Particle Therapy Fighting Cancer

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First idea by Robert Wilson in 1946

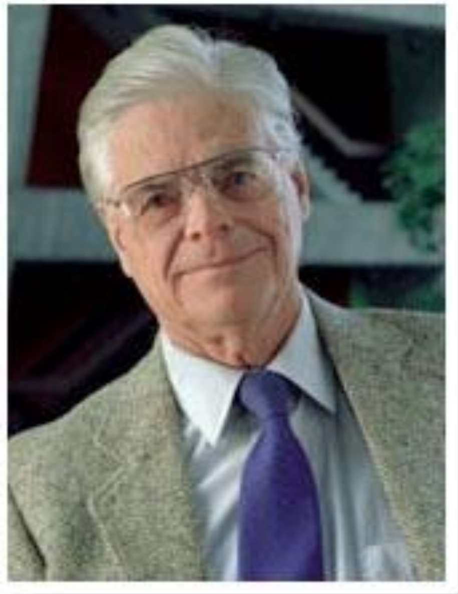
Radiological Use of Fast Protons

ROBERT R WILSON
Research Laboratory of Physics, Harvard University Cambridge, Massachusetts
Accepted for publication in July 1946.

Except for electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators.

Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 MeV (million electron volts) and perhaps as high as 400 MeV. The range of a 125 MeV proton in tissue is 12 cm., while that of a 200 MeV proton is 27 cm. It is clear that such protons can penetrate to any part of the body.



Robert Wilson

"The Visionary"

- **In 1946 Harvard physicist Robert Wilson suggested:**
  - Protons can be used clinically
  - Accelerators are available
  - Maximum radiation dose can be placed within the tumor
  - Proton therapy provides sparing of normal tissues
  - Modulator wheels can spread narrow Bragg peak

Robert R. Wilson (1914-2000)
Radiotherapy using charged particles

1946 Ion therapy for deep seeted tumors (R.Wilson paper)
1954 Lawrence Berkeley Laboratory, USA starts proton therapy
1957 Uppsala starts proton treatment
1975 Lawrence Berkeley Laboratory, USA
starts using heavy charged particle

1990 **Opening of 1st Hospital Proton Therapy in Loma Linda (USA)**
1993 Start of Carbon Ion Therapy in Chiba (Japan)
1996 Proton therapy starts in Villingen/Switzerland

1997 Carbon ion Radiotherapy starts at the University Hospital of Heidelberg, Germany at GSI in Darmstadt
2009 Heidelberg Ion Therapy Center (HIT)

CNAO, Hyogo, Gunma, MedAustron,…

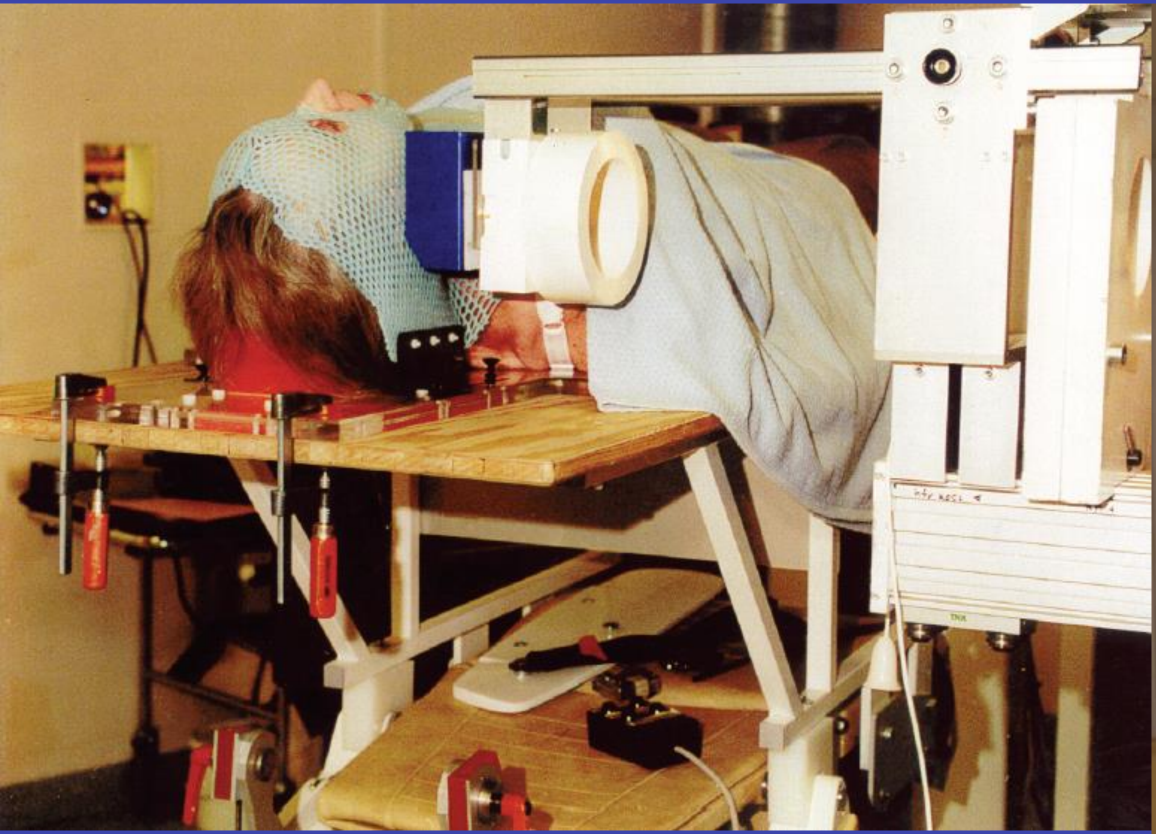
Fundamental Research

Clinical Research

Clinical Application

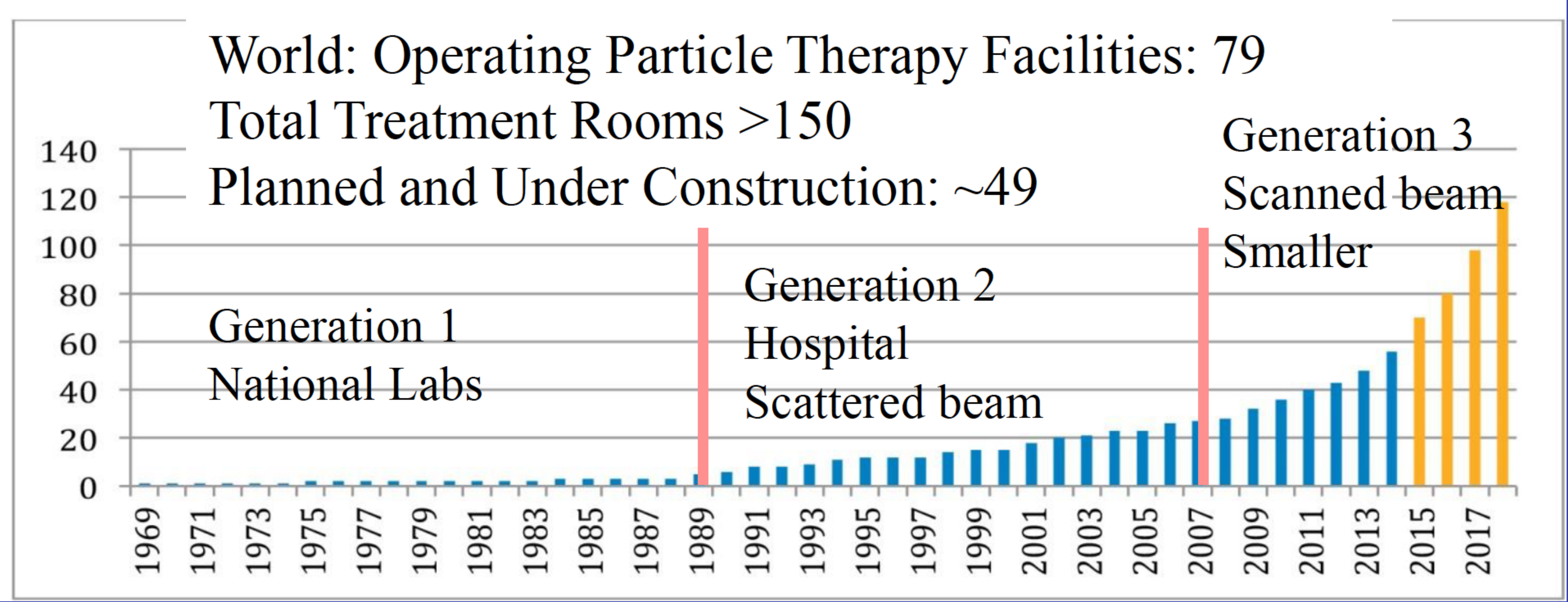
Patient Treatment

in Labs

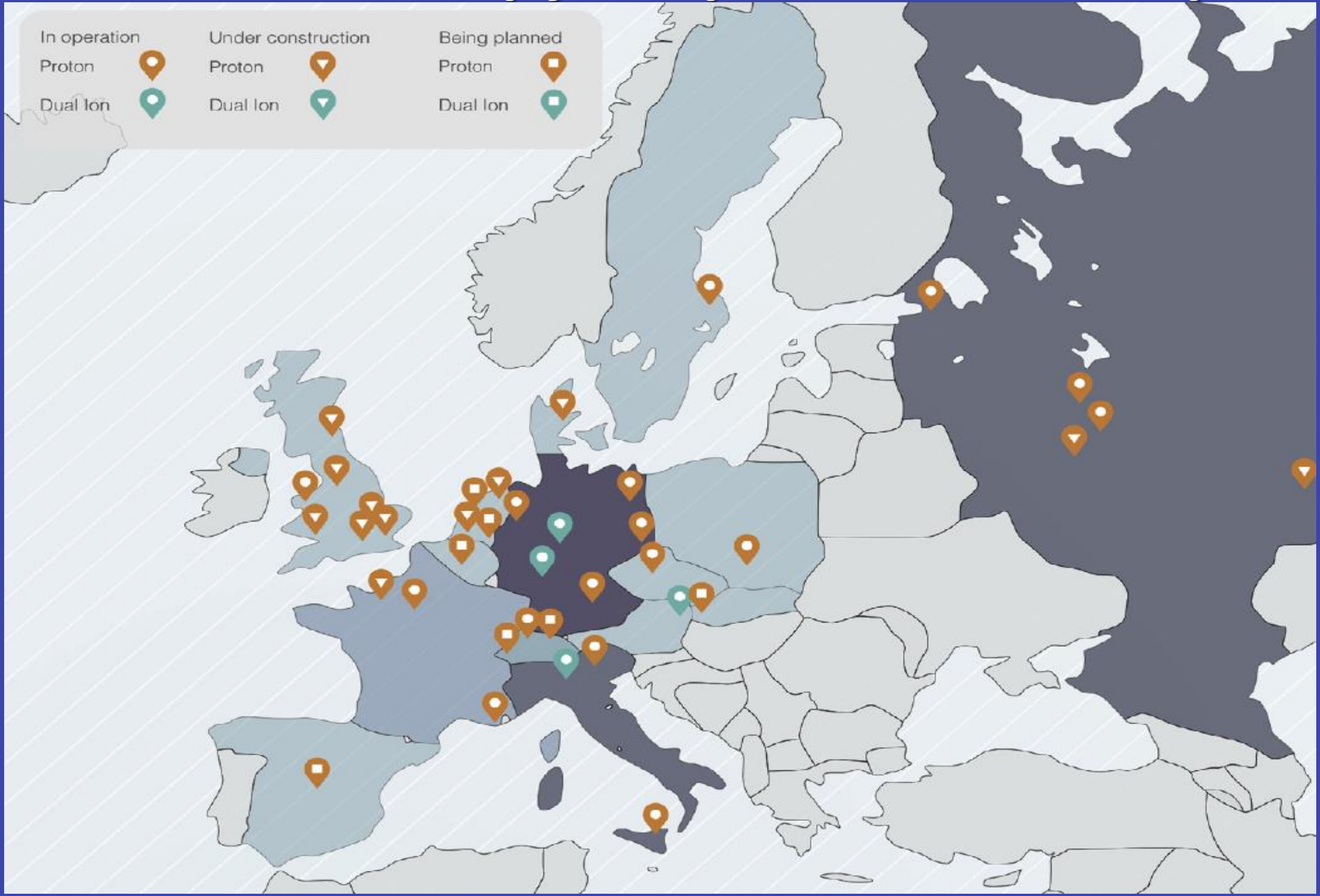


in Hospital

Patient Treatment



Particle Therapy in operation in Europe



The Advantage
of
Protons Relative Photons

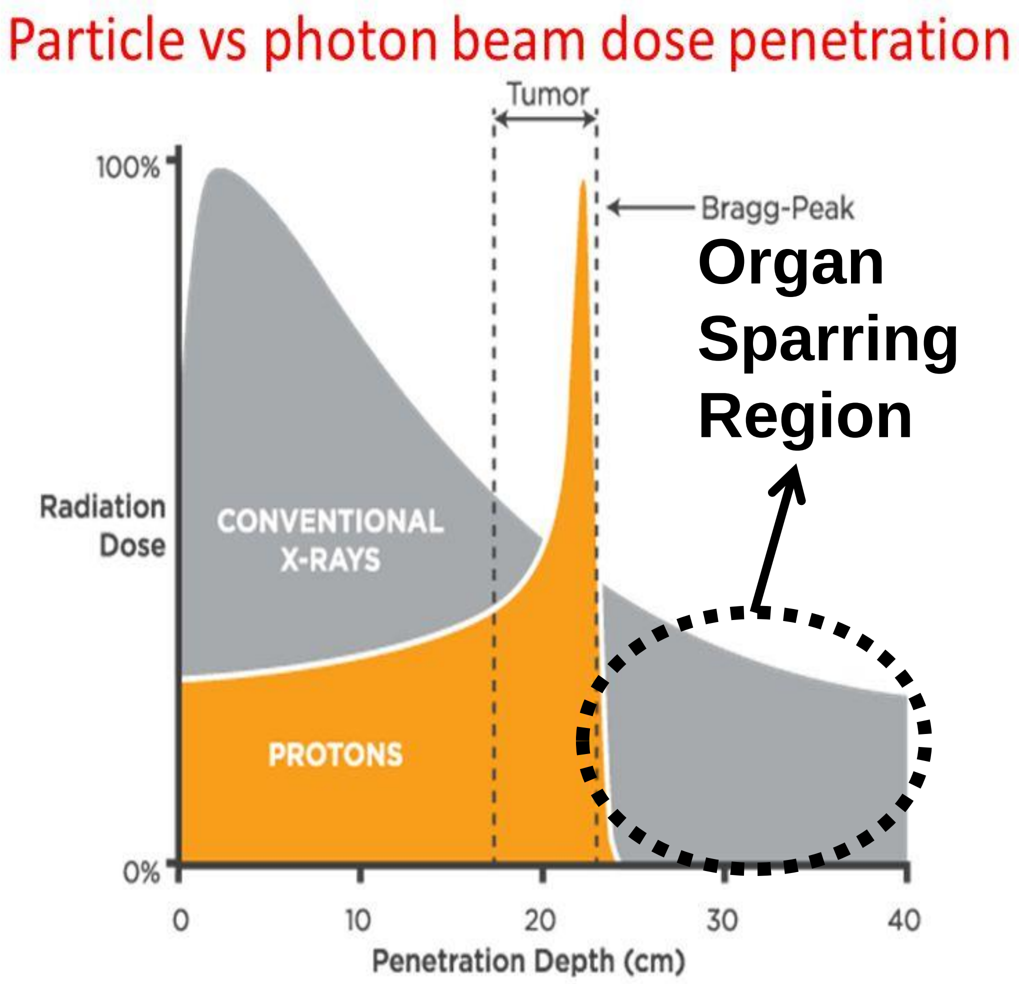
Proton Depth Dose Properties

Bethe-Bloch equation of ionisation energy loss by charged particles

$$-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I.(1-\beta^2)}\right) - \beta^2\right]$$

The beauty of the Bragg peak

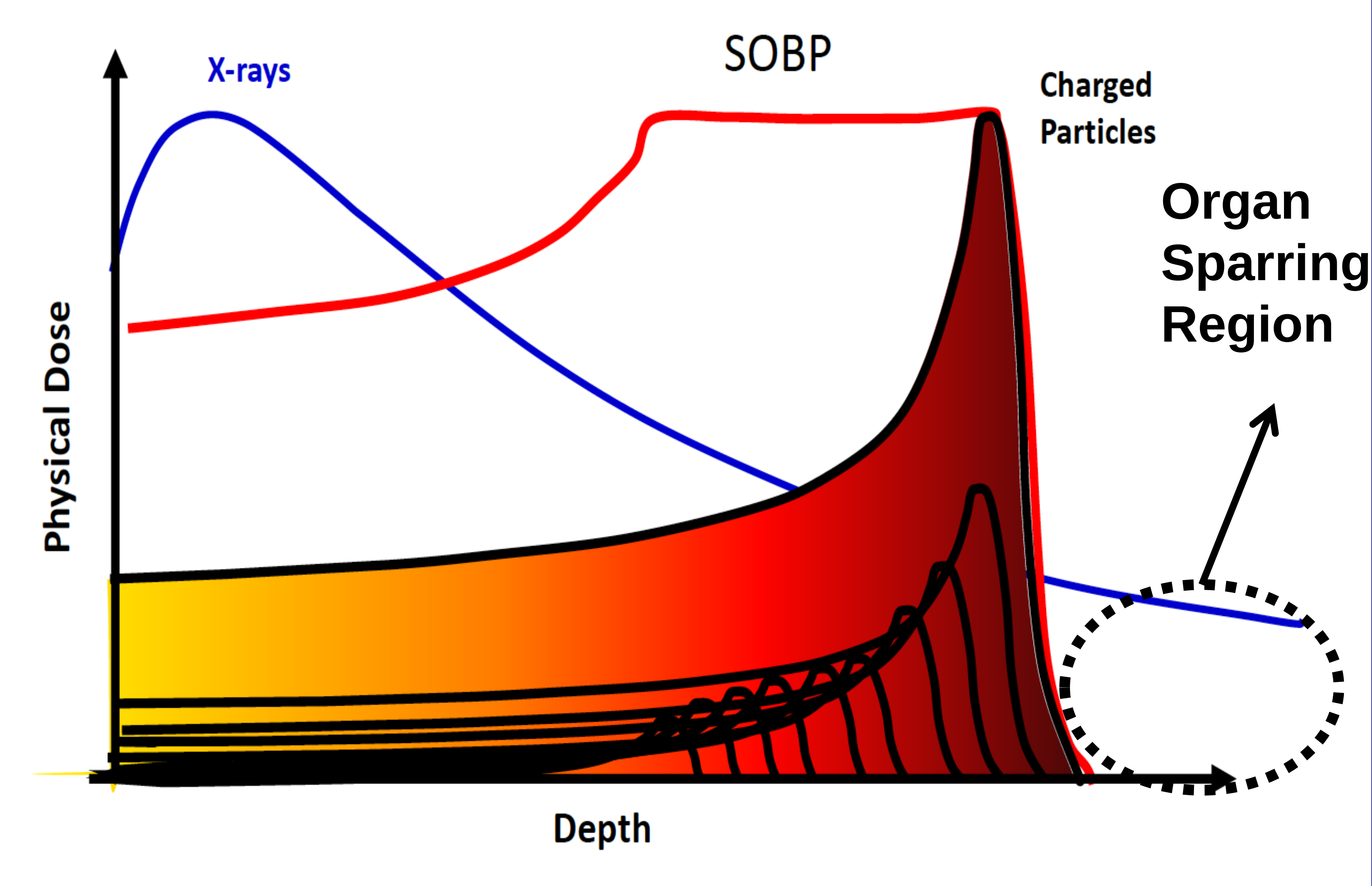
- **Relatively low entrance dose (plateau)**
- **Maximum dose at depth (Bragg peak)**
- **Rapid distal dose fall-off**



Clinical Proton Beams

Clinical Beams
Are delivered as a series of pristine mono-energetic Bragg Peaks

creating an **SOBP**
Spread-Out Bragg Peak

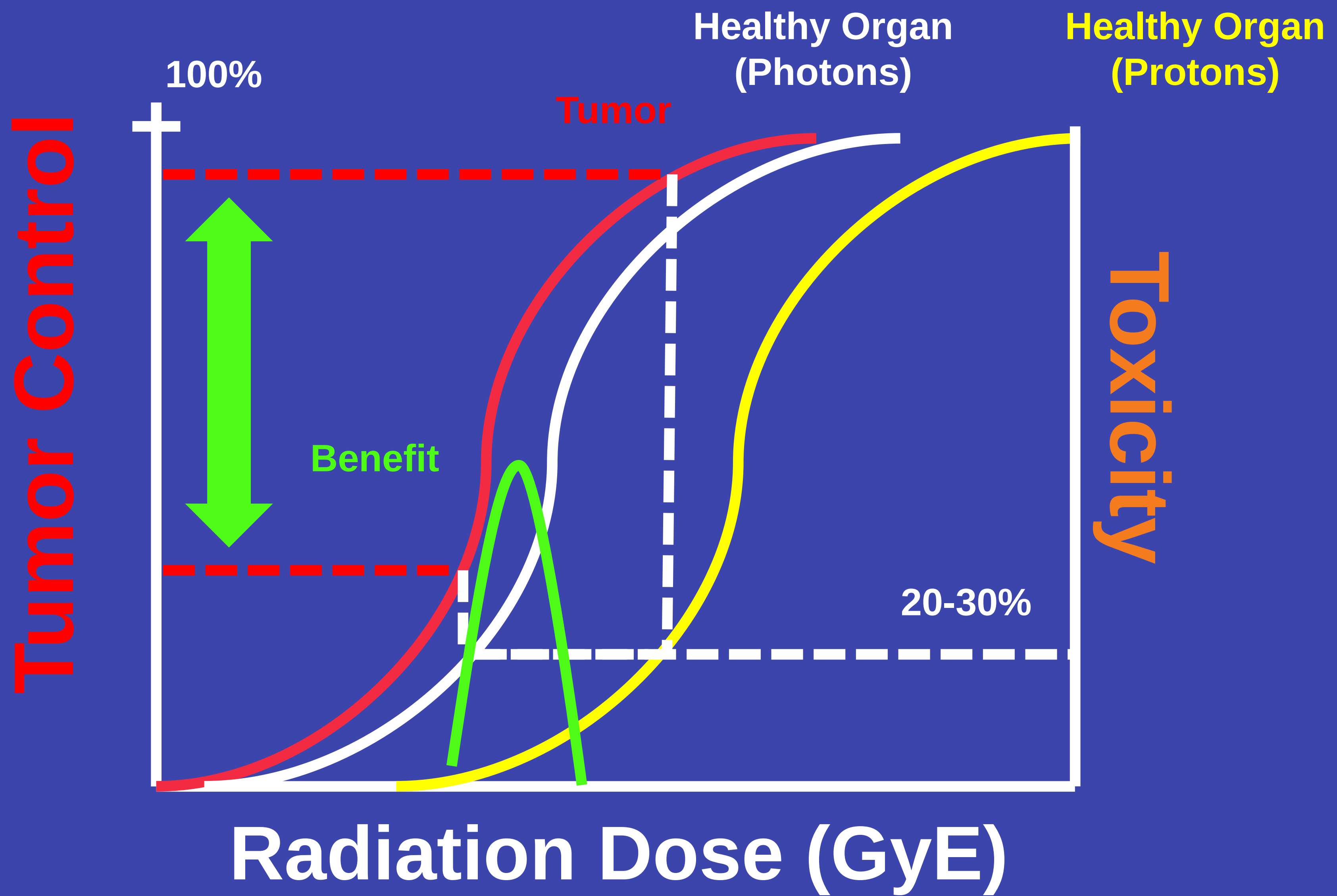


"There is no advantage whatsoever to irradiating uninvolved healthy tissue"

Dr. Herman Suit
Harvard / MGH Proton Center (1)

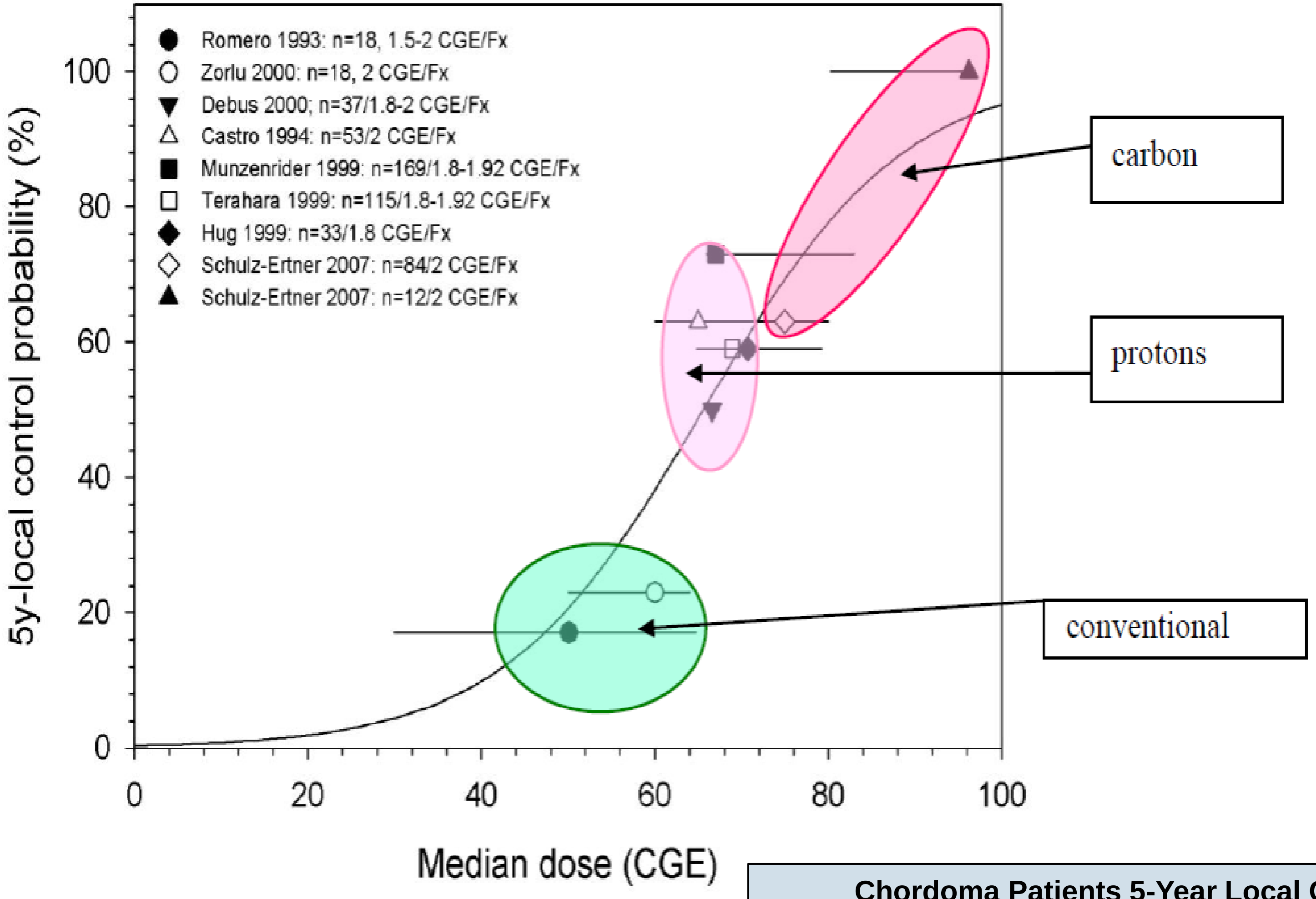
(1) Herman Suit, "The Grey Lecture 2001: Coming Technological Advances in Radiation Oncology," International Journal of Radiation Oncology Biology Physics 53 No. 4 (2002): 798-809.

Quantifying the Advantage of Proton Therapy



Advantage of Particle Therapy

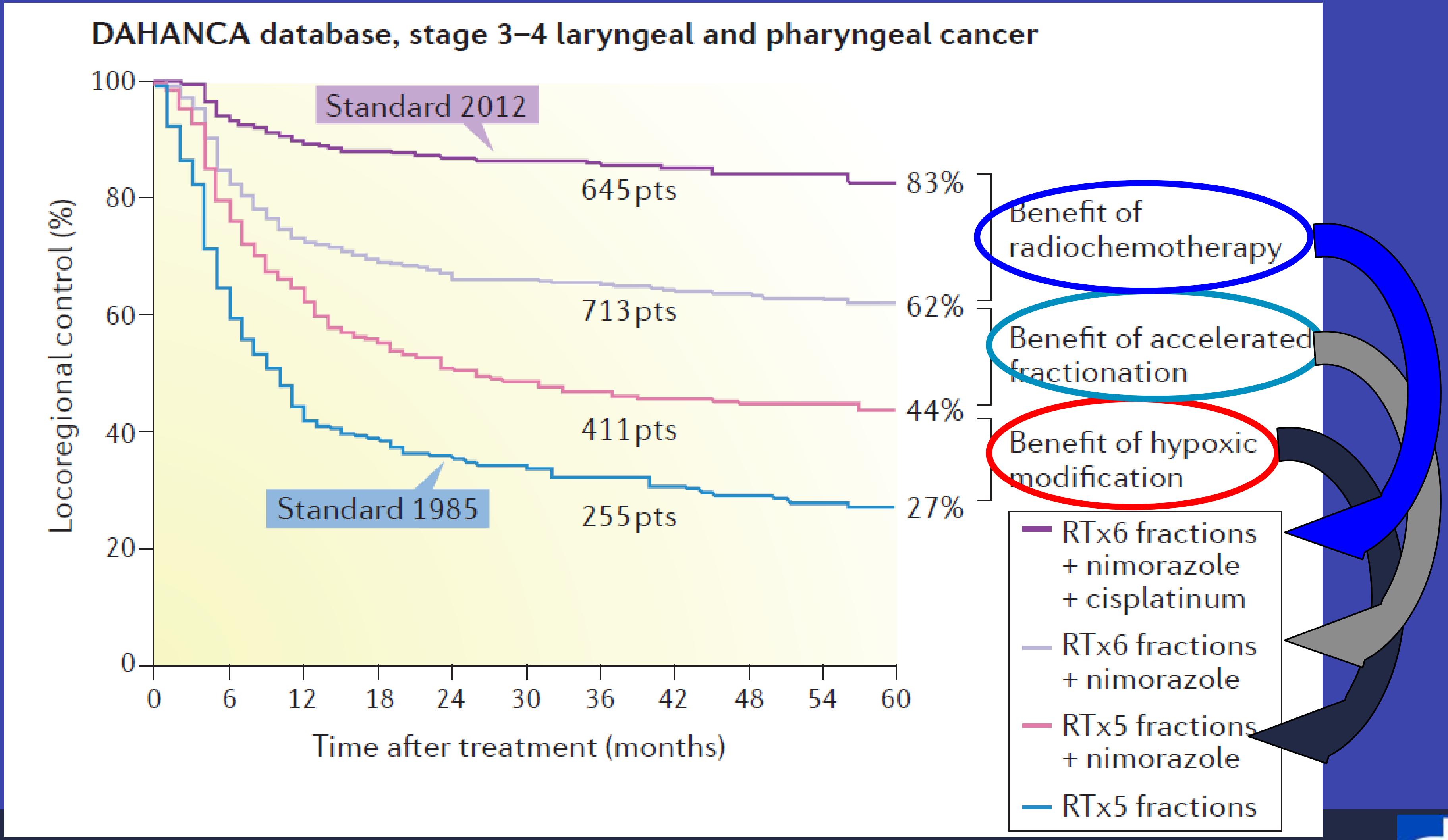
GSI – Darmstadt/Heidelberg Hospital, Germany



Chordoma Patients 5-Year Local Control (source: Schulz-Ertner, Int J Radiat Oncol Biol Phys. 2007)

Photon (X-ray)Therapy Facilities

DAHANCA: DAnish Head And Neck CAncer Group



Ion therapy: advantages

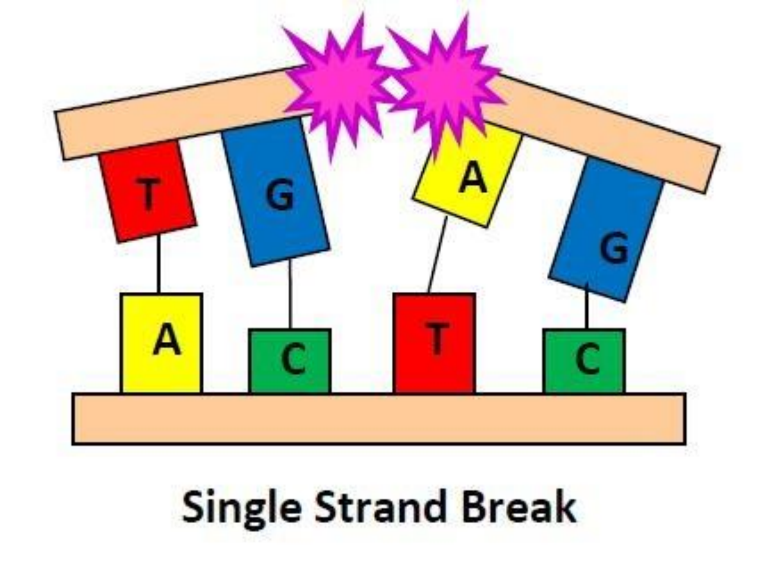
Heavy ions are **more effective than protons or X-rays** in attacking cancer.

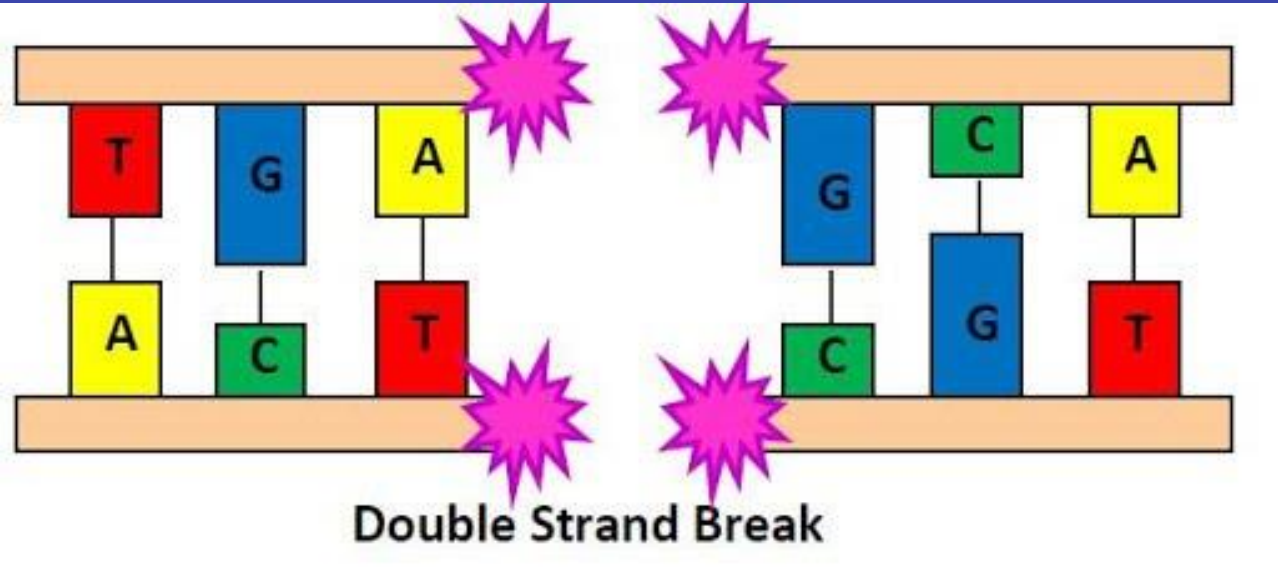
The particle (or X-ray) breaks the DNA; multiple breaks kill the tumour cell. However, the key mechanism is DNA self-repair by the body cells.

- Protons and X-rays cause single-strand breaks that are easy to repair.
- Ions produce more ionisations per length and may cause double-strand breaks that are much more difficult to repair.

Heavy ions allow for lower doses, are effective with radio-resistant tumours (low oxygen content), and might reduce metastasis that are the main cause of mortality.

So far, 2/3 of cases treated at the mixed facilities (HIT, CNAO, etc.) are with carbon.



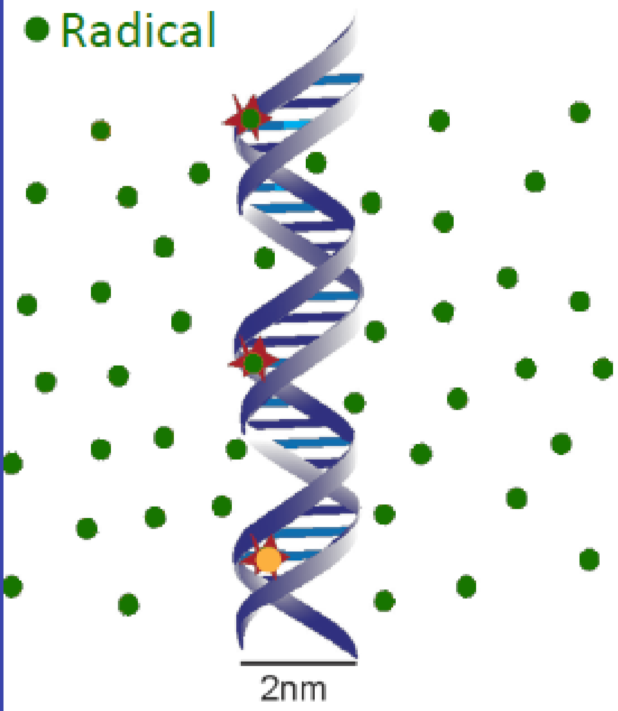


Double Strand Breaks is what makes ions more effective in treating cancer

What about

Biological Advantage of Ions?

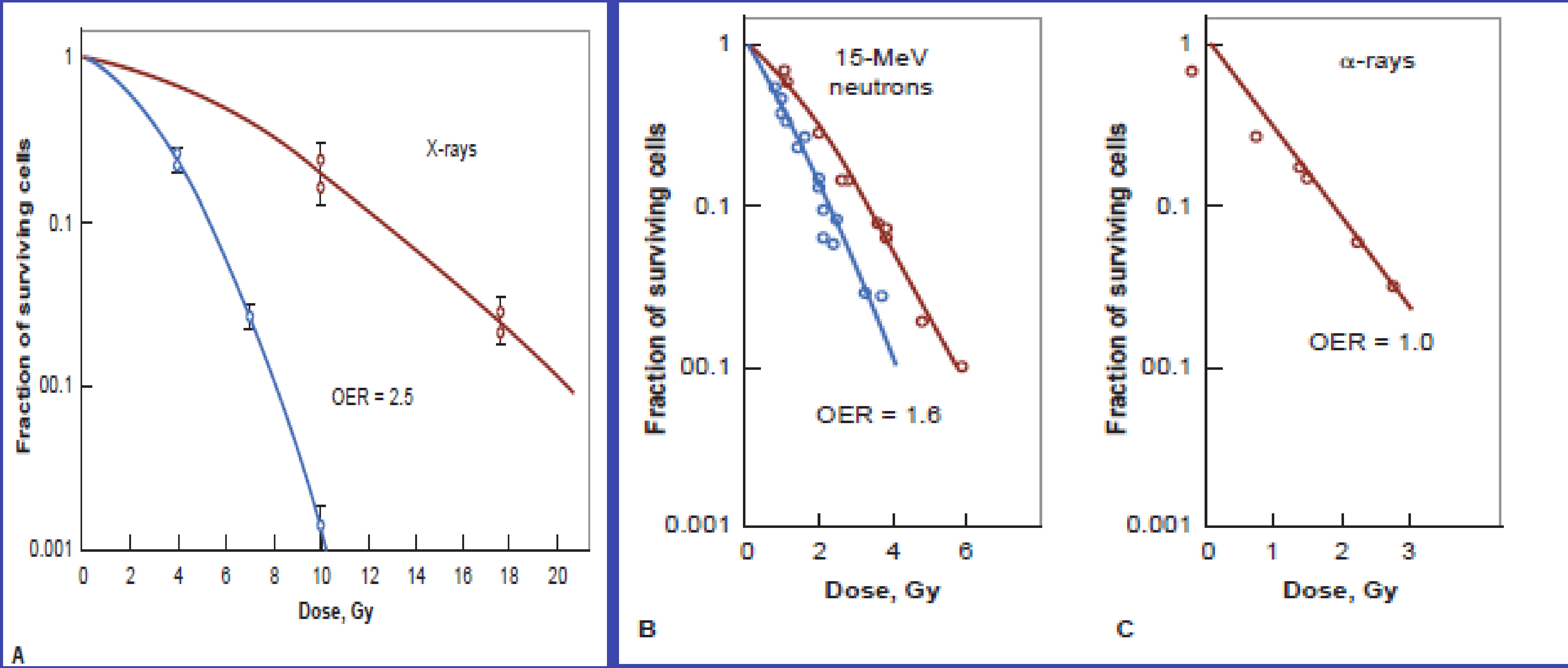
Photons | **Protons** | **Carbon Ions**



γ-radiation

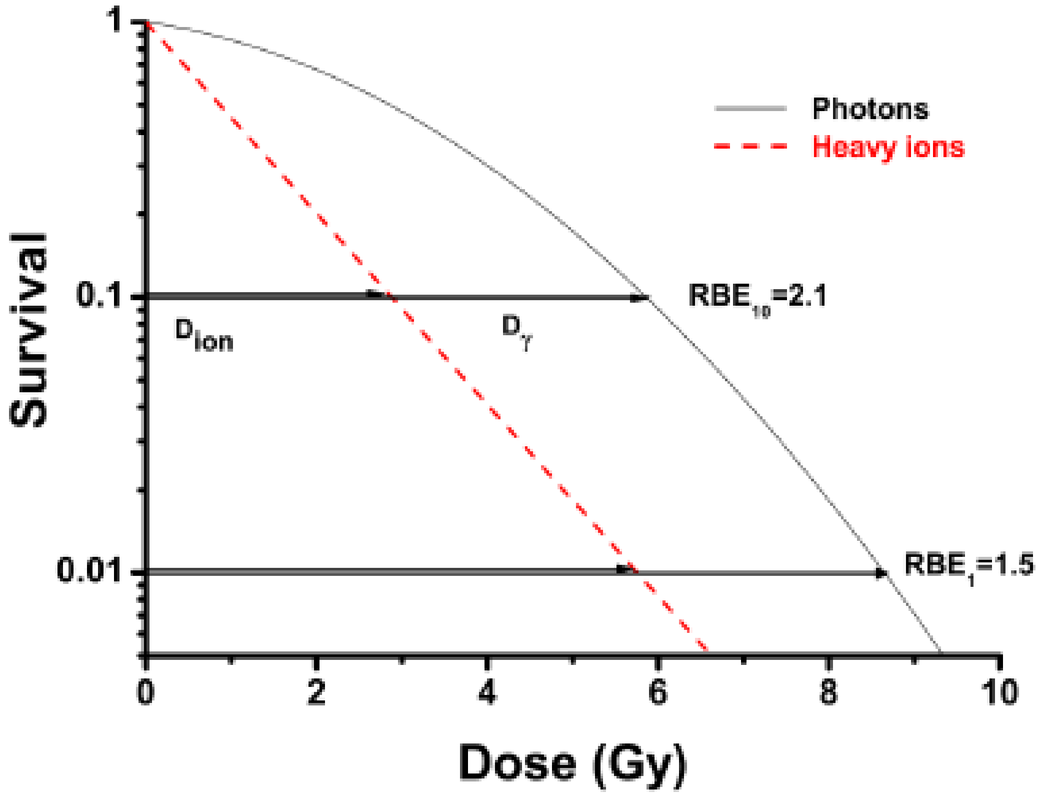
Low and homogeneous ionization density / radical production
→ Random distribution of indirect damage
→ Easier to repair by cell!

Oxygen Effect and LET Dependency



LET and RBE Dependency

Radiation Type/Quality –Relative Biological Effectiveness (RBE)

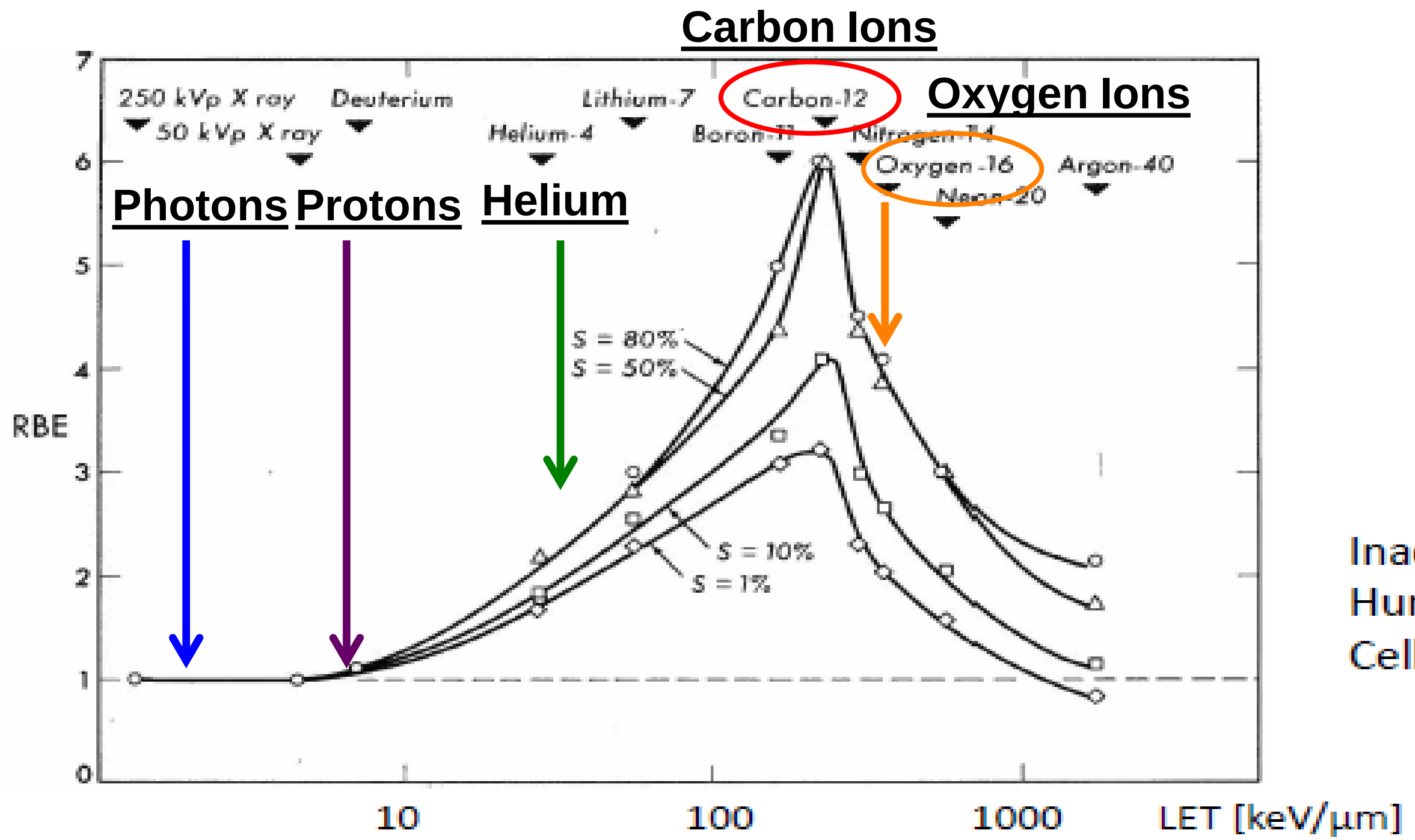


$$RBE = \frac{D_{ref}}{D_{particle}}\bigg|_{iso-effect}$$

- RBE depends on:
  - Dose
  - Particle Type
  - Cell Line
  - Biological Endpoint
  - LET (Reminder: $LET_{\Delta} = \frac{dE}{dl}_{\Delta}$)

LET and RBE Dependency

Quantitative LET-dependency of RBE

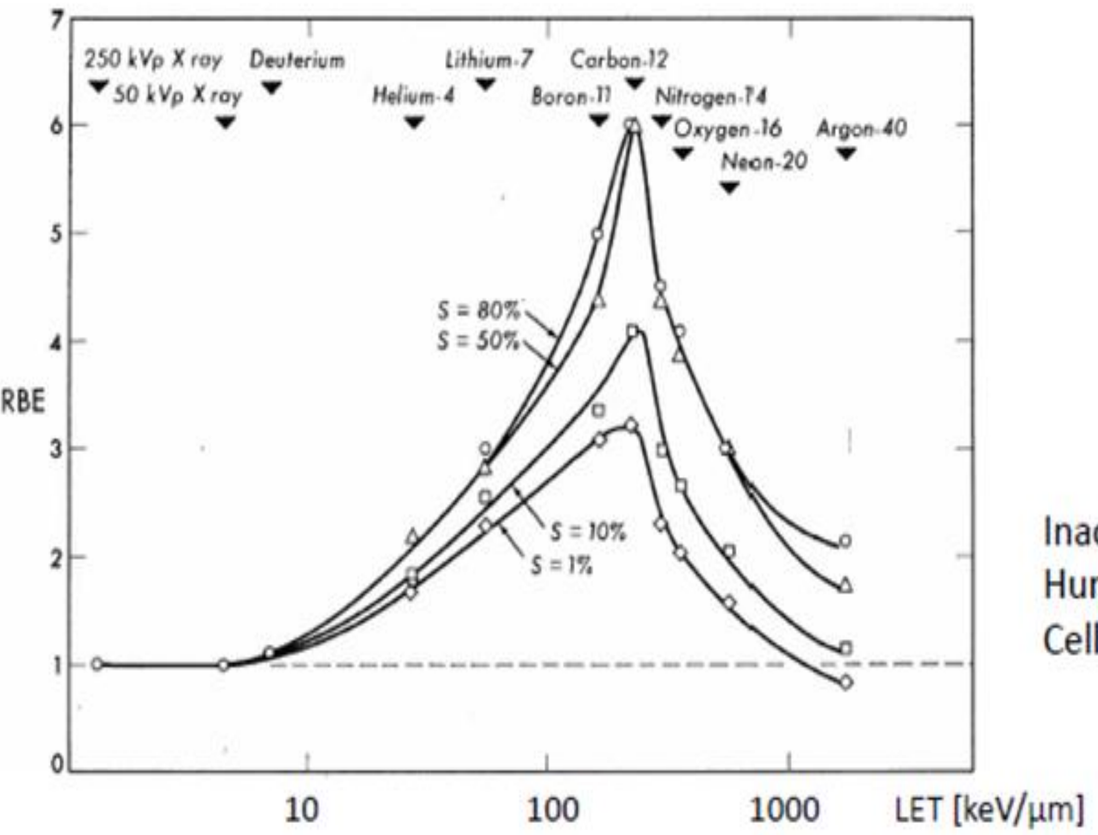


Inactivation of Human Kidney Cells (T-10)

RBE drops after peak due to „Overkill-Effect“

Reminder: $RBE = \frac{D_{ref}}{D_{particle}}\Big|_{iso-effect}$

LET and RBE Dependency
OER Dependency on LET



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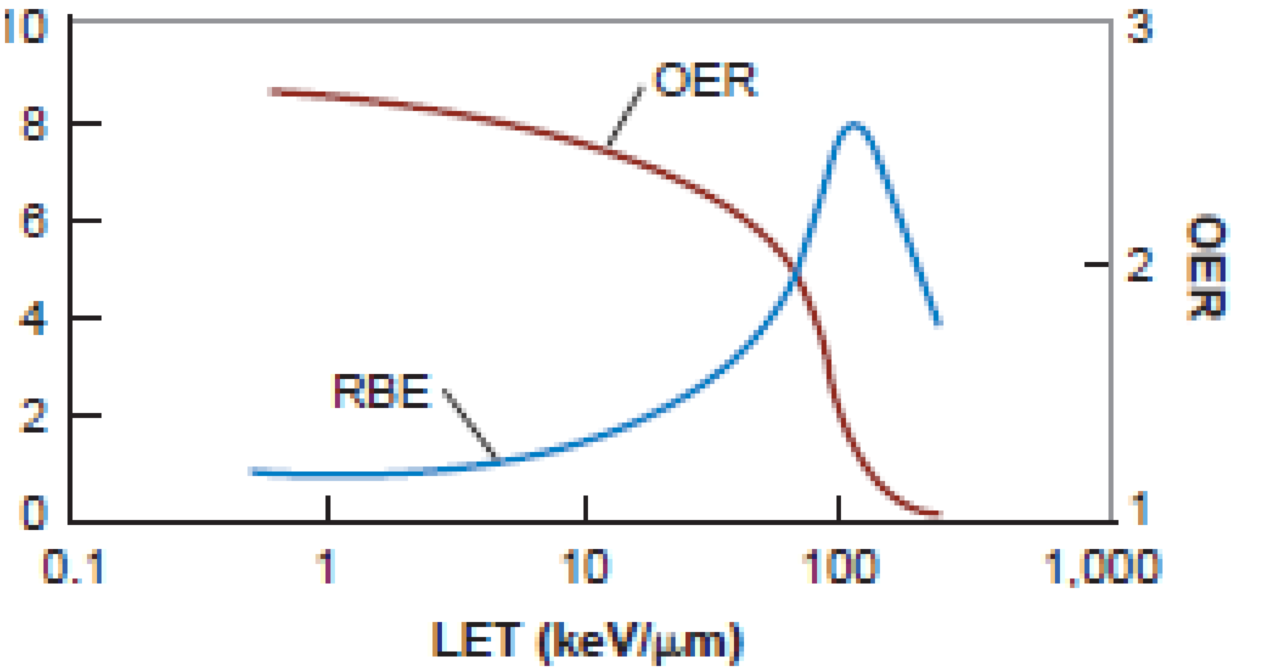
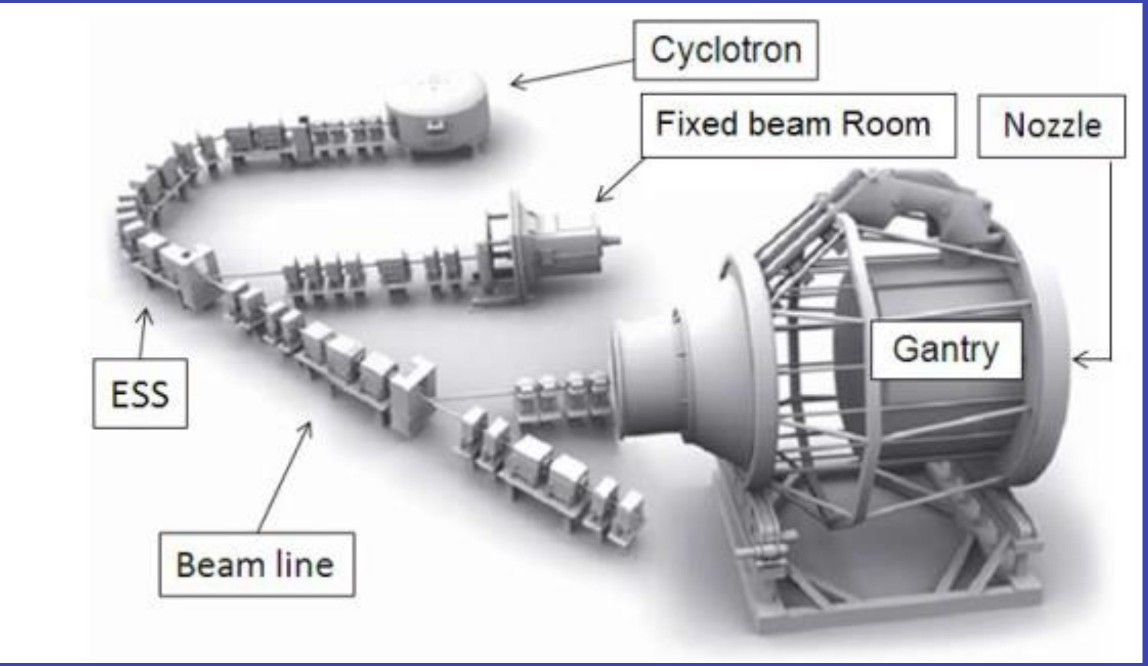


Proton and Ion Beam Therapy Facilities

Current Proton Accelerators

- Cyclotron
- Synchrotron
- Linear Accelerator

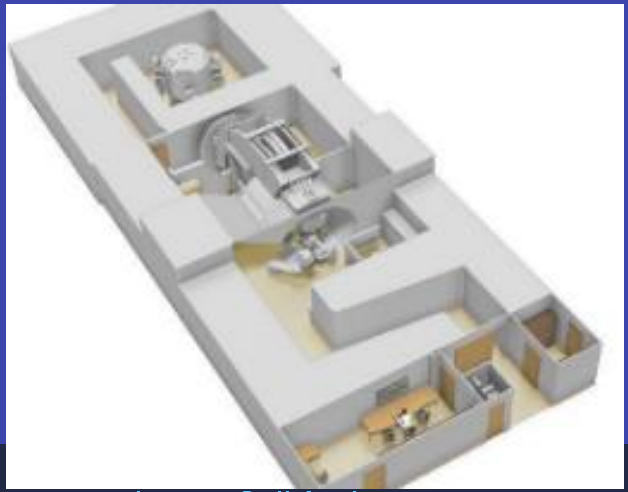
Proton therapy accelerators: cyclotrons



At present, the cyclotron is the best accelerator to provide proton therapy reliably and at low cost (4 vendors on the market).

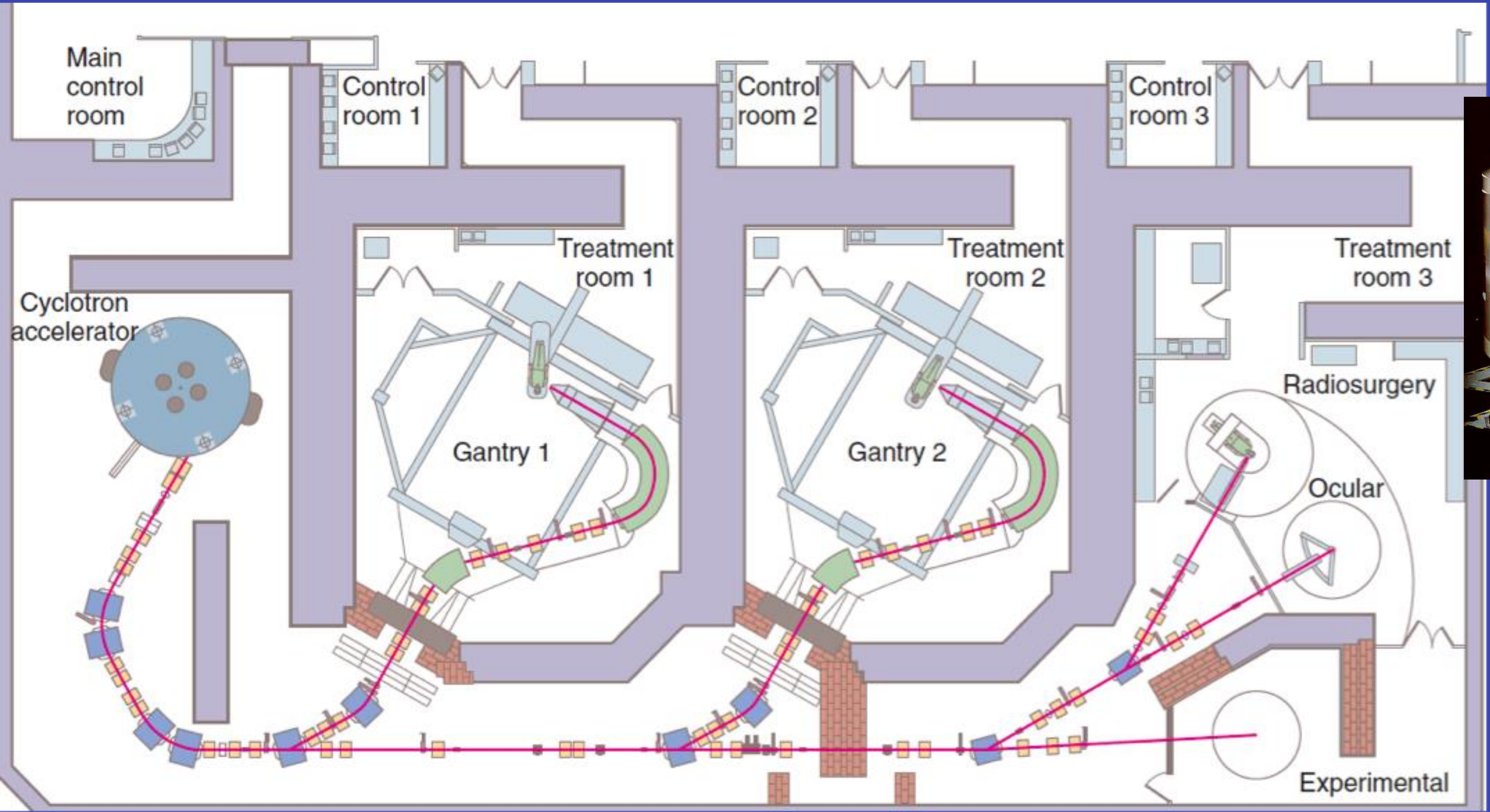
Critical issues with cyclotrons:

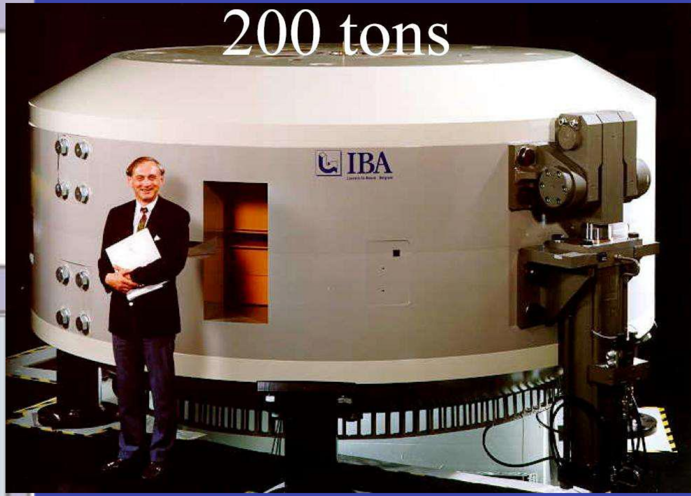
1. Energy modulation (required to adjust the depth and scan the tumour) is obtained with degraders (sliding plates) that are slow and remain activated.
2. Large shielding



ProteusOne and ProteusPlus turn-key proton therapy solutions from IBA (Belgium)

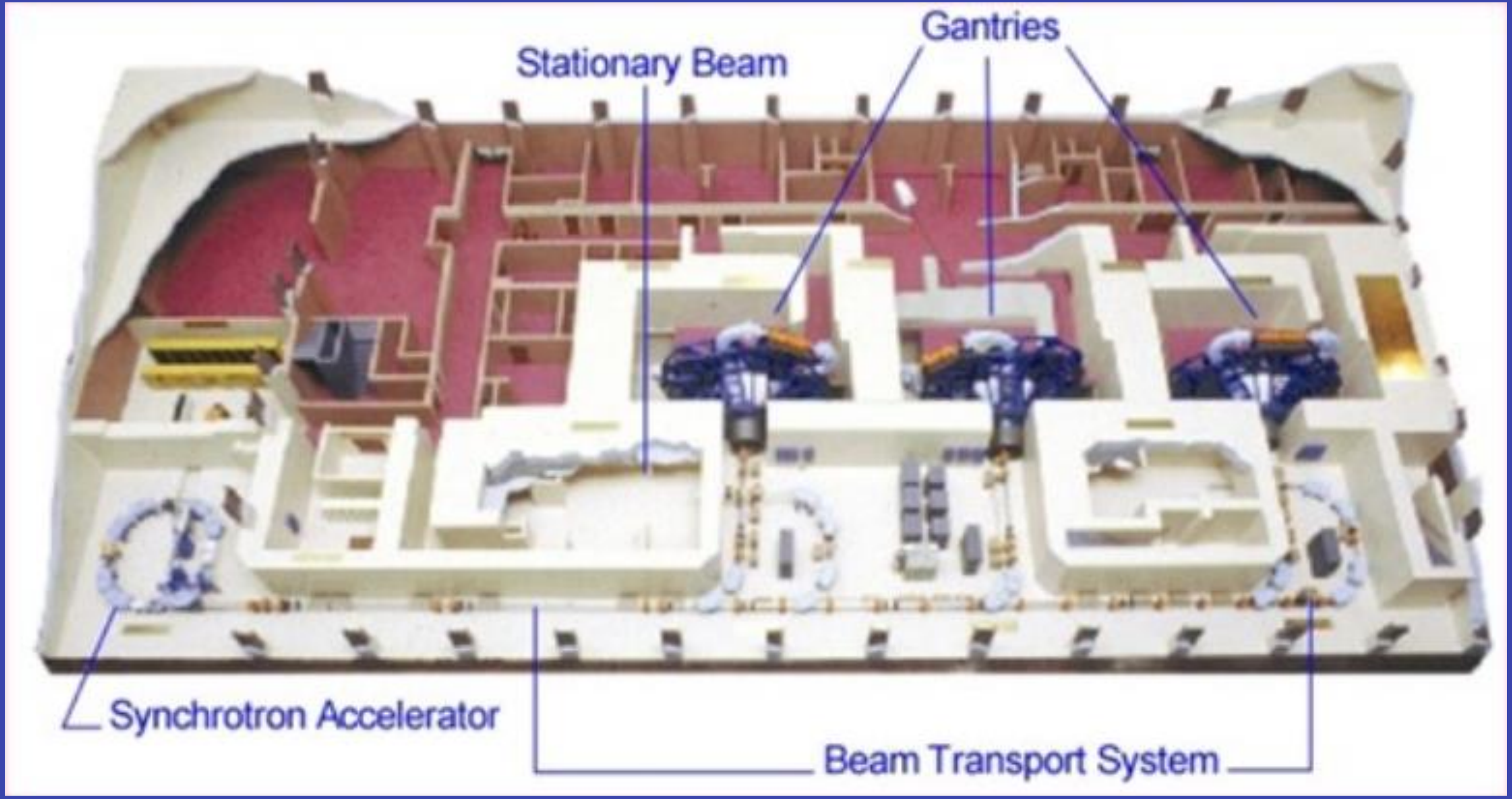
Francis H. Burr Proton Therapy Center, MGH 1997 Boston





IBA
diameter 4 m

Loma Linda University Proton Therapy Center 1990 (Synchrotron)



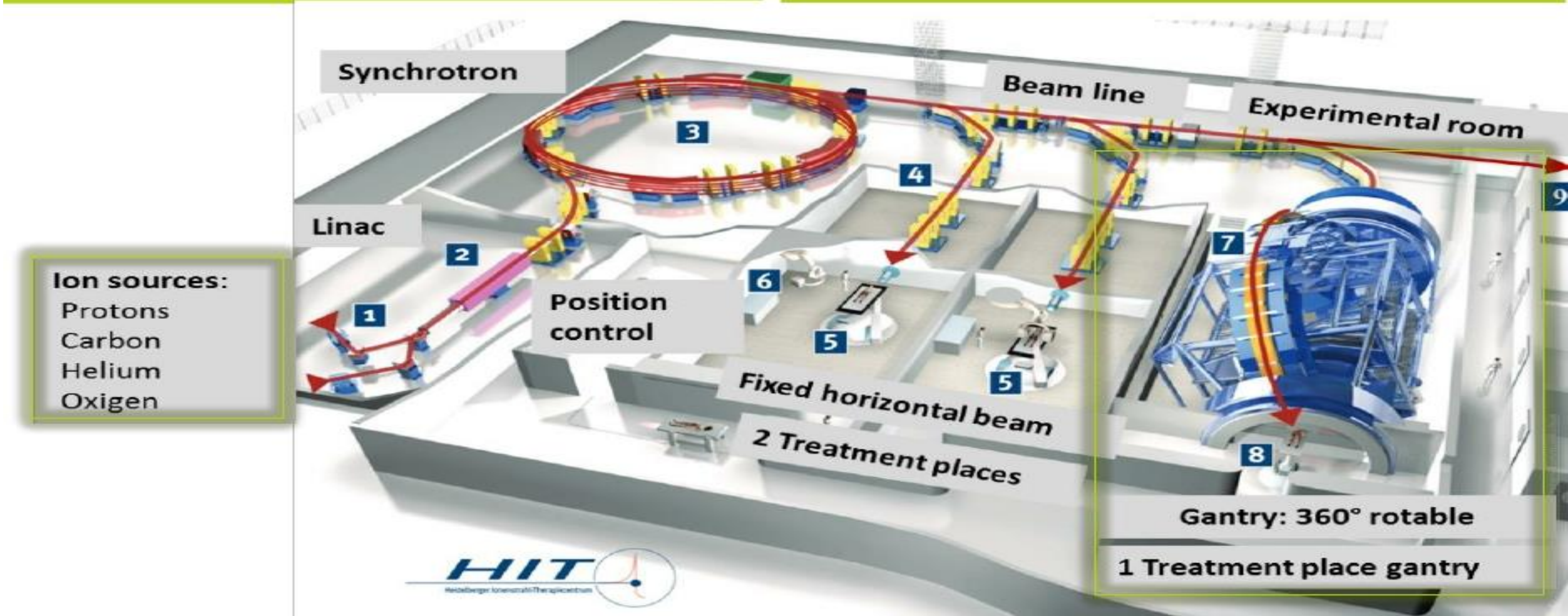
3 cork-screw-type gantries

passive scattering beam delivery

HIT: Heidelberg Ion Therapy Center

- HIT is Europe's first combined treatment facility using **protons and heavy ions** for radiation therapy.

- HIT is the world's first heavy ion treatment facility with a **360 ° rotating beam delivery** system (gantry).



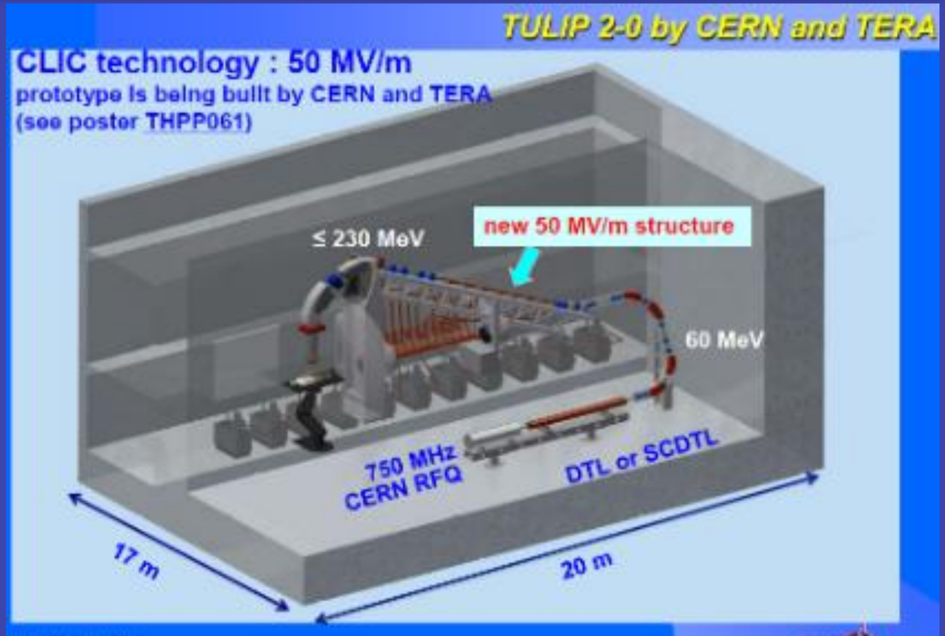
Alternative solutions: the linear accelerator

The TERA Foundation launched and directed by U. Amaldi is promoting accelerators for cancer therapy since 1992. It has launched in 1995 a collaboration with CERN for the development of a proton therapy linac operating at high frequency (3 GHz) and high gradient (30-50 MV/m) reaching 230 MeV in 25 meters.

The development is now continued by ADAM (an AVO company)

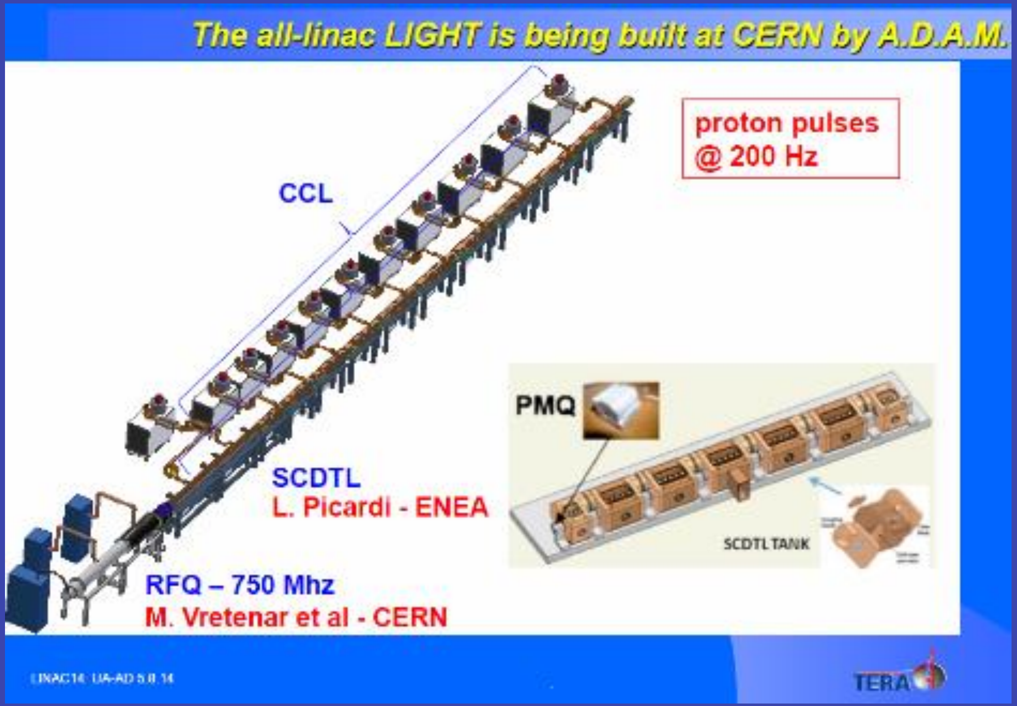
The LIBO prototype structure and accelerating cells (CERN)

Advantages of a LINAC:
- High repetition frequency with pulse-to-pulse energy variability
- Small emittance, no beam loss.



The TULIP concept using CLIC high-gradient cavities – 15 meters

The LIGHT linac by ADAM (being assembled and built in a CERN test area) – 25 meters



Linac Image Guided Hadron

Next Generation Facilities

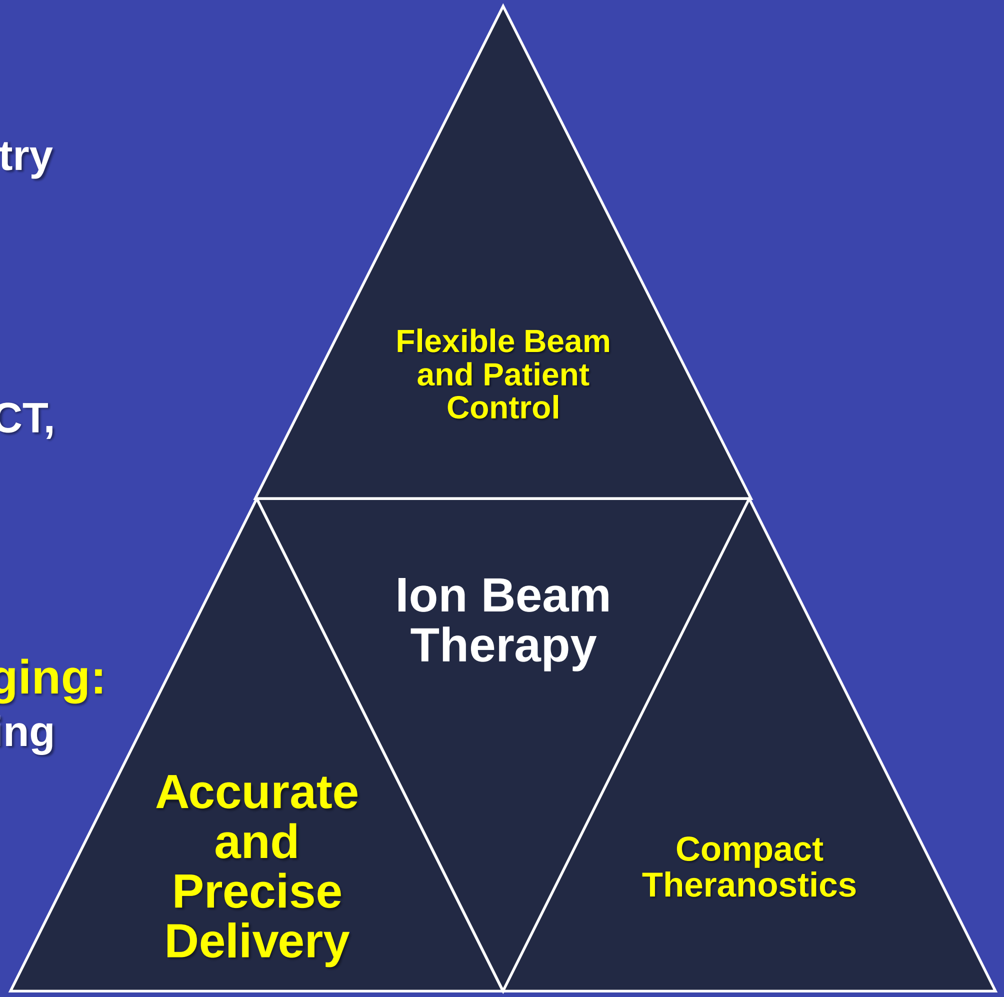
- **Compactness**: Superconductivity
- **In-Room Imaging**: a) Anatomy, b) Beam
- **New Therapy Protocols**: FLASH

RT Requirements for Ion Therapy

1. **Flexible Beam and patient control:**
   - Allow multiple beam angle delivery (partial rotating gantry and robotic couch)
   - Allow high dose rate delivery (FLASH)

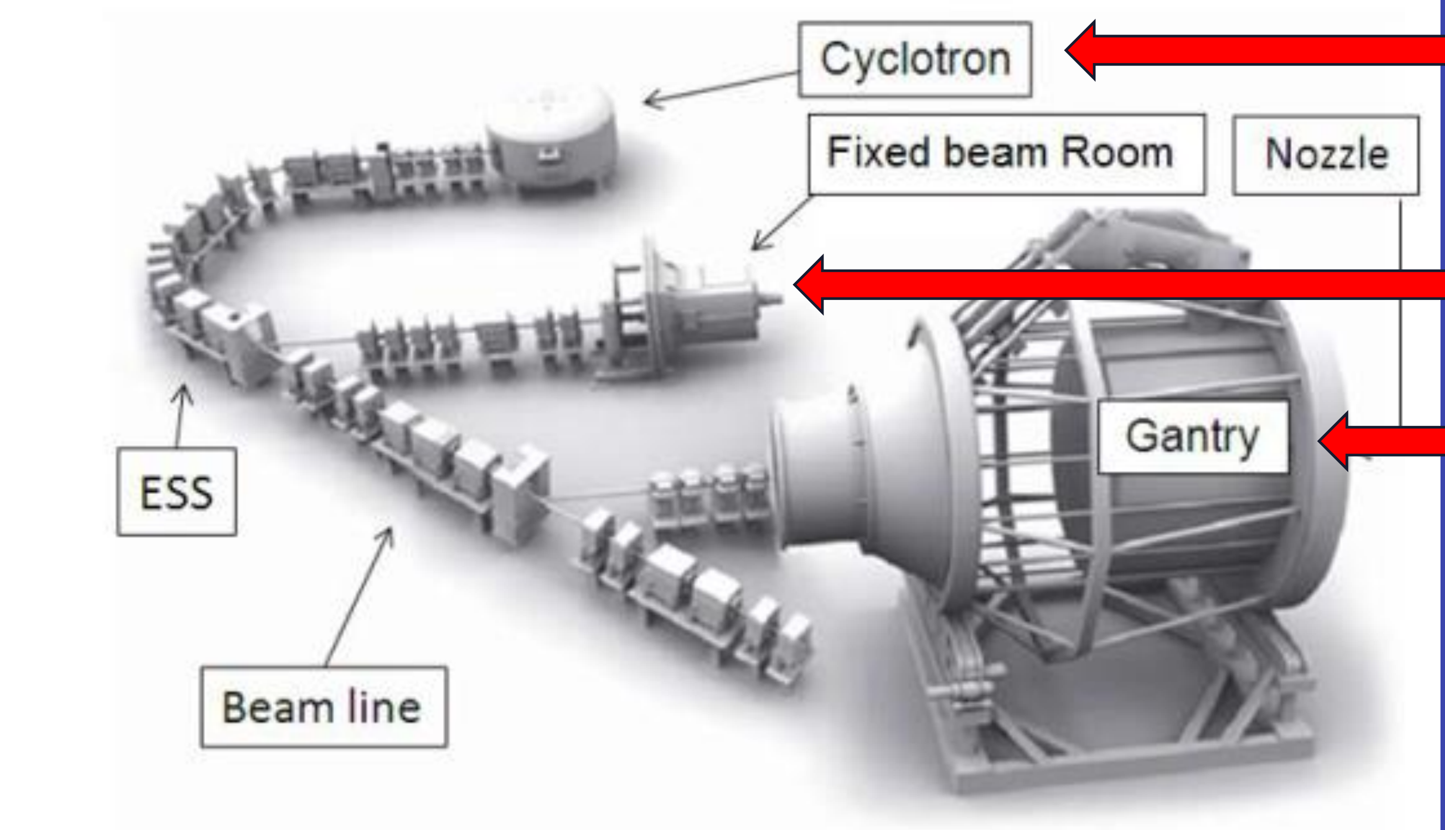
2. **Accurate and Precise delivery of the dose:**
   - Allow anatomical monitoring with in-room imaging (CBCT, MRI, fluoroscopy,etc)
   - Allow beam monitoring with in-room prompt gamma, Cerenkov radiation, etc

3. **Compact Theranostics – combining Therapy and Imaging:**
   - Compact design to allow integration with in-room imaging and beam monitoring



Flexible Beam and patient control:

Allow multiple beam angle delivery (partial rotating gantry and robotic couch)



Compact Cyclotron
Reduces footprint

Fixed Beam-Line
Non-flexible but cheap

Rotating Gantry
Flexible but expensive (University Centers)

Complicated Cancers
You need rotating Gantry

Proton Therapy Market

Single Room → Multi-Room (3-4 Rooms)

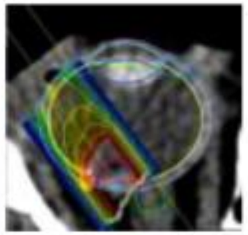
Private Proton TherapyFacility — University Hospital/Academic Center

PROTON INDICATIONS

What Cancers Can Protons Treat?

Classic indications:

- Base of skull tumors
- Eye (uveal) melanomas
- Brain tumors
- Pediatric tumors
- Spinal / Paraspinal tumors
- Prostate cancers

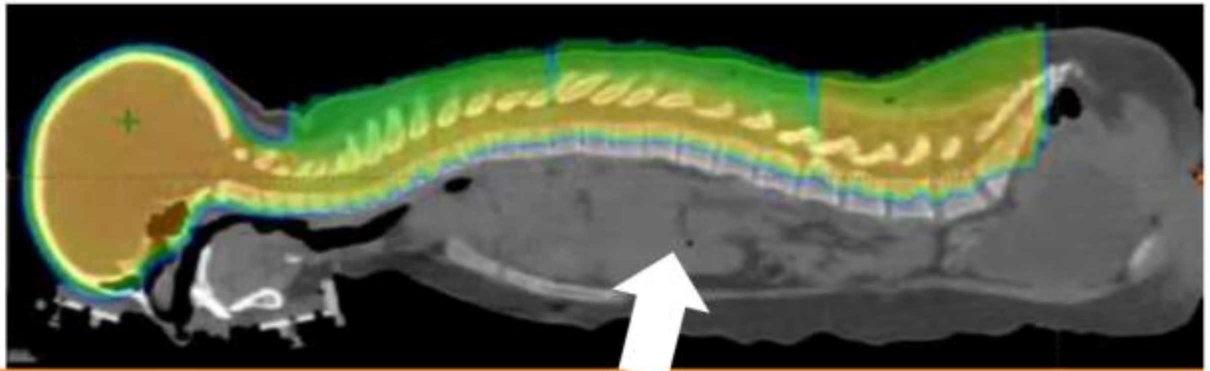


- Lung
- Liver
- Breast
- Esophagus
- Pelvic tumors
- Large sarcomas
- Mediastinal tumors
- Reirradiation of recurrent tumors

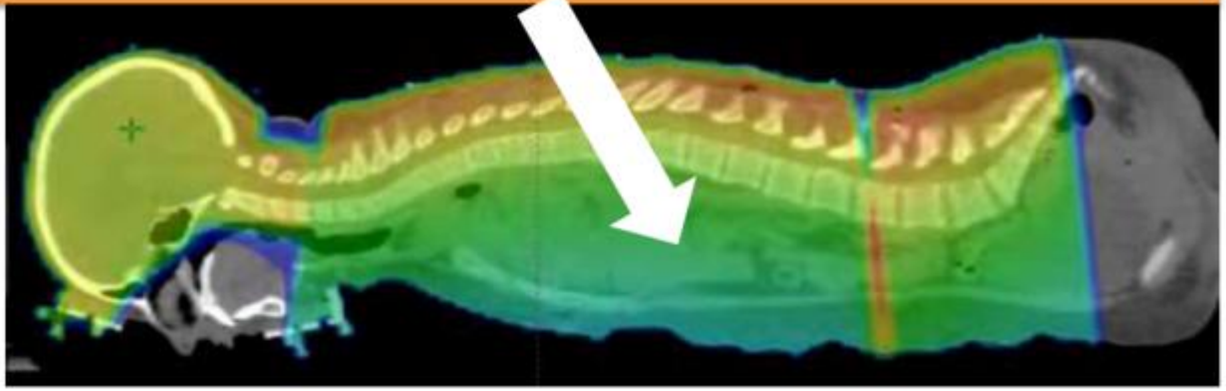
The Value of Protons

Protons are **physically superior** to X-rays:

Protons STOP



Protons avoid unnecessary radiation to heart, lungs, intestines delivered by X-rays



X-Rays do not stop

Continue to travel into normal tissues beyond the target

FLASH Radiotherapy

Is normal tissue sparing

Radiation "In a FLASH"

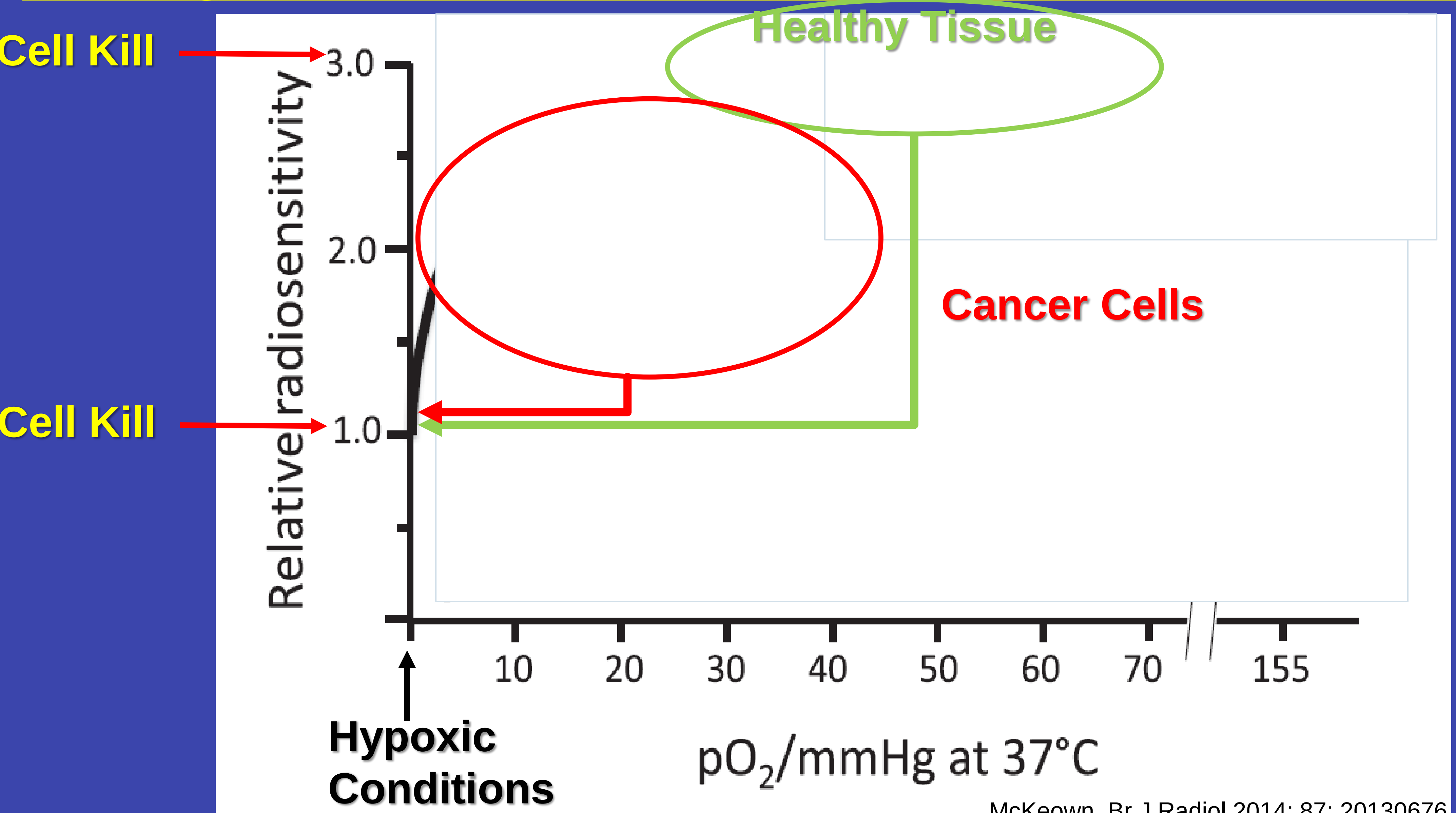
360 days of Sun on the Beach.

360 days of Sun given in 1 day!!

FLASH

BLOCKS O_2 damage during radiation!

Oxygen (O_2) Sensitizes Cells to Radiation



McKeown, Br J Radiol 2014; 87: 20130676

Thank You for Your Attention ☺

QUESTIONS….

DKFZ Group

Relaxing!