Received: 17 November 2023 | Revised: 24 May 2024 | Accepted: 13 June 2024

DOI: 10.1002/cac2.12582

CANCER COMMUNICATIONS Open Access

REVIEW

Evaluation of sodium borocaptate (BSH) and boronophenylalanine (BPA) as boron delivery agents for neutron capture therapy (NCT) of cancer: an update and a guide for the future clinical evaluation of new boron delivery agents for NCT

Rolf F. Barth[1] | **Nilendu Gupta**[2] | **Shinji Kawabata**[3]

[1]Department of Pathology, The Ohio State University, Columbus, Ohio, USA

[2]Department of Radiation Oncology, The Ohio State University, Columbus, Ohio, USA

[3]Department of Neurosurgery, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka, Japan

Correspondence
Nilendu Gupta, Department of Radiation Oncology, The Ohio State University, Columbus, Ohio 43210, USA.
Email: nilendu.gupta@osumc.edu

Abstract

Boron neutron capture therapy (BNCT) is a cancer treatment modality based on the nuclear capture and fission reactions that occur when boron-10, a stable isotope, is irradiated with neutrons of the appropriate energy to produce boron-11 in an unstable form, which undergoes instantaneous nuclear fission to produce high-energy, tumoricidal alpha particles. The primary purpose of this review is to provide an update on the first drug used clinically, sodium borocaptate (BSH), by the Japanese neurosurgeon Hiroshi Hatanaka to treat patients with brain tumors and the second drug, boronophenylalanine (BPA), which first was used clinically by the Japanese dermatologist Yutaka Mishima to treat patients with cutaneous melanomas. Subsequently, BPA has become the primary drug used as a boron delivery agent to treat patients with several types of cancers, specifically brain tumors and recurrent tumors of the head and neck region. The focus of this review will be on the initial studies that were carried out to define the pharmacokinetics and pharmacodynamics of BSH and BPA and their biodistribution in tumor and normal tissues following administration to patients with high-grade gliomas and their subsequent clinical use to treat patients with high-grade gliomas. *First*, we will summarize the studies that were carried out in Japan with BSH and subsequently at our own institution, The Ohio State University, and those of several other groups. *Second*, we will describe studies carried out in Japan with BPA and then in the United States that have led to its use as the

List of Abbreviations: AA, Anaplastic astrocytoma; ABNS, Accelerator-based neutron source; BBB, Blood brain barrier; BMRR, Brookhaven Medical Research Reactor; BNCT, Boron Neutron Capture Therapy; BPA, Boronophenylalanine, a di-hydroxyl boryl derivative of phenylalanine; BSH, Sodium Borocaptate or di-sodium undecahydro-mercapto-*closo*-dodecoborate; DCP-AES, Direct Current Plasma – Atomic Emission Spectroscopy; EORTC, European Organization for Research and Treatment of Cancer; FDA, US Food and Drug Administration; GBM, Glioblastoma multiforme; KURRI, Kyoto University Research Reactor Institute; LAT1, L-type aminoacid transporter-1; LET, Linear Energy Transfer; MST, Mean survival time; OSU, The Ohio State University; PDT, Photodynamic therapy; ppm, Parts per million; $T_{1/2}$, Half life; TMZ, Temazolomide; XRT, External Beam radiation therapy.

primary drug that is being used clinically for BNCT. *Third*, although there have been intense efforts to develop new and better boron delivery agents for BNCT, none of these have yet been evaluated clinically. The present report will provide a guide to the future clinical evaluation of new boron delivery agents prior to their clinical use for BNCT.

KEYWORDS
Boron neutron capture therapy (BNCT), boronophenylalanine (BPA), brain tumors, head and neck cancer, sodium borocaptate (BSH)

1 | BACKGROUND

This review focuses on the two drugs that have been used clinically for boron neutron capture therapy (BNCT). The first drug, di-sodium undecahydro-mercapto-*closo*-dodecoborate ($Na_2B_{12}H_{11}SH$), commonly known as sodium borocaptate (BSH) (Figure 1), was used clinically in Japan as a boron delivery agent for BNCT of patients with brain tumors [1, 2]. The second drug was a di-hydroxyl boryl derivative of phenylalanine, known as boronophenylalanine (BPA) (Figure 1). BPA was used initially to treat patients with cutaneous melanomas [3] and subsequently patients with brain tumors [4], which is the focus of this review. Interested readers are referred to the publications of Kato et al. [5], Kankaanranta et al. [6], and Hirose et al. [7] for the use of BNCT to treat tumors of the head and neck region. BNCT is based on the nuclear capture and fission reactions that occur when the stable isotope, boron-10, is irradiated with low-energy (0.025 eV) thermal neutrons to produce boron-11 in an unstable form, which undergoes instantaneous nuclear fission to produce high-linear energy transfer (LET) alpha particles (stripped down helium nuclei) and recoiling lithium-7 nuclei, as shown below [8].

$$^{10}B+n_{th}[^{11}B]\begin{matrix}\nearrow {}^{4}He+{}^{7}Li+2.79\ MeV\ (6\%)\\ \searrow {}^{4}He+{}^{7}Li+0.48\gamma+2.31\ MeV(94\%)\end{matrix}$$

Prior to 2015, the only source of these neutrons was nuclear reactors, but since then, they have been produced by specially designed accelerator-based neutron sources (ABNSs), which now are being used extensively in Japan [9].

Inorganic boron compounds were first used clinically by Asbury et al. [10], Goodwin et al. [11] in Sweet's laboratory and by Farr et al. [12] in the early 1960's in an attempt to develop more selective boron delivery agents. Soloway et al. [13] at the Massachusetts General Hospital (MGH, Boston, MA, USA) focused on two sulfhydryl-containing boron hydride anions, $B_{12}H_{11}SH^{-2}$ and $B_{10}Cl_8(SH)_2^{-S}$. There are major biological differences between the $B_{12}H_{12}^{-2}$ anion and its mercapto counterpart $B_{12}H_{11}SH^{-2}$, which has the potential to form mixed disulfides with sulfide groups of various proteins [13]. Based on this, biodistribution studies were carried out by Soloway et al. [13] in tumor-bearing mice, and samples of tumor and blood were taken from individual animals. The tumor localizing properties and tumor:blood boron concentration ratios were sufficiently high to suggest that the $B_{12}H_{11}SH^{-2}$ anion of $Na_2B_{12}H_{11}SH$ was the most promising of all the compounds that had been evaluated [13]. Upon his return to Japan, Hiroshi Hatanaka, a neurosurgeon who had been a visiting scientist in Soloway's laboratory, initiated a clinical trial in patients with brain tumors [1, 2]. More detailed information relating to Hatanaka and Farr's early studies initially was provided by Barth et al. [8] in their first comprehensive review article on BNCT. Interested readers are referred to a more recent review by Barth et al. [14] of results obtained using reactor neutron sources for the treatment of high-grade (III-IV) gliomas and recurrent tumors of the head and neck region.

2 | HATANAKA'S CLINICAL STUDIES OF BNCT FOR THE TREATMENT OF BRAIN TUMORS

Between August 1968 and March 1985, Hatanaka et al. [1, 2] treated a total of 77 patients with malignant brain tumors of varying histopathologic types, and among these, 40 purportedly were high-grade gliomas. Initially, patients had de-bulking surgery to remove as much tumor as possible, followed at varying time intervals thereafter with BNCT. Neutron irradiation was carried out at four different Japanese nuclear reactors producing low-energy (0.025 eV) thermal neutrons. Due to their limited depth of penetration, this required that irradiation be administered following removal of a portion of the skull and reflection of the overlying skin flap [1, 2]. This was done in order to increase the depth of penetration of the thermal neutrons and to prevent damage to the skin, which would have occurred if it had not been reflected. Initially, BSH

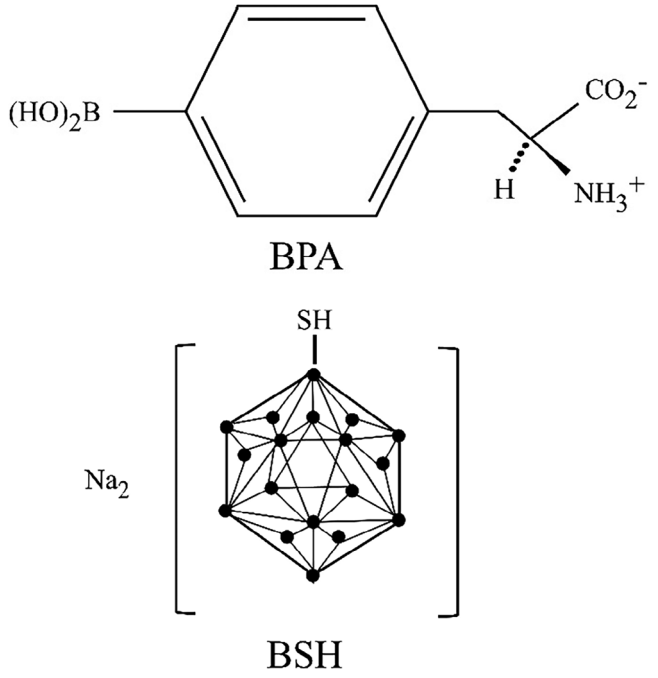

FIGURE 1 Chemical Structure of boronophenylalanine (BPA) and sodium borocaptate (BSH).

was administered via the carotid or vertebral arteries [1, 2] and subsequently intravenously, although it is unclear when this transition occurred. Among the first group of 77 patients that had been treated, those with cortical or subcortical tumors had a 5-year survival rate of 58% and a 10-year survival rate of 29% [1, 2]. As it turned out, these survival data were too good to be true. Most likely, the majority of these patients probably had lower grade rather than high-grade gliomas. The fact that they were of lower grade was substantiated by a recent case report by Kamano et al. [15] on a patient with a diffuse astrocytoma, who had been treated by Hatanaka. BSH was administered via the left internal carotid artery (80 mg/kg) the night before treatment and BNCT was carried out using an unspecified nuclear reactor, which required a radiation time of 5.5 h. The histopathology of the original tumor was unknown, but presumably it was a low-grade glioma, which was apparent when the patient's tumor recurred 7 years later. The patient underwent a second resection of a tumor mass, the histopathology of which revealed grade III radiation damage but no viable tumor cells [15]. The patient subsequently survived for a total of 32 years following BNCT with a reasonably good quality of life. This case report supports the prevailing view that the unusually long survival times of Hatanaka's patients were in large part due to the fact that they had lower rather than higher grade gliomas. Be that as it may, his results were impressive enough to stimulate an interest in BNCT, which had fallen into decline following studies at the MGH [10, 11] and Farr et al.'s [12] unsuccessful clinical trials in the 1950's. Following Hatanaka et al.'s encouraging reports [1, 2], clinical studies were initiated in a number of countries, including the United States, Finland and several other European countries, using either BSH or the more promising drug, BPA. Based on clinical studies carried on patients with cutaneous melanomas by Mishima et al. [3, 16, 17] and the experimental brain tumor studies of Coderre et al. [18, 19] at the Brookhaven National Laboratory (Upton, NY, USA), a clinical trial was initiated. Based on the clinical studies of Chanana et al. [4] and Elowitz et al. [20], BPA became the drug of choice for BNCT.

Almost 10 years later, Hatanaka et al. [21] provided an update on their original report [2]. As of December 1992, 119 patients with gliomas of varying grades had been treated using BSH as the boron delivery agent [21]. Eighteen out of 87 patients, treated on or before May 1987, had lived longer than 5 years, and 9 of them had lived longer than 10 years out of 53 patients operated on or before May 1982. Among the latter, 2 had died at 12 and 17 years following BNCT. Based on these results, it was concluded that BNCT could produce "cures" of what had been regarded as incurable high-grade brain tumors. Sadly, Hiroshi Hatanaka died in May 1994, but in 1997 Nakagawa et al. [22] published an update on their clinical studies using BSH as the boron delivery agent to treat patients with gliomas of varying grades. Between 1968 and 1997, a total of 149 patients received BSH as part of their treatment with BNCT following de-bulking surgery. Among these, 64 patients had a diagnosis of glioblastomas (GBM), 39 had lower grade anaplastic astrocytomas (AA), 17 had grade I or II astrocytomas, and 29 had other tumor types. Finally, there were 29 patients with other types of brain tumors. The patients with gliomas had an overall response rate of 64%. The 2-year survival rate was 12% for patients with GBMs and 56% for patients with AAs. A more realistic picture of the histopathologic diagnoses of Hatanaka et al.'s 173 patients [1], treated between 1968 and 1985, subsequently was provided by Nakagawa et al. [22]. Of those patients who lived more than 3 years, only 10 had GBMs, 14 had AAs, and 9 had low-grade astrocytomas, and the histopathology of the remainder was not specified. Based on this, Hatanaka et al.'s original report [1] of long-term survivors of patients who purportedly had GBMs was based in part on the erroneous histopathologic classification of their tumors. However, the 3-year survival rate of these patients was at least as good as, if not somewhat better than, those patients who had received conventional therapy consisting of surgery and radiotherapy with or without chemotherapy with bis-chlorethyl-nitroso-urea (carmustine) during the same time period. The sum and substance of all of the above was that Hatanaka et al.'s clinical results were sufficiently promising to result in

significant funding from both the National Institutes of Health and the Department of Energy to support BNCT-related research and further clinical trials in the United States.

3 | CLINICAL STUDIES CARRIED OUT IN JAPAN USING BSH AS A BORON DELIVERY AGENT

The only other clinical study carried out in Japan to evaluate BSH as a boron delivery agent was that of Takagaki et al. [23], which consisted of a group of 11 patients who purportedly were diagnosed with GBM. All of these patients had received BSH at a dose of 20 mg/kg body weight at 2.5-16 h prior to surgical removal of their tumors. Boron concentrations in tumor and blood were determined quantitatively by prompt gamma spectroscopy and qualitatively at the cellular level by alpha track autoradiography. There was considerable variability in the brain tumor boron concentrations both quantitatively and qualitatively at varying time intervals following the 90-minute infusion of BSH. Variability in large part was due to differences in the time intervals between BSH administration and debulking surgery, which ranged between 2.5 h and 19 h. As might be expected, there was great variability in the blood boron concentrations, which ranged from 1.6 to 26.6 ppm, and in the tumor boron concentrations, which ranged from 0.5 to 8.6 ppm. These very low tumor boron concentrations would have limited the depth of penetration of thermal neutrons to 12.8 cm. However, no details relating to the neutron irradiation procedure itself were provided. It was very confusing that the biodistribution study involved 11 GBM patients, but the survival data were reported for 16 patients, and no explanation for this inconsistency was provided by the authors. A 3-year survival rate of 31% was reported for 16 patients and a 2-year survival rate of 50% for 8 patients. Plain and simple, these numbers do not add up! Again, the survival data seemed too good to be true. The most likely explanation for the discrepancy was that some patients in the study had lower grade rather than high-grade GBMs, which also had been the case with Hatanaka et al.'s patients [1]. It is noteworthy that these results were never confirmed in another study by this or any other group.

4 | OTHER CLINICAL STUDIES USING BSH AS A BORON DELIVERY AGENT

To the best of our knowledge, the largest therapy study outside of Japan to evaluate BSH as a boron delivery agent for BNCT of patients with high-grade gliomas was carried out by Sauerwein et al. [24] as a European Organization for Research and Treatment of Cancer (EORTC) study 11961 at the Petten High Flux Reactor located in Petten, the Netherlands. As of the time of the writing of their final report, a total of 30 patients had been entered into the study, but only 26 had received BNCT. Neutron irradiation was given in 4 fractions on 4 consecutive days. One day prior to the first irradiation, 100 mg of BSH/kg body weight were administered intravenously. On the following days, both the amount of BSH and its time of administration were modified to attain an average blood boron concentration of 30 parts per million (ppm) over the 4 fractions of BNCT. Of the 26 patients who received BNCT, the mean blood boron concentration over the 4 days was 30.2 ppm. Only one patient developed serious radiation treatment-related toxicity following BNCT. Acute radiation toxicity involving the brain was slightly less than that observed following conventional external beam photon radiation, and late toxicity outside of the brain was mild. The mean survival time (MST) of the all of the patients was not significantly different from one another. All of the patients either died of recurrent brain tumors or had recurrent brain tumors at the time of writing of their final report [25]. The MST of the patients deemed not candidates for BNCT was 6.5 months, and they all died due to local progression of their GBMs. It was concluded that additional studies were necessary in order to come to a definitive conclusion as to the suitability of BSH as a boron delivery agent. To the best of our knowledge, the only other clinical study using BSH was that of Burian et al. [26] in Czech Republic. A total of 5 patients were treated at the epithermal neutron facility at the LVR-15 reactor at the Nuclear Research Institute Rez (Rez, Czech Republic), but the number of patients was not high enough to evaluate the efficacy of BNCT.

Hideghéty et al. [27] carried out a phase I EORTC 11961 clinical trial in a group of 10 patients to evaluate the blood, tumor and selected normal tissue boron concentrations at 12 h following intravenous infusion of BSH at doses of either 100 or 22.9 mg/kg body weight. The average tumor boron concentration was 19.9 ± 9.1 ppm for the patients who were treated with 100 mg of BSH/kg body weight group and 9.8 ± 3.3 ppm for those with 22.9 mg of BSH/kg body weight. The corresponding tumor:blood concentration ratios were 0.6 ± 0.2 and 0.9 ± 0.2 for the patients who were treated with 100 and 22.9 mg of BSH/kg body weight, respectively. The average brain boron concentrations were reported for 4 patients who were treated with 100 mg of BSH/kg body weight group, and the mean was 6.6 ± 2.6 ppm. However, 3 or more tumor tissue samples were taken from only 3 patients. In contrast, as had been reported by Goodman et al. [28], anywhere between 3 and 10 samples were taken from different parts of the same tumor for all of the glioma patients (Figure 2).

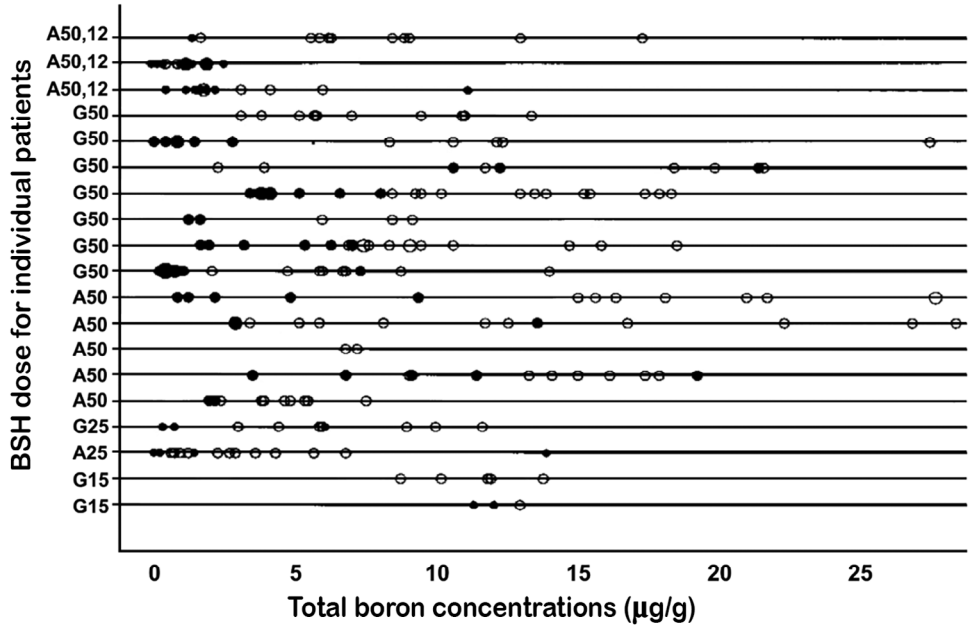

FIGURE 2 Dot plot of total boron concentrations (µg/g) in tumor and normal brain samples for individual patients with either astrocytomas (A) or glioblastomas (G). Patients received sodium borocaptate at a dose of 15, 25, or 50 mg/kg body weight, and tissues were sampled 3-7 h following termination of the infusion except for 3 patients with astrocytomas, from whom tissue samples were taken after 12 h (A50,12). Normal brain boron concentrations are indicated by •, and tumor boron concentrations by ◦. Larger circles (○/●) indicate 2 identical concentrations, and the largest circles (◯/⬤) indicates 3 identical concentrations.

The larger number of samples allowed determination of the great variability in the uptake of BSH in different regions of the tumor, which would have a major impact on the radiation doses delivered to different regions of the tumor.

5 | PHARMACOKINETIC AND TISSUE BIODISTRIBUTION STUDIES OF BSH CARRIED OUT IN THE UNITED STATES

The disappointing clinical results obtained using BSH could have been predicted, based on a number of pharmacokinetic studies, and amongst these the most detailed one was carried out by a group at The Ohio State University (OSU) Medical Center (Columbus, OH, USA) [28]. This study, funded by the US Department of Energy, consisted of a group of 25 patients (10 men and 15 non-pregnant women), 21 years of age or older, with pre-operative diagnoses of GBMs or AAs. Twenty-two of them were patients at the Beijing Neurosurgical Institute (BNI, Beijing, China), which at that time saw the largest number of patients with high-grade gliomas than any other institution in the world, and 3 were patients at the OSU Medical Center. Of the 25 patients, 19 had tumors that were subsequently confirmed by histopathologic examination in the Department of Pathology at OSU to be either GBMs or AAs. These 19 patients constituted the study population, and the remaining 6 had neither of these two types of brain tumors and therefore were excluded from the study. The study plan had been reviewed and approved by the Human Subjects Review Committee of OSU and the US Food and Drug Administration (FDA), which assigned an Investigational New Drug number (34687) to BSH. Since a major part of this study involved Chinese patients at the BNI, the study also received approval by the relevant Chinese health authorities, including the Ethics Committee of the BNI, the Beijing Municipal Health Authority, which has jurisdiction over the BNI, and the Drug Bureau of the People's Republic of China, the Chinese equivalent to the US FDA. Most importantly, because this was a biodistribution and pharmacokinetic study, it had no influence on the type of surgery performed or the type of adjuvant therapy administered after surgery. The BSH drug (#672422, assigned by the Cancer Chemotherapy National Service Center) was synthesized and purchased as a drug substance from Centronics, Ltd. (Croydon, UK). The patients in this study were stratified into 3 groups and received 15 mg (3 patients), 25 mg (3 patients), or 50 mg of boron (13 patients), which corresponded to 26.5, 44.1, or 88.2 mg of BSH/kg body weight. The drug was infused intravenously in 500 mL of normal saline over 1 h. Since the report of Goodman et al. [28] was published in *Neurosurgery*, which still is not an open-access journal, unfortunately it has not reached a

broad audience of readers, and therefore the results are summarized as follows.

Blood boron concentrations were highest at the end of the infusion and then decreased tri-exponentially over the remaining 5 days [28]. For boron doses of 15, 25, and 50 mg/kg body weight, the corresponding blood boron concentrations at 6 h following administration were 20.8, 29.1, and 62.6 μg/mL. The maximum solid tumor boron concentrations for a boron dose of 50 mg/kg body weight at 3-7 h after administration were 17.3 ± 10 μg/g of tumor for AAs and 17.1 ± 5.8 μg/g for GBMs. When averaged over all tumor samples of AAs and GBMs at 3-7 h after infusion, the tumor boron concentrations were 11.9 μg/g, while the normal brain tissue boron concentrations were 5.5 ± 3.9 μg/g brain for AAs and 4.6 ± 5.1 μg/g for GBMs. The corresponding tumor:normal brain boron concentration ratios were 3.8 and 3.2, respectively. Samples of mixed normal brain and tumor had lower concentrations of boron than those of tumor. Following a dose of 50 mg/kg body weight, blood boron concentrations decreased from 104 μg/mL at 2 h to 63 μg/mL at 6 h, and the muscle and skin boron concentrations were 39.2 μg/g and 43.1 μg/g, respectively, during the sampling period of 3-7 h. Taking all of the tissue and blood boron concentrations together, the best tumor boron concentrations were seen at a boron dose of 25 mg/kg body weight at 3-7 h following the end of administration of BSH. Normal brain tissue boron concentrations were consistently lower than tumor boron concentrations. However, tumor boron concentrations were lower than those required for a tumoricidal effect, and there was significant variability within different regions of the same tumor (Figure 2), as well as variability in the uptake of BSH from patient to patient, thereby making any estimate of the radiation dose delivered to the tumor very difficult, if not impossible. Based on these findings, it was concluded that intravenous administration of a single dose of BSH would not be sufficient for a successful therapeutic effect.

6 | STUDIES COMBINING BSH AND BPA AS BORON DELIVERY AGENTS

Based on the clinical studies of several other groups, summarized by Goodman et al. [28], clinical interest in BSH as a boron delivery agent for BNCT of patients with high-grade gliomas almost completely ended. Subsequently, BPA became the only drug that today is being used clinically, with the exception of several reports describing the combination of BSH and BPA. The rationale for this was that the uptake of BSH was dependent upon a breakdown of the blood-brain barrier (BBB) within the tumor, while in contrast the uptake of BPA was dependent upon upregulation of the L-type amino acid transporter-1 (LAT1) in tumors [29, 30]. As recently reported by Watanabe et al. [31], there was an association between tumor expression of LAT1 and the potential efficacy of BNCT. In the first study using a combination of BSH (5 g) and BPA (13 g), Kawabata et al. [32] described the clinical results obtained in 2 patients, one of whom had a GBM and the other a "glial" tumor, which were infused intravenously for 1, 12, and 1 h before neutron irradiation. A marked reduction in tumor volume was seen by magnetic resonance imaging (MRI) at varying numbers of days following BNCT. However, no long-term follow-up information was provided. In a second and more extensive study by Kawabata et al. [30], a total of 21 patients with malignant gliomas, the grades of which were not reported, were treated using a combination of BSH (100 mg/kg) and BPA (700 mg/kg), which were infused intravenously prior to neutron irradiation. The MST was 15.6 months for this cohort versus 10.3 months for 27 patients who had received external beam radiation therapy (XRT). In a second arm of the study, 10 patients received BNCT using both BSH and BPA as boron delivery agents, followed by XRT consisting daily fractions of 2 Gy for a total dose of 20-30 Gy. The MST was 23.5 months for this group compared to 14.1 months for those who only received BNCT, clearly indicating a significant therapeutic gain associated with the combination of BNCT and XRT, as had been reported by Barth et al. [33] in an experimental study combining BNCT with external beam photon irradiation using F98 rat glioma model [34].

7 | PHARMACOKINETICS AND BIODISTRIBUTION STUDIES OF BPA

The pioneering studies by Mishima et al. [3] led to the introduction of BPA as a clinical boron delivery agent for BNCT of patients with cutaneous melanomas [35]. Initially, this was administered peri-lesionally [3] and subsequently intravenously to patients with cutaneous melanoma involving other regions of the body [16]. Coderre et al. [18, 19] were the first to demonstrate that BPA, initially administered orally by gavage and subsequently intravenously, was effective in treating Fischer rats bearing intracerebral implants of the 9L gliosarcoma, which is highly immunogenic [34]. These studies laid the groundwork for the most comprehensive clinical pharmacokinetic and tissue biodistribution studies of BPA in patients with GBM carried out by Elowitz et al. [20]. Varying doses (130-250 mg/kg body weight) of a fructose complex of BPA were administered intravenously 2-3 h prior to the start of the craniotomies of 16 patients with GBMs. Blood samples were taken during and after a

2-hour infusion of BPA. Multiple samples of tumor, normal brain and scalp were taken at surgery for boron determinations. Blood clearance was biphasic with the first phase (re-distribution) having a half-time ($T_{1/2}$) of ~1.2 h lasting 30-40 min and with the second phase (elimination) having a $T_{1/2}$ of ~8.2 h. There was a high degree of variability in the tumor boron concentrations of multiple samples taken from the same patient, as well as patient-to-patient variability [20]. Similarly, tumor:blood boron concentration ratios were highly variable [20] and appeared to be related to the cellularity of the samples [36, 37]. Normal brain boron concentrations were either less than or equal to those seen in the blood. Tumor:blood boron concentration ratios were highly variable from patient to patient and ranged from 0.3 to 3.5. However, the data obtained were encouraging enough to initiate a phase I/II clinical trial between 1994 and 1998 in the Medical Department of the Brookhaven National Laboratory using the Brookhaven Medical Research Reactor (BMRR) [4, 38]. The median time to progression and median survival time of 37 patients treated using the BMRR were 31.6 weeks and 13.0 months, respectively. Local control and survival times were similar to those of historical controls at the time the study was carried out between 1994 and 1999 [38]. These clinical results probably could have been predicted based on the biodistribution and tumor boron concentrations reported by Elowitz et al. [20] and the relation of boron concentrations to tumor cellularity reported by Coderre et al. [36]. Nevertheless, they laid the groundwork for a number of clinical studies carried out in Japan [39–41], Finland [42], Sweden [43], and the United States [4, 44] for patients with brain tumors. The clinical study carried out in Sweden was noteworthy in that the dose of BPA was increased to 900 mg/kg body weight and the duration of its infusion was increased to 6 h [45]. A total of 12 patients were treated with BNCT, 11 of whom also received Temazolomide (TMZ). The median survival time from initial diagnosis was 22 months [46, 47]. This suggested that the increased dose and prolonged infusion time of BPA and the inclusion of TMZ enhanced the efficacy of BNCT. In contrast, shorter survival times were reported by the Japanese [48] and Finnish groups [49], of patients treated at the same time who had received lower doses and shorter infusion time of BPA than the Swedish patients.

However, there is a paucity of other data similar to those reported by Goodman et al. [28] on the tumor versus normal brain uptake of BSH and those reported by Elowitz et al. [20] on the tumor versus normal brain uptake of BPA in patients with brain tumors. More recently, Hiratsuka et al. [35] have presented a brief review on the pharmacokinetics of BPA in the blood following a two-stage infusion of 500 mg/kg of BPA (400 mg/kg BPA for 2 h and 100 mg/kg for 1 h) during neutron irradiation. However, no tumor boron concentrations were reported. Koivunoro et al. [50] carried out a biokinetic analysis of tissue boron-10 concentrations in a group of 98 patients with gliomas who received a 2-hour intravenous infusion of BPA at doses ranging from 290 to 450 mg/kg. Blood samples were taken at 20-min intervals until the end of irradiation. A closed 3-compartment model was used to predict the changes in the total boron concentrations as a function of time in brain and tumor tissues during BNCT treatments. Although all of the calculated tumor:normal brain boron concentration ratios were in a very narrow range of 2.0-2.5, there was considerable variability in the calculated average tumor boron concentrations ranging from 44 to 93 mg/g tumor. Since these were calculated and not quantitatively determined boron concentrations, nothing could be said about the intra-tumoral variability of the boron concentrations, as had been determined by direct boron measurement of multiple samples from the same tumor, as reported by Elowitz et al. [20]. To the best of our knowledge, only Elowitz et al. [20] had determined the intra-tumoral variability of boron concentrations following the intravenous administration of BPA in patients with brain tumors. It would be of great interest if such a study could be carried out in glioma patients who have received BPA prior to their initial surgery, a subset of whom ultimately might be candidates for BNCT. Finally, and potentially very important, was the recent report of Kondo et al. [51], indicating that 3-dihydroxyboryl phenylalanine was 100 times more water soluble than 4-dihydroxyboryl phenylalanine. This practically means that the 3-BPA would not need to be complexed with fructose or sorbitol in order to increase its solubility prior to intravenous administration.

8 | CLINICAL STUDIES IN JAPAN AND FINLAND USING BPA FOR THE TREATMENT OF HIGH-GRADE GLIOMAS AND RECURRENT TUMORS OF THE HEAD AND NECK REGION

The clinical results of the Brookhaven clinical trial [4, 38] led to the studies in Japan [40, 41], Finland [42], and Sweden [45–47] for patients with high-grade gliomas and in Japan [5, 7] and Finland [6] for recurrent tumors of the head and neck region. Over the next 25 years, a large number of patients have been treated, initially using nuclear reactors as neutron sources and ABNSs since 2012 in Japan [52–54]. In the present review we have focused more on the pharmacokinetics, pharmacodynamics and tumor biodistribution of BPA. Following the first clinical studies in the United States using BPA [4, 38, 44], BNCT for high-grade gliomas was initiated in Japan using BPA at

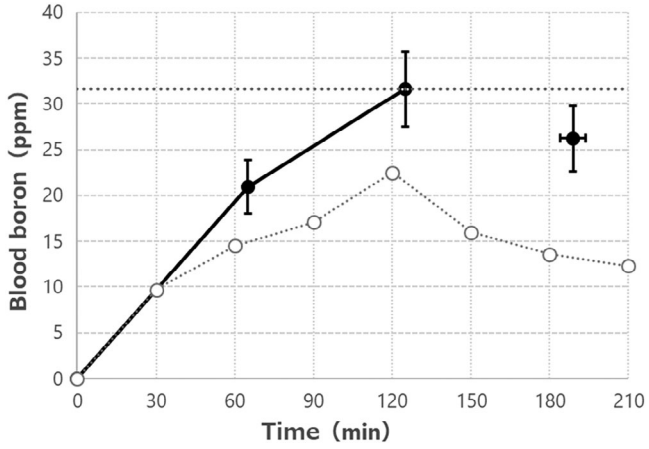

FIGURE 3 Blood boron concentrations from a phase II clinical trial of accelerator-based BNCT for malignant gliomas [64] (solid line) and from a previous study by Elowitz et al. [20] (dotted line). BPA (SPM-011) was administered intravenously at a dose of 400 mg/kg body weight over 2 h, followed by a continuous infusion of BPA at a dose of 100 mg/kg body weight until the completion of neutron irradiation. Neutron irradiation with ABNS was started 2 h post the initiation of BPA infusion (200 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 2 h + 100 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 1 h). The duration of irradiation was carefully managed to ensure the scalp irradiation dose did not exceed 8.5 Gy-Eq. Abbreviations: ABNS, accelerator-based neutron source; BNCT, boron neutron capture therapy; BPA, boronophenylalanine.

a dose of 250 mg/kg, administered intravenously over 1 h [40, 41]. The group at the University of Tsukuba (Ibaraki, Japan) [9], led by Matsumura, continued their clinical trial using the same protocol and the Japan Research Reactor-4. Researchers at Osaka Medical and Pharmaceutical University (Takatsuki, Osaka, Japan) [55] and Kyoto University Research Reactor Institute (KURRI, Kumatori-cho, Osaka, Japan) [56] conducted BNCT clinical trials for patients with recurrent malignant gliomas using the same dosing protocol for BPA alone or in combination with BSH at the KURRI. In a subsequent trial, 700 mg/kg of BPA was administered as a continuous 6-hour infusion for patients with newly diagnosed malignant gliomas [56]. Based on its safety and efficacy, the same protocol also had been used for the treatment of patients with high-grade, difficult-to-treat, high-grade meningiomas [57, 58]. In a study involving 15 patients with recurrent head and neck cancers, treated at the KURRI between June 2004 and February 2006, the total dose of BPA-fructose was 500 mg/kg body weight (400 mg/kg administered at a constant rate of 200 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 2 h prior to irradiation, followed by the remaining 100 mg/kg during irradiation). The blood boron concentration immediately after irradiation averaged above 25 ppm and maintained at a constant blood concentration during during irradiation [56]. In contrast, the blood boron concentration immediately after irradiation in 5 patients treated with 250 mg/kg of BPA (fructose solution) could not be maintained at 20 ppm. The average boron concentration in whole blood immediately after irradiation in 8 patients treated with 500 mg/kg was 19.5 ppm, compared with an average of 30.4 ppm before irradiation, showing pre- and post-irradiation variability [56]. By reducing the intravenous dose rate from 200 to 100 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ of BPA during irradiation, the blood boron concentration could be maintained at 20 ppm. If discrepancies between the pre-dose prescription and post-dose evaluation were large, the treatment would be suboptimal and could cause serious clinical problems such as adverse or ineffective treatment due to over- or under-delivered doses. This was done in order to obtain approval for BNCT from the Japanese Ministry of Health, Labor and Welfare (Tokyo, Japan).

From 2005 to 2012, BPA was administered at a dose of 400 mg/kg for 2 h prior to neutron irradiation, followed by its continuous administration at 100 mg/kg during irradiation in patients with recurrent high-grade meningiomas [57, 58]. The BPA used in the clinical trials carried out in Japan was either a fructose complex or sorbitol complex of BPA. The latter has the trade name of SPM-011, which was developed by Stella Pharma J.V. Co. Ltd. (Osaka, Japan). Complexing L-D-sorbitol with BPA made it easier to dissolve and more stable than the fructose formulation that had been used in the past. The fructose complex was used for BNCT of patients with gliomas [55, 59], meningiomas [57–60], head and neck cancers [5, 6, 61], cutaneous and extra-cutaneous melanomas [35, 60], and Pagets disease of the vulva and perenium [35]. The sorbitol complex was used for patients with meningiomas [57, 58], glioblastomas [59], and recurrent tumors of the head and neck region [61]. During accelerator-based neutron irradiation, it was mandated by the Japanese regulatory authorities to infuse BPA during irradiation in order to maintain the whole blood ^{10}B concentration at 20 ppm (Figure 3). This was used as a surrogate for the tumor boron concentration, since tumor boron concentration could not be measured in real time. Most recently, a clinical trial has been initiated at Gachon University, Gil Medical Center (Gachon, Republic of Korea) for the treatment of patients with recurrent high-grade gliomas using an ABNS [62]. The patients received BPA at a total dose of 500 mg/kg infused over 3 h (166 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$) followed by neutron irradiation, which was administered 1 h after termination of the infusion. The maximum calculated normal brain radiation doses of 9, 11 or 13 Gy-Eq [63]. However, at the time of this writing, no clinical results relating to this trial have been reported.

9 | STRATEGIES FOR IMPROVING THE DELIVERY OF BSH AND BPA

As reported by Hatanaka et al. [21], BSH initially was administered intra-arterially via the carotid or vertebral arteries at a dose of 30-50 mg/kg body weight the night before neutron irradiation. At some unknown point later in time the route was changed to intravenous administration at a BSH dose of 60-80 mg/kg body weight [65]. Subsequently, in the EORTC 11961 clinical trial [25], BSH at a dose of 100 mg/kg body weight was administered intravenously 8-14 h prior to each neutron irradiation and a dose of 1 mg/kg body weight was administered during irradiation in order to achieve a blood boron concentration of 30 ppm. After infusion of BSH, the tumor:blood concentration ratio was 1.2 ± 0.4, and the corresponding tumor:normal tissue boron concentration ratios varied from 3.6:1 to 1:1 depending upon the tissue. BNCT was performed in 4 fractions on 4 consecutive days. Horn et al. [66] carried out a detailed study on the pharmacokinetics and tissue distribution of BSH in a group of 10 patients with either astrocytomas or GBMs. BSH at a dose of 25 mg/kg body weight was administered intravenously over 1 h, and craniotomies and tumor resections were carried out at varying time intervals ranging from 3 to 18 h following termination of the infusion. Average tumor boron concentrations ranged from 4.7 to 16.6 μg/g tumor weight, but there were no data on intra-tumoral variability. Tumor:blood boron concentration ratios ranged from 0.318 to 3.357, and 6 of the 10 patients had tumor:blood boron concentration ratios of 1:5 or greater, which was considered the necessary ratio for effective BNCT. Based on these findings, it was concluded that the most advantageous time interval between BSH infusion and BNCT was 12 h. However, and most importantly, the retention of BSH in the kidneys was very high and potentially nephrotoxic if repeated infusions of BSH were given [66]. The intravenous route of administration was used in all of the other pharmacokinetic and biodistribution studies of BSH, as summarized by Goodman et al. [28].

The clinical studies combining BSH and BPA also have been summarized by Miyatake et al. [59] and more recently by Cheng et al. [67] who included a very useful table summarizing the clinical studies described in this section. There has been a great variability in the clinical protocols employed for the dosage and timing for the administration of both BSH and BPA, and surprisingly the optimum dosing and timing regimens have yet to be determined. As has been described by Miyatake et al. [55] and Kawabata et al. [64], a two-step administration of BPA based on blood boron concentrations was employed to stabilize blood and presumably tumor boron concentrations during the irradiation procedure. Again, pharmacokinetic and tumor tissue distribution studies, such as those reported by Elowitz et al. [20] and Goodman et al. [28], could provide important data to support this approach.

10 | ANIMAL STUDIES TO OPTIMIZE THE DELIVERY OF BSH AND BPA

Barth et al. [68–70] and Yang et al. [71–74] have carried out extensive studies to optimize the delivery of BSH and BPA using the F98 rat glioma model. They compared the intravenous route of administration to intra-carotid administration for BSH and BPA with or without BBB disruption. This was achieved by the intra-carotid infusion of a hyperosmotic solution (25%) of mannitol prior to the intra-carotid administration of either BSH or BPA [70]. The lowest tumor boron concentrations were seen in rats that received either BSH or BPA intravenously (12.9 and 20.8 μg/g, respectively). The highest concentrations, almost 4-fold greater, were seen in rats that received BSH or BPA by intracarotid administration combined with BBB disruption (48.6 μg/g and 94.5 μg/g, respectively). The MST of F98 glioma-bearing rats that received either BSH or BPA by intravenous injection followed by BNCT were 33 and 37 days, respectively, and by intra-carotid injection were 40 and 52 days, respectively. The greatest increase in MST was seen in rats that received BPA by intra-carotid administration combined with BBB disruption (95 days). Based on the studies described above, it was concluded that maximizing the concentrations of BPA by intra-carotid administration combined with BBB disruption increased the physical radiation dose from 33.84 Gy to 119.67 Gy with a corresponding increase in the MST, as indicated above. Furthermore, optimizing the mode of delivery of BSH and BPA has significant impacts on tumor boron concentrations, MSTs, and the physical radiation and relative biological effective (RBE) doses delivered to the tumor.

Although Hatanaka et al. [1, 2] initially administered BSH by intra-carotid administration, this probably was clinically too challenging, and they eventually settled on the much easier intravenous route of administration. To the best of our knowledge, other than Hatanaka et al.'s early protocol that employed intra-arterial administration of BSH, this route has never been investigated clinically using BPA. The one exception was a pilot study carried out by Cruickshank et al. [75] comparing tumor uptake of BPA in one patient who received intravenous administration of BPA and in another patient who received intra-carotid administration of BPA combined with BBB disruption. However, no further studies were reported

using this approach. These data suggest that there still may be a role of BSH and BPA combined with some alternative methods to clinically enhance their delivery to brain tumors. This could include osmotic opening of the BBB [76] by means of pulsed or focused ultrasound [77–79]. Although BBB disruption has been employed by intracarotid administration of cytoreductive chemotherapeutic agents by Priest et al. [76], it still has not been widely accepted by the neurosurgical community [79].

11 | EVALUATION OF NEW BORON DELIVERY AGENTS FOR BNCT

One of the most important priorities for the advancement of BNCT as a cancer treatment modality is the development of new and better boron delivery agents. Hattori et al. [80] recently have described in detail how such agents should be evaluated in vitro and in vivo. The latter include acute toxicity of a single dose, boron uptake in various organs, and in tumor-bearing small animals by means of direct [81] or inductively coupled plasma atomic absorption spectroscopy [82] and cellular localization within tumor cells using techniques such as secondary ion mass spectrometry [82, 83] and alpha track autoradiography [84]. In the case of boron delivery agents, these should be intrinsically non-toxic, and most importantly, dose escalation studies should be carried out to determine the maximum non-toxic attainable tumor boron concentration in tumor-bearing animals. Once these studies have been completed, studies in large animals such as non-tumor-bearing dogs could be initiated. These should include toxicologic evaluation, normal tissue biodistribution, pharmacokinetics and ideally neutron irradiation of the target site. Such studies were carried out by Hatanaka et al. [85] in their evaluation of BSH. Detailed clinical evaluation of BSH, as previously described in this review, was carried out by Goodman et al. [28], which could serve as a guide on how promising new boron delivery agents might be evaluated clinically (Table 1).

The preclinical evaluation of BPA has been described in detail by Mishima [16]. As summarized by Barth [86], Mishima et al.'s [87] initial studies were carried out in Duroc pigs that have a propensity to develop cutaneous melanomas and subsequently in melanoma-bearing hamsters. BPA was administered intravenously, and subsequently the tumor site was irradiated with neutrons, which resulted in complete disappearance of the melanomas [3]. Based on this, a clinical trial was initiated in patients with cutaneous melanomas by means of perilesional injection of BPA, followed by neutron irradiation, which resulted in complete regression of the tumor. Similar results were obtained in several other patients with cutaneous melanomas, and these results subsequently led to the animal studies carried out by Coderre et al. [19] and the clinical study by Elowitz et al. [20], as described earlier in this review. These animal studies subsequently paved the way for the clinical trial carried out in the Medical Department of the Brookhaven National Laboratory [4]. Nowadays, the requirements for a phase I trial, as described by Eisenhauer et al. [88], have gone far beyond that which was required for BSH and BPA. These requirements present a much greater challenge for the future clinical development of new boron delivery agents for BNCT.

12 | WHERE DO WE GO FROM HERE?

There is a broad consensus of opinion among clinicians that at present, BPA is the primary boron delivery agent that can be used for the treatment of cancer patients. That is not to say that BSH or derivatives of it might not be useful in the future as a boron delivery agent for certain types of tumors [89]. What is especially attractive about BSH is that it has 12 boron atoms per molecule, and this provides a strong incentive to develop new delivery agents incorporating the BSH molecule. Hundreds of potential boron delivery agents for BNCT have been described in the chemical and biologic literature [90–101]. There are many excellent reviews covering this topic, and the earliest of these were those of Hawthorne [94] and Soloway et al. [98], among the later are those of Zhu et al. [101], Barth et al. [102], and the most recent ones are those of Couto et al. [93], Jililian et al. [95], Sawuerwein et al. [96], Oloo et al. [103] and Monti-Hughes et al. [104]. Yet, despite this voluminous literature relating to boron delivery agents for BNCT, to the best of our knowledge, none of these agents have been evaluated in any animals larger than mice and rats. The one exception was a tetrakiscarborane carboxylate ester of 2,4(a,b-dihydroxyethyl)-deuteroporphyrin IX [105], also known as boronated protoporphyrin (BOPP) which was synthesized by Kahl et al. [106] and was evaluated in mice [107], rats [107], and dogs [105, 108]. Biodistribution studies were carried out in C6 glioma-bearing mice [107] and 9L glioma-bearing rats [109], which revealed that BOPP had attained a tumor:normal brain boron concentration ratios of up to 400:1 [109]. Based on toxicologic [105], pharmacokinetics [108], and tissue biodistribution studies [108] that were carried out in dogs, it was concluded that BOPP did not have clinically significant toxicity [105]. Furthermore, pharmacokinetic and tissue biodistribution studies suggested that BOPP might be suitable as a sensitizing agent for photodynamic therapy (PDT), which is another binary therapeutic modality [107]. Based on these preclinical studies, Rosenthal et al. [110, 111] and Stylii

TABLE 1 A stepwise guide for the clinical evaluation of new boron delivery agents.[a]

Study goal	Samples to collect and analyze
Pharmacokinetic studies with at least 3 dose levels of the boron delivery agent	Sampling of blood and urine for 120 h following administration of the boron delivery agent. Blood samples should be collected at the start of the infusion, and at 15 and 30 min and 1, 2, 4, 7, 13, 24, 48, 72, 96 and 120 h following the infusion to calculate the pharmacokinetic and excretory profiles of the agent
Define excretion profile of the boron delivery agent	Sampling of urine for each 24-hour interval for 5 days.
Boron in tumor	Multiple samples of the resected tumor, as well as infiltrating and necrotic tumor and a mixture of tumor and normal tissues.
Extra-tumoral boron determinations	Sampling of the skin, bones and muscles during surgery

[a]As reported by Goodman et al. [23] for the evaluation of BSH, patients should be informed that all the following steps will not have any impact on their treatment. The evaluation of new boron delivery agents might require modification, based on their expected uptake, pharmacokinetics and requirements of the relevant drug regulatory authorities.

et al. [112, 113] initiated a Phase I Australian clinical trial of BOPP as a photosensitizer for PDT of patients with recurrent high-grade gliomas. BOPP was administered intravenously followed by intracerebral PDT delivered to the site of the tumor in patients with recurrent GBMs. Although there was a modest increase in patient survival times, it was concluded that infiltrative tumor cells invariably resulted in tumor progression, leading to death of the patients. However, as far as we can determine, there were no further studies using BOPP as a photosensitizer for PDT in patients with high-grade gliomas. Similarly, no clinical studies ever were initiated to evaluate BOPP as a boron delivery agent for BNCT. Rejection of BOPP as a boron delivery agent may have been based on studies in 9L gliosarcoma-bearing rats, which revealed unacceptable toxicity following intravenous administration and great variability in tumor boron concentrations following intracerebral administration by convection-enhanced delivery [109].

To the best of our knowledge, no other boron delivery agents have been used clinically for BNCT other than BSH, which was first used by Hatanaka et al. [1], and BPA, which was first used by Mishima et al. [17]. The detailed clinical study with BSH, which was carried over 25 years ago by Goodman et al. [28], provided a guide for future clinical studies to evaluate new boron delivery agents that have been shown to be promising in dogs and ultimately in humans. Based on the studies described above, it should be possible to reach a conclusion as to whether other agents should be a candidate for clinical use. New delivery agents will then require the submission to the appropriate local and national health authorities of all of the data obtained from the studies described above, including adverse events in animals that could be attributed to their administration. However, up to the present time, no agent other than BPA has reached this stage.

One of the advantages that Barth et al. [68–70, 114] and Yang et al. [71–74] have had in the preclinical evaluation of BSH, BPA, carboranyl porphyrins, nucleosides, and boronated epidermal growth factor receptor (EGFR)-targeting monoclonal antibodies [102] was that they could carry out not only biodistribution studies but also therapy studies. These initially were carried out using the BMRR and subsequently at the Massachusetts Institute of Technology Research Reactor (MITRR). Unfortunately, the BMRR was decommissioned many years ago, and MITRR, to the best of our knowledge, has not been used for BNCT studies since those carried out by Coderre et al. [18, 19], Barth et al. [69, 70], and Yang et al [71, 74] over 15 years ago. It remains to be determined if the new BNCT treatment facilities that have ABNSs also can be used for animal studies. Hopefully they can, and this would greatly advance therapeutic evaluation of the most promising of the myriad of boron delivery agents that have been described in the chemical and biological literature [90–101]. This is of paramount importance since the future success of BNCT largely depends on the development of new and better boron delivery agents than BPA and BSH, each of which has a number of significant shortcomings.

The theoretical advantage of BNCT compared to other radiotherapeutic modalities is that in theory it is the radiation oncologists' ideal type of radiation therapy, in that it specifically targets malignant cells and spares normal cells. However, this is not only an advantage but also a significant challenge, especially in using BNCT to treat patients with high-grade gliomas. The biodistribution studies by Elowitz et al. [20] with BPA and by Goodman et al. [28] with BSH in patients with GBMs and AAs revealed that there was significant variability in the uptake of these boron delivery agents in different samples of the same tumor. There are many reasons for this varibility, including the extensive phenotypic and genotypic cellular

heterogeneity and their invasive properties, the admixture of necrotic and non-necrotic regions within the same tumor, and perhaps most importantly the complex tumor microenvironment [115].

High-grade gliomas are the most difficult of all human cancers to treat by virtue of the fact that they are highly infiltrative of the normal brain and have a highly immune-suppresive microenvironment [116]. All of these variables may have a significant impact on the cellular uptake of chemotherapeutic agents, and more specifically the two boron delivery agents BSH and BPA, which have been used clinically. The optimum method, dosing and timing to deliver BSH and BPA has yet to be determined, and at the present time the only reliable indicator of their efficacy is patient survival time. There are a number of different regimens for the delivery of BPA [117], but only one of them has been evaluated at the time of their first surgical resection although positron emission tomography imaging of 18-fluoro-BPA has provided some useful information on tumor uptake [117]. However, it is incapable of detecting the variability of cellular uptake of BPA, and uptake alone can be very misleading. As reported by Kawabata et al. [118] using the F98 glioma model, carboranyl porphyrins were administered intracerebrally to F98 glioma-bearing rats by convection-enhanced delivery. The tumor uptake of carboranyl porphyrins, as determined by direct current plasma-atomic emission spectroscopy (DCP-AES), was many times greater than that of BPA administered intravenously [69, 70], and yet the survival times were very similar to those obtained following intravenous administration of BPA [118]. An explanation for this was provided by postmortem microscopic examination of the brains of these rats, which revealed that the apparent high tumor uptake of carboranyl porphyrins was attributable to uptake by tumor-infiltrating macrophages and not the tumor cells [118]. This observation provides a caveat to the studies carried out by Elowitz et al. [20] with BPA and by Goodman et al. [28] with BSH, that high tumor boron uptake, as determined by a method such as DCP-AES, does not provide an accurate picture of the actual cellular uptake of the boron delivery agent. Support for this was provided by Coderre et al. [36] who related the boron concentrations with cellularity indices of 107 tumor samples. They found that tumor boron concentrations ranged from 2.7 to 41.3 μg ^{10}B/g over the range of BPA doses that were administered. There were poor associations between the mean tumor boron concentration for each patient with the dose delivery regimen for BPA and therapeutic regimens [4, 38]. This will be a major challenge for the future clinical success of identifying a boron delivery agent that will be effective for BNCT of patients with recurrent, high-grade gliomas.

13 | CONCLUSIONS

To re-emphasize, the purposes of this review were twofold. *First*, to summarize the clinical pharmacokinetic and biodistribution studies that have been carried out with BSH and BPA and how these have led to clinical trials for treating patients with high-grade gliomas. *Second and third*, and equally as important, to provide a template, as described in Table 1, on how new boron delivery agents might be evaluated before being used clinically to treat patients. The evaluation of BPA, as described by Elowitz et al. [20] and Coderre et al. [36] and of BSH by Goodman et al. [28] provides a plan for the future clinical evaluation of the most promising of the hundreds of boron delivery agents that have been described in the chemical and biological literature [91–102]. Sadly, none of these, except for BOPP [107, 119], have reached the stage of clinical evaluation, and this was for PDT rather than BNCT. As reported by Elowitz et al. [20] and Goodman et al. [28], both BPA and BSH are less than ideal boron delivery agents for BNCT of patients with GBMs due to the great variability in their uptake in different regions of the same tumor. This variability unquestionably accounts for the less than curative clinical results obtained in treating patients with the most challenging of all human cancer, high-grade gliomas. The logistics of carrying out such clinical studies have been described by Elowitz et al. [20] and in even more detail by Goodman et al. [28]. Unfortunately, however, both studies were published in the non-open access journal, *Neurosurgery*, and this has significantly limited their accessibility, even today. We hope that this review, will make available to a broad audience of readers interested in BNCT of what needs to be done to evaluate the most promising of the hundreds of boron delivery agents that, as of yet, are still in an early stage of pre-clinical evaluation. Conceivably, clinical studies of promising boron delivery agents initially could be carried out in patients with recurrent tumors of the head and neck region, where multiple samples could be taken in different regions of the same tumor. This is done by a surgeon, who is able to extend the margins of tumor resection when guided by a surgical pathologist in order to remove all of the tumor. The future success of BNCT is dependent upon the development of new and better boron delivery agents for not only brain tumors and head and neck cancers but also other types of cancers.

The various challenges that make BNCT clinical trials very complex to design, implement, and get meaningful clinical results have been summarized by Gupta et al. [120]. One of the most significant challenges is that different boron delivery agents probably will have very different uptake pharmacokinetic and pharmacldynamic profiles

in tumors and normal tissues. While it is common to report average boron concentrations in the tumor and critical structures, the micro-dosimetric impact of this high-LET radiation therapy is completely dependent on how unformly the ^{10}B is distributed within the tumor. Perhaps even more important is that all of the tumor cells presumptively must have the required amount of boron to sustain a lethal $^{10}B(n,\alpha)^{7}Li$ capture reaction. To date, BNCT clinical trials have not focused on evaluating and standardizing the optimal boron dosing delivery regimen. Unfortunately, this has resulted in variations in the clinical results obtained in these trials. Not surprisingly, this has limited the enthusiasm of a large group of radiation oncologists for BNCT as a cancer treatment modality. If BNCT is to be widely accepted as a cancer treatment modality, there must be standardization of various aspects of the design of clinical trials, and implementation and reporting of their results. Most importantly, there is a need for a future plan to carry out multi-institution clinical trials, which have been the key to success in developing new cancer treatment modalities. This could become a reality with the increasing number of ABNSs in Japan, China, and hopefully in other countries.

AUTHOR CONTRIBUTIONS

The majority of the manuscript was written by Drs. Barth and Gupta, and Dr. Kawabata contributed the sections reviewing the studies with BPA.

ACKNOWLEDGMENTS

The present report is dedicated to the memory of Professors Hiroshi Hatanaka and Yutaka Mishima in recognition of their pioneering clinical contributions in making BNCT a cancer treatment modality, to Professor Emeritus Albert H. Soloway in recognition of his pioneering studies in the design and synthesis of a variety of boron compounds, including BSH, as potential delivery agents for BNCT and in celebration of his 98th birthday, and finally in memory of our friend and recently deceased colleague, Joseph Goodman, who was the leader of the pioneering study summarized in the present manuscript.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

No external funding supported this review manuscript

DATA AVAILABILITY STATEMENT

As a review publication, no data are presented in this publication.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

ORCID

Nilendu Gupta https://orcid.org/0000-0003-0461-0570

REFERENCES

1. Hatanaka H, Amano K, Kamano S, Sano K. Clinical experience of boron-neutron capture therapy for malignant brain tumors (1968 - 1985). In: Hatanaka H, editor. Boron neutron capture therapy for tumors. Japan: Nishimura Niigata; 1986:447–449.
2. Hatanaka H, Kamano S, Amano K, Hojo S, Sano K, Egawa S, et al. Clinical experience of boron-neutron capture therapy for gliomas-a comparison with conventional chemo-immuno-radiotherapy. In: Hatanaka H, editor. Boron neutron capture therapy for tumors. Japan: Nishimura Niigata; 1986:349–378.
3. Mishima Y, Honda C, Ichihashi M, Obara H, Hiratsuka J, Fukuda H, et al. Treatment of malignant melanoma by single thermal neutron capture therapy with melanoma-seeking 10B-compound. Lancet. 1989;2(8659):388–389.
4. Chanana AD, Capala J, Chadha M, Coderre JA, Diaz AZ, Elowitz EH, et al. Boron neutron capture therapy for glioblastoma multiforme: interim results from the phase I/II dose-escalation studies. Neurosurgery. 1999;44(6):1182–1192; discussion 92-3.
5. Kato I, Fujita Y, Maruhashi A, Kumada H, Ohmae M, Kirihata M, et al. Effectiveness of boron neutron capture therapy for recurrent head and neck malignancies. Applied Radiation and Isotopes. 2009;67(7, Supplement):S37–S42.
6. Kankaanranta L, Seppala T, Koivunoro H, Saarilahti K, Atula T, Collan J, et al. Boron neutron capture therapy in the treatment of locally recurred head-and-neck cancer: final analysis of a phase I/II trial. Int J Radiat Oncol Biol Phys. 2012;82(1):e67–e75.
7. Hirose K, Konno A, Hiratsuka J, Yoshimoto S, Kato T, Ono K, et al. Boron neutron capture therapy using cyclotron-based epithermal neutron source and borofalan ((10)B) for recurrent or locally advanced head and neck cancer (JHN002): An open-label phase II trial. Radiother Oncol. 2021;155:182–187.
8. Barth RF, Soloway AH, Fairchild RG. Boron neutron capture therapy of cancer. Cancer Res. 1990;50(4):1061–1070.
9. Matsumura A, Asano T, Hirose K, Igaki H, Kawabata S, Kumada H. Initiatives Toward Clinical Boron Neutron Capture Therapy in Japan. Cancer Biother Radiopharm. 2023;38(3):201–207.
10. Asbury AK, Ojemann RG, Nielsen SL, Sweet WH. Neuropathologic study of fourteen cases of malignant brain tumor treated by boron-10 slow neutron capture radiation. J Neuropathol Exp Neurol. 1972;31(2):278–303.
11. Goodwin JT, Farr LE, Sweet WH, Robertson JS. Pathological study of eight patients with glioblastoma multiforme treated by neutron-capture therapy using boron 10. Cancer. 1955;8(3):601–615.
12. Farr LE, Sweet WH, Robertson JS, Foster CG, Locksley HB, Sutherland DL, et al. Neutron capture therapy with boron in the treatment of glioblastoma multiforme. Am J Roentgenol Radium Ther Nucl Med. 1954;71(2):279–293.

13. Soloway AH, Hatanaka H, Davis MA. Penetration of brain and brain tumor. VII. Tumor-binding sulfhydryl boron compounds. J Med Chem. 1967;10(4):714–717.
14. Barth RF, Vicente MG, Harling OK, Kiger WS, 3rd, Riley KJ, Binns PJ, et al. Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer. Radiat Oncol. 2012;7(1):146.
15. Kamano S, Matsuyama M, Minamimura K. A Case of Diffuse Astrocytoma with 32-year Survival after Boron Neutron Capture Therapy. NMC Case Rep J. 2020;7(4):211-215.
16. Mishima Y. Selective Thermal Neutron Capture Therapy of Cancer Cells Using their Specific Metabolic Activities—Melanoma as Prototype. In: Mishima Y, editor. Cancer Neutron Capture Therapy. Boston, MA: Springer US; 1996:1–26.
17. Mishima Y, Ichihashi M, Hatta S, Honda C, Yamamura K, Nakagawa T, et al. First human clinical trial of melanoma neutron capture. Diagnosis and therapy. Strahlenther Onkol. 1989;165(2-3):251–254.
18. Coderre JA, Glass JD, Fairchild RG, Micca PL, Fand I, Joel DD. Selective delivery of boron by the melanin precursor analogue p-boronophenylalanine to tumors other than melanoma. Cancer Res. 1990;50(1):138–141.
19. Coderre JA, Joel DD, Micca PL, Nawrocky MM, Slatkin DN. Control of intracerebral gliosarcomas in rats by boron neutron capture therapy with p-boronophenylalanine. Radiat Res. 1992;129(3):290–296.
20. Elowitz EH, Bergland RM, Coderre JA, Joel DD, Chadha M, Chanana AD. Biodistribution of p-boronophenylalanine in patients with glioblastoma multiforme for use in boron neutron capture therapy. Neurosurgery. 1998;42(3):463–468; discussion 8-9.
21. Hatanaka H, Nakagawa Y. Clinical results of long-surviving brain tumor patients who underwent boron neutron capture therapy. Int J Radiat Oncol Biol Phys. 1994;28(5):1061–1066.
22. Nakagawa Y, Kyonghon P, Kitamura K, Kageji T, Minobe T. Long Term Follow up in Patients Who Underwent Boron Neutron Capture Therapy. In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in Neutron Capture Therapy: Volume 1. Boston, MA: Springer US; 2001:141–144.
23. Takagaki M, Oda Y, Miyatake S, Kikuchi H, Kobayashi T, Sakurai Y, et al. Boron neutron capture therapy: preliminary study of BNCT with sodium borocaptate (Na2B1 2H1 1SH) on glioblastoma. J Neurooncol. 1997;35(2):177–185.
24. Sauerwein W, Moss R, Hideghéty K, Stecher-Rasmussen F, De Vries M, Reulen H-J, et al. Status Report on the European Clinical Trial of BNCT at Petten (EORTC Protocol 11961). In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in Neutron Capture Therapy: Volume 1. Boston, MA: Springer US; 2001:81–86.
25. Wittig A, Hideghety K, Paquis P, Heimans J, Vos M, Goetz C, et al. Current clinical results of the EORTC-study 11961. Res Develop Neutron Capture Therapy. 2002.
26. Burian J, Marek M, Rataj J, Flibor S, Rejchrt J, Viererbl L, et al. Report on the first patient group of the phase I BNCT trial at the LVR-15 reactor. In: Sauerwein WM, Raymond M, Wittig A, editor. Research and Development in Neutron Capture Therapy. 12592002. p. 27–32.
27. Hideghéty K, Sauerwein W, Wittig A, Götz C, Paquis P, Grochulla F, et al. Tissue uptake of BSH in patients with glioblastoma in the EORTC 11961 phase I BNCT trial. J Neurooncol. 2003;62(1-2):145–156.
28. Goodman JH, Yang W, Barth RF, Gao Z, Boesel CP, Staubus AE, et al. Boron neutron capture therapy of brain tumors: biodistribution, pharmacokinetics, and radiation dosimetry sodium borocaptate in patients with gliomas. Neurosurgery. 2000;47(3):608–621; discussion 21-2.
29. Detta A, Cruickshank GS. L-amino acid transporter-1 and boronophenylalanine-based boron neutron capture therapy of human brain tumors. Cancer Res. 2009;69(5):2126–2132.
30. Kawabata S, Miyatake S, Nonoguchi N, Hiramatsu R, Iida K, Miyata S, et al. Survival benefit from boron neutron capture therapy for the newly diagnosed glioblastoma patients. Appl Radiat Isot. 2009;67(7-8 Suppl):S15–S18.
31. Watanabe T, Sanada Y, Hattori Y, Suzuki M. Correlation between the expression of LAT1 in cancer cells and the potential efficacy of boron neutron capture therapy. J Radiat Res. 2022.
32. Kawabata S, Miyatake S, Kajimoto Y, Kuroda Y, Kuroiwa T, Imahori Y, et al. The early successful treatment of glioblastoma patients with modified boron neutron capture therapy. Report of two cases. J Neurooncol. 2003;65(2):159–165.
33. Barth RF, Grecula JC, Yang W, Rotaru JH, Nawrocky M, Gupta N, et al. Combination of boron neutron capture therapy and external beam radiotherapy for brain tumors. Int J Radiat Oncol Biol Phys. 2004;58(1):267–277.
34. Barth RF, Kaur B. Rat brain tumor models in experimental neuro-oncology: the C6, 9L, T9, RG2, F98, BT4C, RT-2 and CNS-1 gliomas. J Neurooncol. 2009;94(3):299–312.
35. Hiratsuka J, Kamitani N, Tanaka R, Yoden E, Tokiya R, Suzuki M, et al. Boron neutron capture therapy for vulvar melanoma and genital extramammary Paget's disease with curative responses. Cancer Commun (Lond). 2018;38(1):38.
36. Coderre JA, Chanana AD, Joel DD, Elowitz EH, Micca PL, Nawrocky MM, et al. Biodistribution of boronophenylalanine in patients with glioblastoma multiforme: boron concentration correlates with tumor cellularity. Radiat Res. 1998;149(2):163–170.
37. Coderre JA, Morris GM. The radiation biology of boron neutron capture therapy. Radiat Res. 1999;151(1):1–18.
38. 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(1-2):101–109.
39. Nakagawa Y, Pooh K, Kobayashi T, Kageji T, Uyama S, Matsumura A, et al. Clinical review of the Japanese experience with boron neutron capture therapy and a proposed strategy using epithermal neutron beams. J Neurooncol. 2003;62(1-2):87–99.
40. Miyatake S-I, Kawabata S, Hiramatsu R, Kuroiwa T, Suzuki M, Ono K. Boron Neutron Capture Therapy of Malignant Gliomas. In: Chernov MF, Muragaki Y, McCutcheon IE, Kesari S, editors. Intracranial Gliomas Part III - Innovative Treatment Modalities. S.Karger AG; 2018;32:0.
41. Suzuki M. Boron neutron capture therapy (BNCT): a unique role in radiotherapy with a view to entering the accelerator-based BNCT era. Int J Clin Oncol. 2020;25(1):43–50.
42. Joensuu H, Kankaanranta L, Seppala T, Auterinen I, Kallio M, Kulvik M, et al. Boron neutron capture therapy of brain tumors:

clinical trials at the finnish facility using boronophenylalanine. J Neurooncol. 2003;62(1-2):123–134.
43. Pellettieri L, B HS, Rezaei A, Giusti V, Skold K. An investigation of boron neutron capture therapy for recurrent glioblastoma multiforme. Acta Neurol Scand. 2008;117(3):191–197.
44. Busse PM, Harling OK, Palmer MR, Kiger WS, 3rd, Kaplan J, Kaplan I, 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(1-2):111–121.
45. Capala J, Stenstam BH, Skold K, Munck af Rosenschold P, Giusti V, Persson C, et al. Boron neutron capture therapy for glioblastoma multiforme: clinical studies in Sweden. J Neurooncol. 2003;62(1-2):135–144.
46. Skold K, H-Stenstam B, Diaz AZ, Giusti V, Pellettieri L, Hopewell JW. Boron Neutron Capture Therapy for glioblastoma multiforme: advantage of prolonged infusion of BPA-f. Acta Neurol Scand. 2010;122(1):58–62.
47. Skold K, Gorlia T, Pellettieri L, Giusti V, H-Stenstam B, Hopewell JW. Boron neutron capture therapy for newly diagnosed glioblastoma multiforme: an assessment of clinical potential. Br J Radiol. 2010;83(991):596–603.
48. Kawabata S, Hiramatsu R, Kuroiwa T, Ono K, Miyatake S. Boron neutron capture therapy for recurrent high-grade meningiomas. J Neurosurg. 2013;119(4):837–844.
49. Kankaanranta L, Seppälä T, Koivunoro H, Välimäki P, Beule A, Collan J, 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(2):369–376.
50. Koivunoro H, Hippelainen E, Auterinen I, Kankaanranta L, Kulvik M, Laakso J, et al. Biokinetic analysis of tissue boron ((1)(0)B) concentrations of glioma patients treated with BNCT in Finland. Appl Radiat Isot. 2015;106:189–194.
51. Kondo N, Hirano F, Temma T. Evaluation of 3-Borono-l-Phenylalanine as a Water-Soluble Boron Neutron Capture Therapy Agent. Pharmaceutics. 2022;14(5):1106.
52. Dymova MA, Taskaev SY, Richter VA, Kuligina EV. Boron neutron capture therapy: Current status and future perspectives. Cancer Commun (Lond). 2020;40(9):406–421.
53. Malouff TD, Seneviratne DS, Ebner DK, Stross WC, Waddle MR, Trifiletti DM, et al. Boron Neutron Capture Therapy: A Review of Clinical Applications. Front Oncol. 2021;11:601820.
54. Skwierawska D, Lopez-Valverde JA, Balcerzyk M, Leal A. Clinical Viability of Boron Neutron Capture Therapy for Personalized Radiation Treatment. Cancers (Basel). 2022;14(12):2865.
55. Miyatake S, Kawabata S, Yokoyama K, Kuroiwa T, Michiue H, Sakurai Y, et al. Survival benefit of Boron neutron capture therapy for recurrent malignant gliomas. J Neurooncol. 2009;91(2):199–206.
56. Ono K, Masunaga S-i, Kinashi Y, editors. Neutron irradiation under continuous BPA injection for solving the problem of heterogeneous distribution of BPA. Advances in neutron capture therapy 2006 Proceedings of 12th international congress on neutron capture therapy; 2006; Japan.
57. Lan TL, Lin CF, Lee YY, Lin KH, Chang FC, Lin SC, et al. Advances in Boron Neutron Capture Therapy (BNCT) for Recurrent Intracranial Meningioma. Int J Mol Sci. 2023;24(5):4978.
58. Takai S, Wanibuchi M, Kawabata S, Takeuchi K, Sakurai Y, Suzuki M, et al. Reactor-based boron neutron capture therapy for 44 cases of recurrent and refractory high-grade meningiomas with long-term follow-up. Neuro Oncol. 2022;24(1):90–98.
59. Miyatake SI, Wanibuchi M, Hu N, Ono K. Boron neutron capture therapy for malignant brain tumors. J Neurooncol. 2020;149(1):1–11.
60. Hiratsuka J, Kamitani N, Tanaka R, Tokiya R, Yoden E, Sakurai Y, et al. Long-term outcome of cutaneous melanoma patients treated with boron neutron capture therapy (BNCT). J Radiat Res. 2020;61(6):945–951.
61. Hirose K, Sato M. Clinical Results and Prognostic Factors in Boron Neutron Capture Therapy for Recurrent Squamous Cell Carcinoma of the Head and Neck Under the Japan National Health Insurance System: A Retrospective Study of the Initial 47 Patients. Int J Radiat Oncol Biol Phys. 2024.
62. Bae Y-s, Kim D-S, Seo HJ, Han J-U, Yoon HJ, Hwang JJ, et al. Advances of LINAC-based boron neutron capture therapy in Korea. AAPPS Bulletin. 2022;32(1):34.
63. www.ClinicalTrials.gov. A Multi-centered, Radiation Dose Escalation, Open, Exploratory, Phase 1/2a Clinical Trial on the Safety, Efficacy and Pharmacokinetic Characteristics of BNCT(Boron Neutron Capture Therapy) in Patients With Recurrent High-grade Gliomas 2023 [cited 2023 2023-02-21]. Available from: https://clinicaltrials.gov/study/NCT05737212#study-overview
64. Kawabata S, Suzuki M, Hirose K, Tanaka H, Kato T, Goto H, et al. Accelerator-based BNCT for patients with recurrent glioblastoma: a multicenter phase II study. Neurooncol Adv. 2021;3(1):vdab067.
65. Nakagawa Y, Hatanaka H. Boron neutron capture therapy. Clinical brain tumor studies. J Neurooncol. 1997;33(1-2):105–115.
66. Horn V, Slansky J, Janku I, Strouf O, Sourek K, Tovarys F. Disposition and tissue distribution of boron after infusion of borocaptate sodium in patients with malignant brain tumors. Int J Radiat Oncol Biol Phys. 1998;41(3):631–638.
67. Cheng X, Li F, Liang L. Boron Neutron Capture Therapy: Clinical Application and Research Progress. Curr Oncol. 2022;29(10):7868–7886.
68. Barth RF, Yang W, Bartus RT, Moeschberger ML, Goodman JH. Enhanced delivery of boronophenylalanine for neutron capture therapy of brain tumors using the bradykinin analog Cereport (Receptor-Mediated Permeabilizer-7). Neurosurgery. 1999;44(2):351–359; discussion 9-60.
69. Barth RF, Yang W, Rotaru JH, Moeschberger ML, Boesel CP, Soloway AH, et al. Boron neutron capture therapy of brain tumors: enhanced survival and cure following blood-brain barrier disruption and intracarotid injection of sodium borocaptate and boronophenylalanine. Int J Radiat Oncol Biol Phys. 2000;47(1):209–218.
70. Barth RF, Yang W, Rotaru JH, Moeschberger ML, Joel DD, Nawrocky MM, et al. Boron neutron capture therapy of brain tumors: enhanced survival following intracarotid injection of either sodium borocaptate or boronophenylalanine with or without blood-brain barrier disruption. Cancer Res. 1997;57(6):1129–1136.

71. Yang W, Barth RF, Bartus RT, Rotaru JH, Moeschberger ML, Ferketich AK, et al. Improved survival after boron neutron capture therapy of brain tumors by Cereport-mediated blood-brain barrier modulation to enhance delivery of boronophenylalanine. Neurosurgery. 2000;47(1):189–197; discussion 97-8.
72. Yang W, Barth RF, Carpenter DE, Moeschberger ML, Goodman JH. Enhanced delivery of boronophenylalanine for neutron capture therapy by means of intracarotid injection and blood-brain barrier disruption. Neurosurgery. 1996;38(5):985–992.
73. Yang W, Barth RF, Rotaru JH, Moeschberger ML, Joel DD, Nawrocky MM, et al. Enhanced survival of glioma bearing rats following boron neutron capture therapy with blood-brain barrier disruption and intracarotid injection of boronophenylalanine. J Neurooncol. 1997;33(1-2):59–70.
74. Yang W, Barth RF, Rotaru JH, Moeschberger ML, Joel DD, Nawrocky MM, et al. Boron neutron capture therapy of brain tumors: enhanced survival following intracarotid injection of sodium borocaptate with or without blood-brain barrier disruption. Int J Radiat Oncol Biol Phys. 1997;37(3):663–672.
75. Cruickshank G, Detta A, Green S, Lockyer N, Ngoga D, Ghani Z, et al. Et-14 * Optimisation of Boronophenylalanine (Bpa) Delivery and Lat1 Expression for the Clinical Application of Boron Neutron Capture Therapy (Bnct) in Glioblastoma. Neuro-Oncology. 2014;16(suppl 5):v82–v.
76. Priest R, Ambady P, Neweult E. Actr-23. Safety of Intra-Arterial Chemotherapy with Osmotic Opening of the Blood-Brain Barrier. Neuro-Oncology. 2018;20(suppl_6):vi16–vi.
77. Burgess A, Hynynen K. Drug delivery across the blood-brain barrier using focused ultrasound. Expert Opin Drug Deliv. 2014;11(5):711–721.
78. Power EA, Rechberger JS, Gupta S, Schwartz JD, Daniels DJ, Khatua S. Drug delivery across the blood-brain barrier for the treatment of pediatric brain tumors - An update. Adv Drug Deliv Rev. 2022;185:114303.
79. Uluc K, Neuwelt EA, Ambady P. Advances in Intraarterial Chemotherapy Delivery Strategies and Blood-Brain Barrier Disruption. Neurosurg Clin N Am. 2022;33(2):219–223.
80. Hattori Y, Andoh T, Kawabata S, Hu N, Michiue H, Nakamura H, et al. Proposal of recommended experimental protocols for in vitro and in vivo evaluation methods of boron agents for neutron capture therapy. J Radiat Res. 2023;64(6):859–869.
81. Barth RF, Adams DM, Soloway AH, Mechetner EB, Alam F, Anisuzzaman AK. Determination of boron in tissues and cells using direct-current plasma atomic emission spectroscopy. Anal Chem. 1991;63(9):890–893.
82. Dai Q, Yang Q, Bao X, Chen J, Han M, Wei Q. The Development of Boron Analysis and Imaging in Boron Neutron Capture Therapy (BNCT). Mol Pharm. 2022;19(2):363–377.
83. Smith DR, Chandra S, Barth RF, Yang W, Joel DD, Coderre JA. Quantitative imaging and microlocalization of boron-10 in brain tumors and infiltrating tumor cells by SIMS ion microscopy: relevance to neutron capture therapy. Cancer Res. 2001;61(22):8179–8187.
84. Woollard JE, Blue TE, Curran JF, Mengers TF, Barth RF. An alpha autoradiographic technique for determination of 10B concentrations in blood and tissue. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment. 1990; 299(1-3):600–605.
85. Hatanaka H. Boron-neutron Capture Theory For Tumors: Nishimura Co. Ltd.; 1986:463.
86. Barth RF. From the laboratory to the clinic: How translational studies in animals have lead to clinical advances in boron neutron capture therapy. Appl Radiat Isot. 2015;106:22–228.
87. Mishima Y, Ichihashi M, Tsuji M, Hatta S, Ueda M, Honda C, et al. Treatment of malignant melanoma by selective thermal neutron capture therapy using melanoma-seeking compound. J Invest Dermatol. 1989;92(5 Suppl):321S–325S.
88. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. J Clin Oncol. 2000;18(3):684–692.
89. Laird M, Matsumoto K, Higashi Y, Komatsu A, Raitano A, Morrison K, et al. Organosilica nanoparticles containing sodium borocaptate (BSH) provide new prospects for boron neutron capture therapy (BNCT): efficient cellular uptake and enhanced BNCT efficacy. Nanoscale Adv. 2023;5(9):2537–2546.
90. Ali F, S Hosmane N, Zhu Y. Boron Chemistry for Medical Applications. Molecules. 2020;25(4):828.
91. Beck-Sickinger AG, Becker DP, Chepurna O, Das B, Flieger S, Hey-Hawkins E, et al. New Boron Delivery Agents. Cancer Biother Radiopharm. 2023;38(3):160–172.
92. Calabrese G, Daou A, Barbu E, Tsibouklis J. Towards carborane-functionalised structures for the treatment of brain cancer. Drug Discov Today. 2018;23(1):63–75.
93. Couto M, Alamon C, Nievas S, Perona M, Dagrosa MA, Teixidor F, et al. Bimodal Therapeutic Agents Against Glioblastoma, One of the Most Lethal Forms of Cancer. Chemistry. 2020;26(63):14335–14340.
94. Hawthorne MF. The Role of Chemistry in the Development of Boron Neutron-Capture Therapy of Cancer. Angew Chem, Int Ed Engl. 1993;32(7):950–984.
95. Jalilian AR, Shahi A, Swainson IP, Nakamura H, Venkatesh M, Osso JA. Potential Theranostic Boron Neutron Capture Therapy Agents as Multimodal Radiopharmaceuticals. Cancer Biother Radiopharm. 2022;37(5):342–354.
96. Sauerwein WAG, Sancey L, Hey-Hawkins E, Kellert M, Panza L, Imperio D, et al. Theranostics in Boron Neutron Capture Therapy. Life (Basel). 2021;11(4):330.
97. Seneviratne DS, Saifi O, Mackeyev Y, Malouff T, Krishnan S. Next-Generation Boron Drugs and Rational Translational Studies Driving the Revival of BNCT. Cells. 2023;12(10):1398.
98. Soloway AH, Tjarks W, Barnum BA, Rong FG, Barth RF, Codogni IM, et al. The Chemistry of Neutron Capture Therapy. Chem Rev. 1998;98(4):1515–1562.
99. Yamamoto T, Nakai K, Matsumura A. Boron neutron capture therapy for glioblastoma. Cancer Lett. 2008;262(2):143–152.
100. Yinghuai Z, Lin X, Xie H, Li J, Hosmane NS, Zhang Y. The Current Status and Perspectives of Delivery Strategy for Boronbased Drugs. Curr Med Chem. 2019;26(26):5019–5035.
101. Zhu Y, Hosmane NS. Nanostructured boron compounds for cancer therapy. Pure and Applied Chem. 2018;90(4):653–663.
102. Barth RF, Mi P, Yang W. Boron delivery agents for neutron capture therapy of cancer. Cancer Commun (Lond). 2018;38(1):35.

103. Oloo SO, Smith KM, Vicente M. Multi-Functional Boron-Delivery Agents for Boron Neutron Capture Therapy of Cancers. Cancers (Basel). 2023;15(13):3277.
104. Monti Hughes A, Hu N. Optimizing Boron Neutron Capture Therapy (BNCT) to Treat Cancer: An Updated Review on the Latest Developments on Boron Compounds and Strategies. Cancers (Basel). 2023;15(16).
105. Tibbitts J, Fike JR, Lamborn KR, Bollen AW, Kahl SB. Toxicology of a boronated porphyrin in dogs. Photochem Photobiol. 1999;69(5):587–594.
106. Kahl SB, Koo MS. Synthesis of Tetrakis-Carborane-Carboxylate Esters of 2,4-Bis-(Alpha,Beta-Dihydroxyethyl)-Deuteroporphyrin-Ix. J Chem Soc, Chem Commun. 1990;(24):1769–1771.
107. Hill JS, Kahl SB, Kaye AH, Stylli SS, Koo MS, Gonzales MF, et al. Selective tumor uptake of a boronated porphyrin in an animal model of cerebral glioma. Proc Natl Acad Sci U S A. 1992;89(5):1785–1789.
108. Tibbitts J, Sambol NC, Fike JR, Bauer WF, Kahl SB. Plasma pharmacokinetics and tissue biodistribution of boron following administration of a boronated porphyrin in dogs. J Pharm Sci. 2000;89(4):469–477.
109. Ozawa T, Afzal J, Lamborn KR, Bollen AW, Bauer WF, Koo MS, et al. Toxicity, biodistribution, and convection-enhanced delivery of the boronated porphyrin BOPP in the 9L intracerebral rat glioma model. Int J Radiat Oncol Biol Phys. 2005;63(1):247–252.
110. Rosenthal MA, Kavar B, Hill JS, Morgan DJ, Nation RL, Stylli SS, et al. Phase I and pharmacokinetic study of photodynamic therapy for high-grade gliomas using a novel boronated porphyrin. J Clin Oncol. 2001;19(2):519–524.
111. Rosenthal MA, Kavar B, Uren S, Kaye AH. Promising survival in patients with high-grade gliomas following therapy with a novel boronated porphyrin. J Clin Neurosci. 2003;10(4):425–427.
112. Stylli SS, Kaye AH. Photodynamic therapy of cerebral glioma–a review Part I–a biological basis. J Clin Neurosci. 2006;13(6):615–625.
113. Stylli SS, Kaye AH. Photodynamic therapy of cerebral glioma - a review. Part II - clinical studies. J Clin Neurosci. 2006;13(7):709–717.
114. Barth RF, Yang W, Wu G, Swindall M, Byun Y, Narayanasamy S, et al. Thymidine kinase 1 as a molecular target for boron neutron capture therapy of brain tumors. Proc Natl Acad Sci U S A. 2008;105(45):17493–17497.
115. García-Montaño LA, Licón-Muñoz Y, Martinez FJ, Keddari YR, Ziemke MK, Chohan MO, et al. Dissecting Intra-tumor Heterogeneity in the Glioblastoma Microenvironment Using Fluorescence-Guided Multiple Sampling. Mol Cancer Res. 2023;21(8):755–767.
116. Baig S, Winkler F. A holistic view of the malignant organism we call glioblastoma. Cell. 2024;187(2):271–273.
117. Miyatake S, Kawabata S, Kajimoto Y, Aoki A, Yokoyama K, Yamada M, 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 neuroimages. J Neurosurg. 2005;103(6):1000–1009.
118. Kawabata S, Yang W, Barth RF, Wu G, Huo T, Binns PJ, et al. Convection enhanced delivery of carboranylporphyrins for neutron capture therapy of brain tumors. J Neurooncol. 2011;103(2):175–185.
119. Kahl SB, Koo M-S. Synthesis and Properties of Tetrakis-Carborane-Carboxylate Esters of 2,4-BIS-(α,β-Dihydroxyethyl) Deuteroporphyrin IX. In: Allen BJ, Moore DE, Harrington BV, editors. Progress in Neutron Capture Therapy for Cancer. Boston, MA: Springer US; 1992:223–226.
120. Gupta N, Gahbauer RA, Blue TE, Albertson B. Common challenges and problems in clinical trials of boron neutron capture therapy of brain tumors. J Neurooncol. 2003;62(1-2):197–210.

How to cite this article: Barth RF, Gupta N, Kawabata S. Evaluation of sodium borocaptate (BSH) and boronophenylalanine (BPA) as boron delivery agents for neutron capture therapy (NCT) of cancer: an update and a guide for the future clinical evaluation of new boron delivery agents for NCT. Cancer Commun. 2024;44:893–909. https://doi.org/10.1002/cac2.12582