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Original paper

Exploring Boron Neutron Capture Therapy for non-small cell lung cancer

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ABSTRACT

Boron Neutron Capture Therapy (BNCT) is a radiotherapy that combines biological targeting and high LET radiation. It consists in the enrichment of tumour with ^{10}B and in the successive irradiation of the target with low energy neutrons producing charged particles that mainly cause non-repairable damages to the cells.

The feasibility to treat Non Small Cells Lung Cancer (NSCLC) with BNCT was explored. This paper proposes a new approach to determine treatment plans, introducing the possibility to choose the irradiation start and duration to maximize the tumour dose. A Tumour Control Probability (TCP) suited for lung BNCT as well as other high dose radiotherapy schemes was also introduced.

Treatment plans were evaluated in localized and disseminated lung tumours. Semi-ideal and real energy spectra beams were employed to assess the best energy range and the performance of non-tailored neutron sources for lung tumour treatments.

The optimal neutron energy is within [500 eV–3 keV], lower than the 10 keV suggested for the treatment of deep-seated tumours in the brain. TCPs higher than 0.6 and up to 0.95 are obtained for all cases.

Conclusions drawn from [Suzuki et al., Int Canc Conf J 1 (4) (2012) 235–238] supporting the feasibility of BNCT for shallow lung tumours are confirmed, however discussions favouring the treatment of deeper lesions and disseminated disease are also opened. Since BNCT gives the possibility to deliver a safe and potentially effective treatment for NSCLC, it can be considered a suitable alternative for patients with few or no treatment options.

Introduction

Boron Neutron Capture Therapy (BNCT) is a binary form of experimental radiotherapy based on the administration of a drug able to concentrate ^{10}B in the tumour more than in healthy tissues, and on the successive irradiation of the target with low energy neutrons [1]. The exploited reaction is the neutron capture in ^{10}B, which has a cross section of 3837 b at thermal energies. The neutron capture gives rise to high LET radiation, generating an alpha particle and a ^{7}Li nucleus with ranges in tissues comparable to a cell diameter. As the energy deposition is spatially confined in the cells where neutrons are captured, dose delivery is selective at a cellular level without requiring the irradiation field to tightly match the shape of the target. This characteristic makes BNCT a potential option for tumours that cannot be surgically removed nor treated with a fractionated photon-therapy or stereotactic ablative body radiation therapy (SABR) protocol because of their location, stage or patient overall status.

The tumours affecting lungs are one of the most common causes of death for cancer in the world. Given that BNCT combines biological targeting and high LET radiation, its application to lung malignancies would offer the following advantages:

a. The possibility of delivering a hypofractioned or even a single-fraction treatment.
b. The ability to treat micrometastatic or diffuse disease.

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c. To disregard those complex techniques that manage the respiratory motion during conventional external radiotherapy, because the cell damage depends on the boron localization.

A preclinical study to assess normal lung tolerance to BNCT was performed in small animals at MIT (USA) with the aim to understand the human lung toxicity observed during cranial treatments [2].In Japan, preclinical studies demonstrated that BNCT was feasible for malignant pleural mesothelioma (MPM) and between 2008 and 2012 patients affected by MPM were treated using epithermal neutron beams, without causing toxicity to the healthy lung and the other involved tissues [3].

At University of Pavia (Italy), a study of BNCT for pulmonary metastases form colon adenocarcinoma is ongoing. Boronophenylalanine biodistribution studies in a rat model showed that the ratios between the boron concentration in tumour and in normal lung are suitable for a safe and effective treatment [4]. These results were recently complemented by those of Trivillin et al. [5], showing that absolute boron concentration values in lung metastases are therapeutically useful either for protocols employing BPA or decahydrodecaborate (GB-10) alone or in combination. Within the context of the treatment of non-surgically resectable lung metastases, biodistribution and radiotolerance BNCT studies in a normal lung sheep model are being also carried out considering an explanted organ irradiation protocol.[1]

The present paper presents the results of the analysis of different BNCT irradiation protocols for some clinical scenarios of lung cancer. The evaluation of the potential application of BNCT has been extended to non-small cell lung cancer (NSCLC), a tumour that showed good response to hypofractionated, high dose radiotherapy schemes (i.e. SABR). The selected cases, however, were not eligible for this therapy because of the tumour proximity to critical organs at risk. These cases are: a localized early stage NSCLC in the upper side close to the costal wall, a deep localized early stage NSCLC tumour located close to the trachea and proximal bronqui, and a theoretical case of oligometastatic disease encompassing the whole lung volume.

Semi-ideal epithermal neutron sources from 100 eV to 6 keV were evaluated to give indications about the optimal characteristics of the neutron source conceived for lung BNCT. Moreover, the spectra of two constructed or projected neutron beams tailored for brain tumours were tested.

One novelty of our approach is to determine the optimum start time and duration of the irradiation using the boron concentration–time profiles in healthy lung and in tumour. In order to evaluate the potential effectiveness of the proposed treatments a suitable tumour control probability model for the treatment of NSCLC with BNCT has also been introduced and validated.

Based on the application of the mentioned radiobiological model and following currently used clinical SABR criteria and experience, some treatment plans delivered in a single BNCT session were assessed and those most promising were thoroughly discussed.

Materials and methods

Different clinical scenarios were taken into account in order to explore the possibility to treat with BNCT a wide range of patients who would have few possibilities with the current clinical options. In the following subsections, the computational and theoretical models introduced in this work are presented in detail, and the evaluation criteria to assess candidate plans are finally described.

[1] Ongoing lung autotransplant study in sheep.

The thorax model

The computational tool used to create the anthropomorphic model of the patients and to analyse the results of the irradiation simulations is a beta version of the Treatment Planning System developed in Argentina. By means of the optimized geometrical reconstruction method called MultiCell, an accurate volumetric model can be generated from the patient CT images by combination of multiple-sized parallelepiped cells suitable for MCNP code [6]. In this way, the total number of cells can be kept relatively low, while ensuring a high precision in the reconstruction. Figure 1 shows an example of a MultiCell reconstruction of a human thorax that evidences the use of different sized cells.

Anthropomorphic models were segmented in the relevant tissues with atomic composition and density taken from ICRU 46 report [7]. Volumes of interest are automatically coded into MCNP.

A superimposed mesh grid of 125 mm^3 is used to calculate the different dose components and a subsequent interpolation is performed to assign the dose values to each pixel of the images. The results are then properly weighted and summed to calculate the total dose.

The neutron sources

The epithermal beams designed for the treatment of deep-seated tumours have energies centred around 10 keV [8]. However, as high energy neutrons deliver higher doses in the first layers of tissues, organ such as the skin and the spinal cord may limit the dose administered to the tumour in case of thorax irradiation.

In this work, several semi-ideal neutron beams were tested on the human thorax models in order to explore advantages and drawbacks related to the extensive irradiation of NSCLC with neutrons. The energy of these sources was sampled from Gaussian distributions with mean energies of 100 eV, 500 eV, 1 keV, 3 keV and 6 keV, and standard deviations of 0.02 keV for mean energies up to 1 keV, and 0.2 keV for the others.

Based on the conclusions drawn from the aforementioned semi-ideal beams, two realistic neutron spectra from existing or projected BNCT facilities were selected from literature and evaluated. The first realistic beam, named MIT-SPECT, is based on the published energy spectrum of the MIT-II epithermal reactor beam developed for BNCT [9]. The beam spectrum is characterized by 95% of the neutrons in the [0, 10 keV] energy range, and approximate 20% between 500 eV and 3 keV. The second realistic beam, named CNEA-MEC, is based on one of the energy spectra published by Capoulat et al. [10]. for an accelerator based epithermal neutron beam that is being designed in Argentina to treat deep-seated GBM tumours with BNCT. In this case, 90% of the neutrons are between 0.2 eV and 20 keV, and almost 30% in the [500 eV–3 keV] energy range. The spectrum of these realistic neutron beams are presented in Fig. 2. Sources particles were sampled uniformly in a plane and particle direction set monodirectional normal to that plane.

Simulations for both semi-ideal and realistic beams were carried out normalizing their corresponding thermal neutron flux peaks in water to 5×10^9 n cm^{-2} s^{-1}. Particle transport was performed without explicitly considering the unavoidable gamma contamination of the beam. However, the contribution of this radiation component to the total dose was taken into account by increasing 50% the induced gamma dose in tissues from H and B.

For localized NSCLC, the beam was set circular with a 10 cm diameter. For multiple metastatic NSCLC the source diameter was increased to 20 cm in order to encompass the lung volume completely. If necessary, a 30 mm thick boronated polyethylene frame was added to the port to reduce the port free area and to