

UNIVERSITY OF HELSINKI

REPORT SERIES IN PHYSICS

HU-P-D160

# **Finnish dosimetric practice for epithermal neutron beam dosimetry in boron neutron capture therapy**

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ACADEMIC DISSERTATION

*To be presented, with the permission of  
the Faculty of Science of the University of Helsinki,  
for public examination in Auditorium CK112,  
Exactum, Gustav Hållströmin katu 2 B  
on April 24<sup>th</sup>, 2009, at 12 o'clock noon*

Helsinki 2009

ISSN 03556-0961  
ISBN 978-952-10-4231-7  
ISBN 978-952-10-4232-4 (pdf version)

Helsinki Print House  
Helsinki 2009

J. Uusi-Simola: Finnish dosimetric practice for epithermal neutron beam dosimetry in boron neutron capture therapy, University of Helsinki, 2009, 38 pp. + appendices, University of Helsinki, Report Series in Physics, HU-P-D160, ISSN 03556-0961, ISBN 978-952-10-4231-7, ISBN 978-952-10-4232-4 (pdf version).

Classification (INSPEC): A2940, A2970J, A8760J, A8760M, B7520C

Keywords: medical physics, radiotherapy, BNCT, epithermal neutrons, dosimetry

## **Abstract**

Boron neutron capture therapy (BNCT) is a form of chemically targeted radiotherapy that utilises the high neutron capture cross-section of boron-10 isotope to achieve a preferential dose increase in the tumour. The BNCT dosimetry poses a special challenge as the radiation dose absorbed by the irradiated tissues consists of several dose components with different relative biological effectiveness. Dosimetry is important as the effect of the radiation on the tissue is correlated with the radiation dose. Consistent and reliable radiation dose delivery and dosimetry are thus basic requirements in order to ensure patient safety, comparability of results between different BNCT centers and to enable comparison with other treatment modalities. The established international recommendations for radiotherapy dosimetry are not directly applicable to BNCT. The existing dosimetry guidance for BNCT provides recommendations for the dosimetric methods but also calls for investigating for complementary methods for comparison and improved accuracy.

In this thesis the quality assurance and stability measurements of the neutron beam monitors used in dose delivery are presented. The beam monitors were found not to be effected by the presence of a phantom in the beam and that the effect of the reactor core power distribution was less than 1%. The weekly stability test for the beam monitoring system with activation detectors has been generally reproducible within the recommended tolerance value of 2%.

An established toolkit for epithermal neutron beams for determination of the dose components is presented and applied in an international dosimetric intercomparison. The measured quantities (neutron flux, fast neutron and photon dose) determined by the groups participating the intercomparison were generally in agreement within the stated uncertainties. However, the measurement uncertainties were large, ranging from 3-30% (1 standard deviation (SD)), depending on the method and depth of measurement, emphasising the importance of dosimetric intercomparisons if clinical data is to be compared between different centers.

Measurements with the Exradin type 2M ionisation chamber have been repeated in the epithermal neutron beam in the same measurement configuration over the course of 10 years. The presented results exclude severe sensitivity changes to thermal neutrons that have been reported for this type of chamber.

The feasibility of microdosimetry and polymer gel dosimetry as complementary methods for epithermal neutron beam dosimetry are studied. For microdosimetry the comparison of results with ionisation chambers and computer simulation showed that the

photon dose measured with microdosimetry was systematically lower than with the two other methods. The disagreement was within the uncertainties. For neutron dose the simulation and microdosimetry results agreed within 10% while the ionisation chamber technique gave 10-30% lower neutron dose rates than the two other methods. The response of the BANG-3 gel was found to be linear for both photon and epithermal neutron beam irradiation. The need for consistent procedures with gel dosimeters was emphasised to ensure reliable results. The dose distribution normalised to dose maximum measured by MAGIC polymer gel was found to agree well with the simulated result near the dose maximum while the spatial difference between measured and simulated 30% isodose line was more than 1 cm. In both the BANG-3 and MAGIC gel studies, the interpretation of the results was complicated by the presence of high-LET radiation.

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## List of original publications & statement of involvement

This thesis is based on the following publications, which are referred to in the text by their Roman numerals I-VI

- I I. Auterinen, T. Serén, P. Kotiluoto, J. Uusi-Simola and S. Savolainen, Quality assurance procedures for the neutron beam monitors at the FiR 1 BNCT facility, *Appl. Radiat. Isot.* 61, 1015-1019 (2004).
- II I. Auterinen, T. Serén, J. Uusi-Simola, A. Kosunen and S. Savolainen, A toolkit for epithermal neutron beam characterisation in BNCT, *Rad. Prot. Dos.* 110 (1-4), 587-593 (2004).
- III P. Binns, O. Harling, W. Kiger III, P. Munck af Rosenschöld, V. Giusti, J. Capala, K. Sköld, I. Auterinen, T. Serén, P. Kotiluoto, J. Uusi-Simola, M. Marek, L. Viererbl and F. Spurny, An international dosimetry exchange for boron neutron capture therapy, Part I: Absorbed dose measurements, *Med. Phys.* 32, 3729-3736 (2005).
- IV J. Uusi-Simola, T. Serén, T. Seppälä, A. Kosunen, I. Auterinen and S. Savolainen, Dosimetric comparison at FiR 1 using microdosimetry, ionisation chambers and computer simulation, *Appl. Radiat. Isot.* 61, 845-848 (2004).
- V J. Uusi-Simola, S. Savolainen, A. Kangasmäki, S. Heikkinen, J. Perkiö, U. Abo Ramadan, T. Seppälä, J. Karila, T. Serén, P. Kotiluoto, P. Sorvari and I. Auterinen, Study of the relative dose response of BANG-3 polymer gel dosimeters in epithermal neutron irradiation, *Phys. Med. Biol.* 48, 2895-2906 (2003).
- VI J. Uusi-Simola, S. Heikkinen, P. Kotiluoto, T. Serén, T. Seppälä, I. Auterinen and S. Savolainen, MAGIC polymer gel for dosimetric verification in BNCT, *J. Appl. Clin. Med. Phys.* 8, 114-123 (2007).

All publications included in this thesis are the results of a combined effort. In Study I, the author participated in the ionisation chamber measurements and in the analysis and interpretation of the data from the ionisation chamber measurements. In Study II, the author participated in the testing and measurements of ionisation chamber part of the toolkit. In Study III, the author participated in the measurement and analysis of the data as the part of Finnish contribution. In Studies I-III the author revised the articles critically and approved the final version to be published. In Studies IV-VI the author participated in devising the concept, the design of the study, in the measurements and in the analysis and interpretation of the data. Studies IV, V and VI were written by the author of this thesis.

To the author's knowledge, these study results have not been used in other Ph.D. theses.

## **Aims of the study**

The aim of this thesis was to examine the existing dosimetric practice and to establish the possibilities of potential complementary dosimeter types for epithermal neutron beam dosimetry.

The specific aims of the study were as follows:

- 1) To present the routine quality assurance procedure and stability measurements to ensure the reliability of the beam monitoring system at the FiR 1 epithermal beam in Finland. (Study I)
- 2) To present and apply a dosimetric toolkit for epithermal neutron beam characterisation in BNCT. (Studies II and III)
- 3) To use TEPC based microdosimetry to measure the neutron and the photon dose at FiR 1 BNCT facility and to compare the results with doses measured using dual ionisation chamber technique and calculated using DORT computer code. (Study IV)
- 4) To study the response and to evaluate the additional information that could be obtained by using polymer gels in BNCT dosimetry. (Studies V and VI)

In addition, stability results with ionisation chamber measurements (Kosunen et al. 1999) are presented spanning the years 1997-2007.

# 1 Introduction

The concept of boron neutron capture therapy (BNCT) was first introduced by Locher (1936). BNCT is a form of chemically targeted radiotherapy. It utilises the high neutron capture cross-section of boron-10 isotope at low (thermal) neutron energies to achieve a preferential dose increase in the tumour volume. In BNCT boron is first selectively accumulated into the tumour by a tumour-specific boron carrier. The tumour and its surroundings are then irradiated with epithermal neutrons. Neutrons slow down (thermalise) in tissue and undergo capture reaction with the boron, causing an increased dose in the areas where the boron is concentrated.

The general aim of radiotherapy is to deliver sufficient radiation dose to the intended target to provide a therapeutic effect while minimizing the complications on healthy tissue. The limit of the therapeutic dose is dictated by the tolerance of the surrounding healthy tissues. The challenge in this is that the difference between the therapeutic dose and the tolerance of the healthy tissue is generally small. Also, there is typically a strong dependence between the radiation dose and the effect – either therapeutic effect on tumour or adverse effect on healthy tissue. The effects and success of radiotherapy are thus ultimately dependent on the accuracy of the delivered radiation dose. This is reflected in the 2.5-5% (1 SD) accuracy recommendations for the patient dose for external radiotherapy (ICRU 26, IAEA 2000).

The accuracy of radiation dose imposes requirements on all parts of the radiation treatment procedure. The uncertainty associated with each individual step in the treatment procedure increases the overall uncertainty. The role of dosimetry in the treatment chain is focused on two aspects: beam calibration and verification of the calculated dose. Beam calibration is a procedure where the relationship between the beam monitors and the dose components of the beam are determined under well-defined standard conditions (IAEA 2001, Voorbraak and Järvinen 2003). Dosimetry under non-standard conditions is performed in order to verify the correctness of treatment planning system (TPS) calculations.

To ensure the comparability and critical appraisal of the results from various pre-clinical radiobiological experiments, as well as the clinical trials, carried out in various epithermal neutron beams, it is of crucial importance that the basic characteristics of the neutron beam (beam geometry, neutron and photon spectra, absorbed dose and fluence distributions) are determined in a coherent and reproducible way. Consistent dosimetry is also a requirement for a reliable comparison with conventional radiotherapy or other treatment modalities. In addition, the safety of treatments requires that the beam dosimetry is accurately related to the readings of appropriate beam monitors.

The above sets the requirement that the basic dosimetric methods must be traceable to the international measurement system. The international recommendations or Codes of Practice for radiotherapy dosimetry, currently available for conventional photon and electron beam therapy, and for (fast) neutron therapy (IAEA 1997; 2000) are not applicable to BNCT due to the complexity of the mixed neutron and photon fields. The guidance on acceptable dosimetric procedures specific to BNCT has been provided by a joint effort of eleven European institutional partners (Voorbraak and Järvinen 2003). Apart

from the recommended dosimetric methods, the pursue for complementary dosimetry methods is motivated by the need for comparable measurements and more accurate methods for dosimetry in BNCT (Voorbraak and Järvinen 2003).

In the Finnish BNCT project the dosimetric efforts have been previously reported in six Ph.D. theses. As a part of his thesis Kosunen (1999) evaluated the feasibility of the dual ionisation chamber method in the BNCT dosimetry and studied the accuracy of the calculated dose distribution in phantoms in epithermal neutron beam. Reasonable accuracy in determining photon and neutron absorbed doses with the dual ionisation chamber method was found. Intercomparisons and validation procedures were recommended for BNCT TPS's due to lack of standard dosimetric methods and large uncertainties in the measured dose. Aschan (1999) investigated the use of thermoluminescent dosimeters (TLD) to determine the photon and neutron dose components of the absorbed dose. In BNCT beams she reported 16% and 20% (1 SD) accuracy in measuring neutron and photon absorbed dose, respectively, enabling *in vivo* measurements. Beam characterisation measurements using Si(Li) diode, dual ionisation chambers and TLDs with comparison to calculated results were presented as part of the work by Kortensniemi (2002). He concluded that the TLD and ionisation chamber methods are functional, but that the accuracy should be improved and found the accuracy of Si(Li) detector suitable for neutron fluence measurements. The estimation of boron concentration in blood during treatment was the topic of Ryyänen (2002). She found several kinetic models to be accurate for the determination of the boron concentration and recommended their parallel use to enhance the estimation. The topic of the thesis by Seppälä (2002) was the calculational model of FiR 1 epithermal neutron beam for treatment planning in BNCT. The beam model was found to be accurate for use in the TPS and the computer simulation results were used in the assessment and development of dosimetric methods and dose planning procedure. Kotiluoto (2007) reviewed computational radiation transport methods and summarised the results of a newly developed radiation transport code MultiTrans. For BNCT the MultiTrans code was found to model the neutron dose and the reaction rates accurately, but the photon dose disagreed with the results obtained with other methods.

The current work presents quality assurance and stability measurements of the neutron beam monitors (Study I). An established toolkit for epithermal neutron beams for determination of the dose components is presented (Study II) and applied in an international dosimetric intercomparison (Study III). The feasibility of microdosimetry and gel dosimetry as dosimetric as complementary methods for epithermal neutron beam dosimetry is studied (Studies IV-VI). Also, stability results with ionisation chamber measurements (Kosunen et al. 1999) are presented spanning the years 1997-2007.

**Table 1.** The dose components in tissue in an epithermal neutron beam and their source reactions. Example methods for determining the dose components and their reported uncertainties are listed. The relevance of each dose component for the treatment can be appreciated through their contribution to the total biologically weighted dose in normal brain (healthy tissue) and target (tumour).

Dose component	Dose due to (particle)	Dose deposited locally* (yes/no)	Particle due to (reaction)	Reaction due to (particle)	Example method of measurement	Measured quantity	Required calculated result for method	Reported uncertainties (1 SD) of dose component (range, %) <sup>¤</sup>	Main source of uncertainty	Biologically weighted dose at FiR 1 <sup>£</sup> Normal brain (%)	Target (%)
D <sub>γ</sub>	Photon	No	<sup>1</sup> H(n,γ) <sup>2</sup> H <sup>†</sup>	n <sub>th</sub>	Mg(Ar) IC	D <sub>γ</sub>		2.4-10	Response to n <sub>th</sub>	33.5	6.4
D <sub>n</sub>	Proton	Yes	<sup>1</sup> H(n,n')p	n <sub>fast</sub>	TE(TE) IC	D <sub>γ</sub> + D <sub>n</sub> + D <sub>N</sub>	Neutron spectrum, n <sub>th</sub>	15-30	Uncertainty in D <sub>γ</sub>	4.2	0.8
D <sub>N</sub>	Proton	Yes	<sup>14</sup> N(n,p) <sup>14</sup> C	n <sub>th</sub>	Foils	Reaction rate	n <sub>th,calc</sub>	1.4-7.4 <sup>&amp;</sup>		16.2	3.1
D <sub>B</sub>	α, Li-ion	Yes	<sup>10</sup> B(n,α) <sup>7</sup> Li <sup>‡</sup>	n <sub>th</sub>	Foils	Reaction rate	n <sub>th,calc</sub>	1.4-7.4 <sup>&amp;</sup>		46.1	89.8

\* Within appr. 10 μm from reaction site

<sup>†</sup> Also photon component in the incident neutron-photon beam

<sup>‡</sup> Also a negligible source of 2.2 MeV photons

<sup>§</sup> Less accurate result can be obtained without calculated n<sub>th</sub>

<sup>&</sup> For thermal neutron fluence n<sub>th</sub>

<sup>¤</sup> In phantom at reference point. Rogus et al. (1994), Raaijmakers et al. (1995), Liu et al. (1996), Kosunen et al. (1999), Munck af Rosenschöld et al. (2003) and Riley et al. (2003)

<sup>£</sup> % of total dose at 2.5 cm depth, 11 cm diameter beam aperture, blood boron-10 concentration 12 ppm (IAEA 2001)

## 2 Epithermal neutron beam dosimetry

The epithermal neutron beam used in clinical BNCT irradiations generates four absorbed dose components in the irradiated tissue:

- (1) the photon dose  $D_\gamma$
- (2) the fast neutron dose  $D_n$
- (3) the nitrogen dose  $D_N$
- (4) the boron dose  $D_B$ .

The photon dose is delivered by electrons created in photon interactions in the tissue. The photon dose is due to both the photon component present in the incident beam and the photons created in the neutron capture reaction by hydrogen  $^1\text{H}(n,\gamma)^2\text{H}$  in tissue. The fast neutron dose is mainly delivered by recoil protons from neutron scatter in hydrogen  $^1\text{H}(n,n')p$  by fast and epithermal neutrons. The nitrogen dose is due to neutron capture reaction in nitrogen  $^{14}\text{N}(n,p)^{14}\text{C}$  and is delivered by protons. The combined fast neutron and nitrogen dose is also called the neutron dose. The boron dose is due to boron neutron capture reaction  $^{10}\text{B}(n,\alpha)^7\text{Li}$  and the dose is deposited by alpha-particles and recoiling lithium ions. The boron neutron reaction gives also a minor contribution to the photon dose, although it can be ignored due to its low prevalence over the hydrogen capture reaction.

The meaning of different dose components from the clinical perspective can be appreciated through the information in Table 1. 90% of the total absorbed dose to the target (tumour) is delivered by the boron dose component only. The therapeutic dose to the tumour is limited by the undesired absorbed dose to the normal brain tissue. 54% of the dose to normal brain is due to the combined photon, fast neutron and nitrogen dose and the remaining 46% is due to the boron dose. It is evident that from the clinical perspective it is desirable to minimize the dose from the photon, fast neutron and nitrogen dose components while maximising the boron dose to the intended target.

It is necessary to determine separately each of the four dose components as they have different absorbed dose distributions and relative biological effectiveness (Zamenhof et al. 1975). This poses a challenge for the dosimetry.

The dosimetric quantities of interest for determining the four dose components are the photon absorbed dose, the fast neutron absorbed dose and the thermal neutron fluence (Voorbraak and Järvinen 2003). All the dose components can be determined from these quantities as the thermal neutron fluence gives rise to the nitrogen and boron absorbed doses. The photon and fast neutron absorbed doses are generally measured using the dual ionisation chamber technique based on ICRU Report 45 (1989) for clinical fast neutron beam dosimetry, and the thermal neutron fluence is measured by using activation detectors (Rogus et al. 1994, Raaijmakers et al. 1995, Kosunen et al. 1999, Munck af Rosenschöld et al. 2003, Riley et al. 2003).

## 2.1 Toolkit for epithermal neutron beam dosimetry

A complete and portable set of dosimetric hardware and methods for determining neutron spectrum in air and dosimetric quantities of interest in phantom has evolved from the experience of the Finnish BNCT project (Study II). Dual ionisation chamber method is used to determine the photon and the combined fast neutron and nitrogen absorbed dose (ICRU 45, Kosunen et al. 1999). A magnesium ionisation chamber with argon gas (denoted as Mg(Ar)) is used for the photon dose measurements. The ionisation chamber is assumed to be insensitive to neutrons in the epithermal neutron beam. Ionisation chamber made from A-150 tissue-equivalent (TE) plastic and filled with tissue-equivalent gas (denoted as TE(TE)) is used to determine the neutron dose. Both detectors are calibrated in a  $^{60}\text{Co}$  beam. Their relative sensitivity to the photon radiation of the epithermal neutron beam were determined through calibrations in water in  $^{60}\text{Co}$  beam and 6 MV photon beam of a medical linear accelerator (Kosunen et al. 1999). In order to calculate the absorbed dose from the signal of the TE(TE) ionisation chamber, the change in the chamber's response in the epithermal neutron beam relative to the calibration beam needs to be taken into account. To calculate this correction factor, the neutron spectrum at the measurement location must be known.

The neutron spectrum and thermal neutron fluence determination require both measurements with activation detectors and calculated results from a treatment planning program or general radiation transport code. The ratio of the measured and calculated reaction rates are used to correct the calculated neutron fluence.

The thermal neutron sensitivity of the nominally neutron insensitive Mg(Ar) ionisation chamber has been reported to increase over time (Raaijmakers et al. 1996, Munck af Rosenschöld et al. 2003). At the Finnish FiR 1 BNCT facility, Mg(Ar) ionisation chamber measurements have been performed in the same measurement geometry over the course of 10 years. Results of these measurements are reported in this study.

## 2.2 Dosimetric intercomparison

BNCT is still an experimental form of radiotherapy and while a recommendation (Voorbraak and Järvinen 2003) exists, there is no standardised method for the epithermal neutron beam dosimetry. The aim of dosimetric intercomparisons in general is to establish the accuracy and precision of dosimetry and to assess the consistency between centers (Nisbet et al. 1998). By using a standard measurement technique and measuring system, differences in the way that different centers carry out their dosimetry can be assessed (Nisbet et al. 1998). Dosimetry intercomparisons are recognised to be effective in revealing the presence of errors (WHO 1988). The aim of the dosimetric intercomparison for BNCT (Study III) was to identify differences in determining the different dose components between the participating groups. If the differences in the measured dose quantities can be quantified, it would enable meaningful comparison of the experimental and clinical results between different BNCT groups.

In Study III, dosimetry comparisons was reported for three clinical centers in Europe, located at the Nuclear Research Institute (NRI) Rez (Czech Republic), VTT Espoo (Finland), and Studsvik Nyköping (Sweden) as well as for the center at MIT Cambridge (USA). The work describes the first step of the investigation, which are the results of dosimetry measurements between the various clinical centers that were performed in the four different epithermal neutron beams. The second step is to provide conversion factors to enable evaluation of total weighted dose between the participating centers (Riley et al. in print).

Measurements were made both in air and in phantom. Epithermal neutron flux as well as photon and fast neutron kerma rates were measured in air and the thermal neutron flux together with the photon and fast neutron absorbed dose rates were measured in phantom. A large, rectangular water-filled box of minimum linear dimensions  $40 \times 40 \times 20 \text{ cm}^3$  was used as the common phantom with the beam impinging on the  $40 \times 40 \text{ cm}^2$  face.

The principal method for determining the absorbed dose in tissue is to measure the photon and fast neutron dose directly using dual ionisation chambers and activation foils to separately account for the boron and thermal neutron dose (Rogus et al. 1994, Kosunen et al. 1999, Munck af Rosenschöld et al. 2003, Riley et al. 2003). At Rez, the use of Si(Li) diodes and TLDs is preferred (Marek et al. 2000). Activated foils were counted using HPGe detectors at each host facility and then cross checked with subsequent measurements back at the visitor's home center. Applying the dosimetry techniques that are standard clinical practice for each facility the absorbed dose was determined for the three radiation components in the host's most commonly used field under same conditions

## **2.3 Complementary dosimetry methods in epithermal neutron beam**

Dual ionisation chambers and activation detectors are often used and recommended (Voorbraak and Järvinen 2003) to determine the basic dosimetric quantities in epithermal neutron beams. Because of the unsatisfactory uncertainties and dependence on calculated results, the current methods need validation and improvements (Rogus et al. 1994, Raaijmakers et al. 1995, Kosunen et al. 1999, Munck af Rosenschöld et al. 2003, Riley et al. 2003, Voorbraak and Järvinen 2003). There are several dosimeter types and methods for BNCT dosimetry, including the examples shortly introduced in the following.

TLDs of several different types have been applied in BNCT (Perks et al. 1988, Raaijmakers et al. 1995, Liu et al. 1996, Aschan et al. 1999, Gambarini et al. 2004, Burgkhardt 2006). To determine both neutron and photon absorbed doses, two detectors with different photon and neutron sensitivity are needed. The signals can be separated into photon and neutron dose components as in dual ionisation chamber technique.

Fission counters,  $\text{BF}_3$  counters, boron lined proportional counters and  $^3\text{He}$  proportional counters can be used for the detection of thermal neutrons (Tattam et al. 1998, Voorbraak and Järvinen 2003, Riley et al. 2004). The method is based on measuring the pulses or current produced by fission or neutron capture reactions of the respective isotope ( $^{235}\text{U}$ ,  $^{10}\text{B}$  or  $^3\text{He}$ ).

The use of Si(Li) semiconductor detectors is based on a lithium converter plate where reaction  ${}^6\text{Li}(n,\alpha){}^3\text{H}$  occurs. The semiconductor detector is used to measure the signal from the alpha and triton particles and can be used to determine the relative thermal neutron fluence distribution (Kortesniemi 2002, Marek and Viererbl 2004).

Measuring radiation dose with alanine detectors is based on electron paramagnetic resonance (EPR) spectrum of the crystalline amino acid alanine. Radiation induces stable radicals in alanine whose relative amount can be measured using EPR spectrum. The alanine is sensitive to neutrons and in order to be used as photon dosimeter in BNCT, the response due to neutrons needs to be taken into account (Marralle et al. 2008). EPR dosimetry can also be applied with lithium-containing formates and dithionates and offer a possibility to measure the absorbed dose from photons and thermal neutrons in the epithermal neutron beam (Lund et al. 2004).

### **2.3.1 Microdosimetry**

Microdosimetric method using a tissue equivalent proportional counter (TEPC) can be applied to measure the photon dose and the neutron dose (Wuu et al. 1992, Kota et al. 2000, Burmeister et al. 2001). Also the boron dose can be measured as a special application using a TEPC with  ${}^{10}\text{B}$  incorporated into the wall and gas of the detector (Wuu et al. 1992). Unlike in the dual ionisation chamber method, the counter is operated in pulse mode. The pulse height difference between the events related to the photon dose and the neutron dose enables the separation of these dose components. The calibration of the detector relies either on an internal radiation source or in a distinct feature (proton edge) of the measured pulse height spectrum. In the epithermal neutron beams used for BNCT treatments the estimated uncertainties for the determination of photon and neutron absorbed are 6-7% and 6% (1 SD), respectively (Wuu et al. 1992, Kota et al. 2000, Burmeister et al. 2001). The uncertainty for the neutron dose compares favourably to the 15-30% (1SD) range of uncertainties reported for the dual ionisation chamber method (Rogus et al. 1994, Raaijmakers et al. 1995, Kosunen et al. 1999, Munck af Rosenschöld et al. 2003, Riley et al. 2003). Published comparisons have shown differences in absorbed doses measured using different methods. In a recent study (Burmeister et al. 2003) microdosimetric method was compared with results from ionisation chamber, TLD and activation foil measurements and a computer simulation in two different epithermal neutron beams. Differences were found especially in the boron dose (10-20% difference), but also in the neutron and photon dose, when determined using the different techniques. In Study IV TEPC based microdosimetry was applied to measure the neutron dose and the photon dose in a large water phantom at the FiR 1 BNCT facility. The results were compared with doses measured using dual ionisation chamber technique and with doses calculated using DORT computer code.

### 2.3.2 Gel dosimetry

Polymer and Fricke gel dosimeters have been introduced as a potential tool for the dosimetry of BNCT (Farajollahi et al. 2000, Gambarini et al. 2000). Ionising radiation induces changes in these dosimeters (polymerisation in polymer gel dosimeters and oxidation of ferrous ions into ferric ions in Fricke gel dosimeters) that can be quantified using for example magnetic resonance imaging (MRI) or optical scanning. The main advantages are that the dosimeter is tissue equivalent in main elemental composition and that the method enables experimental determination of three dimensional dose distribution in various volumes.

In Study V, BANG-3 (MGS Research Inc.) gel vials from three production batches were irradiated with 6 MV photons of a Varian Clinac 2100 C linear accelerator and in the epithermal neutron beam of the Finnish BNCT facility at the FiR 1 nuclear reactor. The gel is tissue equivalent in main elemental composition and density, and its R2 relaxation rate is dependent on the absorbed dose. The R2 relaxation rate map of the irradiated gel vials was measured with a 1.5 T MRI scanner using spin echo sequence. The absorbed dose of neutron irradiation was calculated using DORT computer code, and the accuracy of the calculational model was verified by measuring the photon dose with TLDs and  $^{55}\text{Mn}(n,\gamma)$  activation reaction rate with activation detectors.

Polymer gel dosimeter known by the acronym MAGIC was tested for evaluation of its use in BNCT dosimetry in Study VI. A large (diameter 10 cm, length 20 cm) cylindrical gel phantom was irradiated in the epithermal neutron beam at the FiR 1 nuclear reactor. The neutron irradiation was simulated with a Monte Carlo radiation transport code MCNP. Gel samples from the same production batch were also irradiated with 6 MV photons from a medical linear accelerator to compare dose response in the two different types of beams. The irradiated gel phantoms were imaged using MRI to determine their R2 relaxation rate maps. The measured and normalised dose distribution in the epithermal neutron beam was compared to the dose distribution calculated by the computer simulation.

### 3 Beam monitors and quality assurance

The beam calibration is a procedure where the relationship between the beam monitors and the dose components of the beam are determined under well-defined standard conditions (IAEA 2001, Voorbraak and Järvinen 2003). The task of the beam monitors is to establish an unambiguous relation between significant free-beam parameters and the radiation field generated in the target, a phantom or a patient. From clinical treatment perspective, the beam monitors are used to measure the radiation dose given to the patient. Thus the accuracy and precision of the given radiation dose is directly dependent on the reliability of the beam monitors.

Requirements for a beam monitoring system at a neutron irradiation facility for BNCT have been given in the Recommendations for the Dosimetry of Boron Neutron Capture Therapy (Voorbraak and Järvinen, 2003). The quantities to be monitored are the epithermal neutron fluence and fluence rate, the epithermal neutron fluence spatial uniformity and the photon fluence and fluence rate. Double redundant monitoring for the epithermal fluence rate is required. The impact of the presence of patient or phantom in the beam should be minimal on the monitor reading. As the main tool of the periodic quality control of a beam monitor system repeated measurements for the ratio of the beam monitor count rate to the reaction rate of activation foils (primarily  $^{55}\text{Mn}(n,\gamma)$ ) in a quality control phantom are suggested.

The beam monitoring system at FiR 1 consists of four  $^{235}\text{U}$  fission chambers placed at different positions around the beam collimator. Two of the chambers (N1 and N4) monitor only epithermal neutrons and two chambers (N2 and N3) monitor the whole neutron energy range. Photon radiation is monitored by a single ionisation chamber. The beam monitoring system described in detail by Tanner et al. (1999). The beam monitoring system is used also in all dosimetric work to form a common reference between the measurements.

#### 3.1 Sensitivity and stability of beam monitors

As described in detail in Study I, the sensitivity and stability of the beam monitors at FiR 1 were studied with activation detector and ionisation chamber measurements.

Sensitivity of the beam monitors to a target in the beam was checked by remotely placing the PMMA phantom with 20 cm diameter and 24 cm length into the beam aperture with one end of the cylinder facing the beam. The reactor was running at the power level used in the clinical irradiations.

The sensitivity of the beam monitors to the power distribution in the reactor core was studied by significantly varying the height positions of the reactor control rods and observing the ratio of the signals from TE(TE) and Mg(Ar) ionisation chambers inside a large water phantom at 2 cm and 8 cm depths relative to the three different neutron and one photon monitor channel count rates.

The stability and reproducibility of the beam monitors are routinely checked before each patient irradiation by gold and manganese activation foils irradiated at 2 cm depth along the central axis in the cylindrical PMMA phantom. The reaction rates are scaled to the reference monitor count rate and compared to the reference values. Also the ratios of signal from beam monitors ( $N1/N2$  and  $N3/N1$ ) are compared to reference values.

Calibration of the beam monitors for different reactor power levels are needed since several types of measurements are performed at lower power levels than those used in patient irradiations. Due to saturation phenomenon in the pulse counting system of the beam monitors, extrapolation to full power cannot be simply done by scaling the results by the monitor count rate ratio. Through activation method it is possible to establish an unambiguous relationship between the monitor count rate and neutron flux. The gold and manganese reaction rates at 2 cm depth in the cylindrical PMMA phantom were measured at 100, 50 and 10 kW and compared to the values obtained at full power (250 kW).

## **4 Results**

### **4.1 Toolkit for epithermal neutron beam dosimetry**

Although a recommendation exists, there is no single internationally accepted standard method for dosimetry in epithermal neutron beams. Study II presents a complete example of the hardware and methods required to determine basic epithermal neutron beam characteristics. This mobile toolkit has evolved from the experience of the Finnish BNCT project and has been used in BNCT facilities worldwide.

### **4.2 Dosimetric intercomparison**

International dosimetry exchange for BNCT in which four facilities participated (Study III) is a part of the effort to enable comparison of clinical data between different BNCT centers. The measured quantities (neutron flux, fast neutron and photon dose) determined by the participating groups were generally in agreement within the stated uncertainties.

To provide quantitative comparison of the doses measured by the participants, scaling factors were provided. The factor was calculated separately for each dose component by scaling the depth dose data measured by MIT so that it matched (sum of the squared residuals minimised) the values measured by the participating institute. The scaling factors are given in Table 2. The scaling factors for the MIT dose components are unity. The dosimetric team from MIT performed measurements at all the other three institutes participating in the intercomparison, so MIT results were used as the reference out of convenience. One specific feature in the results is the lack of scaling factor for fast neutron dose for FiR 1. This is because the measurements at FiR 1 did not yield any fast neutron dose. The standard method at FiR 1 with the dual ionisation chambers is to measure absorbed total neutron dose to brain tissue. For the purposes of this study the fast neutron dose was determined by subtracting the nitrogen dose from the measured total neutron dose. The total neutron dose measured by us agreed within uncertainties with the results from a SERA computer simulation and was consistent with previously reported results measured in a similar setup (Kosunen et al. 1999).

The measurement uncertainties (Table 3) were large, ranging from 3-30% (1 SD), depending on the method and depth of measurement and the possibility of clinically significant systematic differences in the absorbed dose specification by individual groups exists. Normalising the dose components to the results obtained using a single method in all beams could improve the precision. The results emphasise the importance of dosimetric intercomparisons in BNCT if clinical data is to be compared between different centers.

**Table 2.** Scaling factors needed to multiply the results of measurements for each dose component to match the results measured by MIT. The MIT results are chosen as the reference based on convenience and does not imply that the MIT results are more accurate than the others.

	MIT	Studsvik	VTT	NRI
Thermal neutron	1.00	1.04	0.96	1.00
Photon	1.00	1.00	0.99	1.12
Fast neutron	1.00	0.70	-	1.01

**Table 3.** Measurement uncertainty estimated on the three dose components for the groups participating in the dosimetric intercomparison.

Absorbed dose component	Uncertainty (1 SD) %			
	MIT	Studsvik	VTT	NRI
Thermal neutron flux	4.0-6.5	3.0-4.0	5.0	10
Photon	4.4	6.0	6.0	20
Fast neutron	30	25	21	5.0

### 4.3 Ionisation chamber response stability

At FiR 1, measurements with the Exradin type 2M ionisation chamber (ser. no. 183) have been repeated in the same measurement configuration over the course of 10 years. The measurements were performed in the cylindrical extension (Ø 20 cm, length 20 cm) of a large cubic water phantom at 2.5 and 6.0 cm depths along the center-line of the beam and the results were calculated according to the methodology presented by Kosunen et al. (1999). The measurement parameters and results are collated in Tables 4 and 5. Calibration factor for air kerma for the ionisation chamber have been determined by STUK Radiation and Nuclear Safety Authority in a  $^{60}\text{Co}$  beam. The change in the chamber's sensitivity to the predominantly 2.2 MeV photons present in the phantom in the epithermal neutron irradiation have been determined through calibrations in water in  $^{60}\text{Co}$  beam and 6 MV photon beam of a medical linear accelerator. Beam monitoring system has been used to scale the current measured with the ionisation chamber to the reference monitor unit count rate.

**Table 4.** Photon absorbed dose measurements at 2.5 cm depth in the cylindrical extension of a water phantom between years 1997 and 2007. The calibration coefficients have been determined for the IC (Exradin M2, ser. no. 183) by STUK Radiation and Nuclear Safety Authority in a  $^{60}\text{Co}$  beam. Beam monitor unit rates were used to normalise the dose to reference conditions.

Date	Measurement conditions			Reference (250 kW) conditions			Difference to 1997 (%)
	Calib. coeff. (mGy/nC)	Current (pA)	MU (cts/s)	MU (cts/s)	Current (pA)	Dose rate (Gy/h)	
Dec 1997	36.93	51.91	35185	34852	51.42	6.80	-
Aug 2004	36.70	56.14	33895	32034	53.06	6.98	2.5
Sep 2005	36.70	55.58	33298	32034	53.47	7.03	3.3
Feb 2006	36.70	54.39	32884	32034	52.99	6.97	2.4
Dec 2007	36.77	59.01	35235	32034	53.65	7.07	3.9

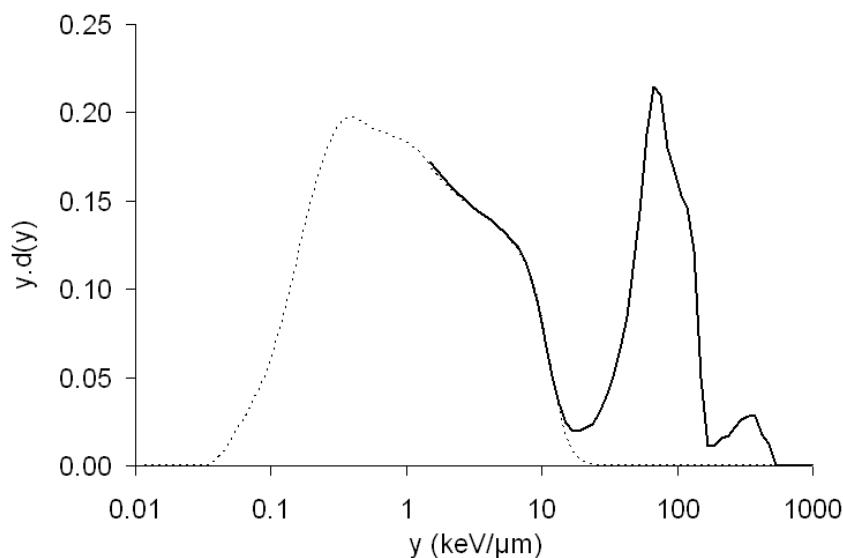
**Table 5.** Photon absorbed dose measurements at 6.0 cm depth in the cylindrical extension of a water phantom between years 1997 and 2007. The calibration coefficients have been determined for the IC (Exradin M2, ser. no. 183) by STUK Radiation and Nuclear Safety Authority in a  $^{60}\text{Co}$  beam. Beam monitor unit rates were used to normalise the dose to reference conditions.

Date	Measurement conditions			Reference (250 kW) conditions			Difference to 1997 (%)
	Calib. coeff. (mGy/nC)	Current (pA)	MU (cts/s)	MU (cts/s)	Current (pA)	Dose rate (Gy/h)	
Dec 1997	36.93	37.44	35064	34852	37.22	4.92	-
Aug 2004	36.70	39.73	33967	32034	37.47	4.93	0.1
Sep 2005	36.70	35.54	33175	32034	34.32	4.51	-8.4
Feb 2006	36.70	39.78	32874	32034	38.76	5.10	3.5
Dec 2007	36.77	42.71	35239	32034	38.83	5.11	3.9

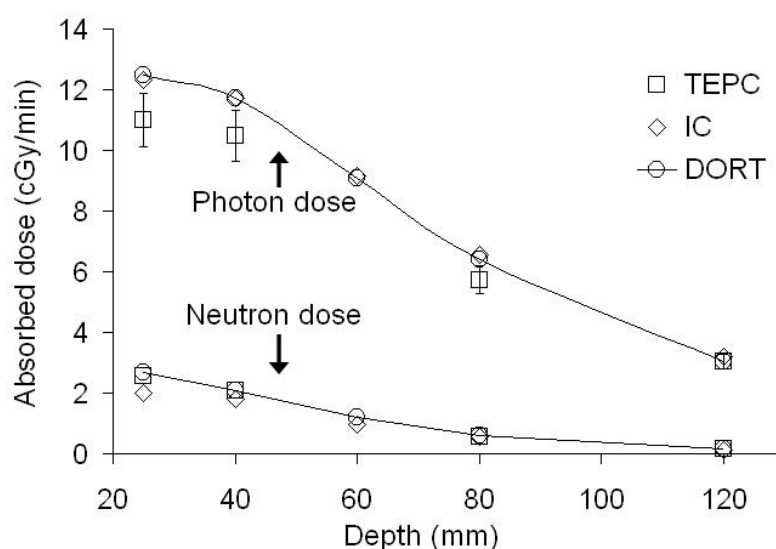
#### 4.4 Complementary dosimetry methods in epithermal neutron beam

Microdosimetry is a suitable measurement method for comparisons with dual ionisation chamber method because microdosimetry is reported to have lower uncertainty in neutron dose measurement and because the method is fundamentally different in respect of detector calibration and separation of photon and neutron dose components. Example of a measured microdosimetric spectrum and its separation into photon and neutron dose components by fitting a reference spectrum from a  $^{60}\text{Co}$  source is shown in Figure 1. Comparison of the results obtained with ionisation chambers, microdosimetry and computer simulation are reported in Study IV. The measured and calculated doses are shown in Figure 2. For photon dose the results from the computer simulation and the ionisation chamber measurements agree within the experimental uncertainties. The photon dose measured with microdosimetry is systematically lower than with the two other

methods. For neutron dose the simulation and microdosimetry results agree within 10% while the ionisation chamber technique gives 10-30% lower neutron dose rates than the other two methods.

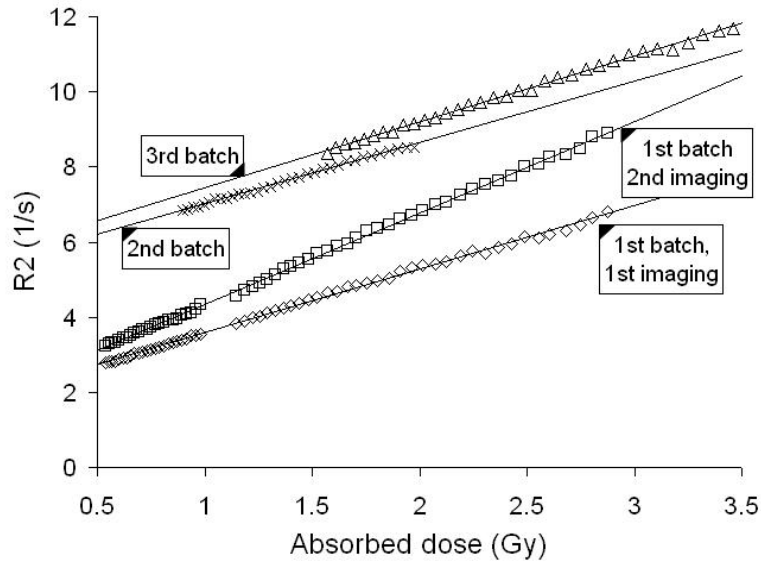


**Figure 1.** Measured microdosimetric (lineal energy) spectrum (solid line) at 25 mm depth in a water phantom in the epithermal neutron beam at FiR 1. Photon spectrum from a  $^{60}\text{Co}$  photon beam (dashed line) was used to extrapolate the spectrum below the lowest measured value and to separate the spectrum into areas corresponding to photon and neutron absorbed dose.



**Figure 2.** Depth dose profiles at the beam center-line measured with microdosimetry (TEPC), dual ionisation chambers (IC) and calculated with DORT computer code. Error bars (8%) are only indicated for the photon dose measurements with the TEPC.

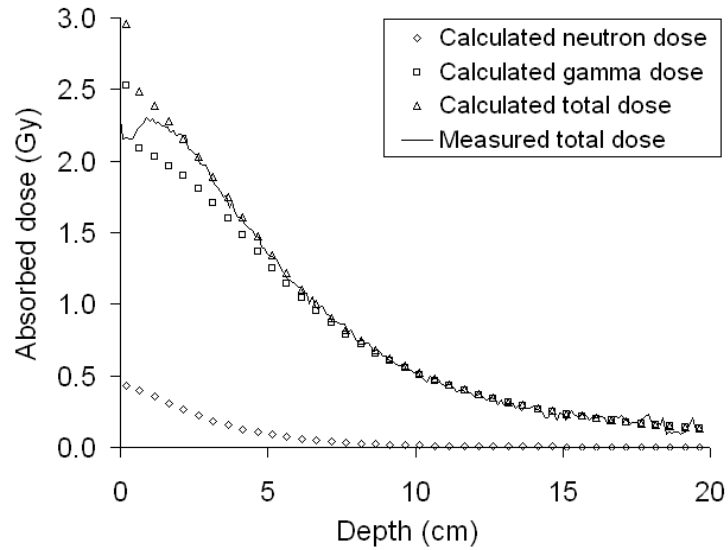
BANG-3 polymer gel dosimeter measurements (Study V) were performed in photon and epithermal neutron beams. The gel response in photon beam was shown to be linear up to the highest used dose of 3.5 Gy. The dose response as the function of absorbed dose in photon irradiation is shown in Figure 3. It shows the results from three different gel production batches and also the dependence of the response on the time between the irradiation and readout of the gel. The dose response in the epithermal neutron beam was also shown to be linear. The calculated depth dose distribution and a representative gel measurement normalised to the calculated total dose is shown in Figure 4. The pyrex glass gel containers were found not to be ideally suited for epithermal neutron beam measurements due to the presence of thermal neutron capturing boron-10, causing uncertainties in the simulated results. For both photon and epithermal neutron beam irradiations the gel sensitivity was shown to differ between different gel batches and also depend on the time between irradiation and MRI imaging highlighting the need for consistency and planning in all the procedures when applying the gel dosimeters.



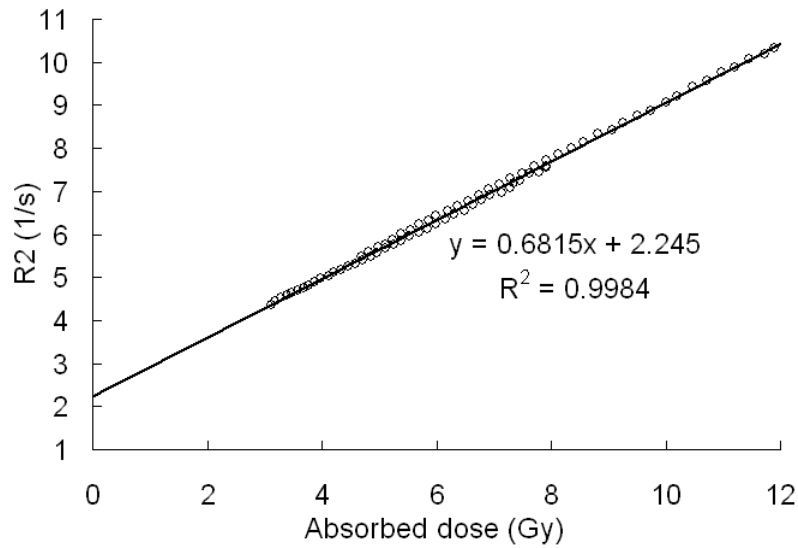
**Figure 3.** Measured relaxation rate of the BANG-3 gel vials from three different production batches as the function of calculated dose in a 6 MV photon beam. The gel vials from the first batch were imaged twice: 5 h and 8 days after irradiation. Lines from the least squares fit to the measured data are also shown.

The MAGIC polymer gel dosimeters used in Study VI were prepared from a single gel batch and irradiated and imaged at scheduled intervals. The gel response in photon irradiation was found to be linear while a 3% difference in sensitivity between the two applied dosimeters was observed as shown in Figure 5. In epithermal neutron irradiation a boron-free quartz glass container was used. The measured dose distribution normalised to the dose maximum shown in Figure 6 was found to agree well near to the dose maximum, while the spatial difference between simulated and measured 30% isodose line was more than 1 cm. The dose response of the gel in the epithermal neutron beam appeared to be

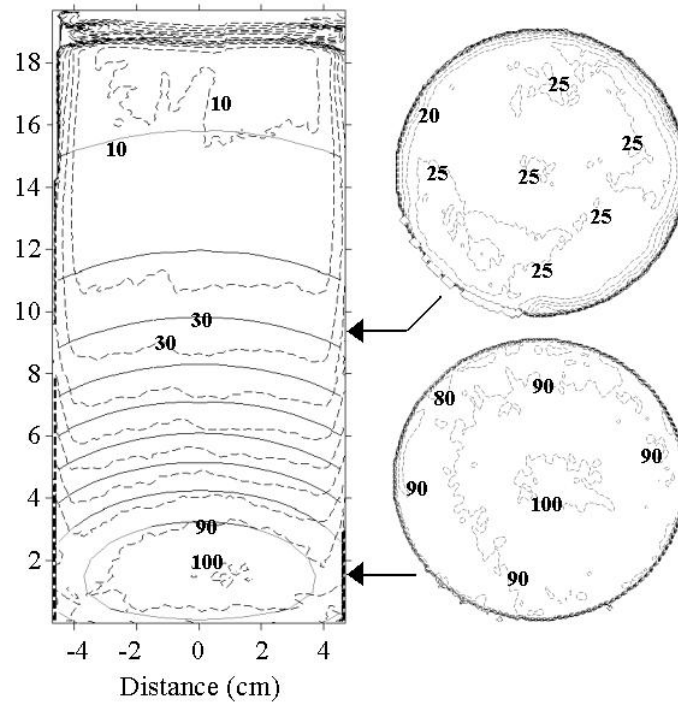
higher near the dose maximum where also the contribution from the high-LET (linear energy transfer) particles is highest (20% of the total dose).



**Figure 4.** The depth dose curve at the  $^{252}\text{Cf}$  epithermal neutron beam in a water phantom calculated with DORT computer code and the measured response of the a BANG-3 gel dosimeter normalised to the calculated total dose.



**Figure 5.** Response of two MAGIC polymer gel vials irradiated with 6 MV photons in a water phantom. A line is fitted to the data using the least squares method. The equation and the correlation coefficient are shown.



**Figure 6.** Left-hand side shows the comparison of calculated (solid line) and measured (dashed line) isodoses at 10% intervals along the center cross-section of the gel cylinder in irradiated the epithermal neutron beam. Representative axial measurement results at the positions indicated by the arrows are shown on the right-hand side

## 4.5 Beam monitors and quality assurance

Main results from the quality control measurements in Study I regarding the beam monitors are threefold. (1) The beam monitor count rate was not affected by the presence of phantom in the beam and the sensitivity change for the reactor core power distribution is less than 1%. (2) The activation reaction rates normalised to the primary beam monitor has generally been reproducible within  $\pm 2\%$ . The standard deviations are 1.6% and 1.7% for Mn and Au reaction rates respectively. (3) Non-linearity correction was determined to take into account the saturation effect in the pulse counting electronics which occurs at high pulse rates. This correction factor for the beam monitor units to allow comparison of measurements performed at different reactor powers. The correction factor to scale the results to the nominal 250 kW reactor power for the most commonly used monitor unit channel (N1) was 1.11 for the three tested reactor power levels of 100, 50 and 10 kW.

## **5 Discussion and conclusions**

### **5.1 Epithermal neutron beam dosimetry**

#### **5.1.1 Dual ionisation chamber method**

Dual ionisation chamber technique is recommended as the reference method to determine the beam profile for photons in air and in phantom and to measure neutron and photon absorbed dose for beam calibration (Voorbraak and Järvinen 2003). The drawback of the dual ionisation chamber method are the uncertainties related to the dose determination and having to rely on calculated parameters (neutron spectrum at the measurement point) for the determination of the (fast) neutron dose. The estimated 6.3% (1 SD) uncertainty for the measured absorbed photon dose arises mainly from the uncertainty in determining the chamber's response to thermal neutrons. The response of the non-hydrogenous Mg(Ar) chamber to thermal neutrons has been reported to change with time. For the neutron absorbed dose, the 21.5% (1 SD) estimated uncertainty in the measured dose arises mainly from the uncertainty of the photon dose, which is subtracted from the total dose measured by the TE(TE) chamber.

The photon sensitivity factors of the ionisation chambers are used to take into account the difference in the chambers' response to the photons in the epithermal neutron beam relative to the photons of the beam the chambers were calibrated in. These factors have been assumed to be unity (Rogus et al. 1994, Raijmakers et al. 1995) or have been estimated from measurements in high-energy photon beams from clinical linear accelerators (Raaijmakers et al. 1996, Kosunen et al. 1999). As elaborated by Munck af Rosenschöld et al. (2002), the response of the ionisation chamber depends on the energy and angle distribution of the photon fluence, and these can be different in epithermal neutron beam than in either the photon beam of a clinical linear accelerator or  $^{60}\text{Co}$  photon beam used in the calibration. Furthermore, placing the ionisation chamber into the phantom causes a perturbation in the electron fluence. In the epithermal neutron beam introduction of the ionisation chambers changes the photon production rate due to difference hydrogen density between the phantom material and the detector. Correction factors taking into account the above-mentioned factors have been calculated with Monte Carlo simulations at Studsvik BNCT facility in Sweden (Munck af Rosenschöld et al. 2002). The correction factor was found to vary with depth and to differ from the photon sensitivity factors derived from measurements in high-energy photon beams from clinical linear accelerators. As the beam characteristics and phantom geometries differ between BNCT facilities, the correction factors should be determined for each individual BNCT beam. The results indicate that, in order to reduce the measurement uncertainty, the experimentally determined photon sensitivity factor should be replaced with a measurement-depth dependent correction factor taking into account the perturbation effects caused by the detector in the phantom.

Raaijmakers et al. (1996) studied the thermal neutron sensitivities of ionisation chambers and TLDs used in the dosimetry of BNCT. They found out that the three tested nominally neutron insensitive Mg(Ar) chambers (Exradin type 2M) displayed some sensitivity to thermal neutrons ( $0.139\text{--}0.367 \times 10^{-12} \text{ Gy cm}^2$ ) and that during the course of one year, the sensitivity of one of the chambers increased by 70%. The cause of the thermal neutron sensitivity and its increase was suggested to be due to chemical corrosion or contamination of the chamber wall. The increase in sensitivity for the same type of chamber was also observed by Munck af Rosenschöld et al. (2003). Thermal neutron sensitivity was found to be  $4.103 \times 10^{-12} \text{ nC cm}^2$  ( $0.169 \times 10^{-12} \text{ Gy cm}^2$ ) and it changed by a factor of two in one year. The chamber was filled with argon gas during storage, but the drift continued so that approximately 25% of the response at 3 cm depth in phantom was due to thermal neutrons.

In the measurements presented in this thesis the Mg(Ar) ionisation chamber has been assumed to be insensitive to thermal neutrons. This assumption is supported by calculations showing a negligible kerma rate for magnesium due to thermal neutrons (Raaijmakers et al. 1995) and the good agreement of the measured and calculated photon and neutron doses (Kosunen et al. 1999). The uncertainty for the photon dose due to the thermal neutron sensitivity was estimated to be 6.0% (1 SD) (Kosunen et al. 1999).

The thermal neutron fluence rate at FiR 1 along the central axis of the cylindrical water phantom is  $2.3 \times 10^9$  and  $1.0 \times 10^9 \text{ cm}^{-2} \text{ s}^{-1}$  at 2.5 and 6.0 cm depth, respectively (Seppälä 2002). Assuming the smallest thermal neutron sensitivity of the values reported above, the dose due to thermal neutrons would be 1.15 and 0.50 Gy/h at 2.5 and 6.0 cm depth, respectively. If the 3.9% increase in the photon dose between 1997 and 2007 measurements reported in this study were due to increase in the chamber thermal neutron sensitivity, the required increase in the thermal neutron sensitivity would be 28% at 2.5 cm depth and 38% at 6.0 cm depth. The observed changes in the measured photon dose during the span of ten years excludes severe thermal neutron sensitivity changes of 50–100% per year, as reported by Raaijmakers et al. (1996) and Munck af Rosenschöld et al. (2003).

### 5.1.2 Complementary dosimetry methods

Compared to the dual ionisation chamber method, microdosimetry provides an independent method to measure photon and neutron absorbed dose. The detector can be calibrated with its own internal radiation source (americium-244, emits alpha particles) or using a feature in the measured pulse height spectrum of the mixed photon and neutron beam. The microdosimetric method does not require knowledge of the neutron spectrum and both the photon and the neutron dose can be determined from a single measurement. With the system used in Study IV, two measurements with different amplification settings are still needed, as the pulse-heights in the spectrum span five orders of magnitude. However, the commercially available proportional counter (model LET- $\frac{1}{2}$ , Far West Technology, CA, USA) made from tissue-equivalent plastic is too sensitive to be used in epithermal neutron beams at the power levels used in patient irradiations. Also, the need to

process the measured pulse height spectrum to obtain the absorbed photon and neutron doses may be considered a drawback. Smaller, less sensitive proportional counters have been applied in epithermal neutron beam dosimetry (Burmeister et al. 2001, Moro et al. 2006). TEPC made from brain tissue equivalent A-181 plastic has been applied to measure absorbed radiation dose to brain tissue (Burmeister et al. 2002). Dual TEPC technique introducing a second counter with walls loaded with boron has been applied to determine boron dose in addition to photon and neutron absorbed doses (Wuu et al. 1992, Kota et al. 2000, Burmeister et al. 2001, De Nardo et al. 2004). Apart from TEPC's, microdosimetric measurements can be performed with semiconductor or gas electron multiplier (GEM) detectors (Bradley et al. 2001, Farahmand et al. 2004)

Apart from determining the absorbed dose, the microdosimetric spectrum can also be used to assess the biological effectiveness of the radiation (ICRU 36). That has been done in epithermal neutron beams (Burmeister et al. 2001, Hsu et al. 2003, Endo et al. 2004). The relative biological effectiveness (RBE) determined from microdosimetric spectrum can be used in assessing the results from radiobiological experiments in BNCT, such as the determination of RBE for crypt cell regeneration in mice in epithermal neutron beams (Gueulette et al. 2005).

The published uncertainty estimates related to dose measurements in epithermal neutron beams using TEPC microdosimetry are 6.1-6.7% for photon and 6.0-6.1 for neutron dose component, presumably referring to an interval of 1 SD (Kota et al. 2000, Burmeister et al. 2001). These uncertainty estimations do not take into account the perturbation effects of the dosimeter in the phantom. As with ionisation chambers, the difference in the hydrogen content between the detector and the phantom will cause a change in the rate of photon production in the neutron capture reaction in hydrogen. The effect on photon fluence estimated by Munck af Rosenschöld et al. (2002) for the dual ionisation chambers (-4.7% and -6.3% (1 SD) for TE(TE) and Mg(Ar) chamber, respectively, at 3 cm depth at the epithermal neutron beam in Studsvik, Sweden). The effect can be expected to be of the same order of magnitude for the commercially available TEPC detector as its physical size is comparable to that of the ionisation chambers used in Munck af Rosenschöld's study. However, unlike in the dual ionisation chamber method, in microdosimetry increased uncertainty in the photon dose component does not directly affect uncertainty in the neutron dose component. This is because in microdosimetry the neutron dose is obtained by separating the microdosimetric spectrum into photon and neutron dose components, and not by subtracting the photon dose from the total dose. The perturbation effect can be expected to be less significant for a smaller detector such as the miniaturised dual TEPC for BNCT dosimetry reported by Moro et al. (2006). The miniature detector has two cylindrical TEPC's with 0.53 mm<sup>3</sup> active volumes built within the end of a 2.7 mm by 200 mm sleeve. It has been verified to accurately measure photon dose in a <sup>60</sup>Co beam up to 20 Gy/h dose rates (Moro et al. 2006). The 2.7 mm outer diameter of that detector can be compared to the 5 mm diameter of the miniature TEPC reported by Burmeister et al. (2001), to the 19 mm diameter of the commercially available TEPC detector (Far West Technology, CA, USA) and to the 11.5 mm diameter of the Mg(Ar) ionisation chamber (Exradin model M2).

The value of gel dosimeters is not in absolute dosimetry, but in its potential to determine two- or three-dimensional radiation dose distributions. Gel dosimeters are divided into Fricke and polymer gel dosimeter groups. The response of the Fricke gels are based on the ferrous sulphate Fricke solution in a gel matrix (Gore et al. 1984). When Fricke solution is irradiated, water decomposition occurs and various reactions lead to the conversion of ferrous ions ( $\text{Fe}^{2+}$ ) to ferric ions ( $\text{Fe}^{3+}$ ). Changes in the ion concentration affect the T1 relaxation rate of water protons. The observed change is dose dependent and can be imaged using MRI or optical measurements. Main drawback of the Fricke gel is that the diffusion of the ferrous and ferric ions deteriorates the dose distribution and constrains the time between the irradiation and the measurement of the dose response. Polymer gel dosimeters introduced by Maryanski et al. (1993) can be imaged days or weeks after irradiation and do not suffer from the blurring of the dose distribution over time. Various different Fricke and polymer gel dosimeters exist with differences in composition and properties (McJury et al. 2000, Chu 2001).

Fricke gel dosimeters have been applied by one research group (Gambarini et al. 2000, 2002, 2004, 2007) in epithermal neutron beam to determine separately photon dose, fast neutron dose, nitrogen dose and boron dose. This has been achieved by using four different Fricke gel dosimeter compositions and by correcting for the relative sensitivity of the gel to the particles inducing the different dose components. The estimated uncertainties of the dose components determined with this method have not been reported to the author's knowledge, but the gel dosimetry results have been verified to agree with TLD measurements and with doses calculated by Monte Carlo simulation (Gambarini et al. 2004). The uncertainty for Fricke gel dosimetry for photon radiotherapy has been estimated to be 5% (MacDougall et al. 2002). Applying Fricke gel dosimetry to BNCT introduces additional uncertainties such as estimating the gel response to dose components other than the photon dose.

The benefit of polymer gel dosimeters over Fricke gels in BNCT is that the dose distribution is stable over days after irradiations and thus do not require prompt reading after irradiation (Maryanski et al. 1993). Polymer gel dosimeters are commercially available (MGS Research Inc., CT, USA) or can be prepared relatively easily from their basic ingredients. Apart from Studies V and VI, the polymer gel dosimeters have been studied in an epithermal neutron beam by Farajollahi et al. (2000). They added boron to the polymer gel to determine the absorbed dose enhancement due to boron neutron capture reaction and compared the enhancement to results calculated with computer simulation.

Polymer gel dosimetry has found applications in radiotherapy due to its capability to 2D measure dose distributions. Other desirable properties of the gel dosimeters include high spatial resolution, tissue equivalence in terms of density and elemental composition and freedom in choosing detector size and geometry. In gel dosimetry measurements the dosimeter itself can act as the phantom. Gel dosimeters of different sizes and geometries are relatively easy to prepare as the geometry is defined by the gel container. When using gel dosimetry to determine doses in electron or photon radiotherapy, the gel response can be determined for example by using a  $^{60}\text{Co}$  photon source or in the radiotherapy beam itself by relating the results to calibrated ionisation chamber measurements. Determining the gel dose response in radiation beams with contribution from high-LET particles is

more challenging (Ramm et al. 2000, Jirasek and Duzenli 2002, Gustavsson et al. 2004, Baker et al. 2008). The response has been found to depend on the LET of the particle. The LET response studies have been performed in proton and carbon ion beams, where the main contribution of the doses is due to high-LET particles. At the FiR 1 epithermal neutron beam the contribution of high-LET particles to total dose is at most 20% at 2 cm depth and decreases with depth, so that the dose due to high-LET radiation is 3% at 10 cm depth. In both the BANG-3 and MAGIC gel studies, though the response to total dose (BANG-3) appeared linear and the relative dose distribution measurement agreed with the simulation (MAGIC), the interpretation of the results is still complicated by the presence of high-LET radiation.

### 5.1.3 Uncertainty of the dose to the patient

Accurate measurements of the neutron fluence and photon and neutron dose components in a phantom is desirable at least for the purposes of beam calibration, beam characterisation and TPS verification. However, in BNCT treatment the absorbed dose to the irradiated tissues depends also on the patient positioning and the local concentration of boron. The uncertainty of the patient dose due to the uncertainties in dosimetry, positioning and boron concentration estimation has been presented in the work by Kortensniemi (2002). The results show that the combined uncertainty of the total absorbed dose to normal brain tissue without boron is 7% (1 SD) at the reference point (depth of maximum thermal neutron fluence). When the boron dose is included, the uncertainty is 18% (1 SD). If the uncertainty related to dosimetry is assumed to be zero, the combined uncertainty for absorbed dose with boron dose included is still 15% and 14% (1 SD) in normal brain tissue and in the target tissue, respectively.

The main source of the patient dose uncertainty in BNCT treatment is the estimation of boron concentration in the irradiated tissue. The boron concentration in blood is measured (Laakso et al. 2001) before and after irradiation. The boron concentration in blood during the irradiation is estimated for each patient (Ryynänen et al. 2000, Kortensniemi et al. 2004). The boron concentration in the tissues of interest is estimated from tissue-to-blood ratios (Coderre and Morris 1999). This last step is the main source of the uncertainty in determining the physical absorbed radiation dose in the patient (Kortensniemi 2002). In addition, the RBE-weighted radiation dose is obtained by applying weighting factors to the different physical dose components according to radiation type and, in the case of boron dose, tissue of interest (IAEA 2001).

In order to improve the estimation of boron concentration in tissues application of position emission tomography (PET), prompt gamma spectroscopy (PGS),  $^{10}\text{B}$  MRI and  $^1\text{H}$  MRI spectroscopy have been suggested. PET study using a boron carrier labelled with  $^{18}\text{F}$  can provide data on the extraction of boron carrier to the tumour and other tissues (Kabalka et al. 1997). PGS can provide information on the biodistribution of boron during irradiation (Verbakel et al. 2003). Proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) has been studied with the aim of *in vivo* quantification of boron carrier (Zuo et al. 1999, Timonen et al. 2005). Magnetic resonance imaging and spectroscopy of isotopes  $^{10}\text{B}$  and

$^{11}\text{B}$  have the potential for real-time monitoring of boron concentration in the patient, but requires special hardware and suffers from low sensitivity (Bendel et al. 2001, Wittig et al. 2008).

The most important issues for the future of BNCT are focused mostly on optimising and improving the biological and chemical aspects the treatment. In a recent review Barth et al. (2005) named four issues for which development is critical for BNCT: more selective and effective boron delivery agents, methods to provide semiquantitative estimates of tumour boron content, improvement of clinical implementation of BNCT and randomised trials to demonstrate the clinical efficacy.

## **5.2 Quality control measurements**

The EU Council Directive on Health Protection (97/43/EURATOM) applies also to exposure of patient as part of their treatment. The directive requires that appropriate quality assurance programmes including quality control measures are implemented. In the recommendations for dosimetry of BNCT (Vorbraak and Järvinen 2003) presents a set of quality control procedures related to the beam calibration and patient dosimetry to meet with the requirement. The recommended tests are listed in Table 6. In addition to the quality assurance procedures, the recommendations include requirements for beam monitors. These include establishing the linearity of the beam monitor system relative to the dosimetric quantities and limiting the impact of patient or phantom on the monitor reading to less than 2%.

The constancy of the neutron energy spectrum in air serves also as a test of the simultaneously used beam monitors. The measurement is justified by the possible slight change of neutron spectrum with the change of fuel element positions within the reactor core. Thus, if the reactor cycle is longer than one year, the recommended annual test would be relevant only as a check for the different beam monitor channels.

Beam calibration is the procedure where the relationship of the dosimetric quantities of the radiation beam to the beam monitor units is determined in a reference position under standard conditions. The dosimetric quantities in the recommendations are photon and fast neutron absorbed dose and thermal neutron fluence. The photon and fast neutron doses are to be determined with dual ionisation chamber method and verified with supplementary method such as TLDs, microdosimetry or semiconductor detector. The thermal neutron fluence is recommended to be determined with a set of three activation detectors. The recommended phantom is a water phantom with PMMA walls with minimum dimensions of  $40 \times 40 \times 20 \text{ cm}^3$ . The measurement point is defined at the thermal neutron fluence maximum at the central axis of the beam.

Depth absorbed dose with ionisation chambers or neutron fluence with activation foils or Si(Li) diode is to be determined annually.

The recommended annual beam monitor tests are repeatability and linearity measured with activation detectors. A weekly stability test with activation foils is also recommended.

**Table 6.** Recommended (Voorbraak and Järvinen 2003) functional performance characteristics to be tested, tolerance values and test frequencies, with respect to radiation output of BNCT facilities.

Performance characteristics	Tolerance value	Test frequency	Method
Constancy of neutron energy spectrum	$\pm 10\%$	Annually and for each reactor cycle	Measurement with 10 or more different activation detectors. Deviation of reaction rates relative to a reference reaction rate measurement.
Beam calibration		Annually and for each reactor cycle	Thermal neutron fluence, fast neutron absorbed dose, photon absorbed dose. In phantom.
Depth absorbed dose or neutron fluence	$\pm 5\%$ *	Annually	Dual ionisation chambers, activation foils or Si(Li) diode.
<i>Beam monitoring system</i>			Repeated measurements for the ratio of the detector count rate to the saturation count rate of activation foils
Repeatability	0.5%		
Linearity	0.5%		
Stability	2.0%		
Uniformity of radiation field			
Indication for central axis for beam entry	2 mm	Weekly or for each patient	Check of laser beam.

\* Reproducibility of dose and fluence per reference monitor reading.

The recommended annual test for the uniformity of radiation field is not well defined. It is explained in the recommendations only as “agreement of measurement and calculation for all dose components tested one initially”. This test appears to come from the work of Rassow et al. (2001), where it is described in more detail. Rassow et al. explain that beam uniformity and depth absorbed dose characteristics of BNCT radiation field must be measured only once initially. The quality assurance program is then to verify that the (intermediate) neutron energy spectrum is stable over time, which ensures that the depth absorbed dose characteristics does not change. Also, if the neutron energy is stable, any change in beam uniformity can be considered irrelevant for the example beam in the article of Rassow et al. The recommendation appears to call for annual calculation of dose components under reference conditions taking into account any changes in neutron spectrum and comparing the results to existing set of initial measurements. If beam uniformity could change without affecting the neutron spectrum, additional measurements for determining possible changes in the beam uniformity are needed. Rassow et al. lists the parameters to be determined as the same that are measured for medical linear accelerators, such as width of beam penumbra. It can be questioned whether the parameters defined for medical linear accelerators are relevant for epithermal neutron beams due to fundamental differences in these radiation sources.

The quality assurance procedures at FiR 1 BNCT facility documented as part of the quality manual for BNCT treatments and are based on the recommendations (Voorbraak and Järvinen 2003). The neutron energy spectrum is measured annually with an activation detector set. The constancy of the spectrum is estimated by calculating ratios of two different reactions and comparing those to reference values. The tolerance is set to  $\pm 2\%$ . Beam calibration is performed annually in reference points both in air and in phantom. Neutron dose and photon dose are determined with the dual ionisation chamber technique.

Additionally a pair of activation detectors is used in phantom to measure thermal and epithermal neutron flux. The beam depth profile is tested by measuring photon absorbed dose with Mg(Ar) ionisation chamber and thermal and epithermal neutron flux with a activation detector pair. Beam radial profiles at 25 mm and 60 mm depth are measured with Mg(Ar) ionisation chamber and Mn activation detector. Deviation of  $\pm 5\%$  of the photon absorbed dose or neutron fluence from the reference values are accepted. The beam monitoring system is tested annually for linearity and repeatability with activation detector measurements. The tolerance value for these measurements is 0.5%. In addition, the stability of beam monitors are checked with activation detectors with weekly measurements with tolerance set to 2%. Laser beam indicators for the beam central axis are checked weekly and deviations of up to 2 mm are accepted.

The beam quality assurance procedures defined in the quality manual of the FiR 1 BNCT facility are consistent with the recommended procedures (Voorbraak and Järvinen 2003). The beam uniformity, which is ambiguously defined in the recommendations, is tested by measuring depth profile of photon absorbed dose with ionisation chamber and thermal and epithermal neutron flux with a pair of activation detectors. In addition, radial beam profiles at 25 mm and 60 mm depth are measured with Mg(Ar) ionisation chamber and Mn activation detector.

## 6 Summary

BNCT is still an experimental form of radiotherapy practiced in a few research centers worldwide. Although recommendations and comparisons have been published, there are still no standardised methods for epithermal neutron beam dosimetry and calibration. Standardisation of dosimetry is a foundation which would enable robust and direct comparison of clinical and other results between different research centres. In this thesis (1) the existing dosimetric practices and quality assurance at FiR 1 were presented and studied, (2) established dosimetric methods were compared in an international dosimetry exchange program, (3) two relatively new methods of dosimetry in BNCT - microdosimetry and polymer gel dosimetry – were evaluated at FiR 1.

**Study I** presents quality assurance test for the neutron beam monitors at FiR 1. Beam monitors were found to be insensitive to presence of patient or phantom in the beam. The sensitivity to changes in the reactor core power distribution was found to be less than 1%. The deviation of the beam monitor checks have typically been of the order of 2% or less. These results are within the recommended tolerance values (Voorbraak and Järvinen 2003). Some measurements are performed at lower reactor power levels than those used at patient irradiations. Correction factor for the non-linearity of the primary beam monitor is determined to relate low power measurements to the reference reactor power.

The dosimetric toolkit at FiR 1 for measuring photon dose, total neutron dose, neutron spectrum and neutron flux locally and at other research centers is reviewed in **Study II**. Measurements are based on dual ionisation chamber technique and activation detectors. The analysis of the results requires calculated values for the neutron spectra at the measurement locations and as such the method does not provide a fully independent method for neutron flux and dose determination.

**Study III** is an international comparison of absorbed dose measurements for BNCT. Neutron fluxes and absorbed dose are measured both in air and in a water filled phantom. The comparison is performed by one team (MIT) visiting three clinical BNCT centers in Europe and an European team from VTT/REZ visiting MIT. Each participant performs measurement according to their appropriate to their local practices. In the different beams the agreement is generally consistent with the estimated uncertainties. However, systematic differences of up to 10% are observed between groups in determining the biologically weighted dose to brain tissue in an example and the difference should be considered clinically significant.

Doses at FiR 1 epithermal neutron beam are determined by microdosimetry, ionisation chambers and computer simulation and compared in **Study IV**. The study includes the first results of microdosimetry applied in FiR 1 beam. The differences in the absorbed dose are within the limits of the stated uncertainties.

In **Study V** BANG-3 type polymer gel dosimeters are evaluated for BNCT dosimetry. The response of the gel dosimeters to the total absorbed dose in the epithermal neutron beam is linear. However, the magnitude of the response relative to photon irradiated samples varies between different gel dosimeter batches. The linearity of the dose response implicated that BANG-3 gel dosimeters are suitable for measuring relative 2D dose distributions.

**Study VI** contains the evaluation of the relatively inexpensive and easy to prepare polymer gel known by the acronym MAGIC in BNCT dosimetry. The dose response of the gel was studied by irradiating gel samples in both the epithermal neutron beam and in a pure photon beam. The gel phantoms were imaged using MRI and the normalised dose distribution was compared to the dose distribution calculated by computer simulation. The properties of the gel makes it suitable for the determination of 2D relative dose distributions in large volumes and complex geometries.

Significant increase in the thermal neutron sensitivity as an aging phenomenon of the Mg(Ar) type ionisation chambers has been reported by two authors. As the ionisation chamber is assumed to be insensitive to neutron, increase in its sensitivity would cause significant additional uncertainties in determined with the dual ionisation chamber method. Photon dose measurements with the Mg(Ar) ionisation chamber have been performed at FiR 1 BNCT facility. Observed changes in measured photon dose between years 1997 and 2007 at FiR exclude severe sensitivity changes of 50-100% per year, as reported by the two authors.

## Acknowledgements

The investigations presented in this thesis were carried out as a part of the Finnish BNCT project. I am obliged to Prof. Juhani Keinonen, Ph.D., the Head of the Department of Physics of the University of Helsinki and Doc. Juhani Ahovuo, Ph.D., and Jyrki Putkonen, M.Sc.Tech., former and current Heads of the HUS Medical Imaging Center of the Helsinki University Central Hospital for providing excellent research facilities.

Several people have contributed to my thesis to whom I am very grateful. Especially I wish to express my sincere gratitude to

Docent Sauli Savolainen, Ph.D., Antti Kosunen, Ph.D., and Docent Sami Heikkinen, Ph.D., my supervisors, for the insight, guidance and excellent support. Their expertise and enthusiasm was the driving force behind this thesis.

Docent Maunu Pitkänen, Ph.D., and Docent Mikko Tenhunen, Ph.D., the official reviewers, for the constructive remarks that markedly improved this thesis.

I warmly acknowledge all the co-authors of the adjoining publications, especially Iiro Auterinen, M.Sc.Tech., Tom Serén, Lic.Tech., Petri Kotiluoto, Ph.D., Tiina Seppälä, Ph.D., Johanna Karila, Ph.Lic., and Docent Aki Kangasmäki, Ph.D. I wish to thank Docent Mika Kortensniemi, Ph.D., and Hanna Koivunoro, M.Sc. for the discussions, collaboration and interest in my work. Thanks are also due to Toni Ihalainen, Ph.Lic., Janne Hämäläinen, M.Sc.Tech, Eero Salli, Ph.D., Marjut Timonen, M.Sc. and all my colleagues in HUS for the nice and educative working atmosphere. I wish to equally thank all the physicists, doctors, nurses and other personnel involved in the Finnish BNCT project – I feel privileged to have had the opportunity to work in that truly multidisciplinary environment.

Finally, the warmest thanks to my dear wife Daniela for her love and patience, and to my daughter Emilia, an endless source of joy and energy.

The financial support of the Academy of Finland, the State Subsidy for University Hospitals, University of Helsinki, the EC (A code of practice for dosimetry of Boron Neutron Capture Therapy (BNCT) in Europe, Contract No. SMT4-CT98-2145) are gratefully acknowledged.

April 2009

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## References

- Aschan, C., Toivonen, M., Savolainen, S., Seppälä, T., Auterinen, I., Epithermal neutron beam dosimetry with TL dosimeters for boron neutron capture therapy, *Rad. Prot. Dos.* 81, 47-56, 1999.
- Aschan, C., Applicability of thermoluminescent dosimeters in x-ray organ dose determination and in the dosimetry of systemic and boron neutron capture radiotherapy, Ph.D. thesis, University of Helsinki (1999), HU-P-D77.
- Baker, C., Quine, T., Brunt, J., Kacpersek, A., Monte Carlo simulation and polymer gel dosimetry of 60MeV clinical proton beams for the treatment of ocular tumours. *Appl. Radiat. Isot.* 2008 [in print]
- Barth, R., Coderre, J., Vicente, M., Blue, T., Boron neutron capture therapy of cancer: current status and future prospects, *Clin. Cancer Res.* 11, 3987-4002, 2005.
- Bendel, P., Koudinova, N., Salomon, Y., In vivo imaging of the neutron capture therapy agent BSH in mice using  $(^{10}\text{B})$  MRI, *Magn. Reson. Med.* 46, 13-17, 2001.
- Bradley, P., Rosenfeld, A., Zaider, M., Solid state microdosimetry, *Nucl. Instrum. Methods Phys. Res. B.* 184, 135-57, 2001.
- Burgkhardt, B., Bilski, P., Budzanowski, M., Böttger, R., Eberhardt, K., Hampel, G., Olko, P., Straubing, A., Application of different TL detectors for the photon dosimetry in mixed radiation fields used for BNCT, *Rad. Prot. Dos.* 120, 83-86, 2006.
- Burmeister, J., Kota, C., Maughan, R.L., Waker, A., Miniature tissue-equivalent proportional counters for BNCT and BNCTEFNT dosimetry. *Med. Phys.* 28, 1911-1925, 2001.
- Burmeister, J., Kota, C., Maughan, R., Waker, A., Riley, K., Wielopolski, L., Application of TEPC microdosimetry to boron neutron capture therapy, *Rad. Prot. Dos.* 99, 351-352, 2002.
- Burmeister, J., Riley, K., Coderre, J., Harling, O., Ma, R., Wielopolski, L., Kota, C., Maughan, R., Microdosimetric intercomparison of BNCT beams at BNL and MIT, *Med. Phys.* 30, 2131-2139, 2003.
- Chu, W., Radiation dosimetry using Fricke-infused gels and magnetic resonance imaging, *Proc. Natl. Sci. Coun. Repub. China B.* 25, 1-11, 2001.
- Coderre, J., Morris, G., The radiation biology of boron neutron capture therapy, *Radiat. Res.* 151, 1-18, 1999.
- De Nardo, L., Seravalli, E., Rosi, G., Esposito, J., Colautti, P., Conte, V., Tornielli, G., BNCT microdosimetry at the tapiro reactor thermal column, *Rad. Prot. Dos.* 110, 579-586, 2004.
- Endo, S., Onizuka, Y., Ishikawa, M., Takada, M., Sakurai, Y., Kobayashi, T., Tanaka, K., Hoshi, M., Shizuma, K., Microdosimetry of neutron field for boron neutron capture therapy at Kyoto university reactor, *Rad. Prot. Dos.* 110, 641-644, 2004.
- Farahmand, M., Bos, A., De Nardo, L., van Eijk, C., First microdosimetric measurements with a TEPC based on a GEM, *Rad. Prot. Dos.* 110, 839-843, 2004.
- Farajollahi, A., Bonnett, D., Tattam, D., Green, S., The potential use of polymer gel dosimetry in boron neutron capture therapy. *Phys. Med. Biol.* 45, N9-14, 2000.
- Gambarini, G., Monti, D., Fumagalli, M., Birattari, C., Salvadori, P., Phantom dosimeters examined by NMR analysis: a promising technique for 3-D determinations of absorbed dose. *Appl. Radiat. Isot.* 48, 1477-1484, 1997.
- Gambarini, G., Agosteo, S., Marchesi, P., Nava, E., Palazzi, P., Pecci, A., Rosi, G., Tinti, R., Discrimination of various contributions to the absorbed dose in BNCT: Fricke-gel imaging and intercomparison with other experimental results. *Appl. Radiat. Isot.* 53, 765-772, 2000.

- Gambarini, G., Birattari, C., Colombi, C., Pirola, L., Rosi, G., Fricke gel dosimetry in boron neutron capture therapy. *Rad. Prot. Dos* 101, 419-422, 2002.
- Gambarini, G., Klamert, V., Agosteo, S., Birattari, C., Gay, S., Rosi, G., Scolari, L., Study of a method based on TLD detectors for in-phantom dosimetry in BNCT, *Rad. Prot Dos.* 110, 631-636, 2004.
- Gambarini, G., Daquino, G., Moss, R., Carrara, M., Nievaart, V., Vanossi, E., Gel dosimetry in the BNCT facility for extra-corporeal treatment of liver cancer at the HFR Petten. *Rad. Prot. Dos.* 126, 640-644, 2007.
- Gore, J., Kang, Y., Schulz, R., Measurement of radiation dose distributions by nuclear magnetic resonance (NMR) imaging, *Phys. Med. Biol.* 29, 1189-1197, 1984.
- Gueulette, J., Binns, P., De Coster, B., Lu, X., Roberts, S., Riley, K., RBE of the MIT epithermal neutron beam for crypt cell regeneration in mice, *Rad. Res.* 164, 805-809, 2005.
- Gustavsson, H., Bäck, S., Medin, J., Grusell, E., Olsson, L., Linear energy transfer dependence of a normoxic polymer gel dosimeter investigated using proton beam absorbed dose measurements. *Phys. Med. Biol.* 49, 3847-3855, 2004.
- Hsu, F., Tung, C., Watt, D., Microdosimetric spectra of the THOR neutron beam for boron neutron capture therapy, *Rad. Prot. Dos.* 104, 121-126, 2003.
- International Atomic Energy Agency (IAEA), Absorbed dose determination in photon and electron beams: an international code of practice, 2nd edition, IAEA Tech. Rep. Series 277 (Vienna, IAEA, 1997).
- International Atomic Energy Agency (IAEA), Absorbed dose determination in external beam radiotherapy: An international Code of Practice for dosimetry based on standards of absorbed dose to water, IAEA Technical Report Series No. 398 (Vienna, IAEA, 2000).
- International Atomic Energy Agency (IAEA), Current status of neutron capture therapy, IAEA-tecdoc-1223 (Vienna, IAEA, 2001).
- International Commission on Radiation Units and Measurement (ICRU), Determination of absorbed dose in a patient irradiated by beams of X or gamma rays in radiotherapy procedures, Report 26 (Bethesda, MD: ICRU Publications, 1976).
- International Commission on Radiation Units and Measurement (ICRU), Microdosimetry, Report 36 (Bethesda, MD: ICRU Publications, 1983).
- International Commission on Radiation Units and Measurement (ICRU), Clinical neutron dosimetry part I: determination of absorbed dose in a patient treated by external beams of fast neutrons, Report 45 (Bethesda, MD: ICRU Publications, 1989).
- Jirasek, A., Duzenli, C., Relative effectiveness of polyacrylamide gel dosimeters applied to proton beams: Fourier transform Raman observations and track structure calculations. *Med. Phys.* 29, 569-577, 2002.
- Kabalka, G., Smith, G., Dyke, J., Reid et al. Evaluation of fluorine-18-BPA-fructose for boron neutron capture treatment planning, *J. Nucl. Med.* 38, 1762-1767, 1997.
- Kortesniemi, M., Solutions for clinical implementation of boron neutron capture therapy in Finland, Ph.D. thesis, University of Helsinki (2002), Report Series in Physics, HUP-D95.
- Kortesniemi, M., Seppälä, T., Auterinen, I., Savolainen, S., Enhanced blood boron concentration estimation for BPA-F mediated BNCT, *Appl. Radiat. Isot.* 61, 823-827, 2004.
- Kosunen, A., Kortesniemi, M., Ylä-Mella, H., Seppälä, T., Lampinen, J., Serén, T., Auterinen, I., Järvinen, H., Savolainen, S.: Twin ionisation chambers for dose determinations in phantom in an epithermal neutron beam. *Radiat. Prot. Dos.* 81, 187-94, 1999.

- Kosunen, A., Metrology and quality of radiation therapy dosimetry of electron, photon and epithermal neutron beams, Ph.D. thesis, Helsinki (1999), STUK-A164
- Kota, C., Maughan, R., Tattam, D., Beynon, D., The use of low-pressure tissue equivalent proportional counters for the dosimetry of neutron beams used in BNCT and BNCTEFNT. *Med. Phys.* 27, 535-548, 2000.
- Kotiluoto, P., Adaptive tree multigrids and simplified spherical harmonics approximation in deterministic neutral and charged particle transport, Ph.D. thesis, Espoo (2007), VTT Publications 639.
- Laakso, J., Kulvik, M., Ruokonen, I., Vähätalo, J., Zilliacus, R., Färkkilä, M., Kallio, M., Atomic emission method for total boron in blood during neutron-capture therapy, *Clin. Chem.* 47, 1796-1803, 2001.
- Linko, S., Revitzer, H., Zilliacus, R., Kortensniemi, M., Kouri, M., Savolainen, S., Boron detection from blood samples by ICP-AES and ICP-MS during boron neutron capture therapy, *Scand. J. Clin. Lab. Inv.* 68, 696-702, 2008.
- Liu, H., Greenberg, D., Capala, J., Wheeler, F., An improved neutron collimator for brain tumour irradiations in clinical boron neutron capture therapy, *Med. Phys.* 23, 2051-2060, 1996.
- Locher, G., Biological effects and therapeutic possibilities of neutrons, *Am. J. Roentgenol. Radium. Ther.* 36, 1-13, 1936.
- Lund, E., Gustafsson, H., Danilczuk, M., Sastry, M., Lund, A., Compounds of  $^6\text{Li}$  and natural Li for EPR dosimetry in photon/neutron mixed radiation fields, *Spectrochim. Acta. A Mol. Biomol. Spectrosc.* 60, 1319-26, 2004.
- MacDougall, N., Pitchford, W., Smith, M., A systematic review of the precision and accuracy of dose measurements in photon radiotherapy using polymer and Fricke MRI gel dosimetry, *Phys. Med. Biol.* 47, R107-21, 2002.
- Marek, M., Viererbl, L., Flibor, S., Burian, J., Rejchrt, J., Validation of the epithermal neutron beam at LVR-15, in *Proc. of the 9th International Symposium on Neutron Capture Therapy, ISNCT*, Osaka, Japan, 2000, p. 41-42.
- Marek, M., Viererbl, L., Spatial characterization of BNCT beams, *Appl. Radiat. Isot.* 61, 1051-1055, 2004.
- Marrale, M., Brai, M., Gennaro, G., Bartolotta, A., D'Oca, M., The Effect of gadolinium on the ESR response of alanine and ammonium tartrate exposed to thermal neutrons, *Radiat. Res.* 169, 232-239, 2008.
- Maryanski, M., Gore, J., Kennan, R., Schulz, R., NMR relaxation enhancement in gels polymerised and cross-linked by ionizing radiation: a new approach to 3D dosimetry by MRI. *Magn. Reson. Imaging* 11, 253-258, 1993.
- McJury, M., Oldham, M., Cosgrove, V., Murphy, P., Doran, S., Leach, M., Webb, S., Radiation dosimetry using polymer gels: methods and applications, *Br. J. Radiol.* 73, 919-29, 2000.
- Moro, D., Colautti, P., Gualdrini, G., Masi, M., Conte, V., De Nardo, L., Tornielli, G., Two miniaturised TEPCS in a single detector for BNCT microdosimetry, *Rad. Prot. Dos.* 122, 396-400, 2006.
- Munck af Rosenschöld, P.M., Ceberg, C.P., Capala, J., Sköld, K., Persson, B.R.R.: Reference dosimetry at the neutron capture therapy facility at Studsvik. *Med. Phys.* 30, 1569-1579, 2003.
- Nisbet, A., Thwaites, D., Sheridan, M., Dosimetric intercomparison of kilovoltage X-rays, mega-voltage photons and electrons in the republic of Ireland, *Radiother. Oncol.* 48., 95-101, 1998.
- Perks, C., Mill, A., Constantine, G., Harrison, K., Gibson, J., A review of boron neutron capture therapy (BNCT) and the design and dosimetry of a high-intensity, 24 keV, neutron beam for BNCT research, *Br. J. Radiol.* 61, 1115-1126, 1986.

- Raaijmakers, C.P.J., Konijnenberg, M.V., Verhagen, H.W. and Mijnheer, B.J.: Determination of dose components in phantom irradiated with epithermal neutron beam for boron neutron capture. *Med. Phys.* 22, 321-329, 1995.
- Raaijmakers, C.P.J., Watkins, P.R.D., Nottelman, E.L., Verhagen, H.W., Jansen, J.T.M., Zoetelief, J. and Mijnheer, B.J.: The neutron sensitivity of dosimeters applied to boron neutron capture therapy. *Med. Phys.* 23, 1581-1589, 1996.
- Ramm, U., Weber, U., Bock, M., et al., Three-dimensional BANG gel dosimetry in conformal carbon ion radiotherapy. *Phys. Med. Biol.* 45, N95-N102, 2000.
- Rassow, J., Stecher Rasmussen, F., Voorbraak, W.P., Moss, R.L., Vroegindeweij, C., Hideghéty, K., Sauerwein, W., Comparison of quality assurance for performance and safety characteristics of the facility for Boron Neutron Capture Therapy in Petten/NL with medical electron accelerators. *Radither.Oncol.* 59, 99-108, 2001.
- Riley, K., Binns, P., Harling, O., Performance characteristics of the MIT fission converter based epithermal neutron beam, *Phys. Med. Biol.* 48, 943-958, 2003.
- Riley, K., Binns, P., Ali, S., Harling, O., The design, construction and performance of a variable collimator for epithermal neutron capture therapy beams, *Phys. Med. Biol.* 49, 2015-2028, 2004.
- Riley, K., Binns, P., Harling, O., Albritton, J., Kiger, S., Rezaei, A., Sköld, K., Seppälä, T., Savolainen, S., Auterinen, I., Marek, M., Viererbl, L., Nievaart, V., Moss, R., An international dosimetry exchange for BNCT Part II: Computational dosimetry normalizations, *Med. Phys.* in print.
- Rogus, R., Harling, O., Yanch, J., Mixed field dosimetry of epithermal neutron beams for boron neutron capture therapy at the MITR-II research reactor. *Med. Phys.* 21, 1611-1625, 1994.
- Ryynänen, P., Kortenesniemi, M., Coderre, J., Diaz, A., Hiismäki, P., Savolainen, S., Models for estimation of the  $(10)\text{B}$  concentration after BPA-fructose complex infusion in patients during epithermal neutron irradiation in BNCT, *Int. J. Radiat. Oncol. Biol. Phys.* 48, 1145-1154, 2000.
- Ryynänen, P., Kinetic mathematical models for the  $^{111}\text{In}$ -labelled bleomycin complex and  $^{10}\text{B}$  in boron neutron capture therapy, Ph.D. thesis, University of Helsinki (2002), Report Series in Physics, HU-P-D102.
- Seppälä, T., FiR 1 Epithermal neutron beam model and dose calculation for treatment planning in neutron capture therapy, Ph.D. thesis, University of Helsinki (2002), Report Series in Physics, HU-P-D103.
- Tanner, V., Auterinen, I., Helin, J., Kosunen, A., Savolainen, S., On-line neutron beam monitoring of the Finnish BNCT facility. *Nucl. Instrum. Meth. Phys. Res.* A422, 101-105, 1999.
- Tattam, D., Allen, D., Beynon, T., Constantine, G., Green, S., Scott, M., Weaver, D., In-phantom neutron fluence measurements in the orthogonal Birmingham boron neutron capture therapy beam, *Med. Phys.* 25, 1964-1966, 1998.
- Timonen, M., Kankaanranta, L., Lundbom, N. et al.,  $^1\text{H}$  MRS studies in the Finnish boron neutron capture therapy project: detection of  $^{10}\text{B}$ -carrier, L-p-boronophenylalanine-fructose, *Eur. J. Radiol.* 56, 154-159, 2005.
- Verbakel, W., Sauerwein, W., Hideghety, K., Stecher-Rasmussen, F., Boron concentrations in brain during boron neutron capture therapy: in vivo measurements from the phase I trial EORTC 11961 using a gamma-ray telescope, *Int. J. Radiat. Oncol. Biol. Phys.* 55, 743-755, 2003.
- Voorbraak, W. and Järvinen H., Recommendations for the dosimetry of boron neutron capture therapy (BNCT), The Netherlands, NRG Petten (2003), NRG Report 21425/03.55339/C

- Wittig, A., Michel, J., Moss, R. et al. Boron analysis and boron imaging in biological materials for Boron Neutron Capture Therapy (BNCT), *Crit. Rev. Oncol. Hematol.* 68, 66-90, 2008.
- World Health Organisation (WHO), Quality assurance in radiotherapy, WHO, Geneva, 1988.
- Wuu. C.S., Amols, H.I., Kliauga, P., Reinstein, L.E., Saraf, F., Microdosimetry for boron neutron capture therapy. *Radiat. Res.* 130, 355-359, 1992.
- Zamenhof, R., Murray, B., Brownell, G., Wellum, G., Tolpin, E., Boron neutron capture therapy for the treatment of cerebral gliomas, theoretical evaluation of the efficacy of various neutron beams, *Med. Phys.* 2, 47-60, 1975.
- Zuo, C., Prasad, P., Busse, P., Tang, L., Zamenhof, R., Proton nuclear magnetic resonance measurement of p-boronophenylalanine (BPA): a therapeutic agent for boron neutron capture therapy, *Med. Phys.* 26, 1230-1236, 1999.