ACCSCIENCE PUBLISHING

Advances in Radiotherapy & Nuclear Medicine

REVIEW ARTICLE

# Boron neutron capture therapy and its potential in paediatric oncology: A narrative review

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## Abstract

Boron neutron capture therapy (BNCT) involves the use of a boronated pharmaceutical that accumulates in tumours to a greater extent than in surrounding normal tissues. When the tumour is exposed to a flux of epithermal neutrons, neutron capture by boron-10 produces high-linear-energy-transfer alpha particles and lithium-7 nuclei with short ranges, which can kill boron-containing tumour cells while limiting energy deposition farther from the capture site. While BNCT was first conceptualised 90 years ago, widespread clinical implementation was delayed because the original neutron sources were nuclear reactors and few clinically useful boronated drugs were available. Recently, accelerators producing adequate neutron flux of appropriate energy have become available, and more suitable pharmaceuticals have been developed, creating new opportunities for clinical implementation. BNCT has attractive characteristics for paediatric radiotherapy, and preliminary modelling suggests potential dosimetric advantages and a reduced risk of radiation-induced second cancers. The magnitude of any clinical benefit remains uncertain, as BNCT biological dose modelling is complex, normal tissue receives radiation from non-boron components of BNCT, and whole-body tissue exposure has not been evaluated. Here we review the potential benefits of BNCT in children, teenagers and young adults. Detailed clinical research programmes will be needed to evaluate the feasibility, value and toxicity of BNCT in paediatric practice.

***Keywords:*** Boron neutron capture therapy; Paediatric oncology; Children, teenagers and young adults; Radiotherapy; Late normal tissue toxicity; Quality of life

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**Citation:** Lopez Martinez S, Vivekananthan C, Amos RA, Gillies CSM, Gaze MN, Moss R. Boron neutron capture therapy and its potential in paediatric oncology: A narrative review. *Adv Radiother Nucl Med*. 2026;4(3):026330037. doi: 10.36922/ARNM026330037

**Received:** August 12, 2026

**Revised:** September 16, 2026

**Accepted:** September 21, 2026

**Published online:** September 28, 2026

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## 1. Introduction

There has been a major resurgence of interest in boron neutron capture therapy (BNCT), as recent technical developments have made a previously impractical treatment option increasingly feasible for routine clinical use. Like other forms of radiotherapy, BNCT aims to treat cancer by delivering a therapeutic dose of ionising radiation to localised tumours to control or eradicate them, while keeping radiation exposure to surrounding healthy tissues as low as reasonably achievable to reduce the risk of both early and

late radiation-related toxicity. However, BNCT has the potential to further improve the therapeutic ratio. Unlike conventional external beam radiotherapy with photons or protons, which minimise the damage to healthy tissues via careful planning and image-guided delivery, BNCT uses a two-step process[1]:

(i) Administration of a pharmaceutical containing the stable boron isotope boron-10 ($^{10}B$) that accumulates in tumour cells (most commonly sodium borocaptate [BSH] and/or 4-borono-L-phenylalanine [BPA][2]), and
(ii) Irradiation with thermal or epithermal neutrons that are captured by $^{10}B$ with high probability, triggering a nuclear reaction producing alpha particles and lithium-7 ($^{7}Li$) nuclei with ranges comparable to the diameter of a single cell.

The aim to minimise the dose delivered to healthy organs at risk (OARs) for patients undergoing radiotherapy is always important, but it is of particular significance when treating paediatric patients due to the greater radiosensitivity of growing and developing organs, and the risk of radiation-induced second cancers later in life, with implications for long-term morbidity and mortality.[3] For this reason, proton beam therapy (PBT), which may decrease irradiation of OARs, is currently favoured for selected children and for teenagers and young adults (TYA).[4,5]

The development of BNCT raises important questions regarding its role in paediatric oncology. Although the biological and physical characteristics may offer some theoretical advantages in certain clinical indications, its place within management strategies alongside conventional radiotherapy techniques is uncertain. This narrative review provides a broad overview of the current evidence relating to BNCT with a particular focus on potential application in paediatric oncology and challenges to implementation. A pragmatic literature search was performed via the PubMed, Google Scholar, and Web of Science databases with terms including "BNCT," "boron neutron capture therapy," "paediatric," "pediatric," "oncology," "children," "teenage and young adult," and tumour-specific terms. As there was limited published evidence of the use of BNCT within paediatrics, paediatric clinical studies were prioritised, while relevant adult studies were also included when relevant to potential paediatric applications. Reference lists of review articles and clinical studies were also screened to identify additional literature. The literature was reviewed through August 2026. Given the narrative scope of this review, a formal systematic-review methodology was not used.

## 2. History and mechanism of boron neutron capture therapy

Despite the potential for clinical benefit, the field of BNCT remained investigational for decades after its initial conception in 1936 by Gordon Locher.[6] Locher[6] proposed the potential of using neutrons for therapeutic purposes, suggesting that thanks to the ease with which neutrons traverse matter and penetrate to disrupt atomic nuclei (particularly with isotopes like $^{10}B$), if these isotopes could be caused to accumulate in tumour cells and then irradiated with thermal neutrons, the reaction would release high linear energy transfer (LET) particles (alpha and lithium nuclei). Their ranges in tissue are comparable to the size of a cell, making them capable of destroying cancer cells while sparing surrounding healthy tissues.[6,7] A schematic of the reaction showing the average ranges and dose deposition compared to the size of a glioblastoma cell is shown in Figure 1.

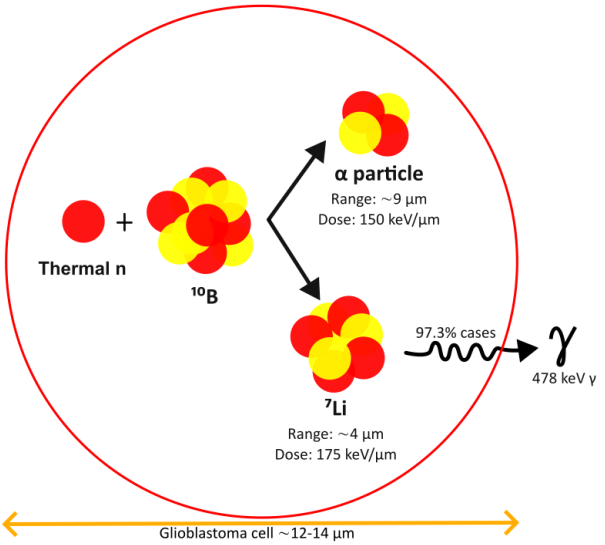


**Figure 1.** Schematic of the mechanism of delivery of boron neutron capture therapy, where a thermal neutron is captured by the $^{10}B$ isotope, producing an alpha particle and a recoiling $^{7}Li$ nucleus. In most cases, the recoiling ion is produced in an excited state, and it then emits a 478 keV prompt gamma ray. The reaction ranges are shown compared to glioma-cell dimensions. Figure created by the authors with Inkscape. The energy deposition values and particle ranges were obtained from Jin et al.[1] The representative glioblastoma cell size was based on the diameter of U87 cells reported in the BioNumbers database.[8,9]

At that time, the only sources of neutrons suitable for BNCT (having the correct energy and flux) were nuclear fission reactors. However, clinical use of such reactors, typically located far from hospital facilities, was extremely

challenging. Reactor-based BNCT uses neutrons that arise directly from the reactor core by filtering and moderating the primary beam. This created several practical problems, not only with the costs and safety challenges associated with operating these reactors, but also because they were not designed specifically for BNCT.

The limitations of the early reactor-based approach were demonstrated by the first clinical BNCT studies, undertaken at Brookhaven National Laboratory in collaboration with Massachusetts General Hospital and the Massachusetts Institute of Technology between 1951 and 1961.[10] These studies used reactor-derived thermal neutron beams and evaluated several early boron compounds, including a $^{10}$B-enriched sodium tetraborate (borax) and, later, the less toxic sodium pentaborate, in an attempt to identify an agent with suitable pharmacological and tumour-targeting properties. Most treated patients had malignant glioma. Clinical outcomes were disappointing, and clinical irradiation was discontinued as the approach did not demonstrate an advantage over the treatments available.[10]

These first experiences identified two principal limitations. First, externally delivered thermal neutrons were strongly attenuated by the scalp, skull, and superficial brain tissue, resulting in inadequate neutron penetration to deep-seated intracranial tumours. Attempts to compensate by increasing the incident thermal neutron fluence increased, in turn, the dose to the scalp and overlying normal brain tissue, producing excessive normal-tissue damage. Second, the boron compounds available at the time did not provide the selective boron distribution required for a favourable therapeutic ratio. Consequently, it was difficult to deliver an adequate boron dose to the tumour while maintaining an acceptable normal-tissue dose. [11,12] Despite these unsatisfactory first experiences, accelerator-neutron sources using proton or deuteron beams have been developed over recent decades, allowing for accelerator-based BNCT (AB-BNCT) facilities that are already being integrated into hospitals.[13-15] This change in source has sparked a true renaissance in this treatment modality, which was cemented by the approval of the technique as a clinical therapy covered by the National Health Insurance in Japan in 2020.[16] More recently, clinical BNCT has been initiated within a special medical tourism pilot zone in Hainan, China[17]; whereas in Finland [18], South Korea [19], Taiwan [20] and other countries, AB-BNCT is currently confined to clinical trials and developmental programmes without nationwide regulatory approval.[21]

The BNCT treatment workflow begins with the patient being administered a boron-containing pharmaceutical which is preferentially taken up in tumour cells. While the boron concentration is elevated, the tumour site is irradiated with a beam of epithermal neutrons. As shown in Figure 2, $^{10}$B has a high neutron-capture cross-section at thermal energies, which decreases with increasing neutron energy, implying that a clinically suitable BNCT beam must therefore provide epithermal neutrons energetic enough to reach the tumour (a problem already observed in the first BNCT experiences[11]), while preserving a high probability of interaction.

Following neutron capture, the boron nucleus decays to $^{7}$Li and helium-4 (alpha particle). These energetic ions have a high LET and, because of their short path length, deposit their energy within each $^{10}$B-loaded cell at the location of capture. Therefore, the dose is maximised in the tumour, where the boron concentration is highest.

Although this is the main mechanism of dose delivery in BNCT, BNCT dosimetry is intrinsically complex because the delivered dose is the sum of several components: the high LET boron dose from the boron capture reaction ($D_B$), proton recoil dose from elastic interaction with hydrogen ($D_N$), proton dose from nitrogen capture of thermal neutrons ($D_H$), and low-LET photon dose both from 2.22 MeV prompt gammas which originate via hydrogen capture of neutrons, and $\gamma$ contamination in the field ($D_\gamma$). Each of these has distinct microdosimetric characteristics and biological effectiveness, which can all be summarised in **Equation 1**:

$$D_{bw} = CBE_B \times D_B + RBE_N \times D_N + RBE_H \times D_H + RBE_\gamma \times D_\gamma, \quad (1)$$

where $D_{bw}$ is the biologically weighted dose, measured in photon-equivalent dose (Gy-eq); the dose components are defined as above, $RBE_\gamma$, $RBE_H$ and $RBE_N$ are the relative biological effects of gamma, hydrogen interactions, and nitrogen interactions, respectively. $CBE_B$ is the neutron compound biological effect (CBE). CBE is used for boron dose instead of relative biological effectiveness (RBE) because of the dependence of boron-dose effectiveness on the boron carrier, tissue type, boron distribution, biological endpoint and irradiation conditions. Consequently, the weighting factors used in BNCT are protocol-specific and should not be interpreted as universal conversion factors.

Often, treatment is prescribed to maximise the normal-tissue dose within the tolerable range. However, as with the weighting factors, different protocols use different dose constraints. For example, one BPA-based head and neck BNCT protocol used $CBE_B$ values of 2.5 for skin and 4.9 for oral mucosa, together with $RBE_N = 3.0$, $RBE_H = 3.0$ and $RBE_\gamma = 1.0$. In that protocol, the maximum dose was

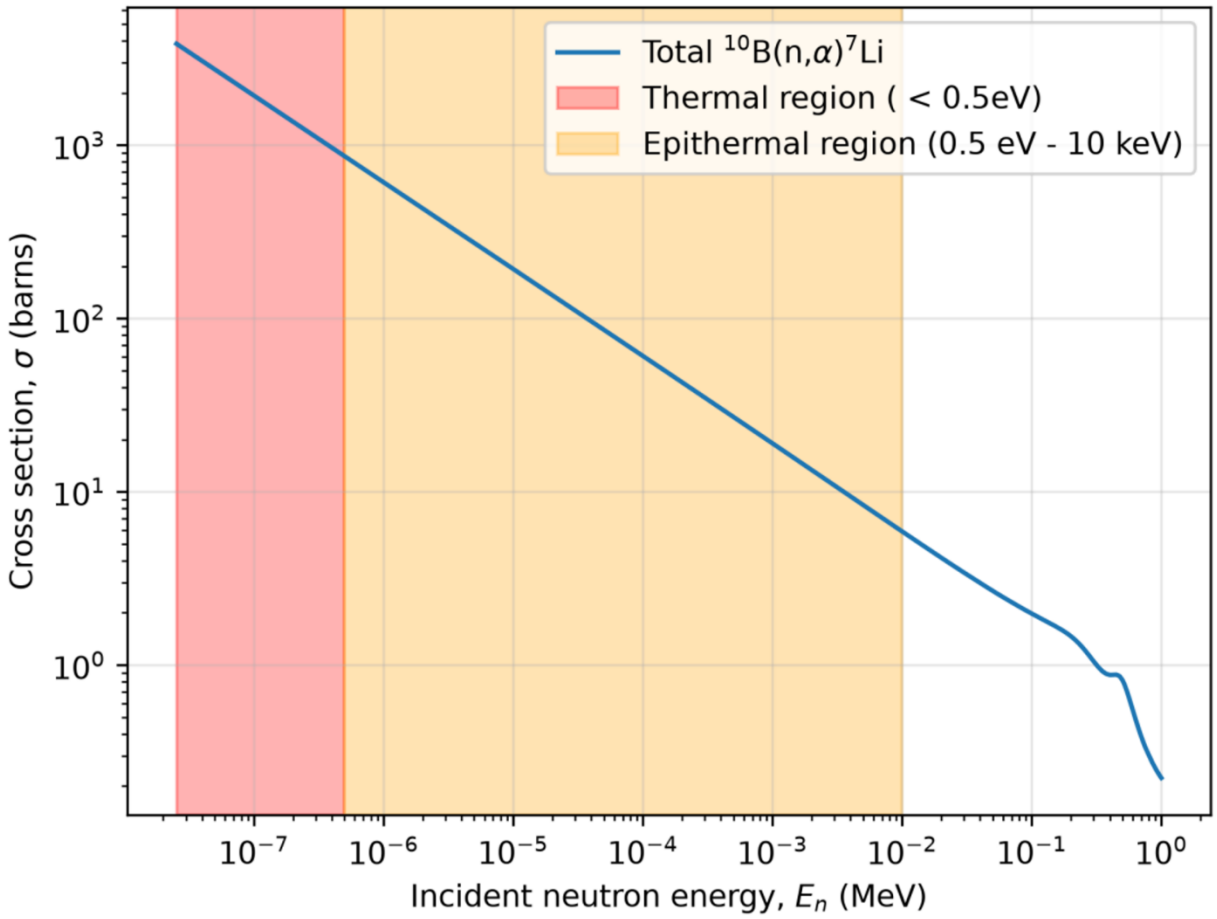


**Figure 2.** Neutron capture cross sections for the therapeutic $^{10}B(n,\alpha)\,^7Li$. The thermal ($E_n < 0.5$ eV) and epithermal ($0.5$ eV $\leq E_n \leq 10$ keV) neutron energy regions are shaded. Figure created by the authors using data from the IAEA Neutron Cross-Section Standards, 2006 evaluation/ENDF/B-VII standards Sub-Library.[22]

constrained to <10–12 Gy-eq for skin or oral mucosa.[23] A different head and neck BNCT protocol applied tolerable normal-tissue doses of 15 Gy-eq for skin, 12 Gy-eq for pharyngeal mucosa, 9 Gy-eq for brain and 5 Gy-eq for the eyes.[24] Such variation in weighting factors, dose constraints, treatment sites, boron agents and dose-reporting methods complicates direct comparison of toxicity and clinical outcomes across studies.

As with all radiation-based cancer treatments, understanding where the dose is being deposited is of great importance. BNCT dosimetry currently relies on models of boronated drug uptake which are matched to the patient by taking periodic blood samples. This indirect measurement of dose is done because currently there is no way to directly measure the delivered dose.

In 93.7% of the boron capture events, the lithium ion is initially in an excited state ($^7Li^*$) which almost immediately de-excites with the emission of a 478 keV prompt gamma. A schematic representing this is shown in Figure 1. These gammas are of sufficient energy that they can easily escape from the patient and be detected externally. Since the neutron capture, gamma emission, and dose deposition can be considered to occur at the same position, it is possible to infer the dose deposition profile from the spatial gamma distribution. Methods for translating this principle into clinically actionable dose verification are discussed later.

## 3. Potential for paediatrics

In the United Kingdom (UK), cancers in children and TYA account for approximately 1% of all cancers[25,26] and radiotherapy is used in approximately one third of these cases.[27,28]

Management of children and TYA requires very careful multidisciplinary teamwork both to select the

optimal, typically multimodality, treatment strategy, and support patients through a treatment course that is both tolerable and acceptable. This is done with input from a multidisciplinary team which includes, but is not limited to, surgeons, clinical oncologists, paediatric oncologists, anaesthetists, specialist nurses, therapeutic radiographers, medical physicists, dosimetrists, and play specialists.[27]

Specific considerations in treating this population with radiotherapy include motion management, use of anaesthesia to facilitate treatment delivery and adapting treatment to be age-appropriate and acceptable to younger patients, such as personalised immobilisation masks and play therapy.[29]

The twin aims of radiotherapy in children and TYA are to achieve disease control and to minimise the adverse effects on normal tissues and organs. Cancer treatment is continuously evolving in paediatrics to make treatment more effective, more acceptable, and less invasive, while reducing the psychological and physical burden of treatment.

A key consideration in paediatric oncology is the long life expectancy following successful treatment. In the UK, 84% of children diagnosed with cancer (between 2012–2016) survive for at least 5 years, while among young people aged 15–24 years, 83% survive for at least 10 years (diagnosed between 2007–2011) and 74% survive for at least 20 years (diagnosed between 1997–2001).[25,26] As increasing numbers of children and young people survive cancer for prolonged periods, the long-term consequences of treatment become increasingly important. It is essential therefore that advances in treatment aim not only to improve survival but also to minimise treatment-related morbidity and its longer-term impacts on health and quality of life.

The relatively recent migration of radiotherapy delivery techniques from photon-based radiotherapy to PBT for many paediatric indications is based more on reducing normal tissue complications than it is on increasing cure probability. As many late effects are driven by normal tissue dose, improved selectivity of target irradiation could translate into an improved long-term quality of life. Techniques to produce highly conformal individualised radiotherapy plans include adaptive planning, high-dose-rate brachytherapy in rhabdomyosarcoma, and linear accelerator-based arc therapy techniques to improve lung sparing in total body irradiation.[29] Approaches including precision targeting with stereotactic radiotherapy and molecular radiotherapy are being explored and utilised, and concomitant use of immunotherapy and other biologic agents may also modify radiotherapy use.[30] However, these techniques do not eliminate irradiation of normal tissues.

Proton beam therapy has a broad range of paediatric indications and has been optimised and well integrated into clinical practice. The evidence base is mature, and the infrastructure is reasonably accessible in multiple higher-income countries.[31] Generating multifield conformal plans for tumours of varying sizes and depths is straightforward compared to the complexities of modelling dose with BNCT.

Protons have a modestly higher RBE of approximately 1.1 compared to photons. High LET radiation achieves a higher rate of ionisation per unit distance, leading to an increased number of double-stranded DNA breaks.[32] This interaction is independent of oxygen concentration, increasing its RBE with a smaller differential radiosensitivity between tumour cell types. Theoretically, high LET radiation should be more effective at treating hypoxic, radiation-resistant tumours.[33]

Molecular radiotherapy targets specific markers on cancer cells and is well established for use in tumour groups such as thyroid and neuroblastoma. In contrast to therapeutic radionuclides, $^{10}$B is a stable, non-radioactive isotope, and therefore does not deliver dose through radioactive decay after administration. In BNCT, the boron dose is generated through the neutron capture reaction $^{10}B(n,\alpha)^{7}Li$, which only happens in regions where boron is exposed to neutron fluence. Thus, boron present in healthy tissues outside the neutron field, for example in the kidneys, would not itself produce substantial boron-capture dose. Nevertheless, boron uptake in healthy tissues within or near the irradiated volume contributes to normal-tissue dose and must be considered during treatment planning.

Another potential advantage of BNCT is the smaller number of treatment sessions relative to conventional fractionated proton or photon radiotherapy. Many protocols deliver treatment over one or two sessions, possibly reducing the burden and risks associated with repeated immobilisation and general anaesthetic[1].

In children, recurrence after a full course of radiotherapy presents a challenge, and the scope for re-irradiation is limited as protons still deliver significant dose levels to healthy tissue. Favourable tumour-to-normal $^{10}$B uptake may permit delivery of a higher biologically effective tumour dose while limiting dose to adjacent normal tissues, making it an attractive option for salvage in heavily pretreated disease.

Boron neutron capture therapy has so far been used only rarely in paediatric practice. The unique combination of high LET radiation limited to an area of disease which has accumulated a pharmaceutical offers the prospect of much reduced healthy tissue damage. These qualities

make it an appealing modality to explore in children and TYAs where, for example, dento-facial deformity following conventional radiotherapy in head and neck tumours [34], and neurocognitive and endocrine effects following central nervous system tumour irradiation are well documented.[35]

As with all treatment approaches, BNCT may have both advantages and disadvantages, and its clinical use requires careful assessment of whether it provides an overall net benefit. The principal potential advantages and disadvantages of BNCT are summarised in Table 1.

**Table 1. Principal potential advantages and disadvantages of boron neutron capture therapy in paediatric practice based on evidence from published reviews and clinical reports[1,2,13–15,32,33,36–41]**

| Aspect | Potential advantages | Potential disadvantages |
|---|---|---|
| Tumour selectivity | Potentially selective cell-level irradiation when $^{10}B$ accumulates preferentially in tumour cells | Achieving a uniform, high tumour-to-normal boron concentration ratio is difficult; intratumoral heterogeneity can reduce efficacy |
| Radiobiology | High linear-energy-transfer particles, potential effectiveness against radioresistant and hypoxic tumour cells | Normal-tissue boron uptake; limited ability to mitigate via fractionation |
| Normal tissue sparing | Micrometre-range particle path length limits damage to nearby cells, useful near critical structures | Mixed radiation components make dose calculation and prediction more complex than standard radiotherapy |
| Treatment course | Fewer treatment sessions than external beam radiotherapy | Optimal dose, fractionation, and retreatment protocols remain uncertain |
| Clinical role | Potential use for recurrent or previously irradiated tumours with few alternative treatment options | Limited evidence in paediatric population and teenagers and young adults |
| Drug delivery & imaging | Clinically used boron agents and positron emission tomography-based uptake assessment support patient selection | Current agents have imperfect specificity; imaging does not fully reflect cellular distribution |
| Infrastructure | Accelerator-based neutron sources enable hospital deployment | High cost, specialised facilities, and limited centre availability |
| Planning & quality assurance | Advanced Monte Carlo planning improves accuracy | Dosimetry and biological effectiveness factors remain uncertain and poorly standardised |
| Safety & regulation | Limited acute toxicity reported | Regulatory approval and long-term toxicity not established |

There are several difficulties with introducing BNCT as a therapeutic option in paediatric practice. First, there are no accelerator-based neutron sources in most countries, and second, there is very limited evidence and experience in children. There is also substantial heterogeneity across adult studies with different infrastructure, boron compounds, drug administration and planning methods, which makes it difficult to synthesise the evidence consistently and produce a standardised protocol for paediatric clinical trials.[42] These and other challenges are further developed in **Section 5**.

## 4. Published clinical experience of boron neutron capture therapy in paediatric oncology

Published clinical experience of BNCT in children remains very limited and consists predominantly of small case series, compassionate-use reports and historical institutional experience rather than prospective clinical trials. The available studies are heterogeneous in tumour type, previous treatment, and BNCT technique, limiting conclusions regarding safety and efficacy. Table 2 provides a summary of published clinical reports of BNCT in paediatric patients.

**Table 2. Summary of published clinical reports of BNCT in paediatric patients**

| Study | Study design | Paediatric sample size (*n*) | Pathology | Boron agent | Neutron source | Dose | Response | Survival | Graded toxicity (CTCAE where applicable) | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| Nakagawa *et al.*[41] | Clinical case series | 23 | 3 GBM, 6 anaplastic astrocytomas, 7 PNET; 6 pontine gliomas, 1 anaplastic ependymoma | BSH | Reactor-based intraoperative BNCT | Cohort-level dose not reported; cases individually dosed | Anaplastic ependymoma: no recurrence | Anaplastic ependymoma: 10-year RFS; others not reported | Not reported | Not reported |
| Chen *et al.*[43] | Compassionate use case series | 5 | 3 recurrent GBM, 2 DMG | BPA | THOR | Variable fractionation; Median prescription dose 15.7 Gy-E (range 6.3–29.0) | 10 treated sites: 1 near-CR, 3 PR, 4 SD, 2 PD (at 1–3 months) | Median progression-free interval: 3.8 months | CTCAE v5.0 used, but grading not reported. Side effects: mild symptoms of increased intracranial pressure, hair loss in irradiated areas | Median 5.3 months (range 3.1–9.7) |
| Chen *et al.*[36] | Compassionate use case series | 4 | 1 high-grade glioma, 1 ganglioglioma, 2 diffuse midline gliomas | L-BPA | THOR | Two fractions, 5–10 Gy-E per fraction, approximately 1 month apart | 3 PR, 1 SD | Not reported for paediatric subgroup | Radiation necrosis ($n = 1$, grade not reported, previous hypofractionated radiotherapy considered to be the cause) | MRI at 4 weeks after BNCT and then every 1–3 months; paediatric subgroup follow-up duration not separately reported |
| Huang *et al.*[37] | Compassionate use case series | 6 | Recurrent DMG | BPA | NTHU atomic reactor | Two fractions, 5–10 Gy-E per fraction; mean tumour dose 16.41 ± 4.80 Gy-E. | 3 PR; 3 SD (MRI assessment at 1 month) | Mean OS 6.39 months (range 5.27–7.51) Mean RFS 4.35 months (range 2.21–6.49) | CTCAE v5.0 used, but grading not reported. Side effects: hair loss, radiation necrosis ($n = 1$, grade not reported; previous hypofractionated radiotherapy considered to be the cause) | Initial post-treatment MRI at one month and subsequent 3-monthly follow-up until death |
| Liao *et al.*[44] | Case report | 1 | Recurrent paediatric sialoblastoma | BPA | Reactor | First BNCT: mean dose 21.66 Gy-Eq. Second BNCT: mean dose 26.39 Gy-Eq | CR after first fraction Partial response after second fraction | 23-month PFS Alive at 52 months | Grade 2 mucositis | 52 months |

Note: Patient overlap is present between the cohorts reported by Chen *et al.*[43] and Chen *et al.*[36] Potential additional overlap with the cohort reported by Huang *et al.*[37] should be considered when interpreting the cumulative sample size. Abbreviations: BNCT: Boron neutron capture therapy; BPA: Boronophenylalanine; BSH: Sodium borocaptate; CR: Complete response; CTCAE: Common Terminology Criteria for Adverse Events; DMG: Diffuse midline glioma; GBM: Glioblastoma; Gy-E/Gy-Eq: Gray-equivalent; L-BPA: 4-borono-L-phenylalanine; NTHU: National Tsing-Hua University; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PNET: Primitive neuroectodermal tumour; PR: Partial response; RFS: Recurrence-free survival; SD: Stable disease; THOR: Tsing-Hua Open Pool Reactor.

The potential of BNCT to reduce normal tissue exposure has led to interest in whether it can reduce the risk of radiation-induced secondary malignancies. Suzuki *et al.*[45] performed a treatment planning study and modelled the lifetime attributable risk (LAR) of secondary cancers for different modalities in nine paediatric, teenage and young adult patients with central nervous system tumours. The modelled results indicated a statistically significantly lower LAR with BNCT. BNCT doses were converted to biologically effective dose using assumed tissue-specific RBE and CBE values and α/β ratios of 10 Gy for tumour and 3 Gy for normal tissues.

The generalisability of these findings is limited because LAR was estimated using mathematical prediction models rather than observed clinical outcomes. The analysis included only bone, brain, and soft tissue and did not review whole-body exposure, so it is not possible to generalise to other anatomical sites. The targeted monoclonal antibody bevacizumab and steroids have been utilised to minimise the risk of radiation necrosis and oedema, respectively.[36,43]

The reported response to BNCT in children is derived from very small sample sizes with indeterminate significance. However, overall, some level of response is recorded, whether a partial response or stable disease.[37,43] There are also reports of variable $^{10}B$ uptake in the brainstem gliomas of younger children. Outcomes from larger trials in adults with glioblastoma multiforme have shown more promising results with comparable outcomes to conventional external beam radiotherapy when used in the primary setting and for recurrence.[42] Table 3 summarises tumour types within paediatric oncology where BNCT may offer an advantage over conventional external beam radiation, including a description of the evidence base providing rationale.

## 5. Current and future challenges and limitations

Paediatric oncology is complicated by the wide variety of histological tumour types, anatomical diversity of tumour localisation, range of stages and biological factors affecting risk stratification, differing ages of patients, and its relative rarity, meaning that phase III trials are usually conducted in many centres internationally. All these factors tend to limit innovative treatment assessments to early-phase trials in only a few specialist centres, meaning that patients need to travel long distances to take advantage of them.

The RBE for BNCT is comprised of the dose contributed by boron, nitrogen, hydrogen, and gamma rays and CBE, which is a value to account for boron accumulation within cells. Conventional dose modelling with the linear-quadratic formula is difficult to apply to BNCT as radiation is delivered in a single large dose, and comparisons using equivalent dose in 2-Gy fractions (EQD2) are not straightforward because of the complex biological response to high-LET radiation.[45]

There is a need for greater international collaboration and consensus on BNCT techniques and reporting standards so that research outputs can be pooled and systematically analysed to support development of standardised treatment protocols. Delivering BNCT safely to children is contingent on the development of specialist infrastructure, robust governance and staff training in BNCT dosimetry and neutron-facility operations. As noted above, BNCT is entering a new phase, driven by the clinical deployment of accelerator-based neutron sources, new generations of boron delivery agents, and more sophisticated treatment-planning systems. Nevertheless, its translation into routine clinical practice remains

**Table 3. Scenarios in which BNCT may offer an advantage over current treatment modalities**

| Tumour type | Value of BNCT | Evidence base |
|---|---|---|
| Diffuse midline/brainstem glioma | Infiltrative tumour; dose limitations in reirradiation; critical OAR tolerance, e.g., brainstem | Limited direct paediatric clinical evidence [37] |
| High-grade glioma | Infiltrative disease; limited salvage options; dose limitation in reirradiation; critical OAR tolerance, e.g., brainstem, optic tract | Limited direct paediatric clinical evidence; extrapolation from adult studies [41] |
| Ependymoma | Dose limitation in reirradiation; critical OAR tolerance | Isolated paediatric clinical evidence.[41] |
| Embryonal CNS tumours | Dose limitation in reirradiation | Limited paediatric clinical evidence. [41] |
| Other paediatric intracranial tumours | Late effects/secondary malignancy implications | Paediatric modelling/ planning evidence. [46] |
| Recurrent paediatric sialoblastoma | Risk of late dentofacial abnormalities after EBRT | Isolated clinical evidence. [44] |

Abbreviations: BNCT: Boron neutron capture therapy; CNS: Central nervous system; EBRT: External beam radiotherapy; LET: Linear energy transfer; OAR: Organ at risk.

constrained by scientific, technical, clinical, and ethical challenges. Many of these limitations are amplified in paediatric oncology, where tolerance for uncertainty is low, and the priority given to long-term safety is high.[3]

### 5.1. Boron delivery agents and tumour heterogeneity

The therapeutic selectivity of BNCT relies on achieving high and relatively homogeneous concentrations of $^{10}B$ in tumour cells compared with surrounding normal tissues, typically expressed as tumour-to-blood and tumour-to-normal tissue ratios. In current practice, BPA and BSH remain the main clinical agents, but both have important limitations. BSH shows limited tumour selectivity and heterogeneous intra- and extracellular distribution, while BPA often requires high dosing and shows appreciable inter- and intra-tumour variability in uptake.

"Third-generation" boron carriers, including small molecules, peptides, liposomes, polymers, nanoparticles, and antibody–drug conjugates, are being developed to improve tumour targeting, nuclear localisation, and systemic tolerability. However, nearly all pharmacokinetic and toxicity data derive from preclinical models and adult clinical cohorts. Age-dependent differences in blood–brain barrier function, organ perfusion and metabolism mean that simply extrapolating adult dosing and timing regimens to children risks both under-treating tumours and increasing normal-tissue dose.[1,47]

Spatial and temporal tumour heterogeneity constitute another fundamental biological constraint. Differences in transporter expression, vascular density, hypoxia, and microenvironmental factors can produce "cold spots" with low boron concentration that may drive local failure despite apparently adequate macroscopic dose. This is particularly concerning for infiltrative paediatric brain tumours, where disease often extends beyond radiologically visible margins. Addressing this requires robust, clinically usable methods to image and quantify boron distribution *in vivo* (e.g. 4-borono-2-[$^{18}$F]fluoro-L-phenylalanine positron emission tomography) and to understand how heterogeneity evolves over time.

### 5.2. Neutron sources and beam characteristics

Early clinical BNCT depended on research reactors such as the FiR 1 (Finland)[48], RA-6 (Argentina)[49], or THOR (Taiwan)[50], which provided high-quality neutron spectra but were geographically limited and presented substantial regulatory, safety, and public-acceptance barriers. While the development of compact, accelerator-based epithermal neutron sources has been transformative, designing these facilities and their beam-shaping assemblies (BSAs) is technically demanding.

The 2023 report of the International Atomic Energy Agency (IAEA) sets out the roles and requirements of a BSA. The report specifies that a BSA should provide: an adequate epithermal neutron flux ($\phi_{epi} \geq 5\times10^{8}\,\mathrm{cm}^{-2}\cdot\mathrm{s}^{-1}$); an optimised neutron energy spectrum, which contains "thermal" neutrons below the energy of 0.5 eV if the beam is meant to treat shallow tumours, or between 0.5 eV and 10 keV for an "epithermal" beam (suitable for deeper cancers), and low fast-neutron contamination (energies above 10 keV); suitable depth–dose characteristics; and minimal accompanying gamma dose.[51]

Treatment depth is an important determinant in the feasibility of BNCT in oncology. Thermal neutrons have limited tissue penetration; therefore, epithermal neutrons are preferred for clinical use as they penetrate further into tissue before falling into the thermal range.[52] The depth at which BNCT can deliver a favourable therapeutic dose is dependent on tumour depth, patient anatomy, the distribution of boron, and beam characteristics.

Several dosimetric metrics measured in phantoms are used to characterise the therapeutic performance of a BNCT beam. Key metrics include the following:

- The advantage depth (AD) is the depth at which the tumour dose would fall below the maximum dose to healthy tissue; it measures effective beam penetration.[53]
- The advantage ratio is the integrated tumour dose divided by the integrated normal-tissue dose from the surface to AD.[50]
- The advantage depth-dose rate is defined as the dose rate at AD. That is the rate of maximum dose to healthy tissue.[53]
- The therapeutic depth or treatment depth, like AD, measures the depth at which the tumour dose falls to half the maximum dose to healthy tissue. It serves as a strong indicator of clinically meaningful depth.[53]

In addition to these phantom-based metrics, there are several in-air beam-quality metrics that are used to determine the achievable treatment dose rate and therefore the treatment time. Common metrics include epithermal neutron flux $\Phi_{epi}$, the thermal-to-epithermal flux ratio $\Phi_{th}/\Phi_{epi}$ (which should be low at beam exit to minimise superficial boron dose), fast-neutron and photon contamination (usually specified as dose per unit epithermal neutron flux, $D_{fast}/\Phi_{epi}$ and $D_{\gamma}/\Phi_{epi}$, respectively). Representative recommended limits are $< 2\times10^{-13}\,\mathrm{Gy\,cm}^{2}$ per epithermal neutron for each component. These contaminants contribute to normal-tissue dose without providing the selective boron-dose advantage of the $^{10}B(n,\alpha)\,^{7}Li$ reaction.[54]

All of these metrics are used to define the therapeutic performance of BNCT beams, and these values can vary according to beam characteristics and boron distribution within tissues.[55] This has clinical implications for appropriate patient selection. Studies in head and neck cancer have demonstrated that deeper-seated tumours may receive lower doses, although accelerator-based epithermal neutron sources improve the potential for treating deeper disease.[23,56]

Furthermore, these beam-quality metrics and beam-shaping assemblies are typically optimised using adult head or torso phantoms.[54,57] In children, smaller cranial dimensions, thinner skulls, and different tissue compositions alter neutron moderation and dose distributions, potentially shifting the depth of maximum therapeutic dose and changing the relative exposure of critical structures such as hippocampi, optic pathways and the pituitary. By analogy, a Monte Carlo study in PBT using age and sexspecific paediatric wholebody phantoms has shown clinically relevant differences in organ doses and secondaryneutron exposure compared with adult models, underlining the importance of ageappropriate phantoms for dose and risk estimation.[58] Dedicated BNCT Monte Carlo studies and experimental validation in paediatric anthropomorphic phantoms will therefore be required to ensure that beam designs and BSAs are genuinely appropriate for paediatric anatomy and radiobiological constraints.

Finally, accelerator-based BNCT capacity remains limited worldwide. The IAEA Accelerator Knowledge Portal lists 33 BNCT facilities worldwide as of September 2026[59]; however, this database includes facilities at different stages of development and should not be interpreted as a count of centres currently delivering clinical BNCT. On the other hand, the International Society of Neutron Capture Therapy (ISNCT) clinical-centre directory lists only nine centres providing active clinical BNCT services in China, Japan, South Korea, and Taiwan, while explicitly excluding facilities still under construction.[60] This limits patient access, slows prospective data collection and complicates worldwide efforts to standardise beam-quality criteria and quality-assurance procedures.

### 5.3. Dosimetry, treatment planning, and dose verification

As explained in **Section 2**, BNCT dosimetry is intrinsically complex because the delivered dose arises from several components. Clinical dose calculations therefore require not only a precise description of the mixed neutron–photon field but also assumptions about CBE and RBE that remain incompletely defined for many tissues and tumour types, and are even questioned as resulting in artificially high tumour dose values and failing to meet their goal of establishing an explanation of the outcomes of BNCT and a comparison to other therapies.[38,39] These uncertainties are particularly problematic in children, whose developing organs may differ from adults in radiosensitivity and repair capacity.

Substantial advances have been made in Monte Carlo-based dose calculation, patient-specific modelling and beam dosimetry for accelerator-based sources. Compact neutron/gamma detectors, cell-based dosimeters, prompt-gamma spectroscopy systems, and epithermal flux monitors are being developed and validated[40], with the aim of characterising all four major dose components (see **Equation 1**) in clinically relevant geometries. In parallel, dedicated quality-assurance approaches for the gamma component, such as optically stimulated luminescent dosimeters, have been evaluated on clinical AB-BNCT systems and shown to provide stable, linear, and reproducible measurements suitable for routine quality assurance.

A major unresolved gap is reliable *in vivo* or real-time verification of boron dose and spatial dose deposition during treatment. The 478 keV photons emitted during boron capture reactions provide a direct signal that can be measured, as the capture, gamma emission, and dose deposition all occur in the same location. Thus, imaging the spatial distribution of these gammas would in principle allow inference of the boron dose distribution. This approach, known as prompt gamma imaging, has been recognised for decades as the most promising route to direct, in-treatment dose monitoring in BNCT. The 2023 IAEA monograph on advances in BNCT notes that the implementation of these techniques will be important and is likely to be a field of active research for the foreseeable future.[51]

One of the earliest studies to propose the use of prompt gamma rays was conducted by Tetsuo Matsumoto and Otohiko Aizawa in 1988. They investigated a prompt-gamma measurement method using a high-purity germanium (HPGe) detector, which has high energy resolution, and examined differences in gamma-ray emission profiles at different boron concentrations.[61] They continued developing this work and demonstrated appreciable differences in the gamma spectrum between phantoms with different $^{10}B$ concentrations as early as 1991.[62] This line of work was continued, with more groups proposing techniques utilising HPGe detectors.[63]

These methods were never translated into clinical practice, and thus, several other detector concepts have been explored. For example, high-resolution scintillation

detectors[64–66] have been used to demonstrate reconstruction of boron distributions in phantoms. However, count rates remain low and spatial resolution is limited by the collimator geometry. To overcome the efficiency penalty of heavy collimation at high gamma energies, collimatorfree Compton camera systems have been proposed and are under active development, having experimentally demonstrated separation of the 478 keV gammas and visualised boron targets under neutron irradiation[67]. In a more clinically focused study, the iTED Compton imager array successfully imaged 478 keV gammas from BPAtreated cancer cells, claiming sensitivity below 1 μg of $^{10}$B.[68,69] Nonetheless, no prompt gamma imaging system has yet achieved routine clinical implementation, principally because of the intense and spectrally complex background combined with the stringent operational requirements of a clinical environment.

For paediatric patients, treatment tolerances are tighter, target volumes are smaller, and more conservative organ-at-risk constraints than in adults are essential. Thus, the absence of reliable *in vivo* dose verification is particularly consequential. Without real-time confirmation that boron dose is being deposited at the intended location and magnitude, clinicians must apply larger safety margins, which directly reduces the normal-tissue sparing that constitutes BNCT's primary theoretical advantage in children. Resolving this verification gap is therefore not merely a technical desideratum but a prerequisite for the confident clinical translation of BNCT to paediatric oncology.

### 5.4. Ethical, regulatory, and logistical considerations in children

Children are recognised as a vulnerable population in clinical research and are subject to heightened protections in trial design and oversight. For paediatric BNCT, the balance between potential benefit and uncertain long-term risk is especially delicate. In most current scenarios, BNCT is offered only after standard therapies, including surgery, chemotherapy, and conventional radiotherapy or proton therapy, have failed, and prognosis is poor. This context may support ethical justification for offering BNCT within carefully controlled protocols, but it also complicates assessment of late toxicity and secondary cancer risk, as many patients will not survive long enough for these events to manifest.

Regulatory pathways for BNCT covering accelerator-based neutron sources, treatment-planning systems and novel boron agents are still evolving. For paediatric indications, regulators and ethics committees are likely to require more stringent preclinical safety data, age-appropriate pharmacokinetics, and robust long-term follow-up plans than for adult trials.

Practical considerations are also non-trivial: younger children may need sedation or general anaesthesia during immobilisation and irradiation; treatment rooms and workflows designed around adult patients may not be child-friendly; and families often face substantial travel and logistical burdens to reach one of the few BNCT centres worldwide. Although BNCT may involve fewer irradiation sessions than conventional EBRT, irradiation time does not necessarily reflect the overall time for the procedure. The steps involved in the treatment workflow, including induction of anaesthesia and recovery, may result in a prolonged treatment episode with implications for the patient and teams involved. The overall procedure time and anaesthetic time should therefore be considered when evaluating the practical advantages of BNCT in children, particularly if treatment takes place over multiple sessions.[70]

Radiation protection considerations include neutron activation of the patient following BNCT. Neutrons interact with elements in healthy tissues and can generate residual radioactivity following irradiation, although evidence from adult studies suggests the resulting exposure is low.[71,72] The implications of interactions with implantable medical devices are unknown. This may be particularly relevant in paediatric oncology where central venous access ports and cerebral shunts may be in use, although evidence evaluating this issue in paediatric patients is currently limited.

Another potential limitation of BNCT application that requires comprehensive evaluation is whole-body radiation exposure. Neutrons may scatter outside of the beam and contribute dose to tissues distant from the target volume alongside photon radiation. This is particularly relevant in smaller paediatric patients as a greater proportion of the body could be exposed to this scattered radiation. Comprehensive whole-body dose evaluation would be needed to provide further evidence of the impact on secondary malignancy risk.

Equity of access is a further concern. AB-BNCT facilities are capital-intensive and currently concentrated in a small number of high-resource settings. Integrating BNCT into paediatric oncology networks would require dedicated referral pathways, harmonised protocols, and mechanisms for long-term outcome tracking across institutions and borders. Without such infrastructure, there is a risk that paediatric BNCT remains a highly specialised option available only to a small subset of children, further limiting the evidence base needed to define and, if justified, expand its role in paediatric cancer care.

## 6. Conclusion

Approximately 75 years after BNCT was first used for patient treatments at Brookhaven National Laboratory in collaboration with Massachusetts General Hospital and the Massachusetts Institute of Technology, advances in AB-BNCT systems and the introduction of novel boronated pharmaceuticals make this modality a potential clinical reality in a number of facilities around the world. However, despite the potential therapeutic benefit, clinical experience in children and TYA remains limited.

To establish the role of BNCT in paediatric radiation oncology will require dedicated research programmes for children and TYA, appropriate clinical and technical infrastructure, and multicentre international collaborations. These programmes should ideally be closely linked with recognised paediatric radiotherapy centres that have the expertise in paediatric supportive care and established pathways for referral and accommodation.

Furthermore, methods for improving accuracy, reproducibility, efficiency, efficacy, and safety should be the focus of continued medical physics research. Priority areas should include, among others: dose calculation for treatment planning; treatment planning techniques; direct verification of delivered dose from detection of nuclear interaction byproducts; improved imaging of drug uptake and tumour response; image guidance, immobilisation, and treatment delivery workflows; quality assurance procedures; biological modelling and outcomes prediction. These innovations will require the development and validation of novel technologies to enable their clinical implementation. Standardisation of absolute dosimetry protocols, prescribing and reporting of dose, and clinical workflows will facilitate multi-institutional clinical trials.[51] The advent of AB-BNCT has created new opportunities for the clinical development of BNCT. As with proton and ion-beam therapy, its ultimate role will depend on identifying the tumour types and patient groups for whom it offers a meaningful therapeutic advantage over established treatments. Selected paediatric and TYA indications may represent promising priorities for future prospective investigation, but this must be established through carefully designed clinical studies.

## Acknowledgments

None.

## Funding

Sergio Lopez Martinez is funded by the EPSRC-funded UCL Centre for Doctoral Training in Intelligent, Integrated Imaging in Healthcare (i4health) (EP/S021930/1). The funders had no role in the design, interpretation, writing, or decision to submit this review.

## Conflict of interest

Richard Amos is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The remaining authors declare no competing interests.

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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

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