Neutrones para la salud en Pavia desde el reactor hasta el acelerador

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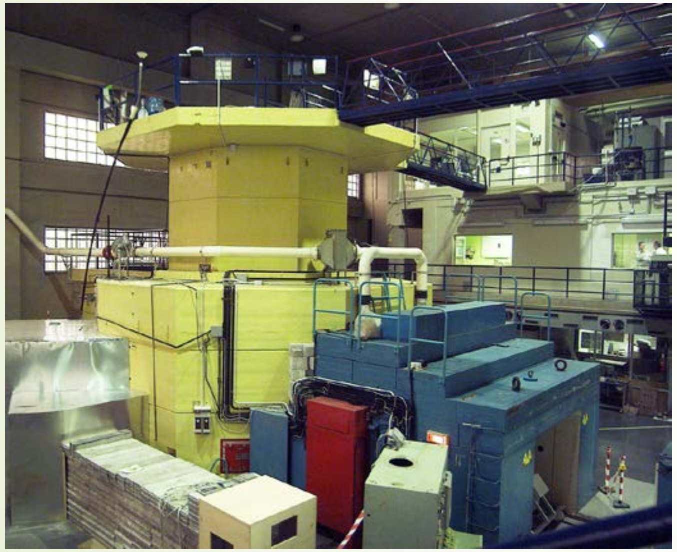
JORNADAS DEL CUIA EN ARGENTINA *9a. Edición*
Terapia por Captura Neutrónica en Boro (BNCT)
Neutrones para la Salud

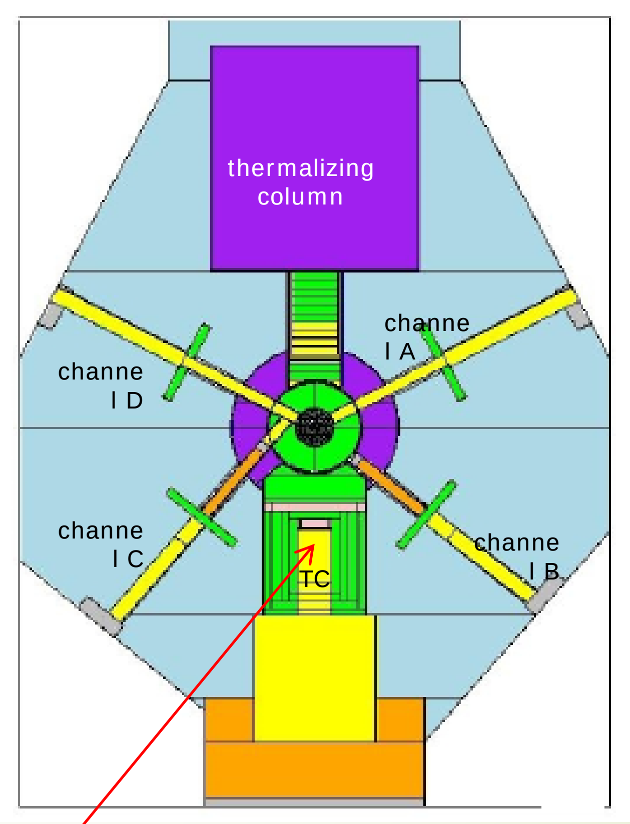
20 de Abril de 2017
Universidad Favaloro
Buenos Aires

24 de Abril de 2017
Universidad Nacional de San Martín
Buenos Aires

BNCT @ TRIGA Mark II reactor



Steady-state power: 250 kW



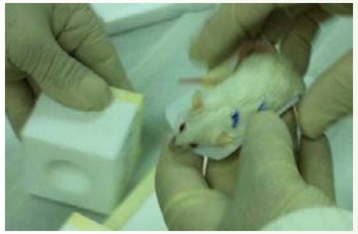
$\varphi \approx 10^{10} - 10^{9}\ cm^{-2}s^{-1}$ thermal neutron field

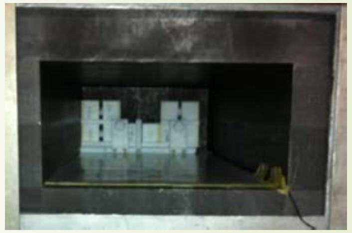
Our research is funded mainly by the National Institute for Nuclear Physics (INFN) and by the Ministry of University and Research (MIUR)

BNCT @ TRIGA Mark II reactor

- Disseminated liver metastases: TAOrMINA project

- Test of toxicity and effectiveness of BNCT by irradiating cell cultures and animal models of rats and mice treated with new boron compounds
  - Disseminated lung metastases
  - Mesothelioma
  - Limb osteosarcoma





- research of new boron carriers: boron up-take measurements in vitro and vivo in animal models
- in vivo boron dose imaging system based on Zinc Cadmium Thelluride

Installation of an accelerator based BNCT system in the Italian Hadron Therapy Center in Pavia

TAOrMINA project

Trattamento Avanzato Organi Mediante Irraggiamento Neutronico e Autotrapianto

Advanced Treatment of Organs by Neutron Irradiation and Auto-graft

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++Dipartimento di Biologia Animale, Università di Pavia e Centro di studio per l'Istochimica, CNR Pavia
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The project was funded by
National Institute for Nuclear Physics (INFN)
since 1988

Collaborators:
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S. Matteo Policlinc of Pavia

The research was leaded by
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D. Cossard, D. Chiaraviglio
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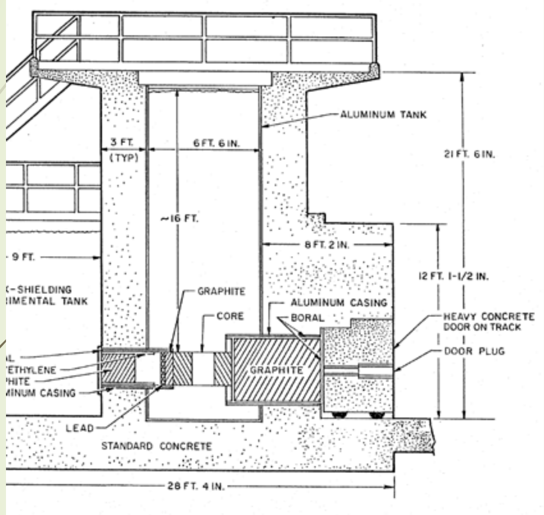
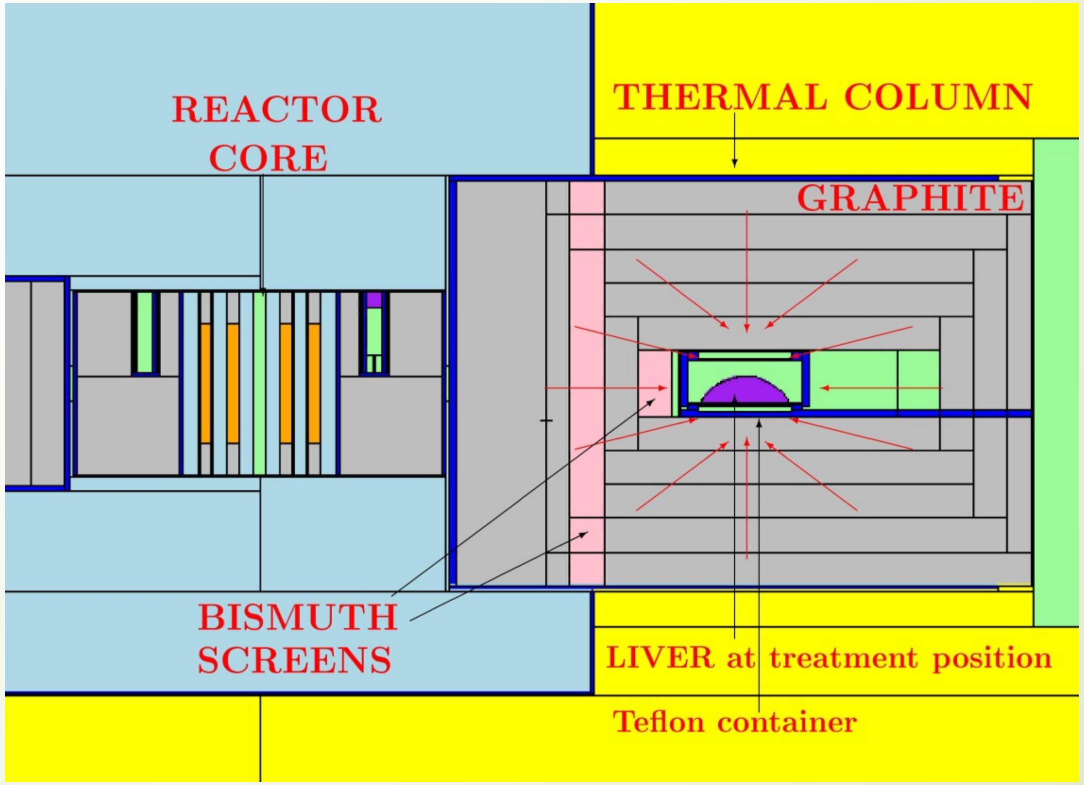
D.M. Ferguson (Mayo Clinic, Rochester, Min. USA)
A. De Bari, S. Manera, A. Venturelli, A. Losi
(LENA, University of Pavia)

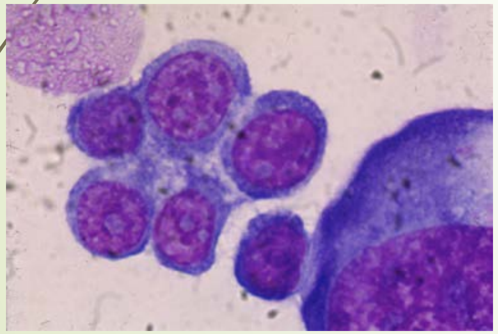
The irradiation facility



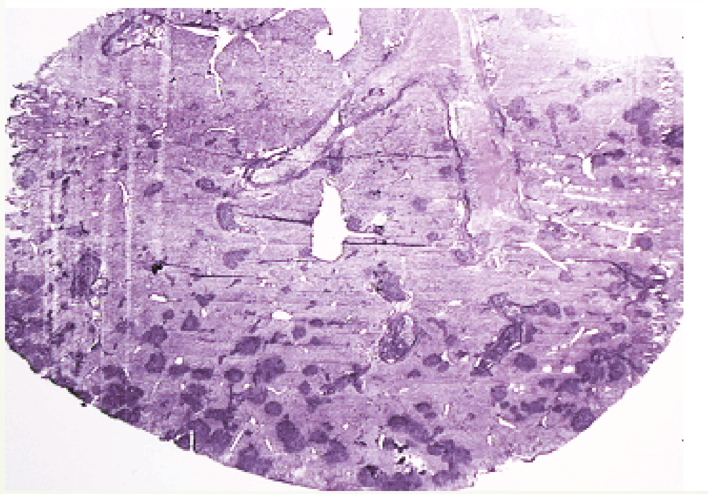


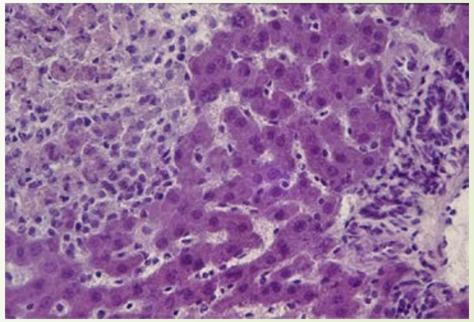
Animal model of liver metastases

- Rats: BD-IX (syngeneic) 250 gr
- Colon carcinoma cell line: DHD/K12/TRb
- Injected cells: 20.10^6
- Site of injection: spleen
- Technical aspects: right portal branch clamping during injection; splenectomy at the end of injection



DHD/K12/TRb cells



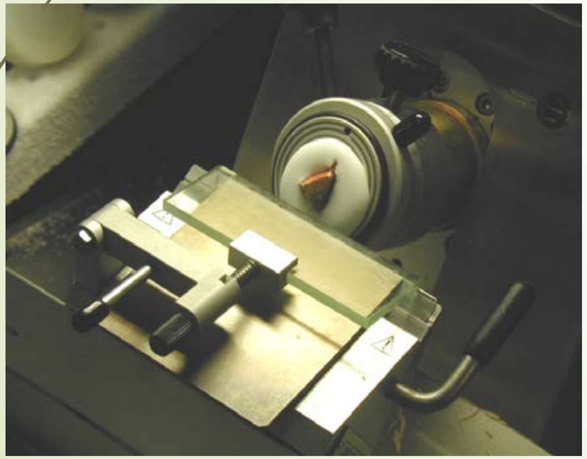


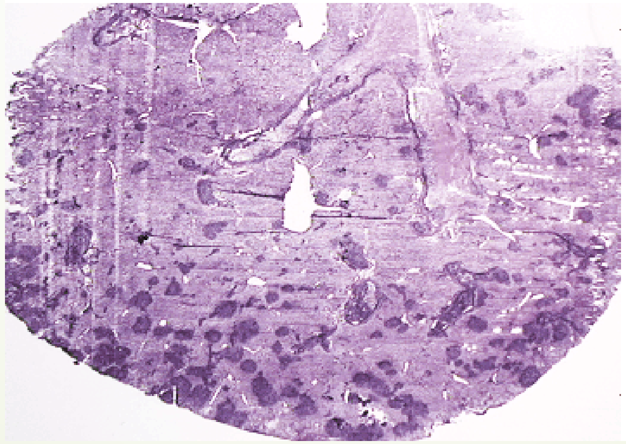
Rat liver with metastases

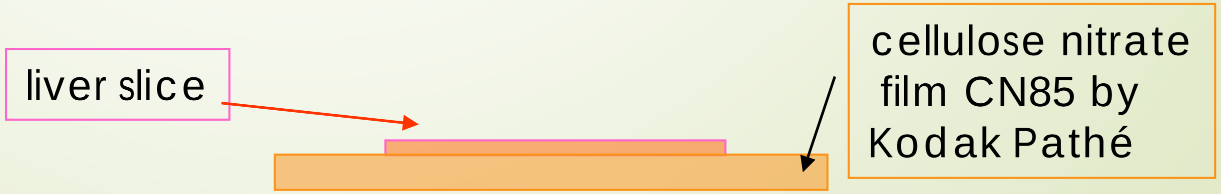
Boron up-take: neutron autoradiography

After BPA administration at a dose of 300 mg/Kg body weight rats were sacrificed at different interval time and liver frozen in the liquid nitrogen

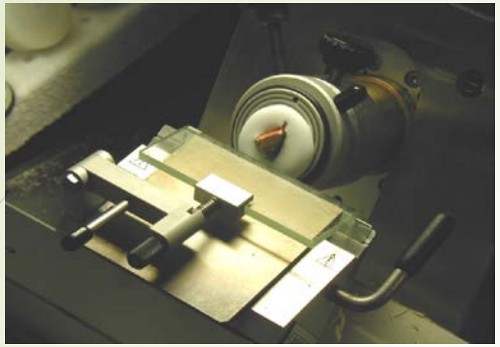
Thin slices of frozen liver were cut using a Leica cryostat at –20°C; one slice, 10 μm thick, was deposited on glass for morphological analysis by standard ematoxilin-eosin stining; the next one (40 μm thick) was put directly on a Cellulose Nitrate film (CN85 by Kodak Pathé) for neutron radiography and the last one on a mylar disk for boron concentration measurement.

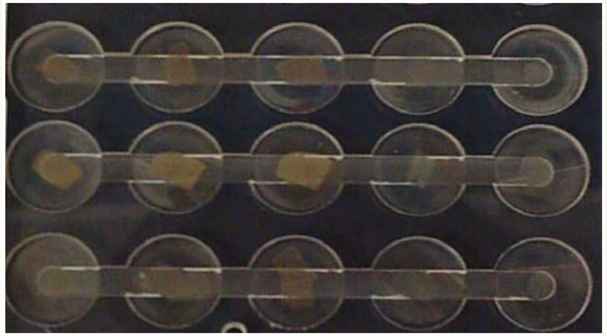


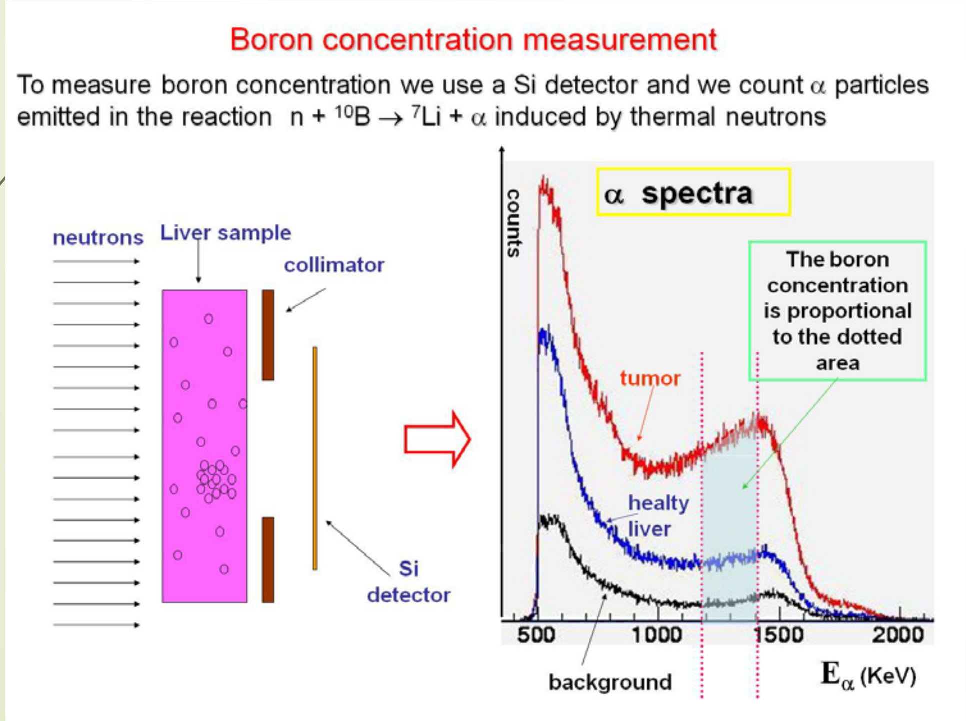


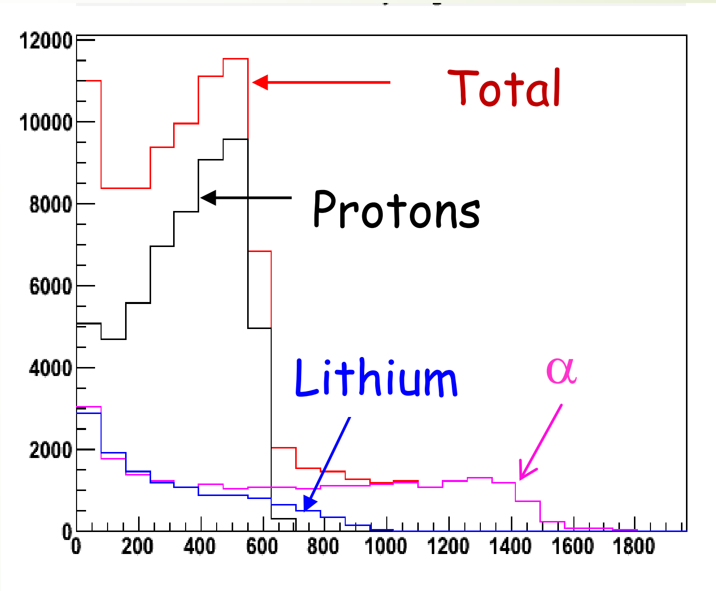


Boron up-take: charged particles spectrometry



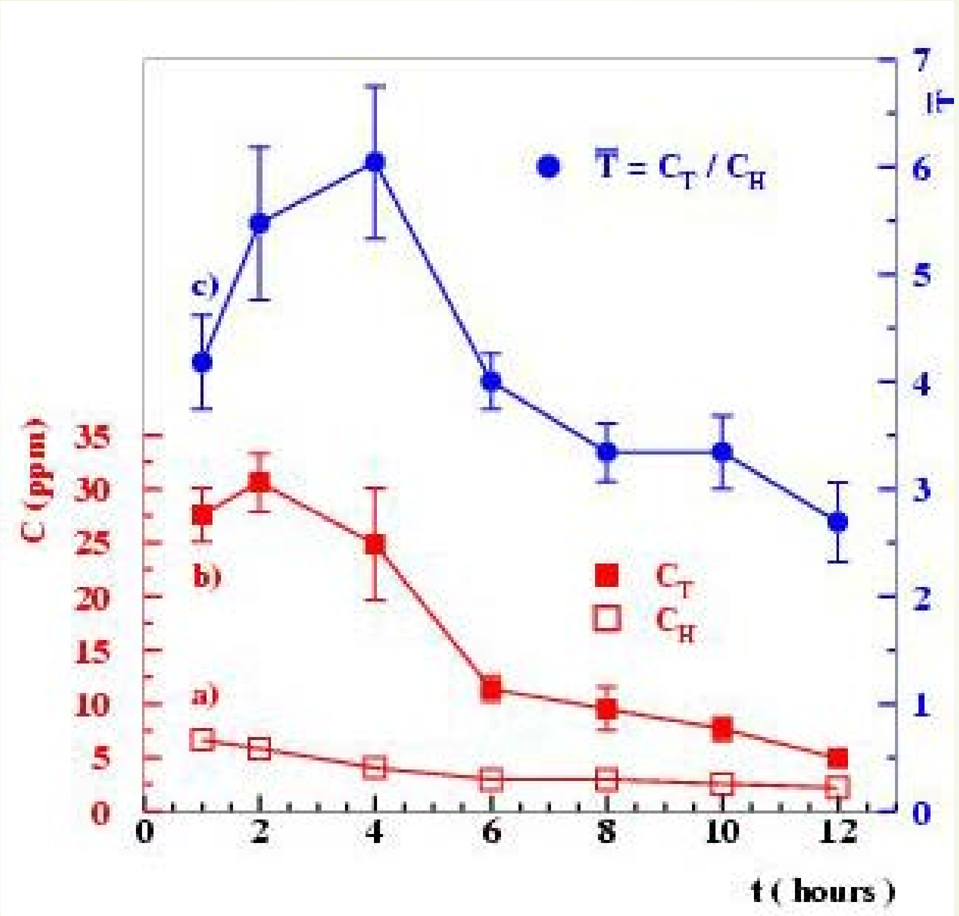






S. Altieri S. Bortolussi Radiat Environ Biophys (2013) 52:493–503

Boron up-take: in the animal model

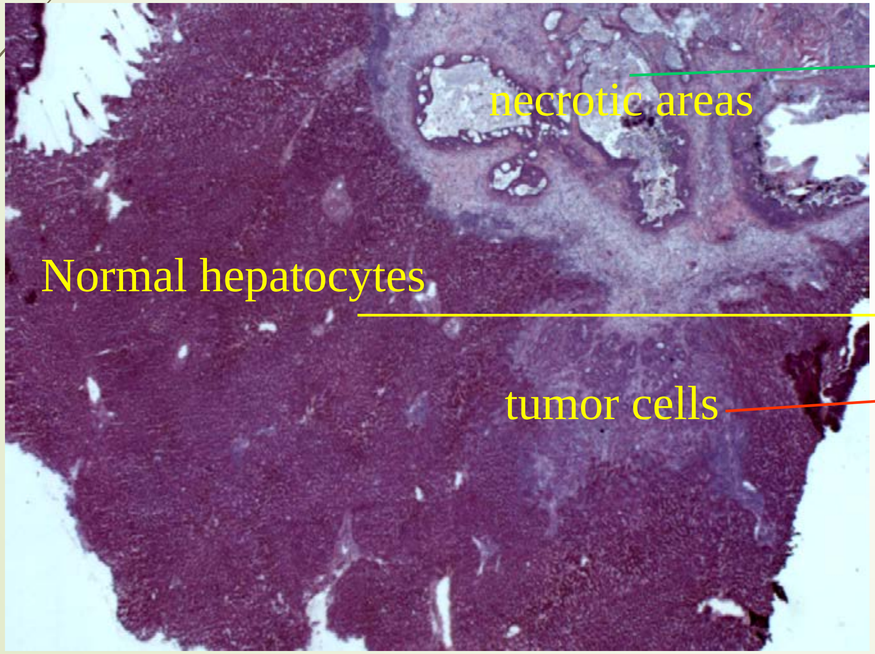


In the time interval from 2 to 4 hours after BPA perfusion the boron concentration in tumour (CT) presents the highest values and the ratio of boron concentration in tumor over normal tissue (T) is at the maximum value of 6

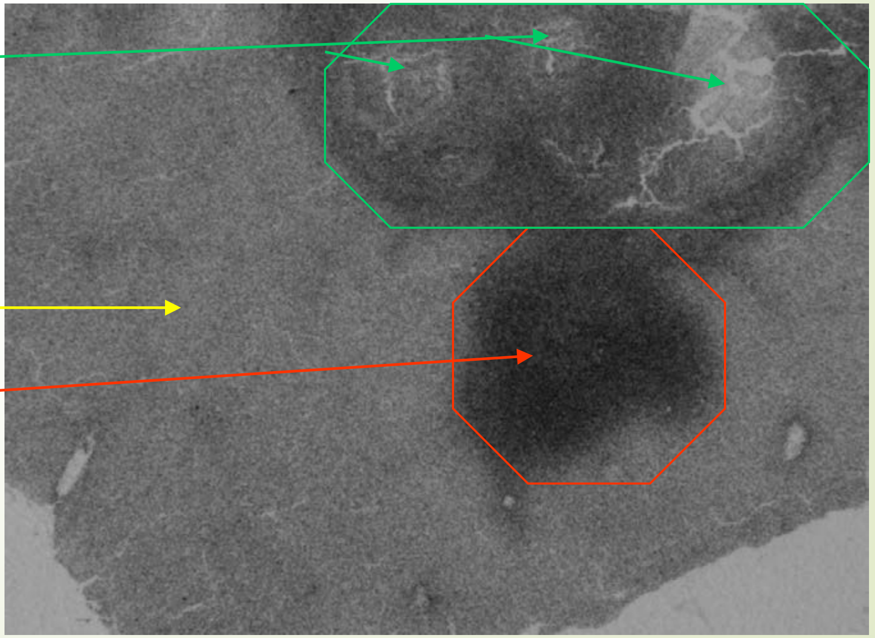
Boron up-take: in patients

BPA was administered at a dose of 300 mg/Kg body weight, during surgery, through a colic vein; the infusion was 2 hours long. To measure Boron concentration some biopsies were taken both from healthy and tumour tissues. Alpha Spectrometry and Neutron Autoradiography showed a selective Boron absorption in metastases (50 ppm in tumours and 8 ppm in liver tissue)

histology



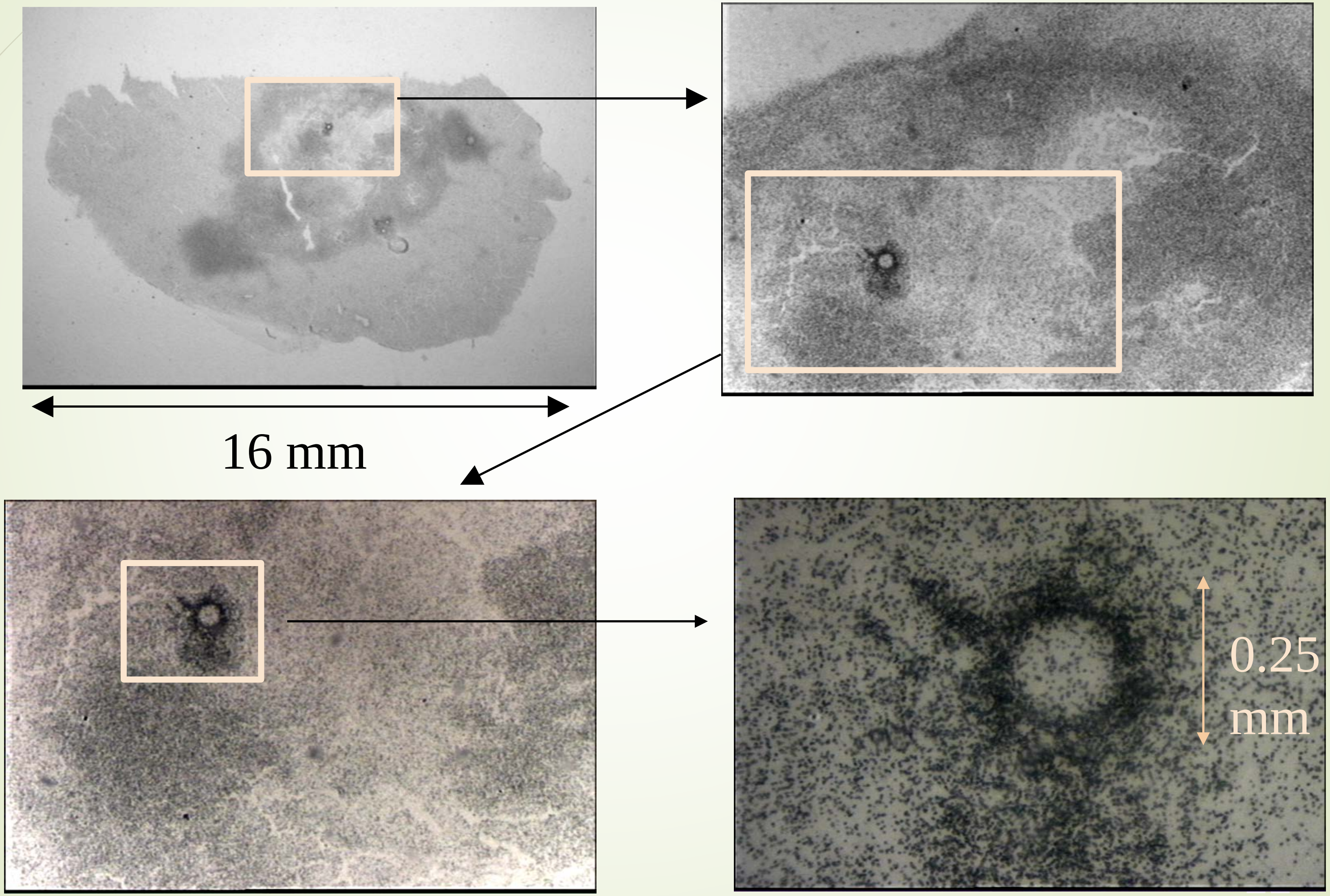
neutron autoradiography



S. Altieri et al. Applied Radiation and Isotopes 66 (2008) 1850– 1855

Boron up-take: in patients

Boron absroption in a very little metastasis

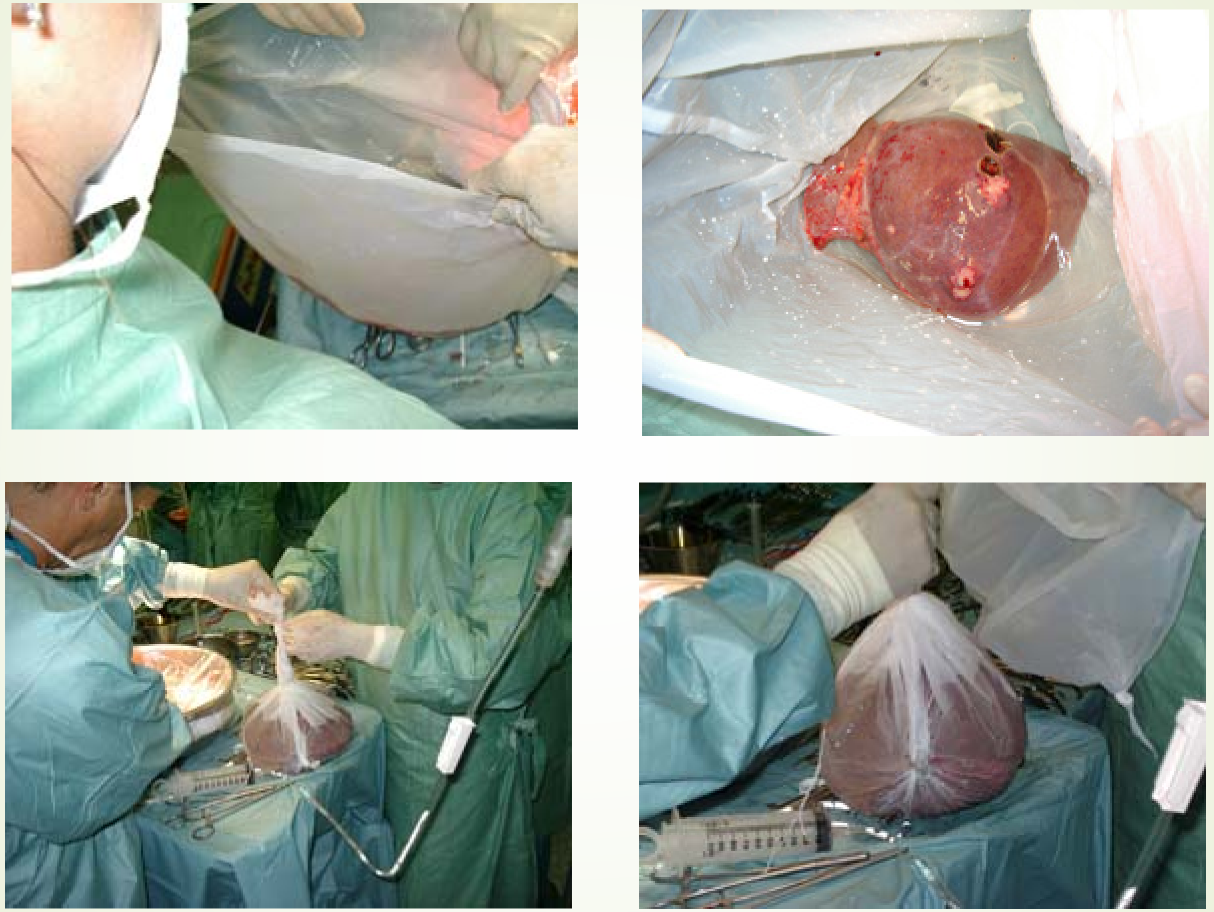


Liver explantation

Liver-out

Washing and Refrigeration

Teflon bag



Teflon container

At the reactor

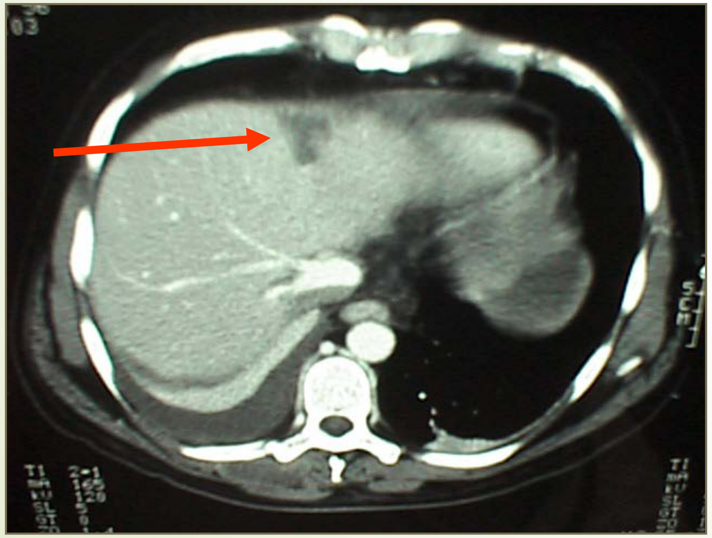
Pushing the liver into the reactor

Pushing the liver into the reactor

Liver back to the surgery room

The outcome of the treatment

7 days after treatment the CT scanning evidenced the liver in normal condition while the metastases appeared in a necrotic state



Arrows indicate the necrotic zones detected after BNCT

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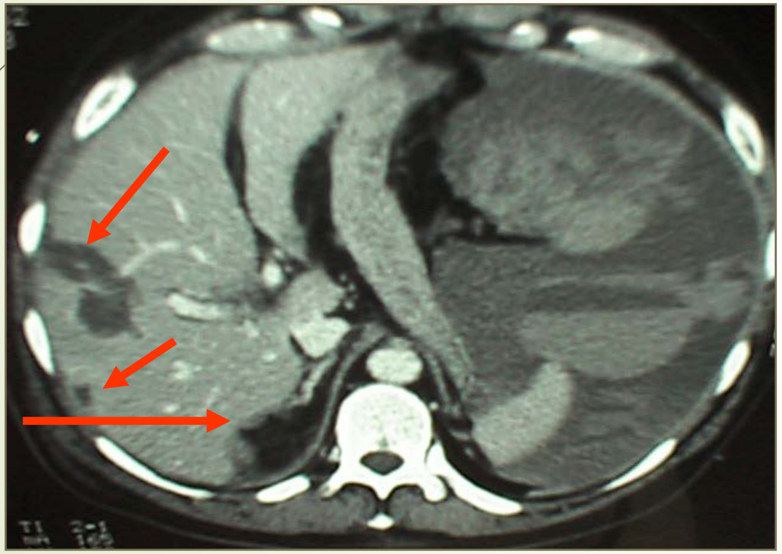

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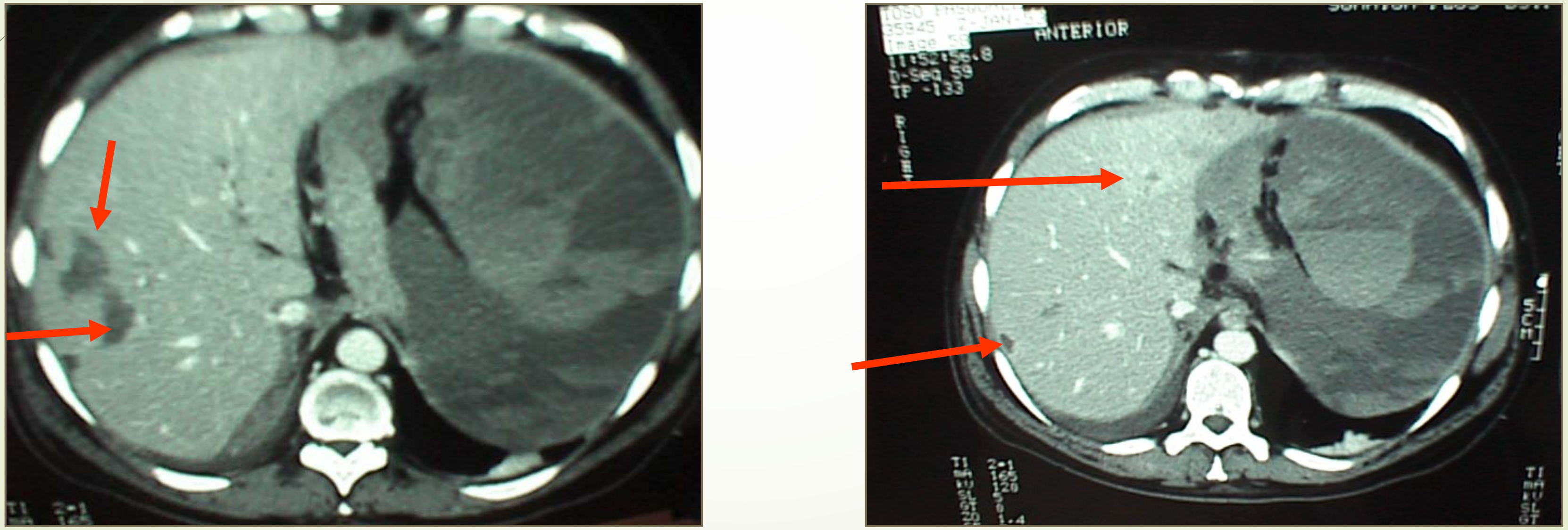
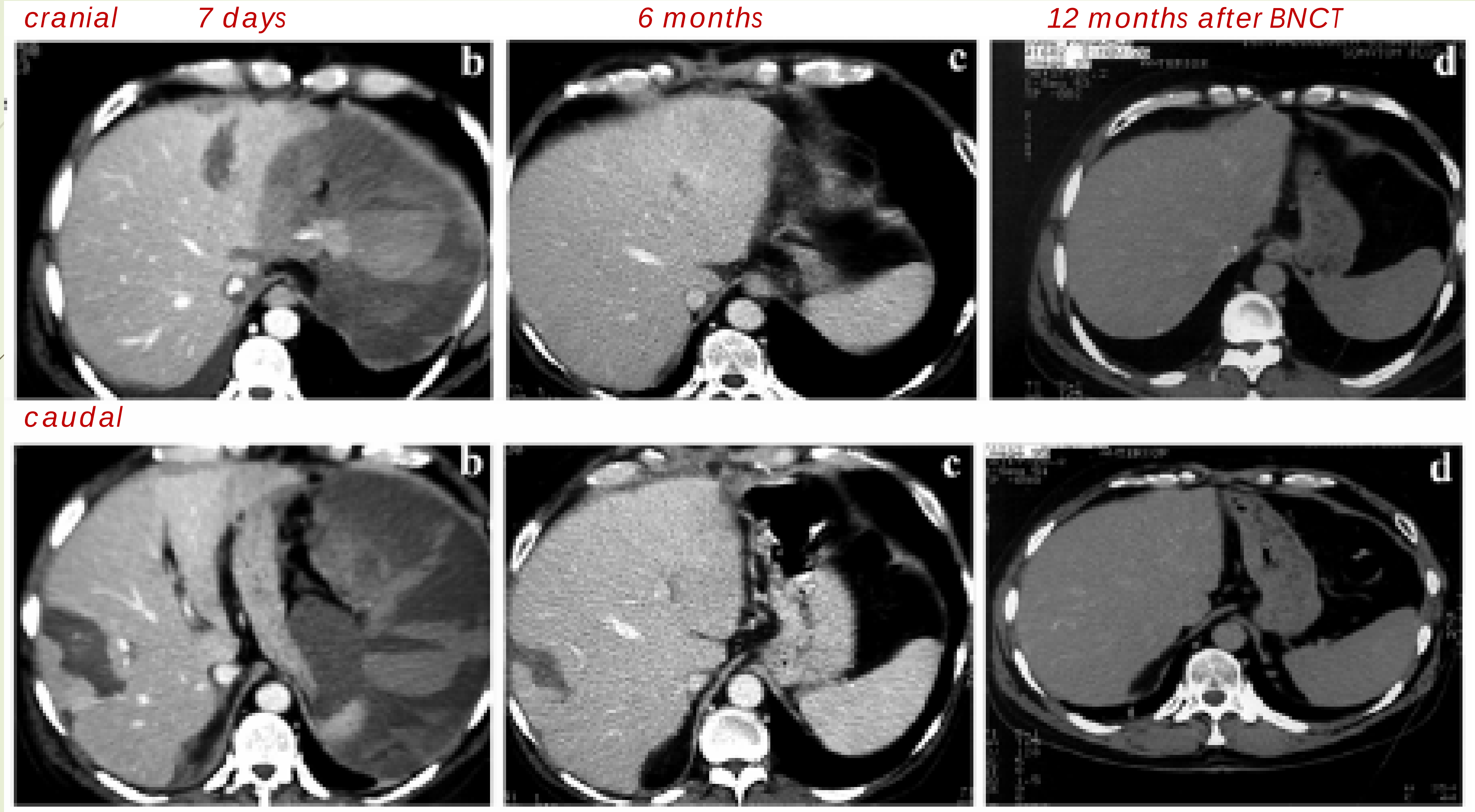


Arrows indicate the necrotic zones detected after BNCT

The outcome of the treatment



Sequence of CT images of liver in the first patient after BNCT; evolution at different times of the metastases towards necrosis with final substitution by normal tissues

The outcome of the treatment

The first patient (TP) was a male, 48 years old, with 14 syncronous metastases of a colon carcinoma operated 7 months before.

All clinical anomalies and biochemical alterations disappeared within some weeks and the patient was discharged in the 40th p.o.day.

Before leaving the Polyclinic he recovered all of his functions and his general condition was good.

On Top of the reactor after BNCT

Befor BNCT he was a therminally hill patient with a few months of live expectancy

After BNCT he survived 44 months with a good quality of life

He died because of diffuse recurrences of his intestinal tumour

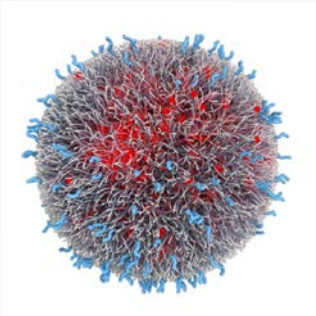
BNCT after Taormina project

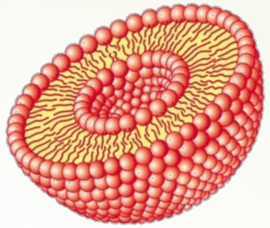
Now we are working on other kind of tumours that can be treated by external beams

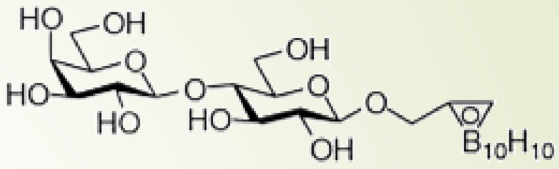
- Animal models:
  - Disseminated lung metastases
  - Mesothelioma
  - Limb osteosarcoma

- Research of new boron carrier: boron up-take measurements in vitro and vivo in animal models
- Test of toxicity and effectiveness of BNCT by irradiating of cell cultures, and animal models of rats and mice treated with new boron compounds

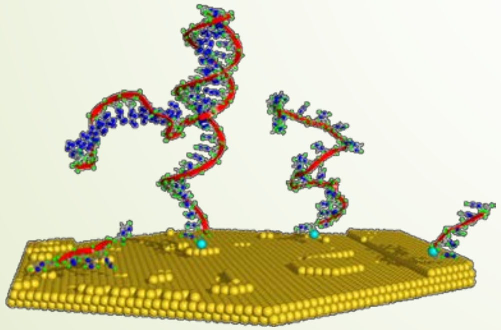
New borated formulations

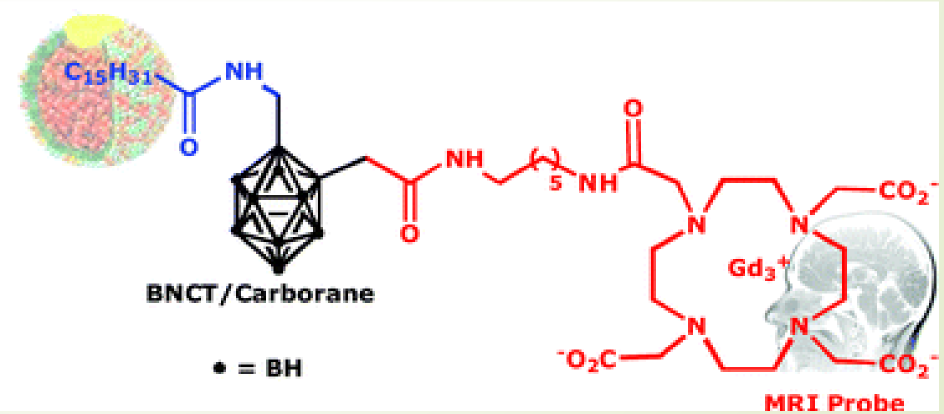






- In vitro test of uptake
- In vitro test of effectiveness (survival curves)
- In vivo test of selectivity (imaging and quantitative measurements)
- In vivo test of effectiveness (small animal irradiation)

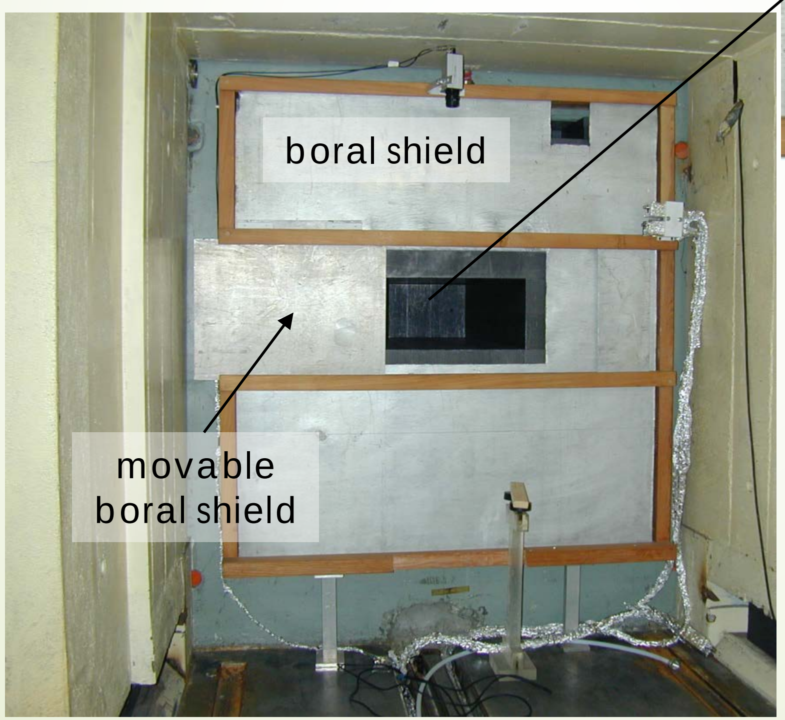


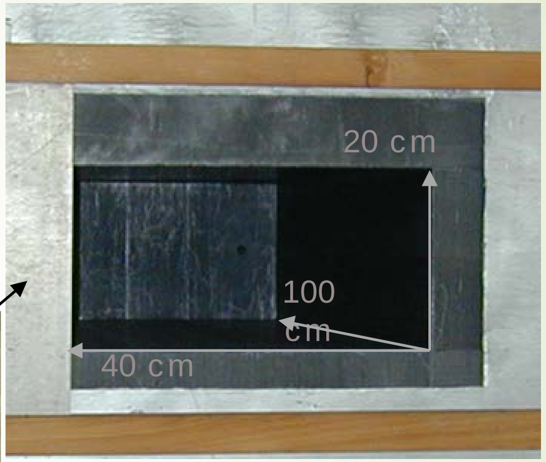


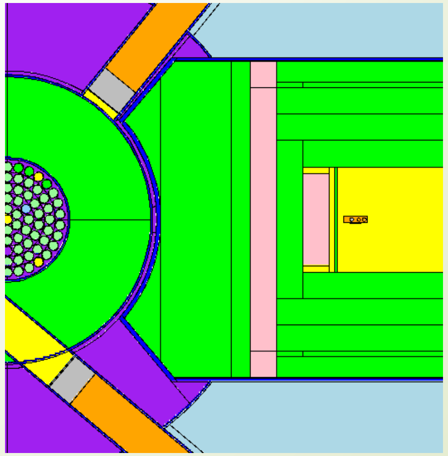
New borated formulations

- *University and INFN of PAVIA: Test in vitro and in vivo with new formulations , boron measurements, cell cultures and animal irradiation (S. Altieri)*
- *University of TORINO: new Boron carrier with Gd –B-LDL for MRI (S. Aime)*
- *University of NOVARA: polimeric nanoparticles and liposomes (L. Panza)*
- *University of FIRENZE: liposomes and nanoparticles functionalized with B (S. Ristori)*
- *Universitiy of POTENZA: boronated porphirines (G. Ricciardi)*

The irradiation position in the thermal column



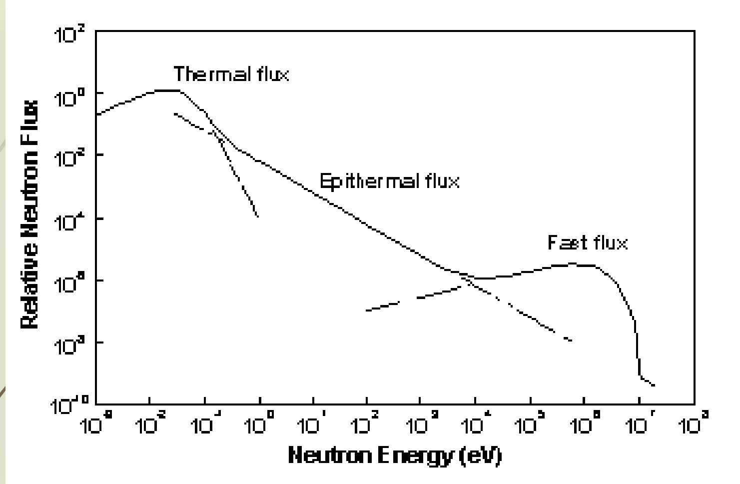




Characterization of the irradiation position: neutron flux

multifoil activation + unfolding algorithm

nuclear reactor broad energy spectrum



Energy range	Detector	Technique
Thermal (< 0.5 eV)	1/v detector	Cd + bare foils
Epithermal (0.5 eV – 10 keV)	Resonance detector	Multifoil set-up
Fast (> 10 keV)	Threshold detector	B + covered foil

$$R = \int_0^\infty \sigma_f(E)\left(\frac{\Psi_f(E)}{\Psi(E)}\right)\Psi(E)\,dE = \int_0^\infty \sigma_f(E)\,P_f(E)\,\Psi(E)\,dE$$

⇨ discrete equation

$$R = \sum_{j=1}^{NG} a_j \phi_j$$

multiprobe set

NG = energy intervals
NF= number of measured reactions (detectors)

$$\begin{bmatrix} a_{11} & a_{12} & a_{13} & \cdots & a_{1\,NG} \\ a_{21} & a_{22} & a_{23} & \cdots & a_{2\,NG} \\ a_{31} & a_{32} & a_{33} & \cdots & a_{3\,NG} \\ \vdots & \vdots & \vdots & & \vdots \\ \vdots & \vdots & \vdots & & \vdots \\ a_{NF1} & a_{NF2} & a_{NF3} & & a_{NF\;NG} \end{bmatrix} \begin{bmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \\ \vdots \\ \phi_{NG} \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ \vdots \\ \vdots \\ R_{NF} \end{bmatrix}$$

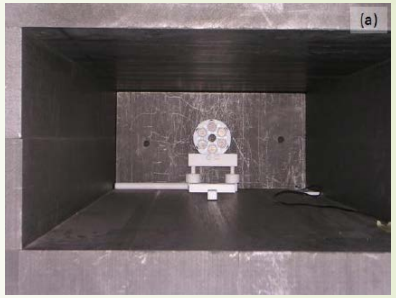
⇨

$$[A][\Phi] = [R]$$

Characterization of the irradiation position: neutron flux

experimental set-up

	probe	energy range of primary responce
bare foils	$^{55}Mn(n,\gamma)^{56}Mn$	thermal
	$^{197}Au(n,\gamma)^{198}Au$	thermal
Cd-cover	$^{115}In(n,\gamma)^{116}In$	1 eV resonance
	$^{197}Au(n,\gamma)^{198}Au$	5 eV res.
	$^{186}W(n,\gamma)^{187}W$	18 eV res.
	$^{55}Mn(n,\gamma)^{56}Mn$	340 eV res.
	$^{63}Cu(n,\gamma)^{64}Cu$	1 keV res.
B-sphere	$^{115}In(n,n')^{115m}In$	> 0.3 MeV

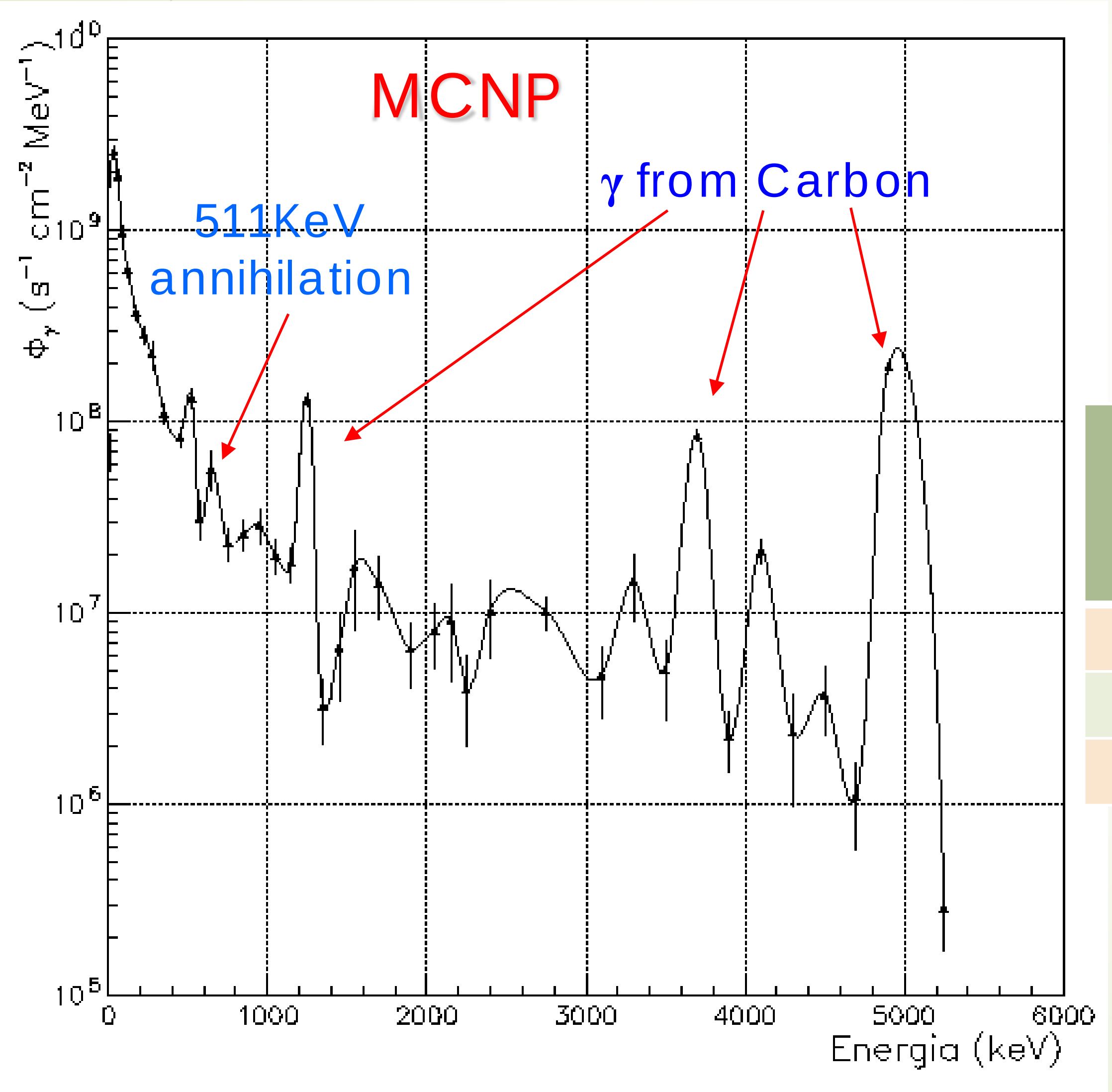


POS 1

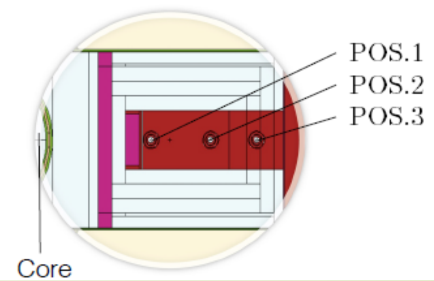
Energy range	Neutron Flux measurements ($cm^{-2}\ s^{-1}$)	Total σ %
< 0.414 eV	1.2E+10	2.5
0.414E eV - 10.7 eV	7.9E+07	3.1
10.7 eV - 1.58 keV	1.2E+08	6.1
1.58 keV – 17.3 MeV	3.7E+07	11.5

Characterization of the irradiation position: gamma dose

in collaboration with University and INFN of Palermo
alanine dosemeters

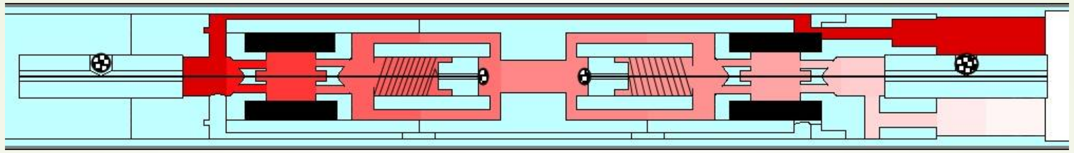


Position in CT	Gamma dose - rate (Gy/h)
1	5.3
2	2.8
3	2.1

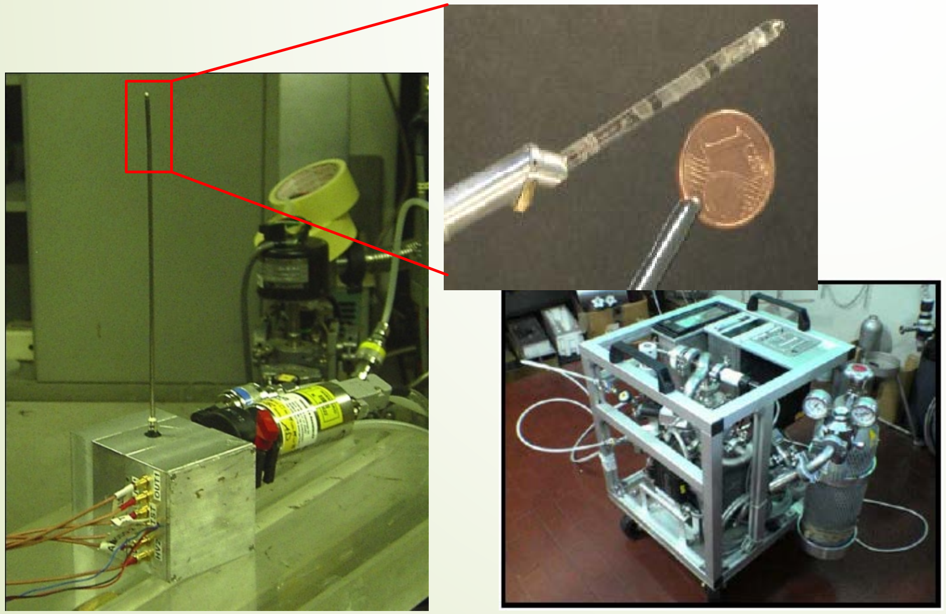


Characterization of the irradiation position: microdosimetry

microdosimetric measurements (mini-TEPC[LNL])



- twin sensitive volumes: 0.6 mm^3; at the atmospheric pressure 1 μm simulated site
- reliable operation in high intens radiotherapy fields (Nice, Catania-LNS, Frascati-LNF)
- cathodes of A-150 plastic and ^{10}B-enriched A-150 plastic (50 ppm)
- TE propane gas



Characterization of the irradiation position: microdosimetry

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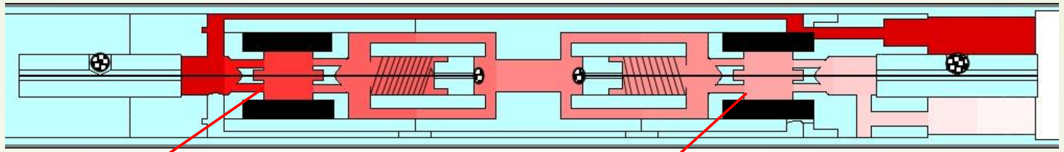
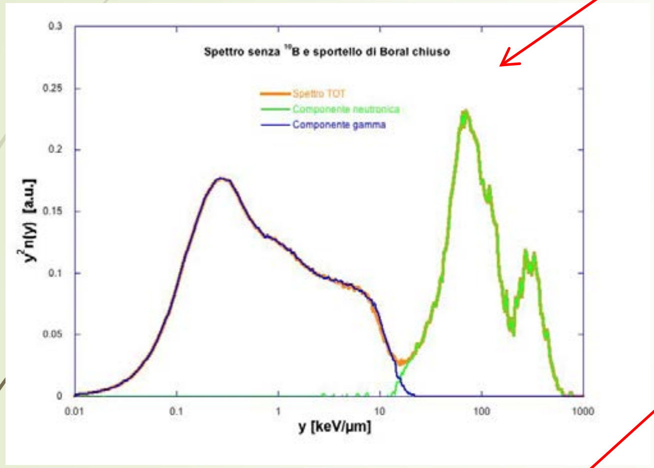
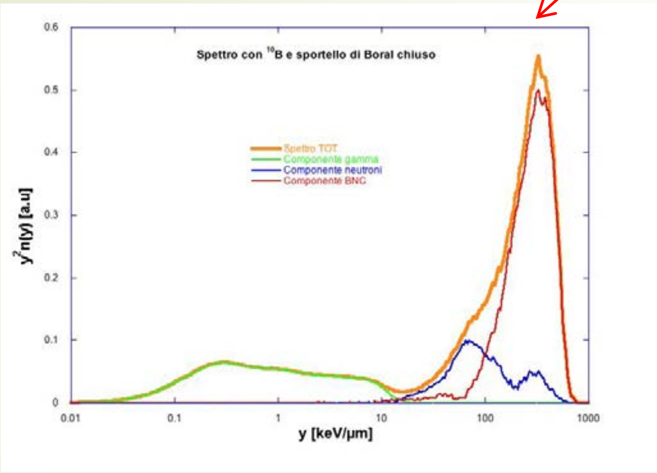
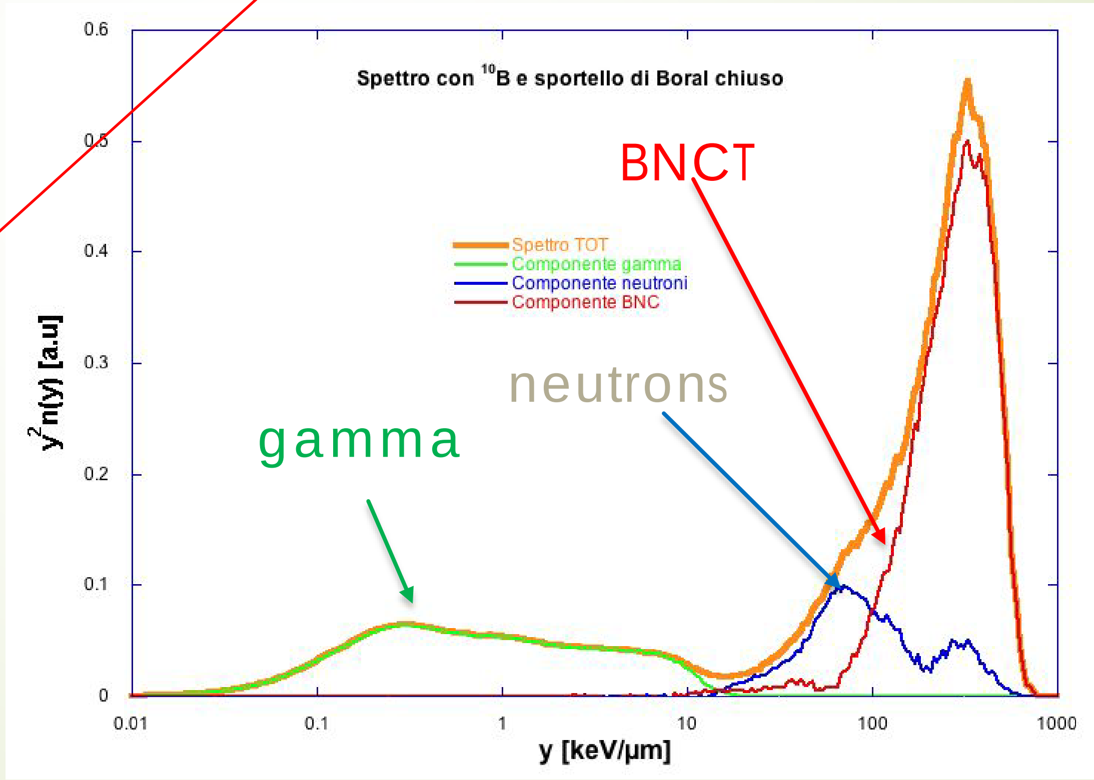




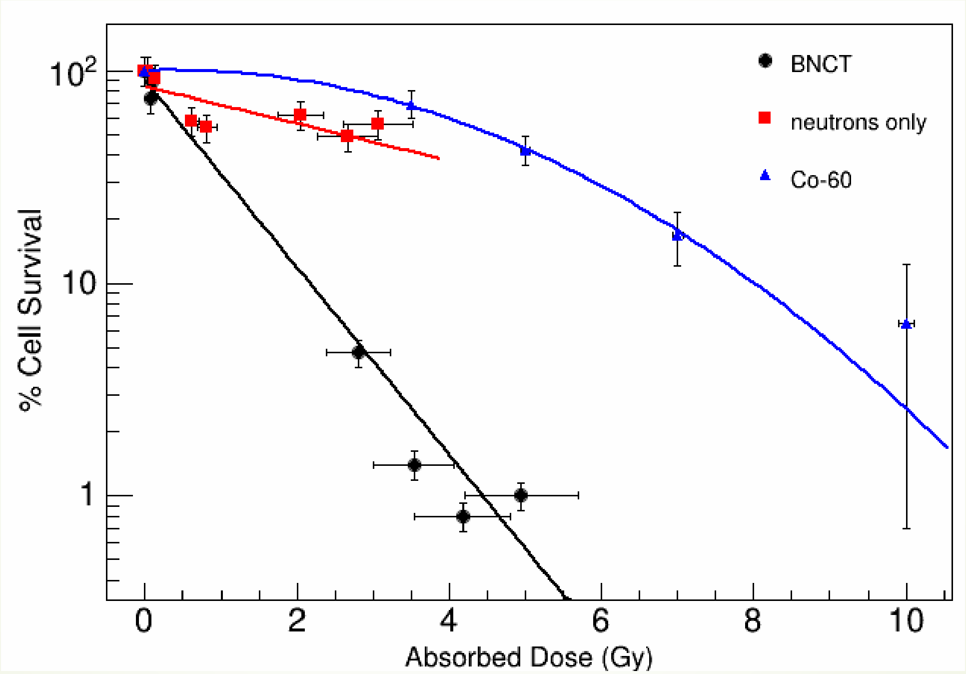


Dose components



Colautti et al., Applied Radiation and Isotope (2013)

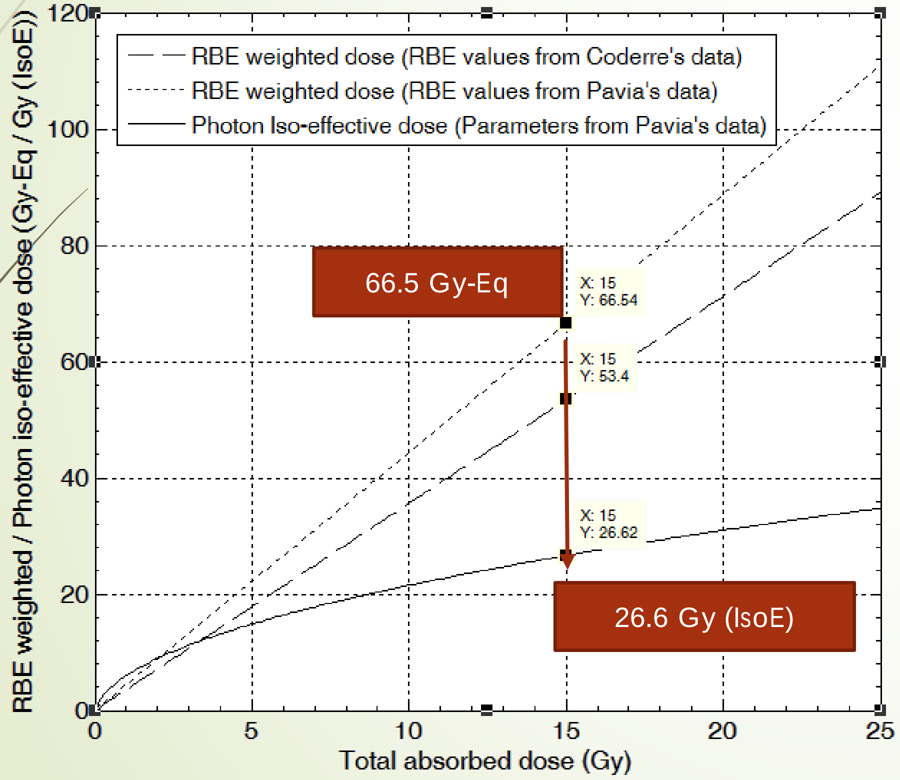
Cell survival studies



Study of BNCT effectiveness on the DHD cell line compared to gamma rays and neutron irradiation without B.

Photon isoeffective dose

- S.Gonzalez and G.Santa Cruz, Rad Res, 178, 2012, 609-621
- Parameters for isoeffective dose model taken from the UMR survival curves



For osteosarcoma, 15 Gy of total absorbed dose correspond to RBE-dose of 66 Gy-Eq (or 53 Gy-Eq with Coderre values) but to 27 Gy (IsoE).

BNCT of Thoracic Tumors

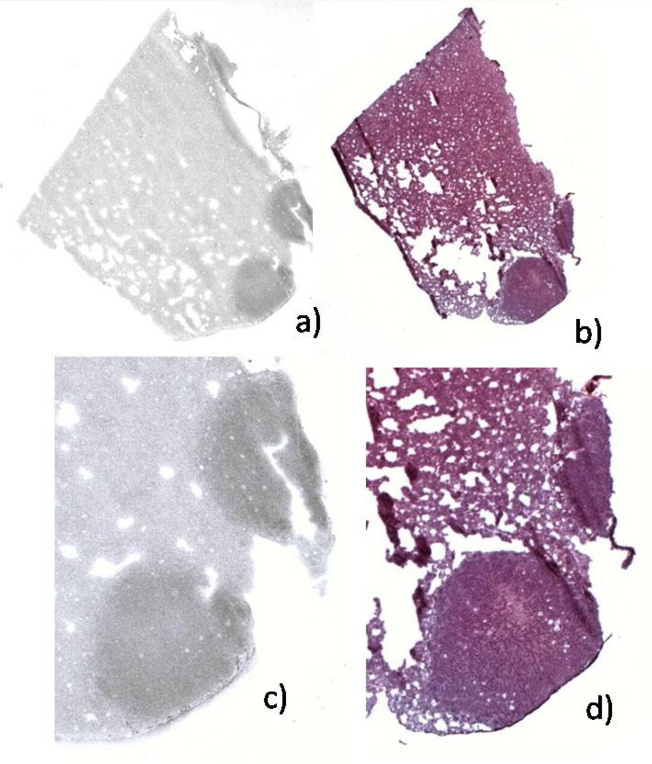
Feasibility of BNCT for diffuse lung tumors:

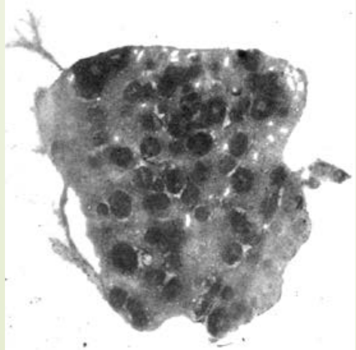
- BPA pharmacokinetics measured on animal models bearing lung metastases
- in vitro and vitro-vivo survival studies
- Test of effectiveness and toxicity of BNCT by irradiation of rats and mice with lung metastases and treated with boron.

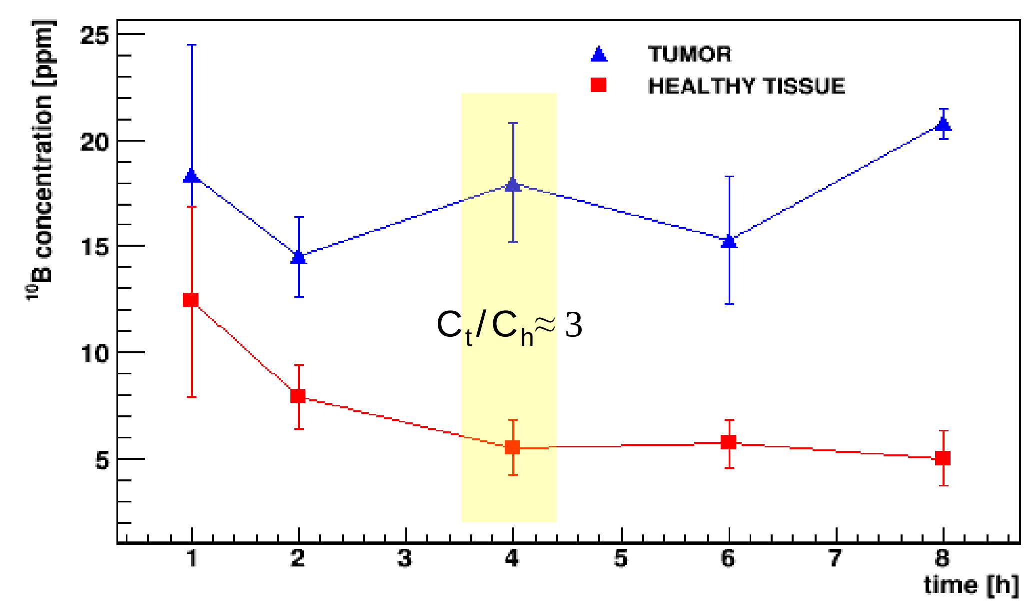
Feasibility of BNCT for mesothelioma:

- in vitro and vitro-vivo studies

Lung metastases in BDIX rats with BPA







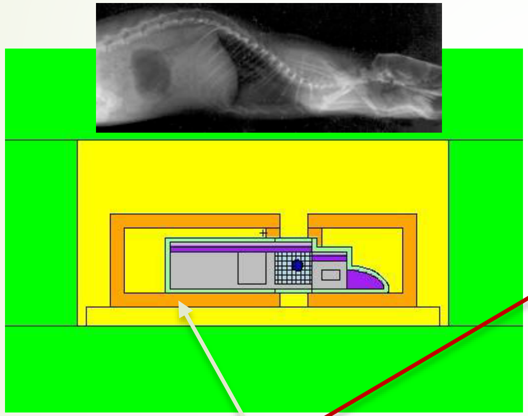
After 300 mg/kg of BPA intra-peritoneal injection there is a selective Boron up-take in this animal model; starting from 4 hours after the infusion a concentration ratio ≈ 3 tumoru/lung is obtained

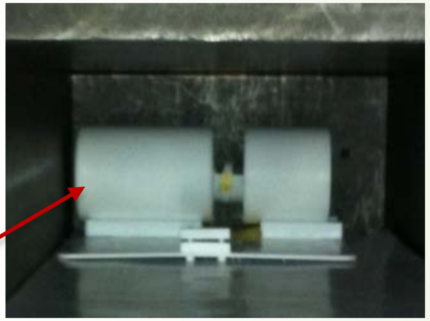
S. Bortolussi et al., Appl. Rad. Isotop. 69 (2011)

Effectiveness of BNCT in rats +BPA

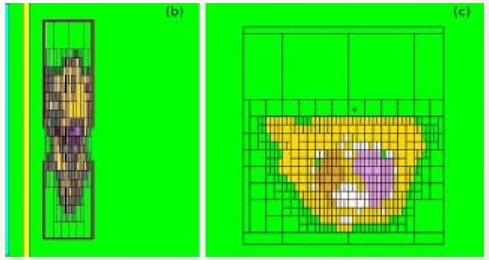
In collaboration with CNEA and INL

Geometrical MCNP rat model





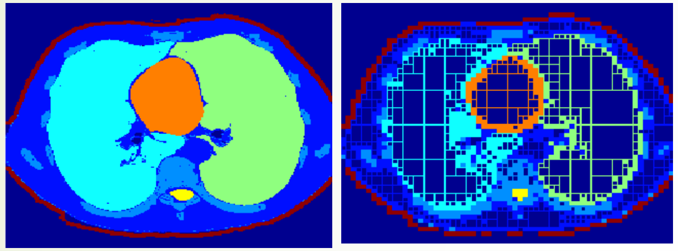
Voxelized rat model

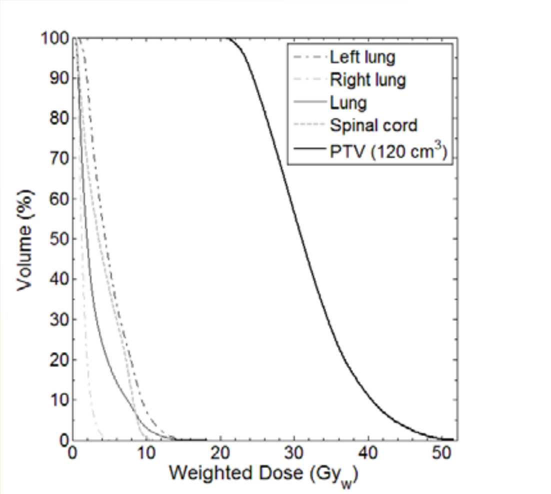


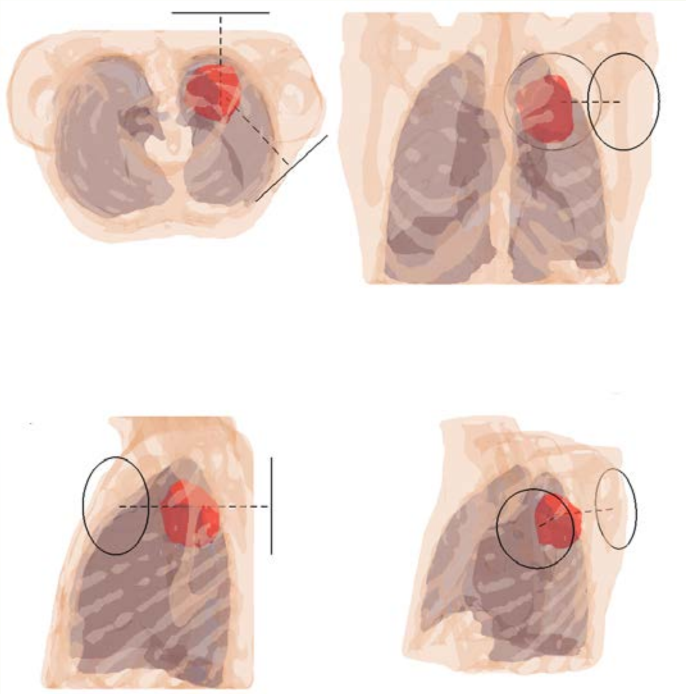
^{6}Li neutron shields

95% $^{6}Li_2CO_3$
ρ≈ 0.75 g/cm^3 15 mm thick

Treatment Planning for lung BNCT







in collaboration with CNEA

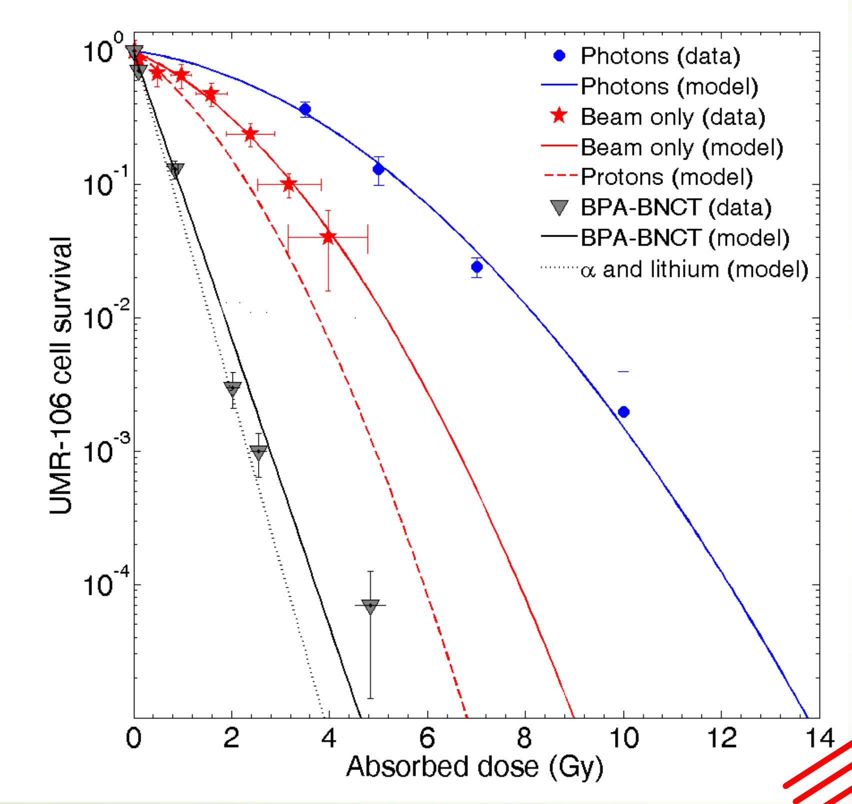
BNCT of Limb Osteosarcoma

Highly malignant tumor, it is the most common primary malignant tumor of the skeleton. OS **infiltrates in the healthy tissue**.

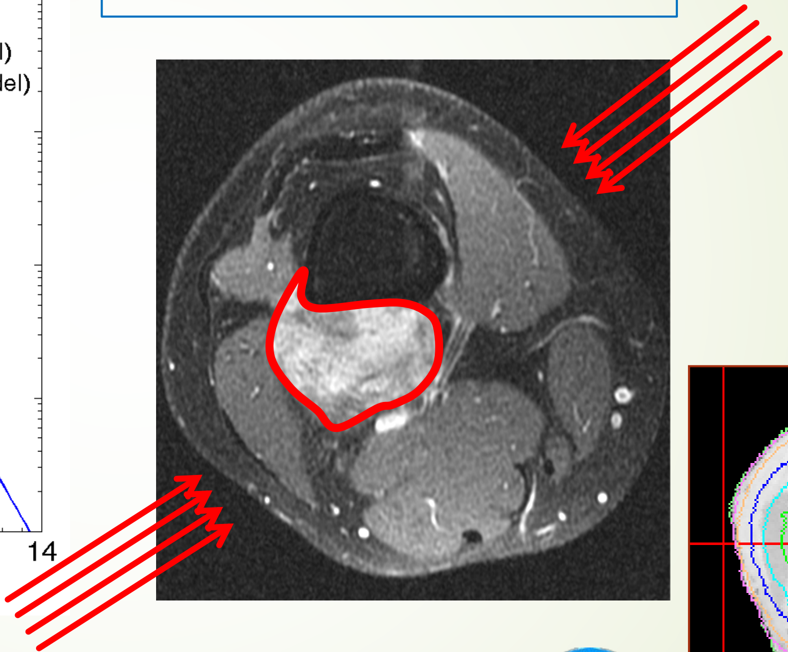
- average age of the patients ~ 19 years.
- the global mean survival at 5 years is 55-70%
- metastases reduce the survival at less than 30%
- AGGRESSIVE SURGERY with amputation or limb salvage procedures (but still very disabling)

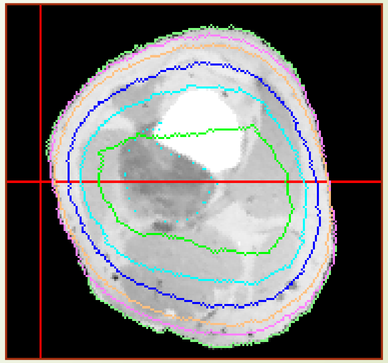
BNCT as ADJUVANT THERAPY

BNCT of Limb Osteosarcoma



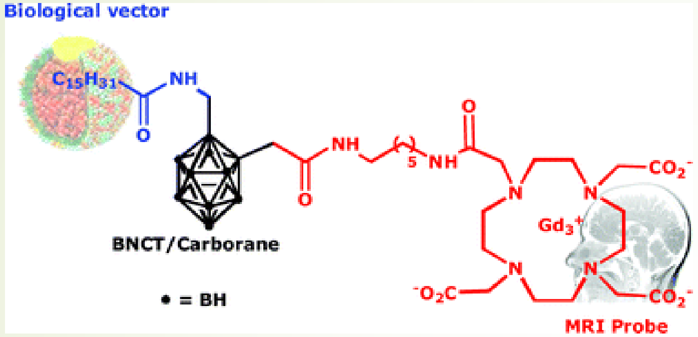
1% survival level
RBE = 2.2
CBE = 5.3

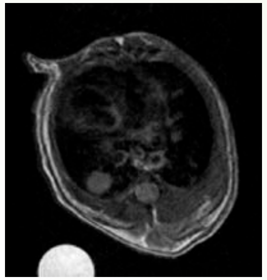


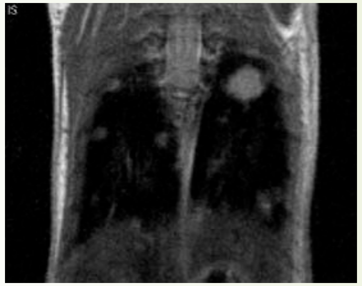


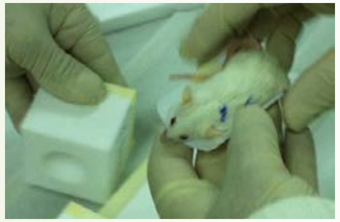
NCTPlan treatment planning in collaboration with

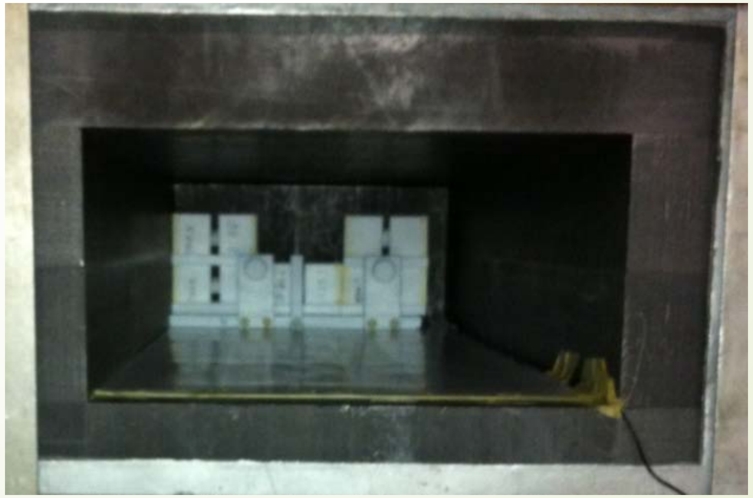
BNCT effectiveness in mice+Gd-B-LDL



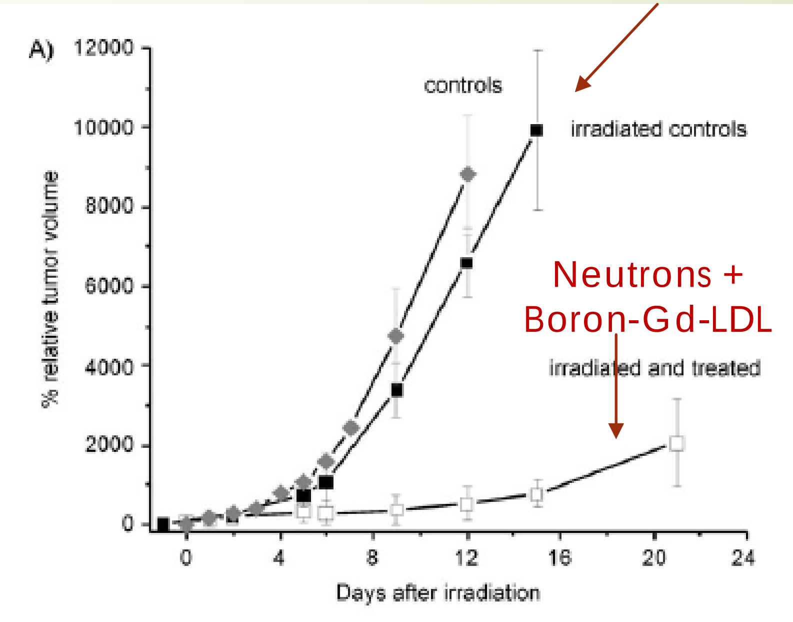








Boron-Gd-LDL: B16F10 melanoma bearing C57BL/6 mice



The tumour growth was followed for 20 days after irradiation by MRI. Although both control groups showed exponential growth in tumour volume, tumour growth was significantly lower for the first 12 days after treatment in the treated group (Figure 4A and B). At this time, both control

S. Geninatti-Crich et al., Chemistry -a European Journal, 17(30), 8479–8486, 2011

Boron imaging by SPECT

The effectiveness of BNCT treatment depends on the radiation dose deposited locally by the capture reaction on ^{10}B.

This dose is proportional to the ^{10}B concentration and to the thermal neutron flux which are present in the volume at the time of irradiation.

However, the local and real time measurement of these quantities is a big challenge, not yet solved in the BNCT community.

$$D \propto \int n_B \sigma \varphi dV$$

D = dose
n_B = density of B10 nuclei
σ = microscopic cross section of B10 capture reaction
φ = neutron flux
V = volume where the dose is delivered

$$n + {}^{10}B \rightarrow \begin{cases} {}^{7}Li \quad + \alpha + 2.79\,MeV \quad 6.1\% \\ \left({}^{7}Li\right)^{*} \quad + \alpha + 2.31\,MeV \quad 93.9\% \end{cases}$$

$$\downarrow \rightarrow {}^{7}Li + \gamma\,(0.478 MeV)$$

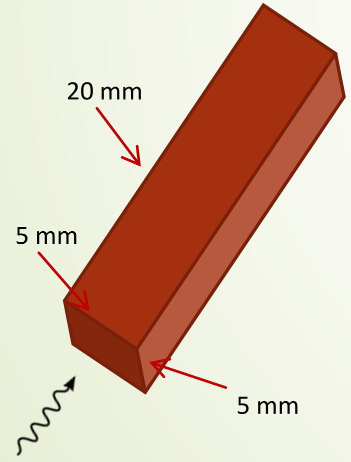
Boron imaging by SPECT CdZnTe detector

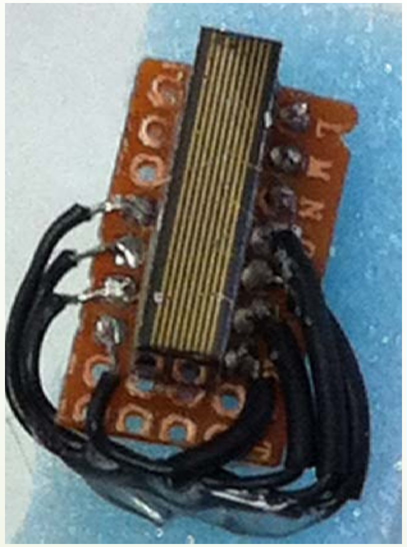
IMEM-CNR
Parma

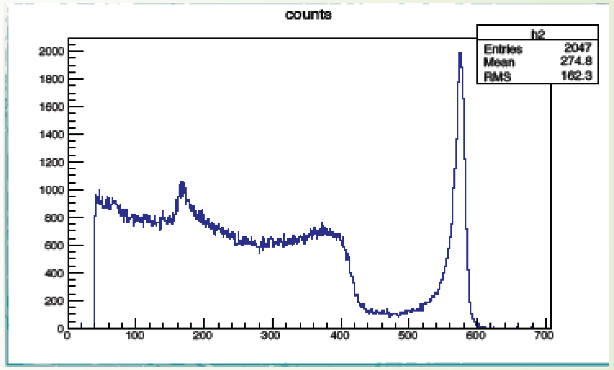
Institute of Materials for Electronics and Magnetism

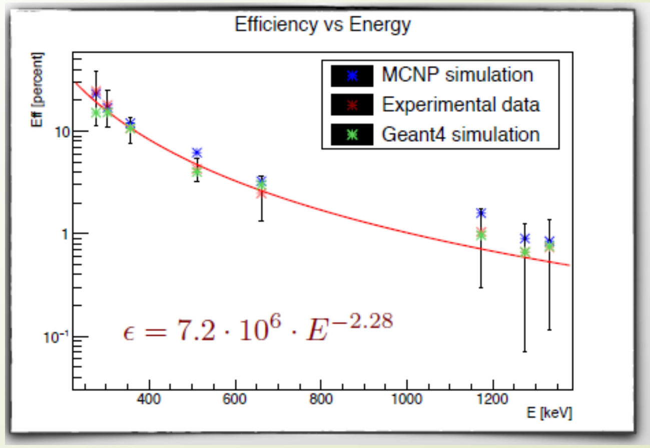
Italian National Research Council

1D detector under test: a drift strip detector 0.5 x 0.5 x 20 mm^3



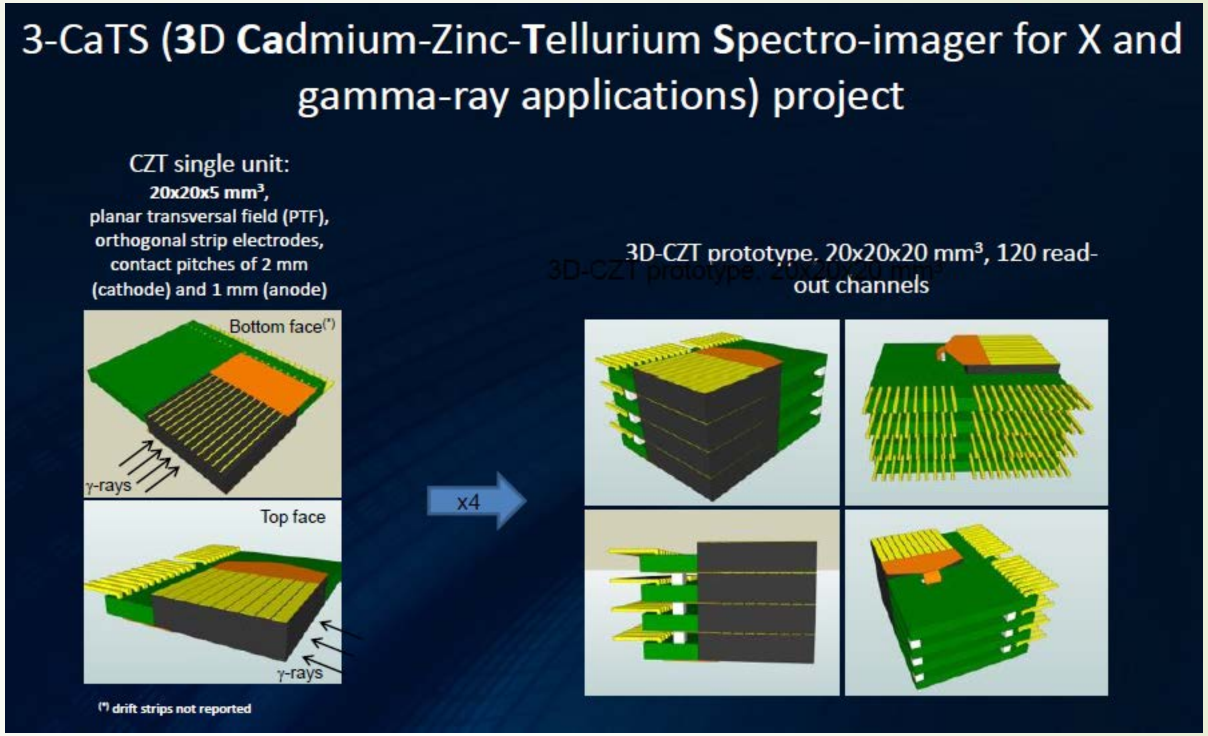






Boron imaging by SPECT

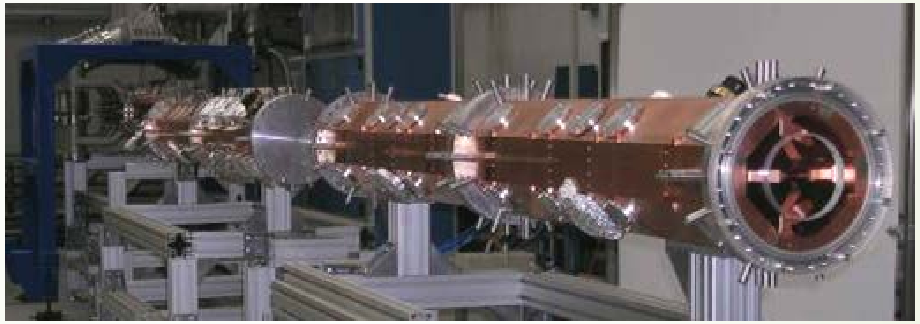
INFN, Pavia Unit,
University of Pavia,
INAF – IASF Bologna,
University of Palermo,
IMEM-CNR, Parma
Due2lab Parma

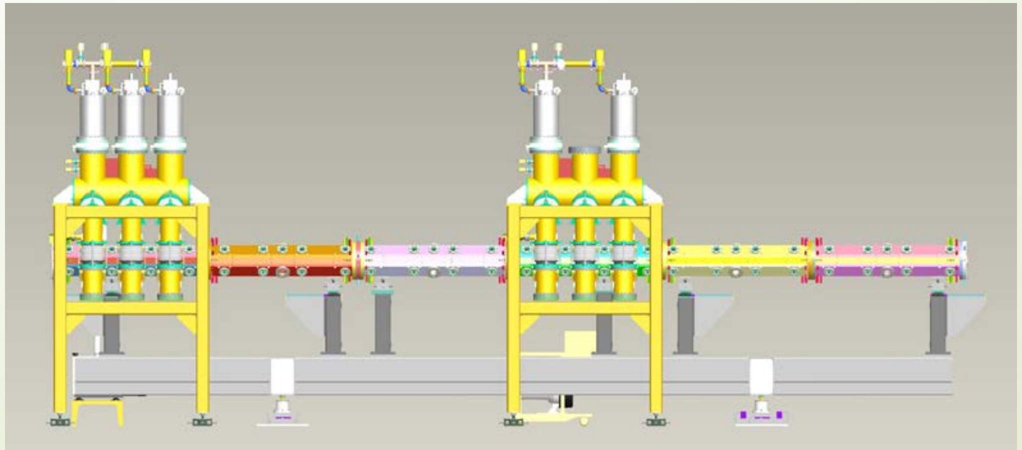


INFN has recently founded a 2-year project named 3CaTS (high performance 3D Cadmium-Zinc-Telluride spectro-imager for X and gamma-ray applications) whose goal is to develop and build an innovative highly segmented prototype of a CZT to prove and evaluate its performance as spectrometer with 3D spatial resolution capabilities suitable for different spectroscopic imaging application in the range from few tens of keV up to MeV, including the BNCT-SPECT.

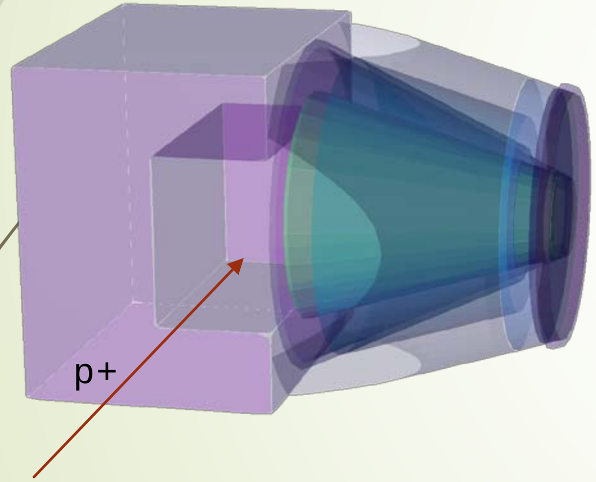
RFQ-based BNCT

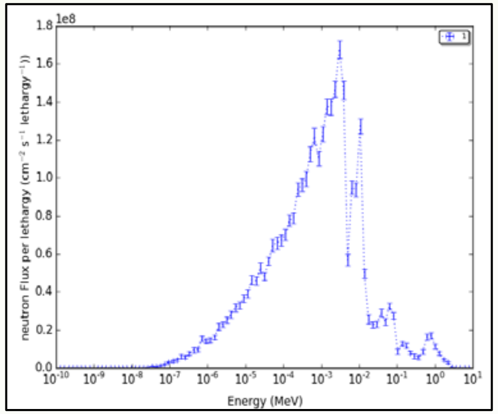
- 5 MeV proton RFQ
- 30 mA
- Be target





Tailoring of a neutron beam around 1 keV



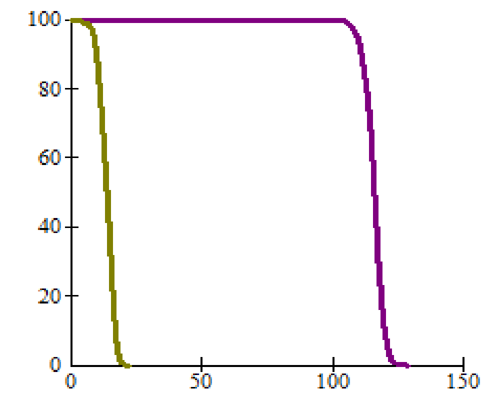


IAEA FIGURES OF MERIT

Flux $2.8 \cdot 10^{9}$ cm^{-2} s^{-1}

Fast cont $8.9 \cdot 10^{-13}$ Gy cm^{2}

Gamma cont $3.7 \cdot 10^{-13}$ Gy cm^{2}

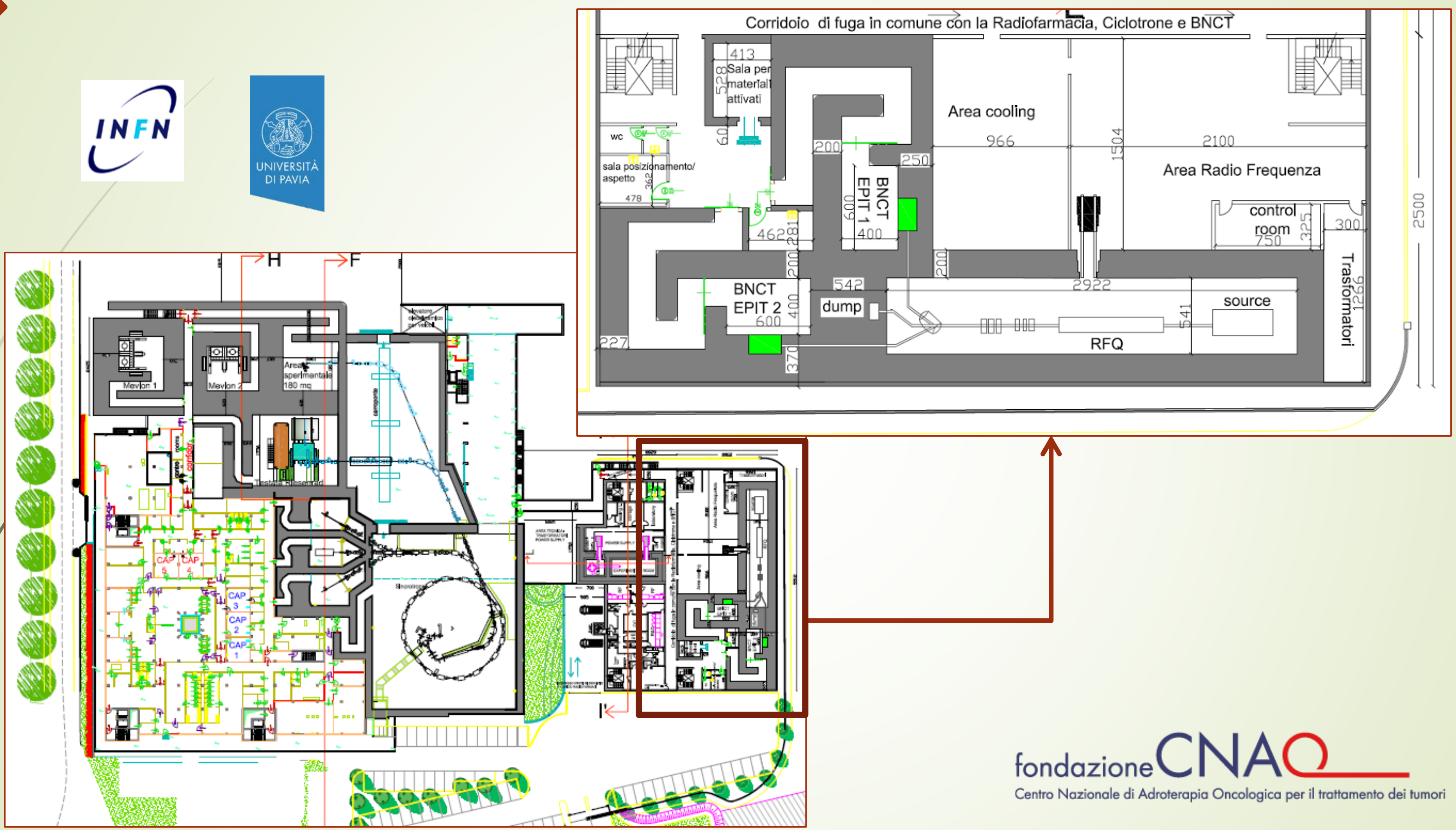


The prescription of 22 Gy_Eq to skin, leads to a minimum dose to tumour of 99.3 Gy_Eq, a maximum dose of 129 Gy_Eq, with a good uniformity in all the tumour volume.

BNCT at CNAO

INFN

UNIVERSITÀ DI PAVIA



fondazione CNAO

Centro Nazionale di Adroterapia Oncologica per il trattamento dei tumori

Italian BNCT network: main components

- *University and INFN of PAVIA: Test in vitro and in vivo with new formulations , boron measurements, cell cultures and animal irradiation (S. Altieri)*
- *University of TORINO: new Boron carrier with Gd –B-LDL for MRI (S. Aime)*
- *University of NOVARA: polimeric nanoparticles and liposomes (L. Panza)*
- *University of FIRENZE: liposomes and nanoparticles functionalized with B (S. Ristori)*
- *Universitiy of POTENZA: boronated porphirines (G. Ricciardi)*
- *University of Palermo: gamma dosimetry (M. Marrale)*

  and SPECT (L. Abbene)
- *LNL-INFN: RFQ (A. Pisent)*

Italian BNCT network: main components

International collaborations

- *CNEA, Argentina: very active researchers exchange for computational dosimetry, treatment planning, beam design, B concentration measurement methods inter-comparison, BNCT efficacy and toxicity on animal models,*
- *INL, Idaho, USA: neutron spectrometry in irradiation facilities*
- *HUCH, Helsinki University Central Hospital and FIR 1, Finland*
- *QEH,University Hospital, Birmingham*
- *Okayama University (Y. Ichikawa)*
- *China* Funded project in the frame of the Executive Programme of Scientific and Technological Cooperation between Italy and China for the years 2016-2018. Italian Ministry of Foreign Affairs and International Cooperation (MAECI). Project: NEU_BEAT (Neutron Beams for Cancer Treatment). Collaboration on:

-New materials for neutron beams design
-Treatment Planning calculations
-Computational dosimetry
-Integration of BNCT and heavy ion therapy

Part of BNCT Pavia group

Physicists at work

Silva Bortolussi
Francesca Ballarini
Nicoletta Protti
Ian Postuma
Setareh Fatemi
Cinzia Ferrari
Laura Cansolino
Saverio Altieri

Thank you

saverio.altieri@unipv.it

http://www.bnct.it