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REVIEW PAPER

Boron neutron capture therapy (BNCT) in Finland: Technological and physical prospects after 20 years of experiences

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Abstract Boron Neutron Capture Therapy (BNCT) is a binary radiotherapy method developed to treat patients with certain malignant tumours. To date, over 300 treatments have been carried out at the Finnish BNCT facility in various on-going and past clinical trials. In this technical review, we discuss our research work in the field of medical physics to form the groundwork for the Finnish BNCT patient treatments, as well as the possibilities to further develop and optimize the method in the future. Accordingly, the following aspects are described: neutron sources, beam dosimetry, treatment planning, boron imaging and determination, and finally the possibilities to detect the efficacy and effects of BNCT on patients.

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Introduction

Boron neutron capture therapy (BNCT) is an experimental targeted radiotherapy method that has been actively researched in Finland since 1992 [1–8]. From 1993 to 1997, the FiR 1 research reactor in Otaniemi (Espoo, Finland) was constructed as a treatment facility [9], and the clinical trials started in May 1999 with primary glioblastoma patients [1]. Since then, over 200 patients with malignant brain or head and neck tumors have been treated at the facility [1–4,8,10].

In BNCT, the boron (^{10}B) carrier compound is usually administered by an intravenous infusion. In the absence of neutrons, the boron compound is a non-toxic and non-radioactive agent that accumulates into cancer cells. After a period of time, boron is optimally located in the tumour cells, while the healthy tissue has a lower boron concentration. The tumour site is irradiated with neutrons, which thermalize in tissue and interact with the ^{10}B nuclei. As a result, high linear energy transfer (LET) alpha and lithium particles are produced, destroying the surrounding cell. In the Finnish trials, intravenously administered L-boronophenylalanine–fructose (l-BPA-F) has been used as the boron carrier, and the patient is irradiated with a beam of epithermal neutrons from the reactor without craniotomy or performing other surgical procedures.

The prerequisite for successful BNCT is to concentrate a sufficient amount of ^{10}B in the tumour cells and to irradiate the patient with neutrons at a high enough intensity and within a suitable energy range, enabling the boron neutron capture reaction to occur. Accordingly, it is important to validate and optimize the behaviour of the boron biodistribution, the energy distribution of the neutron field and the set positioning (Fig. 1). The boron concentration ratio between tumour and healthy cells is crucial, for example, for 20–30 ppm boron concentration 3–4 concentration ratio is needed for the 10^9 neutrons/cm^2/s collimated neutron flux. A great deal of effort has been invested in treatment planning to maximize the benefit to the patient. The Finnish FiR 1 epithermal neutron beam [9] has been characterized extensively using various dosimetric methods, phantom materials and geometries [11], and measured and calculated doses have been compared to validate the quantitative beam source model and its application in the treatment planning [12,13]. A custom-made patient positioning system including a treatment table, beam aperture simulator and positioning lasers has been developed and constructed [11], and the effect of positioning uncertainty on the doses has been studied with Monte Carlo simulations. An image registration protocol for BNCT has been created [14]. Furthermore, the combined uncertainty of the physical dose has been estimated by combining data from different relevant factors [11].

According to International Commission of Radiation Units and Measurements (ICRU), the uncertainty of the dose to the patient in external radiotherapy should not exceed 5%, the recommendation from literature being below 3% [15]. These facts set high objectives for reliability and accuracy in the patient positioning in addition to the boron level definition and beam dosimetry in BNCT. The majority of European research groups involved in the development of BNCT have prepared the report "Recommendations for the Dosimetry of Boron Neutron Capture Therapy (BNCT)" published by the Nuclear Research & consultancy Group (NRG) [16]. The report covers the guidelines for the basic characterization and dosimetry of the epithermal (and thermal) neutron beams used in BNCT. However, this report includes no guidelines for determining boron biodistribution or dose planning calculations. In the future, microdosimetric approaches, quantitative *in vivo* imaging before, during and after the treatment, as well as taking full advantage of computational methods are expected to change the situation [17]. There are also some prospects to find better carrier compounds and optimize the delivery strategies to bring boron efficiently and selectively to the target cells [6,18–22].

In this review, the following aspects will be described: neutron sources, beam dosimetry, treatment planning, boron imaging and determination, and finally the possibilities to detect the BNCT effects on patient, the emphasis being on the research and technical development carried out in Finland during the last 20 years.

Neutron sources

At our TRIGA (Training, Research, Isotopes, General Atomics) Mark II type FiR 1 reactor-based BNCT facility, fission neutrons are slowed down to the epithermal energy range using FLUENTAL™ (69 w-% of AlF_3, 30 w-% of metallic Al, 1 w-% ^{7}LiF) moderator material developed at VTT [9]. The moderated neutrons are collimated and gamma-shielded with bismuth into the high intensity forward directed (current to fluence ratio 0.77) epithermal neutron beam with low gamma, thermal neutron and fast neutron contamination. The beam characteristics and intensity have been confirmed with the measurements performed by the Finnish dosimetry team and by visiting teams from Idaho National Laboratory, Idaho USA [23], Nuclear Research Institute (NRI) Rez Czech Republic [24] and MIT USA [25]. The advantage of using a TRIGA reactor for BNCT is its stability and reliability in addition to the high neutron intensity and low background radiation of the treatment beam [26]. None of the patient treatments has been cancelled or postponed due to reactor related problems during the history of BNCT in Finland.

One of the drawbacks in using a nuclear reactor as a BNCT neutron source is obviously its location in non-hospital environment, even though in Finland the reactor is located only 15 min away from the nearest hospital unit. Also, since the beam position is stationary, the patient needs to be directed and rotated in the treatment fields. To address this issue, for nearly three decades, the development of Accelerator Based Neutron Sources (ABNS) has been of interest, because ABNS could be safely installed in hospitals [19,27–32]. Development of the ABNS for BNCT comprises of three challenging tasks [28]. Firstly, a high power accelerator for producing a high-current particle beam is required. Secondly, an appropriate target for producing neutrons needs to be developed with an efficient heat removal system. Thirdly, in order to reduce the initial neutron energy down to the optimal range for BNCT, a beam shaping assembly (BSA) must be designed.

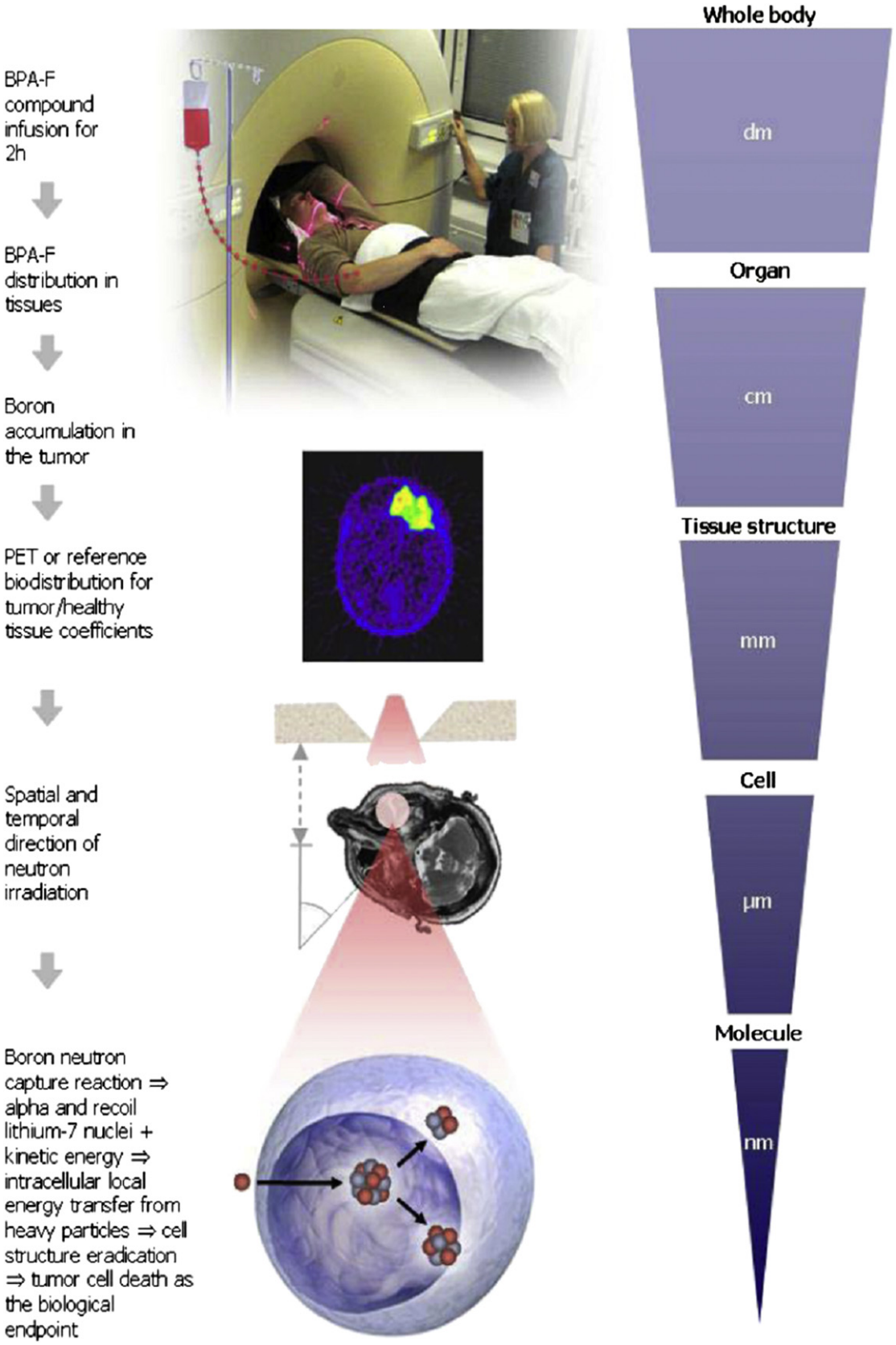

Figure 1 The fundamental dosimetric process of BNCT occurs at the cellular level due to the short path lengths of alpha and lithium recoil nuclei produced in the boron neutron capture reaction. Macroscopic distribution of the boron carrier in tissues is temporally optimized for the irradiation, the tumor having maximal boron uptake compared to the healthy tissue.

The optimal neutron beam energy for treating deep-seated tumours with BNCT is from 4 eV to 40 keV [24–28,30,32,34–37,40–43]. A common problem for neutron sources used for BNCT is that it is not possible to produce a high neutron flux directly at the optimal epithermal energy range. In addition, considerable moderation of the source neutrons is always required. A neutron beam can be moderated, for example, by placing a tissue equivalent material (bolus) on the patient's skin to treat more superficial tumours [26]. During the moderation, neutron intensity is reduced and consequently, the proton accelerator for ABNS for BNCT needs to be operated at much higher power than for example a proton therapy accelerator. The $^{7}Li(p,n)^{7}Be$ neutron source with 2.5 MeV protons at 20 mA current for BNCT requires 400 times more powerful accelerator than used at a typical proton therapy unit with up to 250 MeV protons operated typically at 500 nA.

Neutron producing reactions can be induced by accelerated protons, deuterons or tritons targeting ^{7}Li, ^{9}Be, ^{13}C, ^{12}C, ^{2}H or ^{3}H nuclei. Probably the most studied ABNS application is the $^{7}Li(p,n)^{7}Be$ reaction at around 2.5 MeV proton energy, because a sufficiently low accelerator current (10 mA) is required for producing a high intensity of reasonably low energetic (<1 MeV) neutrons. Such BNCT beams with functional lithium targets and beam shaping assemblies have been developed or are under development at the University of Birmingham in the UK [33], the Institute for Physics and Power Engineering in Obninsk Russia [30] and the Atomic Energy Commission of Argentina in Buenos Aires [34]. The Cyclotron-Based Epithermal Neutron Source (CBENS) built at the Kyoto University Research Institute (KURRI) by Sumimoto Heavy Industries [35] produces neutrons through the $^{9}Be(p,n)^{9}B$ reaction utilizing a 30 MeV proton beam at 1 mA current. Such a powerful neutron source also results in strong activation of the materials within the device. In addition, there are difficulties in reducing the unwanted fast neutron and photon components from the clinical neutron beam [36]. Furthermore, there is a plan to apply a 5 MeV proton beam line for thermal neutron BNCT at Legnaro Laboratories of National Institute of Nuclear Physic (INFN) in Italy [37]. The neutrons are intended to be produced by $^{9}Be(p,xn)$ reactions, where a neutron yield of 10^{14} s^{-1} of <3.2 MeV neutrons is expected. ABNS with a beryllium target for a high flux (>10^{9} neutrons/cm^{2}/s) thermal neutron beam for skin melanoma BNCT have been developed in the project [37–39]. Also $^{2}H(d,n)^{3}He$ or $^{3}H(d,n)^{4}He$ fusion based neutron sources have been suggested for BNCT use [40–43].

To date, all the clinical BNCT trials have been carried out using reactor-based neutrons due to the high thermal or epithermal neutron flux of order 10^{9} neutrons/cm^{2}/s [27]. However, while we do not have an ABNS development project in Finland, we recognize that there is no doubt that realizing ABNS is one of the determining factors in how fast BNCT will be established as routine clinical treatment.

Beam dosimetry

To assure the reliability and consistency of dosimetry and the metrological traceability of calibrations, the dosimetry procedures in radiation therapy follow international guidelines [44–48]. For uncommon and specific type of radiotherapy modalities, such as BNCT, no uniform international dosimetry guidance exists so far. The work towards coherent BNCT dosimetry procedures was started in 1998, when a European project for a Code of Practice of epithermal neutron beams in BNCT was launched [49]. The recommendations of the projects were published in 2003 [16]. The absorbed dose must have a metrologically traceable link to the international dosimetry standards also in BNCT (Fig. 2). In dosimetry of epithermal neutron beams, a reasonable accuracy in the determination of photon and neutron doses has been achieved using ionization chambers [50–52]. The dual ionization chambers are recommended and often used to determine photon and (fast) neutron dose in a mixed photon and epithermal neutron beam [16,50–54]. The method is based on ICRU recommendations for fast neutron beam dosimetry [47,55], which are not directly applicable to the epithermal neutron beams used in BNCT.

During the establishment of systematic dosimetry procedures in the dosimetry of radiation therapy, the importance of quality assurance (QA) has been emphasized [15,45]. The American Association of Physicists in Medicine

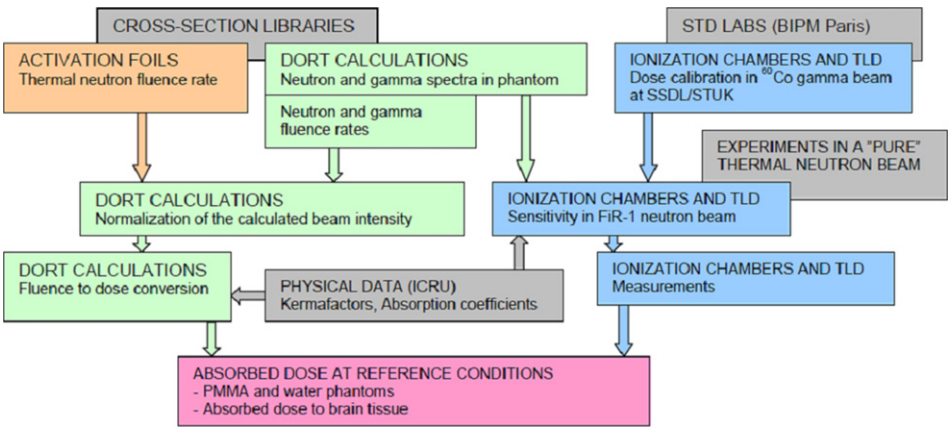

Figure 2 Relation and use of different dosimetric methods. In BNCT the physical dose must have a metrologically traceable link to the international dosimetry standard.

(AAPM) published recommendations for a comprehensive QA for radiation therapy in 1994, and in 1997, the European Society for Therapeutic Radiology and Oncology (ESTRO) presented a frame for a quality system based on the guidelines of the International Standardization Organization (ISO) [56,57]. In the BNCT community, the validity of quality-oriented treatment procedures has been recognized [58], and the baselines for a dosimetry quality program have been presented by Rassow *et al*. [59] and by Järvinen and Voorbraak [16]. Beam quality assurance procedures at the Finnish FiR 1 BNCT facility have been outlined [60].

In the Finnish BNCT program, we use an Exradin T2 ionization chamber made of A-150 tissue equivalent plastic and flushed with tissue equivalent gas (referred to as the TE(TE) chamber) to measure total neutron and photon dose. An Exradin M2 magnesium ionization chamber flushed with argon gas (Mg(Ar) chamber) is used to measure the photon dose. The ionization chambers are individually calibrated for absorbed dose to water in ^{60}Co gamma radiation beam [51,53,61]. For the TE(TE) chamber the relative sensitivity for neutrons is determined according to general Bragg-Gray cavity theory following the ICRU formalism [47]. The Mg(Ar) chamber is constructed purely from non-hydrogenous materials and is assumed to be insensitive to neutrons at all neutron energies [50]. Thus the photon dose determination does not require information of the neutron spectrum. The neutron sensitivity of photon chambers has been investigated in other studies, where also non-zero values have been acquired [51,53,61]. These results demonstrate that the assessment of relevant dosimetry factors in a mixed field is potentially sensitive to specific measurement set-up, and thus careful considerations are required when analysing the acquired experimental data. The absorbed doses from the neutrons cannot be measured directly. Measurements with activation detectors and semiconductor diodes produce reaction rates and neutron fluence rates which are converted into doses by application of the kerma factors [62,63].

Microdosimeters based on a solid state semiconductor detector or a proportional counter can be applied in BNCT dosimetry to measure the total neutron and photon dose [64—67]. However, the use of the commercially available proportional counter (1/2" TEPC, Far West Technology) is limited to measurements at low beam intensity [68,69]. Smaller miniature proportional counters have been built to eliminate the problem of pulse pile-up at higher beam intensities [70,71]. Silicon diode based microdosimeters have a high potential for use in BNCT, since all dose components in the mixed field can be measured on-line with a single small detector [72]. However, the optimal characteristics of the semiconductor detectors for BNCT are still under development. The construction of the detector includes a layer of suitable converter material attached to the surface of a p-n junction diode where the converted charged particles can be detected and measured [72—74].

Other methods applied in photon and neutron dosimetry for BNCT beam include thermoluminescent dosimeters (TLD) [52,75—80], Fricke and polymer gel dosimeters [81] and alanine detectors [82]. TLDs have been used in the Finnish BNCT project for *in vivo* dose verification of the calculated patient doses [83]. Polymer gel detectors have also been used to determine boron dose component [84]. In the Finnish BNCT project we have studied two types of polymer gel dosimeters and applied gel dosimetry to measure the relative total dose distribution [85,86]. Superheated drop detectors, fission counter, BF_3 counters, boron lined proportional counters and ^{3}He proportional counters can be used for the detection of neutrons [16,27,87].

Treatment planning

The main potential and inspiration of BNCT is that the therapeutic effects emerge at the cellular level. BNCT dose calculation requires careful calculation of nuclear interactions of neutrons with the tissue elements and thus, elemental composition of tissues within patient geometry needs to be modelled. In the Finnish BNCT practice, the patient models are created semiautomatically based on information from the computed tomography (CT) or manually based on magnetic resonance (MR) images. The clinical target volume (CTV) is determined based on contrast-enhanced T1-weighted MR images, while also T2-weighted MR images and positron emission tomography (PET) images are frequently utilized [2,3]. For accurate patient modelling and dose calculation, the data from different imaging modalities is combined.

Image registration

In our BNCT image registration protocol [14], the CT image set of the first treatment fraction defines the baseline for the images coordinate system. In the case of two head and neck BNCT fractions, dose planning CT images are taken for both fractions. When the new CT studies are registered with the first reference CT study, *an intra-modality registration* is carried out. *Inter-modality image registration* is performed between different image modalities (MRI/CT/PET). In the latter cases, the image similarity metrics based on the direct comparison of gray levels (like normalized correlation) cannot be utilized in the optimization of the registration parameters, because the intensities in the different imaging modalities do not correlate linearly.

Instead, we apply Mattes implementation of mutual information metrics [88—90]. This metric is optimized with Powell method based on Brent line search [91] and three rotation and three translation parameters (3D rigid transform). In order to decrease the possibility of finding a local maximum of mutual information metric instead of the global maximum, a *multi-resolution approach* is applied. In the multi-resolution approach, the registration is performed first at a coarse scale. The registration parameters from the coarse scale are used as start values of the optimization at a finer scale. The optimization of the metric is carried out using physical coordinates instead of voxel coordinates. The pixel spacing, image position and direction cosines which couple the voxel coordinates to physical coordinates are extracted from DICOM (The Digital Imaging and Communications in Medicine) image files [92]. Hence the estimation of scale parameters (relation of voxel sizes in different studies) is not necessary, which reduces the dimensionality of search space of the optimizer.

Multiresolution approach has been widely proven to provide faster, more robust and more accurate computation of the registration parameters [93,94]. Successive registrations are needed, for example, when images taken at one point of time are first registered with each other, and then, possibly months or years later, these registered images are re-registered with the new images — either for the purposes of new treatment planning or registration aided detection of change [95,96].

The use of 3D rigid transform for registration from different modalities requires careful positioning of the patient for imaging. In the case of head-and-neck cancer patients, it is crucial to avoid different bending of neck. Fixation masks, tattooed points and external markers should be used to assist the patient positioning [14]. We have applied rigid transformations instead of elastic transformations based on thin plate or elastic body splines [87]. It would be difficult to automate elastic registration to work robustly, and to restrict the corrected deformations only to the differences due to patient positioning. Additionally, rigid transformations are faster to optimize. Therefore our protocol is presently based on the careful patient positioning and on the use of rigid 3D transform.

The registration results are verified using multiplanar reconstructions and comparing anatomical features using visual interactive tools based on the Visualization Toolkit [97]. Final verification of the registration is done in the treatment planning software with cubically resampled data. The verification is done by comparing the segmented structures (skin, bones, brain, medulla, air cavities) of one CT image set on the other CT image set.

The in-house developed software [98] used in the registration is based on the Insight segmentation and registration toolkit (ITK) [99,100] and the Visualization Toolkit (VTK). As a future work, it is important to study the impact of the inaccuracies in the image registration on the dose estimation accuracy. If seen necessary, the registration errors can possibly be decreased by extending the registration environment with deformable (non-rigid) transformations or improving patient fixation systems. The approach based on the in-house developed software and open source toolkits (ITK and VTK) enables further development and optimization of the registration framework.

Dose calculation

So far, only Monte Carlo (MC) based treatment planning systems (TPS) have been applied in clinical BNCT. Four MC -based TPSs have been developed for BNCT use: the NCT_Plan developed at Harvard and MIT [101], The Simulation Environment for Radiotherapy Applications (SERA) developed at Idaho National Laboratory (INL) and Montana State University (MSU) [23,102], the THORplan developed at Tsing Hua University in Taiwan [103], and the JAEA computational dosimetry system (JCDS) developed at Japan Atomic Energy Agency (JAEA). The MC methods are often very time consuming, which has led to interest in the application of faster deterministic methods [23], such as the simplified P_n approach [104].

The dosimetric calculations are often performed with the extensively benchmarked and validated multipurpose software, Monte Carlo N-Particle Code (MCNP) [105] or respectively, the 2- or 3-dimensional discrete ordinate method based DORT (two-dimensional discrete ordinates (deterministic) transport) and TORT (three-dimensional discrete ordinates (deterministic) transport) codes [106,107]. The SERA system uses its own MC code, seraMC, for neutron and photon transport calculations. In the Finnish BNCT project, the MCNP or the DORT codes are applied for the simple geometry dosimetric calculations, and the SERA code for the clinical treatment planning [1,13,50,108—110]. The epithermal neutron beam of the FiR 1 reactor has been modelled with the DORT code [12]. The beam model includes neutron and photon transport from the reactor core through the moderator and collimator structures towards beam aperture. The neutron and photon energy and angular distribution obtained with the DORT are converted to a beam model for MCNP and SERA by averaging the forward current for 47 neutron energy groups and 20 photon energy groups. For each energy group, separate angular distributions by 10 cosine cut points in the forward direction have been defined [110]. Neutron models of TPS have been normalized to measurements using diluted AuAl (1w-%, Au) foils in the cylindrical PMMA phantom at the depth of 2.0 cm [12]. The normalization factor of the computational beam model is the ratio of independently measured and computed ^{197}Au(n,ã) activation reaction rates. The neutron energy distribution of FiR 1 beam models in phantoms has been verified by comparing the measured and computed activation reaction rates of ^{197}Au(n,ã) and ^{55}Mn(n,ã), which have different neutron energy response for thermal and epithermal neutrons. The use of Au and Mn activation measurements in the experimental verification of the epithermal neutron beam is relevant, since the calculated thermal neutron induced dose components form 90—95% of total dose at the depths from 0.5 to 10 cm in a phantom in the FiR 1 beam.

Different MC techniques have been compared to evaluate BNCT dose calculations. The different cross-section forms used in the MCNP and SERA have been shown to cause notable discrepancy in the dose calculation in low (25 meV) and high (1 MeV) energy neutron beams [111,112], while in the clinical epithermal neutron beam the most crucial neutron-induced boron and nitrogen doses and the photon dose agree within 4% or better [13]. Moreover, discrepancy between the dose calculations may originate rather from the use of different fluence to dose conversion factors or different dose calculation methods chosen in MCNP or in SERA [113].

Boron imaging and determination

The boron concentration level affects directly the boron neutron capture reaction intensity and further the dose to the tumour and the brain. In the Finnish clinical BNCT practice, the whole blood-boron concentration is routinely determined during and after BPA-F infusion from periodic blood samples using inductively coupled plasma-atomic emission spectrometry (ICP-AES) [11,114—117]. The time period between the measurements before and after the irradiation can be even 30 min. It has therefore been necessary to find a way to predict the blood-boron level

between the measurements and during the irradiation [108]. Pharmacokinetic models have been used to calculate the whole blood-boron concentration during irradiation [11,118,119]. In Finland, a bi-exponential model fit using the Levenberg–Marquardt method has been implemented to provide blood-boron concentration estimates directly for the treatment data flow during the BNCT procedure [11,108]. The boron concentration in tumour and brain tissues are estimated assuming constant boron concentration ratios for blood-to-tumour (1:3.5) and blood-to-brain (1:1) [120], being around 17 ppm and 59.5 ppm (for 400 mg/kg BPA-F infusion) in healthy tissue and tumour, respectively, at the time of the irradiation [1–8]. The accuracy of the boron estimation has been tested on patients with 290–450 mg/kg BPA [1–3,8]. Coderre *et al*. [120] and Elowitz *et al*. [121] measured boron concentration invasively in surgical samples after BPA-F infusion. In patients with suspected or confirmed glioblastoma multiforme, the results of the histological findings indicated mean blood-to-tumour boron concentration ratios from 1.4 to 4 [120,121] and a high variation in the blood-to-tumour boron concentration ratio inside particular tumours [121]. To date treatment planning codes in BNCT do not factor in the patients' individual characteristics with respect to the varying levels BPA uptake into tumours. Consequently, new non-invasive methods are needed to determine and monitor boron concentrations in the tumour and the surrounding healthy tissues.

Molecular based boron imaging

Many studies have examined the suitability of positron emission tomography (PET) for the determination of boron concentration in tumour and healthy tissues for the needs of treatment planning [122–126]. Such PET studies were conducted using ^{18}F-labelled BPA (^{18}F-BPA). In Finland, ^{18}F-BPA PET has been used to monitor the suitability of patients for BNCT by estimating the accumulation of BPA in the tumour [2,8]. The ^{18}F-PET has been performed for patients whenever the PET modality and ^{18}F-BPA tracer have been available. The administered activity of ^{18}F-fluoro-L-BPA tracer has typically been 160–240 MBq and tumour-to-normal tissue ratios have been evaluated from static emission scans obtained 20–40 min following injection. In the cases when ^{18}F-PET was performed, the tumour-to-corresponding contralateral normal tissue ratio of the standardized uptake values of at least 2.5 has been required as an inclusion criteria of Finnish head and neck cancer BNCT trial.

Several magnetic resonance (MR) techniques have been proposed for boron carrier detection. These include ^{11}B or ^{10}B magnetic resonance imaging (MRI) and MR spectroscopic methods [127–130]. Recently, ^{19}F MRI and magnetic resonance spectroscopy (MRS) has also been used to detect ^{19}F-labelled BPA [131,132]. However, to our knowledge none of these ^{11}B, ^{10}B or ^{19}F MRI/MRS methods for boron detection have been tested in human or implemented in clinical BNCT.

The possibility to apply clinically widely used proton MR spectroscopy (^{1}H MRS) for selective BPA-F detection was proposed by Zuo *et al*. [133]. They reported that aromatic proton signals of BPA resonating at the chemical shift range of 7.0–7.5 ppm can be detected *in vivo* at 1.5 T. In theory, this offers possibilities to study the spatial and temporal distribution of BPA and BPA concentration in the brain non-invasively using a typical MR imager without any need for special instrumentation. The aromatic proton signals of BPA enable detection of the boron carrier because, with typical measurement settings (voxel size and measurement duration), normal brain metabolite signals do not overlap with them. MRS imaging (MRSI) of BPA-F with animals at high magnetic field has been studied by Bendel *et al*. [134,135]. In addition, BPA quantification at 1.5 T and 3.0 T using ^{1}H MRS has been studied with phantoms [136,137].

In Finland, the possibility to apply ^{1}H MRS and MRSI for *in vivo* BPA-F detection has been studied [136]. ^{1}H MRS and/or 3D ^{1}H MRSI measurements were conducted ten patients on the day of BNCT at 1.5 T (nine patients) or 3.0 T (one patient). The patients had glioblastoma multiforme, anaplastic astrocytoma gradus III or head and neck cancer. For nine patients, MRS/MRSI was performed after the treatment, and for one patient MRSI study was started before the end of the BPA-F infusion and ended after the end of the infusion. In three patients, the signals in the aromatic region of tumour spectrum were detected. It appears that in favourable cases, it is possible to detect BPA *in vivo* after the BPA-F infusion or after the BNCT [138] (Fig. 3 and Fig. 4). However, because the shape and position of the detected signals do not exactly match the BPA spectrum detected in the *in vitro* conditions, unambiguous assignment of BPA is somewhat difficult. The opportunity to perform MRS immediately after the end of BPA-F infusion for a larger patient group is needed in order to evaluate the actual suitability of ^{1}H MRS for more exact BPA detection and quantification for treatment planning purposes. Using higher magnetic field strengths (3.0 T or even higher) for MRSI the likelihood of detecting low BPA concentrations *in vivo* would improve. In our work, a 3.0 T MRS study was performed for only one out of ten patients. In this case, the MRS was performed approximately 2 h after BNCT and no signals were detected from tumour spectrum aromatic region. In our previous phantom study [139] 3D acquisition-weighted PRESS (position resolved spectroscopy sequence) MRSI was suggested to be a feasible method for *in vivo* BPA evaluation in clinical conditions. We applied this method for six patients at 1.5 T and the signals in the aromatic region were detected in the tumour MRSI spectra of two patients. However, use of MRS for exact BPA quantification *in vivo* would be challenging even if MRS were performed immediately after BPA infusion and modern MRI systems with higher magnetic field were available, but MRSI could be useful for selecting patients for BNCT.

Prompt gamma detection of boron determination

In 94% of boron neutron capture reactions, a prompt 478 keV gamma photon is created. Measuring this gamma radiation from the patient during the BNCT treatment gives the possibility to monitor and quantify the delivered radiation dose and its distribution during the treatment [140–143]. Possibilities to construct a real time 3D imaging

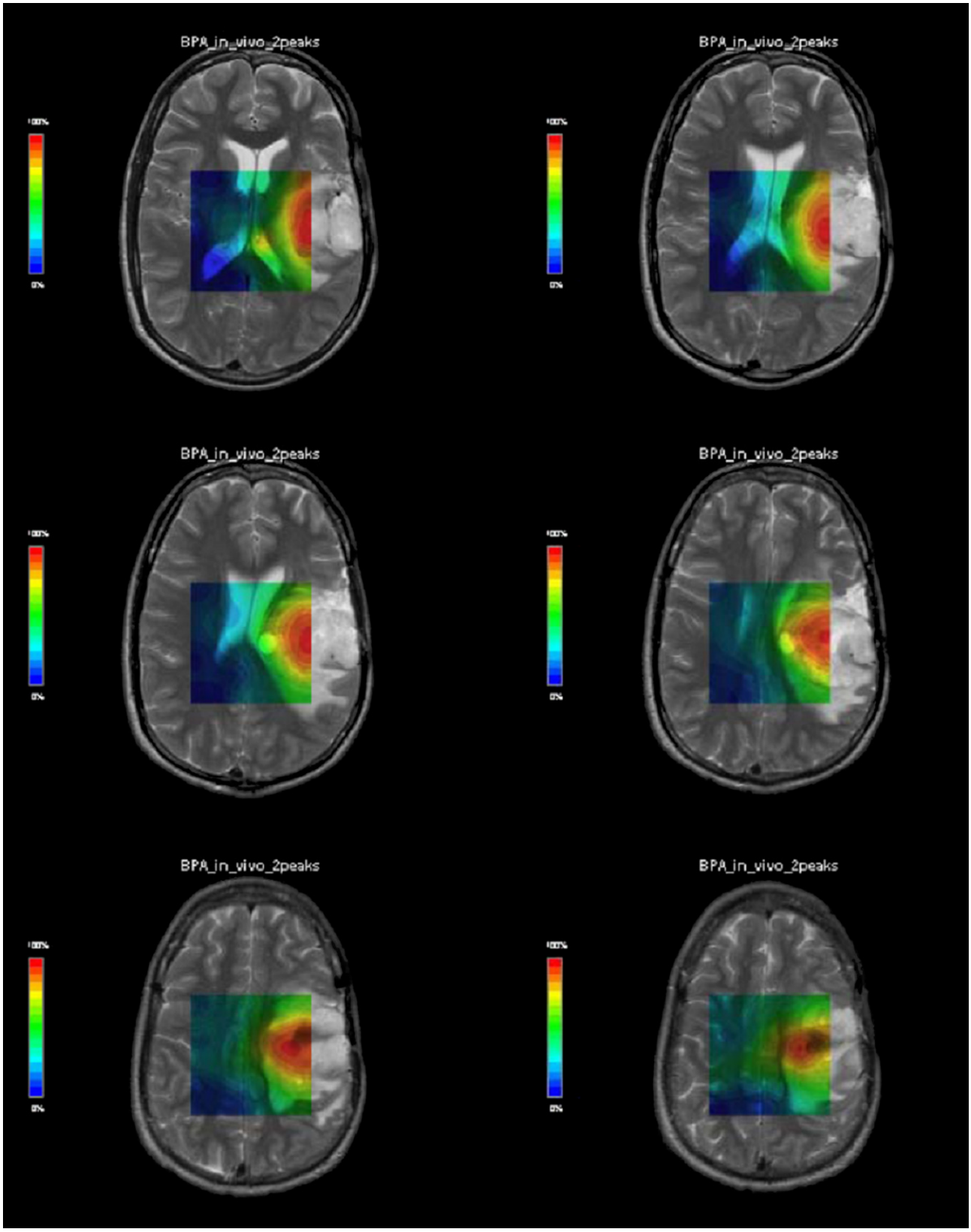

Figure 3 The 3D ^{1}H MRSI metabolite maps of a patient with glioblastoma multiforme [136]. The metabolite maps are based on the Gaussian line shape fitting of two peaks detected in the aromatic region 1.5 h after BNCT. This kind of imaging could give an objective exclusion criterion for BNCT. If no indicative signal is detected from the volume of interest located in a region feasible for good quality MRS, then boron is not accumulating sufficiently in the tumor to reach an appropriate radiation dose level in BNCT.

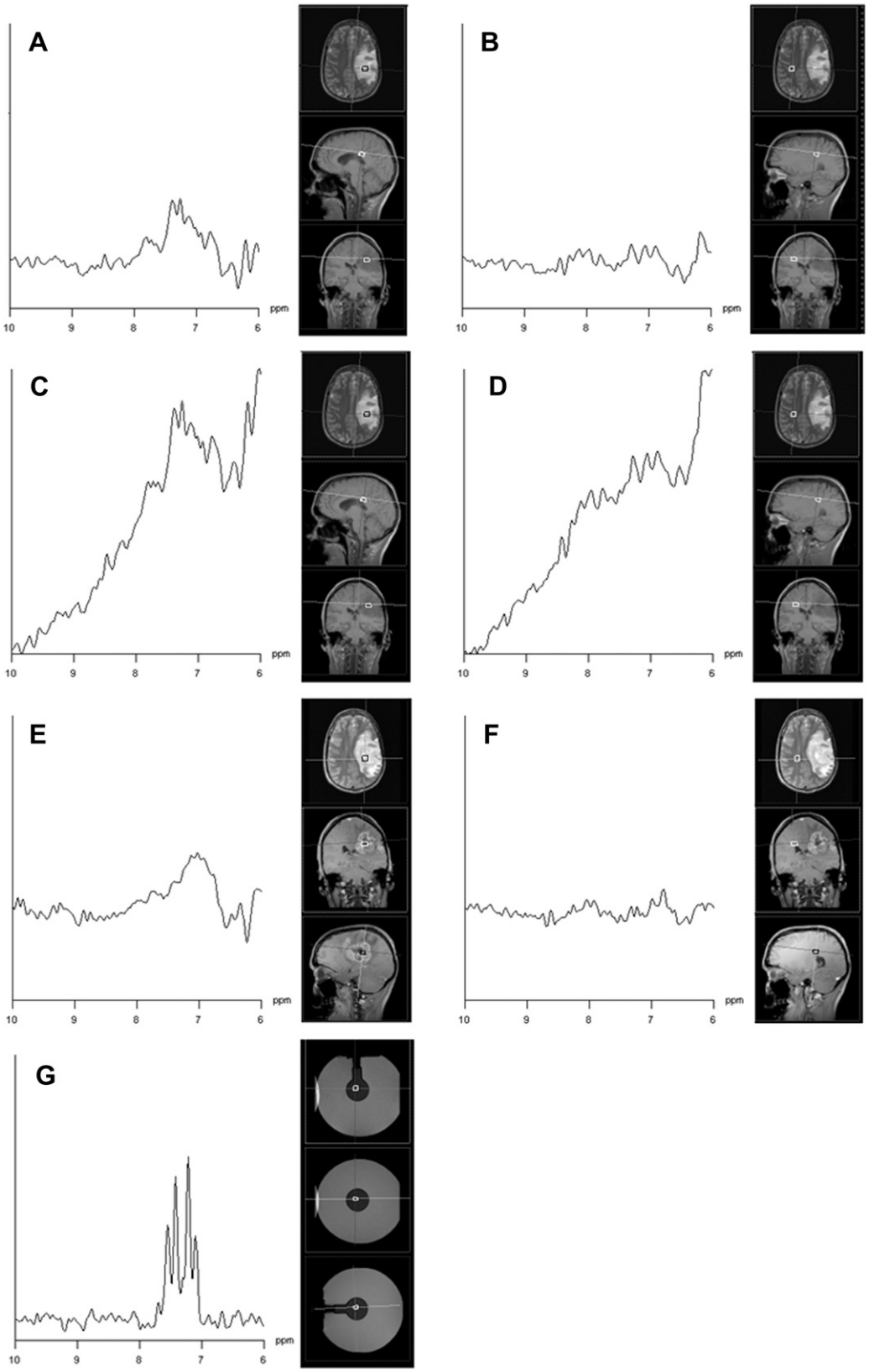

Figure 4 The aromatic region of the 3D ^{1}H MR spectra measured from tumor (A) and contralateral brain tissue (B) 1.5 h after BNCT in patient with glioblastoma multiforme [136]. In the spectra A and B, baseline correction has been applied. The same data without baseline correction is shown in the spectra C and D for comparison. Two signals can be detected in the tumor spectrum (A). The tumour (E) and contralateral brain tissue (F) spectra measured one month after BNCT and a spectrum measured from 3.0 mM BPA aqueous solution (with 10.1 mM creatine) (G) are also shown.

device to be used in BNCT treatments have been studied, but is still in the development phase, since the process is demanding for several reasons: the neutrons and other radiation present in the treatment room, the overall low signal-to-noise ratio and the shortness of the treatment and thus imaging time. In particular the prompt 2.2 MeV gamma rays from hydrogen neutron capture reactions with the induced annihilation peak at 511 keV disturb the measurement and the compton edge can give an important contribution to the background on the 478 keV region and must be taken into account.

In 2002, tests with a boron phantom were performed at the Finnish BNCT reactor both with CdZnTe and Si detectors [144]. The CdZnTe detector appeared promising, being able to detect the required boron signal from the background noise. However, the estimated time needed to produce an image was long compared to the treatment time of a patient. Similar results were achieved in Japan, where both HPGe and CdZnTe detectors were tested [145]. Also, optimization of the collimator dimensions was studied, the results indicating that a 1 cm tumour could be detected using an array of detectors [146]. The germanium detector produces good signal and high quality single point measurements have been achieved [140,141,147], but the required space and cooling systems appear to be too extensive to be used in clinical setting. An Argentinean research group has designed and tested a $LaBr_3$(Ce) detector system producing 1 cm^3 voxel images with 21 $\times$ 21 voxels [148,149]. With this prototype, spectra from a phantom containing a tumour were measured and an image with 1 cm^2 pixels was successfully reconstructed.

During the past ten years, considerable technological improvements have been achieved in both the detector efficiency (electronics, material, signal processing) and shielding of gamma and neutron radiation. At present we are designing and constructing a new prompt gamma camera in Finland. Development of monitoring the dose distribution during the treatment will enable taking BNCT to the next level in terms of predictability and patient safety, as the observation on the exact amount of boron in the tumour as well as in the healthy tissue allows for precise dose calculations.

Diffusion imaging in the detection of BNCT effects in patients

In order to improve BNCT treatments, it is essential to detect the changes in the tumour area and normal tissue as early as possible, and to correlate the findings to the different dose components of the irradiation. MRI and PET studies are used to follow up the response of radiation therapy. Mostly, the follow up of the BNCT patients are based on T2-weighted and gadolinium-enhanced T1-weighted MRI scans. The survival curves are used to determine the "efficiency" of BNCT. However, when a new treatment modality is used for cancer treatment, the acute changes should be especially followed up with modern imaging techniques in order to understand, for example, the effect of different LET-components in the tumour and normal tissues. Conventional imaging techniques seem to be too conservative to detect small changes, which would be essential to understand the mechanisms of complicated irradiations such as BNCT.

Possibilities of using diffusion MRI imaging for tumour grading, definition and response to therapy by estimating changes in Apparent Diffusion Coefficient (ADC) have been widely researched. However, the results appear to overlap and inconclusive for brain tumours [150–152]. For head and neck tumours, ADC may predict the response to therapy (chemoradiation therapy) [153]. Compared to the typical degree of diffusion weighting (*b*-value of 800–1000 s/mm^2), a higher *b*-value (e.g. 4000 s/mm^2) can yield additional information and thus increase significantly the sensitivity to detect an early response [152]. Additionally, instead of mono-exponential diffusion analysis, alpha index to model diffusion heterogeneity may be beneficial in assessing the tumour response. However, this has only been reported when assessing the tumour infiltration in rat brain [154] and human high-grade gliomas [155]. Functional Diffusion Maps (fDM) is a promising biomarker to predict early response to therapy, whereas the mean ADC for a ROI is insufficient. Pre-clinical animal models suggest that ADC is suitable to predict the efficacy of therapeutic response, while it does not assess the response [156]. With fDM it is possible to obtain voxel-wise information about the response to the therapy in both brain [157–159] and head and neck tumours [160].

In Diffusion Tensor Imaging (DTI) directional information about the diffusion is obtained, resulting in anisotropy indices e.g. fractional anisotropy (FA), planar anisotropy (commonly abbreviated as CP) and linear anisotropy (CL) maps. It has been suggested that infiltrative changes can be observed either by visualizing displacement, interruption or widening of the white matter tract in FA-maps or by tractography [161]. FA can be probably used to differentiate tumour recurrence from radiation necrosis in brain tumours and provide a non-invasive alternative to histological diagnosis and craniotomies [162]. In animal models the FA, CP and CL have proven to be capable of defining the tumour border [163,164].

In our preliminary study that aimed to assess the response to BNCT from pre- and post-treatment images from ADC and FA maps, the swelling of the brain caused co-registration problems and the tumour tissue may not have been fully aligned. However, it should be feasible to develop a robust co-registration method once more patients are acquired for the study [151]. Feasibility of diffusion imaging in assessing the response to BNCT and conventional radiation therapy should be studied.

Discussion

From the patient clinical trials carried out so far in Finland, results indicate a clear potential for clinical efficacy and safety of BNCT [1–4,10]. The technological aspects of the treatments are a substantial subject of research since standardization of the treatment process and development of patient imaging and monitoring are essential, if the recommendations on strictness and accuracy of the absorbed dose in radiotherapy are to be followed [15,20,44,46,47,49,55–57,59,165–168].

Currently, BNCT beam dosimetry is mainly based on ionization chambers and activation detectors, while other methods such as microdosimeters or gel dosimeters are applied as complementary methods for either absolute or relative dose measurements. Dose measurements still rely partly on results from computer simulations, such as the calculated neutron spectrum at the point of measurement. Thus, the possibilities in research to improve the management and measurement of the epithermal neutron field energy distribution should be continued.

Furthermore, a more detailed knowledge and monitoring of the boron biodistribution would be beneficial for selecting patients for treatments, treatment planning, dose calculations and in estimating the effectiveness and side effects of the treatments. For this purpose, a variety of methods including diffusion imaging, spectroscopy and prompt gamma imaging are under development. The success of BNCT also depends on developing new treatment schemes, such as combining BNCT with photon radiation therapy [10,169] and on the development of new boron carrier drugs [21,170–173]. It also seems inevitable that in order incorporate BNCT treatment facilities into hospitals and thus to enable more extensive clinical use of BNCT in the future, development of efficient accelerator based neutron sources is required.

Finally, development in boron neutron capture therapy is an interdisciplinary effort requiring an extensive scientific community with expertise in medical and nuclear physics, reactor engineering, chemistry, pharmacology, clinical radiology, neurology and oncology. To reach the full potential of BNCT, pursuing basic research and technical development should be continued. In Finland, this objective has been promoted over two the last two decades, with work provided by an established research community, professional expertise and dedicated technical infrastructure.

Conflict of interest

None.

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References

[1] Joensuu H, Kankaanranta L, Seppälä T, Auterinen I, Kallio M, Kulvik M, et al. Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine. J Neurooncol 2003;62:123–34.

[2] Kankaanranta L, Seppälä T, Koivunoro H, Saarilahti K, Atula T, Collan J, et al. Boron neutron capture therapy in the treatment of locally recurred head-and-neck cancer: final analysis of a phase I/II trial. Int J Radiat Oncol Biol Phys 2011; 99:97–100.

[3] Kankaanranta L, Seppälä T, Koivunoro H, Välimäki P, Beule A, Collan J, et al. l-Boronophenylalanine-mediated boron neutron capture therapy for malignant glioma progressing after external beam radiation therapy: a phase I study. Int J Radiat Oncol Biol Phys 2011;80:369–76.

[4] Kouri M, Kankaanranta L, Seppälä T, Tervo L, Rasilainen M, Minn H, et al. Undifferentiated sinonasal carcinoma may respond to single-fraction boron neutron capture therapy. Radiother Oncol 2004;72:83–5.

[5] Barth RF, Soloway AH, Fairchild RG, Brugger RM. Boron neutron capture therapy for cancer. Realities and prospects. Cancer 1992;70:2995–3007.

[6] Barth RF, Yang W, Rotaru JH, Moeschberger ML, Boesel CP, Soloway AH, et al. Boron neutron capture therapy of brain tumors: enhanced survival and cure following blood-brain barrier disruption and intracarotid injection of sodium borocaptate and boronophenylalanine. Int J Radiat Oncol Biol Phys 2000;47:209–18.

[7] Barth RF, Soloway AH, Brugger RM. Boron neutron capture therapy of brain tumors: past history, current status, and future potential. Cancer Invest 1996;14:534–50.

[8] Kankaanranta L, Seppälä T, Koivunoro H, Saarilahti K, Atula T, Collan J, et al. Boron neutron capture therapy in the treatment of locally recurred head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:475–82.

[9] Auterinen I, Hiismäki P, Kotiluoto P, Rosenberg RJ, Salmenhaara S, Seppälä T, et al. Metamorphosis of a 35 years old TRIGA reactor into a modern BNCT facility. In: Proceedings of frontiers in neutron capture therapy, La Jolla, United States; 2001. p. 267–75.

[10] Kankaanranta L, Saarilahti K, Makitie A, Valimaki P, Tenhunen M, Joensuu H. Boron neutron capture therapy (BNCT) followed by intensity modulated chemoradiotherapy as primary treatment of large head and neck cancer with intracranial involvement. Radiother Oncol 2011;99:98–9.

[11] Kortesniemi M. Solutions for clinical implementation of boron neutron capture therapy in Finland. PhD thesis. University of Helsinki, Helsinki; 2002.

[12] Seppälä T. FiR 1 epithermal neutron beam model and dose calculation for treatment planning in neutron capture therapy. PhD thesis. University of Helsinki, Helsinki; 2002.

[13] Koivunoro H, Seppälä T, Uusi-Simola J, Merimaa K, Kotiluoto P, Serén T, et al. Validation of dose planning calculations for boron neutron capture therapy using cylindrical and anthropomorphic phantoms. Phys Med Biol 2010; 55:3515–33.

[14] Salli E, Seppälä T, Koivunoro H, Kankaanranta L, Asikainen S, Savolainen S. Co-registration of the BNCT treatment planning images for clinical practice. In: Proceedings of international congress on neutron capture therapy, Kagawa, Japan; 2006. p. 64–6.

[15] International Commission on Radiation Units and Measurement (ICRU). Determination of absorbed dose in a patient irradiated by beams of X or gamma rays in radiotherapy procedures. ICRU Publications; 1976. Report 24.

[16] Järvinen H, Voorbraak WP, editors. Recommendations for the dosimetry of boron neutron capture therapy (BNCT). The Nuclear Research and consultancy Group NRG; 2003. Report 21425/03.55339/C.

[17] Välimäki JP, Lampinen JS, Kuronen AA, Ilvonen SA, Stepanek J, Savolainen SE. Comparison of different cell-cluster models for cell-level dosimetry. Acta Oncol 2001; 40:92–7.

[18] Barth RF, Coderre JA, Vicente MG, Blue TE. Boron neutron capture therapy of cancer: current status and future prospects. Clin Cancer Res 2005;11:3987–4002.

[19] Barth RF. Boron neutron capture therapy at the crossroads: challenges and opportunities. Appl Radiat Isot 2009;67:S3–6.

[20] International Atomic Energy Agency (IAEA). Current status of neutron capture therapy. IAEA; 2001. Report IAEA-TECDOC-1223.

[21] Feakes D. Chemistry and pharmacology of agents for BNCT. In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in neutron capture therapy. Kluwer Academic/Plenum Publishing Corporation; 2001. p. 23–34.
[22] Wu G, Barth RF, Yang W, Lee RJ, Tjarks W, Backer MV, et al. Boron containing macromolecules and nanovehicles as delivery agents for neutron capture therapy. Anticancer Agents Med Chem 2006;6:167–84.
[23] Nigg DW. Computational dosimetry and treatment planning considerations for neutron capture therapy. J Neurooncol 2003;62:75–86.
[24] Marek M, Viererbl L. Spatial characterization of BNCT beams. Appl Radiat Isot 2004;61:1051–5.
[25] Binns PJ, Riley KJ, Harling OK. Epithermal neutron beams for clinical studies of boron neutron capture therapy: a dosimetric comparison of seven beams. Radiat Res 2005;164: 212–20.
[26] Seppälä T, Collan J, Auterinen I, Serén T, Salli E, Kotiluoto P, et al. A dosimetric study on the use of bolus materials for treatment of superficial tumors with BNCT. Appl Radiat Isot 2004;61:787–91.
[27] Tattam DA, Allen DA, Beynon TD, Constantine G, Green S, Scott MC, et al. In-phantom neutron fluence measurements in the orthogonal Birmingham boron neutron capture therapy beam. Med Phys 1998;25:1964–6.
[28] Blue TE, Yanch JC. Accelerator-based epithermal neutron sources for boron neutron capture therapy of brain tumors. J Neurooncol 2003;62:19–31.
[29] Barth RF, Joensuu H. Boron neutron capture therapy for the treatment of glioblastomas and extracranial tumours: as effective, more effective or less effective than photon irradiation? Radiother Oncol 2007;82:119–22.
[30] Yanch JC, Zhou XL, Shefer RE, Klinkowstein RE. Accelerator-based epithermal neutron beam design for neutron capture therapy. Med Phys 1992;19:709–21.
[31] Barth RF, Soloway AH, Alam F, Clendenon NR, Blue TE, Mafune N, et al. Pre-clinical studies on boron neutron capture therapy. Basic Life Sci 1989;50:95–105.
[32] Wang CK, Blue TE, Blue JW. An experimental study of the moderator assembly for a low-energy proton accelerator neutron irradiation facility for BNCT. Basic Life Sci 1990;54: 271–80.
[33] Culbertson CN, Green S, Mason AJ, Picton D, Baugh G, Hugtenburg RP, et al. In-phantom characterisation studies at the Birmingham accelerator-generated epithermal neutron source (BAGINS) BNCT facility. Appl Radiat Isot 2004;61: 733–8.
[34] Kreiner AJ, Thatar Vento V, Levinas P, Bergueiro J, Di Paolo H, Burlon AA, et al. Development of a tandem-electrostatic-quadrupole accelerator facility for BNCT. Appl Radiat Isot 2009;67:S266–9.
[35] Tanaka H, Sakurai Y, Suzuki M, Masunaga S, Kinashi Y, Kashino G, et al. Characteristics comparison between a cyclotron-based neutron source and KUR-HWNIF for boron neutron capture therapy. Nucl Inst Meth Phys Res B 2009;267: 1970–7.
[36] Tsukamoto T, Tanaka H, Yoshinaga H, Mitsumoto T, Maruhashi A, Ono K, et al. A phantom experiment for the evaluation of whole body exposure during BNCT using cyclotron-based epithermal neutron source (C-BENS). Appl Radiat Isot 2011;69:1830–3.
[37] Esposito J, Colautti P, Fabritsiev S, Gervash A, Giniyatulin R, Lomasov VN, et al. Be target development for the accelerator-based SPES-BNCT facility at INFN Legnaro. Appl Radiat Isot 2009;67:S270–3.
[38] Ceballos C, Esposito J. The BSA modeling for the accelerator-based BNCT facility at INFN LNL for treating shallow skin melanoma. Appl Radiat Isot 2009;67:S274–7.
[39] Ceballos C, Esposito J, Agosteo S, Colautti P, Conte V, Moro D, et al. Towards the final BSA modeling for the accelerator-driven BNCT facility at INFN LNL. Appl Radiat Isot 2011;69:1660–3.
[40] Verbeke JM, Vujic JL, Leung KN. Neutron beam optimization for boron neutron capture therapy using the D-D and D-T high-energy neutron sources. Nucl Technol 2000;129:257–78.
[41] Koivunoro H, Bleuel DL, Nastasi U, Lou TP, Reijonen J, Leung KN. BNCT dose distribution in liver with epithermal D-D and D-T fusion-based neutron beams. Appl Radiat Isot 2004;61:853–9.
[42] Reijonen J, Leung KN, Firestone RB, English JA, Perry DL, Smith A, et al. First PGAA and NAA experimental results from a compact high intensity D-D neutron generator. Nucl Inst Meth Phys Res A 2004;522:598–602.
[43] Durisi E, Zanini A, Manfredotti C, Palamara F, Sarotto M, Visca L, et al. Design of an epithermal column for BNCT based D-D fusion neutron facility. Nucl Inst Meth Phys Res A 2007;574:363–9.
[44] Wambersie A, Van Dam J, Hanks G, Mijnheer BJ, Battermann JJ. What accuracy is needed in dosimetry? IAEA; 1991. Report IAEA-TECDOC-734. pp. 11–35.
[45] IAEA Technical Report Series. Absorbed dose determination in external beam radiotherapy, an international code of practise for dosimetry based on absorbed dose to water. IAEA; 2000. Report 398.
[46] Broerse JJ, Mijnheer BJ, Williams JR. European protocol for neutron dosimetry for external beam therapy. European clinical neutron dosimetry group (ECNEU). Br J Radiol 1981; 54:882–98.
[47] International Commission of Radiation Measurements and Units (ICRU). Clinical neutron dosimetry part I: determination of absorbed dose in a patient treated by external beams of fast neutrons. ICRU Publications; 1989. Report 45.
[48] American Association of Physicists in Medicine, Task Group 51. Protocol for clinical reference dosimetry of high-energy photon and electron beams. Med Phys 1999;26:1847–70.
[49] Stecher-Rasmussen F, Auterinen I, Beddoe A, Goncalves I, Järvinen H, Kosunen A, et al. A code of practice for the dosimetry of BNCT in Europe. In: Proceedings of 7th international symposium on neutron capture therapy. Zürich: Elsevier Science B.V.; 1997.
[50] Kosunen A, Kortesniemi M, Ylä-Mella H, Seppälä T, Lampinen J, Serén T, et al. Twin ionisation chambers for dose determinations in phantom in an epithermal neutron beam. Radiat Prot Dosim 1999;81:187–94.
[51] Rogus RD, Harling OK, Yanch JC. Mixed field dosimetry of epithermal neutron beams for boron neutron capture therapy at the MITR-II research reactor. Med Phys 1994;21: 1611–25.
[52] Raaijmakers CP, Konijnenberg MW, Verhagen HW, Mijnheer BJ. Determination of dose components in phantoms irradiated with an epithermal neutron beam for boron neutron capture therapy. Med Phys 1995;22:321–9.
[53] Munck af Rosenschold PM, Giusti V, Ceberg CP, Capala J, Skold K, Persson BR. Reference dosimetry at the neutron capture therapy facility at Studsvik. Med Phys 2003;30: 1569–79.
[54] Riley KJ, Binns PJ, Harling OK. Performance characteristics of the MIT fission converter based epithermal neutron beam. Phys Med Biol 2003;48:943–58.
[55] International Commission on Radiation Units and Measurement (ICRU). Neutron dosimetry for biology and medicine. ICRU Publications; 1977. Report 26.
[56] Kutcher GJ, Coia L, Gillin M, Hanson WF, Leibel S, Morton RJ, et al. Comprehensive QA for radiation oncology: report of AAPM radiation therapy committee task group 40. Med Phys 1994;21:581–618.

[57] Thwaites D, Scalliet P, Leer JW, Overgaard J. Quality assurance in radiotherapy. European society for therapeutic radiology and oncology advisory report to the commission of the european union for the 'Europe against cancer programme'. Radiother Oncol 1995;35:61—73.
[58] Sauerwein W, Hideghety K, de Vries M, Watkins P, Vroegindeweij C, Grabe S, et al. The necessity and possibilities for standardization in medical application of BNCT. Abstracts of eighth international symposium on neutron capture therapy for cancer; 1998.
[59] Rassow J, Stecher-Rasmussen F, Appelman K, Garbe S, Morrissey J, Moss R, et al. Quality assurance for clinical dosimetry of the European trial on BNCT in Petten. In: Proceedings of eighth international symposium on neutron capture therapy for cancer, La Jolla, United States; 1998.
[60] Uusi-Simola J. Finnish dosimetric practice for epithermal neutron beam dosimetry in boron neutron capture therapy. PhD thesis. University of Helsinki, Helsinki; 2009.
[61] Raaijmakers CP, Watkins PR, Nottelman EL, Verhagen HW, Jansen JT, Zoetelief J, et al. The neutron sensitivity of dosimeters applied to boron neutron capture therapy. Med Phys 1996;23:1581—9.
[62] Kaita K, Serén T, Auterinen I. First characterisation of the Finnish epithermal beam using activation detectors. In: Larsson B, Crawford J, Weinreich R, editors. Advances in neutron capture therapy. Elsevier Science B.V.; 1997. p. 353—6.
[63] Chadwick MB, Barschall HH, Caswell RS, DeLuca PM, Hale GM, Jones DT, et al. A consistent set of neutron kerma coefficients from thermal to 150 MeV for biologically important materials. Med Phys 1999;26:974—91.
[64] Kota C, Maughan RL. A dosimetry system for boron neutron capture therapy based on the dual counter microdosimetric technique. Bull Cancer Radiother 1996;83:173.
[65] Bradley PD, Rosenfeld AB, Allen BJ, Kobayashi T, Sakurai Y, Kota C, et al. Application of silicon diode arrays for microdosimetry for BNCT and FNT. In: Proceedings of frontiers in neutron capture therapy, La Jolla, United States. Kluwer Academic/Plenum Publishing Corporation; 2001. p. 615—21.
[66] Uusi-Simola J, Serén T, Seppälä T, Kosunen A, Auterinen I, Savolainen S. Dosimetric comparison at FiR 1 using microdosimetry, ionisation chambers and computer simulation. Appl Radiat Isot 2004;61:845—8.
[67] Agosteo S, Colautti P, Fanton I, Fazzi A, Introini MV, Moro D, et al. Study of a solid state microdosemeter based on a monolithic silicon telescope: irradiations with low-energy neutrons and direct comparison with a cylindrical TEPC. Radiat Prot Dosim 2011;143:432—5.
[68] Burmeister J, Kota C, Maughan RL. Dosimetry of the boron neutron capture reaction for BNCT and BNCEFNT. Strahlenther Onkol 1999;175:115—8.
[69] Burmeister J, Kota C, Maughan R, Riley K, Harling O, Wielopolski L, et al. Microdosimetry studies at the BMRR and the MITR-II using miniature tissue-equivalent proportional counters. In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in neutron capture therapy. Kluwer Academic/Plenum Publishing Corporation; 2001. p. 581—6.
[70] Burmeister J, Kota C, Maughan RL, Waker AJ, Riley K, Wielopolski L. Application of TEPC microdosimetry to boron neutron capture therapy. Radiat Prot Dosim 2002;99:351—2.
[71] Moro D, Colautti P, Lollo M, Esposito J, Conte V, De Nardo L, et al. BNCT dosimetry performed with a mini twin tissue-equivalent proportional counters (TEPC). Appl Radiat Isot 2009;67:171—4.
[72] Rosenfeld AB. Semiconductor dosimetry in BNCT. In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in neutron capture therapy. Kluwer Academic/Plenum Publishing Corporation; 2001. p. 557—63.
[73] Pospisil S, Sopko B, Havránková E, Janout Z, Konicek J, Mácha I, et al. Si diode as a small detector of slow neutrons. Radiat Prot Dosim 1993;46:118.
[74] Kaplan GI, Rosenfeld AB, Allen BJ, Coderre JA, Kobayashi T, Maughan RL , et al. Semiconductor detectors for inphantom thermal neutron flux and boron dose measurements in BNCT and fast neutron therapy. In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in neutron capture therapy. Kluwer Academic/Plenum Publishing Corporation; 2001. p. 1175—80.
[75] Perks CA, Mill AJ, Constantine G, Harrison KG, Gibson JA. A review of boron neutron capture therapy (BNCT) and the design and dosimetry of a high-intensity, 24 keV, neutron beam for BNCT research. Br J Radiol 1988;61:1115—26.
[76] Aschan C, Toivonen M, Savolainen S, Seppälä T, Auterinen I. Epithermal neutron beam dosimetry with thermoluminescence dosemeters for boron neutron capture therapy. Radiat Prot Dosim 1999;81:47—56.
[77] Aschan C. Applicability of thermoluminescent dosimeters in X-Ray organ dose determination and in the dosimetry of systemic and boron neutron capture radiotherapy. PhD thesis. University of Helsinki, Helsinki; 1999.
[78] Liu HM, Hsu PC, Liaw TF. Gamma dose measurement in a water phantom irradiated with the BNCT facility at THOR. Radiat Prot Dosim 2001;95:353—8.
[79] Gambarini G, Klamert V, Agosteo S, Birattari C, Gay S, Rosi G, et al. Study of a method based on TLD detectors for in-phantom dosimetry in BNCT. Radiat Prot Dosim 2004;110: 631—6.
[80] Burgkhardt B, Bilski P, Budzanowski M, Bottger R, Eberhardt K, Hampel G, et al. Application of different TL detectors for the photon dosimetry in mixed radiation fields used for BNCT. Radiat Prot Dosim 2006;120:83—6.
[81] Gambarini G, Agosteo S, Marchesi P, Nava E, Palazzi P, Pecci A, et al. Discrimination of various contributions to the absorbed dose in BNCT: fricke-gel imaging and intercomparison with other experimental results. Appl Radiat Isot 2000;53:765—72.
[82] Schmitz T, Blaickner M, Schutz C, Wiehl N, Kratz JV, Bassler N, et al. Dose calculation in biological samples in a mixed neutron-gamma field at the TRIGA reactor of the University of Mainz. Acta Oncol 2010;49:1165—9.
[83] Karila J, Seppälä T, Serén T, Kotiluoto P, Auterinen I, Aschan C, et al. The TL analysis methods used to determine absorbed gamma doses in vivo for the BNCT patients treated at FiR 1. Appl Radiat Isot 2004;61:793—7.
[84] Farajollahi AR, Bonnett DE, Tattam D, Green S. The potential use of polymer gel dosimetry in boron neutron capture therapy. Phys Med Biol 2000;45:N9—14.
[85] Uusi-Simola J, Savolainen S, Kangasmäki A, Heikkinen S, Perkiö J, Abo Ramadan U, et al. Study of the relative dose-response of BANG-3 polymer gel dosimeters in epithermal neutron irradiation. Phys Med Biol 2003;48:2895—906.
[86] Uusi-Simola J, Heikkinen S, Kotiluoto P, Serén T, Seppälä T, Auterinen I, et al. MAGIC polymer gel for dosimetric verification in boron neutron capture therapy. J Appl Clin Med Phys 2007;8:114—23.
[87] Davis MH, Khotanzad A, Flamig DP, Harms SE. A physics-based coordinate transformation for 3-D image matching. IEEE Trans Med Imaging 1997;16:317—28.
[88] Collignon A, Maes F, Delaere D, Vandermeulen D, Suetens P, Marchal G. Automated multi-modality image registration based on information theory. In: Bizais Y, Barillot C, Di Paola R, editors. Information processing in medical imaging. Kluwer Academic Publishers; 1995. p. 263—74.
[89] Wells 3rd WM, Viola P, Atsumi H, Nakajima S, Kikinis R. Multi-modal volume registration by maximization of mutual information. Med Image Anal 1996;1:35—51.

[90] Mattes D, Haynor DR, Vesselle H, Lewellyn TK, Eubank W. Nonrigid multimodality image registration. In: Sonka M, Hanson KM, editors. Medical imaging 2001: image processing; 2001. p. 1609—20.
[91] Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical recipes in C: the art of scientific computing. 2nd ed. Cambridge University Press; 1992. pp. 412—9.
[92] The American College of Radiology (ACR), National Electrical Manufacturers Association (NEMA). Digital imaging and communications in medicine (DICOM). NEMA Standards Publications PS3-1993; 1994.
[93] Pluim JPW, Maintz JBA, Viergever MA. Mutual information matching in multiresolution contexts. Im Vis Comp 2001;19: 45—52.
[94] Maes F, Vandermeulen D, Suetens P. Comparative evaluation of multiresolution optimization strategies for multimodality image registration by maximization of mutual information. Med Image Anal 1999;3:373—86.
[95] Burdett J, Stevens J, Flugel D, Williams E, Duncan JS, Lemieux L. Increased sensitivity to pathological brain changes using co-registration of magnetic resonance imaging scans. Acta Radiol 2006;47:1067—72.
[96] Erickson BJ, Mandrekar J, Wang L, Patriarche JW, Bartholmai BJ, Wood CP, et al. Effect of automated image registration on radiologist interpretation. J Digit Imaging 2007;20:105—13.
[97] Schröder WJ, Martin KM, Lorensen WE. The design and implementation of an object-oriented toolkit for 3D graphics and visualization. In: Proceedings of IEEE visualization '96, San Francisco, United States; 1996. p. 93—100.
[98] Van Leemput K, Hämäläinen J. A cross-platform software framework for medical image processing. In: Proceedings of medical image computing and computer-assisted intervention — MICCAI. Saint-Malo, France: SpringerLink; 2004. p. 1091—2.
[99] Yoo TS, Ackerman MJ, Lorensen WE, Schroeder W, Chalana V, Aylward S, et al. Engineering and algorithm design for an image processing Api: a technical report on ITK—the Insight Toolkit. Stud Health Technol Inform 2002;85:586—92.
[100] Ibáñez L, Schroeder W. The ITK software guide 2.4. Kitware, Inc.; 2005.
[101] Zamenhof R, Redmond E2, Solares G, Katz D, Riley K, Kiger S, et al. Monte Carlo-based treatment planning for boron neutron capture therapy using custom designed models automatically generated from CT data. Int J Radiat Oncol Biol Phys 1996;35:383—97.
[102] Nigg DW, Wemple CA, Wessol DE, Wheeler FJ. SERA - an advanced treatment planning system for neutron therapy and BNCT. Trans ANS 1999;80:66—8.
[103] Li HS, Liu YW, Lee CY, Lin TY, Hsu FY. Verification of the accuracy of BNCT treatment planning system THORplan. Appl Radiat Isot 2009;67:S122—5.
[104] Kotiluoto P, Hiisamäki P, Savolainen S. Application of the new MultiTrans SP3 radiation transport code in BNCT dose planning. Med Phys 2001;28:1905—10.
[105] Briesemeister JF. MCNP - a general Monte Carlo code N-particle transport code, Version 4C; 2000. Computer program.
[106] Rhoades WA, Childs RL. The DORT two-dimensional discrete ordinates transport code. Nucl Sci Eng 1988;99:88—9.
[107] Rhoades WA, Simpson DB. The TORT three-dimensional discrete ordinates neutron/photon transport code (TORT version 3), ORNL/TM-13221; 1997. Computer program.
[108] Ryynänen PM, Kortesniemi M, Coderre JA, Diaz AZ, Hiismäki P, Savolainen SE. Models for estimation of the (10)B concentration after BPA-fructose complex infusion in patients during epithermal neutron irradiation in BNCT. Int J Radiat Oncol Biol Phys 2000;48:1145—54.
[109] Koivunoro H, Auterinen I, Kosunen A, Kotiluoto P, Seppälä T, Savolainen S. Computational study of the required dimensions for standard sized phantoms in boron neutron capture therapy dosimetry. Phys Med Biol 2003;48:N291—300.
[110] Kotiluoto P. Adaptive tree multigrids and simplified spherical harmonics approximation in deterministic neutral and charged particle transport. PhD thesis. VTT, Espoo; 2007.
[111] Wojnecki C, Green S. A preliminary comparative study of two treatment planning systems developed for boron neutron capture therapy: MacNCTPlan and SERA. Med Phys 2002;29: 1710—5.
[112] Durisi E, Koivunoro H, Visca L, Borla O, Zanini A. Comparison of different MC techniques to evaluate BNCT dose profiles in phantom exposed tovarious neutron fields. Radiat Prot Dosim 2010;138:213—22.
[113] Koivunoro H, Kumada H, Seppälä T, Serén T, Kotiluoto P, Auterinen I, et al. Evaluation of SERA and JCDS dose determination methods and comparison to reaction rate measurements in phantom. In: Proceedings of 14th international congress on new challenges in neutron capture therapy, Buenos Aires, Argentina; 2010. p. 250—2.
[114] Kortesniemi M, Seppälä T, Auterinen I, Savolainen S. Enhanced blood boron concentration estimation for BPA-F mediated BNCT. Appl Radiat Isot 2004;61:823—7.
[115] Coderre JA, Morris GM. The radiation biology of boron neutron capture therapy. Radiat Res 1999;151:1—18.
[116] Laakso J, Kulvik M, Ruokonen I, Vähätalo J, Zilliacus R, Färkkilä M, et al. Atomic emission method for total boron in blood during neutron-capture therapy. Clin Chem 2001;47: 1796—803.
[117] Linko S, Revitzer H, Zilliacus R, Kortesniemi M, Kouri M, Savolainen S. Boron detection from blood samples by ICP-AES and ICP-MS during boron neutron capture therapy. Scand J Clin Lab Invest 2008;68:696—702.
[118] Ryynänen P. Kinetic mathematical models for the ^{111}In-labelled bleomycin complex and ^{10}B in boron neutron capture therapy. PhD thesis. University of Helsinki, Helsinki; 2002.
[119] Ryynänen P, Kangasmäki A, Hiismäki P, Coderre J, Diaz AZ, Kallio M, et al. Non-linear model for the kinetics of ^{10}B in blood after BPA-fructose complex infusion. Phys Med Biol 2002;47:737—45.
[120] Coderre JA, Chanana AD, Joel DD, Elowitz EH, Micca PL, Nawrocky MM, et al. Biodistribution of boronophenylalanine in patients with glioblastoma multiforme: boron concentration correlates with tumor cellularity. Radiat Res 1998;149: 163—70.
[121] Elowitz EH, Bergland RM, Coderre JA, Joel DD, Chadha M, Chanana AD. Biodistribution of p-boronophenylalanine in patients with glioblastoma multiforme for use in boron neutron capture therapy. Neurosurgery 1998;42:463—9.
[122] Imahori Y, Ueda S, Ohmori Y, Kusuki T, Ono K, Fujii R, et al. Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. J Nucl Med 1998;39:325—33.
[123] Imahori Y, Ueda S, Ohmori Y, Sakae K, Kusuki T, Kobayashi T, et al. Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I. Clin Cancer Res 1998;4:1825—32.
[124] Imahori Y, Ueda S, Ohmori Y, Sakae K, Kusuki T, Kobayashi T, et al. Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part II. Clin Cancer Res 1998;4:1833—41.
[125] Aihara T, Hiratsuka J, Morita N, Uno M, Sakurai Y, Maruhashi A, et al. First clinical case of boron neutron capture therapy for head and neck malignancies using 18F-BPA PET. Head Neck 2006;28:850—5.
[126] Nichols TL, Kabalka GW, Miller LF, Khan MK, Smith GT. Improved treatment planning for boron neutron capture

therapy for glioblastoma multiforme using fluorine-18 labeled boronophenylalanine and positron emission tomography. Med Phys 2002;29:2351—8.
[127] Kabalka GW, Tang C, Bendel P. The role of boron MRI in boron neutron capture therapy. J Neurooncol 1997;33:153—61.
[128] Bendel P, Zilberstein J, Salomon Y. In vivo detection of a boron-neutron-capture agent in melanoma by proton observed 1H-10B double resonance. Magn Reson Med 1994; 32:170—4.
[129] Bendel P, Sauerwein W. Optimal detection of the neutron capture therapy agent borocaptate sodium (BSH): a comparison between 1H and 10B NMR. Med Phys 2001;28:178—83.
[130] Campanella R, Capuani S, Fasano F, Maraviglia B. Double resonance NMR imaging of BSH. In: Proceedings of research and development in neutron capture therapy, Bologna, Italy. Moduzzi Editore; 2002. p. 963—5.
[131] Porcari P, Capuani S, D'Amore E, Lecce M, La Bella A, Fasano F, et al. In vivo (19)F MRI and (19)F MRS of (19)F-labelled boronophenylalanine-fructose complex on a C6 rat glioma model to optimize boron neutron capture therapy (BNCT). Phys Med Biol 2008;53:6979—89.
[132] Porcari P, Capuani S, D'Amore E, Lecce M, La Bella A, Fasano F, et al. In vivo 19F MR imaging and spectroscopy for the BNCT optimization. Appl Radiat Isot 2009;67:S365—8.
[133] Zuo CS, Prasad PV, Busse P, Tang L, Zamenhof RG. Proton nuclear magnetic resonance measurement of p-boronophenylalanine (BPA): a therapeutic agent for boron neutron capture therapy. Med Phys 1999;26:1230—6.
[134] Bendel P, Margalit R, Koudinova N, Salomon Y. Noninvasive quantitative in vivo mapping and metabolism of boronophenylalanine (BPA) by nuclear magnetic resonance (NMR) spectroscopy and imaging. Radiat Res 2005;164: 680—7.
[135] Bendel P, Margalit R, Salomon Y. Optimized 1H MRS and MRSI methods for the in vivo detection of boronophenylalanine. Magn Reson Med 2005;53:1166—71.
[136] Timonen M. Proton magnetic resonance spectroscopy of a boron neutron capture therapy 10B-carrier, L-p-boronophenylalanine-fructose complex. PhD thesis. University of Helsinki, Helsinki; 2010.
[137] Yamamoto Y, Isobe T, Yamamoto T, Shibata Y, Anno I, Nakai K, et al. T2 corrected quantification method of L-p-boronophenylalanine using proton magnetic resonance spectroscopy for boron neutron capture therapy. Appl Radiat Isot 2009;67:S345—7.
[138] Timonen M, Kankaanranta L, Lundbom N, Collan J, Kangasmäki A, Kortesniemi M, et al. 1H MRS studies in the Finnish boron neutron capture therapy project: detection of 10B-carrier, L-p-boronophenylalanine-fructose. Eur J Radiol 2005;56:154—9.
[139] Timonen M, Kankaanranta L, Lundbom N, Kortesniemi M, Seppälä T, Kouri M, et al. Acquisition-weighted MRSI for detection and quantification of BNCT 10B-carrier L-p-boronophenylalanine-fructose complex, a phantom study. J Radiat Res 2009;50:435—40.
[140] Munck af Rosenschold PM, Verbakel WF, Ceberg CP, Stecher-Rasmussen F, Persson BR. Toward clinical application of prompt gamma spectroscopy for in vivo monitoring of boron uptake in boron neutron capture therapy. Med Phys 2001;28: 787—95.
[141] Verbakel WF, Sauerwein W, Hideghety K, Stecher-Rasmussen F. Boron concentrations in brain during boron neutron capture therapy: in vivo measurements from the phase I trial EORTC 11961 using a gamma-ray telescope. Int J Radiat Oncol Biol Phys 2003;55:743—56.
[142] Verbakel WF. Validation of the scanning-gamma-ray telescope for in vivo dosimetry and boron measurements during BNCT. Phys Med Biol 2001;46:3269—85.
[143] Wittig A, Malago M, Collette L, Huiskamp R, Buhrmann S, Nievaart V, et al. Uptake of two 10B-compounds in liver metastases of colorectal adenocarcinoma for extracorporeal irradiation with boron neutron capture therapy (EORTC Trial 11001). Int J Cancer 2008;122:1164—71.
[144] Auterinen I, Anttila K, Kotiluoto P, Serén T, Savolainen S, Kosunen A, et al. Experiments and simulations for prompt-gamma imaging of boron and hydrogen neutron capture reactions in boron neutron capture therapy. In: Proceedings of the XXXVII annual conference of the Finnish physical society, Helsinki, Finland; 2003.
[145] Kobayashi T, Sakurai Y, Ishikawa M. A noninvasive dose estimation system for clinical BNCT based on PG-SPECT—conceptual study and fundamental experiments using HPGe and CdTe semiconductor detectors. Med Phys 2000;27: 2124—32.
[146] Ishikawa M, Kobayashi T, Sakurai Y, Kanda K. Optimization technique for a prompt gamma-ray SPECT collimator system. J Radiat Res 2001;42:387—400.
[147] Munck af Rosenschöld P, Minarik D, Östlund C, Ljungberg M, Ceberg C. Prompt gamma tomography during BNCT — a feasibility study. J Inst 2006;1:P05003.
[148] Valda AA, Minsky DM, Kreiner AJ, Burlon AA, Somacal H. Development of a tomographic system for online dose measurements in BNCT (Boron neutron capture therapy). Braz J Phys 2005;35.
[149] Minsky DM, Valda AA, Kreiner AJ, Green S, Wojnecki C, Ghani Z. First tomographic image of neutron capture rate in a BNCT facility. Appl Radiat Isot 2011;69:1858—61.
[150] van Westen D, Latt J, Englund E, Brockstedt S, Larsson EM. Tumor extension in high-grade gliomas assessed with diffusion magnetic resonance imaging: values and lesion-to-brain ratios of apparent diffusion coefficient and fractional anisotropy. Acta Radiol 2006;47:311—9.
[151] Kuusela L, Sipilä O, Lundbom N, Kankaanranta L, Savolainen S. Diffusion tensor imaging using rigid co-registration in assessing the effect of boron neutron capture therapy on brain tissue. Int J CARS 2009;4:311—55.
[152] Mardor Y, Pfeffer R, Spiegelmann R, Roth Y, Maier SE, Nissim O, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. J Clin Oncol 2003;21:1094—100.
[153] Kim S, Loevner L, Quon H, Sherman E, Weinstein G, Kilger A, et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clin Cancer Res 2009;15:986—94.
[154] Bennett KM, Hyde JS, Rand SD, Bennett R, Krouwer HG, Rebro KJ, et al. Intravoxel distribution of DWI decay rates reveals C6 glioma invasion in rat brain. Magn Reson Med 2004;52:994—1004.
[155] Kwee TC, Galban CJ, Tsien C, Junck L, Sundgren PC, Ivancevic MK, et al. Intravoxel water diffusion heterogeneity imaging of human high-grade gliomas. NMR Biomed 2010;23: 179—87.
[156] Moffat BA, Hall DE, Stojanovska J, McConville PJ, Moody JB, Chenevert TL, et al. Diffusion imaging for evaluation of tumor therapies in preclinical animal models. MAGMA 2004; 17:249—59.
[157] Moffat BA, Chenevert TL, Lawrence TS, Meyer CR, Johnson TD, Dong Q, et al. Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. Proc Natl Acad Sci U S A 2005;102: 5524—9.
[158] Hamstra DA, Rehemtulla A, Ross BD. Diffusion magnetic resonance imaging: a biomarker for treatment response in oncology. J Clin Oncol 2007;25:4104—9.

[159] Hamstra DA, Galban CJ, Meyer CR, Johnson TD, Sundgren PC, Tsien C, et al. Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. J Clin Oncol 2008;26:3387—94.
[160] Galban CJ, Mukherji SK, Chenevert TL, Meyer CR, Hamstra DA, Bland PH, et al. A feasibility study of parametric response map analysis of diffusion-weighted magnetic resonance imaging scans of head and neck cancer patients for providing early detection of therapeutic efficacy. Transl Oncol 2009;2:184—90.
[161] Young RJ, Knopp EA. Brain MRI: tumor evaluation. J Magn Reson Imaging 2006;24:709—24.
[162] Kashimura H, Inoue T, Beppu T, Ogasawara K, Ogawa A. Diffusion tensor imaging for differentiation of recurrent brain tumor and radiation necrosis after radiotherapy—three case reports. Clin Neurol Neurosurg 2007;109:106—10.
[163] Lope-Piedrafita S, Garcia-Martin ML, Galons JP, Gillies RJ, Trouard TP. Longitudinal diffusion tensor imaging in a rat brain glioma model. NMR Biomed 2008;21:799—808.
[164] Zhang J, van Zijl PC, Laterra J, Salhotra A, Lal B, Mori S, et al. Unique patterns of diffusion directionality in rat brain tumors revealed by high-resolution diffusion tensor MRI. Magn Reson Med 2007;58:454—62.
[165] Thwaites DI, Burns DT, Klevenhagen SC, Nahum AE, Pitchford WG. The IPEMB code of practice for electron dosimetry for radiotherapy beams of initial energy from 2 to 50 MeV based on air kerma calibration. Phys Med Biol 1996; 41:2557—603.
[166] Brahme A. Dosimetric precision requirements in radiation therapy. Acta Radiol Oncol 1984;23:379—91.
[167] Bleehen N, Glatstein E, Haybittle J, editors. Radiation therapy planning. Marcel Dekker; 1983.
[168] Kosunen A. Metrology and quality of radiation therapy dosimetry of electron, photon and epithermal neutron beams. PhD thesis. University of Helsinki; 1999.
[169] Yamamoto T, Nakai K, Nariai T, Kumada H, Okumura T, Mizumoto M, et al. The status of Tsukuba BNCT trial: BPA-based boron neutron capture therapy combined with X-ray irradiation. Appl Radiat Isot 2011;69:1817—8.
[170] Nigg DW. Current trends and progress in the physics of BNCT. In: Hawthorne MF, Shelly K, Wiersema RJ, editors. Frontiers in neutron capture therapy. Kluwer Academic/Plenum Publishing Corporation; 2001. p. 13—21.
[171] Geninatti-Crich S, Alberti D, Szabo I, Deagostino A, Toppino A, Barge A, et al. MRI-guided neutron capture therapy by use of a dual gadolinium/boron agent targeted at tumour cells through upregulated low-density lipoprotein transporters. Chemistry 2011;17:8479—86.
[172] Kimura S, Masunaga S, Harada T, Kawamura Y, Ueda S, Okuda K, et al. Synthesis and evaluation of cyclic RGD-boron cluster conjugates to develop tumor-selective boron carriers for boron neutron capture therapy. Bioorg Med Chem 2011; 19:1721—8.
[173] Cappelli A, Valenti S, Mancini A, Giuliani G, Anzini M, Altieri S, et al. Carborane-conjugated 2-quinolinecarboxamide ligands of the translocator protein for boron neutron capture therapy. Bioconjug Chem 2010;21:2213—21.