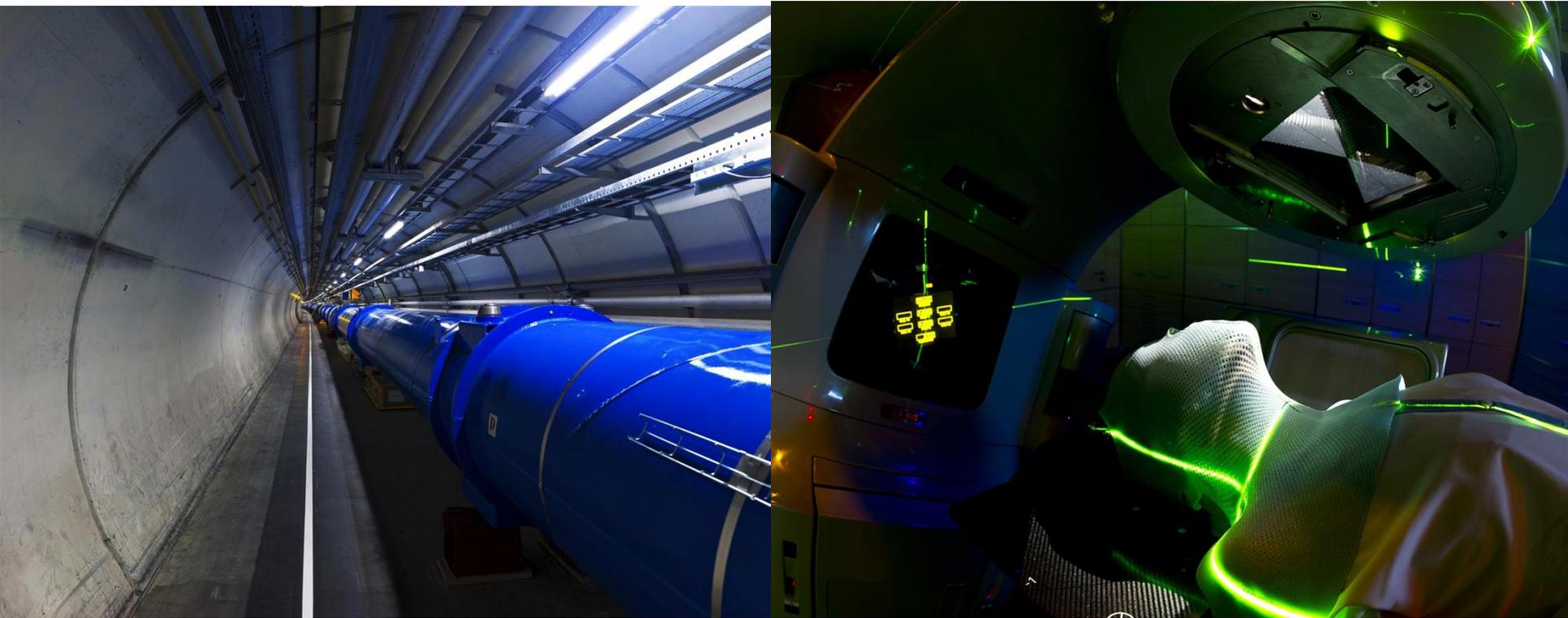


# From Physics to Medical Applications

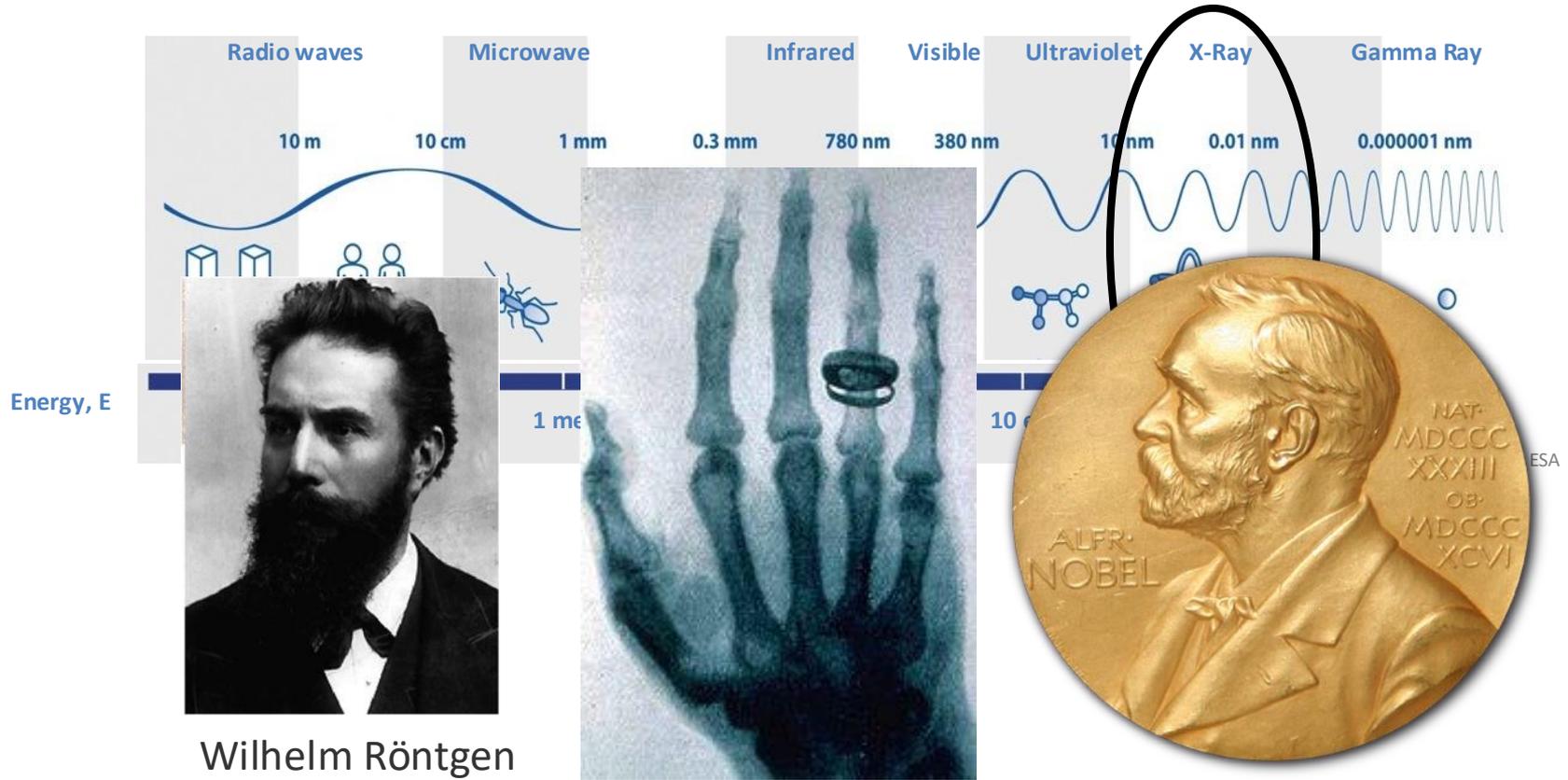


Manjit Dosanjh, 7<sup>th</sup> August 2024

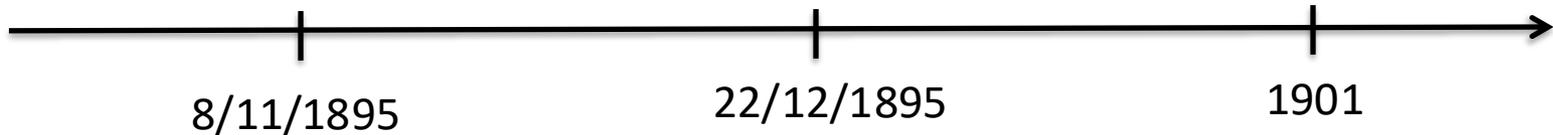
[Manjit.Dosanjh@cern.ch](mailto:Manjit.Dosanjh@cern.ch)



# Modern medical physics.....beginnings



Wilhelm Röntgen

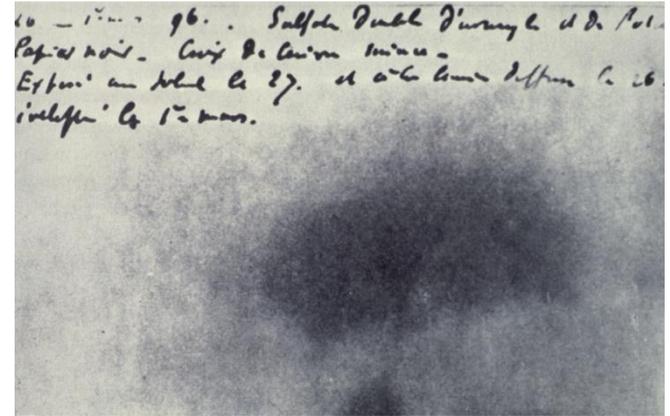


.....beginnings

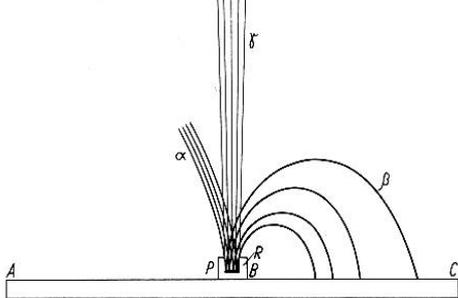


Henri Becquerel

**1896:**  
**Discovery of natural radioactivity**

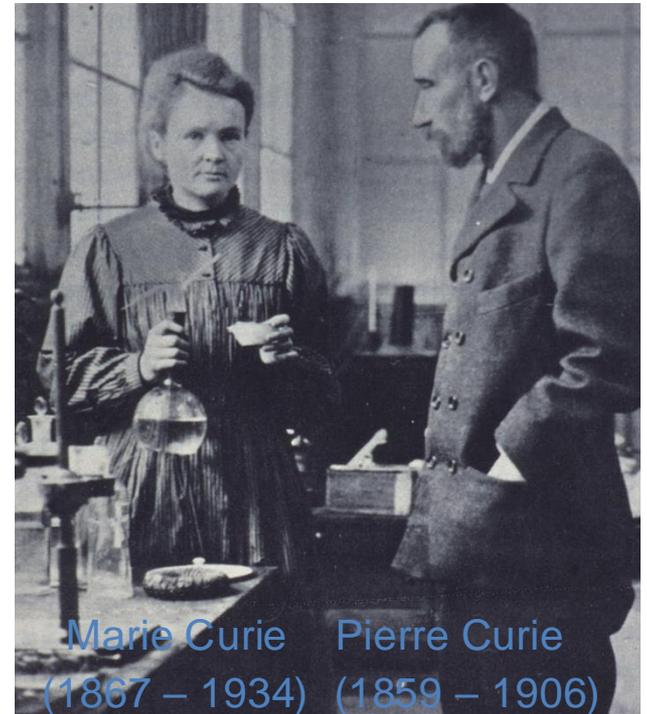


Thesis of Mme. Curie – 1904  
 $\alpha$ ,  $\beta$ ,  $\gamma$  in magnetic field



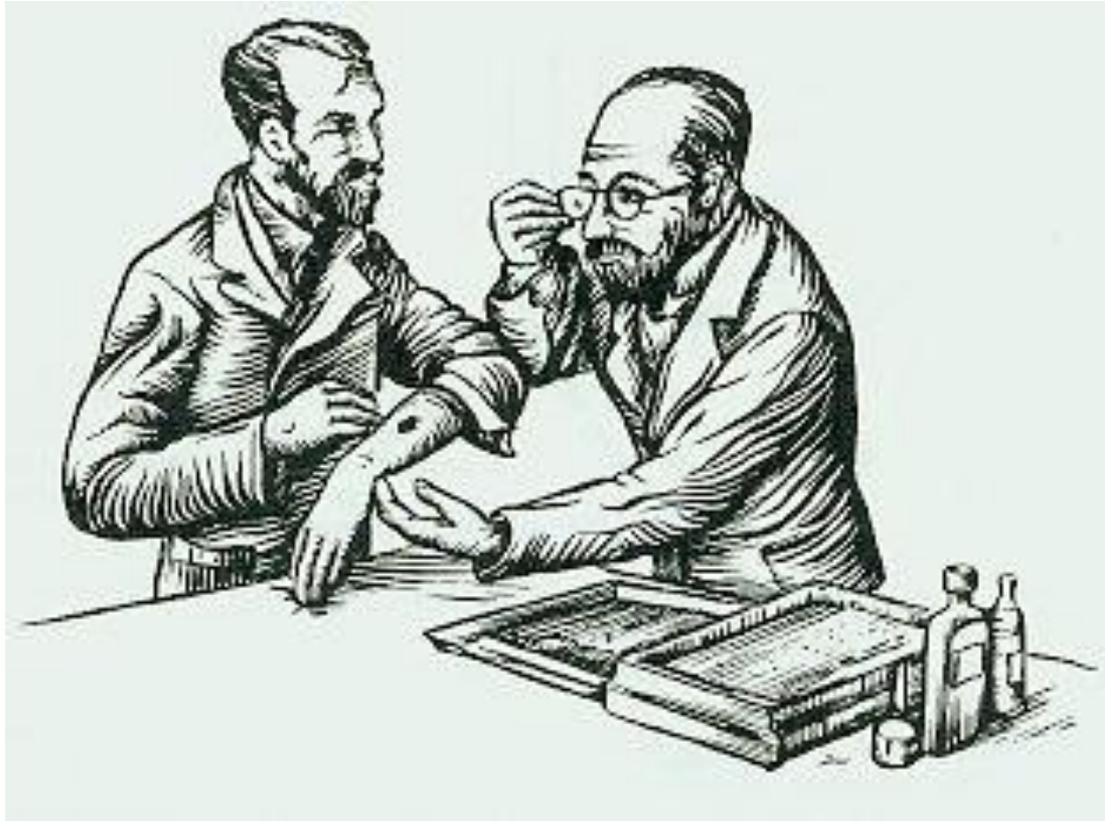
**1898: Discovery of radium**

**used immediately for “Brachytherapy”**



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

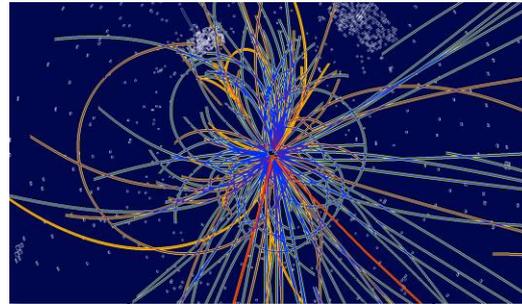
# First radiobiology experiment



Pierre Curie and Henri Becquerel



# CERN and Physics Technologies



Detecting  
particles

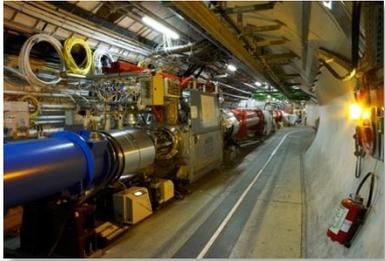
Accelerating  
particle beams



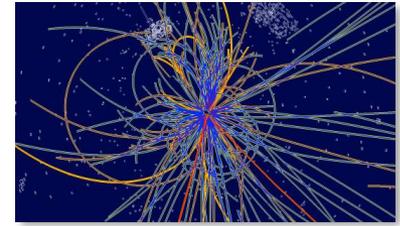
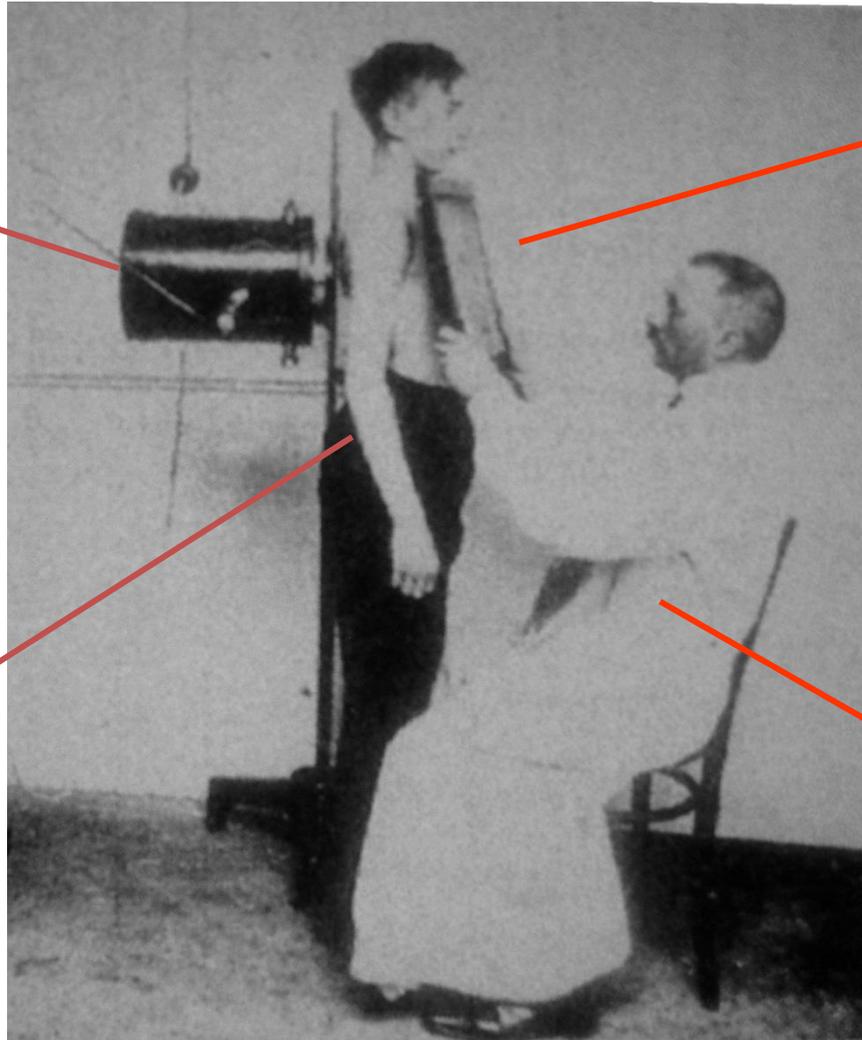
Higgs

Large-scale  
computing (Grid)





**X-ray source**



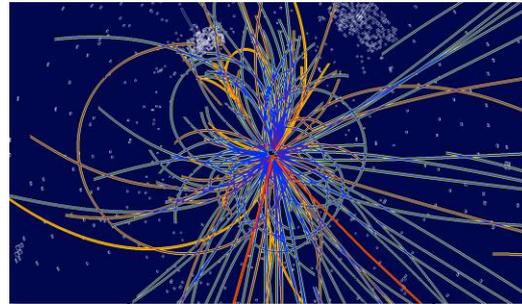
**Detector**



**Pattern Recognition System**

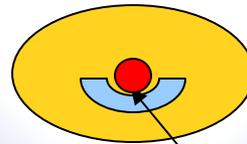
**Object**

# Physics Technologies helping health



Detecting particles

Accelerating particle beams



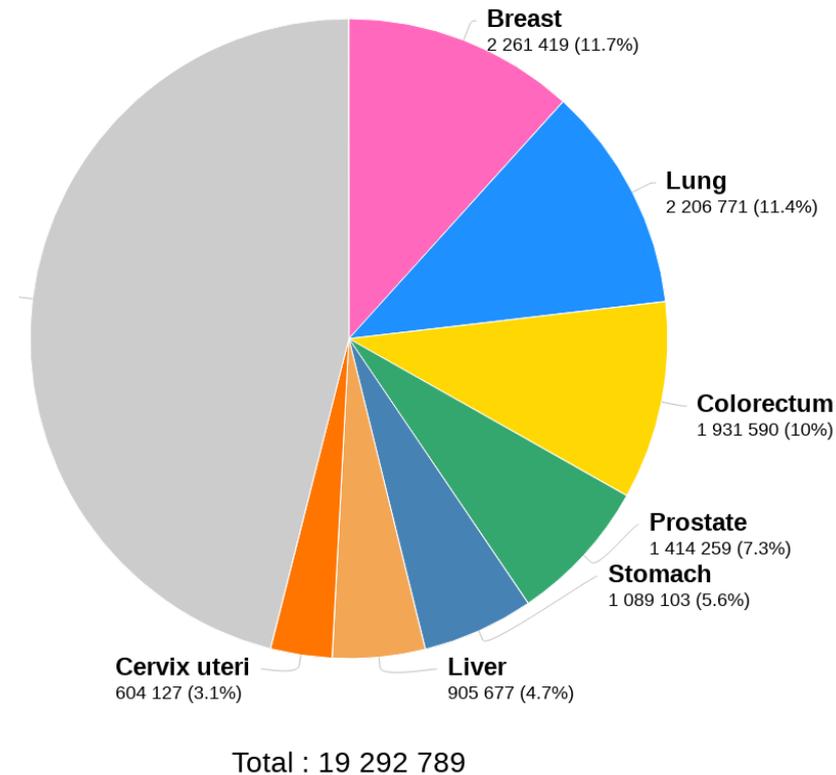
**CANCER**

Large-scale computing (Grid)



# Cancer is a growing global challenge

- Globally **19.3** million new cases per year diagnosed and **9.96** million deaths in **2020**
- 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)

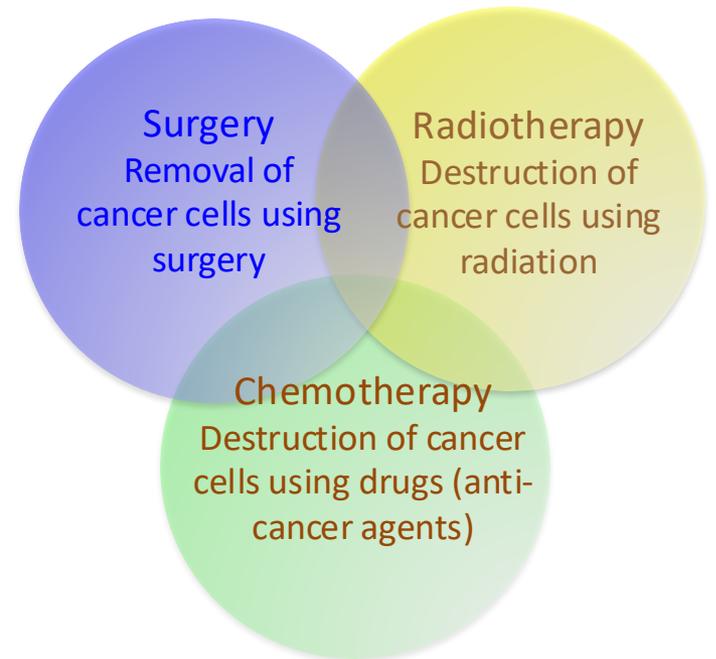


*Data source: GLOBOSCAN 2020*

**Radiation therapy is a key tool for treatment for about 50% patients**

# What is Cancer?

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



# 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**.



Early Diagnosis

Local Control

Fewer Side-effects

# Detectors and art of seeing.....

## Particle Detection

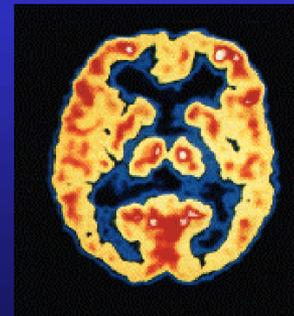


## Imaging

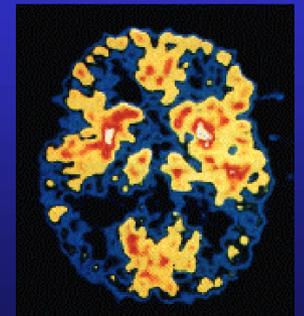


X-ray, CT, PET, MRI

Brain Metabolism in Alzheimer's Disease: PET Scan



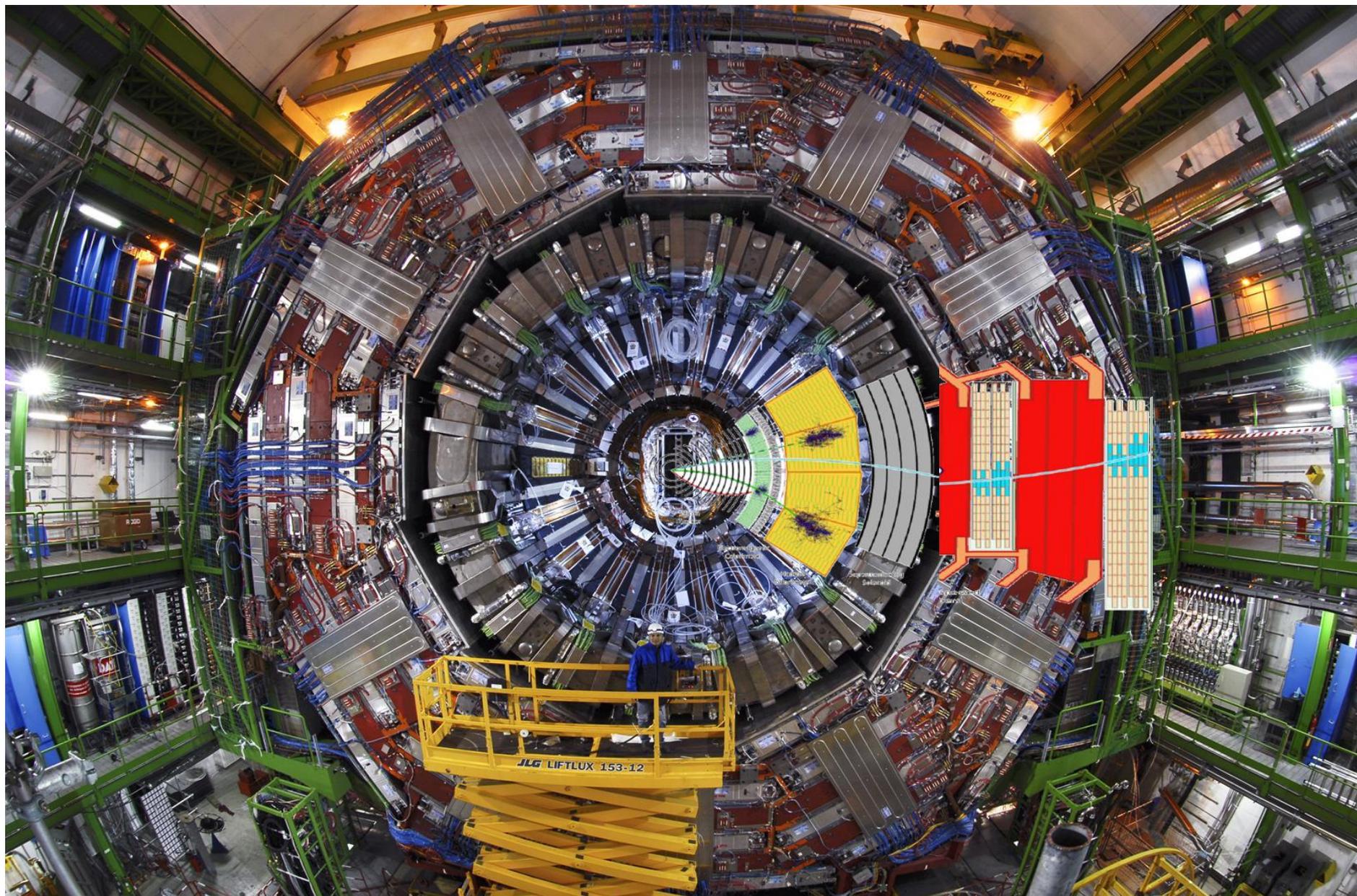
Normal Brain



Alzheimer's Disease

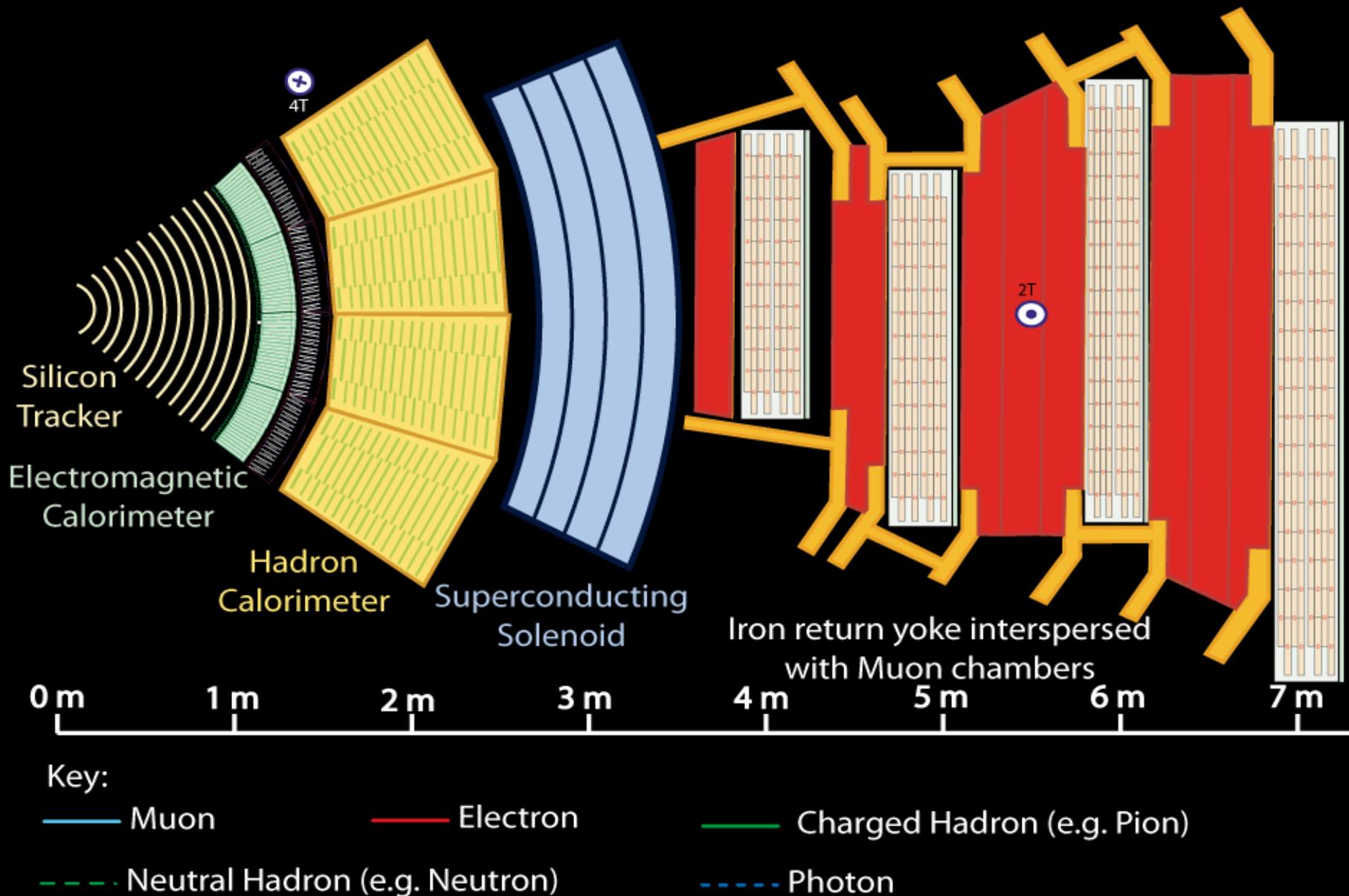


# 200 Mpix 3-D camera taking 40 million photos/second!

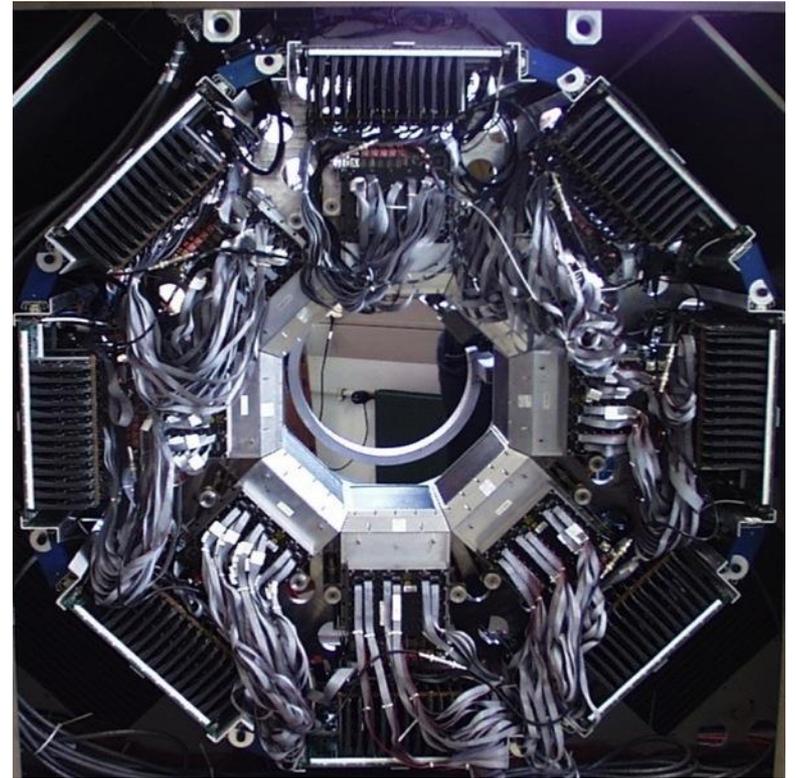




# A slice through the CMS Detector



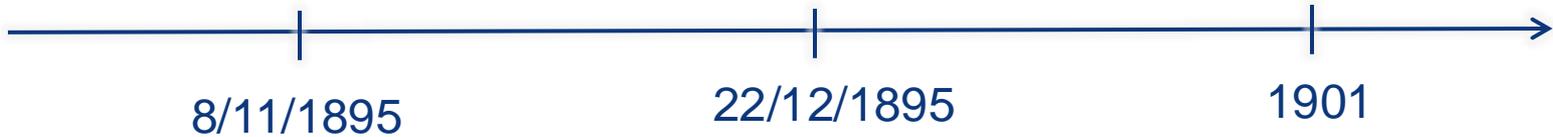
# The detector challenge



# X-ray imaging



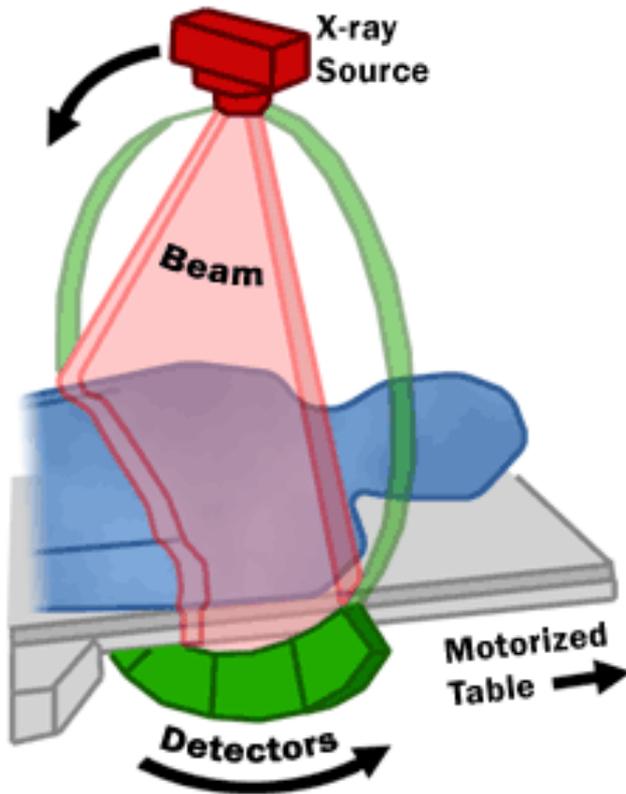
Wilhelm Röntgen



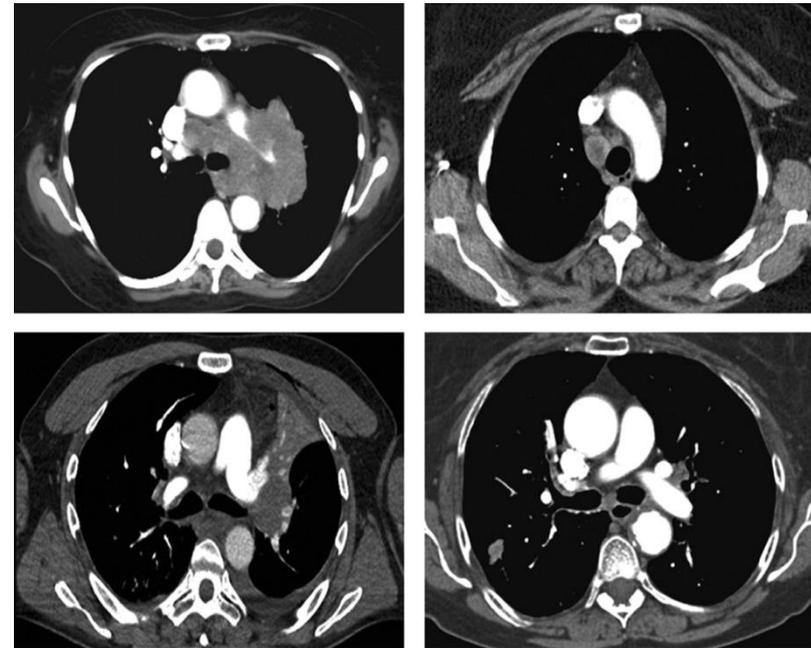
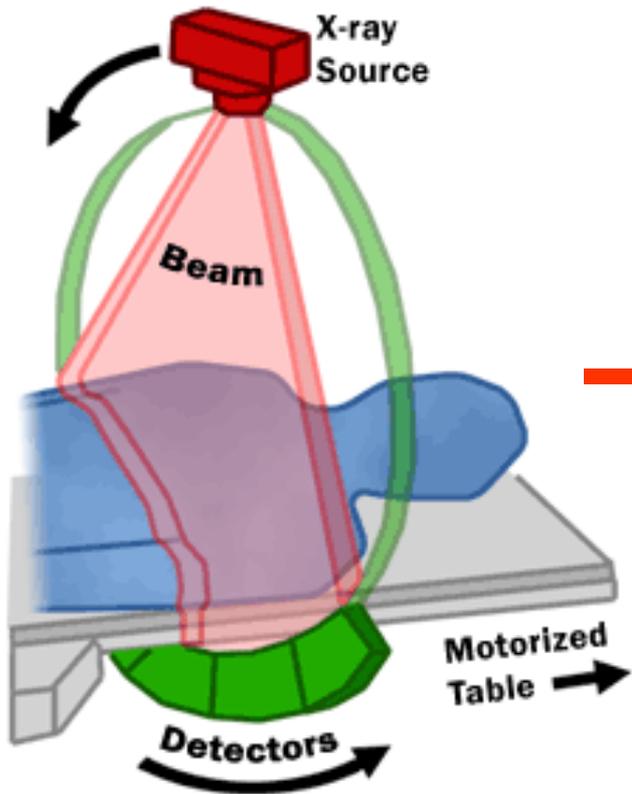
First time we could see beneath the skin without cutting open the patient

# CT – Computed Tomography

## *3d X-rays imaging*



# CT – Computed Tomography

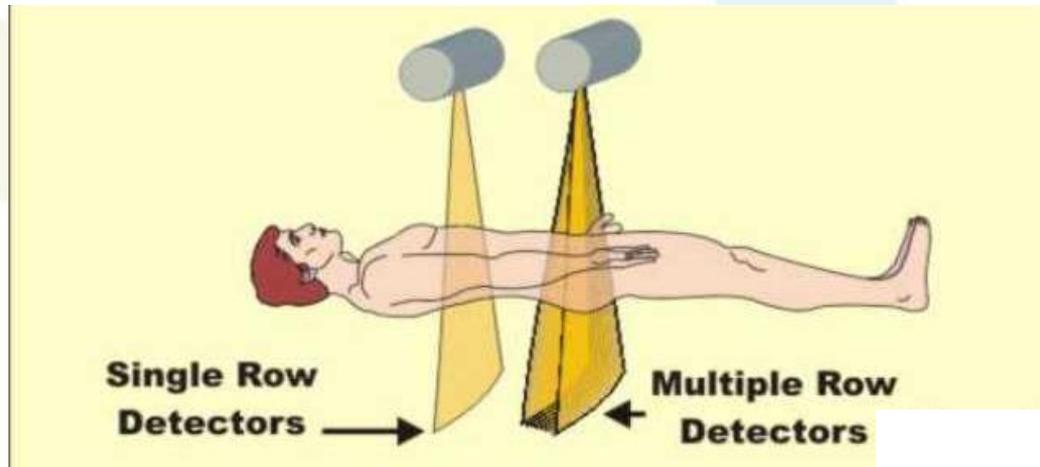


*“3D-imaging”*

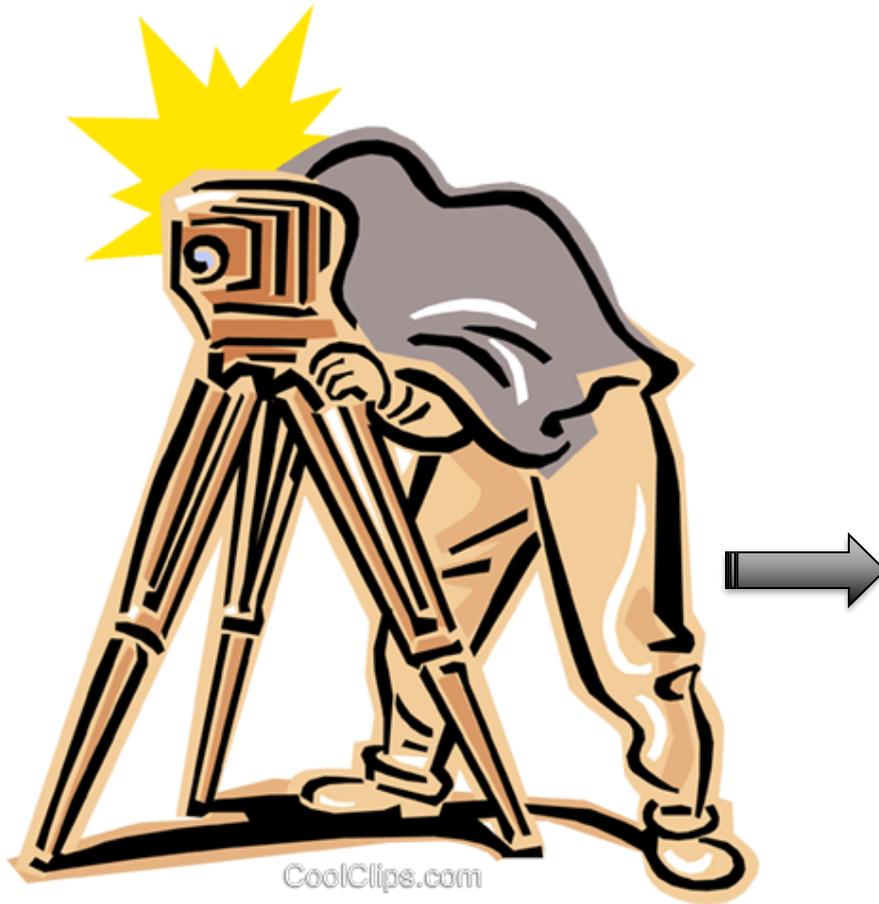
# X-ray CT is a key driver of change in medical imaging

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

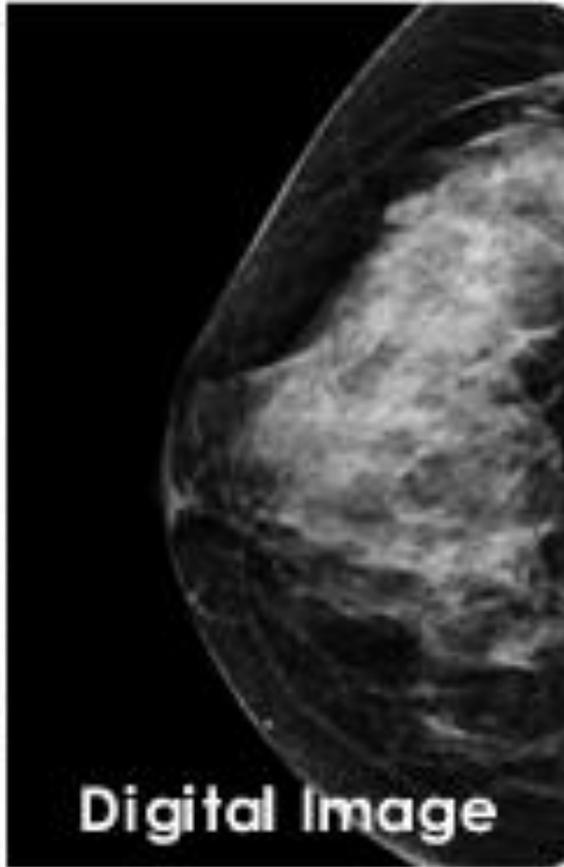
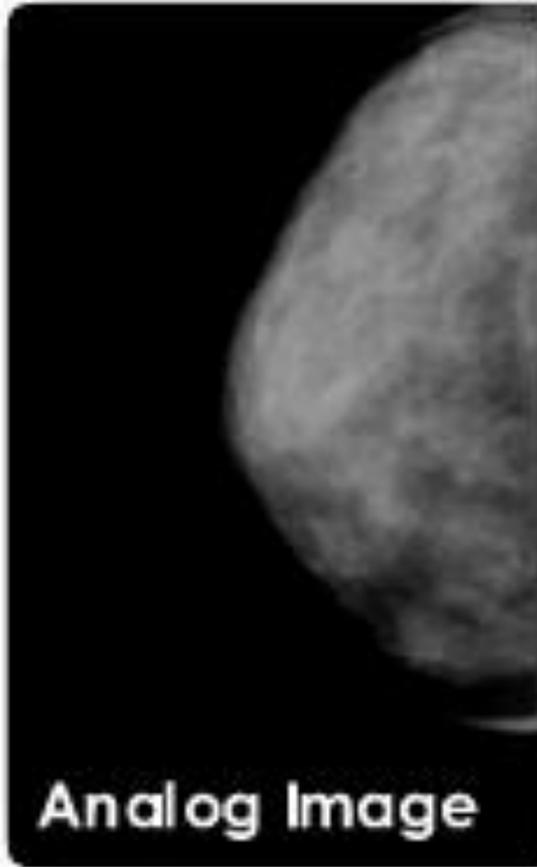


From black and white photos

To

Modern High-Tech photography

# Towards digital colour x-ray imaging



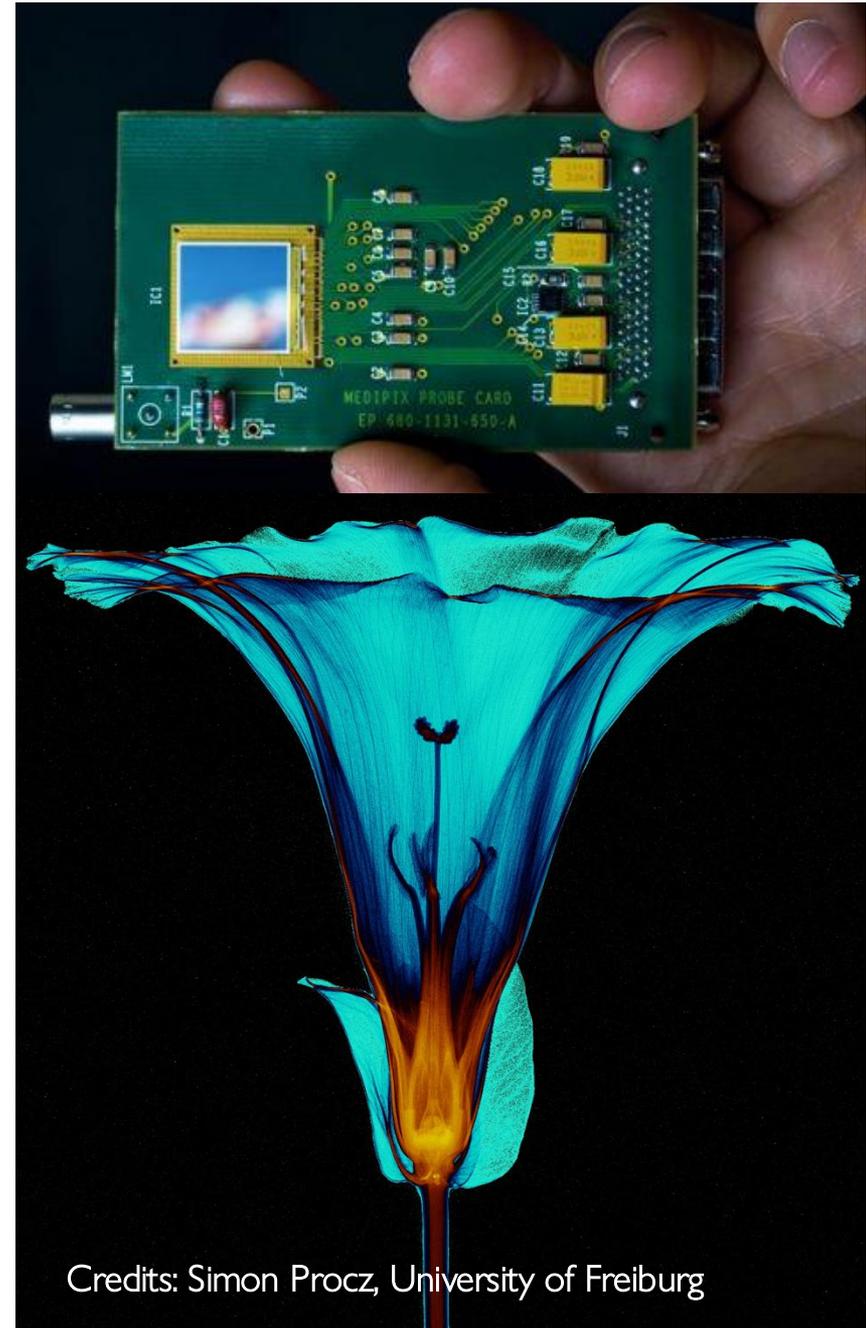
# Medipix

- High Energy Physics original development:

- Particle track detectors
- Allows counting of single photons in contrast to traditional charge integrating devices like film or CCD

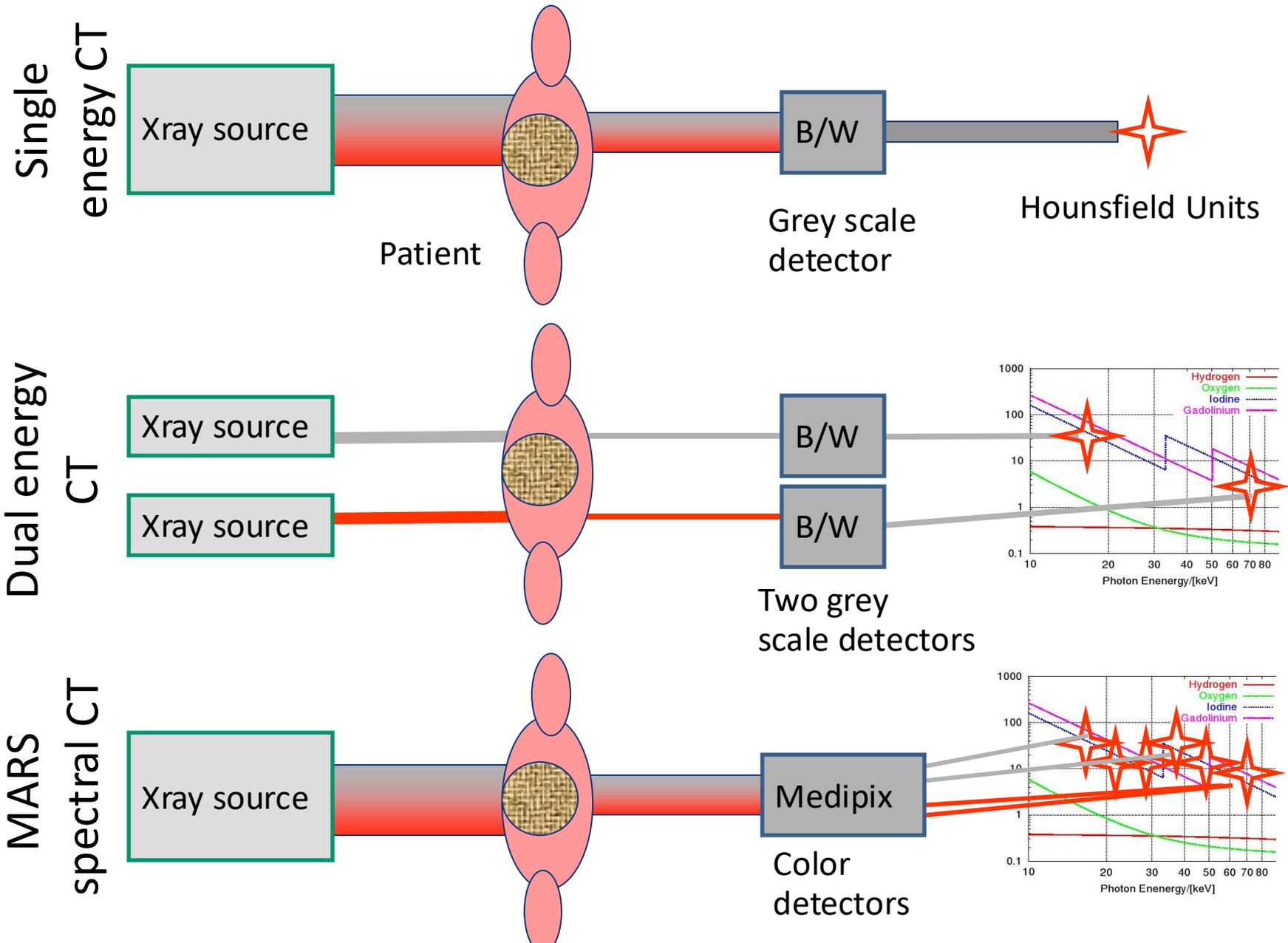
- Main properties:

- 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



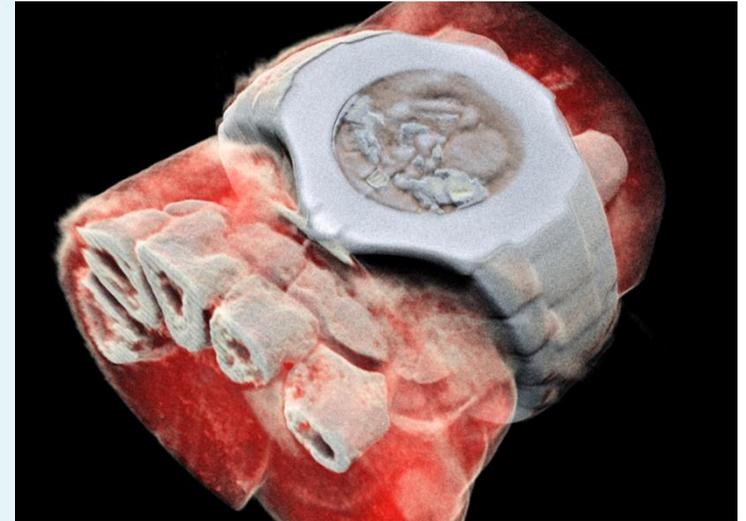
# Spectral CT is now possible

## Medipix All Resolution System

Energy resolution

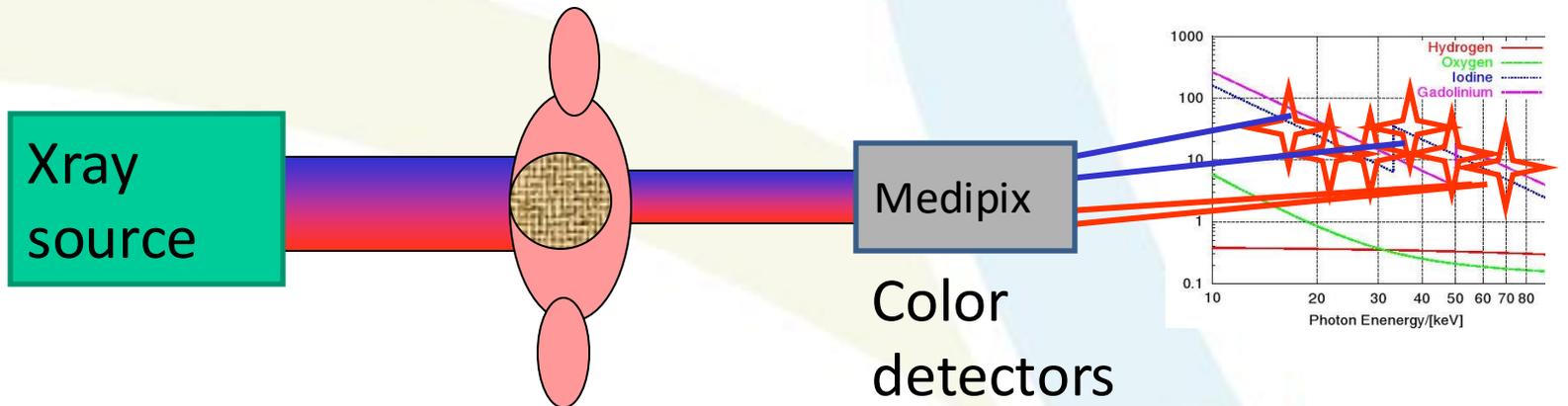
Spatial resolution

Temporal resolution

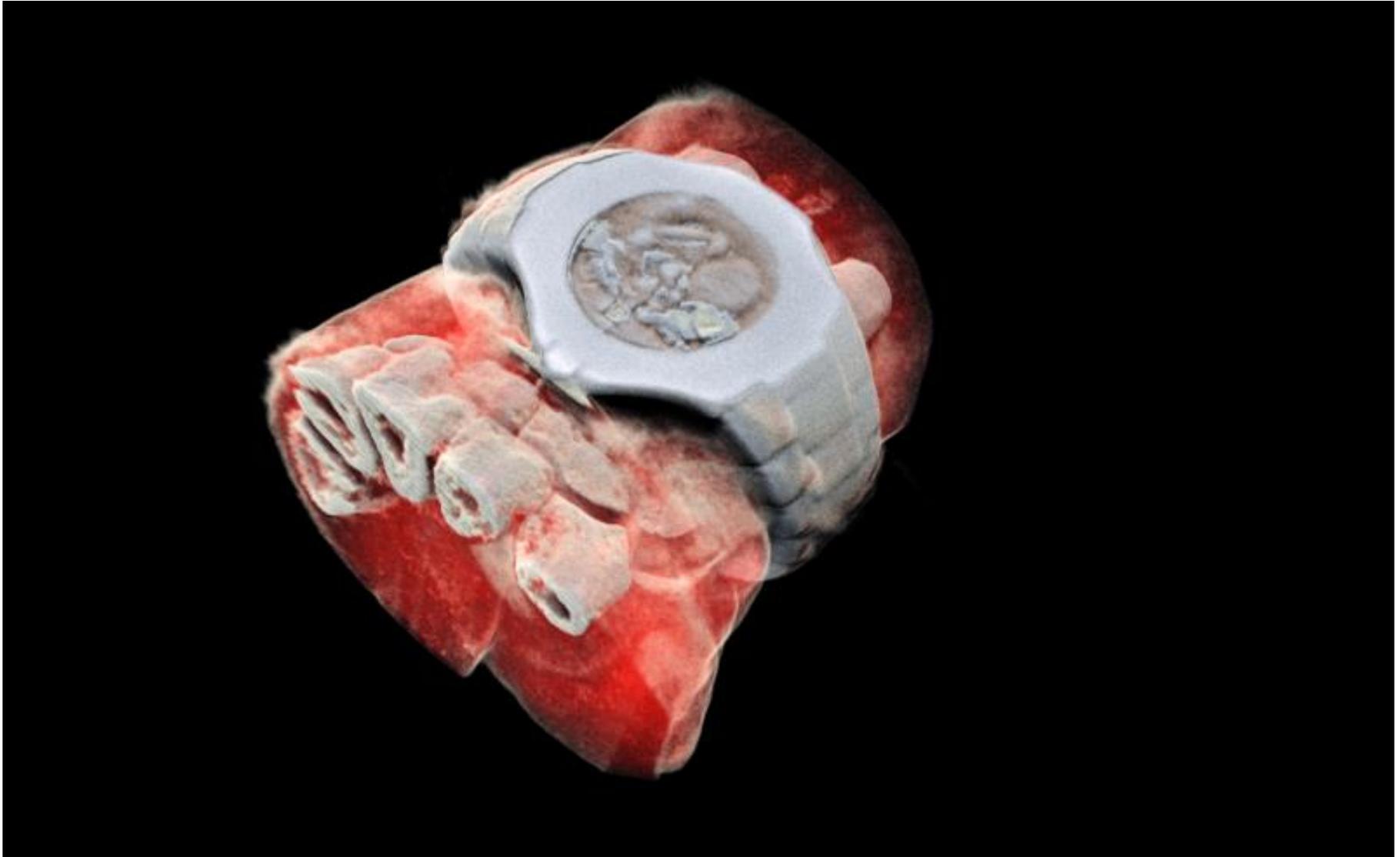


First 3D colour x-ray human image

MARS  
spectral CT

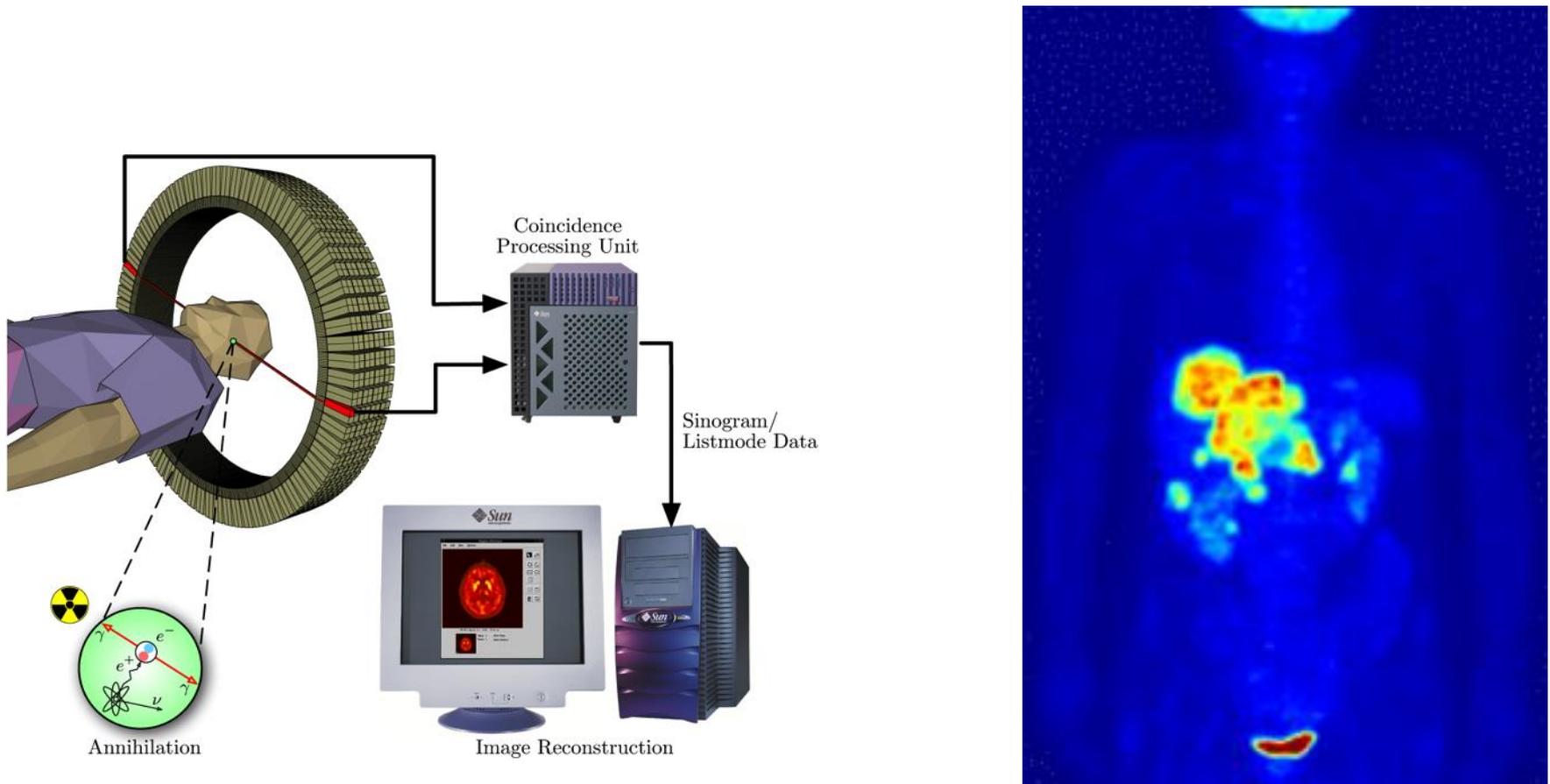


# First 3D human colour x-ray image (2018)



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)

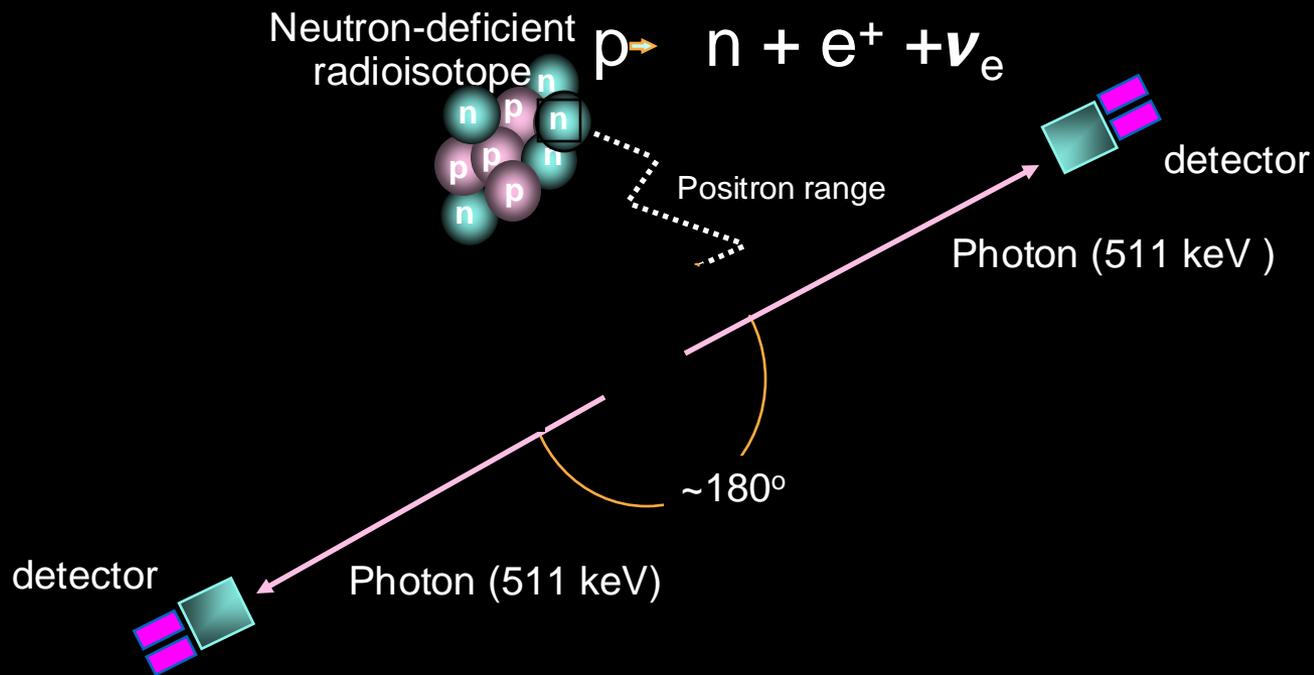
# Positron Emission Tomography



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

1974 the first human positron emission tomography

# Positron Emission Tomography

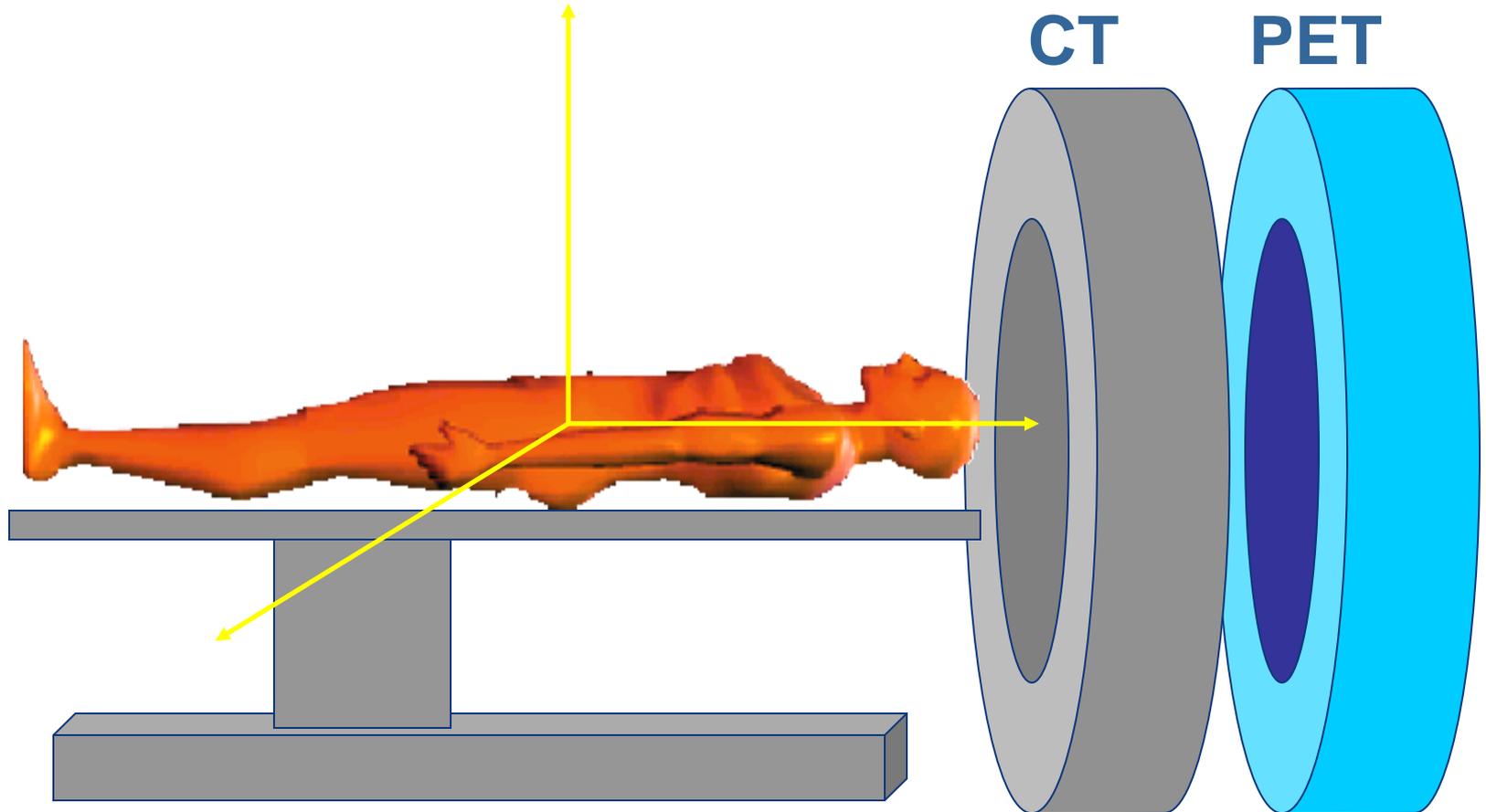


# PET – How it works

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

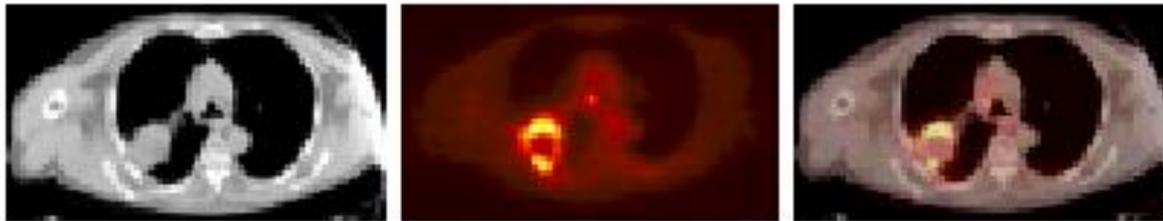
# Concept of PET-CT

*David Townsend*



# 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.



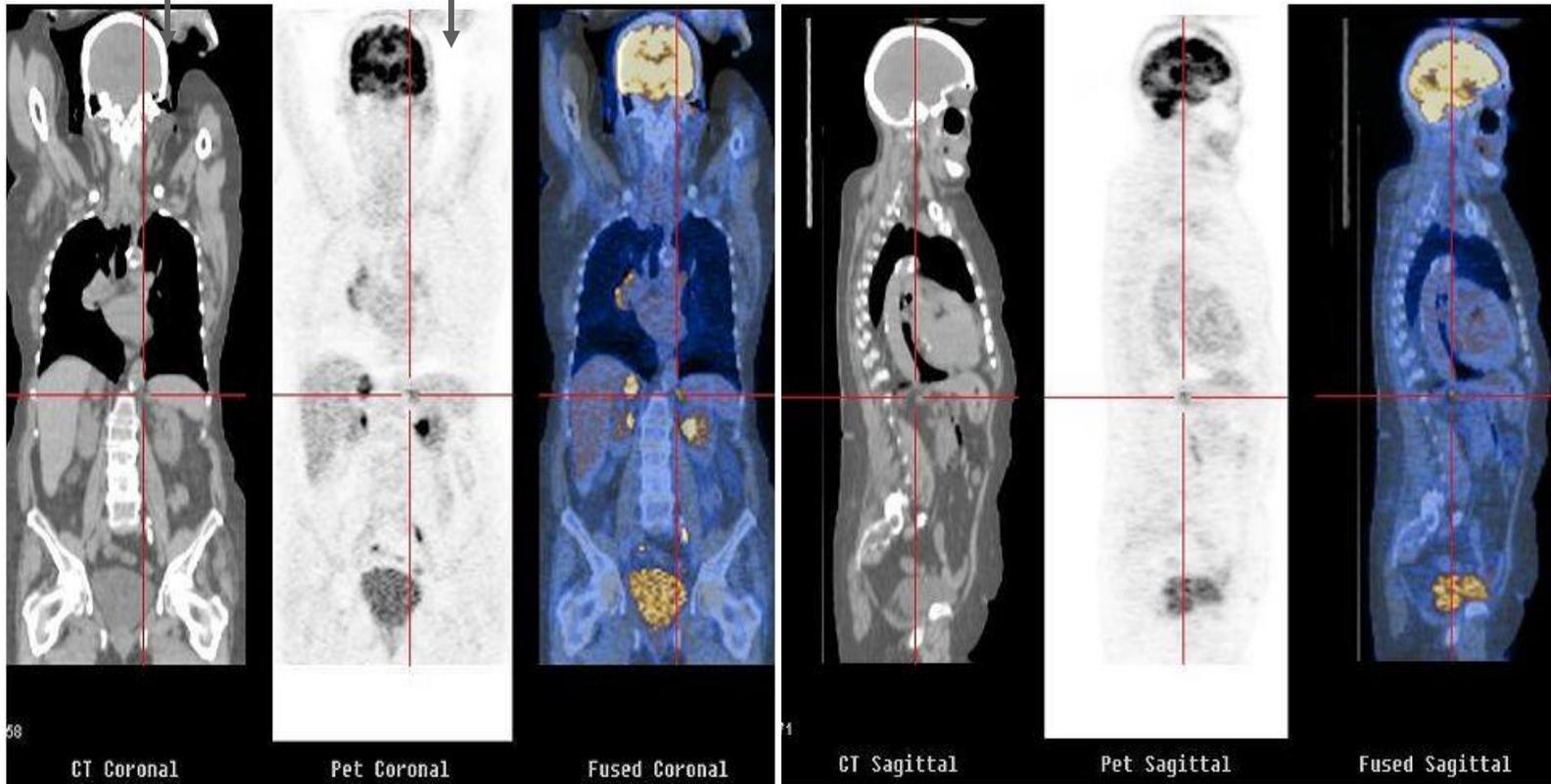
*Courtesy of David Townsend*

# Multimodality imaging: CT with PET

## Combining anatomic and functional imaging

morphology

metabolism

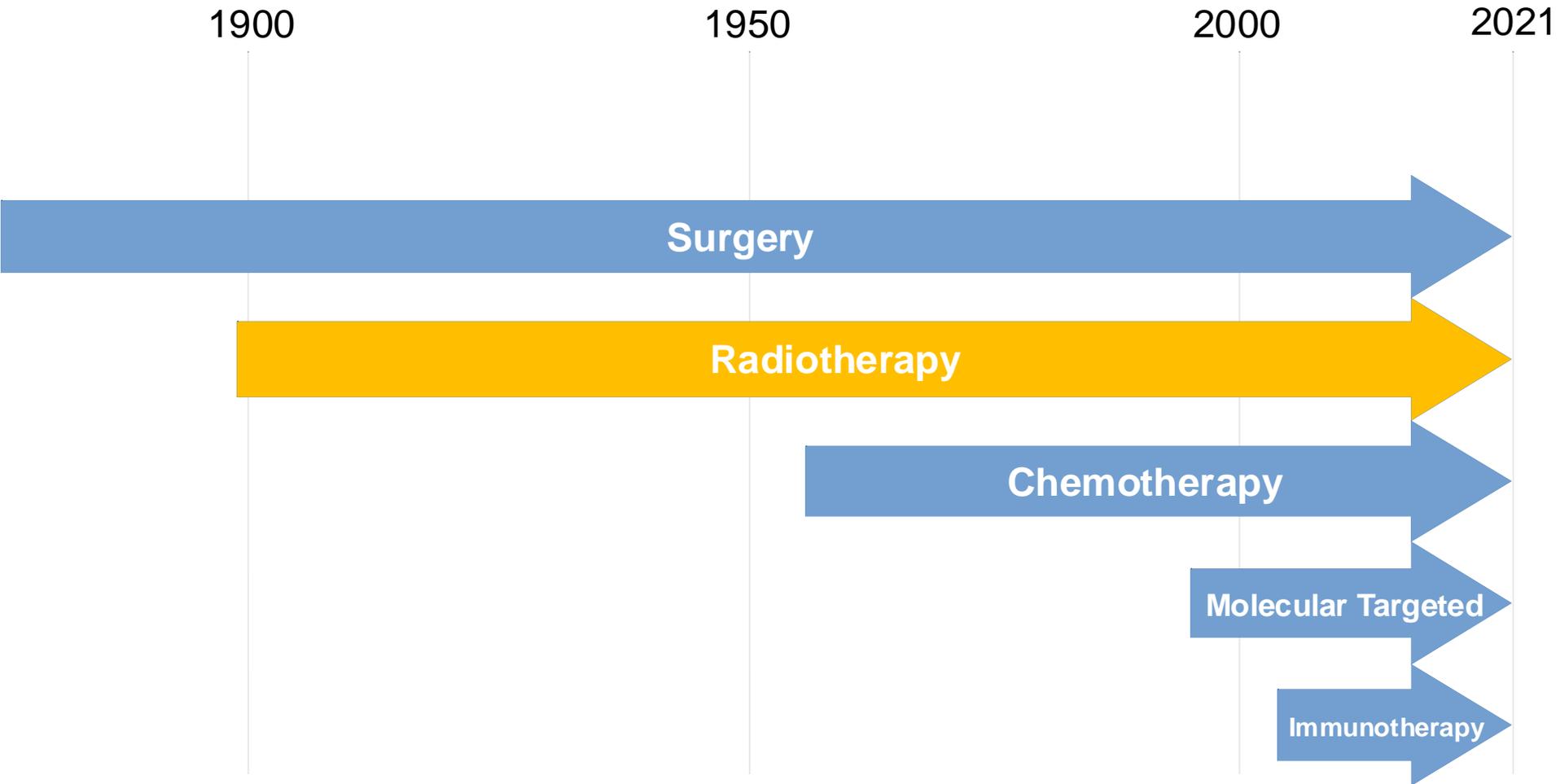


David Townsend, UK Physicist



**European NoVel Imaging Systems  
for ION therapy**

# How do we treat cancer?

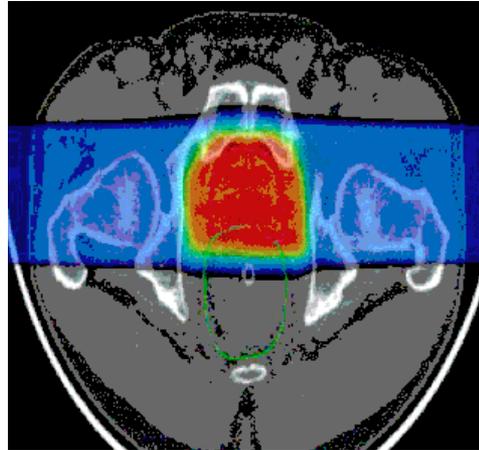


# Treatment options

Surgery



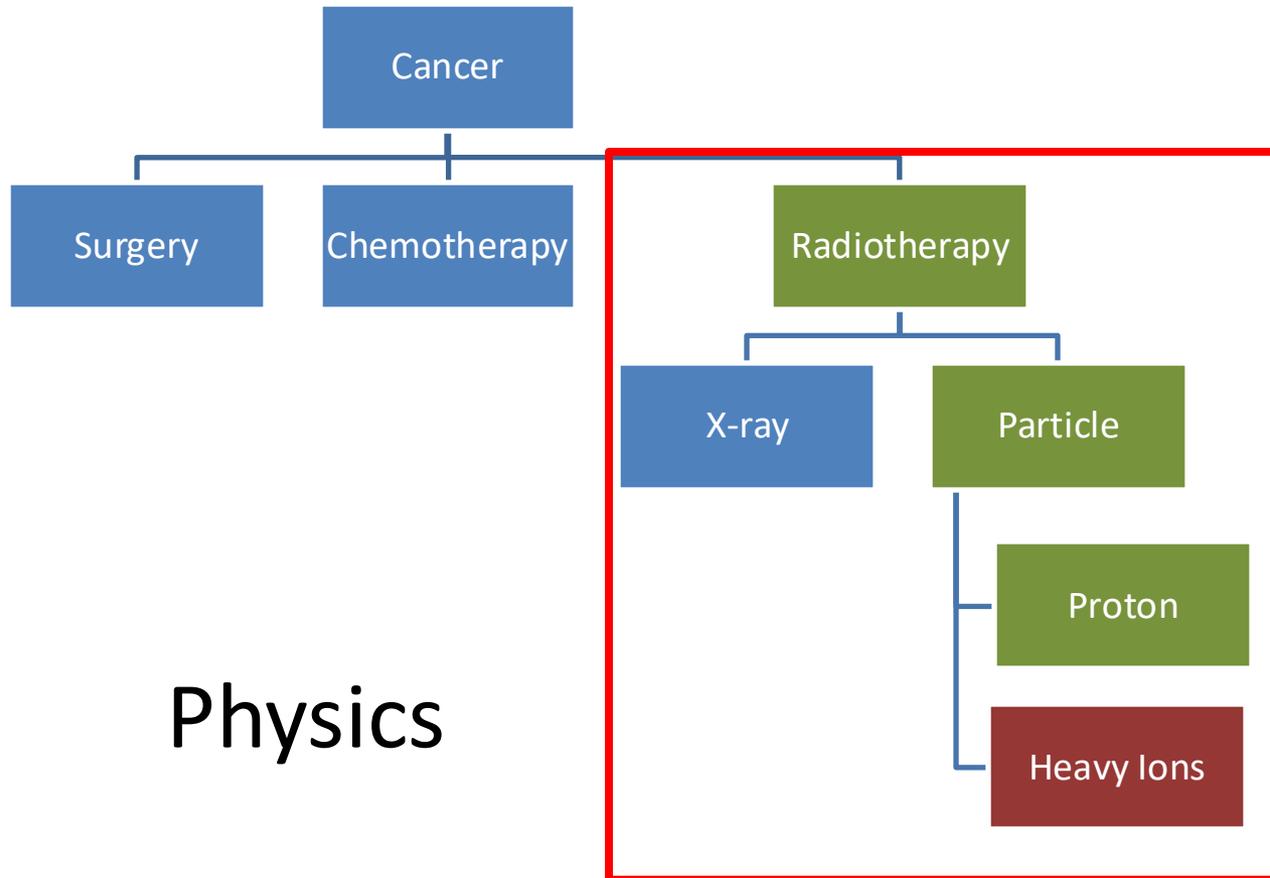
Radiotherapy



Chemotherapy (+ others)



# Cancer treatment options



Physics

# Radiotherapy in 21st Century

## 3 "Cs" of Radiation

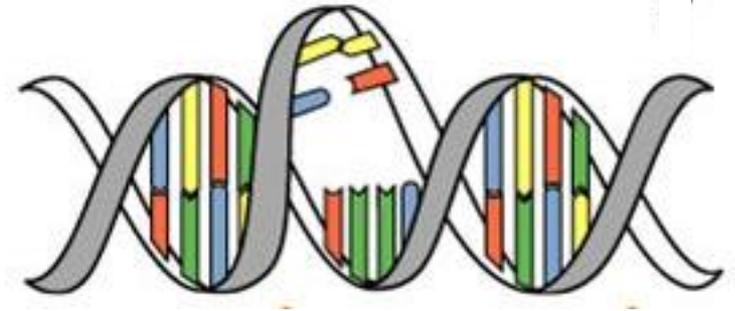
**Cure** ( about 50% cancer cases are cured)

**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

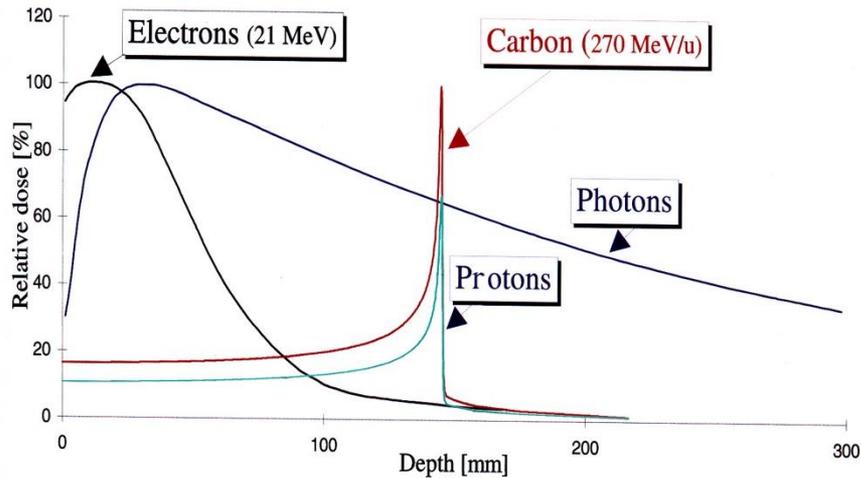


### Aims of Radiotherapy:

- 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 - 400 MeV/u hadrons



Varian True Beam e- linac



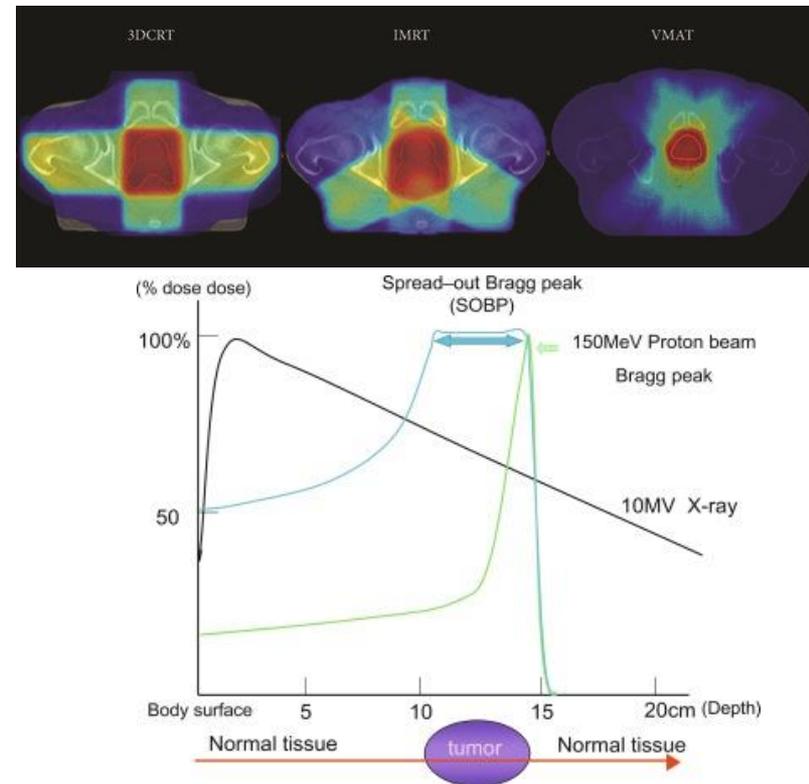
Heidelberg Ion Therapy Centre



# Goal of Radiotherapy

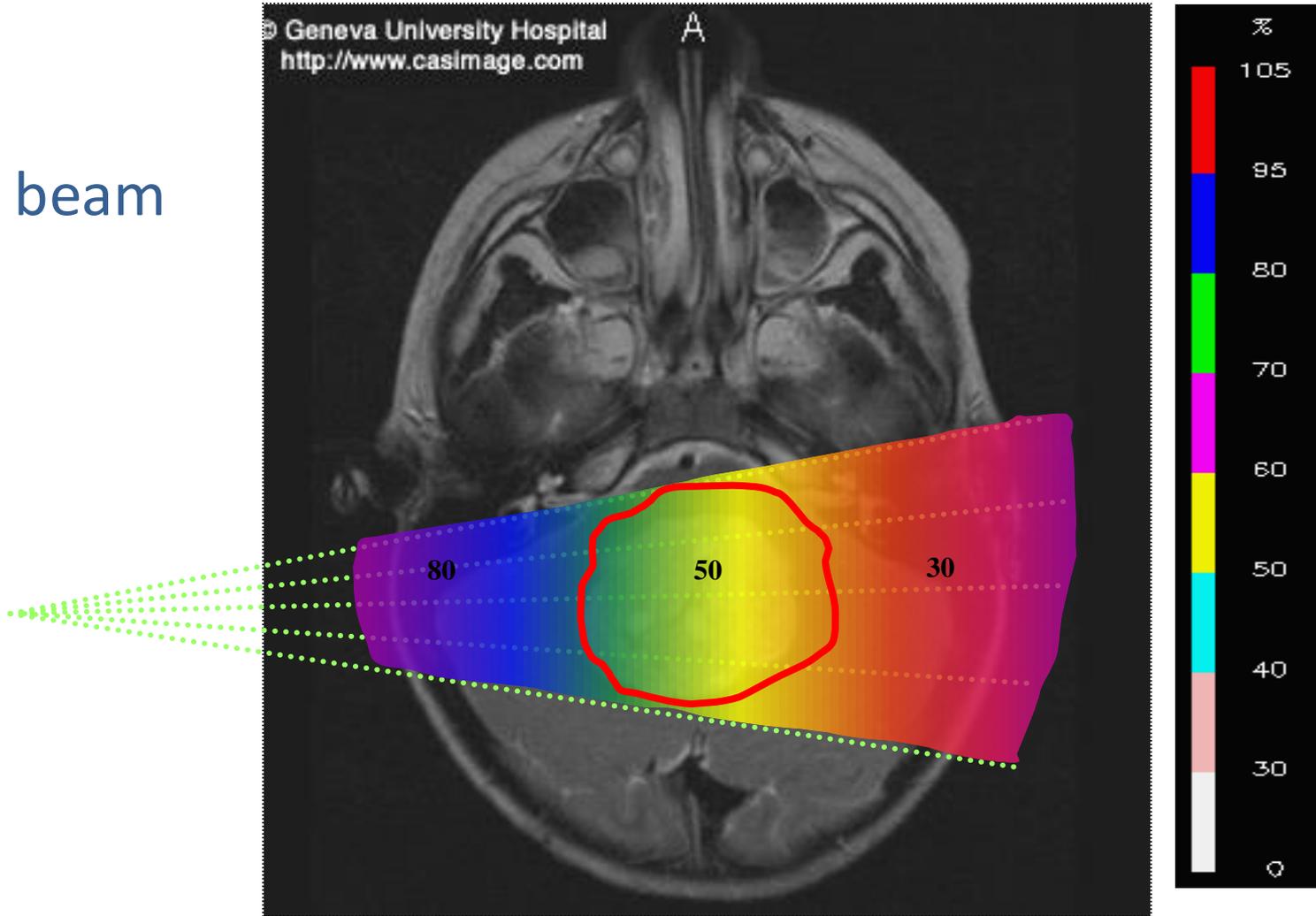
**Holy Grail: Deliver as much radiation dose to the tumour whilst minimising the dose to normal healthy tissue.**

- Better targeting – improved imaging
- Improving dose conformity to tumour through IMRT/VMAT.
- Using the Bragg Peak in hadron therapy.
- Fractionation – delivering treatment across 20-30 fractions.



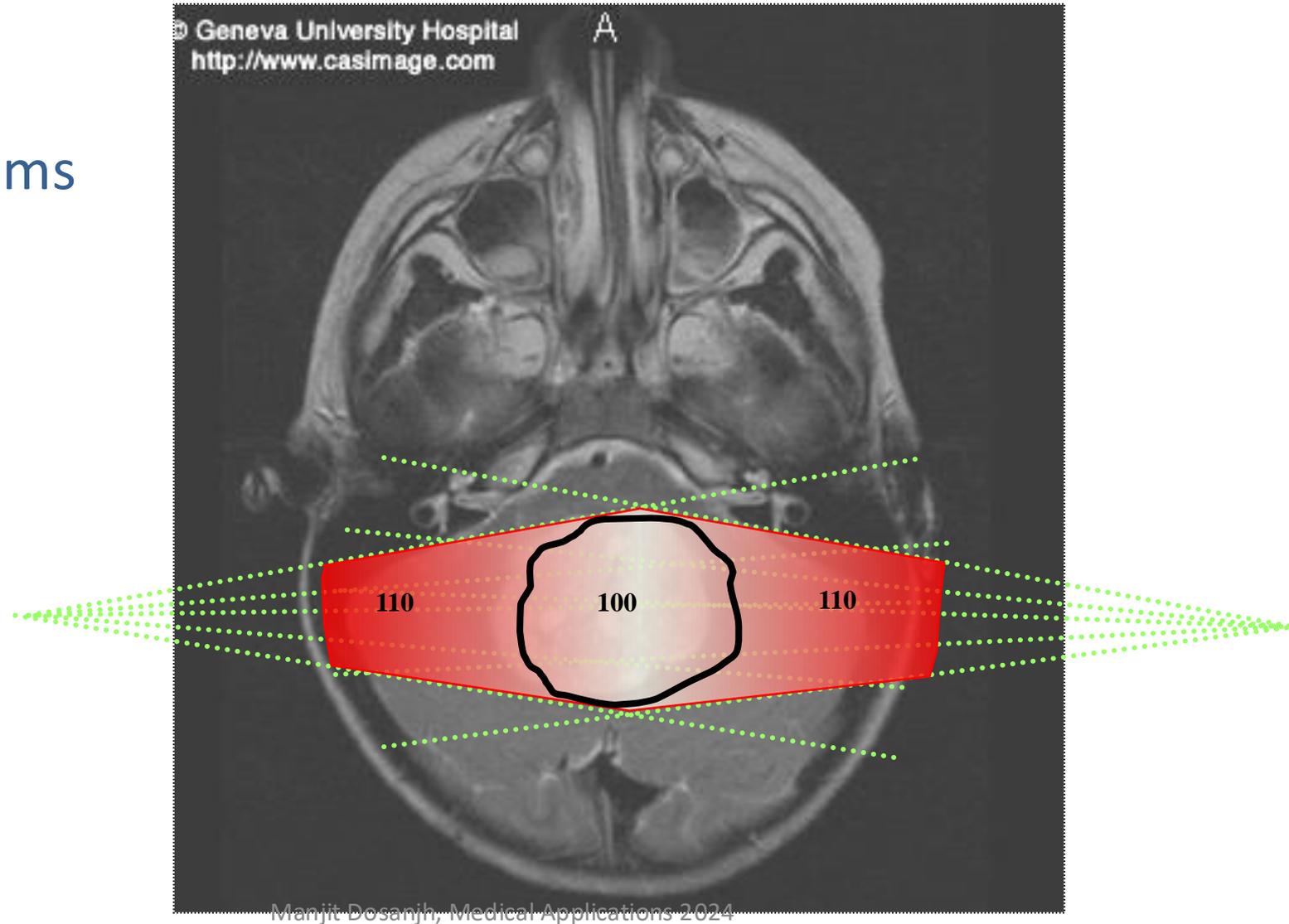
# Classical Radiotherapy with X-rays

single beam

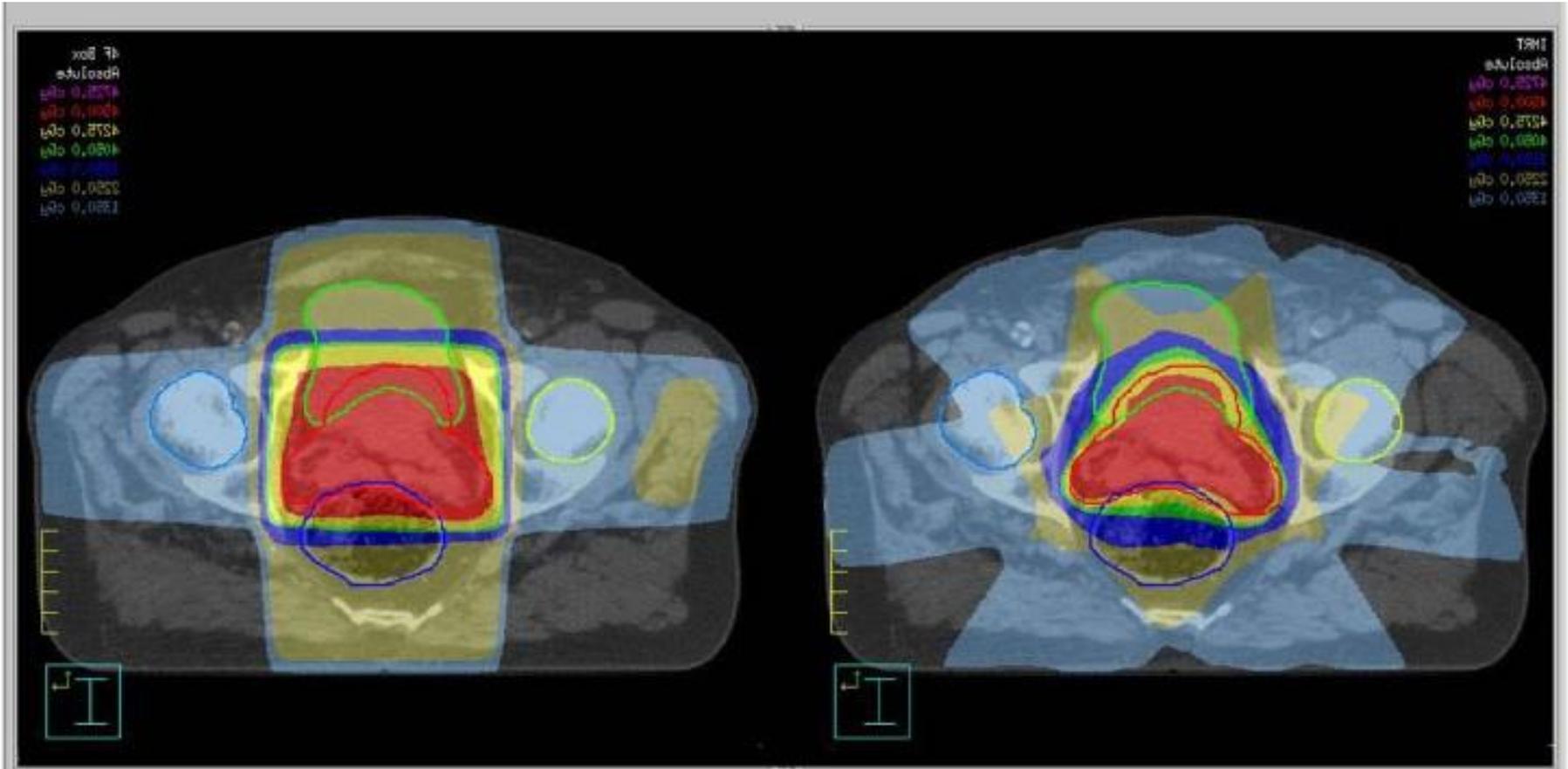


# Radiotherapy with X-rays

two beams



# Improved Delivery

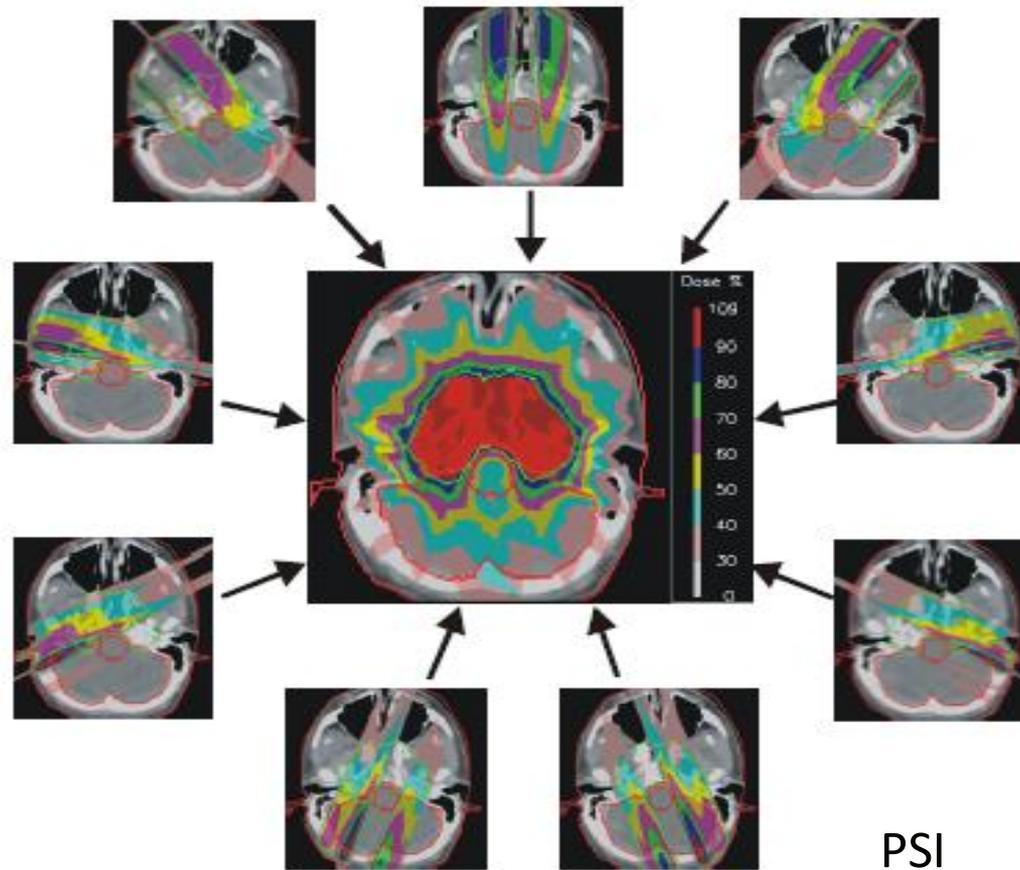


1990s: 4 constant intensity fields

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

# Intensity Modulated Radiation Therapy

9 NON-UNIFORM FIELDS



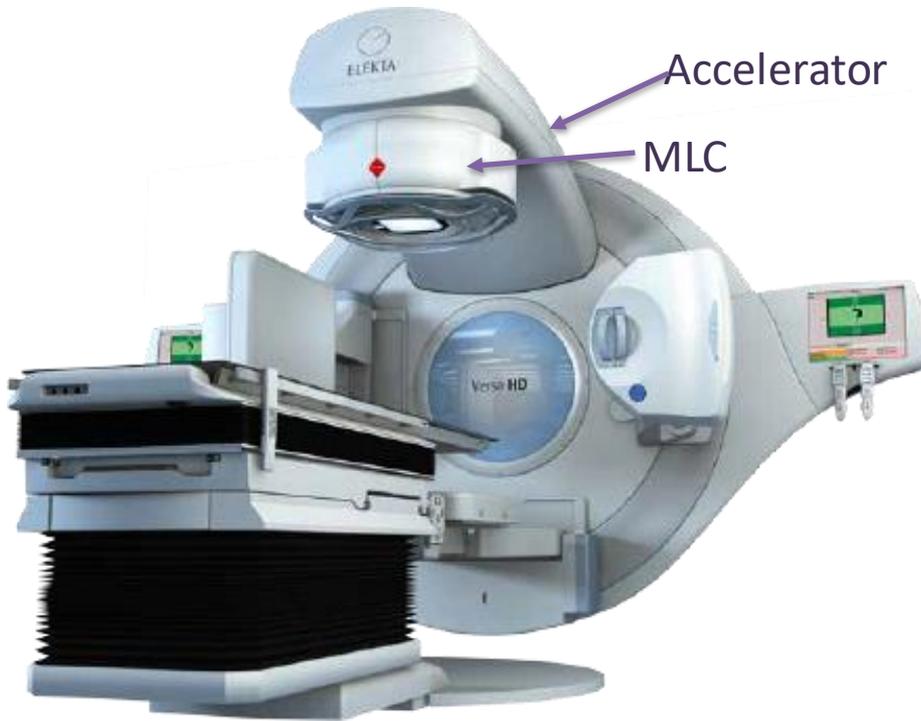
60-75 grays (joule/kg) given in 30-35 fractions (6-7weeks)  
to allow healthy tissues to repair:

90% of the tumours are radiosensitive

# The most widely available accelerator

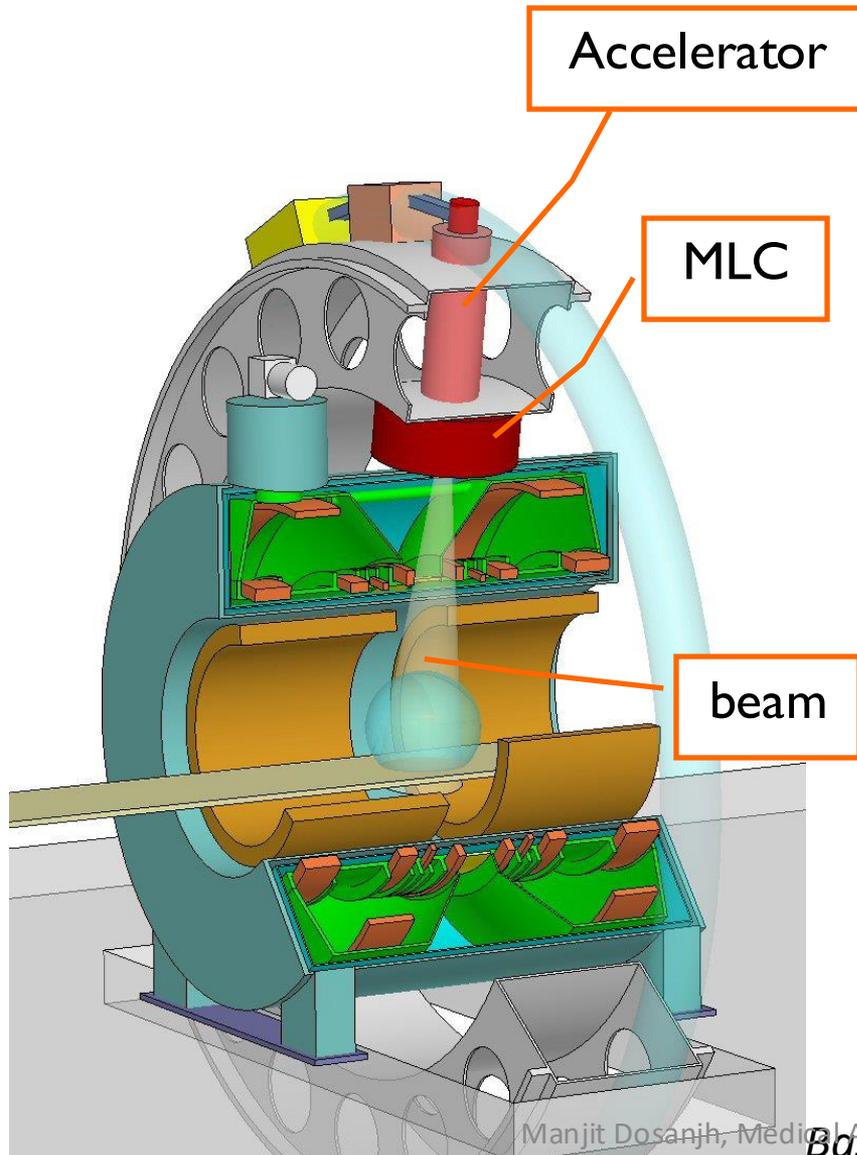
Electron Linac (linear accelerator) for radiation therapy treatment of cancer)

More than 18,000 in use



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

# Concept of MRI guided accelerator



Seeing what you treat at the moment of treatment

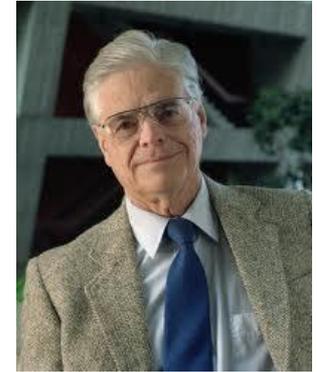
Bringing certainty in the actual treatment

# 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??**

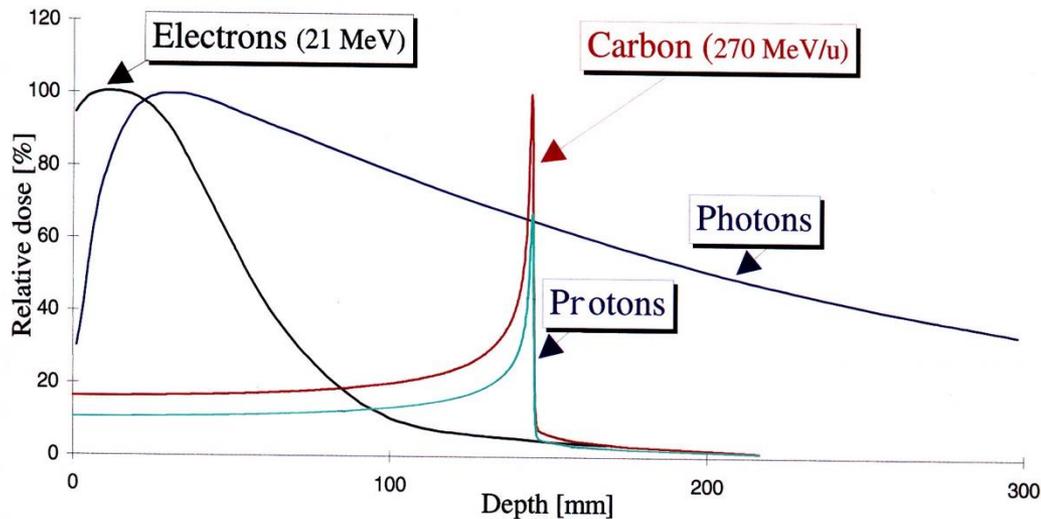
# Hadron Therapy



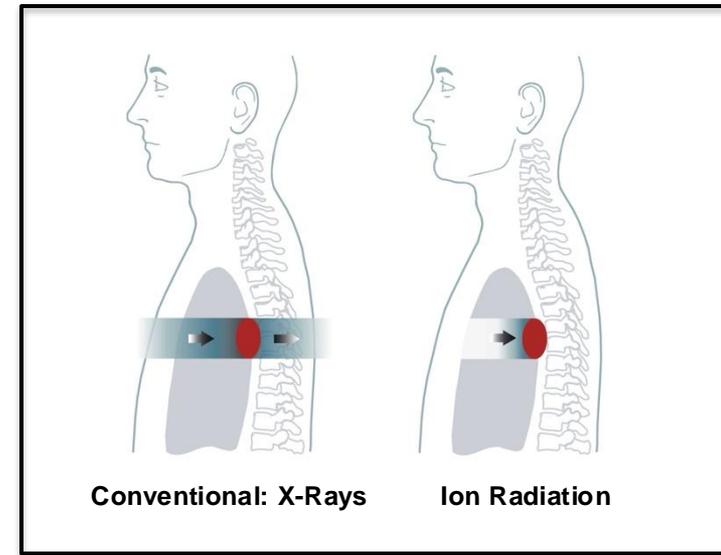
Robert Wilson  
Fermi Lab

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



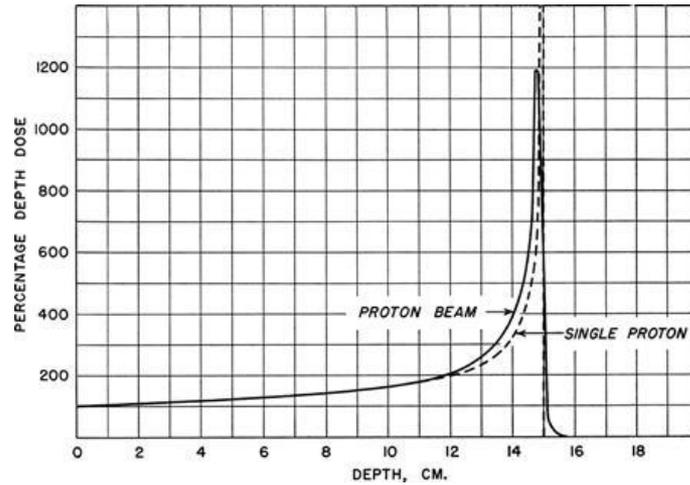
Depth in the body (mm)



1932 - E. Lawrence  
First cyclotron



1946 – proton therapy  
proposed by R. Wilson



Sept 1954 – Berkeley treats  
the first patient



From physics .....

**E. Lawrence  
First cyclotron**



**Lawrence brothers  
Physicist and Doctor**

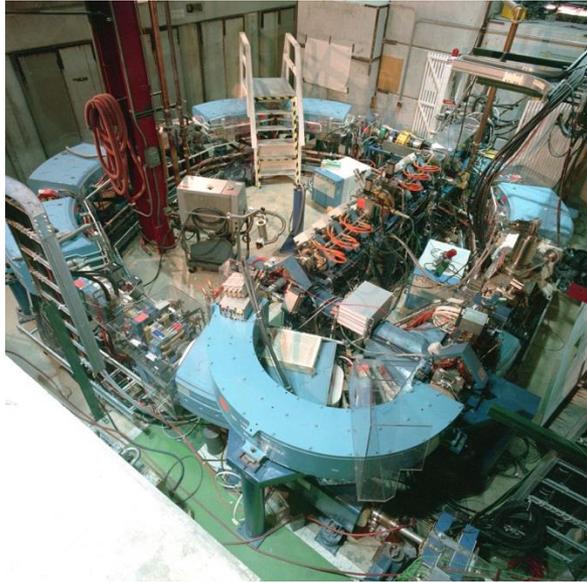


**Sept 1954 – Berkeley  
Treats first patient**



**Importance of collaboration.....**

**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

# Key Milestones of Hadrontherapy

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



**360<sup>0</sup> Gantry**



# The Darmstadt GSI 'pilot project' (1997-2008)



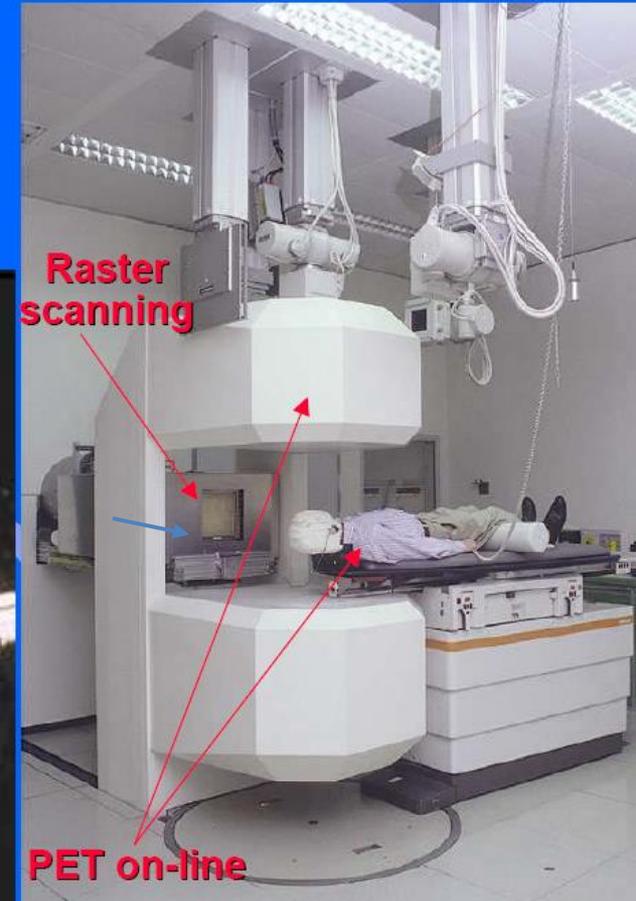
**G. Kraft**

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

**G. Kraft**

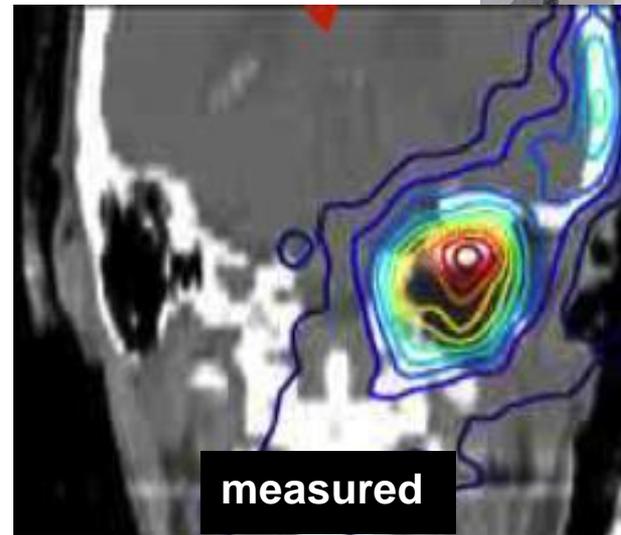
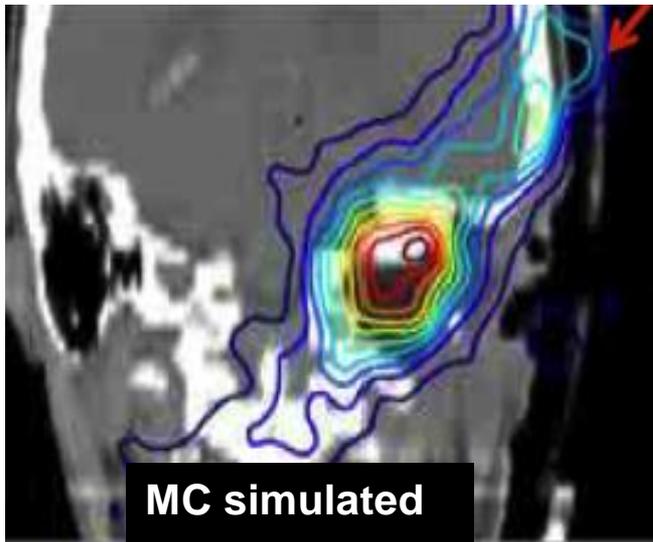


**J. Debus**

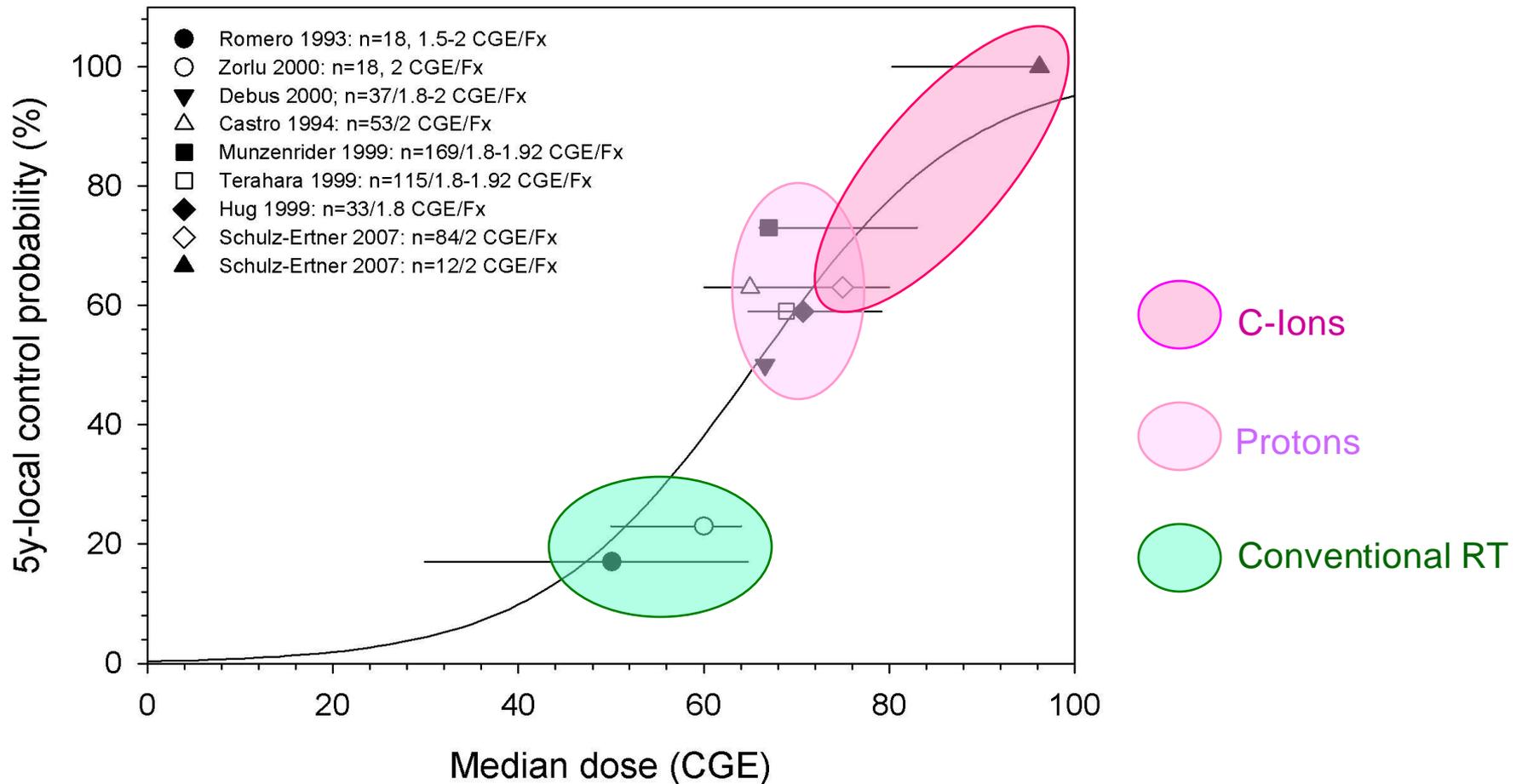


# Real-time monitoring

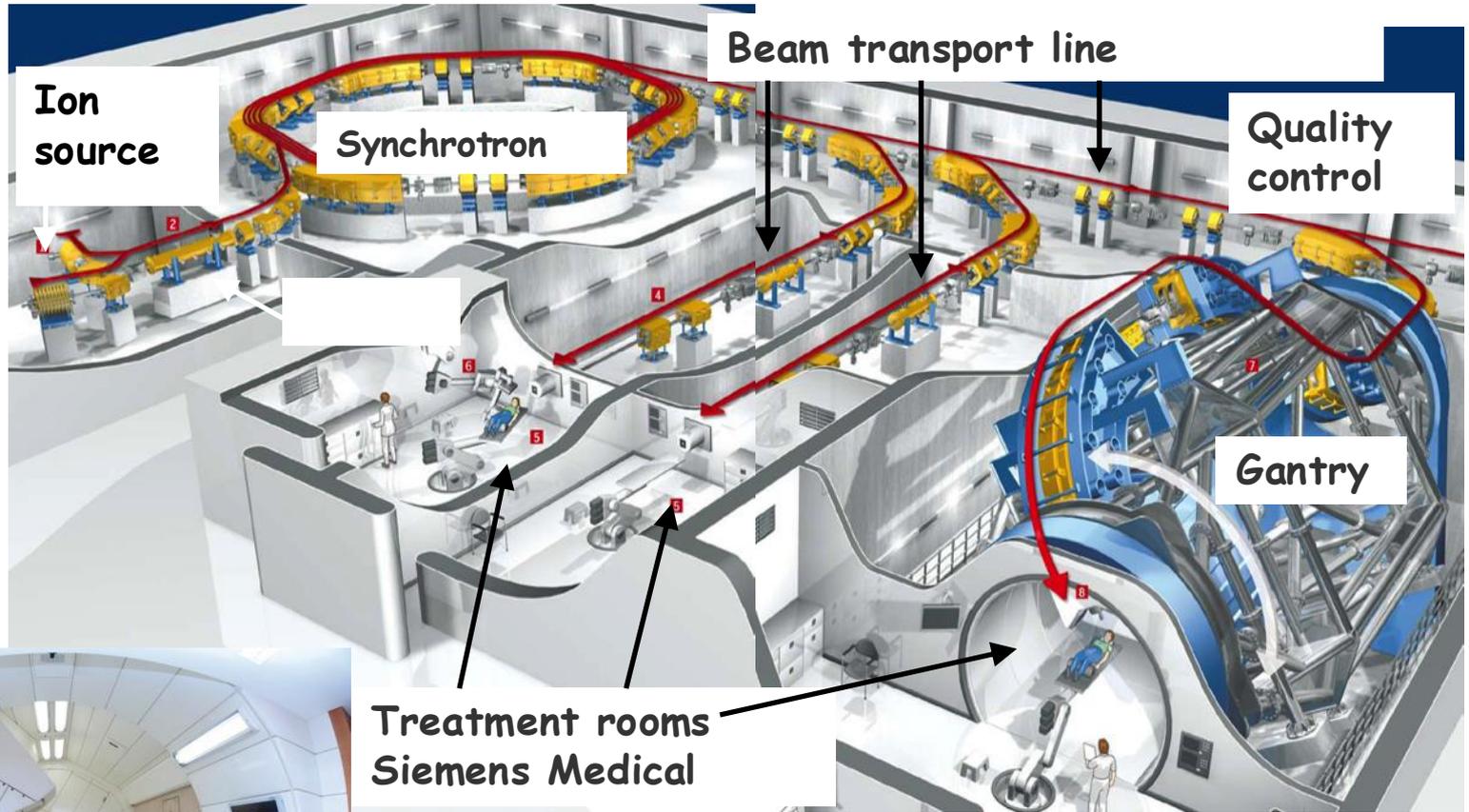
- In-beam PET @ GSI (Germany)
- MonteCarlo simulations
- Organ motion



# Tumour Control Rate: Chordomas



# HIT - Heidelberg



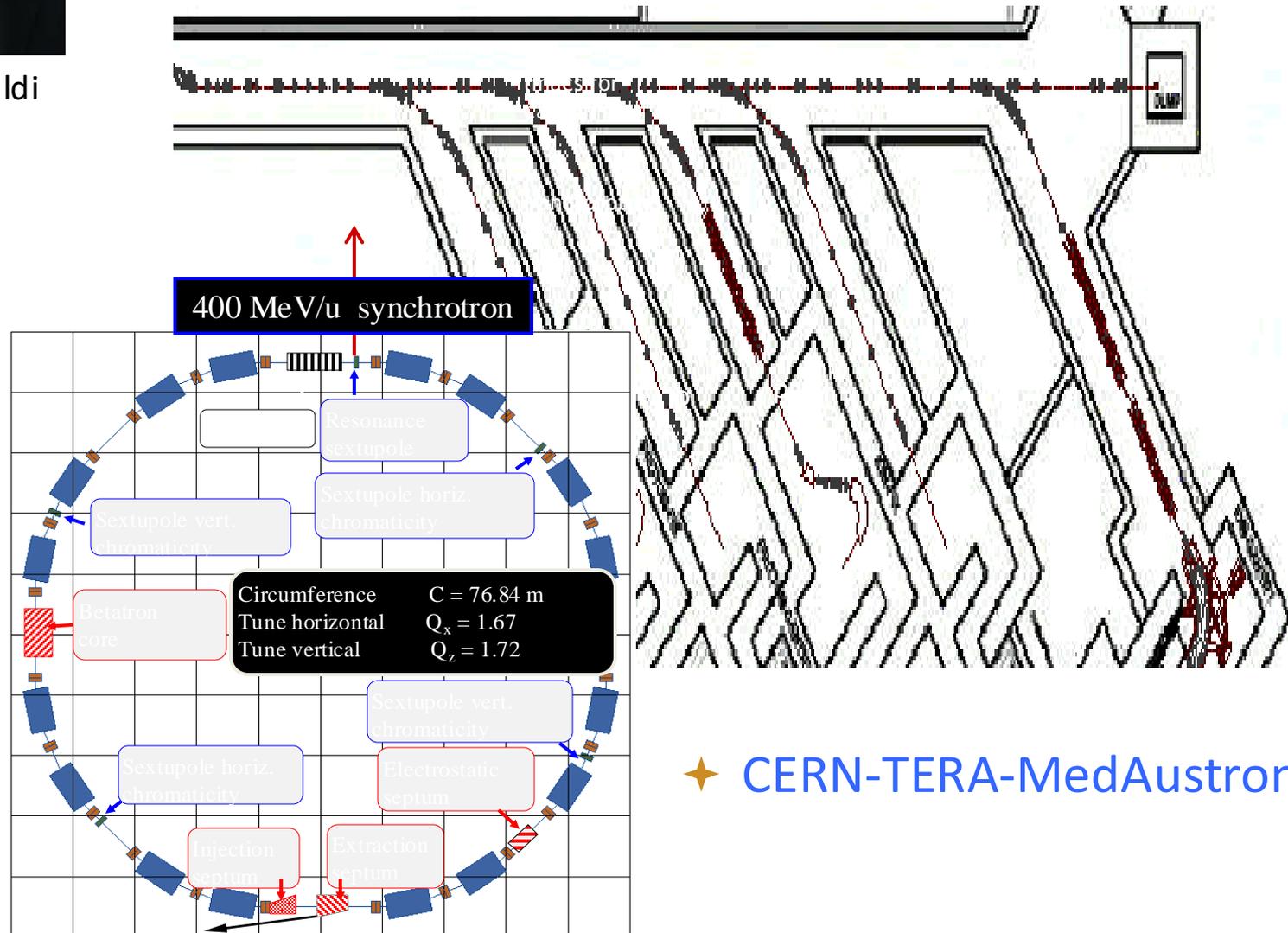
Carbon facilities in Europe: first was HIT  
in Heidelberg – started treating patients in 2009

Manjit Dosanjh, Medical Applications 2024



Ugo Amaldi  
TERA

# PIMMS at CERN (1996-2000)



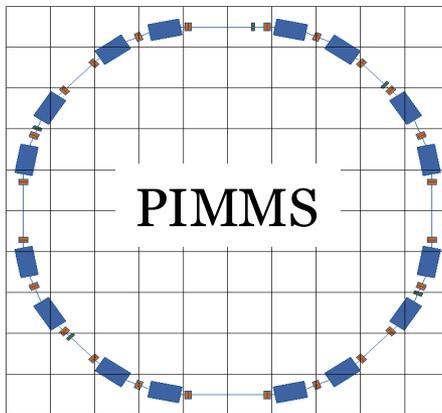
✦ CERN-TERA-MedAustron

# PIMMS study at CERN (1996-2000)



Treatment , CNAO, Italy  
2011

1996-2000  
PIMMS study



MedAustron, Austria 2019



# From PIMMS study to clinical reality



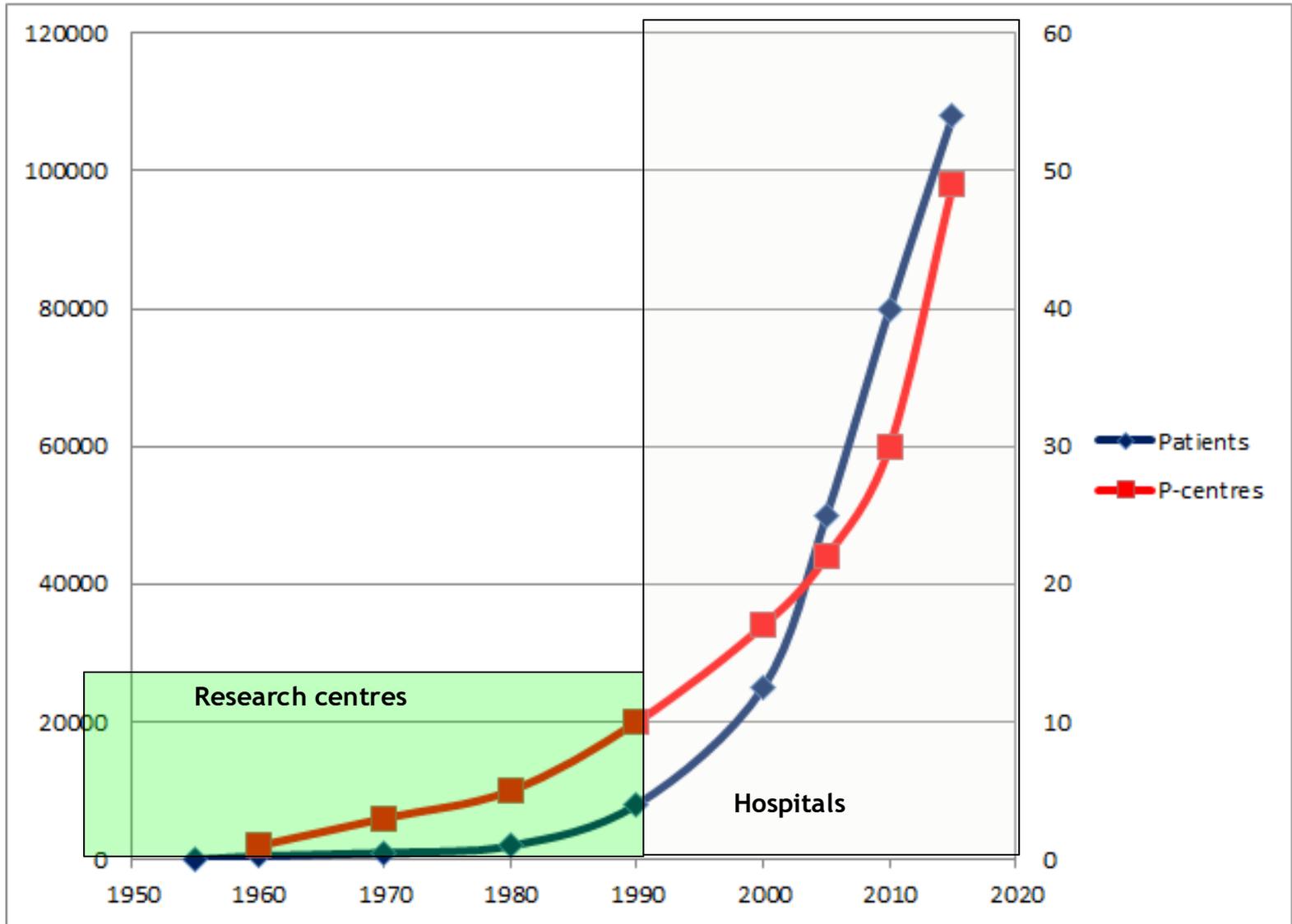
First patient with carbon ions Nov 2012



Treatment started in 2016

**TERA celebrated 30 years on 16 September 2022**

[Data from [www.ptcog.ch](http://www.ptcog.ch)]



# Particle Facilities Facilities in Europe in 2023



# Particle Therapy facilities in clinical operation in 2023



Proton facilities (in red) and 14 carbon therapy facilities (in blue) ***PTCOG, 2024***

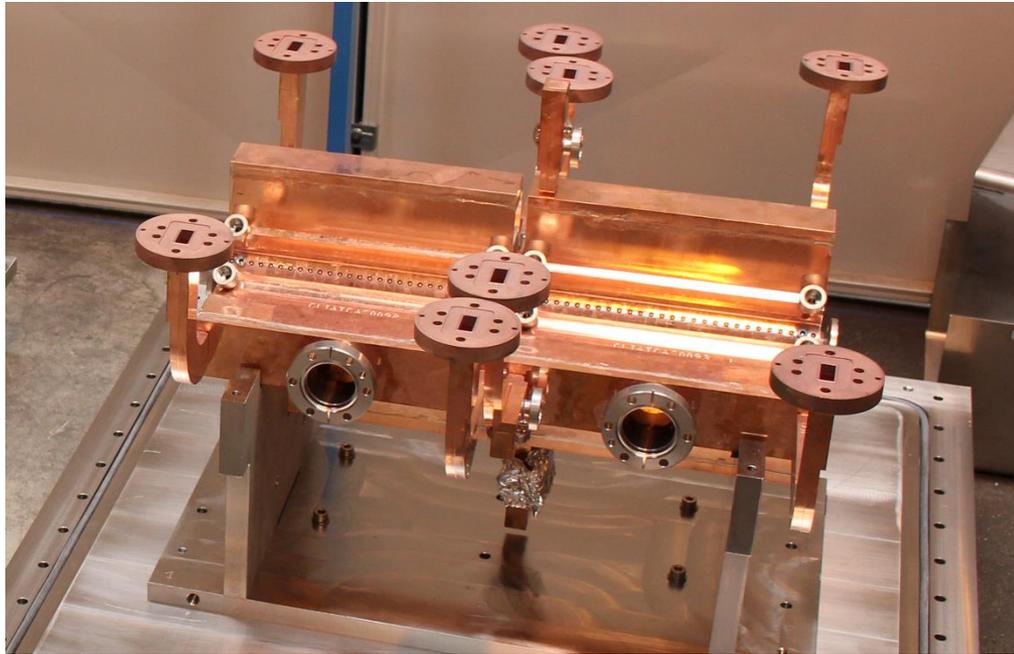
# Much more still needs to be done

- 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

# VHEE (Very High Energy Electrons)

# 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



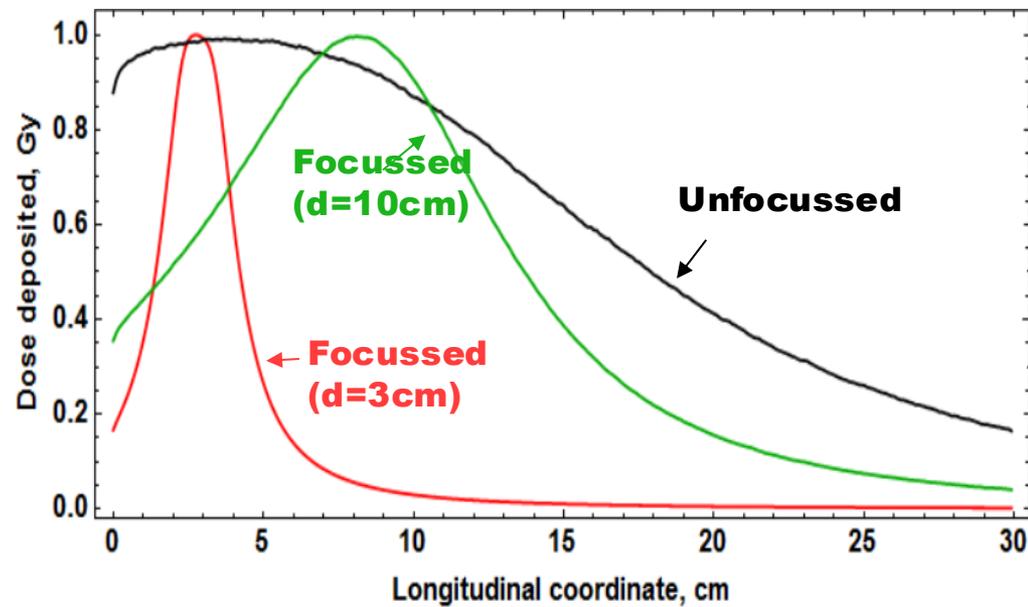
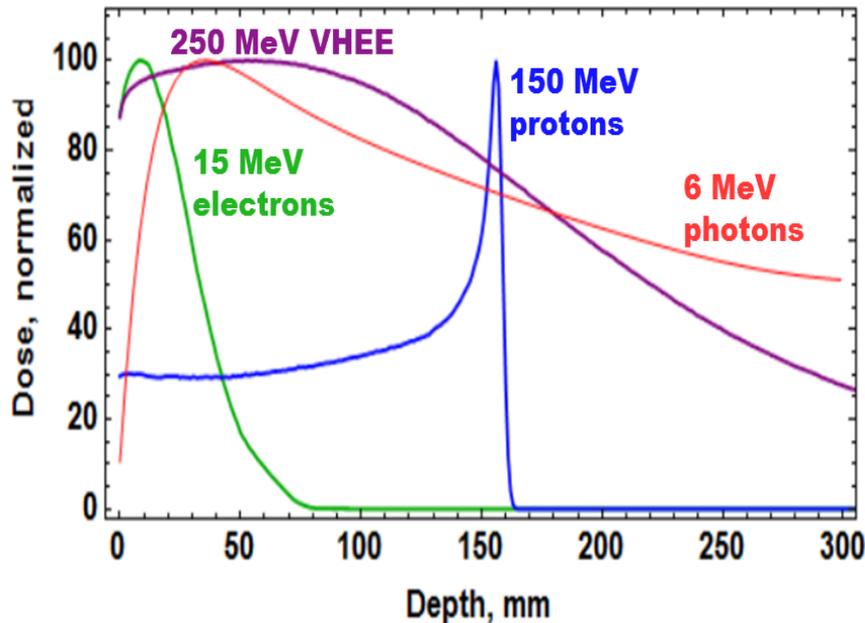
**CLIC RF X-band cavity prototype (12 Ghz, 100 MV/m)**

**Compact Linear Collider**

Manjit Dosanjh, Medical Applications 2024

# VHEE

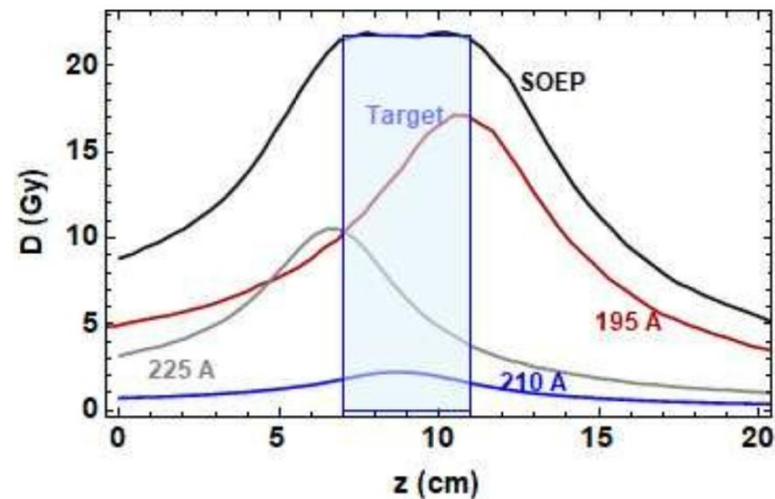
- Their ballistic and dosimetric properties can surpass those of photons, which are currently the most commonly used in RT.
- Their position compared to protons need to be evaluated, but they can be produced at a reduced cost.



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

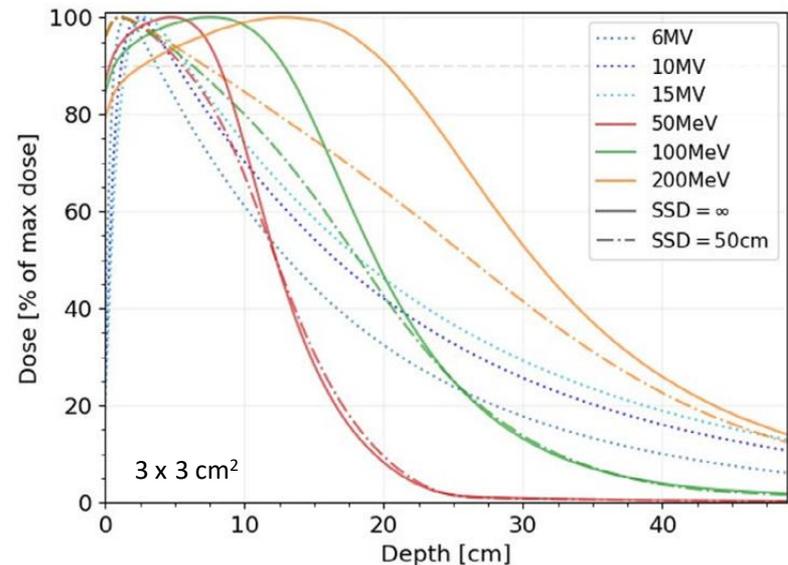
# Very High Energy Electron (VHEE) Radiotherapy

- Favourable characteristics compared to clinical electron beams such as :
  - Increased range within the patient
  - Sharper lateral penumbra
  - Relative insensitivity to tissue heterogeneities
- Possibility for pencil beam scanning or strong focussing (to create an 'electron peak')
- Numerous studies show VHEE can provide generally superior treatment plans compared to state-of-the-art photon RT.
- VHEE facilities would be more compact and cost-effective in comparison to proton and ion therapy facilities.



# Very High Energy Electron (VHEE) Radiotherapy

- Recently revived interest in using VHEE (50-250 MeV e-) for RT due to:
- Advances in high-gradient accelerator technology (e.g. CLIC X-band RF cavities  $\sim 100$  MV/m, and laser-wakefield acceleration  $\sim$ GV/m);
- Using the FLASH effect for deep-seated tumours – technologically easier to produce high intensity electron beams compared to photons or hadrons.





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



UNIVERSITY OF  
OXFORD

# Glimpse of FLASH THERAPY - 2014

## First Proof-of-Concept with low-energy e<sup>-</sup>

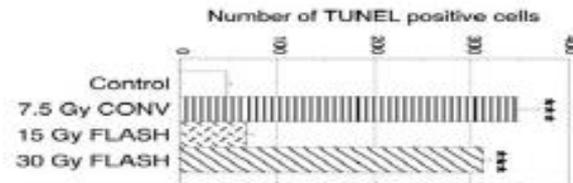
Sci Transl Med 6: 245ra93, 2014

- **FLASH spared normal lung tissue** at doses known to induce fibrosis in mice exposed to conventional dose-rate irradiation (CONV).

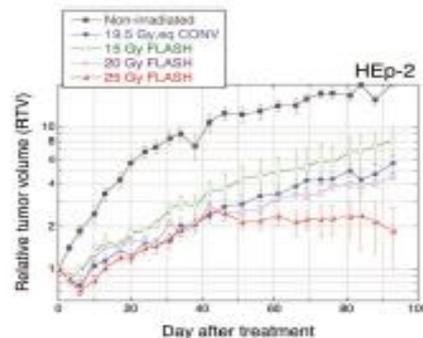


Visualisation of collagen invasion (Masson trichrome staining)  
Healthy      Fibrosis      Healthy

- **FLASH spared smooth muscle cells** in arterioles from radio-induced apoptosis.

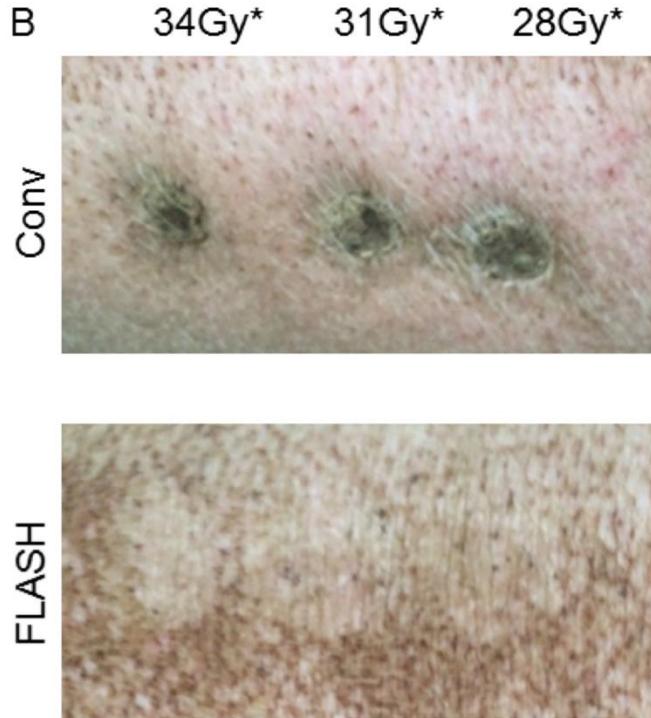


- No difference between FLASH and CONV with regard to tumor growth inhibition.
- However, **normal tissue sparing by FLASH** allowed dose escalation without complications, resulting in complete tumor cure in some xenograft models.



# The FLASH Effect – gaining huge momentum

Vozenin MC, De Fomel P, Petersson K, Favaudon V, Jaccard M, Germond JF, Petit B, Burki M, Ferrand G, Patin D, Bouchab H, Ozsahin M, Bochud F, Bailat C, Devauchelle P, Bourhis J. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. Clin Cancer Res. 2019 Jan

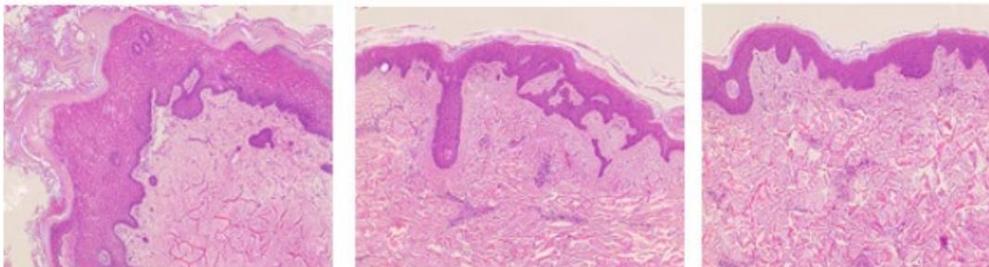


- Apparent sparing of healthy tissue when dose is delivered at **ultrahigh dose rates (UHDR) of > 40 Gy/s.**
- Healthy tissue sparing observed in virtually all radiation modalities.
  - ✓ Majority of experiments/trials with low energy electrons and shoot-through protons.
- So far, 2 human trials:
  - Skin lymphoma with 6 MeV electrons (CHUV, 2019).
  - Bone metastases with 250 MeV (shoot-through) protons (Cincinnati, 2020). Pain relief and not curative
  - Further trials are ongoing

34 Gy Conv

34 Gy FLASH

Control



**FLASH mechanism is still not fully understood.**

# Clinical Translation (2019): Treatment of a first patient with FLASH-radiotherapy,

**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 tissues



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)



Original Article

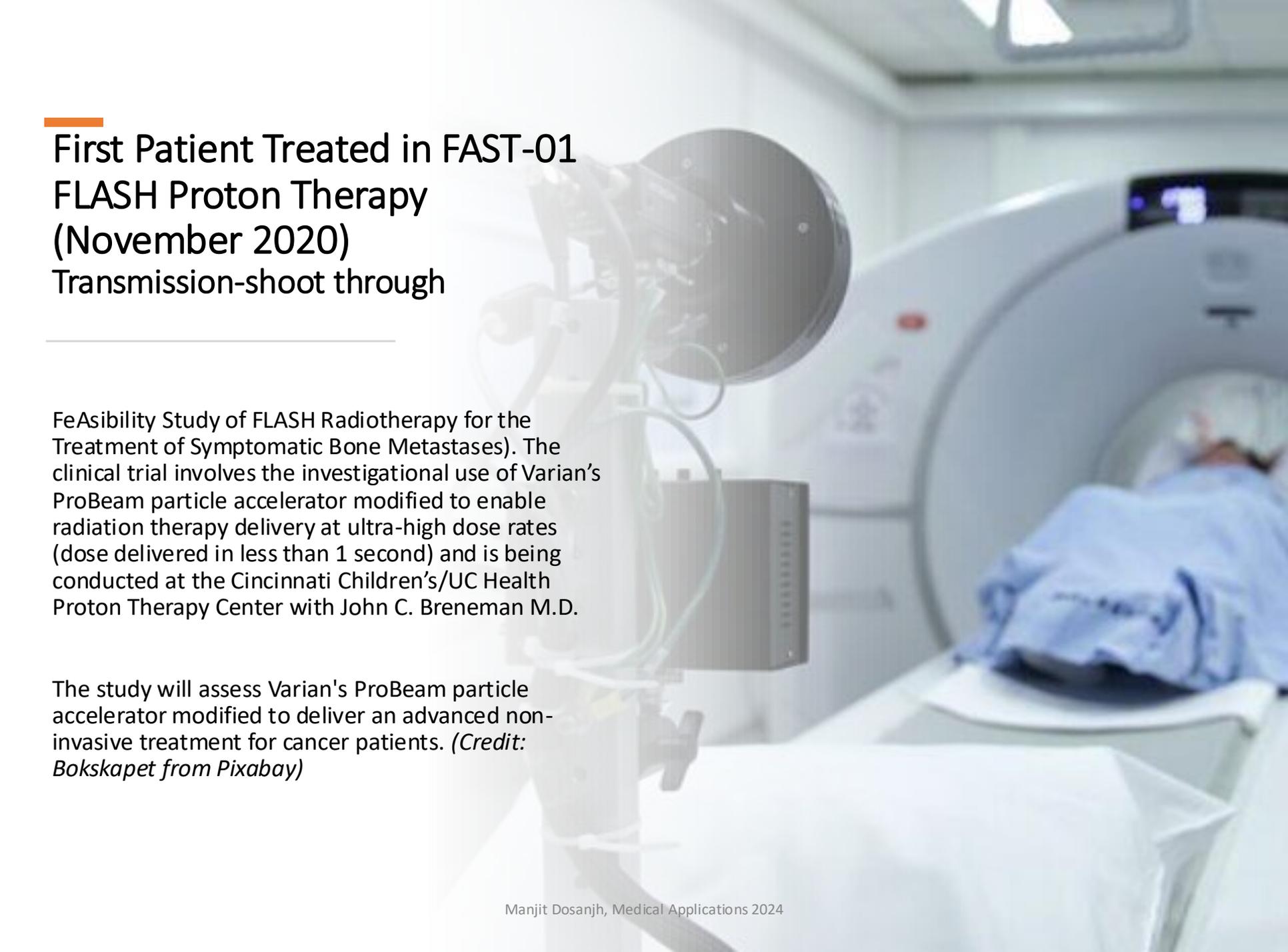
## Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis<sup>a,b,\*</sup>, Wendy Jeanneret Sozzi<sup>a</sup>, Patrik Gonçalves Jorge<sup>a,b,c</sup>, Olivier Gaide<sup>d</sup>, Claude Bailat<sup>c</sup>, Frédéric Duclos<sup>a</sup>, David Patin<sup>a</sup>, Mahmut Ozsahin<sup>a</sup>, François Bochud<sup>c</sup>, Jean-François Germond<sup>c</sup>, Raphaël Moeckli<sup>c,1</sup>, Marie-Catherine Vozenin<sup>a,b,1</sup>

<sup>a</sup>Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; <sup>b</sup>Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; <sup>c</sup>Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and <sup>d</sup>Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland



**Fig. 1.** Temporal evolution of the treated lesion: (a) before treatment; the limits of the 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

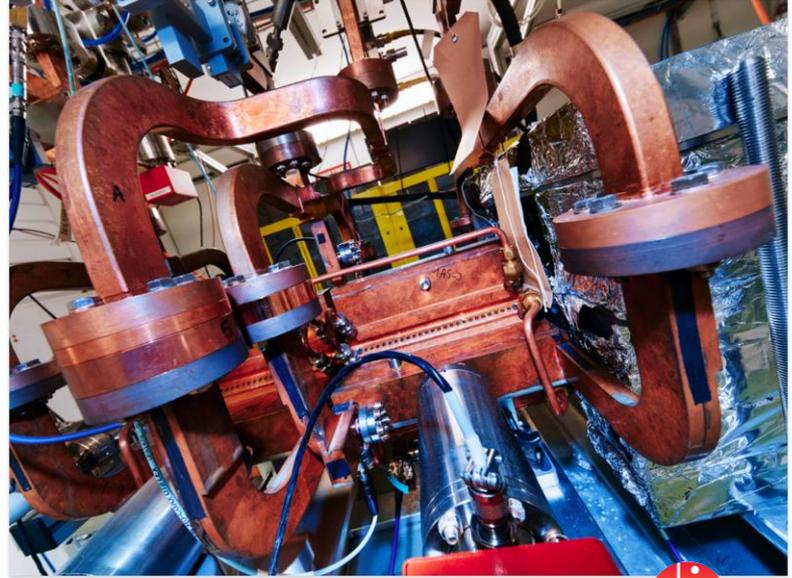
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FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases). The clinical trial involves the investigational use of Varian's ProBeam particle accelerator modified to enable radiation therapy delivery at ultra-high dose 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.

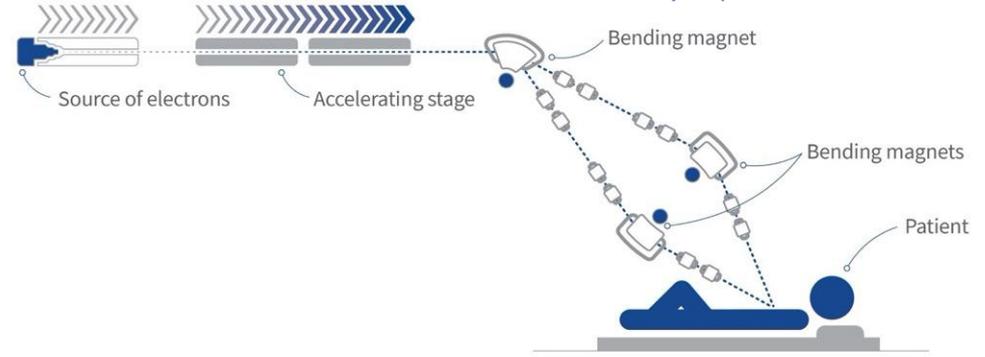
The study will assess Varian's ProBeam particle accelerator modified to deliver an advanced non-invasive treatment for cancer patients. *(Credit: Bokskapet from Pixabay)*

# CERN – CHUV collaboration on FLASH VHEE therapy

CLIC technology for a FLASH VHEE facility being designed in collaboration with Lausanne University Hospital CHUV



Close-up of the Compact Linear Collider prototype, on which the electron FLASH design is based (Image: CERN)



An intense beam of electrons is produced in a photoinjector, accelerated to around 100 MeV and then is expanded, shaped and guided to the patient.

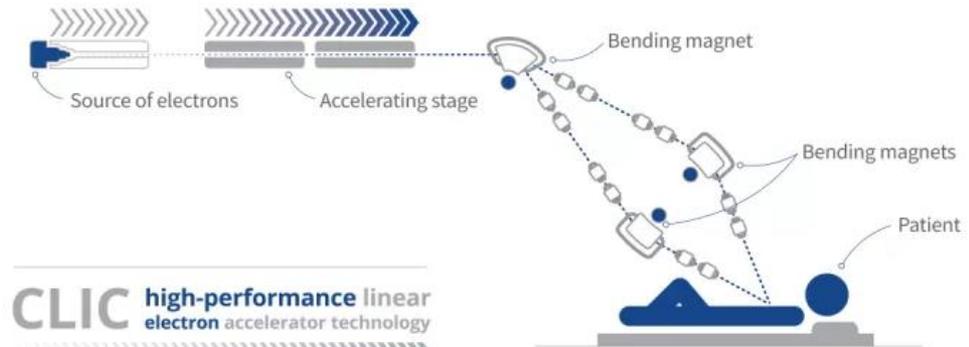
The design of this facility is the result of an intense dialogue between groups at CHUV and CERN.

Jean Bourhis from CHUV:  
“The clinical need that we have really converges with the technological answer that CERN has.”

Walter Wuensch (CERN)

# Very High Energy Electron (VHEE) Radiotherapy

- CERN and CHUV Hospital collaboration to build the first clinical VHEE machine – DEFT (Deep Electron FLASH Therapy).
- Construction and commissioning scheduled for 2025 and clinical trials planned to start in 2027.
- Other VHEE FLASH facilities planned: Stanford (PHASER) and Sapienza, Rome (SAFEST), add Lumitron/UC Irvine and ongoing developments in UK.



**CLIC** high-performance linear electron accelerator technology

**FLASH**  
treatments of  
large and  
deep-seated  
tumours



**< 200 ms**

Full dose  
is delivered by a beam  
of electrons  
in less  
than 200 ms

More healthy  
tissue  
spared



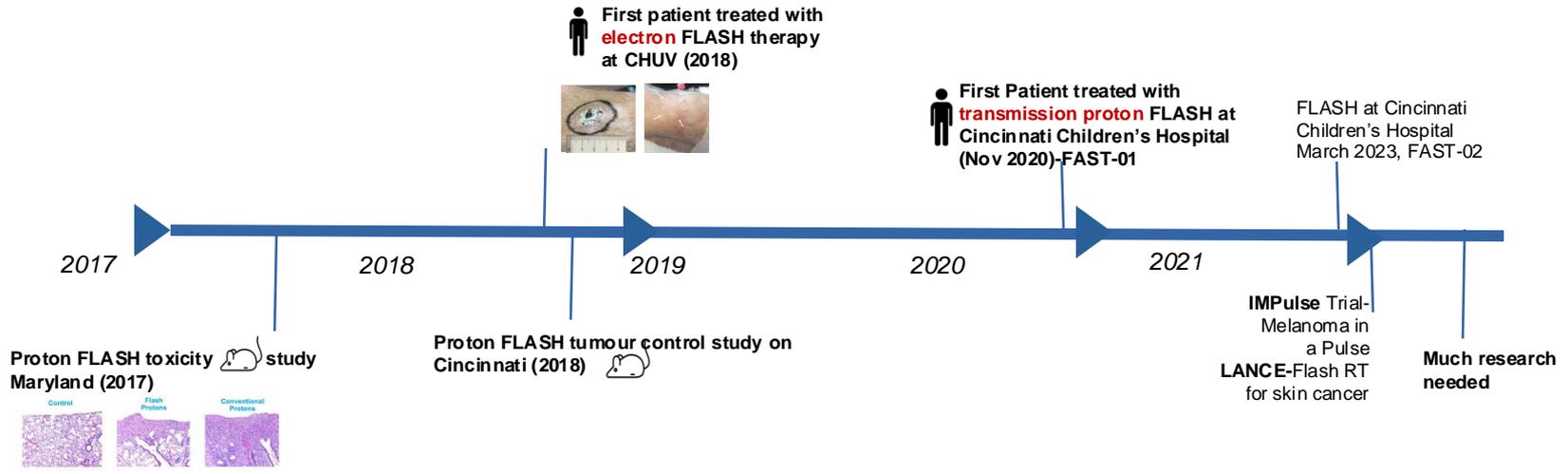
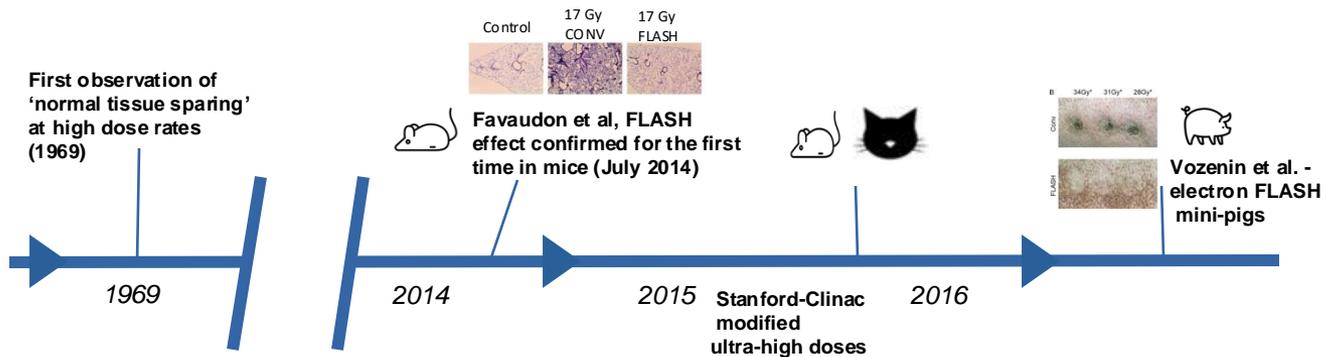
**Innovative  
Radiation Therapy  
with Electrons**



Centre hospitalier  
universitaire vaudois



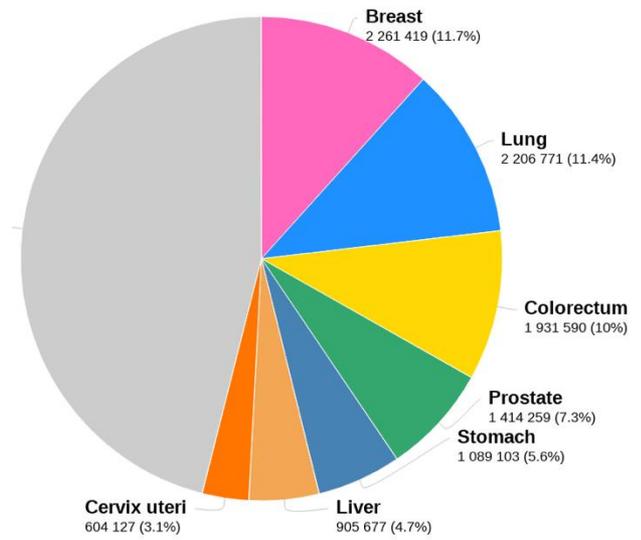
**THERYQ**  
HEALTH



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

## Cancer is a growing global challenge

- In 2020 globally **19.3** million new cases per year diagnosed and **10** million deaths
- By 2040 this will increase to **27.5** million new cases per year and **16.3** million deaths
- **70% of these deaths** will occur in low-and-middle-income countries (LMICs)
- **9 out of 10 deaths** for cervical cancer and **7 out of 10** breast cancer are in LMICs



Total : 19 292 789

*Data source: GLOBOSCAN 2020*

**Radiation therapy is a key tool for treatment for 50-60% patients**

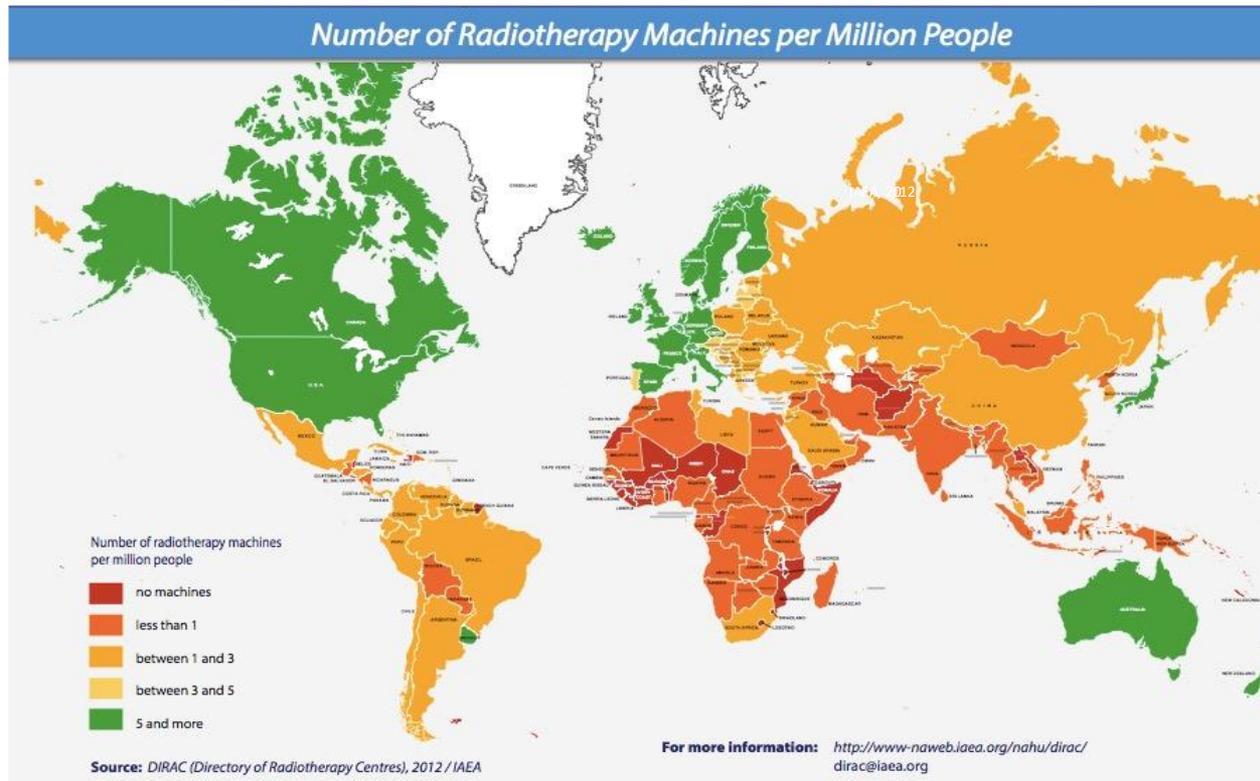
# The Problem:

## Much of the world has limited or no access to Radiation Therapy

**Even though RT is one of the most useful tool** for cancer cure or pain-relief:

- Inadequate supply of RT linear accelerators (Linacs)
- Gap greatest in low-middle income countries (LMICs)
- **Only 10%** patients in Low Income Countries have access to RT

# IAEA 2012 data showing huge disparities in global access



Most of the current 18,000 RT units are in HIC (High-Income Countries)

# Number of people per functioning machine in countries in Africa

## But there are dramatic disparities in Access

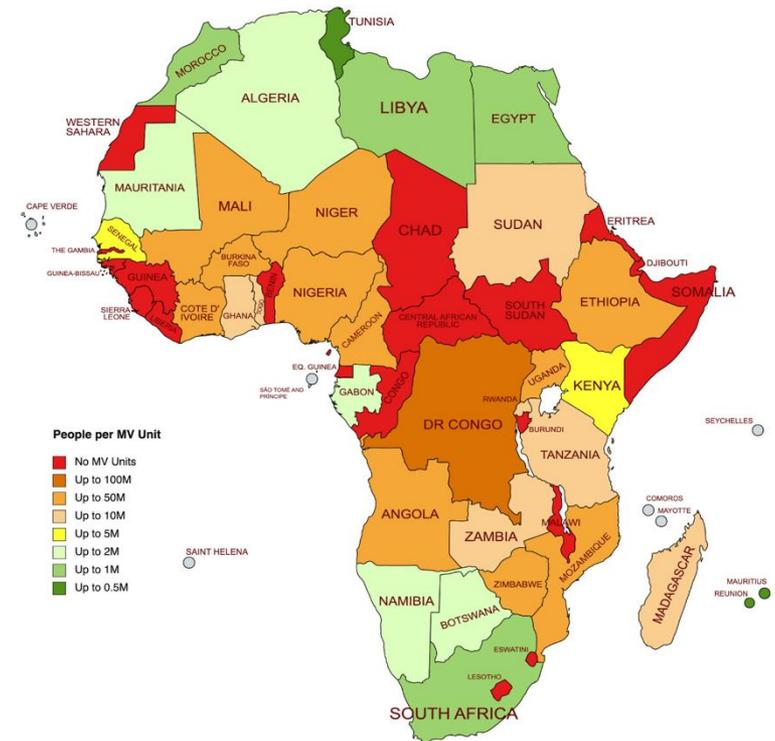
**Africa:** 420 MV RT units for around **1.4 billion** people  
**1 machine per 3.5 million people**

**US:** 3879 MV RT units for around **340 million** people  
**1 machine for 86,000**

**UK:** 357 MV RT units for around **68 million** people  
**1 machine per 190,000**

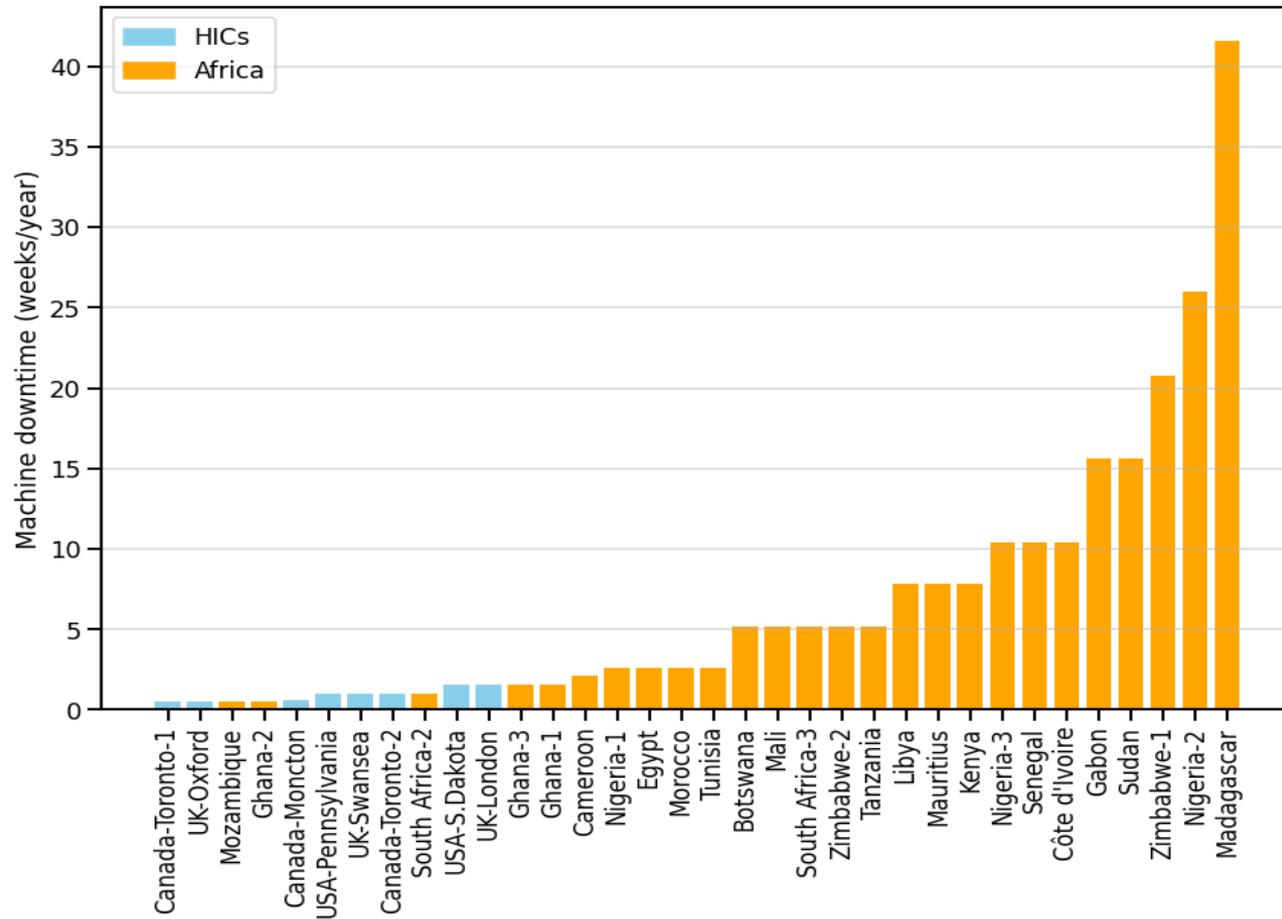
**Switzerland:** 85 for **8.8 million** people  
**1 machine for 100,000**

- By 2030, there will be **1.4 million** new cases of cancer and there will be **1 million** cancer deaths in Africa
- In 2019 only **28** countries had RT facilities
- In 2024 there 34 countries
- Over **60%** are in **just 3 countries:** South Africa, Egypt and Morocco
- 20 countries have none



Created with mapchart.net  
© International Cancer Expert Corps (ICEC) 2023

# Downtime in weeks comparison African and HICs



## Current status of RT

- Current Linacs provide very good treatment both in terms of technical capability and throughput.
- However current LINAC technology is **complex, labour intensive, and expensive** to acquire, install, operate and service
- Linac technology requires **strong, robust and reliable infrastructure** (power, clean water, supply chain etc.) to operate
- Many Linacs are purchased or deployed in Africa and LMICs without sufficient **training**. Many are never used or not close to their capacity
- Linac **servicing** can be slow and very expensive. Service contracts are expensive and not always purchased. Long down times (months or more).
- Can we use technology developments to address the current challenges and make RT more widely available?

# Project STELLA (Smart Technologies to Extend Lives with Linear Accelerators)

The Project STELLA is dedicated to:

- Expanding access to high quality cancer treatment globally
- Developing an innovative and transformative radiation therapy treatment system
- Driving down the cost out of RT and cancer care
- An enhanced training, education and mentoring program that catalyzes RTT implementation in the global context





**[cern.ch/virtual-hadron-therapy-centre](https://cern.ch/virtual-hadron-therapy-centre)**

Manjit Dosanjh, Medical Applications 2024

# Interactive Material

- <https://youtu.be/ICWTaa5zhMQ> (improving access to Treatment)
- <https://www.youtube.com/watch?v=WhgDZKr9GQQ> (from particle physics to medicine)
- [https://lnkd.in/da\\_sa-5q](https://lnkd.in/da_sa-5q) Global Health: Enhancing Access to Cancer Radiation Therapy
- Imaging and hadron therapy animation
  - <http://cds.cern.ch/record/1611721?ln=en>
  - <http://cds.cern.ch/record/2002120>
- 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>
    - FLASH An innovative electron radiotherapy technology
      - <https://videos.cern.ch/record/2762058>
      - <https://videos.cern.ch/record/2295068>

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