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Abstract

Each year more than 3000 Canadians are diagnosed with brain cancers like glioblastoma multiforme or recurrent head and neck cancers, which are difficult to treat with conventional radiotherapy techniques. One of the most clinically promising treatments for these cancers is boron neutron capture therapy (BNCT). This procedure involves selectively introducing a boron delivery agent into tumor cells and irradiating them with a neutron beam, which kills the cancer cells due to the high-linear energy transfer radiation produced by the $^{10}B(n,\alpha)^{7}Li$ capture reaction. The theory of BNCT has been around for a long time since 1936, but has historically been limited by poor boron delivery agents and non-optimal neutron source facilities. Although significant improvements have been made in both of these domains, it is mainly the advancements of accelerator-based neutron sources that have led to the expansion of over 20 new BNCT facilities worldwide in the past decade. Additionally in this work, particle and heavy ion transport code system simulations, in collaboration with the University of Tsukuba, were performed to examine the effectiveness of the Ibaraki BNCT beam shaping assembly to moderate a neutron beam suitable for BNCT at the proposed prototype Canadian compact accelerator-based neutron source (CANS) site, which uses a similar but slightly higher energy 10 MeV proton accelerator with a 1 mA average current. The advancements of CANSs in recent decades have enabled significant improvements in BNCT technologies, allowing it to become a more viable clinical treatment option.

Key words: accelerator-based neutron production, boron neutron capture therapy (BNCT), cancer therapy, cancer, compact accelerator neutron source (CANS)

1. Historical progression of boron neutron capture therapy

Boron neutron capture therapy (BNCT) is a radiotherapy used to treat and eliminate cancer by inducing a localized nuclear reaction inside the tumor cells of a patient. While interest in this area of treatment has increased substantially over the past few decades due to the development of accelerator-based neutron sources, the idea of using neutron capture therapeutically has been around for a much longer time. Immediately following the discovery of the neutron in 1932, research began on the biological implications of neutron capture and its ability to be used therapeutically. The two expected results of tissue neutron irradiation were elastic collisions in the bulk of most tissues, mainly due to hydrogen nuclei, and neutron capture reactions in specific areas of the body where there were small amounts of atoms with high neutron absorption cross sections, such as boron [1]. The theorized medical use cases included the ability to destroy cancer cells in patients or kill disease-producing bacteria by introducing trace amounts of a non-toxic strong neutron-absorbing element in the tumor or infected body regions and bombarding them with slow neutrons [1]. Despite a strong theoretical understanding of neutron capture, which forecasted many future opportunities, limited technology and physical research restricted immediate adoption of neutron capture-based applications.

BNCT was first used in vitro in 1938 to kill and stop the growth of cancer tissue [2]. Small sections of cancer obtained from mice were suspended in boric acid, bombarded with slow neutrons, and re-implanted into the mice. Samples treated with both boric acid and neutrons had significant reductions in the ability to grow after implantation, samples treated with just neutrons had a mild reduction in growth, and samples treated with boric acid experienced no changes

in growth [2]. This experiment highlighted the viability of BNCT as a cancer treatment in vitro, and indicated that it could be used in vivo given there was a way to supply the tumor with a sufficient boron concentration that was substantially higher than the surrounding healthy tissue. Human clinical trials of BNCT first began in 1951 at the Brookhaven Graphite Research Reactor for the treatment of glioblastoma multiforme (GBM) [3]. In the first experiment with 10 patients, a bismuth shield was used to reduce gamma radiation exposure, and borax injected intravenously, was used as the boron delivery agent. While the results were clinically encouraging, the boron concentration was too low and the neutrons had insufficient energy and flux to achieve significant tissue penetration. In the second clinical application, a more robust treatment facility was designed at the reactor, which increased the thermal neutron flux by a factor of 15, and additionally a higher intravenous dosage of borax was administered [3]. Similarly, BNCT clinical research took place at the Massachusetts Institute of Technology from 1959 through 1961 with 18 patients diagnosed with GBM. This set of clinical trials used newly synthesized boron compounds *p*-carboxyphenylboronic acid and sodium perhydrodecaborate, which achieved higher tumor:brain specificity due to their high partition coefficient in the aqueous phase [4]. Despite these innovations, all the patients died within 11 months, a result that represented no significant improvement compared to traditional radiation or surgical resection. Upon post-mortem inspection of 14 patients, the cause of death in nine of the patients appeared to be radiation necrosis, characterized by coagulation of devitalized tissue and severe blood vessel damage, which was believed to be caused by higher than expected levels of boron circulating in blood vessels [5]. Despite previous encouraging results of tumor size reduction, a lack of successful patient outcomes or major breakthroughs led to the discontinuation of clinical trials at the Brookhaven National Laboratories and Massachusetts Institute of Technology in 1961 [6].

With human BNCT trials halted, research continued in mice, transplanted with ependymoblastomas, to screen for boron delivery compounds that were non-toxic and contained a moiety that enabled them to attach inside tumor cells [4]. The first compound to achieve the desired tumor:blood differential of >1 was borocaptate sodium (BSH, $NaB_{12}H_{11}SH_2$), which achieved tumor:blood ratios that ranged from 1.4 to 20.0 [7]. With this newly synthesized compound, human clinical trials of BNCT began in Japan in 1968, led by neurosurgeon Hiroshi Hatanaka [6]. In a trial of 38 people with glioblastoma treated with BNCT between 1968 and 1985, the 5-year survival rate was 19% for the total group; however for the 12 patient subgroup, which had their tumors located superficially in the maximum therapeutic depth (<6 cm deep), the 5-year survival rate was 58% [8]. Additionally, it was realized at this time that the survival rate of patients with deep-seated tumors could be greatly improved by using epithermal neutrons rather than thermal neutrons, as they had superior tissue penetration. While these results reinvigorated interest in BNCT, many concerns were raised with Hatanaka's result, including lack of patient randomization, lack of uniformity in histological tumor grading, and most critically, lack of time standardization for pre-treatment surgery, administration of the capture agent, and irradiation [9]. In a later analysis of a small sample of 12 Americans treated with BNCT in Japan from 1987 to 1994, it was determined that BNCT did not provide significant improvements in survival compared to traditional radiotherapies, when the prognosis and tumor pathology for each individual patient was accounted for [10]. Despite some conflicting opinions on treatment success, BNCT re-emerged as promising radiotherapy for cancer, specifically of the head, neck, and brain; however more work was still required to optimize neutron production and further improve the tumor specificity of boron-containing agents.

During this time, in 1972, another boron delivery agent for BNCT was emerging, *p*-boronophenylalanine (BPA). This non-toxic, L-DOPA analogue was of particular interest for the BNCT treatment of melanomas due to the fact that L-DOPA is a metabolic precursor in the formation of melanin. Therefore, by taking advantage of the accentuated melanogenesis in melanomas, a considerably high concentration of boron could be accumulated in the tumor relative to the surrounding healthy tissue [11]. While surgery is currently the primary treatment of malignant melanomas, it is not always a feasible option when working with metastatic tumors or a medically inoperable patient. Of the 22 patients treated for melanoma with BNCT between 1987 and 2001, there were promising results with good tumor control, long survival times, and only a few patients who faced severe skin damage and required additional post-operative care [12]. In later animal experiments and clinical trials, it was determined that BPA could also be used as a suitable boron delivery agent for GBM BNCT treatments as sufficiently high tumor:brain tissue boron concentration differentials were achieved (>3) [13]. With relatively effective boron delivery agents available, recommendations were made that more work should be done to study accelerator-based neutron sources so that they could be used to effectively produce thermal and epithermal neutrons directly in a hospital setting [11].

Interest in BNCT re-ignited in the 1990s and 2000s following the discovery of new boron delivery agents that were able to effectively target tumor cells and results that continued to demonstrate some anti-cancer effects. Research has restarted in the United States and also began in Argentina, Taiwan, and Europe, including Finland, Sweden, and the Czech Republic [14]. More recently, interest in BNCT has centered around the study of using compact accelerator-based neutron sources (CANSs) for neutron production due to their lower cost, smaller hospital-sized footprint, and the fact that many nuclear reactors used for research have been shutdown or are on the verge of closure [14]. The first accelerator-based neutron source used for BNCT was the C-BENS facility in Kyoto, Japan built in 2009. While Japan, with its seven accelerator-based BNCT facilities at various stages of clinical trials, physical testing, and construction, is the only country where human patients can currently be treated, construction and deployment of similar facilities are underway in Finland, Argentina, China, and South Korea, with further plans for development in Russia, Italy, and Israel [15]. Despite growing worldwide interest in BNCT and accelerator-based neutron

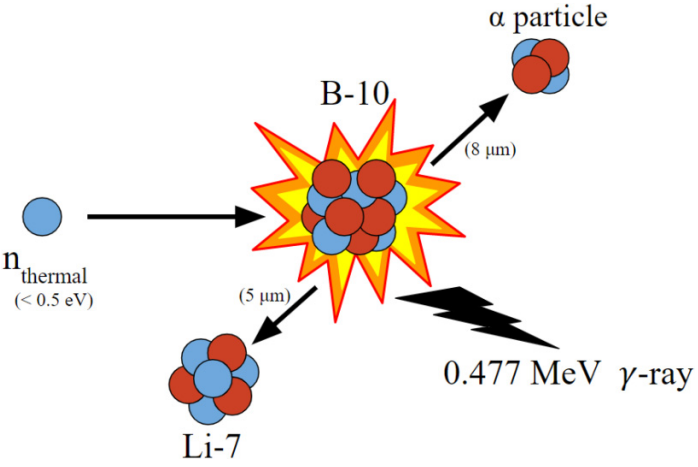
sources, there is currently no facility in Canada conducting relevant research (clinical or pre-clinical). This has led some Canadian scientists to start a national movement with the goal of building a CANS with BNCT capabilities in Canada [16].

2. Therapeutic mechanism of action

Currently, radiotherapies serve as a crucial tool in treatment of various cancers. It is estimated that approximately 50% of cancer patients will receive some form of radiation therapy throughout the course of their treatments [17]. These radiation treatments can be accomplished using high-energy photons (X-rays or gamma rays) or particle radiation (electrons, protons, or neutrons). This radiation causes DNA damage in the cancer cells, which prevents further cell division from occurring. If the cellular machinery is unable to repair the damage, it will lead to cell death by apoptosis, necrosis, mitotic catastrophe, autophagy, or senescence [18]. However, these radiation techniques are not cancer-specific and can lead to DNA damage in healthy cells located around the tumor. Therefore, successful radiation treatments will sufficiently irradiate tumor cells with the proper dosage while simultaneously minimizing the radiation dose applied to non-cancerous cells. One method to improve these treatments is to incorporate drugs that specifically target and interfere with cancer cell signal transduction and DNA repair, causing them to become more radiosensitive, but leaving healthy cells unaffected and capable of repairing damage [19]. BNCT is an emerging, effective radiotherapy treatment that allows for the targeted radiation dosing of cancerous cells while leaving most normal cells unaffected. This procedure is of particular interest for head, neck, and brain cancers, such as GBM, which have a high mortality rate and currently lack robust treatment protocols. It is estimated that of the approximately 3000 Canadians diagnosed with brain or central nervous system cancers each year, 80% will die as a result of it [20]. Overall, BNCT takes advantage of the nuclear reaction boron-10 undergoes when it captures a low-energy neutron, cancer-specific boron delivery agents, and boron's unique neutron capture characteristics to cause radiation damage enclosed within the cancerous cell with minimal harm to the surrounding tissues.

BNCT is a viable radiotherapy due to the nuclear reaction non-radioactive boron (^{10}B) undergoes when it captures a low-energy thermal neutron (Fig. 1) [21]. In this ^{10}B(n,α)^{7}Li reaction, the resultant recoiling lithium nucleus and alpha particle have a high linear energy transfer (LET), ≈175 and 150 keV μm^{-1}, respectively, over a combined range of approximately 12–13 μm [22]. It is an important characteristic that this reaction produces high LET, which is densely ionizing, because it causes substantial biological damage to occur over the particle pathway when compared to sparsely ionizing, low-LET radiation such as gamma and X-rays [23]. Due to the enhanced efficiency of killing cells, high-LET radiation is classified as having a high relative biological effectiveness, approximately 1.5–3 times higher, when compared to low-LET radiation [24]. Additionally, the short particle track lengths of the produced lithium nucleus (5 μm) and alpha particle (9 μm) causes the high-energy radiation to be deposited over a short

Fig. 1. Resultant products and their corresponding track lengths produced in the ^{10}B(n,α)^{7}Li reaction.



distance, roughly the diameter of a single cell. This quality ensures that damage is contained in the boron-containing cells with minimal damage to surrounding healthy cells [25]. Therefore, the specific qualities of the nuclear reaction and produced particles that occur during BNCT are crucial for its prospects as a targeted cancer treatment.

BNCT is a binary system that requires sufficient concentrations of boron-10 to be delivered to cancer cells and proper amounts of neutron irradiation to achieve successful results. Effective boron delivery agents are required to achieve cancer-specific targeting, the main benefit of BNCT over traditional radiotherapies. The general requirements of boron delivery agents are (*i*) low cellular toxicity, (*ii*) high uptake in the tumor (20–35 μg ^{10}B/g), (*iii*) a high tumor:normal tissue concentration differential (around 3–5 times), and (*iv*) low clearance in tumors so that the concentration differential can be maintained throughout the irradiation period [26]. Due to a lack of any major innovations and pharmaceutical investment, BPA and BSH continue to be the main clinical method of delivering boron to tumor cells, commonly as a BPA–fructose complex. However, some research is being completed with the goal of incorporating boron delivery agents into tumor-targeting compounds, such as porphyrins, nucleic acids, peptides, proteins, antibodies, carbohydrates, and liposomes [27]. Nonetheless, advancements in future boron delivery agents will only benefit BNCT treatments and improve the ability to selectively target cancer cells.

Boron is the element at the forefront of neutron capture-based therapies due to the low relative abundance it has in living tissues and its relatively large neutron capture cross section. The amount of boron naturally present in human cells is very low, with about 12–32 mg total boron in a 70 kg adult male [28]. This is extremely low when compared to elements like hydrogen, nitrogen, carbon, and oxygen, which account for over 95% of body mass [29]. Due to the low baseline amount of boron, it is an element that can be introduced in high concentrations to specific areas, relative to surrounding tissue. Neutron capture cross section, specifically for slow or thermal neutrons, is another important factor that must

be considered in neutron capture therapies. The larger the capture cross section is for an element, the easier it is for that atom to absorb a neutron and undergo a reaction. For thermal neutrons with an energy of 0.025 eV, boron-10 has a neutron capture cross section of 3837 barns (b, 1 barn $= 10^{-24}$ cm^2), which is significantly higher than other common body elements like hydrogen, nitrogen, carbon, and oxygen that have thermal neutron capture cross sections of 0.33, 1.86, 0.00387, and 0.00019 b, respectively [30, 31].

Despite these elements possessing very low neutron capture cross sections, their dosimetry component cannot be ignored when calculating the total BNCT dose applied to the patient as they represent a significant portion of the body's natural composition. Therefore, in addition to the high-LET radiation produced by the boron component, $^{10}B(n,\alpha)^7Li$, the low-LET gamma radiation produced when hydrogen captures a thermal neutron $^1H(n,\gamma)^2H$, the high-LET proton of a recoiling hydrogen nuclei when it collides with a fast neutron $^1H(n,n')^1H$, and the high-LET radiation of the released proton or carbon-14, when nitrogen captures a neutron, $^{14}N(n,p)^{14}C$, must be accounted for [25]. However, when a more tissue-penetrating epithermal neutron beam is used rather than a thermal beam, many of these undesirable reactions can be avoided because the higher speed of the epithermal neutrons and corresponding decrease in neutron cross section of hydrogen and nitrogen at those energies means that epithermal neutrons are seldom captured [9]. Overall, the large neutron capture cross section that boron has for low-energy neutrons and its low natural abundance in tissues, enables it to be a strong candidate as the capture agent for neutron capture-based therapies.

3. BNCT neutron sources

The ability for delivery agents to deliver boron to cancerous cells preferentially over healthy cells is an important consideration for treatment; however neutron production and irradiation remain the paramount factors influencing treatment success. Some desirable characteristics of a neutron beam facility for BNCT include high beam purity to minimize gamma ray and fast neutron contamination, high beam intensity to deliver appropriate neutron dose in approximately 30 min, well collimated to allow ample positioning around the body with minimal collateral dose, and a well-shielded irradiation room with patient viewing, communication, and control system reliability to ensure the patient receives the prescribed dose without any inadvertent exposure [25]. Historically, neutrons have been generated from reactor-based neutron sources. Two general methods were used to obtain appropriate energy neutrons for BNCT from reactor sources, (*i*) they were directed from a reactor core to a location where the patient could be treated, or (*ii*) thermalized neutrons generated in reactor were used to cause a fission reaction with an external, subcritical array of fuel, termed as fission converter, to generate new neutrons that were subsequently moderated and used to treat the patient [22]. The second method, proposed in 1993, allowed for better control of neutron generation, including the ability to create a higher energy epithermal neutron beam [32]. While reactor-based sources often provide higher intensity neutron fluxes compared to other sources, they are more expensive, require significantly more infrastructure, licensing, and maintenance, and are typically located away from hospitals and city centres, which complicates clinical trials and reduces patient access [14]. Due to these limitations, alternative neutron sources were required if BNCT is to become a common cancer treatment around the world. Areas of particular interest were isotopic sources, such as ^{252}Cf that is a strong neutron emitter, spallation sources, which bombard heavy elements with high-energy protons, and low-energy proton accelerators that use targets such as lithium or beryllium [9]. Currently, the development of low-energy proton accelerator-based neutron sources remain the top priority for improving the practicality and robustness of BNCT treatments.

Development of CANS technology has led to a resurgence of BNCT as a viable cancer treatment. A CANS, not to be confused with a spallation source, produces neutrons through low-energy proton bombardment of a light element target (typically beryllium or lithium) by the following reactions $^7Li(p,n)^7Be$ and $^9Be(p,n)^9B$ [15]. The four major components of a CANS are (*i*) proton accelerator, (*ii*) target for the proton beam, which acts as the proton-to-neutron converter, (*iii*) a beam shaping assembly (BSA), and (*iv*) resultant neutron beamlines leading to instrument stations for research, industrial purposes, or clinical work. The design of the first three components play a critical role in producing neutrons with both suitable energy and flux for cancer treatment. Accelerator-based BNCT (AB-BNCT) facilities provide many benefits when compared to traditional reactor sources, including that AB-BNCT facilities can quickly be turned on and off depending on when neutrons are needed, they do not produce large amounts of radioactive waste, AB-BNCT facilities are cheaper to install, easier to maintain, require significantly less infrastructure, and licensing, and due to their smaller footprint AB-BNCT systems can be installed directly in hospitals, which increases patient access and hospitals likely already have a radiotherapy department trained to use accelerators for various treatments [33]. Currently, Japan is the only country where AB-BNCT neutron sources have been approved for clinical use and is also the only country where BNCT is a medical treatment option covered by health insurance [34]. Although Japan was the first country to employ AB-BNCT treatments, there are many AB-BNCT facilities around the world at various stages of development, construction, and commissioning [35], including recently constructed facilities in Dongguan, China [33] and Helsinki, Finland [36]. While accelerator-based neutron sources have widely been embraced by the global BNCT community, the variations in design, including accelerator type, proton energy, proton current, target material, and neutron beam moderation (see Table 1), highlight the lack of standardization in technique and underscore that large amount of research is still required to ensure treatment outcomes are optimized.

4. BSA

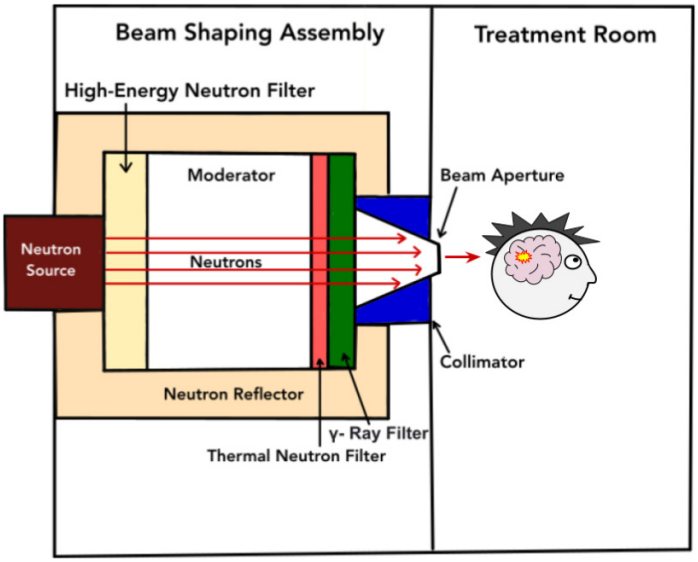
Naturally, the target material and design geometry used in an accelerator-based neutron source have a large

Table 1. Some accelerator-based BNCT (AB-BNCT) facilities around the world that have been constructed, are under construction, or are in development listed with their proton beam parameters (energy and current) and target material used for neutron production.

Facility name	Country	Proton energy (MeV)	Average current (mA)	Target material	Reference
CNEA	Argentina	1.45 (deuteron)	30	Beryllium or ^{13}C	[37]
NeMeSis	Spain	2.1	30	Lithium	[38]
Budker Institute of Nuclear Physics	Russia	2.3	10	Lithium	[39]
CNAO	Italy	2.5	10	Lithium	[40]
Edogawa Hospital BNCT Center	Japan	2.5	20	Lithium	[15]
National Cancer Center Hospital	Japan	2.5	20	Lithium	[41]
N. N. Blokhin NMRCO	Russia	2.5	10	Lithium	[42]
SARAF	Israel	2.5	20	Liquid-lithium	[43]
Xiamen Humanity Hospital	China	2.5	10	Lithium	[44]
Helsinki University Hospital	Finland	2.6	30	Lithium	[36]
Shonan Kamakura General Hospital	Japan	2.6	30	Lithium	[45]
University of Birmingham	United Kingdom	2.6	30	Lithium	[42]
Dongguan People's Hospital	China	2.8	20	Lithium	[46]
Nagoya University	Japan	2.8	15	Lithium	[47]
Dongguan Neutron Science Center	China	3.5	10	Lithium	[48]
INFN LNL	Italy	5	30	Beryllium	[49]
iBNCT	Japan	8	10	Beryllium	[50]
CIAE	China	14	1	Beryllium	[51]
A-BNCT	South Korea	10	8	Beryllium	[52]
C-BENS KURNS	Japan	30	1	Beryllium	[53]
Kansai BNCT Medical Center	Japan	30	1	Beryllium	[54]
STBRC	Japan	30	1	Beryllium	[55]
PC-CANS	**Proposed in Canada**	**10**	**1**	**Beryllium**	[16]

influence on system performance, including neutron moderation and extraction methods. However, after the target, there is still opportunity to optimize the final neutron yield through the clever design of a BSA, consisting of a moderator, reflector, gamma filter, neutron filters, collimator, and protective shielding (Fig. 2). Materials are chosen for the BSA based on their neutron scattering and neutron capture cross section characteristics. The main role of the BSA is to create a neutron beam suitable for BNCT both in terms of energy and flux, based on the desired values outlined in the IAEA-TECDOC-1223 (see Table 2) [21], and to guide them efficiently through the beam aperture and onto the patient in the irradiation room. However, it is important to note that this technical document is mainly referred to for preliminary assessments of beam efficiency and is currently under revision as it was published in 2001 with a focus on the use of reactor-based neutron sources, rather than the accelerator-based neutron sources, which have since emerged as the predominant source of generating neutrons for BNCT. The BSA also serves a role to remove gamma rays and non-useful neutron radiation (fast neutrons and thermal neutrons) contamination to minimize the radiation dose applied to the patient that does not contribute to the boron neutron capture process in the tumor. The design elements of a BSA will vary significantly depending on neutron source and desired beam characteristics for the cancer being treated. For example, while a thermal neutron beam may be suitable for melanomas or superficial

Fig. 2. General schematic of a BNCT treatment facility, including the various parts of a beam shaping assembly that neutrons must pass through as they travel from source to patient.



brain tumors, when applied with a craniotomy, it has poor tissue penetration due to rapid attenuation, and is therefore not appropriate for deep-seated brain tumors [9]. However, an

Table 2. Neutron energy definitions, neutron flux, and gamma ray and fast neutron dose per epithermal neutron values that are desired for BNCT treatments of deep-seated tumors outlined in the IAEA-TECDOC-1223.

Specified BNCT parameter	Defined/desired value
Thermal neutron	<0.5 eV
Epithermal neutron	0.5 eV–10 keV
Fast neutron	>10 keV
Epithermal neutron flux	$>5 \times 10^8$ n/cm^2 s
Epithermal neutron flux/thermal neutron flux	>20
Gamma ray dose per epithermal neutron	$<2 \times 10^{-13}$ Gy cm^2/n$_{epithermal}$
Fast neutron dose per epithermal neutron	$<2 \times 10^{-13}$ Gy cm^2/n$_{epithermal}$

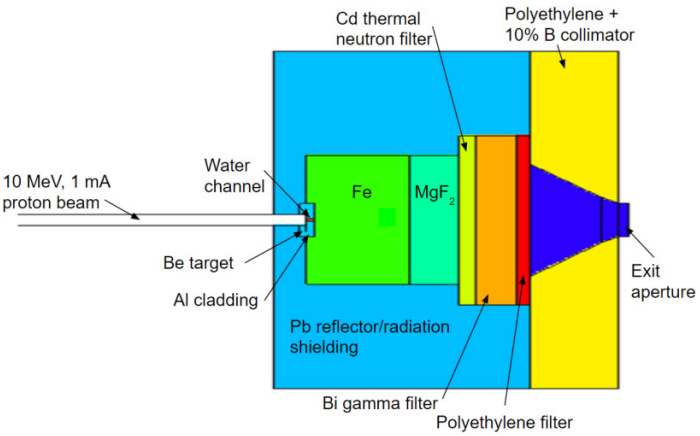
epithermal neutron beam will offer better penetration and achieves a peak thermal neutron flux a few centimetres below the tissue surface as the tissue itself acts as a moderator [56]. Additionally, different BSA designs will be required if neutrons are obtained directly from a reactor core, a fission converter, or accelerator-based sources, with various proton energies and current to account for different neutron energies and fluxes. A well-designed BSA that has been thoroughly tested, with both simulations and physical experiments, is essential for successful BNCT outcomes.

Neutrons produced at the target material can have high energies ranging from 100 keV to approximately 28 MeV [15]. These high-energy neutrons are not suitable for BNCT and must be moderated to <10 keV energies. An ideal moderator material will have a high scattering cross section for high-energy neutrons (fast), a low neutron scattering cross section in the desired energy range (epithermal), and a small neutron absorption cross section to prevent the loss of neutron density and minimize the production of gamma radiation. [39]. Since the cross section of materials can change significantly over higher neutron energy ranges, combinations of materials are commonly used to maintain moderation performance. For example, aluminum (Al), iron (Fe), and nickel (Ni) moderate efficiently in the 10 keV–10 MeV range by elastic scattering, while fluorine (F) moderates efficiently from 10 keV to 5 MeV range due to elastic and inelastic scattering. Therefore, a material like aluminum fluoride (AlF_3) is often used to ensure consistent moderation [57]. Overall, the moderator is a crucial element of the BSA to produce neutrons suitable for BNCT.

All of the neutrons produced at the target material following proton bombardment do not move in a forward, uniform motion, but rather disperse in all directions. To take advantage of these dispersing neutrons and use them to increase the neutron flux in the forward direction, a reflector is installed around the moderator. The ideal properties for a neutron reflector are low absorption cross section, and a high elastic scattering cross section for epithermal neutrons [39]. These properties enable reflectors to have high coefficients of reflection, also known as albedo, for epithermal neutrons, meaning that when neutrons are radiating outwards, away from the beam path and they reach the reflector–moderator interface, they are more likely to be reflected back into the moderator rather than be allowed to continue on their original path [58]. Some common materials used as reflectors are lead and graphite. Heavy elements are typically used as their large mass, relative to that of a neutron, prevent significant reductions in neutron speed from occurring during the elastic collision, thereby maintaining the majority of the neutron's initial kinetic energy [15]. While the neutron reflector does not play a direct role in modifying neutron energies, it is crucial in re-directing scattered neutrons from the target to increase neutron beam intensity.

BSAs are also designed to have filters for thermal neutrons, fast neutrons, and gamma rays to remove harmful radiative contaminants, which improves the neutron beam quality for BNCT. Unlike the moderator, which is designed to slow all neutrons and shift the entire neutron spectrum, these filters have a specialized function that target specific beam components. For example, when deep-seated tumors are treated, a thermal neutron filter should be used. Since these neutrons have poor tissue penetration, they are unlikely to reach the tumor and contribute to the boron capture reaction. Therefore, they increase the total radiation dose applied to the patient while providing no therapeutic benefit. Thermal neutron filters, such as lithium (^{6}Li), boron (^{10}B), or cadmium (^{113}Cd), have very high thermal neutron absorption cross sections (940, 3837, and 19852 b, respectively [30]) compared to other neutron energies, and therefore cause a decrease in the final thermal neutron flux, but allow higher-energy neutrons in the beam to transverse the filter mostly unperturbed [57]. Additionally, since lithium has a higher probability of interacting with epithermal neutrons at the lower end of the energy range (0.5 eV) rather than epithermal neutrons at the higher end of the energy range (10 keV), a lithium filter can act to increase the average epithermal neutron energy with a trade-off of slightly decreasing beam intensity [59]. While the moderator is capable of slowing a significant portion of neutrons to the desired epithermal energy range, often times some fast neutrons remain. To prevent these high-energy neutrons, which do not significantly contribute to the boron capture reaction, from depositing large amounts of unnecessary radiation on the patient, a fast neutron filter is used. Fast neutron filters are commonly composed of iron and aluminum due to the relatively large inelastic neutron scattering cross sections they have at higher fast neutron energy values [15]. In addition to preventing excess

Fig. 3. Cross section of a beam shaping assembly design that incorporates similar materials used in the iBNCT geometry paired with PC-CANS proton beam parameters.



radiation, as fast neutrons are slowed by the filter, they become epithermal neutrons, which results in an increased final epithermal neutron flux [60]. A gamma filter is used to remove any produced gamma ray contamination present in the neutron beam to minimize unnecessary radiation doses. Heavy elements, high-density elements, and high-Z elements are best at shielding gamma radiation, so elements like tungsten, bismuth, and lead are commonly used. In the case of BSA designs, while gamma shielding is an important safety consideration, it should not be implemented to the detriment of the epithermal neutron beam. With this consideration, bismuth is commonly used as a gamma filter as it has good shielding properties and also has a relatively low neutron capture cross section [57]. The use of different materials with special nuclear properties allow specific aspects of the neutron beam to be modified and contaminants removed, and to enable better BNCT standards of care.

The final components of a BSA are the collimator and external radiation shielding. A collimator further reduces undesirable radiation and is required to converge the neutron beam to enable precise targeting of tumor during the BNCT irradiation period. Typically, the circular beam aperture of the collimator has a diameter of 12–14 cm; however, larger size apertures could be used for different types of cancer or large tumors [21]. The collimator usually has a trapezoidal shape and is commonly composed of materials like lead, bismuth, or lithiated/borated polyethylene [57, 60]. While external shielding does not affect the properties of the neutron beam, it is used as a precautionary measure to protect the patient, clinicians, facility staff, and the environment from passive radiation leakage. The collimator is able to act as a radiation shield on the side facing the patient, so lead and concrete are typically used on the top, bottom, and other sides of the BSA to prevent dangerous gamma and neutron radiation escape [57]. Although excessive radiation exposure can have harmful effects, a well-designed BSA will not only deliver the proper neutron dose to the patient but also protect them and others from unnecessary radiation damage.

5. Planned and current facilities

Throughout the various BNCT facilities around the world that have already been built, are under construction, or are just in the planning phase, exist a diverse set of BSAs. These designs, which optimize the neutron beam for BNCT, are rigorously tested and chosen based on proton energy and current at the neutron production source. As such, the accelerator type and target material are important factors that must be considered due to the effect they can have on neutron output. So, although accelerator-based neutron sources offer a variety of benefits for BNCT compared to reactor sources, they do present a new set of variables that must be examined.

In present technology, beryllium (Be) or lithium (Li) is chosen as the target material for low-energy accelerator-based neutron sources. In general, Be is used when proton energies exceed 5 MeV and Li targets are used for proton energies that are less than 3 MeV [61] Cyclotron accelerators are currently being used for clinical trials in two clinics in Japan. In addition to cyclotron technology, other accelerators, such as electrostatic and radio frequency quadrupoles, are being employed in BNCT facilities in Argentina, Japan, Russia, Finland, USA, UK, and Israel [62]. A summary of some BNCT research and clinical facilities that have been constructed, are under construction, or are under development, as well as their proton beam characteristics and target material can be seen in Table 1. Some facilities share the same beam properties as they use a very similar design, or purchase their neutron source from the same company. For example, Helsinki University Hospital, Shonan Kamakura General Hospital, and University of Birmingham all purchased their accelerator-based neutron source from Neutron Therapeutics, while Xiamen Humanity Hospital and the National Center of Adrotherapy Oncology (CNAO) all use a neutron source from TAE Life Sciences. Finally, C-BENS at Koyoto University, Southern Tohoku BNCT Research Center and Kansai BNCT Medical Center either developed their neutron source alongside, or purchased their neutron source from Sumitomo Heavy Industries [45]. Overall, while accelerator-based neutron sources provide many benefits for neutron production in BNCT compared to nuclear reactors, they do have new parameters that must be examined and appropriately chosen.

6. BNCT progress in Canada: prototype Canadian CANS

Since the closure of the National Research Universal Reactor in Chalk River in 2018, there has been a reduction in the availability of neutrons to perform research in Canada. As a replacement reactor would require considerable infrastructure and be expensive, some work has been done to examine an alternative neutron source option, specifically a CANS [16]. A large-scale CANS site would require a significant investment and a lot of planning and time to effectively satisfy all the neutron research needs of Canada. Therefore, in the near-term, a cost-effective proof of concept prototype Canadian CANS (PC-CANS) is being recommended. While this proposed PC-CANS station is designed for general neutron-based research techniques, it would also provide an opportu-

Table 3. Thermal neutron flux, epithermal neutron flux, fast neutron flux, total neutron flux, and epithermal neutron flux/thermal neutron flux measured using PHITS simulations in air conditions at the end of the aperture with the iBNCT beam shaping assembly and PC-CANS proton beam parameters (10 MeV, 1 mA).

Neutron flux	Simulation result
Thermal neutrons	6.73×10^6
Epithermal neutrons	4.27×10^8
Fast neutrons	4.63×10^7
Epithermal neutron flux/thermal neutron flux	63.45

nity to be used as a neutron source to establish a preliminary BNCT facility in Canada. This would be the first of its kind in Canada and would enable pre-clinical research to facilitate future developments. As BNCT research is not the main objective of the site, but rather a supplementary feature, the proton beam parameters and produced neutrons would not be optimized for BNCT. Therefore, to begin research, it would not be as simple as replicating a previously published accelerator-based BNCT design or buying a system from an industry company like Sumitomo Heavy Industries, Hitachi, Neutron Therapeutics, or TAE Life Sciences. Additional work would be required to ensure that BSA is able to moderate neutrons suitable for BNCT, with the proposed PC-CANS proton beam characteristics of 10 MeV and 1 mA average current.

Conducting physical measurements through experimentation is impractical, both in terms of time and money, when designing preliminary BNCT BSA prototypes, therefore computer simulation programs, such as Monte Carlo N-Particle or particle and heavy ion transport code system (PHITS) [63], are used. These Monte Carlo-based programs are the gold standard in the fields of radiation sciences and medical physics for modeling the efficiency of a BSA to attenuate a particle beam to certain specifications without having to construct it physically. Thus far, in collaboration with the University of Tsukuba, preliminary PHITS simulations, using in-house experimental neutron source data, have been performed with the BSA installed at the Ibaraki BNCT (iBNCT) facility [64]. Figure 3 highlights a generalized schematic of the iBNCT geometry and materials used as neutron moderators and filters. The iBNCT BSA design, which has been thoroughly evaluated and has undergone pre-clinical testing, produces compelling results, based on the desired values given by the IAEA-TECDOC-1223 (see Table 2), when combined with the planned PC-CANS proton beam parameters (see Table 3). Of all the BNCT facilities already constructed or planned around the world (see Table 1), the iBNCT facility in Tsukuba, Japan and its BSA was of particular interest to the PC-CANS initiative as they both use a beryllium target for neutron production and operate at similar-scale proton energies, 8 and 10 MeV, respectively. Although the iBNCT facility has an average proton current higher than 1 mA, it would likely only affect the intensity of the achieved neutron flux and not significantly affect neutron moderation performance.

Despite the fact that no previous BNCT research has been completed in Canada, either with simulations or actual neutron sources, significant strides have been made due to the PC-CANS initiative. With proper funding and continued research, Canada could join several other countries in adopting this radiotherapy for the current treatment of head and neck cancers, GBM, malignant melanoma, and the possible treatment of other cancers in the future.

7. Conclusions

BNCT has improved dramatically since the idea was first conceived by Locher in 1936. Often plagued by lackluster and controversial clinical success, research in this field has cycled through periods of high interest to times where it seemed like little progress was being made and major breakthroughs were few and far between. However, due to worldwide interdisciplinary collaboration, including nuclear medicine, pharmacology, oncology, and physics, consistent improvements have been made both in boron delivery agents and neutron production. For example, although BPA and BSH remain the only approved compounds for boron delivery in BNCT, modest research progress has been made with biomolecules. Additionally, significant improvements have been made in the understanding of boron distribution using boron imaging, such as PET with ^{18}F-labeled BPA, allowing for better dose quantification and enhanced treatment planning [22]. Arguably, the most significant development for BNCT in the past couple of decades has been the implementation of CANSs. These CANSs have started a neutron source renaissance as many old reactors begin to close their doors as they are decommissioned. They provide a small, cheap, and easy to license and install neutron source alternative that will enable more research, both pre-clinical and clinical to occur, which will facilitate continuous improvements in BNCT methodologies and patient outcomes.

Furthermore, Canada has had a rich history in the application of neutrons, having been a world leader in material research using neutron beams for over 70 years [65] and in novel cancer therapies, with the world's first cancer treatment with Cobalt-60 radiation taking place at Victoria Hospital (London, ON, Canada) in 1951 [66]. With such a strong history in neutron physics and radiation oncology, BNCT research provides Canada a perfect opportunity to continue this tradition and join other countries at the leading edge of development for an emerging cancer radiotherapy. Through

national scientific collaborations to bring a CANS to Canada, initiatives like PC-CANS provide a great reason to explore the field of BNCT, and determine how an AB-BNCT facility could be established in Canada.

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The authors declare there are no competing interests.

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