Requirements for Boron Neutron Capture Therapy (BNCT) at a Nuclear Research Reactor

Wolfgang A.G. Sauerwein and Ray L. Moss

BNCT TEAM

The European BNCT Project

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Printed in The Netherlands

Foreword

On 11-12 November 2005, a workshop took place in Prague entitled "Requirements for BNCT at a Nuclear Research Reactor", which was funded by the JRC's Enlargement and Integration Action. (E&IA). The intention of the workshop was to exchange knowledge between the EU BNCT programme at the HFR Petten and other existing clinical and preclinical research programmes on BNCT throughout Europe, with the special aim to transfer information towards groups and places that are preparing their own national BNCT projects.

The future of nuclear research institutes will depend on their ability to open research programmes into new areas and to link nuclear technologies with other applications. Medicine is one of the most interesting but also sensitive areas for such multidisciplinary work. Boron Neutron Capture Therapy (BNCT) is a dedicated and well-known topic that demonstrates such a link in an exemplary way.

This book expands on some of the topics presented at the workshop. It is intended to support scientists, clinicians and politicians that are interested to develop a local or national BNCT activity.

We would like to thank the Joint Research Centre of the European Commission, which has strongly supported the workshop and the publication of this book but especially some of the research activities and technological developments that can be reported here. We also thank Jiri Burian, Victor Nievaart and Andrea Wittig for the tremendous efforts they made to prepare the workshop.

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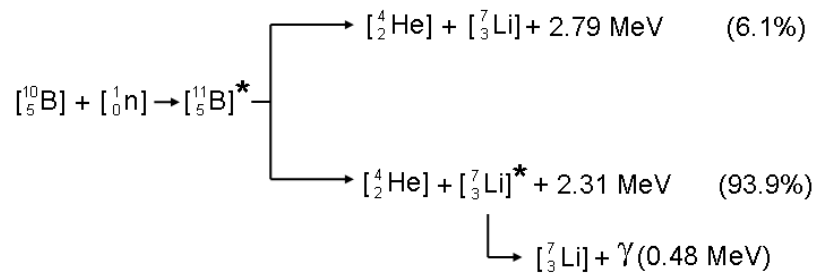
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1. Introduction
W. Sauerwein, R.L. Moss

Boron Neutron Capture Therapy is a binary form of radiation therapy using the high propensity of the non-radioactive nuclide boron-10 to capture thermal neutrons resulting in the prompt nuclear reaction $^{10}B(n,\alpha)^{7}Li$. The products of this reaction have high linear energy transfer characteristics (α particle approximately 150 keVμm^{-1}, ^{7}Li-nucleus approximately 175 keVμm^{-1}). The path lengths of these particles are in the range of 4.5 μm to 10 μm: hence resulting an energy deposition limited to the diameter of a single cell. Theoretically, therefore, it is possible to selectively irradiate those tumour cells that have taken up a sufficient amount of ^{10}B and simultaneously spare normal cells. The basic nuclear reaction in shown in more detail below:

$$[^{10}_{5}B] + [^{1}_{0}n] \rightarrow [^{11}_{5}B]^{*} \begin{cases} \rightarrow [^{4}_{2}He] + [^{7}_{3}Li] + 2.79\ \text{MeV} & (6.1\%) \\ \\ \rightarrow [^{4}_{2}He] + [^{7}_{3}Li]^{*} + 2.31\ \text{MeV} & (93.9\%) \\ \quad\quad\quad \hookrightarrow [^{7}_{3}Li] + \gamma\ (0.48\ \text{MeV}) \end{cases}$$

Shortly after the discovery of the neutron by Chadwick in 1932 [1] and the description of the $^{10}B(n,\alpha)^{7}Li$ reaction by Taylor and Goldhaber 1935 [2], the basic idea to use neutron capture reactions in cancer treatment was published by Locher in 1936 [3]. The first clinical applications in humans were performed in the USA from 1951 to 1961 [4], but were considered a failure. In 1968, Hatanaka started to treat patients suffering from malignant glioma [5]. He used the drug BSH and a thermal neutron source for intra-operative irradiation, which resulted in long survival in some of his patients. His pioneering work led to an increased interest around the world for investigating BNCT further. In 1987, BPA was introduced by Mishima in Japan to treat superficial melanoma with BNCT [6].

In the early 1990s, epithermal neutron sources were developed in the USA and Europe to treat deeper-seated tumours. These facilities created the conditions to start controlled perspective clinical trials in Brookhaven, Petten and Cambridge (MA) in 1996. These were soon followed by the creation of similar facilities in Finland, Sweden, the Czech Republic, Japan and Argentina where patients were treated. A far different approach was applied at Pavia where the thermal column at the TRIGA reactor was used to treat explanted livers with multiple metastases from colo-rectal cancer.

Despite all these activities, BNCT has still to be considered as an experimental modality and further research activities are mandatory to develop this promising idea to a clinically available therapy. To perform the clinical trials that are mandatory for such development, additional radiation facilities are necessary. This book addresses in particular the needs of such facilities and the on-going activities in Europe at nuclear research institutions interested in BNCT.

These developments are of increasing importance as some of the first epithermal neutron facilities mentioned above have been de-commissioned or under threat of closure. More often than not, these closures are due to political and economical reasons and not due to the clinical results.

The use of a research reactor for patient treatment is not only dependent on the engineering and physics aspects, but also on the regulatory issues strongly depending on national laws. The clinical trials themselves are highly complex, applying to a human patient "new", non-commercially available drugs and an irradiation beam not used in conventional radiotherapy. Some contributions in this book

attract the attention on these aspects that have to be considered at the moment at the moment when first discussions start if a nuclear research facility may host BNCT.

BNCT results in a highly complex dose distribution with different dose components having different biological effects. This challenging side of BNCT is addressed from the point of view of radiation biology and medical physics.

The key factor for success and failure in BNCT is the collaboration between very different disciplines, ranging from nuclear physics to surgery; from chemistry to radiation oncology; and from mathematics to radiation biology. Such a diverse collection of intellect requires dedicated coordination structures to develop the synergies needed to move forward. As an example, the Italian national programme on pre-clinical BNCT activities is included in this monograph.

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2. Organisational Aspects

BNCT requires the collaboration of specialists from different disciplines, who will have a very different education and, consequently, a different professional culture. At a first glance the combination of nuclear technology and medicine would appear to be the principle components, however other specialities have to contribute, which cannot be easily included in these two areas. The fact that individuals with no medical training will have to collaborate in the treatment of a patient is a major hurdle that cannot be overcome by organizational tools alone. This chapter describes aspects of organisational structure and of quality management based on the experience made in the European BNCT project in Petten that may be of general interest for groups who are developing a BNCT programme. Furthermore, due to the fact that either a new drug or a new radiation beam or a new facility will be used, special efforts have to be made on quality management, in order that the set-up at the facility and the personnel involved comply with similar practices in conventional radiotherapy departments. Currently worldwide, BNCT when applied to patients has to be seen as clinical research and hence has to fulfil and follow all legal and institutional requirements for this purpose, which may be different from one country to another. The principles however are internationally agreed and when selecting partners for BNCT, it must be assured that everybody complies with the regulatory requirements.

2.1 Interdisciplinary collaboration at a BNCT facility
W. Sauerwein, R.L. Moss

From a principle point of view and no matter worldwide, the application of BNCT in human patients needs 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. By treating patients a high responsibility and a risk associated with the resulting liability will be on each individual participant and institution. Such a situation can only be handled through contractual agreements, which must define unambiguously, the responsibilities and tasks of all the partners. It is recommended that all procedures are written in the form of Standard Operating Procedures (SOP) according to Good Clinical Practice.

In this chapter, the most important partners are enumerated and their tasks are briefly listed. These should be seen as indicative only and will certainly need to be adapted to reflect the local situation.

The Hospital – The Medical Partner
Patient treatment can only be performed together with a hospital and competent medical staff. Furthermore, the experimental nature of BNCT at present makes it mandatory that the hospital must have an academic background, with experience and a well-established reputation in oncology. To select such a hospital, it must be taken into consideration that in most countries clinical research may only be carried out by physicians and/or institutions with specialist qualifications, registered to perform clinical trials.

Radiotherapy
BNCT is one of the most complex forms of radiotherapy. Therefore, when starting a BNCT project, the participation of a radiation-oncology department is mandatory. It is a great advantage, if the radiotherapist involved already has some experience in treating patients with fast neutrons. Unfortunately, such 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 also must be taken into consideration that BNCT is not in the mainstream of current research in radiotherapy. In fact the

high complexity of BNCT requires tremendous effort and longer lead times regarding preparation and gaining sufficient knowledge prior to a clinician being able to safely apply BNCT to a patient. The situation is more difficult because no real clinical training on BNCT can be offered easily to a radiation oncologist willing to start in BNCT.

The main tasks where the radiation oncologist, who is in charge of BNCT, is involved are as follows:
- 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 take all necessary steps to obtain legal and ethical permits and licenses required for the implementation of the medical tasks for BNCT at a research reactor.
- to coordinate the work of the different participants, defining structure and organization of the clinical study and patient treatment. All staff members involved in patient treatment from 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.
- to organize the supply of medical consumables (e.g. gloves etc.) and drugs necessary for medical emergencies occurring in patients at the reactor site.
- to coordinate the treatment performed according to the approved protocol.
- to provide the proper and appropriate information about the treatment to the patients and to obtain the signed informed consent form.
- 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 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 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 accept the beam, before the patient is treated and for the duration of the irradiation, following the check-outs and physicist's reports
- to accept responsibility for the starting time and duration period of the irradiation of the patient, based on data provided by the persons responsible for correct data handling.
- to start the irradiation
- to take 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 take the overall responsibility for the medical aspects of the treatment. The radiotherapist 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 document all actions and all relevant data obtained concerning the patient. The hospital stores the patient's file according to the legal requirements (normally 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.

Medical Physics
The role of the medical physicist is to assure quality and safety of the medical use of ionizing radiation. The medical physicist supports the physician in his/her 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. Some aspects of the work are described in the EU Directive 97/43/EURATOM [1] and where the function is called the Medical Physics Expert. In all countries, special training leading to a formal registration is obligatory. However, such training normally does not include the special aspects of neutron dosimetry and never the special aspects of BNCT. Hence, collaboration between the medical physicist and reactor physicist is a pre-condition to treat a patient with BNCT. The reactor physicist will normally not fulfil the legal requirements to take over the responsibility for patient treatment.

It may be necessary and pragmatic to delegate tasks deriving from medical physics to one of the staff members of the reactor. However, the liability remains with the Medical Physicist, which makes the contract defining the collaboration very important.

The major tasks of the Medical Physicist are:
- to define and describe step by step, the dosimetry needed to fulfi l the requirements of the treatment protocol.
- to define and describe step by step, the quality assurance for all medical physics aspects of the treatment.
- to delegate tasks to staff members of the reactor as described in detail in the SOPs and to supervise their performance
- to design and approve the forms for documentation of the measurements, the recording and reporting of treatment planning and the actual treatment. This includes the physics 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.
- to be present at all treatments of patients and to participate at the preparation of the treatments for each individual patient.
- to be responsible for treatment planning calculations, for controlling the results and for the approval of the plan concerning the physical data.
- to perform the quality control calculations with the treatment planning system.
- to calculate in advance 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. The Medical Physicist also calculates the time of start and end of irradiation based on the analysis of boron concentration in blood.
- to calculate from the approved treatment plan, the data for correct positioning of the patient.
- to calculate the actual dose given to the patient on the basis of the boron concentration of blood taken before and after the irradiation.
- to document all actions and data obtained from the measurements and calculations, which have to be archived by the participating hospital.
- to establish and apply a quality control system for clinical dosimetry, including regular checks of different devices (for example, the on-line monitoring equipment).
- to participate in every relevant meeting and audit concerning the treatment of patients and the radioprotection of the medical area at the reactor.

Pharmacy
Currently, the available boronated compounds for BNCT are experimental drugs and cannot be used without special permission of 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 at the participating hospital is mandatory. The pharmacy has to be licensed to handle and prepare the experimental drugs and needs the necessary equipment to perform the analyses for the quality control.

The need of this experienced partner who has to be licensed for this special task cannot be stressed high enough.

The pharmacy organises the drug supply. Supplying companies must produce the compound according to Good Manufacturing Practice (GMP), which will include a drug master file and written procedures for preparation and quality control of the final product and its intermediates. Additional requirements need to be fulfilled if the drug is imported from another country.

The responsibility for the final preparation of the infusion applied to the patient, 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. All actions have to be documented following the legal requirements.

Other medical disciplines
The performance of BNCT requires not only the above mentioned specialists but also: surgeons, who select, operate, prepare and provide the follow-up of the patients; anaesthetists; pathologists and diagnostic radiologists familiar with the procedure; nurses to take care of the patient; ambulance drivers to take the patient to the reactor, etc.

To perform clinical trials, additional substantial resources and personnel must be available, e.g. data manager, monitors, external experts for audits, study nurses, radiographers and others.

The Reactor – The Nuclear Partner
The owner of the reactor has in addition to his "normal" tasks and duties specific responsibilities and liabilities towards the patient. The owner has to realise that when a patient is treated at the reactor, the reactor becomes a medical instrument, which adds a different dimension to the owner's normal nuclear activities.

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 cooperation but especially about all changes that may influence the treatment.

The reactor owner therefore:
- is responsible for the reactor, the delivery of neutrons, the BNCT facility and the working environment around the facility, i.e. security, radioprotection and safety,
- is responsible for ensuring that these facilities function correctly and that the associated working conditions conform to recognized standards,
- ensures that the quality assurance of the facility, measurements and presentation of data, e.g. check-outs, prompt gamma ray analysis, dosimetry, etc., conforms to acceptable standards,
- nominates a central contact person, who acts as liaison officer between the BNCT technical group at the reactor site and the medical staff.

The tasks can be listed in more detail according to the following topics.

The reactor
The owner of the reactor:
- is responsible for the safe functioning of the BNCT facility and the production of neutrons,
- ensures that the reactor operates as required and that the neutrons are delivered at the defined energies and fluences,

- is responsible for the maintenance and upkeep of the facility, and ensures that these are accomplished punctually,
- defines the schedule of the reactor and informs the radiation oncologist on interruptions in reactor operation
- informs reactor personnel of pending treatment, of 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 during treatment,
- collates and documents relevant information and data

The Beam
The owner of the reactor:
- 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 (if applicable),
- 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 clinicians,
- performs a check out according to a defined checklist described in the relevant Standard Operating Procedures (SOP's) before the facility is used for irradiation.
- 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.)

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,
- installs all infrastructures on patient Radiation Protection, following the legal requirements,
- establishes a contract with the participating hospital concerning the radiation protection of the medical personnel,
- informs the external personnel coming to the reactor site for purposes of BNCT of reactor safety measures, including reactor hall evacuation procedures,
- 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 should include the availability of suitable working space on-site,
- 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). The beam users are obliged to follow the instructions from the reactor staff regarding non-medical aspects
- monitors and records the radioactivity of the patient after treatment,

Boron analysis
It is advised that equipment is available to measure the boron concentration in blood during the treatment, for example a prompt gamma ray facility. Other means to measure boron in blood, e.g. ICP-OES, may be an alternative provided the results become available in a reasonable time. The maintenance of the facility must be organized and its correct function needs to be controlled and documented.

Coordination

BNCT is a highly complex type of radiotherapy, requiring a multi-disciplinary and multi-institutional effort. It must be organised in a strict and regulated way so as not to have any uncertainties in responsibility, liability, safety and legal issues. Such an organisation can only function efficiently if a dedicated coordination structure is established.

References

[1] Health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, EU Council Directive 97/43/EURATOM (30th June 1997),

2.2 Regulatory affairs and Licensing for a BNCT facility

W. Sauerwein

One of the most complex organisations realized to perform BNCT was created for the BNCT trials performed at the European Commission's HFR in Petten. Some major aspects of the regulatory work is described here in the sense of a "worst case scenario". The multinational situation in Petten will provide information including bottlenecks, which also would apply nationally.

Organisational structure and administrative obstacles

The project in Petten was formulated such that 6 different hospitals from 5 different countries (Austria, France, Germany, Switzerland and The Netherlands) enter patients into the studies [1]. Because of the high costs, in the second protocol, the number of participating hospitals was reduced to 2 from 2 countries (Germany and The Netherlands). The treatment was performed by the Department of Radiotherapy of the University of Essen (Germany) at the HFR Petten, which is owned by the European Commission and located in The Netherlands. During the period of treatment, patients were hospitalised at the Vrije Universiteit medische centrum VUmc in Amsterdam. The studies were carried out following approved protocols of the European Organisation for Research and Treatment of Cancer (EORTC) BNCT Study Group [2]. The monitoring and data management of the trial were performed by the NDDO Oncology (Amsterdam) and the EORTC (Brussels). The studies were financed by the European Commission's Framework Programmes (FP4 and FP5) and money from the budgets of the participating institutes. The treatment in Petten was carried out in co-operation with the Joint Research Centre (JRC) of the European Commission and the Netherlands Energy Research Foundation (ECN), under the overall clinical responsibility of the Department of Radiotherapy of the University of Essen which also provided the Medical Physicist. The co-operation of all these institutions, their different tasks and responsibilities were agreed by contract. The overall structure, indicating the principal functions and relevant responsible institutes, is shown in Figure 2.2.1.

To obtain approval for such a complex multi-national project was extremely difficult and time consuming. The initial application to the Dutch Health Ministry 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 unambiguously the issues that had to be addressed. 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.
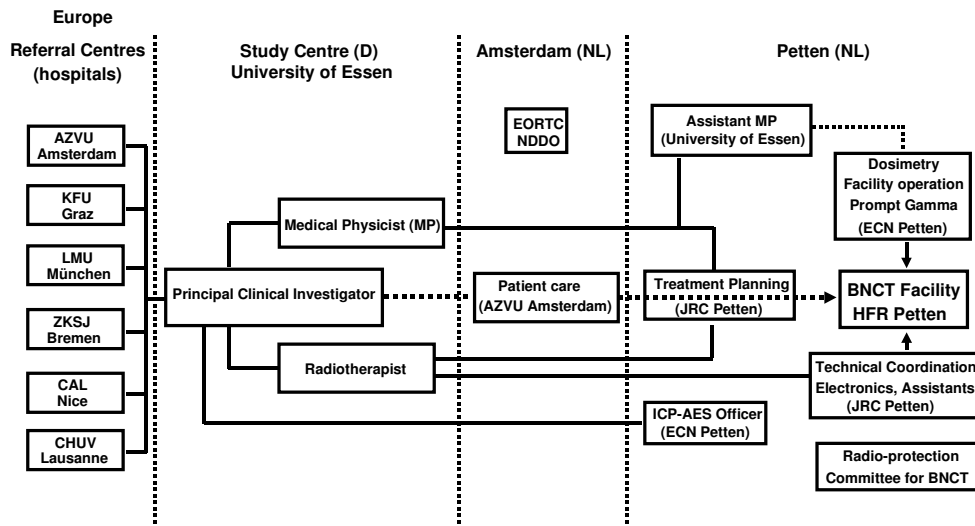
Figure 2.2.1 : Organisational Structure for the BNCT Trials at Petten
(for abbreviations see footnote)[3]

The issues, which finally had to be solved are listed briefly below:

- 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 following the relevant ICH guidelines [3] as published by the European Medicines Agency (EMEA) [4]
  - 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.

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[3] AZVU - Academisch Ziekenhuis Vrije Universiteit, Amsterdam
  KFU - Karl-Franzens-Universität, Graz
  ZKSJ - Zentralkrankenhaus St.-Jürgen-Straße, Bremen
  LMU - Ludwig-Maximilians-Universität, München
  CAL - Centre Antoine Lacassagne, Nice
  CHUV - Centre Hospitalier Universitaire Vaudois, Lausanne
  NDDO — New Drug Development Office
  JRC — Joint Research Centre, European Commission
  ICP-AES — Inductively Coupled Plasma - Atomic Emission Spectroscopy
  ECN — Netherlands Energy Research Foundation (later named NRG)

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

- Personnel and Institutional related:
  - o licensing of foreign physicians to treat patients in The Netherlands, being themselves staff members of a non-Dutch institution (Essen University, Germany),
  - o enabling a non-Dutch Medical Physicist to be responsible and liable for Medical Physics at the HFR Petten,
  - o 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,
  - o applying the appropriate rules for radio-protection of the patients and the staff, respecting both German and Dutch regulations,
  - o concluding contracts, subcontracts, associated contracts, collaboration agreements, etc. with all involved parties, following the rules established by the European Commission for Shared Cost Actions.

An overview of the agreements, which had to be drawn up between the various parties is shown schematically in Figure 2.2.2, where the complexity of the interactions is more than apparent.

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.
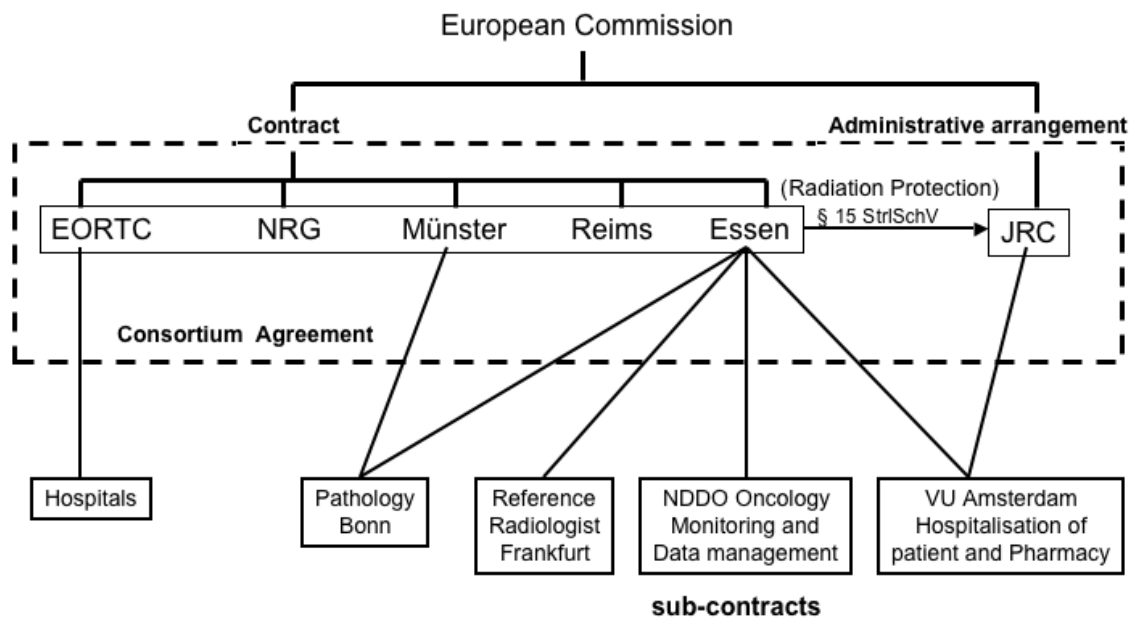
Figure 2: Schematic Overview of the concluded inter-institutional contracts

Insurance
Special care has to be paid to establish insurance cover for, at least, the following aspects:

- Nuclear incidents
- Insurance for patients in clinical trials
- Liability for reactor staff interacting with patients/being involved in patient treatment
- Liability for staff members from the hospital working at the reactor
- Liability for further specialists needed, who are not staff from the hospital or the reactor
- Accident cover for hospital staff during travel to the reactor and work at the reactor
- Accident cover for patients between hospital and reactor

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[2] Sauerwein W., Zurlo A. on behalf of the EORTC Boron Neutron Capture Therapy Group (2002): The EORTC Boron Neutron Capture Therapy (BNCT) Group : achievements and future projects. EJC 38, S31-S34

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) http://www.ich.org/cache/compo/276-254-1.html

[4] European Medicines Agency (EMEA) http://www.emea.europa.eu/

2.3 Quality Assurance for BNCT

W. Sauerwein, J. Rassow, F. Stecher-Rasmussen

The EU Council Directive on Health Protection 97/43/EURATOM requires radiotherapy quality assurance programmes for performance and safety of radiation units, including testing of performance characteristics on a regular basis (quality control).

Whilst all BNCT facilities worldwide are presently located at a nuclear research reactor, they are nevertheless, to all intents and purposes, radiotherapy units. Following local and/or national regulations, the BNCT facilities have been licensed to treat patients. Therefore, as part of the licensing procedure, QA procedures, or at least well-documented procedures, are needed in which the testing of certain performance characteristics, especially all dosimetry aspects, as well as treatment planning, is written down as Standard Operating Procedures or similarly accepted procedures. As an attempt to generate dosimetry guidelines a European Consortium has produced recommendations for the dosimetry of BNCT [1].

International Standards for Quality Assurance in Radiotherapy
The performance of BNCT requires the application of national and international rules of safety and quality assurance for nuclear research reactors, for radiation protection, for radiotherapy and for clinical trials.

The nuclear reactor part is well defined and understood as well as aspects of radiation protection, although specific requirements from reactor safety conditions impose design and safety considerations beyond the conditions of accelerator based facilities. The application of established standards and rules for radiotherapy to BNCT, however, is challenging and few publications have been dedicated to this subject [2-4]. There are no international standards dedicated to BNCT, it is therefore a highly important task to transfer - as far as is possible – analogously rules from conventional radiotherapy to BNCT. This work should be done in a very close collaboration with the national regulatory authorities and supervising bodies.

In particular, it is recommended to establish quality assurance of safety provisions and functional performance characteristics conform to the most recent concepts and regulations of IEC publications or applicable national standards. The following IEC standards and technical reports will help for guidance:

For safety
IEC 60601-2-1 Ed.2:1998 [5] Medical electrical equipment - Part 2-1: *Particular requirements for the safety of electron accelerators in the range 1 MeV to 50 MeV.*

This international standard establishes requirements to be complied with by manufacturers in the design and construction of electron accelerators for use in radiotherapy and defines type tests and site tests. Places limits on the degradation of equipment performance beyond which it can be presumed that a fault condition exists and where an interlock then operates to prevent continued operation of the equipment.

*For performanc*e
Acceptance tests:
IEC 60976: 2007 [6] *Medical electrical equipment - Medical electron accelerators - Functional performance characteristics*. EC 60976 applies to medical electron accelerators when used, for therapy purposes, in human medical practice.

This standard has been developed to medical electron accelerators, which deliver a radiation beam of either X-radiation or electron radiation with nominal energies in the range 1 MeV to 50 MeV at maximum absorbed dose rates between 0.001 Gy s^{-1} and 1 Gy s^{-1} at 1 m from the radiation source and at normal treatment distances between 50 cm and 200 cm from the radiation source. Therefore careful interpretation is needed prior to apply aspects of the standard to an epithermal neutron beam. It describes measurements and test procedures to be performed by the manufacturer at the design and construction stage of a medical electron accelerator, but does not specify acceptance tests to be performed after installation at the purchaser's site. The accompanying report, IEC 60977, however, does suggest that many of the test procedures are appropriate for acceptance tests. The measurement conditions described in the standard from 2007 differ from those previously in use. This applies particularly to the phantom position for measurements and the measurement of distances from the isocentre. These new conditions should also be used whenever possible in BNCT. This standard specifies test procedures for the determination and disclosure of functional performance characteristics, knowledge of which is deemed necessary for proper application and use of a medical electron accelerator and which are to be declared in the accompanying documents together with the greatest deviation or variation to be expected under specific conditions in normal use. In an analogous way the expected deviation and variation of a (epi)thermal beam should be defined prior clinical applications.

An important aspect has been introduced by IEC 60976, which recognized that inaccuracies in the test methods must be allowed for when assessing performance. However, it is not advised to combine the errors into an overall performance tolerance but recommended to keep them separate in the expectation that more accurate test methods will be evolved. It is especially mentioned that this standard does not intend in any way inhibit the future development of new designs of equipment which may have operating modes and parameters different from those described herein, provided that such equipment achieves equivalent levels of performance for the treatment of patients. The latter sentence applies to BNCT. It is assumed in this standard that the irradiation facility has an isocentric gantry, which is not the case in BNCT. It is however explicitly mentioned that where the equipment is non-isocentric, the description of performance and test methods may need to be suitably adapted.

Consistency tests:
IEC/TR 60977 Ed. 2.0:2008. *Medical electrical equipment - Medical electron accelerators - Guidelines for functional performance characteristics* [7]. IEC/TR 60977 applies to medical electron accelerators when used, for therapy purposes, in human medical practice.

This technical report applies to medical electron accelerators which deliver a radiation beam of either X-radiation or electron radiation with nominal energies in the range 1 MeV to 50 MeV at maximum absorbed dose rates between 0,001 Gy s^{-1} and 1 Gy s^{-1} at 1 m from the radiation source and at normal treatment distances between 50 cm and 200 cm from the radiation source. This second edition likewise follows on the issue of a second edition to the disclosure standard IEC 60976 in 2007. It includes the addition of performance guidelines relating to several relatively new technologies introduced within the last few years, including dynamic beam delivery techniques, such as moving beam radiotherapy, intensity modulated radiation therapy (IMRT), image guided radiotherapy (IGRT), and programmable wedge fields (PWF). Also included are stereotactic radiotherapy (SRT)/stereotactic radiosurgery (SRS) and the use of certain electronic imaging devices (EIDs), but of course does not mention BNCT.

Data transfer and data handling, coordinates and scales:
IEC 61217 Consol. Ed. 1.2:2008. *Radiotherapy equipment - Coordinates, movements and scales* [8].

IEC 61217 applies to equipment and data related to the process of tele-radiotherapy, including patient image data used in relation with radiotherapy treatment planning systems, radiotherapy simulators,

isocentric gamma beam therapy equipment, isocentric medical electron accelerators, and non-isocentric equipment when relevant. The object of this standard is to define a consistent set of coordinate systems for use throughout the process of tele-radiotherapy, to define the marking of scales (where provided), to define the movements of equipment used in this process, and to facilitate computer control when used. The problems raised by this international standard are of high importance for BNCT, especially when hospital based systems (CT, MRI, treatment simulators) are used to prepare a patient for BNCT at the reactor.

Radiotherapy treatment planning systems (RTPS):
IEC 62083 Ed. 1.0: 2000. *Medical electrical equipment - Requirements for the safety of radiotherapy treatment planning systems* [9].

An RTPS is principally a software application, and the object of this standard is to establish the requirements for features, associated documentation, and testing of the software. This standard applies to the design, manufacture and some installation aspects of an RTPS, i.e.:
- for use in radiotherapy treatment planning in human medical practice;
- that imports data either through input by the operator or direct from other devices;
- that outputs data either in printed form for review or direct to other devices;
- and which is intended to be used under the authority of appropriately licensed or qualified persons, by operators having the required skills and training; maintained in accordance with the recommendations given in the instructions for use, and used within the environmental and electrical supply conditions specified in the technical descriptions.

Treatment room:
IEC/TR 61859 Ed. 1.0:1997. *Guidelines for radiotherapy treatment rooms design* [10].

This technical report applies only to those aspects of the installation ensuring the safety of the patient, the operator and other persons during the radiotherapy equipment use. The installations considered are those in which are located radiotherapy equipment delivering ionizing radiation used for therapeutic purpose, such as medical electron accelerators, gamma beam therapy equipment and gamma-ray after-loading equipment. It should be considered when designing the radiation room for BNCT.
Quality control programmes, especially for medical electron accelerators are adopted internationally as the already quoted IEC publications. BNCT must follow the same or similar procedures. Furthermore, in following such procedures, this will increase the confidence and reassurance of radiation measurements at the BNCT facility and hence the accuracy of the dose given to the patient.

With respect to quality control procedures related to the beam calibration and patient dosimetry (functional performance characteristics) it can be stated that despite the relatively more complex dosimetry of BNCT, many performance and safety characteristics associated with medical electron accelerators show dependencies on irradiation and operational parameters that are not relevant for BNCT facilities. In fact, quality control for BNCT facilities covers less parameters than that for accelerators [2]. It is therefore or should be somewhat more trivial to set up a BNCT quality control procedure than for a medical electron accelerator. This is because a BNCT facility has only one constant primary radiation quality, a nearly constant absorbed dose rate (at least during the period of treatment, e.g. during a reactor cycle such as at the HFR Petten, where the fluence rate decreases 6% over 24 days [11], just one fixed horizontal beam without gantry and no beam modifying devices, apart from a few different collimator sizes. Rassow et al. [2] showed in detail the comparison between the performance and safety characteristics of medical electron accelerators and a BNCT facility, and in particular for dose delivery, as well as against stray radiation.

Recommendations for a quality control programme, i.e., the functional performance characteristics to be tested, their tolerance values and test frequencies, are given in Tables 2.3.1 -2.3.3. The parameters

are strongly based on the work of Rassow et al [2] and on adopting a sensible approach towards realistic measurable parameters.

The beam calibration for all radiation components shall be carried out initially and, in principle, need not be repeated. However, for reassurance and credibility it is recommended to repeat the comprehensive, initial beam calibration on an annual basis or under certain circumstances, when, for example, important modifications have been introduced in the core configuration. It should not be, as in medical electron accelerators, where similar initial measurements are performed once and only once during the acceptance test. For a nuclear research reactor, where beam characteristics can be influenced by changes in the configuration of the reactor core, e.g. fuel loading and experimental set-up, a more pragmatic approach is needed.

The BNCT Irradiation Facility at Petten
The practical transfer of some of the above mentioned aspects will briefly be reported at the example of the BNCT irradiation facility in Petten, where the treatment of the patient takes place at the HFR, 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.

To satisfy the requirements for BNCT, a specially designed filtered beam tube and irradiation room have been built at one of the eleven horizontal beam tubes located around the reactor. The radiation room has been constructed and equipped to reflect as close as it was reasonably possible in such an environment, the standards and practices associated with conventional radiotherapy centres. Installed equipment includes cameras, intercoms, microphone, electro-optical laser positioning devices, therapy table, on-line beam monitors and instrumentation to monitor the patient's pulse and oxygen pressure in the blood during the irradiation.

Table 2.3.1:   Functional performance characteristics according to IEC 60976 as relevant for BNCT treatment (for medical electron accelerators recommended tolerance values taken from IEC/TR 60977 or, if energy dependent, to be declared by the manufacturer, for BNCT actual values of the Petten beam). For parameters of depth absorbed dose characteristics and uniformity of radiation field, which must be measured only once initially, it is part of the quality assurance program to verify that the energy spectrum of intermediate neutrons is stable ($<\pm$ 2%, long: monthly, short: weekly) and the input for calculations of dose components is correct and results are not changing in time (monthly).

Performance characteristic	Medical electron accelerator	BNCT at nuclear reactor
Dose monitoring system (two totally independent detectors for the sole or at least the most two relevant dose components) • reproducibility • proportionality • stability of calibration throughout the week	• two transmission ionisation chambers (X-radiation, electrons) • 0.5% (6-monthly) • 2.0% (6-monthly) • 2.0% (weekly)	• two fission chambers [f_1, f_2] (neutrons) • two Geiger-Müller counters [GM1, GM2] (gamma-radiation) • 0.5% (weekly) • 0.5% (6-monthly) • 2% (weekly, short: daily)
Depth absorbed dose characteristics • depth dose maximum • penetrative quality (depth of 80% dose) • relative surface dose	• maximum deviation from declared value • (energy dependent) cm • 3 % or 3 mm (short: weekly) • (energy dependent) % (all: 6-monthly)	• agreement of measurement and calculation for all dose components tested only once initially • (calculated) cm • (calculated) % • (calculated) % (all: monthly)
Uniformity of radiation field • square radiation fields (ratio maximum to mini-mum dose in the flattened area in 10 cm depth of phantom) • symmetry within square radiation fields • maximum ratio of absorbed dose anywhere to central axis in plane of depth dose maximum • penumbra of radiation fields (distance of 80% to 20% dose points	• (for X-rays) • 106 % (≤ 30 cm x 30 cm) • 110 % (> 30 cm x 30 cm) • 103 % (all: 6-monthly, short: weekly for X-radiation) • 107 % (≤ 30 cm x 30 cm) • 109 % (type test) (> 30 cm x 30 cm) • (energy dependent) mm (6-monthly for X-radiation)	• agreement of measurement and calculation for all dose components tested only once initially • (calculated) % • (calculated) % • (calculated) % • (calculated) mm • (calculated) mm (all: monthly)
Indication of central axis for entry X-ray beam entry electron radiation exit X-ray beam	• 2 mm • 4 mm • 3 mm (all: monthly)	• 2 mm (weekly, resp. for each patient)
Movements of patient table • maximum difference of table height for different load	• 5 mm (monthly, if important)	• 2 mm (weekly, resp. for each patient)

Table 2.3.2: Safety requirements for equipment functions according to IEC 60601-2-1 Ed.2, as relevant for BNCT treatment. (Interlock causing prevention of irradiation if a device is not correctly pre-selected, displayed or adjusted. Automatic termination if safety tolerance limit is exceeded)

Requirement	Medical accelerator	BNCT at nuclear reactor
• Monitoring absorbed dose (capable for termination)	• double monitoring system: $\pm$ 5% deviation	• double monitoring system $\pm$ 5% deviation
• Controlling timer	• 120% t_{plan} or $\Delta t = 0.1$ min (the greater)	• 102% t_{plan} ($\Delta t \approx 0.4$ min)
• Control of equipment use	• control by key (or pass word) • treatment room door switch	• the same (as for medical electron accelerators)
• Starting conditions	• key use • preselection of all operating parameters: ready state • all interlocks closed • start by operator only	• the same
• Interruption	• possible for later continua-tion without re-selection of operating parameters	• the same
• Termination	• stop of irradiation (and movements) with return to preparatory state (re-selection necessary) • automatic stop if operating parameters are adjusted	• the same
• Abnormal termination	• specific display of cause • warning • no further use possible without key	• the same
• Programmable electronic sub-systems (PESS)	• specific requirements	• the same

The electrical installation has been carried out according to the Dutch safety regulations of NEN 3134(21) on medical installations of Class S2 [12].

Additional instrumentation, critical to the operational safety of the facility, includes radiation monitors and safety interlock systems to control the critical structural components and radiation components, such as the filtered beam components, the beam shutters, the radiation beam, the dose rate in and around the facility, as well as automatic closure of the beam shutters if room entrance procedures are violated. The room has been designed with the safety of the patient and personnel uppermost.

The performance standard of the required work and operational equipment, especially with respect to its accuracy, reliability and quality, have been implemented to conform with accepted standards in quality assurance and control.

Table 2.3.3: Safety requirements against stray radiation according to IEC 60601-2-1 Ed.2, as relevant for BNCT treatment

Requirement	Medical electron accelerator	BNCT at nuclear reactor
• Protection against stray radiation	• Specific requirements (for X-radiation and electron irradiation)	• Automatic actions for gross malfunction of Ar-filter • Ratio of indicated values from GM counter to fission chamber
• Leakage radiation through beam limiting devices and in patient plane (area M: $\phi = 2$ m)	• 2% D_{max} (at central axis in phantom at normal treatment distance [NTD] for 10 cm x 10 cm radiation field) • average 0.5% D_{max} in plane M (with shielded residual aperture)	• 8% D_{max} (free beam measurement with TE/TE ionisation chamber for collimato $\Phi = 12$ cm) • 0.7% D_{max} (without shielded residual aperture, thus with backscatter)
• Leakage radiation outside area M in patient plane	• maximum 0.2% D_{max} • average 0.1% D_{max} • maximum 0.05% D_{max} (neutrons) • average 0.02% D_{max} (neutrons)	• < 0.001 $D_{T,max}$ (for closed primary and secondary shutter) ($\hat{=}$ < 2 μSv/h anywhere in the treatment room)
• Leakage radiation outside patient plane	• 0.5% D_{max} in 1 m distance from electron path way and reference axis • 0.05% D_{max} (neutrons)	
• Emission of ionizing radiation after termination due to induced radioactivity	• dose equivalent integrated between 10 s and 10 min after termination • 10 μSv in 5 cm from surface of equipment • 1 μSv in 1 m from surface of equipment	• dose equivalent integrated between 10 s and 10 min after termination • 10 μSv in 5 cm from surfac of phantom • 0.9 μSv in 1 m from surfac of phantom
	• dose rate equivalent averaged between 10 s and 3 min after termination • 200 μSv/h in 5 cm from surface of equipment • 20 μSv/h in 1 m from surface of equipment	• dose rate equivalent averaged between 10 s and 3 min after termination • 75 μSv/h in 5 cm from surface of phantom • 7.5 μSv/h in 1 m from surface of phantom

The design of the whole facility has been 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 has been reviewed and positively assessed by the appropriate national body at the Ministry of Social Affairs (SZW), who assessed the facility on the basis of site-visits and documentation, which described the facility in detail, including the justification for BNCT, its conformance with the requirements of radiation protection and the organisational structure, where the medical and radio-protection responsibilities are clearly defined.

Prior the first patient treatment, the facility had a site-visit by an independent physician with great personal expertise in clinical applications of BNCT, which resulted in several optimisation steps.

In 1998 the facility became a licensed Quality Management (QM) site according to ISO 9001. The audit was carried out by JRC QM officers, who looked at, amongst other topics, the documented files on design, manufacture, testing, operation and maintenance. Documentation files consisted of:

- Items (lists of components on design, function, geometrical description and safety features);
- Function (functional descriptions);
- Design (calculations, as-built engineering drawings and lists of drawings);
- Manufacture (fabrication and control plans from various manufacturers, materials certificates and manufacturer's name);
- Testing (functional tests, carried out at the manufacturer or at Petten, plus installation and commissioning tests);
- Operation (operating manuals and check-out procedures on all technical issues);
- Maintenance (facility maintenance, especially the critical components, such as the argon system and where appropriate, strict maintenance programmes, as described by the HFRs Periodical Preventive Maintenance system);
- All relevant up-to-date documentation is found in controlled and approved Source Files.

Standard operating procedures

Standard Operation Procedures (SOP) describe step-by-step all relevant procedures concerning the performance of BNCT and the execution of the clinical trial, following the guidelines of Good Clinical Practice [13, 14]. All SOPs are collected in one dossier that has to be available at any time for each staff member.

As an example the main items of the actual SOP's at the Petten BNCT facility are listed below, for 2 items ("General" and "Treatment at the HFR and Follow-Up") all SOPs are mentioned.

1 General
      101 Documentation
      102 Language
      103 Code for information release to press, radio and television
      104 Addresses of investigators and staff members
      105 PTB clock time
2 Ethics
3 Preparation for a Study
4 Treatment Preparation and Surgery
5 Treatment at the HFR and Follow-Up
      501 Free Beam Characterization
      502 Neutron beam facility maintenance
      503 Communication between Facility Operator and medical staff
      504 On-line beam monitoring and beam shutter control
      505 BNCT-Wing at the HFR Petten - provisions and procedures
      506 Neutron beam facility operation
      507 Boron Analysis by Prompt Gamma Ray Spectroscopy
      508 Positioning of patient
      509 In-vivo dosimetry
      510 Calculation of beam monitor units and irradiation time
      512 Timing of BSH infusion in relation to projected treatment time and amount to be administered
      513 Health physics check of patient and hospital staff
      514 Irradiation summary
      515 Reactor hall evacuation
      516 Transport of patients
      517 Security checks for patients and accompanying personnel at the JRC site and the reactor
      519 Patient preparation for BNCT at Petten

For clinical trials as well as for physical measurements, the clock time is sometimes an important factor. This is particularly important for BNCT using neutron activation monitors as part of the beam calibration system. In order to exclude misunderstandings, the legal clock time for Germany was used, given by radio as Central European Time from the Physikalisch-Technische Bundesanstalt (PTB). Radio controlled clocks were available at the places where it was necessary SOP 105).

Clinical trials

Quality management for clinical trials is mainly regulated by guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. ICH guidelines are submitted to the Committee for Human Medicinal Products (CHMP) for endorsement once they have reached Step 2 or Step 4 of the ICH Process. The CHMP, in consultation with the European Commission decides on the duration for consultation with interested parties (up to 6 months). The European Agency for the Evaluation of Medicinal Products (EMEA) publishes and distributes the Step 2 guidelines for comments. At Step 4 the guidelines are endorsed by the CHMP and a timeframe for implementation is established (usually 6 months). The guidelines are subsequently published by the European Commission in the Rules Governing Medicinal Products in the European Union (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm). Step 2 and Step 4 guidelines are available from the EMEA site on the Internet:
(http://www.emea.europa.eu/htms/human/ich/background.htm).

Concerning the use of unregistered medicaments and the description of all the regulatory aspects, which have to be taken into consideration, cannot be the aim of this brief overview. Nevertheless, this very important aspect, the competence and time needed to handle it correctly has to be especially emphasized. It furthermore has to be underlined that in BNCT in addition to the drug aspect the use of a non-conventional radiation beam will add a supplementary challenge for regulatory authorities. The time needed to have a trial protocol accepted cannot be overestimated. It is strongly recommended to start these procedures already during the early discussions when a BNCT facility might be built. A close collaboration with the regulatory authorities is mandatory from the beginning.

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2.4 Radiation Protection
W. Sauerwein, R.L. Moss

The European clinical trial (EORTC 11961) of BNCT for glioblastoma patients started at Petten in October 1997 [1]. The treatment of a patient and the potential exposure of personnel to ionising radiation require by the national Nuclear Energy Law that the JRC (as licence holder of the HFR) must ensure that radiological protection and monitoring of all personnel, including external staff, is provided and that the correct radiation protection measures are taken and followed.

Due to the structure of the European trial, where the treatment takes place at a facility in the Netherlands under the responsibility of clinicians from Germany, it had to be demonstrated that measures taken satisfy both German and Dutch radioprotection laws. To respect both laws, a BNCT radioprotection committee was formed under the chairmanship of an independent radioprotection expert, with members representing all disciplines in the trial. A contractual agreement had to be signed between the German institute (University of Essen) and JRC Petten to guarantee that procedures to be followed complied with German radioprotection regulations (Strahlenschutzordnung §20).

During BNCT, both the patient and the supporting treatment tools, such as mask and therapy table, become radioactive. As such, measurements of the patient and surrounds are taken at regular intervals

after treatment, checked and an appropriate form completed and reported to the BNCT Radioprotection Committee.

As at the HFR, BNCT worldwide is performed using mixed neutron/gamma beams at nuclear research reactors. The mixed beam must be thoroughly and regularly characterised, using dosimetry techniques in addition to those of conventional radiotherapy. Furthermore, the complex beam and subsequent dose distribution in the patient are modelled using treatment planning codes based on programs developed for nuclear applications, e.g. MCNP [2].

To improve radiological protection of the patient and staff, investigations are continuously in progress to fully characterise the beam (using activation foils, ionisation chambers, TLDs) and to determine the boron distribution in the patient using on-line prompt gamma ray spectroscopy.

To conform with the Dutch regulations on radio-protection, a 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 any external authority. The Committee consists of members from each discipline in the BNCT group, and is chaired by an independent expert in radio-protection.

Due to the fact that German staff from Essen University Hospital need to work at Petten, German regulations on radio-protection, especially application of the radio-protection decree: §20 StrSchV (Strahlenschutzverordnung), which regulates the activities of German staff in foreign institutions, had to be contractually agreed. The decree defines regulations on supervision of the staff, personal dosimetry, rules of behaviour, etc.

Radio-protection includes the issuing of personal dosimeters (type: universal dosimeter) to all staff, finger or ring dosimeters to the radiotherapists, and pen dosimeters to participants classified as visitors, eg. nurse(s) and relatives of the patient [3]. Furthermore it is necessary to measure and record all material in and out of the reactor and perform activation measurements on all material used in patient treatment. The patient is an exceptional case, of course, and it is not required that a personal dosimeter is issued to the patient. However, following treatment, the patient is monitored for radioactivity. So far, the reported radiation doses received by the staff are well below the allowable limits.

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3. The BNCT Irradiation facility

3.1 General requirements
R.L. Moss

The design and construction of an irradiation facility in a nuclear research reactor environment for the BNCT treatment of patients suffering from cancer is a very demanding task. The concomitant, complex, legal and regulatory implications have been discussed in earlier Chapters. From the engineering and physical viewpoint, the general requirements to house a complete facility in the confines of a reactor building are:

i) there should be a sufficient and adequate fluence rate of neutrons that emanate through a large diameter beam tube, that itself preferably faces a large source area of the neutron source.

ii) there must be suitable space at the exit side of the beam, to accommodate a large working area for building the irradiation room.

iii) the facility should be freely accessible such that the patient, who may be unable to walk, can be readily and easily brought into the irradiation room from outside.

Furthermore, outside the reactor building confinement:

iv) there should be space allocated outside the reactor building to house facilities for the reception and preparation of the patient prior to entering the facility for treatment. However, this latter condition, providing that there is sufficient space within the reactor building, may apply to within the building.

The basic design can be broken down into specific components, which formed the basis of one of the 2 Working Groups held at the Prague Workshop, entitled: "How to build up an irradiation facility for BNCT". The Working group defined the following 9 components, based on the schematic simplification, shown below:
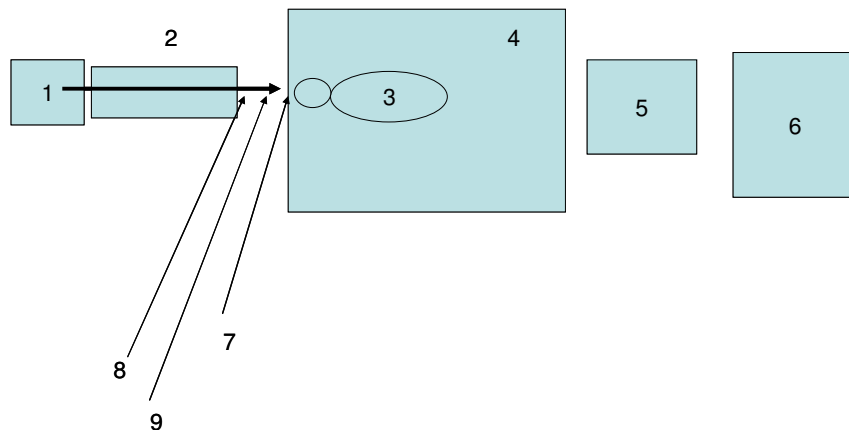
where each numbered component represents:

1. Reactor
2. Beam tube
3. Patient
4. Irradiation room
5. Control room

<ol start="6">
Reception area
Beam dosimetry/characterisation
Beam monitors
Beam shutter

1. The Reactor

In BNCT, there is no singly-available reactor-type that may be regarded as the ideal reactor to develop a BNCT facility. Over the decades a wide variety of reactor-types have been utilised, as the neutron source for a BNCT facility. The closest single design could be a TRIGA, however even this may vary in power and configuration, e.g. utilisation of the thermal column or beam tube.

2. The beam tube

The neutrons, and gammas, emanating from the reactor, need to be moderated, filtered and/or attenuated, such that the required beam intensity and average neutron energy are within the requirements, which themselves can vary depending on the type of tumours to be treated. It is recommended in most cases, that an epithermal neutron beam (neutron energies between 0.5 eV and 10 keV) is the most desirable beam with respect to having the greatest potential for the treatment of many tumour types, especially deep-seated ones. Consequently, following a meeting held in June 1999 in Vienna at the IAEA, which was attended by most of the prominent actors in BNCT from around the world, it was generally agreed, in the form of recommendations and as written within the accompanying report [1], that the neutron-gamma beam at the beam exit should have the following properties:

Table 3.1.1: Recommended beam parameters

Parameter	nomenclature	IAEA recommendation [1]
Epithermal beam intensity	Φ_{epi} (n/cm^2 s)	$> 1.0 \times 10^9$
Fast neutron dose per epithermal neutron	D_f / Φ_{epi} (Gy-cm^2 / n)	$< 2.0 \times 10^{-13}$
Gamma dose per epithermal neutron	D_γ / Φ_{epi} (Gy-cm^2 / n)	$< 2.0 \times 10^{-13}$
Ratio between thermal flux and epithermal flux	Φ_{th} / Φ_{epi}	< 0.05
Ratio between neutron current and neutron flux	J / Φ_{epi}	> 0.7

To achieve these properties, a filtered beam tube is designed that contains materials and/or liquids, which can modify the source neutrons and gammas to provide the required beam. The methods used to design the beam and typical materials are discussed in more detail in the next Chapter. The final design is usually a trade-off between beam intensity and the unwanted contaminants in the beam, i.e. fast neutrons and gammas. The economics also play a role, as some filter materials, which may do a better job, may be more expensive than lesser performing materials.

3. The patient

The type of tumour to be treated will also influence the beam design, whether an epithermal beam or thermal beam is required. Also whether the patient can only be treated in a horizontal position or seated, will influence the design. It should be noted here that the treatment of explanted organs, e.g. liver, is a special case and is not discussed in this context.

4. The irradiation room

If a patient is to be treated in a horizontal position, and especially if brain tumours are to be treated, there should be sufficient space, such that the treatment table can be rotated ±90 degrees about the beam axis. Preferably, the central beam axis should be at least 1m vertically above the floor. The room itself should contain most if not all facilities expected in a conventional radiotherapy room, e.g. cameras, laser positioning devices, ease-of-access, etc.

5. The control or observation room

The patient and the facility need to be monitored. Monitoring equipment such as, puls-oxymeters, TV monitors, microphones, radiation level instrumentation, radiation monitors measuring the beam characteristics, all need to be housed in an area or room, where the medical and physics staff can comfortably sit and observe the patient and radiation beam parameters. Such a room should be next to the irradiation room and be at least 10m^2.

6. Reception area or building

Next to, or outside but close to the entrance to the reactor, an area or dedicated building should be available, where the patient can be received prior to treatment. It will be necessary to prepare the patient, e.g. infusion of the drug, change of clothing, medical examination. The area or building should also have the provisions of an office, for the medical staff, a waiting room, for accompanying relatives, as well as,, of course, a WC.

7. Beam dosimetry/characteristion

The radiation beam is a mixture of neutrons, of all energies, and gamma rays. The beam must be thoroughly characterised, as part of any quality assurance system, as well as, being absolutely necessary, in order that accurate and reliable calculations, especially for treatment planning can be performed. There are a variety of techniques available to characterise such a beam. In section 3.3 below, this is described in more detail. The irradiation room should be designed such that any eventual measurements can be readily carried out.

8. The beam monitors

A beam monitoring system must be available that can measure the radiation beam during treatment and have the capacity to automatically close the beam when the required radiation dose is achieved or when an emergency situation occurs. As in conventional radiotherapy, all safety systems should be backed-up by an independent, second device acting in case of failure of the first. In BNCT, a beam monitoring system normally consists of four beam monitors: two ^{235}U fission chambers (neutron counters) and two GM-tubes (gamma ray counters), which are located close to the beam line, usually in the wall of the beam tube or in the (fixed) collimator, downstream from any beam shutter. The automatic opening and closing of the beam should be controlled by the fission chambers, according to a pre-set number of monitor counts which correspond to the required boron dose delivered at the dose group identification point in a patient. Both fission chambers are pre-set to close the shutters, which are automatically triggered when the target counts are reached. The fission chambers, as well as the GM-tubes, should be monitored and the counts and count rates displayed on two independent computer systems. As an additional back-up for beam shutter closure, i.e. if the monitoring system fails, a timer should be 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.

9. Beam shutter

Depending on the reactor-type utilized, a beam shutter or shutters are necessary, such that the radiation can be stopped or reduced sufficiently in intensity, such that staff can enter the irradiation room. Some reactors, such as the HFR at Petten, operate 24 hours a day, as such the beam shutters must open and close without any mutual effect on the operation of the reactor and to reduce radiation levels to levels where the staff can enter the room. At some facilities, such as low

power, TRIGA reactors, the reactor itself is shut-down as part of the treatment procedure. Beam shutters are generally made of layers of lead and borated or lithiated polyethylene. Opening and closing of the beams must be performed remotely, with emergency back-up facilities to shut the shutters, if the power supply fails. The shutters must be equipped with interlock devices to enable automatic shut-down when the required dose is achieved or in emergencies. If necessary, it should be possible to close the beam shutter(s) manually, if any electrical failure occurs. As a last resort, the beam operator has the mandate to instruct the reactor operators to scram the reactor.

Radiation levels for Personnel

Radiation protection remains the overriding safety feature of any facility, whether it is for medical purposes or not. As such, it is recommended that the radiation levels around the radiation facility, where medical and physics staff members are positioned during treatment, must be as low as reasonably achievable (ALARA), ie. < 5 μSv/hr.

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3.2 Design
R.L. Moss

For a reactor-based facility, the neutrons travelling down the beam emanate from the fission process in the reactor core following fission of uranium-235 in the reactor fuel. As a consequence of using a reactor-based beam, gamma rays as well as neutrons of all energies are present in the beam, which themselves, in sufficient quantities, can give significant doses to the healthy tissue. The unwanted contaminants can be removed from the beam by taking advantage of the nuclear characteristics of certain materials, referred to as moderators, filters or attenuators. Through interactions and/or collisions in the materials, a neutron, either loses some of its energy, is deflected completely out of the beam, is captured by the nuclei of the material, or, at preferred energies, is allowed to traverse the material through characteristic "windows". A variety of filter materials can be considered in order to optimise the beam properties. Despite there being a wealth of materials available, e.g.: Al, Al_2O_3, D_2O, S, AlF_3, Fe, Be, BeO, Ti and PbF_2, as well as commercial products such as Teflon and Fluental^{TM}, which all moderate the high energy neutrons; Bi, Ar, Pb and PbF_2, for attenuating gamma rays; and ^{10}B, Cd and ^6Li for eliminating slow neutrons; it is virtually impossible to produce the "ideal" beam. A compromise is usually reached whereby there is a trade off between the desired neutron fluence and the beam contaminants [1].

Calculational tools

The calculational methods used to design a beam are usually based on deterministic or stochastic theories. The most common computer codes are respectively discrete-ordinate methods, e.g. DOT, and Monte Carlo methods, e.g. MCNP [2] or the extended version, MCNPX. For simulation of particle transport with Monte Carlo, detailed information regarding the interaction properties of the particle and the media through which the particle travels are required. Unlike the deterministic method, e.g. DOT, which solves the transport equation for the average particle behaviour, MCNP(X) obtains an answer by simulating individual particles. Each particle history is started by creating the particle with position and energy coordinates according to a specified source distribution. The particle travels a certain distance and undergoes an interaction, determined by the probability of interaction based on the total interaction cross-section. The type of interaction and the resulting particles are determined by the interaction cross-sections at that point. MCNP(X) must therefore include cross section libraries for calculating the probability of a particle interacting with the medium through which it is transported.

The cross section for each interaction is dependent on the incident particle, its energy, and the material it travels through. As the number of particles and interactions (called 'histories') increases, the quality of the reported average behaviour of the system improves, meaning that the statistical uncertainty decreases. However, often a very large number of histories are necessary to obtain an accurate estimate of the parameters to be calculated. As simulating more histories become time consuming, different techniques called variance reduction techniques are often used to improve the calculation efficiency. Nevertheless, with the advent of more powerful computers and workstations, calculation times are becoming less of an issue.

BNCT facilities
A tabulated summary of the important parameters of a number of facilities that have been designed and installed at various nuclear institutes around the world are given in Table 3.2.1. It can be immediately seen that no 2 facilities are the same. This is primarily due to the fact that BNCT facilities have been designed and installed on existing reactors built for other purposes. Consequently, the designer of each facility has had to make the optimum design that is greatly influenced by the surrounding structure. Nevertheless, most of the facilities listed do satisfy the requirements listed in Table 3.1.1.

Table 3.2.1: Beam characteristics for various BNCT facilities around the world

	MIT FCB, USA		Studsvik Sweden	FiR-1 Finland	BMRR USA	Rez Czech Rep	HFR EC, NL	JRR-4 Japan	KUR Japan	THOR Taiwan
	w/o filter	Li filter								
Φ_{epi} (10^9 n cm^{-2} s^{-1})	5.3	2.5	1.4	1.2	1.1	0.60	0.33	2.2	0.46	1.7
Photon contamination	3.6	4.6	12.6	0.9	1.5	10.8	3.8	2.6	2.8	1.3
Fast neutron contamination (10^{-13} Gy cm^2)	1.4	2.3	8.3	3.3	2.6	16.9	12.1	3.1	6.2	2.8
Beam diameter (cm)	12		14x10	14	12	12	12	12	15	14
Positioning angle (°)	180		180	< 180	180	< 180	180	< 180	< 180	180
Medical room area (m^2)	14			6.4	20	8.8	12.2	7.8	27	20

Process conditions
As well as the beam characteristics, there are additional requirements on the working environment and the needs of the medical staff.

Radiation room
The room must provide sufficient space and means to position the patient comfortably, must satisfy medical requirements, with respect to electrical standards and provisions, and must provide a reasonable hospital-like environment.

In the irradiation area or room, no special conditions are required above the normal reactor hall environment. The temperatures and pressures of the important components are monitored by appropriate provisions. No specific requirements are demanded on these components as part of any experiment.

With respect to therapy, the only process restraint, as specified by the radiotherapists, is that the beam must be able to be closed or the background radiation levels reduced to within acceptable limits, within 15 seconds say, e.g. in case intervention is required by the medical staff.

Observation/control area
This area, located outside the irradiation room, must have the suitable means to observe and monitor the beam and the patient, and provide sufficient space and means to accommodate a minimal number of staff during the treatment, e.g. the radiotherapist, the medical physicist, the facility operator, the physicists and the technical support staff.

Patient preparation facilities
A facility should be available and located preferably outside the reactor building, but close to the irradiation room, where there must be sufficient space to provide an enclosed area to receive and prepare the patient for treatment. Additional space for a waiting room and office space for medical staff should also be available.

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3.3 Beam characterisation
F. Stecher-Rasmussen

Introduction
In a general sense, beam characterisation comprises a number of aspects within the field of BNCT dosimetry. These are:

1. Determination of the beam characteristics for the purposes of source term validation of computer simulations.
2. Determination of beam energy parameters needed for the measurement of the relevant dosimetry quantities.
3. Determination of the different dose components of the beam, related to the beam monitors, for the purpose of beam calibration.
4. Validation of treatment planning calculations.

For the sake of clarity, however, in this document only the first two aspects are discussed.

As an attempt to generate dosimetry guidelines a European Consortium has produced recommendations for the dosimetry of BNCT, including beam characterisation, and an extensive overview of the available methods [1].

Objectives
The objective of beam characterization in this document is the determination of beam characteristics for the purposes of source term validation, and the determination of beam energy parameters ("beam quality specifiers") needed for the measurement of the relevant dosimetry quantities. This includes the determination of beam geometry defined by spatial distribution of relative values of the relevant dosimetry quantities, and the determination of the energy and angular distributions of the gamma rays

and neutrons, in air as well as in phantom. The angular distribution is determined indirectly by determining the spatial distribution at a number of distances from the beam exit port.

A validated neutron and gamma-ray source term is needed as an input for the treatment planning calculations. The source term is obtained by computer calculations taking into account the geometrical arrangement and the material composition of the beam limiting device as precisely as possible. The beam geometry and the spectral source term determined by calculations must be adjusted by experimental data.

Selection criteria and discussion
The selection criteria and available techniques and counting systems for the determination of the beam spatial distribution and the neutron and gamma-ray spectrum are discussed in the following sections. More detailed information on the methods themselves is compiled in [1].

Beam geometry
Information on the beam geometry of a mixed field of epithermal neutrons and photons, free in air, is obtained from the relative beam profile measurements (i.e., measurements of the relative lateral distribution of a given quantity) of neutrons and gamma rays at different axial positions (A1, A2, in Figure 3.3.1). Detectors have to be selected that are insensitive to the other radiation components except that being measured, or for which it is easy to eliminate (by absorbers or an electronic circuit) neutrons in the case of measuring gamma-rays and gamma-rays in the case of measuring neutrons. The profile has to be determined in steps that are relatively small in comparison to the beam width. This requires detectors with an active detector volume of such dimensions that sufficient spatial resolution can be achieved for at least 5 measuring points over the beam width. The number of axial positions in which measurements have to be performed, depends on the divergence of the beam. Measurements in extra positions are needed for parallel beams in which the patient treatment will not be restricted to the positions P1 and P2 (Fig.3.3.1), generally chosen as close as possible to the beam port.
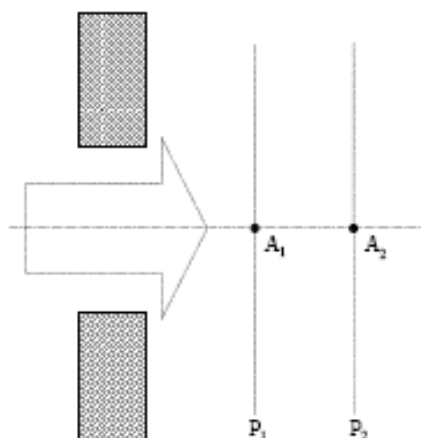
Fig. 3.3.1: Schematic diagram of the determination of beam geometry. Profile measurements free-in-air are performed at different axial positions (A1, A2, …) in lateral directions perpendicular to the beam axis as indicated by lines P1 and P2. The beam is incident through the aperture from the left.

The selected detector should cause negligible perturbation of the measured field, or the perturbation must be sufficiently small that corrections can be easily made. The detector must have an efficiency which allows operation under normal beam conditions. Measurements at beam conditions that are significantly different from clinical conditions should be avoided whenever possible.

Easy commercial availability of the detector system is an important selection criterion, as is the need for simple unfolding of the physical quantity from the measured detector signal. An overview of

detector systems commonly used among active European BNCT centres is given in [1]. A selection of techniques has been tested extensively at the parallel neutron beam of the HFR in Petten in the Netherlands and the more diverging beam FiR1 at Espoo in Finland (see Appendix A in [1]). Experts experienced in the characterisation of their home beam have performed measurements at the other beam, using the same techniques but their own equipment and approach [2]. The differences in approach concern mainly different compositions of stacks of activation foils and use of different build-up and ^{6}Li caps in the case of ionisation chambers. The Bonner sphere and proton recoil techniques, although tested at other BNCT facilities, are applied on a regular basis at Rez facility in the Czech Republic [1] only.

To characterise the spatial distribution of neutrons in the beam, neutron activation monitors, ionisation chambers, thermoluminescence detectors (TLD) and semiconductor detectors are mostly used. Several other methods are also available, such as fission chambers, proton recoil, alpha recoil, and ^{3}He- and BF$_3$ counters, but these are not applied on a large scale.

Neutron energy spectrum
The spectral characterisation of epithermal neutron beams is realised by the adjustment of a calculated neutron spectrum with experimental data. Calculations, selection of the experimental approach, and spectrum adjustment technique will be addressed separately.

Calculations
The calculation of the neutron spectrum with computer codes such as DORT or MCNP should include both a proper simulation of the chosen beam set-up and a high accuracy of simulation of the perturbation of the field due to the presence of the detector(s). The number of energy groups should not be chosen too small. Also the lower and upper energy side of the spectrum should be represented by a number of groups. This will lead to longer computer running times but will avoid inter- and extrapolation procedures later. Proper use of inter- and extrapolation procedures require physical insight and experience.

Measurements
In general, neutron spectrum measurements are performed for the beam axis only, starting at the beam port, and, depending on the beam type, at one or more distances away from the beam port.
The experimental procedures are selected in accordance with the following criteria:

- small mutual perturbation of the monitor materials
- sufficient efficiency under normal beam conditions
- simple discrimination of gamma rays
- simple unfolding of the physical quantity from the measured detector signal
- acceptable uncertainty, good stability and good reproducibility
- accurate modelling of the detector set-up in the computer simulation
- traceability of measurements to appropriate standards.

As mentioned before, measurements should be performed at clinically relevant beam fluence rates. Measurements at significantly different fluence rates should be avoided whenever possible.

The most applied experimental methods for the determination of a neutron spectrum, material activation and Bonner sphere monitoring, are both integral methods. They give no direct information about the number of neutrons with a specific energy. The measured responses are integrated over a neutron energy interval and irradiation time.

In the case of the irradiation of activation monitors in a neutron field, the activation cross section function and the local neutron spectrum determine the energy interval. A set of different activation

materials covers different energy intervals. In the case of Bonner sphere monitoring, a detector sensitive for thermal and epithermal neutron is situated in the centre of a paraffin or polyethylene moderator sphere with a particular diameter. Different sphere diameters result in different levels of neutron moderation as a function of the neutron energy. Here one detector and a series of spheres represent a set of neutron detectors with different spectral sensitivities (different energy intervals).

The measured reaction rate of an activation monitor represents the product of fluence rate function and cross section function, the count rate of the detector inside the Bonner sphere represent the product of fluence rate and response function for the particular sphere. This means that fluence rate is related the chosen cross-section or response function. Therefore differences in neutron spectrum and correction for the contribution of thermal neutrons can be expressed well as relation between reaction rates instead of fluence rates.

A review of the experimental measurement methods is given in Appendix 2 of [1] and practical examples of the determination of the neutron spectrum can be found in Appendix 3 of [1]. Sets of activation detectors ("Spectrum sets") of different composition with and without a cadmium cover have been tested at the BNCT beams in Finland, The Netherlands and The Czech Republic. Also measurements with boron spheres have been performed at these places. Proton recoil measurements have been performed in Petten and Rez, only with limited success. A disadvantage of Bonner sphere and proton recoil monitoring is that they are applicable only at low power, which leads to inaccuracies in scaling to full power (depending on the reactor and beam monitor instrumentation) over this range.

Adjustment procedure
Data obtained from measurements can be used as input for neutron spectrum adjustment. For example, the reaction rates obtained from a neutron spectrum produced by neutron transport calculations are adjusted to the reaction rates obtained from experiments with a set of activation detectors or/and the count rate measured with a detector in the centre of different Bonner spheres.

The adjustment method should provide optimal estimates for the neutron spectrum with assigned uncertainties. Therefore criteria for the selection of the adjustment procedure are:

- an internationally accepted adjustment code, based on correct physics background and mathematics procedures that takes into account the uncertainties in the input data, and furthermore, that is freely available
- experimentally tested and internationally recommended (e.g. by the IAEA) cross-section library
- reliable uncertainty data for reaction rates, cross section data and for the calculated neutron spectrum.

Modern codes, based on a generalised least squares method (GLS), give optimal estimates for the neutron spectrum with assigned uncertainties at a stated level of confidence. However, these codes require the covariance information of the input data (measured reaction rates, calculated neutron spectrum, cross sections). Complete sensitivity analyses have been performed only for a limited number of neutron fields and unfortunately not for a BNCT beam.

A very popular computer program used for neutron spectrum adjustment is the code SAND–II. This program applies a simplified least squares method in logarithmic space and determines the neutron spectrum by iterative adjustments. Several variations of this program are used in practice, e.g. SANDBP [3] and SANDP01 [4]. The usual version of SAND II does not calculate any uncertainty for the various energy regions of the neutron spectrum and, therefore, no covariance information is needed.

The various versions of the SAND-II code use cross-section libraries in a large number of energy groups (640 groups). In general, the neutron spectra, calculated by MCNP or by other codes, are available in fewer groups. Usually no spectrum information is available for thermal neutrons and very fast neutrons. This means that extra spectrum information has to be added to get proper adjustment for these energy regions. A usual approach is to extrapolate the spectrum information below the cadmium cut off of 0.5 eV with a Maxwellian shaped spectrum. For energies above 1 MeV, a fission spectrum is introduced. The approach for the Petten beam as well as the FiR1 beam has been described in [5]. The method has to be applied very carefully and needs a certain amount of physical insight and experience. Extra information on spectrum shape could be avoided by performing neutron spectrum calculations in a larger number of energy-groups. This would require calculations with much greater number of particles, unfortunately leading to long computer-running times but is preferred above extrapolation.

Gamma-ray energy spectrum
Spectrum characterisation of the gamma-ray component in the beam is carried out free in air as close to the beam port as possible, but limited by the dimensions of the shielding applied around the used detector.

Criteria for the technique to determine the gamma-ray energy spectrum are:
- Sufficient efficiency of the detector under normal beam conditions, resulting in count-rates that can be processed by the electronic counting chain without loss of information. In practice, reduction of the detector count-rate will be needed and can be achieved through shielding around the detector provided with a small collimator or use of a reflector in the beam that scatters a part of the beam to a detector outside the beam.
- Simple discrimination of neutrons
- Accurate modelling of the detector set-up in the computer simulation
- Simple unfolding of the beam gamma-ray spectrum from the measured gamma-ray spectrum
- Good stability and reproducibility of the detectors to be used.

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3.4 Boron analysis
F. Stecher-Rasmussen, W. Sauerwein, R.L. Moss

BNCT dosimetry requires an accurate and a fast method to measure the ^{10}B-concentration in blood during treatment. Ideally this should be available close to the treatment room. The most convenient method using the nuclear technology available at a reactor is prompt gamma-ray analysis (PGRA) [1], which will be described here in more details.

As an example, at the HFR in Petten the PGRA facility is located at a beam tube (HB7) close to the BNCT facility (HB11) in the reactor hall.

Prompt gamma-ray analysis (PGRA) is a fast method for measuring the average ^{10}B-content of macroscopic samples. The method has been used to measure the ^{10}B-concentration in samples for Boron Neutron Capture Therapy since many years [2-7]. The principle of PGRA is based on gamma-ray spectroscopy following neutron capture in ^{10}B. The recoiling ^{7}Li-nuclei from the ^{10}B(n,α)^{7}Li reaction decay to the ground state of 7Li by the emission of 478 keV photons. The emission rate of the photons is proportional to the reaction rate of the neutron capture reaction and therefore carries information of the ^{10}B-concentration.

Sample preparation is quite simple and very fast. For liquid samples (e.g. blood, urine) a fixed volume (1.00 ml) is injected into a standard vial and then weighted. Tissue samples are just weighted. The vials are positioned in a sample changer, which allows for automatic measurements of 24 samples in one run. A typical measuring time is 5 min per sample, for a SD of about 0.5 ppm ^{10}B.

Quality control of the Petten 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 through means of measurements of calibration samples. During PGRA the content of the ^{10}B line for an unknown sample is calibrated against ^{10}B-reference samples with known ^{10}B-concentrations. Inter-calibration between PGRA and Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) is mandatory for the detection of possible systematic errors; therefore selected samples have been measured in Petten by both methods at regular intervals.

For BNCT dosimetry, PGRA is an important tool to correct the treatment planning for changes in the ^{10}B-concentration during BNCT. The measured ^{10}B-concentration from BPA in the blood of a patient is used to adjust the hypothetical idealized pharmacokinetic curve to the actual situation. This allows a readjustment between beams of the calculated exposure time (from treatment planning) during a BNCT treatment according to the actual blood-boron concentration of the patient. To make such adjustment during the treatment, a very quick analytical method is mandatory, as this is the case for PGRA.

In addition to the application for BNCT dosimetry, PGRA is also a powerful tool for quality control of the compounds BSH and BPA, for pharmacokinetic studies, and for boron uptake studies.

The present PGRA facility at the HFR provides fast (about 5 min per sample), accurate (standard deviation about 0.5 ppm) and non-destructive measurements of ^{10}B-concentrations down to 1 ppm, suited for a large number of macroscopic samples (0.4 – 1.0 ml) of tissue, blood and urine. The major limitation of this method, the relatively large sample size, might be further reduced by improvement of the shielding and the geometry of the facility to decrease the background in the gamma-ray spectra. PGRA measures the integral ^{10}B-concentration within a sample; therefore it cannot show any inhomogeneities of the ^{10}B-concentration within a possibly inhomogeneous sample. Such inhomogeneities can be relevant in BNCT as the tissue volume which can be measured with PGRA is far bigger than the sub-volumes contributing to the boron neutron capture reaction. Other methods [8], however, are capable of measuring the boron distribution on a microscopic scale.

A further application of PGRA for BNCT includes the possibility of in-vivo gamma-ray spectroscopy of the patient during treatment [9-11] The gamma-ray telescope can provide in-vivo dosimetry and measurement of ^{10}B-concentrations, averaged over a volume of several cm3 and over a time interval of about 2 min. This method, however, needs further improvement for implementation in a clinical routine.

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4. Medical Aspects

4.1 Medical physics (Clinical dosimetry)

P. Munck af Rosenschöld

The purpose of this section is to briefly discuss topics of interest to radiotherapy personnel who participate in any aspect of boron neutron capture treatment planning and delivery. The expression "clinical dosimetry" refers to the process of converting dosimetric quantities from the reference conditions to that of the individual patient. For a discussion on the process of dosimetry under reference conditions see, for instance, [1-4].

1. Commissioning of treatment planning computers
2. Absorbed dose calculations
3. Radiobiological considerations
4. Quality assurance of clinical dosimetry
5. References

Commissioning of radiotherapy treatment planning computers

Treatment planning systems (TPS) are widely used in radiotherapy absorbed dose calculation in patients, and needs to be commissioned for the purpose. In order to commission the TPS several tests are required. In [5], the most common errors found in radiotherapy TPS were summarized as follows:

(a) A lack of understanding of the TPS
(b) A lack of appropriate commissioning (no comprehensive tests)
(c) A lack of independent calculations checks

Well-structured proposals for test procedures for radiotherapy treatment planning programs have been presented in various reports in the literature; notably [6-8]. In principle, the first step involves an *acceptance test*, in which the program is tested in order to confirm that the TPS performs according to its manufacturer's specifications. If the specifications are vague or missing, there is little need for, and indeed ability to design, an acceptance test. Typically, an acceptance test may involve the input of CT or MRI data, the creation and display of 3D objects, and performing a dose calculation and review the output for a standard treatment case. Of particular interest and importance for BNCT is the ability of the treatment planning system to identify and assign different material description to delineated regions of the patient model, as this is required for accurate neutron transport and dosimetric calculations. The following step involves a *commissioning* – in which a number of tests are performed that are generally subdivided into nondosimetric and dosimetric tests. Performing what is referred to as nondosimetric tests are well motivated considering that modern treatment planning systems includes many functions that are not directly related to dosimetric calculations, but still are of great importance for patient safety. The overall goal of the commissioning process is to determine the capability and limitations of the TPS as well as provide the user with experience and training in using it. Some of the commissioning test data can subsequently serve as reference data to be used in the periodic quality assurance tests of the TPS.

Absorbed dose calculation

A commissioned treatment planning system (TPS) is generally used for radiotherapy absorbed dose calculation. Both the geometry and the material content of the irradiated body in an epithermal neutron beam have great impact on the dose distribution. The TPS ability to account for these effects correctly could be verified in phantom experiments. The commissioned TPS should be used to derive conversion factors from the reference conditions to the actual patient. The treatment planning programs used in BNCT has been discussed in literature [9, 10]. The absorbed dose of a single

treatment field to a patient (D_{pat}) of the dose component i to be delivered is given by the simple relation:

$$D_{pat,i} = \left(\frac{D_{pat,i}}{D_{ref,i}} \right)_{TPS} \cdot \left(\frac{D_{ref,i}}{M} \right)_{Measured} \cdot M \qquad \text{(Eq. 4.1.1)}$$

where M is the total number of beam monitor unit counts, $D_{ref,i}/M$ is the measured absorbed dose of component i per beam monitor count under reference conditions, and the $D_{pat,i}/D_{ref,i}$ ratio is calculated using the TPS. Note that for $i=boron$ and $i=nitrogen$ $D_{ref,i}$ is replaced by $\phi_{ref,i}$ (i.e. the thermal neutron fluence determined under reference conditions). Out of practicality, it is often assumed that kerma equals absorbed dose – this is certainly a reasonable assumption for the neutron residuals. To a first approximation $D_{pat,boron}$ is directly proportional to the macroscopic boron concentration, however, at boron concentrations of the order of 10-20 µg/g suppression of the neutron fluence becomes a factor that needs to be addressed [11]. Knowledge of the blood-boron concentration allows an indirect estimation of the boron concentration in other tissues through tissue-to-blood ratios obtained in previous biodistribution studies. The approach in BNCT has therefore been to measure the boron content in blood as a function of time [12].

The boron concentration in a certain region can affect the neutron fluence, and thus the resulting absorbed dose in another region. This fact can lead to both over- and underestimations of the absorbed dose in different structures in the treated volume. For instance, if a too high boron concentration in the brain parenchyma is assumed, the absorbed dose delivered to the blood vessels may be underestimated (as the neutron fluence is underestimated). The use of techniques such as positron emission tomography [13], magnetic resonance spectroscopy [14] and prompt gamma spectroscopy (PGS) has been proposed for use [15], aiming to reduce dosimetric uncertainties.

Radiobiological considerations
A patient receiving BNCT is exposed to a number of absorbed dose components with different radiobiological effectiveness [16]. In order to plan and evaluate treatments in the TPS it is of interest to derive a biologically effective absorbed dose D_{bw}, which is a function *(f)* of the four important dose components:

$$D_{bw} = f\left(D_\gamma, D_p, D_n, D_B \right) \qquad \text{(Eq. 4.1.2)}$$

where D_γ is the photon absorbed dose, D_n is the fast neutron absorbed dose, D_p and D_B are the absorbed doses delivered by charged particles from neutron capture reactions in nitrogen and boron, respectively. Note that photons produced in neutron reactions contribute to the photon absorbed dose (irrespective of the reaction site). It is of great interest to determine the function in equation 4.1.2 for patients that have received BNCT. In clinical BNCT, a simplified approach has often been taken by assigning "weighting factors" taken equal to the relative biological effectiveness (RBE) of each absorbed dose component. The absorbed doses and weighting factors are multiplied and summed, giving an approximation of Eq. 4.1.2 that is referred to as the Total Biologically Weighted BNCT Dose [17]:

$$D_{bw} = D_\gamma \cdot w_\gamma + D_p \cdot w_p + D_n \cdot w_n + D_B \cdot w_c \qquad \text{(Eq. 4.1.3)}$$

and the factors denoted w are the corresponding weighting factors for the absorbed dose components [17]. Eq 4.1.3 gives a biologically weighted absorbed dose (D_{bw}) in units Gy; however, this has been a source of confusion in BNCT literature, where it has often been denoted in "units" Gy (w) or less strictly as RBE-Gy or Gy-Eq (see [18], for a discussion on the notation used in a selection of BNCT related articles). The mathematical operation in Eq. 4.1.3 assumes that the components are biologically

independent of each other, i.e. that there are no synergetic effects, which has not been proven to be the case. In addition, this mathematical operation fails to take into account that the weighting factors as determined from the radiobiological experiments refer to a specific end point.

The biological effect related to the boron absorbed dose (D_B Eq. 4.1.2) depends not only on the linear energy transfer of the emitted particles but also on the microscopic (sub-cellular) distribution of the boron compound. Thus, for a given macroscopic boron absorbed dose, the biological response may differ for different boron compounds. It is however, convenient in the clinical procedure to calculate the macroscopic boron absorbed dose in an organ or region and to include the radiobiological implication of the microdistribution of the boron compound in the weighting factor (w_c Eq. 4.1.3). An inhomogeneous tumour uptake of the boron compound suggests that average tumour absorbed doses are of limited clinical relevance, as this may be the absorbed dose delivered to only a subpopulation of the tumour cells. This conclusion is very important with respect to clinical dosimetry, in which it is advisable to focus on healthy tissue tolerance rather than on macroscopic (averaged) tumour absorbed doses for dose prescription in BNCT.

Quality assurance of clinical dosimetry
Safety and efficacy in radiotherapy require verification of the planned and delivered radiation absorbed dose to each individual patient [7, 19]. A simple test in order to verify that treatment time/monitor unit calculation is reasonable, should be performed before each treatment; a calculation of the absorbed dose to the dose maximum for each field serves as an absolute minimum. More elaborate tests, involving calculation of absorbed dose off-axis and addition of several treatment fields are certainly of interest but may be difficult to perform in BNCT [20], for a system applied to conventional photon radiotherapy). *In vivo* dosimetry has been made compulsory in some European countries as a result of a recent EU directive[4]. Radiotherapy should be verified using a detector that provides relevant information on the absorbed dose delivered to the patient. Preferably, the *in vivo* dosimetry procedure should give a direct measure of the delivered dose without corrections, which can be compared with the primary dosimetry system, i.e. the TPS. Ideally, the measurements should give on-line information on the delivered absorbed dose, enabling the medical physicist to monitor the treatment. Finally, the detector or detectors should not cause a significant alteration of the planned dose distribution. In clinical practice, only activation measurements using detectors placed on the skin of the patient have been used as a tool for verification of BNCT [21–23]. It has been shown using Monte Carlo methods that the activity induced in the wire can be directly related to the delivered absorbed dose at the dose maximum after applying corrections and assuming that the boron concentration in tissue is known. This is probably due to the fact that the induced activity is largely governed by back-scattering of neutrons from the thermal neutron fluence maximum [23]. Another method of great interest for in vivo dosimetry in BNCT is the based on the prompt gamma spectroscopy principle, which is the only method that has the potential for on-line measurement of all dose components in clinical BNCT (except for the clinically least important fast neutron absorbed dose). Previous investigations have been directed mostly towards measurements of the boron uptake, and the full potential of PGS as an *in vivo* dosimeter has yet to be investigated.

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4.2 Radiobiology

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Introduction

The concept that boron could be used as part of a novel form of targeted radio-therapy was first raised in 1935 because of the high cross section of the stable nuclide boron-10 (^{10}B) for slow or thermal neutrons. Thus, providing that ^{10}B can be targeted preferentially to tumour tissue relative to normal tissues, the basis of the therapy would depend on the following reaction:

$$^{10}\text{B} \ + \ ^{1}\text{n} \ = \ ^{7}\text{Li} \ + \ ^{4}\text{He} \ + 2.79 \text{ MeV}.$$
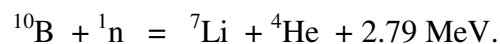
The two products of this fission reaction, an alpha-particle and a lithium-ion would have the advantage of a very limited range in tissue, 9 µm and 5 µm, respectively, so that there will be selective irradiation of cells/tissues containing boron-10. These two fission products are also high linear energy transfer (LET) products (196 keV/µm for the α-particle and 162 keV/µm for the Li-ion). Thus, providing that energy delivery is to important targets within a cell, they are more biologically effective than conventional x- or γ-rays and are almost as equally effective against oxygenated cells as the hypoxic cells, found in tumours.

In addition to the need to find boron carriers that will deliver ^{10}B preferentially to tumour cells, there is also a need for adequate thermal neutron delivery to the site of the tumour, at depth in tissue. This has lead to the development of reactor based, filtration derived, epithermal neuron beams, which can vary considerably in their physical characteristics in terms of dose-rate and the contamination of the epithermal neutron component of the beam with fast neutrons and γ-rays.   The eventual beam composition frequently becomes a compromise in order that the requirement, to produce an acceptable flux of thermalised neutrons at depth in tissue, is achieved. Thus the physical dose characteristics of the different epithermal neutron beams developed for BNCT will differ and some of these differences will have important implications for the biological effectiveness of the beams, this has relevance for both therapy and safety. These physical factors might even be modified if the configuration of the reactor core is changed in relation to the filtration system used to provide the epithermal neutron beam. This makes it mandatory to develop simple biological approaches to compare the different beams designed for clinical use.

Concept of biologically weighted dose

In order that the biological effectiveness of a novel radiation source might be compared with the dose that would be delivered by conventional x-irradiation therapy, the concept of weighted radiation dose

was introduced. In the case of BNCT this is more complex since, by definition, this represents a mixed field irradiation modality and thus weighting factors are required for some if not all of the different dose components that make up the total radiation dose. In addition to the radiation dose from the $^{10}B(n,\alpha)^7Li$ reaction there is also a need to take into account two additional capture reactions, namely, the capture of neutrons by tissue nitrogen and hydrogen:

$$^{14}N \ + \ n \ = \ ^{14}C \ + \ p \ (580 \ keV)$$

and

$$^{1}H \ + \ n \ = \ ^{2}H \ + \ \gamma \ (2.2 \ MeV)$$
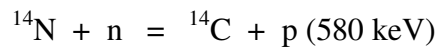
even though these capture reactions occur at only a small fraction of the rate of boron-10. The reaction products are high LET protons and γ-rays, respectively. Other major contributions to the physical dose are high LET recoil protons from fast neutron interactions with hydrogen and incident γ-rays in the reactor based epithermal neutron beam. Simplistically, the conventional photon equivalent dose of any BNCT irradiation will be the product of the physical epithermal neutron beam dose times a weighting factor (wf), plus the physical boron capture related dose times the compound biological effectiveness factor (CBE). Thus:

photon equivalent dose = physical epithermal beam dose. wf + physical 'n, α' dose. CBE

Compound biological effectiveness factor

The determination of this factor, for different normal tissues and its estimation for different tumour models, is an essential part of any compound development programme. Brief details are only included here for completeness. The value of this parameter represents the collective relative biological effectiveness (RBE) of the α-particles and Lithium-ions from the fission reaction, relative to photons, multiplied by a factor that is related to the micro-distribution of boron in tissues. This micro-distribution factor, which is compound and tissue specific, may also depend on the compound administration protocol, and is related to the wasted, biologically ineffective, dose from the $^{10}B(n,\alpha)^7Li$ reaction. Such studies are best carried out using a high flux thermal neutron beam, such as the thermal neutron beam on the Brookhaven Medical Research Reactor [1], since the CBE factor is not dependent on the physical characteristics of the neutron source. The use of a thermal neutron beam, with adequate collimation of the beam and total body shielding, permits the local irradiation of normal and tumour tissues in rodents [1, 2]. This is an additional advantage when relatively small amounts of any new boron-10 delivery agent are available.

Some general principles can be best illustrated by a comparison of the effects of the boron delivery agents p-boronophenylalanine (BPA) and borocaptate sodium (BSH) on the central nervous system (CNS), using a rat spinal cord model. However, it should be fully recognised that the CBE or weighting factors obtained for the CNS, are not applicable to other normal or tumour tissues. BSH does not cross the normal intact blood brain barrier and thus products of the $^{10}B(n,\alpha)^7Li$ reaction are restricted to the lumen of blood vessels. This boron distribution severely limits the biological effectiveness of the fission products. This even applies to the radiation effect in the CNS (selective white matter necrosis), which has a vascular pathogenesis. The CBE or weighting factor of approximately 0.5, relative to photon irradiation, is due to wasted physical dose. BPA, on the other hand, crosses the blood brain barrier allowing a more uniform dose distribution to target cells. This results in a higher CBE factor of approximately 1.3 [3]. However, variations in the dosing schedule for BPA can result in marked differences in the boron distribution between the vascular lumen and the CNS parenchyma. This is reflected by changes in the CBE factor; the higher the blood levels are relative to the CNS parenchyma, the lower the CBE factor [4].

The physical radiation doses have to be calculated in order to determine the CBE values. These calculated doses are based on the blood boron content. For the two boron carriers mentioned above

this represents a reliable surrogate for tissue and blood boron levels in a range that can be determined with accuracy. For the next generation of boron carriers e.g. porphyrin-mediated boron neutron capture therapy [5] the blood boron levels are likely to be very low at the time of irradiation, at the detection limit of detection systems and are thus not a totally reliable basis for the determination of CBE factors. Methods of assaying boron levels in tissues, *in situ,* will need to be developed.

Weighting factors for epithermal neutron beams

As already highlighted, a reactor based epithermal neutron beam is a mixture of both high and low LET dose components. The high LET components are either induced as a consequence of the $^{14}N(n,p)^{14}C$ reaction or as recoil protons, $^{1}H(n,n,)p$, from the spectrum of the fast neutron contamination, of variable energy, of these beams. The low LET component is also a combination of induced γ-rays, $^{1}H(n,\gamma)^{2}H$, and γ-irradiation within the incident beam. The proportion and dose-rate of this combined photon dose component will vary between epithermal neutron sources and with depth in tissue. Although it would be an advantage to determine weighting factors for each of these beam components, in practical terms it is only possible to obtain estimates of the weighting to be applied to the combined high LET components, in terms of a relative biological effectiveness factor (RBE), and an appropriate dose reduction factor (DRF) for the low dose-rate low LET components. Thus:

photon equi. beam dose = physical high LET dose . RBE + physical low LET dose . DRF

assuming, as is presently the case, that the different components to the total radiation dose behave in a way that is independent of each other. Of these parameters the most extensively understood is the variation in the biological effectiveness of γ-rays with dose-rate. Due to the repair of sublethal irradiation damage with time, for prolonged exposures with low dose-rate γ-rays they become progressively less effective when compared with γ-rays with a dose-rate of 1 Gy/min or more. This can be clearly illustrated by examining the effects of different dose-rates on the clonogenic survival of cells *in vitro*. For a given radiation dose the level of cell survival increases as the dose-rate is reduced (Figure 4.2.1). In this example for a clonogenic cell survival of <1% of unirradiated controls, the DRF for an equivalent effect would be < 0.7 for dose rates of <0.16 Gy/min. The γ-ray dose-rates for the present generation of clinical epithermal neutron beams are in the range 0.16 – 0.086 Gy/min, clearly indicating that these γ-rays would be less biologically effective than those delivered at approximately 1 Gy/min.

When BNCT is used for the treatment of glioblastoma, then the dose-limiting normal tissue is the central nervous system. The radiation response of this tissue along with many other tissues has been shown to depend on dose-rate. This is demonstrated by an increase in the dose associated with a 50% incidence of radiation-induced myelopathy (ED_{50}), as the dose-rate declines in two species, the rat and the pig (Figure 4.2.2). When these ED_{50} values are normalised, relative to the value for irradiation at a dose-rate of between 1-2 Gy/min, then there is a linear relationship between dose-rate (log scale) and the DRF. For dose-rates < 0.1 Gy/min, comparable with existing epithermal neutron beams, the DRF is < 0.8.
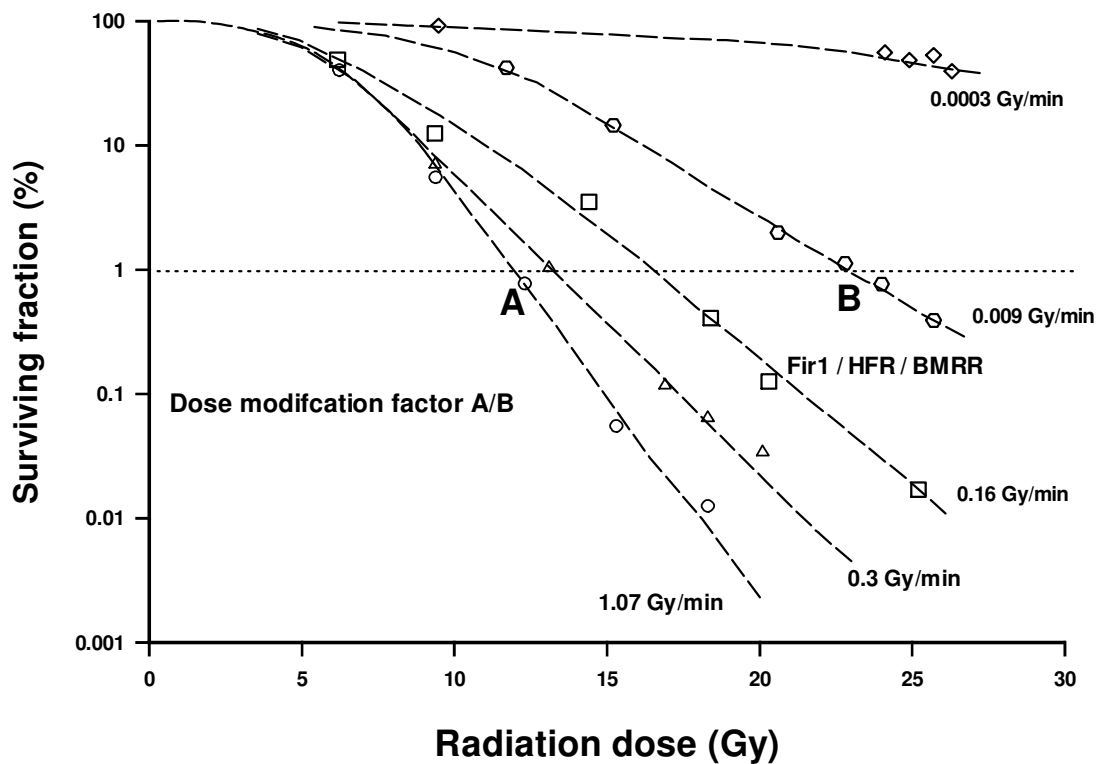
Figure 4.2.1:   *In vitro* cell survival curves for Chinese Hamster cells after irradiation with ^{60}Co γ-rays at various dose-rates. The dose-reduction factor is the ratio of doses to produce the same effect from different dose-rates. The dose-rates of γ-rays in typical clinical epithermal beams (e.g. FiR 1; HFR; BMRR) are in the range 0.16 – 0.009 Gy/min. Redrawn from Bedford and Mitchell [6].

The percentage physical dose contributions from γ-rays for three different epithermal neutron beams are given in Table 4.2.1, along with the maximum dose-rates. From Figure 4.2.2 it is possible to determine the appropriate DRF, which declines with the decline in dose-rate. The DRF used has an impact on the calculated RBE for the high LET components to these beams; use of an inappropriately high value will produce an inappropriately low value for the RBE.

Table 4.2.1: Variation in the γ-ray characteristics of three different epithermal neutron beams that have been used clinically for BNCT

Beam (Location)	FiR 1 (Helsinki)	HFR (Petten)	BMRR (Brookhaven)
γ-ray contribution (%)	71.5	66.8	60.2
Dose-rate (Gy/min)	0.0789	0.035	0.017
Dose-rate reduction factor	0.6	0.5	0.45
	-	(1.0)*	(1.0)*

* DRF values assumed by the centres involved

Figure 4.2.2: Variation in the ED_{50} for radiation-induced myelopathy in the pig ($\triangle$) and rat ($\ominus$) as a function of dose-rate. The ED_{50} values for dose-rates of < 1.0 Gy/min are expressed as a ratio of the 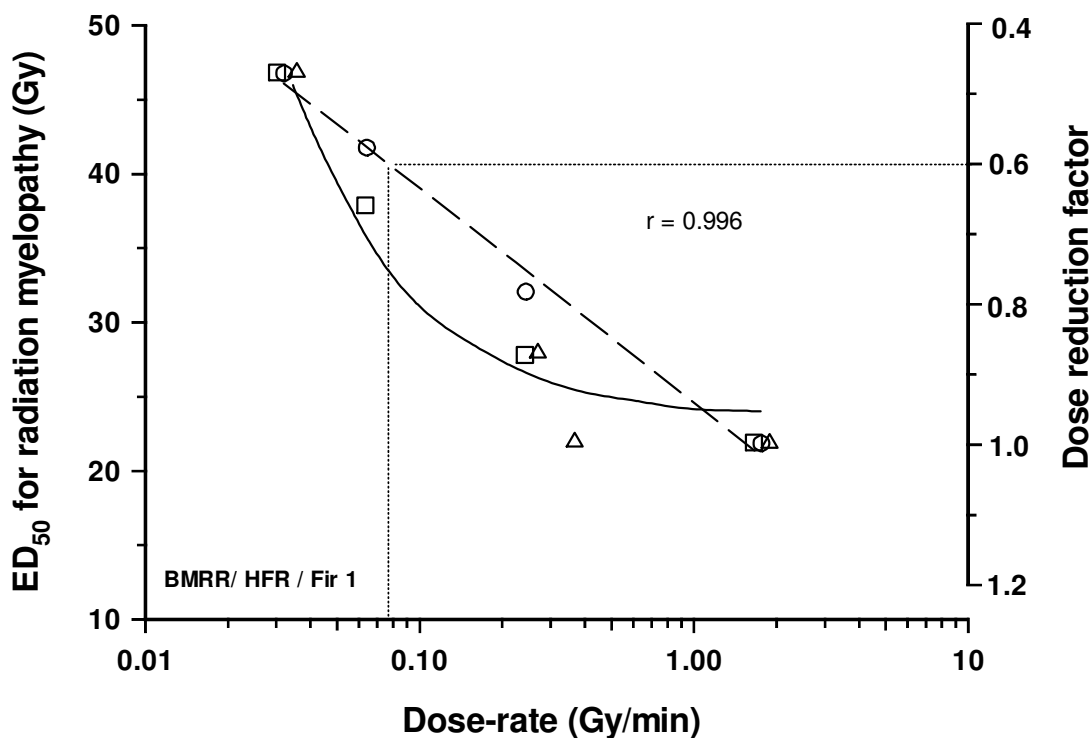highest dose–rate of approximately 1.8 Gy/min (Dose reduction factor – DRF). The DRF ($\bigcirc$) was linearly related to the dose-rate, correlation co-efficient 0.996. Hopewell et al., unpublished data.

Comparison of the biological effectiveness of different epithermal neutron beams

The most comprehensive study, to determine the weighting factors for an epithermal neutron beam, was on the clinical FiR 1 beam line of the VTT based reactor close to Helsinki. The study in Beagle dogs was specifically designed to study the CNS because of the clinical intension to treat patients with glioblastoma. The dose-response relationship was obtained for a range of endpoints after local irradiation of the whole brain; these included sequential changes on magnetic resonance imaging (MRI), post-mortem morphological and histological changes. The effects of irradiation with single doses of epithermal neutrons were directly compared with those produced by 6 MV x-rays, both sets of animals were from the same supplier and the dogs were followed up by the same group of investigators [7]. This avoided the use of historical x-ray data, collected from Beagle dogs [8], following hemi-brain irradiation. Fikes' data [8] had previously been used by two other groups of investigators (for review, see [9]). The additional difficulty in these studies was that local epithermal neutron irradiation of the brain of dogs was combined with the administration of either BSH or BPA, making the determination of weighting factors for the beam more difficult to resolve with accuracy because of the number of unknowns involved.

Frequently, reference is made to these studies in dogs as being 'normal tissue tolerance' studies and not investigations aimed at obtaining weighting factors. This raises questions as to the comparability of the radiation sensitivity between dog and human brain and an endpoint in a dog, which might be accepted as representing 'tolerance' in man. There were also marked differences in the radiation response of Beagle dogs irradiated with photons to the whole brain or hemi-brain, which cannot be explained by the difference in the volume of brain tissue irradiated (Table 4.2.2). The dogs used by Fike et al. [8] showed significantly more neurological damage for comparable doses than the dogs used by Benczik et al [7]. However, for what were considered comparable changes on CT and MRI [9], the dogs in the study by Fike et al. [8] were apparently more radiation resistance i.e. showed less changes

on CT than the dogs used by Benczik et al [7], which showed more changes on MRI, although it should be noted that CT is considered to be a less sensitive technique in the evaluation of changes in the CNS. This reinforces the view that historical controls should not be used, particularly when different parameters, in this case CT vs. MRI changes are used to evaluate the equivalence of two radiation modalities.

The results of the studies by Benczik et al. [7] indicated that the RBE, weighting factor, of the FiR 1 beam varied between 1.2 and 1.4, depending on the endpoint used for the evaluation, with multiple permanent contrast enhancement on T1-weighted images having an RBE of 1.3 ± 0.1. If the DRF of the low dose-rate γ-rays associated with this beam were assumed to be 0.6, then the RBE of the combined high LET component of this beam would be 3.9 ± 0.2 for the same endpoint.

Table 4.2.2: Comparison of photon dose-effect parameters for the dog.

Parameter	Benczik et al.[a]	Fike et al.[b]
Photon energy	6MV	4MV
Imaging	MRI	CT
Neurological LD$_{50}$	>>16Gy[c]	15.7 (15.3-16.1) Gy
[a] Focal change on T2-w MRI	11.0 ± 1.1 Gy	
[b] >1% volume low density		13.5 (12.0-15.2) Gy
[a] Diffuse change on T2-w MRI	10.8 ± 0.94 Gy	
[b] >5% volume low density		15.4 (14.5-16.4) Gy

[a] Benczik et al. [7] quoted doses at the 100% iso-dose
[b] Fike et al. [8] calculated doses at the 100% iso-dose (original publication quoted 95% iso-doses)
[c] Only 40% of dogs showed minor neurological signs (2 of 5 animals irradiated with 16 Gy)

In an additional analysis [7], the dose-effect related incidence for the different endpoints after epithermal neutron irradiation, were converted into photon equivalent doses based on the weighting factors developed and used clinically for the epithermal neutron beam at BMRR; namely 1.0 for low LET γ-ray component and 3.2 for the high LET component of the beam. The use of the BMRR weighting factors for the FiR 1 beam consistently produced an over-estimate to the equivalent photon dose received when compared with the actual data for dogs irradiated with 6 MV x-rays as is illustrated for both single and multiple permanent contrast enhancing lesions on MRI (Figure 4.2.3). The average over-estimate of the photon equivalent dose using the BMRR weighting factors for the FiR 1 beam was 12%. This would imply an under-dosage of patients in this case. However, it does imply the inherent dangers of using weighting factors obtained for one epithermal neutron source to another, no matter how similar they may appear from a physical dose component point of view.
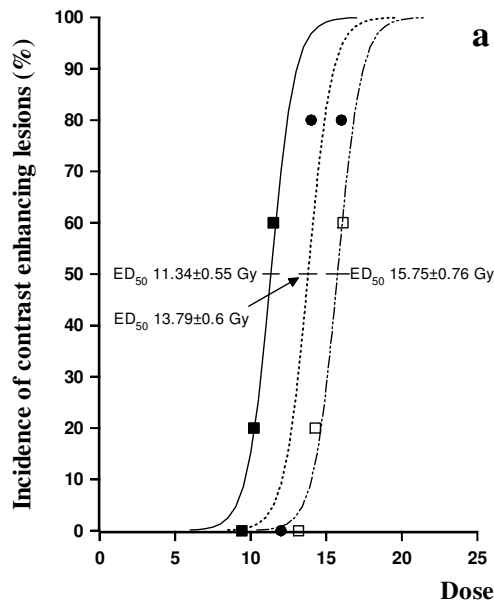

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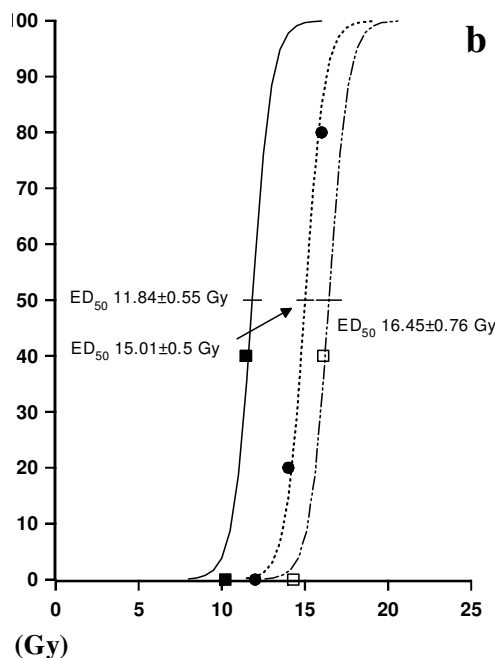
Figure 4.2.3: Dose-related incidence of either (a) single or (b) multiple contrast enhanced lesions on T1-weighted magnetic resonance images in the brain of dogs after irradiation with either epithermal neutrons (■) from the FiR 1 beam or from 6 MV x-rays (●). The photon equivalent doses for the different physical epithermal beam doses used in this study were also calculated using the weighting factors developed for the BMRR (□). These weighted doses produced ED_{50} (± SE) values that were significantly higher than the experimentally observed ED_{50} values for photon irradiation.

Large animal studies of the type undertaken on the BMRR, Petten and FiR 1, while pointing to the need for the biological calibration of epithermal neutron beams, are not practical for many centres apart from the costs involved. A simple *in vitro* cell survival model, to enable the biological comparison of neutron beams used for BNCT research, was initially described in 2001 [10]. Briefly, V79 cells were irradiated in suspension at different depths (20 – 65 mm) in a water-filled cylindrical phantom. Over the period of irradiation the temperature of the water was kept at 4°C, this prevents any repair of sublethal irradiation damage over the variable exposure times and thus the need to correct for the variable dose-rates of different reactor based beams is removed; DRF 1.0.

The use of this model can best be illustrated by reference to a recent comparison of the biological effectiveness of the moderated accelerator based epithermal neutron beam at the University of Birmingham, UK, and the reactor based epithermal neutron beam at Studsvik Medical, Sweden [11]. At all depths in the phantom, the biological effectiveness of the Studsvik beam, for a given dose, was always greater than that for the Birmingham beam. For both beams the survival data obtained for irradiation at 50 mm and 65 mm depths in the phantom was comparable and has been combined in this analysis. Also cell survival curves, down to a level of 0.1% were not complete, specifically for the Birmingham beam. This was due to the very low dose-rates (0.58 – 1.04 Gy/hr, depending on depth) resulting in very long exposure times, compared with the comparatively higher dose-rates at Studsvik (8.2 –16.2 Gy/hr). Extrapolation of the cell survival curves was based on the linear and quadratic parameters fits to data points available (Figure 4.2.4). The ratio of doses for the same level of cell survival was independent of the depth in the phantom, 1.3, 1.3 and 1.33 for a depth of 20, 35 and 50 plus 65 mm, respectively. However, the dose-ratio did depend on the levels compared, from 1.41 at 10% to 1.25 at 0.1%. These differences seem to be related to the differences in the fast neutron contribution, to the total dose, in the Studsvik beam (Table 4.2.3), the difference being 51% at 20 mm

and 83% at 65 mm depth, while the difference in the total high LET contribution is 24-26%. This similar difference in the high LET content of the beam, with depth, might be a simple explanation as to why the dose-ratios for a given level of cell survival are independent of the depth in the phantom. However, more inter-comparisons are required before any definitive general conclusions can be drawn.
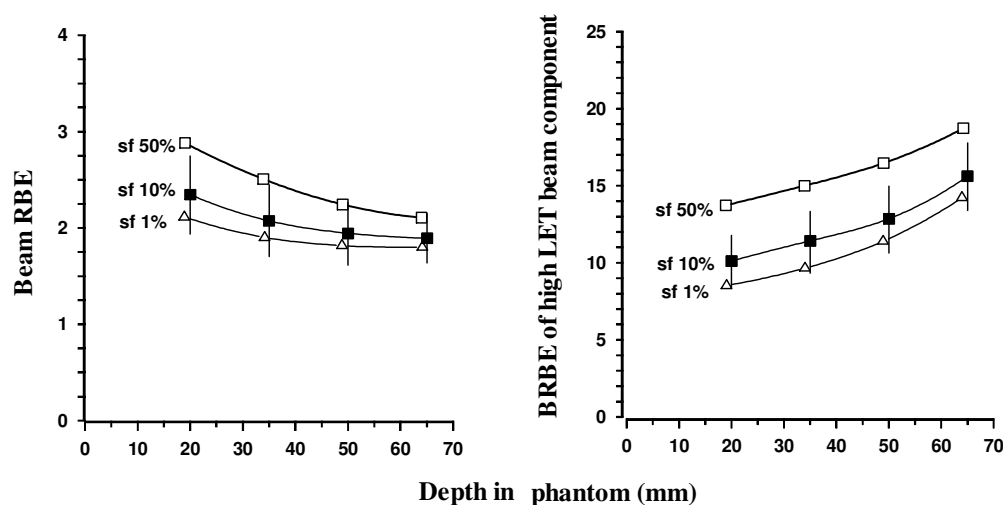

Figure 4.2.4: Variation in the RBE of V79 cells, relative to 250 kVp x-rays, of the Studsvik reactor based epithermal neutron beam with depth in water filled phantom, with the water at 4°C. Values are given for the total beam (left) and the high LET component of the beam (right) assuming a DRF of 1.0 for the low LET component of the beam. Values at three levels of cell survival presented, error bars indicate ± SE for a 10% level of cell survival. Redrawn from Mason [11].

In addition to the irradiations with epithermal neutrons at Studsvik and Birmingham, V79 cells were also x-irradiated at high (42 Gy/hr) and low (1.62 Gy/hr) dose-rates with the cells at 4°C. The cell survival curves for these two sets of conditions were comparable and thus the data were combined to compare with data for cell survival after irradiation with epithermal neutrons, in order to obtain RBE values for the beams. In addition, assuming a DRF of 1.0 in this instance because repair is prevented over the period of irradiation, the RBE for the high LET component of the different beams was determined. In the case of the example illustrated, the RBE of the Studsvik beam, showed a tendency to decline with depth in the phantom (Figure 4.2.4a), as would be consistent with the decline in the high LET component of the total dose. The reduction was approximately 60% from 20 mm to 65 mm depth (Table 4.2.3). The RBE also declines with the level of effect at which it was calculated. The separate evaluation of the RBE for the high LET component to the beam showed an increase in values with depth in the phantom. However, the numerical values are much higher than those usually associated with protons, although they do decline with increasing level of effect at which the RBE was calculated. This is in line with expectation for a high LET radiation and the values would be even lower for the level of cell survival normally associated with the development of normal tissue reactions.

Table 4.2.3: Varying proportional contributions of high and low LET components to the total dose with depth for epithermal neutron beams at Studsvik (1) and Birmingham (2).

	Depth in phantom (mm)			
Dose component	20	35	50	65
^{14}N capture (1)	6.0	6.0	5.2	4.3

(2)	7.0	6.4	5.4	4.3
Fast neutrons (1)	8.8	4.4	2.7	1.8
(2)	4.3	1.4	0.6	0.3
Total high LET (1)	14.8	10.4	8.0	6.1
(2)	11.3	7.8	5.9	4.6
Total low LET (1)	85.2	89.6	92.0	93.9
(2)	88.7	92.2	94.1	95.4

The most marked difference in the dose distribution between the Studsvik (1) and Birmingham (2) epithermal neutron beams was in the relative contribution from recoil protons from fast neutrons in the incident beam

While the routine practice of BNCT assumes that the different components of the mixed field irradiation act independently of each other, one possible interpretation of the above finding is that there is an interaction between high and low LET radiations. Only a relatively small increase in the biological effectiveness of γ-rays when given in combination with a high LET radiation, relative to γ-rays alone would significantly reduce the apparent RBE of the high LET component of this mixed beam irradiation.
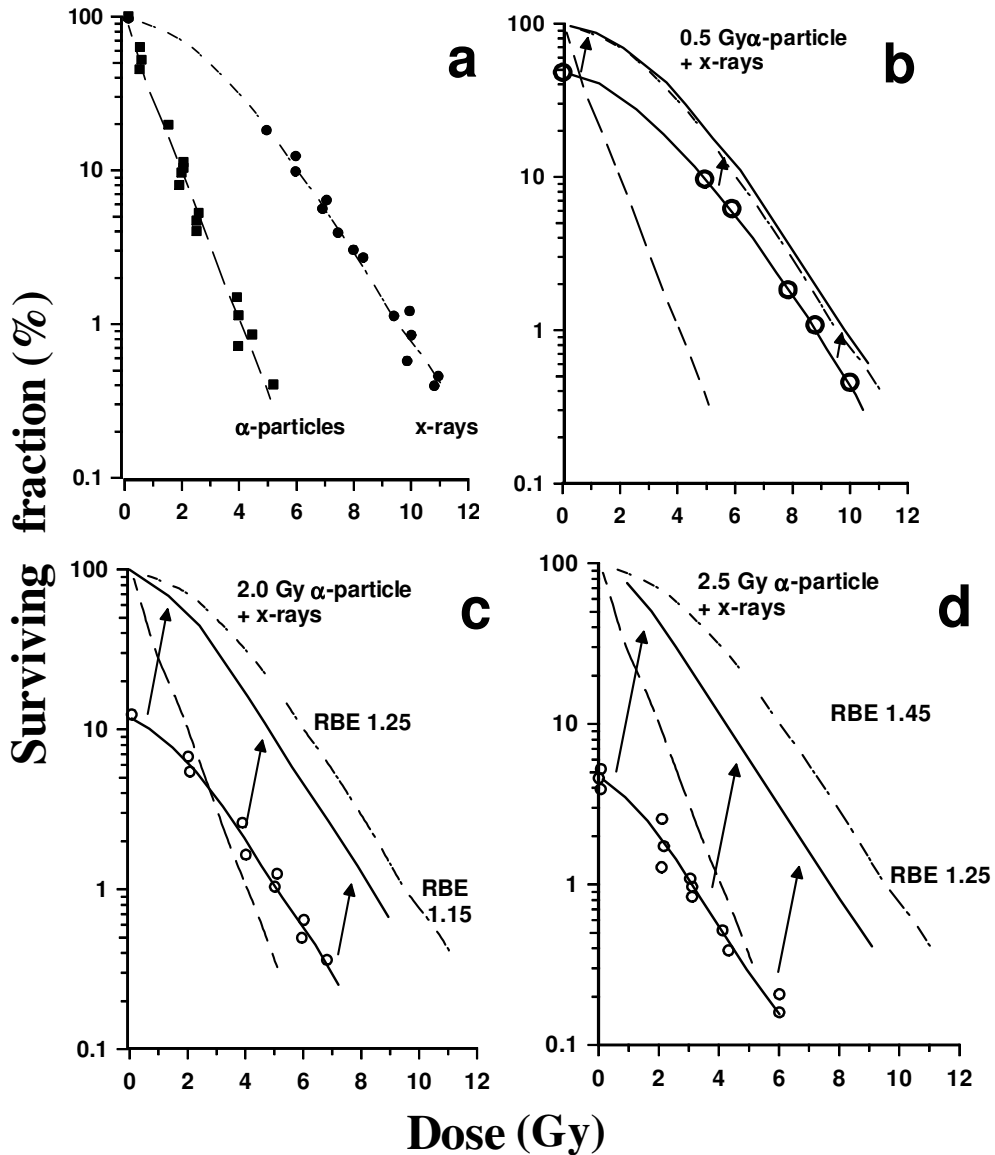
Figure 4.2.5: Clonogenic cell survival curves for V79 cells after with either (a) x-rays [3 Gy/min] or α-particles [0.35 Gy/min; 140 keV/µm] alone or with a fixed dose of α-particles [(b) 0.5 Gy, (c) 2.0 Gy or (d) 2.5 Gy] followed by a variable dose of x-rays. For these combined irradiations the curve for each irradiation type is given as a reference. For these combined irradiations, the actual data (O-O) has been normalised to 100% cell survival (—). The RBE values result from the comparison of this normalised data with x-irradiation alone. Redrawn from McNally et al.[12].

Interaction between high and low LET radiations

While of considerable importance for BNCT, the potential interaction between high and low LET radiations has not been extensively studied nor directly investigated in relation to BNCT. The sequential irradiation of V79 cells with fixed doses of either fast neutrons or ^{238}Pu α-particles (140 keV/µm), prior to exposure to high dose-rate x-rays [12, 13], has provided the closest approximation to BNCT irradiation conditions. For x-rays and α-particles given separately the RBE of the α-particles, relative to x-rays was approximately 6.0, 3.0 and 2.4 for clonogenic cell survival levels of 50%, 10% and 1%, respectively (Figure 4.2.5a), well below those calculated above for the high LET component

of the Studsvik epithermal neutron beam. When 0.5Gy of α-particles, which reduces clonogenic cell survival by 50%, is given prior to x-rays the resulting cell survival curve for x-rays is still curvilinear. Normalisation of the data back to an initial 100% shows the x-ray (with 0.5Gy of α-particles) cell survival curve to be unchanged from x-rays alone (Figure 4.2.5b). This is not the case when the initial α-particle dose is increased to either 2.0 or 2.5 Gy. The RBE of x-rays, combined with the higher dose of α-particles had an RBE of 1.25 when compared with x-rays given alone (Figure 4.2.5d). McNally et al. [13] concluded that "alpha-particles do cause damage capable of interacting with x-ray damage". However, the relationship is not a simple one, it depending on the relative mix of high and low LET radiation.

Conclusions

The determination of tissue specific CBE factors, the parameter that represents the biological effectiveness of the $^{10}B(n,\alpha)^7Li$ reaction products, needs to be a mandatory part of any development programme for new boron capture agents. The CBE factor provides an indication of the uniformity of the boron distribution within a tissue and is tissue specific. Thus CBE factors for a tissue, using existing boron carriers, cannot be used with safety in other tissues.

The biological effectiveness of reactor based epithermal neutron beams, relative to conventional x-rays, will be specific to that beam and weighting factors developed for another beam should not be extrapolated directly for use on other facilities, no matter how similar the physical characteristics of the two beams might appear. For example the application of weighting factors for brain tissue, developed for clinical use at BMRR, to experimental studies in dogs irradiated on the FiR 1 reactor beam provided a 12% over-estimate of the experimentally derived photon equivalent dose. While such differences may appear small, the steepness of tissue dose-response curves is such that had this estimate been in the opposite direction then serious over-dosage would have resulted.

For practical reasons appropriate normal tissue studies in large animal models may not be possible, however, before the clinical use of a new epithermal neutron beam, a biological calibration of that beam, relative to a centre that has had good clinical experience, is essential. This can best be carried out using a standardised *in vitro*, cell survival, model. This can provide an indication of the biological effectiveness of the new facility against the old and also eliminate well-known effects, related to dose-rate for low LET radiations, by storing the cells at 4°C over the period of irradiation. Such cell survival studies have already indicated an additional complication in that high LET radiation cause damage capable of interacting with x-ray damage in such mixed field irradiations. This should be an important area for future research since patient treatment planning is presently based on the premises that the different components of the mixed field irradiation in BNCT act totally independently of each other.

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4.3 Drug

4.3.1 Good Manufacturing Practice (GMP) production for BSH and BPA
O. Kriz

For effective application of BNCT for the treatment of cancer, it is necessary to use a proper carrier for the ^{10}B isotope. Currently, only two compounds, from the many tens designed for this purpose, are used in clinical tests, i.e. sodium mercaptododecaborate (BSH) $Na_2[^{10}B_{12}H_{11}SH]$ and L-4-borononophenylalanine, L-4-$(HO)_2^{10}B$-C_6H_4-$CH_2CH(NH_2)CO_2H$ (BPA), [1].

BSH   BPA
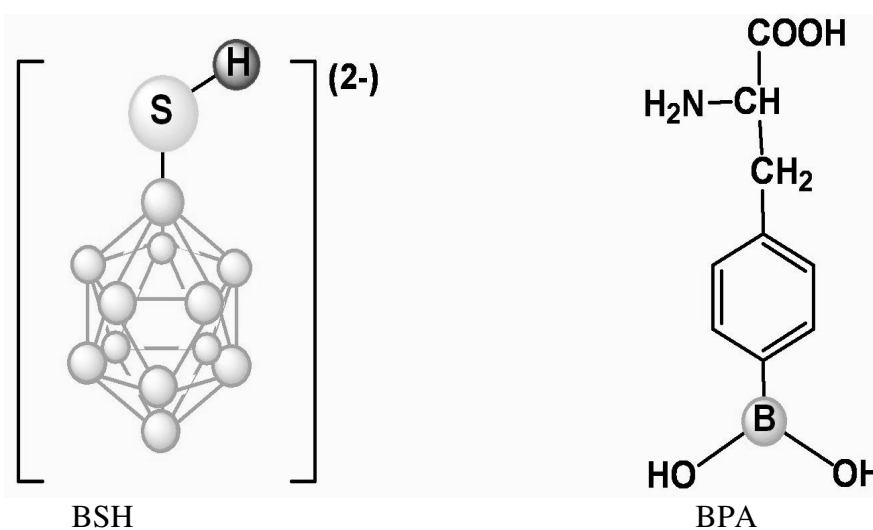
Neither compound is the ideal candidate for this sophisticated therapy as regards to their clinical use. The rate of the drug distribution between tumour-healthy tissue and tumour-blood, as well as persistence of both compounds in the tumour tissue, does not allow for the optimal conditions for

BNCT. Other compounds with better tissue distribution are more toxic or unstable. Several studies from the last decade show tetracarboranylporphyrins as promising future carriers, with which better results could be achieved. These compounds have already become one of the most studied systems. One example to demonstrate their potential, i.e. nickel tetra-carboranylphenylporhyrin, which contains 22% of boron in the molecule, shows significantly lowered toxicity and from biodistribution tests in mice, tumour:normal brain and tumour:blood differentials in the range of 10 and 250, 4 days after application, were found [2]. Another group of promising species are derivatives of metallacarboranes and anionic clusters (e.g. I, II, III), that have been tested as novel effective virostatics [3].

I   **II**   **III**
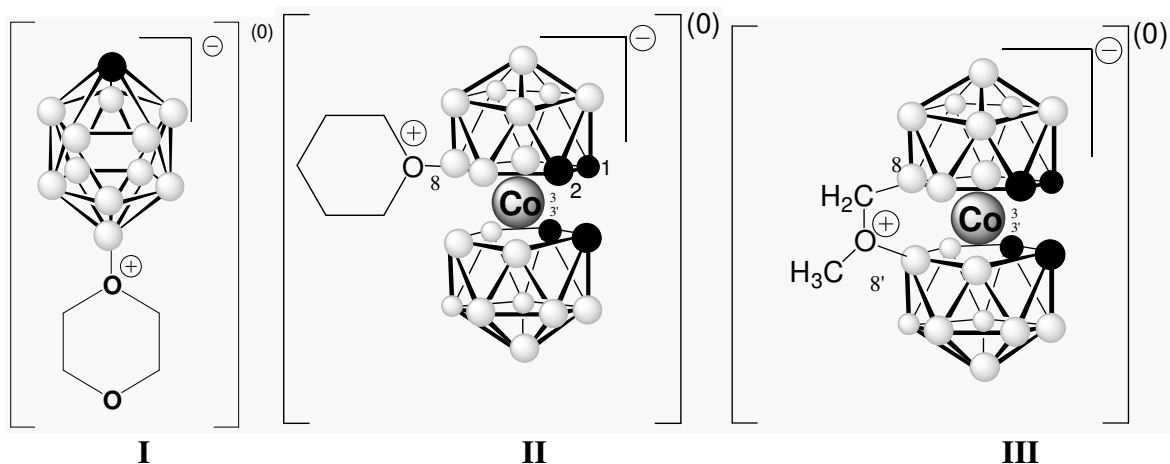
The exhaustive and expensive tests that precede the clinical use of new prospective drugs often take more than five years of intensive work. Over this period of time, BPA and BSH will remain the only drugs available for human BNCT tests. This implies that the two commercial drugs must satisfy high quality demands of the GMP certificate.
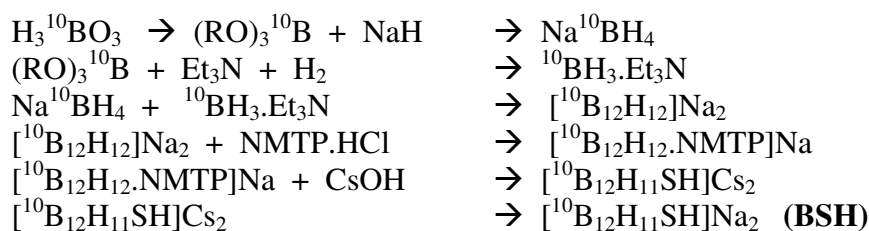
The principle of the production of drugs for human treatment is to manufacture medical products so as to ensure that they fit for their intended use, comply with the requirements of the Marketing Authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The accomplishment of this quality objective is the responsibility of management. It requires participation of the staff in different departments and at the levels within the company by the company's suppliers and by the distributors. To achieve the quality objective in a reliable manner means that the producer must correctly implement a system of Quality Assurance incorporating Good Manufacturing Practice and thus Quality Control. The whole process should be fully documented and monitored. In addition, all parts of the Quality Assurance System require competent personnel, laboratories, manufacturing, equipment and facilities.

As mentioned above, BSH and BPA are at present the only ^{10}B bearers used in human BNCT clinical tests. The first reported but unreliable synthetic method leading to $Na_2[^{10}B_{12}H_{11}SH]$ (BSH) was based on the reaction of hydrated $(H_3O)_2[^{10}B_{12}H_{12}]$ with liquid H_2S at an elevated temperature and higher pressure. Robust synthesis of BNCT drugs is one of the basic demands of Quality Assurance. At present, BSH of a high quality standard is produced by Katchem Ltd. using a procedure developed at the Institute of Inorganic Chemistry of the Czech Academy of Sciences, by the following scheme:

$$H_3{}^{10}BO_3 \rightarrow (RO)_3{}^{10}B + NaH \rightarrow Na{}^{10}BH_4$$
$$(RO)_3{}^{10}B + Et_3N + H_2 \rightarrow {}^{10}BH_3.Et_3N$$
$$Na{}^{10}BH_4 + {}^{10}BH_3.Et_3N \rightarrow [{}^{10}B_{12}H_{12}]Na_2$$
$$[{}^{10}B_{12}H_{12}]Na_2 + NMTP.HCl \rightarrow [{}^{10}B_{12}H_{12}.NMTP]Na$$
$$[{}^{10}B_{12}H_{12}.NMTP]Na + CsOH \rightarrow [{}^{10}B_{12}H_{11}SH]Cs_2$$
$$[{}^{10}B_{12}H_{11}SH]Cs_2 \rightarrow [{}^{10}B_{12}H_{11}SH]Na_2 \text{ } \textbf{(BSH)}$$

NMTP = N-methylthiopyrrolidon

The course of each step is monitored and checked and intermediates are purified by proper procedures. The same robust route has been elaborated for the synthesis of BPA. The original way to synthesise L-BPA started from p-tolueneboronic acid and led to racemic 4-boronophenylalanine. L-BPA was obtained by optical resolution of the racemate. This procedure is relatively cheap and readily feasible in bulk. The product was not quite optically pure and contained pyrogenic endotoxins which must be totally removed. One of the modern syntheses of L-BPA submitted by Katchem Ltd. that satisfies the rules of the GMP is shown in the following scheme:

$$L\text{-Phe} + I_2 \rightarrow 4\text{-}I\text{-}C_6H_4CH_2CH(NH_2)CO_2H$$
$$4\text{-}I\text{-}C_6H_4CH_2CH(NH_2)CO_2H + ROH + BOC \rightarrow 4\text{-}I\text{-}C_6H_4CH_2CH(NHBOC)CO_2R$$
$$H_3^{10}BO_3 + ROH + LB \text{ (Lewis base)} \rightarrow (RO)_2^{10}BH$$
$$4\text{-}I\text{-}C_6H_4CH_2CH(NHBOC)CO_2R + (RO)_2^{10}BH \rightarrow$$
$$\rightarrow (RO)_2^{10}B\text{-}C_6H_4CH_2CH(NHBOC)CO_2R$$
$$(RO)_2^{10}B\text{-}C_6H_4CH_2CH(NHBOC)CO_2R \rightarrow (HO)_2^{10}B\text{-}C_6H_4CH_2CH(NH_2)CO_2H$$
$$\rightarrow L\text{-}\textbf{BPA}$$
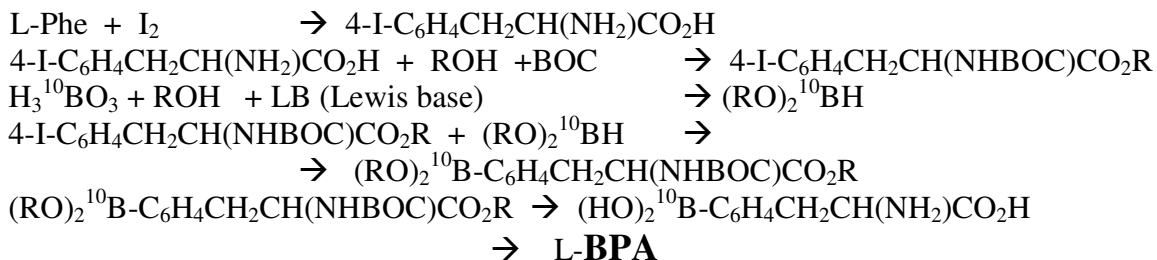
The quality of the product is the degree to which the internal characteristics satisfy the requirements for the given purpose. Therefore, for a ^{10}B carrier for BNCT cancer treatment, it is quality given by confirmation of identity, chemical purity, isotope purity and microbiological purity of final solution for the infusion. Further factors, which determine applicability of the drug for the treatment is the toxicity, stability and price. As a rule, the last three are more influenced by the substance of the drug.

Factors influencing the quality of BSH and BPA (Ishikawa diagram)
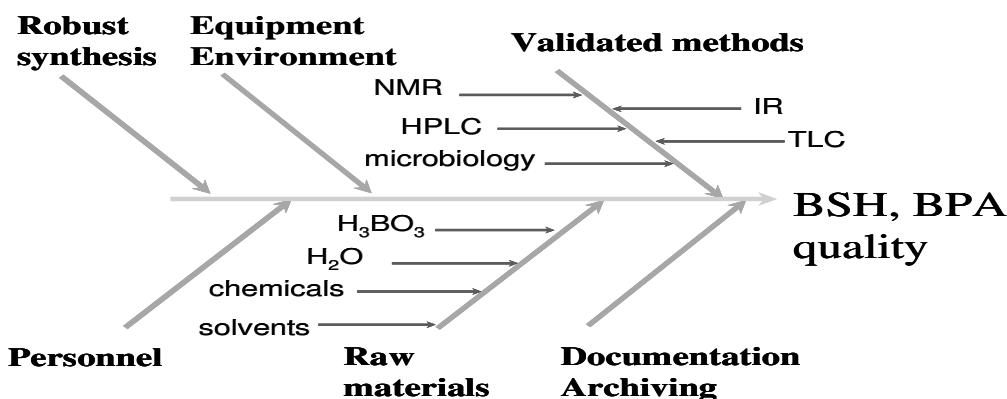
The Ichikawa diagram illustrates the way to Quality Assurance and Good Manufacturing Practice for medicinal products. Robust synthesis means not only exactly defined procedures but also that the production and control operations are clearly specified. All necessary controls on intermediate products, and any other in-process controls and validation are carried out. The finished product is correctly processed and checked according to the defined procedures. The medicinal product is stored, distributed and handled so that quality is maintained throughout its shelf life. During the whole procedure of synthesis, analyses and handling, procedures of self-inspection and quality audit currently evaluate the effectiveness and applicability of the Quality Assurance system.

Qualified personnel are essential for the establishment and maintenance of a satisfactory system of quality assurance. The production should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any employee should not be so extensive as to present any risk to quality. There must be an organization scheme. People in responsible positions should have specific duties with written descriptions and adequate authority to

implement their responsibilities. Such duties may be delegated to designated deputies. There should be no failure in the responsibilities of personnel with the application of Good Manufacturing Practice philosophy.

The laboratories and manufacture of BPA and BSH, as well as the equipment, is located, adapted and maintained to suit the operations of the production and analyses of drugs for human medicine. The organizational set-up and design should minimize the risk of errors and permit effective cleaning and maintenance in order to avoid any adverse effect on the quality of products. For each step or test, particular glassware or stainless steel kettle is used. Packaged BPA is stored in a special box at temperatures up to $20^{o}C$, BSH is refrigerated at $+4^{o}C$.

Production should be performed and supervised by competent people. Therefore, all handling of materials and product, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded. All incoming materials are supplied by stable qualified producers or dealers and should be checked to ensure that the consignment corresponds to the order. At the final stages of the BSH or BPA production, the guaranteed quality of ultra pure water plays an important role. Especially, the selection of a stable supplier of water helps to avoid problems with oxidized products in BSH and intermediates in its synthesis.

Good documentation and archiving is the essential part of the Quality Assurance system and complies with GMP philosophy. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications describe in detail the conditions which the product must meet, the starting materials, intermediates and packaging material used for the final drug. Manufacturing Formulae, Processing and Packaging Instructions state all started materials and the procedure of production and packing. Standard Procedures give directions for performing some operations such as cleaning, clothing, environmental control, sampling, testing or handling of equipment. Records provide a history of each batch of product, including its distribution and all other relevant circumstances regarding the quality of the final product. Therefore, due to correct and complete documentation, "*…it should be possible for an inspector (or a customer), maybe four or five years hence, to look at the records of the work and determine easily why, how and by whom the work was done, who was in control, what equipment was used, the results obtained, any problems that were encountered and how they were overcome*" (D. L. M. Weller ,1988).

The Department of Quality Control is the most relevant institution of each GMP producer. Quality Control is concerned with sampling, specification and testing, as well as the organization, documentation and release of product. The objective is that materials are not released for use, nor a product allowed for sale or supply, until their quality has been judged satisfactory. Quality Control is not only the pursuit of laboratory tests but is part of all decisions which may concern the quality of the product. Therefore, the independence of Quality Control from production is a fundamental condition for satisfactory function of this tool.

For Quality Control of raw materials, intermediates and the final product, validated analytical methods are used. All starting material used for the manufacture of BSH and BPA is of an analytical grade, stable and from reliable suppliers. During each batch of synthesis, it is necessary to do step-by-step control. HPLC and GC analyses combined with high field multinuclear NMR techniques are proper tools for this purpose. Generally, for prompt and simple current analysis in some stages of the syntheses, TLC is very useful. For the final product, a HPLC analysis is used for confirmation of identity and determination of critical impurities. IR spectra are typical for BPA and BSH; jointly with ^{1}H, ^{10}B (by BPA also ^{13}C). NMR spectra identify the individual compounds and ^{10}B enrichment of the boron present. ^{10}B elemental analysis is used for the determination of active substance of BSH or BPA

in the product. LAL test is used as the proof for the absence of endotoxins and the shelf-life test of stability confirms the expiration date of at least two years.

Quality Assurance and GMP for the production of existing [10]B carriers are necessary for the efficiency of present Boron Neutron Capture Therapy. The currently produced and clinically tested compounds, BSH and BPA, once manufactured, can be used for BNCT for at least another five years, which is the minimum time necessary before new, more promising drug may appear.

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4.3.2 Pharmaceutical issues
C.M. van Rij, A.J. Wilhelm, P.M. Bet

Introduction
Medicinal products should be produced in accordance with the principles and the guidelines of Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in The European Community, Volume IV). In Annex 13 of the EEC GMP detailed guidelines are given for investigational medicinal products.

Documentation
One of the premises is a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

This Product Specification File should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following documents:

- Specifications and analytical methods for starting materials, packaging materials,
- intermediate, bulk and finished product.
- Manufacturing methods
- In-process testing and methods
- Approved label copy
- Relevant clinical trial protocols and randomization codes, as appropriate
- Relevant technical agreements with contract givers, as appropriate
- Stability data
- Storage and shipment conditions

Quality Control of the starting material

BPA and BSH are purchased from a certified supplier and every batch is provided with a Certificate of Analysis. This includes tests on identity by NMR, IR spectroscopy and elemental analysis of the ^{10}B content. Purity is monitored by HPLC analysis.

The Quality Control section of the laboratory of our pharmacy confirms the identity of the material by determining the melting point and by performing IR spectroscopy. Purity is checked by an HPLC method (> 98%) and endotoxines were measured with a chromogenic kinetic method (< 0.025 IE/mg). L-BPA content was determined by optical rotation and the degree of enrichment was determined by prompt-gamma ray spectroscopy (PGRS).

If all quality control test are within specifications, a certificate of analysis is prepared and the batch is released for manufacturing.

The shelf-life of the BSH and BPA raw material is set to 1 year. This shelf life is extended with one year after retesting the material on purity by HPLC.

Manufacturing
The application of GMP to the investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of the clinical trial are not affected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. The facility used for preparation of these medications requires a GMP manufacturing license if the handling of the investigational product is more complicated than dissolving and/or adding to a higher volume of intravenous fluids. At present, all investigational products used in BNCT are administered intravenously, which means that manufacturing should take place either under aseptic conditions, or the product must be sterilized in its final package.

Environment and personnel
Aseptic manufacturing of medicinal products requires specific conditions. Preparation must take place in a laminar flow cabinet (class A environment), which should be placed in a class B background environment. Monitoring of the aseptic conditions is required, together with the aseptic preparation skills of the technicians (according to annex 1 Manufacturing of sterile products). All personnel involved should be adequately trained. Manufacturing of products to be sterilized should take place in a class C or D environment.

Validation
Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production. Premises and equipment on the other hand are expected to be validated. Validation of the aseptic manufacturing process should be performed using media fillings. Sterilising processes are required to be completely validated.

Shelf-life investigation
To determine the shelf-life of the investigational product, a validated, stability indicating method (normally HPLC analysis) should be used. The shelf-life investigation should take place with at least two different batches of investigational product, prepared on different days by different personnel using different batches of ingredients. The shelf-life is the time when the 95% confidence interval of the concentration of the active ingredient crosses the 95% limit.

Packaging and labelling
Investigational medicinal products are usually packed individually for each subject included in the clinical trial. Packaging materials should undergo normal quality controls used for routine production.

Labelling demands much more information than routine labelling. The obligatory information is also stated in the GMP annex 13.

Release by a Qualified Person
The process of manufacturing and quality control as well as the finished product should be checked by a Qualified Person, QP. This QP is to release every batch of investigational medicinal product personally. This provision is laid down in Annex 16 of the EU Guide to GMP. Release by a QP is for ensuring that the batch has been manufactured in accordance with the principles and guidelines of EC GMP and to ensure that in the event that a defect needs to be investigated or a batch recalled, the QP is readily identifiable.

If the investigational medicinal product is produced outside the European Union, the import into the EU should also be accompanied by a QP-release of every batch. The holder of an EU import license should provide a QP to check the process of manufacturing and quality control. After verification of the fulfilment of requirements to commence a clinical trial (see art 9 of the Directive 2001/20/EC) the investigational drugs can be distributed to the study sites.

Distribution
The distribution of medicinal products should be in accordance with the rules of Good Distribution Practice, GDP. The GDP rules aim at maintaining the quality of the medicinal product during storage and transport. The GDP provides regulations about receipt, storage, deliveries, returns and emergency recalls. These processes should be part of a quality system with trained personnel, written instructions, adequate premises and equipment and internal auditing. All handling should be documented and transfer from one party to another should be accompanied by documentation. This documentation must be readily available in case of a recall. Maintaining the right temperature conditions is an important factor to ensure quality. The medicinal products requiring controlled temperature storage should also be transported by appropriate means. Temperature logs should be available for both storage and transportation. There should also be an emergency plan available for urgent and non-urgent recalls. In case of a recall, all destinies should be immediately identified and contacted with proper instructions.

4.4 Clinical trials of the EORTC BNCT Group

A. Wittig, L. Collette, W. Sauerwein

Trial strategies

In order to establish a new treatment modality for clinical use, preclinical investigations and early (phase I-II) clinical trials must first show results supporting the principle underlying the mechanics of that treatment's activity and its safety to patients. This is necessary in order to obtain permission from the regulatory authorities and the scientific rationale to conduct more advanced and larger scale (phase III) clinical trials that will eventually lead to the acceptance of the new modality as a routine treatment in hospitals. The conduct of clinical trials is strictly regulated by national laws and international guidelines e.g. guidelines of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [1], the rules for good clinical practice (guideline E6(R1)), and the Rules Governing Medicinal Products in the European Union [2] or the regulatory guidance of the U.S. Food and Drug Administration [3]

These complex rules were primarily developed to allow data to be collected for new drugs but have been extended to any new medicinal products and therapeutic procedures for humans. The trial strategy to develop a new treatment has been well established for drugs. However, a clear design for clinical trials to test and implement a binary treatment modality such as Boron Neutron Capture Therapy (BNCT) is missing. The EORTC BNCT Group aimed to develop such a strategy for clinical trials with the goal to establish BNCT as a treatment modality [4].

The concept underlying treatment with BNCT differs from that of conventional radiotherapy. BNCT can irradiate an extended area where microscopic disease is expected to be present. Unlike conventional radiotherapy, the selective damage to the tumour cells is not achieved by the direct action of the primary beam but is obtained by the neutron capture reactions releasing high LET-particles where ^{10}B-atoms are present. The therapeutic effect occurs only when the ^{10}B-atoms, delivered to the tumour by a dedicated compound are irradiated with thermal neutrons.

BNCT uses an irradiation beam that is not established for clinical practice and that produces a complex dose distribution with high and low LET components. To date, only a nuclear reactor can produce an epithermal neutron beam with the fluence needed for BNCT. This involves the use of technical equipment that is not initially aimed for clinical applications and which may thus need special licensing for that particular application.

Furthermore, BNCT needs a boron carrier to be injected in the patient. This boron carrier must also undergo standard clinical testing like all other investigational drugs. In contrast to other anticancer drugs however, a compound used for BNCT does not on its own have any therapeutic effect but is exclusively aimed at transporting ^{10}B-atoms to tumour cells. Consequently, conventional methods and trial designs are not strictly applicable to test such compound. A prerequisite for BNCT is a selective accumulation of the ^{10}B-carrying compound in the tumour. Therefore, knowledge on the biodistribution of the compound is a prerequisite to develop such a treatment option and may be used as a surrogate endpoint for early clinical testing of boron carriers. A trial with that endpoint could serve a first in a human proof-of-principle trial, but can also help to identify organs at risk, an information that is a needed prior to applying both drug and irradiation together since their joint application carries a greater risk of serious harm to patients.

All these aspects make clinical trials in BNCT a challenging task for the clinical scientists as well as for the regulatory authorities and require strict quality control.

To overcome these issues, the EORTC BNCT Group designed three different prospective early clinical trials [5]:

1. EORTC 11001: "^{10}B-uptake in different tumours using the boron compounds BSH and BPA". This was a translational research/phase I clinical trial. that aimed to identify tumour entities that may be treated with BNCT by demonstrating a selective uptake of the compounds sodium mercaptoundecahydro-closo-dodecaborate (BSH) or para-boronophenylalanine (BPA) or both by these tumours [6].

2. EORTC 11961: "A phase I clinical trial: Postoperative Treatment of Glioblastoma with BNCT at the Petten Irradiation Facility". The aim of the trial was to establish a safe BNCT irradiation by identifying the maximum tolerated irradiation dose for glioma patients [7,8].

3. EORTC 11011: "Early phase II study on BNCT in metastatic malignant melanoma using the boron carrier BPA". This phase II trial was designed as a first multicentre trial to be performed in a similar way at Harvard/MIT and Essen/Petten. The protocol included a biodistribution study and a treatment study performed in 2 fractions aimed at establishing therapeutic treatment activity. The protocol had to be terminated due to difficulties in patient recruitment and lack of financial resources after the time period foreseen for the trial.

Study protocol and monitoring

The protocols were reviewed and approved by the EORTC Protocol Review Committee. They were also reviewed and accepted by the Ethics Committees of each participating hospital and for the first protocol (EORTC 11961) by a specialists' ethics committee (KEMO) established to give advice to the Dutch Ministry of Health.

The independent running and data management of the trial EORTC 11961 was performed by the NDDO Oncology (Amsterdam). For the other two protocols the EORTC Headquarters ensured consistency of the collected data. In trial 11961, all treatments were performed in at the HFR Petten but multiple international centres recruited and followed their patients after BNCT. All GCP requirements were met before a recruiting centre was initiated and was allowed to begin patient accrual. All centres received an initiation visit made by a representative from NDDO/EORTC and a representative from the Study Centre Essen (Study Coordinator). In each centre, all departments involved in the protocol and treatment were visited (e.g. neurosurgery, neurology, radiology and the pharmacy) and all study procedures were reviewed with responsible personnel and explained. All essential study documents were obtained (Curriculum vitae of all persons involved, laboratory norms and quality control certificates, correspondence and approval of the Ethics Committees and a copy of the written informed consents (WIC)) prior initiation. All Case Report Forms (CRFs) in trial EORTC 11961 were monitored on-site, with 100% data verification. Evaluation of the patient's Quality of Life was requested by KEMO and was initially performed by the EORTC Quality of Life Study Group. Because a Quality of Life evaluation is not designed for a phase I trial, this part of the study was however abandoned after the second cohort.

In trial 11961 a Supervisory Board composed of 4 independent specialists (2 radiotherapists, 1 neurologist, 1 radiobiologist) had been established by the EORTC BNCT Study Group. This board acted as the independent review body that had final decision on the dose escalation steps, was responsible for the quality assurance of the study, (including that of the radiotherapy performed at Petten) and gave advice on matters of clinical, ethical and technical bearing. The Supervisory Board also reported to the Dutch Ministry of Health after a treatment period of 2 years. A reference pathologist (Prof. Dr. O.D. Wiestler, Bonn, Germany) was appointed to independently review all histopathological samples. Similarly, a reference radiologist (Prof. Dr. med. F.E. Zanella, Frankfurt, Germany) was appointed to independently review all radiological images of the brain (CT and MRI) obtained for the patients from the diagnostic image through to the end of the follow-up period.

Trial 11001 is a monocentric trial. The Institute for Medical Informatics, Biometry and Epidemiology, University Duisburg-Essen performed independent computerized and manual consistency checks. In case of inconsistencies, queries were issued until resolution. The EORTC Headquarters was responsible for performing quality audits that aimed to evaluate the local facilities available to the responsible investigators for performing clinical trials, to ensure that the clinical trial was conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice and the applicable regulatory requirement(s) (ICH/CPMP GCP Guidelines), to assess the consistency of the data reported in the central database located in Essen with the source data, and to check that all (serious) adverse events have been properly reported.

Study medication

For the trials, the ^{10}B-enriched compounds BSH and/or BPA were used, formulated in vials each containing 1000 mg of the substance. After disappointing experiences with several supplying companies, it became possible in the frame of an FP5 project to establish a reliable drug support at a high quality level [10]. The compounds were produced according to a drug master file and a written procedure for preparation and quality control of the final product and its intermediates. + GLP compliance! The material was then imported into The Netherlands by the Pharmacist of the Vrije Universiteit medische centrum (VUmc) in Amsterdam. Quality control data were provided with each batch imported.

In the laboratory of the VUmc pharmacy, final quality control checks were performed, e.g. for BSH the following tests were mandatory prior to release the batch:

- Identification of the study medication. Test for the presence of sodium and identification of the product by infrared absorption spectrophotometry.
- Absence of oxidation products: This was tested by high-pressure liquid chromatography. The material met the requirements if the total of the oxidation products was less than 2%,
- Absence of bacterial endotoxins (pyrogens): This was tested by Limulus Amoebocyte Lysate test. The material met the requirements if it contained less than 0.025 IE pyrogens/mg BSH.
- Assay of the study medication: These tests were carried out at NRG Petten under the auspices of the VUmc pharmacist according to written procedures:
  o The BSH content was tested. The material met the requirements if the total amount of BSH in each tested vial was 95-105% of stated,
  o The degree of ^{10}B-enrichments was tested. The material met the requirements if the degree of enrichment was >95%.

The responsibility for the quality control and for the release of the substance for clinical use was delegated to two different pharmacists. If the batch met all requirements, it was released for clinical use by the pharmacist with an expiry date one year after initial testing. The substance had to be re-tested every year for degradation products by high-pressure liquid chromatography. The substance was sent to the collaborating hospital together with a certificate of analysis provided by the pharmacist of the VUmc and with a declaration that the material is suitable for clinical use. Before administration to the patient, the compound was dissolved according to standard operating procedures under aseptic conditions and filtered through a sterile 0.22 μm filter. The material remained stable for at least four hours at room temperature and had to be administered within that time.

Informed consent procedure

Written informed consent of patients is a prerequisite before they can be registratered in clinical trials. In trials 11961 and 11011, which included a biodistribution study as well as a BNCT treatment study, all patients signed a t Written Informed Consent (WIC) before surgery, a second WIC before

registration for BNCT treatment and in trial 11961 only, where patients were recruited from international sites, the patients signed a third WIC to the treating radiation oncologist before the actual BNCT treatment in Petten. All centres used the same WIC documents, which were translated into the local language and adapted to the requirements of each local Ethics Committee. All patients also consented to storage, testing and research on their tissue and blood samples as applicable in the respective trial protocols.

Insurance

Insurance of the patients had to be arranged to cover the liability of the sponsor and of any participating parties for bodily injuries and property damages caused to persons subject to the clinical investigations and related to the investigations. Special attention had to be given to the national regulations in France (article L 2097 du Code de la Santé Publique, modifié par la Loi 94.630 du 25 Juillet 1994; Loi du 20 décembre 1988 et son décret d'application du 27 septembre 1990, décret no. 91.440 du 14 Mai 1991), Austria (Arzneimittelgesetz AMG §32 (I) Zi 11 und Zi 12) and Germany (§ 40 Absatz 1 Nr. und Absatz 3 AMG). In recent years, since the EU Directive on Clinical Trials/Medicine for Human Use came into effect in May 2004, these national purposes were extended to most of the EU countries, further increasing the costs for international trials. The EORTC insurance programme covered all patients entered on behalf of EORTC in EORTC studies. Within the European Union this insurance programme covered the EORTC as the sponsor, the investigators and all local hospital staff taking care of patients entered in the EORTC BNCT studies.

Documentation

All data were handled following GCP guidelines. All documents directly related to the trial (i.e. patient identification codes, protocol, documentation, case report forms, approvals) are filed in the Study Centre Essen until at least 2 years after the last future marketing application of BSH/BPA (assuming the compounds will be successful and marketed; note: this is required by ICH-GCP), but not shorter than 30 years. All centres are required to archive all study documents as well as the patient files for the same period

Care is taken to protect the anonymity of the patients with regard to data collection. As the hospital in Essen in many cases was both, the patient registration and the study management centre, as well as the medical treatment (BNCT) centre for all patients, a strict separation of data collected for treatment purposes and for the trial purpose had to be established.

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4.5 Patient care
K. Hideghéty, B. Hahn

Implementation of boron neutron capture therapy for patients requires special procedures. All the necessary equipment and infrastructure for medical supply, both for nuclear and medical emergencies, in a highly technical surrounding at a nuclear reactor site, must be available. Conditions have to be established for performance of fractionated radiation with high geometric accuracy, for administration of the boron compound, and for blood sampling around and during BNCT. In addition, a close cooperation has to be organised between the institutions and hospitals participating in patient preparation, transportation, treatment, patient care and follow up. Finally, the psychological aspects of applying an experimental, highly complex therapy modality partly outside of hospital environment need to be taken into account. Extra consideration must be exercised at the BNCT facility to put the patient and his/her partner/companion at ease. There are basically 3 different sections to be considered from the point of view of these needs:

- a dedicated area to be used as the medical unit, similar to any hospital wing in a modern Radiation Oncology department,
- the irradiation facility and
- special provisions for the treatment
- communication with the patients

Dedicated medical area
The patient should be received at the reactor site in surroundings covering his needs and providing the necessary support to the clinicians taking care of the patient.

There should be a separate room for consultation and any medical examinations, e.g. when the patient is first seen by the physician or for any control throughout treatment, to take blood and to infuse the boron compound, as well as to treat the patient in case of a medical problem. This room is equipped like any general practitioner's office with the possibility to perform basic physical examinations, e.g. physical examination of heart and lung, eye and ENT region (light source), basic neurological status, and to assess parameters such as blood pressure, ECG, etc. For BNCT, the boron compound may have to be infused in this room, requiring the need for an infusion pump. In addition, basic equipment to handle a medical emergency has to be available, such as a defibrillator, oxygen supply, puls-oxymeter and all necessary medication. The selection and maintenance of the medical equipment is the task and responsibility of the clinical partner. Interested readers and researchers may want to gather further information in our respective SOP's or may want to consult propositions how to deal with medical emergencies issued by their local or national authorities. Any scientific publications on medical

emergencies a small selection of these as mentioned in the annotations to this chapter are recommended, as if any medical emergencies occur there will be all sorts of emergencies and they will not be specifically linked to the BNC-treatment.

Furnishing should include a desk, chairs, examination couch for supine position, which should be comfortable enough to allow the patient to rest. Enough storage possibilities for drugs, stationery, etc, have to be foreseen. All the necessary material should be located easily at hand. It has to be realized that there will be medical waste contaminated with patient fluid, which has to be considered as infectious material (blood, syringes, bloodied gloves), as well as sharp instruments such as needles. All this material must be disposed of properly following national rules on medical waste, usually in dedicated medical waste bins.

In order to avoid possible radioactive contamination of the patient's personal clothing, it is advisable for the patient to change clothes to be used during irradiation only.

Appropriate sanitary installations have to be considered for both staff and patients. For handicapped patients, there should be sufficient accessibility for a wheelchair and supporting staff.

A waiting and reception area for the patient, and in many cases his/her family too, should be located in the same building, where they should feel welcomed and made at ease with comfortable chairs and furnishing. There may be long waiting times for the family, hence be sure to provide coffee and other refreshments, as well as reading material, including information on BNCT. It may need to be taken into consideration that for security reasons, a member of the local staff may need to be present in this building at all times.

Additional space, which could be a separate office, has to be provided for the physician. The office should be equipped with adequate telecommunication devices: telephone, fax and internet. This is essential for such a non-hospital based facility, as the clinician may need support and supplementary information from the hospitals having access to all patient related data, such as medical history, laboratory parameters, images and support from specialists at different locations. A close contact is required with the pharmacy for the preparation of the boron compound.

According to the local situation at the facility, easy access for the patient to the treatment room has to be foreseen. Most importantly the atmosphere for the patient should be as reassuring as possible because patients might be anxious or not at ease when arriving at a nuclear research facility with a technical surrounding, including security and safety procedures not commonly found in a hospital environment.

The Irradiation Facility
The irradiation room should reflect a treatment room in a conventional radiotherapy department. A safe and reproducible positioning of the patient is mandatory. This includes a dedicated treatment table, and an adequate patient positioning system. The materials used should not contain elements that could be activated by thermal neutron irradiation. Laser light devices are commonly used to define the coordinate system of the radiation room in order to translate the information coming from diagnostic images and treatment planning into the positioning of the patient for the irradiation. During the treatment the patient has to be under continuous observation, which includes visual (TV cameras) and audial (microphone/ speakers) monitoring. From experience, it is necessary to monitor vital (patient) parameters, for example by puls-oxymeter or ECG. In case of long irradiation times, the possibility to speak to the patient (telling the time) and to play music, even to the patient's own choice, is helpful. It is obvious that the equipment to deal with any medical emergency has to be readily available close by.

Special Provisions

Regular blood sampling is necessary prior, during and after each irradiation. At some facilities, where very long irradiation times may be necessary and there is no possibility to close the beam by means of a mechanical shutter, it might be necessary to install an on-line blood sampling system that can be handled from outside the irradiation room. However, it is most likely that irradiation times are suitable to perform the blood sampling before and after each irradiation beam. The collected blood has to be measured for boron concentration in a very short time (few minutes). The most convenient technique is prompt gamma ray analysis (PGRA). Chemical analysis for example, by Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES) will need more time prohibiting the correction of the irradiation time in the case of an unexpected boron concentration.

Prior to the patient leaving the treatment room and prior to leaving the reactor site, radioprotection measurements have to be performed to evaluate the activation of the patient and to exclude any contamination. The instruments, for example a standard portable dosimeter, and the place to perform these measurements should be available and conveniently located.

Any action related to the patient has to be documented accordingly, which includes at least taking photographs of the positioning, but may include a video of the whole irradiation. All these documents will have to be archived following the national rules for medical archiving and strictly respecting the confidentiality rules in place for all medical actions.

Communication with the patient

Detailed information should be provided in an easily, understandable form about the treatment, about the procedures including the nuclear reactor and its associated safety measures. This should be repeated and the explanation facilitated using written material with images and a video, which could be handed over to the patient and his family. It is highly advisable to include the patient and the family members in the preparation procedure and to encourage them to take an active role during BNCT.

4.6 Treatment planning
V. Nievaart, G.G. Daquino

Treatment planning (TP) programs are required in order to predict the dose and/or particle fluxes given to the patients. Since most BNCT treatment beams are reactor-based, the treatment planner has not only to determine the dose induced by neutrons but also from gammas. Most of the gammas already present in the beam are originating from the reactor core. Neutrons induce a dose in tissue due to reactions with ^{10}B, hydrogen (giving recoiling protons and gammas) and nitrogen (producing protons). Thus in total there are four dose components. Since neutrons are involved, the most experienced method of calculating the doses and fluxes in complex geometries from patients is based on the Monte Carlo technique. This chapter presents the Monte Carlo based TP systems which are used or under development for BNCT. As well as discussing the Monte Carlo TP programs used in BNCT Petten, some accompanying studies are discussed which are closely related to this matter.

Description of BNCT TP systems used in BNCT in Europe

This section gives an overview with descriptions of the 3 Monte Carlo based radiotherapy TP software developed, used and applied in European BNCT facilities. Other treatment planning programs exist, such as in Japan and Taiwan, but are not described here.

BNCT_rtpe

In 1988, at the INEEL (Idaho National Engineering and Environmental Laboratory), a special-purpose medical image based Monte Carlo system optimised specifically for radiotherapy with epithermal neutron BNCT was first applied. This initial effort led to the collaboration with the University of Utah, Department of Computer Science. The outcome of this collaboration was the BNCT_edit system [1]. In 1994, BNCT_edit was replaced by an improved system, BNCT_rtpe (BNCT Radiation Treatment Planning Environment) [2]. BNCT_rtpe was developed by the INEEL in collaboration with the Montana State University (MSU) Deparment of Computer Science. This code inherited the experience gained with BNCT_edit. In addition, new sophisticated characteristics were implemented, such as the Non-Uniform Rational B-spline (NURBS) approach to image-modality-independent reconstruction of patient geometry from medical images [3]. BNCT_rtpe is the TP system used in the treatment of GBM patients at Petten. All the treatments of the patients in the first trial (in all 4 cohorts) have been planned through the use of BNCT_rtpe. This TPS is able to reconstruct the human head from the CT (or MRI) scans of the patient. The code Bnct_rtpe [4] provides a Graphical Unit Interface (GUI), which helps the user to construct the B-splines related to a number of "bodies", identified on the image slices. After loading the image data, the bodies are identified by hand (skin, brain and several organs at risk, like eyes, pituitary and salivary glands, optic chiasm). Then, considering the medical prescriptions, the target is identified also on the slices. The GUI provides also the possibility to represent automatically the B-splines generated. In particular, it is possible to represent the bodies produced as separately as in the whole structure. Figure 4.6.1 represents all the bodies as plotted in the reconstruction window of Bnct_rtpe. The material composition for the previous bodies is selected from a standard library.

An input file (.input extension), ready to be processed by the transport calculation code connected to this TPS, the rtt_MC, is written, containing the information on the type of beam used (spectrum, flux, and so on). Therefore, this part constitutes the pre-processor of the Monte Carlo transport calculation. After the rtt_MC calculation, the results are presented using three different support programs: XCONTOURS, DOSE and EXCEL. XCONTOURS furnishes also the isodose curves related to the rtt_MC calculation, superimposing them on the CT slice images. The default coordinate reference system used in BNCT_rtpe is made with the X and Y axis on the CT plane and the Z axis entering the view.

Figures 4.6.2 and 4.6.3 show some examples of the isodose curves related to the physical boron dose and the total weighted dose respectively.

The DOSE program permits to represent the depth-dose curves (weighted and physical doses) related to the centreline of the beam and the dose-volume histograms related to all the regions of the model. The DOSE utility program scans the output file of rtt_MC (.out file); the same file is scanned by EXCEL in order to acquire useful data for further calculations. In fact the dose rate data are inserted manually from rtt_MC into the TP Spreadsheet for the predefined positions (organs at risk). The spreadsheet calculates the irradiation time and the doses for all beam components given a prescribed physical dose at the prescription point. Another important feature, also present in the other TPSs, is the evaluation of the doses delivered to the so called organs at risk, such as the pituitary gland, the salivary glands, the eyes, the optic chiasm, the inner ears and the thalamus. The positions of the organs at risk are defined by the user during the pre-processing phase. Afterwards, the system calculates the doses and fluences in these check points.
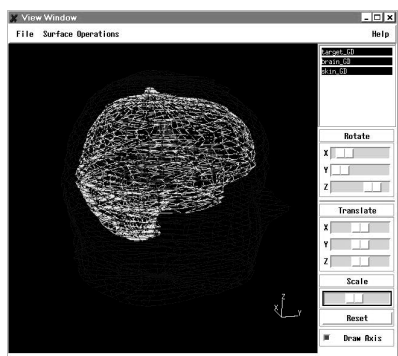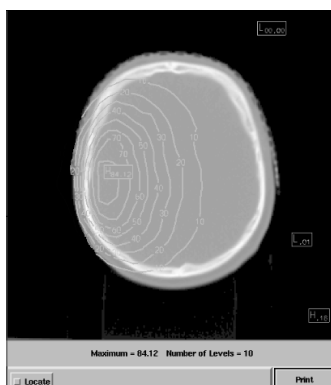
Figure 4.6.1: Reconstruction window in Bnct_rtpe.
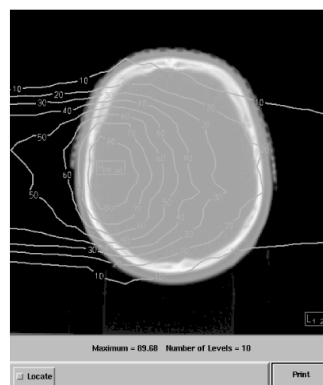

Figure 4.6.2: Boron isodose curves

Figure 4.6.3: All components (weighted) isodose curves

SERA

The SERA (Simulation Environment for Radiotherapy Applications) TP system consists of seven modules that can be run independently. From the first module, which converts a set of CT or MRI images into a specific internal format, to the last one, which displays the computed doses, the SERA system is a stand-alone package. The SERA software can be divided into three main parts:

1. Modelling of the patient's geometry using manual and semi-automated tools from CT and MRI images.
2. Computation of the dose within the geometric model with SeraMC, the Monte-Carlo-based radiation transport code developed by the INEEL. Actually, this is a subset of routines taken from the old Morse Monte Carlo code.
3. Contouring and display of the computed doses onto the original set of medical images.

SeraModel is the image editor that allows the user to determine either manually or semi-automatically regions of interest through the whole set of medical images. The reconstruction technique used is based on a pixel-by-pixel uniform volume element, named "univel" [5]. The resolution of the model is therefore limited to that of the original medical image, allowing very accurate representation of the patient's geometry that usual analytical surface representations cannot afford.

A list of predefined bodies such as brain, skull, tumour, ventricles, etc. is available and refers to files that contain all the information required for radiation transport (elemental composition, RBE factors of the various dose components, etc.). Several editing modules are available in seraModel for making the completion of this task easier either manually or automatically [6].

A single module, seraCalc, is implemented in the core of the TP system for computing the radiation transport of each field into the univels geometry created from the modules described previously. This interface allows the user to input parameters for creating an input file to the Monte Carlo calculation tool, seraMC.

The remaining modules of SERA system deal with the editing and display of the dose components computed by seraMC (also called post-processing phase). seraPlan allows the user to statistically combine up to four fields and/or up to six fractions from several independent seraMC calculations in order to produce single effective doses. The dose combination is performed by weighting each specified field dose component by the appropriate weighting factor, source strength, boron concentration and exposure. The calculated doses, normalised to unit exposure, unit source strength and unit boron concentration are then edited. seraDose is the dose contouring utility that displays the

two-dimensional isodose curves edited by seraPlan superimposed over the original set of medical images.

NCTPlan
NCTPlan is the last version of a series of TPS designed and implemented at MIT since 1990 [7]. In 1996, MacNCTPlan [8] was released with many features that are still present in NCTPlan.

MacNCTPlan is an interactive TPS coupled to the MCNP4B Monte Carlo radiation transport code [9]. It can be subdivided into two distinct parts: Part I provides the graphical environment for the construction of 3D mathematical solid models from 2mm-slice medical images, while Part II furnishes the environment for determining the dose patterns and for displaying the isodose contours superimposed on the corresponding CT images of the patient's head.

As the use of some MCNP features not involved in BNCT calculations increases the run time, enhancements to the ordinary version of MCNP4B have been performed within collaborative work between LANL and MIT/Harvard [10].

In the first part of MacNCTPlan, the 3D mathematical model of the patient's head is created from a set of 2D images, making use of the voxel reconstruction technique. In this method, each plane of medical image data is partitioned into squares of regular size before being mathematically stacked to construct a large 3D array of 11,025 cells of 1 cm^3 volume. A material file should be prepared for the material assignment to each cell of the 3D model. To this purpose, two sets of 256x256x8 bits CT images are required. The first set is done without the iodinated contrast agent (I- stack) and is used to determine the tissue type that will make up the material of the 3D model for MCNP calculations. The second set of images is performed with an iodinated agent (I+ stack) that causes the tumour and oedema to be more visible on the computed images for the tumour outline process. Gd-enhanced MRI images can also be used for identifying and locating the tumour and the oedema. This region is drawn on the slices where it appears and saved in a separate text file to be used with the I- stack of images.

Once the target region has been defined, the user should select with a proper pointing option the region of interest (ROI), which contains the tumour. The ROI should include areas of soft (tumourous and healthy) tissue, skull and air. In fact, these are the four available elemental materials that fill the irradiation volume for the radiation transport calculations. Special care is taken when assigning the ^{10}B concentration to the normal and cancerous soft tissue. This operation is called "test study" in the MIT-Harvard protocol, where tissue samples are taken one week before the BNCT and 2-3 h after the boron drug infusion. Blood samples are taken just prior and after the irradiation, help to properly scale the blood boron-time curve. This way, the ^{10}B concentrations in the soft tissues are assigned, supposing that no boron is going to concentrate in the bone and air.

The source definition is quite simple, as it consists of a virtual plane source in a fixed position in reference to the 3D model. Therefore, once the user changes the orientation of the beam, the software supposes that the 3D model remains in the same position, while the source plane definition is going to be changed.

Once the 11025 cells model is created, a FORTRAN 77 program, called MPREP, provides the MCNP input deck from a series of files. These files contain all the information required for computing the doses in the irradiation volume such as the material file, the spatial, angular and energy characteristics of the neutron and photon beams, the flux tallies and the flux-to-dose conversion factors (based on the neutron KERMA factors for normal brain) [11] for each desired dose component. In order to take into account the effect of the binding of individual nuclei on the interaction between thermal neutrons and the considered materials, S(α,β) tables evaluated at 300K for hydrogen in light water are included for all materials making up the patient's head model.

MacNCTPlan part II provides the graphical environment for deriving the dose patterns from the results of the radiation transport calculations performed by MCNP and displaying the results in one- or two- or three-dimensional form.

MacNCTPlan calculates the dose rate for the whole CT volume. A 3D interpolation process is used to interpolate the voxel-dose-rate to each pixel of the images, prior to any display [8]. This is due to the fact that the 1cm^3 resolution of the MCNP model is far from the about 1mm^3 resolution of the MRI (or CT) scanning. In this phase, also a Fourier Transformation and a ramp filter is applied to the 3D dose matrix, in order to reduce the spatial dose gradients due to the Monte Carlo statistic fluctuations.

Cumulative-Dose-Volume Histograms (DVHs) for arbitrary tumour or normal tissue volumes can be generated as well. A cumulative dose volume histogram is the distribution of the percent of tissue volume exposed at or above a certain dose or dose rate within a region of interest.

An interesting feature of MacNCTPlan is the calculation of the maximum dose as a function of the ^{10}B concentration for each individual beam orientation. This information can be used for adjusting the calculated dose rate with the actual ^{10}B concentration during the irradiation.

MacNCTPlan provides also the effects of a multi-beam irradiation, linearly combining each individual beam according to its weight (generally defined in function of the beams irradiation time difference).

NCTPlan is the new PC-based version of MacNCTPlan [12, 13]. The necessity to integrate the entire process on one computing platform and requirements for upgrading the predecessor led to the development of this code. The object-oriented programming offered several changes in the GUI (multiple windows for modelling analysis and dose displays, etc.). In view of the integration philosophy, MPREP has been integrated in NCTPlan. In addition, NCTPlan can superimpose isodose contours on two orthogonal planes of the CT volume and update these in real-time as the orientation of the planes changes.

BDTPS
Another TP system, which is still under development, but well-advanced is BDTPS (Boron Distribution Treatment Planning System) developed jointly at the JRC-Petten (The Netherlands) in collaboration with the University of Pisa (Italy).

However, the synthesis of ^{18}F-^{10}B-FBPA, performed independently at the Prefectural University of Medicine in Kyoto [14] and at the University of Tennessee [15, 16] in 1996, should be really considered a milestone in BNCT research and allowed for starting a new field of research activities: the development of the BNCT TP system (TPS) based on the PET boron distribution data.

The main BDTPS added value is the implementation of a software architecture based on three strictly dependent models: the 3D, the Monte Carlo (MC) and the Boron (B) models. The 3D model is constructed through the CT slice of the patient's organ (for example, the head in the Petten GM trial). The pixel-based 3D model contains the regions to be evaluated during the Monte Carlo simulations. Like in SERA, each region is assigned its own unique identifier (ID), which serves as reference for the automatic reconstruction of the MC model. Therefore the MC model is also pixel-based. The big advantage of this approach is the best achievable preciseness, but, on the other hand, creates some problems from the calculation time point of view.

Several improvements have been achieved recently in the acceleration of the Monte Carlo neutron transport. For example, a speed-patch-tally has been developed by MIT and LANL scientists in order to upgrade the tracking speed with MCNP-4B. Moreover, MCNPX, the extended version of MCNP,

contains a special type of tally, called mesh tally, which enables an acceleration up to 10000 times in comparison to the standard lattice tally.

The geometry in BDTPS is defined using a lattice grid, based on the regions IDs assignment, which is independent of the boron distribution acquired through the PET scanning. In fact, during the validation of BDTPS, it has been demonstrated that the boron concentration does not influence the neutron transport, even if sharp spatial differences of the boron concentrations are present in small volumes.

The option to assign a boron concentration to each macro-region is maintained in BDTPS, in order to take into account the boron affection on the neutron transport in case of very large region definition.

The PET boron data is collected in a data structure, called B model, which should be perfectly coupled to the MCNP model, because the combination of these two models provides in the post-processing the proper evaluation of the boron dose distribution, based on the real macroscopic ^{10}B localization in the patient tissues.

Discussion and conclusion

Several Monte Carlo based treatment planning systems have been used tested and/or developed for BNCT. They play an important role in irradiation protocols.

Apart from differences due to specific mathematical algorithms, all have demonstrated their usefulness within the decision-making process related to the choice of the proper irradiation beam identification. However, all of them are characterized by a long process, most of the time requiring a lot of effort and time from the treatment planner.

To find a good combination of beams manually and to optimise the beam weights is difficult when dealing with patients suffering from lesions spread throughout the whole brain. The advantage of mathematical procedures, such as the Simplex method, can accelerate the comparison of different sets of beams for which it is known that each combination is the best possible configuration concerning the beam times. Previously, most of the available treatment planning time was spent on weighting each beam correctly for a certain combination and only a few different sets of beams could be investigated. Future studies will deal with testing and applying other possible optimisation schemes and investigating how to calculate more quickly many different beam locations and orientations. Linear optimisation has provided useful beam combinations, which were never considered before. In comparison with treatment plans obtained earlier for patients with many lesions, a reduction of the total irradiation time of 30% can already be achieved. A shorter treatment time in BNCT is favourable, not only for the comfort of the patient but also for the fact that the boron concentration in the tumours decreases with time.

Finally, specific TPS to integrate the real ^{10}B distribution into the Monte Carlo model have been validated for specific phantom geometries take into account the boron micro-distribution through the PET data, while only a single averaged value per voxel can be assigned using, for example, SERA.

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5. A preclinical research programme: The Italian Research Project in BNCT
L. Cionini

As an example of a national programme on BNCT in all its completeness, the Italian research programme is a recommended example on how to approach such a multi-disciplinary topic requiring input from many institutions within a single country.

The Project highlighted initially the importance of the research activities in BNCT and proposed a programme with the following objectives:

1) Search for new molecular systems as boron carriers

The characteristics required to these new systems include:
> a) high selectivity for tumour cells
> b) high loading capability in the tumour cells
> c) low toxicity
> d) suitable solubility in water

To this aim, it is desirable to have molecules containing a boronated moiety, possibly with an elevated number of boron atoms, conjugated with another portion, which could contribute to give to the compound some or all the properties listed above. In particular, it should be able to selectively accumulate a large amount of boron atoms inside the tumour cells.

2) Definition of methods to assess pharmacokinetics and in vivo distribution of boron carriers

The study of these molecular systems should assess:
> a) their toxicity and pharmacological pattern
> b) their biodistribution at the cellular and tissue level
> c) their effect on the radiobiological damage induced by thermal neutrons on cell cultures and animal models
> The expected results of this research aim:
> d) to verify the presence of a differential ratio of boron distribution, able to selectively damage the tumour cells
> e) to define the optimal modality of delivery of the boron compounds and the optimal timing to perform the irradiation
> f) to allow a calculation of the neutron dose based on the real boron distribution

3) Optimization of dosimetry methods for the characterization of neutrons beams and for the evaluation of the absorbed dose.

During BNCT treatments, as well as the therapy dose due to the charged particles emitted in the reactions with ^{10}B, the absorbed dose in tissue is determined also by the secondary radiations produced by the neutron reactions with the isotopes of the tissue itself. The reactions mainly responsible for the thermal neutron released energy in tissue are: $^{1}H(n,\gamma)^{2}H$ and $^{14}N(n,p)^{14}C$. Moreover, there is a dose contribution also due to the fast component of the beam. The relative contributions to the total absorbed dose of the secondary radiation emitted in the above reported reactions also change point-to-point in the exposed volume, and depend on the neutron energy spectrum, on beam geometry and on the size and dimension of the irradiated volume

The achievement of the objectives described above require besides the availability of thermal and epithermal neutron sources with suitable characteristics, the collaboration of a multidisciplinary group

including chemists, physicists, biologists, engineers, pharmacologists, radiation oncologists, neurosurgeons and pathologists.

A research group was formed in Italy several years ago with the contribution of components from all the disciplines mentioned earlier. The group was formed by research units established in 5 Italian University locations:

1) the Pisa Unit, including the Radiotherapy Division and the Department of Nuclear and Mechanical Engineering of the University of Pisa with the cooperation of the CNR Institute of Clinical Physiology (Pisa);
2) the Vercelli Unit, including the research group of Organic Chemistry of the Dept. of Chemical, Alimentary, Pharmaceutical and Pharmacological Sciences of the University of Eastern Piedmont;
3) the Florence Unit, including the Cell and Radiation Biology Laboratory and the Section of Chemistry of the University of Florence in cooperation with the Occupational Toxicology Unit (ASF);
4) the Milan Unit, including the Laboratory of Gel and TLD Dosimetry of the Medical Physics Group of the Department of Physics of the University of Milan;
5) the Perugia Unit, including the Departments of Physics of the Universities of Perugia, Rome "La Sapienza" and Rome "Tor Vergata", with the collaboration of the Biological and Animal Experimentation Management Service of the ISS (Istituto Superiore di Sanità);

and with the collaboration of the team work of the TAPIRO Reactor at ENEA Laboratories (Casaccia).

In the frame of two previous projects, the separate Units have developed and validated several study techniques with the two boron carriers applicable in clinical use, namely BPA and BSH.

The following main results have been achieved, so far:
- the synthesis of two boron classes of carboranes-carbohydrates derivatives
- the realization of the first Italian epithermal column at the TAPIRO reactor for experimental BNCT of cell cultures and laboratory animals
- the realization of a new epithermal column to be used for clinical BNCT
- the realization of an original system for the dose calculation in patients based on the information of boron distribution provided by PET and MRI
- the study of alternative methods to produce magnetic resonance images of BPA and BSH, and on the use of PET to evaluate *in vivo* the pharmacokinetics of BPA labelled with ^{18}F
- the development of an innovative method based on gel dosimetry to obtain the spatial dose distribution of the various dose components in high fluxes of thermal/epithermal neutrons
- the development and characterization of two animal models with implanted melanoma and glioma for experimental BNCT
- experiments on BNCT with BPA as boron carrier on cell cultures of glioma and melanoma lines and on animal models implanted with the same cell lines.

This study group has therefore achieved the necessary knowledge and expertise to develop the study of new boron carrier molecules, to perform their characterization and to use them in experimental BNCT and to translate into patients affected by glioblastoma and melanoma the study techniques used in the animal model and to make effective the realization of an Italian centre of BNCT at ENEA (Casaccia) Laboratories.

Consequently, the Italian national project developed in a next phase the following objectives:

Objective 1: *Selection of new molecular systems as boron carrier having characteristics better than BPA*

The activities will focus on:

A) the synthesis of polyfunctional molecules, containing a saccharidic moiety conjugated with a boron cluster and, possibly, to other compounds useful for a further functionalization of the derivative such as amino acids or hydrophilic structures to increase the water solubility.

B) the formulation of liposomes with hybrid derivative carborane-carbohydrate

C) the introduction of probes into these structures to monitor "in vivo" their pattern using imaging techniques such as magnetic resonance imaging (MRI), computer tomography (CT) and positron emission tomography (PET).

D) Synthesis of auto-assembled nanoparticles containing a boronated compound namely a carborane. Block co-polymers already proved to maintain their properties even after conjugation with chemotherapy agents, have been selected to this purpose. The synthesis of two families of polymers has been planned. A first group will use block co-polymers constituted by an hydrophylic moiety of polyethylene glycol and an hydrophobic part of polycaprolactone. In this case each polymer molecule will contain a carborane cage. In the second group of compounds a polyethylene-glycol will be bound to a co-polymer containing multiple units of amino acids such as aspartic acid, lysine or serine. These polyamino acids have a large number of functional groups allowing the introduction of many carborane cages.

Objective 2: *Pharmacological characterization of the new molecules in comparison to BPA*

The pharmacological characteristics of the molecules made available during the first year, will be tested on the animal model of implanted glioma (Wistar rat), using the same methodology already applied with BPA in the previous MIUR[5] projects for different values of dose, flux, infusion rate.

A) Toxicity will be evaluated on the cardiovascular and the central nervous systems. The effects on the CNS will be evaluated with functional and compartmental neuropharmacology criteria.

The effects on the cardiovascular systems will be assessed on *ex vivo* preparation of spontaneously beating atria of guinea pig, testing the chronotropic and inotropic effect. The responses will be recorded isometrically. To evaluate the vasodilative effect, the response of the thoracic portion of the aorta of rats will be recorded isometrically.

The assessment of the neurological damage will be done according to compartmental and functional neuropharmacology parameters.

B) Boron concentration in samples of tumour and healthy tissue of the glioma and melanoma animal models (Wistar rat implanted with Glioma F98 cells and mice C57BL/6 bearing B16-F10 melanoma) will be assessed using the methods of mass spectrometry as CE-EI-MS and ICP-MS. The mapping of intracellular boron content will be done using the technique of localised spectrometry SIMS (Secondary Ion Mass Spectrometry) on treated cell layer.

(All the experimental procedures will be carried out following the guidelines of the European Community Council Directive 86-609.)

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[5] Italian Ministry for University, Education and Research (MIUR)

Objective 3: *Application of new molecular boron carriers in experimental BNCT studies with melanoma and glioma models*

The study of the available molecular carriers will be done on cell cultures of Glioma (F98), Melanoma (B16-F10) and endothelium (HUVEC), and on the animal models of implanted glioma and melanoma.

A)   Cell Cultures Studies: To characterise the cytotoxic and proliferative damage the following parameters will be used: survival and reproductive integrity indexes, cytofluorimetric assay of DNA content and of the cell distribution in the cell cycle, DNA strand break evaluation, clonogenic test and induced apoptosis. The study of the damage of the endothelial cells (HUVEC) will include the cytotoxic and antiproliferative effects induced by the boron carrier molecules and the modification of these effects induced by thermal neutrons with or without these molecules

B)   Studies on the animal model- The effects of BNCT on the animal model of glioma will be assessed on the normal tissue and on the tumour with histopathological and immunochemical techniques, with cell kinetics techniques, with tests on the clonogenic potential and on the number of residual generations. The effects of BNCT with the new boron carriers will be compared with those obtained with BPA, considered as the standard reference compound. The results will be used to plot dose-effect curves. The residual clonogenic activity of irradiated cells, after their re-inoculation in the animal model, will also be assessed at various BNCT doses.

This part of the study will be performed by the Unit of Dep. of Oncology of Pisa University in collaboration of the CNR Institute of Clinical Physiology and the Dep. of Clinical Physiopathology of University of Florence.

Objective 4: *Application of imaging techniques for boron carrier detection*

The goal of this part of the project is to evaluate the use of PET and MRI to study the pharmacokinectics and biodistribution of the Boron carrier molecules

A)   PET - The PET imaging will be used to study the *in vivo* pharmacokinetics of BPA on the animal model. The use of PET will be both to achieve quantitative information on the boron carrier distribution and to characterize the metabolic activity of the implanted tumour. The labelled analogue of BPA, ^{18}F-BPA will be used as radiotracer for the first objective and ^{18}F-fluodeoxiglucose (^{18}F-FDG) for the second one; both evaluations will be done prior and after BNCT. A new small field scanner (microPET) installed recently at the Institute of CNR Clinical Physiology will be available for this study producing a significant increase in the spatial resolution particularly useful for small animal studies. The labelled BPA synthesis will be performed using the CNR IFC facility, composed by a PETtrace GE Cyclotron and 4 shielded boxes for radiotracer research synthesis. The information on boron localization and uptake *in vivo* will be used in the treatment planning system based on Monte Carlo simulation developed by the Unit of Nuclear and Mechanic Engineering of Pisa for the dose calculation.

B)   MR - This part of the project will be devoted to the NMR characterization of the new molecules and to the development of protocols for the MR imaging of Boron carriers in vivo and for localized proton spectroscopy. The main activity will be done with BPA and BSH: the MRI images will be obtained with double resonance techniques for BSH, while BPA will be imaged by the ^{19}F signal of ^{19}F-BPA.

This part of the project will include:

a) Quantitative MR imaging: a method to characterize quantitatively the images, by means of a correlation with the concentration of boron at different points of the sample.

b) Volume selective spectroscopy: the main task will be to develop techniques able to collect data in shorter time. For BSH a sequence will be developed, implemented and checked to perform a localized spectroscopy which simultaneously allows a coherence transfer from proton to boron and back. For BPA, VSE sequences for proton spectroscopy and for localized ^{19}F spectroscopy of F-BPA will be developed.

c) Combined tomography-spectroscopic studies: a protocol combining the informations provided by the two previous methods will be designed.

This step of the study will be performed by the Unit of Perugia, in collaboration with the NMR/micro-imaging Laboratory of the Italian Institute of Health (ISS, Rome)

Objective 5: *Characterization of the new epithermal column of the TAPIRO reactor for BNCT on cell cultures and on animal models and for its future application on patients*

This activity of the project is dedicated to the characterization of the new epithermal column, in condition of treatment, to quantify the various components of the radiation in the irradiation position. Activation and bubble detectors will be used to determine the neutron flux distribution and its energy spectrum at the end of the collimator both in air and in a tissue-equivalent phantom. The evaluation of photon and fast neutron doses will be performed using the "twin detectors" technique (two ionization chambers, one of them almost insensitive to neutrons, will be used to separately measure these two dose components). A detection system, operating at room temperature, for the on-line and *in vivo* evaluation of the thermal neutron flux and of the neutron boron capture dose will be set up. The realization of the instrumentation required for the use of the TAPIRO reactor in clinical BNCT will be completed.

Part of the project will also be devoted to define the requirements for the design of a clinical BNCT Unit at TAPIRO reactor (ENEA Laboratories). These requirements will concern the areas devoted to the patient reception, to the treatment set up and immobilization, to the radiation delivery and to the clinical support in case of emergency. This design will require an interchange with the other BNCT European centres (particularly in Finland, Sweden and Netherlands)

Objective 6: *Development of dosimetry techniques and application of BNCT treatment planning system*

The proposed dosimetry methods are mainly based on gel dosimeters (Fricke-XylenolOrange-infused-gel or polymer gel dosimeters) made up in the laboratory and optically analysed by means of an imaging instrument designed and constructed during a previous MIUR project. Studies will be carried out on the protocol for dosimeter preparation, utilisation and analysis, with the aim of optimising the reliability of the obtained dose measurements. Fricke gel dosimeters will be mainly utilized, but studies on the suitability of polymer gels, more stable in time after irradiation, will be carried out. The imaging method will be optimised and the dedicated software (utilizing MATLAB® code) for obtaining dose images from the detected light-transmittance images will be extended. The method for separating the different dose components in phantoms will be bettered and its reliability for application to small phantoms will be studied.

Further developments will also be done on dosimetry based on thermoluminescence dosimeters (TLD). The results obtained with gel dosimeters (dose images) will be intercompared with the results obtained, in some positions in the phantoms, with TLDs, activation foils and twin ionisation chambers and also with Monte Carlo simulations developed with the collaborators of ENEA (Bologna), of Milan Polytechnic and of an INFN Unit in Turin.

The beam of the new epithermal column of TAPIRO reactor and all the neutron beams utilised for experiments will be characterised with the described methods: photon and fast neutron doses and epithermal and thermal neutron fluences will be measured.

Measurements of absorbed doses in phantoms of interest for BNCT will be performed. Phantoms will be prepared having suitable shape and composition, made with gel containing a concentration of ^{10}B similar to that in human healthy tissue after ^{10}B supplying and eventually also regions with concentration of ^{10}B similar to that accumulated in tumour tissue. The images of the various secondary dose components will be obtained.

The above work will be carried out by the Unit of the Department of Physics of the University of Milano. A collaboration is active with the Department of Nuclear Engineering of the Polytechnic of Milan for the utilization of activation techniques and of ionisation chambers and for the preparation of polymer gels in specific laboratory. Moreover, measurements and intercomparisons will be performed in European centres where BNCT clinical applications are in course, in particular at the European Centre of Petten (Netherlands) and at the reactor of Rez (Prague).

Some measurements will be performed in connection with the Unit of Pisa for the *in vitro* studies on cellular models (Glioma F98 line). Cell irradiations will be accomplished in phantom, and the various dose contributions will be measured, in order to perform cell studies in exposure conditions comparable to the real situation of human head treatments and to assess the radiobiological effects (proliferation assay and cytotoxicity) according to the absorbed dose.

This objective also includes the completion and the improvement of the innovative Boron Distribution Treatment Planning System (BDTPS) developed by the DIMNP of Pisa. This treatment planning system is based on the real distribution of the boron-10 in the tumour cells obtained through PET images correlated with 3D CT or MRI images of the patient's head. The activity developed in this part of the project will concern the completion of the software for brain treatment (further experiments on cell cultures and small animals will be requested to complete the treatment protocol) and on its user friendliness in close collaboration with the medical personnel. The software will also be extended to the treatment planning for liver tumours.

The DIMNP will also continue to study the use of gadolinium as neutron capture agent in cancer therapy. The isotope ^{157}Gd, already used in Magnetic Resonance Imaging (MRI) as contrast agent, is characterized by an exceptionally high thermal neutron capture cross section and by the selectivity of some Gd-carrier molecules in binding to the tumour cells. The isotope ^{158}Gd, a product of neutron capture, decays to its fundamental state emitting Auger electrons which deposit their energy within a range of some tens of nanometers. If the majority of the Gd nuclei are bound to the DNA, its selective destruction can be effectively achieved. The research activity will be focused on the computer simulation of this phenomenon, improving the computational model and employing the most up-to-date Monte Carlo codes.

Objective 7: *Definition of the requirements to realise a BNCT clinical unit.*

This part of the project will be devoted to define the requirements for the design of a clinical BNCT unit at the TAPIRO reactor (ENEA Laboratories). These requirements will concern the areas devoted

to the patient reception, to the treatment setup and immobilization, to the radiation delivery and to the clinical support in case of emergency. The design will require an interchange with the other BNCT European centres and will be done by the University of Tor Vergata in Rome.

This proposal has been submitted to the Italian Ministry for University, Education and Research (MIUR) for funding

6. Current Situation in Europe

At the time of the Workshop held in Prague in November 2005, there were only 2 BNCT facilities in Europe where BNCT clinical trials were in progress: at the HFR Petten (NL) and the FiR-1 Otaniemi (Finland). The former was the first location in Europe in October 1997, where BNCT treatment was performed. At the latter, treatment started in 1999. Elsewhere, at the LVR-15 reactor in Rez (CZ), patients were treated from 2000-2004, but no patient treatments have taken place since that period. Whilst at the R2-0 reactor at Studsvik (Sweden), a very active BNCT programme, which started in 2001, had unfortunately to stop in 2005, due to the closure of the reactor for economical reasons. In 2002, at the TRIGA reactor of Pavia University (Italy), the extra-corporal treatment of liver cancer on 2 patients was performed. Since then no other treatments have taken place. Both BNCT irradiation facilities at the 2 reactors in Rez and Pavia are still functional. Nevertheless, throughout Europe a number of BNCT studies are at various stages of development. Current programmes are in progress in Hungary, Poland, Italy, Germany, Romania, Bulgaria, Ukraine, Lithuania, Russia and Slovakia. It should also be noted that at Birmingham University (UK), a BNCT facility has been built around the Dynamitron accelerator, which would be the first BNCT facility at a non-reactor centre. However, future utilisation of this facility is currently unsure.

Elsewhere, worldwide, where clinical trials have been recently or are currently running, BNCT facilities are available in the USA at the MIT reactor (Cambridge, MS), in Japan at both the JRR-4 reactor of JAERI and the KUR reactor, Kyoto and at the RA-6 reactor Bariloche (Argentina). BNCT facilities are also well developed at the THOR TRIGA reactor of Tsing Hua University at Tsinchu in Taiwan, at Washington State University, USA (animal studies only) and at the fast reactor of ENEA at Casaccia Italy. BNCT projects are also under consideration in other countries, including South Korea, Thailand and China.

However, it is apparent that there is some effect in progress in many, primarily Eastern European countries to develop BNCT. The chapter here presents brief reports on the current BNCT programmes in Europe.

The first part (sections 6.1 to 6.4) concerns those European centres were BNCT is or has been performed recently, with the second part (sections 6.5 to 6.14) presenting those programmes were BNCT is under development or under serious consideration. Lastly, in section 6.15, the summary of the second Working Group held at the Prague meeting, and entitled: "Designing your own BNCT Programme", is given.

6.1   The BNCT Facility at the European Commission's High Flux Reactor (HFR) in Petten (The Netherlands)

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Introduction
In the early 1990s, the European Commission granted support for research into BNCT throughout Europe. As part of this support, a BNCT facility was designed at the European Commission's HFR Petten, located approximately 60 km north of Amsterdam on the North Sea coast. The facility was to be used as the test bed for a European BNCT programme.

The HFR Petten and the BNCT facility
The High Flux Reactor (HFR) is a powerful 45 MW, light water cooled, multipurpose research and materials testing reactor with particularly high reliability and availability [1]. The reactor is owned and

managed by the JRC's Institute for Energy (IE) and operated by the Nuclear Research and consultancy Group (NRG) at Petten. The HFR's primary goal is to perform irradiation experiments for testing nuclear fuels and components for the European civil nuclear power programmes. The reactor is also a significant producer of radioisotopes, providing approximately 60% of the European market.

The BNCT facility is located on one of the 12 available horizontal beam tubes, namely HB11. The radiation beam consists of a predominately epithermal neutron beam with a fluence rate of 3.8 x 10^8 n/cm^2/s. The gamma dose in the free beam is 1.1 Gy/h. The irradiation room and observation area, are shown schematically in Figure 6.1.1. Outside the reactor building a BNCT-Wing was built to receive and prepare patients for BNCT (see Figure 6.1.2). The separate buildings are linked via the reactor's emergency exit, which serves as direct patient access to the BNCT irradiation room, thus avoiding contact with normal reactor operation and surroundings.

The design of the irradiation beam and filter system consists of materials placed inside the beam tube, between the reactor and the patient treatment position. The filter materials and thicknesses to produce the radiation beam consist of 15cm Al, 5cm S, 1cm Ti, 0.1cm Cd and 150cm liquid Ar. The therapy position is 5.5m from the reactor core and the filtered beam is some 3m in length. Consequently, the beam is very parallel, i.e. it has a high forward directionality, giving an advantage in the penetration of neutrons into tissue and less dose to the surface of the patient. Furthermore, the patient can be positioned without restrictions some 30cm from the beam opening with no loss in beam intensity. The resulting beam is very stable. The conversion of the HFR in 2006 from high enriched uranium (HEU) to low enriched uranium (LEU) has influenced negligibly the beam's performance.

In addition, at the neighbouring beam tube HB7, a pure thermal neutron beam is available to perform high accuracy prompt gamma ray spectroscopy, which is used to determine the amount of boron in blood and tissues of patients during treatment or for post-treatment studies.

Clinical Trials at the HFR
The first patient irradiation by BNCT in Europe took place at the HFR in October 1997. The project was such that 6 different hospitals from 5 different countries (Austria, France, Germany, Switzerland and The Netherlands) enter patients into the study. The treatment is performed by the Department of Radiotherapy of the University of Essen (Germany). During the period of treatment, patients are hospitalised at the "Vrije Universiteit" medical center (VUmc) in Amsterdam. Clinical trials are carried out following approved protocols of the European Organisation for Research and Treatment of Cancer (EORTC). The monitoring and data management of the trial are performed by the New Drug Development Office (NDDO) of the EORTC. The study received financing from the European Commission, within the BIOMED II Programme. 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 Petten). The overall clinical responsibility lies with the Department of Radiotherapy of the University of Essen which also provides the Medical Physicist. The licence for the facility, granted by the Dutch Ministry of Health, is held by the VUmc in Amsterdam. The co-operation of all these institutions, their different tasks and responsibilities are agreed by contract [2].

Current trials include EORTC Trial 11961: Postoperative Treatment of Glioblastoma with BNCT at the Petten Irradiation Facility and EORTC Trial (11011) [3]. Early phase II study on BNCT in metastatic malignant melanoma using the boron carrier BPA. Future plans include the treatment of liver metastases by irradiating the explanted organ. Other research projects include testing of new boron compounds through cell culture experiments and small animal experiments. Experiments have also been performed to test the feasibility of BNCT for rheumatoid arthritis.
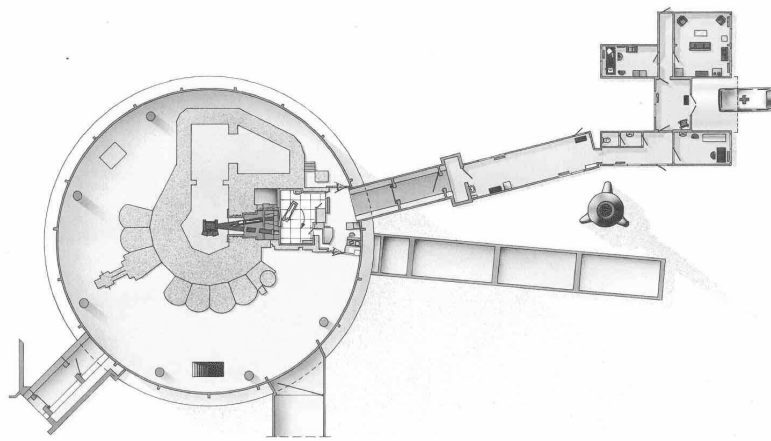
Figure 6.1.1: Cross-section through the HFR containment building, showing the BNCT facility, the reactor vessel, the irradiation room and the location outside the containment building, of the BNCT-Wing
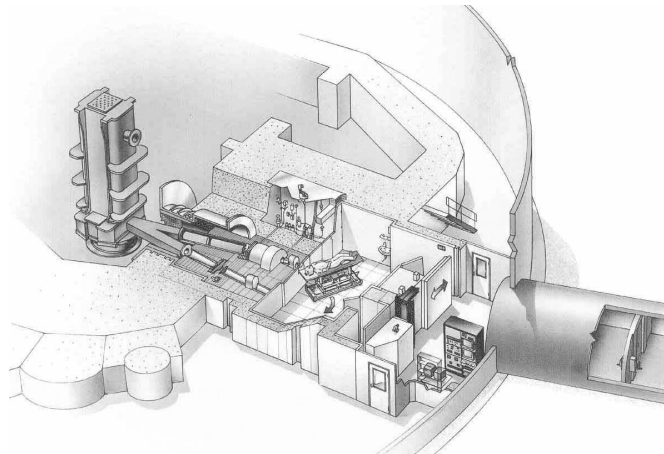

Figure 6.1.2: Overview of the facility, showing the reactor vessel, beam tube HB11, irradiation room (plus patient), the observation/control area and emergency exit.

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6.2 Ongoing Clinical BNCT Trials in Finland

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Introduction

Clinical BNCT has been administered in Finland since May 1999, when the first patient, diagnosed with glioblastoma, was treated. BNCT is given at a dedicated BNCT facility, Fir-1, located at Otaniemi, Espoo, a few kilometers from the largest hospital in Finland, the Helsinki University Central Hospital (HUCH).

The FiR 1 Reactor and the BNCT facility

The FiR 1 nuclear reactor is a light-water moderated 250 kW Triga Mark II reactor, equipped with Fluental™ moderator to produce a high yield of epithermal neutrons. The reactor was used for nuclear research and isotope production until the mid 1990's, when the reactor site was reconstructed. The site now harbours dedicated space for BNCT simulation, boron carrier infusion, boron laboratory and neutron irradiation. BNCT treatments are given in collaboration between the VTT (Technical Research Centre of Finland), Helsinki University Central Hospital, and Boneca Corporation, founded in 2002 to advance and to support BNCT research in Finland.

Clinical Protocols in Finland

BNCT as postoperative radiation therapy in glioblastoma

The first clinical protocol (P-01) was initiated in 1999. This trial was based on the pivotal experience gathered at the Brookhaven National Laboratory (BNL), Upton, New York. As in the studies carried out at the BNL, the target disease of the P-01 protocol is glioblastoma multiforme, and L-boronophenylalanine (L-BPA) is used as the boron carrier. L-BPA is administered at the dosage of 290 mg/kg, complexed with fructose and infused at a constant rate over 2 hours. Blood boron concentrations are monitored at about 20 minute intervals using inductively coupled plasma-atomic emission spectrometry (ICP-AES). The neutron irradiation time is adjusted based on the measured blood boron concentrations to achieve the planned target dose (1). All patients undergo debulking surgery prior to BNCT. None of the patients have received conventional radiotherapy or cancer chemotherapy before BNCT administration, which is carried out within 6 weeks from brain surgery. The average normal brain dose remained at about 5 Gy (W) in the first 18 patients treated, while high weighted single-fraction radiation doses were obtained in the planning target volume [1].

The P-01 protocol was amended in 2002 after the first 12 patients were treated to allow dose-escalation on L-BPA. This was based on the hypothesis that dose-escalation of BPA might result in a larger planning target volume dose and gross tumor dose without a marked rise in the normal brain tissue dose than the 290 mg/kg dose, and thus hopefully in improved survival. The L-BPA dose was increased stepwise first to 330 mg/kg (n=1), and then to 360 mg/kg (n=3), 400 mg/kg (n=3), 450 mg/kg (n=3), and 500 mg/kg (n=3) keeping the boron infusion duration constant (as 2 hours). A maximum of 9 patients was allowed to be treated at the dose of 500 mg/kg or at one level lower than the maximum tolerated dose. The protocol was amended in 2005 to allow treatment of 12 to 24 further glioblastoma patients at the dosage of 450 mg/kg or 500 mg/kg to investigate safety and efficacy of BNCT given following infusion of a high dosage of BPA. Accrual to the P-01 protocol is still ongoing, and the treated patients are being actively followed up (see Table 6.2.1).

BNCT following full conventional radiation therapy in the treatment of malignant brain tumors

Since many brain tumour patients seek for BNCT treatment only at the time of brain tumour recurrence and when all conventional therapies have been exhausted, we wished to investigate whether BNCT might be feasible in this group of patients. Re-irradiation of the brain following full dose conventional radiotherapy is hazardous and may lead to severe complications including radiation necrosis of the brain. Since the normal brain dose remains generally low with BNCT, it is possible that BPA-mediated BNCT might be feasible even following full-dose prior conventional photon irradiation. We initiated a study protocol (P-03) addressing this question in 2001. The planned number of patients to be treated is 22. The study participants have been diagnosed with either glioblastoma or

anaplastic astrocytoma. The protocol requires that tumour recurrence is confirmed both by radiological imaging and histology. As safety measures, the protocol requires a time interval of at least 6 months between the date of BNCT and the last date of conventional irradiation, and the normal brain peak dose computed to a volume of 1 cm^3 is limited to a maximum of 8 Gy (W). The protocol also requires that the prior conventional photon irradiation has been delivered using conventional fractionation (1.8-2.0 Gy/day, 5 days per week) to a cumulative dose of 50 to 60 Gy.

The L-BPA dose is 290 mg/kg given over 2 hours in the P-03 protocol. The protocol was amended in 2005 to allow stepwise dose escalation of L-BPA after the first 10 patients were treated at the dose of 290 mg/kg. The subsequent L-BPA dosage levels were 350 mg/kg (n=3), 400 mg/kg (n=3), and 450 mg/kg (n=3) keeping the L-BPA infusion duration as 2 hours. In case grade III or grade IV toxicity is encountered in one of the 3 patients treated per dose level, 2 further patients will be entered at the same level to determine the maximum tolerated dose. A maximum of 6 patients will be treated at the dosage of 450 mg/kg or at the level one lower than the maximum tolerated dose level. To date, 13 patients have been treated in the P-03 protocol, and BPA dose escalation is ongoing.

BNCT in the treatment of locally recurred head and neck cancer

Thus far the great majority of patients treated with BNCT have been diagnosed with glioblastoma, and knowledge on the efficacy of BNCT in the treatment of other types of human cancer remains limited. We treated a patient who had large, rapidly growing undifferentiated sinonasal head and neck carcinoma with a palliative intent using BNCT in February 2003. Following BNCT the tumor shrank markedly in volume resulting in a good palliative effect in this single patient who had inoperable cancer treated with a full dose of prior conventional radiation therapy [2]. Only moderate adverse effects, consisting mainly of mucosal toxicity, were associated with BNCT. The experience from this single patient encouraged us to initiate a clinical trial protocol in head and neck cancer (BNCT-HN). The first patient was treated in the BNCT-HN trial in December 2003, and at the time of this writing 12 patients with locoregionally recurred head and neck cancer have been entered. The study patients are required to have inoperable head and neck cancer, treated with prior conventional radiation therapy. This trial was amended in 2005 to accrue further 12 to 24 patients to allow better estimation of safety and efficacy of BPA-mediated BNCT in the treatment of inoperable, locally recurred head and neck cancer.

In the BNCT-HN protocol L-BPA is infused at the dosage of 400 mg/kg over 2 hours. Unlike in P-01 and P-03, BNCT is given twice. The second BNCT treatment is administered 3 to 5 weeks after the first one to allow adequate time for the oral mucosa to heal from radiation mucositis prior to the administration of the second BNCT. The oral mucosal membrane peak physical irradiation dose, as computed to the maximum volume of 1 cm^3, is limited to less than 6 Gy for each of the 2 BNCT treatments, and the average planning target volume normal tissue dose is limited to less than 10 Gy (W). To date, 12 patients have been entered to the trial, and accrual is ongoing.

BNCT in clinical practice

We aim to give most BNCT within the context of formal study protocols, since the safety and efficacy of BNCT in the treatment of human cancer is still incompletely known. There are, however, patients who are not eligible for the ongoing trials, or trial entry is not feasible for logistic reasons. We have, therefore, treated also a number of patients (mainly with head and neck cancer) outside of the ongoing clinical trials.

A total of approximately 80 patients have now received BNCT at the FiR 1 BNCT facility, most of them in the trials. The patient accrual in the ongoing research protocols was slow in 1999 to 2003, but improved substantially in 2004 to 2005. We currently provide BNCT at a rate of approximately 40 treated patients per annum, and the clinical demand for BNCT appears to be increasing. However, thorough evaluation of BNCT in clinical trials is mandatory prior to its wide-spread adoption to the clinical routine. It is also of great importance to explore novel modifications of BNCT including new boron carriers and the use of BNCT in combination with other existing cancer therapies. Thus far, many of these approaches have remained unexplored.

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Table 6.2.1 Summary of the ongoing BNCT trials at FiR 1 (as of 18/12/2005)

Study disease	Target group	BPA dose	BNCT	Planned no.	Number

				of patients	treated
P-01 Glioblastoma	No prior RT, BNCT given after surgery	290-500 mg/kg (dose escalation)	Single treatment	Max 55	34
P-03 Glioblastoma Anaplastic astrocytoma	Recurrent cancer, after surgery and conventional RT (50-60 Gy)	290-450 mg/kgh (dose escalation)	Single treatment	Max 20	13
BNCT – Head and Neck (HN)	Inoperable cancer	400 mg/kg, full dose prior RT given	Two treatments 3-5 weeks apart	Max 30	12

6.3 BNCT at the LVR-15 Reactor

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Introduction

In 2000, clinical trials on BNCT started at the LVR-15 reactor of NRI at Rez. An epithermal neutron beam, an irradiation and a control room, both equipped with appropriate devices, were constructed. The internationally-recognized software NCTPlan is utilized for computational dosimetry and treatment planning. At the horizontal LVR channel, a prompt gamma ray analysis (PGRA) system is operated for BNCT purposes. The clinical trial concerns the glioblastoma tumour. The protocol was prepared and approved by the state authorities. Patient selection, sampling of tissues, BSH dosage were assessed. Interesting results of the clinical trials were received for the first group of five patients.

The LVR-15 reactor and the BNCT facility

A beam of epithermal neutrons was constructed at the LVR reactor, replacing the existing thermal column [1]. The measurement techniques and characterization of the beam are described in [2]. In the beam final design, standard materials as aluminum, aluminum fluoride, lead, titanium and lithium were used. The current free beam parameters are: $\Phi_{epi} = 7.13 \times 10^8$ /cm^{2}s, $\Phi_{fast} = 6.1 \times 10^7$ /cm^{2}s, $D_\gamma = 1.98$ Gy/h. The configuration at LVR-15 rector is shown in Figure 6.3.1.

The BNCT facility consists of an irradiation room and a control room. The irradiation room is equipped with appropriate devices, such as laser, TV camera, intercom and patient treatment table. All information for communication with the patient, monitoring and control of the beam are monitored in the control room.

Boron concentration measurements: a PGRA facility for determination of ^{10}B in biological samples was built inside the reactor hall. The measurements were validated for the ^{10}B concentration values by the ICP method.
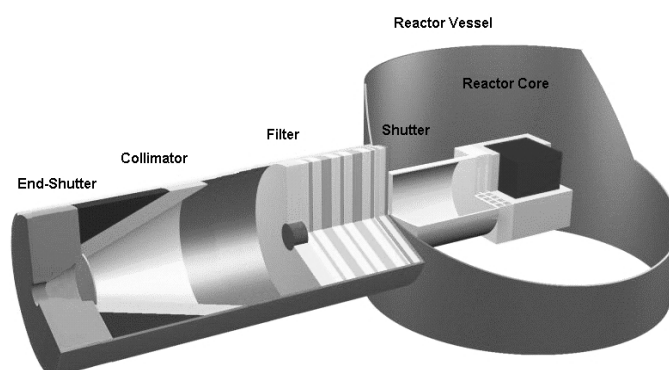

Figure 6.3.1: Configuration of epithermal beam at LVR-15 reactor

Treatment planning: the treatment planning software is one of the most important aspects of the BNCT procedure. The treatment planning code NCTPlan, an internationally-recognized treatment planning program, was chosen [3]. CT and MRI scans are acquired for identification of the tumour and healthy tissues. It serves as input to the MCNP Monte Carlo transport calculations (with known source and materials file). The different contributions to the total dose (boron, fast neutrons, gamma rays, nitrogen) are calculated by the code. RBE-weighted iso-doses for normal brain and for tumour are plotted as the output of the code.

Clinical Trial
The protocol specifying the BNCT treatment of glioblastoma with BNCT at the LVR was approved in 2000. Inclusion criteria were specified for patient selection. The preoperative period was used to study BSH pharmacokinetics. BSH is administered to the patient 12 hours before the operation and blood concentration is measured at regular intervals. Samples are taken at the time of operation and BSH concentration is measured. BSH has been administered at an amount of 100 mg/ kg body weight.

Considering the fact that the irradiation time in LVR reactor is rather long and therefore repair of healthy tissue could take place during irradiation, it was decided to perform the treatment in one fraction, despite the fact that a long time irradiation is not comfortable for the patient.

The aim of a Phase I trial is to establish the safe dose for healthy brain tissue. There is a chance that patients may benefit from BNCT even for the specified starting dose. However, the therapeutical effect is supposed not to be negligible for the final steps. A Phase II trial to investigate the effectiveness of this new modality is planned in parallel with the final dose, if an unacceptable frequency of serious adverse events is not observed.

The domestic supplier Katchem Ltd. produces the BSH (as well as L-BPA). The quality of the product is in the agreement with Test of Quality Control required by this project.

Ten patients with a clinical diagnosis of glioblastoma multiforme received i.v. infusion of BSH within 1 h. Blood samples were taken after the BSH administration; the urine was continuously collected. Tissues sampled during the operation (starting about 12 h after BSH infusion) were taken.

The tissue samples were measured by Inductively Coupled Plasma - Mass Spectroscopy (ICP-MS). Samples of the blood and urine were measured using PGRA. Results are very individual as shown by the ^{10}B concentration versus time profiles in Fig.2. The following ^{10}B concentrations were found: Tumour 15 – 30 µg/g tissue, skin 7 - 15 µg/g, bone and brain healthy tissue 1µg/g approximately.
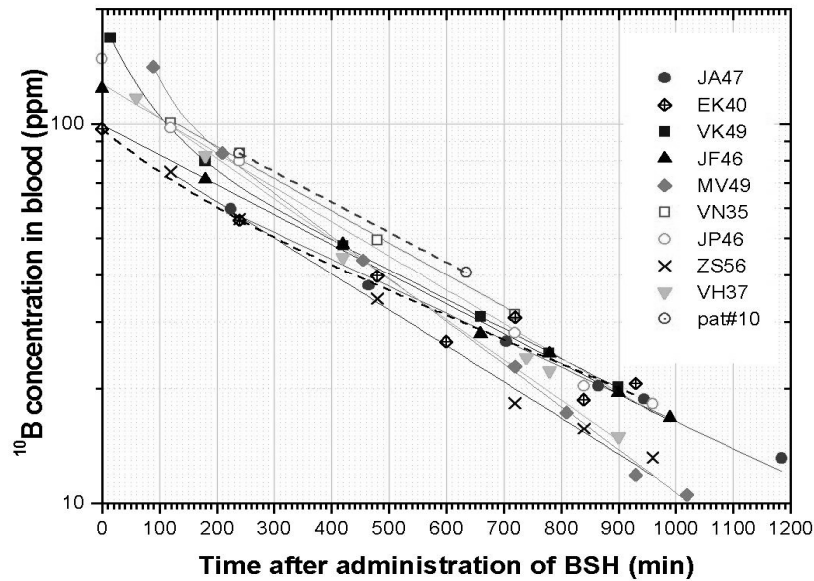
Figure 6.3.2: Blood ^{10}B concentration

Conclusions

The study showed relatively good tolerance of BNCT performed under the above described conditions. Considering that the level of the radiation dose to the target volume in a Phase I study is low and the number of patients was not high enough, an evaluation of the efficacy of BNCT under the above described conditions awaits further study.

Further progress awaits the synthesis of a new substance with high biological effectiveness. For the next period, it is planned to continue clinical trials with a mixture of the present boron agents (BSH+BPA). However, it is not decided yet as to which types of disease the new protocols will be oriented (glioblastoma, melanoma brain metastases, primary melanoma).

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6.4 BNCT activities at Pavia University

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Introduction

Lung carcinoma is the first cause of death for tumour in the west world; current techniques are not effective, new approaches have to be experimented. The very encouraging results obtained with BNCT application to liver metastases through autotransplant [1], convinced the group of Pavia to explore the possibility to apply BNCT to cure diffused lung metastases.

Boron uptake studies

One of the principal requirements for BNCT applications is represented by the possibility to obtain higher ^{10}B concentrations in metastases compared with those in lung healthy tissue. A rat model with lung metastases has been developed to study the time distribution of ^{10}B concentration in tissues. To obtain pulmonary metastases, colon-carcinoma cells from DHD/K12/TRb line [2] are intra-splenic injected in syngeneic BDIX rats. Twenty-eight days after tumour induction, boronphenylalanine is intra-peritoneally administered and the animals are sacrificed at various time intervals from the BPA infusion. The lungs are taken and frozen in liquid nitrogen. Several couples of neighbouring samples are cut using a Leica cryostat: a section is deposited on a mylar disk for boron concentration measurement by ^{10}B(n,α)^{7}Li α spectrometry [3], the adjacent section is deposited on glass for morfological analysis by standard staining, and the last one is submitted to neutron autoradiography. Boron concentration measurements spectrometry on very thin slices are in progress. The available neutron source is the 250 KW Triga Mark II thermal reactor of the Pavia University. Other studies concern neutron trasport by MCNP and MCNPX: a human chest model is being developed, in order to compare extracorporal irradiation in a suitable neutron field and irradiation by external collimated beams.

Low resolution boron imaging

A precise knowledge of the boron concentration, both in tumour and healthy tissues, is an essential requirement for the BNCT treatment. Many methods are used to detect the boron signal coming from biological samples, but the knowledge of the percentages of different kinds of tissues present in the sample is needed. In the case of liver or lung metastases, for example, tumour and normal cells, blood cells and necrotic material can be simultaneously present inside a metastatic nodule with diameter of few millimetres. Therefore, neutron autoradiography has been used for boron imaging. Thin slices of frozen sample are cut at 20° C; one slice, 10 μm thick, is deposited on glass for morphological analysis; the adjacent one is put directly on a Cellulose Nitrate film (CN85 by Kodak Pathé) for neutron radiography. After neutron irradiation, the CN85 film is etched for 20 minutes in a 10% NaOH solution at a temperature of 60°C. Figure 6.4.1 represents an example of neutron autoradiography of rat lung: the darker zones correspond to metastatic zones, thus showing a selective boron uptake into the tumour.
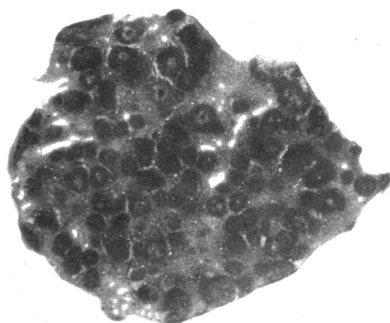

Figure 6.4.1: Neutron autoradiography image of a thin slice of rat lung with colon-carcinoma metastases after BPA infusion. Darker zones represent tumour nodules with high ^{10}B concentration.

BNCT to diffused liver metastases

Starting from an idea proposed by Pinelli [1], a long term research program began in 1987 to study the feasibility of BNCT application to explantable organs. In the project, named TAOrMINA (Advanced Treatment of Organs by Means of Neutron Irradiation and Auto-transplant), have been involved INFN (National Institute of Nuclear Physics) section of Pavia, the Department of Nuclear and Theroretical Physics, the Depatment of Surgery (Division of Hepato-pancreatic Surgery) and the Department of Animal Biology of the Pavia University, the Centre of study for Histochemistry (CNR) and the IRCCS S. Matteo Policlinic of Pavia. The physical and surgical works has been coordinated by Pinelli and Zonta respectively. Their novel method is dedicated to the therapy of patients with diffuse, unresectable cancer in vital organs eligible for transplantation. The therapeutic concept is based on the neutron irradiation of the isolated organs, put in an irradiation position obtained in the Thermal Column of the reactor (Fig.6.5.2a). The facility has been shielded with Bismuth screens to lower the gamma radiation coming from the core. The first research has been addressed to the cure of liver metastases from colon-adenocarcinoma. Besides, an accurate method to measure boron concentration in tissues has been developed [3]. As an example Figure 6.4.2b reports the boron concentration in the healthy liver (C_H) and in the colon carcinoma liver metastases (C_T) for a rat model. The ratio T= C_T/ C_H is also represented.

Two patients have been treated by TAOrMINA method. The outcomes of these treatments have been reported by A. Zonta in [4]. The first patient (48 years old, male) was treated in December 2001, the second (39 years old, male) on July 2003. Both presented more than ten liver metastases from a carcinoma resected months before. The last patient suffered from a cardiomiopathy, and a cardiac failure caused his death in the 31st p.o. day. The autopsy clearly showed how the metastatic nodules had been replaced by necrotic tissues. The first patient was discharged in the 40th p.o.day. In the site of previous metastatic lesions typical CT images showed massive necrosis that were gradually substituted by normal liver tissue. He survived 44 months with a good quality of life, and died on august 2005 because of diffuse recurrences of the colon tumour.
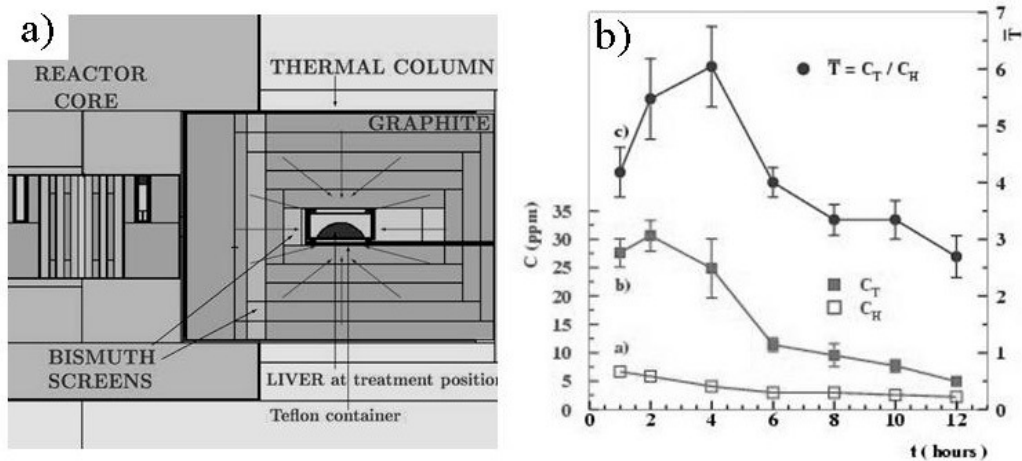

Figure 6.4.2: a) Structure of the modified thermal column with liver at the irradiation position
b) Boron concentration distribution as a function of time interval between BPA infusion and rat sacrifice: □ in the healthy rat liver and ■ tumour tissue; ● boron concentration ratio between tumour and healthy tissues

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6.5 BNCT programme in Hungary

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Introduction
Although epithermal neutrons for clinical irradiation facilities are needed for the approach of treatment of glioma, melanoma and other kinds of tumours by BNCT, thermal neutrons from smaller and less expensive low power research reactors have an important function for further development and application of BNCT. A part of the study of the fundamental radiobiological processes, responsible for the achievement of the therapeutic gain of BNCT, consists of the irradiation of cell cultures and small test animals with thermal neutrons.

Taking this into account, the Institute of Nuclear Techniques (INT) of the Budapest University of Technology and Economics, together with the National Institute of Oncology (NIO) joined the European Collaboration on BNCT. The contribution of Hungary to the European BNCT project comprises a pre-clinical radiobiological study with thermal neutrons − utilizing a low power research reactor − promoting the clinical implementation of BNCT and extending the possibility of the clinical application of BNCT to other tumours than glioma.

In this paper we summarize our contribution to the European BNCT research so far, as well as our present activity and future plans.

BNCT facility at the nuclear reactor of the Institute of Nuclear Techniques (INT), Budapest University of Technology and Economics
INT has a 100 kW power Light Water Reactor (LWR). Preliminary chemical and biological experiments were performed for BNCT studies with thermal neutrons at one of the horizontal beam channels of the reactor (equipped with a special neutron-γ filter) in co-operation with several national institutes and universities [1].

The nuclear reactor has a large irradiation tunnel. At the time of the preliminary experiments, this tunnel was equipped with a special thermal neutron and γ-radiation filter in the frame of EC WP3, in order to obtain a final BNCT irradiation field with optimum beam parameters [3]. The filter and the reactor core can be seen in Figure 6.5.1.

The measured parameters of this final BNCT irradiation field at 100 kW reactor power are as follows (the uncertainty of the data below is in all cases less than 10%):

- Thermal neutron fluence rate ϕ_{th} (E<0.5 eV) $1.23E9 \ cm^{-2} \ s^{-1}$
- Epithermal neutron fluence rate ϕ_{epi} (E=0.5 eV −1 MeV) $7.07E7 \ cm^{-2} \ s^{-1}$
- Fast neutron fluence rate ϕ_{f} (E>1 MeV) $7.03E6 \ cm^{-2} \ s^{-1}$
- γ dose rate   1.3 Gy/h

- ϕ_{th} / ϕ_f (E>1 MeV)   ~ 175

The neutron and γ doses in the targets are monitored. The neutron dose is measured by neutron activation detectors, while the γ-dose by TLD detectors.

Activities performed in Hungary in the field of BNCT
Within the European Collaboration on BNCT, the following research activities have been carried out:

    a) *The Hungarian Natural Institute of Oncology with co-operation of INT performed a multidisciplinary research of BNCT (1990-1997)* [2, 3]: biological evaluation of BNCT in melanomas on B-16 melanoma cultures and on C57 black mice transplanted with B-16 melanoma. Moreover, BNCT human melanoma xenograft has also been performed using either $Cs_2B_{12}H_{12}SH$ or ^{10}B-phenylalanine.

    Areas under investigation included the synthesis of compounds, preparation of boron-containing monoclonal antibodies, biological evaluation of BNCT (efficacy, normal tissue tolerance of BNCT, combined treatment of BNCT and chemotherapeutic agents, analysis of immunosuppressive effect of BNCT) and the analysis of molecular mechanism of α-radiation.
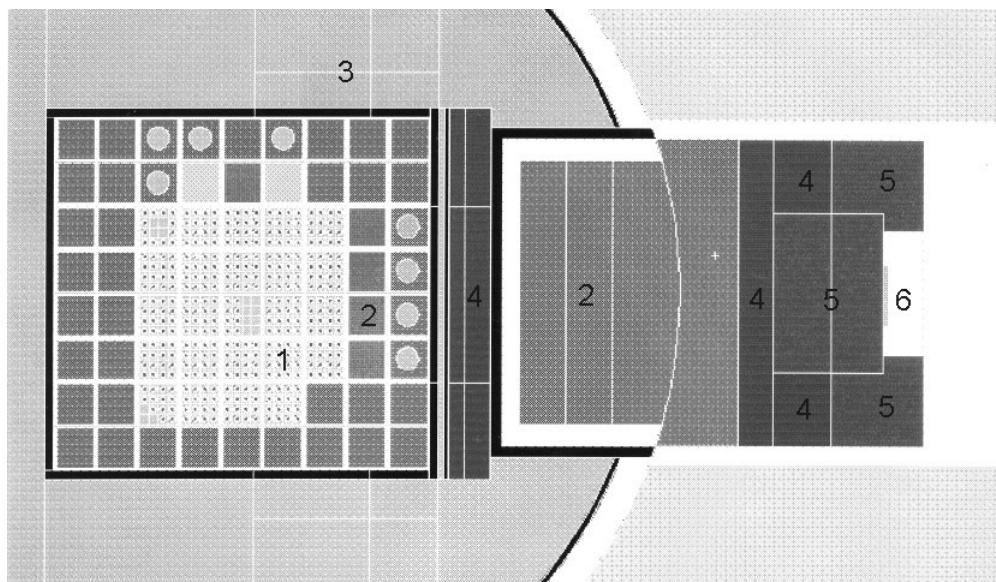

Figure 6.5.1: The final BNCT irradiation facility at the nuclear reactor of INT, Budapest University of Technology and Economics [1: fuel elements; 2: graphite; 3: light water; 4: heavy water; 5: bismuth, 6: irradiation cavity]

    b) *Participation in development of European recommendations for BNCT dosimetry (CoP)* in the frame of EC WP4 (in co-operation with 11 European Laboratories/ Institutes) [4]. The outcome of the project was a document providing detailed guidelines with proven methods for the basic characterisation and dosimetry of epithermal (and thermal) neutron beams, to be used for treatment of cancer patients by BNCT at European research reactors and accelerators. The guidelines apply to the dosimetry in the beams used in pre-clinical research as well as in clinical trials on human patients. The objective was to ensure the level of accuracy, reliability, reproducibility and traceability that is generally required in radiotherapy. The end of the project was *December, 2003.*

c) *Preparation of a proposal in the frame of EU WP6:* (in cooperation with five EU countries/Institutes, including the Chemical Research Center of the Hungarian Academy of Sciences) to investigate the properties of the newly synthetised boronated porphyrins [5], and to develop a new protocol with this compound for combined PDT (Photodynamic) and BNCT therapy.

Future plans

Our future plans in the field of BNCT research include the following topics:

a) Dose response curves of various test chemicals using human and mouse melanoma cultures (cells survivals, plating efficiency).
b) Therapeutic efficacy of combined BNCT and porphyrins, phtalates treatment on transplanted melanoma and tissue cultures.
c) The effect of α irradiation on the DNA (strand breaks) and chromosomes (chromosome aberration)
d) The effect of BNCT and porphyrins, phtalates on the tumoral and cellular immuno-response of B16 transplanted animals.

For realization of the above topics, EC support (e.g. in the frame of an EC project) is required.

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6.6 Development of Neutron Source for BNCT at the Kyiv Research Reactor

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Introduction

The WWR-M Kyiv Research Reactor (KRR) is a light water moderated and cooled tank-type reactor with a beryllium reflector. The reactor currently uses 36% enriched uranium-235 WWR-M2 fuel assemblies, each of which consists of an outer hexagonal tube and two inner cylindrical tubes. The nominal thermal power is 10 MW. The neutron flux in the core is about 10^{14}n/cm^{2}s. Today the KRR is used for various purposes: neutron physics (5 horizontal beam tubes), solid state and material structures studies, radioisotope production (vertical channels), and other applications. Horizontal tube no.10, which is currently used for fundamental investigations as a thermal column, can be demounted rather easily due to its construction as two graphite blocks rolling on rails (see A and B in Figure

6.6.1). This channel is planned to become an epithermal neutron source with parameters that meet the requirements of BNCT.

Planned activities

The concept of the source consists in the transformation of the reactor radiation into epithermal radiation using specially selected moderators, filters, collimators and shielding. The spatial configuration of these source elements and material compositions may be determined by Monte Carlo neutron and photon calculations taking into account both the peculiarities of the KRR system and the nuclear properties of the source materials in the modified thermal column.

Preliminary calculations using the MCNP-4C code have shown [1-3] that the best neutron beam parameters can be obtained at the KRR using the horizontal beam tube no.10, with the following configuration and material components (see Fig. 6.6.1):

➢ a Fluental or Al+CF$_2$ moderator, 50 - 60 cm long in the beam direction, arranged abutting the thermal column bottom with each side confined by a divergent natural nickel conical reflector;
➢ a 274 cm long convergent conical borated polyethylene collimator, coated on the inside with a 3.152 cm layer of natural nickel, which reduces the beam from 108 cm in diameter (at the moderator surface) to an outlet diameter of 4 cm (at the position of a potential patient); and
➢ a 4-6 cm long nickel-60 filter located close to the beam outlet.

It is necessary to carry out the detailed calculations on the system (moderator, collimator, shielding, etc.) needed to transform the existing thermal column into epithermal taking into account both the actual structural features of the KRR and all demands concerning parameters of the epithermal beam, required by BNCT (intensity of epithermal neutron flux, specific fast neutron and photon doses, etc.). Tests are planned to evaluate the main calculation results by means of experimental measurements.

The expected results of this activity are the following:
1. Selection of optimal construction and materials of moderators, reflectors, collimators, filters, converters, shielding for creation at the KRR of epithermal neutron source with parameters required by BNCT (with HEU and LEU fuel) on the basis of calculations and experimental measurements of intermediate results.
2. Estimation of the influence of the planned changes on nuclear safety.
3. Analysis of the influence of the epithermal neutron spectrum on the dose distribution in phantoms.
4. Elaboration of proposal for designing the neutron source for BNCT at the KRR.

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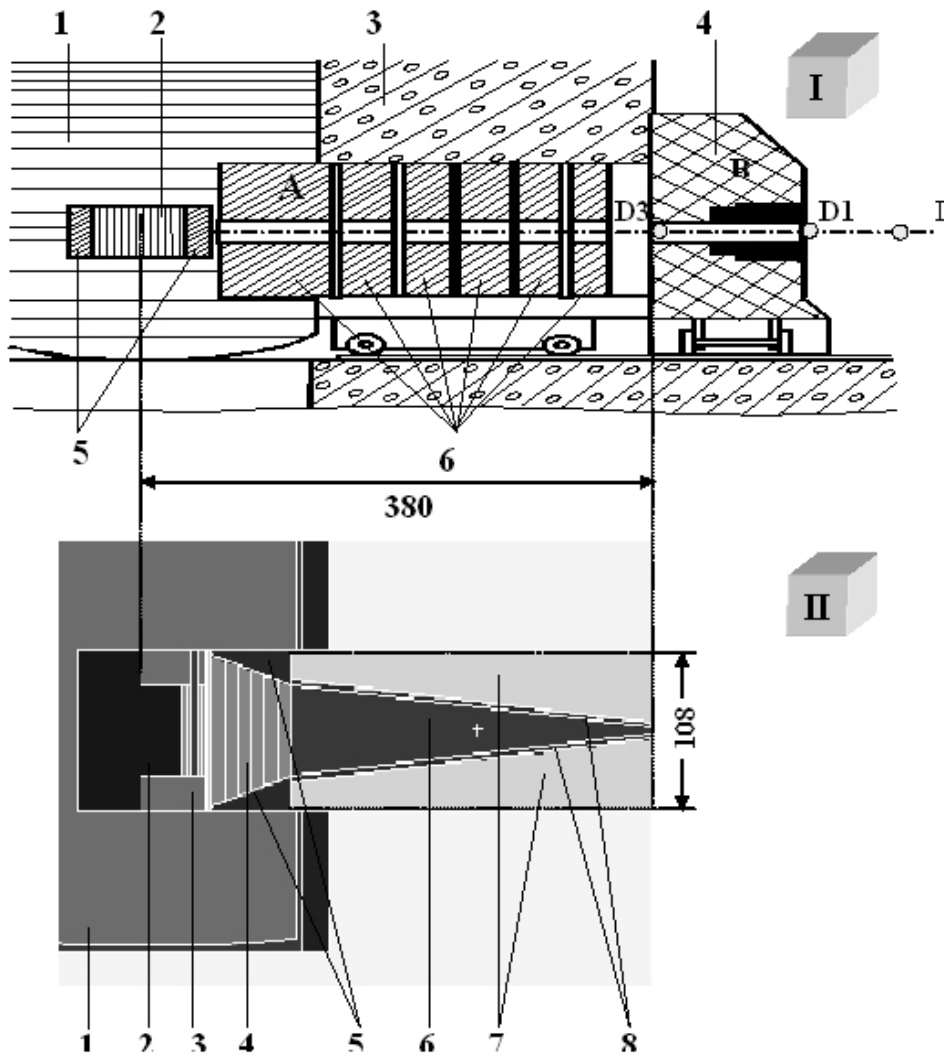
Figure 6.6.1: KRR thermal column (dimensions in cm)

I – TC (until reconstruction): A– the first block, B – the second block. 1– water, 2 – core, 3 – concrete, 4 – paraffin, 5 – beryllium reflector, 6 – graphite. D1, D2, D3 – detector positions in the MCNP calculations.

II – Geometry for MCNP calculations (vertical cross section through the core centre): 1– water, 2 – core, 3 – beryllium reflector (source), 4 – moderator, 5 – reflector, 6 – air, 7 – borated polyethylene, 8 – natural nickel layer.

6.7 Developing BNCT at the Reconstructed IRT Research Reactor

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The Research Reactor IRT-2000

The research reactor IRT-2000 site is arranged on the eastern open and flat part of Sofia (see Figure 6.7.1). It is a water-moderated water-cooled pool type reactor. The reactor was built and put into operation in 1962. In accordance with the requirements of the Bulgarian Safety Authority, the reactor was temporarily shut down in 1989 for increasing the level of nuclear and radiation safety. The Bulgarian safety authority and the Institute for Nuclear and Nuclear Energy (INRNE) proposed in 1999 a large-scale programme for its further development. The Council of Ministers took in 2001 a decision for refurbishment of the IRT-2000 research reactor into a reactor of low power.

The decision for refurbishment of the reactor aims to satisfy the society needs for the development and sustainability of nuclear science, skills and knowledge for the development of applied methods and studies.

Future utilization

The research reactor IRT-2000 will be reconstructed into a reactor of low power 200 kW. According to the non-proliferation requirements, the previously used high-enriched fuel will be replaced with low-enriched fuel.

The future utilization of IRT-200 aims to develop and preserve the nuclear science, skills, and knowledge and refers to:

- Education of students and training of graduated physicists and engineers in the field of nuclear science and nuclear energy;
- Implementation of applied methods and research;
- Development of Boron Neutron Capture Therapy (BNCT) facility.

There will be seven horizontal and six vertical experimental channels for irradiation of samples and other experimental studies. The BNCT facility will be installed on channel N. 1.

BNCT Facility Design

A 3D MCNP transport calculation has been carried out for the design of a BNCT facility. On the basis of these results the reactor core was arranged in order to gain the highest possible neutron flux. The material compositions and geometries most appropriate as a source for BNCT have been selected.

Additional equipment is planned for the construction of the facility with a well-filtered and collimated neutron beam. The necessary medical facilities (e.g. patient preparation, patient irradiation room and patient monitoring room, blood-measurement laboratory) at the reactor facility are also planned.
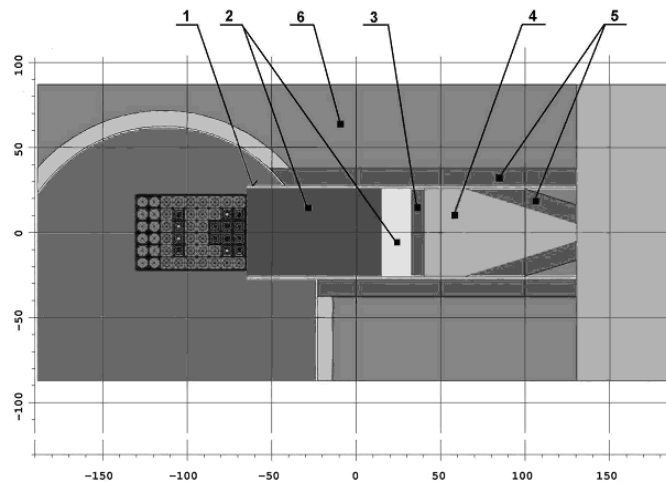
Figure 6.7.1: The BNCT channel : 1. Vessel of Channel; 2. Filter (80 cm Al + 17 cm CF2 + 0.04 cm Cd); 3. Lead Shielding; 4. Collimator; 5. Lead Shielding of Channel; 6. Concrete; 7. Core

The channel for BNCT (see Figure 6.7.1) will be made of a stainless steel plate, 15 mm thick, with a rectangular profile of size 700x550 mm^2 welded onto the pool bottom section wall. The channel face will be made of stainless steel sheet of 2 mm thickness and on the poolside face will be reinforced by screwed-on aluminium plate of 9 cm thickness, which at the same time will form the first part of the neutron filter. The whole channel will be coated by lead of thickness 10 cm. Among the analyzed configurations the filter with 80 cm aluminium (including 9 cm aluminium plate of channel) + 17 cm CF$_2$ + 0.04 cm Cd followed by 8 cm of lead has been recognized as the most acceptable. It is combined with lead collimator, which has 10 cm thickness, inner diameter of 70 cm, length of 90 cm and slope of 17˚.

For a reactor power of 200 kW and the selected filter and collimator it is estimated that the epithermal neutron flux should be equal to ~ $0.9 \cdot 10^9$ n/cm^{2}s. The dose of fast neutrons in tissue per epithermal neutron is estimated as $1.95 \cdot 10^{-11}$ cGy.cm^2.n^{-1}. The dose of gamma rays per epithermal neutron is estimated as $1.98 \cdot 10^{-11}$ cGy.cm^2.n^{-1}.

Collaboration and support
The development of BNCT facility on the research reactor IRT will be carried in close collaboration with leading medical and research institutions from Bulgaria and abroad. INRNE intends to have closer collaboration with IE of JRC Petten, the Netherlands, INFN Italy, FIRR Helsinki, Finland and NRI Rez, Czech Republic. Collaboration with national medical institutes is absolutely necessary. As a first step in this direction the design of medical facilities for patient preparation, diagnostics as well as the irradiation monitoring systems will be prepared together with the Medical University, Sofia and the Medical University, Varna. The Union of the Bulgarian Radiotherapists supports the idea for BNCT treatment.

The project for reconstruction is supported by the Bulgarian Government. It is also partially financed by the EC PHARE program under project BG 5812.01.01 "Innovation of the Radiation Monitoring Systems", the Project BG 5812.01.01 "Technical Assistance" and by IAEA under project BUL/4/014 "Reconstruction of Research Reactor". Currently a proposal has been submitted for a project under EC PHARE Programme for 2006-2008 "Strengthening of the Bulgarian Nuclear Medicine Potential. BNCT development and application at Nuclear Scientific and Experimental Centre".

The financial support on the national and international level gives assurance in development of the BNCT facility, and its application in medical treatment.

Future activities
BNCT working teams are going to be created in order to:
- Establish closer collaboration with national institutions like Universities, hospitals, NRA and Ministry of Health;
- Involve more physicists and medical specialists in the working team;
- Strengthen the international collaboration with institutions where BNCT is applied;
- Build BNCT facility;
- Train the working team to be capable of applying BNCT;
- Draft the BNCT treatment protocol.

6.8 Irradiation Facilities for BNCT at the Research Reactor Maria in Poland

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Introduction
A BNCT research programme started in Poland in 2001, in collaboration of the Institute of Atomic Energy in Świerk and the Institute Maria Curie Oncology Centre in Warsaw. The MARIA reactor in Świerk is to be used as the neutron source for the planned Polish BNCT facility. The general concept was to start up at the same time the construction of the neutron beam line and a research programme. For this reason, it was decided to construct also a second, subsidiary facility (called BIMA) for thermal neutron irradiation of living tissues inside the reactor. The facility was specially designed for a research project devoted to studies on chemistry and pharmacology of new boron compounds for NCT.

The Maria Reactor
The multipurpose high flux research reactor MARIA is water and beryllium moderated, a pool type reactor with graphite reflector and pressurised channels containing concentric six-tube assemblies of fuel elements. The reactor reached its first criticality in December 1974. It was in operation until 1985 when it was shut down for modernization. The modernization encompassed refurbishment and upgrading of technological systems. In particular, the efficiency of ventilation and cooling systems was improved. In 1993 the MARIA reactor was put into operation again. In February 2005, 84 MR-6 type fuel assemblies with 36% enrichment in U-235 were supplied and actually only MR-6 type fuel assemblies with 36% enrichment in U-235 were loaded in the reactor core. Now there are two kinds: the old with 540g contents of U-235 and the new with 430g contents of U-235.

The reactor has been designed with a high degree of flexibility. The fuel channels are situated in a matrix containing beryllium blocks and enclosed by lateral reflector made of graphite blocks in aluminium cans. The MARIA reactor is equipped with vertical channels for irradiation of target materials, a rabbit system and six horizontal neutron beam channels. The nominal power of the reactor is 30 MW(th), thermal neutron flux is 4.0×10^{14} n cm^{-2}s^{-1}, and the output thermal neutron flux at the horizontal channels is $3 - 5 \times 10^{9}$ n cm^{-2}s^{-1}. The main areas of reactor application are production of radioisotopes, testing of fuel and structural materials for nuclear power engineering, neutron radiography, neutron activation analysis, neutron transmutation doping and research in neutron physics. In 2005 the reactor completed 35 operation cycles at power levels from 20 kW to 30 MW, with an overall operation time of 3830h [1].

Planned BNCT activities

The underwater neutron line for BNCT was mounted along the H2 horizontal beam tube axis of the reactor. It consists of two pneumatic caissons, designed as suitably shaped, welded aluminium boxes, coupled with a pneumatic emptying/refilling system. During the irradiation the caissons are filled with nitrogen and then refilled with water, in order to restore the biological shield of the reactor [2].

The auxiliary facility called BIMA enables irradiation of living tissues with thermal neutrons inside the reactor. The facility was designed as two concentric pipes. The internal 9m long pipe is equipped with automatic allocation for standard containers used for cell cultures in biological research. The external pipe, filled with water, is part of a system of precise stabilisation of temperature all along the container ($\pm$ 0.5°C, independently of external conditions). The facility is mounted on the reactor basket with the irradiation point positioned just behind the graphite reflector of the reactor, where practically all neutrons are well thermalized. The measured thermal neutrons flux at the full power of the reactor was equal to φ_{th}=1.2 x 10^9n cm^{-2}s^{-1}. The lower end of the facility (750mm along the pipe), is shielded from gamma radiation by four thick lead rings. This ensures acceptably low value of the ratio of gamma dose rate to neutron flux, which is about D_γ/φ_{th}≈5 x 10^{-14}Gy·cm^{2}n^{-1}.

The construction of a neutron beam-line inside the reactor and the BIMA facility completed the first stage of the BNCT project in the IAE. Measurements of the neutron energy spectrum performed at the front of the channel H2 confirmed that the dominating component in the spectrum is associated to thermal neutrons. Therefore, the next important stage will be the construction of the fission converter at the exit of H2 channel. Afterwards, the suitably designed filter/moderator system will create the required therapeutic epithermal beam. The mass of the ^{235}U in the converter will be deeply subcritical, so the neutron multiplication ratio will be much below one. The balance of neutrons can be improved by the use of a reflector around the converter.

Because of technical conditions at the reactor MARIA the converter has to be placed near the channel exit and head of a patient. Moreover, it is not possible to place the filter-monitor, F/M, the system and set-up for the positioning of the patient along the beam centreline, due to spatial limitations. Therefore, the F/M system had to be placed out of the axis of the duct and the fission converter. The fast neutron beam is expected to be geometrically heterogeneous, so the proposed bent geometry of the F/M system has an important advantage, because the main gamma flux, originated from the reactor core and emerging directly from the reactor duct, is scattered outside the therapeutic position (see Figure 6.8.1).
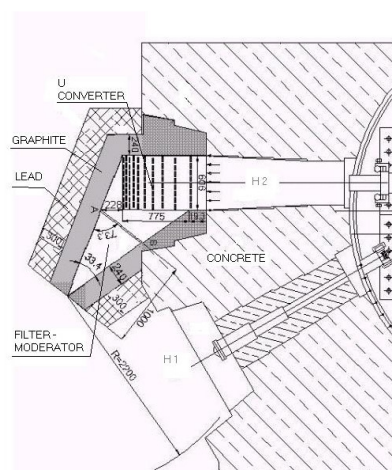

Figure 6.8.1: Schematic view of the fission converter and filter-moderator system at the reactor MARIA in Poland

The fission converter concept has been the subject of several neutron and gamma simulation studies (converter, neutron filter/moderator, photon filter) performed in the Institute of Nuclear Physics in Krakow [3]. The possibility of obtaining an epithermal neutron beam of the required efficiency, spatial

homogeneity and low contamination has been the main considered issue. The unique design of the therapeutic beam set-up has been proposed for the specific geometrical conditions of the irradiation room at the reactor. The numerical calculations revealed that it was possible to realise the epithermal neutron source with acceptable parameters. At the current stage of the source optimisation process, the available "in-air" beam intensity reaches $\varphi_{epi} = 0.3 \times 10^9 cm^{-2}s^{-1}$, assuming incident thermal neutron flux of $10^{10}cm^{-2}s^{-1}$. Both fast neutron and photon contamination are maintained below assumed limits i.e. $2 \times 10^{-13}Gy\ cm^2$. The experience gained during the optimisation performed up to now indicated that further increase of the epithermal beam intensity would be still achievable.

Status and Future Plans
At present, the BNCT line is used for research, with three on-going projects:
1. The use of non-diluted activation detectors with proper modification of self-shielding correction factors.
2. The use of recombination chambers and high pressure chambers filled with different gases for determination of dose equivalent in phantom and for separation of dose contributions from different radiations.
3. Application of special miniature thermoluminescence detectors for thermal/epithermal neutrons (in ^{6}LiF miniature holders) and ^{7}LiF:Mg,Cu,P detectors for estimation of the non-neutron component of the radiation fields. The detectors are produced in Poland, in the Institute of Nuclear Physics in Krakow.

The future of the BNCT project in Poland depends mostly on medical justification. The most important is strengthening the collaboration with oncology physicians, and getting the know-how concerning the medical part and treatment planning. This knowledge has to be gained in international collaboration, which must include training for the interested medical doctor(s) and for young medical physicists.

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6.9 Evaluation of HDR Cf-252 brachytherapy unit use for BNCT

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Introduction
Brachytherapy is a mode of radiation treatment of cancer where the radiation source is delivered in the tumour or close to the tumour. This treatment is predominantly used for gynaecological applications. Traditionally, the gamma emitting sources are broadly employed in the clinic. However, neutrons have radiobiological advantages over pure gamma sources, especially for purely oxygenated, radio-resistant tumours.

The use of unique HDR Cf-252 unit was initiated in Lithuanian Oncology Center in 1989. Over the period 1987-2000 more than 1,468 patients with locally advanced or advanced cancers were treated:

Breast – 350
Gynecology – 839
Mobile tongue and flour of mouth – 82
Rectum – 94
Eesophagus – 34
Prostate – 30
Soft tissue sarcomas – 12
Malignant gliomas – 27

From this large clinical experience, it can be concluded that gamma-neutron Cf source is effective for treatment of many locally advanced cancer sites. However, the analysis of post treatment loco-regional failures shows the necessity to boost the dose on the periphery, especially for gynaecological and malignant glioma patients.

The HDR Cf-252 unit
The main characteristics of Cf-252 source are presented in Table 6.9.1.

Table 6.9.1: ^{252}Cf Spontaneous Fission Properties

Half life	2.645 years
Specific activity	536.3 Ci/gram
SF branching fraction	3.092 %
Neutron emissions	3.768 neutrons/fission
Mean neutron spectrum energy	2.13 MeV
Prompt γ multiplicity (mean)	~ 10/fission
Average prompt γ energy	0.7 – 0.9 MeV
Total prompt γ energy	6.7 – 0.9 MeV

The parameters of the gamma spectra are tabulated in the Table 6.9.2.

Table 6.9.2: Photons from Spontaneous Fission of ^{252}Cf Abundance (photons/µg-s)

Energy (MeV)	Prompt γ	Equilibrium Fission Product γ	Total
0.0 – 0.5	3.3×10^{12}	1.3×10^{12}	4.6×10^{12}
0.5 – 1.0	1.7×10^{12}	4.0×10^{12}	5.7×10^{12}
1.0 – 0.5	7.7×10^{11}	1.9×10^{11}	1.7×10^{11}
1.5 – 2.0	4.2×10^{11}	3.5×10^{11}	7.7×10^{11}
2.0 – 2.5	2.2×10^{11}		2.2×10^{11}
2.5 – 3.0	1.1×10^{11}		1.1×10^{11}
3.0 – 3.5	5.6×10^{10}		5.6×10^{10}
3.5 – 4.0	3.0×10^{10}		3.0×10^{10}
4.0 – 4.5	1.7×10^{10}		1.7×10^{10}
4.5 – 5.0	8.2×10^{9}		8.2×10^{9}
5.0 – 5.5	4.9×10^{9}		4.9×10^{9}
5.5 – 6.0	1.8×10^{9}		1.8×10^{9}
6.0 – 6.5	1.0×10^{9}		1.0×10^{9}

		Total $= 1.322$ x 10^{13} photons/µg-s

The neutron spectrum is presented in the Figure 6.9.1. The normalized dose rate curves of encapsulated Cf-252 point source in water are shown on the Figure 6.9.2

The Russian-made HDR remote "afterloader" with three wires driven in three channels Cf-252 sources was used for brachytherapy treatments. The central source can be moved in 15 possible steps of 1cm each. The unit is originally designed for 0.3 – 1.5 - 0.3 mg of Cf-252 initial activity loading in the channels. Because of the last sources change in 1998, the equipment at present stage is suitable only for experimental set up. The exterior view of the unit is shown in Figure 6.9.3.
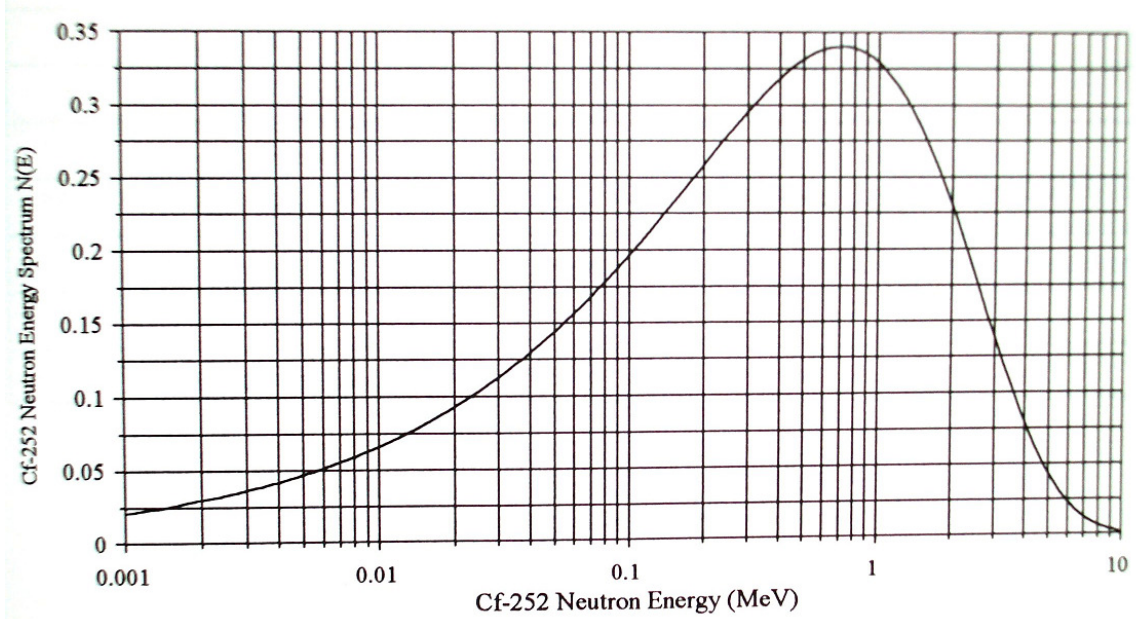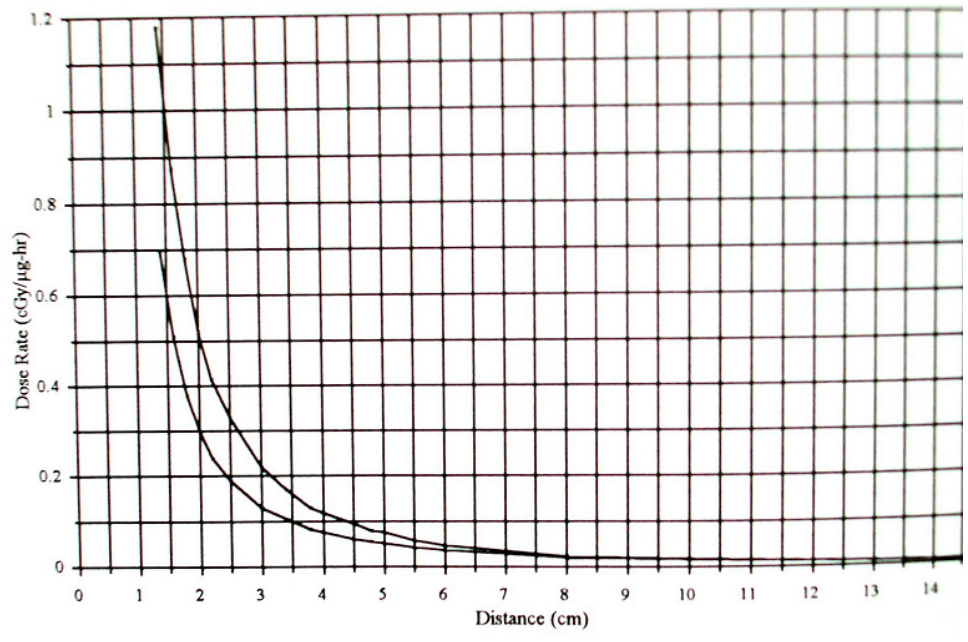

Figure 6.9.1: Watt Fission Spectrum of Cf-252

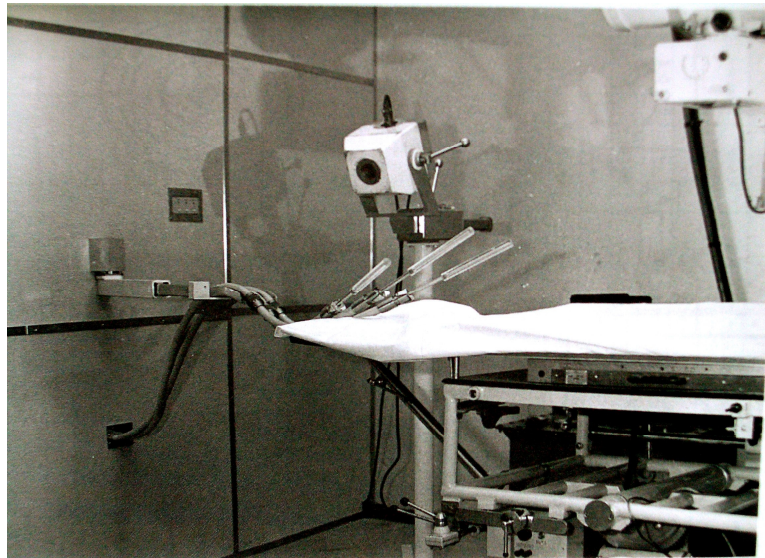Fig. 6.9.2: Measured Cf-252 neutron and photon dose rates vs distance


Fig. 6.9.3: The home-made HFR Cf-252 source loader

Future plans

The authors see two possible ways of using this equipment for BNCT:

1. The redesign of the sources housing and delivery system (see Figure 6.9.4). This way it can accommodate more activity, approximately 1g of initial activity source. Additional room shielding, beam collimation and moderation of neutron fluence are also needed. After these modifications, Cf-252 source can be used as external source of neutrons for BNCT similarly to traditional reactor based BNCT.

2. To deliver boron compounds directly to the treatment sites – gynaecology or gliomas case in such a way that the tail of low energy neutrons for BNCT can boost the lack of dose at the edge of treatment volume.

Absolute and relative dosimetry as well as treatment planning solutions is essential in both cases.
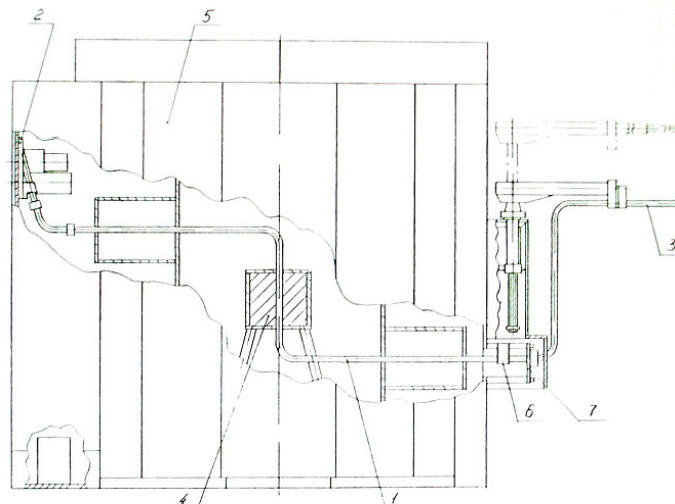
Storage container of Cf-252 sources. 1. One of three channels. 2. Driver. 3. Source guide hose 4. Central lead shield. ;

Fig. 6.9.4: Redesign of the source housing and delivery system

6.10   Developing the method of neutron capture enhanced fast neutron therapy in Obninsk, Russia

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Introduction
Medical Radiological Research Center (MRRC) is the leading institution in the Russian Federation dealing with the problems of medical radiology. The main fields of scientific activity cover fundamental and clinical radiobiology, radiation oncology, nuclear medicine, radiation diagnosis and therapy, radiation epidemiology.

An important study line is the use of neutrons for treatment of oncological patients. More than 500 patients with head and neck tumours, breast cancer and some other types of tumours have been treated at the therapeutic neutron beam of the BR-10 nuclear reactor (Institute for Physics and Power Engineering, Obninsk) [1]. The results of three- and five-year survival studies evidenced the promising effectiveness of radiation therapy schemes with fast reactor neutrons.

Current Situation
Clinical experience obtained at the BR-10 reactor permitted to start similar studies with other neutron sources in Obninsk:

1. reactor WWR-c: 15 MW, mean neutron energy ~1 MeV, fast neutron flux = 5 x 10^9n/cm^{2}s, epithermal neutron flux = 3 x 10^9n/cm^{2}s;
2. accelerator KG-2.5: mean neutron energy ~2.3 MeV, epithermal neutron flux = 1.5 x 10^9n/cm^{2}s;
3. reactor BARS-6: continuous and pulse modes, mean neutron energy ~1.44 MeV, pulse duration ~65 µs;
4. pulsed neutron generator ING-031: ^{3}H(d,n)^{4}He, neutron energy ~14 MeV, pulse duration ~1 µs, variable pulse frequencies 1-100 Hz.

Dosimetry
Paired ionization chambers (TE and magnesium, Exradin), activation and fission track detectors, thermoluminescence dosimeters, FBX chemical dosimeter have been used in dosimetry studies. Calculations are based on MCNP Monte Carlo code. This permitted to obtain values of neutron and gamma dose rates and energy distribution of neutrons in air and in tissue-equivalent phantoms. Special moderators were constructed for thermalisation and space modification of the initial neutron beam.

Biological samples
Several biological objects and end points have been included in the studies: strains of bacterial and yeast cells with different reparation genotypes, hematopoietic stem cells of mice, human lymphocytes and Chinese hamster ovary cells (chromosomal aberrations), tumour bearing laboratory animals (melanoma B-16, sarcoma M-1).

A combined modality of treatment has been developed on the basis of experimental and theoretical assessments as well as on the experience in clinical application of the fast reactor neutrons. In particular, after the administration of the compound containing the neutron capturer, the tumour area is irradiated not only by the thermal neutrons but also by a neutron beam with a wide energy spectrum in which both slow and fast neutrons are produced. Thermalisation of the neutron flux can provide an additional absorbed dose via neutron capture events. The realization of this method induces 60-80 % of absorbed dose due to fast neutron therapy and 20-40 % due to neutron capture therapy [2].

At present the main studies are the following:

1. experimental and calculation dosimetry of neutron, gamma-neutron fields for BNCT;
2. development of equipment for neutron beams (filters, moderators, collimators) dedicated to fast neutron and boron neutron capture therapy;

3. pharmacokinetics of compounds for neutron capture therapy;
4. radiobiological effect of neutrons and boron neutron capture events.

Pharmacokinetic studies of compounds include:
5. synthesis of BSH labelled with radioactive iodine for visualisation of compound distribution in the body. The results demonstrate that adopting radioisotope techniques in BNCT practice allows following the kinetics of boron compound accumulation and elimination in the body of patient. Development of this method considerably simplifies the selection of patients and planning of BNCT [3];
6. selection and studies of biodistribution of novel boron compounds;
7. development of methods to increase the boron compound accumulation in tumour (local heating, infrared and red light irradiation of tumour zone) [4].

Planned activities

In 2006 year we planned the construction of a medical block at the reactor WWRc (see Figure 6.10.1) and starting radiobiological and pre-clinical studies of neutron capture therapy enhancement of fast neutron therapy at this facility. Radiobiological studies with the use of different biological samples at accelerator KG-2.5 are carried out. The studies of distribution of boron compounds labelled with radioactive iodine in the body of tumour bearing laboratory animals, the search of methods for increasing of boron compounds accumulation in tumour and development of schemes for individual planning of BNCT will continue.

In the Medical Radiological Research Center and other institutes of Obninsk there is considerable experience and high-qualified personnel for the development of fast neutron and neutron capture therapy.

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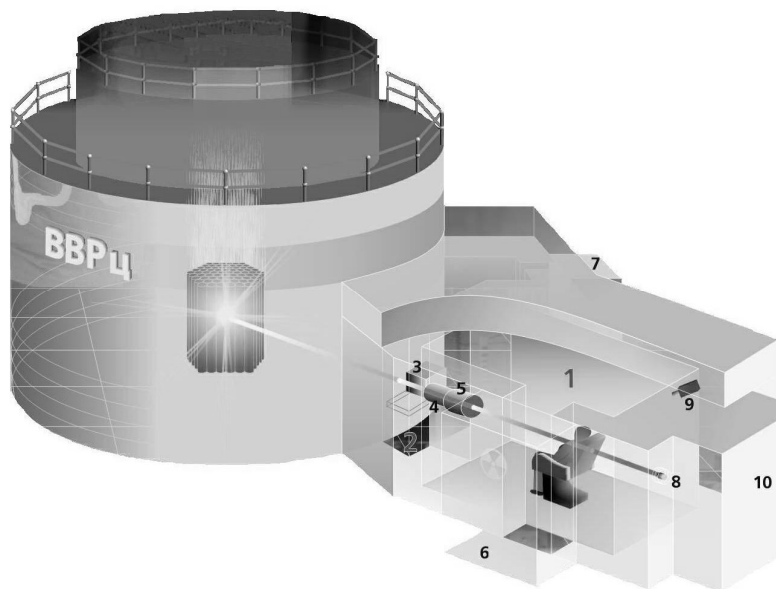
Figure 6.10.1: Model of medical block for realization of neutron capture therapy enhancement of fast neutron therapy at the WWR-c reactor

6.11 Accelerator epithermal neutron beams for BNCT at CC SR

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Introduction

Cyclotron Centre of Slovak Republic (CC SR) is a facility in Bratislava encompassing radionuclide production, production of radiopharmaceuticals, radiopharmaceutical research, eye hadron therapy, an experimental beam for BNCT and other physical and technical applications. At the CC SR there is also a nuclear medicine department for patient examination with positron emission tomography (PET) and a single photon emission computerized tomography (SPECT).

CC SR is being built in two main pavilions. The construction of the first pavilion with PET centre (now BIONT a.s.) is finished. The PET centre consists of a laboratory for positron radionuclide production by cyclotron CYCLONE 18/9, laboratory for production of PET radiopharmaceuticals and of nuclear medicine department in PET centre with PET/CT and PET/SPECT/CT gamma cameras. The CYCLONE 18/9 is a proton/deuteron cyclotron with extracted beam intensities on internal targets up to 18MeV/100 µA protons or 9MeV/50 µA deuterons and up to 30µA protons or 15 µA deuterons on external target.

The building of the second pavilion with cyclotron DC72 started at the beginning of 2006. The DC72 is a proton and heavy ion cyclotron with extracted beams of energy/intensity 72MeV/50µA and 30MeV/100 µA of protons and beams of multiple charged ions up to $^{129}Xe^{18+}$ respectively. The proton beam of 72MeV/50µA is used mainly for the eye tumours therapy and for the BNCT experimental work. The beam of 30 MeV/100 µA protons is used for SPECT radiopharmaceutical production of ^{123}I and ^{81}Rb. Therapeutic radiopharmaceuticals based on the alpha emitter ^{211}At are produced using a beam of alpha particles.

Accelerator neutron beams for BNCT

One of the problems in wider application of BNCT in clinical practice is to have an appropriate epithermal neutron source. At present nuclear reactors as neutron sources are used for BNCT. Due to well known reasons, the operation of nuclear reactors is not optimal in a clinical environment and accelerator sources of neutrons are more attractive. A serious disadvantage of accelerator neutron sources for BNCT is their relatively low intensity of epithermal neutron [1].

An experimental neutron beam for BNCT using the accelerator (AENS) has been developed at CC SR to produce epithermal neutrons. The design of AENS was calculated by the Monte Carlo code MCNP4B.

The main parts of the AENS design are: target, reflector and moderator [2], filter and beam aperture [3]. Designs of the AENS were calculated for three proton beams at CC SR: 72 MeV/50μA (DC72), 30 MeV/100μA (DC72) and 18 MeV/100μA (Cyclone 18/9). Primary neutrons are generated by interaction of 72 MeV or 30 MeV protons with Pb target, while 18 MeV protons can interact with the target $H_2{}^{18}O(Ag)$ for the production of ^{18}F. Differential thick target yield for Pb(p,xn) was taken from [4] (70 MeV protons) and from [5] (30 MeV protons). Angular energy distribution of neutron emission from $H_2{}^{18}O(Ag)$ target was calculated by MCNPX code [6].

The designs of AENS for various proton beams differ mainly in the size of beam aperture. The smaller AENS assembly (45 cm beam aperture) was used for the 18MeV/100μA proton beam. The middle-sized AENS assembly (60 cm beam aperture) was used for the proton beam of 30 MeV/100μA and both the middle- and large-sized (95 cm beam aperture) AENS assemblies were used for the 72MeV/50μA proton beam. The large AENS assembly is shown in Figure 6.11.1.

The design and the material composition of the reflector system, moderators, filters and beam aperture were calculated taking into account the following basic requirements of free-in-air neutron beams:

- the peak of epithermal neutrons is around 10 keV;
- the ratio of epithermal neutron fluence (energy region of 0,6 eV-10 keV) to fast neutron fluence (energy region above of 10 keV) is a factor of about 10;
- the thermal neutron fluence (energy region below 0.6 eV) is negligible in comparison to the epithermal neutron fluence.
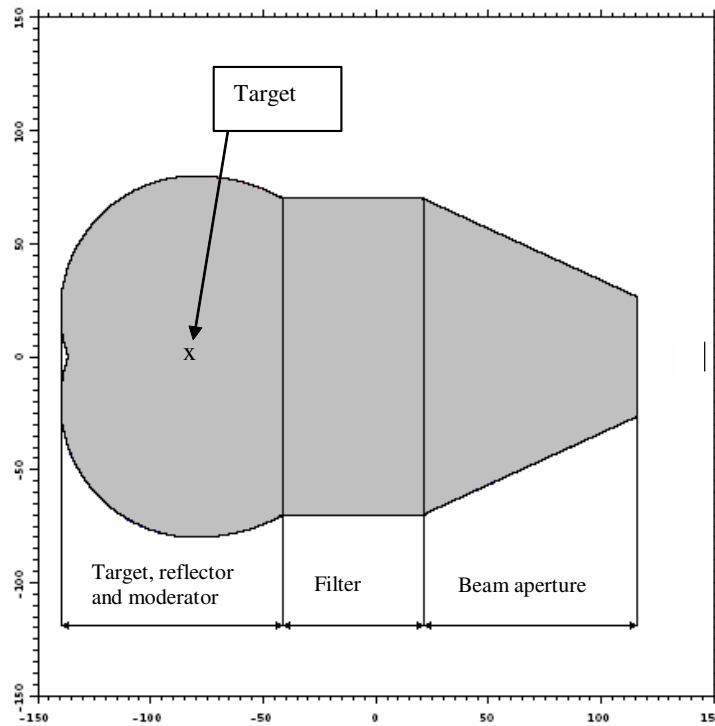
Figure 6.11.1: Sketch of the AENS for BNCT with long beam aperture

Energy spectra of neutron flux density at AENS assembly exit for proton beams 72 MeV/50μA (long and middle beam aperture), for proton beam 30 MeV/100μA (middle beam aperture) and for proton beam 18 MeV/100μA (short beam aperture) are shown in Figure 6.11.2.
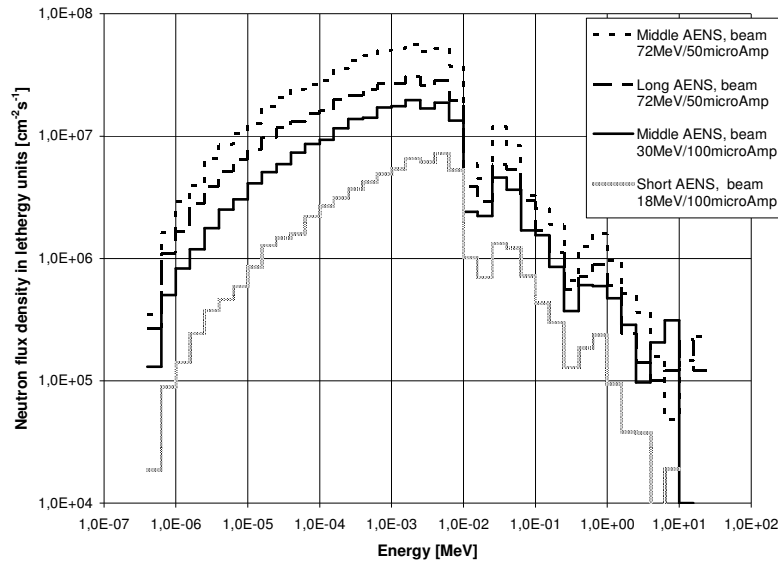

Fig.6.11.2: Neutron energy spectra at the exit of AENS

All investigated designs of AENS produce epithermal neutron energy spectra with peaks at 5 keV. The ratio of the sum of epithermal and fast neutrons and the number of thermal neutrons can be evaluated by integration of the neutron energy spectra across energy intervals of interest. Free beam characteristics, such as integral values of thermal, epithermal and fast neutron flux for various designs of AENS are given in Table 6.11.1.

Table 6.11.1: Integral values and ratios of thermal F_{therm}, epithermal F_{epi} and fast F_{fast} neutron flux [cm^{-2} s^{-1}] produced by AENS in proton beams of CC SR

Proton beam	72MeV/50μA		30MeV/100μA	18MeV/100μA
AENS assembly for BNCT	Long	Middle	Middle	Short
Target	Pb	Pb	Pb	$H_2^{18}O(Ag)$
Neutron emission from target [s^{-1}]	3.0×10^{13}	3.0×10^{13}	1×10^{13}	1.7×10^{12}
Φ_{therm} at beam exit	2.7×10^5	3.5×10^5	1.3×10^5	1.9×10^4
Φ_{epi} at beam exit	3.2×10^8	5.8×10^8	1.9×10^8	5.9×10^7
Φ_{fast} at beam exit	2.8×10^7	4.5×10^7	2.0×10^7	6.5×10^6
Φ_{epi} / Φ_{fast} at beam exit	11.2	13.0	9.7	9.1
Φ_{epi} : 30 cm from beam exit	2.8×10^7	5.8×10^7	1.9×10^7	9.2×10^6
Ratio of Φ_{epi} at beam exit to 30 cm distance	11.4	10.1	10.3	6.4

Taking into account that the minimum required epithermal neutron flux density for BNCT is about of 3 x 10^8 cm^{-2}s^{-1} [7], only the proton beams 72MeV/50μA with the large- and middle-sized AENS assemblies can be used for BNCT in CC SR.

In general a configuration of 30MeV proton cyclotrons with beam intensity higher than 200μA and the middle AENS assembly can be also used for BNCT. The 30MeV cyclotrons for radionuclide production with proton beam intensity of 300μA are commonly installed at clinics with nuclear medicine departments.

The next step in the building of an epithermal neutron beam for BNCT at CC SR is to construct and then experimentally verify the characteristics of the chosen design of the AENS assembly for BNCT.

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6.12 Boron Neutron Capture Therapy at the TRIGA Mainz

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Introduction

Boron Neutron Capture Therapy (BNCT) for explantated organs shall be established at the TRIGA Mainz [1], a project which was first realized at the TRIGA Pavia, Italy [2]. The main objective of this project is to build up an irradiation facility for BNCT of explantated organs, for molecular targeted radiotherapy and other biological and medical purposes at the TRIGA Mainz. This would be the only facility with a thermal and epithermal neutron field of this kind in Germany and could be used for biological and medical research being attractive for international and national research groups.

The thermal column of the TRIGA Mainz shall be reconstructed to allow the irradiation of an organ with thermal and epithermal neutrons and to establish an irradiation facility for medical purposes at the reactor facility. The aim is to reduce as much as possible the gamma contamination by shielding the external photon irradiation in the thermal column and to receive a thermal and epithermal neutron irradiation field with a neutron flux distribution over the organ which produces a low dose gradient in the organ.

Figure 6.12.1: TRIGA MARK II Mainz: 100 kWth steady state; 250 MWth pulse mode

Future activities

As first step, the optimal design of the thermal column for biological and medical purposes is under investigation. This is performed by mathematical modelling using MCNP [3] and ATTILA [4]. The calculations are validated by measurements of the neutron flux and gamma dose in the thermal column and other locations inside the reactor tank.

Suitable dosimeters for the measurement of the neutron flux, neutron energy spectra and different doses in the thermal column are selected [5]. Several dosimeters for the measurements of a relatively small gamma dose in strong neutron fields are tested free-in-air and in phantoms. The characterization of the neutron field by in-air and in-phantom measurements is planned to be performed using different techniques.

On the basis of the calculations and the measurements, the thermal column will be adapted. After the reconstruction, the irradiation field will be calibrated and the beam quality will be verified. Equipment to handle and monitor the explanted organ or other biological samples must be developed. This includes the confinement for the organ, a rotation and cooling system and an online monitoring of the physical quantities. The safety, the reliability and the documentation must be guaranteed to assure a safe working environment and a qualified technique.

To determine the boron concentration and distribution in tissue or blood, the neutron auto-radiography and the Prompt Gamma Neutron Activation Analysis (PGNAA) shall be installed, tested and qualified at the TRIGA Mainz. The results of both methods shall be compared. Additionally the therapy treatment planning software will be installed, tested and adapted to the applications at the TRIGA Mainz. The first trials with SERA have already been carried out [6].

The schedule for the project is summarized in Table 6.12.1. The following steps have already been investigated:

- Measurement of the neutron flux and the photon dose at the thermal column
- Test of detectors (different kinds of TLD, such as CaF_2:Tm material, LiF-Pairs, ^{6}LiF-Detectors, Au-foils)
- Simulations with ATTILA: modeling and first calculations
- Development of a phantom: measurements of the surface and depth dose of neutrons and gamma irradiation
- Establishment of neutron auto-radiography: tests of different films, dependent on the neutron flux and the development conditions
- Installation and testing of the treatment planning software SERA

The project will be carried out in cooperation with different departments of the University Mainz, the University Hospital Essen, the University Münster, the STEAG encotec Essen GmbH, the Forschungszentrum Karlsruhe and the Physikalische Technische Bundesanstalt Braunschweig. International collaboration will also be sought.

Table 6.12.1: Schedule of the planned BNCT project at the TRIGA Mainz

No.	Description
1	Beam design analyses (mathematical modeling using MNCP and ATTILA)
2	Verification of the results obtained from ATTILA and MCNP calculations with measurements (before and after modification of the thermal column)
3	Test of different detectors to measure the neutron flux, neutron energy spectra, neutron and gamma dose.
4	Characterization of the neutron field by in-air and in-phantom measurements in the thermal column (before and after its modification)
5	Modification of the thermal column
6	Construction of the confinement for the organ
7	Installation and test of the online monitoring
8	Beam calibration, quality control and documentation
9	Installation and test of neutron auto-radiography
10	Installation and test of the PGNAA

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6.13 BNCT at the TAPIRO Reactor

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Introduction

Nuclear reactors employed for BNCT experimentation are thermal reactors, except for the TAPIRO reactor at the ENEA Casaccia centre, near Rome (Italy) [1].

TAPIRO is a small and very compact low-power fast-flux research reactor. Its maximum power is 5 kW (4.3×10^{14} neutrons/s) and the maximum neutron flux at the core centre is about 3×10^{12} cm$^{-2} \cdot$s^{-1}. Its first criticality was achieved in 1971. The core is cylindrical (12.58 cm diameter and 10.87 cm height), made of 93.5% enriched uranium metal in a uranium-molybdenum alloy, helium cooled and it is surrounded by a copper reflector. About 170 cm thick biological shield models the outer round shape of the reactor. Both the shield and the reflector are crossed by a number of irradiation channels that penetrate very close to the core. The largest channel is what was originally called the "thermal

column" and it has been dedicated to BNCT research since about 1998 employing both thermal and epithermal neutron beams. More recently, a new epithermal column has been designed for clinical purposes. For these applications the neutron source energy spectrum had to be modified by reducing the fast component and increasing the epithermal (or thermal) component.

Experimental facilities
Two experimental facilities (a thermal and an epithermal column) are currently employed at the TAPIRO reactor aimed at dosimetry and animal experiments.

A thermal neutron experimental facility [2] has been designed and is exploited by the LNL (Legnaro National Laboratory, Padua, Italy) for research dedicated to boron compounds for skin melanoma. For this purpose, the facility is being used to irradiate cells and mice for radiobiological studies and to test instrumentation for neutron microdosimetry studies. The irradiation cavity (about $14\times14\times24$ cm^3) is approximately located in the middle of the thermalizing structure.

A collimated epithermal beam (0.4 eV -10 keV) for BNCT research has been set up to irradiate rats with glioblastoma and to test instruments and methods for radiation dosimetry. The irradiation volume is a parallelepiped-shaped chamber (about $40\times40\times80$ cm^3) and it is placed at the moderating structure exit within the biological shield. The area of the incident beam is 10×10 cm^2. However this facility is not suitable for patient irradiations because the irradiation cavity is too small at its location is not accessible for clinical use.

The epithermal therapeutic facility: design and construction
For clinical purposes a new epithermal column for the treatment of certain kinds of non-superficial tumour (typically brain gliomas) has been designed [3] and is being constructed in collaboration with the University of Pisa (Italy). The irradiation position needed to be moved from within the biological shield (in the experimental epithermal facility mentioned above) to outside the biological shield. The calculation design tool employed was the Monte Carlo code MCNP [4]. The final column design contains: a compressed AlF$_3$ epithermal moderator (density of 1.85 g·cm^{-3}) packed into aluminium boxes, a nickel reflector surrounding the moderator and the cavity following the moderator itself, a long lead collimator followed by an enriched lithiated polyethylene neutron absorber and a small protruding nozzle to improve the patient's position. The epithermal neutron flux (about 8×10^8 cm^{-2} s^{-1}) and the other free beam parameters calculated at the collimator opening (area of 10×14 cm^2) [3] are similar to other facilities used for BNCT trials [5].
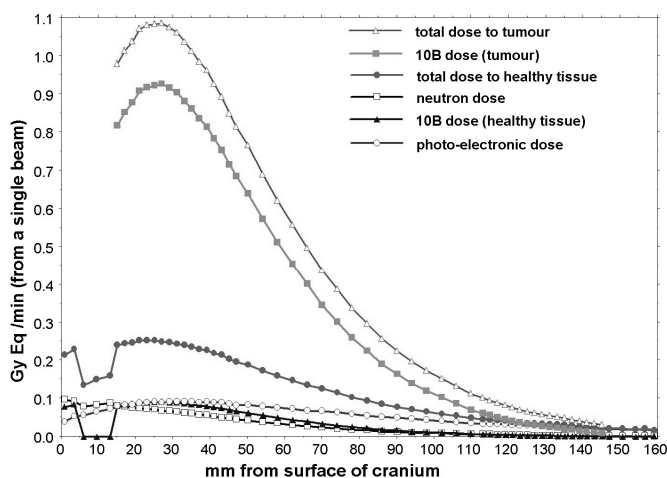

Figure 6.13.1: Profiles of dose components to healthy tissue and tumour

The realistic anthropomorphic phantom "ADAM" [6] was included to evaluate the dose profiles (see Figure 6.13.1) and the therapeutic parameters in the cranium. The dose components considered are: the boron dose, the neutron dose (including both recoil protons and protons from neutron capture in ^{14}N) and the photo-electron dose. RBE factors of 3.2 and 1.0 were used for neutrons (at all energies) and photons respectively. CBE factors are those generally accepted for BPA and brain gliomas (2.5 for skin and tissue under skin, 1.3 and 3.8 for normal and tumour brain tissue) [7]. For a single beam lateral irradiation the maximum dose rate to healthy tissue (ADDR) is 0.252 GyEq/min situated in the brain near the maximum tumour dose, that is a treatment time of 50 min using the constraint of a maximum 12.6 GyEq to healthy tissue. The peak therapeutic ratio is 4.30 at a depth of 13 mm in the brain (27 mm in the cranium). The advantage depth is 86 mm and therapeutic depth is 66 mm (measured from the skin surface). These calculated therapeutic parameters are quite satisfactory for such a low power source and they were evaluated with a conservative hypothesis for the ^{10}B concentration (10 µg/g in brain and 35 µg/g in tumour).

The construction of the epithermal column for patient treatment is nearly completed. The moderator and the reflector assembly have been already set up (see Figure 6.13.2), while the collimator and the neutron absorber are under construction. The beam aperture will be square instead of rectangular (as originally designed). As for the absorber, it has been made of lithiated polyethylene with natural lithium (instead of enriched, as designed) because it is easier to find and its absorbing performances will be sufficient during the beam characterization. According to the characterisation, the absorber might be improved in function of the clinical trials. Moreover, it was desired to maintain some flexibility both in the neutron spectrum (some AlF$_3$ boxes of different thicknesses are available) and in the beam aperture (the outer part of the collimator is movable) to allow for the eventual treatment of organs of different sizes.
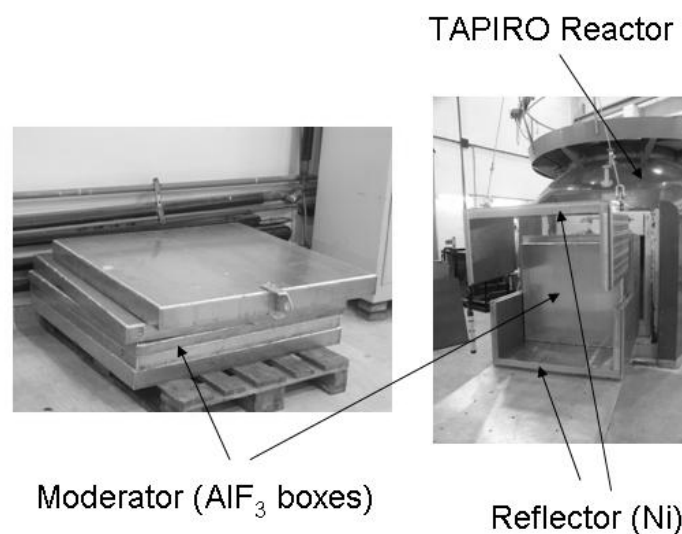

Figure 6.13.2: Construction of the therapeutic epithermal column. Pictures of the moderator and reflector assembly

Future activities
According to the BNCT experiments at TAPIRO with the thermal and epithermal columns, it has been shown that TAPIRO, in spite of its low power of 5 kW, is able to provide an epithermal beam of good quality and of sufficient intensity to perform patient irradiations. The construction of the therapeutic epithermal column is nearly completed. The design of the shielding for the beam characterization is now in progress. The characterization of the beam will begin soon and extensive investigations will be performed by both Italian and foreign research centres. Further applications of the epithermal facility

will be considered, such as the extra-corporal treatment of liver cancer (following the Pavia experience).

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6.14   Boron Neutron Capture Therapy (BNCT) - State of the Art in Romania

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Introduction

Romania, the country in south-eastern of Europe, with 22 millions of inhabitants (July 2003) has a general mortality of 11.4% (2002) and a cancer incidence of about 260 new cases every 100,000 inhabitants. From this, 60 to 80% of the new cases must be treated by radiotherapy, which means about 34,000 new patients needing radiotherapy.

The Institute of Oncology Bucharest was set up in 1949. It was the first unit in Romania where cancer treatment was designed to be multimodal, integrating surgery, radiation therapy and chemotherapy.

The main activities performed in the Institute of Oncology are:

- Diagnostic and Multimodal treatment of cancer patients;
- Scientific medical research;
- Educational activities involving students and postgraduates, pending on "Carol Davila" Medicine University;
- Coordination of cancer care in the South and Eastern part of Romania.

The institute structure is composed of:

- Surgery Departments (2);
- Chemotherapy Departments (3);
- Pediatric Oncology Department;
- Radiotherapy Departments (3);
- Laboratories for different analysis and investigations;
- Laboratory of Radiotherapy with high energy;
- Compartment of Medical Physics and Dosimetry
- Research Laboratories (Cancer biology, Cancer - genesis, Radiobiology);
- Teaching Department.

The equipment in the laboratories of radiotherapy with high energy consists of:

- 2 LINACS, 2 cobalt units, 2 HDR afterloaders, 2 Simulators;
- 2 Treatment planning system: PINNACLE and PLATO;
- Dosimetry equipment for absolute dosimetry, 3D field analyzer, portable radiation monitors; in vivo dosimetry equipment (for external beam therapy as well as for brachytherapy).

The staff of the laboratories of radiotherapy with high energy consists of 14 medical doctors specialized in oncology and radiotherapy, 6 medical physicists, 30 medical technicians and assistants.

Planned activities
In July 2005 the Government of Romania organized and sponsored the contest "Programs of Excellency in Research". In this competition, the Institute of Oncology won with the Complex Projects of Research and Development with the title: "The Study, the Research and the Approach of Boron-10 Neutron Capture Therapy in the Oncological Clinic of Radiotherapy". In this project, the coordinator institution is the Institute of Oncology "Prof.Dr.Al.Trestioreanu", Bucharest and the Director of Programme is Prof. Rodica Anghel, M.D, PhD. The partners in this project are:

- National Institute for Research-Development of Nuclear Physics and Engineering "Horia Hulubei", Bucharest;
- Autonomous Administration for Nuclear Activities - Nuclear Researches Branch, Pitesti;
- Clinical Institute "FUNDENI", Bucharest;
- "Victor Babes" Foundation.

The present experience of the consortium is:

- Experience in classical radiotherapy (with gamma, X and electron beams, including stereotactic and total body irradiation);
- Experience in radiobiology and cell-culture;
- Experience for producing of thermal and epithermal neutrons (TANDEM Linear Accelerator and Nuclear Reactor);
- Experience in spectroscopic analysis and dosimetry of thermal and epithermal neutrons.

The staff of this project include more than 70 persons: radiotherapists; medical doctors; medical physicists; nuclear physicists; chemists, research workers in different fields such as biology, radiobiology, cell cultures, veterinary medicine. The budget of this project is 400,000 €.
The proposed objectives are:

- The technical premises for the implementation of the boron-10 neutron capture therapy

in Romania.

- The generation and the characterization of the neutron beam used in the boron-10 neutron capture therapy.
- The characterization of the incorporation model of the macromolecule containing boron-10 at the tumor cell level, as compared with the metabolism in normal cells.
- BNCT preclinical study in animals with implanted tumors.
- The establishment of radiation doses developed in the studied target volume.
- The creation of a preclinical therapeutic protocol extrapolated in humans.

The steps proposed for the project realisation follow a logical and methodological that should be the basis in the application of BNCT in Romania. Each step gives important data for the next step. It starts with a detailed study on the technical and intellectual resources existent at the moment and needed for the implementation of BNCT. Different types of tumour high affinity macromolecules should be analyzed, attaching a higher ^{10}B concentration. Studies on normal and tumour cells should follow, and then experiments on animals. Afterwards, cell cultures and tumours should be irradiated with neutrons previously characterized in function of the boron capture optimization. The results of this project should end with a preclinical treatment protocol, further extended in human patients.

The project could be characterized by:

- total research, aiming to stimulate the experimental progress in biomedical research, by improving the generation, standardization, data acquisition and analysis;
- promotion and monitoring of non-invasive or minimal invasive technique.

One of the main project aims is to enable the transfer of research results into the clinical treatment of major affections, such as cancer.

6.15 Designing your own BNCT Programme

During the workshop in Prague, the participants were asked to define for a hypothetical BNCT facility a strategy for a BNCT Programme. After an introduction given by Wolfgang Sauerwein, participants had to develop in 2 groups Mission, Vision, Success Factors and Guiding Principles for "their own" BNCT Programme.

The results from these 2 groups are summarized below.

BNCT Centre "ABC"

Our Mission (What business are we in?)
Our mission is to further optimise and develop the potential of BNCT through interdisciplinary research to make BNCT a treatment modality.

Our Vision (What do we want to be recognized?)
We aim at being the leading BNCT Centre and by doing so acting as Reference Centre for developments in this field

We would like to be recognized as those who are
- introducing a new effective treatment
- improving clinical applications for hopeless patients
- modernizing the national cancer treatment strategy
- developing new application for reactors

- respectable scientists able to get EU-funded

What five things do we need to concentrate on to make that happen?
    (*our success factors*)
We need
- to find money
- to establish an efficient project management with QA in all steps of the project
- to create good multidisciplinary collaborations with reliable and motivated partners
- to build good communication between all partners and a good relationship with authorities and media
- to integrate the project in a "Cancer Research Frame" (BNCT should not be a separate "category")

Our guiding principles
- High motivation of the partners with same goals and proper background
- Clear definition of responsibilities, rules and objectives
- Honest partnership on scientific basis
- Open and wide collaboration at inter and national scale
- Acceptance of competence limits
- Keeping deadlines
- Good communication and personal relationship
- No fears for failure

BNCT Centre "XYZ"

Our Mission (What business are we in?)
Developing a reactor based Neutron Capture Therapy for Cancer

Our Vision (What do we want to be recognized?)
We aim at being
- the Reference Centre for BNCT
- an important innovative research activity within our Institutes/Universities
- a group, who sticks to his commitments
- a project, which opens the future in the field

What six things do we need to concentrate on to make that happen?
    (*our success factors*)
- Boron analysis
- Patient treatment
- Improved Communication
    - Information on tasks
    - Meetings
    - Progress-Reports
    - SOP's
- Improved interaction with partners
    - Satisfaction
    - New partners
- Strategy for future
- Publications

Our guiding principles
- The general principles of medical ethics
- The generally accepted professional rules and guidelines to achieve the standards of quality and safety
- Open and unbiased collaboration
- Good organizational structure
- Beneficial for all partners

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Abstract
An international workshop, funded by the JRC¿s Enlargement and Integration Action, took place in Prague in 2005 entitled ¿Requirements for BNCT at a Nuclear Research Reactor¿. The intention of the workshop was to exchange knowledge between the EU BNCT programme at the HFR Petten (EC, NL) and other existing clinical and preclinical research programmes on BNCT throughout Europe, with the special aim to transfer information towards groups and places that are preparing their own national BNCT projects. The future of nuclear research institutes will depend on their ability to open research programmes into new areas and to link nuclear technologies with other applications. Medicine is one of the most interesting but also sensitive areas for such multidisciplinary work. Boron Neutron Capture Therapy (BNCT) is a dedicated and well-known topic that demonstrates such a link in an exemplary way. This book expands on some of the topics presented at the workshop. It is intended to support scientists, clinicians and politicians that are interested to develop a local or national BNCT activity.

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