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Current status of neutron capture therapy

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FOREWORD

There are about 6000 new glioblastoma multiform brain tumours diagnosed each year in the United States of America alone. This cancer is usually fatal within six months of diagnosis even with current standard treatments. Research on boron neutron capture therapy (BNCT) has been considered as a method of potentially curing such cancers.

There is a great interest at under-utilised research reactors institutions to identify new medical utilization, attractive to the general public.

Neutron capture therapy is a true multidisciplinary topic with a large variety of individuals involved. This publication attempts to provide current information for all those thinking about being involved with NCT, based on the knowledge and experience of those who have pioneered the treatment. It covers the whole range of NCT from designing reactor conversions or new facilities, through to clinical trials and their effectiveness. However, since most work has been done with boron capture therapy for brain tumours using modified thermal research reactors, this tends to be the focus of the report.

One of the factors which need to be addressed at the beginning is the timing of the further development of NCT facilities. It should be emphasised that all current work is still at the research stage. Many of those now involved believe that there is little need for many more research facilities until such time as the treatment shows more promising results. For this and other reasons discussed in the report, very serious consideration should be given by research reactor owners and operators before spending large sums of money converting their facilities for NCT.

Papers presented at the Technical Committee Meeting on Current Issues Related to Neutron Capture Therapy, held in Vienna from 14 to 18 June 1999, are given in the annexes. The contribution of the participants to the drafting of this publication is gratefully acknowledged.

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EDITORIAL NOTE

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OVERVIEW

Rationale and history

Conventional radiation therapy involves the use of high-energy X ray or electron beams. This form of radiation is termed "sparsely ionizing" and is described as having a low linear energy transfer (LET) since the energy depositions in tissue as ionizations are spatially infrequent. A higher absorbed dose to tumour relative to normal tissue is achieved by precise geometric target localization, judicious computer-aided treatment planning and accurate beam delivery systems. Radiotherapy also attempts to exploit the subtle differences in the sensitivity to fractionation between tumour and normal tissues at the biological level.

The biological response to ionizing radiation also depends on the type of radiation and is characterized by its relative biological effectiveness (RBE). Over the energy range of therapeutically used X rays, typically 100 kV to 25 MV, approximately the same physical dose needs to be delivered at different energies to reach a given biologic endpoint, resulting in similar RBEs. High LET radiations, however, result in biologic damage that is generally larger per unit dose than for X rays, resulting in an elevated RBE. Hence a lower dose is required to achieve an equivalent effect.

Neutron capture therapy (NCT) is a technique that was designed to selectively target high LET heavy charged particle radiation to tumours at the cellular level. The concept of NCT was first proposed shortly after the discovery of the neutron by Chadwick in 1932 and the elaboration of the unusually large thermal neutron capture cross-section of the naturally occurring isotope ^{10}B by Goldhaber in 1934. He discovered that ^{10}B had an unusually high avidity for absorbing slow or "thermal" neutrons (energy <0.1 eV). Immediately after capturing a thermal neutron ^{10}B briefly becomes ^{11}B, then immediately disintegrates into an energetic alpha particle back to back with a recoiling ^{7}Li ion. These particles have a combined range in tissue of 12–13 µm (comparable with cellular dimensions) and a combined average kinetic energy of 2.33 MeV. The nuclear reaction that describes the foundation of boron neutron capture therapy (BNCT) is shown in Figure 1.

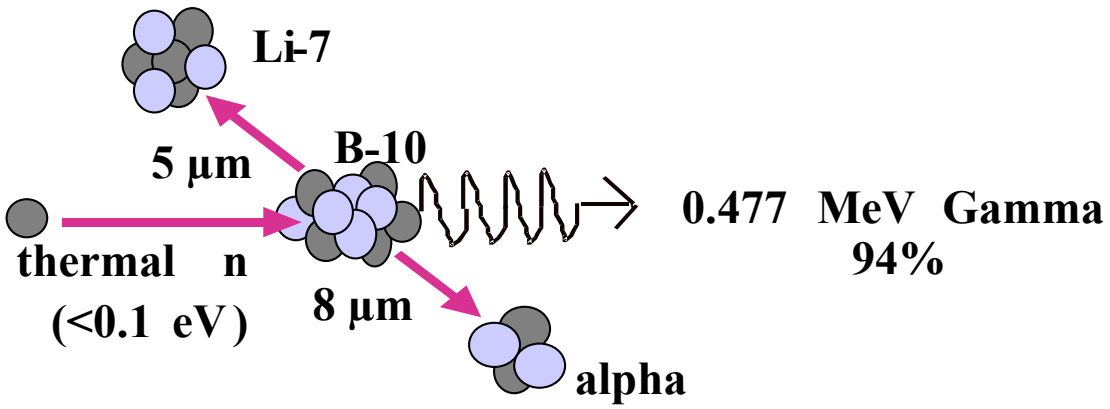

Fig. 1. Nuclear reaction utilized in BNCT. A ^{10}B nucleus absorbs a thermal neutron and promptly emits a back to back ^{7}Li ion and a ^{4}He (alpha) particle. The combined range of 12–13 µm is similar to mammalian cell dimensions.

Gordon Locher first proposed the principle of BNCT as early as 1936. He postulated that if boron could be selectively concentrated in a tumour and the volume then exposed to thermal neutrons, a higher radiation dose to the tumour relative to adjacent normal tissue would result. Targeting is primarily accomplished by selectively concentrating the boron drugs in the tumour rather than by aiming the beam. Therein lies the rationale for the clinical implementation of the concept of BNCT.

BNCT incorporates the targeting principles of chemotherapy and the anatomical localization principles of conventional radiotherapy but with three distinct advantages:

- Current boron compounds at the required concentrations are non-toxic.
- The time interval between drug administration and neutron irradiation can be chosen to maximize the concentration differential between tumour and normal tissue.
- Only the tissues located around the tumour volume are exposed to significant neutron activated boron damage.

Following the earliest suggestions that BNCT might be useful for the treatment of human cancers, interest developed regarding the application of BNCT to primary high-grade brain tumours — glioblastoma multiforme (GBM). It was postulated that the reduction of the blood brain barrier (BBB) in the vicinity of tumour could be exploited to selectively increase the concentration of boron in the brain tumour over normal brain. Initially sodium tetraborate (borax), was used as the vehicle for boron. Perhaps the early interest in applying BNCT to high-grade primary brain tumours stemmed from the fact that this was a cancer with a very poor prognosis. This would ensure that BNCT, even if minimally successful, would nevertheless appear superior to ineffective conventional therapies.

This led to the first clinical trials of BNCT at the Massachusetts General Hospital (MGH) and at the Brookhaven National Laboratory (BNL) using thermal neutrons. These early trials from 1959–1961 demonstrated neither significant prolongation of life nor any evidence of therapeutic efficacy.

The problems that became evident included unacceptable scalp reactions, brain capillary necrosis in isolated cases and persistent disease attributed to insufficient beam penetration.

In an effort to reduce these problems, the MGH initiated a third trial of BNCT at the Massachusetts Institute of Technology Research Reactor (MITR-I) with maximum surgical debulking of the tumour prior to BNCT and irradiation through a reflected scalp and bone flap window. Indeed, the MITR-I research reactor, commissioned in 1958, was designed with a vertical, downwardly-orientated thermal neutron beam in order to facilitate such intraoperative irradiations. As in the earlier BNL trial, there was no evidence of any prolongation of survival with BNCT.

Enhancing selectivity has been an ongoing challenge to chemists developing newer boron compounds with improved concentration ratios. Boron-10 carriers were developed that yielded more favourable tumour-to-brain concentration ratios than were obtainable with borates. Significant boron compounds subsequently used have included sulfhydryl–containing polyhedral borane (BSH) and borated phenylalanine (BPA) with improved tumour to normal tissue boron-10 concentration ratios. Notwithstanding these improvements, a small subset of American patients with confirmed glioblastoma multiforme treated by Hatanaka were

reviewed by Laramore. These patients had no extended survival as compared to historical controls.

In addition to the BNCT treatments of brain tumours as discussed above, Mishima in Japan has employed boronated chlorpromazine and boronated phenylalanine (BPA) (a precursor for melanin) for BNCT of cutaneous malignant melanoma (MM). Mishima has documented clinical tumour regressions in response to BNCT and recorded normal skin and subcutaneous reactions.

More recently, attention has focused on the use of more penetrating epithermal neutron beams in an effort to reduce scalp reaction without the complications of craniotomy. The first BNCT epithermal neutron beam irradiation of a human subject was conducted at the MITR-II research reactor in1994. Because it was felt that inadequately rigorous studies had been conducted to characterise the biological effects of BNCT in humans, let alone the biological effects of epithermal neutrons, it was decided to limit the initial clinical trials to peripheral melanomas. At the same time the first BNCT trial for central nervous system (CNS) tumours was initiated utilising an epithermal neutron beam located at BNL's BMRR reactor.

Conclusion on clinical aspects

BNCT is currently being optimised and evaluated for safety and efficacy in Japan, the U.S. and Europe. At this point BNCT should be regarded as an investigational therapy and patients should only be treated in well designed phase I or phase II clinical trials. A major difficulty facing BNCT is the lack of successful drug development. BNCT is a complex therapy in which interdisciplinary interaction amongst many professionals in indispensable. Major regulatory difficulties should also be taken into consideration when thinking of introducing a clinical BNCT program.

The results of all Phase I (toxicity) and Phase II (efficacy) studies have not yet shown any advantage of BNCT to justify Phase III studies (BNCT randomised against best current practice).

Physics and radiobiology of BNCT

Two different neutron beams are commonly used in BNCT: thermal beams for which therapeutic benefit is limited to shallow depths, and epithermal beams where, with multiple beams, this effect may extend to 8 to 10 cm.

Both types of beams include contributions by fast, epithermal, and thermal neutrons, as well as gamma rays from the neutron source and from the capture and scattering of neutrons in the beam line structures.

In addition to this incident radiation, further radiation components are produced within the body in the form of boron disintegration products, epithermal and fast neutrons, protons from nitrogen capture reactions and gamma rays from hydrogen capture reactions. At every tissue location, the total physical dose consists of the 'boron dose', the fast neutron dose, the nitrogen capture proton dose, and the sum of the gamma doses. The dosimetry of BNCT, therefore, requires the careful analysis of the different components of the radiation field.

To predict a biological effect, the dose arising from each of these four components must first be multiplied by an appropriate weighting factor to account for differences in relative

biological effectiveness and then combined. As will be discussed, the nature of these weighting factors is complex.

Since it is only the 'boron dose' that is the tumour-selective component, the remaining radiation components in the beam should be kept at a minimum. This constitutes an important challenge in beam design. For details on dose components, refer to Section 8.

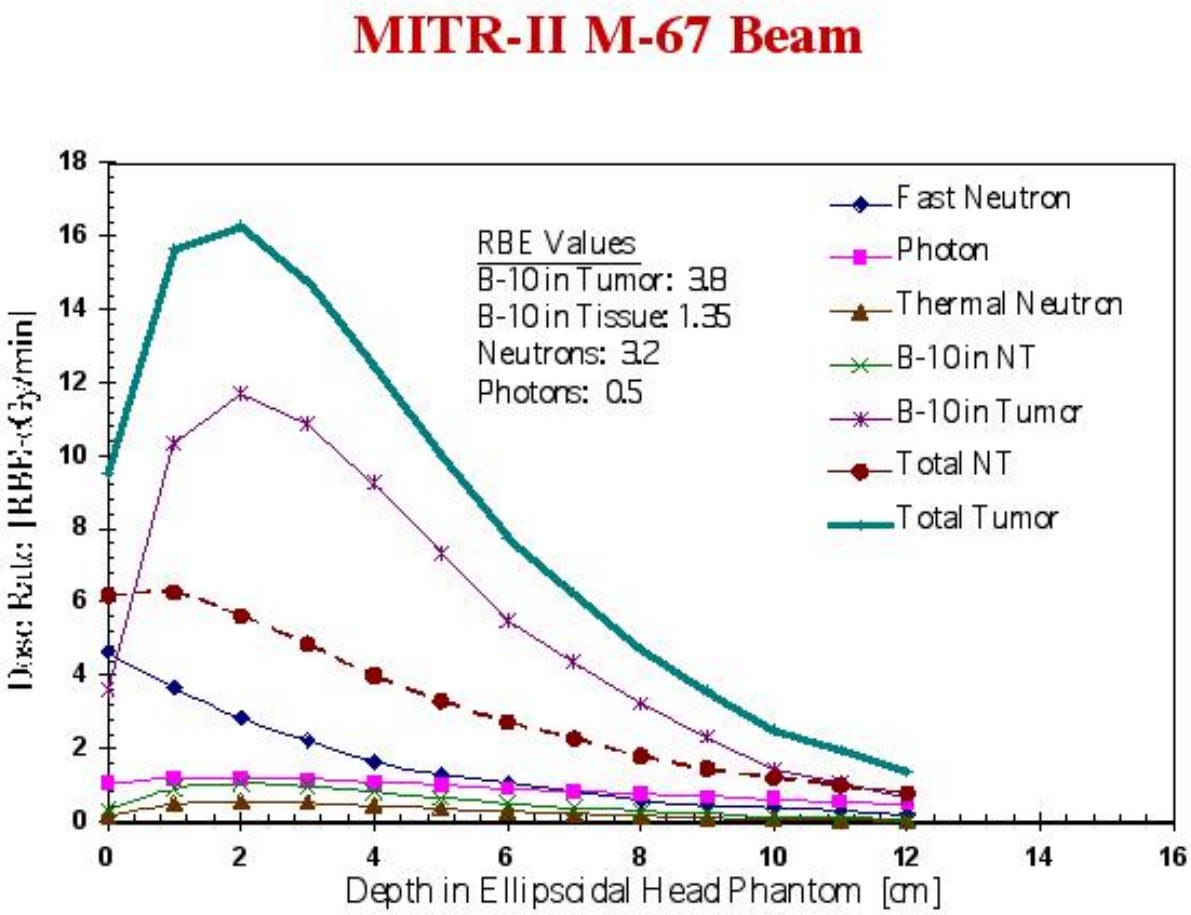

Fig. 2. Weighted depth dose curves showing the various components.

In addition to the above considerations of beam quality, the beam should also be sufficiently intense to ensure that treatment times remain within reasonable limits. This facilitates the procedure for the patient and reduces the problem of patient motion during treatment. It should be realized that whereas conventional radiotherapy fractions are administered within a period of about 10 minutes, current clinical BNCT treatments often extend to a few hours per fraction.

Ongoing and future developments of BNCT

In the year 2000, it is anticipated that a new fission converter-based epithermal beam will be ready for clinical studies at the MITR-II research reactor. It is anticipated that Phase-II (studies of efficacy) and subsequent Phase-III (comparison with best standard practice) studies

will be conducted using this new beam facility. Using the new beam, clinical irradiations could be shortened from the current 3–3 1/2 hours to approximately 5–10 minutes per field. It should be noted that a number of fields may be required in one day to complete a treatment. In addition to facilitating patient setup and increasing patient comfort during BNCT irradiations, the much higher beam quality of this facility compared to the existing epithermal beam should increase the ratio of tumour to tissue dose by a factor of two.

In 1997, a Phase-I clinical BNCT program for glioblastoma multiforme was initiated by a European collaboration at the research reactor facility in Petten, Netherlands. This program uses the boron compound BSH, administered intravenously on four consecutive days, followed by four consecutive daily epithermal neutron irradiations. By mid 1999 the European collaboration program had treated approximately 15 patients.

In 1998, the BNCT research group in Finland commenced a Phase-I clinical trial of BNCT for glioblastoma multiforme using the boron compound BPA-fructose for increased solubility. The protocol involves single BPA administrations followed by single fraction epithermal neutron beam irradiations.

BNCT programs in the Czech Republic, Sweden, and Argentina using BPA and epithermal neutrons, may be initiated in the year 2000, while a new epithermal irradiation facility at the JAERI Research Reactor in Japan should initiate clinical irradiations in the year 2000.

While new irradiation facilities are likely to become available, future success in BNCT is totally dependent on the development of better compounds. Research in this area is independent of the research reactor and its associated personnel and requires the expertise of boron chemists and pharmacologists.

In this document, the terms BNCT and NCT are used interchangeably because much of what is discussed is applicable to NCT regardless of the neutron capture element. However, most work to date has been carried out with boronated compounds.

1. DESIRED NEUTRON BEAM PARAMETERS

1.1. General beam properties

Before addressing the practicalities of current and potential sources of neutrons, how to modify reactors and how to condition beams, it is first necessary to establish the beam characteristics desired for NCT.

For NCT, an adequate thermal neutron field has to be created *in the boron-labelled tumour cells within a prescribed target volume*. This means that for target volumes well below the surface, epithermal beams will generally be best, while for target volumes near the surface, thermal beams will suffice.

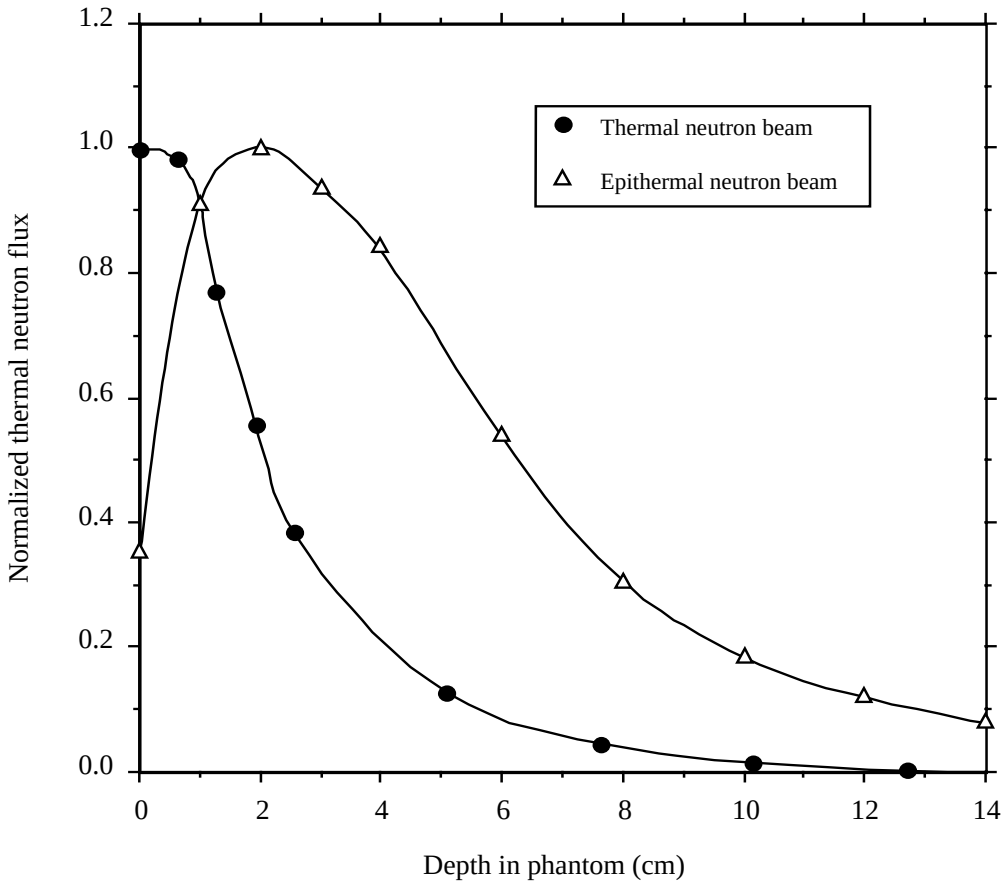

Fig. 1.1. Comparison of flux-depth distributions for thermal and epithermal neutrons.

Figure 1.1. shows that an epithermal beam entering tissue creates a radiation field with a maximum thermal flux at a depth of 2–3 cm, which drops exponentially thereafter. The penetration of the beam can be increased by increasing the average energy of the epithermal neutrons and by increasing the forward direction of the beam, especially with small beam sizes. In contrast to the epithermal beam, which shows a skin-sparing effect, the thermal flux falls off exponentially from the surface.

Thus, thermal neutron irradiations have been used for melanoma treatments in the skin, as well as with open craniotomy for glioma treatments. In general, however, the current trend for treatment of patients with brain tumours is to use epithermal neutron beams.

Radiobiology research for NCT, on the other hand, requires access to both thermal and epithermal beams. Clinical facilities can be used to study the effects of epithermal irradiation, but when studying the effect of boron carrier compounds using cell cultures or small animals, a pure thermal neutron field is preferred.

Most epithermal beams are accompanied by, and produce, other radiations that are not selectively absorbed by labelled cells, and therefore contribute to both normal and tumour tissue damage. It is clearly desirable to reduce these radiations as much as possible in the incident neutron beam. Since the bulk of the report will focus on patient related aspects, it can be stated that the beam design objective is to deliver an epithermal neutron fluence within a reasonable treatment time and to produce the desired thermal neutron fluence at tumour depth with minimal other radiations present.

The two principal beam characteristics of interest are intensity and quality. Beam intensity will be the main determinant of treatment time. Beam quality relates to the types, energies, and relative intensities of all the radiations present.

1.2. Epithermal beam intensity

For the purposes of reporting beam intensity, the common definition for an epithermal energy range should be used, namely 0.5 eV to 10 keV. If other energy limits are used, they should be clearly reported.

Current experience shows that a desirable minimum beam intensity would be 10^9 epithermal neutrons cm^{-2} s^{-1}. Beams of 5×10^8 n cm^{-2} s^{-1} are useable, but result in rather long irradiation times.

When aiming at higher intensities ($>10^{10}$) the advantages of shorter irradiation times must be weighed against those of improved beam quality. Where there is a choice to be made, most practitioners would rather have better quality rather than more intensity, within the constraint of having a reasonable treatment time (possibly extending up to one hour). Requiring immobilization of patients for significantly longer times reduces the clinical acceptability of BNCT as a therapy.

Tumour boron concentration will affect the requirements for beam intensity. If the boron concentration can be raised from the currently values, the beam intensity requirement (or treatment time) will be reduced proportionately. On the other hand, if the beam intensity is too low, it may be difficult to maintain the necessary boron concentration in the tumour for the total irradiation time required. To avoid unduly lengthy irradiation times, fractionation may be considered as an alternative. It could also provide opportunity for boron compound retargeting.

1.3. Incident beam quality

Beam quality is determined by four parameters under free beam conditions. They are discussed below in order of importance.

1.3.1. The fast neutron component

In BNCT the energy range for fast neutrons is taken as >10 keV. Fast neutrons, which invariably accompany the incident beam, have a number of undesirable characteristics such as the production of high LET protons with a resulting energy dependence of their induced biological effects. Therefore, it is one of the main objectives of BNCT beam design to reduce the fast neutron component of the incident beam as much as possible.

Another major objective is clearly to have as high an epithermal flux as possible. In existing facilities the range of dose from this component is from 2.5 to 13×10^{-13} Gy cm^2 per epithermal neutron. A target number should be 2×10^{-13} Gy cm^2 per epithermal neutron.

1.3.2. The gamma ray component

Because of the energy range of the gamma radiation, it results in an non-selective dose to both tumour tissue and a large volume of healthy tissue. Hence it is desirable to remove as much gamma radiation from the beam as possible. Since there are also (n,γ) reactions occurring inside the patient, the importance of this component in the incident beam is somewhat reduced. Nevertheless, a target number for this should be 2×10^{-13} Gy cm^2 per epithermal neutron**.** The range in existing facilities is from 1 to 13×10^{-13} Gy cm^2 per epithermal neutron.

1.3.3. The ratio between the thermal flux and the epithermal flux

To reduce damage to the scalp, thermal neutrons in the incident beam should be minimized. A target number for the ratio of thermal flux to epithermal flux should be 0.05.

1.3.4. The ratio between the total neutron current and the total neutron flux

This ratio provides a measure of the fraction of neutrons that are moving in the forward beam direction. A high value is important for two reasons: (1) to limit divergence of the neutron beam and thereby reduce undesired irradiation of other tissues, and (2) to permit flexibility in patient positioning along the beam central axis. A high ratio means that the epithermal neutron flux very close to the beam port opening will change only slightly with distance from the port. In cases where the body of the patient must be positioned perpendicular to the beam axis, this will permit a patient to be positioned somewhat farther from the port. This will increase the depth dose and facilitate patient positioning without seriously diminishing the available incident beam intensity.

A target number for this ratio should be greater than 0.7.

1.4. Beam size

Circular apertures of 12 to 14 cm diameter are being used in the present clinical trials. However, sizes of up to 17 cm have been proposed for irradiation of brain tumours. Other cancers in the body might require even larger apertures.

These maximum sized apertures are reduced in accordance with the tumour size and position as determined by the treatment planning requirements.

2. NEUTRON SOURCES FOR CAPTURE THERAPY

2.1. Possible sources of neutrons

At present, facilities available for NCT clinical trials are limited, and the only neutron sources for clinical NCT are (thermal) research reactors. Because of this, efforts have been made to modify a number of existing reactors for NCT, with a few new research reactor design projects being started. Since a reactor is usually used for many other applications besides NCT, conflicts or limitations on the NCT work often arise. Additionally, most reactors are separated from hospitals, and their use for clinical trials can present some difficulties. For these reasons, there has been some research regarding the installation of NCT facilities at hospitals. Sources of neutrons suggested for this purpose have included dedicated single-purpose reactors, accelerator-based neutron sources, and the use of ^{252}Cf sources.

2.2. Converted thermal reactors using spectrum shifting and filtering

Most facilities currently involved with NCT are general purpose research reactors which have been modified for this application. There are two basic methods to get the appropriate neutron flux at the treatment location outside of a thermal reactor. These are broadly termed *spectrum shifting* and *filtering*.

Spectrum shifting moderates the fast neutrons leaking from the core down to an appropriate lower energy for NCT. This means either epithermal or thermal energy neutrons. When a reactor has a large aperture irradiation facility such as a thermal column, then the spectrum shifting method is usually used, either by itself or in combination with a filter. In a reactor where only a rather narrow and long beam tube is available, the filtering technique must be used. Filtering transmits neutrons of the desired energy while blocking those of other energies. Generally, filtering is more wasteful of neutrons so that a much higher original source flux is needed. If one compares the neutron flux at the irradiation position relative to the reactor power, the shifting technique gives a much higher flux-to-power ratio than the filtering technique. A review of facilities currently in operation indicates that spectrum shifting, supplemented by filtering, is used much more frequently than filtering alone.

2.3. Fast reactors

While the majority of nuclear reactors potentially available for NCT are thermal reactors, a few fast reactors are also found [2.1]. Since the initial source of neutrons at the irradiation position is fast neutrons leaking from the core, a fast reactor can have much higher flux-to-power ratio than a thermal one of the same power. Indeed, it appears that a 5 kW fast reactor can produce sufficient epithermal neutrons for patient treatment. The low power and compact core of a fast reactor permit a very compact NCT facility. However, the fast reactor needs highly enriched uranium (HEU) fuel, the limited availability of which restricts its likely application. In addition, experience with the application of fast reactors to NCT is very limited.

2.4. New reactor designs

The idea of a newly constructed reactor for BNCT has some attraction. The most positive arguments compared to converting existing facilities are that it can be built near a hospital, in a large population centre where the therapy is needed. In addition, patient treatment considerations can be incorporated from the beginning, thereby providing the highest level of care and comfort. The efficiency of such a facility can be very high.

Not surprisingly, a new research reactor where NCT has been considered from the beginning is likely to be much more efficient in a number of respects, and would probably use the spectrum shifting concept. Reference 2.2 discusses the design of such a facility for a hospital. If its design is optimized, sufficient neutron flux at multiple irradiation positions can be available even at low power. In addition, it can have an integrated facility for prompt gamma neutron activation analysis (PGNAA) of boron in blood. Facilities for microscopic boron distribution measurement, and a thermal neutron beam for NCT research using in vitro cells and small animals, and superficial tumour therapy could also be incorporated. From the technical point of view, designing an extremely safe and effective reactor specifically for NCT is very feasible. However, for a dedicated NCT reactor, an important factor that should be considered is that of public acceptance because of its installation in a medical centre.

Estimates of experts indicate that the construction of new BNCT facility costs about 5–7 million Euro, whereas adaptation of an old one costs 2–4 million Euro.

2.5. Fission converters

The deficiency of a thermal reactor compared to a fast reactor from the viewpoint of the flux-to-power ratio can be partially compensated for by the use of a fission converter. In essence a typical fission converter consists of a row of fuel elements located in the beam line but away from the reactor core. The fission converter absorbs thermal neutrons from the core and generates a beam of fast neutrons, which when appropriately moderated and filtered, produces a high intensity, high quality epithermal beam source much closer to the treatment position. The advantages and disadvantages of fission converters are discussed in detail in the next section.

2.6. Accelerators

An accelerator would be a useful NCT neutron source in a hospital for several reasons. First, accelerators are much more acceptable to the public than reactors. Second, it generally involves fewer complications with respect to licensing, accountability and disposal of nuclear fuel. It can also be switched on and off. However, it must be recognized that the technology is not yet proven. The radiofrequency quadrapole (RFQ) accelerator is considered as the most promising method. The RFQ can be used to generate a high current of protons with an energy slightly higher than the threshold (1.88 MeV) for the ^{7}Li (p,n) ^{7}Be reaction. The resulting neutrons generally require less moderation than those from a reactor.

2.7. Californium

An intense ^{252}Cf source would provide a very compact NCT facility, but it would need frequent replacement of the expensive ^{252}Cf because of the 2.6 year half-life of the isotope. In addition, a source of the order of 1 g would be needed, which would be very difficult to obtain.

It should be noted that either an accelerator or a ^{252}Cf neutron source could be combined with a subcritical assembly to boost the neutron intensity. However, while this might have better public acceptance than reactors because of inherent criticality safety, to a certain extent many of the advantages of accelerators and sources are lost by adding the subcritical assembly. In addition, neutron moderation and filtration would be required.

Table 2.1. Comparison of the advantages and disadvantages of possible neutron sources

SOURCE	TYPE	ADVANTAGES	DISADVANTAGES
Nuclear reactors (Clinically used for NCT)	Existing reactors, Thermal column[1)]	•Spectrum shifting •High flux-to-power ratio	• Separated from hospital • Interferes other utilization
	Existing reactors, Beam tube [2)]	•Filtering •Low flux-to-power ratio	
	New conventional reactors	•Adaptation of thermal column type for NCT is recommended	
	Dedicated new NCT reactors	• In the hospital • Integrated facility for NCT • Sufficient flux at multiple positions • Extreme safety	• Difficulty with public acceptance
	Thermal reactors	• Partial recovery of low flux-to-power ratio by a fission converter (if possible) • Availability of much experience	• Low flux-to-power ratio
	Fast reactors	• High flux-to-power ratio • Compact facility	• HEU is needed • Very limited experience
Accelerators[3)] (Not yet used for NCT)	Source alone	• No expected difficulty with public acceptance when installed at a hospital	
	With subcritical assembly	• Criticality safety	• Additional complexity with both an accelerator and a subcritical core
^{252}Cf source (Not yet used for NCT)	Source alone	• Compact equipment	• Large amount of ^{252}Cf needed.
	With subcritical assembly	• Criticality safety	• Frequent replacement of ^{252}Cf

(1) Reactor having a large irradiation facility such as thermal column;
(2) Reactor having only narrow and long beam tubes;
(3) The use of a large scale accelerator is not considered.

REFERENCES TO SECTION 2

[2.1] AGOSTEO, S., et. al. Design Of Neutron Beams For Boron Neutron Capture Therapy In A Fast Reactor (Annex 5).
[2.2] JUN, B.J., LEE, B.C., Suggestion for an NCT Reactor in the Hospital (Annex 5).

3. REACTOR AND BEAM DESIGN CONSIDERATIONS

Having briefly described the possible sources of neutrons for NCT, the rest of the report will focus on where the most experience has so far been gained, namely the conversion of existing research reactors. Typically, this has meant modifying or adding components such as the reflector, a beam port or thermal column, shielding, collimators and filters in order to try to obtain a beam of the intensity and quality needed. Key aspects of reactor modification and beam conditioning are discussed. Much of the discussion is also relevant to the design of new reactors.

3.1. Core reflector

Most existing thermal research reactors have reflectors to optimize the core efficiency. Clearly, the need to provide a source of fast neutrons for the spectrum shifting moderator, or the filter, demands that the reflector must be removed from that part of the core. This means that a careful analysis of the core neutronics needs to be undertaken prior to this modification, and more fuel may be needed as a consequence.

3.2. Spectrum shift vs. filtered beam

While spectrum shifting using a moderator has proven to give a higher efficiency in producing an epithermal beam than filtering, the choice of which technique to use is typically determined by the existing reactor design. The former method requires the availability of a large opening in the shield such as that often used for a thermal column. Figure 3.1 shows a typical example. If the reactor does not have such a space then a higher powered reactor (>10 MW) with a beam port has the option of filtering the beam. Alternatively, part of the shielding can be opened up or removed to provide space for a spectrum shifter.

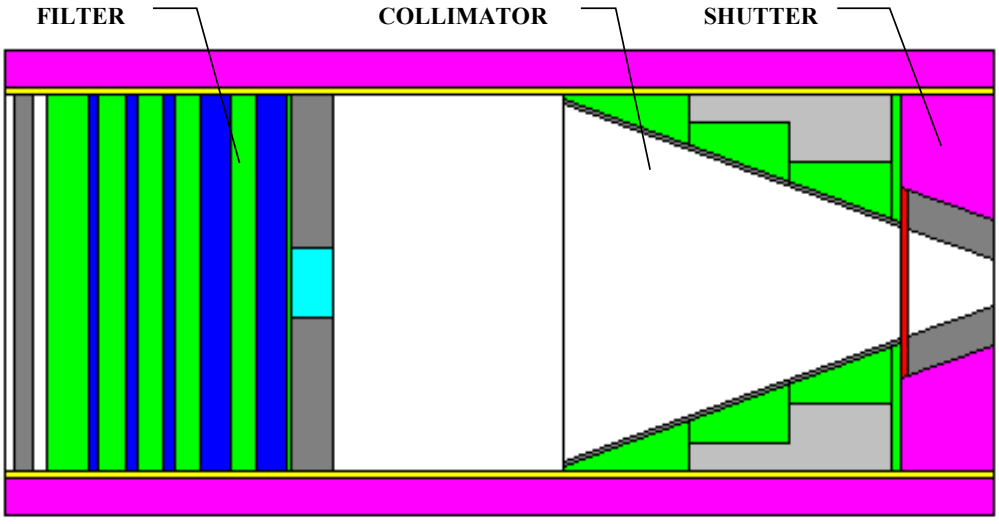

Fig. 3.1. Typical spectrum shift arrangement.

3.3. Core-to-patient distance

For spectrum shift facilities, the moderator has to be placed as close to the reactor core as possible to maximize the input of fast neutrons. A shorter distance from core to patient will thereby result in a higher epithermal flux at the dose point. In addition, it will allow the reactor core to subtend a larger angle allowing the production of a converging beam of higher

intensity. However, the core-to-patient distance is often limited by the need to accommodate features such as a fission converter, moderator, filters, collimators, and shutters. Certainly, increasing the distance from the reactor to the patient beyond the thickness of the existing shield decreases the available flux and should be avoided if possible. Therefore, every effort should be made to fit all beam-conditioning components and shutters within the existing shielding dimensions (Figure 3.2). Some facilities have successfully opened up their existing reactor shielding in order to provide a larger beam aperture, and shorter core-to-patient distance.

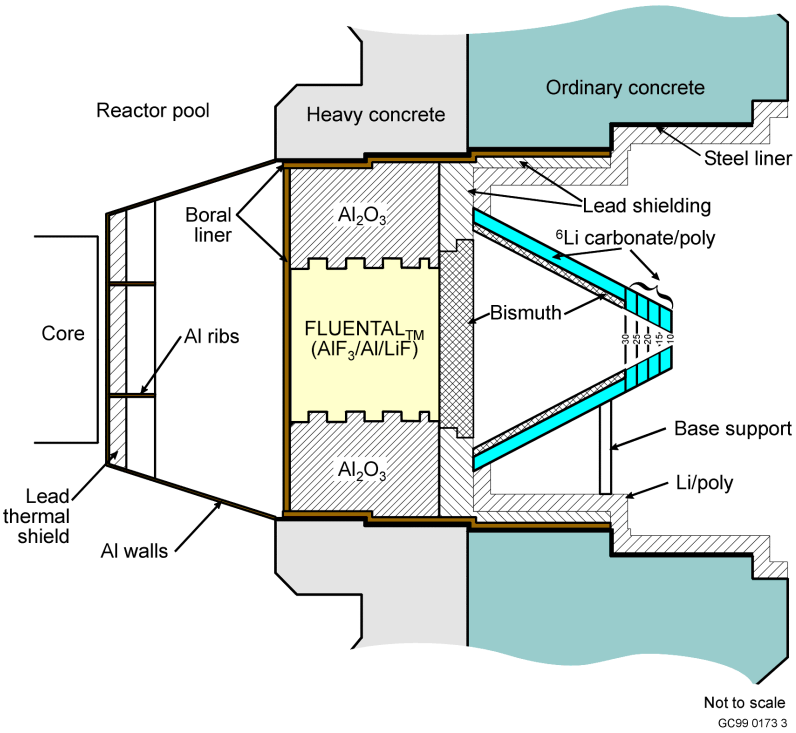

Fig. 3.2. Example of an effort to minimize core to patient distance.

Practically, the beam components, the moderator and collimator, need a length of about 1 to 2.5 meters. This gives the desired position for irradiating the patient supposing that the patient and the personnel can be shielded from the undesired radiation from the reactor core.

For filtered beam facilities the core to patient distance is usually dictated by the original design of the reactor and is not as critical because of the inherent higher current to flux ratio.

3.4. Beam intensity and current-to-flux ratio

Increasing beam intensity is achieved by surrounding the beam with an appropriate reflector and tapering it from a wide to a narrow aperture. Suitable reflector materials for this are those with high scattering cross section and high atomic mass (resulting in little energy loss). They include Pb, Bi, PbF_2.

A forward-directed beam with a current-to-flux ratio of greater than 0.7 helps to deliver a higher intensity neutron beam at a distance from the reactor shield face. This allows greater flexibility in positioning the patient. The use of collimators (see 3.8 below) can be used to improve the current to flux ratio of the final incident beam.

Increasing the distance between the core and the patient will improve the current to flux ratio for a given beam diameter. Hence, for reactors which use the filtering method rather than the spectrum shift method, a very forward directed beam is the natural result of a long, narrow penetration through the biological shield. The filtering components can be installed in the beam tube and the beam can then be transported long distances without further sacrifice in intensity. The longer distance between the core and the patient may offer additional space for beam shutters.

It is important to note that removing as many fast neutrons as possible, and using a beam delimiter to improve directionality, will not necessarily maximize the dose delivered at depth. MCNP modeling has shown that hardening the spectrum slightly by adjusting the thickness of the moderator results in better beam penetration. It also has shown that attempts to improve the directionality of the beam too much can remove so many neutrons that the intensity of the beam is reduced, lowering the dose delivered to the target volume. Optimal conditioning of the beam for a given case may be dependent on the detailed geometry of the target volume.

In the final analysis, the quest for high intensity is perhaps not as important as the production of a sharply defined, high quality epithermal beam, which limits the whole body dose to the patient. With small enough whole body doses, treatment in multiple fractions can be given, compensating for lower epithermal beam intensity.

3.5. Undesirable radiation components in the incident epithermal beam

One of the key aspects of reactor conversion and beam design is to maximize the desired epithermal neutrons while minimizing the healthy tissue dose from all other radiations in the incident beam.

3.5.1. Gamma contamination

Materials such as Pb and Bi, which are relatively transparent to neutrons, may be placed in the beam to reduce gamma rays originating from the reactor core, but these will nonetheless somewhat reduce neutron beam intensity. Bismuth is nearly as good as lead for shielding gamma rays, while having a higher transmission of epithermal neutrons. However, caution is necessary in handling neutron-irradiated bismuth, because of the buildup of ^{210}Po, a bone-seeking alpha emitter created by neutron capture in ^{209}Bi with subsequent beta decay of ^{210}Bi. Encapsulation of the bismuth is highly recommended.

Outside of the neutron beam area, high-density concrete (mixed with iron minerals) can be used to reduce gammas. Steel and iron can be protected from neutrons by shielding containing ^{10}B or ^{6}Li, to prevent neutron activation of these components with subsequent emission of hard gamma rays. It should be noted that ^{10}B emits a low energy capture gamma ray (478 keV) but ^{6}Li does not and its use is to be preferred in locations close to the patient.

3.5.2. Thermal neutron contamination

For epithermal neutron beams, it is desirable to limit thermal neutron contamination by filtering. Filter materials for thermal neutrons require either elements with ^{6}Li or ^{10}B (1/v cross sections) or Cd (0.4 eV resonance). The 1/v cross section materials may deplete the lower energy part of the epithermal neutron spectrum, but Cd produces a high energy (7 8 MeV) capture gamma ray which is difficult to control and cadmium oxide represents a health hazard.

3.5.3. Fast neutron contamination

In the spectrum shift type facilities, the objective is to moderate as many fast neutrons (>10 keV) as possible down to the desired epithermal energies. In the filter type facilities, fast neutrons are removed by filtration. Moderators and filters are discussed below.

3.6. Moderators

Moderation of fast neutrons is best accomplished by low atomic mass materials. Any moderator or filter materials chosen must not decompose in a high radiation field, nor produce moisture. Any neutron activation products from the materials should be short lived. Suitable candidates are Al, C, S, Al_2O_3, AlF_3, D_2O, and $(CF_2)_n$. Combinations of Al followed by Al_2O_3 or AlF_3 downstream are very efficient because the O and F cross-sections fill in the valleys between the energy resonance peaks of Al. Fluental™ was developed by the technical Research Centre of Finland [3.1] and stands up well to radiation, but is very expensive. Teflon™ is susceptible to radiation damage, but even so, may be acceptable when exposed to the relatively modest neutron fluences projected for the facility over its anticipated lifetime.

3.7. Filters

Reference 3.2 analyses various materials that may be helpful for reactor facilities desiring to use the filter methodology. The objective is to start with a very high intensity beam from a high power reactor and filter out all but the neutrons with energies of 0.01 to 10 keV from the reactor beam. This can be done with thick neutron filters of natural or isotopically enriched materials, for which an interference minimum in the total neutron cross section exists in this epithermal energy range.

The total cross section of ^{60}Ni isotope has the deep and wide interference minimum in the energy range from several eV to 10 keV and therefore this material is useful for BNCT purposes. To suppress the neutron groups with energies above 10 keV a set of additional filter materials must be used. Materials such as the isotopes ^{32}S, ^{10}B and others may be used.

By using the 99.5% enriched ^{60}Ni isotope (112 g cm^{-2}) as the main filter component and ^{32}S (54 g cm^{-2}) and ^{10}B (1.15 g cm^{-2}) isotopes as additional filters, a beam with an energy range of 0.01 to 9 keV may be obtained with a purity in the main neutron group of about 92%.

If the above filter design is modified by the addition of some 99.7% enriched ^{54}Fe (50 g cm^{-2}) isotope, a filtered neutron beam may be obtained with approximately 96% of the neutrons in the energy range of 0.01 to 6 keV.

3.8. Collimators

Collimators inside the shielding should reflect neutrons back into the beam. Therefore, neutron reflecting type materials are used. Collimators that are used near the beam exit are beam delimiters and should absorb rather than reflect neutrons. Interchangeable exit collimators having different size inner bore diameters can be used to delimit the final size and divergence of the beam delivered at the patient treatment position. These collimators are made with B_4C or $^6Li_2CO_3$ dispersed in polyethylene. Epithermal neutrons striking the wall of the collimator are thermalized and captured with minimal emission of hard gamma rays, which could shower the patient.

3.9. Shutters

A dedicated NCT reactor that can be started up and brought to full power quickly and reproducibly might not need a shutter. However, the need for continuous operation of the reactor or other characteristics of the reactor operation can dictate the installation of one or more beam shutters. Even with the reactor shut down, a shutter may be required to protect personnel working in the treatment area from radiation from the core and long lived radioactive components along the beam line.

The extra space required for a shutter needs to be taken into account in the design of the irradiation facility. To save space along the beam direction, the filter/moderator can be arranged to move into the space in the beam line vacated by the shutter when it moves into the open position. Another important consideration is the loading capacity of the building structure supporting the weight of the shutter and the available crane capacity required to assemble the shutter. This is not a trivial problem, since the dense materials comprising the shutter can weigh many tons.

A combination of fast acting and slow acting shutters achieve a balance between requirements for quick termination of high dose levels and reduction of low level residual dose at the patient position. The fast acting shutter can be thinner and lighter. Also, the use of a fission converter may require a separate shutter to prevent undesired burnup of the converter fuel.

One shutter design involves pumping water, containing boron, in or out of a tank placed in the beam. This has the advantages of remote storage capability in the open beam configuration, and mechanical simplicity compared with controlled movement of massive blocks.

Under power failure, shutter mechanisms should fail in the closed position (i.e. use gravity to close the shutter).

3.10. Fission converters

Fission converters have a number of advantages when it comes to modifying a reactor for NCT and they have the potential to make almost any research reactor NCT-capable. Fission converters may also increase beam quality and intensity sufficiently well to enable the effective use of NCT on tumours located elsewhere in the body.

A layer of fissile material in the beam re-uses the thermalized neutrons which otherwise would contaminate the beam or would be discarded. Perhaps more importantly, they allow the patient to be placed much closer to the neutron source and ultimately increase epithermal fluxes by factors of about 5 to 10 at the patient position.

On the negative side, a fission converter will increase costs significantly. There is added complexity in the design and construction of the beam line as well as in regard to licensing of the fissile material, and to operations and maintenance. Additional procedures and training of personnel will be required. The typical fission converter will generate about 50–100 kW of heat and therefore will need an additional cooling system. It will certainly take up premium space immediately adjacent or near to the reactor. Finally, the fission converter creates an additional safety hazard and an added source of spent fuel and radioactive waste. Figure 3.3 shows a fission convector installation.

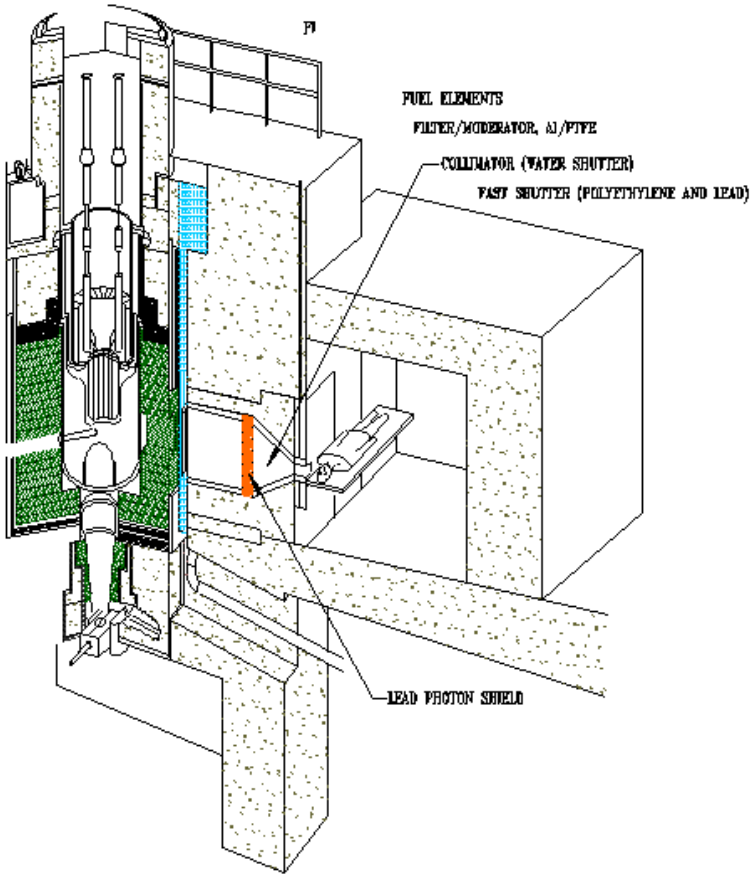

Fig. 3.3. Example of a fission converter system.

3.11. Reactor beam design analysis

Beam design requires a great deal of safety analysis prior to any submission of the facility change to the licensing authority for approval.

The Monte Carlo code, MCNP, has been demonstrated to be very useful for the detailed design of a beam facility and gives excellent agreement with measured values of spectra and flux. However, it can be very laborious to use at the early stages when a variety of potential configurations are being studied. Therefore, for design optimization studies a 2 or 3 dimensional transport code is more convenient.

The adaptability of the 2-D ordinate transport code DOT for the design of a neutron beam for BNCT was verified during the design of the JRR-4 neutron beam facility. The neutron spectra and neutron fluxes calculated by DOT were in good agreement with those measured by the foil activation method using Au, Au covered by Cd, Cu and Ni foils.

3.12. Beam monitoring

Control of patient exposures depends upon periodic calibration of the neutron beam, as well as maintaining stability of the beam during irradiations. There are many factors that can cause a variation in the neutron beam from a research reactor. These include fluctuations in power level, changes in the core flux distribution with burnup and unanticipated events such as a sticking shutter, an object falling into the beam line, or a shift in a filter position. In addition, it is desirable to reproducibly quantify the total irradiation received in order to enable patient to patient comparison. For these reasons, it is very important to monitor the emerging neutron beam fairly near the patient. Fission chambers, which can be modified to increase their sensitivity to epithermal neutrons, are often used for this purpose.

A useful beam monitoring system should provide the following capabilities:

(1) The system should accurately track and record the cumulated neutron fluence incident on the patient during BNCT irradiations.
(2) In conjunction with ^{10}B pharmacokinetic data supplied in real time, the system should accurately track the cumulated patient dose during irradiation.
(3) The system should continuously monitor the complete status of the epithermal beam with regard to instantaneous neutron flux, beam energy, beam position, and cumulative patient dose.
(4) The system should provide redundancy in monitoring beam energy, beam position, and neutron flux.
(5) The system should be able to respond to interruptions of the irradiation despite the fact that under those circumstances the ^{10}B blood concentration profile becomes discontinuous.
(6) The beam monitor detectors should accurately measure incident neutron flux irrespective of the albedo conditions relating to the presence of the patient.
(7) The system should time stamp any abnormal incidents during the irradiation that are reflected by perturbations in the count-rates of the beam monitors.
(8) The computer and the power supply to the data acquisition system and detectors should operate under the protection of an uninterruptable power supply.

In addition to the on-line monitoring, it is also necessary to have a reliable means of calibrating the intensity of thermal and epithermal neutron beams used in research and in clinical applications of BNCT. This is normally done by irradiating foils in these beams. It should be noted that these monitoring and calibration devices must meet the requirements of agencies involved in radiotherapy regulation.

As an example of an epithermal beam monitoring system, at the MIT Research Reactor there are four ^{235}U fission detectors arranged in opposing pairs in the penumbral region of the 15 cm diameter circular beam. One set of opposing detectors is bare, thereby primarily monitoring thermal neutron flux, while the other set is covered by epoxy/Li-6 shields, thus sampling the 1/v portion of the epithermal neutron spectrum. The detectors are shielded from scattered neutrons returning from the patient by a 5 cm thick borated paraffin-wax delimiter. This ensures that the detectors exhibit only 1–2% changes in response with or without a patient present. Each pair of detectors independently measures the epithermal or thermal neutron flux, while the ratio of responses of opposing detectors monitors the beam position. Finally, the ratio of responses of bare vs. epoxy/Li-6 covered detector pairs approximately monitors the relative energy of the beam.

REFERENCES TO SECTION 3

[3.1.] ASCHAN, C., et al., TL Detectors in BNCT Dosimetry (Annex 5).

[3.2.] GRITZAY, O.O, MURZIN, A.V., Analysis Of The Possibility Of Using The Reactor Filtered Neutron Beam Formed By Ni-60 Filter For BNCT (Annex 5).

4. IRRADIATION FACILITY OPERATION AND MANAGEMENT

Aside from the technical aspects of NCT, there are a large number of reactor management and operations factors that must be considered. Since they can have a significant impact on the facility, they need to be carefully considered by institutions which are thinking of entering this field.

4.1. Operation of the facility

4.1.1. Reliability

A reactor facility that is being used for NCT must have a high degree of reliability. Long term reliability is needed to enable patients to be scheduled without fear of postponement or cancellation. In addition, it is clearly important to avoid potential interruptions during patient treatment because of reactor difficulties.

4.1.2. Availability

Many research reactors are under-utilised, and availability may not be a problem. However, facilities which have tended to become involved with NCT are those which are generally more pro-active and have a variety of other missions. NCT requires a significant amount of reactor time, not just for the therapy, but also for such things as the necessary design work, licensing, facility modifications, testing, and calibrations.

4.1.3. Single versus multiple users

If NCT is not the sole program using the reactor, then consideration must be given to the impact on other programs using the facility. There may be a gain or loss of income due to reprioritization of reactor time. Policies will need to be developed to resolve scheduling conflicts and priority of user requirements. Finally, the impact of the NCT facility design on other reactor irradiation facilities needs to be evaluated.

4.1.4. Continuous versus intermittent operations

There are a number of options to minimize the time that a reactor is shut down for each NCT therapy run. One of these is to have a simulator room for patient set up (discussed later). An alternative is to provide shutters with sufficient shielding to access the NCT therapy facility at full power operation without excessive personnel exposure.

4.2. Personnel at the NCT facility

There are generally three groups of people involved at the irradiation facility site. These are the reactor operations staff, the NCT operations staff, and the medical staff. This section will briefly discuss the staff needed and some of their key responsibilities.

Tasks needing staffing at the facility include:

(1) NCT facility design, modification and testing;
(2) Reactor operations;
(3) NCT facility preparation;
(4) Dosimetric analysis of the beam;

(5) Standard health physics work involving the treatment facility and the personnel involved;
(6) Analytical computational work associated with facility design, beam and phantom dosimetry;
(7) Medical Physics
(8) Medical care including all appropriate specialities
(9) Drug preparation;
(10) Evaluation of the boron concentration in the patient;
(11) Patient preparation and positioning;
(12) supervision of the patient status.

4.2.1. Staffing needs

Once an NCT facility is operational, reactor operations and health physics tasks will not require many more staff than those normally associated with running the facility. However, there is a lot of work initially associated with reactor facility modifications to enable NCT to be used, and more staff may be needed. One or two people may need to be dedicated to the NCT operations group during routine operations.

The NCT therapy facility itself is best manned by a team comprising a reactor operations person to control reactor-related shutters and doors, a health physicist for initial entry surveys, a medical physicist and assistants for patient positioning, dosimetry and to measure the concentration of boron in the blood.

While most of the medical staff will be involved at the hospital, those at the reactor facility during treatment should comprise at least, a radiation oncologist, a medical physicist, and a nurse accompanying the patient. It will be necessary to have medical staff permanently on-site during treatment.

The above staff requirements refer to personnel needed during patient treatment. However, it should be noted that during the pre-clinical phase for new facilities, many additional staff, such as radiobiologists to perform cell cultures may be required.

4.2.2. Responsibilities

In most cases the NCT facility will be located at a non-hospital site and remote from the hospital where most of the associated medical staff are located. Therefore, it is important to define a personnel structure with clear responsibilities, duties, and tasks. As discussed below, clear communication lines between the NCT facility personnel and medical staff should be established.

Reactor safety is always the responsibility of the reactor manager while the safety and welfare of the patient is the responsibility of the physician. The medical team is clearly responsible for all the medical aspects.

The NCT facility technical manager should be a member of staff who has a clear understanding of the constraints on reactor operation and clinical issues. This manager is responsible for co-ordination of all tasks at the facility. This person should act as a liaison officer. The technical manager has to ensure that medical staff requirements can be implemented.

The technical manager is also responsible for implementation of a quality assurance (QA) program. The QA program should include regular maintenance, scheduled inspections, and periodic testing of the NCT facility components.

4.3. Technical co-operation and communication

Since NCT requires the participation of many specialized teams from a wide range of disciplines, close co-operation, strong communications and a clear delineation of responsibilities are indispensable for assuring success.

4.3.1. Between reactor operation and medical team

These two groups are the principal arms of this treatment modality. They work together at each phase of the project, Including design and operation all of the therapy facilities.

Another important communication line is that between the reactor management and medical staff regarding patient scheduling and reactor availability.

4.3.2. Between facility staff and regulatory authorities

This includes all the other departments or agencies which can contribute to the success of this technique. Adequate communication with the regulatory authorities, who are responsible for issuance of the licences and approvals to perform NCT at the reactor site is of vital importance. This includes both the reactor licensing and the medical therapy licensing authorities. Contact should be sought at an early stage with all relevant authorities, including those associated with the legal, insurance and liability issues.

4.3.3. Between the facility staff and the public

The pro-active dissemination of current and correct information about the NCT project through the media is considered by many to be essential for a successful program.

4.3.4. Between countries

While NCT is currently being conducted at relatively few institutions, more are interested in the possibility of becoming involved; therefore international co-operation is very important. All concerned Member States are encouraged to establish and maintain strong communication links for co-operation through other international organizations and societies or the IAEA. The International Society of Neutron Capture Therapy and its bienniel meetings clearly have an important role in this area to learn from the best experience of the practicing centres, and to minimize mistakes.

However, exchange of experience and knowledge between the advanced NCT centres also must be maintained, in order to share new methods and techniques. Of particular value here is the list server maintained by MIT (bnct@bnctmva.mit.edu).

Mention should also be made of the related web sites available in the Internet. A good starting point is http://www.bnct.org/. There are many links to other NCT programs from this site.

4.4. Procedures

Prior to starting NCT, all procedures including those related to normal and abnormal conditions, and training should be written, approved, and made available for all reactor operators and the NCT facility staff. The operating procedures should cover the step by step instructions which clearly define all those operations which may affect the beam parameters.

Of particular importance are the procedures dealing with abnormal events. These may arise from the reactor, patient or external event. In each instance, patient welfare will have priority; individual responsibilities for such eventualities must be clearly delineated.

Radiological protection procedures should be integrated with the radiological protection code of practice to ensure that reactor operators and medical staff will not be unduly exposed.

4.5. Training

Although reactor operators should not interfere with the medical treatment process, they should be trained on the different operation aspects of the NCT so that they become well aware of the implication of normal reactor operations that may affect beam parameters.

The NCT facility medical staff should be trained to become familiar with the appropriate reactor procedures, especially the safety aspects. In particular, they should be trained in emergency procedures so that emergency response becomes clear to all the NCT staff. Analogously, reactor personnel should be trained on what is expected of them in a medical emergency situation.

Periodic emergency drills should be planned and implemented, feedback assessed and actions to improve emergency response taken.

4.6. Required facility resources

This section is intended to provide an overview of the additional resources needed to perform BNCT which are above and beyond those usually available at reactors.

4.6.1. Physical layout and space

Since there is a need to transfer patients in and out of the treatment facility via a special vehicle or ambulance, vehicle accessibility needs to be considered. Sometimes this ease of accessibility requirement may be in conflict with the reactor facility's requirements on radiological safety and physical security. To fulfil both requirements, careful design of the facility arrangement is needed.

Similarly, many reactors are limited with respect to the space around thermal columns and beam ports. However, sufficient physical space should be made available for patient treatment. There should be space in front of the beam port to position the patient comfortably, ease of access to the facility for patient and facility staff, sufficient space outside the treatment room to monitor the patient and the beam, and sufficient space inside or outside the reactor building to receive and prepare the patient for treatment (Fig. 4.1).

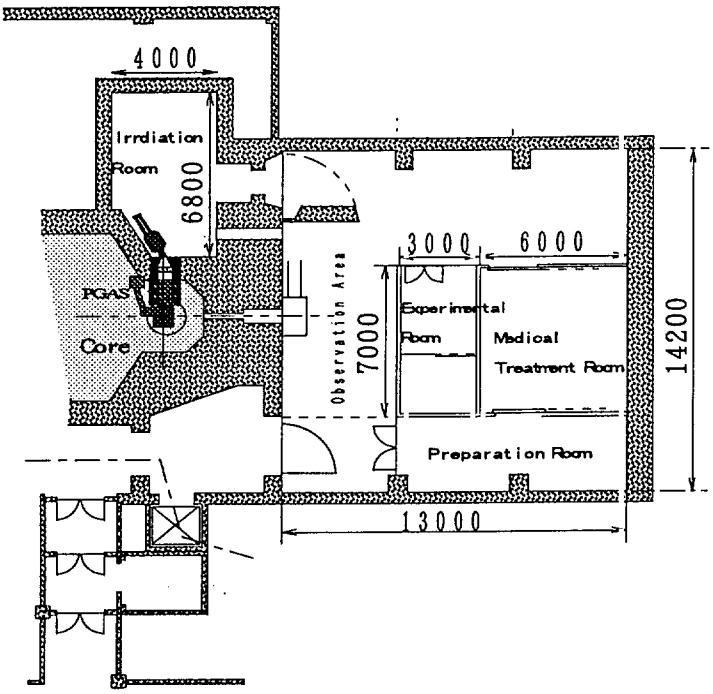

Fig. 4.1. An illustration of the need for patient treatment space around the reactor facility.

4.6.2. NCT radiotherapy infrastructure

For the NCT facility, at least the following infrastructure requirements are needed:

4.6.2.1 Patient treatment room

The patient treatment area should be a closed, shielded room which can meet applicable standards for medical facilities, including temperature control, ventilation, and aseptic conditions. It may be necessary to check that the electrical installations satisfy both medical and reactor standards. The room will need to be supplied with: adequate communication devices such as TV cameras, an intercom and microphone; a therapy table or chair constructed of non activating material

This room also serves as a barrier to prevent radiation from affecting medical and reactor operations personnel during treatment sessions. The treatment room must be large enough to accommodate the patient gurney aligned at any angle from -90^{o} to $+90^{o}$ with respect to the emerging (horizontal) epithermal beam. Appropriate shielding need to be designed and constructed to achieve basic safety standards. Such shielding may weigh many tons and requires consideration early in the design phase and may be very difficult to accommodate at an existing reactor facility. Space and floor loading problems may be exacerbated should a heavy beam shutter be required.

Access to the room should consider ease of patient entrance and quick access for medical staff in case of patient emergency

Any equipment placed near the beam, such as the patient gurney, or beam alignment and monitoring equipment, should also be covered with neutron absorbing material to inhibit

neutron activation of these items. Other items, such as pillows, cushions, and restraints, should be tested for susceptibility to neutron activation before being used with a patient.

4.6.2.2 Simulation

It is recommended to have a patient/beam simulation room within the vicinity. This enables a large amount of set up to be performed away from the actual beam. It allows more normal reactor operation as well as providing a way of allowing the patient to become used to the reactor environment.

4.6.2.3 Medical staff requirements

The medical staff associated with the work will have requirements such as office space and storage space for medical equipment and supplies.

4.6.2.4 Personal dosimetry

All NCT staff must be equipped with personal dosimeters to satisfy radiological protection requirements for both nuclear and medical regulations.

4.6.2.5 On-line-beam monitoring system

An on-line-beam monitoring system is required to detect any changes in the beam parameters during treatment. Such a system must be integrated into a fully automated beam shut-off system (either beam shutter or reactor scram).

4.6.2.6 Blood boron concentration measurement system

Fast and accurate boron concentration measurements in patient blood during treatment is absolutely essential for the NCT facility. This usually means a prompt gamma neutron activation analysis (PGNAA) system or an ICP system.

4.6.3. Floor loading

Since the NCT facility is usually located in the same area with other neutron beam experimental equipment, the floor loading of this area should be considered carefully. A multipurpose reactor will require an additional beam shutter. This shutter will give significant additional load to the floor that might not have been previously considered.

4.7. Geographical factors

Several geographical factors have to be considered when choosing a reactor to convert into an NCT facility, or when siting a new facility.

4.7.1. Proximity of a medical centre

Since NCT treatment requires pre and post treatment in the hospital or medical facility, a short distance between NCT facility and academic hospital with experience and reputation in oncology is preferable. This condition is also needed because of the frequent contact and meetings required between the reactor operation and the medical staff prior to treatment.

4.7.2. Proximity of an airport

In any one country or region there is most likely only going to be one NCT facility. To achieve optimum use of this facility, it should be located in a strategic location. Ideally, this will be near an airport for easy access from the whole country or region.

4.7.3. Easy access to NCT facility

Besides the short distance to the nearest hospital or medical facility, in many countries traffic and road conditions must also be factored into the choice.

4.8. Non-technical considerations

4.8.1. Public acceptance

As with any reactor, public acceptance is an issue that must be considered when converting a nuclear reactor for NCT or for building a new reactor for NCT. The use of the reactor for NCT could be used as an argument for acceptance of this reactor as a medical treatment facility. There are also ethical issues associated with NCT. In particular, NCT treatment involves the irradiation of human subjects. This is also true of other therapeutic procedures such as nuclear medicine, gamma therapy, and brachytherapy. What is different about NCT is that it involves irradiation by neutrons which is an unfamiliar subject to the public. The public tends to be more accepting of radiation therapy than of nuclear reactors in general. Gaining public acceptance is not an easy task, because often public perception of nuclear matters is based on personal feelings rather than scientific facts. Care must be taken to help people understand that if benefits of a reactor facility for NCT are demonstrated these should outweigh the perceived disadvantages of a reactor facility.

4.8.2. Ethical issues

The acceptance and registration of a treatment protocol must be achieved before any medical study can commence. The more this proposed treatment deviates from standard clinical practice, the more safeguards will be mandatory to ensure the freedom of choice for the patient and full disclosure of all known or potential risks entailed in the treatment and its late morbidity. The time required to formulate such a protocol and receive approval may be long — of the order of a year. In some countries, on the basis of the available evidence, this may not be accepted at all.

Another ethical issue involves the use of animals in NCT research. Again, while some are opposed to such research, the biological variability of mammalian tissue to NCT cannot be determined from physical dosimetry or cell culture studies

4.8.3. Economics

Cost is a very important factor in developing and operating an NCT facility. Conversion of an existing reactor facility could cost from a few hundred thousand to several million US$, depending on the extent of modification, availability of materials, and design capability. Constructing a new nuclear reactor specifically designed for NCT would likely cost at least twice as much as a conversion (several $US million to tens of millions).

Operating costs for an NCT facility would exceed those of a typical research reactor. All the normal costs of operating a reactor (personnel, supplies, and maintenance) are involved plus costs specifically associated with the NCT facility. Beyond the initial capital costs, operating costs for the NCT facility could easily be several tens of thousand $US per patient.

4.8.4. Licensing

A reactor will require special licensing and certification to perform NCT. Specifically the reactor license, which is governed by the appropriate regulatory agency, will have to include NCT as a major use of the facility. For a new reactor facility siting approval is an important factor to consider as part of the licensing process. In addition, permission will have to be obtained from the appropriate health authority to perform NCT on human patients.

4.8.5. Liability

Medical liability issues are another major factor with which most research reactors do not normally have to deal. Because of the treatment of human subjects, an NCT facility will have to deal with the same liability issues as any other medical facility.

4.8.6. Administration approval and support

The approval and support of the upper administration of the reactor facility's organization is crucial for a successful NCT program. Without this continued approval and support, the NCT facility is in jeopardy of its existence. Administrative support ensures that financial and liability issues do not become an obstacle to continued NCT treatment.

5. PHYSICAL DOSIMETRY OF BNCT: DETERMINATION OF BEAM PARAMETERS

5.1. Introduction

The issues of physical dosimetry for BNCT can be considered in two parts:

(1) "Beam calibration," which involves the determination of dose in a phantom and the corresponding beam monitor calibration factor normalized to reactor power.
(2) "Measurement of physical dose distributions," which involves characterizing the beam by measuring the depth-dose distribution, off-axis profiles, etc.

In contrast to the X rays and electrons produced in conventional radiotherapy, the radiation field produced in BNCT consists of four distinct radiation components possessing different biological weighting factors. Consequently, it is necessary to quantify each of these radiation components separately using special dosimetry procedures such that meaningful biologically-weighted doses can be determined for different normal and tumour tissues.

5.2. Radiation components in BNCT

Given an incident radiation beam consisting of neutrons and photons, the four dose components produced when the beam enters tissue are:

(1) The gamma dose: the dose due to gamma rays accompanying the neutron beam as well as gamma rays induced in the tissue itself. In the latter case, hydrogen in tissue absorbs thermal neutrons in $^{1}H(n.\gamma)\,^{2}H$ reactions and emits 2.2 MeV gamma rays.

(2) The neutron dose: epithermal and fast neutrons cause "knock-on" recoil protons from hydrogen in tissue in $^{1}H(n.n')p$ reactions resulting in locally deposited energy from the recoiling protons.

(3) The proton dose from nitrogen capture: ^{14}N in tissue absorbs a thermal neutron and emits a proton in a $^{14}C(n,p)^{14}N$ reaction. Dose results from locally deposited energy from the energetic proton and the recoiling ^{14}C nucleus.

(4) The dose due to the ^{10}B fission reactions: ^{10}B absorbs a thermal neutron in a $^{10}B(n,\alpha)^{11}B$ reaction. The energetic emitted alpha particle and the recoiling ^{7}Li ion result in locally deposited energy averaging about 2.33 MeV. About 94% of the time the recoiling ^{7}Li ion is produced in an excited state and de-excites in flight, emitting a 477 keV gamma ray. In the remaining events, the ^{7}Li is emitted in the ground state with no gamma ray emission Because the emitted gamma rays are about two orders of magnitude less prevalent and about half the energy of the 2.2 Mev gamma rays from hydrogen capture, they can be ignored from a dosimetry perspective, although they are frequently utilized for ^{10}B analysis purposes.

5.3. In-air beam measurements

The epithermal and fast neutron and gamma doses can be measured “in-air” or “in-phantom.” In-air measurements are most useful for a general characterization of epithermal neutron beams, whereas in-phantom measurements are necessary for providing data for

comparison with computational treatment planning codes. Such phantoms can be cylinders or cubes, made of solid PMAA or PMAA-walled filled with water, into which the ion chambers and gold/cadmium foil stacks can be inserted; or, they can be more anthropomorphic in design. For historical reasons such phantoms have usually approximated the dimensions of the human head.

5.3.1. Measurement of thermal neutron flux

The nitrogen dose and boron-10 dose are not measured directly but are calculated from measured thermal neutron flux using the kerma approach. (Ref.: the ICRU 57 (1998)). For thermal neutron flux measurement, the bare and cadmium covered gold foil technique is employed as described in the ASTM standard procedure.

5.3.2. Measurement of neutron & gamma dose

The fast and epithermal neutron and gamma dose components are measured using the dual ionization chamber technique originally described by Attix and more specifically for BNCT by Rogus. Typically, a tissue-equivalent ionization chamber measures both neutron and gamma dose with roughly equal sensitivity, while a graphite walled chamber measures only gamma dose. Absorbed doses are derived in each case. The chamber readings are corrected for various factors and the subtraction of the graphite chamber dose reading from the tissue-equivalent chamber dose reading yields separately the epithermal/fast neutron and gamma doses.

Figure 5.1. shows a photograph of the fibreglass walled water filled anthropomorphic dosimetry phantom used at one NCT reactor. Also shown are the ionization chambers that are inserted into the tubes within the phantom and irradiated in the beam. The ionization chambers can be moved in and out by remotely controlled stepping motors.

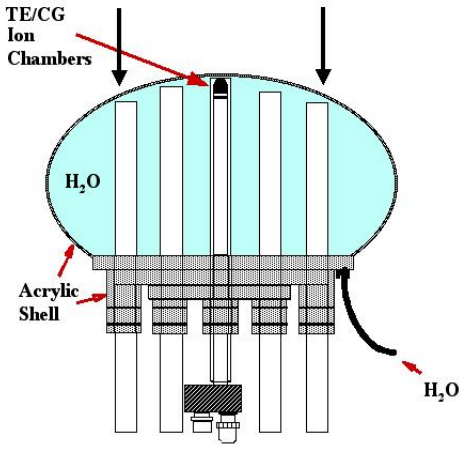

Fig. 5.1. A fibreglass walled water filled anthropomorphic dosimetry phantom used for beam calibrations at the MIT research reactor.

Fig. 1.1. (Section 1) shows the results of typical in-phantom beam measurements for the epithermal neutron beam at the MIT Research Reactor. The measurements were made along the central axis of the beam in the phantom shown in Fig. A. The gamma and neutron doses

were measured as described using dual ionization chambers. The measured thermal neutron fluxes were converted to the nitrogen capture and ^{10}B dose-rates assuming 30 ppm concentration. Each dose component is then weighted by a corresponding biological weighting factor, as shown.

The ionization chambers and their associated electrometers should be periodically (e.g. annually) calibrated by a dosimetry standards laboratory. In addition, prior to every use, the ion chambers should be assessed for constancy of response using devices containing ^{137}Cs or ^{60}Co sources, as is the routine practice in conventional external beam radiotherapy. For the analysis of the activated gold foils in the thermal neutron flux measurement, an intrinsic germanium gamma spectrometer is used and its absolute response may be calibrated using a ^{57}Co foil. The ^{57}Co foil should be periodically sent to a radioactivity standards laboratory for calibration.

5.4. Calibration of the on-line beam monitor system

In order to calculate the number of monitor units (MU) to be delivered to the patient for each field of a BNCT treatment, the on-line beam monitor system needs to be calibrated against the physical dose measured in-phantom and normalized to reactor power level. This can be done at the same time as the central-axis, biologically-weighted dose determinations are made. However, only the total biologically-weighted dose at the maximum location is used for this purpose.

5.5. Measurement of physical dose distributions

The calibration of the beam, and the subsequent monitor calibration, usually refers to the dose determination at a specific reference point in a phantom, usually the depth of maximum absorbed dose.

The measurement of dose distributions characterising the beam, such as a depth-dose distribution, or off-axis profile, is a necessary step in BNCT dosimetry. This not only enables the determination of the characteristics of the impinging radiation field but it also prepares the data to be used for patient dose calculation during the treatment planning process. The measured set of data is also the benchmark against which computer calculations can be compared and form part of the QA system of the entire BNCT procedure. It is acknowledged that these measurements can be tedious in low flux beams, but their necessity has to be stressed.

5.6. Uncertainties in BNCT dosimetry

Rogus (83) has analysed in detail the inherent uncertainties in the dosimetry procedures described above. He has estimated that the thermal neutron flux can be measured with an expanded uncertainty ($k = 2$) of 5–7%, and the nitrogen and ^{10}B doses calculated. The uncertainties in these dose values are difficult to estimate. Epithermal/fast neutron and gamma doses can each be measured with expanded uncertainties ($k = 2$) of 15–20%. These may seem large but it is hoped that with further work in the future they will be reduced.

No national or international standards currently exist defining procedures for the determination of dose in BNCT. However, the European Collaboration is conducting a thorough review and evaluation of different methods of physical dosimetry for BNCT aimed toward the preparation of a European "Code of Practice for the Dosimetry of BNCT."

6. RADIOBIOLOGY

6.1. Introduction

Radiations used for therapy initiate ionizing events in or around living cells. These ionizing events may result in cellular injury from which the cell may recover, lose its reproductive capacity or die. The eventual outcome is dependent on multiple factors, including:

- The type of radiation applied (electromagnetic and its energy; particles and their mass; charge and energy).
- The physical dose applied, the dose rate and the amount of each application (the fraction size).
- The characteristics of the cell affected by the ionizing event (its reproductive rate, stage in the cell cycle, degree of oxygenation).

The radiobiology of BNCT is more complicated than the radiobiology of other radiation therapy modalities. This is due to the fact that the radiation field in BNCT consists of several separate radiation dose components, with different physical properties and biological effectiveness. The magnitude of the radiation dose components changes, even within a given experimental setup, with the amount of boron present, the type of boron compound used and the position within the setup.

6.2. Dose components in BNCT

At each point of interest in the patient, one can identify four components contributing to the absorbed dose:

- the gamma dose, D_γ
- the neutron dose, D_n
- the high-LET proton dose, from nitrogen capture reaction, D_p
- the "boron dose", D_B

Due to the rapid attenuation of the epithermal or thermal neutrons in the tissues, the relative contributions of the four components vary significantly throughout the normal tissues at risk and in the target volume.

It is then difficult to predict the outcome of the treatment and/or the complications by simple evaluation of the absorbed dose at one or a few points. The dose-volume histograms (DVH) for each dose component provide useful information but their clinical significance in BNCT needs to be established.

Boron dose is evaluated assuming a homogeneous distribution of the boron atoms in the different parts of the tissues of interest and in the different sub-cellular structures. It is recognised that this is an important operational assumption, but no alternative approach is possible. Boron concentration in peripheral blood is the only measurable quantity during patient treatment. The tissue boron concentration is then derived from tissue-to-blood concentration ratios previously obtained for different normal tissues from animal experiments and patient observations.

6.3. Dosimetry

Although this section deals with radiobiology, the following points should be stressed because they are relevant for the interpretation of the results:

(1) *Measurements* Due to the fact that the design of biological experiments and their interpretation depend strongly on the magnitude of the physical doses for each of the above dose components, the determination of the latter are of great importance. It is desirable that internationally agreed standard measurement conditions are developed and validated, and applied to as many existing beams as possible.

(2) *Calculations* For the dose components induced gamma rays, recoil protons, thermal neutrons and their derived components, nitrogen capture and boron capture, calculations are often easier to carry out than physical measurements. It is necessary that the assumed composition of the exposed tissue be standardized, and reported. Where possible tissue compositions should be in agreement with those given by ICRU [6.1.].

(3) *Biological dosimetry* Epithermal neutron beams are complex and differ from centre to centre in neutron spectra, beam divergence, incident gamma contamination, and intensity. It is therefore desirable to characterize neutron beams not only by physical measurements, but also by biological dosimetry. It is therefore recommended that a set of experiments should be carried out, in order to further characterize a beam. These experiments, when carried out under identical conditions, should provide a level of confidence in the properties of the beam similar to that achieved with the different fast neutron beams, carbon ion beams and proton beams. The primary aim would be to validate the dosimetry on a biological level. With experience from a sufficient number of institutions, the results from existing beams to a new epithermal neutron beam could be transferred more easily, thus avoiding time consuming experiments for researchers at the new beam.

A recommended first series of inter-comparison experiments should consist of a cell colony formation assay, incorporating the following general considerations:

- Cells should be in suspension in small volumes.
- Irradiation should be carried out in a phantom of simple geometrical shape and appropriate material, allowing irradiation from the side and from the top, depending on the emergence of the beam.
- Cells should be irradiated at different positions within the phantom.
- Irradiation should be carried out in the absence of boron, and in the presence of two different concentrations of boron in the form of ^{10}B-enriched boric acid.

It would be advantageous if agreement could be reached on the cell line and the phantom shape and material. Some such experiments have already been carried out between institutions, but not yet to an extent that any general conclusions concerning the transfer of data from one beam to the next can be drawn. In addition, experiments utilizing *in vivo* systems such as intestinal colonies can be recommended.

For understanding organ response, it would be desirable to use systems where the response of a whole organ could be evaluated (e.g. brain and spinal cord). Such experiments

with epithermal beams would usually require large animals, as small animals would receive a lethal whole-body dose.

6.4. Factors affecting biological effects

6.4.1. Relative biological effectiveness (RBE)

RBE is defined as the ratio of doses of a reference radiation (currently cobalt-60 gamma rays) to a test radiation that will produce the same biological endpoint in a given system [6.2–6.3]. The RBE is a function of the radiation quality (LET).

The RBE varies, often within large limits depending upon dose level, biological system, fractionation and dose rate, experimental conditions (e.g. hypoxia etc.). Therefore it is not possible to assign a single RBE value to a given radiation quality, e.g. fast neutrons, low energy protons or α-particles. Determinations of RBE are always associated with an experimental uncertainty.

6.4.2. Compound biological effectiveness (CBE) or compound factor (CF)

The concept of RBE is valid only when the quantity *absorbed dose* can be defined, i.e. when the averaging procedure implicit in the definition of absorbed dose is applicable.

For the boron dose in BNCT the concept of absorbed dose cannot be applied because of the inhomogeneous distribution of the boron compounds and the short range of the α-and lithium particles. Therefore the RBE cannot be defined and the influence of an inhomogeneous distribution of the boron atoms cannot be determined. Only the product of these two components, RBE and boron distribution, can be assessed for a given tissue and experimental conditions. This product is currently referred to as Compound Biological Effectiveness (CBE) or Compound Factor (CF), although these terms have been used inconsistently in the literature.

6.4.3. Dose reduction factor for the gamma component (DRF-γ)

During protracted irradiation the damage caused by the gamma component of the dose will undergo repair during the time of the irradiation. A low dose rate may result in the need for a dose reduction factor, DRF-γ. This is incorporated in the weighting factor for gamma rays w_γ.

6.5. From experimental RBE and CBE to biological weighting factors, w

As indicated above, the concept of RBE, and CBE or CF are valid only for well specified conditions. In clinical situations the choice of the boron weighting factor w_B will be influenced by the CBE or CF. The choice of the remaining three weighting factors will take into account their respective RBEs. The biological weighting factors are used as a guide to treatment prescription and institutional inter-comparisons. Selection of the weighting factors requires judgement by the radiobiologist and the radiation oncologist.

The terminology used to report the BNCT dose in weighted units should follow the ICRU convention as closely as possible (see Section 8). When the biological weighting factors have been selected for each one of the four dose components, the total biologically weighted dose, in Gy, becomes:

$$D_{bw} = w_c.D_B + w_\gamma.D_\gamma + w_n.D_n + w_pD_p$$

6.6. Dose fractionation

Fractionation plays a major role in enhancing conventional radiotherapy. With the high LET radiations inherent in BNCT any effect of fractionation arising from repair are likely to be minimal. This assumption is supported by experimental results.

Standard photon radiation therapy for glioblastoma is usually delivered in daily fractions (5 days/week) of 1.8–2.0 Gy to a cumulative dose of 55–60 Gy. BNCT, on the other hand, has generally been delivered in a single fraction. Some of the considerations that justify fractionation with conventional therapy are clearly not applicable to BNCT. With boron concentrations in the range of 20–30 μg ^{10}B/g, 85 to 90% of the total biologically weighted dose to the tumour will be from high-LET radiation. Tumour hypoxia, and tumour cell cycle-dependent radiation sensitivity are of relatively minor importance in BNCT-mediated tumour control. In tumours treated by thermal beams there is unlikely to be any advantage in fractionation.

In an *epithermal neutron* beam at depth in the normal brain, the gamma component of the total dose can be as high as 40–50%, due primarily to the $^{1}H(n,\gamma)^{2}H$ reaction in tissue. Fractionation would be expected to be of benefit in allowing for the repair of photon-induced sub-lethal damage as well as allowing for re-population of rapidly growing normal tissues in the treatment field such as mucosa or skin.

Experimentally, conditions that roughly approximate the clinical situation with respect to the relative proportion of low and high-LET dose components have been simulated in the rat spinal cord using thermal beam-only irradiations. Here the radiation mix was ≈53% high-LET and ≈47% low-LET, which is close to that which is likely to occur at depths of >5 cm in the human brain during BNCT. At the ED_{50} level of effect for radiation induced myeloparesis, a relatively small sparing effect (≈14%) was seen when a single dose exposure was compared to four equal fractions (93). The effect was most pronounced in comparing single and 2-fraction exposures. The degree of sparing observed was less than would be expected if the low-LET component of the dose had been fully repaired. This study indicates that there would probably be no practical advantage, in terms of normal CNS sparing, in moving from a two-fraction to a four-fraction BNCT protocol and that fractionating BNCT should not focus on sparing of normal tissue but on re-targeting.

Re-targeting of boron to a new subset of tumour cells during a fractionated BNCT regimen could be of benefit due to the dependence of the dose distribution from the $^{10}B\ (n,\alpha)\ ^{7}Li$ reaction on the distribution of the particular boron compound at the cellular and sub-cellular level. This re-targeting is similar in concept to the repeated administration of chemotherapeutic drugs which accesses cells not previously affected.

6.7. Dose escalation

In BNCT the dose escalation can be achieved by modifying two factors:

- the irradiation or exposure time
- the boron concentration at the time of irradiation

The four dose components in all tissues or organs increase linearly with the exposure time as long as the treatment time is short compared with the biological half-life of boron

(about six hours). Treatment time of a few hours would reduce the potential efficacy of BNCT due to loss of boron.

The boron dose increases approximately linearly with the concentration of boron in tissues. This is true as long as there is no self-shielding due to high boron concentrations. As a result of the change in boron dose, the relative contribution of the four dose components at any point will be modified. Systemic toxicity might limit the administration of boron. Increasing the amount of administered boron will not increase the boron dose in tumour cells which do not incorporate boron.

Dose escalation in clinical trials needs to be preceded and supported by radiobiological experiments. The effect of increasing the treated volume is difficult to assess experimentally in animal models, since the situation is totally different in patient geometry.

6.8. Experimental evaluation of biological effectiveness factors

The approach to experimental determination of these biological effectiveness factors has been recently reviewed [6.4.]. The general approach is as follows: (1) for each tissue, define a quantifiable endpoint or response to irradiation; (2) determine the dose response to a photon reference radiation; (3) determine the dose response to the neutron beam only; and (4) determine the dose response to the neutron beam in the presence of the boron compound. Once these dose response relationships have been determined, it is possible to estimate a number of useful quantities: (1) the RBE of the beam alone, (2) the RBE of the high-LET components of the beam (nitrogen capture dose plus the fast neutron recoil proton dose), (3) the biological effectiveness factor for the particular boron compound. This approach assumes that dose can be considered as a linear physical quantity within the ranges used in biological systems. Alternatively, experiments at two different boron concentrations yield the same results.

A measure of the RBE for the neutron beam can be obtained, in the absence of boron, by comparing the neutron beam dose with the X ray dose sufficient to produce an isoeffect in a given biological system. The result can be expressed as in [Eq. 1], where ED_{50} is the physical absorbed dose which results in a 50% incidence of the biological endpoint under evaluation. This assumes that the beam dose comprises gamma plus a combined "proton dose" as described above and that the RBE of the gamma component is 1. The beam RBE is the ratio of the X ray dose and the beam dose at the ED_{50} effect level [Eq. 2].

[Eq. 1] {["proton" dose] + [gamma dose]} = X ray ED_{50} dose

[Eq. 1b] beam RBE = [X ray ED_{50} dose]/{ ["proton" dose] + [gamma dose]

[Eq. 2] ["proton" dose]["proton" RBE] + [gamma dose] = X ray ED_{50} dose

[Eq. 2b] "proton" RBE ={[X ray ED_{50} dose] – [gamma dose]}/ ["proton" dose]

[Eq. 5] X ray ED_{50} dose = [Beam dose][Beam RBE] + [$^{10}B(n,\alpha)^{7}Li$ dose][CBE factor]

[Eq. 6] CBE factor = { [X ray ED_{50} dose] — [Beam dose][Beam RBE] }/ [$^{10}B(n,\alpha)^{7}Li$ dose]

An estimate of the RBE for the high-LET components of the beam can be obtained in the absence of boron from the same data by expressing the result as in [Eq. 3] and solving for the "proton" RBE as shown in [Eq. 4]. Experimentally, the CBE factor can be evaluated by

first comparing the effect of the beam alone to the effect of a reference radiation to obtain an estimate of the beam RBE or of the high-LET components of the beam as described above. Thermal neutron irradiation, with boron compound present, to a total dose producing the same ED_{50} endpoint is represented by [Eq. 5]. Solving [Eq. 5] for the CBE factor produces [Eq. 6].

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[6.4.] CODERRE, J.A., et al., The Radiadiobiology of Boron Neutron Capture Therapy: Are "Photon-Equivalent" Doses Really Photon-Equivalent? 1999 (Annex 7).

7. CLINICAL DOSIMETRY OF BNCT: PATIENT DOSE CALCULATION AND TREATMENT PLANNING

7.1. Introduction

In contrast to high-energy X ray radiotherapy, the transport of epithermal neutrons is more sensitive to the shape and composition of the patient's body and involves a more complex assortment of radiation components having differing biological weighting factors which therefore need to be considered separately. ^{10}B in tissues may cause significant thermal neutron flux depression which in turn influences most of the other radiation components. Finally, because the ^{10}B pharmaceutical has a concentration/time profile that is different for every patient, in those facilities which have relatively weak epithermal beams (where irradiation times are long) on-line monitoring of the ^{10}B concentration in blood is necessary and the required monitor units can require recalculation during the treatment. For these and other reasons, most practitioners have decided to utilize the Monte Carlo simulation technique for BNCT computerized treatment planning [7.13–7.17].

The dosimetry requirement for clinical BNCT can be considered to consist of three distinct modules:

(1) Physical dosimetry employing an appropriate phantom;

(2) Monte Carlo based treatment planning;

(3) Software to merge the on-line beam monitor readings, treatment planning parameters, and the continually varying blood ^{10}B concentration to provide the monitor units.

Module 1 was dealt with earlier; this section concentrates on modules 2 and 3.

7.2. General issues relating to BNCT computerized treatment planning

7.2.1. Data input/output

There are a minimum of four tissues that should be taken into account in a treatment planning calculation. These are brain, skin, bone, and tumour. Since their radiation transport properties are very similar, the hydrogen and ^{10}B concentrations are of greatest importance in a Monte Carlo calculation. The inclusion of ^{10}B enables the Monte Carlo calculation to approximately correct for the effects of thermal neutron flux depression[1]. Internal air cavities should also be included in the calculation [7.13]. For compliance with evolving BNCT standards, it is recommended that all elemental compositions and physical densities of tissues modelled in the treatment planning calculations should be based on *ICRU-46* data [7.26].

BNCT treatment planning systems should incorporate the display, analysis, and data and graphics interface features common to state of the art external beam radiotherapy treatment planning systems. These could include various provisions for quantitative image analysis, beams-eye-view displays, three dimensional rendering and visualisation, annotation; merging separate treatment plans in the same patient (e.g. merging conventional radiotherapy and

[1] To avoid thermal neutron flux depression due to the presence of high concentrations of ^{10}B its concentration during irradiation should not differ by more than about 20-30% from that assumed in the treatment planning phase, since it has been observed that the thermal flux at the mid-line of a head phantom is depressed by approximately 0.5%/ppm of global ^{10}B concentration.

BNCT treatment plans), and image data communication compatibility with various CT and MRI systems.

BNCT treatment planning system should be capable of displaying isodose contours superimposed on corresponding anatomical image planes, and dose-volume histograms (DVH). Because BNCT dose is dependant upon the boron concentration, which differs in tumour and normal tissue, and because tumour cells may be closely intermingled with normal tissues, it is difficult to display all the necessary isodose contours in the traditional manner as in conventional radiotherapy. In BNCT there are at least two separate dose distributions that need to be displayed, one for tumour tissue and another for normal tissue. This is illustrated in Fig 7.1, which shows a two-field treatment plan.

It should be emphasized that in BNCT treatment planning, the assumption is usually made that there is a fixed ratio of boron between tumour and blood, although there is substantial evidence that the boron distribution at the tumour cell level is heterogeneous. Furthermore, isodose displays for normal tissues should be further subdivided when there are different biological weighting factors from tissue to tissue; this is especially true for the boron dose component.

7.2.2. The dose calculation procedure

There are two basic philosophies on how Monte Carlo based treatment planning should be used to calculate dose.

One approach models the patient with fairly high spatial resolution (from CT, MRI, etc). The Monte Carlo calculation based on such a model directly tallies energy depositions within the various tissues from which dose is then derived. This is the most straight forward calculation procedure, but usually requires very long computation time.

The second approach models the patient more coarsely, typically with a mesh size of 5–10 mm resolution (see Fig. 7.2), and calculates the neutron and gamma fluxes within these mesh regions. These fluxes are then converted to doses using flux-to-kerma rate conversion factors [7.16–7.18]. For the assumption that kerma is equal to absorbed dose to be true for the gamma component, the mesh size should not be less than 5 mm in size.

Each approach has its own merits. The former approach is more accurate although computationally time consuming but the latter is still judged appropriate for clinical use considering the remaining uncertainties involved The Monte Carlo-based BNL and Harvard-MIT BNCT treatment planning systems use the second approach.

Three dimensional deterministic radiation transport methods, such as the 3-D discrete ordinates code TORT, have also been shown to be potentially useful in BNCT treatment planning [7.19–7.20].

7.3. Available treatment planning systems

There are two computer codes currently used for clinical BNCT treatment planning. These are the Idaho National Energy and Engineering Laboratory's *SERA* [7.16, 7.17] and Harvard-MIT's *MacNCTPLAN* [7.13, 7.14].

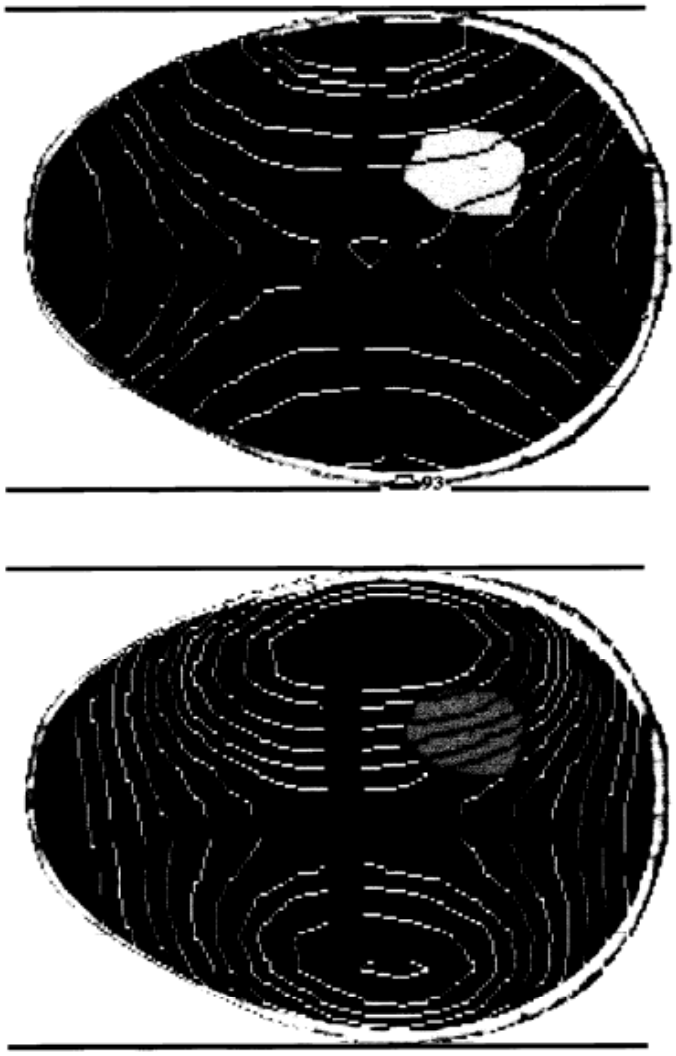

Fig. 7.1. Treatment plan for a two-field BNCT irradiation, computed for BPA assuming a tumour-to-blood ration of 3.5:1 and 15 ppm of boron-10 in blood for the MIT Fission Converter Beam (FCB). The top figure shows isodose contours (in unit of total biologically-weighted dose) in normal tissues; the figure below shows isodose contours in tumour tissue — assuming it could be located anywhere within the brain. The percentages for the tumour isodose contours are normalised to the 100% (maximum dose) point in normal tissue.

Both systems employ the Monte Carlo method and were designed specifically for BNCT. These are available cost free to users for experimental, non-commercial purposes. Both codes are evolving and are supported to various degrees by their originating research groups.

The general purpose Monte Carlo code *MCNP* [7.21] has also been tested for BNCT dose calculations but not for patient treatment planning. *MCNP* is a public domain code, written for a wide range of diverse radiation transport applications. As such, it contains a large

amount of computational overhead which facilitates relatively foolproof geometrical specification, provides extensive internal checking for operator errors, ensures compatibility with many nuclear cross section data sets, etc. This, however, results in greatly reduced computational speed. However, *MCNP* is supported by a large computational radiation transport research group at Los Alamos National Laboratory (LANL), is extensively validated against experimental data and is in continual evolution and improvement as part of LANL's internal computational methods development program and as outside users request added features.

7.4. Computational accuracy and QA of a BNCT treatment planning system

The concept of computational accuracy is problematic since "accuracy" implies comparison against an accepted standard. However, for BNCT dosimetry no computational or physical dosimetry standards have yet been developed. Nevertheless, judicious intercomparisons should be conducted prior to clinical use.

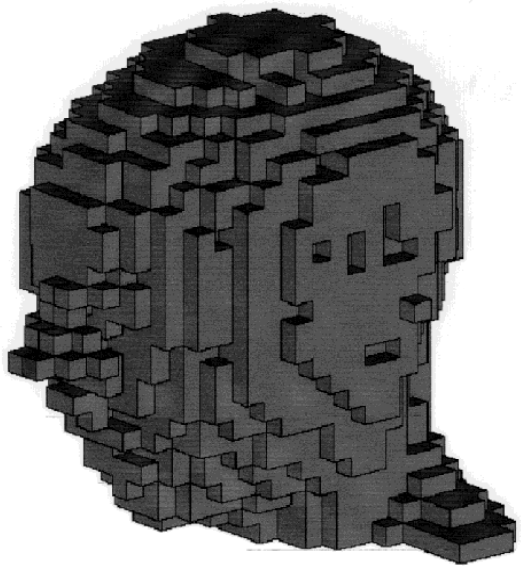

Fig.7.2. Monte Carlo computational phantom on which the treatment plan of Fig 1 is based, using a 10 mm x 10 mm x 10 mm calculation mesh. The model consists of four materials (normal tissue, tumour tissue, bone and air), automatically determined from CT scans by thresholding and contouring, automatically synthesised into the geometrical model from CT scans using the Harvard-MIT developed treatment planning program MacNCTPLAN.

First, any calculations should be compared against the specific facility's experimental dosimetry. A suggested approach is to compute and measure the fast neutron and gamma doses and the thermal neutron flux along the central axis of the beam and for some off-axis points within a simple phantom. Such a phantom could consist of a PMMA-walled water filled cylinder or cube with cross-sectional dimensions approximately double the diameter of the neutron beam, into which ion chambers and activation foils can be inserted. Such computational vs. experimental data should currently be in agreement to within approximately 5–7% for the thermal neutron flux (for which the standard ASTM measurement procedure exists), and within approximately 15–20% for fast neutron and gamma doses. These are currently the estimated expanded uncertainties (k = 2) [Ref. ISO] for gold foil and mixed-field ion chamber dosimetry [7.23]. As methods for physical dosimetry in BNCT are further refined the agreement criteria with physical measurements should be made more stringent.

Second, a comparison of computational results against a computational BNCT "standard test problem" is recommended. The MCNP Monte Carlo code is considered to be the most suitable code for calculating accurately BNCT dose distributions which can be used as a benchmark for other codes [7.16]. As an initial effort at creating such a benchmark for computational dosimetry in BNCT, central axis dose-depth data have been computed at Harvard-MIT in collaboration with LANL using MCNP and an analytical model of an ellipsoidal water filled anthropomorphic head phantom for which simple descriptive analytical equations are published [7.25].

7.5. Conversion of treatment plans to delivered monitor units

After an optimized treatment plan has been generated for a patient it is necessary to determine the number of monitor units which need to be set to terminate the irradiation after the prescribed dose has been delivered.

Different approaches exist to accomplish this, but as an example, the method to be described is the method adopted by the Harvard-MIT program and is illustrated in Fig 7.3. Three phantom environments are shown. The top one represents the *physical* phantom in which the physical dose components are determined; the *middle* one represents a mathematical model of the physical phantom generated by the treatment planning code (MacNCTPLAN); the *bottom* one represents the "patient" to whom BNCT is delivered. The goal is to determine the number of monitor units (MU) that need to be delivered to this patient to achieve the biologically-weighted prescription dose. First, the maximum biologically-weighted dose is determined in the physical phantom containing an estimated ^{10}B concentration and the corresponding beam monitor count-rate in cpm is recorded. Second, a maximum biologically-weighted dose is computed using the Monte Carlo method for the *physical calibration phantom*, assuming a typical anticipated ^{10}B concentration. Third, an optimized Monte Carlo treatment plan is generated for the patient, also including the anticipated ^{10}B concentrations for each individual field delivered. The ratio between the two maximum biologically-weighted dose values from the two Monte Carlo calculations is determined for each field to be delivered. These ratios are called "dose transfer factors" Finally, on the assumption that the physically determined doses are the "gold standard", the required MU values for each field to be delivered are calculated using the equation:

Monitor Unit Counts = Monitor Count-Rate x $(D_2/D_3)/D_1$ x Prescription Dose

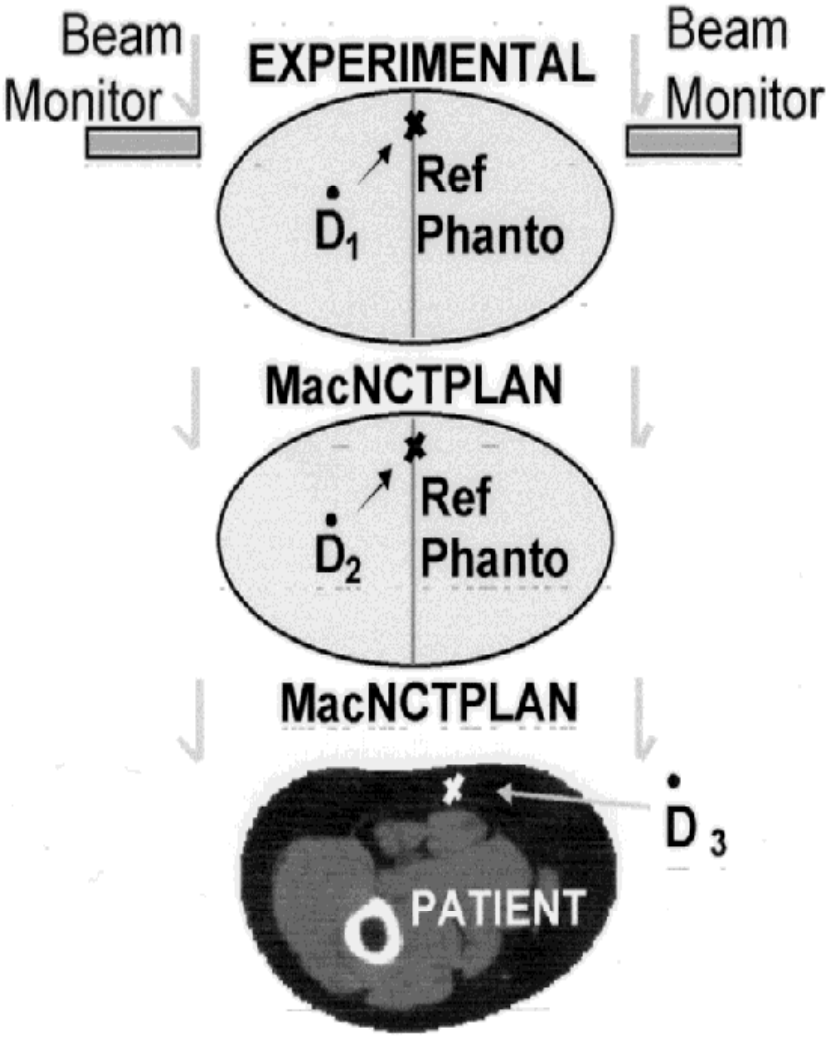

Fig. 7.3. Scheme developed at Harvard-MIT for transformation of physical dose measurements in a phantom to prescribed monitor units to deliver a dose to a patient undergoing BNCT. The "D" values are biologically-weighted dose-rates at the maximum dose locations in each case while the cpm is the beam monitor counting-rate.

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8. DOSE AND VOLUME SPECIFICATION FOR REPORTING BNCT: AN IAEA-ICRU INITIATIVE

8.1. Need for harmonization in reporting

BNCT has been applied since the fifties in Brookhaven, since the early sixties at MIT, and since the late sixties in Japan. However, it is fair to say that, after more than 40 years, the value of the technique is far from being apparent, and even that no definitive conclusion, positive or negative, has been drawn so far. The rationale of BNCT is certainly exciting. There are few examples in the history of radiation therapy, where selective irradiation at the cellular level is administered.

One of the reasons (not the only one of course) for "reluctance" or "scepticism" against the BNCT technique is partly a lack of clarity and rigor in the way of reporting both patient classification, the clinical results and the technical conditions.

Today, only few centers are applying BNCT worldwide and, even among them, there is a lack of agreement on the way of reporting the treatments. Harmonization in reporting is indeed a matter of concern of the International Society for Neutron Capture Therapy (ISNCT).

The ICRU (International Commission on Radiation Units and Measurements) has for several decades been involved in promoting harmonization in methods of reporting radiotherapy applications.

The most widely used contribution of the ICRU is Report 50 on "Prescribing, Recording and Reporting Photon Beam Therapy", published in 1993 [8.4]. A Supplement to Report 50, which includes recent developments in the field has been published in November 1999 as Report 62 [8.6].

ICRU recommendations for reporting have also been produced for brachytherapy; interstitial [8.5], intracavitary radiotherapy, [8.2]. Recommendations on electron and proton beam therapy are in preparation.

Wide consultation at previous meetings of ICRU, ISNCT and the IAEA was used to try to reach an agreement for reporting BNCT treatments.

8.2. Dose reporting

Two important considerations are relevant to dose reporting.

8.2.1. The standard or reference radiotherapy modality

The first consideration deals with the fact that photon beam therapy is for the moment (and will remain in the foreseeable future) the "standard" or "reference" radiotherapy modality. More than 80% of radiotherapy patients are treated today with photons (alone or in combination with another radiotherapy technique). A large experience has been built up worldwide over about 50 years with megavoltage photons. The value, or the relative merits, of BNCT will be evaluated by comparison with conventional photon beam therapy.

It is thus important, when comparing the BNCT technique and the results, that the same definitions and the same concepts be used as in conventional photon beam therapy, and that the same general approach for specifying the dose for reporting be followed. In addition,

BNCT could benefit from the experience gained over the years with conventional radiation therapy.

It is however recognised, that BNCT has unique properties and thus some new concepts or terms need to be introduced. However, these new concepts or terms should be compatible with the existing ones, and conventional methods of reporting, should be retained as much as possible.

8.2.2. Prescribing versus reporting

The second consideration deals with the difference of attitude or approach required when prescribing as distinct from reporting a treatment.

Prescription of the treatment is the responsibility of the radiation oncologist in charge of the patient. Prescription is based on clinical experience and judgement; it should of course also be based on accurate and documented knowledge of the existing technical irradiation conditions. The responsibility of the radiation oncologist is to "integrate" all available information. At the end, he has to provide a simple prescription of e.g. absorbed dose level or so many monitor units, or so much irradiation time. Each radiation oncologist has his own terms of reference, past experience, and way of thinking which could influence final prescription.

In contrast, the requirements for **reporting** are totally different. The aim of reporting is to describe the treatment in such a way that the "readers" (i.e. the different groups of readers, in the different centres, commissions or organisations) can understand what has actually been done, and evaluate the clinical results based on reliable information. This implies the use of the same language, definitions, concepts, the same general approach and the same method for specifying the dose. Otherwise any meaningful exchange of information becomes impossible.

In summary, when prescribing the treatment, the radiation oncologist has some degree of freedom implied in his responsibility. In contrast, when reporting, a uniformity or agreement on terms, concepts, language and approach is essential, otherwise reporting a treatment is likely to be meaningless.

This distinction being made, it is obvious that using the same definitions of terms, the same concepts and the same approach for prescribing and reporting makes the situation much easier and reduces the risk of confusion and error.

It has never been the aim nor the task of the ICRU to influence the prescribed dose, the other aspects of treatment prescription, nor to encourage radiation oncologists to depart from their traditional treatment techniques.

8.3. Reporting clinical data

Three types of data can be identified when reporting a treatment in oncology (a radiotherapy treatment in general or in particular a BNCT treatment):

- patient-related data,
- radiotherapy data,
- data which are specific to BNCT.

Complete and reliable oncological and other clinical data should be reported for any oncological treatment (not only in radiation therapy). The need for a complete clinical record is obvious and does not need to be stressed. In particular, tumour extent and grading should be reported according to international classification systems [8.9, 8.10].

The ICRU concepts of GTV and CTV should be used, since they are general oncological concepts [8.4, 8.6].

8.3.1. Gross tumour volume (GTV)

The gross tumour volume (GTV) is the gross palpable or visible/clinically demonstrable location and extent of the malignant growth.

The GTV may appear different in size and shape, sometimes significantly, depending on which examination technique is used for evaluation, e.g. CT versus MRI for some brain tumours. The technique used for evaluation of the GTV thus has to be reported.

A GTV may be confined to only part of an organ, or involve a whole organ (e.g. in the case of multiple metastases to the brain). It is not possible to define a GTV after a macroscopically complete surgical resection, situation which is common in BNCT.

8.3.2. Clinical target volume (CTV)

The CTV is a tissue volume that contains a demonstrable GTV and/or sub-clinical malignant disease at a certain probability level. This volume thus has to be treated adequately in order to achieve cure.

Delineation of the GTV and CTV is based on general oncological principles, and is independent of any therapeutic approach. In particular, it is not specific to radiation therapy. Delineation of the GTV and CTV *must precede* the selection of the treatment modality and the subsequent treatment planning procedures.

8.4. Reporting absorbed dose in BNCT

Since BNCT is still a complex experimental technique, reporting at "Level 3 [8.5] is needed. Several types of difficulties are raised when specifying dose for reporting BNCT.

At any point in the irradiated tissues, one can identity four components contributing to the absorbed dose:

- The gamma ray dose, D_γ
- The neutron dose, D_n
- The high-LET proton dose from nitrogen capture reaction, D_p
- The “boron dose", D_B

The relative contribution of the different dose components varies significantly with depth, the type of boron compound and the irradiation conditions.

The magnitude of the four components contributing to the absorbed dose should be reported at each point of interest in the patient. The gamma-, neutron-, and proton doses can

be combined and reported together as the "beam dose", D_{beam}. They are related to the beam characteristics.

The "boron dose" that results from the boron (n,α) reaction cannot be determined or evaluated directly. The “boron dose” is evaluated and reported assuming a homogeneous distribution of the boron in the tissues of interest. The boron concentration in the tissues is derived from blood measurements assuming appropriate tissue-to-blood ratios. The blood concentration and the tissue-to-blood ratios which have been used for dose evaluation must be reported.

The homogeneity of boron incorporation at the cellular level (especially for malignant cells) is the main issue in BNCT. The number of alpha particles traversing the cells vary from one cell to another. The "averaging process", which forms the basis of the concept of absorbed dose, is then not applicable.

8.5. The RBE problem and the biologically weighted dose, D_w

The different dose components, at each point of interest have their own "radiation quality", thus their own RBEs. These dose components thus cannot be simply added. Furthermore, it should be stressed that the RBE of a given radiation quality, compared to conventional gamma rays is not a single value but depends on several factors such as absorbed dose, fractionation, dose rate, biological system and endpoint.

It is necessary to apply "weighting factors" to the different dose components of the BNCT beam to enable the radiation oncologist to

- apply the clinical experience gained with conventional photon beam therapy to BNCT
- compare results from different institutions applying BNCT
- derive as a first approximation the BNCT dose to prescribe

Adjustment will need to be made for differences in time-dose patterns

One of the main challenges in BNCT is to select, among all observed RBE values, the weighting factors for the different beam components, which would be the most relevant for the clinical application.

The following symbols are proposed: w_γ w_n, w_p, w_c. The weighting factor w_c (**c** for **c**ombined) combines the effects of heterogeneous microdistribution of the boronated compound as well as the RBE arising from the high LET α and Li particles.

If the beam dose D_{beam} is reported, the corresponding weighting factor, w_{beam}, should also be reported.

Individual weighting factors should always be reported. This would allow subsequent reevaluation of the total weighted BNCT dose, D_{bw}, if better data should become available.

The sum of the products:

$$W_\gamma D_\gamma + w_n D_n + w_p D_p + w_c D_B$$

is the **total biologically weighted dose** in BNCT (symbol D_{bw}, special unit Gy) (**bw** for **b**iologically **w**eighted) and should always be reported. It is the quantity, which should be used when comparing the doses delivered by BNCT and conventional photon beams for protocols or for individual patients.

8.6. Reference point(s) and volumes for reporting BNCT

To facilitate comparisons with other radiation therapy techniques (and in particular conventional photon beam therapy), the specification points for reporting should be selected primarily in relation to anatomical points or the PTV (see below) instead of in relation to the technique (e.g. maximum dose points, beam axes).

In addition to the two purely oncological concepts defined above (GTV and CTV), the concept of planning target volume (PTV) was developed by the ICRU [8.4]. This concept is applicable to radiation therapy in general and also to BNCT.

8.6.1. Planning target volume (PTV)

The PTV is a geometrical concept used for treatment planning; it is defined to select appropriate beam sizes and beam arrangements to ensure that the prescribed dose is actually delivered to all parts of the CTV.

Delineation of the PTV is difficult and is a matter of compromise. It implies the experience, the judgement and the responsibility of the radiation-oncologist. The difficulty results from the presence of "organs at risk".

Delineation of the PTV depends on the limitations of the irradiation techniques. Therefore, the PTV for BNCT may be different from the PTV for a photon treatment (in the same way as a PTV for brachytherapy differs from a PTV for conventional photon therapy). Comparison of the sizes and shapes of the PTV may be one factor, among others, to compare the respective merits of different radiotherapy techniques.

The different causes of uncertainty for which an additional safety margin is needed around the CTV are analyzed and listed in ICRU Report 62 [8.6]. In BNCT, at least three courses of uncertainty arise. The first one is related to patient-beam positioning. Due to the fixed beam geometry and the extended treatment times, uncertainties with respect to patient positioning are exacerbated in BNCT. Secondly, in BNCT, an additional uncertainty is related to boron distribution in space and time. A third uncertainty arises from the magnitude of the various weighting factors.

8.6.2. The reference point and the ICRU approach for reporting dose

- A point is selected at the centre (or in the central part) of the PTV: it is the **ICRU reference point**.
- The four components of the absorbed dose at the Reference Point shall always be reported.
- The best estimate of the **maximum and the minimum** dose and at other clinically relevant points in the PTV should be reported. From the dose-volume histograms, average

dose values can be derived for the four dose components. The clinical relevance of these average dose values needs to be further evaluated.

The boron dose and the biologically weighted dose are critically dependent on the boron concentration, The boron concentrations assumed must be explicitly stated when reporting any of these doses.

8.7. Organs at risk (OR)

The organs at risk ("critical normal tissues") are normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose.

The organs at risk should be identified. In case of BNCT treatment of brain lesions, different parts of the CNS can be identified as organs at risk.

Any movement of the organs at risk as well as uncertainties in patient-beam positioning must be considered. In addition, all of the uncertainties described above for the PTV must be considered. A margin must be added to the OR volume to compensate for these variations and uncertainties. This leads, in analogy with the PTV, to the concept of **planning organ at risk volume (PRV)**. The PTV and PRV may overlap.

8.7.1. Dose reporting for organs at risk

- For each organ at risk, when part of the organ or the whole organ is irradiated above the accepted tolerance level, the *maximum dose* should be reported;
- The *volume* receiving more than the accepted tolerance dose should be evaluated from the dose-volume histograms.

8.8. Additional information specific to BNCT

As stressed in the different ICRU Reports, the treatment modality, the technical conditions, the physical and computational dosimetric methods must be clearly and completely described, using accepted definitions of terms and concepts. In the case of BNCT, technical conditions to be reported include: route of drug administration, period of drug administration, interval between drug administration and start of the irradiation, duration of the irradiation, variation of boron concentration during irradiation, etc. Only under these conditions can the reported dose values be interpreted in a correct and reliable way.

In particular, the different factors listed in ICRU Report 50 (page 44) to describe the treatment technique should be reported, in addition, tissue compositions contained in ICRU Report 48 [8.3] should be used for dose calculation.

Complete and reliable information would allow eventual re-evaluation of the doses if better numerical values of the implied quantities become available.

In addition to the reference points recommended above for reporting and needed for a useful exchange of clinical information, other points directly related to BNCT technique may be important to identify; they depend on the local treatment conditions and policy applied in the department. *Recording* and *reporting* the doses at these additional points may be useful at the local level, for specific studies, such as QA programs, and for inter-comparisons between different BNCT centres.

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Note: References 1–8 are ICRU reports on dose reporting.
References 9–10 are references on pathological staging

9. CLINICAL

9.1. Cancer

Cancer, was known to exist in antiquity; the appearance of infiltration, like legs of a crab, gave rise to the name “cancer” in the times of Galen (130–200 A.D.). However, with increasing longevity of the population resulting from improved control of epidemic and infectious diseases, it leapt into prominence in the twentieth century.

The cure of cancer has become a realistic expectation in developed countries over the last decades. Using the American Cancer Society figures for 1991 [9.1], for a population of 250 million, 1 million invasive cancers (4 per 1000) and 600 000 non-melanomatous skin cancers occurred. The skin cancers are almost invariably cured. Of the invasive cancers, 30% are widely disseminated and receive multi-modality therapy predominantly for palliation. The 70% that are confined loco-regionally will be treated primarily by surgery and radiotherapy. Of these, 56% will be cured, while 44% recur with little expectation of subsequent cure. These figures emphasise that of 1 million invasive cancers, 400 000 should be cured with the existing modern technology. Similar figures resulted from a European study.

Cancer cure is best practised in a multidisciplinary environment with surgery, radiation oncology and medical oncology co-operation. These modalities are frequently used concurrently to obtain optimal results.

Repeat treatment of a site by a single modality including especially radiotherapy, is seldom successful and is usually accompanied by a high morbidity to the patient. This applies to BNCT and conventional radiotherapy where vascular damage may result in local necrosis.

9.2. Malignant astrocytomas (gliomas) of the brain

These tumours arise from the supportive (glial) cells of the neurones of the brain — the astrocytes.

Different histological classification systems exist which recognise groups of tumours divided according to the degree of dedifferentiation (change from the normal cell appearance under a microscope). These are broadly divided into **low grade astrocytomas**, more frequently seen in childhood in the cerebellum which is anatomically a separate part of the brain, involved mainly in control of balance and motion. In this site, management by surgery and, when indicated, adjuvant radiotherapy is associated with a good prognosis. When these tumours occur in the main portion of the brain, the cerebrum (supratentorial brain), seen in adulthood, the outlook is poorer but a 5-year survival of about 40–50% can be expected [9.2, 9.3] with combined surgical and radiotherapy management.

Treatment of **high-grade astrocytomas** is the main field of activity for BNCT therapy. These tumours comprise about 40% of all brain tumours which in turn are 1.5% of all cancers seen [9.1]. ***Thus, as about 4000 cancers occur per year per million population, about 24 can be expected to be high grade astrocytomas***. These tumours are highly anaplastic (large changes from the normal cell appearance). When these cellular changes are accompanied by necrosis, the name *glioblastoma multiforme (GBM)* is applied to this subset of malignant astrocytomas. While 5-year survivals are meaningful in low grade astrocytomas, these are so uncommon in high grade tumours that median survivals are used; typically 36 month for anaplastic tumours without necrosis and only 8.6 months for GBM [9.4]. Even with better

prognostic factors (younger age, good performance status, etc.), these patients rarely survive 5 years. No reference is made to the term 'cure' often reliably used in other cancers.

9.3. New directions in GBM treatment

Studies to determine the effect of increasing the radiation dose above 60Gy or the addition of single or multiple agent chemotherapy, have failed to demonstrate significant benefit from the drug. [9.5]. Adjuvant BCNU may offer a benefit in a small subset of patients [9.6].

Hyperfractionation studies (increased number of smaller fractions of radiotherapy administered more than once a day) have mostly been negative and, when positive results have been obtained, the median survivals still remained under one year [9.7].

Hyperbaric oxygen administered with radiotherapy has theoretical advantages for the treatment of hypoxic tumours. The necrosis in GBM is seen to be evidence of probable hypoxia. No significant advantage was seen in the study conducted by Chang [9.8] using this method of sensitisation with a median survival of 38 weeks. The oxygenomimetic drug, misonidazole, also failed to demonstrate any significant improvement.

9.4. Neutron capture results for GMB

9.4.1. Thermal neutrons — after resection

In North America, the first clinical trial of BNCT for patients with GBM was initiated at Brookhaven National Laboratory's (BNLS) Graphite Research Reactor (BGRR) in 1951 [9.9]. From 1959 to 1961 a series of patients with intracranial tumours received BNCT at the Brookhaven Medical Research Reactor (BMRR). Another group of patients with malignant gliomas was treated at a reactor at the Massachusetts Institute of Technology (MIT) during 1959–1961. These trials used four different boron compounds and a variety of surgical interventions. Results from the BNL and MIT studies were disappointing and all clinical trials of BNCT in the United States were stopped. The disappointing results were attributed inadequate penetration of the thermal neutron beams, the only kind of neutron beam then available, and poor localization of boron in the tumour: tumour-to-blood ^{10}B concentration ratios were less than 1 [9.9–9.11]. Efforts to deliver therapeutic neutron fluences to a tumour at considerable depth in the brain sometimes resulted in severe damage to the scalp. In retrospect, it is now considered that high boron concentrations in the blood contributed to the damage to the vascular endothelium [9.12]. These studies have subsequently proved to be a source of medico-legal litigation.

9.4.2. Thermal neutrons — intraoperative

In Japan, intraoperative treatment with thermal neutrons of a wide variety of brain tumours progressed empirically, lead by the late Hiroshi Hatanaka who began clinical BNCT in 1968 at the HTR (Hitachi training reactor). Their results comprise the largest series of patients treated with BNCT in the world. Their early results were reported as encouraging [9.13–9.15]. One hundred and forty-nine patients were entered into this treatment program [9.13].

The main goal of the clinical trials in Japan was to prove the efficacy of BNCT as an adjuvant to surgery. Their approach is based on the ability of BSH to cross into the disrupted

blood brain barrier surrounding the resected tumour, an area with the highest risk of tumour recurrence. Patients with malignant gliomas were treated using the boron delivery agent, sulfhydryl borane $Na_2B_{12}H_{11}SH$ (BSH) and thermal neutron irradiation. Four reactors (JRR-3; Reactor of Japan Atomic Energy Research Institute, MuITR; Reactor of Musashi Institute of Technology, KUR; Research Reactor Institute of Kyoto University, JRR-2; Reactor of Japan Atomic Energy Research Institute) were authorized for medical use.

These clinical results have been subjected to repeated subset analysis as the initial reports included a variety of brain tumours with differing prognoses. Laramore et al [9.16] identified 14 patients who had been referred from the USA. Of these, data were available on 12 patients. Their median survival of 10.5 months was the same as matched controls and the normal therapy outcome expected from conventional treatment. Nakagawa analysed all of the initial patient results and obtained a 12% two-year survival for the grade IV GBM patients [9.17].

The Kyoto University Reactor experience of a subsequent (1990–1996) cohort of 44 patients of whom 31 had GBM similarly resulted in a median survival time of 11 months for the GBM group [9.18].

No randomized controlled studies have yet been performed.

9.4.3. Epithermal neutrons — after resection

In the 1980's, improvements in neutron beams and boron compounds allowed reconsideration of BNCT. Studies recommenced in 1994 in the US. The treatments are given with a closed skull using epithermal beams. These beams are able to penetrate the superficial tissues of the scalp and skull to reach the tumour. The theoretical advantage of epithermal beams is that they can treat the GBM cells found at a distance from the main tumour mass as well as deep seated tumours. Both BPA and BSH are being used in these trials.

The primary objective of the protocols was to evaluate the safety of BPA-F mediated BNCT in patients with GBM. As a secondary objective, the palliation of GBM by BPA-F mediated BNCT would be assessed. Between September 1994 and June 1999, 54 patients were treated with BPA-F based BNCT at the BMRR. These patients were treated on a variety of drug dose escalation protocols that test the tolerance of the CNS to this therapy. Of 28 patients treated under protocol 4 (the most recent data available) at Brookhaven National laboratory 11 received single field therapy with a median survival of 14 months while the 17 patients with larger tumour volumes (37 cc against 18 cc) treated with two fields had a median survival of 10.5 months [9.19].

MIT also started a protocol at this time, first treating cutaneous melanomas then adding GBM. This study was also testing the tolerance of the CNS to BPA-F mediated BNCT. No results are available to date.

In Europe, at Petten, a Phase I trial testing the tolerance of the CNS to BSH mediated BNCT was also started and 10 patients have been treated. In June 1999 the first patient in the Finnish trial was treated.

9.4.4. Clinical trials

Table 9.1. Summaries of BNCT clinical trials that are currently being conducted in the world

Country	Number of Patients	Clinical Phase	Drug	Histology	Craniotomy	Date
Japan	207	II	BSH/BPA	Astrocytomas	Yes	-/68-
	23	II	BPA	Melanoma	Yes	-/68-
US-BNL	54	I/II	BPA-F	GBM	No	8/94-
US-MIT/Harvard	26	I	BPA-F	GBM/melanoma	No	8/94-
Petten	10	I	BSH	GBM	No	10/97-
Finland	1	I	BPA	GBM	No	6/99-

9.5. Conclusion

In the 50 years since the proposal of BNCT, the basic treatment has remained resection plus 60Gy in daily fractions. A number of modifications of this regimen by increased dose, increased fractions, radiation sensitisation and chemotherapy have been tried and have failed to significantly improve the dismal prognosis.

BNCT studies are applicable to only a small group of cancer patients. From a population of 1 million, i.e. 4000 cancer patients, only 24 cases of high grade astrocytomas are likely to occur. Of these 24, a number will prove unsuitable for BNCT intervention as their level of consciousness or performance status will be incompatible with maintaining the treatment position for the duration required. Other patients would have good prognostic factors such as the absence of necrosis, making them ineligible for an ethical clinical Phase I/II study. Thus it can be expected that under 20 patients per million population per year would even be eligible for such studies. In countries where other clinical research on GBM is ongoing, patient accrual will be further impaired.

Results to date for the 320 patients treated in BNCT studies, similar to other promising interventions, have not demonstrated any significant benefit for these patients.

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10. ADDENDUM ON PHARMACOLOGICAL ASPECTS OF BNCT

10.1. Optimizing delivery of boron-containing agents to brain tumours

Considerable effort has been directed towards the design and synthesis of low and high molecular weight boron delivery agents to target brain tumours. Until recently, however, little effort has been directed towards developing strategies to maximize their uptake by tumours and concomitantly to minimize normal brain and blood levels. The intravenous route is currently being used clinically to deliver both BSH and BPA. Although this is convenient, it may not be ideally suited for delivering high and low molecular weight agents to brain tumours. Strategies for enhancing the delivery of drugs to brain tumours can be classified broadly as invasive, pharmacologic, or physiologic [10.1, 10.2]. Invasive techniques include direct intratumoural injection [10.3], the implantation of sustained release polymers [10.4], convection enhanced delivery [10.5], and hyperosmotic (1.373 m Osmol) mannitol-induced disruption of the BBB (6,7). Pharmacologic approaches include the use of small, lipid soluble molecules and liposomes with diameters <50 nm (which will traverse the BBB), and the bradykinin agonist, RMP-7, a synthetic nonapeptide that has been reported to selectively open the BBB within brain tumours [10.8]. Physiologic strategies include the use of pseudo-nutrients such as insulin like growth factor -1 (IGF-1), cationic antibodies, and chimeric peptides [10.9].

The BBB normally prevents the passage of ionized, water soluble drugs that have molecular weights >180 Da. Even if the main bulk of the brain tumour has a permeable vascular endothelium, the brain around tumour, which contains invasive tumour cells, has decreased permeability to anti-tumour agents. Endothelial cell clefts in microvessels of the tumour may vary widely from normal to abnormal within different regions of the same tumour, indicating the complexity of the tumour vasculature. Neuwelt et al. [10.6, 10.7] have strongly advocated the use of hyperosmotic mannitol-induced blood brain barrier disruption (BBB-D) to enhance the delivery of cytoreductive chemotherapeutic agents in patients with brain tumours. Their most recent data suggest that this approach can significantly enhance the survival of patients with primary central nervous system lymphomas [10.10]. However, on the negative side, BBB-D combined with the intra-arterial administration of cytoreductive chemotherapeutic agents has been associated with increased toxicity [10.11]. The possibility to time the neutron irradiation in this binary form of therapy to allow clearance of the drug from normal tissue (assuming the drug is retained in tumour) may make the capture reaction the ideal “activator” to avoid this toxicity. Pharmacodynamic studies have shown that agents with rapid blood clearance, moderate lipophilicity, and low neurotoxicity are more effectively delivered by the intra-arterial route [10.12]. This has important clinical implications for both BPA and BSH, which currently are being used in clinical trials of BNCT for patients with glioblastomas.

Enhancing the delivery of either BPA or BSH can have a dramatic effect both on increasing brain tumour boron uptake and therapeutic efficacy. Since BNCT is a binary system, normal brain boron levels only are of significance at the time of irradiation, and high values at earlier time points would be inconsequential.

Barth et al carried out BNCT studies at the Brookhaven National Laboratory to compare the therapeutic efficacy of i.v. versus i.c. administration of BPA or BSH with or without BBB-D using the F98 rat glioma model [10.13]. These results convincingly demonstrated that a significant therapeutic gain could be obtained by optimizing boron compound delivery; this

has important implications for both the ongoing clinical trials with BPA and BSH, as well as those that may initiated in the future. In the future, optimization of boron compound delivery will be an integral part of the pre-clinical and clinical evaluations of new capture agents for BNCT.

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APPENDIX

STATUS AS OF JAN. 2000 OF RESEARCH REACTOR FACILITIES FOR NEUTRON CAPTURE THERAPY

Facilities currently performing clinical trials

Finland

FiR — Extensive materials analysis and development. Clinical trials began in 1999.

Japan

JRR4 — JAERI — New modified irradiation facility, capable of changing from thermal to epithermal beam.

KUR — Kyoto University — New modified irradiation facility, capable of changing from thermal to epithermal beam.

Netherlands (EU)

HFR — Petten. Treatment began in October 1997.

United States of America

BMRR — Brookhaven National Laboratory. Installation of a fission converter completed.

MITR — MIT — Installing a new facility with a fission converter.

Facilities under construction or being modified for NCT

Argentina

RA-6 — Beam ready for patients probably in 2000.

Czech Republic

LVR1 — Testing beam configurations, trying to increase flux.

Italy

TAPIRO — Fast reactor — NCT research, small animals and compounds.

United States of America

WSU — Washington State University — Mainly for large animal (dogs) and boron compound research.

University of California Davis (formerly McClellan reactor)

Modified shield to enable NCT.

New facilities under construction which include NCT capabilities

Morocco

Thailand

Facilities performing feasibility analysis for NCT

Indonesia

Checking the suitability of their research reactors.

Kazakhstan

WWR-K — Studies only.

Republic of Korea

HANARO

New, purpose built reactor.

Sweden

R2-0 — Beam filter designed.

Ukraine

Development of filters.

NOTE: Many other facilities are thinking about NCT or awaiting evidence of effectiveness.

Annexes
1–9

Annex 1
NEUTRON BEAM PARAMETERS

General considerations for neutron capture therapy at a reactor facility

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Abstract. In addition to neutron beam intensity and quality, there are also a number of other significant criteria related to a nuclear reactor that contribute to a successful neutron capture therapy (NCT) facility. These criteria are classified into four main categories: Nuclear design factors, facility management and operations factors, facility resources, and non-technical factors. Important factors to consider are given for each of these categories. In addition to an adequate neutron beam intensity and quality, key requirements for a successful neutron capture therapy facility include necessary finances to construct or convert a facility for NCT, a capable medical staff to perform the NCT, and the administrative support for the facility. The absence of any one of these four factors seriously jeopardizes the overall probability of success of the facility. Thus nuclear reactor facility management considering becoming involved in neutron capture therapy, should it be proven clinically successful, should take all these factors into consideration.

1. INTRODUCTION

Neutron capture therapy (NCT), and especially boron neutron capture therapy (BNCT), has had a varied history over the past half century. Early trials in the 1950s and 1960s were largely unsuccessful [1]. By contrast the treatments in Japan since the late 1960s have been relatively successful [2], although not widely accepted among the scientific community and certainly not among the medical community. Other than the Japanese work there was a general moratorium on NCT research from the early 1960s to the mid-1980s. Currently clinical trials are underway in four sites in the United States, Netherlands, and Finland.

If these clinical trials prove successful and the procedure receives formal approval, the question arises as to where NCT treatment would be available and at what type of facility. Currently and perhaps ultimately the answer to the second question is a nuclear reactor. Where such a reactor should be located is strongly dependent on accessibility of patients requiring NCT treatment. Ideally there would be a number of reactors adapted for NCT treatment at locations scattered throughout the populated regions of the world.

The concept of such a large number of reactors adapted for NCT treatment begs three more questions: (1) How can an existing research reactor be converted into a reactor with NCT capability? (2) Or what design features would be optimal if a new reactor facility were being built specifically for NCT? (3) What other considerations are necessary for a successful NCT facility? Discussed below are some of the nuclear design, operating, medical, and non-technical factors that must be considered in order to answer these three questions.

A preliminary question is why get involved with NCT at all? The answer to this question likely falls into one or both of two categories, humanitarian and financial. It is a charitable thing to be involved in extending people’s life span and improving their quality of life by an activity such as NCT treatment. The second reason may be more self-serving. Many

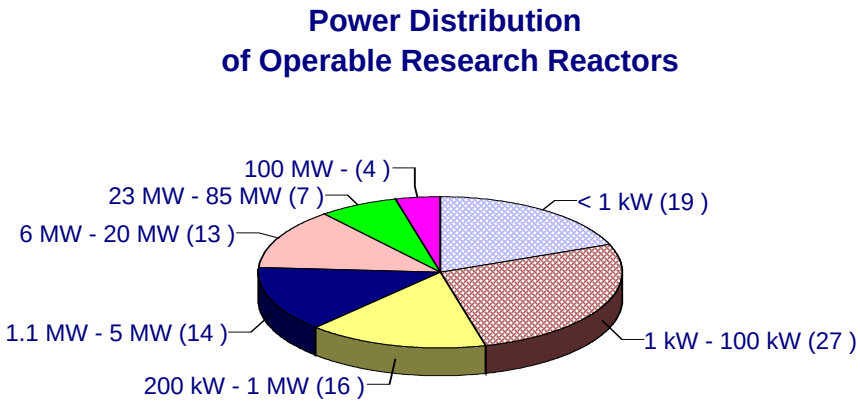

Fig. 1. Power distribution of operable research reactors.

research reactors have very limited budgets and are interested in becoming involved in revenue-producing activities. Some research reactors are in jeopardy of being shut down, often because of operations costs or level of use, and are looking for a "saviour" project to perpetuate their existence. As will be seen, this reason alone is insufficient for becoming involved in NCT.

2. NUCLEAR DESIGN FACTORS FOR NCT

Although NCT has been proposed using ^{252}Cf sources, accelerators, and nuclear reactors, nuclear reactors have by far the majority of NCT experience and proven research results. Basically ^{252}Cf sources, even with converter plates, do not produce an intense enough beam in a reasonable treatment time. Very large and expensive accelerators are required to produce a high, reliable neutron beam strength. Only nuclear reactors will be discussed further in this paper.

A logical question then is what type of nuclear reactor is the best for NCT? The answer to this question lies primarily in determining what types of reactors can produce an adequate strength and quality of radiation beam for NCT. Whether converting an existing reactor or designing a new reactor for NCT, there are some specific principles to consider. The two primary radiation-related requirements for NCT are a sufficiently high intensity epithermal neutron source and an excellent beam quality. In particular, an optimal NCT beam has an adequate epithermal neutron flux with relatively low contributions from fast neutrons, gamma rays, and other in-patient doses.

General consensus [3] is that an epithermal neutron fluence of about $1x10^{13}$ n*cm^{-2} is required for successful NCT. For an epithermal neutron flux of $1x10^{10}$ n*cm^{-2}*s^{-1}, a very reasonable treatment time of only about 17 minutes is necessary. An epithermal neutron flux of $1x10^{9}$ n*cm^{-2}*s^{-1} requires a treatment time of about 3 hours. To some extent these parameters rely on reactor power. Reactors with power levels as low as 100 kW have produced beams which meet some or all of the above parameters. About half of the research reactors in the world have power levels greater than a few hundred kW (see Figure 1), although power level alone is not a sufficient condition for a successful NCT beam.

There are several undesirable components of the NCT beam due to fast neutrons, thermal neutrons, gamma rays from the reactor core, capture gamma rays produced along the beam, and three in-patient radiation sources: gamma rays from neutron capture in hydrogen, protons from the (n,p) reaction in nitrogen, and proton recoil by neutron scattering from hydrogen. It is generally considered to be desirable to have a fast neutron dose to epithermal fluence ratio of less than about $1x10^{-10}$ Gy*cm^2 [4] and a gamma ray dose to epithermal fluence ratio of less than about $2x10^{-11}$ Gy*cm^2 [5].

Another important factor is the neutron current-to-flux ratio, which affects the penetrability of the neutrons into the patient. A high ratio is indicative of a more forwardly directed beam, with a ratio of 1.0 being monodirectional and 0.5 being isotropic.

Converter plates have been designed and tested and have shown that they can improve the intensity of the beam. This is not without its cost since converter plates must be shielded, sufficiently subcritical, and often generate enough heat that they must be cooled. They also take up space that may not be available in reactor conversion.

Although the focus of NCT beams is primarily on epithermal neutrons, it should be noted that highly thermal neutron beams are desirable for NCT research with cells or small animals (few cm in size) or for surface or near-surface tumours.

Two other important properties of an NCT beam, the core-to-patient distance and the cross-sectional area that the beam intersects the core, are somewhat related. Both a small beam diameter and a long core-to-patient distance decrease the epithermal neutron flux at the patient and increase the neutron current-to-flux ratio. A compact reactor design is optimal to produce a sufficient NCT beam. A better NCT beam may also be able to be attained by a change in the reactor moderator or reflector, particularly if this decreases the core-to-patient distance, but these factors also affect core criticality and so may have an offsetting effect.

What type of irradiation facility has these features? Small diameter beam tubes are not adequate. Calculations [6] at Oregon State University have shown that both a radial and a tangential beam port (20 cm stepped down to 15 cm, 3 m long) at a 1 MW reactor produce a beam that is about an order of magnitude too low for a reasonable NCT beam. This is primarily because the neutron flux decreases about four orders of magnitude over the 3 m distance.

Thus primarily thermal columns have been modified to achieve optimal beam characteristics. An existing thermal column is easiest to modify, as was done at FiR-1 [7]. It is possible, although expensive, to cut a large hole in the concrete shield to add an NCT facility as was done at the McClellan TRIGA reactor in California.

In NCT design there is also a need to consider other general reactor design features, such as negative temperature coefficient, cooling, shielding/beam stop, and overall reactor safety, as is the case for any reactor.

Without extensive analysis the effect of the particular type of fuel, moderator, and reflector combination on the NCT beam is difficult to assess. In general, though, the harder the reactor spectrum, the easier it should be to produce the required epithermal beam at the patient location.

There are a number of different types of research reactors that might be considered for NCT, although the author’s experience is mainly with TRIGA reactors. [8,9]. TRIGA reactors

of several hundred kW or more are generally well suited for NCT. Several TRIGA reactors are currently being (McClellan, Washington State University) or have been previously been (FiR-1) modified for NCT. Several other reactor designs have been proposed, including such diverse features as a dual epithermal and thermal beam [10,11], an eccentric core [12], and a square slab design [13].

3. FACILITY MANAGEMENT AND OPERATIONS FACTORS FOR NCT

There are also important operating characteristics that must be considered for an NCT facility. An obvious one is operating hours and scheduling. Availability for NCT may be considerably different than for research. Furthermore, unless it is a dedicated NCT facility, the reactor will need to be available for other research uses beside NCT, such as education, isotope production, and instrumental neutron activation analysis. In this case the NCT facility design cannot displace facilities for other applications. Also worthy of consideration is continuous versus intermittent use. In this regard, can the reactor facility be kept at power while personnel are in the patient treatment room?

A key issue regarding an NCT facility is the definition of responsibility and authority. In the event of an unusual situation, who has the authority to abort the treatment procedure? The best arrangement would be for *both* the principal reactor administrator *and* the physician in charge to each individually have this authority.

Staffing considerations are important, because in addition to the regular reactor staff, there must be a large contingent of medical staff, medical physicists, and other personnel for the NCT set-up and treatment.

Technical co-operation between reactor and medical staff, between technical and non-technical staff, among different technical disciplines, and among international investigators and treatment centers is important for the overall success of NCT.

It is imperative that procedures for normal and abnormal operation conditions, radiological protection, reactor safety, and their associated training be in place. The procedures should be clear and complete step-by-step instructions.

An NCT facility should be located such that patient and medical staff accessibility is not an issue. Often that means a location near a major hospital or medical center with an airport in the vicinity.

4. FACILITY RESOURCES FOR NCT

There are facility-related factors to consider for an NCT facility at a reactor. Several of these relate to the physical space required for the NCT facility. Chief among these is a radiotherapy infrastructure, which includes a patient treatment facility with proper accessibility to the beam, accurate patient positioning, calibration and on-line beam monitoring, and patient comfort features. Other considerations are a patient preparation facility, ideally a patient simulation room identical to the patient treatment room, medical laboratories, and patient safety and shielding.

Personnel-related features of the NCT facility include an adequate and qualified medical staff, personnel dose minimization, patient treatment planning, sanitation, emergency response evacuation of patients and medical staff, and communications between reactor operations and medical staff.

An on-line boron (for BNCT) assay system is critical to the operation of an NCT facility, since boron levels in the blood limit the dose that can be given to the patient.

5. NON-TECHNICAL FACTORS FOR NCT

There are also non-technical factors to consider, not the least of which is cost (renovation or new construction and also operating costs). Conversion costs for an NCT facility could vary from a few hundred thousand to several million US$. A new reactor specifically designed for NCT could cost from a few million to tens of millions of US$.

The facility must be well maintained and reliably operated. Medical liability issues are a major factor with which most research reactors don't normally have to deal. Public acceptance issues must be considered, as for any nuclear facility being built or undergoing major renovation. An NCT facility will generally require licensing by the appropriate reactor regulatory agency and by the appropriate health regulatory agency. There are also ethical issues associated with NCT, namely in the treatment of human subjects and in the use of laboratory animals for NCT research.

An NCT facility incurs liability factors that are not present for most reactors which are not involved in medical treatment. These factors must be carefully addressed before beginning NCT treatment.

Another strongly required consideration for an NCT facility is the approval and support of the administration under which the reactor facility functions. Consideration for starting a new NCT facility without this support is strongly discouraged.

6. CONCLUSIONS

To date NCT therapy has been conducted only in Japan. Clinical trials are currently underway at Brookhaven National Laboratory and Massachusetts Institute of Technology in the United States, at Petten in the Netherlands, and at the Technical Research Centre of Finland. The success of these trials will strongly determine the future of NCT and the need for other NCT treatment facilities.

An NCT facility could be built as part of a comprehensive nuclear medicine center that provides, in addition to NCT, nuclear medicine diagnostic and therapeutic services and palliation treatment, all on an outpatient basis.

Reactor designs have been shown to be adequate to produce the NCT beam characteristics considered essential. There are existing reactors throughout the world that potentially could be converted for NCT. Other factors mentioned in this paper should be considered as factors to be seriously addressed, but not as insurmountable obstacles. The bottom line, if NCT clinical trials prove to be successful, is that for a price reactors can be made available for NCT treatment.

There are four keys to the success of an NCT treatment facility, assuming clinical feasibility is demonstrated. These factors are an adequate neutron beam intensity and quality, necessary finances to construct or convert a facility for NCT, a capable medical staff to perform the NCT, and the administrative support for the facility. The absence of any one of these factors seriously jeopardises the overall success of the facility.

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Annex 2
REACTOR AND BEAM DESIGN CONSIDERATIONS

BNCT facility at the RA-6 reactor

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Abstract. The RA-6 is an open pool MTR type reactor with 500 Kw nominal power, using fuel elements enriched to 90 %. It was designed and constructed fully in Argentina and is owned and operated by the C.N.E.A. at the Bariloche Atomic Center. In this work the analysis of the different alternatives, depending on the main features of a research reactor (type, power, shielding, etc.) , are showed to design a BNCT facility. After that, the different steps followed to produce the epithermal beam at the RA-6 are presented:

- Because only small modifications were required, the first stage was the arrangement of a thermal beam to test and validate our calculation methods and to gain expertise in the different experimental techniques to design and characterise the epithermal facility.
- A basic design of the epithermal device was performed, analysing different and relative sizes of the materials conforming the neutron filter to optimise the neutron spectrum and the absolute value of the epithermal flux at the beam port. This design was used also to make preliminary studies regarding the nuclear safety and solve potential licensing problems.
- A complete design of the internal filter was presented to the Regulatory Authority and after some feedback the filter was constructed and mounted. During this stage a very simple (without any geometry complexity) external port was used to test the free beam facility and to get a complete on phantom dosimetry .
- Using the previous results the new beam port was designed, built and mounted by November 1998, the final characterisation of the facility is being currently performed.

Preliminary results of this job for the free beam are:
$\phi_{epithermal}$ = 1.1 E9 n / cm^2 seg (0.5 eV < E < 10 KeV)
D_{fast} / n_{epi} = 7.5 cGy cm^2 / n_{epi}
$D\gamma$ / n_{epi} = 3.0 cGy cm^2 / n_{epi}5.
The next goal will be to optimise the irradiation room to adequate the facility to irradiate patients.

Introduction

The RA-6 reactor located at Bariloche Atomic Center, is a pool type one with 500 kW of nominal power and U 90 % enriched fuel owned and operated by C.N.E.A.. It is mainly devoted to research, development and teaching activities. It has five neutron irradiation beam channels and a thermal column (removed).

Due to its small power and a suitable operation schedule (usually one single experience each time) the alternative selected for getting an epithermal irradiation facility was to approach, as close as possible, to the reactor core by removing the external thermal column; instead of using one of the irradiation tubes. In order to fulfil this criteria no shutter system was considered in the design. The reactor shutdown is used as the shutter.

Because only small modifications were required, the first stage was the arrangement of a thermal beam to test and validate our calculation methods and to gain expertise in the different experimental techniques to design and characterise the epithermal facility.

The epithermal beam facility was then designed [1] and built replacing the old thermal column (internal and external). Figure 1 shows a plant view of the complete facility including the material composition of the neutron filter, the port and the external shield.

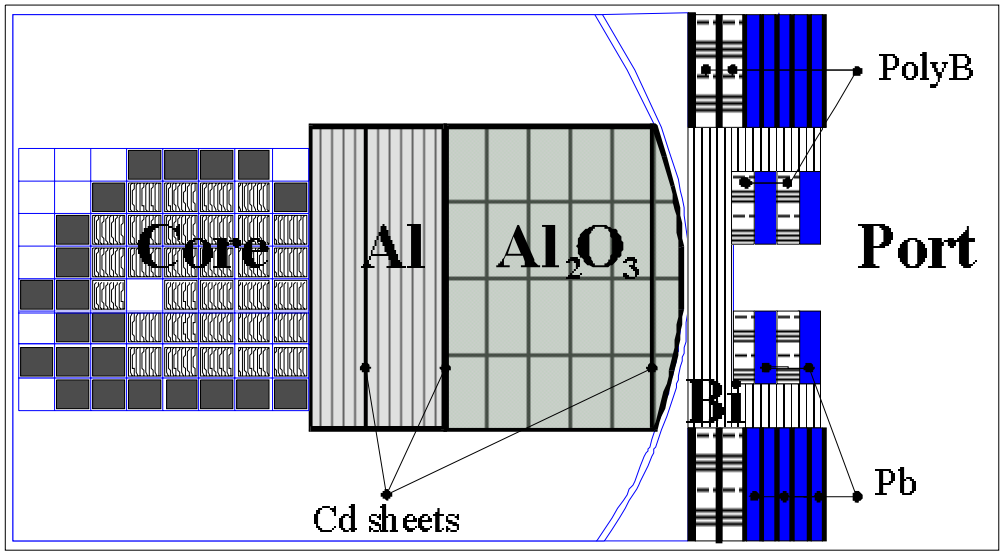

FIG. 1. Plant view of the epithermal facility.y

1. FREE BEAM MEASUREMENTS AND SPECTRUM ADJUSTMENT

1.1. Monte Carlo simulation

The main features of the calculation process were:

- Coupled neutron-gamma calculation with MCNP4B [2] and cross sections based on ENDFB6 data library.
- Point detector tallies at the beam centre and at several positions near the external shielding (for neutrons and photons).
- A detailed neutron and photon source in the core was obtained through a KCODE calculation.
- Neutron spectrum in 29 energy groups was calculated at the beam centre (2 thermal / 15 epithermal / 12 fast).
- Photon doses were calculated by using the ICRP-21 flux-to-dose rate conversion factors. The calculated photon doses rate at the beam centre agree within 20 % with the measured ones.

1.2. Neutron and gamma characterization

Multiple activation detectors (Diluted, 0.1 mm, bare and Cd covered foils of Mn, Au, Cu, In and pure, 0.127 mm, Cd covered foils of Sc, Ag, In), with different energy response, were irradiated at the beam center, and the induced activities were measured by gamma spectroscopy for neutron energy characterisation. The gamma dose rate was measured at the beam centre, with TLD's 700 and paired ionisation chambers.

1.3. Spectrum adjustment

Figure 2 shows the calculated and adjusted neutron flux at the beam centre. Measured activities and calculated spectrum were adjusted with the NMF-90 package [3]. Some of the results and remarks were:

- The IRDF-90/NMG-G was upgraded, including self-shielded data for pure epithermal reactions.
- Group input uncertainties were evaluated conservatively, regarding their statistical errors, and the group to group correlation were assumed exponential on a lethargy exponential scale. Reaction rate uncertainties were lower than 10 % and actual correlation were considered and evaluated.

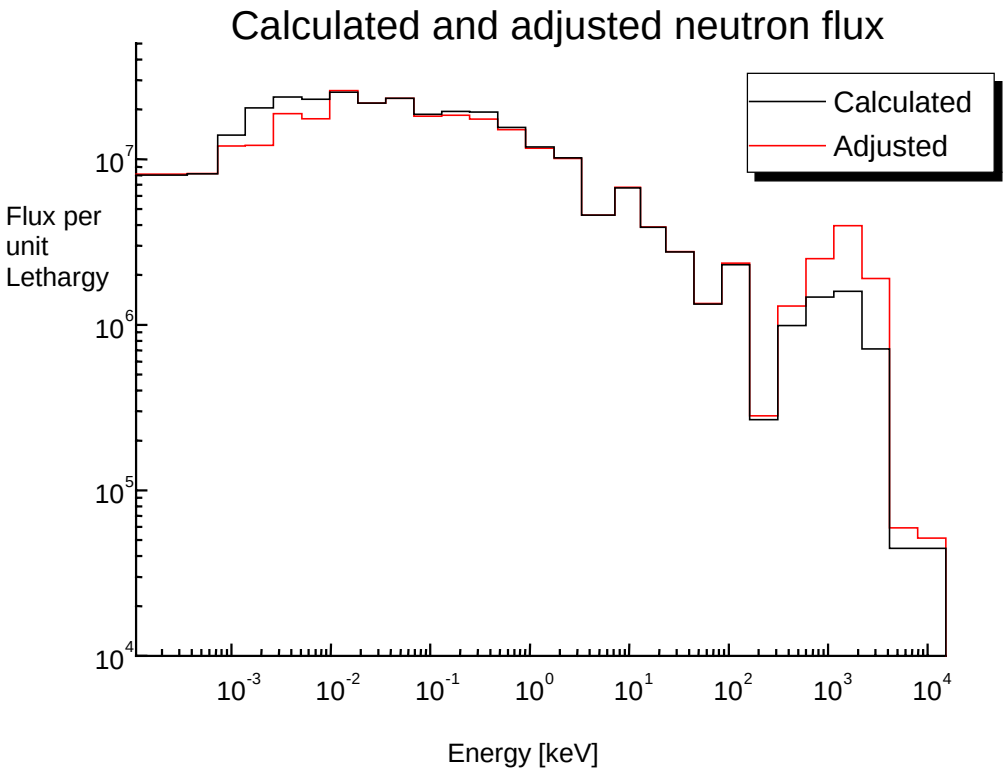

FIG. 2 Calculated and adjusted neutron flux.

A reasonable value (1.3) for χ^2 /N resulted from the adjustment.
— Large (~ 2) adjustment factors resulted in few groups of the fast energy region.
— Sensitivity analysis was performed but integrated flux values remained between their estimated errors.

1.4. Free Beam Parameters

The free beam parameters evaluated from the adjusted spectrum and group calculated KERMA factors are showed in the Table I:

Table I. Free Beam Parameters

Epithermal flux (0.5 ev — 10	(0.32 ± 9 %) 10^{9} n/ cm^{2} seg
Fast neutron dose (> 10 kev)/ n_{epi}	(11.3 ± 16 %) 10^{-13} Gy/ n cm^{2}
photon dose / n_{epi}	(7.5 ± 13 %) 10^{-13} Gy/ n cm^{2}
thermal flux (< 0.5 ev) / n_{epi}	0.07 ± 22 %

2. IN PHANTOM MEASUREMENTS

To make these measurements we used a 17.3 cm diameter and 20.5 cm long cylindrical water phantom. The gamma dose and the fast neutron dose rates inside the phantom were evaluated using the paired ionisation chambers method [4]. The thermal neutron flux was measured using bare and Cd covered gold foils. The N^{14} and B^{10} dose rates were calculated through the measured thermal neutron flux (0–0.45 eV) and the corresponding KERMA factor. Boron concentrations of 30 ppm in tumour and 8.6 ppm (1–3.5 tumour to healthy tissue ratio) in healthy tissue and Nitrogen concentration of 1.8% (in brain) were used. Figure 3 shows the absorbed dose in the center axis of the phantom.

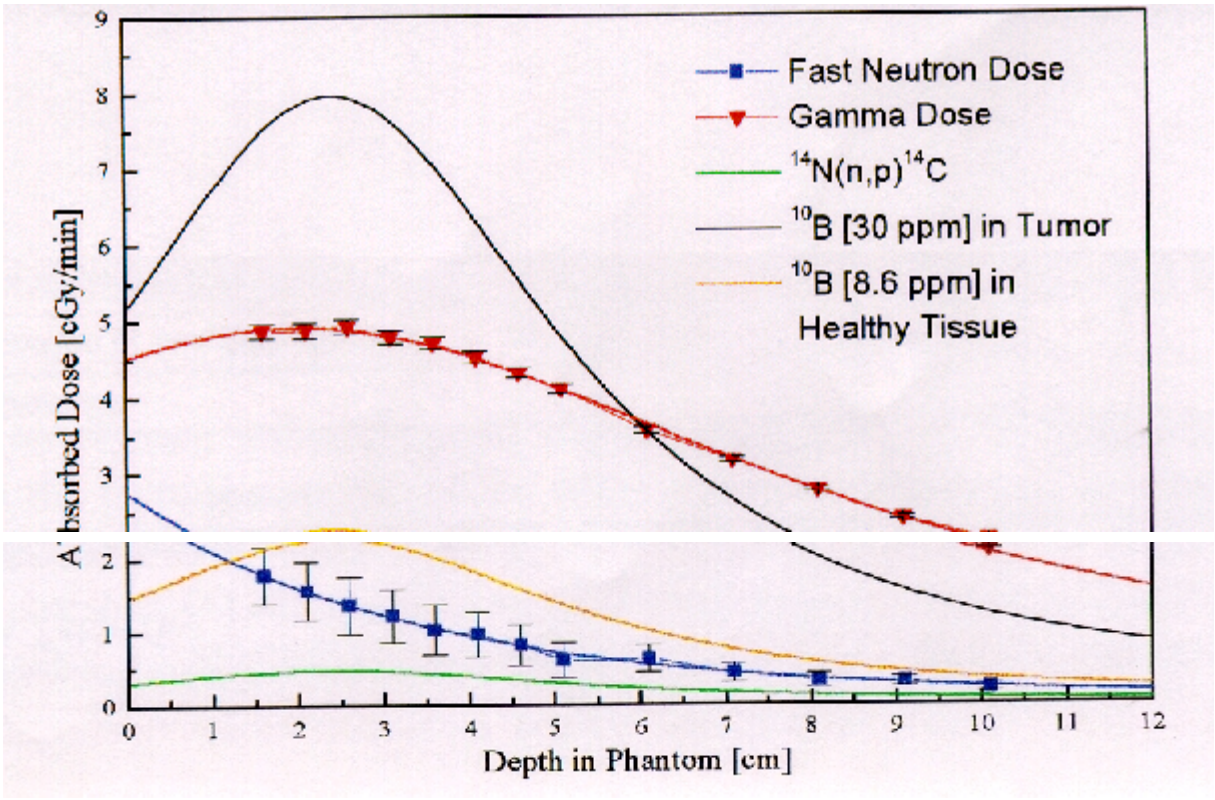

FIG 3. Absorbed dose in phantom.

The estimated uncertainties for gamma and fast neutron dose at 3 cm depth in phantom are showed in Table II:

Table II. Uncertainties For Photon And Fast Neutron Dose In Phantom

Source	Uncertainty in photon dose (%)	Uncertainty in fast neutron dose (%)
Electrometer	1	1.5
Calibration of Graphite chamber	1	3.5
Calibration of TE chamber	0.1	4.5
Relative sensitivity of Graphite	2.5	6
Relative sensitivity of TE chamber	0.1	5
Thermal response of Graphite	1.5	5
Thermal response of TE chamber	0.2	22
Positioning of chambers	1.3	2.6
Reactor power	1	1
Displacement correction factor	0.5	0.5
Thermal flux	0.5	4
Total uncertainty	**4**	**24**

The most relevant contribution to the fast neutron dose uncertainty is due to the uncertainty in the thermal response of the tissue equivalent chamber. The uncertainty in this parameter is assumed to be about 50%; around a mean value between reported values for the same kind of chamber, [4] and our own roughly estimated one: 9.0E-20 C/min/ncm^{2}s. For the Graphite chamber a reported value [4] for an identical chamber was used: 1.45E-20 C/min/n/cm^{2}s.

Considering as RBE factors for gamma dose, fast neutron dose, N^{14} dose and B^{10} dose 1, 3.2,3.2 and 3.8 [5] respectively, and 1.3 for B^{10} in healthy tissue; the beam quality factors are: AD = 6.8 cm; AR = 2.8 and ADDR = 16.25 cGy/min. Figure 4 shows the RBE dose in the center axis of the phantom.

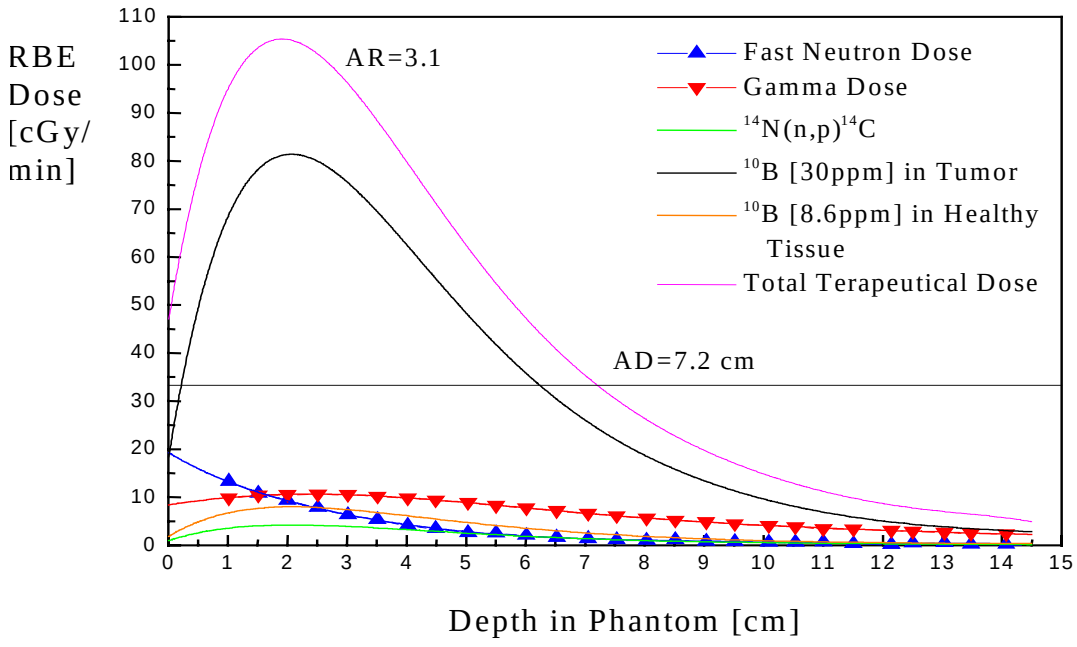

FIG 4. RBE dose in phantom.

3. BEAM OPTIMIZATION AND CHARACTERIZATION

During November 1998 the cylindrical port was replaced by a new one as showed in Figure 5; and characterised following a similar procedure than with the previous beam.

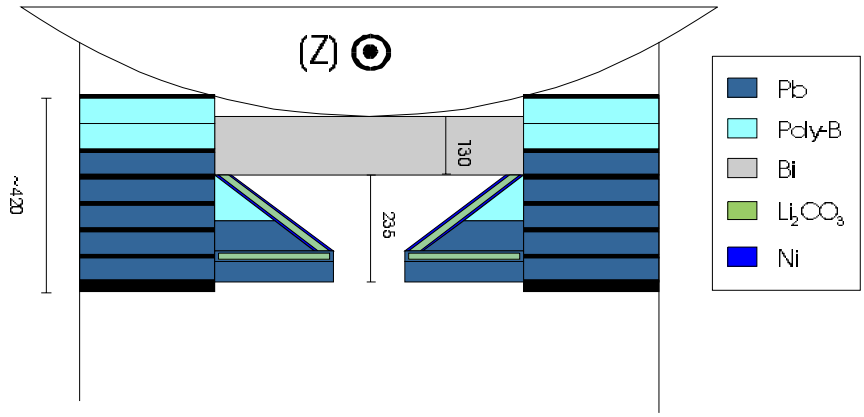

FIG 5. Conical port.

Free beam parameters preliminary evaluated with gold foils and paired ionisation chambers are given in Table III.

Related absorbed and RBE doses in phantom, measured as indicated in the previous section are showed in Figures 6 and 7.

Table III. Free Beam Parameters For The Conical Port

	Epithermal flux (0.5 ev — 10	$1.1 * 10^{9}$ n/ cm^2 seg
	Fast neutron dose (> 10 kev)/ n_{epi}	$7.5 * 10^{-13}$ Gy/ n cm^2
	photon dose / n_{epi}	$3.0 * 10^{-13}$ Gy/ n cm^2
	thermal flux (< 0.5 ev) / n_{epi}	0.03

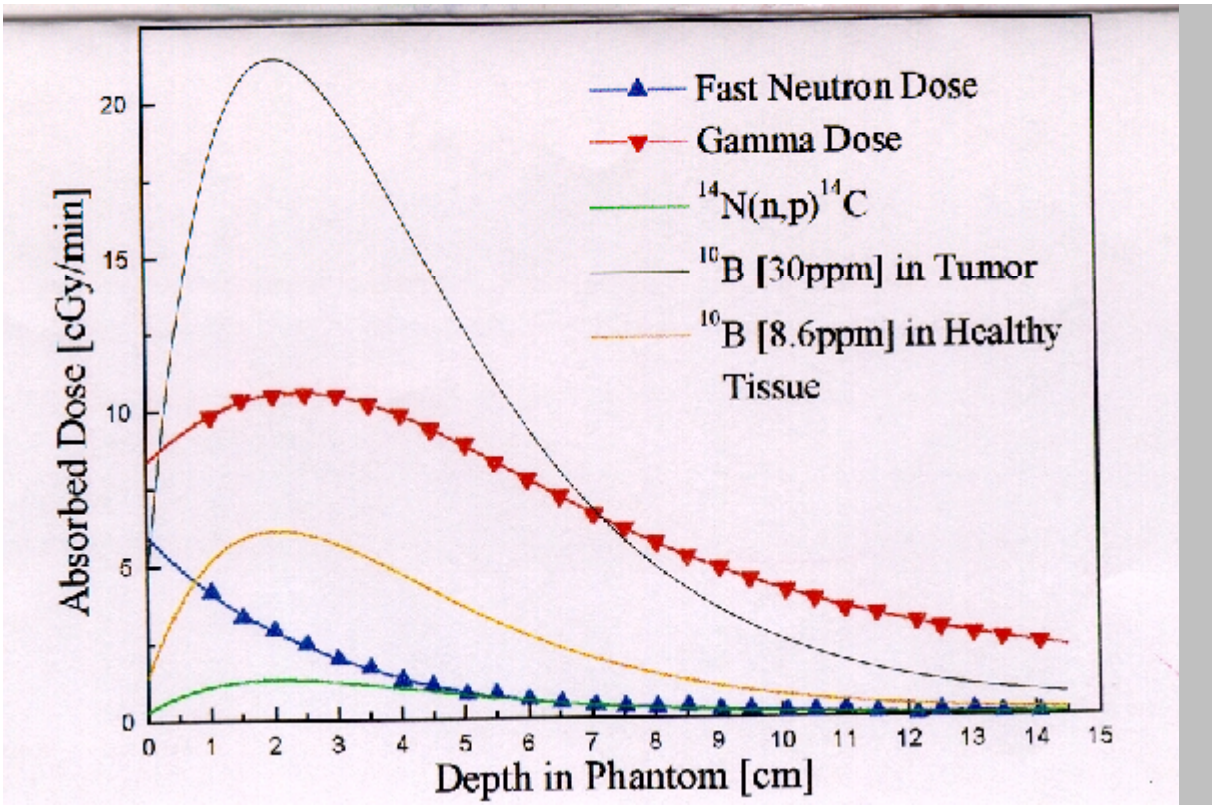

FIG 6. Absorbed dose in phantom for the conical port.

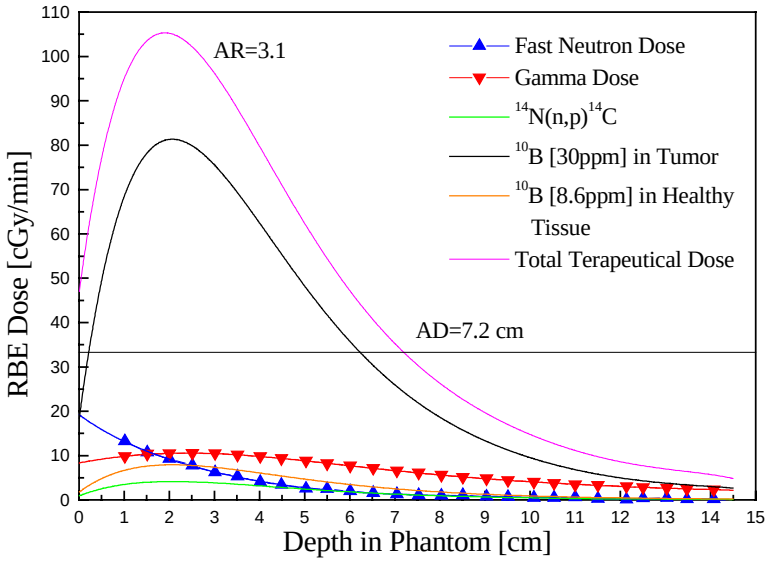

FIG. 7. RBE dose in phantom for the conical port.

The beam quality factors for the optimized beam are: AD=7.2 cm; AR=3.1 and ADDR = 33.3 cGy/min. With this new configuration, a significant increase in the ADDR has been reached, together with a small improvement in AD and AR.

Due to the associated increase in the thermal flux within the phantom, fast neutron dosimetry is, in this new configuration, strongly affected by the thermal response of the TE ionisation chamber. Figure 8 shows relative change in gamma and neutron dose rate due to

relative change in thermal response of the TE chamber (K_T) and the Graphite chamber (K_C); considered as independent parameters, for a thermal flux of 1.0E9 n/cm^{2}s.

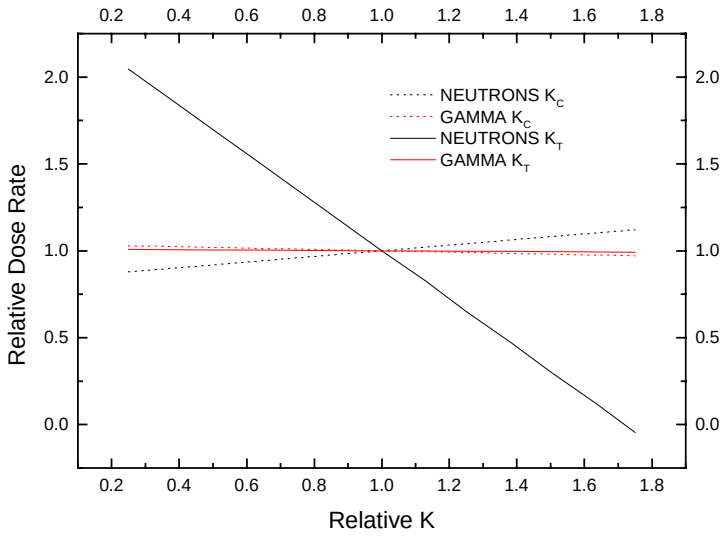

FIG. 8. Relative dose rate vs. relative change in the thermal neutron sensitivity for both chambers at a thermal flux of 1.0 E9 n/cm^{2}s, using as reference values of K_{TE}=9E-20 C/min/n/cm^{2}s and K_C=1.5E-20 C/min/n/cm^{2}s.

K_C has nearly negligible influence on both dose rates; but neutrons dose rate changes approximately 75% due to a 50% change in K_{TE}. This parameter should then be determined in a more precisely way.

In order to achieve the possibility of lateral irradiation, assuming a distance of 10 cm between the beam port and patient's head, the beam quality was also evaluated by in phantom measurement at 10 cm of the beam exit surface. Results are showed in Figure 9.

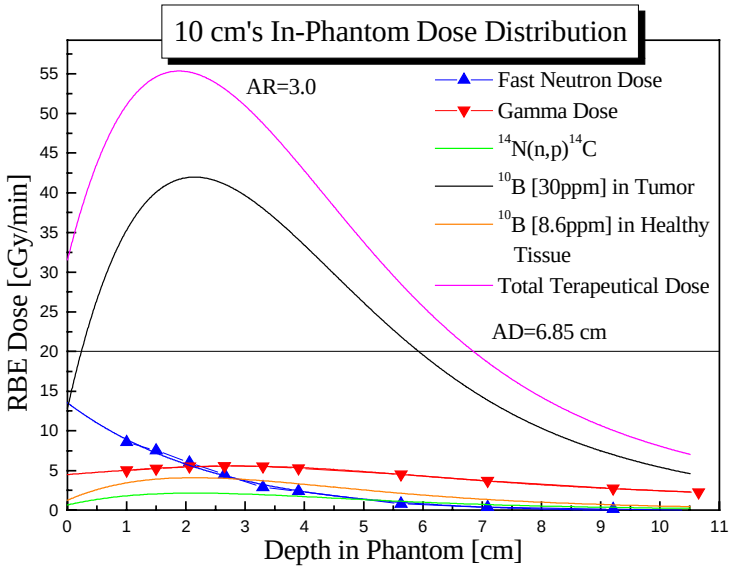

FIG. 9. In phantom RBE doses at 10 cm from beam exit surface.

The most relevant modification observed in the beam quality parameters, at 10 cm from the beam port surface is the reduction in the ADDR from 33.3 cGy/min to 20.5 cGy/min. Another alternative which is being studied is a non symmetric port as is showed in Figure 10.

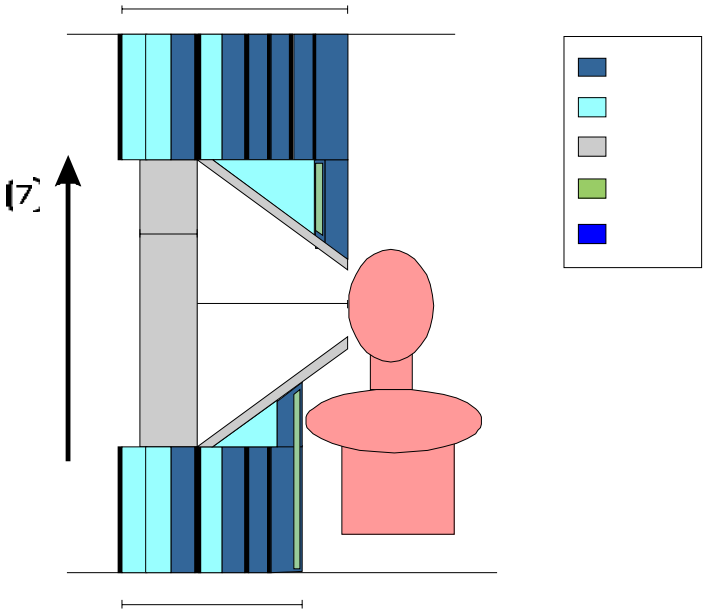

FIG. 10. Port's proposed design for lateral irradiation situation.

4. IRRADIATION ROOM

Irradiation room plant is showed in Figure 11.
An internal borated polyethylene shielding of 10 cm thickness was chosen, together with an external shielding of 50 cm thickness of concrete.

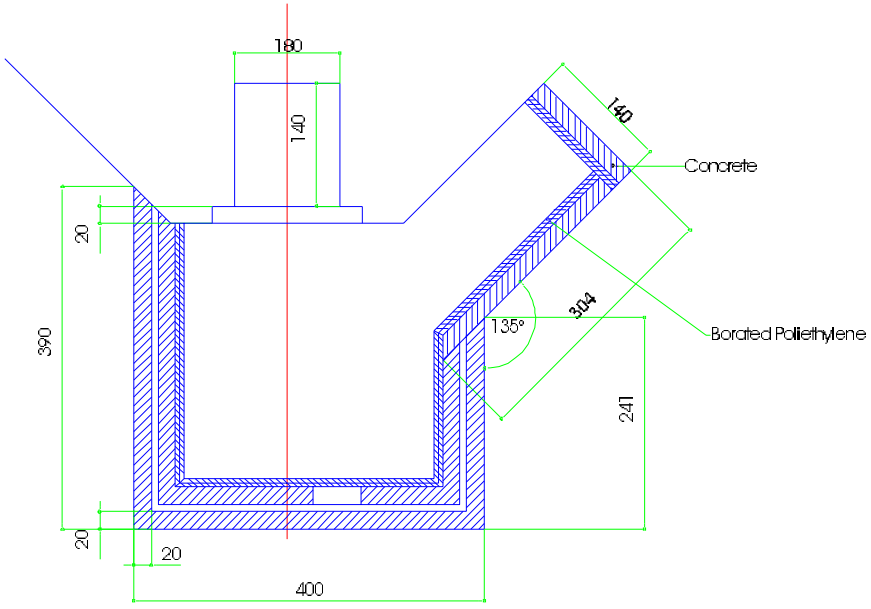

FIG. 11. Irradiation room.

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Feasibility study to develop BNCT facility at the Indonesian research reactor

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Abstract. Survey to the Indonesian research reactors and its supporting facilities have been done in order to check possibility to install BNCT facility. Oncologists from several hospitals have been informing about the BNCT treatment for tumours and they give a positive response to support utilisation of the BNCT facility. Several aspects required to support the BNCT treatment have also been identified and related activities on that matter soon will be initiated. The interim result in our survey indicated that utilisation of the 30 MW Multipurpose reactor would not be possible from technical point of view. Further study will be concentrated to the TRIGA reactor and an epithermal neutron beam facility at the thermal column of this reactor will be designed for further work.

INTRODUCTION

Three research reactors are available in Indonesia, operated by National Nuclear Energy Agency of the Republic of Indonesia (BATAN). Those three reactors are: TRIGA Bandung reactor 2 MW located at Bandung, TRIGA Kartini reactor 250 kW at Yogyakarta and Multipurpose Research Reactor 30 MW at Serpong. Using those three reactors, especially Triga Bandung and Multipurpose Research Reactor RSG-GAS, radioisotope for nuclear medicine has been produced and then distributed to the hospital. Up to know 19 hospitals in Indonesia have been facilitated with nuclear medicine unit.

Support of BATAN to develop and to enhance nuclear medicine in Indonesia have got a good respond by hospital, especially hospital at the near by research center operated research reactor. Some hospitals are also used as a teaching hospital of the university in those cities. Based on this condition a good relationship has been settled between BATAN, hospital and Faculty of Medicine of that University.

In the last two years, BATAN has considered that utilisation of the research reactor should be improved. One of the ideas is development of the BNCT facility at one of the research reactors. In the other hand oncologist reported that incidence for cancerous tumours and certain brain tumours in Indonesia is high enough. For example data from Sardjito Hospital in Yogyakarta stated 30 brain tumour patients in 1998 have been treated using combination of ***surgery***, and photon irradiation and the result were unsatisfied.

Feasibility study to develop BNCT at the Indonesian Research Reactor is being done. With support of the Japan Atomic Industrial Forum (JAIF) one Japanese expert on BNCT facility has been assigned to support feasibility study to develop BNCT at the RSG-GAS reactor or at the TRIGA Kartini reactor. With support of the Japan Atomic Energy Research Institute (JAERI) author has a chance to visit BNCT facility in Japan and also to gather latest information on the BNCT technology, especially on the preparation of the reactor and beam design to facilitate BNCT treatment facility.

In regard of the purpose, author as a person who is responsible for feasibility study of the BNCT in the Indonesian Research Reactor is willing to attend on the IAEA TCM on current issue related to Neutron Capture Therapy to gather latest information on this technology

1. RESEARCH REACTORS IN INDONESIA

Three research reactors are available in Indonesia, those reactors are: TRIGA type reactor Bandung, Kartini (TRIGA) reactor Yogyakarta, and Multipurpose Research Reactor (MTR-type) RSG-GAS located in Serpong Nuclear Research Center[1]. Further detail description and also its status are described below.

TRIGA reactor in Bandung

TRIGA reactor Bandung has been operated since 1964. On the early period of its operation the reactor has a nominal power of 250 kW. Last 1971, the reactor was then upgraded to 1000 kW with replacement of the reactor core and its fuel elements; instrumentation and other related process system equipment. The TRIGA Bandung reactor has utilized for radioisotope production purposes, neutron beam experiment and also training for reactor operator; as well as doing some reactor physics experimental activities. This reactor has 4 beam tubes, 3 radial and 1 tangential tube, thermal column and thermalizing column.

Since at the beginning of the reactor project being initiated, close cooperation between BATAN and University (Bandung Institute of Technology and Padjadjaran University) has been settled. Base on that situation, the reactor has been also used as a versatile tool by students as well as researcher from the university together with BATAN's staff. It can be stated also that Research and Development (R & D) on nuclear technology in Indonesia has been started using this reactor.

Several types of radioisotopes have been produced using this reactor. Radioisotope for medical purposes, such as: ^{131}I and ^{99}Mo/^{99m}Tc. Other radioisotope has been produced either for hydrology (^{82}Br) or R & D on agriculture; ^{32}P.

This reactor has a laboratory for NAA and equipped with a nuclear counting system as well as personnel to perform neutron flux measurement and neutron dosimetry. A big hospital with nuclear medicine facility is available around 5 km from the reactor site. This hospital is also used as a teaching hospital by faculty of medicine, Padjadjaran University.

Up to 1990, medical radioisotope as well as radioisotope for other purposes in Indonesia were fulfilled by this reactor. When the new reactor RSG-GAS, 30 MW and the radioisotope laboratory in Serpong become in operation, radioisotope required for medical as well as for industry and other purposes where then fulfill by this new reactor. Since then the TRIGA reactor in Bandung is mainly used to perform R & D on new radioisotope and also this reactor is used as a backup when the RSG-GAS reactor in the shut down period. Nowadays, reactor TRIGA in Bandung is being upgraded to be operated for 2 MW power level. The activities are being done and it expected will be finalized within next 2 year.

Kartini reactor in Yogyakarta

Kartini research reactor is a 100 kW TRIGA operated since 1979 in Yogyakarta. Modification on the instrumentation system has done last 1997 and the reactor system has

also modified to improve reactor operation at 250 kW power level. This reactor is equipped with in-core as well as in reflector irradiation facilities. The irradiation facilities are equipped also with rabbit system and also gamma spectrometry system as well as delayed neutron-counting system. So that this reactor can be used to perform NAA (Neutron Activation Analysis) and also U-Th analysis (using delay neutron counting technique) from the ore. This reactor has 4 beam tubes, these tubes is equipped with γ and neutron radiography and sub-critical assembly. The thermal column and thermalizing column are available in the reactor, see Figures 1 & 2.

The Kartini reactor is operated by Yogyakarta Nuclear Research Center, which is very closed relationship with Gadjah Mada University. Based on this situation, the Kartini reactor is used as a training facility for student from the Gadjah Mada University.

Several hospitals, both government as well as private are located near by this reactor facility in the distance less then 10-km. Faculty of Medicine of the Gadjah Mada University uses the government hospital also as a teaching hospital.

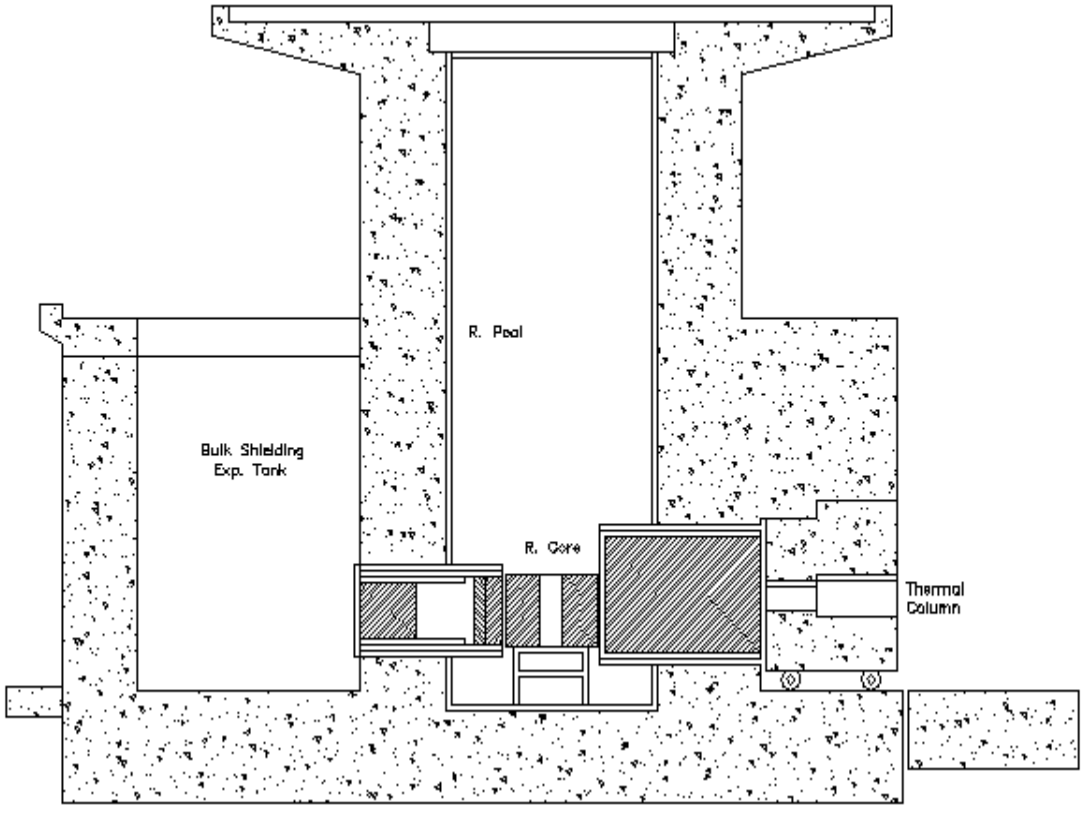

FIG. 1. Vertical cross-section of the TRIGA Kartini reactor.

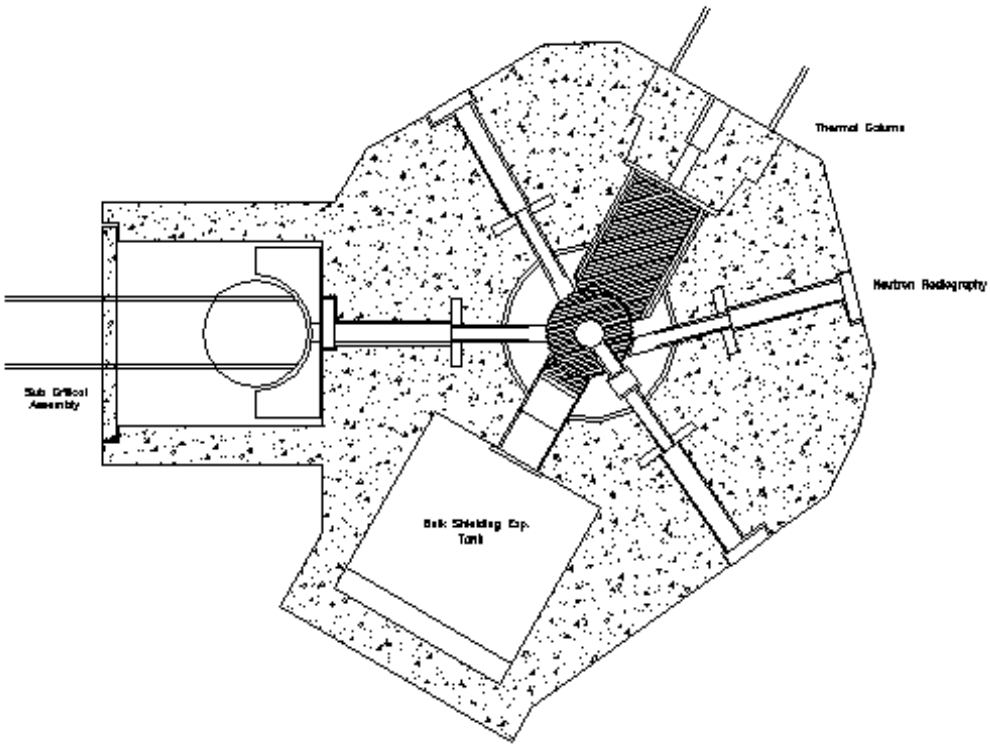

FIG. 2. Horizontal cross-section of the TRIGA Kartini reactor.

Multipurpose research reactor RSG-GAS

The RSG-GAS reactor is located in Serpong Research Center, it has nominal power 30 MW. The RSG-GAS reactor is a plate type/MTR type reactor using LEU fuel in form of U_3O_8-Al. This reactor is equipped with irradiation facility as well as equipment for neutron beam experimental purposes, see Figure 3.

This reactor was officially inaugurated on August 1987 and reactor utilization for radioisotope production was started on December 1990. Up to know this reactor produced the entire radioisotope used in Indonesia, either for medical purposes as well as for industrial purposes. Some of the radioisotopes produced from this reactor are also exported to foreign country. The reactor equipped with 6 beam tubes, one of this up to know is still unused. The other beam tubes used for radioisotope production (^{125}I), and neutron beam experiments purposes, i.e. neutron radiography, powder diffractometer, triple axis spectrometer, neutron guide tube, etc.

This reactor is also has a facility for fuel element irradiation under high pressure and temperature condition as occurred in the NPP. This reactor has equipped with a power ramping facility, a facility to stimulate power ramping on the BWR or PWR fuel element under irradiation condition.

This reactor is located in Serpong, a suburb of Jakarta for about 35-km in Southwest direction. Several big hospitals either private or government own are available in Jakarta, however due to traffic condition in near by Jakarta, at least one and half hour is required to go from the nearest hospital in Jakarta to the reactor facility in Serpong.

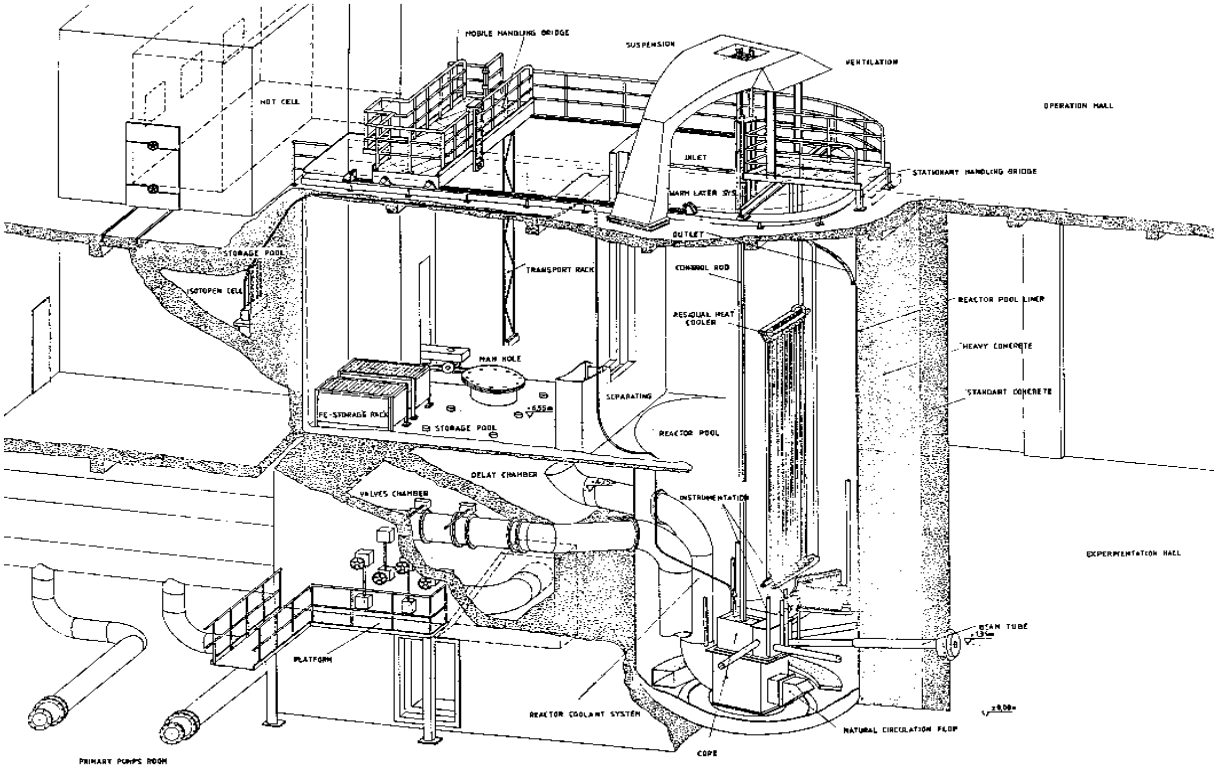

FIG. 3. Isometric drawing of the RSG-GAS reactor.

Survey to the Indonesian research reactor for the BNCT treatment facility have done with the following criteria:

(a) Neutron flux requirement: neutron flux might be used at the front of beam tube or other facility should be around 10^8 — 10^9 n/cm^2.s for thermal or epithermal [2,3]. It was considered also possibilities to modify such of beam-tubes arrangement if it would be needed to reach that requirement. It was considered also volume of the beam and available space in front of beam tube to allow activities for BNCT treatment.

(b) Reactor utilization program: Since the BNCT treatment requires preparation in the reactor area/ room, neutron as well as gamma beam shutter is absolutely needed, other wise reactor should be started up and shut down to perform this treatment or single purpose only.

(c) Supporting facility: The most important supporting facility is neutron flux measuring laboratory and boron concentration measurement facility. All of the reactor facilities have a laboratory to perform neutron flux as well as neutron spectrum measurement. The available equipment to measure boron concentration in the tissue as well as in the blood is ICP-MS, and this equipment is available in Serpong facility.

(d) Potential users of the BNCT/hospital: Positive response of the medical staff in the hospital, their expertise as well as facility available on that hospital is considered as a supporting items to decide utilization of the reactor for BNCT.

With a support of JAIF, a BNCT expert of JAERI has visited Indonesia and spent around one week at the RSG-GAS reactor in Serpong beginning of this year. He has performed intensive discussion with the Indonesian reactor engineered and he explains basic

requirement for the BNCT facility. He has visited also TRIGA reactor in Yogyakarta and performed technical discussion with reactor engineers and medical doctor/oncologist of the Sardjito hospital and Faculty of Medicine, Gadjah Mada University. With support from JAERI, Japan, author has spent 2 weeks in JAERI facility to gather further detail information regarding BNCT technology, and he has also visited several institutions operated these facilities. During his visit to Japan, discussions with specialist expert on neutron beam design as well reactor engineers have been done in order to finalise decision on which reactor the BNCT facility will be installed.

Result on this survey indicated that the RSG-GAS reactor is not suitable to perform BNCT treatment due to some reasons:

(a) Neutron beam as well as volume of the neutron beam available in the front of beam tube is only 10^7 and it is not sufficient [4]. Beam-tube modification is very difficult and also not possible since utilization program of the reactor.

(b) Neutron and gamma beam shutter is required because other wise reactor utilization program will be disturbed by BNCT treatment. However, construction of the beam shutter in this room/hall is not possible since limitation on available space on this area as well as bearing capacity of that floor is limited.

(c) Transportation of the patient being treated from hospital to the reactor facility is rather difficult since arrangement of the reactor building, and also traffic from Jakarta to the reactor site vice versa are not comfortable.

Since the RSG-GAS reactor is not suitable for the BNCT facility, other two TRIGA reactors are considered to be used for that purposes. Further activity on preparation of the beam design for BNCT will be concentrated to the TRIGA reactor. Using TRIGA reactor, BNCT facility should be installed in front of the thermal column. Availability of the supporting facility as well as a good response of oncologist and other medical staff of the Sardjito hospital and Gadjah Mada University to the BNCT program is indicating that utilization of TRIGA reactor in Yogyakarta will be feasible.

2. FURTHER STEP ON BNCT ACTIVITY IN INDONESIA

The BNCT facility in Indonesia is planned in operation within next 5 years from now on. Based on the literature survey referring to the other facilities now is available [2,3,5,6] or being available in the near future [7], epithermal neutron beam is more preferable rather than thermal neutron beam. To follow on the tendency, BNCT facility for the Indonesian TRIGA reactor is planned to use epithermal neutron beam.

Since the BNCT program has started, several activities now were identified and also initiated. The main activities can be described as follows:

Beam design

The thermal column of TRIGA reactor will be modified to produce epithermal neutron beam required for the BNCT facility. Material in the thermal column will be changed in order to get epithermal neutron beam. As the first step, the reactor physics calculation using Monte Carlo code MCNP is initiated. To get a better result and also to speed up the calculation process, shifter material or moderator and also photon g-shield have used in the Finnish reactor [8] will be considered. Calculation model as described by Matsumoto [9,10] will be

applied on this work. Completion of this work will be followed with the next step to perform engineering design to prepare basic and detail design. Preparation of the reactor physics calculation as well as engineering activities of the neutron beam design is planned for two years. This activity will be followed by construction, testing and commissioning of the equipment, including also phantom measurement.

Neutron dosimetry and treatment planning

At the reactor facility, neutron flux and spectrum measurements have done using foil and wire activation detectors. Laboratory with nuclear counting system is available, included also sample changer to perform multiple sample analysis. Neutron flux measurement using SPND is also used in the experimental facility. Since manpower to perform these activities is also available, the most important activity to be done in the field of neutron dosimetry is improvement on accuracy and to speed up the measurement result. The other aspect of dosimetry for BNCT as described by Watkin [11] will be considered and prepared. Dose treatment planning can be done through calculation process and it will be checked or verified using measurement.

B concentration measurement

B concentration in tissue and blood can be measured using PGAA and ICP-MS/AES. Up to know PGAA system is still under designed, although this activity previously is planned to detect other light element in the air pollutant. It is expected that within 5 years from now, the equipment is ready and well-trained personnel are available to determine B concentration in tissue as used in other facility [12]. The ICP-MS is available and also well-trained personnel are ready to perform light element identification and measurement.

Radiobiology and pre-clinical experiment

Radiobiology and pre-clinical experiment for animal will be continued, as previously done using TRIGA reactor in Bandung. This experiment should be done in co-operation with medical doctor or oncologist to get better result.

3. CONCLUSIONS

Feasibility study to develop BNCT facility at the Indonesian reactor has been done and a good response from the potential user has considered. Results of this study can be found as follows:

- BNCT study in Indonesia is being started and it is planned that the facility will be available within next 5 years.
- TRIGA reactor will be used instead of multipurpose RSG-GAS, epithermal neutron beam will be chosen rather than thermal neutron.
- Neutron beam design activity is being started with reactor physics calculation and it will be followed with an engineering activity.
- Other activities on neutron dosimetry, boron concentration measurement, and other aspects are also being initiated.

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Suggestion for an NCT reactor in the hospital

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Abstract. The concept of neutron capture therapy is older than 60 years, but a specific tool in the hospital has not yet been realised. Accelerators are supposed to be promising, but the technology has not been proven yet and a new method or facility to measure the boron concentration in the samples from patients quickly is needed. Installing a new reactor in the metropolitan medical center is deemed very hard because of public acceptance, but designing an extremely safe and effective reactor is possible by using proven technologies. Its review indicates that 10^{10} n/cm^2–s of epithermal flux at the irradiation position can be obtained at 200–300 kW by optimised design. Multiple irradiation positions are available in a reactor. The low power results in low values of excess reactivity, fuel burnup, decay heat, radiation inventory, construction and operation cost, etc. The reactor also provides the prompt gamma neutron activation analysis measuring boron concentration. The neutron diffraction technique gives more than 10^7 n/cm^2-s of thermal neutron flux for this purpose at 100 kW with low background.

1. INTRODUCTION

Neutron capture therapy (NCT) is a potentially effective treatment method for radio-resistant and highly invasive tumors such as glioblastoma or melanoma. Its efficacy using B-10 (BNCT: Boron NCT) has been partially demonstrated in Japan[1,2,3] using thermal neutrons. Early stage clinical trials using epithermal neutrons of BMRR (Brookhaven Medical Research Reactor)[BNCT web of BNL] shows that patient survival after a single BNCT dose is comparable to or slightly better than survival after modern standard therapy. Significantly enhanced survival by epithermal BNCT has not been demonstrated yet, but the quality of the patients' life is much better and the enhanced result is expected by the dose optimization trials that are undergoing. Due to the poor penetration of thermal neutrons into tissue, the thermal NCT needs the reopening of the skull for irradiation and its efficacy is proven only for superficial tumors. While thermal neutron irradiation facilities are needed for research, the trend for patients' treatment has definitely been toward epithermal NCT.

The neutron source for the BNCT should provide facilities for patients' irradiation and prompt gamma neutron activation analysis (PGNAA). The PGNAA is not considered so inevitable because a reactor for the NCT usually has it and other methods, such as inductively coupled plasma — atomic emission spectroscopy (ICP-AES) can be utilized at the research stage. For routine treatments in a hospital, however, a quick and accurate method measuring B-10 concentration to control the irradiation is needed. At present, the PGNAA is the only method available for this purpose. ICP-AES can give better accuracy than the PGNAA but it needs several hours for sample preparation for a measurement. Accelerators are believed as promising epithermal neutron sources for the NCT, especially from the viewpoint of public acceptance for their installation in hospitals. The technology, however, has not been proven yet and no suggestion has been found for the quick measurement of B-10 concentration.

At present, the only proven neutron sources for the NCT are research reactors. Many efforts to optimize reactors for the NCT are found. While many of them are to modify existing reactor facilities, conceptual designs for new reactors are also found. If a very good chemical compound for the NCT is found, or if the efficacy of the NCT is sufficiently verified by a currently available compound, a neutron source readily installable in a medical center will be in demand. Obtaining public acceptance for the new installation of a reactor in a metropolitan hospital is deemed very hard. But it is believed that the technology to design an extremely safe low power reactor is well established, and the public opinion to such reactors is not so

bad. Reviewing such technologies and summarizing the basic design concept of a reactor optimized for the NCT in a hospital (NCTR), is worthwhile, therefore, for the readiness, because patients of malignant cancer cannot wait.

The basic requirements for an NCTR should be considered from safety, especially considering public acceptance, and economics points of view. A higher flux-to-power ratio (FPR) is the first priority because it is closely related to both of safety and economics by permitting lower reactor power and shorter irradiation time. The low power and short operation time cause low burnup of fuel, low radiation inventory of the core and surrounding materials, low excess reactivity, low burden in cooling and shielding, little engineered safety features, etc. The highest FPR achievable is roughly estimated through the review of NCT neutron sources of reactors. The basic feature of the NCTR is suggested. Since the NCTR should also provide PGNAA system(s), a method to achieve sufficient thermal neutron beams for the PGNAAs at low reactor power is also suggested.

2. REVIEW OF THE NCT NEUTRON SOURCES OF REACTORS

It is widely accepted that the neutron spectrum closer to the 10 keV mono-energy with sufficiently low gamma background is the better to allow deeper penetration of neutrons minimizing damage to normal cells. Since the actual spectrum cannot be mono-energy and the neutron above 10 keV causes proton recoil the actual peak energy is usually lower than 10 keV. The epithermal neutron flux at the irradiation position should be as high as possible to minimize irradiating time. If the patient moves during the irradiation, places other than the target are irradiated. Therefore, the patient is put under anaesthesia during the irradiation. The concentration distribution of a chemical compound for the NCT varies as time goes on, and the time interval for optimum irradiation is limited. While one of the currently available boron compounds — BSH or BPA is used, the upper limit of thermal neutron fluence to brain cancer is about 10^{13} n/cm^2. When an epithermal neutron beam irradiates the tissue, the peak thermal neutron flux inside the tissue is about three times of incident epithermal neutron flux. Therefore, the epithermal neutron flux of 10^9 n/cm^2-s needs about 1 hour of irradiation time.

Constantine[4] summarized methods to obtain epithermal neutrons in existing reactors. His suggestion can be applied to a new NCTR design as well. If possible, the preferred method is spectrum shifting. Fission spectrum neutrons are slowed down below 10 keV but not to very low energy until they reach to the irradiation position. This method is possible when the reactor has a wide area emitting neutrons such as a thermal column. In a reactor where only rather narrow and long beam tubes are available, neutrons and gamma rays from the core are filtered to permit more transmission of epithermal neutrons, but the FPR is very low as shown at HFR Petten in Table 1.

The refining method of neutrons in a given reactor core condition, in which spectrum shifting of fast neutrons and shielding of thermal neutrons and gammas are included, is alsoimportant. Spectrum shifters are also summarized in reference 4. It should have large scattering cross-section above 10 keV, but small cross-section below 10 keV. Its mass number should not be large or small. From the cross-sectional point of view, Ni-64, which is used for the conceptual design of the Russian reactor[6], is very close to the ideal case except a window around 25 keV, but its natural abundance is only 0.926 %. Other Ni isotopes have far different cross-section characteristics. Its mass number is rather large to slow down fast neutrons. Therefore, it can be used as a good filter rather than a spectrum shifter. Aluminum and sulfur are practical candidates.

Table I. Reactor epithermal neutron sources

Reactor	Power	Flux	Material(s)	Method	Remarks
KUR	5 MW	1.5E9	Al+D_2O	Shift	D_2O for thermal NCT
JRR-4	3.5 MW	1.7E9	Al+D_2O	Shift	D_2O for thermal NCT
BMRR	3 MW	2.7E9	Al+Al_2O_3	Shift	
		1.9E10	Fission converter	Shift	Calculated
MITR	5 MW	2.6E8	S+Al	Shift	Below core
		1.3E10	Fission converter	Shift	Calculated, horizontal
HFR	45 MW	3.3E8	Al+S+Ti+Ar	Filter	Petten
TRIGA	250 kW	1.3E9	AlF_3	Shift	Finland
MuITR	100 kW	4.1E8	Al+Al_2O_3	Shift	TRIGA
Cho	300 kW	3.2E9	AlF_3	Shift	Conceptual
Russian	300 kW	4.8E9	Ni-64	Filter	Conceptual, HEU fluid fuel, fast core

Since both have windows above 10 keV, Al_2O_3 or AlF_3 are used to block these windows. AlF_3 adopted at the Finland TRIGA[7] facility which was recently built among the reactors in the Table 1, will be used at Georgia Tech. in the USA and Studsvik in Sweden, and Cho[8] used it for his conceptual reactor design.

Since the BMRR is the only reactor in the world built specifically for the NCT, it has the best beam capability among existing facilities. If the FPR is compared, however, a TRIGA II in Finland has the highest value, which is 1.3×10^9 n/cm^2-s at 250 kW. The modification study of MuITR[9], which is a TRIGA II as well, shows slightly lower value of 4.1×10^8 n/cm^2-s at 100 kW, which may be caused by the use of a different spectrum shifter — Al and Al_2O_3 instead of the AlF_3 used in Finland. While a conceptual thermal reactor designed by Cho has 3.2×10^9 n/cm^2-s at 300 kW, a conceptual fast reactor using fluid fuel designed by the Russians has 4.8×10^9 n/cm^2-s at the same power. Since the Russian design is a fast core, its flux could be much higher if proper spectrum shifting is adopted. Cho's design also demonstrates that multiple irradiation positions for the NCT — at least four, is possible. The FPR of Cho's design is about two times that of Finland's TRIGA, which may be explained that completely new design without any restriction to modify an existing reactor, could enhance the FPR. Furthermore, if the fission converter is employed to Cho's design, the flux could be much enhanced. The author[10] estimated that about 1×10^{10} n/cm^2-s of flux could be obtained by a 200 – 300 kW reactor power. The Chinese design[11] showed 1.2×10^{10} n/cm^2-s at 300 kW.

3. PGNAA IN AN NCTR

The NCTR should also have sufficient thermal neutron beams for PGNAAs. The NCT and PGNAA facilities were recently installed in JRR-4[12]. The beam for the PGNAA comes through a neutron guide tube. The measuring time for the B-10 concentration is expected within a few minutes by about 1×10^7 n/cm^2-s of flux at the sample position. A cold neutron source or neutron guide tube at an NCTR, however, cannot be expected. An other option is the filtering method, but the background is rather high, the thermal flux at the sample position

may not be high enough at a low power NCTR, and a beam tube can only be used for one PGNAA system. Should an NCTR have multiple NCT ports, more than one PGNAA systems would be needed. The combination of filtering and diffraction is found in MITR[13], where neutrons of higher energy than (002) mode diffraction are filtered away by a sapphire.

For the design of the PGNAA system at HANARO[14], which is 30 MW multipurpose research reactor, all modes of diffraction and focussing but without any filtering, are adopted. Since the direction of the diffracted beam is far away from the incident beam, the fast neutron and gamma background at the sample position is expected to be very low. It is believed that if this concept is applied to the NCTR, the neutron flux for the PGNAA will be sufficient and multiple systems can be installed at one beam tube. The beam for the PGNAA will be vertically diffracted (45° Bragg angle) by 2 mm thick pyrolytic graphite (PG) plates from a spare white beam (upper and lower parts of the beam area, 2×7 cm^2 each) of a dedicated beam tube. The analyses and experiments confirm that the flux at the sample position will be 3×10^8 n/cm^2-s. If all conditions are the same, except the reactor power, 3×10^6 n/cm^2-s is expected at 300 kW NCTR. The 45° Bragg angle is chosen in HANARO due to the limited space, but the peak flux weighted by 1/v reaction occurs at around 11.6° of Bragg angle, which is about three times of that by 45°, which was confirmed by the measurement at the HANARO CN port[15]. Furthermore, the nose flux can be higher by the dedicated design, the distance from the nose to the PG can be shorter, and the beam area to be diffracted can be wider. Though the estimation is very rough, it can be safely said that the flux will be more than 1×10^7 n/cm^2-s at 100 kW. The spectrum of the diffracted beam is composed of several lines. The energy band of each line is very narrow, which means that all other energy neutrons pass the PG. Therefore, multiple beams for the PGNAA systems can be obtained by slightly different Bragg angles as shown in Fig. 1. It shows the top view of this concept and two beams are reflected horizontally. If the third one is needed, that beam can be diffracted to upward.

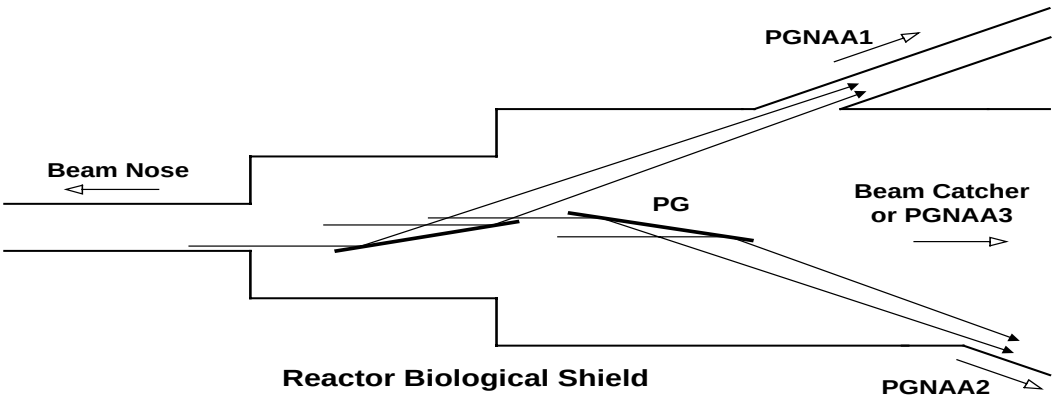

FIG. 1. Diffracted PGNAA beams for an NCTR..

4. SUGGESTED FEATURE OF THE NCTR

If it is assumed that the epithermal neutron flux at the irradiation position is 1×10^{10} n/cm^2-s at 250 kW, the irradiation time is about 6 minutes and the power generation is 90 MJ, which is approximately equivalent to 3×10^{18} fissions or 2.5×10^{-3} g burnup of U-235. If the reactor has three irradiation positions (remaining one side for PGNAAs), and operates four

times/day and 300 days/year, up to 3,600 patients could be treated with less than 2.5 g burnup of U-235 in a year. Its initial fuel in the core could be used for the lifetime of the reactor without any refuelling. The core is cooled by natural convection of pool water. An in-pool N-16 decay tank[16] will maintain the pool-top radiation level sufficiently low and a small plate type heat exchanger cools the pool water. In case of a pool failure accident, the core is safely cooled by natural convection of air. All reactor systems, except radiation monitoring and ventilation systems, run only limited time — say less than an hour/day, because the preparation for irradiation and post irradiation works consume much more time than the irradiation. The majority of radwaste during the normal operation is very low level filters and ion exchangers of the pool water purification system, and filters of the ventilation system.

The reactor should also be safe against abnormal reactivity insertion or failure in the reactivity control. J.K. Kim[17] suggested a subcritical reactor multiplying intense neutron source with the expense of periodic replacement of Cf-252. Even if the reactor reaches criticality, however, we can limit its power generation far below safety criteria without any engineered reactivity control. For the case of power burst reactors, prompt insertion of large reactivity to obtain pulse shaped power behavior, is their normal operation mode. A reactor has thousands of safe pulsing records. This fact sufficiently confirms safety against reactivity insertion. For the case of a TRIGA-ACPR[18] with rated power of 300 kW for steady state operation, its peak power reaches more than 20,000 MW with full width half maximum (FWHM) of 4–5 ms and the power generation is more than 100 MJ in a pulsing. Air cooled fast burst reactors (FBR)[19] also generate similar pulsing power with shorter FWHM and higher peak power. In these cases the neutron generation in a single pulse could be more than that for a NCT treatment. Therefore, the pulsing operation could directly be utilized for the NCT if very short irradiation time is required. But it is not recommendable because of possible fear to the public by prompt super-criticality. These pulsing operation needs a certain amount of excess reactivity to reach prompt supercritical. Since the prompt temperature defect of the fuel during the pulsing operation is much more than the reactivity worth inserted, the reactor immediately turns itself to sub-critical status. As far as the excess reactivity is maintained below a limited value at this kind of reactors, even though all control rods are accidentally withdrawn, promptly or slowly, and the reactor shutdown mechanism has failed, its power generation cannot exceed the safety limit due to the inherent safety feature. If this small excess reactivity cannot compensate the lifetime fuel burnup, a small amount of burnable poison could be mixed in the fuel. Natural erbium is used as a burnable poison in some TRIGA fuels.

An option under debate is the fractionation since it is more effective to control tumours than a single lumped irradiation in conventional radiotherapy. Should the fractionation be the standard NCT or the time for a single lumped irradiation be longer, say 20 minutes instead of six, the reactor power could be lowered more. The lower rated power needs the lower excess reactivity in case of a reactor having a large power defect, which consequently enlarge the safety margin.

Its operation time should also be limited to keep the radiation inventory in the core as low as possible and to keep the minimum excess reactivity for operation. Operation only during irradiation is recommended. It reduces the shielding requirement for the shutter, thereby increases neutron flux at the irradiation position. The square wave operation mode is found in research reactors, and quick and reliable startup is possible by computer control.

Though the reactor power is low and operation time is extremely limited, it can be effectively utilized for neutron activation analysis (NAA) and low level radioisotope

production. The NAA facility can also be utilized for the track analysis to determine cell level boron distribution. So as to provide a certain level of thermal neutron flux for PGNAAs and the above mentioned applications, the best reflector — beryllium should be used for a part. Heavy water is not recommendable as a reflector because it causes additional burdens in reactor management. The core should be as compact as possible without any irradiation hole causing neutron loss in the core. All control rods should be fuel followers. Since the excess reactivity is very small, all control rods will be almost withdrawn during operation, and thereby the core only has fuel and coolant.

So as to judge economics of a reactor mentioned above, the cost of other oncological treatments could be referred[20]. The X ray conformal radiotherapy (CRT) which uses more than six cross-fired X ray beams, costs about US$11 million for the accelerator and the first gantry, and about US$2 million for each added gantry. If it is considered that a reactor could have at least three irradiation positions and its operation cost would be much lower than an accelerator, it is economically competitive as far as the efficacy of the NCT is proven.

5. CONCLUSIONS

Designing an extremely safe NCTR is possible by using already proven technologies. An optimized low power reactor could be an effective tool to be used in a medical center. It provides high epithermal neutron flux at multiple positions, PGNAAs for the determination of boron concentration to control irradiation, NAA including track analysis for the cell-wise boron distribution, low level radioisotope production, etc. It is an integrated facility for the NCT and could be used for other medical demands. The reactor itself is safe in any anticipated accident conditions because of low power, limited operation time, low excess reactivity and inherent safety feature of large prompt negative temperature coefficient. Its operation and management cost would be lower than that for the equivalent medical accelerator.

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Annex 3
IRRADITION FACILITY OPERATION AND MANAGEMENT

Boron neutron capture therapy: An interdisciplinary co-operation

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Abstract. The international (European) undertaking in BNCT in the Netherlands has required close scrutiny of the organisational structure required to establish BNCT facilities. The multidisciplinary co-operation and the tasks of the participants in the hospital (Radiation Oncologist, Medical Physicist, Pharmacist and other medical and paramedical staff) and those attached to the reactor) are described. The organisational structure and regulatory aspects required for the international functioning of the Petten treatment facility are provided for guidance to new projects in this field.

1. INTRODUCTION

The first clinical trial in Europe of Boron Neutron Capture Therapy (BNCT) had to be prepared and performed in a multinational scale whereby a unique facility available for BNCT is localised in one country (The Netherlands) and is operated by an international team of experts under the leadership of a German radiotherapist, treating patients coming from different European countries [1,2]. Hence, from the beginning it was evident that a very specialised organisational and contractual structure had to be created. From a principle point of view, the application of BNCT in human patients needs everywhere in the world a multi-institutional and multi-disciplinary co-operation, which should be initiated as soon as a facility i.e. a research reactor decides to investigate the possibility to perform patient treatment. Furthermore, due to the fact that a new drug, a new radiation beam and a new facility will be used, special efforts have to be made on quality management, in order that the setup at the facility and the personnel involved comply with similar practices in conventional radiotherapy departments.

In this article, some aspects of the organisational structure and of the quality management for the European project in Petten is given that may be of general interest for groups who are interested to establish a BNCT facility.

2. THE HOSPITAL

Obviously, patient treatment only can be performed together with a hospital and competent medical staff. Furthermore, the experimental nature of the present BNCT trials makes it mandatory that the hospital must be an academic hospital with experience and reputation in oncology. By searching such a hospital, it must be taken in consideration, that in some countries the possibility to perform clinical research is limited to especially certified physicians or institutions.

2.1. Radiotherapy

BNCT is a modality that performs radiotherapy in one of the most complex ways imaginable. Therefore, from the beginning the participation of a radiation-oncology department is mandatory. It is a great advantage, if the radiotherapist involved already has some experience in fast neutron therapy. Unfortunately, this treatment is only performed at a few places worldwide. It will be difficult to find such an experienced person willing to invest a major part of his time in BNCT. It must be taken into consideration, that BNCT is not accepted by the majority of radiotherapists as a modality that should be investigated. The poor reputation of BNCT is due to several facts, including its very specific history [3]; the fact that most of the publications on clinical aspects of BNCT are usually written not respecting the established standards for radiotherapy and the high complexity of the achieved dose distribution, which is judged to be uncontrollable.

The main tasks of the radiotherapist who is in charge of BNCT are:

- to organise a medical structure, which will allow patient irradiation in a non-medical environment distant from a hospital, including training of staff members.
- to co-ordinate the work of the different participants, defining structure and organisation of the clinical study and patient treatment. All staff members involved in patient treatment of all participating institutions are obliged to follow his instructions independent of their affiliation, and to communicate with him on a regular basis.

- to specify and provide the medical equipment and to control the functioning of any such equipment. He has to organise the supply of medical consumable (e.g. gloves etc.) and drugs necessary for medical emergencies occurring in patients at the reactor site
- to provide the proper and appropriate information about the treatment to the patients and to obtain the signed informed consent form.
- to take all steps necessary to obtain legal and ethical permits and licenses required for the implementation of the medical tasks for BNCT at a research reactor
- to take the overall responsibility for the medical aspects of the treatment. He is responsible and liable for the whole treatment and for each individual patient
- to prepare and to provide the appropriate data for the evaluation data sheets and to describe the actions in details, and furthermore to write and update the Standard Operating Procedures (SOP) concerning his work
- to prepare all relevant clinical data for treatment planning, i.e. to define the target volume and the organs at risk, and to approve the final treatment plan
- to take the blood samples from the patients for prompt gamma analysis or other purposes
- to be responsible for the positioning of the patient for the irradiation
- to co-ordinate the treatment performed according to the approved protocol
- to accept the beam, before the patient is treated and for the duration of the irradiation, following the check-outs and physicist's reports, as defined in the relevant SOP
- to accept responsibility for the starting time and duration period of the irradiation of the patient, based on data provided by the persons that are responsible for correct data handling
- to start and to finish the treatment, by taking the responsibility to physically activate the opening and closing of the beam shutters. The treating radiotherapist takes the responsibility for the safe and precise irradiation provided that it is ensured by the owner of the reactor and the medical physicist that the facility is operating in a safe and reliable manner
- to take overall responsibility for the welfare of the patient whilst at the reactor site (including concomitant disease, and arising acute symptoms)
- to decide on the timing and the amount of boron compound to be administered to the patient based on the calculations and measurements performed by others
- to document all actions, and all relevant data obtained concerning the patient, the radiotherapy department stores the patient’s file according to the legal requirements, for at least 30 years
- to participate in every meeting and audit at each level concerning the BNCT study, including the radioprotection of the medical area and staff at the reactor site

2.2. Medical physics

In general terms, the role of the medical physicist is to assure quality and safety of the medical use of ionising radiation. The medical physicists support the physicians in their task to treat patients by providing all necessary physical and technical data to perform a safe and precise treatment and to control all technical equipment involved in the patient treatment.

The major tasks of the Medical Physicist will be:

- definition and description, step by step, of the dosimetry needed to fulfil the requirements from the protocol
- definition and description, step by step, of quality assurance from all medical physics aspects of the treatment
- delegation and supervision of the performance of the tasks described in detail in SOPs, which are formally approved by the Medical Physicist to the staff members designated by the owner of the reactor and supervision of their work
- approval of proper forms of documentation of the measurements, the recording and reporting of treatment planning and the actual treatment. This includes the physical part of Standard Operating Procedures (SOP) and Case Report Forms (CRF), and the definition of quality control of the irradiation, including calibration and dosimetry requirements (regular measurement of the beam parameters, check of the equipment for controlling the irradiation area), treatment planning, determination of the start and duration of irradiation, and support of those actions that physically involve the patient, e.g. positioning the patient in the beam.
- immediately inform the responsible radiotherapist and all other decision making staff members about all changes influencing the treatment defined in the study protocol
- participation in every relevant meeting and audit concerning the treatment of patients and the radioprotection of the medical area at the reactor
- presence at all treatments of patients and participation at the preparation of the treatments for each individual patient.
- responsible for performing treatment planning calculations, for controlling the results and for the approval of the plan concerning the physical data. The overall medical responsibility of the radiotherapist is to approve the final plan
- performance of control calculations with the treatment planning system according to the relevant SOP
- calculation in advance of the duration of each irradiation (expressed in time and in beam monitor units) based on the individual patient planning factors and on the actual beam monitor calibration. He also calculates the time of start of irradiation based on the prompt-gamma analysis of the blood samples
- calculation from the approved treatment plan of the data for correct positioning of the patient
- calculation of the actual dose given to the patient on the basis of the boron concentration of blood taken before and after the irradiation
- documentation of all actions, and data obtained from the measurements and calculations which have to be archived by the participating hospital
- Quality control: Performance of measurements for clinical dosimetry and quality control according to the relevant SOPs, including regular checks of different devices (for example on-line monitoring equipment)

It may be necessary and pragmatic to delegate tasks deriving from medical physics to nuclear physicists or other staff members committed by the reactor owner.

2.3. Pharmacy

All of the available compounds for BNCT are experimental drugs and cannot be used without special permission by the national agency responsible for new drugs in medicine. To handle such issues, the participation of an experienced pharmacist and of a well-equipped pharmacy in the participating hospital is extremely useful. The pharmacy should be used to handle experimental drugs and have the necessary equipment to perform the analyses for the quality control.

The pharmacist will organise the drug supply. Supplying companies must produce the compound according to a drug master file and should have a written procedure for preparation and quality control of the final product and its intermediates. The material needs then to be imported into the country where BNCT will be done. Quality control data have to be provided with each batch that is imported.

In the laboratory of the pharmacy, the following quality control checks should be performed:

- identification of the study medication by appropriate methods
- absence of oxidation products or other impurities
- absence of bacterial endotoxins (pyrogens). This is tested by Limulus Amoebocyte Lysate test [4]
- the degree of boron-10 enrichment

The responsibility for the quality control and for the release of the material for clinical use needs to be delegated to two different pharmacists. If the batch meets all requirements, the pharmacist releases it for clinical use with a defined expiry date after initial testing.

Before administration to the patient, the infusion of the drug needs to be prepared for the individual patient, following the prescription of the radiotherapist. All actions have to be documented following the legal requirements.

Concerning the use of unregistered medicaments, the description of all the regulatory aspects, which have to be taken in consideration, cannot be the aim of this brief overview. Nevertheless, this very important aspect, the competence and time needed to handle it correctly is especially emphasised [5–8].

2.4. Other medical specialists

To perform BNCT more then the already mentioned specialists are mandatory. Neurosurgeons select, operate, prepare and follow the patients. Pathologists and diagnostic radiologists familiar with the procedure are critical. To perform clinical trials a substantial resources and personnel must be available, e.g. data manager, monitors, external experts for audits, research nurses, radiographers... In any case, the availability of an ethics committee must be guaranteed.

3. THE OWNER OF THE REACTOR

The owner of the reactor is responsible for the reactor, the delivery of neutrons, and the BNCT facility, in general, including the working environment around the facility, i.e.

security, radioprotection and safety. He is responsible for ensuring that these facilities function correctly and that the associated working conditions conform to recognised standards. He ensures that the quality assurance of the facility, measurements and presentation of data, e.g. check-outs, prompt gamma ray analysis, dosimetry, etc., conform to acceptable standards. He provides a central contact person or liaison officer between the BNCT technical group at the reactor site and the medical staff. His tasks in more detail include:

The reactor

The owner of the reactor is responsible for the safe functioning and production of neutrons for the BNCT facility. He ensures that the reactor functions as required and the neutrons are delivered at the preferred energies and fluences. He is responsible for the maintenance and upkeep of the facility, and ensures that these are accomplished punctually. He is the co-ordinator for the schedule at the reactor in order to perform the treatment, checks the reactor schedule and any possible interruptions in reactor operation, and informs the radiotherapist accordingly and promptly. He informs his personnel of pending treatment, the personnel required, the irradiation (treatment) schedule and objectives, and activates the necessary actions to prepare for treatment, as well as, ensuring that the necessary support and materials are available and present for treatment. He collates and documents all information and data from the day's activities, and reports in the relevant source document.

The Beam

He is responsible for the condition and operation of the filtered neutron beam facility, which comprises the safety instrumentation and interlocking system, the complete filter system and the different shutters. He is therefore responsible for the supervision of the non-medical part of the therapy facility, which also includes direct-line of communication with the reactor operating staff, medical physicists and beam users. He performs a check out according to a defined checklist described in the relevant SOPs before the facility is used for irradiation. The check out includes a control of the function of the safety interlock system, the filter system and the beam shutters. He performs regular checks of the communication system of the irradiation room, the lasers and the equipment for placement of the patient in the radiation beam (irradiation table, fixation devices etc.) as described in detail in the relevant SOPs.

Working environment, security and radiation protection

The owner of the reactor is responsible for the safe working conditions of the reactor and the working environment. He installs all infrastructures on Patient Radiation Protection, following the legal requirements. He establishes a contract with the participating hospital concerning the radiation protection of the medical personnel. He informs the external personnel coming to Petten for purposes of BNCT of reactor safety measures, including reactor hall evacuation procedures. He ensures that the needs of medical staff working at the reactor are fulfilled in order that they may perform their duties safely and efficiently; this includes the availability of suitable office and working space on-site. He is responsible for all security measures at the reactor site, including movement on-site of staff members from the hospital and patient, plus accompanying person(s). He is responsible for escorting and co-ordinating the movement of the patient and medical staff on the reactor sites. He monitors and records patient radioactivity after treatment. He is also responsible for the guidance of beam users and the patient out of the building in the event of a reactor hall evacuation

The owner of the reactor provides the infrastructure for all co-workers to allow them to perform their tasks. It will be mandatory to install communication structures that guarantee

regular exchange of information on all aspects of the co-operation but especially about all changes that may influence the treatment. He ensures that quality assurance of its work follows his own standards (for example ISO 9001) respecting whenever it may be applicable the current recommendations of Good Clinical Practice and Good Laboratory Practice for Trials on Medicinal Products in the European Community [5–8] or the equivalent national legal requirements and of course, the guidelines for reactor safety.

He informs the beam users immediately about malfunctions influencing the neutron beam conditions or safety conditions. He guides the beam users on questions concerning the operation of the beam shutters, on the safety measures of the facility and on general reactor safety questions (for instance in case of reactor hall evacuation).

The owner of the reactor, after having received information from the reactor operators about changes in reactor conditions (planned or unplanned), transmits this information immediately to the beam users.

The beam users are obliged to follow the instructions from the facility operator regarding non-medical aspects.

Prompt gamma facility

It is advised that a prompt gamma facility is available in order to be able to measure the boron concentration in blood during the stay of the patient at the reactor [9]. Reactor staff members shall organise the construction of such a facility and its handling. The maintenance of the facility must be organised and its correct function needs to be controlled. Other means to measure boron in blood, e.g. ICP-AES, may be an alternative provided the results become available in a reasonable time.

5. ORGANISATIONAL STRUCTURE AND REGULATORY ASPECTS

The project at the High Flux Reactor HFR in Petten has been formulated such that 6 different hospitals from 5 different countries (Austria, France, Germany, Switzerland and The Netherlands) enter patients into the study. The Department of Radiotherapy of the University of Essen (Germany) performs the treatment at the HFR Petten, which is owned by the European Commission and located in The Netherlands. During the period of treatment, patients are hospitalised at the University/Academic Hospital "Vrije Universiteit" (AZVU) in Amsterdam. The study is carried out following an approved protocol of the European Organisation for Research and Treatment of Cancer (EORTC) BNCT Study Group. The New Drug Development Office (NDDO) of the EORTC performs the monitoring and data management of the trial. The study is financed as a Shared Cost Action by the European Commission, within the BIOMED II Programme [10]. The treatment in Petten is carried out in co-operation with the Joint Research Centre (JRC) of the European Commission and the Nuclear Research and Consultancy Group (NRG) in Petten, under the overall clinical responsibility of the Department of Radiotherapy of the University of Essen which also provides the Medical Physicist. The co-operation of all these institutions, their different tasks and responsibilities are agreed by contract.

To obtain approval for such a complex multi-national project was extremely difficult and time consuming. The initial application to the relevant national medical authority in the Netherlands was submitted in 1995. The complexity of the procedure was primarily due to the uncertainties in identifying the appropriate authorities in the Netherlands, as well as in the other European countries involved. Even the ministries themselves who deal with health

policy, could not answer or identify the issues that had to be addressed and resolved clearly. No European approach is available due to the fact that medical applications fall under national law and that there is no harmonisation on the European level.

The issues, which had to be solved, are listed briefly here.

Reactor related:

— licensing of the reactor as a facility for patient treatment,
— licensing of the facility which is not part of a hospital to irradiate patients,
— gaining local approval on safety aspects, both nuclear and conventional, at the reactor site.

Protocol related:

— establishing the EORTC BNCT Study Group,
— reconciling the different points of view of different ethics committees in different countries,
— gaining approval of the study protocol by different review boards at different levels in a multitude of institutions,
— handling a non-registered drug to be used in different countries following the study protocol,
— regulating the execution of the study protocol as well as the operation of the facility by appropriate Standard Operating Procedures respecting the rules of Good Clinical Practice [11].

Patient related:

— obtaining insurance for patients following different national procedures,
— building up the local infrastructure for patient care, travel and nursing, including all anticipated emergencies.

Personnel and Institution related:

— licensing of foreign physicians (EU and non-EU) to treat patients in The Netherlands, being themselves staff members of a non-Dutch institution (Essen University, Germany),
— enabling a non-Dutch Medical Physicist to be responsible and liable for Medical Physics at the HFR Petten,
— identifying the different actions performed by persons coming from different institutions in different countries in order to establish and delineate the responsibility, and hence liability, towards the patient; furthermore to describe the tasks of all participants, and to create and approve the appropriate agreements and contracts to define such structures,
— applying the appropriate rules for radio-protection of the patients and the staff, respecting both German and Dutch regulations,
— concluding contracts, subcontracts, associated contracts, collaboration agreements, etc. with all involved parties, following the rules established by the European Commission for Shared Cost Actions.

Furthermore, in the Netherlands alone, the following governmental bodies (with Dutch abbreviations in brackets) had to be involved:

- Ministry of Health, Welfare and Sport (VWS)
- Ministry of Economic Affairs (EZ)

- Ministry of Social Affairs (SZW)
- Ministry of Environment (VROM)
- Ministry of Foreign Affairs (BZ)
- Central Ethics Committee on Medical Research (KEMO)
- Health Inspectorate for the province of North Holland
- Mayor's Office of the Community of Zijpe.

In the other countries, as well as on the European level, similar interactions were necessary without any possibility of co-ordination.

General Aspects of Quality Management and Safety Assessments

BNCT at the HFR Petten is performed respecting the European, National Dutch and whenever it is possible, the National German rules of safety and quality assurance for nuclear research reactors, for radioprotection, for radiotherapy and for clinical trials. In particular, quality assurance of safety provisions and functional performance characteristics conform to the most recent concepts and regulations of IEC publications and/or DIN standards for medical electron accelerators:

For safety: IEC 601-2-1:1981[12](identical with DIN 6847-1[13]), newest draft: DIN-IEC 62C/148/CDV:1995-12[12]

For performance:

— acceptance tests: IEC 976: 1989-10[14], identical with DIN 6847-4:1990-10[15]
— consistency tests: DIN 6847-5:1997-07[16](compare also IEC 977[17])

And for treatment planning systems:

— or performance (consistency tests): DIN 6873-5: 1993-08[18]
or — as far as is possible — transferred analogously.

From other differing aspects, the following publications were also considered: DIN 6847-2:1990-03[19]; DIN 6847-3:1980-03[20,21]; DIN VDE 0750-1:1991-12[22]; DIN VDE 0750-207:1986-10[23,24]; IEC601 [25-28].

All relevant procedures concerning the performance of BNCT in Petten and the execution of the clinical trial are described by Standard Operation Procedures (SOP), following the guidelines of Good Clinical Practice [5,6,11]. The dossier of SOPs contains step-by-step descriptions of some 55 procedures. A copy of the dossier is in possession of each participant of the Shared Cost Action.

The reporting of dose is made following as close as possible to the standards used in conventional radiotherapy [29–31].

For the clinical trial, as well as for physical measurements, the clock time is sometimes an important fact. In order to exclude misunderstandings, the legal clock time for Germany is used, given by radio as mid-European time or mid-European summer time from the Physikalisch-Technische Bundesanstalt (PTB). Radio controlled clocks are available at the places where it is necessary.

6. SUMMARY

The current trial at the HFR Petten has demonstrated that a highly complex type of radiotherapy, BNCT requiring a multi-disciplinarian and multi-institutional effort, must be organised in a strict and regulated way so as not to have any uncertainties in responsibility, liability, safety and legal issues. It is apparent, that the structure, which brings together medicine and nuclear technologies, is not necessarily specific to the multi-national approach realised in Petten being a site owned by the European Commission. The structure is applicable to national projects, and the paper presented here may be seen as a guideline to any group about to set up a facility to perform BNCT at a reactor site. The next step would be a recommendation to write a documented guideline for BNCT trials.

ACKNOWLEDGEMENTS

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Introducing BNCT treatment in new treatment facilities

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Abstract. The physical and radiobiological studies that should be performed before the initiation of BNCT are discussed. The need for dose-escalation versus response studies in large animal models is questioned. These studies are time consuming, expensive and legally difficult in some countries and may be dispensable.

Considerable effort is being made, in different countries, to construct new neutron sources for boron neutron capture therapy (BNCT) with epithermal neutrons. Due to the particular properties of the production of neutrons, which differs between each of the facilities, it is very pertinent to ask when such a facility can be used for treating patients. This question is of fundamental importance for giving a positive answer to the question whether the treatment of a patient is ethically permissible. The potential harm inflicted to the patient must be seen in relation to the severity of the disease and the potential impact of the treatment on the course of the disease.

New treatment modalities need to be tested for their potential damage to healthy tissue. In clinical trials, this is usually done by dose escalation schemes. This is usually carried out in a Phase I clinical trial. The dose (of, e.g., a chemotherapeutic agent) is increased stepwise from a level known to induce only minor damage in animals, until dose-limiting toxicity signs are found in patients. The maximum tolerated dose in animals is usually backed off from considerably when entering a new chemotherapeutic agent in clinical Phase I trials.

In radiotherapy, the same principle pertains. Here, radiation dose is increased step-wise. Due to the fact, however, that prior radiotherapy of the healthy tissue exposed might result in a reduced tolerance to additional exposure, BNCT can in most cases only be applied when no prior treatment with radiotherapy has been done. This is different from most Phase I trials with chemotherapeutic agents. In order to ethically justify the exchange of a proven radiotherapeutic treatment with an experimental treatment, the dose level prescribed must be close to the limit of exposure for the tissues to be exposed.

In many of the tissues exposed to damaging conditions, the effect of the damage is often only seen after long observation periods, and sometimes without early warning signs. Especially in the tissue of the CNS, damage occurs with lag times of many months. It was therefore considered essential that realistic models for damage to healthy CNS tissue were tested prior to the initial treatment of patients. These studies comprised of a great number of large animals which were observed for over a year, or until they developed significant life-deteriorating damage. For the facility at the High Flux Reactor of the Joint Research Centre in Petten, The Netherlands, 42 dogs were entered into this study[1]. The study took around two years to be completed. The study resulted in a safe radiation dose for the treatment of the first group of patients in protocol EORTC 11961. At the same time, the starting radiation dose for the trial was high enough to expect some effect on the treated disease.

Clearly, a program in which large animals are treated prior to the treatment of patients, is extremely costly, and difficult to implement. Furthermore, it would require that a clinical study in patients is started only several years after the completion of a facility. It would therefore be of great value if ways could be found how to avoid the performance of such a

study. Its ethical justification is poor unless all information concerning past experiences from all sources has been collected and analysed.

It is therefore suggested here that all available information on the physical properties and radiobiological effects of the neutron sources should be collected.

Specifically, information about the following radiobiological aspects of BNCT in epithermal neutron beams should be brought together and exchanged:

(a) physical dosimetry and geometry of the beams free in air

(b) dosimetry in the different experimental set-ups c. through f.

(c) dose-response functions from cell culture experimental models

(d) dose-response functions from experiments in small animal models

(e) dose-response functions from experiments in large animal models

(f) dose-related effects of patient treatment

The items a. through e. are the steps achieved so far in all epithermal neutron beams used for patient treatment.

Inter-comparison between the physical properties and the radiobiological effects of fully tested neutron sources might serve as a predictive tool for new, or not yet fully tested neutron sources.

A predictive tool will require a few assumptions, which ideally should be tested experimentally. Until such experiments are carried out and resulted in appropriate conclusions, the data already available should be tested for the following hypotheses:

(1) Are doses in BNCT additive when multiplied by uniform RBE/CF values?

(2) In larger organs, are doses best represented by point values or by volume-integrated values?

With a predictive tool, the investigation of the radiobiological effect of new neutron sources, which is expensive, time-consuming, and legally as well as ethically problematic, might be considerably reduced. The time lag between finalising a neutron source and making use of it for the benefit of patients might thereby be shortened.

In addition, information will be gained how the increase of the boron concentration in healthy tissue might effect the total radiation dose which can be delivered safely.

It should therefore be the aim of future exchange and discussions to evaluate whether the above steps a. through d. might be sufficient to allow the initiation of patient treatment with all reasonable safety for the patient. If this is the case, step e. could be avoided. This would have great beneficial impact for the initiation of the treatment of patients, as step e. is very time-consuming, very expensive, legally difficult in some countries, and ethically problematic.

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Annex 4
BEAM DELIVERY

Epithermal neutron beam for BNCT research at Washington State University

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Abstract. A new filter has been designed and analysed for the Washington State University TRIGA™ research reactor. Optimum balance of epithermal flux and background KERMA was obtained with a Fluental™ and alumina filter. The epithermal neutron flux calculated by the DORT transport code was approximately 9×10^{8} n/cm^2–s with a background KERMA of about 3×10^{-13} Gy/n/cm^2. Operation of the beam for animal testing is expected to commence in 2000.

1. INTRODUCTION

Veterinary radiation oncology researchers at the Washington State University (WSU) School of Veterinary Medicine have made major contributions to the understanding of the *in vivo* radiobiology of Boron Neutron Capture Therapy (BNCT) over the years. For example, the large animal model studies of normal brain tissue tolerance in BNCT conducted by this group [1] provided a key component of the radiobiological basis for the resumption in 1994 of human BNCT trials in the US. Those studies used the epithermal-neutron beams available at Brookhaven National Laboratory and at the Petten facility, in The Netherlands, with technical support form the Idaho National Engineering and Environmental Laboratory (INEEL) in several areas of physics, biophysics, and chemistry. Recent attention has been focused upon the development of a more convenient and cost effective local epithermal-neutron beam facility for BNCT research and boronated pharmaceutical screening in large animal models at WSU. The design of such a facility, to be installed in the thermal column region of the TRIGA™ research reactor at WSU, was performed in a collaborative effort [2,3] of WSU and the INEEL. Construction is now underway.

2. FACILITY DESCRIPTION

Figure 1 shows an overall plan of the WSU research reactor facility. The new epithermal-neutron beam extraction components will be located in the thermal-column region of the reactor-shielding monolith. The original graphite has been removed from this region and is being replaced with a new epithermal-neutron filtering, moderating, and collimating assembly as shown in Figure 2. The 1MW reactor core is suspended from a movable bridge above the pool. It can be positioned directly adjacent to a hollow truncated aluminum cone that extends horizontally into the reactor pool from the tank wall on the upstream side of the filtering and moderating assembly. Neutrons emanating from the core travel into the filtering and moderating region. The spectrum is tailored in this region such that most neutrons emerge

with energies in the epithermal energy range (0.5 eV – 10 keV). Downstream of the filtering and moderating region is a bismuth and lead gamma shield, followed by a conical neutron collimator composed of bismuth surrounded by lithiated polyethylene. Provision is made for several different exit port aperture sizes as shown. A heavily shielded concrete beam stop and treatment room will be located just outside of the thermal column opening in the reactor shield wall, as shown in Figure 3.

A key distinguishing feature of the WSU facility is the use of a new, high efficiency, neutron moderating and filtering material, Fluental^{TM}, developed by the Technical Research Centre of Finland [4]. Fluental^{TM} is manufactured by hot isostatic pressing of a mixture of 69% (by weight) aluminium fluoride, 30% aluminium, and 1% lithium fluoride. A block of this material, having a thickness in the beam propagation direction of 0.64m and transverse dimensions of approximately 0.6m, is surrounded by aluminium oxide to produce the neutron filtering and moderating region shown in Figure 2.

3. PERFORMANCE ESTIMATES AND DISCUSSION

DORT [5] radiation transport design calculations for the coupled core and filter-collimator assembly indicate that an epithermal neutron flux of approximately 10^9 n/cm^2-s at a reactor power of 1 MW will be produced at the exit port of the collimator. The background neutron KERMA (a measure of the fast-neutron contamination) for the beam is calculated tobe approximately 3×10^{-13} Gy/n□cm^2. The calculated neutron spectrum at the collimator exit port is shown in Figure 4. The computational methods used for this design were previously validated against measurements performed for a similar neutron beam facility that is already

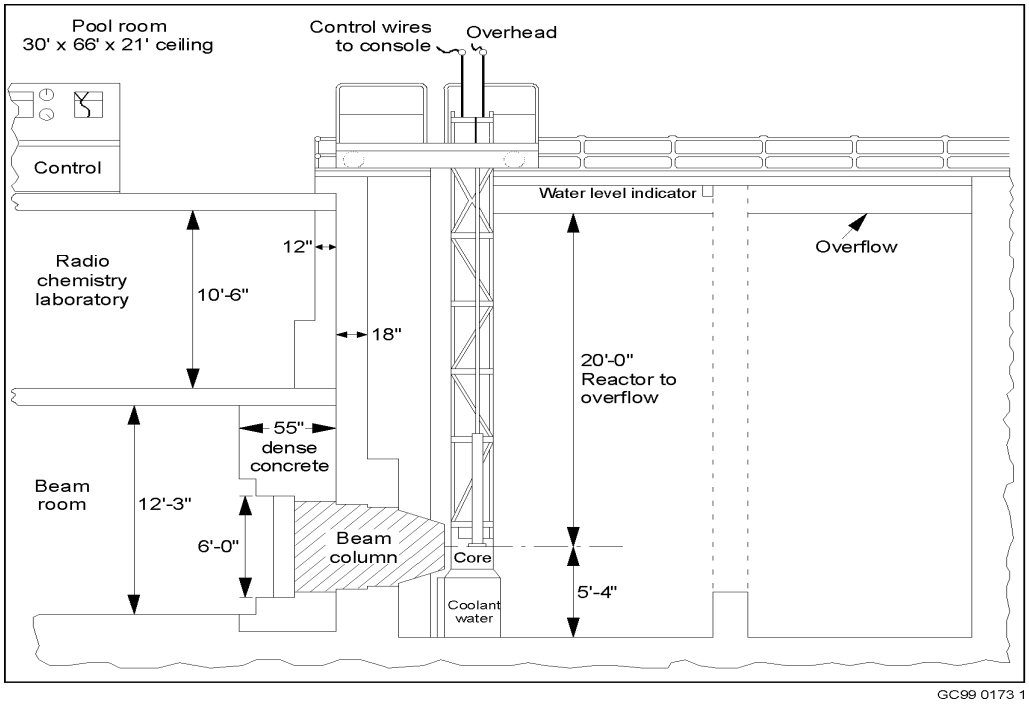

Figure 1. Elevation plan sketch of the Washington State University Research Reactor.

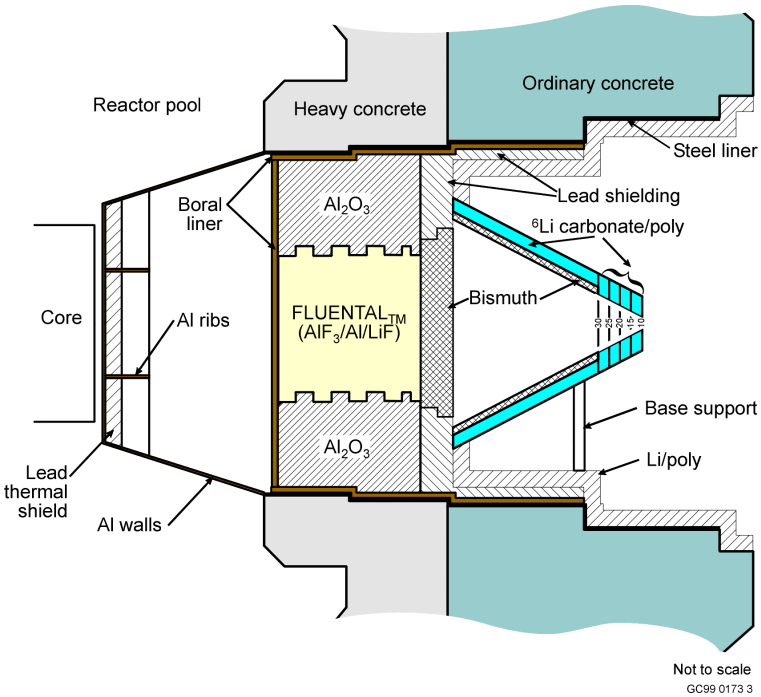

Figure 2. Washington State University column assembly with epithermal-neutron filter.

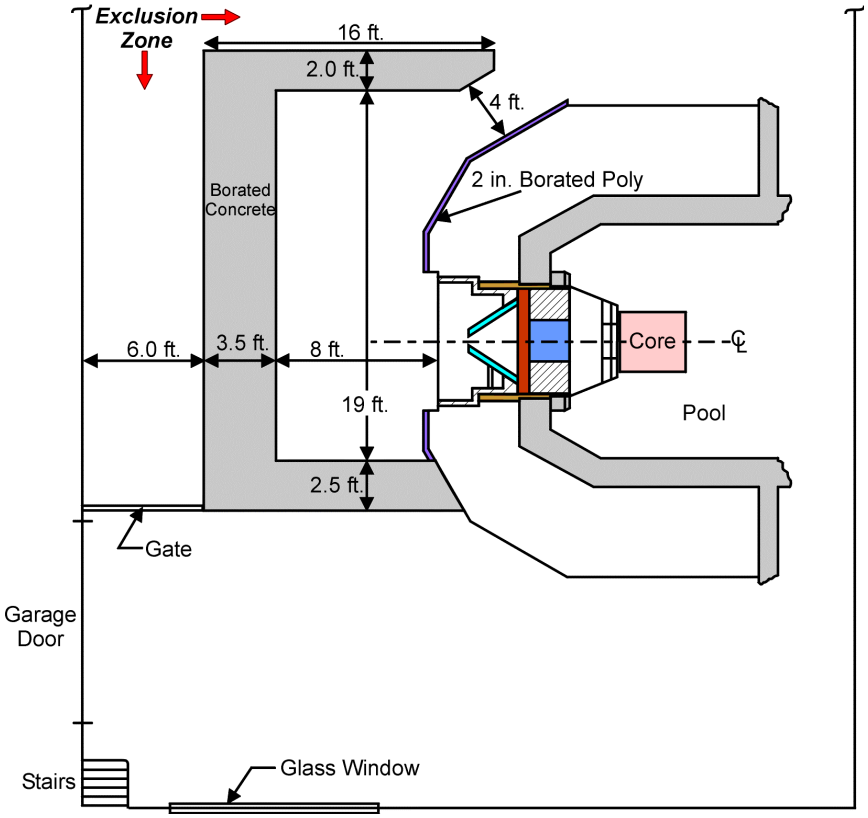

Figure 3 Approximate WSU beam stop layout.

in operation at the FiR1 TRIGA™ research reactor in Finland [6]. Additional validation calculations for the WSU application were performed using the MCNP [7] Monte Carlo code.

An additional key feature of the WSU beam facility design is the provision for adjustable filter-moderator thickness to systematically explore the radiobiological consequences of increasing the fast-neutron contamination above the nominal value associated with the baseline system described above. This is an important clinical issue for BNCT. Thinner filter/moderator arrangements will produce epithermal beams having correspondingly harder spectra and greater levels of fast-neutron contamination. The components shown in Figure 2 are designed for relative ease of disassembly and re-assembly compared to other reactor-based epithermal-neutron facilities that are currently in operation. Thus it will be possible to have a number of different filter/moderator arrangements over the life of the facility.

Construction of the new WSU beam facility was started in 1998 with initial testing scheduled for late 1999. Operation for animal research applications is anticipated in 2000 and beyond. The WSU facility will be the third clinical-scale epithermal-neutron source for BNCT research in the US.

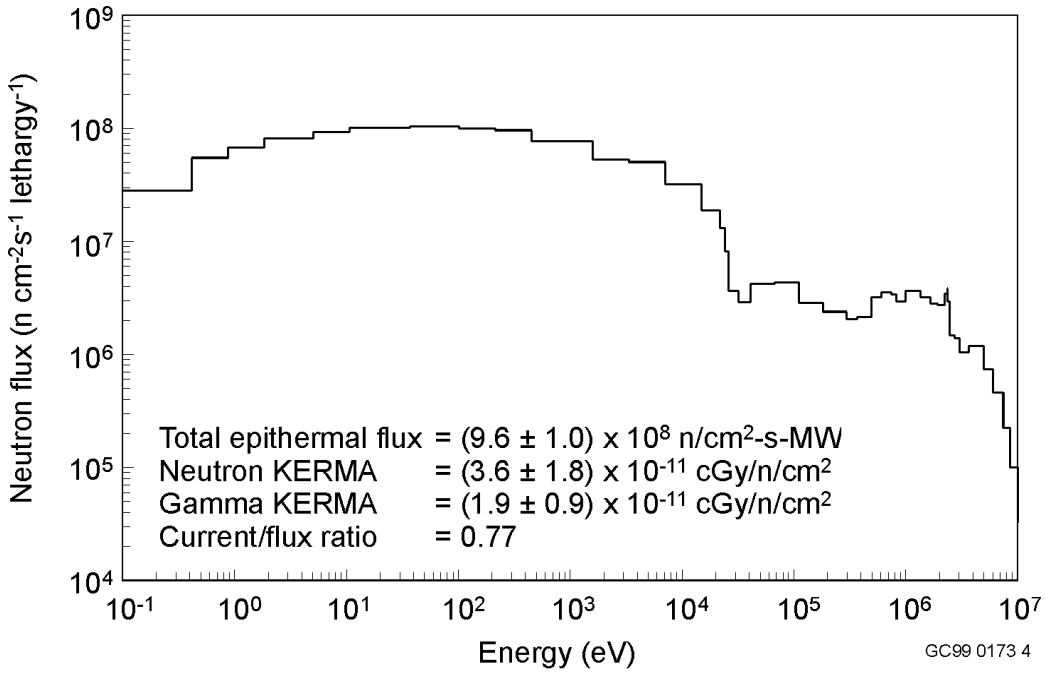

Figure 4. Calculated WSU epithermal neutron beam neutron spectrum at the collimator exit.

ACKNOWLEDGEMENT

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Design of neutron beams for boron neutron capture therapy in a fast reactor

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Abstract. The BNCT (Boron Neutron Capture Therapy) technique makes use of thermal or epithermal neutrons to irradiate tumours previously loaded with ^{10}B. Reactors are currently seen as a suitable neutron source for BNCT implementation, due to the high intensity of the flux they can provide. The TAPIRO reactor, that is located at the ENEA Casaccia Centre near Rome, is a low-power fast-flux research reactor that can be useful employed for this application. In this work computer simulations were carried out on this reactor to obtain epithermal and thermal neutron beams for the application of BNCT in Italy in the framework of a specific research program. Comparisons with measurements are also reported. Using the MCNP-4B code, Monte Carlo calculations were carried out to determine the materials suitable for the design of the thermal and epithermal columns. Various arrangements of reflector and moderator materials have been investigated to achieve the desired experimental constraints. On the basis of these calculations, a thermal column was designed and installed in the TAPIRO reactor to perform preliminary experiments on small laboratory animals. For the planning of a therapy treatment of gliomas on larger size animals, several material configurations were investigated in the search for an optimal epithermal facility. The aim of the present study is to indicate how a fast research reactor can be successfully modified for generating neutron beams suitable for BNCT applications.

1. INTRODUCTION

Cancer treatments are faced with the crucial problem to selectively preserve healthy tissue and to eradicate all malignant cells. To this aim, Boron Neutron Capture Therapy (BNCT) seems to have good prospects. BNCT is a highly-selective binary technique for the treatment of localised infiltrating cancers, such as grade III and IV gliomas in the human

brain. BNCT is based on the $^{10}B(n,\alpha)^{7}Li$ reaction that occurs when a non-toxic boron compound is selectively taken up by tumour cells and irradiated with thermal neutrons. The high-LET α particle emitted, having a range of about one cell diameter, allows specific cell killing in the host tissue to be achieved.

One of the major problems raised by the BNCT technique is to obtain a suitable beam of neutrons in terms of intensity and energy spectrum. The neutron flux must meet several requirements simultaneously. The preferred characteristics of the neutron beam are:

- high thermal neutron flux intensity at the tumour site for reducing the irradiation time;
- low high energy neutron component for sparing the healthy tissue;
- low gamma ray dose;
- high forward component (current to flux ratio).

A thermal neutron beam can be very effective for the treatment of surface tumours such as skin melanoma, but it cannot be used for the treatment of deep pathologies, due to its limited penetration depth. Neutron sources providing an epithermal spectrum ranging from 0.4 eV to 10 keV are being considered for clinical use for the treatment of deep-seated tumours such as gliomas.

Reactors are currently seen as the most suitable type of neutron source for BNCT implementation, due to the high intensity of the flux they can provide. In the framework of a specific national research program [1] the irradiation experiments on animal tumours are planned in the TAPIRO fast research reactor [2]. For this purpose the feasibility to obtain suitable neutron beams in the main experimental column of the TAPIRO reactor is investigated by means of Monte Carlo simulations. Firstly the neutron spectrum exiting from the reactor reflector was calculated with MCNP — version 4B [3]. The simulation results were compared with experimental measurements performed with a set of Bonner spheres.

Then a thermal neutron irradiation facility (composed of layers of graphite) was designed and installed in the reactor to perform preliminary experiments on small laboratory animals. Finally, an epithermal column was designed using MCNP to simulate several moderator, reflector and shielding configurations to arrive at the final model, using the DSA technique for variance reduction (see for example [4]). In order to have a flexible arrangement of the facility, the thermal and the epithermal columns are arranged on two different trolleys, which can be separately driven into the cave of the borate concrete shield, depending on the required experimental condition.

In this work, the design of a modification to the low-power fast-flux reactor TAPIRO to provide optimised neutron beams is presented.

2. THE TAPIRO REACTOR

The TAPIRO reactor, that is located in the ENEA Casaccia Centre near Rome, is a highly enriched uranium-235 fast neutron facility. Since 1971, it has been used for fast reactor shielding experiments, biological effects of fast neutrons, etc. [2]. A sketch of the reactor is shown in Figs. 1 and 2.

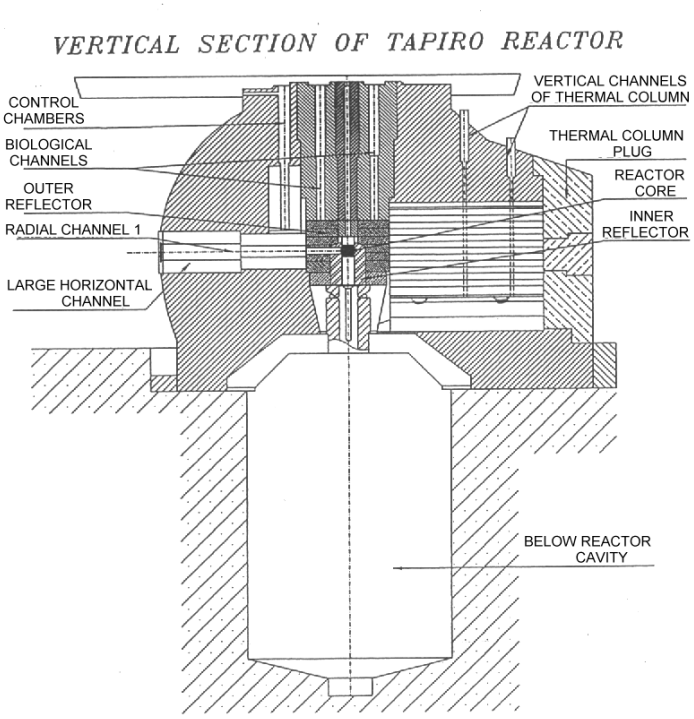

FIG. 1. Vertical section of the TAPIRO reactor.

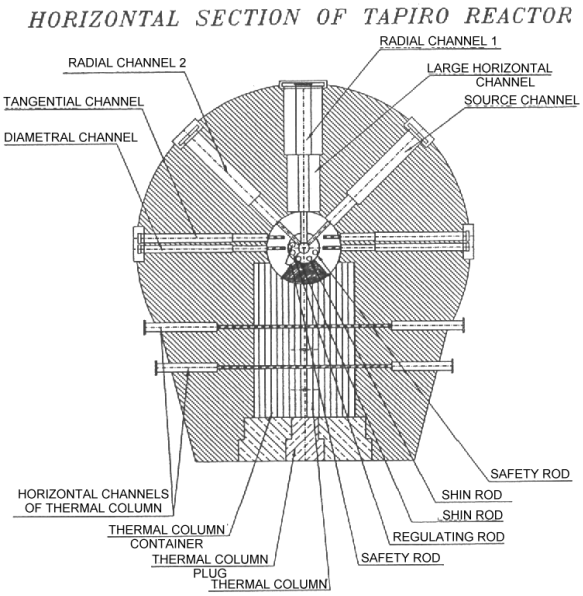

FIG. 2. Horizontal section of the TAPIRO reactor.

The nominal power is 5 kW (thermal) and the core centre neutron flux is 4×10^{12} $cm^{-2}\cdot s^{-1}$**.** The reactor has a cylindrical core (12.58 cm diameter and 10.87 cm height) made of 93.5 % enriched uranium metal in a uranium-molybdenum alloy (98.5 % U, 1.5 % Mo in weight) which is totally reflected by copper. The copper reflector (cylindrical-shaped) is divided into two concentric zones: the inner zone, up to 17.4 cm radius, and the outer zone up to 40.0 cm

radius. The height of the reflector is 72.0 cm. The outer zone of the reflector contains a removable sector which was filled with alumina (Al_2O_3, density 1.3 g/cm^3) (the “alumina window”). The reactor is surrounded by borate concrete shielding about 170 cm thick.

3. CALCULATIONAL TECHNIQUE: MCNP AND DSA

Monte Carlo is one of the most powerful instruments available to design BNCT facilities. The main reason for its advantage over deterministic methods is its capability to represent complex geometry and to model radiation streaming. It is also able to faithfully model the basic neutron cross-section data. However by its very nature, Monte Carlo can only estimate a response to some statistical error; the more differential a response in space, energy or angle, the higher this error. If we wish to calculate a neutron spectrum in reasonable detail, this requires estimating a large number of fluxes, each occupying a narrow energy group. Consequently the statistical error may be large.

Analogue Monte Carlo means, within the constraints of the cross-section data and of the geometrical model, a simulation of reality. With analogue Monte Carlo, the source-detector attenuation may be so large that no neutrons actually score, or so few neutrons that the statistical error is too high. Under these circumstances techniques called "variance reduction methods" provide a lower statistical error in a given computing time. A variety of such methods exist; they can be divided into two general classes: biasing and population control methods. Each variance reduction method requests a range of user-defined parameters and for a given response there exist an optimum set of parameters that provides a minimum statistical error in a given computing time. Parameters that are near optimum for one response may be far from optimum for another response. Thus although standard Monte Carlo methods may treat problems involving a high attenuation, they do so only by calculating a single response at a time. The DSA (Direct Statistical Approach), which has been under development for many years [4], aims to optimise splitting and Russian roulette parameters employed in control of the track population in both space and energy. An important characteristic is that, by means of a single integral parameter (the "quality factor"), the DSA allows the user to evaluate during the iterative optimisation procedure when he has reached the region of the optimum. The DSA currently employs as vehicle the widely used code, MCNP-4B. The DSA provides a way to optimise a calculation to more than one response of interest. In practice in a given computing time, the sum of the squares of the fractional errors of the responses is minimised; this for responses that may differ by orders of magnitude (as for example in a flux spectrum) or that may be in different units (a flux, a reaction rate, a dose, etc.) [5].

In the design of BNCT facilities we wish to know both the thermal, epithermal and fast components of the neutron flux spectrum in reasonable detail at the irradiation position, as well as the gamma ray dose. Thus the multiple response optimisation feature of the DSA is particularly appropriate to BNCT applications.

4. COMPARISON OF LEAKAGE NEUTRON FLUX MEASUREMENTS WITH MCNP RESULTS

After preliminary calculations performed by MCNP-4A [6], a more detailed simulation of the TAPIRO reactor was performed by MCNP-4B, in order to produce a final configuration. The nuclear data file used was based on ENDF-B/6.

No direct on-line measurement of the reactor power is available. Furthermore as the neutron flux leaking from the outer reflector of the reactor at the alumina window acts as a source term for the thermal and epithermal columns, it was considered important to make

experimental comparisons at this position so as to have some idea of the uncertainty of this source term. The experimental verification of the calculated neutron source term was carried out by making activation measurements. The purpose was to determine the neutron spectral fluence at the exit of the alumina window of the reactor. Neutron spectrometry was performed with a set of five Bonner spheres of different diameters, designed at the Nuclear Engineering Department of the Polytechnic of Milan. Gold foils were placed at the centre of the Bonner sphere moderator (polyethylene). Care was taken to exactly position the sphere on the axis of the neutron beam at the centre of the alumina window. The gamma activity of the irradiated foils was measured with a NaI (2"x2") scintillator. The neutron spectrum was then determined by an unfolding method. The data unfolding of the Bonner spheres was carried out with an iterative code based on the theories of spectra adjustment, as discussed in more details in [7]. At each step, the code aims to reduce the χ^2 arising from the experimental data, while limiting the modifications of the group fluxes with respect to the values of the previous iteration. The initial guess is a constant lethargy distribution; the maximum number of iterations is fixed in advance according to the accepted χ^2 value.

The results obtained are compared with Monte Carlo calculations that included a detailed description of the detector set-up, by modelling the complete configuration (reactor and Bonner spheres) in three dimensions with MCNP. In Fig. 3 a three dimensional vertical section of the facility obtained by means of the SABRINA code [8] is shown. Due to the lack of complete information on the composition of the concrete shielding, the influence of different compositions of the concrete shielding on the calculated reaction rates was investigated.

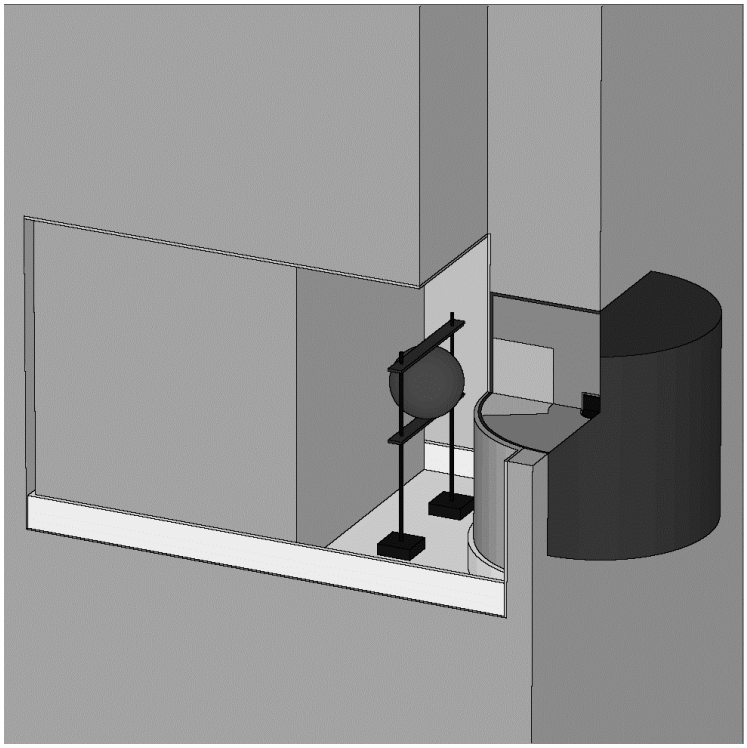

FIG. 3. Schematic 3-D view of the detector set-up (from right to left: cylindrical copper reflector, reactor core, alumina window, Bonner sphere on the iron trolley; all surrounded by the concrete shield).

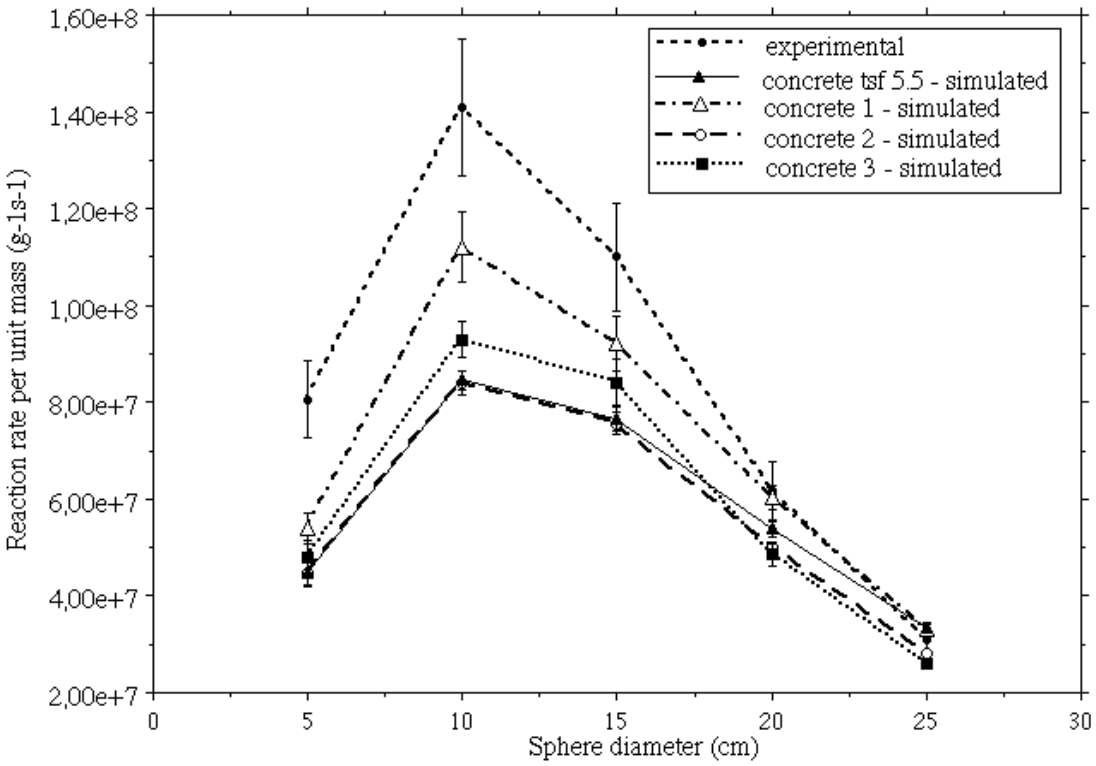

FIG. 4. Comparison between the experimental data and the MCNP calculations.

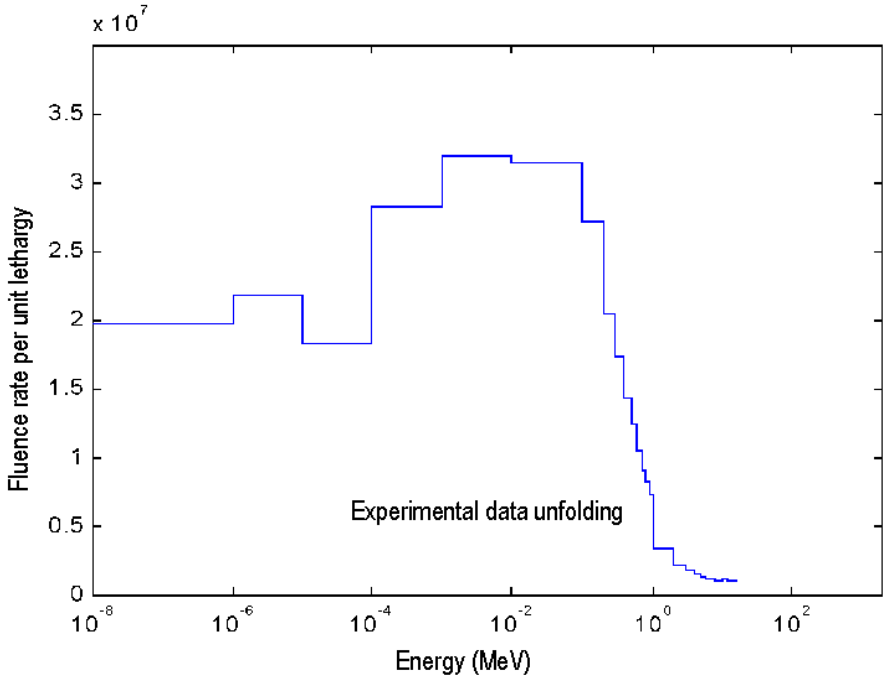

FIG. 5. Experimental spectral fluence at the alumina window position.

A comparison between the experimental data and the MCNP activation calculations is plotted in Fig. 4. Differences between calculated and experimental results were found:

especially for the two smallest spheres the calculations underestimated the results. The experimental spectral fluence at the alumina window position is shown in Fig. 5.

5. THE THERMAL COLUMN

Firstly a thermal column was designed and installed in the TAPIRO reactor to perform preliminary experiments in view of the planning of a therapy treatment of gliomas on small laboratory animals. MCNP-4B has been used to model the radiation transport of neutrons and photons within a number of different geometrical configurations. The simulations aimed to calculate a thermal flux (< 0.4 eV) inside a 18×18×18 cm^3 irradiation field which is located in the middle of the structure, inside a 13 cm thick lead γ-shield in order to have a very low γ-background. A schematic view of the moderating structure (composed of layers of graphite) is illustrated in Fig. 6.

Experimental studies are currently in progress to perform preliminary measurements of the spatial distribution of absorbed dose in small dosimeters placed at various locations inside a tissue-equivalent phantom at the irradiation field position in order to discriminate the contributions of the different components of the irradiation field.

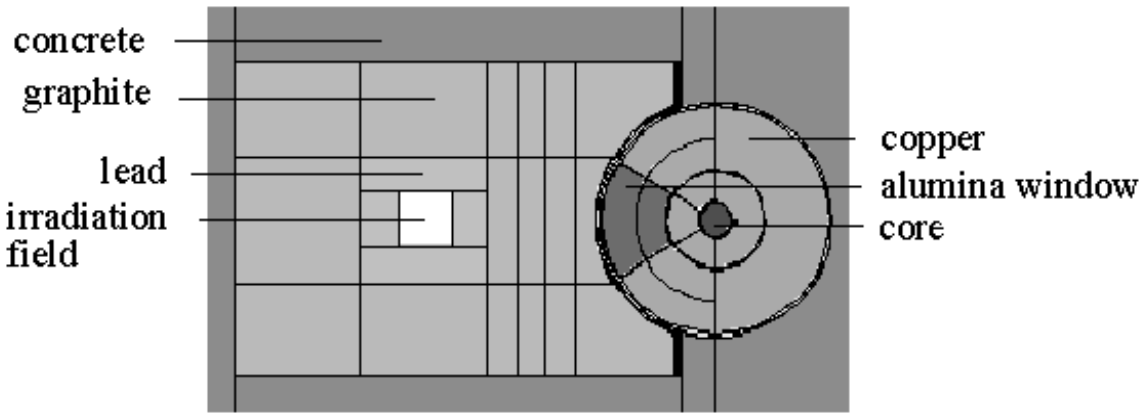

FIG. 6. Horizontal section of the thermal column.

6. EPITHERMAL COLUMN: RESULTS FOR DIFFERENT SPECTRAL SHIFTER CONFIGURATIONS

It is generally accepted by the BNCT research community that an epithermal neutron beam (energy range of 0.4 eV to 10 keV) with minimal contaminants from gamma rays and thermal (< 0.4 eV) and fast (> 10 keV) neutrons is desirable to treat deep-seated tumours because of its penetration and skin-sparing properties. The reference parameters required for an acceptable BNCT beam are summarised as follows [9]:

⇒ *epithermal flux*: "as high as possible" but in any case higher than 5×10^{8} $cm^{-2}\cdot s^{-1}$;
⇒ *fast neutron kerma*: less than 5×10^{-13} $Gy\cdot cm^2$ per unit epithermal neutron flux;
⇒ *gamma kerma*: less than 3×10^{-13} $Gy\cdot cm^2$ per unit epithermal neutron flux.

An extensive parametric study of the moderating and shielding materials was carried out in order to obtain the near optimum epithermal neutron beam performances. Several material configurations have been investigated using MCNP-4B to achieve the desired experimental conditions. The maximum depth available for the epithermal column is 160 cm (distance from

the external surface of the reflector), reserved for filter/moderator materials and including the irradiation chamber to be simulated. The general configuration for the simulations is shown in Fig. 7.

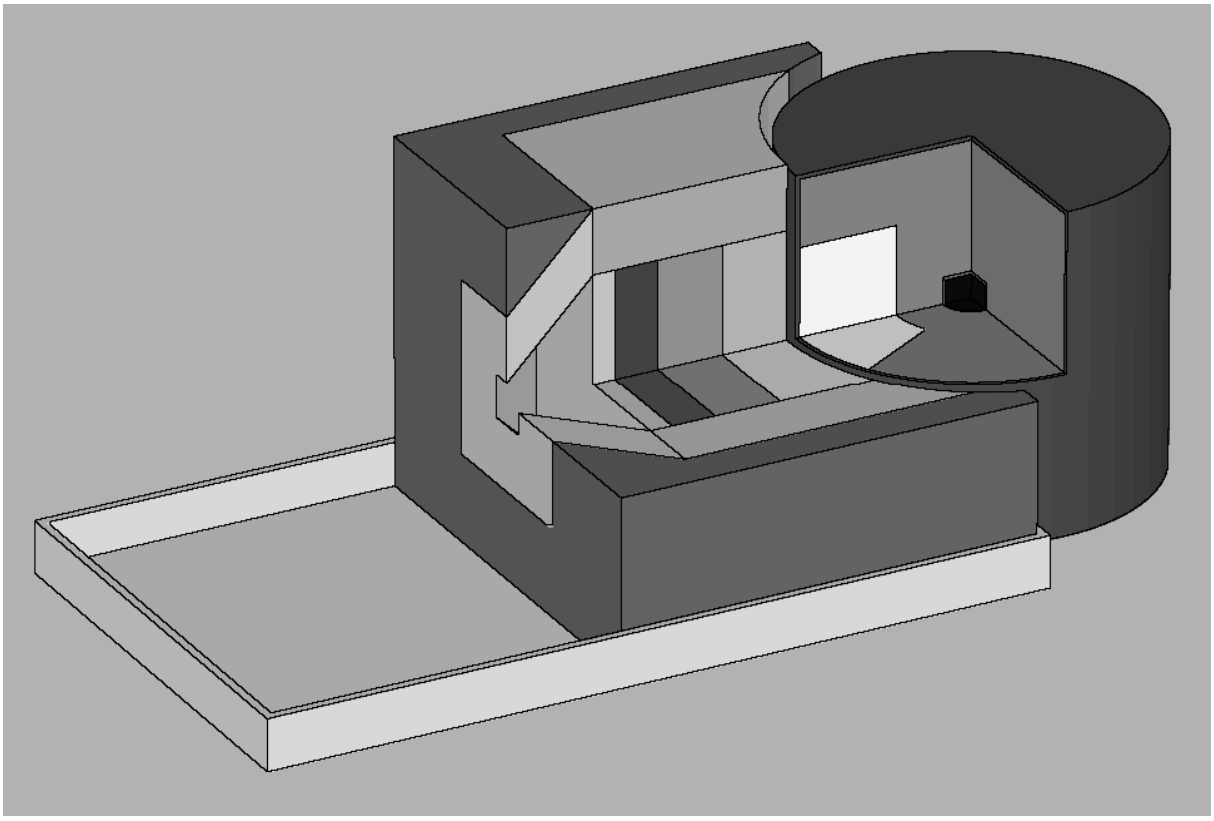

FIG. 7. D section of the epithermal column (from right to left: cylindrical copper reflector, reactor core, alumina window, moderators surrounded by the nickel reflector, lead gamma shield and collimator; all surrounded by the concrete shield and located on the iron trolley).

The following data have been calculated at the exit of the collimator, averaged over a 10×10 cm^2 irradiation surface:

- thermal, epithermal and fast neutron flux components;
- mean cosine of the angle between the neutron direction and the normal to the surface;
- fast neutron kerma in water ($Gy \cdot s^{-1}$), divided by the neutron epithermal flux ($cm^{-2} \cdot s^{-1}$);
- gamma kerma in water ($Gy \cdot s^{-1}$), divided by the neutron epithermal flux ($cm^{-2} \cdot s^{-1}$).

Various materials for use in designing a moderator for a medical epithermal beam were investigated. Epithermal neutron beams of adequate intensity and quality for therapy may be achievable by use of filter/moderators such as Al/AlF_3 and $CF_2/AlF_3/Al$, which produce broad-spectrum epithermal neutron beams because of their greater attenuation of fast than of epithermal neutrons. Further downstream after the filter/moderator region, there is a 0.4 mm-thick cadmium thermal neutron shield, a 5 cm-thick lead gamma ray shield, followed by a lead collimator. The entire structure is surrounded by a nickel reflector of 15 cm thickness. Outside the reflector there is heavy borate concrete. With regard to the CF_2 some doubts exit because it seems that neutron irradiation could damage this material.

The MCNP calculation results are summarised in Table I. The best results so far were obtained with the configuration (5).

Neutron spectra from configurations (4) and (5) are plotted in Fig. 8. The comparison between these two cases shows the influence of the AlF_3 density on the neutron spectra, above all on the fast component.

Table IV. MCNP calculation results at the exit of the beam collimator for different moderator configurations

	Φ_{th} ($cm^{-2}\cdot s^{-1}$)	Φ_{epith} ($cm^{-2}\cdot s^{-1}$)	Φ_{fast} ($cm^{-2}\cdot s^{-1}$)	Fast neutron kerma /Φ_{epith} ($Gy\cdot cm^2$)	Gamma kerma/Φ_{epith} ($Gy\cdot cm^2$)
(1) AlF_3 (25 cm) Al (15 cm)	5.66×10^{6}	3.02×10^{9}	5.19×10^{8}	6.50×10^{-13}	8.15×10^{-14}
(2) CF_2 (5 cm) AlF_3 (15 cm) Al (20 cm)	6.82×10^{6}	2.64×10^{9}	3.88×10^{8}	5.30×10^{-13}	1.01×10^{-13}
(3) CF_2 (10 cm) AlF_3 (15 cm) Al (15 cm)	7.46×10^{6}	2.33×10^{9}	2.46×10^{8}	3.95×10^{-13}	1.08×10^{-13}
(4) AlF_3 (40 cm)	5.89×10^{6}	2.76×10^{9}	3.85×10^{8}	5.65×10^{-13}	1.05×10^{-13}
(5) AlF_3 (40 cm)	7.73×10^{6}	2.52×10^{9}	2.30×10^{8}	3.62×10^{-13}	1.06×10^{-13}
Target parameters		*> 5×10^{8}*		*< 5×10^{-13}*	*< 3×10^{-13}*

(1), (2), (3), (4): AlF_3 density = 1.4 g/cm^3 - (5): AlF_3 density = 1.7 g/cm^3

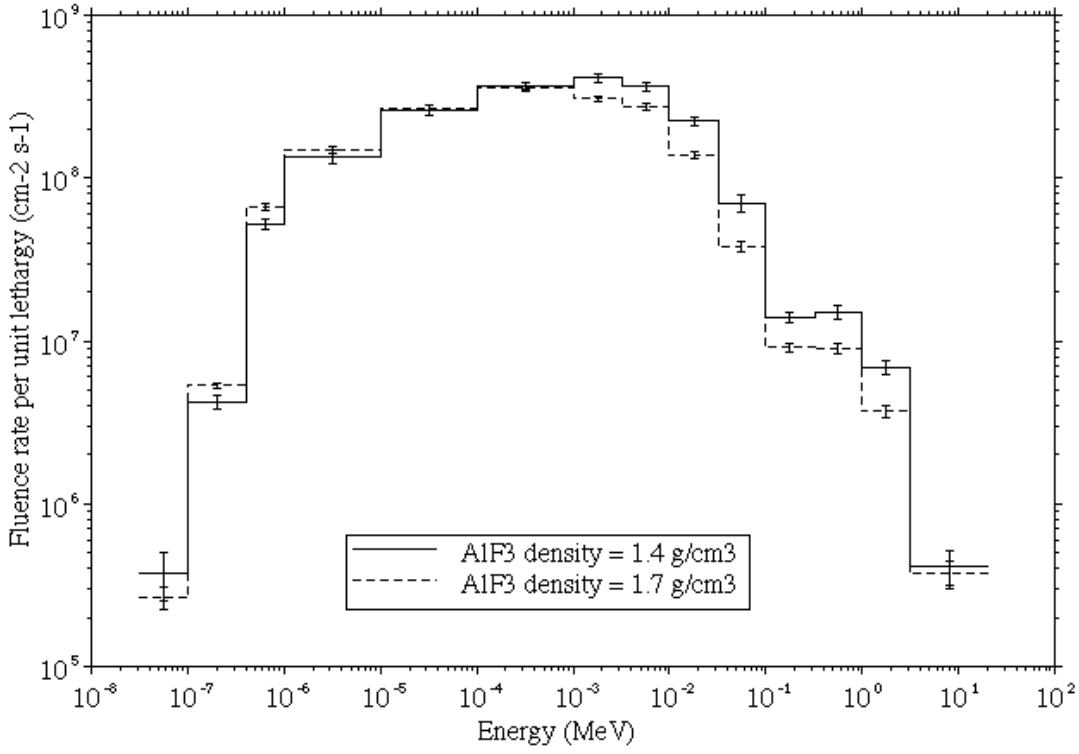

FIG. 8. Neutron spectra at the collimator exit: dotted line configuration (5), continuous line.

7. CONCLUSIONS

This work confirms that the low-power fast-flux reactor TAPIRO could be modified and usefully employed for BNCT applications. In this study the BNCT requirements on the neutron intensity, the neutron spectrum and the dose rates were simultaneously taken into account.

With regard to the thermal column, experimental studies are currently in progress to perform preliminary measurements at the irradiation field position of the designed thermal facility in view of the planning of a therapy treatment of gliomas on small laboratory animals.

With respect to the epithermal column, AlF_3 and CF_2 seem to be good moderators; the epithermal flux level is sufficient to reach target parameters notwithstanding the fact that the TAPIRO reactor power is much smaller than that of thermal experimental reactors (e.g. a 1 MW TRIGA). The MCNP calculations show that an epithermal column could be installed in the TAPIRO reactor; before the end of the year the designed epithermal facility will be constructed and the reactor will be used as a neutron source to perform significant experiments first on brain phantoms and then on laboratory animals.

In order to have a flexible arrangement of the facility, the thermal and the epithermal columns are arranged on two different trolleys, which can be separately driven into the cave of the borate concrete shield, depending on the required experimental condition.

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The experience from the construction of BNCT facility at the LVR-15 reactor

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Abstract. The BNCT project at LVR-15 reactor of NRI for treatment of human brain gliomas is before start of clinical trials. A survey of present conditions is included, the attention is devoted to BNCT facility with epithermal neutron beam first of all. The different materials for filter composition were studied, the calculational methods have been used for the determination of neutron and gamma rays in the reactor geometry. Some configurations were experimentally verified. The effort for improvement of epithermal neutron beam parameters in configuration 1998 was concentrated to block of filters remodelling, improvement of collimator-shutter geometry, the choice of optimal reactor core edge configuration. Awaited results from experiment in June 1999 are described.

1. INTRODUCTION

The BNCT interdisciplinary group in the Czech republic decided as a first priority to initiate the glioma clinical trial at the LVR reactor of NRI. The principal aim now is to prepare the Phase I trial, to establish maximum tolerated dose by healthy tissue when irradiating with BSH drug. The activity has been concentrated in this final stage also on improvement of the parameters of the beam. The treatment protocol was prepared and put forward to corresponding authorities for approval.

2. BNCT PROJECT

The development and construction of BNCT facility were realised at **LVR reactor** of NRI Rez. The LVR-15 is a light water reactor with enriched fuel (36 %) and standard thermal power 10 MW. This, on commercial basis running reactor, is used for material testing experiments at water loops and rigs, for radio-pharmaceuticals production, irradiation of silicon crystals, for basic and applied research at horizontal channels, and for BNCT as a source of epithermal neutrons. A beam of epithermal neutrons has been constructed at the LVR empty space of thermal column as described in Fig 1.

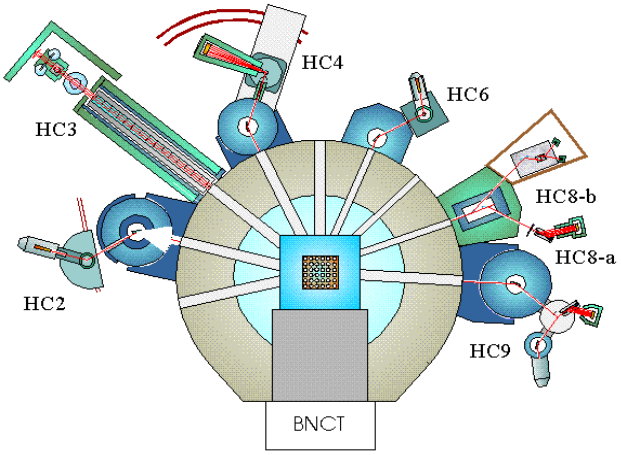

FIG. 10. BNCT at LVR-15 reactor.

The main drawback of our arrangements is a rather long distance between the core and irradiation point (about 4 m).Design principles and development of **epithermal beam** will be described in separate chapter. The monitoring system has been used for **physical dosimetry**, the information from detectors for both neutrons and gamma rays has been collected by an on-line system controlled by a program implemented on a PC. The **irradiation room** from concrete blocks covered by boronated polyethylene is equipped by laser alignment devices, TV camera, intercom, patient treatment table. Outer observation facilities, including PC, TV monitor, beam operating console, communications for patient are installed in **control room**. The internationally-recognised software MacNCTPLAN for computational dosimetry and **treatment planning** is utilised. A **prompt gamma analysis system**, PGA, has been designed and is operated for BNCT purposes at horizontal channel of LVR-15. Good agreement between PGA and standard ICP method was obtained, boron concentration 1 ppm in blood is measurable. The **Protocol** specifying treatment of glioblastoma with BNCT at the LVR has been prepared in details. The domestic supplier Katchem Ltd. is able to produce **boron compound** BSH (as well as L-BPA). The quality of the product is in the agreement with Test of quality control asked in EU project.

3. EPITHERMAL NEUTRON BEAM

For BNCT a high intensity and high quality epithermal neutron beam has to be designed. Low background contamination from fast neutrons and photons has to be reached. Both stochastic methods (as Monte Carlo MCNP code) as well as deterministic method (as TORT discrete ordinates code) can be used as computational tool.

3.1. General principles

Appropriate materials for **filter/moderator** have to offer high resonance scattering cross section in the fast energy range, low cross section in the epithermal range. The filter should absorb thermal neutrons, production of gamma has to be controlled. Acceptable cost of material is supposed. The materials have to be without decomposition in radiation field, without high long term radioactivity, without moisture during long time operation. The following materials as Al, C, S, Al_2O_3, AlF_3, D_2O, $(CF_2)_n$ — Teflon are often used. The combination Al with Al_2O_3 or AlF_3 is very efficient. Cross sections of elements F and O cover the valleys between resonance peaks of Al, due to light mass the moderation is very effective. The appropriate **reflector** can reduce transverse leakage out of the filter, it increases the intensity of the beam. The materials with high scattering cross section and high atomic mass (little energy loss) are used. The lead with low photon production and lower cost is preferred. For **thermal neutron filter** either elements ^{10}B and ^{6}Li with 1/v absorption cross section or Cd with 0.4 eV resonance are appropriate. **Gamma shielding** against fission gammas and gammas from inner parts as Ti, AlF_3, Cd close the configuration usually.

3.2. The configuration 1998

Several assemblies have been designed and experimentally tested during some last years with the aim to determine parameters both of the free beam and the beam inside the phantom [1]. The techniques used for measurement were described in the paper of La Jolla symposium [2]. The configuration 1998 is demonstrated in Fig.2. and described in [3]. Fast neutrons escaping the core and reflector are transported through the empty inner shutter (can be filled by water) to block of filters. Epithermal neutrons are collimated and transferred through the outer shutter to the irradiation point. The block of filters consists of B_4C thin layer, lead-5cm, ten layers aluminium and aluminium fluoride, total thickness 61 cm (35 cm Al, 26 cm AlF_3), lead-11 cm. There is 1 cm Ti and B_4C thin layer just behind Al-C collimator. The

characteristics of the beam measured in 1998 are rather low for clinical purposes (Φ_{epi} = 1.82 10^8 n/cm^{2}s for free beam, Φ_{th} = 4.82 10^8 n/cm^2 s, $D_{f.n.}$ = 0.625 Gy/h, D_γ = 1.87 Gy/h in the phantom at depth 2.5 cm).

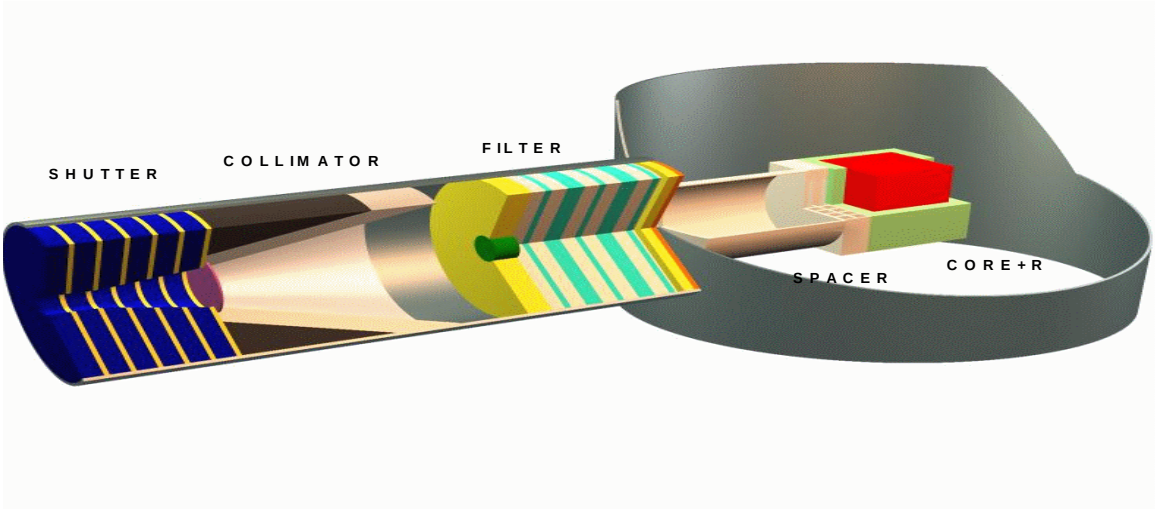

FIG.2. Epithermal neutron beam configuration 1998.

3.3. The configuration 1999

The irradiation time necessary to deliver the treatment dose to the patient at the LVR-15 BNCT facility of configuration 1998 is too long because of the low intensity of the epithermal beam. This was the reason leading to a re-designing of the filter. There are two facts which limit the design. First, the reactor LVR-15 is mostly used for the irradiation of material samples and therefore the core cannot be permanently changed in the way fully satisfying the BNCT requirements. Secondly, the budget which can be used for the new design is limited so that parts of the current filter have to be utilise as far as possible. The final design is therefore a compromise. There were two regions of possible changes which should improve the main characteristics of the beam: — remodelling of core edge, — the changes in the beam parts (filter composition, collimator, shutter).

3.3.1. The core edge

The computational study was realised for the evaluation of different configuration of the core edge. The four fuel elements, air spacers or Be reflectors can be placed to three rows from core to inner shutter. The five variants were taken into consideration, relative fast neutron density flux entering to shutter is understood as coefficient C.

VARIANT	1ST ROW	2ND ROW	3RD ROW	COEFF.
variant 1	air spacers	air spacers	air spacers	C=1
variant 2	Be. refl.	Be refl.	4 fuel el.	C=1.17
variant 3	Be refl.	air spacers	4 fuel el.	C=1.20
variant 4	air spacers	Be refl.	4 fuel el.	C=1.29
variant 5	air spacers	air spacers	4 fuel el.	C=1.56

The influence of the configuration is essential, variant 5 will be used for experimental verification.

3.3.2. The changes in the beam parts.

The **shutter** of configuration 1998 was composed from cylindrical and conical collimators of the total length of 60 cm. It was made of layers of lead and boronated polyethylene. The epithermal neutron flux decreased 80 times when passing through it. The new design of a conical shutter is only 25 cm thick and without the cylindrical part, see Fig.3. Material composition of the walls of conical cavity should ensure a good reflection and low absorption of the epithermal neutrons. Aluminium was supposed to have a good reflective abilities and also to be able shift interacting fast neutron to the epithermal region. As an alternating material lead was also studied. The results shows that the replacement of the 5 cm aluminium by the same thickness of lead resulted in the increase of the epithermal flux by 34%. Additional increase of the wall to 10 cm of lead increased the epithermal flux by 58%. The fast neutron dose ratio to the epithermal neutron was by 5% less in the first case and by 25% in the second.

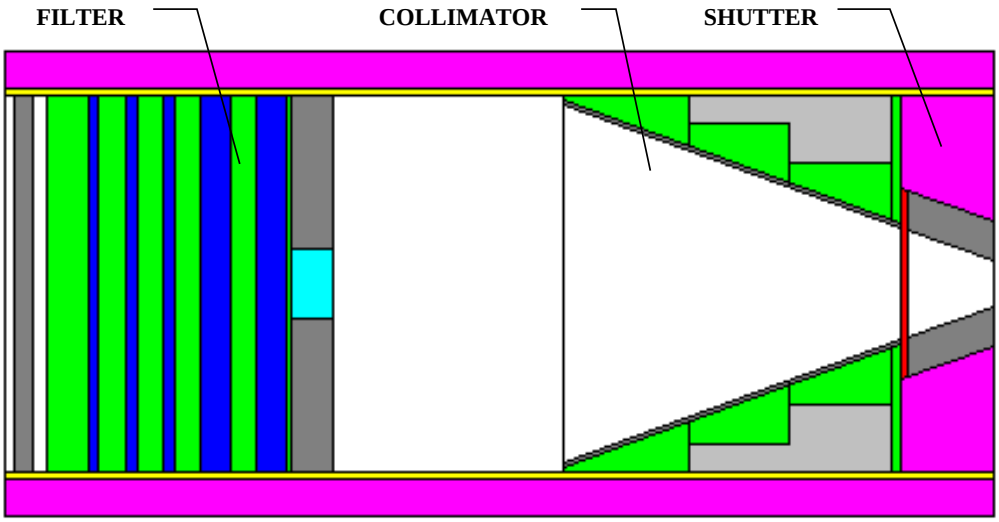

FIG.3. Epithermal neutron beam configuration 1999.

The **beam collimator** is a conical type made of aluminium, the length of it is 90 cm and the diameter changes from 100 cm to 30 cm. To improve its reflecting abilities we tested influence of lead on the inner surface of the collimator. A lead layer of thickness of 10 cm instead of aluminium one resulted in increase of the epithermal neutron flux by 38 %. Even an additional 1 cm layer of lead on the aluminium surface of the collimator caused an increase of 5 %. In the first case the fast neutron dose ratio decreased by 10% and by 3% in the second one. Between the end of filter and the beginning of the collimator there is an empty cylindrical space of 62 cm thick and 1 m in diameter. In case the inner surface of the cylinder had been covered by a 5 cm thick layer of lead the epithermal flux increased by 10 % and fast neutron dose ratio didn’t change. In general, a lead layer of 5–10 cm thick on the reflecting surface in the collimating part of the beam filter caused an increase of the epithermal flux in the beam and lowered the fast neutron dose ratio.

In this stage we also tested the influence of material composition and geometrical arrangement of the **beam filter**. The beam filter consists of a cylindrical blocks of 1 m in diameter, the materials Al, AlF_3, S were considered. We tried to optimise the existing set of blocks to receive the maximum epithermal neutron fluxes with acceptable background of fast neutrons. During the study we received some interesting results for sensitivity different materials in our configuration. For example the adding 5 cm of Al at the beginning of the filter decreased epithermal flux by 20%, and 10 cm of Al by 35%. The ratio of fast neutron dose to epithermal neutron decreased by 8% and 30% respectively. Having extended the variant by a 15 cm sulphur block resulted in the reasonable decrease of the epithermal flux by 43% but the fast neutron dose ratio decreased only by 32%. The present heterogeneous design consists of the alternating blocks of Al and AlF_3, totally 40 cm of Al plus 25 cm of AlF_3.

4. CONCLUSION

The new configuration 1999 will be experimentally verified at the end of June. The essential increase of neutron beam parameters is awaited. It's supposed the irradiation time necessary to deliver the treatment dose to the patient at the LVR-15 BNCT facility will be acceptable, it enable the start of clinical trials.

ACKNOWLEDGEMENTS

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The remodelling outline of the neutron irradiation facility of the Kyoto University research reactor mainly for neutron capture therapy

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Abstract. The Heavy Water Thermal Neutron Facility of the Kyoto University Research Reactor (KUR, full power: *5* MW) was wholly updated in March 1996 mainly for neutron capture therapy (NCT). The performance as a neutron irradiation facility was improved using the epi-thermal neutron moderator of the aluminum-heavy water mixture (AI/D_20 = 80/20 in volume percent), the neutron energy spectrum shifter of heavy water whose thickness changed from 0 cm to 60 cm, and the thermal neutron filters of I mm-thick cadmium and 6.4 mm-thick boral plates. The clinical irradiation utilisation under the fill-power continuous KUR operation was realised employing both the Radiation Shielding System, and the Remote Carrying System for a patient. The safety and utility of the facility were improved due to the Safety Observation System. The KUR Advanced Irradiation System for NCT was organised.

1. INTRODUCTION

The Heavy Water Thermal Neutron Facility at the Kyoto University Research Reactor (KUR, full power: *5* MW) had been constantly utilised for several research fields such as physics, engineering, biology, medics, etc. since the first KUR criticality in June 1964 [1,2]. Fundamental study for neutron capture therapy (NOT) has been continued since 1970 at the KUR. For the physical and engineering research field, the following main results were obtained: (i) design and development of a clinical thermal-neutron irradiation field with low level gamma ray contamination [2], (ii) development of thermal-neutron shielding material using ^{6}LiF with low secondary gamma ray generation [3], (iii) establishment of a measurement method for ^{10}B concentration in tissue by (n, *r)* Prompt Gamma ray Analysis (PGA) [4], (iv) cell-level estimation method of absorbed dose for NCT *[5]*, etc.. These subjects were strongly connected with the thermal neutron irradiation technique and the estimation of ^{10}B absorbed dose in tissue, and were indispensable for the NCT study not only for the fundamental research but also for the clinical trial.

A clinical irradiation for NOT at the facility was carried out in May 1974 for the first time, and it has been regularly performed from February 1990. By November 1995, just before the remodelling, sixty-one clinical trials were carried out for about six years [6]. In the NOT clinical irradiation at the pre-updated facility, the startup and shutdown of the reactor was needed for setting of the patient, etc.. On these experiences, the update of the facility was requested by the clinical irradiation staffs and the users in the other research fields, so as to enable (1) the utilisation under the full-power continuous KUR operation for the increase of the opportunity for NOT clinical irradiation, (2) the utilisation of epi-thermal neutrons to improve the irradiation effectiveness for deep-seated tumour, and (3) the clinical irradiation concurrently with the experiments in the other research fields, etc. [7].

Moreover, the following problems of the old facility had been pointed out; (i) difficulty of the handling for the routine maintenance and checkup, and for the irregular damage, and (ii) risk of the leakage of the cooling light water for the heavy water tank, because of its structure that the heavy water tank was settled on the reactor tank with an 0-ring of about 2 m diameter by thirty-six stainless-steel bolts and the primary cooling water flew through a narrow channel between the both tanks. In regard to these matters, the necessity of the fundamental reconstruction of the whole facility became remarkably recognised, from the viewpoint of the safety and stability of the facility and its usage.

2. CONCEPTION FOR THE REMODELLING

The old facility had a high performance as a thermal neutron irradiation field. On the basis of keeping the advantages of the old facility, the main design subjects for the updated facility, Heavy Water Neutron Irradiation Facility (HWNIF), were chosen as described in the following sections. The design studies were performed mainly by simulation calculations using transport calculation codes for neutrons and gamma rays. The transport calculation codes of "ANISN" and "DOT 3.5" were used for one dimensional and two dimensional simulations, respectively. The proprieties of the simulation calculation codes and the calculation processes were confirmed from the comparison between the measured data and calculation results for the old facility [8].

2.1. Improvement in safety for the facility

From the standpoint of the improvement of the facility safety, the following subjects were carried out.

(1) The heavy water tank was separated from the reactor tank. A cooling system for the heavy water tank was newly settled on the tank. Due to this separation, an air gap was formed between the both tanks. In order to hold argon gas activated in the air gap, "Activated Argon Attenuation System" was installed.
(2) In order to protect the side surface of the reactor tank facing to the facility, and secure the primary cooling water channel for the reactor tank and the thermal shield, a cooling water jacket was newly settled on the reactor tank by welding.
(3) The whole of the HWNIF, from the heavy water tank to the outer lead layer, was made as one component. Exceptionally, the outer lead layer can be independently removed for the maintenance of the cadmium and boral filters, which were installed on the core-side of the outer lead layer.

2.2. Advanced neutron utilization for NOT

In the viewpoint of the advanced utilisation of neutrons in a biomedical field, three kinds of neutron irradiation fields, (i) mainly thermal neutrons, (ii) mix of thermal and epi-thermal neutrons, and (iii) epi-thermal neutrons, were studied according to the following subjects;

(1) the epi-thermal neutron moderator,
(2) the neutron energy spectrum shifter and the thermal neutron filter,
(3) the reflector element of the reactor core,
(4) the cooling water thickness between the reactor tank and the heavy water tank,
(5) absorbed dose distribution in a human body under epi-thermal neutron irradiation, and
(6) the clinical collimators for thermal and epi-thermal neutron irradiation.

2.3. NCT clinical irradiation under the full-power continuous operation

In order to utilize the KUR for NOT clinical irradiation under the continuous operation at the full-power of 5 MW, it is necessary to secure the condition that persons can work in the irradiation room under the KUR operation. A design criterion of the Radiation Shielding System was that a total dose equivalent rate of neutrons and gamma rays was less than 100 μ Sv/hr at the working area in the irradiation room. Moreover, in the viewpoint of the reduction of the working time in the irradiation room, the Remote Carrying System for a patient was

produced. A clinical collimator is settled on this system, then the positioning for the patient are possible outside of the irradiation room previously to a clinical irradiation.

2.4. The design goals of the HWNIF

The design goals for the HWNIF were set as listed below. The numerical values are proper for a free-in-air condition with no irradiated sample at the normal irradiation position, which corresponds to the central point of the bismuth layer surface. The neutron energy regions for thermal, epi-thermal and fast neutrons are defined to be below 0.6eV, from 0.6eV to 10keV and over 10keV, respectively.

(1) Thermal neutron irradiation field: Thermal neutron flux (fluence rate) is more than 3 x l0^9 n/cm^2/s, and the cadmium ratio for gold activation foil (thickness of gold foil is 50 μ m, and thickness of cadmium cover is 0.7 mm) is more than 1,000. The ratio of the incident gamma ray dose to thermal neutron fluence is less than 3 x 10^{-11} cGy/(n/cm^2). For the incident fast neutron dose, the incident ratio to thermal neutron fluence is less than 1 x 10–11 cGy/(n/cm^2).

(2) Mixed irradiation field of thermal and epi-thermal neutrons: Thermal neutron flux is more than 3 x 1 ~ n/cm^2/s, and epi-thermal neutron flux is more than 3 x 108 n/cm^2/s. For the incident gamma ray dose, the ratio is almost the same as that for the thermal neutron irradiation field.

(3) Epi-thermal neutron irradiation field: Epi-thermal neutron flux is more than 3 x 108 nlcm^2/s. The ratios of the incident gamma ray dose and fast neutron dose to epi-thermal neutron fluence are less than 3 x 10'~ cGy/(n/cm^2) and 1 x i0~'^{0} *cGy/(nlcin^2),* respectively.

3. THE HEAVY WATER NEUTRON IRRADIATION FACILITY

Figure 1 shows the outline of the HWNIF. The epi-thermal neutron moderator, the neutron energy spectrum shifter, the thermal neutron filters and the bismuth layer were installed in order from the core side. As the heavy water tank was settled not connectedly with the reactor tank, it can be removed together with the polyethylene layer and the lead layer outside of the tank. The cooling water jackets of 1 cm thickness are attached both to the reactor tank and the heavy water tank. The jacket plates are welded in order to avoid the cooling water leakage. The inner lead layer of 10 cm thickness and the outer lead layer of 20 cm thickness were settled for the gamma ray shielding. This inner lead layer is an effective shielding against the gamma rays from the core side under the maintenance work. Between the inner and outer lead layers, a polyethylene layer is inserted as a supplementary shield against fast neutrons.

3.1. The epi-thermal neutron moderator and the neutron energy spectrum shifter

The installation position of the epi-thermal neutron moderator was restricted to be the inside of the heavy water tank adjacent to the reactor core. From the design study results on priority of the safety and stability, the moderator was decided to be 80%/20% in the mixing volume-ratio of aluminum and heavy water, 60 cm in diameter, and 66 cm in thickness. The periodic structure of 20 mm-thick aluminum plates and *5* mm-thick heavy water gaps was decided, on the expectation of the heat removal by natural-convection. That is because (1) we had much experience for the utilisation and handling of aluminum and heavy water at the old facility, and (2) these materials had been considered as a moderator in some plans for the epi-thermal neutron irradiation field [9,10].

The neutron energy spectrum shifter was decided to be installed on the outside of the epithermal neutron moderator in the heavy water tank. The spectrum shifter is comprised of three shifter tanks of almost 70 cm diameter, whose thickness are 10, 20 and 30 cm in order from the reactor core side. The supply and drain of heavy water are possible independently for the respective shifter tanks. By the combination of “full” and “empty” of heavy water in the three shifter tanks, the total thickness of the heavy water layer can be controlled from 0 to 60 cm in 10 cm increments. The water shutter is a cylinder of 60 cm diameter and 30.5 cm thickness, and it is surrounded by the bismuth neutron scatterer of *5* cm thickness. The tanks of the spectrum shifter and the water shutter are made with 10 mm-thick aluminum plate.

3.2. The thermal neutron filters and the bismuth layer

The installation of two kinds of the thermal neutron filters, the cadmium filter and the boral filter, were decided. These energy characteristics for neutron absorption are different especially in the energy range from thermal neutrons to epi-thermal neutrons. The installation space for the neutron filters is 10 cm thick including the casing, due to those driving mechanisms. In order from the core side, the boral filter and the cadmium filter are arranged. The respective filter thickness are 1 mm and 6.4 mm. The cadmium filter is sandwiched with a 1 mm-thick aluminum plate (for the core-side) and a *5* mm-thick aluminum plate, for the increase in the mechanical strength. The filters can cover the area of 70 cm diameter for the fully-close case, according as the core-side surface of the bismuth layer is 60 cm diameter. The apertures of the both filters can be adjusted continuously from 0 to 62 cm.

The center of the bismuth layer are removable for a rectangle part of 25 cm x 25 cm in square and *5* cm in thickness, and a convex part of 20 cm diameter for *5* cm thickness and 15 cm diameter for 13.4 cm thickness, from the irradiation room side. So, four kinds of the bismuth thickness such as 0, 5, 18.4 and 23.4 cm can be selected at the bismuth center.

3.3. The irradiation modes and the basic irradiation characteristics

Table I shows the measured values of the irradiation characteristics for several irradiation modes at the normal irradiation position [11]. The “irradiation mode” means a condition of the facility-side, such as open or close of the cadmium and boral filters, full or empty of heavy water in the neutron energy spectrum shifter and heavy water shutter tanks, and the thickness of the center part of the bismuth layer. The first and second characters in the symbol defining irradiation mode represent the open or close conditions of the cadmium and boral filters. The character “0” means the filter “opened (not full-closed)”, and the character “C” and “B” mean the cadmium and boral filters “full-closed”, respectively. The four numbers represent the conditions of the tanks of the heavy water shutter and the spectrum shifter, in order from the irradiation-room side. The number “0” and “1” mean “empty” and “full”, respectively. The last character represents the condition of the center thickness of the bismuth layer. The characters “E”, “G”, “F” and “H” mean the thickness of 0, 5~ 18.4 and 23.4 cm, respectively. Usually, the bismuth layer thickness is 18.4 cm, namely, in the “F” condition

3.4. Stability of the KUR operation

The stability as to the power and reactivity of the KUR was experimentally confirmed for the influences of the drain-supply of heavy water in the tanks of spectrum shifter and the heavy water shutter, and the open-close of the thermal neutron filters under the full-power continuous operation at 5 MW. In the estimation about these influences on the KUR stability,

the changes and change rates for the linear power “Lin-N”, the logarithm power “Log-N”, the period monitor, the safety power channels and thermal power, were monitored.

The influences were observed inconsiderably for the spectrum shifter and the heavy water shutter, but hardly for the open-close of the thermal neutron filters. Also, the influences

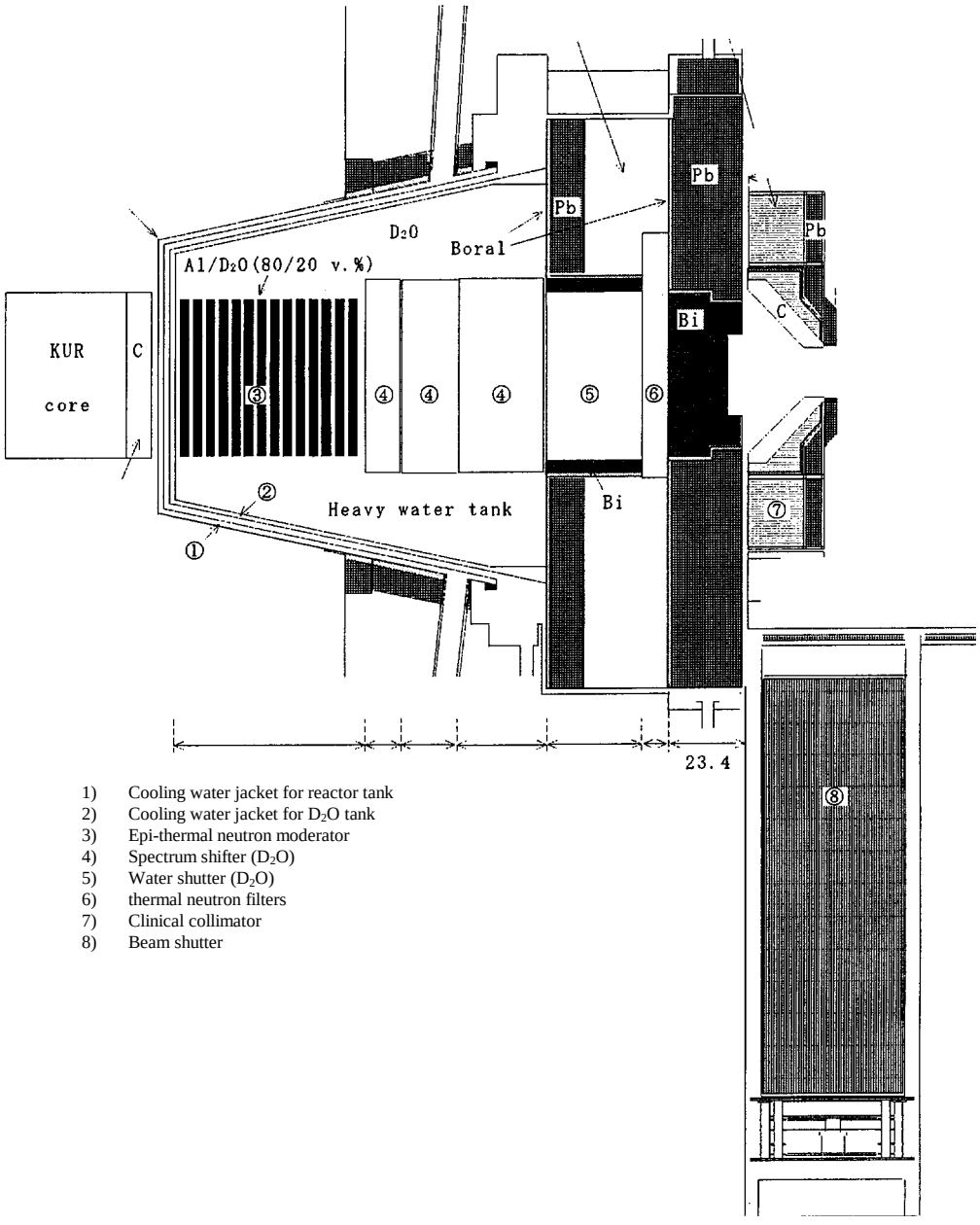

FIG. 1. Outline of the updated Heavy Water Neutron Irradiation Facility.

Table V. Measured values of the neutron fluxes and gamma ray dose equivalent rates at the bismuth surface during the full-power (5MW) KUR operation.

Irradiation mode	D_20 thickness (cm)	Cadmium ratio	Thermal neutron flux ($n/cm^2/s$)	Epi-thermal neutron flux* ($n/cin^2/s$)	Gamma ray dose equivalent Rate (cSv/hr)
00-1111-F	90	790	l.6E+08	4.lE+05	10
00-0111-F	60	700	5.9E+08	l.7E+06	40
00-0110-F	50	650	7.7E+08	2.4E+06	50
00-0101-F	40	400	1.OE+09	5.1E+06	60
00-0011-F	30	160	2.OE+09	2.5E+07	100
00-0010-F	20	51	2.3E+09	9,3E+07	110
00-0001-F	10	22	3.3E+09	3.2E+08	180
00-0000-F	0	9.4	5.OE+09	1.2E+09	330
00-0000-F	0	Almost 1	Not estimable	1.1 E+09	60
OB-0000-F	0	Almost I	Not estimable	4.OE+08	50

Measurements were carried out using the "irradiation rail device".
Neutron fluxes were estimated with gold activation foils, and gamma ray doses were measured with TLD (BeO).
*It is assumed that the epi-thermal neutrons have a pure l/E spectrum.

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of the control rod positions and the accumulated operation time from the reactor startup to a condition change were not observed. For the heavy water drain-supply in the tanks of the spectrum shifter and the heavy water shutter under the full-power operation, the following results were mainly obtained;

(1) Two safety power channels change about 0.02 MW (below 0.5%),
(2) Thermal powers estimated from both the primary and secondary coolant systems change about 0.04 MW (below 1%),
(3) These changes are minus for the supply and plus for the drain, and
(4) These changes are observed during the supply or drain within a few minutes.

Incidentally, the KUR is controlled for the Lin-N signals to be almost constant, within 1%. It was confirmed that the control stability and safety of the KUR are maintained by the condition change of the HWNIF under the full-power continuous operation.

4. OUTLINE OF THE ADVANCED CLINICAL IRRADIATION SYSTEM FOR NCT

Figure 2 shows the layout of the Advanced Clinical Irradiation System supporting NOT. This system consists mainly of (i) the Radiation Shielding System, (ii) the Irradiation Room and the Entrance Shield Door, (iii) the Remote Carrying System and the Medical Treatment Room for a patient, and (iv) the Safety Observation System. Additionally, the Irradiation Rail Device is provided for basic experiments.

4.1. The radiation shielding system

For the efficient radiation shielding at the mixed field of neutrons and gamma rays, it is general to investigate on the following three divisions; (i) epi-thermal and fast neutrons, (ii) thermal neutrons, and (iii) gamma rays. Fast neutrons with the average energy of 2 MeV generated from the reactor core are efficiently shielded due to the absorption by boron-l0, cadmium etc. after the moderation and thermalization.

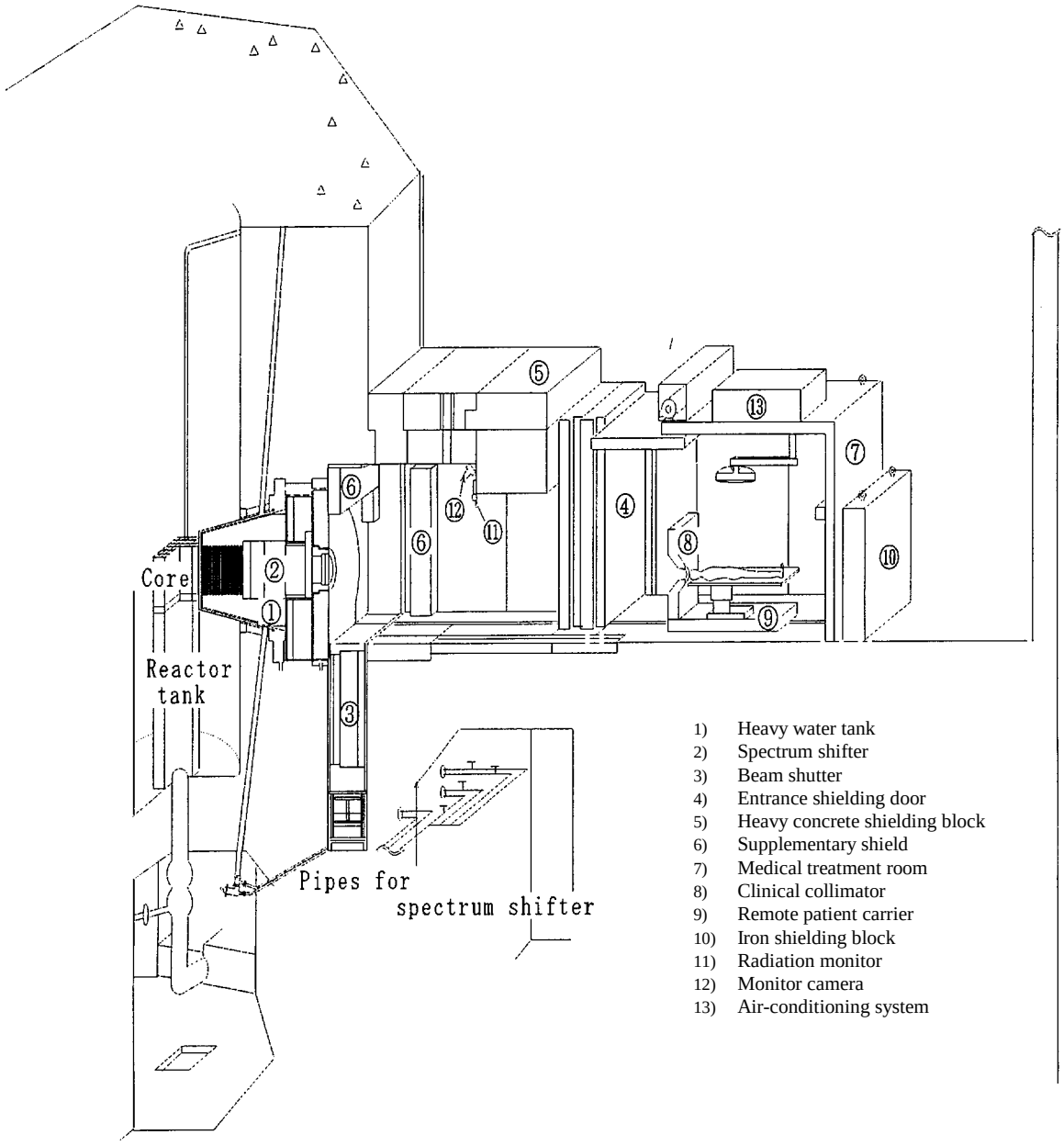


FIG.2. Layout of the KUR Advanced Clinical Irradiation System.

The gamma rays yielded due to the neutron capture, together with the primary gamma rays from the reactor core, are shielded by high-density materials such as lead, bismuth, etc. On the bases of these concepts, the Radiation Shielding System was investigated.

The radiation shielding system consists of (I) the heavy water shutter and the neutron energy spectrum shifter against fast neutrons, (2) the thermal neutron filters of cadmium and boral against thermal neutrons, and (3) the Beam Shutter, the irradiation room and the entrance shield door against neutrons and gamma rays. For the water shutter, light water was thought to be chosen in the conceptual study [11]. However, the available space for the water shutter was decreased to be about 30 cm. The shutter material was changed from light water to heavy water, in the viewpoint of the simplification of the water drain-and-supply system In order to compensate the insufficient radiation shield against fast neutrons, a Beam Shutter was installed outside of the bismuth layer. The beam shutter has a multi-layer structure consisting

of iron, lead, polyethylene, borated-polyethylene. The whole thickness of the Beam Shutter is 74 cm, which is the maximum size in order to install it in the pit space for the radiation shield of the old facility.

The open-and-close operations of these shutters and doors can be done by remote control, and it takes about five minutes in maximum to fully open or close. As workers and researchers enter the irradiation room under full-power continuous KUR operation, the means of the reduction of the induced-radiation especially from activated aluminum were taken prudently.

4.2. The irradiation room and the entrance shield door

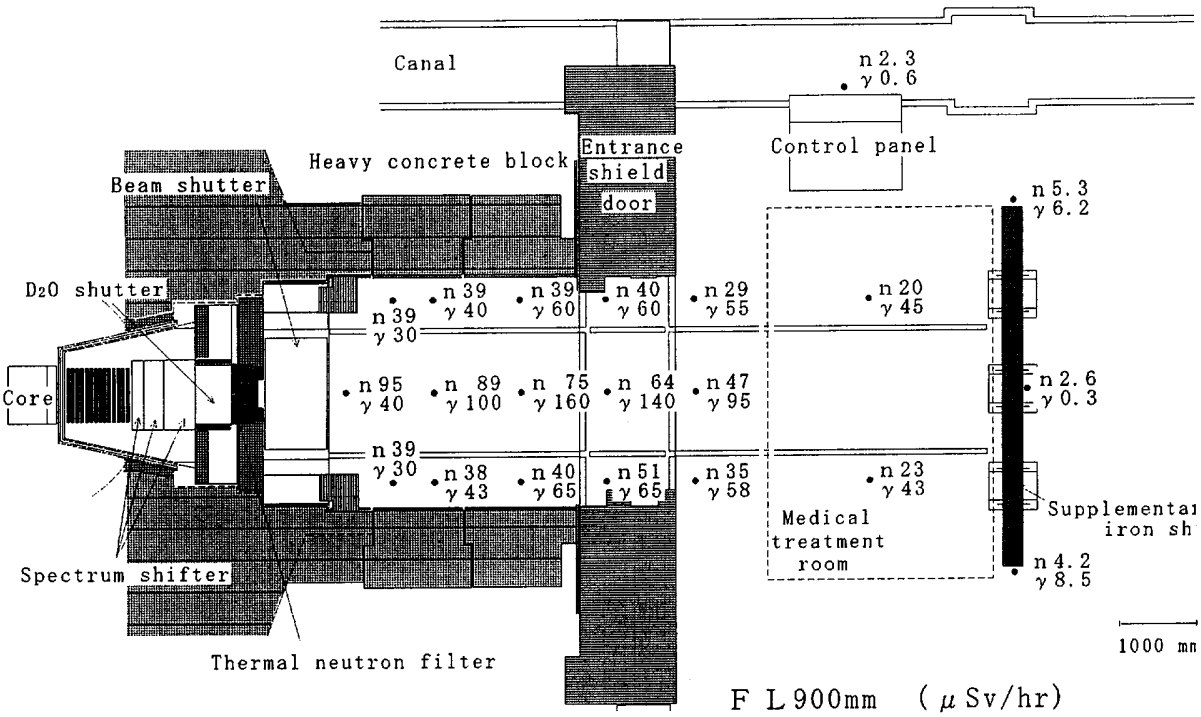
The outline of the updated irradiation room is shown in Fig. 3. For the updated irradiation room, both the inner width and height are 2.4m, the depth is 3.6m for the installation of the remote carrying system. The entrance shield door is sliding-door type and the maximum open size is 2.2m. The door has a multi-layer structure consisting of iron, polyethylene and borated-polyethylene, whose total thickness is 1.2 m, for the improvement of the shielding performance against epi-thermal and fast neutrons. The inside of the irradiation room is overall covered with 1 cm-thick borated-polyethylene, in order to reduce the activation of the structure materials.

Six experimental tunnels are cut through the heavy concrete blocks of the irradiation room; two vertically through the ceiling block and four horizontally through the right and left blocks, are cut through. Additionally, four small tunnels are holed for cables, etc., horizontally through the right and left blocks. The irradiation rail device can be set through one of the horizontal experimental tunnels. The monitor lines for a patient, such as anaesthesia hose, etc., the signal lines for monitor televisions, the other lines for experiment, etc., can be drawn out from the irradiation room through a pit under the entrance shield door.

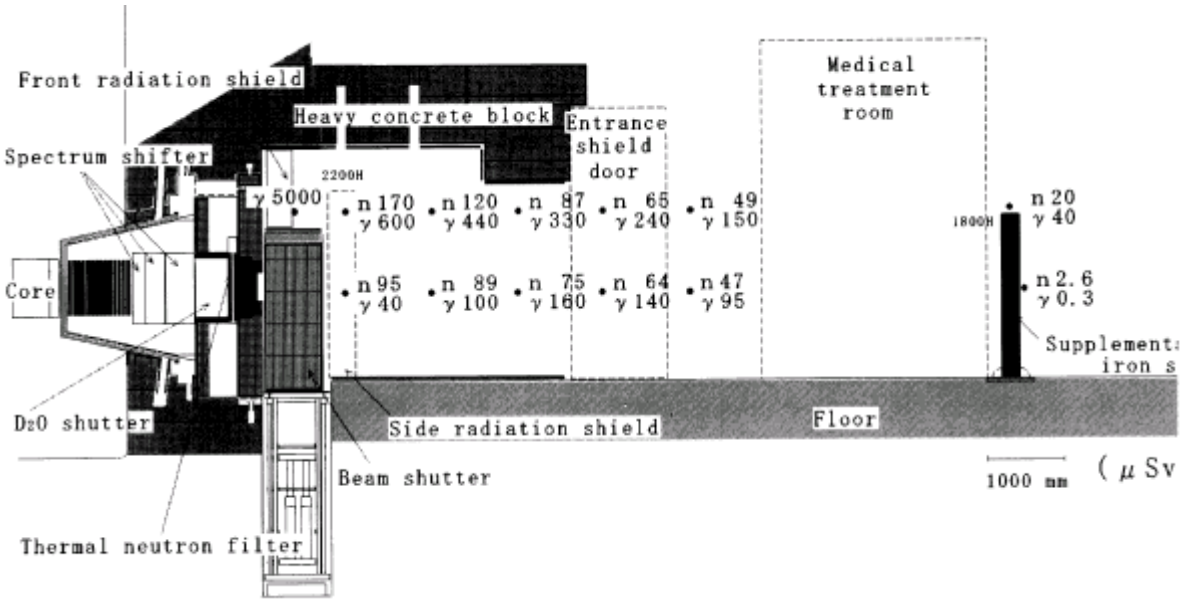
4.3. Dose distributions of the irradiation room under the full-power continuous operation

In order to estimate the exposure dose for the utilisation under the continuous operation, the dose rate distributions inside and around the irradiation room were measured under the full-power operations of *5* MW for the condition of the spectrum shifter and the heavy water shutter tanks “full-filled”, the boral filter “full-close”, the Beam Shutter “close” and Entrance Shield Door “full-open”. A rem-counter and an ionised chamber were used for the dose measurements of neutrons and gamma rays, respectively. The measured dose equivalent rates are shown in Fig. 3. At the 180 cm height from the floor level, where the Beam Shutter does not reach, the doses were higher. At the 90 cm height near the center axis, which corresponded to the normal working area (3 m distant from the bismuth layer surface), the total dose equivalent rate of neutrons and gamma rays was almost 250 μ Sv/hr. This value is larger than the design criterion of 100 μ Sv/hr, due to the addition of the scattered component from the non-shielded areas due to the Beam Shutter. The admittance time per a week will be limited within four hours.

Employing the remote carrying system together with the radiation shielding system, the setting and positioning for a patient is possible at the outside of the irradiation room, and a patient can be carried into the irradiation room by the remote patient carrier, under the full-power continuous operation.



TOP VIEW



SIDE VIEW

FIG.3. Measured dose distribution of neutrons and gamma rays inside and outside of the irradiation room employing the Radiation Shielding Systems under the full-power (5MW) KUR operation.

The carrier moves from the medical treatment room into the irradiation room along the rails. A medical treatment room is settled adjacent to the irradiation room. For the countermeasure against falling bacteria, a bactericidal air-conditioning system is attached on the ceiling in this room. A driving motor for the remote patient carrier is settled in the small pit at the center part under the irradiation room floor-level. The carrier can be remotely moved by electrical power about 90 cm in the irradiation room.

A clinical collimator system and a manual X-Y table are settled on the carrier. A clinical bed with position-control mechanism for up-down and rotation is put on the X-Y table. Then, the positioning to the collimator aperture is easily possible by laser pointers attached on the medical treatment room. Three kinds of the collimator are provided for thermal, mixed and epi-thermal neutron irradiation. Those maximum aperture sizes are 190 mm. These collimators are used together with the inner collimators for several use conditions. The maximum size of irradiated sample treatable by this remote carrying system, is 200 cm in width, 180 cm in height and 2 t in weight.

4.4. The safety observation system

The operation conditions for the HWNIF are always under concentrated observation by the safety observation system. In the standing points of radiation-exposure protection for workers and safety for a patient, the following two interlocks are set. (1) The “open” operation of the entrance shield door is interlocked for the conditions of the beam shutter “close”, the heavy water shutter and the spectrum shifter tanks “full”, during the KUR power larger than 10 kW. (2) The carrier cannot be moved from the waiting position for the condition of the beam shutter “not open”. On the contrary, the beam shutter cannot be closed, for the condition that the carrier is at the irradiation position.

5. CONCLUSION

We completed this remodelling works on the basis of the knowledge for the maintenance and repair of the old facility, the experiences of the NCT clinical irradiation and the basic experiments in many research fields, etc.. In the updated HWNIF of the KUR, the neutron irradiation with various energy spectra, such as mixed irradiation of thermal and epi-thermal neutrons, solo-irradiation of epi-thermal neutrons, are possible using the thermal neutron filters together with the neutron energy spectrum shifter. The utility and application of the facility became remarkably improved for NCT clinical irradiation.

The first NCT clinical irradiation at the HWNIF was performed for a brain tumour with the thermal neutron irradiation mode in November 1996. Fourteen NCT clinical irradiation; four with thermal neutron irradiation mode “00-0011-F” and ten with the mixed neutron irradiation mode of thermal and epi-thermal neutrons “00-0000-F”; thirteen for brain tumour and one for melanoma, were already performed as of June 1999. Solo-irradiation of epi-thermal neutrons is planning to start in near future. From now on, we will promote the more effective utilisation and application of this facility on the basis of the facility safety.

ACKNOWLEDGEMENTS

The updating design study was performed by the direct and indirect supports of many co-operators, as this facility has been originally used by many researchers. The authors thank Mr. Koichi Ono of KURRI for helpful advice about the radiation exposure for the workers under

the construction. The tasks such as the recognition of the updating methods, the pre-employment inspection, etc., were carried out on the collaboration of the KURRI technical staff. Special thanks are due to the co-operators of Hitachi, Ltd., ATOX Co., Ltd., Hitachi Zosen Corporation, Nuclear Fuel Industries, Ltd., Kajima Corporation.

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Medical irradiation facility at JRR-4

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Abstract. The operation of JRR-2, in which 33 cases of medical irradiation were performed for clinical trials of BNCT using thermal neutron beam for malignant brain tumour patients since 1990, was terminated at the end of 1996. In order to transfer the medical irradiation for BNCT from JRR-2 to JRR-4, a new medical irradiation facility was installed at JRR-4 in June 1998. The new facility provide a suitable neutron beam (thermal or epithermal neutron beam) for each medical irradiation. It was verified that both thermal and epithermal neutron beams had enough intensity for a clinical trail of BNCT and very low contamination of gamma ray and fast neutron.

1. INTRODUCTION

A medical irradiation facility for BNCT was installed at JRR-2 in 1990. Since then 33 cases of medical irradiation for clinical trials of BNCT using thermal neutron beam were performed for malignant brain tumour patients by Dr. Hatanaka, Dr Nakagawa's and a group at the Tsukuba University. The operation of JRR-2 was terminated at the end of 1996 because of ageing of reactor components. In order to transfer the medical irradiation for BNCT from JRR-2 to JRR-4, a new medical Irradiation facility was installed at JRR-4.

JRR-4 was constructed in 1965 for the purpose of shielding test of the first nuclear ship in Japan "Mutu". It is a light water moderated and cooled swimming pool type reactor with the maximum thermal power of 3.5 MW. The operation mode is daily operation. It was used for shielding experiment, neutron activation analysis, irradiation test of reactor materials and fuels, production of radioisotop~s4 — silicon doping and education and training of nuclear engineer. At the beginning of l997, the operation was terminated once for modification of reactor system and renewal of utilisation facilities containing installation of the medical irradiation facility, and resumed in January 1999. This paper presents outline of the new medical irradiation facility and results of its characteristic test.

2. OUTLINE OF MEDICAL IRRADIATION FACILITY AT JRR-4

The general arrangement of medical irradiation facility at JRR-4 is shown in Fig. 1. The medical irradiation facility consists of neutron beam facility, medical treatment room and experimental room. And furthermore, a prompt gamma ray analyses system was installed for BNCT.

2.1. Neutron beam facility

The basic design policy of the neutron beam facility is to provide a variety of neutron beams from thermal to epithermal neutron beam. In Japan, thermal neutron beam is needed to continue the conventional BNCT. Fig. 2 shows the neutron beam facility. It consists of heavy water tank, cadmium shutter, collimator and irradiation room. The irradiation angle of patent is possible to adjust within 90 degree to left side, and 60 degree to right side.

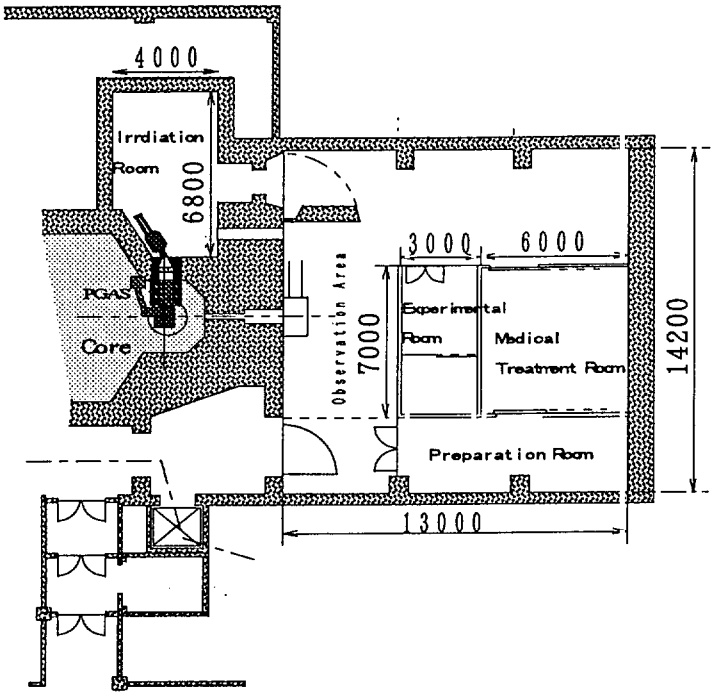

FIG.1. General arrangement of a medical irradiation facility.

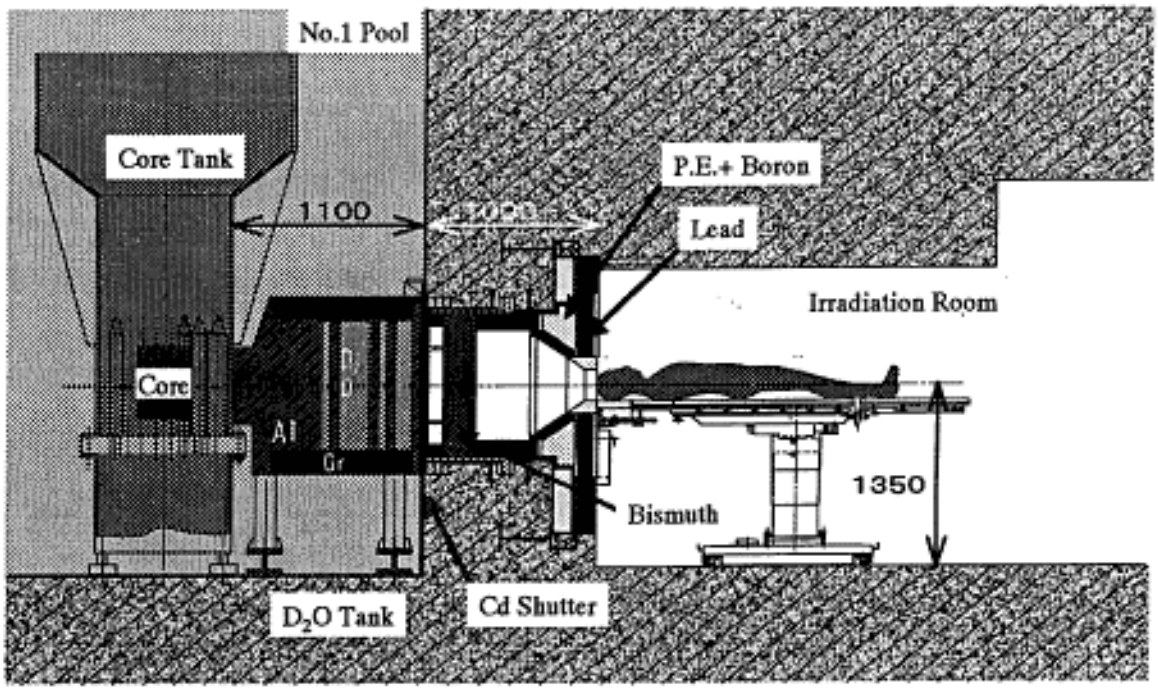

FIG.2. Cross sectional view of neutron beam facility.

2.2. Medical treatment room

The medical treatment room was prepared for pre and post-irradiation surgical operations in the case of BNCT for malignant brain tumour patient using thermal neutron beam. A bed for surgical operation and irradiation, astral lamp, sterilisation lamp, medical sink for sterilisation, etc. are installed in this room.

2.3. Experimental room

Incubator, clean bench, draft chamber, etc. are set in the experimental room for fundamental experiments on BNCT.

2.4. Prompt gamma ray analyses system

A prompt gamma ray analyses system was installed to accurately determine boron concentrations in tumour and blood in a short time. Fig.3 shows the system. A Ni/Ti multilayer supermirror guide tube[(2)] was adopted as a neutron guide tube to obtain higher neutron flux at the measurement position.

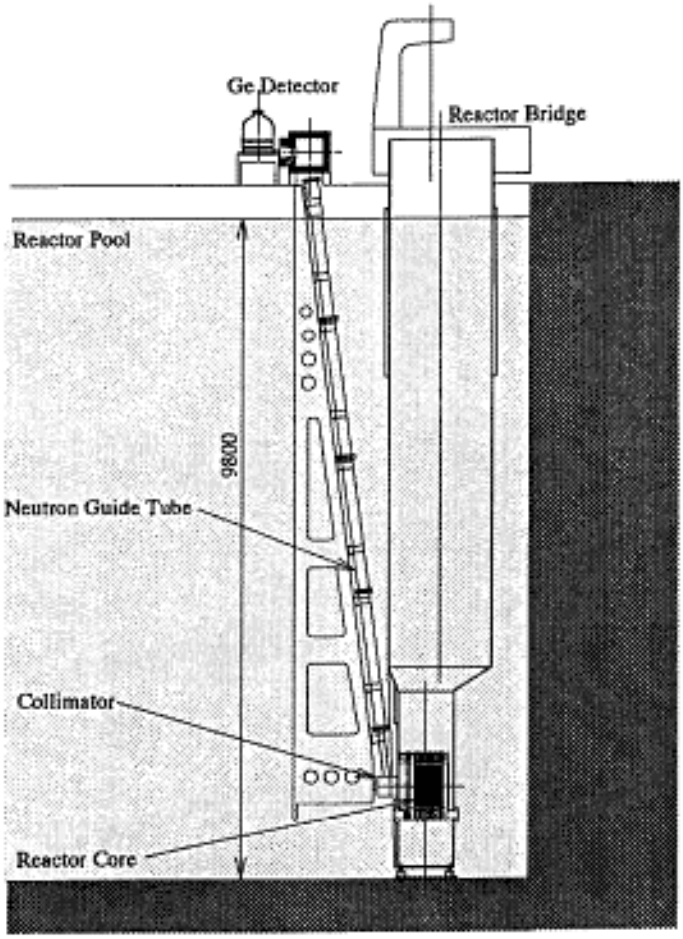

FIG.3. Outline of prompt gamma ray analysis system.

3. NEUTRON BEAM FACILITY

3.1. Objectives of beam design

The objectives of the beam design were set as follows for free beam model:

(1) Thermal neutron flux at beamport (thermal mode): $\geq 1 \times 10^{9}$ n/cm^2/sec
(2) Epithermal neutron flux at beam port (epithermal mode): $\geq 1 \times 10^{9}$ n/cm^2/sec
(3) Gamma ray contamination: $\leq 3 \times 10^{-13}$ Gy cm^2/n
(4) Fast neutron contamination: $\leq 5 \times 10^{-13}$ Gy cm^2/n

3.2. Design optimization

Design optimisation studies were performed for aluminum and heavy water thickness of heavy water tank, position and thickness of bismuth shield, etc. Two dimensional calculations using 2-D discrete ordinate transport code DOT3.[3] and library data based on JENDL3.1[4] (Japanese Evaluated Nuclear Data Library version 3.1) were performed in the design optimisation studies. 21 group neutron and 9 group gamma ray energy structure were used in the calculations.

Dependence of beam performance on aluminum thickness is shown in Fig. 4a and 4b. Increasing the aluminum thickness, the fast neutron contamination in epithermal neutron beam decreases rapidly. Therefore, the aluminum thickness of 75 cm was chosen to reduce fast neutron contamination in epithermal neutron beams, while thermal and epithermal neutron fluxes were enough to satisfy the design objectives.

The thickness of the heavy water layer can be arbitrary chosen from 0 cm to 28 cm by 4 cm step. The maximum thickness is 33 cm. Dependence of beam performance on heavy water thickness is shown in Fig. 5a and 5b. The beam design objectives are practically satisfied for every available heavy water thickness.

3.3. Performance test of beam facility

Performances of the beam facility were verified experimentally for following three typical beam modes ; Thermal Beam Mode I ,Thermal Beam Mode II and Epithermal Neutron fluxes, fast neutron and gamma ray contamination and Cadmium ratio of each beam mode at the beam port are shown in Table 1. Neutron spectra of each beam mode at beam port are shown in Fig. 6–8. The neutron spectra calculated by DOT 3.5 are good agreement with ones measured by foil activation method using Au, Au covered by Cd, Cu and Ni foil. Thermal neutron fluxes shown in Table 1 were measured using Au foils, and epithermal and fast neutron fluxes were determined based on neutron spectra shown in Fig.6–8. The typical neutron beams have very low contamination of fast neutron and gamma ray.

Thermal neutron flux distributions measured by Au foils in a cylindrical head water phantom with diameter of 18.6 cm and height of 24 cm are shown in Fig. 9. In Epithermal Beam Mode, a remarkable peak is observed at the depth of 1.S cm from the surface of phantom. Maximum thermal neutron fluxes of Thermal Beam Mode I, Thermal Beam Mode II and Epithermal Beam Mode are 5.9, 1.5 and 4.0 X l0^9 n/cm^2/sec respectively, and have enough values for clinical trail of BNCT.

4. CONCLUSION

The medical irradiation facility at JRR-4 can provide a wide variety of neutron beams by changing the thickness of heavy water in heavy water tank, and by inserting/removing the cadmium shutter. It was verified that all beam modes have enough neutron beam intensities for BNCT and very low contamination of fast neutron and gamma ray. In addition to the above, accessory equipment and facilities necessary for BNCT were installed at JRR-4.

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Analysis of the possibility of using the reactor filtered neutron beam formed by Ni-60 filter for BNCT

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Abstract. For BNCT we propose the neutron filter for reactor beam having the spectrum with the average energy about 3.5 KeV. This beam may be formed using the thick sample of enriched isotope Ni-60 (99.5 %). This main component has to be accompanied with the set of additional elements to suppress the neutrons above 10 KeV. Here we present the calculations of the transmission function and neutron flux density of such filter with Ni- 60 and Fe, B, S and others, using the evaluated neutron cross sections from the libraries ENDF/B-VI and JENDL-3.2. The analysis of the influence of these additions to suppress the high energy neutrons is fulfilled. There is shown the optimal configuration of such filter on the basis of ^{60}Ni, which is the most convenient for BNCT, as we suppose. We intend to build and test this filter at our WWR-M reactor till the end of this year.

1. INTRODUCTION

As it is well known, the large cross section of thermal neutron interactions with B-10 isotope leading to a slitting of B-10 nucleus onto He and Li together with absorbability of cancerous tumours to take up the boron atoms much more then healthy cells, are the basis of Boron Neutron Capture Therapy method. As ionisation capability of He and Li ions is high, and their runs are short, then the cells, preferably enriched by boron, are killed and the healthy cells are damaged much less. However, as the penetrating capability of thermal neutrons is low, then to reach the cancerous tumours, localised into several centimetre depths, the epithermal neutrons are more suitable. In addition, the use of thermal neutrons carries attendant problems due to the magnitude of the skin dose [1]. Epithermal neutrons have the lower neutron capture rate in hydrogen and it would result in reduction of a skin dose, and moderation of epithermal neutrons within the head would give rise to thermal neutron peak at the cancerous tumour site. As it is shown in paper [2], the most suitable neutrons for BNCT are neutrons with energy in region from 0.1 eV to 10 KeV, because their KERMA factor and hence, the direct tissue damage, is smaller than for thermal or fast neutrons.

Such neutron beams may be formed at nuclear reactors using the thick neutron filters of natural or isotope enriched materials, for which interference minimum in the total neutron cross section exists in energy range from several eV to 10 KeV.

2. KIEV RESEARCH REACTOR

In the Scientific Centre "Institute for Nuclear Research" of UkNAS during the last twenty years at the research WWR-M reactor in Kiev the filtered neutron beam technique was developed very successfully. Availability of ten horizontal channels with the diameter 60 or 100 mm having the neutron fluxes up to 2.10^9 n/cm^2·s at 10 MW of reactor power, the set of isotope enriched and natural materials, such as Sc-45, Ni-60, Ni-58, B-10, Cr-52, S-32, Fe-56, Fe-54, Mn-55, V-51, Ti-48, Si-28, Li-7, Mg-24, make it possible to have the set of 20 quasimonoenergetic neutron beams in the energy region 0.017–610 KeV with the output fluxes about 10^5–10^8 n/cm^2·s. General scheme of the filter set-up at the horizontal channel is shown in Fig. 1.

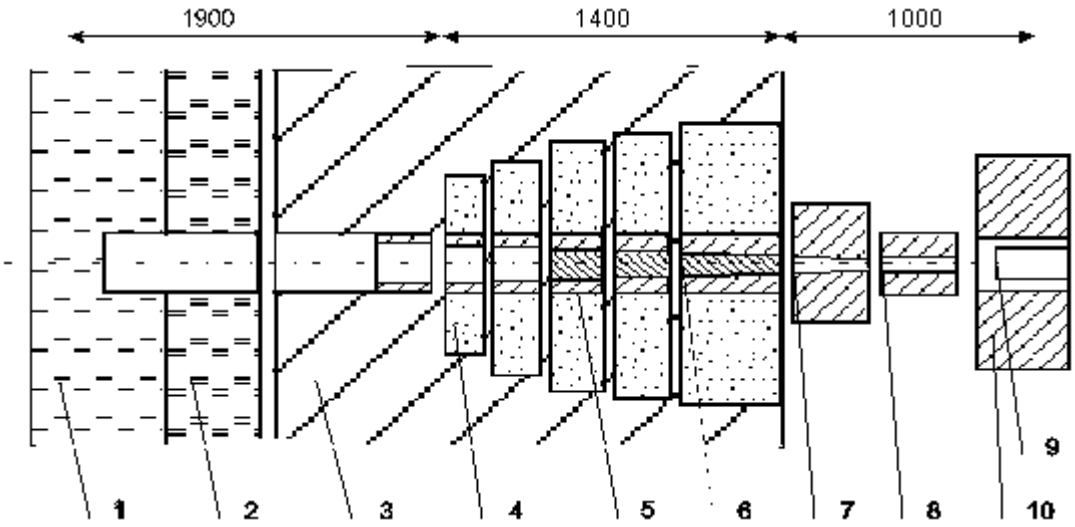

FIG.1. General scheme of the filter set-up at the horizontal channel. 1- core, 2- water, 3- biological shielding, 4- shutters, 5- collimators from lead and paraffin with boric acid, 6- filter, 7- external collimator, 8- intermediate collimator, 9- counter, 10 - shielding.

3. THE CALCULATED RESULTS

The main purpose of this work was the development of compound neutron filters, first of all on the base of Nickel-60 isotope, which allowed to separate from reactor spectrum rather intensive neutron group in energy range from several eV to 10 KeV and at the same time to decrease the contribution of neutron groups with energies above 10 KeV. To choose the components of such filters, the total cross sections of all available materials have been calculated for energy range from 10^{-5} eV to 10 MeV at the temperature 300 K within an accuracy 1% on the basis of the evaluated nuclear data libraries ENDF/B-VI and JENDL-3.2. These calculations have been performed with code packages GRUCON [3,4] and PREPRO-96 [5]. As it can be seen from Fig. 2, where the result of such calculations for the total cross section of Ni-60 isotope is presented, really this isotope has the deep and wide interference minimum in energy range from several eV up to 8 keV and it may be used for BNCT purpose. Of course, the total cross section of Ni-60 isotope has several interference minima, the most deep of which are situated at the energies about 28, 43, 65, 86, 97, 160, 181 KeV and such filter will transmit not only desired neutrons, but the neutron groups with larger energies. They may be suppressed using additional to the basic filter materials.

For the optimisation of the neutron filter components to separate the neutron group with energies from several eV to 8 KeV and to minimise the high energy groups contributions, it was developed a special code package. Simple calculations of neutron transmissions were carried out. The initial neutron spectrum was accepted as 1/E. The real enrichment of the available materials has been taken–for Ni-60 the enrichment is equal to 99.5% and 0.5% of Ni-58.

The components of the most perspective for BNCT purpose filters chosen from all calculated ones are given in Table I. In the last column of this table the absolute neutron flux densities for main neutron group, which may be obtained at Kiev reactor using these filters, are given. Their values have been evaluated by normalisation of the relative neutron flux densities, obtained in the calculations for all these filters to the measured experimental value $6 \cdot 10^6$ n/cm^{2}s for the filter a) [6].

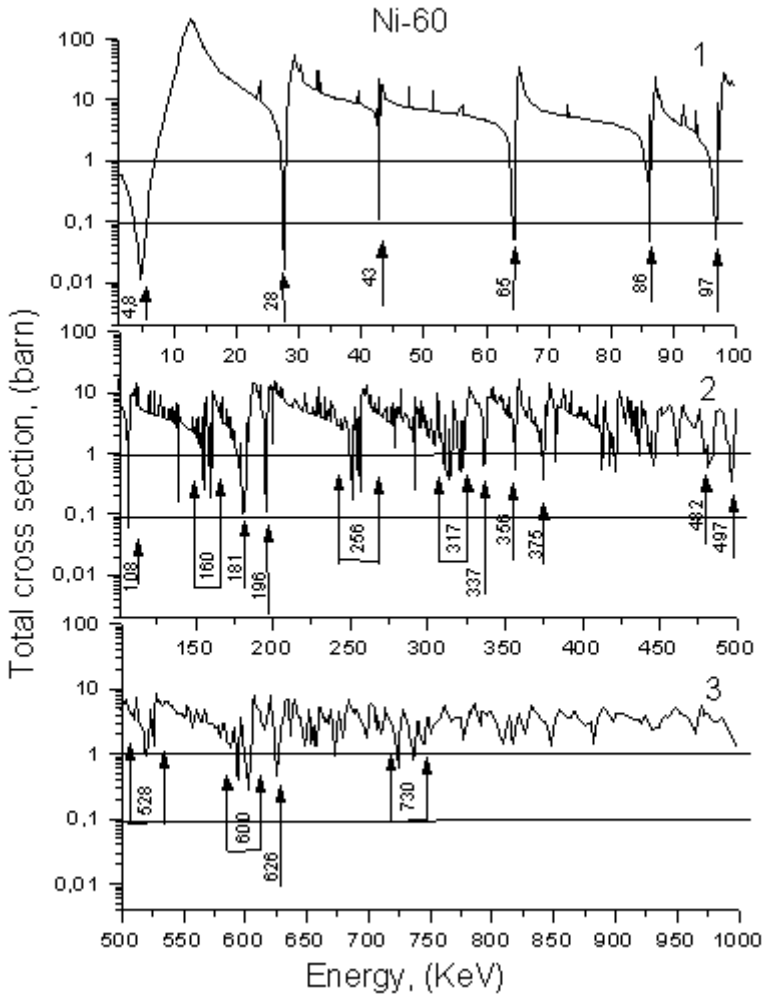

FIG.2. Total cross section for Ni-60 isotope calculated on the basis of ENDF/B-VI.

Table I.

Filter	Relative intensity (in %) of neutron groups (energy in KeV) to the full spectrum flux													
	0.01	24	42	60	82	177	246	327	359	465	489	503	607	762
	10	29	43	65	87	188	317	359	465	489	503	607	762	900
a)	92.3	3.40	0.49	2.39	0.09	0.10	0.27	0.14	0.10	<.01	<.01	0.19	0.15	<.01
b)	92.1	2.89	0.39	2.16	0.26	0.35	0.76	0.18	0.30	0.20	0.12	0.59	0.61	0.27
c)	92.8	1.8	0.48	2.17	0.25	0.17	0.51	<.01	0.59		<.01	0.29	0.60	<.01
d)	95.6	0.67	0.48	1.91	0.19	<.01	0.39	<.01	0.20		<.01	<.01	<.01	<.01
e)	91.2	1.91	<.01	2.42	<.01	0.20	0.67	0.29	0.52	0.22	0.14	0.68	0.76	0.35
f)	93.1	1.44	<.01	2.11	<.01	0.12	0.48	0.35	0.39	0.17	0.11	0.54	0.61	0.28

In Fig.3 the neutron spectra formed in the energy range from 0.01 to 9 KeV with filter compositions are shown. The contributions of the main neutron group and the neutron groups with energies above 10 KeV to the full spectrum flux are given in Table 2.

Table II.

Name of filter	Components of filters in g/cm^2					Neutron flux in 10^6 n/cm^2·s
	Ni-60	S-32	B-10	Fe-54	Sc-45	
a)	212	84	1.15	-	-	6.0
b)	112	54	1.15	-	-	16.32
c)	112	54	1.15	20	-	11.52
d)	112	54	1.15	50	-	9.06
e)	112	54	1.15	-	30	4.14
f)	112	54	1.15	-	40	3.60

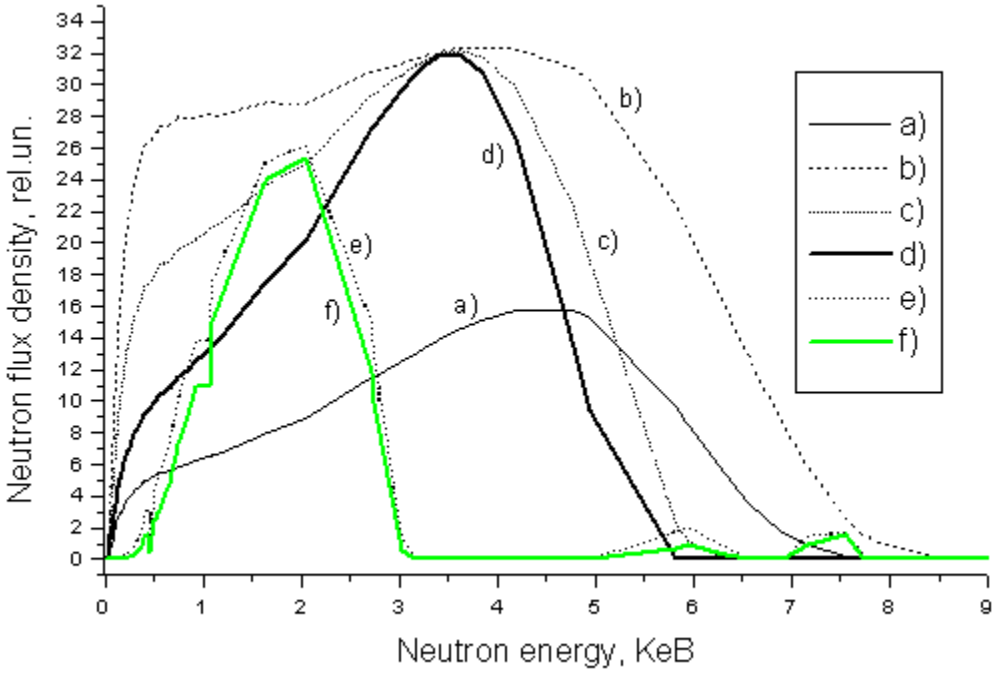

FIG.3. The neutron spectra formed in the energy range from 0.01 to 9 KeV using filter compositions.

4. CONCLUSIONS

- By using as the main component the 99.5% enriched Ni-60 isotope and as the additional ones S-32 and B-10 isotopes, at the reactor beam it may be obtained the filtered neutron beam with the energies 0.01–9 KeV and with the absolute neutron flux density about $1.6 \cdot 10^7$ n/cm^2·s.

- The purity of the main neutron group 0.01–9 KeV is about 92%, and we may move the average neutron energy in the group to higher meanings using the additional filter material Fe-54, or using the additional material Sc-45 we move the average energy in neutron group to lower meanings. At these situations we reduce the intensity of the main group, but it may be useful for different penetrability of neutrons, as it is needed in medical practice. These additions also increase the purity of the main neutron group (up to 96%).

- Additional filter materials (Fe, Sc) may be located at the output collimator, where they may be very quickly changed, while the basic part (Ni-60, B-10, S-32) is located in the reactor channel.

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Annex 5

PHYSICS OF EMERGENT BEAM

Three dimensional measurements of absorbed dose in BNCT by Fricke-gel imaging

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Abstract. A method has been studied for absorbed dose imaging and profiling in a phantom exposed to thermal or epithermal neutron fields, also discriminating between various contributions to the absorbed dose. The proposed technique is based on optical imaging of FriXy-gel phantoms, which are proper tissue-equivalent phantoms acting as continuous dosimeters. Convenient modifications in phantom composition allow, from differential measurements, the discrimination of various contributions to the absorbed dose. The dosimetry technique is based on a chemical dosimeter incorporated in a tissue-equivalent gel (Agarose). The chemical dosimeter is a ferrous sulphate solution (which is the main component of the standard Fricke dosimeter) added with a metal ion indicator (Xylenol Orange). The absorbed dose is measured by analysing the variation of gel optical absorption in the visible spectrum, imaged by means of a CCD camera provided with a suitable filter. The technique validity has been tested by irradiating and analysing phantoms in the thermal facility of the fast research reactor TAPIRO (ENEA, Casaccia, Italy). In a cylindrical phantom simulating a head, we have imaged the therapy dose from thermal neutron reactions with ^{10}B and the dose in healthy tissue not containing boron. In tissue without boron, we have discriminated between the two main contributions to the absorbed dose, which comes from the $^{1}H(n,\gamma)^{2}H$ and $^{14}N(n,p)^{14}C$ reactions. The comparison with the results of other experimental techniques and of simulations reveals that the technique is very promising. A method for the discrimination of fast neutron contribution to the absorbed dose, still in an experimental stage, is proposed too.

1. INTRODUCTION

As known, Boron Neutron Capture Therapy (BNCT) takes advantage of the high cross section of the nuclear reaction of thermal neutrons with ^{10}B:

$$^{10}B(n,\alpha)^{7}Li \qquad (\sigma = 3837\ b)$$

For treatment planning, besides the dose due to the presence of ^{10}B, it is necessary to determine the dose delivered by thermal neutrons in surrounding tissue without boron. In fact, the maximum admitted thermal neutron fluence during treatments is related to the dose in healthy tissue, which has to be within tolerance limits. Presently, the spatial distributions of absorbed dose in BNCT are commonly determined by means of computer simulations, with Monte Carlo or deterministic approach, but the necessary input parameters, which drastically determine the results, are not always satisfactorily determinable and the patient geometry is not easily simulated. Therefore, the experimental determination of the spatial distribution of absorbed doses is very important to support and validate the calculations.

Owing to the different Linear Energy Transfer (LET) of the different kinds of secondary radiation produced by neutron reactions in a medium, the determination of total dose is meaningless and the various contributions have to be separately identified. This result is commonly attained by means of elaborated simulation procedures. In practice, experimental dosimetry usually consists of fluence measurements, possibly complemented by some information about energy spectrum. On the other hand, both fluence and energy spectrum change from point to point in the medium, so that dose knowledge is very complex and difficult.

The here described technique for neutron dosimetry allows absorbed dose imaging and profiling in tissue-equivalent phantoms exposed to thermal or epithermal neutrons, discriminating between various contributions. The proposed technique is based on the imaging, after exposure, of phantoms made with a gel-dosimeter material of proper composition. From differential analysis of images detected in phantoms having convenient differences in the elemental composition, it is possible to separate the various contributions to the absorbed dose.

2. METHOD FOR ABSORBED DOSE IMAGING

As known, in ferrous sulphate solutions ionising radiation starts a chain of chemical reactions which results in the conversion of ferrous ions Fe^{2+} into ferric ions Fe^{3+}. The conversion yield has shown to be proportional, till saturation, to the absorbed dose. Therefore, after ionising radiation, from the variation of some detectable physical parameter depending on the ferrous and ferric ion amounts, the absorbed dose can be indirectly determined. In conventional Fricke dosimetry, the light absorption at about 300 nm is utilised, because such an absorption, negligible before ferrous ion oxidation, results to be proportional to the ferric ion concentration, that is to the absorbed dose. Spectrophotometric analysis has proved to be very reliable. Moreover, the different paramagnetism of ferrous and ferric ions gives an interesting technique for dose measuring: in fact, Nuclear Magnetic Resonance (NMR) analysis gives the possibility of spatial determination of paramagnetic species, because of their different influence on the spin relaxation times of the hydrogen nuclei of the solution. On account of this consideration, the feasibility of measuring 3-D distributions of absorbed dose in Fricke-infused gel-phantoms by NMR imaging has been suggested [1]. The sensitivity of such a technique is lower than that of spectophotometry, but this disadvantage is counterbalanced by the fact that, when ferrous sulphate solution is incorporated into a gel, the

ferrous ion oxidation yield has resulted to be considerably higher. In previous works, we have enquired the feasibility of dose imaging by means of NMR analysis [2] and the possibility of applying such a technique in thermal neutron fields for BNCT [3–6]. The main drawback consisted in the not negligible diffusion of Fe^{2+} and Fe^{3+} ions in the phantom. This effect causes a continuum loss of spatial resolution during the time between irradiation and analysis, so that a prompt phantom imaging after exposure is necessary to achieve good spatial resolution. Very often it is difficult to have such a possibility, in particular when exposures are performed in a nuclear reactor.

Therefore, we have considered an alternative technique for gel analysis, utilising spectrophotometry. The proposed method for gel-phantom imaging is based on transmittance measurements; we have designed and constructed a very simple portable instrument for image detection, which can be quickly assembled near the irradiation facility [7].

2.1. Gel dosimeter and portable imaging instrument

As before pointed to, in sulphuric acid solutions, ferric ions induce absorption peaks, in the UV region, at wavelengths near 300 nm. A considerable enhancement of the sensitivity of optical analysis is obtained by adding to the gel components a proper metal-ion indicator, which yields absorption in the visible spectrum. We have chosen Xylenol Orange ($C_{31}H_{27}N_2Na_5O_{13}S$, Fluka Chemie) which induces an absorption maximum at about 585 nm [8], as shown in Fig. 1. The difference in absorbency, at this wavelength, between irradiated and non-irradiated gels has shown to be linearly correlated to the absorbed dose. Visually, by increasing the absorbed dose, the colour of this Fricke-Xylenol-Orange infused gel (which for the sake of brevity we call FriXy-gel) changes from orange to violet.

The analysis technique is based on transmittance imaging performed by means of a CCD camera. In order to measure transmittance, the phantom to be inspected is composed of a set of piled up gel layers. Each layer consists of a stratum of gel within two transparent polyethylene or mylar films, held by a proper frame of the desired thickness and shape.

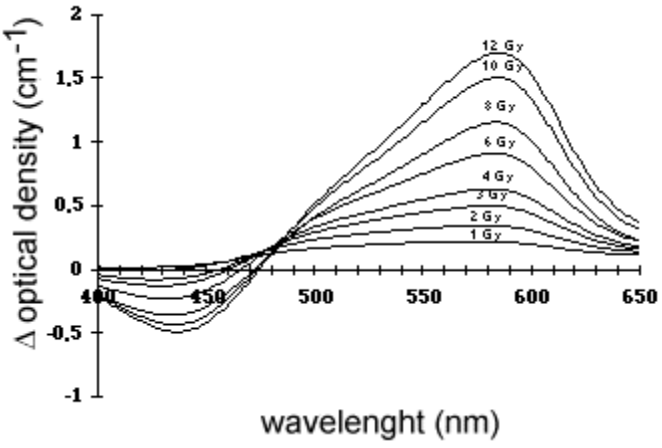

FIG.1. Difference in Optical Density between irradiated gel-samples and reference gel-sample.

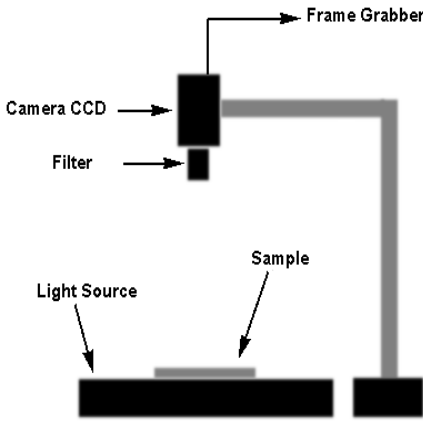

FIG.2. Instrument for imaging.

After exposure of the whole phantom to ionising radiation, each layer is promptly imaged and from the so obtained 2-D images, the 3-D distribution is reconstructed by means of convenient software.The instrument for transmittance image acquisition is composed of a CCD camera, an optical filter, a light diffuser and a PC. The interference filter (585 nm) is placed between the 50 mm camera lens and the CCD detector, to match the wavelength of the absorption maximum. A schematic view of the instrument is shown in Fig. 2.

2.2. Imaging technique

The absorbed dose can be correlated to the difference in Grey Levels (ΔGL) between irradiated and non-irradiated gels. These ΔGL values can be easily converted in differences of absorbency value, or Optical Density (ΔOD) with simple mathematics:

$$\Delta OD = \log_{10}\left(\frac{\Delta GL_{blank}}{\Delta GL_{irr}}\right)$$

The acquired transmittance images include a stripe of transmittance standards, with different optical densities. In a first step, the Grey Level values measured on the strip are utilised to test the stability of the light source and to evaluate possible correction factors. Moreover, with proper software for image elaboration, the Optical Density images can be obtained by means of direct dot elaboration of GL images. Finally, if some gels are exposed to known doses and analysed, then the γ-calibration curve is obtained and transmittance images can be converted into dose images.

For attaining good result reliability, the calibration procedure has to be performed with gel samples arranged in the same preparation, and moreover irradiation and analysis have to be carried out in an interval of time as short as reasonably possible, preferably in the same day. In fact, the stability in time of the gel dosimeter is not high. In a detailed study performed by analysing the dosimeter with NMR imaging [2], we have found good reproducibility of the

time dependence, whose knowledge allows to go up to reliable values. If this dependence has not been determined, by performing near-in-time calibration and analysis, reliable results are obtained.

3. DOSE IMAGING AND PROFILING IN PHANTOMS FOR BNCT PLANNING

3.1. Dosimetry of thermal and epithermal neutrons

The dosimetry of slow neutrons is difficult and particularly complex, because many kinds of energy release mechanisms are involved. In fact, neutrons do not directly produce ionisation in passing through matter: having no charge, they do not interact with atomic electrons, but with atomic nuclei. The deposition of dose by intermediate and fast neutrons in tissue is mainly due to hydrogen recoil nuclei, while thermal and epithermal neutrons release dose mostly through nuclear reactions. Thermal neutrons propagate in matter, till they are captured by an atomic nucleus, with a probability described by the isotope cross section. The cross-sections for such nuclear reactions highly depend upon neutron energy. The reactions are accompanied by the emission of energetic γ-rays or, like for ^{10}B, of ionising charged particles. If a deep tumour has to be treated, epithermal neutron beams are needed. In fact, to make up for the remarkable attenuation of thermal neutrons in tissue, intermediate neutrons are added in the beam, having a proper energy in order to produce a maximum in the thermal neutron fluence at the depth of the tumour. In this case, not only the energy release due to thermal neutrons has to be determined, but also the energy released in tissue by the recoil protons generated by the scattering of intermediate neutrons with hydrogen has to be considered, because its contribution may be significant.

For thermal neutrons, the main contributions to the absorbed dose in tissue come from hydrogen and nitrogen, through the nuclear reactions:

$$^{1}H(n,\gamma)^{2}H \quad (\sigma=0.33\ b) \quad \text{and} \quad ^{14}N(n,p)^{14}C \quad (\sigma=1.81\ b)\ .$$

The first reaction is responsible for dose depositions also far away from the site of interaction while the second one gives local dose deposition. In most common practical conditions, i.e. tissue-volumes with dimensions bigger than few centimetres, the first reaction is strongly dominant. Owing to the dissimilar linear energy transfer (LET) of the different radiation components, and to their different relative biological effectiveness (RBE), the total dose is meaningless, and it is necessary to determine the separate contributions to the absorbed dose of each field component. Possibly, this determination has to be made with 3-D resolution, because the relative contributions of the various dose components change with depth in tissue.

3.2. The FriXy-gel for BNCT

The first general condition for phantom dosimetry is that of achieving good tissue-equivalence of dose absorption in the substitute of which the phantom is composed. In thermal or epithermal neutron fields, this condition requires that the secondary radiation produced by the nuclear reactions is the same as that in tissue. The only possibility to obtain this equality is that of composing a tissue-substitute containing the same isotopes that give in tissue the main contributions to the absorbed dose, in the same percentage.

Since in our standard FriXy-gel the mass percentage of hydrogen is very near to that of most human tissues, in particular of brain tissue, a good tissue-equivalence is obtained for fast neutron energies. Moreover, if a proper amount of nitrogen is added to the gel’s composition,

the dosimeter becomes equivalent to brain tissue for all neutron energies. With the purpose of determining the different contributions to the absorbed dose, we developed FriXy-gels with different elemental compositions. One gel was completely tissue-equivalent, and another one was nitrogen depleted. We also prepared a gel with the same composition of the standard one, but augmented with a concentration of ^{10}B typical for the therapy (30 μg/g). In Tab.1 the various compositions are shown and compared to that of adult brain tissue from ICRU-44 [9].

Table 1. Elemental composition of brain tissue and of developed gels.

	H	***N***	***C+O***	***Others***	
Brain (Adult)		10.7	2.2	85.7	1.4
FriXy-gel + N	10.9	2.2	86.8	0.1	
FriXy-gel standard		11.1	0	88.8	0.1

For various neutron energies, we have related the kerma factors for gel, evaluated utilising data of ICRU-26 [10], to the kerma factors for adult brain from ICRU-46 [11]. The resulted ratios, reported in Fig.3, show a good tissue-equivalence of the gel with nitrogen for all energies. As expected, the gel nitrogen-depleted departs from equivalence for thermal and epithermal neutrons, and this difference in kerma factors is a consequence of the absence of charged particles due to the reaction with nitrogen. Therefore, this gel can be utilised to measure the dose from the γ-rays emitted in the reactions with hydrogen.

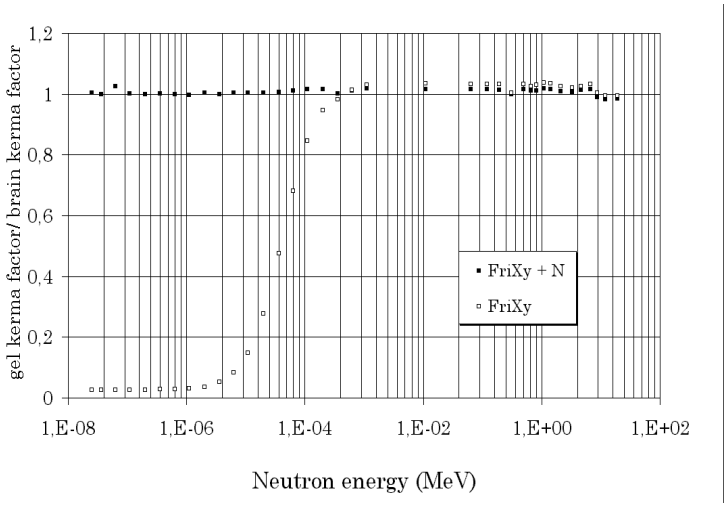

FIG. 2. Ratio between gel and brain kerma factors.

Preliminary calibrations were realised, exposing the three different types of gel to gamma radiation, in order to investigate the gamma sensitivity of the dosimeters with the different compositions. We have found that the sensitivity of the FriXy-gel with boron is slightly lower than that of the standard FriXy-gel, and also lower is the sensitivity of the gel with nitrogen.

3.3. Experimental results with thermal neutrons

In order to check the method for dose imaging and discriminating, some exposures have been made in the thermal column of the fast nuclear reactor TAPIRO, at the ENEA Casaccia Centre near Rome, where a proper thermal column was designed and constructed for BNCT experiments. This facility is a highly enriched ^{235}U research reactor. The nominal power is 5 kW (thermal) and the maximum neutron flux is 4×10^{12} $cm^{-2}s^{-1}$. In the thermal column, the moderating structure, designed by means of MCNP simulations, is composed of 40 cm thick graphite blocks. The structure, whose section is shown in Fig.4a, has a cubic shape. A 10 cm thick lead γ-shield was located inside the graphite, in order to have low gamma background in the irradiation volume, which is a cubic space with sides of about 18 cm. The thermal neutron flux in the thermal irradiation volume, at the maximum reactor power, was $3\cdot10^{8}$ cm^{-2} s^{-1}.

The phantom we have exposed to the neutron field was made up of a polyethylene cylinder (16 cm diameter, 14 cm height) with a coaxial cylindrical hole (6 cm diameter) as shown in Fig.4b. In the hole, four FriXy-gel rectangular layers (3 mm thick) were arranged in each exposure, by alternating gels having different compositions, in order to discriminate between the various contributions to the absorbed dose. We have chosen polyethylene as phantom material, because its hydrogen concentration makes the spatial distribution of the absorbed dose from the g rays emitted in the reaction with hydrogen to be very similar to that in tissue. Moreover, it was more practical than an entire phantom made of gel. In fact, the aim of the experiment was that of investigating the feasibility of such dose measurements and the reliability of the obtained results. When dose determinations in some specific situations will be needed, a convenient phantom will be designed.

In various thermal neutron exposures of the phantom, the FriXy-gel layers (standard, with nitrogen, with boron) were laid one upon another with horizontal orientation.

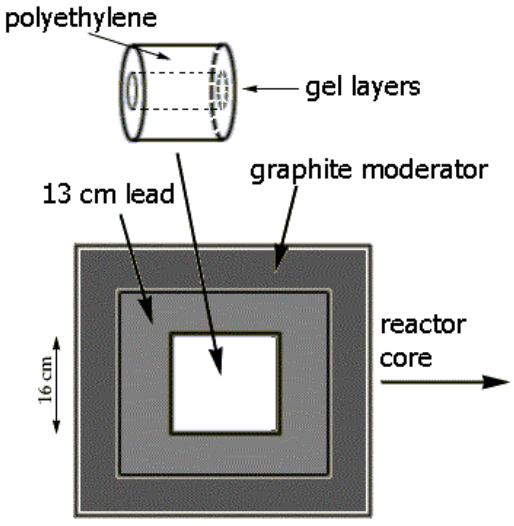

FIG. 3a. Moderator and irradiation set up.

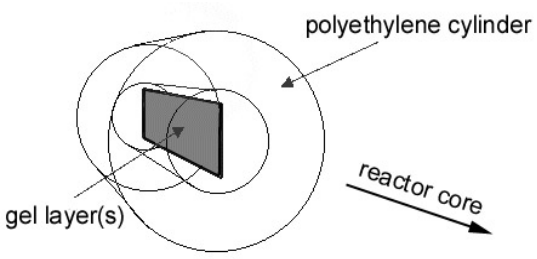

FIG. 3b. Polyethylene phantom.

The empty spaces between the gel and the cylinder were filled up with properly shaped polyethylene pieces, in order to avoid vacuum spaces and to have a good global tissue-equivalence. So, in each position of all the gel layers, the absorbed dose due to the γ rays generated by neutrons in the reactions with hydrogen is the same that would be absorbed, in the same position, in tissue. Moreover, in the gel containing nitrogen, the dose due to the particles generated in the reactions with such nuclei, which is locally released, is absorbed in addition to the previous one, and its value is equal to the corresponding absorbed dose in tissue. Therefore, from differential analysis of images, all contributions to the absorbed dose can be obtained.

In Fig.5, images and Grey-Level profiles of irradiated gels (with boron, standard and with nitrogen) are shown. The visible transversal gradient, showing a lack of symmetry in the thermal neutron field, was found with conventional dosimeters, too. Properly elaborating the images of different gel layers (standard, with nitrogen, with boron) each one normalised with respect to its own calibration, it is possible to image the dose contributions due to gamma radiation and to protons in healthy tissue and the therapy dose from boron. To translate images into dose values, the γ-calibration of each dosimeter gel was utilised; in such a way, the dose due to γ-radiation is directly obtained from standard FriXy-gel, and by means of properly made subtraction operations the γ-equivalent dose of the other secondary radiation can be derived. To obtain the correct values of all doses, the sensitivity of the dosimeter to the various radiation has to be considered. For the standard Fricke dosimeter, it is known that the dosimeter response to high LET protons is lower than that to γ rays, because there is dependence upon LET of the production of OH and H radicals, which determine the radiation-induced oxidation of ferrous ions. The possible LET dependence of the dosimeter with the chemical composition we have prepared deserves to be determined. We have not yet started studying the gel response to protons, because previously we aim to search how to prepare a dosimeter-gel containing the desired amount of nitrogen which presents best characteristics, i.e. best sensitivity and, principally, more reliability and stability in time. So, for the gel with nitrogen we have utilised the γ-calibration with no correction factor. The dose due to ^{10}B (that comes from the energy released both from α particles and ^{7}Li ions) seems to be not well described by the γ-equivalent dose. In a previous experiment [3], where Fricke-infused gels were analysed by means of NMR imaging, we have found that the apparent sensitivity of the gel dosimeter to the secondary radiation from ^{10}B was about one half of that to γ-radiation. So, we have considered that this effect could be present in the case of the FriXy-gel also. We have related the γ-equivalent dose measured in a certain position of the dosimeter to the theoretical

absorbed dose [12] (originating from the α and ^{7}Li particles) evaluated, in the same position, on the basis of the fluence value measured with an activation foil. Then we have brought a correction factor of 0.588 to the γ-equivalent dose to obtain the dose due to ^{10}B. A good determination of the sensitivity of the dosimeter gel to the secondary particles of the ^{10}B reaction is necessary and its study is in program. In Fig.6 the dose profiles are reported.

As mentioned before, in the analysis of images, we have found noticeable trouble coming from the fact that the gel with nitrogen has resulted to have lower higher variation in time, and also if we try to take into account this effect, the reliability of results is lower. It will be convenient to find a best technique to prepare the gel-dosimeter containing nitrogen, in order to achieve unfailing behaviour.

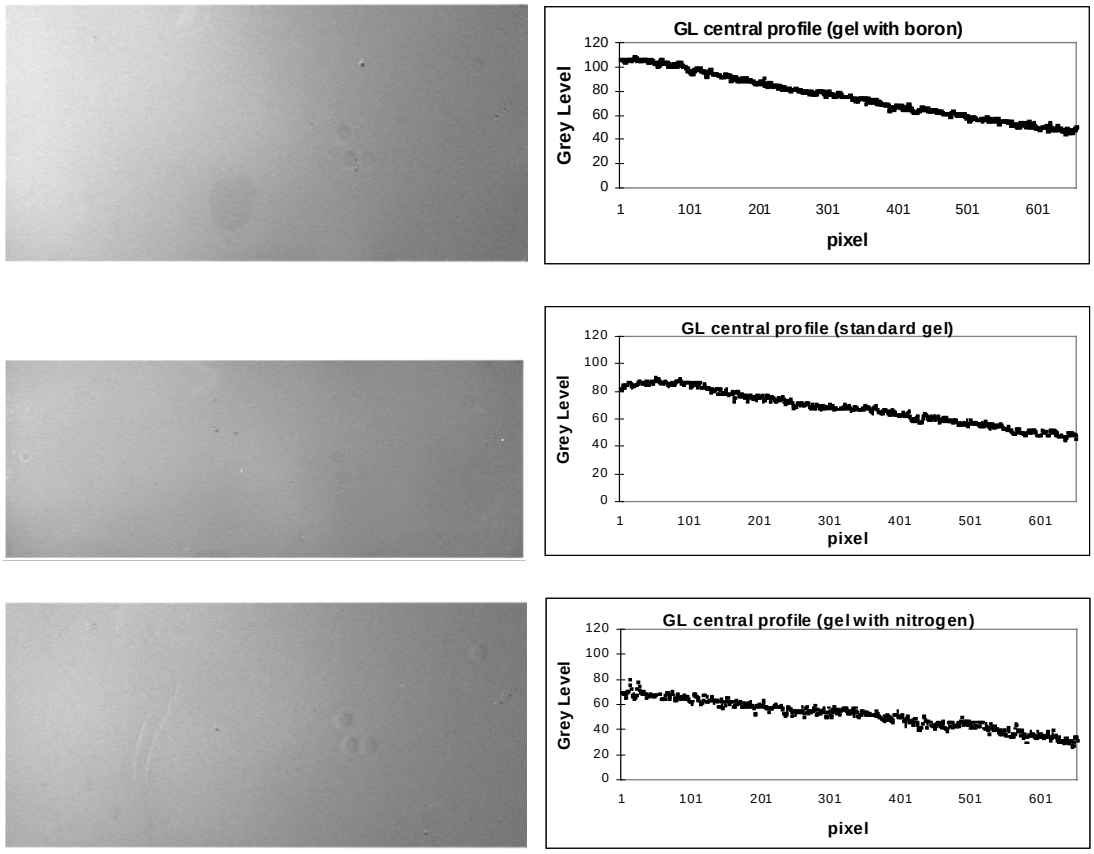

Fig. 5. Transmittance images and Grey Level profiles of gels with the various compositions.

4. INTERCOMPARISON WITH OTHER EXPERIMENTAL RESULTS

To check the validity of the method, some measurements with standard techniques were performed, and the results were inter-compared. In particular, activation techniques and thermoluminescent dosimeters (TLD) were employed. In such measurements, the cylindrical cavity of the phantom was filled with polyethylene, and the dosimeters were located in small hollows, in positions corresponding to gel layers.

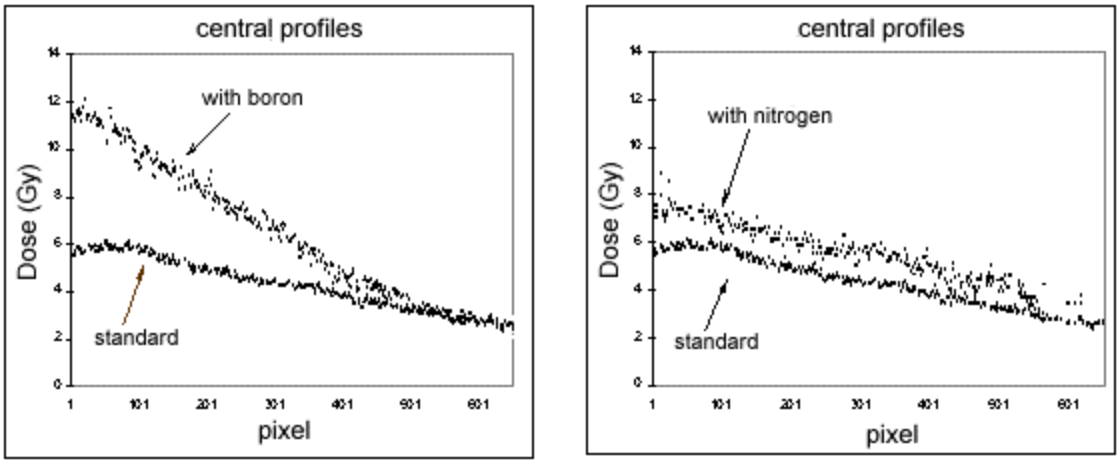

FIG.6. Dose profiles in the various gel dosimeters.

By means of activation technique, thermal neutron fluence values in some positions in the phantom were measured. By means of TLDs, both γ ray dose values and thermal neutron fluences were measured. The activation foils used were made of gold or indium in form of thin disks (1 cm diameter). Foils were located in polyethylene supports, in the same positions of TLD dosimeters (but in separate exposures). In order to determine thermal neutron fluences, two exposures were performed, with foils, in the same positions, naked or screened with Cadmium. The foils were properly oriented in order to avoid mutual shielding. For γ ray dose determinations, TLD-300 chips (CaF_2:Tm) were utilised, whose sensitivity to thermal neutrons is very low, so that up to fluences of the order of 10^{12} cm^{-2} they have a response not affected by thermal neutron contributions. Thermal neutron fluxes in discrete position were measured with TLD-100 chips (LiF:Mg,Ti). The fluence values measured with TLD-100 and with activation foils were very close to each other. Such data were utilised to test the consistency of the various profiles obtained by elaborating gel images.

To compare the results obtained with such dosimeters with the results obtained by elaborating FriXy-gel images, from the dose profiles of gel with boron the profiles (in corresponding positions) of gel without boron were subtracted, after normalisation for gel sensitivity. In such a way, the contribution of γ-rays emitted in the reactions with hydrogen is removed, and the resulting profile is the dose due to reactions with ^{10}B only. The so obtained values are quickly converted into fluence values. The flux profiles are in such a way evaluated. The comparison of the obtained fluxes with flux values measured by means of activation foils and TLDs, as shown in Fig. 7, confirm the reliability of the technique.

5. FINAL CONSIDERATIONS

The described results show that the technique is very promising and induce us to make improvements, in order to achieve higher precision and to get more knowledge.

With regards to the instrument for gel imaging, a refinement is in progress for what concerns image detection and transfer. Moreover, the proper software still in development will give the possibility of compensating for the lack of uniformity in the illuminator and for its instability in the time. The gel behaviour needs to be studied more widely.In fact, exposures in the thermal column of the reactor take long times, of the order of five hours.

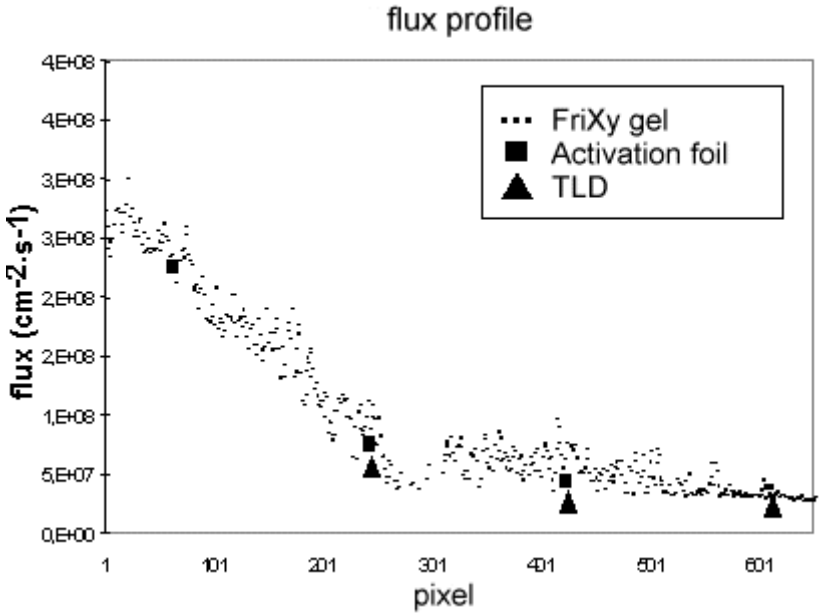

FIG.7. Inter-comparison of flux profile obtained with FriXy-gel and fluxes measured with activation foils and with TLDs.

So, it is necessary to understand how sensitively the gel can undergo modifications in the irradiation time, and how such effect can be taken into account in order to achieve good reproducibility and reliability of results. For achieving the desired amount of nitrogen, we have added the chemical compound Urea to the gel components, but the resulting gel-dosimeter, in addition to a lower sensitivity, has shown higher instability in time. It should be therefore very important to find a better method of preparation of the gel with nitrogen.

Another very important argument, presently in study in our laboratory, is the measurement of the contribution of fast neutrons to the absorbed dose. As said before, in epithermal neutron fields this contribution will be not negligible with respect to the dose from thermal neutrons in tissue without boron. This contribution is mainly due to the recoil protons resulting from inelastic scattering of neutrons with hydrogen nuclei, and its radiobiological effectiveness is different from that of γ-radiation emitted in the reaction, with hydrogen too, of thermal or epithermal neutrons. Therefore the 'total dose' is meaningless, and discrimination is necessary in all situations in which neither contribution is negligible with respect to the other. We aim to face the problem by means of differential analysis of images of absorbed dose in FriXy-gels made with light and with heavy water [13]. The method we are considering and testing is based on the consideration that in heavy-water Fricke solution the ferrous ion oxidation yield is higher than in light-water Fricke solution in a γ ray radiation field, but the opposite situation was found in neutron fields [14,15]. We are investigating the response of a heavy-water FriXy-gel dosimeter, to enquire the possibility of separating the dose from fast neutrons by differential analysis of images obtained by heavy/light-water made gels. The heavy-water gel layer will be made with the maximum thinness compatible with the reliability of images, so to minimise the perturbation of the tissue-equivalence of the phantom. The proper orientation of the gel layer with respect to the neutron beam direction

will be estimated too in order to minimise the perturbation of fast neutron slowing due to the heavy water. This experiment is recently started.

The total and gamma profiles obtained from the images have been compared with calculated profiles found in literature, and the agreement has revealed satisfactory.

APPENDIX

Standard FriXy-gel composition:

ferrous sulphate solution [1 mM $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$], sulphuric acid [50 mM H_2SO_4] and Xylenol Orange [0.11 mM $C_{31}H_{27}N_2Na_5O_{13}S$, Fluka Chemie]in the amount of 50% of the final weight Agarose SeaPlaque [$C_{12}H_{14}O_5(OH)_4$, Fluka Chemie] in the amount of 1% of the final weighthighly purified water [H_2O] in the amount of 49% of the final weight

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Tl detectors in BNCT dosimetry

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Abstract. The main detectors for characterising and controlling of BNCT beams are activation foils and paired ionisation chambers. Thermoluminescent (TL) dosimeters are also of interest because of their following advantages: i) small physical size, ii) no need for high voltage or cables, i.e. stand alone character, and iii) suitability for large scale measurements; with TL dosimeters it is possible to measure depth dose curves and profiles at the same time, with one irradiation. Also, TL dosimeters may be possible detectors for *in vivo* use. At the Finnish BNCT facility, a TL detector MTS-Ns of TLD Niewiadomski & Co. (Krakow, Poland) with an ultra-thin active LiF:Mg,Ti layer for small self-shielding of thermal neutrons was selected for use as a neutron sensitive dosimeter. A TL detector MCP-7s (^{7}LiF:Mg,Cu,P) of the same manufacturer was used for gamma detection because of its high sensitivity to gamma radiation compared to that to high LET radiation. The gamma dose and neutron fluence distributions have been measured in PMMA, water and brain substitute liquid phantoms at the BNCT beam. Gamma dose and neutron fluence profiles measured with TL detectors correlate with those calculated using DORT (Two Dimensional Discrete Ordinates Transport Code) and measured with ionisation chambers. MTS-Ns TL detectors were found to measure accurately (8 %, 1 S.D.) the relative neutron fluence, and therefore to be a useful addition to the activation foils in BNCT neutron dosimetry. Due to the high uncertainty of the thermal neutron sensitivity of the MCP-7s TL detectors, the absorbed gamma doses can be measured with MCP-7s detectors within 20% in the mixed neutron-gamma field of BNCT. The treatments of glioma patients at the Finnish BNCT facility will start in the spring 1999. The doses to the target volume and sensitive organs, i.e. brain, will be calculated individually in the dose planning. Since it is also necessary to monitor the absorbed doses to the head and to the body, *in vivo* dosimeters are used. For clinical practise, when verifying the absorbed doses *in vivo* the used TL and activation foil dosimeters must be placed on the skin of the patient or in accessible cavities. The TL detector MCP-7s will be used in *in vivo* gamma dosimetry. The corrections for the thermal neutron sensitivity of the MCP-7s TL detectors will be made based on the neutron fluence measured with activation foils. The accuracy of approximately 10% can be achieved in those measurement points, in which thermal neutron fluence is negligible and, therefore, no correction for thermal neutron sensitivity is required. This applies to those measurement points in the body, i.e. total body dose.

1.1. INTRODUCTION

Boron neutron capture therapy (BNCT) [1–3] utilises epithermal neutrons for the treatment of malignant tumours. In BNCT ^{10}B is introduced into the tumour cells, and the selective therapeutic dose is delivered by the neutron capture reaction $^{10}B(n,a)^{7}Li$ when exposed to a neutron fluence. In order to evaluate the quality of an epithermal beam for BNCT the desired epithermal neutron fluence and the undesired fast and thermal neutron fluences as well as gamma fluence have to be determined. The gamma dose to tissue when irradiated with epithermal beam is composed of gamma rays present in the beam and from the capture reaction $^{1}H(n,g)^{2}H$.

The main dosimeters for characterising and controlling BNCT beams are activation foils and paired ionisation chambers [4]. In clinical dosimetry, ionisation chambers are commonly used for phantom measurements because of their accuracy and practicality [5,6], but for *in vivo* measurements they are not frequently used because of the high voltage applied and the size of the chambers and the cables attached to them. For BNCT dosimetry, thermoluminescent (TL) dosimeters are of interest because of their following advantages [7]: i) wide useful dose range, ii) small physical size, iii) reusability and therefore, iv) economy, v) no need for high voltage or cables, i.e. stand alone character, vi) tissue equivalence (LiF) for most radiation types, and vii) suitability for large scale measurements; with TL dosimeters it is possible to measure depth dose curves and profiles at the same time, with one irradiation. Also, TL dosimeters may be possible detectors for *in vivo* use.

In previous phantom studies, MCP-7s (^{7}LiF:Mg,Cu,P) and TLD-700 (^{7}LiF:Mg,Ti) TL dosimeters have been used in the gamma dosimetry of BNCT [4, 8–11]. However, as the response of a TL material to thermal neutrons is mainly dependent on the thermal neutron capture cross sections of its constituent elements [12], difficulties have been encountered arising from a small ^{6}Li content in the enriched ^{7}Li. Therefore, Raaijmakers *et al*. [4,13] have applied the method in which the TL detectors are shielded from thermal neutrons using a ^{6}Li containing cap in the epithermal neutron beam of BNCT. Also, a theoretical method for determining correction factors for thermal neutron sensitivity of TL detectors has been developed [14], and used [8,15].

Experimentally observed thermal neutron sensitivities of the traditional TLD-100 (LiF:Mg,Ti) detectors have found to vary [16]. These variations in sensitivity are mainly due to the self-shielding of TL detectors which can vary from few percentages to 50% depending on the geometry, i.e. thickness, of TL detector [17]. Therefore, besides the traditional TLD-100 detectors also two-layer detectors (MTS-Ns) with an ultra-thin active LiF:Mg,Ti layer on a passive base have been used as a neutron radiation sensitive dosimeters for BNCT [8].

In patient studies, it is necessary to monitor the absorbed doses *in vivo* to the head and to the body. TLD-700 dosimeters has been used for gamma dosimetry both in patient studies [18], as well as in healthy tissue tolerance studies with beagle dogs [19]. In the Finnish healthy tissue tolerance study the absorbed gamma doses were measured *in vivo* with MCP-7s detectors [20].

TL detectors can be, and commonly are, used for the absorbed dose measurements performed with the aim to investigate cases where dose prediction is difficult, and not as a part of a routine verification procedure. Among these cases are, for example, new radiotherapies which have been developed for patient treatment during the past decades. Absorbed dose determination in these radiotherapies, e.g. boron neutron capture therapy, is more complicated (see e.g. refs. [4,13]) compared with the traditional external radiotherapy.

High uncertainties may be present in the dose determination due to the patient anatomy, i.e. geometry, the less accurate irradiation source definition or the radiation quality, among the other things. The aim of this work was to study the applicability of TL detectors in BNCT dosimetry.

2. MATERIALS AND METHODS

Based on the observations of our previous study [8], MTS-Ns (LiF:Mg,Ti) and MCP-7s (^{7}LiF:Mg,Cu,P) TL detectors of Dosimeter Niewiadomski & Co. were selected for use for neutron and gamma detection, respectively, in the mixed neutron-gamma field of BNCT. In this work, the absorbed gamma doses were derived as explained in detail elsewhere [8]. Since no thermal neutron shields were used in these measurements, the correction for the thermal neutron sensitivity of the gamma detectors were made based on the theoretical method [14,15]. Neutron fluences were derived as explained in the same study [8], in which a code of practise for relative neutron fluence measurements, performed with TL detectors in the mixed neutron-gamma field of BNCT, has been presented.

The MTS-Ns detectors were prepared by heating in an oven at 400°C for ten minutes. The preparation of the MCP-7s detectors was made by heating the detectors in a Vinten Toledo 654-reader with a reading temperature of 240°C for 40 s. Readout of the dosimeters was made with the same TL dosimeter reader, Vinten Toledo 654. The heating profiles of 135°C for 16 s followed by 40 s at 240°C and 20 s at 340°C (ramp heating) were used for the MCP-7s and for MTS-Ns detectors, respectively. Calibration of the detectors was made by irradiating the dosimeters to the air kerma of 0.5 Gy with a ^{60}Co source at Secondary Standard Dosimetry Laboratory (SSDL) of Helsinki. To get a homogeneous irradiation for individual calibration, all the dosimeters were irradiated in a running wheel with ^{60}Co source (SSDL of Helsinki) and an epithermal neutron beam (TRIGA Mark II research reactor FiR 1 in Otaniemi, Espoo) [21,22].

The measurements with TL dosimeters were performed in cylindrical (diameter 20 cm, length 24 cm) PMMA (polymethylmetacrylate, $(C_5H_8O_2)_n$), water and brain substitute liquid (Liquid B) [23] phantoms at the epithermal neutron beam of the 250 kW TRIGA Mark II research reactor FiR 1. The beam exit aperture diameter was 14 cm. Reactor powers of 130 kW for the MCP-7s detectors and 10 kW for the MTS-Ns detectors were used. The irradiation time was 15 minutes for both detector types. TL detectors used for measurements in the water and in the Liquid B phantoms were inserted in holes in polypropylene discs. These holes were water isolated with paper and self-adhesive tape of polypropylene on both sides of the discs. Also, measurements were performed with MCP-7s TL detectors situated on the surface of the modified BOMAB phantom [24,25]. In these irradiations the reactor power of 250 kW and irradiation time of 20 minutes were used.

3. RESULTS AND DISCUSSION

The uncertainties of the performed gamma dose and neutron fluence measurements are illustrated in TABLE I. The low precision of the gamma dosimeter MCP-7s is mainly due to the reproducibility of the detector: after irradiations in the mixed neutron-gamma field, the reproducibility of the TL readings was found to be only 7% (1 S.D.) [8]. The reason for the poor reproducibility is assumed to be in the high temperature glow peaks of the ^{7}LiF:Mg,Cu,P TL material generated by neutron radiation. These glow peaks are not released during the used annealing procedure: it is recommended by the manufacturer that MCP-7s detectors be prepared by heating at 240°C ± 5°C for ten minutes, but since a sufficiently stable oven was

unavailable to meet this temperature requirement, the preparation was made by heating the detectors in a Vinten Toledo 654 -reader with a reading temperature of 240°C for 40 s followed by the rapid cooling with the normal rate of the heater planchet (from 240°C to 80°C in about 20 seconds). By using a proper oven for annealing, and the recommended (or longer) annealing time with an advanced readout technique and background subtraction method, the reproducibility of the MCP-7s detectors might be reduced considerably (e.g. to be < 1% as in [26–28]) from the obtained 7% [8]. Furthermore, the use of an annealing temperature higher (e.g. 260°C) than the standard 240°C may improve the reproducibility of ^{7}LiF:Mg,Cu,P detectors [29,30].

TABLE I.: The uncertainties present in the gamma dose (MCP-7S) and neutron fluence (MTS-NS) measurements performed with TL detectors.

Specification of the uncertainty, ui	Reference	Estimated u_i (1 SD) %	
		MCP-7s	MTS-Ns
u_1 = u(neutron fluence)	[8]	-	12.5
u_2 = u(gamma dose)	[8]	7.5	-
u_3 = u(correction to neutron sensitivity)	[15]	18	-
u_4 = u(measurement arrangements)	[32]	3	3
$u_5 = u(\text{total}) = (u_1^2+u_2^2+u_3^2+u_4^2)^{1/2}$		20	13

The inaccuracy for the gamma dose measurements is also caused by the high uncertainty (18%, TABLE I) present in deriving the correction factors [14] for thermal neutron sensitivity of the used TL detectors. According to our previous study [8], MCP-7s is less sensitive for thermal neutrons, and therefore more suitable for BNCT dosimetry, than the traditional TLD-700. However, its thermal neutron sensitivity was found to be essentially higher than that based on the literature [31], and therefore a detailed study was performed about its thermal neutron sensitivity [15]. The uncertainty of the thermal neutron correction factor mainly arises [15] from the uncertainty of the spectrum averaged fluence-to-kerma conversion factor, used in theoretical derivation of the correction factor [14]. The uncertainty of the used fluence-to-kerma conversion factor is 10% [32], and it is also one of the major sources of error [8] in deriving the (relative) neutron fluence from the measurements performed with MTS-Ns detectors.

The reproducibility of the MTS-Ns detectors was found to be 6% (1 S.D.) in the mixed neutron-gamma field [8]. The used 400^{o}C high temperature annealing regenerates these detectors completely and residual background readout values do not explain any instability in the detector sensitivities. In our recent study [33] on the response characteristics of the MTS-Ns detectors, the reproducibility of the readout values has been improved by using advanced readout technique with linear heating and glow curve analysis. When performing measurements with large number of consecutive TL detectors in the phantom, the TL detectors may have influence to each others TL readings. Therefore, a Monte Carlo simulation was used to estimate this shielding effect [34]. In the simulations, detectors positions were selected to be the same as those in actual measurements [8] at the BNCT beam of FiR 1.

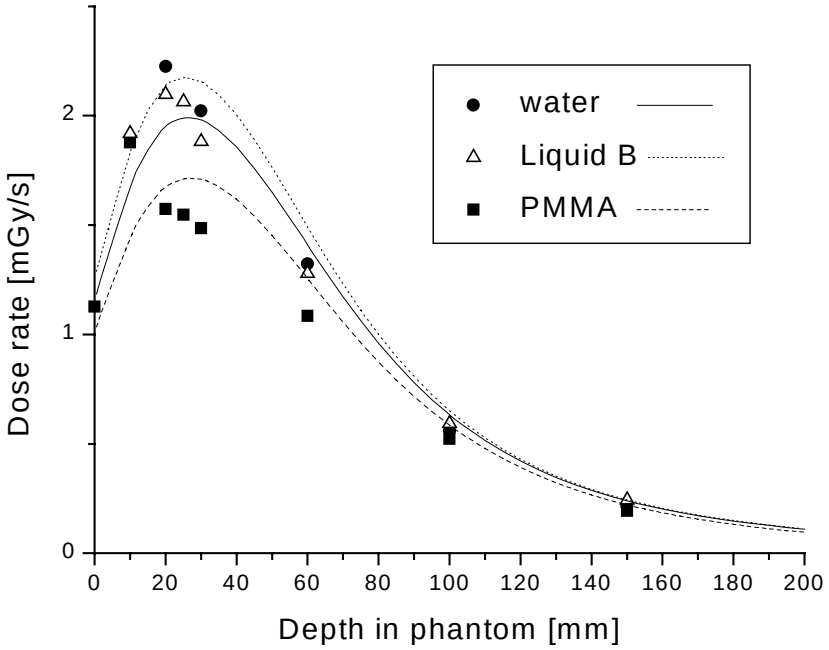

FIG. 1. Depth dose curves for gamma measured (symbols) and calculated (lines) in cylindrical PMMA, water and brain substitute liquid (Liquid B) phantoms. The uncertainty of gamma dose measurements, mainly caused by the uncertainty of the thermal neutron sensitivity, can be even 20% (1 S.D.) at the depth of thermal neutron fluence maximum.

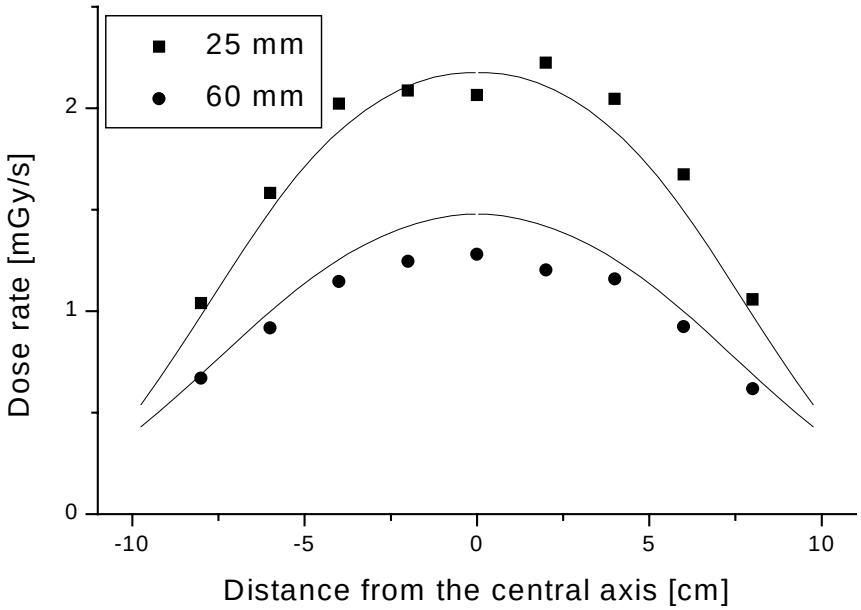

FIG. 2. Measured (symbols) and calculated (solid lines) transverse profiles of the gamma component in the brain substitute liquid phantom at the depths of 25 mm and 60 mm, measured from the phantom surface.

Also, Monte Carlo simulations were used to determine the perturbation of the neutron and gamma fluences caused by the polycarbonate ($(C_{16}H_{14}O_3)_n$) frames, with the aid of which the TL detectors have been fixed in the measurements in the phantom. As a result, no significant fluence differences were found to occur in the cases of thermal and epithermal neutrons or gamma rays: the neutron and gamma fluence rates were similar within 3% for the simulations with and without neighbouring ^{nat}LiF or ^{7}LiF TL detectors and polycarbonate frames at various measurement points in the phantom. The spatial uncertainty of the measurements performed in the water and Liquid B phantoms is ± 0.5 cm due to uncertain positioning of the TL detectors to their thin holder frames.

According to the Burlin cavity theory [35], a one sided cavity effect occurs when irradiating the phantom medium surrounded MCP-7s TL detectors. Because of the one sided effect and the isotropic angular distribution of the gamma rays and secondary electrons, the increase in the dose to the active LiF was estimated to be less than 10% [8]. Therefore, a reduction of 5% was made for the kerma, measured with MCP-7s detectors, to correct for the error caused by the cavity effect. However, the use of thin layer detectors, such as MCP-7s, for the gamma dosimetry should be re-considered because of the uncertainty caused by the cavity effect.

It is found in this work (TABLE I), that even if lower precision, the accuracy of the dose estimations, performed with TL detectors in the phantoms, is not essentially worse compared with that performed with ionisation chambers [36]. However, in the measurements with TL detectors, additional uncertainty may also be caused by detector handling. In this study, detectors were carefully handled, either by mechanical or vacuum tweezers in order to avoid uncertainty. Because it seems that frequently handled TL detectors lose sensitivity when handled with mechanical tweezers [37], the detecting surface of the dosimeters was not touched while using the mechanical tweezers. No cleaning of the used detectors was needed and, therefore, performed. Also, cleaning is good to avoid [37] since it may change the crystalline surface structure and, therefore, response characteristics of the detector.

Depth dose curves for gamma radiation, measured with TL detectors and calculated using DORT (Two Dimensional Discrete Ordinates Transport Code) [38], are presented in FIG. 1. for cylindrical PMMA, water and Liquid B phantoms. FIG. 2. shows transverse profiles of the measured and calculated gamma dose rate components in the brain substitute liquid phantom. Similar comparisons are presented for the thermal neutron fluence distributions measured with TL detectors and activation foils in FIG. 3. and 4. As seen in the figures, the obtained gamma dose and neutron fluence distributions correlate within the uncertainties (TABLE I) with those calculated using DORT code and measured using activation foils, respectively. The absorbed gamma doses measured on the surface of the BOMAB phantom are presented in TABLE II. The measurement points were selected to be the same as those to be used with patients, and representing total body dose. As a comparison, crude estimates calculated with DORT code are also presented (TABLE II), and found to be the same order of magnitude than the measured values. It is concluded that TL detectors are capable for BNCT dosimetry, and therefore they are a useful addition to the more common dosimetric methods used in BNCT. At the Finnish BNCT facility, the absorbed doses to healthy tissues are monitored for the glioma patients. For clinical practice, when verifying the absorbed doses *in vivo*, the dosimeters must be placed on the skin of the patient or in accessible cavities. Based on the results of this study, the TL detector MCP-7s will be used for *in vivo* gamma dosimetry. The corrections for the thermal neutron sensitivity of the MCP-7s detectors will be made based on the neutron fluence measured with activation foils.

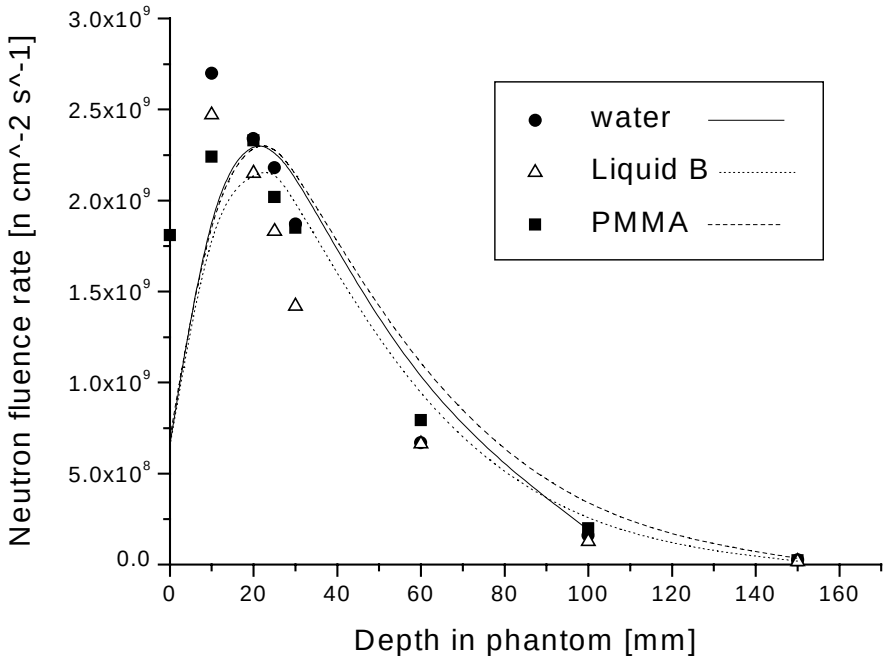

FIG. 3. Thermal neutron fluence (^{6}Li response) distributions as a function of depth measured with TL detectors (symbols) and activation foils (lines) in PMMA, water and brain substitute liquid (Liquid B) phantoms (diameter 20 cm, length 24 cm).

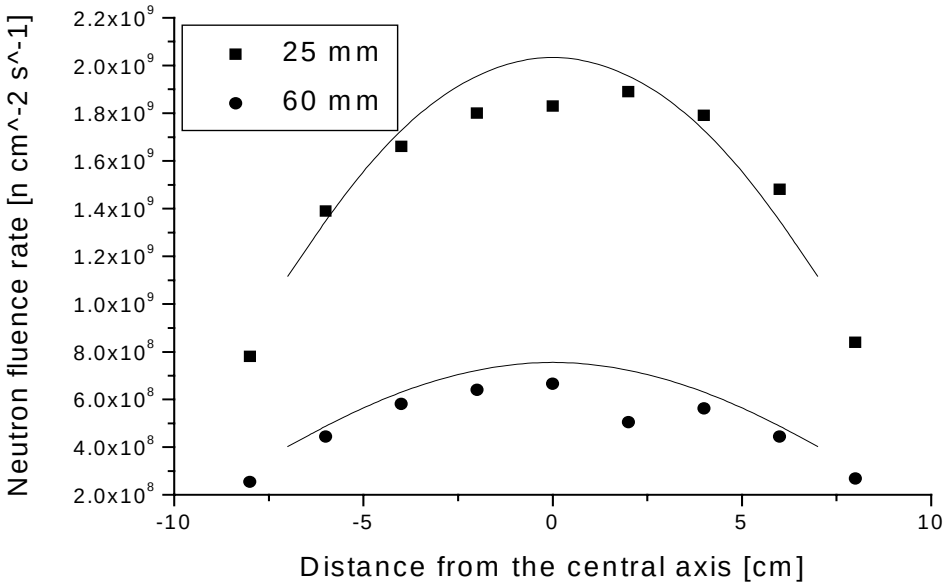

FIG. 4. Transverse profiles of the neutron component in the brain substitute liquid phantom measured with TL detectors (symbols) and activation foils (solid lines).

TABLE II: The measured and calculated absorbed gamma doses to the points situating on the surface of the BOMAB phantom, and representing the total body dose, during the irradiation time of 20 minutes.

	Absorbed gamma dose (mGy)	
	measured	calculated
Thyroid	80 ± 10	100
Sternum	40 ± 5	30
Umbilicus	10 ± 1	30

According to this study, the accuracy of approximately 10% can be achieved in those measurement points, in which thermal neutron fluence is negligible and, therefore, no correction for thermal neutron sensitivity is required. This applies to those measurement points in the body, i.e. total body dose.

5. CONCLUSIONS

In many clinical applications, the use of TL dosimeters is the only available tool for dosimetry. TL detectors are especially useful in difficult geometries where the best use can be made of their advantages such as their stand alone character and small physical size. In this work, the abilities of TL detectors were studied in BNCT dosimetry, in which TL dosimeters were found capable for the gamma dose and neutron fluence measurements.

The uncertainties of TL dosimeters were found to be high but not essentially worse than for the other measurement techniques used in BNCT dosimetry. Also, the precision and accuracy of the absorbed dose measurements performed with TL detectors may be improved by: i) selecting the appropriate detector type for the measurement purpose, ii) using the recommended thermal treatment procedure, and iii) careful handling of the detectors. It is showed in this work that the absorbed gamma doses can be measured with TL detectors within 20% in the mixed neutron-gamma field, which enables *in vivo* measurements at BNCT beams with approximately same accuracy.

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Characteristics of neutron irradiation facility and dose estimation method for neutron capture therapy at Kyoto University research reactor institute

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Abstract. The neutron irradiation characteristics of the Heavy Water Neutron Irradiation Facility (HWNIF) at the Kyoto University Research Reactor Institute (KIJRRI) for boron neutron capture therapy (BNCT), were described. The present method of dose measurement and its evaluation at the KURRI, were explained. Especially, the special feature and noticeable matters were expound for the BNCT with craniotomy, which was applied at present only in Japan.

1. INTRODUCTION

The updating construction of the HWNJF of the Kyoto University Research Reactor (KUR, full power: *5* MW) had been performed from November *1995* to March 1996 mainly for the improvement in neutron capture therapy (NCT) [1,2]. The main aims were (i) improvement in the safety and maintainability of the facility, (ii) improvement in the performance for NCT in the application of both thermal and epi-thermal neutrons, and (iii) the improvement in the utility such as NCT clinical irradiation during the full-power continuous KUR operation, etc.. The KUR Advanced Irradiation System for NCT was organized. The first NCT clinical irradiation at the HWNIF was performed for a brain-tumour patient with the thermal neutron irradiation mode in November 1996. Fourteen NCT clinical irradiation; four with the thermal neutron irradiation mode and ten with the mix irradiation mode of thermal and epi-thermal neutrons, were already performed as of June 1999. Solo-irradiation of epi-thermal neutrons is planning to start in near future. The knowledge and experiences obtained from sixty-one NCT trials before the updating and fourteen trials after that, were reported in the viewpoint of radiation medical physics.

2. THE KUR ADVANCED CLINICAL NEUTRON IRRADIATION SYSTEM

Figure 1 shows the layout of the KIJR advanced clinical irradiation system. This system consists of the HWNIF, the radiation shielding system and the remote carrying system. In the HWNIF, the epi-thermal neutron moderator to increase the epi-thermal neutron component, the neutron energy spectrum shifter and heavy water shutter to control the neutron energy spectrum, are installed inside of the heavy water tank in order from the core side. The thermal neutron filters of cadmium and boral to control the thermal neutron component, and the bismuth layer as a gamma ray filter, are installed outside of the heavy water tank. The neutron irradiation with several neutron energy spectra from almost pure thermal neutrons to epi-thermal neutrons are available at the HWNIF.

The radiation shielding system consists of (i) the heavy water shutter and the neutron energy spectrum shifter against fast neutrons, (ii) the thermal neutron filters of cadmium and boral against thermal neutrons, and (iii) the beam shutter and the entrance shield door for the irradiation room against both neutrons and gamma rays. An open-or-close operation of the radiation shielding system can be done by remote control, and it takes about five minutes. In the standing point of the safety for radiation exposure, the operations of the entrance shield door and the beam shutter are interlocked. As the total dose equivalent rate of neutrons and gamma rays is a little less than *250* kt Sv/hr at the normal working area in the irradiation room

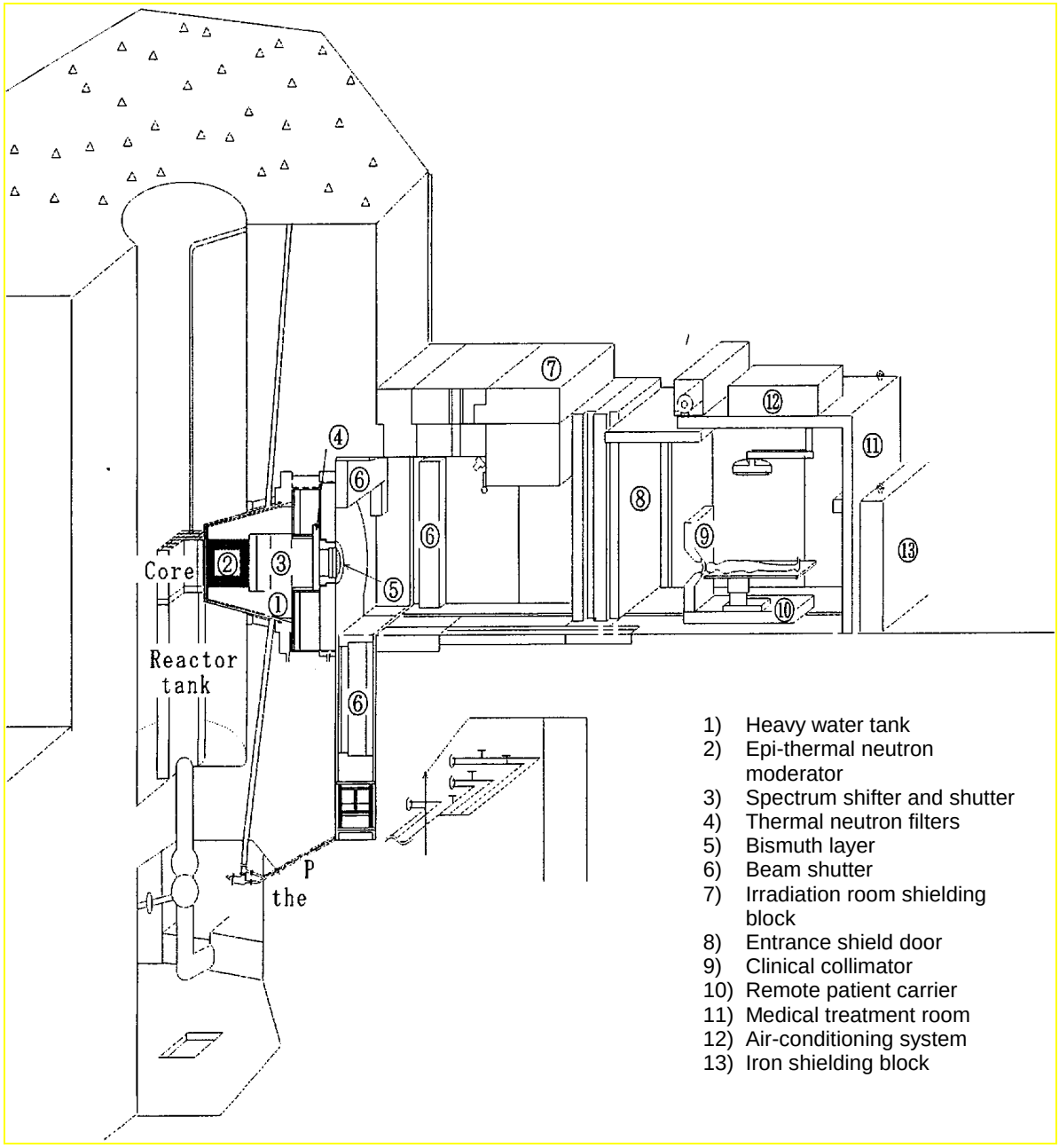

FIG.1. Layout of the KUR advanced clinical irradiation system.

under a continuous KUR operation, the admittance time to the irradiation room should be limited within four hours per a week.

Employing the Remote Carrying System together with the Radiation Shielding System, the clinical irradiation are possible under a continuous KUR operation. The setting and positioning for a patient and the regulation of the monitoring equipment, etc., can be performed outside of the irradiation room. Patient Carrier, employing the X-Y laser pointers, etc. A clinical collimator system and a manual X-Y table are settled on the Remote The positioning of the patient to the collimator aperture is easily possible table, a clinical bed with position-control mechanism for up-down and rotation, Thus, the utility and application of the facility for NCT is remarkably improved.

3. THE IRRADIATION CHARACTERISTICS AT THE NORMAL IRRADIATION POSITION

3.1. Characterization methods

The boundary energies between thermal and epi-thermal neutrons, and between epi-thermal and fast neutrons, are usually fixed to 0.6 eV and 10 keV, respectively, for biomedical uses at the KURRI. Gold foil of 5011 m thickness and 3 mm diameter, and cadmium cover of 0.7 mm thickness are used in the measurement of thermal neutron flux and cadmium ratio. For the estimation of epithermal neutron flux, its energy region is represented by 4.9 eV, which corresponds to the main resonance peak of ^{197}Au (n, γ) ^{198}Au cross section. The epi-thermal neutron flux is calculated as the integrated neutron flux from 0.6 eV to 10 keV, on the assumption that the neutron energy spectrum accorded to a l/E spectrum for the energy range.

Table I.: Measured values of the neutron fluxes and gamma ray dose equivalent rates at the bismuth surface during the full-power (5MW) KUR operation.

Irradiation mode	D_20 thickness (cm)	Cadmium ratio	Thermal neutron flux (n/cm^2/s)	Epi-thermal neutron flux* (n/cm^2/s)	Gamma ray dose equivalent Rate (cSv/hr)	D~ / ~ (cSvI(nlcm^2))
00-0111-F	60	700	*5.9E+08*	l.7E+06	40	l.9E-l1
00-0110-F	50	650	7.7E+08	2.4E+06	50	1.8E-l1
00-0101-F	40	400	l.OE+09	5.IE+06	60	l.7E-ll
00-0011-F	30	160	2.OE+09	2.5E+07	100	l.4E-11
00-0010-F	20	51	2.3E+09	9.3E+07	110	l.3E-1l
00-0001-F	10	22	3.3E+09	3.2E+08	180	1.5E-1l
00-0000-F	0	9.4	*5.OE+09*	l.2E+09	330	l.9E-1l
CO-0000-F	0	Almost 1	Not estimable	1.1 E+09	60	1 .6E-11
OB-0000-F	0	Almost 1	Not estimable	4.OE+08	50	3.5E-l1

Measurements were carried out using the "irradiation rail device".
Neutron fluxes were estimated with gold activation foils, and gamma ray doses were measured with TLD (BeO).
*It is assumed that the epi-thermal neutrons have a pure 1/E spectrum.
For the CO-0000-F and OB-0000-F modes, Dγ/∅epi

In the measurement of gamma ray dose rate, thermo-luminescent dosimeter (TLD) of BeO is used. For the TLD on the commercial base (TLD-170L produced by Matsushita Electric Industrial Co., Ltd.), the BeG powder is encapsulated with borosilicate glass. The sensitivity of the TLD-170L is about I cSv per 10 x 10^{10} n/cm^2 thermal neutron fluence due to the (n, α) reactions of ^{10}B contained in the borosilicate glass. So, we ordered the special TLD encapsulated with quartz glass, which does not contain '^{0}B. Incidentally, the BeO powder for the TLD-170L also has a little sensitivity to low-energy neutrons, because of the ^{6}Li impurity. The thermal neutron fluence of 8 x 1012 n/cm^2 is approximately comparable to 1 cSv gamma ray dose. Though the sensitivity of the special-ordered TLD is improved, we usually use the TLD together with gold foil for the neutron-sensitivity correction.

3.2. Irradiation characteristics for the irradiation modes

The “irradiation mode” means an irradiation condition of the facility. The first and second characters in the symbol defining the irradiation mode, as shown in Table 1, represent the open-close conditions of the cadmium and boral filters, respectively. The character “0” means the filter “opened (not full-closed)”, and the character “C” and “B” mean the cadmium and boral filters “full-closed”, respectively. The four numbers represent the conditions of the heavy water shutter and spectrum shifter tanks, in order from the irradiation-room side. The number “0” and “1” mean “empty” and “full”, respectively. The last character represents the center thickness of the bismuth layer, which is optional among 0 cm, 5 cm, 18.4 cm and 23.4 cm. Usually, the bismuth layer thickness is set to be 18.4 cm, namely in the “F” condition.

The measured irradiation characteristics at the normal irradiation position for the several “irradiation modes” are tabulated in Table 1. The thermal neutron flux at the normal irradiation position is influenced about ±10% by the KUR power, the reactor-core arrangement of the fuels and the reflectors, and the control-rod positions, etc.. The epi-thermal neutron flux is more affected by the reactor-core arrangement than the thermal neutron flux, and the flux fluctuation is empirically thought to be about ± 20%. The estimation of the gamma ray dose rate has the error of ± 20%.

As shown in Table 1, both thermal neutron flux and epi-thermal neutron flux decrease according to the increase of the heavy water thickness. For the standpoint of biomedical uses, we defined three groups of the irradiation modes as follows: (1) thermal neutron irradiation group; the cadmium ratio is over 100, (2) mixed neutron irradiation group; the cadmium ratio is below 100, and (3) epi-thermal neutron irradiation group; the cadmium or boral filters are fully closed. Especially, “00-0011-F”, “00-0000-F” and “CO-0000-F” modes, whose available neutron fluxes are the largest in the respective groups, are defined as the standard irradiation modes, and called “standard thermal neutron irradiation mode”, “standard mixed neutron irradiation mode” and “standard epi-thermal neutron irradiation mode”, respectively.

Figure 2 shows the relative intensities of thermal neutrons, epi-thermal neutrons and gamma rays, and the measured values of the cadmium ratio at the normal irradiation position as functions of the cadmium filter aperture. The epi-thermal neutron intensity hardly changes according to the cadmium filter aperture. On the other hand, the thermal neutron intensity, the gamma ray dose rate and the cadmium ratio decrease as the aperture decreases. It is found that the cadmium ratio can be controlled from approximately I to the maximum value of the respective irradiation mode by changing the cadmium filter aperture. As the gamma ray intensity changes according to the same tendency as the thermal neutron intensity, it is thought that the gamma rays at the normal irradiation position are almost generated from the (n, ~) reactions of the bismuth with thermal neutrons. For the cadmium aperture smaller than about 50 mm, the gamma ray intensity increases as the aperture decreases. The reason is thought to be that the gamma rays generated from the cadmium filter and the component from the reactor core exceed the secondary gamma rays from the bismuth layer for the filter aperture of about 50 mm.

Figure 3 shows the comparison of the neutron energy spectra at the normal irradiation position among the 00-0000-F, CO-0000-F and OB-0000-F modes. These neutron energy spectra were estimated mainly by multi-foil activation method with an adjusting code “NEUPAC” [3], and the estimation error was about 20%. The difference of the energy spectra between the CO-0000-F and OB-0000-F modes, is dependent on the difference of the energy characteristics for the neutron penetration between the cadmium and boral filters.

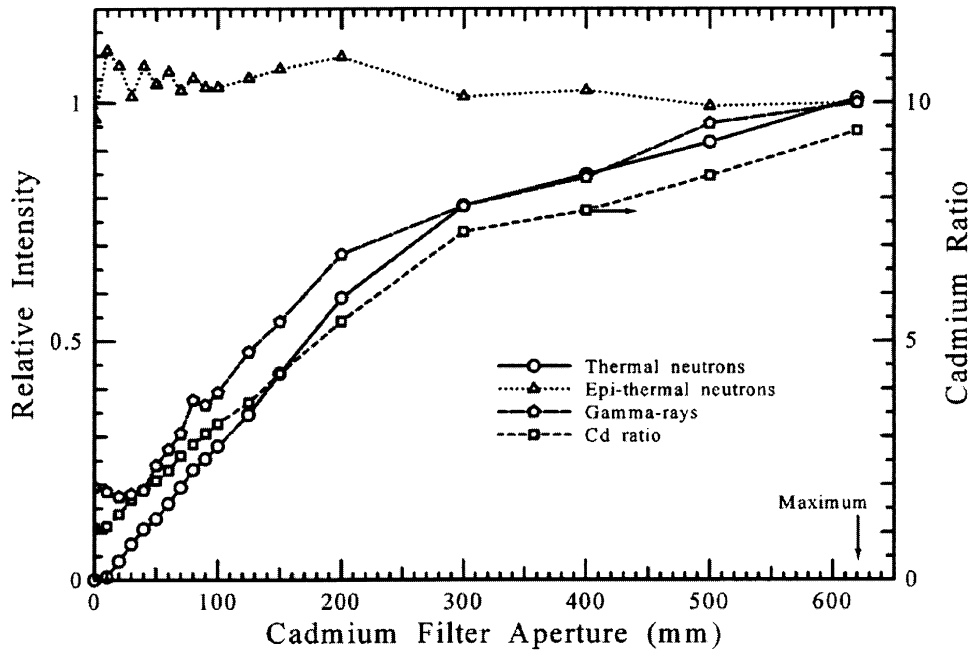

FIG. 2. Measured relative intensities of neutrons and gamma rays, and cadmium ratio at the normal irradiation position depended on the cadmium filter aperture (0 mm: the CO-0000-F mode, 620 mm; the 00-0000-F mode).

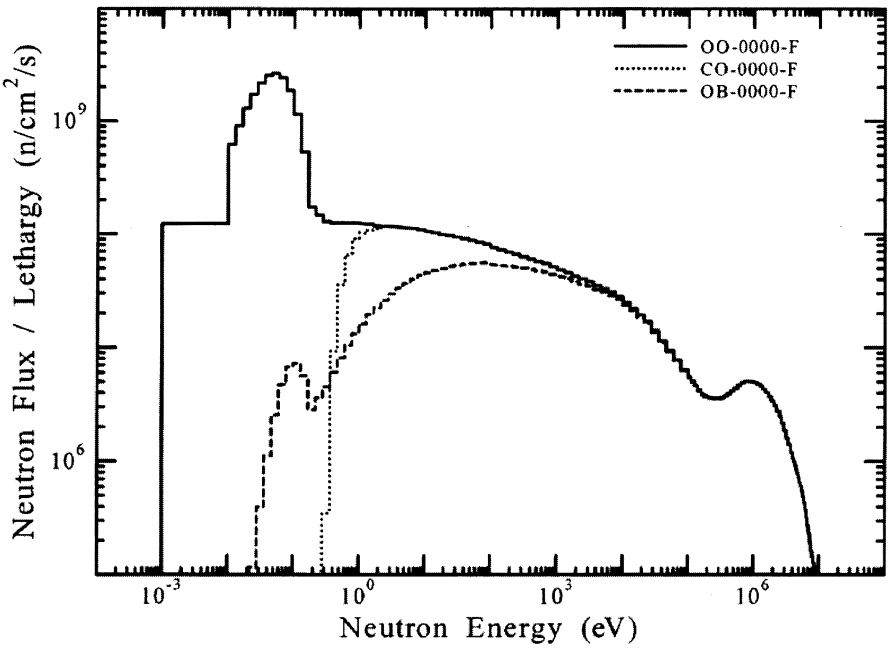

FIG. 3. Neutron energy spectra at the normal irradiation position for the 00-0000-F, CO-0000-F and OB-0000-F modes, estimated by multi-foil activation method

3.3. The dose distribution characteristics for nct clinical irradiation

3.4. Dose distribution in a head phantom

Figures 4 (a) and (b) show the measured depth distributions of thermal neutron flux and gamma ray dose rate in a head phantom for the three standard irradiation modes of 00-0011-F, 00-0000-F and CO-0000-F using the clinical collimator system shown in Fig. 5. The measured data of the old facility is also shown. The used phantom is a water-filled case made with acrylic resin of about 3 ruin thickness, modified a human head. The irradiation field size is 10 cm in diameter.

In the comparison between the 00-0000-F and CO-0000-F modes, the latter thermal neutron flux at the 5 cm depth is 30% of the former one. As the difference between the both modes is mainly generated from whether the thermal neutrons are incident or not, about 30 % of the thermal neutron flux at the 5 cm depth for the 00-0000-F mode is contributed from the moderated thermal neutrons. As the cadmium ratio of the incident neutron beam is smaller, the distribution shape is gentler, the distribution peak position is deeper, and the thermal neutron flux at the deeper part is relatively larger. For example, the depths where the thermal neutron flux becomes 20% of that at the peak position, are about 3.7 cm for the old facility, about 4.5 cm for the 00-0011-F mode, about 5.3 cm for the 00-0000-F mode, and about 8 cm for the CO-0000-F mode. Not only the depth distributions but also the radial distributions are expected to be improved. For the gamma ray dose distributions, the more gamma rays are generated in the phantom according as the thermal neutron flux at the deeper part relatively increases.

3.4. Whole-body exposure dose

Figure 5 shows the measured whole-body distributions of thermal neutron flux and gamma ray dose equivalent rate under an NCT clinical irradiation for the 00-00 1 1-F, 00-0000-F and CO0000-F modes. Three kinds of clinical collimators are provided for thermal, mixed and epi-thermal neutron irradiation. The maximum aperture sizes are 190 mm. The irradiation field sizes were set to be 10 cm in diameter, using the thermal neutron irradiation collimator with a plastic sheet containing ^{6}LiF at 30% in weight for the 00-0011-F mode, and using the mixed neutron irradiation collimator with an inner collimator of polyethylene containing natural LiF at 50% in weight for the 00-0000-F and CO-0000-F modes. On the assumption of the same thermal neutron fluence at the head top, the gamma ray dose equivalents at the respective parts of the human body for the 00-0011-F and 00-0000-F modes, have been applied for NCT, are about one fourth to one third of those for the old

4. THE DOSE MEASUREMENT AND ESTIMATION UNDER BNCT CLINICAL IRRADIATION AT THE KURRI

4.1. Feature of BNCT clinical irradiation with craniotomy

The thermal neutron irradiation is suitable for tumour seated near the surface such as melanoma, but its application is limited for deep-seated tumour, because thermal neutron flux in human body monotonously decreases depended on the depth from the body surface The

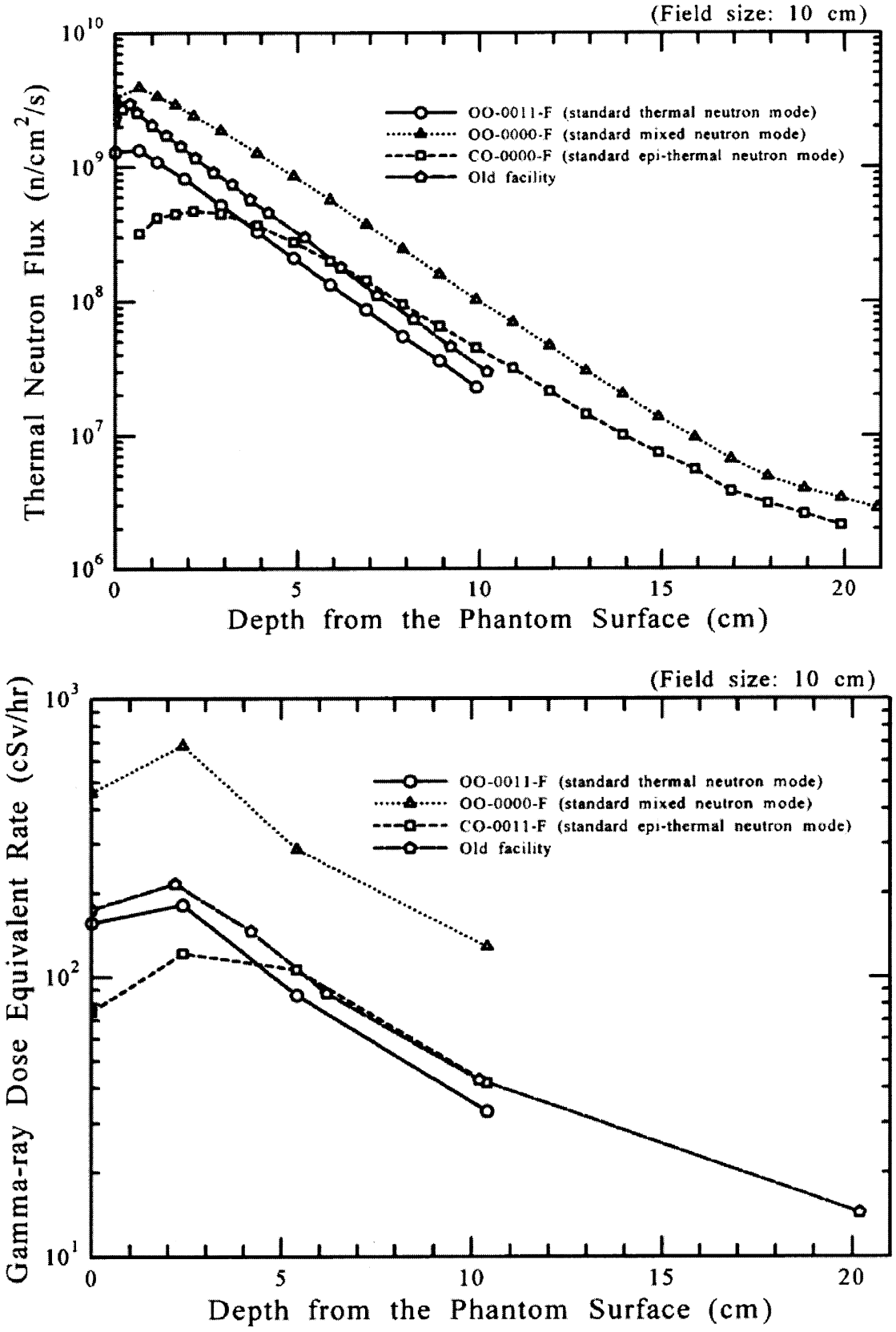

FIG. 4AB. Measured depth distributions along the central axis in a head phantom. a) thermal neutron flux, b) gamma ray dose equivalent rate.

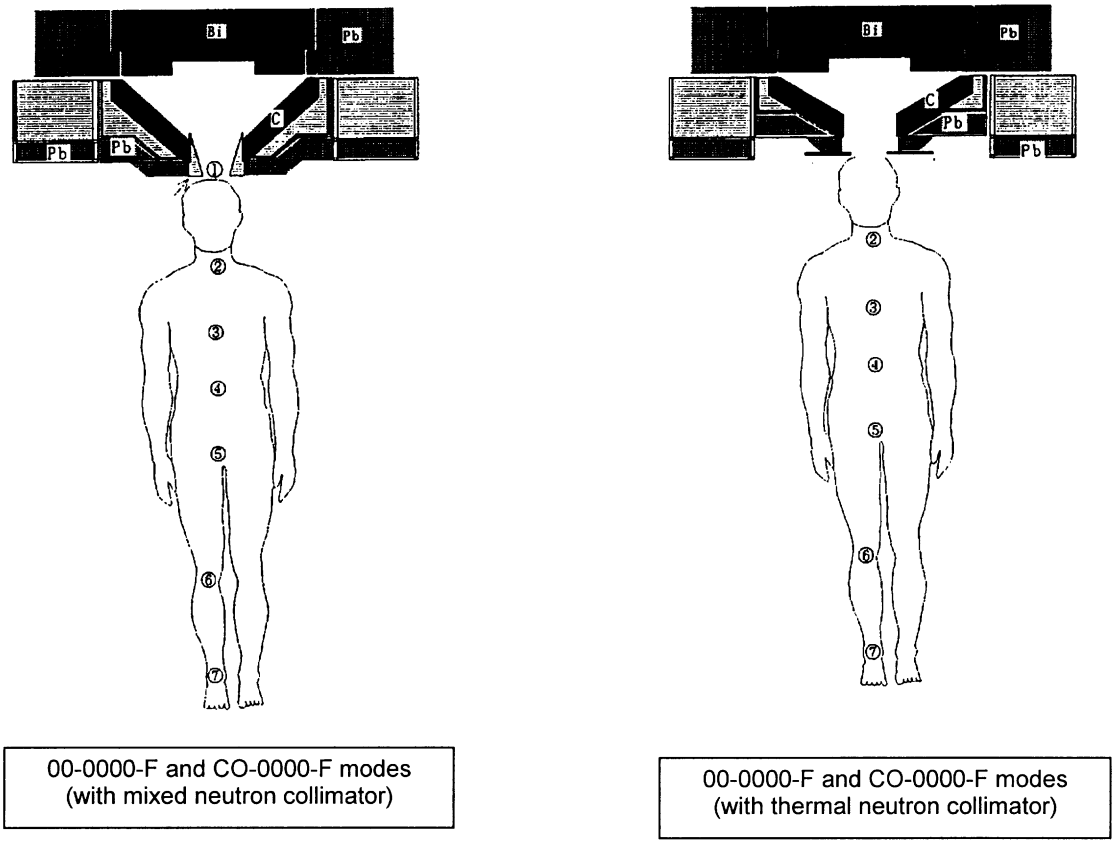

FIG. 5. Measured whole-body distributions of gamma ray dose equivalent rate and thermal neutron flux under NCT clinical irradiation.

BNCT for brain tumour in Japan has been performed together with craniotomy as so-called "under-surgery irradiation", and the demerit of thermal neutron irradiation has been somewhat covered up. From the clinical experiences, the treatable depth for thermal neutron irradiation is thought to be about 5 cm depth from the surface [4]. The other hand, solo-irradiation of epi-thermal neutrons has a characteristic to lower the thermal neutron flux near the surface and relatively increase the flux at the deeper part. This characteristic is a merit for treatment of deep-seated tumour, and it makes the BNCT without craniotomy possible. However, for the case of under-surgery irradiation, the treated part is practically near the surface, and then the shallow part may not be sufficiently irradiated by thermal neutrons with the solo-irradiation of epi-thermal neutrons.

We have been proposing the application of the mix irradiation of thermal and epi-thermal neutrons to NCT, from the viewpoint of the dose-distribution control in human body [5]. Figure 6 shows calculated depth distributions along the central axis in a head phantom for the BNCT with craniotomy using the solo-irradiation of thermal neutrons and epi-thermal neutrons, the mixirradiation of 0.24 and 2 in $\varnothing/_{epi}/\varnothing_{th.}$ The distributions are normalised to be unity at the respective peak positions. In this case, the size of the removed part by craniotomy is S cm in diameter and 3 cm in depth. It is thought that the application of the mix neutron irradiation can cover up the respective demerits of thermal and epi-thermal neutron irradiation. Its application to the actual BNCT has already started using the mix irradiation modes at the updated FWNIF. Moreover, as shown in Fig. 2, the mixing ratio of thermal neutrons to epi-thermal neutrons can be continuously controlled by adjusting the aperture of

the cadmium thermal neutron filter at the updated facility. Then, the intermediate distribution of thermal neutron flux can be tailored between the 00-0000-F mode and CO-0000-F mode shown in Fig.4.

4.2. Dose measurement method

At the KURRI, the dose measurements under BNCT clinical irradiation are performed according to activation method using gold wires for the thermal neutrons, and using TLDs for the gamma rays. The TLD of Mg_2SiO_4(Tb) powder (produced by Kasei Optonix, Ltd.) is enclosed in polyethylene tube in order to put on the irradiated surface. For the whole-body exposure, the commercial-base ThD of BeO (ThD- 1 70L) is used, covered with ^{6}LiF thermal-neutron shielding case.

A process of the dose estimation for the clinical irradiation is as follows;

(1) Before a clinical irradiation, the dose rate distributions of neutrons and gamma rays in a body are estimated by phantom experiments and/or simulation calculations.
(2) Thermal neutron flux is directly monitored at some interested points in the irradiated part using gold wires during the first 15–30 minutes of the clinical irradiation, and the thermal neutron flux distribution in the tumour part is estimated in the reference to the results in (1).
(3) The ^{10}B concentrations in the samples of the patient blood and tissue are measured by prompt gamma ray analysis (PGA) [6], and the concentrations in the tumour part and normal tissue are estimated using the data obtained from the basic experiments and the former clinical irradiation.
(4) Using the data from (2) and (3), the absorbed doses at the interested parts are estimated and the whole irradiation time is decided.

This estimation process is completed about 40–55 minutes after the start of the clinical irradiation.

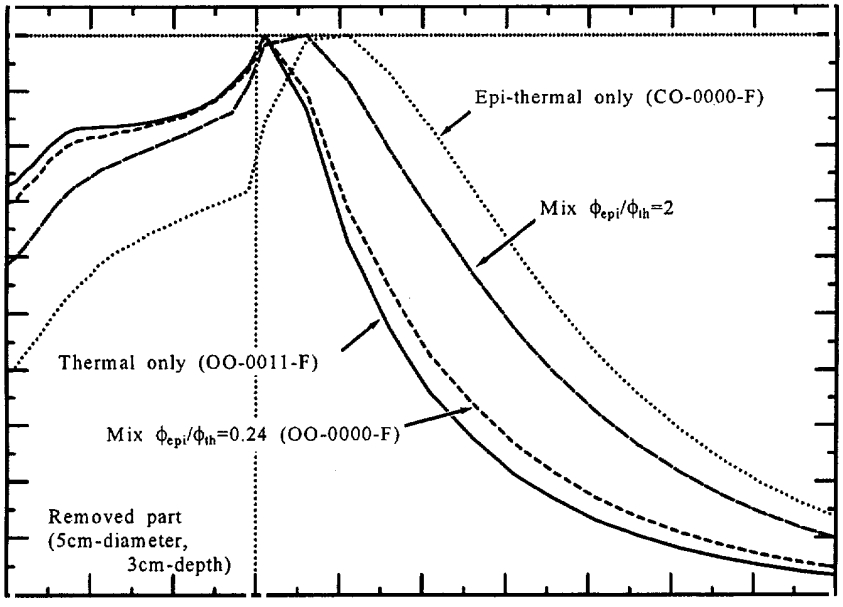

FIG. 6. Calculated depth distributions along the central axis in a head phantom for the BNCT with craniotomy. (The removed part size is S cm in diameter and 3 cm in depth.)

4.3. Dose evaluation methods

The standpoints on the dose estimation in tumour part and normal tissue are different between for brain tumour and melanoma. For brain tumour, the medical doctors attach importance on the total physical absorbed dose, PD (Gy), which almost corresponds to the sum of the physical absorbed doses of $^{14}N(n,p)'^{4}C$ and $'^{0}B(n, a)^{7}Li$ reactions mainly with thermal neutrons, and 'H(n,n)'H reactions mainly with epi-thermal and fast neutrons.

$$PD = (K_N N + K_B B) \Phi_{th} + D_f \quad \text{(eq. 1)}$$

Here, (F ~, is thermal neutron fluence (n/cm^2), D_f is physical absorbed dose due to epi-thermal and fast neutrons (Gy), N is concentration of ^{14}N (%), B is concentration of ^{10}B (ppm), and K_n and K_B are kerma factors of $^{14}N(n,p)^{14}C$ and $^{10}B(n, a)^{7}Li$ reactions (Gy cm^2), respectively. In usual, the D_f is estimated by phantom experiments and/or simulation calculations. Incidentally, it is assumed that the composition of tumour and normal tissue is H:1l.l%, C:12.6%, N:2% and O:74.3%. One of the current criteria for the clinical dose is that the PD is over 15 Gy at the deepest tumour part and under 10 Gy at the surface [7]. The dose estimation for the gamma rays is not included in the equation 1, but the above mentioned dose criterion is decided on the consideration of the gamma ray contribution.

For the case of melanoma, the RBE absorbed dose, RD (RBE Gy) is used.

$$RD = (R_N K_N N + R_B K_B B + G) \Phi_{th} \quad \text{(eq. 2)}$$

Here, R_N and R_B correspond to the RBEs of $^{14}N(n,p)^{14}C$ and $^{10}B(n, \alpha)^{7}Li$ reactions, respectively, and the both RBEs are assumed to be 2.5 [8]. G is the ratio of gamma ray dose to thermal neutron fluence (RB_E Gy)/(n/cm^2), and this is previously estimated by phantom experiments and/or simulation calculations. As the BNCT clinical irradiation for melanoma is performed normally using the thermal neutron irradiation modes, the dose estimations about epi-thermal and fast neutrons are not included. A current clinical dose criterion is that the dose is over 25 RBE Gy for the tumour part and under 18 RBE Gy for the normal skin tissue.

5. CONCLUSION

In the dose report for an BNCT clinical irradiation, the following two data are mainly required; (i) the dose information for the estimation of the therapeutic efficacy, and (ii) the dose report for the estimation of the harmful side-effect. For the data (ii), only the whole-body dose exposure is measured at present time. The dose-exposure estimation both for normal tissue near the irradiated part and for the internal organs, is one of the subjects to be solved near future. For the data (i), the following matters are pointed out at the KURRI;

(1) It takes at least 40 minutes for the dose estimation.
(2) For the BNCT with craniotomy, it is difficult to complete the simulation calculations in a short time just before the start of the clinical irradiation. Because the irradiation geometry becomes fixed just before the irradiation, so the final confirmation for the irradiation condition is difficult.
(3) The thermal neutron flux distribution near the surface is easily affected by the surrounding conditions such as the geometry, etc., especially for the BNCT with craniotomy.
(4) The present estimation method of $'^{0}B$ concentration by PGA is based on the assumption that the concentrations at tumour part and normal tissue are homogeneously equal.

At present, we are considering about the introduction of an on-line dose estimation method using small semiconductor detectors for neutron dose and, a telescope system for gamma ray dose [9]. Also, we are researching the possibility of a PO-SPECT system, which is one of direct, real time and 3-D dose estimation techniques for ‘^{0}B(n, a y)^{7}Li reaction distribution in tissue [10].

The three standard irradiation modes of the HWNIF for NCT are summarized as follows;

(1) the standard thermal neutron irradiation mode, 00-00 1 1-F: tumour seated near the surface, such as melanoma (within a few cm depth).
(2) the standard mixed neutron irradiation mode, 00-0000-F: tumour seated at comparatively deeper part (depth from a few cm to almost 5 cm).
(3) the standard epi-thermal neutron irradiation mode, CO-OOOOF: BNCT for deep-seated tumour with out craniotomy.

The standard mixed neutron irradiation mode is the main current, and its effectiveness is being confirmed for BNCT.

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Development of the epithermal neutron beam and its clinical application for boron neutron capture therapy at the Brookhaven medical research reactor

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Abstract. The failures of the Boron Neutron Capture Therapy (BNCT) trials conducted between 1951 and 1961 were attributed to inadequate penetration of the thermal neutron beams and poor localization of boron compound in the tumour. The epithermal neutron beam at the BMRR was designed and installed to improve the penetration of the neutron beam. The use of this epithermal neutron beam for the clinical trial initiated in 1994 at Brookhaven National Laboratory (BNL) was preceded by the neutron beam optimization and characterization, the validation of the treatment planning software and the establishment of a procedure for treatment plan evaluation and dose reporting and recording. To date, a total of 54 patients have been treated. Our experience in the development of the epithermal neutron beam for clinical BNCT at the BMRR may be useful to other investigators desirous of developing similar programs for cancer therapy.

1. INTRODUCTION

The Brookhaven Medical Research Reactor (BMRR) became operational in 1959 and, soon after, the high flux thermal neutron beam was employed for the clinical trials of BNCT for glioblastoma multiforme (GBM). It became apparent that penetration of the thermal neutron beam was inadequate to deliver sufficient thermal neutron fluence at depth through an intact scalp and skull for effective BNCT [1,2]. Attempts to improve the tumour dose at depth by increasing the thermal neutron fluence resulted in excessive damage to the skin and overlying normal brain tissue. Subsequently it was determined that for deep-seated brain tumours, a beam of epithermal neutrons, defined as neutrons with energies between 0.4 eV and 10 keV, was preferable to a beam of thermal neutrons. In 1988, an epithermal neutron beam based on Al/Al_2O_3 filtration and moderation was designed and installed at the BMRR [3]. This beam was further enhanced both in intensity and in quality in 1992 by reconfiguring the fuel elements in the reactor core [4]. This epithermal neutron beam can deliver a relatively high thermal neutron fluence at depth without causing serious skin damage. These improvements in the neutron beam at the BMRR, and subsequent pre-clinical studies that led to a better understanding of the radiobiology of boronophenylalanine-fructose (BPA-F)-mediated BNCT, resulted in the initiation in 1994 of the current BNCT clinical trials for human GBM at the BMRR using BPA-F and epithermal neutrons [5,6]. To date, a total of 54 patients have been treated.

2. BEAM DELIVERY AND CONTROL

2.1. Epithermal Neutron Irradiation Facility (ENIF) at the BMRR

Figure 1 depicts the horizontal cross-sectional view of the existing ENIF at the BMRR. The present reactor core has thirty-two fuel elements (filled squares in Fig. 1). The reactor core is cooled and moderated by light water. Fission neutrons from the light water cooled reactor core first travel through the graphite reflector. A stationary Bi block wall, 0.19 m thick, shields patients from incident gamma. Downstream from the Bi shield are two empty Al tanks, 4 and 8 cm thick, respectively. The initial epithermal neutron beam development was a joint effort by groups at BNL and INEEL (Idaho National Engineering and Environmental Laboratory). In 1988, Al and Al_2O_3 were selected by Fairchild and Wheeler [3] as the primary moderator and placed in the beam shutter to produce the present epithermal neutron beam. Bismuth shields were cast into the beam shutter and the irradiation port to further reduce the gamma rays at the irradiation port. A 3.8 cm-thick Li-poly shield was added in 1991 to surround the Bi port, and thereby to reduce stray neutrons coming laterally to the irradiation port. In 1992, the epithermal neutron beam was enhanced both in intensity and quality by rearranging the fuel elements in the reactor core to skew the fission neutron fluence rate distribution toward the epithermal port [4].

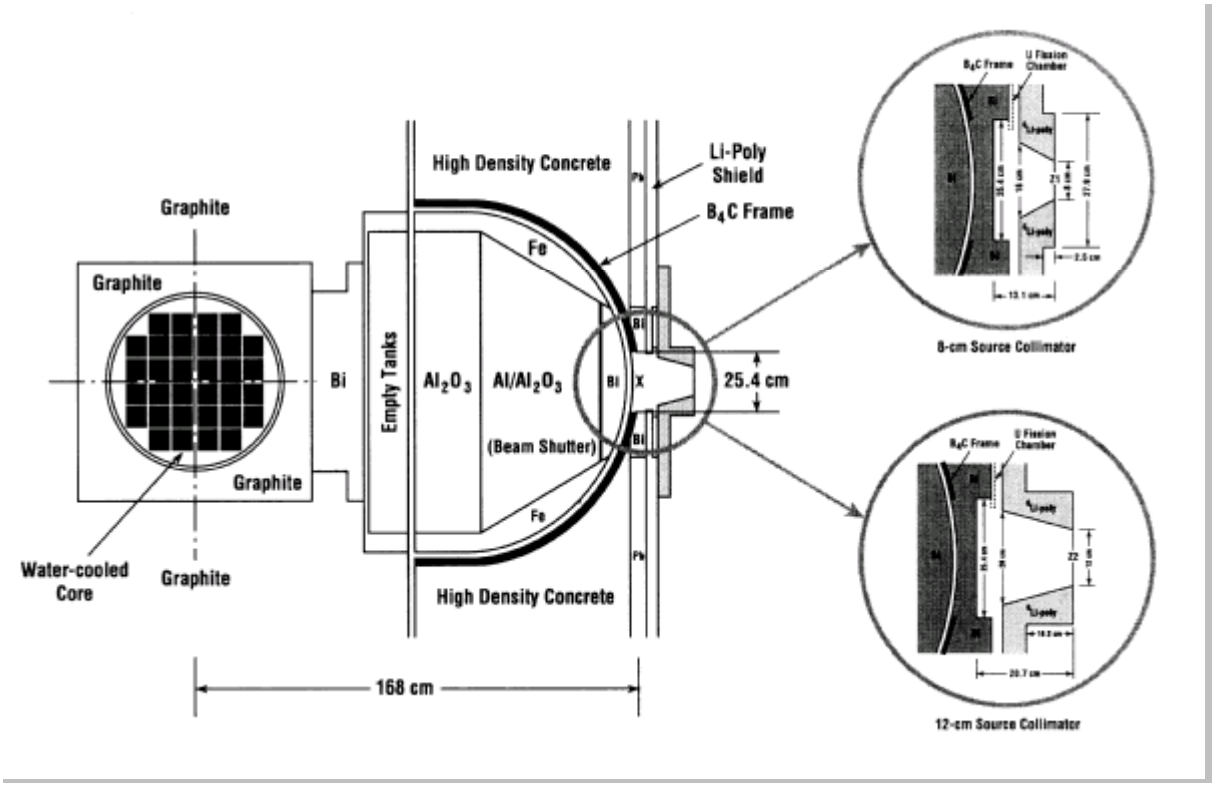

FIG. 1 Horizontal cross-section view of the BMRR epithermal neutrom irradiation facility.

2.2. Beam collimation

The beam at the irradiation port is further collimated and restricted to an aperture of either 8 or 12 cm in diameter [7]. Li-poly, the material selected to build these neutron collimators (Reactor Experiments, Inc., Sunnyvale, California), consists 45 wt% of Li_2CO_3 (93% enriched isotopic ^6Li) powder uniformly dispersed in polyethylene. With a high overall content of ^6Li (7.0 wt%) to absorb thermal neutrons with minimal secondary gamma ray

production and a high content of H (7.9 wt%) to moderate fast neutrons, Li-poly is ideal for collimation of the epithermal neutron beam.

Sequentially, two collimators having the same external cross sectional area (27.9 cm × 27.9 cm), as shown in Fig. 1, were constructed. One is 7.6 cm thick with a conical cavity 16 cm in diameter on the reactor core side tapering to 8 cm facing the patient's head (8-cm collimator) and the other is 15.2 cm thick with a conical cavity 20 cm in diameter tapering to 12 cm (12-cm collimator). Each collimator can be mounted on the Li-poly shield at the irradiation port. The Li-poly shield outside the collimator was thickened to 5.1 cm by adding a 1.3 cm-thick Li-poly frame, which holds either collimator in place. The beam paths along the beam centerline are 13.1 and 20.7 cm from the face of the Bi shield to the irradiation points Z1 and Z2 for the 8-cm and 12-cm collimators, respectively.

2.3. Control of neutron irradiation

The epithermal neutron beam at the BMRR is controlled by a neutron beam shutter system, and in the event of an emergency, the reactor itself may be rapidly shutdown. The reactor nuclear safety system constantly guards against reactor power excursions and is designed to scram or set back (automatically shut down) the reactor if either the power level is too high or the rate of power increase is too fast. The scramming procedures involve the rapid deployment into the core of all the reactor’s control rods resulting in a shutdown of neutron production in the core.

The emerging epithermal neutron beam at the irradiation port is interrupted by the mechanical beam shutter systems with assemblies that can be raised and lowered hydraulically inside a vertical cavity to control the irradiation. When the shutter is lowered, a high-density concrete section of the shutter blocks the beam between the reactor core and the patient location. When the shutter is raised, the filter/moderator section of the shutter is between the reactor core and the patient location and an epithermal neutron beam is produced. A failure in the hydraulic system would result in the shutter falling by gravity to the lowered position in about 10 seconds, blocking the beam. The shutter can be controlled either by the reactor operator in the control room or from a remote panel near the observation window for the treatment room.

Two uranium fission chambers are mounted, one upward and one downward at the corners of the bismuth irradiation port in a non-perturbing and non-perturbable configuration. A change in the position or spatial distribution of the beam due to the shutter position can therefore be detected by comparing the reading from these two chambers. These chambers primarily display the flux intensity of epithermal neutrons in the beam. During neutron irradiation, these chambers are interfaced to a computer to monitor the neutron beam with respect to intensity and symmetry. Integral chamber readings and appropriate ratio calculations are displayed at 20-sec intervals.

3. BEAM CHARACTERIZATION

Extensive measurements were performed to characterize the intensity and quality of the epithermal neutron beam.

3.1. Measurements of energy spectra

Energy spectra of the epithermal neutron beam were measured at the face of the Bi port (X in Fig. 1) by the INEEL group using foil activation and proton-recoil spectrometry [8]. In

the epithermal energy region 0.4 eV to 10 keV, a set of foil materials were chosen, each with a single dominant resonance cross-section peak: ^{115}In/1.46 eV, ^{197}Au/5 eV, ^{186}W/18 eV, ^{59}Co/132 eV, ^{55}Mn/340 keV, and ^{63}Cu/580 eV. The resonance foil assembly consisted of a stack of activation foils and a side shield composed of the same material, and a Cd shield. For neutron energy range of 0.6 eV to 20 keV, measurements were made using ^{63}Cu detectors whose response was modified through spectrum tailoring with ^{6}Li filter. The ^{63}Cu stack assembly was arranged with copper foils alternated between lithium metal enriched in ^{6}Li and a ^{10}B back shield. Measurements in the epithermal and fast regions were accomplished by tailoring the neutron spectrum with a ^{10}B filter, using the ^{235}U fission and ^{238}U capture reactions as detectors. Fast neutron energy range was also determined from the reaction ^{115}In(n,n') with a threshold at 530 keV. To suppress the neutron capture reaction rate, the indium foils were placed inside a ^{10}B spherical shell. All activation foil assemblies were irradiated at the center of the Bi port. The induced gamma activities were measured and neutron activation rates were derived from the measured gamma activities. Neutron flux data were derived from the activation data by two approaches: 1) using just the resonance reaction rate data to derive the value of the incident flux for neutrons at the energy of the primary resonance and 2) using all the activation data simultaneously to derive the neutron spectrum over the measured energy range. Because narrow energy peaks and fine structure may not be revealed in the calculated spectrum or the spectrum measured by foil activation, proton-recoil spectrometry measurements with hydrogen-filled proportional chambers were carried out to obtain high-resolution neutron spectral data over the energy range from 100 keV to 2 MeV. A composite neutron spectrum was produced based on the analysis of all the measurements. This neutron spectrum provides the basis for the neutron source plane that is used in the treatment planning software for the clinical trial at the BMRR.

3.2. Dosimetric measurements

3.2.1. Dosimetric methods

In-air and in-phantom measurements of thermal and epithermal neutron fluxes, gamma and fast neutron dose rates were performed at the patient irradiation port. Bare and Cd-covered Au foils (0.00127 cm thick and an average diameter of 0.8 cm) are used to measure the thermal and epithermal neutron fluence rates. Induced activity of each Au foil was measured with NaI(Tl) well-type detectors. Depleted U-coated fission chambers (TGM Detectors, Inc., Waltham, Massachusetts) were also used to measure the epithermal neutron fluence rate in air at the irradiation aperture. These cylindrical chambers are 0.6 cm in diameter and 4 cm long. During experiments, these chambers were covered with 2 mm-thick Li metal (95% enriched isotopic ^{6}Li) to shield them from thermal neutrons.

The technique of mixed-field ionization chamber dosimetry, based on the methodology of Attix [9], was used for gamma and fast neutron absorbed dose measurements in air. The ionization chambers are from Far West Tech., Inc. (Goleta, California); one is essentially neutron insensitive with a graphite wall containing circulating CO_2 gas (2 cm^3 sphere with a wall thickness of 3.02 mm), and the other is gamma and neutron sensitive with an A-150 tissue equivalent (TE) plastic chamber containing circulating methane based TE gas (1 cm^3 sphere with a wall thickness of 1.27 mm and 3.56 mm-thick equivalent cap). This technique enables an accurate separation of the absorbed doses due to gamma rays and fast neutrons in the beam. Both chambers were calibrated by irradiation with a ^{137}Cs source at Far West Tech., Inc. These chambers were covered with ^{6}LiF thermal neutron shields, which were made with two cylindrical tubes of 0.0794 cm-thick Cellulose Acetate Butyrate, separated by 0.4 mm-thick ^{6}LiF (95% enriched isotopic ^{6}Li) compressed powder and sealed at each end.

The gamma absorbed dose distributions in the phantom were measured by LiF-700 TLD rods (Harshaw Chemical Company, Solon, Ohio). The TLD-700 is made of isotopically enriched lithium-7 fluoride (99.93% enriched isotopic ^{7}Li, 1 mm x 1 mm x 6 mm). These TLD rods still contain a small amount of ^{6}Li impurities, which strongly respond to thermal neutrons in the phantom. Thermal neutron response of these TLD rods were determined by comparing the readings resulted from the irradiation at the thermal neutron irradiation facility at the BMRR and at the calibration ^{60}Co source at BNL.

Table I shows the measured beam parameters in air at various irradiation points. The fluence rate of epithermal neutrons drops rapidly as a function of the distance from the irradiation point X (Fig.1) of the Bi shield. The intensities at Z1 and Z2 (Fig.1) are about 1/2 and 1/3 of the intensity at X, respectively. After collimation, the beam quality (D_{fast}/n_{epi} and D_{γ}/n_{epi}) is somewhat worse because fast neutrons tend to be more forward directed than epithermal neutrons, and because additional gamma rays are produced within the collimator. Therefore, during the collimation process the reduction of epithermal neutrons is greater than that of fast neutrons and gamma rays. On the other hand, because of collimation, the beam directionality (J_{epi}/ϕ_{epi}) is improved. J/ϕ is the angular fluence rate weighted cosine of the emergent neutrons at a half space; J/ϕ is 0.5 for an isotropic beam and 1.0 for a parallel beam. The new collimator produces a lower intensity and somewhat more "contaminated" beam, however the beam is more forwardly directed.

TableI. Measured in-air beam parameters at various irradiation points for 3 MW reactor power

Parameter	X	Z1	Z2
ϕ_{epi} ($cm^{-2}s^{-1}$)	$(2.7\pm0.16)\times10^{9}$	$(1.4\pm0.84)\times10^{9}$	$(0.84\pm0.05)\times10^{9}$
D_{fast}(Gyh^{-1})	4.2±0.63	2.3±0.35	1.4±0.21
$D\gamma$(Gyh^{-1})	0.96±0.05	0.78±0.04	0.60±0.03
D_{fast}/n_{epi}	$(4.3\pm0.7)\times10^{-13}$	$(4.5\pm0.73)\times10^{-13}$	$(4.8\pm0.78)\times10^{-13}$
$D\gamma/n_{epi}$	$(1.0\pm0.08)\times10^{-13}$	$(1.5\pm0.12)\times10^{-13}$	$(2.0\pm0.16)\times10^{-13}$
J_{epi}/ϕ_{epi}	0.56	0.72	0.80

3.2.2. Phantom

The main purpose of phantom dosimetry is to measure the neutron and gamma fluence rate and absorbed dose distributions. Phantom dosimetry provides information, which can be used to verify a simulated source model. Once validated experimentally, the source model can be used to calculate treatment plans for each individual patient. A 14 cm Lucite cube phantom was used for dosimetric experiments at the BMRR-ENIF [7]. The 2744 cm^3 cube is similar to the volume of the head. Because of its simplicity, dosimetric experiments can be repeated with a minimum of errors due to positioning uncertainties. Also because of its well-understood elemental composition, an accurate Monte Carlo simulation can be made.

Three sets of 1.59 cm diameter Lucite rods were arranged in the phantom. The first set has 0.0254 cm wide slits to accommodate bare Au foils located at 3.5, 7.0, and 10.5 cm depths of each rod. The second set has 0.254 cm wide slits to accommodate Cd capsules with Au foils in them, located at corresponding depths of each rod. The third set has 0.159 cm

diameter holes to accommodate TLDs, located at corresponding depths of each rod. Three dimensional dosimetric information for the thermal neutron fluence and gamma absorbed dose rates at these nine locations, can be obtained using this phantom.

4. IMPLEMENTATION OF THE TREATMENT PLANNING SOFTWARE

A BNCT treatment planning system developed at INEEL was chosen for the clinical trials at BNL [10]. Results of energy spectrum measurements as well as the in-air dosimetric measurements were used to design a simulated neutron source plane at the irradiation port. Using this neutron source plane, the neutron and photon transport computations of the treatment planning system is validated by phantom dosimetric measurements and by other independent computations using the Monte Carlo N-Particle Transport Code [11].

A treatment planing procedure was developed for the clinical trial. It includes: 1) contrast-enhanced MRI scans of a patient's head; 2) construction of a head model with defined anatomical regions; 3) neutron and photon transport computations; 4) estimation of the absorbed dose; 5) identification of optimal treatment plan; 6) patient positioning; and 7) dose reporting and recording (post-treatment evaluation). Treatment plan evaluation is based on the criteria set in the dose escalation protocols. These criteria, listed in the order of importance, are as follows: 1) prescribed reference dose and average brain dose; 2) dose to sensitive sites; 3) minimum target dose; 4) minimum tumor dose. Within constrains of the reference dose, average brain dose, and dose to sensitive sites, the treatment plan is optimized to deliver the highest minimum target dose. The criteria used in the treatment plan evaluation are the essential components of the post-BNCT report. In addition, we have performed very detailed dose calculations for each patient, including the dose to each hemisphere and to cerebellum etc. This detailed dose information will provide the basis for evaluating the radiobiology of the BPA-mediated BNCT.

In order to increase the thermal neutron fluence at depth, the 12-cm collimator replaced the 8-cm collimator after the first 15 patients. We have employed 1, 2 or 3 fields of irradiation to improve the dose distribution and to escalate dose in the on-going clinical trial. Fig. 2 shows the isodose contours for normal brain resulting from 1-field (left), 2-field (center), and 3-field (right) irradiation.

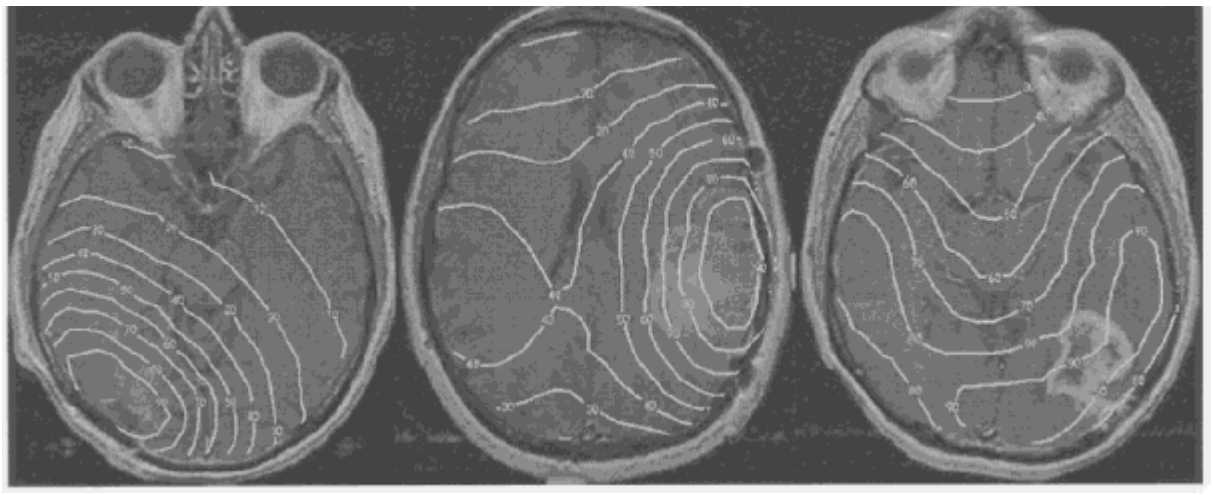

Fig. 2 Isodose contours for normal brain resulting from 1-field (left), 2-field (center), and 3-field (right) irradiation.

5. SUMMARY

The epithermal neutron beam at the BMRR was designed and built to improve the neutron beam penetration for BNCT of malignant glioma. The implementation of this neutron beam for clinical use included several major steps. First, the neutron beam was characterized in terms of intensity and quality by extensive measurements and simulations. Second, a treatment planning software was installed and validated by dosimetric measurements and simulations. Third, a procedure was established to evaluate the treatment plan and to report and record the radiation doses. The overall effectiveness of the neutron beam depends on many parameters including its intensity and quality, as well as the treatment irradiation geometry. The experience gained with the use of this beam in more than 50 patients led us to design a new epithermal neutron beam that will enable us to further optimize the treatment in neutron capture therapy.

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Code of practice BNCT dosimetry: A European project

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Abstract. The guidelines followed for the dosimetry of BNCT in the European research reactors have been finalised by a consortium of 11 institutions. The work programme anticipated is outlined and the present status described.

1. INTRODUCTION

Boron Neutron Capture Therapy (BNCT) is a new form of radiotherapy expected to be beneficial to cancer patients with glioma, a type of brain tumour. The first European clinical trials with BNCT on glioma patients have started in Petten, The Netherlands, in October 1997. Other European countries, Finland, United Kingdom and Czech Republic, are approaching clinical trials, and pre-clinical BNCT-studies are progressing in Portugal and Hungary. To ensure the comparability and critical assessment of the results from pre-clinical radiobiological experiments and from clinical trials on human patients, it is of crucial importance that the basic characteristics of the neutron beam (beam geometry, neutron and gamma ray spectra, absorbed dose and fluence distributions) are determined in a coherent and reproducible way. The existing international recommendations on radiotherapy dosimetry are not applicable to BNCT. Therefore, accepted dosimetric procedures are urgently needed to provide credibility and reliability for BNCT, to the benefit of the patients and to facilitate the recognition and clinical acceptance of this new treatment modality by the radiotherapeutic community and the national health authorities.

2. OBJECTIVES OF THE EUROPEAN COLLABORATION

The objective of the project is to prepare detailed guidelines for the dosimetry of epithermal neutrons to be used for BNCT at European research reactors and accelerators. These guidelines will ensure the level of accuracy, reliability and reproducibility, which is generally required in radiotherapy and which will be of crucial importance for the success and optimisation of the BNCT treatments.

The project is carried out by a consortium consisting of Nuclear Research and Consultancy Group NRG (Petten NL, Xo-ordinator), Netherlands Cancer Institute (Amsterdam The Netherlands), Institute for Advanced Materials of the Joint Research Centre of the Commission of the European Communities (Petten The Netherlands), Radiation and Nuclear Safety Authority (Helsinki, Finland), University of Helsinki (Helsinki Finland), University of Birmingham (Birmingham, United Kingdom), Nuclear and Technological Institute (Sacavém Portugal), Technical University of Budapest (Budapest, Hungary), Nuclear Research Institute (Rez, Czech Republic), Technical Research Centre of Finland (Espo, Finland) and Universitätsklinikum Essen (Essen, Germany).

3. WORK PROGRAMME

The project is limited to the basic problems of the physical dosimetry prior to clinical treatment in order to attain control of the most urgent topics. To meet the objectives, the partners are studying and developing the methodology for the basic BNCT-dosimetry by:

- theoretical review and analysis of the available knowledge,
- selection of the most promising methods and procedures,
- systematic experimental investigations of the most promising methods,
- verification of experimental results by theoretical calculations in order to determine the critical physical parameters affecting the overall accuracy of the measurements,
- selection of recommended dosimetry procedures, and
- systematic intercomparison of the selected dosimetry procedures in the available European BNCT beams.

The project pursues the following dosimetry steps of research:

- characterisation of the mixed neutron-gamma beam emerging free in air from the neutron source (nuclear reactor or particle accelerator);
- characterisation of the mixed field of radiation generated in a phantom exposed to the mixed neutron-gamma beam:

- in a reference phantom under reference conditions;
- in a patient simulation (non-reference conditions);

- characterisation of beam monitors as a tool to establish an unambiguous relation between significant free-beam parameters and the field of radiation generated in a phantom.

As a structured approach the work is divided into work packages. All work packages include both quality control and evaluation of uncertainties.

3.1. Work package 1: Beam characterisation

1.1 Beam geometry
1.2 Spectrum characterisation of the neutron component
1.3 Spectrum characterisation of the gamma ray component

3.2. Work package 2: Beam calibration

2.1 Reference phantom material
2.2 Reference geometry
2.3 Absorbed dose to tissue
2.4 Non-reference conditions
2.5 Thermal neutron fluence rate
2.6 Intercomparison of methods

3.3. Work package 3: On-line monitoring

3.1 Beam monitoring

Work package 4: Writing the code
4.1 Drafting and editing the text
4.2 Referee reading

4. STATE OF PROGRESS

During a kick-off meeting in Petten on 13–14 November 1998 the overall time schedule and a detailed work plan for the next six months were established. The partners are currently in the process of reviewing i/ their own dosimetry procedures and ii/ other dosimetry procedures worldwide in order to select the most promising procedures for further research.

Annex 6
RADIOBIOLOGY

The radiobiology of boron neutron capture therapy: Are "photon-equivalent" doses really photon-equivalent?

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Abstract. Boron neutron capture therapy (BNCT) produces a mixture of radiation dose components. The high-linear energy transfer (LET) particles are more damaging in tissue than equal doses of low-LET radiation. Each of the high-LET components can multiplied by an experimentally determined factor to adjust for the increased biological effectiveness and the resulting sum expressed in photon-equivalent units (Gy-Eq). BNCT doses in photon-equivalent units are based on a number of assumptions. It may be possible to test the validity of these assumptions and the accuracy of the calculated BNCT doses by 1) comparing the effects of BNCT in other animal or biological models where the effects of photon radiation are known, or 2) if there are endpoints reached in the BNCT dose escalation clinical trials that can be related to the known response to photons of the tissue in question. The calculated Gy-Eq BNCT doses delivered to dogs and to humans with BPA and the epithermal neutron beam of the Brookhaven Medical Research Reactor were compared to expected responses to photon irradiation. The data indicate that Gy-Eq doses in brain may be underestimated. Doses to skin are consistent with the expected response to photons. Gy-Eq doses to tumor are significantly overestimated. A model system of cells in culture irradiated at various depths in a lucite phantom using the epithermal beam is under development. Preliminary data indicate that this approach can be used to detect differences in the relative biological effectiveness of the beam. The rat 9L gliosarcoma cell survival data was converted to photon-equivalent doses using the same factors assumed in the clinical studies. The results superimposed on the survival curve derived from irradiation with Cs-137 photons indicating the potential utility of this model system.

1. BNCT DOSE COMPONENTS

In tissue, boron neutron capture therapy (BNCT) produces a mixture of components with differing linear energy transfer (LET) characteristics. Thermal neutron capture by ^{10}B, the $^{10}B(n,\alpha)^{7}Li$ reaction, releases high-LET alpha and lithium particles with a track length in tissue of approximately 10 μm. The interaction of the neutron beam with the nuclei of other elements in tissue will deliver an unavoidable, non-specific background dose, from a mixture of high- and low-LET radiation components, to both tumor and normal tissue. Thermal neutron capture by hydrogen releases a gamma ray through the $^{1}H(n,\gamma)^{2}H$ reaction. The capture of thermal neutrons by nitrogen in tissue, the $^{14}N(n,p)^{14}C$ reaction, releases a high-LET proton with an energy of 590 keV. Contaminating fast neutrons (those with kinetic energies >10 keV) in the epithermal neutron beam produce high-LET recoil protons with similar average energy through collisions with hydrogen nuclei ($^{1}H(n,n')p$ reaction) in tissue. These dose components each vary differently as a function of depth, and could vary considerably between different epithermal neutron beams.

2. WHY EXPRESS BNCT DOSES IN PHOTON-EQUIVALENT UNITS?

Due to the high density of ionizations produced along the particle track, high-LET radiation generates more damage in biological systems than an equal physical dose (in Gy) of low-LET radiation Dose components with different LET characteristics will have different

degrees of biological effectiveness with regard to tumor and to the various normal tissues within the treatment volume, such as the CNS and the skin. To express the total BNCT dose to a given tissue in a common, photon-equivalent unit, each of the high-LET dose components (physical dose in Gy) is multiplied by an experimentally determined biological effectiveness factor. The total, photon-equivalent BNCT dose can then be expressed as the sum of the biological effectiveness-corrected physical absorbed dose components, using a unit defined as the Gray-Equivalent (Gy-Eq). The biological effectiveness factors will be different for different tissues such as tumor, brain or skin. These biological effectiveness factors will also differ among different boron compounds.

Why use photon-equivalent dose units in BNCT? The use of Gy-Eq doses in a dose escalating BNCT clinical protocol allows a consistency in the dose estimation, even if the relative contributions of each different dose component may be changing as the total dose is escalated or as the treatment parameters are changed (e.g., progression from 1-field, to 2-fields, to 3-fields). Perhaps more importantly, the use of Gy-Eq units in BNCT dose estimation allows a comparison of doses delivered at different institutions. The currently available clinical epithermal beams being used for BNCT differ considerably in the relative proportions of the various dose components. Is 10 Gy total physical dose the same at two different treatment centers? Not necessarily. Figure 1 shows an example of two hypothetical epithermal neutron beams. Both beams are used to deliver a reference dose (to 1 cm^3) of 10 Gy to normal brain. Beam 2 has a different mixture of dose components compared to Beam 1; 4 times more fast neutrons, 50% of the thermal fluence, and slightly higher (16%) gamma component. The Gy-Eq doses shown in Figure 1 for both of these hypothetical beams are calculated using the biological effectiveness factors in current use in the Brookhaven clinical trial [1,2]. It is clear that even though the physical doses are the same, the Gy-Eq doses are considerably different: 15 Gy-Eq for Beam 1 versus 20 Gy-Eq for Beam 2.

3. BIOLOGICAL EFFECTIVENESS FACTORS

The dependence of the biological effect on variations in the microdistribution of different boron compounds, and of the same boron compound in different tissues, makes the term relative biological effectiveness (RBE), as generally understood, inadequate for fully defining the biological effectiveness of the $^{10}B(n, \alpha)^7Li$ reaction. RBE is usually defined as the ratio of doses of a reference radiation (generally X rays) to a test radiation that will produce the same biological endpoint in a given system. Measured in this way, the RBE is solely a function of the quality (LET) of the test radiation. In BNCT radiobiology, measured biological effectiveness factors for the component of the dose from the $^{10}B(n, \alpha)^7Li$ reaction have instead been termed compound factor [3] or compound biological effectiveness (CBE) factor (cf. [4]).

The approach to experimental determination of these biological effectiveness factors has been recently reviewed [5]. The general approach is as follows: 1) for each tissue, define a quantifiable endpoint or response to irradiation; 2) determine the dose response to a photon reference radiation; 3) determine the dose response to the neutron beam only; and 4) determine the dose response to the neutron beam in the presence of the boron compound. Once these dose response relationships have been determined, it is possible to estimate a

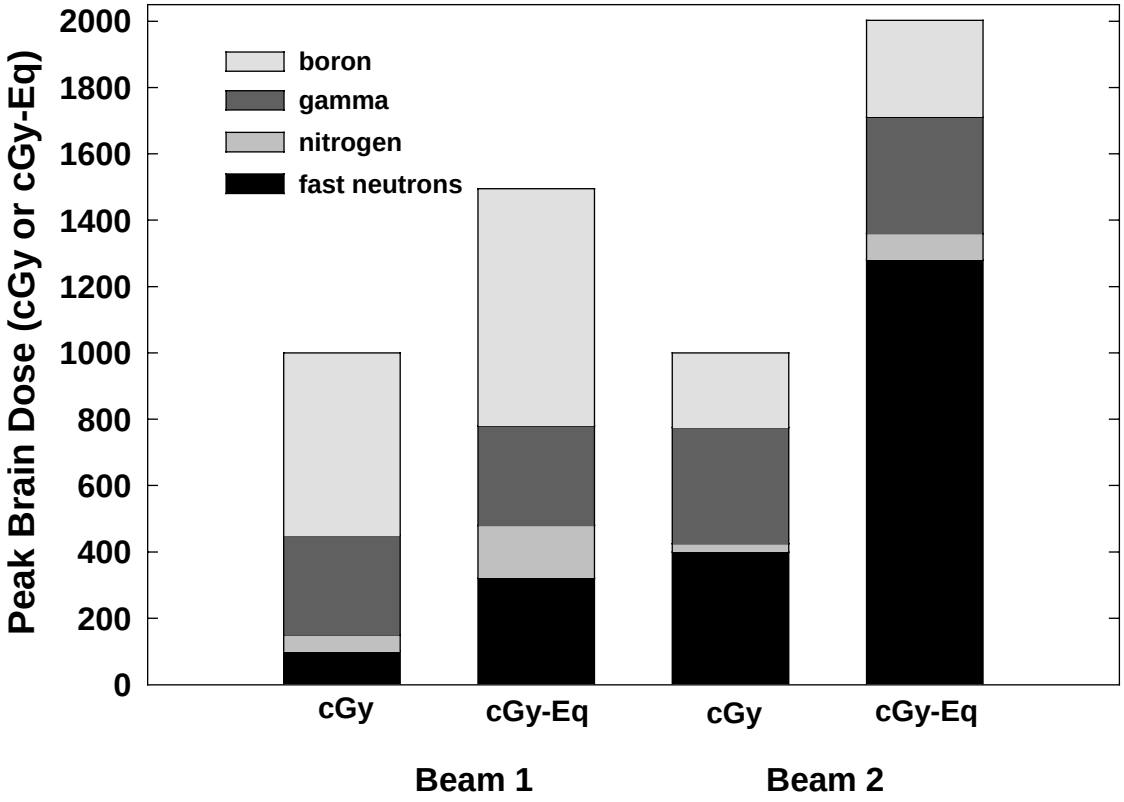

FIG. 1. Comparison of two hypothetical beams with equal peak physical dose in brain, but different photon-equivalent doses.

number of useful quantities: 1) the RBE of the beam alone, 2) the RBE of the high-LET components of the beam (nitrogen capture dose plus the fast neutron recoil proton dose), 3) the biological effectiveness factor for the particular boron compound.

In the following discussion, the "proton dose" is used to refer to the high-LET components of the neutron beam: the 590 keV protons released from thermal neutron capture reactions in nitrogen and the recoil protons resulting from the collision of fast neutrons in the beam with hydrogen atoms in tissue. Because their energies tend to be in the same range, the uniformly distributed effects of the nitrogen capture proton and the fast neutron recoil proton are most conveniently measured as a combined "proton dose".

A measure of the RBE for the neutron beam can be obtained, in the absence of boron, by comparing the neutron beam dose with the X ray dose sufficient to produce an isoeffect in a given biological system. The result can be expressed as in [Eq.1], where ED_{50} is the physical absorbed dose which results in a 50% incidence of the biological endpoint under evaluation. This assumes that the beam dose comprises gamma plus a combined "proton dose" as described above and that the RBE of the gamma component is 1. The beam RBE is the ratio of the x ray dose and the beam dose at the ED_{50} effect level [Eq. 2].

$$\text{["proton" dose]} + \text{[gamma dose]} = \text{X ray } ED_{50} \text{ dose} \qquad \text{[Eq. 1]}$$

$$\text{beam RBE} = \text{[X ray } ED_{50} \text{ dose]/\{ ["proton" dose] + [gamma dose] \}} \qquad \text{[Eq. 2]}$$

An estimate of the RBE for the high-LET components of the beam can be obtained in the absence of boron from the same data by expressing the result as in [Eq. 3] and solving for the "proton" RBE as shown in [Eq. 4].

["proton" dose]["proton" RBE] + [gamma dose] = X ray ED_{50} dose [Eq. 3]

"proton" RBE = [X ray ED_{50} dose — gamma dose]/ ["proton" dose] [Eq. 4]

Experimentally, the CBE factor can be evaluated by first comparing the effect of the beam alone to the effect of a reference radiation to obtain an estimate of the beam RBE or of the high-LET components of the beam as described above. Thermal neutron irradiation, with boron compound present, to a total dose producing the same ED_{50} endpoint is represented by [Eq. 5]. Solving [Eq. 5] for the CBE factor produces [Eq. 6].

X ray ED_{50} dose = [Beam dose][Beam RBE] + $^{10}B(n,\alpha)^{7}Li$ dose][CBE factor] [Eq.5]

CBE factor = { [X ray ED_{50} dose] — [Beam dose][Beam RBE] }/ [$^{10}B(n,\alpha)^{7}Li$ dose] [Eq.6]

The short range of the particles released from the $^{10}B(n,\alpha)^{7}Li$ reaction make the biodistribution of the particular boron compound of critical importance in experiments designed to measure CBE factors. The various experimental conditions under which CBE factors can be measured means that a number of variables will contribute to the overall biological effect. The mode of compound administration, the boron distribution pattern within the cell and within the tissue, the dose per fraction and even the size of the nucleus in the target cell population all may influence the experimental determination of a CBE factor. It is critical that experimental determinations of CBE factors be done under conditions that approximate the clinical situation as closely as possible. For example, studies with BPA in the rat spinal cord have shown that the CBE factor is dependent on blood:spinal cord ratio [6]. For BPA, CBE factor values from 0.66 to 1.33 were obtained depending on experimental conditions.

4. VALIDATION OF PHOTON-EQUIVALENT DOSES

The calculation of Gy-Eq doses delivered to tumor and to normal tissues in BNCT requires estimates of three basic parameters: 1) the boron concentrations in tumor and normal tissues, 2) the CBE factors for that particular boron compound in tumor and in all normal tissues within the treatment field, and 3) the RBE of the high-LET components of the beam itself for tumor and for the normal tissues involved.

Validation of the calculated photon-equivalent doses currently being used in BNCT clinical trials can come from a) animal models, where the effects of Gy-Eq doses delivered during boron neutron capture irradiations can be compared to the known response of the tissue to photon irradiation; or b) from the clinical data, if there are endpoints reached in the BNCT dose escalation trials that can be related to the known response to photons of the tissue in question. The following sections on skin/mucosa, brain, and tumor attempt to bring together data from animal studies and/or the preliminary data from the Brookhaven BNCT clinical trial [1,2,7] to estimate the accuracy of the calculated Gy-Eq BNCT doses.

4.1. Skin/Mucosa

The BNCT program in Japan, in the course of treating human malignant melanoma using BPA and thermal neutrons, has produced important information on the effect of this treatment on human skin [8]. Based on boron measurements in blood and skin, these investigators estimated the boron concentration in the skin at the time of BNCT to be between 1.3 and 1.5 times the concurrent level in the blood. This is in agreement with the data from the Brookhaven clinical biodistribution data [7]. The threshold for moist desquamation in human skin after a single dose of photons was taken to be 18 Gy. By comparing the calculated doses to the skin and the observed incidence of moist desquamation, these authors were able to estimate the biological effectiveness factor for the combined effects of the nitrogen capture reaction and the boron neutron capture reaction as approximately 2.3 to 2.5.

In the Brookhaven BNCT trial, the calculated dose to the scalp is based on the measured boron concentration in the blood at the time of BNCT, assuming a blood/scalp boron concentration ratio of 1.5:1 [1,7,8]. Recent studies in rats have shown that the boron concentration in oral mucosa is twice the concurrent level in the blood [9]. Calculated BNCT doses to mucosa assume this value of two times the blood. For both skin and mucosa, an RBE for beam “protons” of 3.2 is assumed. For mucosa and for skin, a CBE factor of BPA of 2.5 is used [8]. This value is somewhat lower than the CBE factor value of 3.7 measured for BPA with moist desquamation of rat skin as the endpoint [10], which could be related to structural differences in the architecture of the vascular supply between the loose skin of rats and the fixed skin of humans. The CBE factor measured for BPA using ulceration of the undersurface of the rat tongue as a model for oral mucosa was approximately 5 [9].

In photon radiotherapy single-fraction doses of approximately 18 Gy produce moist desquamation, which is generally considered to indicate the tolerance limit in clinical radiotherapy [11]. Single-fraction doses substantially larger than 18 Gy result in critical damage to the vasculature in the underlying dermis resulting in dermal necrosis. Depending upon the photon energy, the maximum tolerance dose for human skin (dermal necrosis endpoint) following a single exposure is estimated to range from 22.5–30.0 Gy [12].

In the series of dog irradiations carried out using BPA-fructose and the epithermal neutron beam at the Brookhaven Medical Research Reactor, the calculated doses to the scalp ranged from 12–20 Gy-Eq. The skin response consisted of epilation, loss of pigmentation and a mild dry desquamation. The dog that received the highest dose developed small areas (1–2 mm) of moist desquamation. In the BNCT clinical trial at Brookhaven, the calculated scalp doses range from 10 to 19 Gy-Eq. The observed effects include only epilation and a mild erythema. In the Brookhaven BNCT clinical trial, there have not been enough documented incidences of side effects to estimate the accuracy of the calculated Gy-Eq doses to mucosa. At least for skin, the available data from dog and human BNCT irradiations indicate that the mild reactions observed to date following calculated BNCT doses, which have all been below 20 Gy-Eq, are consistent with the (lack of) response expected from photon irradiation.

4.2. Brain

The rat spinal cord model has been used to quantify the biological effectiveness of BNCT in the normal CNS [4,6,13]. The late radiation-induced effects seen in the spinal cord following a single fraction of BNCT are similar to those seen in the brain [14]. The sensitivities of the rat

brain and spinal cord to fractionated irradiation are also comparable [15]. The end point of limb paralysis (myeloparesis) for the evaluation of late radiation-induced spinal cord damage is clearly defined while histopathologic and histomorphometric endoints used to assess damage to the brain can be difficult to quantify.

Estimates of the tolerance of the normal brain to fractionated photon radiotherapy were converted to single-fraction equivalent doses using the linear quadratic formalism. For photon radiation, the threshold for necrosis is estimated to be approximately 13.8 Gy. Emami et al. estimated the risk of necrosis for irradiation of various brain volumes [16]. The calculated single-fraction dose producing a 5% risk of necrosis for irradiation of 1/3 of the brain volume is ≈ 14.5 Gy, and for irradiation of the whole volume, ≈ 13.2 Gy. The threshold for somnolence after whole brain radiation is estimated at approximately 7.3 Gy.

The photon-equivalent dose (Gy-Eq) to the normal brain is estimated from the measured boron concentration in the blood at the time of BNCT using a CBE factor for BPA of 1.3 [4], and an RBE of 3.2 for the beam "protons" [1]. The brains of 12 normal dogs were irradiated in the Brookhaven Medical Research Reactor epithermal neutron beam following i.v. infusion of 950 mg BPA/kg as the fructose complex. The maximum dose (delivered to 1 cm^3 of brain at the depth of maximum thermal neutron fluence) ranged from 7.8 Gy (11.8 Gy-Eq) to 11.8 Gy (17.5 Gy-Eq). The average dose delivered to the entire brain ranged from 5.8 Gy (8.5 Gy-Eq) to 8.5 Gy (12.2 Gy-Eq). All dogs were monitored by MRI for brain changes. Six dogs were sacrificed at varying time intervals due to onset of neurological complications. The remaining six dogs were sacrificed for histological analysis at 3 years post-BNCT, having shown little or no MRI changes and no neurological problems. In general, average whole brain doses up to 6.8 Gy (9.8 Gy-Eq) or peak doses up to 9.7 Gy (14.3 Gy-Eq) were well tolerated. Higher doses produced lethal brain necrosis.

Some BNCT patients that received whole-brain doses above 6 Gy-Eq have developed sub-acute side effects (somnolence). The follow-up period is not long enough on this group of patients to draw any conclusions about the accuracy of the calculated Gy-Eq doses. Further analysis, with more clinical response data, is required.

4.3. Tumor

For BPA, a method for the estimation of the boron concentration in tumor based on measured blood boron concentrations has been reported [17]. A morphometric index of the density of viable-appearing tumor cells in histologic sections obtained from samples adjacent to, and macroscopically similar to, the tumor samples used for boron analysis correlated linearly with the boron concentrations. From that correlation it is estimated that ^{10}B concentrations in glioblastoma tumor cells were 3.5–4 times greater than concurrent blood ^{10}B concentrations. The tumor/blood ^{10}B concentration ratio derived from this analysis provides a rationale for estimating the fraction of the radiation dose to viable tumor cells resulting from the boron neutron capture reaction. This method is based on measured boron concentrations in the blood at the time of BNCT without the need for analysis of tumor samples from individual patients. For BPA, a CBE factor value of 3.8 (range 3.6–4.0 for survival fractions of 10%, 1% and 0.1%, respectively) was derived in the 9L rat gliosarcoma model using an *in vivo*/*in vitro* clonogenic assay where intracranial tumors were irradiated *in situ*, surgically removed immediately after irradiation, and plated for colony-forming assay [18]. In summary, Gy-Eq BNCT doses to tumor use the following assumptions: 1) the boron concentration is 3.5 times higher than the concurrent level in the blood; 2) the CBE factor for BPA is 3.8; 3) the RBE for

beam “protons” is 3.2; 4) all tumor cells, including infiltrating cells, take up the same amount of boron; and 5) post-surgical tumor behaves like primary tumor.

Estimates of the magnitude of the dose required to control glioblastoma can be obtained from the photon or fast neutron literature. Stereotactic radiosurgery delivering a 15–35 Gy (20 Gy mean) boost to the tumor after 54–60 Gy of conventional fractionated photon therapy has proved to be locally effective in tumor control in the central portion of the treatment volume [19]. This treatment is roughly equivalent to a 30 Gy single-fraction treatment. Laramore has used the fast neutron experience to estimate that a single-fraction glioblastoma control dose should be in the range of 29–39 Gy-Eq [20].

The minimum tumor doses (deepest part of the contrast-enhancing tumor volume) calculated for the Brookhaven BNCT patients are all over 18 Gy-Eq, with a significant proportion over 30 Gy-Eq. Tumor recurrence has been local in the majority of cases, although extensive tumor necrosis has been documented in histological sections from some patients. Clearly, the Gy-Eq tumor doses are overestimates, or at least not all tumor cells are receiving the estimated doses. There are a number of assumptions behind the estimation of Gy-Eq doses to the tumor involving the delivery of boron to the tumor. Experiments are underway to address each of these assumptions more rigorously.

4.4. Radiobiological Dosimetry

Experimental determination of the RBE factors for the BNCT dose components has, for the most part, been carried out in thermal neutron beam experiments, either in vitro, or in small animals [5]. The exception is the dog work by Gavin [21] using the epithermal neutron beams at the High Flux Reactor, Petten, The Netherlands, and at the Brookhaven Medical Research Reactor. A direct measure of epithermal beam RBE in small animals is difficult due to the high whole body exposure. Build-up material would be required to thermalize the incident neutron beam.

A model system has been developed consisting of cells in culture placed at increasing depths in a lucite phantom in an effort to provide a direct measurement of the RBE of the epithermal neutron beam at the BMRR. Preliminary studies have shown that the technique of using cell survival at depth in a phantom in the epithermal beam can detect differences in beam RBE as a function of depth [22]. A method for direct measurement of the RBE of epithermal neutron beams could be of possible use in a number of applications such as: comparison of the beam RBE from different reactors or accelerator sources; investigation of the influence of dose per fraction on the beam RBE; investigation of whether beam RBE changes as a function of depth. This system may also allow vealidation of Gy-Eq doses. As an example, Figure 2 shows the survival fraction of rat 9L gliosarcoma cells as a function of increasing exposure time in the BMRR epithermal neutron beam. Cell vials were irradiated at depths of 1.0, 2.0, 3.5 and 7.0 cm in the lucite cube phantom. The relative proportions of the various dose components vary as a function of depth and, in addition, vary differently for each depth. Also shown in Figure 2 are survival curves for cells irradiated at 3.5 and 7.0 cm depth in the presence of boric acid at a concentration of 10 μg ^{10}B/ml. The presence of the boron greatly increases the cell kill. Figure 3 shows the dose response of the 9L cells to irradiation with Cs-137 gamma photons. In Figure 3, all of the dose components for the data points in Figure 2 have been multiplied by the appropriate biological effectiveness factors in a preliminary attempt to determine whether this set of factors produces photon-equivalent doses. The CBE factor used for boric acid was 2.3 [23]. Most of the BNCT data points superimpose

on the Cs-137 curve, indicating that the set of RBE and CBE factors do, indeed, generate photon-equivalent doses in this model system. This approach could be of use in further characterization of the response of biological systems to variations in the BNCT treatment parameters.

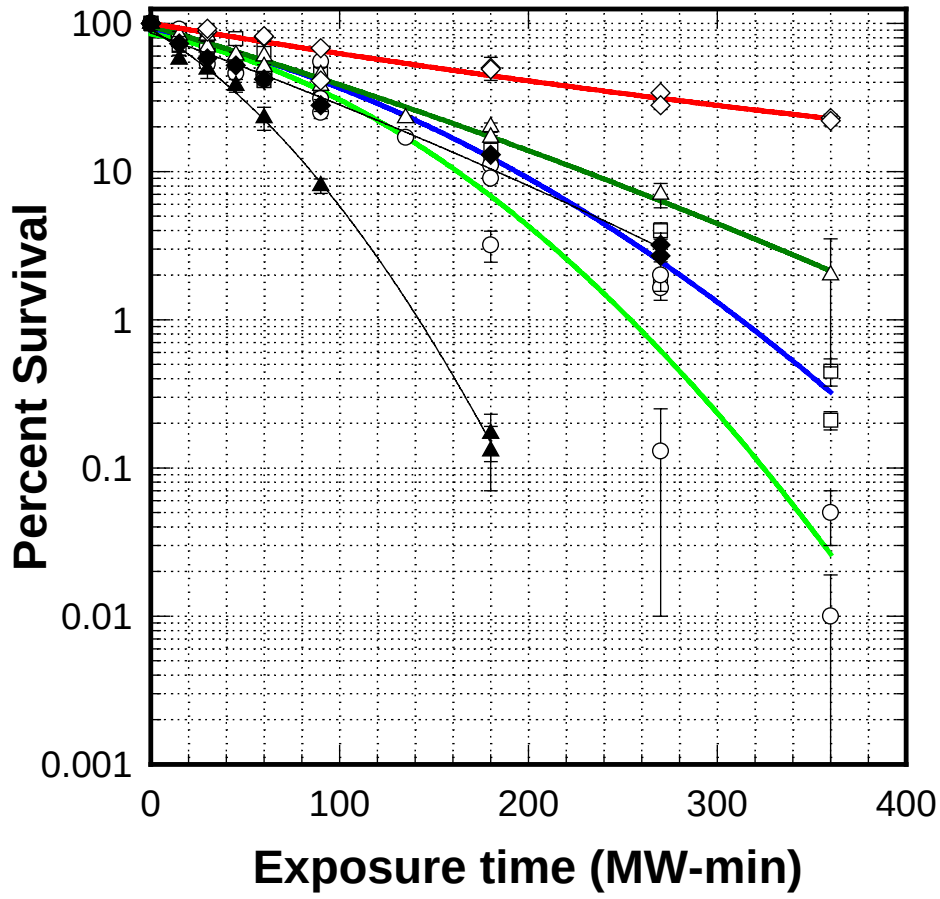

FIG. 2. Survival of rat 9L gliosarcoma cells as a function of exposure in the epithermal neutron beam. Cells were irradiated at various depths in a lucite phantom: open diamonds, 7.0 cm; open triangles, 3.5 cm; open squares, 2.0 cm; open circles, 1.0 cm; filled diamonds, 7.0 cm in the presence of boric acid (10 µg/ml ^{10}B); filled triangles, 3.5 cm in the presence of boric acid (10 µg/ml ^{10}B).

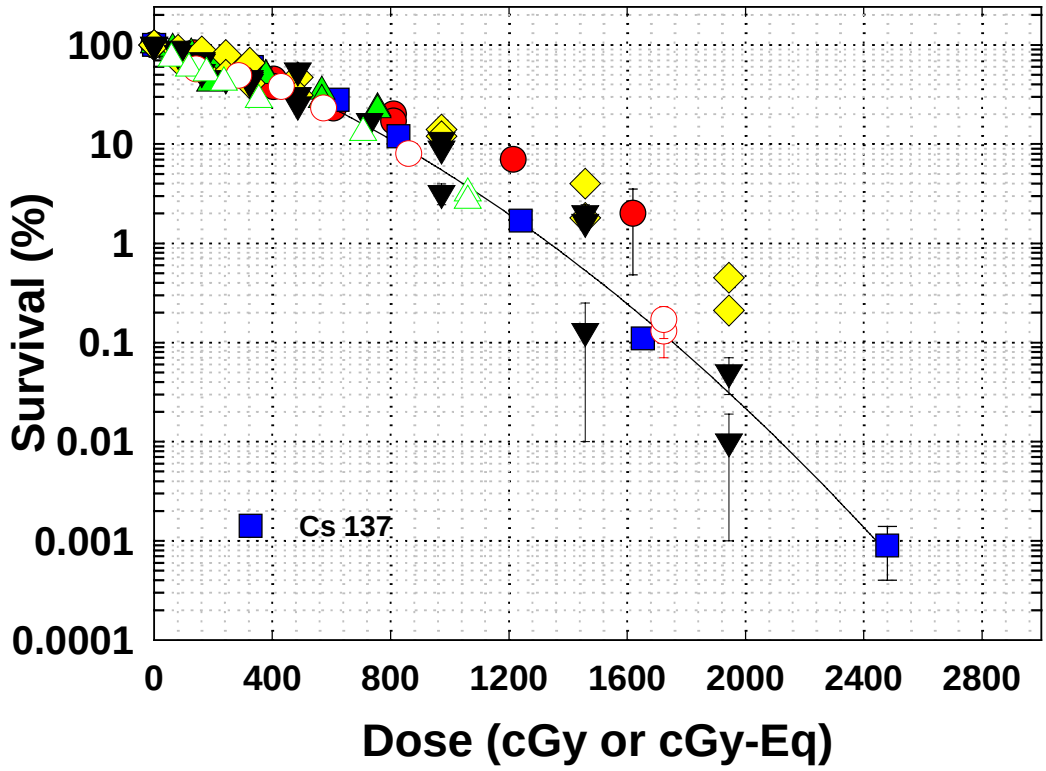

FIG. 3. Survival of rat 9L gliosarcoma cells as a function of exposure in the epithermal neutron beam. Cells were irradiated at various depths in a lucite phantom: triangle up, 7.0 cm; circle, 3.5 cm; diamond, 2.0 cm; triangle down, 1.0 cm; open triangle up, 7.0 cm in the presence of boric acid (10 µg/ml ^{10}B); open circle, 3.5 cm in the presence of boric acid (10 µg/ml ^{10}B). The data shown in Figure 2 was converted to Gy-Eq dose by multiplying the dose components by the following RBE or CBE factors: fast neutrons, 3.2, nitrogen capture, 3.2, boron capture (boric acid), 2.3, gamma, 1.0.

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Annex 7
TREATMENT PLAN

Implementation of BNCT treatment planning procedures

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Abstract. Estimation of radiation doses delivered during boron neutron capture therapy (BNCT) requires combining data on spatial distribution of both the thermal neutron fluence and the ^{10}B concentration, as well as the relative biological effectiveness of various radiation dose components in the tumor and normal tissues. Using the treatment planning system created at Idaho National Engenering and Environmental Laboratory and the procedures we had developed for clinical trials, we were able to optimize the treatment position, safely deliver the prescribed BNCT doses, and carry out retrospective analyses and reviews. In this paper we describe the BNCT treatment planning process and its implementation in the ongoing dose escalation trials at Brookhaven National Laboratory.

1. INTRODUCTION

The mixed radiation field produced during BNCT comprises radiations with various LETs and different relative biological effectiveness (RBE). Due to the short ranges of the two high LET products of the $^{10}B(n,a)^{7}Li$ reaction, the microdistribution of the ^{10}B relative to the cell nuclei is of particular importance for their biological effectiveness [1, 2]. The biological effect of the radiation produced by boron neutron capture may be different for different tissues and boron carriers, and must be adjusted accordingly [3]. The experimentally determined measures of the biological effectiveness of the $^{10}B(n,a)^{7}Li$ reaction have been termed compound adjusted RBE or CBE factor [4, 5]. For estimation of photon-equivalent doses delivered during BNCT, data on spatial distribution of different physical dose components must be related to the patient's anatomy and multiplied by appropriate RBE or CBE factors. Furthermore, as most of these radiation dose components originate from neutron interactions after the incident neutrons have undergone multiple scattering, three dimensional calculations, accounting for particle scattering, are required in order to obtain detailed spatial dose distribution [6]. Monte Carlo stochastic simulation method predominates in current BNCT treatment planning systems [6–8] although deterministic methods may also be applicable [9–11].

A BNCT treatment planning system (TPS) developed at the Idaho National Engineering and Environmental Laboratory [6, 7, 12–15] has been used for the clinical trials at Brookhaven National Laboratory. Using this TPS, we have developed procedures to obtain the optimal irradiation geometry and to evaluate the time of irradiation required to deliver the prescribed BNCT radiation doses. The present work describes the implementation of the treatment planning software in ongoing clinical trials [16], and the BNCT treatment planning procedures.

2. TREATMENT PLANNING SOFTWARE

The TPS provides tools to create a three dimensional model describing patient anatomy and regions of interest [12,13], calculate the complex radiation fields produced during the

treatment [6,7,15], create dose-volume histograms, and co-register the isodose contours with MR or CT images [12,14]. Module 1, BNCT Radiation Treatment Planning Environment (BNCT-Rtpe), provides the graphical interface for semi-automated geometric

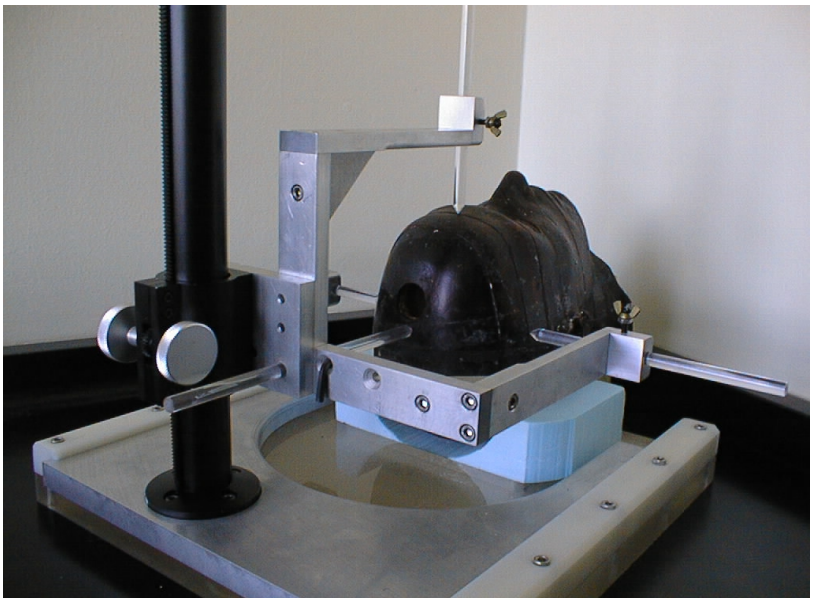

FIG. 1. The stereotactic frame used to identify reference points on the patients' head.

modeling of treatment objects derived from MRI or CT medical imaging modalities [12]. Module 2, Radiation Transport in Tissue by Monte Carlo (rtt_MC) [15], uses the solid model descriptions of the regions of interest, defined by the means of BNCT-Rtpe, to calculate the complex radiation fields present in tissue during the BNCT treatment. The Monte Carlo stochastic process is applied for solving the three dimensional Maxwell-Boltzman transport equations for neutron and gamma particles in simulations of BNCT. After completion of the calculations, rtt_MC saves results including the data needed for isocontour displays and dose/volume histograms in the output files. Module 3, Xcontours [6,14], allows isodose contours to be superimposed on the MRI or CT images of normal tissue or on the target volume. The radiation dose fields are displayed in the original MRI or CT images as dose contours providing an accurate way to view the radiation fields so that the beam location and treatment time can be determined with consideration given to both tumor dose and normal tissue sparing.

3. TEATMENT PLANNING MRI OR CT SCANS

The described TPS accepts both MRI and CT scans as a base for building the head model to be used for Monte Carlo calculations. Nevertheless, excellent soft-tissue contrast resolution makes MRI the preferred modality for BNCT treatment planning. Good visualization of the tumor (contrast enhancing volume) and other anatomical structures allows accurate identification and delineation of the regions of interest and enables more precise estimation of the radiation doses delivered to selected structures. According to recent reports, the total spatial image distortion observed using a 1.5 T MRI machine, within the volume relevant for BNCT treatment planning, are less than 2 mm [17]. This degree of spatial uncertainty is offset by the improved definition of the selected regions of interest provided by MRI based treatment planning.

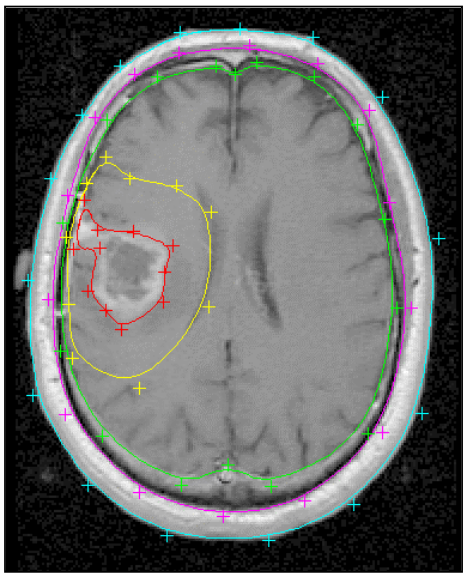

FIG. 2. MRI scan showing transaxial section of a patient's head with control points (+) defining scalp, skull, brain, tumor and target (tumor plus a 2 cm shell) volumes.

Treatment planning MRI brain scans were carried out within seven days prior to the scheduled treatment. Using a specially devised frame (Figure 1) the following reference points were marked with a semi-permanent surgical marker pen on the patient's scalp: vertex, anterior, posterior, left lateral, and right lateral. Radiographic markers were used to visualize the reference points on the MRI images. CT scans were used for those patients who were unable to undergo MRI brain scans. Patients were placed supine on the flat tabletop of the scanning machine and, with help of the marked reference points and the cross-hair lights, the heads were positioned horizontally, parallel to the axis of the scanner. The image files from the simulation MRI or CT scans were transferred via the Internet or on a digital tape to the treatment planning work station (HP 735/125, Hewlett Packard, Palo Alto, CA). The size of the transferred file was checked before and after the transfer to assure that the file had not been altered.

4. GENERATION OF THE THREE DIMENTIONAL MODEL OF THE HEAD

Using InterFormat, an image format conversion program (RadioLogic, Clinton, CT), the image files were translated to an AAPM standard image format [18,19] required by the BNCT-Rtpe. Images of the transaxial sections of the head were displayed by BNCT_Rtpe and the contours of the tumor, as well as the normal structures of interest including scalp, skull, and brain, sinuses were outlined (Figure 2). A 3D model of the patient's head was created using BNCT_Rtpe by a B-Spline reconstruction based on the control points. The rtt_MC module of the treatment planning software used this model, containing all anatomical structures relevant for the subsequent Monte Carlo calculations and regions of interest for which detailed dose characteristics were required. Dose-volume histograms could be generated for any volume defined by control points and reconstructed in the 3D model. After the geometry of the model had been defined, the elemental composition was assigned to each

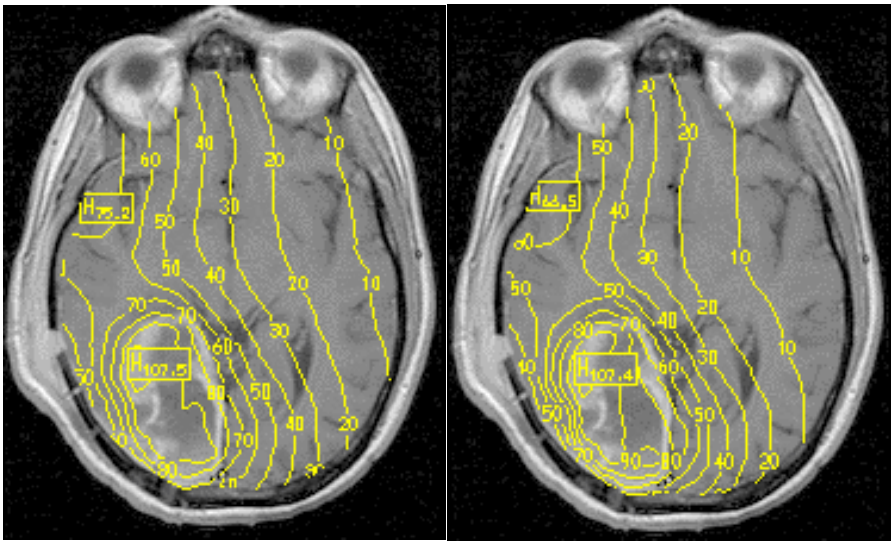

FIG. 3. Examples of isodose contours for normal brain (left panel, 100% =12 Gy-Eq) and tumor (right panel, 100% = 66 Gy-Eq) resulting from treatment plans employing semi-unilateral double-field irradiation. The isodose contours are superimposed on MRI scans showing a transaxial section of a patient's head. The contrast enhancing tumor volume is in the left occipital lobe.

TABLE I. Elemental compositions used in Monte Carlo calculations.

Element	Weight Fraction (%) in		
	Scalp, ref. [20]	Skull, ref [21]	Brain, ref. [22]
H	10.39	4.99	10.56
C	23.74	21.14	13.95
N	2.69	3.99	1.84
O	62.98	43.38	72.59
Na	--	0.10	0.14
P	--	8.08	0.39
Cl	0.21	0.28	0.14
K	--	--	0.39
Ca	--	17.55	--
Mg	--	0.20	--
S	--	0.30	--

5. OPTIMIZATION OF THE DOSE DISTRIBUTION

Optimization of the treatment required calculation of the dose distribution at various irradiation geometries to maximize the radiation dose to the target volume, while keeping the dose to normal tissues within the limits prescribed in the protocol. Variables such as: anatomical feasibility of the patient positioning; dose-volume histograms for the brain and target volume; normal tissue isodose contours; maximum doses and dose-rates to the sensitive structures of the brain; tumor tissue isodose contours; homogeneity of the dose in the target volume; and minimum doses to the target volume, were examined to determine the optimum treatment plan. Also, since the probability of the presence of tumor cells in the ipsilateral hemisphere of patients with unifocal unilateral GBM treated under the current protocol is

higher than anywhere else in the brain, we attempted maximize the neutron flux in the ipsilateral hemisphere and, thereby, to deliver as high a dose as possible to any infiltrating tumor cells there, while sparing the contralateral hemisphere. The results of the Monte Carlo calculations were presented as: 1) isodoses of total BNCT dose over corresponding MRI scans of the brain (Figure 3); 2) isodoses over cross sections of the head model showing the outlined tumor and target volumes; 3) dose-volume histograms for normal brain, tumor and target volumes (Figure 4).

6. FINAL PRE-TREATMENT REPORTS

For the selected irradiation geometry, a table listing the estimated minimum doses for the tumor and target volume and estimated maximum doses for certain normal tissues including retina, basal ganglia, thalamus, optic chiasm, and scalp was prepared. The estimations were based on the results of the Monte Carlo calculations using the following parameters: BMRR epithermal neutron beam high-LET components (fast neutrons, producs of thermal neutron capture in nitrogen) RBE = 3.2; CBE factor for BPA in the brain = 1.3; CBE factor for BPA in the tumor cells = 3.8 [3–5]; CBE factor for BPA in scalp and mucosae = 2.5 [23]. The radiobiological studies leading to these factors have been recently discussed by Coderre and Morris [24]. The average blood ^{10}B concentration expected following infusion of 250 or 290 mg BPA/kg body weight were 11 and 13 ppm, respectively. The ^{10}B concentration used for the tumor cells, brain, scalp, and mucosae were, respectively, 3.5, 1, 1.5, and 2 times the expected blood ^{10}B concentration (23,25,26). The results of pre-treatment radiation dose estimations were used to select the most appropriate treatment plan and to identify the potential side effects expected from the selected plan.

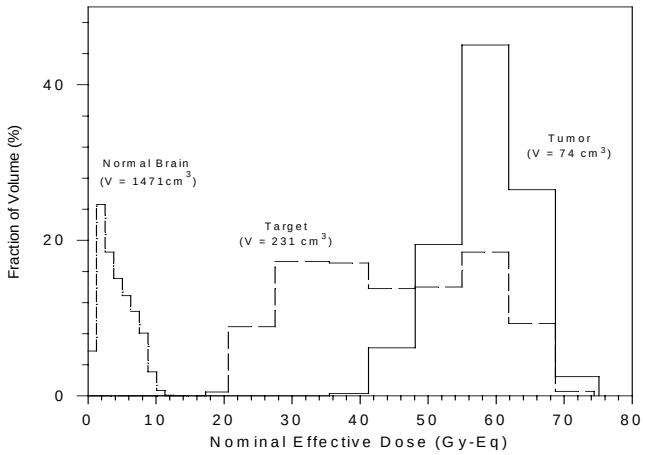

FIG. 4. An example of dose volume histograms for the brain, tumor, and target volumes resulting from treatment plans employing semi-unilateral double-field irradiation.

The following information resulting from the treatment optimization was recorded in order to facilitate the patient positioning and determination of the irradiation time: 1) The *posterior-anterior, left-right and up-down* distances of the "beam entry point" (point where the center of the neutron beam would be expected to enter the scalp as determined by TPS) in relation to the reference triangulation points. These data allowed the entry point to be located and marked on the scalp. This point was then positioned in the center of the beam collimator face. 2) The coordinates of the triangulation points on the patient's head expressed in the

system of coordinates in which the origin (0,0,0) was defined as the center of the beam collimator face. These coordinates provided a means to verify the treatment position by measuring the distances of the triangulation points to the collimator face or positioning lasers. 3) The irradiation time required to deliver the prescribed peak brain dose as a function of the boron concentration in the blood. 4) The corresponding minimum doses to the target volume. 5) The doses to certain sensitive intracranial and extracranial sites as estimated for the expected ^{10}B blood concentrations.

7. PATIENT POSITIONING

Generally on the day before the scheduled BNCT irradiation, the simulation of the treatment position was carried out in a replica of the BMRR epithermal neutron treatment room featuring a transparent mockup of the beam collimator, which allowed verification of the treatment position from the "beam view", and laser positioning crosshair lights [27]. The relative locations of the positioning lasers to the collimator are identical in the irradiation room at the BMRR and in the simulation room replica. The beam entry point was identified and marked on the scalp using the previously obtained data. The patient was placed in the treatment position in such a way that the beam entry point coincided with the center of the beam collimator. The head position was adjusted using the coordinates of the reference triangulation points in relation to the center of the beam collimator. The head position was stabilized by a vacuum pillow (Med-Tec, Orange City, IA) and Velcro straps. The positions of

FIG. 5. A patient shown in a BNCT treatment position at the 12 cm collimator in the simulation room. A deflatable beam pillow and a Velcro strap are used to immobilize the head. Transparency of the simulation room mock-up of the collimator allows verification of the treatment position from the direction of the neutron beam.

the laser cross hairs on the head were marked. The cushioning and support materials used, the table height and position, and the angle between the table and the beam port wall were recorded. Polaroid photographs of the patient in the simulated treatment position were taken. These data were then used to reproduce the patient's position in the BMRR epithermal neutron beam treatment room. Figure 5 shows a GBM patient in the final treatment position in the simulation room. It is necessary that no voluntary effort be required of the patient in

maintaining the desired treatment position during irradiation. Bean pillows proved to be very useful in supporting the patient at the collimator. This kind of support does not depend upon voluntary effort and limits the involuntary movements, so that all the fiducial markers are kept within a margin of 5 mm from the prescribed position. As the BNCT irradiation field is not sharply circumscribed, geometrical uncertainties of this magnitude are acceptable.

8. IRRADIATION

The irradiation time was determined using the irradiation-timetable. Blood ^{10}B concentrations were measured during and after the BPA-F infusion by both direct-current plasma atomic emission spectroscopy (DCP-AES) [28,29] and prompt-gamma ray spectroscopy [30]. The approximate total irradiation time was determined based on the blood ^{10}B concentration measured just before the start of irradiation and the available pharmacokinetic data. During the break in irradiation, at the approximate midpoint of the irradiation (single-field BNCT) or at the completion of each field irradiation (multi-field BNCT), additional blood samples were drawn and the blood ^{10}B concentration was measured. The average ^{10}B concentration during the entire treatment was predicted on the basis of the slope of the curve formed by the blood boron concentrations at the end of infusion, just prior to the start of therapy, and at the break points, using the combined data from BPA-F biodistribution studies and data obtained during this trial. Based on the predicted average ^{10}B concentration, the duration of the remaining part of the irradiation was adjusted to bring the target volume and brain up to the prescribed doses.

During irradiations, patients were observed via closed-circuit television (TV) with images obtained from three video cameras showing the patient in the treatment positions from different angles. Communication with the patient was made possible via an intercom system. One of the TV monitors was used for the continuous verification of patient position. The reference lines coinciding with the laser crosshair and prominent contours of the patient were marked directly on the screen, which allowed easy identification of any deviations from the desirable treatment position. Any significant deviations could be corrected without treatment interruption by directing the patient via intercom to readjust the position as required. If necessary, timed video records were used to estimate possible effects of any patient movements on the total dose distribution.

9. POST-TREATMENT DOSIMATRIC EVALUATION

Upon completion of BNCT, the blood ^{10}B concentration was measured and the actual average blood boron concentration was calculated. The difference between the predicted average and the actual average values seldom exceeded 1 ppm, resulting in less than 1 Gy-Eq difference between the estimated and retrospectively calculated peak normal brain dose. The measured blood ^{10}B concentration and the total time of irradiation were used for the final evaluation of the doses delivered to regions of interest, and to prepare a post-treatment dosimetry report containing the following sections: 1) post-treatment patient dose evaluation sheet listing reactor power, peak thermal neutron fluence, measured boron concentrations in the blood, estimated boron concentrations in the tumor and normal tissues, volumes of the brain, tumor and target, peak dose rate in the brain, peak and average brain doses, average and minimum tumor and target volume doses, maximum doses to selected anatomical structutes; 2) isodose contours overlaid onto images of the brain scans (Figure 3); 3) tumor tissue isodose contours overlaid onto images of the target volume; dose-volume histograms for the brain, tumor and target volume (Figure 4).

There are inherent uncertainties in the estimation of BNCT doses. A large fraction of the radiation dose delivered to both tumor and normal tissues during BNCT originates from the ^{10}B- neutron capture reaction. Therefore, ^{10}B concentrations in various tissues have a great influence on the total radiation dose. Furthermore, in order to relate the radiation doses delivered during BNCT to conventional radiotherapy, all BNCT doses are expressed in Gy-Eq units, which requires appropriate RBE and CBE factors. These factors were mostly derived from animal studies using different endpoints. For instance, the CBE factors for BPA in the brain and in the tumor were obtained from spinal cord irradiation in the rat [5] and from in vivo/in vitro survival experiments using rats with implanted gliosarcoma [3], respectively. It is not known how relevant these models are for spontaneous GBM in cerebral hemispheres of humans treated with BNCT. Each of these values has an inherent uncertainty, which adds to the overall uncertainty in the BNCT dose estimates. Furthermore, only boron concentration in the blood was measured during BNCT. The boron concentration in tumor and normal tissues was assumed based on the previous biodistribution studies and, presently, very little is know about the boron concentration in individuals tumor cells invaiding normal brain away from the main tumor. If different values of RBE, CBE, or boron concentrations are deemed to be more appropriate at some point in the future, then the TPS will enable retrospective recalculations of the BNCT doses using these modified values.

10. CONCLUSION

In BNCT, like in conventional radiotherapy, it is crucial to accurately determine the doses delivered to the tumor and normal tissues in order to optimize the treatment and to analyze its outcome. The procedures described in this paper, combined with the BNCT treatment planning software, provide a means to optimize the irradiation geometry and to calculate the nominal BNCT doses delivered to regions of interest as a function of irradiation time and ^{10}B concentration in the blood. Post-treatment reports, including dose volume histograms for the normal brain, tumor and target volumes, estimations of radiation doses delivered to selected sites in the brain and other tissues, as well as isodose contours superimposed on MRI scans facilitated the evaluation of the treatment outcome.

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Clinical treatment planning for subjects undergoing boron neutron capture therapy at Harvard-MIT

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Abstract. Treatment planning is a crucial component of the Harvard-MIT boron neutron capture therapy (BNCT) clinical trials. Treatment planning can be divided into five stages: (1) pre-planning, based on CT and MRI scans obtained when the subject arrives at the hospital and on assumed boron-10 distribution parameters; (2) subject set-up, or simulation, in the MITR-II medical therapy room to determine the boundary conditions for possible set-up configurations; (3) re-planning, following the subject simulation; (4) final localization of the subject in the medical theray room for BNCT; and (5) final post facto recalculation of the doses delivered based on firm knowledge of the blood boron-10 concentration profiles and the neutron flux histories from precise on-line monitoring. The computer-assisted treatment planning is done using a specially written BNCT treatment planning code called MacNCTPLAN. The code uses the Los Alamos National Laboratory's Monte Carlo n-particle radiation transport code MCNPv.4b as the dose calculation engine and advanced anatomical model simulation based on an automatic evaluation of CT scan data. Results are displayed as isodose contours and dose-volume histograms, the latter correlated precisely with corresponding anatomical CT or MRI image planes. Examples of typical treatment planning scenarios will be presented.

1. INTRODUCTION

To date, twenty eight subjects have received epithermal neutron irradiations in 1–4 fractions following oral or intravenous administrations of 250–400 mg/kg of p-boronophenylalanine (BPA) in the Harvard-MIT phase-I boron neutron capture therapy (BNCT) protocol [1]. Treatment planning for BNCT involves multiple stages. The treatment planning sequence for a subject starts with the examination of medical records and recent CT and MRI scans by the clinical and medical physics team. If the subject complies with the inclusion criteria the procedure and associated risks are explained and informed consent is obtained. Subsequent steps involve the CT and MRI scanning of the subject to generate source images for the computational synthesis of a customized anatomical model for Monte Carlo treatment planning calculations, selection of beam locations and weights, computation of doses by Monte Carlo simulation, clinical assessment of isodose contours, simulation set-up of the subject in the irradiation facility, fabrication of immobilization devices, final refinement of the treatment plan if necessary, conversion of isodose contours and epithermal neutron beam calibration data into the required beam monitor counts to be delivered with each beam, sometimes a ìtest doseî administration of BPA to obtain stereotactically targeted samples of tumor and normal tissues for boron-10 analysis, and, finally, the set-up of the subject in the irradiation facility and the actual delivery of the BNCT irradiation according to protocol.

2. METHODS & MATERIALS

With an approximate knowledge of the tumor target region based on prior CT and MRI films that the subject brings with him/her an estimate is made regarding the approximate orientation of the neutron beams relative to the subject's head. The subject is then taken to the

medical irradiation facility at the MIT Research Reactor and a simulated set-up is done. Aquaplast masks (WFR/Aquaplast, Inc., Wyckoff, New Jersey) — thin plastic anatomy-conforming net-like masks first softened by immersion in hot water — are fabricated with the subject positioned on the irradiation couch to keep the head immobilized during irradiation. The position of the irradiation couch is adjusted to conform to the initially planned irradiation position. CT and MRI scans of the subject's head are acquired with and without contrast (I+ & I-, Gd+ & Gd-). All image sets are fused into spatial registration with each other, facilitated by the subject wearing a fiducial frame (Anatomark, Interneuron, Inc., Lexington, MA). Immobilization through the use of Velcro tape and foam rubber cradles ensures that the subjectís head remains essentially motionless during the acquisition of the CT and MRI scans. For the identification of the tumor and target regions the Gd+ image set is preferred, while to convert the Hounsfield Unit values in the CT images into elementally based materials for the Monte Carlo transport calculations the I- image set is used. The physical and mathematical principles, architecture, operation, and application of the Monte Carlo based BNCT treatment planning code MacNCTPLAN have been described in previous reports [1–5]. The code is written for the Power Macintosh platform using Pascal modules nested within the public domain image processing code NIH Image (v.1.57). The Monte Carlo simulation code MCNP4b [6] is employed to compute the three dimensional dose distributions utilizing the mathematically synthesized model of the subject's head. Initial boron concentrations in normal and tumor tissues are estimated either from previous clinical cases, or from the results of a test dose administration of BPA, from which the blood boron-10 concentration curve is derived as well as boron-10 concentrations in stereotactically obtained tumor and normal tissue samples. These boron concentrations are entered into the Monte Carlo calculation in order to account for thermal neutron flux depression. After isodose contours have been generated, correlation of these with tumor volumes and with sensitive anatomical structures (e.g., retina, optic chiasm, parotid gland, brain stem, etc.) is accomplished by superimposing the isodose contours on corresponding CT or MRI image planes. As a further aid to the clinical interpretation of tumor and normal tissue doses, MacNCTPLAN permits the display of dose-volume histograms (DVHs) defined by manually drawn ROIs. As well as computing isodose contours for the subject, isodose contours are also computed by Monte Carlo simulation for the standard head phantom that is used for the physical in-phantom calibration of the M-67 epithermal neutron beam at the MIT Research Reactor [7,8]. Each of the individually computed dose components contributing to the point of maximum total RBE-dose-rate in the phantom (d-max) is compared to the corresponding measured value, and a Monte Carlo Dose Scaling Factor (MCDSF) is calculated to force the corresponding Monte Carlo dose values to conform to the measured ones. The ratio of maximum normal tissue d-max for a beam oriented in the calibration position in the standard head phantom to the maximum normal tissue d-max of a specifically oriented beam in the subject, for equal boron-10 concentrations, is called the Monte Carlo Dose-Rate Ratio (MCDRR). After a multibeam treatment plan is computed for the subject, application of the MCDSFs and the MCDRR for each beam will normalize the computed d-max in the subject for each individual beam to the physical d-max measured in the standard head phantom. The perceived advantage of this approach is that the Monte Carlo computation is not utilized for predicting absolute doses in the subject, but only for determining a dose transfer factor between a Monte Carlo calculation in a standard head phantom and a Monte Carlo calculation in the subject; while the final conversion of the dose isocontours in the subject to absolute RBE-dose-rates is tied to the physical dose calibration performed in the standard head phantom. During the BNCT irradiation, blood samples are drawn from the subject remotely at frequent intervals and immediately analyzed for boron-10 concentration by prompt-gamma spectroscopy or ICP-AES analysis [9]. As the resulting blood boron-10 pharmacokinetic curve evolves during the

irradiation, the data are entered into a dose monitoring program [10] which utilizes the on-line beam monitor count-rates, previously calibrated against reactor power level and dose in the standard head phantom, the instantaneous boron-10 blood levels, and the previously calculated MCDRRs to compute real time cumulated absolute RBE-dose to the subjectís normal tissue. Following the irradiation, the neutron flux history of the irradiation and the blood boron-10 curve are reanalyzed and a ìtrueî average boron-10 concentration is computed independently for each beam delivered. The treatment plans are finally recalculated using MacNCTPLAN utilizing the true boron-10 concentrations and power histories.

3. RESULTS & DISCUSSION

Fig. 1 shows a photograph of a subject lying on the irradiation couch on top of VacLoc pillows in the irradiation position. The VacLoc pillows (Med-Tec, Inc., Orange City, Iowa) are thick plastic bags filled with very small styrofoam balls which are initially soft and conform to the subjectís anatomy. When a vacuum is drawn on these pillows they maintain the same contours but become rigid. The VacLoc pillows, together with three restraint belts, provide comfortable support and immobilization to the subject's trunk and legs, especially when lateral & longitudinal couch angulations of up to 15 deg. are required. A custom-fabricated Aquaplast mask immobilizes the subject's head. Usually, holes are cut out of the mask over the eyes, nose, and mouth to increase the comfort of the subject. Relative immobilization of the subject's body by the VacLoc pillows is also important from the safety perspective since the subjectís head is independently immobilized by the Aquaplast mask. The neutron beam entrance points and incidence angles are marked on the surface of the masks with the aid of hard copy styrofoam cutouts of orthogonal CT planes centered on the beam axis. Fig. 2 shows such a pair of orthogonal CT images from which the beam entrance point and the required angulations of the supporting baseplate of the irradiation couch were determined. The two beams labelled 1 and 2 are in this instance truly parallel-opposed, although this is unusual. Fig. 3 shows a tumor isocontour RBE-dose plot for an anatomical section passing through the mid-plane of the tumor (a GBM). The assumption was made that the average boron-10 concentration in blood was 15 ppm for the first beam and 10 ppm for the second and that tumor contained 3.5x higher boron-10 concentration than blood or normal brain. Actual intracellular concentrations of boron-10 in tumor and normal brain are sometimes physically measured when stereotactic biopsies of tumor and normal tissues following BPA administration are available using high-resolution alpha-autoradiography [11,12] and more accurate tissue dose distributions can then be recalculated *post facto*. The isodose contours are in units of RBE-cGy and are referenced to the maximum RBE-dose (d-max) in normal tissue. For example, if the prescription dose to normal tissue were 1,000 RBE-cGy, then the 200%î isocontour would correspond to a tumor dose of 2,000 RBE-cGy. Fig. 4 shows the corresponding anatomical plane in which the isocontours represent doses to *normal* tissue. For a 1,000 RBE c-Gy prescription dose, the 50% isocontour would correspond to a normal tissue dose of 500 RBE-cGy. DVH calculations are often done for the orbits, the whole brain, and for the tumor and target volumes.

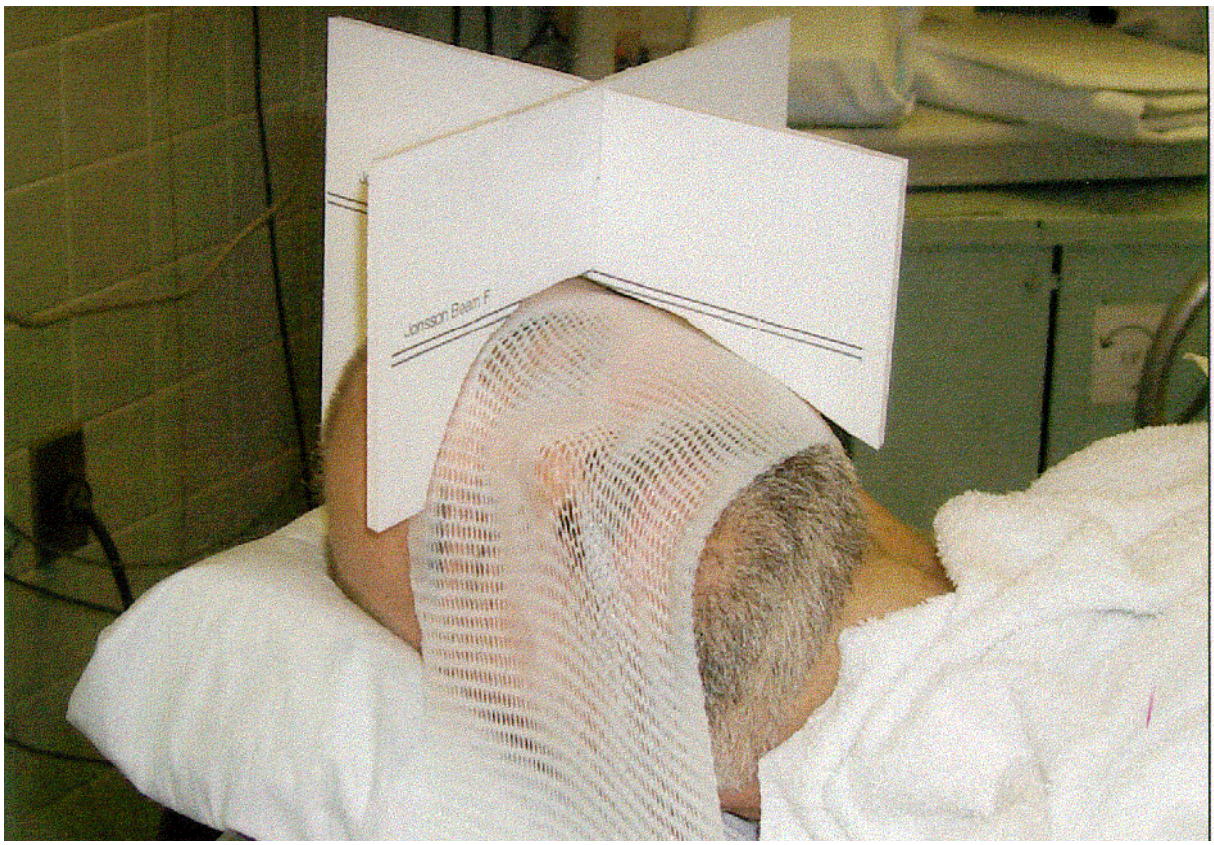

FIG. 1. BNCT GBM protocol subject lying on couch in irradiation position. Aquaplast mask is shown immobilizing the head and styrofoam localization cutouts are seen defining the beamís central axis and entrance point.

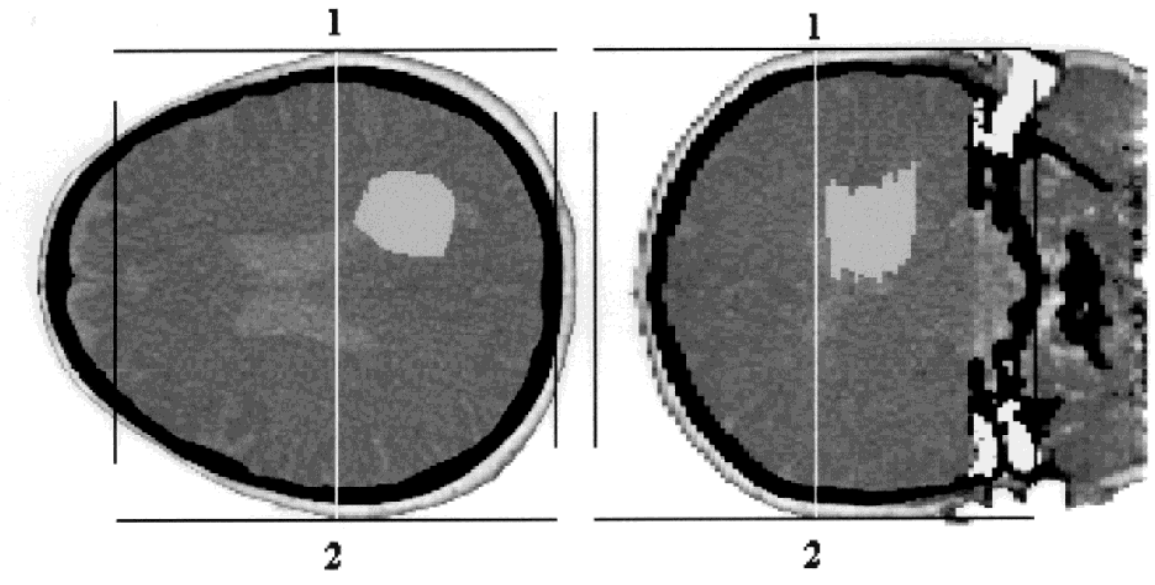

FIG. 2. Coronal & transverse CT images of subjectís head from which styrofoam cutouts are made to determine the beam entrance points on the Aquaplast mask and the required irradiation couch angulations. Beam entrance positions and the necessary angulations of the head relative to the vertically oriented beam axis are shown. The enhancing tumor volume is shown in gray. The M-67 beam has a circular cross section of 15 cm diameter.

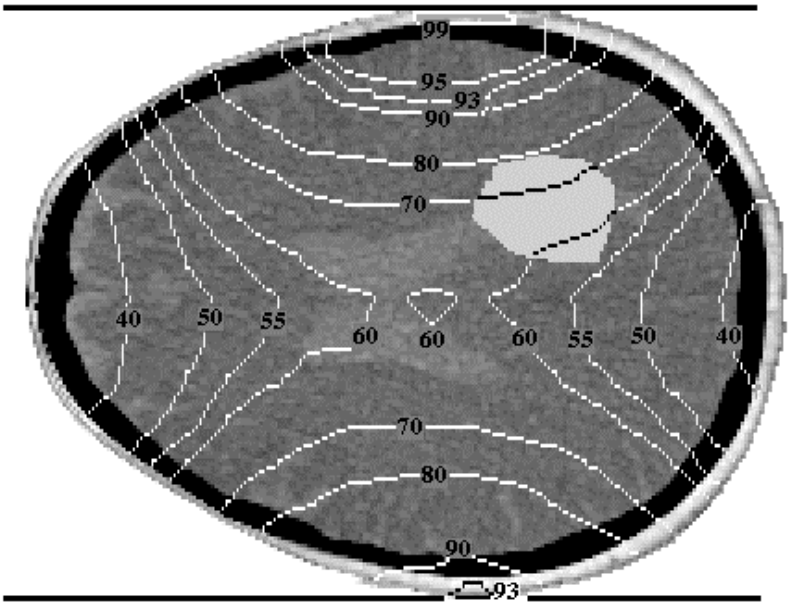

FIG. 3. Isocontour dose plot for an anatomical section passing through the mid-plane of the tumor (GBM). The isocontours, in units of percent RBE-cGy, represent doses to normal tissue with the 100% value corresponding to the ìd-maxî point referred to in the text. The assumption is made that blood & normal brain contain 15 ppm of boron-10 for the first beam delivered & 10 ppm for the second beam. The RBE values assumed are 1.35 for boron-10 dose in normal brain (this the compound-RBE); 3.2 for thermal, epithermal, and fast neutron dose, and 0.5 for gamma dose. The latter was chosen because the irradiations typically extend over a total period of approximately six-eight hours stretched over two consecutive days. The RBE values are fully referenced in [5].

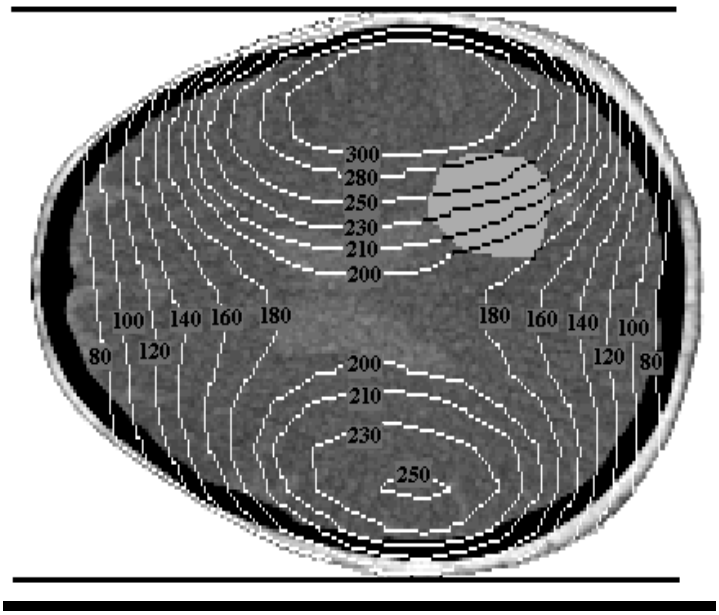

FIG. 4. Isocontour plot for the same anatomical section as in Fig. 3. Here, however, the isocontours, also in units of RBE-cGy, represent doses to tumor tissue. It is assumed that tumor contains 3.5 times higher boron-10 concentration than blood. The boron-10 compound-RBE value assumed for tumor is 3.8, fully referenced in [5]

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SERA — an advanced treatment planning system for neutron therapy

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Abstract. The technology for computational dosimetry and treatment planning for Boron Neutron Capture Therapy (BNCT) has advanced significantly over the past few years. Because of the more complex nature of the problem, the computational methods that work well for treatment planning in photon radiotherapy are not applicable to BNCT. The necessary methods have, however, been developed and have been successfully employed both for research applications as well as human trials. Computational geometry for BNCT applications can be constructed directly from tomographic medical imagery and computed radiation dose distributions can be readily displayed in formats that are familiar to the radiotherapy community. The SERA system represents a significant advance in several areas for treatment planning. However further improvements in speed and results presentation are still needed for routine clinical applications, particularly when optimization of dose pattern is required.

1. INTRODUCTION

The Simulation Environment for Radiotherapy Applications (SERA) system, developed independently by INEEL in collaboration with Montana State University, is entering the applications phase. SERA consists of several modules for 1) image manipulation, 2) model reconstruction based on medical images, 3) dose computations by Monte Carlo simulation, 4) three dimensional model and dose display, 5) two dimensional dose contour display over image slices, 6) planning tools for field and fraction selection, and 7) tools for creation and display of line plots and dose-volume relationships. SERA is currently in initial clinical testing in connection with BNCT trials at Brookhaven[1] and will replace the present BNCT_Rtpe system upon general release in 1999.

The SERA system incorporates a new method for reconstructing patient geometry from medical images and for subsequently tracking particles through this geometry during a Monte Carlo radiation transport simulation[2]. The method, in contrast to the Non-Uniform Rational Bspline (NURBS) method used in BNCT_Rtpe, is based on a pixel by pixel uniform-volume element ("univel") reconstruction of the patient geometry. Fast line rasterization methods, implemented largely with integer arithmetic, are used to allow rapid particle tracking through the univel geometry. Univels along the particle track are investigated, and precise region intersection points can be rapidly calculated as the particle moves from one region to the next. By scaling the univels to match the resolution of the original image data, the geometric fidelity of the NURBS reconstruction method is retained, and the computed doses have similar statistical accuracy. The execution time is reduced by a factor of five to ten. This speedup factor holds even though the new univel model may consist of several million elements. Execution times for the method, with current moderate-priced desktop computing hardware, are in the range of 15–20 CPU minutes per field. Parallelization of the algorithm to, for example, four CPUs would yield computation times in the range of five minutes per field, since the execution speed would scale nearly linearly with the number of CPUs.

A number of other new features are available for the SERA system. For example, a capability to input patient-specific boron localization data derived from PET, as described by Kabalka[3], is under development. The boronated pharmaceutical of interest (in this case boronated phenaylalanine, or BPA) is labeled with ^{18}F, permitting the localization properties of the drug to be observed by PET. This information can be registered with the anatomical images used for the patient geometry construction and thereby incorporated into the treatment planning calculations. Currently, BNCT treatment planning is typically based on the rather simple assumption of a uniform boron concentration within each anatomical region of interest in the model. The new capability thus will offer the potential for increased fidelity in the boron dose computations. In addition, a technique for further increasing the speed of the radiation transport computations that is based on the application of weight windows is under investigation by INEEL collaborators at the University of Michigan[4]. The basic physics modules of SERA will allow incident neutron energies up to 100 MeV, with an explicit treatment of recoil proton transport. This expands the utility of the SERA system into the field of fast-neutron radiotherapy, with or without BNCT augmentation[5].

2. SERA DESCRIPTION

The main menu for SERA is shown in Figure 1. This window may be used to launch the modules of SERA or they may be launched independently. It accommodates an expert mode, and allows global preferences to be set. The main menu provides the ability to launch or close individual SERA components on different displays and to provide command line parameters to a software module when it is launched. At this time, SERA will run on either Linux-based Intel systems or Solaris 2.6 (or newer) systems with high-end video support. Other computer systems will be supported only under special arrangements.

FIG. 1. SERA main menu.

2.1. Image Formatter (seraImage)

Most treatment plans developed with SERA will begin with the **seraImage** formatting module. Its basic function is to convert the original medical image format into the QSH format, which is the internal format used within the SERA modules. QSH is an image file format based on the American Association of Physicists in Medicine (AAPM) standard and described further in the SERA manual located at the Universal Locator Address (URL) http://www.cs.montana.edu/~bnct. The image formatting function will accept unformatted (raw) and QSH formatted images. Images may be deleted, re-arranged, translated, scaled, or rotated. The image header file can also be modified.

2.2. Image Modeling (seraModel)

The purpose of the **seraModel** module is to easily and rapidly divide an image set into regions of interest. The user interface for **seraModel** is shown in Figure 2.

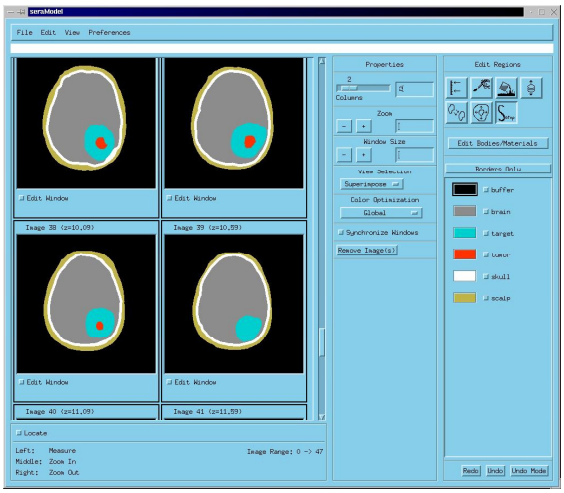

FIG. 2. seraModel user interface.

The image matrix used for display in this program has been generalized to work on systems with different color depths. Images may be viewed at an arbitrary zoom level, in an arbitrary window, and with an arbitrary number of columns.

The **seraModel** module provides many useful image operations, including manual and automatic definition and generation of univel-based regions of interest that form the geometry used by the Monte Carlo radiation transport simulation (**seraMC**). Various tools are provided to aid in the manual/automatic definition of regions including region copying, scaling, overwriting, and painting by fill or borders. Thresholding-based segmenting, 3D region growing, and margin definition operations are also provided. The regions are painted in colors chosen by the user, with an option of viewing just the borders of the regions to see the underlying image. The user can edit regions as small as an individual pixel. These tools are being extended to make region creation by treatment planners as intuitive and efficient as possible. Other features include the ability to:

(1) set and save the preferences for the program,
(2) maintain a list of the recently used files for quick access,

(3) undo one or more operations as may be necessary,
(4) save disk space by transparently reading compressed files,
(5) look at axial, sagittal, and corneal slices, and
(6) use control panels to give the user easy access to important functions.

Another feature of the program saves the regions in a uniform volume element format that lends itself to fast geometry interrogation. A resultant univel (uv/uvh) file format has been developed to describe the voxelized regions.

A set of library routines (libuv) has been written to handle reading and writing the uv/uvh files, and to interrogate the geometry of the bodies represented in these files. The stepping algorithms used for the intersections have increased the Monte Carlo performance by more than a factor of five over the NURBS based algorithm. By maintaining a high resolution set of univels, the accuracy of the simulation is maintained. Additionally, lost particle occurrences are greatly reduced compared to the NURBS geometry interrogation.

2.3. Three Dimensional Viewer (sera3d)

The three dimensional viewer, **sera3d**[6], provides flexible three dimensional displays of the univel-based solid models (see Figure 3) and isodose contour data after all of the bodies are created with **seraModel**. Points, solid regions, hollow regions, or polygonal surfaces can be used to view the geometry. The beam line and selected particle paths may also be displayed in the viewing window. A surface colouring feature for viewing two and three dimensional isodose contours is also provided.

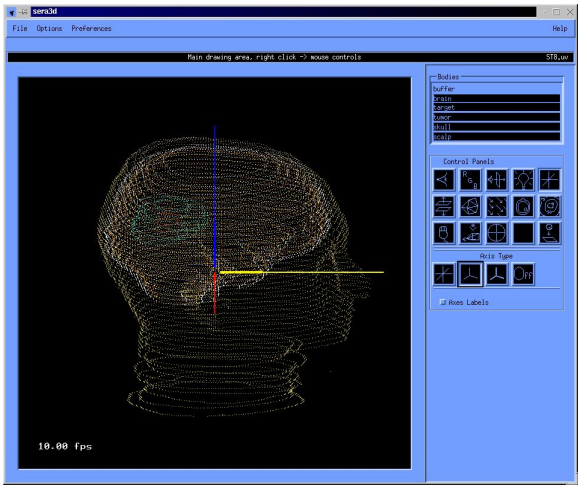

FIG. 3. Three dimensional viewer user interface.

The Open GL graphics standard is used for the **sera3d** three dimensional display. The main purpose of the viewer is to provide the user with a fuller understanding of the proposed treatment plan.

The program will take a segmented uv/uvh file and reconstruct the segmented regions for 3D viewing. Various rendering options provide varying levels of reconstruction performance and detail. Features are provided to further explore the model geometry. User-defined region transparency allows a view through the outer regions to inner regions of interest. Similarly, six orthogonal clipping planes provide a defined "cut" out of the regions to see the regions inside. Full rotational capabilities, various camera positions including a beam-line view, and multiple rendering windows provide additional control.

An additional advancement in the program is the ability to inlay the original medical image into its corresponding location within the reconstructed geometry and to optionally display dose contours on selected planes. The method allows a slice plane to be drawn in an arbitrary direction through the "medical slice volume", resulting in an oblique slice.

This ability has been extended to the loaded beam line, and slices perpendicular to the beamline are now available. It also allows a detailed volume rendering of the original slices.

2.4. Dose Contouring (seraDose)

The **seraDose** (see Figure 4) dose contouring module employs a new locally developed contour library that replaces the contouring libraries used by xcontours, which were supplied by the National Center for Atmospheric Research (NCAR). The addition of the new contouring library allows for more customization of the contour displayed levels. This includes the selection of specific percentage levels at which contour lines are to be placed, the ability to color individual isodoses, and the option of viewing various sizes of contour line labels The user also may save their specific settings in a preferences file for later use.

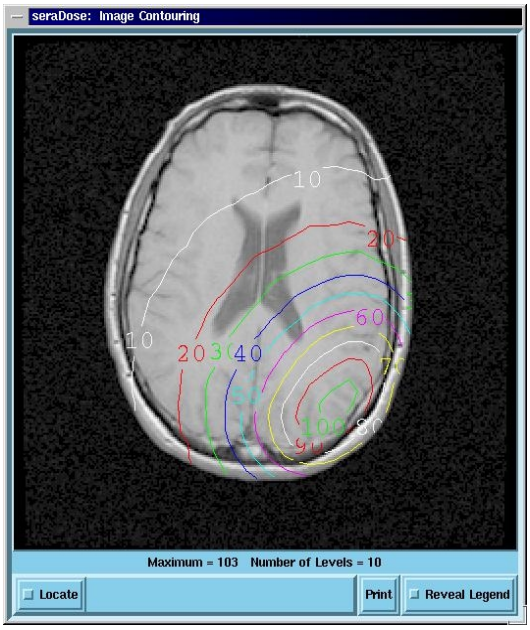

FIG. 4. seraDose display for single image.

The **seraDose** module can display contour color washes in 16, 24, or 32 bit color-depth displays. An image/results directory scheme has been developed for improved file organization and easier manipulation of multiple slices. Finally, **seraDose** can read either raw image files or QSH formatted files.

2.5. Dose Plots (seraPlot)

The **seraPlot** module provides the integrated control of dose-depth and dose-volume plotting utilities that post-process the results of the treatment simulation. The dose-depth and dose-volume utilities read the outputs from the Monte Carlo calculations (**seraMC**) and invoke the xmgr generalized plotting module for each encounter of a line edit and for specified dose-volume edits.

Dose-depth plots can be shown for any or all of the following dose-components:

total dose	Group 1 fluence
boron-10 dose	Group 2 fluence
gamma dose	Thermal fluence
nitrogen-14 dose	Gamma production
hydrogen dose	Ultrafast gamma dose
other dose	

2.6. Field and Fraction Combinations (seraPlan)

The **seraPlan** module allows the user to statistically combine fields and fractions for final treatment planning so that single effective dose can be presented. The user may select between 1 and 6 fractions and between 1 and 4 fields per fraction.

3. DOSE CALCULATIONS

The output from **seraMC** (and other methods) is usually considered to be dose when in fact it is Kinetic Energy Released in Matter (KERMA). In only one instance, the simulation of ultra-fast recoil proton transport (where the incident neutron has energy > 16.9 MeV), is absorbed dose calculated. The KERMA from other charged particles is calculated assuming a uniform macroscopic concentration of the precursor nuclides. The microscopic distribution and charged-particle non-equilibrium is accounted for in the weighted dose by use of an empirical Relative Biological Effect (RBE) or in the case of the boron dose, a Compound Factor (CF). The RBE and CF also includes biological effects which are due to radiation quality. There is no correction from gamma KERMA to gamma dose, which leads to an underprediction or overprediction of gamma dose near boundaries. It is felt that this approximation of dose is adequate for present applications of BNCT.

3.1. Calculation of Pointwise Dose

Patient treatment planning requires the ability to determine pointwise dose. Monte Carlo, in general, computes volume-integrated values since the variance at a single point is infinite. There are methods to determine pointwise dose in Monte Carlo but it is not practical to use these since so much detail is required. In the **seraMC** module, flux and dose is computed as a volume integral for each region. In addition, to provide detail, a virtual edit mesh is imposed over all anatomical regions. This edit mesh consists of an orderly array of cubes, usually with width 10 mm. For every particle path, the contribution to flux and all dose

components for each edit cube intersected by the ray is tallied. After the Monte Carlo simulation, pointwise dose is then determined as a function of the volume-integrated values determined for the edit cubes. The value at a point is determined as a function of the nearest 7 edit cubes in orthogonal directions. The following constraints are assumed to compute each point value.

(1) The flux shape in each orthogonal direction is assumed to be a second order polynomial.
(2) The coefficients of the polynomial are determined using the integral values of the three edit cubes in each orthogonal direction.
(3) The volume integral of all point values within each edit cube is equal to the volume integral value determined in the Monte Carlo process.
(4) At the boundaries of the edit mesh, where there are only two edit cubes, it is assumed that the slope of the function at the boundary is that determined by the two integral values of the cubes.

3.2. seraMC Outputs

Treatment planning requires the use of zero, one, two, and three dimensional outputs. A zero dimensional output is the dose at a single point. This point value may be the minimum dose in the target (treatment volume) which may represent a goal of treatment planning or the point value could represent a constraint in treatment planning.

A one dimensional edit may be a dose-depth relationship, such as shown in the example presented in Figure 5.

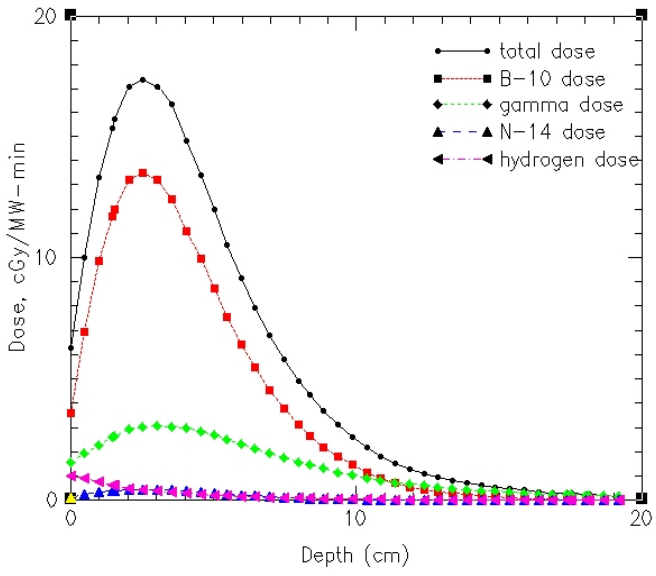

FIG. 5. Dose profile for standard model; 50 ppm boron, 120-mm aperture.

For Figure 5, the boron concentration was set to 50 ppm in the edit even though it was 14.3 in the transport simulation. It is usually assumed that the boron concentration is low enough that the thermal neutron flux is not perturbed by the boron and edits can be obtained for any reasonable boron concentration. If this is not the case and the boron distribution is

known then it can be set to that value for the transport simulation and the flux perturbation would be properly accounted for.

An example of a two dimensional edit is the important isodose display, such as previously presented in Figure 4. To obtain this edit, **seraMC** writes a file consisting of values for a uniform grid, set by the user. This grid is often a 40 by 40 grid over the field of view and the pointwise dose components are written to the file at each grid line intersection. The **seraDose** module then determines the contour lines as interpolated values from the grid points.

An example of a three dimensional edit is the dose-volume integral. The results from this integration provide perhaps the most important information for treatment planning. The dose space is divided into N + 1 percentile bins where N defaults to 10 to give bins of width 10 percent but N can also be set by the user. The additional bin is for dose values exceeding 100% of the reference dose. For each bin and each component, the associated volume is computed. The user specifies a grid width (delta) and the integration is performed over the grid for a specified region or set of regions. The integration is performed at least twice where the grid spacing is halved for successive integrations until the total volume of integration determined by the process differs from the previous integral value by less than a specified epsilon. An example of a cumulative dose-volume plot is provided in Figure 6.

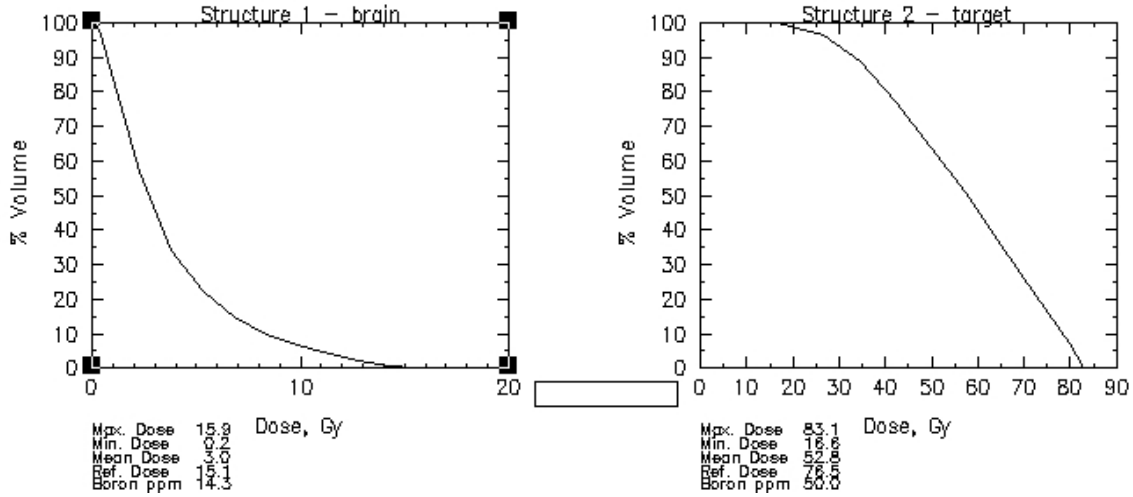

FIG. 6. Dose-volume relationships for standard model.

In addition to volumes for each bin, this edit provides the minimum, maximum, and mean value for each component of dose. These values are mandatory for proper treatment planning. The output for up to 6 plans can be displayed simultaneously for selection by the radiotherapist.

Another important output is the reference dose. The **seraMC** code has several options for determining reference dose. The reference dose can be a specified point, a point at a specified depth along the beam line, or it can correspond to an edit voxel or cluster of edit voxels. If an edit voxel, the reference dose can be the voxel of peak thermal flux or peak weighted dose. One can specify an acceptance region list, for example allowing the reference dose to be in healthy brain but not in the tumor. If the reference dose is an edit voxel it is computed as the mean value of the voxel and a point lying within that voxel could have a

value larger than the voxel value. If the reference volume is more than one voxel then the reference dose is the mean value of the minimum-dose voxel within the reference volume. Typically, the reference volume is some volume in healthy brain and the corresponding reference dose is used to determine the irradiation time such that a certain dose value is not exceeded. The computed reference dose is the concentration and RBE weighted value of dose and is set to be the 100% dose value for contouring and calculation of dose-volume relationships.

Various positioning parameters can be calculated and may be useful in determining the position of the patient relative to the beam. Using the "fiducial" edit one can get the distances (in patient coordinates) from a fiducial marker to the entry point at the center of the beam and to a laser positioning system. One also gets a trace from the marker to the beam exit plane in a direction perpendicular to the plane.

3.3. Optimization

Some work has been done in optimization, or in determining fields etc. such that the tumor control probability is at a maximum and all constraints are met. Manual optimization is a very time consuming process requiring great resource and in the future we plan to automate the optimization process as much as is practical. Optimization is very important because a small increase in minimum target dose can result in a very significant gain in tumor control. For single field applications, positioning the beam such that the distance along the beamline to the center of the target is a minimum is often a good approximation of the optimum single field. As more fields are added, the process becomes much less intuitive and resource intensive, in fact manual optimization becomes an impossible process under time and resource constraints always existing at a particular facility.

A simple example of optimization would be a grid search which can be done manually for single field applications. In this method, the beam orientation is modified in step increments in a range of effectiveness and the orientation yielding the maximum tumor control or other desired goal is selected. As the number of fields increase and the necessary constraints are imposed, this method becomes impractical and more sophisticated approaches are required. One such approach is the differential approach where each beam variable is varied and the differential response is determined. If the response is positive, the search continues in that direction until an optimum or zero differential is determined for each variable. This search is modified by constraints such that situations where the constraint is violated are omitted. This approach has been tried with the doses calculated by a lookup table and it appears to work well. In the future, computer speeds may be such that it would be possible to do this search using Monte Carlo transport. Multiple CPU units would result in linear reductions in the required clock time and it may be possible to find the approximate optimums overnight or even sooner.

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Annex 8
CLINICAL

Medical set-up of boron neutron capture therapy (BNCT) for malignant glioma at the Japan research reactor (JRR)-4

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Abstract. The University of Tsukuba project for boron neutron capture therapy (BNCT) was initiated at the Japan Atomic Energy Research Institute (JAERI) in 1992. The clinical study for BNCT began at the Japan Research Reactor (JRR)-2 of the JAERI in November 1995. By the end of 1998, a new medical irradiation facility had been installed in JRR-4 of that included a new medical treatment room and patient-monitoring area adjacent to the irradiation room. The medical treatment room was built to reflect a hospital-type operation room that includes an operating table with a carbon head frame, anesthesia apparatus with several cardiopulmonary monitors, etc. Following craniotomy in the treatment room, a patient under anesthesia is transported into the irradiation room for BNCT. The boron concentration in tissue is measured with prompt gamma ray analysis (PGA) and simultaneously by inductively coupled plasma atomic emission spectroscopy (ICP-AES) methods. For the immediate pre- and post-BNCT care, a collaborating neurosurgical department of the University of Tsukuba was prepared in the vicinity of the JAERI. The long term follow-up is done at the University of Tsukuba Hospital. Epithermal neutron beam also became available at the new JRR-4. By changing the thickness and/or the configuration of heavy water, a cadmium plate, and a graphite reflector, the JRR-4 provides a variety of neutron beams, including three typical beams (Epithermal mode and Thermal modes I and II). Intraoperative BNCT using the thermal beam is planned to study at the beginning of the clinical trial. The ongoing development of the JAERI Computational Dosimetry System (JCDS) and radiobiological studies have focused in the application of the epithermal beam for BNCT. After obtaining these basic data, we are planning to use the epithermal beam for intraoperative BNCT.

1. INTRODUCTION

A new medical irradiation facility was completed at the Japan Research Reactor (JRR)-4 in the Japan Atomic Energy Research Institute (JAERI) in September 1998. The research project on boron neutron capture therapy (BNCT) for malignant glioma will begin at the JRR-4 in July 1999. The University of Tsukuba project for the clinical study of BNCT was proposed in 1992 in collaboration with Hatanaka and colleagues [1]. The first clinical study, BNCT with a thermal neutron beam and $Na_2{}^{10}B_{12}H_{11}SH$ (BSH), took place from November 1995 to the end of 1996 at JRR-2 in JAERI [2]. The new JRR-4 facility is capable of providing both epithermal and thermal beams, and it has a medical treatment room being prepared for intraoperative BNCT.

2. MEDICAL IRRADIATION FACILITY

2.1. The medical treatment room and the patient-monitoring area

The general arrangement of the medical irradiation facility is shown in FIG.1. The irradiation room, the patient-monitoring area, the laboratory, and the medical treatment (operating) room are located in the basement. The medical treatment room was built to reflect a hospital-type operating room, with the following features: (1) an operating table that can move patient in all three orthogonal directions and in the vertical and horizontal directions; (2) a carbon head frame for use in the irradiation room; (3) an anesthesia apparatus with cardiopulmonary monitors; (4) a washbasin plus sterilized warm water; (5) sterilamps; and (6) on-line TV monitors. Following craniotomy, a patient on the operating table is moved from the medical treatment room into the irradiation room. In the patient-monitoring area, the drip infusion bottles and an urinary bag are observed via TV monitor by the anesthesiologist. The anesthesiologist can observe all the monitors and anesthetic machine used during the craniotomy.

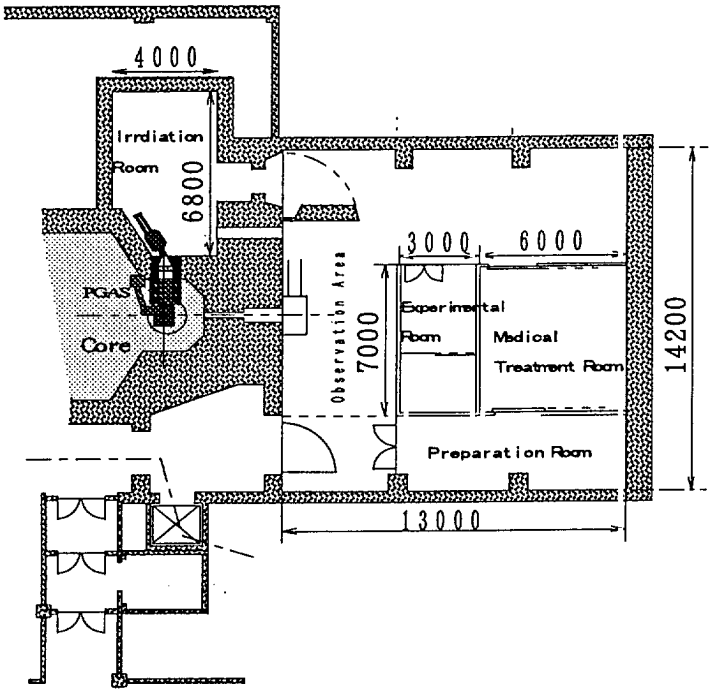

FIG. 1. General arrangement of medical irradiation facility.

2.2. Boron concentration measurement

A prompt gamma ray analysis (PGA) device has been installed on the second floor of the JRR-4. An inductively coupled plasma atomic emission spectroscopy (ICP-AES) device has been installed in the laboratory in the basement. To estimate the irradiation time during the intraoperative BNCT procedure, the measurement of the boron concentration of specimens must be complete within half an hour by using PGA and/or ICP-AES in the JRR-4.

2.3. Beam performance of in the facility at the JRR-4

The JRR-4 irradiation facility can provide a variety of neutron beams by changing the thickness and/or configurations of heavy water, a cadmium shutter, and a graphite reflector (FIG.2). However, three typical beam settings for BNCT have been proposed (TABLE 1). Among the three typical beams, the use of mode II results in similar irradiation time and dose distribution to the beam used at the JRR-2 that had been utilized in a part of the clinical trial by Hatanaka and Nakagawa [1] and also in the first clinical experiences by the University of Tsukuba group [2].

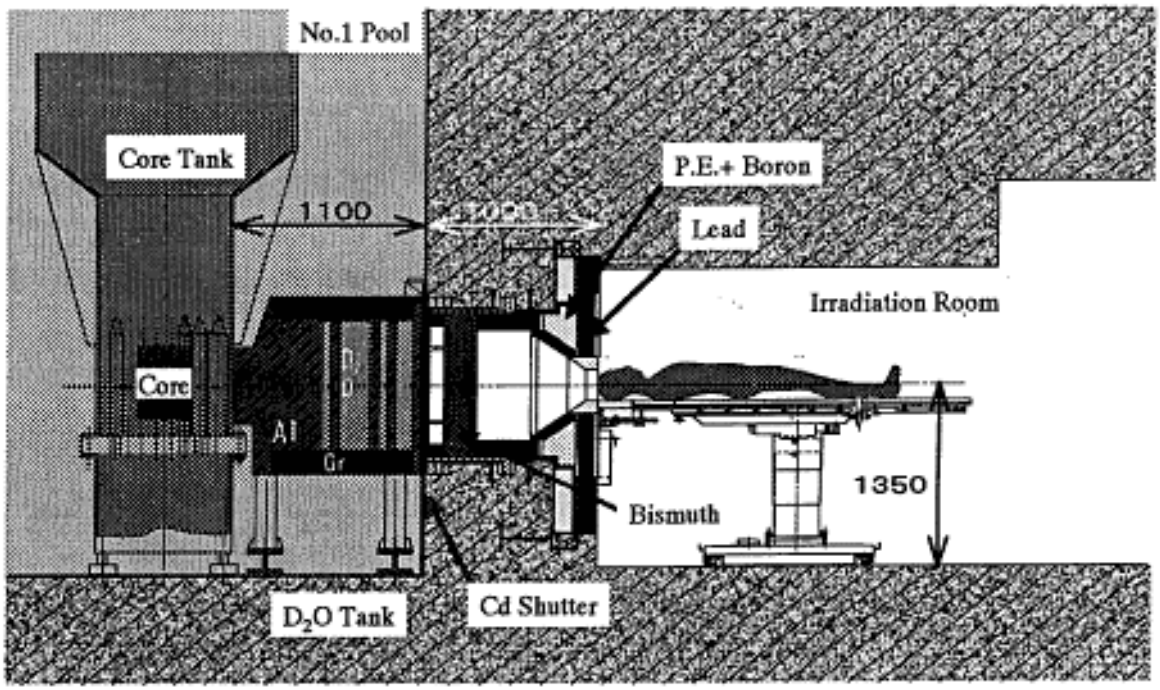

FIG. 2. Cross-section of the medical irradiation facility.

TABLE 1. Beam performance of typical modes of JRR-4

Items		Unit	Epithermal mode	Thermal Mode I	Thermal Mode II	JRR-2
Heavy water		cm	8	12	33	-
Cadmium shutter			on	off	off	-
Bi filter		cm	18	18	18	-
Carbon lining		(7cm)	Yes	Yes	Yes	-
Collimator*		cmcm	15	15	15	-
Neutron flux	Thermal < 0.53eV	n/cm^2sec	3.6×10^8	2.0×10^9	6.5×10^8	1.1×10^9
	Epithermal 0.53-10keV	n/cm^2sec	2.2×10^9	9.0×10^8	3.2×10^7	-
	Fast > 2.6MeV	n/cm^2sec	4.7×10^5	3.6×10^5	5.0×10^4	-
Cadmium ratio			1.15	2.5	13.5	64
Gamma dose rate		Sv/h	2.4	3.6	0.7	0.48

*Collimators in 10 cm and 20-cm diameter are also available

2.4. Dose planning system (JAERI Computational Dosimetry System: JCDS)

A software-based dose planning system is under development for the purpose of precise dose simulation and further investigation of BNCT with an epithermal beam. By the end of May 1999, the beta version of the JAERI Computational Dosimetry System (JCDS) for BNCT became available. This JCDS not only allows dosimetry of the usual non-surgical BNCT, but it also enables physicians to plan the dosimetry for intra-operative BNCT using skin reflection and air void.

2.5. Peri-BNCT care of patients

The initial debulking surgery and boron distribution study are performed at the University of Tsukuba Hospital. The immediate pre- and post-BNCT care is given at Naka Central Hospital, which is located in the vicinity of JRR-4, and long term follow-up is done again at the University of Tsukuba Hospital.

3. PROTOCOL

The new research protocol on boron neutron capture therapy (BNCT) for malignant glioma will begin at the JRR-4 in October 1999. The primary goals of this project are: (1) establishment of the treatment facility, including the treatment room and anesthesia apparatus, for the performance of intraoperative BNCT; (2) establishment of the safety and efficacy of BNCT with BSH and the thermal beams; (3) cross-calibration of the JCDS data with actual measurement results during intraoperative BNCT for optimizing the JCDS; (4) preparation for possible use of the epithermal beam.

3.1. Patient criteria

All patients entered into this study will be seen at the University of Tsukuba Hospital. To be eligible, patients have to fulfill the following criteria [2]:

(1) Histologic proof of anaplastic astrocytoma or glioblastoma and its variants [3]
(2) Karnofsky performance score $\geq$ 70
(3) Age 18 to 70 years
(4) Supratentorial unilateral tumor no deeper than 6 cm from brain surface
(5) Adequate cardiopulmonary, hepatic, renal, and bone marrow functions:
(6) - SGOT<60 IU/ml, Bilirubin<1.5 mg%
(7) - BUN<30 mg/dl, Cr<1.5 mg%
(8) - WBC>2500/mm3, Plt>75000/mm3, no severe anemia
(9) No previous chemotherapy or radiotherapy
(10) No double cancer and no previous therapy for any other cancers
(11) No allergy to BSH
(12) Signed informed consent

3.2. BNCT treatment conditions

Intraoperative BNCT is comprised of: (1) BSH biodistribution study at the first operation for tumor removal, and (2) a second craniotomy and BNCT approximately 2 to 4 weeks following the first operation. In the BSH biodistribution study, 1 g of BSH 12 h before the first operation, then blood is taken up serially for boron concentration analyses. Specimens from various parts of the brain tumor are kept for the measurement of boron level. For BNCT,

100 mg/kg BW of BSH is given with 500 ml of saline for 1 h via intravenous drip infusion. The infusion is initiated 12 h before planned irradiation. The calculation of irradiation time is based on the tumor and blood boron level and the thermal neutron dose that is measured intraoperatively using gold wire and/or foils.

4. DISCUSSION

Malignant gliomas are refractory to all current therapeutic modalities, including surgery, chemotherapy, and radiation therapy. The difficulties of using postoperative radiation therapy to cure patients with malignant gliomas are caused by the low intrinsic radiosensitivity and the diffuse microinvasion within the brain parenchyma around the tumor [4,5]. BNCT, the emerging therapeutic modality for high-grade gliomas, is based on neutron capture reaction between the cold isotope of boron (^{10}B) and the thermal neutron. On capture reaction, ^{10}B atoms disintegrate into high-LET alpha (^{4}He) and Lithium (^{7}Li) particles. Theoretically, tumor affinity of boron compounds and a short path length (-10Lim) would result in selective tumor cell killing with minimum damage to circumscribing normal tissue.

Several years after the early clinical trials of BNCT by Farr et al. [6,7] and Sweet et al. [8,9], Hatanaka and Nakagawa had treated more than 150 patients using intraoperative BNCT with BSH [1]. Recently, American and European clinical trials were initiated using BNCT with epithermal neutrons, which can overcome the steep attenuation of thermal neutrons in the brain [10,11]. Epithermal neutrons can pass through the scalp, the temporal muscle, and the cranial bone and convert to thermal neutrons in tissue. Therefore, epithermal neutrons would improve the amount of thermal neutrons delivered to deep-seated lesions. In the American and European clinical trials, BNCT is performed in a rather non-invasive fashion in which patients are irradiated without skin reflection and general anesthesia. Treatment planning and the assessment of BNCT dose are based on software-based treatment planning systems [12] and/or the accumulated knowledge from clinical biodistribution studies, and animal experiments [13,14]. In intraoperative BNCT, the BNCT dose would be planned based on the previous clinical data of JRR-2, especially with regard to preventing radiation damage. Irradiation time would be decided by calculating the BNCT dose from the actual boron content of the residual tumor and the blood boron level, and the measurement of the withdrawn gold wire. Regarding the validity of the estimated irradiation time (dose) with JCDS, JCDS data should be compared to the intraoperative measurement results, which are calculated from gold wires placed in the surgical field.

It is empirically known that an air balloon placed in a surgical defect of the brain plays a role of being the void for neutron beams and leads to increased dose delivery at the bottom of the surgical defect. Experimentally, an improvement of thermal neutron flux is observed not only in the direction of the beam axis but also in the vertical and horizontal directions (unpublished data). The improvement of dose distribution in deep-seated lesion caused by skin reflection and the void effect is thought to be essential to BNCT with thermal neutrons. Similarly, improved dose distribution would be a considerable gain for future intraoperative BNCT with an epithermal beam. Since intraoperative radiation therapy (IORT) has demonstrated some advantages [15], for example single high-dose targeting radiation, avoids unwanted radiation damage to normal tissues, we think that intraoperative BNCT with an epithermal beam could play an important role in improved clinical results. For that reason we have designed studies that focus on intraoperative BNCT with an epithermal beam to enter the next phase of clinical trials.

5. CONCLUSION

A medical irradiation facility for intraoperative BNCT has been installed in JRR-4. The University of Tsukuba group is preparing for a clinical study to assess the safety of intraoperative BNCT with BSH and a thermal beam at the brand-new facility. Following this clinical study, we are planning to initiate intraoperative BNCT with an epithermal beam.

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Clinical practice in BNCT to the brain

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Abstract. Our concept of Boron Neutron Capture Therapy (BNCT) is to selectively destroy tumour cells using the high LET particles yielded from the 10B(n,α)7Li reactions. The effort of clinical investigators has concentrated on how to escalate the radiation dose at the target point. BNCT in Japan combines thermal neutrons and BSH ($Na_2B_{12}H_{11}SH$). The radiation dose is determined by the neutron fluence at the target point and the boron concentration in the tumour tissue. According to the recent analysis, the ratio of boron concentration (BSH) in tumour tissue and blood is nearly stable at around 1.2 to 1.69. Escalation of the radiation dose was carried out by means of improving the penetration of the thermal neutron beam. Since 1968, 175 patients with glioblastoma (n=83), anaplastic astrocytoma (n=44), low grade astrocytoma (n=16) or other types of tumour (n=32) were treated by BNCT at 5 reactors (HTR n=13, JRR-3 n=1, MuITR n=98, KUR n=30, JRR-2 n=33). The retrospective analysis revealed that the important factors related to the clinical results and QOL of the patients were minimum tumour volume radiation dose, more than 18Gy of physical dose and maximum vascular radiation dose (less than 15Gy) in the normal cortex. We have planned several trials to escalate the target radiation dose. One trial makes use of a cavity in the cortex following debulking surgery of the tumour tissue to improve neutron penetration. The other trial is introduction of epithermal neutron. KUR and JRR-4 were reconstructed and developed to be able to irradiate using epithermal neutrons. The new combination of surgical procedure and irradiation using epithermal neutrons should remarkably improve the target volume dose compared to the radiation dose treated by thermal neutrons.

1. INTRODUCTION

Glioblastoma is a poorly differentiated glioma and considered the most malignant tumour of the brain. It occurs in the white matter of the cerebrum and rapidly grows and invades the normal brain tissue from multiple directions before the time of diagnosis. Most of the patients with such an invasive glioma, not only glioblastoma but also anaplastic astrocytoma and low-grade astrocytoma are beyond the point of curative treatments such as surgery, chemotherapy, and conventional radiotherapy. The proton beam therapy & heavy-ion therapy with Bragg peak have high risk of damage to the surrounding normal brain tissue in the same way with surgical excision. Recent trials using high dose radiation (60-70Gy) therapy show constantly efficient results. However, radiotherapy of the whole brain produced extensive radiation damage. From the viewpoint of the radiation effect and good quality of life after treatment, boron neutron capture therapy (BNCT) is an ideal treatment for malignant brain tumours. [1,2]

2. BASIC PRINCIPLE OF BNCT

We consider BNCT an intercellular internal radiation therapy. Alpha particles (^{4}He) and recoiling lithium-7 (^{7}Li) nuclei yielded from the nuclear reaction between boron-10 and thermal neutron have a high linear energy transfer (LET) and an associated high relative biological effectiveness (RBE). Furthermore, the two particles have a short path length (5–10 mm) which is approximately equal to the diameter of the tumour cells. Selective accumulation of ^{10}B in the tumour cells and corrective irradiation with suitable thermal neutron beam can realise cell levelled destruction of tumour tissue without significant damage to the surrounding brain tissue. It is well known that for a successful treatment in patients with malignant brain tumour, it is essential to secure a sufficient radiation dose (enough alpha

particles & recoiling lithium-7). This depends on the boron compounds that adequately accumulate in the tumour tissue and improvement of neutron penetration in the brain. [3]

3. HISTORY OF BNCT

Clinical trials of BNCT were initiated in 1951 at Brookhaven National Laboratory by Farr et al and developed by Sweet and Sweet et al. at Massachusetts General Hospital/ Massachusetts Institute of Technology. However, after several trials, it was discontinued in 1961 because of the discouraging clinical results. The renewal of BNCT was organised in 1968 by H. Hatanaka in Japan using a new boron compound, BSH ($Na_2B_{12}H_{11}SH$) at HTR (Hitachi training reactor) in Japan. Successively, four reactors (JRR-3; Reactor of Japan Atomic Energy Research Institute, MuITR; Reactor of Musashi Institute of Technology, KUR; Research Reactor Institute of Kyoto University, JRR-2; Reactor of Japan Atomic Energy Research Institute) were authorised for medical use. Besides facilities, evolutionary procedures and new ideal instruments were introduced into the clinical trials. One was the diagnostic procedure such as CT scan and MRI, which made it possible to determine the size and the depth of the tumour with greater accuracy. The other ideal instrument was prompt gamma ray spectrometry developed by Drs. Kobayashi and Kanda· Prompt gamma ray spectrometry has given us more accurate data on the boron concentration in tumour tissue and blood before a decision on the radiation time is made. As various improvements progressed, a more correct radiation plan was made and dose escalation has been tried.

4. RECENT STANDARD TECHNIQUE OF BNCT

In order to improve the neutron penetration of the brain tissue, we de-bulk the brain tumour and make a cavity during a preliminary operation one to two weeks before BNCT. Partial excision of the tumour also minimises the bulk of future narcotised tissue after BNCT. The skin flap must be large enough to allow a large aperture for the neutron beam (12 cm x12 cm). According to the MRI findings, we insert a few gold wires in the tumour or around the tumour for measurement of neutron flux. The tip of the wire must be around the target point. After the operation, we identify the location of the gold wires by CT and/or skull X ray. The day before BNCT, about fifteen hours before neutron irradiation, BSH diluted in 500-ml saline is intravenously infused for 60 minutes by drip infusion. (60~80 mg BSH/kg body weight). The following morning the patient is taken to the reactor. Under general anaesthesia, the patient's skin flap is reopened and the bone flap is removed. After the opening of the dura mater, a piece of the tumour tissue is obtained for boron-10 analysis. We place an additional two or three gold wires on the surface of the brain to measure the neutron fluence on the irradiation field. A thin silastic rubber balloon filled with air is placed into the cavity. The procedure maintains the size of the cavity during neutron irradiation and improves the neutron penetration. Following the closure of the dura matter, a heat-malleable plate of a plastic material containing ^{6}Li-F is applied to the patient's head to protect the skin from the thermal neutron irradiation. This "helmet" has a hole in the center to allow the neutron beam into the tumour-harbouring area of the brain. The beam should be as free as possible from fast neutrons and gamma rays to avoid indiscriminate radiation to the brain. The entire head is covered with sterile plastic drapes to prevent infection. Simultaneous neutron beam monitoring devices are attached on the surface of the brain. Gamma rays are measured by TLD at several points of the body. The patient is moved into the irradiation chamber. Under remote-control general anaesthesia, the head is fixed towards the neutron port and neutrons are delivered. Blood is intermittently drawn from the patient before and after neutron irradiation for boron-10 analysis. Boron concentration in the brain tumour and blood is

measured by prompt gamma ray spectrometry during the irradiation. In order to measure the exact neutron flux at each point of interest, gold wires inserted in the tumour tissue are pulled out at 15–30 minute intervals after the full power operation of the reactor. It is possible to assess the exact neutron fluence at each point of interest. The plan for the remainder of the irradiation is then based on this up-to-the-minute data regarding boron concentration and neutron flux.

5. TIMING OF THE NEUTRON IRRADIATION

Neutron irradiation was designed according to the clinical analysis in our series. T. Kageji et al. reported detailed pharmacokinetics and boron uptake of BSH in a recently issued report.. Neutron irradiation was started between 10 to 20 hours after a single infusion of BSH in consecutive trials. [4] The mean boron concentration before the neutron irradiation in the tumour tissue was 25.8 ppm. The tumour to blood ratio (T/B) was nearly stable at around 1.2 to 1.69 in successful cases. The study showed a significant statistical correlation between boron uptake and time interval from the infusion of BSH. Within the first 10 hours after BSH infusion, malignant glioma tissue contained high level of boron (30–60 ppm), however; the boron concentration in blood showed a higher level than that in the tumour tissue. Hence the T/B ratio was below one. In the 12–24 hours following BSH infusion, the boron concentration in the tumour was above 20 ppm in 56% of malignant glioma patients. The T/B ratio was more than one in 69% and two in 38% of them. These data indicated that the neutron irradiation should be done around 15–18 hours after the BSH infusion. A positive tumour-to-blood ratio and a uniform tumour concentration around 10–40 mg/g ^{10}B are needed for successful BNCT.

6. CASE REPORTS

Case 1. A 50-year-old man developed speech disturbance and right hemiparesis. Cerebral angiography demonstrated tumour stain in the left front-parietal area. He underwent craniotomy and the tumour was subtotally removed. Histological diagnosis was glioblastoma. He received BNCT at MuITR in June 1972. After craniotomy under general anaesthesia, a ping pong ball was inserted into the cavity to improve the neutron penetration. Neutron flux was measured on the surface of the ping-pong ball and on the bottom of the cavity using gold foils. It was 8.8E + 12n/cm^2 and 5.3E + 12n/cm^2 respectively. Boron concentration in the tumour tissue was 15.3pp. and 27.3 ppm in the blood (Fig. 1-a). Retrospective analysis of the radiation dose of boron n-alpha reaction was 7.5-16.8 Gy (physical dose). A follow up CT scan studied 11 years after BNCT demonstrated porencephalic cyst, however, there was no recurrence of the tumour. After 20 years the man was still active as a farmer and holds a driving license at the age of 70 (Fig. 1-b).

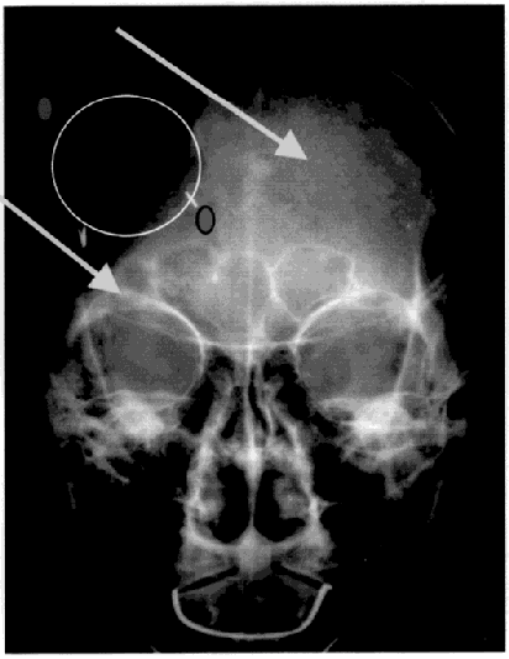


Fig.1.a.Radiation planning

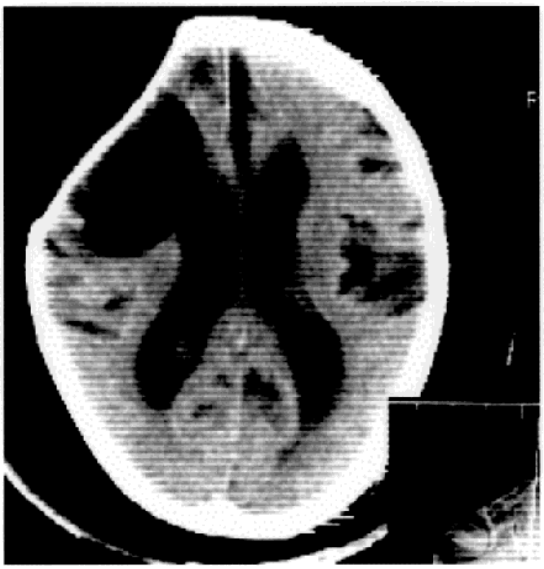


Fig. 1.b. Follow up CT 15 years after BNCT

Case 2. A 60-year-old woman with glioblastoma underwent BNCT at MuITR in July 1977. A ping pong ball was inserted into the cavity and neutron flux was measured on the surface of the ping pong ball and on the bottom of the cavity. It was 1.45E + 13n/cm^2 and 7.5E + 12n/cm^2 respectively. Boron concentration in the tumour tissue was 14.0ppm and 13.3ppm in the blood. According to the retrospective analysis of the radiation dose of boron n-alpha reaction, tumour volume dose was 15.9 Gy (physical dose). Follow up MRI studied 16 years after BNCT demonstrated multi cystic lesion, however, there was no recurrence of the tumour (Fig. 2).

Case 3. An 11-year-old girl had a huge tumour in the right frontal lobe. Histological diagnosis was grade 3 oligo-astrocytoma. BNCT was performed at MuITR in Oct. 1981. Neutron flux measured on the surface of the ping pong ball and on the bottom of the cavity using gold foils was 1.46E + 13n/cm^2 and 6.72E + 12n/cm^2 respectively. Boron concentration in the tumour tissue was 22.1ppm and 11.2ppm in the blood. Tumour volume radiation dose was 23.0 Gy (physical dose). Follow up MRI studied in 1994 demonstrated porencephalic cyst, however, there was no recurrence of the tumour (Fig. 3).

Case 4. A 41-year-old female suffered from headache epileptic seizure and right hemiparesis. A magnetic resonance image (MRI) showed an enhanced mass in the left parietal lobe. She underwent craniotomy and partial resection of the tumour. Histological diagnosis was glioblastoma. BNCT was performed at KUR in Aug. 1992. Two gold wires were inserted around the tumour. Neutron flux was measured on the surface of the brain and at the target point. It was 1.6E + 13n/cm^2 and 4.1E + 12n/cm^2 respectively. Boron concentration in the tumour tissue was 20.0ppm and 11.2ppm in the blood. Retrospective analysis of the radiation dose of boron n-alpha reaction was 13.0 Gy (tumour volume dose). Follow up MRI demonstrated marked decrease of the enhanced lesion (Fig 4).

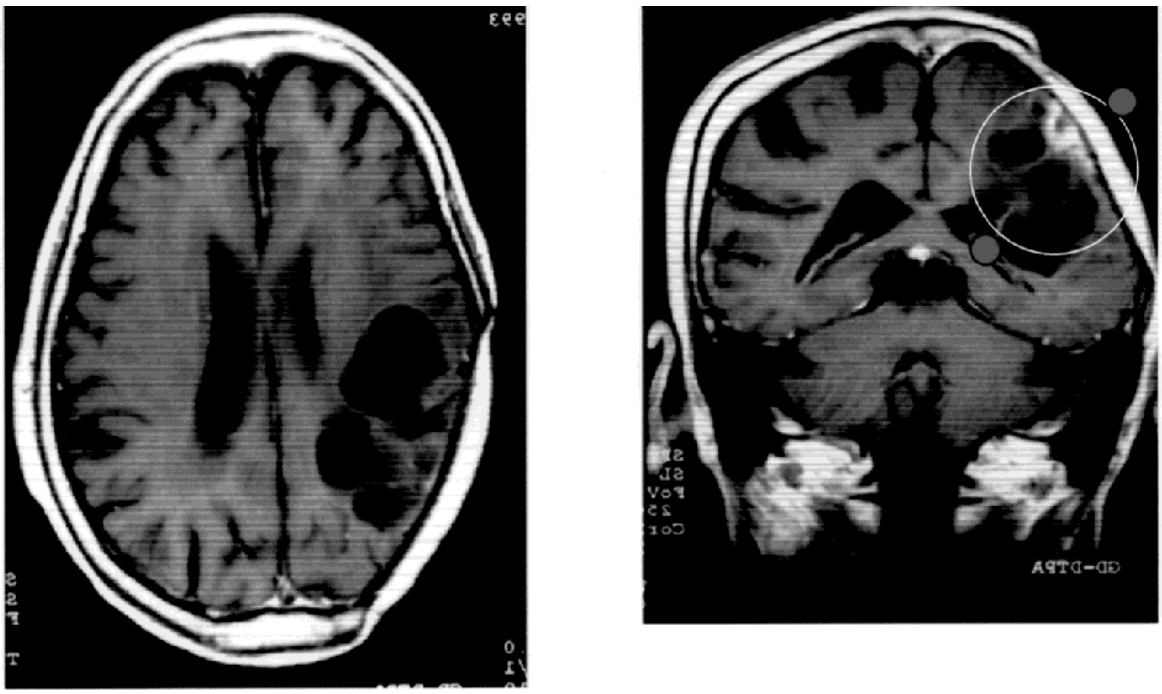


Fig. 2. Follow up MRA after 16 years after BNCT. Boron concentration :14.0 ppm in tumor tissue, 13.3 ppm on blood Radiation time : 140 min . Radiation dose:15.9 Gy (B-10 n-a)

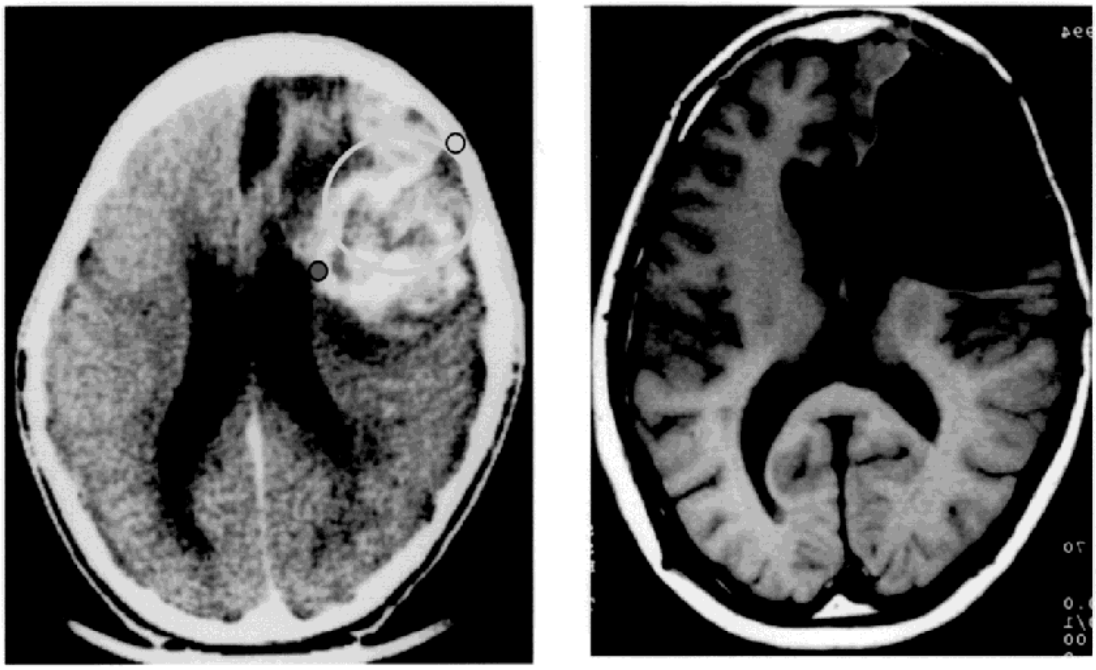
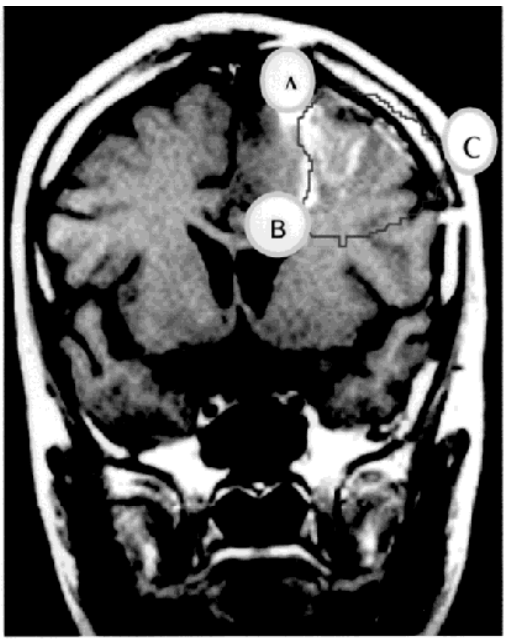


Fig. 3. 11F, Oligo-astrocytoma (G3). Planning (left) Oct. 1981 at MulTR. Follow up MRI (right) in 1994. Radiation dose at target pint was 23Gy.



Radiation planning

Tumor volume radiation dose : **13.0 Gy**

Neutron flux at point

A : 2.31 X 10^9

B : 5.88 X 10^8

C : 2,12 X 10^9

Boron concentration

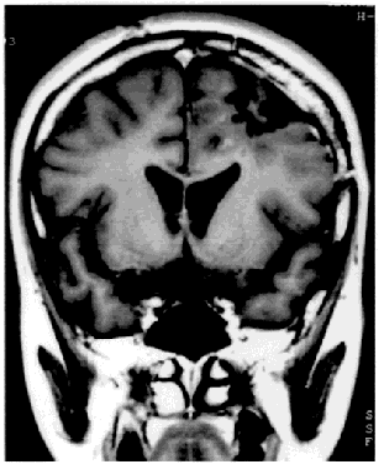


Fig. 4. A 41-year-old female with glioblastoma.. Planning (left) Aug. 1992 at KUR. Follow up MRI (right) 2 years after BNCT. Radiation dose at target pint "B "was 13Gy.

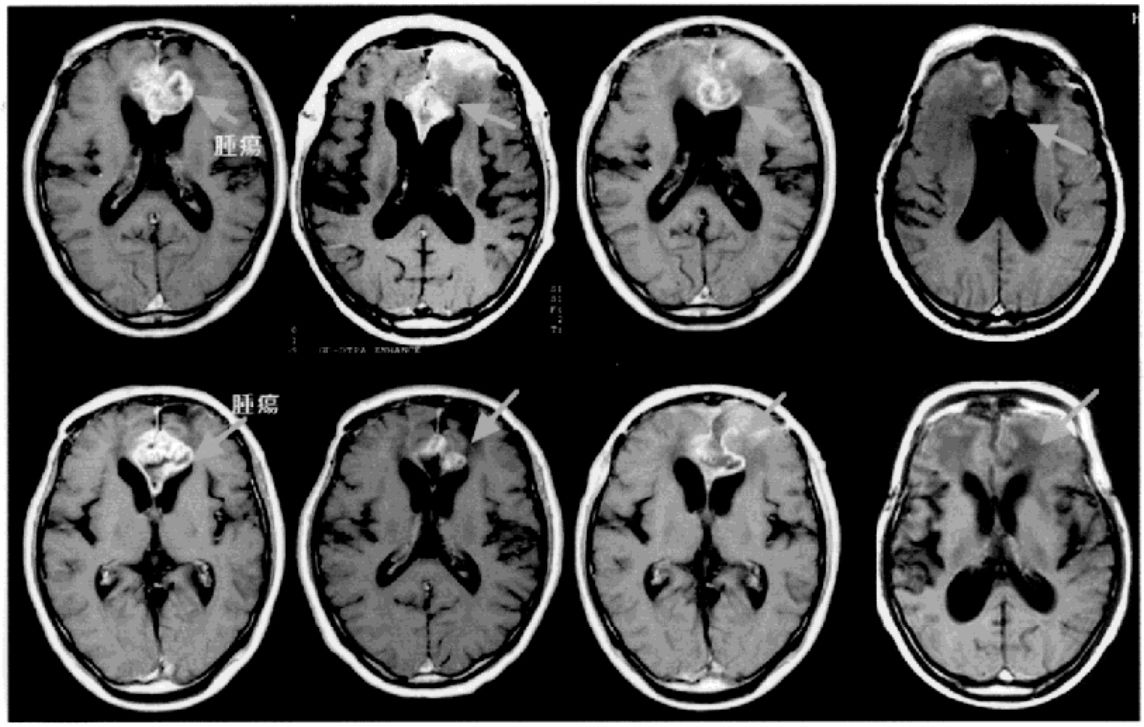


Fig. 5. A 65-year-old man with glioblastoma was underwent in March, 1995 at JRR-2. Follow up MRI BNCT (from leftto right ; pre BNCT, 2weeks, 1 month, 6 months after BNCT) Radiation dose at target pint was 11Gy. Abnormally enhanced lesion gradually decreased (arrow).

Case 5. A 65-year-old man had glioblastoma in the bilateral frontal lobe. He underwent craniotomy and partial resection of the tumour. Histological diagnosis was glioblastoma. BNCT was performed at IRR-2 in March, 1995. Neutron flux was measured using gold wires which were inserted around the tumour. It was 4.2E + 12n/cm^2 at the target point. Boron concentration in the tumour tissue was 31.0ppm and 25.0ppm in the blood. Retrospective analysis of the radiation dose of boron n-alpha reaction was 11.0 Gy (tumour volume dose). Follow up MRI demonstrated a gradual decreasing of the enhanced lesion (Fig 5).

7. CLINICAL OUTCOME

Since 1968, we have treated 175 patients and performed boron-neutron capture therapy (BNCT) using 5 reactors in Japan. There were 83 patients with glioblastoma, 44 patients with anaplastic astrocytoma and 16 patients with low grade astrocytoma (grade 1 or 2). There were 32 patients with other types of tumour. Most of the patients were followed by CT or MRI to study the efficacy of BNCT. Retrospectively we divided the patients into two groups to investigate the prognostic factors. One group (group 1): the patients who lived more than 3 years. The other group (group 2): the patients who lived less than 3 years. We analyzed histology of the tumours, age of the patients, radiation time, boron concentration in the blood, neutron fluences on the surface of the brain at the target point target depth and tumour volume dose in each group.

Table I. Clinical outcome of the patients who lived more than 10 years

Patient	Age	Sex	Histology	T/B ratio	10B in tumour	Tumour volume dose
M.T.	50	M	Glioblastoma	0.56	15.3	13.5
R.N.	60	F	Glioblastoma	1.05	13.3	18.9
T.T.	30	M	Chondrosarcoma	1.07	27.1	11.6
C.U.	47	F	Meningioma	8.95	90.4	13.8
C.Y.	58	F	Meningioma	N.D	N.D	12.5
K.N.	25	M	An. Astrocytoma	1.15	35.2	23.1
T.M.	11	f	An. Astrocytoma	1.43	11.2	14.2
Y.T.	38	F	Glioblastoma	1.42	13.9	15.9
R.K.	56	M	Glioblastoma	1.89	21.6	20.3
M.I.	22	M	Malig. Ependymoma	N.D.	N.D.	14.8
K.K.	39	M	An. Astrocytoma	N.D.	N.D.	15.2
E.M.	48	F	Meningioma	N.D.	N.D.	9.3

CT or MRI demonstrated marked response in 3 to 6 months after BNCT in 60% of the patients with glioma. Twelve patients (four glioblastomas and four anaplastic astrocytomas three meningioma, one chondrosarcoma) lived more than 10 years. Seventeen patients lived more than 5 years. There were two patients with glioblastoma, 10 patients with anaplastic astrocytoma and one with low grade astrocytoma. Out of 143 patients with glial tumours treated by BNCT, 27 lived or have lived longer than 3 years after BNCT. As prognostic factors, grading of the tumour, ages of the patients and target depth were proved as important

factors. However, the most important factor was tumour volume radiation dose demonstrated by boron n-alpha reaction. The tumour volume was calculated on CT or MRI findings. Twenty-eight patients were treated before the induction of CT, therefore the patients were excluded in this study. [5.6]. The tumour volume radiation dose in the patients with grade 2 glioma were 11.5Gy (group 1) vs. 6.7Gy (group 2), 15.6Gy (group 1) vs. 11.8 (group 2) in grade 3 glioma and 18.2Gy (group 1) vs. 9.8Gy (group 2) in glioblastoma patients (table 2).

8. RADIATION NECROSIS

Radiation necrosis was diagnosed by CT and/or MRI; however, it is still considered controversial to diagnose the radiation necrosis after BNCT. Radiation necrosis was determined as follows: low intensity on MRI T-1 weighted image with contrast enhancement (+) and high intensity on T-2 weighted image. Low density area with contract enhancement (+) on CE-CT. Radiation necrosis was found in 19 patients (19/175 10.9%). Fourteen of those 19 patients had clinical symptoms and radiographic change. Nine of the 14 had neurological deficits such as motor weakness and speech disturbance. The patients were treated with a high dose of steroid therapy (Dexamethasone 32-64mg/day was tapered for one to two weeks and changed to prednisolone 10-30mg / day per os). Of these 9, 3 patients' symptoms gradually disappeared after using the steroid treatment. The remaining six patients had permanent mild to slight neurological deficits. The other 5 out of 14 patients had only epileptic seizure within 1 week after BNCT. The remaining five patients had only radiographic change without neurological deterioration. Radiation necrosis demonstrated by CT or MRI was noticed in two months to two years after BNCT. The age of the patients with radiation necrosis is 38.5±19.0 y.o., and the age of the patients without radiation necrosis is 41.8± 18.6 y.o. The radiation time of the patients with radiation necrosis was 254 ± 99 min., as opposed to the radiation time of the patients without radiation necrosis, which was 218 ± 103 min. The boron concentration in the blood of the patients with radiation necrosis was 28± 9 ppm, while the boron concentration in the blood of the patients without radiation necrosis was 22± 10 ppm. The maximum neutron fluence of the patients with radiation necrosis was $2.1x10^{13}\pm 0.6x10^{13}$ n/cm^2; however, the neutron fluence of the patients without radiation necrosis was $1.7x10^{13}\pm 0.8x10^{13}$ n/cm^2. Vascular radiation dose was calculated according to the report by Kitao and Rydin. Only one-third of the ^{10}B (n, a)^7Li radiation occurring in vascular lumen will be absorbed by the vascular endothelium. Lastly, the vascular radiation dose of the patients with radiation necrosis was 21± 8.1 Gy, while the vascular dose of the patients without radiation necrosis was 9.4 ± 5.1 Gy. These data indicated that the maximum vascular dose should be less than 15 Gy.

Table II. Patients surviving more than 5 years after BNCT

Patient	Age	Sex	Histology	T/B ratio	10B in tumour	Tumour volume dose
P.C.	50	M	Glioblastoma	0.75	15.3	13
I.M.	15	F	Rhabdomiosarcoma	3.8	28	11.1
R.T..	4	F	Pontine glioma	N.D	N.D.	10.6
Y.A.	44	M	An. Astrocytoma	1.7	13.4	16.7
Y.S.	37	M	An. Astrocytoma	1.9	25.8	10.1

Table II. (cont.)

T.Y..	39	F	An. Astrocytoma	1.9	30.1	18.3
K.Y..	52	F	Meningioma	N.D.	N.D.	10.3
P.J.	40	F	An. Astrocytoma	1.1	12.8	13.3
K.O..	33	M	An. Astrocytoma	1.3	18.4	17.2
Y.M.	27	M	An. Astrocytoma	N.D.	N.D.	11.5
M.F.	42	F	Meningioma	N.D.	N.D	10.3
N.M.	1.4	F	An. Astrocytoma	1.6	28.6	8.5
R.T	41	F	Glioblastoma	0.8	11.6	16.6
K.Y.	7	M	An. Astrocytoma	N.D.	N.D	7.9
I.O.	8	F	An. Astrocytoma	N.D.	N.D	9.7
T.S.	31	M	An. Astrocytoma	N.D..	N.D	13.8
H.M.	17	M	An. Astrocytoma	2.6	56.1	15.2

Table III. Radiation necrosis and related factors

	Necrosis (+)	Necrosis (-)
Age	38.5 ± 19.0	41.8 ± 18.6
Radiation time	254 ± 99	218 ± 108 (min)
B-10 in blood	28.9 ± 9	22 ± 10 (ppm)
Neutron fluences	21.E ± 0.6	1.7E ± 0.8 (13n/cm^2)
Maximum Vascular dose	21.8 ± 8.1	9.4 ± 5.1 (Gy)

9. NEW PROTOCOL

The tumour volume radiation dose of the last protocol was 10Gy but increased up to 15Gy in the new protocol. Surgical procedures and making a cavity played an important role not only to irradiate with sufficient neutron fluence, but also to avoid radiation side effect. Radiation side effect or radiation necrosis was observed in 10.9 % of our series. The factors related to radiation necrosis were maximum thermal neutron fluence on the brain surface and vascular dose. Therefore, we decided the maximum thermal neutron fluence on the surface of the brain should be below 2.0 + E13 n/cm^2. Vascular dose in the brain tissue near the surface of the brain or maximum vascular dose must be controlled below 15 Gy. To improve the neutron penetration, we decided to utilize epithermal neutron beams. KUR was reconstructed in 1997. Following the shutdown of the JRR-2, JRR-4 was renewed for medical use in 1998. Both reactors have the capacity to yield thermal neutron beam, epithermal neutron beam and

mixed beams. We compared the neutron fluences at the target point and on the surface of the cavity between a case treated by thermal neutron and one by mixed beam (Fig. 3). Thanks to the cavity, neutron penetration was improved ca. 30% even if irradiated by thermal neutron. The new combination of surgical procedure and irradiation using epithermal neutrons should remarkably improve the target volume dose compared to the radiation dose treated by thermal neutrons, seven times without cavity and 3.5 times with cavity.

9.1. Proposed protocol for malignant brain tumours in Japan in 1998

Patient selection
- Patients with glioma grade 3-4
- Less than 70 years of age
- No serious systemic disease
- Good general condition (KPS>70)
- Radiation dose
- Minimum Tumour Volume Dose: 18Gy*
- Target Volume Dose: 15Gy*
- Maximum Vascular Dose < 15Gy

*Physical dose of boron n-alpha reaction
Neutron irradiation using mixed beam of thermal neutron or epithermal neutron beam
Radiation time is decided according to the data of boron concentration in the blood or tumour tissue and neutron flux at the target point and surface of the brain.

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First clinical results from the EORTC Phase I Trial “postoperative treatment of glioblastoma with BNCT at the Petten irradiation facility”

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Abstract. Based on the pre-clinical work of the European Collaboration on Boron Neutron Capture Therapy a study protocol was prepared in 1995 to initiate Boron Neutron Capture Therapy (BNCT) in patients at the High Flux Reactor (HFR) in Petten. Bio-distribution and pharmacokinetics data of the boron drug $Na_2B_{12}H_{11}SH$ (BSH) as well as the radiobiological effects of BNCT with BSH in healthy brain tissue of dogs were considered in designing the strategy for this clinical Phase I trial. The primary goal of the radiation dose escalation study is the investigation of possible adverse events due to BNCT; i.e. to establish the dose limiting toxicity and the maximal tolerated dose. The treatment is delivered in 4 fractions at a defined average boron concentration in blood. Cohorts of 10 patients are treated per dose group. The starting dose was set at 80% of the dose at which neurological symptoms occurred in preclinical dog experiments following a single fraction. After an observation period of at least 6 months, the dose is increased by 10% for the next cohort if less then three severe side effects related to the treatment occurred. The results of the first cohort are presented here. The evaluated dose level can be considered safe.

1. INTRODUCTION

Boron Neutron Capture Therapy (BNCT) is based on the reaction occurring between the non-radioactive isotope ^{10}B and thermal neutrons. A low energy neutron is captured by the ^{10}B-nucleus, which disintegrates into a Li- and He-nucleus, two densely ionising particles with high biological effectiveness and short range in tissue. A selective targeting of this reaction to tumour cells would lead to a highly effective treatment while sparing healthy tissue, resulting in a ”targeted and timed cell surgery” [1]. This innovative idea had been published already by Locher in 1936 [2]. It was not until the 50’s and 60’s that the first clinical trials of BNCT were performed, namely at the Brookhaven National Laboratories and MIT. The results were disappointing due to inadequate boron-compounds and sub-optimal neutron sources but further pioneering clinical applications were performed in Japan in the late 60’s [3]. These applications, which reported some outstanding results, were not in the frame of controlled prospective clinical trials. However, the specific efforts of H. Hatanaka and his co-workers [4,5] led to a reconsideration of clinical applications with BNCT in the United States as well as in Europe. This article reports the initial results of the first European clinical trial, which was started as a multinational effort in 1997, after almost 10 years of preparation [6–11].

The demonstration project, which is financed by the European BIOMED II Program had the objective to investigate the feasibility of BNCT at the High Flux Reactor (HFR) in Petten (NL) following the EORTC protocol 11961 [12,13]. The aim of the study is to investigate the systemic toxicity due to the boron carrier $Na_2B_{12}H_{11}SH$ (BSH) at one given real time pharmacokinetic guided boron blood concentration. Furthermore, the study will detemine the maximal tolerated radiation dose and the dose limiting toxicity of BNCT to healthy tissues in cranial location using the epithermal beam at the BNCT irradiation facility of the HFR [14]. The demonstration project is intended to establish and evaluate the structure of a trans-national co-operation for patient treatment in Europe using a unique facility [15,16].

1. PATIENTS AND METHODS

So far, 14 patients have been entered into the study, 12 males and 2 females coming from five neurosurgical centres in 4 European countries. Mean age of the patients at on study registration was 62 years (51–74). The performance status at inclusion was very good with a median Karnofski index of 90 (70–100). The initial tumour localisation was temporal in 4 cases, frontal in 4 cases, parietal in 1 case, occipital in 1 case, temporo-occipital in 2 cases, temporo-frontal in 1 case and parieto-occipital in 1 case. The average target volume was 135,7 cm^3 (range 29–213 cm^3). Central pathology review at the German Brain Tumour Reference Centre in Bonn revealed Glioblastoma Multiforme (WHO grade IV) in 11 patients and Gliosarcoma (WHO grade IV) in 3 patients.

BSH was administered 13–14 hours prior to surgery at a dose of 1 mg/kg/min. Blood, tumour, skin, brain, muscle, cerebro-spinal fluid and dura samples were taken during the operation. Blood samples continued to be taken regularly during 48 hours after surgery. The boron content was measured by ICP-OE-spectroscopy at Nuclear Research and Consultancy Group NRG Petten [17].

Of the 14 patients 3 had partial, 4 subtotal and 7 complete tumour resection. The three patients with a remaining tumour volume larger than 30 % of the initial tumour size had to be excluded. One patient could not undergo BNCT because of an intercurrent infection and prolonged recovery after the surgery.

The first patient cohort (10 patients) was treated by BNCT with the epithermal beam at the HFR in Petten [18–21] which is owned by the European Commission. The starting radiation dose level, which was derived from previous animal experiments, was set at 8.6 Gy boron neutron capture absorbed dose D_B [22] prescribed at the Dose Group Identification Point (DGIP) [12]. For the other dose components limiting maxima were defined, which were never reached. The DGIP was set at a point that is physically well defined and can be clearly identified in each patient: namely, the maximum of the thermal neutron fluence in the patient. The size of the circular beam was fixed at 12 cm diameter; the distance from the beam exit in the wall to the beam entrance in the patient was 30 cm.

The only variable parameter, the orientation of the patient's head relative to the beam, was selected on the basis of the planning target volume localisation. A single field was used for the treatment of the first 5 patients. The last 5 patients were irradiated with two oblique beams which resulted in two separate thermal neutron fluence peaks, one in the planning target volume in the operated area and one outside. Consequently a larger volume was irradiated in the second five patients but the boron neutron capture absorbed dose, which is defined for a cohort of patients, was the same for the whole group of the 10 patients, namely 8.6 Gy.

The patients travelled to Amsterdam by public transport, where they were admitted to the Department of Neurosurgery of the Academic Hospital of the Vrije Universieit Amsterdam for 1 week. During this period BNCT was performed in 4 fractions on 4 consecutive days, except one case, in whom the third and fourth fractions of irradiation were delivered subsequently on the same day.

The day prior to the first irradiation, 100 mg/kg BSH was administered i.v. at a dose rate of 1mg/kg/min. On the following days both the amount (range 9.5–70.4 mg/kg) and the time point of BSH administration (range 10–25 hours prior to the radiation) were modified in order to achieve an average boron concentration of 30 ppm ^{10}B in blood over the four fractions. The amount, start of the infusion and duration were adapted each day after obtaining the actual pharmacokinetic data (from the regularly taken blood samples) by prompt gamma spectroscopy. In the 10 patients treated mean blood boron concentration over the four fractions of BNCT was 30.3 ppm (range 27.3–32.3 ppm).

On the basis of the measured real boron concentration in blood during the radiation and of the actual delivered monitor units, the absorbed doses from the different physical dose components and the weighted dose were calculated and reported in defined points and volumes. The data were compared to the detected and scored radiation toxicity. The findings on systemic toxicity due to BSH alone have been reported and evaluated separately The

radiation toxicity is recorded and reported as early radiation toxicity if it occurs within 90 days after the end of BNCT, and as late radiation toxicity if it occurs later than 90 days. Four different toxicity scales were used for grading the events. These scales address acute systemic (drug) toxicity, early radiation toxicity, and -- using two scales -- late radiation toxicity. The latter two comprise the EORTC/RTOG (European Organization for Research and Treatment of Cancer / [U.S] Radiation Therapy Oncology Group) scale, which is an established, validated but not very precise method; and the SOMA scale, an improved but not yet validated approach [23]. It allows a more detailed determination of observed effects, for example neurological deficits.

2. RESULTS

2.1. Tissue uptake study

Samplings during surgery resulted in a tumour/blood boron concentration ratio normalised at 100 mg/kg BSH 13 hours after the end of BSH infusion of 0.63 (range 0.26 – 1.3). The results of this tissue uptake study were not used to perform the patient treatment in Petten.

2.2. Toxicity evaluation

With respect to the study drug BSH the following observations were made: One event of serious toxicity was reported and described as possibly related to BSH concerning one patient who developed a grade IV agranulocytosis during the week of BNCT. The agranulocytosis was treated by GSF and resolved within 36 hours. Grade 1 toxicity, regarding haematological changes in 3 cases, erythema and urticaria in 1case, erythema in another 1 case, flash like sensation in 2 cases, nausea and vomiting in 1, hypokaliaemia and hyponatraemia in 1 case were detected and interpreted as possibly related to BSH. Grade 1, 2 and 3 fever possibly related to the study medication occurred in three patients.

Acute radiation toxicity was slightly less than observed in conventional radiotherapy: Mild erythema in 3 cases, focal alopecia in 9 cases, taste change (4 cases), headache, decreased lacrimation, behavioural changes, mild pruritus of an ear, tinnitus (each in one case) and mild dry mouth (2 cases) were reported in the first 3 months after the end of BNCT.

Compared to other treatment modalities in oncology, the acute toxicity of BNCT under the defined circumstances was acceptable.

Late radiation toxicity outside the brain was mild and consisted of: ongoing alopecia (in 5 cases), slight atrophy of the skin (2 patients), skin pigmentation changes, lens opacity, low grade blurred vision, low grade hearing loss, atrophy of oral mucosa, hormonal changes each in 1 patient.

The interpretation of the relationship of neurological events to BNCT proved to be very difficult especially in cases of progressive tumour recurrence. Minor neurological symptoms such as slight incoordination, paresthesia of the right hand and mild dysphasia possibly due to BNCT were completely resolved. A minor intellectual deficit, one grade 1 personality change and in two cases grade 1 headache was considered as possibly related to BNCT. The two neurotoxic events (both grade 3) with headache and psychosis with aggressive behaviour developed probably due to tumour progression and were unlikely to be caused by BNCT.

One serious adverse event was interpreted as probably BNCT related toxicity. In this specific case BNCT was given in November 1997 in four fractions with no evidence of any adverse event. After surgery the patient had discrete motor speech disturbance, which became slowly progressive from March 1998 onwards caused by a recurrent tumour, which was confirmed by MRI. An acute right facial nerve palsy associated with distal paresis of the right arm developed in May 1998. These symptoms were related to a progressive infarction in the perfusion territory of the thalamostriate arteries originating from the middle cerebral artery. At that time the tumour was progressing. Further MRI' s demonstrated tumour progression and an increase of the infarction size. Following a period of worsening neurological symptoms the patient died in December 1998 due to tumour progression. A clear attribution of the symptoms mentioned above either due to the tumour or infarction could not be made. Furthermore the infarction itself may be due to the progressive tumour or due to radiation induced vascular damage to the wall of the thalamostriate arteries.

2.3. Survival

The mean survival of the first patient group at the time of monitoring was 9.5 months after the first surgery for glioblastoma and 8.4 months after the last day of BNCT. Two of the 10 treated patients were alive. All patients with a fatal course died from recurrent disease. The patients who are alive are suffering from tumour recurrence. The outcome is as expected, taking into consideration the criteria for patient selection. The mean survival of the 4 patients not eligible for treatment with BNCT was 6.5 months after the initial surgery. All 4 patients died due to local progression of the glioblastoma.

3. CONCLUSIONS

After careful evaluation of the data, we can conclude that the starting BNCT dose level was safe, but probably high enough to reach the dose limiting toxicity within the frame of this radiation dose escalating trial. The observed toxicity due to BSH i.e. the effects on the haematological system needs further investigations, i.e. a defined dose escalation study investigating the toxic effects of the drug. Early and late radiation toxicity is slightly lower compared to conventional radiotherapy for glioblastoma with photons at a dose of 60 Gy in 6 weeks. The results concerning survival are similar, as expected.

The feasibility of performing BNCT using the epithermal beam at HFR Petten in a multinational approach could be demonstrated. However the therapeutic potential of BNCT cannot yet be evaluated at this point. Glioblastoma multiforme constitutes a good model for a phase I trial giving the opportunity to offer patients with a very poor prognosis and without expected benefit from all currently available treatments a therapeutic modality which at least shortens the treatment time. Glioblastoma multiforme however may not be the disease to judge the utility of BNCT and the therapeutic benefit deriving from BNCT. Future attempts will, therefore, focus on other tumour entities in addition to refining the protocol for glioblastoma patients.

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The Phase I/II BNCT Trials at the Brookhaven medical research reactor: Critical considerations

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Abstract. A phase I/II clinical trial of boronophenylalanine-fructose (BPA-F) mediated boron neutron capture therapy (BNCT) for Glioblastoma Multiforme (GBM) was initiated at Brookhaven National Laboratory (BNL) in 1994. Many critical issues were considered during the design of the first of many sequential dose escalation protocols. These critical issues included patient selection criteria, boron delivery agent, dose limits to the normal brain, dose escalation schemes for both neutron exposure and boron dose, and fractionation. As the clinical protocols progressed and evaluation of the tolerance of the central nervous system (CNS) to BPA-mediated BNCT at the BMRR continued new specifications were adopted. Clinical data reflecting the progression of the protocols will be presented to illustrate the steps taken and the reasons behind their adoption.

1. INTRODUCTION

The first clinical trial of BNCT for patients with GBM was initiated at Brookhaven Graphite Research Reactor in 1951 [1]. From 1959 to 1961, a series of patients with intracranial tumors (all except one, primary malignant brain tumors) received BNCT at the Brookhaven Medical Research Reactor (BMRR). Another group of patients with malignant gliomas was treated at the reactor at the Massachusetts Institute of Technology (MIT) during 1959–1961. These trials used four different boron compounds and a variety of surgical interventions. Results from the BNL and MIT studies were disappointing and all clinical trials of BNCT in the United States were stopped. The disappointing results were attributed to 1) inadequate penetration of the thermal neutron beams and 2) poor localization of boron in the tumor: tumor-to-blood ^{10}B concentration ratios were less than 1 [1–4]. Efforts to deliver therapeutic neutron fluences to a tumor at considerable depth in the brain sometimes resulted in severe damage to the scalp. In retrospect, it is now considered that high boron concentrations in the blood contributed to the damage to the vascular endothelium [2, 4–6]. The late Hiroshi Hatanaka began clinical BNCT in Japan in 1968. Patients with malignant gliomas were treated using the boron delivery agent, sulfhydryl borane $Na_2B_{12}H_{11}SH$ (BSH) and thermal neutron irradiation with an open skull technique. One hundred and forty-nine patients were entered into this treatment program [7]. The median survival for the BNCT-treated group was slightly shorter than the median survival of “the group treated conventionally” [8]. An analysis of patients from the United States who received BNCT in Japan failed to show any significant advantage of BNCT over more conventional approach [9]. Hatanaka and Nakagawa have, however, observed several long term survivors in a subset of BNCT-treated patients [10]. Of 38 patients with grades 3 and 4 malignant gliomas treated between 1968 and 1985, the 5- and 10- year survival rates were 19.3% and 9.6%, respectively. Sixteen of these 38 patients had tumors within 6 cm of the cortical surface. The 5- and 10-year survival rates in this subset of patients were 58.3% and 29.2%, respectively. Such long term survival, even in a highly selected population, has not been observed following conventional therapies.

In the 1980's, improvements in neutron beams and boron compounds allowed BNCT to reemerge in the USA as a potentially useful method for preferential irradiation of tumor. A higher energy ("epithermal") neutron beam is now in place at the BMRR [11, 12]. The higher energy epithermal neutrons are moderated in tissue to become low energy thermal neutrons that can be captured more efficiently by ^{10}B nuclei. Theoretically, the epithermal neutron beam at the BMRR makes it possible to treat deeper supratentorial tumors with BNCT. At the present time there are two boron compounds that are reportedly useful for clinical BNCT, BSH and the amino acid analog *p*-boronphenylalanine (BPA). One of the rationales for the use of BSH in BNCT of intracranial malignancies is that it does not cross the normal blood brain barrier (BBB) [13]. Intracranial tumors are assumed to be devoid of a functioning BBB and expected to preferentially accumulate BSH. It has, however, been reported that the integrity of the BBB in primary and metastatic brain tumors is highly variable (14) which may explain some of the relatively low reported tumor:blood boron concentration ratios following administration of BSH [10, 15, 16]. Moreover, BBB-respecting agents such as BSH will concentrate in the perivascular zones of those regions of the brain, which normally lack a BBB. A uniform intravascular and extravascular boron distribution in tissues lacking a BBB would result in about a three-fold higher radiation dose to the endothelium in these regions from the $^{10}B(n,a)^{7}Li$ reaction than to endothelium in regions where the BBB is intact [5, 17]. The use of the more deeply penetrating epithermal neutrons at the BMRR would produce more neutron capture events at greater depths than would be possible with a thermal neutron beam. A boron carrier that preferentially accumulates in tumor cells independent of BBB function, such as BPA, would therefore, be a better match for epithermal neutrons. In preclinical BNCT studies in rats bearing 9L gliosarcoma, BPA was shown to be superior to BSH [18]. BPA is transported across the blood-brain barrier into the normal brain. The average concentration of boron in the normal brain is between 75% and 100% of that found in the blood, and the average macroscopic concentration of boron in the tumor is 2 to 4 times higher than that in the blood. A soluble complex of BPA and fructose, BPA-F [19] was infused intravenously at doses ranging from 100 to 170 BPA/kg in patients in conjunction with a debulking craniotomy. No adverse effects attributable to BPA-F were observed in these patients [20].

On September 13, 1994, the aforementioned advances in neutron beams and boron compounds led to the beginning of a test of the closed-skull BNCT for human GBM at BNL using BPA-F and epithermal neutrons under US-FDA IND #43,317. The primary objective of this protocol was to evaluate the safety of BPA-F mediated BNCT in patients with GBM. As a secondary objective, the palliation of GBM by BPA-F mediated BNCT would be assessed. Between Sept, 1994 and June 1999, 54 patients were treated with BPA-F based BNCT at the BMRR. These patients were treated on a variety of dose escalation protocols that test the tolerance of the CNS to this new type of binary therapy. In this report we discuss some of the issues considered in the preparation of the clinical trials as well as a historical perspective on how the trials progressed.

2. CRITICAL CONSIDERATIONS

The first of these issues deals with the tolerance of the normal tissues within the field, particularly the brain. The initial tolerances were established based upon data derived from both human and animal exposure to either single doses of photons [21–23] or single treatments with BNCT [24–25]. These studies suggested an upper limit for a safe dose to the whole brain of 10–11 Gy. Smaller volumes of brain, around 14 cm^3, were found tolerate doses of 20 Gy [26].

Glioblastoma multiforme was selected because of the exceedingly poor prognosis, less than 12 months median survival with standard therapy [27]. Maximum tumor depth was determined based on the limited thermal neutron flux to sites deeper than 6 cm. A Karnofsky Performance Status (KPS) of 70 or higher was chosen to minimize potential problems associated with the requirement that patients remain totally still during treatment, which lasts between 45 minutes and 2 hours. A KPS of 70 or higher also allows comparison with the Radiation Therapy Oncology Group (RTOG) database Recursive Partition Analysis (RPA) classes [27]. Patients with prior adjuvant therapies were excluded because of the unknown degree of increased susceptibility of normal brain to BNCT resulting from these treatments.

The decision to administer BNCT in a single fraction was based on the following reasons:

1. All human clinical BNCT data was based on single fraction treatments. The distribution of BPA, particularly to normal brain, following more than one fraction of BNCT is unknown.

2. Results of animal studies to date do not support the hypotheses that multiple fractions either protects normal brain or improve tumor control [28–29].

3. The tolerance of the central nervous system to single-fraction BNCT has not been reached and the possibility of a tumorcidal dose within these tolerance limits has not been explored.

The considerations that lead to the selection of BPA rather than BSH as the boron carrier were described in the introduction. To summarize BPA was found to actively accumulate in 9L gliosarcoma is nontoxic and crosses the blood brain barrier (18–20). As previously described the estimates of normal tissue radiation tolerance thresholds and the probable tumor control doses were based primarily on results of human and animal exposures to single dose of photons or single treatment with BNCT. There are many dose components in BNCT, each with a different relative biological effectiveness (RBE) [30]. The total effective BNCT dose is expressed as the arithmetic sum of RBE corrected absorbed doses of each component using the unit Gy-Eq (Gray-Equivalent). The estimated radiation tolerance thresholds for the average brain dose and maximum doses to basal ganglia, optic chiasm and scalp were 11, 11, 11, and 22 Gy-Eq, respectively. Pre-BNCT GBM debulking was required not only for tissue diagnosis and amelioration of any mass effect but also as a prophylactic measure to soften any single-fraction, high dose BNCT induced increase in intracranial pressure due to radiation-induced sterile tumor inflammation and/or necrosis and edema.

3. PROGRESSION OF THE DOSE ESCALATION IN THE CLINICAL TRIALS

3.1. Toxicity evaluation

The safety of BPA mediated BNCT was the primary objective of this study. CNS toxicity was evaluated based on post-BNCT follow-up reports. The patient information included history and physical examination, total and differential leukocyte counts, routine clinical tests of blood and urine, MRI brain scans, Mini Mental State scores, Karnofsky Performance Status scores, and acute and late BNCT mediated neurotoxicity scores. Grade 3 or grade 4 toxicity, if any, was to be scored as severe toxicity. Death directly related to BNCT was to be defined as grade 5 toxicity. The toxicity criteria and grading systems were based on the Cooperative Group Common Toxicity Criteria and Radiation Therapy Oncology Group

(RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) acute and late radiation morbidity criteria [31].

3.2. Dose escalation

For the first protocol in the dose escalation series a reference dose of 10.5 Gy–Eq was chosen. The reference dose was defined as the dose to a 1 cm^3 volume centered at the maximum of the thermal flux. The reference dose corresponded to the maximum dose, Dmax, when one field was used. Eleven patients were treated with a reference dose of 10.5 Gy-Eq. using an eight centimeter collimator at a reactor power of 2 megawatts (MW). During this time a pilot study, which included patients that did not fit the entry criteria of the first protocol, were given radiation using a reference dose of 12.6 Gy-Eq. No significant CNS side effects were documented in these 15 patients. Two autopsies were performed in this cohort. There was no evidence of histologic damage to the normal brain.

Encouraged by the results from the first 15 patients a new protocol was started with a prescribed reference dose of 12.6 Gy-Eq. The reference dose was then defined as the 1 cm^3 centered at the maximum of the thermal flux outside the tumor volume. The dose escalations were achieved by increasing the dose of BPA, the reactor operating power, the duration of irradiation, and by changing the neutron beam collimator. The increase in the collimator size also allowed for increased dose at depth. In this new protocol a stratifying criteria was established which separated the patients into two groups. Stratification occurred based on target volume. If the target could be treated to a minimum dose of 17 Gy-Eq with one field the patient will be placed on the single field group (protocol 4a). If the target was too big to be covered by the one field then the patient will be placed on the double field group (protocol 4b). A significant increase in the average brain dose was observed when two fields were used as seen in figure 1.

3.3. Increased incidence of side effects

As the dose escalation continued some non-CNS side effects were noted. These effects included, but were not limited to otitis, parotitis, and sinusitis. At this time new radiobiological studies in animals were commissioned to evaluate the boron concentration in other head and neck tissues as well as to test the radiobiological effectiveness of this therapy on skin, mucosae, and glandular tissues. These studies revealed that there was an increase concentration of boron in these head and neck tissues. Further evaluation indicated that the radiobiological effectiveness of BNCT with BPA in the mucosae is higher than previously expected. As new information was uncovered the dose evaluation for treatment planning was revised accordingly.

In protocol 4 there were three acute RTOG grade 3 CNS toxicity documented. These responded rapidly to intravenous decadron infusion. The lesson learned from these three cases was the importance of maintaining a high level of decadron prior to and immediately after the BNCT treatment to avoid pre-treatment brain edema. Eight patients in this group had seizures. All of them had subtherapeutic levels of antiseizure medication during and/or after the procedure. Another lesson learned here was to maintain the level of antiseizure medication therapeutic during and after the treatment. Since we established these policies of premedicating the patients, with therapeutic levels of antiseizure medications and high dose steroids, no seizure or acute grade 3 CNS toxicity has been documented. Results from 10

autopsies in this cohort, with a maximum average brain dose (ABD) of 6 Gy-Eq, revealed that at these doses there was no significant radiation damage to the CNS.

3.4. Tumor response

As the ABD was escalated (Fig 1), the dose to the tumor increased (Fig 2). The time to progression (TTP) from diagnosis did not change significantly from protocol to protocol. The median TTP has not shown any dose response (Fig 3). Survival is not an adequate endpoint since it is dependent on the aggressiveness of the post progression treatment and not on the actual BNCT dose. One parameter that has not seen a perceptible change throughout the protocols is the average blood boron concentration (ABBC) (Fig 4). It is essential to increase the boron concentration in the blood and subsequently in the tumor to take full advantage of this binary therapy.

Salient characteristics of the first five protocols are shown in Table 1. Table 2 summarizes the parameters modified as the doses were escalated.

TABLE I. BNCT clinical trial summary

Protocol	Comments	Number of patients	Reference Dose (Gy-Eq)	Ave. Brain Dose (Gy-Eq)	Min. Tumor Dose (Gy-Eq)	Min. Target Dose (Gy-Eq)
1	9/94	1	10.5	(2.3)	(27)	(16)
2	2/95	10	10.5	<7.5	>20	not specified
3	Pilot study:	4	12.6	<7.5	>20	not specified
4a	1-field 6/96	11	12.6*	<7.5	~30	~17
4b	2- fields 6/96	17	12.6*	<7.5	~30	~17
5	3-fields 10/98	7	15*	<11	>30	~29**

*****Reference outside tumor
**Redefined target

TABLE II. BNCT dose escalation parameters

BPA	250 mg/kg, 290 mg/kg or 330 mg/kg
Reactor Power	2 MW or 3MW
Collimators	8 cm or 12 cm
Treatment Fields	Single, Double or Triple
Treatment Time	38 min to 120 min
Reference Brain Dose	10.5 Gy-Eq or 12.6 Gy-Eq

4. CURRENT PROTOCOLS

Based on the low toxicity seen up to protocol 4, several protocols were designed. Protocol 5 is a continuation of the dose escalation of single fraction BNCT with reference dose of 15 Gy-Eq and escalating ABD up to 11 Gy-Eq. The required minimum target volume dose was 29 Gy-Eq for this protocol. Protocol 6 is two fraction BNCT for patients who do not qualify for protocol 5. This protocol was designed to answer the question of possible advantages of boron redistribution in tumor and potential changes in the tolerance of normal tissues after fractionation. Protocol 7 used double fraction BNCT to treat patients with tumor volumes ≤ 50 cm^3 who had minimally invasive diagnostic biopsy only. This was designed to evaluate possible changes in the CNS side effect profile when treating intact tumors. Protocol 8 used single fraction BNCT to treat patients with recurrent debulked GBM after a single course of radiation. Out of eleven patients accrued in these 4 protocols 7 have been placed in protocol 5, 2 in protocol 6 and one each in protocol 7 and 8.

For the current protocols the target volume definition was changed from the gadolinium enhanced region plus a 2 cm shell around it, to the larger of the postoperative gadolinium enhanced region or the preoperative peritumoral edema and the 2 cm shell that encompasses it. This change reflected our observation that all recurrences occurred locally and their progression followed the preoperative edema volume pattern and data from Kelly et. al.[32]. The initial target volume definition used in the RTOG malignant glioma protocols RTOG-9305 and 9411 was adopted. This included the volume of edema in the target, where the risk for recurrence is highest. It also made the volumes used to report our data consistent with the volumes used in the radiooncologic literature. It is too early to tell what the long term effects in patients accrued under the current protocols will be.

5. CONCLUSIONS

Based on the results from the first 4 dose escalation protocols and 12 autopsies we can conclude that BNCT at doses of up to 6 Gy-Eq using BPA-F at the BMRR is safe. In this group of 43 patients there appears to be no improvement in tumor response as dose escalates, when using TTP as an endpoint. The BPA-F dose has been marginally escalated so far and more aggressive escalation of the boron dose is indicated to improve tumor response. BNCT boron dose optimization trials should continue.

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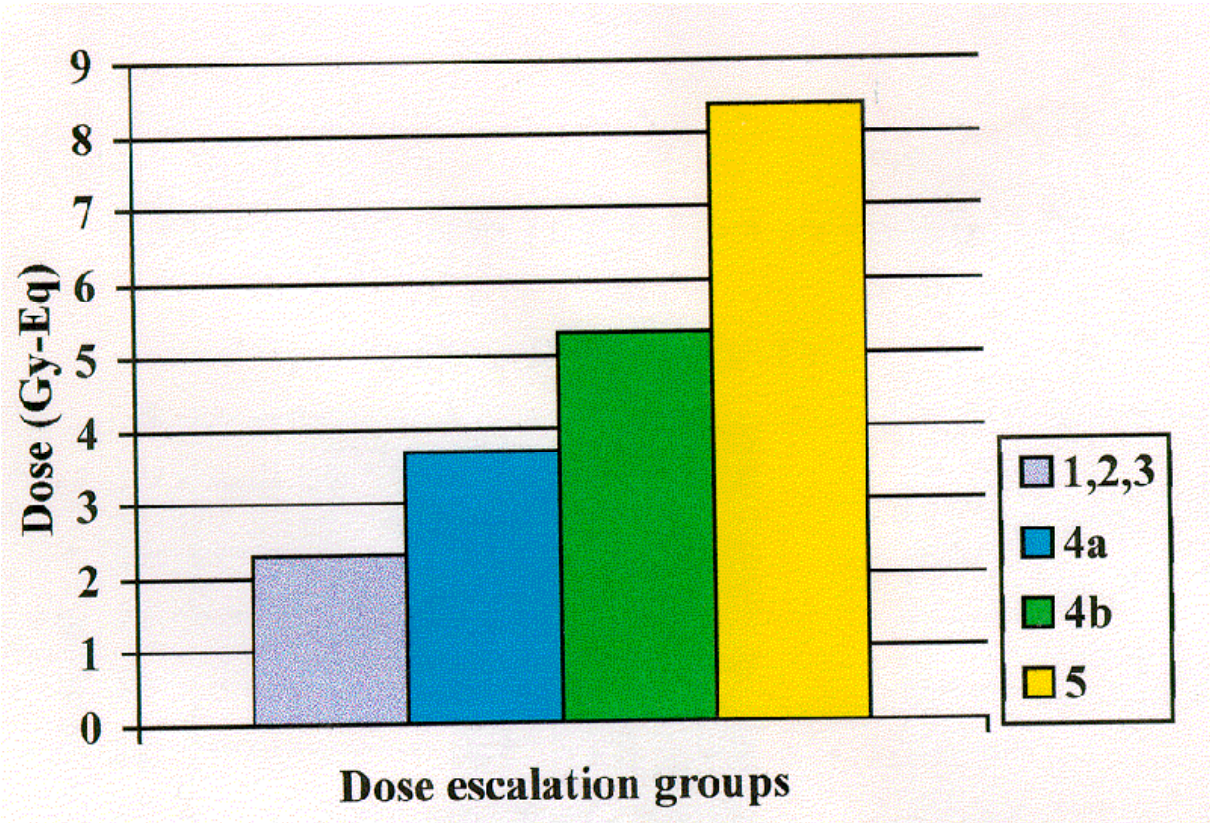

FIG. 1. Average Brain Dose escalation by protocol.

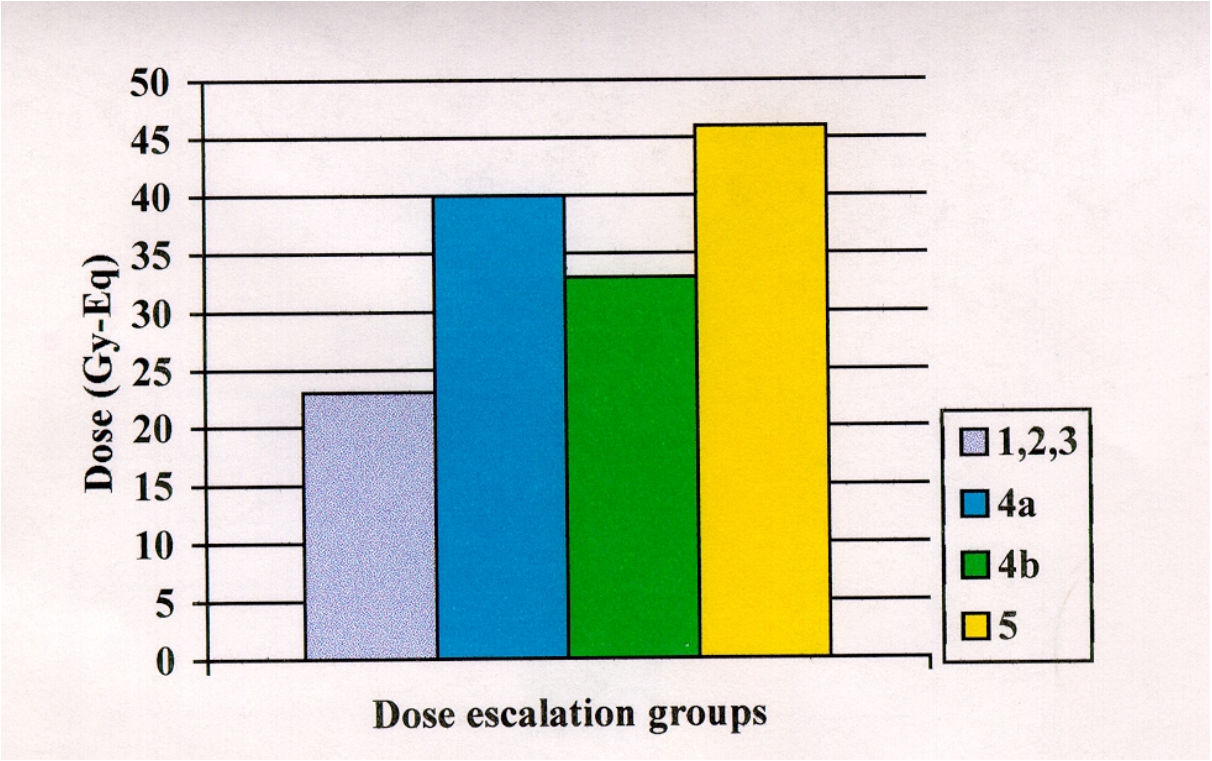

FIG. 2. Minimum Tumor Dose escalation by protocol.

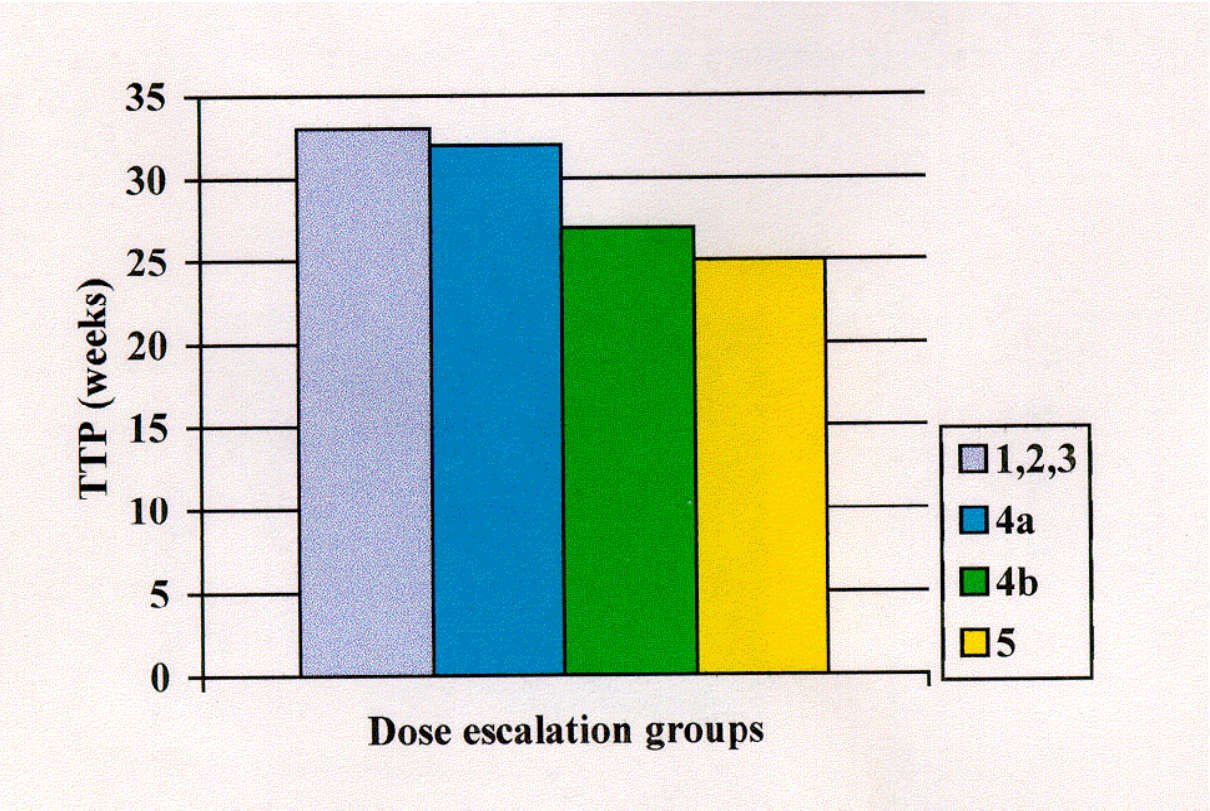

FIG. 3. Time to Progression (weeks) by protocol.

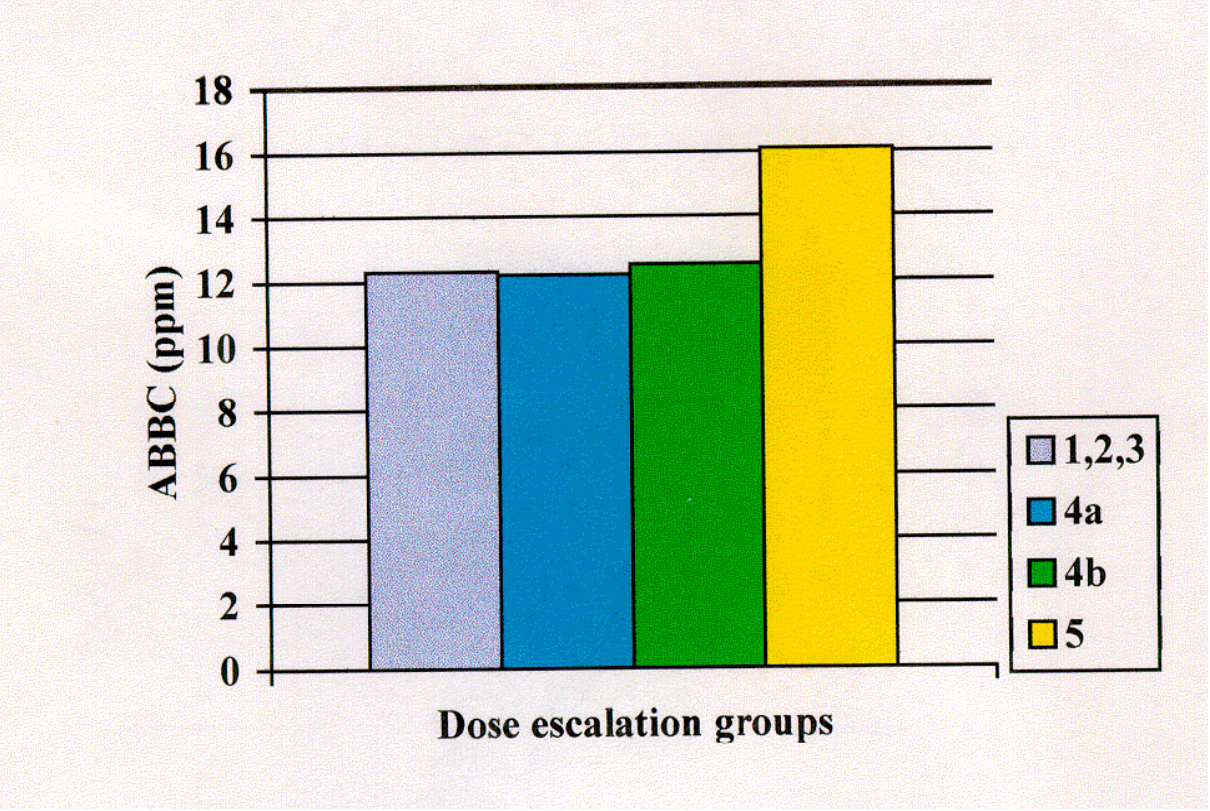

FIG. 4. Average Blood Boron Concentration (ppm) by protocol.

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The BNCT facility at the HFR Petten: Quality assurance for reactor facilities in clinical trials

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Abstract. The first clinical trial in Europe of Boron Neutron Capture Therapy (BNCT) for the treatment of glioblastoma was opened in July 1997. The trial is a Phase I study with the principal aim to establish the maximum tolerated radiation dose and the dose limiting toxicity under defined conditions. It is the first time that a clinical application could be realised on a completely multi-national scale. The treatment takes place at the High Flux Reactor (HFR) in Petten, the Netherlands, is operated by an international team of experts under the leadership of a German radiotherapist, and treats patients coming from different European countries. It has therefore been necessary to create a very specialised organisation and contractual structure with the support of administrations from different countries, who had to find and adapt solutions within existing laws that had never foreseen such a situation. Furthermore, the treatment does not take place in an hospital environment and even more so, the facility is at a nuclear research reactor. Hence, special efforts were made on quality assurance, in order that the set-up at the facility and the personnel involved complied, as closely as possible, with similar practices in conventional radiotherapy departments.

1. INTRODUCTION

The first clinical trial in Europe of Boron Neutron Capture Therapy (BNCT) for the treatment of glioblastoma was opened in July 1997 at the High Flux Reactor (HFR) in Petten, the Netherlands [1,2]. The first patient was treated in October the same year and currently, 10 patients have received treatment. The trial is a Phase I study with the principal aim to establish the maximum tolerated radiation dose and the dose limiting toxicity under defined conditions. It is the first time that a clinical application could be realised on a completely multi-national scale, whereby a unique facility available for BNCT is localised in one country (The Netherlands) and is operated by an international team of experts under the leadership of a German radiotherapist, treating patients coming from different European countries. It has therefore been necessary to create a very specialised organisation and contractual structure with the support of administrations from different countries, which had to find and adapt solutions within existing laws that had never foreseen such a situation.

It was apparent in the early stages of setting up the project, especially during many of the discussions with the Health authorities that quality, and certainly Quality Assurance (QA), would become a critical aspect of the whole trial. This was particularly the case with BNCT, as not only was it a new, experimental treatment about to be performed for the first time in

The Netherlands, and indeed Europe, but it would be performed in a non-hospital environment and in particular at a nuclear research site. It was necessary therefore to comply, as closely as possible, with similar accepted practices in conventional radiotherapy departments.

2. RADIOTHERAPY ASPECTS ON QUALITY ASSURANCE AND SAFETY

The council directive on health protection 97/43/EURATOM (based on recommendation of ICRP-60) requires explicitly appropriate QA programmes for performance and safety of radiotherapy units, including testing of performance characteristics on a regular basis.

Firstly, we should remind ourselves that for clinical trials, Quality Assurance means all those planned and systematic actions that are established to ensure that the trial is performed and the data is generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) [3,4] and the applicable regulatory requirements. Furthermore, in the context of these actions, we should distinguish between Quality Control (QC), which are the operational techniques and activities with the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Regarding GCP, this is the standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that rights, integrity and confidentiality of trial subjects are protected. As part of the GCP guidelines, Standard Operating Procedures (SOPs) are written which give the detailed instructions to achieve uniformity of the performance of each specific function.

3. NUCLEAR ASPECTS ON QUALITY ASSURANCE AND SAFETY

Conducting a clinical trial at a nuclear research centre does not impose in itself that a QA system fulfilling GCP guidelines must be performed. Nuclear installations inevitably themselves have their own QA systems. At the HFR, a Quality and Safety policy exists to maintain the key position of the HFR amongst research reactors worldwide, which can only be achieved and maintained by remaining at a high level of safety and quality in all aspects of operation of the reactor. The quality system is based, amongst others, on the principle of ISO 9001 and the environmental principles in ISO 14000. As part of the QA system, the Quality manual of the HFR describes the quality system and refers to the quality guidelines, procedures and working instructions as collated in the IAM Quality system, the Dutch Nuclear Safety Rules, the QA guidelines of the IAEA, and the HFR Technical Operational Guidebook.

Consequently, when compared, there are inevitably many overlapping similarities existing in both the medical and nuclear QA systems. Hence, the requirement to fulfil GCP for clinical trials at nuclear installations is not that peculiar. As a result, BNCT at Petten is performed respecting European, Dutch and whenever possible, German rules of safety and quality assurance for nuclear research reactors, for radio-protection, for radiotherapy units and for clinical trials [5]. In particular, quality assurance of safety provisions and functional performance characteristics conform to the most recent concepts and regulations of IEC publications and/or DIN standards for medical electron accelerators [6–9] and for treatment planning systems [10] or, as far as is possible, transferred analogously.

All relevant procedures concerning the execution of the clinical trial are described in a file of Standard Operation Procedures. The file of SOPs contains step-by-step descriptions of

some 55 procedures, including all nuclear activities, such as, for example, the reactor hall evacuation in case of a nuclear incident. A copy of the SOP file is in possession of each participant involved in the trial.

4. THE BNCT IRRADIATION FACILITY AT PETTEN

Treatment of the patient takes place at the HFR [11], located at the Joint Research Centre in Petten, The Netherlands. The HFR is a 45 MW, materials testing reactor, with the prime objective to perform experiments on nuclear fuels and materials destined for the European civil nuclear power programmes. In recent years, the reactor has increased its area of application into medicine, in particular radioisotope production, as well as BNCT. For BNCT, a specially designed filtered beam tube and irradiation room was built at one of the eleven horizontal beam tubes located around the reactor [12].

In designing, implementing and reviewing the development of the facility, the required work was carried out in conformance with accepted standards in QA and QC. The design of the whole facility was reviewed critically by the local Reactor Safety and Experimental Assessment Committees, who have the mandate to judge a facility on both its nuclear and conventional safety aspects, including reactor safety and radio-protection of the personnel. The working environment was reviewed by the appropriate regulatory body at the Ministry of Social Affairs (SZW), who assessed the facility on the basis of site-visits and documentation [13] which described the facility in detail, including the justification for BNCT, its conformance with the ALARA (as low as reasonably achievable) principles of radiation protection and the organisational structure, where the medical and radio-protection responsibilities are clearly defined. The facility also underwent a local quality audit, as part of the JRC's mission to become a licensed Quality Management (QM) site according to ISO 9001 during 1999. Finally the facility had a site-visit by an independent physician with personal expertise in clinical applications of BNCT.

The step-by-step procedure in developing such a QA system is given in ISO9001. For an experimental facility, the structure is well defined. When medical procedures, and in particular BNCT procedures, are required, the written and executed procedure is an adaption of the written standard.

For a BNCT facility the procedures described in the following sections are based on the experience at Petten. Whist similarities elsewhere will exist, differences or even non-applicability of some of the procedures will occur.

4.1. Dosimetry

Dosimetry guidelines, as followed in conventional treatment centres, apply to photon, electron or fast neutron facilities. For BNCT facilities, where an epithermal neutron beam is used, the beam (in air) includes fast neutrons (>10keV) and gamma rays. The latter comes from both the beam itself (reactor gammas) and from activation of the in-beam material [13]. In human tissue, containing boron-10 compounds, the beam produces effectively four main dose components, all with different biological effectiveness: the boron neutron capture absorbed dose, the nitrogen neutron capture absorbed dose, the fast neutron absorbed dose and the gamma ray absorbed dose.

Furthermore, the neutron beam emanates from a reactor, which in the case of the HFR, as a strict operating schedule, running 24 hours per day for eleven cycles of 4 weeks each, per

year. Hence due to burnup of the reactor fuel, the intensity of the beam over the scheduled 4 weeks cycle reduces by some 4–5%. Also, the intensity of the beam at the start of each cycle may vary by some ±4% per cycle, due to experimental loading changes in the reactor. Hence, quality assurance of the beam during treatment must follow a strictly controlled procedure, which includes the following steps:

- free beam measurements on a monthly basis, using a multi-foil packet consisting of 12 activation foils,
- on the first day of the treatment week (each patient receives a fraction of radiation on four consecutive days), reference phantom measurements are performed using activation foils, twinned ionisation chambers and a pn-diode,
- the measurements are used to calibrate the on-line monitors (see next section),
- on succeeding days of treatment, the reference phantom measurements are repeated using the pn-diode, twinned ionisation chambers and the in-beam monitors, which are all normalised to the first day's measurements.

Following the QA system, as well GCP, all measurements are written down, controlled and countersigned by the responsible person, documented and later archived. Despite the complexity associated with BNCT dosimetry, QA procedures applied for BNCT infer less radiation and operational procedures than for conventional radiotherapy. Furthermore, reproducibility in BNCT is equivalent with medical accelerators, whilst all safety requirements and equipment functions, including against stray radiation are equivalent.

4.2. Beam monitoring and beam shutter control

The QA concept applied for the BNCT beam, is the same as that established for conventional radiotherapy purposes, but adapted for the special situation at the reactor. All safety systems are backed-up by an independent second device acting in case of failure of the first. The beam monitoring system consists of four beam monitors: two ^{235}U fission chambers (neutron counters) and two GM-tubes (gamma ray counters), which are located in the fixed beam collimator, downstream from the main beam shutter and before the sliding gamma shutter. The automatic opening and closing of the beam shutters is controlled by the fission chambers, according to the pre-set number of monitor counts which correspond to the required boron dose delivered at the DGIP (dose group identification point) [2] in a patient. Both fission chambers are pre-set to close the shutters, which are automatically triggered when the target counts are reached. Fission chamber nr.1 acts as the principal counter, with nr.2 as the back-up. Both chambers, as well as the GM-tubes, are monitored and counts and count rates displayed on two independent computer systems. As an additional back-up for beam shutter closure, a timer is available, with a pre-set time at 2% above the given irradiation time. If called into use, closure of the beam shutters is automatically triggered. If necessary, the beam shutters can be closed by means of a push-button on the beam shutter operations panel. If this fails, due to electrical failure, the beam shutters can also be closed by means of manual mechanical devices [14]. As a last resort, the beam operator has the mandate to instruct the reactor operators to scram the reactor.

The above description is given as an example of the working philosophy of one of the main components in the overall BNCT facility. Similar detailed descriptions exist for other principal components, but for brevity, will not given here.

4.3. Radiation protection

Radiation protection procedures follow the national and international QA systems where responsibility is the most important issue. To conform with the Dutch regulations on radio-protection, an authorised Radio-Protection Committee for BNCT has been formed. The committee has the prime task to review and advise, on a half-yearly basis, the radio-protection methods used for BNCT. If need be, this advice is transmitted to the appropriate regulatory authority.

4.4. BNCT treatment planning

As part of the overall treatment planning procedure, supplementary use is made of the INEEL treatment planning program [15], which is located on 2 separate SUN workstations at JRC. The QA system provides for the necessary documentation, etc. as given in the above sections. As part of the QA system, a quality control procedure for the program involves calculations on two standard test cases, i.e. a standard patient and standard phantom, which are calculated to check for possible non-conformance. The cases are chosen in such a way that all the essential parts of the program are used. At defined periods, the versions on both workstations, whether updated or not, are run for the two standard test cases. A control procedure is followed and performed each time a new version of the program is installed. The procedure includes comparative calculations, back-up steps and SOP updates.

For the patient plans, each treatment plan is calculated in Petten and presented, discussed and agreed at the radiotherapy department of Essen University during their daily audit on treatment planning.

4.5. Patient positioning system

The preparation for the treatment planning is done at the referral hospital, including making of the positioning mask. The CT images are transferred to Petten, where the treatment planning calculations give the geometry of the incident beam to the patient, as well as the beam centre-line entrance and exit points. To position the mask in the required position, a system has been developed based on the QA principle of reproducibility. The frame utilises an open, aluminium framework in which the mask is placed. The step-by-step procedure is described in the relevant SOP, the positioning can be accurately and quickly controlled by the radiotherapist [16].

4.6. Prompt gamma ray analysis

The mean blood-boron concentration during the treatment of the patient is determined by means of prompt gamma ray analysis [17], which is located at Petten on a neighbouring beam tube (HB7) in the reactor hall. A quality control of the facility is performed on the first day of each treatment week, when the resolution of the detector is checked using a ^{60}Co source, and the function and accuracy of the entire system is checked using calibration samples. On the days of patient treatment, the resolution of the detector is checked again, and the set-up is calibrated using standard samples. One blood sample per patient and one calibration sample are later validated by ICP-AES, available at Petten. Again a documented procedure is strictly followed.

4.7. Training of the staff

Prior to treatment of the first patient, a training programme was carried out and repeated on a regular basis, whereby all procedures and actions necessary to perform BNCT have been simulated in "dummy runs". Special attention was paid to emergency situations including both technical and medical failures, such as a reactor hall evacuation emergency and a simulated cardiac arrest of the patient. With respect to a QA system, it has to be demonstrated that staff following a specific training schedule related to the needs of the experiment, i.e. trial.

5. CONCLUSION

The first demonstrations of BNCT in the USA were thwart with danger and were damaging to the patient. The fact that the clinical trials, also here in Petten, take place in a nuclear research reactor, which apart from being conducted in a non-hospital environment, conveys to some people, possible additional dangers. It is therefore of the utmost importance that special attention is given to safety, beyond normal rules, and to the training of staff. This is most poignant when demonstrable strict quality assurance procedures exist, offering guaranteed reliable and safe functioning of the treatment.

Despite the fact that guidelines for QA on health protection may appear only to be applicable to medical applications, they are based on the same principles of QA systems in general. Hence, when compared, there are inevitably many overlapping similarities existing in both the medical and nuclear QA systems. The requirement to fulfil GCP for clinical trials at nuclear installations is therefore not that peculiar. Thus, QA procedures for BNCT at nuclear installations can be, and should be, readily implemented.

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Annex 9
DOSE REPORTING

Determining and reporting the doses in the treatments of glioma patients in the epithermal neutron beam at the Finnish BNCT facility (FIR 1)

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Abstract. The clinical trials of glioma patients at the Finnish boron neutron capture therapy (BNCT) facility (FiR 1) started in May 1999. The doses of the patient in tumour, target volume and sensitive tissues are calculated individually. The calculated doses are calibrated to the reference monitor units according to the ratio of the independently measured and calculated ^{197}Au(n,g) reactions rates at the depth of 20 mm on the central axis of a cylindrical PMMA phantom chosen as the reference geometry. Absorbed doses to the head and body are monitored individually using *in vivo* dosimeters. In BNCT the total dose is the weighted sum of the absorbed doses originating from the neutron and gamma interactions in tissues. The material compositions of the head model for the neutron-gamma transport calculation and kerma factors are based on the ICRU report 46. The doses in the clinical research of BNCT should be reported in such a way that the doses are comparable, traceable and can be recalculated, if underlying information, like weighting factors for dose components, are replaced by new ones. The minimum, maximum, average and reference doses are reported for the tumour, target and normal brain. In addition to the total weighted doses the dose components (boron, gamma, nitrogen and fast neutron dose), weighting factors and estimated boron concentration in these tissues are reported. There are no international recommendations available for BNCT dose calculation or reporting. Therefore the BNCT doses reported in the literature may not be comparable and a careless use of values can lead to over- or underdosing. There is an obvious need for standardisation in the medical application of BNCT. In this paper the methods of dose calculation and reporting of the glioma patients at FiR 1 are described.

1. INTRODUCTION

The clinical trials of glioma patients with boron neutron capture therapy (BNCT) started in May 1999 at the Finnish Research Reactor (FiR 1). Epithermal neutrons are used with boronophenylalanine-fructose (BPA-F) as the ^{10}B carrier. The dosimetric methods for the patient's treatment are based on the practise established in the radiobiological study early in the year 1998 [1,2]. In the dose planning the patient's doses in the tumour, target volume and sensitive tissues of the head are calculated individually in the treatment planning as a function of average ^{10}B concentration in blood during the irradiation. Estimation of the average ^{10}B concentration is based on kinetic models [3] and on taking blood samples before and after irradiation. The blood samples are analysed with ICP-AES [4]. Doses to the head and to the body are monitored using *in vivo* dosimeters [5]. Dose delivery is controlled using the beam monitoring system [6,7].

Like in Finland (FiR 1), epithermal neutron irradiations are used for BNC-treatments in USA (Brookhaven Medical Research Reactor (BMRR) [8] and Massachusetts Institute of Technology Research Reactor (MITR-II) [9]) and in the Netherlands (High Flux Reactor (HFR) [10]. In Japan at the Kyoto University reactor (KUR) thermal neutrons or a mixed field of thermal and epithermal neutrons [11,12] and at Japan Atomic Energy Research Institute (JAERI) [13] thermal neutrons are used for BNCT. The high intensity epithermal neutron beam at FiR 1 has the smallest fraction of fast neutrons and photons of the existing BNCT beams [6,7,14]. The purity of this beam makes it possible to achieve higher tumour dose than elsewhere, since the acceptable normal brain tissue dose limits the irradiation time. To verify/calculate the treatment planning of patients at FiR 1, HFR [15] and BMRR [16] the BNCT_Rtpe/rtt_MC treatment planning program [17] is used. At MITR-II the treatment plans are carried out with the NCTPLAN [18]. At FiR 1 and HFR [19] physical doses are calculated to tissue compositions recommended by ICRU [20]. At BMRR [16] and MITR-II [18] different tissue compositions are used to calculate neutron-gamma transport and kerma factors, for example the brain composition is defined by Brooks et al. [21].

There are no international recommendations for the BNCT dose calculation or reporting. Therefore the BNCT doses in the literature are not always comparable and a careless use of values can lead to over- or underdosing.

In any radiotherapy the physical dose must have a metrologically traceable link to the national and international dosimetry standards. In addition, the uncertainty of the dose delivered to the patient has to be low enough for estimating the effects of the treatment beforehand and analysing afterwards. Accurately characterised neutron and photon spectrum, fluence and dose distributions in a phantom form the basis for a reliable dose delivery to a patient in the BNCT. There is an obvious need for standardisation in medical application of BNCT [22-24]. In this paper we describe the method of dose determination and reporting of the glioma patients at FiR 1.

2. DOSE IN BNCT

The accumulated biodistribution of ^{10}B controls the therapeutic dose distribution i.e. boron dose (D_B) in tissues. The rest of the total dose is composed of the neutron, nitrogen capture (D_N), fast neutron (D_{fast_n}), and the gamma doses(D_g). To estimate the biological

response of the tissues to the combination of all these doses the concept of weighted dose is used [1,2,22]. The weighted dose D_W is a sum of physical dose components (D_i) multiplied by weighting factors (w_i) of each dose component in a tissue. The weighted dose can thus be written [1,2]:

$$D_W = w_g D_g + w_B D_B + w_N D_N + w_{fast\_n} D_{fast\_n}. \quad (1)$$

The unit for absorbed dose (i.e. physical dose) is gray [1 Gy=1 J/kg]. As the weighting factors are dimensionless gray is the unit of both the physical (D_g, D_B, D_N and D_{fast_n}) and weighted dose (D_W). To illustrate the difference of the absorbed and weighted doses, the letter W in parenthesis is added to the symbol Gy writing one space between the symbol and the additional specification for the weighted dose [1 Gy (W)].

3. CALCULATED DOSE

FIG. 1. illustrates the calculated BNCT doses at FiR 1. The scheme is a modification of the program flow for BNCT treatment planning program rtt_MC presented by Nigg et al. [25]. The main elements that the user can influence in the calculation of the BNCT dose at any BNCT facility are neutron-gamma source, head model including tissue compositions, ^{10}B concentration in tissues and weighting factors.

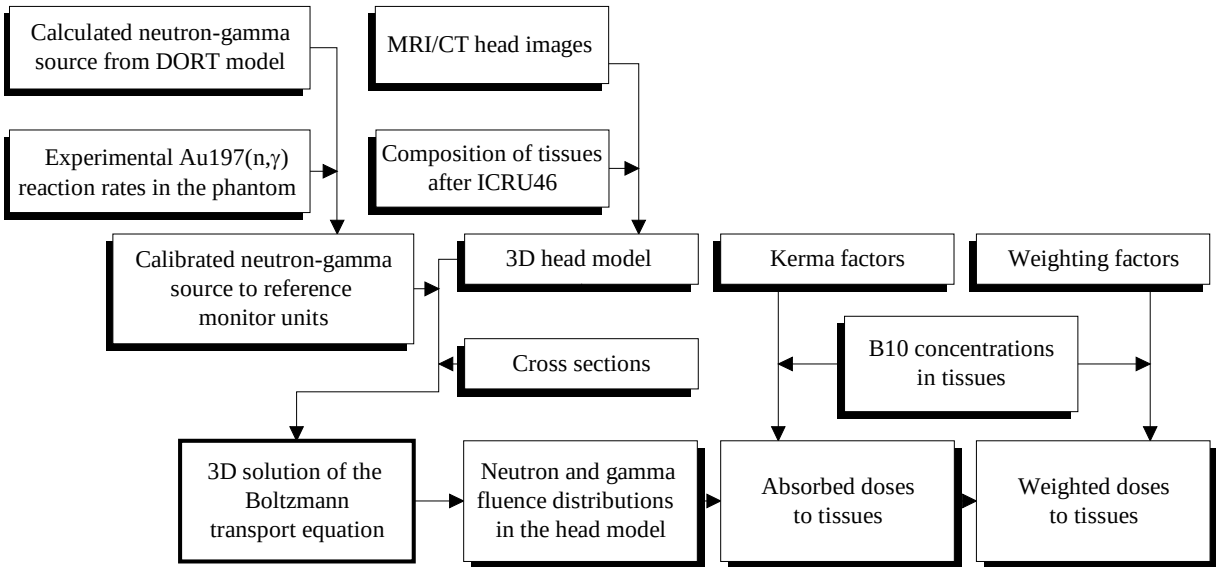


FIG. 1. The scheme for calculating doses at FiR 1.

3.1. Neutron-gamma source

The Finnish BNCT facility (FiR 1) is a low-power 250-kW TRIGA II pool reactor. The beam in its present configuration was completed in November 1997. The FiR 1 beam has a better quality (lower fast neutron and incident gamma dose in tissue) and a more penetrating neutron spectrum. It is believed to deliver a higher value of Tumour Control Probability (TCP) than other existing BNCT beams at shallow depth [14].

The neutron-gamma model for the epithermal treatment beam is one of the basic elements in assuring the reliability of the doses. The FiR 1 beam with different sizes of apertures (Ø8, 11, 14, 17, 20 cm) has been modelled with the DORT (Two dimensional Discrete Ordinates Transport) code [26,27]. The FiR 1 beam model includes the nuclear reactor to generate the fission neutrons, the moderator to moderate the fission neutrons to epithermal energies (with a small fast neutron and gamma contamination), the collimator to collimate the epithermal neutrons to compose a clinical beam, and some surrounding materials, like part of the concrete shielding.

There have been three different geometrical configurations at FiR 1. The beam models for these configurations have the same model of the core, but differ in the moderator thickness or in the beam delimiter or conical collimator arrangement [28–34]. The FiR(K63) beam configuration with the moderator thickness of 63 cm and conical collimator were used in the radiobiological study in 1998 [2,35] and in the clinical trials of the glioma patients so far.

The 67-group coupled P_3 neutron-gamma BUGLE-80 cross section library was used in the DORT calculations. A forward-biased quadrature set (D_{166}) was chosen for the accurate angular calculation at the beam-line from the core to the collimator output. The model has a horizontal cylindrical geometry. The longitudinal central axis of the model passes from the reactor core via the centre of the FLUENTAL^{TM} moderator to the centre of the collimator. The composition of the core was calculated from the burnup of the fuel rods. The biased core loading (fresh fuel in the direction of the BNCT moderator), that was estimated to increase the beam intensity by 30%, was taken into account in the model. The model consists of two parts. The first part of the model, that is seldom changed at FiR 1, includes the core with fuel elements, graphite reflector and water. The second part includes the moderator, collimator, phantom and part of the concrete shield.

The neutron spectra from the DORT model were verified with multifoil measurements at the bismuth face, at the 14 cm free beam exit and at the 11 and 14 cm source planes (50 mm inwards from the exit of the beam aperture) with a water phantom in place [30]. The neutron and gamma distributions in the phantoms were verified with Au/Mn activation foil, twin ionisation chamber and thermoluminescent detector (TLD) measurements [27,33].

The neutron-gamma source description from the DORT calculations is defined for the treatment planning software BNCT_Rtpe/rtt_MC (ver. 2.2/106) [17]. The source model includes the source plane description and the subsequent 50 mm thick layer of collimator that produces the treatment beam. For the source description the directional intensities of the neutrons and photons in the 67-group energy structure from the DORT model were averaged over air of the collimator cone at the radial plane perpendicular to the beam direction. The directional intensities of the source model are described with 10 bins in each energy group.

3.2. Head model for radiation transport calculation

The human head is imaged transaxially with a clinical high-field whole body MR scanner (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) using the standard head coil. Thirty-eight to fifty-seven, depending of the head size, T1 weighted images from the top to the neck are collected with a spin echo sequence (TR=600ms, TE=14ms, FoV=230*230 - 260*260, matrix size 256*256, slice thickness 5.0mm) [36].

For the head model skin, cranium, normal brain (cerebrum and cerebellum), the target and tumour volumes are segmented. The skin volume comprises all the soft tissue that is not

included in the normal brain, target or tumour volumes. The cranium volume, that has the lowest neutron attenuation, includes bone, cartilage and sinuses. The compositions of segmented tissues for transport calculations are defined according to the ICRU Report 46 [20]. The skin is defined as a skin (adult), the cranium as a skeleton-cranium (whole, adult) and the normal brain, target and tumour as a brain (whole, adult) [20] (TABLE I).

In the transport calculation BNCT_Rtpe/rtt_MC uses the cross section data from the ENDF/B (IV/V) library [17].

TABLE I. THE MATERIAL COMPOSITIONS OF THE HEAD MODEL, [20].

Tissue	The elemental composition w-%											Density kgm^{-3}
	H	C	N	O	Na	P	S	Cl	K	Mg	Ca	
Skin	10.0	20.4	4.2	64.5	0.2	0.1	0.2	0.3	0.1			1090
Cranium	5.0	21.2	4.0	43.5	0.1	8.1	0.3			0.2	17.6	1610
Brain	10.7	14.5	2.2	71.2	0.2	0.4	0.2	0.3	0.3			1040

3.3. ^{10}B concentration in tissues

The two-step method to estimate the homogeneous ^{10}B concentration in any tissue uses i) the average ^{10}B concentration ratio of the tissue-to-whole blood and ii) the analysed and averaged ^{10}B concentration in the whole blood during the irradiation session [B-B10]. The patient's blood samples taken before and after irradiation are analysed with ICP-AES [4]. To calculate the average value the ^{10}B concentration in the blood during and after the BPA-F infusion is modelled by kinetic models [3]. The values of the ^{10}B concentration ratios between the tissues and the whole blood for the BPA-F are from the literature and are in clinical use at the BMRR (Brookhaven Medical Research Reactor) [16,37,38]. The ^{10}B concentration ratio of the normal brain-to-whole blood is 1:1, the tumour(target)-to-whole blood 3.5:1 and the skin-to-whole blood 1.5:1 [37].

3.4. Kerma factors and weighting factors for dose calculation

At FiR 1 the ICRU recommendations [20] of the tissue compositions for the kerma factors are used also in calculating the absorbed doses from the neutron and gamma fluences [TABLE I]. The cross sections of the kerma factors are in 94 energy groups taken from the ENDF/B (IV/V) library [17]. On the other hand weighting factors are taken from the BMRR dose weighting scheme [8], which uses the brain composition defined by Brooks et al. [21] for the nitrogen and fast neutron kerma factors. The elemental fraction (percentage by mass) of nitrogen and hydrogen defined by Brooks et al. are 1.84 and 10.6, respectively, and by ICRU 2.2 and 10.7 [TABLE I], respectively. The weighting factors used with the ICRU brain composition for kerma factors are corrected for this difference, giving for nitrogen capture (w_N) 2.68 (=3.2*1.84/2.2) and for fast neutron (w_{fast_n}) 3.16 (=3.2*10.6/10.7), where 3.2 is the weighting factor for both nitrogen capture (N) and fast neutron (fast_n) dose components used in the BMRR scheme. The fast neutron spectra of the BMRR and FiR 1 epithermal beams are so close to each other that the use of the same fast neutron weighting factor in both cases was considered to be justified. Through this correction the derived weighted dose at FiR 1 will in fact be equal to a weighted dose calculated to Brooks brain and weighted with the BMRR factors.

The boron dose (D_B) from the neutron absorption of ^{10}B, is calculated from the neutron fluences and the ^{10}B kerma factors, and the homogeneous ^{10}B concentration in the tissue [17]. The boron dose does not include the boron capture gammas, they are calculated separately to the gamma dose. The weighting factors of boron capture in normal brain, tumour/target and skin are also taken from the BMRR dose weighting scheme and are 1.3, 3.8 and 2.5, respectively [38]. Typical calculated normal brain doses (Ø11cm beam at FiR 1 and $[B\text{-}B10]_{ave}$ 12 μg/g (BPA-F)) in the 1.0 cm^3 volume at the thermal neutron maximum, chosen as the reference point, are 5.0, 5.3, 0.9, and 0.2 Gy/h for gamma (γ), boron capture (B), nitrogen capture (N) and fast neutrons (fast_n), respectively. These values would give the total weighted reference dose rate of 15 Gy (W)/h (=1.0*5.0+1.3*5.3+2.68*0.9+3.16*0.2) to the normal brain.

4. MEASURED DOSE

4.1. Dose calibration to measurements

For the dose calibration of the treatment planning system the source model was first verified [27]. Thereafter the calculated doses were calibrated to the reference monitor units according to the ratio of the independently measured foil and calculated $^{197}Au(n, \ )$ reactions rates at the depth of 2.0 cm in the central axis of a cylindrical PMMA phantom chosen as the reference geometry. The entrance face of the phantom lies in the beam exit plane as is the patient's head in the irradiation.

The source model was verified principally with Au and Mn activation measurements in cylindrical phantoms that consist of three brain tissue substitute materials (Liquid B[39], water and PMMA). An activation cross section file (Act.sigma) generated specially for this purpose was included in the rtt_MC. The program uses this option to calculate the $^{197}Au(n,\gamma)$ and $^{55}Mn(n,\gamma)$ reaction rates in the diluted Au-Al and Mn-Al foils in the model. The cross sections in 640 groups with uncertainties for $^{197}Au(n,\gamma)$ and $^{55}Mn(n,\gamma)$ reactions were taken from the IRDF-90 library [40]. They were condensed into a 94 group structure using the program FLXPRO from the LSL-M2 package [41]. A standard 640-group weighting spectrum was used with a Watt spectrum for fast neutrons, a 1/E spectrum for epithermal neutrons and a Maxwell spectrum for thermal neutrons.

The result of the verification with Au foils showed that inside the phantom the difference from the measurements was within ±5% (1SD). At the surface of the phantom the thermal neutron fluence was overestimated 10%, because of the big size (1 cm^3) of tallies and a steep cross section gradient between air and a tissue substitute material [27]. At this situation the rtt_MC program is unable to interpolate the doses/fluences correctly at the interface. Also IC and TLD measurements in the phantoms showed very good agreement with the calculated values from the treatment planning code [27,33]. The uncertainties of the measured rates (with IC) of absorbed dose to brain tissue in a water phantom were approx. 6% for gamma, and approx. 20% for neutrons at the depth of 25 mm in the phantom when using beam aperture 14 cm.

The epithermal neutron beam from the reactor is monitored with three pulse-mode ^{235}U-fission chambers for the epithermal and thermal neutron fluence rate and one current mode ionisation chamber for the gamma dose rate [6,7,42]. The detectors are monitored on line with a PC-program based on virtual instrumentation to give the primary reference dose. Backup dose monitoring is accomplished by observing stand-alone NIM counters. The intensity

calibration and the link from the dose to the beam monitor units (the calibration factor) was obtained from the ^{197}Au reaction rate measurements in the phantom at the reference geometry. The calculated dose rate $\dot{D}^{calc}_{\mathrm{Re}\,f}$ at the reference monitor unit rate in a patient or a phantom is [27]

$$\dot{D}^{calc}_{\mathrm{Re}\,f} = \frac{r^{meas}_{Au-197}(\dot{MU}_{\mathrm{Re}\,f})}{r^{calc}_{Au-197}(250kW)} * \dot{D}^{calc}(250kW) \qquad (2)$$

where $r^{meas}_{Au-197}(\dot{MU}_{\mathrm{Re}\,f})$ is the measured Au-197 reaction rate at the reference monitor unit rate and $r^{calc}_{Au-197}(250kW)$ the calculated Au-197 reaction rate at the 250kW reactor nominal power in the reference geometry. $\dot{D}^{calc}(250kW)$ is the calculated dose rate at the 250kW reactor nominal power in a patient or a phantom. The number of monitor units MU to be administrated in a phantom or a patient irradiation is [27]

$$MU = t_{\mathrm{Re}\,f} * \dot{MU}_{\mathrm{Re}\,f} = \frac{D}{\dot{D}^{calc}_{\mathrm{Re}\,f}} * \dot{MU}_{\mathrm{Re}\,f} \qquad (3)$$

where D is the planned dose in a patient or a phantom and $\dot{MU}_{\mathrm{Re}\,f}$ is the reference monitor pulse rate.

4.2. *In Vivo* dosimetry

Thermoluminescent (TL) detectors MCP-7s (^{7}LiF:Mg,Cu,P) from TLD Niewiadomski & Co. (Krakow, Poland) are used for *in vivo* gamma detection [32,43,44]. The individual dose monitoring is performed at several measurement points both in the head and in the body. The corrections for the thermal neutron sensitivity of the TL detectors used are made based on the neutron fluence measured at the same point with Mn-Al foils (1 % Mn, Ø 12 mm x 0.2mm, ECN Petten) and wire pieces (2.4 % Mn, Ø 0.03", Reactor Experiments). In the radiobiological study [5], the measured and calculated absorbed gamma doses and thermal neutron fluences were in good agreement. The uncertainty of the neutron fluence measurements is estimated to be 5% (1 S.D.). The uncertainty of gamma dose measurements is approx. 10% (1 S.D.) in those measurement points in the body in which thermal neutron fluence is negligible and, therefore, no correction for thermal neutron sensitivity is performed, and approx. 20–30% (1 S.D.) in the measurement points situated in the head where the mixed neutron-gamma field occurs.

5. AN EXAMPLE OF A TREATMENT PLAN AND DOSE REPORTING

The three dimensional software BNCT_Rtpe/rtt_MC (ver. 2.2/106) [17] was used to make a dose plan in a head model of a healthy volunteer as an example. The thirty-eight MR images were used to construct a three dimensional model of the head. The tumour and target volumes were arbitrarily defined. In the head model skin, cranium, brain, target and tumour were segmented [36].

A one-field dose plan was calculated with the Ø11 cm FiR 1 beam (FiR(K63)). The calculation time for one field (one million histories) was about seven hours on the Linux

operating system with a 200 MHz Pentium Pro. The doses in the tumour/target volume and normal brain tissues were calculated assuming homogeneous boron concentration in the tissues, and ^{10}B concentration ratio of tumour/target-to-blood 3.5:1 and normal brain-to-blood 1:1. The weighted boron dose is about 90% of the total weighted reference dose for tumour and about 45% for normal brain ([B-B10] is 12 ppm) at the thermal neutron maximum i.e. the reference point [FIG. 2]. The weighted dose to tumour cells is about five times higher than to normal brain cells [FIG. 3.]. In one field irradiation as high as 57.5 Gy (W) average target dose can be achieved [FIG. 4.], when average normal brain dose remains at 3.7 Gy (W). In the dose-volume-histogram the normal brain dose includes the normal brain, target and tumour. The minimum, maximum, average and reference doses are calculated and reported for the tumour, target and normal brain. In addition to the total weighted doses the dose components (boron, gamma, nitrogen and fast neutron dose), weighting factors and estimated boron concentration in these tissues are reported.

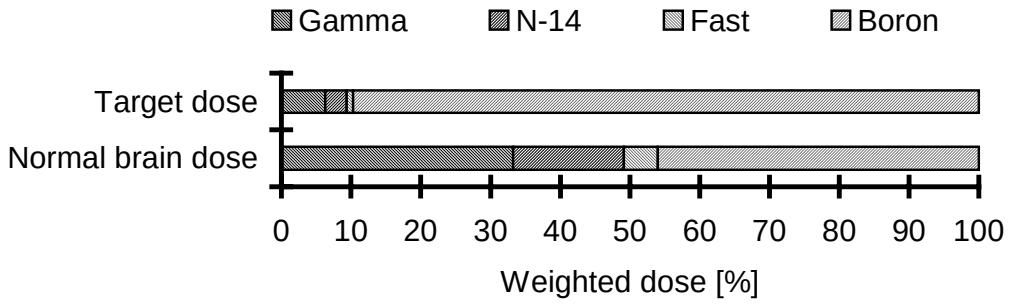
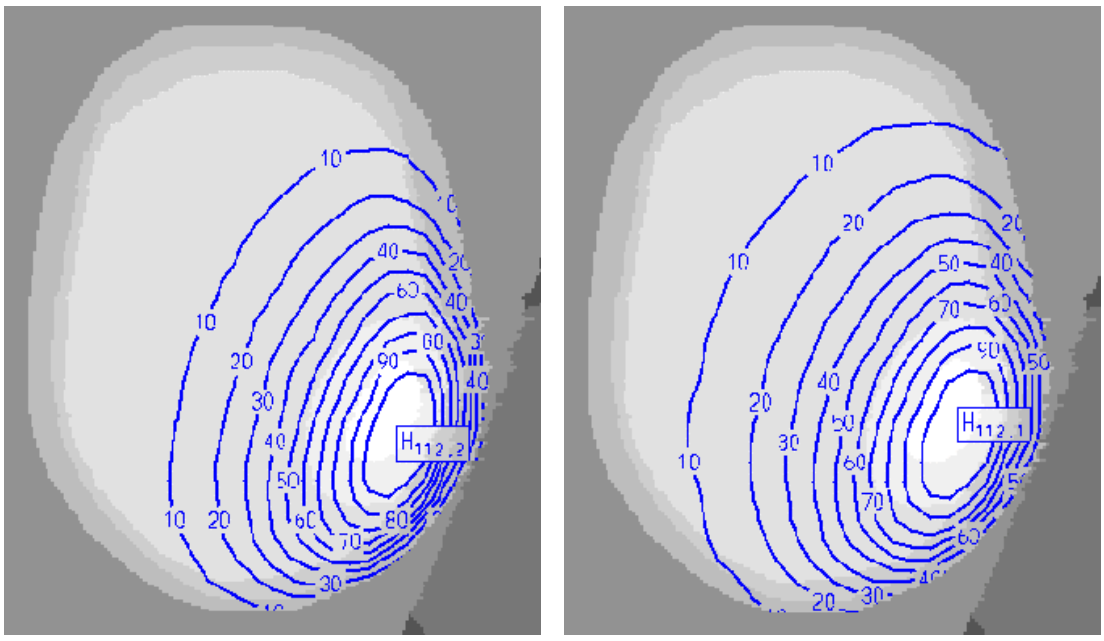


FIG. 2. Relations of weighted reference target and normal brain dose components in the human head. The reference doses are located at the thermal neutron maximum and are averaged over 1cm^3. The one field 11cm FiR 1 beamt is used in the calculation. The ^{10}B concentration in the blood is 12μg/g.



(a) (b)

FIG. 3. Weighted target (a) and normal brain (b) isodoses. At 100% the weighted target dose rate is 78 Gy (W)/h and the normal brain dose rate is 15 Gy (W)/h. The one field 11cm FiR 1 beam is used in the calculation. The ^{10}B concentration in the blood is 12μg/g. Tumour (white) and target are shown.

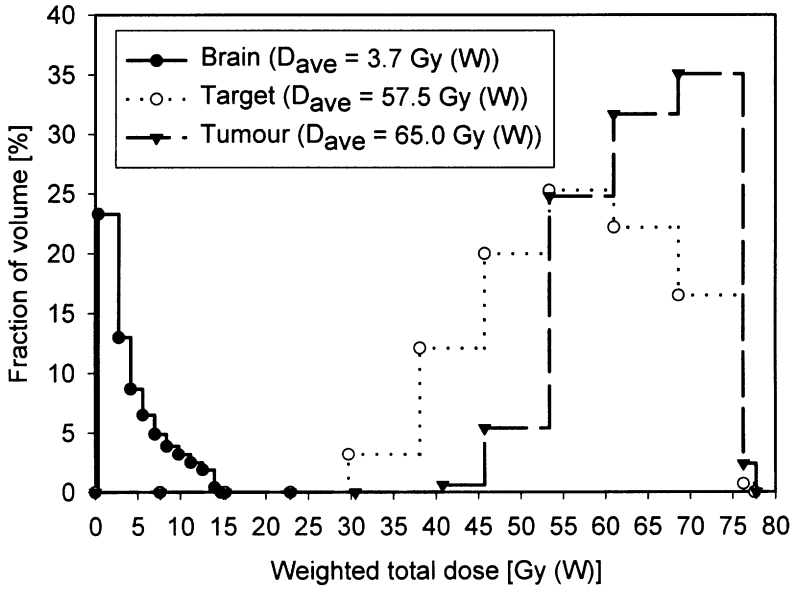


FIG. 4. Weighted normal brain, target and tumour dose volume histograms for the example dose plan. The volumes are for normal brain 1580 cm^3, target 125 cm^3 and tumour 35 cm^3. The one field 11cm FiR 1 beam is used in the calculation. The ^{10}B concentration in the blood is 12μg/g.

6. DISCUSSION AND CONCLUSION

In BNCT the total dose is the weighted sum of the absorbed doses originating from the neutron and gamma interactions in tissues. The doses in the clinical research of BNCT should be reported in such a way that the doses are comparable, traceable and can be recalculated, if underlying information, like weighting factors for dose components, are updated. To make the calculated doses comparable the dose calculation should be standardised. In this paper the methods of dose calculation and reporting of the glioma patients at FiR 1 are described. Our dose reporting scheme is in agreement with the one reported by Sauerwein et al. [22].

The accuracy of dose calculations was verified by phantom measurements beforehand. Activation foils (Au and Mn for epithermal and thermal neutron fluence), twin ionisation chamber technique (tissue equivalent chamber for neutrons and Mg(Ar) for gamma), thermoluminescent dosimeters (LiF:Mg,Ti for (relative) neutron fluence and ^{7}LiF:Mg,Cu,P for gamma) and a SiLi-detector for thermal neutrons were used in an extensive series of dosimetric phantom measurements [30-33]. All the measurements in the phantoms showed very good agreement to the calculated values from the treatment planning code [27,30-34]. The neutron transport calculations in the phantom were verified with the comparison of the calculation codes rtt_MC, MCNP and DORT[45]. The uncertainties of the measured rates (with IC) of absorbed dose to brain tissue in a water phantom were approx. 6% for gamma, and approx. 20% for neutrons at the depth of 25 mm in the phantom when using beam aperture 14 cm.

The DORT code was chosen for neutron source calculation based on the good experience in the modelling of the BMRR epithermal beam [46] where the distance from the reactor core to the beam exit is approximately same as at FiR 1 [47]. Using the fission power

of the reactor (250 kW) the DORT model very accurately predicts the behaviour of the neutron and gamma fields. The position for the source plane of the treatment planning code was chosen between the bismuth collimator and the phantom in a place, where the epithermal neutron fluence is most homogeneous in the radial direction [27].

Changes in the epithermal neutron beam geometry or significant changes in the fuel elements loading will require a new beam model and a new calibrated neutron-gamma source for the dose planning. In addition to calculations complete measurements are required at the free beam exit plane to get an overview of the changes in the neutron spectrum, and in the tissue substitute phantoms (water and PMMA) to verify the calculated dose/fluence distributions of the source model used for the dose calculation in the phantoms and in the patient.

At the low power 250 kW TRIGA reactor the burn up of the fuel elements and the secondary reaction products are insignificant during a one year period, therefore an intensity decrease or neutron spectrum change is not expected. However, the beam intensity and the ratio of epithermal and thermal neutrons are followed by routine measurements. In the routine measurements a few hours before the patient treatment the $^{197}Au(n,\gamma)$ and $^{55}Mn(n,\gamma)$ reaction rates are measured in the reference geometry. If the measured reaction rates differs more than 5% of the reference values, a new calibration factor for the calculation of the monitor units is used.

Using the Au activation detectors it has been experimentally shown that with the beam monitor unit method the neutron fluence in the reference geometry can be administered with a precision of 1–2%. The calibration factors for 11 and 14 cm beams separately were verified from the ratio of measured and calculated $^{55}Mn(n,\gamma)$ reaction rates at the reference geometry. The calibration factors defined from Au/Mn reaction rates agreed within 1.5%, i.e. less than the combined cross section uncertainties. As an other means to verify the stability of the beam monitors an IC-chamber neutron dose measurement in the reference phantom is performed daily after the patient irradiation. The combined uncertainty is estimated to be 6.3 % (1 SD %).

The single fraction weighting factors used clinically in the dose calculation at FiR 1 are the same that are used at the BMRR [37,48], because the BMRR epithermal neutron beam spectrum and intensity are most similar FiR 1 beam [46]. These weighting factors should be used as one set, because the nitrogen and fast neutron weighting factors are calculated assuming the gamma weighting factor one and the nitrogen and fast neutron equal [38]. The weighting factors should also be used with the “correct” tissue composition for the kerma factors.

For example, if weighting factors 3.2 is used both for the nitrogen and the fast neutron dose components with the ICRU brain composition for the kerma factors instead of originally used Brooks brain composition (section 3.4.), the weighted normal brain dose rate would be 0.5 Gy (W)/h higher.

The dosimetry procedure at FiR 1 can be considered to guarantee that the delivered physical doses in the treatments at the Finnish BNCT facility have metrologically traceable links to the international dosimetry standards. The uncertainties in the physical dose components in the BNCT can be estimated.

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