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Logic Estimation of the Optimum Source Neutron Energy for BNCT of Brain Tumors

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ABSTRACT

BNCT is very complicated technique; primarily due to the complexity of element composition of the brain. Moreover; numerous components contributes to the over all radiation dose both to normal brain and to tumor. Simple algebraic summation cannot be applied to these dose components, since each component should at first be weighed by its relative biological effectiveness (RBE) value. Unfortunately, there is no worldwide agreement on these RBE values. For that reason, the parameters required for accurate planning of BNCT of brain tumors located at different depths in brain remained obscure. The most important of these parameters is; the source neutron energy.

Thermal neutrons were formerly employed for BNCT, but they failed to prove therapeutic efficacy. Later on; epithermal neutrons were suggested proposing that they would be enough thermalized while transporting in the brain tissues. However; debate aroused regarding the source neutrons energy appropriate for treating brain tumors located at different depths in brain. Again, the insufficient knowledge regarding the RBE values of the different dose components was a major obstacle.

A new concept was adopted for estimating the optimum source neutrons energy appropriate for different circumstances of BNCT. Four postulations on the optimum source neutrons energy were worked out, almost entirely independent of the RBE values of the different dose components. Four corresponding condition on the optimum source neutrons energy were deduced. An energy escalation study was carried out investigating 65 different source neutron energies, between 0.01 eV and 13.2 MeV. MCNP4B Monte_Carlo neutron transport code was utilized to study the behavior of neutrons in the brain. The deduced four conditions were applied to the results of the 65 steps of the neutron energy escalation study. A source neutron energy range of few electron volts (eV) to about 30 keV was estimated to be the most appropriate for BNCT of brain tumors located at different depths in brain.

1. INTRODUCTION

BNCT is a cancer treatment modality; that when implemented for treating Glioblastoma Multiform (GBM), a fatal brain tumor; patient is first given a ^{10}B–enriched compound, which is selectively localized in the GBM cells at relative concentration to normal cells ≈ 4:1. The patient's head is then irradiated with a neutron beam. During their passage through the different tissues of the head, energetic neutrons are rapidly thermalized by repeated elastic scattering with nuclei of normal element in tissues, until they end up as thermal neutrons. Thermal neutrons are captured by the ^{10}B nuclei, producing excited ^{11}B nuclei, which disintegrates into α-particles, Lithium-7 ions, and in 93.7% of the reactions; gamma photons.

Though the neutron cross-sections for elements in the normal tissues are several orders of magnitude lower than that for ^{10}B, two of these elements; viz, Hydrogen-1 and Nitrogen-14, are present in such high concentrations that their interactions with neutrons contribute significantly to the total absorbed dose in normal tissues. These reactions are: neutron-proton (n,p) reaction with Nitrogen-14; $^{14}N\ (n\ ,\ p)^{14}C$, and elastic scattering reaction with hydrogen; $^{1}H\ (n\ ,\ n)\ ^{1}H$. The last reaction is a double edged weapon. Since on one hand; it is the main reaction helping thermalization of the epithermal source neutrons. Yet on the other hand; it imposes inevitable extra dose the superficial healthy brain tissues.

The radiobiology of BNCT in brain is not yet sufficiently understood, since the relative biological effectiveness (RBE) values of the $^{10}B(n,\alpha)^{7}Li$ reaction, and of the secondary neutron interactions with normal brain tissue constituent elements; were not yet precisely determined. Accordingly; the optimal energy of source neutrons to be use when BNCT is used for treating brain tumors located at different depths in brain is not yet decisively determined.

2. Theory

In order to describe quantitatively the performance of BNCT, and compare the efficacy of different neutron beams; the following figures of merits can be used:-

Advantage Depth (AD)

AD is defined as the depth in brain at which a tumor would receive a radiation dose that is equal to the *maximum* radiation dose received by healthy tissue.

Thus there are two Advantage Depths: *the minimum AD* and *the maximum AD*. Beyond these depths, the tumor would be expected to receive a smaller dose than the maximum delivered to healthy tissue.

Advantage Depth Dose Rate (ADDR)

ADDR is the equivalent-dose rate to tumor defined at the advantage depth. From the previous definition of AD, the ADDR is the maximum equivalent-dose rate to normal tissue (anywhere in the cranium). The ADDR was developed primarily as a clinically meaningful neutron beam intensity criterion for epithermal neutron beam design studies.

Advantage Ratio (AR)

AR is defined as the ratio of the dose to the tumor over the average dose to the normal tissue, integrated from the head surface to the maximum AD.

The AR is a measure of a particular treatment beam's ability to minimize integral dose to normal brain tissue while effectively treating the tumor.

***Therapeutic Depth (TD)* [(48)]**

TD is defined as depth in brain, at which the tumor dose falls below *twice* the maximum dose to healthy tissue. This is an indicator of how efficient a particular neutron beam would be, in treating deeply seated brain tumors.

***Peak Therapeutic Ratio* [(48)]**

It is defined as the maximum tumor dose over the maximum healthy tissue dose.

Therapeutic Gain (TG) [(38)]

It is defined as the total dose released to the tumor, divided by the maximum dose released to normal tissue. It is a measure of the ability of a neutron beam to minimize integral dose to normal tissues while effectively treating a tumor.

This paper conducted a parametric study of a neutron beam as it is transported from the very superficial layer of a head phantom till its target at a brain tumor. The study sought for the optimum source neutrons energy that should be employed when planning Boron Neutron Capture Therapy (BNCT) for tumors located at different depths inside the brain.

3. MATERIALS AND METHODS

In the present work; an energy escalation study using a hypothetical mono-energetic mono-directional neutron source was conducted. The behavior in a head phantom; of the neutron beam emitted by such source at 65 different energies, was investigated and analyzed using the neutron transport Monte_Carlo code MCNP4B. In conclusion, an estimate of the source neutrons energy range that is presumably optimum for BNCT was inferred.

3.1 The Neutron Source

It is a hypothetical thin disc, 11.8 cm in diameter and 0.04 cm thick; figure 1. The output neutron flux is mono-energetic and mono-directional. The energy of the emitted neutrons was specified by the MCNP4B model.

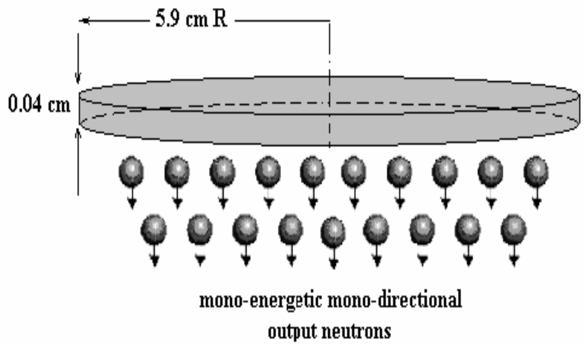
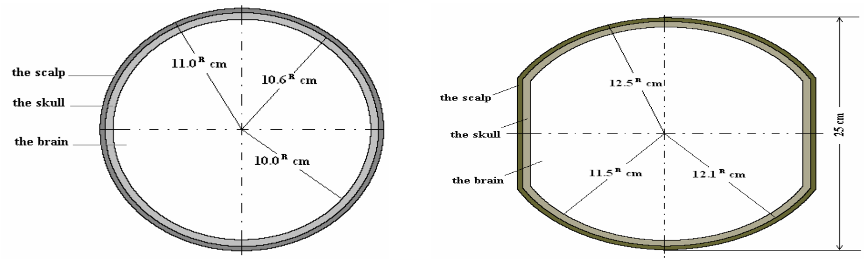


Figure (1): The neutron source.

3.2. The Head Model

It is a barrel shaped volume enclosed by three concentric surfaces. The outer surface is made by the intersection between a sphere (12.5 cm radius) and a cylinder (11.0 cm radius) which axis passes through the center of the sphere; figures 2. Thus, the overall height of the model is 25.0 cm. The intermediate and the inner surfaces are of the same geometrical configuration, but of spherical surfaces radii = 12.1 and 11.5 cm, and cylindrical surfaces radii = 10.6 and 10.0 cm respectively. The *scalp* (the head skin, a layer of 0.4 cm thickness) is represented by the space enclosed between the outer and the intermediate surfaces.



(a) **(b)**

Figure (2): The head model; (a) cross section, (b) and longitudinal section.

The *skull* (the head bones, a layer 0.6 cm thickness) is represented by the space enclosed between the intermediate and the inner surfaces.

The *brain* is represented by the space enclosed by the inner surface. The element composition of the head phantom was taken after the International Commission on Radiation Units and Measurements document (ICRU 46)'s phantom structure for adult head [54].

The neutron source and the head models were assembled as shown in figure 3, being connected via an air-filled "conducting pipe".

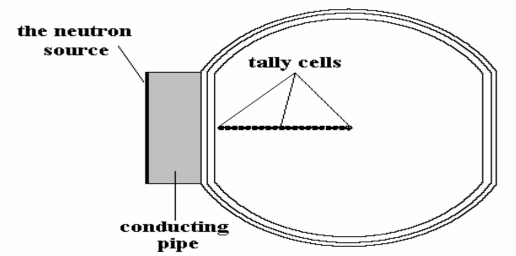
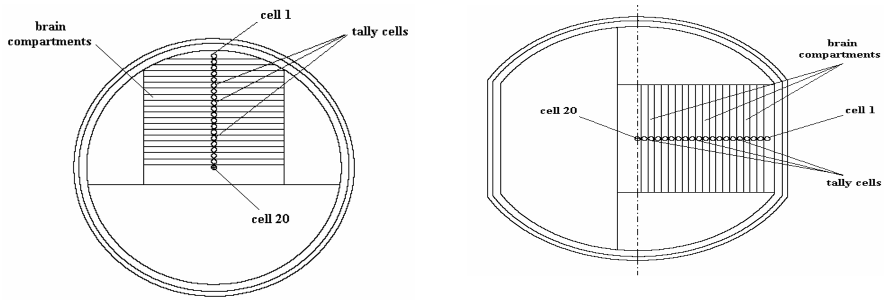


Figure (3): The source-head assembly, showing the tally cells in brain region.



(a) **(b)**

Figure (4): The brain compartments and tally cells; (a) cross section, (b) longitudinal section.

3.3. The MCNP Runs

MCNP runs were conducted, for 65 different source neutron energies. The error for all tallies was kept < 0.05 [58]. The energy boundaries between the arbitrarily called thermal, epithermal, and fast neutrons energies were; 1.484 eV and 1.0825 MeV.

For each MCNP run, the following quantities were tallied: total neutron flux, thermal neutron flux, epithermal neutron flux, fast neutron flux, and total deposited energy.

4. RESULTS AND DISCUSSION

4.1 Postulations on the Source Neutrons Energy

Knowledge regarding the radiobiology of BNCT was used to figure out certain restrictions on the neutron beam behavior in brain, allowing rejecting or accepting particular source neutron energies.

This knowledge can be summarized in the following points:

1. The average neutron capture (n,α) cross-sections of ^{10}B; in the *thermal, epithermal ,* and *fast* ranges of energies are of the orders of: ~1000 barns, ~10 barns [59], and ~1.0 barns [59] respectively.
2. The neutron capture (n,α) cross-section of ^{10}B in the *thermal* and most of the *epithermal* range of energies follows a *1/υ* trend [59].
3. The average neutron cross-sections of the normal elements in brain, in the *thermal* energy range; are typically much less than 1 barn [36], while in the *epithermal* range of energies; are of the order of 10 barns. Among these; ^{1}H and ^{14}N are especially important to consider [59].
4. The summed concentration of ^{1}H and ^{14}N in *normal* brain tissues is of the order of 100,000 ppm, while that of ^{10}B (therapeutically introduced) in *tumor* tissues would be of the order of ~ 40 ppm [30, 54]; i.e. the ratio of concentration of ^{1}H and ^{14}N in *normal* brain tissues, to that of ^{10}B in a *tumor*, would be of the order of ~2000 times.
5. The ^{10}B concentration in *tumor* tissues would be ~ 4 times its concentration in *normal* brain tissues [30].
6. From the definition of the Therapeutic Depth (TD); efficient boron neutron capture therapy (BNCT); necessitates that the equivalent-dose to *tumor* should be at least *twice* the maximum equivalent-dose to *normal* brain tissues elsewhere [48].
7. The Glioblastomas are usually located at 3-7 cm depth inside the brain [49].

From the above considerations; four principal postulations (conditions) on the source neutrons energy and the neutron behavior inside the brain and tumor, were inferred. The results of the 65 MCNP runs were interpreted in lights of these postulations. Those four principal postulations are;

I. The Thermal Fraction of the Total Neutron Flux at Tumor Depth:

For the $^{10}B(n,\alpha)^{7}Li$ interaction rate in tumor to be *equal* to neutrons interaction rate with other normal elements in brain tissues; especially ^{1}H and ^{14}N; the ratio (R) of neutron flux triggering the ^{10}B to the neutron flux triggering ^{1}H and ^{14}N should be;

$$R \approx \frac{10 \times 10}{0.004 \times 1000} \approx 25$$

where;

10: is an approximate concentration of the most neutron-active elements in brain,

10: is an average value for neutron cross-sections of the most neutron-active elements in brain, at *epithermal* range of energies,

0.004: is the ^{10}B concentration (g/100g), in tumor, and;

1000: is the average (n,α) cross-section of ^{10}B in the *thermal* range of energies

Yet; the RBE.s of the heavy charged particles products of $^{10}B(n,\alpha)^{7}Li$ reaction are; at least; *two times* the RBE.s of products of neutrons interactions with ^{1}H and ^{14}N [(64)]. Then; it could be stated that for $^{10}B(n,\alpha)^{7}Li$ equivalent-dose to tumor, to be as *equal* as the [^{1}H + ^{14}N] equivalent-dose (to tumor and nearby tissues), the ratio (R) at the tumor depth; should be ~ *10* (≈25÷2). That's; the thermal fraction of the total neutron flux at tumor depth should be ≥ 0.9.

The first condition on source neutron beam can be formulated as that; *Source Neutrons Energy Should Satisfy that; at Tumor Depth the Thermal Fraction of the Total Neutrons Flux; Should be ≥ 0.9*

Figures 5 (a-d) present plotting for the thermal fraction of the total neutrons flux at different depths in brain; for the 65 source neutrons energies screened. The source neutrons energy range where the mentioned fraction was ≥ 0.9 is specified.

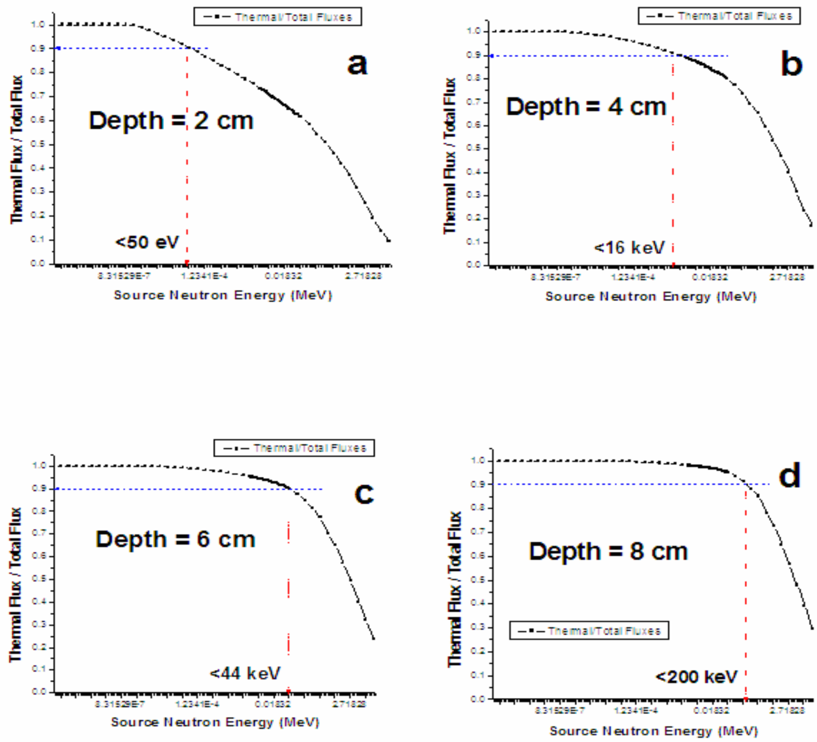


Figure 5 (a-d): The thermal fraction of the total neutrons flux, for the 65 source neutrons energies screened; at different depths.

II. The Ratio of Thermal Neutron Flux at Tumor to the Maximum Thermal Neutron

Flux Anywhere else in Brain (Y)

Ostensibly; this ratio (Y) should be ≥ 0.5, so that when corrected by the factor of *4x* (the relative concentration of ^{10}B in *tumor* to that in *normal* brain tissues); the $^{10}B(n,\alpha)^{7}Li$ interaction rate at tumor site would be at least *twice* its value anywhere else in brain. However; investigating the thermal neutron flux tallies of the 65 MCNP runs, it is found that; for all source neutron energies; the thermal neutrons flux's energy *distribution* and *intensity* were space (depth) dependent. This implies that $^{10}B(n,\alpha)^{7}Li$ interaction rate at a point; would be a function of the *integral intensity* of thermal neutron flux, but also of its energy *distribution* at that point.

Figure 6 illustrates an example for the above fact. It shows that for a source neutron energy of 10 keV; the thermal neutron flux is *softer* (more thermal) at depth = 7 cm than it is at depth = 3 cm. Similar facts could be demonstrated for the entire 65 source neutron energies screened. Recalling that the neutron cross-section of the $^{10}B(n,\alpha)^{7}Li$ reaction follows a *1/v* trend [(59)]; it could be inferred that the *average* $^{10}B(n,\alpha)^{7}Li$ thermal neutron cross-section is *directly proportional* to *depth*, for *all* source neutrons energies.

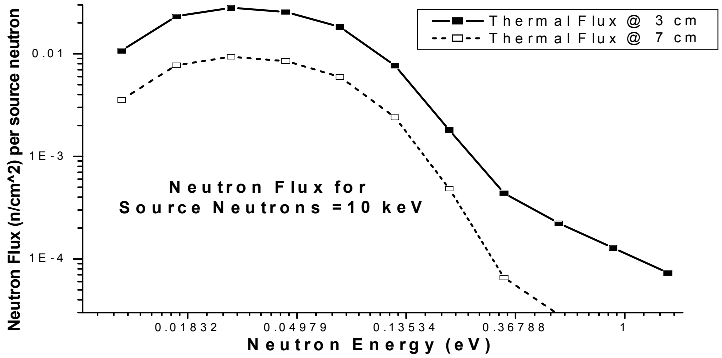


Figure (6): Thermal neutron fluxes' energy distribution at depths of 3 & 7 cm in brain for source neutrons energy = 10 keV.

However; results of the 65 MCNP runs conducted, demonstrated that the *integral intensity* of *thermal* neutron flux; is generally *inversely proportional* to *depth;* figure 7.

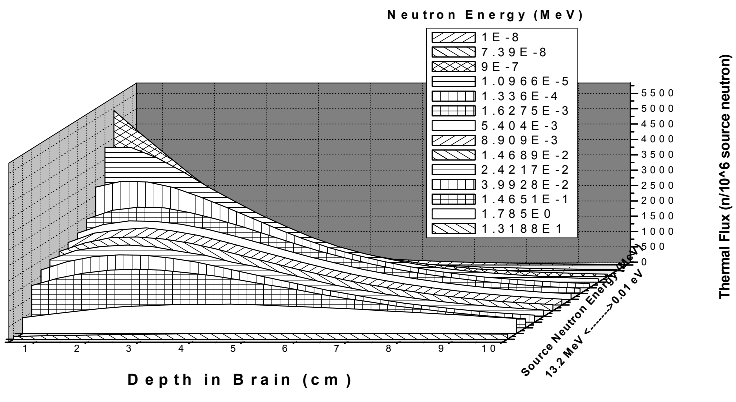


Figure (7): Thermal neutron fluxes at different depths in brain, for different source neutrons energies.

As illustrated in figure 7; the above fact holds valid for all depths beyond 2.0 cm. Recalling that Glioblastomas are usually located at 3-7 cm depth inside the brain [49]; it can be affirmed that; for all brain depths of concern regarding GBMs, the integral intensity of thermal neutron flux is inversely proportional to depth. This guarantees that the *average* $^{10}B(n,\alpha)^{7}Li$ cross-section would always be *greater* at *tumor* depth than it is at the depth in brain where the thermal neutron flux is *maximum*. This palliates the condition of ($Y \geq 0.5$). Consequently; a figure of ($Y \geq 0.25$) proves acceptable.

In conclusion; the second condition on source neutron beam can be formulated as that;

The Ratio of Thermal Neutrons Flux at Tumor Depth to the Maximum Thermal Neutron Flux Anywhere else in Brain; Should be ≥ 0.25

Figures 8 (a-d) present plotting for the ratio between the thermal neutrons flux at different depths in brain, and the maximum thermal neutron flux wherever in brain; for the 65 source neutrons energies screened. The source neutrons energy range where the mentioned ratio was ≥ 0.25 is specified.

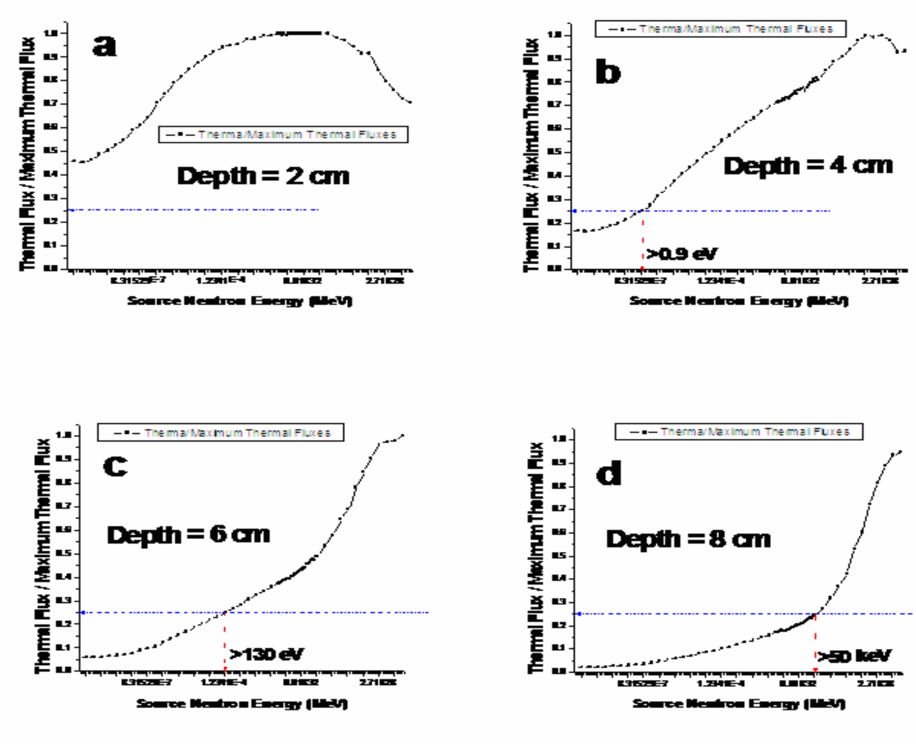


Figure 8 (a-d): The ratio between thermal neutrons flux and the maximum thermal neutrons flux wherever in brain, for the 65 source neutrons energies screened; at different depths.

III. The Ratio of Total Deposited Energy at Tumor to the Maximum Total Deposited Energy

This is the ratio between *total* deposited energy at target *tumor* depth, and the *maximum* total deposited energy anywhere else in *brain*; (E_d/E_{max}). There is not yet a global convention regarding the RBE-values for the various forms of radiation contributing to the total radiation dose to normal brain tissues and to tumor in BNCT, accordingly it shouldn't be more erroneous to entirely ignore the RBE value than to use ill defined ones.

Figure 9 indicates that the value of total deposited energy is, almost invariably, inversely proportional to depth. So, it shouldn't be expected to get the maximum value of total deposited energy; at tumor depth, which is usually located beyond 3 cm. Rather; the source neutrons energy range at which the ratio (E_d/E_{max}) was maximal for each depth in brain, had been determined; figure 10. These ranges should be good indicators of the source neutron energy range optimal for BNCT.

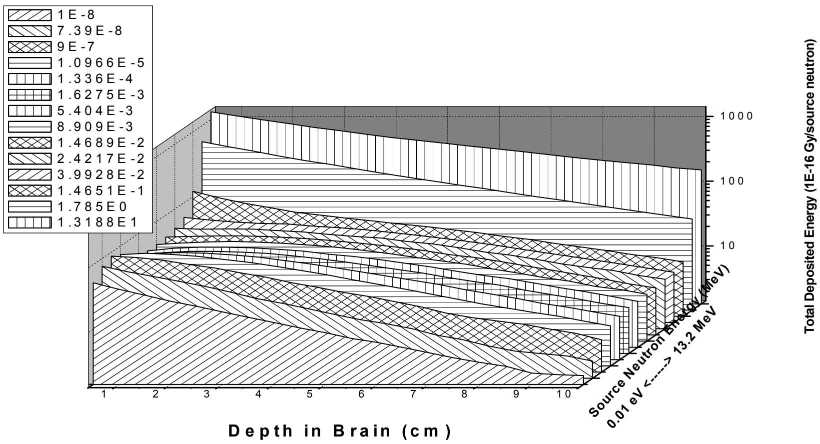


Figure (9): Total deposited energies at different depths in brain, for different source neutrons energies.

In conclusion; the third condition on source neutron beam can be formulated as that;

Total Deposited Energy at Tumor Depth and the Maximum Total Deposited Energy Anywhere-else in Brain; should be Maximal.

Figure 10 (a-d) present plotting for the ratio between the total deposited energy at different depths in brain, and the maximum total deposited energy wherever in brain; for the 65 source neutrons energies screened. The source neutrons energy range where the mentioned ratio was maximal is specified.

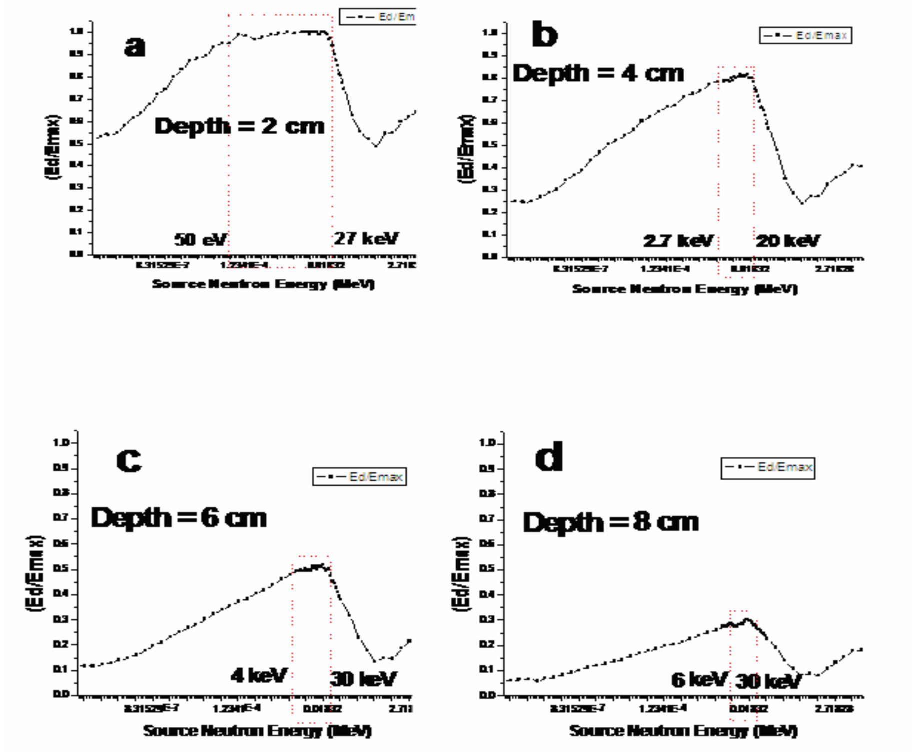


Figure 10 (a-d): The ratio between the total deposited energy (Ed), and the maximum total deposited energy (Emax), for the 65 source neutrons energies screened; at different depths.

IV. Thermal Neutron Flux vs. the Total Deposited Energy at Tumor

Evidently; if the major portion of the *deposited energy* in normal brain tissues and in tumor; were due to the $^{10}B(n,\alpha)$ reaction, then the ratio of the deposited energy (dose) in *tumor* to that in normal *brain* tissues; would be controllable via adjusting the differential concentration of ^{10}B between normal brain tissues and tumor [30].

If the *total deposited energy* plot was following that of *thermal neutrons flux;* then the above condition is believed to have been satisfied. If it wasn't; this should indicate that other than thermal neutrons (i.e. other than the $^{10}B(n,\alpha)$ reactions) are responsible for the major portion of the total deposited energy (dose), which is *undesirable*.

A review of plotting of the thermal neutrons fluxes and the corresponding total deposited energies, at each of the 65 source neutrons energies screened (some are presented in figures 11 [a-f]); would reveal that the curves for the two quantities follow almost the same pattern (i.e. were parallel), at source neutrons energies up to 20 keV. However; at higher energies, the two curves were progressively dissociated; indicating that other than thermal neutrons (i.e. other than the $^{10}B(n,\alpha)$ reactions) were surpassing in energy deposition.

In conclusion; the fourth condition on source neutron beam can be formulated as that;

The Proportion between Thermal Neutrons Flux and Total Deposited Energy All-through the Brain; be Reasonably Constant

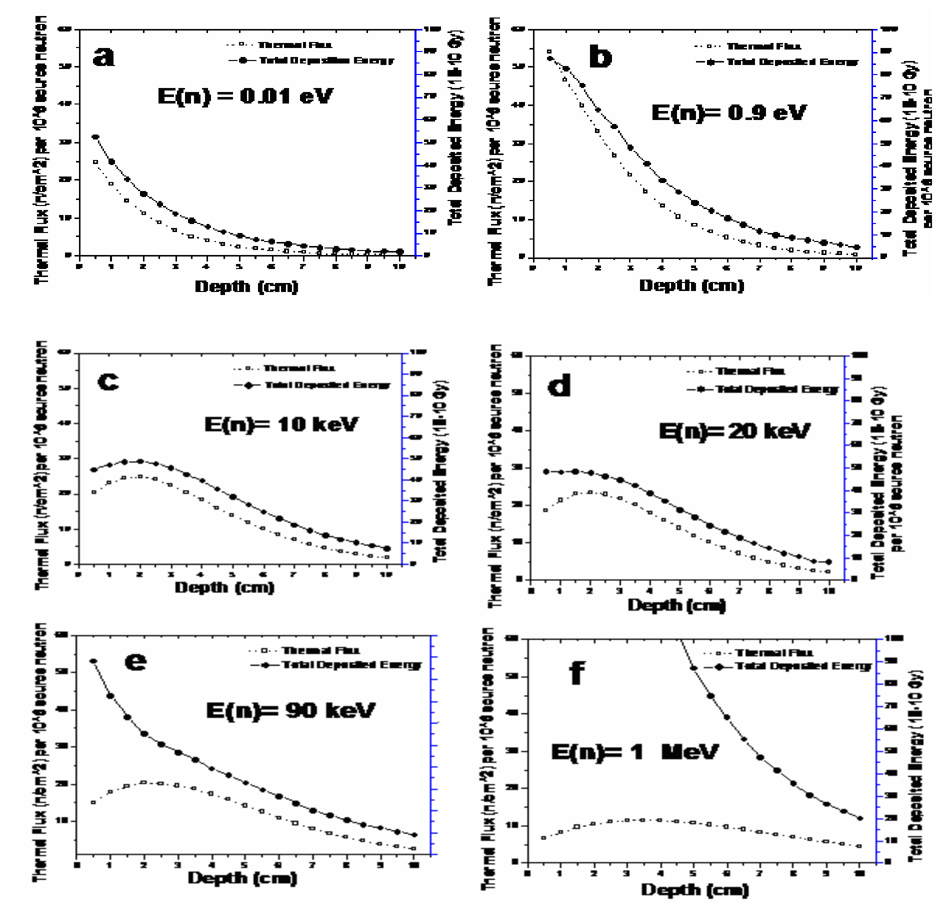


Figure 11 (a-f) Thermal neutron fluxes and total deposited energies at different depths for different source neutrons energies, $E_{(n)}$.

Figures 12 (a-d) present plotting for the proportion between the thermal neutrons flux, and the total deposited energy at different depths in brain; for the 65 source neutrons energies screened. The source neutrons energy range where the proportion between thermal neutron flux and total deposited energy was reasonably constant is specified.

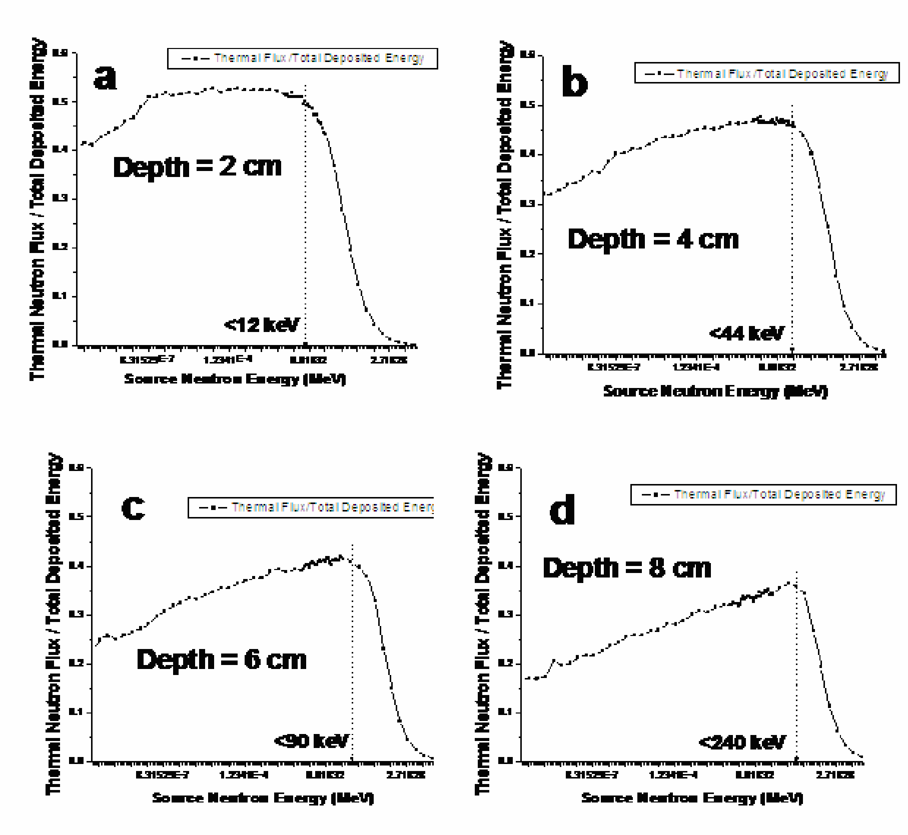


Figure 12 (a-d): The proportion between the thermal flux and the total deposited energy, for the 65 source neutrons energies screened; at different depths.

From figures 5, 8, 10, 12; the source neutrons energy ranges within which each one of the four conditions on source neutron beam was satisfied, were determined. Upper and lower limits for each of these ranges were specified for different depths in brain.

The *narrowest* energy range was chosen for each of the 10 studied depths. Such choice was by selecting the highest value of the lower limits, and the lowest value of the upper limits Table 2 presents these selected source neutrons energy ranges for different depths in brain.

Table (2): The selected source neutrons energy ranges for different depths in brain.

Depth (cm)	Energy Range		Depth (cm)	Energy Range	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
1	1.5 eV	10 eV	6	4 keV	30 keV
2	50 eV	50 eV	7	4 keV	30 keV
3	1 keV	360 eV	8	50 keV	30 keV
4	2.7 keV	16 keV	9	170 keV	30 keV
5	5 keV	20 keV	10	400 keV	36 keV

The contradiction in upper and lower energy limits for depths = 8, 9, 10 cm reflect the difficulty in applying BNCT for the very deeply seated brain tumors. This can be explained on logic basis as follows;

On their way to a deeply seated tumor; source neutrons will interact frequently with the normal elements and ^{10}B in normal brain tissues [(10)]. These interactions are double edged weapon, since; on one hand; they reduce the energy of the neutrons to thermal (thermalization), which is optimal for Boron neutron capture reaction [(10)], yet; on he other hand; a great portion of these neutrons is lost by capturing in the ^{10}B and other nuclei present in normal brain tissues [(10)]. Neutron capture interactions rates for the normal elements in brain tissues, are extreme at *epithermal* range of energies [(10)]. While the $^{10}B(n,\alpha)^{7}Li$ interaction rate is extreme at thermal range of energies. This is known as the ^{10}B self shielding [(65)]. Accordingly; using thermal source neutrons wouldn't be appropriate for very deeply seated tumors; since most of the thermal neutrons would be lost by capture in ^{10}B existent in the more superficial normal brain tissues. Using too energetic (fast) neutrons; wouldn't be appropriate too; since a great portion of such very highly energetic neutrons would be lost by capturing in normal elements of brain before they are enough thermalized (i.e. during transition by the epithermal range).

CONCLUSION

In view of the above results and discussion; it could be presumed that the range of source neutrons energies that is appropriate for BNCT is from few electron volts to about 30 keVs.

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