Present and Future of Hadrontherapy

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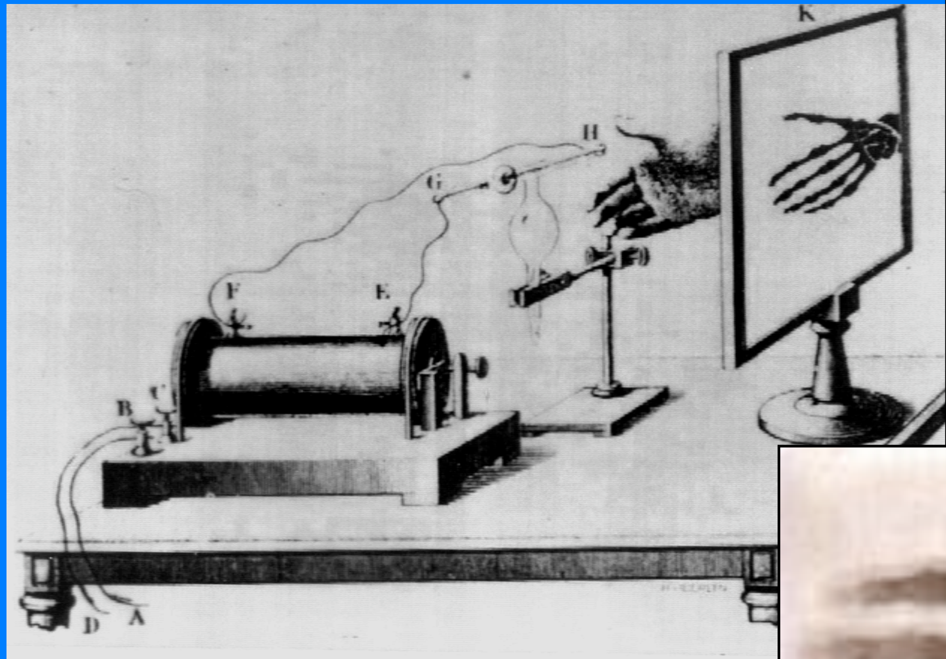
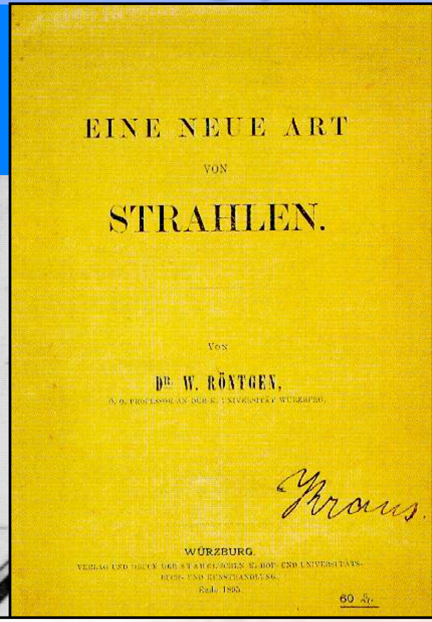
Outline

- Introduction
  - Fundamental research in physics and medical applications
- Conventional radiation therapy
- Hadrontherapy, the new frontier of cancer radiation therapy
  - Proton-therapy
  - Carbon ion therapy
- Some new ideas for the future of hadrontherapy
- Conclusions and outlook

- November 1895 : discovery of X rays

Wilhelm Conrad Röntgen



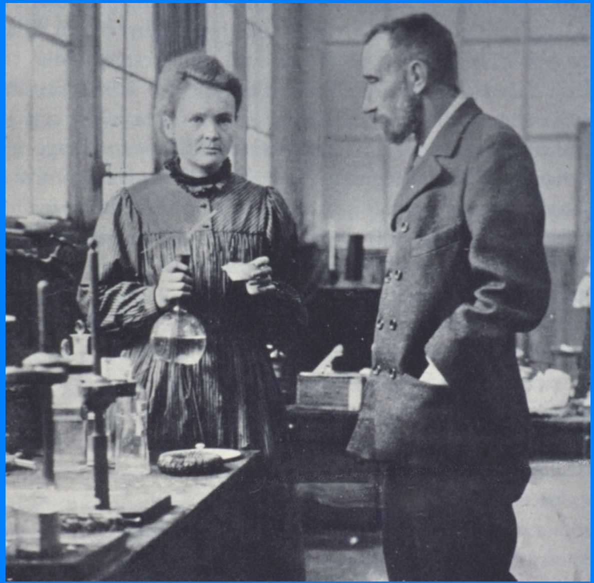


- December 1895 : first radiography
- First application of *photons* to medicine much before Einstein (1905) and the concept of light quanta!

The starting point

• 1896 : discovery of natural radioactivity

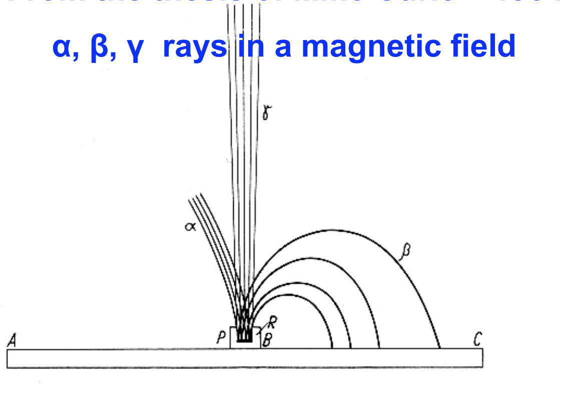
Henri Bequerel

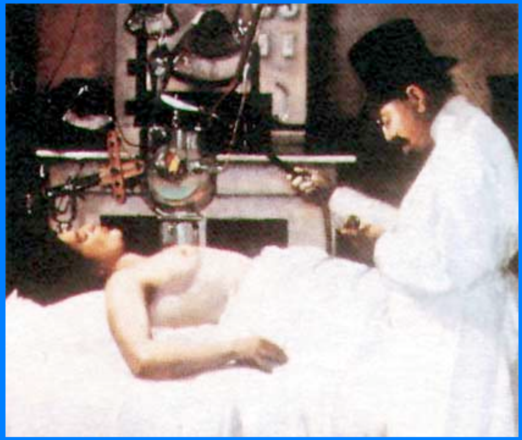


Maria Skłodowska-Curie and Pierre Curie

From the thesis of Mme Curie – 1904

α, β, γ rays in a magnetic field





• 1908 : first attempts of radiation therapy in France

• The name "*curiethérapie*" is still used!

Picture: Dr. Chicolot, Musée de l'Assistance Publique, Paris

STOCKHOLM

1902 1912

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

- **Basic concept: Local control of the tumour!**

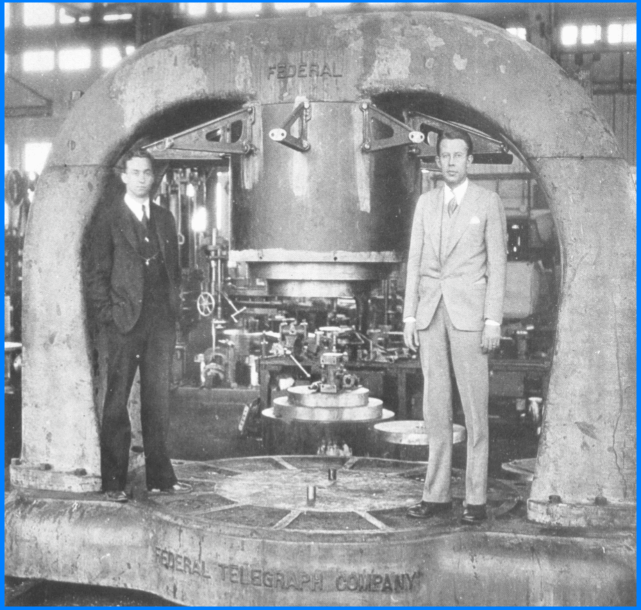
A big step forward…

…in high energy physics and in

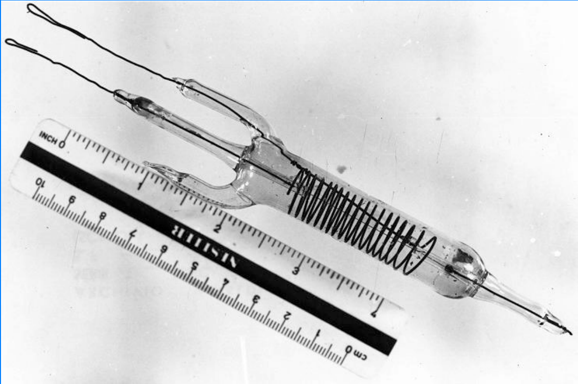
- Medical diagnostics
- Cancer radiation therapy

is due to the development of three fundamental tools

- Particle accelerators
- Particle detectors
- Computers

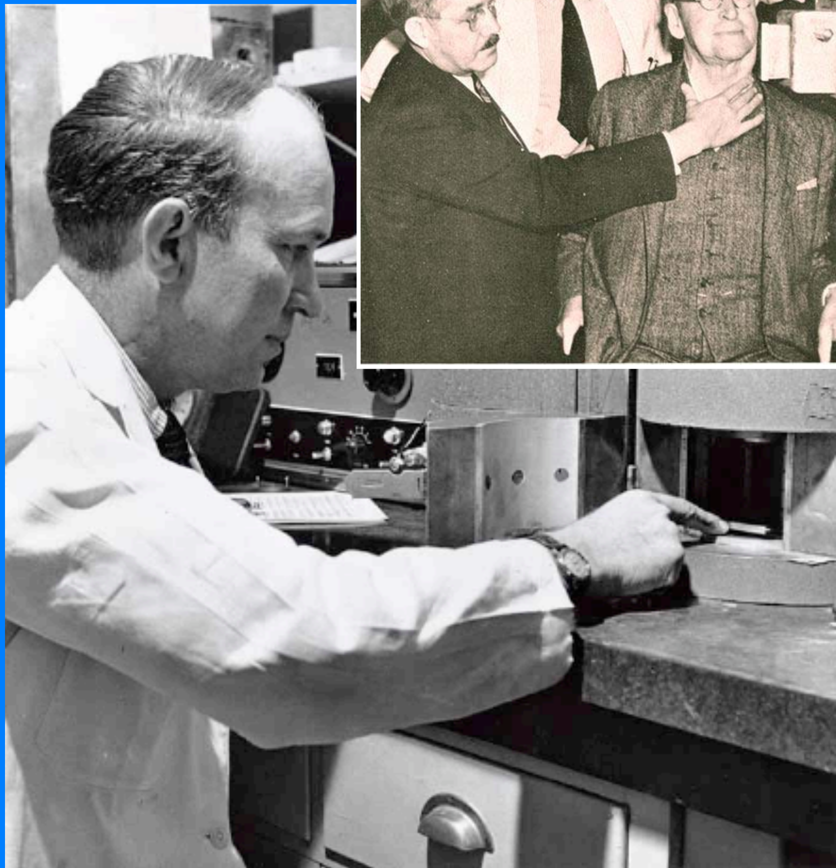


M. S. Livingston and E. Lawrence with the first cyclotron



Geiger-Müller counter built by E. Fermi and his group in Rome

The Lawrence brothers and interdisciplinary research



John H. Lawrence made the first clinical therapeutic application of an artificial radionuclide when he used phosphorus-32 to treat leukemia. (1936)

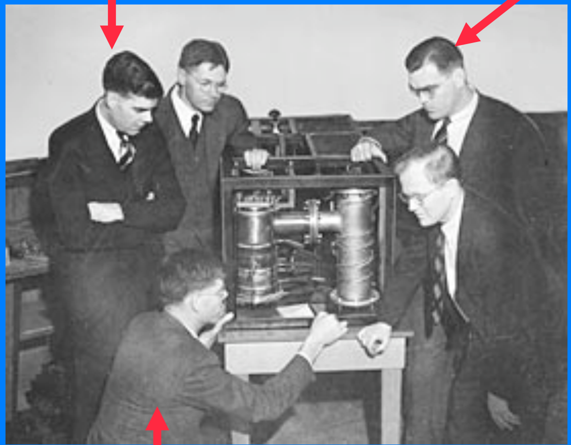
- John Lawrence, brother of Ernest, was a medical doctor
- They were both working in Berkeley
- First use of artificially produced isotopes for medical diagnostics
- First irradiations of salivary gland tumours with neutron beams

An interdisciplinary environment helps innovation!

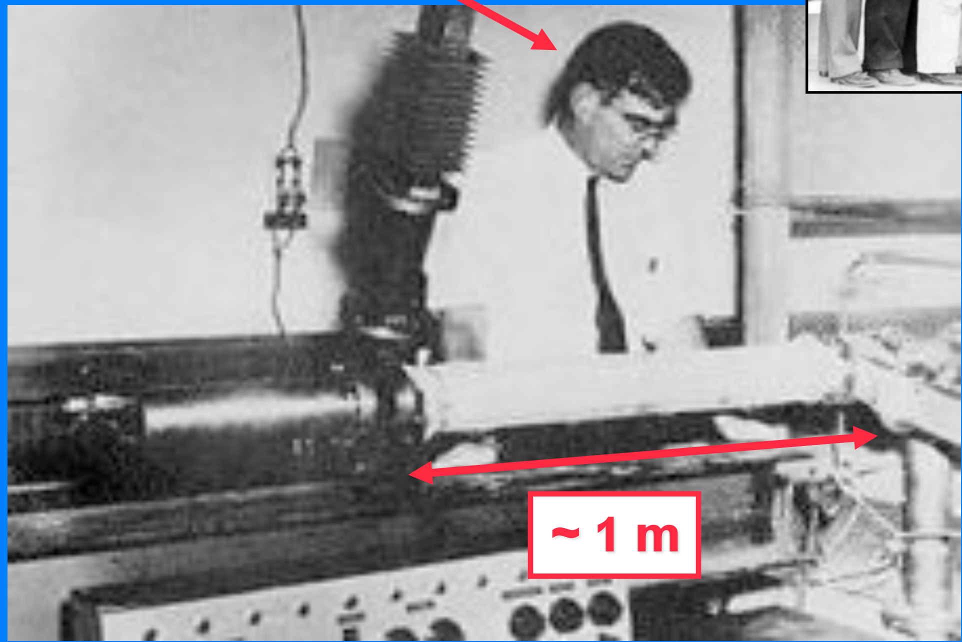
The electron linac

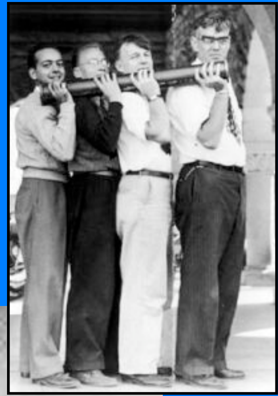
Sigurd Varian

William W. Hansen



Russell Varian





1939

Invention of the klystron

The electron linac is used today in hospital based conventional radiation therapy facilities

1947
first linac for electrons
4.5 MeV and 3 GHz

Accelerators running in the world

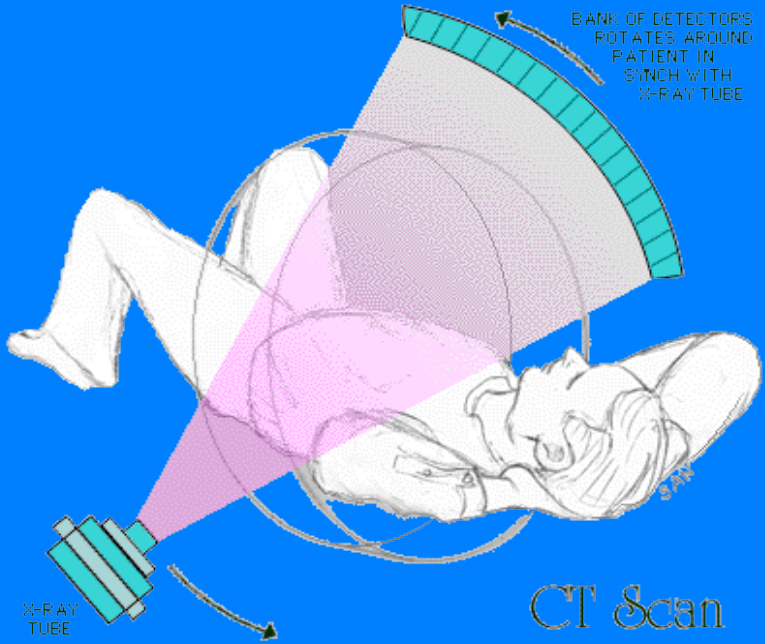
CATEGORY OF ACCELERATORS	NUMBER IN USE (*)
High Energy acc. (E >1GeV)	~120
Synchrotron radiation sources	>100
Medical radioisotope production	~200 } 9000
Radiotherapy accelerators	> 7500 } 9000
Research acc. included biomedical research	~1000 } 9000
Acc. for industrial processing and research	~1500
Ion implanters, surface modification	>7000
TOTAL	> 17500
(*) W. Maciszewski and W. Scharf: Int. J. of Radiation Oncology, 2004	

- **About half are used for bio-medical applications!**

Diagnostics and imaging are essential!

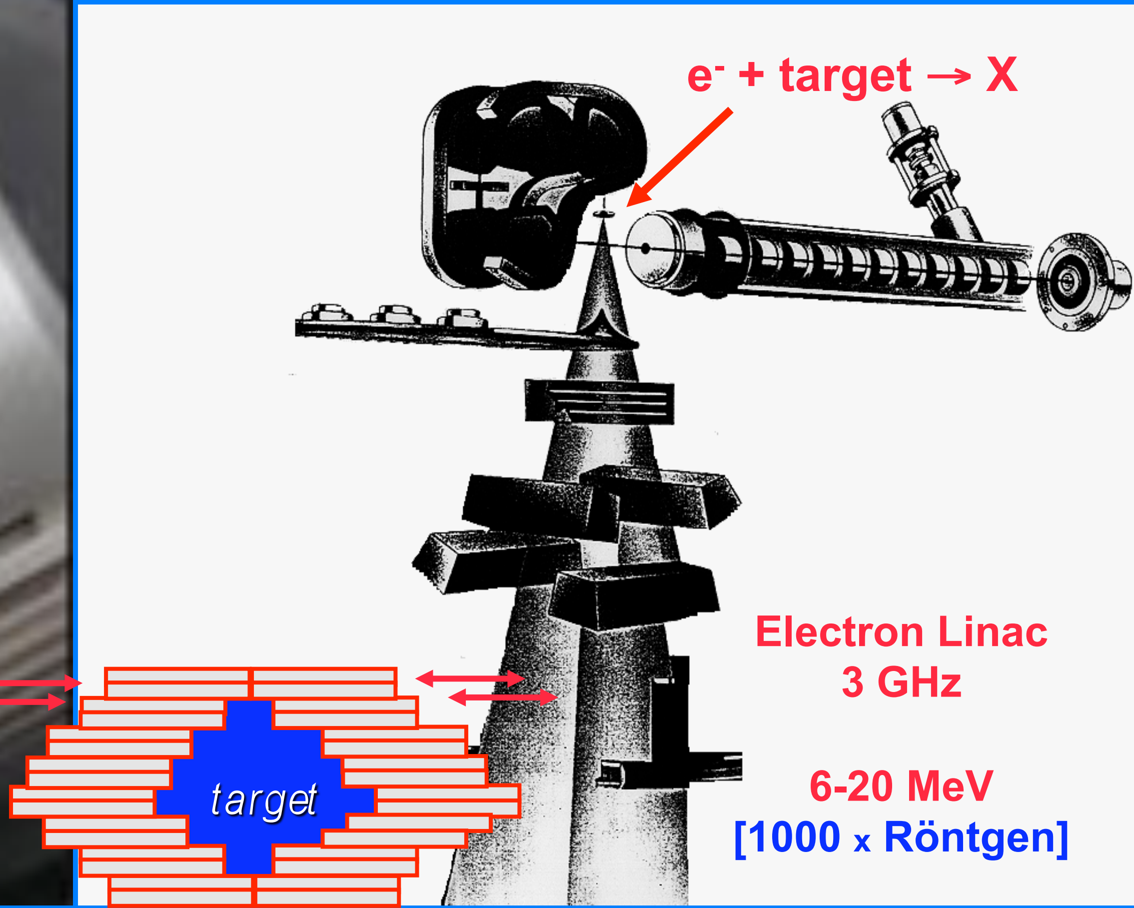
Abdomen

Computer Tomography (CT)



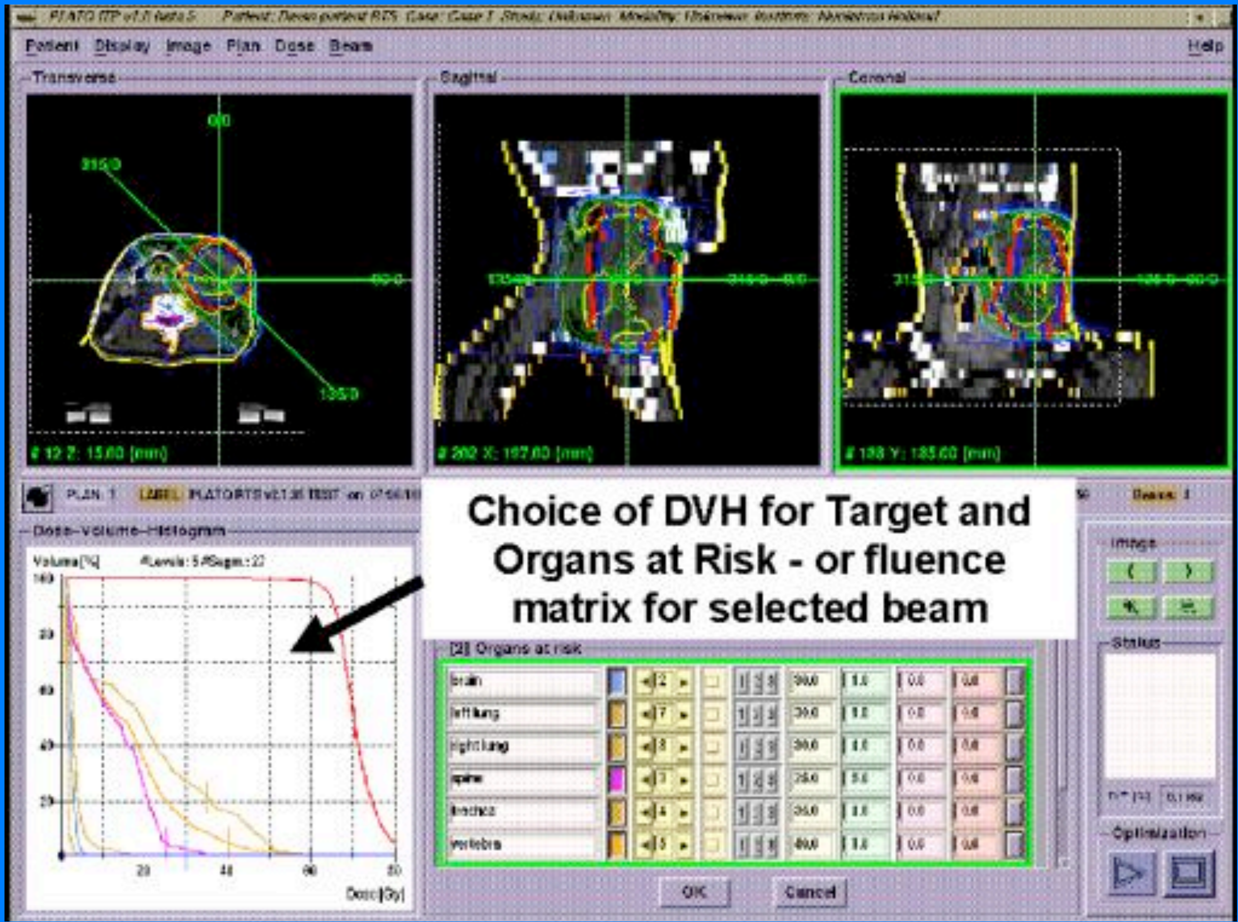
- Measurement of the electron density
- Information on the morphology

Radiotherapy with X-rays



- **Electron linacs to produce gamma rays (called X-rays by medical doctors)**
- **20'000 patients/year every 10 million inhabitants**

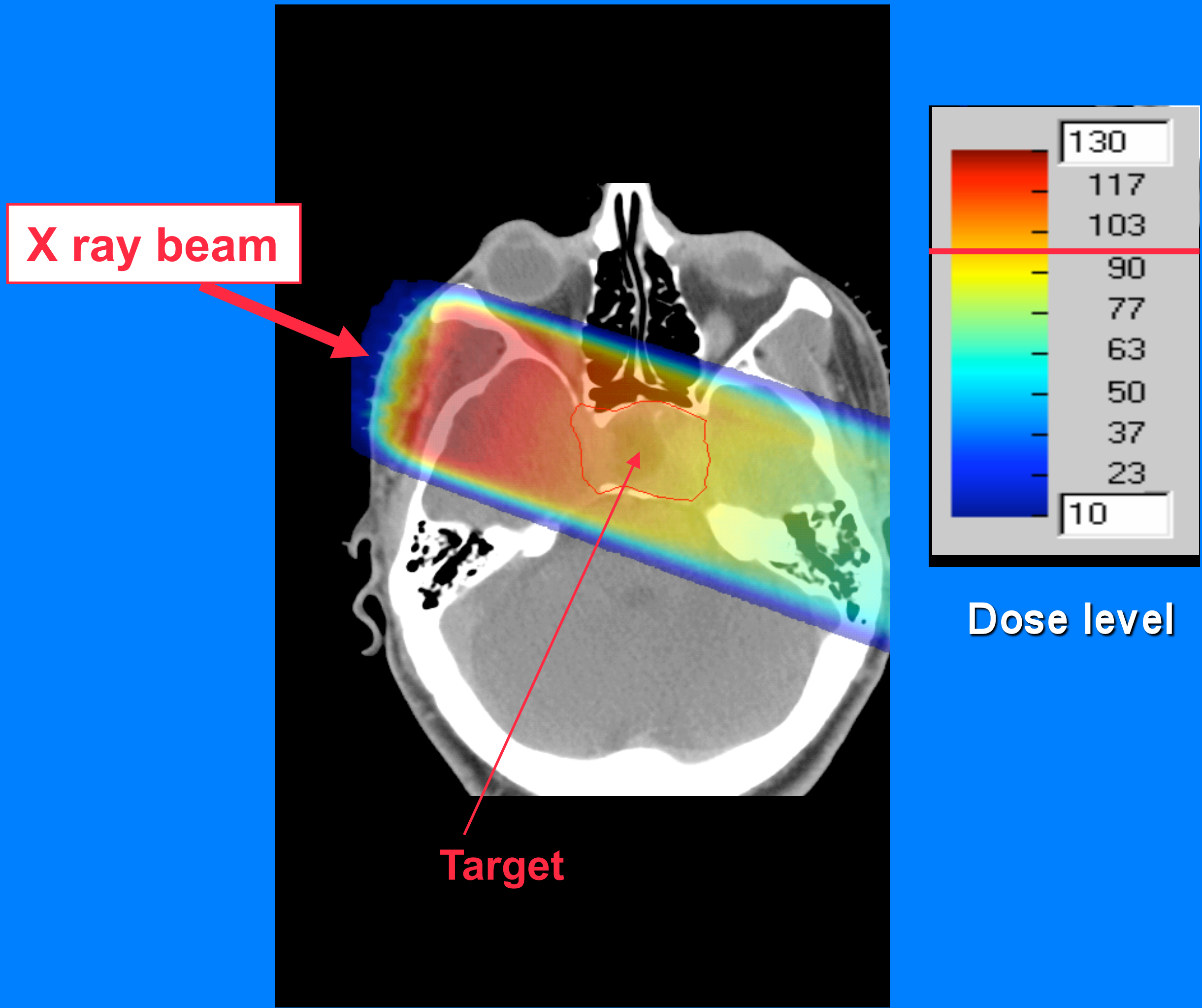
How does it work?



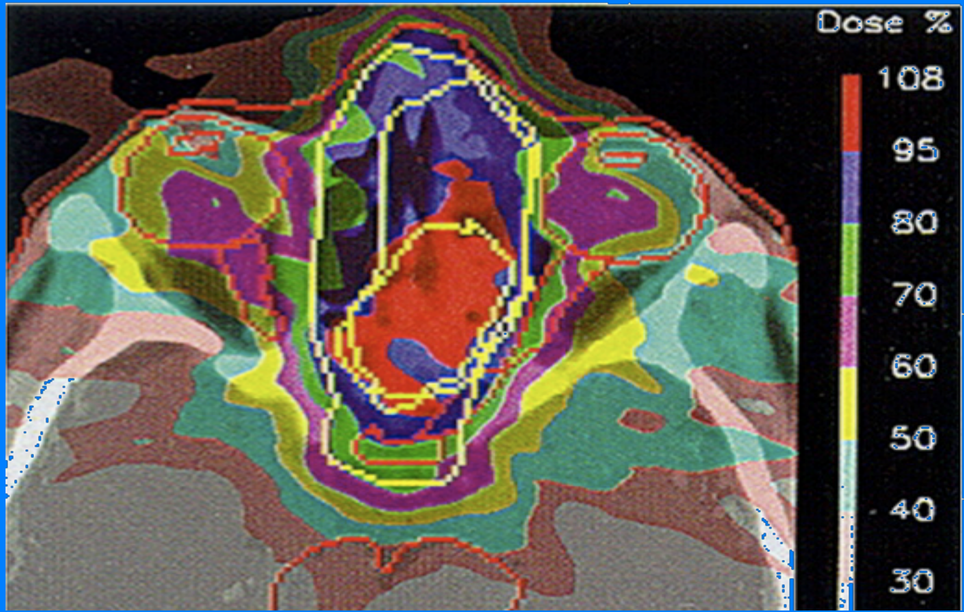
- TC scan data are used to
  - design the volume to be irradiated
  - choose the radiation fields
  - calculate the doses to the target and to healthy tissues

- The dose is given in about 30-40 fractions of about 2 Gray

The basic problem of X ray therapy



An example of dose distribution with X rays



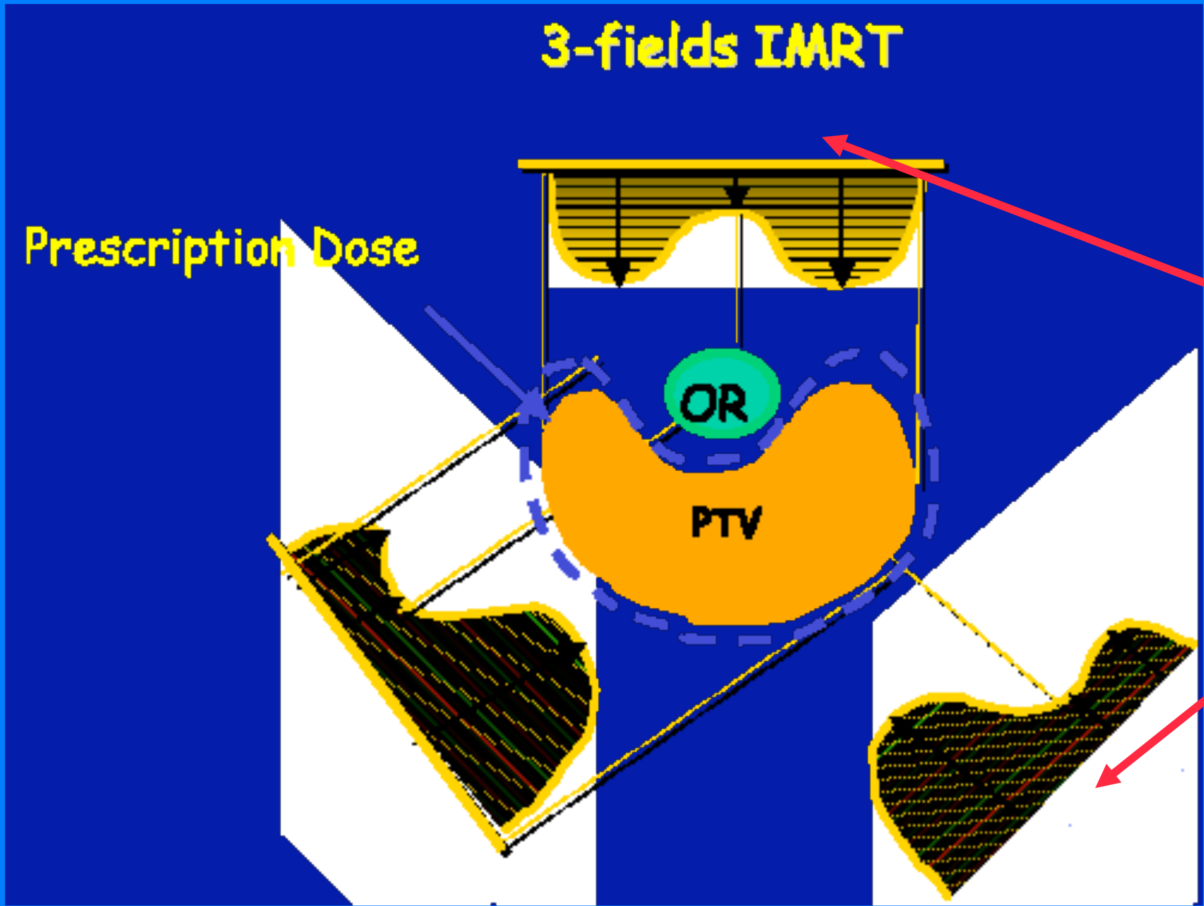
9 different photon beams

Use of many crossed beams to irradiate the target and spare at best the healthy tissues

The limit is due to the dose given to the healthy tissues!

Especially to the organs at risk (OAR)

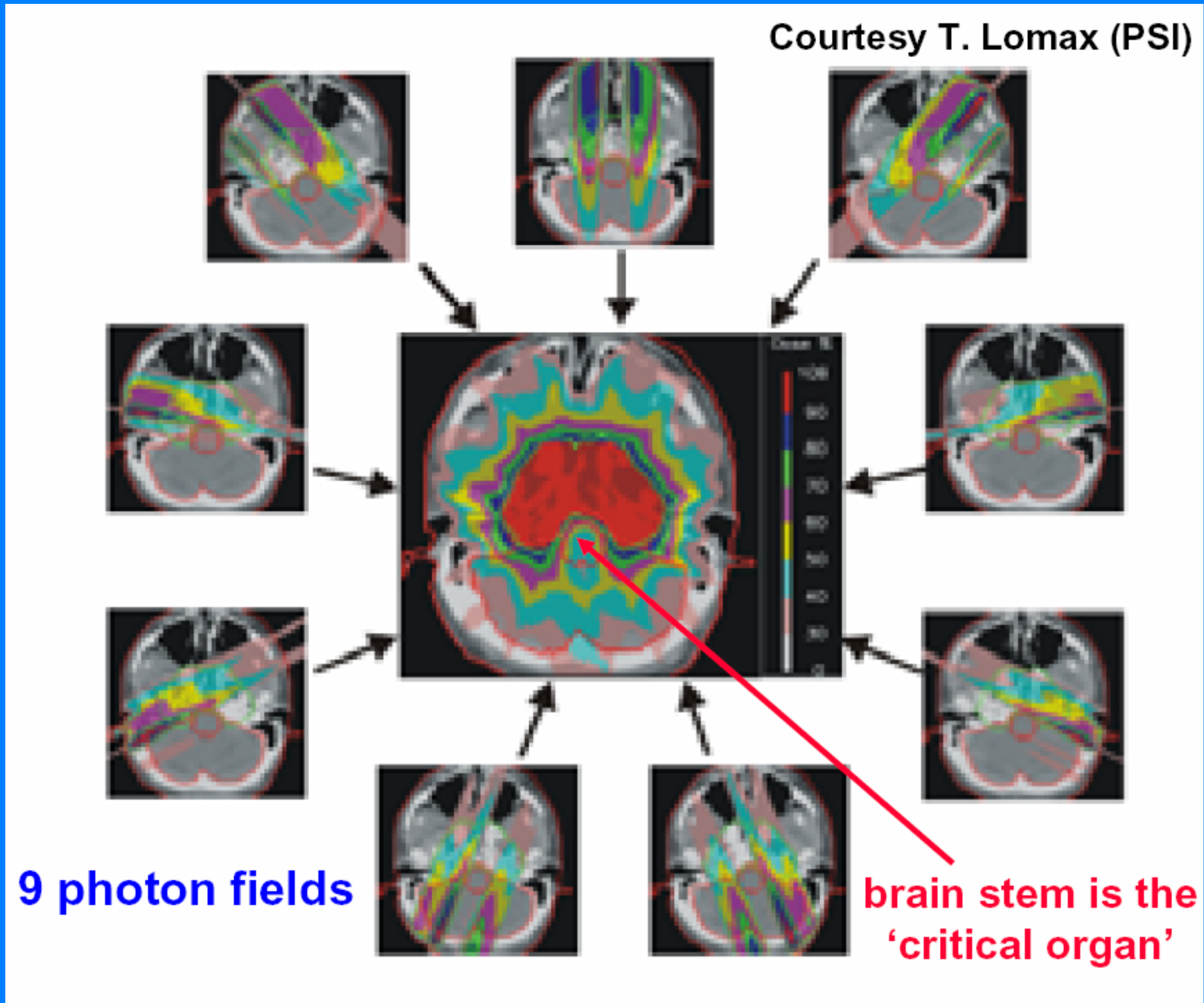
Intensity Modulated Radiation Therapy (IMRT)



Multi leaf collimator which moves during irradiation

- It is possible to obtain concave dose volumes
- Time consuming (used for selected cases)

A step forward towards dose conformation

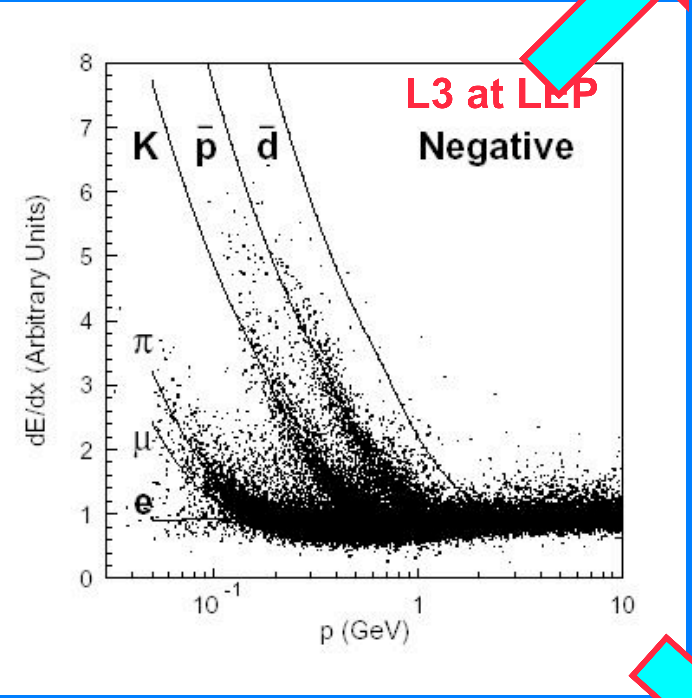


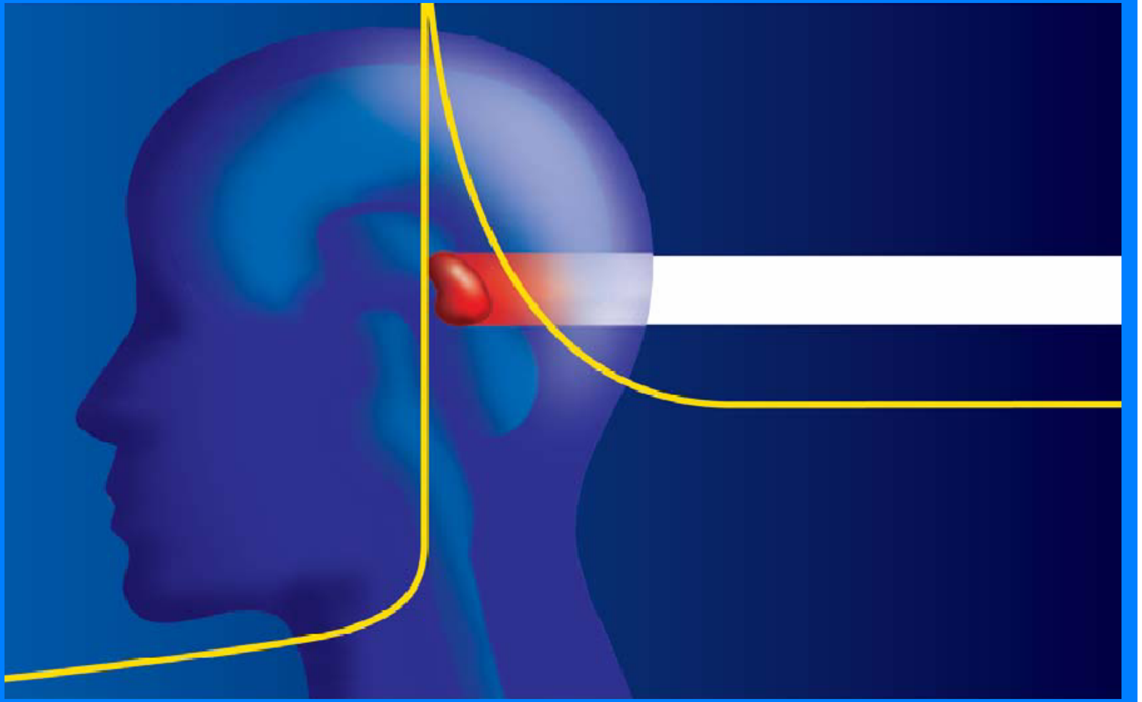
Intensity Modulated Radiation Therapy (IMRT)

Let's go back to physics...

Fundamental physics

Particle identification

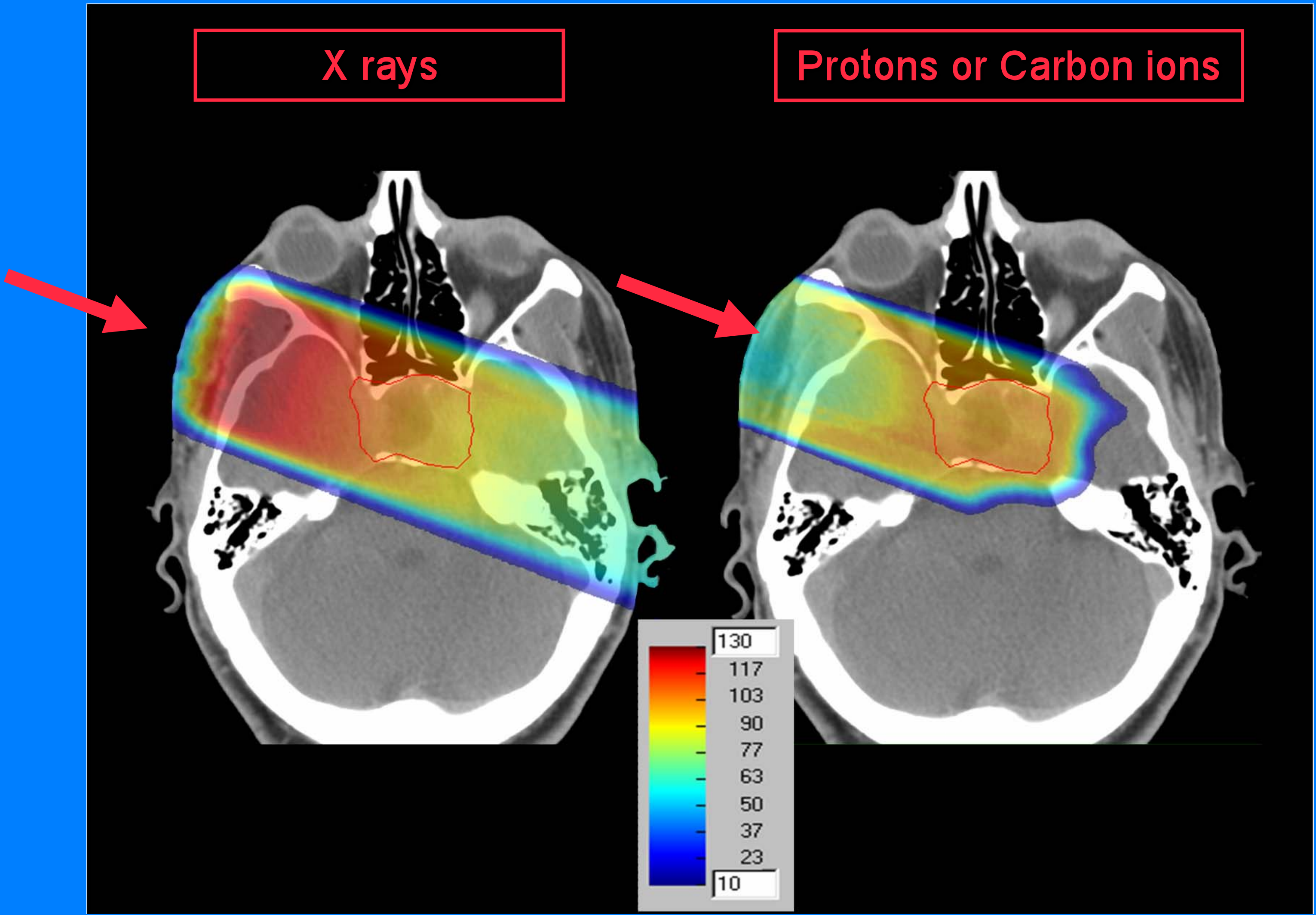




Medical applications

Cancer hadrontherapy

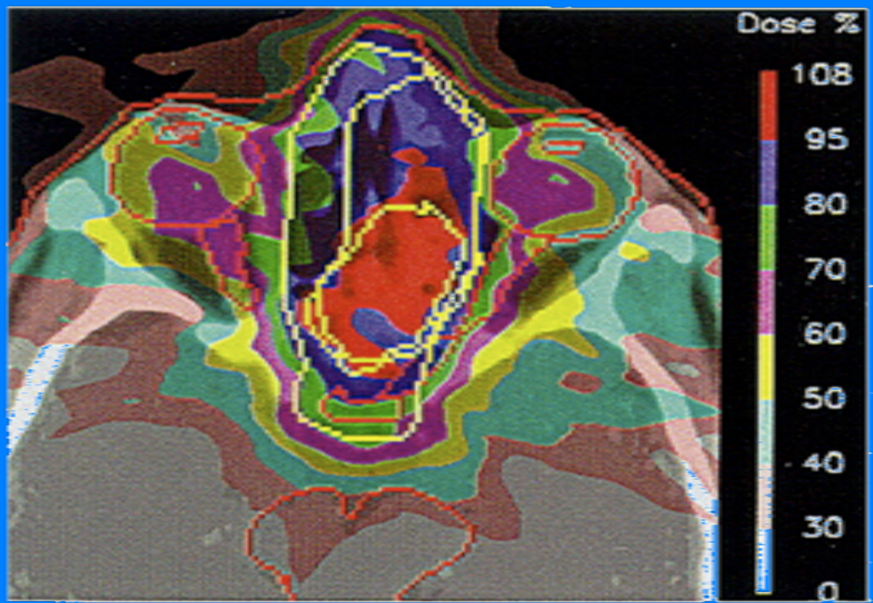
Single beam comparison



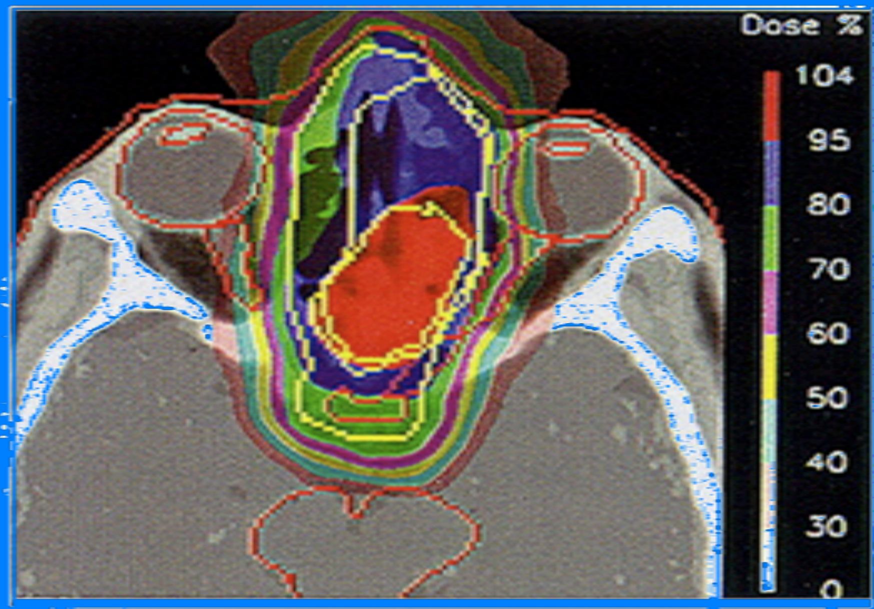
Protons and ions are more precise than X-rays

Tumour between the eyes

9 X ray beams



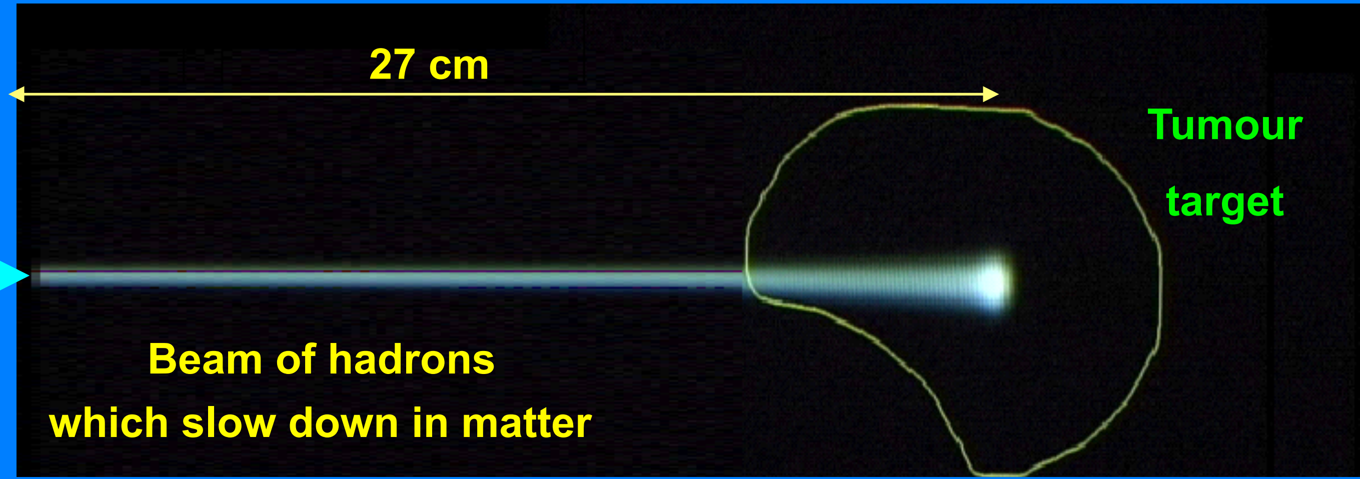
1 proton beam



The basic principles of hadrontherapy

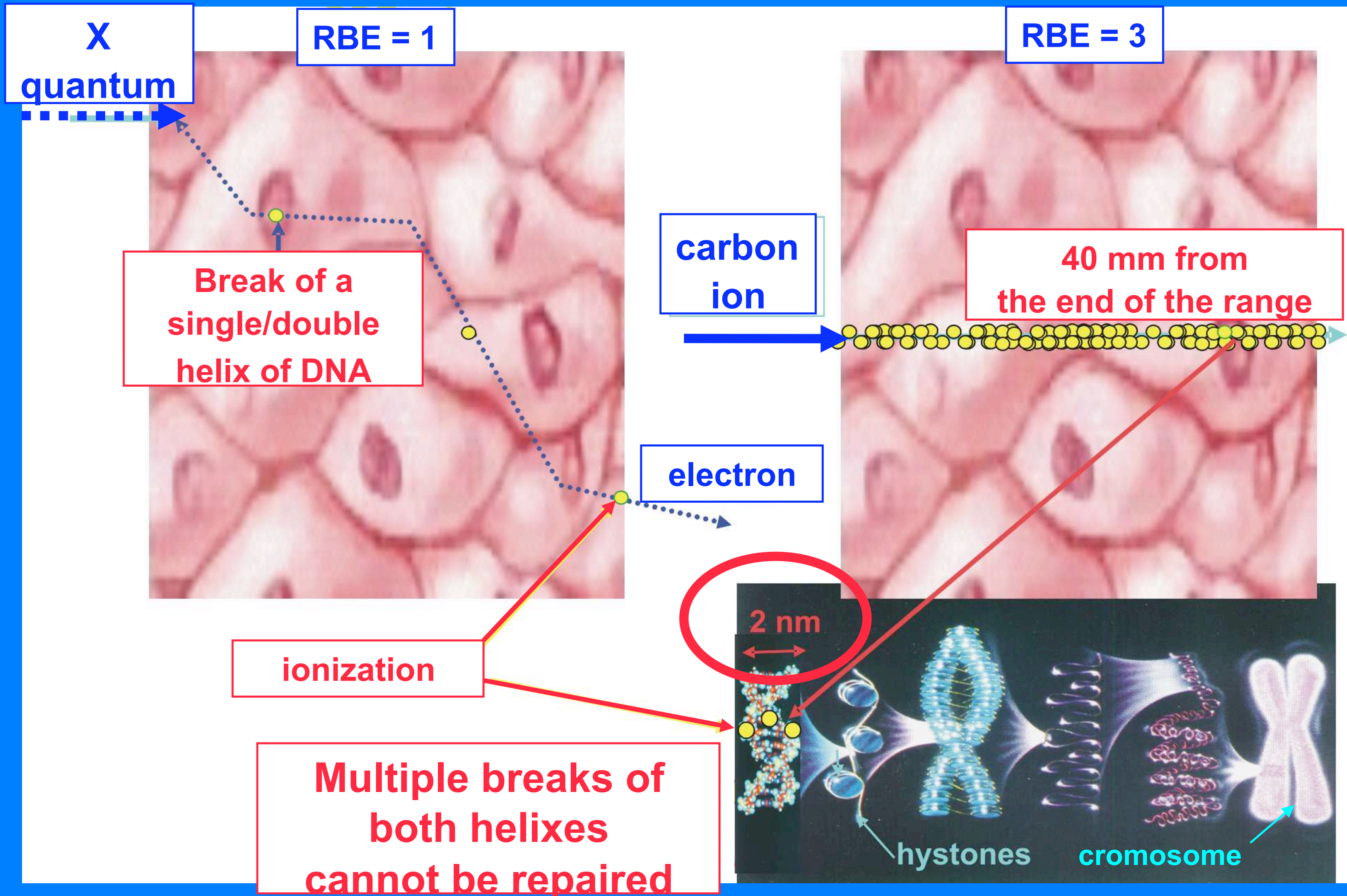
Protons
200 MeV
1 nA

Carbon ions
4800 MeV
0.1 nA



- Bragg peak
  - Better conformity of the dose to the target → healthy tissue sparing
- Hadrons are charged
  - Beam scanning for dose distribution
- Heavy ions
  - Higher biological effectiveness

Why ions have a large biological effectiveness?



The first idea – Bob Wilson, 1946

- Bob Wilson was student of Lawrence in Berkley
- Study of the shielding for the new cyclotron
- Interdisciplinary environment = new ideas!
- Use of protons and charged hadrons to better distribute the dose of radiation in cancer therapy

R.R. Wilson, "Radiological Use of Fast Protons", Radiology, 47 (1946) 487

The beginning of hadrontherpy 1954 at Berkeley

- 1948- Biology experiments using protons
- 1954- Human exposure to accelerated protons and alphas
- 1956 - 1986: Clinical Trials– 1500 patients treated

Cornelius A. Tobias

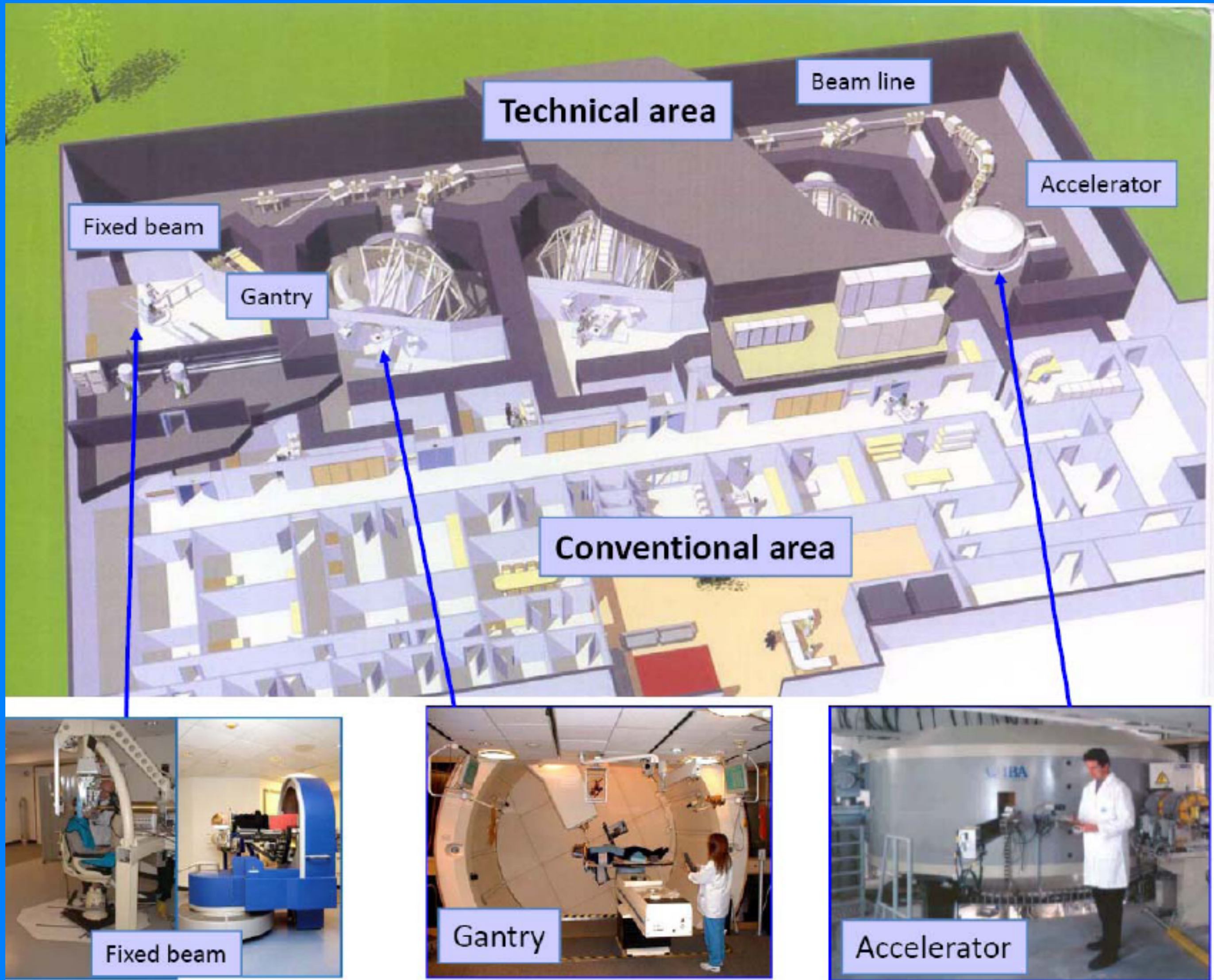
C.A. Tobias, J.H. Lawrence et al., Cancer Research 18 (1958) 121

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

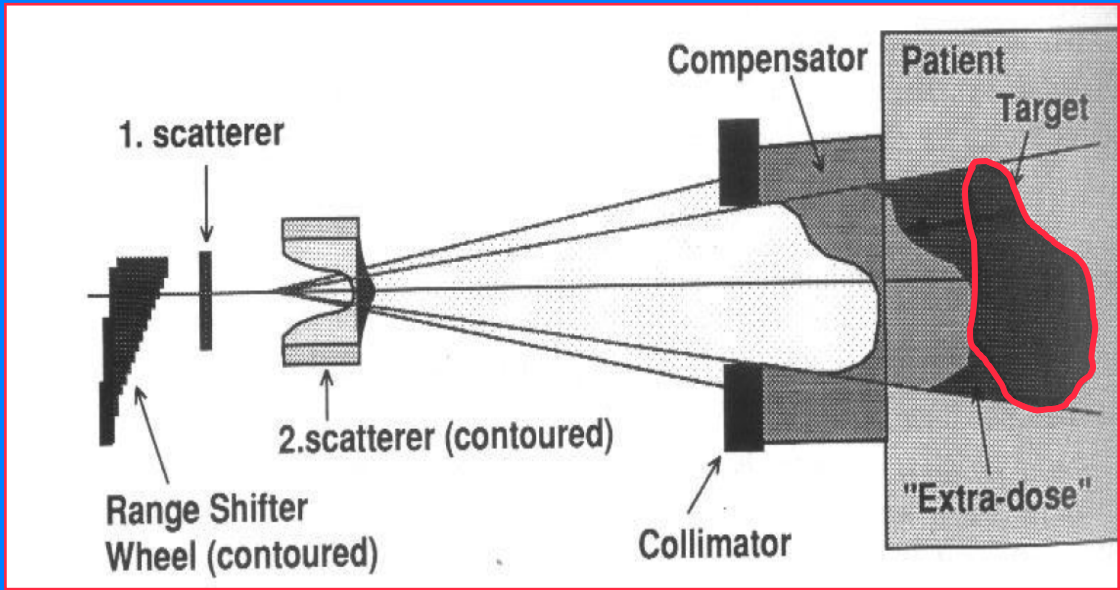
What do we need to treat deep seated tumours?



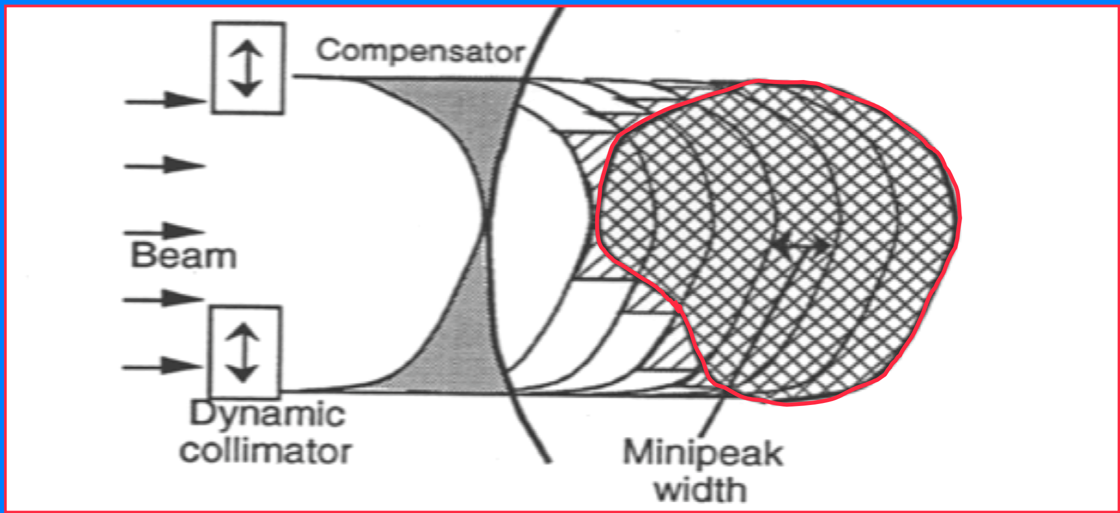
General scheme of a proton-therapy centre. The example reported here is based on the system commercialized by the company IBA (Belgium).

What does a patient see of all that?

Dose distribution (present): passive spreading



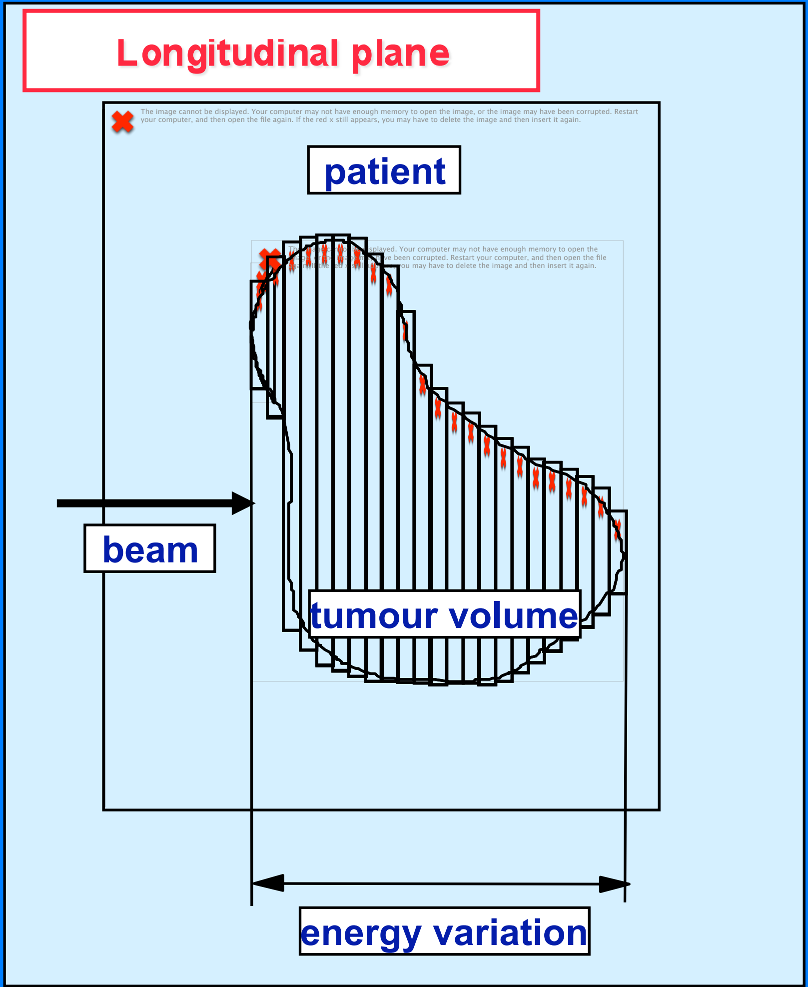
'Double scattering'

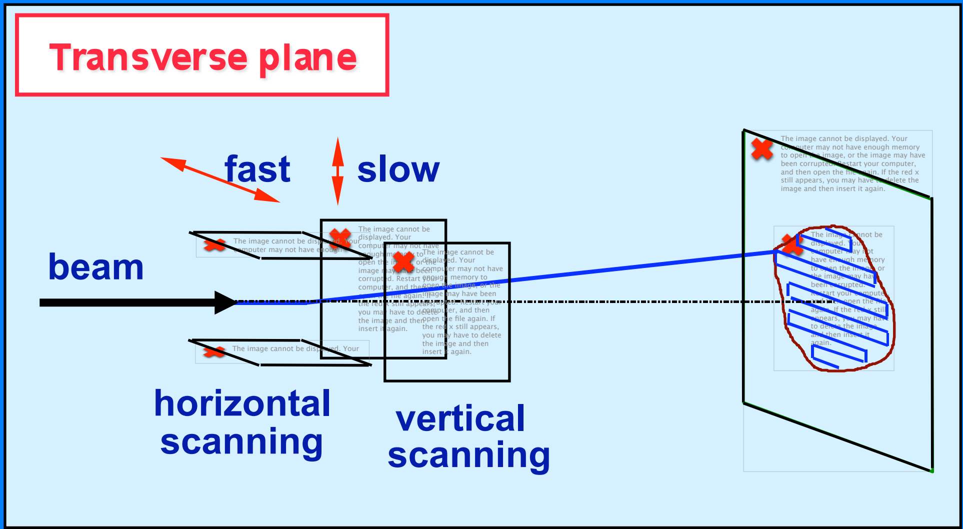


'Layer stacking'

These are the systems uses today in clinical practice!

Dose distribution (future): raster scanning



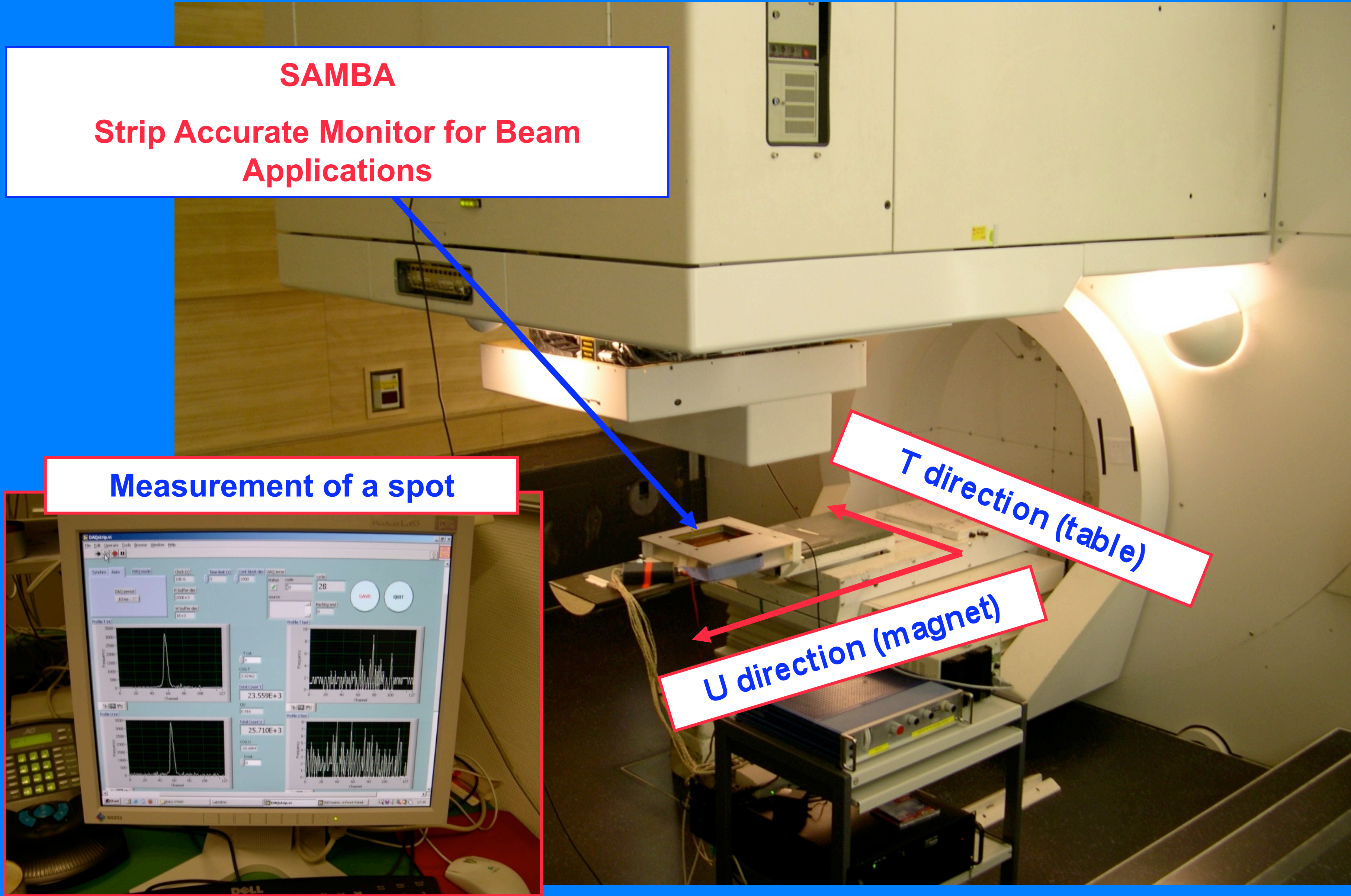


New technique developed and applied for treatments at GSI

The Gantry1 at PSI

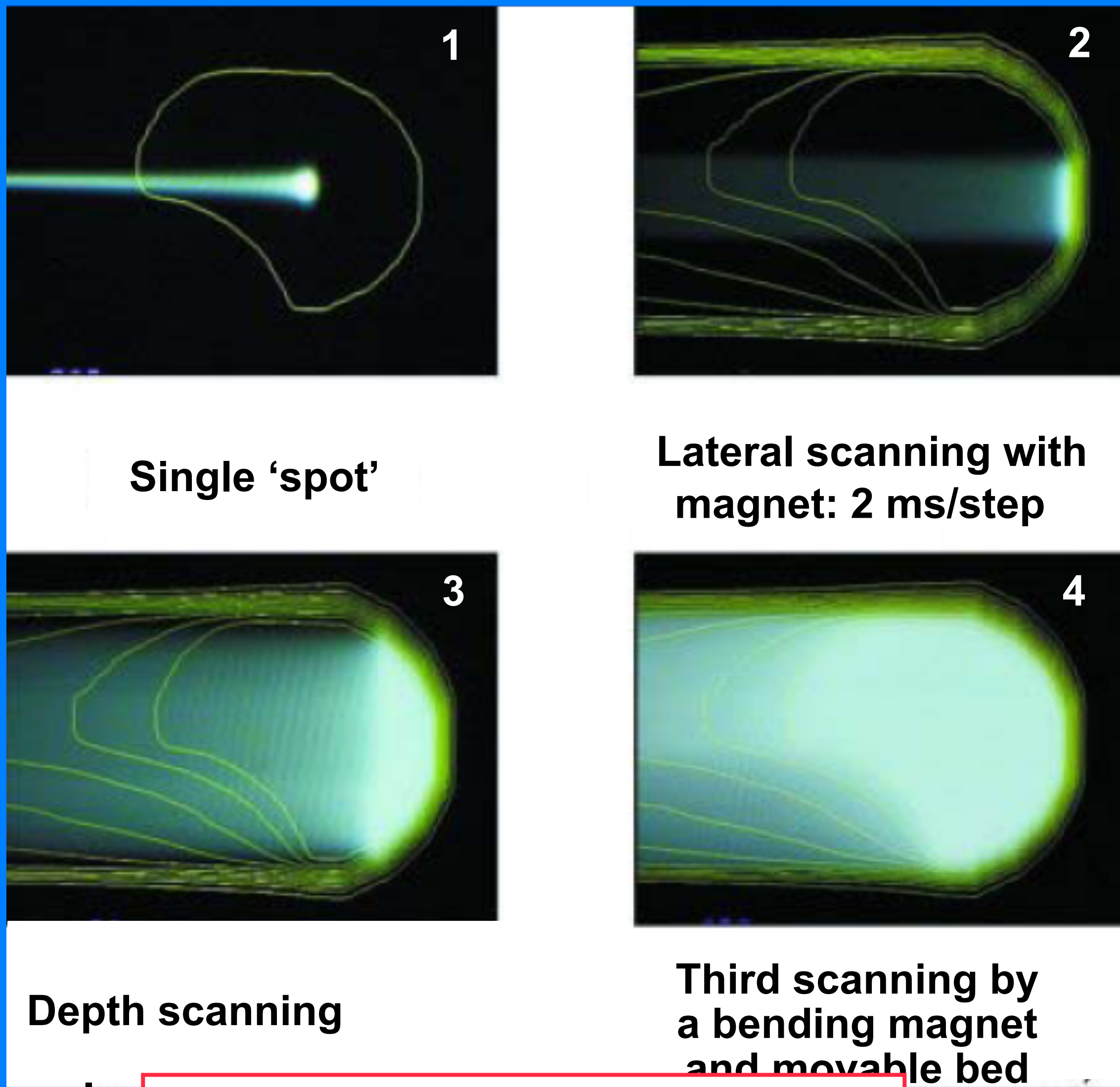
SAMBA

Strip Accurate Monitor for Beam Applications



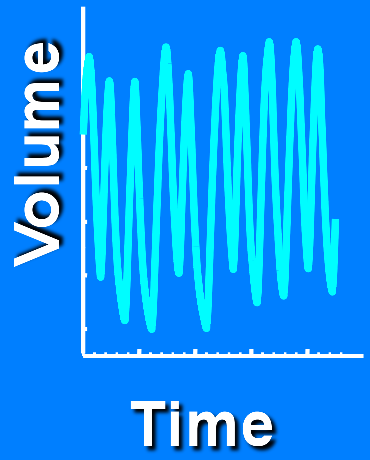
Measurement of a spot

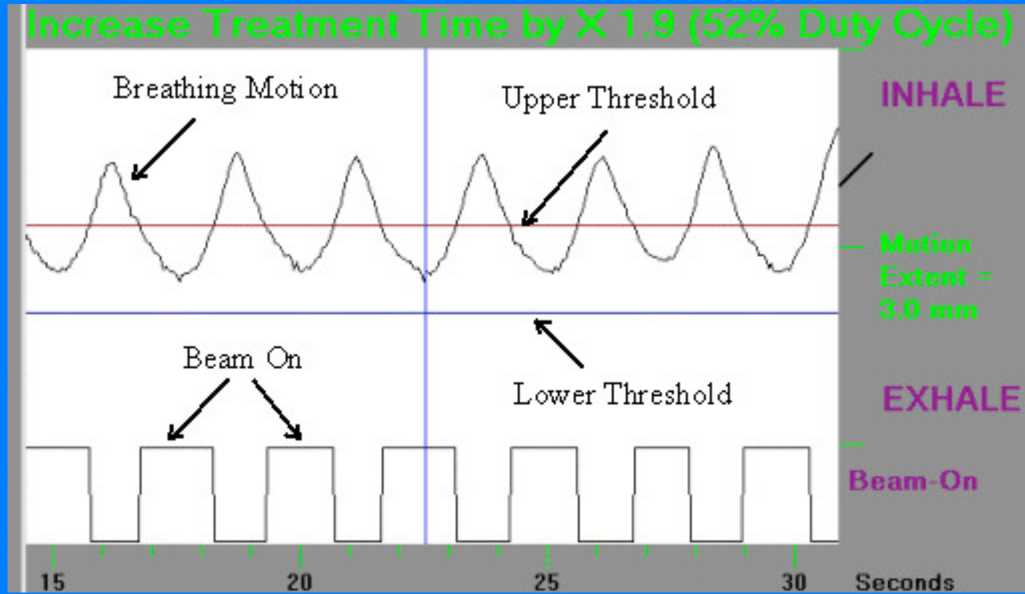
Dose distribution (future): spot scanning



New technique developed and applied for treatments at PSI

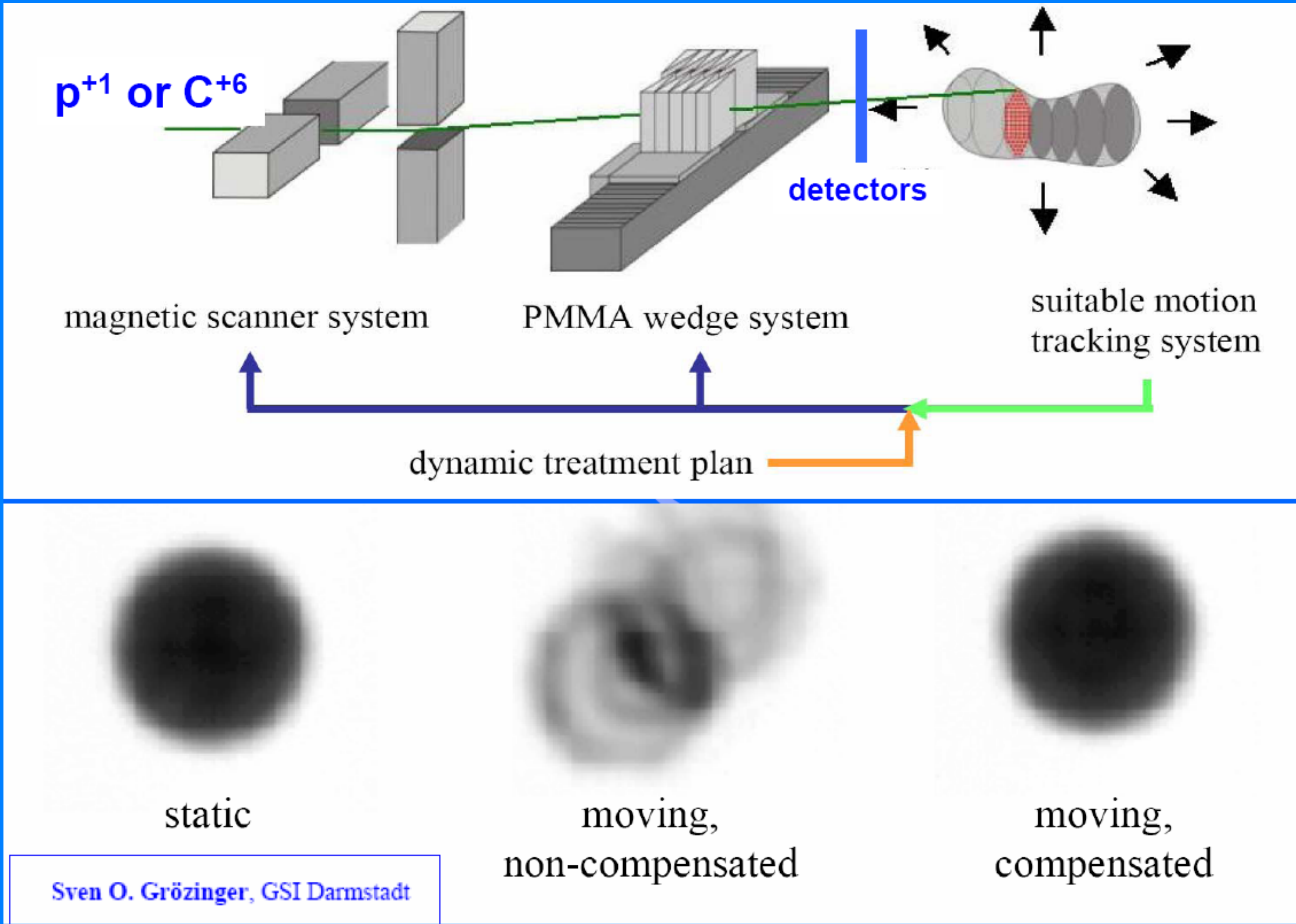
Organ motion (present): respiratory gating





- **The beam reaches the patient only when the "gate" is ON**
- **Synchrotrons: synchronization of the respiration of the patient with the cycle of the accelerator**
- **Technique already in use in Japan (Tsukuba)**

Moving organs (future): organ tracking



Number of potential patients

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

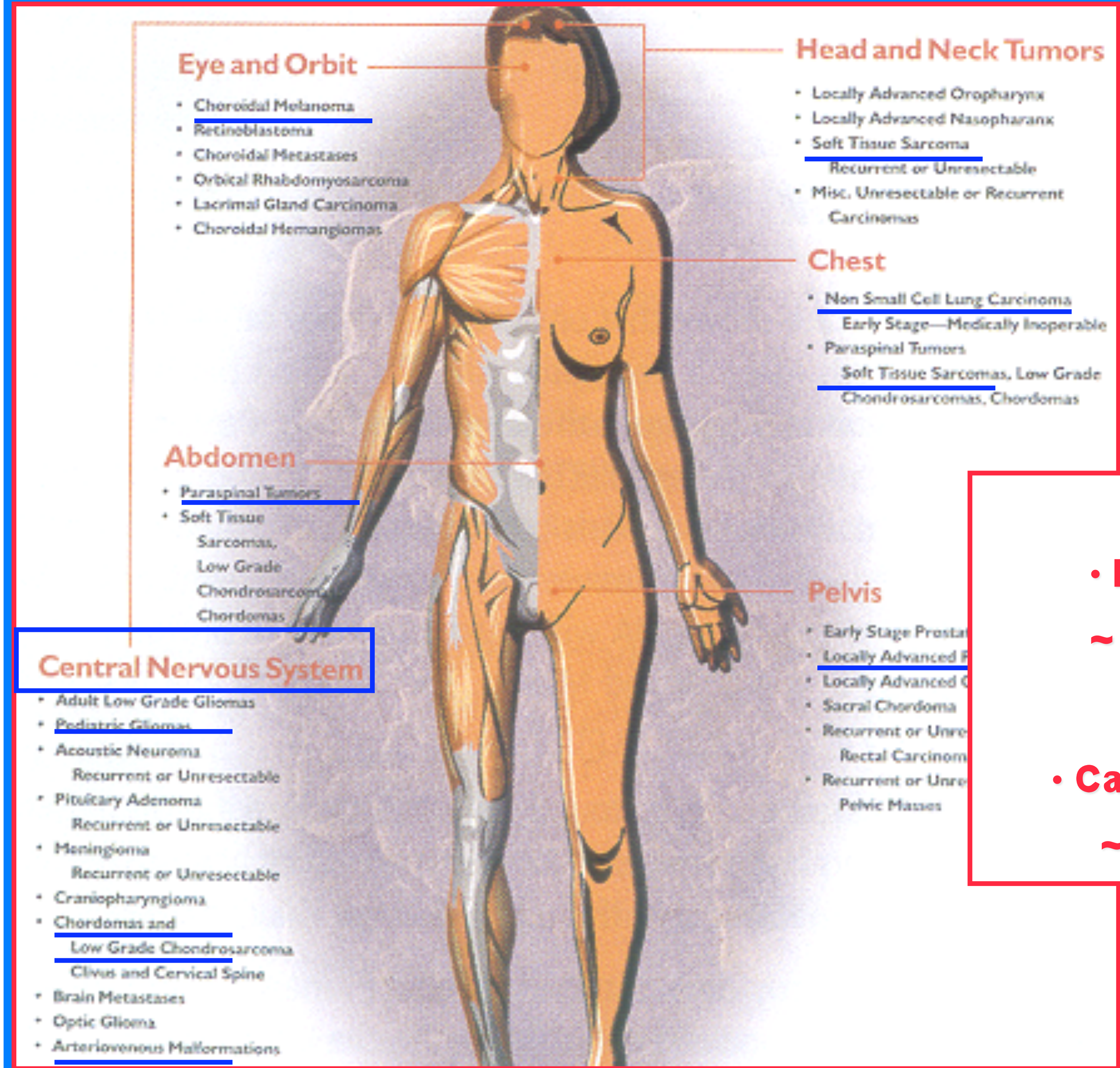
  1 centre

TOTAL about 3'500 pts/year

every 10 M

Results of clinical studies conducted in Italy, France, Germany, Austria and Sweden

The treated sites



Up to present

- **Proton-therapy:**

~ 55 000 patients

- **Carbon ion therapy:**

~ 2 200 patients

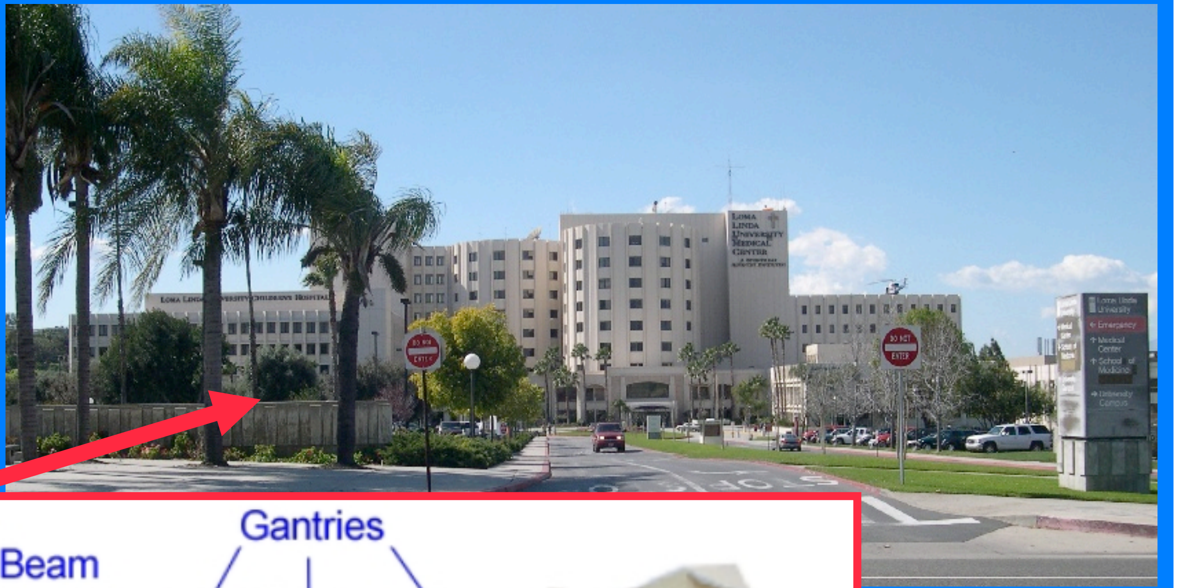
Present and “near” future of hadrontherapy

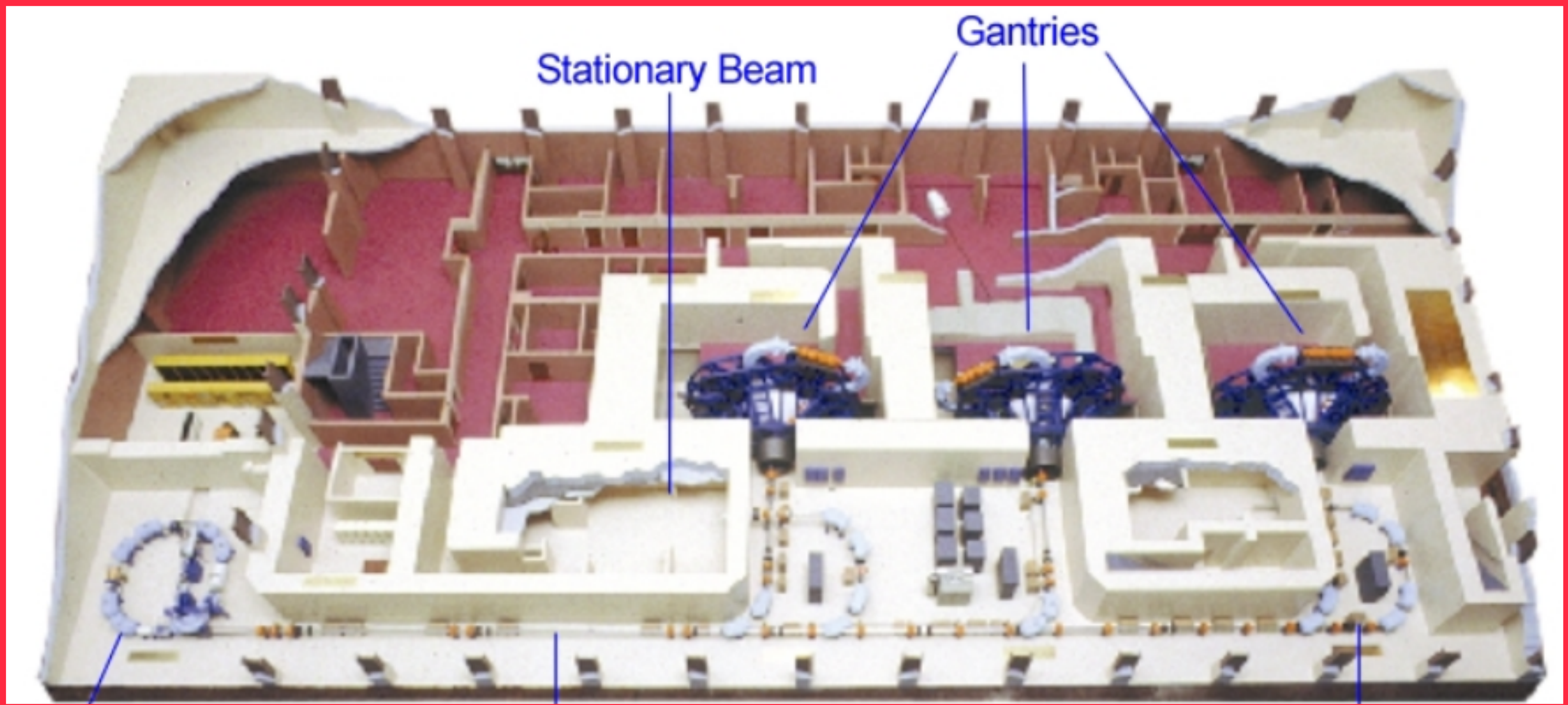
- **Proton-therapy is “booming”!** *(for information see PTCOG, ptcog.web.psi.ch)*
  - Laboratory based centres: Orsay, PSI, INFN-Catania, …
  - Hospital based centres: 3 in USA, 4 in Japan and many under construction (USA, Japan, Germany, China, Korea, Italy, …)
  - Companies offer “turn-key” centres

- **Carbon ion therapy**
  - 2 hospital based centres in Japan
  - Pilot project at GSI
  - 2 hospital based centres under construction: HIT in Germany and CNAO in Italy
  - 2 projects (almost) approved (ETOILE in France and Med-Austron in Austria)
  - European network ENLIGHT

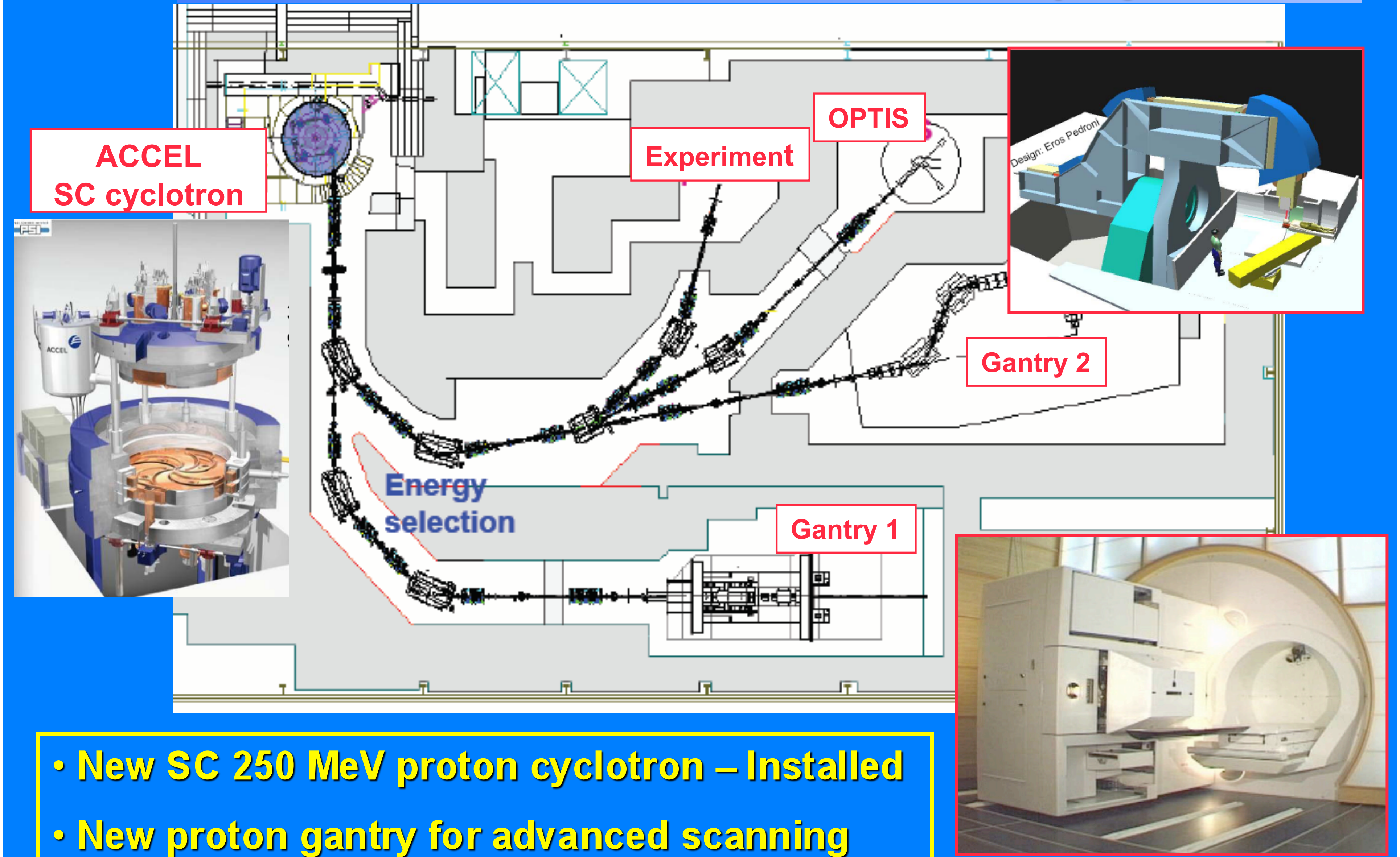
The Loma Linda University Medical Center (USA)

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



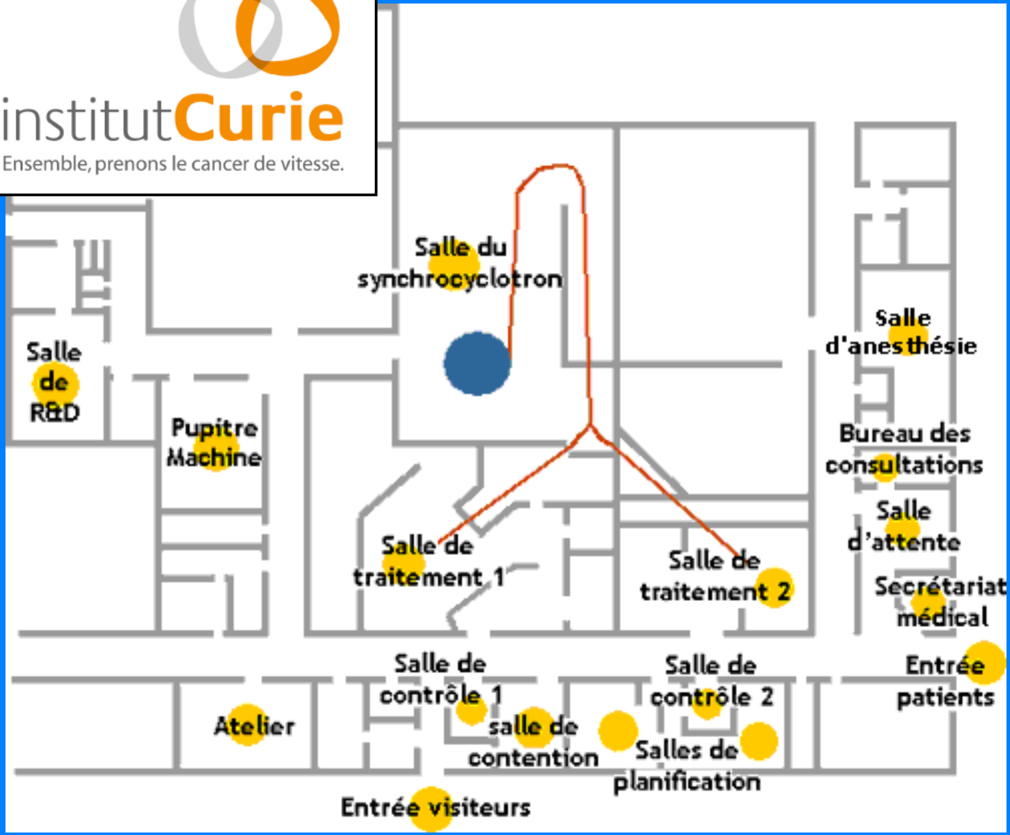


PROSCAN project at PSI



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

Centre de protonthérapie de l'Institut Curie in Orsay

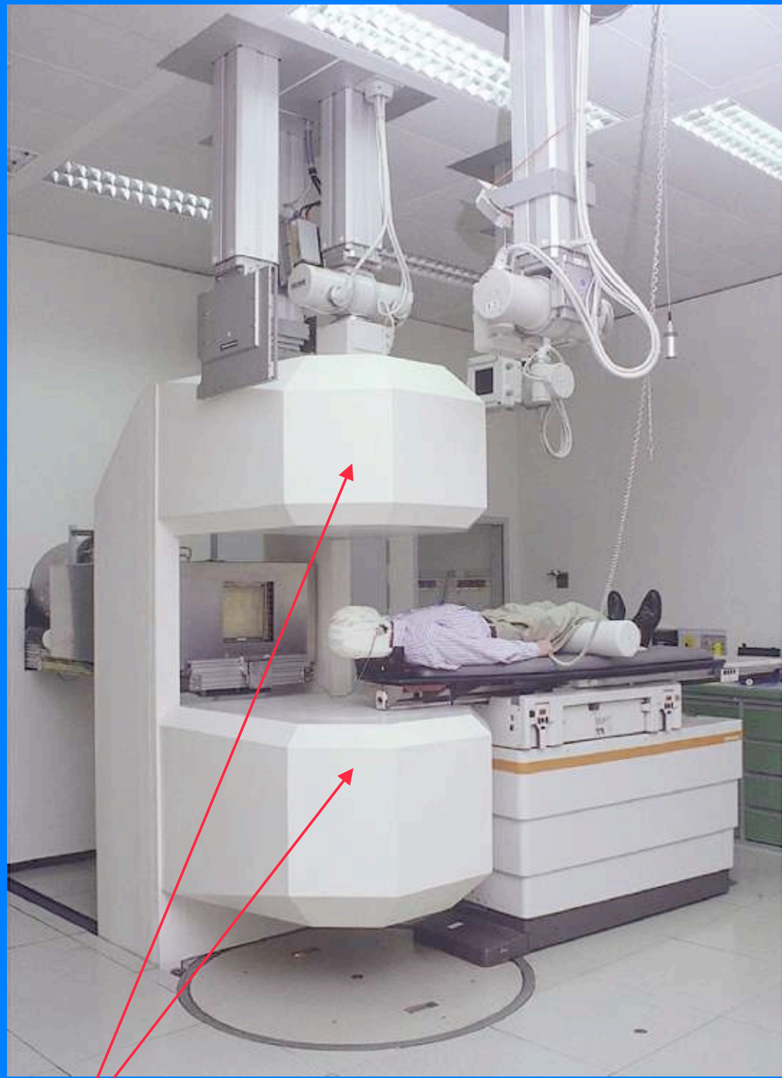


- Active from 1991
- 3766 patients treated (Dec-06)
- Extension (New cyclotron + Gantry by the Belgian company IBA)
- 650 patients par an à partir de 2009

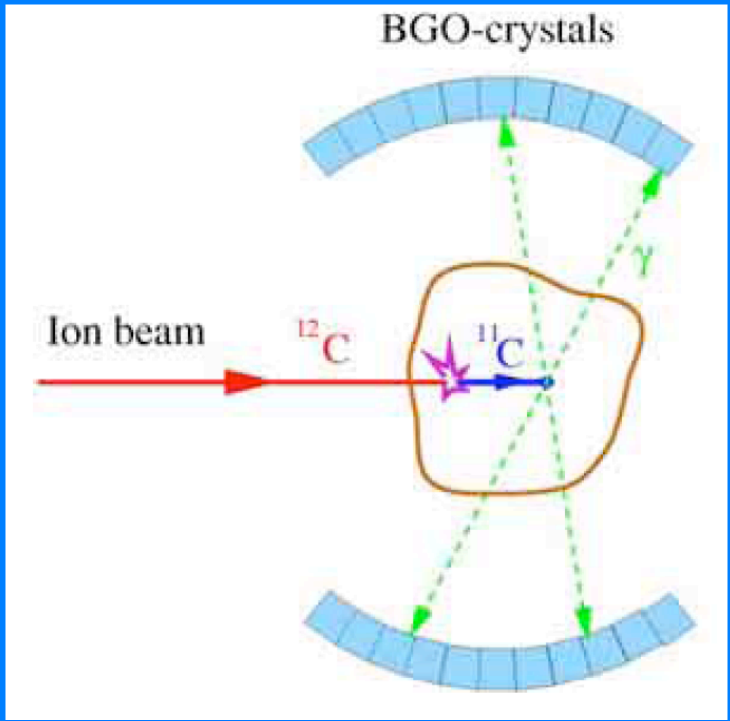
Carbon ion therapy in Europe

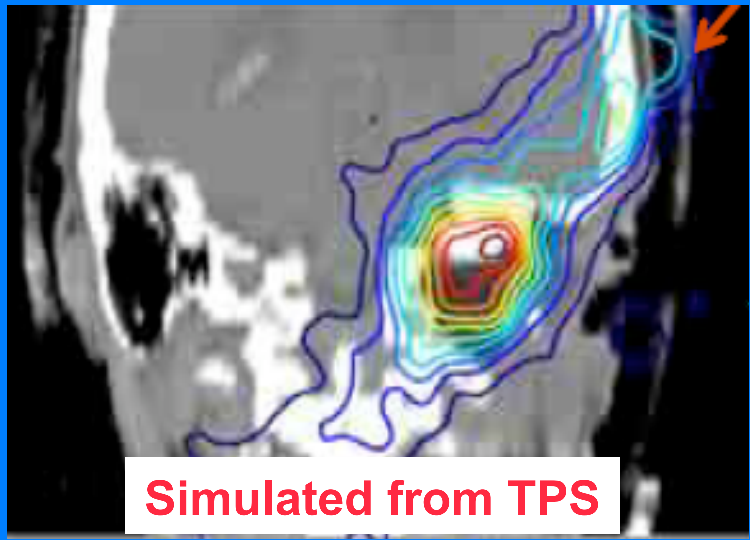
1998 - GSI pilot project (G. Kraft)

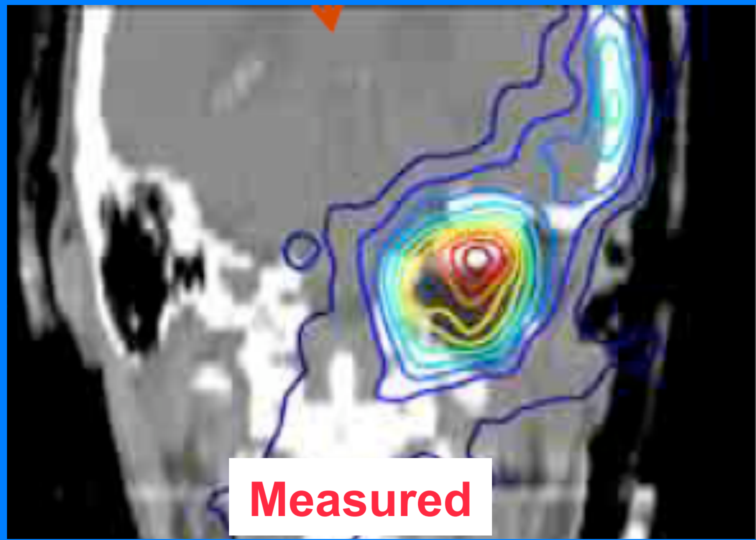
200 patients treated with carbon ions



PET on-beam

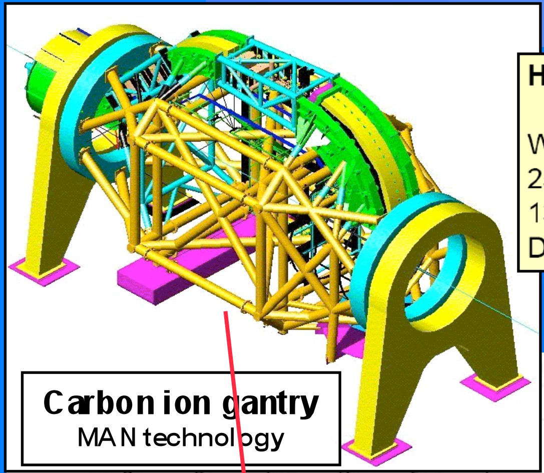






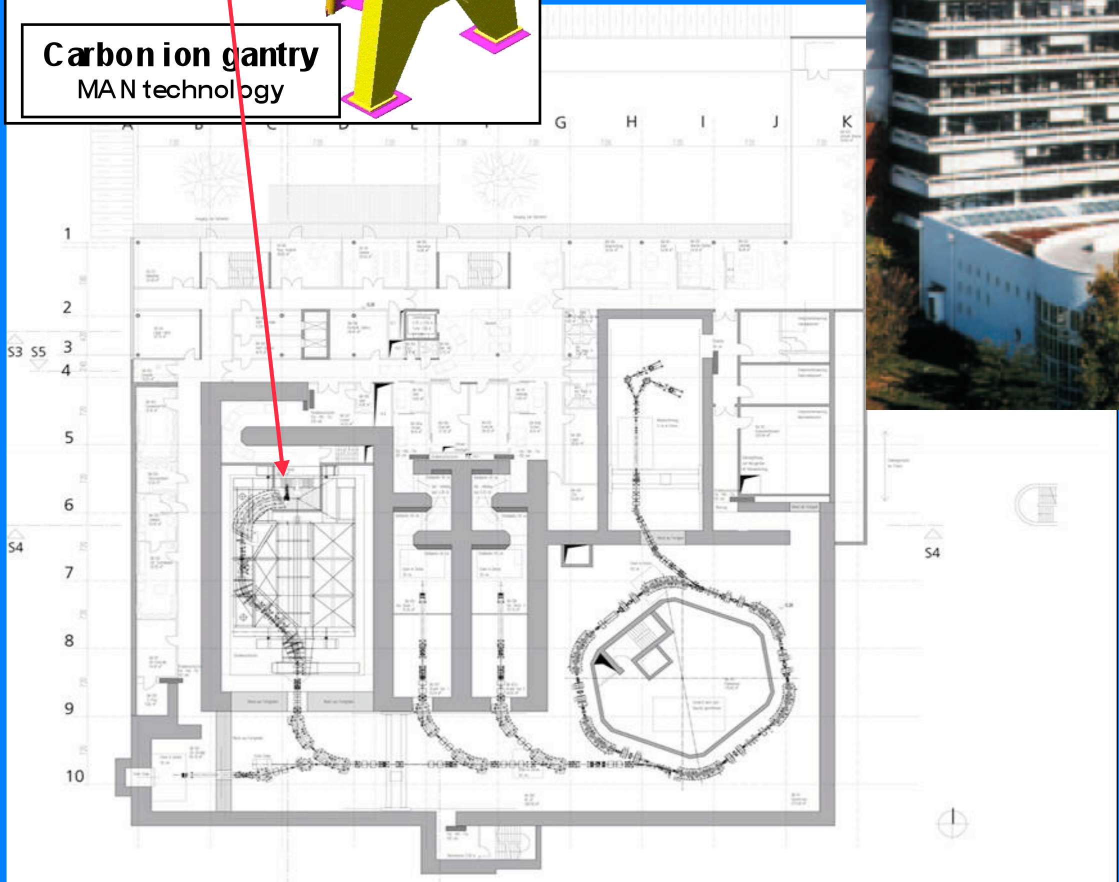
Measurement of the "real" 3D dose distribution given to the patient

HIT – University of Heidelberg



Heavy-ion Gantry

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



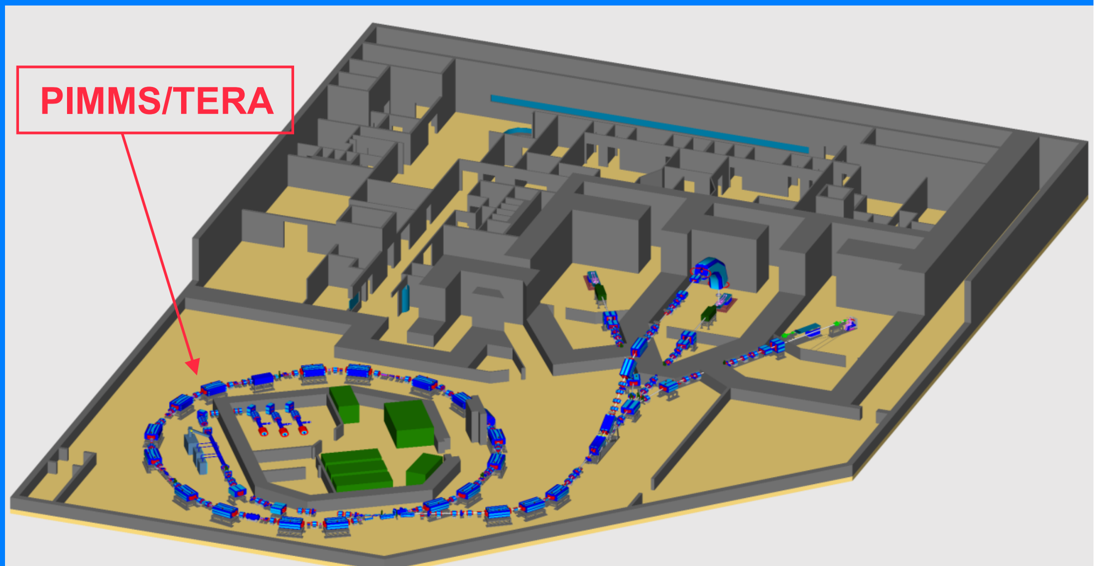
- **Hospital based centre**
- **Project started in 2001**
- **First patient treatment foreseen in 2008**
- **First C-ion gantry**

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

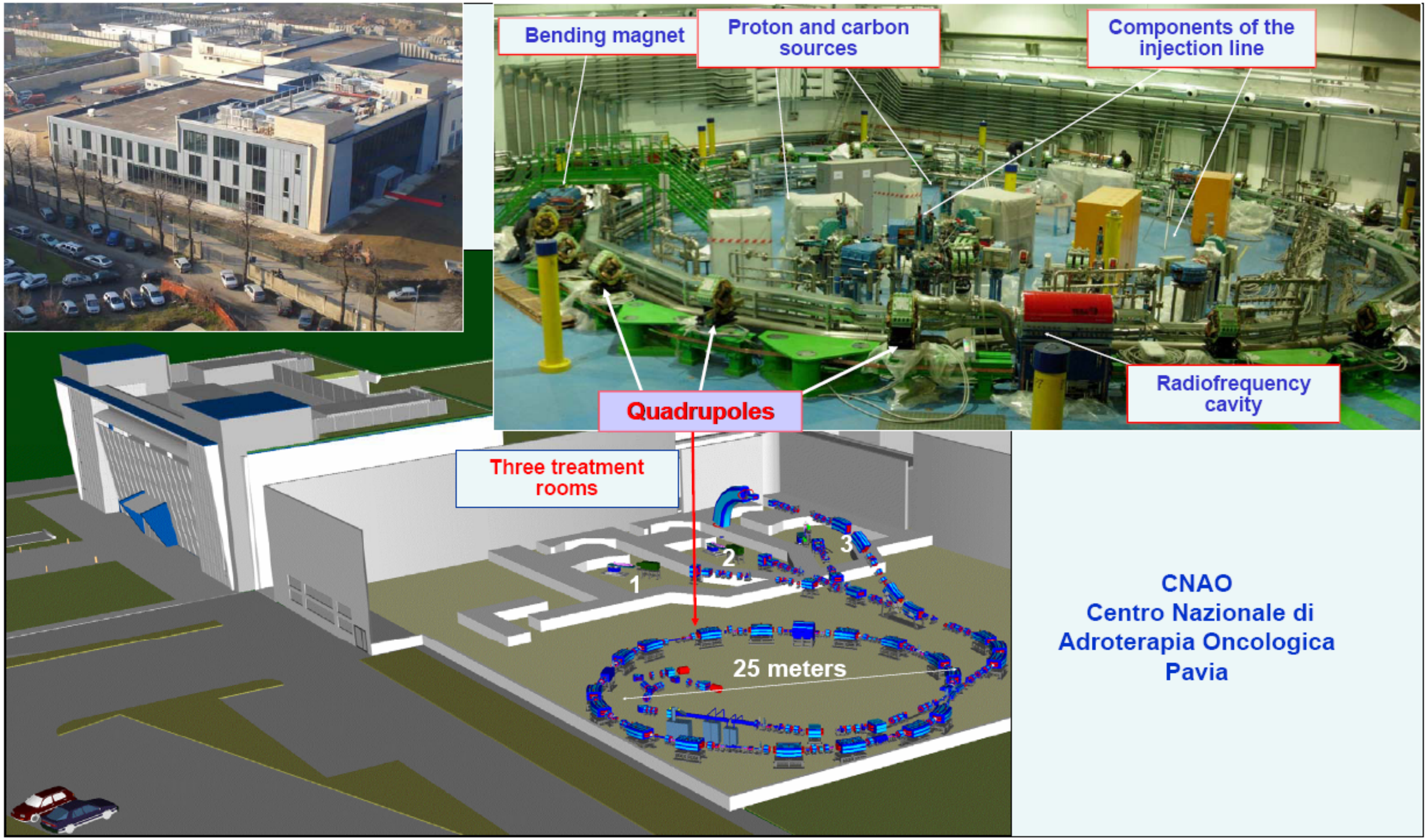


- Collaborations with many research institutes and universities
  - in particular CERN, INFN, PSI, GSI, JRC, Universities of Milan, Turin and Piemonte Orientale

CNAO – Presented at the CERN Open Day April 2008

fondazione CNAO

Centro Nazionale di Adroterapia Oncologica
under construction in Pavia (Italy)



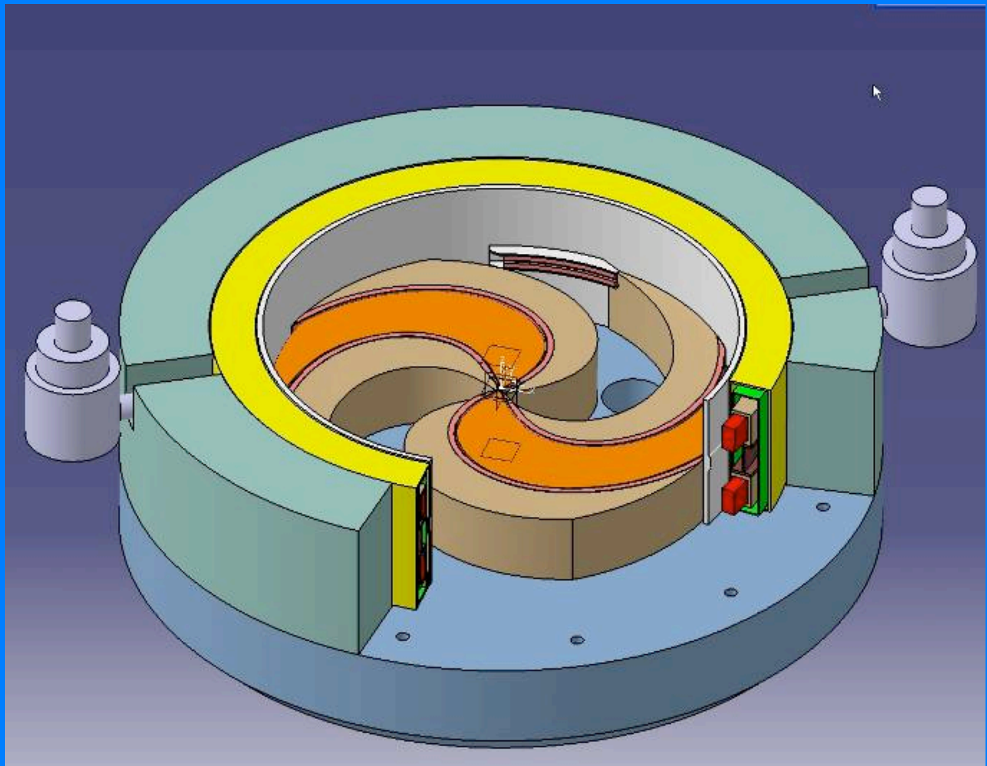
The challenges for the future of hadrontherapy

- Reduce costs, size and complexity
- Improve the quality of the treatment

↓

1. Innovative (possibly compact) accelerators
2. Innovative compact gantries (especially for ions)
3. Techniques for dose distribution (especially to treat moving organs)
4. Synergies with advanced medical imaging
5. Optimization of the available medical resources

A SC cyclotron for carbon ion therapy



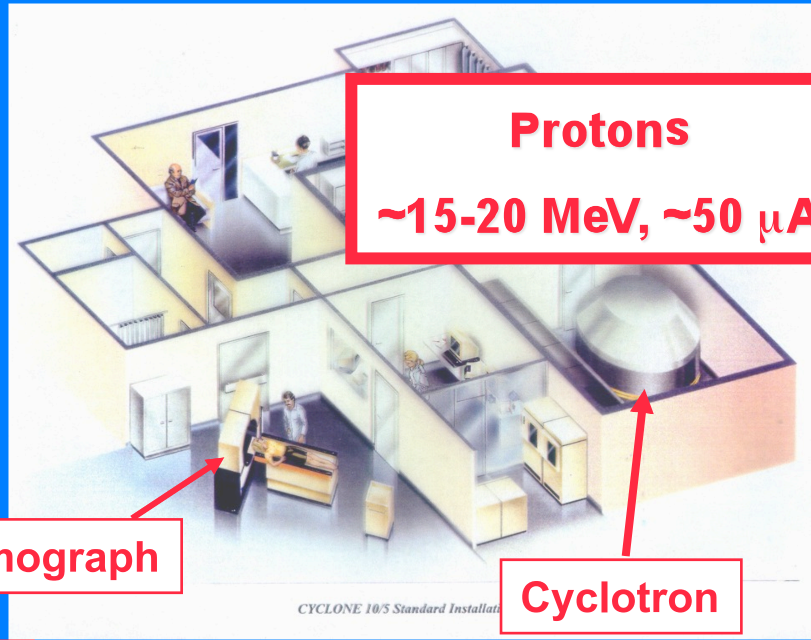
- Superconducting isochronous cyclotron, accelerating Q/M = 1/2 ions to 400 MeV/U (H_2^+, Alphas, $Li6^{3+}$, $B10^{5+}$, $C12^{6+}$, $N14^{7+}$, 016^{8+}, $Ne20^{10+}$)
- Diameter 6.3 meters
- Design by IBA (Belgium)
- The first prototype will be realized in Caen by the Archade consortium

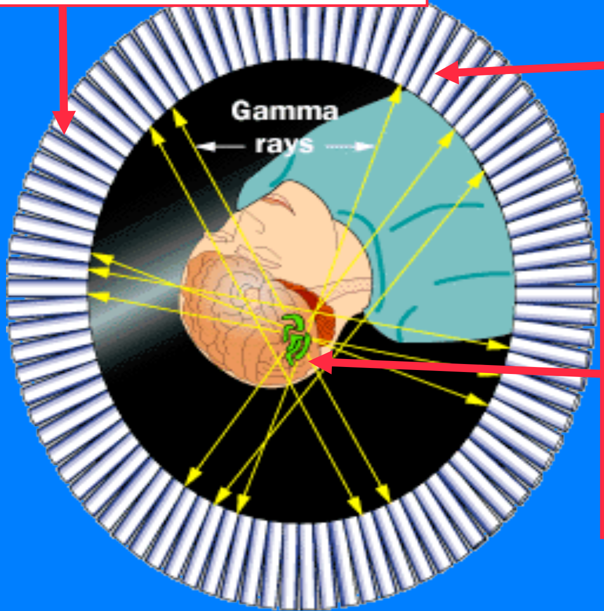
iba

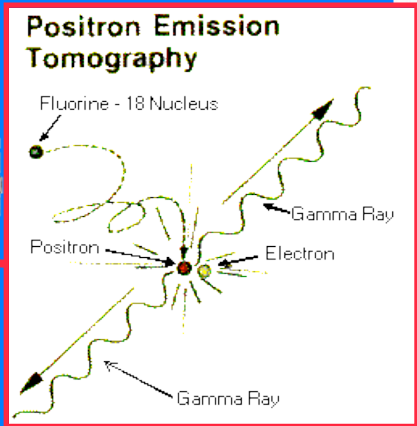
Archade
ADVANCED RESOURCE CENTRE FOR HADRONTHERAPY IN EUROPE

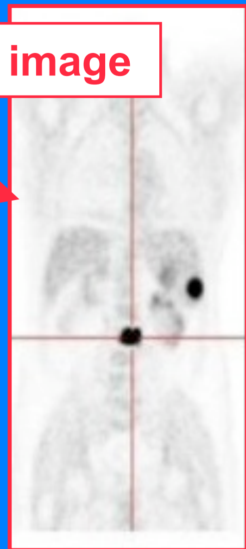
Advanced medical imaging: PET and PET-CT

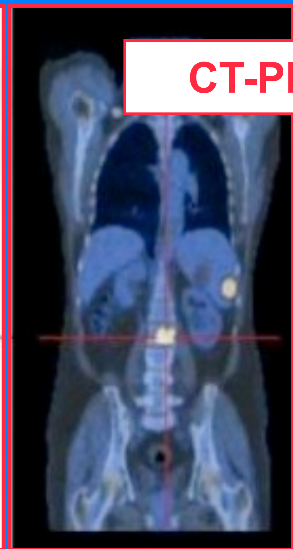
- FDG with ^{18}F is the most used drug (half life 110 minutes)
- Measurement of the density of ^{18}F through back-to-back gamma detection
- Information on metabolism











PET can help for planning in radiation therapy

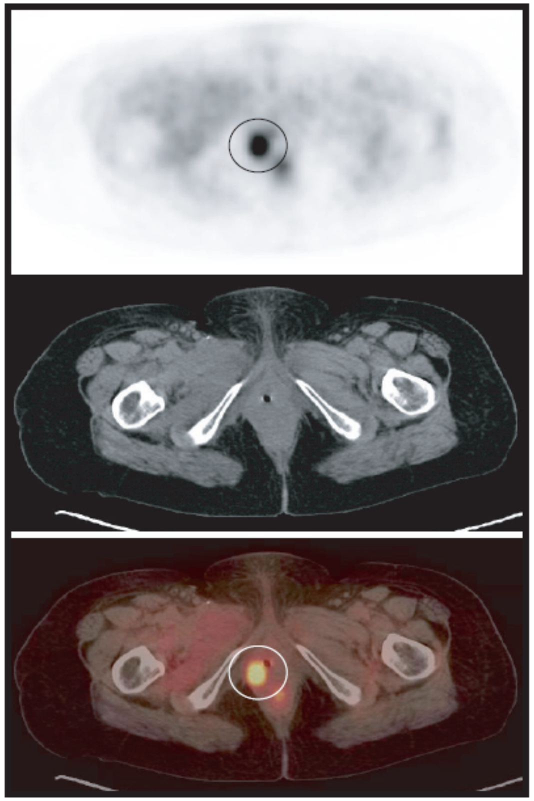
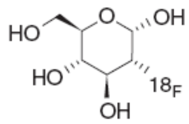
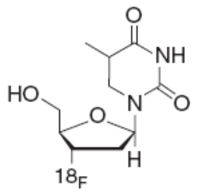
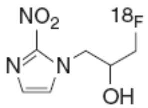
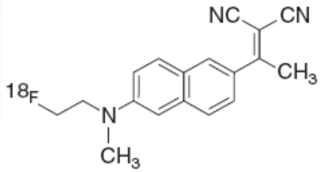


Figure 1 PET, CT, and PET/CT images of a patient with cervical cancer, undetected except on the PET images. (The circles highlight the focal area of FDG uptake, indicative in this case of cervical cancer, on the PET image and the PET/CT overlay image, but no abnormality is seen on the standard CT image.)

Radio labeled tag	Molecular structure	Physiological parameter	Example of clinical use
^{18}F FDG		Glucose utilization	Possible malignancy
^{18}F FLT		Cell proliferation	Possible malignancy
^{18}F MISO		Cell proliferation	Determining radiation exposure
^{18}F FDDNP		Amyloid plaque binding agent	Alzheimer's disease marker

R. Nutt et al., CLINICAL PHARMACOLOGY & THERAPEUTICS,

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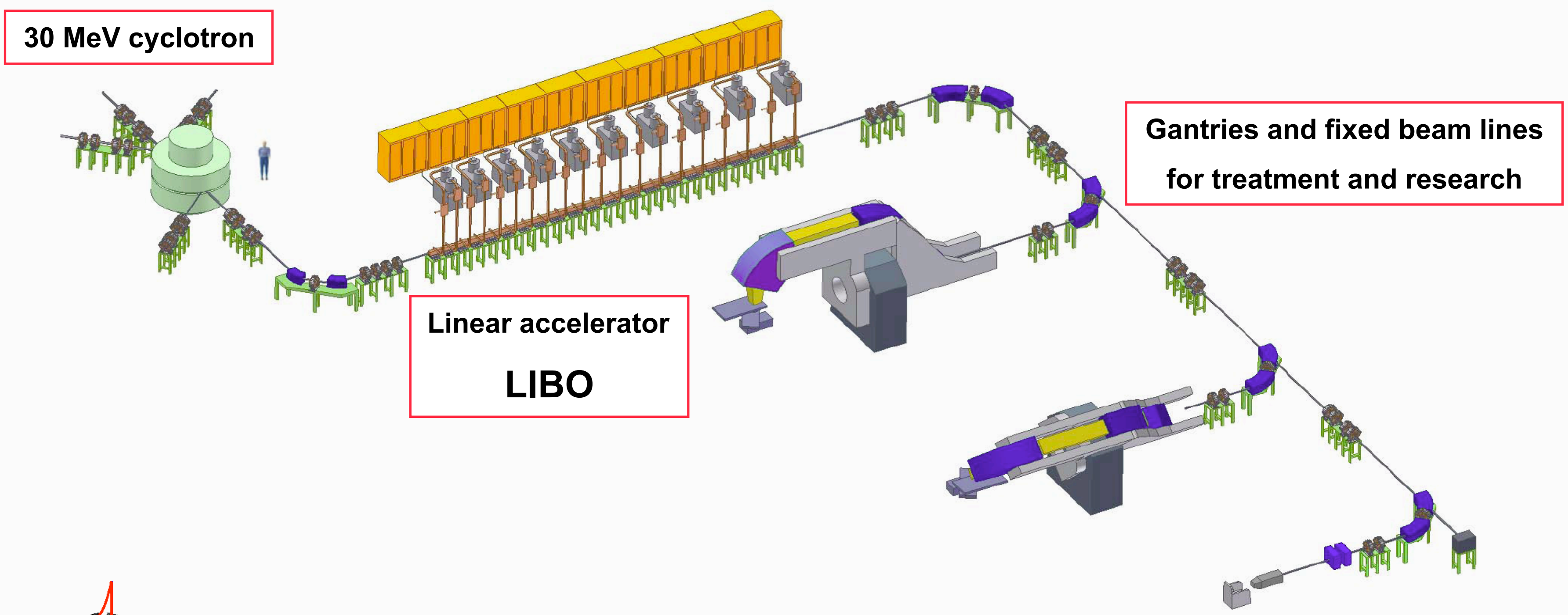
IDRA: a project promoted by the TERA Foundation

IDRA

Institute for Diagnostics and RAdiotherapy



TERA

Three fundamental questions to detect and cure the disease:

When ? — As Soon As Possible

Where ? — As Precisely As Possible

How ? — As Effectively As Possible

<u>One answer :</u>

Multidisciplinary approach

Some examples :

- Non-invasive screening (molecular markers, imaging, …)
- High precision diagnostics (MRI, TC, PET, SPECT, …)
- High precision non-invasive therapy (hadrontherapy, …)

Conclusions and Outlook

- Since the beginning of particle physics, more than one-hundred years go…

Particle physics offers medicine and biology very powerful tools and techniques to study, detect and attack the disease

To fully exploit this large potentiality, all these sciences must work together!

Work is in progress…

Physics is beautiful…

…and useful !