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TOPIC REVIEW

Boron neutron capture therapy for malignant brain tumors

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Abstract

Background Boron neutron capture therapy (BNCT) is tumor-selective particle radiation therapy that depends on the nuclear capture and fission reactions. These reactions occur when a non-radioactive boron isotope (^{10}B) is irradiated with low-energy thermal neutrons to yield high linear energy transfer α-particles and lithium-7 nuclei within a limited path length, i.e., an almost one-cell diameter. The ^{10}B-containing cells can then be selectively destroyed by these potent particles. BNCT has been applied in the field of malignant brain tumors for newly diagnosed and recurrent malignant gliomas (chiefly glioblastomas).
Clinical results These clinical applications of BNCT have been performed with reactor-based neutron sources over the past decades. We also applied reactor-based BNCT for 58 newly diagnosed glioblastomas and 68 recurrent malignant gliomas including 52 glioblastomas. In this review article, we summarize the clinical results from the literature concerning BNCT for these high-grade gliomas (including our research). We also applied reactor-based BNCT for 46 cases of recurrent and refractory high-grade meningiomas, and some of the results will be presented herein.
Future prospects In Japan, neutron sources have been shifted from reactors to accelerators. Phase 1 and 2 clinical trials have been performed for recurrent malignant gliomas using accelerator-based neutron sources, and now fortunately, a cyclotron-based neutron generator has been approved as a medical device by Japanese regulatory authority, as the world's first accelerator-based BNCT system for medical use. We also discuss the future prospects of accelerator-based BNCT in hospitals as therapy for malignant brain tumors.

Keywords BNCT · Glioma · Glioblastoma · Meningioma · PET · Review

Introduction

Principle

Boron neutron capture therapy (BNCT) is a cell-targeting particle radiotherapy that enables the selective killing of malignant cells and the sparing of normal cells. BNCT is a binary approach: a boron-10 (^{10}B)-labeled compound must deliver higher concentrations of ^{10}B to target tumor cells compared to the concentrations delivered to the tumor cells' surrounding normal tissues. This delivery of ^{10}B is followed by irradiation with low-energy thermal neutrons. When a neutron collides with ^{10}B, high linear energy transfer (LET) particles, i.e., α-particles and recoiling ^{7}Li particles, are released within one cell's diameter by the ^{10}B (n, α) ^{7}Li neutron capture reaction [1]. These high-LET particles can destroy sufficient amount of ^{10}B-containing cells without exerting hazardous effects on the adjacent normal cells. Therefore, if sufficient quantities of boron compounds can be made to accumulate selectively in tumor cells with enough contrast to surrounding normal cells, the BNCT becomes an ideal radiotherapy.

The principle of BNCT is depicted in Fig. 1. In the figure, malignant glioma with infiltrative characteristics are the presumed target tumor cells. Neither microsurgery nor sophisticated ion beam radiation therapy such as that used with carbon and proton particles can remove or destroy only tumor cells without damaging surrounding normal cells. In BNCT, after the selective accumulation of a ^{10}B-containing compound in the tumor cells, the tumor cells are irradiated with non-hazardous low-energy thermal neutrons. During this process, spatially selective irradiation with neutrons for tumor cells alone is not required. High-LET particles will

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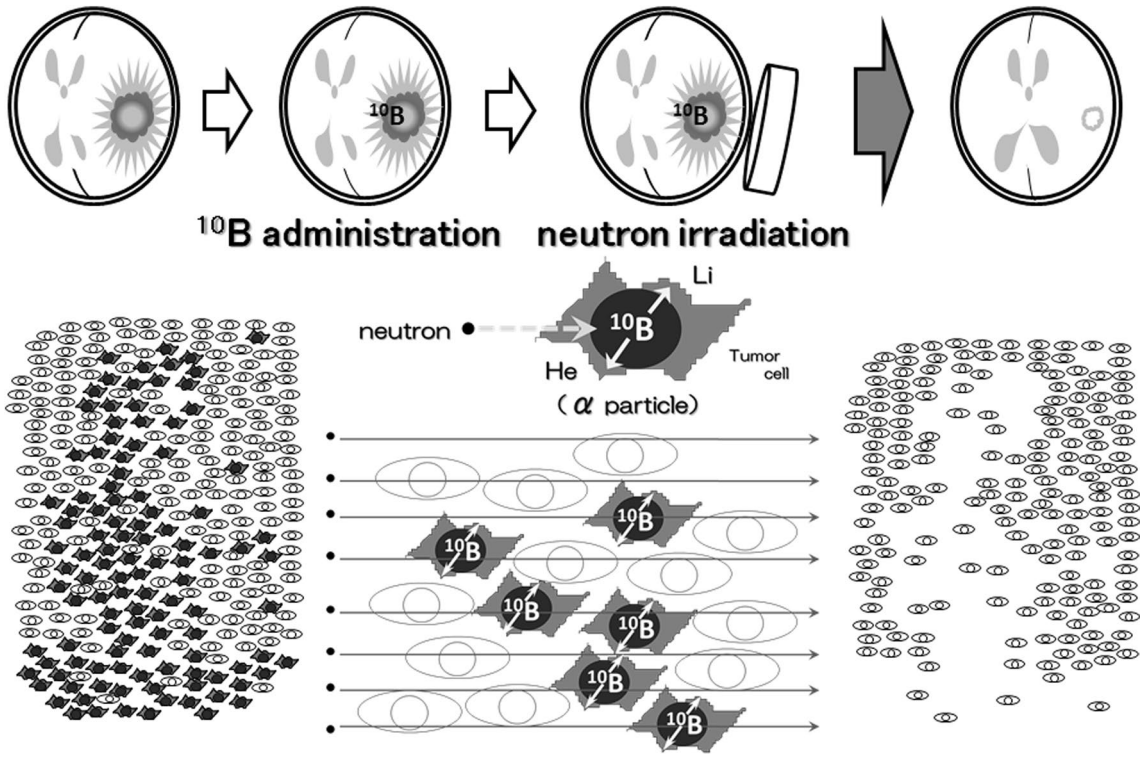

Fig. 1 The principle of boron neutron capture therapy (BNCT). BNCT is a binary approach: a boron-10 (^{10}B)-labeled compound is administered that delivers high concentrations of ^{10}B to the target tumor relative to surrounding normal tissues. This is followed by irradiation with thermal neutrons or epithermal neutrons that become thermalized at depth in tissues. The short range (5–9 μm) of high-LET α-particles and ^{7}Li particles released from the ^{10}B (n, alpha) ^{7}Li neutron capture reaction realizes tumor-selective killing without damage to adjacent normal brain tissue

destroy only a high amount ^{10}B-containing cells and leave the normal surrounding cells intact, as shown in Fig. 1.

History

BNCT has a relatively long history. In 1932, Sir James Chadwick discovered the neutron [2] and was awarded the Nobel Prize in Physics for this discovery. Only 4 years later, Locher published a comprehensive theoretical account of the biological effects and therapeutic possibilities of BNCT [3]. Kruger [4] and Zahl et al. [5] reported animal experiments using BNCT in 1940. The initial clinical interest in and applications of BNCT were focused on high-grade gliomas—chiefly glioblastomas (GBMs) [6, 7]. The first clinical application of BNCT was conducted in the U.S. in the 1950s, at the Brookhaven National Laboratory [8–10], and Sweet and his coworkers at Massachusetts General Hospital performed a clinical study of BNCT from 1960 to 1961 using the Massachusetts Institute of Technology research reactor. They treated 17 cases of malignant gliomas with BNCT, but the outcomes were disappointing; the patients' median survival after BNCT was only 87 days. These unsatisfactory results might have been due to a poor selective accumulation of boron compound in tumor tissues and/or to limited penetration of the thermal neutrons. These problems were eventually resolved, as described below.

Selective accumulation of boron compounds and positron emission tomography (PET) imaging

The selective tumor destruction in BNCT is achieved by the selective accumulation of ^{10}B atoms in tumor cells. Since the 1990s, only two boron compounds have been used clinically for the BNCT of high-grade gliomas. One is the polyhedral boron anion, sodium mercaptoundecahydro-closododecaborate ($Na_2B_{12}H_{11}SH$), commonly known as sodium borocaptate (BSH) [11]; the other is the boron-containing amino acid (L)-4-dihydroxyborylphenylalanine, known as boronophenylalanine (BPA) (Table 1). Each of these boron compound reaches and accumulates in glioma cells or tissues in differing manners [12]. BSH is not delivered into normal brain tissue through an intact blood–brain barrier (BBB), but when the BBB is disrupted, BSH accumulates passively in the interstitial space of glioma tissue. In contrast, BPA preferentially accumulates well into an actively dividing subpopulation of tumor cells via the

Table 1 Clinical results of BNCT for newly diagnosed and recurrent GBM

Medical institution	Treatment dates	Tumor type and no. of patients	Boron compound and (treatment[a])	Clinical outcome[b] mOS	Refs
Brookhaven National Laboratory, Upton, NY, USA	1994–1999	nGBM 53	BPA 250–330 mg/kg in 2 h	12.8 mos	[62–65]
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA	1996–1999 2002–2003	nGBM 20 nGBM 6	BPA 250–350 mg/kg in 1.5 h BPA 14 g/m^2 in 1.5 h	11.1 mos NA	[64, 66, 67] [68]
Universitätsklinikum Essen, Essen, Germany	1997–2002	nGBM 26	BSA 100 mg/kg in 1.7 h	10.4–13.2 mos	[69]
Helsinki University Central Hospital, Helsinki, Finland	1999–2001 2001–2008	nGBM 30 rGBM 20	BPA 290–500 mg/kg in 2 h BPA 290–450 mg/kg in 2 h	11.0–21.9 mos 7 mos.(post-BNCT)	[70] [71]
Faculty Hospital of Charles University, Prague, Czech Republic	2000–2002	nGBM 5	BSH 100 mg/kg in 1 h	NA	[18]
Nyköping Hospital, Nyköping, Sweden	2001–2003 2001–2005	nGBM 29 rGBM 12	BPA 900 mg/kg in 6 h BPA 900 mg/kg in 6 h	17.7 mos 8.7 mos (post-BNCT)	[18, 72–76]
University of Tsukuba, Tsukuba City, Ibaraki, Japan	1999–2002 1998–2007 1998–2007	nGBM 5 nGBM 7 nGBM 8	BSH 100 mg/kg in 1–1.5 h (IO-BNCT) BSH 5 g/body in 1 h (IO-BNCT) BSH 5 g/body in 1 h + BPA or 250 mg/kg in 1 h (BNCT + XRT)	23.2 mos 23.3 mos 27.1 mos	[77] [78] [78]
University of Tokushima, Tokushima, Japan	1998–2000 2001–2004 2005–2008	nGBM 6 nGBM 11 nGBM 6	BSH 64.9–178.6 mg/kg (IO-BNCT) BSH 64.9–178.6 mg/kg (IO-BNCT) BSH 100 mg/kg and BPA 250 mg/kg in 1 h (BNCT + XRT)	15.5 mos 19.5 mos 26.2 mos	[79–81] [79–81] [79–81]
Osaka Medical College, Takatsuki, Japan	2002–2003 2003–2006 2002–2007 2010–2013 2013–2018	nGBM 10 nGBM 11 rGBM 19 nGBM 32 rGBM 10	BSH 5 g/body + BPA 250 mg/kg in 1 h BSH 5 g/body in 1 h + BPA 700 mg/kg in 3 h (BNCT + XRT) BSH 5 g/body + BPA 250 mg/kg in 1 h or BSH 5 g/body + BPA 700 mg/kg in 3 h BSH 5 g/body in 1 h + BPA 500 mg/kg in 3 h (BNCT + XRT + TMZ) BPA 500 mg/kg in 3 h (BNCT + Bev)	14.5 mos 23.5 mos 10.8 mos 21.1 mos (2 yr OS: 45.5%) 12 mos	[17, 24] [24] [27] * [33]**

2 yr OS 2-year overall survival rate, *Bev* bevacizumab, *GBM* glioblastoma, *IO-BNCT* intraoperative BNCT, *mOS* median overall survival, *n* newly diagnosed, *NA* not available, *r* recurrent, *TMZ* temozolomide, *XRT* X-ray treatment

[a]Treatment in the parentheses is not solely external beam BNCT

[b]A range of survival is given in some cases to summarize the survival reported for different cohorts

*Manuscript in preparation. ** Unpublished data

augmented expression of L-type amino acid transporters on the cells, and the accumulation does not depend on BBB disruption [13]. However, some of the BPA inevitably accumulates in normal cells. In BNCT, large amounts of BPA are administered intravenously (Table 1). Empirically, we have observed that an excess amount of intravenously administered BPA recrystallized in the patients' urine a few hours after neutron irradiation and caused a

transient high-grade fever. This adverse event can be prevented by appropriate hydration just after neutron irradiation [14].

BPA accumulation can be visualized and semi-quantified by positron emission tomography (PET). BPA can be labeled with 18-fluorine, which is the tracer used in ^{18}F-BPA-PET imaging. With the ^{18}F-BPA-PET technology, the BPA concentration is readily calculated with the combination of only venous blood sampling, without tumor sampling [15]. This unique PET imaging technique makes it possible to conduct a dose simulation by BNCT prior to neutron irradiation [16, 17]. Representative PET imaging in a GBM case is shown in Fig. 2. This imaging provided the lesion/normal brain (L/N) ratio of BPA at 7.8 for the patient, and the imaging demonstrated that BPA accumulates well not only in contrast-enhanced tumor tissue (indicating the tumor bulk) but also just adjacent to and around the enhanced tumor volume, i.e., in infiltrative tumor tissues. This PET image provides evidence of tumor cell-selective destruction by BPA-based BNCT. The good accumulation of BPA shown by PET imaging ensures the effectiveness of BPA-based BNCT prior to neutron irradiation.

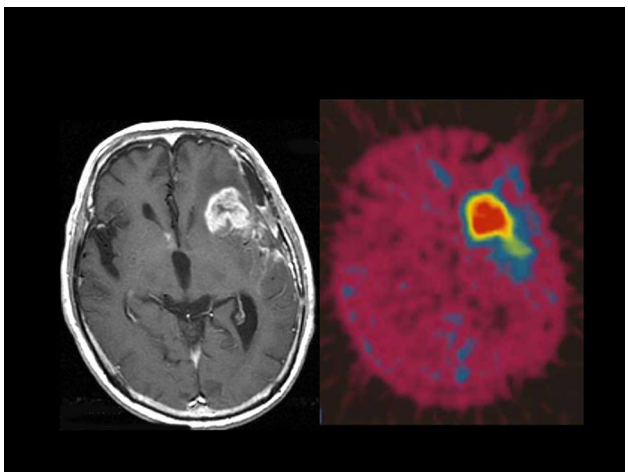

Fig. 2 Contrast-enhanced T1-weighted MRI ^{18}F-labeled BPA-PET image of a representative glioblastoma (GBM) patient. The patient received ^{18}F-BPA-PET to assess the distribution of boronophenylalanine (BPA) and to estimate the boron concentration in the tumor before BNCT without a direct determination of the boron concentration in the tumor. The lesion-to-normal brain (L/N) ratio of the enhanced tumor was 7.8 in this case. Note that even the periphery of the main mass (i.e., the infiltrative portion of the tumor) showed BPA uptake. The L/N ratio of the BPA uptake was estimated from this study and then used for the dose planning. ^{18}F-BPA-PET provided an accurate estimate of the accumulation and distribution of BPA

Clinical results

Newly diagnosed GBMs

Theoretically, the results of BNCT depend on the boron concentration in tumor tissue or tumor cells and the amount of neutrons that reach those sites. We noted the poor early clinical results obtained in the 1970s in the U.S. above; one of the causes of the poor patient outcomes is likely to be the low penetration potency of the thermal neutron beam from the nuclear reactors that were used. As mentioned, the ^{10}B (n, α) ^{7}Li neutron capture reaction is caused by low-energy thermal neutrons, whereas epithermal neutrons (which have the potency to penetrate deeply) can be thermalized at a certain depth within the body. Therefore, after the 1990s epithermal beams were used for BNCT in many reactors around the world. Another reason for the poor results in the early U.S. series is the use of an immature boron compound.

We summarize the BNCT clinical results for GBMs (chiefly newly diagnosed and partly recurrent cases) listed in Table 1. This table is modified from previous reviews [18, 19]. In the 1990s, epithermal beams became available for BNCT for brain tumors in the U.S., Germany, Finland, Sweden, the Czech Republic, Taiwan and Japan. Among the subsequent clinical studies, there were several modifications of the BNCT and the case numbers were quite limited, making a systematic review (meta-analysis) of this field difficult. However, some trends and facts can be learned from this table. As the boron carrier, only BPA and BSH were used in all of the studies. The clinical results of the U.S. studies performed in the 1990s were markedly improved compared to the previous results using thermal beams in the same country. The studies conducted in Europe indicated that the BNCT performed therein provided almost the same level of the results achieved by the Stupp's regimen [20].

In a Japanese series, some investigators (including our group) used BSH and BPA simultaneously. As discussed above, these compounds accumulate in different manners in different subpopulations of glioma cells and tissues. The two compounds used together might compensate for each compound's weak points. Additional X-ray therapy (XRT) was also applied; this seemed to improve the clinical results of BNCT for patients with newly diagnosed GBMs, with the median survival of each study at 23.5–27.1 months. These results are enough good compared to those of a large-scale clinical trial for newly diagnosed GBM [20–22]. The additional XRT might improve the shortage of the prescribed dose in BNCT (especially for deep-seated tumors) and increase the bottom dose due to an uneven distribution of ^{10}B atoms in tumor tissue.

We have completed a prospective multicenter clinical trial of BNCT with additional XRT that used the combination of temozolomide for newly diagnosed GBM (Osaka-TRI-BRAIN 0902, NCT00974987) (manuscript in preparation) [23]. In that prospective study, the median survival was 21.1 months and the 2-year survival rate was 45.5%. Our clinical regimen of BNCT for newly diagnosed GBM is published elsewhere [17, 24].

Recurrent GBMs

Initially, we applied BNCT mainly for recurrent malignant gliomas. Marked tumor shrinkage was observed in neuroimages of our initial patient series [16, 17]. More than 50% of the contrast-enhanced lesions disappeared in eight of 12 cases during the follow-up duration [14, 17]. The survival data from some clinical studies of BNCT for recurrent malignant gliomas are also summarized in Table 1. The median survival times after BNCT alone for recurrent GBM in Table 1 are 7–10.8 months. Large-scale clinical trials of newly diagnosed GBM cases treated with chemoradiotherapy have been reported [20–22], whereas only a few reports about recurrent GBM have been published. It is thus difficult to estimate whether the above-mentioned median survival time achieved by BNCT for recurrent GBM is optimal or not. In 2007, Carson et al. [25] published an excellent article regarding a recursive portioning analysis (RPA) for recurrent gliomas. We then analyzed our BNCT results for recurrent gliomas based on the gliomas' RPA classification, and the results demonstrated that BNCT prolonged the survival of the patients with recurrent malignant glioma in every RPA class; moreover, it greatly prolonged the survival of the patients in poor RPA classes [26]. Our clinical regimen of BNCT for recurrent malignant gliomas is published elsewhere [27].

The most important shortcoming of BNCT for recurrent malignant gliomas is brain radiation necrosis (BRN). Prior to their second radiation treatment at a recurrence, almost all patients with recurrent malignant gliomas have already received nearly 60 Gy XRT as an initial radiotherapy. Even with tumor-selective particle radiation BNCT, BRN often occurs after BNCT in recurrent glioma cases, and the BRN may cause severe brain edema leading to severe neurological deficits and may sometimes be life-threatening. Bevacizumab, an anti-vascular endothelial growth factor antibody, is powerful weapon used to treat BRN [28, 29] and is useful for BRN therapy even after BNCT [30–32]. Figure 3 presents a representative case of recurrent GBM treated by BNCT, followed by a successful treatment of BRN with bevacizumab.

In Japan, bevacizumab is an authorized chemotherapeutic agent under national health insurance coverage, and it can be used in daily practice for both newly diagnosed and recurrent malignant gliomas. Using these advantages, we conducted a pilot clinical study of early bevacizumab administration (immediately after BNCT) for recurrent malignant gliomas [33], and the results demonstrated the prevention of BRN and potential clinical benefits.

High-grade meningiomas

High-grade meningiomas [i.e., World Health Organization (WHO) grades 2 and 3] are very difficult to control. The reported 5-year recurrence rates are 78–84% [34]. In particular, high-grade meningiomas that recur after the initial radiotherapy tend to have poor prognoses. The reported median progression-free survival and median overall survival post-recurrence are 5.2 and 24.6 months, respectively [35]. No standard treatments are established for recurrent high-grade meningioma [36].

We have applied reactor-based BNCT for 46 patients with recurrent high-grade meningiomas since 2005 [37–39]. A representative case is shown in Fig. 4. Like this case, all 46 cases showed good shrinkage of the mass as an initial response by BNCT, but we lost many of the patients due to systemic metastasis and intracranial distant recurrence outside of the neutron irradiation field [37]. Our clinical regimen of reactor-based BNCT for high-grade meningiomas is published elsewhere [37]. We are now performing a randomized control trial of accelerator-based BNCT for recurrent high-grade meningiomas between a BNCT-treatment group and a best-supportive-care group, estimating the progression-free survival as the primary endpoint.

From reactors to accelerators

Until 2012, all clinical BNCT treatments were performed using neutrons generated from a nuclear reactor. BNCT has shown potency for treating gliomas and high-grade meningiomas, and it has also shown promising effects for recurrent and refractory head and neck cancers [40–45]. Despite this potential, BNCT is yet to become a standard treatment modality for many types of cancers. One of the reasons for this is the difficulties surrounding the operation and maintenance of nuclear reactors for clinical BNCT purposes. In the past, more than 10 reactors were constructed and used for clinical BNCT activities in the U.S., Europe, Argentina, and Asia, but there are currently only two reactors (in Taiwan and Japan) that remain in routine operation for clinical BNCT. After the horrific nuclear reactor meltdown caused by the earthquake and tsunami in Fukushima, Japan in 2011, the use of nuclear reactors has become increasingly difficult.

For this reason, the emerging trend is to consider an accelerator-based neutron system for clinical BNCT, as such systems have several proven advantages over a nuclear reactor. An accelerator-based neutron system to

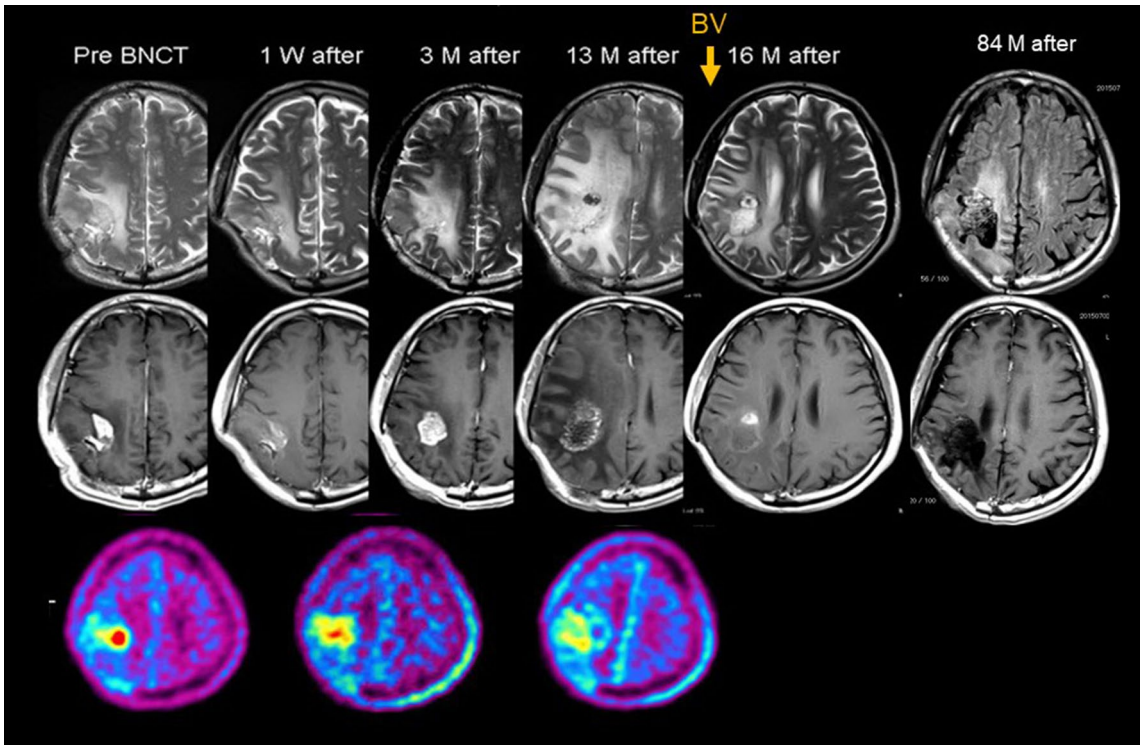

Fig. 3 A representative recurrent GBM case treated by BNCT with successive bevacizumab. The right parietal GBM recurred after standard chemo-radiotherapy. The F-BPA-PET image showed marked tracer uptake in the right parietal region with a 3.8 L/N ratio of the tracer, indicating that the lesion was a recurrent GBM. The patient was treated with BNCT. Periodic MRI showed gradual enlargement of both the enhanced lesion and perifocal edema, whereas F-BPA-PET showed a gradual decrease of the tracer uptake. The final L/N ratio, 13 months post-BNCT, was 2.3. This L/N ratio suggested that the lesion was brain radiation necrosis. The patient was treated with intravenous bevacizumab treatment biweekly (5 mg/kg). After four treatments, MRI showed marked improvement in the perifocal edema and left hemiparesis. The patient is doing well 84 months after the BNCT, without tumor progression or recurrence of the radiation necrosis

be installed and operated in a hospital environment should be compact, economical, safe, secure, and stable. For BNCT, an epithermal neutron flux (neutron energy range of 0.5 eV–10 keV) at $> 1 \times 10^9$ n/cm^2/s is required to treat a patient within 1 h [46]. Several types of accelerators have been developed to produce such neutrons, ranging from low-energy electrostatic accelerators (2–2.8 MeV) [47] and midrange energy linacs (2.5–10 MeV) [48] to high energy cyclotrons (30 MeV) [49]. These systems have been studied vigorously since the 1980s, and their applications for clinical BNCT have only recently succeeded. The two main obstacles that had to be overcome were the target's cooling and the insufficient beam intensity stability.

In March 2020, Sumitomo Heavy Industries constructed a cyclotron-based accelerator neutron source which has been approved by the Japanese Ministry of Health, Labor and Welfare (MHLW). This system accelerates a proton with an energy of 30 MeV and a maximum beam current of 1 mA when striking a beryllium target, generating neutrons. Using this accelerator, phase 1 and 2 clinical trials for recurrent malignant gliomas have been performed since 2012. These were followed by a clinical trial for head and neck cancers.

The new cyclotron-based system was recently approved in Japan for clinical use for head and neck cancers [50]. A Japanese pharmaceutical company that makes good manufacturing practices (GMP)-grade BPA medicine, Stella Pharma Corporation, was approved simultaneously [51]. An investigator-initiated clinical trial for recurrent and refractory high-grade meningioma in a randomized controlled trial using this system is underway, as described above.

With the foundation of decades of dedicated research and development, the future for BNCT is very bright with numerous companies worldwide developing an accelerator-based neutron source. This would expand the clinical BNCT services and ultimately provide a steppingstone in making BNCT a standard treatment modality for various types of cancer.

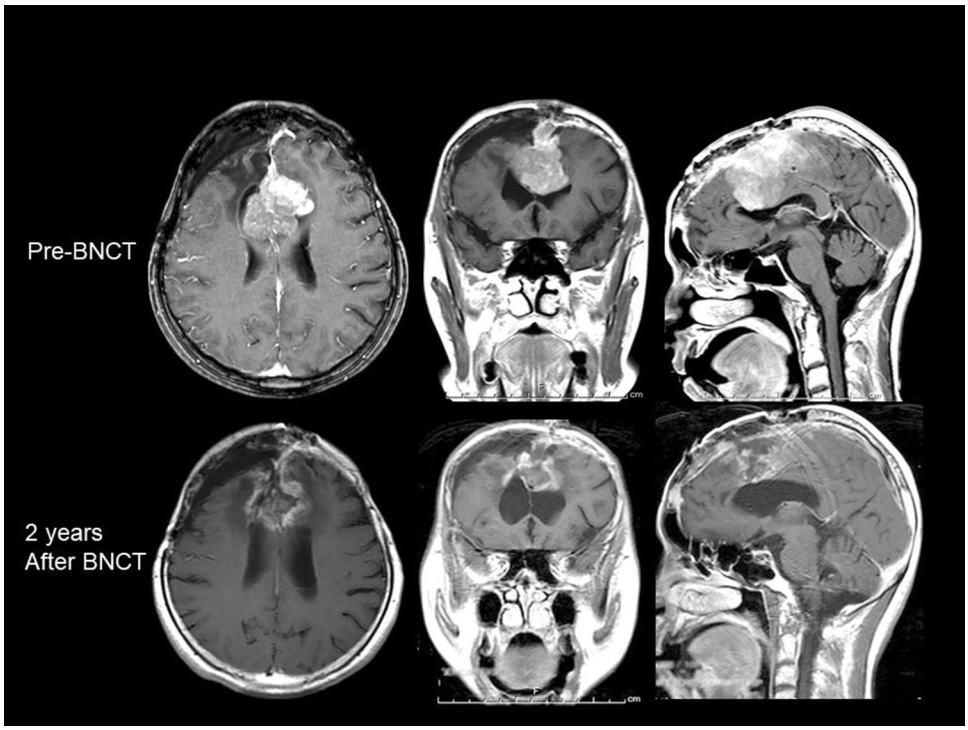

Fig. 4 A representative case of recurrent high-grade meningioma treated with reactor-based BNCT. The patient had recurrent anaplastic meningioma. She underwent three surgeries, plus stereotactic radiosurgery and X-ray treatment. Unfortunately, the lesion recurred and the patient was referred for us for BNCT. At 2 years post-BNCT, the size of the lesion is greatly reduced, with no neurological deterioration

Discussion and future prospects

BNCT has been improved for malignant gliomas, especially in Japan. The major cause of this progress in Japan might be ascribed to the development of F-BPA-PET in Japan. This unique PET technology had been applied for the simulation of BNCT prior to the initial neutron irradiation. The average tumor-to-normal brain ratio of BPA was estimated as 3.5 based on tumor sampling, and this ratio was applied in non-craniotomy BNCT [1]. This method for the estimation of the precise boron concentration in individual tumor tissues is rather uncertain. As noted above, F-BPA-PET provides a more accurate BPA L/N ratio in BPA-BNCT compared to the estimated value of 3.5. In addition, we have routinely used F-BPA-PET after BNCT to assess the lesion activity and to differentially diagnose BRN or pseudoprogression from tumor progression, as shown in Fig. 3 [26]. If worsening of the lesion is recognized on MRI but F-BPA-PET shows decreased tumor activity (as in Fig. 3), radiation treatment should not be administered as an alternative treatment. This correct understanding of lesion activity might lead to the appropriate introduction of bevacizumab for BRN and good clinical results in the use of BNCT for malignant gliomas in Japan.

The development of accelerator-based neutron sources for BNCT occurred only in recent decades. To date, only BSH and BPA have been used in the clinical studies and clinical trials of BNCT for many types of cancers. However, many boron carriers have been constructed and tested in preclinical studies. For example, boron-containing liposomes [52, 53], boronated DNA intercalators [54], boronated porphyrins [55, 56], boronated growth factors and boronated antibodies for their receptors [57–59], a BSH-fused cell-penetrating peptide [60], and polyvinyl alcohol and BPA conjugate [61] have been investigated. Unfortunately, no boron carriers have as yet surpassed the utility of BSH and BPA. If more ideal boron carriers than BSH and BPA are identified, BNCT may well open the next door for ideal cancer treatment. We hope that the next decade becomes a new era of BNCT for many types of cancer.

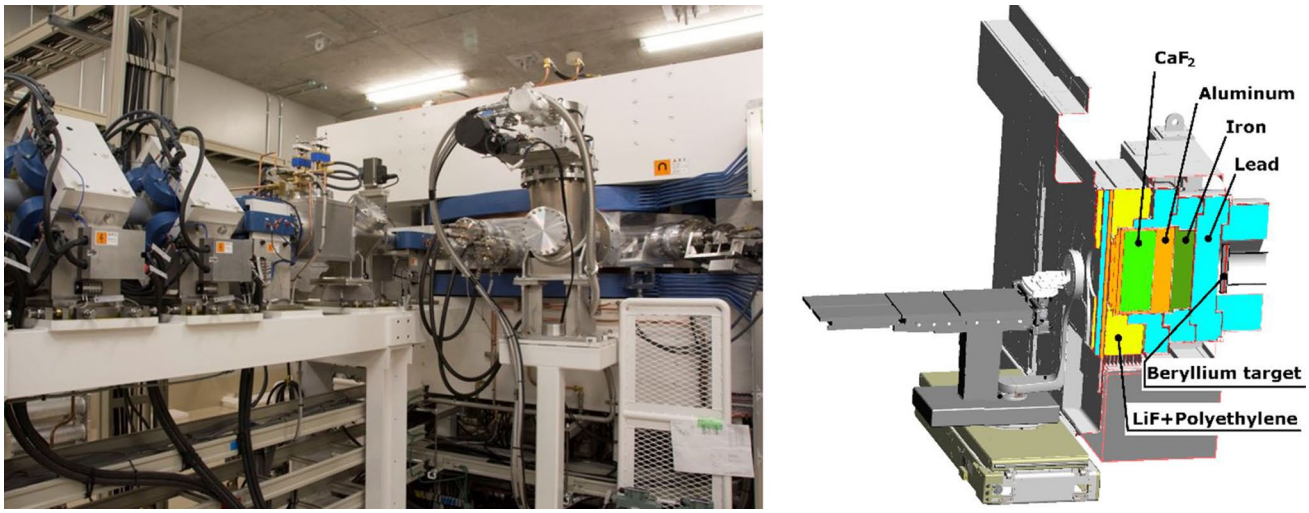

Fig. 5 Left: A photograph of a cyclotron-based accelerator for neutron generation installed in the Kansai BNCT Medical Center in Osaka Medical College. Right: Cross-sectional diagram of the accelerator-based neutron source. By courtesy of Sumitomo Heavy Industries, Ltd., Shinagawa-ku, Tokyo

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

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