Review Article

Side effects of boron neutron capture therapy

ABSTRACT

Boron neutron capture therapy (BNCT) is an innovative cancer treatment modality that selectively eliminates tumor cells while sparing normal tissues. Clinical studies have explored its application across various malignancies, including malignant gliomas, meningiomas, pediatric tumors, head and neck cancers, and melanomas. However, despite its therapeutic potential, BNCT is associated with various adverse effects that differ depending on the tumor type, neutron source, boron delivery agent, and treatment protocol. These adverse reactions pose significant challenges to the broader clinical implementation of this approach. This review systematically examines the adverse effects of BNCT observed in clinical studies, focusing on their underlying mechanisms, contributing factors, and tumor-specific variations. Additionally, it highlights current strategies for managing and preventing these effects and emphasizes the need for further research to address unresolved challenges. This article aims to provide comprehensive insights into the adverse effects of BNCT, supporting the development of safer and more effective treatment protocols and ultimately advancing their role in precision oncology.

KEY WORDS: Adverse effects, boron neutron capture therapy, malignant tumors, precise therapy

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INTRODUCTION

Improving cure rates while minimizing adverse effects (AEs) is the primary objective of modern cancer therapy. Boron neutron capture therapy (BNCT) is a promising tumor-selective treatment modality, offering new possibilities for managing refractory and recurrent tumors. It employs the non-radioactive isotope boron-10 (^{10}B), which undergoes a nuclear reaction upon neutron irradiation to produce high-linear energy transfer (LET) alpha particles (^{4}He) and Lithium-7 (^{7}Li) recoil particles, accompanied by minimal gamma emissions, as illustrated in Figure 1.[1,2] These high-LET particles have a destructive range of $<10\ \mu m$, limiting their effects to boron-containing cells and sparing adjacent healthy tissues. Typically, boron delivery is achieved using borocaptate sodium (BSH) and boronophenylalanine (BPA).[3]

BNCT has been explored in clinical studies across a range of malignancies, including malignant gliomas, malignant meningiomas, childhood malignancies, head and neck malignancies, malignant melanomas, extramammary Paget's disease, hepatocellular carcinomas, and lung cancer. Despite its potential, different types of tumors can exhibit varying AEs with BNCT. Although the tumor's anatomical site plays a significant role in determining these effects, other influencing factors also warrant detailed exploration. Understanding these diverse reactions is crucial for optimizing the therapeutic potential of BNCT across different cancer types.

This review systematically examines the AEs of BNCT, focusing on their mechanisms, influencing factors, and clinical management and prevention strategies. By addressing these challenges, we aim to provide a comprehensive understanding of how to optimize BNCT for broader clinical applications.

GLIOBLASTOMA

Glioblastoma multiforme (GBM) remains one of the most formidable malignancies, with a median survival of only 14 months despite maximal resection, radiotherapy (RT), and adjuvant chemotherapy.[4] BNCT has garnered attention for its ability to selectively target tumor cells while minimizing damage to surrounding healthy tissues, making it particularly promising for recurrent

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GBM. Although the relatively low radiation dose is absorbed by normal brain tissue, concerns regarding potential damage, especially in pre-irradiated patients, remain.

Radiation necrosis

Mechanisms and diagnosis of radiation necrosis after BNCT

Radiation necrosis (RN) is a significant complication of BNCT for malignant brain tumors, particularly in recurrent cases where prior exposure to RT increases susceptibility. RN is driven by inflammatory cytokine release, increased vascular permeability, extracellular edema, and myelin loss, which may lead to small vessel occlusion and hemorrhage.[5] Vascular endothelial growth factor (VEGF) overexpression in reactive astrocytes has been confirmed as a key driver of increased vascular permeability and edema in human[6] and animal[7] studies.

RN may occur without apparent neurological symptoms, making diagnosis challenging.[5] Although biopsy remains the gold standard for diagnosis, its invasiveness limits its clinical utility. Advanced imaging techniques, such as dynamic contrast-enhanced T1-weighted perfusion MRI (DCE-MRI)[8] and fluorine-^{18}-labeled boronophenylalanine positron emission tomography (^{18}F-BPA PET) imaging,[9] offer non-invasive alternatives by evaluating vascular permeability and tumor metabolism. These modalities enhance diagnostic accuracy in distinguishing between RN and tumor recurrence, thereby supporting timely clinical decision-making.

Cases supporting the occurrence of RN in patients with GBM treated with BNCT

Several studies have identified radiation dose, boron accumulation, neutron distribution, and target volume as key contributors to RN development.[10-13] The BN-α dose from the ^{10}B (n,α) ^{7}Li reaction, which is more damaging than gamma radiation, plays a pivotal role in RN development.[11,12] A retrospective study of 159 Japanese patients (1977–2001) reported an RN incidence of 11.9%, with maximum vascular dose identified as the key risk factor.[14] Kageji *et al*.[12] emphasized that maintaining the maximum vascular volume dose below 12 Gy, or ideally under 10 Gy in critical areas such as the speech center, may help reduce the risk of RN. This recommendation was based on a cohort predominantly comprising newly diagnosed patients, suggesting that these thresholds may primarily apply to treatment-naïve brain tissue. A Phase II trial for recurrent glioma set the scalp dose limit at 8.5 Gy-Eq, based on prior safety data, reflecting a more conservative approach in re-irradiated patients.[15] Nevertheless, the evidence base remains limited, and no definitive safe dose thresholds for normal brain tissue in recurrent GBM have been established. Further clinical validation is necessary. However, age, irradiation duration, blood boron concentration, and neutron concentration did not show a statistically significant correlation with RN incidence.

Treatment protocols have a significant impact on the incidence of RN. Kawabata *et al*.[16] compared two strategies in newly diagnosed GBM: BNCT alone and BNCT combined with XRT (20–30 Gy). The combination protocol employed higher BPA doses (700 mg/kg) and longer infusions, which increased the tumor dose but also elevated the RN rates (10/21 cases, 4 symptomatic), likely due to higher exposure to surrounding normal tissues. Interestingly, some studies contradict these *trends*. Pellettieri *et al*.[17] observed no severe AEs in 12 patients with recurrent GBM who received 900 mg/kg BPA for 6 hours at tumor doses of 13–23 Gy-Eq. The absence of severe adverse reactions despite high BPA doses suggests that the correlation between tumor dose and AEs may be more complex and influenced by sample size and patient variability.

Kageji *et al*.[18] reported that approximately half of the patients treated with intraoperative BNCT (IO-BNCT) developed radiation necrosis, whereas none in the non-operative BNCT (NO-BNCT) group exhibited symptomatic RN. Moreover, NO-BNCT was associated with fewer side effects, reduced invasiveness, and better survival outcomes.

Treatment strategies for RN in patients with GBM treated with BNCT

The treatment options for RN include corticosteroids, anticoagulants, vitamin E, hyperbaric oxygen, and surgical resection.[19] However, none of these approaches has shown proven efficacy in controlled trials.[5]

Targeting VEGF is a promising therapeutic approach. Bevacizumab, an anti-VEGF monoclonal antibody, reduces vascular permeability and cerebral edema and has shown efficacy in treating symptomatic RN.[20] Repeat administration has also benefited patients with recurrent RN, whereas asymptomatic cases may only require observation.[19,20]

A randomized trial by Levin *et al*.[5] confirmed the benefit of bevacizumab in RN, with symptom control achieved in three out of seven patients following BNCT. Nonetheless, AEs such as proteinuria, aspiration pneumonia, and thromboembolic complications have been reported, with the severity of proteinuria being potentially dose-dependent.[5,21]

No consensus exists on the optimal dose or duration of bevacizumab therapy; however, administering low-dose bevacizumab every 2-4 weeks until radiological or clinical remission is a common strategy.[20]

Preventive measures remain critical, and dose-reduction strategies include the use of collimators,[16] tumor reduction before BNCT,[22] and non-operative BNCT protocols.[18,23] Additionally, bevacizumab has also been identified as a potential preventive measure for RN.[24]

Neurotoxicity

The neurological AEs of BNCT include cerebral edema, seizures, peripheral motor neuropathy, and somnolence syndrome, and these have been widely reported in clinical studies.

Mechanisms and classification

Neurotoxicity may result from elevated intracranial pressure, aseptic inflammation, or radiation-induced damage to surrounding tissues.[22,25,26] Factors such as tumor volume,[27,28] boron dose,[25] infusion time,[27] and the number of irradiated fields[22,28] are closely linked to the incidence and severity of neurotoxicity. Higher boron concentrations and broader irradiation fields intensify local inflammation and oxidative stress, contributing to blood-brain barrier disruption and neurotoxic effects.[22,25]

Clinical cases and observations

Clinical data show that seizures and cerebral edema are the most common neurotoxic effects of BNCT. In a study involving nine high-grade glioma patients treated with intraoperative BNCT, three experienced seizures.[10] One study comprising 20 patients with GBM and 2 with mesenchymal astrocytoma reported seizures in 18% and cerebral edema in 11% of cases.[25] Similarly, a Swedish study observed 9 seizures in 5 out of 17 GBM patients in 2003 and 12 seizures (grades 1–3) in 7 patients in 2008, with both findings strongly associated with BNCT.[27,29] Interestingly, BNCT has also demonstrated the ability to alleviate cerebral edema without requiring adjuvant drugs, such as steroids or dehydrators.[30]

Somnolence syndrome is a distinct subacute complication that typically presents with fatigue, lethargy, and malaise 1–3 weeks after irradiation and usually resolves within a few weeks.[31] Clinical trials conducted at Harvard-MIT and Brookhaven National Laboratory (1994–1999) identified somnolence syndrome as the most common neurological side effect. It is associated with increased intracranial pressure and stands out because of its transient yet disruptive nature.[28]

In a study involving nine high-grade glioma patients treated with intraoperative BNCT, three experienced acute peripheral motor neuropathy and orbital muscle swelling; one case resolved spontaneously, whereas the others responded to steroid treatment.[10]

Management and mitigation strategies

Neurotoxicity can be mitigated by tumor debulking before BNCT to reduce intracranial pressure from aseptic inflammation and edema.[22] Optimizing the boron dose, infusion protocols, and minimizing irradiated fields are additional measures to limit neurotoxicity.[22,25,27,28]

Blood-bone marrow toxicity

Hematologic toxicity is a notable concern in BNCT, particularly at high BPA doses. In a study by Kawabata *et al*.[16,32] (2002-2006), grade 3/4 myelotoxicity, including reductions in hemoglobin, leukocytes, neutrophils, and platelets, was observed in 11% of patients receiving 250 mg/kg BPA, 17% receiving 500 mg/kg, and 28% receiving 700 mg/kg doses. Radiation dose was identified as a key contributing factor. Management strategies include hematopoietic growth factors to support marrow recovery and dose fractionation to allow for normal tissue repair between sessions.[33,34] Further studies are needed to validate the efficacy of these approaches and to establish standardized protocols for managing hematologic toxicity in BNCT.

Other AEs

Other grade 3/4 toxicities, such as elevated ghrelin, amylase, and creatinine, were reported in newly diagnosed GBM patients treated with BPA, with the incidence varying by dose: 64% (250 mg/kg), 25% (500 mg/kg), and 63% (700 mg/kg).[16,32] Alopecia was one of the most common side effects and was reported in over 80% of cases across studies.[16,25,30]

In a Phase I trial involving 22 patients with recurrent malignant gliomas, Kankaanranta *et al*.[25] observed mild-to-moderate (grade 1/2) AEs in most cases. The most common late-treatment toxic reactions, including fatigue, muscle weakness, cerebral edema, and skin atrophy, were reported in 11% of patients.

HEAD AND NECK CANCERS

Head and neck cancers (HNC) are typically treated with encompassing surgery, RT, and chemotherapy. However, recurrent or metastatic HNCs, particularly in patients who have already received a full dose of RT, pose significant treatment challenges. BNCT offers a promising alternative but carries risks such as carotid blowout syndrome (CBS), radiation osteonecrosis (ORN), and soft tissue necrosis.[35,36]

CBS

CBS is a rare but potentially fatal complication in HNC patients treated with BNCT, with an incidence ranging from 2% to 10% in re-irradiated cases and a fatality rate of 76%.[37-40] Tumor encasement of the carotid artery exceeding 180°, particularly when accompanied by skin invasion, has been frequently associated with CBS risk in BNCT-treated HNC.[38,41,42]

CBS results from damage to the carotid artery wall due to tumor invasion into the vascular shaft, radiation-induced free radical damage, or prior surgical interventions.[42,43] This damage may lead to pseudoaneurysm formation, arterial necrosis, or hemorrhage, which typically manifests as acute transoral[44] or transcarotid[34] hemorrhage and carries high mortality and neurological morbidity.[45] Damage to the tunica, which provides ~80% of the blood supply to the carotid artery wall, is a critical factor contributing to pseudoaneurysm formation or arterial wall necrosis.[42]

Computed tomography angiography (CTA) is essential for pretreatment risk assessment. In high-risk patients, prophylactic embolization or stent placement has proven effective in reducing the incidence of CBS.[34,42,46] For instance, Lan *et al*.[42] reported that prophylactic embolization successfully prevented CBS in two high-risk cases. Early recognition and intervention are critical for improving safety and enabling BNCT to proceed under controlled conditions.

ORN and soft tissue necrosis

ORN and soft tissue necrosis are significant late AEs associated with BNCT, particularly in HNC. ORN impairs both aesthetics and function, presenting as non-healing bone necrosis within irradiated fields unrelated to tumor recurrence.[47] Its pathogenesis is multifactorial and remains poorly understood, with no validated predictive biomarkers.[48]

ORN and related complications have been reported in various BNCT studies. Kato *et al*.[35] reported a case of ORN among six patients with recurrent HNC treated with hyperthermal neutrons. Similarly, Haginomori *et al*.[49] observed grade 1 osteonecrosis in a patient with recurrent squamous cell carcinoma of the temporal bone following two fractionated BNCT sessions. The JHN002 trial identified advanced osteonecrosis of the jaw in one out of 21 patients treated with cyclotron-based BNCT for recurrent or locally advanced HNC.[50,51] In a Phase I/II trial, Kankaanranta *et al*.[52] noted grade 4 soft tissue necrosis (7%) and grade 3 ORN (20%) in 30 patients. Similarly, in a study conducted at the Tsinghua Open Pool Reactor (THOR), one case of advanced ORN and one case of soft tissue necrosis were reported among 12 patients receiving two BNCT fractions for localized or recurrent HNC.[53]

These findings underscore the potential for severe late AEs in patients with BNCT-treated HNC, particularly in cases involving fractionated treatment protocols. However, the occurrence of RN in BNCT-treated patients is acceptable compared to that in patients undergoing re-irradiation. For instance, approximately 11% of patients undergoing re-irradiation with chemotherapy required surgical intervention for jaw osteonecrosis due to radiation-induced ORN.[54] Careful treatment planning and close follow-up remain essential to mitigate these risks.

Laryngeal edema

Laryngeal edema is a potentially serious complication of BNCT, and rare cases require tracheotomy. In the study by Kimura *et al*.,[55] one out of six patients developed laryngeal edema after the second BNCT session, during which both BPA and BSH were administered. The authors cited earlier findings indicating that this combination may increase ^{10}B accumulation,[30] suggesting a potential mechanism for the observed toxicity. Another study suggested that a short interval between photon therapy and BNCT could intensify the severity of AEs, including laryngeal edema.[34]

Other AEs

A wide range of additional AEs has been reported in HNC patients treated with BNCT. Common mild-to-moderate toxicities include dermatologic (such as alopecia or dermatitis), oral (such as mucositis or xerostomia), and metabolic (such as hyperamylasemia) symptoms, as well as fatigue and otitis. Less frequently, serious complications such as pneumonia, osteomyelitis, intracranial infections, and hematologic toxicity have also been observed. These effects vary depending on the tumor site, dose distribution, and prior radiotherapy exposure.[34,44,49,50,52,53,55,56]

Among the late complications, pulmonary toxicity has been documented in a Phase I/II study, with pneumonia occurring in 35% of the patients, including two life-threatening cases.[52] Neurological toxicities, though rare, have included transient aphasia due to cerebral edema and necrosis[57] and grade 3 cerebral neuropathy in two patients in the THOR trial.[34]

Several mitigation strategies have been explored. Shielding critical organs (such as the eyes) with lithium carbonate powder can reduce acute toxicity,[58] whereas feeding tubes improve nutritional support during severe mucositis or dysphagia.[53] Additionally, swallowing rehabilitation has demonstrated functional benefits for patients with treatment-related dysphagia, especially in advanced oral cancers.[59,60] However, reducing the skin dose with Li_2CO_3 pads may prolong the treatment time and compromise therapeutic efficacy,[61] underscoring the need for optimized protection strategies that balance safety and effectiveness.

MALIGNANT BRAIN TUMORS IN CHILDREN

Diffuse midline glioma (DMG), officially classified by the WHO in 2016, is a highly aggressive type of malignant glioma commonly occurring in the brainstem of children. Tumors in this region are considered particularly challenging due to their location in eloquent and surgically inaccessible areas, and conventional treatments have yielded limited success.[62] From 2019 to 2022, six children with recurrent DMG received two sessions of fractionated BNCT followed by bevacizumab; no severe toxicity was reported, except for alopecia, and one case of RN was likely related to prior hypofractionated therapy rather than the BNCT itself.[63] In another Japanese study, 23 children <15 years old with malignant gliomas underwent IO-BNCT, with only one case of mild hemiparesis attributed to RN, further supporting BNCT's favorable safety profile in pediatric patients.[64]

MENINGIOMA

Meningiomas account for over 30% of adult central nervous system tumors.[65] Although typically benign, atypical (WHO grade 2) and anaplastic (grade 3) variants can exhibit aggressive behavior.[66] RT remains a key modality for patients with subtotal resection or those ineligible for surgery; however, the overall prognosis remains limited.[67,68] BNCT provides a promising salvage option, particularly in previously irradiated recurrent cases.

Treatment outcomes and toxicities

Takai *et al*.[69] reported grade 2 RN in 34.1% and grade 3 RN in 13.6% of patients with relapsed high-grade meningioma treated with reactor-based BNCT who received hormonal therapy and bevacizumab, respectively. Bevacizumab has also proven effective in reducing BNCT-related cerebral edema.[70] Severe edema was associated with a low tumor-to-normal (T/N) ratio and a broad irradiation field in one study.[71] Conversely, Tamura *et al*.[72] reported no severe toxicity apart from alopecia in a patient with a T/N ratio of 5.0, underscoring the role of boron distribution in minimizing AEs. Other toxicities include mucositis and transient neurocognitive symptoms.[70,71]

Skull base meningiomas

Due to surgical limitations, skull base meningiomas are particularly well-suited for BNCT. In the study by Takeuchi *et al*.,[73] no RN was observed in nine patients treated with BNCT. Compared to conventional RT or ^{125}I brachytherapy, which can exhibit RN rates as high as 27%,[74] BNCT may represent a safer alternative for managing these challenging cases.

MELANOMA OF THE SKIN

Melanoma is an aggressive malignancy that can spread both locally and distantly. Surgery is the primary treatment for localized cases, but advanced or metastatic melanoma often requires alternative therapies. Despite the inherent radio resistance of melanomas,[75] BNCT has shown promise in cases unresponsive to conventional RT.

Skin toxicity is the most frequent AE of BNCT for melanoma. In a study by Fukuda *et al*.,[76] 16 out of 22 patients experienced skin reactions (mostly grade ≤3 and self-limiting); three developed grade 5 necrosis requiring grafting (graded on a five-point scoring system). In a Phase I/II trial by the Argentinean National Energy Commission, grade 1 acute skin reactions were common, and ulceration occurred in 30% of the evaluable areas (grade 3).[77,78] Similarly, Yong *et al*.[79] reported grade 1–2 acute radiation injury in a BNCT trial using an in-hospital neutron irradiator with no late toxicity. These findings suggest that skin toxicity varies according to the dose, treatment area, and exposure time.[78]

As the dose-limiting organ in melanoma BNCT, the skin limits therapeutic exposure regardless of boron concentration.[77,78] Management involves using lipid colloid or alginate dressings for mild reactions and grafting for severe necrosis.[76,79] Optimizing boron delivery and treatment planning is essential for minimizing toxicity without compromising efficacy.

VULVAR MELANOMA AND EXTRAMAMMARY PAGET'S DISEASE

BNCT has been investigated for vulvar melanoma (VM) and extramammary Paget's disease (EMPD), offering potential advantages in balancing efficacy and toxicity compared to conventional therapies. In the study by Hiratsuka *et al*.,[80] four patients (one VM, three EMPD) underwent BNCT, with moderate skin erosion being the most severe toxicity; additional effects included grade 2 dysuria and grade 1 mucositis. Similarly, Makino *et al*.[81] reported only mild erythema and skin erosion in two elderly patients with EMPD treated with BNCT. These findings suggest that BNCT is generally well-tolerated in patients with VM and EMPD while preserving functional and cosmetic outcomes. Further comparative studies are needed to confirm the clinical value of this drug in these rare malignancies.

LIVER CANCER

BNCT has a favorable safety profile in limited studies involving hepatocellular carcinoma (HCC). In one report, extracorporeal liver BNCT led to rhabdomyolysis and confusion, which were attributed to post-irradiation syndrome involving cytokine-mediated tissue damage.[82,83] Other reports described only mild, transient toxicities, including fever and elevated liver enzymes,[84] or no AEs at all, following selective intraarterial infusion of a ^{10}BSH-based emulsion (^{10}BSH-WOW).[85] These findings suggest that BNCT may be well tolerated by selected patients with HCC. However, its safety profile requires validation in larger controlled studies to guide clinical application and treatment planning.

LUNG CANCER

Due to the shallow penetration of thermal neutrons, BNCT is particularly suitable for superficial or chest wall-located recurrent lung tumors. This approach may benefit patients who are no longer candidates for conventional therapies. Suzuki *et al*.[86] reported two patients with diffuse pleural tumors who were treated with fractionated BNCT. One patient developed grade 2 pulmonary toxicity (fever and chest pain), and radiation pneumonitis was observed in areas receiving >4 Gy-Eq. In another study, a patient with recurrent chest wall lung cancer was treated with two BNCT fractions; no acute or late AEs were observed.[87]

Although BNCT is primarily used for superficial tumors, a simulation study has examined its feasibility for deep-seated lesions, such as non-small-cell lung cancer (NSCLC).[88] These studies emphasize the importance of optimizing boron delivery to selectively target tumor cells and managing respiratory motion to improve therapeutic accuracy.

Despite promising preliminary data, significant challenges remain—particularly the shallow penetration of thermal neutrons. Continued technological advances are essential for the broad application of BNCT to deep lung tumors.

DISCUSSION

BNCT is a novel therapeutic modality that selectively targets tumor cells while sparing surrounding healthy tissues, offering advantages over conventional therapies. However, AEs, ranging from mild to life-threatening and varying based on the tumor type, neutron source, boron agent, and dose distribution, remain a major challenge. The current review focuses specifically on BNCT-related toxicities, excluding the intrinsic pharmacological toxicity of boron compounds, which falls within the realm of pharmaceutical research. Both fatal and nonfatal AEs can significantly affect survival and quality of life, highlighting the need to understand and mitigate treatment-related toxicity.

Table 1 summarizes the AEs of BNCT across different tumor types, emphasizing the variability in the severity and frequency of complications. For example, the role of RN in glioblastoma underscores the delicate balance between efficacy and safety. Despite progress in the use of boron agents and advanced imaging for treatment planning, RN remains a significant complication. These observations highlight the need for further innovation in boron delivery technologies to achieve higher T/N ratios and more uniform boron distribution.

In lung cancer, BNCT has demonstrated safety for superficial chest walls or pleural tumors. However, pulmonary toxicity and limited neutron penetration hinder its application in deep-seated lesions, such as NSCLC. Emerging strategies, such as *in situ* whole-lung BNCT, are under exploration and may expand their utility in managing metastatic disease without extrapulmonary spread.[89]

Severe but rare toxicities, such as CBS and ORN in HNC, highlight the importance of careful patient selection, prophylactic interventions (e.g. embolization), and dose optimization. Although infrequent, these events may cause fatal or irreversible damage, warranting heightened vigilance in high-risk anatomical areas.

The therapeutic potential of BNCT continues to grow, with studies extending to breast, urological, and lung malignancies. Advances in neutron source design and boron delivery chemistry have improved the feasibility of developing deeper

Table 1: Comprehensive summary of BNCT adverse effects across tumor types

Tumor type	Adverse effect	Severity	Mechanism/notes	Management strategies
Glioblastoma	Radiation Necrosis (RN)	Severe	Driven by VEGF overexpression and vascular damage.	Bevacizumab, corticosteroids, hyperbaric oxygen, or surgical excision.
	Neurotoxicity (e.g., Seizures, Somnolence Syndrome)	Moderate to severe	Linked to intracranial pressure changes or aseptic inflammation.	Steroids, supportive care, and proactive boron dose management.
	Hematological Toxicity	Mild to moderate	Dose-dependent; associated with BPA or BSH infusion.	Monitor blood counts; effects are usually reversible.
	Alopecia	Mild	Universal but non-threatening.	No intervention needed; resolves post-treatment.
Head and Neck Cancer (HNC)	Carotid Blowout Syndrome (CBS)	Severe	Caused by vascular invasion and high-dose radiation to the carotid artery.	Prophylactic embolization or stent placement; CTA for risk stratification.
	Radiation Osteonecrosis (ORN)	Moderate to severe	Multifactorial etiology, including fractionated treatment.	Surgical intervention, conservative management, or hyperbaric oxygen therapy.
	Soft Tissue Necrosis	Moderate	Results from high radiation doses to surrounding tissues.	Supportive care; address severe cases with surgical debridement.
	Laryngeal Edema	Moderate to severe	Related to boron dose and combination protocols (BPA + BSH).	Tracheotomy for severe cases; boron dose adjustment.
	Mucositis, Xerostomia	Mild to moderate	Common due to radiation damage to mucosal surfaces and salivary glands.	Topical treatments, hydration, and symptomatic care.
	Pulmonary Toxicity	Moderate to severe	Associated with radiation and fractionated BNCT in treated areas.	
Lung Cancer	Pulmonary Toxicity	Severe	Associated with high doses and radiation pneumonitis in treated areas.	Corticosteroids; precise dose control to minimize lung exposure.
	Radiation Pneumonitis	Moderate to severe	Linked to areas receiving >4 Gy-Eq radiation dose.	Anti-inflammatory agents and careful planning of radiation fields.
Melanoma (Skin)	Skin Ulceration and Necrosis	Moderate to severe	Results from prolonged exposure and high skin dose.	Dressings for mild cases; grafting for necrosis.
	Alopecia	Mild	Non-threatening but universal.	No specific treatment required.
	Radiation Dermatitis	Mild to moderate	Related to superficial radiation exposure.	Topical treatments and patient education.
Liver Cancer	Hepatic Insufficiency, Renal Failure	Severe	Cytokine release from irradiated liver tissue causing systemic inflammatory response.	Supportive care for multi-organ failure; dose fractionation to minimize toxicity.
	Rhabdomyolysis and Confusion	Moderate to severe	Observed in extracorporeal liver BNCT.	Immediate supportive care; cytokine modulation may help.
Childhood Brain Tumors	Radiation Necrosis	Moderate	Rare; associated with prior radiotherapy or high BNCT doses.	Monitoring, and supportive care.
	Neurotoxicity	Mild to moderate	Rare in pediatric cases; mostly reversible.	Steroids or symptomatic management.
Other Cancers (e.g., EMPD)	Skin Erosion	Mild to moderate	Related to tumor location and neutron dose.	Wound care; adjust treatment protocols for highly sensitive areas.

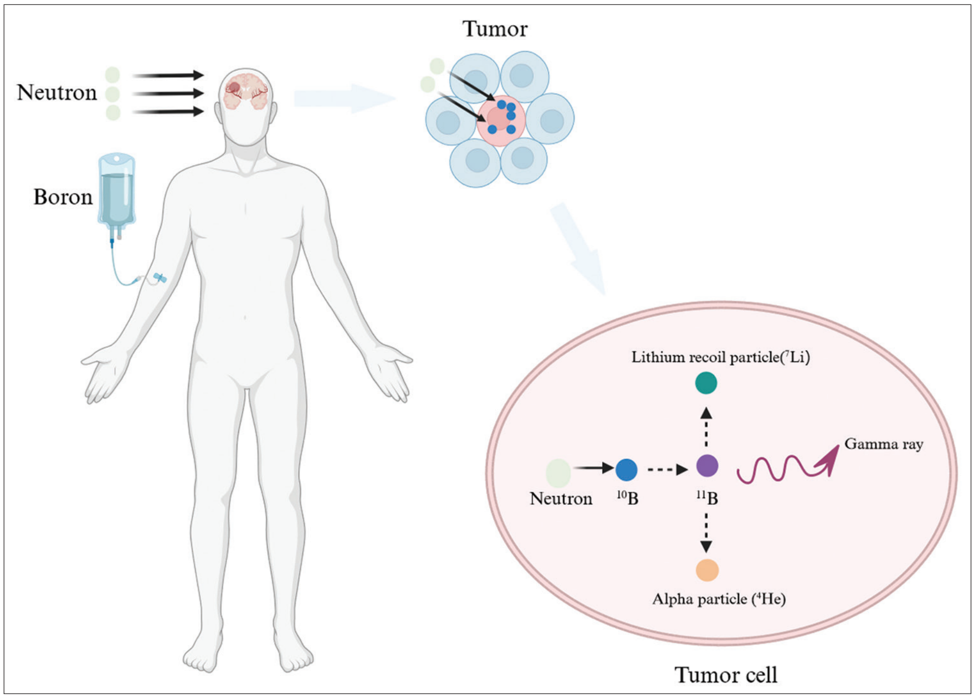

Figure 1: Boron neutron capture process and reaction

targets. However, successful implementation still depends on precise dose control, improved biodistribution, and strategies to mitigate toxicity. The use of BNCT for metastatic or disseminated disease highlights the importance of ongoing research aimed at optimizing treatment protocols and expanding its therapeutic applications.

A central challenge, often referred to as the "BNCT dilemma,"[12] is achieving a sufficient dose for efficacy without surpassing the toxicity thresholds. The variability in inclusion criteria, neutron energy, and boron agent usage across studies also complicates interstudy comparisons. Standardization of clinical protocols and harmonization of patient selection are critical for developing robust, generalizable evidence.

Uneven intratumoral boron uptake,[27] low T/N ratios, limited neutron penetration, and inhomogeneous radiation dose distribution contribute to toxicity. Promising strategies to address these challenges include developing next-generation boron agents with enhanced tumor selectivity, adopting fractionated BNCT protocols to allow for normal tissue recovery, and optimizing neutron delivery. For example, employing superthermal sources and multifield irradiation can enhance dose uniformity.[87] Accelerator-based BNCT systems have enhanced dose precision and accessibility, supporting global clinical trials that will generate essential safety and efficacy data.[90] These platforms will likely shape the next generation of BNCT protocols.

Looking forward, BNCT is increasingly moving toward a multidisciplinary framework that integrates oncology, radiology, and drug development. Combinations with immunotherapy or targeted agents may enhance tumor specificity and overcome resistance, enabling more effective and personalized cancer therapy.[91]

This review has outlined the major toxicities of BNCT and their implications for clinical application. Although BNCT offers reduced systemic toxicity compared to conventional radiotherapy, certain severe reactions, although rare, can offset survival benefits or compromise functional recovery. Ongoing innovations in boron delivery, treatment planning, and patient selection are essential for achieving safe and effective BNCT. Future studies should focus on optimizing this balance to fully realize the transformative potential of BNCT in oncology.

Key messages

This work summarizes and analyzes the adverse effects of BNCT across various tumor types, aiming to provide a practical reference for clinicians and researchers involved in its clinical application and development.

Author contributions

Yushu Zhang was responsible for the conceptualization, study design, literature search, data extraction and synthesis, and drafting of the manuscript. Yufeng Cheng contributed to the conceptualization, provided overall supervision and guidance, and critically revised the manuscript. Both authors approved the final version of the manuscript. Yufeng Cheng serves as the guarantor of the work.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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