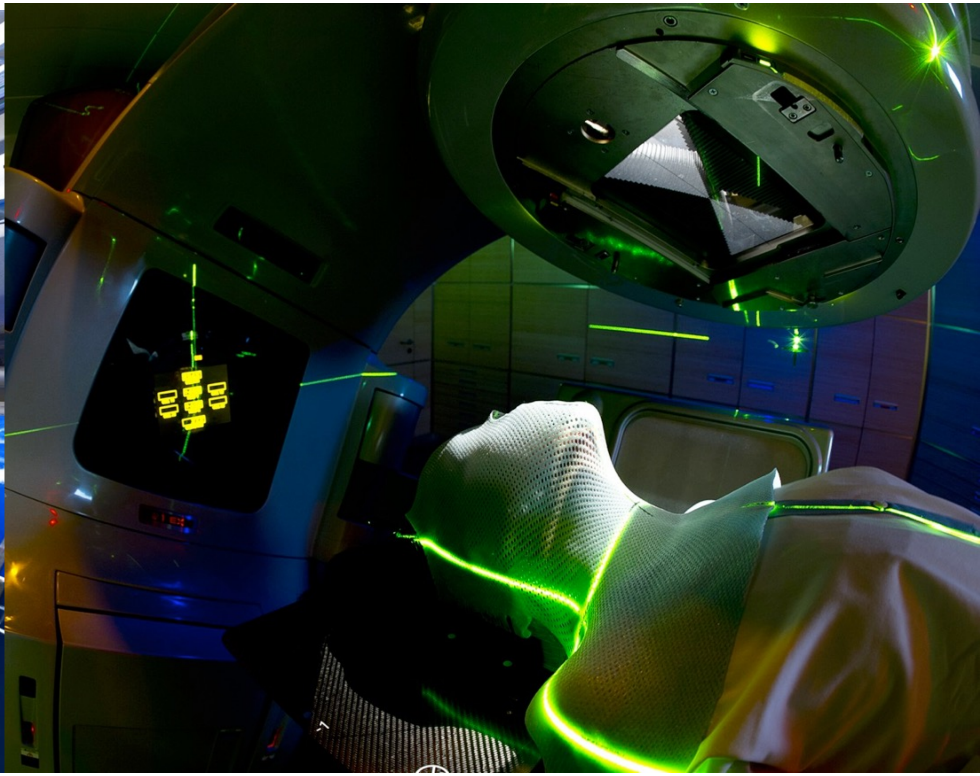
From Physics to Medical Applications



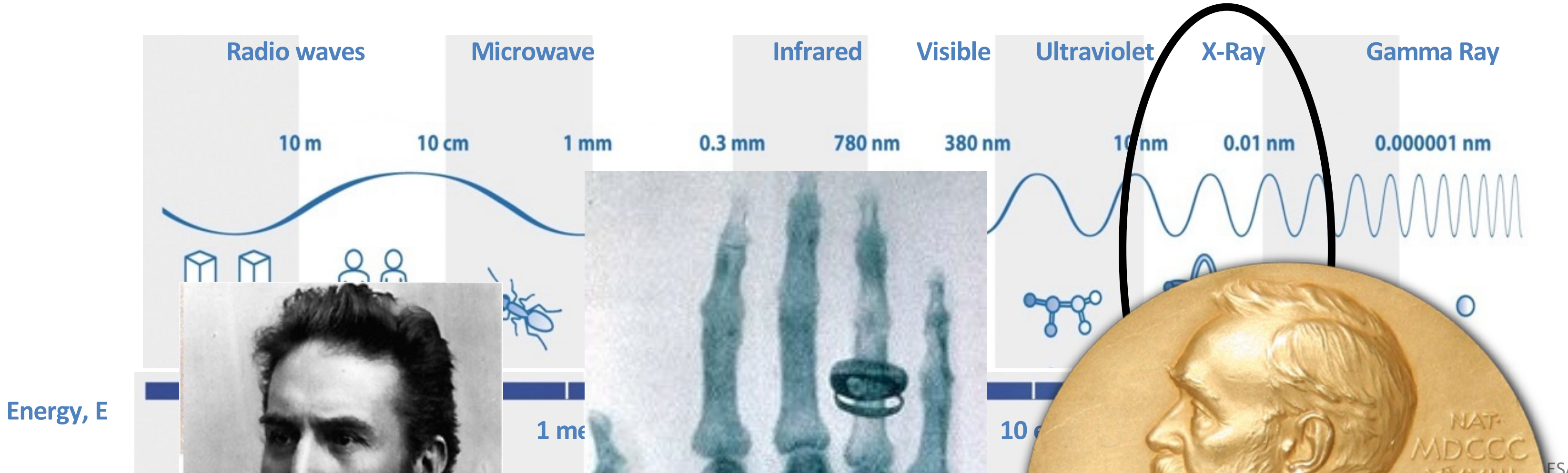
Manjit Dosanjh, 9th July 2024

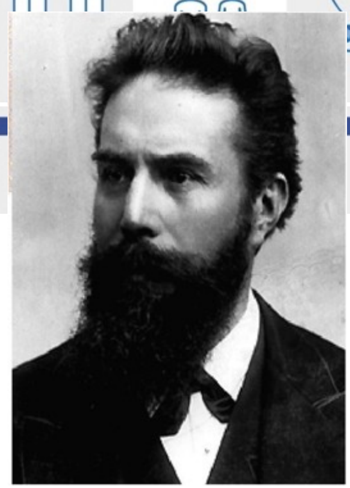
Manjit.Dosanjh@cern.ch

CERN

UNIVERSITY OF OXFORD

Modern medical physics…..beginnings





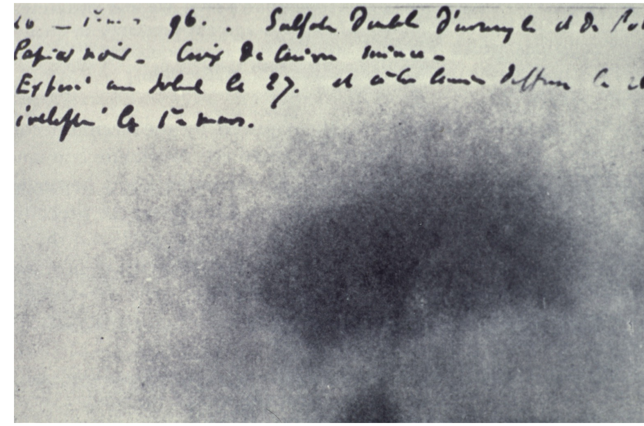
Wilhelm Röntgen

8/11/1895 — 22/12/1895 — 1901

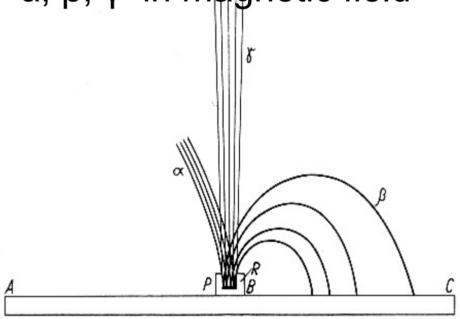
..........beginnings

Henri Becquerel

1896:
Discovery of natural radioactivity

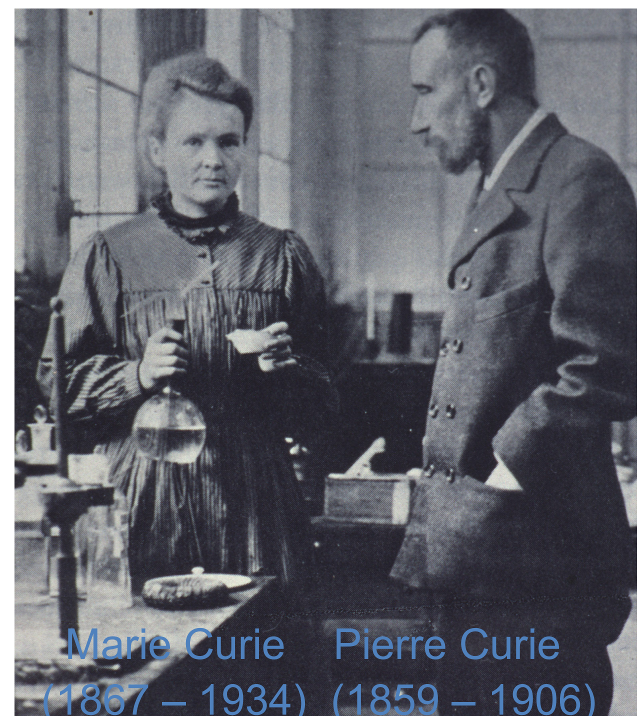


Thesis of Mme. Curie – 1904
α, β, γ in magnetic field



1898: Discovery of radium

used immediately for "Brachytherapy"



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

First radiobiology experiment

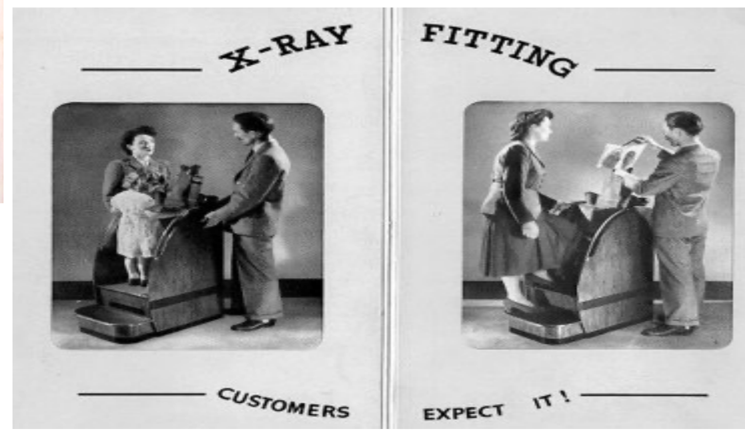
Pierre Curie and Henri Becquerel

Use of Radioactivity for everything….

Par Cinémagazine, 14 février 1935 — https://gallica.bnf.fr/ark:/12148/bpt6k2000628h, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=97956453

Par Radior cosmetics — sitead New York Tribune Magazine, page 12, Domaine public, https://commons.wikimedia.org/w/index.php?curid=35047170

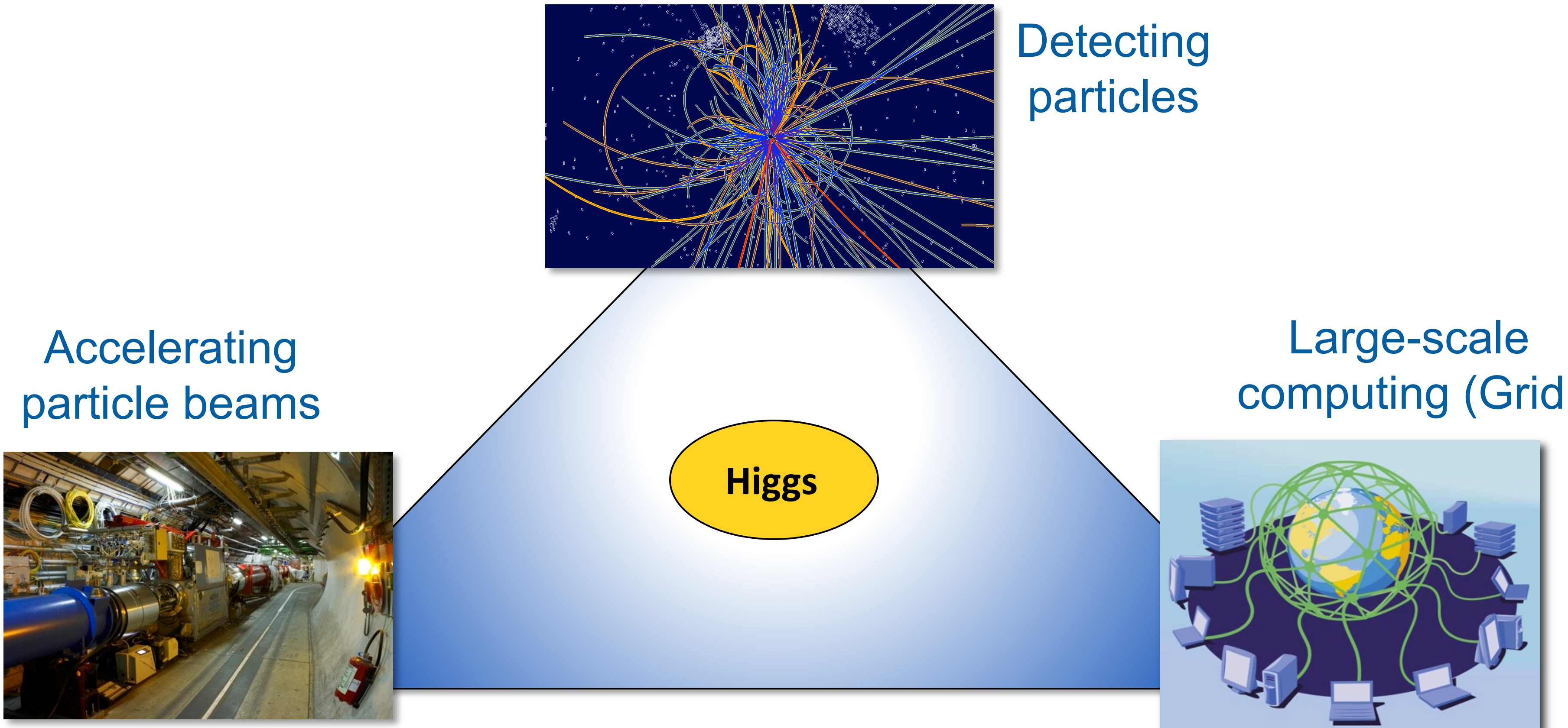
Par Sam LaRussa from United States of America — Radithor, CC BY-SA 2.0, https://commons.wikimedia.org/w/index.php?curid=57841049

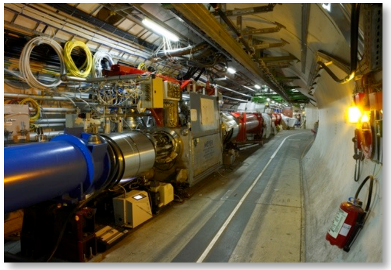


https://www.smh.com.au/national/nsw/from-the-archives-1956-ban-urged-of-x-ray-machines-at-shoe-shops-20210318-p57c1m.html

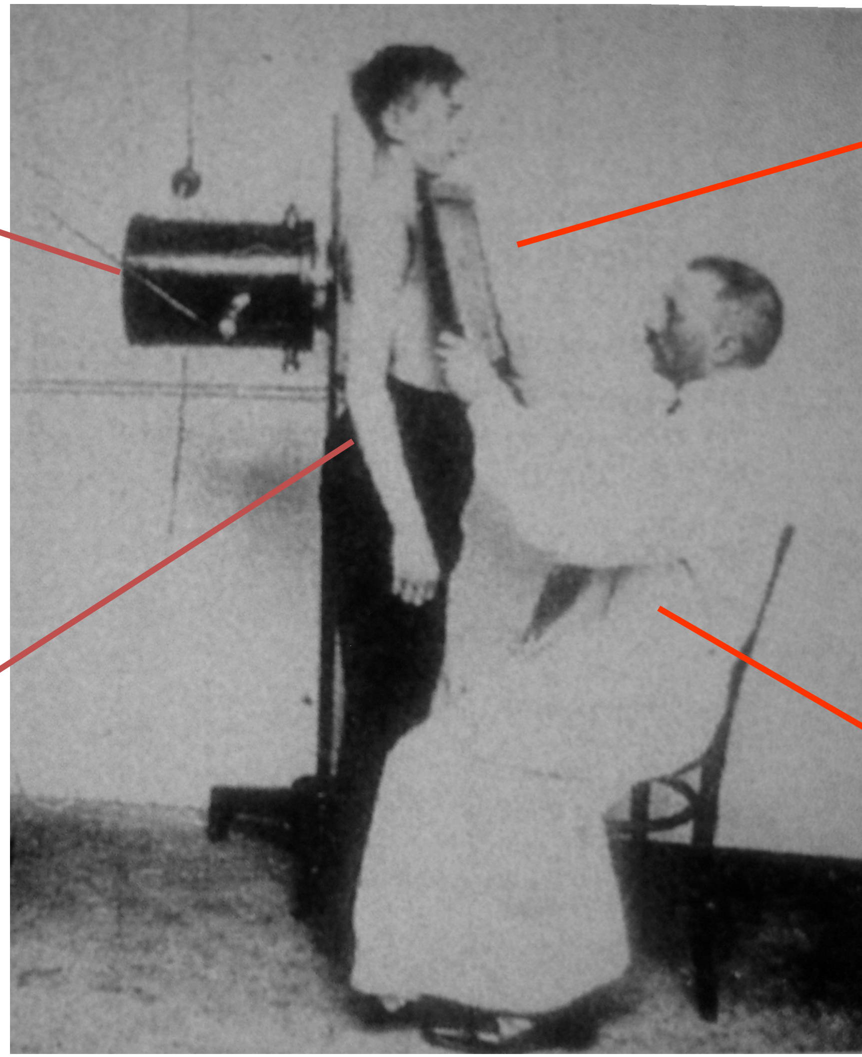
Courtesy of Manuela Cirilli

CERN and Physics Technologies

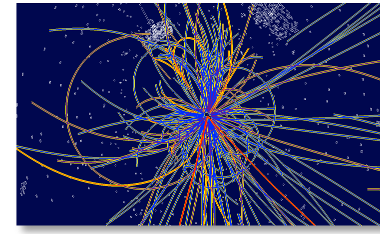




X-ray source



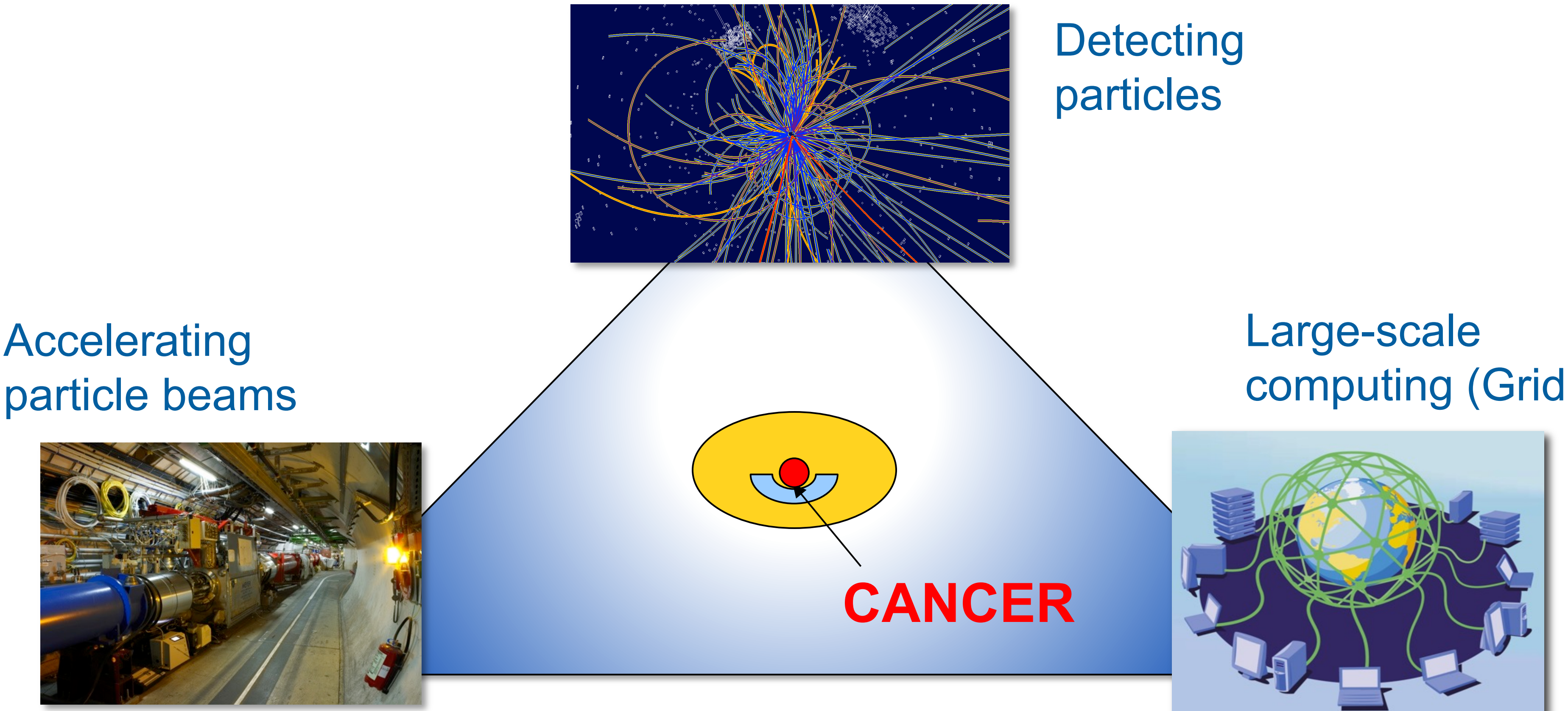
Object



Detector

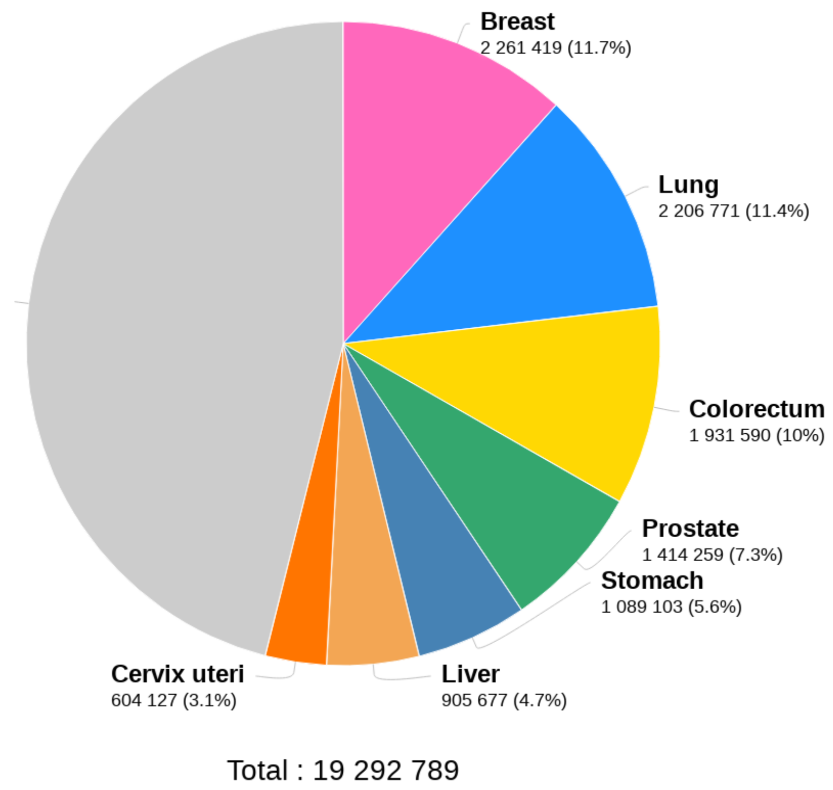
Pattern Recognition System

Physics Technologies helping health



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)

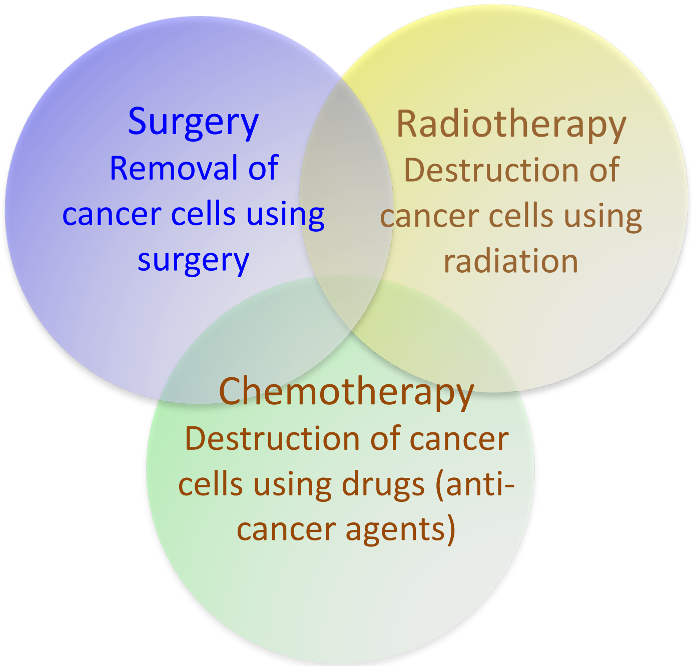


Data source: GLOBOSCAN 2020

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

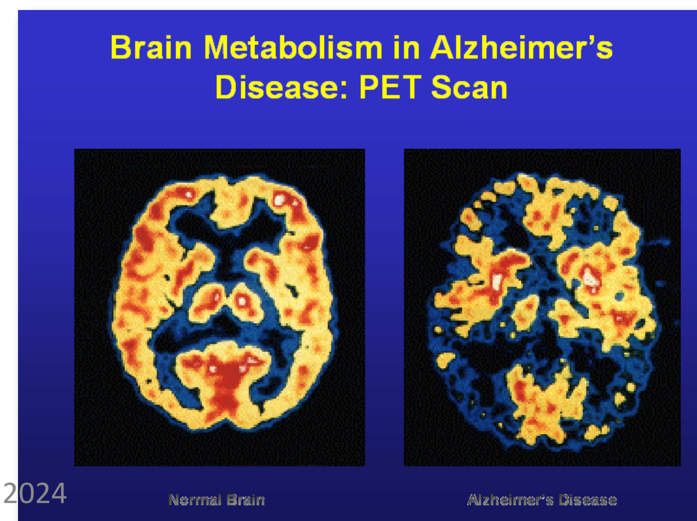
Treatment has two important goals to kill the tumour and protect the surrounding normal tissue. Therefore "seeing" in order to know where and precise "delivery" to make sure it goes where it should are key.

Detectors and art of seeing………

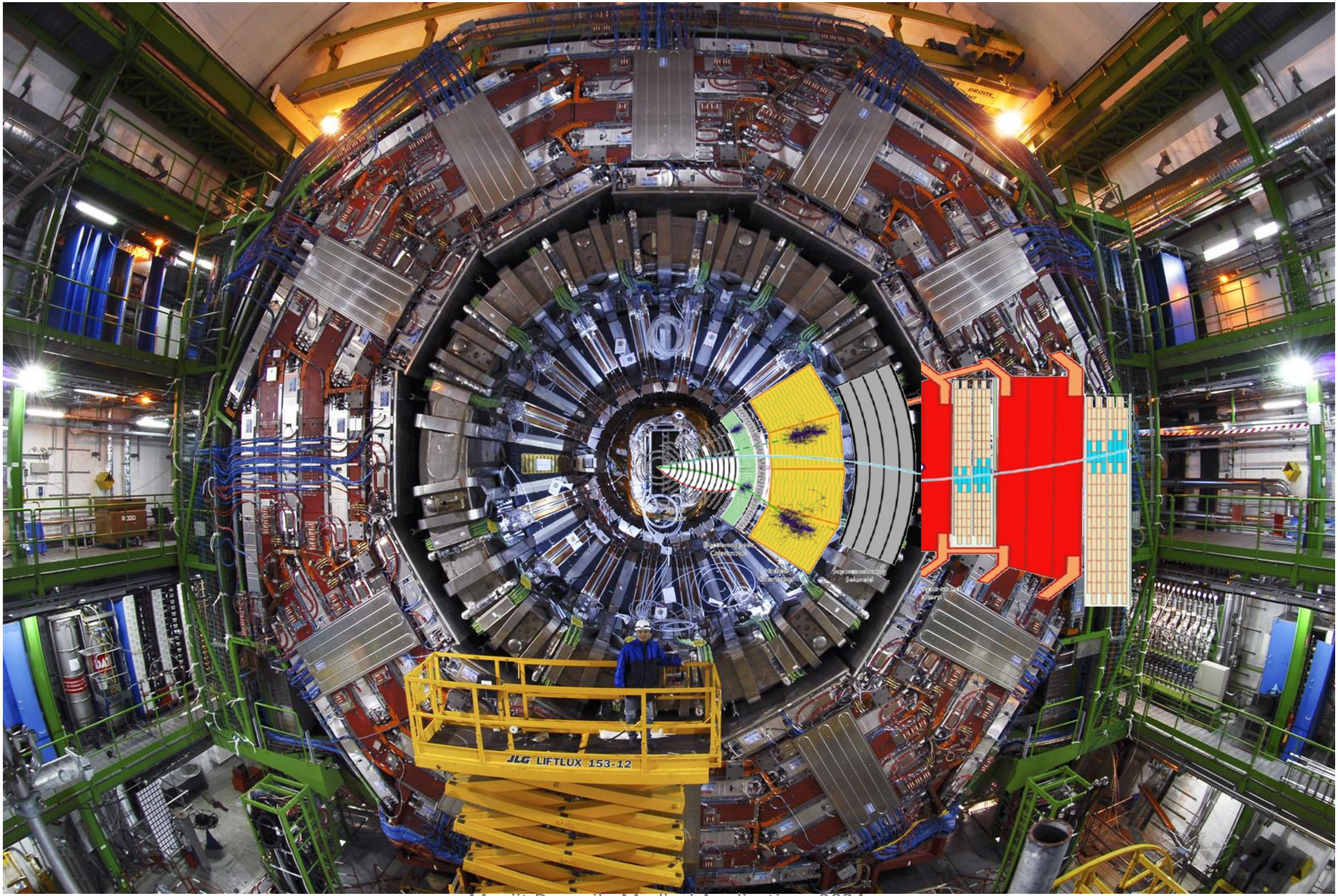
Particle Detection

Imaging

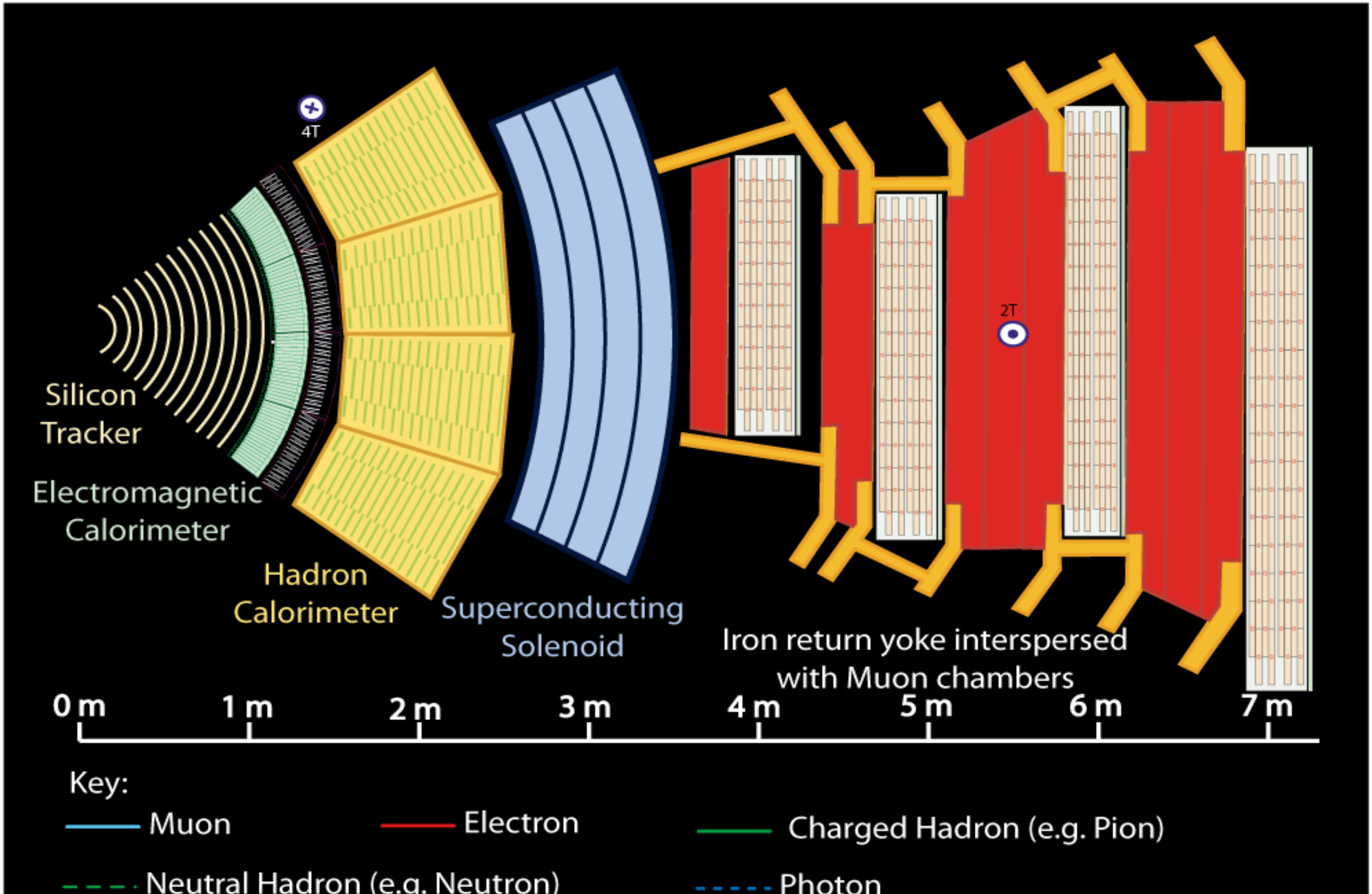
X-ray, CT, PET, MRI



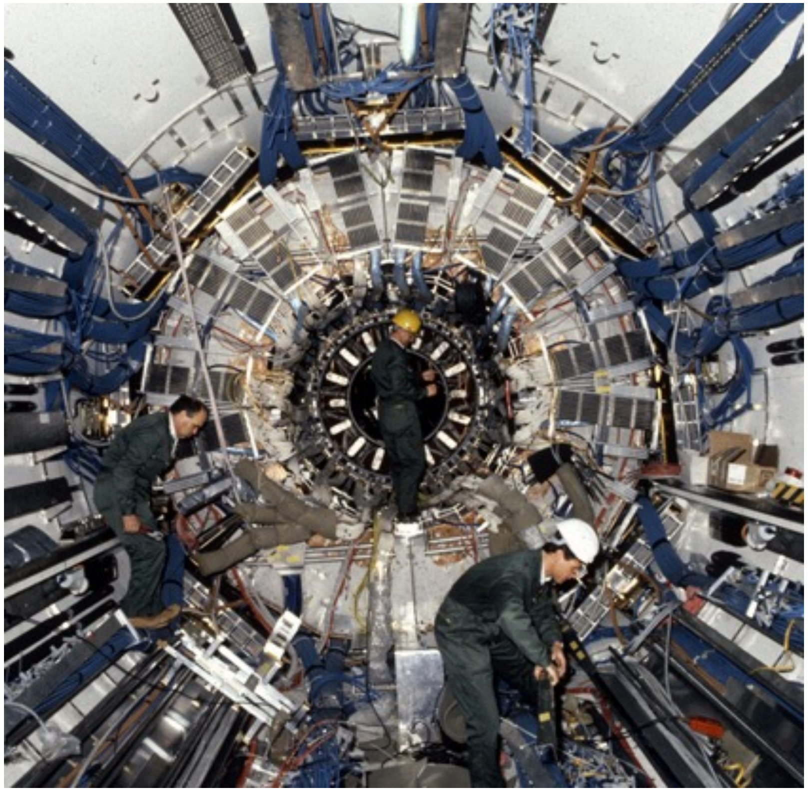
200 Mpix 3-D camera taking 40 million photos/second!

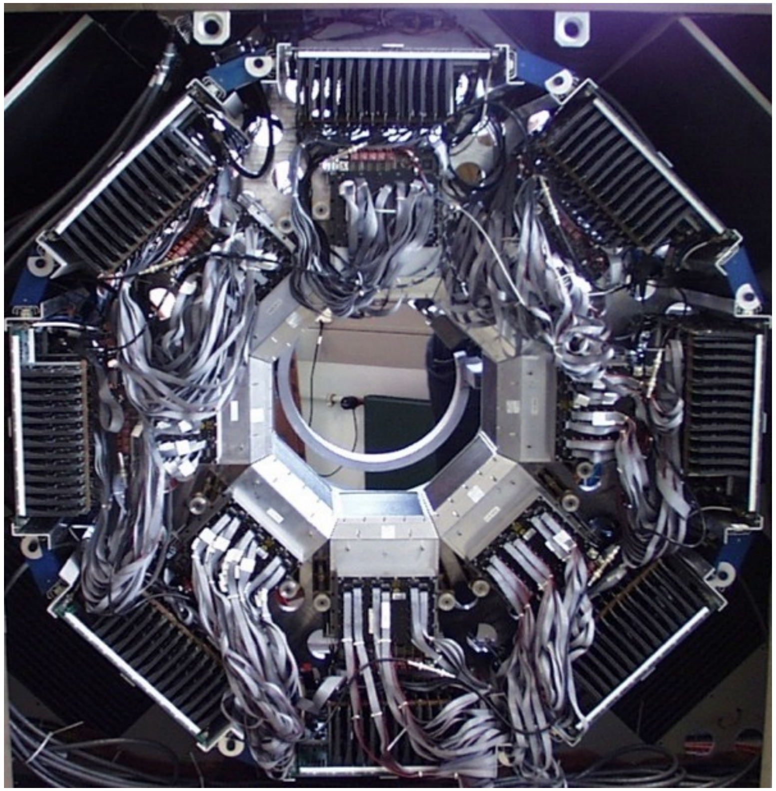


A slice through the CMS Detector



The detector challenge





X-ray imaging

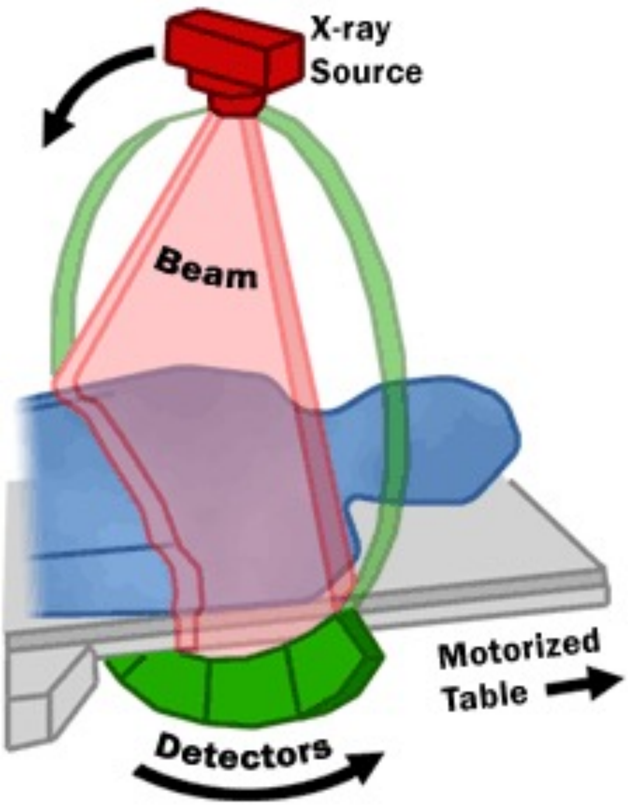
Wilhelm Röntgen

8/11/1895 — 22/12/1895 — 1901

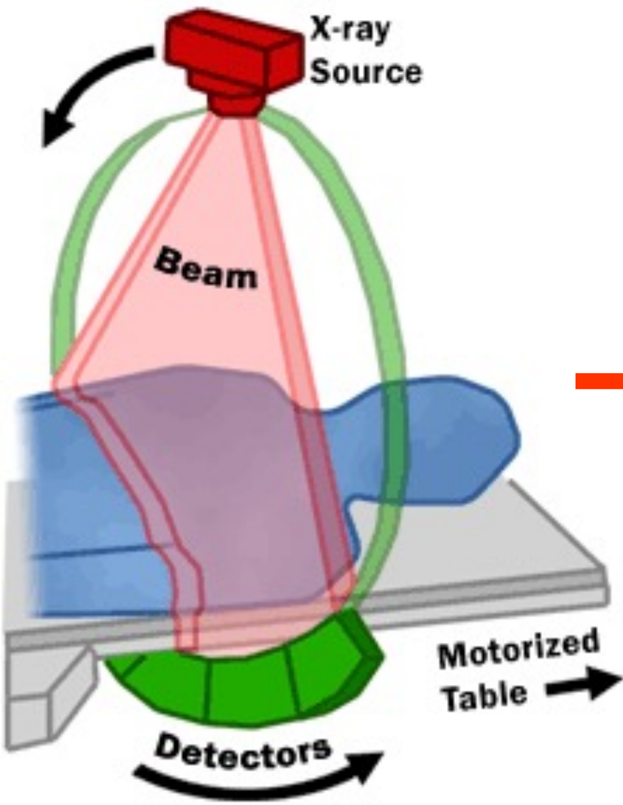
First time we could see beneath the skin without cutting open the patient

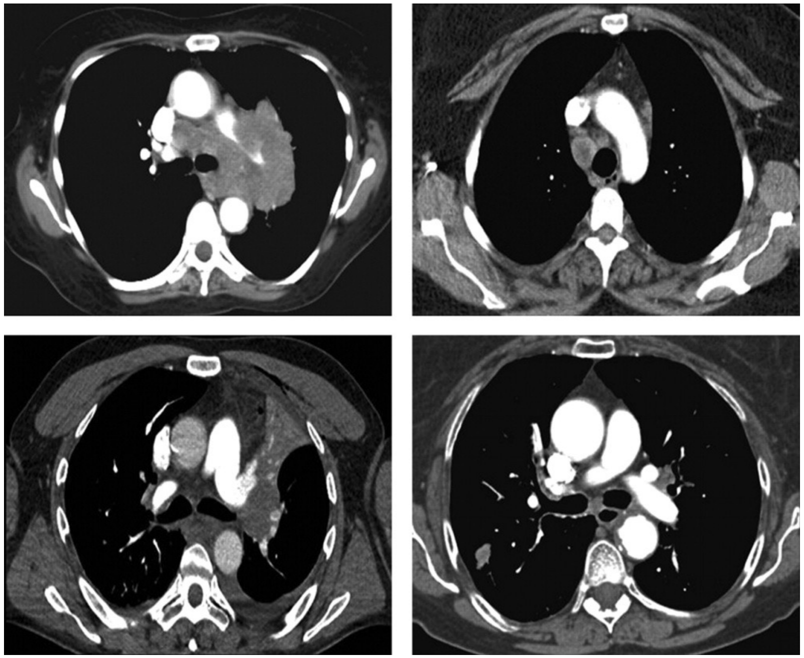
CT – Computed Tomography

3d X-rays imaging



CT – Computed Tomography



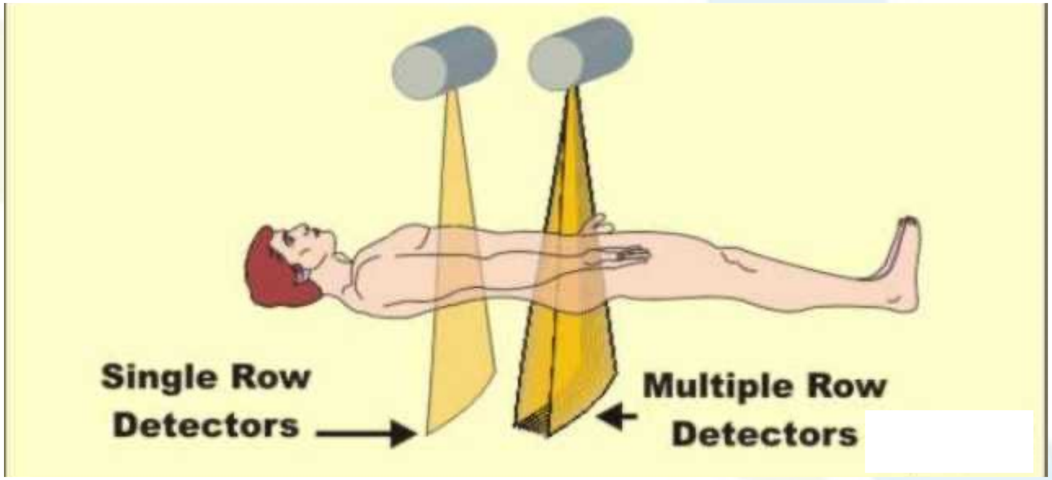


"3D-imaging"

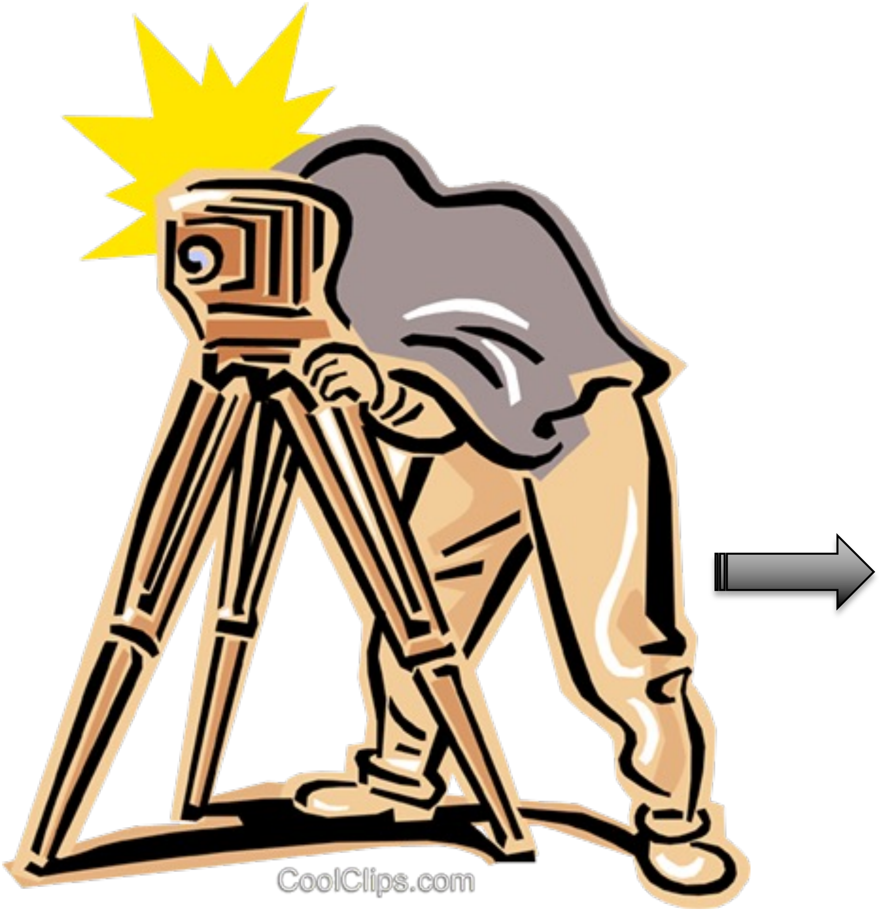
X-ray CT is a key driver of change in medical imaging

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

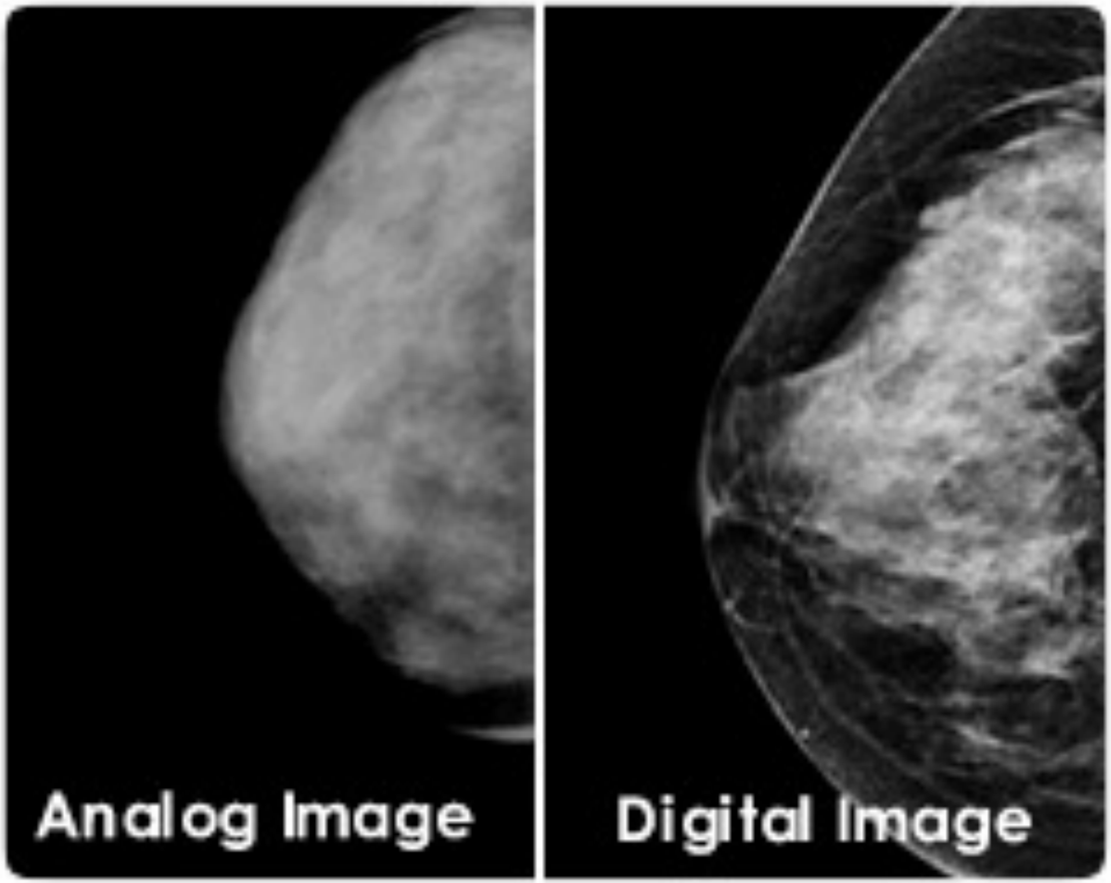


Revolution in Photography



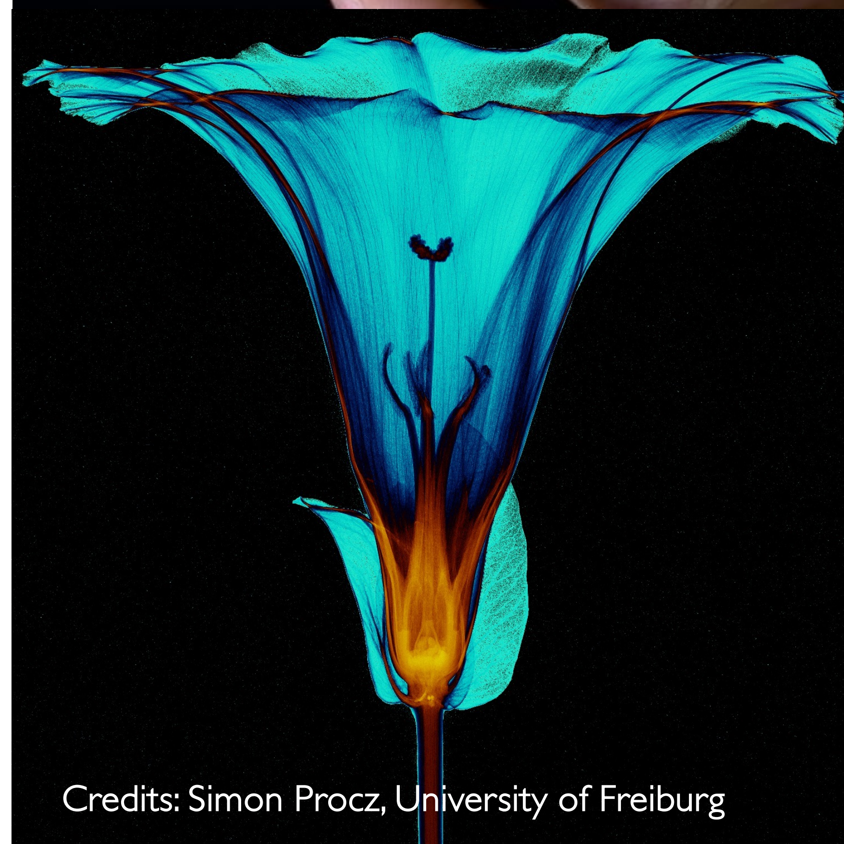
From black and white photos To Modern High-Tech photography

Towards digital colour x-ray imaging

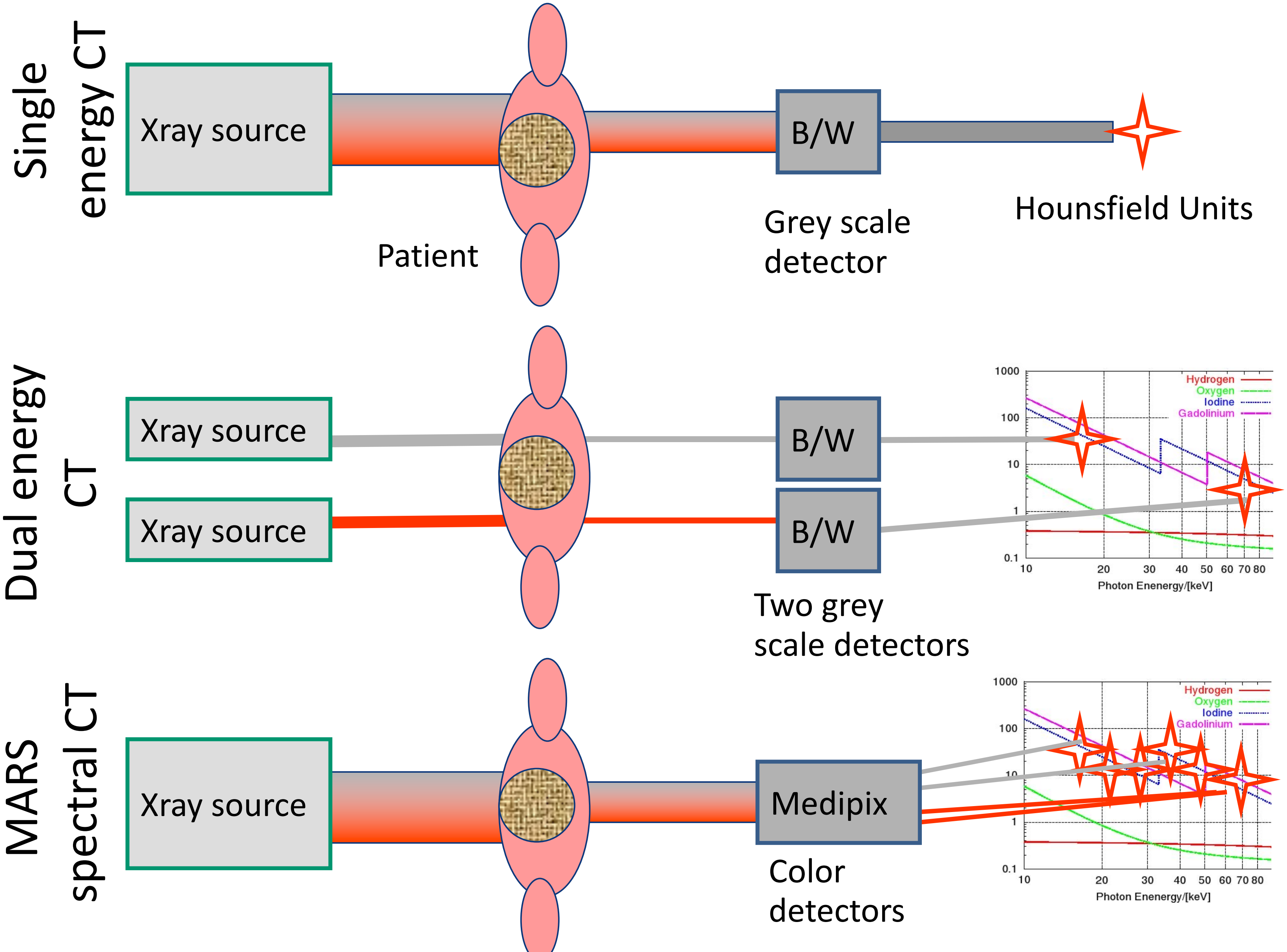


Medipix

- 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



Single- , dual-, and spectral CT



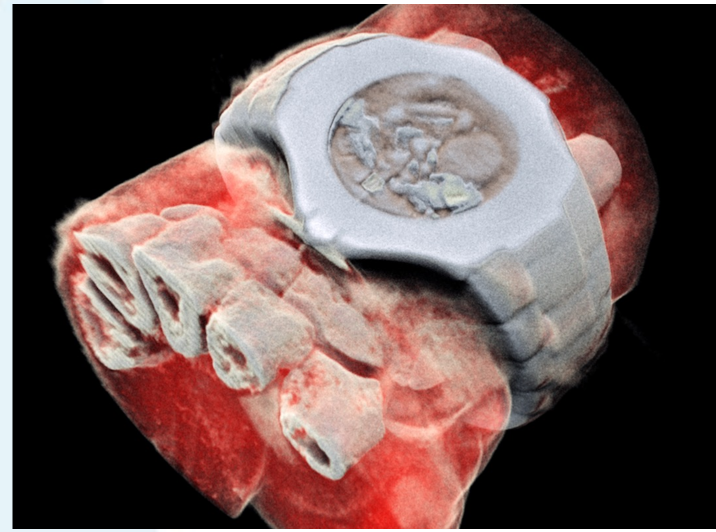
Spectral CT is now possible

Medipix **A**ll **R**esolution **S**ystem

Energy resolution

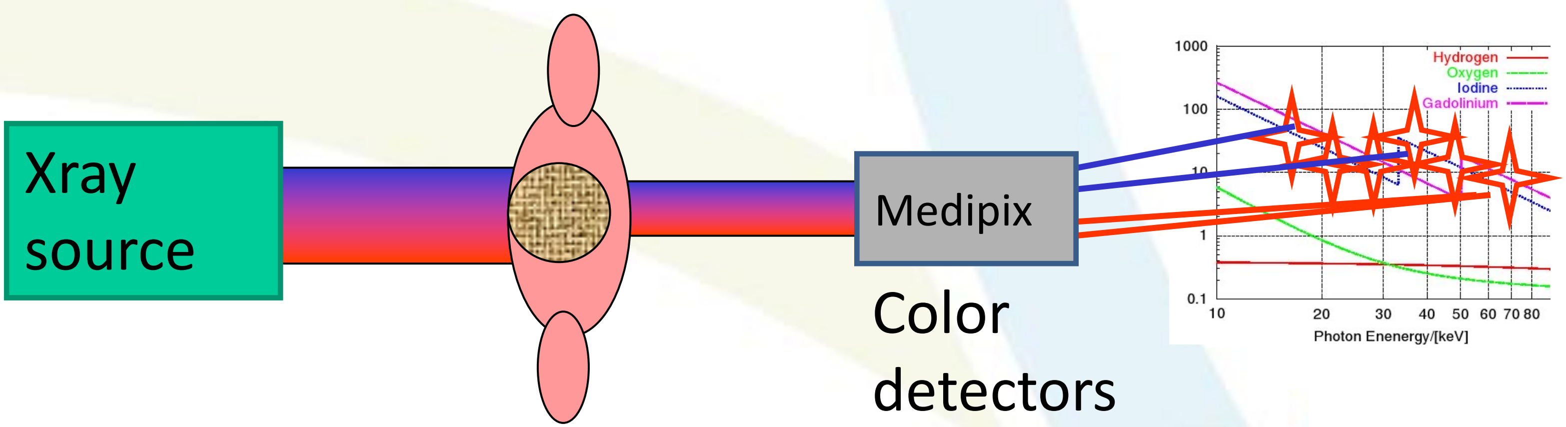
Spatial resolution

Temporal resolution

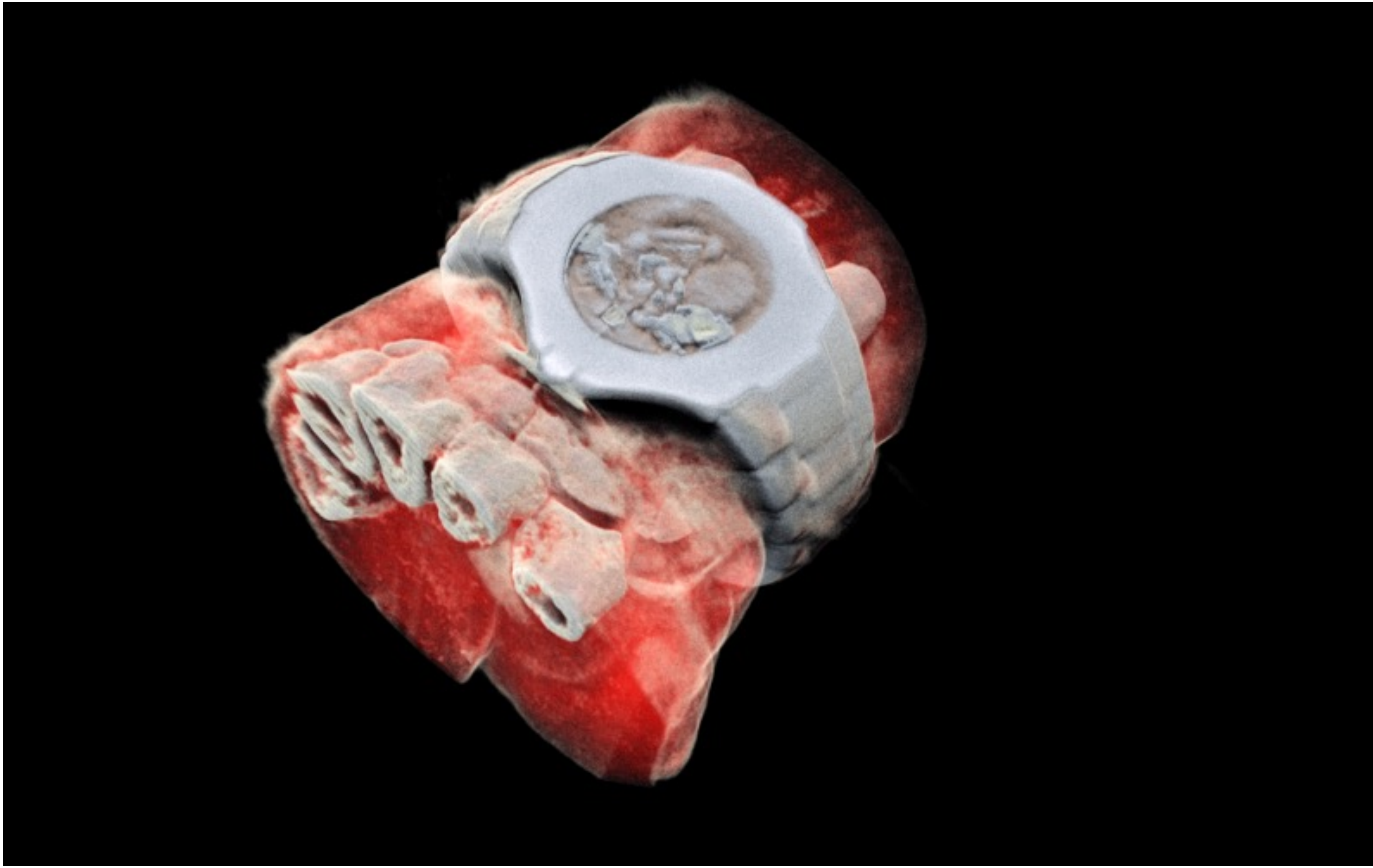


First 3D colour x-ray human image

MARS spectral CT

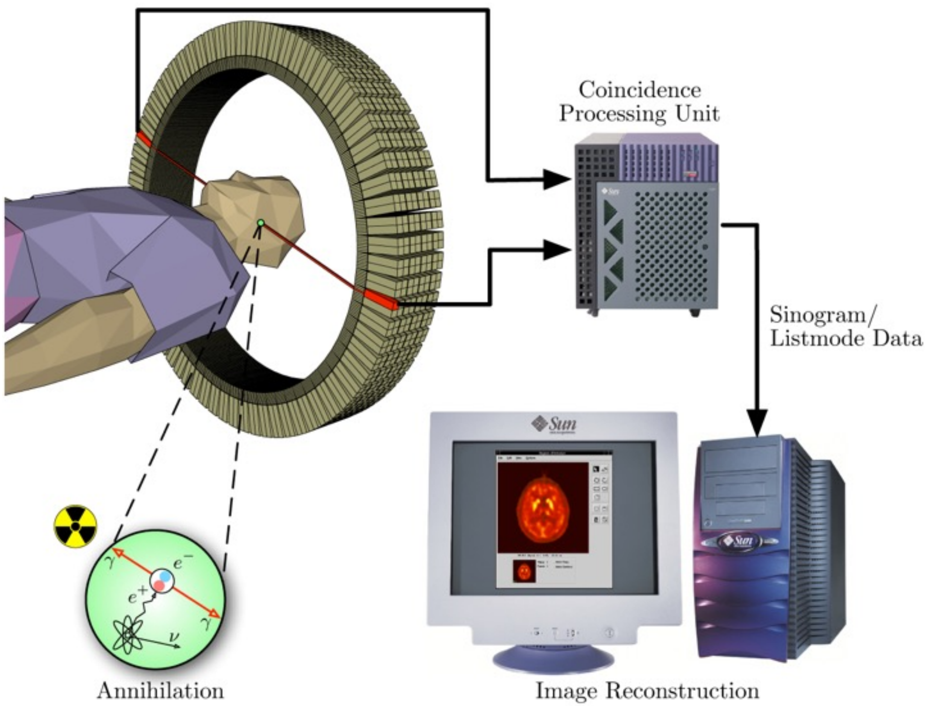


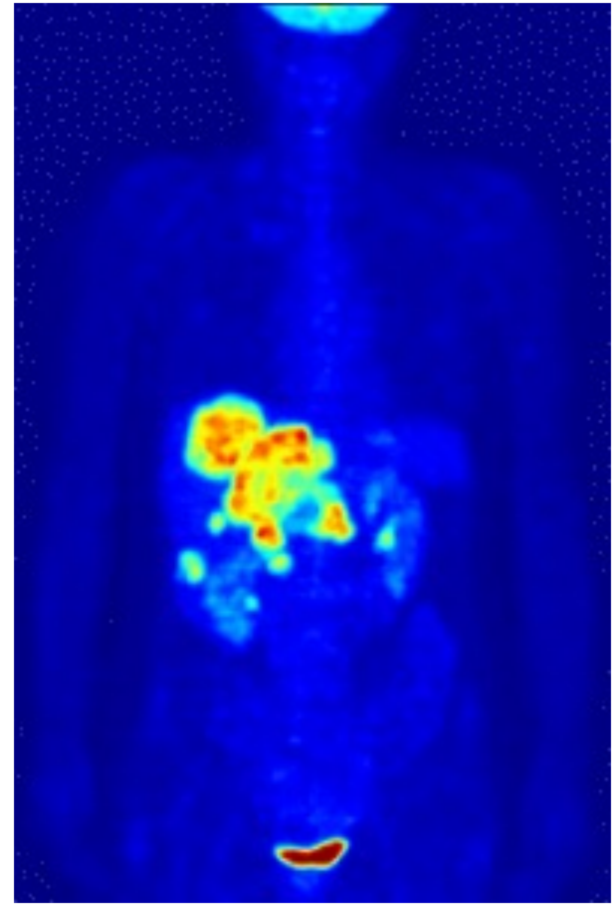
First 3D human colour x-ray image (2018)



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

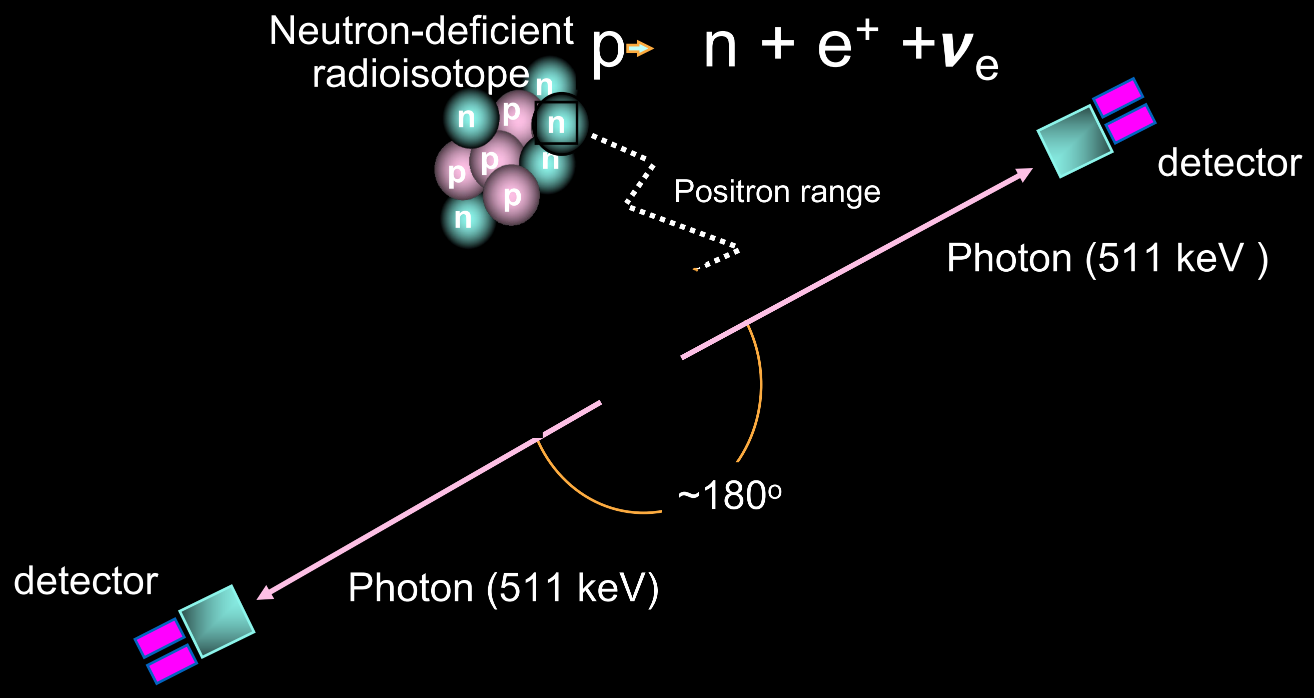




- ^{18}FDG carries the ^{18}F to areas of high metabolic activity
- 90% of PET scans are in clinical oncology

1974 the first human positron emission tomography

Positron Emission Tomography

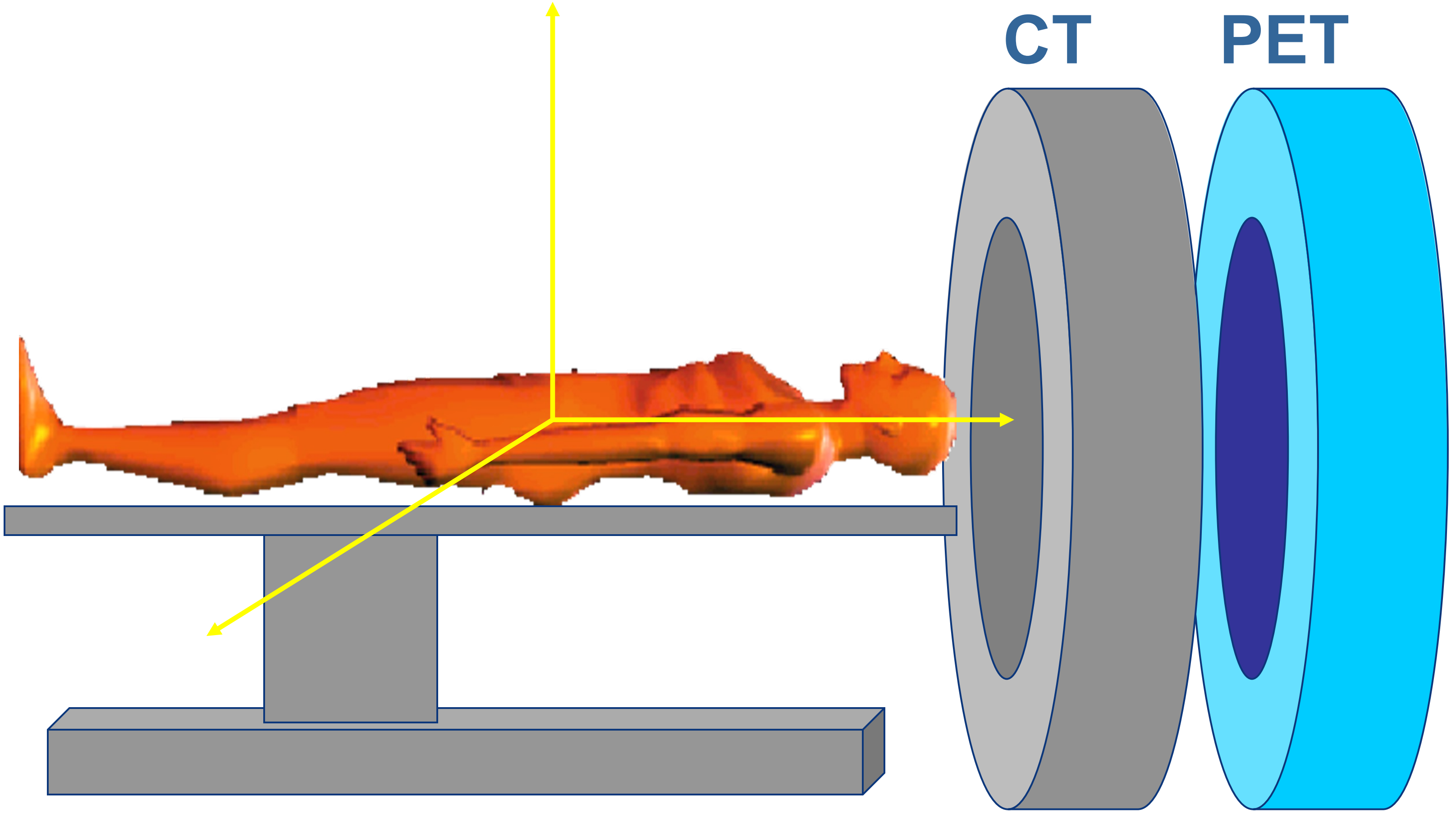


PET – How it works

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

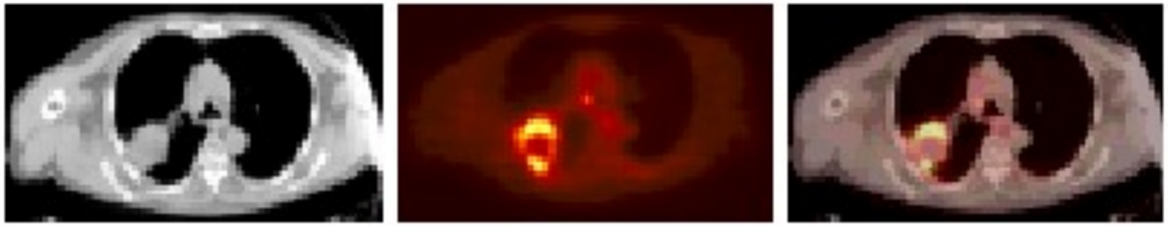
Concept of PET-CT

David Townsend



Multi-modality imaging

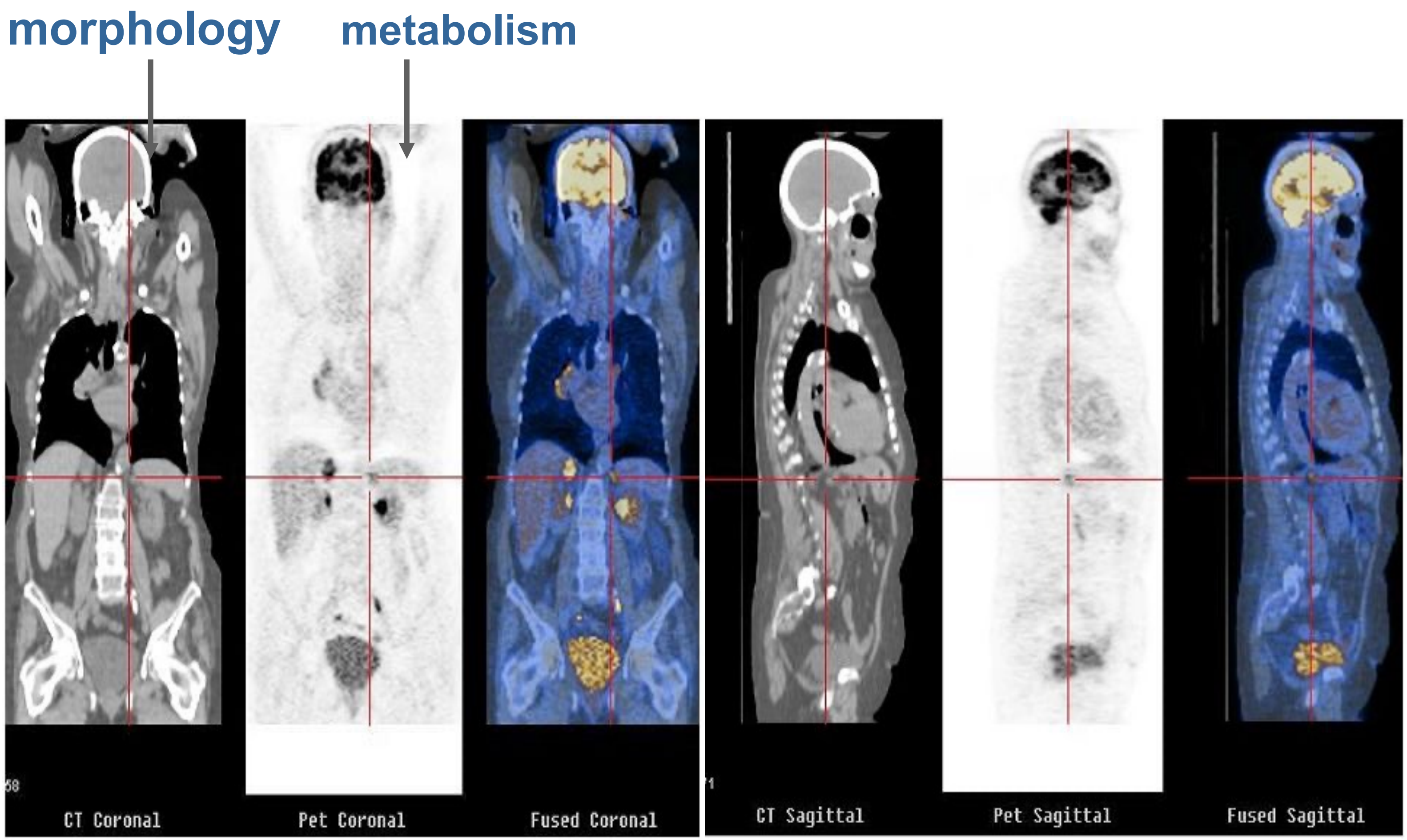
Primary lung cancer imaged with the Dual/Commercial scanner. A large lung tumor, which appears on CT as a uniformly attenuating hypodense mass, has a rim of FDG activity and a necrotic center revealed by PET.



Courtesy of David Townsend

Multimodality imaging: CT with PET

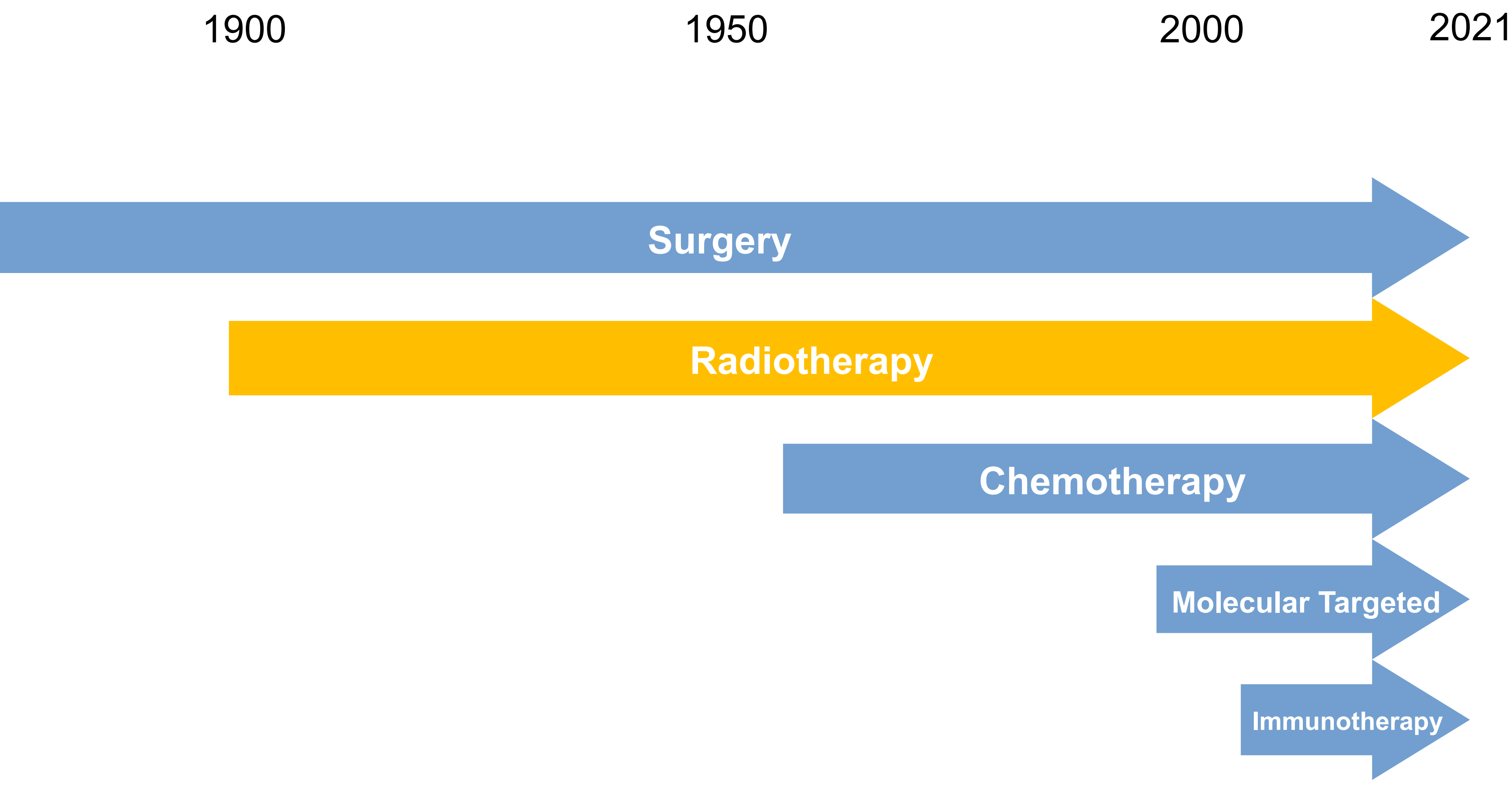
Combining anatomic and functional imaging



David Townsend, UK Physicist


ENVISION
European NoVel Imaging Systems
for ION therapy

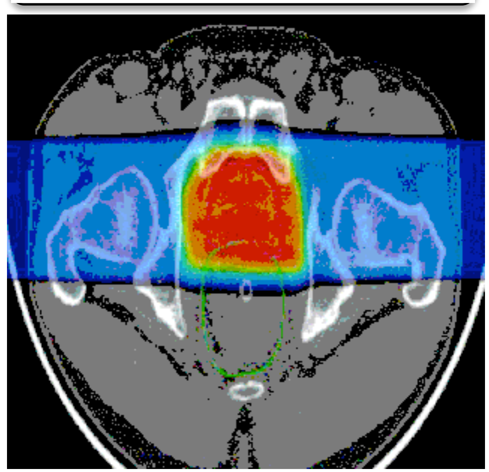
How do we treat cancer?



Treatment options

Surgery

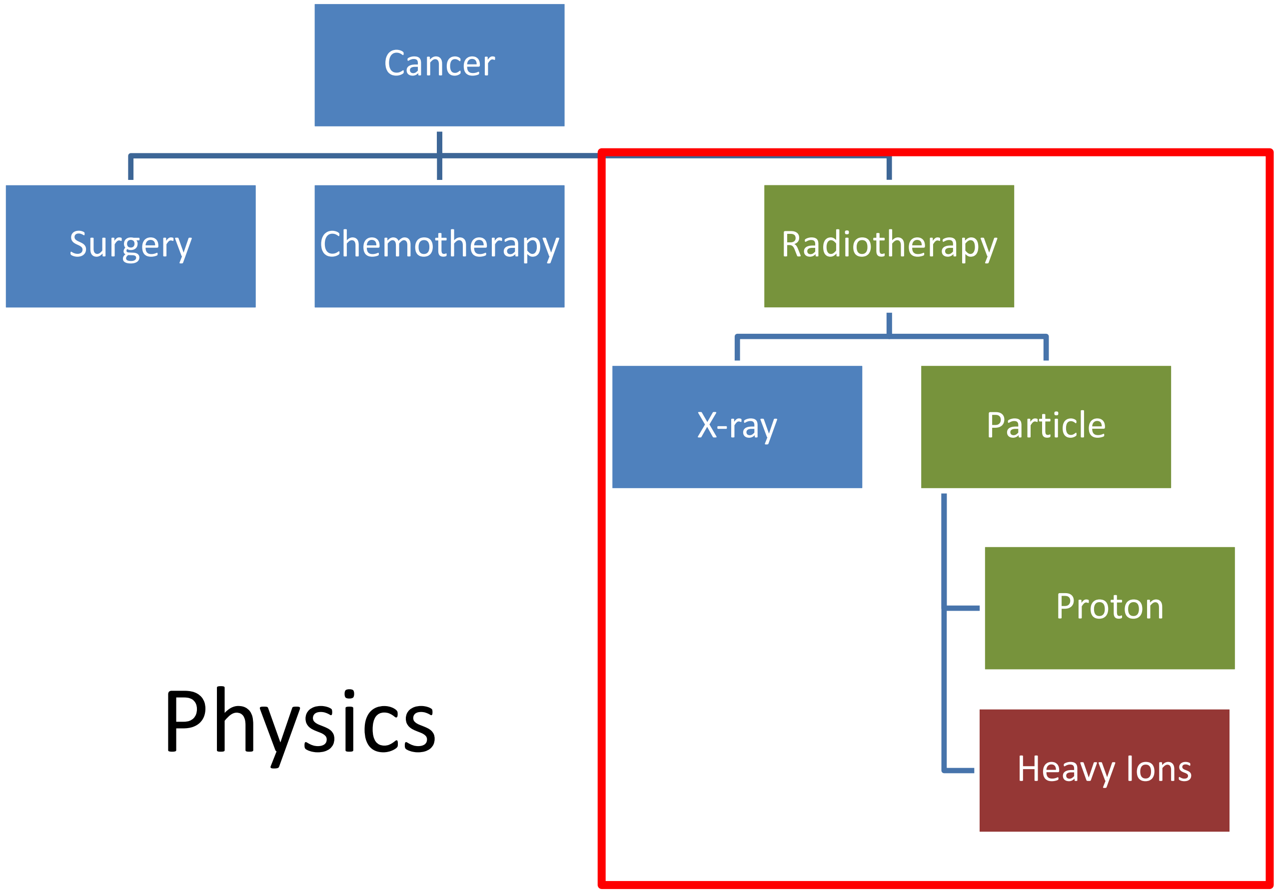
Radiotherapy



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)

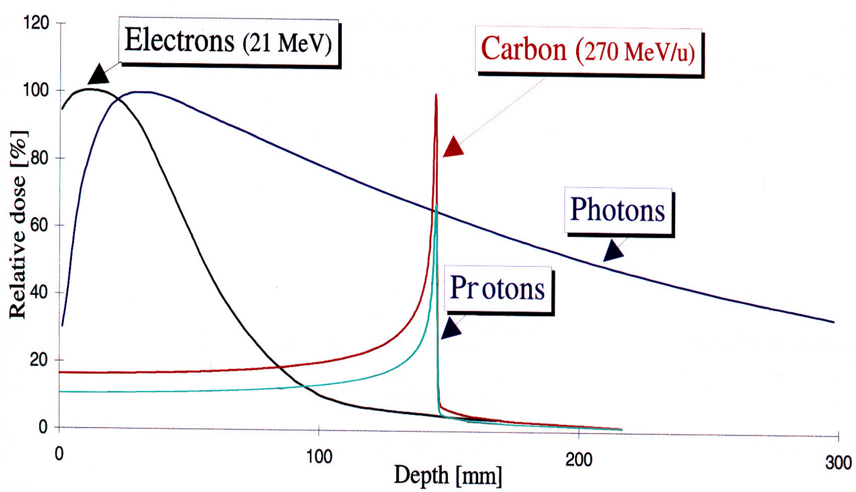
- About 50% patients are treated with RT
- No substitute for RT in the near future
- No of patients is increasing

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 - 400 MeV/u hadrons



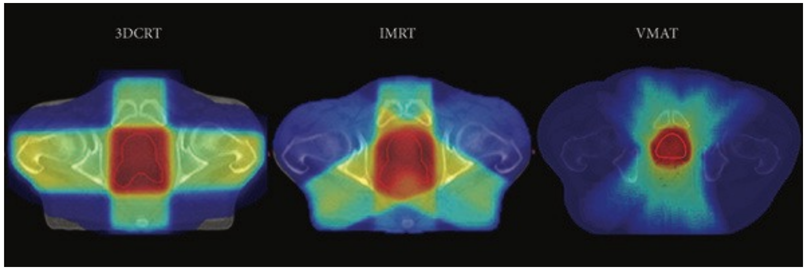
Varian True Beam e- linac

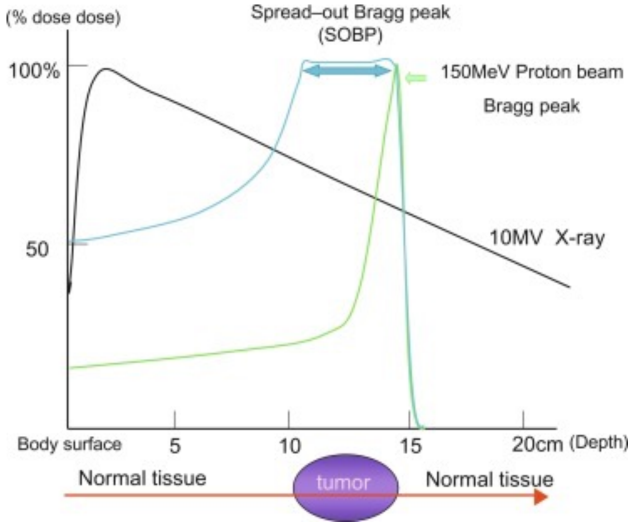
Heidelberg Ion Therapy Centre

Goal of Radiotherapy

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

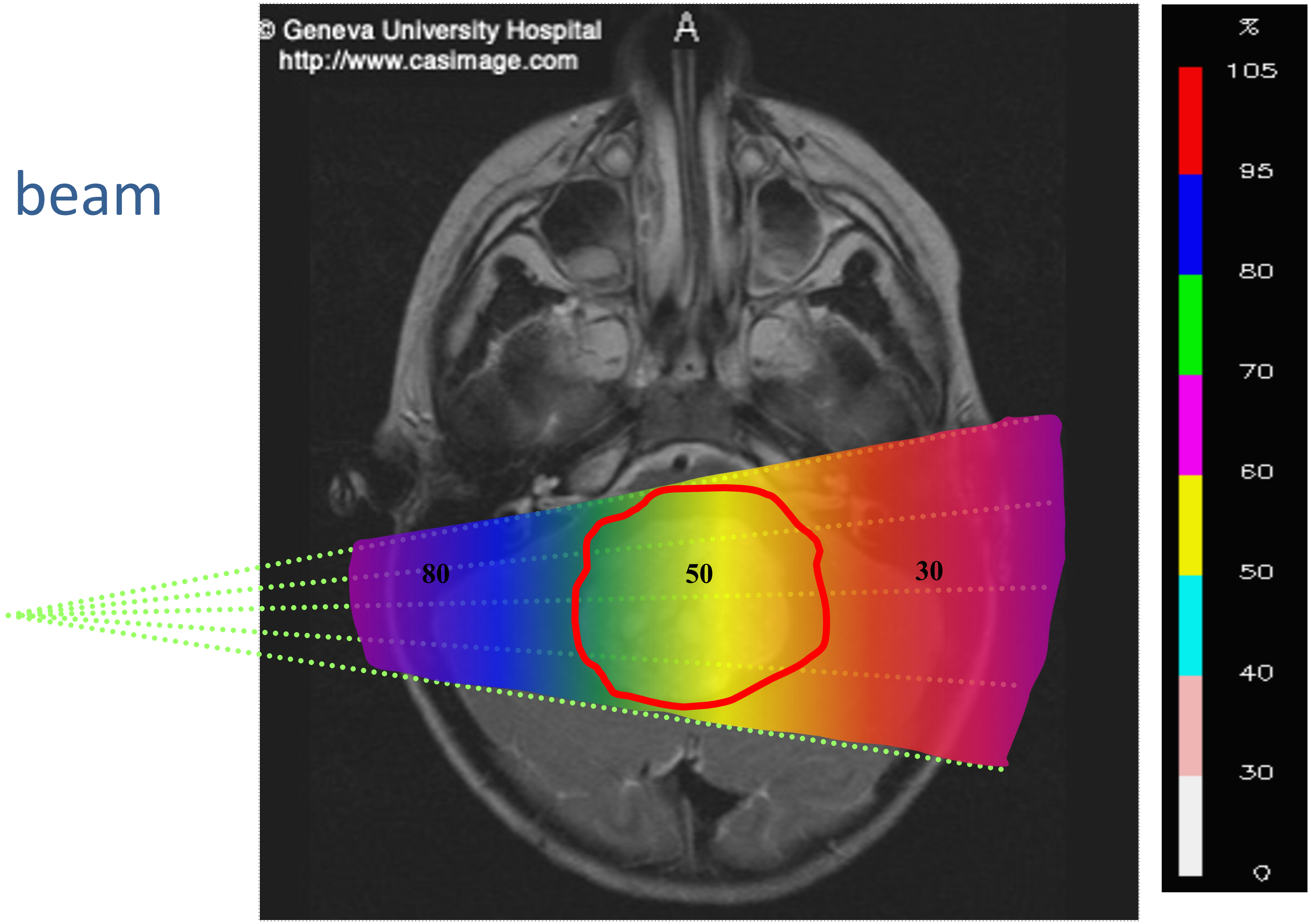
- Better targeting – improved imaging
- Improving dose conformality to tumour through IMRT/VMAT.
- Using the Bragg Peak in hadron therapy.
- Fractionation – delivering treatment across 20-30 fractions.





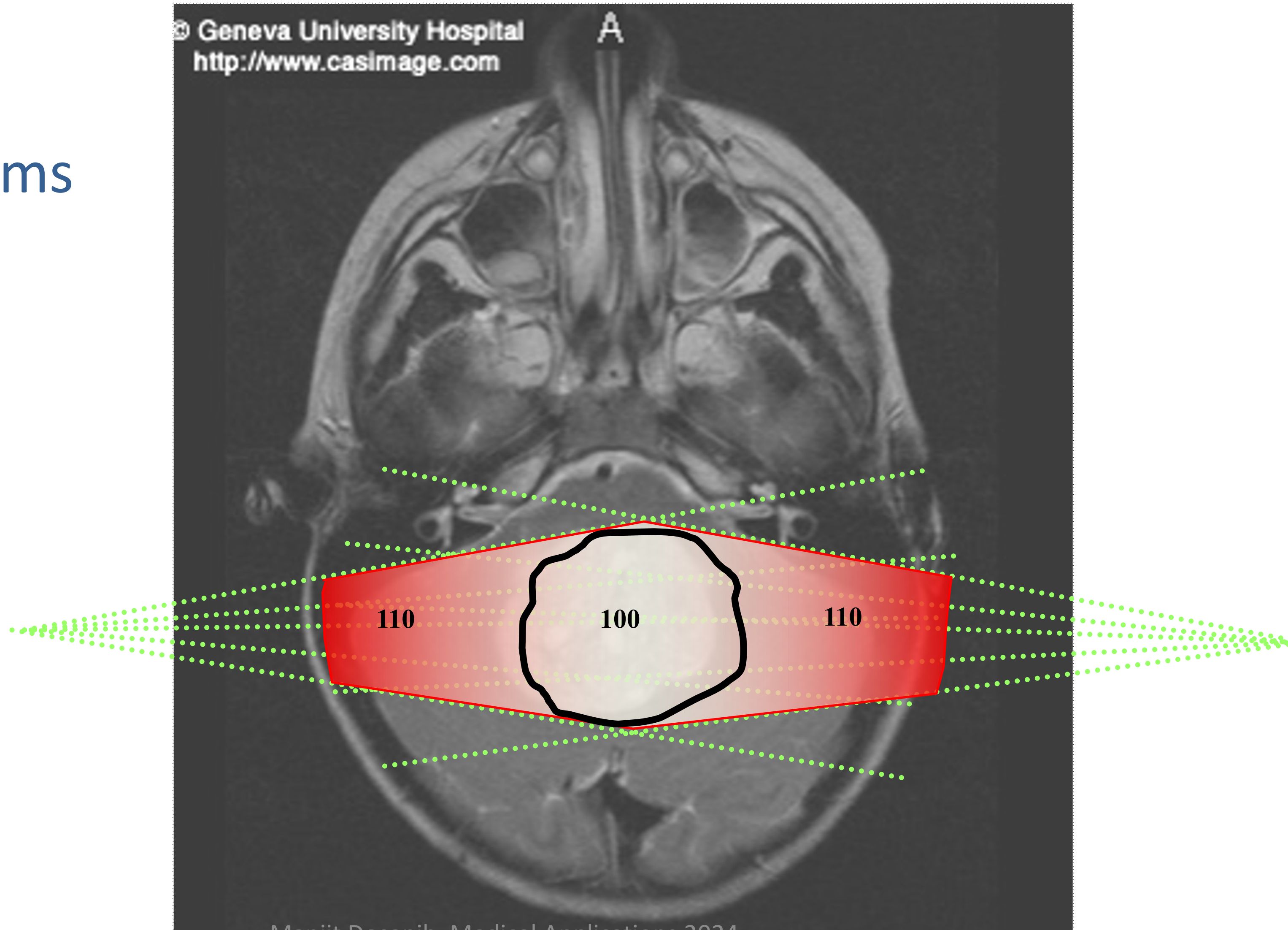
Classical Radiotherapy with X-rays

single beam

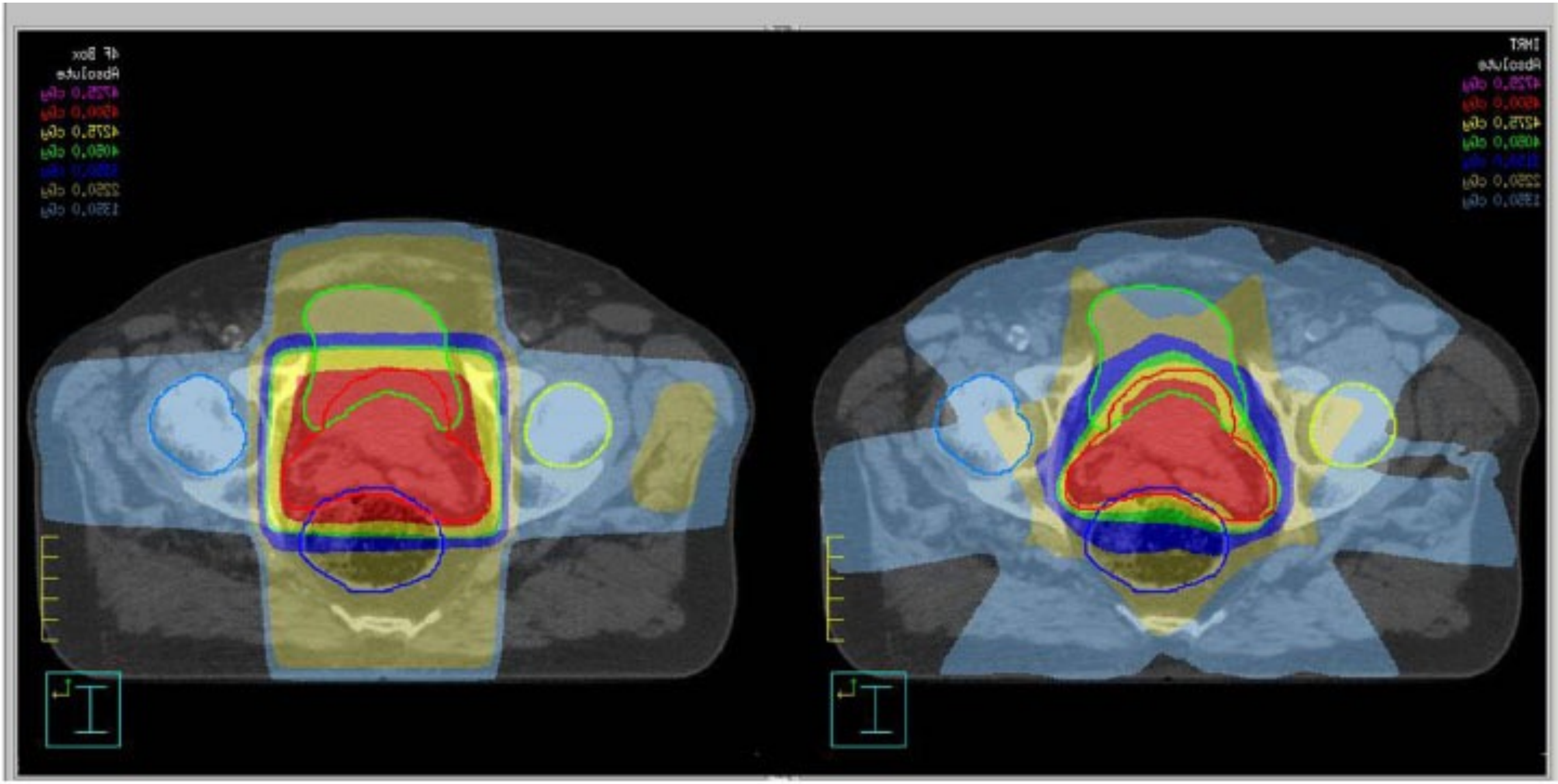


Radiotherapy with X-rays

two beams



Improved Delivery

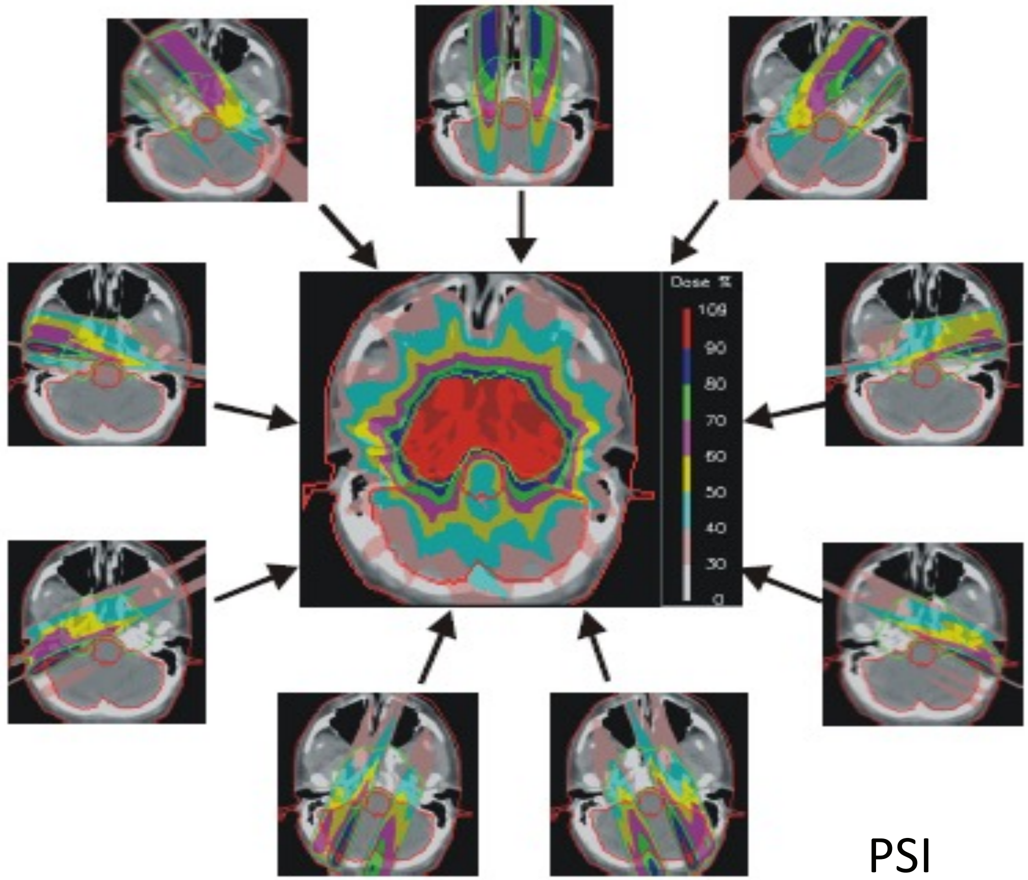


1990s: 4 constant intensity fields

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

Intensity Modulated Radiation Therapy

9 NON-UNIFORM FIELDS



PSI

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

to allow healthy tissues to repair:

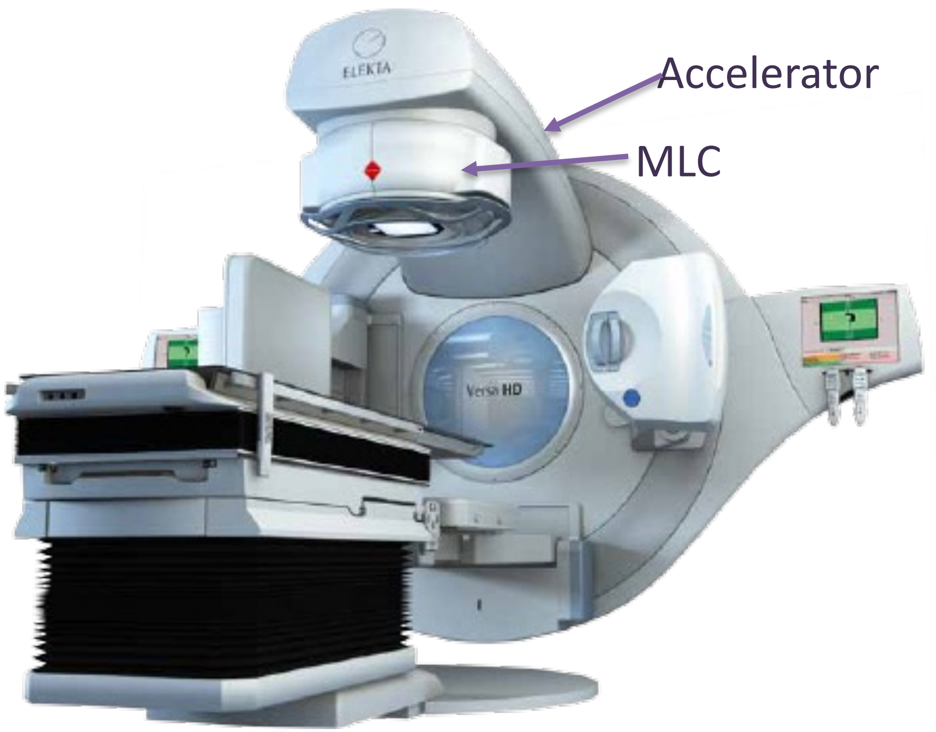
90% of the tumours are radiosensitive

Ugo Amaldi, TERA

The most widely available accelerator

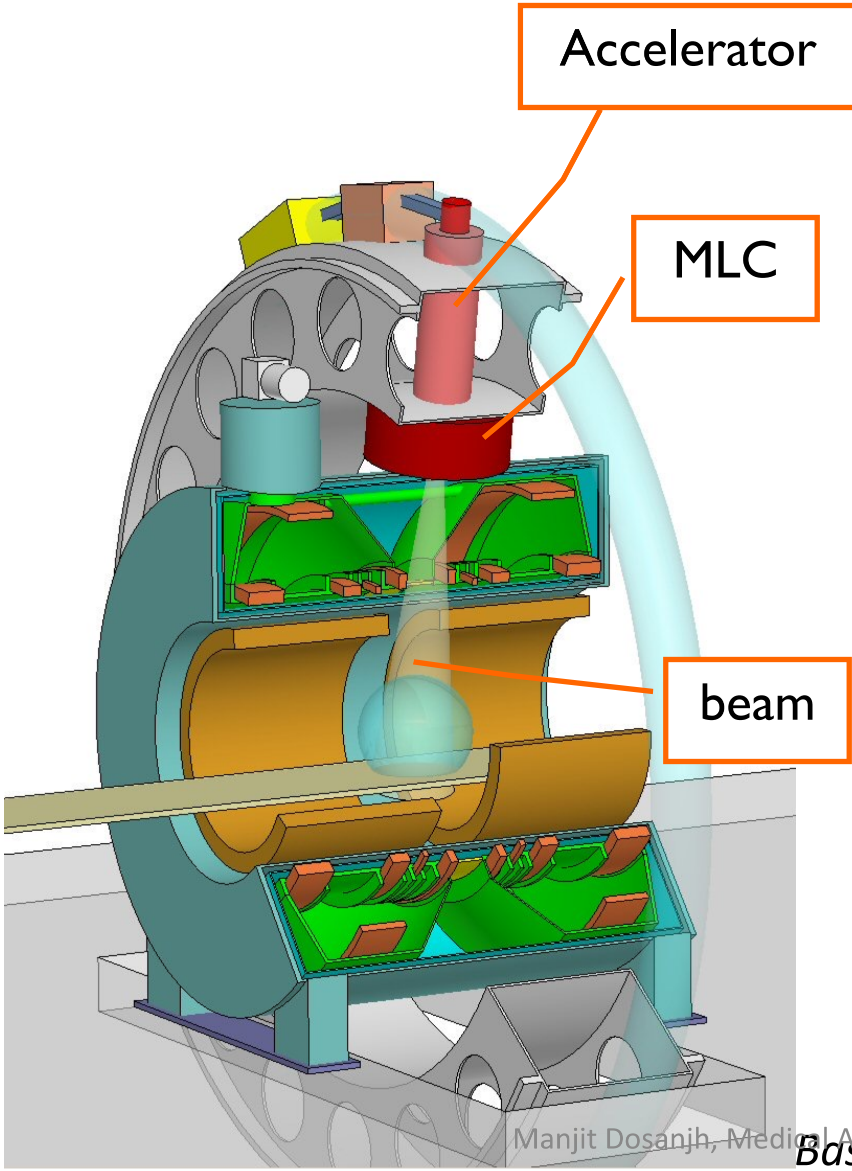
Electron Linac (linear accelerator) for radiation therapy treatment of cancer)

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

Bas Raaymakers, Utrecht, UMC, ENLIGHT

Advances in Radiation Therapy

In the past two decades due to:

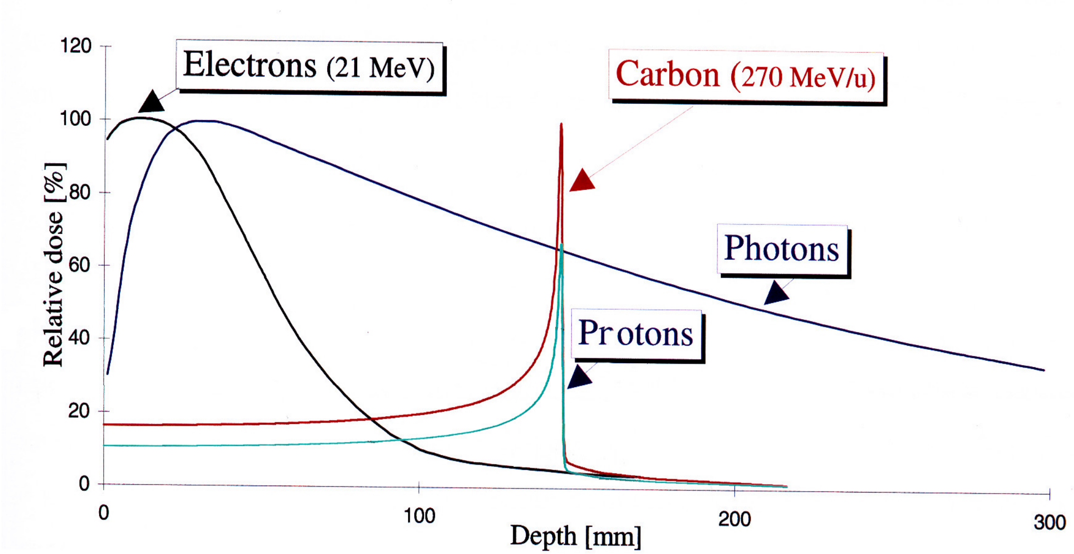
- improvements in imaging modalities, multimodality
- technology, powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
  - MRI-guided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

Hadron Therapy

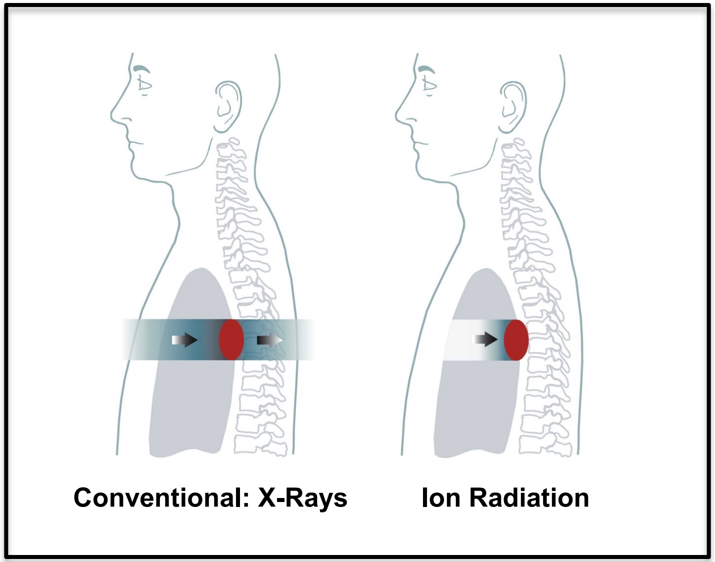
In 1946 Robert Wilson:

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

Robert Wilson
Fermi Lab



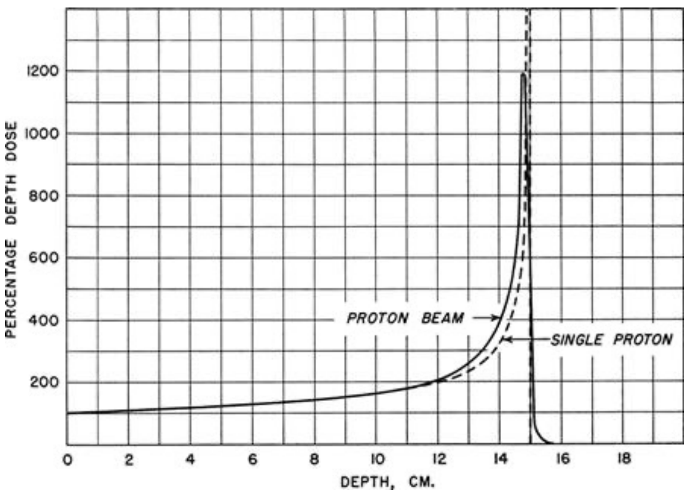
Depth in the body (mm)



1932 - E. Lawrence First cyclotron

1946 – proton therapy proposed by R. Wilson

Sept1954 – Berkeley treats the first patient



From physics ……..

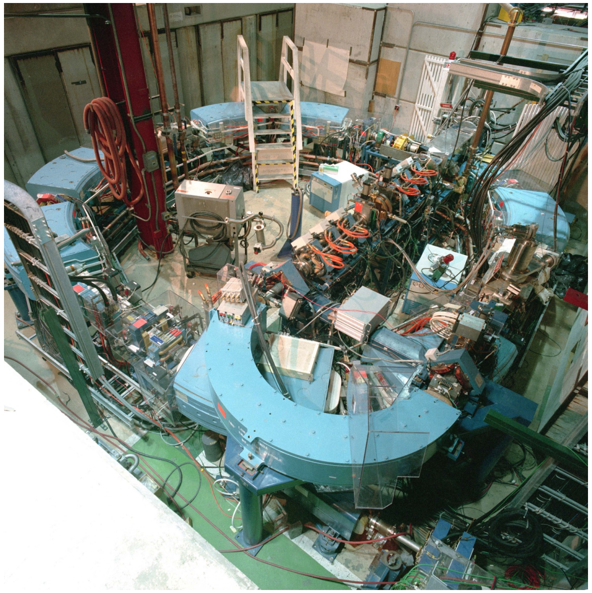
E. Lawrence
First cyclotron

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

360^0 Gantry

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

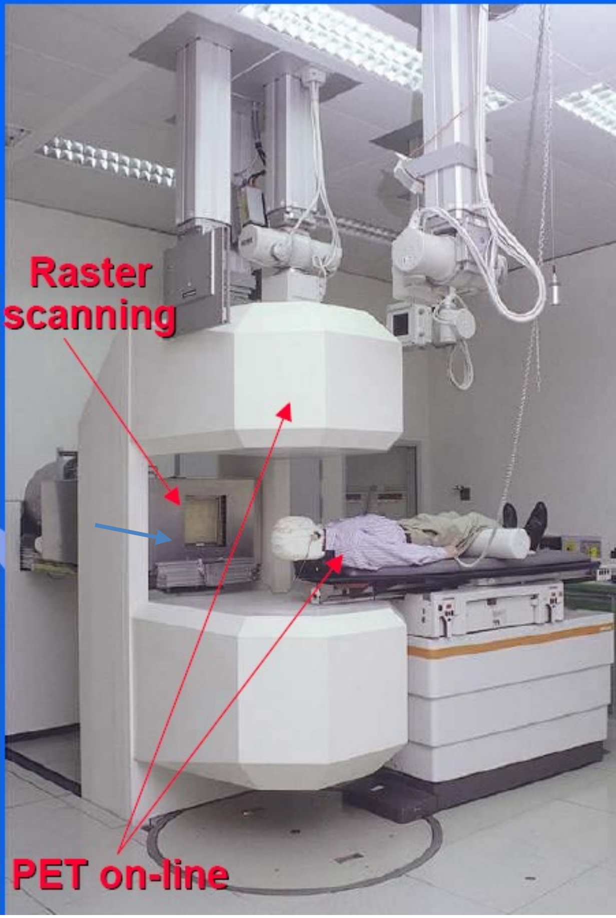
G. Kraft

J. Debus

G. Kraft

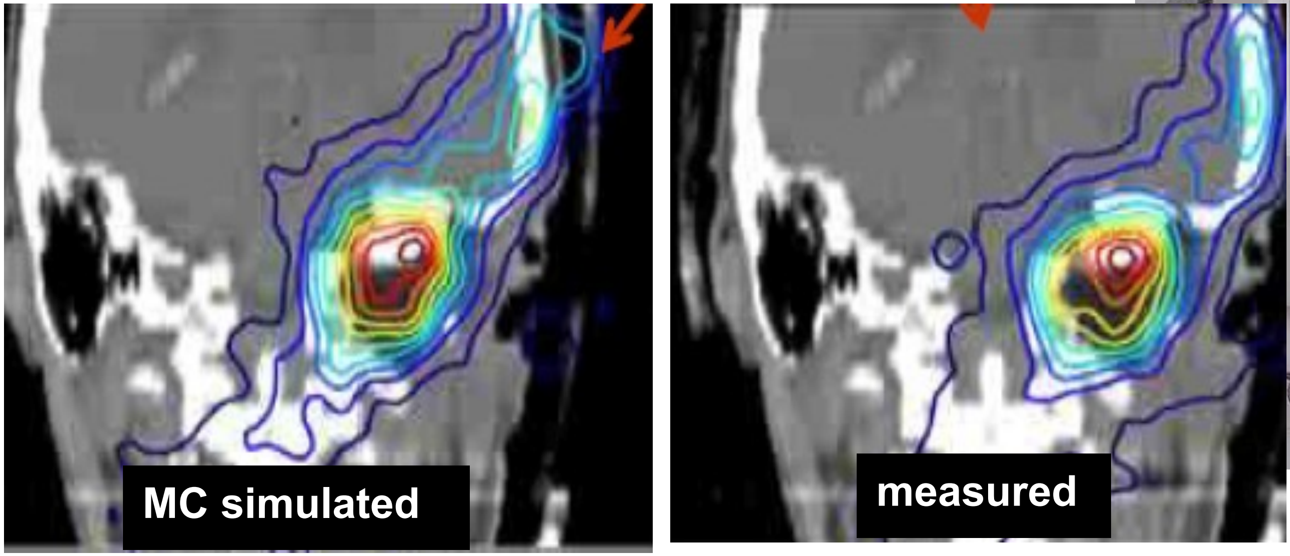
450 patients treated with carbon ions

J. Debus (Heidelberg Univ.)

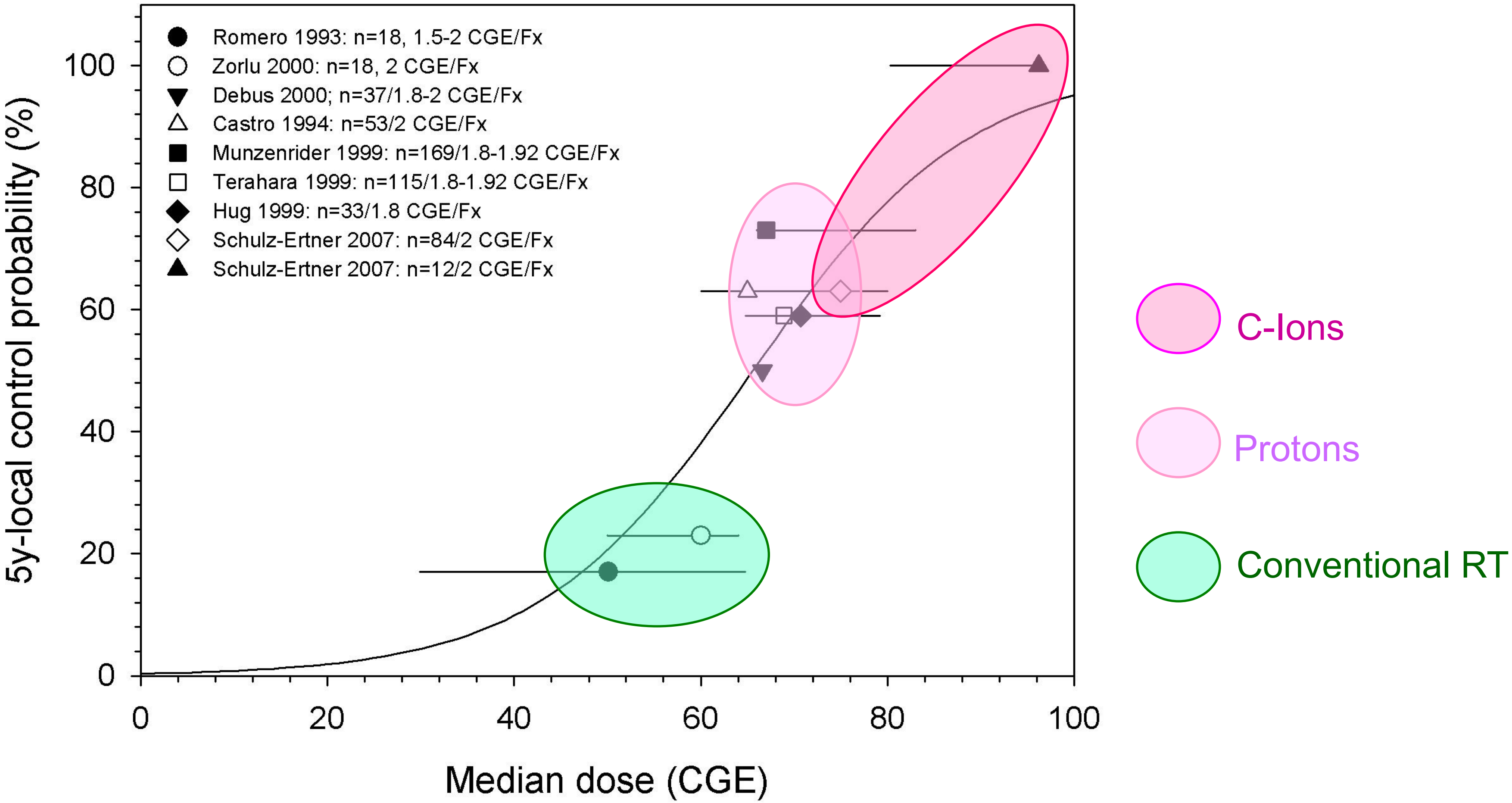


Real-time monitoring

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

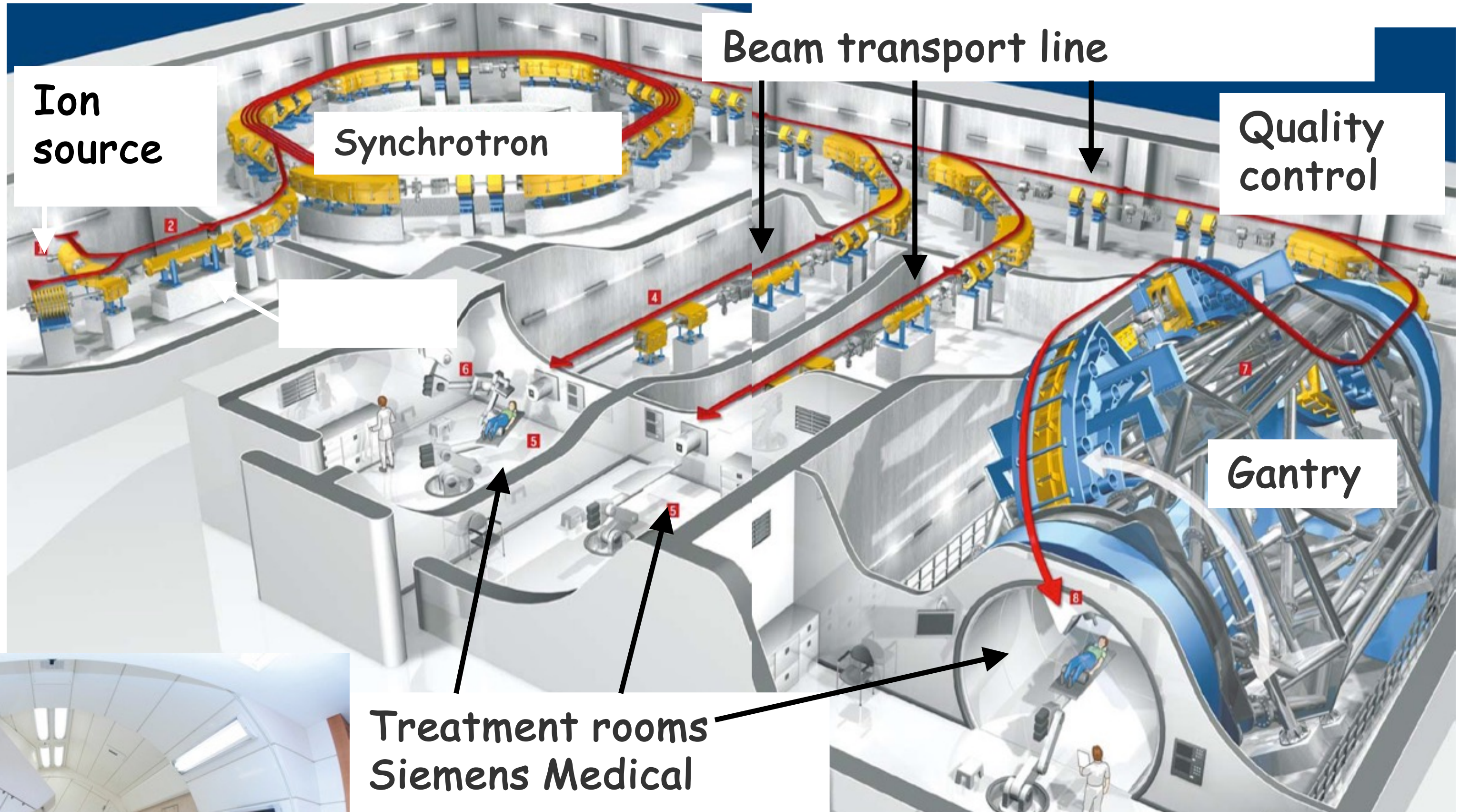


Tumour Control Rate: Chordomas



Schulz-Ertner, IJROBP 2007

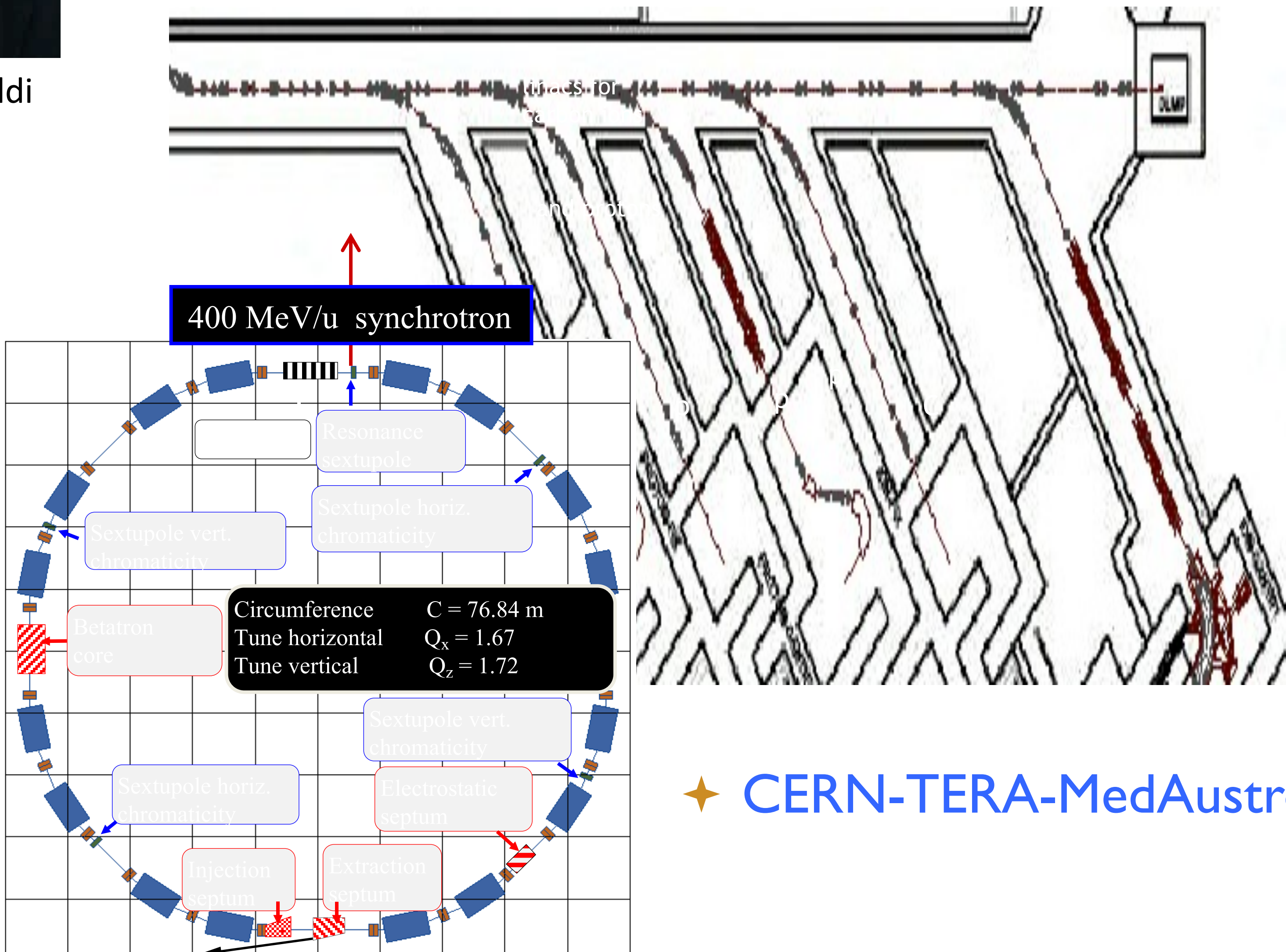
HIT - Heidelberg



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

Ugo Amaldi
TERA

PIMMS at CERN (1996-2000)



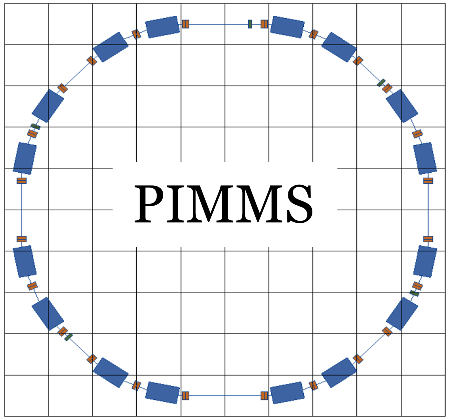
✦ CERN-TERA-MedAustron

PIMMS study at CERN (1996-2000)

Treatment , CNAO, Italy
2011

MedAustron, Austria 2019

1996-2000
PIMMS study



From PIMMS study to clinical reality

TERA

fondazione CNAO

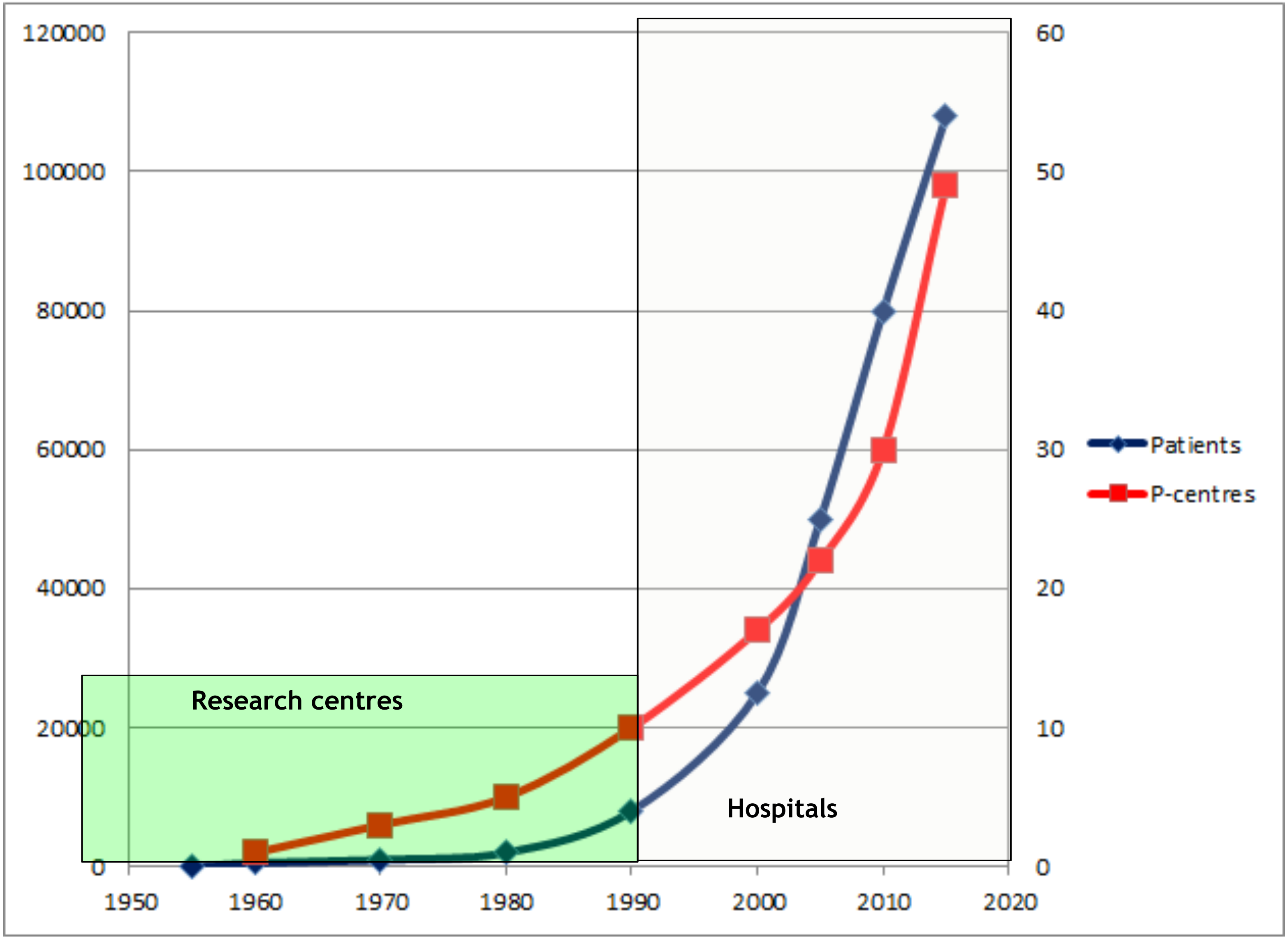
ebg MedAustron

First patient with carbon ions Nov 2012

Treatment started in 2016

TERA celebrated 30 years on 16 September 2022

[Data from www.ptcog.ch]



Particle Facilities Facilities in Europe in 2023

Manjit Dosanjh, Medical Applications 2024

Particle Therapy facilities in clinical operation in 2023

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

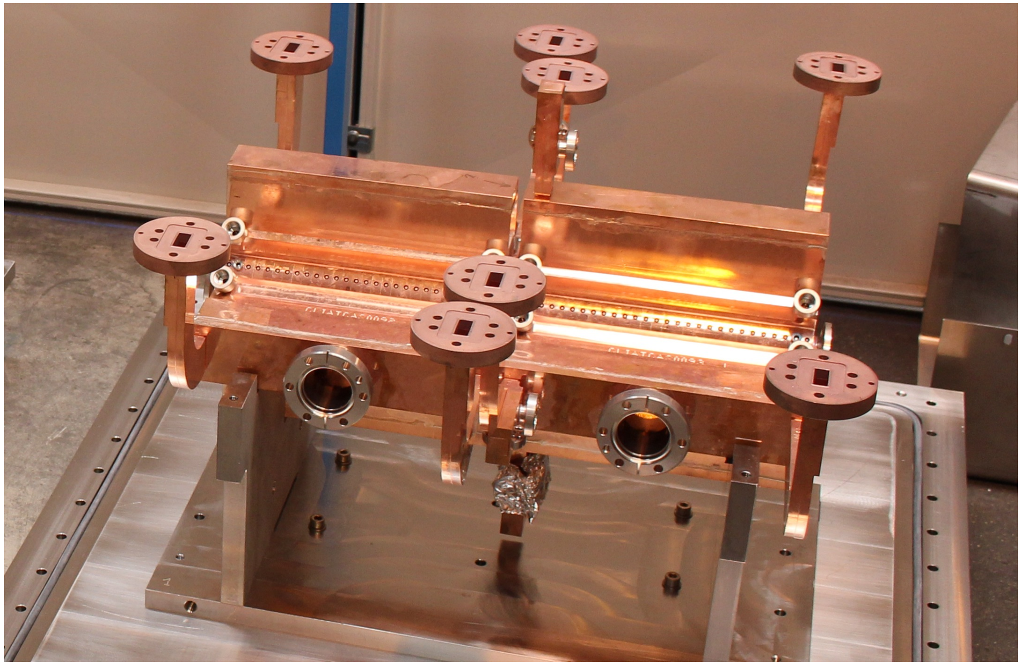
Much more still needs to be done

- 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

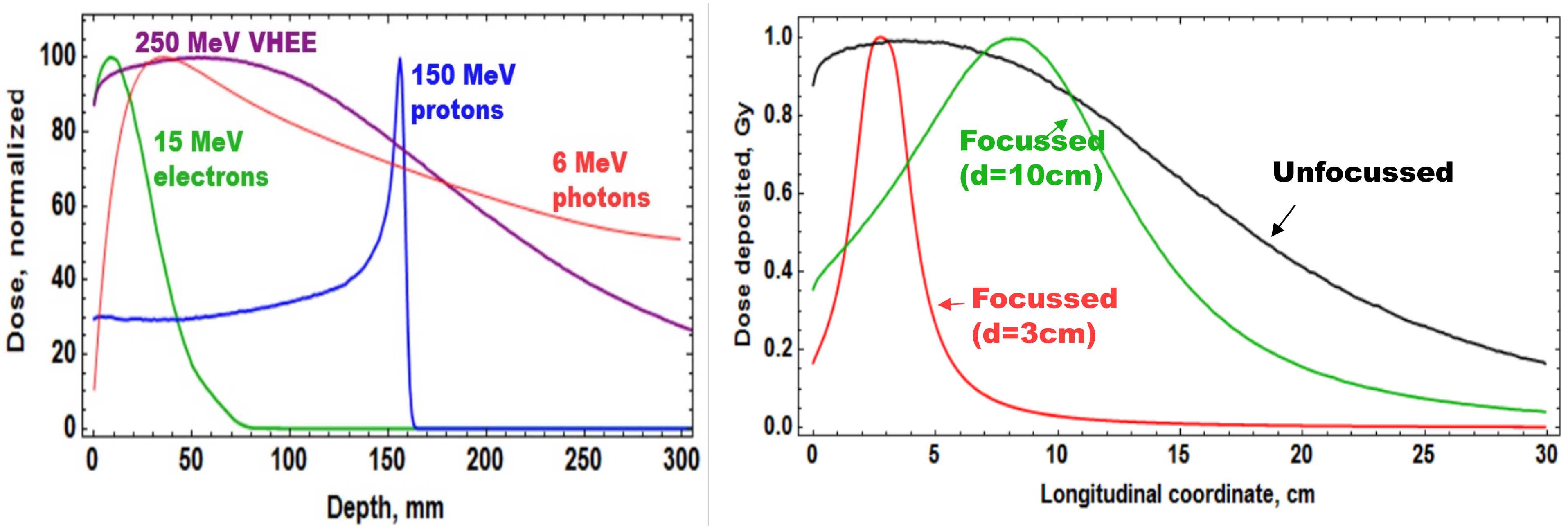


CLIC RF X-band cavity prototype (12 Ghz, 100 MV/m)

Compact Linear Collider

VHEE

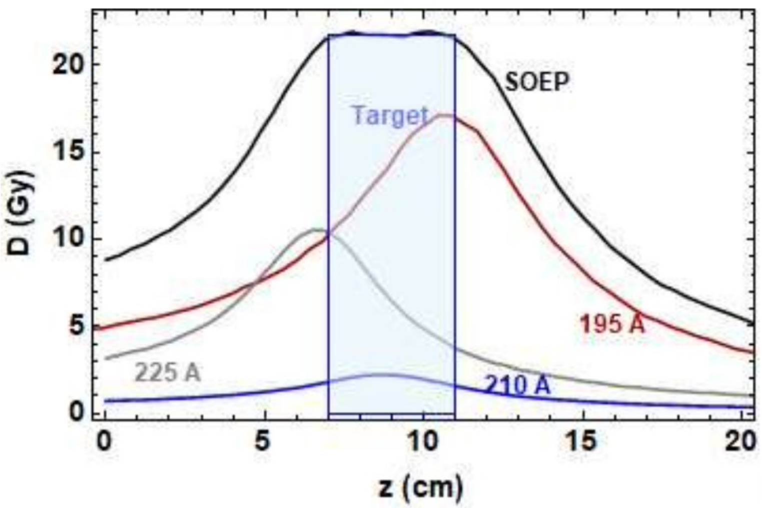
- Their ballistic and dosimetric properties can surpass those of photons, which are currently the most commonly used in RT.
- Their position compared to protons need to be evaluated, but they can be produced at a reduced cost.



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.



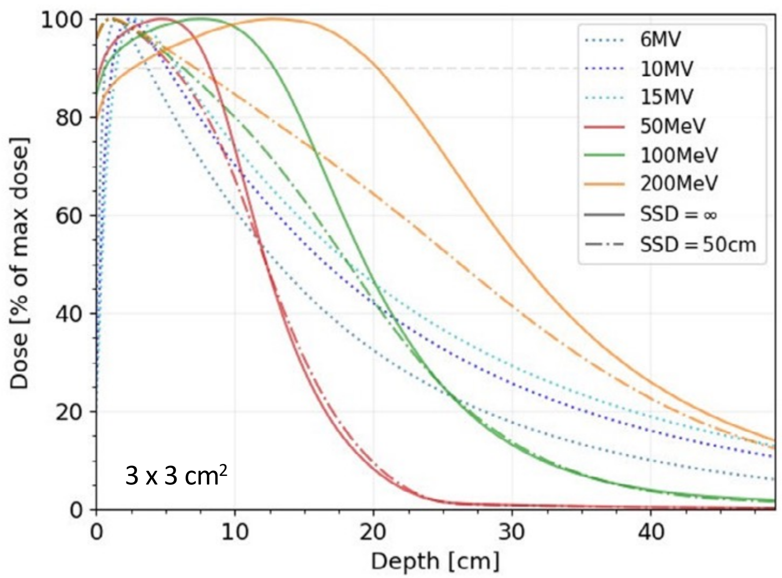
Whitmore et al: Focussed VHEE Beams, 2021

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 ~100 MV/m, and laser-wakefield acceleration ~GV/m);

- Using the FLASH effect for deep-seated tumours – technologically easier to produce high intensity electron beams compared to photons or hadrons.



Böhlen et al: Characteristics of VHEE Beams, 2021

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

CERN

UNIVERSITY OF OXFORD

Glimpse of FLASH THERAPY - 2014

First Proof-of-Concept with low-energy e^-

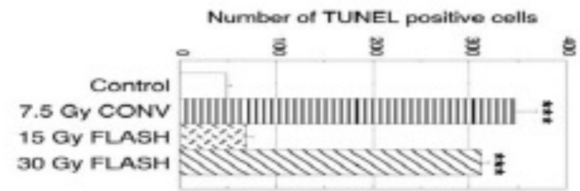
Sci Transl Med 6: 245ra93, 2014

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

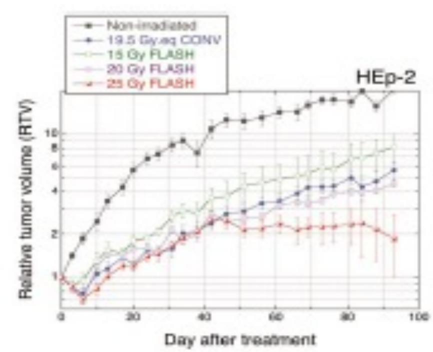
Visualisation of collagen invasion (Masson trichrome staining)

Healthy Fibrosis Healthy

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

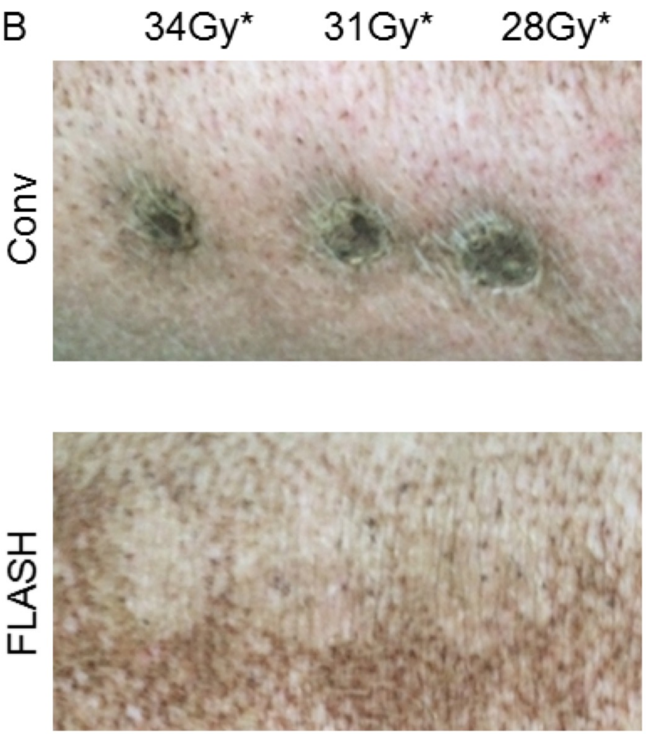


- No difference between FLASH and CONV with regard to tumor growth inhibition.
- However, **normal tissue sparing by FLASH** allowed dose escalation without complications, resulting in complete tumor cure in some xenograft models.



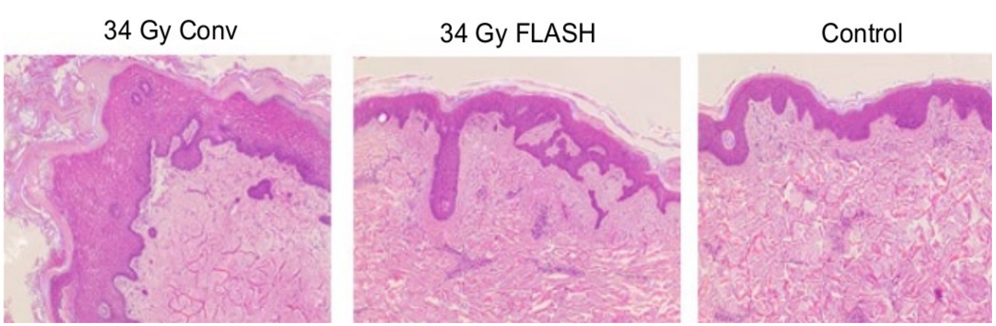
institutCurie

The FLASH Effect – gaining hhuge momentum



Vozenin MC, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond JF, Petit B, Burki M, Ferrand G, Patin D, Bouchaab 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



FLASH mechanism is still not fully understood.

Clinical Translation (2019): 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

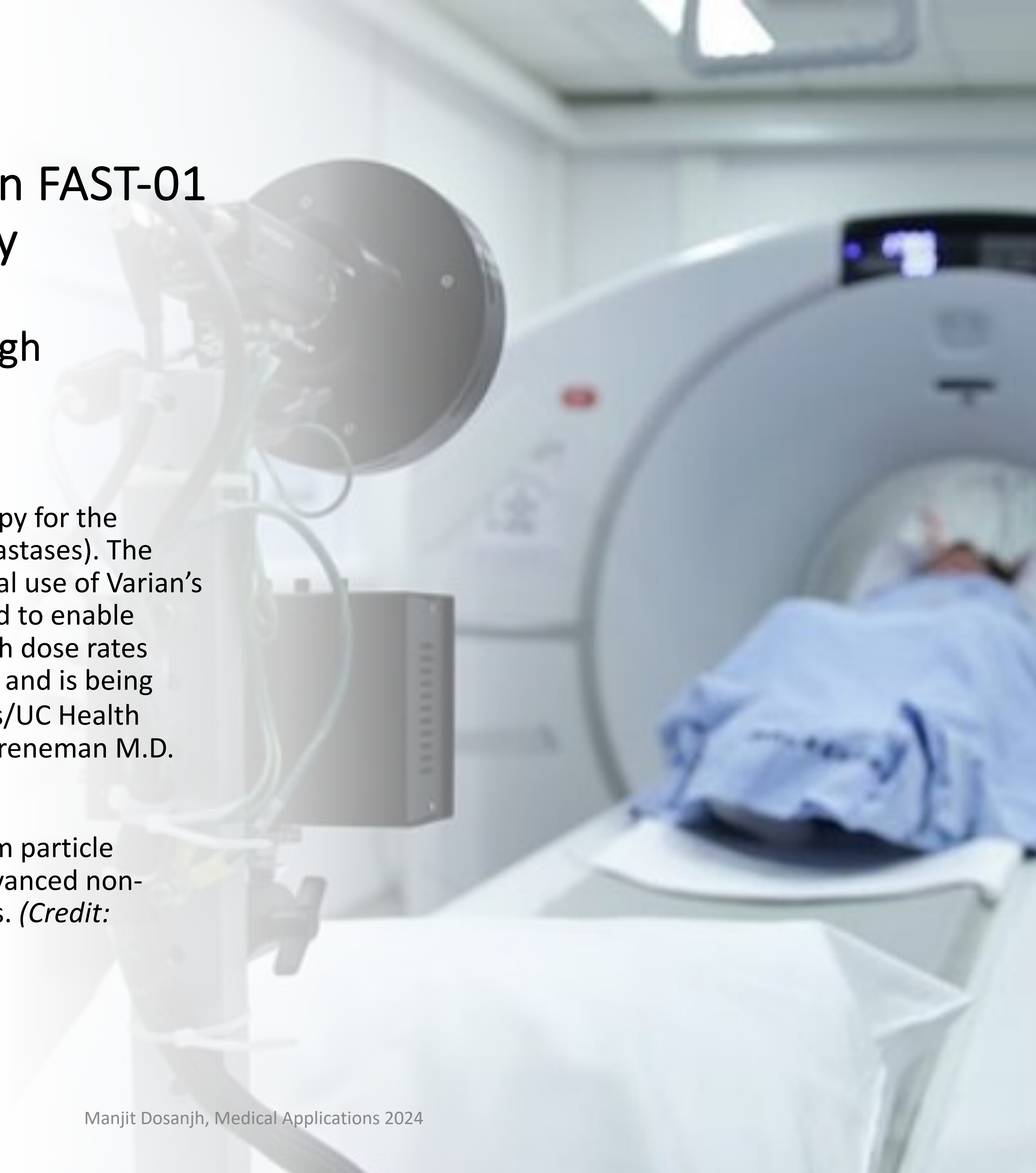
Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

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

Transmission-shoot through

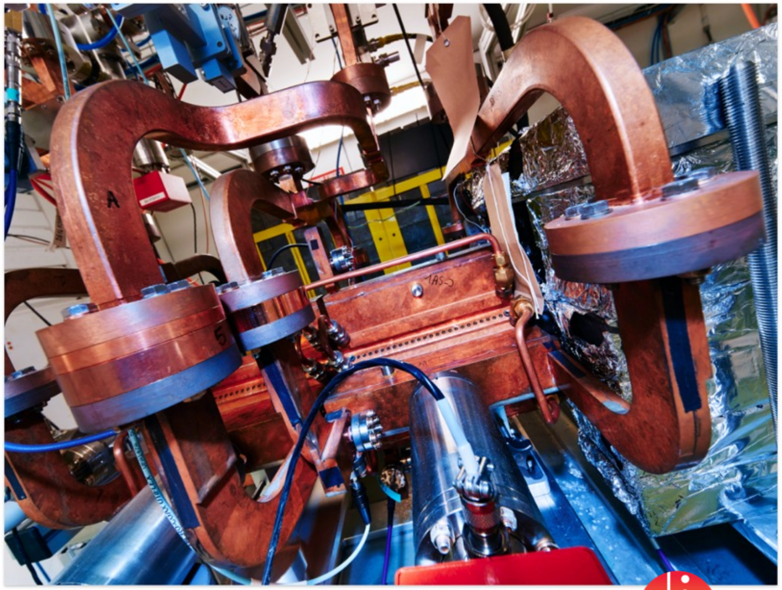
FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases). The clinical trial involves the investigational use of Varian's ProBeam particle accelerator modified to enable radiation therapy delivery at ultra-high dose rates (dose delivered in less than 1 second) and is 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)*

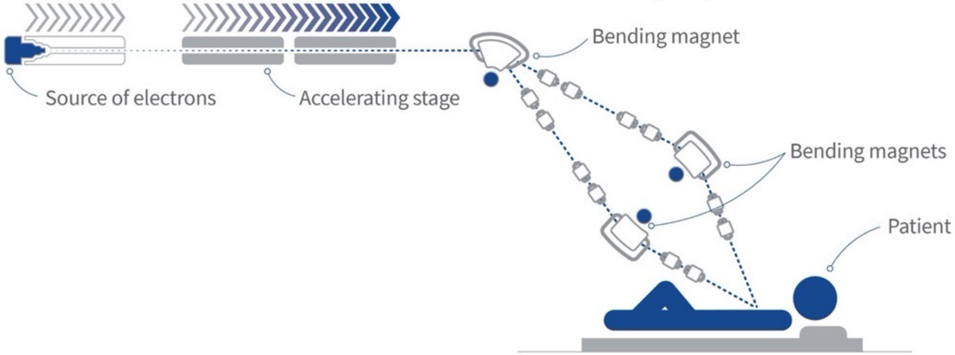


CERN – CHUV collaboration on FLASH VHEE therapy

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.

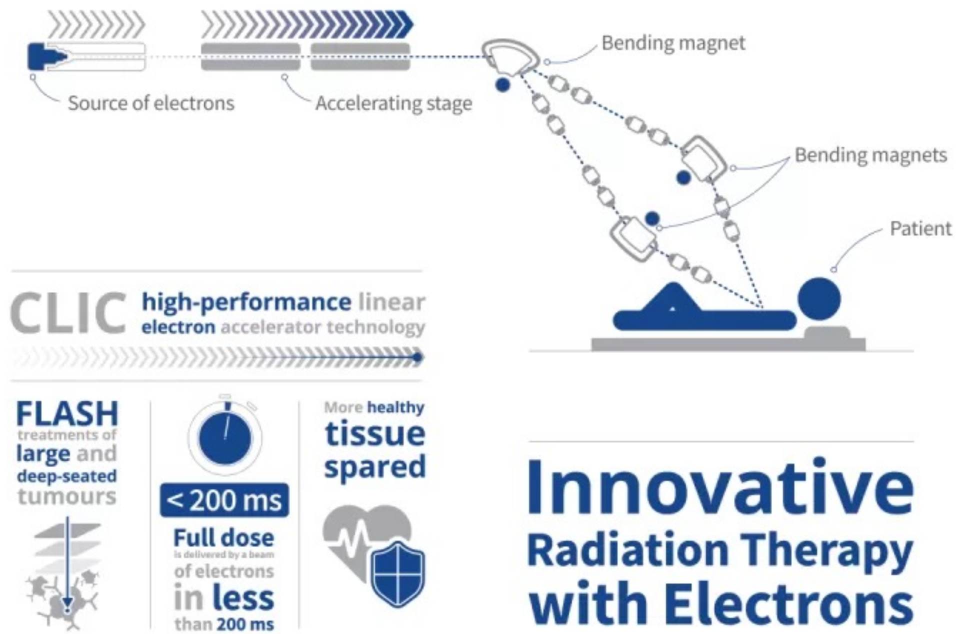
The design of this facility is the result of an intense dialogue between groups at CHUV and CERN.

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

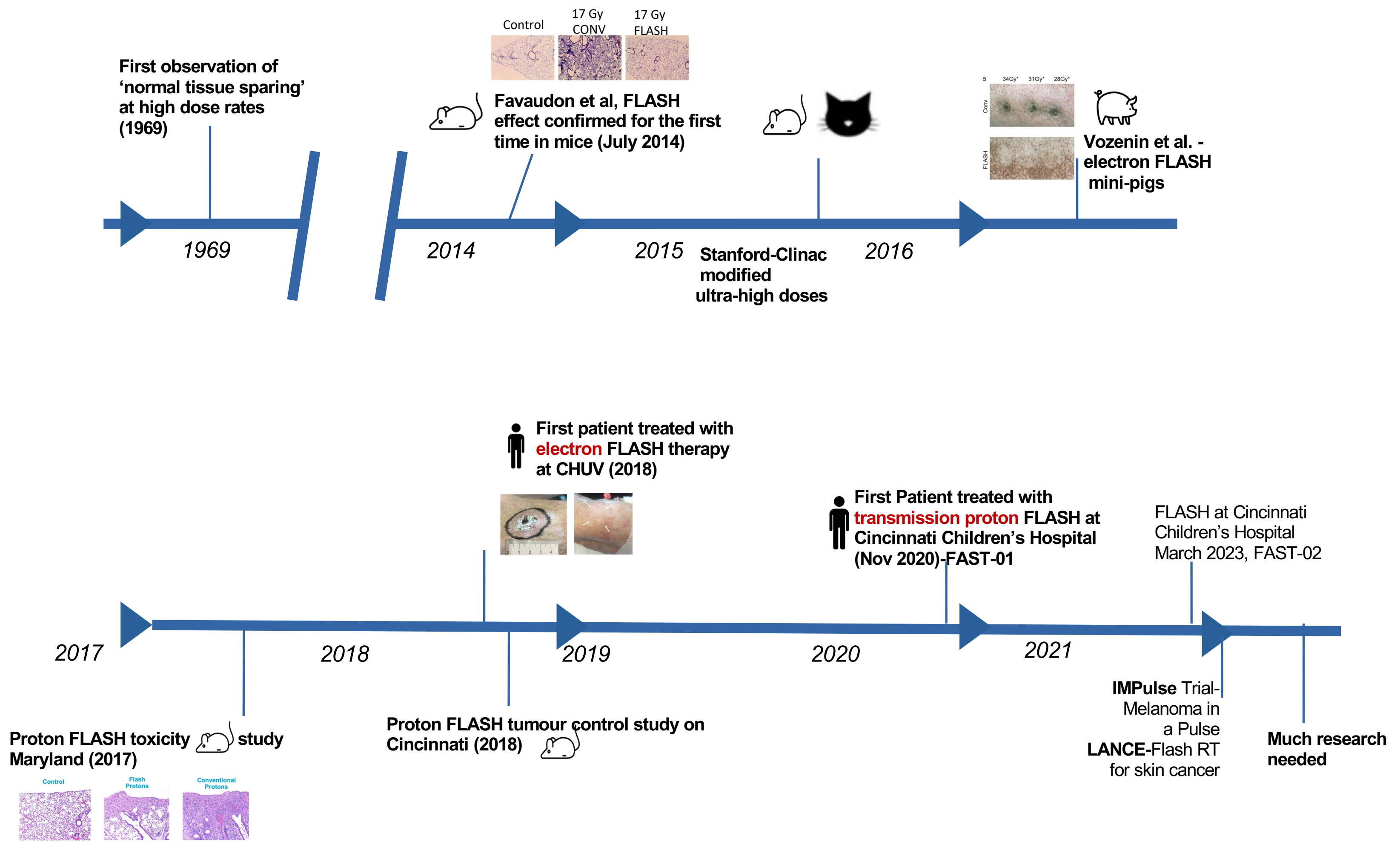
Walter Wuensch (CERN)

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.



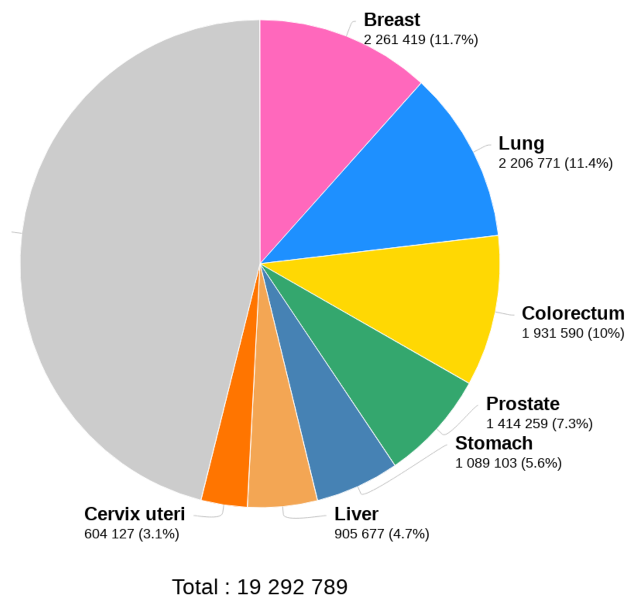
Centre hospitalier universitaire vaudois


First observation of 'normal tissue sparing' at high dose rates (1969)
Control
17 Gy CONV
17 Gy FLASH
Favaudon et al, FLASH effect confirmed for the first time in mice (July 2014)
Vozenin et al. - electron FLASH mini-pigs
1969
2014
2015
Stanford-Clinac modified ultra-high doses
2016
First patient treated with electron FLASH therapy at CHUV (2018)
First Patient treated with transmission proton FLASH at Cincinnati Children's Hospital (Nov 2020)-FAST-01
FLASH at Cincinnati Children's Hospital March 2023, FAST-02
2017
2018
2019
2020
2021
Proton FLASH toxicity study Maryland (2017)
Control
Flash Protons
Conventional Protons
Proton FLASH tumour control study on Cincinnati (2018)
IMPulse Trial- Melanoma in a Pulse
LANCE-Flash RT for skin cancer
Much research needed

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



Data source: GLOBOSCAN 2020

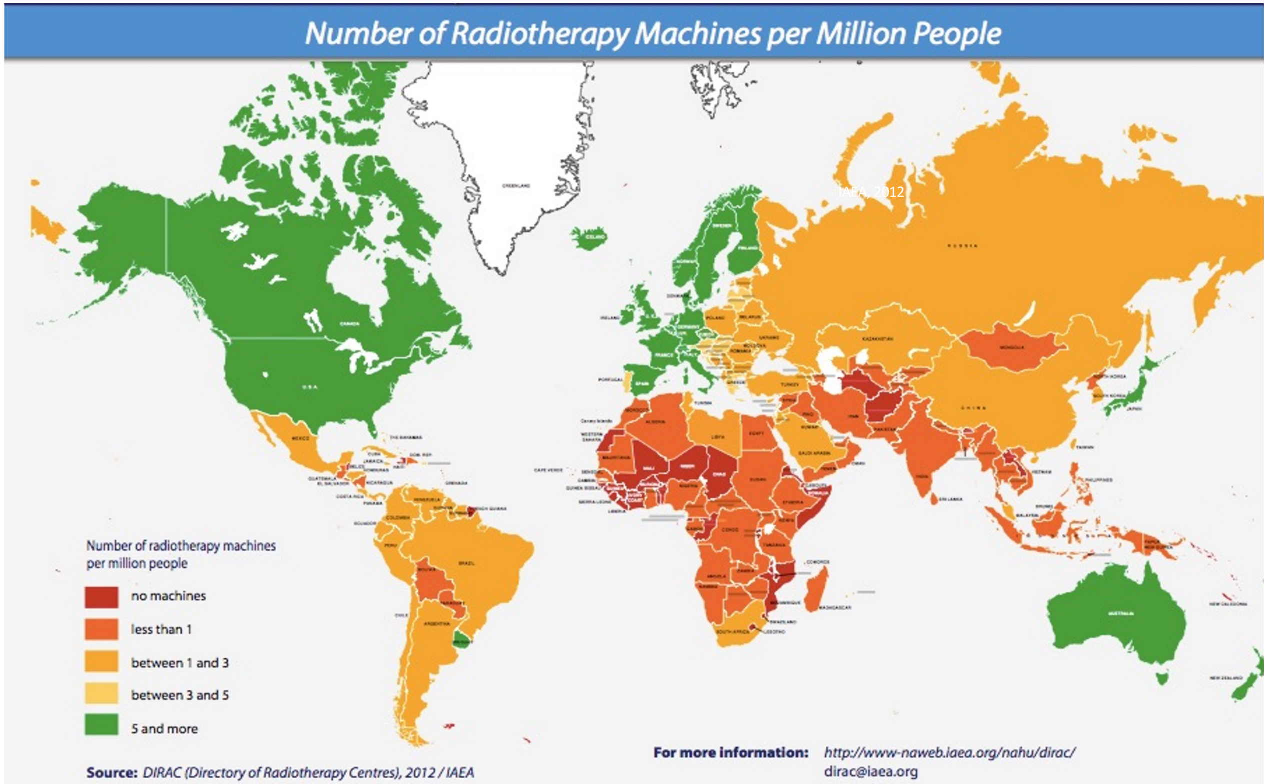
Radiation therapy is a key tool for treatment for 50-60% patients

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



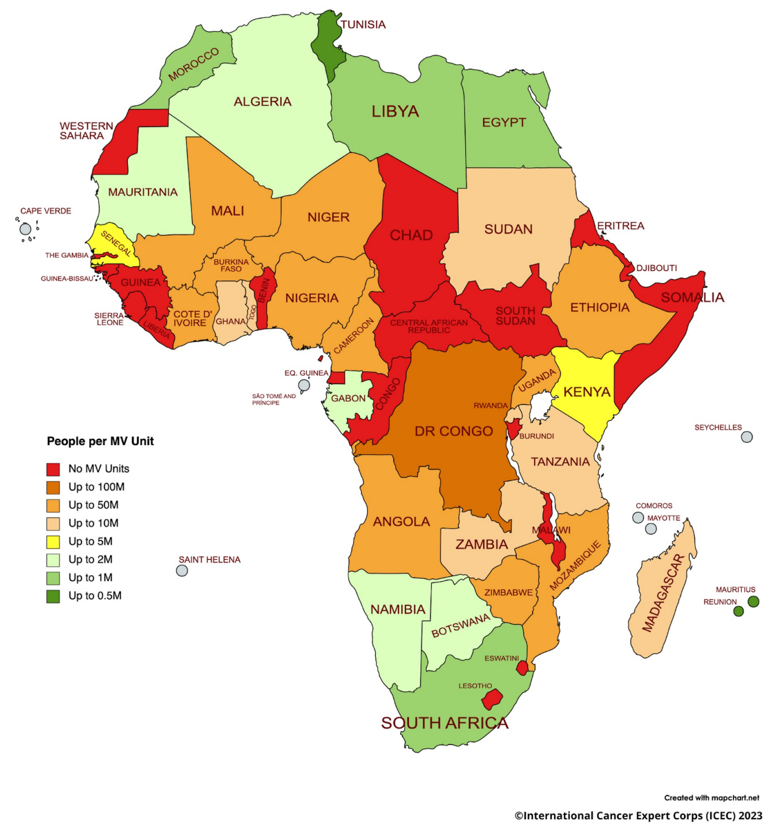
Most of the current 18,000 RT units are in HIC (High-Income Countries)

Number of people per functioning machine in countries in Africa

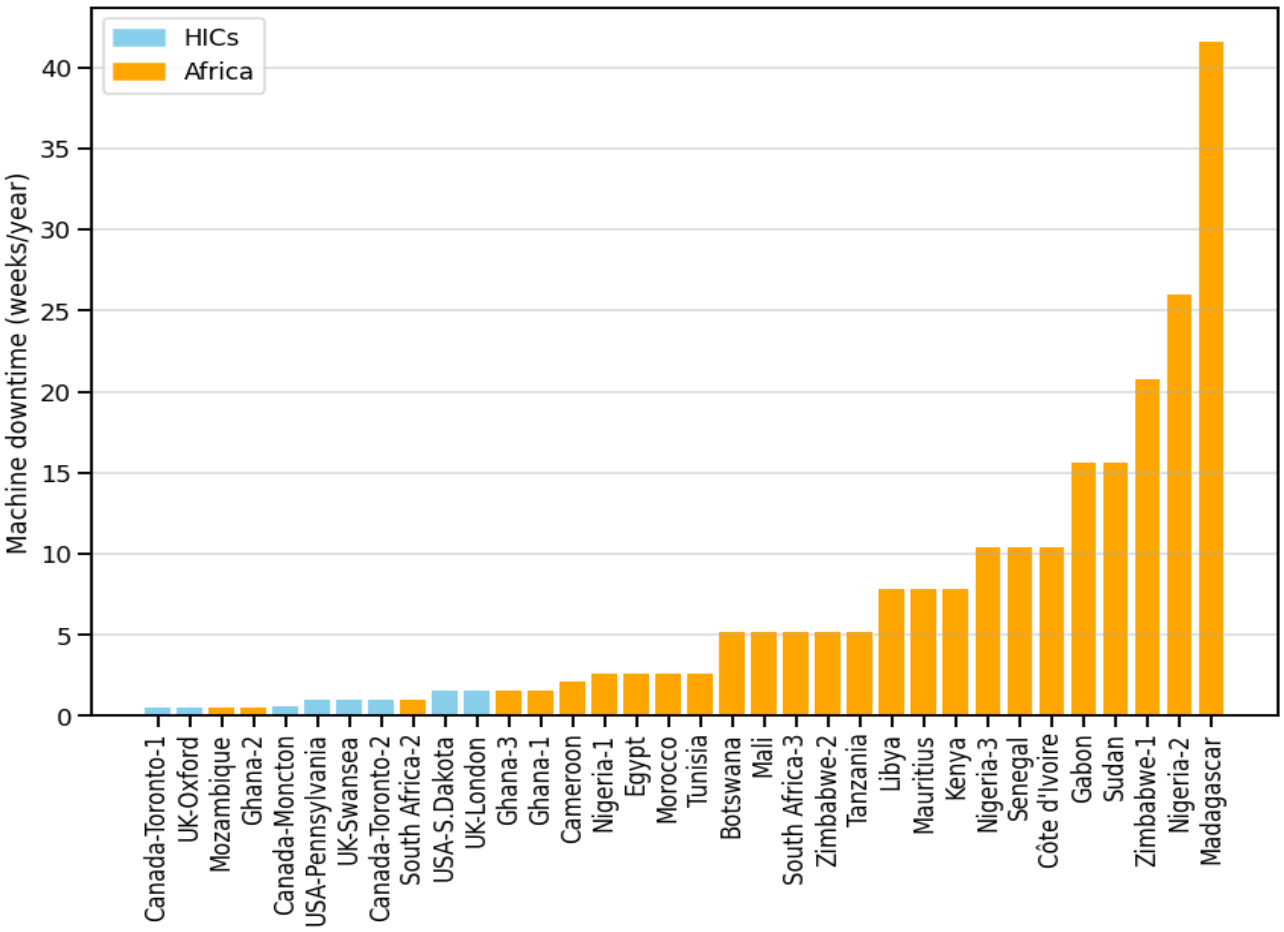
But there are dramatic disparities in Access

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
I 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



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 (**S**mart **T**echnologies to **E**xtend **L**ives with **L**inear **A**ccelerators)

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

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 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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