The validation of the treatment planning system BDTPS through an “in-vivo” comparison

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Introduction.
Boron Neutron Capture Therapy (BNCT) is a therapeutic technique, still under development, which exploits the interaction between thermal neutrons and B¹⁰ isotope administered to the patient using drugs. The reaction $\text{B}^{10}(n,\alpha)\text{Li}^7$ produces two high LET and short range fragments causing tumor cell damage.
BNCT may be useful for treatment of locally advanced tumors that, in addition to the primary tumor mass, show microscopic infiltration into healthy tissue depths.
Correct boron level measurements both in tumor and in normal tissue are fundamental for therapeutic success. The method used in the past consists of an analysis of tissue samples taken during surgery [1][2][3]. However, the need to move towards non invasive techniques led to development of innovative methods. Nowadays, Positron Emission Tomography (PET) is able to provide boron concentration estimations through in vivo information [4][5].
The idea to couple the Treatment Planning System (TPS) to the information on the real boron distribution in the patient is the main added value of the new methodology set-up at DIMNP of University of Pisa, in collaboration with the JRC of Petten (NL). The methodology has been implemented in the new TPS, called BDTPS (Boron Distribution Treatment Planning System) [6], which takes into account the actual boron distribution in the human volume of interest, while the standard TPS assumes a uniform boron distribution, far from the reality.
After an “in-phantom” validation at JRC (Petten) [7], an “in-vivo” validation of BDTPS was possible thanks to a Japanese researchers’ team collaboration.
A Japanese 74 years old woman affected by parotid cancer was the medical case proposed for BDTPS implementation.
Both CT and PET stacks, together with other information about the case, have been provided by the Tokai Research and Development Center of JAERI. Actually, BDTPS was implemented both in standard and in PET-based approach, in order to make possible an exhaustive comparative analysis between the two approaches. The first case, named Back, was necessary to derive the same results of Japanese standard system (JCDS) [8] used for the application.

Materials and Methods.
A 74 years old Japanese woman case affected by a stage IV parotid cancer is the study reference. The objective is to compare the standard approach (adopted with JAEA Computational Dosimetry System - JCDS) and the PET-based procedure. Both runs have been conducted through the Boron Distribution Treatment Planning System (BDTPS), designed as a complete TPS containing all the main characteristics of JCDS (e.g. pre-processing based on CT images of the patient, fiducial markers, organs at risk, Monte Carlo modeling, post processing, etc.). In BDTPS, the boron dose is evaluated on the basis of the real macro-distribution of the boron compound by modules fully integrated into its internal structure.

A. Back.
Hereafter, the approach used with JCDS will be called “Back”. This method consists of five phases:
- 3D reconstruction on CT stack
- T/N evaluation on PET stack
- Assigning the 3D model with two $\text{B}^{10}$ concentrations according to T/N ratio
- Doses and fluences evaluations
- Irradiation time and plan definition
The CT scan of the patient, 60 Kg, was used for the head 3D model reconstruction.
Later on, the patient has been PET-scanned after an infusion of 220 MBq of F-BPA for a period of 40 minutes in order to assess the T/N ratio. Thus, two $^{10}$B concentrations are assigned, one to the tumor and the other to the healthy tissue respecting this ratio. In particular:

- $T/N = 5$
- $[^{10}\text{B}]_{\text{tumor}} = 146.5 \text{ ppm}$
- $[^{10}\text{B}]_{\text{tissue}} = 29.3 \text{ ppm}$

Afterwards, 500 mg of BPA for 60 kg in 3 hours have been infused in the patient and the radiation therapy performed. As neutron source, the Japan Research Reactor N. 4 (JRR-4) was used; it is a 3.5 MW$_{th}$ swimming pool style reactor, moderated and cooled with light water, that uses enriched uranium ETR-type as fuel element.

**B. PET-based approach (BDTPS)**

BDTPS needs the construction of three models of the human zone of interest:

- 3D Model, which takes into account the real geometry through CT images.
- Monte Carlo Model (MC), to simulate irradiation calculation.
- Boron Model, to take into account the heterogeneous boron distribution in the various tissues.

During the MC model construction, the Boron model is formed, hereafter referred as B Model. In fact, each universe in the MC model defines a region, which in turn defines a material with its own average boron concentration and density. Moreover, being MC model built directly from 3D model, this raises the need to have the CT stack perfectly aligned with the PET stack. This is not a requirement in JCDS standard methodology, where the PET scans are used only to assess the T/N ratio. An ad hoc CT-PET alignment work was carried out through the use of the software Amide 0.9.1.

**Results**

The 3D model is composed of 49 CT images, and the tumor extends from CT slice 9 to CT slice 20. We refer to this range because of the presence of high $^{10}$B concentrations that allows us to better appreciate the differences between the two methods. In particular we consider the slice 16 as best representative of the dynamics encountered in the central tumor range. The two approaches comparison shows how the boron dose in the center of the tumor assumes smaller values in the PET-based approach. This is even more evident through the "pixel by pixel" difference between the boron dose rate mappings in the PET-based and the Back methods. In particular, this behavior is highlighted from the slice 14 till the slice 17.

The results of the comparison show that there is an overestimation of the boron dose rate in the tumor center of about 40% in the Back case when compared with PET-based case. The situation is made even clearer if we look at the slice 16, and in particular only to the tumor mass. In fact, considering the area of the rectangle bounding the tumor and evaluating the dose values within the box, a regular surface distribution comes out from the Back approach due to the homogeneous concentration of $^{10}$B . The PET-based approach, instead, shows a central depression as a consequence of the heterogeneous distribution resulting from the activity values recorded in the PET images.

Making the difference (PET)−(Back), the formation of a concave area is representative of the boron dose rate (Gy/h) overestimation in the Back approach.

Because the boron dose rate is one of the parameters from which mainly the treatment planning depends on, according to BDTPS results one can argue an underestimation of the irradiation time in JCDS protocol. This hypothesis is supported by the patient follow-up. In particular, this document shows a recurrence raised about eighteen months later the radiation therapy, placed just where the overestimation is shown by BDTPS.

**Conclusions.**

Previous studies[9][10][11] evidenced the possibility to improve the TPS efficiency, introducing the boron localization in Monte Carlo code. In particular, the use of PET images, obtained through a positron-emitter agent (F18) linked to the boron drug BPA [12], enhances the precision and realism of the results of the treatment planning system applied to Neutron Capture Therapy (NCT) [13] . In fact, the knowledge of the boron distribution in the tissues is a key factor for the precise dose evaluation.

The comparison between the first results obtained with PET-based analysis and those from JCDS Japanese method evidenced the importance of considering PET images and boron distribution at the level of the treatment planning in neutron capture therapies[14].

Moreover, an underestimation of boron dose around the tumor ROI is detected using the PET-based approach. Possible contributions could derive also from the larger, and therefore incorrect, definition of region contour by the radiologist. This implies that the PET data integration in suitable treatment planning allows not only a valid description of the macroscopic boron distribution in various tissues, but gives support in the definition of region contours.

The follow-up of the patient confirms how BDTPS led to results very close to the reality.

**References.**


