Review Article

A brief review on reactor-based neutron sources for boron neutron capture therapy

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Abstract: Neutron sources for boron neutron capture therapy (BNCT) have been based, until few years ago, on fission nuclear reactors; indeed only nuclear reactors were able to produce neutron flux with the right intensity in the range of thermal and/or epithermal energy. At present many centers are substituting reactor sources with accelerator-based neutron sources that can be easily installed in a hospital environment helping the BNCT diffusion as a standard cancer treatment. Although only few reactor-based BNCT sources are still active (Argentine, China, Japan, Taiwan), nonetheless the role played by nuclear reactors was essential for BNCT birth, and the current available reactors will continue to give a fundamental contribution to its further development. In this article we report a brief review of the fission reactor-based neutron sources for BNCT; we focus on the main requirements which this source had to fulfil to be suitable for BNCT applications, not pretending to be exhaustive due to the very broad topic. General requirements for reactor BNCT neutron sources, techniques to produce epithermal neutron beams starting from fission neutrons, and parameters for their performance evaluation will be briefly discussed.

Keywords: Boron neutron capture therapy (BNCT); fission reactors; neutron sources; epithermal neutrons

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Introduction

All boron neutron capture therapy (BNCT) activity, research and clinic, has been done, until few years ago, using fission reactor neutron sources. Usually existing research reactors has been adapted to extract neutron beams useful for boron concentration measurement, for *in vitro* and *in vivo* preclinical experiments and for patient irradiation in suitable treatment rooms built in the reactor hall. There are two exceptions: the Massachusetts Institute of Technology Research Reactor (MITR) and the Brookhaven Medical Research Reactor (BMRR) commissioned in 1950s (1); more recently, in 2010, an in-hospital neutron irradiator (IHNI) was realized in Beijing, China (2,3) and one is in project in Nakhon Ratchasima, Thailand (Sanguansak N, 2018, unpublished data), both based on miniature reactor neutron source (MRNS).

At present only few reactor based BNCT sources are still active (Argentine, China, Japan, Taiwan) (4-7) and many accelerator-based neutron capture therapy (NCT) sources are already built or under installation. Although new accelerator-based sources will surely help BNCT diffusion, nonetheless what played by nuclear reactors was essential for BNCT and the current available reactors will continue to give a fundamental contribution to the further development of BNCT.

In this article, we report a brief review of the fission reactor-based neutron sources for BNCT [High Flux Reactor at Petten in the Netherlands, Studsvik reactor in Sweden, FiR1 reactor in Finland, LVR-15 reactor in

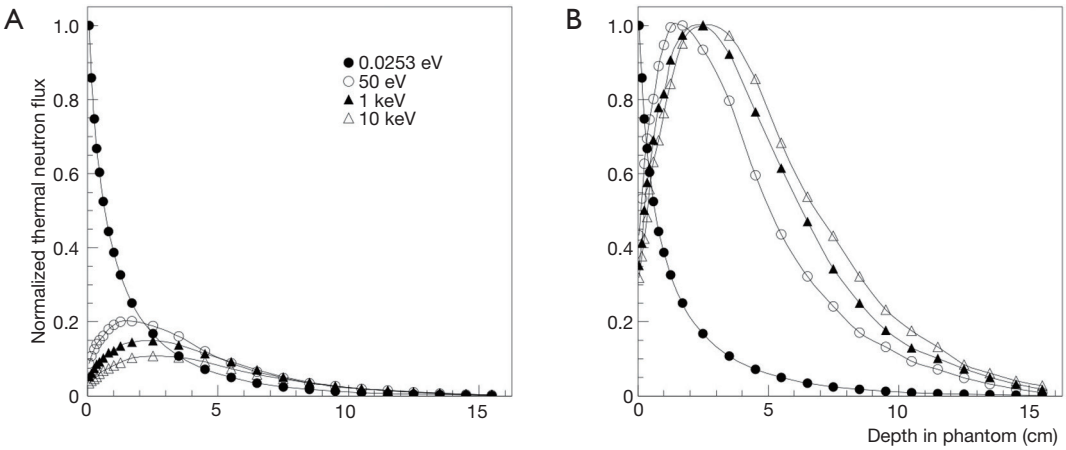

Figure 1 Thermal neutrons profile as a function of the depth in a tissue phantom when irradiated by an ideal parallel thermal neutron beam or epithermal neutron beam; epithermal neutrons show a better penetrability in tissues. As a normalization factor in frame (A) the maximum thermal neutron flux has been used, while in frame (B) the neutron flux maximum for each energy has been used.

Rez, Czech Republic, Kyoto University Research Reactor in Japan, JRR4 at JAER1 in Japan, Musashi Institute of Technology Reactor (KURR) in Japan, McCellan Nuclear Radiation Center Reactor at Davis, California, Washington State University reactor in Pullman, Washington, RA-6 reactor in Bariloche, Argentina, Tsing-Hua Open-pool Reactor (THOR) in Taiwan, Tapiro reactor in Rome, Italy, Triga Mark II of Pavia University in Italy] (8-26). We try to make a list of the different kind of sources and focus on the main requirements which these sources are able to fulfil for BNCT application, not pretending to be exhaustive due to the very broad topic.

General requirements for reactor-based BNCT neutron sources

The majority of reactor sources, realized by modification of existing reactors, use neutrons coming directly from the core (after appropriate moderation and filtration) (27); but there is an example, at MITR-II, that uses a fast neutron converter (FCB) installed in a large thermal neutron beam (28,29).

The first BNCT facilities were realized in the early 1950's and 1960's at Brookhaven National Laboratory (BNL) (29), the first nuclear reactor designed specifically for medical research and therapy and at MIT (MITR-I) with thermal neutron beams (30).

After the unsuccessful results of these trials (30) due to some reasons, among which the low capability of thermal neutrons to penetrate deeply into tissue, research on epithermal neutron beams for BNCT started. *Figure 1* shows the different thermal neutron profile in tissue when a beam of thermal or epithermal neutrons is used. Calculations have been done assuming an ideal parallel neutron beam with different energy (0.0253 eV, 50 eV, 1 keV and 10 keV) impinging on a phantom with a standard soft tissue composition. It is evident that the penetrability in tissues of epithermal neutrons with the possibility to reduce the dose at patient surface are better than that of thermal neutrons; the maximum of thermal flux is reached at a depth of around 2–3 cm with neutron energies from 50 eV to 10 keV.

To be able to treat a patient in a reasonable time (no more than a few tenth of minutes for each irradiation field), taking into account a feasible level of boron concentration of about 30 ppm in the tumor, and to have a high probability to destroy the tumor, a thermal neutron fluence on the order on 10^{12} cm^{-2} is necessary. This means that a neutron flux on the order of 10^{9} $cm^{-2}{\cdot}s^{-1}$, thermal or epithermal, depending on the depth of the tumor, must be produced at the entrance of the patient.

Until a few years ago, before the advent of the accelerator-based neutron sources, the only device that is able to produce neutron sources with this intensity is fission nuclear reactor. Generally these sources were designed and realized at already existing reactors, designed for research or material testing purposes, and not for medical and BNCT applications. For this, BNCT irradiation beams have been realized using the existing horizontal or vertical channels in the reactor biological shield whose thickness increases with the reactor power. This limits the advantages

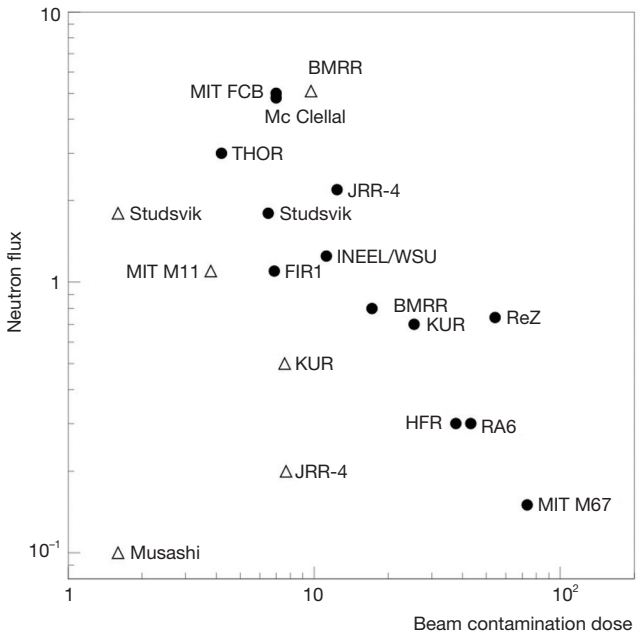

Figure 2 Thermal (empty bullets) and epithermal neutron flux as a function of the beam contamination (undesired dose from photons and fast neutrons) for several NCT beam facilities. The best beams are in the upper left-hand part of the figure (8). Units are: 1,010 $cm^{-2}\cdot s^{-1}$ for thermal nuetron flux, 10^9 $cm^{-2}\cdot s^{-1}$ for epithermal one and RBE Gy cm^2 for contamination dose with RBE equal 1 for photons and 3.2 for neutrons.

coming from the use of high power reactors to have a more intense beam for BNCT due to the decrease of the neutron flux with the increase distance from the core to the beam exit. A way to overcome this is the use of a FCB installed in a position where an intense thermal neutron flux exists. This solution was used at MITR-II to realize an epithermal neutron beam (31,32). Moreover, it effectively reduced the photon contamination produced by neutron capture in the collimator.

In the design of a BNCT beam, beyond the intensity of neutron flux, some other characteristics must be taken into account with the main purpose to not reduce the BNCT selectivity.

Several parameters must be considered in the design of a BNCT beam, among which the most important are:

- The beam intensity to have reasonably short irradiation time, that is compatible with the comfort of the patient to keep a fixed position;
- The beam energy with high penetration capability to allow the treatment of deep seated tumors;
- The purity of the beam to not decrease the selectivity of the therapy that is the reduction of fast and thermal neutrons contamination, as well as that from photons.

A huge number of studies investigated the best ranges for these parameters. At the time in which these studies were carried out BNCT addressed primarily on brain tumors, thus the great majority of these studies used a water or polyethylene head phantom. The parameters to be considered are undoubtedly many, such as: the energy spectrum of the beam, the beam dimension, the collimation, the boron spatial distribution in healthy and cancer tissues (determined by the selectivity of the boron vector), the depth and position of the targeted tumour (33-40).

General guide values for this and other parameters were given for BNCT of brain tumors (41). Recommended values are:

- Fast neutrons contamination: $<2.10^{-13}$ Gy cm^2/n;
- Gamma contamination: $<2.10^{-13}$ Gy cm^2/n;
- Thermal to epithermal neutron flux ratio: <0.05;
- Neutron current to total flux ratio: >0.7;
- Beam radius: 12–15 cm.

Other suggested values reported for epithermal neutron beams (8) assuming borophenylalanine (BPA) as boron carrier and taking into account the radiation relative biological effectiveness (RBE) (1 for photons and 3.2 for neutrons) are as follows:

- Intensity: $\Phi epi > 2.10^9$ $cm^{-2}\cdot s^{-1}$;
- Energy: 0.4 eV < E ≤ 10–20 keV;
- Beam contamination (n+γ): $<2.810^{-12}$ RBE Gy cm^2;
- Beam collimation: $J/\Phi > 0.75$;
- Beam size and shape: adjustable beam size to at least 16 cm with possibilities to adjust beam shape;
- Treatment time: ~10 min per irradiation field;
- Patient and beam positioning: easy beam placement on any part of the body;
- Beam monitoring and control: accurate and reliable systems for neutron fluence delivery to ~1% of prescription;
- Treatment room: well shielded, easy and quick access, audio and visual communication with patients;
- Patient setup and support: separate spaces or rooms for exams, infusions, test setups and irradiation.

To give an idea of the performance of some epithermal and thermal BNCT beams, with respect to beam intensity and beam purity, *Figure 2* reports the thermal and epithermal neutron flux at beam exit as a function of the beam contamination (dose from photons and fast neutrons

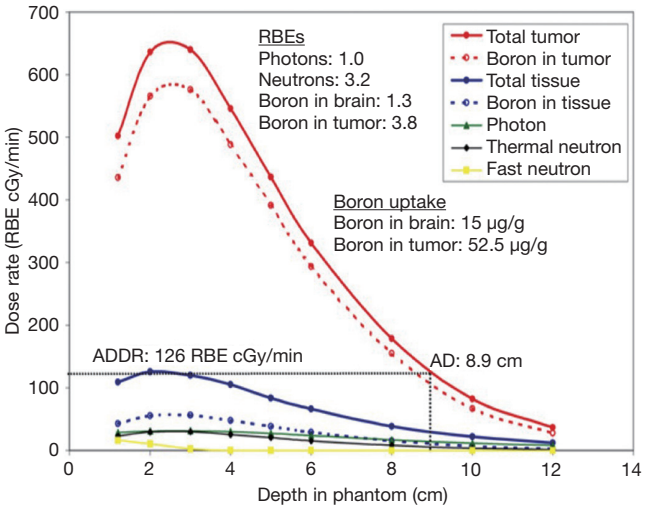

Figure 3 Depth dose rate profile along the beam axis as a function of depth in a head phantom for the MITR-II FCB epithermal beam; different components of BNCT dose and weighting factors are reported (42). MITR, Massachusetts Institute of Technology Research Reactor; FCB, fast neutron converter; BNCT, boron neutron capture therapy.

in normal tissues) (8). The best beams are in the upper left-hand part of the figure.

The ability of a NCT beam to treat deep seated tumors depends on the dose rate profile in the patient body as a function of the depth. In BNCT, the total dose at a point includes many components: the boron dose, the proton dose (by thermal neutron capture in nitrogen and by fast neutron elastic scattering on hydrogen), gamma dose (by gamma contamination of the beam and by (n,γ) reactions (mainly on hydrogen) and inelastic scattering in tissues. The main components of the dose rate are related to the thermal neutron flux, so their profile is similar to that of thermal neutrons. Frequently the biologically weighted dose is used in place of the absorbed dose; in this case the used weighting parameters must be clearly specified. As an example, *Figure 3* shows the depth dose rate profile along the beam axis as a function of depth in a head phantom for the MITR-II FCB epithermal beam (42); different components of BNCT dose and weighting factors are reported.

To evaluate the performance of an NCT beam for the treatment of a tumor, four parameters have been introduced: advantage depth (AD), advantage ratio (AR), advantage depth dose rate (ADDR) and the therapeutic gain (TG). AD is defined as the depth in the phantom at which the absorbed dose by the tumor is equal to the maximum dose delivered to healthy tissue; AR at a particular depth is defined as the ratio between the integral of tumor and normal tissue doses from the surface to the AD; ADDR is the dose rate at the AD, it is equal to the maximum dose rate in normal tissues and can be used to evaluate the irradiation time needed to reach the tolerance dose of normal tissue (33); finally, TG is defined as the ratio between the average dose in the tumor region and the maximum dose to normal tissues. In *Figure 3*, the AD and the ADDR of the beam are 8.9 cm and 126 RBE cGy/min, respectively.

All these parameters are very useful to design an NCT beam; Monte Carlo simulations (40) show that AD is almost independent by the boron concentration for neutron beams in the energy range from thermal up to 10 keV; while it is very sensitive at higher energies, for example at 100 keV. In the same paper (40), the AD as a function of neutron energy has been evaluated for three values of boron concentration (2, 10 and 40 ppm). A maximum value for the AD is reached in the region from few keV to a few tens of keV. Moreover the TG has been evaluated as a function of neutron energy (0.01 eV–1 MeV) for a brain tumour located at a depth of 5 cm and one at 8 cm. Again a maximum of this parameter is reached in the same energy range (few keV to a few tens of keV); showing that this is a good energy range for NCT beams. All simulations were done assuming a fixed value of the tumour/normal tissue concentration ratio of 4.3 and RBE factors of 1.6 and 2.3 for protons and ^{10}B reactions respectively taken by Wallace *et al.* [1994] (38). As a general rule the TG depends on boron concentration and on the boron concentration ratio between tumor and healthy tissues; with higher boron concentrations and higher ratios, the higher values of TG are obtained.

Neutron beams and neutron field for BNCT

Neutrons produced by fission nuclear reactors have a typical spectrum with a most probable energy of 0.7 MeV, a mean energy of 2 MeV and a high energy tail up to about 10 MeV. Due to moderation process this neutron spectrum is changed in a new one with three main components: thermal, epithermal and fast. To produce a neutron beam useful for NCT of deep seated tumors some moderating and filtering materials are used to reduce the thermal and fast components and increase the epithermal one. Usually the principal materials are composed by Al, F, Mg because of the inelastic cross section behaviour characterized by an almost constant value at low energy and a series of resonances at energies higher than a few tens of keV; usually

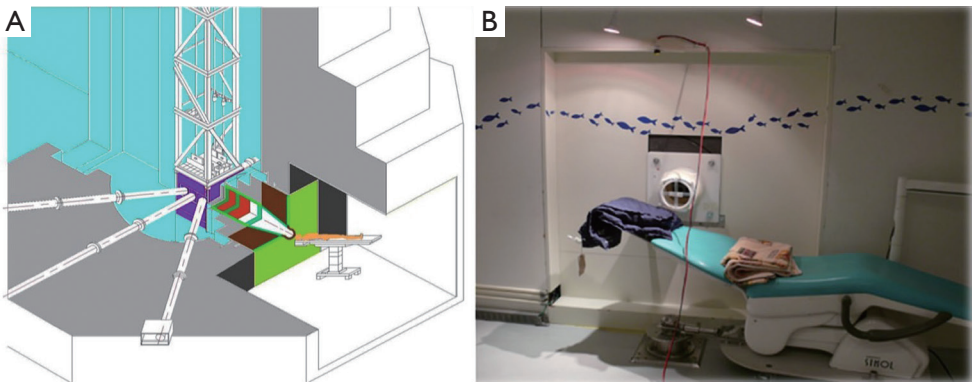

Figure 4 (A) A view of the Tsing-Hua Open Pool Reactor (THOR) and (B) a photo of the treatment room with the treatment couch and polyethylene extension collimator for maintaining treatment position during epithermal neutron irradiation (7).

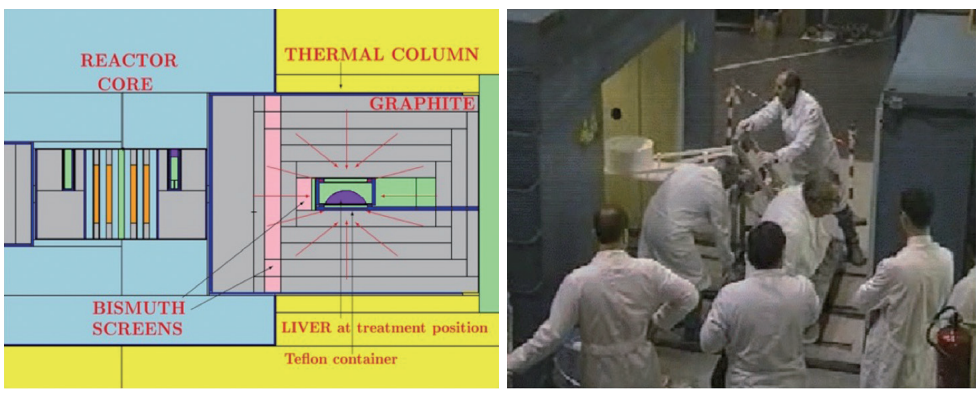

Figure 5 The irradiation position of the liver (left panel) at Triga Mark II reactor of Pavia University; explanted liver (in the cylindrical Teflon container) pushed in the thermal column for the irradiation (right panel).

in a beam shaping assembly (BSA) Pb is used as neutrons reflector. In *Figure 4*, a view of the THOR and a photo of the treatment room are shown (7). A special case of BSA is represented at the Kyoto University Research Reactor Institute (KURRI) (14,15,41). The main part of the BSA is made by Al and D_2O slabs; after this, further containers can be filled with D_2O to shift the epithermal beam to lower energies adding a thermal component.

As last example we report a different approach, with respect to the reactor BNCT facilities cited until now, that was used at University of Pavia. With the aim to apply BNCT to the treatment of spread metastases invading a whole liver, a facility was realized at Triga Mark II reactor to treat an explanted organ. To have the possibility of irradiating the entire organ, not a beam but a neutron field was produced for modifying the existing thermal column to create a channel with the ability to host the explanted organ; a Bi layer was used to shield the gamma radiation coming from the core (24-26). Left panel of *Figure 5* shows the irradiation position of the liver in the thermal column; the right panel shows the explanted liver (in the cylindrical Teflon container) was pushed into the thermal column for the irradiation.

Conclusions

In this article, we have reported a brief review of the fission reactor-based neutron sources for BNCT focusing on the main requirements which these sources are able to fulfil the BNCT application. General requirements for reactor BNCT neutron sources, techniques to produce epithermal neutron beams starting from fission neutrons and parameters for their performance evaluations have been briefly discussed.

There are some reactor-based BNCT centers still treating patients in Argentine, China, Japan and Taiwan. That will continue to give a fundamental contribution for further development of BNCT.

Surely accelerator-based BNCT sources, already built or under installation, will play a major role in the successful diffusion of BNCT as a standard cancer treatment; but the fission reactors have offered, until now, a unique opportunity to show the feasibility and effectiveness of BNCT on many techniques that will be useful for accelerator-based BNCT.

Moreover, nuclear reactors can be very useful to continue BNCT research for instrumentation development, boron concentration measurements in new boron compounds and in *in vitro* and *in vivo* experiments.

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