How radiation protection issues influence the design of a clinical facility for accelerator-based Boron Neutron Capture Therapy

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Abstract. Boron Neutron Capture Therapy (BNCT) is a non-invasive, binary radiotherapy, combining the administration of a borated drug able to accumulate in tumour cells and the irradiation of the patient with low energy neutrons. The capture of a thermal neutron in boron-10 produces two charged particles which lose energy in a few micrometers, causing irreversible damages to the DNA of the cell hosting the reaction. The overall effect is the selective kill of malignant cells, while sparing the surrounding healthy tissues. The context of this work is the project of a BNCT clinical facility based on a proton accelerator coupled to a beryllium target and a Beam Shaping Assembly (BSA) mainly made of lithiated aluminum fluoride in solid form, a new material produced for this purpose. Experimental and computational studies are presented, concerning the main constituent of the BSA and the design of the treatment room. Samples of solid lithiated aluminum fluoride were studied regarding presence of impurities, mechanical resistance and uniformity. The neutron activations of the materials in the Beam Shaping Assembly and in the treatment room and the calculation of the dose distributions in the room and in the patient healthy organs were investigated. The obtained results are useful for the project of the facility, showing how these evaluations are used as a criterion for the beam design. In fact, whereas literature often overlooks the radiation protection perspective in the evaluation of BNCT feasibility studies, focusing mainly on the physical characteristics of the beams, the out-of-field dose, the neutron activation of surrounding materials and the ambient dosimetry are pivotal for the design of a clinical facility.

KEYWORDS: radiotherapy; BNCT; AB-BNCT; patient safety; neutron activation; external dosimetry

1 INTRODUCTION

Boron Neutron Capture Therapy (BNCT) is a non-invasive binary radiotherapy that uses the synergistic action of a borated drug and the irradiation with low energy neutrons, exploiting the high cross section of the (n, alpha) reaction in boron-10 [1]. The possibility to use neutron capture reactions to kill malignant cells was first theorized by the physicist Gordon Locher in 1940, just four years after the discovery of the neutron. Therapies based on such reactions can be extremely selective, thanks to the very short ranges in biological tissues of the charged particles produced, which will lose their energy in paths not exceeding the diameter of a typical cell. This selectivity strictly depends on the possibility to accumulate ^{10}B in tumour with sufficient concentration and with a high tumour-to-normal tissue concentration ratio, using drugs developed on purpose [2].

In BNCT treatments, the patient, after the administration of tumour-targeting boron-enriched drug, is irradiated with low energy neutrons. The probability that a thermal neutron is captured in ^{10}B is much higher than the interactions of neutrons with other elements in biological tissue: the reaction ^{10}B(n,a)^{7}Li has a cross section of about 3840 barns at 0.025 eV, about 2000 times the cross section of the capture in ^{14}N.

The capture reaction in ^{10}B produces an alpha particle and a lithium ion, with high-LET (Linear Energy Transfer) and with ranges in biological tissue of respectively 5 and 9 micrometers. Since these values are comparable with the average cellular diameter, the particles will lose their energy in the cell hosting the reaction, causing irreversible damages to the DNA. Given the higher concentration of boron-10 in tumour comparing to healthy tissues, the overall effect is the selective deposition of a therapeutic dose in cancer while sparing the surrounding normal cells. Thanks to this selective effect, not based on a beam targeting but rather on a biological targeting, BNCT is a potential therapeutic option for the treatment of disseminated, infiltrated or non-operable tumours.

A fundamental branch of present BNCT research concerns the neutron sources, since typical ones, research nuclear reactors, are not easily adaptable to the needs of a clinical treatment. With the last developments of technology, it is now possible to obtain proper neutron beams for BNCT using proton or deuteron accelerators coupled to beryllium or lithium targets. It is thus becoming increasingly relevant the development of BNCT facilities from accelerators, easier to install and maintain in healthcare settings [3]. Worldwide, projects are ongoing to install and use accelerator-based BNCT clinical facilities with neutron sources coming from different machines and targets. Different beam energies and targets produce neutron beams of different spectral characteristics. To obtain a neutron beam suitable for patient treatment, it is necessary to use a Beam Shaping Assembly (BSA): a composition of different geometries and materials to thermalize, filter and collimate the neutrons exiting from the target.

The context of this work is the Italian project of a BNCT clinical facility based on a Radio Frequency Quadrupole proton accelerator, designed and manufactured by the National Institute of Nuclear Physics, coupled to a beryllium target. Such machine delivers 5 MeV protons with a 30 mA current in continuous wave, producing at the target a neutron flux of the order of 10^{12} neutrons per second per square centimeter, through the ^{9}Be(p,n)^{9}B reaction. The maximum energy of the produced neutrons is 3.2 MeV; to obtain an epithermal neutron beam suitable for deep-seated tumours (with peaked energy spectrum between 1 and 10 keV) and collimate the beam, an appropriate BSA was designed. It was previously demonstrated that the best material for the core of the BSA to obtain the desired spectrum is solid lithiated aluminum fluoride [4]. Since only powders of lithiated aluminum fluoride were commercially available, the solid form of the material has been created on purpose at Pavia University. Samples of this new material were obtained through a sintering process, namely the application of heat and pressure, on a proper mix of powders of lithium fluoride and aluminum fluoride.

This work summarizes the experimental and computational studies carried out in my Ph.D., devoted to contributing to the design of a BNCT clinical facility. In particular, the aim is to produce useful results for the construction and equipment of the treatment room, and to show how these evaluations play a role also in the design of the clinical beam itself.

2 LITHIATED ALUMINUM FLUORIDE

Lithiated aluminum fluoride, inserted in the BSA structure and surrounding the Be target, allows obtaining an epithermal flux at the beam port higher than 10^9 neutrons per second per square centimeter, with an acceptable low thermal and fast neutron contamination [data under publication]. Lithiated aluminum fluoride is commercially available only in the form of powder, which is not adequate to build a compact assembly whose moderation properties must be stable in time. For this, a material with high and uniform density is needed. An opportune sintering process on powders of lithiated aluminum fluoride was set up to obtain the solid form of the material. In the procedure for producing the solid material, powders of aluminum fluoride and lithium fluoride are mixed and placed into graphite molds in a special machine where they are compressed while heated. Solid samples of different shapes are obtainable, with variable density depending on the applied pressure and temperature.

To characterize the material from the point of view of trace elements, possible source of residual radioactivity, Neutron Activation Analysis was carried out on powders. Samples of different provenance (industrial-grade or chemical-grade) were exposed to neutrons at the research nuclear reactor TRIGA Mark II of Pavia University [6]. Powders were irradiated for 2 hours in the Central Thimble irradiation facility and for less than a minute in the “Rabbit” channel, to detect respectively long-lived and short-lived isotopes. The spectra of the activated material have been acquired with a hyper-pure germanium detector and the impurities present in the samples have been quantified by gamma spectroscopy. The composition evaluated experimentally has been used to calculate the neutron activation of the BSA, as will be better explained in the corresponding section. The results of the measurements have shown that industrial-grade powders impurities, albeit in higher concentrations, are less concerning about the residual activation. Moreover, they facilitate the sintering process. For these reasons, industrial-grade powder has been chosen to create the constituent of the BSA moderating core.

As the neutron spectrum in the accelerator facility is different than that in the reactor, simulations have been run to evaluate the BSA activation due to a typical patient irradiation. Results confirmed that residual activation of the material is not a concern for the maintenance of the facility [7]. However, to spare the patient and the medical staff from residual radioactivity at the end of the irradiation, studies are ongoing to design a shield, which stops the gamma radiation coming from the BSA. To this end, dedicated calculations have been set-up with the Monte Carlo code PHITS [8], able to run a gamma source from activated materials in the geometry of the problem.

An important evaluation for BSA concerns its mechanical resistance. The aim is to verify that the BSA material, even after a long exposure to neutron irradiation, is able to support its own weight without any break or crack occurring. Obviously, any material dispersion must be avoided, not only due to its residual radioactivity, but also because the moderation of neutrons could be modified, changing the spectral characteristics of the clinical beam. The mechanical resistance is thus an important feature both for staff and patient safety.

To investigate this aspect, sample of solid lithiated aluminum fluoride have been irradiated in the Central Thimble of the Pavia reactor for about 6 hours, exposing them to a total neutron fluence comparable with the one resulting from about 1000 treatments in the future BNCT facility. Then, compression tests were performed on both irradiated and non-irradiated samples, comparing them in terms of the stress-strain curves obtained [9].

Preliminary results indicate a good mechanical resistance of the material, even after the long exposure to neutron irradiation in the reactor. Samples with higher density, despite being more fragile in the production process, show better mechanical properties, in fact they break with higher loads. Quantitative results of these measurements are still under analysis and a second round of measurements to better understand the effects of density is underway. The effect of neutron irradiation also needs further research.

The microstructure of the solid lithiated aluminum fluoride is being investigated as well. Ideally, the material should be perfectly homogeneous and uniform. To study the microstructure, several solid samples with variable density have been produced, and analysed by SEM (Scanning Electron Microscope) [10]. SEM imaging showed that higher density corresponds to a tighter bound of the powder grains, however the uniformity was not satisfactory even in the densest samples. The production process was then modified to optimize the microstructure of the final material. We tested three different procedures: i) with a new method, using a specific machine, to mix the starting powders of aluminum fluoride and lithium fluoride; ii) with the new mixing method and also a thermostatic oven to heat the samples (800 °C for 2 hours) after the production; and iii) with the new mixing but using a lithium fluoride powder that was previously grinded to a microscopic-submicroscopic level. The third procedure produced a uniform sample, with lithium fluoride well distributed in the volume, and was thus selected as the most adequate protocol for the preparation of the material.

3 TREATMENT ROOM

As described in [7], the geometry of the treatment room has been reproduced using different Monte Carlo transport codes, and simulations of a clinical irradiation have been performed to evaluate the quantities of interest concerning dosimetry and neutron activations. With the code MCNP6 [11] the neutron source distributed in the Be target described in [4] was simulated. The patient irradiation time has been conservatively taken equal to 2 hours (while the typical duration of a BNCT treatment is about one hour). To guarantee a robust convergence of the calculations, the simulations have been run for a sufficient time to obtain a relative statistical error lower than 1%.

The following quantities have been investigated: the neutron activation of air, walls and patient, and the dosimetry in air and in the patient.

These quantities have been evaluated changing the materials of the walls of the room, to evaluate the role played by the construction materials in the relevant radioprotection quantities. Concrete, concrete with 5% of natural abundance boron, polyethylene, polyethylene with 7% of natural abundance lithium were tested. From the obtained results, and also considering practical issues such as the facility of construction and the costs of materials, we decided to focus on concrete and borated concrete.

3.1 Neutron activation of the air

Depending on the local regulations on radiation protection, the neutron activation of air can be a very crucial issue in the design of a BNCT clinical facility. The residual specific activity of air in the irradiation room and its dependance on the material of the walls were evaluated. The focus was the neutron activation of argon, in which the beta- emitter Ar-41 with half-life of about 109 minutes is produced. Being argon a noble gas naturally present in air, it is not simple to filter it out from the room, therefore its activation must be lowered as much as possible. Our target was a residual specific activity less than 1 Bq/g.

The first results obtained for this quantity were disappointing, in fact, none of the wall compositions evaluated guaranteed an acceptable air activation. This evaluation prompted a revision of the whole BSA structure, requiring higher collimation. The radioprotection evaluations proved to be a valuable feedback for the beam design, that was tested on its physical properties (intensity, spectrum) and on its therapeutic potential (treatment planning on real tumour cases). Although promising, this beam was not suitable for a clinical facility due to unacceptable air activation. Collaborative work has led to a new BSA structure, whose core was still lithiated aluminum fluoride, but capable of higher collimation.

The results of the simulations with the new beam have indicated borate concrete as the optimal composition for the walls [7]. In fact, boron, through the same BNCT reaction, reduces the thermal neutron flux in the room and thus also the neutron activation.

3.2 Neutron activation of the walls

Since concrete contains elements which can become radioactive under neutron irradiation, also neutron activation of the walls was evaluated. This quantity was simulated by calculating the reaction rates in the element of a mesh superimposed to the walls, to point out the in-depth distribution. By comparing the activation reaction rates of the elements composing the walls in the case of boron-loaded and ordinary concrete, it is possible to observe an important reduction of the residual activation thanks to the presence of boron [7]. This result requires material investigation, as borated concrete may be produced by adding different borated formulations to ordinary concrete, possibly modifying its structural properties. Studies in this sense have been performed by other groups that are currently building BNCT facilities, demonstrating that this material can be produced and used for construction.

3.3 Neutron activation of the patient

The neutron activation of the patients is an important point for the safety of those who will come into contact with them after the treatment, and plays a role for the management of treated patients in the following hours and in the organization of the facility layout. In fact, the design of the building depends on this aspect, for what concerns the need of specific structures such as hot restrooms to store the urine of the treated patients or separate rooms to host patients after irradiation. The residual specific activities of the elements composing the patient soft tissue and urine were evaluated. A phantom representing the patient in a typical position for a clinical treatment was implemented in the simulated geometry of the room. Also in this case, the advantage deriving from the addition of boron in the walls is evident. In fact, with boron-loaded concrete walls, the specific activities at the end of a treatment are overall reduced by 60% and by 40%, respectively in the case of soft tissue and urine elements. Even with borated walls, the obtained results suggest that the need of special restrooms to store urine may be necessary, depending on the local radiation protection regulations but the reduction in activation shows that boron in concrete makes a significant difference.

3.4 In-air dosimetry

Relevant dosimetry quantities have been evaluated in the air of the treatment room, using a mesh reticulating the space to better visualize their distribution [7]. Absorbed dose, equivalent dose and H*(10) or ambient dose equivalent [12] have been evaluated, with or without the phantom representing the patient, for three neutron energy bins: thermal (0 ÷ 0.4 eV), epithermal (0.4 eV ÷ 0.5 MeV) and fast (0.5 ÷ 4 MeV). The dose distributions with walls of borated concrete show a marked reduction compared to the ones obtained with ordinary concrete, confirming the ability of the loaded material in reducing the neutron flux in the room, especially for the thermal component, as expected.

All the dosimetric distributions indicate that the dose is higher perpendicularly along one side of the beam. Such asymmetry can be attributed to the presence of a vacuum channel in the accelerator structure. In order to eliminate this effect, a layer of lithium-loaded polyethylene could be added in the wall in front of the vacuum tube, as a shielding to absorb the excess of neutrons.

3.5 In-patient dosimetry

The doses absorbed in the patient healthy organs have been calculated in the patient phantom in a typical position for a treatment. The total absorbed dose-rates have been calculated through the nuclear reactions that take place in biological tissue irradiated with neutrons, also considering the presence of boron in the healthy organs with a conservative concentration of 15 parts per million. The relevant reactions are: the radiative capture in hydrogen, the elastic scattering in hydrogen, the capture with proton emission in nitrogen and the capture with alpha emission in boron.

The resulting values, also in this case, show a reduction when the walls are simulated as made of borated concrete instead of ordinary concrete. The average reduction for all considered organs is around 20% in the case of a patient treated in the thorax zone, and is even higher when considering a treatment position with the beam on the head-and-neck district.

In this respect, the new beam with higher collimation capabilities ensures a better in-patient dosimetry. It is not possible to define a threshold above which the dose absorbed in an organ is considered too high for the treatment, as the priority is the tumour treatment. Thus, the configuration ensuring the minimum out-of-beam absorbed dose is to be preferred. As for the air activation, also the out-of-field dosimetry using human models are an important tool to evaluate the suitability of a beam for clinical treatments.

4 CONCLUSIONS

Literature on the evaluation of neutrons sources for BNCT often overlooks the radiation protection perspective, focusing only on the physical characteristics of the clinical beam, without considering the peripheral dose, the activation of surrounding materials and the ambient dosimetry. More comprehensive evaluations show the importance of these factors when designing an accelerator-based BNCT clinical facility: the radiation protection viewpoint is a valid tool for the project of beam and of the building. The optimization of the shielding, the evaluation and minimization of the dose received by the organs outside the treatment area, and the control on the activation of the irradiated materials are closely interconnected and must be faced all together. All these aspects are critical not only to design the facility, but also to manage it during its operation. These studies are in line with the present scientific debate on how to establish the clinical potential of a neutron beam for BNCT, and are particularly relevant as the accelerator technology is now spreading BNCT as an accessible radiotherapy treatment in many institutions.

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