Neutron beams implemented at nuclear research reactors for BNCT

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ABSTRACT: This paper presents a survey of neutron beams which were or are in use at 56 Nuclear Research Reactors (NRRs) in order to be used for BNCT, either for treatment or research purposes in aspects of various combinations of materials that were used in their Beam Shaping Assembly (BSA) design, use of fission converters and optimized beam parameters. All our knowledge about BNCT is indebted to researches that have been done in NRRs. The results of about 60 years research in BNCT and also the successes of this method in medical treatment of tumors show that, for the development of BNCT as a routine cancer therapy method, hospital-based neutron sources are needed. Achieving a physical data collection on BNCT neutron beams based on NRRs will be helpful for beam designers in developing a non-reactor based neutron beam.

KEYWORDS: Instrumentation for neutron sources; Instrumentation for particle-beam therapy

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1 Introduction

In Boron Neutron Capture Therapy (BNCT), the patient is injected with a tumor localizing drug containing $^{10}$B and then exposed to a suitable neutron beam. Boron captures thermal neutrons and produces two high Linear Energy Transfer (LET) particles ($^4$He and $^7$Li) that release their energy within the cellular dimension, what is much more effective than low-LET radiation in deactivating tumor cells [1].

BNCT relies on two key factors: a tumor selective boron carrier drug and a suitable neutron source. Research in the area of development of boron-containing delivery agents for BNCT started $\sim$ 50 years ago. The other key to successfully administering BNCT is the neutron source. So far, the only sources for BNCT have been Nuclear Research Reactors (NRRs). Interested readers are referred to the book “Neutron Capture Therapy: Principles and Applications” by Prof. Dr. Sauerwein [2] and also to two comprehensive review papers by R. Barth et al. [3, 4]. An old extensive summary of the possibilities in neutron beam design, development and performance for BNCT was achieved in an international workshop at MIT in 1990 [5]. Similarly, there are some other review papers [6–8].

The first clinical successes were reported by Prof. Dr. Hatanaka et al. [9, 10], later on a number of other groups followed and proved positive effects on patients treated by BNCT [11–20]. After
about 60 years research and development on the reactor-based BNCT, the technical efforts are focused on the accelerator-based neutron sources to be installed in hospitals [21–26].

BNCT requires neutron beams of suitable energy and intensity and low gamma background. To achieve such a beam, a spectral Beam Shaping Assembly (BSA) must be designed and installed between the neutron source and the patient [1] (see figure 3). The BSA generally consists of neutron moderator, neutron reflector, thermal neutron filter, gamma filter, and collimator. The shapes, dimensions and materials of a BSA are highly dependent on the neutron source specifications such as mean energy and source strength.

This paper presents a survey of neutron beams which were or are in use at NRRs in order to be used for BNCT, either for treatment or research purposes. The paper mainly will investigate 56 NRRs with regard to various choice and combinations of their BSA materials, beam parameters and the special use of nuclear fuel in BSA as a fission converter. Achieving a comprehensive data collection on BNCT based on NRRs will be helpful for beam designers in developing a non-reactor based neutron beam.

2 BNCT physical mechanism

Figure 1 shows a schematic view of what happens in BNCT. The fundamental reaction between boron and thermal neutrons is:

\[ n_{th} + ^{10}\text{B} \rightarrow ^{7}\text{Li}(0.84\text{ MeV}) + \alpha(1.47\text{ MeV}) + \gamma(0.48\text{ MeV}) \quad (93.7\%) \quad (2.1) \]

\[ n_{th} + ^{10}\text{B} \rightarrow ^{7}\text{Li}(1.01\text{ MeV}) + \alpha(1.78\text{ MeV}) \quad (6.3\%) \quad (2.2) \]

Capturing a thermal neutron, \(^{10}\text{B}\) promptly disintegrates into two high LET particles: an alpha particle and a recoiling lithium nucleus with 9 and 5 \(\mu\text{m}\) range in tissue, respectively [1].

The energy deposited by the \(^{10}\text{B}(n,\alpha)^{7}\text{Li}\) reaction is called the boron dose (\(D_B\)). In addition to boron dose, three further main dose components are produced within the tissue in BNCT treatment.

![Figure 1. BNCT cell-killing mechanism.](image)
These principally undesired doses are generated by (1) incident and secondary gamma rays, $D_γ$; (2) the thermal neutron dose ($D_N$), i.e., the dose resulting mainly from thermal neutron capture in nitrogen $^{14}$N$(n_{th},p)^{14}$C, and (3), the fast neutron dose ($D_{fn}$), i.e., the dose from recoil protons [1]. The total biologically weighted dose is the sum of these four dose components with the corresponding weighting factors ($w_i$):

$$D_w = w_γD_γ + w_BD_B + w_ND_N + w_{fn}D_{fn}$$

(2.3)

Accepted values of the biological weighting factors are 1 for gamma dose, 3.2 for both thermal and fast neutron dose, 3.8 for boron dose in tumor and 1.3 for boron dose in normal tissues, respectively [1]. The goal of radiation therapy is to maximize tumor dose while minimizing exposure to normal tissue. Accordingly, the Therapeutic Gain (TG), i.e., the ratio between the tumor dose and the maximum dose to the normal tissue has been defined. Higher TG means better condition for therapy [1].

3 The qualified neutron beam for BNCT

In BNCT, an adequate thermal neutron field has to be created within the boron labeled tumor cells. Figure 2 shows a comparison of thermal neutron flux-depth distributions for different incident neutron energies [8].

![Figure 2](image_url)

**Figure 2.** Depth-distribution for monoenergetic neutron pencil beams of different energies [8].

As can be seen, an epithermal beam entering brain tissue creates a radiation field with a maximum thermal flux at a depth of 2–3 cm, which drops exponentially thereafter. In contrast to the epithermal beam, a thermal beam entering tissue falls off exponentially from the surface. The depth distribution of the thermal field can be influenced by the incident neutron energy which is, however, limited to a maximum of 10 keV; for higher neutron energies, the KERMA coefficient increases to prohibitive values. This indicates that a thermal neutron beam is suitable for treatment of superficial tumors, while for treatment of deep-seated tumors, only an epithermal neutron is suitable. In both, epithermal and thermal BNCT neutron beams, fast neutrons and gamma rays are considered as the
beam contaminations which should be limited to the desired values. The required BNCT beam parameters are presented in table 1 [27]. Beside thermal and epithermal entrance neutron beams, the utilization of hyper-thermal neutrons (neutrons with energy range from 0.1 eV to 3 eV) was also studied in order to improve the thermal neutron flux distribution at depth in a living body [10, 28].

| Table 1. Neutron beam parameters recommended by the IAEA for BNCT [27]. |
|---------------------------------------------------------------|
| **Thermal BNCT** | **Epithermal BNCT** |
| Parameter | Recommended value | Parameter | Recommended value |
| $\phi_{\text{thermal}}$ (cm$^{-2}$s$^{-1}$) | $> 10^9$ | $\phi_{\text{epithermal}}$ (cm$^{-2}$s$^{-1}$) | $> 10^9$ |
| $\phi_{\text{thermal}} / \phi_{\text{total}}$ | $> 0.9$ | $\phi_{\text{epithermal}} / \phi_{\text{thermal}}$ | $> 20$ |
| $D_{\text{epithermal+fast}} / \phi_{\text{thermal}}$ (Gycm$^2$) | $< 2 \times 10^{-13}$ | $D_{\text{fast}} / \phi_{\text{epithermal}}$ (Gycm$^2$) | $< 2 \times 10^{-13}$ |
| $D_{\text{gamma}} / \phi_{\text{thermal}}$ (Gycm$^2$) | $< 2 \times 10^{-13}$ | $D_{\text{gamma}} / \phi_{\text{epithermal}}$ (Gycm$^2$) | $< 2 \times 10^{-13}$ |

Fast energy $E > 10$ keV  
Epithermal energy $0.5$ eV $< E < 10$ keV  
Thermal energy $E < 0.5$ eV

4 Beam Shaping Assembly (BSA)

In order to apply BNCT successfully, the primary spectrum of the neutron source must be modified to the required neutron beam (table 1) using an appropriate BSA. Figure 3 shows the schematic view of a BSA. In this section different parts of BSA are introduced.

![Figure 3. Schematic view of a common BSA.](image)

4.1 Moderator

The fission neutron spectrum produced in a reactor core contains many fast neutrons. These fast neutrons should be moderated and reach the desired epithermal energy range of about 0.5 eV to 10 keV. In epithermal BNCT, the moderator should have a high fast neutron scattering cross-section ($\Sigma_{s,\text{fast} \rightarrow \text{epi}}$) and low epithermal neutron scattering and absorption cross-sections ($\Sigma_{r,\text{epi}}$) so that the value of $\Sigma_{s,\text{fast} \rightarrow \text{epi}} / \Sigma_{r,\text{epi}}$ parameter is as high as possible. As well, they should have a low fast neutron absorption cross-section because fast neutrons will be removed from the spectrum and cannot contribute anymore to the lower energy regions. A good moderator also must not become the source of a strong photon field and if so, the energies should behave low energies which can
be removed [1]. The macroscopic cross-sections of some candidate moderators which are used in different BNCT facilities are presented in table 2 [29].

| Material | $\Sigma_{s,\text{fast}}$ | $\Sigma_{s,\text{epi}}$ | $\Sigma_{s,\text{fast} \rightarrow \text{epi}}$ | $\Sigma_{s,\text{epi} \rightarrow \text{th}}$ | $\Sigma_{r,\text{fast}}$ | $\Sigma_{r,\text{epi}}$ | $\Sigma_{r,\text{fast} \rightarrow \text{epi}}$ | $\Delta\Sigma_{r}$ |
|----------|-------------------|------------------|-----------------|----------------------|-------------------|----------------|------------------|----------------|
| $\text{AlF}_3$ | 0.340 | 0.268 | 0.012 | 0.005 | 0.013 | 0.005 | 0.005 | 2.296 |
| $\text{AlF}_3/\text{Al}^*$ | 0.247 | 0.186 | 0.012 | 0.003 | 0.012 | 0.004 | 0.004 | 3.227 |
| $\text{MgF}_2$ | 0.251 | 0.308 | 0.010 | 0.005 | 0.011 | 0.005 | 0.005 | 2.056 |
| $\text{Al}$ | 0.112 | 0.080 | 0.002 | 0.001 | 0.002 | 0.001 | 0.005 | 1.560 |
| $\text{D}_2\text{O}$ | 0.259 | 0.322 | 0.038 | 0.032 | 0.002 | 0.032 | 0.005 | 1.183 |
| Ti | 0.204 | 0.269 | 0.003 | 0.000 | 0.032 | 0.005 | 0.010 | 0.524 |
| V | 0.364 | 0.447 | 0.005 | 0.000 | 0.032 | 0.000 | 0.000 | 0.497 |

* A 30% Al plus 70% AlF$_3$ mixture

The moderators consisting of fluoride have the highest value of $\Sigma_{s,\text{fast} \rightarrow \text{epi}}/\Sigma_{r,\text{epi}}$ parameter, hence, fluoride has been considered as an important element as a moderator in BNCT. It has a low neutron absorption cross-section and low energy threshold of inelastic scattering, as shown in figure 4.

![Figure 4](image)

**Figure 4.** Neutron reaction cross-section of fluorine.

Especially, Fluental™ (Al 30% + AlF$_3$ 69% + LiF 1%) is a suitable neutron moderator material developed at Technical Research Centre of Finland (VTT) [30]. It provides very good spectrum shifting to the epithermal neutron region with a good fast neutron cutoff (figure 5 [31]).

Heavy water is another material that was used as a neutron moderator [32, 33]. In the JRR-4 reactor, four separate heavy water tanks were used to operate independently; thus, the optimum heavy water thickness could be selected for both thermal and epithermal beams to meet the requirement of various treatment depths. The tanks were installed along with a cadmium filter which was set to change the beam condition from the thermal to the epithermal mode (figure 6 [33]).
Figure 5. Neutron flux per unit lethargy for different epithermal neutron filters at a TRIGA reactor [31].

Figure 6. The heavy water system and BSA in JRR-4 [33].

4.2 Reflector

Neutrons that initially are scattered in the moderator may leak out before reaching the energies of interest. This loss can be substantially reduced by surrounding the moderator with a reflector. The reflector returns neutrons that collide first in the moderator but leak out before slowing down and also deflect neutrons that miss the moderator upon streaming from the source. In addition, the (n,2n) reaction in the reflector contributes significantly to the total neutron production [34]. Some materials such as graphite [35], lead [36], BeO [37] and Tungsten/Molybdenum [38] have been considered as neutron reflectors. Lead with low photon production and low cost is a preferred reflector. Lead has also shown a better performance than graphite [36].
4.3 Reflector/moderator geometries

Generally, the reflector is considered as a layer which covers the moderator material, as shown in figure 7. Kasesaz et al. proposed new reflector/moderator geometries including multi-layers and hexagonal lattice. The effects of these geometries were investigated by MCNP4C Monte Carlo code [39]. It was found that the proposed configurations have a significant effect to improve the thermal to epithermal neutron flux ratio which is an important neutron beam parameter. Table 3 presents the values of neutron beam parameters related to some selected cases [39].

![Figure 7](image.png)

**Figure 7.** Top view of four considered reflector/moderator configurations, red: reflector, green: moderator [39].

| Geometry | $\phi_{\text{epi}}$ ($10^{-7}$ cm$^{-2}$ source particle) | $\phi_{\text{epi}}/\phi_{\text{thermal}}$ | $D_{\text{fast}}/\phi_{\text{epi}}$ ($10^{-13}$ Gycm$^2$) |
|----------|------------------------------------------------|---------------------------------|-------------------------------|
| A        | 12.5                                           | 35.1                            | 0.151                          |
| B        | 16.7                                           | 24.7                            | 0.120                          |
| C        | 13.9                                           | 222.2                           | 1.571                          |
| D        | 11.6                                           | 427.7                           | 1.775                          |

4.4 Fast neutrons, thermal neutrons and gamma filters

In order to obtain an epithermal neutron beam with high quality, thermal and fast neutron filters have to be used. The flux of fast neutrons can most effectively be decreased and transformed to an epithermal flux by Al or its fluoric compounds [40]. Cadmium, Gadolinium, and materials enriched with $^{10}$B or $^6$Li have high thermal cross-sections, but care must be taken about an additional generation of gamma radiation (B, Gd, Cd) and of fast neutrons (Li). Figure 8 shows the total neutron cross-section of these materials. In addition to thermal and fast neutrons, gamma rays must be suppressed. Pb and Bi are the common gamma filters widely used in BNCT beam lines [1, 27, 34, 41–43].

4.5 Fission converter technique

The fission converter approach is a method to convert thermal neutrons to fission neutrons. To do this, e.g., arrays of nuclear fuel elements (fresh or spent fuel highly enriched in $^{235}$U) are placed in
the reactor thermal zone. Thermal neutrons in the thermal zone induce fission processes and thereby fast neutrons which are then moderated and filtered to epithermal energy. Finally, a high intensity epithermal neutron beam is produced close to the treatment position. Suitable fission converter approach enable thermal research reactors to provide high intensity and high quality epithermal neutron beams [2].

A lot of neutronic and engineering design studies are needed for having a fission converter-based epithermal neutron beam. The first fission converter beam for BNCT was constructed at the MITR [44]. W.S. Kiger III has performed the neutronic study of MITR for providing a fission converter-based epithermal beam. After extensive studies on moderator, filter and collimator, he proposed a beam with high epithermal neutron flux (about $1 \times 10^{10}$ cm$^{-2}$s$^{-1}$ at the patient position), and low contaminations with fast neutrons and photons (less than $2 \times 10^{-11}$ cGycm$^{-2}$) [45]. S. Sakamoto has performed further studies to provide a beam with better epithermal neutron flux ($1.91 \times 10^{10}$ cm$^{-2}$s$^{-1}$), low cost, enhanced safety and flexibility [46]. An engineering design including satisfyingly steady state and accident criteria design were also performed [47]. Some other fission converter-based beams were designed at BMRR [48], McClellan Nuclear Research Center (MNRC) [49], MURR [50], MARIA [51], JSI [31], OSURR [52], MuITR [53] and KRR [54]. Figure 9 shows a plan view of some fission converter-based beam lines.

5 NRRs for BNCT

As mentioned above, NRRs were the first neutron sources used in clinical BNCT and a lot of knowledge about BNCT has been derived from the experience in NRRs. Even low power NRRs like TRIGA reactors can provide a sufficient neutron flux after appropriate adaptation.

A comprehensive data collection on BNCT based on NRRs will be helpful for beam designers in developing a new neutron beam. There are 56 nuclear research reactors around the world that have been used for BNCT, either for treatment or research purposes only. Table 4 presents the list of these reactors.
Figure 9. Plan view of the some fission converter-based beam line at: (a) MIT [55], (b) BMRR [56], (c) MNRC [49], (d) IMNSR [57].
Table 4. List of all NRRs that have been considered for BNCT.

| No. | Reactor   | Country     | Power (MW) | Ref. |
|-----|-----------|-------------|------------|------|
| 1   | BGRR      | U.S.A.      | 28         | [58] |
| 2   | BMRR      | U.S.A.      | 3          | [1]  |
| 3   | BTU       | Hungary     | 0.1        | [59] |
| 4   | BER-II    | Germany     | 10         | [60] |
| 5   | Dalat     | Vietnam     | 0.5        | [61] |
| 6   | DIDO      | U.K.        | 25         | [62] |
| 7   | FiR-I     | Finland     | 0.25       | [63] |
| 8   | FRJ-2     | Germany     | 23         | [148]|
| 9   | FRM-I     | Germany     | 4          | [64] |
| 10  | FRM-II    | Germany     | 20         | [65] |
| 11  | FRMZ      | Germany     | 0.25       | [66] |
| 12  | GTRR      | U.S.A.      | 5          | [67] |
| 13  | HANARO    | Korea       | 0.03       | [68] |
| 14  | HFR       | Netherlands | 45         | [69] |
| 15  | HIFAR     | Australia   | 10         | [147]|
| 16  | HTR       | Japan       | 0.1        | [118]|
| 17  | IEA-R1    | Brazil      | 5          | [70] |
| 18  | IHNI      | China       | 0.03       | [71] |
| 19  | IMNSR     | Iran        | 0.03       | [27] |
| 20  | IRT MIFI  | Russia      | 2.5        | [72] |
| 21  | IRT-Sofia | Bulgaria    | 0.2        | [73] |
| 22  | ISIS      | France      | 0.7        | [149]|
| 23  | ITU       | Turkey      | 0.25       | [74] |
| 24  | JRR-1     | Japan       | 0.05       | [151]|
| 25  | JRR-2     | Japan       | 10         | [118]|
| 26  | JRR-3     | Japan       | 10         | [118]|
| 27  | JRR-4     | Japan       | 3.5        | [33] |
| 28  | JSI       | Slovenia    | 0.25       | [31] |
| 29  | KARTINI   | Indonesia   | 0.25       | [75] |
| 30  | KRR       | Ukraine     | 10         | [76] |
| 31  | KUR       | Japan       | 5          | [77] |
| 32  | LENA      | Italy       | 0.25       | [78] |
| 33  | LFIR      | Netherlands | 0.03       | [79] |
| 34  | LVR-15    | Czech republic | 10       | [80] |
| 35  | MARIAP    | Poland      | 30         | [40] |
| 36  | MINTR     | Malaysia    | 1          | [81] |
| 37  | MITR      | U.S.A.      | 5          | [82] |
| 38  | MNRC      | U.S.A.      | 2          | [49] |
| 39  | MOATA     | Australia   | 0.1        | [150]|
| 40  | MuIITR    | Japan       | 0.1        | [53] |
| 41  | MURR      | U.S.A.      | 10         | [50] |
| 42  | OSTR      | U.S.A.      | 1          | [83] |
| 43  | OSURR     | U.S.A.      | 0.5        | [52] |
| 44  | PBF       | U.S.A.      | 20         | [84] |
| 45  | R2-0      | Sweden      | 1          | [85] |
| 46  | RA-1      | Argentina   | 0.04       | [86] |
| 47  | RA-3      | Argentina   | 10         | [87] |
| 48  | RA-6      | Argentina   | 0.5        | [88] |
| 49  | RPI       | Portuguese  | 1          | [89] |
| 50  | SMNSR     | Syria       | 0.03       | [90] |
| 51  | TAPIRO    | Italy       | 0.05       | [91] |
| 52  | THOR      | Taiwan      | 1          | [92] |
| 53  | TRR       | Iran        | 5          | [93] |
| 54  | WWR-K ALMATY | Kazakhstan | 6          | [94] |
| 55  | WSU       | U.S.A.      | 1          | [95] |
| 56  | YAYOI     | Japan       | 2          | [96] |
5.1 NRRs for BNCT in America

The first clinical trials of BNCT were performed at Brookhaven Graphite Research Reactor (BGRR) in 1951 using beams of thermal neutrons [9]. A few years later, from 1959–1961, Brookhaven Medical Research Reactor (BMRR) and Massachusetts Institute of Technology Reactor (MITR) were designed and used for BNCT, and a series of patients were irradiated. In all cases, no survival with BNCT was observed. The major problems were attributed to inadequate penetration of thermal neutron beams, little known dose distribution, and lacking localization of boron in the tumor. As a consequence, clinical trials of BNCT in U.S.A. were stopped [9, 97], but could be restarted in the 1990s at BMRR and MITR [98, 99]. The new epithermal beam with low fast neutron and gamma contaminations at MIT was able to penetrate the superficial tissues without causing too strong a damage and to build up a thermal neutron field in deeper-seated tumor with sufficient intensity [99].

Experimental modality and research activities were also performed in (MNRC) [49], RA-6 [88], RA-3 [87], OSTR [83], OSURR [52], PBF [84], RA-1 [86], GTRR [38] and WSU [95]. Table 5 represents the materials used in BSA structure of Americas BNCT facilities. The plan view of some of these BSAs are presented in figure 10. The measured or calculated beams parameters are presented in table 6.

| Reactor | BSA materials used in BNCT beams in America (FC=Fission Converter). | Ref. |
|---------|------------------------------------------------------------------|------|
| BMRR    | Al/Al₂O₃/Cd/Bi/Pb/Li-Polyethylene                                 | Yes  [5] |
| GTRR    | D₂O/Bi/Al/Al₂O₃/Pb/Cd/Li-Polyethylene/Concrete                   | Yes  [50] |
| MNRC    | Graphite/Al/AlF₃/Pb/Cd/Bi/Li-Polymer/LiF/Heavy concrete           | Yes  [49] |
| MITR    | Al/PTEF/Cd/Pb                                                    | Yes  [82] |
| MURR    | Pb/Graphite/Al/Al₂O₃/Cd/Li-Polyethylene/High density concrete    | Yes  [100] |
| OSTR    | D₂O/S/L₂CO₃/                                                     | No   [83] |
| OSURR   | Al/Graphite/Lead/PbF₃/Cd/Concrete                               | Yes  [101] |
| RA-1    | Al/Graphite/Cd                                                   | No   [86] |
| RA-3    | Bi/Pb/Fe/Zircalloy-4/Cd/Paraffin                                | No   [87] |
| RA-6    | Al/Al₂O₃/Pb/Cd/Bi/B-Polyethylene                                | No   [1] |
| WSU     | Pb/Al/Boral/Al₂O₃/Fluental/Bi/Li-Polyethylene/B-Polyethylene/Concrete | No   [1] |

5.2 NRRs for BNCT in Asia

After the first failure in U.S.A., BNCT in Asia was pioneered by Japanese. It was started at Hitachi Training Reactor (HTR) by Prof. Dr. Hatanaka [103] from 1968 to 1975 when this reactor was closed permanently. Thereafter, Musashi Institute of Technology Research Reactor (MuITR) was used for BNCT in Japan until 1989. This reactor was shut down because of a reactor pool leakage [13]. Kyoto University Reactor (KUR) was another reactor in Japan which was established in 1964. The first clinical study of BNCT at the thermal neutron irradiation facility of this reactor was performed in May 1974 [32]. In the period from 1974 to 1995, only thermal neutron irradiations could be delivered at this facility, hence, BNCT was applied in cases of malignant melanomas and open-laid brain tumors only. From 1995 to 1996, the thermal neutron irradiation facility at the KUR was remodeled and neutron energy spectra from almost pure thermal to epithermal became
Figure 10. Plan view of the some BSA in America: (a) BMRR [56], (b) MIT [55] (c) WSU [95], (d) RA-6 [88].

Table 6. Calculated (C) or Measured (M) parameters of some American BNCT beams.

| Reactor | Mode    | M/C | $\varphi_{\text{thermal}}$ ($\times 10^6$ cm$^{-2}$s$^{-1}$) | $\varphi_{\text{epi}}$ ($\times 10^6$ cm$^{-2}$s$^{-1}$) | $\varphi_{\text{fast}}$ ($\times 10^7$ cm$^{-2}$s$^{-1}$) | $D_{\text{fast}}/\varphi_{\text{epi}}$ ($\times 10^{-13}$ Gycm$^2$) | Ref. |
|---------|---------|-----|-------------------------------------------------|---------------------------------|-----------------|---------------------------------|-----|
| BMRR    | Epithermal | C   | 0.14                                           | 0.68                            | 3               | 2.6                             | [102]|
|         | M       | 0.19 | 0.88                                           |                                 | 4.1             | 2.7                             |     |
|         | M       | 510  | -                                              | -                               | -               | -                               |     |
| MITR    | Epithermal | M   | 1.16                                           | 3.71                            | 14              | 1                               | [102]|
|         | C       | 0.97 | 4.29                                           |                                 | 15.8            | 0.9                             |     |
| MNRC    | Epithermal | C   | -                                              | 5                               | -               | 200                             | [49]|
|         | Thermal  | C   | 56                                             | -                               | -               | -                               |     |
| WSU     | Epithermal | C   | 0.09                                           | 0.27                            | 1.1             | 2.6                             | [102]|
|         | M       | 0.3  | 0.3                                            | 1.2                             | 2.8             |                                 |     |
| RA-6    | Epithermal | C   | 0.28                                           | 0.68                            | 4.3             | 7.9                             | [102]|
|         | M       | 0.33 | 0.65                                           | 4.4                             | 9.1             |                                 |     |
| RA-3    | Thermal  | M   | 9                                              | -                               | -               | -                               | [87]|

Available [104]. In a clinical trial 23 children under 15 years were treated including 4 patients under 3 years [16].
Japan Research Reactor No. 4 (JRR-4) is one of the other reactors which were used for BNCT. Modification of JRR-4 for core conversion began in 1996, and its medical irradiation facility was installed for BNCT and the reactor was adopted to generate epithermal as well as thermal neutron beams. Clinical BNCT trials were started at JRR-4 in 1998 with the thermal neutron beam. At the later stage of intraoperative BNCT (since 1999), the epithermal beam was used in JRR-4. However, in December 2007, a crack in a graphite reflector of the reactor core was found on a weld of the aluminum cladding. JRR-4 was stopped until February 2010 for replacement of the graphite reflector. After restarting BNCT in 2010, 3 patients were treated.

Because of the March 2011 East Japan earthquake and tsunami, JRR-4 was stopped again with no prospect of restarting [105].

Another research reactor in Asia which has been used for BNCT is the Tsing Hua Open-Pool Reactor (THOR). It is a 2 MW research reactor at National Tsing Hua University (NTHU) in Hsinchu and is the only epithermal neutron source for BNCT research in Taiwan. The first epithermal neutron beam of THOR was built in 1998. It was built by removing the removal portion of the graphite blocks (see figure 11 [106]).

![Figure 11](image)

**Figure 11.** The horizontal cross-section of the THOR epithermal neutron beam [106].

The beam was used for conducting cell and animal experiments related to BNCT drug developments. THOR was shut down for renovation of a new epithermal neutron beam for BNCT in January 2003. In November 2003, concrete cutting was finished for getting closer to the core and for a larger treatment room. Figure 12a shows the top view of THOR new beam design [92]. Treatment of patients was started in August of 2010 in this reactor. Up to September 2016, 22 patients were treated [107].

Also IHNI in China has started human therapy with 6 patients up to December 2016 [108]. IHNI is the only reactor for BNCT which is installed at a hospital site.

Experiments and research activities were also performed in Syria [90], Indonesia [75], Korea [68], Vietnam [61] Malaysia [81] and Iran [27, 41, 43, 93, 109–115].

Prof. Dr. A. Pazirandeh (from Tehran University) and Dr. M.K. Marashi (from NSTRI) initiated BNCT research in Iran in 1990s. Their research was about the use of a beam tube of Tehran Research Reactor (TRR) to produce a proper neutron beam for BNCT [109, 116, 117]. The results showed that the final neutron flux was not sufficient for BNCT. Since then, no attempt was made to design a
proper neutron beam at TRR. In 2010, BNCT research has been restarted focusing on TRR thermal
column [41, 43, 93, 110], construction of a head phantom [111] and evaluation of beam parameters
inside of the phantom volume [112]. Simulations have shown that, an epithermal neutron beam can
be achieved at the thermal column exit if all graphite blocks are removed from the thermal column
and replaced by an appropriate BSA, but in practice, it was impossible to remove all graphite blocks
due to the high gamma dose caused by the reactor. So, the arrangement of graphite blocks has been
modified and a thermal neutron beam has been generated instead of epithermal neutron beam. More
details about the TRR BNCT project are provided in [93]. In addition to TRR, there are also some
MCNP design studies of thermal and epithermal neutron beams at the Isfahan Miniature Neutron
Source Reactor (IMNSR) [27, 57]. Table 7 shows the materials used in BSA of NRRs in Asia. The
plan view of some BSAs in Asia are presented in figures 12 and 13. Some measured or calculated
beam parameters are presented in table 8.

| Reactor | BSA compositions | FC | Ref |
|---------|------------------|----|-----|
| HANARO  | Bi/Polyethylene/Cd/Si/Pb | No | [68]|
| IHNI    | Epithermal mode: Al/Al$_2$O$_3$/Pb/Bi/C, thermal mode: Bi/Ph/C/PE(Pb) | No | [71]|
| IMNSR   | H$_2$O/AlF$_3$/Al/Al$_2$O$_3$/Bi/Pb/Cd/Be/Air | Yes | [57]|
| IMNSR   | Epithermal mode: Be/Al/Fluental/Cd/Bi, thermal mode: Be/Al/CF$_2$/Bi/Pb | No | [27]|
| JRR-2   | Graphite/Polyethylene/B$_4$C/Bi/LiF/Pb | No | [118]|
| JRR-4   | Al/D$_2$O/Cd/Bi/Li-Polyethylene/B-Polyethylene | No | [1]|
| KARTINI | Al/Ni/Bi/Li$_2$CO$_3$-Polyethylene/Barite concrete | No | [75]|
| KUR     | Al/D$_2$O/Bi/Pb/Polyethylene/B-Polyethylene/Cd | No | [77]|
| MuITR   | Al$_2$O$_3$/Bi/Pb/Concrete | Yes | [53]|
| SMNSR   | Al/Fluental/Bi/Li$_2$CO$_3$-Polyethylene/Cd/Pb | No | [90]|
| THOR    | Al/Fluental/Pb/Bi/Li-Polyethylene/Heavy concrete | No | [92]|
| TRR     | Pb/Graphite/Al/Bi/Cd/Concrete | No | [41]|
| TRR     | Pb/Graphite/Concrete/Boral | No | [43]|
| YAYOI   | Fe/Pb/Graphite/Bi/B-Paraffin/Polyethylene | No | [96]|

5.3 NRRs for BNCT in Europe

The first European clinical trial of BNCT was carried out from 1997 to about 2003 at the Petten
High-Flux Reactor (HFR) in the Netherlands [1]. It used a transmission filter consisting mainly of
liquid Ar and therefore realized a concept completely different from the other reactors. The clinical
trials at Petten were followed by treatments at the TRIGA reactor FiR-1 in Finland [121], CZ
Check republic [80], Sweden [85] and Italy [91]. Biological and dosimetric research activities were
performed in Germany [122–124] U.K. [62], Portugal [89], Poland [40], Ukraine [76], Slovenia [31],
Bulgaria [73, 125] and Hungary [59].

FiR-1 reactor in Finland was a 250 kW TRIGA reactor which was, permanently closed after
more than 50 years of operation. Between 1999 and 2012, about 249 patients with head and neck
cancer, primary and recurrent brain tumors and melanoma were treated in this reactor [4]. Joensuu
et al. have reported on 18 patients with brain tumor. The results have supported continuation of
clinical research on BNCT [126]. Kankaanranta et al. has also reported on 30 patients with operable
Figure 12. Plan view of the some BSA in Asia: (a) THOR [92], (b) KUR [119], (c) IMNSR [27], (d) IHNI [71], (e) TRR [43].

Table 8. Some Calculated (C) or Measured (M) parameters of Asian BNCT beams.

| Reactor | Mode       | M/C  | $\varphi_{\text{thermal}}$\((\times 10^8 \text{ cm}^{-2}\text{s}^{-1})\) | $\varphi_{\text{epi}}$\((\times 10^9 \text{ cm}^{-2}\text{s}^{-1})\) | $\varphi_{\text{fast}}$\((\times 10^7 \text{ cm}^{-2}\text{s}^{-1})\) | $D_{\text{fast}}/\varphi_{\text{epi}}$\((\times 10^{-13} \text{ Gycm}^2)\) | Ref. |
|---------|------------|------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------|------|
| KUR     | Epithermal | C    | 0.03                                           | 0.35                                             | 3.2                                              | 7.2                             | [102] |
|         |            | M    | 2.05                                           | 1.14                                             | 2.5                                              | 1.7                             |       |
| JRR-4   | Hyper thermal | C    | 18                                             | 0.81                                             | 2.3                                              | 1.8                             | [102] |
|         |            | M    | -                                              | 1.69                                             | -                                                | 2.8                             | [92]  |
| THOR    | Epithermal | M    | 0.65                                           | -                                                | 2.2                                              | 0.65                            | [41]  |
|         | Thermal    | C    | 5.6                                            | -                                                | -                                                | -                               | [43]  |
| IHNI    | Epithermal | C    | 0.156                                          | 0.4                                              | 3.6                                              | 5.6                             | [71]  |
|         | Thermal    | C    | 20.14                                          | 0.91                                             | 2.56                                             | -                               | [71]  |
head and neck cancer. The results show that 76% of patients responded to BNCT, 21% of them had tumor growth stabilization and 3% had progress [19, 20].

R2-0 research reactor in Sweden was another BNCT center in Europe. Capala et al. reported about the treatment of 17 patients with brain tumor [127, 128]. The elemental compositions of each reactor BNCT BSA are shown in table 9. The plan views of some BSAs in Europe are presented in figure 14. Some measured or calculated beam parameters have been presented in table 10.

6 From reactors to accelerator-based BNCT

After gaining some experience in the different fields of BNCT during about 60 years, today’s efforts to use BNCT as a routine radiotherapy focus on the hospital-based neutron sources such as proton accelerator facility [21–26, 131–134], neutron generators [42, 135–137] and $^{252}$Cf radioisotope [138–140].

Figure 13. Plan view of the some BSA in Asia: (a) Musashi [120], (b) YAYOI [96], (c) ITU [74], (d) Syria [90], (e) IRT [73].
Table 9. BSA materials used in BNCT beams in Europe (FC=Fission Converter).

| Reactor | BSA composition | FC | Ref. |
|---------|----------------|----|-----|
| BTU     | Graphite/Bi/Polyethylene | No | [59] |
| DIDO    | Al/S/Ar/B/Ti/Polyethylene/Pb/He/D_2O | No | [62] |
| FiR-1   | Fluental/Boral/Bi/Pb/Li-Polyethylene/Al | No | [121] |
| HFR     | Cd/Al/Ti/S/Ar/Polyethylene/Pb/Heavy concrete | No | [69] |
| IRT-MIFI| Graphite/Steel/Pb/Zirconium | No | [129] |
| IRT-Sofia| Al/Al_2O_3/Graphite | No | [125] |
| JSI     | Graphite/Al/PbF_2/Fluental/Cd/Bi/Boral/Li_2CO_3-Polyethylene/Concrete | Yes | [31] |
| KRR     | Be/Fluental/Ni/B-Polyethylene | Yes | [76] |
| LVR-15  | Al/AlF_3/Pb/B-Polyethylene | No | [80] |
| MARIA   | Graphite/Pb/Al/AlF_3/Cd/Bi | Yes | [51] |
| R2-0    | Al/Bi/Teflon/D_2O/Polyethylene B-Pb/Li | No | [130] |
| RPI     | Be/Al/Pb/Polyethylene/Concrete | No | [89] |
| TAPIRO  | AlF_3/Ni/Pb/Li-Polyethylene-Concrete | No | [91] |

Figure 14. Plan view of the some BSA in Europe: (a) HFR [69], (b) DIDO [62], (c) FiR-1 [63], (d) TAPIRO [91].
Table 10. Calculated (C) or Measured (M) parameters of some European BNCT beams.

| Reactor | Mode   | M/C | $\phi_{\text{thermal}}$ ($\times 10^8 \text{cm}^{-2}\text{s}^{-1}$) | $\phi_{\text{epi}}$ ($\times 10^9 \text{cm}^{-2}\text{s}^{-1}$) | $\phi_{\text{fast}}$ ($\times 10^7 \text{cm}^{-2}\text{s}^{-1}$) | $D_{\text{fast}}/\phi_{\text{epi}}$ ($\times 10^{-13} \text{Gy/cm}^2$) | Ref. |
|---------|--------|-----|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----|
| HFR     | Epithermal | M   | 0.07                                           | 0.37                                           | 7.5                                              | 11                                              | [102] |
|         |        | C   | 0.04                                           | 0.32                                           | 4.7                                              | 6.4                                              |     |
| FiR-1   | Epithermal | M   | 0.72                                           | 1.07                                           | 3.4                                              | 1.5                                              | [102] |
|         |        | C   | 0.66                                           | 1.03                                           | 3.2                                              | 1.4                                              |     |
| LVR-15  | Epithermal | M   | 0.38                                           | 0.65                                           | 5.5                                              | -                                                | [80]  |
| TAPIRO  | Epithermal | C   | 0.0566                                         | 3.02                                           | 51.9                                             | 6.5                                              | [91]  |
| KRR     | Epithermal | C   | 0                                             | 3–5                                            | -                                                | -                                                | [76]  |

Neutron generators are devices which contain a compact linear accelerator. They can produce neutrons using the reaction $T(d,n)^4\text{He}$ or $D(d,n)^3\text{He}$. However, the d-T-reaction generates high energy neutrons (14 MeV) which are difficult to moderate; and the d-D reaction does not deliver a high neutron flux. Their advantages are the smallness of these neutron generators, their relatively low price and the possibility to install them in a hospital environment [37, 42, 135, 141].

$^{252}\text{Cf}$ sources need more frequent source replacement due to a short half-life of 2.6 years. It decays either by alpha particle emission or by spontaneous fission with branching ratio of 96.9% to 3.1%, respectively. Furthermore, for BNCT a source of the order of 1 g would be needed which is very difficult to obtain. A treatment trial in Thailand using $^{252}\text{Cf}$ interstitially for cervix carcinoma in combination with boron could not be continued. Thus, the use of $^{252}\text{Cf}$ is not realistic [142, 143].

In contrast to reactors, accelerators can be easily turned on and off. Their operation and management cost would be lower [2]. Recently Japanese unveiled several accelerator-based BNCT facilities to treat tumors [144–146] — as an example, see figure 15. The main advantage of hospital-based accelerators is related to their better acceptance by the clinicians in comparison with NRRs. The main challenge in the use of accelerators for BNCT is that the particle current to create a sufficient neutron flux should be greater than 10 mA which needs high technology components. It is clear that the spectrum of neutrons generated in accelerator-based neutron sources must be modified to obtain the required epithermal beam using a proper BSA.

Figure 15. Unveiled accelerator-based BNCT equipment at national cancer center in Tsukiji [145].
7 Conclusions

All our knowledge about BNCT is indebted to research made in NRRs. The results of about 60 years research in BNCT and also the demonstrated advantages of this method for treatment of cancers show that to develop BNCT as a routine cancer therapy, a non-reactor based neutron source is needed. Achieving a comprehensive data collection on BNCT based on NRRs will be helpful for beam designers in developing a hospital-based neutron beam.

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