Nuclear Physics meets Medicine and Biology: Boron Neutron Capture Therapy

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Abstract
BNCT is a tumour treatment based on thermal-neutron irradiation of tissues enriched with ^{10}B, which according to the ^{10}B(n,α)^{7}Li reaction produces particles with high Linear Energy Transfer and short range. Since this treatment can deliver a therapeutic tumour dose sparing normal tissues, BNCT represents an alternative for diffuse tumours and metastases, which show poor response to surgery and photontherapy. In 2001 and 2003, in Pavia BNCT was applied to an isolated liver, which was infused with boron, explanted, irradiated and re-implanted. A new project was then initiated for lung tumours, developing a protocol for Boron concentration measurements and performing organ-dose Monte Carlo calculations; in parallel, radiobiology studies are ongoing to characterize the BNCT effects down to cellular level. After a brief introduction, herein we will present the main activities ongoing in Pavia including the radiobiological ones, which are under investigation not only experimentally but also theoretically, basing on a Monte Carlo code recently extended to simulate cell killing.

1 Introduction

"The difficulties disappear, however, if it be assumed that the radiation consists of particles of mass 1 and charge 0, or neutrons" [1]. Only four years after the neutron discovery by Sir James Chadwick, Locher provided a detailed description of the biological effects expected from neutron irradiation and proposed to use the neutron capture reaction on ^{10}B for therapeutic purposes [2]. More specifically he cited ''the possibility of destroying or weakening cancerous cells, by the general or selective absorption of neutrons by these cells. In particular there exist the possibilities of introducing small quantities of neutron absorbers into the regions where it is desired to liberate ionizing energy. A simple illustration would be the injection of a soluble non-toxic compound of boron, lithium, gadolinium or gold into a superficial cancer, followed by bombardment with slow neutrons''. Boron Neutron Capture Therapy (BNCT) is indeed an experimental radiotherapy based on thermal neutron irradiation of tumour cells previously enriched with ^{10}B, which has a very high cross section (3837 barn at thermal energies) for the ^{10}B(n,α)^{7}Li reaction. This reaction gives rise to an alpha particle and a Li ion of short range (9 and 5 μm, respectively), which deposit most of their energy in the same cell where they were produced. BNCT can be a valid option to treat patients affected by tumours that are not surgically operable and do not show positive response to chemotherapy nor to conventional radiotherapy, such as diffuse primary tumours and metastatic disseminations. The selective Boron uptake by the tumour cells is one of the key issues of BNCT, since it allows delivering a potentially therapeutic dose to the tumour with a substantial sparing of the surrounding normal tissues.

The history of BNCT has been long and sometimes complicated. The first clinical applications took place at the beginning of the 1950s in the USA at BNL and MIT for cerebral gliomas, which were treated with a borated compound named Borax and irradiated with reactor thermal neutrons [3]. The

outcomes were not satisfactory, mainly due to the low penetration of thermal neutrons and the low selectivity of the Borated compound; the trials were stopped in 1959. Better results were obtained in the late 1960s in Japan, thanks to new compounds with higher selectivity [4]. Although in terms of survival the results were not better than those with conventional radiotherapy, the high number of treated patients (120) was a great stimulus for the researchers to continue. In 1994 a new clinical trial started at BNL in Brookhaven, where the use of epithermal neutrons allowed to achieve a better penetration, sparing the skin and delivering a higher dose to the tumour, thanks to the neutron thermalization in the first tissue layers (skin and scalp) [5,6]. Furthermore, a new generation of borated compounds was developed such as BPA-f (boronophenylalanine-fructose complex), which is able to carry the Boron atoms inside the cells penetrating the cell membranes. In the same period, a trial for cutaneous melanoma and another one on intra-cerebral melanoma or glioblastoma started at MIT [7,8]. At the end of the 1990s a similar research program started in Petten, the Netherlands, for cerebral tumours [9], and similar trials were initiated in Sweden and Finland [10,11]. In 2001 and 2003 two patients affected by liver metastases were treated in Pavia with the auto-transplantation technique, which will be described in the next section [12,13]. In 2003 a trial for skin melanoma started in Argentina [14], and a trial for brain metastases was initiated in Petten. Analogous research works were developed in Czech Republic, South-Korea, Taiwan and Russia. At the moment the trials for brain tumours are going on mainly in Japan, together with a new research on lung. Lung tumours are now one of the most interesting targets for BNCT, and the activity in Pavia is currently focused on this organ. Concerning other tumour types, projects have been developed for liver (e.g. Argentina, Germany and Japan), head and neck cancers (e.g. Finland and Japan) and oral tumours, and other malignancies such as osteosarcoma are under evaluation. Particularly interesting seem the outcomes of a Finnish clinical trial on head and neck inoperable recurrences. Over the first 12 patients, with a median follow-up of 31 months, 10 responded to BNCT and 2 had tumour growth stabilization for 5.5 and 7.6 months. The median duration of tumour control was 10 months, and the median survival time was 13 months. Three patients were alive at the time of the analysis (follow-up of 30, 31 and 36 months), one of them without cancer recurrence and with a good quality of life [15].

After reporting on the clinical experience in Pavia for liver metastases, this paper will provide an overview of the main BNCT-related activities currently ongoing in Pavia (i.e. Boron concentration measurements, organ dose simulations in humans, animal irradiation and radiobiological studies), where the research is now focused on lung tumours. Lung carcinoma is indeed the main cause of cancer mortality worldwide; however, despite the recent introduction of new therapeutic agents, little progress has been achieved in terms of survival, and the prognosis for these patients remains poor. BNCT can therefore be a valid option for the treatment of diffuse lung tumours and lung metastases, which generally show a poor response to both surgery and chemotherapy. Among the various activities, particular attention will be devoted to computational radiobiology studies at sub-cellular and cellular level, for which a mechanistic model and a Monte Carlo code originally developed for chromosome aberration induction has been recently extended and applied to the simulation of tumour cell death following enrichment with ^{10}B and thermal neutron irradiation like in a typical BNCT treatment.

2 BNCT in Pavia: the clinical experience on liver with the auto-transplantation technique

Within the TAOrMINA project, in December 2001 for the first time in the world an isolated liver affected by colon-carcinoma metastases, previously loaded with a ^{10}B compound, was irradiated with thermal neutrons at the Triga Mark II reactor of the University of Pavia [12,13]. The procedure consisted of three main phases: 1) *early surgical phase*, including a 2-hours liver perfusion with a solution of ^{10}boronophenylalanine (^{10}BPA), two biopsies of both metastatic and normal hepatic tissue to verify a favourable (that is, higher than 4:1) ^{10}B concentration ratio between the samples, and finally the hepatectomy with contemporary starting of an extra-corporeal circulation; 2) *radiotherapeutic phase*, during which the isolated liver was washed and chilled, transferred to the thermal column of the

reactor and irradiated isotropically for about 10 minutes; 3) *late surgical phase*, in which the liver was reconnected to the patient and the extra-corporeal bypass was removed. The patient was a 48-years-old man with 14 liver metastases, operated seven months before. The whole procedure lasted 21 hours, and the ratio between the ^{10}B concentration in the tumour and that in the healthy tissue was close to 6:1. In 2003 a second patient, a 39-years-old male affected by 11 hepatic metastases already operated, underwent the same procedure, which lasted 18 h 40'.

The location for liver irradiation was built inside the thermal column of the reactor, where the γ background coming from the core was lowered by means of two bismuth screens (overall thickness = 20 cm); the gamma dose was measured by BeO TLD dosimeters, whereas the neutron flux was measured by Au and Cu wires/foils ($1.4x10^{10}$ thermal neutrons cm^{-2} s^{-1} in air). The Boron concentration was evaluated basing on alpha-particle spectrometry coupled to neutron auto-radiography; more details on this method will be provided in the next section. With a neutron fluence of $4x10^{12}$ n cm^{-2}, for both patients the absorbed dose was 18±1 Gy in the tumour and 6±0.3 Gy in the healthy liver, whereas the ^{10}B concentration ratio between tumour and healthy tissue was 5.9 for the first patient and 5.6 for the second one. For the irradiation, the liver was placed inside two Teflon bags and positioned in a Teflon container, which was transported to the irradiation channel by a semi-automatic trolley. Halfway through the irradiation time, the Teflon container was rotated by 180° using a remote control, to increase the uniformity of the thermal neutron flux distribution inside the organ.

During the first three weeks after the treatment, both patients were affected by a dramatic but totally reversible "post-irradiation syndrome", mediated by the release of a large amount of cytokines as an effect of cellular necrosis. In the same period of time, a similar evolution of the liver lesions was observed for both patients, with necrotic areas appearing in the regions that were occupied by tumour nodules before the treatment. During the fourth week the clinical evolution of the two cases became different: while the second patient, who was suffering from a cardiomyopathy, died on the 33th p.o.d. following severe circulatory complications, the first one progressively returned to normal laboratory values (including neoplastic markers and the residual liver function) and was discharged after 40 days in a good state of health. Twenty months after BNCT a CT scan showed a tumour recurrence, which was removed surgically. Unfortunately, thirty-three months after BNCT multiple recurrences appeared, for which chemotherapy, immunotherapy and surgery resulted ineffective, leading to the patient death 44 months after the BNCT treatment. Such recurrences are likely to be due to cells that at the moment of irradiation were quiescent, thus non-proliferating and unable to uptake and retain adequate levels of BPA. This hypothesis was confirmed by experiments with *in vitro* cell cultures, which revealed the presence of neoplastic cells spared by neutron irradiation and restoring a tumour population [13].

3 BNCT in Pavia: ongoing research activities on lung tumours

3.1 Boron concentration measurements

The selective killing of tumour cells, which is a fundamental requirement for any anti-cancer therapy, in BNCT can be achieved thanks to the selective uptake of ^{10}B in tumour cells with respect to normal ones; a reliable ^{10}B concentration measurement both in tumour tissues and in normal ones is therefore a crucial step in view of a BNCT treatment plan, in order to identify the conditions that will deliver a therapeutic dose to the tumour sparing the normal parenchyma. Many methods were developed to measure ^{10}B concentrations in biological samples, including inductively coupled plasma atomic emission spectrometry (ICP-AES), ICP-mass spectrometry (ICP-MS), and prompt-gamma neutron activation analysis (PGNAA). [16]. Whatever method is used, it is essential to know what kind of tissues are present in the analysed samples, since tumour cells, normal cells and necrotic areas can be simultaneously present in a metastatic sample. This is the reason why in Pavia a quantitative approach based on alpha-particle spectrometry is coupled to a qualitative approach based on neutron autoradiography.

The qualitative analysis [17] requires to cut couples of tissue sample slices; for each couple, the first slice (70 μm thick) is deposited on a sensitive film for neutron autoradiography, whereas the second one (10 μm thick) is deposited on glass for morphological analysis. The samples deposited on the films are irradiated with thermal neutrons, and the high-LET particles coming from the $^{10}B(n,\alpha)^{7}Li$ reaction induce latent tracks, which are visualized by etching. The protocol for lung samples consists of irradiating the films and then etching them in a NaOH solution. Figure 1 shows a comparison between a histological preparation and a neutronigraphic image of two subsequent tissue slices.

Concerning the quantitative analysis, the method applied in Pavia is based on the energy spectrum of the charged particles produced in the $^{10}B(n,\alpha)^{7}Li$ reaction [16,18]. Tissue samples treated with BPA are irradiated in the thermal column, in a position where the thermal neutron flux is of the order of 10^{9} cm^{-2} s^{-1} . Since the slices are 70 μm thick, they are thicker than the range of the alpha particles. Therefore the energy spectra are not Gaussian peaks, and the determination of the ^{10}B concentration requires a deep analysis including information on the stopping power of alpha particles in tissue. In addition to the alpha-particles and the ^{7}Li ions originated by the $^{10}B(n,\alpha)^{7}Li$ reaction, protons from the $^{14}N(n,p)^{14}C$ reaction are also present due to the Nitrogen atoms naturally contained in the cells. Selecting an energy window of 1110-1350 keV allows to discriminate against Nitrogen protons and ^{7}Li ions. The absolute ^{10}B concentration (in parts per million or ppm, that is micrograms of Boron atoms per gram) is then calculated as:

$$[^{10}B]=KC\ \Delta E/(\eta\sigma\varphi S\Delta(\rho x))\ . \qquad (1)$$

K is a normalization constant, C represents the experimental counts in the energy range ΔE, η is the geometrical efficiency of the apparatus, σ is the microscopic cross section of the (n,α) reaction, φ is the thermal neutron flux, S is the tissue sample surface seen by the detector through the collimator, and $\Delta E/\Delta(\rho x)$ is the alpha-particle stopping power in (dry) tissue. The experimental error associated to this method is of the order of 10%, and the lower limit of detection is about 0.5 ppm, due to the natural ^{10}B background in tissue. The main advantage of this method is the ability to measure the ^{10}B concentration as well as the ^{10}B distribution in a 2-D tissue slice, and to directly correlate the macroscopic spatial information to the histology of the analyzed specimen. Further details on this method can be found elsewhere [16,18].

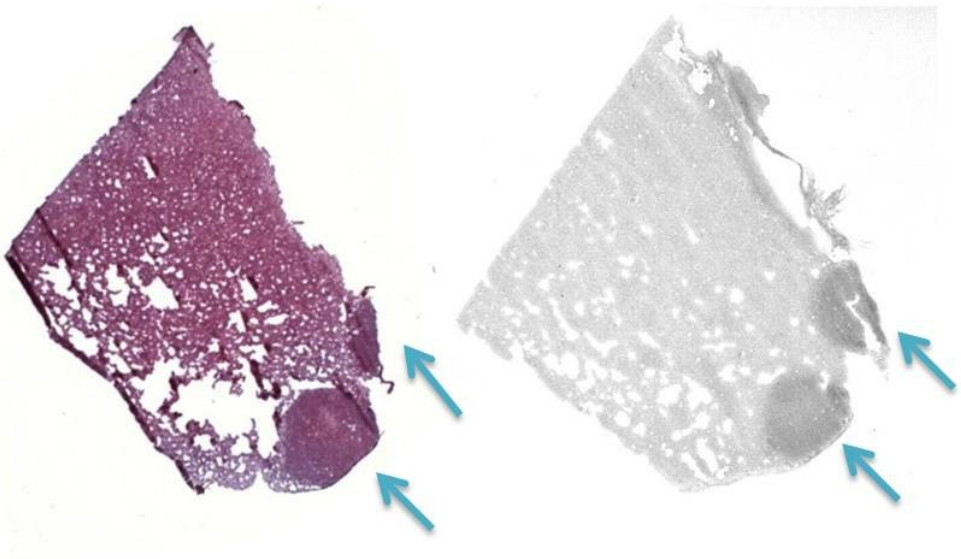

Fig. 1: Comparison between the autoradiography and the histological preparation (standard hematoxilin-eosin staining) of two subsequent slices cut from a rat lung with induced metastases and treated with BPA. a) neutron autoradiogram, b) histology (enlargement: 10 x). The arrows indicate the tumour nodules, which are darker in the neutron autoradiogram because the boron concentration is higher in the tumour cells.

3.2 Simulation of human lung irradiation

In Pavia the WIDEST1 research project, funded by INFN (National Institute of Nuclear Physics) and MIUR (Ministry of University and Scientific Research), is aimed to explore the possibility of irradiating the whole lung using external, collimated epithermal neutron beams, and BPA as a ^{10}B carrier. This way the patient will not undergo the complicated auto-transplantation procedure, and the neutrons, thermalized in the first tissue layers, would not be much attenuated thanks to the lung low density (about 0.3 g/cm^3). To verify whether a proper dose distribution can be obtained in the lung and to test whether the surrounding sensitive organs can be spared, a Monte Carlo simulation study was performed with the MCNP code (version 4c2) coupled to the ADAM anthropomorphic phantom, which was irradiated with two ideal neutron beams (antero-posterior and postero-anterior), mono-energetic and collimated, with dimensions of 11 x 26 cm^2. [19,20]. A schematic representation is reported in Fig. 2. While the thermal neutron flux obtained with a thermal neutron source (0.0253 eV) resulted to be about three times higher at the body surface with respect to the lung, the thermal neutron flux obtained with a 1 keV epithermal source resulted to be very advantageous, being three times lower in the skin with respect to the lung and remaining uniform in the lung. Assuming a ^{10}B concentration of 25 ppm in the tumour and 5 ppm in the healthy lung, the physical dose to the tumour resulted to be about two times the dose to the normal lung, mainly due to the relatively high gamma contribution. A ratio of about 3.5 was obtained considering only the contribution of the charged particles. However, the ratio between the dose in the tumour and that in the normal lung further increases up to 5 weighing the various dose components by the corresponding biological factors, that is the Relative Biological Effectiveness (RBE) and the Compound Biological Effectiveness (CBE). In particular, the dose delivered to normal lung following an irradiation of 15 minutes with a neutron flux of 1.75x10^9 neutrons/(cm^2 s) would be 4 Gy-Eq in the central section of the lung, highly consistent with literature prescriptions on the lung tolerance doses. These results obtained with an ideal beam indicate that the treatment of lung tumours by multiple (external) epithermal neutron beams could be feasible, since the low density of the lung allows for a quite uniform dose distribution in the whole organ.

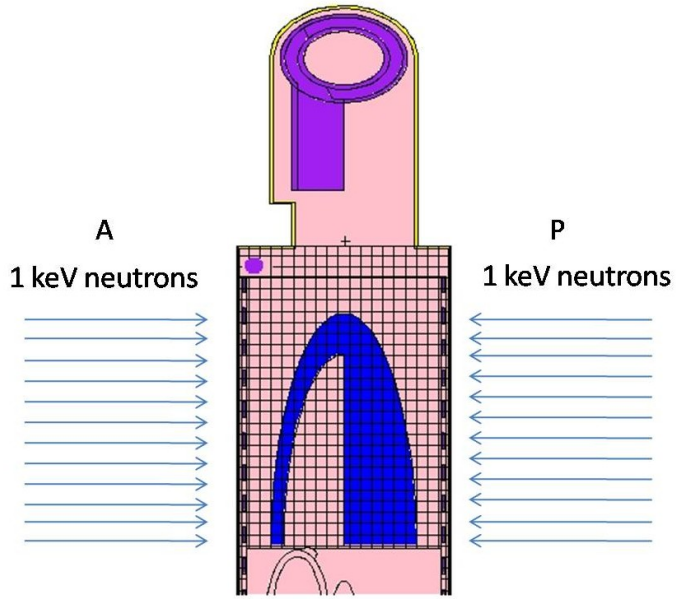

Fig. 2: ADAM model used as an input for MCNP to simulate the irradiation of the entire lung by collimated external epithermal neutron beams. The figure shows the irradiated region and the two opposite ideal beams used to calculate the dose delivered to each tissue. The 1 keV neutrons are perfectly collimated, and leave the spine outside the irradiation field

3.3 Animal irradiation

An investigation on the *in vivo* BNCT effectiveness has been planned, consisting of the irradiation of rats affected by lung metastases in the thermal column of the Triga Mark II reactor of the University of Pavia. The rats will be inserted in a shielding box with a window for lung irradiation, with the main aim of proving that the tumour can be treated sparing the normal tissues, investigating the radiation-induced changes in the lung histology, and verifying the increase of the animal surviving time. As a necessary step before starting the experiments, the MCNP code (version 4c2) was applied to the calculation of organ dose distributions in a rat model phantom [21], which was simulated as a cylinder with internal geometrical structures representing the various organs: skin (modelled as a 0.5 cm thick external cylinder), lungs, oesophagus, intestine, heart, spine, kidneys and brain, with the various materials defined according to ICRU-46; the lungs were divided into 0.125 cm^3 cubic voxels, in order to obtain a detailed map of the dose absorbed in the region of interest. The rat model was inserted into different shielding boxes of variable shape and thickness, with different dimensions of the lung window; Fig. 3 shows a representation of the rat model simulated with MCNP. The following parameters were considered to evaluate the shielding effectiveness: tolerance doses in the healthy tissues, uniformity of the thermal neutron flux distribution in the lung, and dose-volume histogram (DVH) in the healthy lungs when delivering to the tumour a therapeutic dose of at least 40 Gy-Eq.

The simulations were validated by comparisons with measurements performed with a simplified rat model consisting of three polyethylene cylinders (body, neck and head) with a copper wire along their principal axis, inserted in a Teflon cylindrical box. The thermal neutron flux was measured with the activation method basing on the $^{63}Cu(n,\gamma)^{64}Cu$ radiative capture reaction, following 1h irradiation at 250 kW perpendicularly to the longitudinal axis of the thermal column, which is a 1 m long channel with a section of 40x20 cm^2. The simulations were in good agreement with the measured thermal neutron flux, both in air and in the phantom. The shielding configuration that best fulfilled the aforementioned criteria was a 1.5 cm thick cylindrical container filled with Lithium carbonate, with a 4 cm window for lung irradiation; the box must be rotated by 180° halfway during the irradiation time. Under these conditions, the following results were obtained: 1) the calculated ratio between the maximum and the minimum thermal neutron flux in the lungs was 1.5, indicating a good uniformity; 2) with a ^{10}B concentration of 77 ppm in the tumour and 22 ppm in the normal lung, an irradiation time of 12 minutes was sufficient to deliver at least 40 Gy-Eq to the tumour.

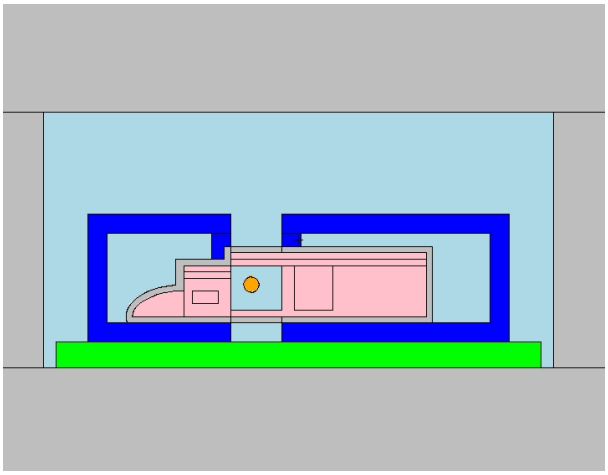

Fig. 3: Longitudinal section of the rat model designed with MCNP geometry, with the neck and the body modelled as cylinders, and the head modelled as an elypsoid; the latticed cylinder inside the body represents the lungs, whereas the outer structure is the shielding box with a window for lung irradiation

With this treatment plan, the doses to the considered normal tissues were lower than the tolerance doses with the only exception of the kidneys, for which an additional shielding can be considered; in particular, the mean dose to the normal lung was 5.9 Gy-Eq. The mean weighted dose to the tumour was 49±4 Gy-Eq, implying a ratio between dose to the tumour and dose to the healthy lung higher than 8. These results indicate that the rat irradiation in the thermal column is feasible, allowing to deliver a therapeutic dose to the tumour sparing the normal tissues in a time that is highly compatible with the anaesthesia. A shielding box with the characteristics described above has already been constructed, and the animal irradiation will start soon.

3.4 Radiobiology: experiments and simulations

To better understand the effects of a BNCT treatment down to the cellular level, *in vivo* and *in vitro* radiobiology studies are ongoing in Pavia since several years. While *in vivo* studies are focused on BD-IX rats [22], the *in vitro* activity is devoted to different tumour cells including DHDK12TRb (DHD) cells, a rat coloncarcinoma cell line that induces metastases either in the liver or in the lung, depending on the injection site. In particular the Boron uptake as a function of BPA concentration and time of treatment and the Boron washout as a function of temperature and time after BPA deprivation have been characterized in a recent work, as well as the survival of DHD cells following irradiation with either gamma rays, or thermal neutrons without previous Boron uptake, or thermal neutrons following Boron uptake. A detailed description can be found elsewhere [23].

The *in vitro* cell survival studies have been recently integrated by an activity of computational radiobiology at sub-cellular and cellular level. More specifically, a mechanistic model and a Monte Carlo code originally developed for radiation-induced chromosome aberrations - that is incorrect rejoining of chromosome fragments - in normal cells have been extended to simulate the survival of DHD cells following enrichment with ^{10}B and subsequent irradiation with thermal neutrons, like in a typical BNCT treatment. The model/code for chromosome aberration induction, which was initiated in 1997 [24,25], relies on the following basic assumptions: 1) chromosome aberrations arise from DNA clustered lesions, each lesion giving rise to two independent chromosome free-ends; 2) only pairs of free ends created within a threshold distance *d* will join and thus take part in the process of aberration formation. These assumptions rely on the evidence that, on average, 1 Gy of (low-LET) radiation induces about 40 DNA double-strand breaks (DSBs) per cell, but less than 1 aberration per cell; it is therefore very likely that, among the many initially induced DNA breaks, only those that are severe enough (like clustered ones) and close enough are involved in DNA damage mis-repair and thus in the formation of chromosome aberrations. Up to now, the model has been validated for the induction of the main chromosome aberration types in normal lymphocytes exposed to X- or γ-rays [26], light ions such as protons and alpha particles [27], and heavier ions like Carbon, which is nowadays of great interest for tumour hadrontherapy, and Iron, interesting for space radiation research [28,29]. The agreement between simulations and literature experimental data supports the model assumptions on the mechanisms governing chromosome aberration induction, including the fundamental role of clustered DNA damage and the step-like distance dependence for the interaction probability between two (clustered) DNA lesions. Furthermore, the model has been applied to predict the induction of Chronic Myeloid Leukaemia following exposure to low-LET radiation [30] and the induction of chromosome aberrations in astronauts exposed to space radiation [31]. A detailed description of the simulation methods is beyond the scope of this paper, and can be found elsewhere [24-32].

Basing on an experimental observation concerning the link between chromosome aberrations and cell death [33], the model was recently extended to simulate radiation-induced cell death adopting a one-to-one relationship between the average number of "lethal aberrations" (i.e., dicentrics, rings and deletions) per cell and –lnS, being S the fraction of surviving cells. More specifically, for each considered dose value D the fraction of surviving cells was calculated as $S(D) = \exp[-LA(D)]$, where LA(D) is the (simulated) average number of lethal aberrations (dicentrics+rings+deletions) per cell following a dose D. Although the observation by Cornforth and Bedford was specifically related to normal fibroblasts exposed to X rays, in the present work this approach was applied not only to low-LET radiation but also to intermediate- and high-LET particles, both for normal cells and for tumour

ones. The starting point consisted of reproducing the experimental outcomes obtained by Cornforth and Bedford, that is survival of normal cells following X-ray irradiation. Figure 4 shows the simulated dose-response curve for cell survival obtained as described above, as well as the corresponding experimental data on AG1522 normal fibroblasts exposed to X rays; the agreement between simulations and data validates the model for the survival of normal cells exposed to X rays, and more generally low-LET radiation.

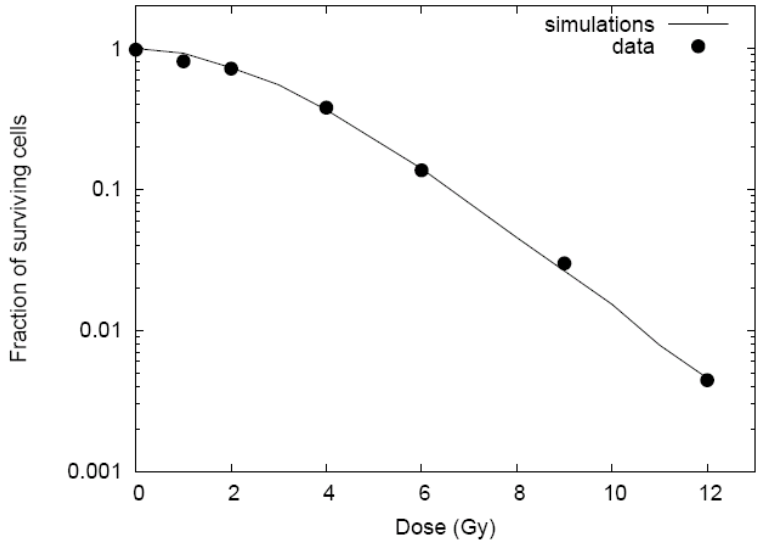

Fig. 4: Survival of normal cells exposed to X rays; the line represents the model prediction, whereas the points are literature data for comparison taken from ref. [33].

As a second step, the same approach was applied to simulate the survival of normal cells exposed to intermediate and high LET radiation such as protons and alpha particles, which are both involved in BNCT. The simulation outcomes were compared with literature data on V79 cells exposed to either 0.64 MeV protons [34], or 3.2 MeV alpha particles [35], corresponding to an average LET in water of 35 keV/μm and 120 keV/μm, respectively (results not shown here); the agreement between simulations and data provided a validation of the model for the survival of normal cells exposed to a monochromatic, parallel field of protons or alpha particles. The final step of the present work consisted of extending the code to simulate the survival of tumour cells exposed to a BNCT treatment, that is enrichment with ^{10}B and subsequent irradiation with thermal neutrons. Since in a Boron-rich tissue thermal neutrons deposit their energy mainly through the reactions $^{10}B(n,\alpha)^{7}Li$ and $^{14}N(n,p)^{14}C$, where the energies of the involved particles are 1.47 MeV for alphas (corresponding to an average LET in water of ~190 keV/μm), 0.84 MeV for ^{7}Li (~160 keV/μm) and 0.59 MeV for protons (~38 keV/μm), in the simulations the irradiation was directly reproduced by means of alpha particles and protons; ^{7}Li was treated like an alpha particle since the LET values of these particles are both quite high, thus implying no significant difference in terms of biological effectiveness. To reproduce a typical BNCT scenario, the code was purposely modified to allow the simulation of a mixed field of protons and alpha particles; furthermore, each particle was made start from a random position inside the cell with a random direction, to reproduce a uniform intra-cellular distribution of the ^{10}B and ^{14}N atoms. Figure 5 shows the simulated cell survival curves following exposure either to 0.59 MeV protons (to simulate thermal neutron irradiation of cells not enriched with ^{10}B), or to a mixed field of 1.47 MeV alpha particles and 0.59 MeV protons, to simulate thermal neutron irradiation of boron-enriched cells. The experimental data reported for comparison are relative either to DHD cells exposed to thermal neutrons (but not pre-treated with ^{10}B), or to DHD cells enriched with ^{10}B and subsequently exposed to thermal neutrons [23].

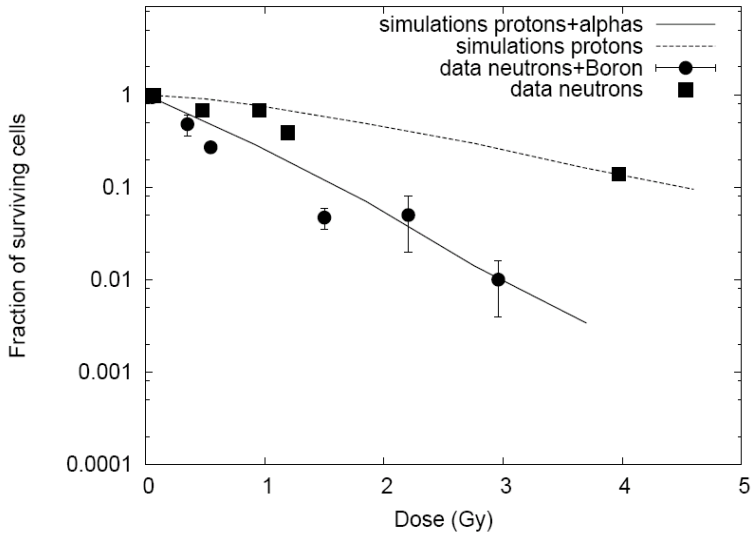

Fig. 5: Fraction of surviving DHD cells following either exposure to thermal neutrons without ^{10}B pre-treatment (upper curve), or enrichment with ^{10}B and subsequent exposure to thermal neutrons (lower curve). The lines represent model predictions, whereas the points are experimental data taken from ref. [23].

4 Concluding remarks

After a brief introduction on some historical and clinical aspects of BNCT, the state of the art of the main activities ongoing in Pavia was presented. Such activities, which are currently focused on lung BNCT research, include Boron concentration measurements by neutron autoradiography and alpha spectrometry, organ dose simulations with the MCNP code and radiobiology studies, both experimental and theoretical. While the organ dose simulations indicate that the treatment of lung tumours by external neutron beams (epithermal for humans and thermal for rats) could be feasible, radiobiology studies are mainly aimed to the quantification of cellular Boron uptake and washout, as well as the characterization of cell death following enrichment with ^{10}B and neutron irradiation.

Cell death was investigated not only experimentally but also theoretically, purposely extending a Monte Carlo code originally developed for radiation-induced chromosome aberrations. The agreement between simulations and cell survival data provided a validation of the model; a possible future development for this kind of activity is the evaluation of (non-lethal) damage in normal cells, which is an important issue not only for BNCT but for any tumour treatment.

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