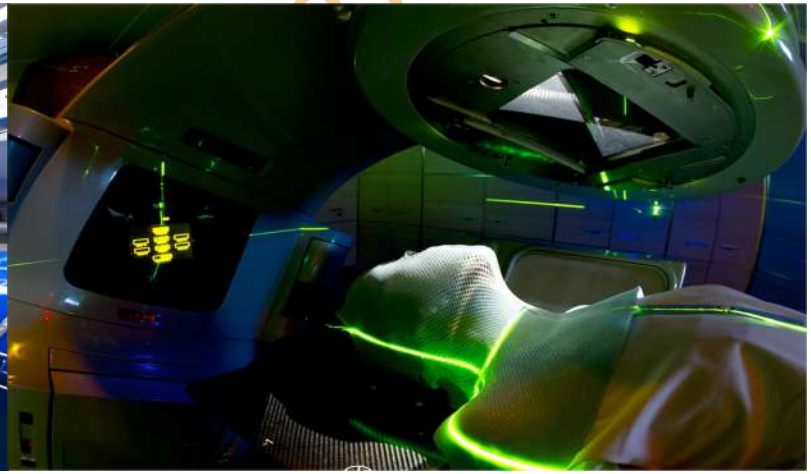
HITRI plus
Heavy Ion Therapy Research Integration

Cancer and Particle Therapy Overview



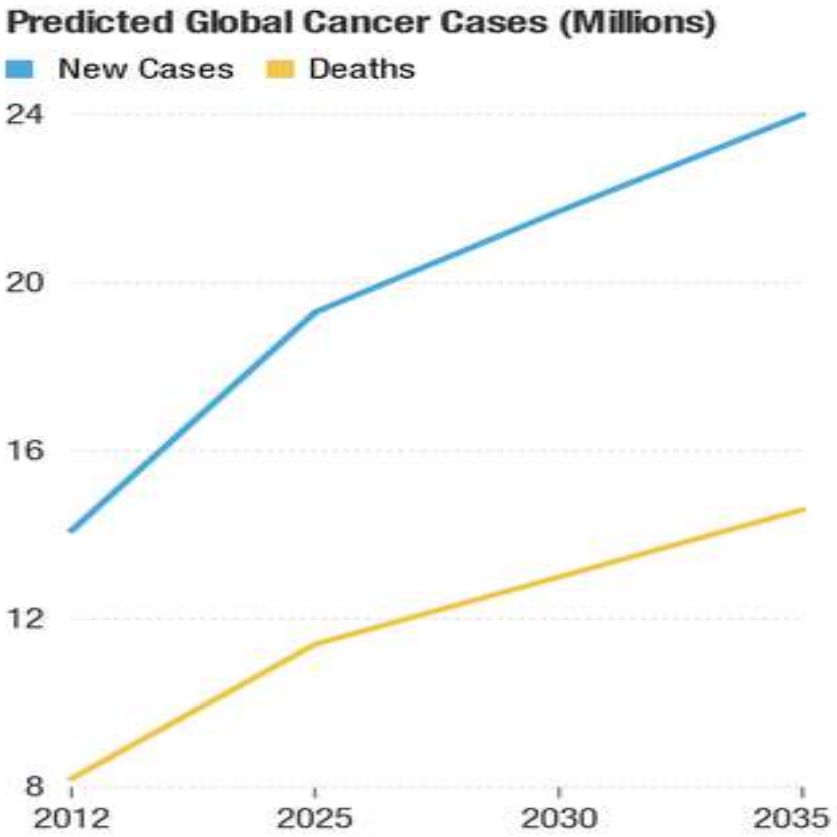
MANJIT DOSANJH CERN, SEEIIST AND UNIVERSITY OF OXFORD
ENLIGHT COORDINATOR

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

cern.ch/virtual-hadron-therapy-centre

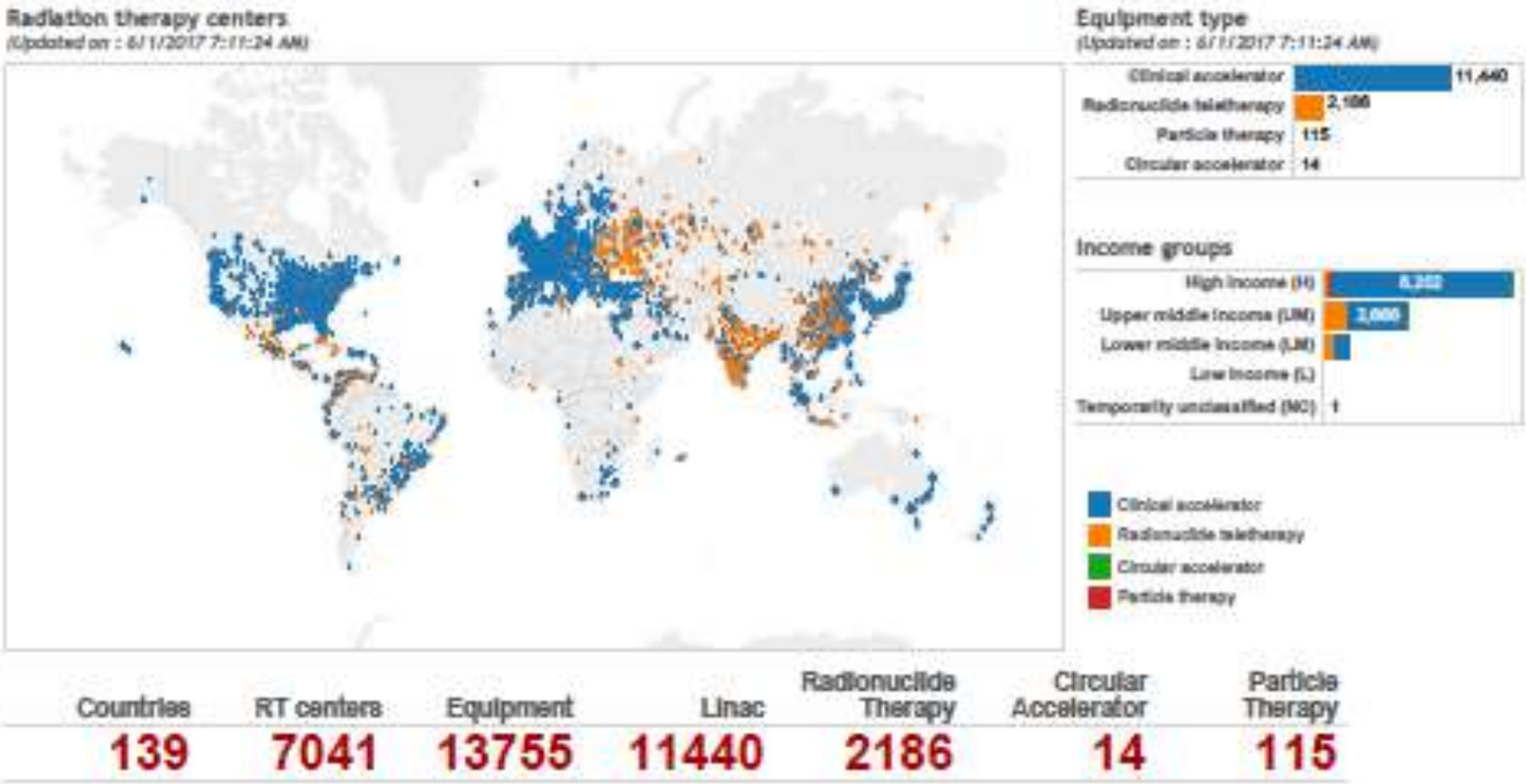
Cancer is a growing global challenge

- Globally **18** million new cases per year diagnosed and **9.6** million deaths in **2018**
- This will increase to **27.5** million new cases per year and **16.3** million deaths by **2040**
- **70% of these deaths** will occur in low-and-middle-income countries (LMICs)



Radiation therapy is a key tool for treatment for over 50% patients

World wide radiotherapy coverage



Countries	RT centers	Equipment	Linac	Radionuclide Therapy	Circular Accelerator	Particle Therapy
139	7041	13755	11440	2186	14	115

Cancer Treatment and Improving Outcomes

Ideally one needs to treat:

The tumour

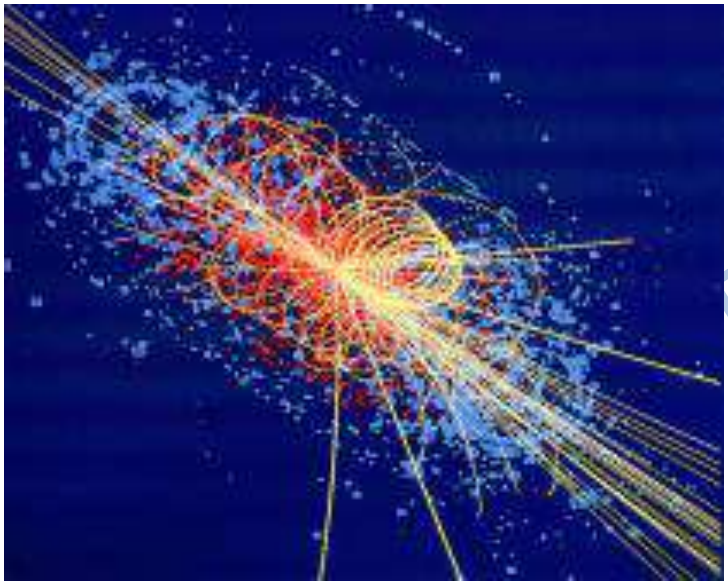
The whole tumour

And nothing **BUT** the tumour

Treatment has two important goals to kill the tumour and protect the surrounding normal tissue. Therefore "seeing" in order to know where and precise "delivery" to make sure it goes where it should are key.

No treatment without detection!

Particle Detection

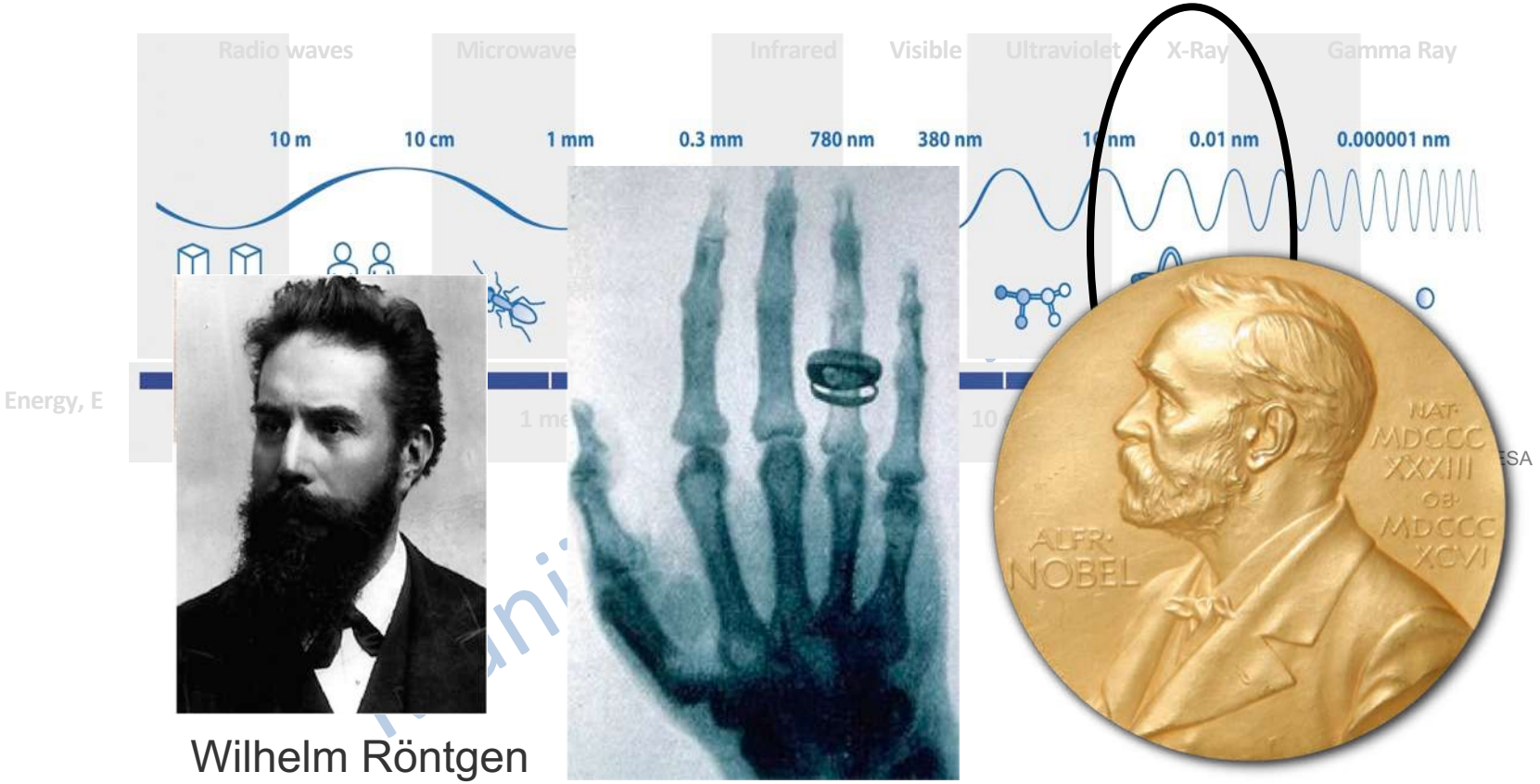


Imaging

X-ray, CT, PET, MRI

Art of seeing……

X-ray imaging



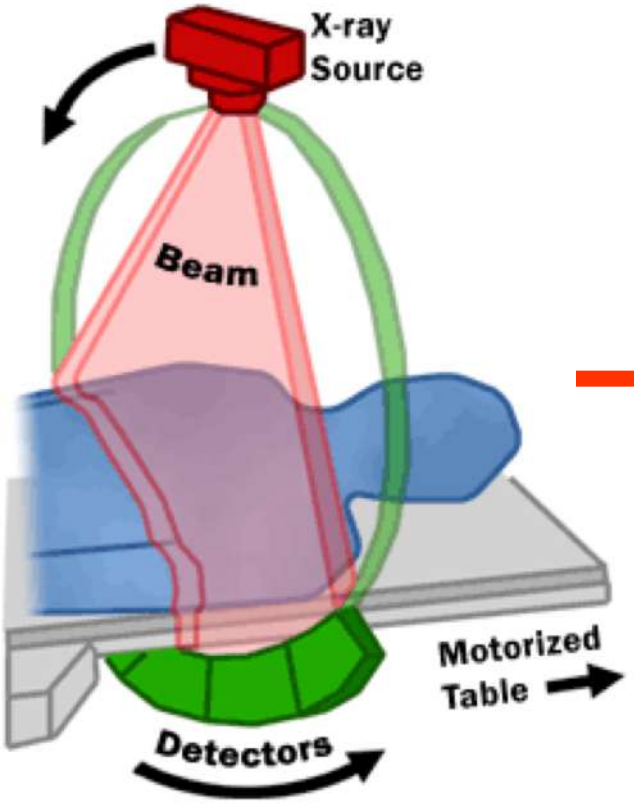
Wilhelm Röntgen

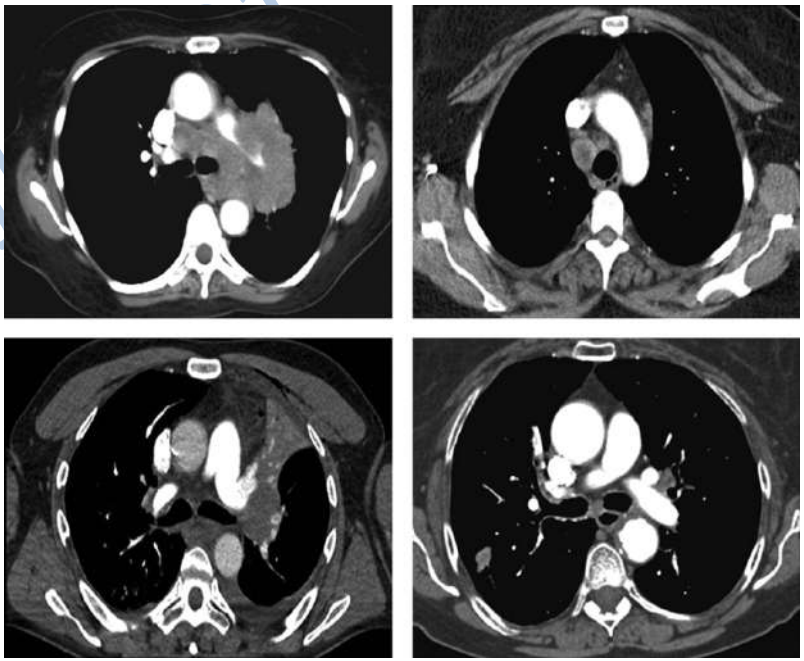
8/11/1895

22/12/1895

1901

Choice of Imaging is Computed Tomography



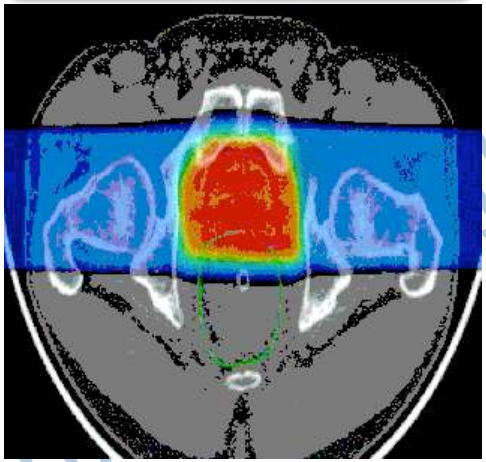


"3D-imaging"

Treatment options

Surgery

Radiotherapy



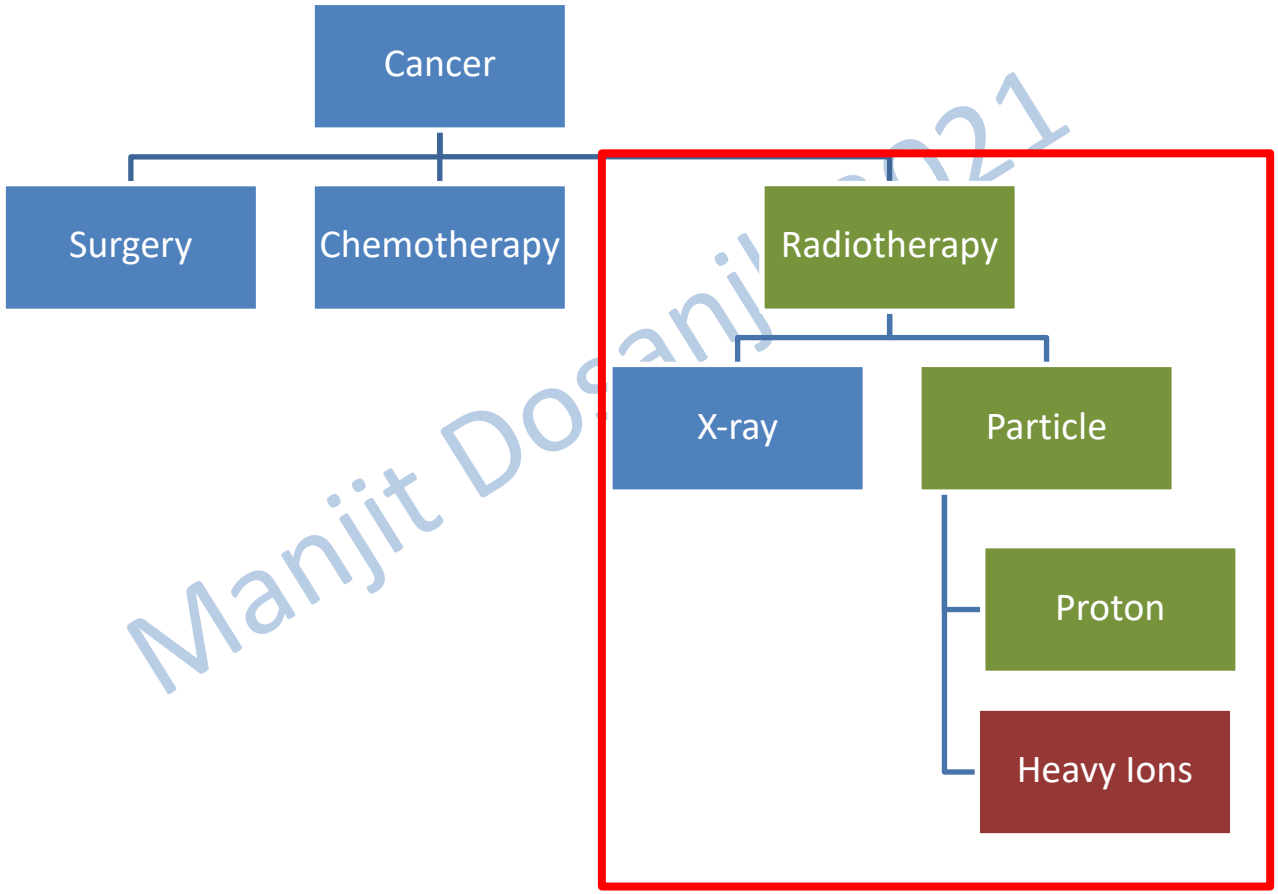
X-ray, IMRT, Brachytherapy, Hadrontherapy

Chemotherapy (+ others)

Hormones; Immunotherapy; Cell therapy; Genetic treatments; Novel specific targets (genetics..)

AIM:
Survival, Quality of life

Cancer treatment options



Radiotherapy in 21st Century

3 "Cs" of Radiation

Cure (about 50% cancer cases are cured)

Conservative (non-invasive, fewer side effects)

Cheap (about 10% of total cost of cancer on radiation)

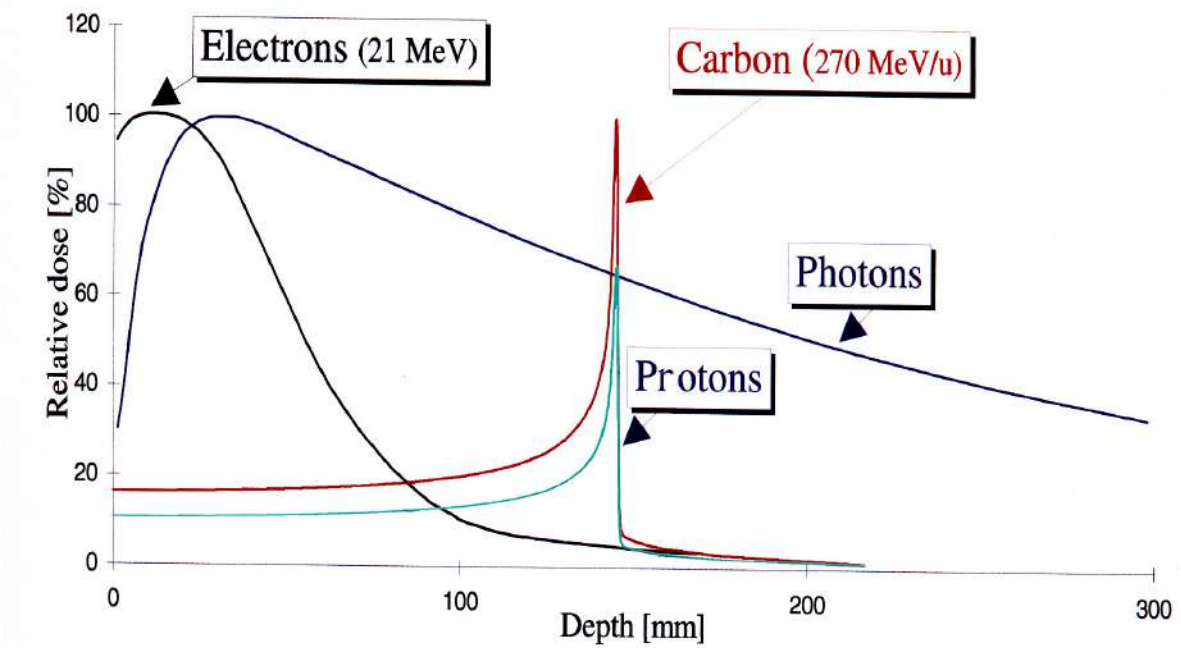
- About 50% patients are treated with RT
- No substitute for RT in the near future
- Number of patients is increasing

Aims of Radiotherapy:

- Irradiate tumour with sufficient dose to **stop cancer growth**
- **Avoid complications** and **minimise** damage to surrounding tissue

Current radiotherapy methods:

- 5-25 MV photons
- 5 - 25 MeV electrons
- 50 - 300 MeV/u hadrons

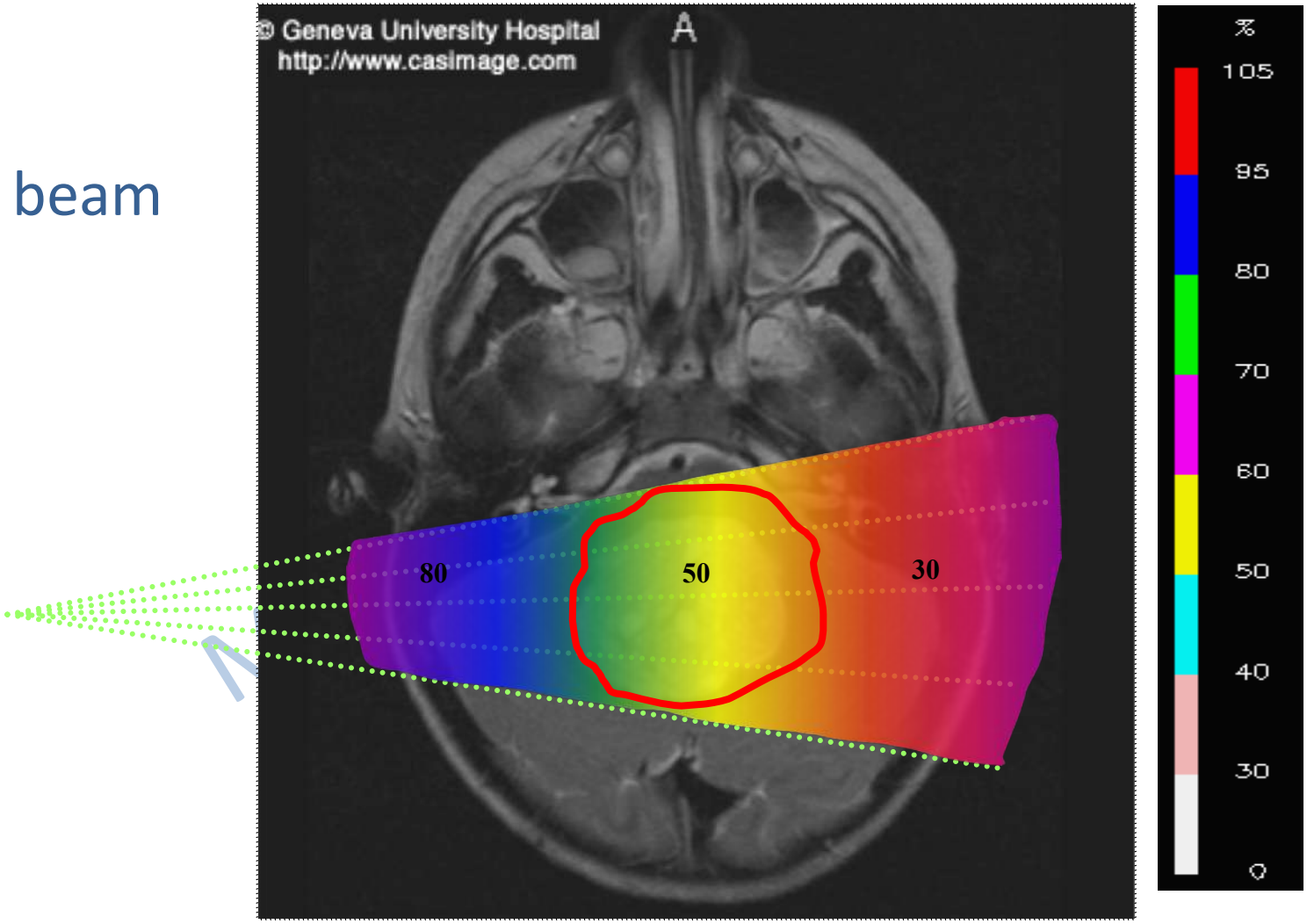


Radiation Therapy Today

- Key radiation therapy delivery systems
  - Cobalt 60 machines
  - Linear accelerators (Linacs)
  - Brachytherapy
  - Image-guided radiotherapy (IGRT); MR-guided etc.
  - **Particle therapy (proton and carbon, other ions)**
  - FLASH therapy (emerging field)

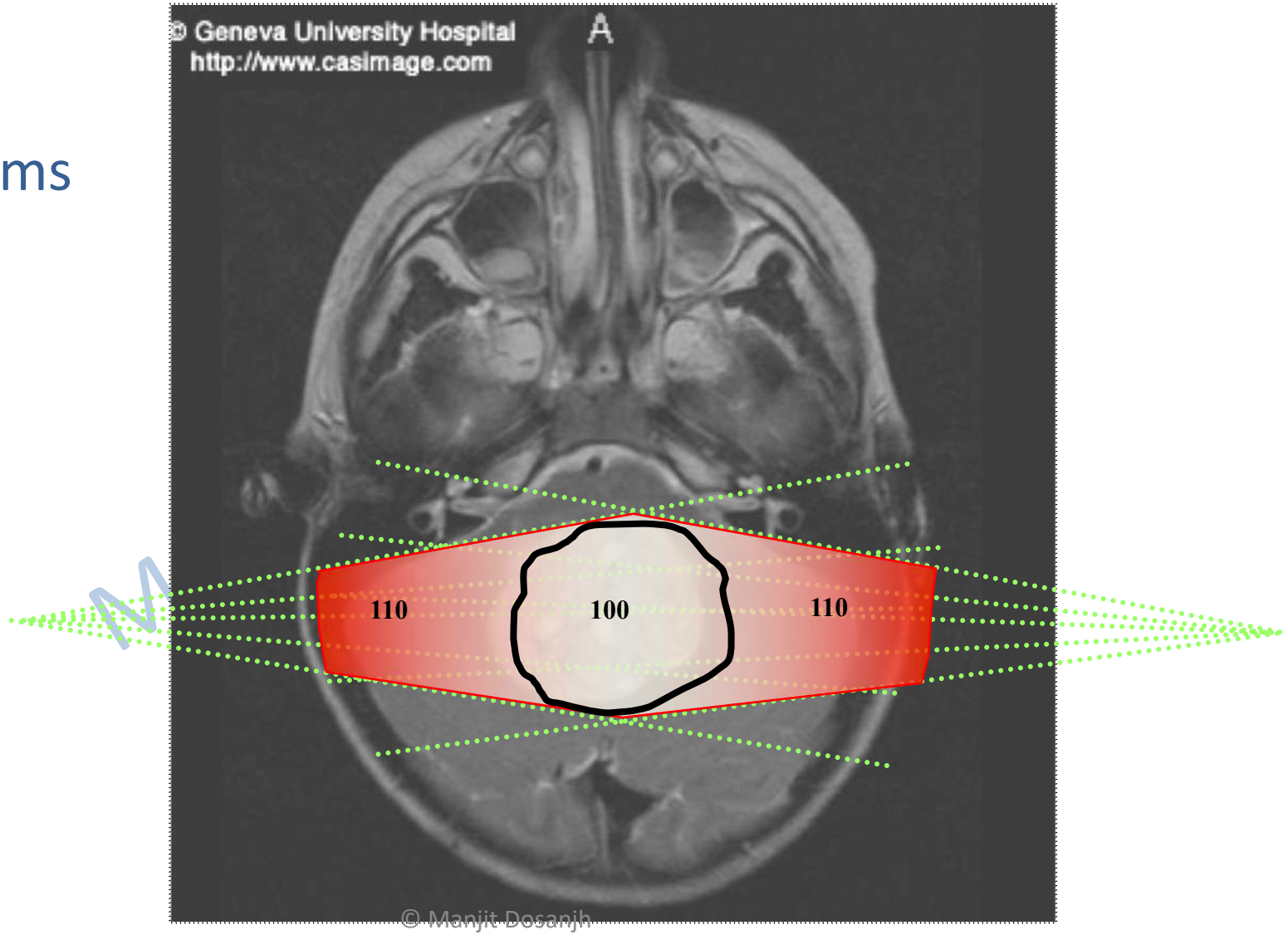
Classical Radiotherapy with X-rays

single beam

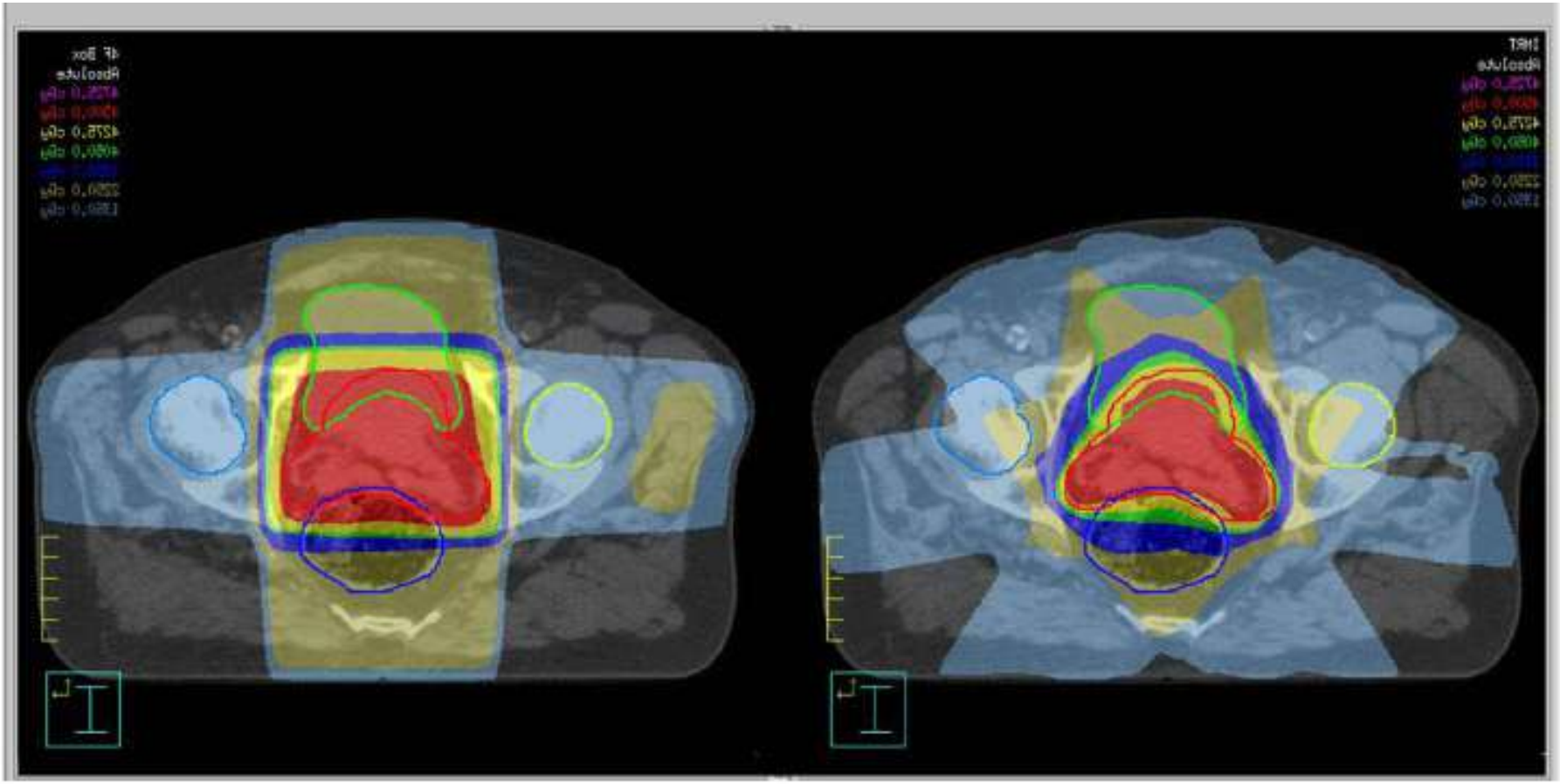


Radiotherapy with X-rays

two beams



Improved Delivery

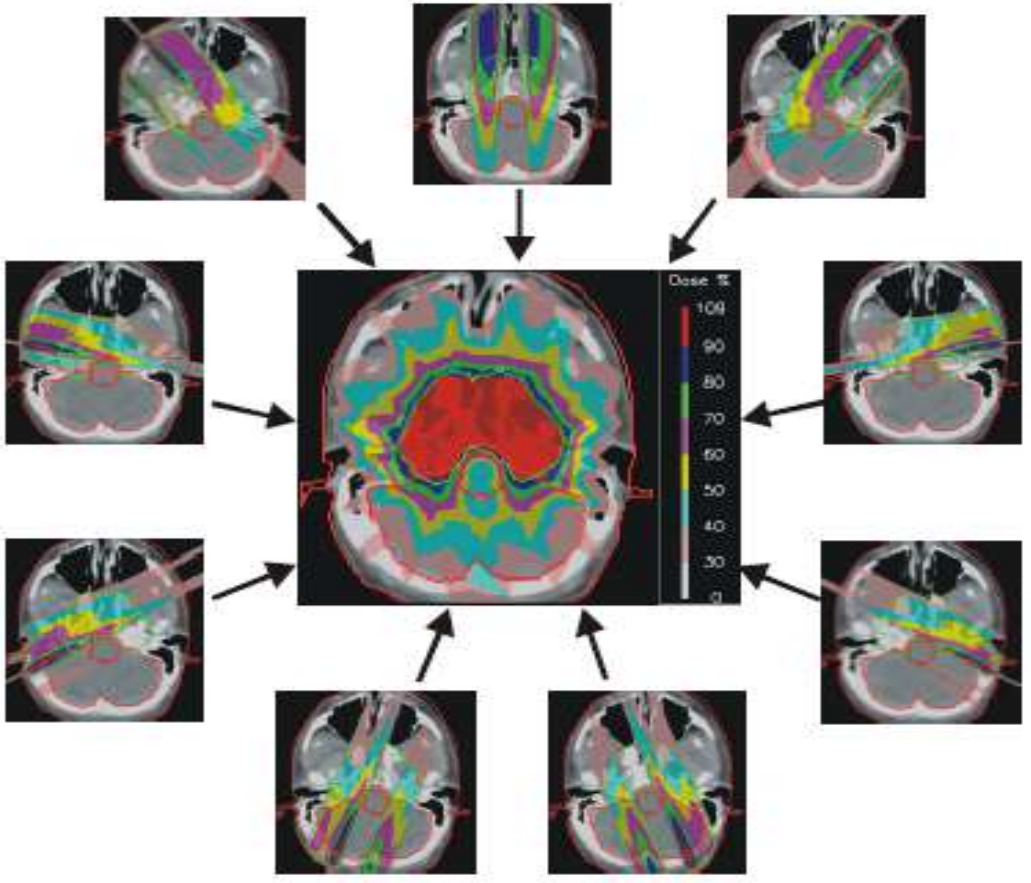


1990s: 4 constant intensity fields

Current state of RT: Intensity Modulated Radiotherapy (IMRT) – Multiple converging field with planar (2D) intensity variations

Intensity Modulated Radiation Therapy

NON-UNIFORM FIELDS



PSI

60-75 grays (joule/kg) given in 30-35 fractions (6-7weeks)

to allow healthy tissues to repair:

90% of the tumours are radiosensitive

Advances in Radiation Therapy

In the past two decades due to:

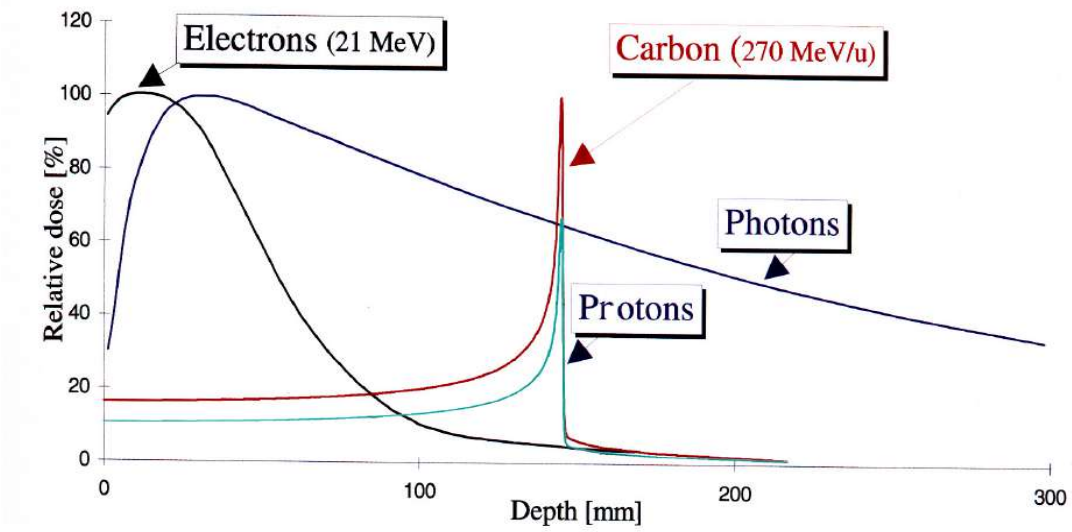
- improvements in imaging modalities, multimodality
- technology, powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
  - MRI-guided Linac therapy
- Is Hadron/Particle Therapy the future?

Hadron Therapy

In 1946 Robert Wilson:

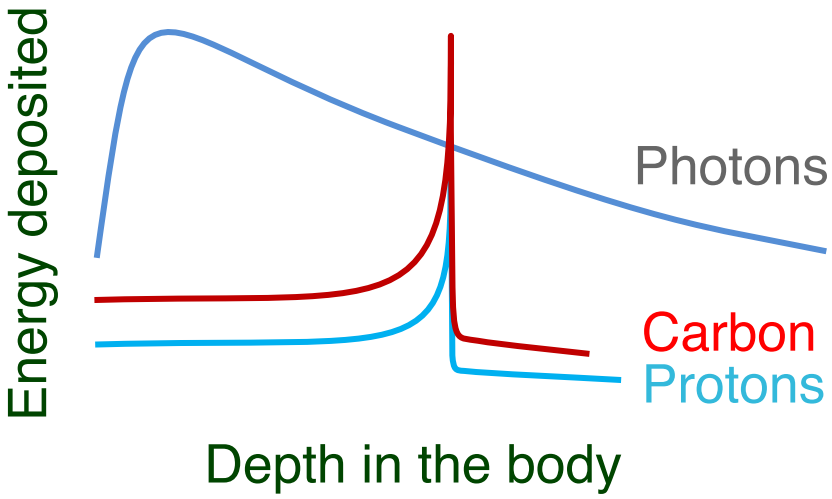
- **Protons can be used clinically**
- **Accelerators are available**
- **Maximum radiation dose can be placed into the tumour**
- **Particle therapy provides sparing of normal tissues**

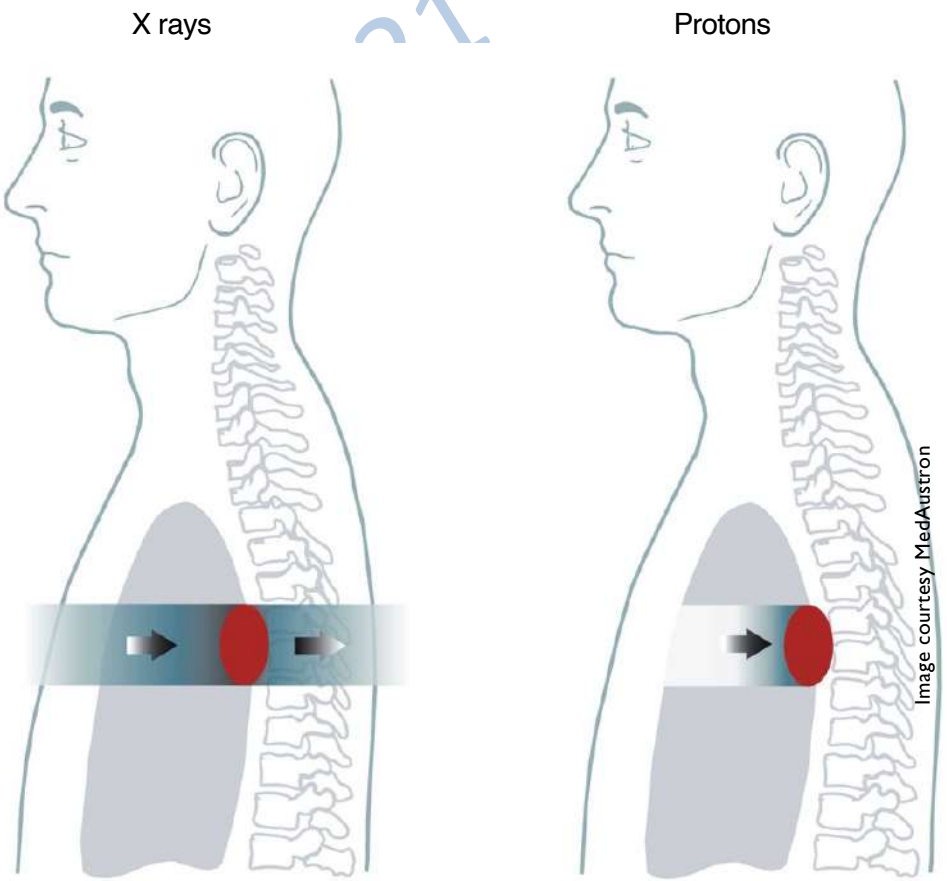
- Tumours near critical organs
- Tumours in children
- Radio-resistant tumours



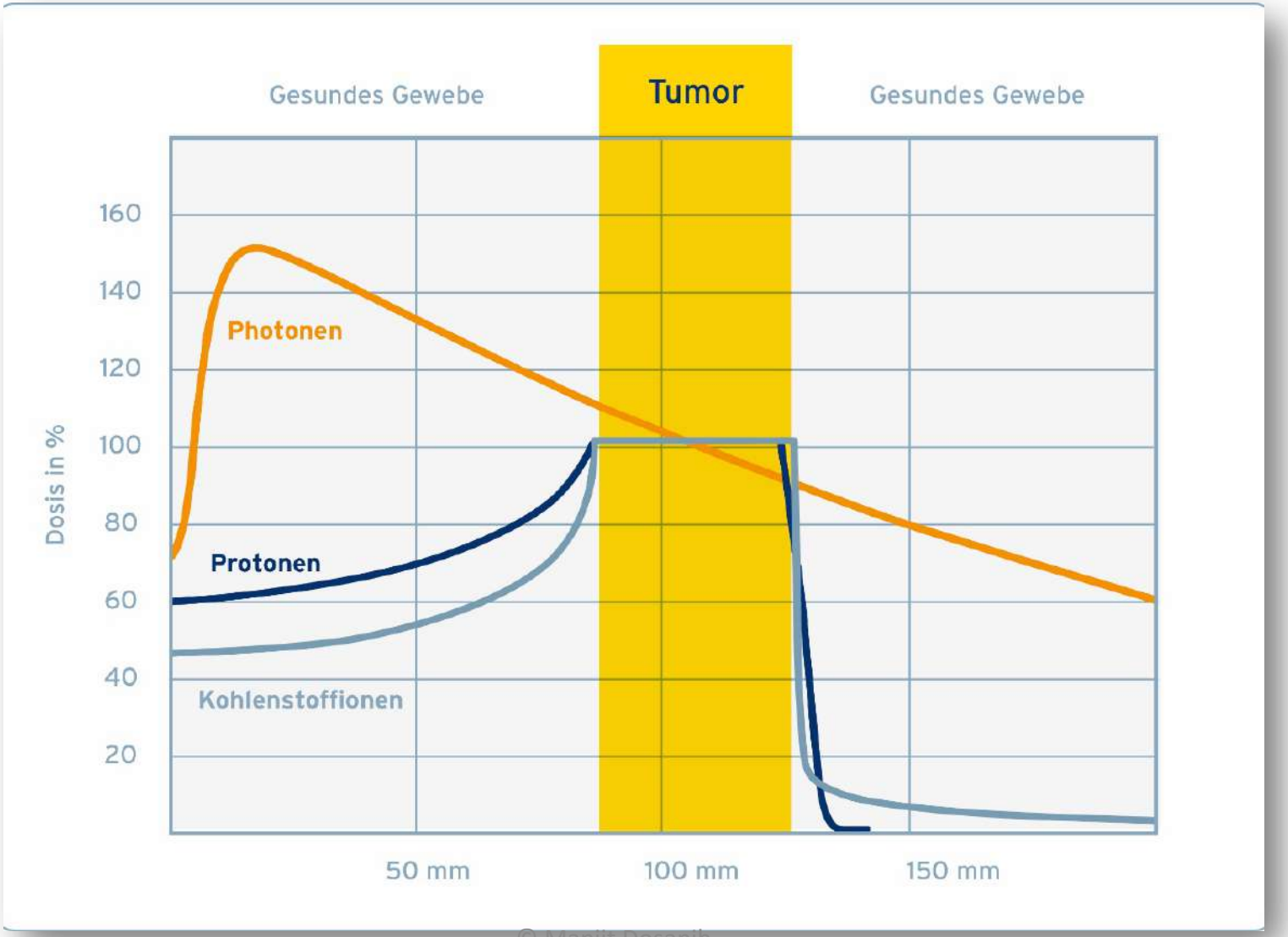
Depth in the body (mm)

Hadron therapy

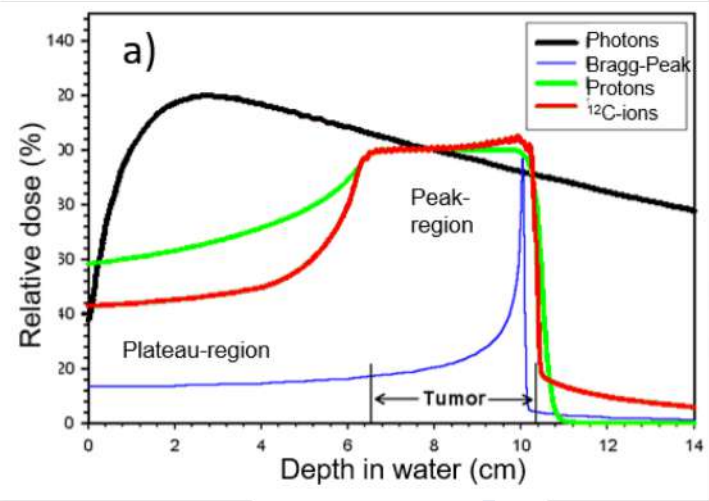


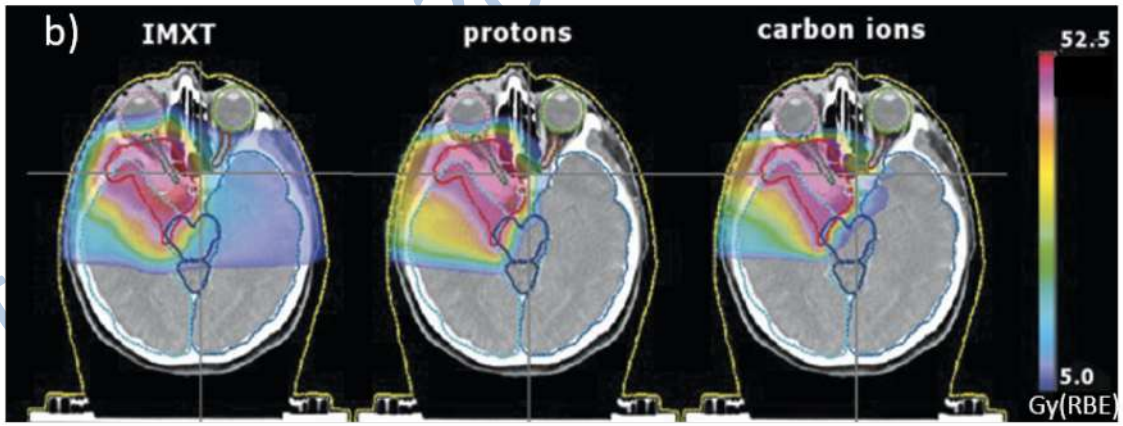


Hadron Therapy



Particle/Hadron Therapy?

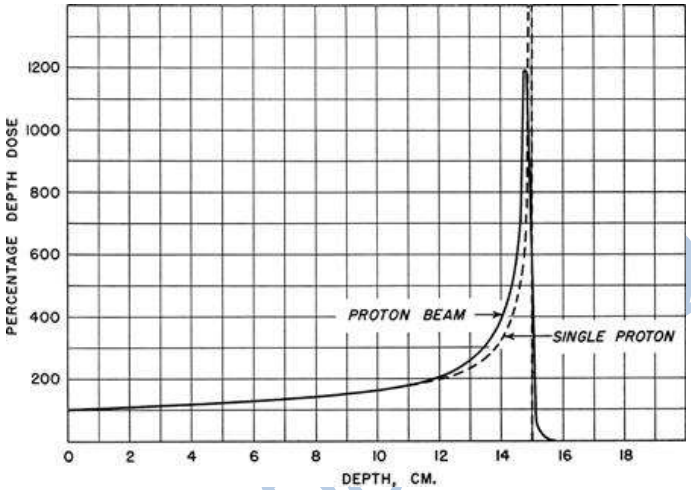




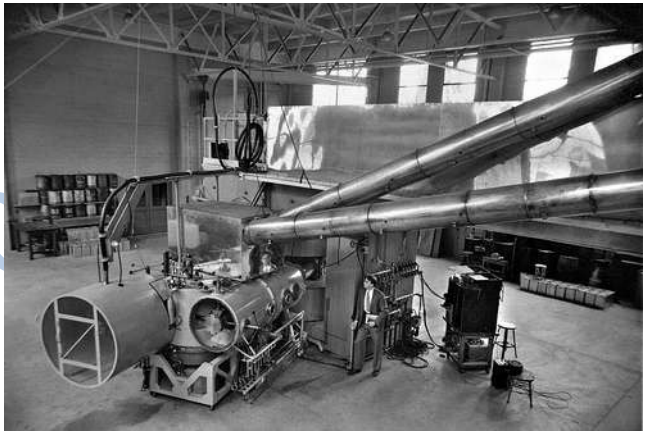
Depth dose profiles in water (a) and treatment plans (b) comparing photons, delivered with the most advanced intensity modulation RT (IMXT), and state-of-the-art scanned protons and ^{12}C ions, showing the increased tumour-dose conformity of ion therapy due to the characteristic Bragg peak (a).

1932 - E. Lawrence
First cyclotron

1946 – proton therapy
proposed by R. Wilson



1954 – Berkeley treats
the first patient



From physics……..

3 crucial years for HT

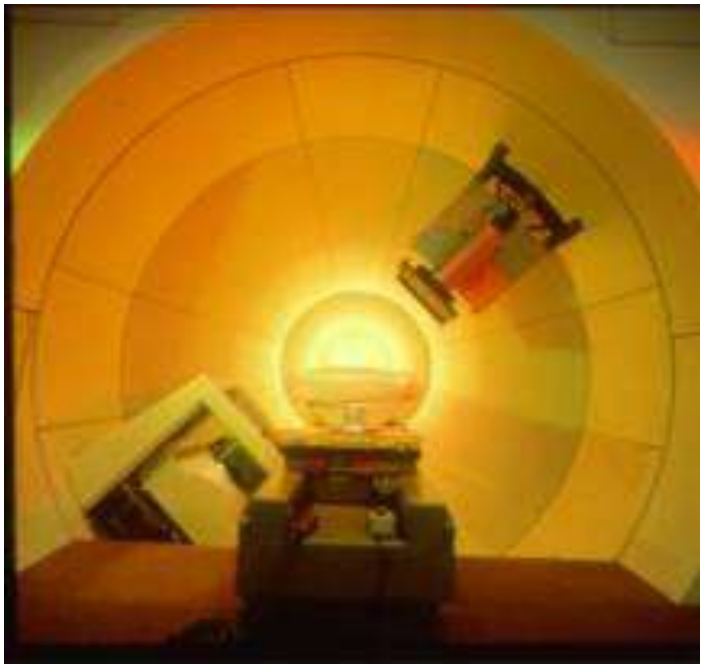
In the years 1992-1994 the rate of progress changed:

- 1992 at Loma Linda first proton patient
- 1993 MGH (Boston) orders the first commercial proton therapy centre
- 1993 GSI starts the carbon ion 'pilot project'
- 1994 HIMAC first carbon ion patient

Key Milestones of Hadrontherapy

1991 — First hospital based *Proton* facility
Loma Linda University Medical Center, CA, USA

360^0 Gantry



HIMAC in Chiba is the pioneer of carbon therapy

Yasuo Hirao

First patient1994

Hirohiko Tsujii

Since the cells do not repair. less fractions are possible

HIMAC: reduced fractions! Even single fraction

The Darmstadt GSI ‘pilot project’ (1997-2008)

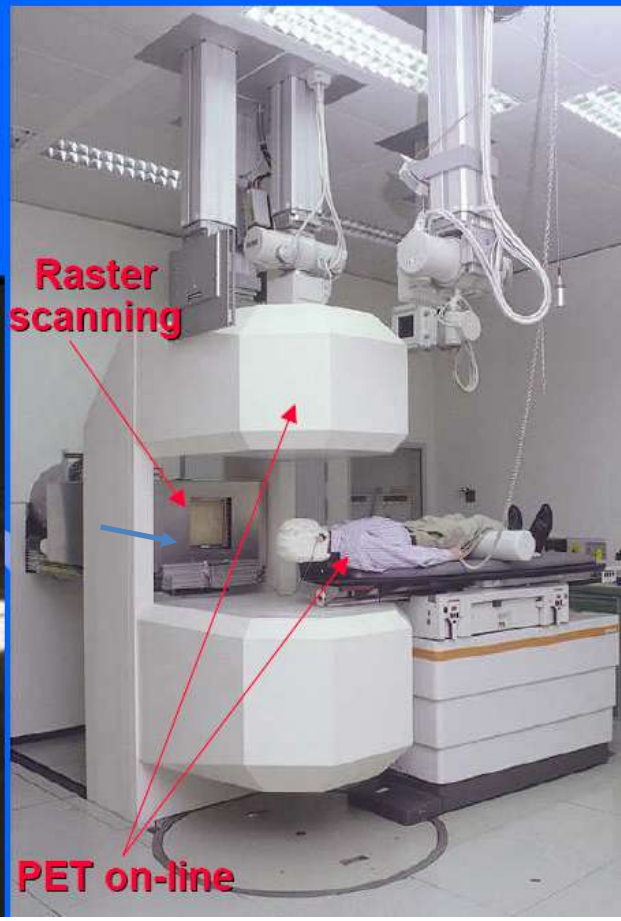
G. Kraft

J. Debus

G. Kraft

450 patients treated with carbon ions

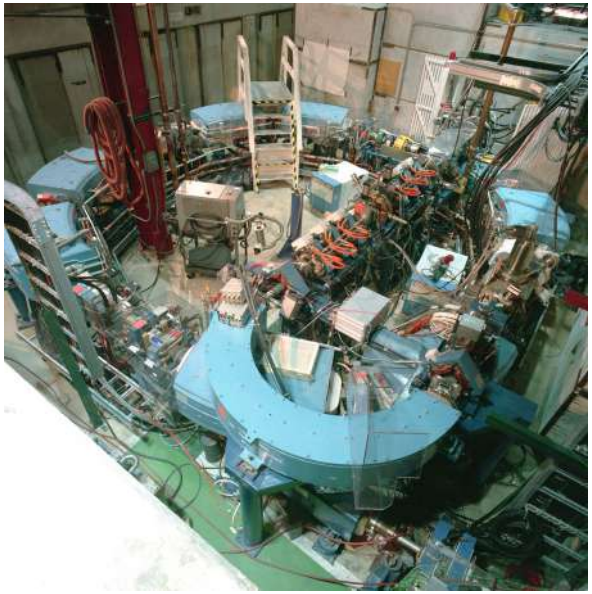
J. Debus (Heidelberg Univ.)



1993- Loma Linda USA (proton)

1994 – HIMAC/NIRS Japan (carbon)

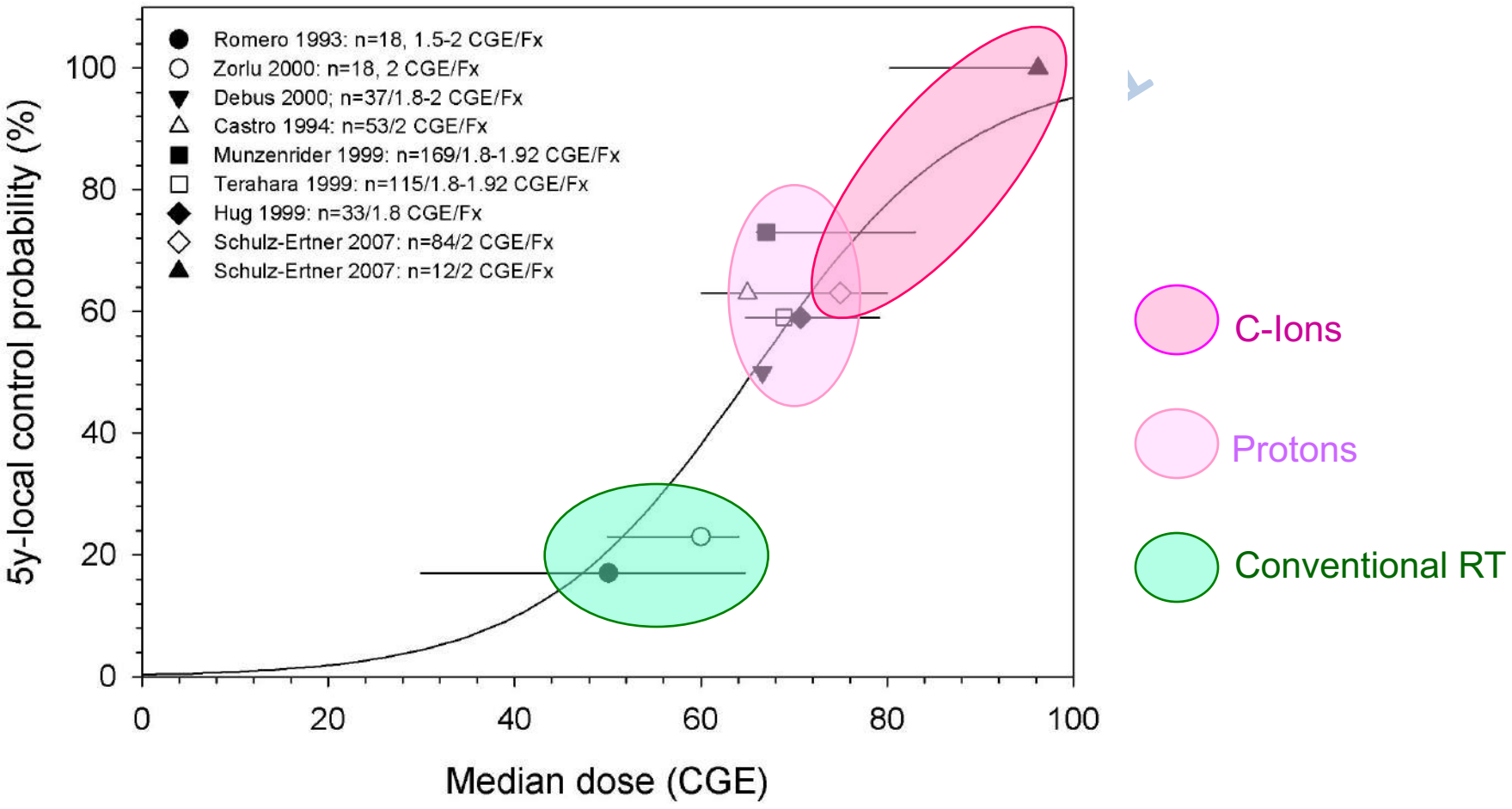
1997 – GSI Germany (carbon)



First dedicated clinical facility

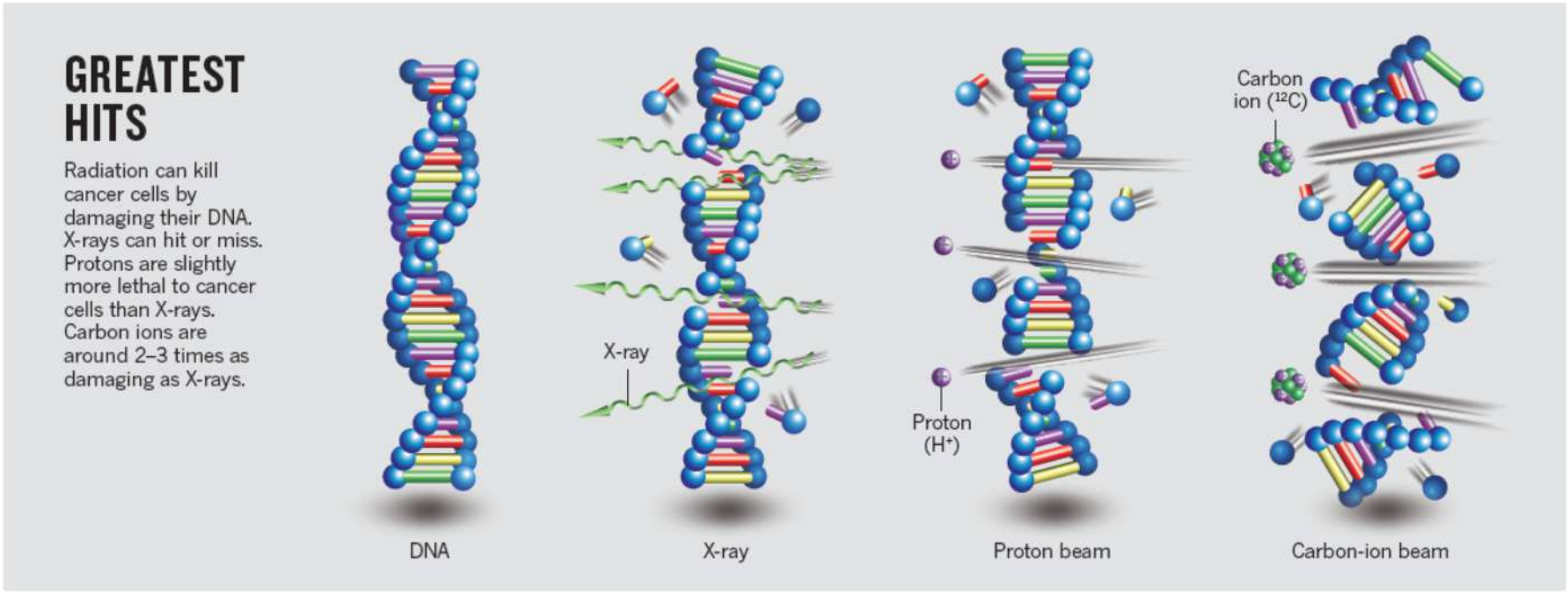
Three crucial years for PT……to clinics

Tumour Control Rate: Chordomas



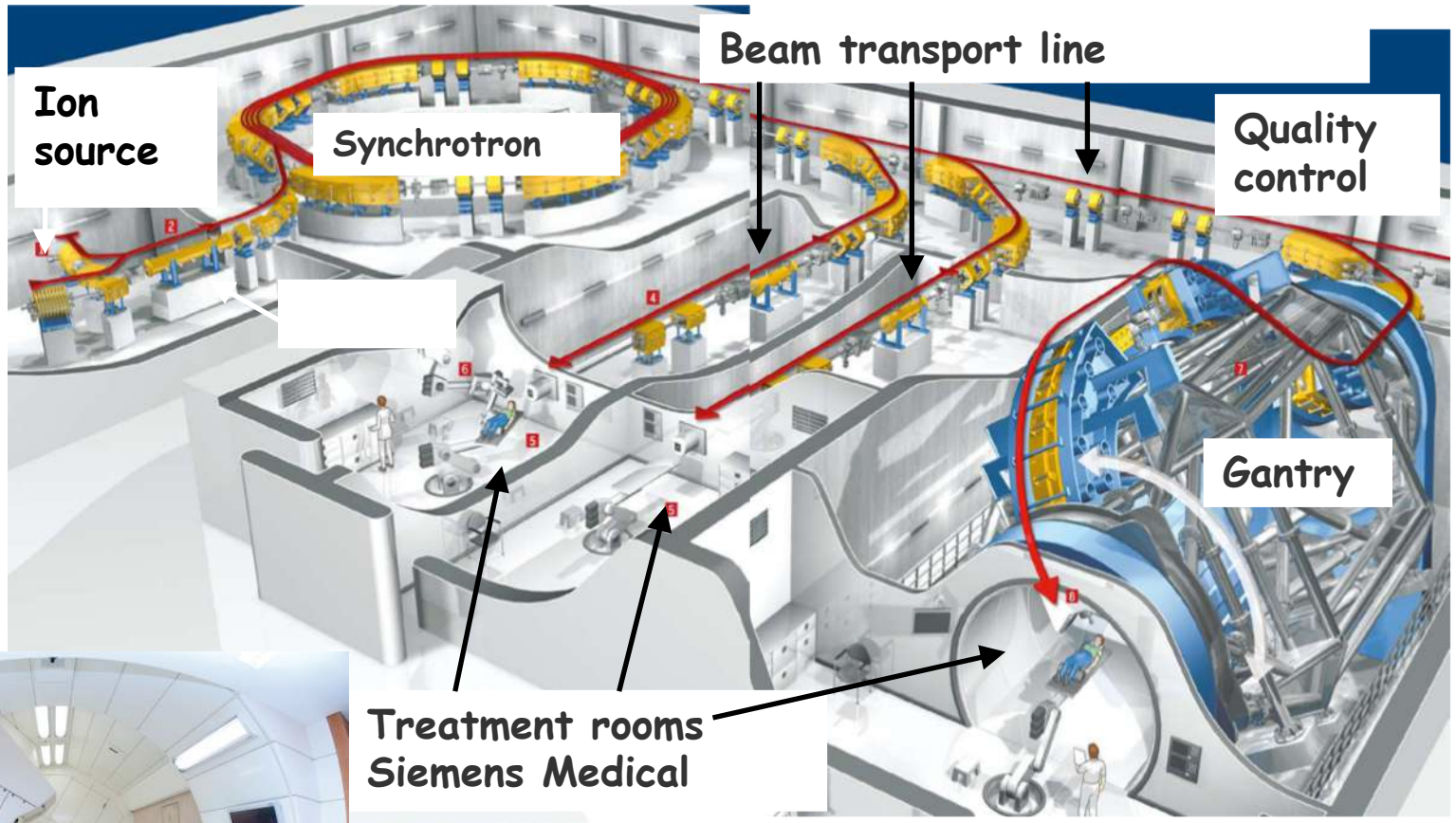
Schulz-Ertner, IJROBP 2007

DNA **X-rays** **Protons** **Carbon ions**



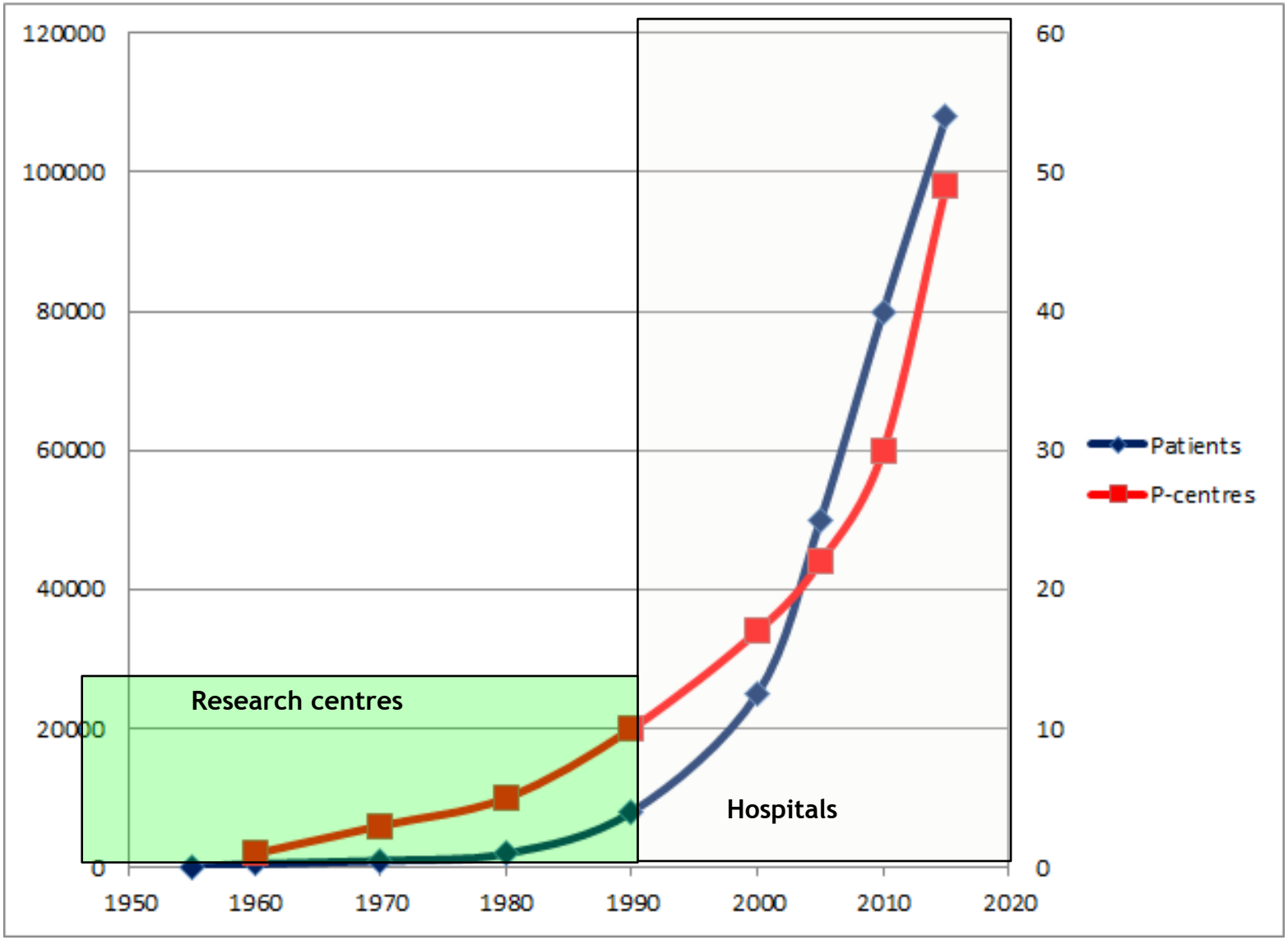
Marx, Nature, 2014

HIT - Heidelberg

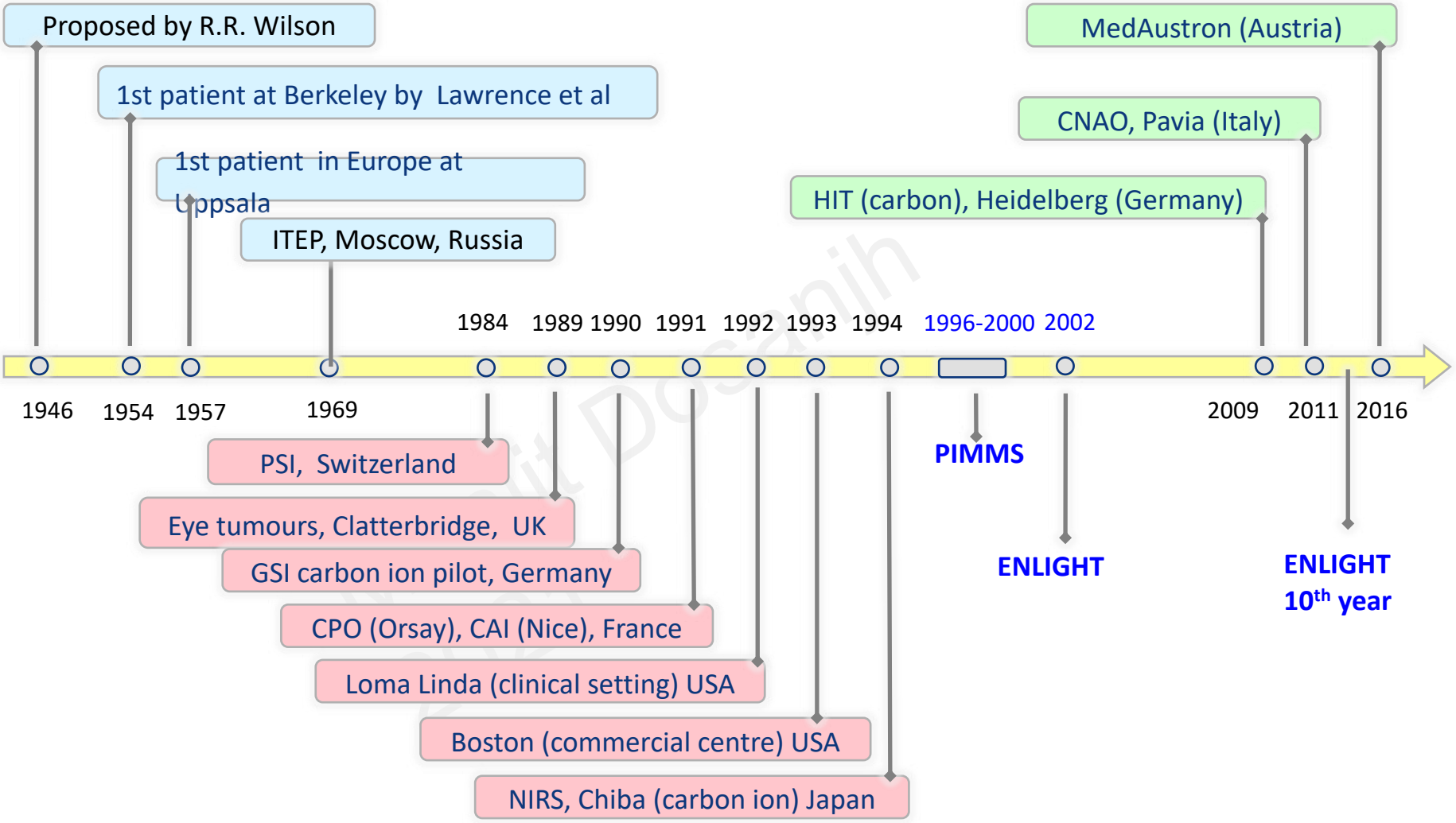


Carbon facilities in Europe: first dual ion clinical facility - started treating patients in 2009

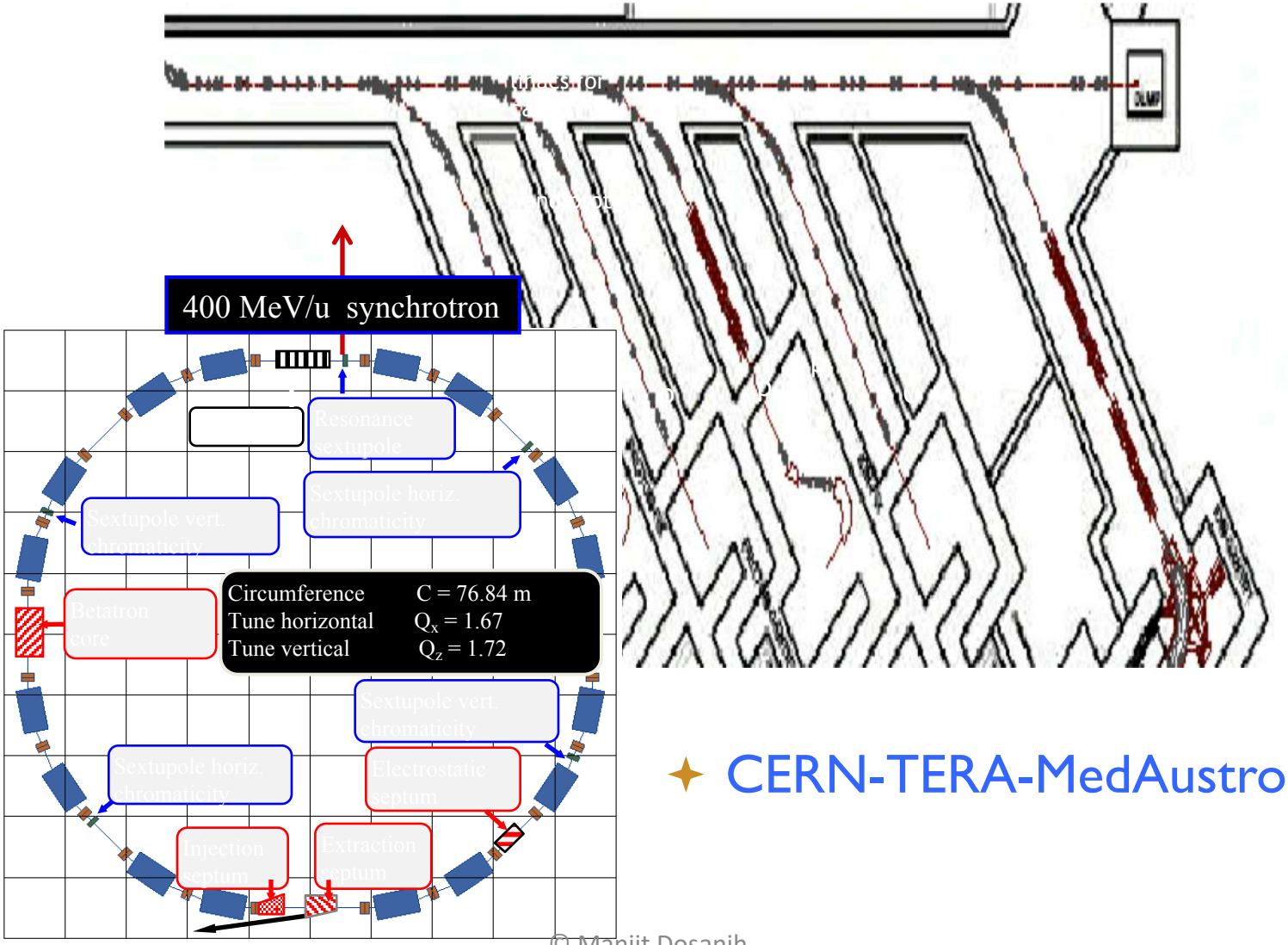
[Data from www.ptcog.ch]



Particle therapy: a short history

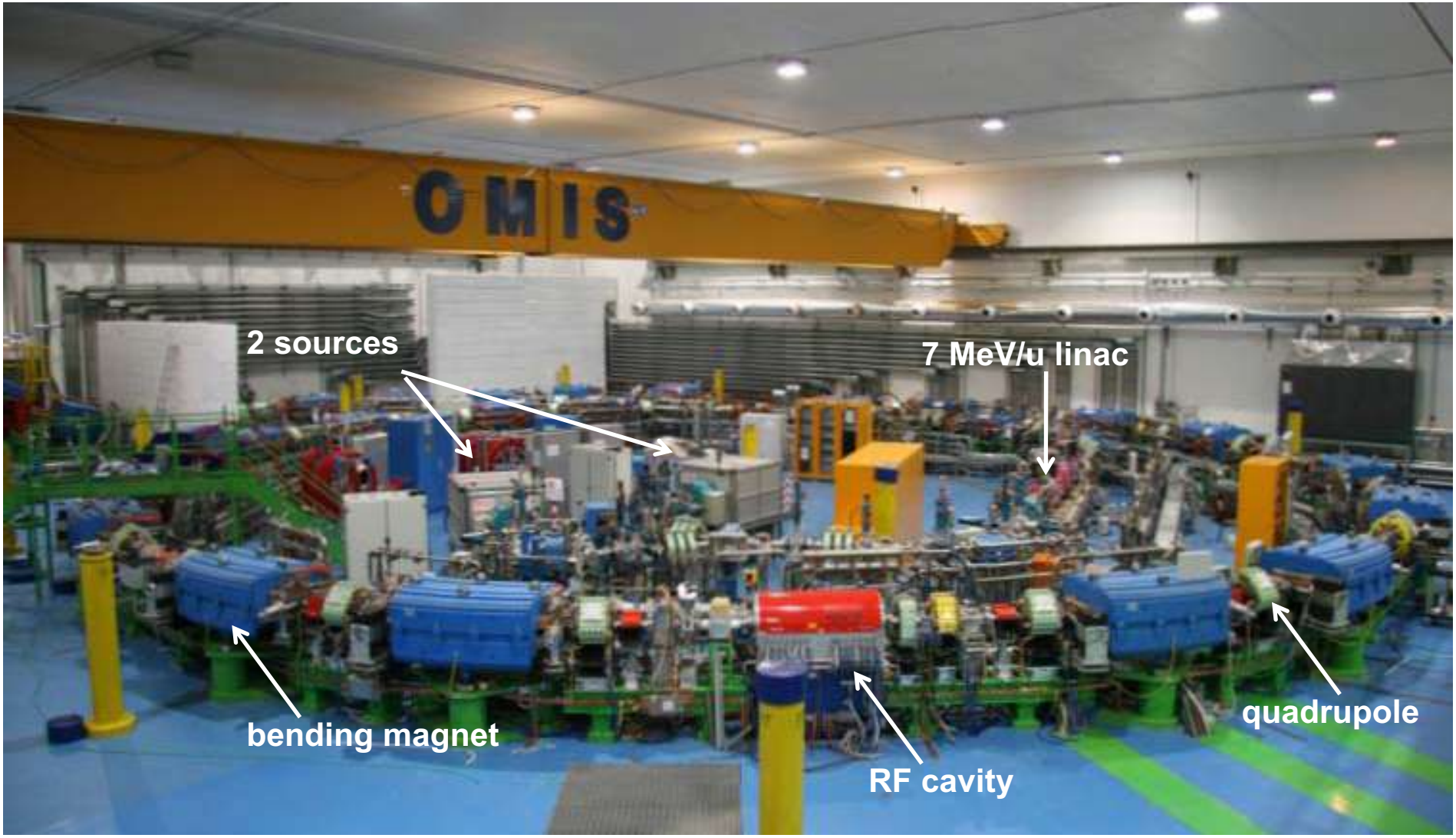


PIMMS at CERN (1996-2000)



- CERN-TERA-MedAustron

CNAO: Pavia, Italy

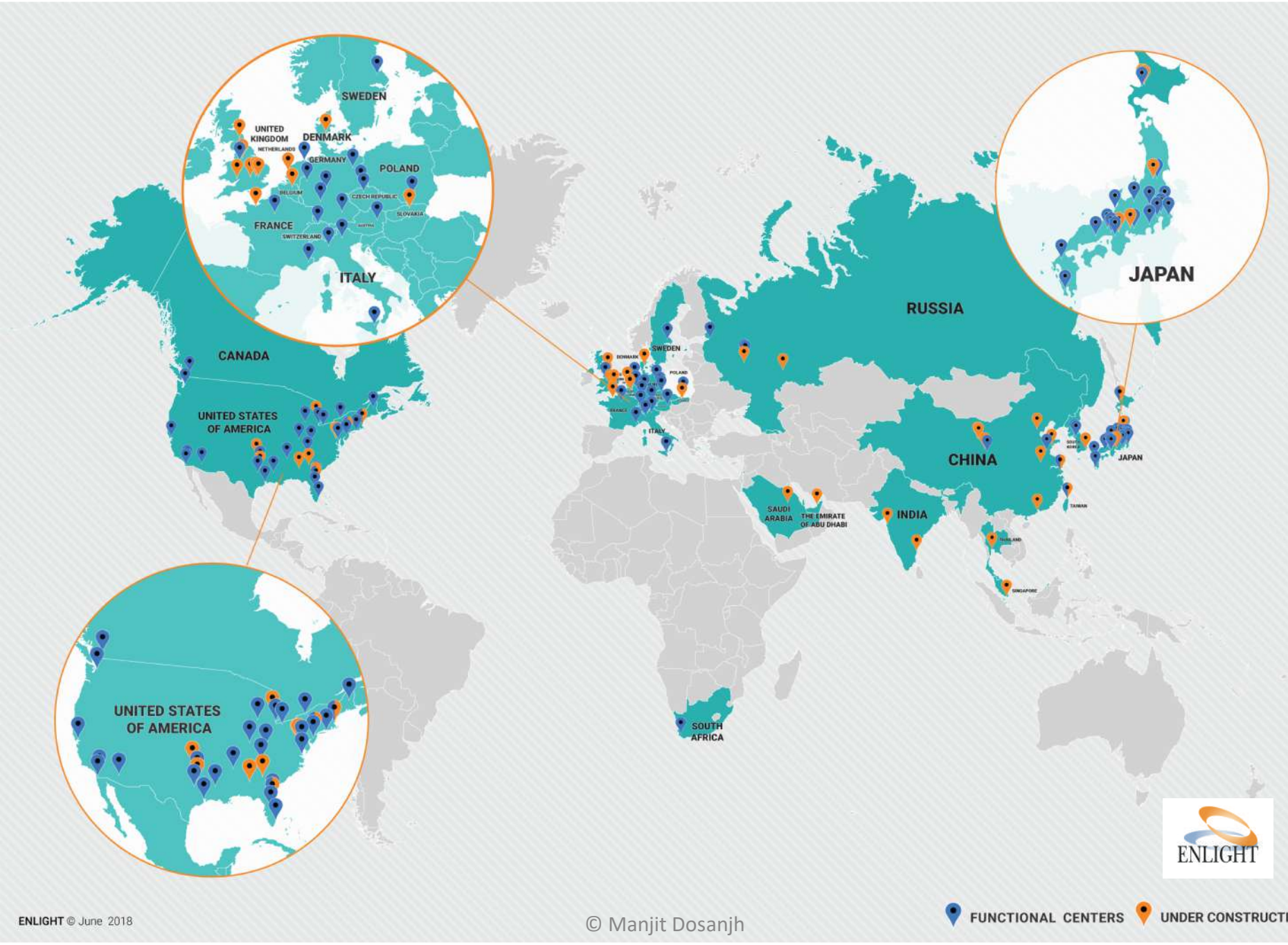


Started treating patients in 2011

MedAustron, Wiener Neustadt, Austria

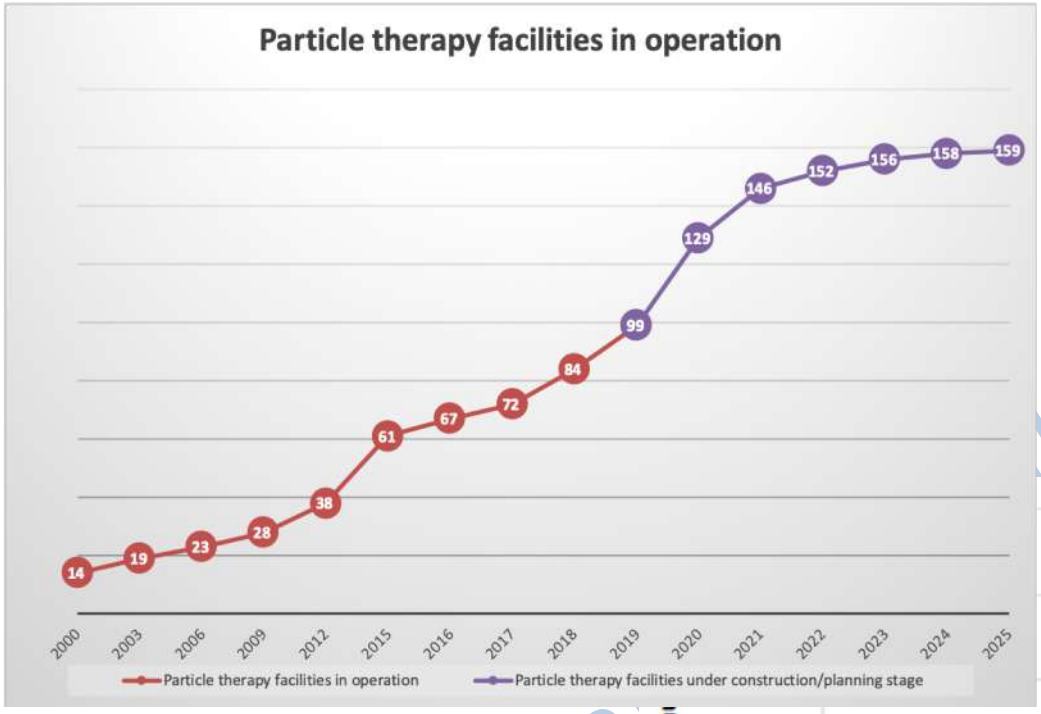
Started treating patients in December 2016

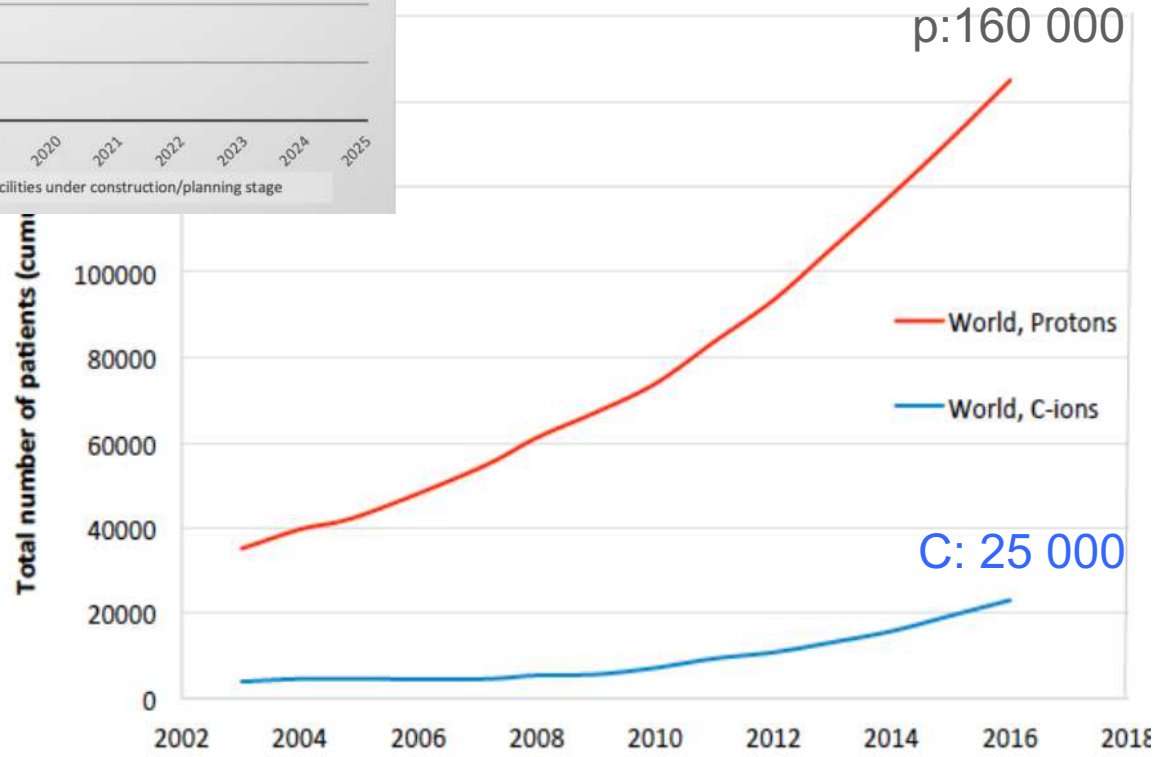
Facilities in operation in Europe 2020



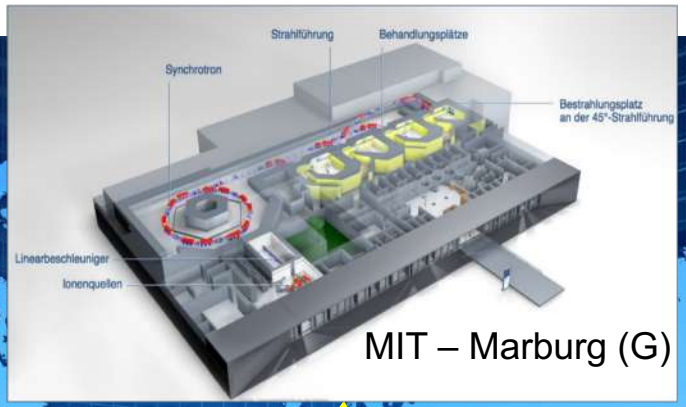
ENLIGHT © June 2018

Centres and patients worldwide





Multi-ions clinical facilities in the World



MIT – Marburg (G)

HIT – Heidelberg (G)

3 centres in China

6 centres in Japan

CNAO – Pavia (I)

MedAustron – Wien (A)

New Developments

FLASH Therapy with all particles?

FLASH therapy is an experimental treatment modality delivering radiotherapy at ultra-high dose rates to treatment volumes in typically <1 second.

Treatment of a first patient with electron FLASH-radiotherapy (CHUV group)

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland

5.6 MeV linac adapted for accelerating electrons in FLASH mode

15 Gy with 10 pulses **in 90 ms**

3.5 cm diameter tumour, multiresistant cutaneous

Appears that instantaneous dose Induces a massive oxygen consumption and a transient protective hypoxia in normal issues

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

Varian *FlashForward* Consortium

Varian's FlashForward™ Consortium is formed from institutions around the world to establish preclinical study designs, develop technical solutions, and share research protocols to help advance the science and clinical translation of FLASH therapy.

World's First FLASH Clinical Trial
Feasibility Study of FLASH Proton Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01)

A standard palliative dose fractionation regimen of 8 Gy in a single fraction is delivered with a 250MeV transmission proton beam at FLASH dose rates. **Cincinnati Children's Hospital Medical Center** (PI: Dr. J. Breneman). The design of the follow-up trial FAST-02 is underway.

Clinical FLASH Protons

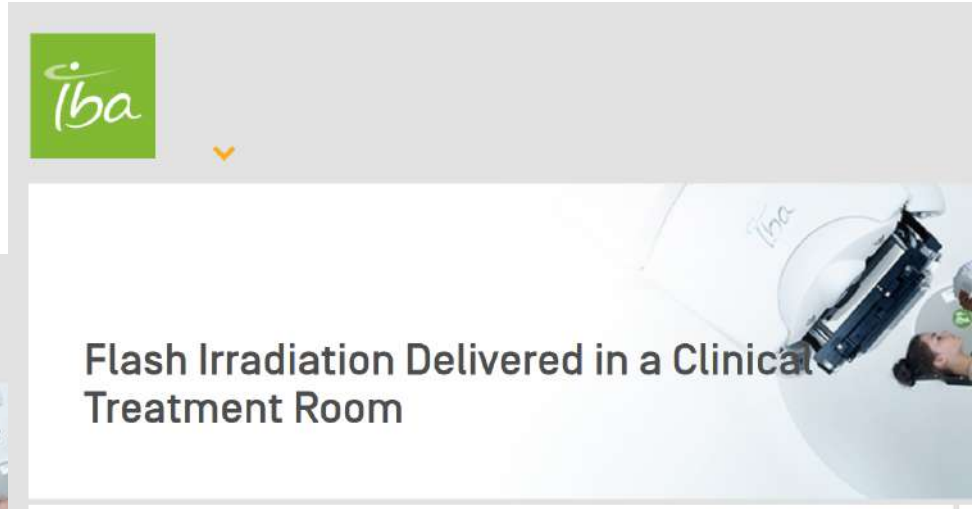
- Manufacturers setting up clinical beams

Flash Irradiation Delivered in a Proteus®ONE Treatment Room

Proton therapy / 11.06.2019

Successful Ultra High Dose Rate delivered at Isocenter in IBA's compact proton therapy solution

Louvain-la-Neuve, Belgium, 11 June 2019 – IBA (Ion Beam Applications SA), the world's leading provider of proton therapy solutions, is pleased to announce the first Flash irradiation in an IBA Proteus®ONE compact gantry treatment room at the Rutherford Cancer Centre Thames Valley in Reading, United Kingdom, on June 8, 2019. This represents another major milestone for IBA and its medical and research partners in their work to lead the development of Flash irradiation.



Flash Irradiation Delivered in a Clinical Treatment Room

Proton therapy / 08.03.2019

Successful Flash Irradiation at Isocenter in IBA's Proteus® Solution Gantry Room

Louvain-la-Neuve, Belgium, 8 March 2019 – IBA (Ion Beam Applications SA), the world's leading provider of proton therapy solutions, is pleased to announce the first Flash irradiation in an IBA gantry treatment room at the University Medical Centre Groningen (UMCG) in The Netherlands. This achievement represents a major milestone in the work that IBA and its medical and research partners are engaged to bring Flash irradiation to clinical treatment.

Summary

- **Dose-rate** has a significant impact on radiobiological response

- Recent data has shown that at dose-rates around >40 Gy/s (FLASH Exposures) **normal tissue can be protected**

- An underpinning role for **oxygen dependent chemistry**

- Further studies are on-going to fully define the impact of total dose, spatial patterning, total exposure rate and **radiation quality** on response

Particle therapy + immunotherapy

Does Heavy Ion Therapy Work Through the Immune System?

Marco Durante, PhD,* David J. Brenner, PhD,† and Silvia C. Formenti, MD‡

*Trento Institute for Fundamental Physics and Applications-National Institute for Nuclear Physics, University of Trento, Trento, Italy; †Center for Radiological Research, Columbia University Medical Center, New York, New York; and ‡Department of Radiation Oncology, Weill Cornell Medical College, New York, New York

Received Aug 10, 2016, and in revised form Aug 21, 2016. Accepted for publication Aug 25, 2016.

International Journal of Radiation Oncology biology • physics

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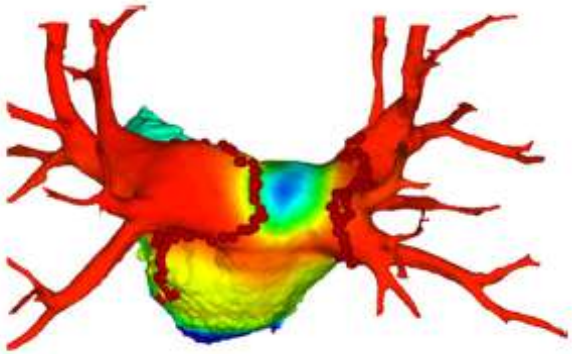
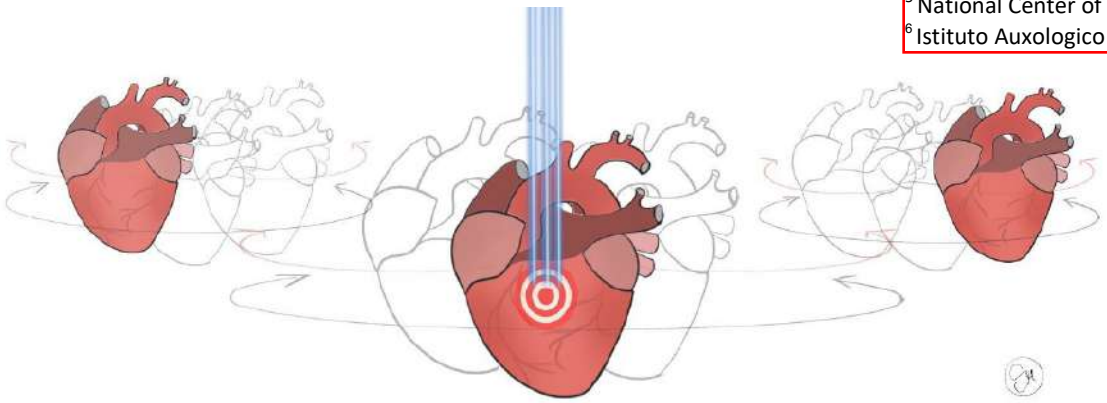
Non oncological application: ventricular arrhythmia(CNAO)





Non-invasive Proton Radiotherapy for Refractory Ventricular Tachycardia in advanced heart failure: first in-man case.

Veronica Dusi[1,2], MD, PhD; Viviana Vitolo[5], MD; Laura Frigerio[1,3], MD; Rossana Totaro[1,3], MD; Adele Valentini[4], MD; Amelia Barcellini [5],MD; Alfredo Mirandola[5], PhD; Giovanni Battista Perego[6], MD; Michela Coccia [3], MD , Alessandra Greco[3], MD, Stefano Ghio[3] ,MD, Massimiliano Gnecchi [1,2], MD, PhD; Luigi Oltrona Visconti[3] , MD, Roberto Rordorf[1,3]MD.

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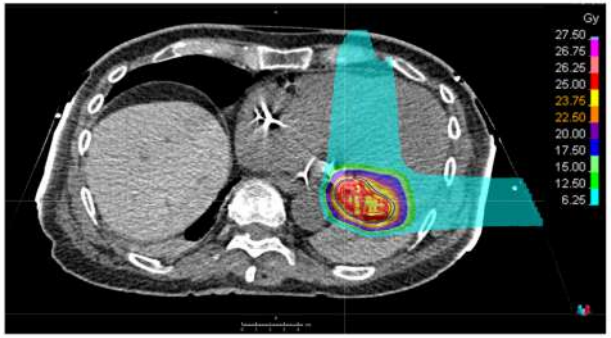
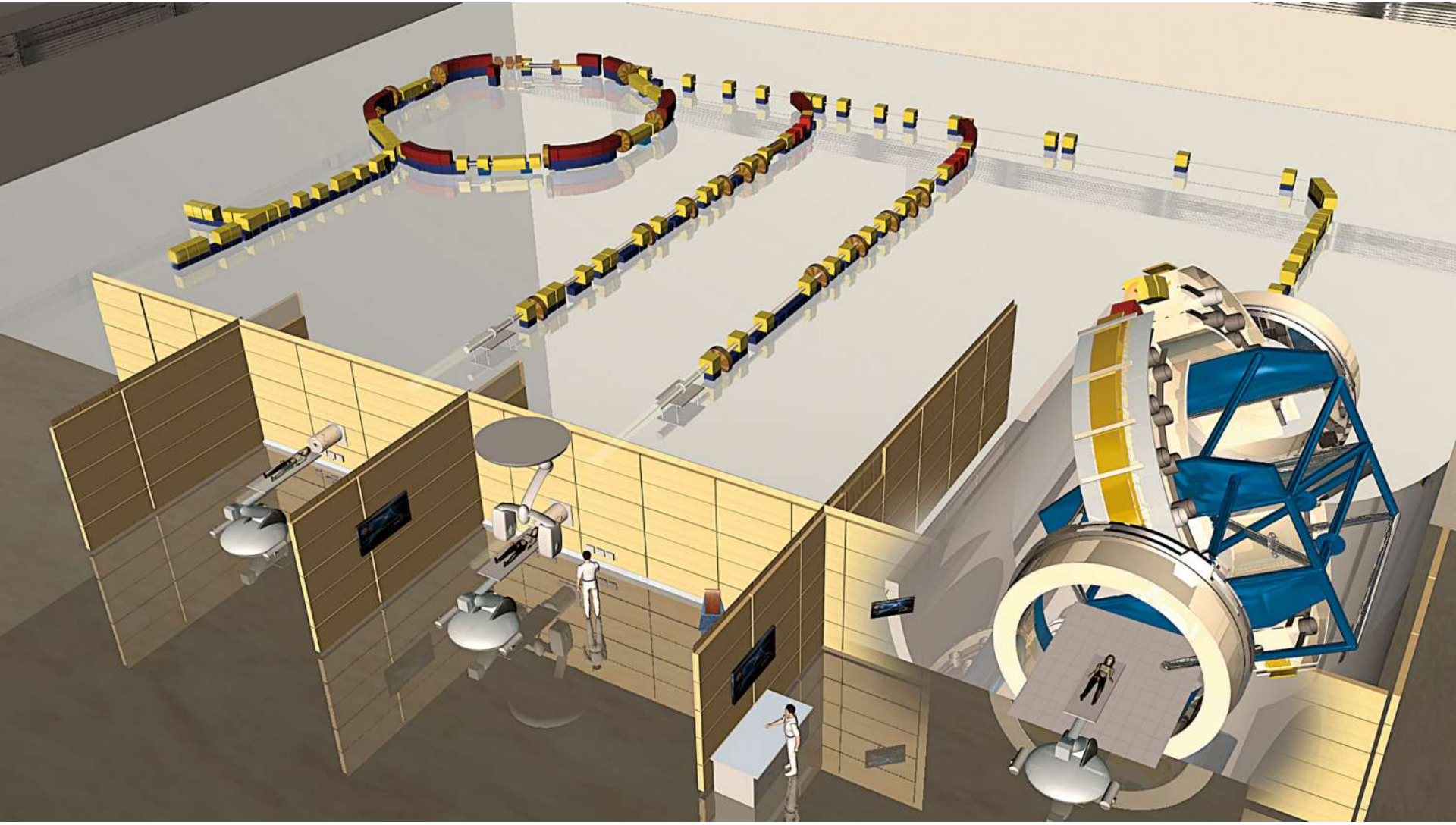


Much remains to be done ……..

Challenge

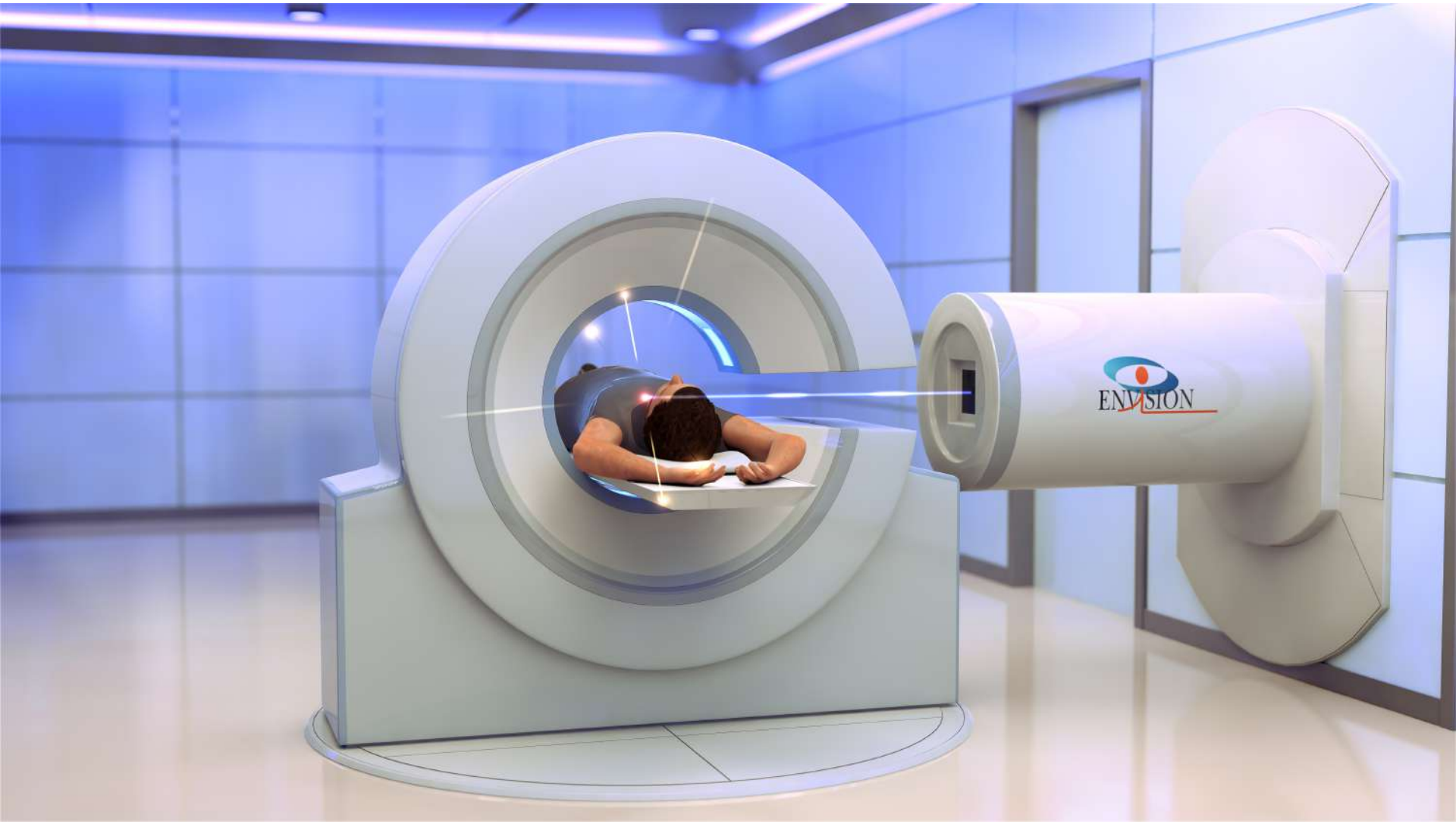


Smaller, simpler, cheaper

Challenge

More compact, cheaper, energy efficient

Challenge



precision

Challenge

Safer and more effective therapy

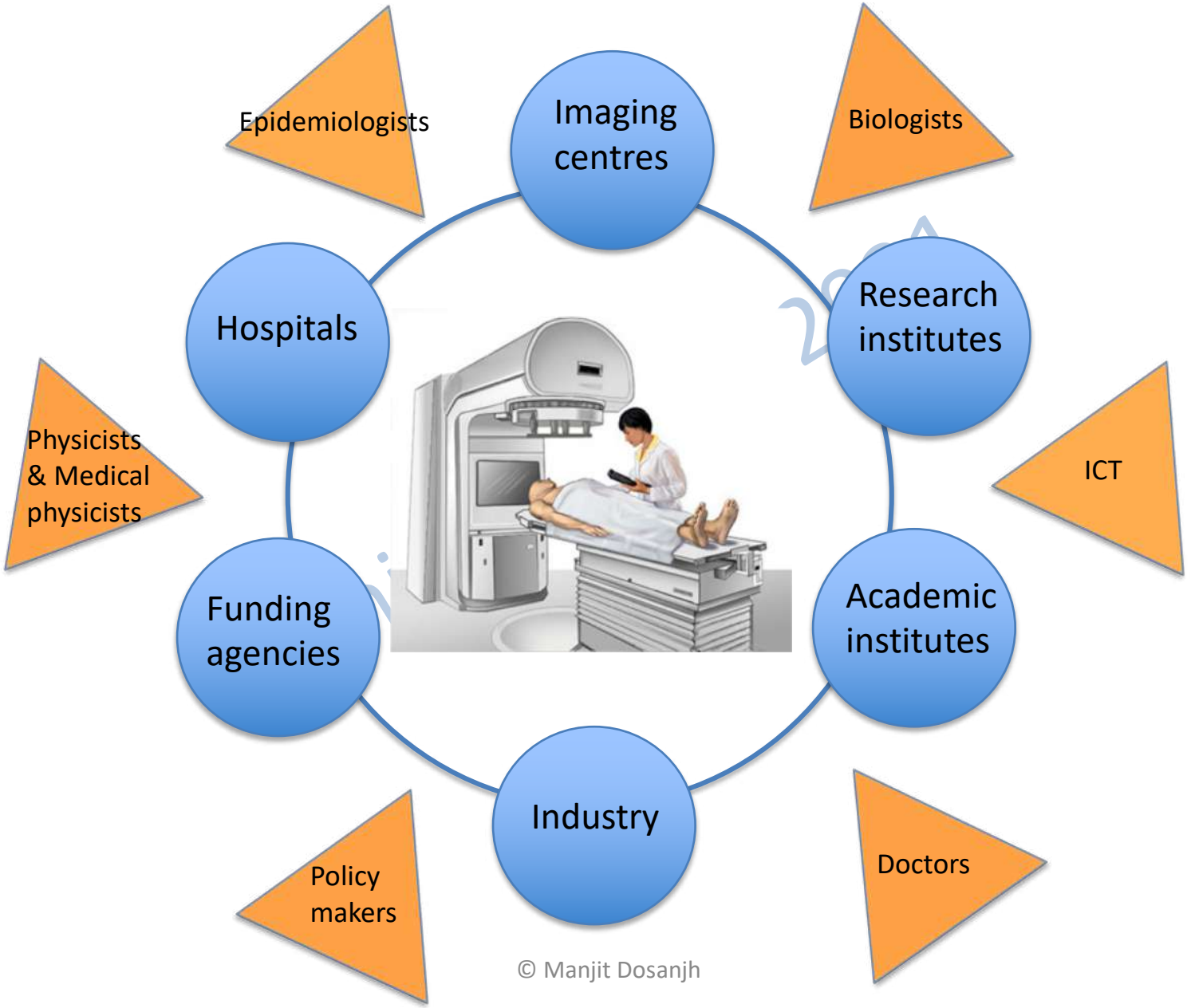
Challenge

Clinical trials: protons, carbon, ions, multi-centric

Much more still needs to be done

- Treat the tumour and only the tumour
  - ⇒ Imaging and dose delivery: control and monitor the ideal dose to the tumour
  - ⇒ Minimal collateral radiation "outside" the tumour
  - ⇒ Minimal radiation to nearby critical organs
  - ➢ Even if the tumour is moving
- Compact: Fit into a large hospital
  - ⇒ Accelerator: smaller, simpler, cheaper
  - ⇒ Gantry: compact, cheaper, energy efficient
- Be affordable
  - ✓ Capital cost ?
  - ✓ Operating costs ?
  - ✓ Increased number of treated patients per year ?
- Wish list from community
  - ✓ Improve patient through-put
  - ✓ Increase effectiveness
  - ✓ Decrease cost
- New ideas being explored

ENLIGHT-Collaboration is key (see 18:00 talk)



The need for SEEIIST? (Prof Ristova's talk follows)

ENLIGHT

Where it all started…..

Thank you to the ENLIGHT community and the collaborators whose slides and research I have used for this presetation

"This material was prepared and presented within the HITRIplus Heavy Ion Therapy MasterClass school, and it is intended for educational purposes to facilitate students;
people interested to use any of the material for any other purposes (such as other lectures, courses etc) are kindly requested to please contact the author
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HITRI plus
Heavy Ion Therapy Research Integration

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