Journal of Neuro-Oncology **62:** 7–17, 2003.

Fission reactor neutron sources for neutron capture therapy – a critical review

Otto K. Harling and Kent J. Riley
Nuclear Engineering Department, Nuclear Reactor Laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA

Key words: neutron capture therapy beams, critical review

Summary

The status of fission reactor-based neutron beams for neutron capture therapy (NCT) is reviewed critically. Epithermal neutron beams, which are favored for treatment of deep-seated tumors, have been constructed or are under construction at a number of reactors worldwide. Some of the most recently constructed epithermal neutron beams approach the theoretical optimum for beam purity. Of these higher quality beams, at least one is suitable for use in high through-put routine therapy. It is concluded that reactor-based epithermal neutron beams with near optimum characteristics are currently available and more can be constructed at existing reactors. Suitable reactors include relatively low power reactors using the core directly as a source of neutrons or a fission converter if core neutrons are difficult to access. Thermal neutron beams for NCT studies with small animals or for shallow tumor treatments, with near optimum properties have been available at reactors for many years. Additional high quality thermal beams can also be constructed at existing reactors or at new, small reactors. Furthermore, it should be possible to design and construct new low power reactors specifically for NCT, which meet all requirements for routine therapy and which are based on proven and highly safe reactor technology.

Introduction

To date the overwhelming majority of research and clinical studies in neutron capture therapy (NCT) have used neutron beams generated by fission reactors. Undoubtedly, this is due to the fact that there are already many high intensity reactor neutron sources operating worldwide. Reactors which have been or are being used for NCT studies include the Massachusetts Institute of Technology Research Reactor (MITR) [1–3], the Brookhaven Medical Research Reactor (BMRR) [4,5], the High Flux Reactor at Petten in the Netherlands [6], the Studsvik reactor in Sweden [7], FiR1 reactor at the University of Helsinki, Finland [8], the LVR-15 reactor at NRI in Rez, Czech Republic [9,10], the Kyoto University Research Reactor in Japan [11,12], JRR4 at JAERI in Japan [13], and the Musashi Institute of Technology Reactor in Japan [14]. Other reactor-based facilities for NCT which have been constructed or are being constructed include the McCellan Nuclear Radiation Center Reactor at Davis, California [15], Washington State University reactor in Pullman, Washington [16], the RA-6 reactor in Bariloche, Argentina [17] and the Taiwan Research Reactor in Taiwan, Republic of China [18]. Design activities for reactor-based NCT neutron sources are in progress in several countries including Korea, Slovenia, Russia and the Peoples Republic of China.

In this paper, we provide a review of the status of fission reactor beams for NCT. We will start by summarizing the physics and other desirable requirements for NCT neutron beams and then compare some currently available reactor beams with these requirements. A currently available high performance epithermal neutron beam will be compared with a theoretical optimum reactor-based beam. Options for the construction of reactor-based NCT facilities will be briefly discussed and examples given of two approaches to reactor-based beams. No attempt has been made in this paper to compare reactor-based beams and accelerator produced

beams for NCT. An objective comparison of reactor and accelerator sources is not a trivial undertaking.

Technological approaches to NCT beams at reactors

The BMRR and the MITR are the only two reactor facilities that were designed and constructed specifically for NCT. The BMRR [4,5] was designed with two horizontal beams and the MITR [2,3] with one vertical beam. Both facilities were initially designed for thermal neutron NCT. One of the BMRR's beams was later converted to an epithermal beam. Similarly, the MITR thermal beam was converted to an epithermal beam (M67) and following completion of the epithermal fission converter beam (FCB), in 2000; this beam has been rebuilt into a thermal beam. All other current NCT beams have been constructed by making appropriate modifications to reactors. Most if not all such modifications were designed to produce epithermal neutron beams which could be used to irradiate deep-seated tumors without the need for surgery to reflect surface tissues. The exceptions to this trend are in Japan, where the initial US experience with intraoperative thermal neutron irradiations was continued and refined. Recently, however, the newest Japanese NCT facilities have been constructed to allow irradiations with thermal, epithermal or mixed energy neutron beams [11–13].

Two general approaches to modifying reactors for epithermal NCT have been used. In most modifications, the core neutrons have been accessed directly by removing as much moderator as possible on one core face and adding a large area beam line with filter moderators, thermal neutron and photon shielding and some collimation. The other approach to modifying existing reactors has been to use a large area thermal neutron beam, which is often found in the thermal column of research reactors, to drive a fission converter that produces the neutron source for the epithermal beam. The rest of the beam line is then similar to those facilities which use the core directly as a source. Beam shutters are used in some of these designs while in others, especially at the lower power reactors, which can often be dedicated exclusively to NCT irradiations, beam shutters may not be essential. Beam shutters usually result in some increases in the overall length of the epithermal beam line, and this can therefore have a significant effect on the intensities available at the patient position. However, beam shutters are important for limiting dose to the clinical staff and in decoupling other reactor uses from the needs of the NCT irradiations.

A good example of a reactor conversion, which uses the core directly in a low power 250 kW TRIGA reactor, is the Finnish facility at FiR1 [8]. This epithermal beam facility has an intensity of 1.1×10^9 n cm^{-2} s^{-1}, a low specific beam contamination (physical dose per unit of neutron fluence) of 2×10^{-13} and 0.5×10^{-13} Gy cm^2, respectively for fast neutrons and gamma rays and good collimation, $J/\phi = 0.77$. Figure 1a shows an isometric drawing of the irradiation facility at FiR1. The main components of the beam line are labeled in Figure 1b.

There is currently one operating fission converter based epithermal neutron irradiation facility, the FCB [1] at the MITR. Other fission converter based facilities have been designed and one is under construction [15]. Figure 2 shows an isometric view of the FCB with the main components labeled. The converter, currently 10 spent MITR fuel elements, operates at 83 kW of fission power with the MITR at 5 MW. This could be increased to the license limit of 250 kW by using different fuel and by increasing reactor power to 10 MW. Currently an application is pending with the USNRC for a 20% increase in reactor power. Shutters are used to decouple the operation of the FCB from other uses of MITR. A patient collimator mounted at the end of the beam line is sufficiently long to allow patient positioning for every conceivable target location on the human body. The epithermal beam, with a 16 cm diameter circular collimator aperture, has an intensity of 5×10^9 n cm^{-2} s^{-1}, specific beam contamination of 1.2×10^{-13} Gy cm^2 and 3.2×10^{-13} Gy cm^2, respectively for fast neutrons and gamma rays and very good collimation $J/\phi = 0.84$.

In recent years, no new reactors specifically designed for NCT have been constructed. However, existing reactors have been able to provide adequate beams for NCT research. If in the future NCT can be shown to be an improved form of therapy new reactor-based designs for NCT would be worthy of consideration. These designs could be based on existing well proven technology for low power ultra safe reactors [19,20]. Extrapolating from actual experience and from design studies, it is likely that a reactor source with a power less than 100 kW could be designed to produce an epithermal neutron beam which combines the intensity and beam quality desired for routine therapy. In the next section, we discuss the requirements for neutron beams to be used in limited clinical studies and for routine therapy.

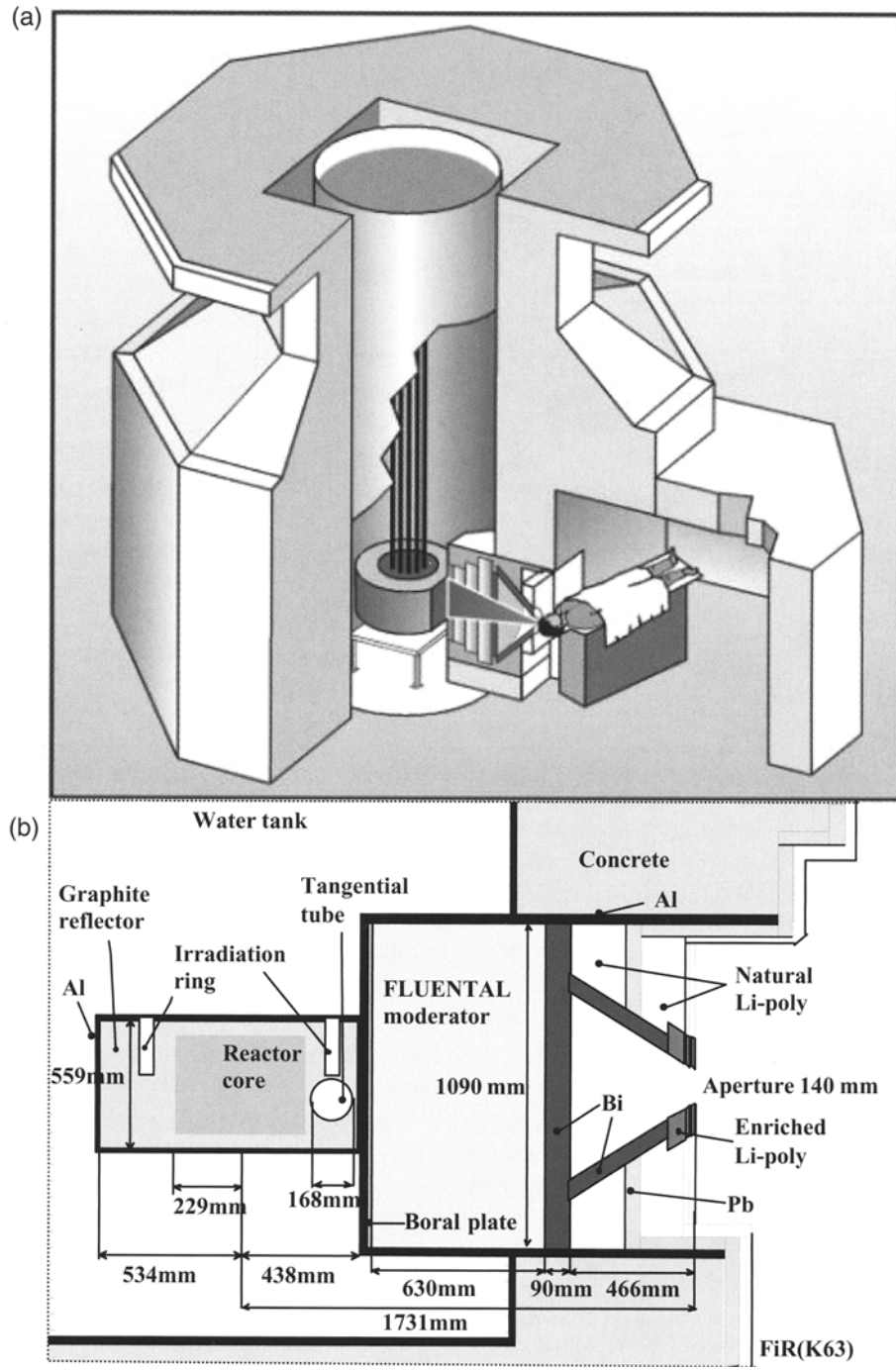

Figure 1. FiR1 epithermal neutron irradiation facility at the 250 kW reactor of the Technical University of Helsinki. (a) Is an overall isometric view of the irradiation facility and (b) provides a labeled and dimensioned drawing of a side view of the beam line.

Requirements for NCT neutron beam facilities

Table 1 provides our suggestions for the desirable characteristics of reactor-based neutron beams. Two energy ranges epithermal, $0.4\,\text{eV} < E < 10\,\text{keV}$ and thermal, $0 < E < 0.4\,\text{eV}$, are listed in the table to bring some realism to this characteristic. One justification for specifying a range of neutron energies is that NCT is of the greatest potential utility for the treatment of tumor cells which are widely dispersed in normal tissue. This implies that relatively large volumes of normal tissue would be treated by NCT without seriously damaging

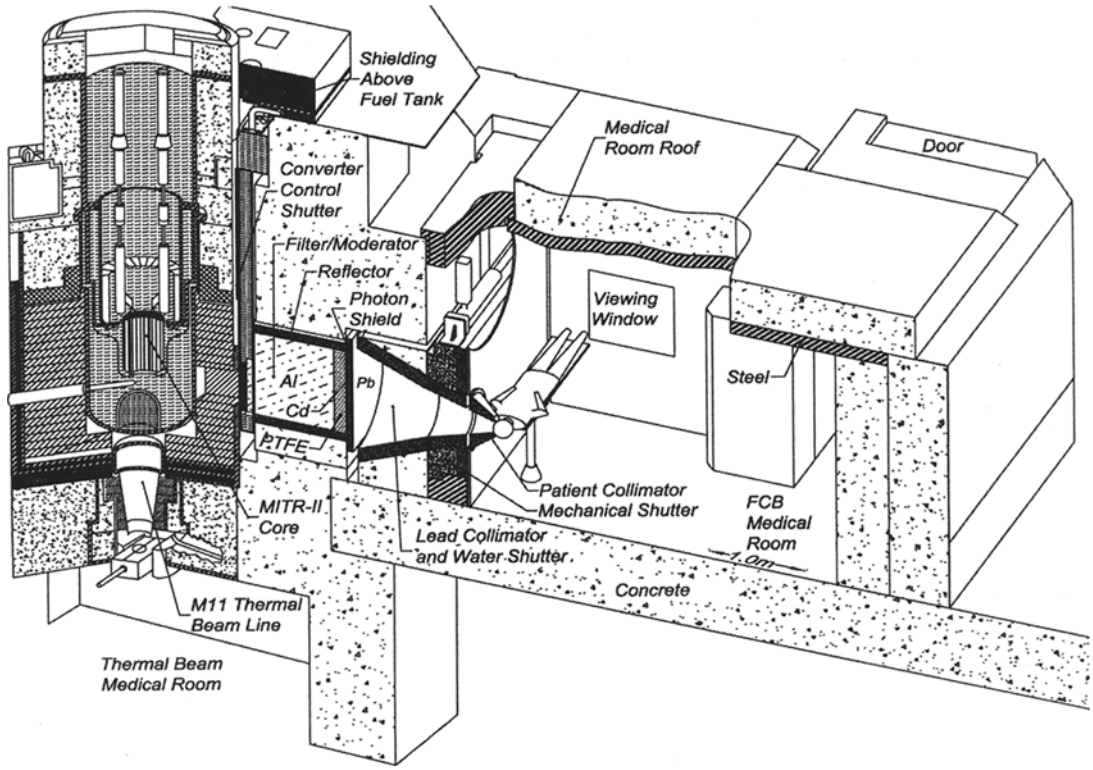

Figure 2. An isometric view of the MITRR showing the new fission converter-based beam and the original vertical thermal neutron irradiation facility. Major components are labeled.

Table 1. Suggestions for the desirable properties of thermal and epithermal neutron beams for NCT

	Epithermal neutron beams	Thermal neutron beams
Energy	$0.4\,\text{eV} < E < 10\,\text{keV}$	$0 < E < 0.4\,\text{eV}$
Intensity	$>2 \times 10^9\,\text{n cm}^{-2}\,\text{s}^{-1}$	$>0.5 \times 10^9\,\text{n cm}^{-2}\,\text{s}^{-1}$
Contamination	$\lesssim 2.8 \times 10^{-13}\,\text{RBE Gy cm}^2$ for gamma and fast neutron	$\lesssim 2.8 \times 10^{-13}\,\text{RBE Gy cm}^2$ for gamma and fast neutron
Collimation (J/ϕ)	>0.75	—
Advantage depth	>9 cm	>4 cm
Beam size	0 to >16 cm diameter	0 to >16 cm diameter

Intensities are estimated for one-field irradiations to tolerance, about 12.5 RBE Gy, in 30 min or less using an advanced capture compound.

the normal tissue. For example in the case of glioblastoma multiforme (GBM) it is likely that the whole brain or at least one hemisphere will require treatment to eliminate microscopically dispersed viable tumor cells. This suggests that there is no single ideal neutron energy for an epithermal beam. Furthermore, it has been shown that a wide range of epithermal neutron energies can produce useful therapeutic ratios (TRs) at most depths in human targets [21]. Another reason, a practical reason, for specifying a range of energies is that there is no way to use a reactor to produce anything but a wide range of epithermal energies if adequate

intensity for NCT is to be achieved. Beams with thermal neutron energies are also listed in the table because such beams are useful in the treatment of superficial malignancies, for intraoperative NCT and for small animal experiments.

Suggested intensity requirements in the table are based on the completion of a single field irradiation in a patient in less than ~30 min with an advanced capture compound which produces a high 10 : 1 ratio for boron in tumor relative to normal tissue. In estimating the desired intensity or flux we have assumed the following. A tolerance dose of 12.5 (RBE) Gy, boron concentration of 5.25 ppm in critical normal tissue for a brain irradiation using epithermal neutrons and 7.9 ppm for skin in a thermal neutron irradiation. The relative biological effectiveness factors (RBEs) are 1.0 for photons, 3.2 for neutrons, and 1.35, and 2.5, respectively for boron in brain and skin tissue. These RBEs are being used in several BNCT brain cancer trials which use the compound boronated phenylalanine (BPA). Several beam placements are generally used for NCT irradiations especially for brain irradiations. Therefore, the suggested ~30 min irradiation time for one field translates into more than one hour for the typical brain treatment comprised of two or three fields. We suggest that this is acceptable for low through-put clinical trials such as are currently in progress at various NCT research centers. However, intensities, which are considerably higher, for example, 2–5 times higher, will be very desirable for routine NCT therapy.

Contamination in the NCT beams should be low compared to the inherent, non-discriminating dose components from neutron capture in hydrogen and nitrogen. These unavoidable adventitious dose components are $\sim 2.8 \times 10^{-12}$ RBE Gy cm^2 for brain irradiations again using RBEs of 1.0 and 3.2, respectively for gammas, fast neutrons and recoil protons from neutron capture in nitrogen.

Collimation, conveniently specified as the neutron current to flux ratio (J/ϕ), is important in limiting collateral dose and in reducing the effects of positioning errors in the axial or beam direction. Good collimation also increases useful beam penetration under conditions where the beam size is smaller than the target [21].

The advantage depth (AD) [22] is a figure of merit, which provides information on the maximum depth for which the TR, dose to tumor divided by peak dose to normal tissue, is greater than one. The AD must be larger than the maximum tumor depth for effective therapy.

Beam size and collimator configuration at the patient position should allow flexibility in treating any accessible site on the body. Clinical irradiations have to date focused on brain and peripheral melanoma irradiations. Variable beam sizes up to ~16 cm are desirable for brain irradiations to permit irradiation of the entire brain. The average lateral dimension, ear to ear, of the adult human head, including skin and scalp, is 16 cm. For brain irradiations the AD should be >8 cm in order to produce a TR greater than 1 at the brain midline. In fact ADs 9 cm or greater are important for treating deep-seated disease in the central nervous system. With high TRs achievable using advanced boron capture compounds it is conceivable that larger targets than the human brain can be treated. Therefore, beams of greater size than 16 cm could be useful. Other sites such as lungs, liver, female breast, and prostate are potential future targets for NCT.

Current beams and ideal beams

Figure 3 is a plot, which shows the free in-air epithermal flux *versus* the sum of the RBE weighted specific dose from gamma plus fast neutron contamination for several reactor-based neutron beams around the world. These in-air figures of merit are a measure of a beam intensity and purity and provide a convenient way to compare the various beams. Although in-phantom figure of merit such as those described earlier are more indicative of the therapeutic properties of a given beam, they are not often available on a common basis for direct comparison. Measured in-air data for epithermal neutron beams that are currently operative are shown with solid symbols. The Studsvik facility is presently operating, but measured data is not yet available, and has therefore not been included in Figure 3. Beams which are in the design phase, under construction or have been decommissioned are shown with open symbols. A vertical dashed line, at 2.8×10^{-12} RBE Gy cm^2, indicates the unavoidable non-selective dose components in an NCT brain irradiation. This adventitious dose is due primarily to neutron capture in the hydrogen and nitrogen of the target tissue. The figure also has two nearly horizontal solid curves which represents the minimum intensity required to irradiate a patient to tolerance, assumed to be 12.5 RBE Gy, in a 30 min irradiation, for two capture compounds. The lower curve is for

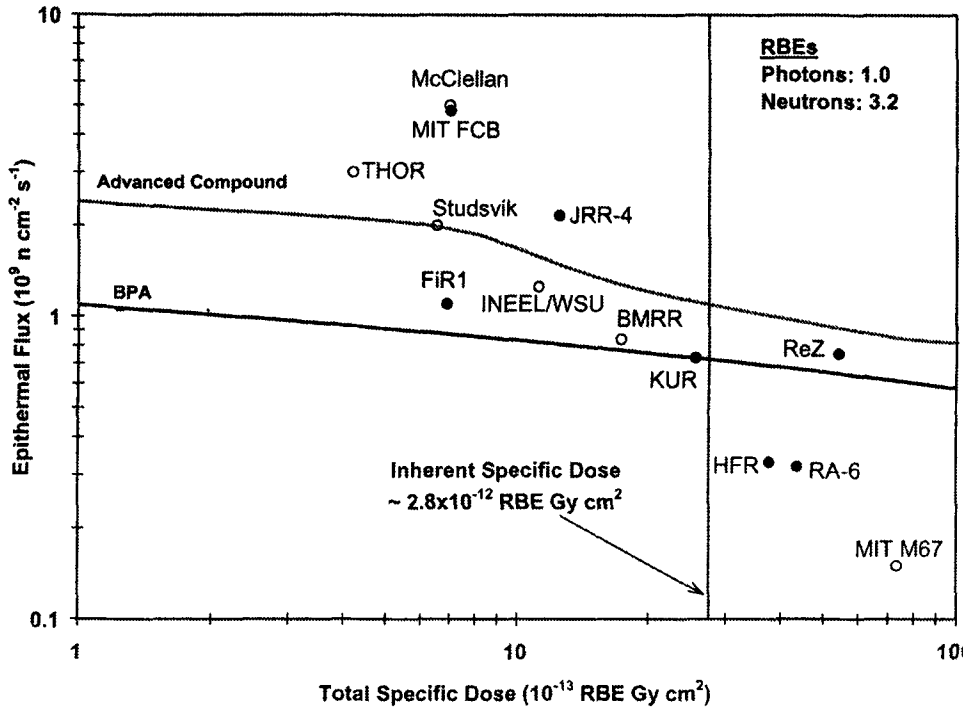

Figure 3. Neutron flux and specific dose from photons and fast neutrons in the beam are plotted for several NCT beam facilities around the world. Those labeled with solid circles, • refer to measured data in epithermal neutron beams that are currently in operation. Hollow circles, ○ refer to epithermal neutron facilities which are under construction, planned, or which have been decommissioned. The dashed vertical line at 2.7×10^{-12} RBE Gy cm^2 represents the unavoidable non-selective dose components created from neutron interactions in tissue. The nearly horizontal curves represent the intensities which are required to complete a single field irradiation to tolerance in 30 min, assumed to be 12.5 RBE Gy for two different capture compounds. The lower curve is for a currently available compound such as BPA and assumes 15 ppm of boron in tissue while the upper curve is for an 'ideal' compound with 5.25 ppm boron in tissue. The best beams are in the upper left-hand part of the figure. The RBEs are those which are currently being used in brain irradiations with the BPA compound.

a currently available compound such as BPA assuming boron concentrations of 15 ppm in tissue and 52.5 ppm in tumor. These numbers are consistent with concentrations observed using BPA-F infusions of 350 mg kg^{-1} over 1.5 h. The upper curve is for an advanced compound, which has a 10/1 ratio of boron in tumor relative to normal tissue and 5.25 ppm normal tissue concentration. The dashed vertical line and solid nearly horizontal lines define regions in the upper left-hand part of the figure which we suggest as the desirable goal for NCT beam performance. The figure shows the importance of high intensity with low beam contamination especially in the case of advanced capture compounds with high tumor to normal tissue boron concentration ratios.

Advanced compounds with improved T/N boron ratios and high purity beams provide better TRs and increased effective treatment depths or ADs. These conditions also imply the need for epithermal beam intensities in excess of 2×10^9 n cm^{-2} s^{-1} to limit treatment times to ~30 min. Intensities several times higher than 2×10^9 n cm^{-2} s^{-1} would be needed for high through-put routine therapy.

Figure 3 shows that it has been possible to design and construct high quality reactor-based epithermal neutron beams, which allow treatments of deep-seated tumors in a reasonable time, <30 min when using advanced and highly tumor selective capture compounds. One of the currently operating beams, the MIT FCB, has a sufficiently high intensity and beam quality to allow high through-put routine treatments with advanced compounds. The facility currently under construction at McClellan and the facility designed for THOR are also expected to have beam characteristics

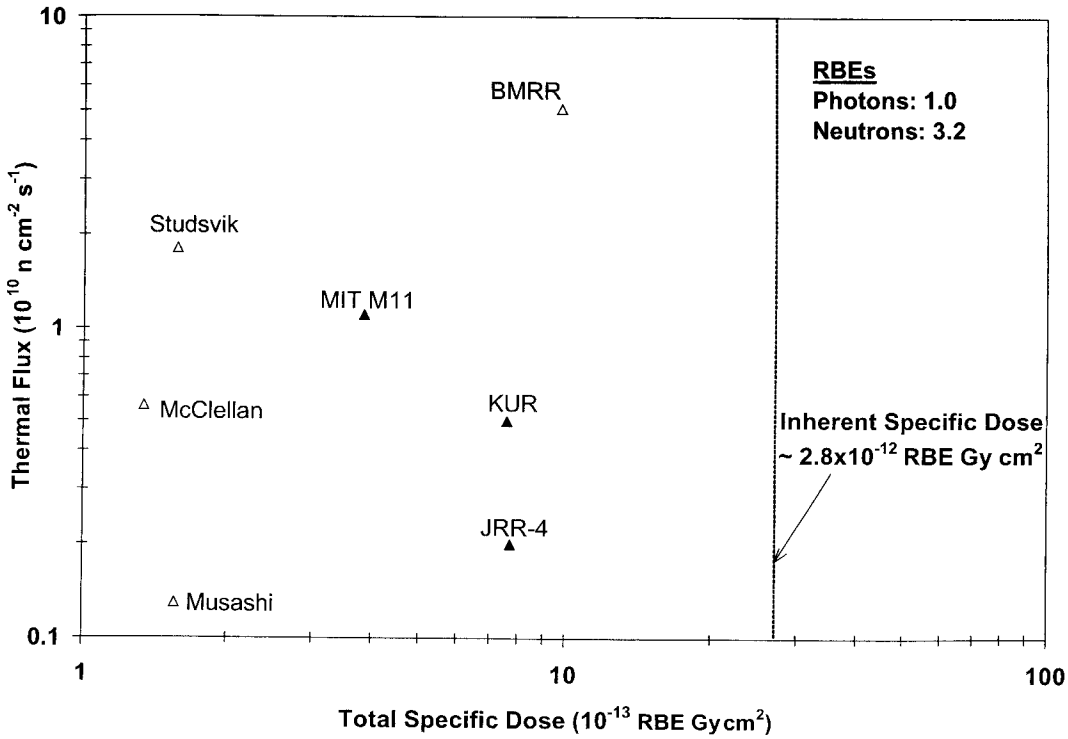

Figure 4. This figure provides the in-air intensities of existing, solid triangles ▲, and planned or decommissioned, hollow triangles △, thermal neutron irradiation facilities. The vertical dashed line indicates the inherent non-selective dose components from neutron irradiations. All of these facilities have sufficient intensity to reach a tolerance dose of 12.5 RBE Gy in less than 30 min using an advanced compound. The RBEs are the same as were used in Figure 3 for epithermal neutrons. Figure 4 shows that a number of reactor-based thermal neutron irradiation facilities have been constructed which meet and exceed the criteria summarized in Table 1. In fact, most of these facilities have high enough intensity and beam quality to make them well suited for high through-put irradiations of small animals or shallow tumors in human targets.

suitable for high through-put routine therapy, and it is possible that some of the other existing beam facilities can be significantly increased in intensity without a decrease in beam quality. Intensity can also be traded for further filtration. For example, a ^{6}Li filter can be used to shift the location of the thermal neutron peak over a few centimeters as has been demonstrated at Studsvik [7], and thereby optimize the TR at a depth which gives the best expectation of tumor control.

Figure 4 provides the in-air intensities and the RBE weighted specific dose of existing, planned and decommissioned thermal neutron irradiation facilities for NCT [7,11–15,23–25]. The vertical dashed line indicates the inherent non-selective dose components from neutron irradiations. Figure 4 shows that a number of reactor-based thermal neutron irradiation facilities have been constructed which meet and exceed the criteria for purity and intensity summarized in Table 1. In fact, most of these facilities have high enough intensity and beam quality to make them well suited for high through-put irradiations of small animals, cell cultures or shallow tumors in human targets.

Thermal neutron beams suited for NCT are relatively easy to construct at reactors and many small and medium-sized research reactors could be used for this purpose.

Other applications of NCT, for example boron neutron capture synovectomy or BNCS [26], and prompt gamma neutron activation analysis for ^{10}B analyses in biological samples [27], can be carried out very effectively at small and medium-sized research reactors. In BNCS, the boron concentrations in the target tissue are an order of magnitude higher than in the case of boron NCT for cancer. This implies that much lower intensity and lower beam purity is required for

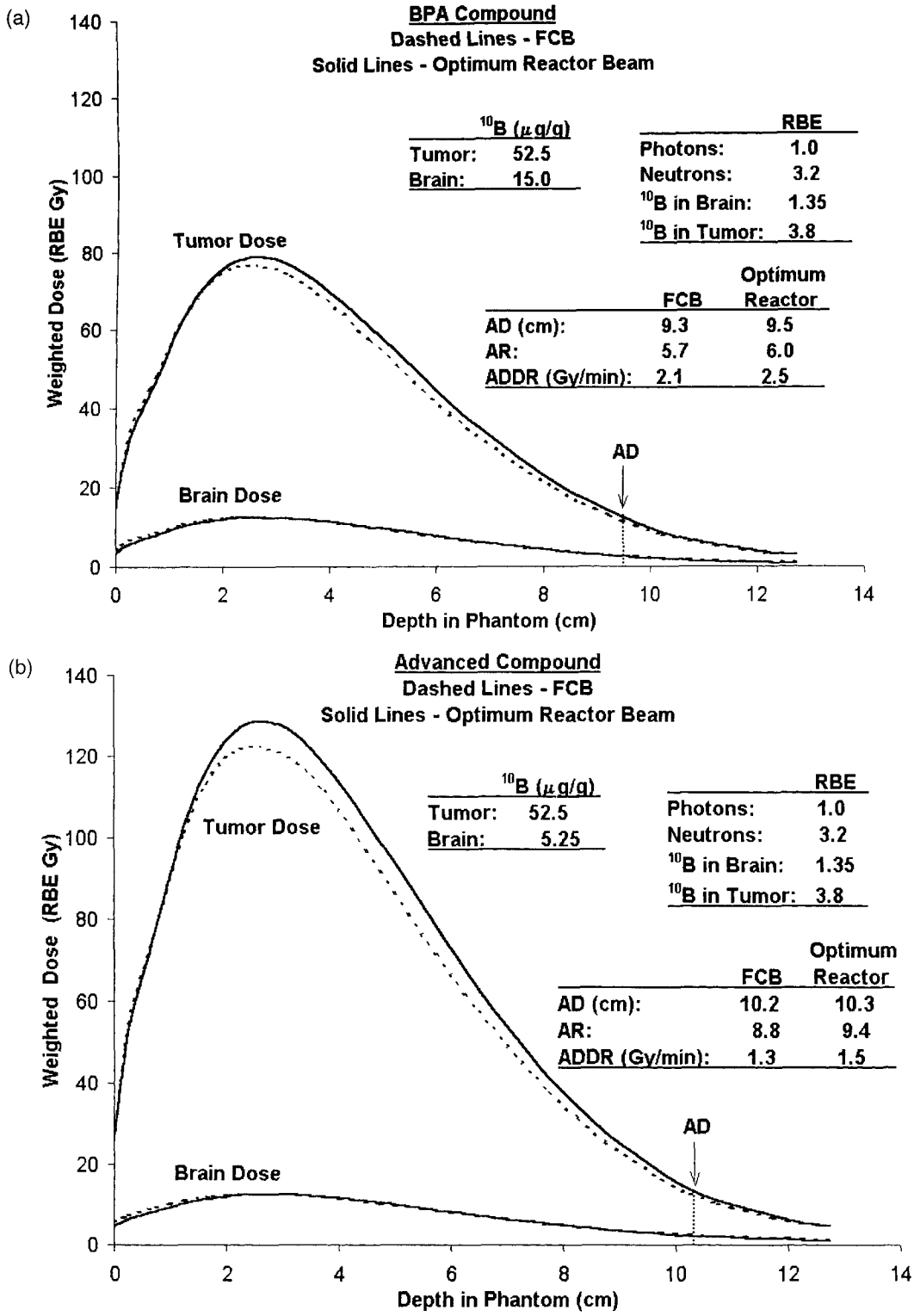
(a)
BPA Compound
Dashed Lines - FCB
Solid Lines - Optimum Reactor Beam
10B (μg/g)
Tumor: 52.5
Brain: 15.0
RBE
Photons: 1.0
Neutrons: 3.2
10B in Brain: 1.35
10B in Tumor: 3.8
FCB
Optimum Reactor
AD (cm): 9.3 9.5
AR: 5.7 6.0
ADDR (Gy/min): 2.1 2.5
Tumor Dose
Brain Dose
AD
Weighted Dose (RBE Gy)
Depth in Phantom (cm)
(b)
Advanced Compound
Dashed Lines - FCB
Solid Lines - Optimum Reactor Beam
10B (μg/g)
Tumor: 52.5
Brain: 5.25
RBE
Photons: 1.0
Neutrons: 3.2
10B in Brain: 1.35
10B in Tumor: 3.8
FCB
Optimum Reactor
AD (cm): 10.2 10.3
AR: 8.8 9.4
ADDR (Gy/min): 1.3 1.5
Tumor Dose
Brain Dose
AD
Weighted Dose (RBE Gy)
Depth in Phantom (cm)

Figure 5.

BNCS than for BNCT. Thermal or epithermal beams of $\sim 10^8$ n cm^{-2} s^{-1} should be adequate for BNCS. Such beams with adequate purity can readily be produced at small and medium power research reactors.

To illustrate how closely the dose *versus* depth distributions for one of the best current epithermal neutron beams compares with the distribution for a theoretically optimum reactor-based beam we have compared these in Figure 5a,b. The optimum reactor beam has an intensity which varies as $1/E$ with no thermal ($E < 0.5$ eV) and fast neutron ($E > 10$ keV) or photon contamination. This optimum reactor beam is compared with the MIT FCB using two capture compounds. Collimation for both beams is assumed to be the same as for the FCB [1], or $J/\Phi = 0.84$. Figure 5a presents the results for the currently available BPA compound assuming, $T/N = 3.5$ ppm, and 15 ppm and 52.5 ppm boron concentration respectively in normal tissue and tumor. Doses are in RBE Gy for a hypothetical irradiation to a maximum normal tissue dose of 12.5 RBE Gy. Brain RBEs are used. Figure 5b presents the dose distributions for an advanced compound, $T/N = 10$ with 52.5 ppm boron in tumor and 5.25 ppm in normal tissue.

Figure 5a,b shows only a small difference between the performance of the FCB and an optimum reactor beam. The peak tumor doses for the FCB and optimum reactor beam differ by 3% and 5.6%, respectively for BPA and an advanced compound. The fractional difference is greatest when comparing performance using the advanced compound. This is expected since the fraction of dose delivered to normal tissues from the inherent beam contamination increases when the boron dose to normal tissues decreases as a result of the improved T/N boron concentration ratio provided by the advanced compound. Similar conclusions were reached in another study [28]. The TR, dose to tumor/maximum dose to normal tissue, is a good measure of the expected performance of a beam. In Figure 6, we have plotted the TR for the FCB and the optimum reactor beam with BPA and the advanced compound. There is only a small difference between the TRs obtained with the FCB and the theoretically optimum reactor beam. These results clearly indicate that some existing epithermal neutron beams closely approach the theoretical optimum NCT dose distribution for a fission reactor source.

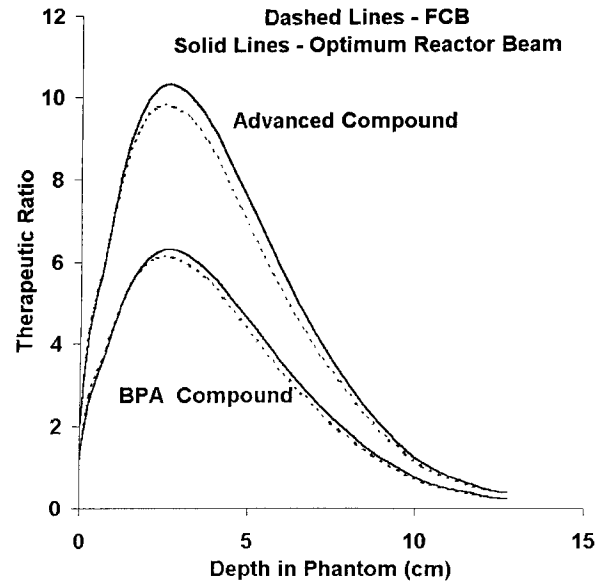

Figure 6. This figure shows the TR (dose to tumor/maximum dose to normal tissue), for hypothetical brain irradiations using the MIT FCB and an optimum reactor-based beam. The TR is calculated as a function of depth using the results shown in Figure 5a,b.

Summary

In this paper, we have critically reviewed the current status of fission reactor sources for NCT. Epithermal neutron beams are emphasized but thermal neutron beams are also discussed. Recently several epithermal neutron irradiation facilities have been constructed which combine near theoretically optimum beam purity with intensities which are well suited to clinical studies. One of these facilities also has adequate intensity for routine high through-put therapy and another such facility is under construction. It has been demonstrated that reactor-based epithermal neutron irradiation facilities with near optimum characteristics can be

Figure 5. (a) is a comparison with the FCB and an optimum reactor-based beam for a brain irradiation using the BPA capture compound, which has a T/N boron concentration ratio of 3.5. Boron concentrations are assumed to be 15 and 52.5 ppm, respectively in normal tissue and tumor. RBE values used in (a,b) are 1.0, 3.2, and 1.35, respectively, for photons, thermal neutrons and fast neutrons and boron in normal tissue. (b) compares irradiations with the FCB and an optimum reactor-based beam using an advanced capture compound which has a 10/1 ratio of boron in tumor to normal brain, 52.5 ppm and 5.25 ppm, respectively. The irradiation times to achieve a tolerance dose, assumed to be 12.5 RBE Gy, are 4.1 and 6.7 min, respectively using BPA and an advanced compound.

designed and constructed at existing low and medium power research reactors. Furthermore, based upon current technology and experience, it should be possible to design and construct new ultra-safe, low power reactors specifically for routine epithermal neutron based NCT. Incremental improvement in the clinical utility, of even the best current beams, is possible and desirable. For example, further improvements in the dose/depth profile may be achievable with added collimation and with filtration to modify the low energy portion of the epithermal neutron spectrum. Beam intensity will invariably be reduced significantly while specific contamination will increase. Therefore, these strategies for improvements in beam performance are most suited to high intensity beams with low contamination. In addition variable beam filtration and optimized collimator designs can be implemented at a relatively low incremental cost. Reactor produced thermal neutron beams for NCT with high purity and high intensity have been available for many years at low and medium power research reactors. These beams are well suited for small animal studies and for treatment of shallow tumors. Additional thermal neutron beams for NCT research and clinical applications are relatively easy to construct at existing research reactors.

Acknowledgements

The US DOE has provided partial support for the studies reported here under contract numbers DE-FG02-97ER62489 and DE-FG02-96ER62193.

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Address for offprints: Otto K. Harling, Massachusetts Institute of Technology, 138 Albany Street, Cambridge, MA 02139, USA; Tel.: (617)253-4201; Fax: (617)253-7300; E-mail: oharling@mit.edu