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Accelerator-based epithermal neutron sources for boron neutron capture therapy of brain tumors

Thomas E. Blue[1] and Jacquelyn C. Yanch[2]
[1]*Nuclear Engineering Program, Mechanical Engineering Department, The Ohio State University, Columbus, OH;* [2]*Department of Nuclear Engineering and Whitaker College of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA*

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Summary

This paper reviews the development of low-energy light ion accelerator-based neutron sources (ABNSs) for the treatment of brain tumors through an intact scalp and skull using boron neutron capture therapy (BNCT). A major advantage of an ABNS for BNCT over reactor-based neutron sources is the potential for siting within a hospital. Consequently, light-ion accelerators that are injectors to larger machines in high-energy physics facilities are not considered. An ABNS for BNCT is composed of: (1) the accelerator hardware for producing a high current charged particle beam, (2) an appropriate neutron-producing target and target heat removal system (HRS), and (3) a moderator/reflector assembly to render the flux energy spectrum of neutrons produced in the target suitable for patient irradiation. As a consequence of the efforts of researchers throughout the world, progress has been made on the design, manufacture, and testing of these three major components. Although an ABNS facility has not yet been built that has optimally assembled these three components, the feasibility of clinically useful ABNSs has been clearly established. Both electrostatic and radio frequency linear accelerators of reasonable cost (~\$1.5 M) appear to be capable of producing charged particle beams, with combinations of accelerated particle energy (a few MeV) and beam currents (~10 mA) that are suitable for a hospital-based ABNS for BNCT. The specific accelerator performance requirements depend upon the charged particle reaction by which neutrons are produced in the target and the clinical requirements for neutron field quality and intensity. The accelerator performance requirements are more demanding for beryllium than for lithium as a target. However, beryllium targets are more easily cooled. The accelerator performance requirements are also more demanding for greater neutron field quality and intensity. Target HRSs that are based on submerged-jet impingement and the use of microchannels have emerged as viable target cooling options. Neutron fields for reactor-based neutron sources provide an obvious basis of comparison for ABNS field quality. This paper compares Monte Carlo calculations of neutron field quality for an ABNS and an idealized standard reactor neutron field (ISRNF). The comparison shows that with lithium as a target, an ABNS can create a neutron field with a field quality that is significantly better (by a factor of ~1.2, as judged by the relative biological effectiveness (RBE)-dose that can be delivered to a tumor at a depth of 6 cm) than that for the ISRNF. Also, for a beam current of 10 mA, the treatment time is calculated to be reasonable (~30 min) for the boron concentrations that have been assumed.

Introduction

Clinical trials of boron neutron capture therapy (BNCT), on-going in the US, Europe and Japan, will evaluate the safety and efficacy of this modality in the treatment of human tumors. Should these trials prove successful, the development of BNCT into a routine therapeutic modality will then depend, in part, on the availability of suitable neutron sources that are compatible with installation in a hospital environment. A low-energy accelerator-based neutron source (ABNS) has the potential for meeting the requirements for a clinical

BNCT facility. This paper reviews the generation of epithermal neutron fields with ABNSs for the treatment of brain tumors through an intact scalp and skull. An ABNS for intra-operative BNCT and BNCT-enhanced fast neutron therapy (FNT) are discussed in [1,2], respectively.

Accelerators offer a number of potential advantages over reactor-based neutron sources for clinical applications. First, accelerators can be easily turned off when the neutron field is no longer required. This, and the fact that neutrons are not produced via a critical assembly of fissile material, means that licensing and regulations associated with maintaining the neutron source are substantially simplified. Second, the variety of neutron-producing reactions that are accessible to accelerators, allows for a number of neutron energy source spectra to be produced. Consequently, for some accelerator types, a number of clinically useful epithermal neutron fields can be produced by the same accelerator, and the neutron flux energy spectrum of the field can be tailored to the spatial characteristics of a particular patient's tumor. Third, the capital expenses of an accelerator-based BNCT system will be substantially lower than those associated with installation of a reactor system in or near a hospital. And finally, accelerators have been prominent features of radiotherapy departments in hospitals for years; clinicians have a long-standing and comfortable experience with such devices for patient irradiation. It is likely that accelerator hardware for BNCT irradiations could be sited within an existing radiotherapy room with the addition of extra shielding.

The development of ABNS for BNCT has been underway since the 1980s. The initial activity toward this end began in the United States with work at The Ohio State University, the Massachusetts Institute of Technology, the University of Missouri, and Idaho National Engineering and Environmental Laboratory [3–9]. Later important contributions were made by researchers at the Georgia Institute of Technology, Lawrence Berkeley National Laboratory, and Idaho State University [10–14]. Recently, federal funding for the development of ABNSs for BNCT has been reduced in the United States, and significant advances are being made in other parts of the world [1,15–21], perhaps most notably at the University of Birmingham in the United Kingdom [22–24].

An ABNS for BNCT is composed of a number of components: (i) the accelerator hardware for producing a high-current charged particle beam, (ii) an appropriate neutron-producing target and target heat removal system (HRS), and (iii) a moderator/reflector assembly to render the flux energy spectrum of neutrons produced in the target suitable for patient irradiation. Progress has been made on the design, manufacture and testing of various components of the ABNS, and upon component subparts. Although a facility has not yet been built which has physically assembled all the parts in their optimum configuration, clinically useful accelerator-based neutron fields are clearly feasible.

The bulk of the early effort in accelerator-based BNCT was devoted to the design and testing of moderator/reflector assemblies to determine if neutron fields having the desired characteristics for patient irradiation could be generated. Development of the accelerator hardware and the target and target HRS are not as advanced. The following document describes the progress that has been made with respect to the various ABNS components. Trade-offs that have been made in total ABNS design will be identified, and a number of design options that may be made in the future will be discussed.

Accelerators for BNCT

A small number of accelerator types have been proposed as potential candidate accelerators and low-current versions of some of these accelerators have been used for evaluation of various moderator/reflector designs. However, the consensus among accelerator engineers and physicists is that there is no technical reason that machines capable of generating the currents needed to deliver therapy in reasonable times could not be built. That is, the limitation is financial and not technical [25].

Cyclotrons

Accelerators can generally be classified as being linear or recirculating. A cyclotron is an example of a recirculating accelerator. Recirculating accelerators can be very compact, efficient and cost effective, because a particle is accelerated through the same accelerating structures many times, gaining energy incrementally with each traversal of the structure, until it achieves the desired energy and is extracted. The advantages that are achieved by repeatedly using the same accelerating structures in a recirculating accelerator do not come without disadvantages. Among the disadvantages is that recirculating accelerators are generally limited to lower beam currents than linear accelerators. Also, the magnet systems, which are necessary for recirculation, can be large, expensive, and power consuming, and particle extraction can be difficult.

The recirculating accelerator, which is of a physical size to be useful in hospitals for BNCT, is the cyclotron. Indeed, cyclotrons are presently used in hospitals for the production of positron-emitters and for fast neutron radiation therapy. Both these applications require charged particle beams of higher energy, but significantly less current, than beams that are thought to be optimum for an ABNS for BNCT. Generally speaking, the combination of accelerated particle energy (a few megaelectronvolt) and beam current ($\sim$10 mA) that is required for BNCT is far from the conventional operating regime for cyclotrons. Thus, cyclotrons are unlikely candidates as accelerators for accelerator-based BNCT. However, as previously discussed, cyclotrons that are used for FNT can be used for BNCT-enhanced FNT, without modification. Only the accelerator target needs to be modified [2].

Linear accelerators

Linear accelerators can be classified as being electrostatic linear accelerators or radio frequency (rf) linear accelerators. As the name implies, in an electrostatic linear accelerator, the charged particle beam is accelerated by an electrostatic field. In contrast, in an rf linear accelerator the charged particle beam is accelerated by a time-varying induced electric field.

Electrostatic linear accelerators

Electrostatic linear accelerators are generally well suited to physics investigations with various low-energy charged particles, because electrostatic linear accelerators can be used to accelerate particles of various charges and masses to various energies. An example of an electrostatic linear accelerator is the Van de Graaff accelerator, which for many years was the accelerator of choice in many physics departments across the country. More relevant to the discussion at hand is the electrostatic accelerator that has been built for BNCT research in the laboratory for accelerator beam applications (LABA) at The Massachusetts Institute of Technology (MIT) [26]. The LABA accelerator has proven to be an excellent tool for evaluating the usefulness of various charged particle target reactions for BNCT at various particle energies. It is built in a tandem configuration, which means that negative ions are accelerated from the ion source (which is held at ground potential) to a stripping foil (which is held at positive potential). At the stripping foil, the accelerated negative ions are stripped of their electrons, leaving positively charged ions, which are further accelerated to the target which, like the source, is held at ground potential. The accelerating potential is generated in a Van de Graaff accelerator by physically transporting charge on a moving belt. The charging structure for the LABA accelerator is more modern and compact and comprises two assemblies of aluminum electrodes separated by insulators. The LABA accelerator has generated beam currents exceeding 1 mA at a proton energy of 1.5 MeV [27]. This accelerator is of a compact and lightweight design; modifications rendering the design capable of generating a combination of beam currents and energies that are sufficient for clinical BNCT are not expected to lead to significant increases in either size or weight of the device.

The tandem configuration is advantageous in that for the same electrostatic potential, the accelerated beam energy is twice what it would be if the accelerator were not set up in a tandem configuration. Also, the ion source is at ground potential. A potential disadvantage of the tandem configuration is the limited lifetime of the stripping foil at high beam currents. For example, for the LABA accelerator approximately 2–70 mA-h of negative ions can strike the stripping foil before it must be replaced. The LABA accelerator uses a carousel containing 82 foils that can be moved into place. A more general disadvantage of electrostatic accelerators is that they can suffer from electrostatic breakdown, which is exacerbated for proton accelerators by counterstreaming electrons (electrons that travel in the opposite direction as the protons in the beam). Counterstreaming electrons not only induce breakdown, but also increase the current that must be supplied by the charging structure to maintain the accelerating potential. At LABA, this problem has been solved by the LABA accelerator's tandem configuration and by the use of tiny permanent magnets placed on the accelerating electrodes so that electrons are swept out of the beam before they can contribute to a substantial loss of current.

The possibility of electrostatic breakdown resulting from counter-streaming electrons can also be mitigated by increasing distances between differently charged structures in electrostatic linear accelerators. This approach has been adopted by the designers of an electrostatic quadrupole (ESQ) accelerator at Lawrence Berkeley Laboratory (LBL) that at one point in time was being refurbished for BNCT [12]. In addition to making the ESQ accelerator large, in this accelerator, ESQ focusing is used to limit the beam diameter throughout the length of the accelerator and to inhibit counterstreaming electrons. This is especially important for the ESQ, because it is not built in a tandem configuration. Because it does not employ stripping foils, it is suitable for prolonged operation at high currents. This accelerator has been estimated as ultimately being capable of accelerating up to 50 mA of 2.5 MeV protons. However, it is huge. It is housed within a tank that is 2.4 m in diameter and 6.1 m in length. In fairness to this accelerator type, it must be said that a 2.5 MeV proton ESQ-accelerator that would be built especially for BNCT could be more compact, with tank dimensions of 2–3 m diameter and 3 m length [12]. However, in comparison to the LABA accelerator that has a tank that is only 1.0 m in diameter and 3.0 m in length, such an accelerator would still be large.

Finally, a Dynamitron linear electrostatic accelerator has operated at the University of Birmingham at an energy of 2.8 MeV with a current of 1.25 mA. Clinical BNCT is planned for this accelerator. As we shall discuss in later sections of this paper, decreased neutron field quality can be traded off for shorter treatment times, or alternatively, lower beam current requirements. The Birmingham neutron field is included in our assessment of field quality for various ABNS designs, so that the reader can understand the tradeoffs that have been made at the University of Birmingham in this regard.

Rf linear accelerators

In rf linear accelerators, the charged particles are accelerated by an induced electric field, which varies in space and time. Rf linear accelerators are constructed so that the space-time behavior of the electric field that is experienced by the accelerated particles is always of one sign. This synchronization must exist along the length of the accelerator, and since the relationship between particle position and time depends on particle mass and charge, rf linear accelerators are designed to accelerate a particular species of ion to a particular output energy. Therefore, rf linear accelerators are not appropriate for evaluating various charged particle-target reactions for BNCT, as has been done at LABA. However, rf linear accelerators may be very appropriate for clinical BNCT, once an appropriate charged particle and charged particle energy has been identified.

An advantage of rf linear accelerators is their compact size and potential for high current operation. Since the electric field strength for breakdown is much larger for the high frequencies at which rf linear accelerators operate than for electrostatic operation, rf linear accelerator can generally be made smaller than electrostatic accelerators for the same particle energy and peak current. However, the operating costs for rf linear accelerators exceed the operating costs of comparable electrostatic accelerators, due to the rf linear accelerators' larger power consumption. Their power consumption is larger, because power must be supplied to the rf accelerator, not only to accelerate the beam, but power must also be supplied to drive the rf currents in the accelerating structure, which induce the accelerating electric field. These currents lead to ohmic heating, which is a mechanism for power loss.

Efforts are underway to build and test an rf accelerator, that is designed specifically for BNCT. The proton linac that was first recognized as being capable of fulfilling the requirements on particle energy and beam current for an ABNS for hospital-based BNCT is the radio frequency quadrupole (RFQ) [28,29]. It has been demonstrated, at appropriate particle energies, that RFQs can produce peak currents that exceed the demands for average current for clinical BNCT. These demonstrations of peak current capability have been made, for the most part, for pulsed mode operation, with low duty factors (fraction of the time the beam is on).

While demonstrations of peak current capability, which exceed 10 mA for operation in pulsed mode, provide convincing evidence for the scientific feasibility of continuous (cw) operation at currents greater than 10 mA, the extension of the RFQ linac structure to cw operation is a challenging endeavor. CW operation at currents larger than 10 mA has been accomplished in only a few research-oriented projects [30,31], none of which involved a commercially viable accelerator for hospital-based BNCT. A small and inexpensive rf accelerator is needed for BNCT, which meets, but does not greatly exceed, the needs for BNCT. Such an rf accelerator, named the accelerator based epithermal neutron source (ABENS), is under development at Linac Systems [32]. The ABENS accelerator combines an RFQ linac structure in series with an rf quadrupole focused rf drift tube (RFD) linac structure. The RFD linac structure is designed specifically to increase the acceleration efficiency, and thereby reduce the rf capital costs and the operational costs for linac structures in the few-MeV range. At an approximate cost of \$1.5 M, the ABENS accelerator is designed to be 0.6 m in diameter and 3 m in length, with a weight of about 1500 kg and is expected to produce a 10 mA beam of 2.5 MeV protons.

Target and target HRSs

Targets

Design and development of targetry for BNCT requires a balance of neutronic, mechanical, and thermal considerations. Above all targets must produce a sufficient number of neutrons when irradiated by a suitable ion beam. The charged particle beam striking the target should be as large as possible to spread the heat load, but still must remain small enough to limit losses of those neutrons generated near the edges of the target. Because the charged particle beam generates heat as it is stopped in the target material, a target HRS must be designed which keeps the target cool and mechanically stable. This entire target and cooling assembly must be integrated into the moderator/reflector assembly without adversely affecting the neutron field either by reducing the flux or by altering the desired neutron energy spectrum.

Table 1 lists properties of several neutron-producing charged-particle reactions proposed for use in accelerator-based BNCT. The bulk of the effort devoted to designing moderator/reflector assemblies for BNCT has concentrated on the ^{7}Li(p,n)^{7}Be reaction at bombarding energies of approximately 2.5 MeV. Neutron production from this reaction is high and the relatively soft (low-energy) spectrum requires less moderation than those generated in other reactions. Smaller moderator lengths usually translate to fewer neutron losses via leakage and solid angle effects, and consequently a larger fraction of the neutrons produced in the reaction is available for use at the patient position. Investigators have studied if there are advantages in either increasing or decreasing the proton energy above or below 2.5 MeV [6,9,11,14,15,24]. References [14,15] establish that neutron field quality is poor just above threshold in comparison with the field quality that can be obtained for reasonable proton beam currents at 2.5 MeV. Otherwise, there is no consensus with regard to operating at energies that are either slightly below or slightly above 2.5 MeV [11,24].

Unfortunately, while the ^{7}Li(p,n)^{7}Be reaction is excellent neutronically, the mechanical, chemical, and thermal properties of lithium metal make it a poor candidate for a target. As shown in Table 1, the melting point of pure lithium metal is low; the risk of target failure is thus high although designs based on an operating liquid lithium metal target are possible. These are most feasible with vertically-oriented beams. Another difficulty with lithium is its poor thermal conductivity, which means removal of heat from the target is inefficient, further jeopardizing target integrity. And finally, lithium is a very reactive metal, forming compounds immediately upon exposure to air. Fabrication of a pure metal target must be performed in an inert environment allowing no contact with air as the target is formed, placed in the cooling configuration and installed on the accelerator beam line.

Investigators have studied the potential of alternate targets [6,10,21,33,34]. Use of beryllium and carbon targets overcomes these difficulties in manufacture and cooling. Melting points are much higher and thermal conductivities are superior to lithium. Neutronically, however, use of Be or C represent a compromise since, at the bombarding energy required to generate the same neutron yield as observed with the ^{7}Li(p,n)^{7}Be reaction, the average neutron energy is much higher. Thus, more extensive moderators are required, which leads ultimately to fewer neutrons per unit accelerator current at the patient position.

Table 1. Characteristics of four charged-particle reactions considered for accelerator-based boron neutron capture therapies

Reaction	Bombarding energy (MeV)	Neutron production rate (n/min-mA)	Calculated average neutron energy at 0° (MeV)	Calculated maximum neutron energy (MeV)	Target melting point (°C)	Target thermal conductivity (W/m-K)
^{7}Li(p,n)	2.5	5.34×10^{13}	0.55	0.786	181	85
^{9}Be(p,n)	4.0	6.0×10^{13}	1.06	2.12	1287	201
^{9}Be(d,n)	1.5	$1.3 \times 10^{13*}$	2.01	5.81	1287	201
^{13}C(d,n)	1.5	1.09×10^{13}	1.08	6.77	3550	230

*Varies by a factor of three in the literature; this value was determined by comparing simulation and experimental values.

Target HRS design

A number of methods for target cooling have been proposed and examined to greater and lesser degrees. No matter which target or target HRS is considered, the peak heat flux (power per unit area) on the target is an important parameter. One approach to achieving adequate cooling of the target, is to expand the charged particle beam spot size on the target, thereby reducing the heat flux on target. It has been shown that 2.5 MeV protons can be expanded to large diameter with static magnetic elements in beam transport systems [35]. Even if the beam is expanded, target cooling is technically challenging. Target HRSs that are based on (i) submerged-jet impingement [36] and (ii) the use of microchannels have emerged as viable target cooling options [12,14].

Submerged jet impingement
Submerged jet impingement involves the injection of coolant, via one or more nozzles, through a region of the same fluid onto the target backing (the cooled surface which supports the target) or onto the back of the target itself, if the target needs no backing. This approach has been experimentally investigated at MIT LABA using both light water and liquid gallium as the coolant [36,37]. Also, target cooling via submerged-jet impingement has been implemented at the University of Birmingham Accelerator Facility using heavy water as the coolant [38]. Gallium has a number of characteristics that render it superior to water as a coolant for submerged jet impingement. For instance, gallium's much larger thermal conductivity and much higher boiling point mean that heat can be removed from the target backing with gallium at higher heat fluxes than with water as the coolant. Thus, with gallium as the coolant, for a given beam current, the target can be smaller without exceeding the target HRS heat flux capability.

Microchannel HRS
Lawrence Berkeley Laboratory has pioneered the development of a microchannel target HRS for accelerator based BNCT [12]. A microchannel HRS is fundamentally a finned structure with an enhanced area for heat transfer due to the microchannel fins. In the LBL HRS design, coolant passages that are essentially rectangular in cross section, with 0.5 mm width and 6 mm height, are machined at 2.25 mm intervals within the target backing [12]. These coolant passages (microchannels) run across the width of the target backing. The microchannels are arranged in groups of six (creating five fins) with supports between the groups. Due to the nature of the microchannel structure, with its alternating pattern of groups of channels and supports, and because the coolant flow through the microchannel is tangential to the target surface (in contrast to perpendicular to the target surface, as it is for submerged jet impingement), the target can be separated from the coolant by as little as 1 mm, without compromising the target HRS structural integrity. For a lithium target, because the lithium metal is so close to the coolant, the lithium can be maintained below its melting temperature. Consequently, a HRS based on microchannel technology is quite appropriate for solid lithium targets. Although the convective heat transfer coefficient and the heat flux capability may be smaller for a water-cooled microchannel HRS than for a HRS based on submerged jet impingement with gallium, the upbeam surface of the target backing can be maintained at sufficiently low temperatures to prevent the lithium target from melting. As an example, for the LBL design of a microchannel target HRS according to calculations and measurements, the target HRS can maintain a lithium metal target below the lithium melting temperature for beam heat fluxes as large as 6 MW/m^2.

Moderator assembly

The goal of moderator/reflector assembly design is to create a neutron field, which is maximally beneficial to the patient given constraints on accelerator beam energy and current. Since there is no single set of neutron field assessment parameters that is universally accepted, the performance of the various designs of an ABNS for BNCT will be assessed relative to the performance of an ISRNF for BNCT.

Idealized standard reactor neutron field

The neutron flux energy spectrum for the ISRNF has the following characteristics: zero flux for neutron energies below 0.5 eV, zero flux for neutron energies above 10 keV and a neutron flux energy spectrum that varies inversely with neutron energy (a so-called $1/E$ flux energy spectrum) for neutron energies between 0.5 eV and 10 keV. Two additional assumptions are made. One is that the ISRNF is not contaminated with gamma rays. The other is that the ISRNF is perfectly collimated (i.e. neutrons are monodirectional, with a direction of motion which is parallel to the moderator/filter central axis.) The ISRNF is chosen as a standard in an article (by Harling et al.) that reviews fission reactor sources [39], because it very nearly describes the best reactor neutron fields for BNCT. It is important to note, however, that the ISRNF does not represent the ultimate neutron field for BNCT, in terms of field quality. In fact, we shall see later in this paper that some ABNS neutron fields are predicted to be of better quality.

Neutron field assessment parameters

Although there is no single set of neutron field assessment parameters that is universally accepted, there is some commonality among the sets of assessment parameters that are used. First of all, neutron field assessment parameters can be classified as being of two types, in-air or in-phantom. For both types of assessment parameters, there are at least two parameters per assessment parameter set. One of the parameters of the set is an indicator of field quality and the other parameter is an indicator of field intensity. The article by Harling et al. [39] evaluates reactor fields on the basis of in-air parameters, and the interested reader is referred to that article for an example of a set of in-air neutron field assessment parameters. In this article, we will restrict our attention to in-phantom assessment parameters. Two different sets of in-phantom neutron field assessment parameters are used. One set was developed at OSU and the other set was developed at MIT.

The assessment parameters that were developed at OSU are the tumor dose (D_{tumor}) and the treatment time (T) [40]. D_{tumor} assesses field quality. As D_{tumor} was originally developed at OSU, it is the high linear energy transfer (LET) absorbed dose that can be delivered to the tumor without exceeding the tolerance of normal tissue, for irradiation from some particular aspect. T assesses field intensity (or lack thereof). It is the time a patient can be irradiated without exceeding normal tissue tolerance at any point in the brain. The set of neutron field assessment parameters, D_{tumor} and T, has been adopted by others [13], with the modification that D_{tumor} has been generalized to be an RBE-dose (H_{tumor}), which includes a contribution from gamma rays. Although moderator/reflector assembly design work at OSU has been based on maximizing D_{tumor}, while maintaining T at reasonable values [41], we present H_{tumor} results here, in order to be consistent with the work of others, who take credit for gamma-ray dose contributing to the control of gliomas.

The assessment parameters that were developed at MIT for evaluation of ABNS performance include the advantage depth (AD) and some estimate of the total tumor dose rate [26]. The AD assesses field quality. It is the depth at which the tumor RBE-dose equals the maximum allowable RBE-dose to healthy tissue. For any tumor located at depths in tissue less than the AD, the tumor/healthy tissue RBE-dose ratio will be greater than 1. To assess field intensity, the total RBE-dose rate to tumor at a depth in tissue of 4 cm is used.

RBEs, CBE, and boron concentrations

For consistency with the paper by Harling et al. [39], we have assumed that for brain the RBE for photons (RBE γ) is 1.0, the RBE for neutrons (RBE_n) is 3.2, and that the compound biological effectiveness (CBE), the product of the compound factor and the RBE, is 1.35. The RBE's for the tumor are assumed to be the same as those that are listed above. The CBE for tumor is assumed to be 3.8. We have used two sets of boron concentrations in our calculations. One set (15 ppm for normal tissue and 52.5 ppm for tumor) was chosen to match the values that were used in the paper by Harling et al. [39]. The other set (7.5 ppm for normal tissue and 40 ppm for tumor) was chosen to match the values that were assumed in previous work at MIT comparing the performance of alternate targets. Fortuitously, the values for RBEs and boron concentrations, which were used by Harling et al. [39], are consistent with those that were chosen by researchers at the University of Birmingham [24]. However, it should be noted that in their calculations, the Birmingham researchers assumed that the CBE is 1.3 for normal tissue as opposed to the slightly more pessimistic value of 1.35 that is used herein.

Target and moderator/reflector assembly evaluation

Just as there is no single set of neutron field assessment parameters that is accepted as standard, there is no single moderator/reflector assembly that is accepted as best. Apart from the differences in moderator/reflector assembly design that arise from differences in neutron field assessment parameters (such as optimizing D_{tumor} as opposed to H_{tumor}) [42], differences in moderator/reflector assembly design arise as a consequence of different choices which have been made regarding target and bombarding particle type and energy. Also, constraints that are imposed by the available (or hypothesized) accelerator regarding the maximum beam current on target affect the moderator/reflector assembly design. As we have mentioned previously, one can trade-off neutron field quality in favor of operation at a lower beam current.

Comparison of neutron field assessment parameters for ABNS and ISRNF

^{7}Li(p,n)^{7}Be reaction with Fluental/PbF$_2$ moderator/ reflector assembly. Important early contributions to ABNS moderator/reflector assembly design were made at OSU [3,5] and MIT [7,8], where D_2O, aluminum/D_2O mixtures and BeO were investigated as moderator materials in combination with alumina, lithium carbonate, and lead reflectors. Fluental is a patented material with composition AlF_3(69mass-%), aluminum (30mass-%) and LiF [43] that was developed in Finland for reactor-based BNCT. Fluental was first suggested as a useful moderator material for an ABNS by Nigg et al. [44]. It was pioneered at LBL [12] as a moderator material for the ^{7}Li(p,n)^{7}Be reaction. Presently, Fluental is being considered for use at the University of Birmingham with a graphite reflector [24]. At OSU, the moderator/reflector assembly design has evolved (at least temporarily) to consist of a Fluental moderator, which is surrounded by a PbF_2 reflector [41]. Results of calculations are presented below for this moderator/reflector material combination for a moderator, which is 30 cm thick axially and 31 cm in diameter and is surrounded by an annular reflector, which is radially 31 cm thick. The calculations assume that a 10 mA beam of 2.5 MeV protons is perpendicularly, and uniformly, incident on a 25 cm diameter lithium-7 target. Furthermore, the calculations assume that the head phantom, with the boron concentrations that were previously identified (15 ppm for normal tissue and 52.5 ppm for tumor), is irradiated from the superior aspect. The geometry of the moderator calculation is shown in Figure 1. The moderator/reflector assembly materials are assumed to be pure.

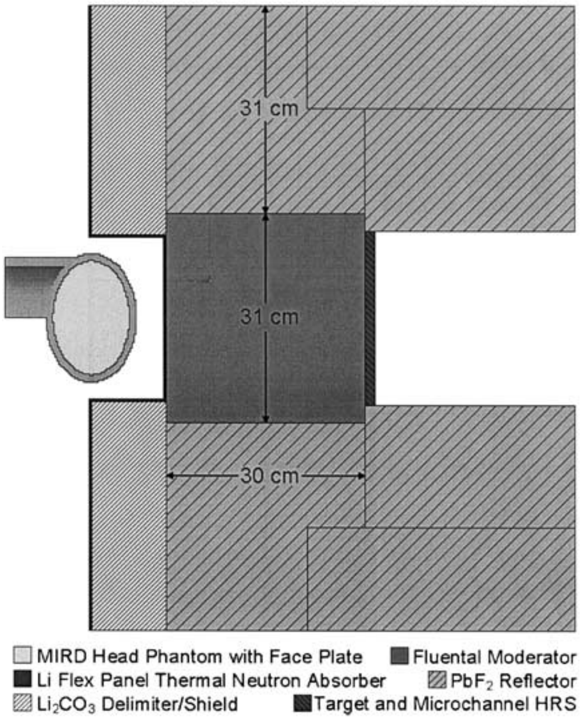

Figure 1. Moderator assembly with a Fluental moderator, which is 30 cm thick axially and 31 cm in diameter and is surrounded by an annular PbF_2 reflector, which is radially 31 cm thick. A 25 cm diameter lithium-7 target and a MIRD head phantom, irradiated from the superior aspect are included in the figure.

Figure 2 shows a comparison of H_{tumor} *versus* depth inside the skull for this ABNS neutron field and for the ISRNF irradiating the same phantom. From the results of this calculation, one can see that the value of H_{tumor} at 6 cm is significantly larger (4100 vs. 3400 RBE cGy) for the ABNS than for the ISRNF. The treatment time, which is the time for which the RBE-dose to normal tissue equals 12.5 RBE Gy (the normal tissue tolerance that is assumed by Harling et al.), is calculated to be 31 min for irradiation in a single fraction. This treatment time could be reduced to 23 min, by reducing the moderator axial thickness to 25 cm. In fact, H_{tumor} would increase slightly if this were done. However, D_{tumor} would decrease, and since D_{tumor} has historically been the optimization parameter at OSU, we choose to compare the ISRNF with a moderator assembly that has been optimized for this field assessment parameter.

With the irradiation geometry that is described above, the quality of the neutron field for an ABNS for BNCT exceeds the quality of the neutron field for the ISRNF. This is in part a consequence of the different neutron energy spectra of the neutron fields for these two neutron sources. It may also be a consequence of the fact that, in the ABNS calculational model, the head phantom is placed within a neutron field delimiter/shield. In this geometry, neutrons can enter the head phantom from its sides. In contrast, for the ISRNF calculational model, the head phantom is irradiated by a disk source in air with neutrons that are perpendicularly incident on the phantom.

The AD that we calculate for the ISRNF is less than that calculated by Harling et al. (8.8 cm vs. 9.6 cm). This may be a consequence of differences in the head

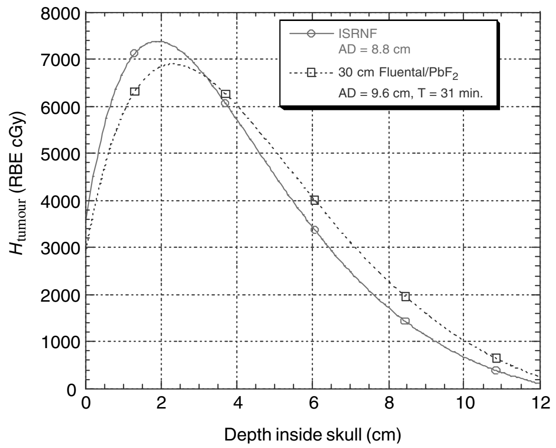

Figure 2. A comparison of H_{tumor} *versus* depth inside the skull for ABNS neutron field with Fluental/PbF_2 moderator/reflector assembly and for the ISRNF irradiating the same phantom. The value of H_{tumor} at 6 cm is significantly larger (4100 vs. 3400 RBE cGy) for the ABNS than for the ISRNF. The treatment time, which is the time for which the RBE-dose to normal tissue equals 12.5 Gy, is calculated to be 31 min for irradiation in a single fraction for a 10 mA proton beam current.

phantom model and irradiation geometry or in neutron kerma factors. However, the comparison of neutron fields (ABNS vs. ISRNF) is generally valid and from the comparison one can conclude that an ABNS can produce a radiation field of better quality than the radiation field for the ISRNF. This conclusion is consistent with the work of others. Wheeler et al. [45] compared the calculated performance of three existing reactor facilities and an ABNS design by LBL called the LBL-ESQ. The basis of comparison was a predicted tumor control probability (TCP). The LBL-ESQ moderator assembly design included a moderator region that was comprised of aluminum and aluminum fluoride. With this moderator material, the TCP for the LBL-ESQ was calculated to be significantly larger than the TCP for the reactor facilities for maximum healthy tissue RBE-doses on the order of 12.5 RBE Gy.

Finally, it should be stated that the Fluental/PbF_2 moderator/reflector assembly that has been analyzed is only a moderator assembly design. Difficulties may be encountered regarding the chemical toxicity of PbF_2 or the expense of moderator assembly materials (at the requisite purity) that demand design modifications. One would hope that in making such modifications only small sacrifices would have to be made regarding the quality of the ABNS neutron field.

Flexible D_2O/graphite moderator/reflector assembly. Moderator assembly material chemical toxicity and cost has been considered in recent neutron field design efforts at the MIT-LABA. In addition, these studies have focused on the design of a flexible moderator/reflector assembly that could be: (1) used with a number of different neutron-producing charged particle reactions and bombarding particle energies, (2) useful for irradiation of larger or smaller tissue volumes, and (3) easily and quickly modified to either harden or soften the epithermal neutron field. The ability to easily modify the flux energy spectrum and thus the penetrability of the neutrons would allow some tailoring of the neutron field for each treatment scenario. For example, a more energetic spectrum might be desired for irradiation of a tumor located deep within the tissue whereas a softer, less-penetrating spectrum would be desirable for sparing deeper tissue when irradiating a tumor near the surface.

A variety of materials used as either moderator/filter or reflector materials in the BNCT community were considered and computer simulation was used to evaluate the dosimetric effect of each combination in an ellipsoidal phantom composed of material that was brain-equivalent from the viewpoint of elemental constituents and mass density. Simulation of the effect of each combination of materials and dimensions was performed for each of the neutron-producing reactions listed in Table 1. Boron concentrations in tumor and healthy tissue were 40 and 7.5 ppm, respectively, and RBE and CBE values assumed were those described above.

The optimization process led to a final design comprising a 20 cm diameter cylindrical D_2O moderator surrounded by an 18 cm-thick graphite reflector (see Figure 3). The moderator length was 27 cm but the neutron-producing target could be moved within the D_2O to effectively reduce the extent of moderation. While heavy water did not consistently out-perform other moderator candidates (such as Fluental or BeO) for all reactions, the flexibility of being able to easily move the target within the moderator was an important consideration. Performance characteristics of the assembly design for each of the four neutron-producing reactions are shown in Table 2. Note that the moderator length in each case is different. As described above, this would be accomplished by moving the target assembly closer to the patient within the heavy water moderator. Also, it should be remembered that the boron concentrations that are assumed for normal

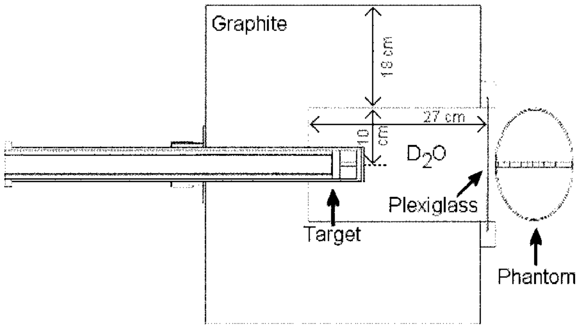

Figure 3. Schematic of MCNP geometry used to compare reflector and moderator materials. The dimensions shown here correspond to the existing LABA assembly. The target material, the moderator diameter, length, and material, and the reflector material were varied in the simulations.

Table 2. Figures of merit using 18-cm thick lead or graphite reflectors with the hardest and softest neutron spectra. Moderation was by a 20-cm diameter cylinder of D_2O of varying lengths. The uncertainties in the figures of merit were calculated by propagating the dose rate uncertainties from the simulations.

Length of D_2O (cm)	Advantage depth (cm)	Tumor dose rate @ 4 cm (RBE-cGy/min-mA)	Ratio of fast and tumor dose rates @ 1 cm
1.5 MeV d-Be, lead reflector			
20	5.3 ± 0.5	13.0 ± 0.5	0.38 ± 0.03
25	6.3 ± 0.8	7.5 ± 0.3	0.28 ± 0.04
27	6.4 ± 1.1	5.7 ± 0.2	0.27 ± 0.04
1.5 MeV d-Be, graphite reflector			
20	5.1 ± 0.2	13.7 ± 0.2	0.35 ± 0.01
25	6.2 ± 0.3	7.5 ± 0.1	0.21 ± 0.01
27	6.1 ± 0.3	6.2 ± 0.1	0.19 ± 0.01
30	6.3 ± 0.4	4.8 ± 0.1	0.14 ± 0.01
2.5 MeV p-Li, lead reflector			
21	9.1 ± 0.2	44.7 ± 0.5	0.041 ± 0.002
2.5 MeV p-Li, graphite reflector			
21	8.3 ± 0.2	44.3 ± 0.5	0.026 ± 0.002

brain and tumor in calculating the entries in Table 2 are different than those that are assumed by Harling et al. [39]. We estimate that correcting for these differences (in order to better compare with the AD for the ISRNF with the standard boron concentrations) decreases the ADs that are shown in Table 2 by a small factor (∼2%).

Orthogonal neutron field. Researchers at the University of Birmingham are attempting to create an ABNS for BNCT using an existing Dynamitron linear electrostatic accelerator that is capable of producing a few milliamperes of proton beam current. Their work is unique because they are attempting to create a clinical facility using an existing accelerator. Consequently, they are faced with constraints on beam current and beam orientation (the beam is directed vertically downward) which challenge their design. They have assumed in their calculations that their accelerator can produce protons with energies up to 3 MeV and beam currents as large as 5 mA [22]. With these limitations, they have optimized a moderator assembly. For ease in patient positioning, and because of concerns about placing the target, target HRS, and moderator assembly above the patient [23], they have investigated the potential for extracting a neutron field with a horizontal center line (with the appellation orthogonal neutron field) from a moderator assembly and target, where the target is bombarded with a vertical beam. With this physical arrangement, they have concluded that a proton beam energy of 2.8 MeV incident on a lithium target is optimum.

Their optimization was performed first with a D_2O/graphite moderator/reflector assembly [23], and more recently with a (AlF_3/Al/LiF)/graphite moderator/reflector assembly [24]. With the (AlF_3/Al/LiF)/graphite moderator/reflector assembly the advantage depth is calculated to be 8.0 cm. The treatment time is calculated to be 164 min for treatment in a single fraction with a beam current of 1 mA. For larger beam currents, the treatment time would decrease in proportion to the reciprocal of the beam current. In particular, one can see that for a beam current of 10 mA (as assumed in calculations at OSU), the treatment time would be only 16 min. This treatment time is less by about one-half than the corresponding treatment time (31 min) as calculated by researchers at OSU for the Fluental/PbF_2 moderator assembly that is shown in Figure 1 for a lithium target bombarded with 2.5 MeV protons. It is unclear whether the differences in the AD (8.0 cm vs. 9.6 cm) and treatment time are a consequence of differences in the neutron field geometry relative to the proton beam (orthogonal vs. collinear), differences in reflector materials, or differences in moderator axial thickness. Also, differences in the AD and treatment time may be due to differences in the calculational models (such as phantom geometry and orientation and kerma factors). However, the general trend is one that has been experienced by all ABNS researchers: as one reduces the millampere-minutes of beam on target that is required for therapy, then the quality of the neutron field is decreased.

Conclusion

In conclusion, through the efforts of a number of investigators, progress has been made towards the development of an ABNS for BNCT. In addition to studies which have been undertaken for 2.5 MeV protons incident on a lithium target, studies have been undertaken to investigate the potential for using other targets, such as beryllium, with protons and other projectile particles, or a lithium target with incident protons of greater or lesser energies. The studies that have been undertaken have gone beyond simple analyses of particle yield, and neutron and photon transport through moderator assemblies. Analyses have begun to consider the ABNS system as a whole, with attention being paid to capabilities and costs of accelerators, target and target HRSs, moderator assemblies, and the resulting neutron field quality and intensity. It appears, through the accumulated results of the various researchers, that a number of rather small design windows exists where an ABNS can be built for reasonable cost, which will generate a neutron field of sufficient intensity for clinical treatment of brain tumors with BNCT. In particular, for 2.5 MeV protons incident on a lithium target, the quality of the neutron field can be designed to exceed the quality of the ISRNF.

This paper has considered only the potential for building an ABNS for BNCT based on low energy light ion accelerators that are suitable for installation in an existing hospital. We have not included in our considerations the potential of using light ion accelerators that are injectors to larger machines in high-energy physics facilities. Such accelerators are not constrained by limitations on energy, current, size, and cost that limit accelerators that would be suitable for siting in hospitals. Also, we have not considered a concept that may be suitable for siting in hospitals that is based on the production of photo-neutrons by bremsstrahlung X-rays created by electron beams impinging on high atomic number targets in a heavy water filled tank [46].

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Address for offprints: Thomas E. Blue, The Ohio State University, 206 West 18th Ave., Columbus, OH 43210, USA; Tel.: (614) 292-0629; Fax: (614) 292-3163; E-mail: blue.1@osu.edu