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Review Article

# Latest Advances in Boron Neutron Capture Therapy for Intracranial Glioblastoma

**Yi-Wei Chen[1,2,3,4]*, Pei-Fan Mu[5], Ting-Yu Huang[6], Ko-Han Lin[7], Po-Shen Pan[8], Jen-Kun Chen[9], Hong-Ming Liu[10], Meng-Hao Wu[11], Fong-In Chou[10]**

[1]Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei City, Taiwan
[2]Department of Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan
[3]Department of Medical Imaging and Radiological Technology, Yuanpei University of Medical Technology, Hsinchu City, Taiwan
[4]College of Nuclear Science, National Tsing-Hua University, Hsinchu City, Taiwan
[5]College of Nursing, National Yang Ming Chiao Tung University, Taipei City, Taiwan
[6]Department of Nursing, Taipei Veterans General Hospital, Taipei City, Taiwan
[7]Department of Nuclear Medicine, Taipei Veterans General Hospital, Taipei City, Taiwan
[8]Department of Chemistry, Tamkang University, New Taipei City, Taiwan
[9]Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes, Miaoli County, Taiwan
[10]Department of Nuclear Science and Technology Development, National Tsing-Hua University, Hsinchu City, Taiwan
[11]Department of Radiation Oncology, Mackay Memorial Hospital, New Taipei City, Taiwan

## Abstract

**Objective:** Glioblastoma (WHO classification Grade IV) is a highly malignant brain tumor with a high propensity for recurrence even after standard treatments. Patient death is inevitable, as the available methods are largely ineffective for remediation and treatment once recurrence has occurred. This review presents recent advancements in boron neutron capture therapy (BNCT) that have allowed for its clinical use in treating glioblastoma. **Data Sources:** We retrospectively reviewed the results of clinical trials and articles published in the past 30 years worldwide. **Study Selection:** All included studies addressed the use of BNCT to treat high-grade gliomas, including glioblastoma. **Results:** The development of boron-containing agents exhibiting specificity and improvements in technologies that generate neutron sources have led to the clinical use of BNCT for treating tumors. BNCT involves the delivery of a boron-10-containing drug specifically to tumor cells, followed by irradiation with low-energy thermal neutrons to generate two biologically active particles (helium [α particle] and lithium nuclei). Although these particles are highly effective at destroying cells, their field of destruction is limited to the tumor cells. Therefore, BNCT serves as an excellent mode of targeted particle therapy for tumors, particularly those that are infiltrative. The published articles reviewed here demonstrate the gradual refinement of the BNCT technique and prolonged survival for glioma patients compared to conventional treatments. **Conclusion:** With continued improvements, BNCT may become the first-choice treatment for malignant infiltrative glioblastoma in the near future.

**Keywords:** Boron neutron capture therapy, glioblastoma, particle therapy, quality of life, radiotherapy

**Address for correspondence:** Dr. Yi-Wei Chen, Department of Oncology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Beitou District, Taipei City 11217, Taiwan.
E-mail: chen6074@gmail.com

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## Introduction

Malignant glioblastoma, the most common brain tumor in adults, is a great clinical challenge because of its high propensity for recurrence even after standard treatment. Following complete resection, enhanced radiation therapy, and standard oral chemotherapy, the mean survival time is 14–16 months. Data from the Taiwan Cancer Registry show that of the 718 Taiwanese patients newly diagnosed with malignant brain tumors in 2019, 325 had Grade IV malignant glioblastoma.[1] Recent advances in molecular diagnostics have enabled the identification of important prognostic factors for the posttreatment progression of highly malignant tumors,[2,3] including the mutational status of isocitrate dehydrogenase 1 and the presence or absence of $O^6$-methylguanine-DNA methyltransferase. However, breakthroughs in glioblastoma therapy are still extremely limited. Specialized treatment modalities have emerged recently, including targeted therapy with bevacizumab for the inhibition of tumor angiogenesis and the use of tumor treating fields for destruction control. While these approaches offer hope for the treatment of malignant glioblastoma, an urgent need remains for major advances in these treatment modalities.

Radiotherapy is an effective cancer treatment method that has been used for decades. Since the discovery of X-rays by German physicist Wilhelm Conrad Röntgen in 1895, X-rays and other forms of radiation have been widely applied clinically for treating tumors. Polish-born French physicist and Nobel laureate Marie Curie, best known for her pioneering work on radioactivity, isolated the radioactive elements polonium (Po) and radium (Ra) from pitchblende, marking the beginning of the medical use of radiation. Modern radiation therapy, which uses X-rays (photons), causes substantially less damage to normal tissues than earlier radiation treatment due to important developments in radiotherapy equipment. However, the effectiveness of radiation therapy on certain tumors has reached an impasse imposed by the need for new radiation sources with better tumor-destroying effects. Laboratory studies investigating the effects of photon therapy on glioblastoma have found that radiation causes limited damage to these tumor cells.[4] With the arrival of the era of particle therapy, novel therapies such as proton therapy and heavy-particle (carbon ion) therapy have shown promise for treating tumors. However, proton therapy does not offer a substantial advantage over conventional photon therapy in terms of tumor damage, with relative biological effectiveness of only 1.1 times that of photon therapy. The main advantage of proton therapy lies in its superior physical dose distribution (Bragg Peak Phenomenon),[5] which reduces the damage to normal brain tissue. Although the biological effects of heavy-particle therapy is 3–5 times that of photon therapy,[5] clinical experience shows that it inflicts a certain amount of damage to normal neural tissue in the brain, making it unsuitable for improving glioblastoma treatment.

Boron neutron capture therapy (BNCT), a specialized type of targeted particle radiation therapy, involves the targeted delivery of a boron-10-containing (10 is a mass number) drug to tumor cells, followed by irradiation with low-energy thermal neutrons. Boron occurs in nature mainly as boron-11, and boron-10 is a nonradioactive isotope. In response to neutron capture, boron-10 undergoes nuclear fission to produce helium (α particle) and lithium nuclei. In addition to exerting excellent tumor annihilation effects, these products also possess an extremely small field of action (5–10 μM), limiting their effects to the diameter of a single tumor cell. Thus, BNCT is a targeted particle therapy capable of generating high intratumor destructive energy [Figure 1]. The concept of tumor destruction through BNCT was proposed by Gordon Locher in 1936,[6] less than a decade after the discovery of uncharged nuclear particles, later named neutrons, by British physicist James Chadwick in 1932. However, the preferential administration of boron-10-containing drugs to tumors and the satisfactory generation and control of thermal neutron beams were not possible during this era due to technological limitations. Nevertheless, this tumor treatment concept, known as a "magic bullet" approach, has intrigued investigators since its inception, inspiring active investigation in a variety of fields.

## Boron Neutron Capture Therapy Development Worldwide

In the 1950s, the first-ever human clinical trial of BNCT was conducted on a malignant infiltrative glioblastoma. Because malignant glioblastoma of the brain causes immense physical and emotional suffering to patients and their families, Dr. William H. Sweet, a neurosurgeon at Massachusetts General Hospital, collaborated with experts

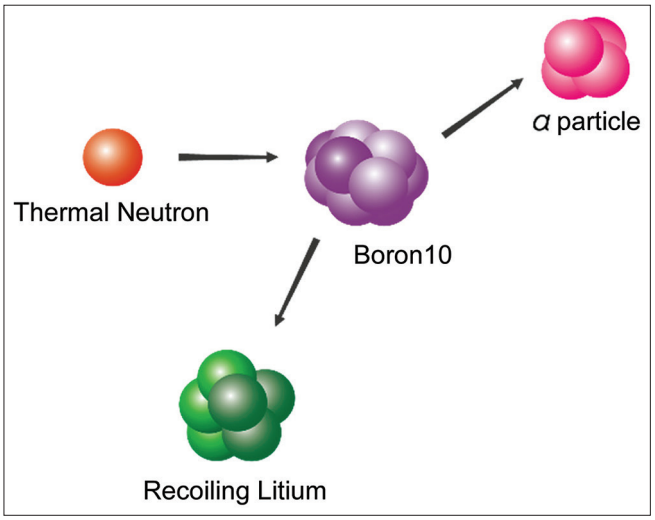


**Figure 1:** Principle of BNCT. Boron-10 atoms, which possess a larger capture cross-section than other atoms, are irradiated with thermal neutrons. When a boron-10 atom absorbs a thermal neutron, it disintegrates into two particles (α particle and lithium nucleus) with strong tumor-destroying ability. BNCT: Boron neutron capture therapy

at the Massachusetts Institute of Technology and Harvard Medical School to perform the first human clinical trial of BNCT for malignant glioblastomas using the Brookhaven Graphite Research Reactor.[7,8] Because of the multitude of unexplored variables in this first-ever trial, including the immaturity of nuclear engineering techniques for the generation of thermal neutrons and the nonspecificity of boron-containing drugs, satisfactory efficacy was not observed, and the trial was terminated early. Dr. Hiroshi Hatanaka, a professor of neurosurgery at Teikyo University in Tokyo who had participated in the BNCT trial, believed that this novel treatment method had potential advantages for the treatment of malignant brain tumors. Therefore, he introduced the concept and techniques of BNCT in Japan, where he initiated further research and development. Upon his return to Japan, Dr. Hatanaka assembled a multidisciplinary team of experts from fields including nuclear engineering, pharmaceuticals, and clinical medicine. After rectifying the shortcomings of the initial trial led by Dr. Sweet,[9] he conducted Japan's first human clinical trial of BNCT on brain tumors in 1968, using sodium borocaptate (BSH) as the boron-containing drug. The promising clinical effects achieved in this trial prompted substantial progress in BNCT research in Japan and even led to the official approval of BNCT as a standard cancer treatment (recurrent head-and-neck cancer only) by the Ministry of Health, Labor, and Welfare of Japan in May 2020. Studies in other developed countries have also investigated BNCT for the treatment of malignant brain tumors and reported satisfactory effects [Table 1].[10-18]

In Taiwan, the use of BNCT for the treatment of malignant brain tumors was initiated in March 2017 and is currently implemented for compassionate use in accordance with Article 3-1 of the Regulations on Human Trials promulgated by the Ministry of Health and Welfare of Taiwan. An application for approval of special medical care must be filed for each case to the Institutional Review Board of Taipei Veterans General Hospital of Taiwan and the Taiwan Food and Drug Administration. Upon approval, BNCT can be performed as a salvage measure for patients with recurrent malignant brain tumors and mainly targets patients with recurrent glioblastoma. At Taipei Veterans General Hospital, the boronated amino acid L-4-[10] boronophenylalanine (BPA) is used as the boron delivery agent for BNCT. In BPA, the essential amino acid phenylalanine is the carrier for boron-10. Such amino acid-type drugs are taken up as nutrient sources and consumed in large quantities by tumor cells to maintain their division and proliferative functions, thereby concentrating the reactions in BNCT [Figure 2]. Currently, pharmaceutical manufacturers in Taiwan can manufacture this drug, which can be subsequently provided to hospitals for use in BNCT. As of February 2022, the neural tumor team at Taipei Veterans General Hospital has made arrangements and provided care for more than 100 Taiwanese patients with malignant brain tumors to undergo BNCT as salvage therapy. Initial observations of patient responses have been consistent with the findings of relevant studies in Japan. In addition to exerting clear antitumor effects, BNCT also improved the quality of life of patients and did not produce severe side effects, which has boosted the confidence of the treatment team. The central nervous system tumor team at Taipei Veterans General Hospital has also rendered assistance to brain tumor patients from other countries, including Australia, Spain, and Japan. Satisfactory treatment effects were also observed in these patients, confirming the superior quality of this treatment and establishing the prominent role of Taiwan in administering international humanitarian aid.

BNCT implementation in Taiwan has confirmed the value of a pretreatment assessment through positron emission tomography (PET) using 4-borono-2-$^{18}$F-fluoro-phenylalanine as the radiotracer ferric binding protein (FBPA)-PET). After the administration of FBPA by injection, PET scanning is performed on regions of BPA accumulation. The standardized uptake value (SUV) of the tumor, which reflects tumor activity, divided by the SUV of normal tissue (T/N ratio) is an important indicator used for pre-BNCT evaluation [Figure 3]. BNCT studies conducted worldwide show that significant treatment effects can only be achieved with a T/N ratio >2.5. A T/N ratio close to 1 indicates no distinct difference in tracer uptake between the tumor tissue and normal tissue, making BNCT ineffective. PET scanning using an amino acid-based tracer provides multiple advantages over conventional glucose-based tracers. Because glucose uptake is high in both normal brain

**Table 1: Worldwide reports of boron neutron capture therapy treatment for malignant glioblastoma**

| Country | Number of patients (years) | Medication and dose | Median survival (months) | References |
|---|---|---|---|---|
| United States | 53 (1994-1999) | BPA (250-330 mg/kg) | 12.8 | 9,10 |
| United States | 20 (1996-1999) | BPA (250 or 350 mg/kg) | 11.1 | 11,12 |
| Switzerland (EORTC) | 26 (1997-2002) | BSH (100 mg/kg) | 10.4-13.2 | 13 |
| Japan | 40 (1998-2008) | BPA (500 mg/kg) | 23.5 (for primary), plus X-ray RT | 14,15 |
| Japan | 15 (1998-2007) | BPA (250 mg/kg + BSH 5 g) | 10.8 (for recurrence), 27.1, plus X-ray RT | 16 |
| Finland | 50 (1999-2012) | BPA (290-400 mg/kg) | 11.0-21.9 (for primary)<br>7.0 (for recurrence) | 17 |
| Sweden | 30 (2001-2007) | BPA (900 mg/kg) | 17.7 (for primary) | 18 |

EORTC: European Organization for Research and Treatment of Cancer, BPA: L-4-$^{10}$boronophenylalanine, BSH: Sodium borocaptate, RT: Radiographic testing

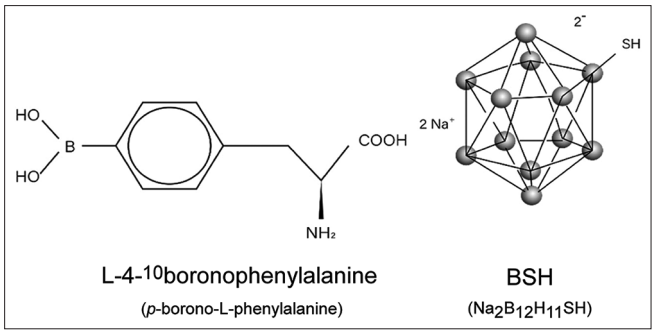


**Figure 2:** BPA, an amino acid (phenylalanine)-type boron-10 carrier drug, serves as a nutrient source and is taken up in large quantities by tumor cells. BSH is a cage-structured drug with 12 corners (one boron-10 atom at each corner) and 20 facets. BSH exerts strong tumor destruction effects but is not taken up by tumor cells due to its water-soluble nature. Thus, BSH is commonly used in combination with BPA in clinical practice. BPA: Boronophenylalanine, BSH: Sodium borocaptate

tissue and tumors, glucose-based tracers do not distinguish the field of tumor activity. Amino acid-based tracers distinguish both the tumor location and activity. In addition, cell uptake of phenylalanine requires mediation by the cellmembrane receptor large-neutral amino acid transporter 1 (LAT-1). Cells that do not express LAT-1 are readily distinguished by their lack of phenylalanine uptake. FBPA-PET also has advantages regarding safety. Conventional photon radiation therapy can cause radiation necrosis in normal brain tissue after 30 fractions of treatment. Using magnetic resonance imaging (MRI), radiation necrosis may be difficult to distinguish from recurrent brain tumor tissue. In contrast, FBPA-PET can determine the tissue type due to the absence of LAT-1 in inflammatory cells.[19]

Conventional photon radiation therapy and particle therapy employ manual positioning to determine the irradiation field. Because malignant brain tumors possess the extremely strong infiltrative ability, the determination of the actual tumor region using the naked eye is difficult and may lead to an inadequate irradiation field that results in recurrence at or beyond the field edge. BNCT is unique in that it automatically targets the tumor region, preventing tumor escape [Figure 4]. The dose distribution of BNCT is concentrated in the region of boron drug uptake by the tumor, thereby avoiding significant exposure to normal tissue [Figure 5].

## Preliminary Effects Achieved with Boron Neutron Capture Therapy for Emergency Treatment of Malignant Tumors in Taiwan

Since March 2017, the central nervous system tumor team at Taipei Veterans General Hospital has been approved for compassionate use of BNCT to treat adult and pediatric patients with malignant brain tumors. By the end of 2019, approximately 30 patients with malignant brain tumors (glioblastoma in 15) had been treated with BNCT. The average dose (range: 20–40 Gy-equivalent) was estimated to be delivered according to the

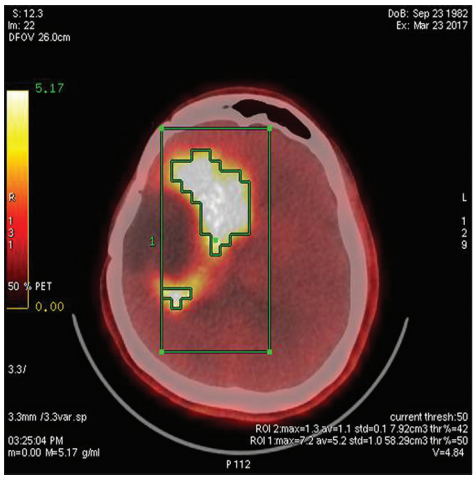


**Figure 3:** FBPA-PET uses 4-borono-2-[18] F-fluoro-phenylalanine as a tracer used to determine the extent and activity of malignant brain tumors before BNCT treatment. We also use tumor SUV/normal tissue SUV as the T/N ratio to indicate the feasibility of BNCT. BNCT treatment is more likely to be effective for a T/N ratio >2.5. FBPA-PET: Ferric binding protein-positron emission tomography, BNCT: Boron neutron capture therapy, SUV: Standard uptake value

gross tumor volume and normal tissue constraints (actual mean tumor dose, 17.44 ± 7.50 Gy-equivalent). Follow-up MRI images obtained at 1–3 months after treatment completion revealed that approximately 50% of patients achieved complete or partial response, 30% achieved stable disease, and only 20% had progressive disease. Median survival among glioblastoma patients was 7.34 months for overall survival, 6.47 months for cancer-specific survival, and 4 months for relapse-free survival. Although glioblastoma had the poorest survival after BNCT of all brain tumor types, these results indicate that BNCT exerts therapeutic effects on terminal malignant brain tumors, a finding consistent with the treatment experiences reported in other countries.[20]

Statistical analysis of the characteristics of 34 patients treated with BNCT for malignant tumors showed that the following parameters were associated with a better prognosis: T/N ratio ≥4, tumor volume <20 mL, mean tumor dose ≥25 Gy-E, MIB-1 ≤40, lower recursive partitioning analysis class, and the use of bevacizumab after BNCT.[21] These factors serve as a reference for predicting the therapeutic effects of BNCT and may aid in identifying patients suitable for BNCT in Taiwan's BNCT group. Tumors in the cerebral region as well as those in the brain stem can be controlled using a multi-fractionated strategy.[22]

A study by a BNCT team led by Dr. Miyatake of Osaka Medical and Pharmaceutical University reported that the majority of brain tumor patients treated with BNCT had received conventional X-ray radiation therapy before BNCT treatment. Therefore, radiation necrosis in the brain may still occur in these patients. Administration of the targeted antiangiogenic agent bevacizumab following BNCT has been suggested for the protection of brain tissue.[23]

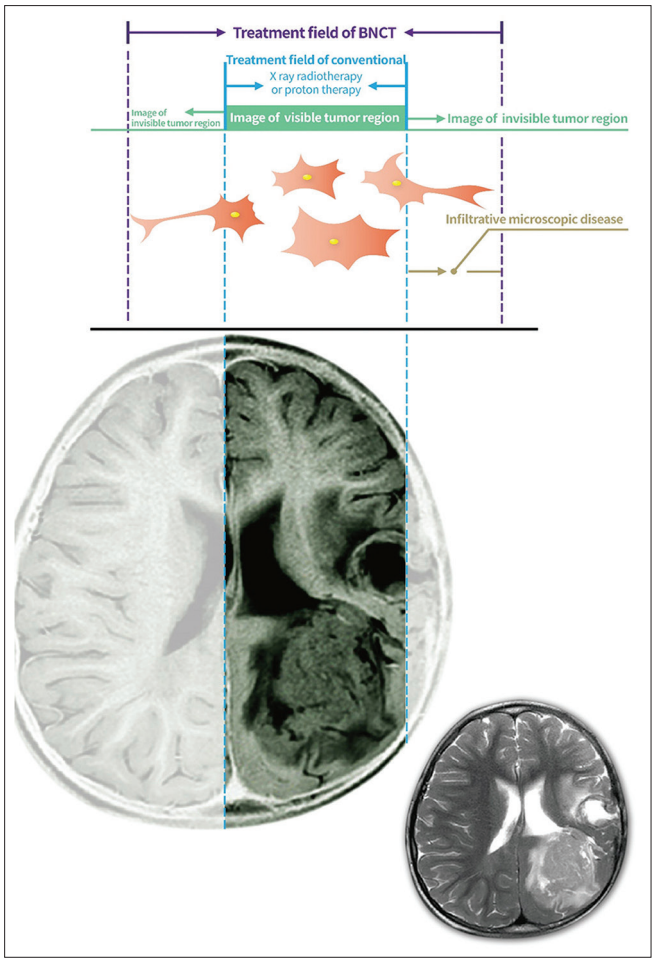


**Figure 4:** BNCT can achieve targeted and comprehensive annihilation of infiltrative tumors provided that the boron-containing drug is uniformly distributed and absorbed within the tumor volume (in both imaging-visible and invisible regions). In contrast, the irradiation field for conventional photon or proton radiotherapy is determined by manual target positioning, which carries a risk of treatment failure due to the absence of irradiation in the tumor region invisible to the naked eye (microscopic tumor infiltrative area). BNCT: Boron neutron capture therapy

Compared to the trials worldwide, the radiation dose administered in Taiwan is somewhat lower because this first clinical trial in Taiwan of BNCT for malignant brain tumors warranted safety precautions.[24]

## Palliative Treatment and Post-Boron Neutron Capture Therapy Nursing Care

Most patients with advanced brain tumors who received BNCT underwent this treatment as palliative care, which aims to relieve symptoms and improve quality of life. In palliative care, BNCT led to significant improvements in patient quality of life and symptom burden at follow-up 1–3-months after treatment.[25] Living with dignity and high quality of life is the aim of post-BNCT care.[26] A holistic approach using a coordinated, multidisciplinary team has been suggested. The efficacy of BNCT brings hope to patients with advanced cancer.

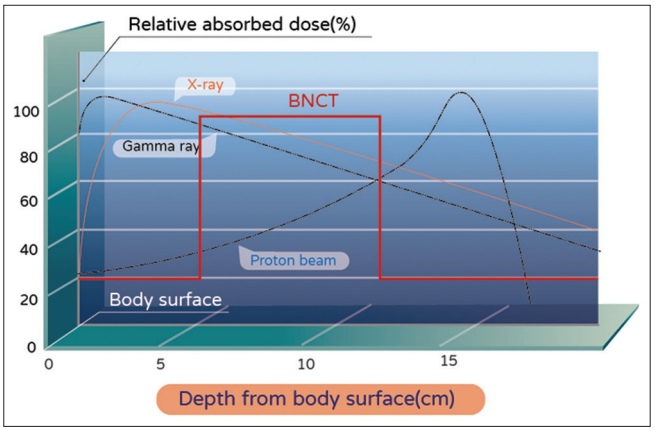


**Figure 5:** The dose distribution of BNCT differs from that of conventional X-ray or proton radiation therapy in that the BNCT dose is only distributed in cells that take in the boron drug (Courtesy from Dr. Hong-Ming Liu of National Tsing Hua University). BNCT: Boron neutron capture therapy

We suggest that post-BNCT care should include the assessment and management of challenging physical symptoms, psychological distress symptoms, health management styles, and family resilience. To support patient engagement, the patient and their family should be encouraged to participate in self-care and agree on a shared plan of action.[27] Patients also benefit from approaches that (1) provide education about their physical experience to them and their families, (2) increase self-care ability, and (3) encourage spirituality, social support, search for meaning, self-achievement, positive emotions, and maintaining significant relationships.[28,29]

## Conclusion

BNCT is a tumor-targeting particle radiation therapy with high biological effectiveness. Its superior tumor destruction and precise targeting abilities decrease damage to normal tissue. However, BNCT is a highly technical procedure that requires collaboration across multiple disciplines, including medicinal chemistry, radiobiology, medical physics, nuclear engineering, clinical oncology, and nursing care, to achieve satisfactory results. We are hopeful that the technical requirements for administering BNCT in clinical practice can be introduced in Taiwan in the near future so that Taiwan may follow in the footsteps of Japan and eventually grant official approval for BNCT as a standard tumor treatment method to benefit more patients.

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### Conflicts of interest

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