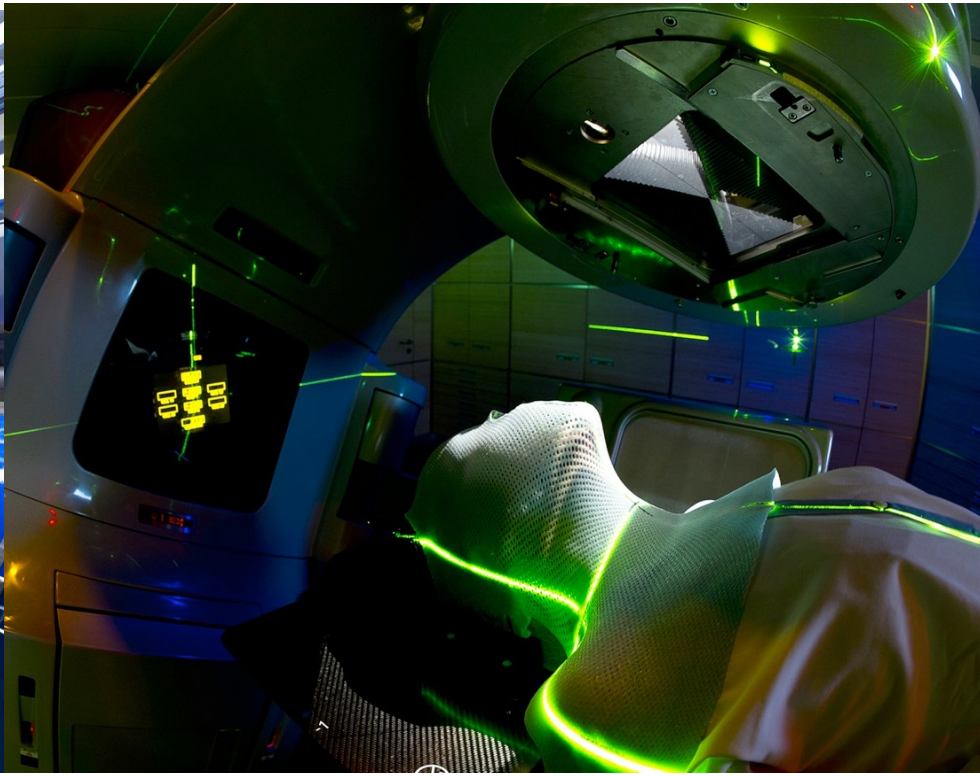
From Physics to Medical Applications



Manjit Dosanjh

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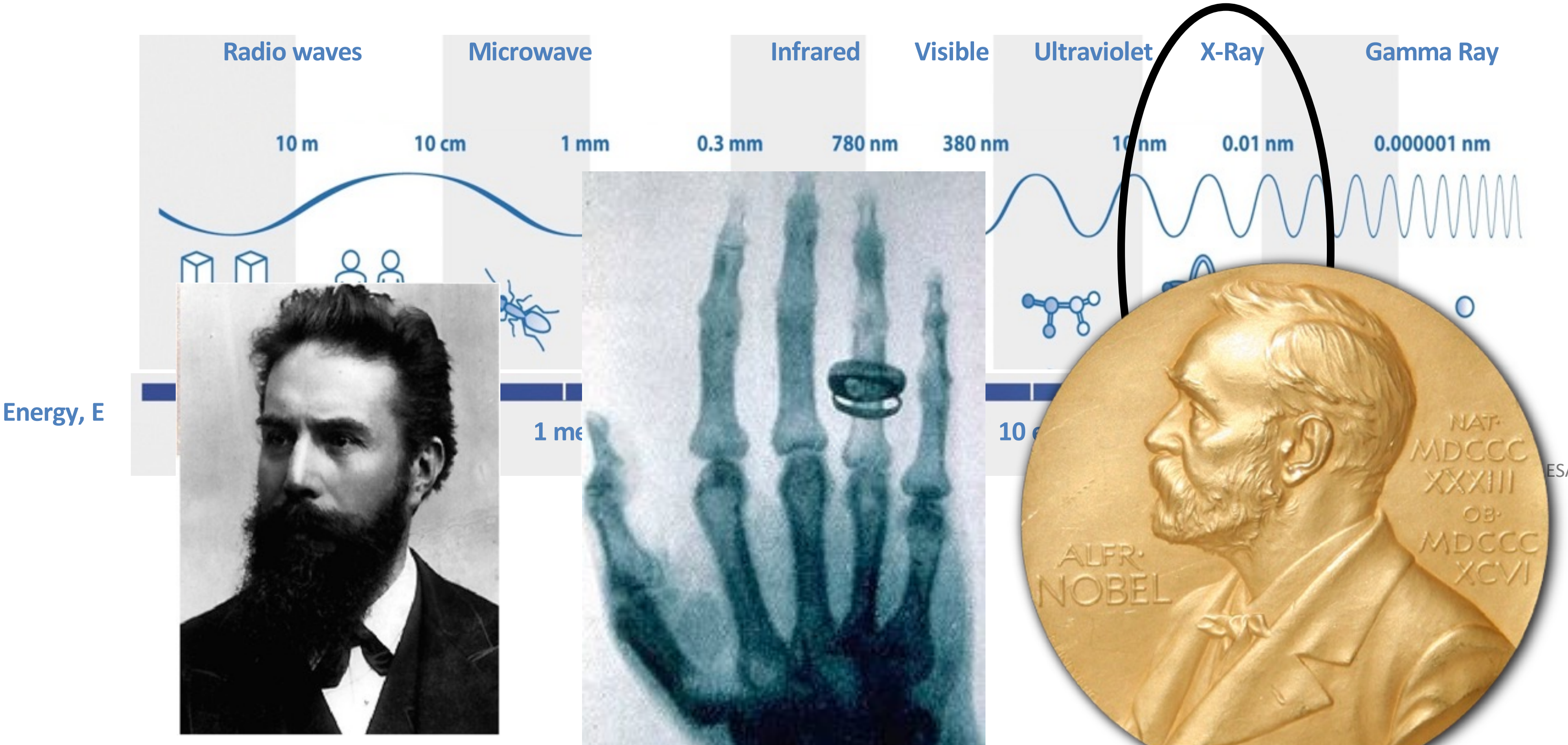
30 May 2022

CERN

UNIVERSITY OF OXFORD

Modern medical physics…..beginnings



Wilhelm Röntgen

8/11/1895

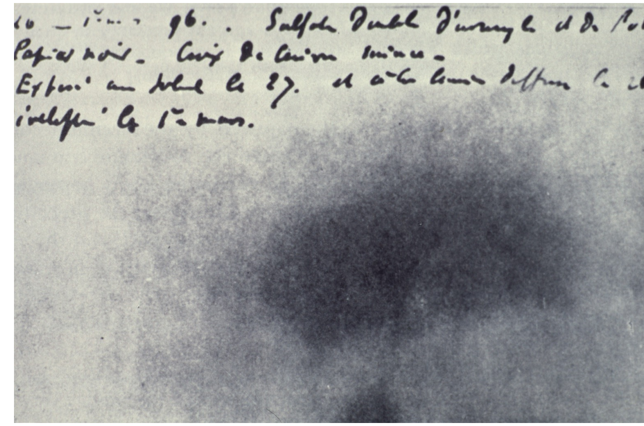
22/12/1895

1901

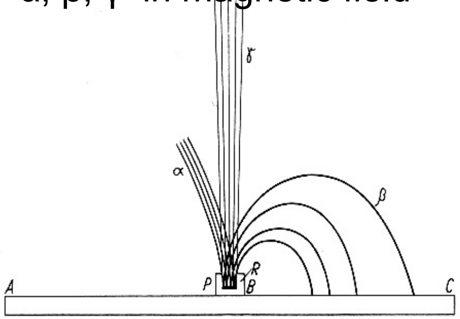
..........beginnings

Henri Becquerel

1896:
Discovery of natural radioactivity

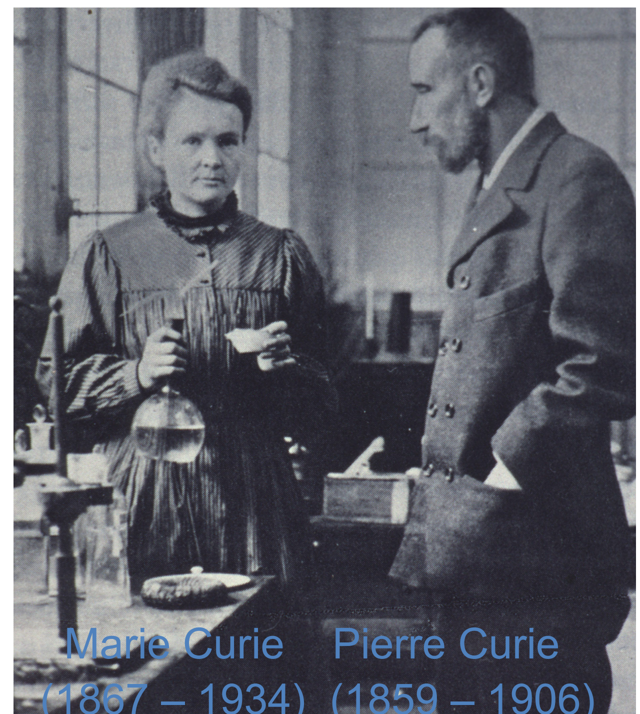


Thesis of Mme. Curie – 1904
α, β, γ in magnetic field



1898: Discovery of radium

used immediately for "Brachytherapy"

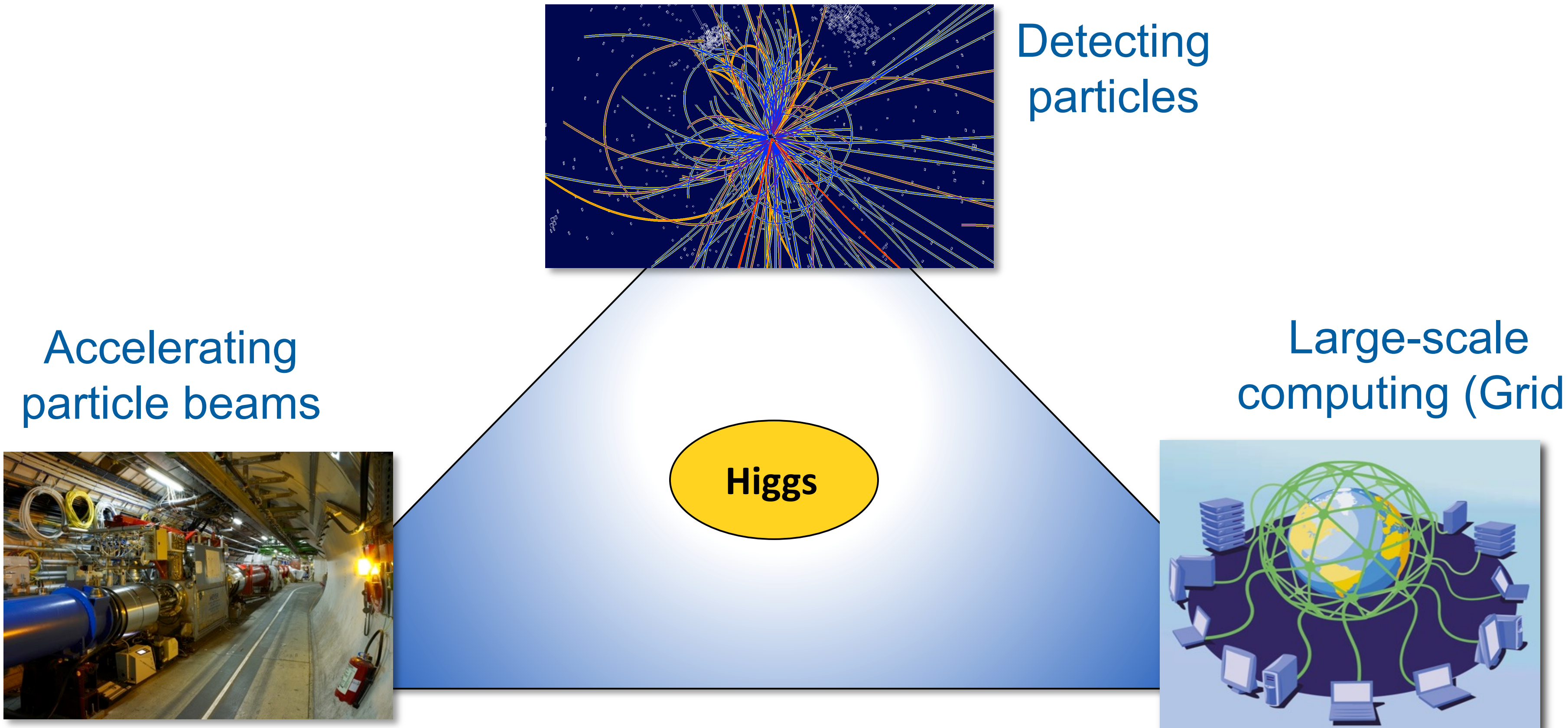


Marie Curie (1867 – 1934) Pierre Curie (1859 – 1906)

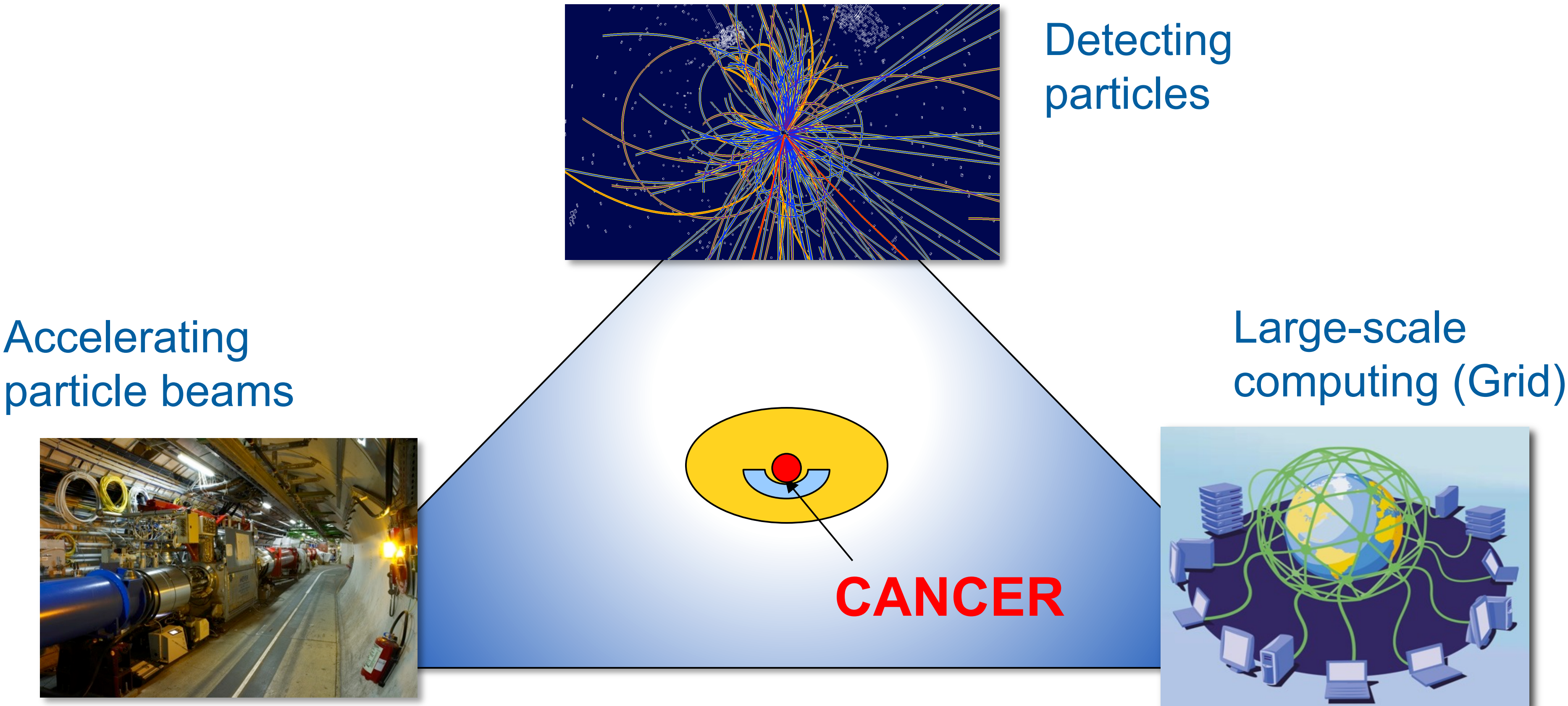
First radiobiology experiment

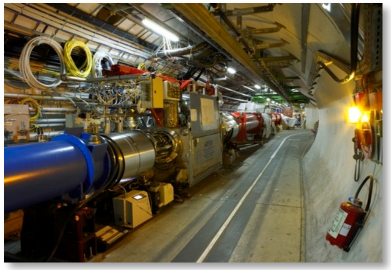
Pierre Curie and Henri Becquerel

CERN and Physics Technologies

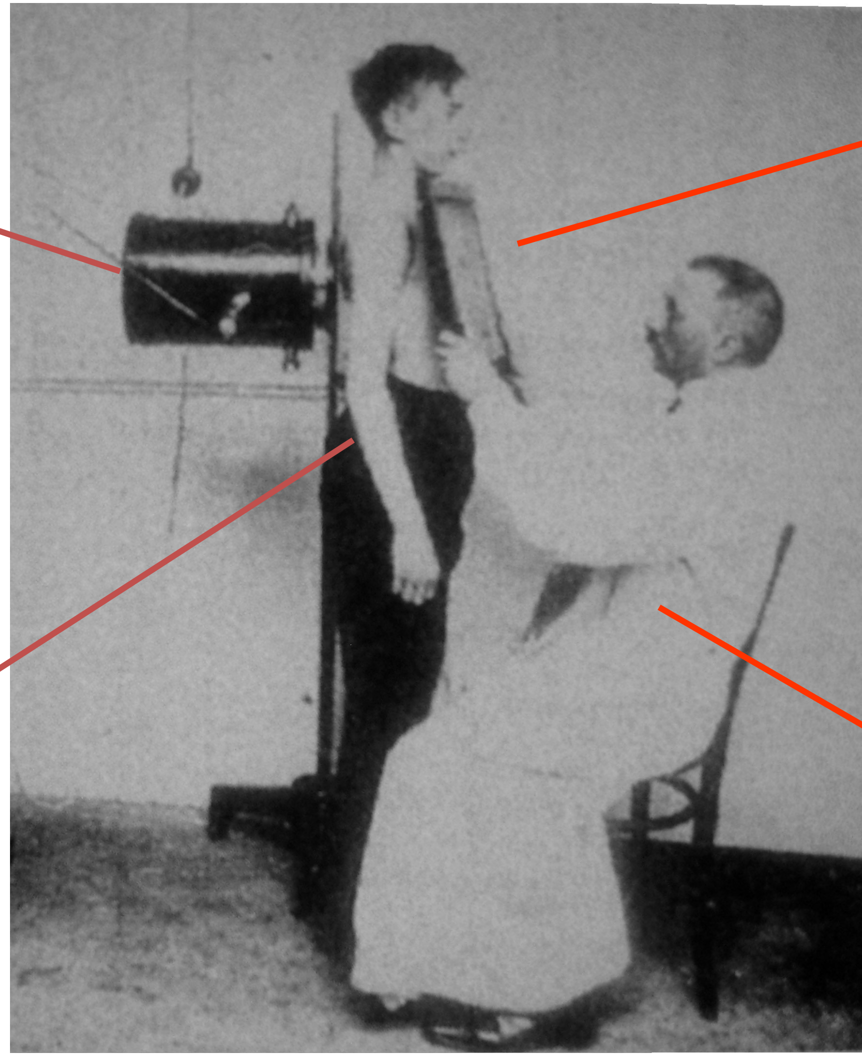


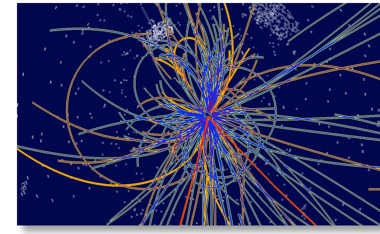
Physics Technologies helping health





X-ray source





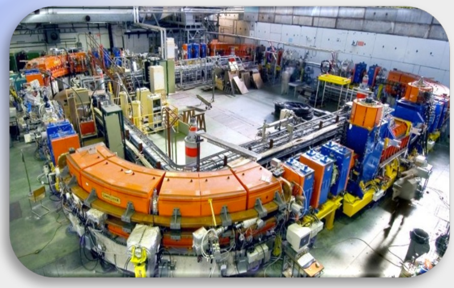
Detector

Object

Pattern Recognition System

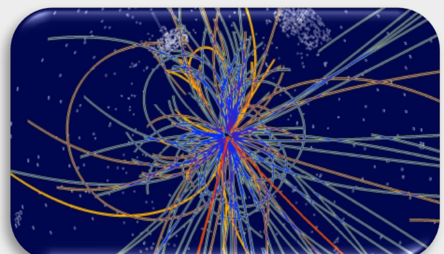
Fourth Pillar: Catalysing collaboration

Accelerating particle beams

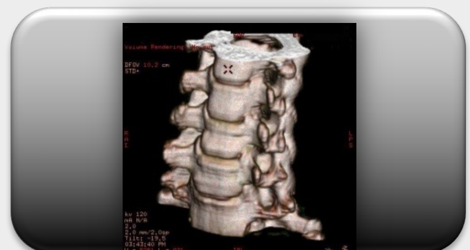


RadTherapy

Detecting particles

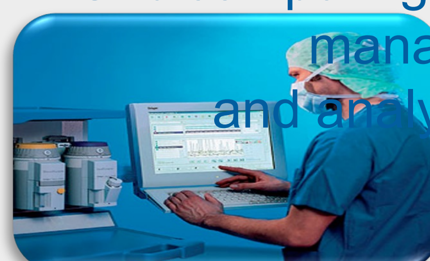


Medical imaging



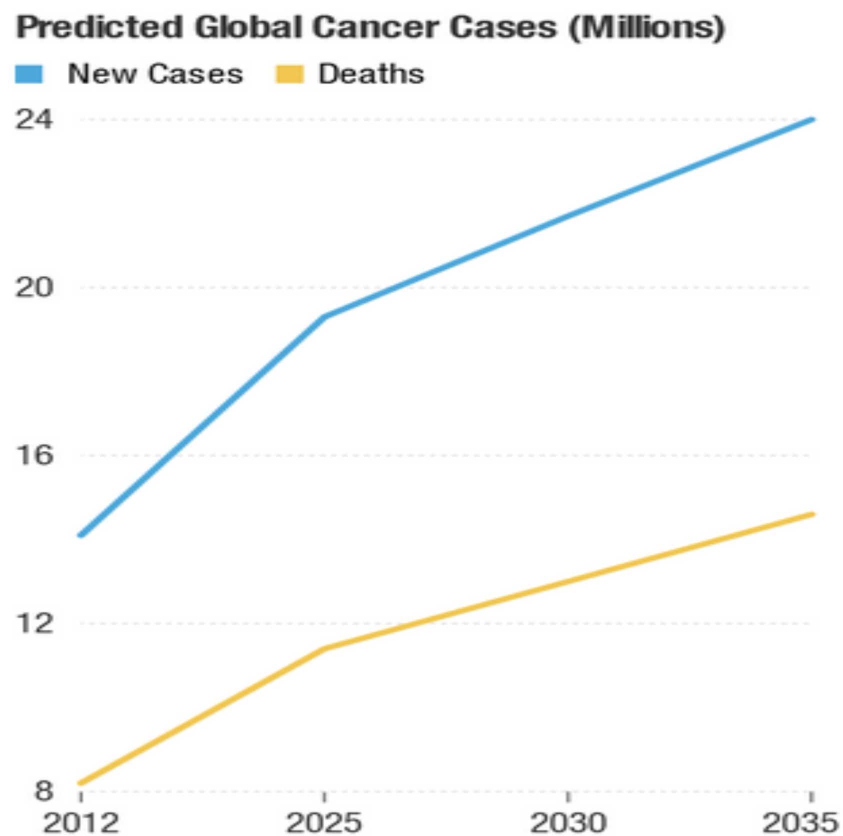
Large scale **computing** (Grid)

Grid computing for medical data management and analysis



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)

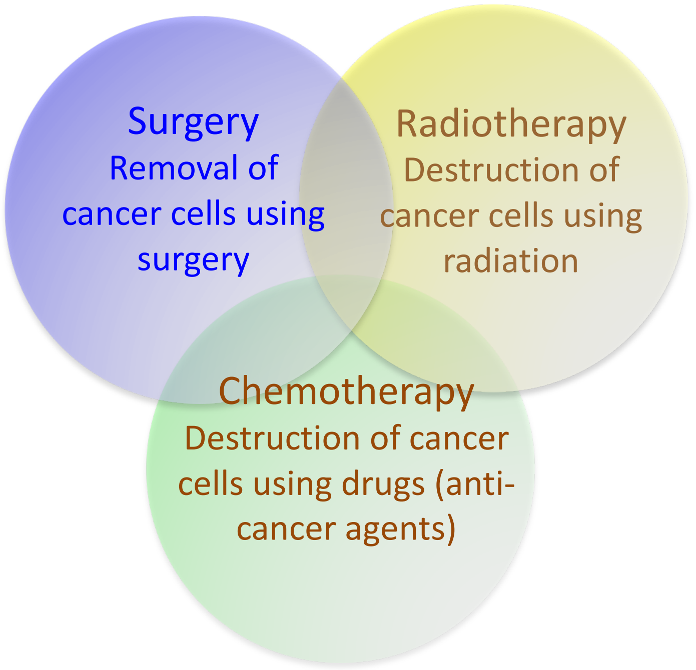


Radiation therapy is a key tool for treatment for over 50% patients

Only 10% of patients in low-income have access

What is Cancer?

- Tumour: what is it?
  - Abnormal growth of cells
  - Malignant: uncontrolled, can spread → cancer



The Challenge of Treatment

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.

Cancer Treatment and Improving Outcomes

Ideally one needs to treat:

The tumour

The whole tumour

And nothing **BUT** the tumour

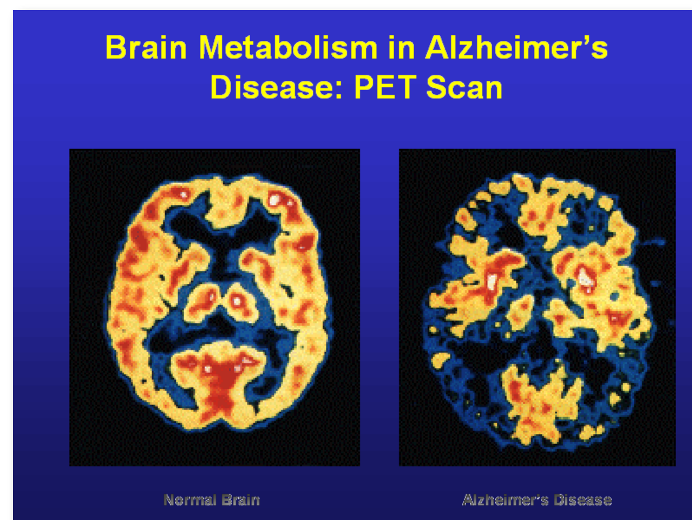
Treatment has two important goals to kill the tumour and protect the surrounding normal tissue. Therefore "seeing" in order to know where and precise "delivery" to make sure it goes where it should are key.

Detectors and art of seeing………

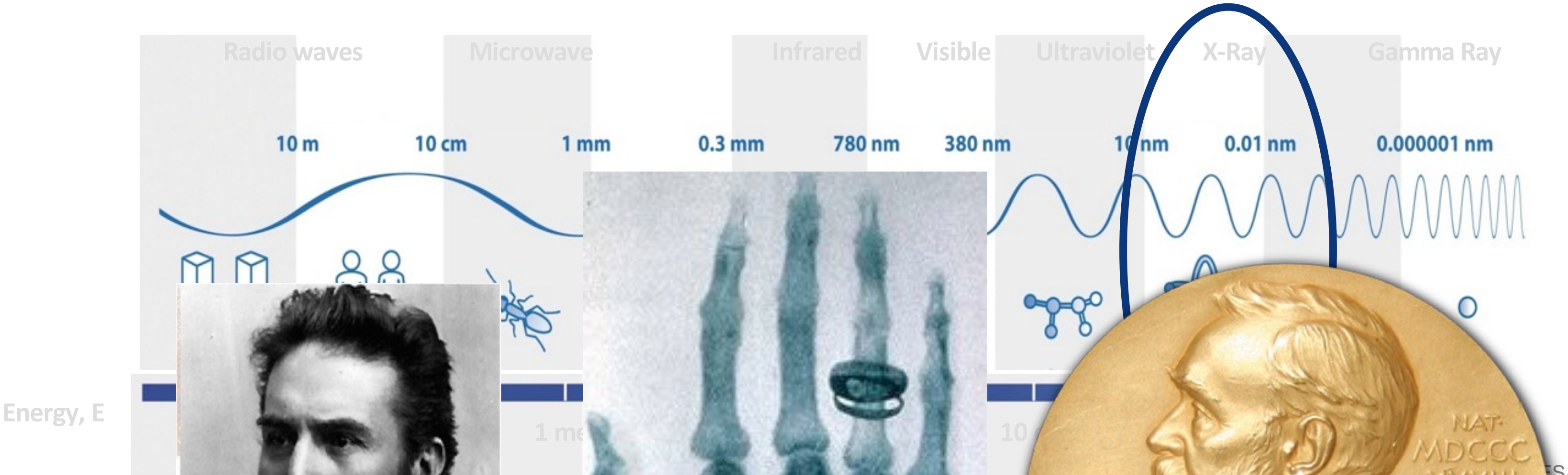
Particle Detection

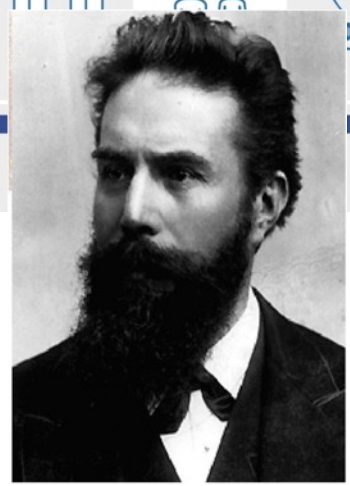
Imaging

X-ray, CT, PET, MRI



X-ray imaging





Wilhelm Röntgen

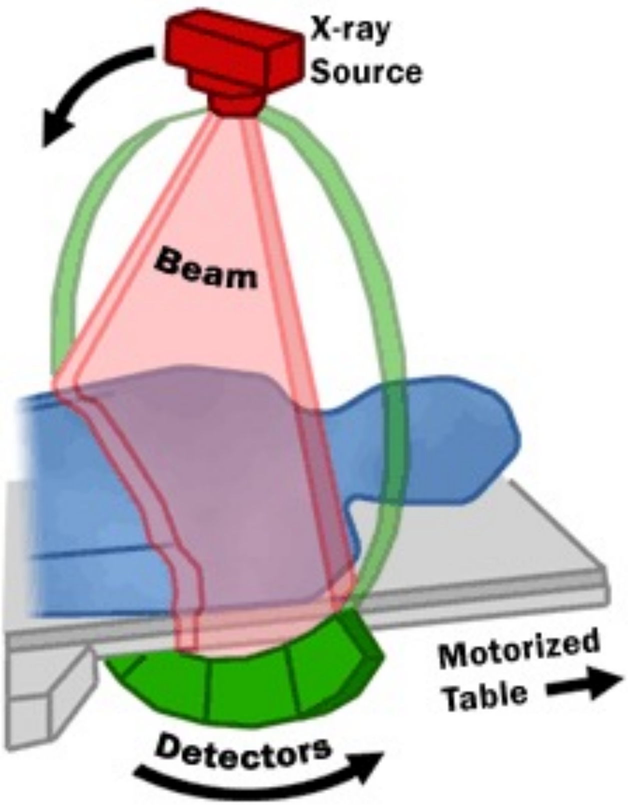
8/11/1895

22/12/1895

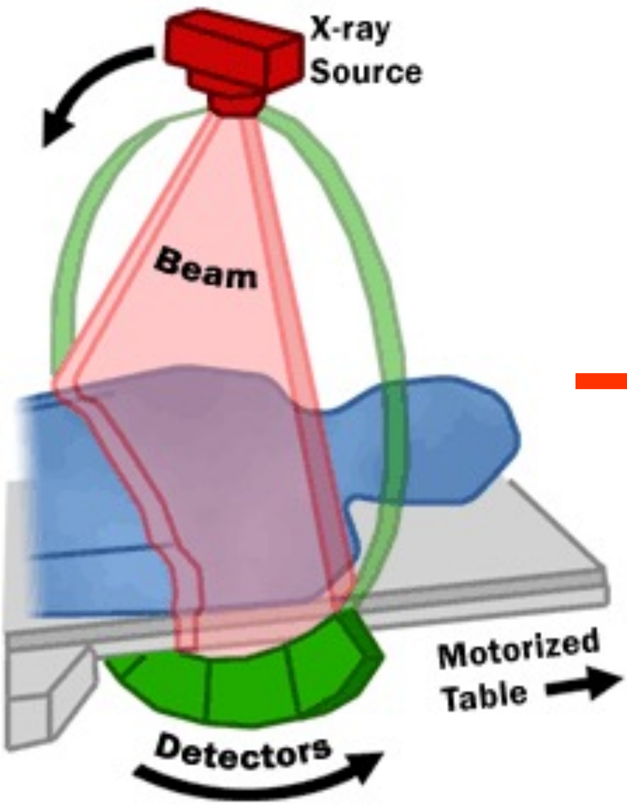
1901

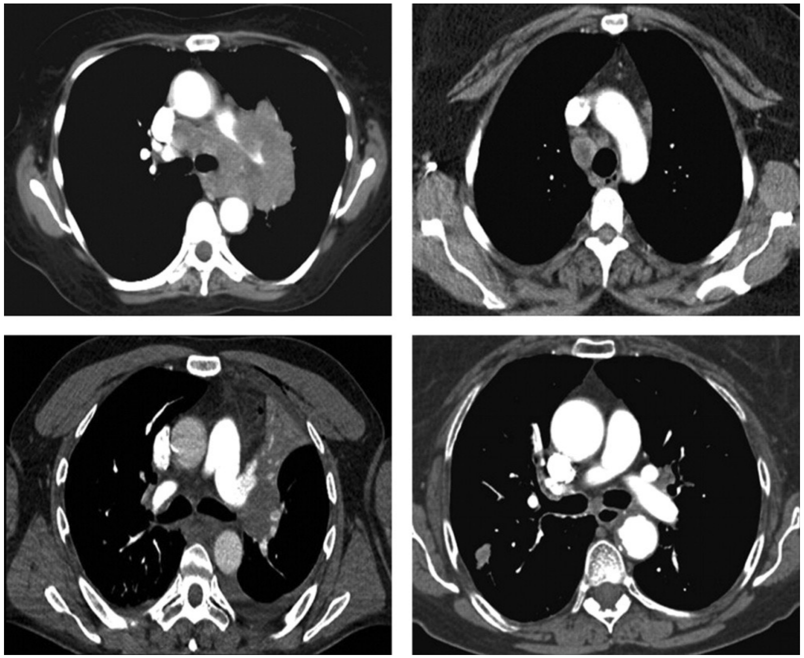
CT – Computed Tomography

3d X-rays imaging



CT – Computed Tomography



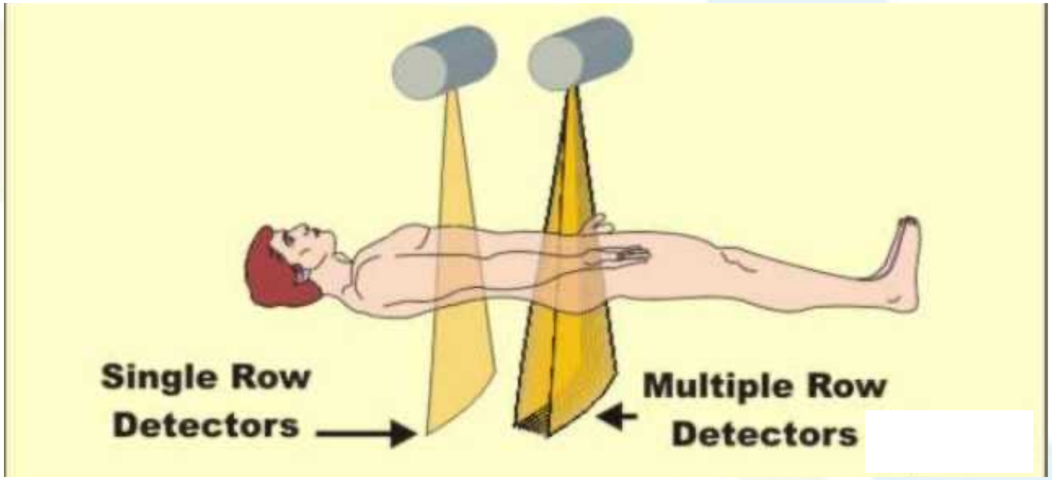


"3D-imaging"

X-ray CT is a key driver of change in medical imaging

2000-2008 “CT Slice War”

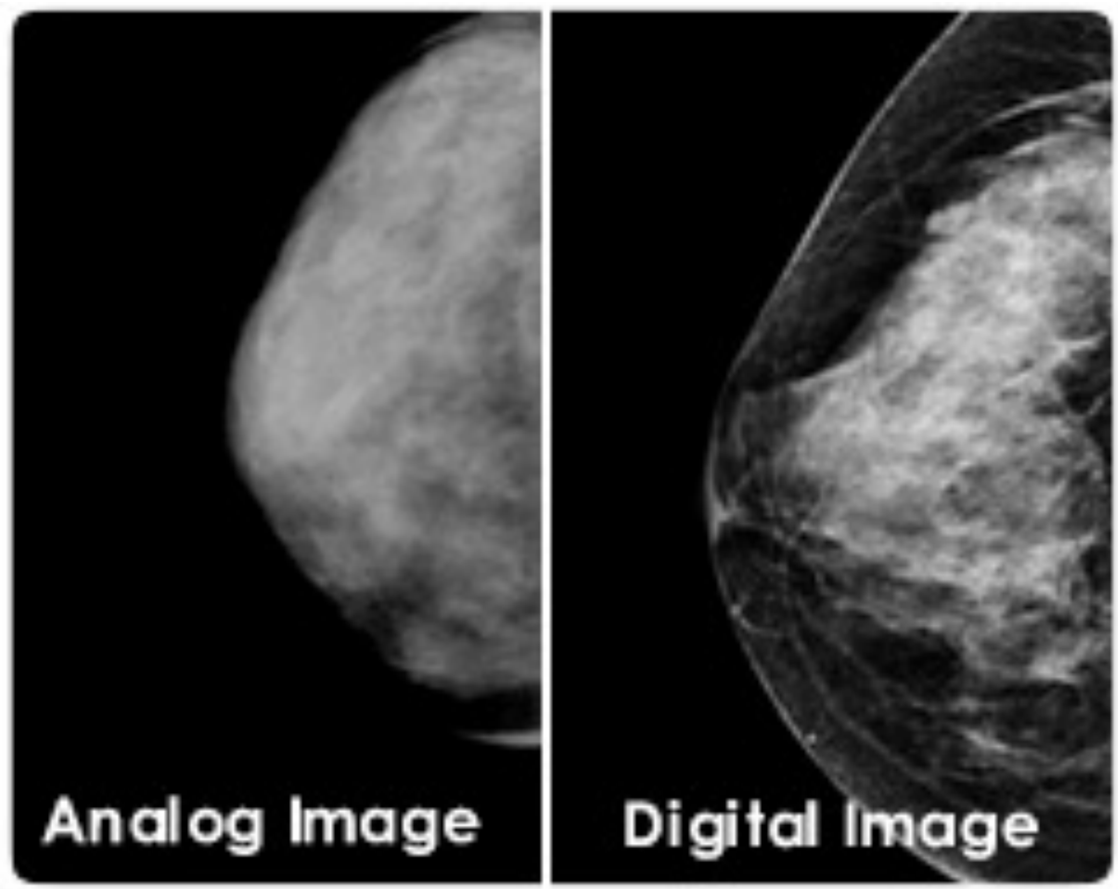
- *CT became very fast with small voxel / pixels*
  - 2000: acquire a single transverse slice per rotation
  - 2012: acquire up to 64-500 slices per rotation



Revolution in Photography

From black and white photos To Modern High-Tech photography

Towards digital colour x-ray imaging

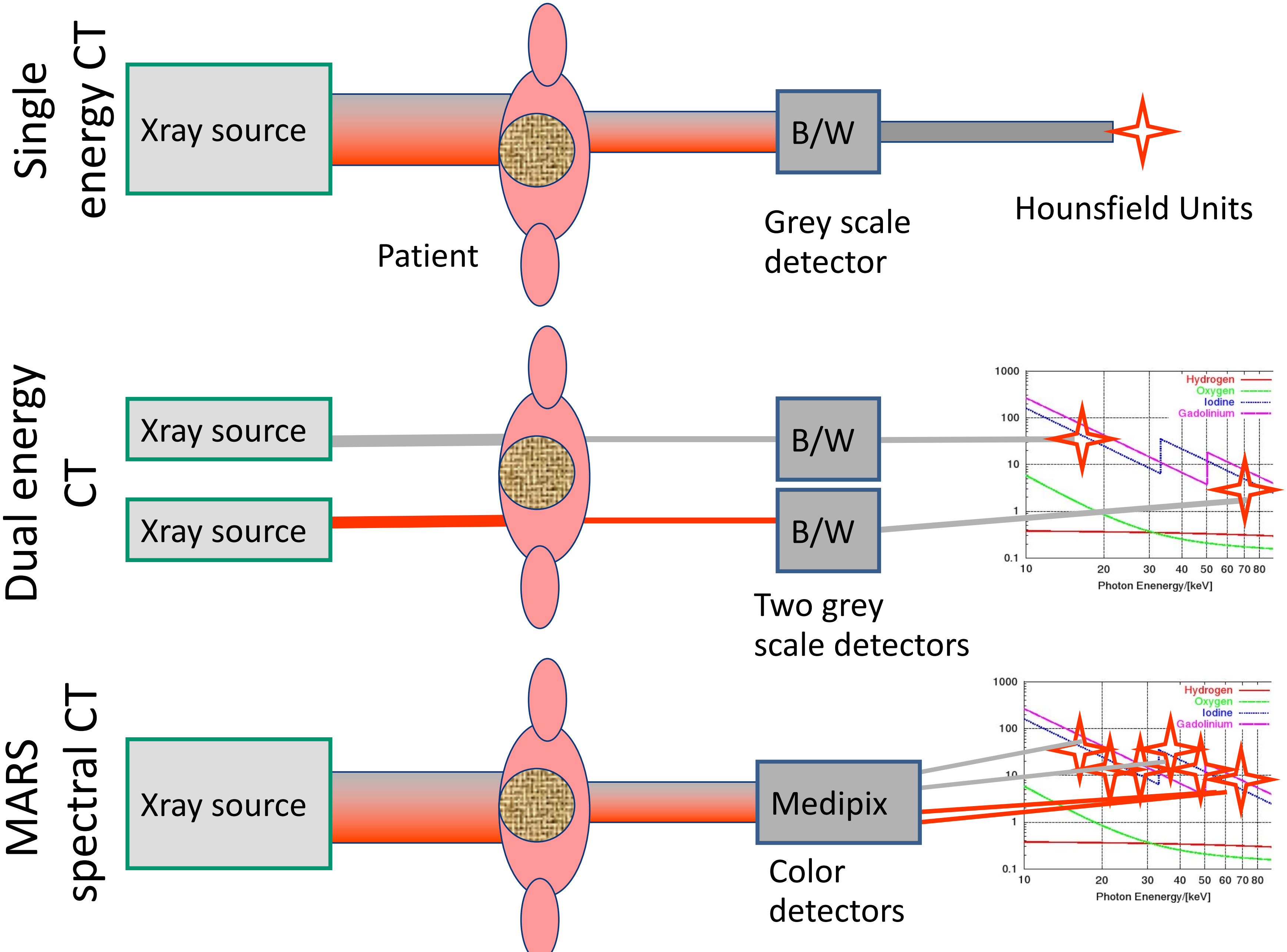


Medipix

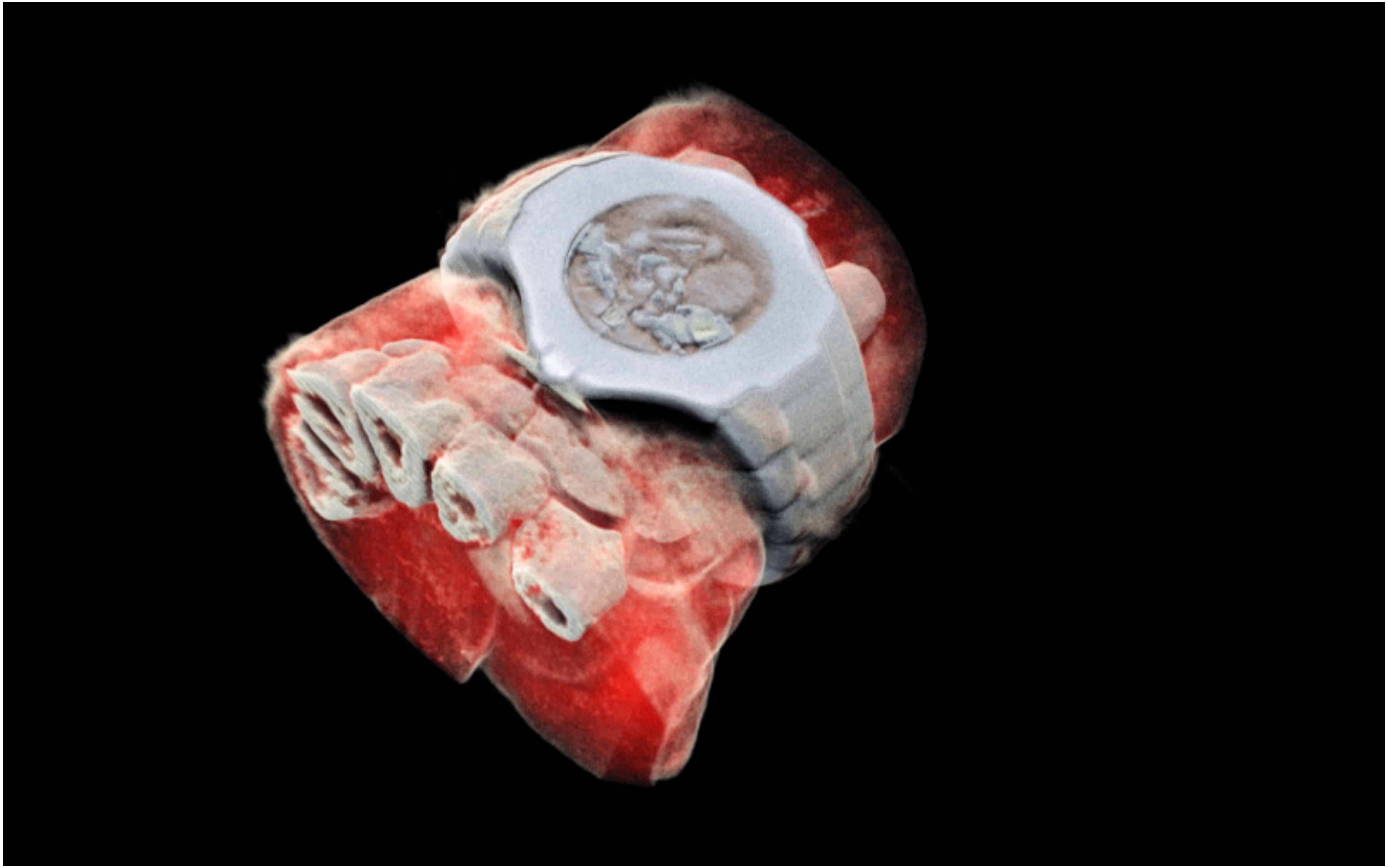
- High Energy Physics original development:
  - Particle track detectors
  - Allows counting of single photons in contrast to traditional charge integrating devices like film or CCD
- Main properties:
  - Fully digital device
  - Very high space resolution
  - Very fast photon counting
  - Good conversion efficiency of low energy X-rays

Credits: Simon Procz, University of Freiburg

Single- , dual-, and spectral CT



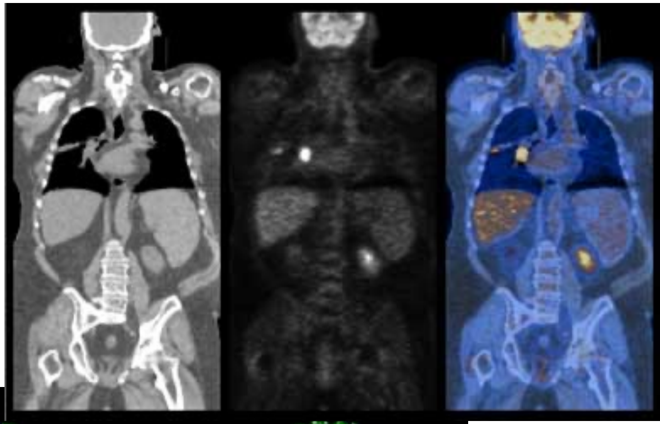
First 3D human colour x-ray image



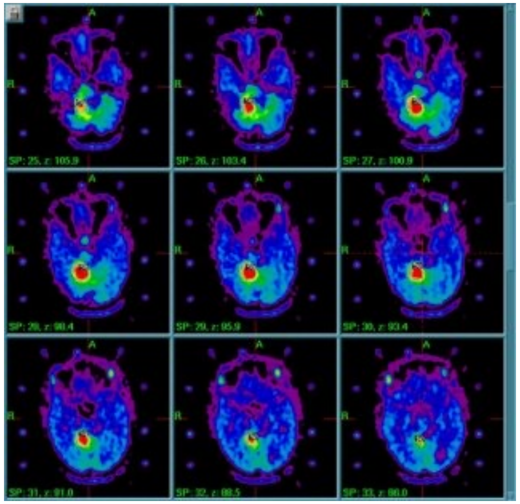
A 3D image of a wrist with a watch showing part of the finger bones in white and soft tissue in red. couples the spectroscopic information generated by the Medipix3 with powerful algorithms to generate 3D images (Image: MARS Bioimaging Ltd)

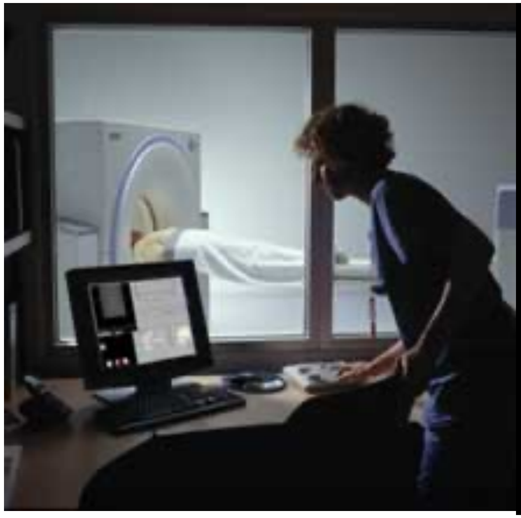
PET: antimatter for clinical use

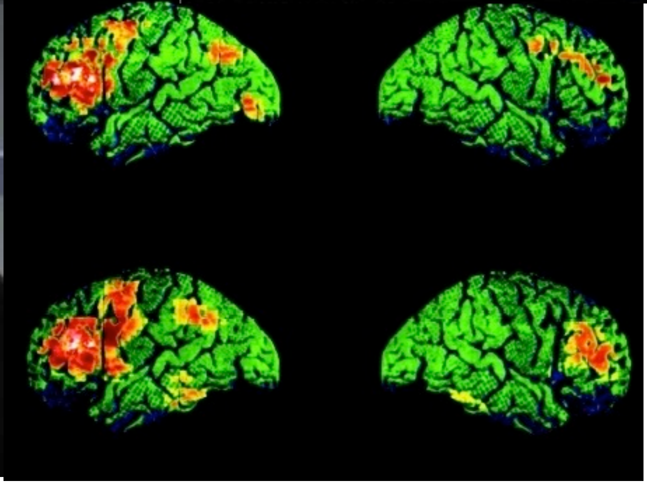
- Not only science-fiction



- Positrons are used in PET:
- PET = Positron Emission Tomography



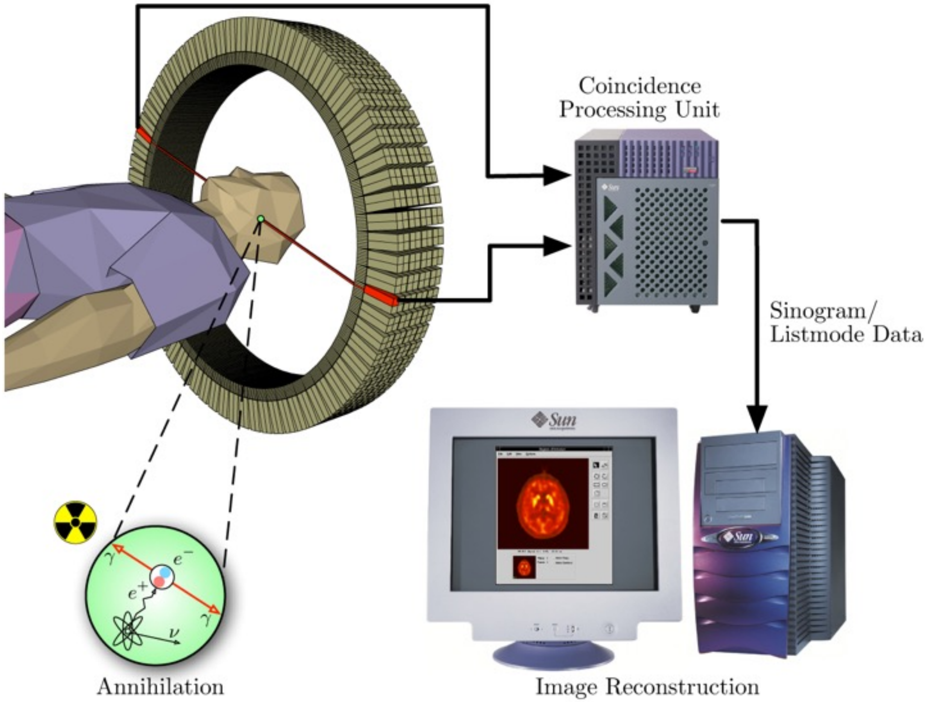


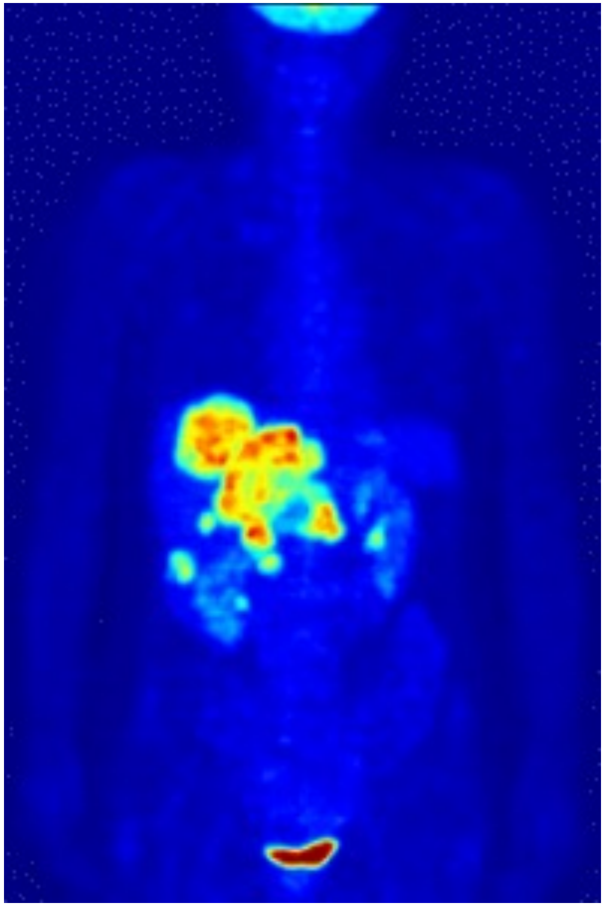


PET – How it works

http://www.nymus3d.nl/portfolio/animation/55

Positron Emission Tomography



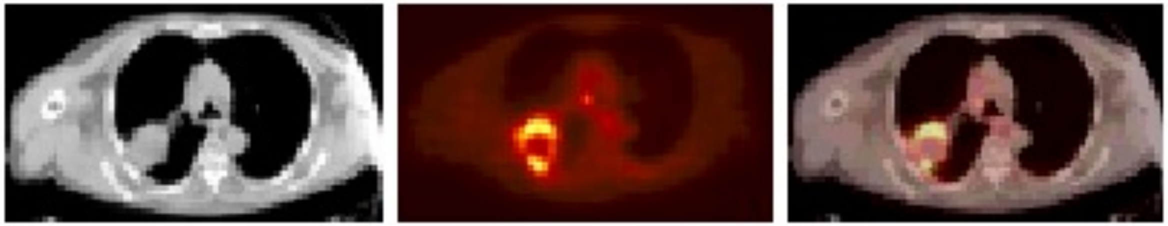


- ^{18}FDG carries the ^{18}F to areas of high metabolic activity
- 90% of PET scans are in clinical oncology

1974 the first human positron emission tomography

Multi-modality imaging

Primary lung cancer imaged with the Dual/Commercial scanner. A large lung tumor, which appears on CT as a uniformly attenuating hypodense mass, has a rim of FDG activity and a necrotic center revealed by PET.

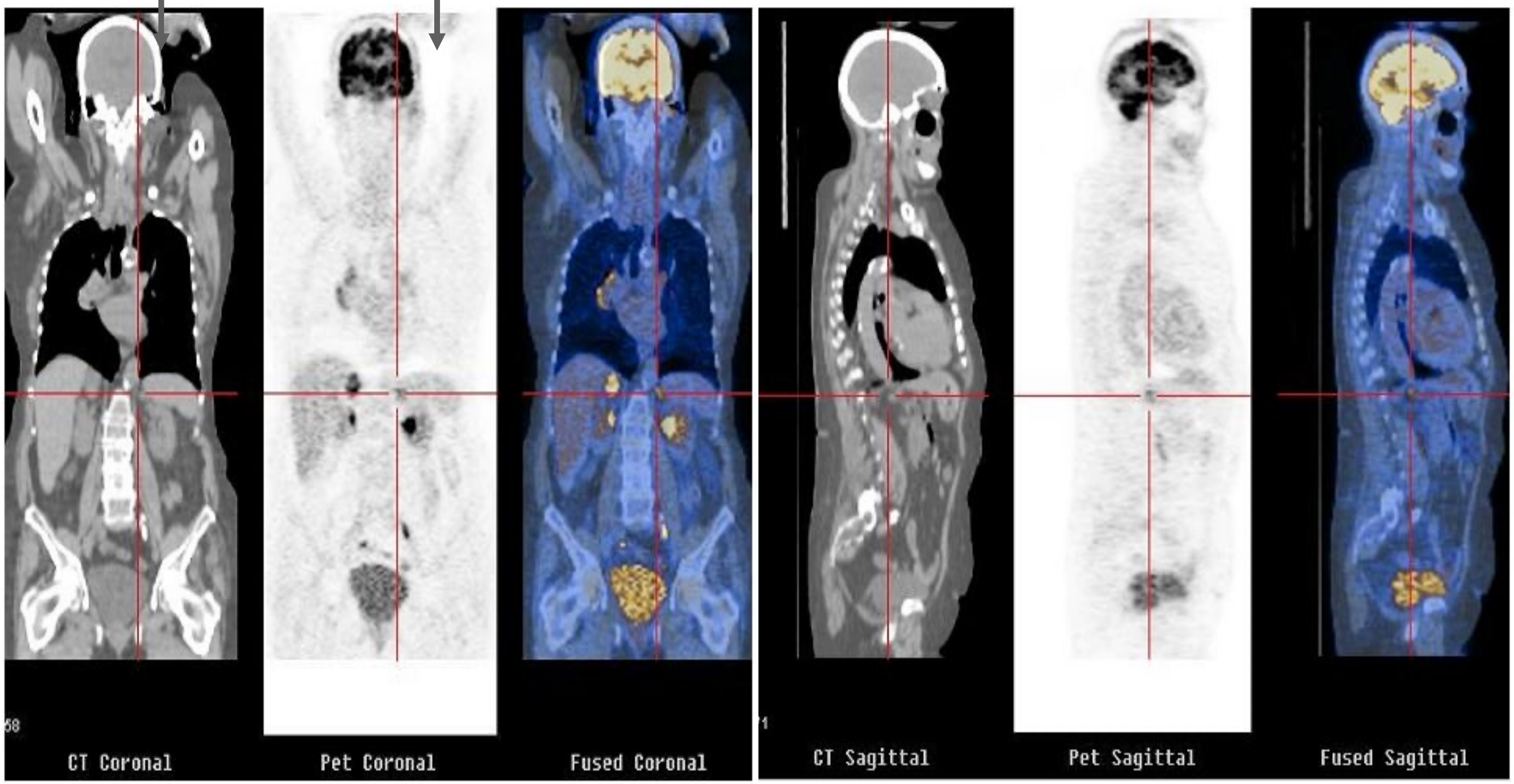


Courtesy of David Townsend

Multimodality imaging: CT with PET

Combining anatomic and functional imaging

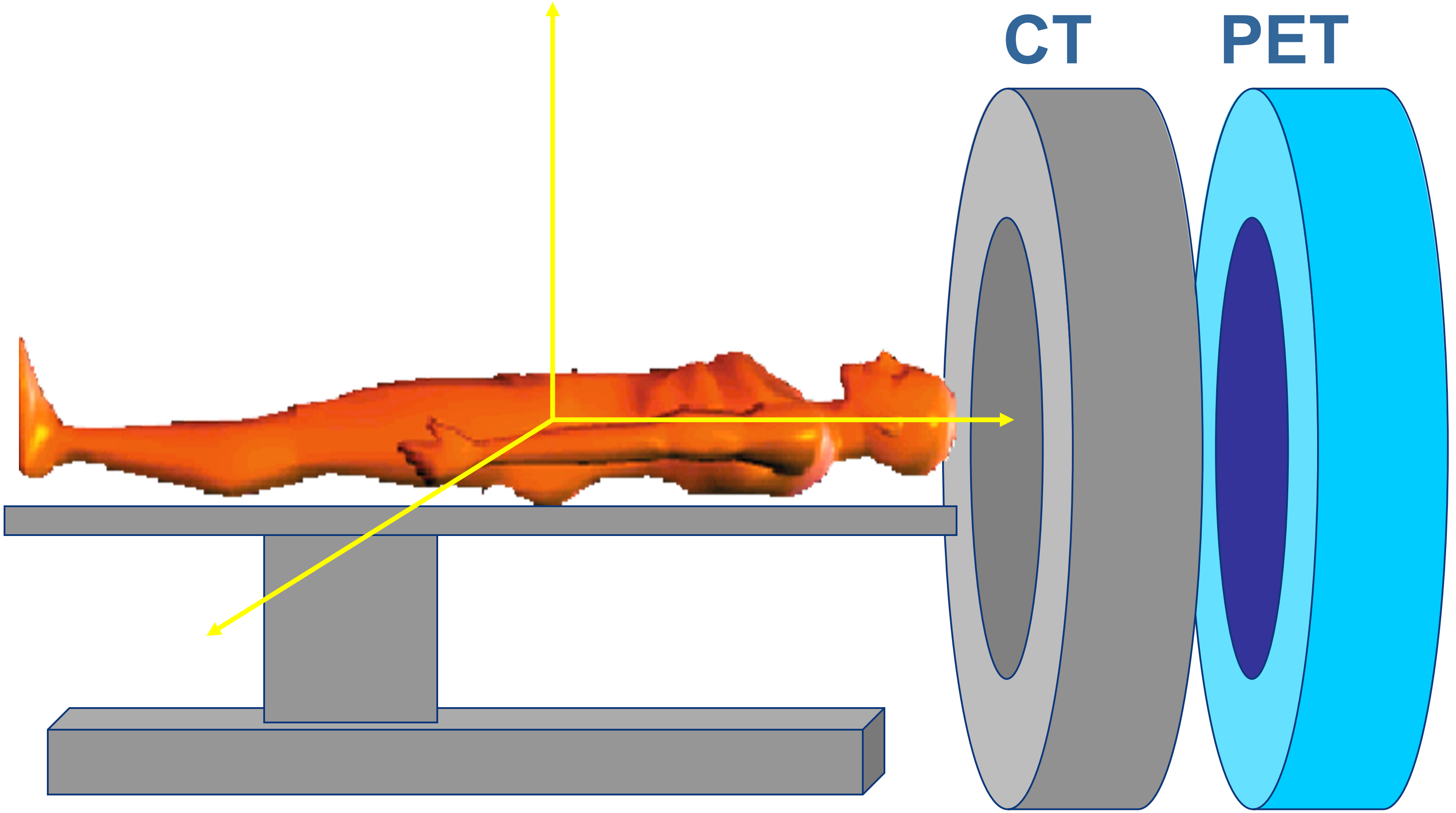
morphology metabolism



David Townsend, UK Physicist

Concept of PET-CT

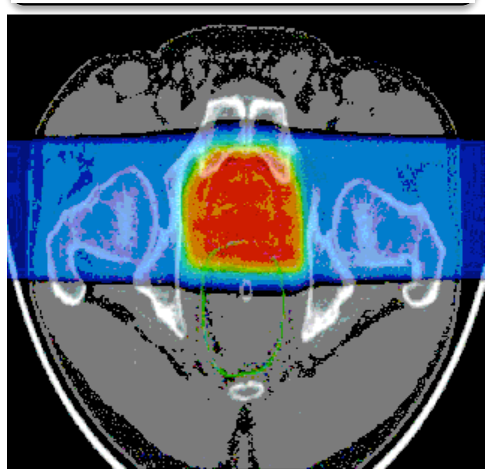
David Townsend



Treatment options

Surgery

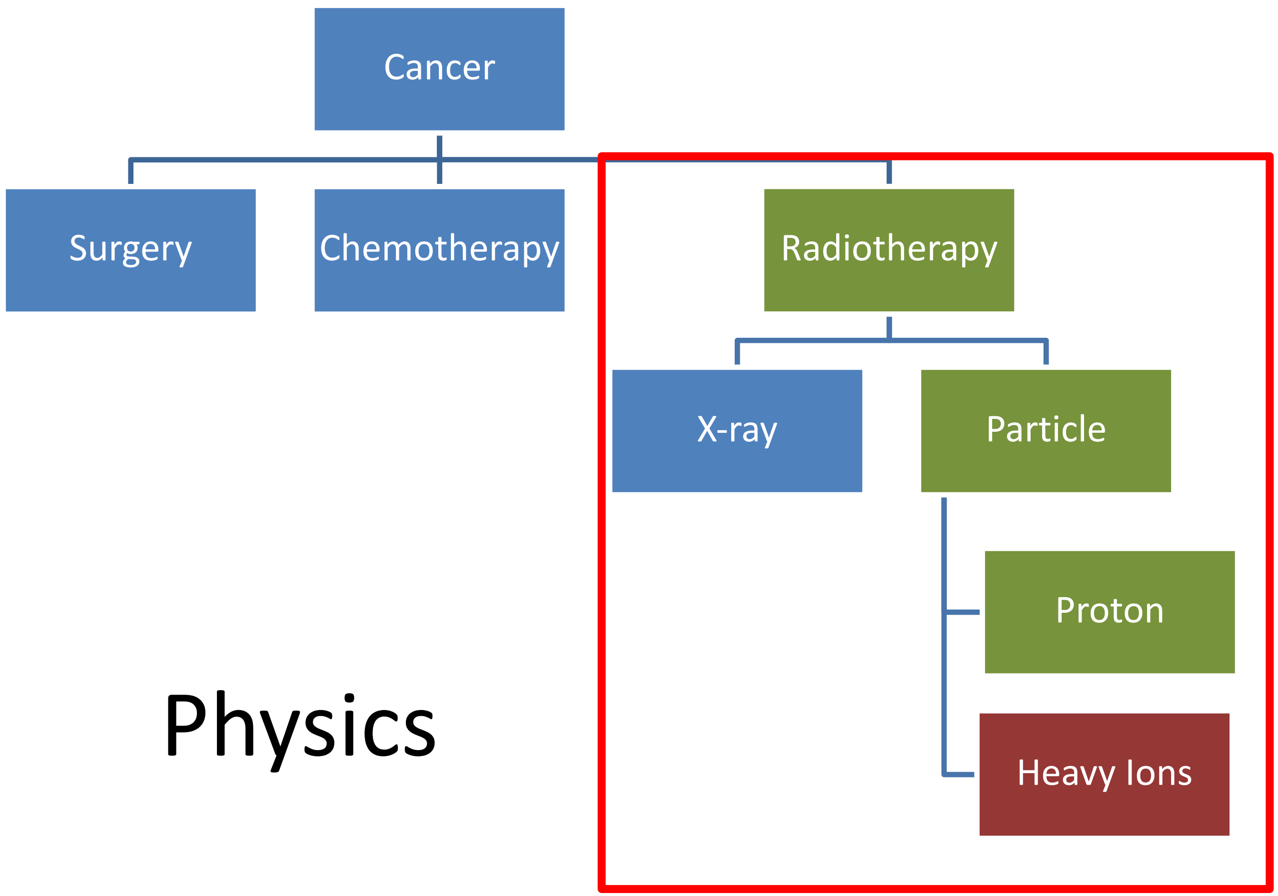
Radiotherapy



Chemotherapy (+ others)

AIM:
Survival, Quality of life

Cancer treatment options



Physics

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)

(J.P.Gérard)

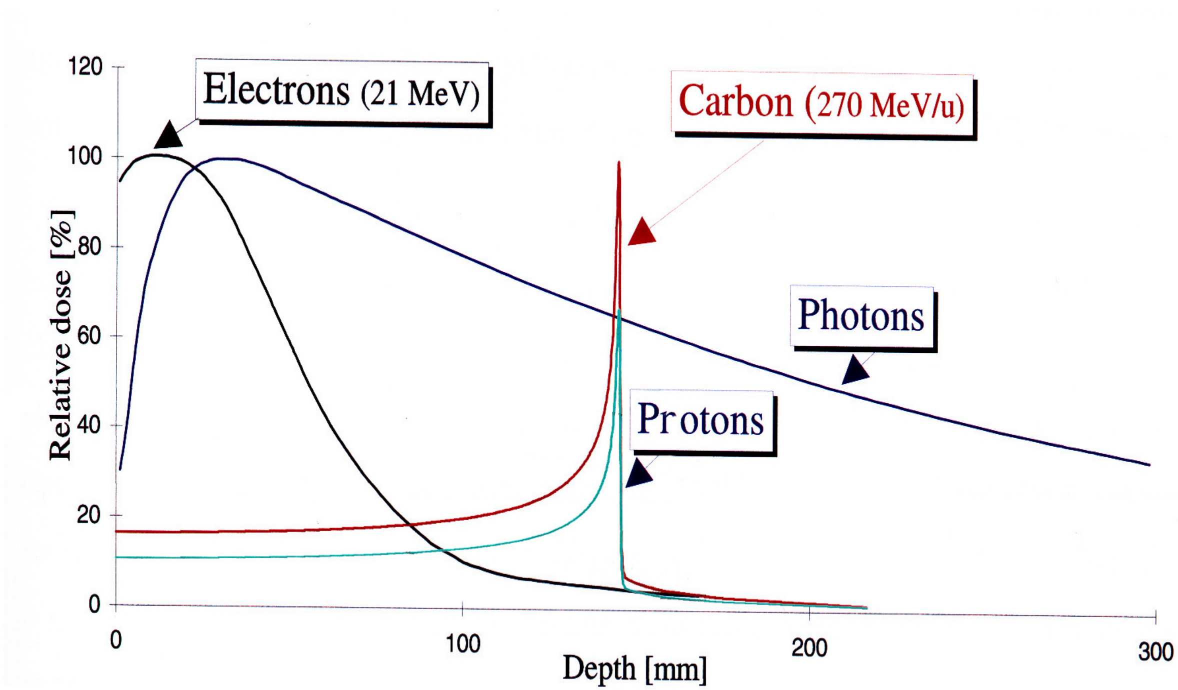
- About 50% patients are treated with RT
- No substitute for RT in the near future
- No of patients is increasing

Aims of Radiotherapy:

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

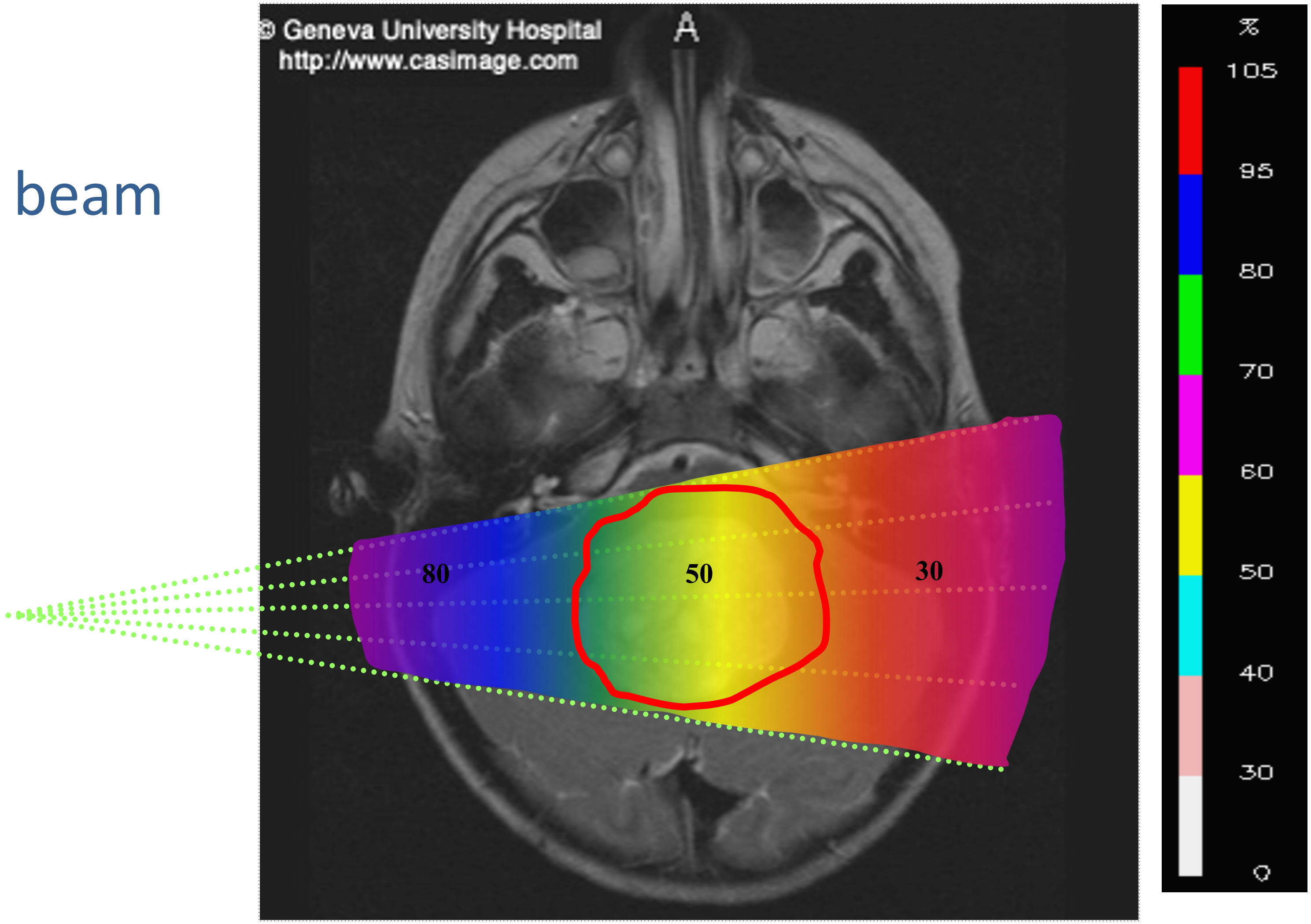
Current radiotherapy methods:

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



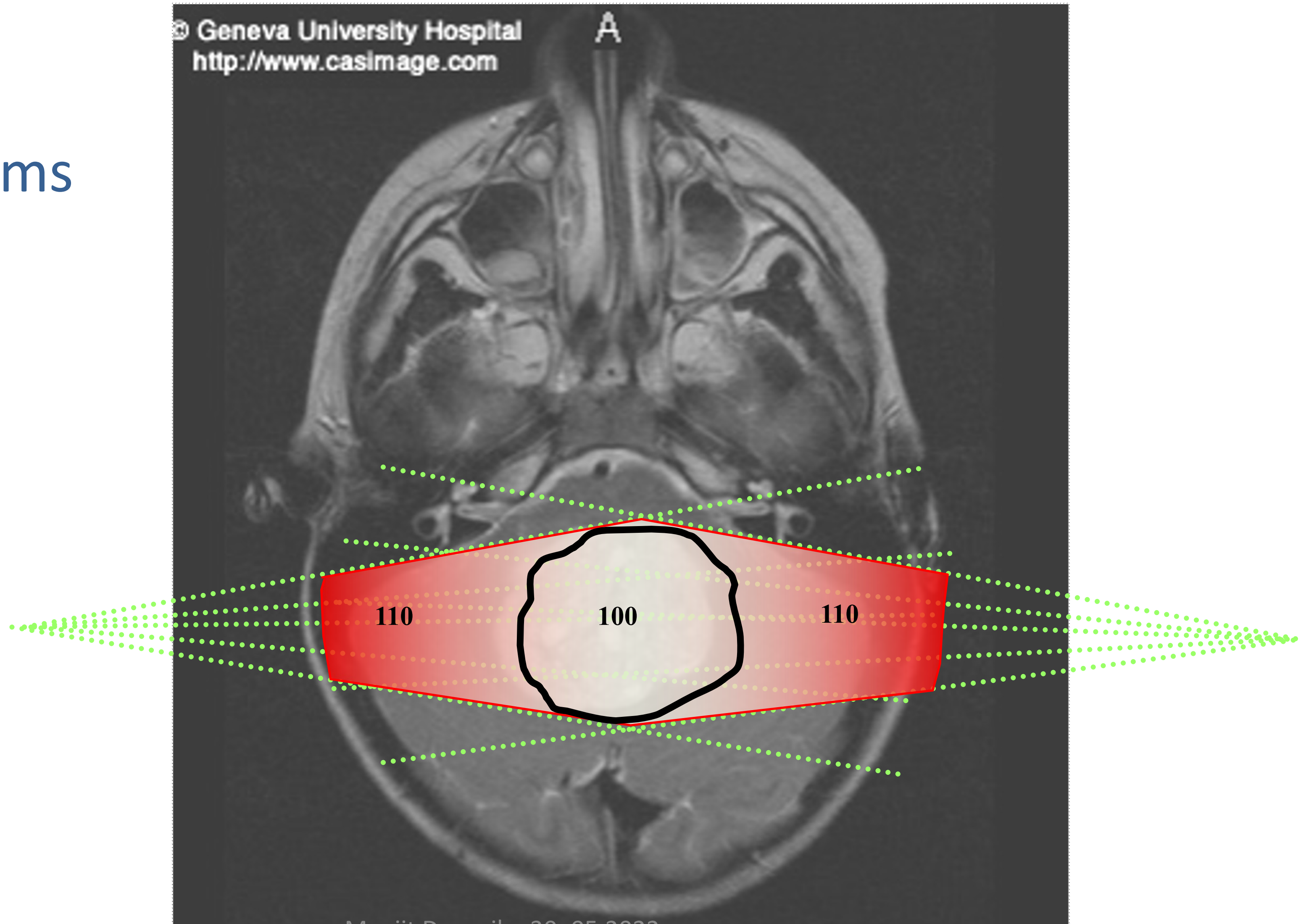
Classical Radiotherapy with X-rays

single beam

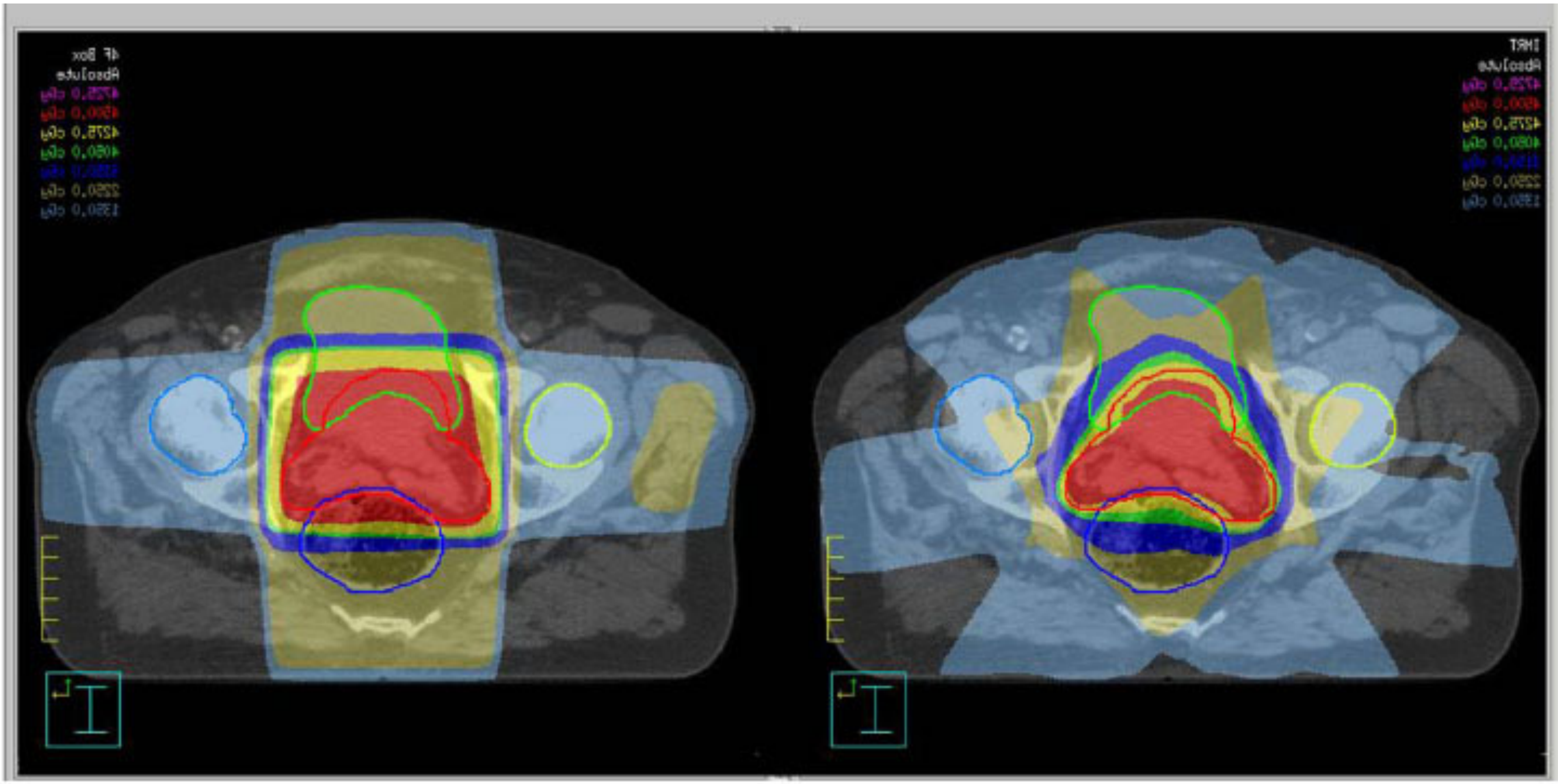


Radiotherapy with X-rays

two beams



Improved Delivery

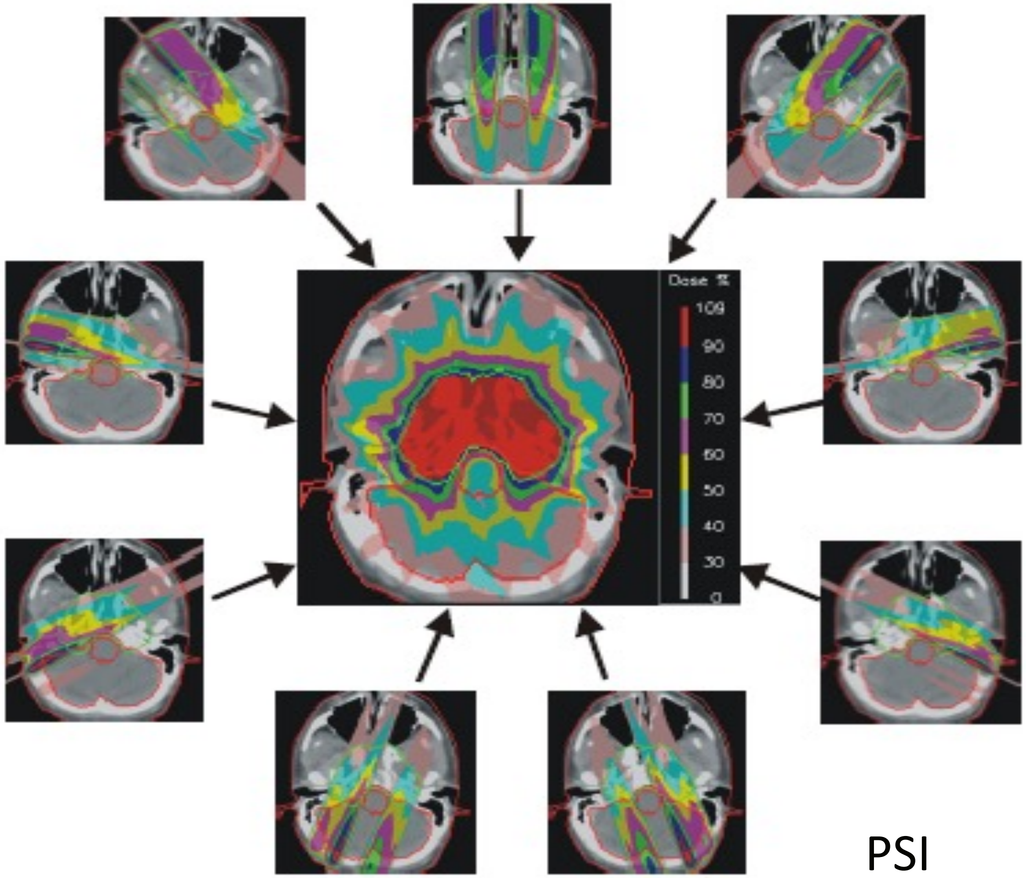


1990s: 4 constant intensity fields

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

Intensity Modulated Radiation Therapy

9 NON-UNIFORM FIELDS



PSI

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

to allow healthy tissues to repair:

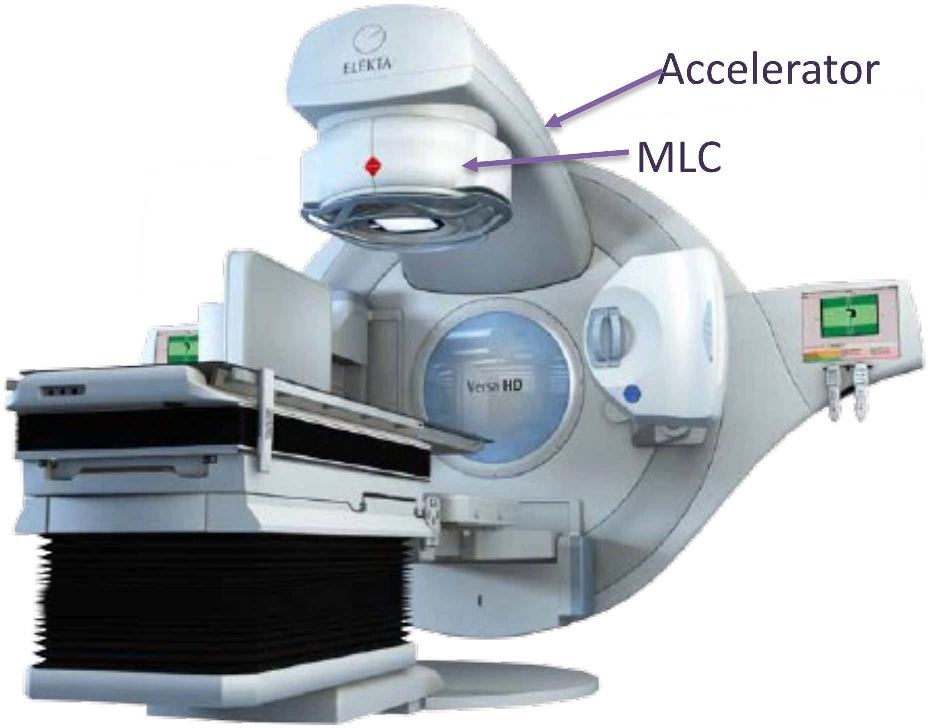
90% of the tumours are <u>radiosensitive</u>

Ugo Amaldi, TERA

The most widely available accelerator

Electron Linac (linear accelerator) for radiation therapy treatment of cancer)

More than 10,000 in use



Widely available in all major hospitals in, specially in high income countries (HIC)

Advances in Radiation Therapy

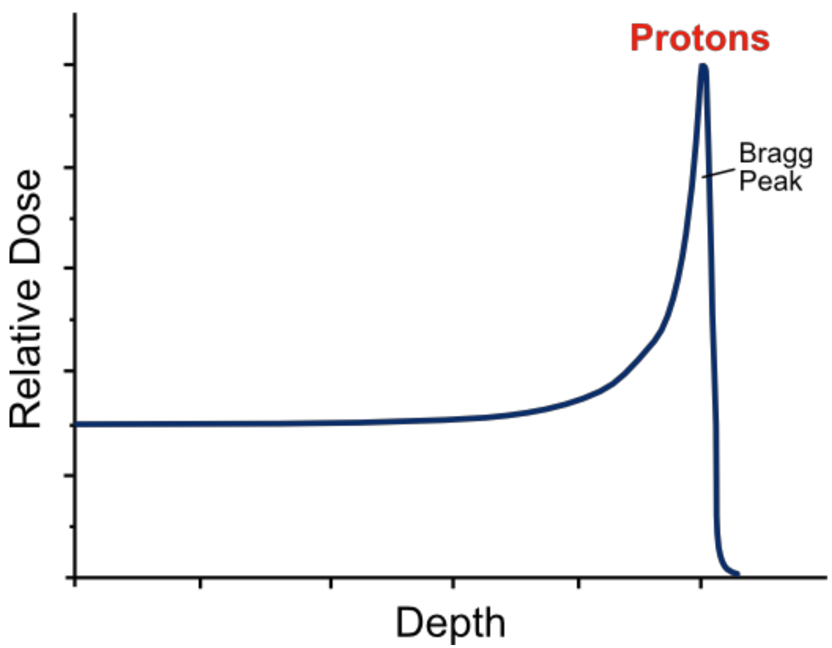
In the past two decades due to:

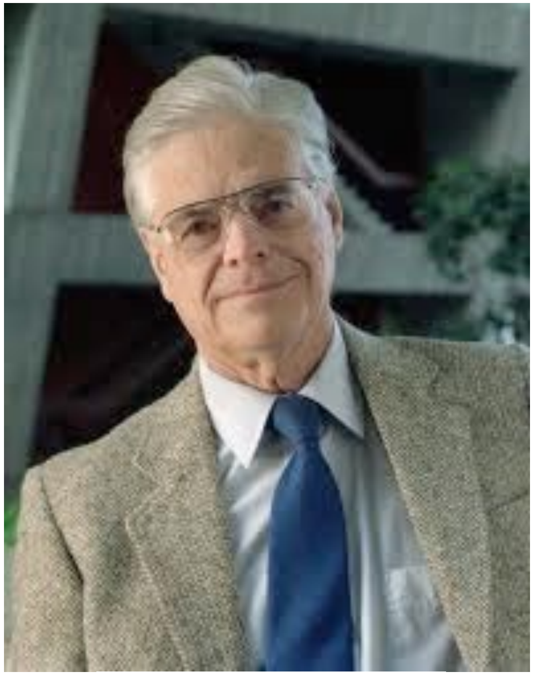
- improvements in imaging modalities, multimodality
- technology, powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
  - MRI-guided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

Why Hadron Therapy?

- 1946: Robert Wilson

  Protons can be used clinically





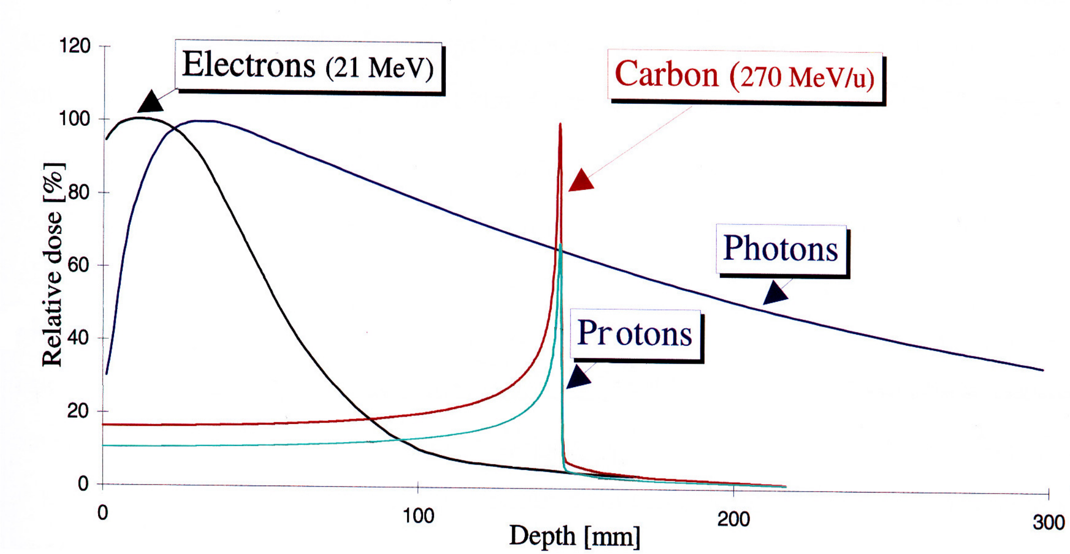
Robert Wilson

Hadron Therapy

In 1946 Robert Wilson:

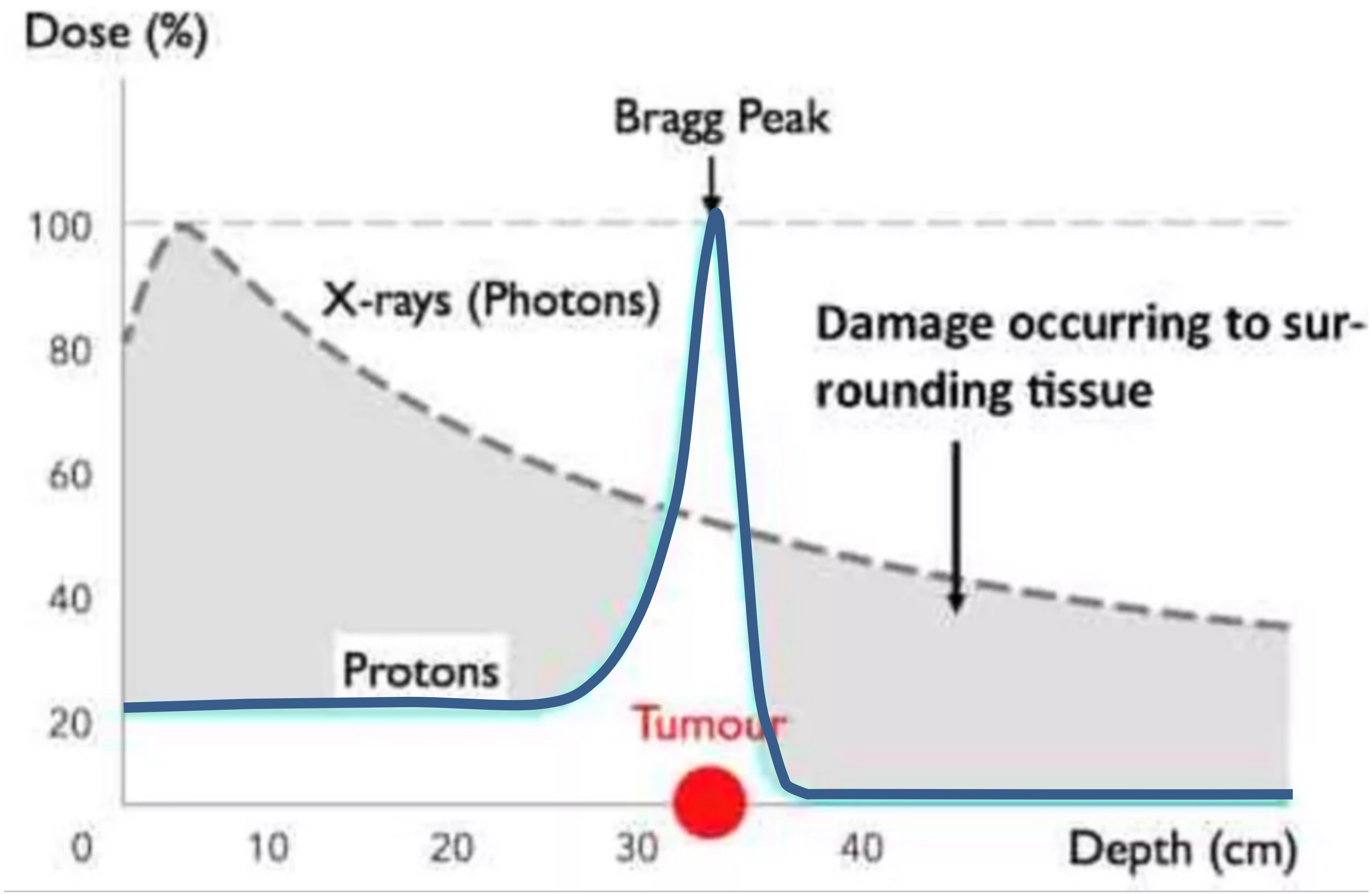
- **Protons can be used clinically**
- **Accelerators are available**
- **Maximum radiation dose can be placed into the tumour**
- **Particle therapy provides sparing of normal tissues**

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

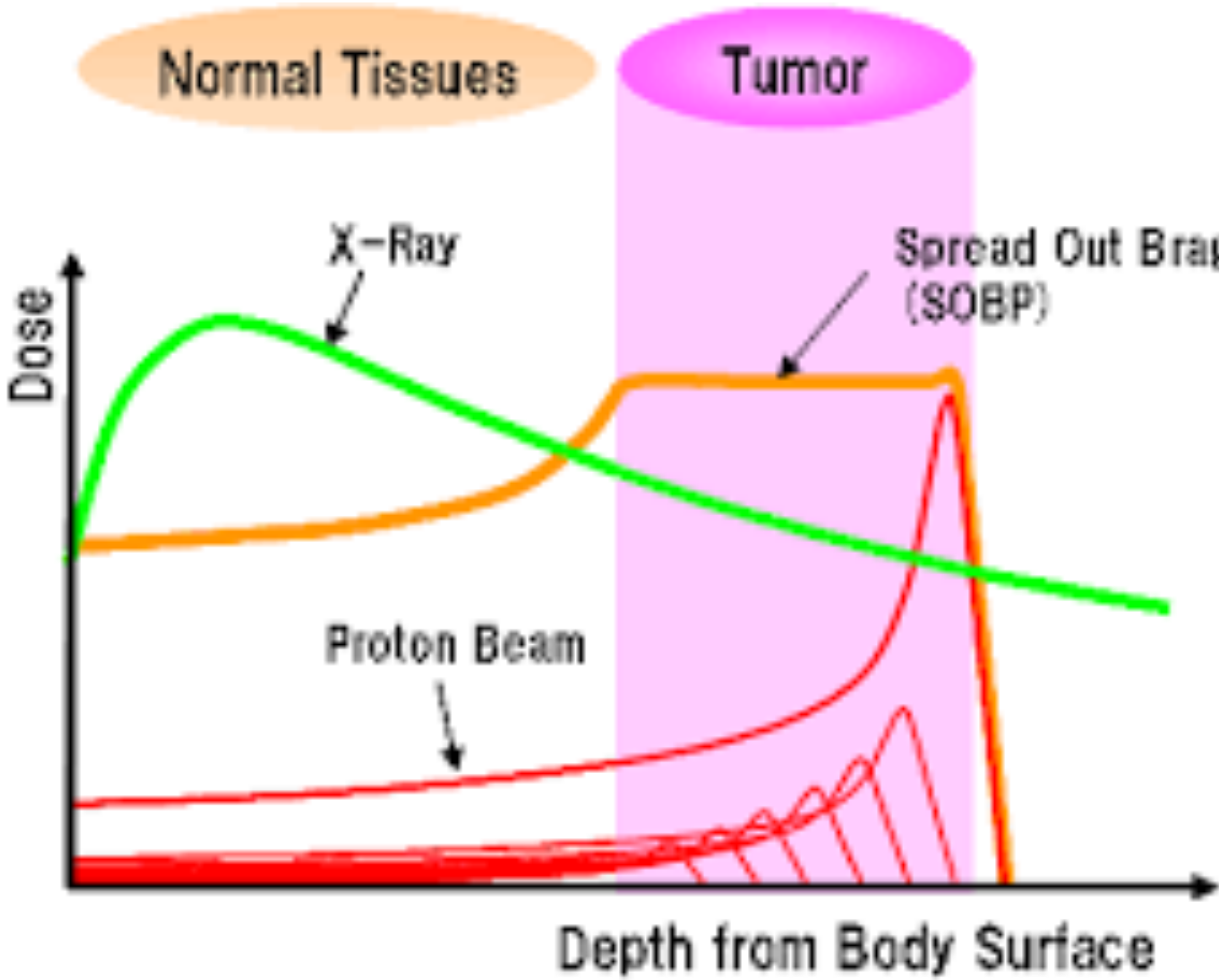


Depth in the body (mm)

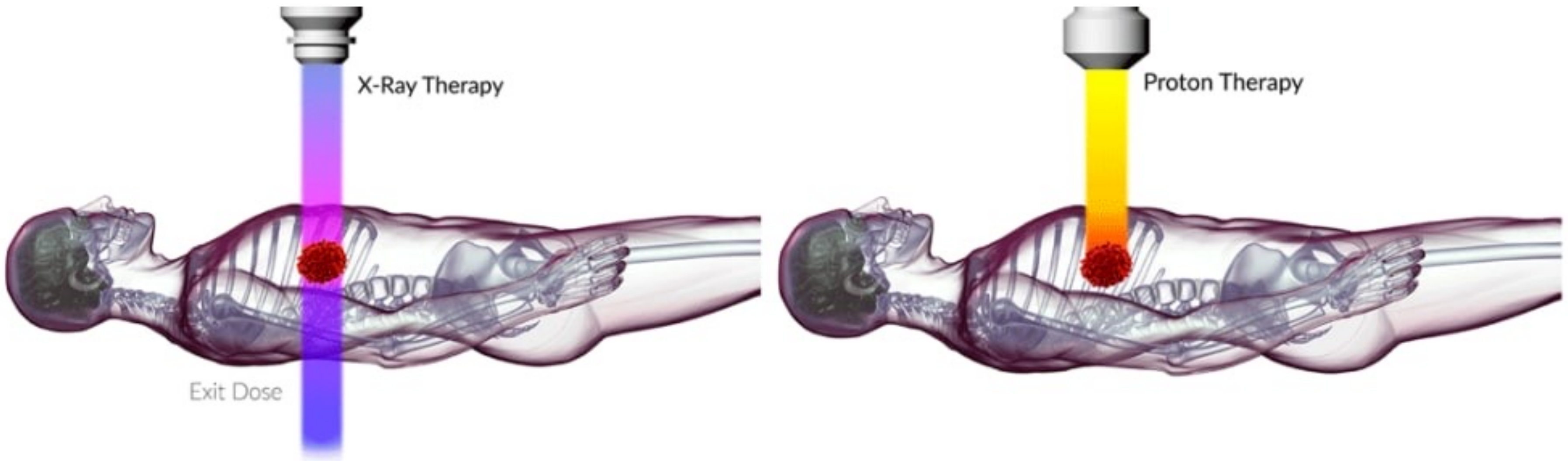
Photons vs. protons



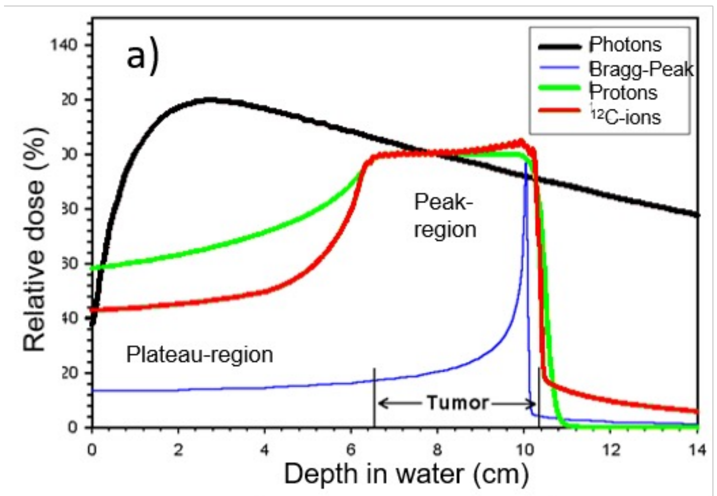
Spread Out Bragg-peak targeting the **tumour**

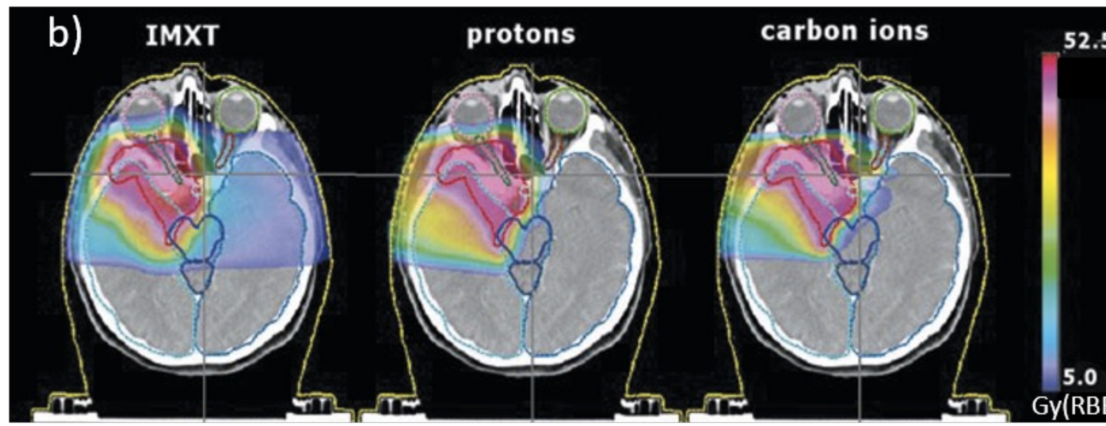


RT vs. PT in human body



Why Particle/Hadron Therapy?



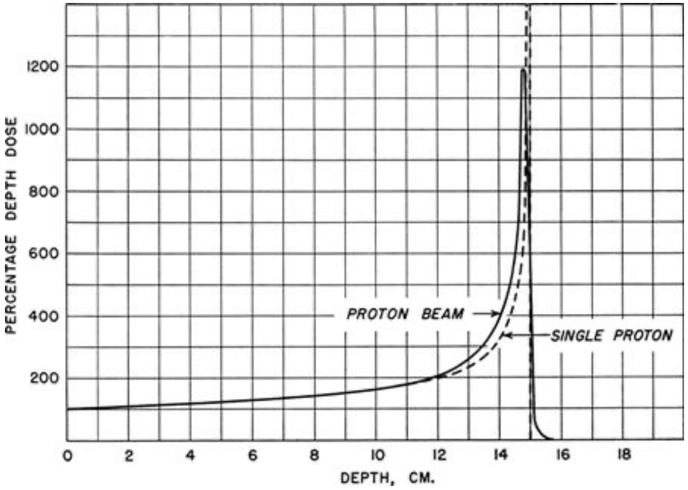


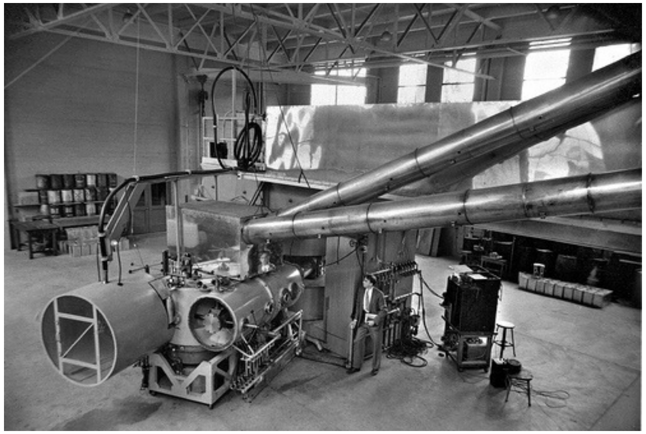
Depth dose profiles in water (a) and treatment plans (b) comparing photons, delivered with the most advanced intensity modulation RT (IMXT), and state-of-the-art scanned protons and ^{12}C ions, showing the increased tumour-dose conformity of ion therapy due to the characteristic Bragg peak (a).

1932 - E. Lawrence First cyclotron

1946 – proton therapy proposed by R. Wilson

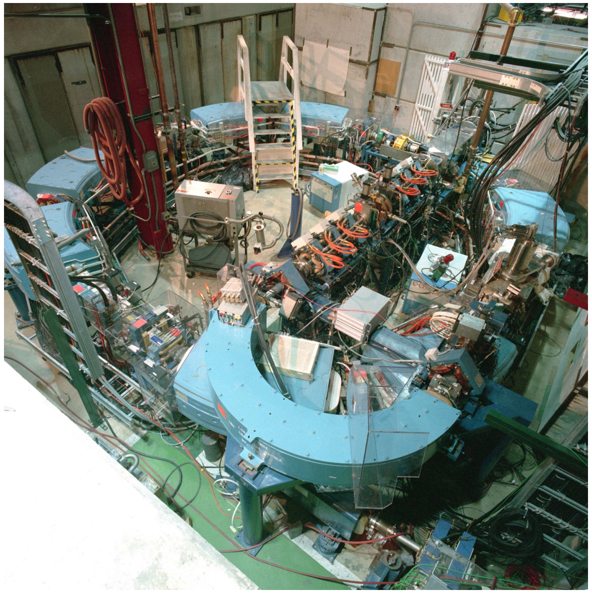
1954 – Berkeley treats the first patient





From physics……..

1993- Loma Linda
USA (proton)



First dedicated clinical facility

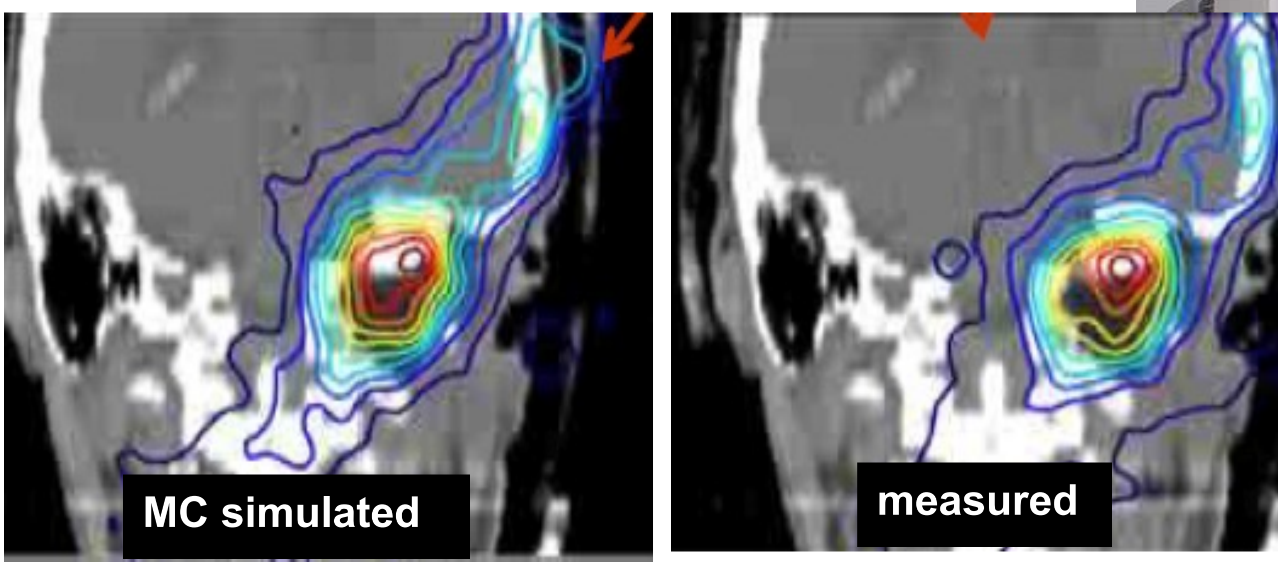
1994 – HIMAC/NIRS
Japan (carbon)

1997 – GSI
Germany (carbon)

Three crucial years for PT........to clinics

Real-time monitoring

- In-beam PET @ GSI (Germany)
- MonteCarlo simulations
- Organ motion



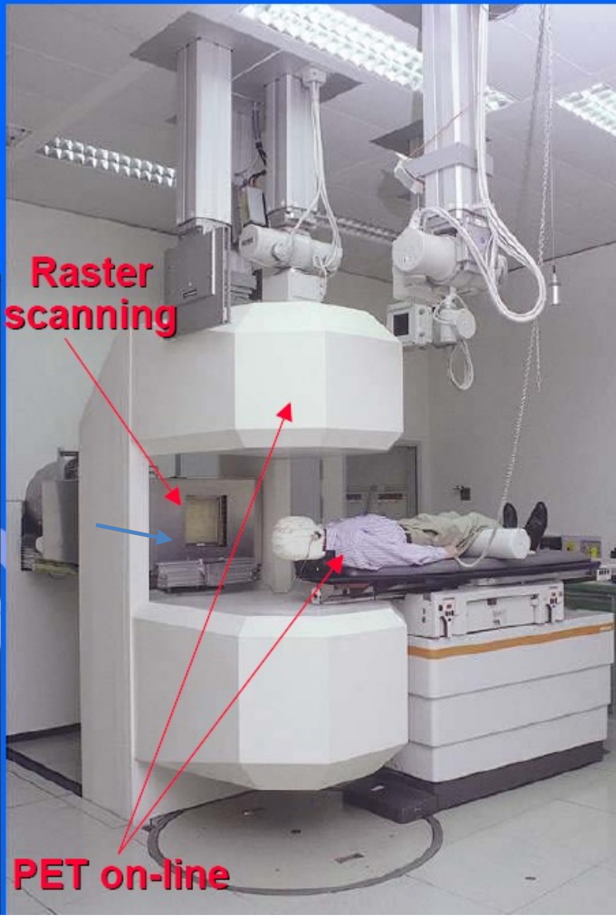
The Darmstadt GSI ‘pilot project’ (1997-2008)

G. Kraft

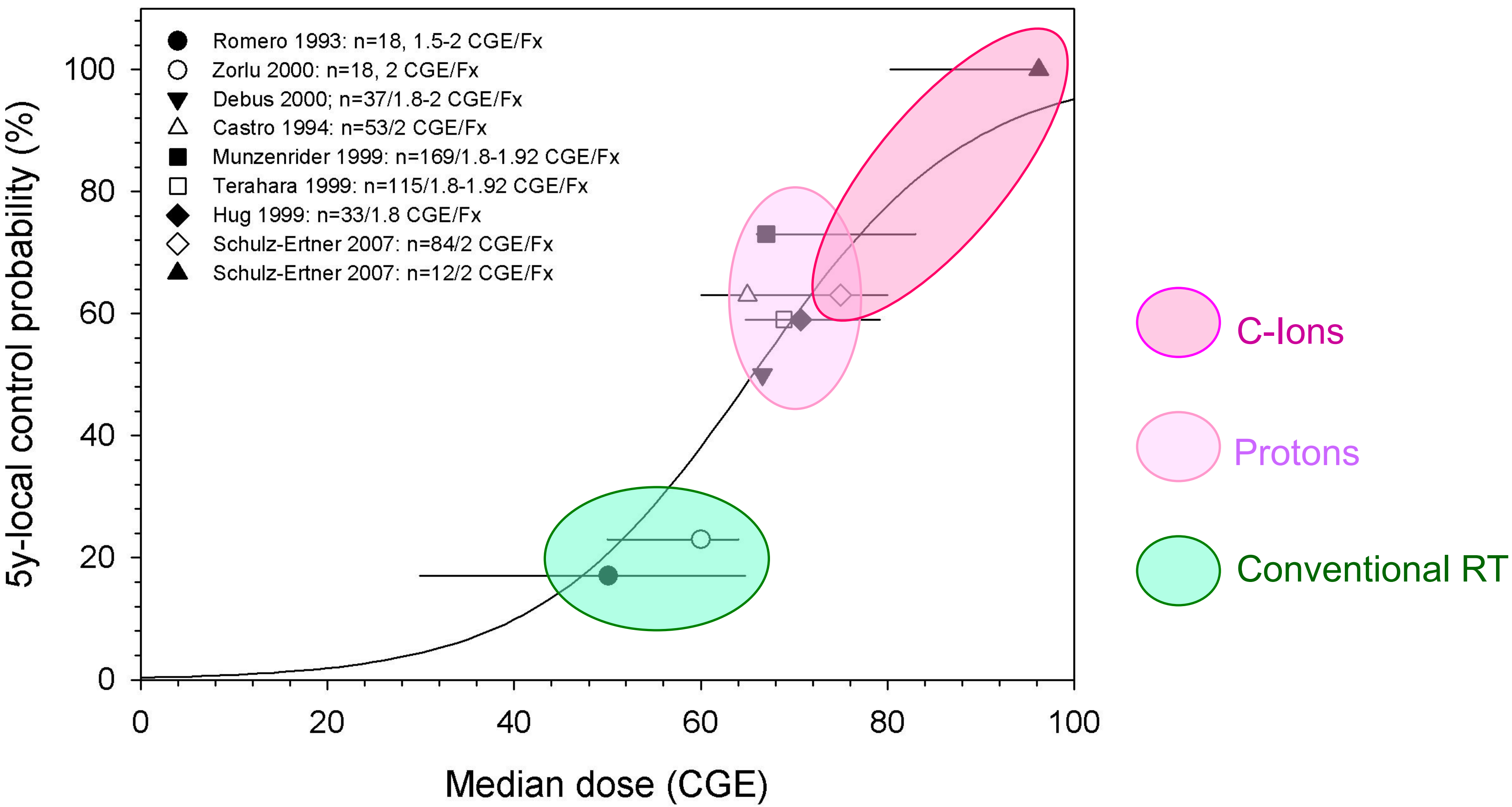
J. Debus

G. Kraft

450 patients treated
with carbon ions
J. Debus (Heidelberg Univ.)



Tumour Control Rate: Chordomas



Schulz-Ertner, IJROBP 2007

Radiotherapy in 21st Century

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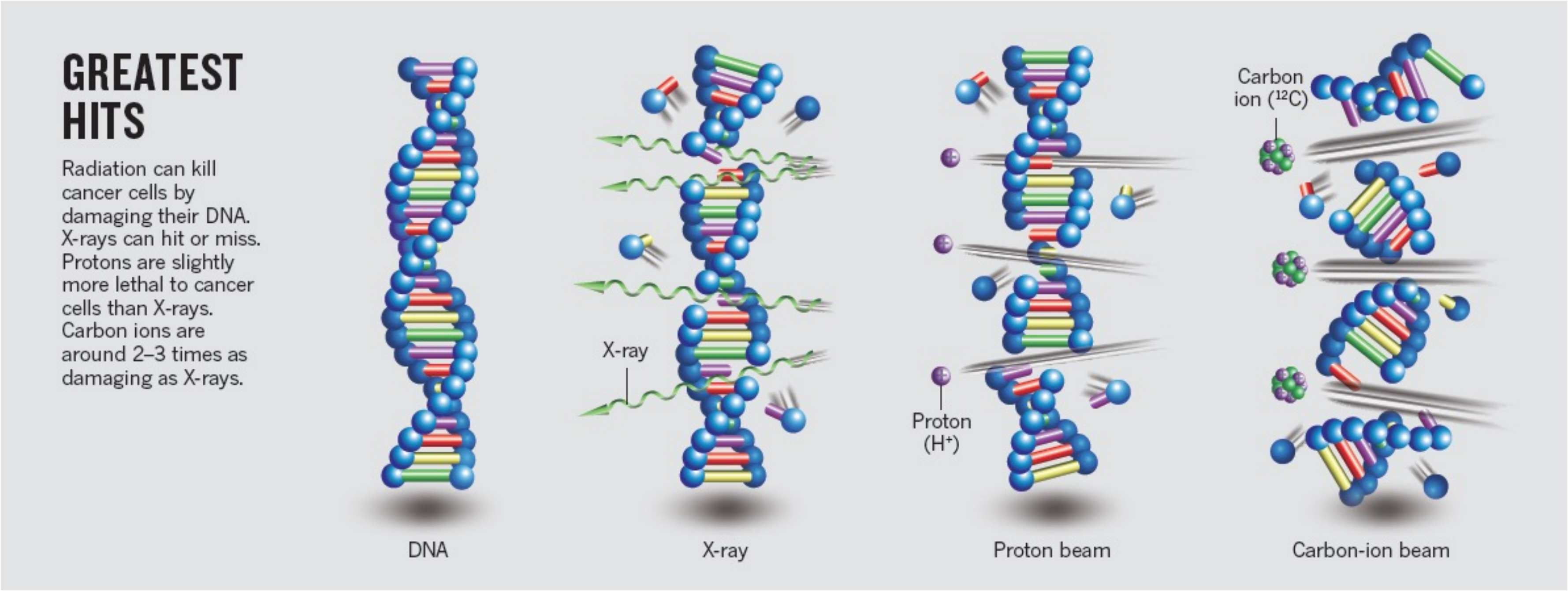
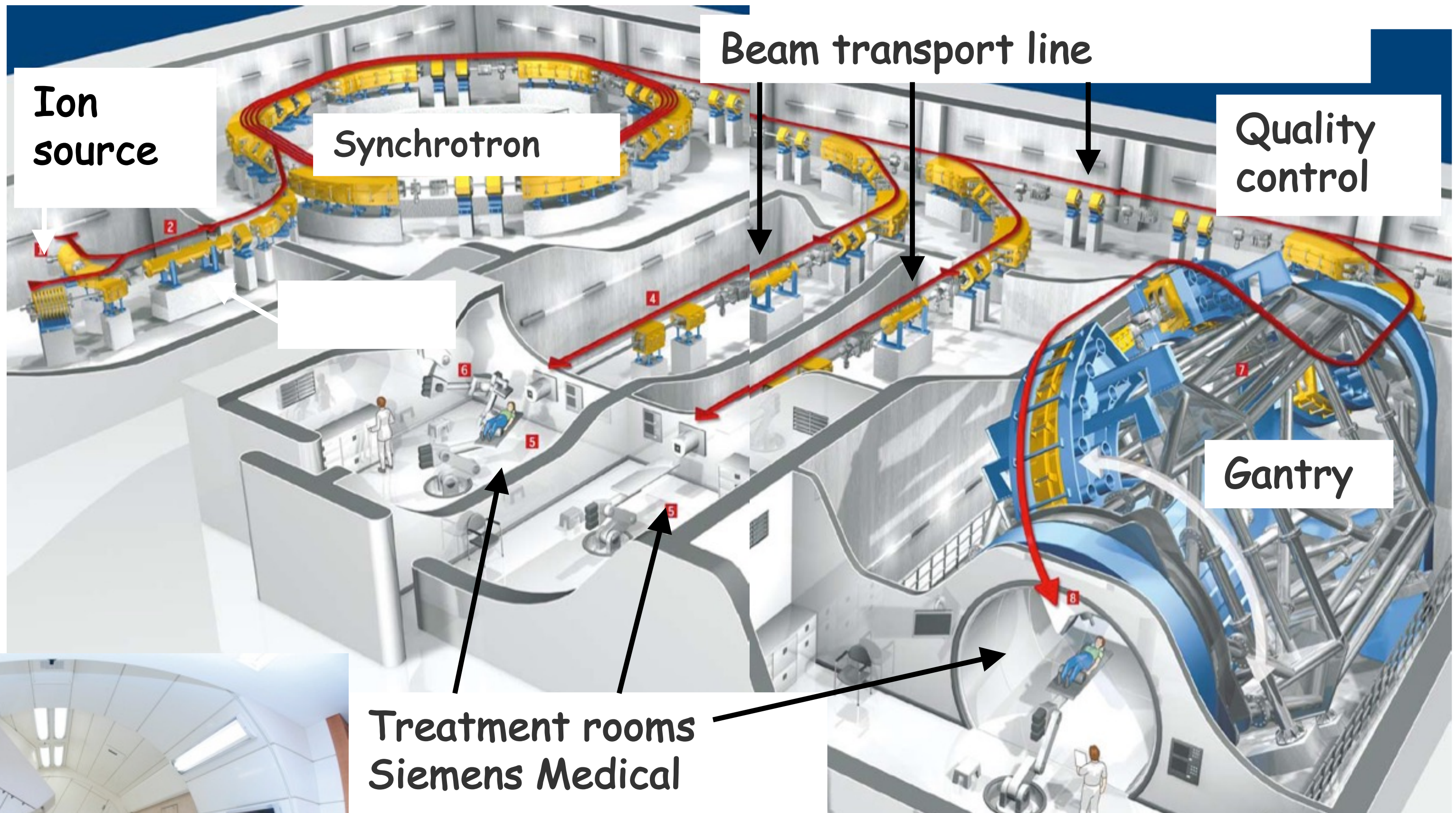
Conservative (non-invasive, fewer side effects)

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

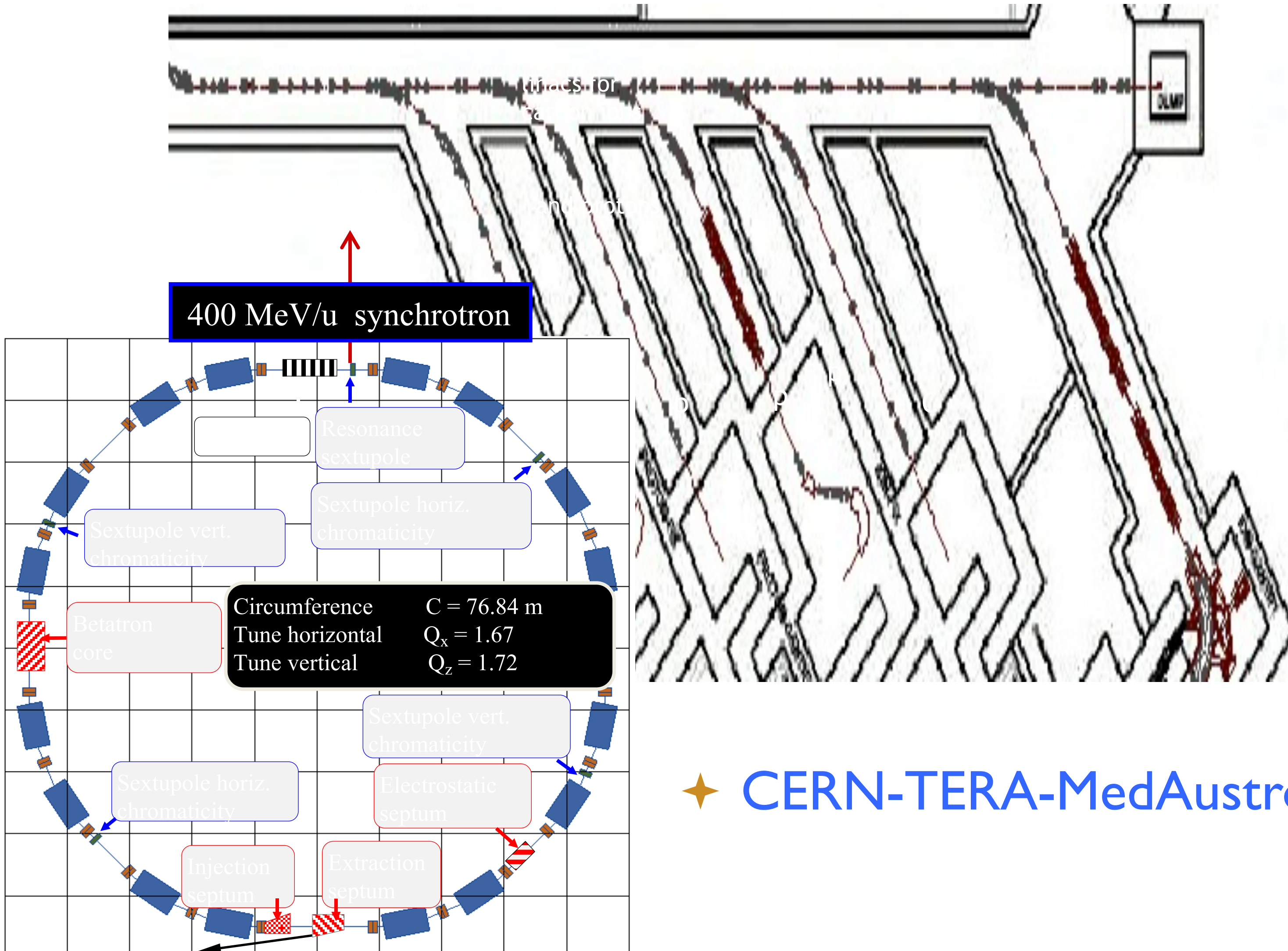


HIT - Heidelberg



Carbon facilities in Europe: first was HIT in Heidelberg – started treating patients in 2009

PIMMS at CERN (1996-2000)



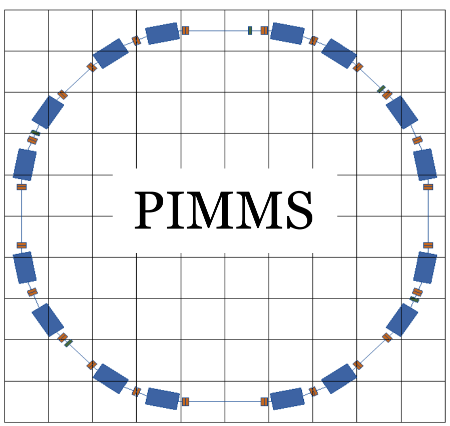
- CERN-TERA-MedAustron

PIMMS study at CERN (1996-2000)

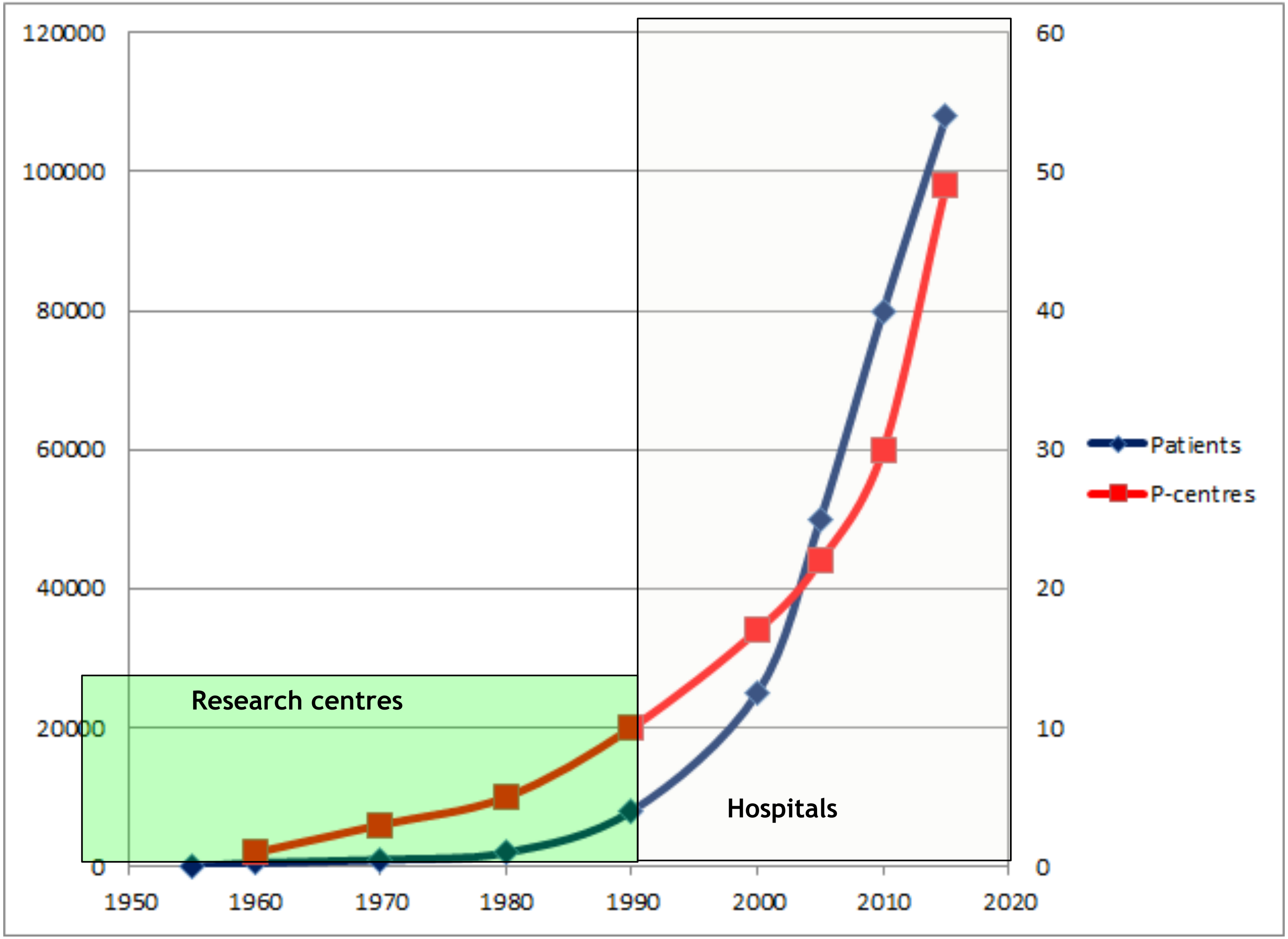
Treatment , CNAO, Italy
2011

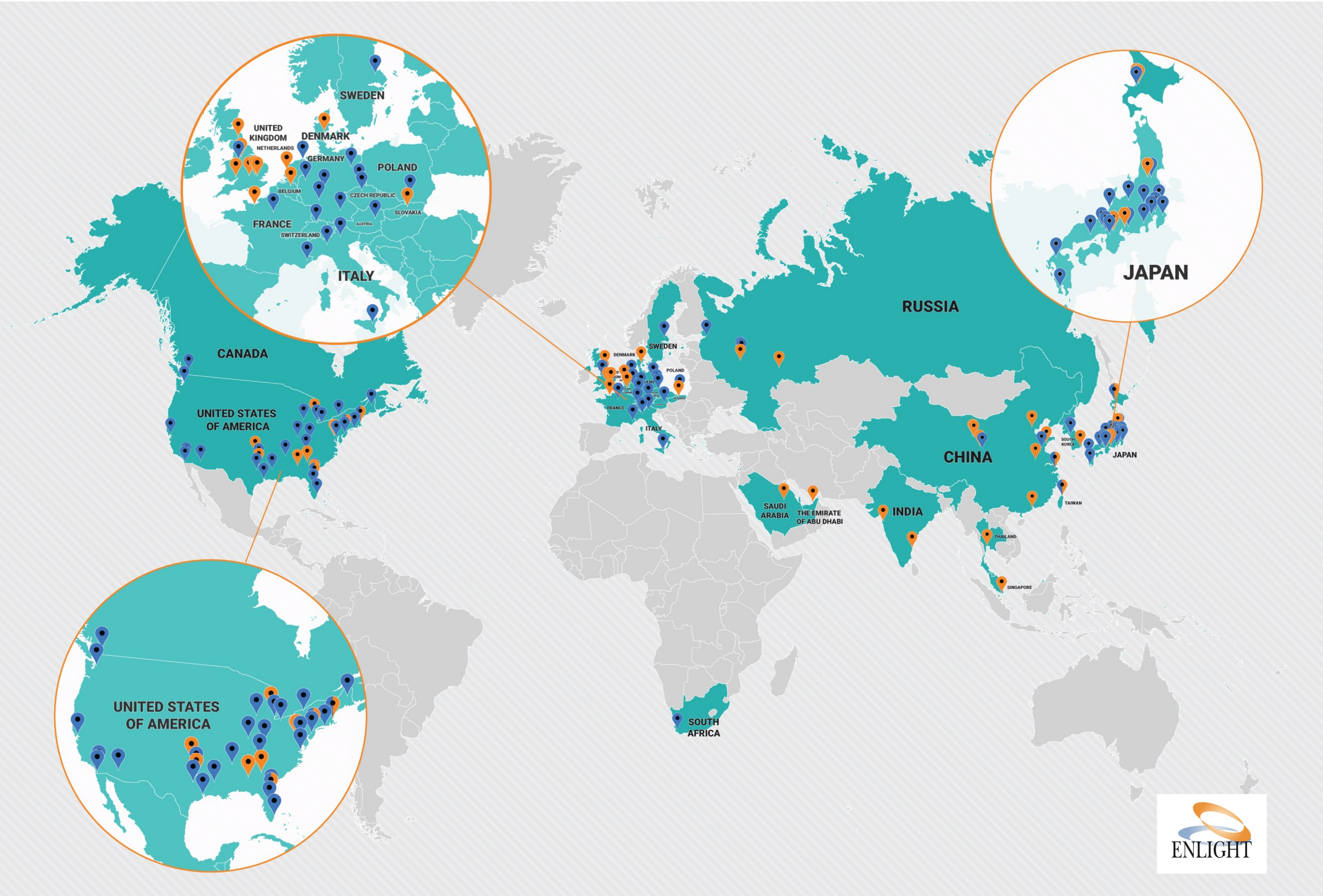
MedAustron, Austria 2019

1996-2000
PIMMS study



[Data from www.ptcog.ch]





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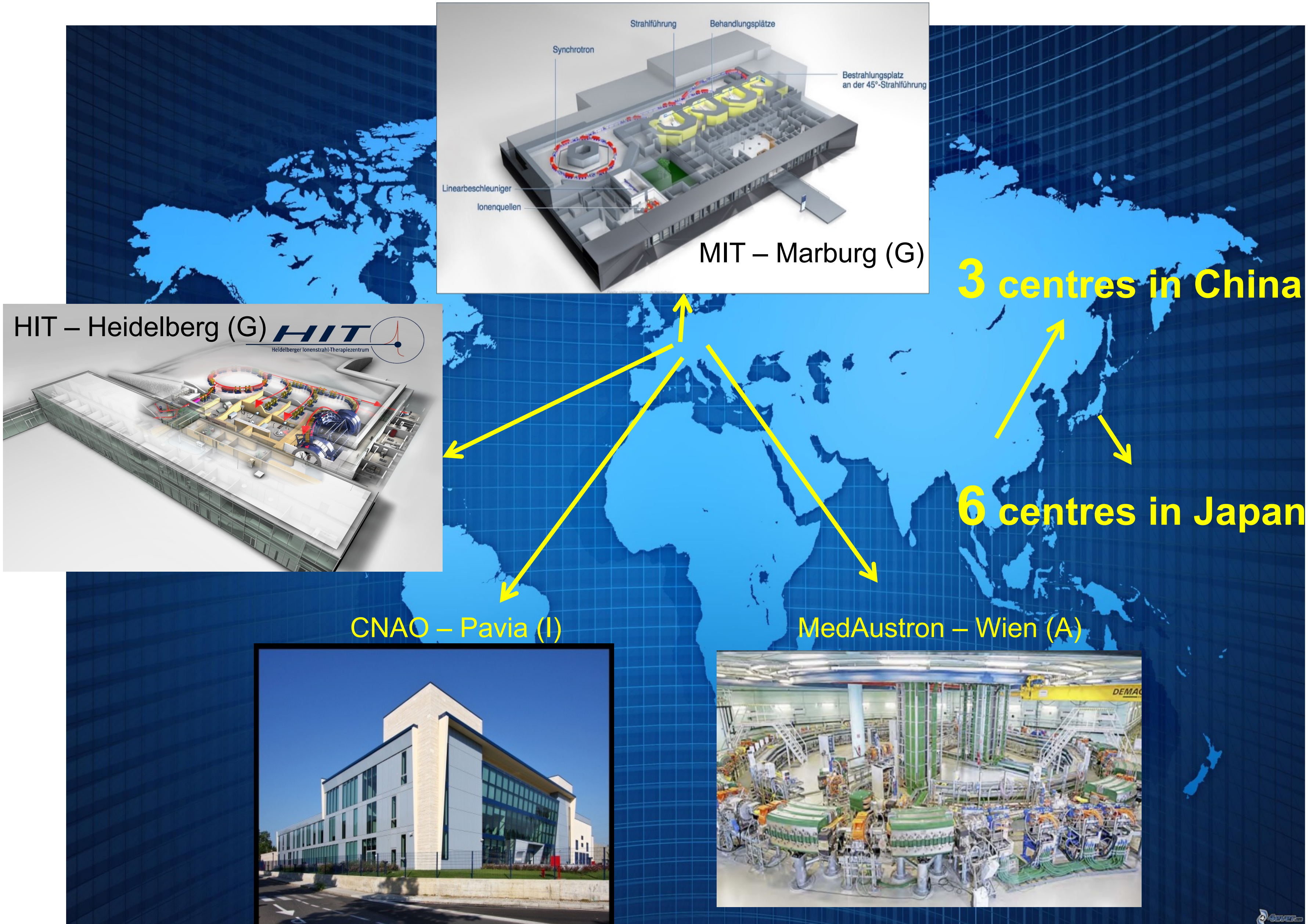
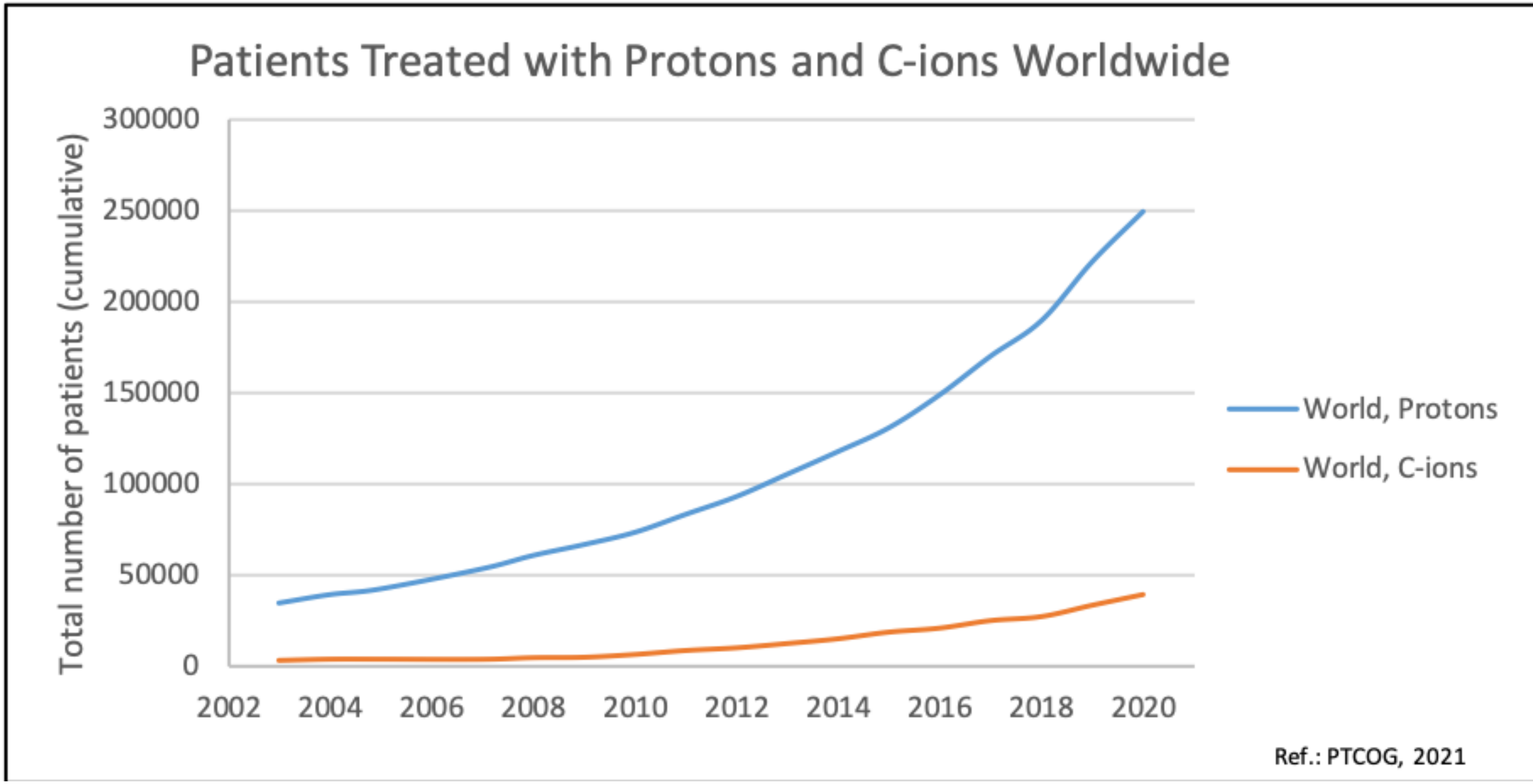
Multi-ions clinical facilities in the World



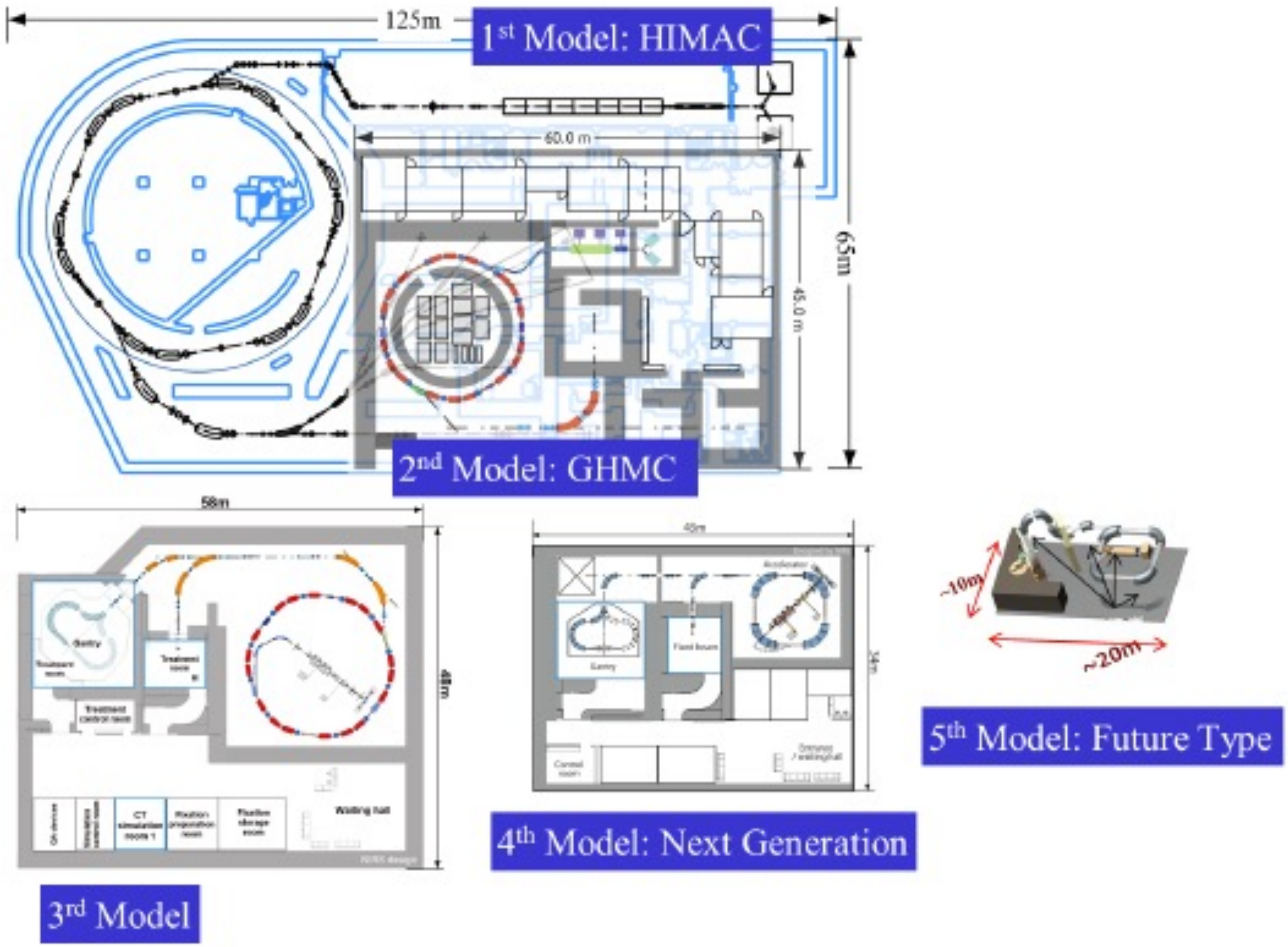
Patient Numbers



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

Plan of Miniaturizing Machine



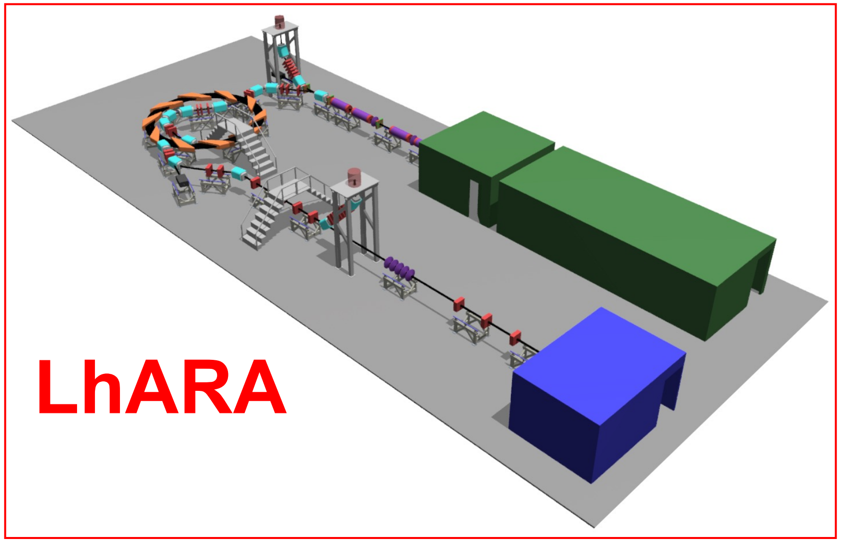
Courtesy of Dr. Kojii Noda

LhARA: Laser-hybrid Accelerator for Radiobiological Applications (K.Long, ICL)

A novel, hybrid, approach:

- High-flux, laser-driven proton/ion source:
  - Overcome instantaneous dose-rate limitation
- Delivers protons or ions in very short pulses:
  - Pulse length 10 – 40 ns
- Arbitrary pulse structure
- Novel plasma-lens capture & focusing
- Fast, flexible, efficient acceleration using FFA:
  - Protons up to 127 MeV p;
  - Ions up to ~33 MeV/u

→ **compact, uniquely flexible facility**



Pre-CDR: CCAP-TN-01; arXiv:2006.00493; submitted to Frontiers in Nuclear Physics, Medical Physics and Imaging

The LhARA consortium

University partners: Imperial College London (CCAP), University of Liverpool, Manchester, University of Strathclyde, Royal Holloway University of London, Queen's University Belfast

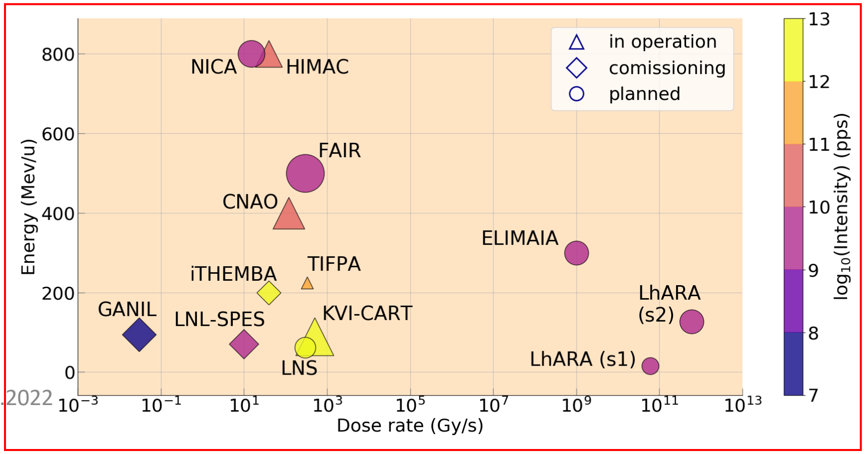
Accelerator institute partners: ASTeC, John Adams Institute for Accelerator Science, The Cockcroft Institute

Laboratory partners: Particle Physics Department, Central Laser Facility, ASTeC, ISIS Neutron and Muon Source

Clinical partners: Oncologists, medical/biophysics, providers — Imperial College Healthcare NHS Trust, 70 Years of the NHS 1948–2018, The Clatterbridge Cancer Centre NHS Foundation Trust

Industrial partners: Maxeler Technologies (Maximum Performance Computing), Corerain, LEO Cancer Care

+ Brm (Phys, Hosp, Cyclotron), NPL, Surrey, Institut Curie



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CERN: Beyond PIMMS to NIMMS

A new accelerator design

Requirements of the ion therapy community, expressed at the Archamps Workshop, June 2018

1. Concentrate on heavy ions (Carbon but also Helium, Oxygen, etc.) because proton therapy is now commercial (4 companies offer turn-key facilities) while ions have higher potential for treatment but lower diffusion.

2. A next generation ion research and therapy accelerator must have:

- ❑ Lower cost, compared to present;
- ❑ Reduced footprint;
- ❑ Lower running costs;
- ❑ Faster dose delivery with higher beam intensity or pulse rate;
- ❑ A rotating ion gantry;
- ❑ Operation with multiple ions (for therapy and research).

An innovative design:

- Can attract a wide support from the scientific community;
- Can increase the exchange SEE-WE and inside SEE thanks to stronger collaboration on scientific and technical issues;
- Can bring modern high technology to the region, with new opportunities for local industry and scientific institutions.

+ Specific requirements for SEEIIST:

- ❑ Easy Industrialization
- ❑ Reliability
- ❑ Simple operation
- ❑ Reduced risk
- ❑ Acceptable time to development

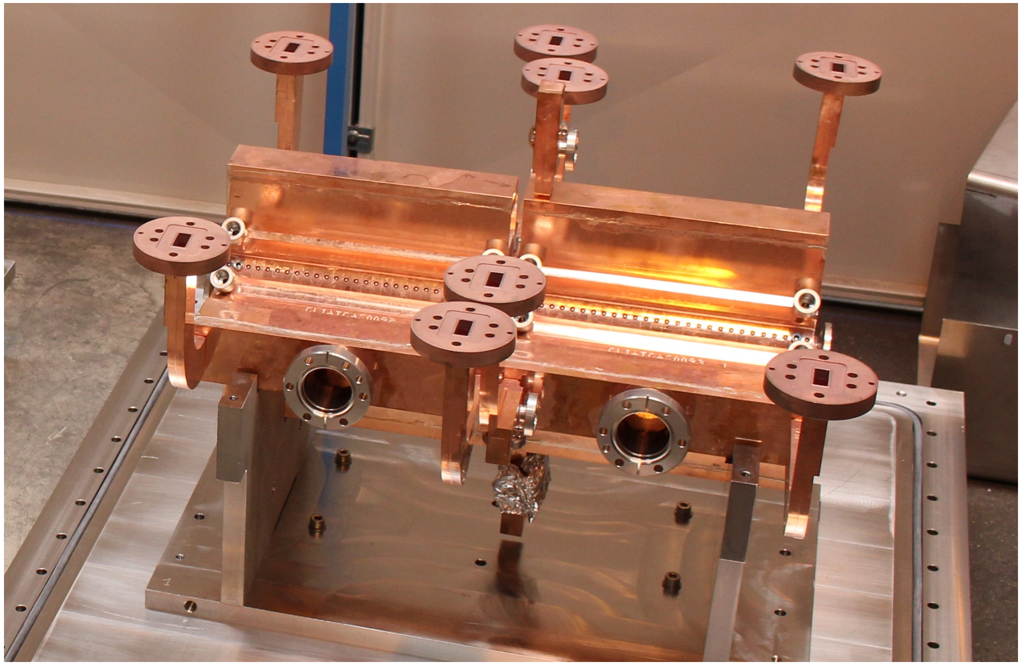
FLASH: a new way of delivering Radiotherapy for treating cancer?

CERN

UNIVERSITY OF OXFORD

New State of the art?

With recent High-Gradient linac technology developments, **Very High Energy Electrons (VHEE)** in the range 100–250 MeV offer the promise to be a cost-effective option for Radiation Therapy

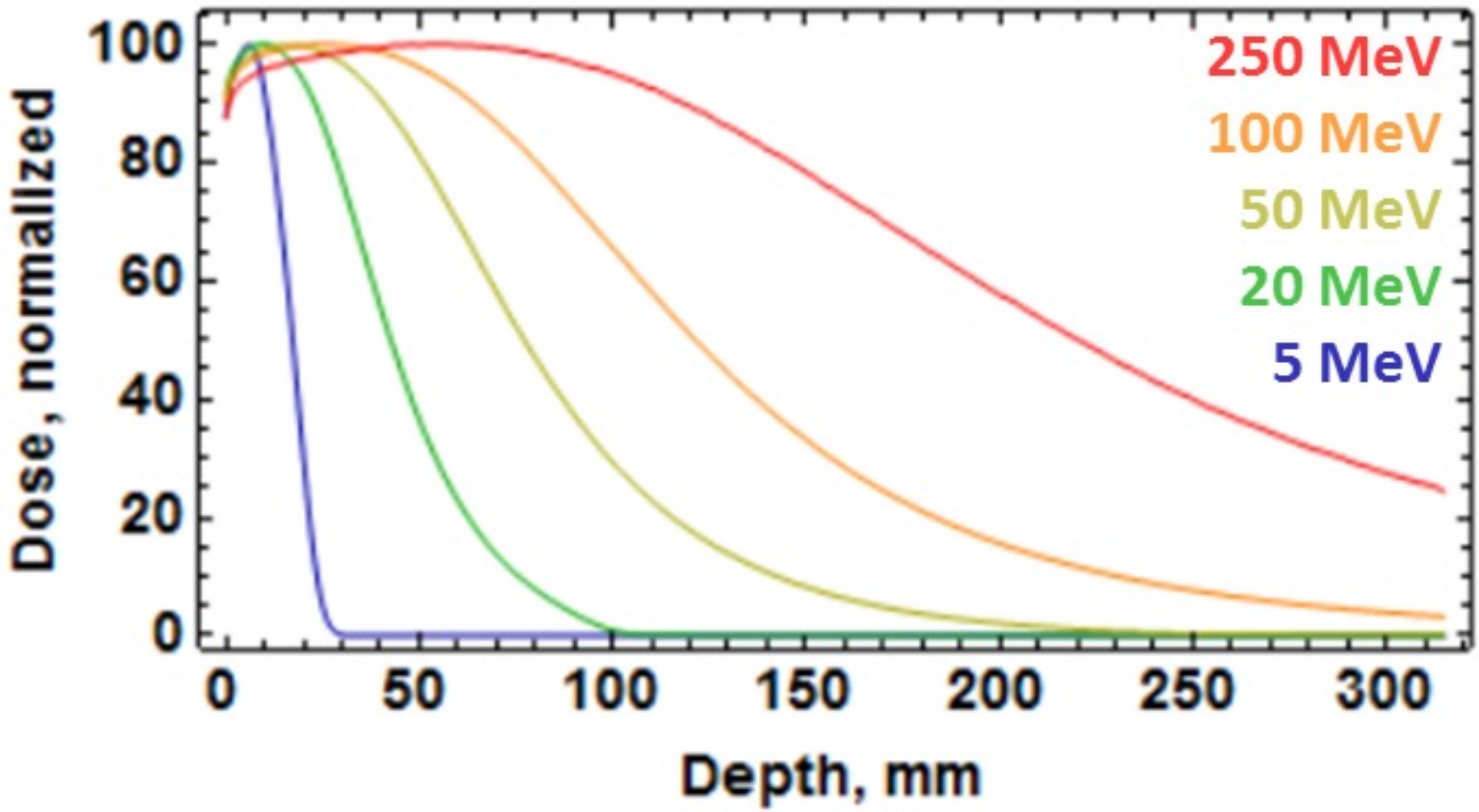


CLIC RF X-band cavity prototype (12 Ghz, 100 MV/m)

Compact Linear Collider

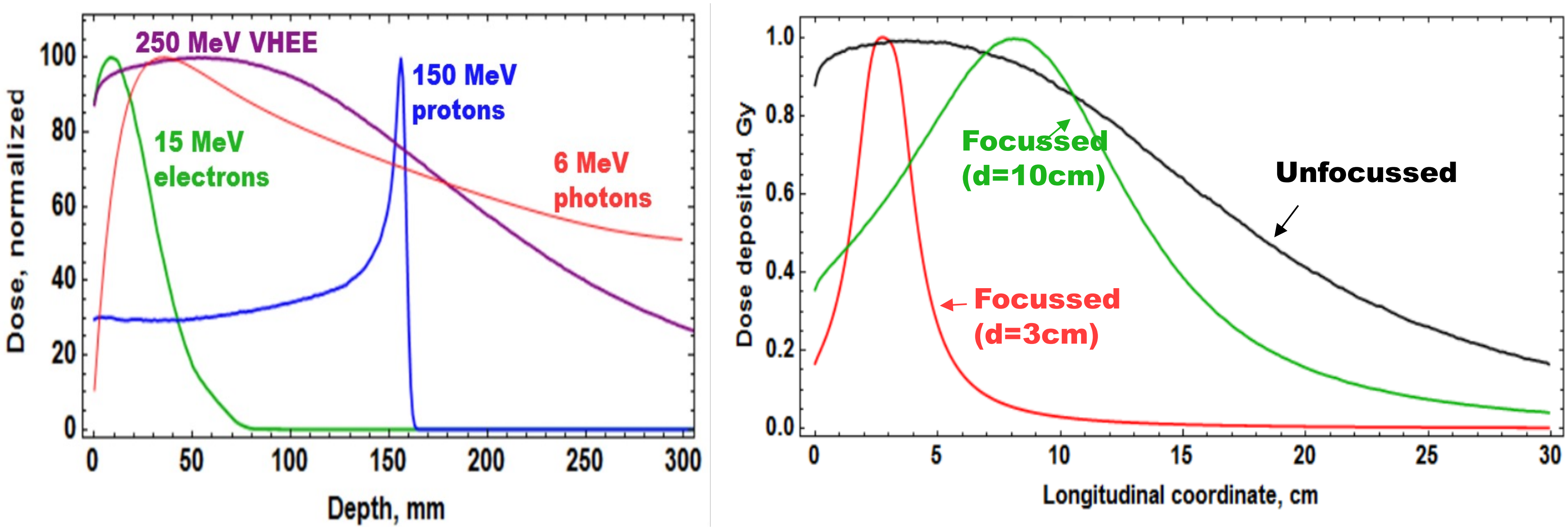
Acknowledge Lagzda

$\sigma = 5$ mm, various energies



VHEE

- Their ballistic and dosimetric properties can surpass those of photons, which are currently the most commonly used in RT.
- Their position compared to protons need to be evaluated, but they can be produced at a reduced cost.



Depth Dose curve for various particle beams in water (beam widths r=0.5 cm)

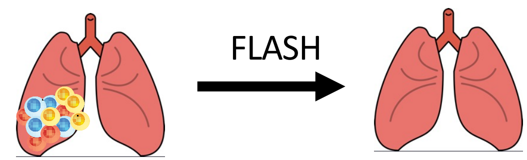
FLASH radiotherapy is based on the observation that healthy tissue is less damaged if treatment occurs very fast

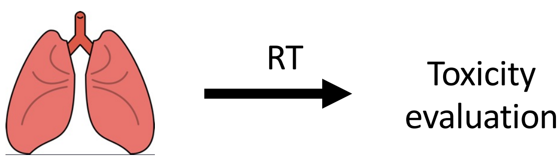
RESEARCH ARTICLE

RADIATION TOXICITY

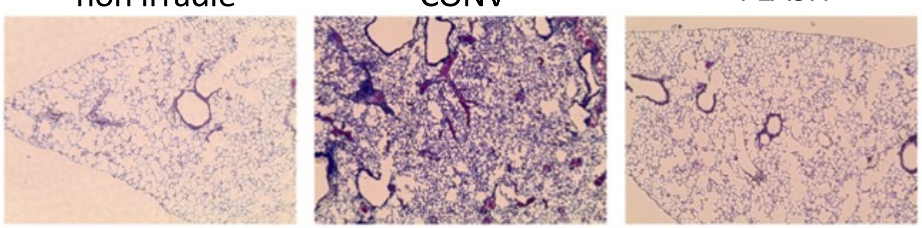
Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2||] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]





Contrôle non irradié	17 Gy CONV	17 Gy FLASH



HEALTHY	FIBROTIC	HEALTHY

Anti-tumor efficacy

FLASH EFFECT

Absence of radiation-induced toxicity in the Normal lung

Treatment of a first patient with FLASH-radiotherapy


Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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

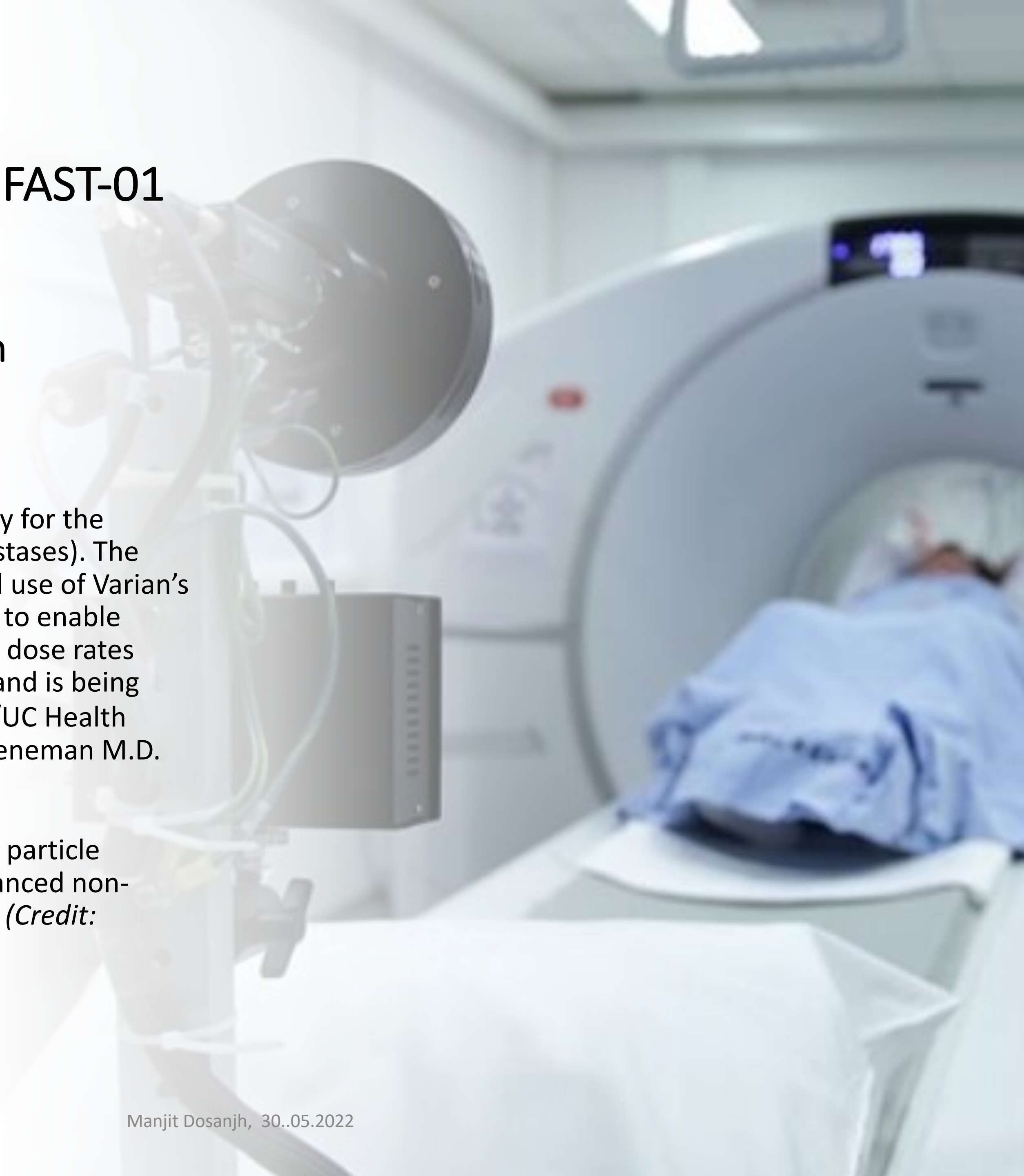
15 Gy with 10 pulses **in 90 ms**

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.

First Patient Treated in FAST-01 FLASH Proton Therapy (November 2020)
Transmission-shoot through



FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases). The clinical trial involves the investigational use of Varian's ProBeam particle accelerator modified to enable radiation therapy delivery at ultra-high dose rates (dose delivered in less than 1 second) and is being conducted at the Cincinnati Children's/UC Health Proton Therapy Center with John C. Breneman M.D.

The study will assess Varian's ProBeam particle accelerator modified to deliver an advanced non-invasive treatment for cancer patients. *(Credit: Bokskapet from Pixabay)*

Where it all started.....

Thank you for listening

cern.ch/virtual-hadron-therapy-centre

Interactive Material

- Imaging and hadron therapy animation
  http://cds.cern.ch/record/1611721?ln=en
  http://cds.cern.ch/record/2002120

- Interactive virtual visit to a hadrotherapy centre:
  http://www.cern.nymus3d.nl/maps#

- PARTNER Marie Curie
  http://cds.cern.ch/record/1384426?ln=en
  http://cds.cern.ch/record/1327668

- ENERVISION Marie Curie
  http://cds.cern.ch/record/1541891

- HITRIplus beam time

  https://www.hitriplus.eu/transnational-access-what-is-ta/

- FLASH An innovative electron radiotherapy technology

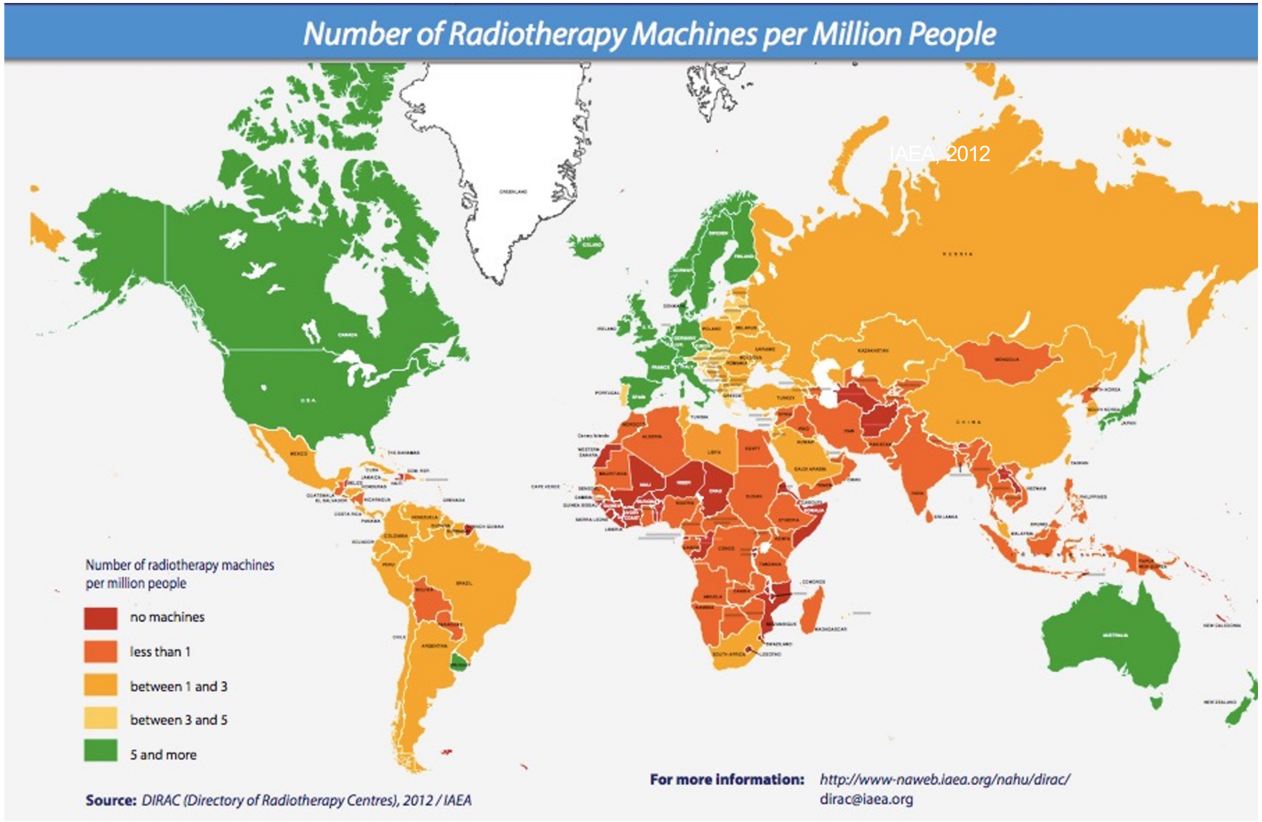
  https://videos.cern.ch/record/2762058

  https://videos.cern.ch/record/2295068

Physics for development……

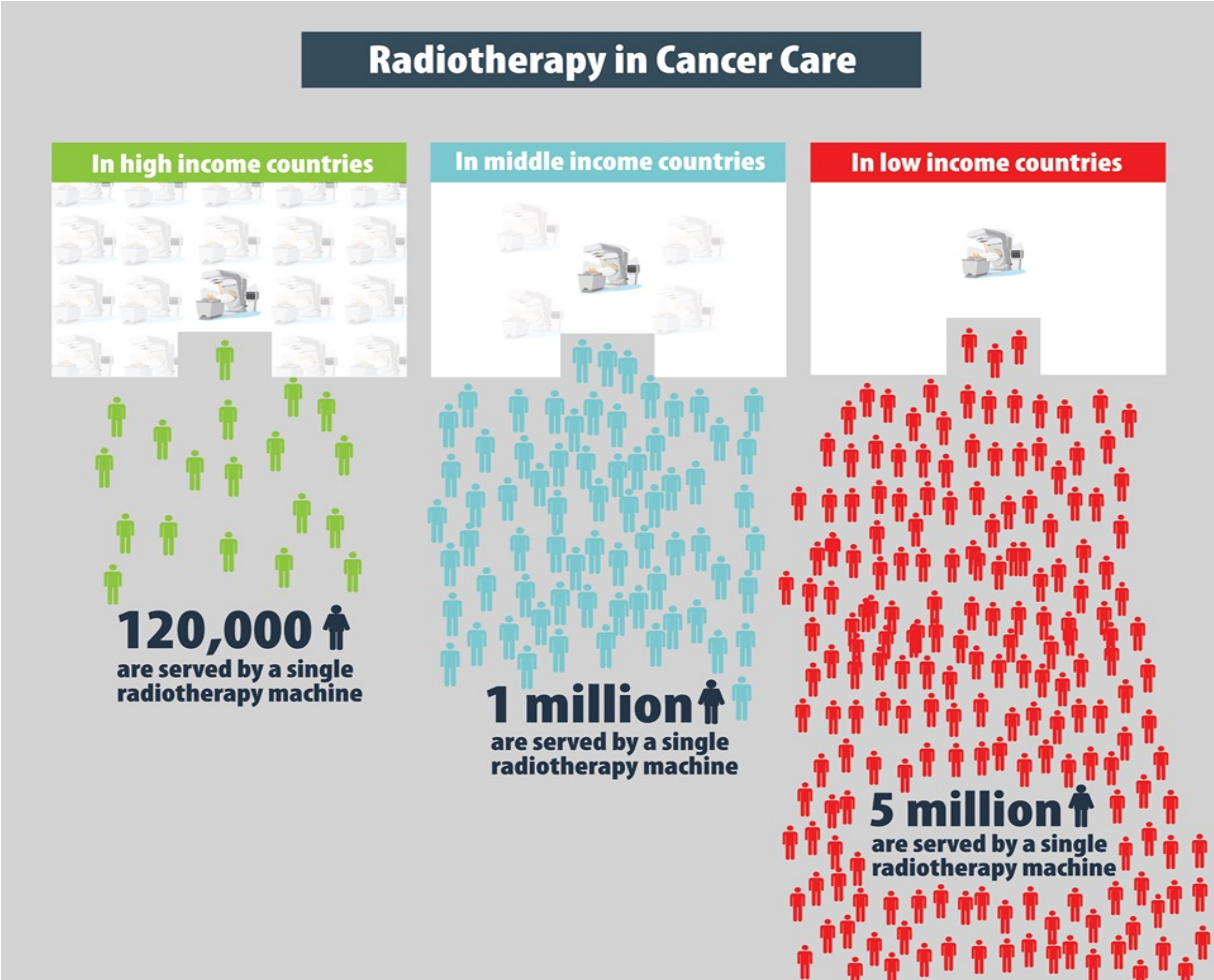
Current Challenge: how to go from almost no radiotherapy to high quality radiotherapy globally:
Challenging Environments

Radiation Therapy is essential part of cancer treatment



However only 10% of patients in low-income regions have access

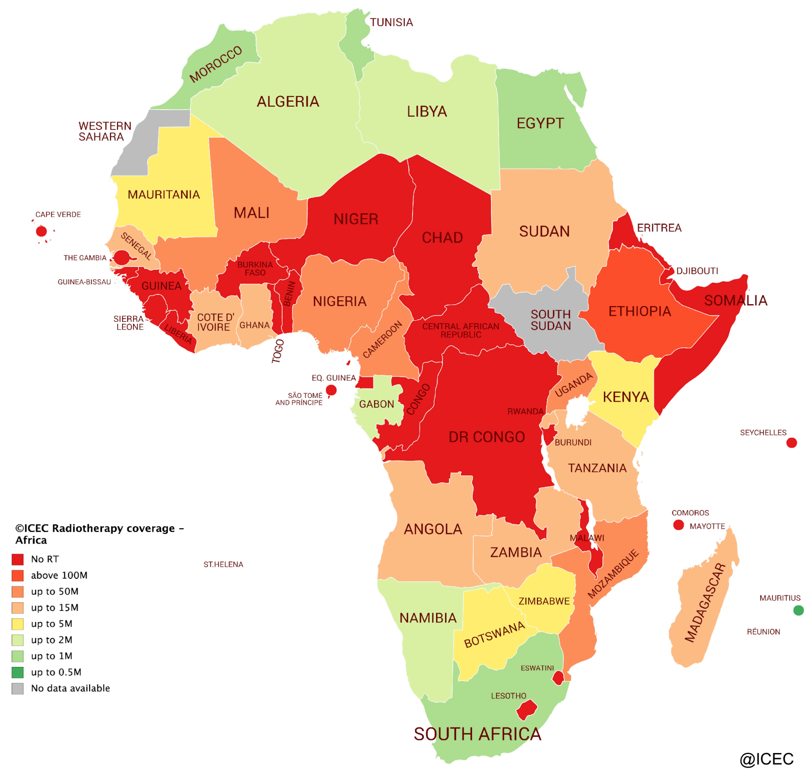
9 out of 10 deaths for cervical cancer & **7 out of 10** breast cancer are in LMICs


Radiotherapy in Cancer Care
In high income countries
In middle income countries
In low income countries
120,000
are served by a single radiotherapy machine
1 million
are served by a single radiotherapy machine
5 million
are served by a single radiotherapy machine

Dramatic Disparity in Access to Radiation Therapy Treatment

- **16.3 million cancer deaths** worldwide in 2040
- **70%** of projected cancer deaths are **in LMICs**
- Radiation Therapy is an **essential treatment** for **over 50% of cancers** resulting in cure or palliation
- LMICs have limited radiotherapy access: Only **10% of patients in low-income** and **40% in middle-income countries** have access to RT

Country	LINACs	Population	People per LINAC
Ethiopia	1	115 M	115,000,000
Nigeria	7	206 M	29,000,000
Tanzania	5	59.7 M	11,900,000
Kenya	11	53.9 M	4,890,000
Morocco	42	36.9 M	880,000
South Africa	97	59 M	608,000
UK	357	67 M	187,000
Switzerland	83	8.6 M	103,000
US	3727	331 M	88,000

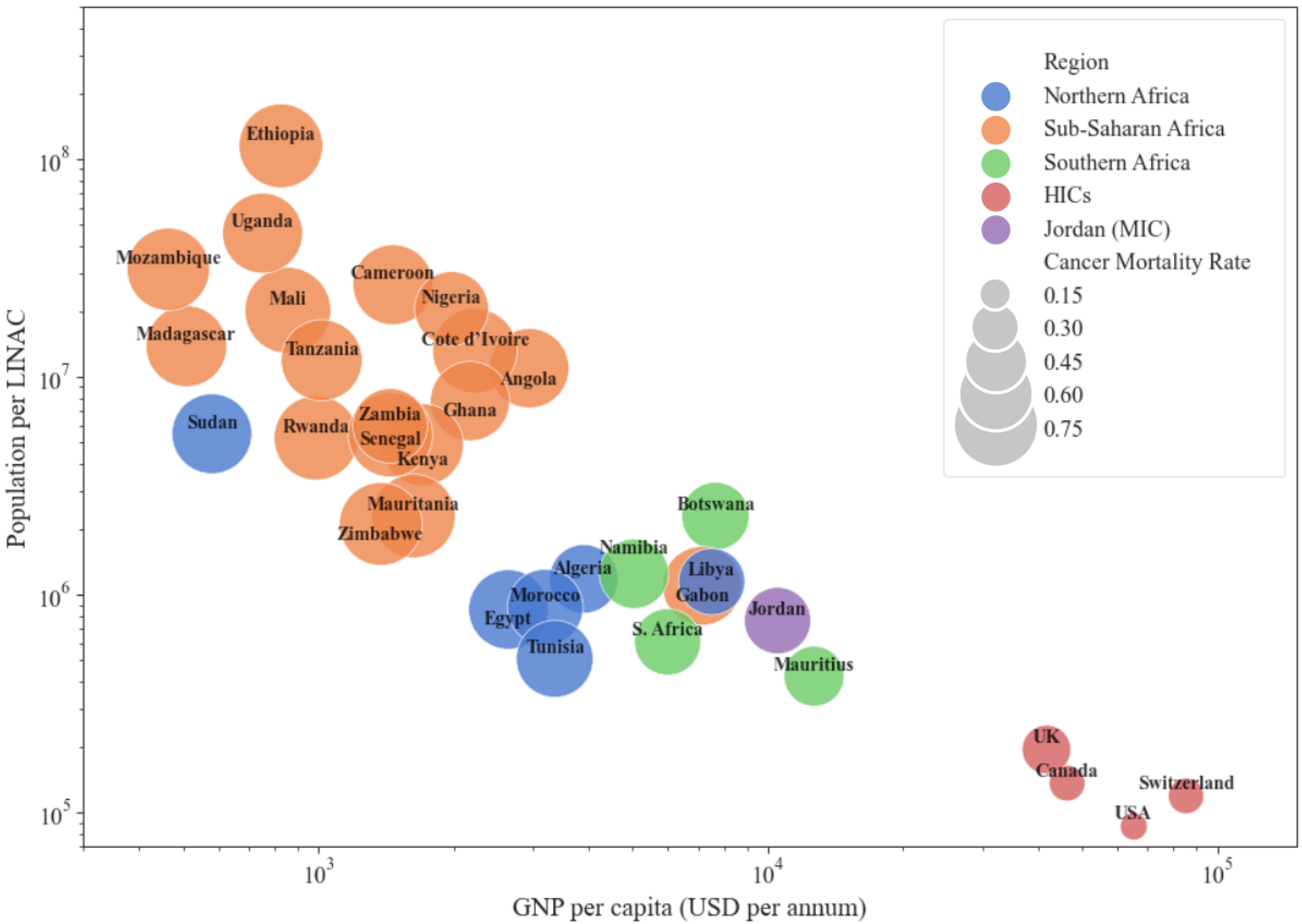


Map showing the number of people per functioning machine in countries in Africa

Current Challenges

- In Africa - 26 of 55 countries have no LINAC-based RT facilities
- Current need is 5000 RT machines
- In 2040 demand will be over 10,000 machines
- RT cobalt-60 technology has environmental and potential security risks
- LINACs are high cost, more complex and labour-intensive to operate and maintain, but offer state-of-the-art treatment

GNP per Capita and the Ratio of Inhabitants to RT Machines and Cancer Mortality Rates



Current treatment technology

- LINAC-based RT is the current technology of choice

But LINAC technology is **complex, labour intensive, and high cost** to acquire, install, operate and service.

Can we use technology developments from HEP to address the current challenges and make RT more widely available?

New LINAC Design Requirements

- First patient treated in 1953 Hammersmith Hospital, UK
- First patient treated in US in 1956, Stanford, with first Varian LINAC
- LINAC technology has not changed remarkably in 50 years

Can LINACs be improved in the future to expand access to RT ?

Medical Linacs for challenging environments

- 1st Design Characteristics of a Novel Linear Accelerator for Challenging Environments, November 2016, CERN
- 2nd Bridging the Gap Workshop, October 2017, CERN
- 3rd Burying the Complexity Workshop, March 2018, Manchester

- 4th Accelerating the Future Workshop, March 2019, Gaborone

CERN

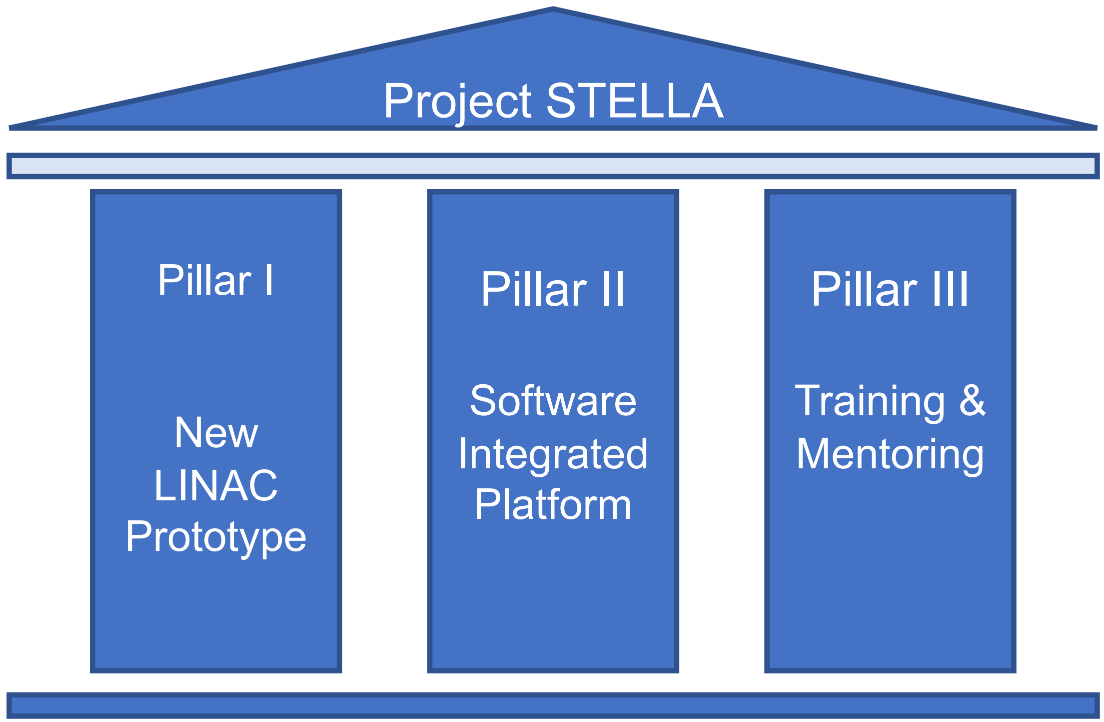
International Cancer Expert Corps
Partnering to transform global cancer care

UKRI Science and Technology Facilities Council

Project STELLA

Smart **T**echnologies to **E**xtend **L**ives with **L**inear **A**ccelerators

Project STELLA is a unique global collaboration involving some of the **best physics** and **medical talent, expertise from leading laboratories in accelerator design** and, importantly, **input and collaboration** from users in **Africa, other LMICs** and **HICs.** The goal of this project is to design disruptive technology for the treatment of cancer patients with radiation therapy.



International Cancer Expert Corps
Partnering to transform global cancer care

CERN

UKRI Science and Technology Facilities Council

Lancaster University

UNIVERSITY OF OXFORD

Collaboration with all African Countries

Innovative Technologies towards building Affordable and Equitable Global Radiotherapy (ITAR)

- **Gather information** from African hospitals/facilities regarding challenges faced in providing radiotherapy in Africa
- **Identify** the challenges with those who live with them day-to-day
- **Create design specifications** for a radiotherapy machine to meet these challenges for an improved design
- Assess applications of **ML, AI and use of cloud-computing** in African and LMIC settings
- **Technical design report** for a prototype

Input from all African countries that have LINAC-based RT

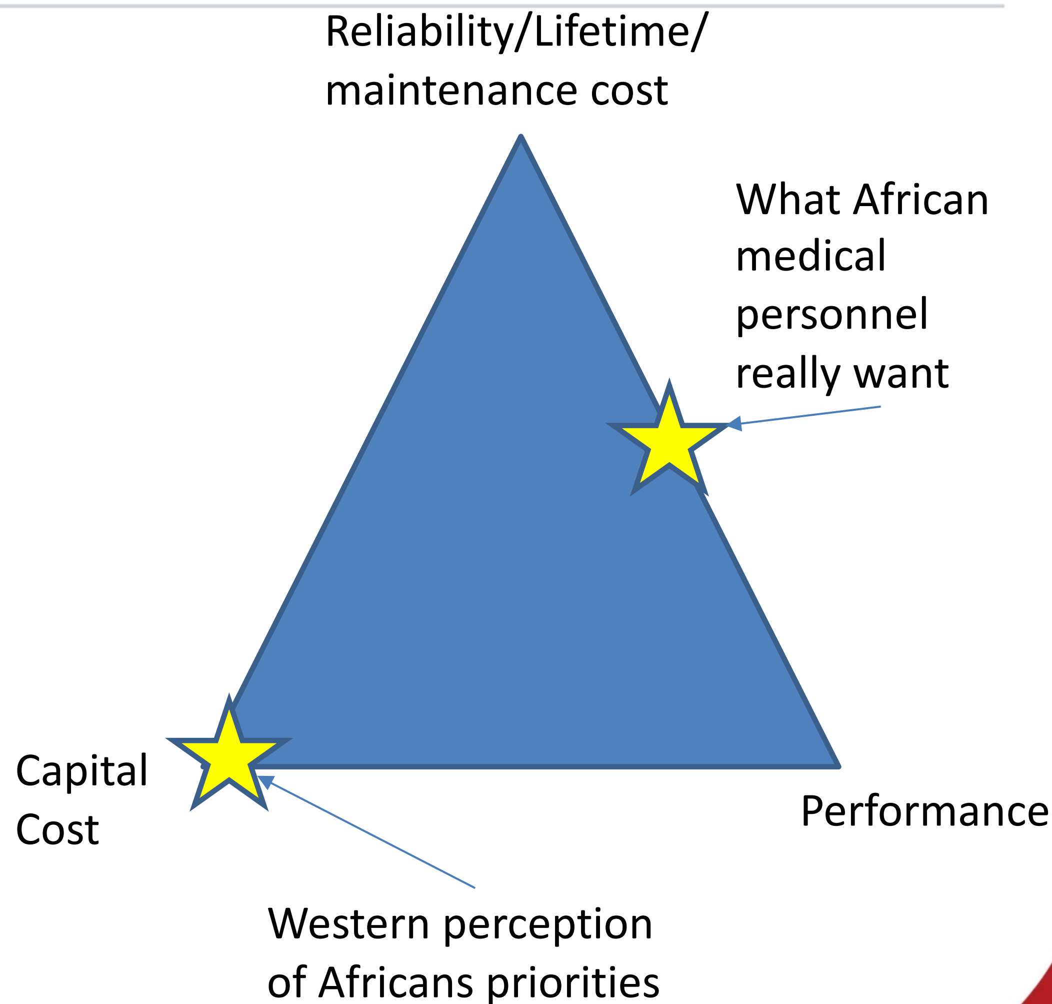
Biggest issues in LMIC hospitals

equality, want , need

Lancaster University

Graeme Burt

- Delays in repairs
- Lack of funds for regular maintenance
- Lack of trained engineers
- Fluctuating electrical supply
- Corruption



What isn't wanted

- Cheap, poorly made linacs and second-class treatments

Ultimate Goal for STELLA

- Robust, modular, reliable and simple to use machines
- Are affordable
- with the aim to: **expand access to RT**

STELLA is looking at innovative design for reduction in acquisition and operating costs ensuring more improved LINAC access and a **mentoring and training program for a sustainable solution**

Such an ambitious project not be possible without collaboration and our colleagues from the grass-roots http://www.iceccancer.org/

Manjit Dosanjh, 30..05.2022