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The ^{9}Be(d,n)^{10}B reaction as a neutron source for Boron Neutron Capture Therapy

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A project aimed at the development of an accelerator facility devoted to **B**oron **N**eutron **C**apture **T**herapy (BNCT) is ongoing at the National Atomic Energy Commission of Argentina [1]. In a first stage of development, the accelerator will be capable of delivering proton or deuteron beams of 30 mA at about 1.4 MeV which is suitable for neutron production through the ^{9}Be(d,n) reaction. In this context, deep-tumor treatment capabilities of neutron beams produced by this reaction have been thoroughly studied in the last few years. Our previous studies based on a Snyder head phantom showed very encouraging results for a neutron field produced by bombarding a thin Be target (8 μm) with a 30 mA beam of 1.45 MeV deuterons.

In this work we evaluate the performance of the proposed neutron source for the treatment of a real patient with diagnosed glioblastoma multiforme (GBM). The patient's head with a 4.2 cm^3 tumor within the occipital lobe of the brain was modeled by 11025 voxels from a computed tomography stack. The absorbed dose rate was computed via the Monte Carlo N-Particle code (MCNP) and the neutron beam direction was determined based on the location of the lesion using the NCTPlan code, a treatment planning code widely used in BNCT. The results derived from the simulations were assessed prescribing 11 Gy-Eq as the peak dose to normal brain, according to clinical protocols.

Preliminary results show that a significant peak dose of 47 Gy-Eq can be delivered to the tumor with the proposed scheme in a single-field irradiation of 60 minutes while keeping the average whole brain dose lower than 4 Gy-Eq. These results are comparable to those obtained with the ^{7}Li(p,n)^{7}Be reaction, which provides a better quality neutron field for BNCT. Moreover, the dose performances obtained with the proposed neutron source are comparable to those achieved in reported phase I/II clinical trials.

These promising results strengthen the prospects for a potential use of the ^{9}Be(d,n)^{10}B reaction for BNCT brain tumor treatments and for the implementation of an operational AB-BNCT facility in Argentina in the relatively short term.

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1. Boron Neutron Capture Therapy (BNCT)

Boron **N**eutron **C**apture **T**herapy (BNCT) is a therapy modality for the treatment of diffuse, infiltrating and very radioresistant types of cancer, such as high-grade glioma, melanomas, recurrent head & neck tumors and other pathologies for which there are only palliative, low-effectiveness or mutilating treatments.

BNCT is perfomed in two steps. First, the patient is administered with a compound tagged with ^{10}B, an isotope with a high thermal neutron capture cross section (3840 barn). This compound preferentially accumulates in tumor cells. Then, the patient is irradiated with an intense neutron beam. Ideally, for deep-seated tumors, the neutron beam must be "epithermal", i.e., with an energy of about 10 keV. Epithermal neutrons are moderated as they penetrate the tissues, reaching the tumor with an energy in the "thermal" (i.e., with an energy < 0.5 eV) range. Then, the capture reaction takes place in the ^{10}B-loaded cells, producing high-LET and low-range radiation - an α particle and a ^{7}Li - whose ranges in biological tissues are comparable to the diameter of a cell. Due to the selectivity of the ^{10}B-carrying compound and the short range of these particles, lethal doses are delivered to tumor tissues, without harming significantly the healthy tissues.

The major challenge in BNCT has been the requirement for a highly-selective cell tumor targeting. So far, there are two ^{10}B-carrying compounds that have been used in clinical trials: sodium borocaptate ($Na_2{}^{10}B_{12}H_{11}SH$ or "BSH") and boronophenylalanine or "BPA". Phase I/II clinical trials using epithermal neutrons and one (or both) of these compounds have been carried out since the 1990s in the US, Japan, Europe, and more recently in Taiwan. Encouraging results have been obtained in high-grade glioma and recurrent head & neck tumor treatments. For a comprehensive and up-dated review of BNCT clinical trials and boron delivery agents, see Barth et. al. [2].

Another (and not less important) challenge in BNCT has been the design and development of sufficiently intense neutron sources capable of producing a clean epithermal spectrum. Only nuclear reactors have been used as neutron sources so far. However, **A**ccelerator-**B**ased (AB) neutron sources are more advantageous in many aspects. First, the neutron spectrum from certain nuclear reactions is much softer than the one coming from fission, which make it easier to generate the "ideal" epithermal spectrum, and hence to produce a neutron field of better therapeutic quality. Also, but not least, because of their much lower cost and level of complexity compared to a reactor based facility, and mainly because they permit in-hospital siting.

On this sector, some neutron-producing reactions have been proposed for BNCT [3] (Table 1). Among them, the ^{7}Li(p,n)^{7}Be reaction is excellent neutronically (i.e., produces relatively low-energy neutrons with a significant cross-section) but the mechanical, chemical and thermal properties of metallic Li make it a poor candidate for a high-power target (such as required for AB-BNCT). It is important to point out that proton currents of about 30 mA with an energy of about 2.3 MeV are required to produce a neutron field intense enough to perform a 1-hour irradiation treatment. This means that a power of almost 70 kW must be safely carried away in order to keep the production target solid, which is a non-trivial challenge from a technological point of view. In this sense, neutron-producing reactions from ^{9}Be or ^{13}C are better candidates for a high-power target, due to the much higher melting points and thermal conductivities of these materials.

Reaction	Bombarding energy [MeV]	Neutron Yield [mC^{-1}]	Average neutron energy at $^{\circ}0$ [MeV]	Target melting point [$^{\circ}C$]	Target thermal conductivity [$W.m^{-1}.K^{-1}$]
$^{7}Li(p,n)^{7}Be$	2.3	$5.8\ 10^{11}$	0.34	181	85
$^{13}C(d,n)^{14}N$	1.5	$1.8\ 10^{11}$	1.08	3550	230
$^{9}Be(d,n)^{10}B$	1.5	$3.3\ 10^{11}$	2.01	1287	201
$^{9}Be(p,n)^{9}B$	4.0	$1.0\ 10^{12}$	1.06	1287	201

Table 1: Characteristics of some neutron-producing reactions considered for accelerator-based BNCT

2. $^{9}Be(d,n)^{10}B$-based neutron sources

In the low-bombarding energy range (i.e., deuterons from 1.0 to 1.5 MeV), the $^{9}Be(d,n)^{10}B$ reaction produces a relatively hard neutron spectrum compared to the other reactions listed in Table 1. However, the use of a thin target (i.e., of a few microns) allows eliminating most of the highest energy neutrons from the spectrum. As an example, the neutron spectra from 1.45 MeV deuterons on a thin and a thick target (i.e., target thickness > range of deuterons in beryllium) are shown in Fig.1.

In the spectra of Fig.1, the neutron production below 0.6 MeV belongs to the sixth, seventh and eighth excited states in the residual nucleus ^{10}B; at 5.11, 5.16 and 5.18 MeV respectively. Higher-energy neutrons, belong to the ground and the first five excited states. The group of states at about 5 MeV become energetically accessible at about 1 MeV deuteron energy and are preferentially populated above this threshold [4]. In this condition, most of the energy released in the reaction is spent in exciting the residual ^{10}B while a few hundred keV are available as kinetic energy for the emitted neutron. Therefore, the strong neutron structure at the lowest-energy range of the spectra is produced.

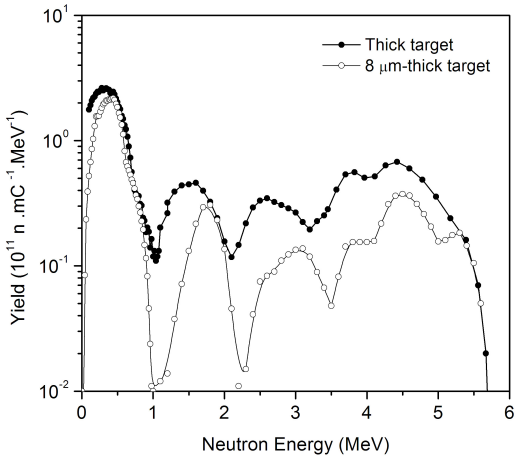

Figure 1: Neutron spectra from 1.45 MeV deuterons on a 8 micron and a thick beryllium target

Due to the energy loss of deuterons, in a thick target most reactions occur at a bombarding energy below the 1 MeV threshold, where in most cases it is only possible to populate the lowest energy states (i.e., to produce high-energy neutrons). In contrast, in the thin target of Fig.1 a

deuteron loses 400 keV at most, and consequently all the (d,n) reactions occur at the bombarding energy range that mostly populates the 5 MeV states. In other words, all the reactions that cannot populate these levels (and hence, most of the highest energy neutrons) are eliminated.

The advantage of using a thin target must be emphasized. The strong contribution of neutrons above 1 MeV energy (present in a thick target) is very difficult to be efficiently epithermalized, without reducing the total neutron flux and/or producing a high fast and thermal contamination after the moderation process. In fact, some authors discarded the use of this reaction for BNCT, due to the high fast neutron contamination produced with a thick target. In this regard, it is important to point out that fast neutrons produce high-LET recoil protons, primarily by scattering on hydrogen present in tissues, which in turn deliver undesirable dose to the healthy tissues. On the other hand, thermal neutrons have a limited penetration depth, not being suitable for deep-seated tumor treatments. A thin target allows reducing considerably the contribution of neutrons above 1 MeV, and hence to improve the therapeutic quality of a ^{9}Be(d,n)-based neutron source for BNCT.

3. Beam Shaping Assembly

An efficient **B**eam **S**haping **A**ssembly (BSA) design is required to produce the epithermal beam. The BSA consisted in a moderating volume made of layers of Al and AlF_3. The moderating volume is delimited by 15 cm thick lead walls, as a neutron reflector. The whole BSA was covered with 4 cm thick natural Lithium Polyethylene (7.5% of Li by weight) as a neutron shielding material. A conical-shaped collimator was added in order to delimit the beam and to facilitate patient positioning. A 30 mA deuteron beam current was considered throughout. A sketch of the BSA design and patient positioning is shown in Fig.2. The length and cross-section of the moderating volume were optimized by means of Monte-Carlo simulations using the MCNP code, in order to obtain the best possible beam quality. The optimization procedure is described in detail in Ref. [5].

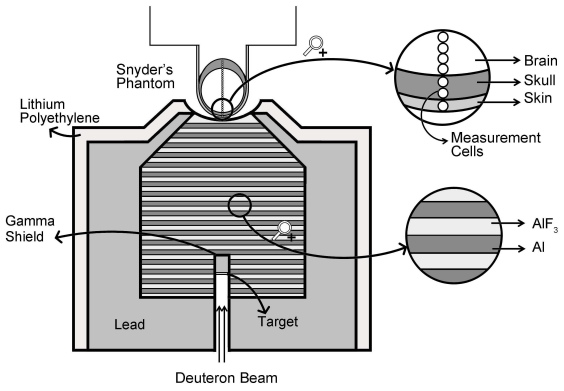

Figure 2: Beam shaping assembly (BSA) considered in this work.

4. Dose calculations and treatment planning assessment for a real glioblastoma case

The treatment planning capability of a neutron source based on a 30 mA deuteron beam of 1.45 MeV on a 8 micron Be target was assessed for a real glioblastoma (GBM) case. For this

purpose, a computed tomography stack image of a patient with a 4.2 cm^3 tumor in the occipital lobe of the brain was considered. The tumor was located at a depth between 2.5 and 3 cm from the skin surface. The computed tomography stack was voxelized using the NCTPlan code [6], and a single neutron field in the posterior-anterior direction was considered. All tissue compositions were taken from the ICRU-46 report, adding the standard boron concentrations to each of them. A standard value of 15 μg/g was adopted for the ^{10}B concentration in blood. ^{10}B concentrations for skin, brain and tumor tissues typically adopted in BNCT [7] are listed in Table 2.

The dose rate in each voxel was computed by means of the MCNP code. In BNCT the total dose is calculated as the radiobiological weighted sum of the boron dose (D_B), thermal and fast neutron doses (D_{ther} and D_{fast}) and the gamma dose (D_γ):

$$D = w_B D_B + w_{ther} D_{ther} + w_{fast} D_{fast} + w_\gamma D_\gamma \tag{4.1}$$

The first component is the dose delivered by α particles and ^{7}Li produced in the boron thermal neutron capture ^{10}B(n,α)^{7}Li. D_{ther} arises primarily from the thermal neutron capture on ^{14}N present in tissues, and D_{fast} stems mainly from neutron elastic collisions on hydrogen, ^{1}H(n,n)^{1}H. The last contribution (D_γ) primarily comes from neutron radiative capture on hydrogen atoms in tissues. The weighting factors for fast, thermal and gamma dose are called Relative Biological Effectiveness' (RBE's). For the boron dose the weighting factor is called Compound Biological Effectiveness (CBE) since it not only depends on the radio-sensitivity of the tissue but also on the applied boron compound and its microdistribution. The adopted weighting factors [8] are listed in Table 2.

Tissue	RBE		CBE	^{10}B tissue-to-blood ratio*
	Gamma	Thermal/Fast neutrons	Boron	
Skin	1	3.0	2.5	1.5
Brain	1	3.2	1.3	1.0
Tumor	1	3.2	3.8	3.5

Table 2: Adopted radiobiological efectiveness', compound biological efectiveness' and ^{10}B concentrations in different tissues. *^{10}B uptake in blood was taken as 15 μg/g throughout.

The treatment planning was assessed setting the maximum dose to normal brain to 11.0 Gy-Eq, which is the maximum tolerable dose to normal brain according to BNCT protocols. At the same time, it was verified that the maximum dose to skin and the mean dose to the whole brain did not exceed the tolerable limits of 16.7 and 7 Gy-Eq respectively. The treatment planning capability of a ^{7}Li(p,n)-based neutron source was also assessed under identical conditions and subjected to the same clinical protocol in order to compare with the proposed ^{9}Be(d,n)-based source.

5. Results and Discussion

Table 3 shows the maximum, mean and minimum doses for tumor and healthy tissues for the proposed GBM case. For comparison, the results obtained with a ^{7}Li(p,n)-based source are included (see Minsky and Kreiner [9]). Doses reported in the phase I/II trials carried out at the

Brookhaven Medical Research Reactor (BMRR) are also included as reference data [8]. The clinical trials at the BMRR included 10 patients diagnosed with a GBM tumor that received a single fraction of BNCT using a single field exposure to the reactor epithermal beam. The RBE's and CBE's are the same as considered for the ^{9}Be(d,n) and the ^{9}Li(p,n)-based sources. The reported ^{10}B uptake in blood ranged from 11.2 to 15.4 μg/g and the tissue-to-blood ^{10}B concentrations were the same as this work. The treatments were carried out prescribing 10.5 Gy-Eq (9 patients) and 13.8 Gy-Eq (1 patient) as the peak dose-equivalent to normal brain. Treatment time and dose per-

Table 3: Maximum, mean and minimum doses for tumor, brain and skin obtained from the treatment planning assessment of the proposed glioblastoma case.

Neutron source	Treatment Time (min.)	Tumor Dose (Gy-Eq)			Normal Brain Dose (Gy-Eq)			Skin Dose (Gy-Eq)		
		Min.	Mean	Max.	Min.	Mean	Max.	Min.	Mean	Max.
$^{9}Be(d,n)^{10}B$	60.4	35.1	42.0	47.2	0.4	3.6	11.0	0.1	3.0	15.4
$^{7}Li(p,n)^{7}Be^{\ddagger}$	38.5	37.0	45.0	51.8	0.5	3.4	11.0	0.2	2.3	13.0
Reference data[§]	45-65	19.8-32.3	*	47.6-64.4	*	1.9-2.6	10.5[†]	*	*	10-16

[‡] 30 mA protons of 2.3 MeV on a metallic Li target (see Minsky and Kreiner [9])

[§] Phase I/II trials on 10 patients at the Brookhaven Medical Research Reactor (see Chadha et. al. [8])

[†] Prescription dose for 9/10 patients. One patient received 13.8 Gy-Eq. * Not reported.

formances obtained with the ^{9}Be(d,n)-based source are comparable to those obtained in the BMRR clinical trials. The mean dose to normal brain is rather higher for the Be case but is still acceptable since it is below the maximum tolerable limit of 7 Gy-Eq. The peak dose to tumor tissue is slightly lower in the Be case, but the value is still acceptable. In this regard it is important to point out that the treatment planning we present here can still be optimized in order to increase this dose. In fact, the neutron field direction was set a priori. A thorough optimization of the patient positioning (also including the use of multiple fields) may improve this dose performance. Preliminary calculations with a Snyder phantom showed that tumor peak doses up to 51 Gy-Eq and up to 57 Gy-Eq are feasible for a similar tumor depth in single and double-irradiation treatments respectively [5].

Compared to the ^{7}Li(p,n)-based source, the treatment time for the ^{9}Be(d,n)-based one is rather longer, due to the relatively low neutron yield ($1.65\ 10^{11}$ against $5.8\ 10^{11}$ neutrons/mC). Nevertheless, the derived value is comparable to those reported for clinical trials, and hence, acceptable. Similar tumor and normal brain doses were achieved with both sources. Moreover, dose-volume histograms (Fig. 3) show a homogeneous tumor dose distribution in both cases.

Skin dose for the Be case is somewhat higher than for the Li one, but the derived value is still within the reference limits. In the Be case, the main contribution to the skin dose is due to boron thermal neutron capture (42%) and fast neutron scattering on hydrogen (36%). Both contributions could in principle be reduced with a thorough BSA optimization.

6. Conclusions

A preliminary evaluation of the brain tumor treatment capability was assessed for a ^{9}Be(d,n)-based neutron source. Encouraging results were obtained for a particular clinical glioblastoma case. Figures of merit regarding homogeneity and doses in tumoral and healthy tissues are comparable to those obtained with a ^{7}Li(p,n)-based source, which produces a more proper spectrum for BNCT. Treatment time and dose in skin are higher in the Be case, but are still comparable to those achieved

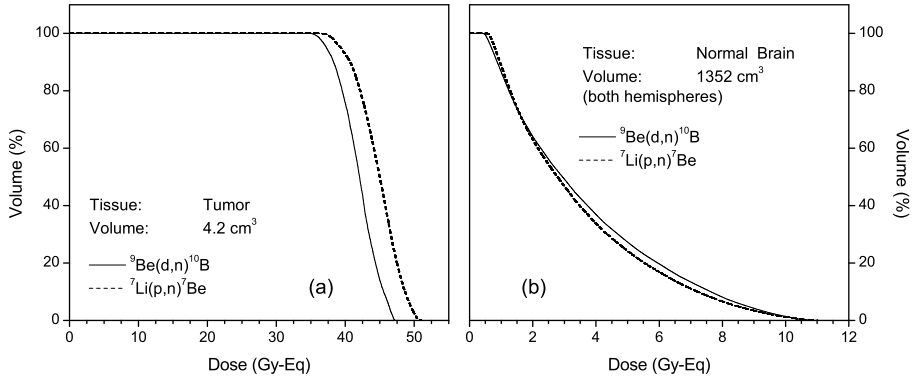

Figure 3: Dose-volume histograms for the proposed GBM case. (a) Tumor (b) Normal brain.

in phase I/II clinical trials at the Brookhaven Medical Research Reactor. A thorough optimization of the beam shaping assembly and patient positioning including the use of multiple fields would improve dose performances and remains as a future work.

Finally, it is important to point out that the design and construction of a high-power target (as required for AB-BNCT) is one of the most important challenges in the implementation of fully operational AB-BNCT facility. The suitable thermal and mechanical properties of Be compared to other target materials allows avoiding most of the complications in this matter. The good treatment capabilities obtained here strengthen the prospects for a potential use of a Be target, and hence, the prospects for the implementarion of a AB-BNCT facility in a relatively short term.

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