TAOrMINA: From the First Idea to the Application to the Human Liver

T. Pinelli, A. Zonta*, S. Altieri*, S. Barni, A. Braghieri, P. Pedroni, P. Bruschi, P. Chiari**, C. Ferrari*, F. Fossati, R. Nano**, S. Ngnitcjeu Tata*, U. Prati*, G. Ricevuti**, L. Roveda* and C. Zonta***

INFN, Pavia and Dept. of Nuclear and Theoretical Physics, University of Pavia, Italy
**Dept. of Surgery, Div. of Hepato-pancreatic Surgery, University of Pavia and IRCCS S. Matteo, Pavia, Italy*
***Dept. of Animal Biology, University of Pavia and Centre of study for Histochemistry, C.N.R., Pavia, Italy*

Summary

A novel method is described for the therapy of patients with diffuse, unresectable cancer in vital organs, which can be submitted to transplant. The therapeutic concept is based on the neutron irradiation of the isolated organ. Until now the research has been addressed to the case of liver metastases responsible of a significant contribution to the poor clinical outcome of colon[1]. Details of the first human treatment are reported and discussed together with the achieved results and the early postoperative follow up of the patient.

Introduction

The treatment of liver metastases secondary to a colon carcinoma poses frequently unsolved difficulties when they are multifocal, diffuse to both lobes or close to vital parts of the organ. In this case surgical resection is impracticable and homotransplant is affected by poor outcome due to neoplastic promoting effect of immune suppressive regimens. Standard chemotherapy is usually not able to prolong significantly the survival of such patients nor external radiotherapy is recommended due to the risks of actinides hepatitis. Besides these therapeutic restraints also the detection and localization of small neoplastic nodules can be difficult, deceptive or incorrect: Therefore even after a local aggressive approach relapse is a frequent event.

Having considered the problem in every way we realized that the total neutron irradiation of the liver removed from the patient could be the only way of destroying all detected and undetected metastases provided they are charged with a ^{10}B compound. The isolated liver is positioned into a thermal neutron field[2] where neutrons, coming from all direction, interact with boron without neglecting any even minimal part of the organ[2].

Material and Methods

In 1987 we started a long-term research whose main objective was to study the possibility to solve the mentioned problem by exploiting the property of tumors to absorb selectively boron from particular solutions injected into the blood circle. BNCT has been experimented in USA, Japan and Europe to treat malignant brain tumors by collimated thermal and epithermal neutrons. Up to now the clinical trials did not produce all expected results[3].

In our case collimated neutron beams are absolutely unfit to realize an effective therapy on the liver in presence of diffused cancerous nodules[2,4].

Preliminary calculations and measurements pointed out[2,4] that a safe and effective treatment is ensured when the ratio (T) of boron concentration in tumor (C_T) over normal tissues (C_H) is 3.5-4 at least:

$$T = \frac{C_T}{C_H} \geq 3.5 \div 4$$

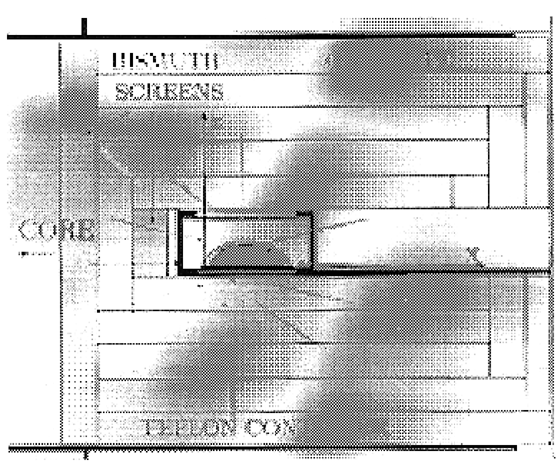

Figure1: Structure of the modified thermal column with liver at the irradiation position.

In particular cases, characterized by high values of boron concentration in tumor, lower values of this ratio can be accepted. Moreover, an adequate treatment requires high flux, good uniformity of the neutron field and negligible background.

In order to fulfill the above conditions, we performed a drastic modification of the reactor thermal column (Figure 1). In particular, the reduction of gamma background allowed getting a clean neutron field (Figure 2), fit to the irradiation of the isolated organ. In parallel, we got the possibility to measure with a good approximation (0.5 ppm) the boron concentration in liver tissues[2,4].

With the aim to verify the fundamental safety condition we studied, for the first time with a significant statistics, the boron uptake by assuming the rat as the experimental model [2,4]. The boron measurement was a crucial and difficult phase of our research. We solved the problem by an original nuclear method based on the range-energy particle relations[4]. Boron concentrations were evaluated by analyzing the particle spectra obtained during the neutron irradiation of tumor and normal tissue samples[2,4]. The experimental analysis of boron uptake evidenced a clear and positive result. Figure 3(a) proves that a safe and effective treatment can be obtained by starting the neutron irradiation in the time interval from 2 to 4 hrs. In Figure 3 (b) we can observe, in addition to T distribution, how in the same interval we can obtain, with a high probability[4], values larger than 4 of the boron concentration ratio in tumor over normal liver.

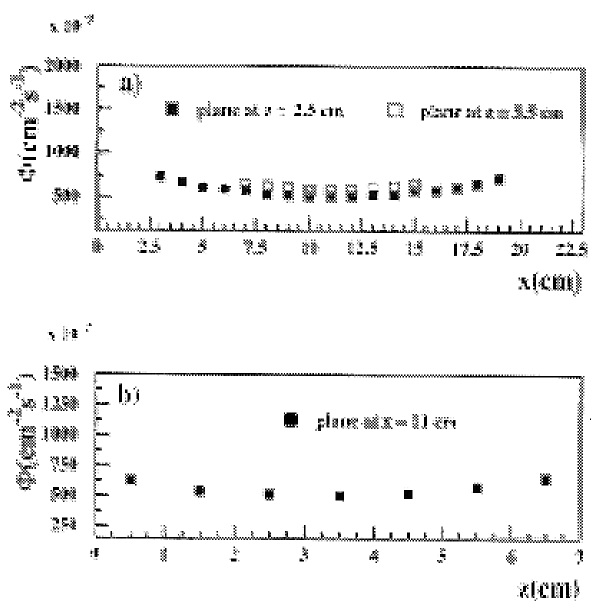

Figure 2: Neutron flux distribution at the irradiation position. x and z are longitudinal (a) and vertical (b) axes of the thermal column.

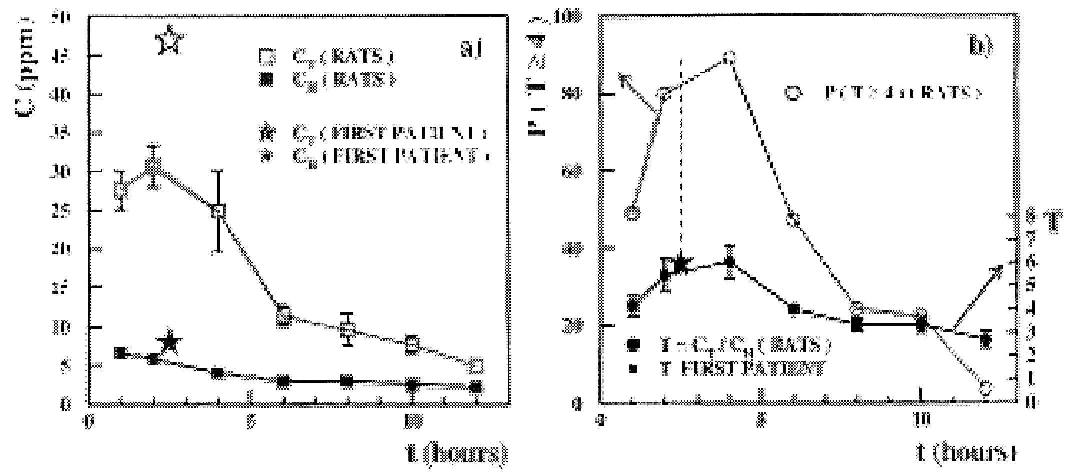

Figure 3: Boron concentration distribution achieved with the rat model (a). Time distribution is shown also for the probability to get a T value higher than 4 (b); t=0 is the mean time boron perfusion period. Stars represent values relative to the Patient at the beginning of n irradiation.

To conclude the check on the feasibility of the project, "in vivo" and in "vitro" pre-clinical trials were performed. We obtained significant and coherent indication from both cells[4] and rat tissues. In particular the microscopic analysis of tumor and normal tissue of rat liver evidenced irreversible damages (apoptosis and necrosis) in cancerous tissue only[4].

First Human Treatment

The first patient was 48 years old, suffering from synchronous diffuse liver metastases from a sigmoid adenocarcinoma resected 7 months before in another Hospital. At the end of a complete course of standard chemotherapy the hepatic situation and clinical conditions appeared worsened. An external US scan showed 6 metastases in both liver lobes, confirmed by a spiral CT. GEC was 63%. At the beginning of the operation an intraoperative US scan revealed the presence of 14 metastases in the liver.

Before removing the liver 750 ml of a 0.14 M solution of BPA-fructose complex (300 mg/Kg b.w.) was injected through colic vain during a period of 2 hrs. After 1 h from the start and at the end of perfusion we collected tumor and liver samples for boron measurement. After boron measurement the treatment plan was formulated. Equivalent doses were calculated by assuming RBE values given in literature[6], and following the indication that BNCT effects are independent from the nature of tumor[7] (Figure 4). At this point the hepatectomy was completed. On the bench the isolated liver was washed with chilled UV solution and then carried to the Reactor Laboratory

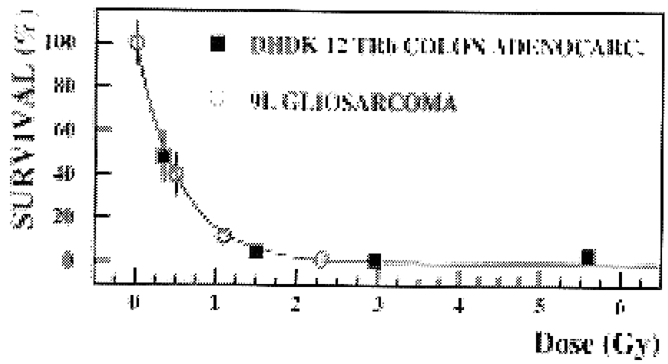

Figure 4:Dose effect study of survival on two different tumor cells.

of Pavia University. Here, by following the treatment plan, the explanted liver was submitted to the thermal neutron irradiation up to reach the fluence of $4x10^{12}$ cm^{-2} (11 min).

Taken back to the operative theatre, the liver was washed again with chilled UV solution and then reconnected to the vascular and biliary stumps of the patient. The procedure required 21 hrs altogether.

The postoperative period presented the following complications in sequence: (1) thrombotic occlusion of the left femoral vein (gradually reabsorbed); (2) renal insufficiency (lasted 10 days with complete recovery); (3) hepatic insufficiency (with clotting defects and Jaundice); (4) left foot drop (compression of common peroneal nerve in bed).

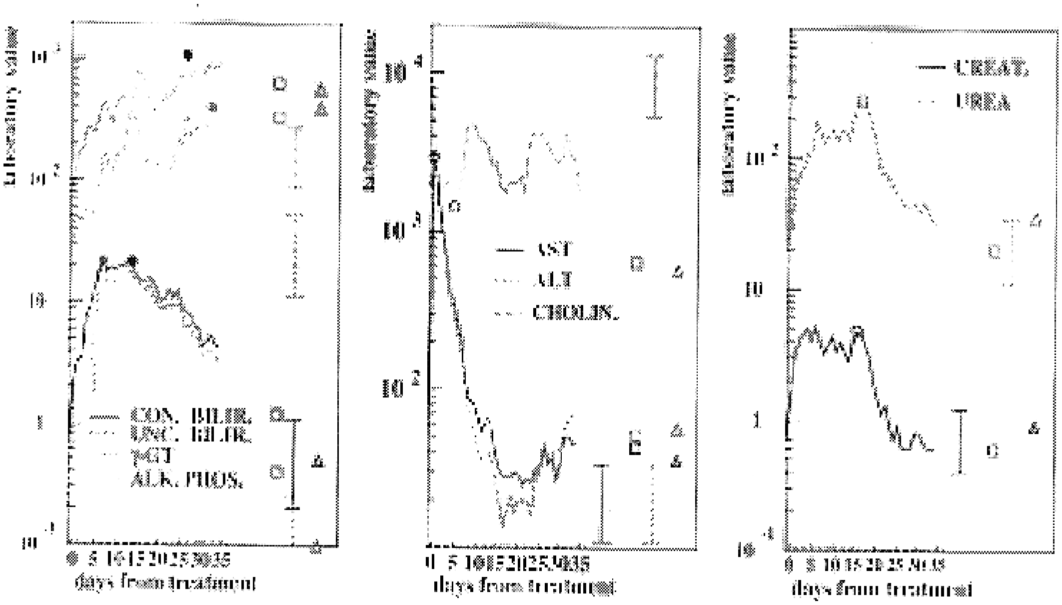

Figure 5: Behavior of some laboratory values vs. time. Preoperative values are indicated at t=-1. Operation day is at t=0. Squares and triangles give values at 90 and 180 days after treatment. The vertical segments are, in the given scale, the ranges of normal values. Circles show the worst values.

At present (7 months from the operation) the patient is in good general condition; laboratory values are good (Figure 5); neoplastic markers are negative. GEC is now 73%. Both spiral CT and PET show absence of metastatic nodules in the liver.

Discussion and Conclusions

The clinical outcome of the first human application of our therapeutic proposal is at present very satisfactory

The most important point of this experience are: (1) a retrospective neutronigraphic analysis of the tissue samples taken at the time of the operation shows that micrometastases as small as 0.25 mm are present and ^{10}B loaded. We consider that this fact supports definitively the necessity of treating the entirely of an isolated organ to avoid the neoplastic relapse; (2) the treatment plan we formulated is coherent with the results obtained during our research as confirmed by Figure 3 and Table I; (3) the early postoperative course was affected by important modifications of several laboratory values, but none of them appears directly related to the effects of liver neutron irradiation. Renal and also hepatic insufficiency should be referred to long-standing veno-venous by-pass, anhepatic condition, and ischemic liver preservation and to a compartimentation syndrome of inferior limbs. Both renal and hepatic conditions recovered almost completely. Now GEC is higher than preoperatively; (4) there is repeated evidence of the radical treatment of liver metastases: Necrotic tissue in the site of previous neoplastic localizations is gradually substituted by normal tissue.

In conclusion thermal neutron irradiation of the isolated liver after ^{10}B loading proved to be a feasible and efficacious therapy without an intrinsic toxicity[8], at price of an important operation to be deserved to selected patients.

Table I: Treatment plan of the first patient.

PATIENT TREATMENT PLAN		**TREATMENT DATA**	
boron concentration (ppm)	absorbed dose (Gy-Eq)	neutron fluence (cm^{-2})	4 10^{12}
normal tissue		time (min)	11
$C_H = 8 \pm 1$	$D_H = 8.6 \pm 0.5$	C_T/C_H	5.9
tumour		D_T/D_H	7.2
$C_T = 47 \pm 2$	$D_T = 62 \pm 2$		

The present-day conditions of our first patient are the best we expected; according to his words he is enjoying again a life of satisfactory quality.

Acknowledgement

INFN funded the project during the entire research. A. Caignard and D, M. Ferguson are acknowledged for their help in inducing tumors in the experimental animal and for her excellent contribution to the preclinical trials respectively. IRCCS San Matteo Pavia, in addition to Hospital facilities, gave financial support also. Gratefully we thank the reactor people and the numerous Technicians for their enthusiastic collaboration and friendship.

TAOrMINA: Advanced Treatment Organs by Means of Neutron Irradiation and Autotransplant

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