Outline

1. **Introduction: a historical overview**
2. **Modern medical diagnostics**
3. **Particle accelerators for medicine**
4. **Conventional radiation therapy**
5. **Basic principles of hadrontherpy**
6. **Present and future of hadrontherapy**
   - Proton-therapy
   - Carbon ion therapy
   - Neutrons in cancer therapy
7. **A tour in a hadrontherapy centre**
8. **Specific topics in hadrontherapy**

Hadrontherapy
from laboratories to hospital based centres

The main goal of radiation therapy

STOCKHOLM

1902 **1912**

Courtesy J.P. Jerard, MD, Nice (France)

Local control of the tumour!

The first facilities

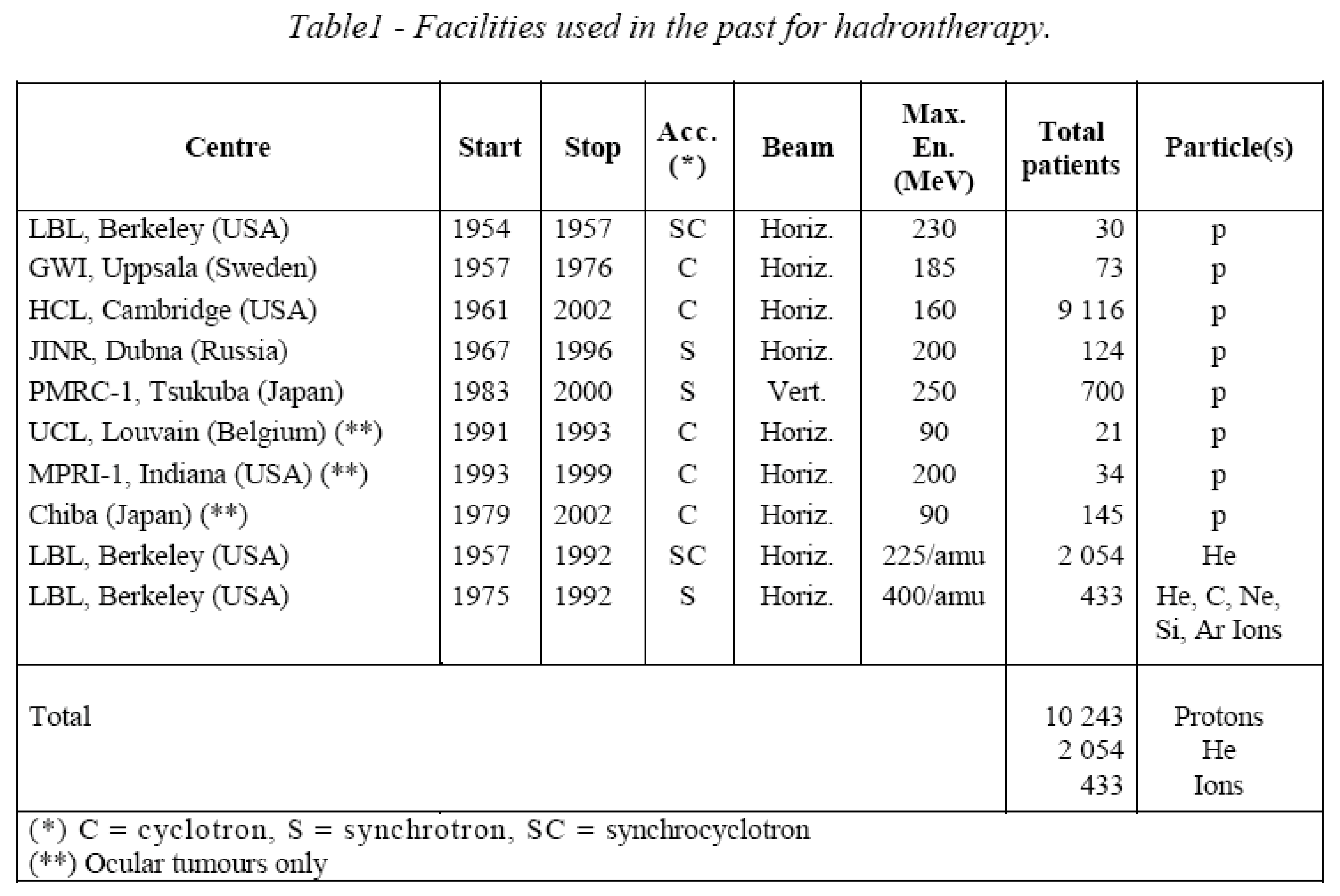


Table1 - Facilities used in the past for hadrontherapy.

Centre	Start	Stop	Acc. (*)	Beam	Max. En. (MeV)	Total patients	Particle(s)
LBL, Berkeley (USA)	1954	1957	SC	Horiz.	230	30	p
GWI, Uppsala (Sweden)	1957	1976	C	Horiz.	185	73	p
HCL, Cambridge (USA)	1961	2002	C	Horiz.	160	9 116	p
JINR, Dubna (Russia)	1967	1996	S	Horiz.	200	124	p
PMRC-1, Tsukuba (Japan)	1983	2000	S	Vert.	250	700	p
UCL, Louvain (Belgium) (**)	1991	1993	C	Horiz.	90	21	p
MPRI-1, Indiana (USA) (**)	1993	1999	C	Horiz.	200	34	p
Chiba (Japan) (**)	1979	2002	C	Horiz.	90	145	p
LBL, Berkeley (USA)	1957	1992	SC	Horiz.	225/amu	2 054	He
LBL, Berkeley (USA)	1975	1992	S	Horiz.	400/amu	433	He, C, Ne, Si, Ar Ions
Total						10 243 2 054 433	Protons He Ions

(*) C = cyclotron, S = synchrotron, SC = synchrocyclotron
(**) Ocular tumours only

Proton therapy centres in operation

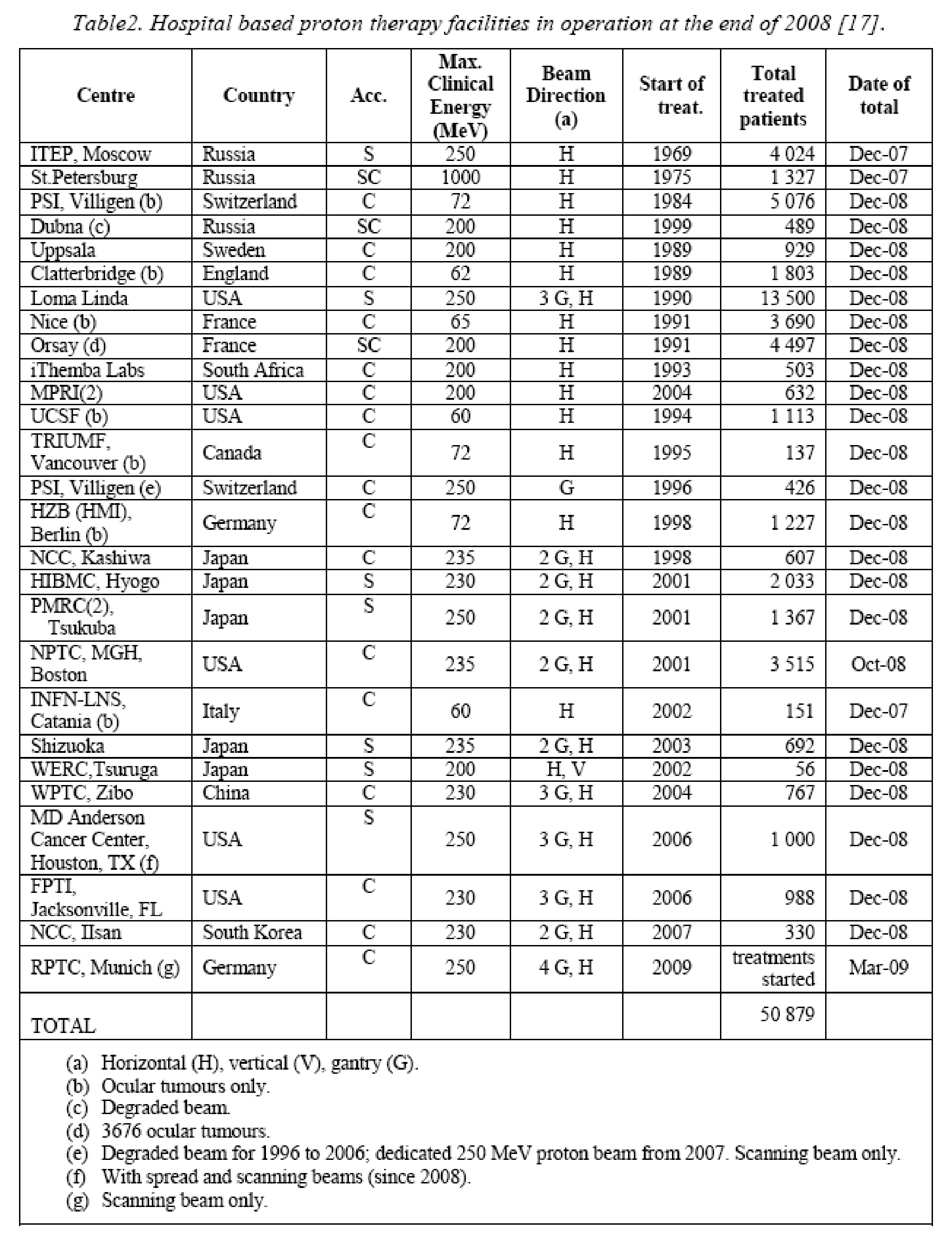


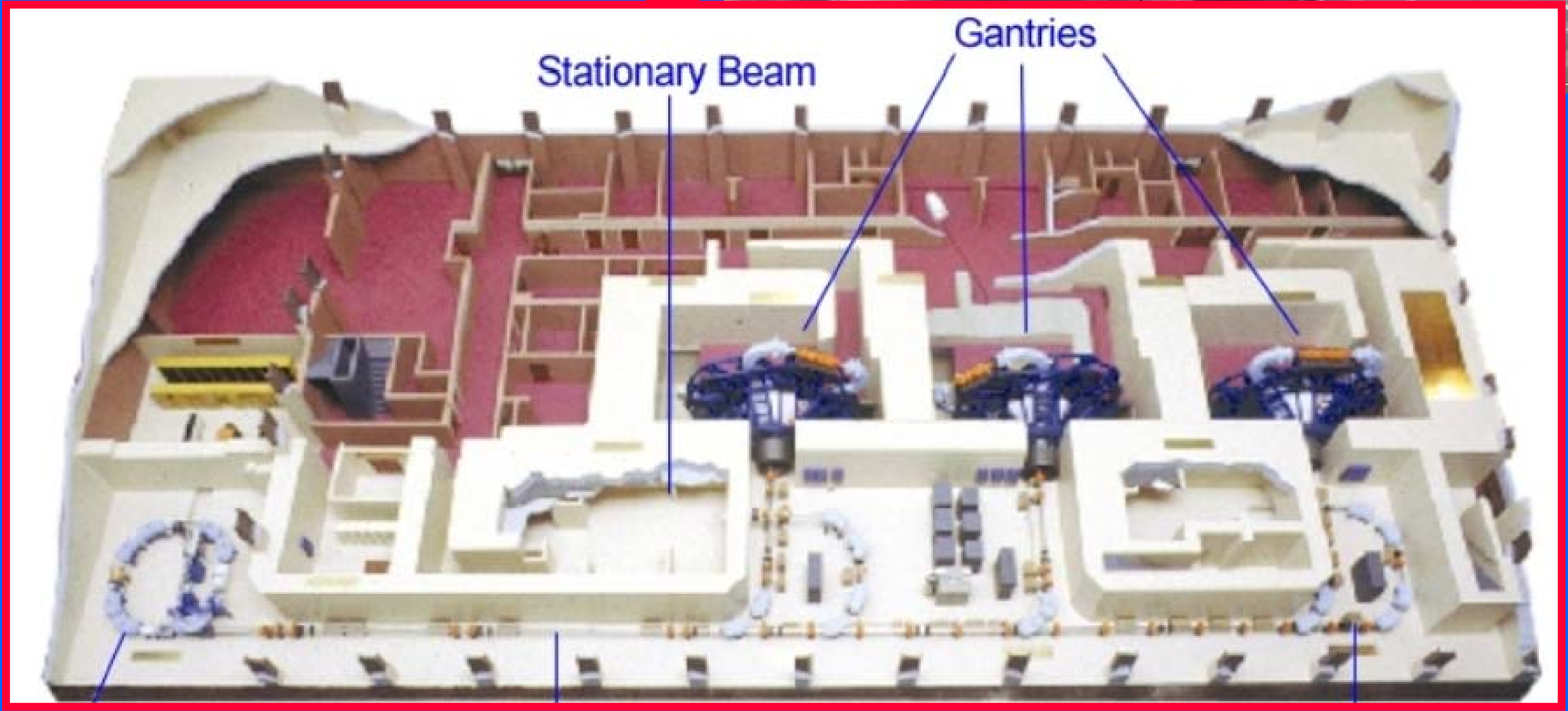
Table2. Hospital based proton therapy facilities in operation at the end of 2008 [17].

Centre	Country	Acc.	Max. Clinical Energy (MeV)	Beam Direction (a)	Start of treat.	Total treated patients	Date of total
ITEP, Moscow	Russia	S	250	H	1969	4 024	Dec-07
St.Petersburg	Russia	SC	1000	H	1975	1 327	Dec-07
PSI, Villigen (b)	Switzerland	C	72	H	1984	5 076	Dec-08
Dubna (c)	Russia	SC	200	H	1999	489	Dec-08
Uppsala	Sweden	C	200	H	1989	929	Dec-08
Clatterbridge (b)	England	C	62	H	1989	1 803	Dec-08
Loma Linda	USA	S	250	3 G, H	1990	13 500	Dec-08
Nice (b)	France	C	65	H	1991	3 690	Dec-08
Orsay (d)	France	SC	200	H	1991	4 497	Dec-08
iThemba Labs	South Africa	C	200	H	1993	503	Dec-08
MPRI(2)	USA	C	200	H	2004	632	Dec-08
UCSF (b)	USA	C	60	H	1994	1 113	Dec-08
TRIUMF, Vancouver (b)	Canada	C	72	H	1995	137	Dec-08
PSI, Villigen (e)	Switzerland	C	250	G	1996	426	Dec-08
HZB (HMI), Berlin (b)	Germany	C	72	H	1998	1 227	Dec-08
NCC, Kashiwa	Japan	C	235	2 G, H	1998	607	Dec-08
HIBMC, Hyogo	Japan	S	230	2 G, H	2001	2 033	Dec-08
PMRC(2), Tsukuba	Japan	S	250	2 G, H	2001	1 367	Dec-08
NPTC, MGH, Boston	USA	C	235	2 G, H	2001	3 515	Oct-08
INFN-LNS, Catania (b)	Italy	C	60	H	2002	151	Dec-07
Shizuoka	Japan	S	235	2 G, H	2003	692	Dec-08
WERC,Tsuruga	Japan	S	200	H, V	2002	56	Dec-08
WPTC, Zibo	China	C	230	3 G, H	2004	767	Dec-08
MD Anderson Cancer Center, Houston, TX (f)	USA	S	250	3 G, H	2006	1 000	Dec-08
FPTI, Jacksonville, FL	USA	C	230	3 G, H	2006	988	Dec-08
NCC, Ilsan	South Korea	C	230	2 G, H	2007	330	Dec-08
RPTC, Munich (g)	Germany	C	250	4 G, H	2009	treatments started	Mar-09
TOTAL						50 879	

(a) Horizontal (H), vertical (V), gantry (G).
(b) Ocular tumours only.
(c) Degraded beam.
(d) 3676 ocular tumours.
(e) Degraded beam for 1996 to 2006; dedicated 250 MeV proton beam from 2007. Scanning beam only.
(f) With spread and scanning beams (since 2008).
(g) Scanning beam only.

The Loma Linda University Medical Center (USA)

- First hospital-based proton-therapy centre, built in 1993
- ~160/sessions a day
- ~1000 patients/year



(Incomplete) list of future new facilities

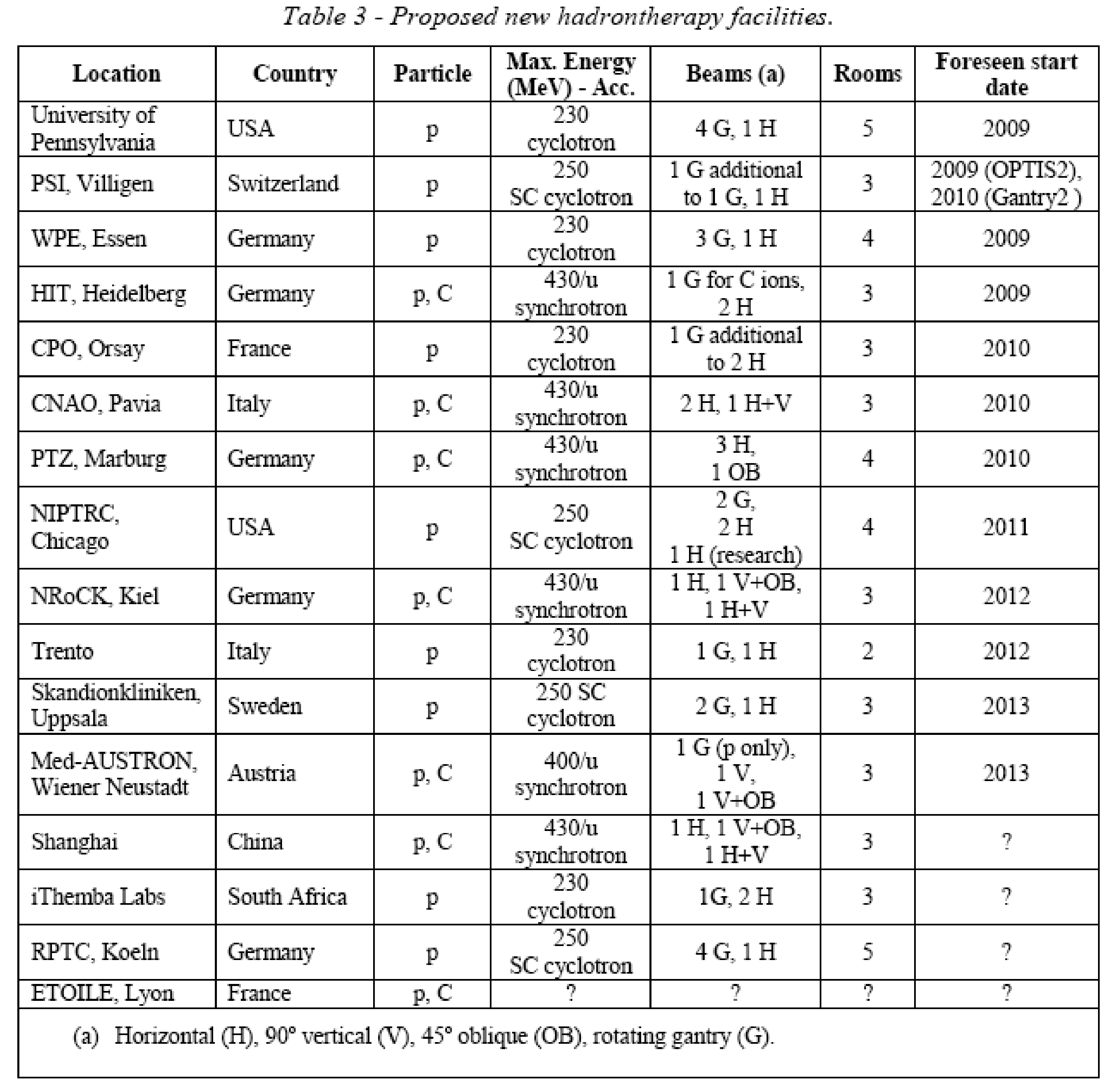
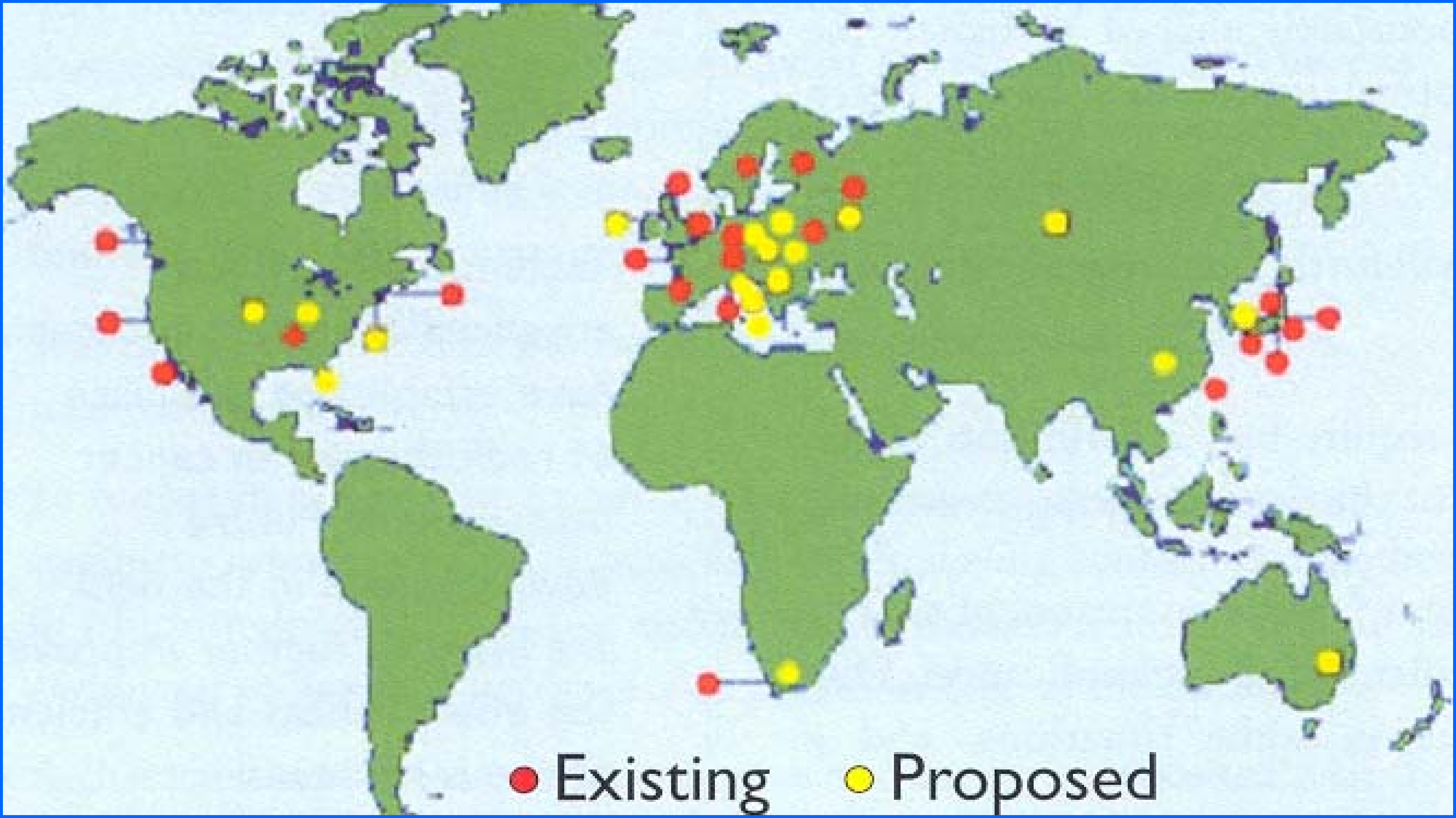


Table 3 - Proposed new hadrontherapy facilities.

Location	**Country**	**Particle**	**Max. Energy (MeV) - Acc.**	**Beams (a)**	**Rooms**	**Foreseen start date**
University of Pennsylvania	USA	p	230 cyclotron	4 G, 1 H	5	2009
PSI, Villigen	Switzerland	p	250 SC cyclotron	1 G additional to 1 G, 1 H	3	2009 (OPTIS2), 2010 (Gantry2)
WPE, Essen	Germany	p	230 cyclotron	3 G, 1 H	4	2009
HIT, Heidelberg	Germany	p, C	430/u synchrotron	1 G for C ions, 2 H	3	2009
CPO, Orsay	France	p	230 cyclotron	1 G additional to 2 H	3	2010
CNAO, Pavia	Italy	p, C	430/u synchrotron	2 H, 1 H+V	3	2010
PTZ, Marburg	Germany	p, C	430/u synchrotron	3 H, 1 OB	4	2010
NIPTRC, Chicago	USA	p	250 SC cyclotron	2 G, 2 H 1 H (research)	4	2011
NRoCK, Kiel	Germany	p, C	430/u synchrotron	1 H, 1 V+OB, 1 H+V	3	2012
Trento	Italy	p	230 cyclotron	1 G, 1 H	2	2012
Skandionkliniken, Uppsala	Sweden	p	250 SC cyclotron	2 G, 1 H	3	2013
Med-AUSTRON, Wiener Neustadt	Austria	p, C	400/u synchrotron	1 G (p only), 1 V, 1 V+OB	3	2013
Shanghai	China	p, C	430/u synchrotron	1 H, 1 V+OB, 1 H+V	3	?
iThemba Labs	South Africa	p	230 cyclotron	1G, 2 H	3	?
RPTC, Koeln	Germany	p	250 SC cyclotron	4 G, 1 H	5	?
ETOILE, Lyon	France	p, C	?	?	?	?

(a) Horizontal (H), 90° vertical (V), 45° oblique (OB), rotating gantry (G).

Hadrontherapy in the world

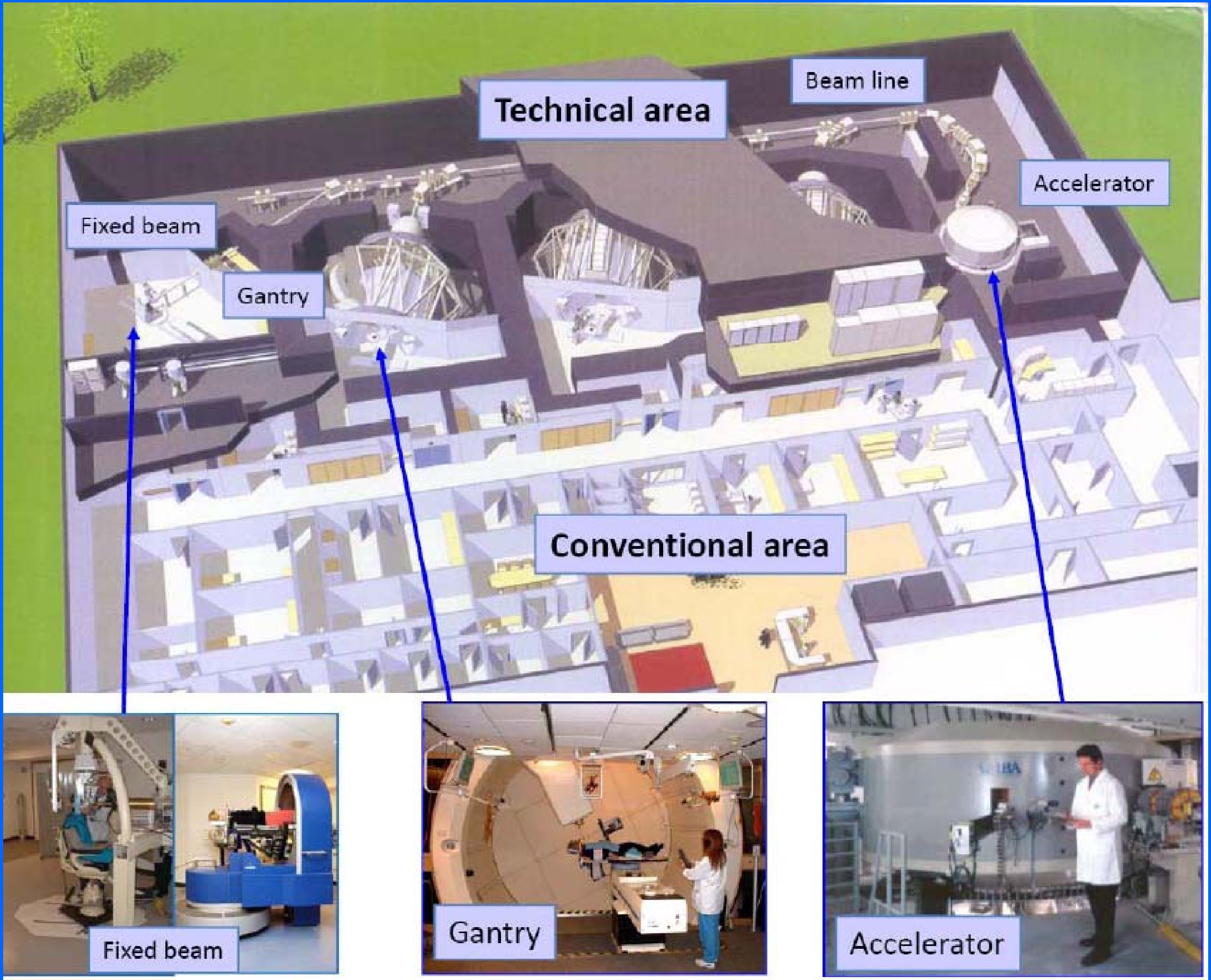


Today there are two main kind of treatments

- Treatment of eye-melanoma
  - Shallow tumour
  - About 65 MeV of energy are needed
  - Relatively small cyclotrons
  - Very high local control
  - Many centres in operation (ex. Centre Antoine Lacassagne in Nice)

- Treatment of deep seated tumours
  - Energies up to about 210 MeV are needed
  - Much larger infrastructure

What do we need to treat deep seated tumours?



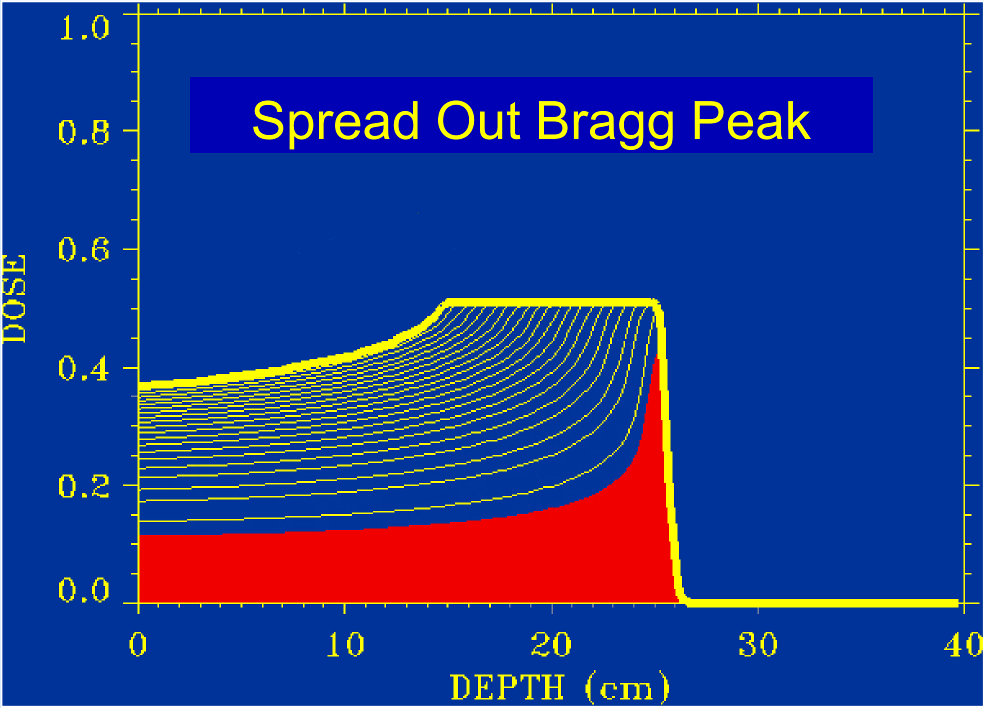
General scheme of a proton-therapy centre. The example reported here is based on the system commercialized by the company IBA (Belgium).

Dose distribution systems: from passive spreading to active scanning

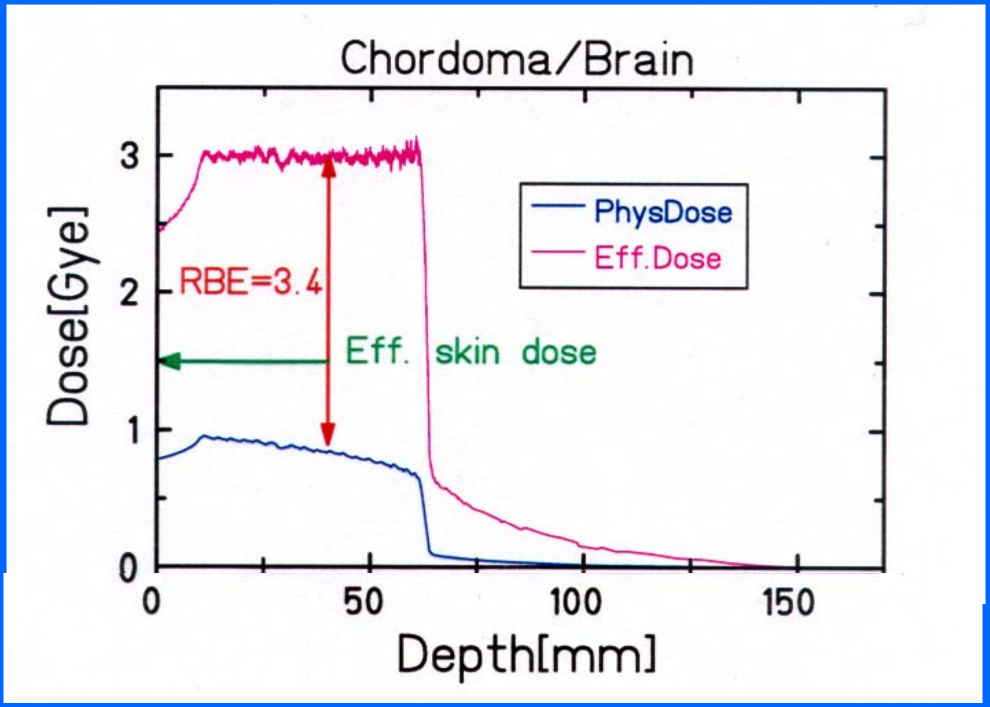
A ganrty for proton therapy

The “SOBP”

- A tumour is much larger (few cm) than the Bragg peak (few mm)
- Particles of different energies have to be used
- Many Bragg peaks have to be superimposed with the right weights to obtain a flat dose distribution (Spread Out Bragg Peak – SOBP)
- For carbon ions the RBE has to be taken into account !

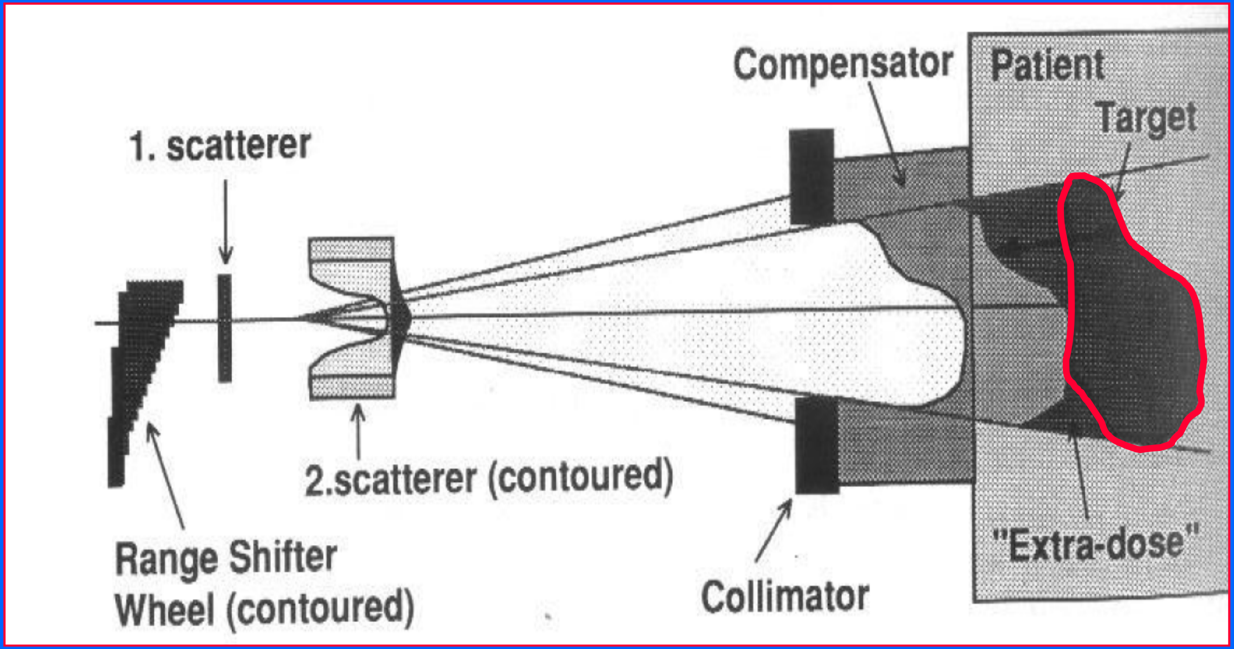


Protons (RBE=1.1)

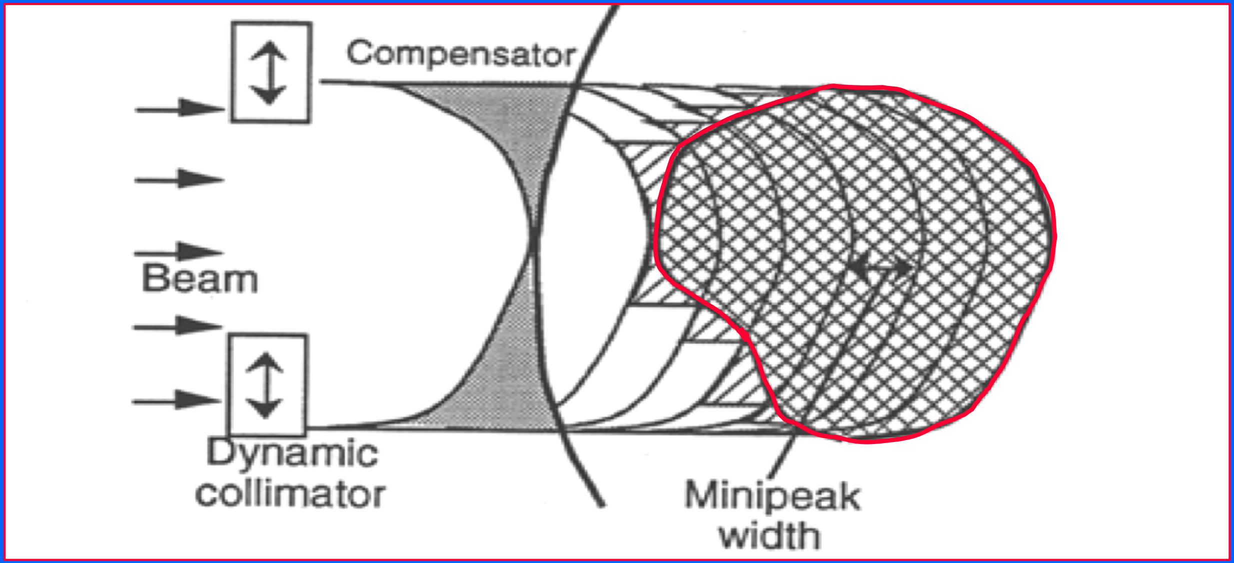


Carbon ions

Dose distribution: passive spreading

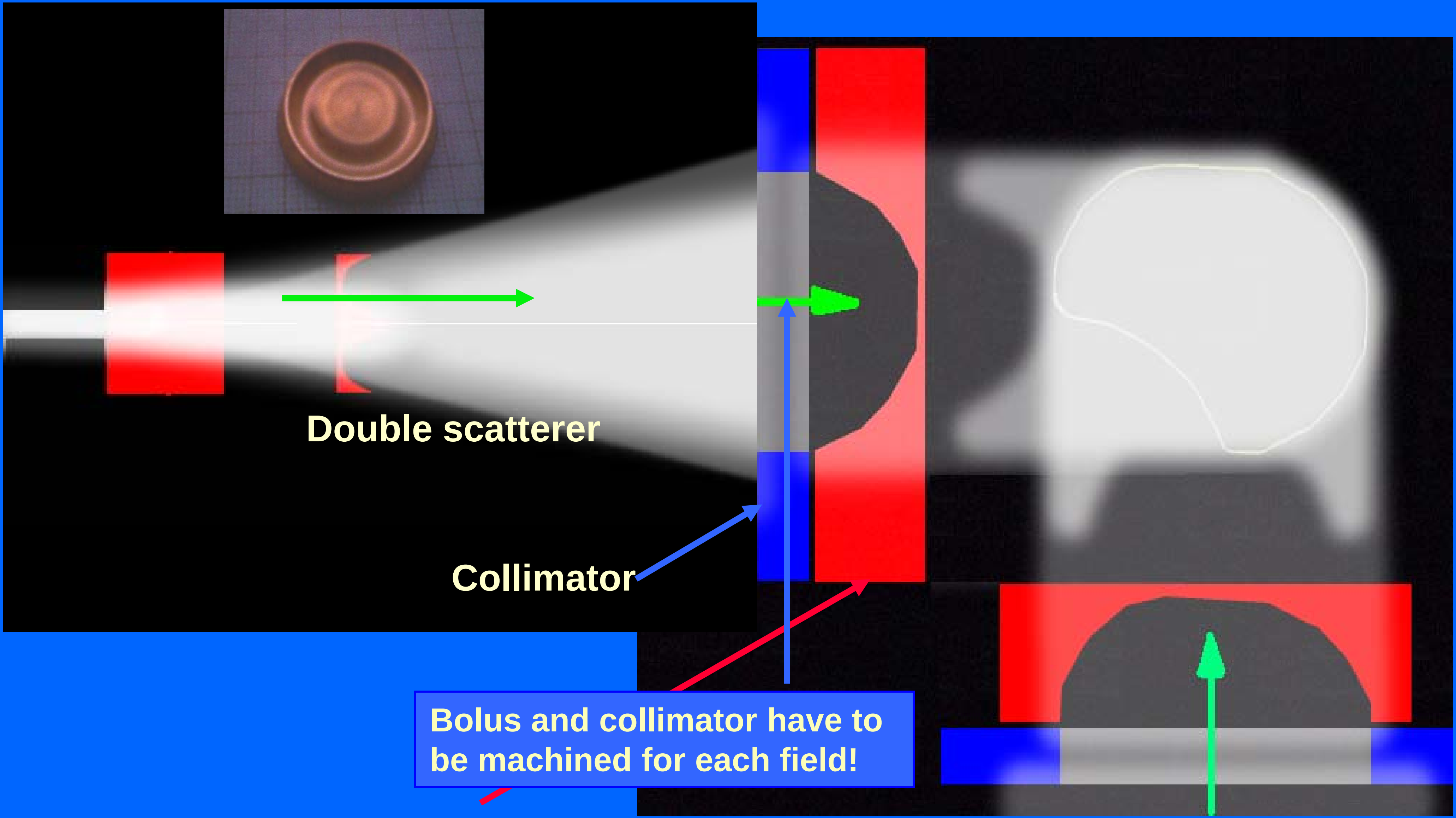


'Double scattering'



'Layer stacking'

Standard procedure: Passive beam spreading with respiratory gating

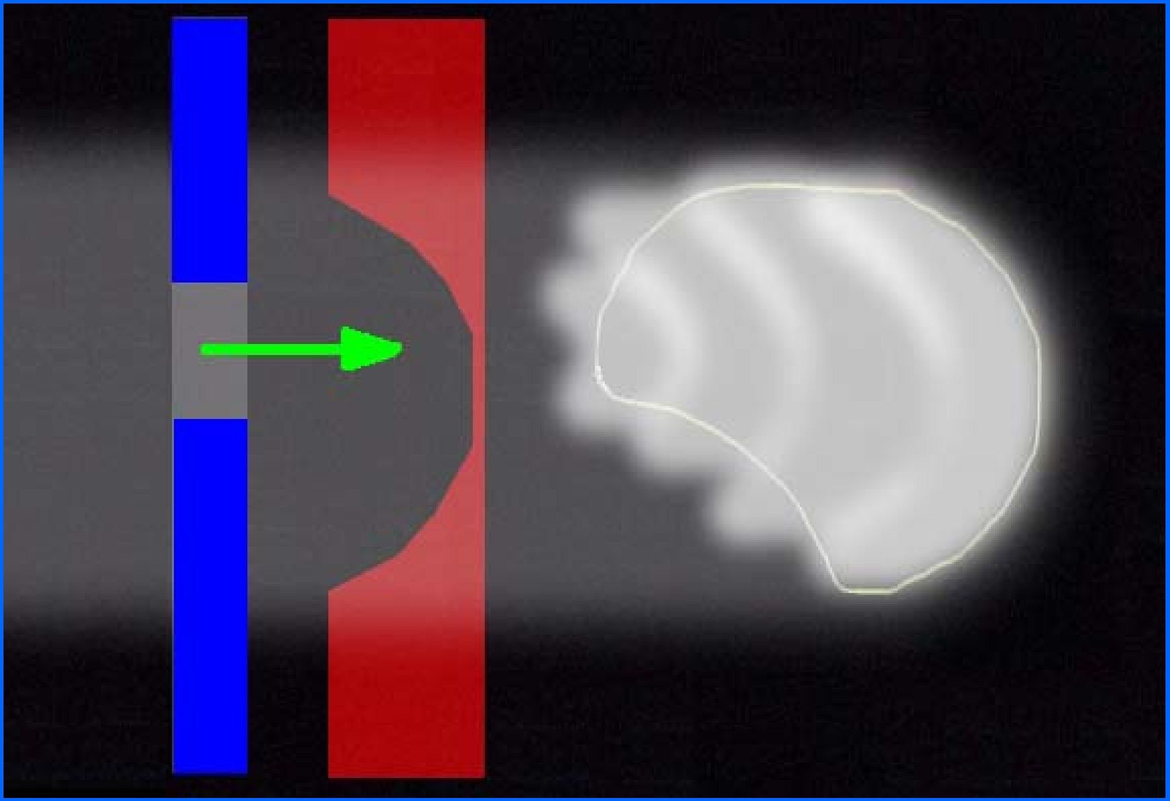


Double scatterer

Collimator

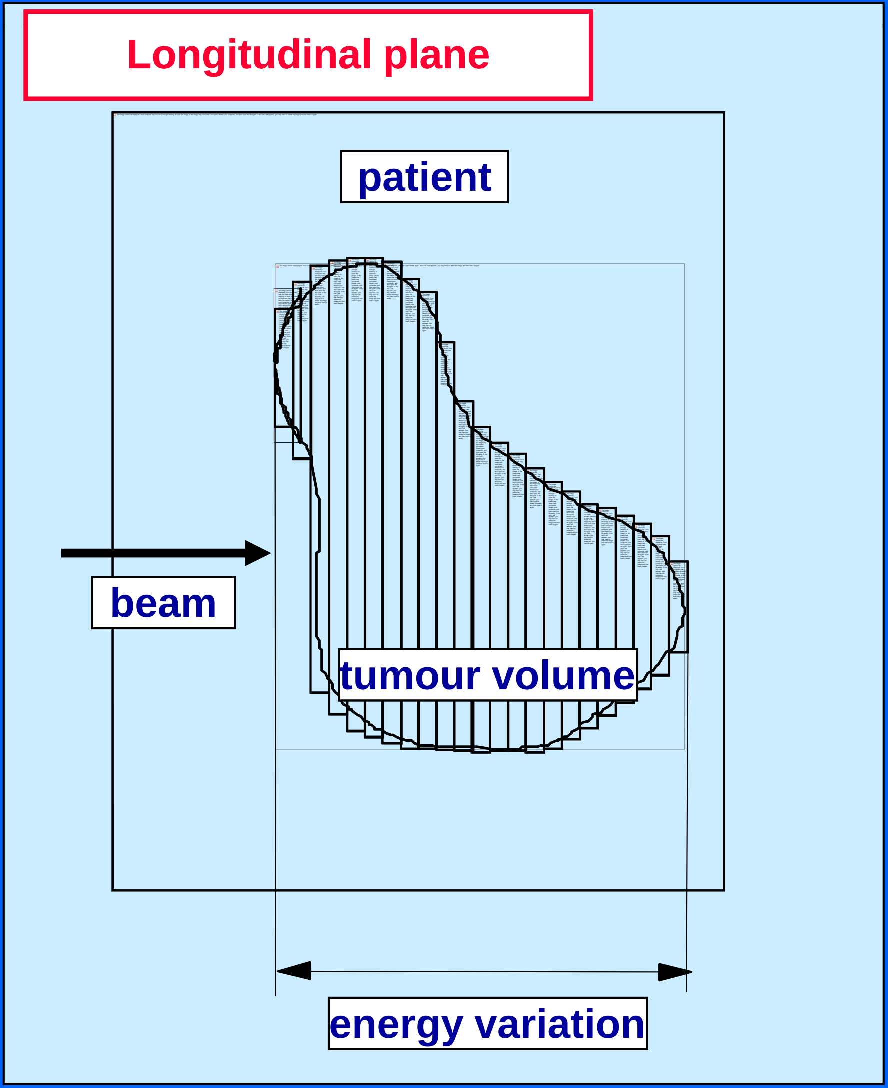
Bolus and collimator have to be machined for each field!

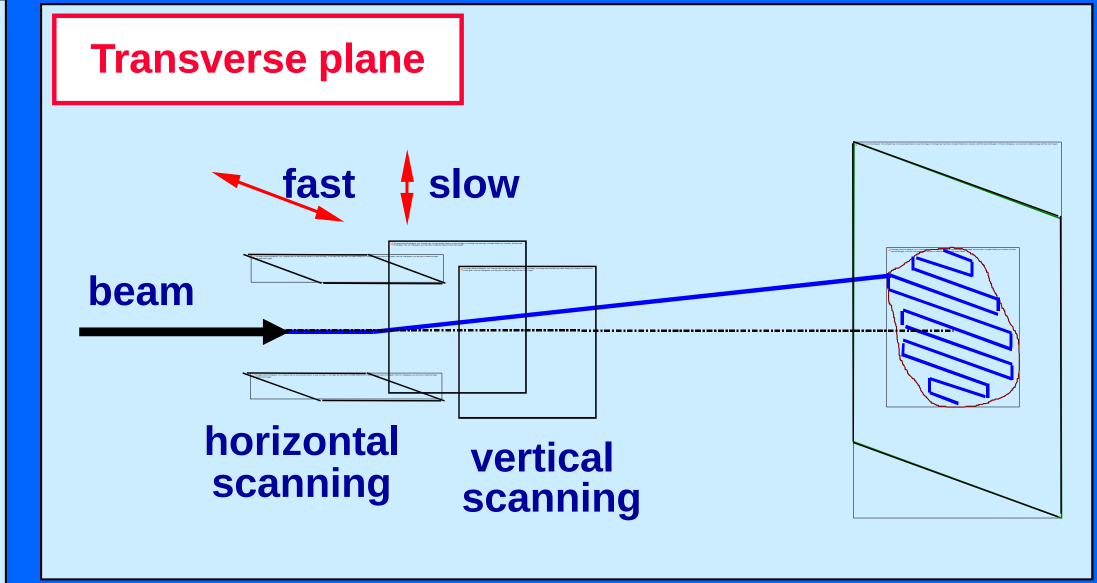
Advanced procedure: layer stacking with respiratory gating

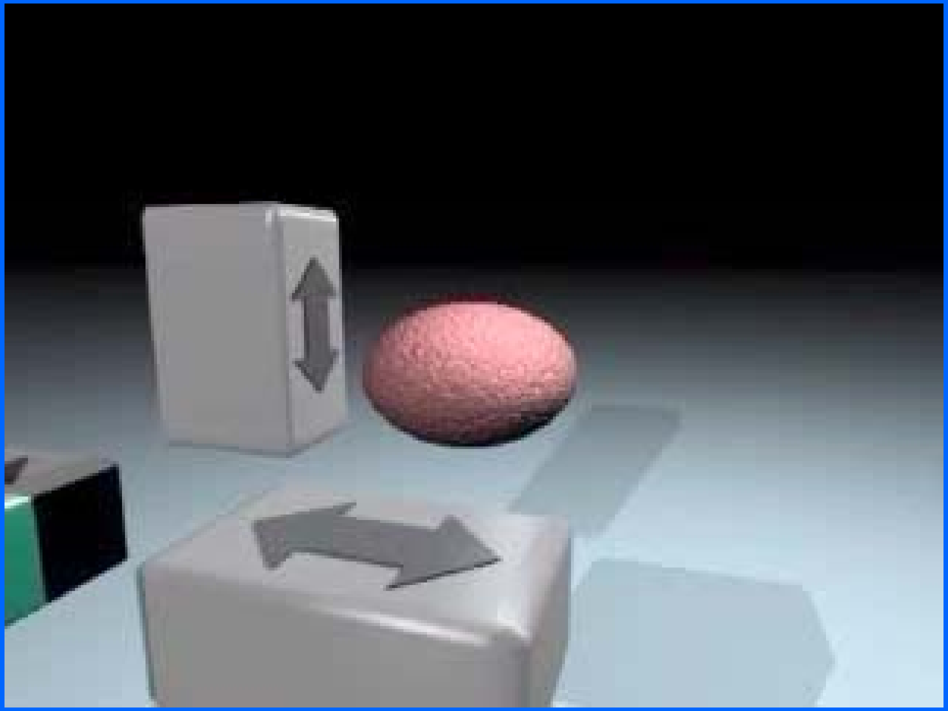


- **Collimator adapted to transverse shape of each slice.**

Dose distribution: active scanning

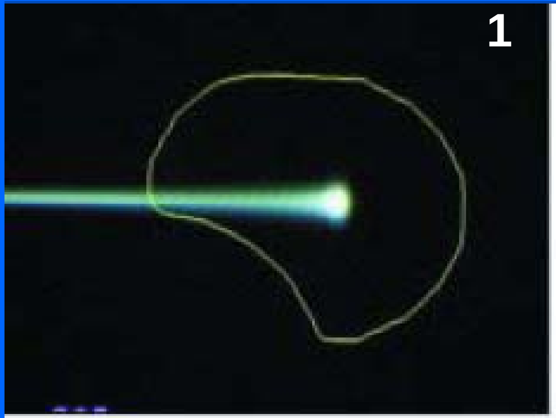




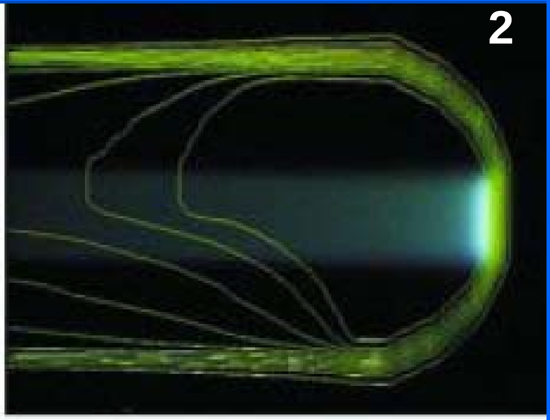


New technique developed mainly at GSI and PSI

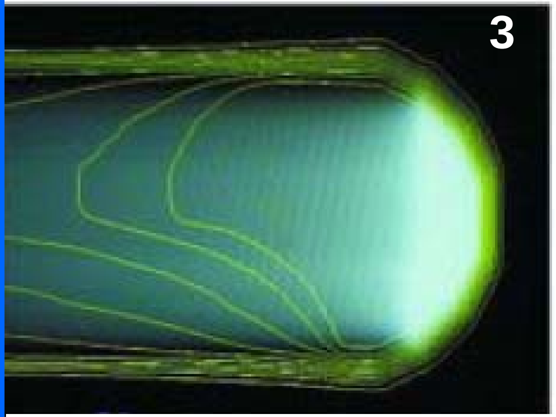
Active "spot scanning" a la PSI



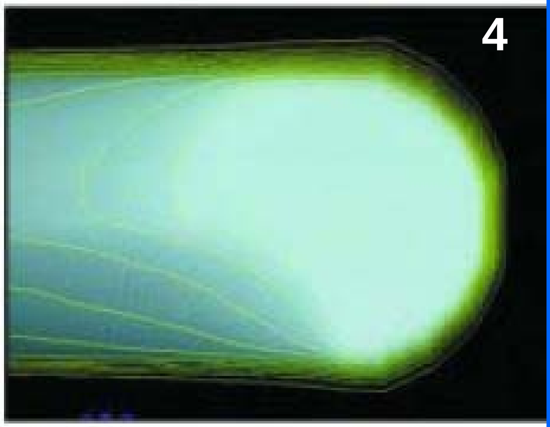
Single 'spot'



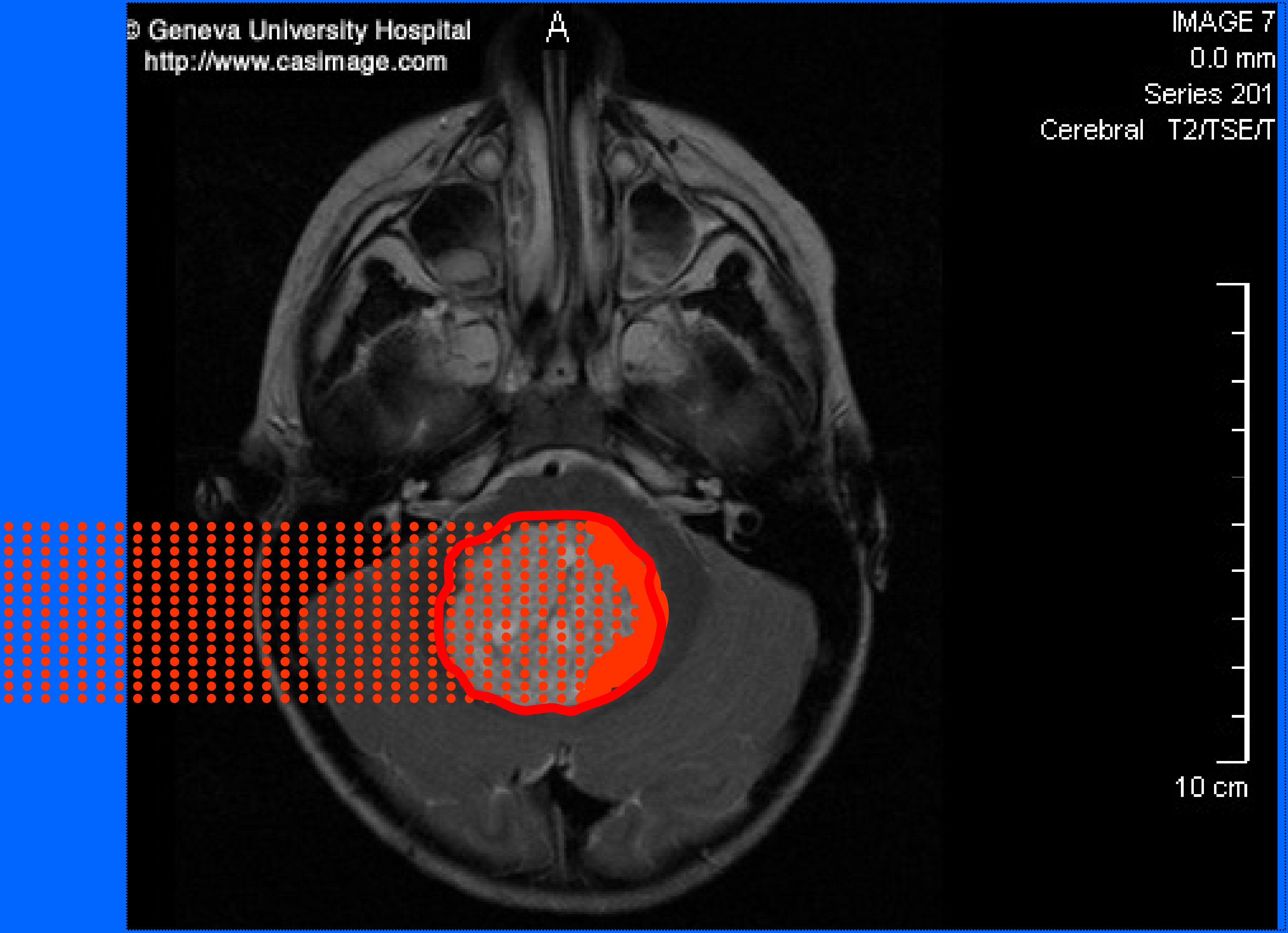
Lateral scanning with magnet: 2 ms/step



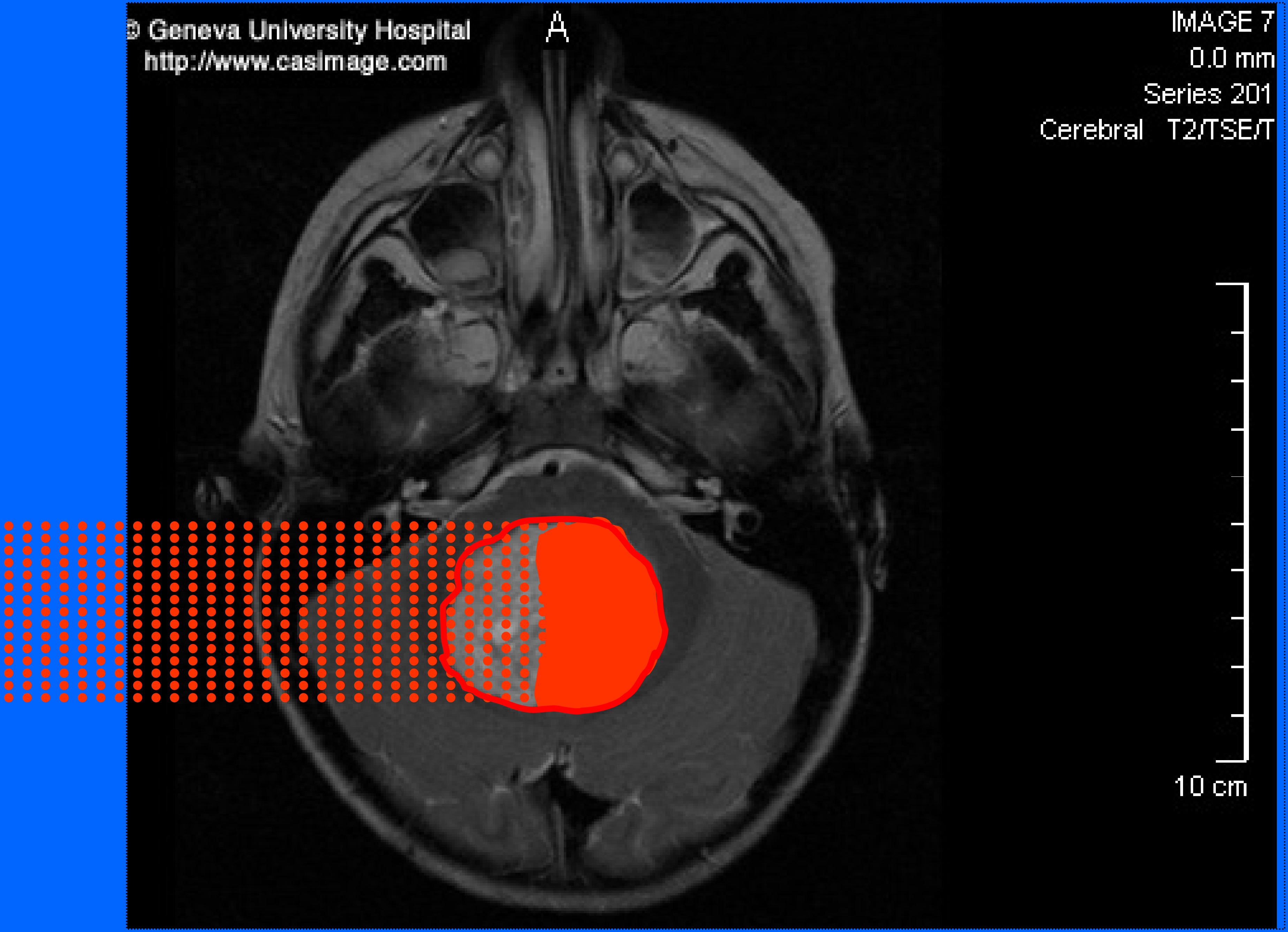
Depth scanning



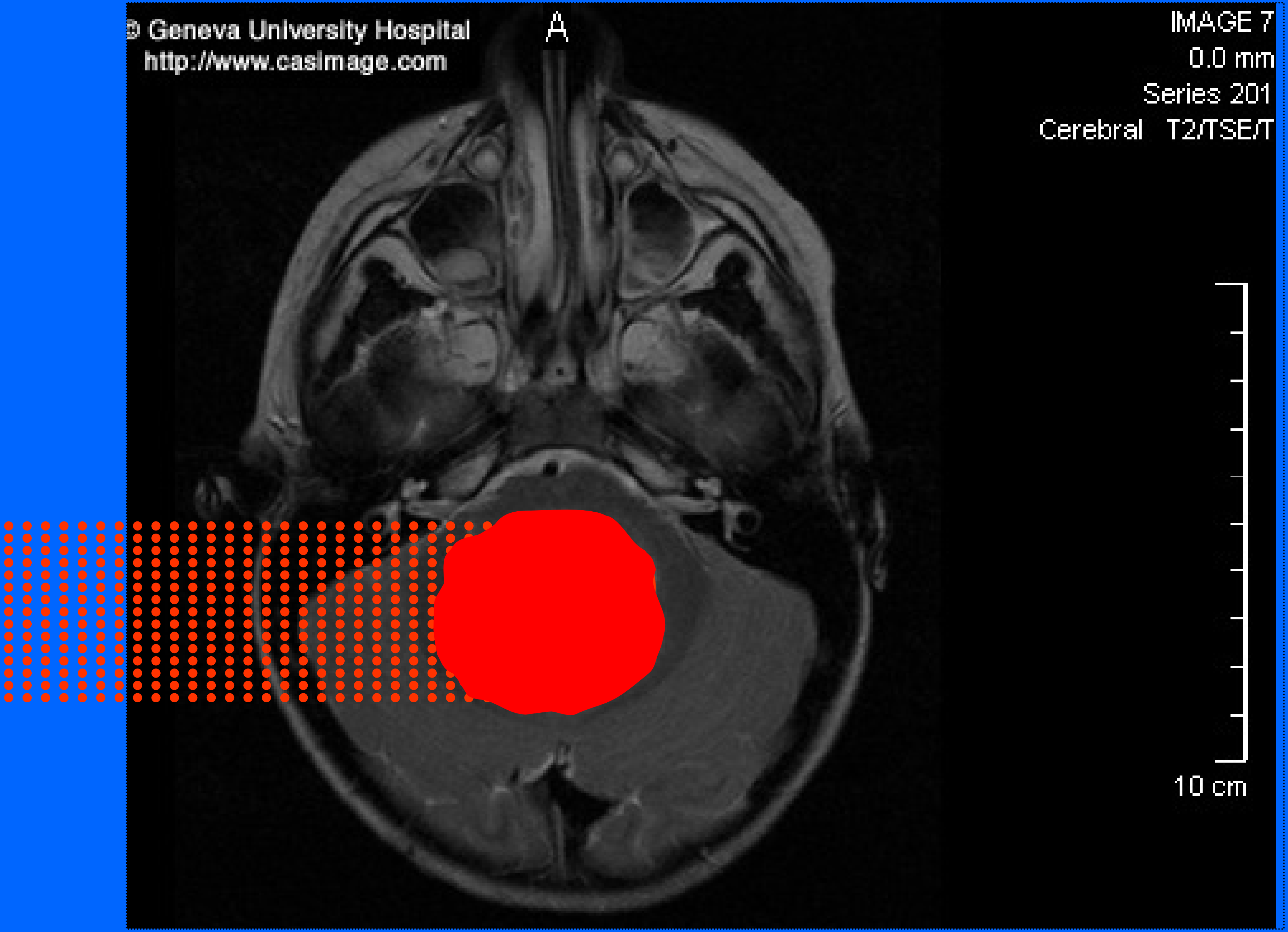
Third scanning by a bending magnet and movable bed



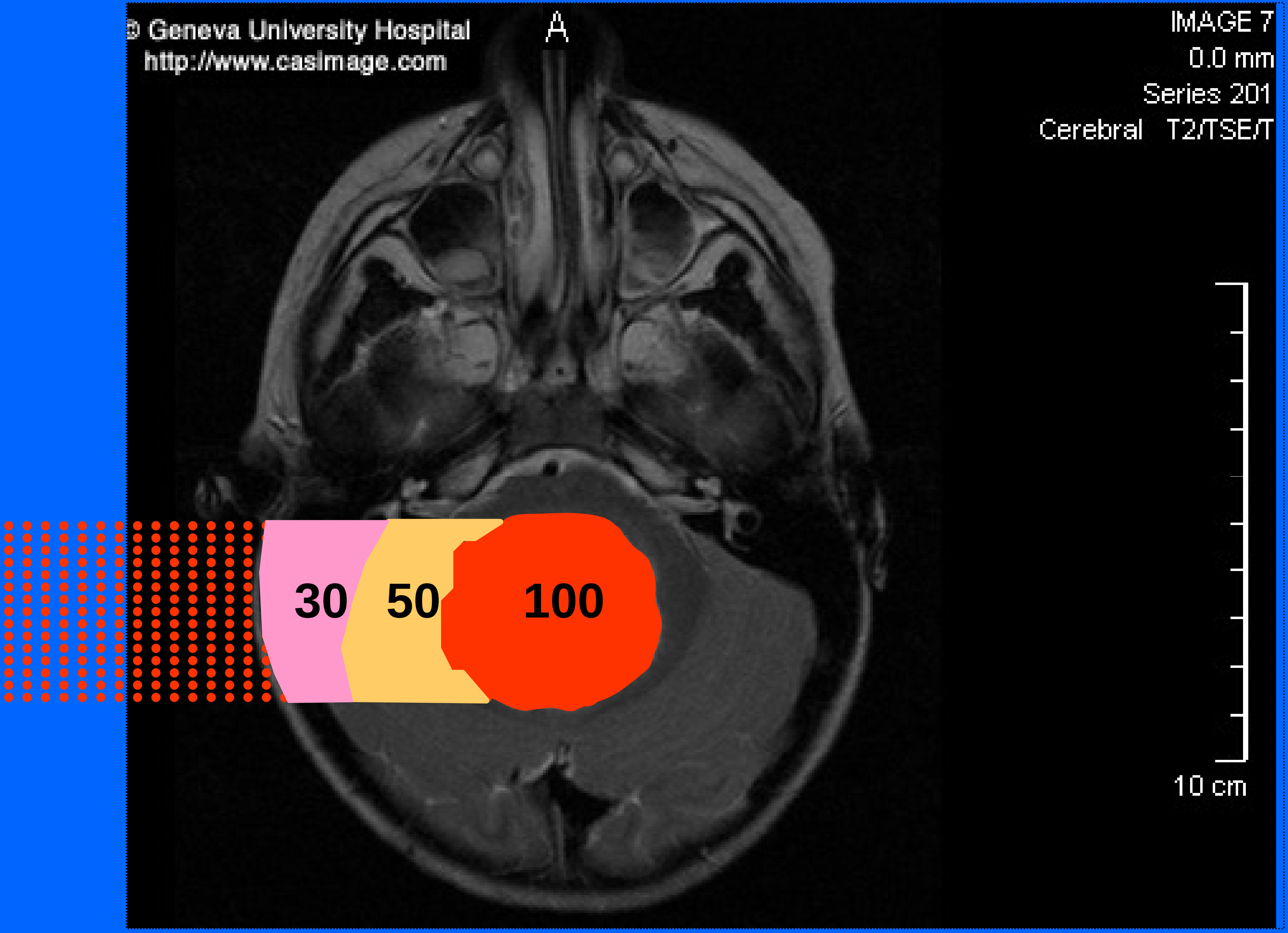
High precision RT with proton beams



High precision RT with proton beams

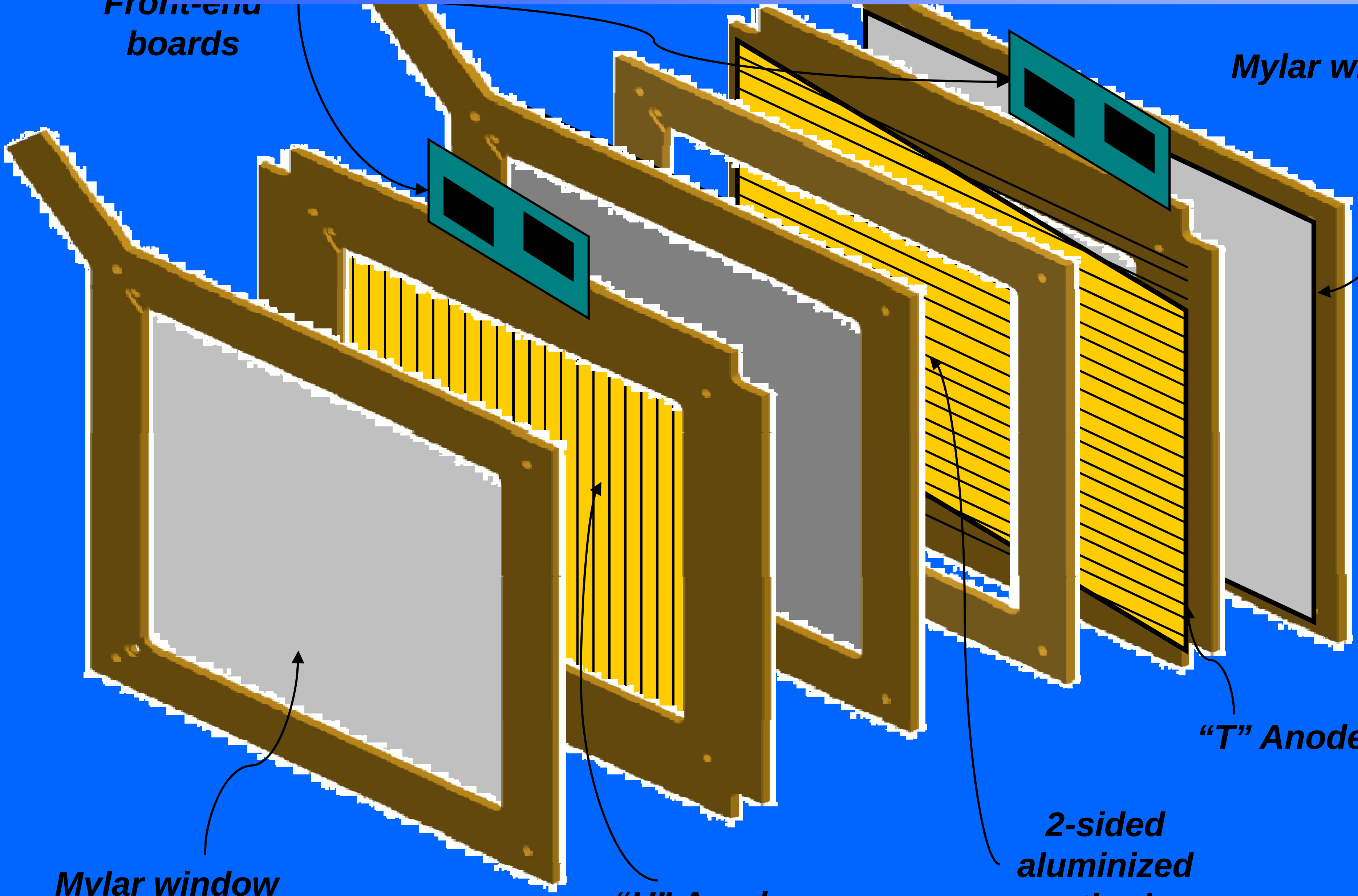


High precision RT with proton beams



High precision RT with proton beams

A detector for spot scanning:
The strip chamber developed by TERA for PSI



Front-end boards

Mylar window

Mylar window

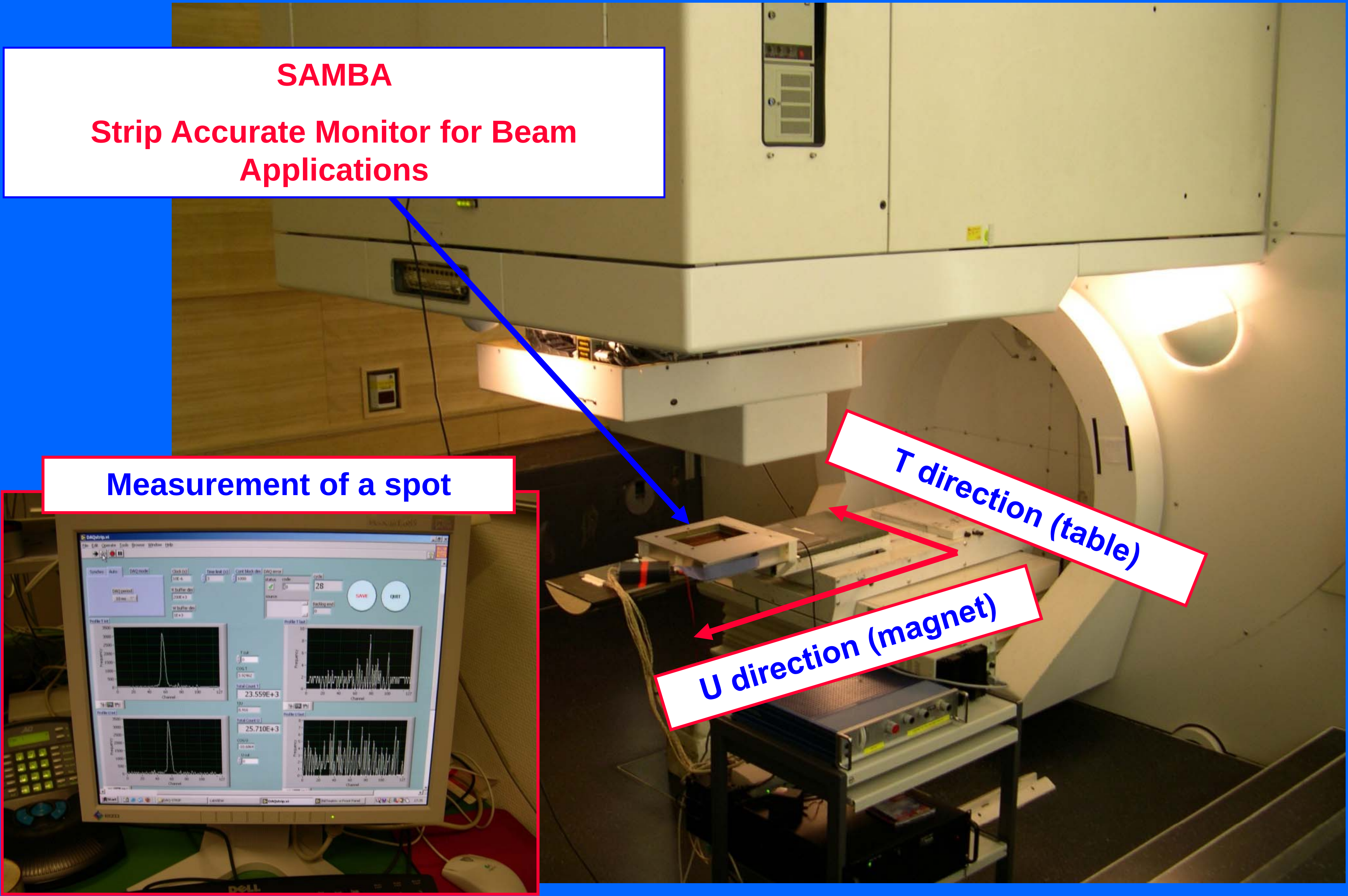
"U" Anode

2-sided aluminized cathode

"T" Anode

In collaboration with University and INFN Torino

Beam tests on Gantry1 at PSI



SAMBA

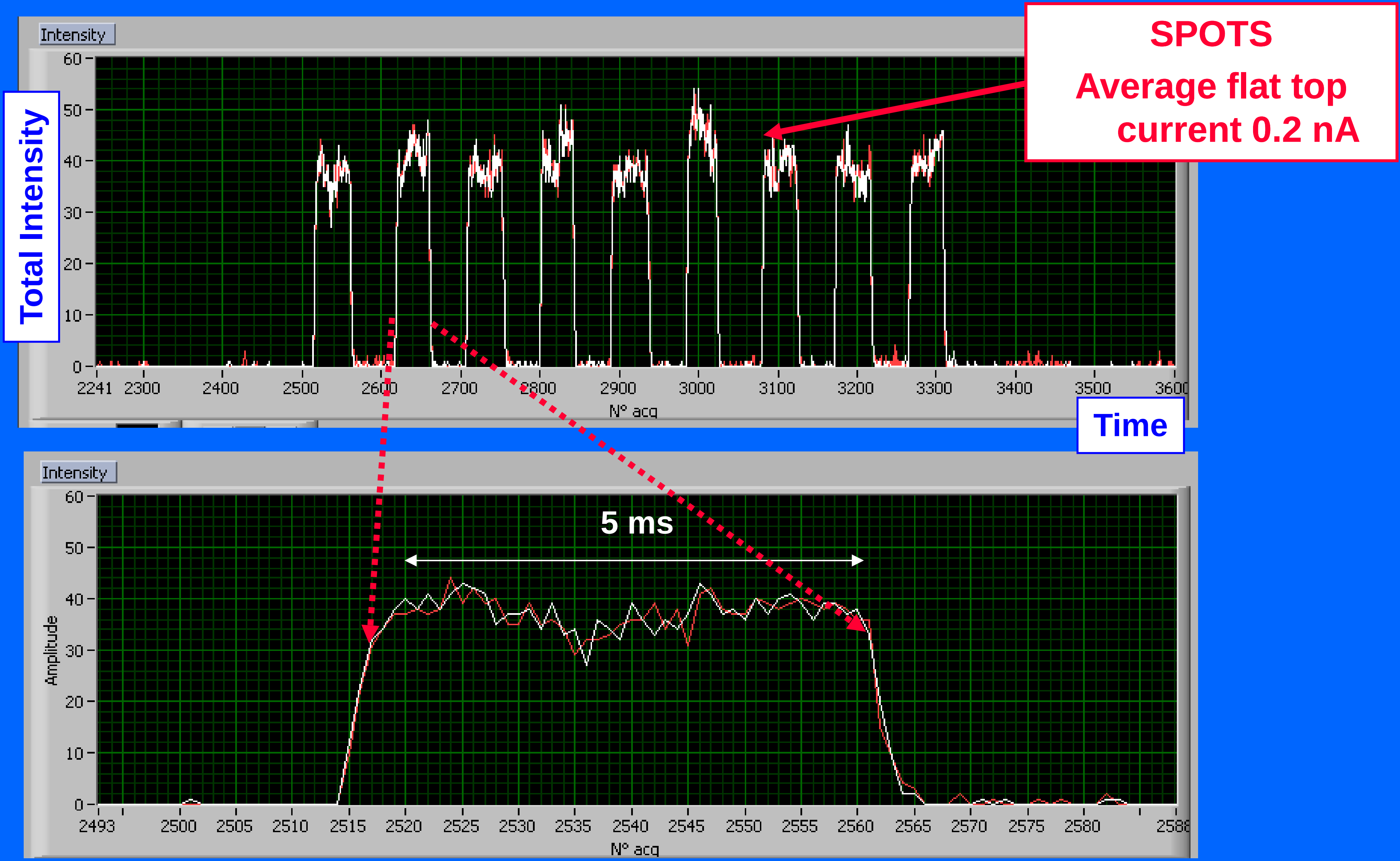
Strip Accurate Monitor for Beam Applications

Measurement of a spot

T direction (table)

U direction (magnet)

Time profile of the clinical beams



Total Intensity

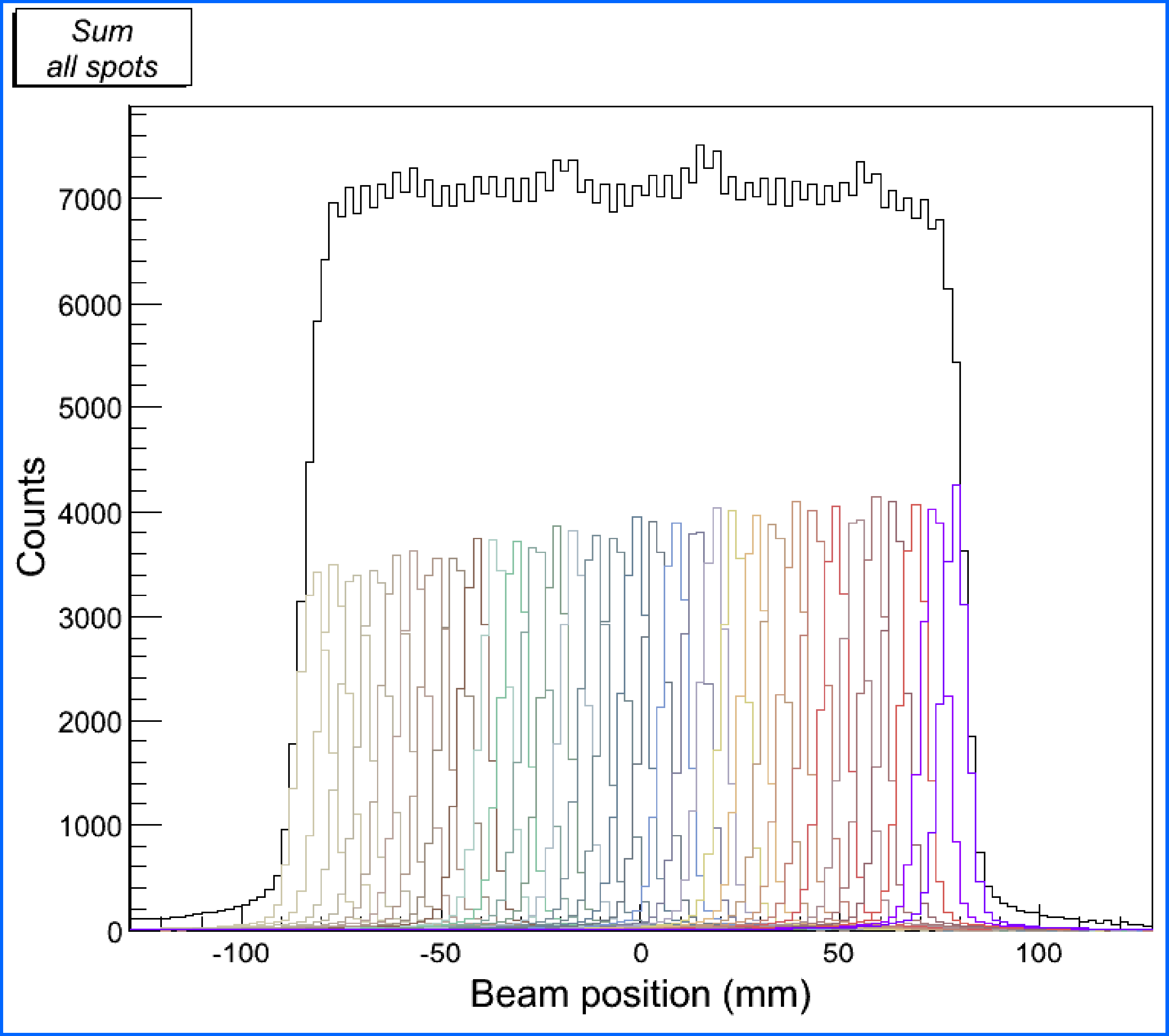
SPOTS

Average flat top current 0.2 nA

Time

5 ms

A line of dose made of spots



Patients and centres

Number of potential patients

Study by AIRO, 2003

Italian Association for Oncological Radiotharapy

X-ray therapy every 10 million inhabitants: 20'000 pts/year

Protontherapy

14.5% of X-ray patients = 2'900 pts/year

Therapy with Carbon ions for radio-resistant tumours

3% of X-ray patients = 600 pts/year

Every 50 M inhabitants

- Proton-therapy

4-5 centres

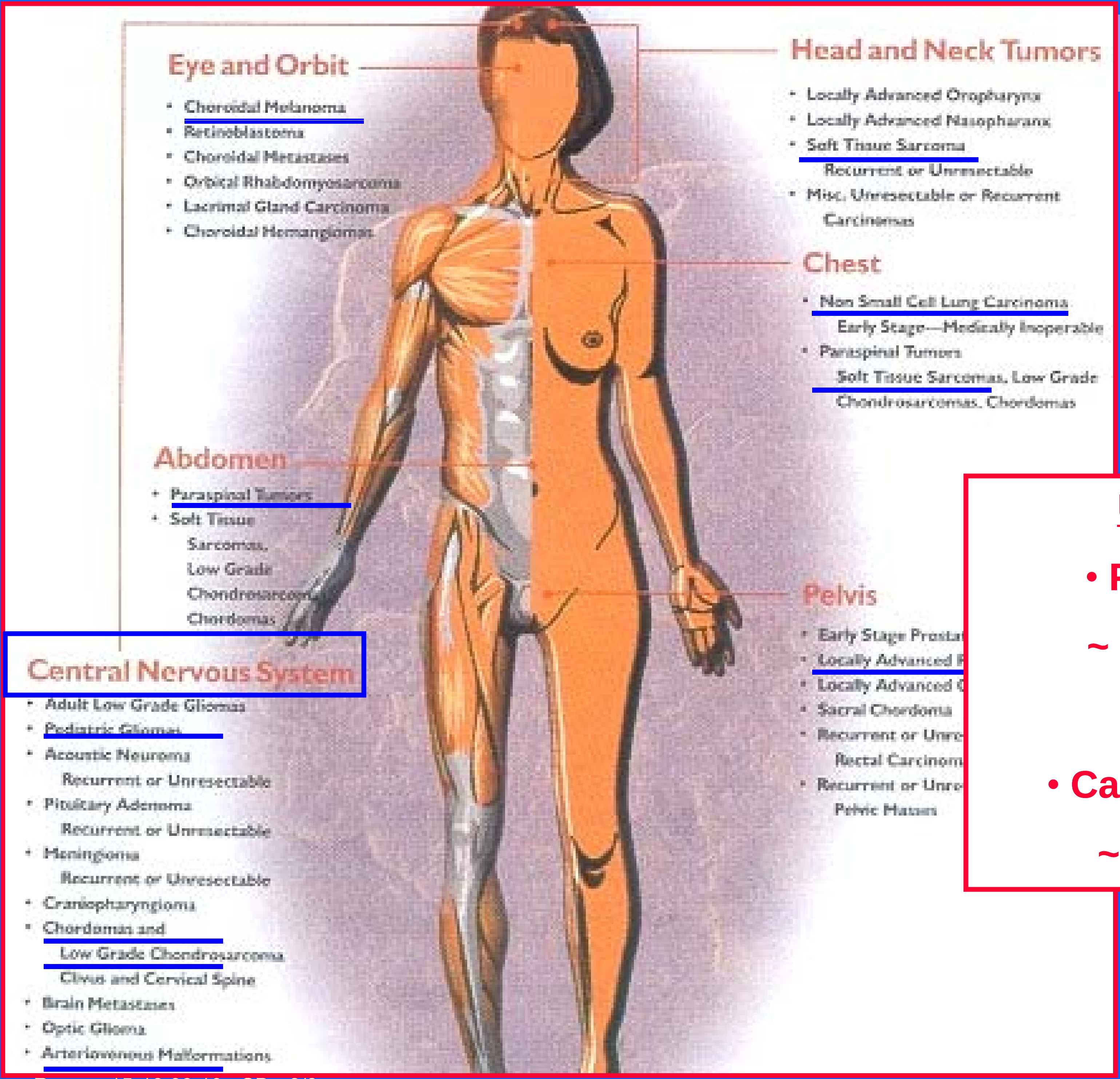
- Carbon ion therapy

1 centre

TOTAL about 3'500 pts/year

every 10 M

The sites



Eye and Orbit

- Choroidal Melanoma
- Retinoblastoma
- Choroidal Metastases
- Orbital Rhabdomyosarcoma
- Lacrimal Gland Carcinoma
- Choroidal Hemangiomas

Head and Neck Tumors

- Locally Advanced Oropharynx
- Locally Advanced Nasopharanx
- Soft Tissue Sarcoma
  Recurrent or Unresectable
- Misc. Unresectable or Recurrent
  Carcinomas

Chest

- Non Small Cell Lung Carcinoma
  Early Stage—Medically Inoperable
- Paraspinal Tumors
  Soft Tissue Sarcomas, Low Grade
  Chondrosarcomas, Chordomas

Abdomen

- Paraspinal Tumors
- Soft Tissue
  Sarcomas,
  Low Grade
  Chondrosarcomas,
  Chordomas

Pelvis

- Early Stage Prosta
- Locally Advanced F
- Locally Advanced C
- Sacral Chordoma
- Recurrent or Unre
  Rectal Carcinom
- Recurrent or Unre
  Pelvic Masses

Central Nervous System

- Adult Low Grade Gliomas
- Pediatric Gliomas
- Acoustic Neuroma
  Recurrent or Unresectable
- Pituitary Adenoma
  Recurrent or Unresectable
- Meningioma
  Recurrent or Unresectable
- Craniopharyngioma
- Chordomas and
  Low Grade Chondrosarcoma
  Clivus and Cervical Spine
- Brain Metastases
- Optic Glioma
- Arteriovenous Malformations

Up to present

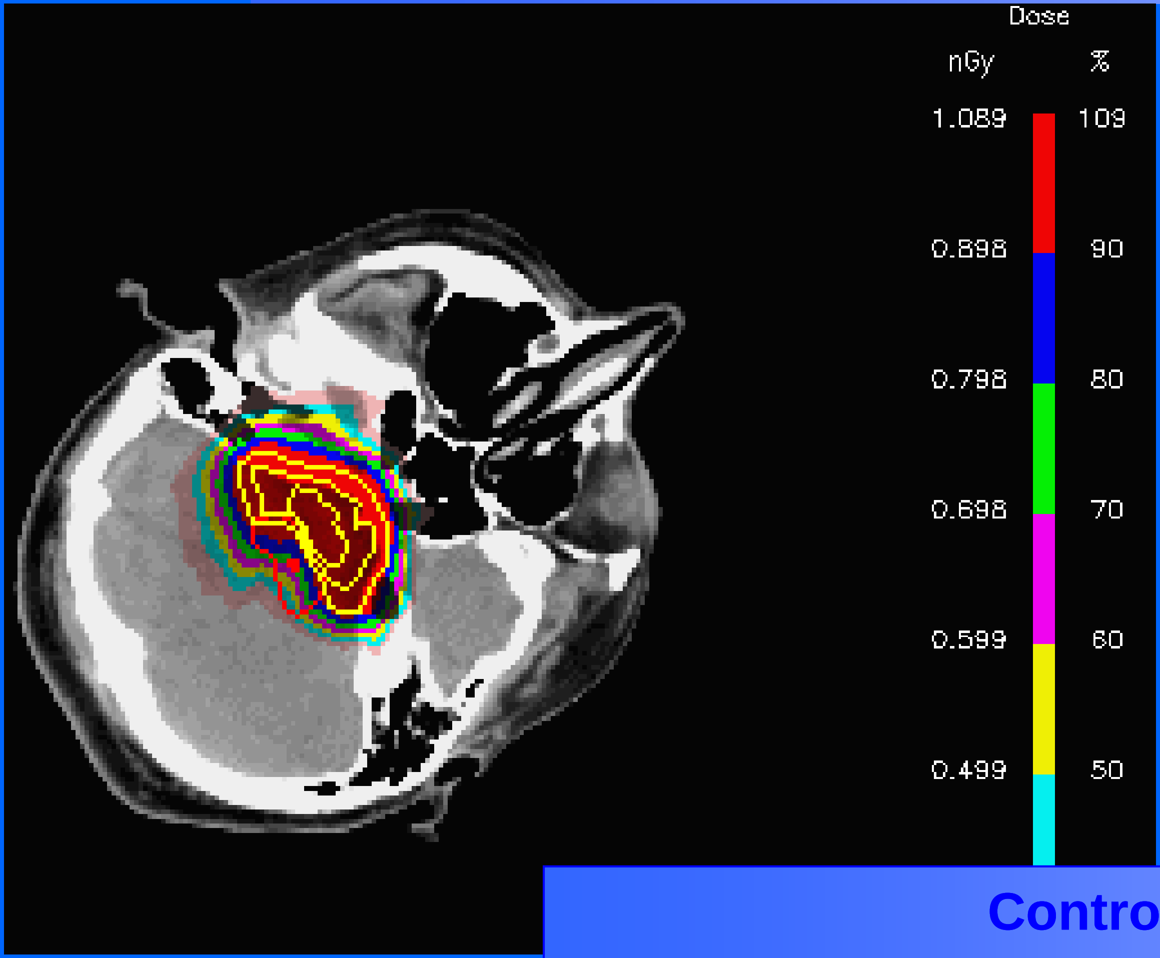
- **Proton-therapy:**

  ~ 55 000 patients

- **Carbon ion therapy:**

  ~ 5 000 patients

Tumours of the central nervous system



Control at 5 years

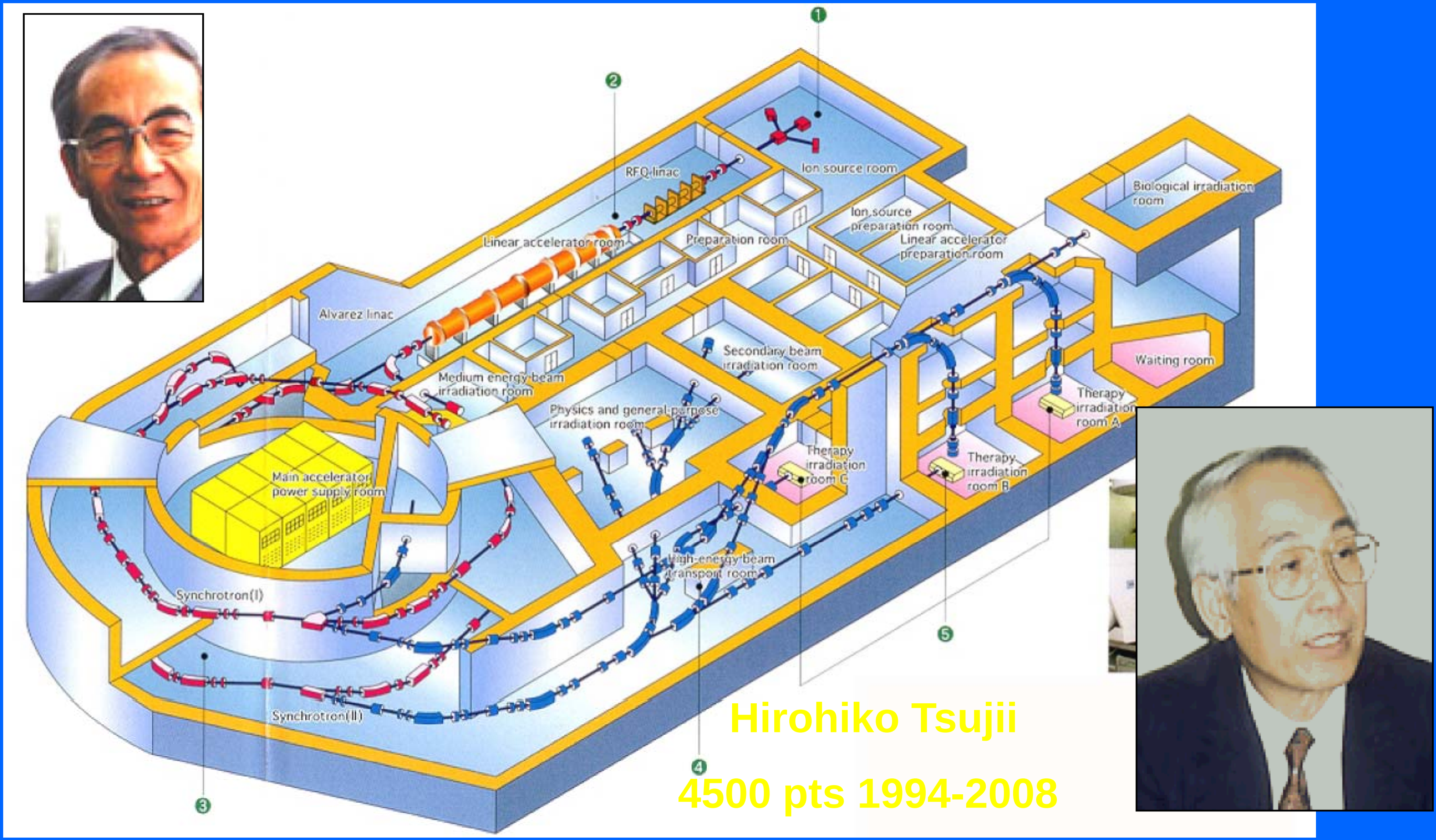
	RT	**Protons**
Chordomas	**17-50%**	**73-83%**
Chondrosarcomas	**50-60%**	**90-98%**

Carbon ion therapy in Japan

HIMAC in Chiba is the pioner of carbon therapy (Prof H. Tsujii)

Yasuo Hirao

[15] Hirao, Y. et al, "Heavy Ion Synchrotron for Medical Use: HIMAC Project at NIRS Japan" Nucl. Phys. A538, 541c (1992)



Hirohiko Tsujii

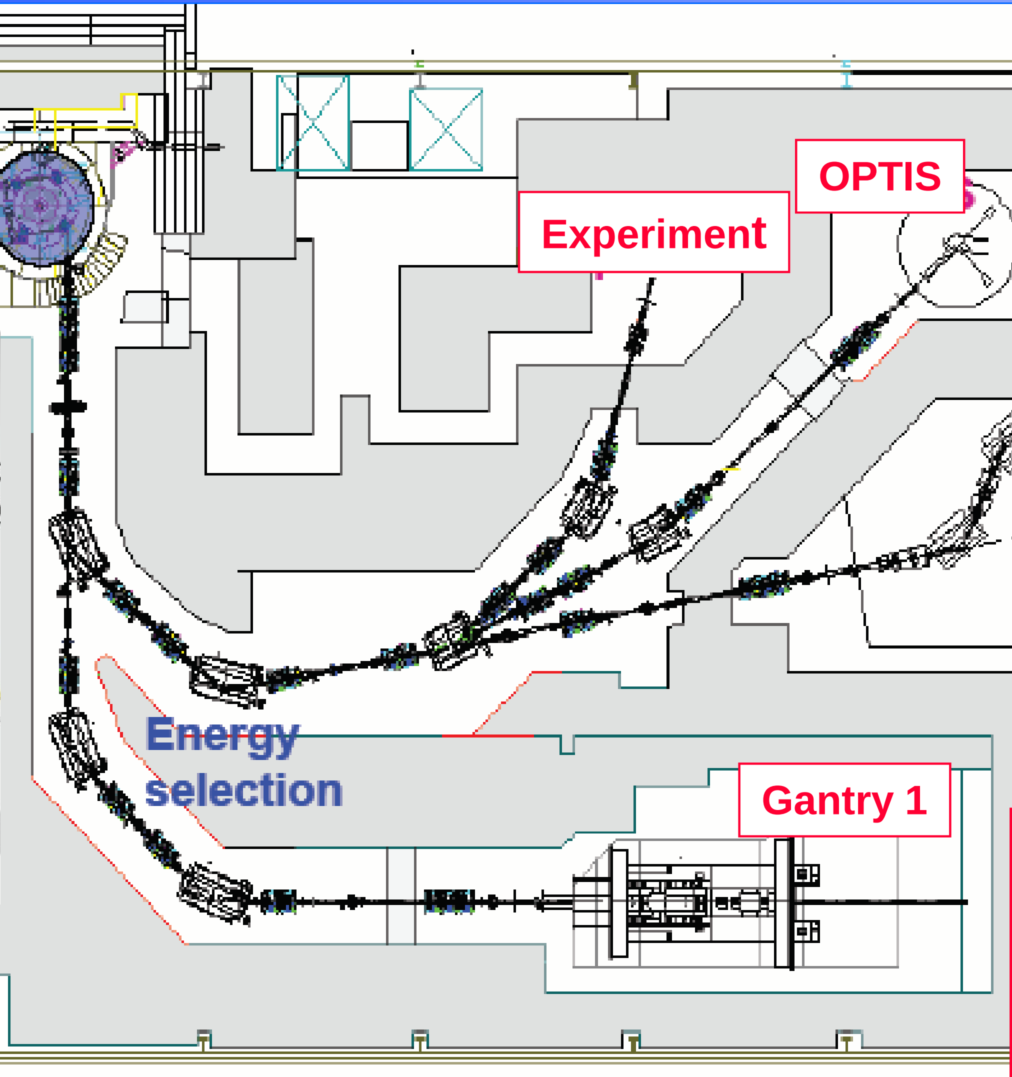
4500 pts 1994-2008

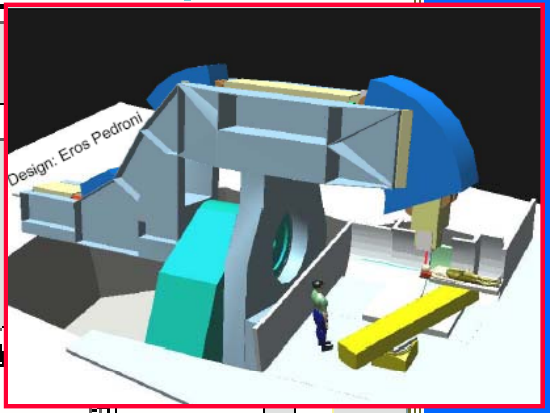
Since the cells do not repair. less fractions are possible

HIMAC: 4-9 fractions!

Hadrontherapy in Europe

PROSCAN project at PSI

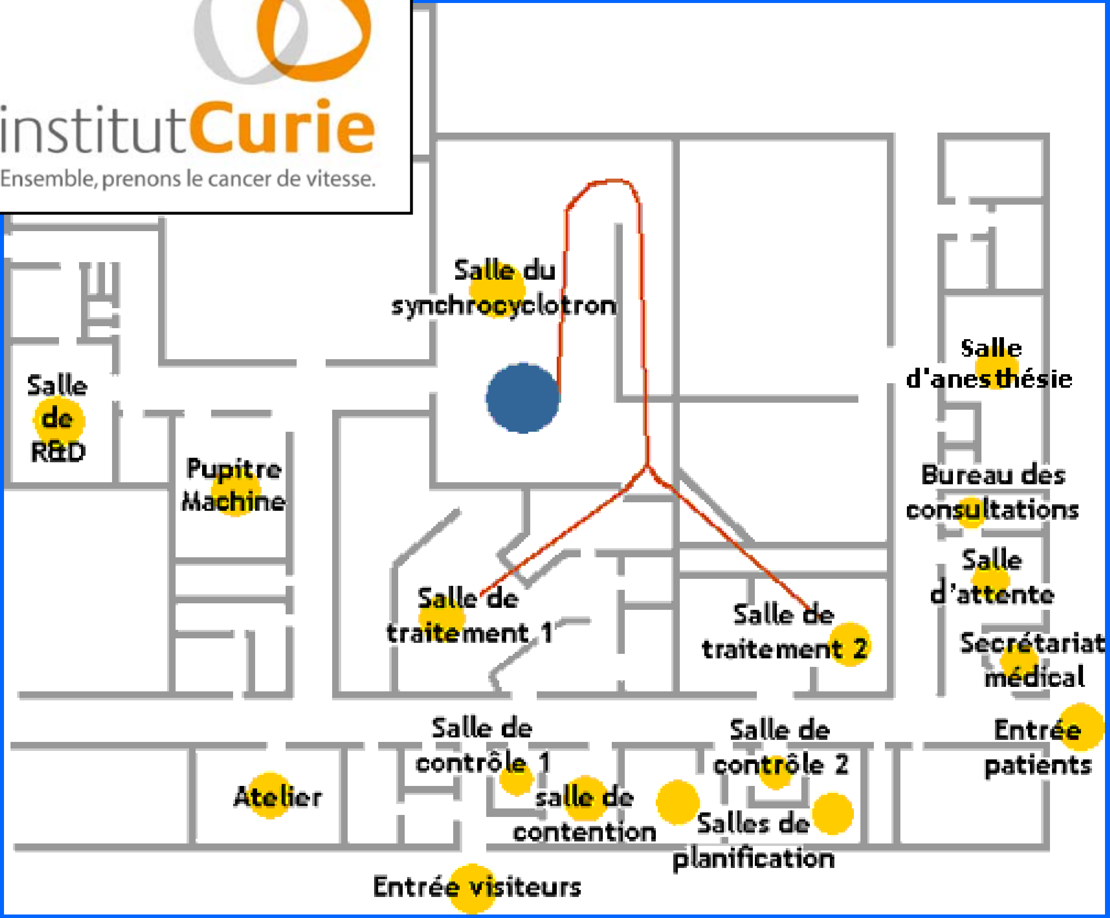


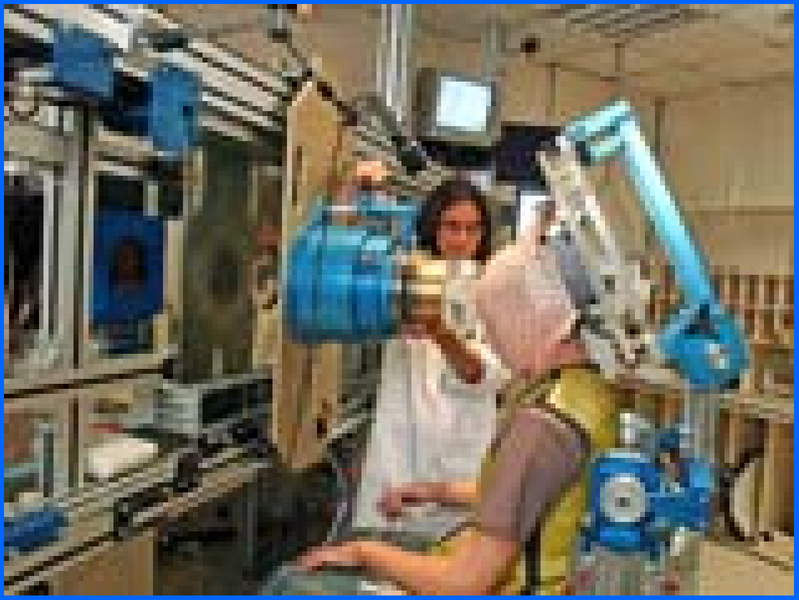


- **New SC 250 MeV proton cyclotron – Installed**
- **New proton gantry for advanced scanning**

Centre de protonthérapie de l'Institut Curie in Orsay

institutCurie
Ensemble, prenons le cancer de vitesse.



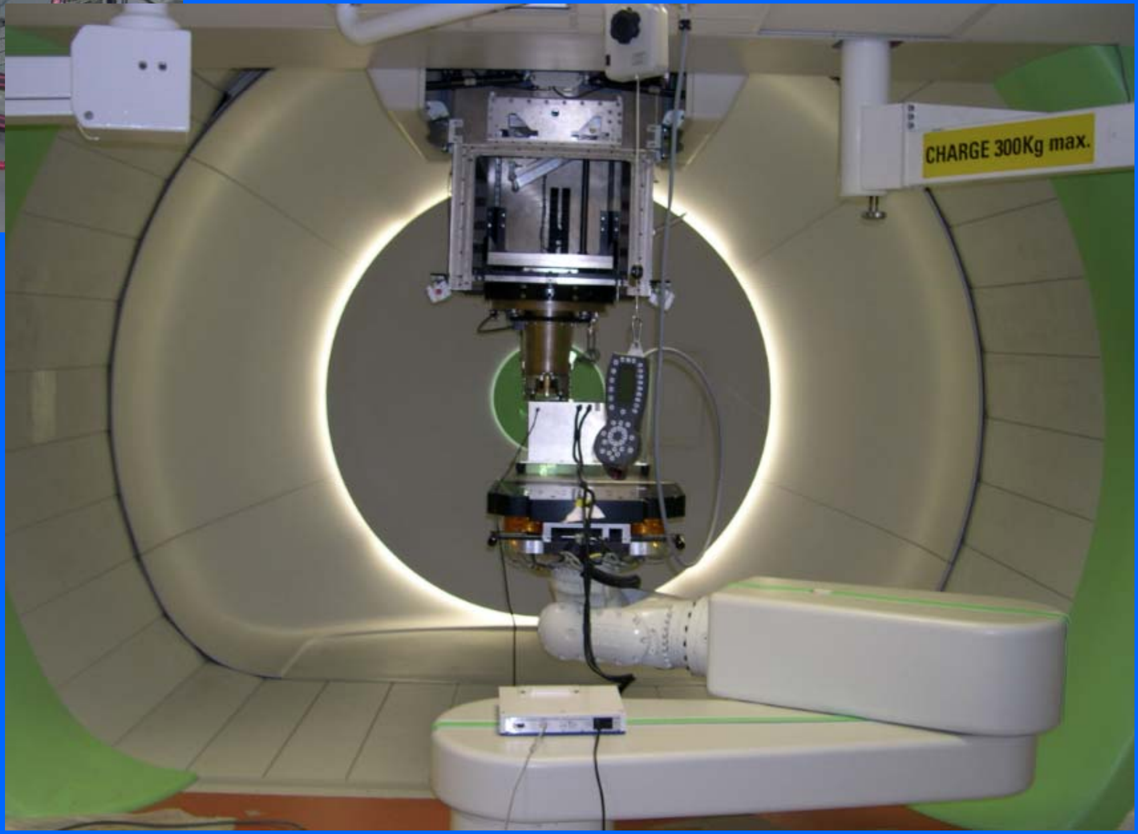


- Active from 1991
- 5000 patients treated (Nov-09)
- 250 pt/year ophthalmology, 100 pts/year deep seated (Head and neck)
- Extension (New cyclotron + Gantry by the Belgian company IBA)

The ‘new’ CPO

- New 230 MeV cyclotron
- Installed in October 2008
- New gantry now under commissioning

- Treatments have not been stopped during the installation of the new cyclotron and the new gantry!
- Treatments with the new equipment + the 2 existing rooms foreseen in 6 months



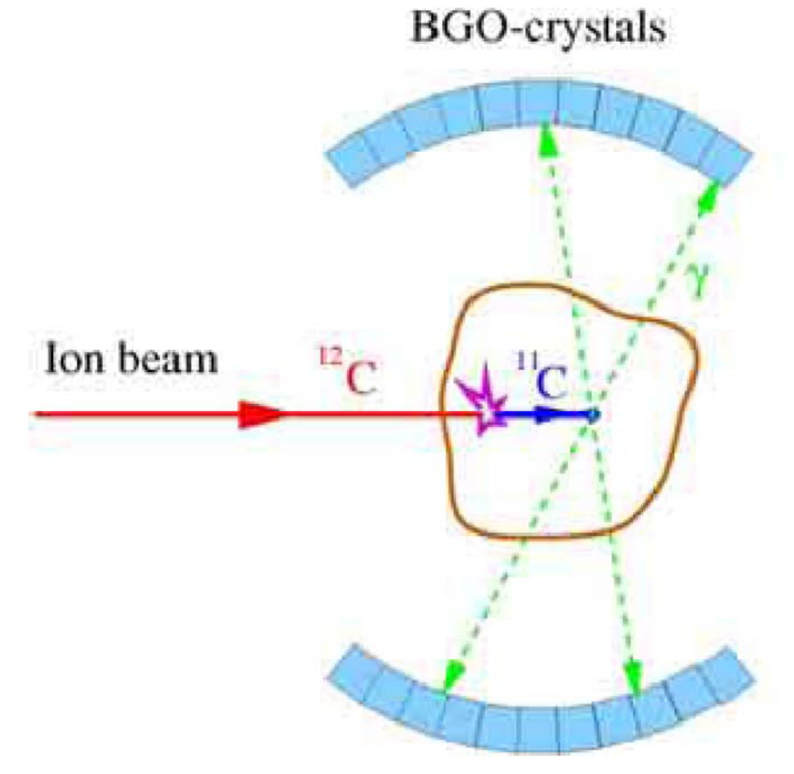
Carbon ion therapy in Europe

1998 - GSI pilot project (G. Kraft)

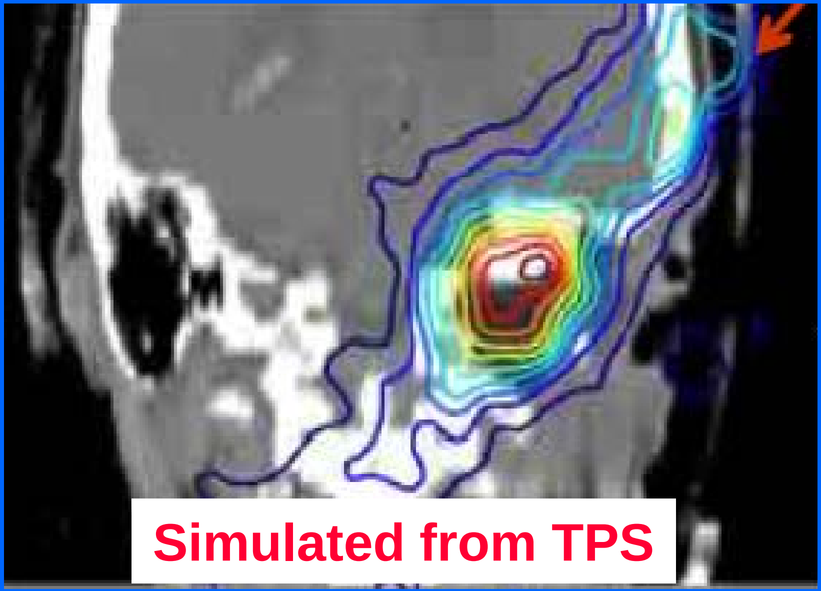
200 patients treated with carbon ions

PET on-beam

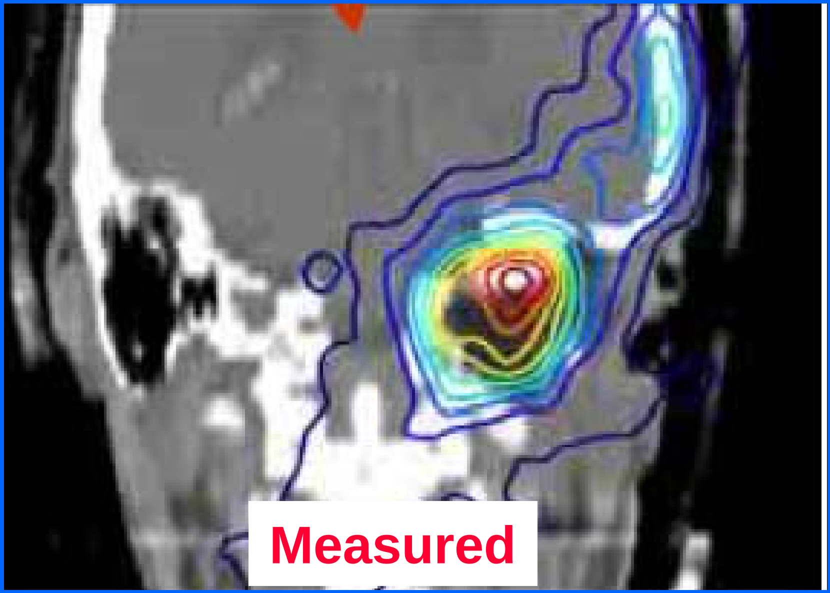
PET on-beam



Measurement of the ”real” dose given to the patient

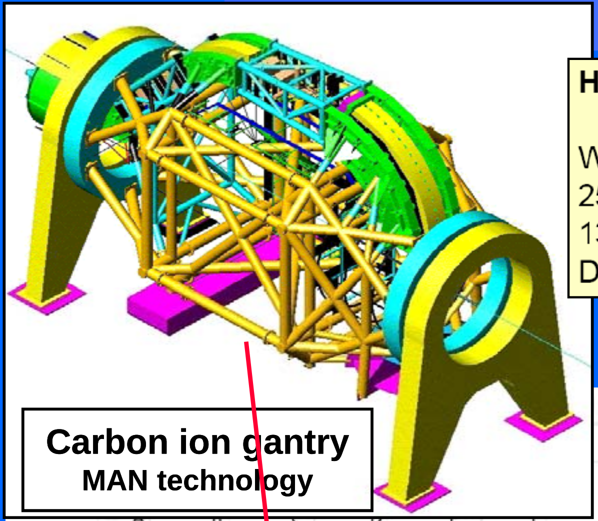


Simulated from TPS



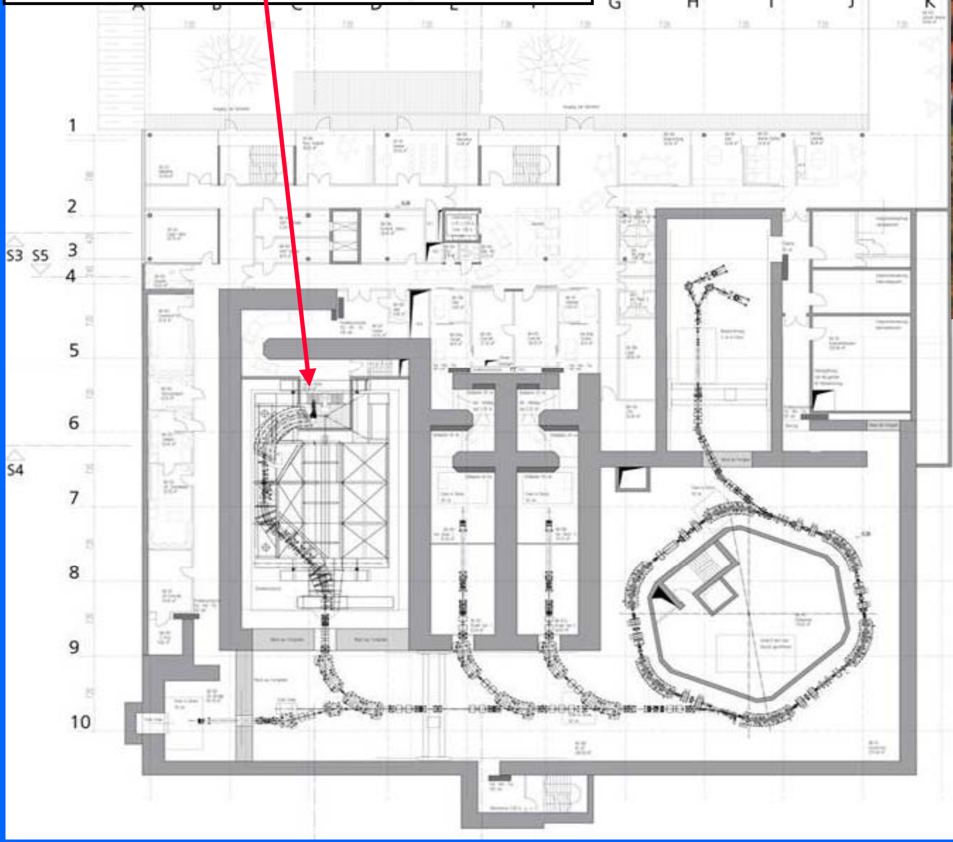
Measured

HIT – University of Heidelberg



Heavy-ion Gantry

Weight: 600 t
25 m long
13 m diameter
Deformation < 0.5 mm

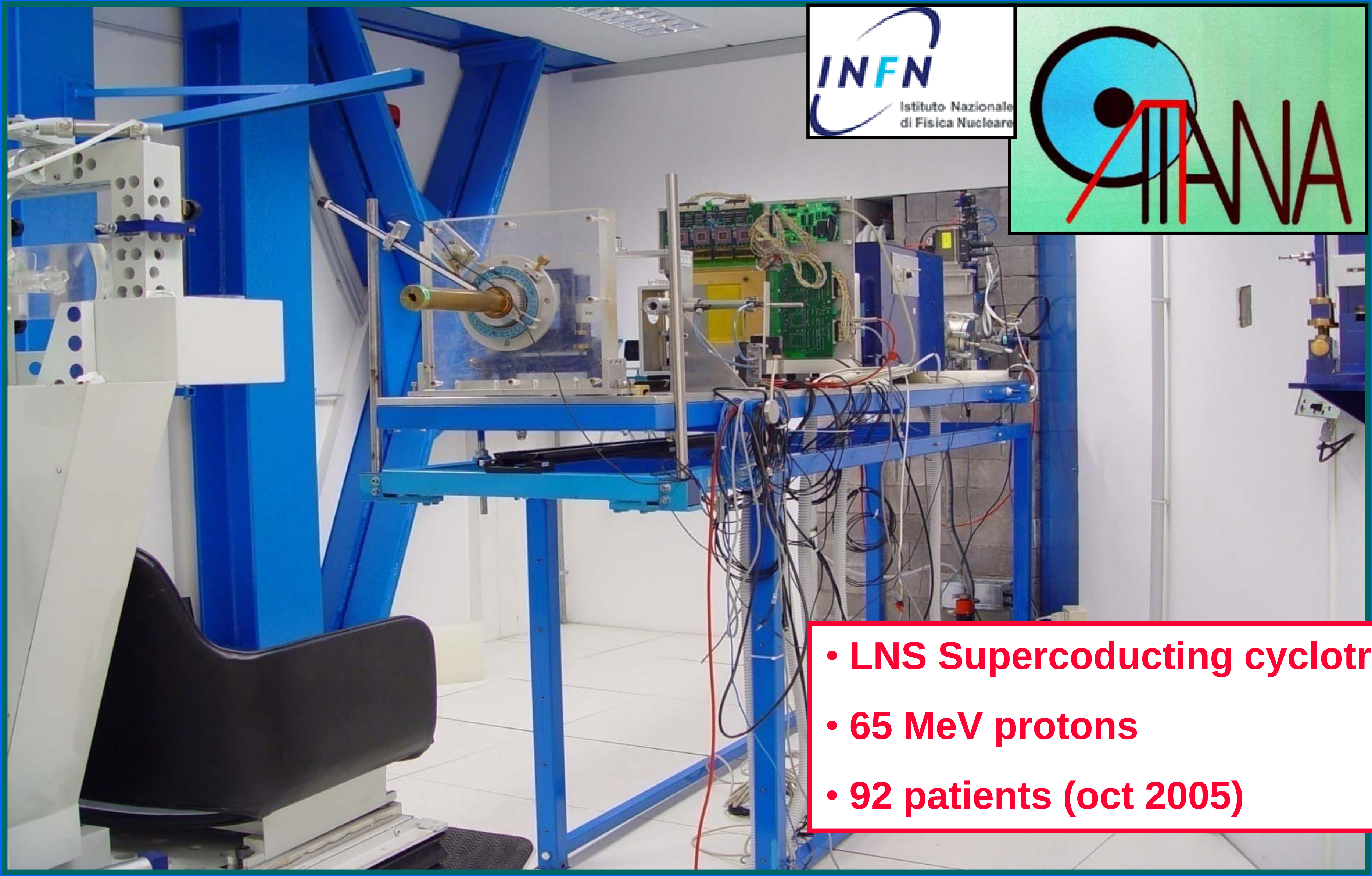



December 2006

- **Hospital based centre**
- **Project started in 2001**
- **First patient treated in November 2009**
- **First C-ion gantry**

Hadrontherapy in Italy

The eye melanoma treatment at INFN-LNS in Catania



INFN
Istituto Nazionale
di Fisica Nucleare

CATANA

- **LNS Supercoducting cyclotron**
- **65 MeV protons**
- **92 patients (oct 2005)**

The TERA Foundation

- **Not-for-profit foundation created in 1992 by Ugo Amaldi and recognized by the Italian Ministry of Health in 1994**

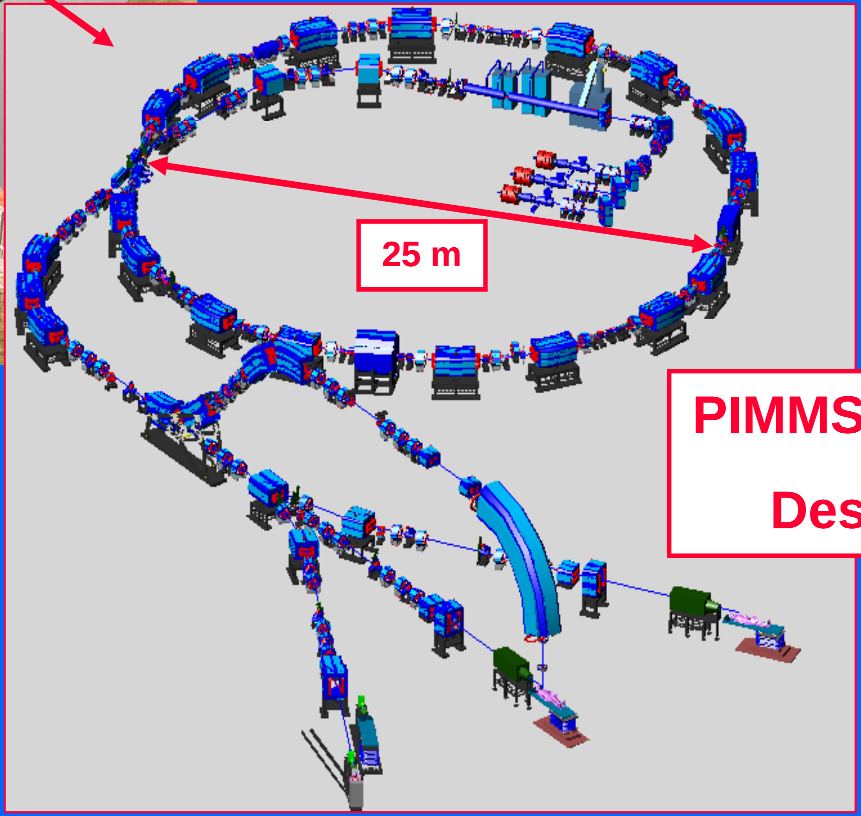
- **Research in the field of particle accelerators and detectors for hadron-therapy**

- **First goal: the Italian National Centre (CNAO) now under construction in Pavia**

Ugo Amaldi

CNAO on the Pavia site

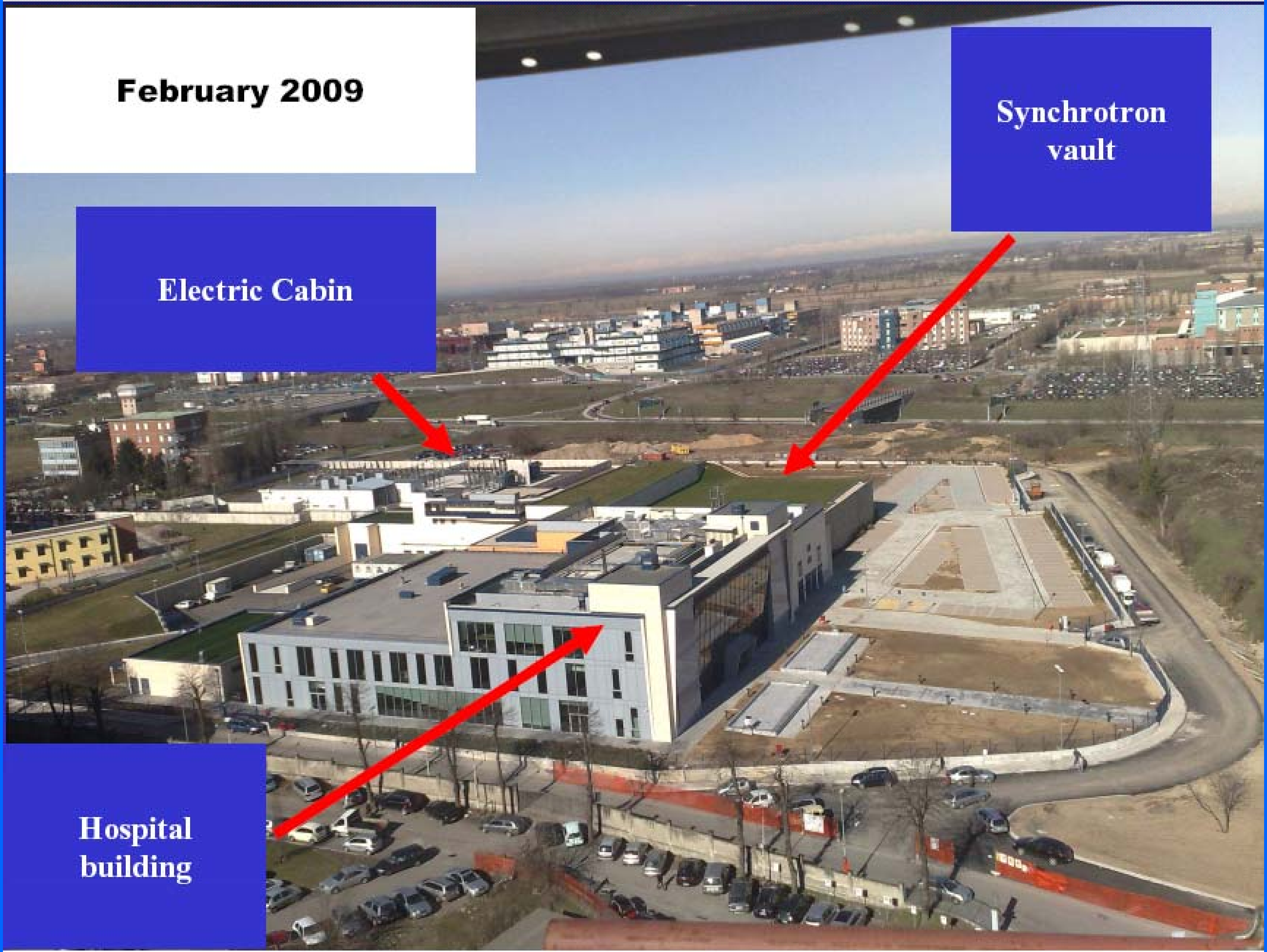
- **Main source of funds: Italian Health Ministry**
- **Ground breaking: March 2005**



PIMMS/TERA Design

- **Hospital based centre**
- **Protons and carbon ions**

CNAO


February 2009

CNAO

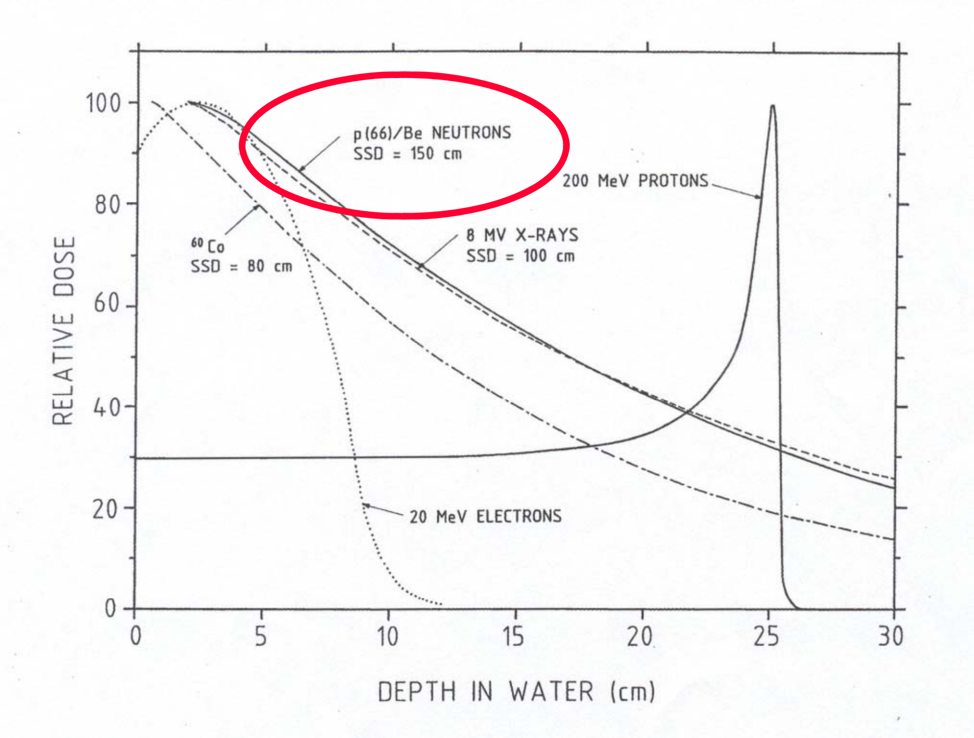
- **Hospital based centre**
- **Project started in 2003**
- **Beams in the synchrotron foreseen in December 2009**

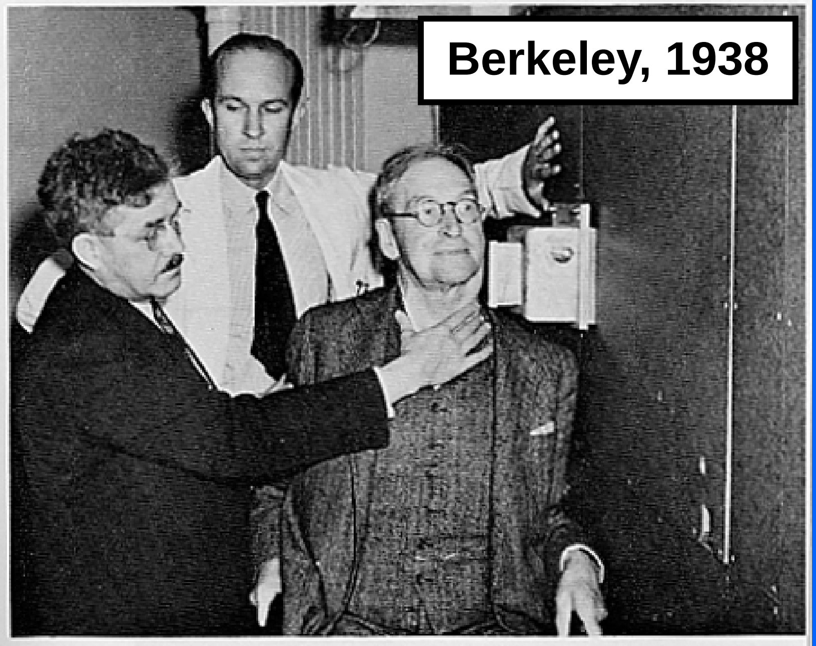

Chair for head and neck

The synchrotron

Neutrons in cancer therapy

Hadrontherapy with fast neutrons



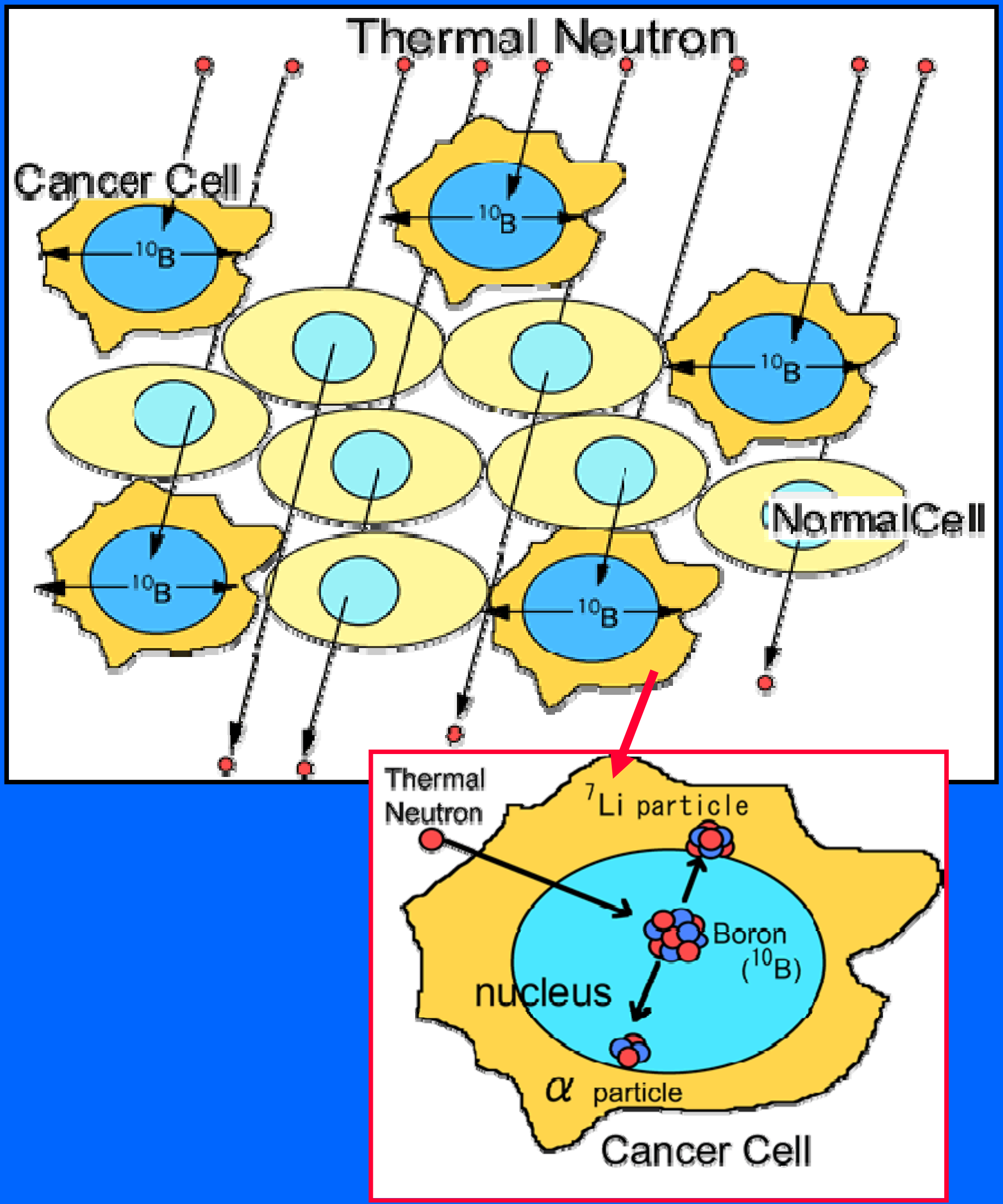


Berkeley, 1938

PLATE 8.4 Robert Stone and John Lawrence treating Robert Penney at the 60-inch neutron port. LBL.

- Neutrons are neutral → no Bragg peak
- MeV neutrons are produced with cyclotrons (p + Be reaction)
- MeV neutrons produce nuclear interactions → high LET radiation
- Used for radio resistant tumours (ex. salivary glands, tongue, brain)
- About 9 centers in the world [ex. Orleans (France), Fermilab (USA)]

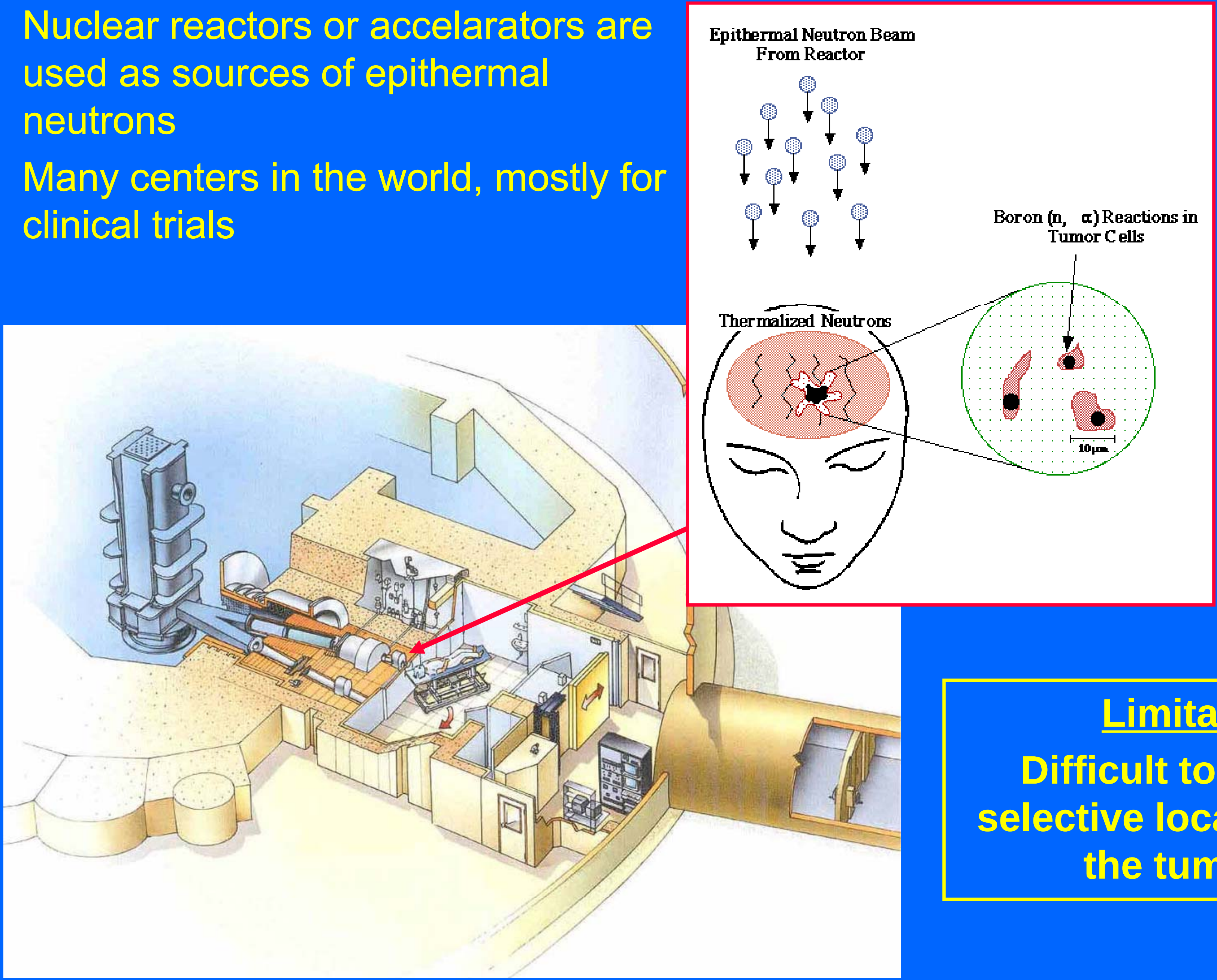
Boron Neutron Capture Therapy (BNCT)



- Concept proposed in 1936 by G.L. Locher (only 4 years after the discovery of the neutron!)
- Bring into cancer cells a nuclide that captures neutrons and disintegrates into high LET fragments
- ^{10}B is used
  - Available (20% of natural B)
  - Fragments of high LET and path lengths approximately one cell diameter (about 12 microns)
  - Well known chemistry

BNCT facilities

- Nuclear reactors or accelarators are used as sources of epithermal neutrons
- Many centers in the world, mostly for clinical trials



<u>Limitation</u>

Difficult to achieve selective localization in the tumour !

End of part VI