Annex 3
IRRADITION FACILITY OPERATION AND MANAGEMENT

Boron neutron capture therapy: An interdisciplinary co-operation

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

1. INTRODUCTION

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

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

2. THE HOSPITAL

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

2.1. Radiotherapy

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

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

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

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

2.2. Medical physics

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

The major tasks of the Medical Physicist will be:

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

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

2.3. Pharmacy

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

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

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

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

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

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

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

2.4. Other medical specialists

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

3. THE OWNER OF THE REACTOR

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

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

The reactor

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

The Beam

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

Working environment, security and radiation protection

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

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

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

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

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

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

Prompt gamma facility

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

5. ORGANISATIONAL STRUCTURE AND REGULATORY ASPECTS

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

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

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

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

Reactor related:

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

Protocol related:

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

Patient related:

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

Personnel and Institution related:

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

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

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

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

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

General Aspects of Quality Management and Safety Assessments

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

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

For performance:

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

And for treatment planning systems:

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

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

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

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

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

6. SUMMARY

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

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