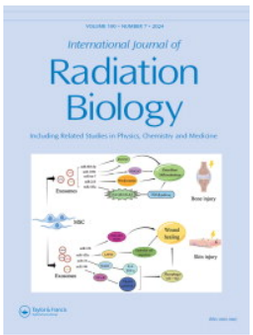

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REVIEW

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A clinician's perspective on boron neutron capture therapy: promising advances, ongoing trials, and future outlook

Shumin Shen[a*], Shanghu Wang[b*], Dachen Zhou[c], Xiuwei Wu[a], Mingzhu Gao[a], Jinjin Wu[a], Yucai Yang[a], Xiaoxi Pan[d] and Nianfei Wang[a]

[a]Department of Oncology, The Second Hospital of Anhui Medical University, Hefei, China; [b]Department of Radiotherapy, Anhui Chest Hospital, Hefei, China; [c]Department of General Surgery, The Second Hospital of Anhui Medical University, Hefei, China; [d]Department of Nuclear Medicine, The Second Hospital of Anhui Medical University, Hefei, China

ABSTRACT

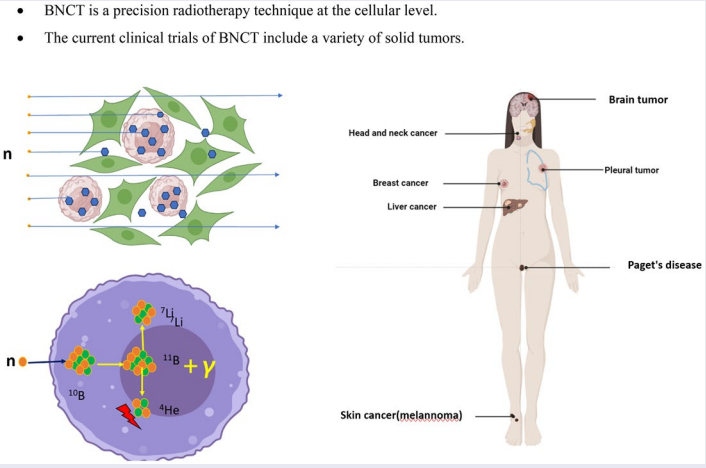
Purpose: This comprehensive review aims to provide a unique clinical perspective on the latest advances and ongoing boron neutron capture therapy (BNCT) trials for various cancers.

Methods: We critically analyzed clinical data from BNCT trials for head and neck cancer, glioblastoma, melanoma, meningioma, breast cancer, and liver tumors. We investigated differences in tumor responses and normal tissue toxicities among trials and discussed potential contributing factors. We also identified the limitations of early BNCT trials and proposed strategies to optimize future trial design.

Results: BNCT has shown promising results in treating head and neck cancer, with high response rates and improved survival in patients with recurrent disease. In glioblastoma, BNCT combined with surgery and chemotherapy has demonstrated survival benefits compared to standard treatments. BNCT has also been successfully used for recurrent high-grade meningiomas and shows potential for melanomas, extramammary Paget's disease, and liver tumors. However, differences in tumor responses and toxicities were observed among trials, potentially attributable to variations in treatment protocols, patient characteristics, and evaluation methods.

Conclusions: BNCT is a promising targeted radiotherapy for various cancers. Further optimization and well-designed randomized controlled trials are needed to establish its efficacy and safety. Future studies should focus on standardizing treatment protocols and addressing limitations to guide clinical decision-making and research priorities.

GRAPHICAL ABSTRACT



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CONTACT Nianfei Wang wangnianfei@outlook.com Department of Oncology, Second Hospital of Anhui Medical University, No. 678 Furong Road, Hefei 230601, China.
*These authors contributed equally to this work

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Introduction

Neutron capture therapy (NCT) is a form of targeted radiotherapy involving a two-step process. First, a stable isotope is selectively delivered to the tumor cells. Subsequently, the tumor is irradiated with low-energy neutrons, inducing a nuclear reaction that generates high-linear energy transfer (LET) particles and gamma rays, which leads to localized cell death. The two main types of NCT are boron neutron capture therapy (BNCT) and gadolinium neutron capture therapy (GdNCT), each of which utilizes different isotopes with unique nuclear capture reactions and emission profiles (Lee et al. 2022).

In 1932, James Chadwick, a researcher at the University of Cambridge, discovered the presence of boron. Soon after, Goldhaber found that bombarding boron with slow neutron production produced alpha particles. In 1936, Locher, a researcher at Swarthmore College, recognized Goldhaber's therapeutic potential and proposed BNCT. From 1940 to 1951, numerous scientists conducted animal experiments to translate the BNCT concept into practice. Interested readers can refer to Sweet's review for more comprehensive information on the early history of BNCT (Sweet 1997).

BNCT provides cell-level targeting by using non-radioactive isotope ^{10}B that accumulates selectively in tumor cells. When low-energy neutrons are absorbed by isotope ^{10}B, it triggers a reaction called boron capture therapy. This reaction causes the isotope to break down into an alpha particle and a ^{7}Li nucleus, emitting particles that generate energy over a limited distance of 7-10 μm. This range happens to match the size of a cell, which allows for targeted destruction of cancer cells while leaving healthy cells unharmed (Figure 1) (Locher 1936). Secondly, α particles and ^{7}Li nuclei exhibit high linear energy transfer (LET) radiation, increasing the relative biological effect (RBE). Charged particles can damage DNA directly, regardless of cancer cell oxygen content. Therefore, BNCT can potentially have a lethal effect on hypoxic tumors (Ono et al. 2019). Furthermore, patients typically undergo BNCT once or occasionally twice, with each treatment lasting 30-60 min.

The neutron sources used in BNCT include reactor reactors and accelerator-based systems. A limited number of reactors remain operational, and many have been decommissioned. Advancements in accelerator neutron source technology have facilitated the rapid development of BNCT. Several countries, including Japan, Finland, Italy, South Korea, China, Great Britain, Russia, Israel, and Argentina, are constructing or planning BNCT centers (Figure 2) (Cartelli et al. 2020; Accelerator-based BNCT projects [date unknown]). In 2009, Sumitomo Heavy Industries, in collaboration with Kyoto University, Japan, achieved a significant milestone by successfully developing a cyclotron-based neutron source. Furthermore, in 2012 Kyoto University conducted the world's first clinical trial of Accelerator-based- BNCT (AB-BNCT). In contrast, in 2020, AB-BNCT received approval to treat recurrent head and neck cancer in Japan, with coverage

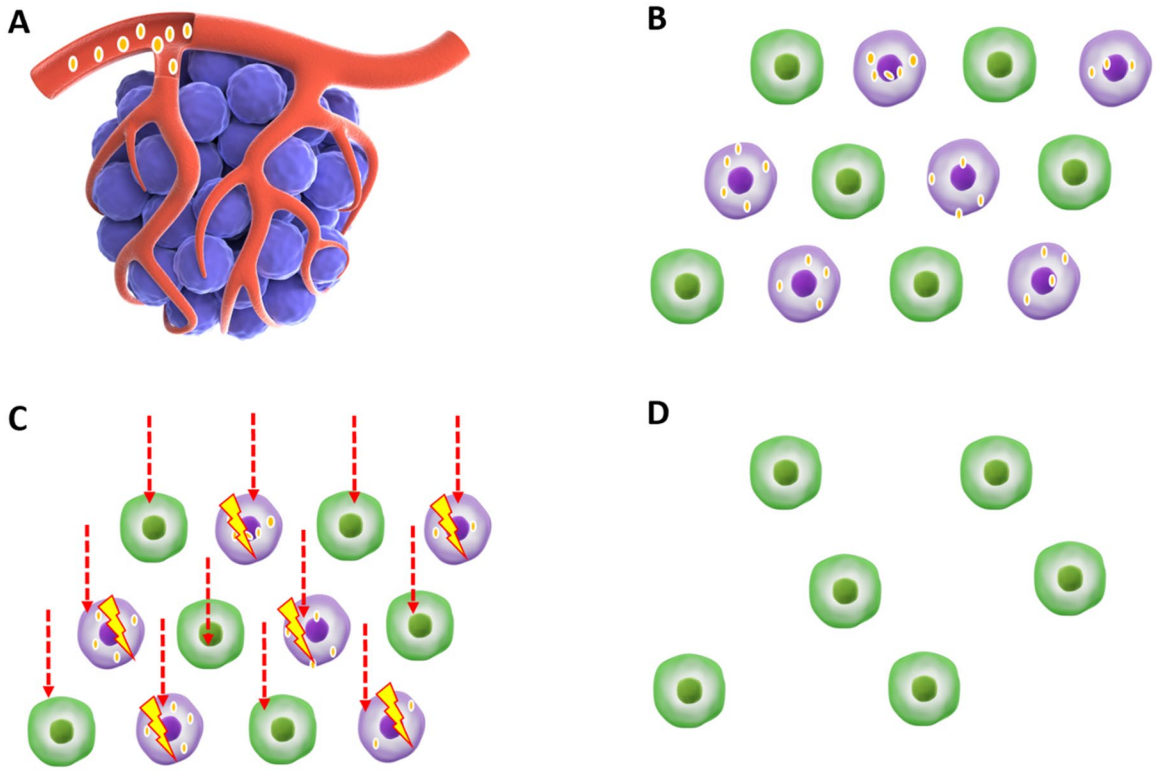

Figure 1. Mechanisms of BNCT in cancer.
Patients were injected intravenously with a boron delivery agent before and sometimes during treatment (A). Cancer cells selectively absorb the boron-delivery agent with little uptake by normal tissues (B). The boron nucleus absorbs neutrons and undergoes nuclear fission, yielding an alpha particle and a ^{7}Li. The range of the particle is 4-7 μm, equal to the diameter of a cell (C). Tumor cells were eliminated following BNCT therapy without causing considerable damage to normal tissue cells (D).

Figure 2. Global AB-BNCT projects: operational status of completed and under-construction facilities.
The figure illustrates the operational status of accelerator-based boron neutron capture therapy (AB-BNCT) projects worldwide that have been completed or are currently under construction. The data used to create this figure was obtained from the official website of the International Society for Neutron Capture Therapy (ISNCT) and is current as of the end of 2022.

provided by health insurance. Finland had initially planned to commence the AB-BCNT clinical trials in 2023 (Porra et al. 2023). However, as of April 2024, we have not found evidence that they have officially initiated the clinical studies.

Several reviews have comprehensively summarized the evolution of boron delivery agents and neutron sources (Luderer et al. 2015; Barth et al. 2018; Farhood et al. 2018; Dymova et al. 2020). This article begins with an overview of BNCT clinical trials registered with authoritative organizations. Subsequently, we examined typical clinical studies focusing on efficacy and treatment-related adverse events, considering the anatomical site and pathological type of tumors.

Introduction to boron delivery agents

Boron compounds have extensive applications in the medical field, including antibacterial, anti-tuberculosis, anti-tumor, anti-parasitic, anti-protozoal, anti-inflammatory, anti-folate, anti-depressant, anti-allergic, anesthetic, and anti-Alzheimer's drugs, as well as proteasome and lipogenesis inhibitors (Leśnikowski 2016; Das et al. 2022). They also play an essential role in neutron capture therapy (Xuan and Vicente 2018). In recent years, researchers have proposed two methods to enhance the effect of proton therapy using boron isotopes: proton–boron fusion therapy (P-BFT) using boron-11 agents and neutron capture-enhanced particle therapy (NCEPT) using boron-10 agents (Tabbakh and Hosmane 2020).

The boron element used in BNCT is ^{10}B because ^{10}B has a higher neutron capture cross-section of 3837 barns than 0.005 barns of ^{11}B (Fithroni et al. 2022). Many studies consider that an ideal boron delivery agent should simultaneously meet the following four conditions: low toxicity; ^{10}B concentration in the tumor exceeds 30 μg/g; its concentration in the cancer is much higher than that in normal tissues, generally considered tumor-to-normal tissue ratio (T/N) > 3; and it is rapidly cleared from the body after BNCT treatment (Sibrian-Vazquez and Vicente 2011; Takagaki et al. 2018; Ali et al. 2020). Unfortunately, no boron delivery agent met all these conditions. For convenience, we also briefly introduce and evaluate boron delivery agents by dividing them into three generations (Figure 3), as in the literature.

First-generation boron delivery agents

As early as the 1950s, compounds such as boric acid, borax, and pentaborate were synthesized. These small-molecule compounds lack tumor-targeting ability and are quickly metabolized out of the body, so they cannot accumulate in tumors. This is an essential reason for the unsatisfactory efficacy of early BNCT clinical studies.

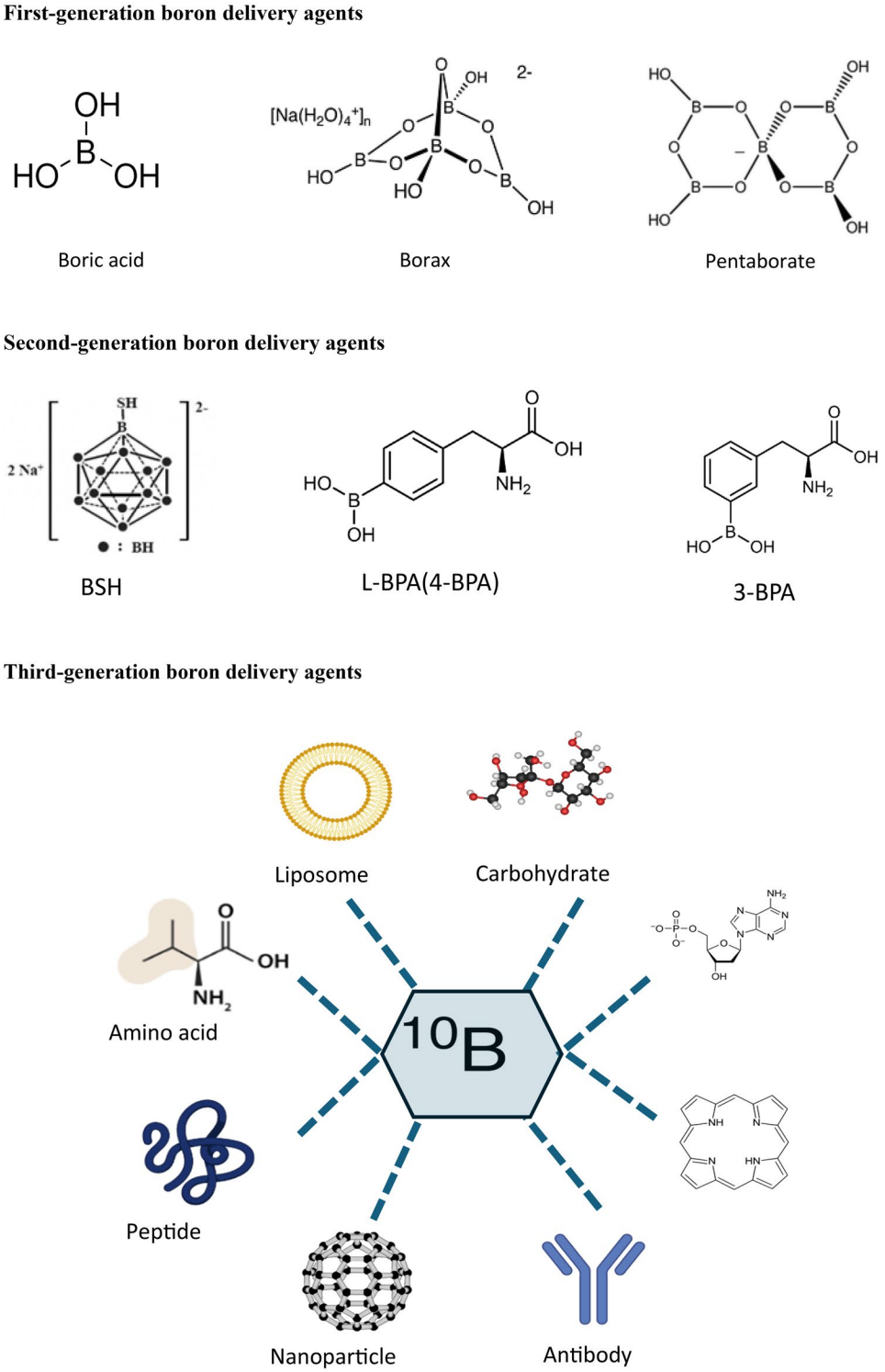

Figure 3. Classification and structures of boron delivery agents for BNCT.
This figure illustrates the development of boron delivery agents for BNCT across three generations. The first-generation compounds, such as boric acid, borax, nanoparticles, and pentaborates, had low tumor selectivity and accumulation. The second generation introduced the clinically successful BPA and BSH, which exhibited improved tumor targeting and lower toxicity than the first generation. The third generation enhances tumor specificity and boron delivery by conjugating BPA and BSH with tumor-targeting moieties. These include amino acids, peptides, antibodies, porphyrins, liposomes, and oligonucleotides.

Second-generation boron delivery agents

These include BPA and BSH (Lamba et al. 2021), two boron delivery agents approved by the FDA for BNCT clinical trials.

BSH

BSH is a cage-like polyhedral borane anion with each molecule containing 12 ^{10}B atoms. BSH can accumulate near brain tumors when the blood-brain barrier (BBB) is disrupted. It was

first discovered by Soloway and Hatanaka in 1967 and was used by Dr. Mishima to treat glioblastoma in 1989 (Sauerwein et al. 2012). Owing to the lack of tumor cell-specific ligands, BSH has low T/N and tumor-to-blood ratio (T/B). Although the mechanism of boron concentration differences in different tissues is not entirely clear, it is generally believed that its small molecular size allows it to diffuse to various organs through blood perfusion and may be affected by physiological barriers such as the blood-brain barrier (Sauerwein et al. 2012).

In the European Organization for Research and Treatment of Cancer (EORTC) clinical trial 11961, the dosage of BSH was 100 mg/kg body weight. Pharmacokinetic analysis showed that the average clearance rate of boron in the blood was 19.8 mL per minute, and the terminal half-life ranged from 44.0 to 92.8 hours, indicating that the elimination of BSH in the body is relatively slow. Side effects that may occur when patients are infused with BSH, such as flushing and nausea, may be related to infusion rates exceeding 1 mg/kg/min (Hosmane 2012). In addition, the variability of boron concentrations in the blood of different patients is considerable, emphasizing the need for individual measurements of blood ^{10}B concentrations during each patient's irradiation to ensure the accuracy and safety of treatment.

BPA

BPA is a boron-containing compound designed for BNCT, including L-BPA (4-BPA) and the recently reported compound 3-BPA. L-BPA was synthesized by Snyder et al. in 1958 and was first used by Dr. Mishima to treat melanoma in 1989 (Mishima et al. 1989). The structure of L-BPA is highly similar to that of phenylalanine, allowing it to be selectively absorbed by tumor cells through the L-type amino acid transport system (LAT-1). BPA has good tumor cell targeting, with higher T/N and T/B values. L-BPA has been applied in BNCT treatment of various tumors, including melanoma, glioma, head and neck tumors, Paget's disease, and breast cancer. Based on the positive results obtained from the JHN002 clinical study (Hirose et al. 2021), L-BPA (SPM-011) was approved for marketing in Japan in May 2020 under the name borofalan (Steboronine ®) for BNCT treatment of unresectable locally advanced or recurrent head and neck cancer (see below). Almost all ongoing clinical studies of AB-BNCT in Japan have adopted borofalan as a boron delivery agent, such as JPRN-jRCT2032230554 (JRCT 2024a), JPRN-jRCT2051210053 (JRCT 2024b), NCT04293289 (ClinicalTrials.gov 2000), JPRN-jRCT2031220410 (JRCT 2024c), JPRN-jRCT1080224974 (Mishima et al. 1989), JPRN-jRCT2051190044 (JRCT 2024d). L-BPA has a low boron content and requires high doses for treatment. It has poor water solubility and may cause hematuria due to crystallization in the urine (Kanno et al. 2021). L-BPA requires fructose or mannitol as the solvent, which limits its use in fructose-intolerant patients. Additionally, studies have shown that BPA is easily degraded by endogenous hydrogen peroxide, leading to loss of boronic acid groups and poor metabolic stability in vivo (Li et al. 2019).

3-BPA is the positional isomer of L-BPA. Comparative studies with L-BPA have shown that 3-BPA has similar biodistribution and tumor-targeting ability. The water solubility of 3-BPA is 125 g/L, more than 100 times that of L-BPA; therefore, it does not require solubilizing sugars during administration. Thus, 3-BPA is expected to replace L-BPA in the near future (Kondo et al. 2022).

Pharmacokinetic analysis showed that BPA clearance in vivo exhibited a biphasic process with a rapid redistribution phase and a slower elimination phase. When BPA is infused, the variability of blood boron concentrations in patients is considerable, emphasizing the need for individual measurements of blood (Dymova et al. 2020) B concentrations during each patient's irradiation to ensure the accuracy and safety of treatment (Sauerwein et al. 2012).

^{18}F-labeled L-BPA

When the boron concentration in a patient's tumor reaches its maximum accumulation, it is a crucial issue for implementing BNCT, as this is the only way to maximize tumor cell killing while simultaneously optimizing the protection of normal tissues surrounding the tumor. Positron emission tomography (PET)-guided BNCT has the potential to overcome this challenge using dual-mode formulations.

In 1991, Ishiwata found that a hydrogen atom on the benzene ring of L-BPA can be replaced by ^{18}F to obtain ^{18}F-BPA (Ishiwata et al. 1991). Various examinations using ^{18}F-BPA PET were reported in the latter part of the 1990s (Mishima et al. 1997; Imahori et al. 1998). ^{18}F-BPA PET can help select patients with good prognoses and support dose distribution calculations. Studies have shown that the higher the ^{18}F-BPA accumulation ratio between the tumor and normal organs, the better the anti-tumor effect and fewer adverse reactions (Nariai and Ishiwata 2012). Generally, the ^{18}F-BPA accumulation ratio between the tumor and normal organs should be 2.5 or higher (Fukumitsu and Matsumoto 2021). However, the method used to achieve this measurement has not been standardized. In addition, other formulations, such as contrast agents for magnetic resonance imaging (boron-gadolinium compounds), are expected to be applied clinically (Shanmugam et al. 2023).

Third-generation boron delivery agents

Although BPA and BSH have achieved a specific efficacy in BNCT-treated patients, neither has reached the standard of an 'ideal' boron delivery agent, and we have described their shortcomings above. Chemists and pharmacists have been committed to synthesizing a variety of potentially highly efficient boron dosing agents. The core concept of the third-generation boron delivery agent design is to improve the tumor targeting of drugs, which has become one of the hottest directions in BNCT research. They are currently being tested in cell and animal models and have no application in clinical trials.

These delivery agents include boron-containing nucleosides (Khalil and Adam 2024), peptides (Nakase et al. 2020), polyamines (Ueda et al. 2021), porphyrins (Hiramatsu et al. 2011), liposomes (Li et al. 2022),

monoclonal antibodies (Yamana et al. 2023), and various types of nanoparticles (Wu et al. 2006; Nakamura and Kirihata 2012; Ban and Nakamura 2018; Ali et al. 2020; Zhang et al. 2023). A recent review by Hong Xu et al. from China Pharmaceutical University introduced a new classification system for boron drugs used in BNCT based on their design strategies. This system categorizes drugs into four distinct types: Cell Membrane Targeting, which utilizes transport mechanisms such as LATs, glucose transporter (GLUT), and peptides to exploit the increased nutrient demands of tumor cells; Nuclear Targeting, where drugs interact with or integrate into DNA, targeting the nucleus for direct damage during neutron capture; Enhanced Permeability and Retention (EPR) effect, leveraging the looser vascular structures of tumors to accumulate large molecules such as liposomes, polymers, or nanoparticles; and Tumor Affinity, employing molecules such as porphyrins that naturally target and accumulate in tumor cells. This classification highlights the diverse mechanisms and design principles underlying the targeted actions of boron drugs in BNCT (Xu et al. 2024).

Early BNCT clinical exploration

In 1951, neurosurgeon WH Sweet conducted a BNCT trial on glioma at Massachusetts General Hospital, using borax as the boron delivery agent. Eighteen patients with gliomas were included in this study. The patients had a median overall survival [(mOS) defined as the time from randomization until death from any cause. The Median Overall Survival (mOS) refers to the survival time at which 50% of the study population has survived.)] for approximately three months (Asbury et al. 1972; Slatkin 1991). In 1968, Hatanaka from Teikyo University, part of Sweet's research team, initiated a clinical study on BNCT brain tumors using sodium borocaptate (BSH). By 1995, 149 patients had undergone treatment in five reactors. This included 64 patients with glioblastoma (WHO grade IV), 39 with anaplastic astrocytoma (WHO grade III), 17 with low-grade astrocytoma (WHO grade I and II), and 30 with other types of cancer. The overall response rate [According to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, the efficacy of cancer treatment can be categorized into four levels: complete response (CR), stable disease (SD), partial response (PR), and progressive disease (PD). The overall response rate (ORR) is defined as the percentage of patients achieving either CR or PR among all treated patients.] (ORR) was 64% among glioblastoma patients, with 7 cases of glioblastoma, 22 cases of anaplastic astrocytoma, and 8 cases of low-grade astrocytoma surviving for over two years. The mOS for patients with glioblastoma, anaplastic astrocytoma, and low-grade astrocytoma was 640 days, 1811 days, and 1669 days, respectively. Six patients, two with glioblastomas and four with anaplastic astrocytomas survived for over ten years. Studies have indicated that the histological grade, patient age, neutron irradiation, neutron injection at the tumor target, and tumor target depth or size are important prognostic factors (Nakagawa and Hatanaka 1997).

A team led by Professor Mishima at Kobe University conducted a study that showed that Professor Mishima and his colleague at Kobe University have conducted a study that shows that L-p-boronophenylalanine (L-BPA) exhibits selective absorption by cancer cells, making it a potential boron delivery agent for clinical trials involving BNCT. The researchers treated 22 patients with melanoma and achieved a promising complete remission (CR) rate of 73% (16 22) (Fukuda et al. 2003).

Overview of recent BNCT clinical trials

Clinical trial registration originated in the 1990s when the United States Congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997. This legislation mandated the National Institutes of Health (NIH) to establish a database for registering NIH-funded clinical trials focused on severe or life-threatening diseases. The ClinicalTrials.gov website was officially launched in February 2000, marking the start of modern clinical trial registration. To understand the current landscape of BNCT clinical trials, we systematically searched the WHO International Clinical Trials Registry Platform using the keywords 'BNCT' or 'neutron capture therapy of cancer.' As of April 25, 2024, our search yielded 56 results. After excluding non-interventional studies, we categorized the remaining trials into two groups: reactor-based BNCT(RB-BNCT) and accelerator-based BNCT (AB-BNCT).

RB-BNCT clinical trials

Our analysis revealed that 30 clinical trials involving RB-BNCT have been registered globally, with Japan leading this way (16 trials). These trials encompass a broad spectrum of malignancies, including head and neck squamous cell carcinoma (SCC), skin angiosarcoma, brain tumors, breast cancer, glioblastoma, glioma, melanoma, pleural mesothelioma, and various skin malignancies (Table 1). Most of these trials were in phase I/II or II, underscoring the early stages of clinical development of RB-BNCT. L-BPA and BSH are the most frequently used boron carriers, with L-BPA being the most prevalent choice. The sample sizes of these trials exhibited considerable variability, ranging from one to 50 participants, with some trials not specifying the number of enrolled subjects. The recruitment status of these trials was also diverse, with some completed, some terminated, some actively recruited, and others yet to commence recruitment.

Notably, while 14 research reactors worldwide have previously conducted BNCT treatments (Moss 1993), most of these facilities have now been decommissioned because of various factors, such as funding constraints, management issues, and policy changes. At present, only a few institutions, such as the Kyoto University Research Reactor Institute (KURRI), Kyoto University Reactor (KUR) in Japan, and National Tsing Hua University (NTHU) with its Tsing Hua Open-pool Reactor (THOR) in Hsinchu, Taiwan, are actively pursuing RB-BNCT clinical research.

Table 1. Globally registered clinical trials of Reactor-based BNCT[¶].

Country or Region	Investigator	Types of Cancer	ID	Phase	Boron carrier	Sample#	Recruitment status
Japan	Nara Medical University	Head and neck SCC (recurrent)	jRCTs051180160	II	NA	7	Completed
Japan	Osaka Medical College	Skin angiosarcoma (recurrent)	jRCTs051180217	II	NA	2	Terminated*
Japan	University of Tsukuba	Brain tumor (recurrent)	UMIN000003692	I/II	L-BPA	2	Completed
Japan	Osaka Medical College	Breast cancer (recurrent)	UMIN000029403	I/II	L-BPA	1	Terminated*
Japan	Osaka Medical College	Glioblastoma (newly diagnosed)	UMIN000002385	II	BSH + L-BPA	32	Completed
Japan	University of Tsukbua	Glioma (high-grade)	C000000298	II	NA	20	Completed
Japan	University of Tsukuba	Glioma (newly diagnosed)	UMIN000003984	NA	L-BPA	20	Recruiting
Japan	Osaka Medical College	Glioma (recurrent)	UMIN000029144	II	NA	4	Terminated*
Japan	Osaka Medical College	Glioma (recurrent)	UMIN000013419	I/II	NA	50	Not yet recruiting
Japan	Osaka Medical College	Head and neck cancer	UMIN000011221	I/II	NA	10	Recruiting
Japan	Kawasaki Medical School	Melanoma	UMIN000005124	NA	NA	4	Completed
Japan	Osaka Medical College	Melanoma (choroidal)	UMIN000029402	I/II	NA	3	Not yet recruiting
Japan	NA	Pleural mesothelioma	UMIN000005478	I/II	L-BPA	20	Recruiting
Japan	Kawasaki Medical School	Skin malignant tumors	UMIN000027541	I/II	L-BPA	3	Completed
Japan	Kawasaki Medical School	Head and neck cancer(recurrent)	jRCTs061180067	I/II	L-BPA	21	Terminated*
Japan	Kawasaki Medical School	Skin malignancies (advanced or recurrent)	jRCTs061180066	I/II	L-BPA	3	Terminated*
Finland	Helsinki University Central Hospital	Head and neck cancer	NCT00114790	I/II	L-BPA	30	Completed
Finland	Helsinki University Central Hospital	Central nervous system tumors	NCT00115440	I/II	L-BPA	22	Completed
Finland	Helsinki University Central Hospital	Central nervous system tumors	NCT00115453	I/II	L-BPA	50	Completed
Finland	Helsinki University Central Hospital	Head and neck cancer	NCT00927147	I/II	L-BPA	17	Completed
Germany	EORTC[&]	Colorectal cancer, head and neck cancer	NCT00062348	I	L-BPA or BSH	NA	Unknown
Germany	EORTC[&]	Melanoma	NCT00085059	II	L-BPA	NA	Unknown
Global	EORTC[&]	Central nervous system tumors	NCT00004015	I	BSH	NA	Unknown
Taiwan	Taipei Veterans General Hospital	Head and neck cancer	NCT01173172	I/II	L-BPA	17	Completed
Taiwan	Taipei Veterans General Hospital	Head and neck cancer	NCT02004795	I/II	L-BPA	NA	Unknown
UK	Cancer Research UK	Central nervous system tumors	NCT01233492	I	L-BPA	NA	Completed
US	Beth Israel Deaconess Medical Center	Melanoma	NCT00002781	I	L-BPA	NA	Unknown
US	Beth Israel Deaconess Medical Center	Central nervous system tumors	NCT00039572	I/II	L-BPA	NA	Completed
US	Beth Israel Deaconess Medical Center	Melanoma	NCT00059800	II	NA	NA	Completed
China	The Third Xiangya Hospital of Central South University	Melanoma	NCT02759536	I/II	L-BPA	NA	Recruiting

[¶]This table is compiled based on data from the International Clinical Trials Registry Platform (https://trialsearch.who.int/). The data retrieval date is April 25, 2024.
[&]: This is a trial sponsor.
[#]If the trial is completed or terminated, the number of patients represents the actual number of participants recruited; otherwise, NA.
BNCT: Boron neutron capture therapy; EORTC: European Organization for Research and Treatment of Cancer; L-BPA: L-p-boronophenylalanine; BSH: Borocaptate sodium; EORTC: European Organization for Research and Treatment of Cancer; NA: Not applicable.

AB-BNCT clinical trials

Japan emerged as a frontrunner in AB-BNCT clinical trials, accounting for 10 of 12 registered studies worldwide. Renowned institutions, such as Osaka Medical and Pharmaceutical University, Southern Tohoku BNCT Research Center, National Cancer Center Hospital, Edogawa Hospital, and the University of Tsukuba, spearheaded these trials. The most common malignancies investigated in these trials included head and neck SCC, glioma, meningioma, malignant melanoma, angiosarcoma, and breast cancer. Most Japanese trials were in phase I or II, with sample sizes ranging from five to 120 participants. The neutron sources employed in these trials were BNCT30, CICS-1, CICS-2, and iBNCT001, whereas SPM-011 was consistently used as the boron carrier.

China and South Korea have also ventured into AB-BNCT clinical research, each with one registered trial. The Chinese trial, spearheaded by Xiamen Honghai Hospital, focused on recurrent head and neck cancer and primary brain tumors using a NeuPex neutron source and NBB-001 boron carrier. Meanwhile, the South Korean Gachon University Gil Medical Center trial investigated recurrent gliomas using a DM-BNCT neutron source and DMX-102 boron carrier (Table 2).

Clinical study of BNCT for different types of tumors

Head and neck cancer

Head and neck cancer is the seventh most prevalent malignancy worldwide, with more than 660,000 new diagnoses and 325,000 deaths reported annually (Gormley et al. 2022). SCC accounts for approximately 90% of all head and neck cancer cases (Vigneswaran and Williams 2014). Between 50% and 60% of patients who undergo standard therapy may experience recurrence or metastasis within two years (Sacco and Cohen 2015),. The treatment of recurrent cancer poses a significant challenge (Chow 2020). In cases where local recurrence cannot be effectively treated with salvage surgery or radiotherapy, the prognosis is unfavorable, and untreated patients typically survive for only 6– 9 months (Chow 2020). Table 3 shows the curative effect of BNCT on recurrent head and neck cancer.

Sixty-two patients underwent BNCT at Kyoto University, Japan. The BNCT dose administered to the skin and oral mucosa was less than 10–12 Gy-Eq. Within six months of the procedure, the ORR of BNCT was 58% within six months after the procedure. The one-year and two-year survival (OS) rates were 43.1% and 24.2%, respectively. The most common acute grade 3 and 4 toxicities observed were hyperamylasemia (38.6%), fatigue (6.5%), mucositis/stomatitis (9.7%), and pain (9.7%). However, all of these toxicities are manageable and controllable (Suzuki et al. 2014).

At Osaka University, Japan, 26 patients with recurrent head and neck cancer, including 19 with squamous cell carcinoma, 4 with salivary adenocarcinoma, and 3 with sarcoma, underwent treatment with BNCT. Among these patients, 12 achieved CR, and 10 achieved partial response (PR) (Kato et al. 2009).

Table 2. Globally registered clinical trials of AB-BNCT.

Country	Investigator	Types of Cancer	ID	Phase	Neutron Source	Boron carrier	Sample[#]	Date of registration	Recruitment status
Japan	Osaka Medical and Pharmaceutical University	Glioma (recurrent)	jRCT2051210053	I	BNCT30	SPM-011	9	2021/7/16	Completed
Japan	Southern Tohoku BNCT Research Center	Head and neck SCC (recurrent)	UMIN000044118	II	BNCT30	SPM-011	120	2021/5/10	Not yet recruiting
Japan	Osaka Medical and Pharmaceutical University	Meningioma (recurrent)	jRCT2051190044	II	BNCT30	SPM-011	18	2019/9/4	Not Recruiting
Japan	Osaka Medical College	Malignant glioma(recurrent)	jRCT2080224670, JapicCTI-194742	II	BNCT30	SPM-011	27	2021/7/19	Completed
Japan	Southern Tohoku BNCT Research Center	Head and neck cancer (recurrent)	jRCT2080224571, JapicCTI-194640	II	BNCT30	SPM-011	21	2019/2/22	Completed
Japan	National Cancer Center Hospital	Skin angiosarcoma (unresectable)	jRCT2031220410, NCT05601232	II	CICS-1	SPM-011	10	2022/10/26	Recruiting
Japan	National Cancer Center Hospital	Melanoma or angiosarcoma	JapicCTI-195062	I	CICS-1	SPM-011	10	2019/12/3	Completed
Japan	National Cancer Center Hospital	Malignant melanoma and angiosarcoma	jRCT1080224974, JapicCTI-195062	I	CICS-1	SPM-011	10	2019/12/3	Completed
Japan	Edogawa Hospital	Breast cancer (recurrent)	jRCTs031220371	I	CICS-2	SPM-011	5	2022/10/7	Recruiting
Japan	University of Tsukuba	Glioblastoma (newly diagnosed)	jRCT2032230554	I	iBNCT001	SPM-011	18	2024/1/10	Recruiting
China	Xiamen Honghai Hospital	Head and neck cancer, primary brain tumor(recurrent)	ChiCTR2300078618	I	NeuPex	NBB-001	16	2023/12/14	Recruiting
Korea	Gachon University Gil Medical Center	Gliomas(recurrent)	NCT05737212	I/II	DM-BNCT	DMX-102	39	2022/12/6	Recruiting

[¶]This table is compiled based on data from the International Clinical Trials Registry Platform(https://trialsearch.who.int/). The data retrieval date is April 25, 2024.
[#]If the trial is completed or terminated, the number of patients represents the actual number of participants recruited; otherwise, NA.
BNCT: Boron neutron capture therapy; NA: Not applicable.

Table 3. BNCT clinical trial of head and neck squamous cell carcinoma.

Research sponsor	Year of Study	Neutron source	Type(s) of cancer/ number of patients	Boron carrier	Main outcomes
Kyoto University	2001-2007	Reactor	rHN 49 urHN 13	BSH and L-BPA	CR 28%, PR 29%; 2yOS 24.2%
Osaka University	2001-2007	Reactor	rHN 26	L-BPA or L-BPA + BSH	CR 46%, PR 38%; Average OS 13.6 m
University of Tsukuba	2003-2007	Reactor	rSCC 10 r-nonSCC 7 urHN 3	L-BPA	CR 55%, PR 35%; 2yPFS 22.4%, 2yOS 31.4%
Helsinki University Central Hospital	2003-2008	Reactor	urHN30	L-BPA	CR 45%, PR 31%; 2yPFS 20%, 2yOS 30%
	2003-2012	Reactor	rSCC 79	L-BPA	CR 36%, PR 25%; 2yPFS 38%, 2yOS: 21%
Taipei Veterans General Hospital	2010-2013	Reactor	rHN 17*	L-BPA	2yLC 20%, 2y OS 47%
Southern Tohoku BNCT Research Center	2016-2018	Accelerator	rHN 22	SPM-011	CR 23.8%, PR 47.6%; 2yOS 85.3%

*Report on the first stage.

BNCT: Boron neutron capture therapy; L-BPA: p-boronophenylalanine; BSH: Na2B12H11SH; CR: complete response; PR: partial response; LC: local control; PFS: progression-free survival; OS: overall survival; 2y: years; rHN: recurrent head and neck carcinoma; urHN: unresectable recurrent head and neck carcinoma; rSCC: recurrent squamous cell carcinoma; r-nonSCC: recurrent non-squamous cell carcinoma.

The University of Tsukuba, Japan University of Tsukuba, conducted a study involving 20twenty patients with head and neck cancer, including 11 patients with non-squamous non-squamous cell carcinoma treated with BNCT. After a five-month follow-up, 11 patients achieved CR, seven earned PR, and two had stable disease (SD). The mean mOS for the patients was 18.8 months. Notably, no severe acute or chronic normal tissue response was observed in these patients (Aihara et al. 2014).

The Helsinki University Central Hospital and Finland Helsinki University Central Hospital conducted a study involving 30 patients with recurrent head and neck cancer who had previously undergone photon RT. These patients were treated with BNCT between 2003 and 2008 and registered under the trial identifier NCT00114790. Among the patients, 26 were treated once with BNCT, whereas four received two treatments. Thirteen patients achieved CR, nine had PR, and six had SD. The median progression-free survival (mPFS) was 7.5 months, ranging: from 5.4 to 9.6 months. The 2-year progression-free survival (PFS) and OS rates were 20% and 30%, respectively.

Additionally, 27% of patients survived for two years without local recurrence. The most frequent acute adverse effects reported were mucositis (54%), mouth discomfort (54%), and weariness (Kankaanranta et al. 2012). The second study enrolled 79 patients with inoperable recurrent head and neck SCC from 2003 to 2012. Among these patients, 95% had previously received radiation therapy, and 71% had undergone surgery. Forty patients underwent a single treatment with BNCT, while 39 received two treatments, with a median interval gap of six weeks between sessions. The CR rate was 36%, the PR rate was 32%, and 25% of the patients had SD. Notably, the study found that BNCT fractionated treatment was more effective than a single treatment, with a CR rate of 50% compared to 19% in the single treatment group. Additionally, the PR rate was 29% in the fractionated treatment group compared with 36% among those who received a single treatment.

The Taiwan Veterans General Hospital enrolled 17 patients with recurrent head and neck cancer who had previously undergone photon RT. Of these, 15 patients underwent BNCT twice, and two underwent therapy once. The initial prescribed dose was 19.8 Gy-Eq, followed by a second dose of 14.6 Gy-Eq. Six of the total patients achieved CR, and another six earned PR. The local control rate at two years was 28%, and the OS rate at the same interval was 47%. One patient with recurrent hypopharyngeal cancer developed grade 4 laryngeal edema accompanied by carotid bleeding (Wang et al. 2018).

In 2020, Southern TOHOKU Hospital, Japan, presented the outcomes of the accelerator-based BNCT (AB-BNCT) clinical trial JHN002 (Hirose et al. 2021). The primary inclusion criteria were patients with recurrent head and neck SCC post-photon radiotherapy and those with non-squamous non-squamous cell carcinoma, who were either ineligible for surgery or had relapsed post-treatment. The participants were administered 400 mg/kg BPM-011BPA, followed by AB-BNCT. The cancer irradiation dose prescribed for the tumor was adjusted based on the maximum mucosal dose of 12 Gy-Eq. The cancer irradiation dose was adjusted based on the maximum mucosal dose of 12 Gy-Eq. Of the 21 enrolled patients who completed BNCT, 8 had squamous cell carcinoma, and 13 had non-squamous cell carcinoma. The primary endpoint ORR was 71.4% (15/21), including a CR rate of 23.8% and PR of 47.6%, which is markedly superior to the efficacy of immune checkpoint inhibitors (ORR < 20% (Borel et al. 2020; Kao and Lou 2019)). Secondary endpoints showed 1- and 2-year PFS rates of 70.6% and 60.5%, respectively, and the 1-year and 2-year OS rates were 94.7% and 85.3%, respectively. There was a 5% (one case) incidence of grade 3 oral mucositis. There were no grade 4 or 5 adverse effects (AEs) apart from temporary hyperamylasemia. Remarkably, the AE rate in this trial was lower than that in previous AB-BNCT studies, possibly because of advanced treatment planning processes, such as target delineation, dose prescription, beam adjustment, and placement optimization (Hirose et al. 2021).

Based on the results of this phase II clinical study, the Japan Greenlit BNCT system was developed by Sumitomo Heavy Industry Co., Ltd., Tokyo, and Steboronine®, a boron-based drug crafted by STELLA Pharmaceutical Company, was designed by Sumitomo Heavy Industry Co., March 2020. Updated safety data from BNCT in March 2022

revealed a median recovery time of 23 days for oral mucositis, 40 days for dermatitis, 58 days for one instance of alopecia areata, and 156 days for another (Hirose et al. 2022).

Following the success of this trial, Japan approved the BNCT system and Steboronine® for treating inoperable recurrent head and neck tumors in March 2020. A new phase II clinical trial (UMIN000044118) with a larger sample size of 120 patients is ongoing to evaluate the efficacy and safety of AB-BNCT using SPM-011 in patients with recurrent head and neck squamous cell carcinoma (UMIN 2021). In China, Xiamen Hongai Hospital has registered a phase I/II clinical trial (ChiCTR2200066473) investigating the safety, tolerability, and preliminary efficacy of AB-BNCT using a NeuPex neutron source and NBB-001 boron carrier in patients with recurrent head and neck cancer and primary brain tumors (ChiCTR 2023). This study aimed to enroll 12 patients and is expected to be completed by December 2024.

Additionally, case studies have documented the use of BNCT for newly diagnosed head and neck cancer. Teruhito Aihara and colleagues from Kawasaki Medical School treated five salivary gland cancer patients. Remarkably, all patients achieved CR within six months post-treatment, with a median CR duration of 24 months and an mOS of 32 months. Leena Kankaanranta and her team from Helsinki University Central Hospital, Finland Helsinki University Central Hospital, managed a patient with an extensive nasal cavity and paranasal sinus carcinoma. The cancer was eradicated post-treatment, and the patient's optic nerve function remained intact (Kankaanranta et al. 2011). Additionally, Kimura Y and associates from Osaka Medical College, JapanOsaka Medical College, used BNCT to treat a 78-year-old patient with a newly diagnosed papillary cystadenocarcinoma of the upper lip, resulting in the complete disappearance of the tumor (Kimura et al. 2009).

Glioblastoma

Based on the WHO classification, glioblastoma (GBM) is the most common and aggressive brain tumor. For patients with GBM who are unable to undergo surgery, the mOS is only four months. In the standard post-treatment, the 1-year OS rate was 41.4%, with an mOS of approximately 14 months (Tan et al. 2020). The primary reason for resistance to photon radiotherapy is the lack of oxygen in cancerous tissues (Chédeville and Madureira 2021). Given that BNCT's efficacy is not contingent on the tumor's intracellular oxygen content, it presents a promising method for GBM treatment.

Since the 1990s, RB-BNCT has been used to treat newly diagnosed recurrent GBM (Table 4). To enhance its efficacy, Japan has refined trial protocols in the following ways: (i) concomitant use of BPA and BSH, (ii) supplemental photon radiotherapy, and (iii) a combination of temozolomide and bevacizumab. Employing these strategies, the mOS for primary GBM patients has risen from 23.5 to 27.1 months, significantly improving over standard treatments (Stupp et al. 2005; Gilbert et al. 2014). Data from Tsukuba University and Osaka Medical College (Tamura et al. 2006; Miyatake et al. 2007) indicated that intraoperative BNCT offers no survival benefit compared to postoperative BNCT in patients with GBM.

JG002 represents Japan's latest open-label multicenter phase II clinical trial that employed AB-BNCT to treat

Table 4. Clinical outcomes of RB-BNCT in the treatment of newly diagnosed and recurrent GBM.

Research sponsor	Year of Study	Type(s) of cancer	Sample Size	Boron carrier/administration	mOS (month)
Brookhaven National Laboratory	1994–1999	nGBM	53	BPA 250~330mg/kg in 2 h	12.8
Beth Israel Deaconess Medical Center	1996–1999	nGBM	20	BPA 250~350 mg/kg in 1.5 h	11.1
	2002–2003	nGBM	6	BPA 14 g/m2 in 1.5 h	NA
Essen University Hospital	1997–2002	nGBM	26	BSA 100 mg/kg in 1.7 h	10.4–13.2
Helsinki University Central Hospital	1999–2001	nGBM	30	BPA 290–500 mg/kg in 2 h	11.0–21.9
	2001–2008	rGBM	20	BPA 290–450 mg/kg in 2 h	7 (post-BNCT)
Charles University College Hospital	2000–2002	nGBM	5	BSH 100 mg/kg in 1 h	NA
Nyköping Hospital (Sweden)	2001–2003	nGBM	29	BPA 900 mg/kg in 6 h	17.7
	2001–2005	rGBM	12	BPA 900 mg/kg in 6 h	8.7 (post-BNCT)
University of Tsukuba	1999–2002	nGBM	5	BSH 100 mg/kg in 1–1.5 h (IO-BNCT)	23.2
	1998–2007	nGBM	7	BSH 5 g in 1 h (IO-BNCT)	23.3
	1998–2007	nGBM	8	BSH 5 g in 1 h + BPA 250 mg/kg in 1 h (BNCT + XRT)	27.1
Tokushima University	1998–2000	nGBM	6	BSH 64.9–178.6 mg/kg (IO-BNCT)	15.5
	2001–2004	nGBM	11	BSH 64.9–178.6 mg/kg (IO-BNCT)	19.5
	2005–2008	nGBM	6	BSH 100 mg/kg and BPA 250 mg/kg in 1 h (BNCT + XRT)	26.2
Osaka Medical College	2002–2003	nGBM	10	BSH 5 g + BPA 250 mg/kg in 1 h	14.5
	2003–2006	nGBM	11	BSH 5 g in 1 h + BPA 700 mg/kg in 3 h (BNCT + XRT)	23.5
	2002–2007	rGBM	19	BSH 5 g + BPA 250 mg/kg in 1 h or BSH 5 g + BPA 700 mg/kg in 3 h	10.8
	2010–2013	nGBM	32	BSH 5 g in 1 h + BPA 500 mg/kg in 3 h (BNCT + XRT + TMZ)	21.1
	2013–2018	rGBM	10	BPA 500 mg/kg in 3 h (BNCT + Bev)	12
Taipei Veterans General Hospital	2017–2019	rGBM	15#	BPA 450 mg /kg	7.34*

Note: This table is adapted from the review by Miyatake SI et al.

n: newly diagnosed; r: recurrent; GBM: glioblastoma; IO-BNCT: Intraoperative BNCT; XRT: X-ray radiotherapy; mOS: median overall survival; TMZ: temozolomide; Bev: Bevacizumab.

All newly diagnosed GMB patients in the table underwent reductive surgery.

#34 patients with malignant brain tumors, including 15 patients with GBM, relapsed after standard treatment and were in critical condition.

*7.34 months is the average rather than the median.

recurrent GBM (Miyatake et al. 2020). Preliminary results were obtained at the 2020 ASCO meeting in 2020. This study enrolled 24 patients with GBM between February 2016 and June 2018, the study enrolled 24 GBM patients, achieving a 1-year OS rate of 79.2% and an mOS of 18.7 months.

The Gachon University Gil Medical Center in South Korea has also initiated a phase I/IIa clinical trial (NCT05737212) to investigate the safety and efficacy of AB-BNCT using the DM-BNCT neutron source and DMX-101 boron carrier in patients with recurrent high-grade gliomas, including GBM (ClinicalTrials.gov 2023). The trial aimed to enroll 39 patients and explore the adequate radiation dose level for AB-BNCT based on confirming the maximum tolerated dose. The estimated completion date is December 2024.

Long-term survivors face a potential risk of developing secondary primary cancers; however, in Japan, the likelihood of this occurrence remains exceedingly low. Since 1968, of the 180 patients diagnosed with malignant brain tumors, only one developed multiple meningiomas within the BNCT target field (Kageji et al. 2015).

High-grade meningioma

Based on the 2016 World Health Organization classification, meningiomas are categorized into three grades: Grade I constitutes 80% of cases and typically has a favorable prognosis. Grade II (comprising 20%– 25%) and Grade III (encompassing 1%– 6%) meningiomas are defined as high-grade meningiomas (HGMs) and are associated with a less favorable prognosis. The prognosis for HGM cases that recurred after photon post-photon radiotherapy deteriorated further, with an mOS of 24.6 months and an mPFS of 5.2 months.

Osaka Medical College has extensively studied BNCT for recurrent HGM. Between 2005 and 2019, the institution treated 44 relapsed HGM cases using BNCT, and the results were disseminated across consecutive publications (Tamura et al. 2006; Miyatake et al. 2007; Takeuchi et al. 2018; Takai et al. 2022). For patients with WHO grade II (20 cases) and III (24 cases) HGM post-surgery, the mOS was 44.4 months and 21.55 months, respectively ($p = .0009$). The mPFS for WHO grade II and III HGM patients was 24.3 and 9.4 months, respectively ($p = .0024$). Notably, grade 2 and grade 3 radiation encephalitis occurred in 31.4% and 13.6% of the patients, respectively. Although it is often assumed that deeper tumors may not respond well to BNCT, seven patients with skull base cancers exhibited positive outcomes (Takeuchi et al. 2018).

Osaka Medical College, Japan, initiated a phase II clinical trial of AB-BNCT to treat HGM and patient enrollment commenced in April 2019 (JRCT2051190044) (Nakahara et al. 2020). This study randomized 18 patients with recurrent HGM into two groups: 12 underwent BNCT treatment, while the remaining six received the best supportive care (palliative care). The primary endpoint of this study was PFS.

Stenstam and colleagues from the Nykoping Hospital, Sweden, documented the successful treatment of two patients with recurrent HGM using BNCT (Stenstam et al. 2007). One patient exhibited a survival duration of 32 months after BNCT post-BNCT, whereas the other survived after a 27-month follow-up.

Brainstem tumor

Pediatric high-grade brainstem gliomas are rare tumors, accounting for 10-20% of all pediatric brain tumors. Patients with these tumors have a mean survival rate of only eight months. Multiple hospitals in Taiwan have documented the treatment of seven patients with terminal brainstem glioma who qualified for emergency and compassionate use. All these patients underwent two fractions of salvage BNCT, receiving doses of 7.22 Gy-Eq and 6.62 Gy-Eq prescribed to the skin, receiving doses of 7.22 Gy-Eq and 6.62 Gy-Eq, respectively. Among the seven patients, one achieved CR, and five achieved PR. Importantly, none of the patients experienced acute or delayed adverse events. Therefore, low-dose fractionated BNCT may be a promising, safe, and effective salvage therapy for patients with terminal brainstem glioma glioma patients (Chen et al. 2022).

Melanoma of the skin

Although melanoma accounts for approximately 10% of all skin cancers, it accounts for approximately 80% of skin malignancy-related deaths attributed to skin malignancies (Siegel et al. 2020). Radiotherapy is an essential treatment option for patients with melanoma who are unable or prefer not to undergo surgery, and radiotherapy is a vital treatment option (Fort et al. 2016). Melanomas are often resistant or insensitive to photon radiation (Im et al. 2020). In contrast, BNCT has shown notable potential for melanoma treatment.

Fukuda reviewed the treatment of 32 patients with cutaneous melanoma using L-BPA as a boron delivery agent at Ohio State University Fukuda reviewed the treatment of 32 patients with cutaneous melanoma using L-BPA as a boron delivery agent from 1987 to 2014. The overall CR rate was 78% (n = 25/32). This included a CR rate of 81% (22/27) for primary cancers and 60% (3/5) for metastatic cancer. Nodular melanoma has a CR rate of 33% (1/3), whereas non-nodular melanoma has a more impressive rate of 87.5% (21/24) (Barth et al. 2018).

Between 2003 and 2007, Argentina conducted a phase I/II BNCT clinical trial that enrolled seven patients with skin melanoma. The dose for the normal skin was capped between 16.5 and 24 Gy-Eq. The ORR and grade 3 skin toxicities were 69% and 69%, respectively, whereas grade 3 skin toxicities were recorded at 30% and (Menéndez et al. 2009).

Kawasaki Medical University administered RB-BNCT to eight patients with melanoma and monitored their progress. The age of the patients at the time of treatment ranged from 48 to 86 years old. Their tumors were located on the plantar or facial regions, were characterized by a clinical stage of cT1-2N0M0, and displayed no regional lymph node involvement. The prescribed minimum dose for the tumor was 25 Gy, whereas the maximum skin dose was 15 Gy. Remarkably, six of the eight patients achieved CR, and two

attained PR, resulting in an ORR of 88%. Three patients succumbed to conditions such as pneumonia or factors related to old age that were not associated with melanoma. However, the remaining five patients continued to lead lives of good quality. No adverse events exceeding grade 2 in severity were reported as adverse events exceeding grade 2 in severity (Hiratsuka et al. 2020).

The Third Xiangya Hospital of Central South University, China, initiated a clinical trial for BNCT treatment targeting melanoma to enroll 30 patients (NCT02759536). However, this trial is still in progress (Yong et al. 2016). The latest public data indicate that at least 22 patients were enrolled (Wang et al. 2022).

The National Cancer Center Hospital in Japan recently completed a phase I study (NCT04293289) to evaluate BNCT drug CICS-1 (SPM-011) safety and efficacy in patients with primary melanoma or angiosarcoma (ClinicalTrials.gov 2000). The results of this study provide valuable insights into the potential of CICS-1 as a novel boron delivery agent for BNCT in melanoma and angiosarcoma treatment. Building on phase I results, a phase II trial (NCT05601232) was initiated to investigate further the efficacy and safety CICS-1 in patients with unresectable angiosarcomas (JRCT 2024c).

Breast cancer

Preliminary clinical data suggest that BNCT may be an effective treatment for locoregionally recurrent breast cancer (Kurosaki et al. 2024). In a case report from the University of Tokyo, Japan, a patient with recurrent breast cancer in the left axillary lymph nodes they have experienced a significant reduction in tumor size and pain relief two months after BNCT treatment with BPA without severe acute toxicities (JRCT 2020).

More recently, Edogawa Hospital, Japan, reported three patients with locoregionally recurrent breast cancer treated with BNCT using the CICS-2 accelerator and SPM-011 (Kurosaki et al. 2024). At 90 days post-treatment, one patient achieved a complete response, while the other two had partial tumor shrinkage. No grade 3 or higher adverse events were observed, and importantly, no evidence of radiation pneumonitis was detected on CT scans.

These early clinical results indicate that BNCT may be an effective and well-tolerated treatment option for recurrent breast cancer. Currently, a phase I clinical trial (jRCTs031220371) is underway at Edogawa Hospital, Japan, to evaluate the safety and efficacy of BNCT using the CICS-2 accelerator and SPM-011 for recurrent breast cancer following radiotherapy (JRCT 2022). The primary endpoint was the incidence of acute adverse events, while the secondary endpoints included the tumor response rate, progression-free survival, and overall survival. This trial, along with future studies, will provide further insights into the potential of BNCT as a treatment modality for recurrent breast cancer.

Extramammary Paget's disease

Extramammary Paget's disease (EMPD) predominantly involves the genitalia, perineum, and perianal regions. Although surgery is the primary treatment modality for EMPD, it often results in organ dysfunction, notably sexual dysfunction, which adversely affects the patient's quality of life. BNCT is a viable alternative treatment for EMPD.

Kyoto University administered BNCT to three newly diagnosed EMPD patients, delivering a tumor dose ranging from 18 to 23 Gy-Eq and limiting the dose to the normal skin mucosa between 6.8 and 8.7 Gy-Eq. All three tumors were entirely eradicated within a six-month timeframe. However, the patient experienced mild-to-moderate radiation dermatitis and discomfort within two months post-BNCT, which resolved rapidly (Hiratsuka et al. 2018). BNCT offers an effective treatment for EMPD, ensuring the preservation of organ function.

Hepatocellular carcinoma and liver metastases

In 2009, Kyoto University documented a case of hepatocellular carcinoma (HCC) in a patient with hepatocellular carcinoma (HCC) who underwent BNCT and transcatheter arterial chemoembolization (TACE) (Suzuki et al. 2007). The patient had a history of hepatitis C cirrhosis and was categorized according to the Child-Pugh B liver function classification. While the right-lobed HCC was managed with BNCT, the left-lobed HCC was treated with TACE. Post-BNCT treatment, the lesion in the right lobe remained stable for 3.5 months.

The University of Pavia in Italy used BNCT to treat two patients who had metastatic liver cancer originating from the colon. In one patient, the tumor demonstrated size reduction and maintained stability for 20 months. Regrettably, another patient succumbed to cardiomyopathy 33 days after the treatment. An autopsy of this patient revealed considerable necrosis within the cancerous region (Zonta et al. 2009).

Hironobu Yanagie and colleagues from the University of Tokyo administered BNCT to a 63-year-old patient with multiple hepatocellular carcinomas in the left lobe of the liver. They used a water-in-oil emulsion containing BSH for treatment. Three months after BNCT, the patient's cancer status remained stable, and there were no treatment-related adverse effects related to the treatment (Yanagie et al. 2014).

Because most patients with HCC have HCC from viral or alcoholic hepatitis, BNCT is a cellular-level radiation therapy that protects normal liver cells from irradiation and ensures treatment safety.

Other sarcomas

The National Cancer Center Hospital in Japan treated two elderly older women diagnosed with scalp hemangiosarcoma using AB-BNCT. Six months after treatment, the tumor completely disappeared. A follow-up study conducted 20 months later revealed no recurrence (Igaki et al. 2022). Futamura et al. of Osaka Medical College, Japan, successfully treated a photon radiotherapy-induced osteosarcoma of the left occipital bone with BNCT (Futamura et al. 2014). Masayoshi Inoue et al. of Osaka Medical School treated a recurrent cervical

malignant nerve sheath tumor, which shrank and was maintained for 24 months after BNCT, significantly relieving brachial plexus compression symptoms (Inoue et al. 2010). Minoru Suzuki et al. of Kyoto University treated two patients with pleural mesothelioma and spindle cell tumors. During BNCT of the chest, two patients did not develop grade 2 or higher radiation pneumonia (Suzuki et al. 2008).

Differences in tumor response and normal tissue toxicity among BNCT clinical trials

The tumor response and normal tissue toxicity observed in BNCT clinical trials can vary owing to a complex interplay of factors, including tumor characteristics, treatment-related factors, differences in BNCT protocols, patient-specific genetic variations, and the study sample size.

Tumor factors, such as pathological type, grade, size, and depth can influence treatment outcomes. For instance, in head and neck cancer trials, patients with non-squamous cell carcinoma generally showed better responses than those with SCC. Similarly, in high-grade meningioma studies, patients with WHO grade II tumors had longer median overall survival and progression-free survival than those with grade III tumors.

Treatment-related factors, such as prior radiotherapy, chemotherapy, or concurrent use of antitumor drugs (e.g. bevacizumab, cetuximab, or temozolomide) and supplementary X-ray therapy during BNCT, can affect treatment efficacy and toxicity. For example, in glioblastoma trials, patients who received BNCT with concurrent temozolomide and X-ray therapy showed improved median overall survival compared to those who received BNCT alone.

Variations in BNCT protocols, including neutron sources, boron delivery agents, and prescription dose habits among clinical centers, can contribute to differences in treatment outcomes. The choice of boron delivery agent (e.g. BPA, BSH, or a combination of both) and administered dose can vary between studies.

Genetic variations can significantly affect radiotherapy's sensitivity and side effects for cancer treatment. Studies have shown associations between specific genetic variations and the response to radiotherapy. For example, XRCC1 polymorphisms have been linked to cancer prognosis after radiotherapy (Gong et al. 2021). Additionally, polymorphisms in DNA repair genes, such as XPC, XPD, and XPG, have been associated with the acute side effects of radiotherapy in patients with head and neck cancer patients (Chang-Claude et al. 2005).

Furthermore, sample size can influence the assessment of efficacy and toxicity in BNCT clinical trials. Studies with smaller sample sizes may need help accurately assessing treatment effects and adverse event rates, while more extensive studies can provide more reliable results.

In conclusion, the observed differences in tumor response and normal tissue toxicity among BNCT clinical trials can be attributed to the complex interplay of factors related to tumor biology, treatment protocols, patient characteristics, genetic variations, and the study sample size. Future studies should aim to stratify patients based on these factors to optimize treatment efficacy and minimize toxicity. Additionally, large-scale multicenter clinical trials should be conducted to obtain more reliable evidence to support the clinical application of BNCT.

Limitations of early BNCT trial design and prospects of future trial

Early BNCT clinical trials faced several challenges and limitations that needed to be addressed to ensure the success of future studies and secure regulatory approval. One major issue is insufficient feasibility assessment, with factors such as patient recruitment difficulties and neutron source malfunctions often leading to premature trial termination. This highlights the need for thorough feasibility evaluations before initiating clinical trials to minimize the risk of study discontinuation. Another limitation lies in the design of the clinical studies, particularly in phase I/II trials. The objectives of these early phase trials often need to be clarified, with numerous observation indicators that may not be relevant to the study's primary goals. To address this issue, future trials should have well-defined objectives and focus on the most pertinent endpoints for each developmental phase. Moreover, BNCT clinical research differs from traditional drug or radiotherapy device studies because it involves a complex combination of hardware, software, and pharmaceutical components. Consequently, effective communication and collaboration among stakeholders, including regulatory authorities responsible for medical devices and drug clinical trials, clinical physicians, physicists, pharmacists, and nuclear medicine experts, is essential for successfully designing and evaluating BNCT clinical trials.

Currently, most BNCT clinical studies aim to verify safety and determine the appropriate dosing (drug and radiation doses) using small, open-label phase I/II trials involving multiple tumor types. Although these studies have provided valuable insights, they have yet to comprehensively assess the efficacy of BNCT. Randomized controlled trials (RCTs) in phase III are the gold standard for evaluating the effectiveness and safety of new treatment modalities, building upon the foundation of phase I/II studies. RCTs require rigorous trial design, strict inclusion and exclusion criteria, adequate sample sizes, and long-term follow-up to generate the most persuasive evidence.

OS is the ideal endpoint for assessing the efficacy of cancer treatments, as temporary tumor shrinkage may not necessarily translate into prolonged OS, a phenomenon frequently observed in anticancer drug research. RCTs are essential to establish BNCT as a viable cancer treatment option.

For BNCT RCTs, it is crucial to use accelerator-based neutron sources to ensure consistency and reproducibility across study sites. The initial study population consisted of patients who failed or could not tolerate conventional treatments, with a focus on specific tumor locations and types. As the evidence base grows, the study population can gradually expand to include patients with newly diagnosed

cancers. The control group received the current standard of care recommended for the investigated cancer types.

In addition to RCTs, long-term follow-up studies are necessary to assess the durability of treatment responses and monitor the potential late toxicities associated with BNCT. These studies provide valuable information about treatment's long-term benefits and risks, which is crucial for guiding clinical decision-making and securing regulatory approval.

To optimize the efficiency and informativeness of BNCT clinical trials, innovative trial designs and statistical methods such as adaptive designs and Bayesian approaches should be incorporated. These approaches can help accelerate the development and approval of BNCT by allowing seamless integration of new data and rapid identification of promising treatment strategies.

In conclusion, while early BNCT clinical trials have provided important insights, they have also revealed several limitations that must be addressed to ensure the success of future studies and to secure regulatory approval. By conducting thorough feasibility assessments, designing trials with well-defined objectives, fostering collaboration among stakeholders, and employing rigorous methodologies, such as RCTs and long-term follow-up studies, future BNCT clinical trials can generate high-quality evidence to support the treatment's efficacy and safety, ultimately leading to improved outcomes for cancer patients.

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Authors' contributions

Nianfei Wang was the one who came up with the idea and designed the study. Shumin Shen, Shanghu Wang, Xiuwei Wu and Dachen Zhou searched the literature and analyzed the data. Mingzhu Gao, Jinjin Wu and Yucai Yang were in charge of visualizing the data. Shanghu Wang, Xiaoxi Pan, and Shumin Shen wrote the paper. Nianfei Wang critically revised it for important intellectual content. All the authors read and approved the final manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors confirm that no generative AI- or AI-assisted technologies were used in the writing of this manuscript or analysis of the data presented.

Disclosure of interest

The authors declare no conflicts of interest.

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Notes on contributors

Shumin Shen, MM, is conducting basic and clinical research in oncology radiotherapy at Anhui Medical University.

Shanghu Wang, PhD, is a Deputy Director of Radiotherapy Department, specializing in clinical research on radiotherapy for lung and esophageal cancer and a Sub-PI for multiple Phase II and III clinical trials.

Dachen Zhou, MD, is specializing in liver cancer and liver transplantation. Previously conducted tumor radiophysics research at Heidelberg University, Germany.

Xiuwei Wu, MD, is focusing on chemotherapy, immunotherapy, and endocrine therapy in oncology.

Mingzhu Gao, MD, is specializing in chemotherapy and immunotherapy for digestive system tumors.

Jinjin Wu, MD, is conducting basic research on colon cancer pathogenesis and clinical translational studies.

Yucai Yang, MD, is engaged in basic and clinical translational research on nanomaterials in oncology.

Xiaoxi Pan, PhD, is focusing on basic and clinical research in radionuclides.

Nianfei Wang, PhD, is specializing in chemoradiotherapy, with a focus on basic and clinical research in digestive system tumors, particularly colorectal cancer and hepatocellular carcinoma.

Data availability statement

These data are made available upon request.

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