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BORON NEUTRON CAPTURE THERAPY

Oncological, Radiobiological, Chemical and Radiation Physics Aspects in the BNCT Technique Present and Future in Italy

Proceedings of the Workshop held in Padua
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RADIATION PHYSICS AND RADIOBIOLGICAL STUDIES

NEUTRON SOURCES

THE ITALIAN HADRONTHERAPY PROGRAMME AND THE BNCT PROJECT

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1. INTRODUCTION

More than two hundred physicians, physicists, engineers and informatics experts form the *Hadrontherapy Collaboration,* which aims at bringing Italy to the forefront of tumour radiotherapy by the beginning of next century and to foster hadrontherapy in Europe. In spring 1991 the *Hadrontherapy Programme* was initiated in the framework of INFN by a report titled "*Per un Centro di Teleterapia con Adroni*" [1]. For this purpose the Milan INFN group was financed by the V Commission of INFN in 1992; since then the socalled "*ATER Experiment*" has grown: it is now formed by groups of 11 INFN Laboratories and Sections. In the six years 1992 - 1997 the overall finacing of this R&D activity amounts to about 3 GLit (about 3 million DM). As indicated in Table 1, ATER is subdivided in four subprojects:

ATER-A	accelerators and related techniques	*Coordinator*	Sandro Rossi,
ATER-E	software developments and networking		Sandro Squarcia,
ATER-I	radiobiology		Giancarlo Gialanella,
ATER-R	detectors, dosimetry and monitoring		Paolo Colautti.

Table 1 - The Projects of the Hadrontherapy Programme

Year	*Project*	*Purpose*	*Promoting Institute (leader underlined)*	*Leader*
1991	ATER	R&D in accelerators, radiobiology, RITA, dosimetry etc.	**INFN**	Ugo Amaldi (CERN e TERA)
1992	CNAO	Costruction in Milano of a National Centre based on a synchrotron for protons and ions	**TERA**+INFN+nine Founding members of the Mirasole Foundation	Sandro Rossi (TERA)
1993	TOP	Construction in Rome of a proton linac	**ISS**+ENEA+INFN +TERA etc.	Martino Grandolfo (ISS)
1993	RITA	Multimedia network for the exchange of medical folders and diagnostic images	**TERA**+INFN+IST +INT+ISS etc.	Vito Vitale (INT- Genova)
1994	PPCI(*)	Costruction of a protonterapy centre based on a cyclotron produced by IBA	**UNIV. FIRENZE** + Members of Consortium	Giampaolo Biti (Un. Firenze)
1995	CATANA	Construction at the existing SC cyclotron of LNS of a proton beam for eye treatment	**INFN-LNS** + Dept. Oftalmology - Catania	Giacomo Cuttone (INFN-LNS)

(*)*Progetto Protoni Centro Italia*

The *TERA Foundation* was created in fall 1992 to collect funds and employ a staff fully devoted to the Hadrontherapy Programme. In 1997 twentythree staff worked fulltime on the TERA projects and the budget of the Foundation was about 1.4 GLit.
The flagship project of TERA is the construction of a Centre which will have both proton and ion beams. In 1993 TERA initiated the RITA project and ISS the TOP project (*Terapia Oncologica con Protoni*). In 1994 the Physiopathology Department led by Giampaolo Biti started to organize a Consortium of Universities and health Centres of the regions around Florence to buy a cyclotron and a gantry from IBA (Belgium) and realize PPCI (Table 1). In 1995 the *Laboratory Nazionali del Sud* (LNS) of INFN decided to use the proton beam extracted from the existing superconducting (SC) cyclotron to treat eye melanomas and macula degenerations. These activities are shortly summarized in this report after a review of what is happening in the world.

2. THE INTERNATIONAL LANDSCAPE

The projects of Table 1, which are independent but coordinated, have to be seen in the world landscape. About 80% of the 18000 protontherapy treatments performed in the world have used beams produced by accelerators constructed for fundamental research in nuclear and particle physics. Out of these cases, 20% are teye melanomas for which various dedicated accelerators exist in Europe. About 10% of the treatments of deep seated tumours have been done at the only fully dedicated facility, the American *Loma Linda University Medical Center.* As far as *ions* are concerned, since 1994 HIMAC treats patients with carbon ions, so that at HIMAC precious information is collected on this new radiotherapy, to be complemented by the results which will be obtained starting in 1998 in GSI (Darmstadt), where the first treatments with a scanning ion beam have been performed in 1997.

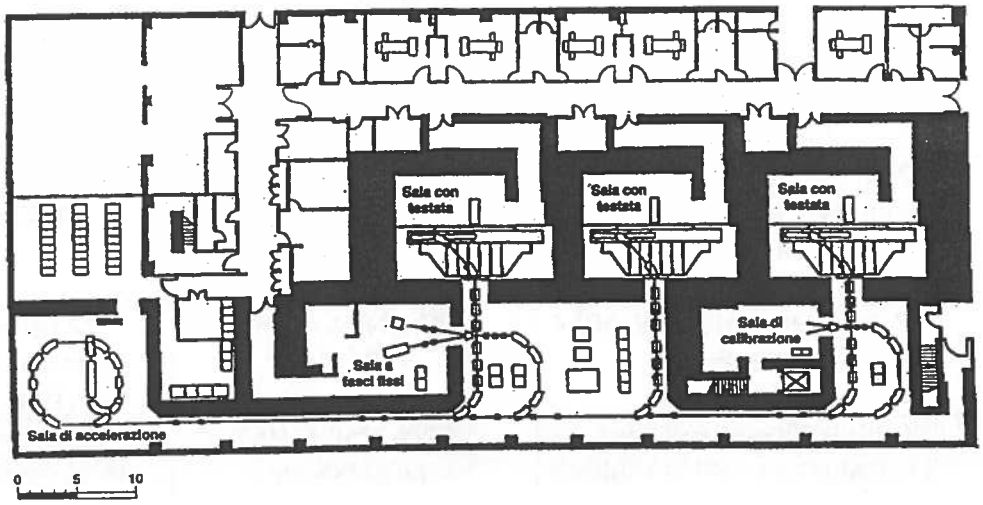

Fig. 1. The Loma Linda Centre is based on a 250 MeV protonsynchrotron and features three gantry rooms and one room for therapy with fixed beams.

When considering only hospital centres fully devoted to the treatment of deep-seated tumours and having more than one treatment room, the world situation is as follows.
In Europe deep hadrontherapy with charged beams is performed in Uppsala and Orsay, at two modified nuclear physics cyclotrons. Thus the recent increase of interest in hadrontherapy throughout Europe is quite natural, as in the year 2002 there will be *five* hospital-based centres

for deep hadrontherapy in the United States and *seven* in Japan, plus one in Taiwan and one in the People Republic of China - which will not be discussed further.

Running at present:

- *Loma Linda = Loma Linda University Medical Center*. This is the first hospital-based protontherapy centre in the world for which a total investment of 80 million $US was granted by public and private funds. It features three isocentric gantries and a room with fixed beams (Fig. 1).
- *HIMAC = Heavy Ion Medical Accelerator Centre* in Chiba, near Tokyo. Built with a total investment of 350 million $US, since 1994 HIMAC treats patients in three rooms with *carbon ions*. About 300 patients had been irradiated by the end of 1997.

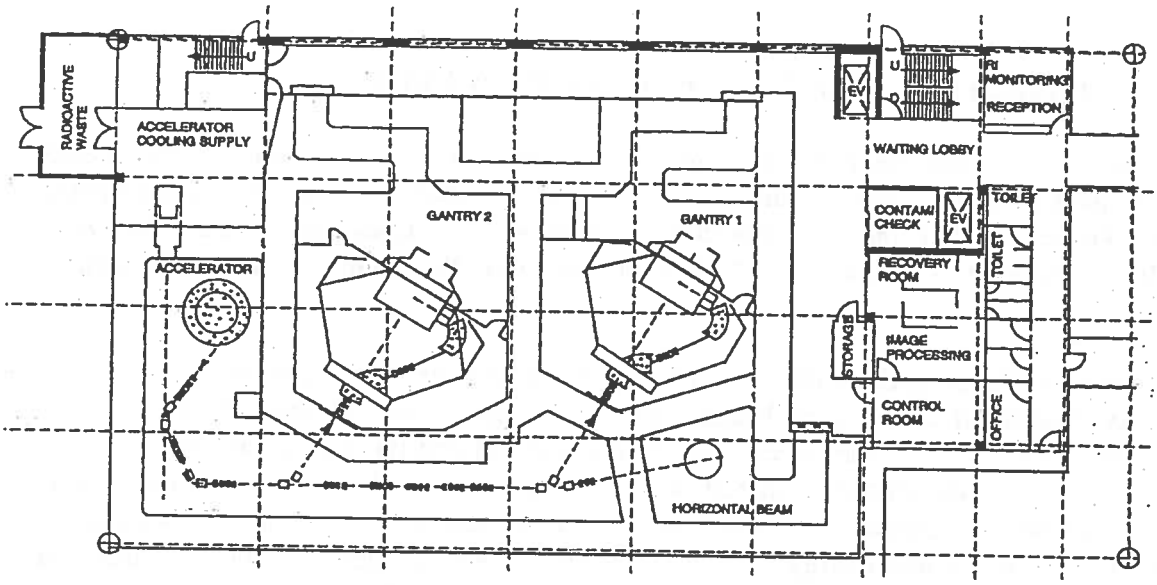

Fig. 2. The layout of the Kashiwa facility is very similar to the one of NPTC in Boston.

Fully financed and under construction:

NPTC = Northeast Proton Therapy Center (Boston, USA). This *protontherapy* centre, built for 46 million $US by the Massachusetts General Hospital (MGH) in Boston, will start treatments in 1998 and aims at tirradiating about 1'000 patients/year. It is based on a cyclotron built by IBA.

TENET - This is the one of the major network of hospitals in the States. It has recently acquired the company PTCA (*Proton Therapy Corporation of America*) and has decide to invest 250 M$ for the construction of three full-fledged centers with cyclotrons and gantries. One of them will be in the San Francisco area.

Kashiwa Centre Proton Treatment Facility - The cyclotron of this *protontherapy* centre (Fig. 2) is being built by IBA in collaboration with the Japanese company Sumitomo. The centre initiate treatments in 1998 with three rooms for protontherapy, two of them equipped with rotating gantries.

Hyogo Charged Particle Facility - Direct follower of HIMAC, this centre is in construction to the North of Kobe by Mitsubishi Electric (Fig. 2). It will start irradiation in 2001 with *proton and carbon ions*. The total investment, which includes a 50-bed hospital, is 275 million $US. This centre (which has two proton gantries, one room with a fixed proton beam and two room for ion treatments) is the most similar to CNAO in structure and objectives.

Shizuoka Cancer Center- Located about 150 km West to Tokio, this centre is financed by the Shizuoka Prefecture for its Cancer Center. It will have *only proton* beams with two gantries and a fixed beam.

KUMPF = Kyoto University Medical Proton Facility - This *protontherapy* centre, to be ready in 2001, is based a synchrotron, a gantry and a fixed horizontal beam.

Wakasa Bay Project - Situated North-East Kyoto, this *protontherapy* centre is supported by the *Science Agency* and the Hitachi will be responsible for the construction of the facility, which has a synchrotron, a gantry and a fixed beam.

Tsukuba Centre - Located near Tsukuba, inside the University Campus, this *protontherapy* centre is fully financed with 70 million $US. The project foresee two gantries rooms and one experimental room. The centre should be ready in the year 2000.

3. THE COMMITTEES OF THE HADRONTHERAPY PROGRAM

In the framework of the Hadrontherapy Programme three Committees, which are "transversal" to the projects of Table 1 and coordinate all the common research and development activities: the *Pathologies and Treatments Committee,* the *Radiobiology Committee* and the *Dosimetry and Microdosimetry Committee*. Due to lack of space only the results of the first Committee will be presented.

Three studies of the potential Italian patients have been performed by physicians of AIRO, the Italian Association of Oncological Radiotherapy. They have been published by TERA in the Blue Book (1994, Ref. 2), the Green Book (1996, Ref. 3) and the Red Book (1997, Ref. 4). The last study (R. Orecchia et al in Ref. 4) shows that about 12'000 persons are diagnosed annually as having a tumour or lesions which could benefit from the treatment with *proton beams* having a maximum energy of 200-250 MeV; for 825 of these patients the treatment with protons is the elective cure; these are classified as Category A patients. The relevant tumour sites and the figures are given in Table 2.

Table 2. Elective indications for protontherapy already clearly supported by clinical data. These patologies are classified in Category A of the three Italian studies. (Column b gives the percentages of treatable tumours and column a the numbers.)

Category A	Patients/y	Treatable with protons	
		a	b
Uveal melanoma	370	370	100 %
Chordoma of the base of skull	30	30	100 %
Chondrosarcoma of the base of the skull	40	40	100 %
Meningioma of the base of the skull	250	125	50 %
Paraspinal tumours	140	140	100 %
Schwannona of the acoustic nerve	300	45	15 %
Hypophysis adenomas	750	75	10 %
TOTAL	**1'880**	**825**	**44 %**

The tumours of Category B are collected in Table 3. Table 2 and 3 show that with *protontherapy* one could treat with advantage about 10 % of all the about 120'000 Italian patients who are nowadays irradiated with X-rays and electrons. Thus about 1% - out of this 10% - have tumours of category A, for which protontherapy is the elective cure (Table 2). The

same percentages would of course apply also to the other nations, whose citizens have similar living habits and, thus, cancer incidences. However studies conducted some time ago at the *European level* are, probably, less conservative and give as conclusion percentages for protontherapy which are in the range 30-40 %.

Table 3. Pathologies which one expects might draw an advantage from protontherapy, but for which further clinical studies of clear validation are required [4].

Category B	Patients/year	Treatable with protons	
		a	*b*
Epithelial brain tumours	900	450	50 %
Brain metastases	1'000	100	10 %
Head and neck tumours	3'060	430	15 %
Salivary glands tumours	370	185	50 %
Undifferentiated tumours of the thyroid gland	65	30	50 %
Lung tumours (NSCLC)	19'800	1'980	10 %
Thymoma	45	5	10 %
Œsophagus tumours	1'900	85	5 %
Biliary tract tumours	2'500	375	15 %
Cancer of the liver	3'850	385	10 %
Cancer of the pancreas	4'500	900	20 %
Retroperitoneal sarcoma	50	25	50 %
Rectal cancer	4'800	1'440	30 %
Uterine cervix cancer	720	360	50 %
Cancer of the bladder	9'000	900	10 %
Prostate cancer	8'800	2'640	30 %
Recurrence of pelvic tumours after surgery	>500	>250	50 %
Solid pediatric tumours	1'400	140	10 %
Non neoplastic pathologies			
Arterovenous malformations (AVM)	130	40	30 %
Macular degeneration of the retina	?	?	?
TOTAL (on about 120'000 treatments/year)	**>63'390**	**>10'720**	**17 %**

Carbon ion beams of 4'800 MeV are particularly indicated for the treatment of deep-seated tumours, which are radio-resistant both to X-rays and to protons. These are about 10 % of all the tumours treated with X-rays, and therefore in Italy about 10'000 patients a year. This approach is substantiated by radiobiological studies and by clinical information gathered with neutrontherapy, but it is not yet clinically proven, since only about 300 patients have been irradiated with carbon ions at HIMAC (Japan). In 1998 in GSI (Darmstadt) the new carbon ion facility will start treating about seventy patients/year. TERA plans to have ion beams at CNAO, presented in the next Section.

4. THE CNAO PROJECT

To illustrate the second of the Italian project appearing in Table 1, it has to be recalled that, from the beginning of 1992[1], TERA is engaged in the design and realization of the hadrontherapy centre CNAO based on a synchrotron which can accelerate protons to at least 250 MeV and carbon ions (A=12) to at least 4800 MeV (i.e. 4800/12 = 400 MeV/u). This will be a centre of excellence devoted to tumour hadrontherapy of more than one thousand patients/year, to clinical research in cancer therapy and to R&D in the fields of radiobiology and dosimetry. The first study was completed in spring 1994 and published in the Blue Book [2]. At the end of 1995 the TERA Foundation has drawn the interest of CERN in the design of an *optimized* synchrotron for light ion therapy initiative to be then built nationally by those European countries who will decide to invest the needed funds. At the beginning of 1996, the CERN management agreed, and a new study of such a synchroton was started at CERN (PIMMS = *Protons and Ions Medical Machine Study*) under the leadership of Philip Bryant. The Project Advisory Committtee is led by Giorgio Brianti. Five TERA staff members and two doctoral students from the AUSTRON Project (Vienna) partecipate in the study, which aims at finding new optimized solutions for the synchrotron and the isocentric proton gantries. GSI, which since long is working in the field of hadrontherapy with ion beams, partecipates with the responsability for the design of the ion injector and of a gantry for carbon ions. A report on this work was recently published [5].

While initiating the European collaboration on PIMMS, TERA offered to six Hospital, oncological Institutes of Milano and Pavia and to three Universities to form a consortium and realize the National Centre for Oncological Hadrontherapy in Milano. The instrument of understanding was signed in June 1996 by

Salvatore Maugeri Foundation - IRCCS, Pavia

TERA Foundation , Novara

European Institute of Oncology - IRCCS, Milan

National Institute for Tumour Research and Cure - IRCCS, Milan

National Neurological Institute Besta - IRCCS, Milan

Ospedale Maggiore Polyclinic - IRCCS, Milan

San Matteo Polyclinic - IRCCS, Pavia

Polytechnical School, Milano

University of Milano

University of Pavia.

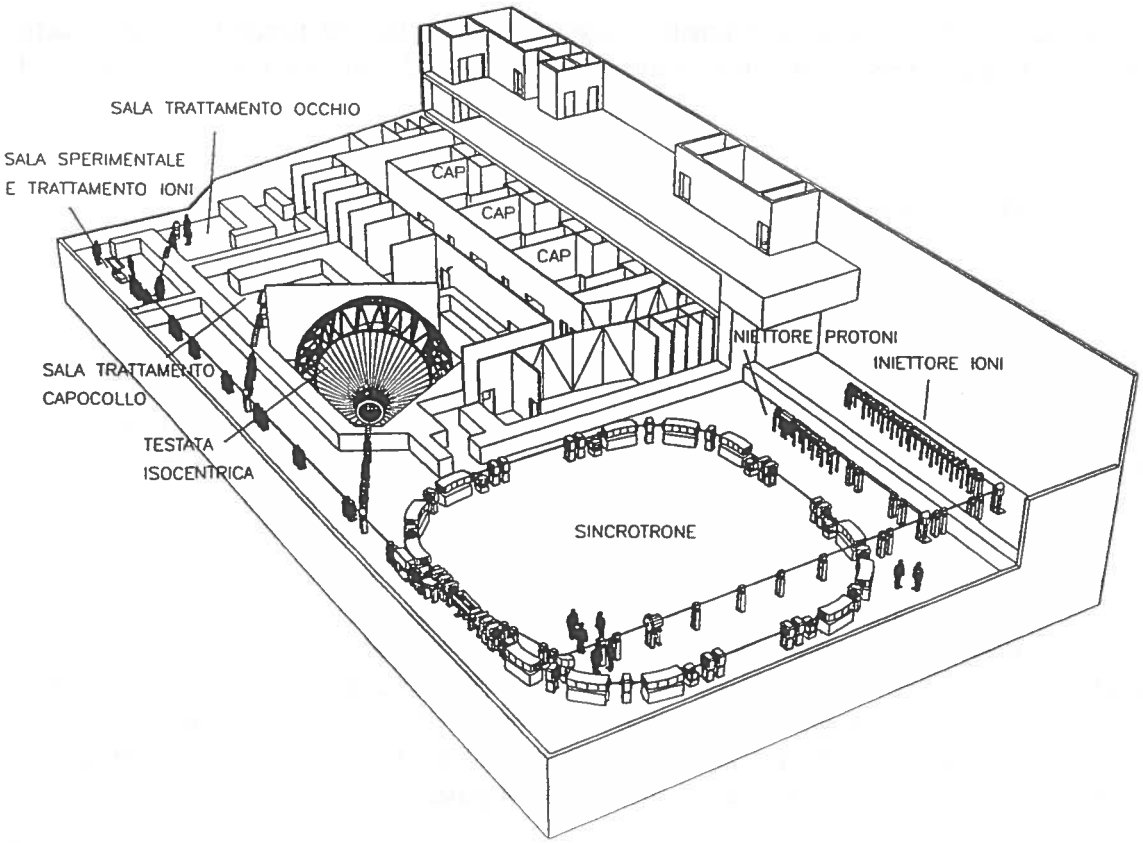

Fig. 3. The CNAO synchrotron will have a diameter of about 22 metres Patients will be treated with protons in three rooms. Initially only one of them will feature a gantry, but the fixed beam room can be transformed in a gantry room. The first carbon ion treatments will be performed with a horizontal beam . Later the building will be extended.

In 1996 the Polyclinic of Milano (Ospedale Maggiore) put at the disposal of CNAO a wonderful site located close to the Mirasole Abbey, South of Milano on the road going to Pavia.

In March 1997, the bylaws of the *Fondazione Medico Scientifica Mirasole*, a no profit Foundation which will be responsible for the construction and the management of CNAO, have been approuved. The ten founding Members are engaged in finding the public (1/3) and private funds (2/3) required for the construction and the initial managemen: in total, including salaries of about 20 people for five years, about 100 GLit (100 MDM). In the long run the Mirasole Foundation income will be sufficient to finance its operation, including the payment of salaries for the personnel (in 1994 about 70 people).

At the beginning of June 1997 Ospedale Maggiore asked 33 GLit (33 MDM) to the Health Ministry, through the government of the Lombardy Region, for the buildings and conventional plants of CNAO. This sum is requested on an already funded law for hospital construction which reserves, over the next six years, about 1200 million kLit to about forty national Institutes (IRCCS) devoted to medical research and health care. Six of these Institutes are founders of the Mirasole Foundation. The response is expected by spring 1998. Since three years TERA has requested to the Charity Compagnia di San Paolo (Turin) 16 GLit (16 MDM) for the synchrotron and the controls and 32 GLit to the Foundation Cariplo (Milano), for the rest of the hightec components of CNAO. San Paolo has already granted the requested

contribution and Cariplo has given a positive answer, waiting for the funds fromthe Health Ministry. If the positive reply will come by middle 1998, CNAO will be completed at the end on 2003.

5. THE RITA NETWORK

The second project of TERA is the creation of an informatics and organisational network, called *RITA (Italian Network for Hadrontherapy Treatment),* which will connect the Associated Centres – distributed throughout Italy and abroad, and situated in the public oncological institutions and in private clinics – with the Centres where proton and ion beams will be made available. Through RITA the specialised medical and physics staff of all the Italian oncological institutes who want to profit from the Hadrontherapy Programme (called above*Associated Centres*) will be connected with the experts of CNAO and of the other protontherapy centres. By using the most modern informatics techniques, they will exchange diagnostics images and discuss each case, so that the patient will travel to one of the centres where hadron beams will be availabel only if the tumour can be treated with a clear advantage. Some of the physicians at these Associated Centres (sometimes after using conventional radiotherapies) will even be able to plan a successive hadron treatment for their patients, which will then be irradiated in one of the hadrontherapy centres. The implementation of the RITA network is already well advanced, since in 1997 the first connection between two oncological centres has been tested and a clinical folder has been produced.

6. THE TOP - LINAC OF ISTITUTO SUPERIORE DI SANITÀ

The Green Book of Ref..2, completed in 1995, responds to the needs of Istituto Superiore di Sanità (Rome). In fall 1993 the Physics Laboratory of ISS, which was since long active in the fields of proton radiobiology and dosimetry, decided to request special funds for the construction of a prototype of a "compact" accelerator (and its rotating gantry) and to finance R&D programmes in the fields of radiobiology, dosimetry, networking, pathology and treatment planning. This programme is now known as the *TOP Project* of ISS, where TOP stands for "Terapia Oncologica con Protoni".
By the initiative of the TERA Foundation, and in the framework of the Hadrontherapy Programme, in the years 1993-1995 four working groups have designed four novel medical proton accelerators: two synchrotrons, a superconducting cyclotron and a high-frequency (3 Ghz) proton linac. They are described in the Green Book [3]. In September 1995 copies of this book were distributed to the members of the Scientific Committee of the TOP project. The decision was to construct the first part of the high-frequency proton linac, whose injector will also be capable of producing PET isotopes. In 1997 an agreement has been signed between ISS and ENEA for the construction of the accelerator. An agreement with TERA is under discussion. The linac will be constructed in Rome on a piece of land situated between ISS and the oncological Institute Regina Elena, which will be responsible for the medical part of the centre.

The initial ISS funds (6 million kLit, i.e. 6 million DM) were allocated in 1994 and appropriated in March 1996 with the understanding that about 80% of this sum has to be spent for the linac. A further contribution of 2.3 million kLit was granted at the end of 1995. Requests for about 10 million kLit are pending; they will allow the completion of the linac

and of three treatment areas, one of them with a rotating gantry.

7. THE PPCI AND CÀTANA PROJECTS

The *Department of Physiopathology* of the University of Florence is forming a Consortium to construct on the University site a protontherapy centre with one gantry. The protons will be accelerated by an IBA cyclotron and the layout will be very similar to the one of the Kashiwa centre, shown in Fig. 2. A second gantry could be addedd later.

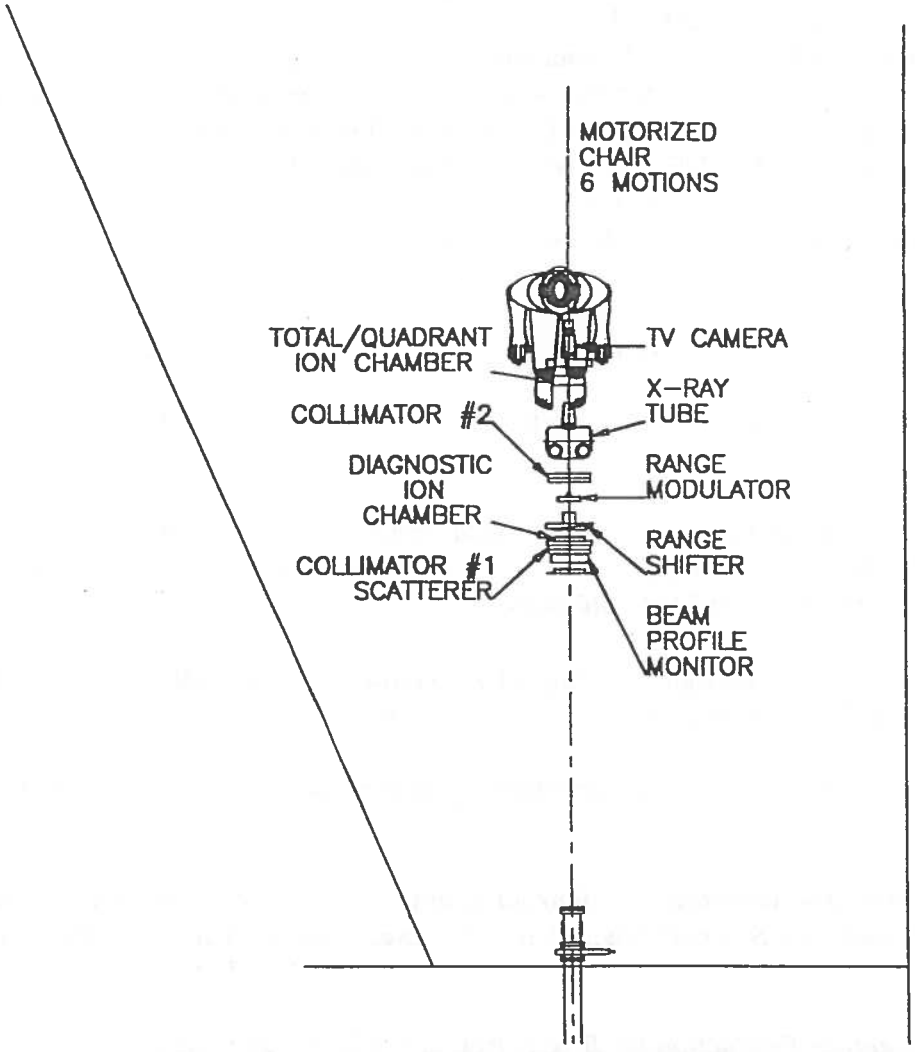

Fig4. The medical proton line of the Laboratory Nazionali del Sud (INFN, Catania).

In Catania the *Laboratori Nazionali del Sud* (LNS - INFN) are trasforming the existing superconducting cyclotron, so that in 1998 a proton beam of 100 MeV will be extracted. INFN has already financed the new medical beam line of Fig. 4, which will allow eye treatments to start in 1999. The first clinical proton beam will thus be operative in Italy before the turn of the century.

8. CONCLUSIONS

By joining forces Italian scientists have been able to launch a very consistent Hadrontherapy Programme, which is formed by independent projects and, since the beginning of 1998, is coordinated by CNA, the *Coordinamento Nazionale Adroterapia*. The Programme has already moved a total of about 20 GLit (20 MDM). The financing of at least some of the large projects of Table 1 should soon be decided.

In parallel other ideas are proposed. In particular at the present meeting a *BNCT project* for the Legnaro National Laboratory of INFN has been presented for the first time. This is a positive step, since the BNCT facility initially included in the CNAO project by S. Agosteo et al [6] had to be left out from the proposal for Mirasole [4, 5] for cost reasons. It is very natural to expect that the R&D activity of the next years for preparing this new facility will be part of the ATER experiment financed by INFN, for which a three year plan (1999 - 2001) is in preparation. Later, in the framework of CNA the project will be another independent construction programme, parallel to the ones listed in Table 1.

References

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PERSPECTIVES OF BNCT IN ONCOLOGY

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In the search for the ideal cancer therapy, Boron Neutron Capture Therapy is one of the most promising new modalities, offering the perspective of the maximum damage to the tumor cells and the maximum sparing of surrounding normal tissues. To realize its potential BNCT requires however that a large number of tecnological and scientific problems are solved. The first clinical attempts of using BNCT in the 1950s (4), failed to show any advantage as the enthusiasm for the exciting theoretical advantage of this new modalitay was not sufficent to overcome the lack of a neutron beam and of a boron compound of suitable characteristics. These premature studies risked to compromise the countinuing interest and the financing and development of further research in that field. Since then many advances have been made in all the major areas that are essential for the ultimate success of BNCT; although more must be done to prove unecquivocally the therapeutic efficacy of this radiotherapy modality, as well as its role and its indications, it is advisable that in any country where radiotherapy is well established as one of the main cancer specialty, a multisciplinary Working Group including physicists, chemists, biologists, ingeniers and radiotherapists is created, to promote within the country the interest in the subject and to actively partecipate in the international scientific effort for BNCT.

Radiotherapy may fail in the local control of tumor for two main reasons: because the dose delivered is not sufficent to kill all cancer cells; or because some cancer cells are missed from the area treated to a cancericidal dose.
Both events must be avoided to achieve the definitive local control and not to have a tumor recurrence. Unfortunately most of the measures aiming to reduce the risk of the first cause of tumor recurrence may at the same time increase the risk of the second one. Increasing the dose requires infact that the volume exposed to the high dose is as small as possible, to avoid an excessive damage of normal tissues and this unavoidably involves a higher risk of marginal misses.
The large majority, if not the totality, of the modern developments of the radiotherapy techniques (conformal RT, stereotactic RT, brachytherapy, adrontherapy) are essentially aimed to increase the dose; and this effect usually occurs as a result of a better ability to concentrate the dose in smaller and irregular deep seated volumes. This has decreased the incidence of sequelae and it has considerably enlarged the indications of radiotherapy, but wether the tumor control probability has increased, is much less clear.
On the radiobiological side, several attempts have been made to envisage treatment modalities (unconventional fractionation schedules, radiosensitizers, radioprotectors) able to selectively damage the cancer cells while sparing the normal tissues. If a large differential damage could be achieved the geometrical sparing of normal tissus would infact became much less relevant. Unfortunately only minimal achievements were made with this radiobological approach. One of the main constraints is that reliable tests able to evaluate the cell kinetics parameters of an individual tumor are still missing.
Recently the concomitant use of radiations and chemotherapy has become very popular, leading to some of the few advances reported in the last years in oncology. It is worth of

mentioning that in most cases the efficacy of the radio chemo therapy combination was to due to a better local control and not to the systemic action of the drug. This potentiation of the efficacy of radiation is usually attributed to the interference of the drug with the repair mechanisms of the cellular radiation damage, but it is also possible that chemotherapy contributes to the better local control, killing the cells missed from the radiation field edges.

In conclusion the clinical experience supports the hypotesis that at least for some tumors there is a strong need of treatment modalities able to increase the dose in a larger area, where the cancer cells are potentially spread, without the constraints due to the risk of healthy tissues damage.

The main potential merit of BNCT is that the radiation dose to the tumor volume and to the normal tissues is not only determined by the geometric shape of the radiation field, but also by the different concentration of boron in the correspondent cells. Thermal neutrons used for BNCT because of their low energy, have infact a very limited number of interactions with the nuclear species commonly found in tissues and therefore result by themselves in a very limited damage; boron has on the contrary a very high cross section for capturing thermal neutrons leading to two particles of a very high LET releasing their energy within a few microns corresponding to the diameter of a cancer cell.
BNCT is therefore a thypical bymodal treatment using two components each being individually innocuous but becoming lethal to the cell when combined.
This simple and schematic process to became a treatment modality for clinical use requires however a large number of conditions wich have been the subject of all the research work done by many scientists in the last 30 years after the first experiments made at Massachusset's General Hospital (1). Most of the problems wich need to be solved and the relative state of art will be presented during this meeting.
Although we are still far from having solved all these problems it is now quite clear where to address the research work and time is mature to proceed to clinical experiments.
The availability of epithermal neutrons made possible to reach tumors relatively deep seated. Important advances have been made in the very complex field of radiation dosimetry and treatment planning of BNCT. Microdosimetry is of particular importance to understand the effects of the high LET particles combined with the other incident and induced radiations. The effectiveness of BNCT not only requires that boron is preferentially concentrated in the tumor but the exact location within the cells is also essential because of the very short track of the particles. Methods to detect the boron concentration in vivo and to determine its cellular localization in vitro on tissue samples are at an advanced stage (7). In the search of boron compounds able to cross the blood brain barrier and to selectively concentrate in the nucleus of tumor cells a very promising approach seems that of boronated nucleic acid precursors and protein components (9); these compounds may infact be selectively used by proliferating tumor cells compared with the normal cells leading to the differential necessary for BNCT. A further field for research is BNCT radiobiology: due to the mixture of radiations contributing to the total dose in BNCT and to the many variables of the radiobiologic effect, the evaluation of relative biologic effectiveness of BNCT is very difficult and may present a large case by case variability (5).
The clinical interest in the use of BNCT was mainly concentrated on the treatment of malignant high grade gliomas; a second clinical target was represented by melanoma. Both tumor are known to be very radioresistant; high grade gliomas although only occasionally metastasizing, are never radically resectable and almost invariably recur locally after high dose radiations and lead to the patient death within 6-12 months; recurrence have been

demonstrated to arise both marginally and centrally. The delivery of higher radiation dose to a large volume of the brain with conventional radiotherapy is inhibited by the risk of normal brain damage and of radiation necroses. The incidence of malignant gliomas in Italy is of 900 new cases per year; this is also the number of patients dying for this disease in the same time interval. If BNCT was only able to save a large amount of these patients any effort for its introduction in the clinical use would be fully justified.

Although the disappearance of malignant gliomas after BNCT was demonstrated in several experimental animal studies (2, 3, 8), convincing data on its efficacy in the clinical use are still scarce. Most of those unsuccesfull results were however attributable to the lack of suitable tools and knowledge.

The largest and most interesting results have been obtained in Japan by Hatanaka (6); his data were the subject of large criticisms and clearly need to be confirmed in a better designed trial. It has to be mentioned however that in a recent update of the japanese series, in a group of 16 patients with grade 3-4 glioma histologically confirmed and seated not deeper then 6 cm, a 5 years survival rate of 58,3% was reported.

Other clinical trials are underway in the US at the Brookhaven Medical Research Reactor, Upton NY and in Europe at the Petten Joint Research Centre, The Netherlands. Results are not available but the feasibility and the safety of this technique have been confirmed by the first data.

The development of a national group in our country devoted to BNCT is therefore justified and desirable.

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BNCT: NEW PERSPECTIVES IN RADIATION THERAPY

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1. BORON NEUTRON CAPTURE THERAPY (BNCT):

Definition: BNCT is performed in two steps: (I) a boron based compound is administered to the patient, when maximal boron concentration in the tumor is achieved, (II) thermal neutrons[1] are delivered on the tumor.
Mechanism of action: The neutron capture reaction produces two energetic particles, $^{4}He_{2}^{++}$ (α particles) and $^{7}Li_{3}+$ that are strongly cell toxic. Due to the short range of these nuclear fragments (5 - 9 μm) mainly those cells that have bound or internalized a B-containing substance are killed.
Therapy: To date clinical applications of BNCT have been to primitive brain tumors and malignant melanoma.Two boron compound have been approved for therapeutical purpose in U.S.: the amino acid p-boronophenylalanine (BPA) and the sodium borocaptate (BSH).

2. BNCT: A REVIEW OF CLINICAL TRIALS.

Shortly after the discovery of neutron, occurred in 1932, Locker proposed using fission products from the ^{10}B neutron capture reaction to treat cancer.

In 1941, studies of boron and lithium neutron capture therapy in mice showed that these nuclides concentrated in tumor cells and produced apparent tumor regression after neutron irradiation.

This led to initial clinical trials in 1952 by researchers at Brookhaven National Laboratory (BNL) in New York: a boron drug was delivered to a series of ten patients with brain tumors and irradiation was carried out with the Brookhaven Graphite Reactor. Between 1959 and 1961 further 16 patients were irradiated at the Brookhaven Medical Research Reactor. In the study conducted by Sweet, from 1961 to 1962, a series of 18 patients were treated at the MIT reactor. These unsuccessful clinical trials of BNCT were abandoned in 1962, primarily because of technological immaturity. The boron drug was a simple inorganic boron compound and did not accumulate selectively in the tumor. Furthermore the reactors at BNL and MIT provided only thermal-neutron beams with such limited depht of penetration that viable tumor was often found at a depht of 2-3 cm after treatment, while surface tissues were over-irradiated. Some patients died from treatment-induced brain swelling because synthetic steroids were not available.
In 1968 Hatanaka, who had been involved with the early US clinical trials, continued BNCT of brain tumors with a new boron compound (borocaptate sodium or BSH) till 1994. More

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[1] *A particle is defined as a thermal particle when itís energy is comparable to that aquired from the processes of thermal excitation. If the particle is free, i.e. without any interaction, itís energy coincide with the kinetic energy.* $E_{kinetic} = mv^2/2$ *were m and v indicate the mass and the speed of the particle respectively. The thermal excitation energy is determined by the following relation:* $E_{thermal} = 3kT/2$ *where k is the Boltzmannís costant and T the absolute temperature (°K). Therefore* $E_{thermal} = E_{kinetic}$ *or* $3kT/2 = mv^2/2$, *applies for the free particles.*

than 160 patients, a variable interval of time after palliative surgery, have been treated by BNCT.
Patients received BSH by intra-artery infusion (more recently by intra-venous (i.v.) infusion) at a dosage of 30 - 50 mg ^{10}B/kg body weight (b.w.). Six to twelve hours later, patients were irradiated with thermal neutrons on the surgical bed. Because of high skin boron concentration, the scalp was reflected before irradiation. Due to low neutron flux irradiation, times of 3 - 5 hours were required in one fraction. After 1985 treatment has been limited to more superficial tumors, since the depht of penetration was no more than 6cm. Hatanakaís results are noteworthy for two reasons. First, out of a total of 38 patients who had grade III and IV gliomas, and 12 of whom had tumors located within 6 cm of the cortical surface, the reported mean survival time was 44 months, the median was 25.6 months, 5 and 10 year survival rates were 19.3% and 9.6% respectively. Second, there was no evidence of radiation injury to normal brain, except for one patient who had received an exceptionally large dose of neutrons.
Nevertheless, Hatanakaís results are difficult to interpret for a variety of reasons. These include the varying time intervals between surgery and administration of the capture agent and irradiation, lack of randomization of patients and most importantly, poor depht of penetration of neutron beam. The above Hatanakaís results have stimulated groups in different countries to initiate clinical programs.

Takagaki treated a group of patients with recurrent advanced glioblastoma multiforme (GBM) by BNCT using BSH and reported increased survival compared to historical control.

Stragliotto, Haritz, Haselberg and Ceberg have carried out biodistribution studies of BSH in patients with GBM who received an i.v. infusion of the compound at varying doses and time intervals prior to surgical resection of their brain tumors. All of these studies have shown that BSH has a higher affinity for brain tumor compared to normal brain, but the chemical and biological basis for this remain yet to be determined.

In the study carried out by Mishima, BPA was injected subcutaneouslys or i.v. to 14 patients with melanoma before irradiation with neutrons. A good local control and moderate skin reactions have been reported.

Preliminary biodistribution data of BPA fructose complex have been reported by Bergland in a series of 7 patients with GBM. Peak tumor boron concentrations ranged from 11 to 26μg/g and normal brain value were <5μg/g.

3. PRECLINICAL STUDIES AND ONGOING CLINICAL TRIALS; PROPOSALS OF STUDY.

The start of conference and the development of international collaborations focussed on BNCT in the 1980s and in the early 1990s, the publication of roughly 40 articles per year since 1993 (from Medline) indicated an increased interest on this subject.
In 1983 the first symposium of the International Society for Neutron Capture Therapy was held at BNL, New York. The next symposium is scheduled for 1998 in San Diego, California. The bilateral, Australian / Japanese BNCT Program for Melanoma treated the first patient in 1987. Also in 1987, a european collaboration on BNCT was formed with two main goals:

implement BNCT of gliomas at the High Flux Reactor in Petten, The Netherlands and create the necessary conditions for BNCT of other cancers and at other facilities. The first International Workshop on Accelerator-Based Neutron Sources was held in 1994 in Jackson (USA).

Preclinical studies: the evaluation of biodistribution and selectivity for the tumor of boron-compounds is the aim of some ongoing studies or proposal of study focussed on BNCT. Preclinical models are studied to evaluate BNCT on tumor of different organs.
At BNL ongoing studies are evaluating the different affinity of tumoral cell colture to BPA, BSH and new boron compounds. Available data indicate that a new boronate porphyrin (BOPP) satisfies most requirements to be an effective compound in BNCT. Kahl reported that in animal studies the ratio of BOPP in tumors and healthy cells was greater than 100:1 and it cleared sufficently fast from the blood. The latter property is relevant in order to avoid vascular damage with irradiation. At the university of California in S.Francisco (UCSF), *in vitro* and animal studies are currently performed to evaluate plasma and tissue kinetics of BOPP. The degree of selective distribution to tumor and toxicity characterization are relevant aims of these studies.

Clinical trials: A phase I/II clinical trial of BNCT is underway at BNL. Fift-teen patients with GBM have received BNCT following 2-hr infusion of 250mg BPA/kg b.w.. Radiation dose ranged from 25 to 52 Gy. There were no acute adverse effects on normal brain.
In 1968 Hatanaka initiated a clinical trial of BNCT for the treatment of brain tumors that was ongoing untill his death in 1994. The trial has been continued by his associate Nakagawa: out of 149 patients treated with BNCT, 64 had gliomas of various grade. Their overall response rate was 64% and median survival of GBM was approximately 21 months.
At UCSF proposals of clinical trials of BNCT were done by Larson: phase I, II, and III studies for patients with GMB or locally advanced head and neck squamous cell carcinoma. Phase I/II studies will evaluate toxicity and activity of BOPP followed by a single dose of BNCT. Phase III will compare the latter with the best fractionated conformal radiotherapy, by x rays from linear accelerator.
The first european clinical trial of BNCT is ongoing at the Research Center of the European Commission in Petten (The Netherland). It is planned the accrual of ten patient with GBM, who have already been operated in their country. Epithermal neutrons of a High Flux Reactor will be delivered.

4. SINGLE DOSE VS FRACTIONATION

It has been discussed whether the neutron doses should be fractionated or not when treating malignant gliomas in Petten. An argument against fractionation is that the highest possible neutron dose should be applied in combination with the highest possible concentration of ^{10}B in the tumor and that these condition will be difficult to achieve repeatedly. Conversely it should be an advantage for the low LET irradiated normal tissue to use fractionated treatments since the normal tissue should then be allowed to recover between the irradiations while this should not be the case for the high LET irradiated tumor cells. It is still unclear how effective a ëretargetingí of BSH is after a previous radiation. There are indications from experiments on mice that BSH is more easily taken up in the brain after a first treatment but this has to be analysed in more detail.

5. LIMITING FACTORS AND FUTURE DIRECTIONS OF BNCT

There are three components necessary for the success of BNCT:
1) a nontoxic boron compound
2) selective and homogeneous assimilation of the boron compound into the tumoral cells
3) activation of the boron compound by neutron with an energy adequate for penetration to the depht of the tumor.

None of these three problems have been completely solved. Nontoxicity and selective distribution of boron compound are somehow related. New boron-containing substances, such as monoclonal antibodies, nucleosides, growth factors, liposomes and thioureas have potential to be used in clinical trials with BNCT. Nevertheless none of them appears completely safe for clinical use and their biodistribution is currently under evaluation on preclinical models.

Previous clinical test with BSH-based BNCT against gliomas showed that thermal neutrons do not have a good penetration across the skull. Epithermal neutrons have an enrgy range higher than the thermal neutron and are suitable for BNCT, expecially for the deep-seated tumors. At the university of Whashington itís under evaluation the sequence of epithermal and fast neutrons. In some case this sequence is expected to result in a dramatic increase of tumoral control probability.

Overcoming these limiting factors it will become a priority the availability of neutron sources other than nuclear reactors. Accelerators delivering a neutron flux sufficent for medical treatment are in advanced stage of study. Basically two proper neutron sources can be considered:

1) the collision of a deuteron beam with a Tritium target products a 14 MeV monoenergetic neutron beam and an Helium ion. It is possible to obtain this reaction by compact shaped machinary, supplied with mobile or rotating head, with a dose rate of 10 - 15 cGy/min, at the isocenter of 100cm and with an half-value layer (HVL) of 9.5cm. During the irradiation a big amount of heat is produced. It is difficult to dissipate all the heat. Moreover tritium, the target, has a short duration.
2) The other source of neutrons is the collision of highly energetic accelerated protons on a target constituted of Berilium. The neutron beams energy ranges from 1 MeV to the same energy of colliding protons.This technics requires a cyclotron to accelerate the protons. Magnetic fields could be used to deviate and collimate the protons to the target located in the gantry. The operative source to skin distance (SSD) of these accelerators is one meter. The higher HVL of the neutrons produced by protons and the greater simplicity of accelerating protons instead of deuterons guided the adoption of the second technic in most units of BNCT.

In 1995 nineteen accelerators and one reactor were operative as sources of neutrons for therapeutical purpose: 3 out of 19 accelerators used the first technic and 16 used the second technic. It is currently under evaluation Californium 252 as a neutron source for brachitherapy of patients with brain lesions. Tools to improve the accuracy of dosimetry and BNCT dedicate computer packages to determine isodose curves are included in developing projects.

Combined treatments: A general approach for BNCT, whatever type of tumor is considered, could in the future be initially to try different combinations of surgery, external radiation, chemotherapy, hypertermia or other suitable modalities and in some way combine them with BNCT. For example, metastases with limited spread or with rather well-known localization, possible to be included in the applied neutron field, could be targeted with boron-containig tumor seeking agents for BNCT. Targeting boron-containing macromolecules might in most cases bind to tumor cells in well vascularized regions of the tumor. The targeting process

could be complemented with a treatment modality, e.g. external radiotherapy, that inactivate the remaining cells in less vascularized regions of the tumor. It is expected that clinical trials will be done to develop treatment combinations that fulfil the requirements of attacking both the primary tumor and the spread of metastases.

6. CONCLUSIONS

BNCT is an example of medical issue showing fluctuations of interest. Although this therapeutical technique was set up 50 years ago, it does not play a definite role in cancer treatment and a general consensus on it has not been reached.
Which are the causes of such a phenomenon?
I believe that a multidisciplinary approach is mandatory to face successfully the technical and methodological problems of modern medicine.
This is a typical example in which cooperation of different competences including physics, chemistry, radiobiology, radiotherapy, pharmacology, diagnostic techniques and clinical management is required.
Hatanakaís trials in which patients were irradiated on their open skull and Zontaís original experiments performed in Pavia on the isolated liver lead us to reflect on the reasons that prevented any attempt of loco-regional administration of boron compounds.
Conversely the wide toxicity of boron compounds employed till now, was a limiting step to the adoption of this technique, which appears little objectionable from a theoretical point of view but it is true that pharmaceutical companies did not appear interested in this field.
But does an individual route to medical research exist today?
We do not believe.
We do not believe that today, because of the availability of neutron beams suitable for therapy, we are closer to the solution.
We do not believe that, because diagnostic techniques allow a 3D-imaging of the target and an almost perfect simulation of the treatment is feasible, the problem can be solved.
Despite radiotherapy provides us with high-tech tools, we cannot assume that the goal is achieved.
We mean that till we speak alone and sometimes discuss *inter nos*, like in this occasion, but without a daily involvement of the overmentioned abilities and other experts such as pathologists, molecular biologists and obviously the clinicians, we and others will continue to face recurrently the problem. The solution will appear very close but something will lack to achieve it.
When a proper boron compound will be available, BNCT, hadrontherapy and the modern radiotherapy could provide the best results if, in addition to selectively hitting the tumor volume, we will be able to schedule our hits keeping into account the specific cell kinetics of the target neoplasm. Moreover better results will be obtained when we will overcome *ex iuvantibus* drug dosing criteria and will discover the biological rules to optimize the combination of surgery, chemotherapy and radiotherapy.
A combinatory approach seems to be time-consuming and too expensive to find out the best therapeutical approach. Further wide studies are required after which an application is expected.
We greatly admire those researchers actively operating in the field and whose work results in a big collection of data and indications that enable improvements in decision making; nevertheless, we think that only by reversing the approach we could overcome the distressing problem of cancer therapy.

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CUTANEOUS MELANOMA: NATURAL HISTORY AND BORON NEUTRON CAPTURE THERAPY

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Melanomas are tumors arising from melanocytes, specialized cells of the neural ridge that during embryonic development migrate to their final destination: the skin, uvea, meningeal membranes or entodermic mucosae. Melanomas may therefore arise in these tissues, though most of them (90%) are cutaneous.

The incidence of cutaneous melanoma appears closely related to ethnic factors, ranging from 0.2 per 105 per year, among Asian and Oriental peoples,to 40 per 105 per annum in Queensland. Although no reliable data for Italy are available in the Veneto region its incidence is 8-9 per 105 per annum. The incidence of this tumor has increased all over the worldwide during the last 30 years, at a much greater rate than all other tumors types, except for lung neoplasms in women (1-5).

In USA the risk of developing a melanoma has increased while it was 1/600 in 1950, it is expected to rise to 1/90 in 2000. This great increase may partly be explayned by its early diagnosis and current screening campaigns. UVBs are probably a triggering factor in subjects with a fair complexion, who are the most prone to genomic injury from sun rays (short and intense exposures) (6).

Cutaneous melanoma almost exclusively affects wealthy white people. While there is no significant difference in its incidence in males and females its appears to be gender-linked, the tumor developing mainly on the trunk in men and the legs in women (7).

Primary cutaneous melanoma may have a biphasic or monophasic growth pattern. The former characterised by a first stage known as ìradial growth phaseî, with melanocytes proliferation in the epidermis, followed by subsequent neoplastic infiltration of the dermis and subcutaneous tissue, named ìvertical growth phaseî. Only the vertical growth phase has the maximal metastatic potential that is closely related to the tumor thickness (Breslow) and Clarkís level (8-10).

According to their growth pattern, these neoplasms can be classified as follows:

Superficial spreading melanoma (SSM), which usually arises from a pre-existing benign naevus and makes up roughly and represents 70% of cases; it shows a slow initial phase (radial growth), followed by accelerated diffusion (vertical growth phase).

Nodular melanoma (NM), which affects 15-30% of patients and usually arises on intact skin; it has an aggressive behavior ìab initioî, due to the almost exclusively vertical component of its growth.

Lentigo maligna melanoma (LMM), which has a low-frequency (4-10%), and usually appears on the face of elderly people; it has a prolonged (years) radial phase, followed by ensuing nodules that are the expression of the vertical growth phase.

Acral-lentiginous melanoma (ALM), which accounts for 2-8% of cases and arises on the palms of the hands, and soles of the feets and ungual bed; it has a biological aggressiveness (8-10).

Malignant melanoma may spread distally through the lymphatics (regional and distant nodes) and blood vessels (lung, liver, bone, CNS metastases).

The most widely used staging system for melanoma is the TNM (11), that takes into account all the most important prognostic factors (tumor thickness and nodes status) in terms of disease-free survival and enables its management to becustom-tailored.
The treatment of choice is surgical excision, with a disease-free margin of 1 cm for T1 and T2 tumors, 2 cm for T3 and 3 cm for T4. ìSentinelî node biopsy should be undertaken for all the lesions thicker than 1 mm in order to evaluate the risk of metastases. If at histology lymphnodes metastasis is confirmed, a formal therapeutic dissection should be performed.
Melanoma cells may not only spread to regional nodes but may also cluster and grow along the lymphatic vessels, becoming palpable sub-cutaneous nodules in around 5% of cases. These nodules are considered ìsatellitesî if confined within 2 cm from primary, and ìin-transit metastasesî if they extend further. The management of these lesions is a challenging issue, as all the lymphatic basin tributary to the tumor has to be treated. At present, the best results are achieved by lipofascectomy for head and neck, trunk and limb-root tumors, while limb lesions below the upper third are amenable to hyperthermic antiblastic perfusion (12).
The vast majority of patients have local recurrence after these well-standardised treatments (40%) and usually do not respond to systemic chemotherapy. They can therefore be considered for experimental therapies.
Boron neutron capture therapy (BNCT) utilizes the reaction occurring when the 10B nuclei are irradiated with low-energy neutrons which are captured by the nuclei, forming the 11B, that spontaneously disintegrates into a 4He (alpha) and a 7Li particle. One or two particles traversing the nucleus are enough to determine clonogenic death.
Different molecular carriers (monoclonal antibodies, phenylalanine etc.) can deliver boron into the cells. The tumor bearing tissue is then irradiated with thermal neutrons and the ensuing cell damage propagates to within 10 microns.
ìIn vitroî studies with this technique showed that of melanoma, soft tissue sarcoma and glioma cells are extremely vulnerable (13-14).
In USA from 1951 through 1961 the first clinical trial was carried on patients with high grade gliomas. The results reported were very poor, due to accumulation and retention of boron in healthy brain at higher concentration than neoplastic tissue. The development of new vectors allowed to achieve a better penetration into the cells and to ìre-thinkî the clinical use of BNCT. Moreover, BNCT proved to be more active than X-rays at the same level of absorbed doses in inducing DNA damage, when measured with the so-called ìcomet-assayî (15).
It has been shown in rats with melanoma metastatic to the brain, that tumors have a higher 10B1-p-boronphenylalanine (10B1-BPA) uptake than healthy tissue, and that the survival of animals treated with the drug was significantly improved when compared to that of animals given external beam radiotherapy (16).
In order to ameliorate, in terms of selectivity, the efficacy of BNCT, some authors advocte the use of monoclonal antibodies targeting tumor-specific antigens, such as BsAbB8, that cross-reacts with human melanoma and glioma cells (17-18).
Few studies on the clinical application of BNCT for humans have been reported in literature. Currently the Brookhaven National Laboratory (BNL) and Massachusetts Institute of Technology (MIT) are conducting two clinical trials on BNCT for high grade gliomas and melanoma, respectively (19). In Japan, Hiratsuka (20) treated one case of melanoma with BNCT with 10B1-BPA and obtained a complete response with low toxicity, while Fukuda (21) tretated 6 melanoma patients (1 with metastases and 5 who were candidates for ampuatation), and reported complete responses in four. Moreover, since 1987, Mishima has treated 12 melanoma patients with lymphnode metastases, and observed tumor regression and no nodal re-growth after 1 year of follow-up (22).

The European Collaboration Group on BNCT has started to pursue this approach, but only at a level of pre-clinical research (23).

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PHOTOTHERAPY OF PIGMENTED MELANOMA WITH VISIBLE LIGHT AND PORPHYRIN RELATED PHOTOSENSITIZERS: POSSIBLE SYNERGISM WITH BNCT

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1. INTRODUCTION

Photodynamic therapy (PDT) is a promising experimental treatment for neoplastic disease based on the ability of tumour tissues to retain some photosensitizer with a certain degree of selectivity; hence, photoactivation of the photosensitizer by visible or near infrared radiation leads to tumour necrosis by the production of cytotoxic species (Jori et al., 1990). So far the clinical studies used heterogenous porphyrin preparations, hematoporphyrin derivative and Photofrin II, as photosensitizer (Kessel, 1990).
A main factor controlling the response of tumour to PDT is represented by the penetration depth of the incident light into the irradiated tissue in order to ensure an efficient photoactivation of the sensitizer localized in the malignant lesion. The process is modulated by the absorption coefficient of the given tumour, as well as by the light-scattering properties of the tissue constituents (Patterson et al., 1991). Both factors generally decrease with increasing wavelength; in the far-red region (700-850 nm) the interaction of light with lightly pigmented mammalian tissues is dominated by scattering (Marchesini et al., 1989) as only very weak residual absorption bands of hemoproteins are residually present. On the other hand, in heavily pigmented tissues absorption of far-red light by melanin is still significant, thereby strongly reducing the depth of light penetration (Svaasand et al., 1990). This explains the insensitivity of such pigmented tumours to PDT with porphyrin-type photosensitizers that exhibit a modest absorbance in this spectral region.
In order to explore the possibility of extending the use of PDT to the treatment of pigmented melanoma we have employed naphthalocyanines as phototherapeutic agents. Naphthalocyanines display intense absorption in the 780-800 nm interval (ε = 3-5 x 10^5 M^{-1} cm^{-1}) and are efficient photosensitizers of biological systems (Firey and Rodgers 1987).

2. PHARMACOKINETIC STUDIES

As an experimental model we selected B16 pigmented melanoma subcutaneously transplanted to C57/BL6 mice by injection of 20 µl of a cell suspension containing 10^6 cells. When the tumour volume was in the range of 0.02-0.04 cm^3 the B16 tumour-bearing mice were intravenously injected with 1 mg/kg of bis(di-isobutyloctadecylsiloxy)-2,3-naphthalocyanatosilicon (isoBO-SiNc) incorporated into DL-dipalmitoylphosphatidylcholine (DPPC) liposomes prepared by sonication as previously described (Cuomo et al. 1990). At 24 h after dosing,the mice were sacrificed and the isoBO-SiNc in the serum and other tissues was measured by a spectrophotofluorimetric procedure (Cuomo et al., 1990).
The pharmacokinetic behaviour of the photosensitizers is shown in Table 1

Table 1 - Recoveries of isoBO-SiNc from selected tissues (μg of drug per g) and serum (μg/ml) of C57/BL6 mice bearing a B16 pigmented melanoma at various times after injection of 1 mg/kg photosensitizer

Time (h)	Serum	Liver	Tumour	Skin
1	13.64±0.99	6.03±1.78	0.57±0.30	0.23±0.03
3	6.03±0.50	8.13±1.07	0.43±0.17	0.32±0.05
6	5.28±0.29	10.53±0.68	0.44±0.14	0.32±0.07
24	0.69±0.08	10.97±0.85	0.57±0.16	0.52±0.06
48	0.21±0.11	9.78±1.25	0.58±0.13	0.50±0.08
168	nd*	8.74±1.34	0.08±0.01	0.46±0.03

*Not detectable.

The clearance from serum was relatively fast with no residual dye detected at 1 week after injection. On the other hand, large amounts of isoBO-SiNc were accumulated and slowly eliminated by liver with similar recoveries at 3 h, 24 h and 1 week. This behaviour has been reported for other hydrophobic dyes (Jori 1992). The maximal accumulation of the photosensitizer in the tumour was observed at 24 or 48 h after injection. However the targeting of melanoma by isoBO-SiNc was characterized by very poor selectivity since the isoBO-SiNc concentration in the skin (which represents the peritumoral tissue) was similar to that found in the tumour.

3. PHOTOTHERAPY STUDIES

For experimental PDT studies we have used mice bearing B16 pigmented melanoma injected with 1 mg/kg liposome-bound isoBO-SiNc. Phototreatment was performed at 24 h after administration of the drug. The tumour area was directly exposed to 776 nm light from a diode laser which was operated at a fluence rate of 300 mW/cm^2 for a total light fluence of 520 J/cm^2. In a parallel set of experiments the same protocol was immediately followed by a further 776 nm laser irradiation at 550 mW/cm^2 and 200 J/cm^2 (which raises the intratumoral temperature to 44.4• C) (Biolo et al., 1996). For each group the effectiveness of the treatment was evaluated by comparing the rate of tumour growth of the irradiated mice with that observed for control mice transplanted simultaneously with the phototreated mice but not exposed to light and not injected with isoBO-SiNc. The tumour size was measured daily by means of a caliper. Individual tumour volumes (V) were calculated by assuming a hemiellipsoidal structure for the tumour nodule and measuring the two perpendicular axes (a and b) and the height (c). Application of the relationship $V = 2/3\pi$ (a/2 x b/2 x c) provided the tumour volume. The time to reach a defined tumour volume was calculated for the individual tumours.

The pigmented melanoma exhibited an appreciable response to PDT which was characterized by a transient tissue swelling and edema, followed by a local necrosis of both the treated tumour and the overlying skin tissue.

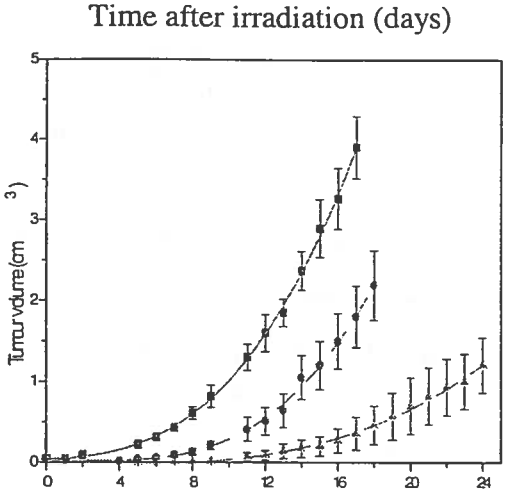

Figure 1 - Rate of tumour growth for mice injected with isoBO-SiNc (1 mg/kg) and after 24 h irradiated with: 300mW/cm^2 and 520 J/cm^2 of 776 nm light (●); 300mW/cm^2 and 520 J/cm^2 of 776 nm light followed by 550 mW/cm^2 and 200 J/cm^2 of 776 nm light (▲). Comparison with the rate of tumour growth in untreated and unirradiated mice (■). Each point represents the average of seven mice ± SE.

Fig.1 shows the rate of tumour growth as a function of the post irradiation time. Clearly the application of PDT induced only a modest delay of tumour growth. On the other hand, a marked increase of the tumour growth delay to about 13 days was caused when the first 776 nm treatment was followed by the second irradiation. This shows that the photoinduced thermal processes have an effect which is additional to that initially induced by a neat photodynamic treatment. Our findings agree with observations by other authors (Anderson et al. 1981) indicating that the application of hyperthermia to a PDT-treated tumour immediately after irradiation potentiates the overall effects. In our experimental model, to obtain a confined temperature increase, we took advantage of the well-known property of melanin to convert a large fraction of the absorbed light into heat (Polla et al. 1982). This may cause a localized rise in the temperature of the melanin microenviroment.

Recently, in order to further exploit the potential of phototherapeutic modalities for the treatment of highly pigmented tumours, we investigated the association of conventional PDT with high peak power (HPP) laser irradiation, and in particular with a Q-switched Nd:YAG laser delivering pulses of 1,064 nm light. This wavelength is absorbed by melanin and can induce the selective photothermolysis of melanosomes (Anderson et al., 1989), provided the Nd:YAG laser is operated in a submicrosecond pulsed regime so that the photoexcitation of the endogenous chromophore occurs in a time scale that is shorter than the thermal relaxation time in the irradiated tissue (Anderson and Parrish 1983). In this way, the resulting temperature increase is spatially confined in the microenvironment of the melanin and the resulting fragmentation of melanosomes takes place without any detectable damage of the surrounding tissue compartments (Anderson et al., 1989).

The phototherapeutic studies were performed when the tumour diameter was in the range of 0.4-0.6 cm. B16 melanoma bearing mice were irradiated with 1,064 nm light from the

Nd:YAG laser at 500 or 650 mJ per pulse (HPP). In one group of mice at 24 h after isoBO-SiNc injection (1mg/kg) the tumour area was exposed to 774 nm light from an Argon-pumped dye laser which was operated at a fluence rate of 300 mW/cm^2 for a total light fluence of 520 J/cm^2 . This PDT treatment was performed, in other two groups, also before or after the tumours had been exposed to 1,064 nm light from the Nd:YAG (650 mJ). In a parallel set of experiments a sequential treatment involving HPP and PDT (with the same irradiation conditions mentioned above) was followed by an immediate further 774 nm-laser irradiation at 550 mW/cm^2 and 200 J/cm^2. The effect of these different irradiation protocols are summarized in Table 2.

Table 2 - Effect of different irradiation protocols on tumour regrowth

Photosensitizer 1mg/kg	Irradiation protocol	Mice tumour free-time (days)	Regrowth delay (days)*
-	HPP	0	3.7
isoBO-SiNc	PDT	2	6.3
isoBO-SiNc	PDT + HPP	2	7
isoBO-SiNc	HPP + PDT	9	16.4
isoBO-SiNc	HPP + PDT + HT	22	34.6

HPP : High Peak Power irradiation from Nd: YAG laser, 1064 nm, 650 mJ per pulse
PDT : Photodynamic Therapy from dye laser , 774 nm, 300 mW/cm^2 , 520 J/cm^2
HT : Hyperthermia from dye laser, 774 nm, 550 mW/cm^2, 200 J/cm^2
** Difference between the growth time for treated and control mice. The growth time is the time interval for the tumour to grow to a volume of 1 cm^3 from the size at the time of irradiation (0.03-0.04 cm^3). The growth time of control mice was 11 days.*

Clearly, the application of PDT immediately before HPP induced only a modest delay of tumour growth, which was essentially identical with the effect of PDT alone (see Table 2). On the other hand, a marked increase of the tumour growth delay to about 16 days was caused when the PDT treatment was performed immediately after HPP. The regrowing tumour was still sensitive to combined HPP/PDT irradiation followed by a further irradiation under conditions which were known to raise the tissue temperature to 44.4• C (Biolo et al., 1996). In actual fact, the overall tumour regrowth was delayed to 34.6 days (Table 2).
Our data clearly show that the combined application of different therapeutic modalities is a necessary requirement for obtaining an efficient response of pigmented melanoma especially for eradicating the tumour. In this connection, BNCT appears to offer promising features, since boron-porphyrins can be readily synthesized and are likely to keep a high affinity for this

tumour type: so far, porphyrins or analogues of different chemical structure have generally been accumulated by tumours in significant amounts. The research in this field should obviously be focused on the definition of the modalities which enhance the synergism between PDT (and/or PTT) and BNCT.

4. ACKNOWLEDGMENT

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AN INNOVATIVE PROCEDURE TO TREAT UNRESECTABLE LIVER TUMOURS BY THE BORON NEUTRON CAPTURE THERAPY

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1. SUMMARY

The unsolved problem of an effective treatment of diffused liver metastases is the target of our research. In a number of cases indeed, no traditional therapy is presently available to face such a pathology. Our project is based on the following sequential phases: liver explantation and boron enrichment of the organ, irradiation into a thermal neutron field , liver grafting into the same donor (liver autograft).The irradiation of the isolated liver gives the significant advantage to preserve the remaining organs from radiation damage and will distinguish our procedure from any previous experience in the field. The therapy could be possible and effective also in the case of tumour metastases disseminated to both lobes or in inaccessible parts of the liver. As usual, the therapy is based on the ionizing effect produced inside the cell by the passage of $^{4}He, ^{7}Li$ ions released in the final state of the nuclear reaction

$$^{10}B + n \rightarrow ^{4}He + ^{7}Li + 2.792Mev \qquad (1)$$

We describe the development of the various phases of our interdisciplinary research and report the main respective results. In particular we give for the first time statistically significant results on the selective boron absorption by tumour tissue. In addition we show an original demonstration of BNCT effects on metastatic liver which was irradiated and reimplanted.

2. FEASIBILITY OF THE TREATMENT

The feasibility of the treatment is conditioned by the following conditions:
1) Boron concentration must be larger in the tumour than in the healthy tissues. The problem is to get the possibility of lethal doses absorbed by the tumour while the dose in the remaining tissues is lower than the tolerance level[1,2,3].
2) Uniform distribution of neutron flux inside the entire organ.

The Boron concentration in the tumour must be higher than a threshold value depending on the quality of irradiation facility and the elementary composition of the organ to be treated. We calculated (Table I) the doses absorbed in tumour and healthy tissues in correspondence of various Boron concentrations. The calculus took into consideration all neutron induced

reactions. Assuming the thermal neutron fluence $\Psi = 10^{13} cm^{-2}$, we used the following equations:

$$D_H = 9.8 + 0.9 C_H$$
$$D_T = 9.8 + 0.9 T C_H \qquad (2)$$

D_H, D_T, C_H and C_T being the doses and ^{10}B concentrations (ppm) in healthy and tumour tissues respectively, T is defined as the Boron concentration ratio in tumour over healthy tissues: $T = \frac{C_T}{C_H}$.

The quantity 9.8 Gy is the total dose induced by processes different from reaction (1), including the low gamma background of 1.6 Gy obtained by improving the reactor thermal column as described in section 4. We assume 20 Gy as the tolerance dose[2] for healthy tissues and 50 Gy as the valid dose to obtain tumour cells irreversibly damaged, then we can calculate the minimum useful value of T by inserting the values $D_H = 20, D_T = 50 Gy$ in equations (2). We find:

$$T = 3.9 \quad C_H = 11.3 \ ppm \quad C_T = 44.6 \ ppm$$

In conclusion, we need for a safe irradiation $T \geq 3.9$. In correspondence to such a value, tumour tissues must hold a ^{10}B minimum concentration around 45 ppm, necessary to minimize the undue doses mainly induced by proton and gamma radiation from $^{14}N(n,p)^{14}C$ and $^{1}H(n,\gamma)^{2}H$ reactions respectively.

Table 1

Doses for neutron fluence $\Psi = 10^{13} cm^{-2}$

Process	Dose (Gy)
$^{1}H(n,\gamma)^{2}H$	5.6
$^{14}N(n,p)^{14}C$	2.2
$^{10}B(n,\alpha)^{7}Li$	0.9*
$^{35}Cl(n,\gamma)^{36}Cl$	0.4
γ – background	1.6
Dose in healthy tissues	**Dose in tumor**
19 Gy	56 Gy**

* Dose with 1 ppm ^{10}B concentration

** ^{10}B 10 ppm, T = 5

3. SURGICAL TECHNIQUE

The procedure of liver autograft in the experimental animal consists of three sequential phases:

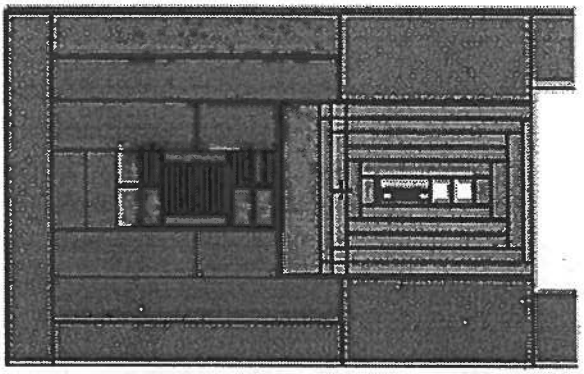
- Mobilization of the liver by dissecting all connections with the surrounding structures preserving the vascular (portal v., hepatic a., infra hepatic cava v., supra hepatic cava v.) and biliar (choledocus) connections.

- removal of the liver which is perfused with refrigerated electrolyte solution and then submitted to "ex vivo" treatment. In the meantime the animal is maintained on extracorporeal circulation(cava-cava and porta-cava bypass).
- Liver replacement into the same "donor" animal and anasthomosis of the four previously mentioned vessels and choledocus.

After the standardization of these phases we could assess the maximum and mean survival during the anhepatic phase. The particular technique of extra corporeal circulation we employed, allowed to carry out a prolonged procedure (over 8 hours in the swine) without the use of systemic heparin.
The above time is largely sufficient to allow the use of the boron neutron capture therapy as the intermediate step of the entire procedure.
The technique was validated on the swine (about 80 procedures), then successfully employed in clinic (5 patients). In the rat series of experiments, the liver autograft was carried out with microsurgical technique , using two different syngeneic animals as donor and recipient.

4. THE IRRADIATION FACILITY

We decided to modify the structure of the thermal column of the reactor Triga Mark II of the University of Pavia to reach two objectives:
a) To get a thermal neutron field with a very low gamma background.
b) To obtain a low noise irradiation position that allows a high counting sensibility of alpha particles. We measure boron concentration in hepatic tissues by analyzing spectra of particles produced in reaction (1).
After having completely emptied the thermal column vessel of the reactor, we realized a new optimal structure by a convenient distribution of moderating and screening materials according to the simulations performed by MCNP4A code.
Fig. 1 shows the new thermal column configuration with the indication of the explanted liver at the irradiation position. We measured the distributions of the neutron flux and Cadmium ratio inside the irradiation facility and, by using TLD detectors, we measured also the doses produced by the pure gamma ray background. Such measures evidenced a relevant improvement of gamma background being its value reduced from 350 to 8.1 Gyh^{-1}; the neutron flux and thermalisation degree are still quite satisfactory[3] .



5. BORON DISTRIBUTION IN HEPATIC TISSUES

A relevant world-wide activity is presently devoted to optimize the tumour selective boron uptake. New methods and new boron compounds as Liposomes, Saccharide porphyrins, immuno proteins are tested[(3)].
After some preliminary test with Boronphenylalanine (BPA) and Dodeca-borane (BSH), our group is facing the problem by using a model of colonic liver metastasis in the rat and BPA as boron carrier. BPA we are using is 95% ^{10}B enriched being supplied by Boron Biologicals Inc. Raleigh, NC, USA.

Our procedure is the following:
- Tumour induction in the rat by inoculating 10^6 cells of a line established from a rat colon carcinoma chemically induced in a BD-IX strain rat[4].
- Ten days later, the boron compound solution (300 mg per Kg) is intravenously injected to enrich the hepatic tissues.
- After a time t the animal is sacrificed and its liver is extracted, perfused with glucose 5% solution and then frozen.
- Samples both of tumours and healthy tissues are cut according to a common established geometry and submitted to histologic analysis.
- Both kinds of samples, tumour and healthy, are then positioned inside the reactor thermal column and singly irradiated in such a way that the alpha particles released from the entire sample undergoing the reaction (1) can be counted.

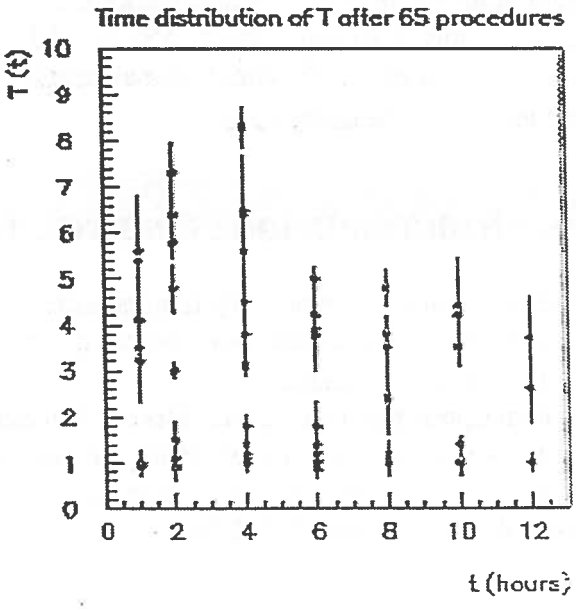
The counting is accomplished by a spectrometric apparatus front the sample, including as particle detector a thin silicon diode whose pulses are elaborated by a conventional electronic line. The detector thickness and the electronic elaboration are such to discriminate all possible particles except alphas from the mentioned reaction.
Then we evaluate, for each sample, the average boron concentration by a double comparison of α spectra with those achieved by analytical and Monte-Carlo methods respectively[5].
We realized a satisfactory sensitivity for Boron concentration measurement by our method: $\sigma_B = 0.5 ppm$.

6. RESULTS AND DISCUSSION

The survival time during the anhepatic phase resulted largely compatible with the time of neutron irradiation:

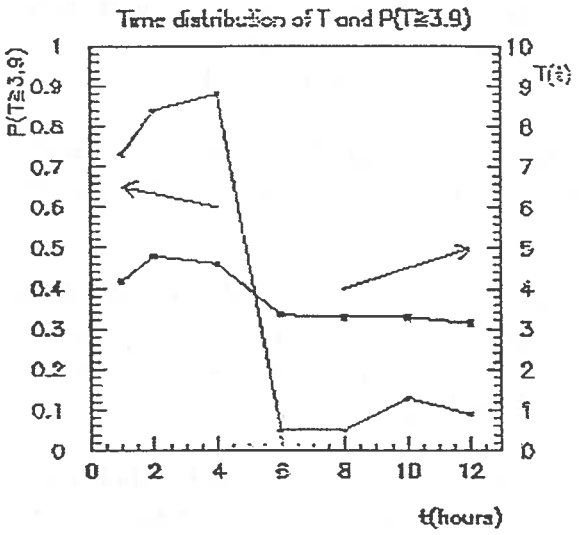
$S_{Max} = 32h$ (maximum survival during the anhepatic phase)
$S_{Mean} = 24h$ (mean survival during the anhepatic phase)
$S_{Wh} > 8h$ (survival during procedures without the use of systemic heparin)
$t_{Irr} = 715 sec$ (time of irradiation to give the tumour tissues 50 Gy)

Fig. 2 shows T distribution versus t as obtained by 68 procedures. Each point refers to the single rat and gives the T value averaged over several liver samples; t=0 represents the moment of BPA injection. The result is statistically significant and represents, up to now, the most exhaustive analysis of boron uptake in the field of BNCT.. All $T \cong 1$ values reported in figure derive from rats whose liver resulted tumour free after an unsuccessful inoculation. Tumour sample counting has been corrected in such a way to report its value to the case of tissue entirely consisting of tumour cells.



As regarding ^{10}B concentration threshold in tumour tissues, we evaluated that a percentage around 70% of rats present C_T higher than 40 ppm in the time interval $2 \leq t \leq 6$ *h*.

In *Fig. 3* we can observe the time distribution of $P_{T \geq 3.9}$. This function represents the probability to achieve, at the time t, a T value larger than 3.9. At the same figure we report also the distribution of T(t) mean value.



We describe at least some preliminary microscopic observations to evaluate the irradiation damages in the boron enriched tissues:

- Two hours after the irradiation, the samples present a very active presence of Kupffer cells whose density seems larger in the tumour than in the healthy tissues (Fig 4)
- In the internal volume of the metastatic nodules, the radiation damage appears relevant (apoptosis state). This feature can support the assumption that the Boron absorption is not limited to the cells forming the external surface of the tumor (Fig. 5).
- Fig. 6 shows the ultrastructure of the rat liver parenchyma after 3 days from treatment and reimplantation. Several metastatic carcinoma cells present pattern (asterisks)both at sinusoid (a) and nodule (b) level. None of such a condition has been observed in healthy tissues up to now.

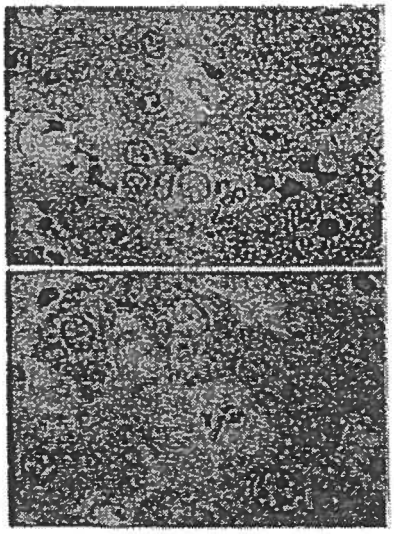


Fig. 4

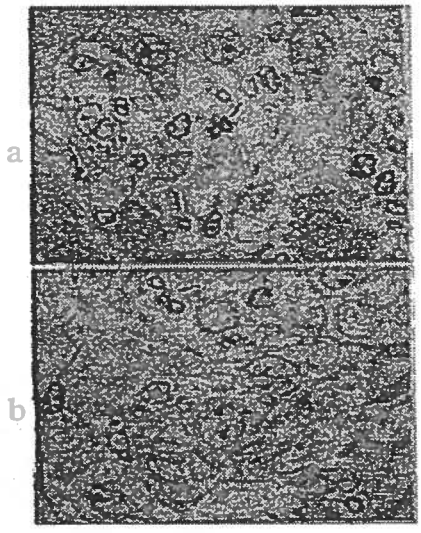


Fig. 5

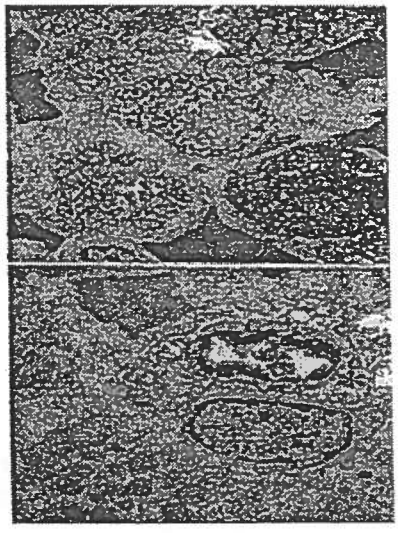


Fig. 6

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SYNTHESIS OF BORONATED COMPOUNDS FOR BNCT

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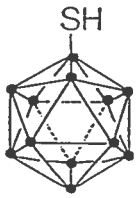
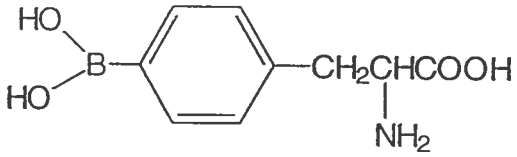
Boron neutron capture therapy (BNCT) was first proposed in 1936 as an application to the treatment of human tumors[1] but early attempts to use this protocol were unsuccessful[2-4]. The failure was attributed to vascular damage due to the high boron concentration caused by nonselective uptake of boronated drugs.



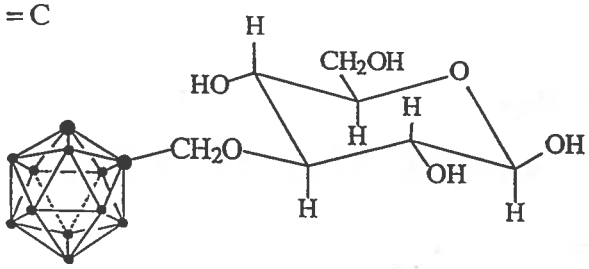
(1) BSH



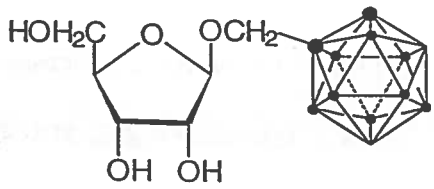
(2)

Recently, encouraging results, have been obtained by Japanese authors[5] using borocaptate (BSH **1**) and 4-(dihydroxyboryl)phenylalanine (BPA **2**) in the treatment of brain tumors and malignant melanoma in human patients. Consequently, the increased attention for BNCT has stimulated the synthesis of new boronated drugs. Is important to note that to minimise damage to normal tissues, the quantity of boron in the tumor (30 μg ^{10}B/gr of tumor) must exceed that of surrounding normal tissue by a factor exceeding 3.[6-8] Therefore in view of preparation of more selective boron drugs. Some point are required for development of new products: bioactivity, lipophilicity, high tumor uptake, uptake inside the cell membrane, high tumor/blood ratio, low toxicity. Thus various carrier molecule have been used to deliver boron to tumor cell

• = B
● = C

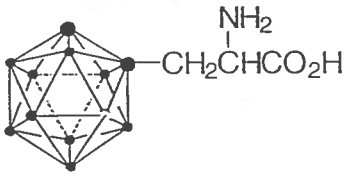


(3) 3-o-(o-carboran-1-ylmethyl)D-glucose

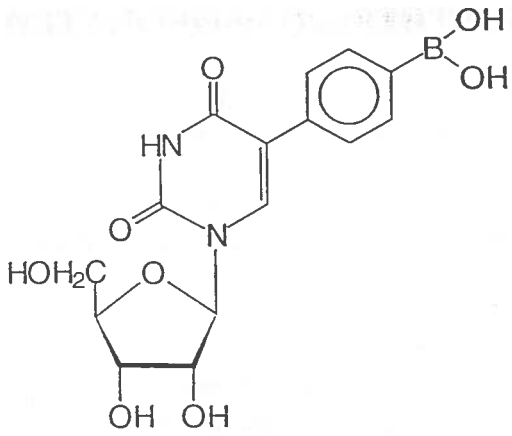


(4) ribofuranosyl carborane

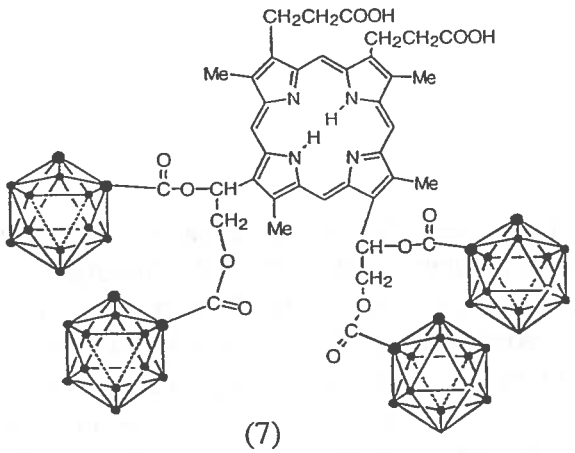
thereby including carbohydrates [9-11] (**3**) (**4**), amino acids [12-17] (**5**),



(5) *o*-carboranylalanine



nucleosides [18-20] (**6**), antisense agents [21], porphyrins [22] (7) antibodies,[23-24] and liposomes[25]. Now, the only drug (BPA) is under investigation for clinical trials in the U.S.[26].



(7)

Some carboranyl analogues of phenylalanine [14, 16] are corrently being evaluated as potential BNCT agents. More innovative syntheses of some potential drugs for BNCT will be discussed.

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MONOCLONAL ANTIBODIES AS ^{10}B-DELIVERING AGENTS FOR BORON NEUTRON CAPTURE THERAPY OF TUMORS

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Boron neutron capture therapy (BNCT) represents a binary approach to cancer treatment, in which a physiologically targeted compound containing ^{10}B is delivered to the tumor. When ^{10}B is irradiated with low energy thermal and epithermal neutrons, the resulting nuclear reaction produces alpha particles with high linear energy transfer and radiobiological effectiveness which are able to destroy a wide variety of biological active molecules like DNA, RNA and proteins. One of the most important goal of cancer therapy is to achieve a high degree of selectivity with destruction of all malignant cells without damaging the normal surrounding tissues. In theory, this ideal selectivity might be achieved by a two-component system, each constituent of which is nonlethal and mostly accumulated in the malignant cells, but whose combination could be lethal to neoplastic cells and spare normal ones. In the BNCT approach, the two independent components of the system are represented by the neutron flux in the tumor area and in the surrounding tissue, and by the boron concentration in neoplastic and normal cells. The neutron flux in the irradiated volume depends primarely on the type of neutron beam, as neutrons with thermal energies cannot penetrate into the depth of a target to reach deeper lying tumors, while epithermal neutrons would allow deeper lying tissue to be reached more efficently, and at same time would reduce the dose deposition in the surface tissues. The boron accumulation in the tumor, as well as its residual concentration in healthy tissue is influenced by the choice of compound, its route of administration and the time interval between administration and treatment (1). On this regard, many attempts have been made to develop tumor-selective boron compounds for BNCT, but their general lack of a highly preferential accumulation in tumor tissues has risen several criticisms. Nonetheless, at present two boron compounds are in clinical use: the first is a polyhedral borane for treatment of gliomas and the second is a tyrosine analogue and a melanin precursor to be used against melanomas (1).

A category of molecules that appears very interesting as boron-delivering agents is represented by monoclonal antibodies (mAb) directed against tumor-associated antigens (TAA). In fact, the high specificity of the antigen-antibody reaction, in conjunction with the large panel of recently identified TAA (2-4), makes these molecules highly attractive as tools to selectively accumulate ^{10}B at the site of tumor mass. Moreover, a good experience has already been acquired in using mAb to target drugs, radioisotopes and toxins to cancer cells. As it is currently held that for cell surface antigens 10^9 ^{10}B atoms per cell are required to obtain a lethal reaction in the cell nucleus, and assuming an antigen site density of 10^6 per tumor cell, this implies that approximately 1000 ^{10}B atoms should therefore be linked to each antibody molecule to achieve a therapeutic effect. During the past years many chemical approaches have been developed to link boron-containing compounds to antibody molecules. Initial research focused on the synthesis of a low molecular weight hetero-bifunctional boron compound containing 10 boron atoms per molecule (5). While this compound could be efficently linked to mAb, the objective of 1000 boron atoms per antibody molecule could be achieved only by boronating 100 separate reaction sites on the antibody, but this procedure brought about a so marked alteration in the mAb structure that they lost their immunoreactivity (5). To bypass this problem, a boronated polymer having more than 1000 B

atoms per polymeric unit was synthesized and covalently linked to mAb by means of two heterofunctional reagents (6). The resulting immunoconjugates contained several thousands B atoms per antibody molecule and retained their *in vitro* immunoreactivity. However, intravenous or intraperitoneal inoculation of these conjugates showed that they had lost their *in vivo* tumor-localizing properties and accumulated primarely in the liver. Although several other chemical procedures have been tried (7-12), at present direct boronation of mAb does not appear a feasible approach, as conjugation results in either a poor boron content or reduced immunoreactivity associated with increased liver uptake. More recently, new and more promising strategies have been developed, involving the production of bispecific mAb which bind simultaneously to two different antigens, a TAA and a boronated macromolecule. This approach might provide a means to concentrate large amounts of boron to tumor cell-wall antigens without the use of covalent bonds and chemical conjugation reactions (13-16). Finally, by taking advantage of the high-affinity binding of currently available mAb to TAA such as the carcinoembryonic antigen (CEA), immunoliposomes have been prepared. These structures consist of liposomes, which can carry large amount of a ^{10}B-compound, conjugated to a mAb that is able to specifically direct the complex to the tumor. Immunoliposomes have been shown to deliver the ^{10}B-compound to target neoplastic cells and to exert an inhibitory effect on tumor cell growth following thermal neutron irradiation *in vitro* (17, 18). Moreover, although intravenous injection of immunoliposomes is not feasible because of liver accumulation and poor tumor targeting, it has been recently reported that their direct intratumoral injection inhibited tumor cell growth with thermal neutron irradiation *in vivo* (19), thus opening new hopes for the use of mAb in a BNCT approach to cancer treatment.

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^{10}B COMPOUNDS NMR IMAGING FOR BNCT

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1. INTRODUCTION

The effectiveness of ^{10}B neutron capture therapy depends on the capability to monitor the localisation and the concentration of boron compounds before irradiation. This is to choose the best irradiation delay time, that is the delay during which there is the maximum ^{10}B concentration in the tumour cells and the minimum one in the safe tissue.
As ^{10}B is not a natural emitter it is not possible to detect it directly with the usual nuclear medicine methods. However with techniques such as PET one can detect the distribution of boron compounds which are marked with beta emitters such as ^{18}F in boronophenylalanine **(1)** but in this case the ^{10}B compound drug -kinetics can be altered with respect to the drug-kinetics of the not-marked compound. Furthermore a PET investigation doesn't give any information about the chemical selectivity of the examined compounds. Other methods, such as "prompt gamma ray spectroscopy" **(2)** require the irradiation of the sample to analyse the results of the capture processes. So, it is obvious that such procedure makes it impossible to monitor the distribution of the boron compounds in order to determine the best delay time of neutron irradiation. On the other hand, methods like colorimetry **(3)** or inductively coupled plasma-atomic emission spectroscopy (ICP-AES) **(4)** require the extraction of blood samples, or of tissues for the analysis. In any case, the spatial resolution that can be obtained with these methods is relatively low and can provide only a partial idea of the selectivity of the ^{10}B enriched compounds with respect to the tumour area.
Nuclear Magnetic Resonance, with the recent development of tomography and spectroscopy "in vivo" techniques, has found an application field of great interest in medical diagnostics. In fact such techniques are neither invasive nor destructive. They do not imply the use of ionising radiations and, at the same time, they allow the selection of a certain nuclear species and a good resolution of soft tissue. Moreover, they produce an accurate determination of the spatial volumes and a continual monitoring for metabolic and functional studies. However other features make NMR a powerful and unique tool of investigation. In fact the signal of magnetic resonance depends on a series of physical parameters such as nuclear spin density, nuclear relaxation times, chemical shifts, indirect dipolar coupling constants, and diffusion coefficients that permit to obtain a great deal of chemical and physical informations. Therefore NMR tomography and spectroscopy are the ideal methods of quantification and localisation of the BNCT compounds in organs. However, as the signal to noise ratio (S/N) in a NMR investigation depends on several factors (on the magnetic field intensity, on the number of resonant spins, on their gyromagnetic ratio and on relaxation times), it is impossible to detect ^{10}B through standard NMR techniques. In fact this nucleus is characterised by a gyromagnetic ratio about 9.3 times smaller than that of the hydrogen (the most sensitive in NMR) and (as ^{10}B is a quadrupolar nucleus) by relaxation times that broaden the NMR line and strongly reduce the ^{10}B sensibility even at high magnetic fields.

2. METHOD AND RESULTS

We have overcome all the difficulties concerning ^{10}B detection by developing same original methods in Double Resonance **(5-8)** which make it possible to observe indirectly the signal of the insensitive nuclei by exploiting their indirect dipolar J-coupling with hydrogen nuclei. Because such J interaction is of short range, it is possible to select the protons linked to the less sensitive nuclei by suppressing the signals of the other non-interesting nuclei (biological water, fat) in a sample. The double resonance method is based on the modulation of the proton SEDOR (Spin Echo Double Resonance) **(9)** signal caused by the scalar J coupling between protons and less sensitive nuclei. Such modulation is generated through the simultaneous irradiation of the two nuclear coupled species. By means of a preliminary study of the indirect dipolar coupling interaction between hydrogen nuclei and the ^{10}B ones and a FIT of the experimental SEDOR data, we have obtained the value of the J-coupling constant, that characterises the coupling between ^{10}B and hydrogen nuclei in BSH **(10)**. Such results had never been reached before, not even by exploiting spectrometers in high resolution and very intense magnetic fields, because ^{10}B quadrupolar moment broadening the NMR line, hides the fine structure of indirect dipolar coupling. As to tomography methods, we have made the first map representing the ^{10}B in BSH distribution in two different concentrations in aqueous solution **(11-13)**. These images represent the spatial distribution of the boron nuclei in a sample and are characterised by the S/N ratio of proton images, because the indirect imaging and spectroscopy methods developed by us imply the detection of the protons coupled to the rare nuclei only. Besides, the method allows the suppression of all the uncoupled nuclei by means of the coupling constant of the selected bound.

These first results obtained "in vitro" at a low field (0.7 T) have aroused considerable interest in NMR international research; as a matter of fact, after our first publication about ^{10}B other foreign research groups have taken an interest in the problem of ^{10}B compounds detection for BNCT. In particular an Israeli research group has recently applied our method revealing the in vivo (on a mouse) spectra of the ^{10}B in BSSH concentrated in a tumour **(14)**. These researchers have not made then an "in vivo" image, because, according to them, the relaxation times of the protons bound to the ^{10}B atoms **(15)** are prohibitive to reach such purpose. We do not agree with the Israeli group, and basing ourselves on our first studies on H-^{10}B relaxation times **(16)** we have now the target to obtain some "in vivo" results. Then we have implemented the sequence on a NMR spectrometer that uses a large bore magnet to make possible same experiments on little guinea-pigs. The magnetic field intensity is 7T, so we can have a further increase of sensibility compared to that we have obtained at low field. Moreover we have set up a probe working at the hydrogen and ^{10}B frequencies, required by a 7T magnetic field.

Finally NMR, by the use of Double Resonance techniques of indirect ^{10}B revelation, allows the monitoring of the boron compounds used in BNCT, with a sufficient spatial and temporal resolution to optimise therapeutic techniques, both for the choice of the most selective compound for a tumour, and for the choice of the dose and suitable irradiation time.

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DOSIMETRY FOR BNCT

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1. INTRODUCTION

The dosimetry for BNCT is particularly complex. It involves many kinds of investigations that we can divide into two main categories, which are partially overlapping:
a) characterisation and monitoring of neutron source and beam,
b) determination of absorbed dose in phantoms (for beam calibration and for therapy planning) and in vivo (for beam control during exposure).
Both points a) and b) require that many aspects be taken into consideration, because the BNCT radiation field is mixed (thermal neutrons, fast neutrons and γ-rays). Moreover, the dosimetry of thermal neutrons is difficult and not exhaustively studied. Therefore, a standard protocol for BNCT dosimetry has not yet been settled, and it is worthy of further research.
Within the European collaboration on BNCT, a project[1] has recently started aimed to define guidelines on acceptable dosimetric procedures; they underline the urgency of attaining such results, in order to give credibility and reliability to the clinical research and to get the success of the BNCT treatment. The objectives of this collaboration project are (i) beam characterisation free in air, (ii) beam calibration in phantom and (iii) on-line monitoring. Both reactor and accelerator-based neutron sources will be considered. The programme will proceed with the following activities:

- analytical review of the available knowledge about this topic,
- experimental investigations of the most promising methods,
- determination of the critical physical parameters, by verification of experimental results with theoretical calculations
- systematic comparison of dosimetry procedures.

Many research groups are working in Europe, in USA and in Japan, to set up proper dosimetric techniques or to establish suitable calculation methods and models.

2. SOURCE AND BEAM MONITORING

The characterisation of the beam is necessary to properly plan treatments. Moreover, during exposure doses and dose rates have to be carefully checked, because also small errors may result in ineffective treatment or in overcoming normal tissue tolerance. It is convenient that source and beam dosimetry are made separately, in order to have quicker control and easier readjustment possibility.
A variety of techniques are utilised for neutron beam dosimetry, but each of them requires further investigation.
For the neutron component of the field, the more simple technique is based on activation foil measurements which, however, allow only an integral evaluation over the energy spectrum of neutrons and, moreover, do not cover all the energy ranges of interest for BNCT. Activation foils can profitably provide thermal neutron fluxes. Other techniques are utilized, like pulse fission counters, but always giving fluence information, from which the absorbed dose is

calculated. For computer simulations, on the opposite, also the neutron spectrum has to be known.
Proton recoil counters are widely utilised, allowing the characterisation of neutron spectrum above about 30 keV. But gas-filled detectors are suitable for low intensity fluxes. Solid state detectors have shown more promising characteristics. Other techniques are in development. BF_3 counters are employed for relative neutron fluence measurements with also beam profile information. Bonner Spheres allow fluence and dose measurements with spectral discrimination, for neutron energies ranging from thermal up to about 20 MeV. Bubble dosimeters are very promising, foe their insensitivity to γ-rays.
The photon component of the beam is inspected by means of Geiger-Müller counters, of ionisation chambers, of photographic emulsions, or also of thermoluminescent dosimeters (TDL). Improvements of such dosimetric techniques are in study, aimed at increasing the dosimeter insensitivity to neutrons and the reliability of their response.

3. ABSORBED DOSE

The absorbed dose in BNCT is mainly due to thermal neutrons, but not negligible contributions come from the fast-neutron component of the beam and from the γ-rays of reactor core and of surrounding activated materials.
Neutrons do not directly produce ionization in passing through matter. Having no charge, they do not interact with atomic electrons, but with atomic nuclei. The interactions occur through nuclear forces, which have short range; then, the interaction probability is low, and neutrons traverse large thickness before thermalising.
The reactions occurring with fast neutrons are spallation and nuclear reactions, and the absorbed dose in tissue is due to the ionization produced by the particles emitted in these reactions. Below the threshold for nuclear reactions (a few MeV) the elastic interactions of neutrons with atomic nuclei are important; with light nuclei, the energy lost is large and the recoil nuclei produce ionization. This effect in particularly significant in tissue, where the lightest nucleus (that of hydrogen) is abundant.
Thermal neutrons propagate in matter like a gas, till they are captured by an atomic nucleus. The probability of this process is a characteristic of each isotope, described by its cross section. The capture is accompanied by the emission of energetic γ-rays or, like for ^{10}B, of ionizing charge particles.
If a deep tumour is treated, epithermal neutron beams are needed. In fact, to make up for the remarkable attenuation of thermal neutrons in tissue, intermadiate neutrons are added in the beam, having a proper energy in order to produce a maximum in the thermal neutron fluence at the depth of the tumour. In this case, also the energy released in tissue by the recoil protons generated by the scattering of intermediate neutrons with hydrogen has to be considered, because its contribution may be significant.
The dissimilar linear energy transfer (LET) of the different radiation components, and the dependence on LET of the relative biological effectiveness (RBE) of radiation, make necessary to determine the contributions to the absorbed dose of each field component. Possibly, this determination has to be made with also three-dimensional resolution, because the relative contributions of the various dose components change with depth in tissue. Also the absorbed dose coming from neutron capture changes with depth, in a way that strongly depends upon the neutron energy spectrum. In fact, besides the therapeutic reaction $^{10}B(n,\alpha)^7Li$ occurring in tissue where ^{10}B is selectively accumulated, the main contributions

come from the reactions $^{14}N(n,p)^{14}C$ and $^{1}H(n,\gamma)^{2}H$. The cross-sections for such nuclear reactions highly depend upon neutron energy. Moreover, also the γ-rays generated in these reactions give a contribution, with lower LET, to the absorbed energy.
From the above description, it is clear that a good determination of absorbed doses in BNCT is very difficult, both in experimental approach and in calculations.

4. WORK PROGRAM

Our research group is pointed to set up a dosimetric protocol with suitable features for the therapy program of Italian collaboration. For source and beam monitoring, a choice will be made based on the experience of the other European research groups, choosing the more effective techniques, compatibly with the available financial support.
For the dosimetry in phantom, a technique will be developed that is now in study in our laboratory. In this technique, tissue-equivalent phantoms are prepared, which act by themselves as dosimeters. The phantom material is a tissue-equivalent matrix in which a proper chemical solution is incorporated, acting as dosimeter. The so composed phantoms are analysed, after exposure, with a suitable technique allowing the 3-D measurement of the absorbed dose.
Up to now, in our experiments the tissue equivalent matrix consists of a gel obtained with the polysaccharide AgaroseSeaplaque. The incorporated chemical dosimeter is an aqueous solution whose main constituent is a ferrous sulphate solution. The 3-D measurements of absorbed dose are done by means of Nuclear Magnetic resonance (NMR) imaging. In fact, in ferrous sulphate solutions the ionising radiation produces a conversion of ferrous ions Fe^{2+} into ferric ions Fe^{3+}. The conversion yield has shown to be proportional, before saturation, to the absorbed dose. Ferrous and ferric ions, both paramagnetic, present different magnetic moments. In aqueous solutions, NMR analysis gives the possibility of spatial determination of paramagnetic species, because of their different influence on the spin relaxation times of hydrogen nuclei. In particular, in our case, a linear dependence of the relaxation rates of hydrogen nuclei on absorbed dose is evident[2].
Preliminary measurements were performed in order to inquire the possibility of determining the relative contribution of ^{10}B on the absorbed dose[3] or the feasibility of obtaining isodose curves in boronated phantoms[4][5]. The obtained results are promising, and they have given to us some addresses for future research. In Fig.1 the isodose curves are shown from the NMR imaging of a boronated gel phantom (8 cm diameter, 15 cm height) exposed in the thermal column of a reactor.

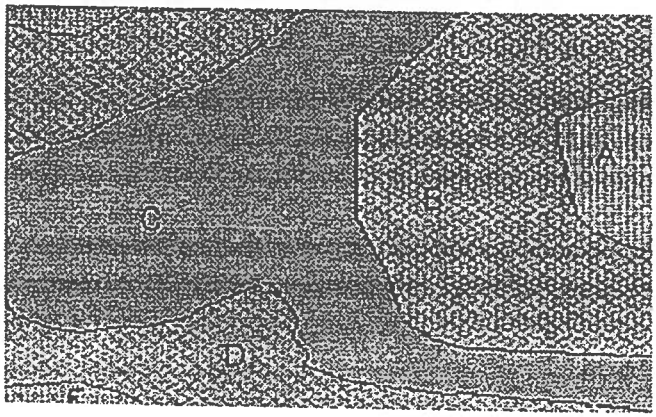

Fig. 1 - Contour plot of the NMR image of a boronated gel phantom after exposure to thermal neutrons.

We are now setting up an alternative technique of measurement, based on optical analysis in substitution of NMR imaging, with which the 3-D determination of absorbed dose is obtained with better sensitivity and better spatial resolution, moreover utilising simpler and less expensive instrumentation compared to NMR analysers. The technique will be described later. In Fig.2 an example of image taken with this promising technique is shown.

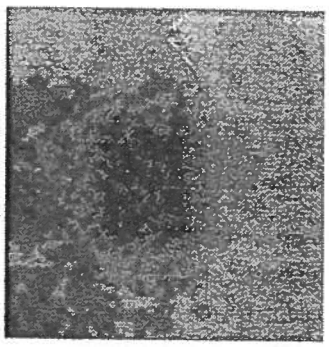

Fig. 2 - Image of absorbed dose in a gel phantom after exposure to a collimated γ-ray beam. The size of the image is 25 mm x 25 mm.

Different gel compositions will be studied, aimed at obtaining gel dosimeters with different sensitivity to the different components of the radiation field, in order to make differential measurements.
The goal of the research is to establish a method for the 3-D measurement of the absorbed dose in tissue-equivalent phantoms, with the possibility of discriminating between the contributions of the different radiation components with different LET. At least, we aim at obtaining 3-D information on the total γ-dose, on the dose from neutrons in tissue without ^{10}B and the dose due to ^{10}B.

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TUMOUR AND HEALTHY TISSUES DOSE CALCULATION USING MONTE CARLO CODE AND PET INFORMATIONS ON BORON DISTRIBUTION IN TISSUES

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1. INTRODUCTION

In BNCT the neutron beam simulation is essential in order to know doses to healthy tissues, blood and tumour, taking into account the different quantities of boron in various tissues. In fact it is impossible to perform direct dose measurements into patient brain.
As a consequence of the previous statement, two fundamental goals have to be reached:
- the possibility to use a fast and reliable calculation method, enough accurate;
- the ability to perform a real tissue boron distribution evaluation.
Therefore, the first problem that we met in simulating the neutron irradiation of brain tissues was the choice of the most suitable code. The main constraints are:
1) irreducibly three-dimensional geometry;
2) objects with very complex contours;
3) very irregular real boron distribution.
The best solution to meet these constraints is the use of a Monte Carlo code. The use of this kind of calculation method by our group, is supported by the know-how on the use of this type of code, acquired in the field of radiation engineering, mainly in shielding and nuclear fusion calculations [1].
The principal calculation codes now used in clinical trials by BNCT community are:
1) MCNP-4A, which represents now one of the most reliable Monte Carlo codes for transport equation solution [2].
2) Rtt_MC (or only rtt), developed at INEL, particularly for the BNCT [3].
MCNP-4A code is continuously developed in Los Alamos National Laboratories (LANL) and it deals with the transport of neutrons, photons and electrons. It has been used at MIT in the simulation of trials, carried out on MITR-II reactor. The second code is named Radiation Transport in Tissue (rtt) and is used in the analysis of trials, in progress at BNL [4]. Both these codes have been utilized at JRC of Petten, in order to define the BNCT treatment planning [5].
As regards the second goal, it is very difficult to acquire reliable boron and dose distribution through direct measurements on patients. Therefore, we need a simulation tool.
To meet this purpose, we have developed an original calculation system (CARONTE System [6]) able to connect the Monte Carlo code, MCNP-4A, with the information regarding the boron distribution, acquired through BNCT-oriented PET scans, and to plot the resulting doses.

2. THE RESEARCH ACTIVITY RESULT: THE CARONTE SYSTEM

At the University of Pisa, in close collaboration with Genova University, a research group started, in 1996, to work on BNCT. Its research activity performed an extensive literature

search [6] and critical review.. This activity brought to the issue of a report on BNCT feasibility study in our Country [7]. In the same time particular research works started on experimental neutron stereodosimetry and on the BNCT simulation by means of codes, and, in particular, by MCNP-4A code.

The model, that we have developed, concerns the brain structure, because we have focused (until now) our study on the glioblastoma multiforme case. It has geometry and composition as close as possible to the anatomic ones and it contains information about the real distribution of boron in tissues in order to meet the second goal outlined at the beginning of the first paragraph.

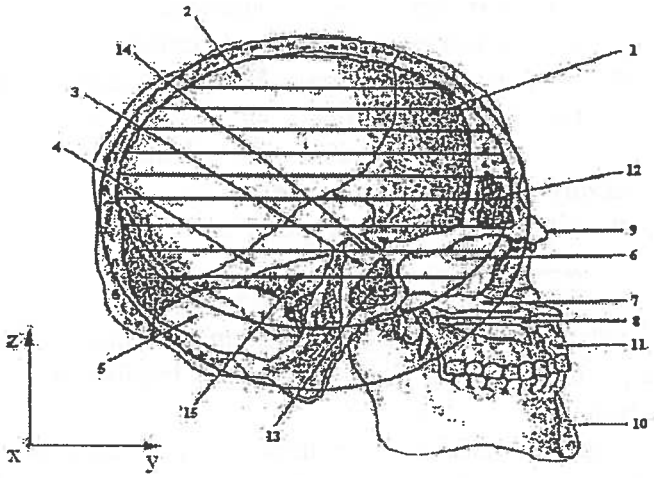
In particular a brain model, made of two non-concentric ellipsoids (Fig. 1) [8] and divided by some transaxial sections, has been assumed. Horizontal lines indicate various brain sections (slices). This model allows to consider the brain composition and the variable thickness of the skull.

- *internal ellipsoid*

$$\left(\frac{x}{6}\right)^2+\left(\frac{y}{9}\right)^2+\left(\frac{z}{6.5}\right)^2-1=0 \qquad (1)$$

- *external ellipsoid*

$$\left(\frac{x}{6.8}\right)^2+\left(\frac{y}{9.8}\right)^2+\left(\frac{z+1}{8.3}\right)^2-1=0 \qquad (2)$$



NOTE - The central sagittal plane of the head model superimposed on a human skull cross section. This figure shows how the head model simulates a human head. Red arrows indicate reference coordinate system 1. frontal; 2. parietal; 3. sphenoid; 4.temporal; 5.occipital; 6.ethmoid; 7.vomer; 8.palatine; 9.nasal; 10.mandible; 11.maxilla; 12.frontal sinus; 13.sphenoidal sinus; 14.sella turcica; 15. internal auditory meatus

***Fig. 1.** Two non-concentric ellipsoids phantom model, with transaxial slices, containing information on brain material and on boron distribution and concentrations [8]. On the left hand the equations, related to the two ellipsoids, are reported.*

Using this structure it is possible to construct a brain model through the insertion of slice information, referred to the boron distribution; as regards the other elements in brain tissue, we have used the "brain" material, found in literature (and generally accepted). These data are reported in Table 1 [9], together with the "skull" and "muscle" materials.

Table 1. ***Percentages of elements present in brain, skull and muscle material [9].***

Elements (% by weight)	«Brain»	»Bone»	«Muscle»
H	10.6	5.0	10.2
C	14.0	14.0	12.3
N	1.84	4.0	3.5
O	72.5	45.0	72.89
Ca	---	21.0	0.01
P	0.39	11.0	0.2
Cl	0.14	---	---
K	0.39	---	0.3
Na	0.14	---	0.08
Mg	---	---	0.02
S	---	---	0.5
Density (g/cm^3)	1.047	1.5	1.040

The last material can be used also for other kinds of tissue (like skin). In fact, we plane to upgrade this model in the case of other cancers, like melanomas.
In a previous article [10] we have described a first rough application of this particular model to a phantom, constituted by the double non-concentric ellipsoids structure (eqs. 1 and 2) and of three transaxial slices, in order to construct a brain model, that contains information on:
- brain material (through values presented in table 1);
- uniform boron distribution, by means of data inserted into slices, like that plotted in Fig. 2.
Figure 2 represents the central slice, passing through the center of the inner ellipsoid, *ad hoc* depicted through a commercial graphic program (PaintShop), in order to simulate the PET output.

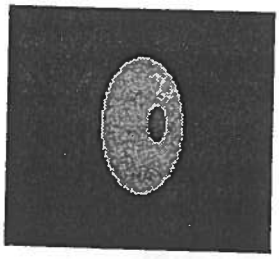


Fig. 2. Central slice inserted in the model represented in Fig. 1

The skull region is not represented in the figure, but it is present into the model used by CARONTE, in order to allow a correct neutron transport calculation.
The green ellipse represents a section of the inner ellipsoid, whereas the red ellipse indicates a section of the tumour region. Colours characterize the boron concentration present in the zone (red more). The developed System CARONTE is able to translate information present in Fig. 2 into values of boron concentration and to insert these data in brain model, represented in Fig. 1; furthermore, the complete model is converted into an input file for MCNP-4A code.

3. MAIN CHARACTERISTICS OF CARONTE

CARONTE System interacts with MCNP-4A code in the preprocessing and postprocessing phases.
In the first one it is able to construct a head model, like that described in the previous paragraph, containing the anatomic data and the brain boron distribution. Boron local levels are supplied, by our System, reading the slices concentration data through the normalization of the max colour value present in the figure.

Then MCNP-4A code makes neutron/photon transport calculations and provides an output file, containing all needed results. This file is heavy to read and, in general, very extended. Therefore CARONTE provides the capability of depicting tallies results (*doses* and *fluences* in MCNP cells) in a form similar to that normally used in clinical routine. In fact it depicts the isodose and isofluence surfaces, using the colour scale, reported in [6]. This section constitutes the postprocess phase.
As regards the preprocessing phase, in case of uniform distribution, data are provided by the biodistribution studies. The same operation seems to be possible using data obtained from the PET, PGRA or NRM scans. These non-invasive imaging techniques, adequately biased, seems to be able to describe the real boron distribution into the tumour and healthy brain regions.
CARONTE System allows the direct transfer of the particular PET output files to the MCNP-4A code in order to perform all the necessary calculations.
The Kyoto Team has recently demonstrated the feasibility of this type of analysis by PET scans, utilizing BPA, labeled with ^{18}F, as boron carrier [11]. Through the very kind collaboration of these Japanese scientists, it was possible to apply CARONTE System to PET slices obtained for a glioblastoma multiforme case at Kyoto Hospital. It is important to note that CARONTE System can operate either with a ".raw" image file or directly with the pixel values present in the original PET output file of PET scans. This model avoids any information loss, but needs to preprocess the original file, in order to translate the pixel values into boron concentration data.
In both cases, during the preprocessing phase, the user must define a series of parameters (answering to the code requests), which are fundamental for the construction of the model. These parameters are connected to the geometry setup of the PET slices into the brain model.
These data are provided directly to MCNP-4A code, that makes calculations in relation to tallies defined as input items. It is possible to use default tallies or to add new user tallies. The default calculations are related to:
1) neutron and photon fluence into the brain model;
2) doses inherent into BNCT, that is to say:
- dose from $^{10}B(n,\alpha)^{7}Li$ reaction (therapeutic dose);
- dose from $^{14}N(n,p)^{14}C$ reaction;
- dose from $^{1}H(n,n')^{1}H$ reaction (in the case of epithermal beam);
- dose from $^{1}H(n,\gamma)^{2}H$.

These ones are the main nuclear reactions which occur into brain and skull materials [12]. The last three are considered undue doses. CARONTE System has also other particular features, like the IMAGES program, which allows to compare the original image and the transferred image to MCNP-4A code, in order to make a rough visual control of the correct transfer.
Now CARONTE is still in a rough graphic state, because now it runs only in a DOS session. We are
improving the System allowing it to run also in WINDOWS 95 environment, adding several interactive options. Further explanations can be found in the provisional form of its Manual [6].

4. CARONTE APPLICATIONS AND RESULTS

CARONTE has been applied to a test case, whose central slice is reported in Fig. 2, and to the cited human glioblastoma multiforme case (Kyoto) [11]. We have carried out 14 runs

(BNCT01÷14) on the test problem and 12 runs (BNCT15÷26) on the Kyoto case, changing four parameters, i.e.:
- Source-to-Skin Distance (SSD);
- neutron beam origin (right or left);
- neutron beam spectrum at the irradiation port;
- infused BPA dose (1500÷3500 mg).

In Fig. 3 we represent the isodose surfaces for the BNCT04 run (test problem) and one of the runs (BNCT16) related to the Kyoto problem. We assumed:
- ipsolateral source (red arrows indicate the beam origin);
- SSD equal to 30 cm;
- epithermal neutron beam (Petten beam);
- 2500 mg of infused BPA.

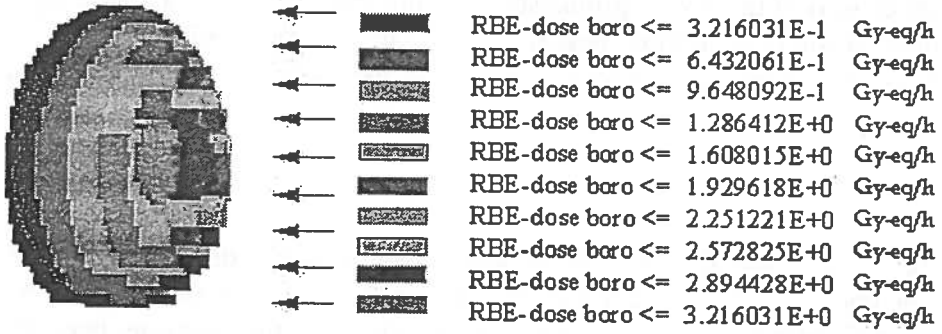


Fig. 3. Boron isodose surfaces related to the slice reported in figure 2 (BNCT04 run)

These results are similar to those obtained at INEL using rtt_MC code [3] in the analysis of a Labrador dog head [13] with an uniform boron distribution (Fig. 4). We have used, in both cases, the same colour scale. Looking at these cases, it is clear that an uniform boron distribution (with two different concentration only in tumour and in surrounding regions), provides a typical boron dose distribution, with radially decreasing isodose surfaces.

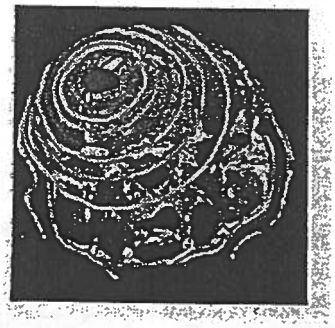


Fig. 4. Boron isodose curves related to a uniform boron distribution assigned to a Labrador dog head model (rtt_MC) [13]

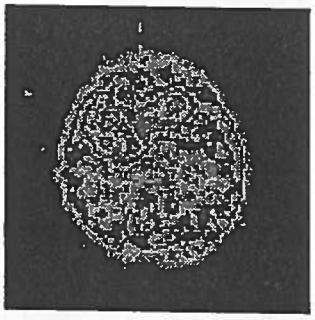
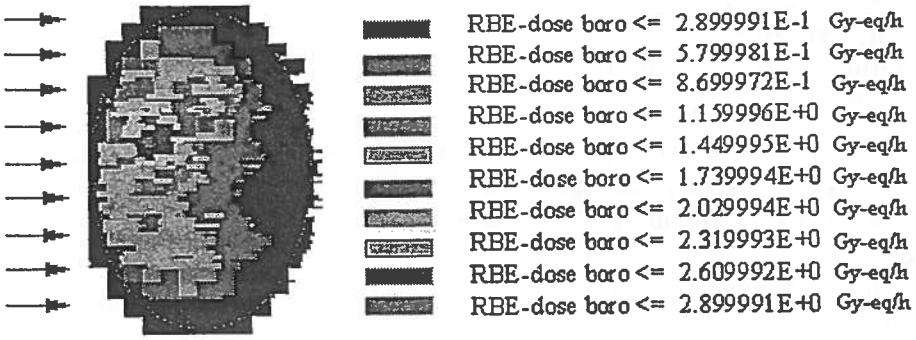


Fig. 5. Central PET slice for the Kyoto glioblastoma multiforme case [11]

Figure 5 shows the central PET slice of the Kyoto case [11]. We have adopted the same colour scale used in Fig. 2. Observing Fig. 5, it is clear that the REAL boron distribution, recorded by PET scanning, is quite different from the uniform case. As a consequence, the dose distribution will be very different from the radially decreasing isodose surfaces, which characterize the uniform boron distribution. The capability to take into account the real boron distribution is the most important and innovative feature that characterizes CARONTE

System and that remarks it among other codes [13]. The boron isodose surfaces of Fig. 6, obtained by a CARONTE run (BNCT16), are related to ipsolateral irradiation (red arrows



indicate the beam origin) of the Kyoto glioblastoma multiforme case, with an SSD equal to 30 cm, an epithermal neutron beam (Petten beam) and 2500 mg of infused BPA.

Fig. 6. Boron isodose surfaces related to the real boron distribution of Fig. 5 (BNCT16 run)

5. DISCUSSION

Observing Fig. 6, we may note that, in case of deep tumour distribution, it is very difficult to irradiate the whole cancer region. In fact, the right appendix of the tumour shown in Fig. 5, is weakly interested, although it presents a boron concentration near the max one, because of the shielding effect of the boron atoms present in the anterior region. A Parallel-Opposed (POP) irradiation seems to be adequate in this case, as demonstrated in Fig. 7 (BNCT18 run), where the beam is coming from the right. We can recognize that the right appendix of the tumour receives, now, a sufficient boron dose.

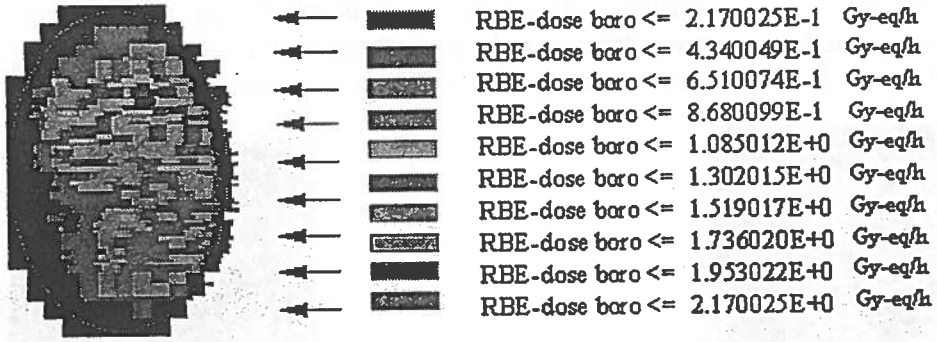


Fig. 7. Boron isodose surfaces in the Kyoto case with a controlateral beam (BNCT18 run)

We have already discussed the problems concerning the trials carried out on the test geometry (Fig. 2) in a previous paper [10].

Analysing now the results obtained from the CARONTE application to Kyoto PET scans (BNCT15 to BNCT26 runs), other aspects can be emphasized:

1) SSD parameter is not much relevant on the dose values.

2) Monoenergetic beams (35 eV and 2 KeV) are very efficient, because they produce Therapeutic Gain (TG = ratio between the minimum dose to the tumour and the maximum dose to the healthy tissue) around 2. These monoenergetic beams are, obviously, only a theoretical guess.

3) Fast neutron spectrum produces TG values around 1. The booster (supplementary dose) produced, at the end of the neutron flight, by the boron reaction, is interesting, in order to raise

the TG value. This kind of spectrum will be produced by accelerators, that seem to be more easily used in the existing hospital facilities than reactors.
4) Further investigations are necessary about the BPA dose levels influence on retention factors.

6. CONCLUSIONS

The simulation of the neutron behaviour into the brain is essential in order to know the doses distributions due to BNCT. To perform this goal, it is necessary to use a Monte Carlo code (e.g. MCNP-4A code), inserting into input data a boron distribution as close to the real one as it is possible.
In order to meet this target, we have developed the CARONTE System, which is able to connect the Monte Carlo code to the boron information present in the PET slices. It seems to be possible to use, as information tool, also the data obtained by PGRA or NRM, but it is necessary to perform further research work.
Twenty-six different CARONTE simulations, considering a circular section beam, with a diameter of 9.2 cm, and changing four fundamental parameters, have been carried out. The results have been discussed in the previous paragraph.
From these results it is clear that a software package, like CARONTE, is very important for establishing the treatment planning in a way coherent with the real patient situation after boron infusion. We stress that all these results can be obtained only by calculations, saving serious expenses and without irradiating any patient.

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MICRODOSIMETRY FOR BNCT

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1. INTRODUCTION

BNCT radiation dosimetry is complex, since it has to take into account the dose due both to the external radiation field and to the fission products of ^{11} B* (the excited isotope of boron created by the absorbtion of thermal neutron by the isotope ^{10}B) and of ^{15}N* (the excited isotope of nitrogen created by thermal neutron absorption by ^{14}N). Living cells experience radiation events of very different LET, ranging from few tenth of keV/µm (2.2 MeV gamma rays) to about 300 keV/µm (^{7}Li ions of 870 keV of energy). Moreover, since the neutron spectrum changes with the depth, the radiation LET spectrum is different at different depths in tissue. The LET spectrum can even change with the time, since the accelerator-based BNCT beam features can not be assumed constant in the time. Since radiation of different LET has different biological and therapeutic effectiveness, a simple dose monitoring is therefore not enough to optimize the therapeutic treatment. It is necessary to monitor the relative variation of all the different LET components.
In order to prepare a reliable therapeutic plan it is then necessary to calculate the biological dose, by multiplying the physical dose by a weighting factor which depends on the quality of the radiation, namely on the LET spectrum of the radiation. However, the biological effectiveness of a radiation is better correlated to the linear energy density measured in microscopic cavities, simulating meaningful biological targets, rather than to LET [1]. Microdosimetry is just dealing with that.
Microdosimetry is not the attempt to define the dosimetry in very small sites (dosimetry is already defined in an infinitive small volume), but the attempt to introduce the finite volume of interaction as fundamental concept for the biological action of radiations [2]. Differently with respect to dosimetry, which deals with expectation values, microdosimetry deals with the energy fluctuations in the volume of reference [3]. Therefore the LET concept, which is an expectation value, turns in y (lineal energy), which has the same physical dimension of the LET, but it is a stochastic variable. Spectroscopic monitoring about the interaction of radiation with tissue is given by microdosimetry with the help of tissue-equivalent gas proportional counters (TEPC). Microdosimetry is based on a full conceptual and mathematical framework stemming from the probability theory. Appropriate physical quantities have been defined and their relationships described. Despite of providing full satisfactory radiation action models, microdosimetry succeeded, if not to conciliate, at least to link practical radiation quality investigations in medicine with more basic quantitative assessments of radiation action.
Several attempts have been done to apply microdosimetric concepts in BNCT. The references of such studies are quoted in the paper of Solares and Zamenhof [4].

2. THE BORATED TEPC MONITOR

The prince instrument to measure the microdosimetric stochastic variables is the tissue-equivalent proportional counter (TEPC). In figure 1 the sketch of cylindric TEPCs constructed at LNL. The cylinder, the cathode of the gas counter, is made of conductive tissue-equivalent plastic Shonka A-150. The anode wire is surrounded by a field grid which assures the electronic avalanche, generated in a pulse, is uniformly distributed along the wire and close to it. The counter cavity simulates the volume V in the biological sample. Ionisation events, which occur in the cavity because of the radiation, generate electrons which drift towards the anode wire where they accelerate, because of the intense electrical field near the anode, and produce secondary ionisation. Because of this amplification mechanism, even one original electron can be detected. If the ionisation yield is significantly more than one, it is proportional to the imparted energy ε in the sphere cavity. The factor of proportionality is W (the mean energy expended to create an ion pair). The gas filling the cavity is made tissue-equivalent mixing together different gases. Two gas mixtures are generally used: methane-based mixture (64.4% methane, 32.4% carbon dioxide, 3,3% nitrogen) and propane-based mixture (55.0% propane, 39.6 carbon dioxide, 5.4 nitrogen). Because of the low density of the gas with respect the biological tissue, the radiation interaction with the gas cavity is equivalent to the interaction with a volume V much smaller in size. At 20 °C of temperature, 1 cm in propane-based mixture is equivalent to 1μm in tissue when the gas pressure is 5.56 kPa (41.7 Torr). Similarly the methane-based mixture at 9.52 kPa (71.4 Torr) of pressure. The counter can be continuously flushed with fresh gas-mixture at the given pressure to assure gas gain constancy in time. The cathode wall is cut longitudinally into two pieces. Therefore, like a motor-hood, it can be opened for ordinary or special maintainance actions. The alpha source support rotates around the stem to allow for the insertion of the alpha beam into the counter during the calibration measurements. Height and diameter of the counter cavity are equal (13 mm), therefore the cavity mean chord is the same as that one of a sphere of equal diameter.

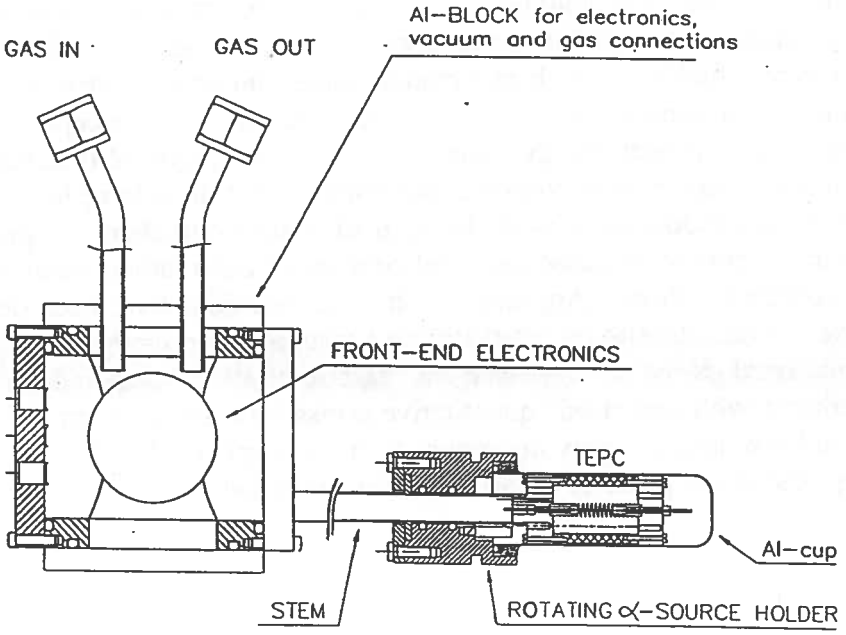

Figure 1. The 13 mm cavity TEPC counter constructed at Legnaro Laboratories.

In figure 2 a microdosimetric spectrum collected with the counter of figure 1 is shown. The radiation field was a collimated neutron beam of the reaction d(4.5 MeV)+Be. In figure 2 the spectrum collected with our detector (new TEPC) is compared with that one of a spherical commercial counter (the LET 1/2" counter of the Far West Technologies). The events due to gamma rays have been subtracted in order to emphatise the differences of the two spectra. Only minor differences can be observed. They are due to the differences in the chord distribution of a spherical cavity in comparison with a right cylinder cavity.
For experimental studies with the thermal column of Legnaro Laboratories, a modified design of such counter could be used. The SHONKA A-150 wall can be loaded with ^{10}B in order to simulate the microdose spectrum experienced by the cell which has been previously charged with ^{10}B. Walls with different contents of ^{10}B can be prepared and easily substituted in the counter. Even the filling gas mixture can be loaded with ^{10}B at the wished concentration. The flowing gas system can be easy modified to change the quantity of ^{10}B inside the counter. ^{10}B only in the wall, or only in the gas cavity, or in both can simulate the y-spectrum experienced by the biological structure, simulated by the TEPC cavity, when the living cell has been charged of ^{10}B only in the membrane and cytoplasm, or only in the nucleus or in both.
The possibility of make use of concepts and experimental methodics of the classical approach of microdosimetry shows some unexpected fruitful prospectives, if applied to BNCT. Using properly designed boronated TEPC's, the analysis of the microdosimetric spectra, together with additional beam monitoring measures and experimental informations about the boron distribution in cells or tissues can focus appropriate therapeutic strategies. In 1992 Wuu et al. [5] at BNL, first analised microdosimetric spectra obtained from a 2.5cm diameter TE Rossi-type proportional counter with 50 ppm of ^{10}B incorporated into the 3 mm thick Shonka plastic wall, filled with a propane-based TE gas mixture with the addition of boron trifluoride in a amount equivalent to 50 ppm of ^{10}B. It was exposed to the epithermal beam of the BMRR at reduced power levels between 0.1 and 5 kW to avoid pulse pile-up. In such a way the counter simulates the simple situation of a boron-doped cell surrounded by medium with uniform boron uptake. In a successive improvement of the methodic, Kota and Maughan [6] showed also that it was possible, changing only the simulated volume in a TEPC, to obtain information about the probability of lethal effect on a cell deriving from different loadings of boron, in the nucleus and cytoplasm or only in the membrane.

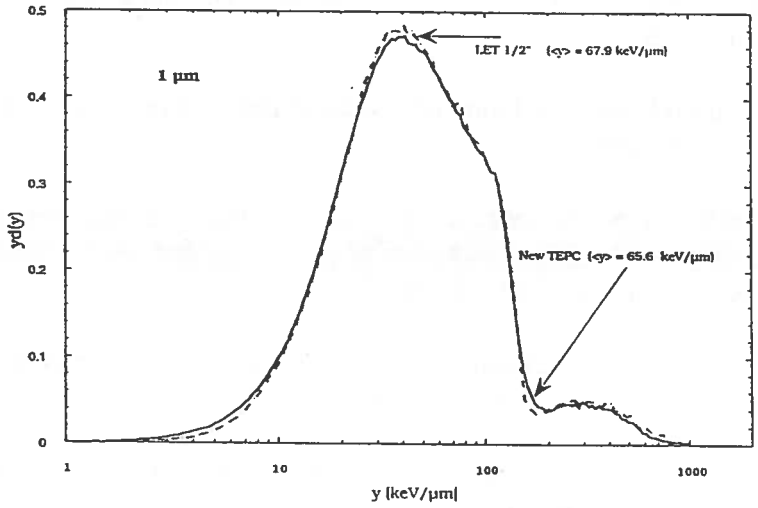

Figure 2. Comparison of a spectrum collected with our TEPC and with a commercial spherical TEPC.

Preliminary experimental studies with reduced beam intensities can be performed with figure 1-like detectors. However, the future therapeutic facility will use intense beams to treat a patient. A typical therapeutic beam could be of $10^9 cm^{-2} s^{-1}$, which would give rise to about 10^7 events per second in the counter of figure 1. Which such intense beams the monitoring can be performed only with minicounters of 1 mm^3 of cavity. Which such counters reasonable counting rates could be experienced.
In figure 3 the LNL mini-TEPC of 1 mm^3 of cavity is shown. The counter is drawn in two positions rotated of 90°. In position A it is possible to see the big T-shaped cavity in which the ^{244}Cm α^- source can be inserted and the gas-in duct. Just beneath the source cavity, one can see the small cylindrical cavity which is the 1mm sensitive volume of he counter. In position B the electrode connections and the gas-out duct.
The counter of figure 3 has been designed for monitoring a proton terapeutic beam. However, it can be costructed with 1 mm thin borated cathode to monitor a BNCT therapeutic beam and to investigate the beam qualiy variation in the first centimeters of tissue.

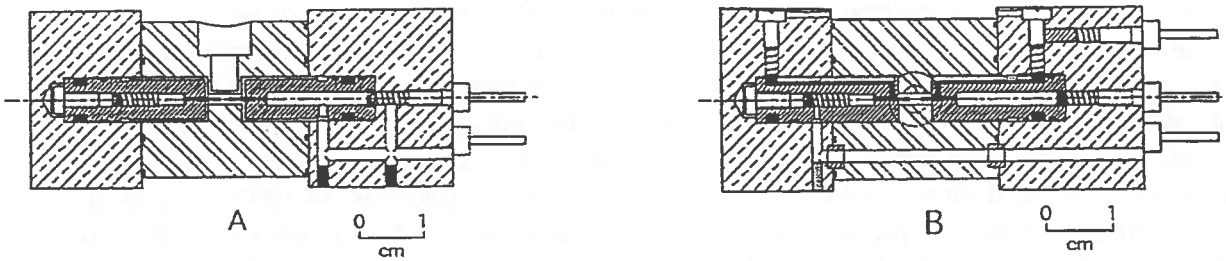

Figure 3. The mini-TEPC in construction at LNL

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RADIOBIOLOGICAL FEATURES OF BNCT

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Radiotherapic treatments, as well as chemotherapy, unavoidably entail the exposition of normal tissues and organs included in the irradiated volumes. Tissues with high proliferative activity show higher radiosensitivity and will develop acute damage, those with low or absent proliferation, more radioresistant, can develop later damages. The maximum radiation dose one can administrate to the neoplasia is limited to the injury induced on the healthy tissues and, if they are very radiosensitives, the restriction is higher.

Several strategies, based both on technical improvement and on biological hypothesis, are employed to deliver the maximum damage on the neoplastic tissues, with maximum sparing of the healthy ones. One of these is the selective targeting of radiations in the tumour cells (1). Though targeting strategies have a limited clinical use at present, the increasing number of targeting agents creates a growing interest about the future use of these techniques. *The radiobiology of targeted radiotherapy is therefore likely to be of increasing importance.*

The first example of targeted radiotherapy is the therapy with ^{131}I, had been employed for the radicalization of thyroid carcinoma surgery or for the treatment of metastases. The limitations of these therapies is due to the request of selective metabolic ways to uptake the radionuclide in the cancer cells. In recent years monoclonal antibodies have attracted attention as targeting molecules of cytotoxic agents, including radionuclides; however, the need for specific epitopes on the cell tumour surface and the poor penetration of the molecules reduce their clinical usefulness

At present many studies are performed on the search of molecules able to vehiculate specific cytotoxic groups in the tumour cells, with small dimensions and higher diffusion ability (1).

Besides direct targeting of radionuclides in the tumour cells, other possibilities is to introduce an agent which become cytotoxic when activated by another. These "binary strategies" allow the separation of cell targeting from the cell damage, making easier to assess the time of high agent concentration in tumour cells or the high tumour/healthy cell ratio, and permit the planning of appropriate treatment. The known examples of binary strategies are the boron neutron capture therapy (BNCT) and the photodynamic therapy (PDT).

Theory of BNCT was formuled in 1936, few years after the discovery of neutrons (2). After the confirms of the feasibility of this technique and of its cell lethality, the first clinical trials was undertaken between 1951 and 1962 in brain tumours. The failure of these treatments and the severe side effects induced by radiations are commonly referred to the poor selectivity of boron carrier compounds for tumour tissue, to the low penetration of thermal neutrons and to the impossibility to control cerebral edema due to the lack of dexamethazone, employed later (3).

At all these reasons must be added the lack of strict radiobiological studies about the effects of these irradiation techniques on healthy and tumour tissues, in terms of early acute response and later tolerance and/or complications.

The radiobiology of radiotherapy with conventional beams (ß rays and photons) provided, in the years, an accurate characterization of the "quality" of radiations, in terms of Linear Energy Transfer (LET), Relative Biological Effectiveness (RBE), etc.; the interaction with the biological matter have been also studied in depth, with the research on the Dose Rate (DR)

and oxygen (OER) effects, the development of models able to describe the response of cells to radiations, the effects of different modalities of dose fractionation etc.
Moreover, all the events following the release of energy from radiation to matter have been studied: the damage which, during the asymptomatic (preclinical) phase, is at physical chemical, biochemical and molecular level, and becomes clinically evident when it involves cells, tissues, organs and finally the whole organism. During these events, if the injury has been subletal, the repair mechanisms can operate and the repopulation of tissues can be obtained.
All these phases have been studied, by means of research analyzing the modifications of several parameters at morphological (qualitative and quantitative), ultrastructural, biochemical, cell kinetics, molecular.level (4-7)
Almost all these studies must be still performed for the BNCT, and the available knowledge about the BNCT effects is inadequate to understand all the phenomena developed in the irradiated tissues.
Studies in the bio-oncology field regards a matter, the neoplastic growth, in which a lot of variables plays an important role. Neoplastic growth essentially depends on: number of stem cells, growth fraction (GF), time of cell cycle (Tc) and cell loss (CL). Many other factors can modify the growth, both as promoting agents (oncogenes, growth factors, p53 mutations, microenvironmental factors and others) and limiting ones (oncosuppressor genes, growth factor inhibitors, apoptosis, microenvironmental factors, necrosis and others).
When this complex system is exposed to a cytotoxic agent, its expected response (cell death or clonogenic death) is in turn influenced by several factors variable case-by-case, promoting (high intrinsic radiosensitivity, high proliferative activity, vascularization, microenvironmental factors etc.) or limiting (mutations, repair/repopulation processes, concentration of -SH groups, necrosis etc.).
The resulting dishomogeneity of response causes the fact, well known in oncology, that tumours in the *same* clinical stage, with the *same* istopathological classification, treated with the *same* therapy show *different* response and *different* clinical outcome.
With the aim to discriminate in advance patients with different response probability, that need for different therapeutic schedules, many potential predictiive tests have been developed, to analyze the radiosensitivity of the irradiated tissue, the modification of cell kinetics, the induced cell death or "programmed" cell death (apoptosis), the microenvironmental, cytogenetic, molecular and immunological factors. Some of these tests can be used during radiotherapy (8-10).
It is clear that a system with a so high biological complexity and several mechanisms of response must be studied in depth and each model utilized must be accurately characterized in its biological aspects to understand the significance of the modifications induced by radiations.
It is worth noting that the radiobiology of BNCT is much more complex than conventional radiations radiobiology, depending on:

- filters and shields of sources, variables case-by-case, that produces different dose from different components who compose total dose;
- use of thermal or epithermal neutrons;
- boron concentration in the tumour and cancer/healthy tissue and cancer/blood boron concentration ratios;
- structure and composition of tumour;
- its anatomical architecture versus healthy tissue;
- intracellular localization of boron.

As consequence of these variables, in the last 20 years RBE values between 1.5 and 6.4 have been obtained in different studies. According to Lam's hypotesis (11) the RBE_{BNCT} is the sum of RBEs of various components:

$RBE_{BNCT} = f_{n,\alpha}\, RBE_{n,\alpha} + f_{n,p}\, RBE_{n,p} + f_{n,\gamma}\, RBE_{n,\gamma} + f_{i\gamma}\, RBE_{i\gamma} + f_{fn}\, RBE_{fn}$

where $f_{n,\alpha}$ = dose from $^{10}B(n,\alpha)^{7}Li$, $f_{n,p}$ = dose from $^{14}N(n,p)^{14}C$, $f_{n,\gamma}$ = dose from $^{1}H(n,\gamma)^{2}H$, $f_{i\gamma}$ = dose from incident γ and f_{fn} = dose from fast n.

Only the doses from nitrogen and hydrogen capture are relatively constant from system to system. The other components may vary widely in function of boron concentration and of filtration system of the beams. Moreover, a sinergistic effects, rather than simply additional, cannot be excluded.

As regards to the targeting of boron in the cancer cells, it must be considered that boron carrier molecules are uptaken in the cells by diffusion from blood and there is a decreasing concentration with the increase of the distance from capillaries. In tumour tissues the growth rate is higher than the angiogenesis one, with the presence, in extended cancers, of anoxyc and necrotic areas in which the molecules cannot arrive. The consequent dishomogeneity in the distribution of the boron compounds causes a lower probability of death for the cells located in areas with low concentration of boron. In this case may be hypotesized the administration of combined therapy (i.e. BNCT+PDT for melanoma, BNCT+radio/chemotherapy for others), with the aim to kill also the cells who can escape from boron effects (1).

The effects of different boron carriers leads to introduce a further variable named "compound factor" (CF). For the BSH in brain tumours a value of 0.37±0.06 has been calculated: the low value of this factor is due to the exclusion of the molecule from the normal brain by the blood-brain barrier (BBB) (12).

The use of fractionation in BNCT is largely discussed. Very few experimental data are available about this topics and the discussion turn around the presence/absence of shoulder in the dose-effect curve of α particles. A preliminary experiment, with two doses of BSH and two exposition of brain to thermal neutrons, demonstrate an increase of boron concentration in healthy brain, probably caused from a BBB alteration following the first irradiation, that may induce a higher injury in the healthy tissue after the second one (13).

At present also the animal models in BNCT studies appear largely insufficient to define the tissue response to BNCT: i.e. a study on Harding-Passey melanoma (heavily pigmented) in BALB/c mice demonstrates that the 83% of total dose is due to the boron capture and that the dose requested for the 50% of tumour control is the half of that requested for X rays (14.7 Gy vs. 29 Gy). But, *also in these optimal conditions*, in which the boron carrier molecules are easily excluded from unpigmented skin, the total body dose results 1.3 Gy, about 10% of tumour dose. Moreover, the neutron fluence needed to administer the dose shows a 20% variability, due to the dishomogeneity of boron distribution and neutron flux (14).

These data, reported only as examples of the plentiful literature on BNCT, demonstrate the need for an accurate biological characterization of the *in vivo* effects of this suggesting technique. The words of Ronald Dorn (15) appear very appropriate to conclude this brief communication:

1. How much of an advantage is gained in using *epithermal neutrons rather than thermal ones*? and *in which system* is this advantage of most usefulness?
2. *Is fractionation an advantage*? and does this advantage (or disadvantage) vary with *tumour type, beam quality and boron compound?*
3. How does *normal tissue tolerance* to BNCT compare to tolerance to conventional radiation therapy?

4. What are the *tolerable levels* of the various radiations present in an epithermal neutron reactor beam?

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NANODOSIMETRY FOR BNCT

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1. INTRODUCTION

BNCT beam monitoring is feasible by using a microdosemeter [1]. Spectra of absorbed energy in micrometric volumes can be in fact properly weighted to give a dose correction factor to calculate the biological dose. The weights are extracted by comparing microdosimetric spectra with a large ensemble of radiobiological data. However, microdosimetry describes the radiation action only with good approximation. We still ignore the physical parameter the biological effectiveness is correlated to. If such a parameter exists it would be appear by experimental measurements at nanometre level, since the fate of an irradiated cell depends on molecular mechanisms which take place, after irradiation, at nanometre level. The possibility to find such a physical parameter is always at the horizon of radiation physicists. Its knowledge would allow for a complete theory of radiation biological action. Radiation therapies, which use complex radiation fields like BNCT, would take great advantage from such a theory. The description of energy deposition event distributions in nanometric sites is called nanodosimetry.

2. NANODOSIMETRY AND TRACK-NANODOSIMETRY

Calculations and phenomenological studies [2] suggest that the physical parameter which drives the radiation action has to be sought in the ionisation pattern around a charged particle track .

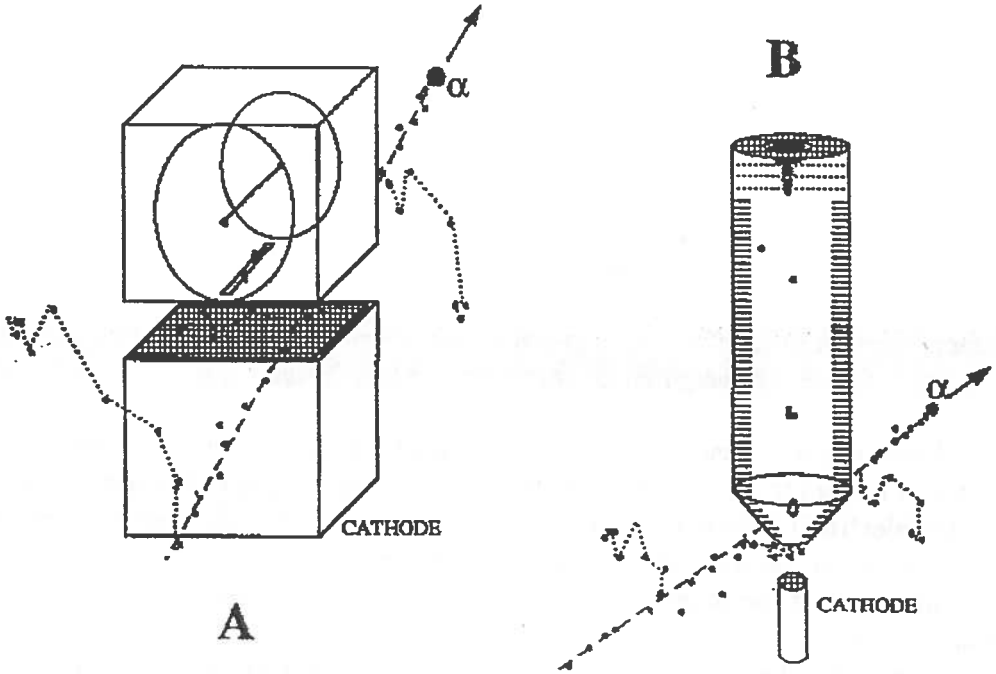


Figure 1. Two detectors for track-nanodosimetry developed at Legnaro.

The ionisation cluster distributions and their variations with the distance from the particle track could explain the radiation action mechanisms and answer to plenty of why's about the biological effectiveness of different radiations. We call track-nanodosimetry the investigation of the ionisation event fluctuations in nanometric volumes positioned at a given distance from the charged particle track.

Experimental track-nanodosimetry can be performed in several different ways. The aim is measuring the ionisation event distribution in a tissue-equivalent gas volume the dimensions of which are nanometric, at density 1 gr/cm^3. Since the track structure is much larger than such a volume, the ionisation event distribution varies with the volume position with respect to the track. Therefore an other aim is measuring how the ionisation distribution changes departing from the ionising particle track.

In figure 1 two detectors, fabricated at Legnaro Laboratories for such aims, are sketched. In figure 1A the particle passes through two electrodes which define a small drift region. A cylindrical proportional counter is enclosed in the anode cube. A thin slit connects the proportional counter and the drift region. Electrons created beneath the slit drift into the proportional counter, where they originate an electronic avalanche. The pulse spectrum collected with such a detector is proportional to the initial number of electrons. With such a detector we have measured the mean ionisation yield in nanometric volumes at a given distance from the track of a ^{244}Cm α-particle [3].

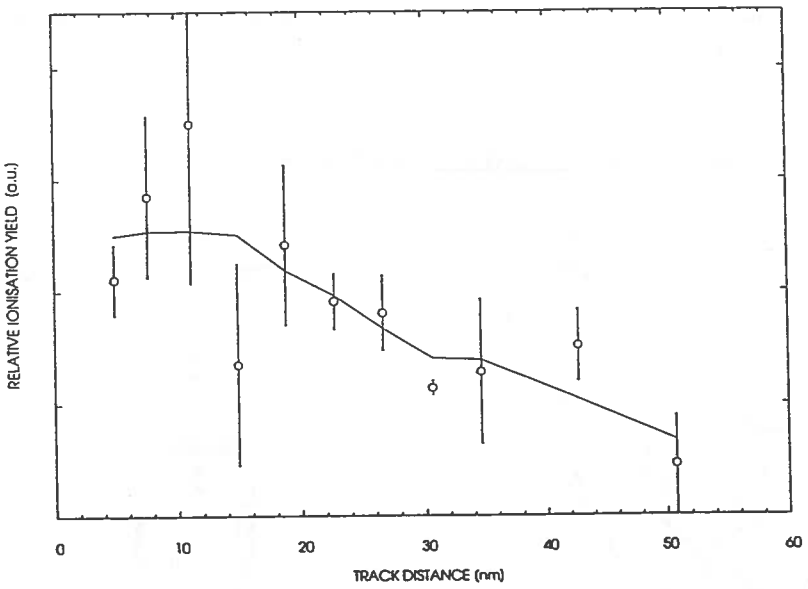


Figure 2. Mean ionisation yield of a ^{244}Cm α-particle in a nanometric volume (see text). The line is a weighted fit of the experimental data.

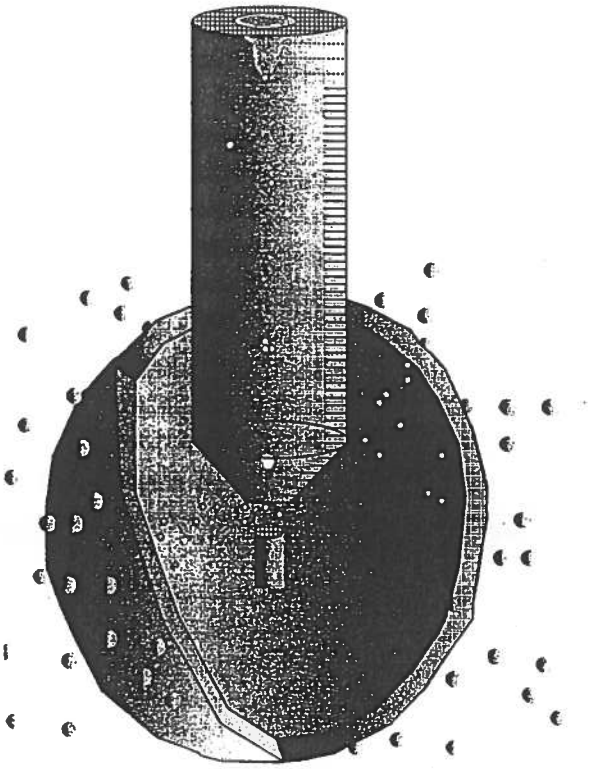
In figure 2 the relative mean ionisation yield in a volume of 3 x 11 x 66 nm^3 is plotted against the mean distance of the volume from the particle track. The experimental data are sensitive to the variation of the electrical field in the drift region [3]. However, they are consistent with the hypothesis that there is an almost flat region of 10-20 nm around the particle track. This finding would point out that the mean ionisation around a track depends only on the primary ionisation linear density.

The gas counter avalanche statistics is very broad when few initial electrons are multiplied by a large gas gain factor. Therefore the initial electron statistics is masked, it can not be measured properly with the detector of figure 1A. In order to check the finding of figure 2

with better resolution and precision and to perform ionisation cluster size distribution measurements, we have designed the counter in figure 1B. In such a counter the electrons, created in between the cathode and the hole, are made to drift along a drift column in order to separate them. The electrons arrive at the multi-stage proportional counter, positioned at the end of the drift column, well separated in time. Therefore, they generate in the proportional counter electron individual avalanches which can be detected separately. With a fast electronics it is then possible to count the electrons one by one. The counter will be able to measure not only the mean ionisation yield, but even the ionisation cluster distribution with resolution of 1 electron.

3. A POSSIBLE DETECTOR FOR BNCT NANODOSIMETRY

The detector of figure 1B is not yet operative. We think that first track-nanodosimetric measurements at high resolution will be performed in one year.
In figure 3 there is the sketch of a detector able to monitor the BNCT beam at nanometre level. The sensitive volume of the nanometric detector of figure 1B is surrounded of a sphere of boronated tissue-equivalent plastic to simulate the irradiation conditions of a chromatin fibre inside the body of a patient. The large cavity, filled with tissue-equivalent gas, minimises the so-called wall effects, that means the spectral distortions due to the different density of the wall with respect to the sensitive volume of the counter. Thermal neutrons of the therapeutic beam are absorbed by the sphere. Secondary charged particles generated in the sphere-wall cross randomly the gas cavity originating clusters of ionisation events inside the nanometric sensitive volume of the counter. Therefore this counter will be not a track-nanodosimeter, but a high resolution nanodosimeter.



Nanodosimetry and track-nanodosimetry are still frontier science. A lot of research is still necessary to develop reliable nano-detectors. Moreover, experimental radiation physics at nanometre level is just at the beginning. Several questions are still without answer. However, nanodosimetry promises to have a large positive impact on the radiation action understanding, this could improve all the hadron therapy and especially the BNCT therapy.

Figure 3. *The sketch of a possible detector for BNCT nanodosimetry.*

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EXPERIMENTAL STUDY ON BIOLOGICAL EFFECTIVENESS OF LOW ENERGY ACCELERATED CHARGED PARTICLES: FROM 'BROAD BEAMS' TO 'COUNTED PARTICLES' LIMIT.

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1. INTRODUCTION

Over the recent years an increasing interest in radiation biology research is being devoted to the attempt of relating the initial energy deposition events to the observed biological effects. Increased knowledge of the biological effects induced by radiations with 'different quality' can provides constraints for identifying the radiation physical characteristics relevant to their biological action. This information is important both to radiation protection and to medical applications for the better definition of the therapeutical tumor treatments with charged particles and neutrons. In particular, the knowledge of the biological effectiveness of *a* particle beam will contribute to determine which dose can be administred to the target volume (including the tumor and the healthy tissues) without inducing unacceptable damage.
As far as a BNCT treatment it concerns, it would be necessary to identify the different components of the 'biological effective dose' in the target volume and to quantify the biological response to these different dose components in such that the tumor receives the maximum dose avoiding unacceptable damage to healthy tissue. Such a goal could be achieved with an adequate physical, dosimetric and radiobiological characterization of the different beam components in the different elements of the target volume.

To contribute in the understanding of the biological action of charged particles, we have undertaken since many years a systematic investigation of the effectiveness, in terms of cellular and molecular damage in mammalian cells, of low-energy (high-LET) ions at the radiobiological irradiation facilities we have set up at the light ion 7 MV Van de Graaff CN accelerator and at the heavy ion 16 MV XTU Tandem accelerator of the Laboratori Nazionali di Legnaro-INFN , Legnaro -Padova, Italy [refs.1, 2].
The facilities, characterized by high flexibility in dose-rate and energy as well as high homogeneity of monoenergetic 'broad-beams' and reproducibility of irradiation conditions, enable irradiation in air, at atmospheric pressure and controlled temperature, of cultured mammalian cells growing as a monolayer attached on mylar foils, with the chosen ion beam.

In this report we briefly present the low-energy light ion radiobiological results obtained in conventionally 'broad-beam' conditions and we discuss on planned activities on experimental opportunities offered by the 'microbeam facilities', taking also into account the recently installed microbeam facility at the 2 MV AN2000 VdG accelerator of the Laboratori Nazionali di Legnaro-INFN , Legnaro-Padova, Italy [3].

2. LOW-ENERGY LIGHT ION RADIOBIOLOGY

We have undertaken since many years, in the framework of collaborative experiments, mainly with the Istituto Superiore di Sanità- Roma, a systematic comparative analysis of the

biological effectiveness of different accelerated charged particles as a function of LET in inducing cell inactivation, *hprt* mutation and DNA dsb (considered as crucial lesions) in V79-753B Chinese hamster cells.
In our early works we have shown, giving the first experimental evidence, that low-energy protons (in the LET range 7 - 38 keV/μm) are more effective than alpha particles at the same LET for inactivation and *hprt* mutation induction in V79-753B Chinese hamster cells [4,5]. Such results have subsequently been confirmed by independent experiments carried out at different European laboratories [6,7]. Parallel experiments on the induction of DNA damage in terms of single- and double-strand breaks not gave, in contrast, any indication of difference in effectiveness for the different radiation considered (X- , gamma-rays, protons, alphas) [8, 9].
Subsequently, in order to extend the investigated proton LET range, we have performed investigation with deuteron beams (in the LET range 13 - 57 keV/μm), that possess twice the range of protons with the same LET and the same velocity, showing, as an unexpected result, that deuterons appear less effective than protons in inducing both the biological end-points inactivation and *hprt* mutation [10,11].
More recently we have started a series of systematic and comparative experiments by using ^{3}He and ^{4}He ions in the LET range 40 - 150 keV/μm.
The results show that the effectiveness for cell inactivation induced by $^{3}He^{++}$ ions increases with the LET up to about 80 keV/μm and then decreases, while for $^{4}He^{++}$ ions rises as the LET increases up to about 100 keV/μm and then decreases, in agreement with literature data. Moreover, a different biological effectiveness can be observed between $^{3}He^{++}$ and $^{4}He^{++}$ ions in the LET range 40-80 keV/μm: the RBE values for $^{4}He^{++}$ ions are in fact lower than those obtained for $^{3}He^{++}$ ions of comparable LET, paralleling our findings with protons and deuterons [10,11].
Furthermore, considering the rejoining kinetics of DNA dsb induced by g-rays, protons and $^{4}He^{++}$ ions after exposure of V79 cell to a dose of 40 Gy, it appears that there are significant differences in the kinetics depending on both radiation type and LET [11], in contrast with the initial yield of DNA dsb findings but paralleling the cellular results.
All the results reported here give indirect experimental evidence that changing the type of ionizing radiation, from sparsely to densely, and increasing the LET there is an increase in the "complexity" of the induced damage. The lesion complexity affects the repair capability and, as a consequence, the final cellular effects. All this underlines a "damage quality" dependent on the "radiation quality".

3. 'COUNTED-PARTICLE' RADIOBIOLOGICAL STUDIES

The use of microbeam facility in radiobiological investigations dates back to few decades concerning the study of the 'individual cell' response to a single or few ('counted') charged particles, contributing to a realistic risk assessment at very 'low dose' (e.g., 'radon indoor' problem).
The achievements in particle accelerator and delivery systems, in radiation detectors, image analyser systems as well as in biological assays offer nowaday unique opportunity to carefully study the individual cell response to a precise number of particles, down to the limit of a 'single particle'per cell, in terms of particle localization, time (between particle tracks), number and energy deposition. Such capability allows one to investigate many important

radiobiological tasks, among which the 'biological effectiveness' of exactly one single particle in terms of cellular and molecular effects, but also the intra-cellular communication, the cell-to-cell communication, the functionality and role of the sub-components of the cell.
In recent years, a number of Laboratories worldwide have developed and are developing microbeam facilities, apparatuses and experimental approaches for irradiation of individual cells *in vitro* with 'counted particles' [12 -19]
Mainly aimed to the applications of nuclear techniques (like, PIXE, RBS, etc.) in different interdisciplinary researches, recently has been installed at the 2 MV AN2000 VdG accelerator of the Laboratori Nazionali di Legnaro-INFN a (magnetically focussed) microbeam [3]. Conditions as close as acceptable to "single (counted) particle irradiation" *in vacuum* have been recently achieved by the LNL accelerator Division and further development are planned for the extraction in air of the 'counted particles'.
Recent microbeam achievements are providing clear evidence of the significantly contribution to a better understanding of the biological consequences of densily ionizing radiations of such non-conventional experimetal approach.
Geard et al [13] show single alpha particles (90 keV/μm) direct trough the cell nucleus cause death (70-85% cell survival) and oncogenic transformation ($5x10^{-5}$) of C3H10T1/2 cells. Pugliese et al. [19] report that the survival probability for single alpha particles (105 keV/μm) travesing the nucleus of Chinese Hamster V79 cells is about 67%, while Folkard et al. [20] show that 5 to 60 protons (3 MeV; 12 keV/μm) through the V79 cell nucleus give a survival probability of about 93 to 47%. Hei et al [21] report that although single alpha particle (90 keV/μm) traversal is slightly cititoxic to human hamster hybrid A_L cells (about 82% survival probability) it is highly mutagenic (110 mutants per 10^5 survivors).

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AN ACCELERATOR-BASED NEUTRON SOURCE FOR BNCT OF SKIN MELANOMA

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1. INTRODUCTION

BNCT of skin malignant melanoma has been developed in Japan since 1972[1]. Primary lesions and unobservable satellite metastasis can be selectively treated with this technique. The clinical results related to 18 patients treated in Japan up to January 1996 are analysed in ref. 1. The survival rate after two or more years resulted to be 78%, regardless the level of melanoma progression. ^{10}B-para-boronphenylalanine (BPA) was used as the boron carrier to the tumour. The patients were irradiated at a research reactor facility for 1-2 hours with thermal neutrons and the related maximum fluences at the tumour sites were in the range[2] $(1.0\text{-}2.0)\times10^{13}$ cm^{-2}.

The design of the accelerator-based neutron source for BNCT of skin melanoma discussed in the present work is described in ref. 3. Neutrons are produced by bombarding a thick beryllium target with 7 MeV deuterons. The target is contained in a heavy water moderator in turn enclosed in a graphite structure. Lead filters are placed on the Faraday cup containing the beryllium target and on the heavy water container to reduce the prompt gamma ray dose. The experimental verification of the accelerator-based source was performed at the CN Van De Graaff accelerator of the Laboratori Nazionali di Legnaro (LNL, Italy). Measurements of thermal fluence uniformity and prompt gamma ray dose at the irradiation position, together with estimates of the neutron fluences inside an Alderson phantom are discussed in the following.

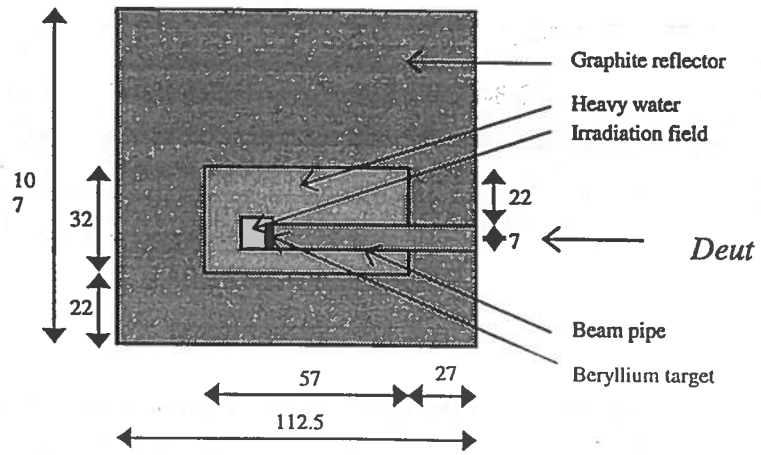

Fig. 1 - A schematic sectional view of the basic structure (not to scale). Dimensions are in cm.

2. SOURCE DESIGN

The source design was performed with Monte Carlo simulations using the MCNP-4A[4] code. The measured double differential distribution of neutrons produced by 7 MeV deuterons impinging on a thick beryllium target[5,6] was considered as the simulation source.

The simulations aimed at obtaining a uniform thermal fluence of 10^{13} cm^{-2} inside a $10x10^2$ cm^2 irradiation field. The cumulative physical dose due to fast neutrons and prompt gamma rays was limited below 2 Gy versus about 20 Gy delivered to the tumour by the $^{10}B(n,\alpha)^7Li$ reaction products.

Fig. 1 shows a schematical view of the moderating structure. In particular, the heavy water container is made of aluminium 1050, the graphite thickness (from the heavy water tank side to the irradiation position) is 22 cm, the beam pipe and the Faraday cup, in which the beryllium target is inserted, are in aluminium 6063. The thicknesses of the lead filters placed on the Faraday cup and on the heavy water tank are 1 cm and 3 cm, respectively. The position of the irradiation field is on the lateral surface of the graphite structure. Thermal neutrons not included in the irradiation field are shielded by a LiF layer 3 mm thick, covering the remainder of the lateral surface.

The physical dose due to the different components of the irradiation field (i.e. thermal and fast neutrons, prompt gamma rays) were calculated by considering a soft tissue phantom (surface 50x50 cm^2, thickness 10 cm), placed in contact with the graphite structure surface. The phantom was centered at the irradiation field position and was subdivided into cubic cells (10x10x10 cm^3). A layer 3 mm thick (simulating the treatment volume), loaded with 50 μg g^{-1} of ^{10}B, was considered in the cell adjacent to the irradiation position, while the ^{10}B concentration in the remainder of the phantom (normal tissue) was 10 μg g^{-1}. The results are listed in Tab. 1. It should be mentioned that the lead filters attenuate the prompt gamma ray and the fast neutron dose by about 45% and 50%, respectively.

Table 1 - Neutron and prompt gamma ray dose rate per unit deuteron current (Gy h^{-1} mA^{-1}) to the tumour (3 mm thick) and to the normal tissue of the soft tissue phantom (see text).

	Tumour	Normal tissue	
^{10}B content (μg g^{-1})	50	10	
		Behind tumour	Average
$^{10}B(n,\alpha)^7Li$	37.93 ± 0.87	2.29 ± 0.87	1.49 ± 0.05
$^{14}N(n,p)^{14}C$	2.34 ± 0.05	0.71 ± 0.02	0.46 ± 0.02
Fast neutrons	2.46 ± 0.27	1.07 ± 0.12	0.77 ± 0.14
Prompt gamma rays	8.91 ± 0.53	6.28 ± 0.18	3.92 ± 0.18
Total	51.64 ± 1.05	10.35 ± 0.90	6.64 ± 0.23

3. EXPERIMENTAL

The neutron measurements were performed at the CN Van De Graaff accelerator of the LNL. The deuteron energy and nominal current were 7 MeV and 100 nA, respectively. The deuteron current impinging on the beryllium target was measured with a Faraday cup connected to a

charge integrator and equipped with an electron suppressor. The charge integrator stability was checked in all measurements by placing a BF_3 proportional counter at a fixed position close to the graphite moderator. The result of a single measurement was accepted when the ratio of the BF_3 counts to the measured charge was consistent with the whole set of measurements.

The thermal and epithermal (0.4 eV-10 keV) fluence rates were measured at various positions inside the irradiation field with activation techniques using bare and cadmium-covered indium foils. In particular, a grid of nine activation foils equally spaced by 2 cm was used to assess the thermal fluence uniformity inside the 10x10 cm^2 irradiation field. The gamma activity of the irradiated foils was measured with a 2"x2" NaI scintillator. The counting and normalisation uncertainties were estimated separately, using the method described in ref. 7.

It should be pointed out that the measurements were performed with a stainless steel heavy water container, because that of aluminium[8] had to be removed, as D_2O pollution was observed. In particular, as the utilized aluminium 1050 alloy was not passivated, a non negligible amount of aluminium hydroxide was produced because of corrosion. The ratio of the average thermal fluence in the irradiation field with an aluminium tank to that with stainless steel is about 2.6, as results both from MCNP calculations and measurements[7,8].

The fluence rate spatial distribution in the irradiation field was also calculated with MCNP, by strictly reproducing the geometry of the experimental structure and of the In foil grid. Fig. 2 shows the measured and calculated fluence rate per unit deuteron current at the considered positions.

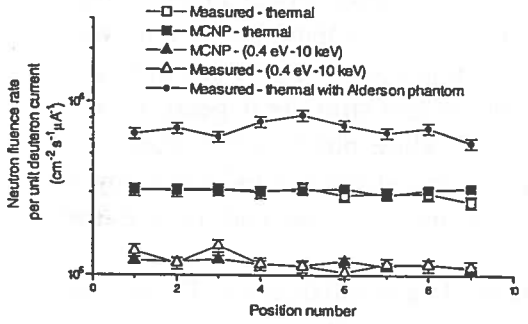

Fig.2 - Neutron fluence rate per unit deuteron current at various positions inside the irradiation field with and without and Alderson phantom.

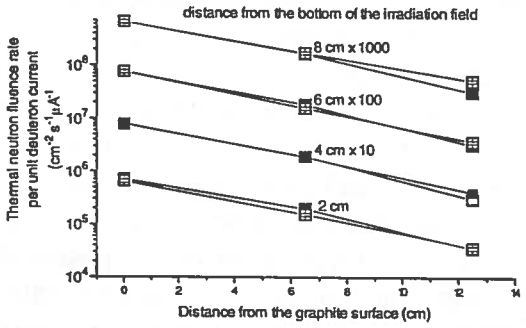

Fig. 3 - Neutron fluence rate per unit deuteron current at various positions inside an Alderson phantom. Solid symbols: MCNP, open: experim.

The thermal neutron fluence rates were also measured inside an Alderson phantom (type: ART). The zone covered by the 10x10 cm^2 irradiation field was investigated. A cadmium layer 1 mm thick was used to shield the lateral surface of the moderating structure outside the irradiation field. Different sets of bare and Cd-covered indium foils were placed at 0 cm, 6.5 cm and 12.5 cm from the surface of the graphite moderating structure, between two contiguous Alderson phantom sections. The considered sections were positioned at 2 cm, 4 cm, 6 cm and 8 cm from the bottom of the irradiation field. The thermal neutron fluence rates per unit deuteron current at the positions adjacent to the graphite surface with the presence of the Alderson phantom are shown in Fig. 2. It was observed that the presence of the Alderson

phantom contributes to increase the thermal fluence at the tumour position, because of neutron reflection.The measured thermal fluence rates averaged over all positions with and without the Alderson phantom resulted to be $(6.9\pm0.8)\times10^5$ cm^{-2} s^{-1} μA^{-1} and $(3.0\pm0.2)\times10^5$ cm^{-2} s^{-1} μA^{-1}, respectively, emphasising that the thermal fluence increased of a factor 2.4 because of reflection. The measured thermal fluence rates inside different Alderson phantom sections at various distances from the graphite reflector are shown in Fig. 3. The results of a simulation in which the Alderson phantom was considered are also shown.

The prompt gamma ray dose was measured at the irradiation position with ^{7}Li TLDs, whose response was assessed up to 7 MeV photons. Repeated measurements were performed to estimate the measurement uncertainty. The configuration of the moderating structure refers to the aluminium heavy water tank without lead filters. The resulting air kerma rate was 4.06 ± 0.04 Gy h^{-1} mA^{-1} and can be compared the dose rate of 3.82 ± 0.20 Gy h^{-1} mA^{-1} calculated at the irradiation position without phantom. The prompt gamma ray dose values listed in Tab. 1 take into account the contribution of prompt gamma rays produced in the ^{10}B loaded soft tissue and, although they refer to a configuration with lead filters, are larger than the measured data.

4. CONCLUSIONS

The accelerator-based thermal neutron source here described can provide the dose necessary for the treatment of melanoma (20 Gy) in one hour with a deuteron current of 530 μA and a ^{10}B concentration into the tumour of 50 μg g^{-1}. The cumulative prompt gamma ray and fast neutron dose (averaged over the whole phantom) is 2.5 Gy. A reflection effect given by the presence of a phantom and increasing the thermal fluence at the irradiation position, was observed. The measured ratio of the thermal fluence with the phantom to that without is 2.4 (in agreement with the calculated value) . It is obvious that this effect strongly depends on the irradiation geometry. Anyway, it should be taken into account while planning the treatment dose. Moreover, it can be exploited to design appropriate reflecting structures to be employed during the irradiation, in order to increase the therapy thermal fluence and reduce the necessary deuteron current and/or the exposure time.

The agreement of the measurements with the calculated data is satisfactory. The results of measurements of the fast neutron energy distribution are given in ref. 7.

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TAPIRO AND TRIGA ENEA'S REACTORS AS NEUTRON SOURCE FOR BORON NEUTRON CAPTURE THERAPY

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1. INTRODUCTION

Reactors are currently seen as the most suitable type of neutron source for BNCT implementation, due to the high intensity of the flux they can provide. Neutron sources with epithermal spectrum are being considered for clinical use, because thermal neutrons have limited penetration depth and cannot be used for the treatment of deep pathologies.
The preferred characteristics of the neutron beam are:

- high epithermal flux intensity for reducing the irradiation time;
- low/high energy neutrons component for sparing the healthy tissues;
- low thermal neutron component which causes undue dose on surface tissues;
- low gamma ray flux;
- high forward component (current to flux ratio).

In this work, beside a brief description of TRIGA characteristics for a BNCT activity, the design of a modification for the low-power fast-flux TAPIRQ reactor to have an optimized epithermal flux is presented.
The spectrum-adapter calculations, performed by MCNP, are presented in a specific paper.

2. THE TRIGA REACTOR

The TRIGA RC-1 reactor [1] (see fig. 1) is a pool thermal reactor whose core is placed inside a cylindrical graphite reflector, on an aluminium vessel, filled up with demineralized water, that develops the function of moderator, of cooling mean of the core and of biological shield. Fuel is composed of cylindrical elements formed by a ternary alloy of Zr-H and uranium enriched at 20% in ^{235}U (about 4.5 kg of ^{235}U). Therefore moderation is assured not only by cooling water but also by zirconium hydride of the alloy which is also responsible of the prompt high negative temperature coefficient. The reactor is controlled by four control rods: 2 shims, 1 safety and 1 regulating rod. An Am-Be source provides for the controlled and gradual initiation of the chain reaction. The removal of thermal power produced by the core is effectuated by natural water circulation. Water of the pool, to which such power is yielded, is kept at constant temperature by a suitable cooling circuit provided with heat exchanger and cooling towers.
It is also possible to irradiate electronic components under voltage in the central thimble and in the rotary specimen rack in particular conditions (covered cables, insulated samples).

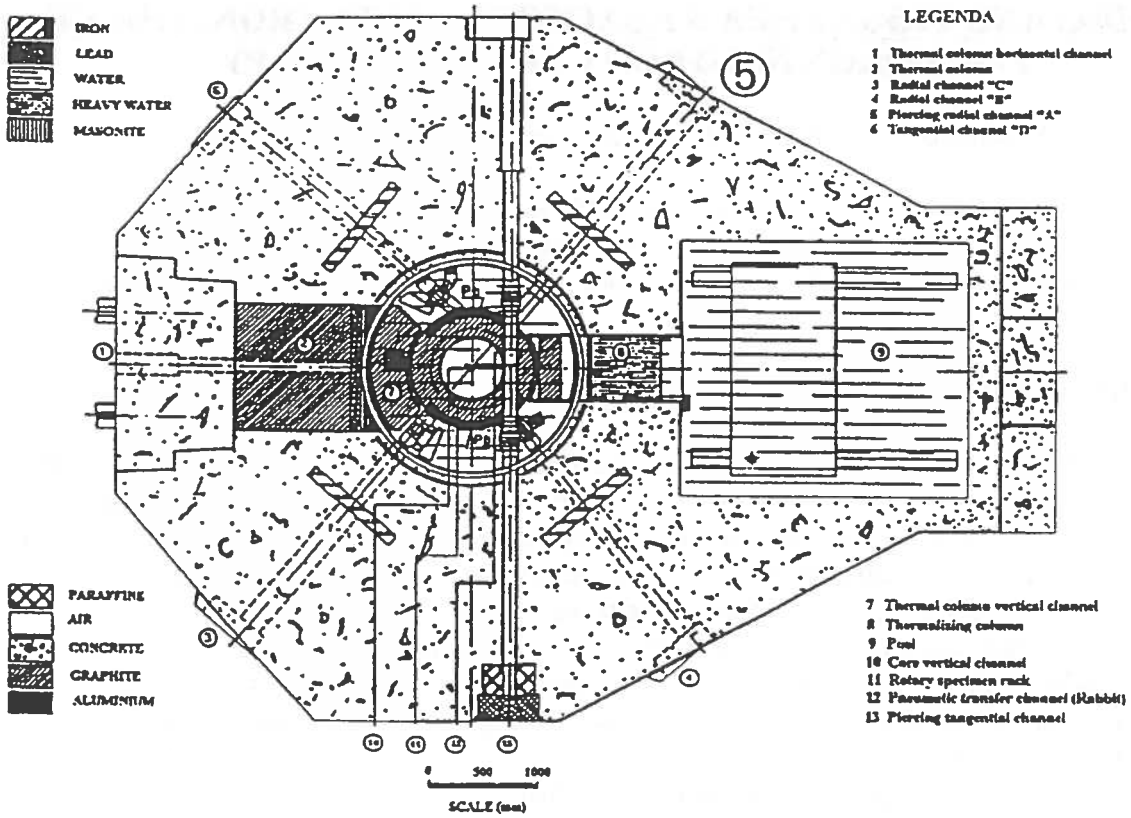

Fig. 1 - TRIGA RC-1 horizontal section.

An accurate neutron flux calibration by means gold foils was carried out in the whole reactor core after first criticality and it is repeated in the irradiation facilities whenever fuel burn-up restoration is accomplished. TL dosimeters, beryllium oxide sintered discs, were used to characterize gamma dose in the main experimental facilities. Reactor building is provide with a radiochemical laboratory were irradiated material may be manipulated. In this laboratory is placed the terminal station of pneumatic transfer system (RABBIT), used for short mean life radioisotopes production. It is also equiped with 3 chemical hoods and lead shields.

3. BNCT PROGRAM FOR TRIGA REACTOR

To employ ENEA TRIGA reactor in the BNCT on malignant brain tumor, reactor researcher staff have studied [2] the possibility to use the piercing radial beam to have a neutron thermal flux in the irradiation position of about $3\text{-}10^8$ n/cm^{2}s (see fig. 1, channel 5).
Inside piercing beam, a neutron collimator (2400 mm of total lenght and 50 mm of outside diameter) will be introduced.
To stop gamma and neutron radiation outside beam tube during preparation phase of human patient, a lead rotating shutter (350 mm lenght, 660 mm diameter provided of 50 mm diameter hole to align with piercing beam axis) will be installed in a cavity purposely realized in the concrete of the reactor external biological shield.
In the external part of neutron collimator a graphite box has been foreseen (minimum graphite thikness: 400 mm; about internal volume sufficient to introduce a cavy animal or the patient head). The graphite box will be installed in asymmetric position to piercing beam axis to

avoid, as much as possible, gamma irradiation and to have only neutron irradiation. Inside graphite box has been calculated an uniform neutron flux distribution (due to neutron scattering and albedo) more than 10^8 n/cm^{2}s (3 10 n/cm s) that is enough for the BNCT purposes.

4. THE TAPIRO REACTOR

The TAPIRO reactor, that is located in the ENEA Casaccia Center near Rome, is a highly enriched uranium-235 fast neutron facility [3]. Since 1971, it has been used for fast reactor shielding experiments, blanket studies, biological effects of fast neutrons and so on. A sketch of the reactor is shown in fig. 2.

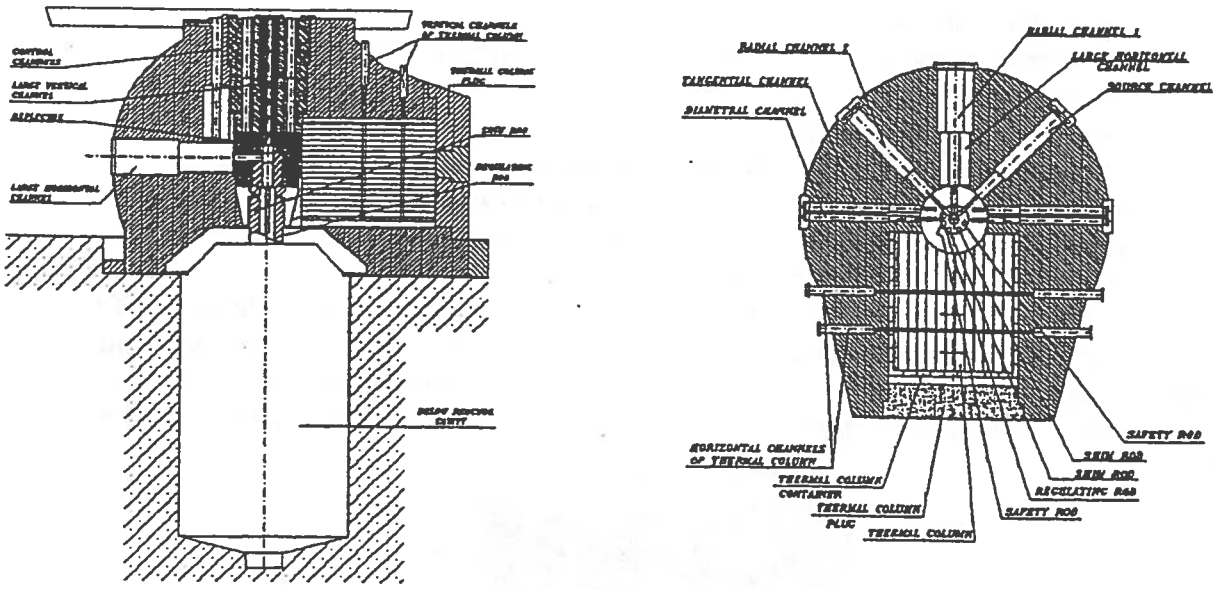

Fig. 2 - TAPIRO reactor. Left: axial vertical section.
Right: horizontal section with experimental channels view.

The nominal power is 5 kW (thermal) and the maximum neutron flux is $4 \cdot 10^{12}$ n/cm^{2}s.
The reactor has a cylindrical core (12.58 cm diameter and 10.87 cm height) made of an uranium- molybdenum alloy (98.5% U, 1.5% Mo in weight) which is totally reflected by copper. The outer copper reflector (cylindrical-shaped) is divided in two concentric zones: the inner zone, up to 17.4 cm radius, and the outer zone up to 40.0 cm radius. The height of the reflector is 72.0 cm. A section of the outer zone of the reflector can be taken away or replaced by a convenient material. The graphite blocks of the thermal column can be replaced by weakly moderating materials, such as Al_2O_3, graphite and D_2O, to obtain an "epithermal column", a sort of spectral shifter, useful for BNCT.
The reactor is surrounded by a borate concrete shielding about 170 cm thick.
The maximum depth available for the "epithermal column" is 160 (lenght from the external surface of the reflector). The "epithermal column" is set on a trolley, which can be driven into the cave of the borate concrete shielding.

5. TAPIRO EPITHERMAL COLUMN FOR BNCT. RESULTS FOR DIFFERENT SPECTRAL SHIFTER CONFIGURATIONS

The reference parameters to have an acceptable BNCT beam are summarized as follows:
- epithermal flux (1 eV < E_n< 10 keV) : higher than $5 \cdot 10^8$ n/cm^{2}s^{-1}
  (based on a therapeutic dose of 10^{12} n/cm^2 for an irradiation time shorter than one hour);
- fast neutron kerma : less than $5 \cdot 10^{-13}$ Gray cm^2/epithermal neutron;
- gamma kerma : less than $3 \cdot 10^{-13}$ Gray cm^2/epithermal neutron.

Some configurations have been investigated iteratively to achieve the desired experimental conditions [4].
The following data have been calculate5 at the exit of the last material, averaged over a disk surface having a radius of 10 cm:

- thermal, epithermal and fast flux components;
- flux weighted energy;
- mean cosine of the angle between the beam neutron direction and the normal to the surface;
- the current to flux ratio (J/ϕ);
- fast neutron kerma in water defined ad the energy deposition in water by fast neutrons (Gy·s^{-1}) divided by the epithermal flux (n/cm^{-2}s^{-1});
- gamma kerma in tissue defined as the energy deposition in tissue by gammas (Gy·s^{-1}) divided by the epithermal flux (n/cm^{-2}s^{-1}).

In a first configuration (similarly to the scheme reported in fig. 3) the removable sector of the outer reflector was filled with alumina (AI_2O_3, density 3.96 g/cm^3). The spectral shifter consists of layers of aluminum, alumina, cadmium, with a bismuth gamma shield, reflected by a layer of nickel. The final collimation is provided by a bismuth cone surrounded by concrete shield.

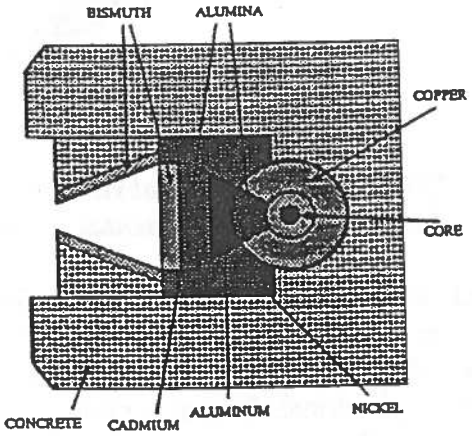

Fig. 3 - Horizontal section of the TAPIRO reactor in the configuration number 1.

This solution gets a profitable value of (J/4) despite of a low epithermal flux at the collimator exit.
Some alternative configurations have been investigated. One of them consists of layers of aluminum, heavy water, a cadmium foil and a bismuth gamma shield. The entire column is surrounded by a nickel reflector. In the original work the collimator was made of nickel, but this material produces a too high gamma dose; so it has been substituted with a bismuth one (configuration number 2).
An epithermal flux about 6 10~ n/cm s has been obtained.

To avoid the troubles related to the heavy water handling, a similar configuration, in which this material has been substituted by graphite, has been investigated (configuration number 3). The final results of all the investigated configurations are summarized in Table 1.

Config.	Position	ϕEpith ($n/cm^{-2}s^{-1}$)	ϕFast/ϕEpith	J/ϕ	Fast neutron kerma ($Gy \cdot cm^2 n^{-1}$)	Gamma kerma ($Gy \cdot cm^2 n^{-1}$)
1	At the collimator exit	$2.54 \cdot 10^{8}$	$2.16 \cdot 10^{-2}$	0.70	$0.91 \cdot 10^{-13}$	$0.47 \cdot 10^{-13}$
2	At the collimator exit	$5.96 \cdot 10^{8}$	$7.73 \cdot 10^{-2}$	0.70	$2.50 \cdot 10^{-13}$	$0.38 \cdot 10^{-13}$
3	At the collimator exit	$4.70 \cdot 10^{8}$	$6.89 \cdot 10^{-2}$	0.70	$3.02 \cdot 10^{-13}$	$0.34 \cdot 10^{-13}$
Target parameters		$> 5 \cdot 10^{8}$	---	---	$< 5 \cdot 10^{-13}$	$< 5 \cdot 10^{-13}$

6. CONCLUSIONS

From this preliminary study it is possible to conclude that:

a) the MCNP calculations show that an epithermal column could be installed in the TAPIRO reactor, instead of the thermal one;

b) the epithermal flux level is sufficient to reach the target parameters even if the TAPIRO fast source reactor power is much lower than a typical thermal experimental reactor power (i.e. a TRIGA having a power of 1 MW);

c) significant experiments on brain phantoms could be performed without difficulties;

d) other optimization studies should be performed to achieve better parameters, mainly concerning the beam collimation.

The facility could be also intended as an experimental mock-up for the use of highly enriched uranium in low power reactor for BNCT.

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More detailed informations about TRIGA and TAPIRO BNCT program are in the [2] and [4] references, available nearby the meeting organizer secretary's office.

USE OF AN INNOVATIVE MONTE CARLO TECHNIQUE TO CALCULATE NEUTRON SPECTRA IN BNCT – APPLICATION TO THE TAPIRO REACTOR

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1. VARIANCE REDUCTION IN MONTE CARLO AND THE DSA

Monte Carlo is the most powerful instrument available to design BNCT facilities, be they reactor– or accelerator–based. The main reason for its advantage over deterministic methods is its capability to represent complex geometries and to model radiation streaming. It is also able to faithfully model the basic neutron cross–section data (although if very narrow resonances or cross–section windows are present, they may possibly not be sampled in the transport). However by its very nature, Monte Carlo can only estimate a response to some statistical error. The more differential a response in space, energy or angle, the higher this error. If we wish to calculate a neutron spectrum in reasonable detail, this requires estimating a large number of fluxes, each occupying a narrow energy group. Consequently the statistical error may be large.

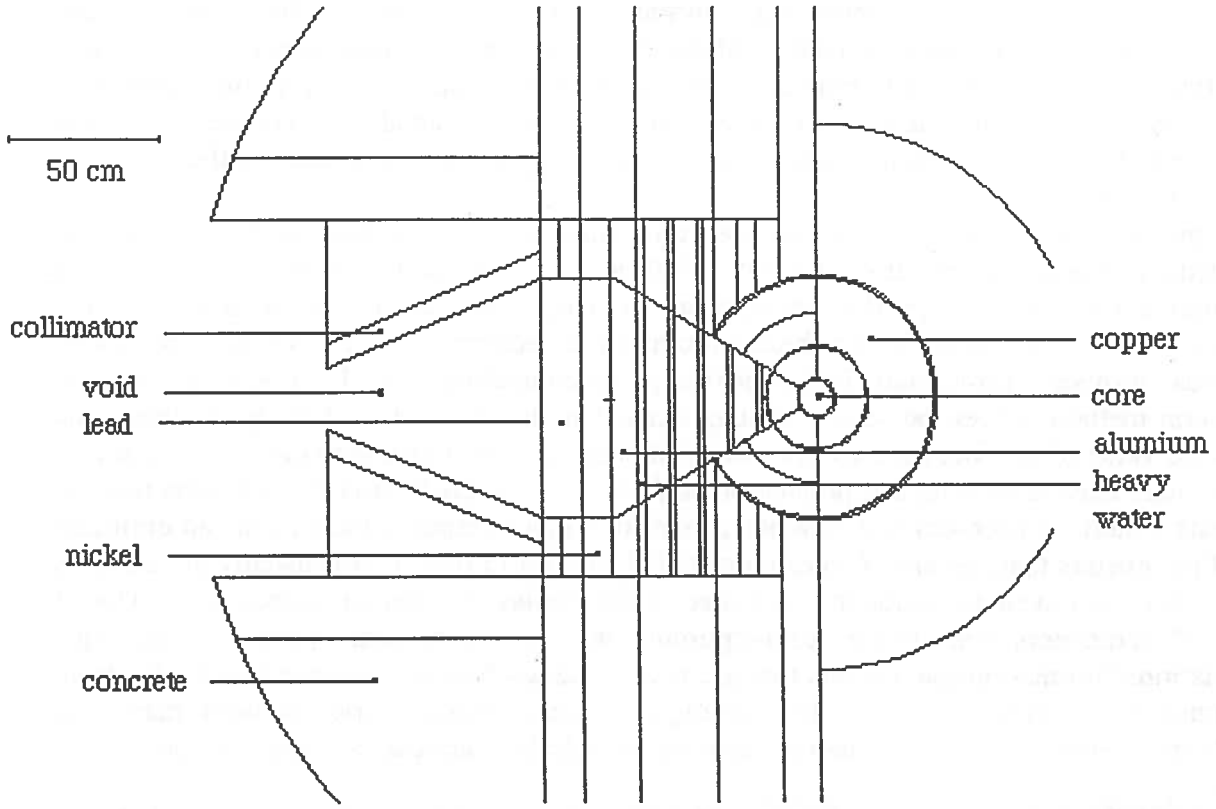
Analogue Monte Carlo means, within the constraints of the cross–section data and of the geometrical model, a simulation of reality. With analogue Monte Carlo, the source–detector attenuation may be so large that no neutrons actually score, or so few neutrons that the statistical error is too high. Under these circumstances techniques called "variance reduction methods" provide a lower statistical error in a given computing time, T. In general, variance reduction methods lower the second moment and thus the error whilst leaving unaltered the expected value of the first moment. A variety of such methods exist; they can be divided into two general classes: biasing and population control methods. Each variance reduction method requests a range of user–defined parameters and for a given response there exists an optimum set of parameters that provides a minimum statistical error in time T. It is usually not obvious what this optimum set is, although it is linked to the adjoint function, or "importance". Use of a set of parameters that are far from optimum may be worse than running an analogue calculation. Furthermore parameters that are near optimum for one response may be far from optimum for another response. Thus although standard Monte Carlo methods may treat problems involving a high attenuation, they do so only by calculating a single response at a time.

Control of the track population is a completely general variance reduction method that is applicable to a very wide range of transport problems. The DSA (Direct Statistical Approach), which has been under development for many years (see for example refs. 1,2,3,4), aims to optimize splitting and Russian roulette parameters employed in control of the track population in both space and energy (or to optimize cell starting weights in the presence of biasing methods – ref. 3). An important characteristic is that, by means of a single integral parameter (the "quality factor"), the DSA allows the user to evaluate during the iterative optimization procedure when he has reached the region of the optimum. The DSA currently employs as vehicle the widely–used code, MCNP4B (ref. 5).

A recent development has been to extend to more than one response (ref. 6). This was realised by normalizing the second moment function coefficients using the squares of the respective

first moments (ref. 6). In practice in a given computing time, the sum of the squares of the fractional errors of the responses is minimized; this for responses that may differ by orders of magnitude (as for example in a flux spectrum) or that may be in different units (a flux, a reaction rate, a dose, etc.).
It is not obvious that an optimization of the variance reduction parameters to several responses would be particularly advantageous in the case that the responses are spatially distant from one another. Instead when the responses are spatially near, indeed if they occupy the same spatial location, it seems possible that a multi–response optimization may hold advantages over a number of single response optimizations. The latter situation obtains in the design of BNCT facilities where we wish to know both the thermal, epithermal and fast components of the neutron flux spectrum in reasonable detail at the irradiation position, as well as the gamma ray dose. Thus the multiple response optimization feature of the DSA is particularly appropriate to BNCT applications.

Fig. 1. TAPIRO; geometry; horizontal section

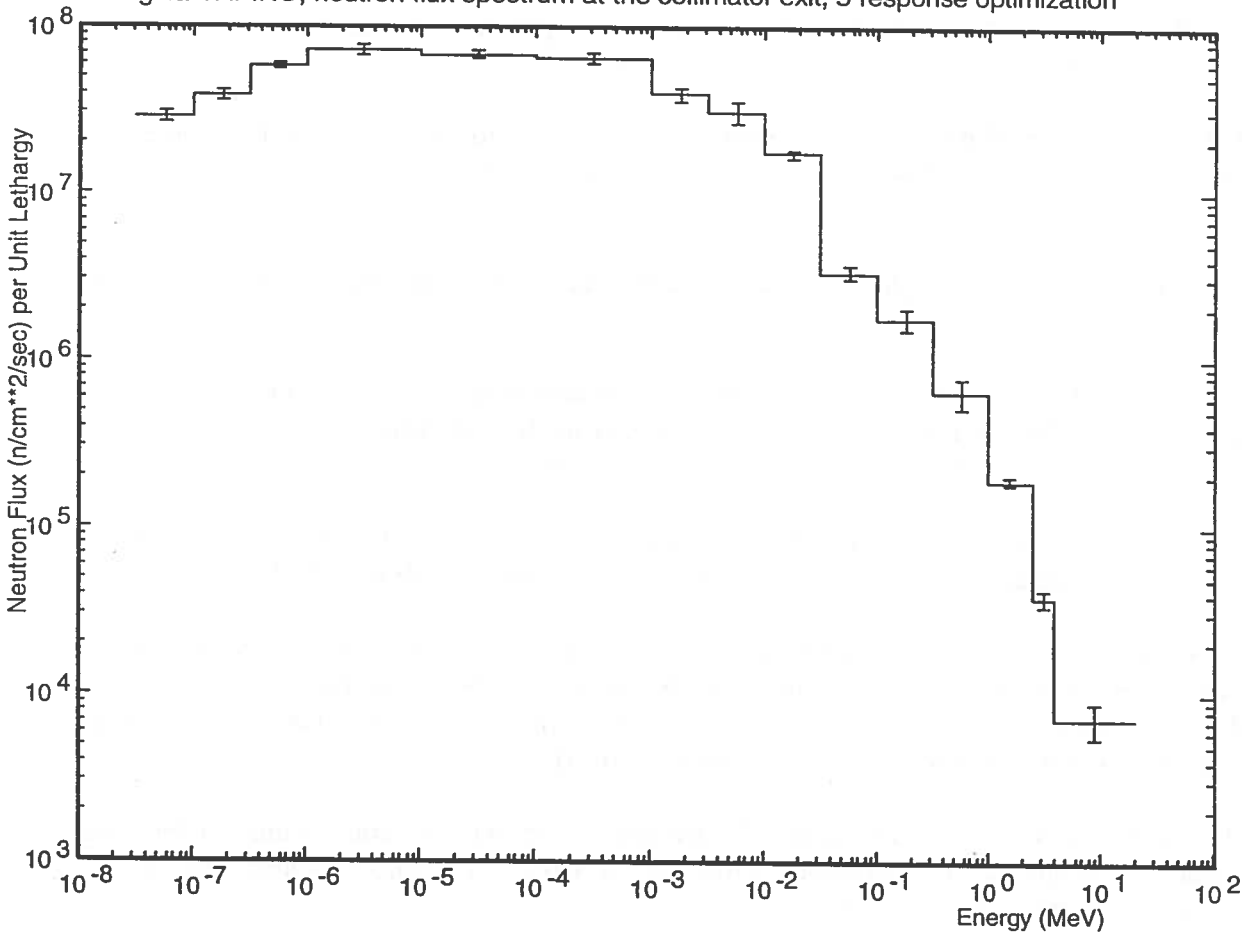


2. APPLICATION TO A SPECTRUM SHIFTER FOR THE TAPIRO FAST ASSEMBLY

TAPIRO at ENEA Casaccia is a fast assembly with core radius 6.3 cm and height 10.87 cm with 93.5% enriched U metal and a Cu reflector. A sector of the concrete shield and outer reflector has been replaced by a "spectrum shifter" whose role is to provide an epithermal neutron spectrum. That considered here, suggested by Rief *et al.* (ref. 7), is a sequence of five modules, each consisting of 2 cm of D_2O and 8 cm of Al, followed by 11.5 cm of Al, 0.4 mm of Cd and 13 cm of Pb, all surrounded by a Ni reflector (Fig. 1). Following the Pb, there is a graphite collimator which restricts the neutron beam to a 10 cm radius aperture. Note that this

configuration is not the final one – the collimator material was subsequently changed to Bi to lower the thermal neutron flux (ref. 8).
A multi–response optimization was carried out by dividing the neutron flux into 5 groups: < 0.32 eV, 0.32 – 1 eV, 1 eV – 10 keV, 10 keV – 1 MeV and > 1 MeV. In Fig. 2 the resulting flux spectrum at the collimator exit is shown. We see that the statistical error is reasonably satisfactory over the whole energy range. Thus the DSA multi–response algorithm produced variance reduction parameters that calculated a flux spectrum over 4 orders of magnitude. Further details of this calculation are in ref. 6.

Fig. 2: TAPIRO; neutron flux spectrum at the collimator exit; 5 response optimization



The DSA codes have recently been rewritten to reduce the "book–keeping" time for multiple responses. The new codes were applied to the optimization of four responses at the collimator exit: the neutron flux < 1 eV, 1 eV – 10 keV, > 10 keV, and the gamma ray dose, so as to verify possible savings in computing time with the multi–response optimization, that were reported in ref. 6. The multi–response optimization gave a 20% saving during the generation phase and a 50% saving for the running phase with the generated optimum variance reduction parameters. However as observed in ref. 6, the main saving is in "human" time, four optimization procedures being substituted by a single one. In this context it may be mentioned that the multi–response algorithm has been successfully applied to a numerical dosimetry problem involving 84 responses (ref. 9).

3. CONCLUDING REMARKS

– The multi–response feature of the DSA is particularly useful in BNCT facility design.
– The DSA codes currently employ some IMSL routines. This constraint could be removed.
– The DSA is currently being extended to n–particle transport (protons, pions, electrons, etc.) and to energy ranges up to GeV.

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ACCELERATOR-BASED BNCT: CURRENT STATUS AND PERSPECTIVES

SOLONE Collaboration

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1. INTRODUCTION

Promising results in the treatment of various tumor diseases with Boron Neutron Capture Therapy (BNCT) justify increasing efforts to improve the two components of the therapy, the ^{10}B carriers and the neutron beams [1]. In particular, recent developments in the accelerator technology are making realistic the possibility of setting up high-quality, safe and cost-effective epithermal neutron sources based on accelerators. We describe here such progresses; in the following, we discuss the different approaches and the related problems towards accelerator-based BNCT, analyzing the solutions currently investigated and those potentially interesting for future developments. In particular, we compare the characteristics of various proton- and deuteron-induced reactions that can be used for neutron production for BNCT. Some of these reactions have been recently studied at the 88" cyclotron of Lawrence Berkeley National Laboratory (LBNL) by a collaboration between the INFN group "Solone" (Bari) and the LBNL group involved in the development of an accelerator-based BNCT facility. Finally, we give an overview of the different types of accelerators that can be used to produce epithermal neutron beams for the treatment of glioblastoma multiforme, as well as other forms of deep-seated tumor.

2. EPITHERMAL NEUTRON BEAMS BY ACCELERATORS

Analyses [2,3] of the BNCT dose deposition in tumor versus normal tissues show that the therapeutic effect would be optimized by using a monoenergetic neutron beam, with the energy chosen on the basis of the tumor depth. In fig.1a the ratio between the dose released to the tumor and the maximum dose to normal tissues is shown as a function of neutron energy, for a tumor located at a depth of 5 cm inside the brain [3]. In the simulation, a concentration of 10 and 43 ppm of ^{10}B in blood and tumor, respectively, has been assumed (these are typical values for BPA). The optimal neutron energy, corresponding to the maximum dose ratio is, in this case, around 4 KeV; for lower energies the neutrons thermalize at depths smaller than the tumor location, while for higher energies the recoiling protons lead to a rapid increase of the dose released to the normal tissues, in particular at the brain surface. The dose deposition versus depth in the brain, in the case of 4 KeV neutron beams, is shown in fig.1b.
Although in practice monoenergetic neutron beams of few KeV cannot be produced, it is clear that one should try to approach such a condition to optimize the therapeutic effect. In this respect, an important role can be played by the choice of the moderator and filter assembly

necessary to reduce to the desired energy the neutrons produced in reactors. However, a great step forward could derive by the use of an accelerator as an intense neutron source. With a suitable choice of the neutron-producing reaction, in fact, it is possible to obtain low energy neutrons (E_n<1 MeV) which, even after the moderation process, retain a narrow energy spectrum and a negligible contamination of the high energy component. Together with the possibility of producing neutron beams of superior quality with respect to nuclear reactors, accelerators offer the advantage of fewer safety problems related to radiation hazards, thus enabling the installation of BNCT facilities in metropolitan areas and even in hospitals. Moreover, the relatively low construction and running costs of accelerators allow for a wider diffusion of the centers for the application of the therapy. For these reasons, the interest in accelerator-based BNCT and in the related research has been rapidly increasing in the past few years.

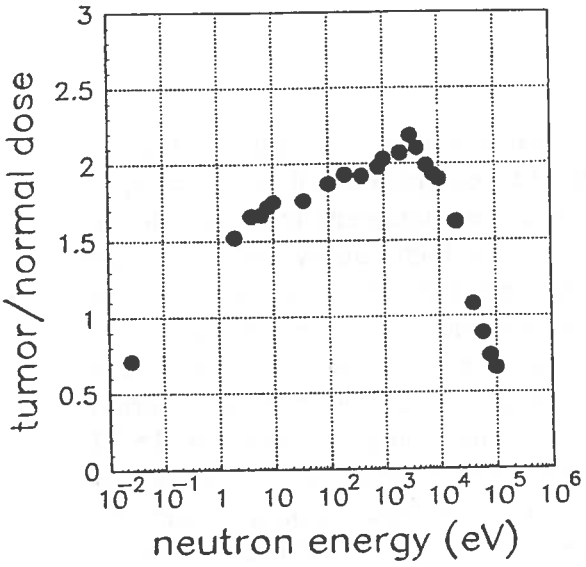

Fig. 1a

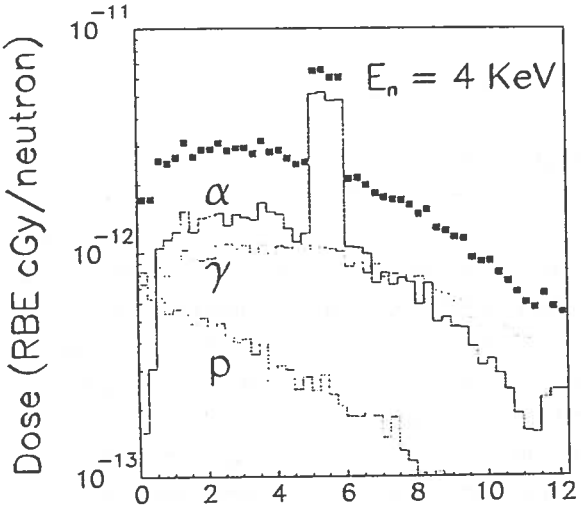

Fig. 1b

Fig. 1: a) Ratio between the dose to tumor and the maximum dose to normal tissues as a function of neutron energy. b) Dose distribution in the brain for a neutron beam of 4 KeV energy.

3. NEUTRON-PRODUCING REACTIONS

An accelerator-based neutron source relies upon a proton or deuteron-induced reaction on a suitably chosen target. The choice of the beam energy and of the target is mainly dictated by the following requirements:

- low energy neutron emission;
- low energy of the incident proton or deuteron beam;
- high neutron yield.

The first condition optimizes the therapeutic effect, since an initial low energy distribution results, after moderation, in a narrow epithermal neutron beam and in a small contamination of high energy neutrons. The second condition minimizes the size and the cost of the accelerator. This is usually not in contradiction with the first condition, since a lower incident energy often implies a lower energy of emitted neutrons. On the contrary, the third requirement, connected to the limitations in the proton or deuteron beam currents that can be

accelerated, usually implies higher incident energy. Although priority should be given to the optimization of the dose deposition, a compromise between the different needs must be searched. To this aim, it is important to rely on the accurate knowledge of the energy spectrum and yield of neutrons emitted in the reactions. Furthermore, extensive simulations of the needed moderation process have to be performed before drawing any conclusion on the optimal reaction, and economic considerations should also be taken into account in the choice of the right solution for the accelerator.

A collaboration between the INFN group "Solone" and the Nuclear Science and Accelerator and Fusion Research Divisions of LBNL has recently undertaken a systematic study of potentially interesting neutron producing reactions. The experiments are performed at the 88" cyclotron of LBNL with low-energy proton and deuteron beams. Neutrons of energy as low as 100 KeV are detected by means of 5 cylindrical liquid scintillator cells 5" in diameter and 2" thickness [4], placed at various angles around a thin-wall aluminum scattering chamber. Neutron yield and energy spectra have been measured for (p,n) and (d,n) reactions characterized by a positive or slightly negative Q-values, and for incident energies of 1.5 and 2.5 MeV for deuteron and proton beams respectively. The characteristics of some of the investigated reactions are reported in Table 1.

Table 1: Nuclear reactions of potential interest for BNCT

Reaction	$E_{p,d}$ (MeV)	Q-value (MeV)	Tot. Yield (n/• C)	E_n (MeV)	Y(E_n>1 MeV) (%)
$^{7}Li(p,n)^{7}Be$	2.5	-1.64	$9.8x10^{8}$	0.6	0
$^{9}Be(p,n)^{9}B$	2.5	-1.85	$3.9x10^{7}$	0.4	0
$^{9}Be(d,n)^{10}B$	1.5	4.36	$7.6x10^{7}$	0.45	40
$^{12}C(d,n)^{13}N$	1.5	-0.28	$3.2x10^{7}$	0.55	0
$^{13}C(d,n)^{14}N$	1.5	5.33	$2.1x10^{8}$	0.7	30

The $^{7}Li(p,n)^{7}Be$ reaction is characterized by a very high neutron yield even for proton energies slightly above the reaction threshold, due to a strong resonance at 2.3 MeV. Extensive simulations of the moderation process [5] show that the optimal proton energy for this reactions may lay in the range 2.3-2.5 MeV. In this region the peak of the neutron energy spectrum is low (E_n<700 KeV), whereas for higher proton energies the gain in the yield is offset by the necessity of a heavier moderation process which lowers the quality of the epithermal neutron beam. Important projects of accelerator-based BNCT facilities are based on the $^{7}Li(p,n)^{7}Be$ reaction at 2.5 MeV, in particular the BNCT project at LBNL [6]. Proton beam current requirements are in the range 1-20 mA, depending on the choice of the moderator, the optimization of the reflector and the beam quality requirements. Although very convenient in terms of neutron energy spectrum and yield, the $^{7}Li(p,n)^{7}Be$ reaction presents some drawbacks. The low melting point of the Li target (170 °C) requires a target cooling system capable of dissipating several kW of power. Moreover, the abundant production of ^{7}Be (lifetime of about 50 days) requires safety systems for the accelerator and appropriate arrangements for the targets disposal.

On the contrary, the $^{9}Be(p,n)^{9}B$ reaction does not produce radioactive residues and, most importantly, does not require an efficient cooling system, due to the high melting point of the Be target. However, the neutron yield in this reaction becomes interesting for BNCT applications only for proton energies larger than 3 MeV, with an optimal energy in the range

3-4 MeV. The $^{9}Be(p,n)^{9}B$ reaction at 4 MeV is the primary choice in the MIT project [8,12], with needed beam currents of the order of few mA. The disadvantages of the $^{9}Be(p,n)^{9}B$ reaction are associated with the larger dimensions, and consequently higher costs, of the accelerator and, especially, with the neutron energy spectrum which, above E_p=3 MeV, is contaminated by a high energy component (>1 MeV).
The $9Be(d,n)^{10}B$ at E_d=1.5 MeV, recently proposed as an intense source of low energy neutrons [7], is characterized by an abundant production of 400 KeV neutrons, but a 40 % contamination of 3.6 MeV neutrons makes this reaction inadequate for use in BNCT. A detailed analysis of other reactions is forthcoming [9]. Many of them are characterized either by a low yield, or by a sizeable contamination of high energy neutrons. One reaction, however, deserves attention because of the high yield and the relatively small contamination of high-energy neutrons: the $^{13}C(d,n)^{14}N$ at E_d=1.5 MeV. Despite of the low energy of the deuteron beam, the total neutron yield is large (only a factor of 5 smaller than the 2.5 MeV Li(p,n) reaction). Moreover, the main peak in the neutron energy is around 700 KeV, similar to the Li(p,n) reaction, and the contamination is concentrated at neutron energies slightly above 1 MeV. Other advantages that make this reaction potentially interesting for BNCT are the low energy of the deuteron beam (< 2 MeV), the high melting point of the C target (4000 °C) and, finally, the stable reaction residue which does not present problems of radioactive target disposal. Extensive simulations of the moderation process for this reaction are now being performed. It seems likely to obtain good quality epithermal neutron beams with deuteron currents between 50 and 100 mA, which is within the reach of the available accelerator technology. Further measurements, however, are needed to confirm these results, and to optimize the choice of deuteron energy and of the moderator for this reaction.

4. ACCELERATORS FOR BNCT

The main feature required to an accelerator for BNCT is the high intensity of the proton or deuteron beam. Because of the low incident energy, in fact, it is necessary to accelerate beam currents of the order of milliamperes or, in some cases, of tens of milliampers. On the other hand, the low energy requirement for the primary beam constitutes an advantage in terms of complexity, size, maintenance and costs of the accelerator. Different kinds of accelerators are being developed which should be capable of delivering proton or deuteron beams of the necessary intensity. A list of their main features is reported in Table 2.

Table 2: Accelerators for BNCT

Accelerator	Energy (MeV)	Beam Current (mA)	Length (overall) (m)	Ref.
ESQ	2.5	100	1.7 (3)	[11]
Tandem	4.1	5	3.1 (4.3)	[12]
RFQ (ANL)	3	100	4 (5)	[15]

The Electrostatic Quadrupole (ESQ) accelerator consists of a series of accelerating electrodes which, by suitably designed shape and polarity, also exert a strong focusing effect. The main feature is that high beam currents can be accelerated without the need of large gradients between the electrodes. In principle, this type of accelerator is simple and reliable. Some particular engineering solutions of the electrode insulation and cooling, together with new compact power supplies, may allow to build high-current ESQ accelerators of the size of a desk.Various prototypes of ESQs have already been built and tested, and proton or deuteron

beams of currents as high as 100 mA have been successfully produced [10]. Although originally proposed for other purposes (namely as injectors for tokamac fusion reactors), ESQs coupled with a target system may represent a compact and rather inexpensive low-energy neutron source, easy to install and operate. A full scale ESQ accelerator for BNCT applications is currently under construction at LBNL [6]. The accelerator is expected to deliver up to 60 mA of protons at a maximum energy of 3 MeV. The use of the ^{7}Li(p,n) reaction will allow to produce an epithermal neutron beam of higher quality and comparable intensity relative to the currently available beam at the Brookhaven Medical Research Reactor, with estimated treatment time less than an hour. The accelerator is planned to deliver the first proton beams in 1999.

The Tandem accelerator is a more conventional type of low-energy electrostatic accelerator, consisting of a uniform-gradient accelerating tube, with a positive high-voltage terminal in the middle. Negative ions are produced in the source and accelerated towards the center where, going to a stripper foil, they become positive and can be accelerated away from the center. Some limitations in the beam currents, inherent in conventional designs and mainly connected to mechanically-charged high voltage generators, have been overcome by using an appropriate source and a high current solid-state power supply. As an example, Newton Scientific Inc. (NSI) has designed a tandem Accelerator capable of producing proton or deuteron beams of 4.1 MeV and currents up to 4 mA. The accelerator, installed at the MIT Nuclear Engineering Department, will be used to produce epithermal neutrons through the ^{9}Be(p,n)^{9}B reaction at 4 MeV [12,13]. The accelerator is now being tested for use in BNCT and in BNCS (Boron Neutron Capture Synovectomy), an application of neutron boron capture for the treatment of rheumatoid arthritis. The drawback of this solution is that it is unlikely that the Tandem technology will easily allow to produce beam currents larger than 10 mA. Moreover, the costs associated with the constructions and operation (stripper foils, insulating gas, etc...) seem not to make this type of accelerator very suitable for a widespread use as a neutron source in BNCT.

The Radiofrequency Quadrupole (RFQ) accelerator is based on the property of mechanically modulated quadrupole electrodes to simultaneously accelerate and focus particle beams with the radiofrequency fields. Because of the strong focusing produced by the electrode structure, RFQs are very attractive as high-current accelerators, and for this reason they are used as injectors for particle and heavy-ion accelerators in research and in industrial applications [14]. Several considerations enter in the determination of the accelerator parameters, in particular the radio-frequency and the electrode voltage. While RFQs operated with high frequencies (~2 GHz) are very compact, the use of lower frequencies gives stronger focusing, less difficulties in the electrode mechanical tolerances and, in general, allows higher current limits. Furthermore, a low frequency RFQ can have substantially lower costs since it does not require the use of klystron as radiofrequency generator.

An RFQ accelerator for BNCT applications has been designed at the Argonne National Laboratory [15] and its features are reported in Table 2. In the project, the accelerator is expected to deliver up to 100 mA of proton or deuteron beams at energies up to 3 MeV, and can therefore be used in conjunction with either the Li(p,n) or the Be(p,n) reaction to produce intense epithermal neutron beams.

The Solone group is currently examining the possibility of a similar solution for an accelerator-based BNCT facility. Preliminary calculations indicate that it should be possible to accelerate deuteron beams of around 100 mA of current at 2 MeV with an RFQ accelerator operated at 120 MHz. Combined with the ^{13}C(d,n) reaction, this accelerator could produce a neutron beam of intensity and quality comparable to other existing or proposed projects.

Furthermore, the low energy of the deuteron beam and the use of a low frequency would keep the size and costs of the accelerator to a reasonably low level. More accurate information on the reaction and more detailed calculations are needed before concluding on the feasibility of this solution.

5. CONCLUSIONS

Clinically-useful levels of intensity and spectral purity of the epithermal neutron beams appear to be quite feasible using variuos types of accelerator-based neutron sources. However, the choice of the optimal solution has still to be investigated; this is the task for the near future.

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NEUTRON BEAMS FOR THE BNCT AT LNL PERSPECTIVES

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To produce the required fluxes of thermal/epithermal neutron for the BNCT application, with an accelerator-based source, is a formidable task commonly understood to require several tens of mA of 2.5 to 5 MeV protons on a lithium or beryllium target that can withstand the bombardment. In the frame work of the next five-years plan of INFN, the Laboratori Nazionali di Legnaro (LNL) have been proposed the construction of a facility for the production of radioactive beams (RIBs) based on an high-intensity proton accelerator. Besides the RIBs production, a neutron beam for the BNCT applications is also planned.

1. INTRODUCTION

The international community is showing growing interest in high intensity linacs for scientific, industrial and social applications. Proton linacs with final energies of about 1 GeV and CW operation are proposed for secondary beams production, tritium production, nuclear waste transmutation or energy production in sub-critical accelerator driven reactors. The beam intensities vary for different proposed application and are ranging from 10 to 100 mA.
In the frame work of the Italian participation to the project of a high intensity proton facility for the energy amplifier and nuclear waste transmutations, LNL is involving in the design and construction of prototypes of the injection system of the 1GeV linac that consists of a RFQ (5 MeV, 30 mA) followed by a 100 MeV linac. This program has been already financially supported and the work is actually in progress.
In this context, the LNL has been proposed a project for the construction of a second generation facility for the production of radioactive ion beams (RIBs) by using the ISOL method. The final goal consists in the production of neutron rich RIBs with masses ranging from 80 to 150 by using primary beams of protons, deuterons and light ions with energy of 100 MeV and 100 kW power (see Fig. 1). This project is proposed to be developed in about 10 years from now and intermediate milestones and experiments are foreseen and under consideration for the next INFN five year plan (1999 - 2003). In such period of time is proposed the construction of a proton accelerator of 10 MeV energy and 30 mA current, consisting of a RFQ (5 MeV, 30 mA) and a linac (10 MeV, 30 mA), and of a neutron area dedicated to the RIBs production and to the neutron physics. The RFQ it will be of the same type of that designed for the high intensity project mentioned above. An intense R&D program on high intensity accelerator techniques and targetry is already in progress.

2. THE ACCELERATOR

The sequence RFQ-DTL (Drift Tube Linac) is, by far, the most used scheme for proton linacs in the energy range of 10 - 100 MeV. In our design both DTL and RFQ operates at the main linac frequency of 352 Mhz; in this way we avoid any frequency jump, and the bore hole

inside the DTL structure can be kept large enough to have a good margin between beam dimensions and machine acceptance. The beam design specifications of the proposed accelerator are summarized in Table 1.

Table 1 - Beam specifications

Kind of particle	p	
Output energy	100	MeV
Duty cycle	100	%
Beam current	30	mA
Norm. beam emittance	1	π mm mrad

The RFQ structure is, nowadays, the natural choice for the low energy part of any linear accelerator. It is very efficient up to the energy of few MeV giving a transmission in excess of 90% of the continuos beam coming from the source at energies of few tens of keV.
The acceleration efficiency of the RFQ falls down very rapidly in the range of 1 to 10 MeV and it is mandatory to change structure. As usual we consider a DTL as following accelerating segment and the transition has been put at 5 MeV trading off the RFQ low efficiency at the end of the structure with the higher DTL shunt impedance at its beginnings. The DTL shows a good efficiency up to hundreds of MeV. In Table 2 the main linac characteristics are summarized.

Table 2 - Main parameters of the linac.

	Unit	RFQ	DTL
Input energy	MeV	0.05	5
Output energy	MeV	5	100
Beam current	mA	30	30
RF frequency	Mhz	352.2	352.2
Total length	m	5.3	80
Transmission	%	94.6	100
RF power diss.	MW	0.6	8.3
Beam loading	MW	0.15	2.8
Quad. diss.	MW	-	0.6

3. THE NEUTRON BEAMS

As explained above, at LNL is planned to have for the year 2003 a neutron area equipped with a proton accelerator of 10 MeV and 30 mA. Besides the activities related to the RIBs production, a neutron beam dedicated to the BNCT application is also foreseen. Moreover, for the BNCT application a lower energy proton accelerator (up to 5 MeV) is sufficient and the RFQ above described is a very suitable accelerator to produce high intensity neutron beams.

The reaction ^{7}Li (p,n)^{7}Be has been proposed as an accelerator-based source of neutrons for the BNCT. This reaction displays a large resonance in the forward direction around 2.3 MeV which extends to about 2.5MeV. The angular distribution of the produced neutrons shows a pronounced peak at zero degree. The neutron yield (per incident proton) between 0^0 and 30^0

is about 4×10^{-3} (n/p) so that, in our case, an intensity of the order of 7×10^{14} (n/s) is expected. These neutrons have to be slowed down in energy, by using a moderator/reflector assembly, by roughly 2 - 4 orders of magnitude for BNCT application since the neutron distribution from the target peaks in the energy range of 400 to 800 keV. In fact, a generally accepted useful neutron energy range for treating deep-seated tumors is 1 eV to 10 keV. After the filtering process in the moderator/reflector assembly a flux of the order of 10^{11} (n/s cm^2) suitable for the BNCT application is expected.

4. CONCLUSIONS

The possibility of disposing of a neutron facility for the BNCT application at LNL within the year 2003 become rather realistic, but still depend upon the decision concerning the next five years plan of INFN. A part such a considerations, in the frame work of the high intensity proton linac project a first prototype (in alluminum) of the RFQ accelerator (5 MeV, 30 mA) has been designed and constructed. The prototype has been recently delivered and actually is under RF measurements in the laboratory. After measurements shall we proceed to the construction of the final RFQ that is planned to be ready in two years. Its features will fulfil completely the requirements for a neutron beam dedicated to the BNCT application.

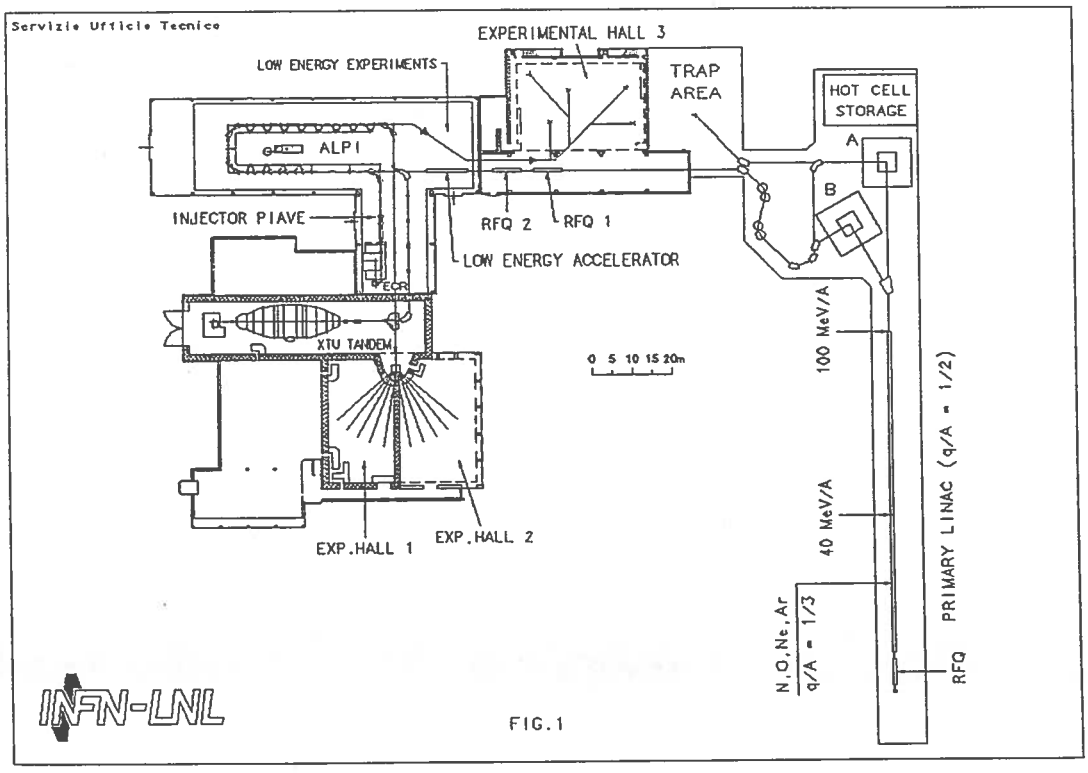

FIG. 1

5. ACKNOWLEDGMENTS

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