PART III:

Particle therapy of cancer

The HOLY GRAIL of Radiation Therapy

Ideal Situation

Provide a lethal dose to the tumor

and

Spare perfectly the surrounding healthy tissue

In Practice

Deposit the radiation dose more precisely in the target volume with less dose in the surrounding healthy tissues.

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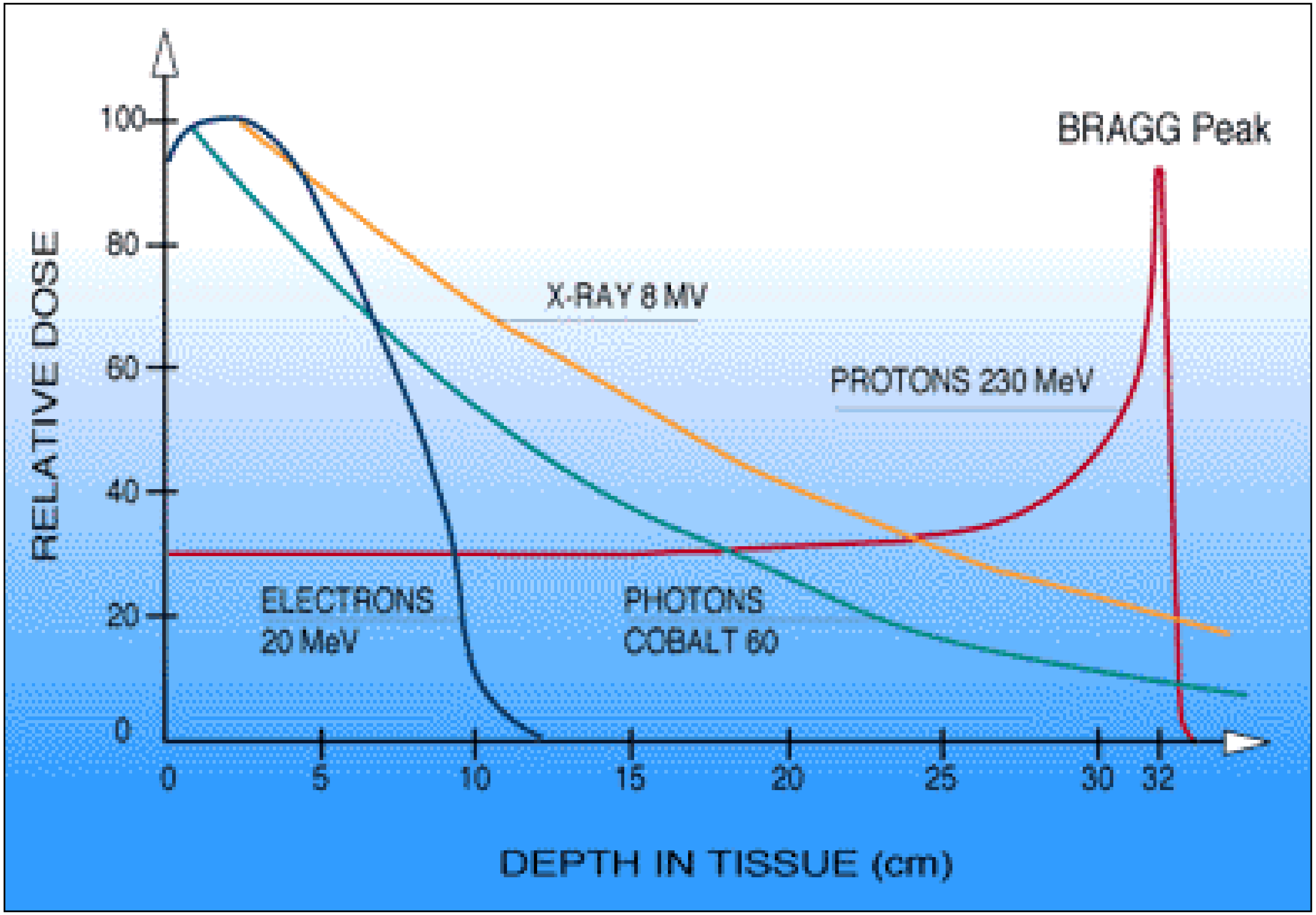
The depth dose curve distributions



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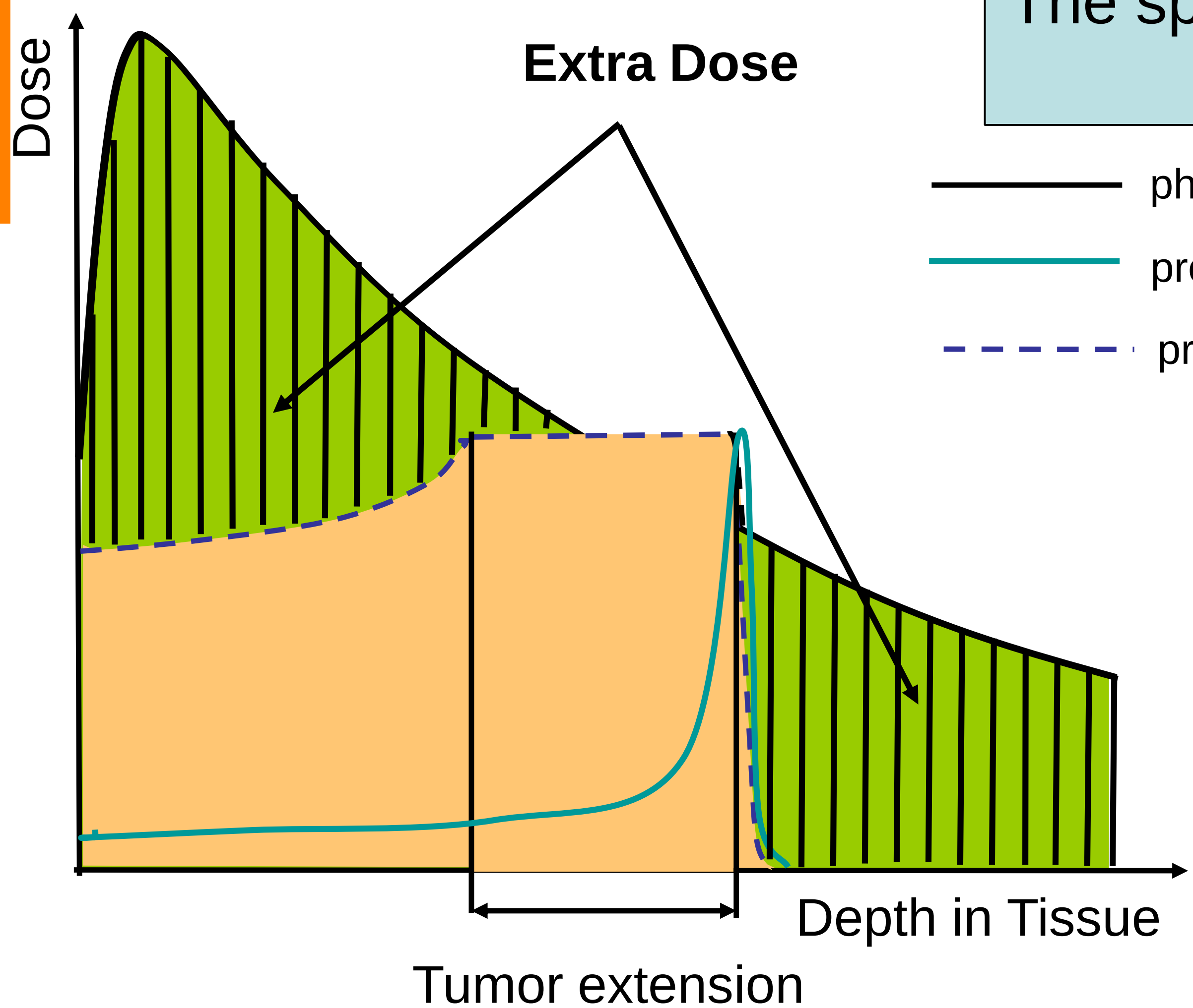
Photon-Proton dose distribution comparison



The spread out Bragg peak (SOBP)

- Position of the Bragg peak depends on beam energy
- Incomming energy modulation $\Rightarrow$ SOBP
- No dose downsteam of tumor
- Lower dose upstream of tumor

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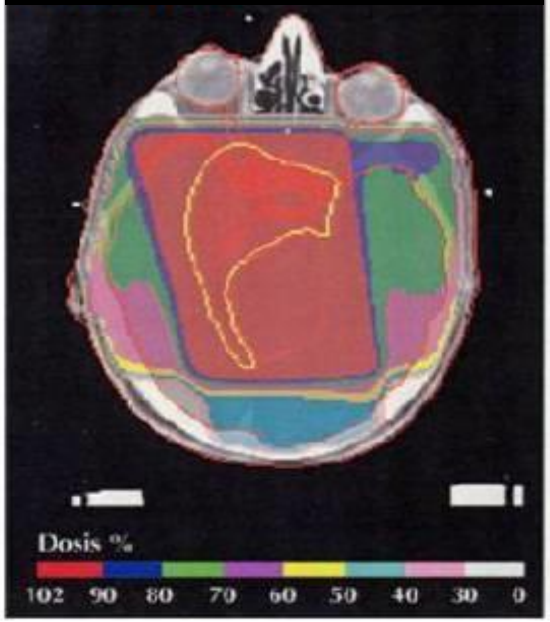
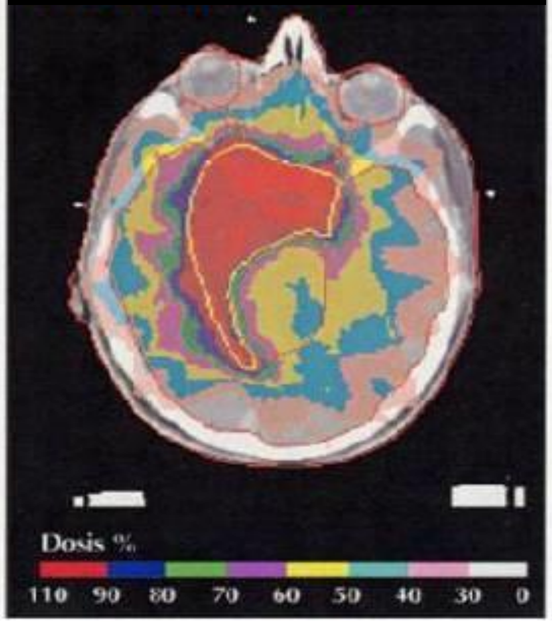
Particle Therapy: Comparing PT & Conventional RT

Main advantage of the Bragg peak => more precise conformal mapping of the tumor volume

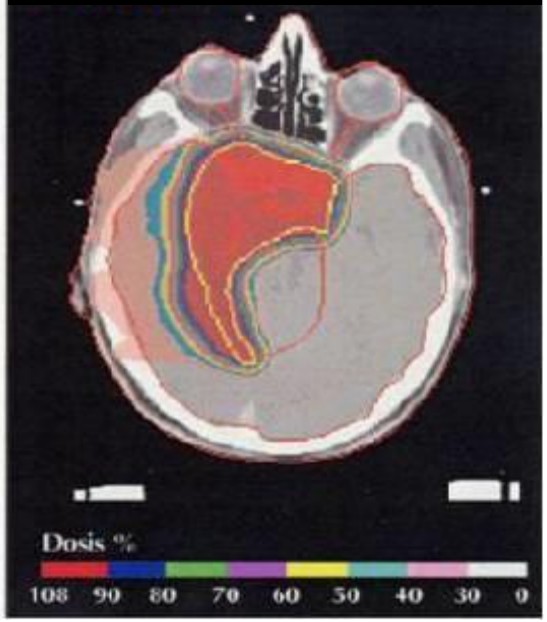
Photon	IMRT Photon	Proton



Conventional Radiotherapy



IMRT = Intensity Modulated Radio Therapy



Scattering technique

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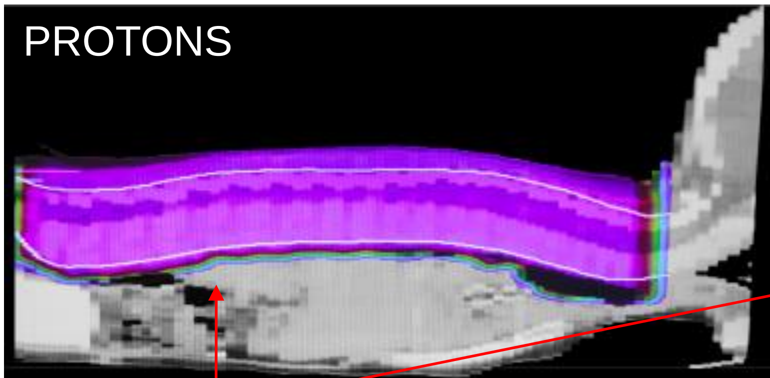
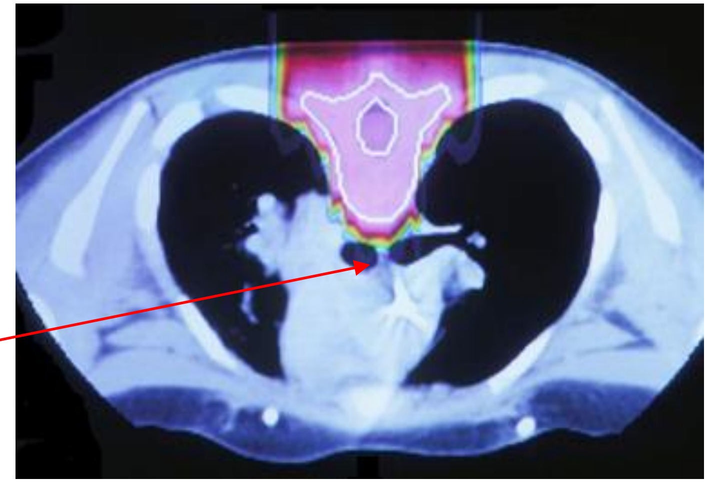
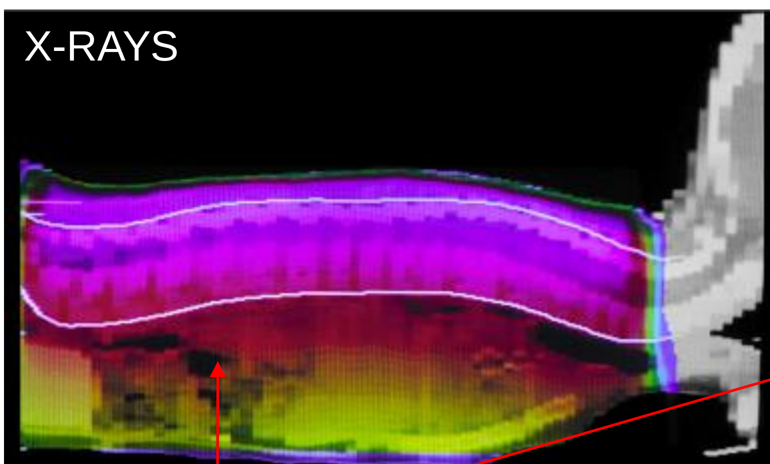
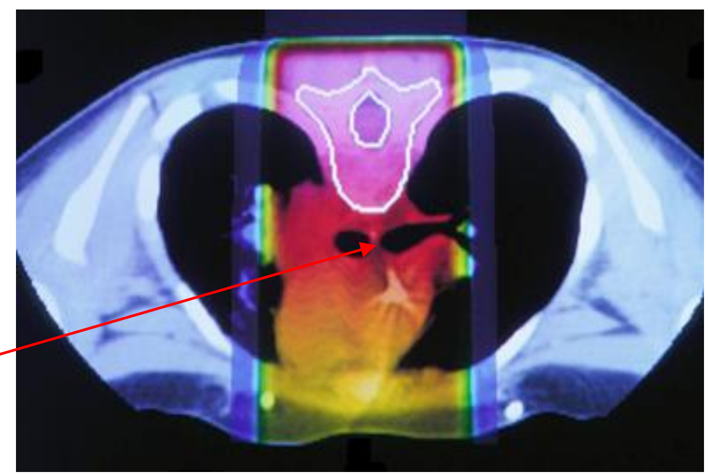
Medulloblastoma Treatment X-Rays vs Protons





Low or No Dose Released Here



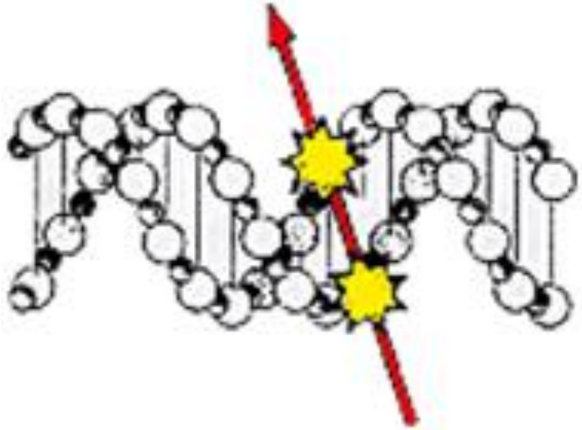


High Dose Released Here

Radiobiological effects of ionizing radiation

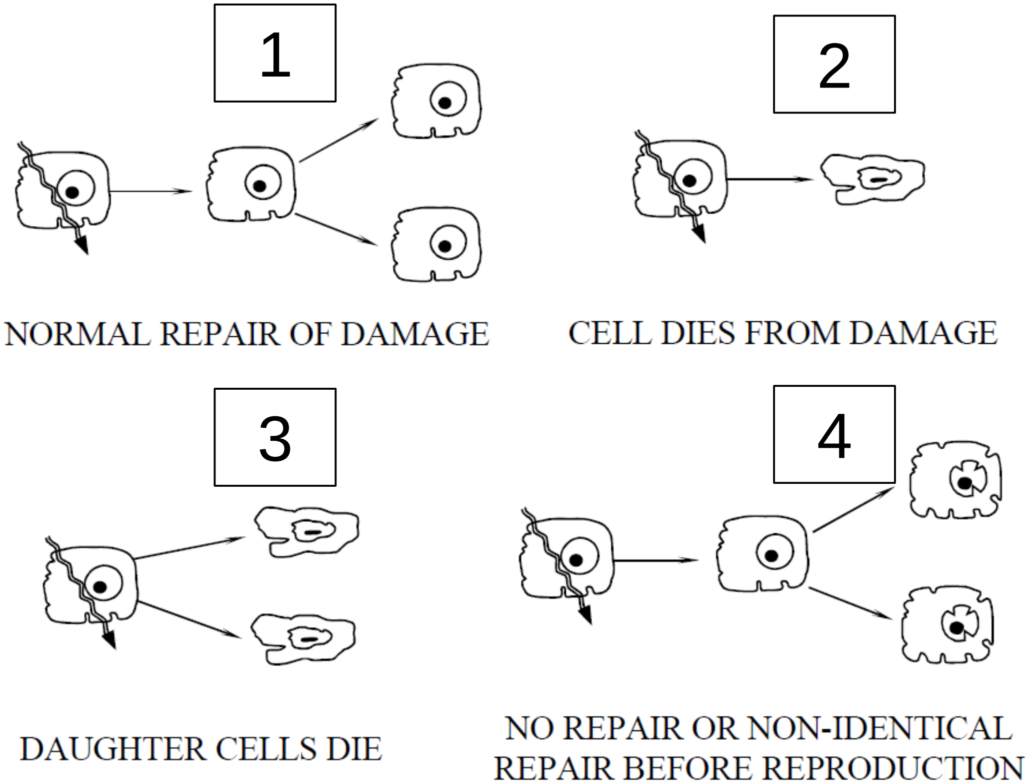
Complex mechanism depending on several factors

- Type and state of irradiated cells (O_2, SS or DS DNA)
- Type and energy of incident radiation (LET)
- Quantity of radiation per mass unit (dose)



The objective is to break the DNA in the tumor cell such that it can not repair itself

Possible effects of on the cells



1 => apply fractions

2 or 3 => wanted

4 => not wanted => may induce secondary tumors in healthy tissues => avoid by applying multiple fractions

Tumor cells have less repair capability => apply fractions so that healthy cells can repair

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Relative Biological effect of Protons vs Carbon

- **LET ⇒ Linear Energy Transfer**
  - Fast protons and photons ⇒ low LET radiation
  - Carbon, neutrons and slow protons ⇒ high LET radiation
- **Low LET**
  - Relatively uniform distribution of dose
  - DNA is broken by oxidizing radicals created in water/tissue (indirectly)
- **High LET**
  - High density of ionization events along particle track
  - DNA is broken by direct ionization events
- **OER ⇒ Oxygen Enhancement Ratio**
  - Low LET radiation more effective in a oxygen-rich environment
  - Tumors are less oxygenated (less vascularized)
  - Healthy tissue is higher oxygenated (well vascularized)
- **High LET ⇒ Relative Biological effectiveness (RBE) is higher**

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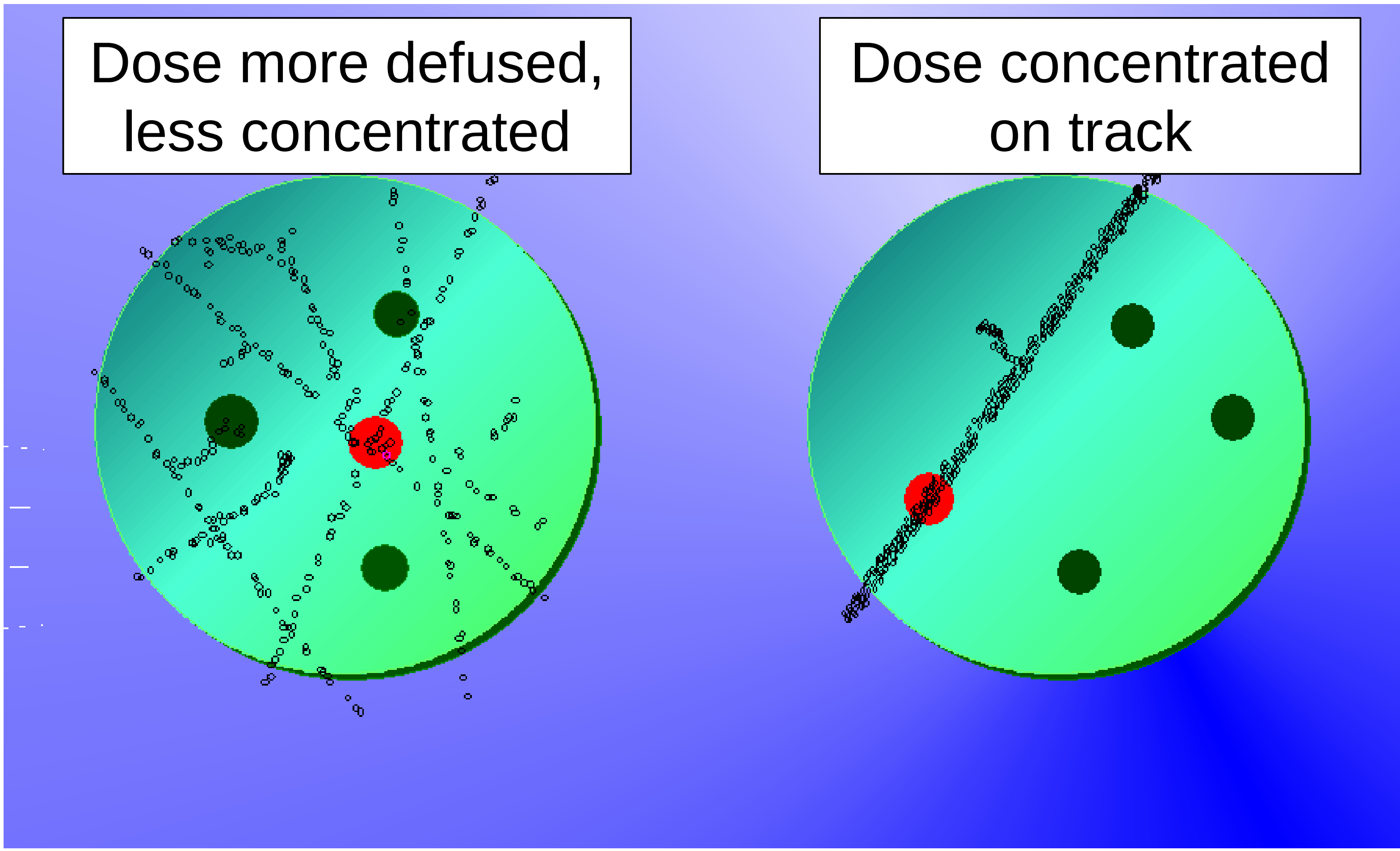
LET: Linear Energy Transfer

Photons, Fast Protons | Neutrons, Carbon ions

Low LET | High LET



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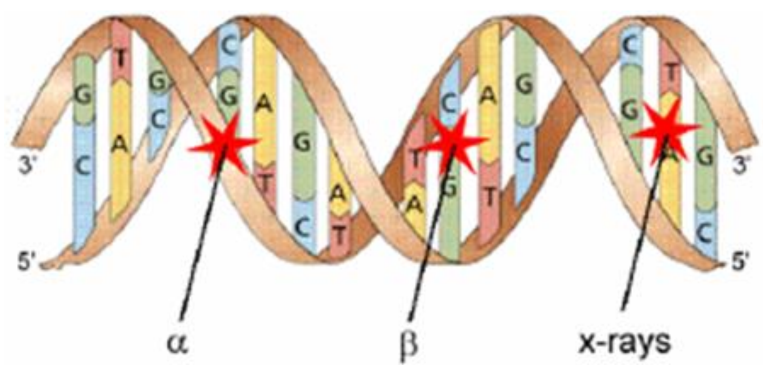
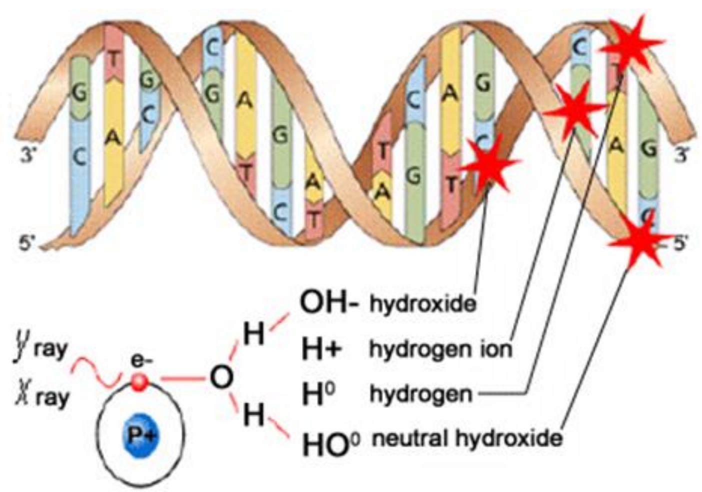
Two types of radiation damage

Direct: High LET particles (C,α, slow n, p or β) have frequent interaction over a short distance; they break directly DNA strands due to massive but local destruction. Whatever the state of the cell, enzymes generally cannot repair the DNA.

Indirect: Low LET particles (γ,X,fast n, or β) induce radiolysis in the cell. The chemically very reactive free radicals destroy the DNA strand. The presence of O2 increases the production of free radicals, therefore the radio-sensitivity of the cells to low LET radiation Indirect effects are dose and state of cell dependant.





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OER ⇒ A famous experiment of Dr. Gray

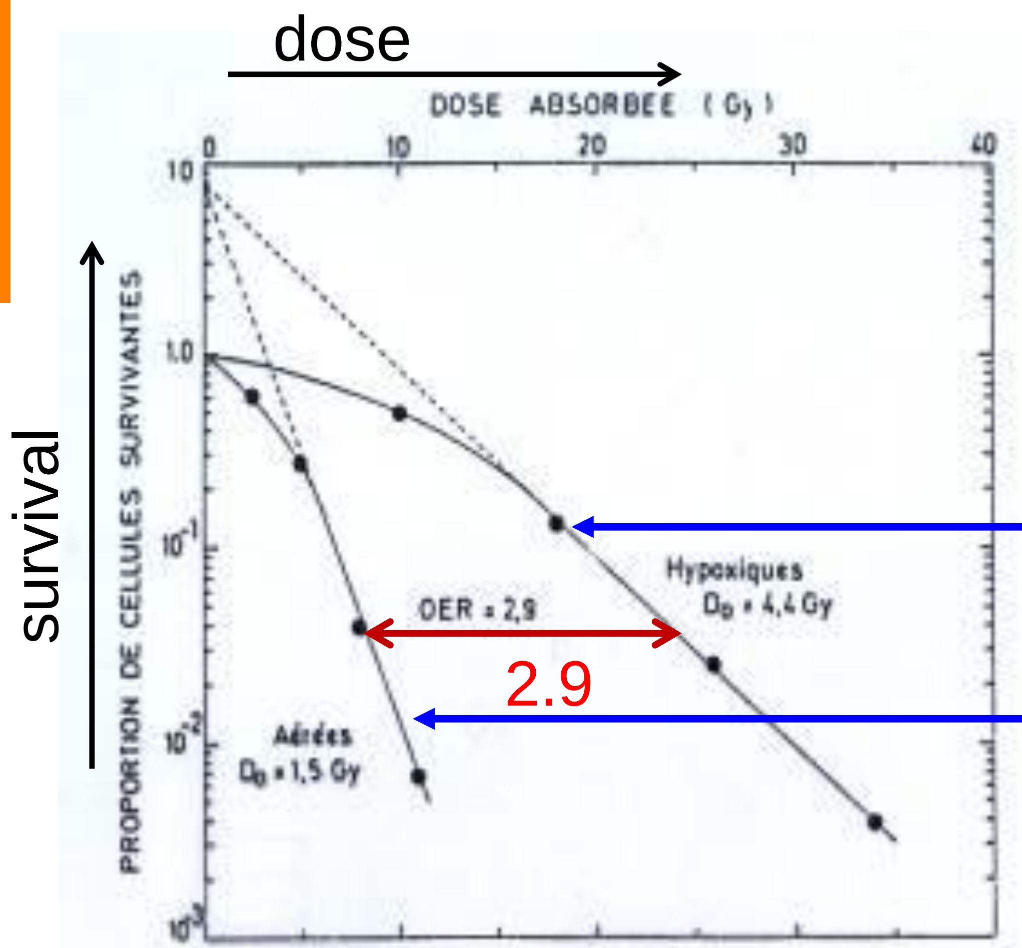

Figure VII.1
Courbes de survie obtenues, *in vitro*, pour des cellules mammaires EMT6 de souris, après irradiation par rayons gamma, en hypoxie et dans des conditions normales d'oxygénation. *La forme* des courbes de survie est la m'me dans les deux cas, mais la *dose* nécessaire pour

Cell survival rate as function of absorbed dose

1) Oxygen poor condition (tumor)

2) Normal oxygen condition

OER = 2.9

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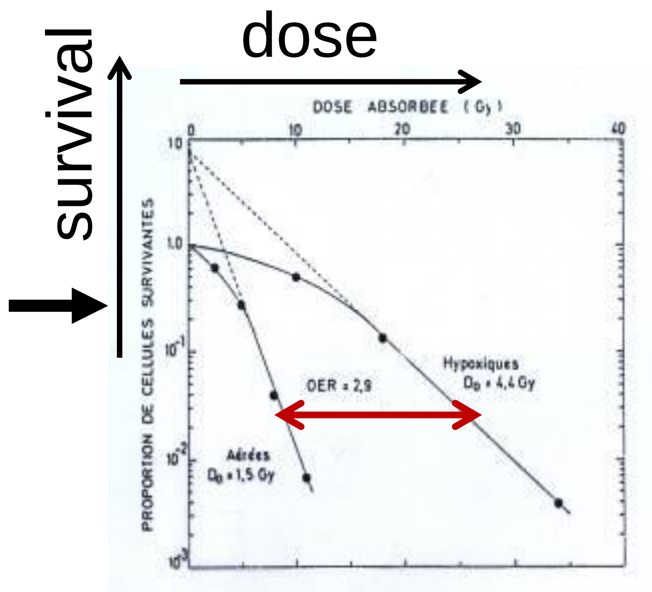
Oxygen Enhancement Ratio

Low O_2-level in tumors =>Carbon beams even better than proton beams

Low -LET

OER for low LET

= 3

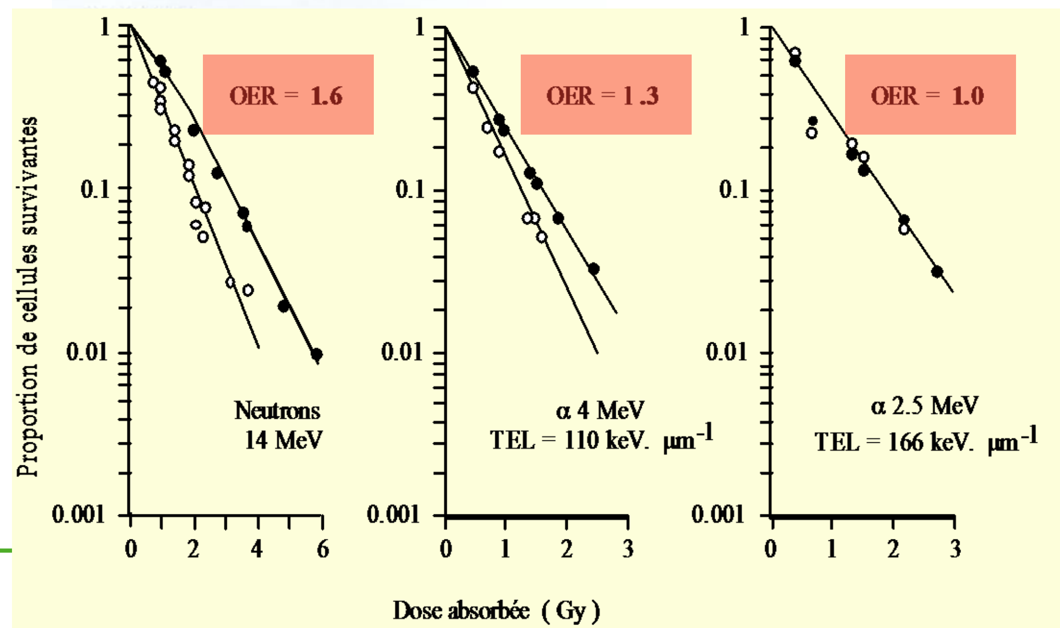


OER decreases as the LET increases

High -LET

OER for high LET

= 1 - 1.7



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Main Specifications of a Proton Therapy System

1. **Ability to reach the tumor**

- Range in patient: up to 32 g/cm²
- Range modulation:up to full range, with steps of 0.5 g/cm²
- Field size: up to 30 x 40 cm

2. **Ability to reach the from any selected direction**

- Isocentric Gantry
- Precise, robotic patient positioner

3. **Ability to reach the tumor accurately**

- Penumbra: maximum 2 mm at skin
- Distal dose falloff: maximum 1 mm above physical limit
- Patient positioner accuracy and reproducibility: 0.5 mm for small displacements
- Gantry accuracy and reproducibility: 1 mm radius circle of confusion
- Patient alignment methods: lasers, light fields, X-rays

4. **Ability to verify and control the dose deposition using IC's**

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Accelerator parameters driving the technology choice

- Energy: defines the range in the patient (230 MeV enough)
- Energy definition: defines the range accuracy and the distal falloff
- Beam current: defines the dose rate (10^{11} p/sec enough (10 nA))
- Beam current stability and noise: defines ability to use wobbling and scanning
- Accurate and fast beam current control: needed for conformal therapy

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Cyclotrons for Proton & Carbon therapy?

- In 1991, when IBA entered in PT, the consensus was that the best accelerator for PT was a synchrotron
- IBA introduced a very effective cyclotron design, and today the majority of PT centers use the cyclotron technology (Not only IBA but Accel/Varian, Still Rivers Systems/Mevion)
- Over these 15 years, users came to appreciate the advantages of cyclotrons:
  - Simplicity & reliability
  - Intense, continuous (non pulsed) beam current
  - Lowest cost and size
  - But, most importantly, the ability to modulate rapidly and accurately the proton beam current

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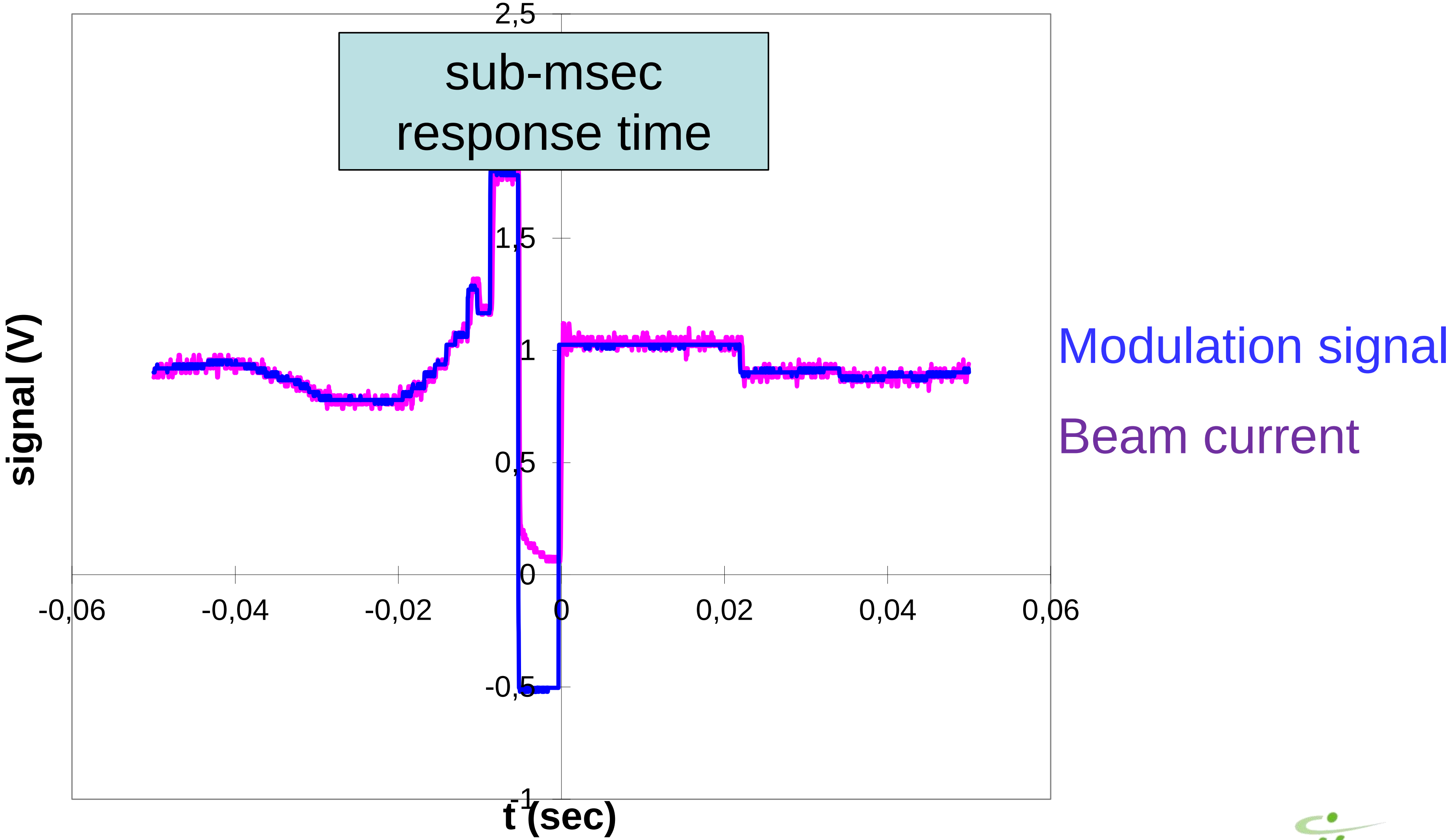
Real oscilloscope measured signals



Why is fast current modulation important?

- A big issue with scanned beam is the motion of the target during irradiation
- If you cannot control accurately and rapidly the current ,or if the beam is slowly pulsed , your only choice is step-and-shoot (spot scanning)
- Assuming a 10 mm (FWHM) beam spot size, a 50% overlap and a 20 Hz pulse rate, the maximum scanning speed will be 0.2 m/sec
- With this speed, for a large size tumor, repainting many time each layer is not really an option
- In contrast, with a cyclotron you can scan at 20 m/sec and rescan many times each layer

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Change of energy?

- Cyclotrons are simpler at fixed energy
- Energy change by graphite degrader at waist after cyclotron exit, followed by divergence slits and energy analyzer
- This very effectively decouples the accelerator from the patient
- Fragmentation products are effectively eliminated in slits and ESS
- Yes, neutrons are produced, but ESS is well shielded and the average beam currents are very low > little activation
- How fast? 5 mm step in energy in 100 msec. Respiration cycle is 2…4 seconds => 100 msec is fine

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Accelerators for proton therapy: two alternatives

Small synchrotron

+ *Advantages*
  + Naturally variable energy
– *Disadvantages*
  – Current limited if low energy injection
  – Beam current stability & low noise is difficult on small synchrotrons
  – Fast and accurate beam current control difficult to achieve
  – More complex with negative impact on availability

Compact cyclotron

+ *Advantages*
  + No physical current limitation
  + Beam current stability & noise specifications currently achieved on small cyclotrons
  + Fast and accurate beam current control over 1000/1 range easy to achieve
  + Low complexity, resulting in highest availability
– *Disadvantages*
  – Variable energy requires external Energy Selection System

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A Proton Therapy Facility is like a small Hospital

- A proton therapy system is much more than only an accelerator
- It is a complex, multi-room system, filling a hospital building.
- The total investment is around 100 M€, of which 45 M€ for the equipment
- Many people (doctors, therapists, physicists, nurses) work daily in a PT facility
- A PT facility can treat 1500 patients/year and generate revenues in the order of 30 M€/year!

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Main Sub-systems of a cyclotron based PT facility

- 230 MeV isochronous cyclotron
- Energy Selection System (ESS)
- Beam Transport and Switching System
- Isocentric Gantries (typically 3) and one Fixed Beam Line
- Nozzles for matching the beam wrt the required treatment (scattering, wobbling or scanning, diagnostics)
- Robotic Patient Positioners
- Software Control and Safety System

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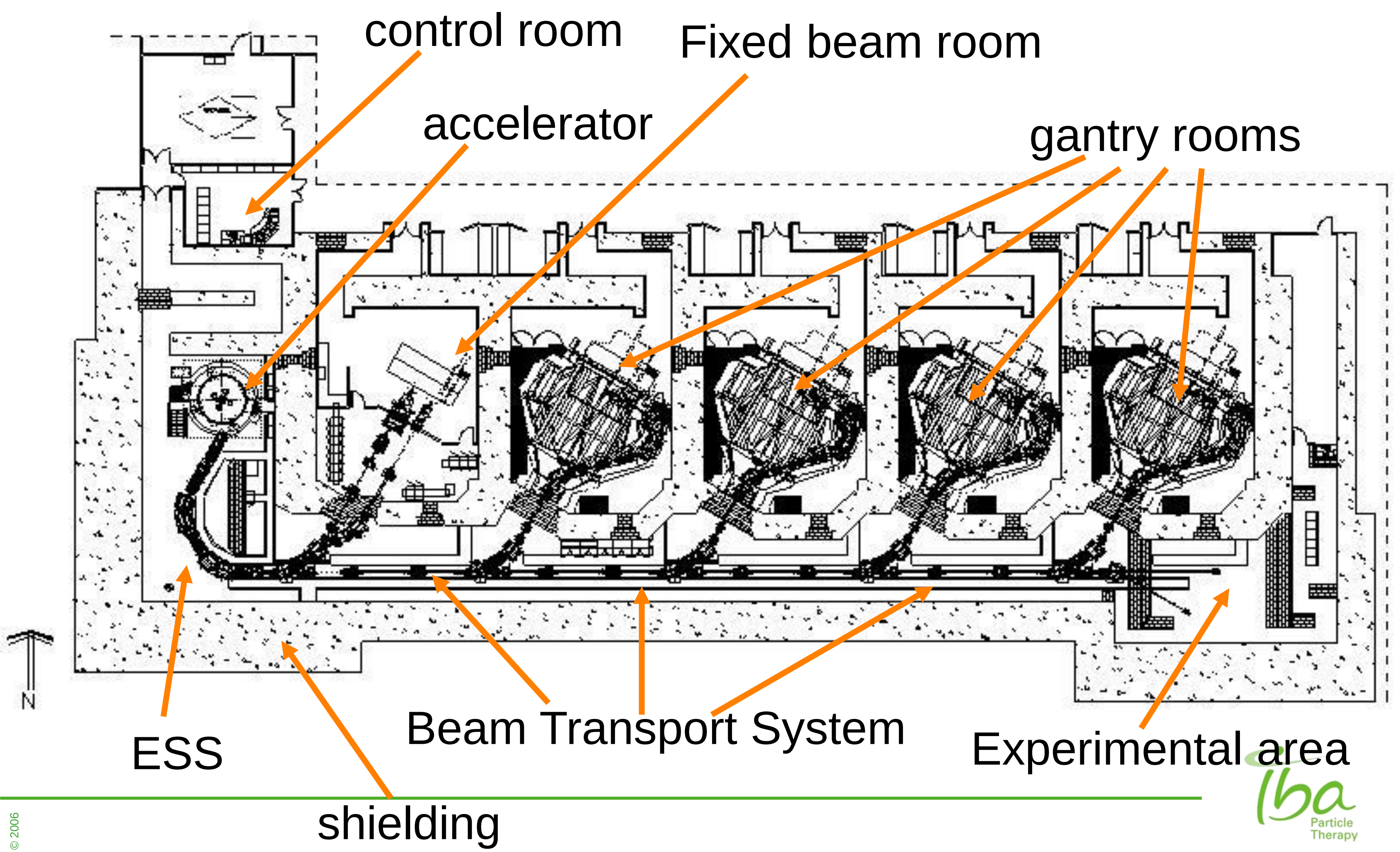
Typical Proton Therapy Facility Layout



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Proton therapy center

€30-55 millions for equipment
€45-100 millions for the center

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The 230 Mev Cyclotron at MGH in Boston

Protons only

Fixed energy

200 tons

∅ = 4.7 m

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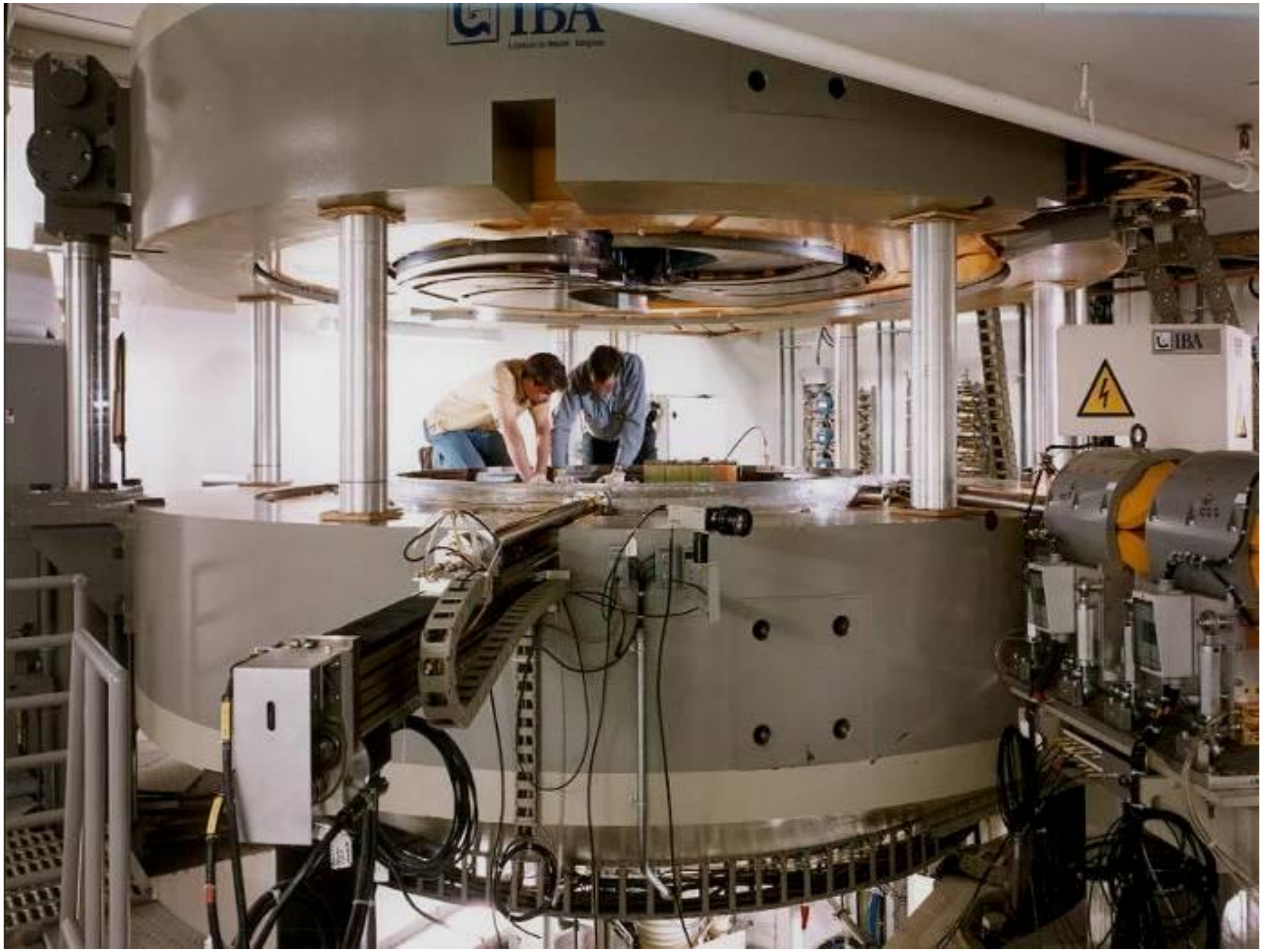
Cyclotron Opens in the Median Plane for easy access



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C230 inside view: spiral sectors with elliptical gap

Spiral sectors => better vertical focusing
Elliptical gap => high B-field and easier extraction

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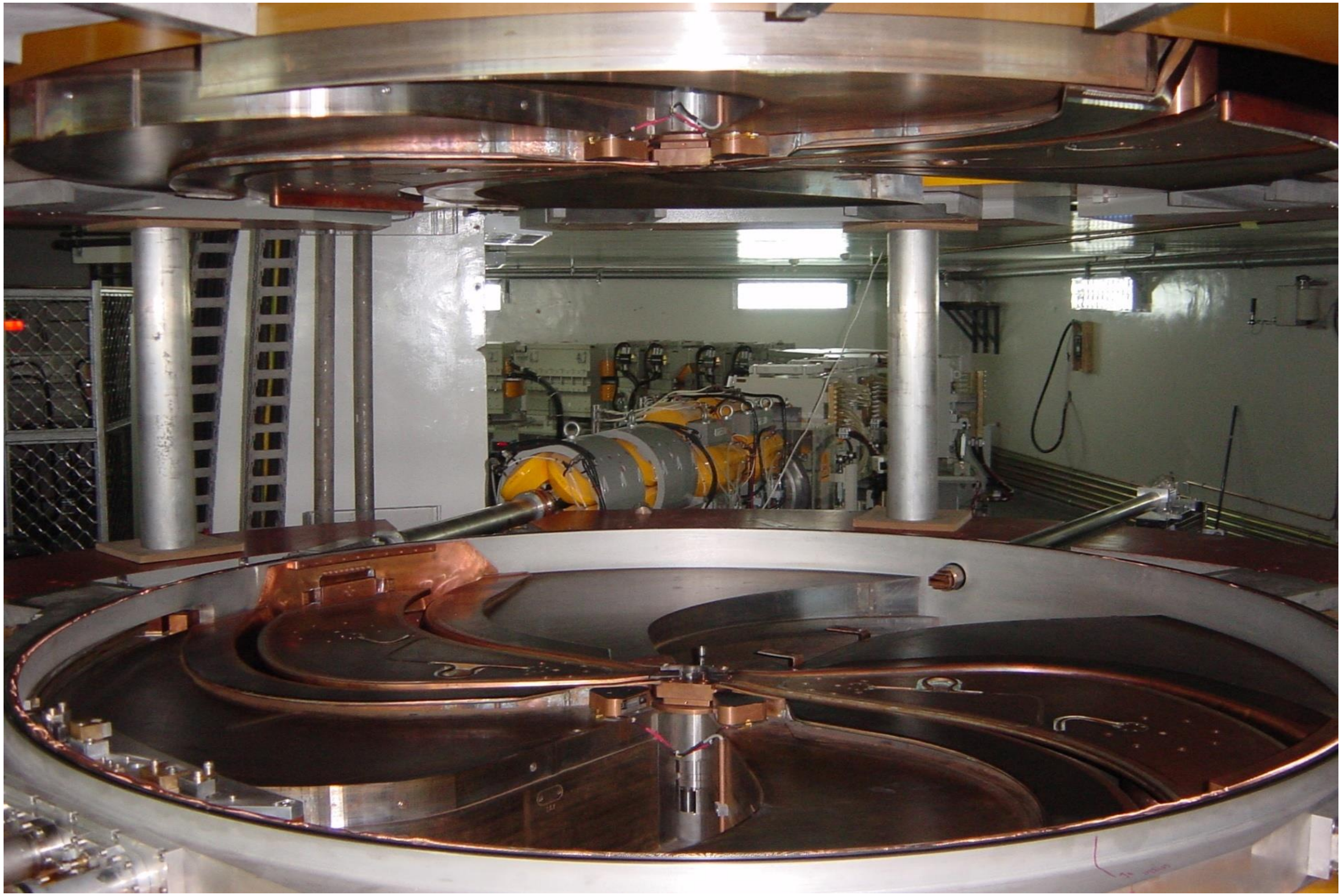
IBA PT subsystems : the Cyclone 235

Another view from the inside…



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Zoom on cyclotron center

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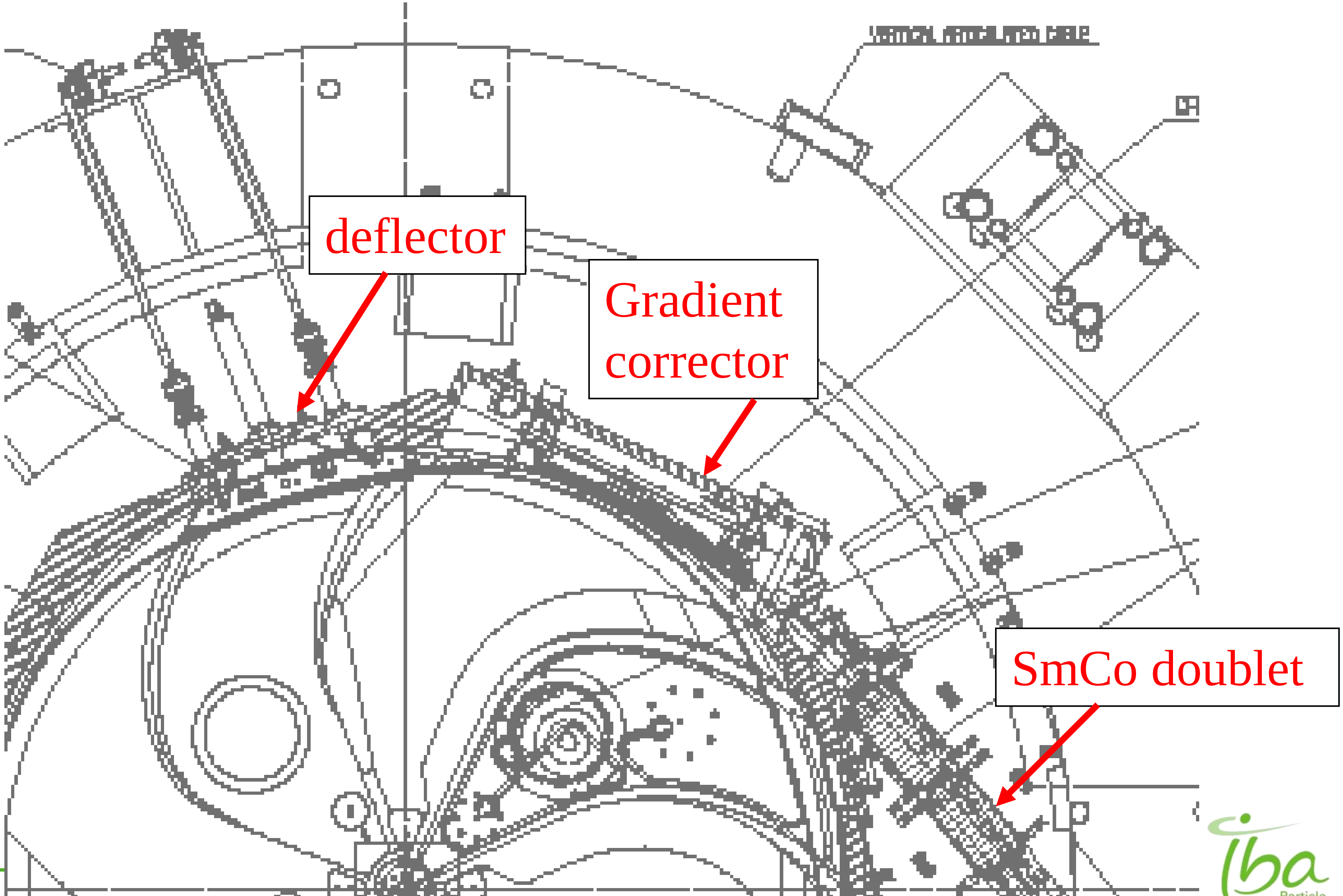
Extraction from the C230 cyclotron



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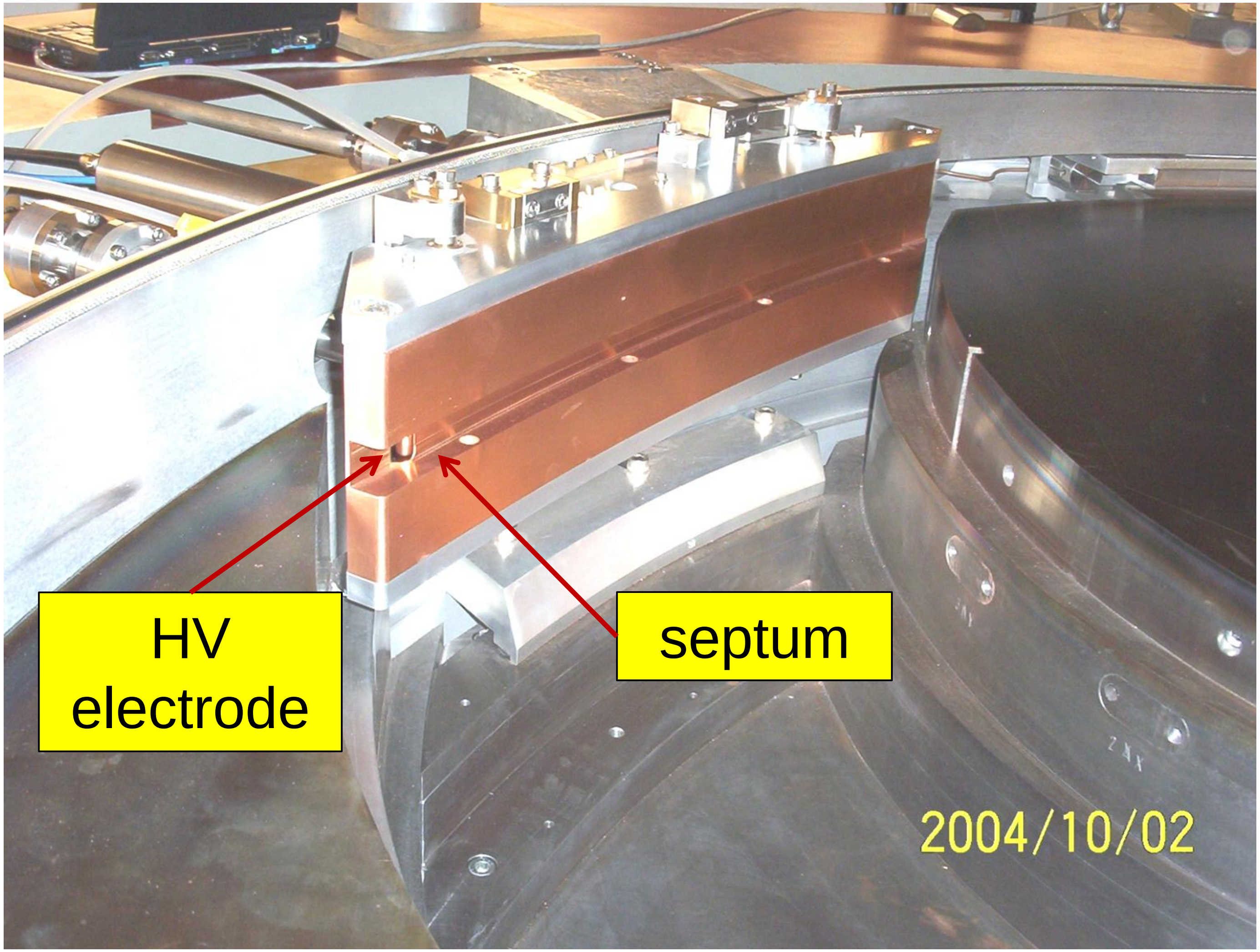
Electrostatic Deflector



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C235 Permanent Magnet Doublet

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The Energy Selection System

- Carbon wedge is used for coarse energy definition
- Emittance slits are used to define the emittance of the transmitted beam
- Analyzing magnet system defines accurately the range at nozzle entrance
- Laminated magnets and quads allow 10% energy change in 2 seconds

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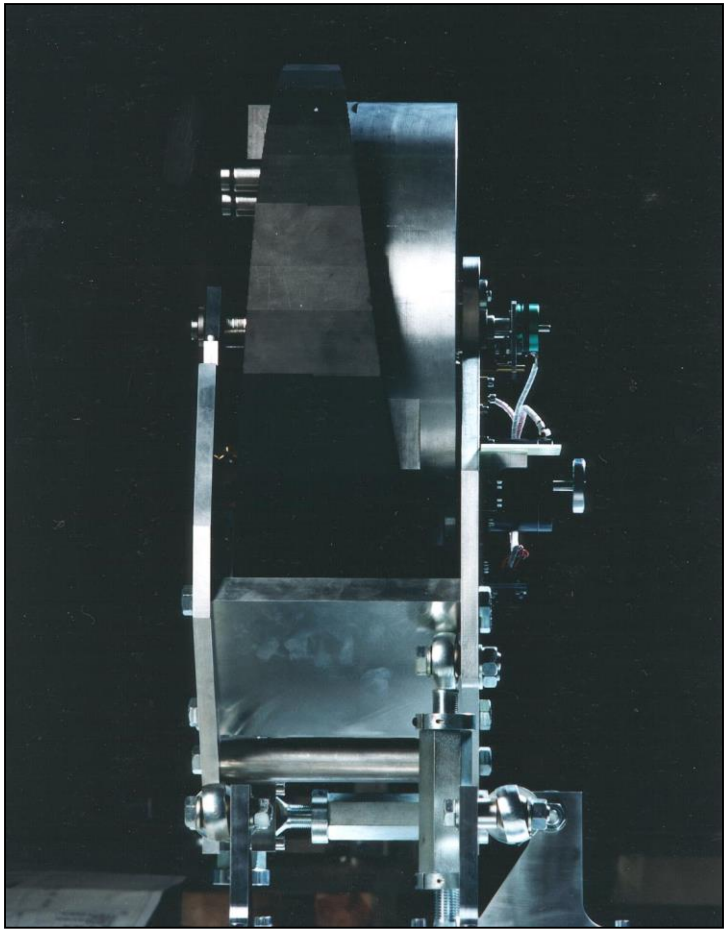
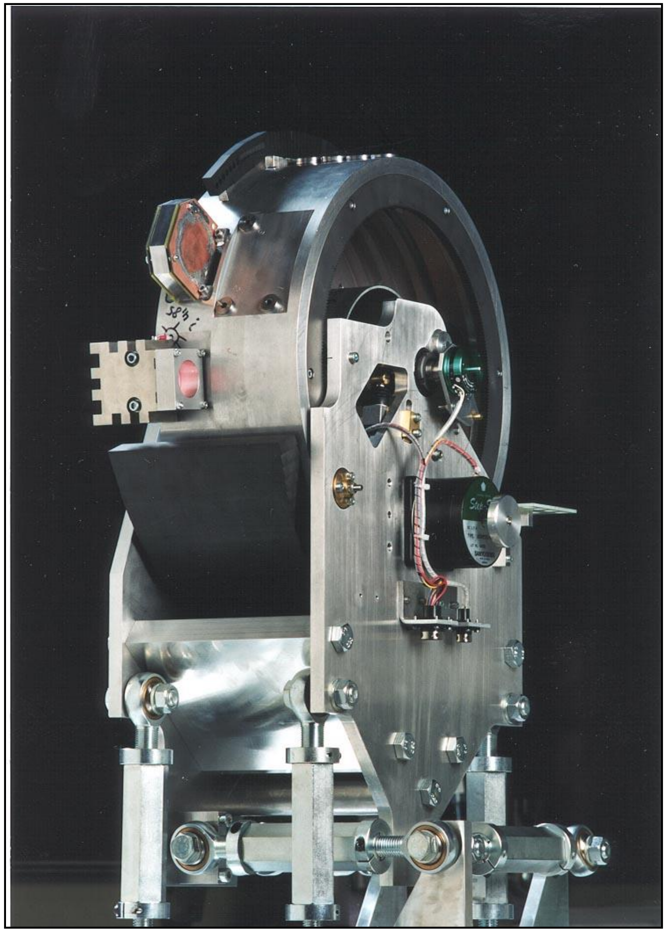
The carbon wedge degrader





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IBA PT subsystems : the beam transport lines.

The energy selection system. WPE, Essen, 2010.

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The Beam Transport and Switching System

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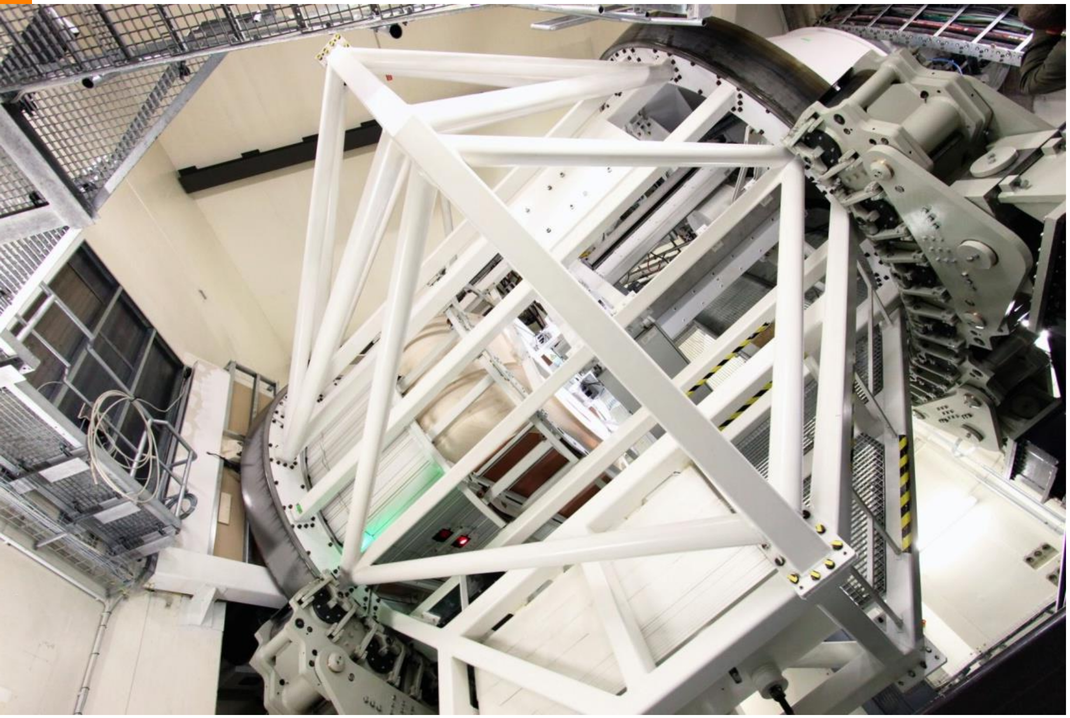
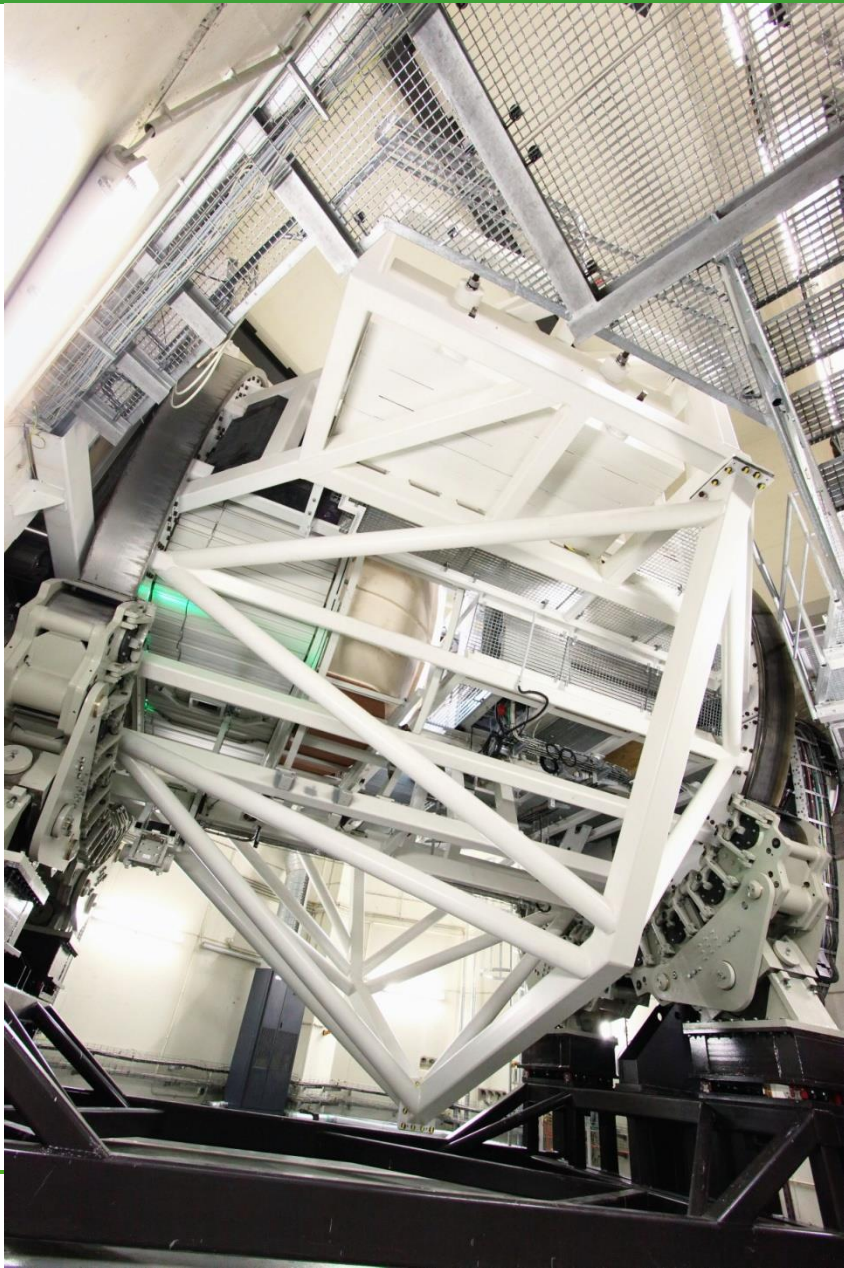
IBA PT subsystems : the treatment rooms.

The isocentric gantry.





About 10 m high

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Gantry Alignment with Theodolites

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The purpose of the nozzle

- Modulate the proton energy (range in patient)
- to spread the proton beam to obtain a uniform dose distribution in a large volume
  - Double scattering for small to moderate fields
  - Wobbling for the largest and deepest fields
  - Pencil Beam Scanning for the most precise conformal mapping
- to measure accurately the dose delivered to the patient
- Provide alignment of the patient with the proton field

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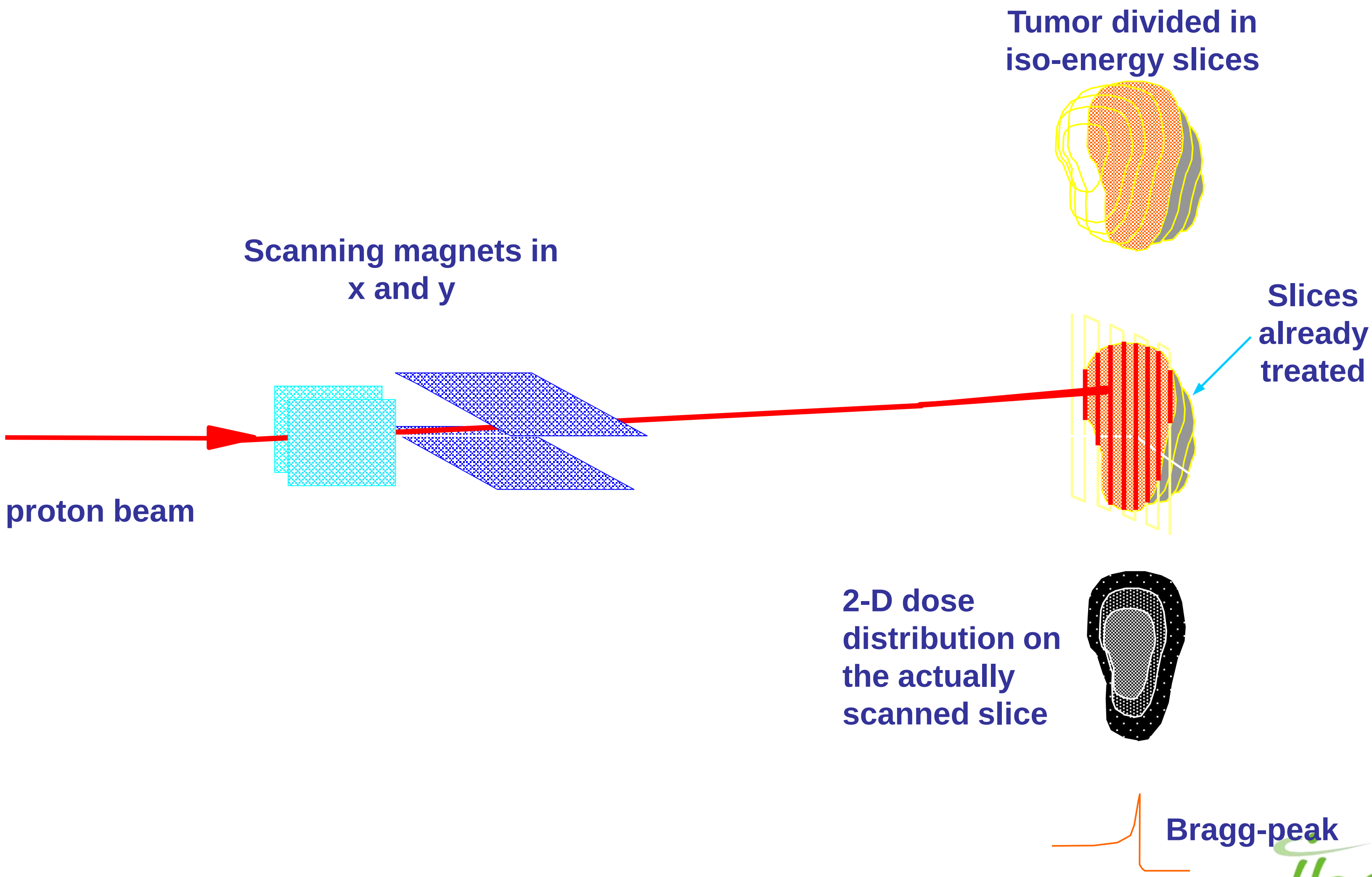
IMPT: Pencil Beam Scanning principle



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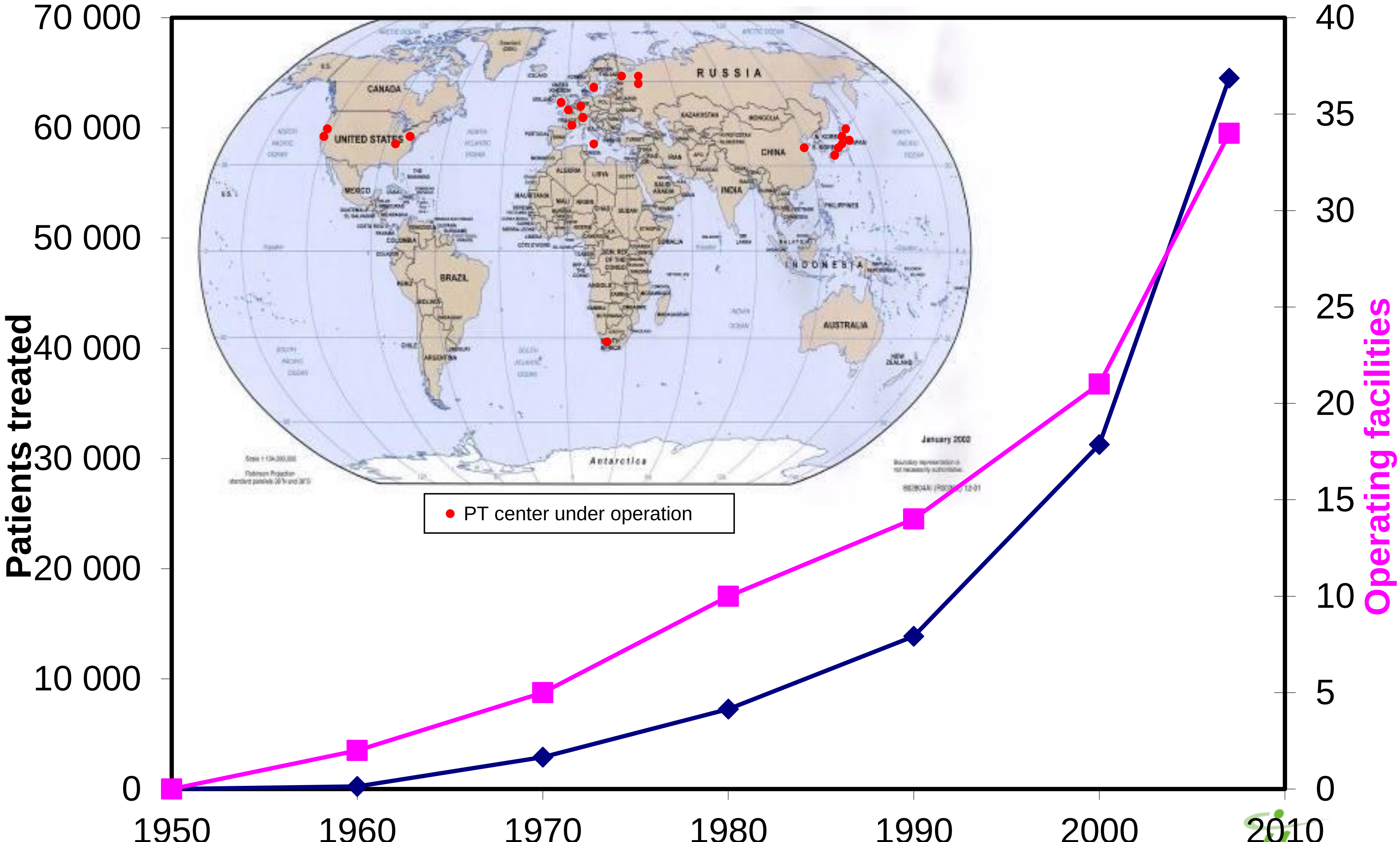
A patient friendly treatment room is important

Proton Therapy is growing rapidly !



Courtesy Janet Sisterson & PTCOG

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More than 20 IBA PT customers in the world

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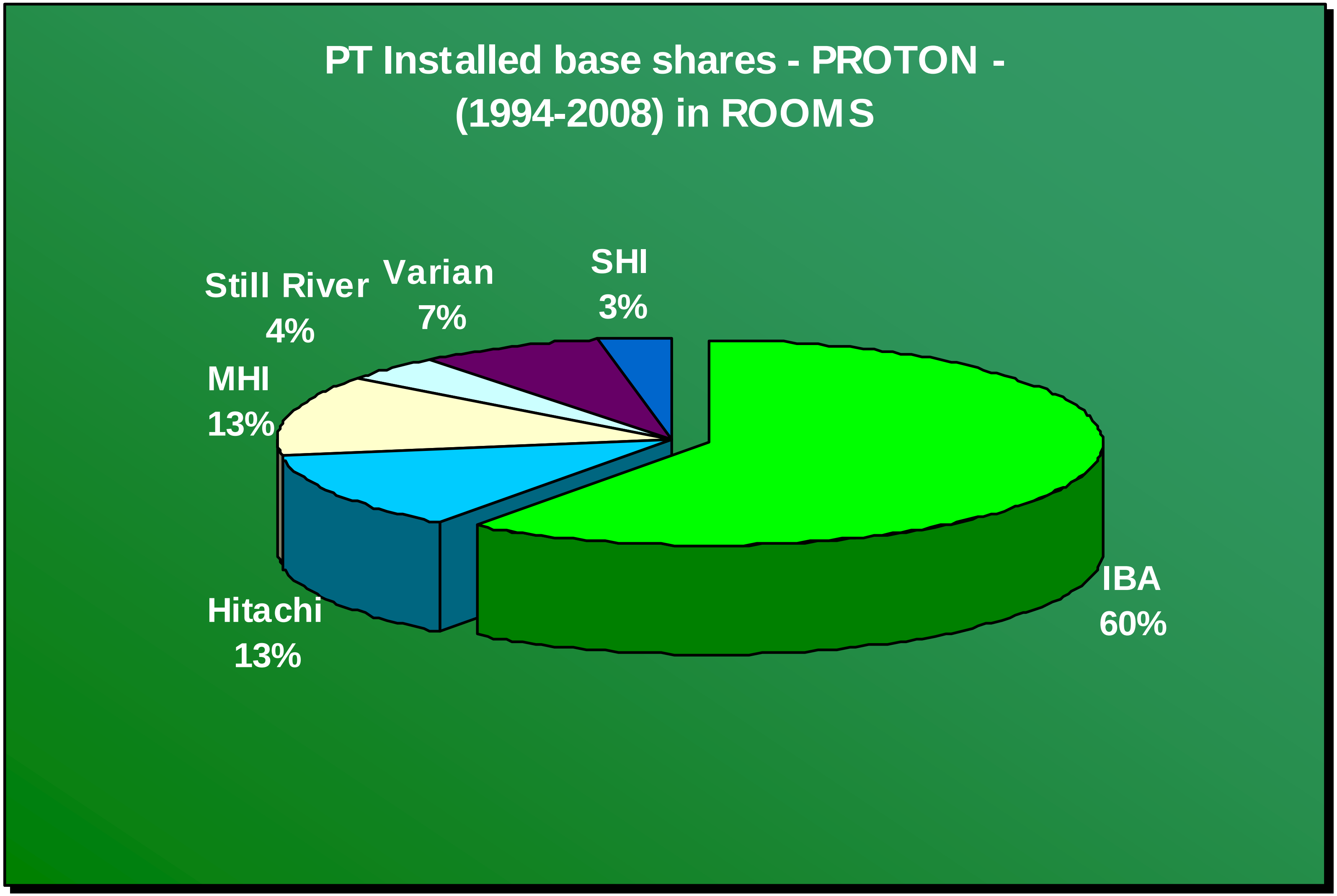
IBA has currently the largest installed base in PT



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The UPHS Particle Therapy Centre, Philadelphia

- The largest Particle Therapy centre to date!
- 4 Gantry Rooms
- 1 Fixed Beam Room
- 1 Experimental Room
- Beam since July 2008

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