Boron Neutron Capture Therapy activity of diffused tumors at Triga Mark II in Pavia

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Abstract

The Boron neutron Capture Therapy research in Pavia has a long tradition: it begun more than 20 years ago at the Triga Mark II reactor of the University. A technique for the treatment of the hepatic metastases was developed, consisting in explanting the liver treated with ^{10}B, irradiating it in the thermal column of the reactor, and re-implanting the organ in the patient. In the last years, the possibility of applying BNCT to the lung tumours using epithermal collimated neutron beams and without explanting the organ, is being explored. The principal obtained results of the BNCT research will be presented, with particular emphasis on the following aspects: a) the project of a new thermal column configuration to make the thermal neutron flux more uniform inside the explanted liver, b) the Monte Carlo study by means of the MCNP code of the thermal neutron flux distribution inside a patient's thorax irradiated with epithermal neutrons, and c) the measurement of the boron concentration in tissues by (n,α) spectroscopy and neutron autoradiography.

1. Introduction: BNCT basic principles

Neutron Capture Therapy (NCT) is a binary form of experimental radiotherapy, which exploits the thermal neutron capture reaction in ^{10}B nuclei: $^{10}B(n,\alpha)^{7}Li$ (2840 b at 0.025 eV, Q-value=2.792 MeV). The therapy is based on the possibility to obtain a selective uptake of boron in the tumour by infusing the patient with specific boron carriers. After a proper time interval, the tumoral cells are loaded with higher boron concentrations with respect to the surrounding healthy tissues. Then, the tumoral target is irradiated with thermal or epithermal neutrons. The charged particles emitted in the reaction $^{10}B(n,\alpha)^{7}Li$ have a short range in tissue: their path is of the order of a cell diameter. This means that the high LET particles cause potentially lethal damages only within the cell in which are generated. This is the principle of the selective effect of BNCT, based on boron biodistribution rather than on the irradiation field. There are some substantial advantages in using this kind of therapy, especially in those cases in which conventional radiotherapy or surgery are not effective. This is the case of disseminated tumours, as metastatic spreads, which are characterized by the invasion of entire vital organs, the presence of small nodules that cannot be detected with diagnostic methods, and the presence of different kinds of tissue inside the irradiation target such as: active tumour cells, healthy tissue, necrosis, etc. Irradiating the whole organ with a uniform neutron field, a higher radiation dose would be delivered to the tumour, taking advantage from the selective boron uptake. In

this way, a detailed knowledge of the tumour morphology and distribution before the treatment would not be necessary.
An example of this situation is represented by the hepatic metastases from colon-adenocarcinoma, that invade the whole liver even after a successful surgical resection of the primitive tumour. Other tumours that have few options to be treated by conventional therapies are the lung diffuse tumours, both metastases and primary, which are one of the main causes of death for cancer in the western world.

In Pavia, the BNCT application to diffuse tumours has a long tradition and has been developed at the TRIGA Mark II reactor. A long study that lead to two clinical application in 2001 and 2003 was developed for the treatment of liver metastases by the auto-transplantation method. It consists in infusing the liver with the boron carrier, explanting the organ and irradiating it in the thermal column of the reactor and finally re-implanting the organ in the same patient. Furthermore, some years ago, a preliminary study for the application of BNCT to diffuse lung study was started. In this case the therapy would foresee an irradiation of the patient thorax using external epithermal neutron beams.

2. BNCT of liver metastases

The long term research to study the feasibility of BNCT application to liver metastases by means of auto-transplantation, began in Pavia in 1987, starting from an idea proposed by T.Pinelli. The project called TAOrMINA (Advanced Treatment of Organs by Means of Neutron Irradiation and Auto-transplantation) involved the INFN section of Pavia, the Department of Nuclear and Theoretical Physics, the Department of Surgery (Division of Hepato-pancreatic Surgery) and the Department of Animal Biology of the Pavia University, the Centre of study for Histochemistry (CNR) and the IRCCS S. Matteo Policlinic of Pavia. The physical and surgical activities were coordinated by T. Pinelli and A. Zonta respectively. [1]

The therapeutic concept is based on the neutron irradiation of the isolated liver in a neutron field produced in the thermal column of the reactor TRIGA Mark II of Pavia University. The column was modified in order to realize a 100 cm long channel with graphite walls, with transversal dimensions of 40 x 20 cm^2. The γ background coming from the reactor core was drastically lowered by inserting two Bismuth screens, both 10 cm thick. The irradiation field was studied by means of the Monte Carlo transport code MCNP [2] and by experimental measurements with the activation method.

In the irradiation position, the thermal flux in air is $1.4 \cdot 10^{10} cm^{-2} s^{-1}$ (±7%), while the epithermal component with energy higher than 0.2 eV is about three orders of magnitude lower. The behavior of the thermal neutron flux in the irradiation position was studied both experimentally (by copper wires activation) and by MCNP simulations. A Teflon phantom to model a human liver was built for experimental measurements in the irradiation position inside the thermal column, and the same phantom was simulated using MCNP (fig.1) [3]. It was modeled as a spherical section with Teflon walls 0.5 mm thick and filled with a liver-equivalent solution. The elemental composition by weight of the solution with 50 ppm of ^{10}B is reported in Tab. 1. The copper wires were positioned along the principal axis of the phantom, and cut into 1 cm segments after irradiation to construct the thermal neutron flux profiles along x, y and z axis inside the liver.

Element	O	C	H	N	P	K	S	Cl	Na	^{10}B	^{11}B
ICRU 46	71.6	13.9	10.2	3.0	0.3	0.3	0.3	0.2	0.2	0.0	0.0
solution	83.86	1.29	10.6	3.0	0.3	0.22	0.3	0.2	0.22	0.0050	0.0222

Tab.1 Elemental composition of the liver-equivalent solution compared to the elemental composition of the liver as reported in the ICRU 46. The values are in percentages by weight.

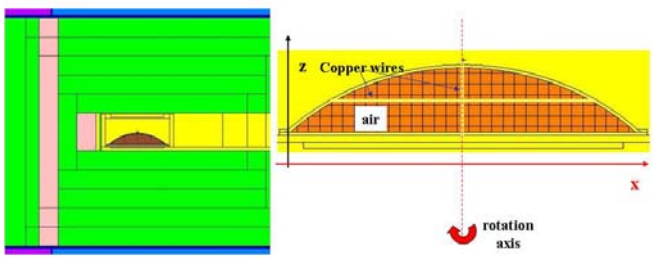

Fig.1 Liver model used to measure and simulate the neutron flux distribution in the irradiation position. Left: a particular of the thermal column with the Bismuth screens and the phantom positioned in the irradiation channel.

The first comparison between simulations and experimental measurements was performed with the experimental phantom without liver solution, with the copper wires in the described position. The simulation reproduced this situation using air to fill the liver model. In fig.2 the thermal neutron flux is plotted along the longitudinal axis of the column (x axis); the agreement between the experimental measurements and the simulation is good. The flux has a linear behavior and decreases of a factor of about 1.5 along a distance of 20 cm. Rotating the phantom by 180° halfway through the irradiation time, the flux distribution becomes perfectly uniform. The distribution of the flux is flat along the transversal and vertical axis of the column also without rotation.

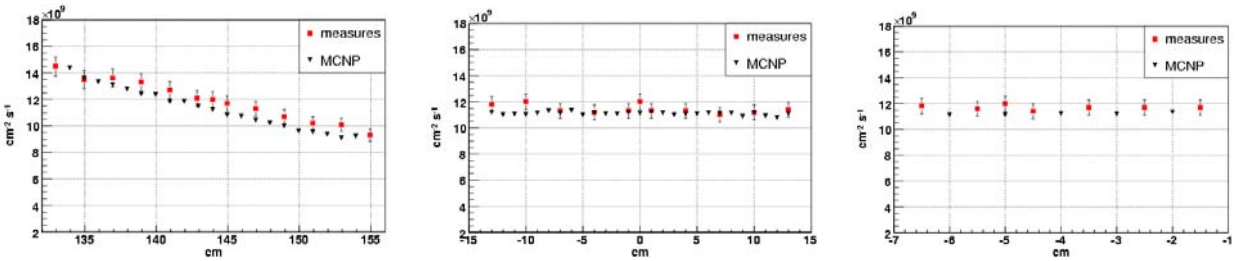

Fig.2 Neutron flux profile along the longitudinal, transversal and vertical axis of the liver model filled with air. The measurements (red) and simulations (black) are overlapped for comparison.

The introduction of the hepatic solution modifies the flux distribution in a way that the ratio between maximum and minimum flux values is about 2 despite the rotation. Due to the high Boron concentration ratio between the tumour and the healthy liver (about 6), it is possible to deliver a lethal dose to the tumour with a substantial sparing of normal tissues, even with a thermal neutron distribution not so uniform. Nevertheless, we tried to obtain a better neutron flux distribution simulating new configurations of the graphite walls around the liver position. After some trials a highly satisfactory result was obtained for the described liver model. Fig.3 shows the configuration of the Thermal Column that ensures a better homogeneity of the flux distribution inside the phantom. Besides the new graphite setup, a layer of a material containing ^{6}Li was put along the phantom Teflon holder, towards the core. The neutron flux distribution obtained with this configuration is reported in fig.4. An important improvement of this new configuration is that the high uniformity of the flux is produced without rotation of the liver.

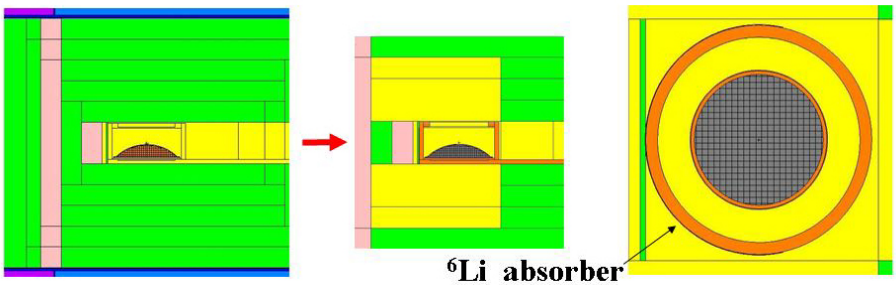

Fig.3 New configuration of the graphite walls around the liver position; right: horizontal section of the liver model inside the Teflon holder; the thin absorber foil that coats the front half of the Teflon holder is indicated.

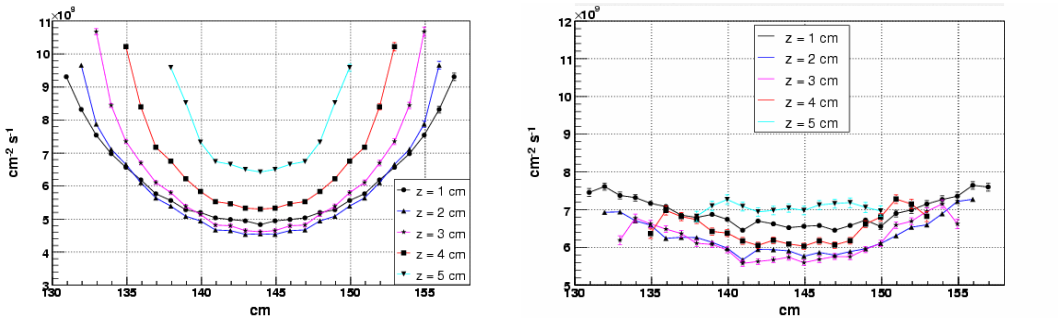

Fig.4 Spatial distribution of the neutron flux inside the liver model along longitudinal axis for different planes along z axis. Left: present column configuration, organ rotated by 180° halfway through the irradiation time; right: in the column configuration shown in the middle picture of fig.3, without rotation. The indicated z planes refer to the distance form the base of the phantom.

The selective boron uptake in the hepatic metastases was proved with a study on an animal model [5]; the hepatic metastases were induced in rats, that were subsequently infused with BPA (Boro-PhenylAlanine). It was found that between 1 and 12 hours from BPA infusion the boron concentration in the metastases was higher comparing to normal tissue, and that between 2 and 4 hours the concentration ratio between tumour and liver was about 6.

In December 2001 and July 2003 two patients affected by diffuse hepatic metastases [6] were treated with this technique. After BPA infusion the liver was removed from the patient, washed from the blood and put into two Teflon bags, and then into the Teflon holder. The holder was carried to the reactor, irradiated for about 10 minutes and then carried back to the hospital for the auto-transplantation. During the explants procedure, after one and two hours from BPA administration, two samples (tumoral and healthy tissues) were taken from the liver and frozen in liquid nitrogen. Thin slices of frozen liver were cut using a Leica cryostat at –20°C; one slice, 10 μm thick, was deposited on glass for morphological analysis by standard ematoxilin-eosin staining; the next one, 40 μm thick, was put directly on a Cellulose Nitrate film (CN85 by Kodak Pathé) for neutron autoradiography [7], and the last one on a mylar disk for boron concentration measurement by α spectrometry. The measurements demonstrated that boron concentration in normal liver was about 8 ppm, while in the tumour was about 45 ppm, with a ratio higher than 5. Neutron authoradiography used for boron bio-distribution imaging showed that the boron concentration values strongly depended on the tissue types (fig.5).

In both patients, about 10 days after the treatment, the CT scan evidenced that liver was in normal conditions, while the adeno-carcinoma metastases appeared in necrotic state. The second patient, who experienced also a vascular complication, was re-operated 31 days after BNCT treatment and a sudden cardiac failure determined his death in the 33rd p.o. day. In the first patient all clinical anomalies and biochemical alterations disappeared within some weeks and he was discharged in the 40th p.o. day. In the site of previous metastatic lesions typical CT images appeared indicative of massive necrosis. Later they were gradually substituted by normal liver tissue. He survived 44 months with a good quality of life, and died because of diffuse recurrences of the intestinal tumour [6].

3. BNCT of diffuse lung tumours

To study the possibility to apply BNCT in the cure of diffuse pulmonary tumours, a BNCT lung project was created in Pavia, supported by Ministry of Education, University and research (MIUR) and INFN, in which Physicists, Medical Doctors and Biologists are involved [8]. One of the aims of this research is to find a method to uniformly irradiate the whole lung using external neutron beams. To this end Monte Carlo calculations were performed using the male anthropomorphic phantom Adam [9,10] in MCNP. As a starting point for simulations, an ideal neutron beam monochromatic and perfectly collimated was chosen. Two plane neutron sources 11 cm large and 26 cm high were simulated, that allowed to irradiate all the right lung volume (fig.6).

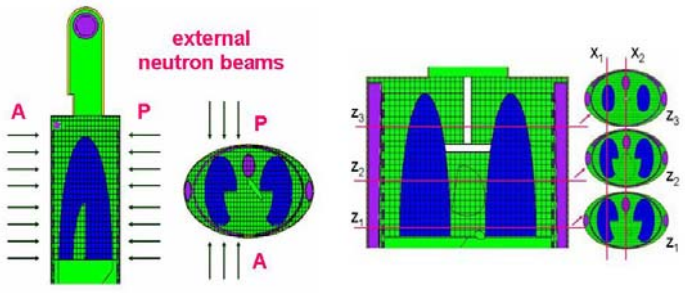

Fig.6 Schematic view of the collimated neutron sources that irradiated the entire lung in the calculations. Neutron flux and dose distributions were calculated along x_1 and x_2 axis for each of the three sections (z_1, z_2 and z_3) at different heights of the lung model. x_1 is inside the neutron beam, x_2 is external.

Fig.7 is a comparison between thermal neutron flux distributions obtained in the lung starting with a 0.0253 eV thermal neutron source (triangles) and with a 1 keV epithermal neutron source (squares). The plot refers to the x_1 axis inside the beam in the z_2 section of the model, at half the height of the lung (see fig.6). As expected, an external source of thermal neutrons is not a proper choice for lung irradiation, while the thermal neutron flux distribution obtained with external epithermal beams is very advantageous. With this solution the neutron flux is three times lower in the skin and in the external tissues than in the lung, and it remains uniform along almost the whole organ.

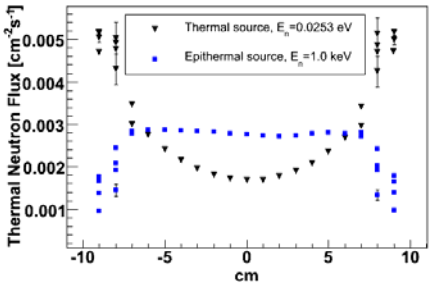

Fig.7 Thermal neutron flux distributions along x_1 and x_2 in the z_2 section. Triangles: distribution obtained with two thermal sources (0.0253 eV); squares: distribution obtained with two epithermal beams (1 KeV).

In fig.8 the different dose components per source neutron are shown; the section of the model is again z_2; on the left there is the beam distribution along x_1 axis (in-beam), on the right the beam distribution along x_2 axis (out of beam). The boron dose component is evaluated assuming 1 ppm of ^{10}B in all the tissues. the γ component is nearly the same along the in-beam and out-beam directions, while the dose from charged particles is at least 3 times higher in the zone directly irradiated by neutron beams.

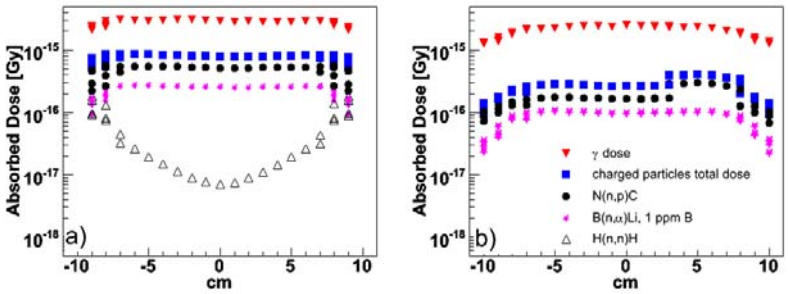

Fig.8 Dose distribution (Gy/source neutron) in z_2 section: along x_1 axis (left), along x_2 axis (right). The dose components are: upside-down triangles: γ dose from $^1H(n,\gamma)^2H$ – circles: $^{14}N(n,p)^{14}C$ – triangles: $^1H(n,n')^1H$ – stars: $^{10}B(n,\alpha)^7Li$ assuming 1 ppm of ^{10}B in all tissues – squares: charged particles total dose.

The boron uptake both in the normal lung and in the pulmonary metastases were studied in a rat model developed on purpose [11]. It was proved that around 4 hours after BPA administration, the ratio between the concentration in tumour and in normal lung is higher than 4. Fig.9 shows a comparison between an histological section and the neutron autoradiography of a successive slice of a rat lung with induced metastases and treated with BPA. The images clearly show that the boron concentration is higher in the metastases (darker structure in both the pictures) than in normal lung.

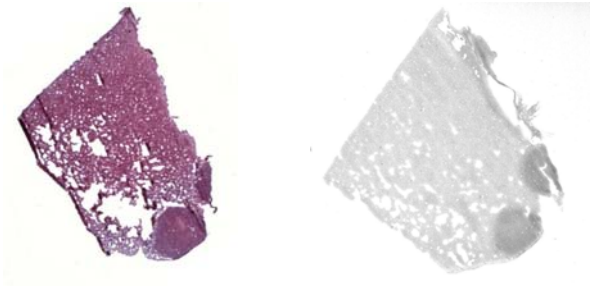

Fig.9 Histological preparation and neutron autoradiography of two successive slices of rat lung with tumoral nodules and treated by BPA: light zones are normal parenchyma, dark zones are metastases.

5. References

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