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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.