PHASE I CLINICAL STUDY ON BORON NEUTRON CAPTURE THERAPY (BNCT)

Principal Clinical Investigator
Prof. Wolfgang Sauerwein

Doktori (PhD) - értekezés

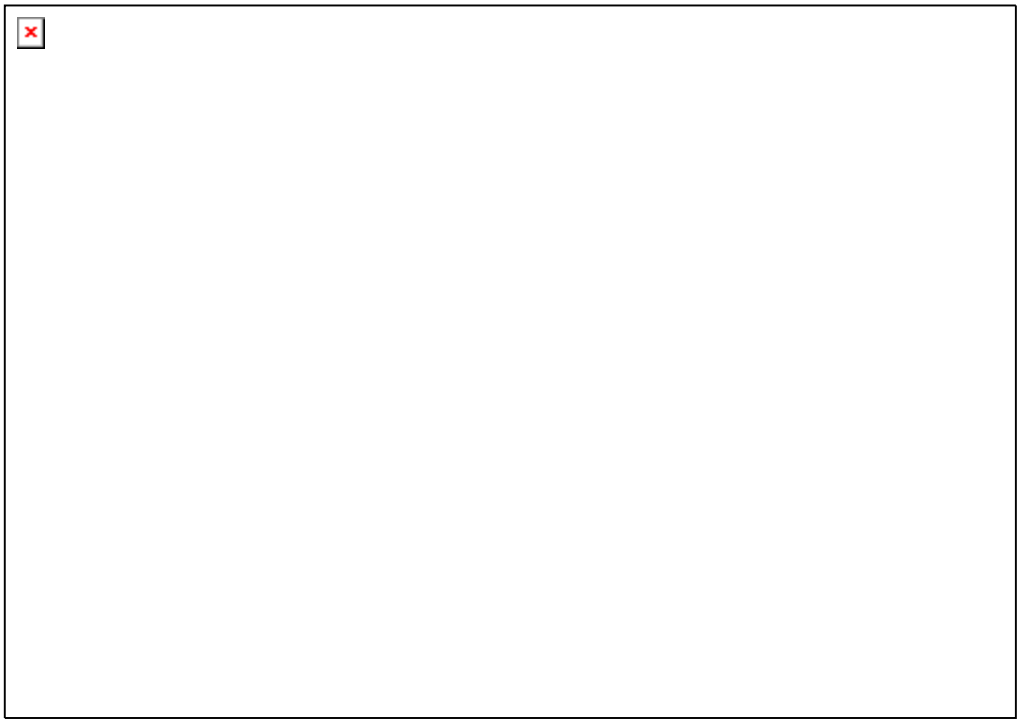
Dr Katalin Hideghéty

A Doktori Iskola vezetője
Professzor Nagy Judit

Témavezető
Professzor Ember István

Pécsi Tudományegyetem, Általános Orvosi Kar, Pécs, 2002.

Contents



1 Introduction

Boron neutron capture therapy (BNCT) is a binary treatment modality, based on the high cross section of ^{10}B to capture thermal neutrons producing two densely ionising particles with high biological effectiveness. In this reaction, the thermal neutron is captured by the nucleus, and the resulting boron-11 nucleus disintegrates spontaneously into a ^{4}He (α) and a ^{7}Li particle. [^{10}B (n, α)^{7}Li] These particles have ranges in tissue of ≈9 μm and ≈5 μm, respectively. The particles have a high Linear Energy Transfer, LET, and an associated high Relative Biological Effectiveness, RBE. One or two particles traversing the cell nucleus suffice to lead to clonogenic death. [1]
The therapeutic potential of this reaction was first recognised by Locher in 1936.[31] Sweet in 1951 suggested its use for the treatment of brain tumours.[59]

The preconditions for clinical use of BNCT are an appropriate thermal neutron delivery facility and a non-toxic boron compound with selective uptake of the targeted tissue i.e. tumour cells.

Image1 BNCT wing at the High Flux Reactor

Image 2. reactor core, HB11 neutron chanel with filters and BNC - treatment room

The boron delivery agent should preferably concentrate within each tumour cell, have sufficiently long biological half-life, resulting high intracellular concentration during the thermal neutron exposure. Up to now two agents are available for clinical investigation, sodium borocaptate (BSH) [54, 60]and boronophenylalanine (BPA),[5] [6]which are being used in clinical trials at epithermal neutron facilities for BNCT of high-grade gliomas and melanomas.

As binary treatment, BNCT allows to optimise the treatment by manipulation of two independent parameters. One parameter is the boron concentration in tumour and healthy tissues in its vicinity. The other parameter is the thermal neutron fluence rate in the tumour and in the surrounding tissue. Damage to tumour tissue and to healthy tissue will be influenced by both of these parameters.

The EORTC BNCT Group conducts the first phase I study on BNCT. It is a radiation dose escalation trial on GBM patients with a constant blood boron level in order to study the feasibility of $Na_2B_{12}H_{11}SH$ (BSH) as boron carrier and to define MTD and DLT of BNCT in cranial localisation. In addition to the tissue uptake and pharmacokinetics of BSH have been studied in the first patient group.[69,70,71, 49] The trial is currently in progress at the European High Flux Reactor in Petten (NL).[35] The study is performed according to the "Boron Neutron Capture Therapy with Glioblastoma Patients at the Petten Irradiation Facility" EORTC 11 961 phase I clinical " protocol.

2 Purposes of this PhD study

It will be demonstrated in the present work what kind of challenges and difficulties should have been overcome in order to investigate whether BNCT a new, complex radiotherapy modality, using epithermal neutrons and BSH as boron compound can be applied in a safe manner for patients in a trans-European set-up.

I. The preparation of the first clinical study in Europe will be presented. In addition to the difficulties defining a phase I trial design in the lack of established rules in the radiation oncology, the special features of BNCT had to be taken into consideration as well.

I/1. Clear definition on the aim of the clinical trial, strategy, end points and evaluation criteria were established as a part of my work. The achieved solutions, furthermore the general conclusions, which could be drawn for clinical research on highly selective new radiation therapy modalities will be described in the present thesis.

I/2. As a part of the clinical trial on BNCT BSH pharmacokinetics and tissue uptake investigation has been performed. In this PhD work, the results of the borocaptate uptake in glioblastoma multiforme and surrounding healthy tissues and its potential contribution on localisation of the energy deposition due to boron neutron capture reactions and its radiotherapeutical relevance will be described.

I/3. In this work the particular dose concept will be analysed which was defined specially for BNCT using epithermal neutron source in order to establish reproducible and comparable dose specification and reporting system as close to the standard

recommendations in radiotherapy as it was possible. The limitations and achievements in the complex dose(s) handling will be pointed out.

II. Interim results in term of dose-effect relationship of the ongoing EORTC 11 961 phase I study will be presented.

III. The conclusion of the interim analysis of the ongoing trial and the direction of further investigations and future perspectives of BNCT will be highlighted.

3 Preparation of the study protocol of the phase I clinical trial at the Petten irradiation facility

For introduction BNCT in Europe into the clinical application careful research had to be conducted on humans according to the generally accepted ethical, scientific and medical rules. There were no defined study methodology available for a completely new radiation approach, which is expected to be highly selective on cellular level.

3.1 Method of early clinical research on a selective radiation modality

The rules to perform early clinical trials in oncology with new drugs in systemic application are well established. In a phase I design the aim is to define the Maximal Tolerated Dose (MTD) and Dose Limiting Toxicity (DLT) (qualitative: organ specificity and quantitative: severity). Usually 3 patients suffering from metastatic tumours receive the drug on the defined (amount/body surface (mg/m^2)) dose level. The acute toxicity (follow up in general 1 month, scoring by standard toxicity scales NCIC-CTC) is detected whilst escalating the dose for 3 patients/cohort.

In radiation oncology in contrast to the drug trials, where the new agent is exposed equally to the whole body, special solutions have to be found due to the localised application of radiation. Furthermore the long-term morbidity detection and evaluation of late sequels of the treatment is mandatory in order to establish a safe dose level for further clinical research.

A particular strategy had to be clearly defined in the lack of well established method for phase I clinical testing of a complex radiation modality in order to:

- create homogeneous patient cohorts from the point of view of prognosis and radiation exposure for the different organs at risk
- prescribe the dose and define the dose escalation
- specify and report the dose in normal tissues
- detect the treatment related side effects and define the late radiation injury as endpoint
- establish dose- biological effect relationship and on that basis predict a safe dose for further clinical research

3.2 Aim of the EORTC 11 961 BNCT Study

The main goal of the trial is to establish

- the qualitative and quantitative radiation Dose Limiting Toxicity (DLT)
- and the Maximum Tolerated radiation Dose (MTD).

of BNCT in cranial localisation to healthy tissues under defined conditions at the HFR-Petten irradiation facility.

- Furthermore the study aims to define the feasibility of using Na2B12H11SH (BSH) as boron carrier. The dose of the study medication is not escalated in this trial.

3.3 Trial Design

Cohorts of patients with glioblastoma multiforme after surgical removal of the tumour undergo the radiotherapy with BNCT (under condition that the inclusion criteria have been met) instead of conventional radiotherapy for the tumour. The toxicity of the treatment is evaluated and the length of survival is recorded.

In addition to a separate investigation on BSH pharmacokinetics and tissue uptake have been performed during the surgery of the first patient group.

3.4 Patient Selection

Glioblastoma is chosen as the target tumour for the following reasons: The tumour is highly resistant to conventional treatment. After surgery, it recurs within the organ of origin, at or close to the original site. Median survival is consistently short even with maximal therapy, and there are no long term survivors, so that a major effect of the treatment on the clinical outcome can be seen during the investigation. Median survival is long enough to detect late effects on normal tissue. Boron uptake in the tumour following administration of BSH, the compound chosen, is well-documented (see below).

The healthy brain tissue receives a smaller dose than tumour tissue during BNCT, due to the confinement of BSH to the blood. Due to the dissemination pattern of GBM the irradiation of a large volume of the brain, even the whole, is acceptable in order to eliminate satellite micro-metastases

3.4.1 Creation of homogeneous population in the point of view of expected outcome

In order to ensure an homogeneous population of patients from the point of view of treatment outcome, we followed the partitioning criteria suggested by Curran et al.[7],

who classified different prognostic factors for median survival, from a mixed population of patients with glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA). In short, the partitioning differentiates between age (50 years of age and older versus under 50 years of age), Karnofsky Performance Scale (70 and higher versus below 70), histology of the tumour (glioblastoma multiforme versus astrocytoma grade III), extent of surgery (partial or total versus biopsy) and ability to work (yes or no; not used as a criterion here). The selected patients have median survival times of 11.4 and 9.2 months, depending on whether they are able to work or not, with a 25% survival of 15.6 and 13.8 months, respectively.

Patients selected would have no or only a very small benefit from conventional radiotherapy.

3.4.2 Definition on tumour characteristic

By defining the inclusion criteria on tumour dependent factors our aim was to create homogeneous patient cohorts with the same radiation exposure for the different organs at risk during anti-cancer treatment to the aim to identify the dose limiting anatomical structures, but at the same time, the local radiation modality must be directed toward the tumour region. The patients suffering from a localised tumour must have theoretical benefit from the intervention under examination, however it is unavoidable to cause serious normal tissue damage in some patients in order to achieve the main objective of a phase I trial.

In the ongoing BNCT study patients are included with solitary, lobar GBM, as confirmed by the reference neuro-pathologist, and with total tumour resection, as confirmed by the reference neuro-radiologist, with patient characteristic defined as class IV according to Curran(1).

<u>Eligibility Criteria</u>

Age 50 years or older at inclusion

Karnofsky Index is equal to or above 70. The patient must be able to travel to The Netherlands by public transport.

Pathological diagnosis of glioblastoma multiforme, confirmed by the reference pathology centre.

Evaluable pre- and postoperative MRI must be available.

Gross total removal of the contrast enhancing tumour is confirmed by postoperative MRI performed within 48 hours after surgery (remaining contrast enhancing tumour volume is $\leq$ 30%). If no MRI is available within 48 hours after surgery, later postoperative MRI may be used, if the Radiological Centre consider it appropriate for the evaluation.

Availability of the beam is confirmed for the planned treatment date. The start of BNCT must be within 6 weeks after surgery.

After relating detailed information on his disease and it’s prognosis, on conventional treatment modalities, on BNCT, on the present study, on the course of the fractionated

BNCT in the Netherlands and its possible side effects, the patient must consent to the radiotherapy and to the follow up. The patient must act as free person.

Patient should be able to travel to The Netherlands by public transport.

Exclusion Criteria

Prior anticancer treatment for the present tumour, chemotherapy, radiation, etc., but excludes corticosteroids and stereotactic biopsy.

Prior radiotherapy to the head and neck.

Prior head surgery with craniotomy, except for the GBM.

Prior head malignancy.

Second contemporary malignant tumour.

Severe dyspnea at diagnosis.

Severe heart disease (congestive heart failure, angina pectoris).

Severe lung disease (obstructive or restrictive lung disease).

Severe gastro-intestinal disease, active peptic ulcer disease.

Severe impairment of liver function (bilirubin, transaminases, alkaline phosphatase >2.5 of the normal range) unless caused by reversible reaction to anti-seizure medication.
Severe impairment of kidney function (blood urea nitrogen, creatinine > 2.5 of upper limit of the normal range).
Uncontrolled endocrine disease.

Serious mental or serious organic brain disease (e.g. pre-existing epilepsy or serious aphasia) or legally incapacitated patients.

4 Tissue uptake study

Boron-10 enriched (>95%) sodium borocaptate was supplied by Boron Biological. The pharmacy of the Academic University "Vrije Universiteit" (VU) prepared the quality control and an injectable pharmaceutical formulation containing lyophilised borocaptate. Quality checks according to standard operating procedure had been performed at the study pharmacy and at The Netherlands Energy Research foundation (NRG) Petten to ensure the stability, purity, ^{10}B enrichment and to exclude pyrogen content of the drug. Quantification of BSH in its ionic form [$(B_{12}H_{10}SH)_{2-}$] as well as of its oxidation products [$(B_{24}H_{22}SH_2)_4$- and $(B_{24}H_{22}S_2O)_4$-] in the lyophilised material was carried out by high pressure liquid chromatography (HPLC). The ^{10}B enrichment was controlled by prompt gamma ray spectroscopy and ICP-AES measurements at NRG Petten. Only certified BSH has been used for human administration.
Fourteen patients (twelve males and two females) weighing 56-109 kg, in the age range between 50 and 74 years, with strong suspicion of operable glioblastoma multiforme were admitted to the study after informed consent was given. None of the patients had reduced function of the kidneys or of the liver, and none suffered from another malignant disease.

The first 10 patients according to the protocol plan were to be infused 14 hours prior to the surgery with 100 mg of BSH/kg body weight dissolved in 500ml physiological solution, into the antecubital vein over the course of 100 minutes (at the rate of 1mg/kg/min). The total amount of borocaptate infused varied between 5000 and 9000 mg.
Three further patients have been administered with a total dose of 2000 mg BSH infused at the same rate. After termination of the BSH infusion, samples of blood (2 ml) were taken into heparinised tubes at times 0, 3, 6, 9, 12, 13, at the time point of tissue sampling and 18, 24 and 48 hours after the end of infusion. The pharmacokinetics analysis of boron concentrations together with the pharmacokinetics analysis of repeated administration of BSH for fractionated BNCT will be reported.
During surgery tissue samples (tumour /central periferic part/, peri-tumoural oedema, non-tumour brain tissue, dura mater, cranial bone, muscle, and skin) for which exposure to the neutron beam during the planned BNCT was expected, were dissected from the tumour location and operation area. Whenever possible, tissue specimens were collected from four different locations in the tumour. The content of boron in samples of blood and tissues was measured by ICP-AES at Petten. The estimated error of BSH detection in tissues by this method (AES) was about 2 %. The detection limit was 0.5 ppm. The boron concentration was normalised and evaluated at 100 mg/kg BSH dose. For evaluation the average total boron concentration ± standard deviation (SD) for each tissue was calculated, when there was more than one sample.

5 BNCT as postoperative radiotherapy

BNCT is administered instead of conventional radiotherapy. The epithermal neutron radiation is performed in a fractionated manner.

BNCT as a radiotherapy modality differs considerably from conventional external radiotherapy. In particular the facilities built for BNCT produce no monoenergetic neutron radiation, but the beam contains incident photons and a certain spectrum of neutrons. The thermal neutrons, which are present in the free beam and the neutrons with higher energy (epithermal, fast neutrons) which slowed down in tissues resulting thermal neutrons in the depth, have capture reactions with different probability with the elements composing the human tissues. Although their rates are small compared to that of boron, on an atom-per-atom basis, the presence of hydrogen and nitrogen in rather high concentrations leads to an unavoidable energy liberation and dose deposition in all tissue exposed to neutrons**.** Obviously the contribution of the different dose components are changing with the depth and the biological effectiveness of them differs from each other in great degree. The concentration and the microscopic distribution pattern of ^{10}B influence the absorbed dose to tissue caused by the neutron capture reaction of ^{10}B.

Consequently the total dose distribution is provided by several dose components. In addition to the boron neutron capture absorbed dose, other biologically relevant dose components to be considered are the absorbed dose from recoil protons from scattering of incident fast neutrons on hydrogen, the absorbed dose from protons emitted by the $^{14}N(n,p)^{14}C$ neutron capture reaction and the absorbed dose from incident photons (gamma radiation) and photons generated in the $^{1}H(n,\gamma)^{2}H$ reaction. The latter are generated in the irradiated volume, but will deposit a radiation dose also to the parts of

the brain not in the beam, and to the rest of the body. The figure 1. shows the contibution of the different dose components for a defined beam setting along the beam line.

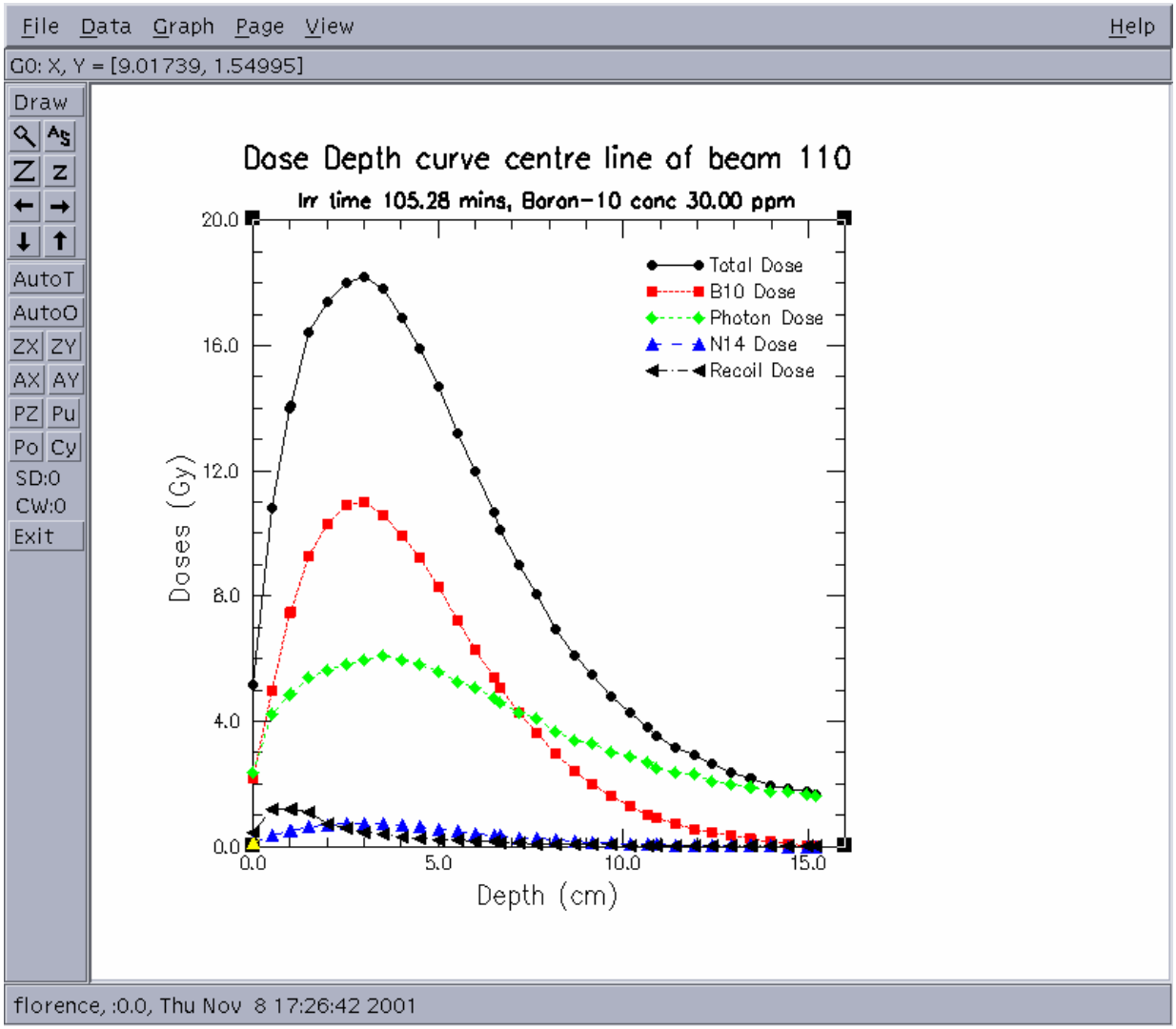


Figure1. Depht dose curves of the different dose component along the beam axis

5.1 Fractionation

The neutron irradiation is given in a fractionation scheme with four fractions in one week. As close as possible to 30 ppm average boron concentration in blood must be achieved over all four fractions.

The reasons for fractionation are the following:

The delivered total dose can be adjusted more closely to the prescribed dose, as the boron concentration at the end of each session is required to compute the dose delivered per session.

There is retargeting of BSH to tumour following repeated BSH administration [12].

Sparing of healthy tissue with fractionation has been observed in the dog experiments. [26] BSH is infused prior to each fraction, at time intervals and amounts described below. Treatment must start within six weeks after surgery. While the patient is in the trial, other anticancer therapies are excluded, unless required by the treatment of recurrence or symptoms.

5.2 Radiation Dose Prescription, Specification and Dose Escalation

5.2.1 Dose specification and reporting

The ICRU recommendation on dose recording and reporting cannot be used directly for BNCT, as the energy is deposited from different radiation qualities, which cannot be added in macroscopic volumes. The different, biological relevant dose components are delivered unequally to microscopic, sub-cellular structures depending on tissue composition, boron-10 spatial concentration and neutron spectrum fluence and distribution. All biological relevant doses are reported in defined points and volumes. The MRI changes of the brain are correlated to the dose distribution.

5.2.1.1 Absorbed dose concept and definitions for BNCT-treatment planning

Prior to start the clinical investigations apart of a suitable neutron delivery device and an appropriate boron carrier drug targeting the tumour cells, the establishment of a system allowing a reproducible and comparable description on energy deposition to biological structures i.e. tissues during BNCT, was essential. However the realistic description of the physical reactions on cellular level is not possible at the present status of knowledge. Real time measurements on ^{10}B distribution with high resolution in the different tissues during the thermal neutron exposure cannot be executed. A pool of reliable data on subcellular boron localisation could not be obtained even in vitro. There are relative high uncertainties by the dosimetry, by the source definition and the dose(s) calculation is limited as well. Therefore the clinical trials on BNCT can be only considered as empirical testing of a bimodal radiation therapy form. In order to define a system of describing and reporting of the energy deposition from different radiation qualities to the human body a special approach have been established. Our intention was to follow as close as possible the terms and definitions currently used in conventional radiation oncology on the basis of international proposals and the generally accepted oncological concepts. At the same time we tried to create a transparent system, which allows the intercomparison of patient treatment results performed at the different facilities. The definitions published in the ICRU reports and ASTM standards have to be taken into account.[14] Nevertheless it has to be stressed that the ICRU recommendations cannot be applied directly and completely in BNCT. Unavoidably special terms had to be introduced and the dose description, reporting system which is recommended by international committees have been adapted and re-defined according to the specialities of BNCT.

5.2.1.1.1 Absorbed dose

The absorbed dose as a macroscopic quantity is the basic parameter for prescribing, recording and reporting a radiotherapeutic procedure. This absorbed dose will be realised in a macroscopic region of specified elemental composition in tissue by energy deposition of secondary particles resulting from interactions of neutrons and gamma rays with the tissue.

In this approach the microscopic dose distributions of short-range high-LET particles (α-particles, Li-particles and protons) are averaged over macroscopic volumes.

5.2.1.1.2 Neutron absorbed dose D_n

The neutron absorbed dose D_n [Gy] is the absorbed dose from recoil protons from the thermal, epithermal, fast neutrons excluding gamma-rays and all particles produced by neutron capture reactions: $^{10}B(n,\alpha)^7Li$ and $^{14}N(n,p)^{14}C$.

5.2.1.1.3 Neutron energy ranges and integral neutron fluence rate (neutron flux)

The following grouping for neutrons of different energy is used:

slow neutrons corresponding approximately

to **thermal neutrons**: $E_{th} \leq 0.414$ eV

intermediate neutrons corresponding approximately

to **epithermal neutrons**: $0.414 \text{ eV} < E_{epi} \leq 9.12$ keV

fast neutrons $9.12 \text{ keV} < E_{fast} \leq 20$ MeV

Thermal neutrons actually have energies of roughly the same order of magnitude of the surrounding media, which is in the order of 0.025 eV. For most of the calculations using INEEL treatment planning program and also MCNP the "thermal energy" group has been taken as $0 \leq E_{th} \leq 0.414$ eV. Quoted thermal fluence rates from calculations are total neutron fluxes ($cm^{-2}s^{-1}$) over this energy range. Within the INEEL treatment-planning program the various dose rates are all evaluated as integral quantities during the particle transport calculation. Consequently a realistic distribution of particle energy is used in the dose rate calculation and the division of neutron energies into 3 broad energy "bins" is arbitrary and provided for user information only [62, 63].

The integral fluence rates per energy group (thermal, epithermal, fast) are defined by:

φ_{th} integral fluence rate of thermal neutrons

φ_{epi} integral fluence rate of epithermal neutrons

φ_{fast} integral fluence rate of fast neutrons

where: $\varphi_{th} = \int_0^E \varphi(E_n) dE_n$ with E= 0.414 eV

$$\varphi_{\text{epi}} = \int_{E}^{E_1} \varphi(E_n) dE_n \qquad \text{with } E_1 = 9.12 \text{ keV}$$

$$\varphi_{\text{fast}} = \int_{E_1}^{E_c} \varphi(E_n) dE_n \qquad \text{with } E_C = \text{cut off energy of the fast neutron spectrum (20 MeV)}$$

$\varphi(E_n)$ is the differential fluence rate (neutrons cm^{-2} s^{-1}) at the neutron energy E_n. The integral fluence rates defined here are not used to derive doses or other quantities used for treatment planning. They are defined for information only.

5.2.1.1.4 . Gamma-ray absorbed dose D_g

The gamma ray absorbed dose D_g [Gy] is due to gamma radiation present in the primary beam and also generated by the $^1H(n,\gamma)^2H$ and other neutron capture reactions in a phantom or patient.

5.2.1.1.5 Nitrogen neutron capture absorbed dose D_N

The nitrogen neutron capture absorbed dose D_N [Gy] is delivered by the secondary protons generated by the $^{14}N(n,p)^{14}C$ neutron capture reaction in a phantom or patient.

5.2.1.1.6 Boron neutron capture absorbed dose D_B

The boron neutron capture absorbed dose D_B [Gy] is delivered by high LET alpha particles and lithium ions from neutron capture of boron-10 by the $^{10}B(n,\alpha)^7Li$ reaction. The absorbed dose caused by boron neutron capture in tissue depends on the ^{10}B-concentration in blood. For the definition of D_B a homogeneous boron distribution in tissue has been assumed.

5.2.1.1.7 Boron-10-concentration c_B

The concentration c_B in the brain is a complicated function of the ^{10}B-concentration in blood. The presence of ^{10}B in the brain has two effects:

1. At a certain concentrations (>10 ppm) the neutron transport is affected and the neutron distribution is altered. For realistic values of ^{10}B concentration the neutron distribution is perturbed insignificantly but for transport calculations a nominal value of 10 ppm ^{10}B is taken as being uniformly distributed throughout the whole brain.

2. For the calculations of the absorbed dose D_B, the ^{10}B-concentration is assumed equal to the ^{10}B-concentration measured in blood.

5.2.1.1.8 Calculation of the absorbed dose from boron capture

The absorbed dose D_B (Gy) can be calculated by the following numerical value equation:

$$D_B[Gy] = \frac{1000}{\rho} \int_0^T \int_0^{E_c} \overline{N}_B \cdot E_{tr}(E_n) \cdot (1-g) \cdot \sigma(E_n) \cdot \varphi_E(E_{n,t}) \cdot dE_n \cdot dt \quad [J \cdot kg^{-1}]$$

ρ - material density [g cm^{-3}]

T - entire irradiation time [s]

t - time integration variable [s]

g - bremsstrahlungs efficancy factor [-] (<0.001) used in the factor (1-g) for conversion of kerma K to absorbed dose D

E_n - neutron energy [MeV]

E_c - cut-off energy of the neutron spectrum [MeV]

E_{tr} - transfer energy to secondary particles per absorption effect [J]

$\overline{N}_B$ - ^{10}B number density [^{10}B atoms cm^{-3}]

$\sigma(E_n)$ - absorption cross section of ^{10}B at energy E_n [cm^2]

$\varphi(E_n)$ - $d\varphi/dE_n$ - spectral neutron fluence rate at energy E_n [$MeV^{-1} \cdot cm^{-2} \cdot s^{-1}$]

If $\varphi(E_{n,t})$ is constant during the irradiation, and if events of non-thermal neutrons can be ignored then the numerical value equation may be reduced to

$D_B[Gy] = 1000\ \Phi\ \overline{c}_B\ k_f \quad [J \cdot kg^{-1}]$

with the explanation of additional symbols:

$$\Phi = \int_0^T \int_0^{E_c} \varphi_E(E_{n,t}) \cdot dt \cdot dE_n = \int_0^T \varphi \cdot dt$$

- spectral neutron fluence rate integrated over the irradiation time T [cm^{-2}]

$\overline{c}_B$ - average ^{10}B concentration during the entire irradiation time T [-]

$k_f = E \cdot \frac{\mu_{tr}}{\rho} =$ neutron kerma divided by neutron fluence [$J \cdot cm^2 \cdot g^{-1}$]

$\frac{\mu_{tr}}{\rho}$ - mass energy transfer coefficient [$cm^2 \cdot g^{-1}$]

Note: Both of these equations evaluate the energy production. Implicitly the assumption is used, that all this transfer energy (exclusively the energy for production of bremsstrahlung) is absorbed locally: The place of the kerma production is per definitionem the place of interaction. The place of absorbed dose is the line along with the energy transfer by the secondary particles to atoms and molecules happens. In the case of BNCT the range of the secondary alpha particles and Li-ions is within 10 μm, thus the energy transfer is in good approximation locally and – together with the bremsstrahlungs efficacy factor < 0.001 – the kerma equals absorbed dose.

For the nitrogen neutron capture absorbed dose D_N, an equation as given for D_B is used. N_N [the ^{14}N atomic density] is constant. For the calculation of D_N, 2.2% by weight nitrogen in brain is used in accordance with ICRU Report 46.

5.2.1.1.9 Total absorbed dose

The total absorbed dose is the sum of all absorbed dose components: $D_T = D_n+D_g+D_B+D_N$

5.2.2 Volumes of interest for BNCT treatment

The target of radiotherapy is the tumour tissue with a certain safety margin. However in a phase I trial the tissues in interest are in fact the normal tissues from the point of view of the study objectives.

The following volumes are chosen according to the definitions given in ICRU Report 50 for the present study:

5.2.2.1 Gross tumor volume (GTV):

The gross tumour volume is defined as gross palpable or visible/demonstrable extent and location of malignant growth. For BNCT the GTV is - if not otherwise specified - the contrast-enhancing volume on pre-surgical contrast-enhanced MRI.

5.2.2.2 Clinical target volume (CTV):

The clinical target volume is defined as a tissue volume that contains a demonstrable GTV and/or sub-clinical microscopic disease, which has to be eliminated. This volume has to be treated adequately in order to achieve the aim of therapy, cure or palliation. It must be defined in plain topographic terms or according to a corresponding code in conformity with the recommendations for GTV.

5.2.2.3 Planning target volume (PTV):

The planning target volume is a geometrical concept and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV. It is a purely geometric concept, and thus cannot be described in anatomic terms. For BNCT the PTV can be taken approximately as the GTV plus a 2 cm thick shell enclosing it. The PTV is to be defined by the radiation oncologist in charge for treatment.

5.2.2.4 Treated volume

In radiotherapy the accepted definition for the treated volume is the volume enclosed by an isodose surface, selected and specified by the radiation oncologist as being appropriate to achieving the purpose of treatment (e.g., tumour eradication, palliation). In this phase I study this definition cannot be applied, hence the treated volume is corresponding to the irradiated volume for the purposes of the trial.

5.2.2.5 Irradiated volume

The irradiated volume is that tissue volume which receives a dose that is considered significant in relation to normal tissue tolerance. The irradiated volume depends on the treatment technique used.

5.2.2.6 Organs at risk

Organs at risk are normal tissues outside the CTV whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose. In BNCT of glioma, apart from the brain, the following organs are to be considered at risk: skin, optic chiasma, eyes, ears, pituitary gland, and salivary glands. They are to be identified on the MRI or CT scans by the Radiotherapy Centre. The absorbed doses on each of these structures have to be reported.

5.2.3 Dose prescription to the Dose Group Identification Point (DGIP)

In this trial the boron neutron capture absorbed dose D_B which is defined for the boron neutron capture therapy of the cohorts of patients is given at a physically defined point. This Dose Group Identification Point DGIP is located where the thermal fluence is a maximum for a given treatment plan; i.e. fluence rates integrated over time for each field and summed over all fields. With this definition the DGIP may lie inside, or outside, of

the PTV. The D_B at the DGIP will be called Maximum Accepted Dose (MAD) and will correspond to the 100% value of the boron neutron capture absorbed dose distribution. For the other dose components a limiting maximum at the DGIP has been defined which must not been exceeded. Radiation dose escalation in this study is done by increasing the MAD. It may be possible for several points to satisfy the definition for DGIP, particularly if multiple fields are used. In this case the point having maximum thermal fluence with the highest fast neutron absorbed dose will be the DGIP.
Under the present technical conditions the number of irradiation fields are limited to two, the field size is defined as 12 cm diameter. The field arrangement is defined to achieve two separated thermal fluence maxima (two DGIPs), one inside the planning target volume, and an one outside of the PTV in the brain.

5.2.4 Dose distribution in defined volumes

In conventional radiotherapy if the absorbed dose is prescribed to a given volume, the corresponding 3-D dose calculation should result a dose distribution as homogeneous as possible, using a reasonable number of fields. In BNCT large macroscopic and microscopic dose heterogeneity is present because of heterogeneity of the boron distribution within the tissues and the relatively steep fall off of the neutron fluence with depth. Therefore the dose in a defined volume cannot be described using the ICRU concept of a ”reference point” and a ”reference dose”. For this trial, the dose distribution in defined volumes will be described by reporting the following dose values:

Minimum dose $D_{x,min}$

The minimum doses are the smallest doses of each dose component, of the total absorbed dose and the biologically weighted dose in a defined volume.

Maximum dose $D_{x,max}$

The maximum doses are the highest doses of each dose component, of the total absorbed dose and the biologically weighted dose in a defined volume.

Average dose $D_{x,average}$

The determination of the average dose is based on the calculation of the dose at each one of a large number of discrete points (lattice points), uniformly distributed in a defined volume. The average dose is the average of the dose values in these lattice points, described by the equation

$$D_{x,average}=1/N\ \Sigma(V)\ (D_{i,j,k})$$

where N is the number of lattice points, i is the column index in this lattice, j is the row index, k is the level index, and $D_{i,j,k}$ is the dose at the lattice point i,j,k located inside the volume V. For BNCT the average doses are reported separately for each doses component, the total absorbed dose and the biologically weighted dose, in the given volume.

Median dose $D_{x,median}$

The median dose is the central value of the doses at all lattice points, when arranged according to magnitude. The median doses of BNCT are reported separately for each doses component, the total absorbed dose and the biologically weighted dose, in the given volume.

Modal dose $D_{x,modal}$

The modal dose is the dose that occurs most frequently at lattice points in the volume concerned. There may be more than one modal dose value, which then makes this concept useless for reporting purposes. The modal doses of BNCT are reported separately for each doses component, the total absorbed dose and the biologically weighted dose, in the given volume.

5.2.4.1 Dose in the PTV, dose at the prescription point

The ICRU Reference Point and ICRU Reference Dose Concept is not applicable for BNCT. In order to obtain a dose, which can be topographically identified, the point at the geometrical middle of the PTV is defined as ”prescription point” for this study. The absorbed doses at this prescription point have to be reported in addition to the $D_{x,min}$, $D_{x,max}$, $D_{x,average}$, $D_{x,median}$ and $D_{x,modal}$.

BNCT relies on the selective accumulation of boron in tumor areas. A therapeutic effect can, however, only be expected if the boron-containing areas also receive a sufficient thermal neutron flux. This implies that a substantial part of the whole brain must be exposed to neutrons.

5.3 Treatment planning

Dose calculations are performed on the basis of a 3D model of the particle transport and neutron scattering with the ***bnct_rtpe/rtt_MC*** code developed specially for BNCT by Idaho National Energy and Environment Laboratory (INEEL). [65, 66] Two volumes are defined in the 3D model of a patient’s head: the brain and the planning target volume. The material composition of the different organs was used for the dose calculation as defined in the ICRU-46. To simulate the particle transport in the patient, a homogenous ^{10}B concentration of 10 ppm is assumed in the whole head. For the evaluation of the doses a homogeneous boron distribution has been assumed in the tumour and in healthy tissues equal to the measured blood boron concentration. Isodose curves throughout the whole head, dose depth curves for each beam together with the dose-volume histograms for the regions of the target and the healthy brain are generated. [62, 63] [64] Figure 2-6. On the special spread sheet all dose components have been indicated in defined points. For evaluation purpose to compare the observed adverse events to applied dose(s) of BNCT case report form on applied dose(s) to the relevant anatomical structures particular to this study has been created.

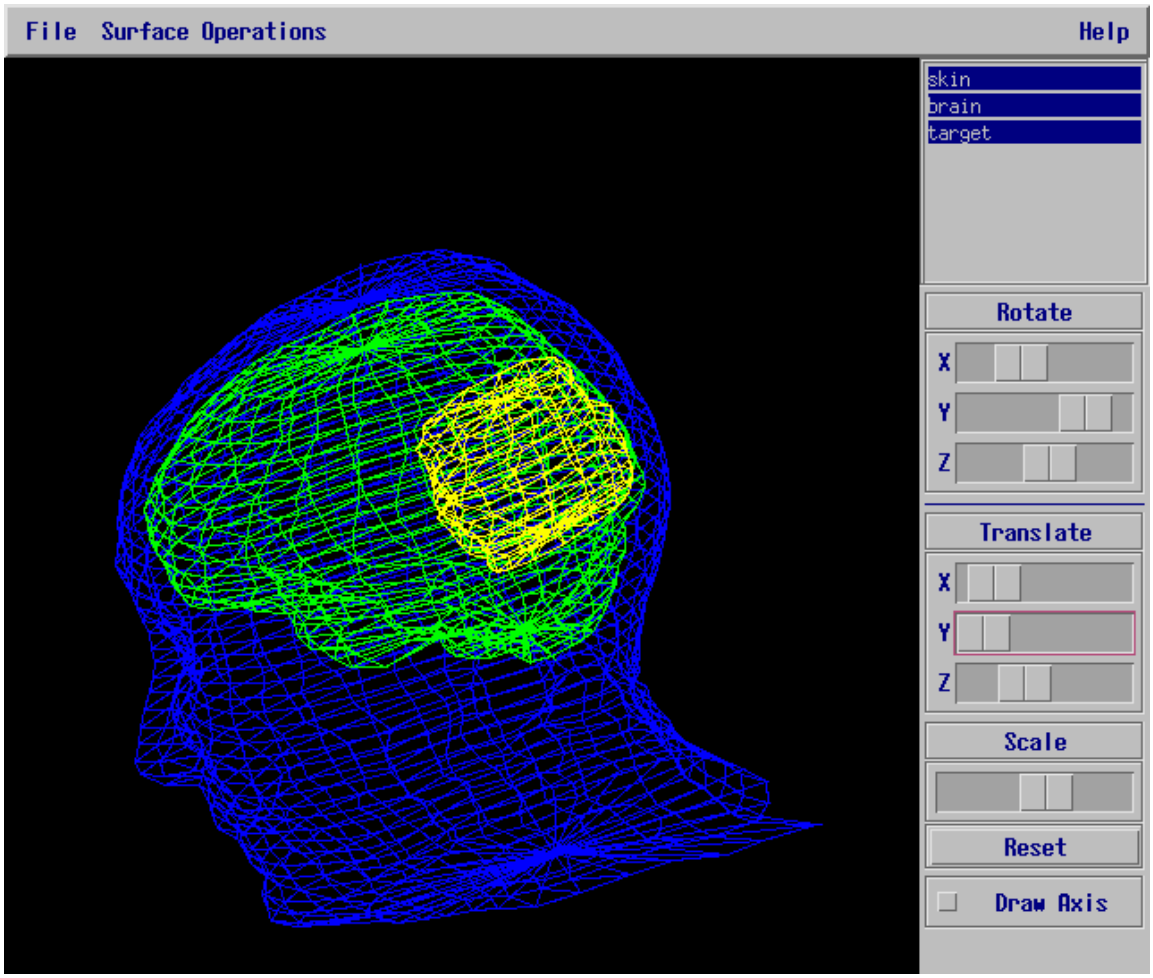


Figure 2. external, brain and planning target indicated for the 3D planning

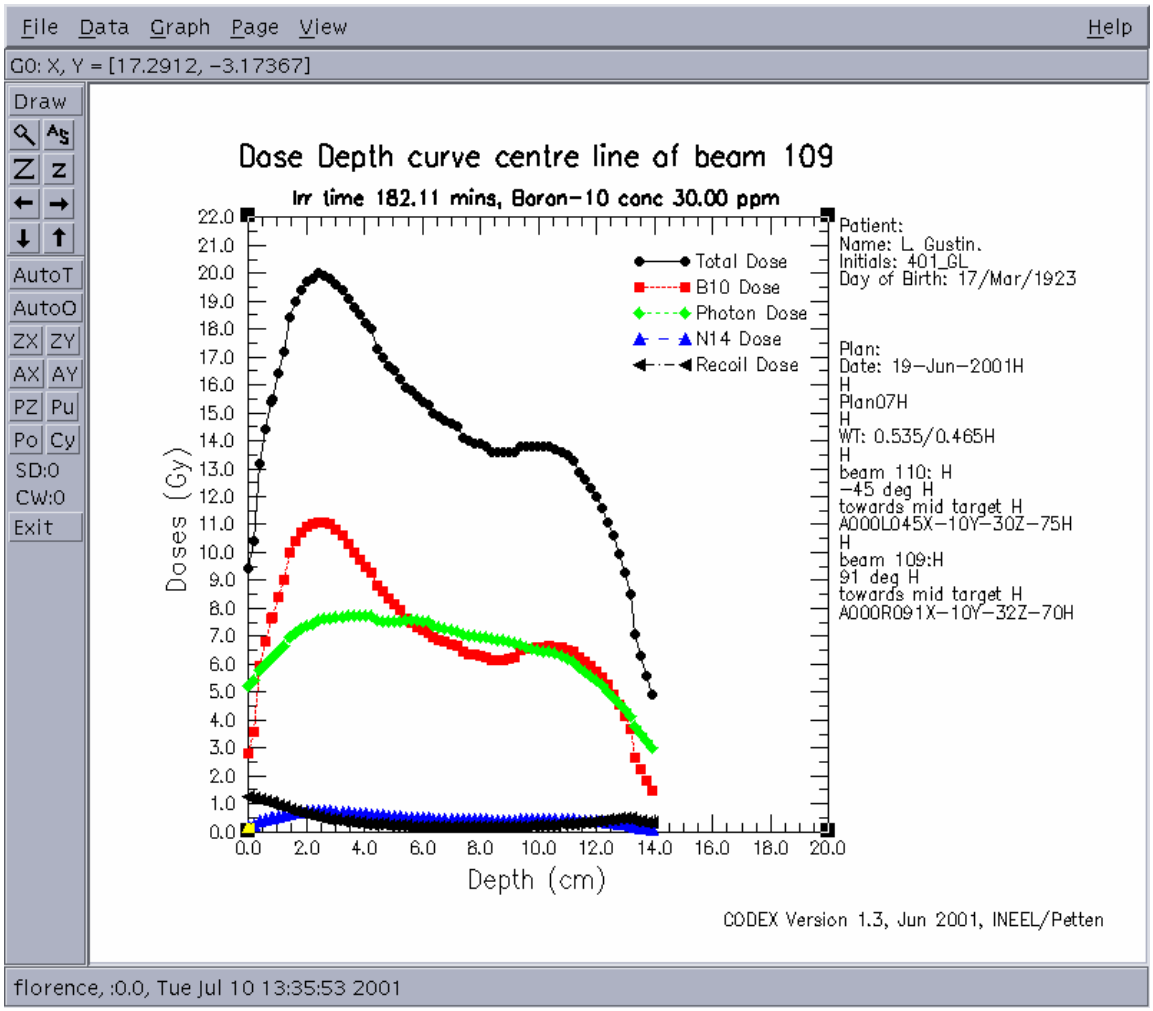


Figure 3. Doses depth curves of a 2 fields plan along the first beam axis

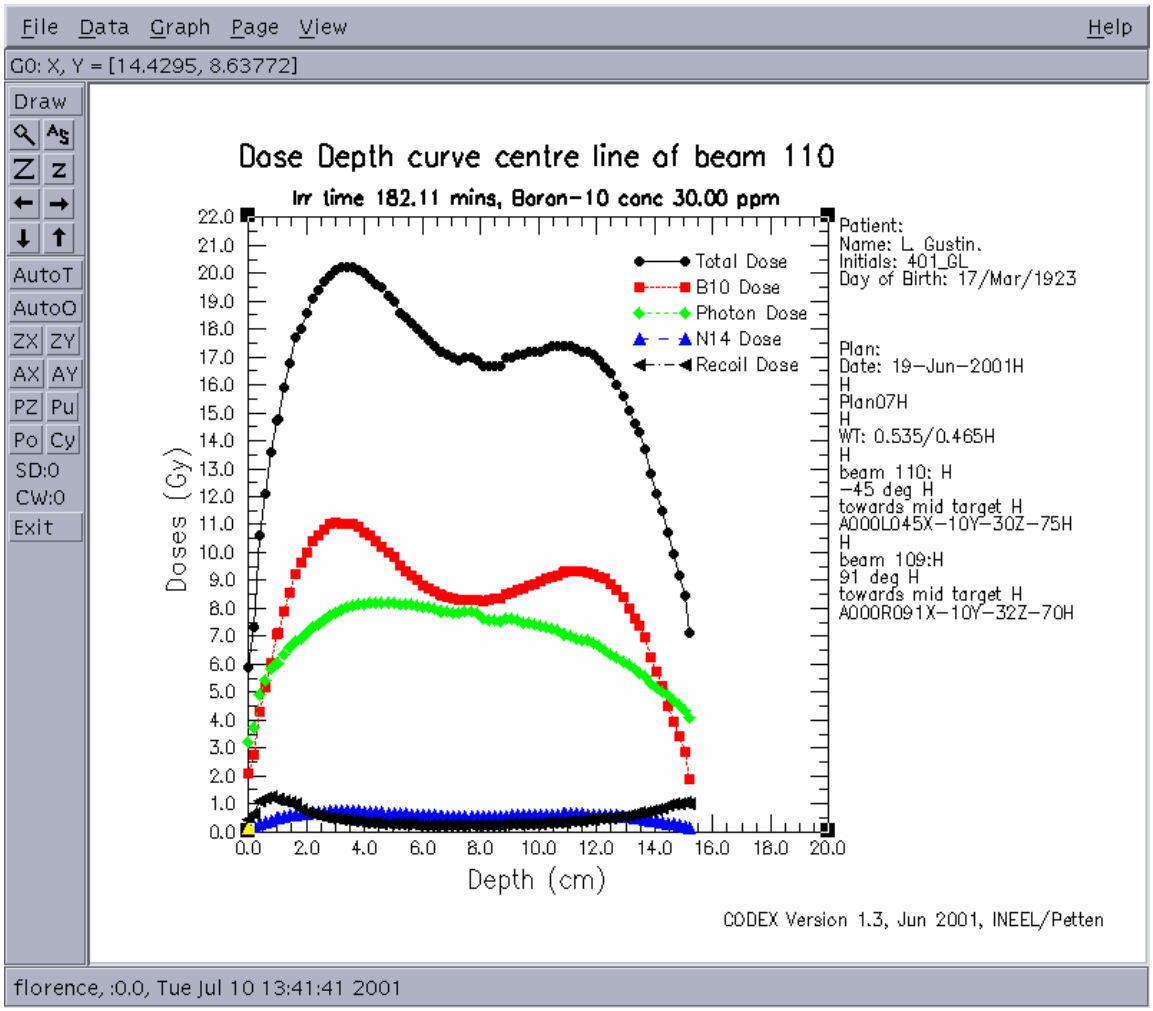


Figure 4. Doses depth curves of a 2 fields plan along the second beam axis

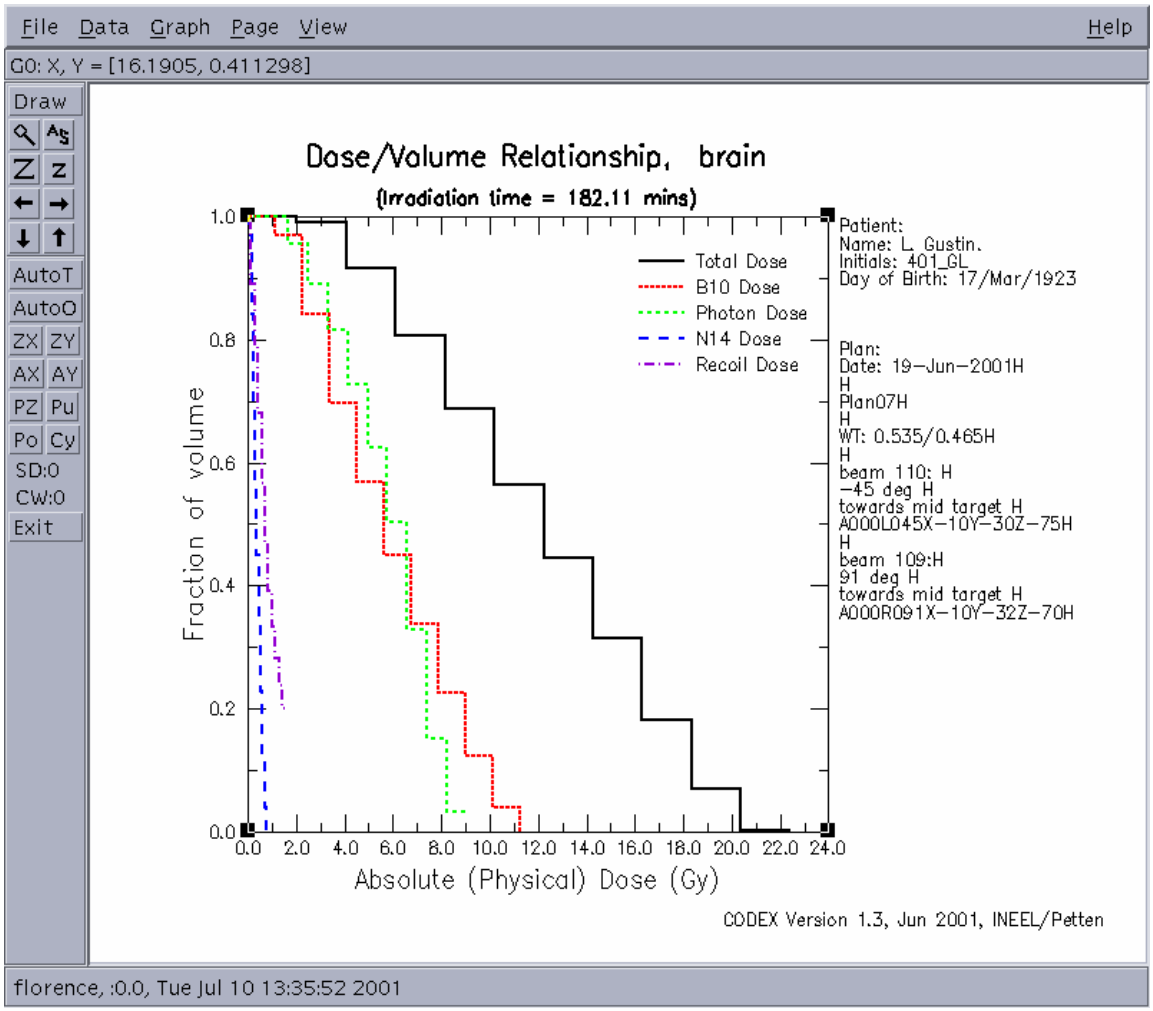


Figure 5. Doses volume histogram for the brain

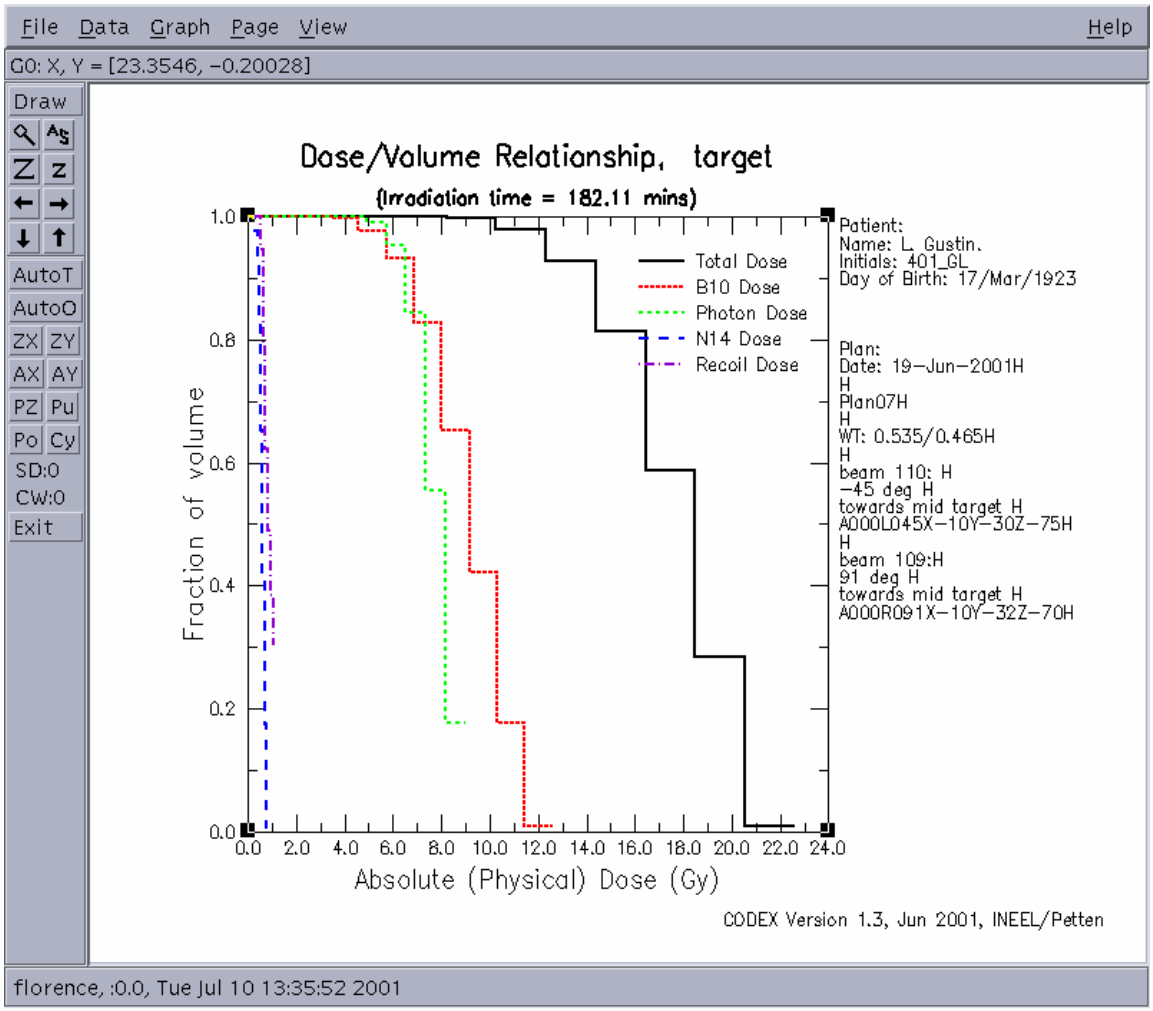


Figure 5. Doses volume histogram for the target volume

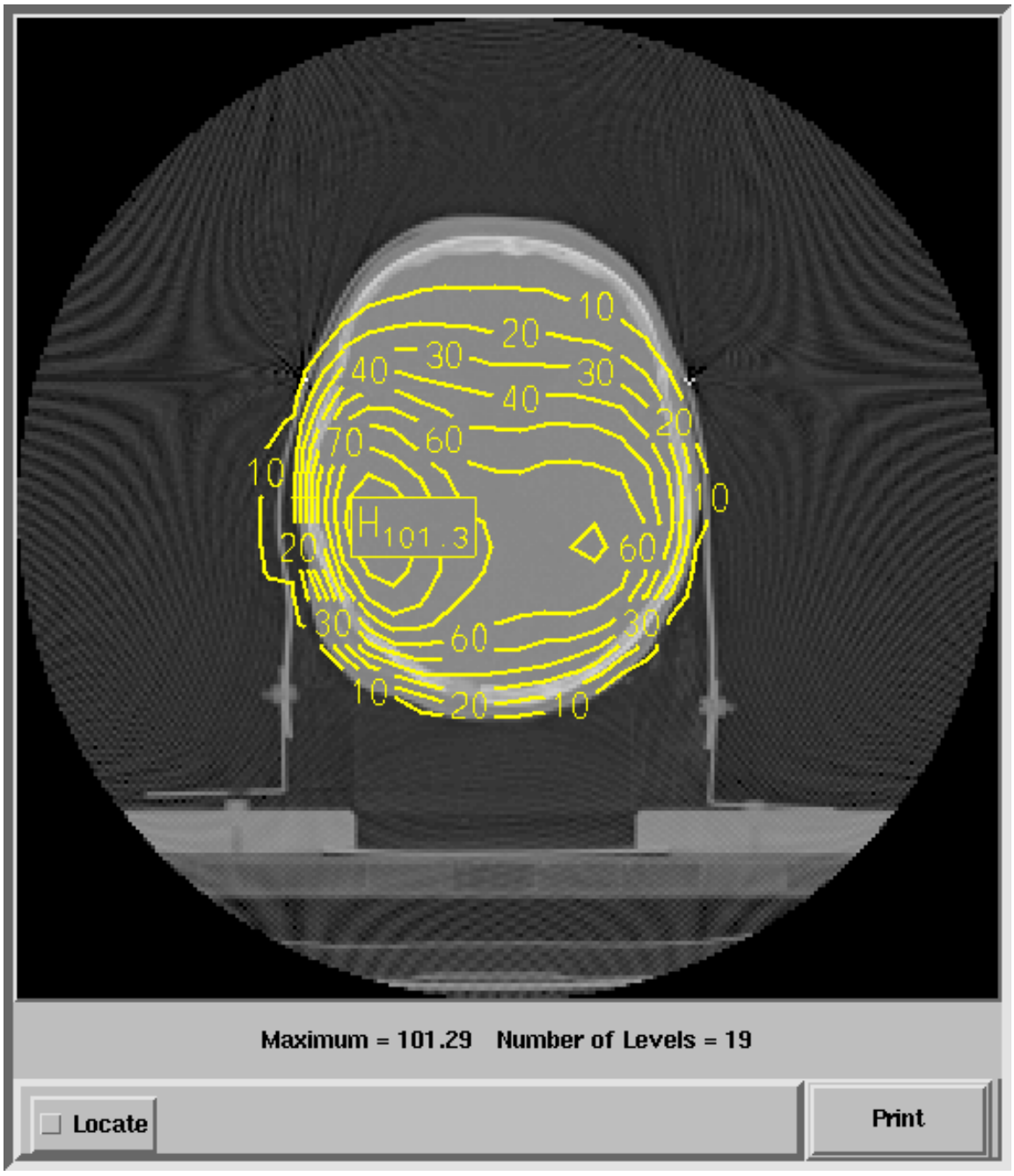


Figure 6. Boron dose distribution on transversal planning-CT scan

5.3.1 Reporting of dose

In this study reporting of the applied dose has always be done by describing the absorbed dose of each dose component. In addition to a biologically weighted dose (D_{WU}) is reported, which is the sum of the different dose components multiplied with their respective biological weighting factors: $D_{WU}=W_{n+N}\cdot D_{n+N}+W_g\cdot D_g+CF_{organ}\cdot D_B$ (W_{n+N} =3.9; W_g C =1; CF =0.37 for the tumor and CF= 0.81 for other tissues)

The doses are reported in

- defined points:
- DGIP: thermal fluence maximum for a given treatment plan
- Dose prescription point: one point at the center of the former tumor area (In order to obtain a dose which can be topographical identified in the target region, the point at the geometrical middle of the PTV is defined for this study.
- at the indicated points relevant to the organs at risk: optic chiasm, thalamic vessels, eyes, ears, pituitary gland, salivary glands, and the skin at beam entrance and exit.
- defined volumes:

  planning target volume and the whole brain volume including the target.

Doses - volume histograms are calculated in the defined volumes, furthermore the minimum, maximum, average, median and modal (D_{min} , D_{max}, $D_{average}$, D_{median}, D_{modal}) of each dose component and the biological weighted dose is reported for evaluation of doses adverse event relationship. Reporting of the applied dose is done by describing the absorbed dose of each dose component. The report of only one "dose equivalent" value may introduce grave errors in the interpretation of data, and hence risk to patients, and shall therefore, be strictly avoided.

5.4 Starting dose and dose escalation steps

The MAD for the starting dose is set at $D_B \leq 8.6$ Gy, $D_n \leq 0.9$ Gy, $D_N \leq 0.6$ Gy and $D_g \leq 5.8$ Gy . D_B should be as close to 8.6 Gy as possible.

The treatment with this absorbed dose led to no neurological symptoms in the healthy tissue tolerance study in dogs.

The dose is to be increased by 10% over that of the previous cohort according to the escalation strategy defined.

A radiation dose escalation strategy peculiar to this study has been established in order to protect the patients having enough time prior to starting the treatment of the next cohort to detect serious late adverse events, meanwhile the study could be finished during an acceptable time period . Some concepts are introduced here to ease definition of the decision rules:
Decision was made on opening the next radiation dose level, on whether a detected radiation toxicity must be considered dose limiting, on the judgement about the closure of the study and reporting of a certain radiation dose as maximum tolerated radiation dose.

Definitions:

Serious Adverse Event (SAE)

- life-threatening events
- events which are disabling or incapacitating
- events which require or prolong hospitalisation
- clinical events or laboratory abnormalities which lead to treatment discontinuation

- death from any reason occurring within 30 days of receiving the radiation therapy with BNCT.

All serious adverse events occurring up to 30 days after the end of radiation therapy with BNCT must be reported within 24 hours. After that period all serious adverse events thought to be at least possibly treatment-related, must be reported.

Unacceptable radiation toxicity:
There is no approved definition of unacceptable late radiation toxicity like for drug toxicity (grade 4). The solution of this problem is to involve independent experts of this field to obtain a maximum of unbiased objectivity

Dose Limiting Toxic Event DLTE
All SAEs, which may be related to the applied radiation dose, must influence the continuation of the trial. There a two factors which should be judged, the relationship to BNCT, and the acceptability or unacceptability of the SAE.

The relationship of a SAE to BNCT: Unrelated – unlikely – possibly – probable - definite
The decision whether a SAE is considered to be a radiation Dose Limiting Toxic Event, DLTE, was judged on the basis of the reported SAE and a detailed report from the investigator and the relevant Reference Centres. The decision whether a certain SAE is an unacceptable event, a radiation dose limiting toxicity had been suggested by the Treating Radiotherapy Centre and was confirmed by the members of the Advisory Board.

Follow-up time: The "minimum follow-up time" is set to six months.

Success
A success is defined for a given observation time as a patient who is observed for at least the minimum follow-up time and who has not developed any DLTE. Also, any patient who is withdrawn from the study after minimum follow-up time without any DLTE is rated as a "success".

Failure
Any patient who developed a DLTE up to the current observation time is considered a "failure".

Dose escalation strategy (70)
D(s) is the current dose, D(s+1) is the next dose and D(s-1) the previous dose.

1. Recruit patients at dose D(s) as long as there are no failures, no (one, two) successes, and less than nine (six, four) patients under study. At three or more successes, do not recruit and wait until every patient under study has been observed for six months. Then, proceed to D(s+1) and start with a new collective.
2. If there is one DLTE and no (one, two, three, four) successes, recruit patients until there are nine (nine, nine, six, four) under study. At five or more successes, do not recruit and wait until every patient under study has been observed for the minimum follow-up

time. If no further DLTEs has been observed, proceed to D(s+1) and start with a new collective.
3. If there are two DLTEs and less than five successes at dose D(s), stop the trial and choose D(s-1) as the limiting dose. At five (six) successes, keep recruiting until there are six (four) patients under study. At seven successes, do not recruit and wait until every patient under study has been observed for the minimum follow-up time. If no further event occurred, proceed to D(s+1) and start with a new collective.

4. As soon as there are three DLTEs at dose D(s), stop the trial and choose D(s-1) as the limiting dose.

The following dose escalation steps are proposed:

		Maximum doses			
Escalation step	% dose increase from previous step	D_n (Gy)	D_N (Gy)	D_g (Gy)	D_B (Gy)
1		0.9	0.6	5.8	8.6
2	10	1.0	0.7	6.4	9.5
3	10	1.1	0.8	7.0	10.4
4	10	1.2	0.9	7.7	11.4

5.5 Toxicity detection and quantification

In order to achieve the aim of the trial the applied dose should be correlated to biological effects, namely to the adverse reactions of healthy tissues. The main problem is the interpretation of the adverse events, the distinction between the therapy related toxic events and the clinical symptoms due to the tumour. Furthermore the toxicity evaluation is more difficult in radiation oncology because there is no final consensus on the tool to be used for grading the severity of the observed morbidity. (EORTC/RTOG early and late radiation morbidity *versus* NCIC CTC *versus* SOMA LENT)

A rigorous follow up with frequent analytical and functional examinations of the possible organs at risk has been defined.

	Week				Month												
	1	2	3	4	2	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18	
Clinical examination	x *	x *	x *	x *	x	x	x	x	x	x	x	x	x	x	x	x	every 3 months
Quality of life	x			x		x				x				x			every 6 months
Mini Mental Status			x		x		x	x		x		x				x	every 6 months
MRI	x				x		x	x		x		x		x		x	every 6 months
Ophthalmologic examination								x				x				x	every 6 months
ENT examination								x				x				x	every 6 months
Hypothalamic-pituitary axis					x		x	x		x		x		x		x	every 6 months

Table 5.5/1

Clinical examination: general clinical examination and neurological examination, *in addition to during the first month follow up blood pressure, ECG, complete blood chemistry and haematology

Quality of life (questionnaire EORTC QLC-C30 and Brain Module)

Ophthalmologic examination: visual acuity, visual field, ophthalmoscopy, slit lamp, ocular pressure

ENT examination: clinical examination including audiometry and evaluation of salivary gland function

Hypothalamic-pituitary axis: prolactin, STH, TSH, T4, FSH, LH; ACTH and fasting cortisol if the patient is not under corticosteroid treatment

Radiation toxicity will be detected with special focus on the following organs: brain, eye, salivary gland, ear, irradiated skin, subcutanous tissue, oral and pharyngeal mucosa

Systemic toxicity is detected from the first drug administration up to 30 days and the adverse events due to the boron compound are graded by the CTC scale based on NCI-CTC (October 1993) and NCIC CTG expanded CTC (21 December 1994). Early radiation toxicity during the first 90 days after radiotherapy is scored using the NCIC-CTC and EORTC/RTOG early radiation morbidity scales. The RTOG/EORTC Early Toxicity Criteria for Eye, Ear, Skin, Mucous membrane, salivary gland, CNS are to be followed for the irradiation site, from the first day of the treatment through day 90. The RTOG/EORTC Late Toxicity Criteria for Eye, Ear, Irradiation Site, Skin, Subcutaneous tissue, Mucous membrane, Salivary gland, Brain, Neurologic are supplemented by relevant items of NCIC-CTC and modified SOMA LENT (Late Effect on Normal

Tissue) categories. The parallel use of three different scoring systems shows the difficulty to chose a single, appropriate scale.

5.6 Tumor response

Patients are evaluable for BNCT-related anti-tumour activity after receiving at least one treatment with BNCT. Disease measurements made from follow-up MRIs are compared to the tumour measurements made from the last MRI made prior to BNCT treatment (the orthogonal dimension of the tumour are measured (the maximal extent of tumour in x-, y- and z-direction)). Tumour measurements from MRIs are performed in a reference radiology institute in Frankfurt by Professor F.B. Zanella and Dr. B. Turowski.

Responses were classified according to 2 scales.
First according to the MacDonald scoring, which corresponds to the WHO system:

- Complete response (CR): disappearance of the enhancing tumor tissue.
- Partial response (PR): <50% decrease of initially enhancing tumor volume after one month to the prior imaging (unchanged or reduced corticotherapy).
- Progressive disease (PD): >25% increase of enhancing tumor or new tumor growth.
- Stable disease (SD): all other situation.

Secondly, responses were classified according to the Zanella scoring. This scoring based on the following criteria and the subjective impression of the two experienced reference neuroradiologists proves an acceptable 'sure subjective' judgement on the tumor response:

- The changes in the signal intensity (increase or decrease) will be described. However it should be noted, that it is not possible to differentiate between the peritumoral radiation induced changes and the tumor progression only on the basis of image morphology.
- The change of the perifocal edema is an indirect sign of tumor response.

On the basis of the above listed objective MRI features the judgement by the two neuroradiologists was classified as following:

- Regressive disease (PR): evidence of decrease or disappearance of tumor on MRI.
- Progressive disease (PD): evidence of increase or new growth of tumor on MRI.
- Stable disease (SD): all other situations.

A short description on the tumor response and damage to the healthy brain (as well as scoring the damage using the SOMA scale) was given as free text.

5.7 Quality management

With respect to the multi-institutional, interdisciplinary and cross-cultural features of the first clinical investigation on BNCT, a special quality management system had to be established. The tasks and responsibilities were specified and allocated. A detailed description on the study procedures, flow charts, organigrams, check lists, study document forms including not only the case report forms, but pre-printed forms for source documents and submission of study material was provided to all participants. Local personal explanation and training was performed in the frame of the initiation site

visits at each patient referral centre. The treatment preparation and performance were exercised as complete dummy runs and evaluated prior to start the study and prior to start the treatment of each patient cohort. Numerous external experts, professional institutions and special boards play active roles in controlling the study documents, data, the different procedures, decisions and evaluation. The interim evaluation during and after the therapy of the first patient group led to a substantial protocol amendment and to improved statistical design.

5.7.1 Dose Monitoring

5.7.1.1 On-line monitoring

One of the major differences in using a nuclear reactor as the radiation source in comparison to a conventional source, such as a cyclotron, is that the beam intensity varies with time due to the burn-up of the fuel in the reactor. For example the reactor in Petten operates in monthly cycles, giving a reduction in beam intensity of 3-5% over a monthly period. Also, depending on the core configuration due to the fuel and experimental loading, there can be cycle-to-cycle variations of up to 15%. It should be noted that over a typical treatment time of 30 minutes to 2 hours these variations are negligible. Nevertheless, it is imperative to know the absolute values of beam intensity, or at least the intensity relative to the reference beam, during the treatment[20]. For treatment planning codes as mentioned here it is virtually impossible to model these fluctuations in output. Therefore it is necessary to apply a monitoring system and not to rely solely on time.

The system should be able to detect parameters such as: neutron spectrum shifts; changes in fluence rates; and changes to the neutron to gamma-ray ratio. As a result, at the HFR Petten facility, a system of monitors has been placed inside the beam tube structure.

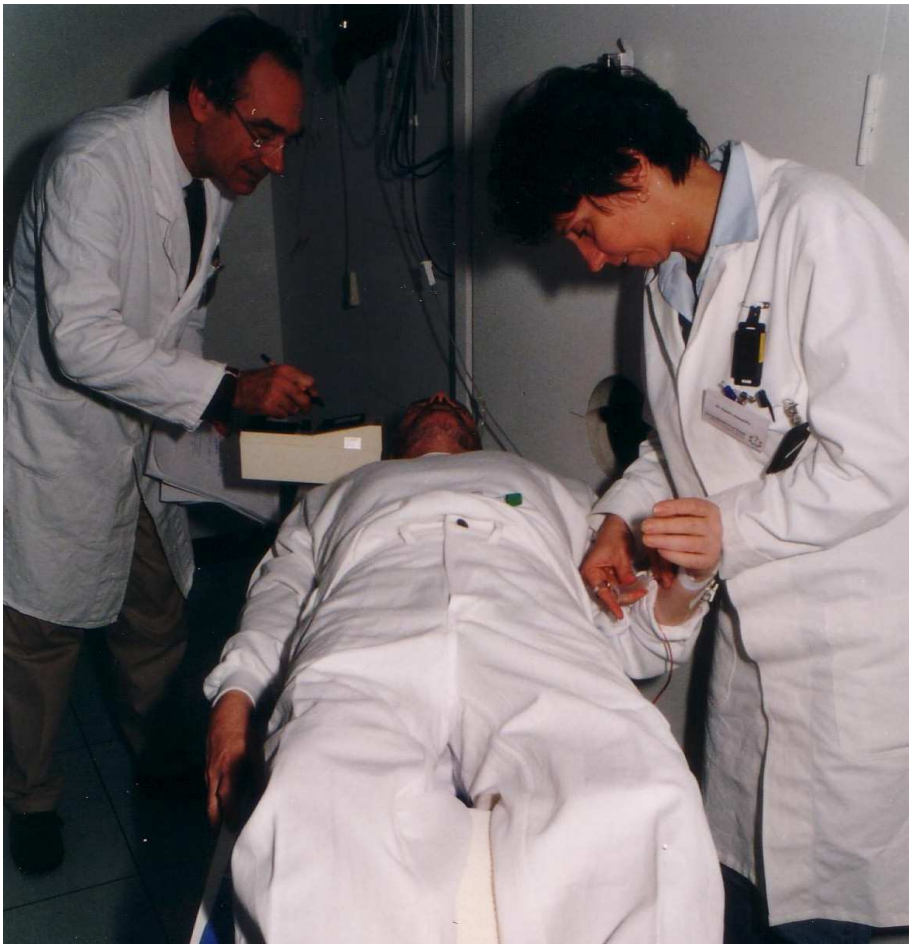


Image 3. Blood sampling after irradiation and radiation measurement at the head

The system consists of a twinned set of cadmium-covered ^{235}U fission counters: Geiger-Müller counters; and ionization chambers. The system of monitors are thus able to measure the epithermal neutron fluence, the fast neutron fluence and the gamma field, and moreover able to detect significant changes in these parameters that could effect treatment conditions. Unacceptable changes in certain parameter result in automatic closure of the main beam shutters, and hence end of treatment[48](71).

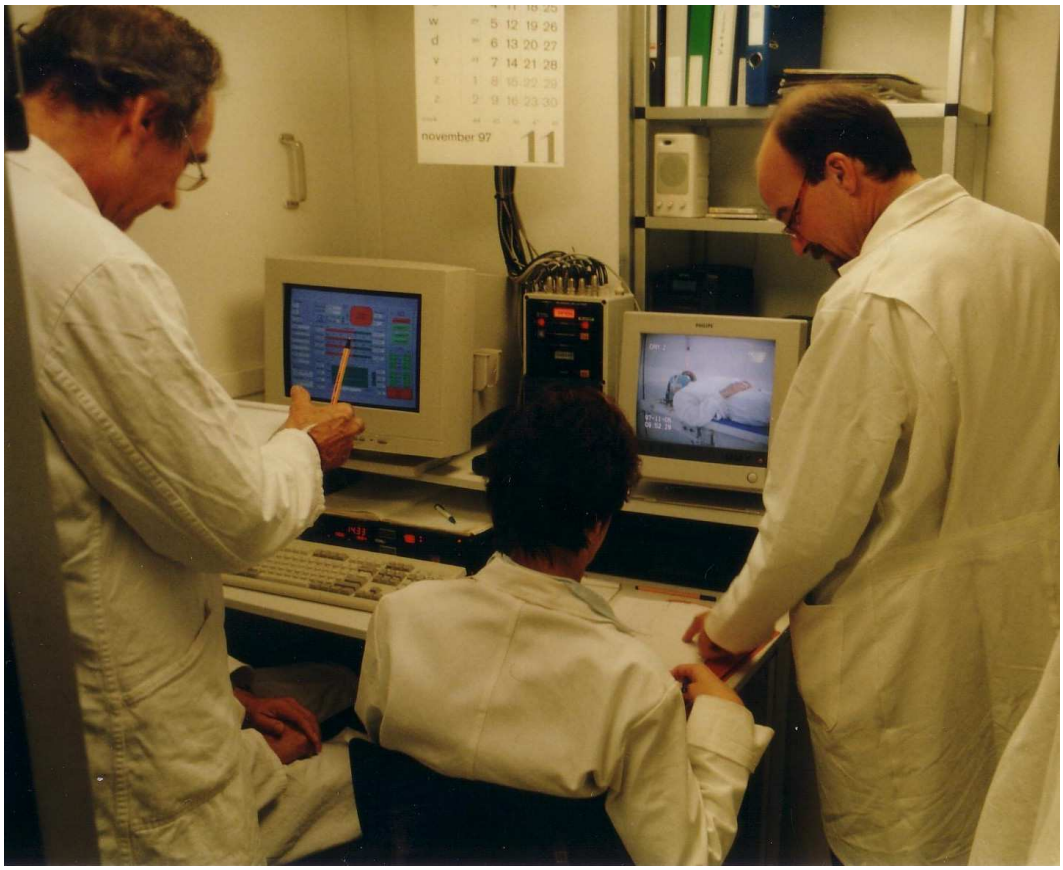


Image 4. Radiation and patient monitoring during neutron exposure

5.7.1.2 Monitor unit computation

The relation between the dose components determined under reference conditions and the monitor reading has been evaluated. It is essential that this relation be checked at least before each patient treatment and also at various other times during a reactor cycle. For the computation of the value of the monitor setting, i.e. the number of monitor units, Mus, for the actual patient irradiation it is therefore necessary to apply a MU-computation program[53-37].

5.7.1.3 Boron-10-blood concentration monitoring

A system has been developed to monitor the ^{10}B-blood concentration [52] of patients receiving BNCT in order to obtain optimal agreement between prescribed and actual boron dose.

As the Li-particle from the $^{10}B(n,\alpha)^{7}Li$ reaction emits a prompt gamma-ray, this photon can be used to determine the reaction rate and thereby the boron concentration. To this purpose, a system for prompt gamma-ray analysis, PGRA, has been developed at a beam tube near to the treatment beam of the High Flux Reactor in Petten. The short data acquisition time (about 5 min) and the ease of sample preparation (injection of 1 ml blood into a standard vial) enable monitoring of the ^{10}B-blood concentration prior to and

after irradiation of patients. By interpolation into the time interval of the irradiation, the mean ^{10}B-blood concentration during patient irradiation, and thereby the actual boron dose, can be determined.

The PGRA system has been extensively used in a healthy tissue tolerance study to measure the ^{10}B-blood concentration of beagle dogs receiving epithermal neutron radiation. The uncertainty in the mean ^{10}B-blood concentration during irradiation, determined from the PGRA measurements, amounted to about 0.3 ppm for the 25 ppm ^{10}B group. By adjusting the start of the irradiation to the individual ^{10}B elimination curves from the PGRA measurements, good agreement (standard deviation: 7% for the 25 ppm group) was obtained between intended and actual ^{10}B-blood concentration during irradiation [27].

The same careful ^{10}B-blood monitoring procedure will also be applied during the actual patient treatment. The procedure includes a protocol for calibration and quality assurance of the PGRA equipment.

6 Results

The study protocol was accepted by EORTC-Protocol Review Committee on 5. August 1996. The protocol have been changed after evaluation on the treatment of the first cohort (10 patients). Several definitions have been stated more precise. The final approval on the amended protocol was obtained on 8 March 1999.

6.1 Patient demographics

The 12 male and 2 female patients had a mean age of 61.2 years (range 51-74) at registration. The tumour histology of glioblastoma multiforme was confirmed after tumour removal by the Study Reference Neuropathology (Prof. Wiestler, Bonn, Germany) in all 14 patients. The actual BSH dose was in average for the first 10 patients 95.59 mg/kg body weight (range 89.7 – 103.9) and 22.93 (20.4 – 27.3) for the last three patients. 1 patient (113) who received only 8.8 mg/kg BSH has been excluded from the evaluation. The basic demographic and BSH administration data are listed in Table 1.

Patient	Gender	Age	Performance status (Karnofsky)	Dose of BSH (mg/kg)
101	M	74	80	103,9
102	M	52	80	101,4
103	M	73	90	100,0

104	M	59	70	98,2
105	M	56	80	90,9
106	F	63	90	95,2
107	F	57	90	89,7
108	M	71	100	92,1
109	M	60	80	94,6
110	M	58	100	89,9
111	M	64	100	20,4
112	M	51	90	21,1
113	M	51	100	8,8
114	M	68	100	27,3

Table 6.1/1 patient demographics and administered BSH

6.2 Boron distribution in tissues

Tumour

The boron content in tumour specimens of individual patients is presented in Table 2.

Pat. N^{o} tissue	101	102	103	104	105	106	107	108	109	110	111*	112*	114*	Average	SD
Blood	48.9	33.7	35.5	28.7	43.01	27.51	29.64	25.08	26.49	40.92	64.37	50.35	27.2	37.03	11,42
Tumour$_{av.}$	34.6	17.74	20.3	17.5	31.57	9.56	7.74	21.50	19.45	12.81	54.00	33.61	28.1	23.73	12,08
SD	7.25		3.37	3.20	7.37	2.10	4.74		6.79		6.71			5.19	-
tumour/ blood	0.71	0.53	0.57	0.61	0.73	0.35	0.26	0.86	0.73	0.31	0.84	0.67	1.03	0.63	-

Table 6.2/1 boron concentration in blood and in the tumour

Boron concentration differences of factors 2 to 4 have characterised the inhomogeneity of the boron uptake in specimens obtained from different parts of the tumour. The inter-patient variability of the tumour boron concentration was higher than the intra-tumour variations. The large SD associated with the averages of all boron concentration

values indicated the high intra- patient variability regarding the boron concentration in the blood and in tumour samples. The tumour:blood ratio at the time point of the tissue sampling, some 12 hours (10-14.25 h) after the BSH infusion, was 0.63 ppm on average and did not exceed unity in all patients, except one.

Boron concentration in normal tissues

Tissue	Average ^{0}B concentration (ppm)	Standard deviation	^{10}B concentration rate (tissue/blood)
blood	37.03	11,4	1.00
skin	45.08	39,51	1.27
muscle	26.14	17,36	0.75
bone	5.57	2,15	0.16
dura	58.52	49,62	1.70
brain	10.33	6,74	0.25
$average_{tumour}$	23.73(±5.19)	12,08	0.63

Table 6.2/2. boron concentration in healthy tissues in the neighbourhood of the tumour

Brain

Boron concentrations in the epitumoural healthy brain tissue varied between 9.4 and 25.04 ppm. In all patients, it was lower than in blood, tumour, and other tissues investigated. On average 4 times higher boron concentration was measured in blood than in the normal brain at the time point of the surgery. However the high SD indicates the uncertainty of the sampling. Whenever the specimen has been dissected from the peritumoural oedema, at the macroscopic margin of the tumour or from larger distances from the tumour tissue, there was large deviation between the boron levels.

Further healthy tissues

There was a clear separation between the boron content of the different healthy tissues. The boron concentration in the cranial bone tissue was consequently very low. The skin and dura samples showed high BSH uptake, however the boron concentration values differed remarkably from patient to patient. At the time point of potential irradiation, the skin and dura to blood boron concentration rates were above 1, i.e. 1.27 and 1.70 respectively. CSF has been collected only from two patients for boron content analysis, but one had to be excluded from the evaluation because of probable blood contamination. Therefore the measured ^{10}B concentration values 30.6 ppm and 2.1 ppm are mentioned only for the sake of totality. Nevertheless the definition of the boron content in the cerebra-spinal fluid is very important, and reliable CSF sampling should be established in further boron uptake studies with different compounds. In the head muscles, ¾ amount of the blood boron concentration was found 14 ± 1 hours after the BSH infusion.

6.3 BNCT at the Petten irradiation facility

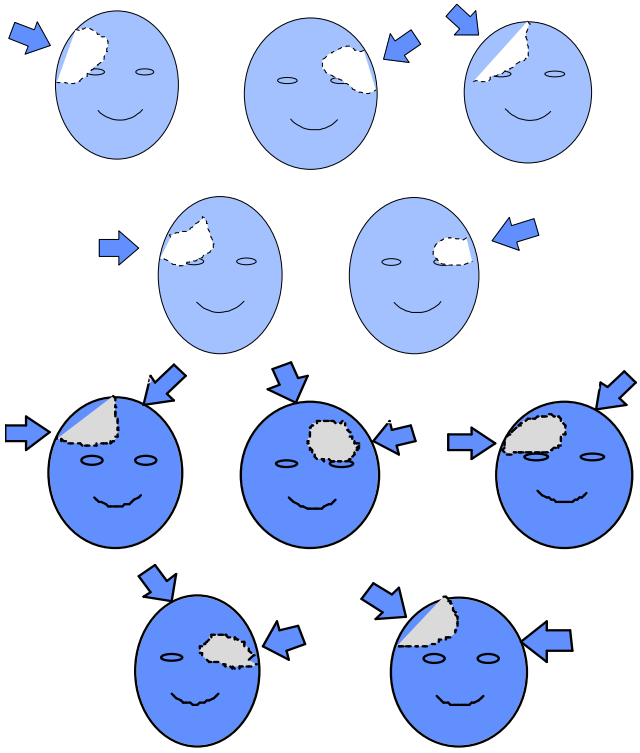
After recovery from surgery the eligible patients were prepared for BNCT. From the 14 patients 3 had partial, 4 subtotal, 7 complete tumour resection. The three patients with a remaining tumor volume larger than 30 % of the initial tumor size had to be excluded. One more patient could not undergo BNCT because of an inter-current infection and prolonged recovery after the surgery.

The first patient cohort (10 patients) has been treated by BNCT at the Petten Irradiation Facility. The preparation for the BNCT planning was started on a strictly defined, uniform way at the Referral Center.
In the Radiotherapy Department a mask with defined landmarks on it was manufactured. Planning CT under fixed conditions was performed with the mask on the patient and the image data have been transferred electronically to Petten. The hard copies have been submitted to Essen. The treating radiotherapist in Essen indicated the target volume and organs at risk on the hard copies, then they were sent to Petten. The planning were performed by the INEEL code. During the planning procedure the medical and the planning teams had intensive communication and much discussions.

The only variable parameter, the orientation of the patient's head to the beam (12 cm of diameter), at 30 cm Wall Skin Distance (WSD), was selected on the basis of the planning target volume localization. A single field was used for the treatment of the first 5 patients. The last 5 patients were irradiated with two beams (12 cm of beam diameter, 30 cm WSD), so that the configuration resulted two separated thermal neutron fluence peaks, one in the PTV in the operated area and one outside of the PTV, in "healthy" brain.

Consequently a larger volume was irradiated in the second five patients but the boron neutron capture absorbed dose, which is defined for a cohort of patients, was the same 8,6 Gy calculated for the whole group of the 10 patients.
The initial tumor localization was reported as: temporal (n=4), temporo-occipital (n=2), temporo-frontal (n=1), occipital (n=1), frontal (n=4), parietal (n=1) and parieto-occipital (n=1)
The average target volume was 135,7 cm^3 (range 29-213 cm^3).

Target volume
Figure 7. shows the scheme of the tumor localization and beam arrangement. The first 5 patients were irradiated with a single beam, the second 5 patients with two tangential beams.
Figure 7.
Scheme of the tumor localization and beam arrangement



The patients traveled by public transport to Amsterdam, where they were hospitalized at the Neurosurgery Ward of the Vrije University during the week of BNCT. BNCT was performed in 4 fractions at the High Flux Reactor Petten. (6-7)

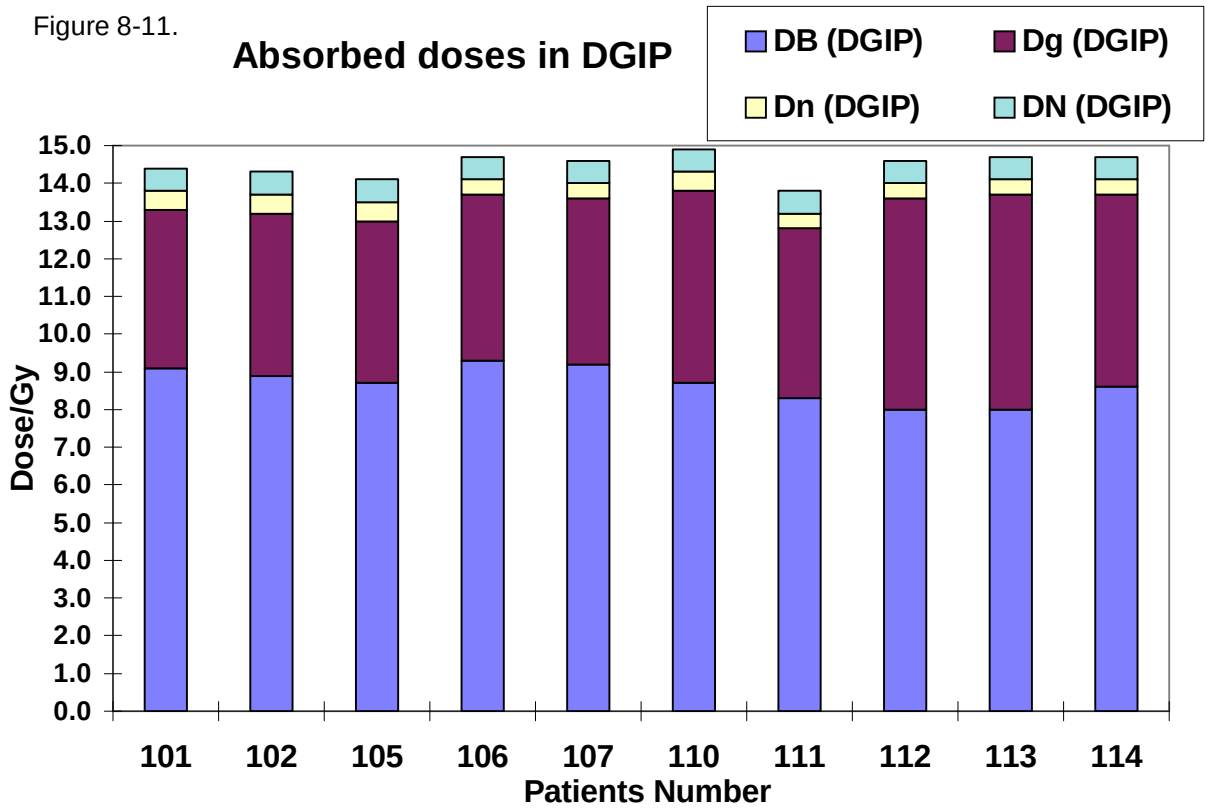
Image 5. patient position and beam for BNCT at HFR

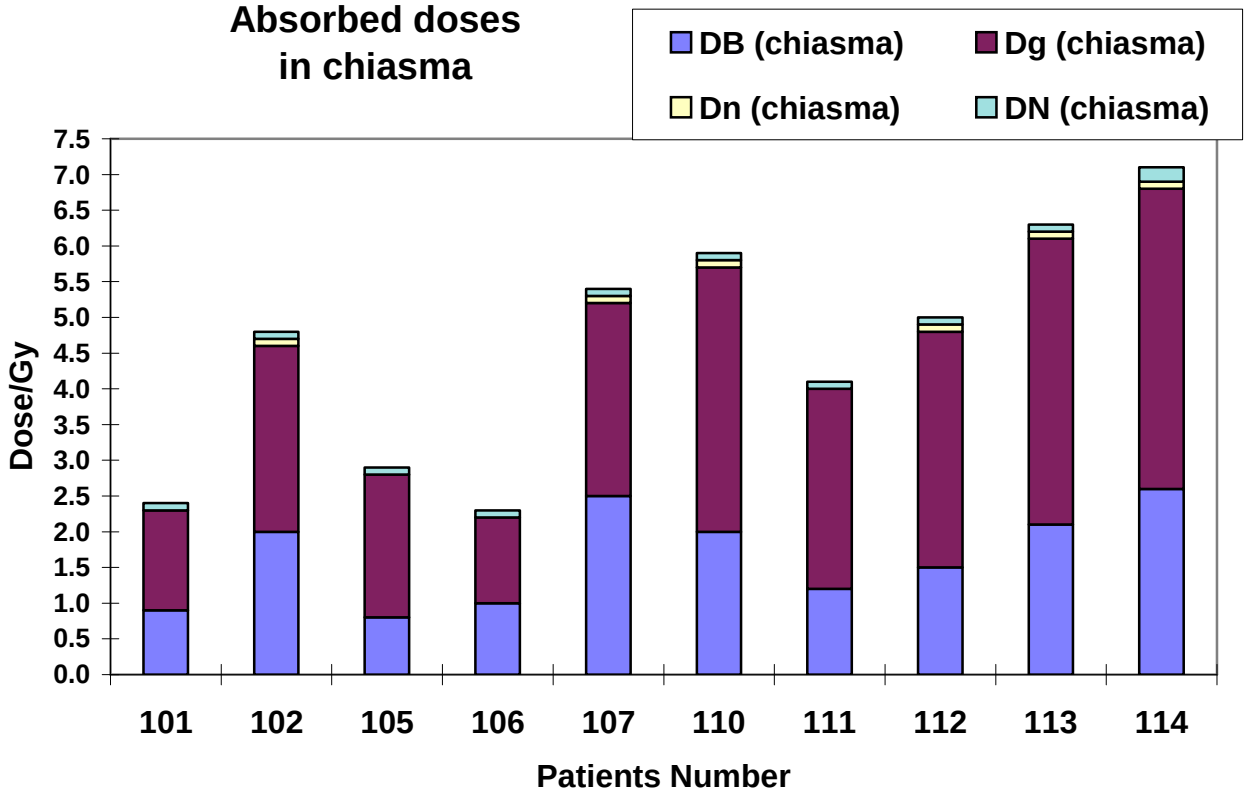
On the day before the day of radiation BSH had been administered i.v. at the speed of 1mg/kg/min. Two parameters were varied, the amount (11 - 100 mg/kg) and the time

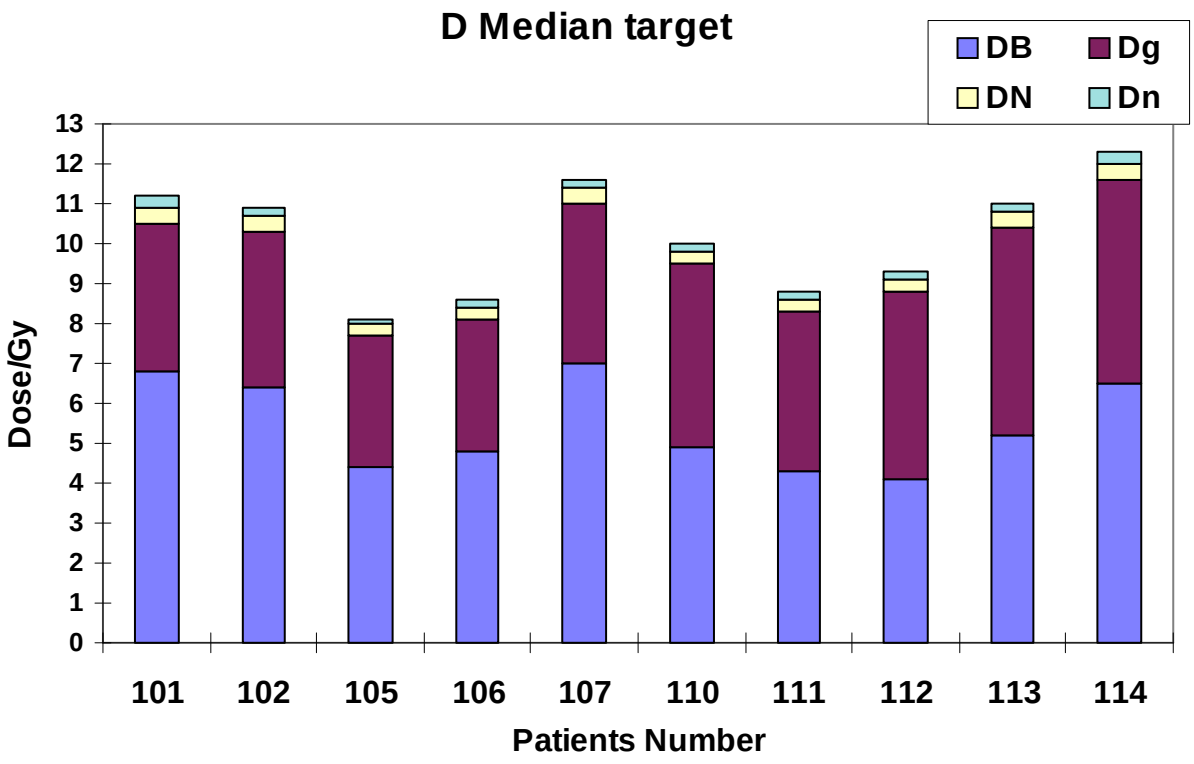
point of administration (10- 25 hours prior to the radiation) in order to achieve an average of 30 ppm ^{10}B concentration in blood over the four fractions. The amount, start of the infusion and duration were prescribed each day after obtaining the actual pharmacokinetic data (from the regularly taken blood samples). In the first cohort of 10 patients an average 30,27 ppm (range 27,3-32,3 ppm) blood boron concentration could be achieved over the four fraction of BNCT. On the basis of the real boron concentration in the blood during the radiation the absorbed doses from the different physical dose components and the weighted dose were calculated and reported in defined points and volumes.

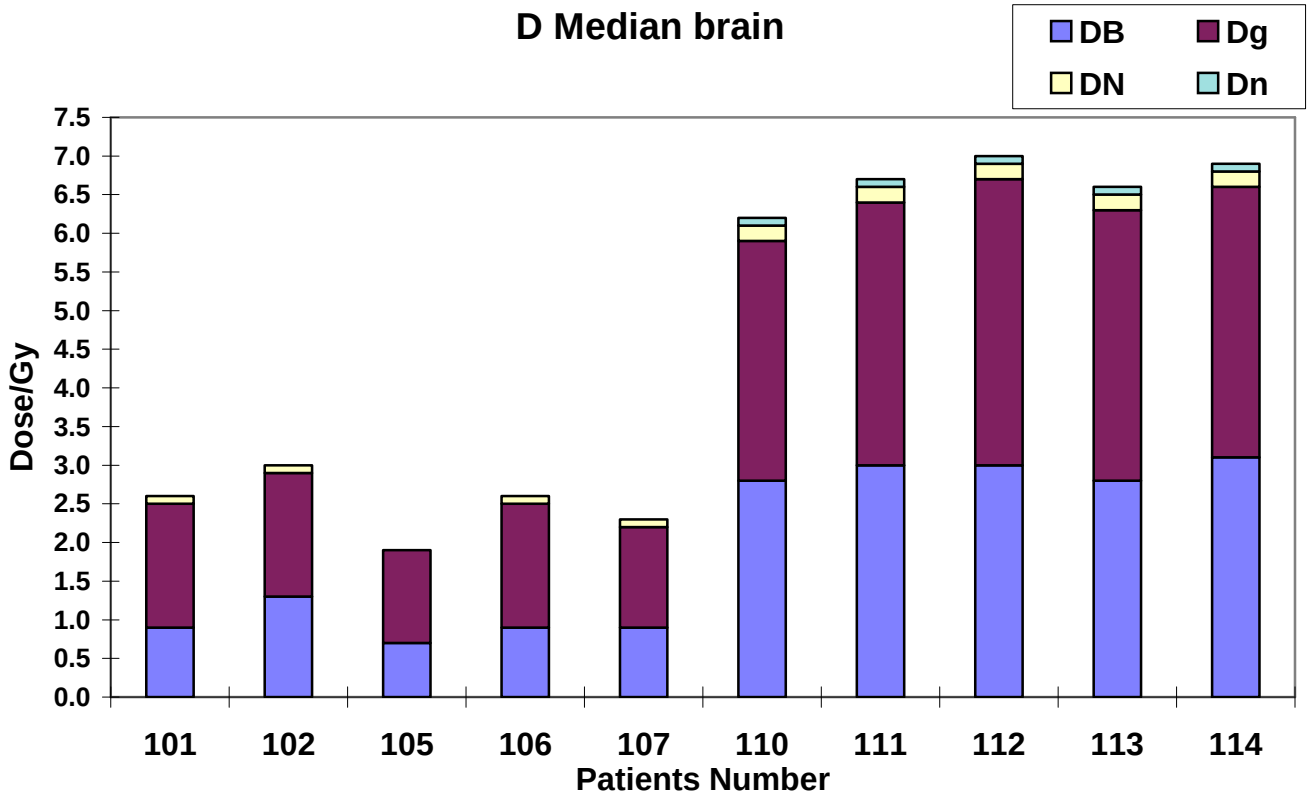
The absorbed doses of the BNCT of the first patient cohort, calculated on the basis of the actual delivered monitor units and measured boron concentration in the blood assuming equal homogeneous boron distribution in the human tissues, are shown in the Figure 2-5. in some of above defined points and volumes as examples. Fig. 2-5

Figure 8-11.




Absorbed doses in chiasma
DB (chiasma)
Dg (chiasma)
Dn (chiasma)
DN (chiasma)
Dose/Gy
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
101
102
105
106
107
110
111
112
113
114
Patients Number


D Median target
DB
Dg
DN
Dn
Dose/Gy
13
12
11
10
9
8
7
6
5
4
3
2
1
0
101
102
105
106
107
110
111
112
113
114
Patients Number



The data described in this PhD thesis have been reported on the CRF by the investigators and have been entered into the study database at NDDO Oncology. The data are quality controlled: data as reported on the CRFs by all investigators have been verified against the source documentation during monitoring visits to the centres. The tumour response data have been taken directly from the reports from the reference radiologists

The prescribed D_B at the DGIP in the group of the first ten patients could be achieved, for the other dose components a limiting maximum at the DGIP has not been exceeded:

Patient No	101	102	105	106	107	110	111	112	113	114
D_B (DGIP)	9.1	8.9	8.7	9.3	9.2	8.7	8.3	8.0	8.0	8.6
D_g (DGIP)	4.2	4.3	4.3	4.4	4.4	5.1	4.5	5.6	5.7	5.1
D_n (DGIP)	0.5	0.5	0.5	0.4	0.4	0.5	0.4	0.4	0.4	0.4
D_N (DGIP)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
D_T (DGIP)	14.4	14.3	14.1	14.7	14.6	14.9	13.8	14.6	14.7	14.7
D_{WU} (DGIP)	11.6	11.8	11.6	11.7	11.7	12.4	11.3	12.3	12.4	12.1

Table 6. 3./ 1: Doses at the dose group identification point of the 10 treated patients.

BNCT has been performed according to the protocol, the planned 30 ppm average blood boron concentration over the four fraction of the irradiation could be approximated.

6.4 Toxicity due to BNCT radiation

6.4.1.1 Hematological Toxicity

During early follow-up

During the early follow-up post-BNCT patients 110 and 112 experienced new occurrence of leucopenia (grade 1) which was considered respectively possibly and probably related to BNCT. Shortly after BNCT patient 111 experienced leucopenia (grade 2) considered unlikely related to treatment.

During the follow-up (visit 1-4) of patient 110 lymphopenia (increase of severity to a grade 2) is considered possibly related to BSH/BNCT.

6.4.1.2 Skin Toxicity

The skin doses were reported at the point along the beam axis of both beam entrance and exit site and at two edge points at the beam entrance site. The first 5 patients were treated by single field at the operated (previous tumor) site, therefore the skin doses were reported at 4 points: at beam entrance (middle of the field), at two points at the beam edge at the entrance site and at beam exit (middle of the field). The second 5 patient of the cohort were treated from two beams. In that cases the skin doses were reported at the above-described points of both beam, altogether at 8 points. In the followings the skin doses of the 10 treated patient at all points are summarized in the table 4.6.4.2/1. In the case of an adverse event which was related at least possibly to BNCT the highest doses among all 4 or 8 points are given.

Skin	D_B	D_g	D_N	D_n	D_T	D_{WU}
Max	4.1	4.2	0.5	1.0	9.7	13.1
Min	0.0	0.5	0.0	0.0	0.7	0.7
Mean	1.7	2.1	0.2	0.4	4.3	5.7

Table: 6.4.1.2./1: Skin doses of the 10 treated patients at the beam axis and four (upper, lower, 2 lateral) edge points corresponding of both beam entrance and exit site.

During early follow-up

During BNCT treatment patient 107 had erythema and slight swelling of the left part of the face (CTC 2/RTOG 2) considered possibly related to BSH/BNCT. As the swelling occurred also outside the radiation field, the Study Centre Essen considers this event as a probable side effect of the corticosteroid treatment.

Patient 107	D_B	D_g	D_N	D_n	D_T	D_{WU}
Skin beam entrance	3.9	3.3	0.4	0.9	8.6	11.8

Table: 6.4.1.2/2: Skin doses of patient 107 at the beam entrance point.

Patient 110 experienced erythema of the skin at the radiation area (CTC 1/RTOG 1) definitely related to BSH/BNCT. During follow-up visit 1-4 the patient 110 has mild pruritus of the ear (RTOG 1) possibly related to BSH/BNCT.

Patient 110	D_B	D_g	D_N	D_n	D_T	D_{WU}
Skin beam entrance	3.1	3.5	0.4	0.9	7.8	10.9

Table: 6.4.1.2/3: Skin doses of patient 110 at the beam entrance point.

During follow-up after BNCT patient 112 experienced erythema (CTC 1/RTOG 1) definitely related to BNCT.

Patient 112	DB	Dg	DN	Dn	DT	DWU
Skin beam entrance	4.1	4.2	0.5	0.9	9.7	13.1

Table: 6.4.1.2/4: Skin doses of patient 112 at the beam entrance point.

Patient 102 experienced erythema while receiving BNCT treatment, however the erythema was considered unlikely related to BSH/BNCT.

The three grade 1 acute events in two patients (110 and 112), which are considered BNCT related by the Study Centre Essen showed no correlation either with any of the dose components nor with the total or weighted dose.

During late follow-up

Patient 105 experienced slight atrophy of the skin (RTOG 1/SOMA 1) considered probably related to BNCT.

Patient 105	D_B	D_g	D_N	D_n	D_T	D_{WU}
Skin beam entrance	3.0	2.8	0.4	0.7	6.9	9.5

Table: 6.4.1.2/5: Skin doses of patient 105 at the beam entrance point.

At visit 6 patient 110 had pigmentation changes (of the irradiation site) and atrophy of the skin (RTOG 1/SOMA 1). Both events were considered probably related to BNCT and resolved before visit 7.

Patient 110	D_B	D_g	D_N	D_n	D_T	D_{WU}
Skin beam entrance	3.1	3.5	0.4	0.9	7.8	10.9

Table: 6.4.1.2/6: Skin doses of patient 110 at the beam entrance point.

The two grade 1 late events in two patients (105 and 110), which are considered BNCT related by the Study Centre Essen showed no correlation either with any of the dose components nor with the total or weighted dose.

6.4.1.3 Alopecia

In nine out of ten patients alopecia was observed. The alopecia started in general during the early follow-up (visit 4-6). For patient 107 no alopecia was observed, this may however be due to the short follow-up of this patient (up to visit 5). In four patients the alopecia has resolved during subsequent follow-up (in patients 101, 105, 111 and 113 the alopecia resolved at visit 7, 7, 9 and 6). The alopecia was always considered at least probably related to BNCT.

Skin doses at beam entrance	D_B	D_g	D_N	D_n	D_T	D_{WU}
Patient 101	3.3	3.0	0.4	0.9	7.6	11.3
Patient 102	3.2	2.6	0.4	0.6	6.7	8.9
Patient 105	3.0	2.8	0.4	0.7	6.9	9.5
Patient 106	3.7	3.1	0.4	1.0	8.2	11.4
Patient 107	3.9	3.3	0.4	0.9	8.6	11.8
Patient 110	3.1	3.5	0.4	0.9	7.8	10.9
Patient 111	3.9	3.2	0.5	0.8	8.4	11.5
Patient 112	4.1	4.2	0.5	0.9	9.7	13.1
Patient 113	3.0	3.8	0.4	0.9	8.2	11.3
Patient 114	3.4	3.3	0.4	0.9	8.0	11.1

Table 6.4.1.3/1: Skin doses to all patients.

Average doses at the skin	D_B	D_g	D_N	D_n	D_T	D_{WU}
For patients with no or resolved alopecia	3.42	3.2	0.42	0.84	7.94	11.08
For patients with irreversible alopecia	3.5	3.34	0.42	0.86	8.08	11.08

Table 6.4.1.3/2: average skin doses in two groups (5 vs. 5 patients), one group with irreversible alopecia and one with no or resolved alopecia.

The occurrence and reversibility of the alopecia showed no correlation either with any of the dose components nor with the total or weighted dose.

6.4.1.4 Toxicity to the eyes/visual system

The doses were reported at the points in the middle of both eyes and at the point represents the chiasma opticum. In the case of an adverse event which was related at least possibly to BNCT the doses of the concerned eye are given. If a change has been observed on both eye equally, the relationship with the BNCT is doubtful, due to the different radiation doses at the two sides, except vision deterioration maybe in correlation of the doses at the chiasma.

Eye	D_B	D_g	D_N	D_n	D_T	D_{WU}
Max	3.7	2.5	0.4	0.3	6.9	8.1

Min	0.0	0.2	0.0	0.0	0.2	0.2
Mean	0.7	1.0	0.1	0.03	1.8	2.0

Table 6.4.1.4/1: Eye (both) doses of the 10 treated patients.

Optic chiasm	D_B	D_g	D_N	D_n	D_T	D_{WU}
Max	2.6	4.2	0.2	0.1	7.0	7.3
Min	0.8	1.2	0.1	0.0	2.3	2.4
Mean	1.7	2.8	0.1	0.1	4.6	4.8

Table: 6.4.1.4/2: Doses at the chiasma opticum of the 10 treated patients.

During early follow-up

During follow-up visit 1-4 patient 110 experienced decreased lacrimation (CTC 2/RTOG 2, and grade 1 at visit 5), respectively possibly and probably related to BNCT.
No representative point was defined for the glandula lacrimalis, but this observation warns to pay attention on secreting glands as organs of risk.

Patient 106 experiences a decrease in visual acuity (to a grade 3) unlikely related to BNCT.

Patient 112 experienced a decrease in vision right after the patient was re-operated for the recurrent GBM.

Patient 112	D_B	D_g	D_N	D_n	D_T	D_{WU}
Right eye	0.5	0.9	0.0	0.0	1.5	1.6

Table: 6.4.1.4/5: Right eye doses of patient 112.

During late follow-up

For patient 105 lens opacity (grade 1) and blurred vision (SOMA 2) were reported at visit 8 and were considered possibly related to BNCT. In this patient the left eye was outside the irradiated area.

Patient 105	D_B	D_g	D_N	D_n	D_T	D_{WU}
Right eye	1.5	1.5	0.2	0.0	3.2	3.7

Table: 6.4.1.4/6: Doses at the right eye of patient 105.

At visit 7 patient 113 had blurred vision (CTC 1/SOMA 2) possibly related to BNCT. In this patient the right eye was outside the irradiated area.

Patient 113	D_B	D_g	D_N	D_n	D_T	D_{WU}
Left eye	1.9	1.7	0.2	0.1	3.9	4.6

Table: 6.4.1.4/7: Doses at the left eye of patient 113.

6.4.1.5 ENT, oral mucosa and salivary gland toxicity

The doses were reported at the points of both inner ears and at the points in the middle of parotis at both sides. In the case of an adverse event which was related at least possibly to BNCT the doses of the concerned ear or salivary gland are given.
If a change has been observed on both ears equally, the relationship with the BNCT is doubtful, due to the different radiation doses at the two sides.

Ear	D_B	D_g	D_N	D_n	D_T	D_{WU}
Max	4.9	3.7	0.6	0.2	8.9	10.1
Min	0.0	0.8	0.0	0.0	1.1	1.1
Mean	1.7	2.2	0.2	0.05	4.1	4.5

Table 6.4.1.5/1: Ears (both) doses of the 10 treated patients.

Salivary gland	D_B	D_g	D_N	D_n	D_T	D_{WU}
Max	1.9	2.1	0.1	0.1	4.0	4.3
Min	0.0	0.2	0.0	0.0	0.2	0.2
Mean	0.5	0.9	0.03	0.01	1.4	1.5

Table 6.4.1.5/2: Salivary glands (both) doses of the 10 treated patients.

During early follow-up

During follow-up visit 1-4 for patient 112 tinnitus was reported (CTC 2/RTOG 3) and was considered possibly related to BNCT.

Patient 112	D_B	D_g	D_N	D_n	D_T	D_{WU}
Right ear	2.7	3.6	0.3	0.0	6.7	7.4

Table 6.4.1.5/3: Right ear doses of patient 112.

During the first 4 weeks post BNCT (visit 1-4) taste change in patient 102 (CTC 1/RTOG 1), 105 (CTC 2 /RTOG 2) and 110 (CTC 1/RTOG 1) is considered possibly related to BSH/BNCT, while in patient 112 the taste change (CTC 1/RTOG 1) is probably related to BNCT.

During the first 4 weeks post BNCT (visit 1-4) both patient 105 and patient 112 experienced a mild dry mouth (RTOG 1) considered probably related to BNCT.

Patient 105	D_B	D_g	D_N	D_n	D_T	D_{WU}
Left salivary gland	0.0	0.9	0.0	0.0	0.9	0.9

Table 6.4.1.5/4: Left salivary gland doses of patient 105.

Patient 112	D_B	D_g	D_N	D_n	D_T	D_{WU}
Right salivary gland	1.4	1.9	0.0	0.0	3.3	3.4

Table 6.4.1.5/5: Right salivary gland doses of patient 112.

During late follow-up

At visit 8 patient 105 had a hearing loss grade 1 of the left ear considered possibly related to BNCT. In view of the radiation doses given to the right and the left ear. Study Centre Essen considers a relationship unlikely.

Patient 105	D_B	D_g	D_N	D_n	D_T	D_{WU}
Right ear	1.0	1.1	0.1	0.0	2.2	2.4
Left ear	0.0	1.0	0.0	0.0	1.1	1.1

Table 6.4.1.5/6: Doses of both ears of patient 105.

Patient 101 had a slight deterioration (right, high tone) on the tone audiometry as well as an increase in hearing loss right (from 10 to 20 db) on speech audiometry at visit 8. The investigator considers this a result of patient's ageing and did not relate it to BNCT treatment.

The bad taste in patient 114 (visit 8) was considered to be not related to BNCT.

At visit 7 for patient 105 a slight atrophy of oral mucosa (RTOG 1/SOMA 1) was specifically reported. The event was considered probably related to BNCT.

6.4.1.6 Abnormalities in hormone levels

Changes in hormone levels were detected at the end of the early follow-up/beginning of late follow-up.

Pituitary gland	D_B	D_g	D_N	D_n	D_T	D_{WU}
Max	2.4	4.1	0.1	0.1	6.6	6.8
Min	0.7	1.3	0.0	0.0	2.4	2.4
Mean	1.5	2.7	0.1	0.1	4.4	4.6

Table 6.4.1.6/1: Doses at the pituitary gland of the 10 treated patients.

For patient 105 a mild decrease in HGH is considered probably related to BNCT (visit 5). A mild HGH decrease in patient 112 was not thought to be related to BNCT (visit 7).

Patient 105	D_B	D_g	D_N	D_n	D_T	D_{WU}
Pituitary gland	0.7	1.9	0.0	0.0	2.7	2.8

Table 6.4.1.6/2: Doses at the pituitary gland of patient 105.

For patient 106 severe decreases in FSH and LH levels are considered possibly related to BNCT (visit 6).

Patient 106	D_B	D_g	D_N	D_n	D_T	D_{WU}
Pituitary gland	1.0	1.3	0.0	0.0	2.4	2.4

Table 6.4.1.6/3: Doses at the pituitary gland of patient 106.

For patient 101 and 105 (for doses of patient 105 see table 4.6.3.6/2) a mild increase in FSH is considered possibly related to BNCT (visit 5).

Patient 101	D_B	D_g	D_N	D_n	D_T	D_{WU}
Pituitary gland	0.9	1.6	0.0	0.0	2.6	2.7

Table 6.4.1.6/4: Doses at the pituitary gland of patient 101.

Patient 114 experienced increased FSH, which was considered unrelated to BNCT (visit 7).

Patient 114	D_B	D_g	D_N	D_n	D_T	D_{WU}
Pituitary gland	2.2	4.1	0.1	0.0	6.6	6.8

Table 6.4.1.6/5: Doses at the pituitary gland of patient 114.

For patient 105 (for doses of patient 105 see table 4.6.3.6/2) and 112 a mild increase of LH is possibly related to BNCT (visit 5).

Patient 112	D_B	D_{WU}	D_g	D_N	D_n	D_T
Pituitary gland	1.4	5.0	3.3	0.1	0.0	4.9

Table 6.4.1.6/6: Doses at the pituitary gland of patient 112.

The increase of LH in patient 114 was considered unrelated to BNCT (visit 7).

Except one case (patient 106 with severe decreases in FSH and LH levels) the hormonal changes were mild increases or decreases, which could be influenced by many factors. No consequent tendency could be observed and no dose-effect relationship was observed. Further observations are needed.

Neurological Toxicity

	D_B max	D_B min	D_g max	D_g min	D_N max	D_N min	D_n max	D_n min	D_T max	D_T min	D_{WU} max	D_{WU} min
Brain D_{max}	9.2	7.7	5.9	3.8	0.6	0.5	1.0	0.6	15.0	12.3	13.0	10.2
Brain D_{min}	0.3	0.0	0.8	0.2	0.0	0.0	0.0	0.0	1.4	0.2	1.2	0.2
Brain D_{median}	3.1	0.7	3.7	1.2	0.2	0.0	0.1	0.0	7.1	1.8	6.2	1.7
Brain $D_{average}$	3.4	1.1	3.6	1.3	0.2	0.1	0.2	0.0	7.3	2.5	6.4	2.2
Brain D_{modal}	1.3	0.4	4.3	0.6	0.1	0.0	0.1	0.0	8.0	0.7	6.7	0.6

Table 6.4.1.7/1: Summary on volume doses of the brain without the target volume of the 10 treated patients.

During early follow-up

At follow-up visit 1-4 patients 110 and 112 experienced behavioral changes (CTC 1) possibly related to BNCT. At visit 6 patient 110 had a personality change (CTC 1/RTOG 1/SOMA 1) possibly related to BNCT.

Patient 112 experienced paresthesia of the right hand (CTC 1/RTOG 1, possibly related to BNCT) during follow-up visit 1-4.

Brain patient 110	D_B	D_g	D_N	D_n	D_T	D_{WU}
D_{max}	8.8	5.5	0.6	0.8	15.0	12.5
D_{min}	0.0	0.4	0.0	0.0	0.6	0.5
D_{median}	2.8	3.1	0.2	0.0	6.2	5.3
$D_{average}$	3.1	3.0	0.2	0.1	6.5	5.5
D_{modal}	1.3	4.3	0.0	0.0	2.2	1.9

Table 6.4.1.7/2: Doses of the brain without the target volume of patient 110.

Brain patient 112	D_B	D_g	D_N	D_n	D_T	D_{WU}
D_{max}	8.2	5.8	0.6	0.9	14.8	13.0
D_{min}	0.3	0.8	0.0	0.0	1.4	1.2
D_{median}	3.0	3.7	0.2	0.1	7.1	6.2
$D_{average}$	3.3	3.6	0.2	0.2	7.3	6.4
D_{modal}	1.2	4.2	0.0	0.0	5.1	4.3

Table 6.4.1.7/3: Doses of the brain without the target volume of patient 112.

Patient 107 is hospitalised for a psychosis (SAE # 6, CTC 3/RTOG 3) unlikely related to BNCT (visit 1-4). The patient also has aggressive tendencies, which are considered unlikely related to BNCT

In patient 111 occipital pain (CTC 1) is possible related to BNCT (visit 2).

Brain patient 111	D_B	D_g	D_N	D_n	D_T	D_{WU}
D_{max}	8.3	5.6	0.6	0.9	14.2	11.9
D_{min}	0.2	0.8	0.0	0.0	1.3	1.1
D_{median}	3.0	3.4	0.2	0.1	6.7	5.9
$D_{average}$	3.4	3.4	0.2	0.2	7.1	6.2
D_{modal}	1.2	3.8	0.0	0.0	4.8	4.0

Table 6.4.1.7/4: Doses of the brain without the target volume of patient 111

Three patients experienced headache starting during the first 4 weeks post BNCT (visit 1-4). The event was thought to be possibly related to BNCT: patient 112 (CTC 3/RTOG 3/SOMA 3) (see table 4.6.3.7/3), patient 113 (CTC 1) and patient 114 (CTC 1).

Brain patient 113	D_B	D_g	D_N	D_n	D_T	D_{WU}
D_{max}	8.3	5.9	0.6	0.8	15.0	13.0

D_{min}	0.1	0.5	0.0	0.0	0.7	0.7
D_{median}	2.8	3.5	0.2	0.1	6.6	5.8
$D_{average}$	3.2	3.4	0.2	0.2	6.9	6.0
D_{modal}	1.2	4.3	0.0	0.0	3.6	4.4

Table 6.4.1.7/5: Doses of the brain without the target volume of patient 113

Brain patient 114	D_B	D_g	D_N	D_n	D_T	D_{WU}
D_{max}	8.7	5.5	0.6	1.0	15.0	12.9
D_{min}	0.1	0.6	0.0	0.0	0.7	0.7
D_{median}	3.1	3.5	0.2	0.1	7.0	6.1
$D_{average}$	3.3	3.3	0.2	0.2	7.0	6.0
D_{modal}	1.3	4.3	0.0	0.0	8.0	6.7

Table 6.4.1.7/6: Doses of the brain without the target volume of patient 114

The headache in patients 104 (increase in severity of pre-existing headache after surgery), 105 (between visit 7-8), 110 (between visit 5-6) and 111 (visit 5) was considered not or unlikely related to BSH or BNCT.

For patient 113 slight incoordination (dys-coordination) was reported (CTC 1/RTOG 1, possibly related to BNCT), which started at visit 5 and had resolved at visit 7.

At recurrence, the GBM often creates similar symptoms, like headache, neurological symptoms, behavioural changes, to the toxicity that is expected due to the irradiation of the brain. Therefore the investigators in quite a large number of neurological adverse events could not distinguish regarding the causality of the symptoms whether they developed due to the growing tumour or due to the BNCT treatment. Although in the majority of the cases the tumour could be the cause of the symptoms, in these cases often a relationship with BNCT could not be ruled out and a relationship 'possibly' was given. However during the evaluation no dose-neurological effect relationship was observed.

During late follow-up

One serious adverse event was interpreted as possibly BNCT related toxicity. In this specific case BNCT was given in November 1997 in four fractions with no evidence of any adverse event. After surgery the patient had discrete motor speech disturbance, which became slowly progressive from March 1998 onwards caused by a recurrent tumour, which had been confirmed by MRI.
An acute right facial nerve palsy associated with distal paresis of the right arm developed in May 1998. These symptoms were related to a progressive infarction in the perfusion territory of the thalamostriate arteries originating from the middle cerebral artery. At that time the tumour was progressing. Further MRI' s demonstrated tumour progression and an increase of the infarction size. Following a period of worsening neurological symptoms the patient died in December 1998 due to tumour progression. A clear attribution of the symptoms mentioned above either due to the tumour or infarction could not be made. Furthermore the infarction itself may be due to the progressive tumour or due to radiation induced vascular damage to the wall of the thalamostriata arteries.

The doses at the area of arteria thalamostriata were calculated retrospectively in three more patients (101, 112 and 114), who were assumed (on the basis of the beam

geometry) to have received relevant doses at these points. All the boron, total and the weighted dose at points representing the arteria thalamostriata were lower for patient 102 than for patient 112 and 114. In addition a larger volume was irradiated for patients 110 –114.

The observed infarction can not be explained by the applied doses in view of the doses the other patients received at that area. The patient had at the same time and at the same area tumour progression, the causal correlation of a blood vessel occlusion should not be completely excluded. Secondly, the dose calculation based on the measured blood boron concentration assumes a homogenous boron distribution in the different tissues. A selective accumulation in special tissues or concentration in special blood vessels and differential individual cellular, subcellular biodistribution may have occurred, resulting in much higher dose in reality, than the calculated values. On the basis of one singular individual event possibly related to BNCT it would be too early to draw far-reaching conclusions.

	D_B (Gy)	D_g (Gy)	D_N (Gy)	D_n (Gy)	D_T (Gy)	D_{WU} (Gy)
Point 1	2.6	2.9	0.2	0.1	5.8	4.8
Point 2	3.1	2.9	0.2	0.1	6.2	5.1
Point 3	3.6	3.3	0.2	0.1	7.2	5.9
Point 4	3.7	3.2	0.2	0.1	7.3	5.9
Point 5	3.5	3.2	0.2	0.1	7.0	5.7
Point 6	3.1	3.0	0.2	0.1	6.4	5.2

Table 6.4.1.8/1: Doses of patient 102 at the points representing the arteria thalamostriata.

Patient	101	102	112	114
Slice considered (table position on CT)	-132	-70	-648	-70
Boron conc. [ppm]	32.2	30.6	27.9	30.2
Boron dose [Gy]	1.8 - 2.7	2.6 - 3.7	3.2 - 4.0	4.3 - 5.2
Total dose [Gy]	4.3 - 5.8	5.8 - 7.3	8.4 - 9.0	9.6 - 10.3
Weighted dose [WU]	3.5 - 4.6	4.8 - 5.9	6.2 - 7.4	7.8 - 9.1

Table 6.4.1.8/2: Range of doses at the 6 points representing the arteria thalamostriata in 4 patients.

Patient 113 has mild dysphasia (RTOG 1). He also had it immediately after surgery, but then it resolved very quickly. Now a possible relation to BNCT is given. The dysphasia resolved at visit 7.

Patient 102 also experienced dysphasia (SAE # 8) (CTC 2/SOMA 3), which is unlikely related to BNCT (probably related to tumour). At the last visit performed (visit 12) the dysphasia is RTOG 3/SOMA 3.

In patient 105 a minor intellectual deficit (RTOG 1/SOMA 1) (visit 8) and dizziness (grade 1) (between visit 8-9) are considered possibly related to BNCT

6.4.1.7 Other toxicity

During early follow-up

Patient 102: Investigator considers constipation possibly related to BNCT (visit 1-4). Study Centre Essen considers constipation unlikely related to BNCT.
Patient 107: Experiences a moderate swelling of the neck, shoulders and throat (investigator suggested a lymphatic cause) for which the investigator had no explanation and was therefore considered possibly related to BNCT (visit 1-4). As the neck, shoulders and their lymphatic region were outside the radiated area a relationship to BNCT Study Centre Essen considers a relationship unlikely.

Patient 110: Fatigue (CTC 1) for two days during BNCT treatment is possibly related to BSH/BNCT. At visit 1-4 investigator considers malaise (CTC 3) possibly related to BNCT for patient 113.

Further increase of already increased SGPT (grade 2) in patient 102 and an increase in bilirubin (grade 2) in patient 112 at visit 5 are possibly related to BNCT. Study Centre Essen considers a relationship unlikely.

During late follow-up

No other toxicity due to BNCT was reported.

6.5 Efficacy and doses in the target volume

6.5.1 Point and volume doses relevant to the target volume

The planning target volume (PTV) was taken approximately as the gross tumour volume (for BNCT it is -if not otherwise specified- the contrast-enhancing volume on presurgical contrast-enhanced MRI) plus a 2 cm thick shell enclosing it. The Study Radiotherapist in charge for treatment defined the PTV.

Patient No	101	102	105	106	107	110	111	112	113	114
D_B (presc.point)	7.5	6.8	4.8	5.3	7.9	5.1	5.1	4.8	5.4	7.8
D_g (presc.point)	4.1	4.2	3.7	3.7	4.2	4.8	4.3	5.2	5.5	5.6
D_n (presc.point)	0.2	0.2	0.1	0.1	0.3	0.2	0.2	0.2	0.2	0.3
D_N (presc.point)	0.5	0.4	0.3	0.3	0.5	0.3	0.3	0.3	0.4	0.5
D_T (presc.point)	12.3	11.6	8.9	9.4	12.9	10.4	9.9	10.5	11.5	14.2
D_{WU} (presc.point)	9.4	9.2	7.2	7.4	9.9	8.7	8.2	8.9	9.6	11.4

Table 6.5.1/1: Doses at the point defined as the geometrical middle of the target volume called prescription point.

	D_B max	D_B min	D_g max	D_g Min	D_N max	D_N min	D_n max	D_n min	D_T max	D_T min	D_{WU} max	D_{WU} min
Target D_{max}	9.4	8.0	5.9	4.4	0.6	0.6	0.9	0.4	15.3	13.8	13.0	11.4
Target D_{min}	4.1	1.0	3.8	1.6	0.3	0.1	0.1	0.0	8.8	2.7	7.4	2.4
Target D_{median}	7.0	4.1	5.2	3.3	0.4	0.3	0.3	0.1	12.2	8.2	10.2	6.7
Target $D_{average}$	7.0	4.3	5.1	3.4	0.4	0.3	0.3	0.2	12.3	8.5	10.3	7.0
Target D_{modal}	7.7	2.9	5.4	3.2	0.5	0.2	0.2	0.1	12.4	6.3	10.3	5.2

Table 6.5.1/2: The range of the doses in the first ten patients from the different dose components in the target volume.

6.5.2 Tumour response

Patients are evaluable for therapy-related antitumour activity after receiving at least one treatment with BNCT. Disease measurements from patient`s MRIs were performed by two radiologist (prof.dr. Zanella/dr. Turowski) of the Neuroradiology Centre. Responses were classified according to 2 scales (see paragraph 3.3). First according to the scale of MacDonald, applying the standard criteria for tumour responses. Moreover, the tumour measurements were graded according to straightforward criteria of Zanella (increasing: any increase in tumour volume, decreasing: any decrease in tumour volume).
The data in table 6.5.2/1 have been taken directly from the reports of the reference radiologists.
Progression was observed at the same date for evaluations according to both scales in all except one patient (patient 113). Of the 10 patients treated with BNCT there were at least 8 patients who's tumour remained temporarily stable following BNCT treatment (Table 6.5.2/1). The best response for patient 111 was PD and the best response for patient 113 was PD or SD, depending on the scale used (see table 6.5.2/1). No PRs or CRs were observed in patients who had remaining tumour following the GBM surgery.

Patient #	Measurements remaining tumor post-surgery	Date last BNCT	Best response after BNCT (MacDonald)	Best response after BNCT (Zanella)	Date tumor progression
101	Complete resection.	30/10/1997	SD	SD	16/03/1998
102	Considered a complete resection after surgery. Later, retrospectively, a tumour rest behind the resected area is observed on the MRI performed post-surgery.	07/11/1997	SD	SD	05/05/1998
105	Complete resection.	19/12/1997	SD	SD	19/06/1998[1]

106	>70% removed.	16/01/1998	SD	SD	09/03/1998
107	Complete resection.	23/01/1998	SD	SD	14/04/1998
110	Complete resection.	01/05/1998	SD	SD	10/07/1998
111	>70% removed.	08/05/1998	PD	PD	13/05/1998
112	>70% removed.	06/06/1998	SD	SD	07/08/1998
113	>70% removed.	26/06/1998	SD	PD	31/08/1998[2]
114	Complete resection.	21/08/1998	SD	SD	02/11/1998

Table 6.5.2/1: Tumor responses and tumor progression date after BNCT according to reference radiologist.

[1]On the MRI of 30/04/1998 the reference radiologist already suspects PD. [2]PD according to Zanella scale on 31/08/1998 and on 19/11/1998 according to the MacDonald scale.

6.5.3 Survival

Survival is calculated from the date the patient was operated for resection of the GBM, as well as from the last date of BNCT treatment (Table 6.5.3/1). For the 4 patients not treated with BNCT (ineligible for the second stage of the study) survival data have also been collected (Table 6.5.3/2).

Patient #	Survival after first surgery for GBM		Survival after the last day of BNCT treatment	
	days	months[3]	days	months[3]
101	343	11.3	313	10.3
102	442	14.5	414	13.6
105	343	11.3	321	10.6
106	209	6.9	165	5.4
107	194	6.4	159	5.2
110	234	7.7	210	6.9
111	327	10.8	304	10.0
112[1]	438	14.4	409	13.4
113	256	8.4	218	7.2
114[2]	376	12.4	331	10.9
Mean	316	10.4	284	9.4

Table 6.5.3/1: Survival of patients treated with BNCT

[1]Patient 112 died on 19/07/99 (after the monitoring visit). [2]Patient 114 died on 17/07/99 (after the monitoring visit). [3]Calculated with one month equals 365/12=30.42 days.

Patient #	Survival after first surgery for GBM	
	Days/	months
103	53	1.7
104	340	11.2
108	326	10.7
109	66	2.2
Mean	196	6.5

Table 6.5.3/2: Survival of patients not eligible for BNCT.

7 Discussion

7.1 History of clinical boron neutron capture therapy

7.1.1 BNCT with thermal neutrons in the United States

The first clinical trials of BNCT were carried out in the United States, with brain tumour patients in the early fifties [61] Thermal neutrons were used and the radiation was performed through the intact skull. The boron compounds used in these initial clinical studies were inorganic water-soluble compounds [55] These drugs have little or no preferential accumulation in tumour tissue; i.e. the tumour-to-blood ratio was smaller than one [56]. When given in combination with poorly penetrating thermal neutron beams, these agents produced excessively high doses at the surface with insufficient doses to the deeper located tumour [60]. The resulting poor outcome stopped in the next decades further clinical trials in the USA.

7.1.2 Therapy in glioma patients with BSH in Japan

In contrast to the first experiences, good results with BNCT in glioma treatment are claimed to be obtained by Japanese groups. Up to September 1994, Hatanaka, Nakagawa, Mishima and Oda have treated a total of 149 patients for glioma with BNCT and BSH as boron drug [22-41]. Only recently, details of doses, boron concentrations, and side effects have been presented in lectures and papers. The compound used in Japan is $Na_2B_{12}H_{11}SH$ (BSH). It was first synthesized by Soloway [57]. Initial uptake studies in mouse tumours led Hatanaka to apply it to BNCT.

Most of the patients treated had undergone surgery for removal of the tumour a few weeks before BNCT. BNCT treatment followed shortly after surgery, the earliest is one week. A number of patients underwent therapy several weeks after the surgery. For the treatment with thermal neutrons, the scalp was reflected, and a bone flap was removed. The cavity left after the initial tumour surgery was filled with ping-pong balls or a silastic rubber balloon, to allow for adequate thermal neutron penetration. A single field was used, directed to the tumour region under intra-operative conditions.

BSH was infused to patients prior to the treatment. About 10 to 18 hours later, boron concentration in blood was about 10 to 20 ppm. Tumour-to-blood ratios between 0.5 and 2 were observed, with absolute boron concentrations in the tumour of 15 to 30 ppm. Irradiation time was determined according to a projected physical dose from the $^{10}B(n,\alpha)^7Li$ reaction.

Long-term tumour control has been observed in several patients, receiving 15 to 20 Gy physical dose to the brain from the $^{10}B(n,\alpha)^7Li$ reaction (). Of a series of 15 long term survivors, about half are claimed to be patients with a grade IV glioma. In about 10% of all patients, enhancing areas on the CT and MRI images are detected; they are interpreted

as radionecrosis [24] Overall 5-year survival rates for patients with glioblastoma and anaplastic astrocytoma (including recurrent tumours) of 25.7% percent have been reported recently by Nakagawa [42].

7.2 BNCT with epithermal neutrons

The type of neutron beam first and foremost determines the neutron energy spectrum, hence the thermal neutron fluence rate in the irradiated volume. The beams utilized in the past in the USA and in Japan were beams in which the neutrons had thermal energies. Therefore, they cannot penetrate to reach deeper-lying tumours. Presently, neutron sources with epithermal neutron energies are being prepared for clinical use. Epithermal neutrons allow to reach deeper-lying tissue more efficiently, and at the same time reduce the dose deposition in the surface tissues. Efforts to install and deploy such beams have resulted first in three facilities world-wide: the Brookhaven Medical Research Reactor (BMRR) at the Brookhaven National Laboratory (BNL), the MITR-II reactor at the Massachusetts Institute of Technology (MIT), the High Flux Reactor (HFR) at the Joint Research Centre (JRC) at Petten, The Netherlands. Recently epithermal facilities for clinical use have been built in Finland, Sweden and Japan.

The compound used in early clinical trials with brain tumours and melanoma malignum in the USA started in 1994, is p-dihydroxyboryl phenylalanine, BPA. The same boron carrier is used in the clinical studies at VTT in Helsinki and in clinical application of BNCT at Studsvik, in Sweden.

I have made an intercomparison on the first three clinical trials on cranial BNCT at the three epithermal neutron sources; at Brookhaven and at MIT in the USA, and at Petten, in Europe. The common goal was to correlate delivered doses to observed biological effects. BNCT is a highly complex binary system; therefore an understanding of the definition of the delivered doses, and of the clinical tools employed to measure effect in the three separately developed trials is essential for the correct interpretation of the overall results.
Brookhaven National Laboratory (BNL) Brookhaven: protocol #4 phase I/II Study to test feasibility and safety of single fraction BNCT using BPA (2)
Harvard University-Massachusetts Institute of Technology Nuclear Reactor Laboratory (H-MIT) Boston: protocol#46,175/#5 phase I Study to test feasibility and safety of BNCT using BPA, normal tissue toxicity, local tumor response in GBM and CNS melanoma (1)
High Flux Reactor (HFR) Petten: protocol 11961 phase I Study to test toxicity of BNCT using BSH, to determine the Maximal Tolerated Dose (MTD) and Dose Limiting Toxicity (DLT) (3-4)
All clinical groups aim to establish the safety of BNCT for brain tumors by defining the toxicity spectrum of the treatment, but there are basic differences between them in terms of the study design, scientific approach, primary and secondary objectives, tools of evaluation and definitions. The present work is restricted to the comparison of the written study designs; the dose prescription, definitions for treatment planning, dose reporting, source quality, dosimetry, treatment conditions, etc. are topics for a separate publication.

Study design of the three ongoing clinical trials is summarized in the table.
table 7.2/1. Study design

site	tumour	age	BNCT	changing para-parameters	fractio-nation	boron carrier
BNL	Gliblastoma multiforme	>18	postop.	1 *vs* 2 fields depen-ding on the tumor depth,	single	**BPA** escalated from 250 up to 495 mg/kg
H-MIT	Gliblastoma multiforme	>18	with me-asurable tumor	radiation dose esca-lated 10%/cohort	single; 2-3 (field/fr.)	**BPA** escalated from 250 up to 350 mg/kg
HFR	Gliblastoma multiforme	>50	postop.	radiation dose esca-lated 10%/cohort	four	**BSH** defined constant blood ^{10}B concentra-tion over the 4 fract.

Drug pharmacokinetic and tissue distribution prior to BNCT is optional at BNL and H-MIT and part of the study at HFR.

The common primary endpoint is to detect radiation toxicity. The definition of the unacceptable morbidity differs considerably in the 3 trials. In Brookhaven the severe, RTOG grade 3-4 toxicity is defined as dose limiting toxicity, while in Boston significant MRI changes, visual field deterioration, severe acute or chronic morbidity are considered as stopping events. At HFR, treatment related life threatening, incapacitating serious adverse events are defined as unacceptable systemic or radiation morbidity.
As secondary endpoints, trends in Karnofsky performance status and in local tumor control are investigated at BNL, the local (short term) response on MRI at H-MIT, and local response and survival are recorded at HFR.

The patient selection is a crucial point for the outcome of the trial. Usually a phase I study population involves patients with diverse tumor types. In the three ongoing trials a special tumor type is selected: histologically confirmed glioblastoma multiforme and, in addition at H-MIT, radiologically documented CNS metastasis of melanoma malignum. The patients should have good performance status (Karnofsky index $\geq$ 70) in every ongoing study. Another important prognostic factor is that the age is limited at HFR $\geq$ 50 years, which defines a less favorable group than at BNL, where the patients above 40 years can be entered; the lower age limit at H-MIT is 18 years. Any comparison with historical control groups according to Curran classification may be misleading taking into consideration the different inclusion criteria at the three sites, which define special subgroups of glioblastoma patients, presumably with different prognosis than the larger, less homogeneous historical control. At BNL the deepest part of the supratentorial, unilateral, unifocal, partially or completely resected tumor must be <6 cm from the surface at BNCT. Furthermore patients are excluded if the precondition to achieve the prescribed minimal target dose without exceeding the peak normal brain dose is not fulfilled. At H-MIT unresectable or measurable residual tumor mass is required for the secondary endpoint, namely for the tumor response. For these patients life expectancy must be at least 3 months. In Europe patients are included with single, supratentorial, lobar lesion, outside major functional areas if the reference Neuroradiology Center confirms that > 70% of tumor volume could be removed. In addition to a good and fast recovery from surgery and the ability to travel to The Netherlands is

required. From the point of view of concomitant diseases and pretreatment the common intention is to exclude any therapy or illness, which could have any relevance on the BNCT morbidity.

However there are considerable differences in the protocols, how it is defined, allowing latitude for the decision of the physician for formulating strictly described exclusion criteria.
At present the treatment (e.g. dose delivery) is not comparable at all, not only because of the different neutron sources, different planning systems and input data, different boron carrier and different conditions of boron compound administration, but because the treatment concepts and study philosophies differ.
The planning target volume defined at BNL based on the postoperative, planning CT as the actual contrast enhanced volume + 2 cm shell around, can be remarkably different from the one delineated by the radiation oncologist at H-MIT using the contrast enhanced volume and using a 2 cm shell around the Gross Tumor Volume (GTV) on the preoperative MRI at HFR. However the relevance of the target definition is also remarkably different in the 3 trials. The prescribed dose is the minimal target biological dose, without exceeding the peak normal brain biological dose in Brookhaven and the normal tissue maximum biological dose in Boston (expressed in different units Gy-Eq; RBE-Gy). The radiation times vary both at BNL and H-MIT to achieve the prescribed biological doses at the measured blood boron concentrations. For treatment planning 3.5/1 tumor/blood and 1/1 healthy tissue concentrations/blood boron concentrations are assumed.
In Europe the leading physical dose component, the boron neutron capture dose, is defined at the ”point” of the thermal neutron fluence maximum for the calculation of the radiation time. The assumed tissue boron concentration is equal to blood concentration = 30 ppm average over the 4 fractions. The amount and timing of the BSH infusion is changed every day in order to achieve the average 30 ppm blood boron concentration over the four consecutive days of the treatment.
The radiation performed at BNL is single-fraction with a collimator size of 12 cm diameter, at a Skin Wall Distance (SWD) = 0 from 1 field if the tumor margin>4-5 cm, or double fields. The patient head is fixed to the wall with tapes. At H-MIT the treatment is given with 1-3 fields using a collimator size of 15 cm, the SWD = 0. For practical reasons (long irradiation time of 2.5-3-hours) the BNCT is performed on two consecutive days (1-2 field/day) using 2 thermoplastic masks for fixation.
At HFR the BNCT is performed in four fractions on 4 consecutive days, collimator size is 12 cm, SWD = 30 cm, and multiple fields can be used. A thermoplastic mask is manufactured for coordinate system correlation and fixation of the patient´s head.
At BNL mandatory anti-seizure medication is prescribed, so that the blood level should be in the therapeutic range and usually 4x4mg/day Dexamethasone is given to the patients. Furthermore during the radiation the patients receive slight sedation by Valium or Lorazepam. At H-MIT no medication is prescribed, the patients are sedated by Valium or Lorazepam during the radiation. At HFR, 3x4 mg/day Dexamethasone must be given during BNCT.
Follow up is done by the referring physician at BNL and in the European trial and by the clinical investigator at Beth Israel-Deaconess Medical Center in Boston. The results are evaluated by the investigators in the USA-trials, whilst in Europe data collection, monitoring and data management are performed by NDDO and evaluated by independent experts and by the Study Center.

Apart from the common physical, neurological examination, blood, urine laboratory tests and MRI, at BNL mini mental score, KPS, steroid dependency and QL, at H-MIT full visual field, in Europe complete ophthalmologic, ENT, endocrine function and QL are followed. The grading of the adverse events is based on different scoring scales in the three ongoing studies using modified RTOG/EORTC early and late radiation morbidity scales, items from NCIC-CTC scales and modified SOMA categories. The image evaluation is done by the investigators in USA as the estimated percentage changes in the contrast enhanced tumor volume on post-BNCT scans and by the Reference Neuroradiology Center in Europe.
In Europe the local response judged according to Zanella and MacDonald classification and by measuring the orthogonal dimensions of the tumor.
For the management of tumor recurrence, at BNL except BNCT fractionated photon radiotherapy, surgery, brachytherapy, photon or proton radiosurgery with or without chemotherapy, immune therapy are allowed, at H-MIT any therapy is allowed.
In the European trial any form of radiotherapy is prohibited for the treatment of recurrence.

7.3 Tissue uptake of BSH

Boron neutron capture therapy is a highly complex binary system, which is determined by the ^{10}B distribution and concentration in the time and space, furthermore by the quality of the neutron facility and radiation parameters.

This study is the only one up to now which provides data on tissue uptake using BSH corresponding to the real clinical situation of BNCT. The BSH dose has been administered in the therapeutical range (100 mg/kg) and the time point of the surgery, i.e. the time point of the tissue sampling was defined similar to the planned time of the epithermal neutron radiation at the HFR Petten. [50, 13] [10] However some uncertainties could be attributed to the multi-centre study design including 5 participating patient referral neuro-surgery centres located in 4 different countries some thousand kilometres distance from the analytical laboratory. In order to improve the reliability and efficacy, a detailed description of the procedure has been provided to all participating institutes. The infrastructure and preparation were checked, the study procedures have been agreed and training in detail during the initiation site visit. In addition to the case report forms, special study documents have been provided (source document forms, submission forms) to achieve the highest unambiguity and uniformity.[43, 44] In spite of these attempts to assure the quality such a trans-European study design proved to be unfavourable for sensitive analytical procedures. The boron content of the tissue samples can be highly influenced by the accuracy of the sampling and by the tissue specimen handling during the surgery and during the transport. All these factors must be taken into account by the interpretation of the bio-distribution data.

7.3.1 Tumour boron concentration

In agreement with published data of Stragliotto *et al.*,[58] (except Horn et al.,[25] who reported small differences between maximal and average boron concentrations in the tumour tissue indicating a quite homogenous distribution of boron in the tumour), there

was relative high intratumoural boron concentration variability was found, which underlines the heterogeneity of the tissue uptake of BSH within the tumour. [30]
[28-19][17, 69] The wide range of the boron concentration, yielded from multiple tumour samples of an individual patient, can be due to various factors. The Brookhaven research group investigated BPA as a boron carrier and found an inverse correlation between the measured boron concentration in the tumour specimen and the proportion of non-tumour tissue (necrotic tissue, normal brain).[6] In contrast, Goodman et al. [16]could not establish any relationship of the boron level in the tumour sample to the cellularity using BSH. The different intracellular boron uptake could be attributed to heterogeneous tumour micro-regions due to unbalanced neovascuralisation and consequent insufficient blood transport function. Therefore, BSH availability may alter in different parts of the tumour tissue. Furthermore the variable insufficient blood supply leads to micro-environmental variations in pH, cellular nutrition and metabolic waste accumulation.
The cellular heterogeneity in terms of different genetic feature, metabolism, expression and activity of regulator proteins and status in the proliferation cycle may contribute to the intracellular uptake of boron carriers and its clearance from the cells, leading to appreciably varying ^{10}B content in the samples taken from different parts of a tumour. BSH is supposed to accumulate intracellulary via passive diffusion.[12, 18-43]
Therefore the balanced inter/inracellular concentration gradient throughout the whole tumour tissue is the main determinant factor to achieve a minimum boron concentration in each tumour cell. Up to now no attention has been paid to the influence of tumour vascularisation on the boron compound delivery. It is well established that the majority of tumour blood vessels are newly formed as a result of angiogenesis triggered by stimulator factors. The neovascularisation is characteristic only in tumour tissues. The abnormal microvascular architecture with insufficient function may be favourable for cancer treatment. Hence, for example, the lack of complete blood brain barrier allows the selective targeting of the malignant cells. But, at the same time the insufficient microcirculation leads to unbalanced BSH transport within the neoplastic tissue. Therefore, investigation of tumour vascularisation on boron delivery from different boron compounds and development of clinical strategies to influence the tumour blood supply and angiogenesis, are of particular interest for optimisation on the selectivity and homogeneity of intracellular tumour ^{10}B uptake. This should be especially considered in other tumour types than brain tumours, where the disadvantage of aberrant vascular structure and spatial heterogeneity in vessels on drug distribution is not compensated by the favour of selective ^{10}B delivery due to functional impairment of the microvascular network.

7.3.2 Healthy tissue uptake

Horn et al [25]classified the non-tumour tissues in which the boron content was measured over the time into two categories. The first was represented by tissues, in which the boron content closely followed the time course of boron blood concentrations, i.e. the muscle and dura. The second tissue group was formed by tissues characterised by low boron retention brain, skin and cranial bone. In this tissue group, boron levels did not exceed 5 µ/g in all sampling time intervals. There was only one exception to this rule: skin concentration measured 3 h after the end of BSH infusion. Our results underline this division of healthy tissues with respect of their boron uptake behaviour. However in our patients, the skin falls in the first category with relatively

high boron concentration at the time point of surgery. We have found high inter-patient variability. But the large standard deviation does not differ from the series of investigations in the literature.[2] [12, 3, 9] [58, 17, 55, 57, 63-68] It can be partly explained by the different individual uptake feature due to different body constitution, feeding conditions, but it shows as well as the enormous sensitivity of the analytic method to the sampling, sample handling and detection technique. In our study some uncertainties could be attributed to the multicentre organisational structure. We can state that in agreement of the results of other research groups, the boron concentration was consequently low in the healthy brain and bone samples and remarkably lower in the muscle than in the blood. At the same time the skin and dura contained 1.3 and 1.7 times more boron respectively than the blood.

Time point of irradiation

In the complex system of BNCT, a significant parameter to obtain therapeutical benefit is the definition of the time point of thermal neutron exposure. Which should be when sufficient boron concentration is in the tumour, lasting during the neutron radiation, and at the same time the ^{10}B concentration should be significantly lower in the blood, as well as in the surrounding healthy tissues. It is very difficult to draw clear-cut recommendations in spite of the numerous publications in the last decades on pharmocokinetic and bio-distribution evaluations.
The inconsistency of the data is attributed to the administration of low amounts of BSH in some of the human experiments, to the different sampling time and period, to the use of different methods for boron detection and for evaluation of plasma pharmacokinetics, to the large variability of intra-tumour boron concentration. [12, 61, 62] [52, 16, 20, 21] [29] In a recent publication from Ohio State University,[16] boron concentration-time profile curves of the different tissue compartments were compared. Under defined conditions, they could not simulate a therapeutically useful boron concentration for glioblastoma and anaplastic astrocytoma. It was found that in all human bio-distribution evaluations, some hours after the BSH infusion, the tumour blood boron concentration ratio is increasing with the time, however the concentration-time profile analysis resulted in substantial deviations regarding the peak ratio and the time point when the tumour: blood boron concentration ratio exceeds unity. This is in contrary to the data from Gabel et al, Nakagawa-Hatanaka and Horn et al, [12, 24, 25] who conclude that the glioma: blood ratio peaks at around 12 hours and remains constant thereafter. In our patients, unfavourable tumour: blood (0.6:1) ratios have been detected at 14 hours after the end of the BSH infusion. These findings are supported by the data of Fankhauser, Stragliotto and Kageji. [58, 29, 11] On the basis of retrospective evaluation of 123 patients treated by BNCT in Japan, Kageji et al suggest neutron irradiation should be around 15-20 hours after the start of BSH infusion. We conclude that besides empirical testing of BNCT and seeking for alternative applications of the boron carriers (intracarotid administration, dose escalation, combination with blood brain barrier disruptive agents, combined administration of BSH-BPA) which are available for clinical use, collection of reliable human pharmacokinetic data and tissue uptake data is essential for further optimisation of this treatment modality.

7.4 Dose handling concept for BNCT

7.5 Presentation of the applied dose

The absorbed dose, as a macroscopic quantity is the basic parameter for prescribing, recording and reporting a radiotherapy procedure. This absorbed dose will be realised in a macroscopic region of specified elemental composition in tissue by energy deposition of secondary particles resulting from interactions of neutrons and gamma rays with the tissue. At present, the approach used in BNCT is to average the microscopic dose distributions of short-range high-LET particles (α-particles, Li-particles and protons) over macroscopic volumes. The American BNCT groups, who started first the clinical research used the sum of biologically weighted dose components expressed in RBE-Gy or Gy-Eq (ie. physical energy deposition from the different radiation qualities absorbed by the material during multiplied with their weighting factor derived from limited animal experiment. I have to underline the misleading character of this type of presentation of the applied dose. All clinical BNCT teams publish their dose assuming homogeneous boron distribution throughout the tumour and throughout the healthy tissue. We do not have data on boron content from a sufficient number of healthy tissue samples obtained from the same patient, therefore the SD of the measured concentrations in the skin, dura, bone, muscle and not affected brain, has never been calculated. Much more data has been collected in the analysis of the boron content of tumour samples. Hence, it appears evident from the literature and from our study that the tumour boron concentration measured over small macroscopical volume varies considerably.

This high macroscopic inhomogeneity should not be neglected.

At the present status of BNCT research:
the ^{10}B concentration can be measured in macroscopic volumes of human samples (fluid samples such as urine, saliva, blood, CSF and in tissue samples)
the neutron transport can be calculated, based on Monte Carlo simulation taking into account the physical characteristics of the given beam (HFR) and the representative atomic constitution of the concerned tissues
the physical absorbed doses from the different dose components can be calculated in 1 cm^3 volume after definition of the atomic composition of the given tissue
the total physical dose and some dose components (photons, neutron spectrum and intensity) can be measured in macroscopic volume

7.5.1 Evaluation on dose components

D_n: Due to the low mean neutron energy at HFR the absorbed dose decreasing steeply in the depth. The maximal value of Dn in skin at the beam entrance was 0.9 ±0.1 Gy in the first , 1.0 ±0.1 Gy in the second, 1.1 ±0.1 Gy in the third cohort and 1.2 Gy in the patient treated at the fourth dose level. In 1 cm depth falls the fast neutron dose to 40% of the maximum, in 2 cm it is under 10%. Therefore the reporting of Dn may not necessary for deep regions at HFR if the radiation time is not prolonged remarkably. The neutron dose should be reported and evaluated carefully at the superficial structures.

D_N: The nitrogen neutron capture absorbed dose is depending on the thermal neutron distribution and the N concentration of the given tissue. The D_N was always under 0.7 Gy throughout the whole study. It should be reported only if due to extraordinary high N

content of a tissue really biologically relevant dose is absorbed.(for example above 0.5 Gy)

Dg: Is a significant dose component at HFR, determined by the incident photons from the beam and by the H capture reaction. This latter depends from the thermal neutron distribution and from the H content of the given tissue. The source definition has an estimated uncertainty regarding the gamma component at about 50%. The Dg calculation should be improved.

D_B: The absorbed dose yielded by boron neutron capture in tissue depends on thermal neutron fluence and on the concentration and the microscopic distribution pattern of ^{10}B. It can not be detected directly during the radiation. Some data have been collected from pharmacokinetic and tissue uptake studies, but neither the resolution nor the reliability are sufficient for direct translation for calculation. For transport calculations a nominal value of 10 ppm ^{10}B is taken as being uniformly distributed throughout the whole brain.

The uncertainty of D_B due to inter-patient and intra-tumoural variations of the tissue boron concentration even on macroscopical level can reach factor 3-5. The uncertainty due to unknown sub-cellular localisation is much higher.

For calculation of D_B for this trial a homogeneous boron distribution in tissue has been assumed equal to the measured boron concentration in blood. It is based on the hypothesis that the absorbed dose caused by boron neutron capture in tissue has the same relationship to the ^{10}B-concentration in blood if the administration of the boron compound (route, rate of infusion, time interval between infusion and neutron exposure) kept constant.

On the other hand in this phase I study the main aim is to define the healthy tissue tolerance. Consistent results of tissue uptake studies confirmed a remarkably lower boron concentration in healthy brain, than in blood, using boron compound BSH. The potential sensitive anatomical structure can be the capillary system, whilst keeping in mind, that the geometrical factor, the distribution of boron can reduce the biological effectivity of the short rage high LET radiation released in blood, to the blood vessel wall.

The neutron transport is affected and the neutron distribution is altered by the proton density and by the concentration of nitrogen and boron in the different tissues. It would be require- able to take into account by the neutron transport and dose calculation as well the real H content of the different structures based on proton density detection on the MRI images. The elemental composition and boron concentration of the volumes, which are contoured in the planning code, can be indicated. However the manual indication of the different anatomical structures on each CT slice is limited due to pragmatic reasons. It is unrealistic to define more than 5-6 volumes, which is enough to achieve sufficient accuracy taking into account the N content. At the therapeutic values (some 10th ppm) of ^{10}B concentration the neutron distribution is perturbed significantly. Real time in vivo imaging of boron distribution is important for precise particle transport calculation and essential for accurate definition of boron dose.

D_T the addition of simple physical doses with different biological effectiveness in a certain point seems to be useless. The reporting of DT can be avoided in the future.

D_{WU} Doubtless the handling of one dose component instead of 3-4 would simplify the dose handling in BNCT. The question is whether is it possible to generate reliable photon equivalent dose definition. The answer is: no. The introduction of a single numbers as „biological weighted dose“ at the present status of knowledge increases enormously the uncertainties of the dose reporting. The biological weighting factors are derived from experimental data with different cell lines or animals, with different endpoints. The individual human boron distribution, which is deciding for the main dose component (D_B) can not be simulated realistically in experimental model. The physical dose calculation of these experiments has a high uncertainty as well. The RBE alone of the fast neutron component using the same endpoint varies in function of the neutron energy, depth, fraction size remarkably.

7.5.2 Dose prescription and radiation parameters

This concept allowed creating quite homogeneous patient cohorts but it is not acceptable any more apart from this phase I radiation dose escalation trial. The aim of the study the establishment of the qualitative and quantitative radiation Dose Limiting Toxicity (DLT) and the Maximum Tolerated radiation Dose (MTD) of BNCT in cranial localisation to healthy tissues under defined conditions at the HFR-Petten irradiation facility can be achieved using the present dose specification. However we can draw a restricted conclusion at the end of the study: with the same BSH administration (i.e. BSH is given 12 hours prior to radiation at a dose rate of 1mg/kg/min at a dose adjusted each day prior to irradiation in order to achieve 30 ppm average ^{10}B concentration over the four fractions) using the same beam (the same neutron spectrum and photon intensity, 12 cm aperture,) the healthy brain can tolerate a certain point dose within six months after BNCT.

For BNCT the thermal neutron delivery of the given beam should be optimised for the individual patient bearing a defined tumour.

The thermal neutron distribution could be more homogeneous in the defined macroscopic target volume (according to ICRU 50) meanwhile the thermal neutron fluence should be kept low outside the target region especially in defined organs at risk using different treatment techniques:
Technique of multi-portal, non-coplanar irradiation using different beam shape and size, special wedges, shielding and bolus material.

The main dose component must be the high LET radiation from BNC reaction (the other dose components should be reduced as low as reasonably possible by:

- improving the facility
- yielding high and long lasting intracellular ^{10}B concentration exclusively in the tumour cells (optimisation of boron compounds)

7.6 Safety of using BSH as boron carrier

BSH has been administered to over 300 patients with brain tumours as single dose prior to surgery or prior to BNCT, over a range of 5 to 102 mg/kg in the frame of the

European collaboration and BNCT treatment in Japan. However, testing the tolerability of BSH has never been the main objective of the different human investigations. The majority of the patients could be evaluated retrospectively for safety. Relevant human toxicity data could be obtained from these separate studies. No drug-related fatalities, life threatening conditions or prolonged side effects have been reported. The feasibility of using BSH in four doses applied on four consecutive days at a maximum dose of 100 mg/kg could be confirmed in the EORTC 11961 phase I trial. Apart from slight changes in the laboratory values and minor transient clinical symptoms, such as flush sensation and grade I nausea and vomiting, only one event of serious toxicity, possibly related to BSH, has been observed out of 25 patients. A grade 4 neutropenia occurred, which was resolved within 36 hours. In 2 cases, 4 times 100 mg/kg BSH was administered without any adverse event. We can conclude in general that BSH up to 100mg/kg single dose and 400 mg/kg cumulative dose is a well tolerated, non-toxic agent. There is also agreement between our observations and those of Stragliotto and Fankhauser in that a high rate of BSH infusion may be critical as far as the appearance of some reversible adverse reactions is concerned.

8 Conclusions

Boron neutron capture therapy is a highly complex binary system, which is determined by the ^{10}B distribution and concentration in the time and space, furthermore by the quality of the neutron facility and radiation parameters.
The approach on the trial design, patient selection, definition on end point, dose escalation strategy and toxicity detection corresponds to criterion of careful introduction of a complex radiation modality into the clinic.
Establishment of a medical infrastructure and appropriate working conditions for an outpatient clinic at the nuclear reactor site applying the European standards and the accepted international rules of radiotherapy provides the basis of the safe patients treatment.
The feasibility of performing BNCT using the epithermal beam at HFR Petten in a multinational approach could be demonstrated. However the therapeutic potential of BNCT cannot yet be evaluated at this point.
Glioblastoma multiforme constitutes a model for a phase I trial giving the opportunity to offer patients with a very poor prognosis and without expected benefit from all currently available treatments a therapeutic modality which at least shortens the treatment time. Glioblastoma multiforme however may not be the disease to judge the utility of BNCT and the therapeutic benefit deriving from BNCT. Future attempts will, therefore, focus on other tumour entities in addition to refining the protocol for glioblastoma patients.
The quality management system proved to be essential to assure the high quality of the study, correct interpretation of the collected data and of patient treatment performance.

After careful evaluation of the data, we can conclude that the starting BNCT dose level was safe but probably not high enough to reach the dose limiting toxicity within the frame of this radiation dose escalating trial. Early and late radiation toxicities are clearly lower compared to conventional radiotherapy for glioblastoma with photons at a dose of 60 Gy in 6 weeks. The results concerning survival are similar, as expected.
The feasibility of using BSH for BNCT has been proved. Further reliable data should be collected on boron bio-distribution on macroscopic and sub-cellular scale (72). As well as the cellular uptake mechanism and the influence of the macro- and micro-environment on it, should be investigated. However, on the basis of the present knowledge, further optimisation on boron delivery can be introduced in clinical research. As a next step, the maximal tolerated dose of BSH and the combined administration of BSH-BPA could be established in humans.

At the same time the optimisation of thermal neutron delivery can improve the results of the empirical clinical investigation on BNCT. In order to increase the accuracy of neutron transport calculation the tissue inhomogeneity i.e. proton density should be taken into account. On that basis the boron dose should be calculated with realistic values of boron concentration of at least macroscopic volumes. To that aim in vivo boron imaging with acceptable resolution should be developed.(73).

The findings of the tissue uptake and pharmacokinetics studies, do not allow to apply their results directly for clinical BNCT. This study claims the need for further investigation on careful boron imaging both in vivo and in vitro. A more realistic boron

dose calculation can open possibilities for further optimisation on BNCT. A better understanding on biological procedures in microscopic volumes may evolve how many tumour cells must be killed in a given stroma-cells pattern, in order to eliminate a certain tumour with BNCT, where the energy is deposited in a range corresponding to a cell diameter.

The phase I study was an important step toward the development of early trial methodology for radiation oncology and served paramount information on BNCT which defines the direction of further investigations on neutron capture therapies.

9 Summary of my personal contribution

In 1995 I was invited to participate as study radiotherapist in the first European clinical invetigation on BNCT supported by the 4th EU framework program. My tasks (working at the Radiotherapy department of Essen University) included in connection to the BNCT research:

1. The establishment of the Study Centre in Essen (as task leader) in details the patient entering into the trial, organisation of drug accounting, participation in writing the treatment protocol, reporting to the different authorities, maintaining the information exchange, and collaboration between the different study groups, different disciplines and different medical fields.
   The BNCT facility is located at Petten, in The Netherlands therefore a trans-European patient treatment had to be created. A multi-national "hospital" has been organised with Neurosurgery Departments and Local Radiotherapy Units (which took care on patient preparation for BNCT planning) at Amsterdam, Bremen, Graz, Munich, Nice, a Neuropathology Department in Bonn, a Neuroradiology Department in Frankfurt, a Treating Radiotherapy Department in Essen, an Outpatient Radiotherapy Unit in Petten and a Pharmacy and an Inpatient Department in Amsterdam.
   In order to make functioning this „European Clinic" a trans-European communication system allowing secure data and image transfer had to be developed and tested. Meanwhile the high quality of the patient treatment and its documentation had to be assured. I have worked out the documentation and archivation system following the requirements of the legal regulation of the different countries and the rules of Good Clinical Practice. I have written the radiology, radiotherapy, anatomy check of patient positioning, drug prescription and administration, patient care and documentation standard operating procedures, furthermore the investigator instruction booklet for the patient referral and patient hospitalising Institutes and for the study center. I performed together with EORTC/NDDO the initiation site visits to all participating hospitals. I have had comprehensive discussions in order to create the basis of treatment planning taking the specialties of BNCT into account.

2. The preparation of the interdisciplinary cooperation and the medical and medical physics aspects in order to create the possibility of safe patient treatment at a non-medical environment at the Petten research reactor.

   I took part in establishing a medical infrastructure and appropriate working conditions for an outpatient clinic at the nuclear reactor site. I have organized the common work of diffent groups at Petten during the patient treatment assuring all necessary information exchange for safe patient BNCT. (Facility, dosimetry, blood boron concentration, patient positioning parameters, treatment reporting) We performed dummy runs of emergency situation as part of the strict quality assurance system defined by the group with my participation.

3. Definition of documentation and data collection particular to the aim of the study

I have written the case report forms with the assistance of NDDO, the submission form and other study document forms. I drafted the project reports for the European Union.

4. I have analysed the data of the first 14 patients entered into the trial together with Martin de Vries and we wrote the Interrim Report on the first cohort. On the basis of data evaluation we pointed out the necessity of major improvement of the study protocol. I have prepared the protocol amendment in order to rationalise and simplify the trial design and state the procedures, definitions more precisely. We defined a radiation dose escalation strategy particular to this study together with Hans Hüsing from the Bio-mathematics Dept. of Univ. Essen. The protocol amendment had been discussed and approved by the Project Co-ordination Committee, by the EORTC Protocol Review Committee and by the Ethic Committees of all participating Hospitals. Obviously I had to re-write the CRFs, Instruction Booklets for the investigators and pre-printed document forms according to the changed protocol. After the evaluation of the first patient group it became obvious that the BSH uptake and PK part of the study is finished. In spite of the ther uncertainties regarding some data obtained from this study the reporting of the reliable data bears remarkable importance due to the limited possibility to perform human PK and tissue uptake investigations. I summerised the conclusions could be drawn from that study.

5. I practically performed the BNCT of 21 patients from planning target volume definition, plan evaluation, patient information, to daily BSH prescription and irradiation on four consecutive days at Petten.

6. After 5 years experiences and intensive work in the field of BNCT and in connection of preparing the study protocols for 3 future clinical trials on BNCT I had some clear suggestions on dosimetry, treatment planning and dose handling.

7. Finally I would like to share with the oncoradiology community as well the general conclusions regarding the qualitative measurement of adverse events, and clinical research methodology on the field of emerging radiotherapy modalities. (I have worked intensively on this field as chairmen of ISNCT committe of standards and quality assurance for clinical BNCT already for some years)

10 Aknowledgement

First of all I would like to thank to Professor István Ember, who has trusted in my research work, accepted me in his scientific school and supported the finalisation of my thesis. I am very grateful to Dr Attila Miseta, who encouraged me and assisted to join to the Hungarian scientific life.

I remember to the long way on clinical research started at Szeged, and I would like to express my gratefulness to all my colleagues supported this work, especially to Professor Olga Ésik, who initiated it and introduced me into the scientific activity. How angry I was, when she let me rewrite my first article again and how grateful I am now to be taught the reliable way of clinical research.

I would like to thank to Germaine Heeren, who showed much earlier than the official politics what does mean the European approach, perspective and she achieved with incredible hard work, that the common knowledge and practice could be available for each European radiotherapist. The impact of Germaines work both on the quality of the routine radiotherapy and research in Europe is unestimetable

During the 6 years – I have spent as study radiotherapist - in the first trans-European clinical BNCT study I have collaborated with a lot of experts of different disciplines coming from different countries, from different culture, having different approaches, but working for the same goal to establish the role of a new, complex treatment modality for cancer patients. It is absolutely impossible to list all the people whom I am grateful for the fruitful cooperation, for the constructive discussions, for the knowledge I have learned, or simply for an important word, encouraging smile and for a human guest in a difficult situation. Nevertheless I try to mention some of them:

Professor Wolfgang Sauerwein, who invited me, who introduced me into the BNCT, who helped much and who requested the lot of work, which resulted the present thesis.

It was very nice to work with you Gundula Franz, Ina Grübel and Terese Henkel and the whole staff of Radiotherapy Dept. of Univ. Essen.

Professor Jürgen Rassow. Dear Jürgen I have learned from you a lot, thank you for that and for all your support.

I am very grateful to the group of Medical Physics Dept. at IG I, who accepted me and supported my work especially to Sigrid Wollmann, Anette Stolzke and Wolfgang Baumhoer.

I would like to thank for the fascinating collaboration for the neurosurgeons, radiotherapists, neurologists radiologists throughout the whole Europe: Prof Brada, prof. Scalier, prof. Klaus Haselsberger, prof. Jan Heimans Claudua Götz, Axel Siefert, prof. Philippe Paquis, Hans Fankhauser, Bernd Turowski.
I have learned from you Martin de Vries paramount information on GCP, on clinical studies. It was fantastic to work with you! I have appreciated your clear approach and I took a lot from you for all of my clinical work.
The farewell to Petten was extremely difficult for me. I am so sorry that we could not form a permanent BNCT staff together at Petten, which could be the only way of clinical BNCT. Nevertheless I would like to thank to everybody working more or less time for BNCT at Petten independent from the Institution (JRC,ECN or later NRG). Ray Moss,

Finn Stecher Rassmussen I could not express my gratefulness for offering a second home at Petten and for all our discussions, for the unforgettable atmosphere, and for the enthusiastic common work. Corine van Vliet, Peter Watkins and Jim Morrisey you should be aware that through our lot of correspondence, argument exchange we have created together the basis of the safe patient irradiation. Pioneering the treatment planning for BNCT, we all invested a lot of work but we have gained valuable knowledge, experience. I am very grateful for the nuclear physicist, engineers and technical staff who provided and controlled the beam and the supplementary measures for BNCT like PGRS:Klaas Ravensberger, Klaas Appelmann and all the HFR staff members. Wilko Verbakel, the gamma telescope is a very important tool, I am happy to have so much discussions in connection to the in vivo measurements. I had very good connection to all medical physicists worked in the project: Stephan Garbe, Cecilia Kessler, Paule Charland, Elvira Finke.
ÖGROThank you Emmanuelle Bourhis, and Andrea Wittig, that you continue the work and for the present collaboration on BNCT.
The European BNCT Study is financially supported by the European Commission *as Demonstration Project* in the form of a Shared Cost Action from the Biomedical and Health Research Program (BIOMED II) of DGXII, contract no BMH4-CT96-0325 and by the Swiss foundation “Neurochirurgie 2001”
I am grateful to the leadership of the University of Kaposvár to Prof. Péter Horn, József Baka and Prof. Imre Repa for creation of the Onkoradiology Department of the Institute of Diagnostic Imaging and Oncoradiology and invited me providing the possibility to use my skills and experiences and for the support of the further scientific work on BNCT.

This thesis have never been written without the understanding, support, love, patience and power of my family.

11 References

1. Barendsen, G.W., *RBE - LET relationships for lethal, potentially lethal and sublethal damage in mammalian cells: implantations for fast neutron radiotherapy.* Bull Cancer/Radiother, 1996. **83**(Suppl 1): p. 15s-18s.
1. Barth, R.F. *Optimizing delivery of boron containing agents to brain tumors*. in *First E.U.-U.S. Workshop on Human BNCT Trials*. 1998. Lund, S: Lund Univ.
2. Ceberg, C.P., *et al.*, *Performance of sulfhydryl boron hydride in patients with grade III and IV astrocytoma: a basis for boron neutron capture therapy.* J. Neurosurg., 1995. **83**.
3. Ceberg, C.P., *Pharmacokinetics and Biodistribution of Boron Compounds.*, . 1994, Lund University.
4. Coderre, J.A., *et al.*, *Selective delivery of boron by the melanin precursor analogue p-boronophenylalanine to tumors other than melanoma.* Cancer Res, 1990. **50**(1): p. 138-41.
5. Coderre, J.A., *et al.*, *Biodistribution of boronophenylalanine in patients with glioblastoma multiforme: boron concentration correlates with tumor cellularity.* Radiation Research, 1998. **149**(2): p. 163-70.
6. Curran, W.J.j., *et al.*, *Recursive Partitioning Analysis of Prognostic Factors in Three Radiation Therapy Oncology Group Malignant Glioma Trials.* Journal of the National Cancer Inst., 1993. **85**(9): p. 704-710.
7. Dewit, L., *et al. A proposal for clinical pilot studies for BNCT*. in *4th International Symposium on Neutron Capture Therapy for Cancer*. 1990. Sydney, Australia: UICC, Abstract-Book.
8. Elowitz, E.H., *et al.*, *Biodistribution of p-boronophenylalanine in patients with glioblastoma multiforme for use in boron neutron capture therapy.* Neurosurgery, 1998. **42**(3): p. 463-9.
9. Fankhauser, H. *Upgrades proposal for initial trial of BNCT in patients in Petten.* in *Approaching clinical trials with BNCT*. 1992. Chavannes-de-Bogis / Nyon: Abstractbook.
10. 69. Fankhauser, H., G. Stragliotto, and P. Zbinden, *Borocaptate Sodium (BSH) Pharmacokinetics in Glioma Patients*, in *Boron Neutron Capture Therapy*, D. Gabel and R. Moss, Editors. 1992, Plenum Press: New York. p. 155-162.
11. Gabel, D., *et al.*, *Pharmacokinetics of Na2B12H11SH (BSH) in patients with malignant brain tumours as prerequisite for a phase I clinical trial of boron neutron capture.* Acta Neurochirurgica, 1997. **139**(7): p. 606-11.
12. Gabel, D. and e. al., *Clinical implementation of neutron capture therapy*, in *European Union. Biomedical and Health Research*, A.-E. Baert, *et al.*, Editors. 1995, IOS Press: Amsterdam, Oxford, Tokyo, Washington. p. 300-301.
13. Gabhauer, R., *et al. J-4 Reporting of BNCT irradiation: Application of the ICRU recommendations to the specific situation in BNCT*. in *Eighth International Symposium on Neutron Capture Therapy for Cancer*. 1998. La Jolla, California USA: Univ. of California Los Angeles, USA.
14. Glass, J. *p-Borono-L-phenylalanine*. in *First International Symposium on Neutron Capture Therapy*. 1983. Brookhaven, Massachusetts.

15. Goodman, J.H., *et al., Boron neutron capture therapy of brain tumors: biodistribution, pharmacokinetics, and radiation dosimetry sodium borocaptate in patients with gliomas [In Process Citation]*. Neurosurgery, 2000. **47**(3): p. 608-21.
16. Haselsberger, K., H. Radner, and G. Pendl, *Boron neutron capture therapy: boron biodistribution and pharmacokinetics of Na2B12H11SH in patients with glioblastoma.* Cancer Res, 1994. **54**(24): p. 6318-20.
17. Haselsberger, K., H. Radner, and G. Pendl, *Na2B12H11SH (BSH) in combination with systemic hyaluronidase: a promising concept for boron neutron capture therapy for glioblastoma.* Neurosurgery, 1996. **39**(2): p. 321-5.
18. Haritz, D., D. Gabel, and R. Huiskamp, *Clinical Phase-I Study of Na2B12H11SH (BSH) in Patients with Malignant Glioma as Precondition for Boron Neutron Capture Therapy (BNCT).* Int J Radiat Oncol Biol Phys, 1994. **28**(5): p. 1175-1181
19. Haritz, D., *et al., Pharmacokinetics and Biodistribution in Patients with Malignant Glioma after Administration of N-Acetylcysteine (N.AC) prior to Borocaptate Sodium (BSH).*1995.
20. Hatanaka, H., *et al. Boron Uptake by Human Brain Tumors*. in *Neutron Capture Therapy. Second International Symposium*. 1986. Tokyo: Nishimura.
21. Hatanaka, H., *et al. Clinical Experience of Boron Neutron Capture Therapy for Malignant Brain Tumors (1968-1985)*. in *Neutron Capture Therapy*. 1986. Tokyo: Nishimura.
22. Hatanaka, H., K. Sano, and H. Yasukochi, *[Boron-neutron capture therapy in brain tumors and other cancers--a radiosurgery]*. Gan To Kagaku Ryoho, 1988. **15**: p. 1115-23.
23. Hatanaka, H. and Y. Nakagawa, *Clinical Results of Long-Surviving Brain Tumor Patients who Underwent Boron Neutron Capture Therapy.* Int J Radiat Oncol Biol Phys, 1994. **28**(5): p. 1061-1066.
24. Horn, V., *et al., Disposition and tissue distribution of boron after infusion of borocaptate sodium in patients with malignant brain tumors.* Int J Radiat Oncol Biol Phys, 1998. **41**(3): p. 631-638.
25. Huiskamp, R., *et al. Large animal model studies of normal tissue tolerance using an epithermal neutron beam and borocaptate sodium.* in *Dose components and biological effects in conventional radiotherapy and neutron capture therapy*. 1992. Essen: Proceedings.
26. Huiskamp, R., *et al. Radiobiology Studies at Petten: Status on Cell Culture, Mice and Dog Experiments*. in *4th International Symposium on Neutron Capture Therapy for Cancer*. 1991. Sydney, Australia: UICC, Abstract-Book
27. Joel, D., *et al., Pharmakokinetics and tissue distribution of the sulfhydryl boranes (monomer and dimer) in glioma-bearing rats.* Strahlenther. Onkol., 1989. **165**(2/3):p.167-170.
28. Kageji, T., *et al., Pharmacokinetics and boron uptake of BSH (Na2B12H11SH) in patients with intracranial tumours.* J Neuro-Oncol, 1997. **33**(1-2): p. 117-30 Issn: 0167-594x.
29. Kraft, S.L. *In-Vivo Uptake Studies in Spontaneous Intracranial Tumours of Dogs.* in *Approaching clinical trials with boron neutron capture therapy*. 1992. Chavannes-de-Bogis / Nyon: Abstractband.
30. Locher, G.L., *Biological effects and therapeutic possibilities of neutrons.* Am. J. Roentgenol. Radium Ther., 1936. **36**(1): p. 1-13.

31. Mehta, S.C. and D.R. Lu, *Interspecies pharmacokinetic scaling of BSH in mice, rats, rabbits, and humans.* Biopharm Drug Dispos, 1995. **16**(9): p. 735-44 Issn: 0142-2782.
32. Mehta, S.C., F.D. Boudinot, and D.R. Lu, *Pharmacokinetics of sodium mercaptoundecahydrododecaborate after intravenous injection in rats.* Drug Metabolism and Disposition, 1995. **23**(12).
33. Mishima, Y., *et al., First human clinical trial of melanoma neutron capture. Diagnosis and therapy.* Strahlenther Onkol, 1989. **165**(2-3): p. 251-4.
34. Moss, R.L., *et al. The completed BNCT facility at the HFR Petten*. in *7th International Symposium on Neutron Capture*. 1996. Zürich: European Commission, JRC.
35. Moss, R.L., *et al., The requirements and development of neutron beams for neutron capture therapy of brain cancer.* J Neuro-Oncol, 1997. **33**(1-2): p. 27-40.
36. Moss, R.L. *Characterisation and Monitoring of the Petten Epithermal Neutron Beam*. in *CLINCT BNCT Workshop*. 1993. Helsinki: Helsinki University of Technology. 44. Moss, R.L., *BNCT Quality System: Quality Assurance and Quality Control Documentation Boron Neutron Capture Therapy at the High Flux Reactor Petten, .* 1997, JRC, Inst. for Advanced Materials, HFR Unit: Petten.
37. Nakagawa, Y., *Boron Neutron Capture Therapy: The Past to the Present.* Int. J. Radiat. Oncol. Biol. Phys., 1994. **28**(5): p. 1217.
38. Nakagawa, Y., *et al., Boron neutron capture therapy for malignant brain tumors in children,* in *Cancer Neutron Capture Therapy,* Y. Mishima, Editor. 1996, Plenum Press: New York and London. p. 725-731.
39. Nakagawa, Y. and H. Hatanaka, *Boron neutron capture therapy. Clinical brain tumor studies.* J Neuro-Oncol, 1997. **33**(1-2): p. 105-15 Issn: 0167-594.
40. Oda, Y., *[Boron neutron capture therapy]*.Nippon Geka Hokan, 1989. **58**(6):p.473-4.
41. Nakagawa, Y. and H. Hatanaka. *Recent Study of Boron Neutron Capture Therapy for Brain Tumors*. in *First International Workshop on Accelerator-Based Neutron Sources for Boron Neutron Capture Therapy*. 1994. Jackson, Wyoming, USA: National Center for BNCT Measurement and Development.
42. Nakagawa,T. and T.Nagai, *Interaction between serum albumin and mercaptoundecahydrododecaborate ion (an agent for boron-neutron capture therapy of brain tumor). I. Introductory remarks and preliminary experiments.* Chem Pharm Bull Tokyo, 1976. **24**(12): p. 2934-41.
43. Nakagawa, Y., *et al. E-49 Determination of BSH ($Na_2B_{12}H_{11}SH$) absorbed in the tumor tissue*. in *Eighth International Symposium on Neutron Capture Therapy for Cancer*. 1998. La Jolla, California USA: Univ. of California Los Angeles, USA.
44. Ono, K., *et al., Radiobiological evidence suggesting heterogeneous microdistribution of boron compounds in tumors: its relation to quiescent cell population and tumor cure in neutron capture therapy.* Int J Radiat Oncol Biol Phys, 1996. **34**(5): p. 1081-6 Issn: 0360-3016.
45. Otersen, B., *Binding, distribution and cellular uptake of Na2B12H11SH (BSH) in tumor tissue of glioma patients: Investigations for boron neutron capture therapy,* in *Inst. f. Organ. Chem.* 1996, University of Bremen.
46. Otersen, B., *et al., Binding and distribution of Na2B12H11SH on cellular and subcellular level in tumor tissue of glioma patients in boron neutron capture therapy.* Journal Of Neuro Oncology, 1997. **33**(1-2): p. 131-9.

47. Rassow, J., *et al. U-47 Quality assurance for clinical dosimetry of the European trial on BNCT in Petten*. in *Eighth International Symposium on Neutron Capture Therapy for Cancer*. 1998. La Jolla, California USA: Univ. of California Los Angeles, USA.
48. Sauerwein, W., *et al., European clinical trials of boron neutron capture therapy for glioblastoma.* Nuclear News, 1998. **41**(2): p. 54-56.
49. Sauerwein, W., *The clinical project at HFR Petten - a status report*, in *Advances in Neutron Capture Therapy*, B. Larsson, J. Crawford, and R. Weinreich, Editors. 1997, Elsevier Science B.V. p. 77-82.
50. Stecher-Rasmussen, F., *et al. U-36 The principles of the clinical dosimetry in the phase I clinical trial of BNCT for glioblastoma-patients at Petten*. in *Eighth International Symposium on Neutron Capture Therapy for Cancer*. 1998. La Jolla, California USA: Univ. of California Los Angeles, USA.
51. Stecher-Rasmussen, F., *et al. Boron Detection for the Petten BNCT Project: Prompt Gamma, ICP-AES, Track Etch and ESI*. in *4th International Symposium on Neutron Capture Therapy for Cancer*. 1990. Sydney, Australia: UICC, Abstract-Book.
52. Stecher-Rasmussen, F., *et al. The feasibility of a clinical thermal neutron facility for boron neutron capture therapy at the ECN argonaut reactor in Petten*. in *7th International Symposium on Neutron Capture*. 1996. Zürich: European Commission, JRC.
53. Soloway, A.H., *et al., Boron chemistry and target cell affinity.* Strahlenther. Onkol., 1989. **165**(2/3): p. 118-120.
54. Soloway, A.H., R.L. Wright, and J.R. Messer, *Evaluation of Boron Compounds for use in Neutron Capture Therapy of Brain Tumors. I. Animal Investigations.* J Pharm Exp Therapeutics, 1961. **134**: p. 117-122.
55. Soloway, A.H., *et al. Chemical Overview of Boron Neutron Capture Therapy*. in *First International Symposium on Neutron Capture Therapy*. 1983. Brookhaven: Brookhaven National Laboratory.
56. Soloway, A.H., H. Hatanaka, and M.A. Davis, *Penetration of brain and brain tumor. VII. Tumor binding sulfhydryl boron compounds.* J. Med. Chem., 1967. **10**: p. 714-717.
57. Stragliotto, G. and H. Fankhauser, *Biodistribution of Boron Sulfhydryl for Boron Neutron Capture Therapy in Patients with Intracranial Tumors.* Neurosurgery, 1995. **36**(2): p. 285-293.
58. Sweet, W.H. and M. Javid, *The possible use of slow neutrons plus boron-10 in the therapy of intracranial tumors.* Transact. Am. Neurol. Ass., 1951. **76**: p. 60-63.
59. Sweet, W.H., *Early history of development of boron neutron capture therapy of tumors.* J Neuro-Oncol, 1997. **33**(1-2): p. 19-26 Issn: 0167-594x.
60. Sweet, W.H., A.H. Soloway, and G.L. Brownell, *Boron-slow neutron capture therapy of gliomas.* Acta Radiologica (Stockholm), 1963. **1**: p. 114-121.
61. Vroegindeweij, C., *et al., Definitions in the INEL treatment planning program and in the meaesurements for BNCT*, . 1997, JRC, Institute for Advanced Materials (IAM): Petten.
62. Watkins, P. *Development of a Treatment Planning Methodology for BNCT at the HFR Petten*. in *CLINCT BNCT Workshop*. 1993. Helsinki: Helsinki University of Technology.
63. Watkins, P., *et al. Use of the BNCT_Rtpe/rtt_MC treatment planning system for BNCT irradiations of human patients at Petten*. in *7th International Symposium on Neutron Capture*. 1996. Zürich: European Commission, JRC.

64. Wheeler, F.J. and D.E. Wessol, *Dose calculation based on image reconstructions*, in *Boron Neutron Capture Therapy*, D. Gabel and R. Moss, Editors. 1992, Plenum Press: New York. p. 143-154.
65. Wheeler, F.J., *Validation studies for the INEL treatment planning software as applied to the Petten BH11 epithermal neutron beam*, . 1995, JRC Petten, Institute for advanced materials: Petten..
66. Hüsing J., Sauerwein W. Hideghéty K., Jöckel K-H. *A scheme for a dose-escalation study when the event is lagged* STATISTICS IN MEDICINE Statist. Med. 2001; 20:3323-3334
67. Rassow J, Stecher-Rassmussen F., Voorbarak W., Moss R., Vroegindeveij C., Hideghéty K.,Sauerwein W. *Comparison of quality assurance for performance and safety characteristics of the facility of Boron Neutron Capture therapy in Petten/Nl with medical electron accelerators* Radiotherapy and Oncology 59 (2001) 99-108
68. Hideghéty K, Sauerwein W, Wittig A., Goetz C., Haselsberger K., Paquis P., Grochulla J. F., Wolbers J., Moss R., Huiskamp R., Fankhauser H., De vries M., Gabel D. *Tissue Uptake of BSH in Patients with glioblastoma in the EORTC 11961 Phase 1 BNCT Trial*, 2002. Journal of Neuro-Oncology, accepted
69. Hideghéty, K., *et al.*, *Postoperative treatment of glioblastoma with BNCT at the Petten irradiation facility (EORTC Protocol 11961).* Strahlenther Onkol, 1999. **175**(Suppl. II): p. 111-114.
70. Hideghéty, K., *et al.*, *Postoperative treatment of glioblastoma with BNCT at the Petten irradiation facility (EORTC protocol 11961).* 1997.
71. Verbakel W., Hideghéty K., Morrissey J., Sauerwein W., Stecher-Rasmussen F. *Towards in vivo monitoring of neutron distributions for quality control of BNCT* , Physics in Medcine and Biology, 2002, vol 47. p 1059-1072