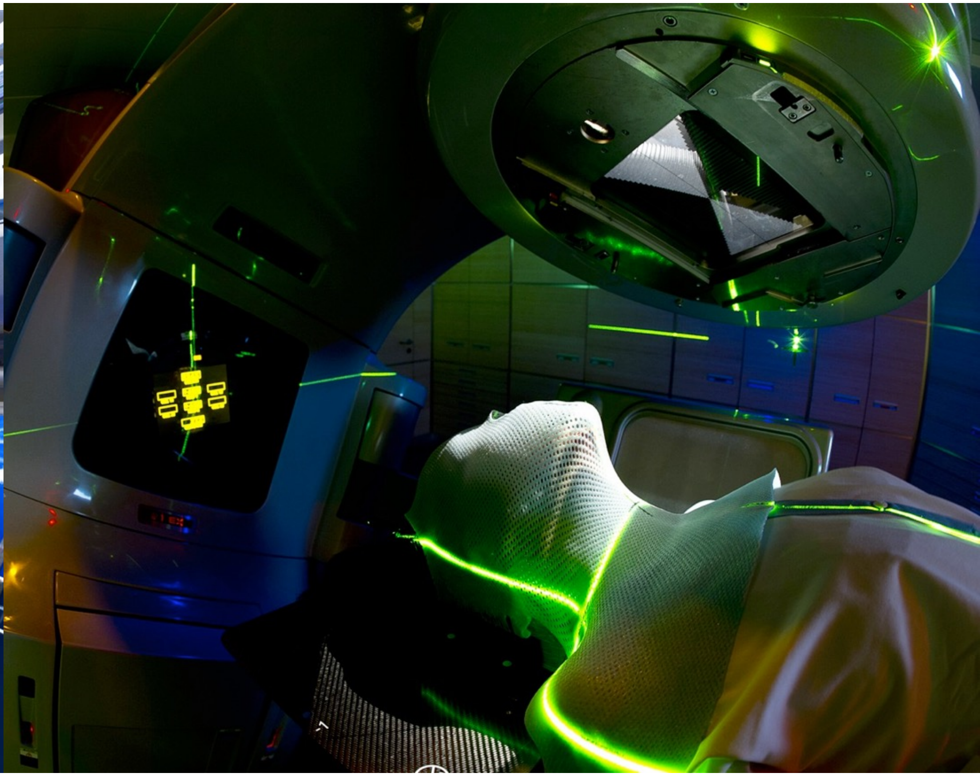
From Physics to Medical Applications



Manjit Dosanjh

Manjit.Dosanjh@cern.ch

9 August 2023

CERN

UNIVERSITY OF OXFORD

Modern medical physics.....beginnings

Wilhelm Röntgen

8/11/1895

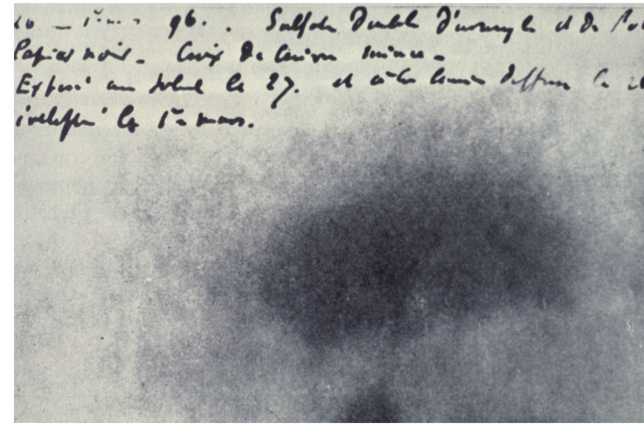
22/12/1895

1901

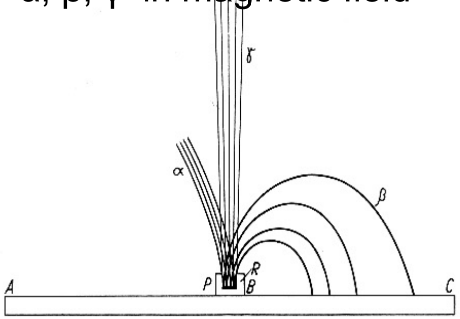
..........beginnings

Henri Becquerel

1896:
Discovery of natural radioactivity

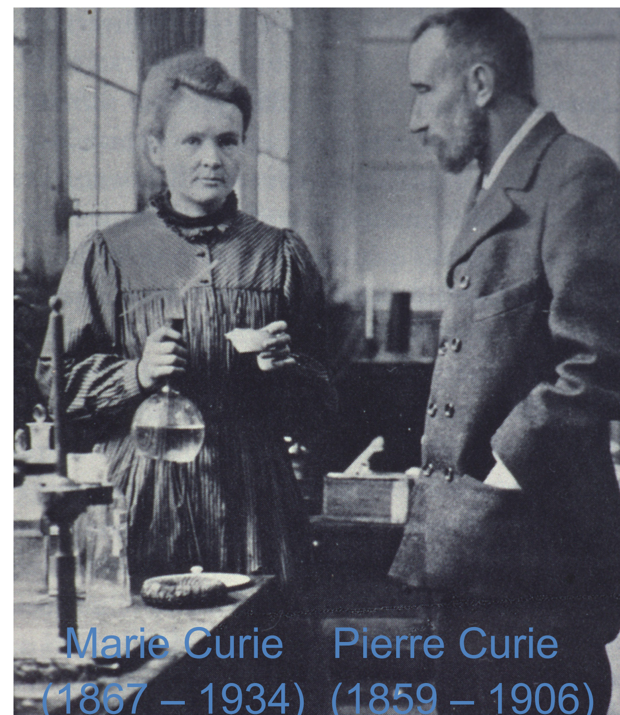


Thesis of Mme. Curie – 1904
α, β, γ in magnetic field



1898: Discovery of radium

used immediately for "Brachytherapy"

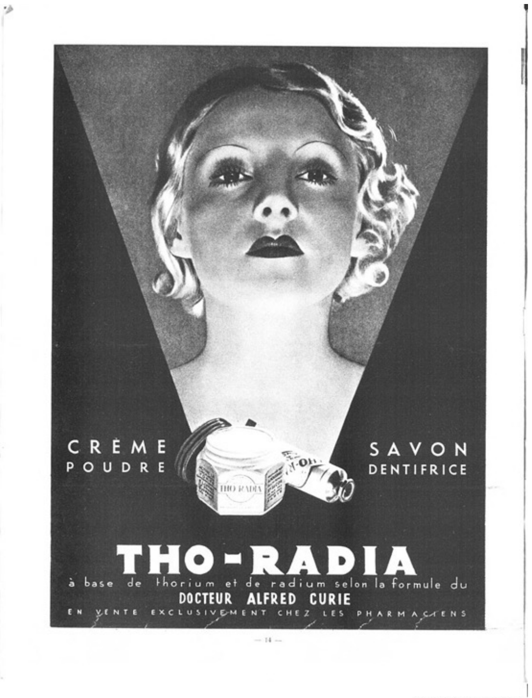


Marie Curie (1867 – 1934) Pierre Curie (1859 – 1906)

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

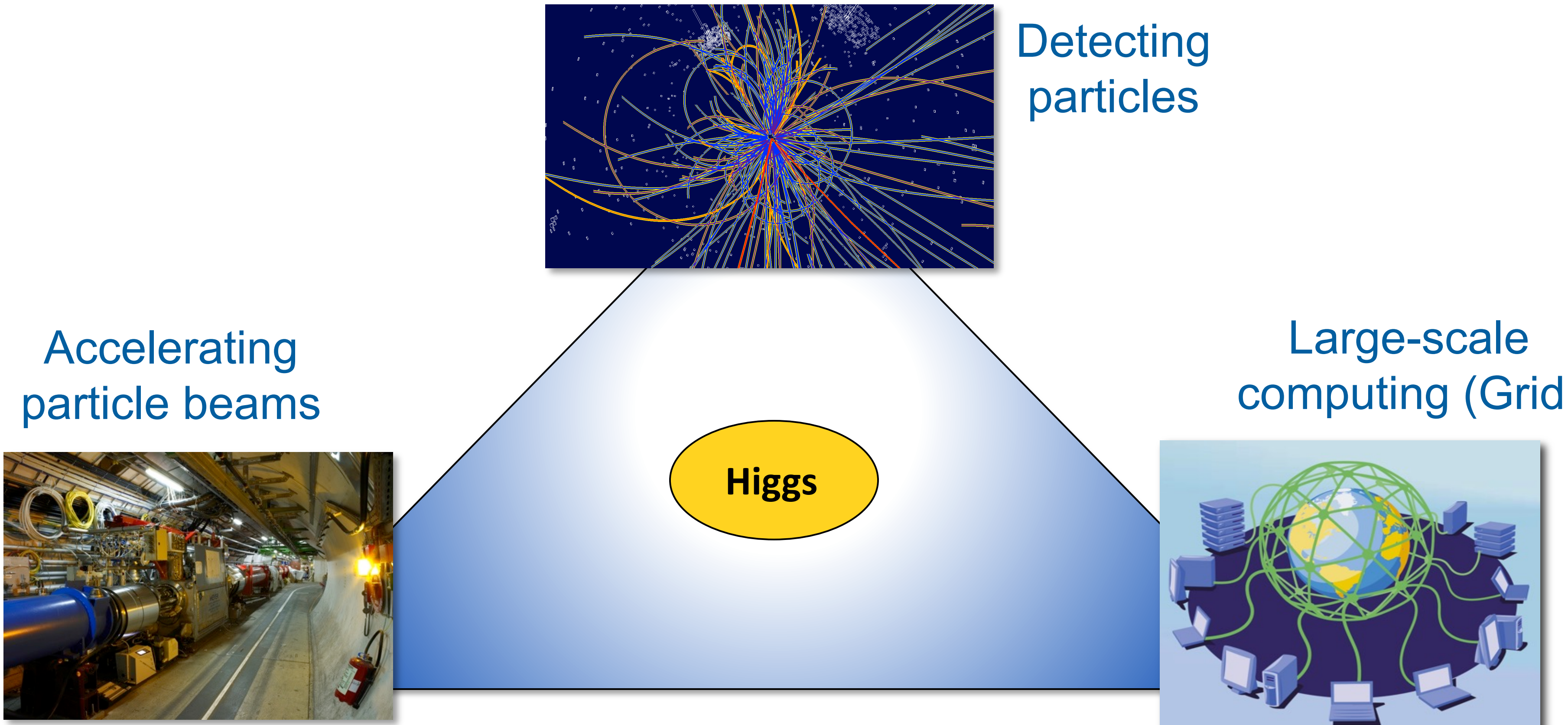
Par Radior cosmetics — sitead New York Tribune Magazine, page 12, Domaine public, https://commons.wikimedia.org/w/index.php?curid=35047170

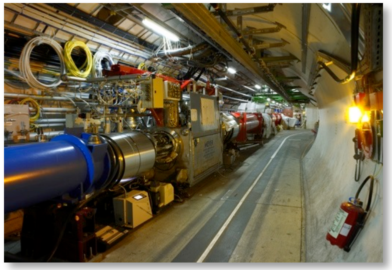
Par Sam LaRussa from United States of America — Radithor, CC BY-SA 2.0, https://commons.wikimedia.org/w/index.php?curid=57841049

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

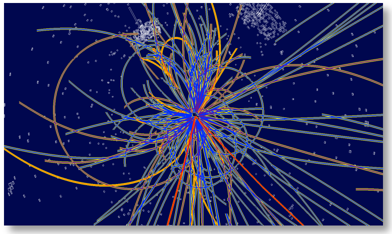
Courtesy of Manuela Cirilli

CERN and Physics Technologies

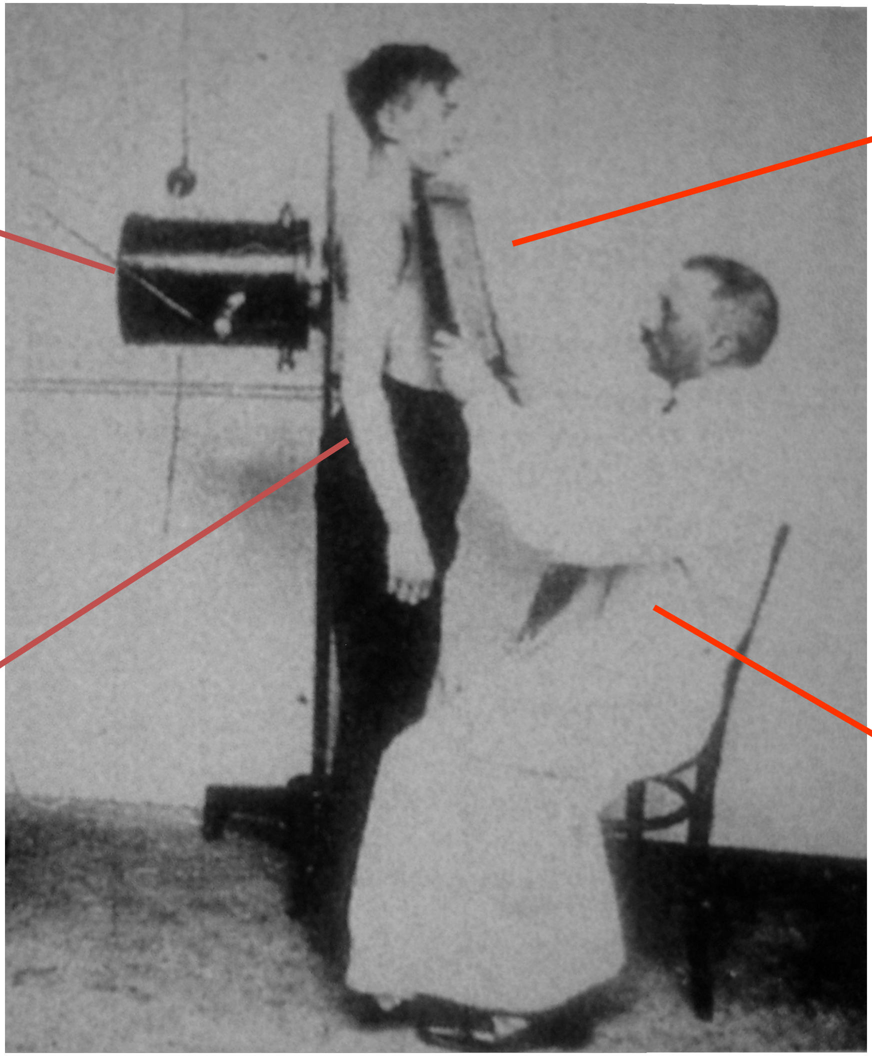




X-ray source



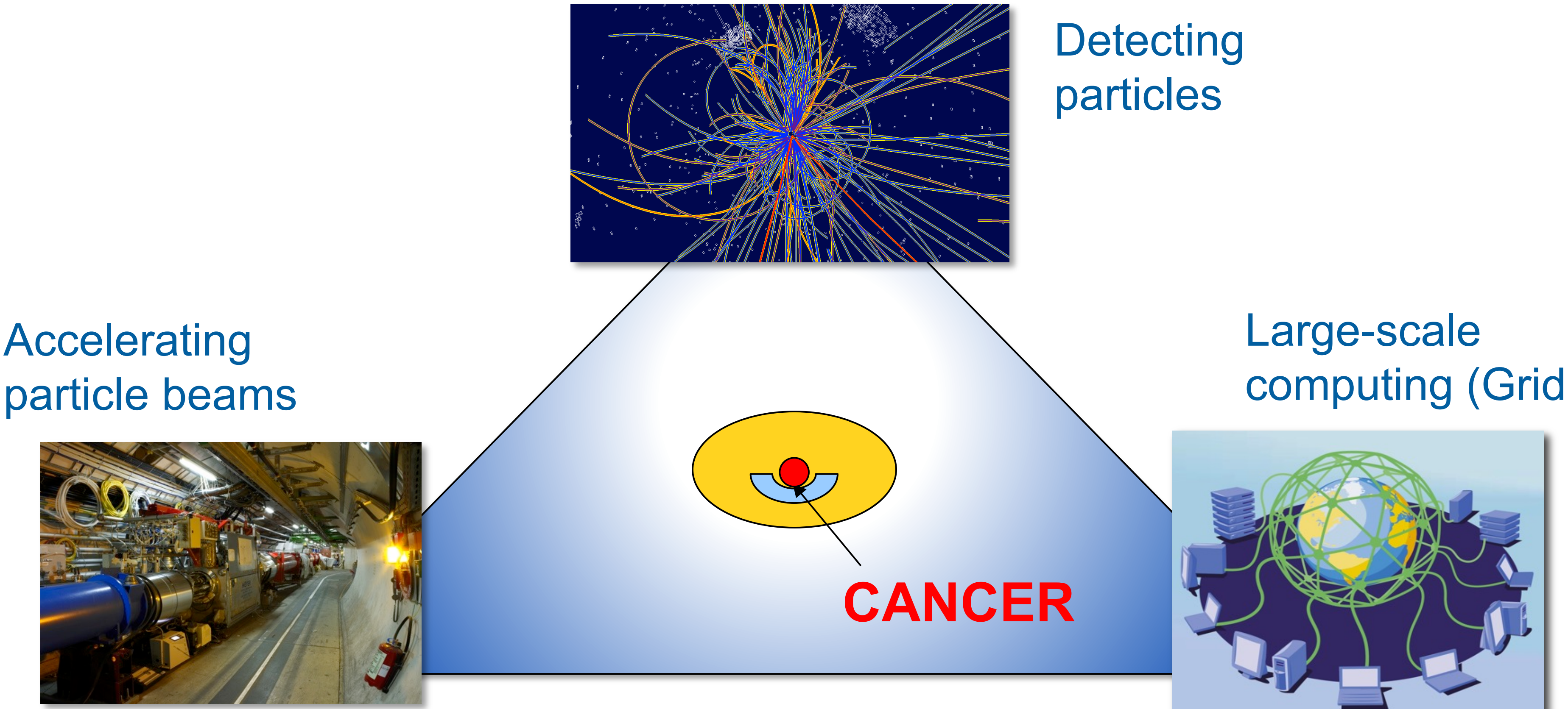
Detector



Object

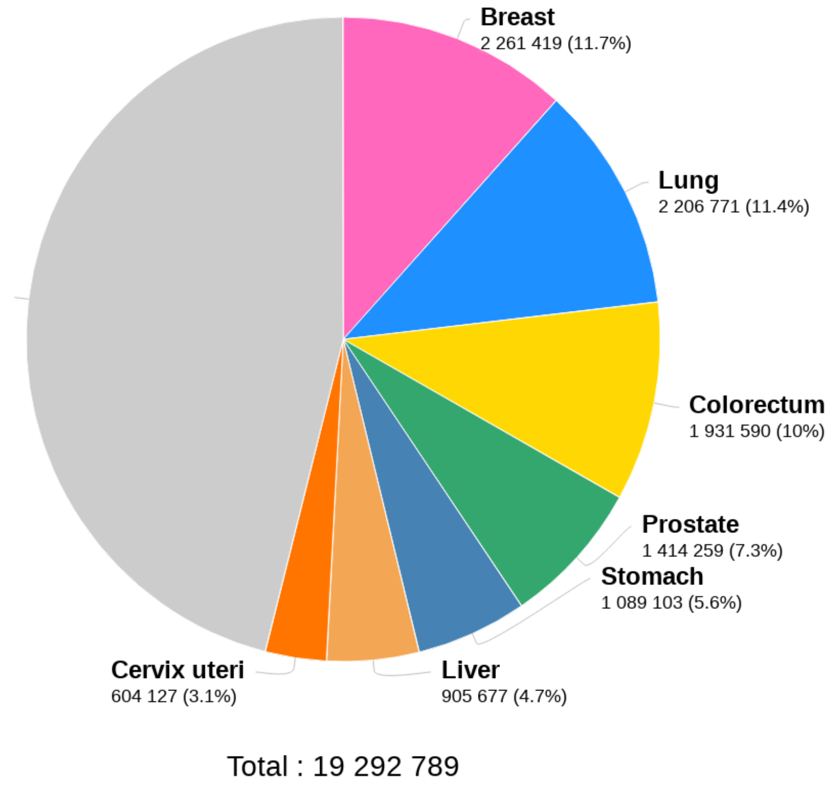
Pattern Recognition System

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)

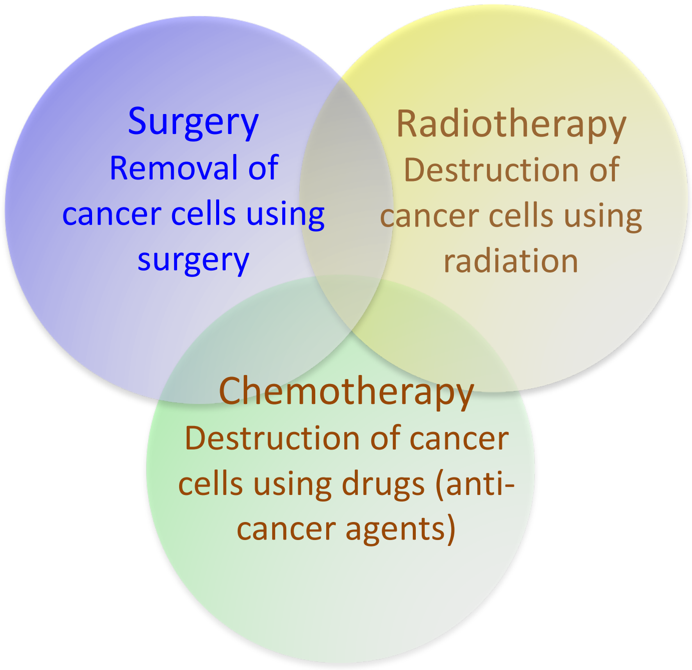


Data source: GLOBOSCAN 2020

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

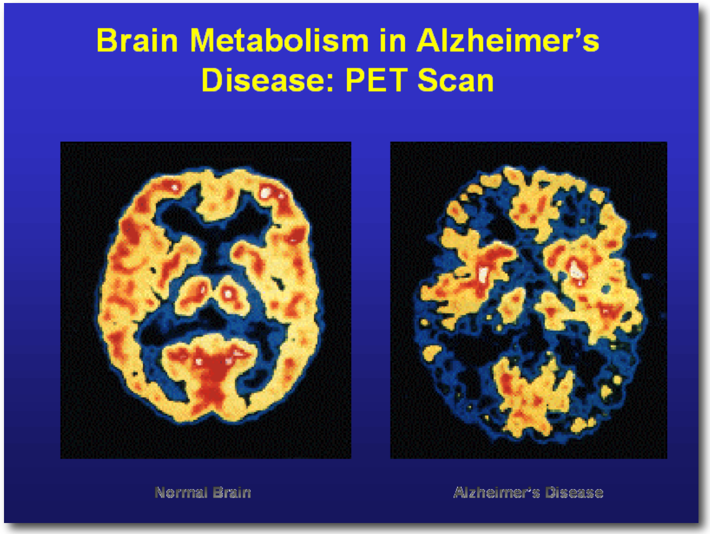
Treatment has two important goals to kill the tumour and protect the surrounding normal tissue. Therefore "seeing" in order to know where and precise "delivery" to make sure it goes where it should are key.

Detectors and art of seeing………

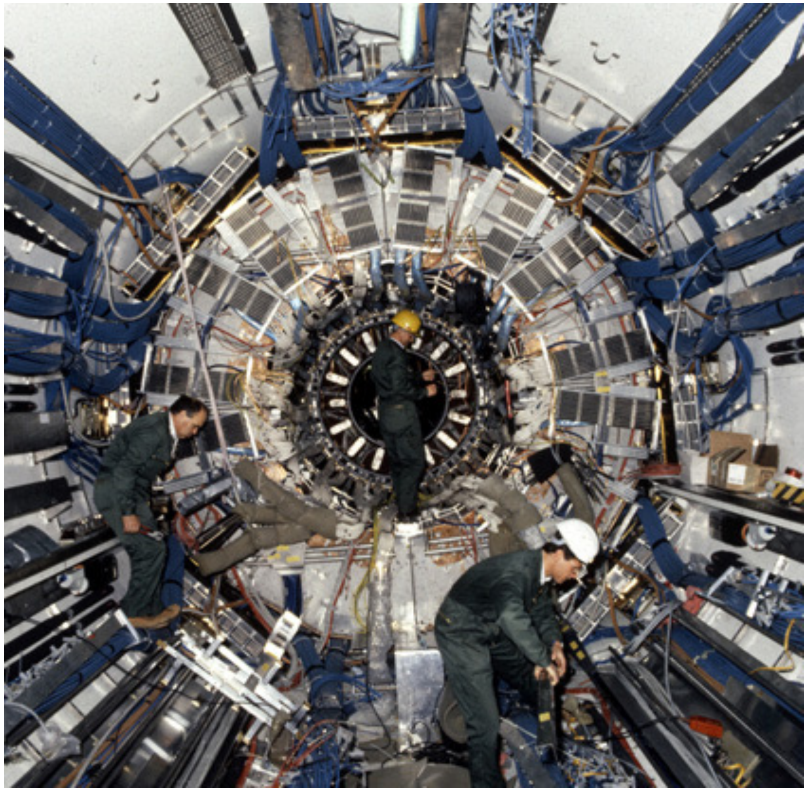
Particle Detection

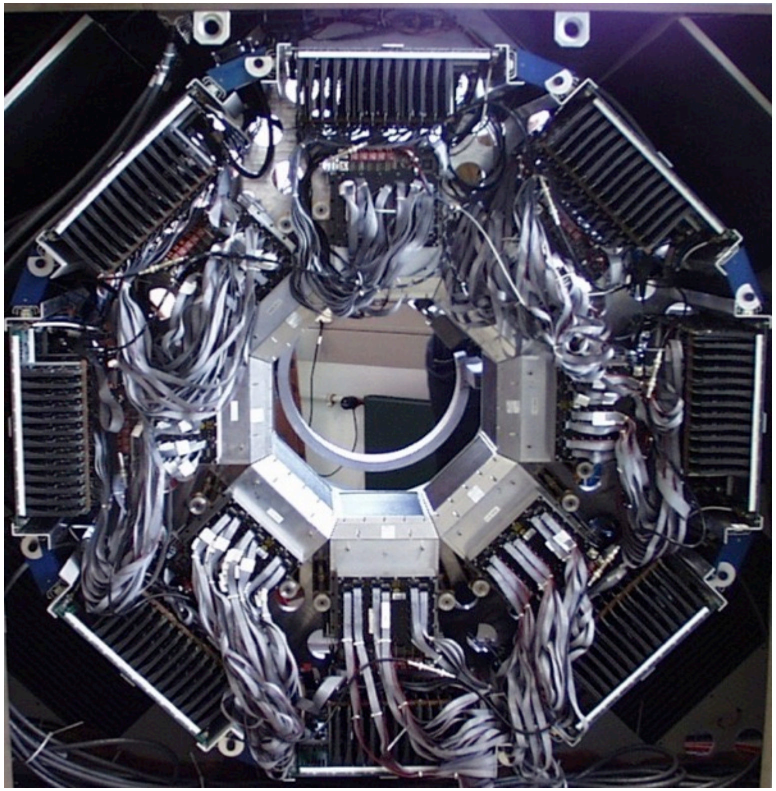
Imaging

X-ray, CT, PET, MRI

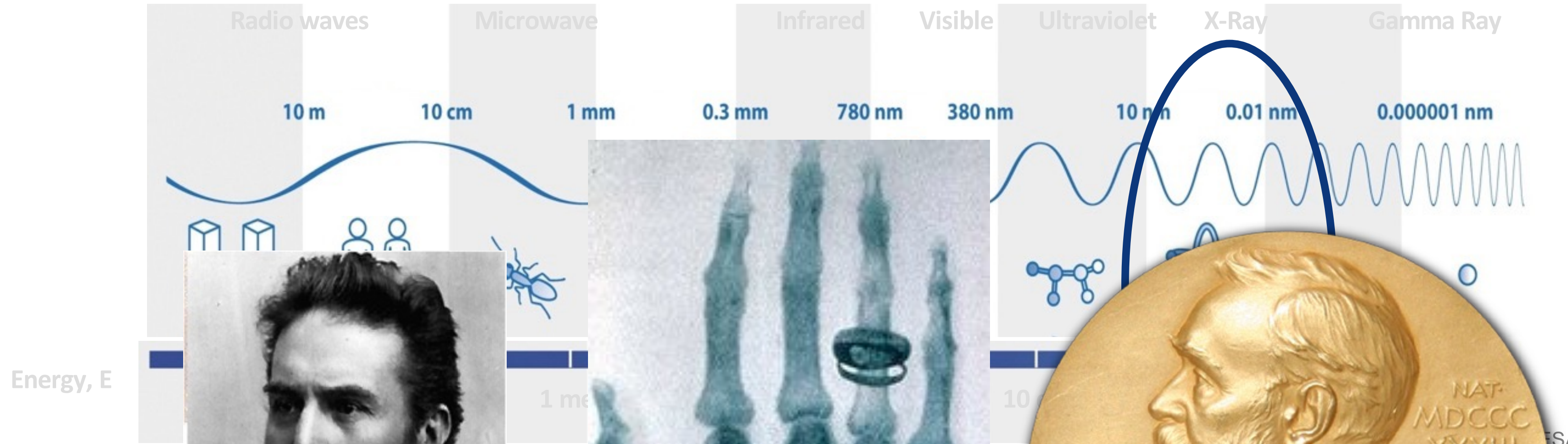


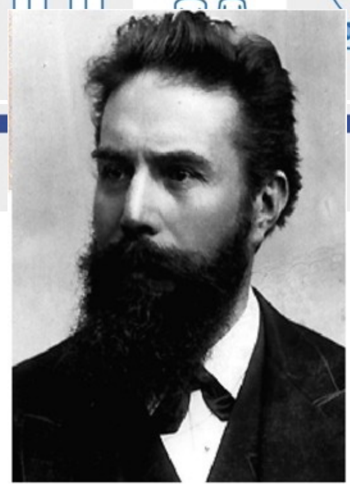
The detector challenge





X-ray imaging





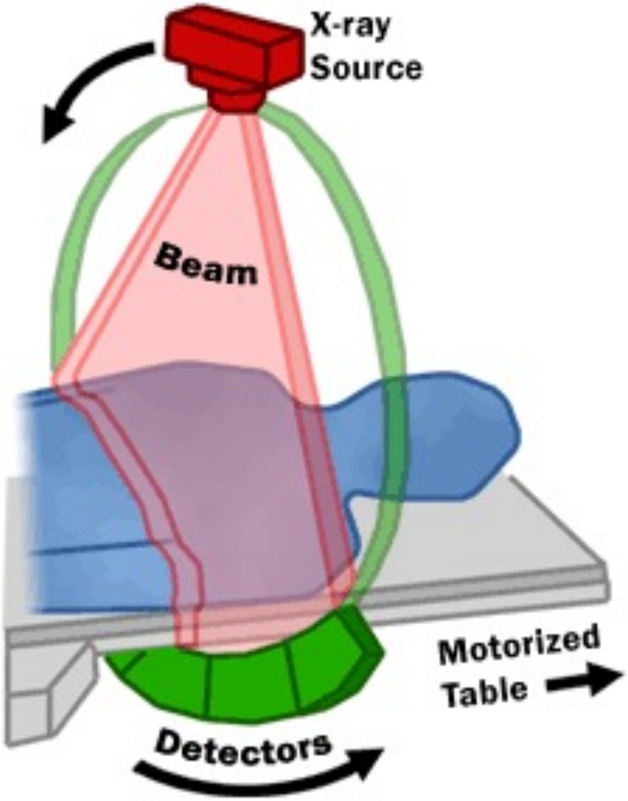
Wilhelm Röntgen

8/11/1895 — 22/12/1895 — 1901

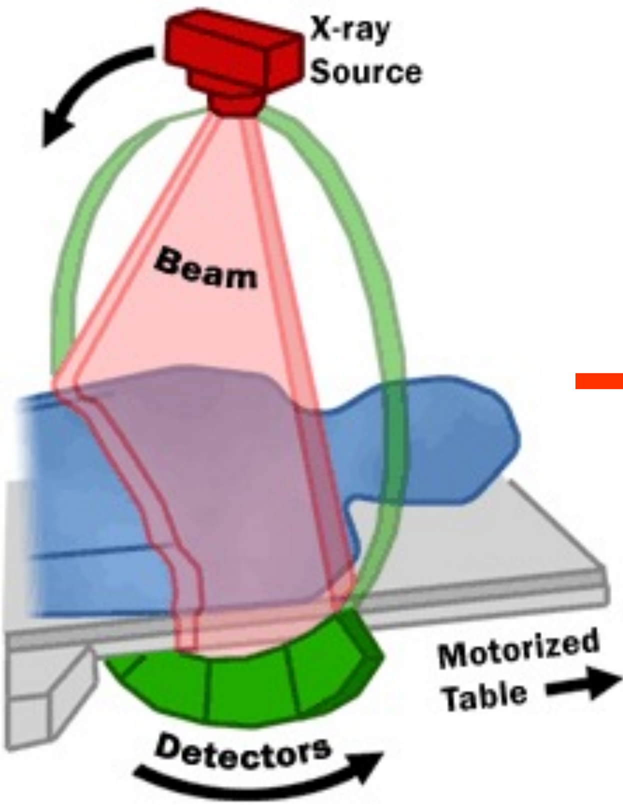
First time we could see beneath the skin without cutting open the patient

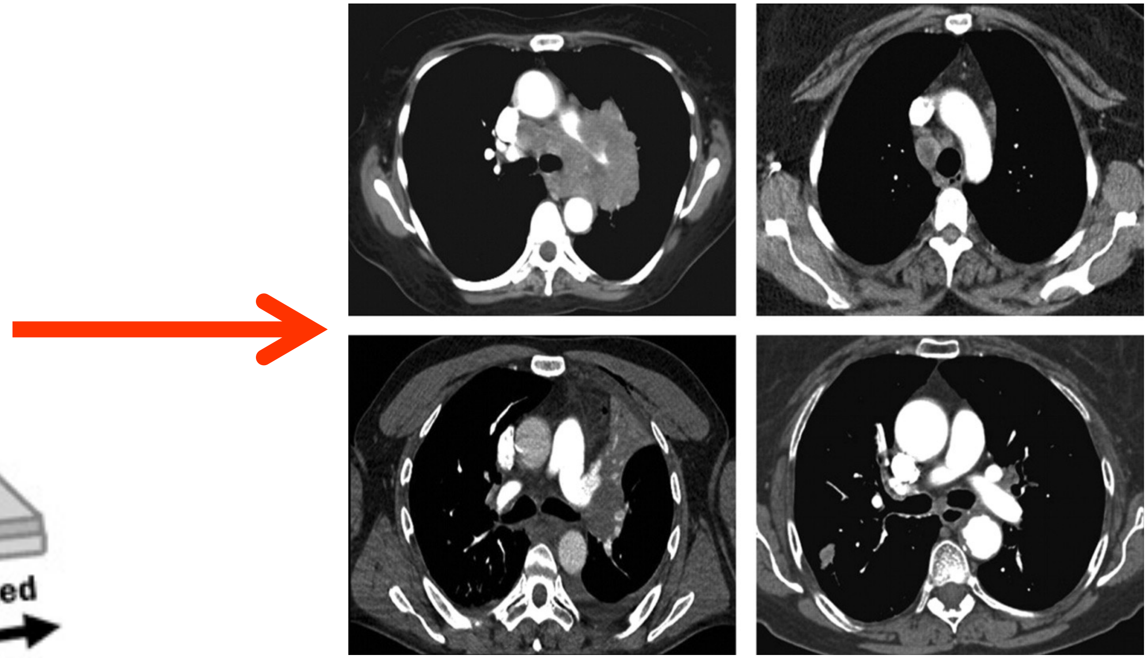
CT – Computed Tomography

3d X-rays imaging



CT – Computed Tomography



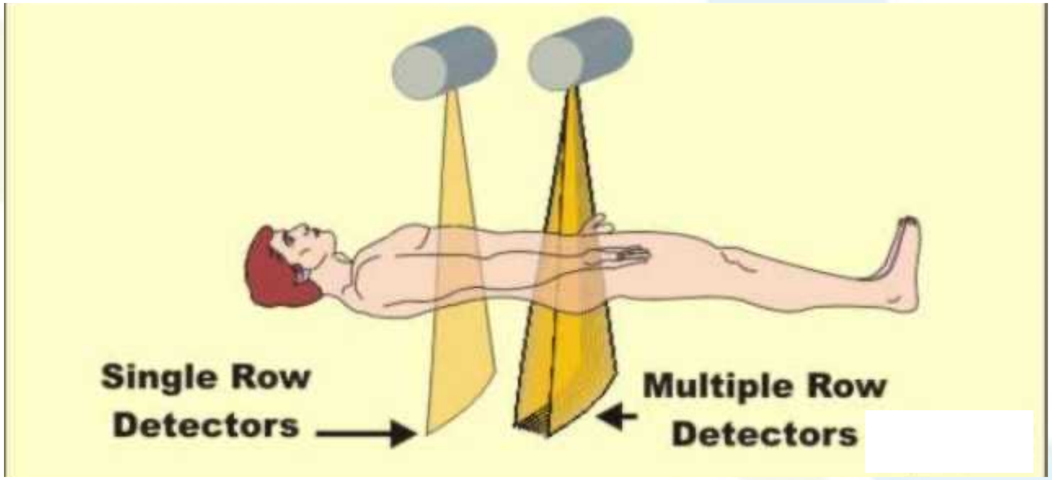


"3D-imaging"

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

2000-2008 “CT Slice War”

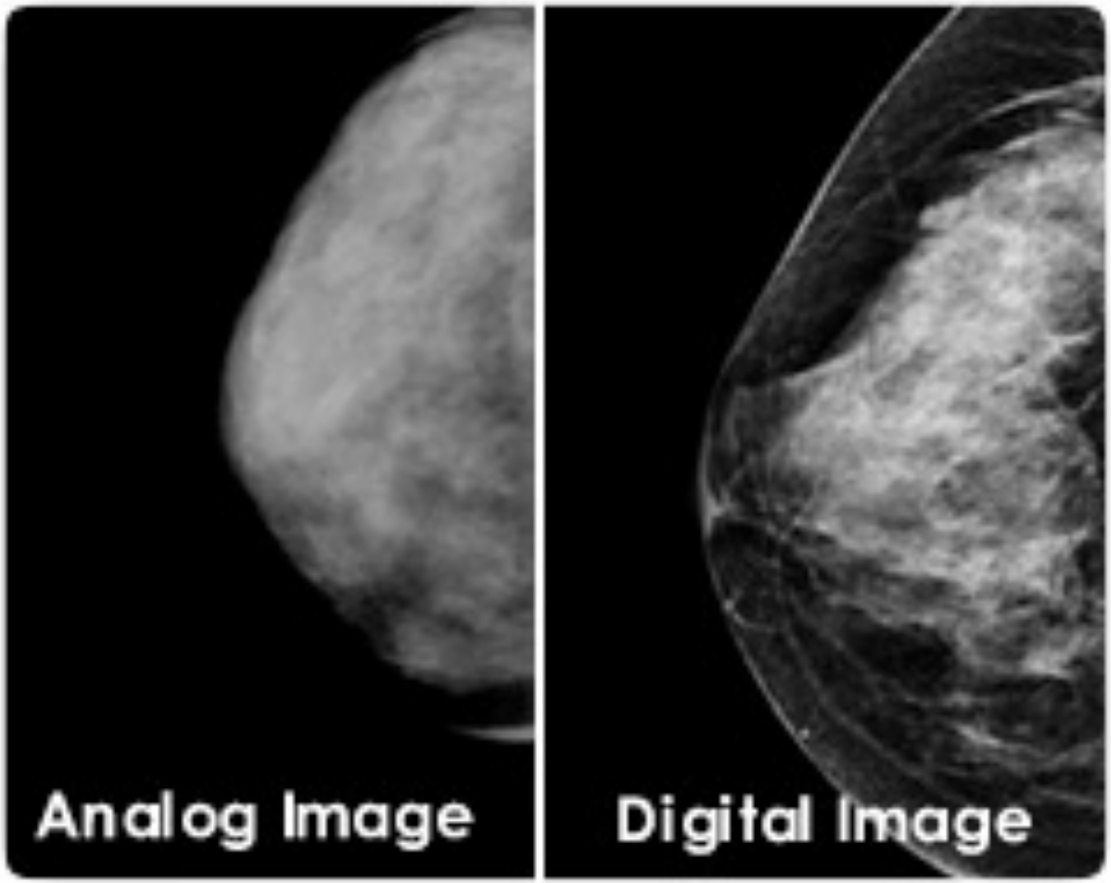
- *CT became very fast with small voxel / pixels*
  - 2000: acquire a single transverse slice per rotation
  - 2012: acquire up to 64-500 slices per rotation



Revolution in Photography

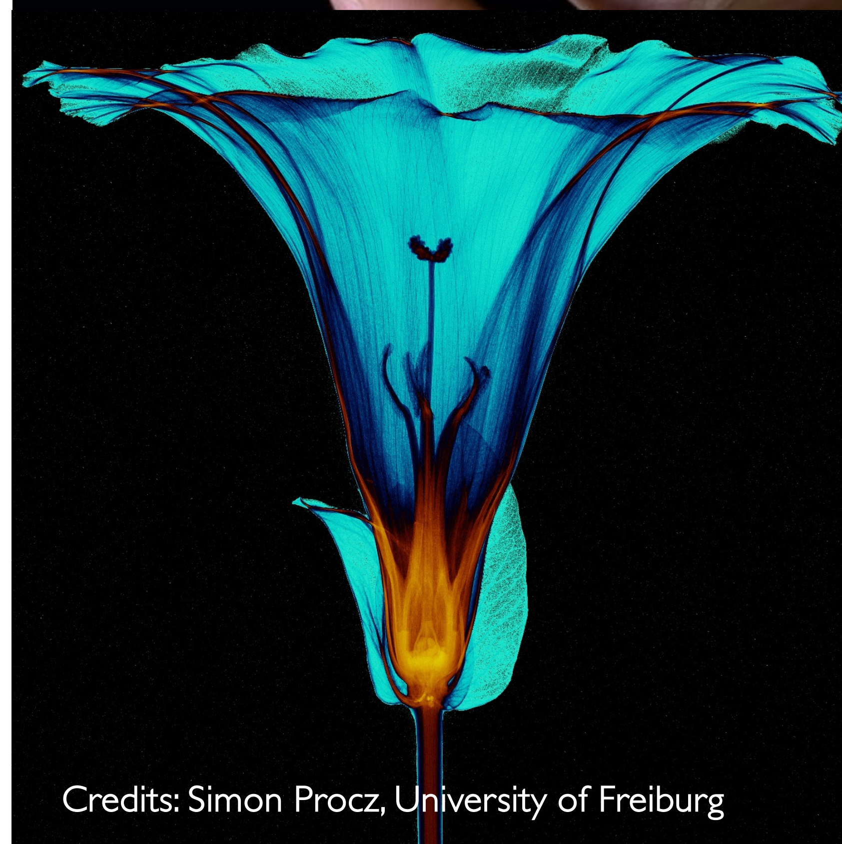
From black and white photos To Modern High-Tech photography

Towards digital colour x-ray imaging



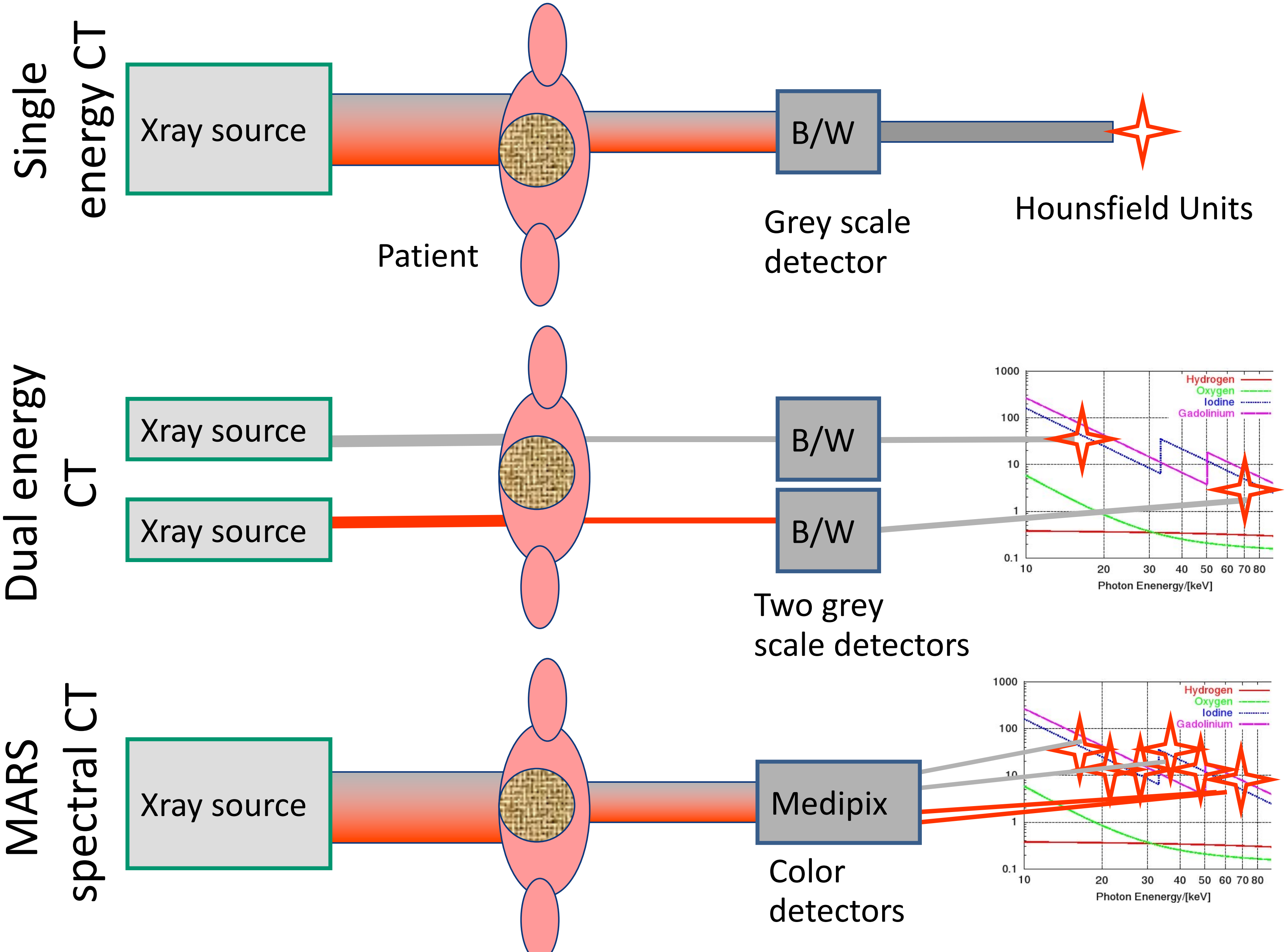
Medipix

- 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



Credits: Simon Procz, University of Freiburg

Single- , dual-, and spectral CT



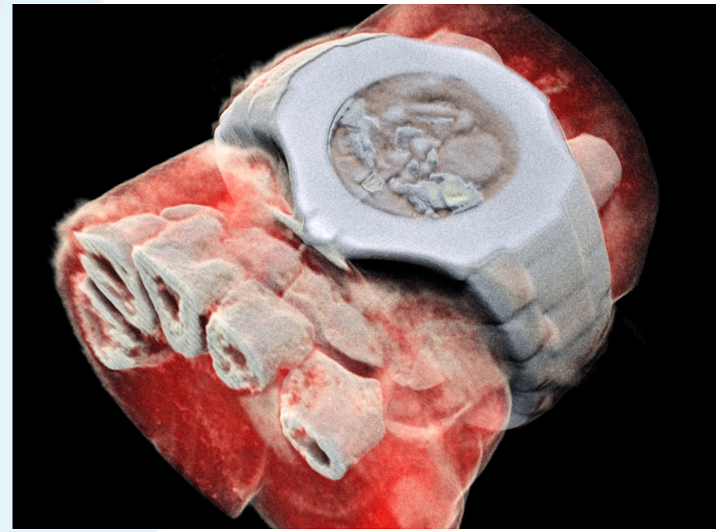
Spectral CT is now possible

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

Energy resolution

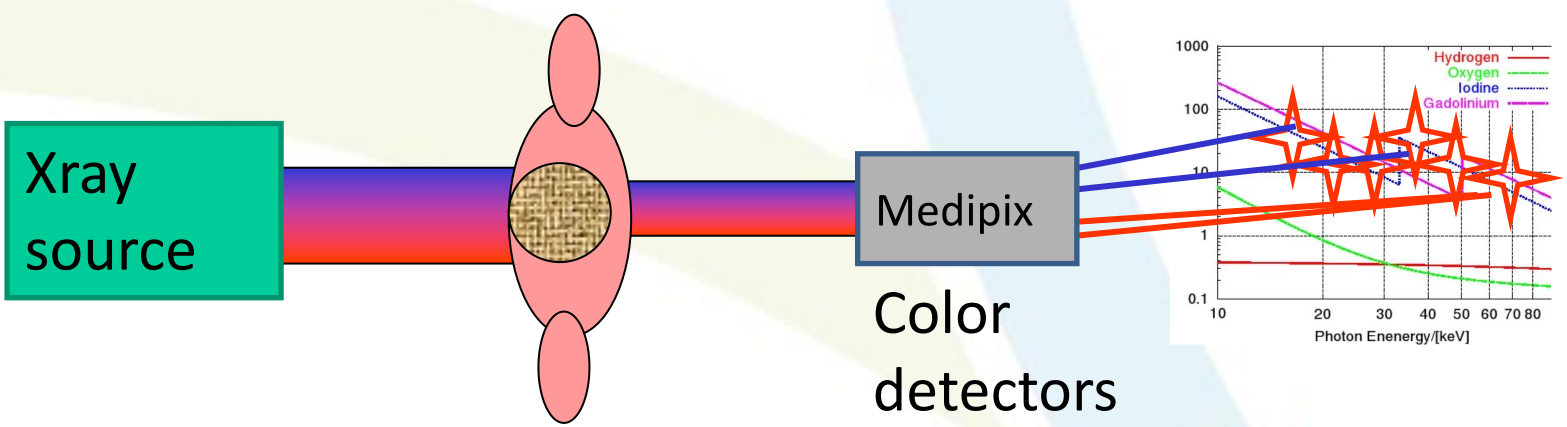
Spatial resolution

Temporal resolution

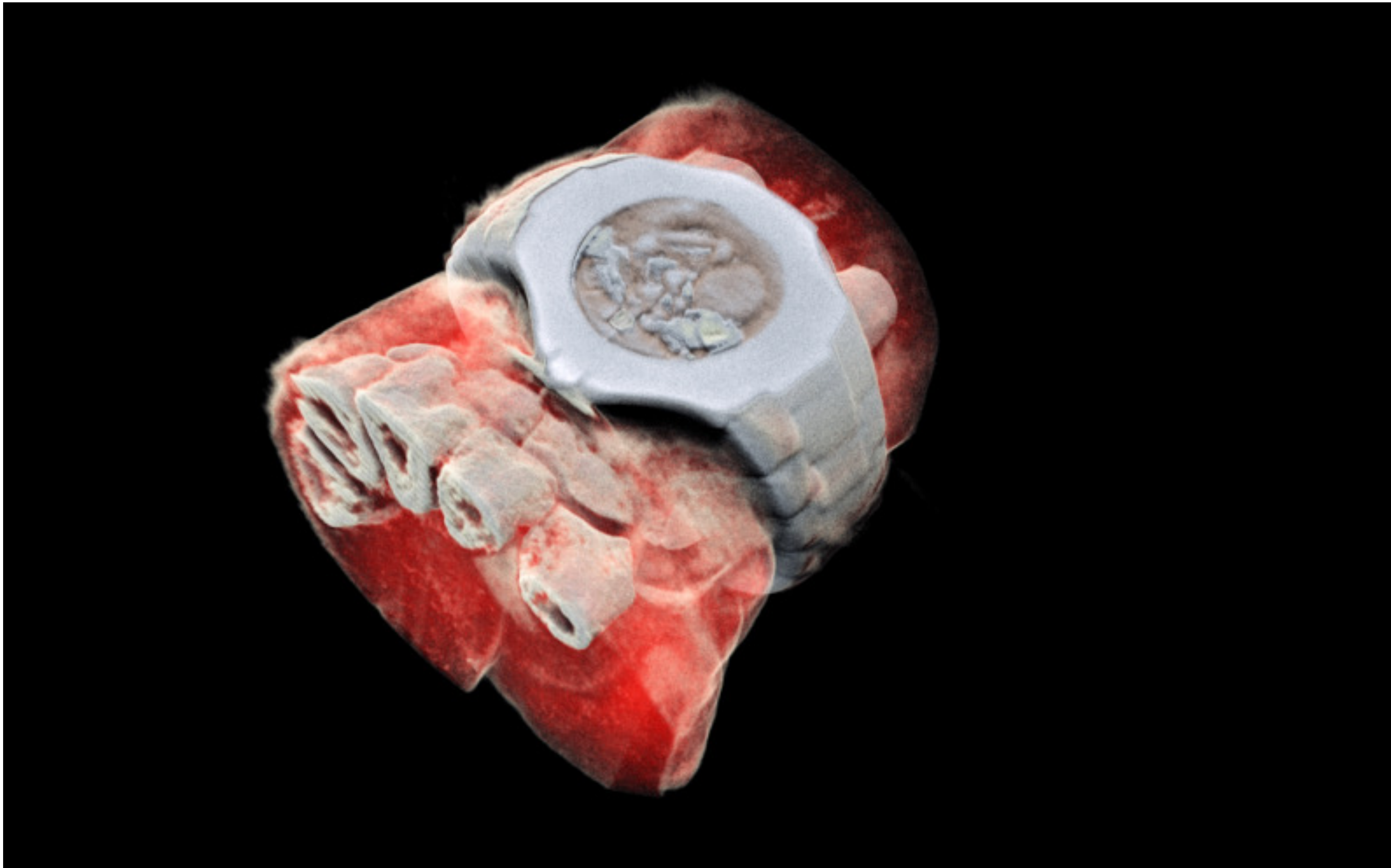


First 3D colour x-ray human image

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)

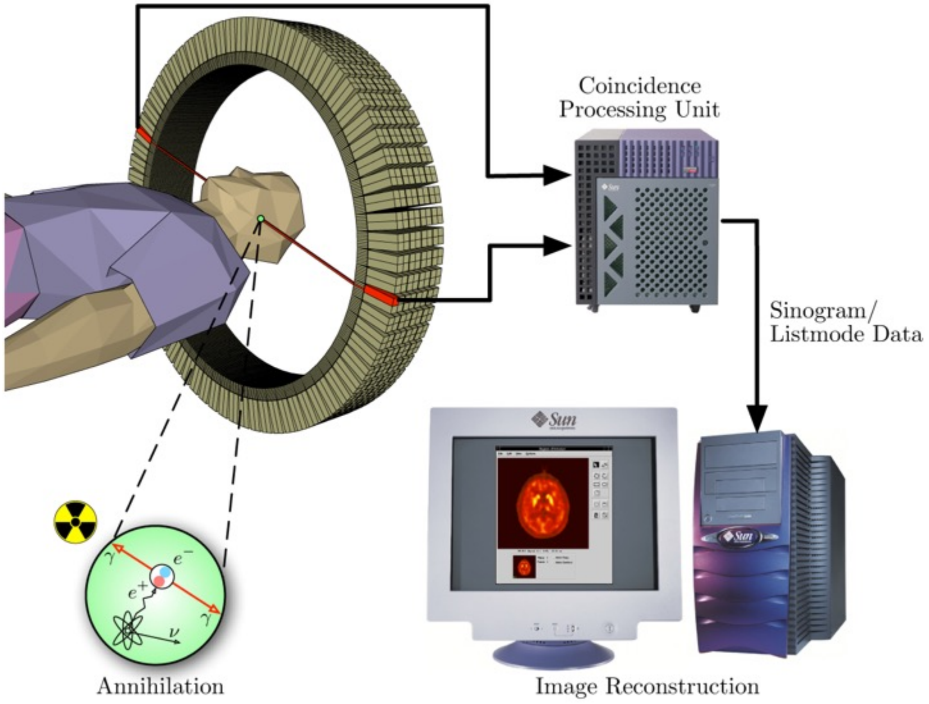
More and more progress…

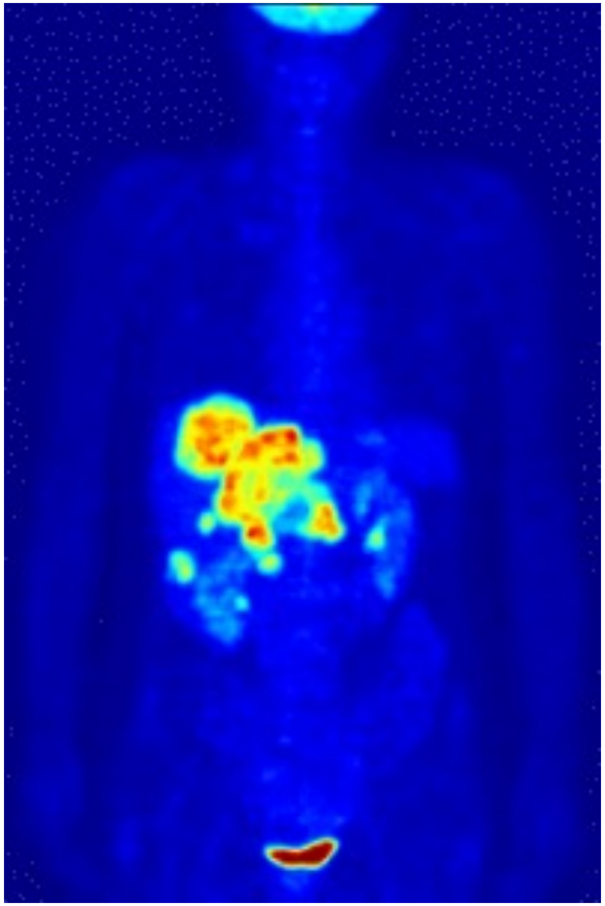
Colour 3D X-ray image of a fatty deposit on an artery (carotid plaque) taken using a Medipix3 detector

mars

Image by Mars Bio-Imaging
Feature article link:
https://rdcu.be/bOFuR

Positron Emission Tomography

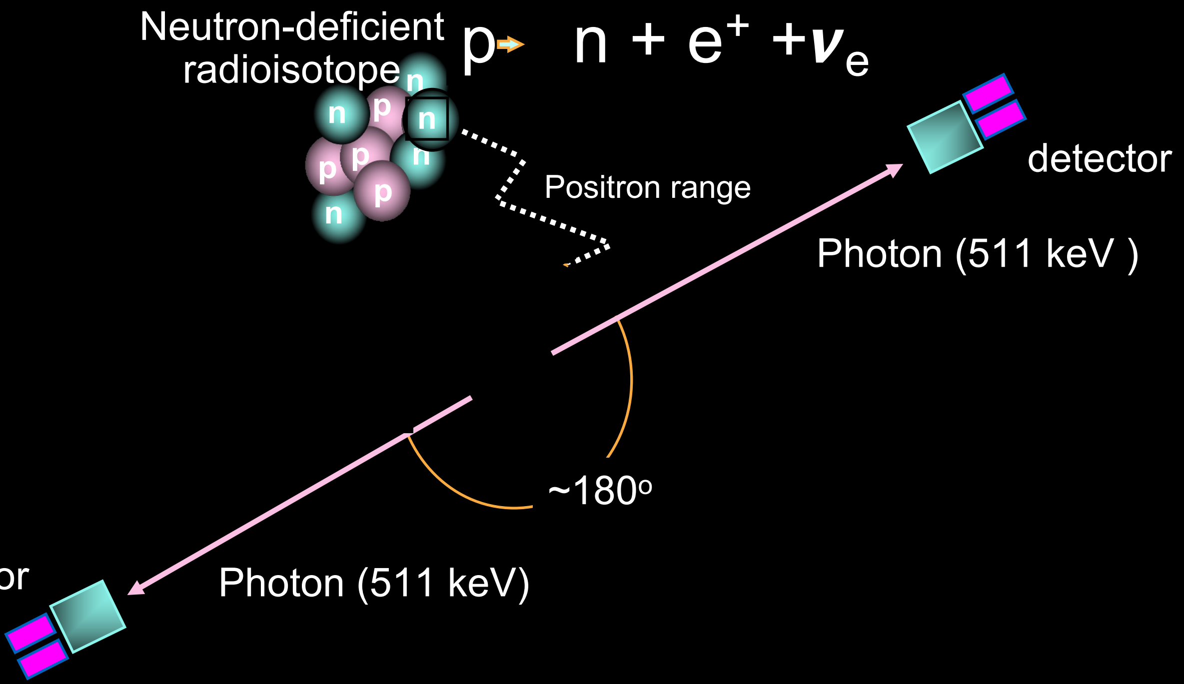




- ^{18}FDG carries the ^{18}F to areas of high metabolic activity
- 90% of PET scans are in clinical oncology

1974 the first human positron emission tomography

Positron Emission Tomography

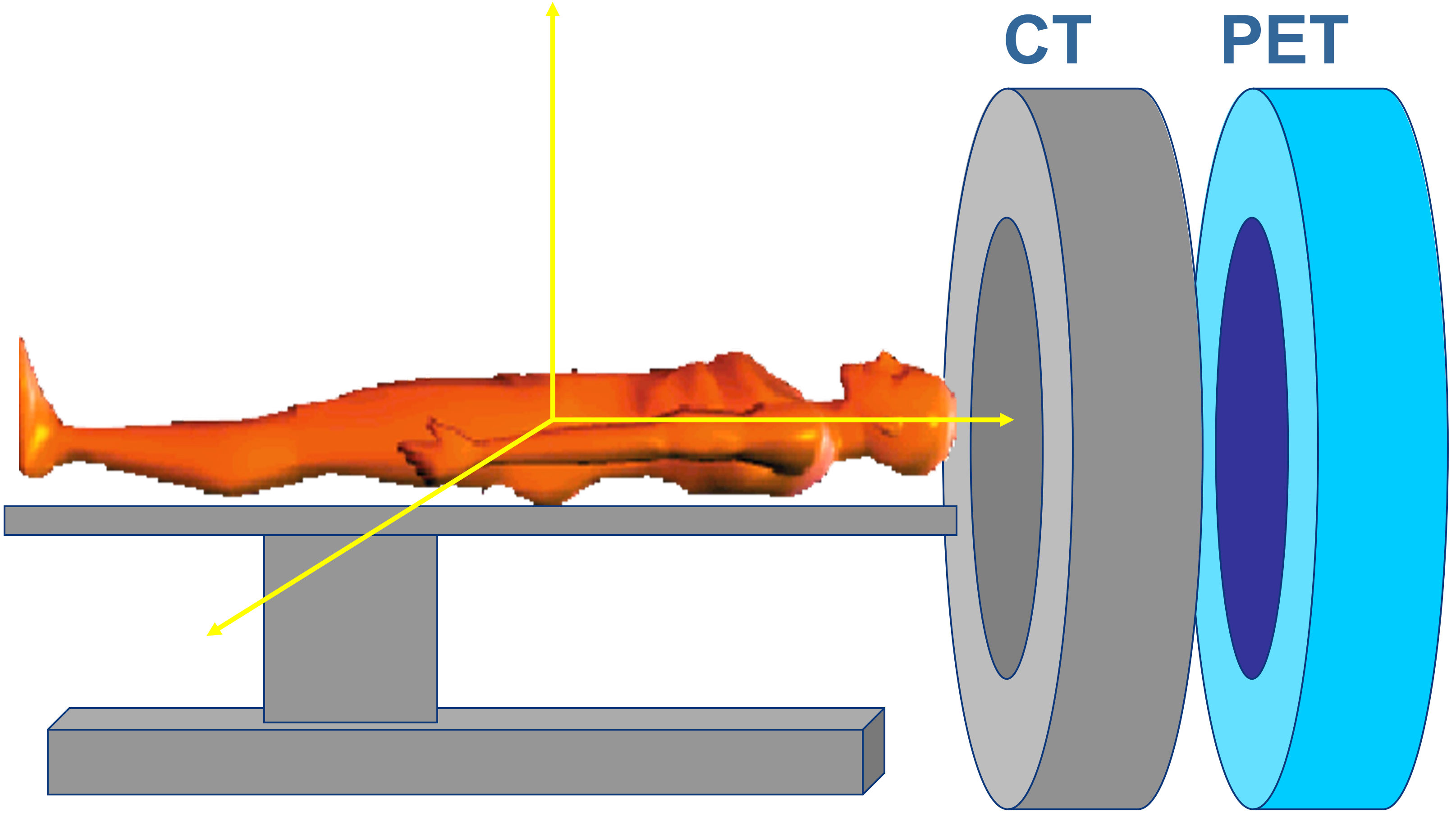


PET – How it works

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

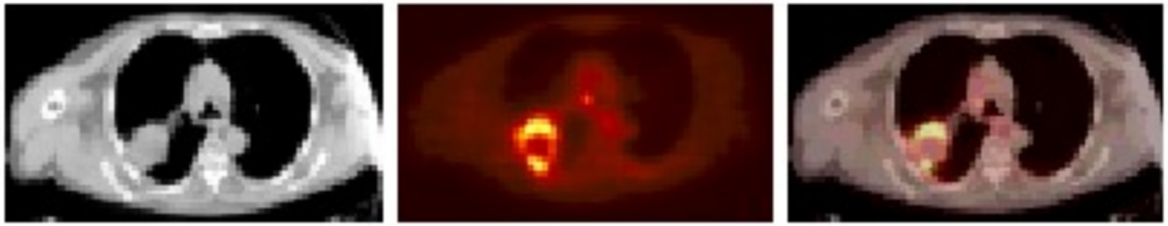
Concept of PET-CT

David Townsend



Multi-modality imaging

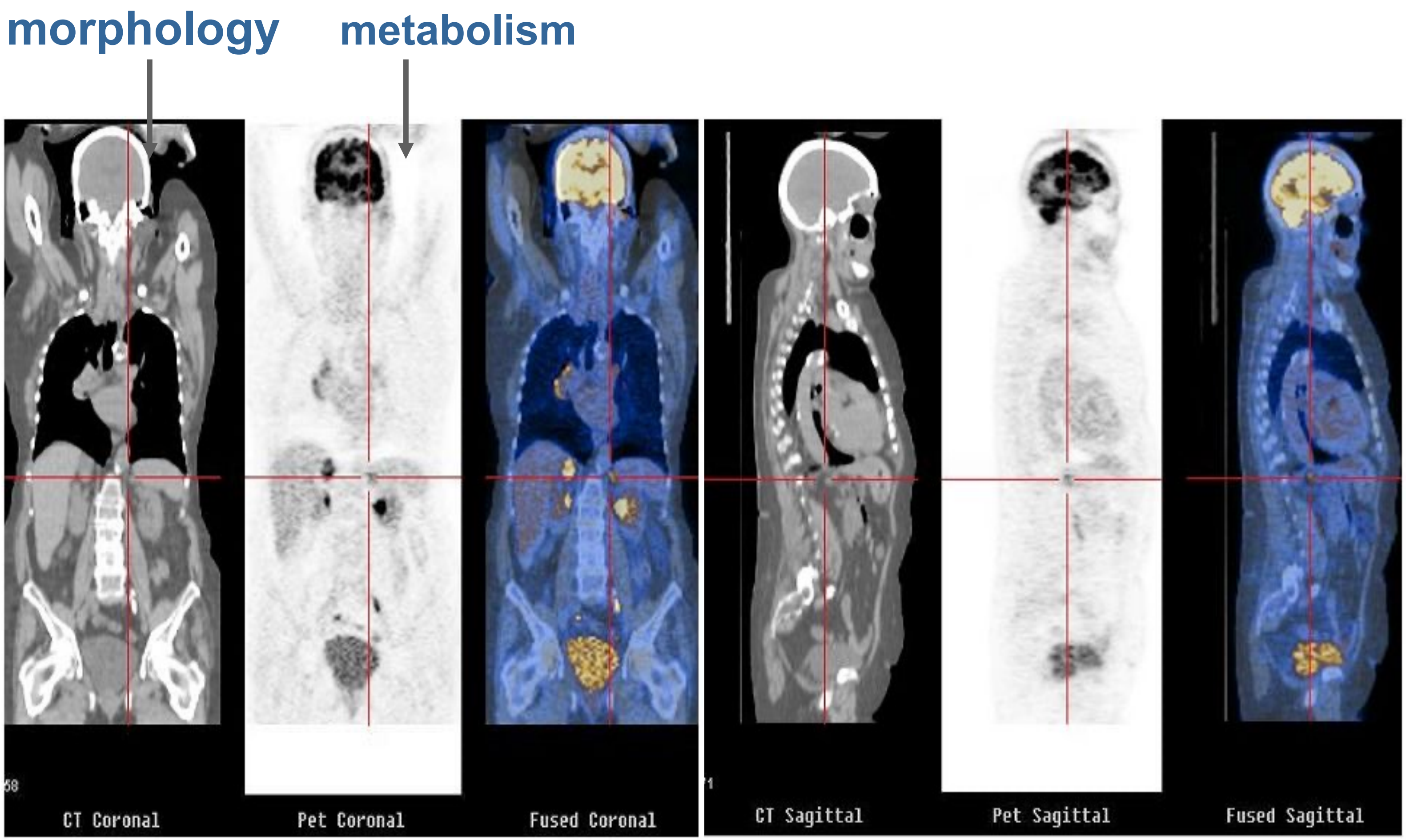
Primary lung cancer imaged with the Dual/Commercial scanner. A large lung tumor, which appears on CT as a uniformly attenuating hypodense mass, has a rim of FDG activity and a necrotic center revealed by PET.



Courtesy of David Townsend

Multimodality imaging: CT with PET

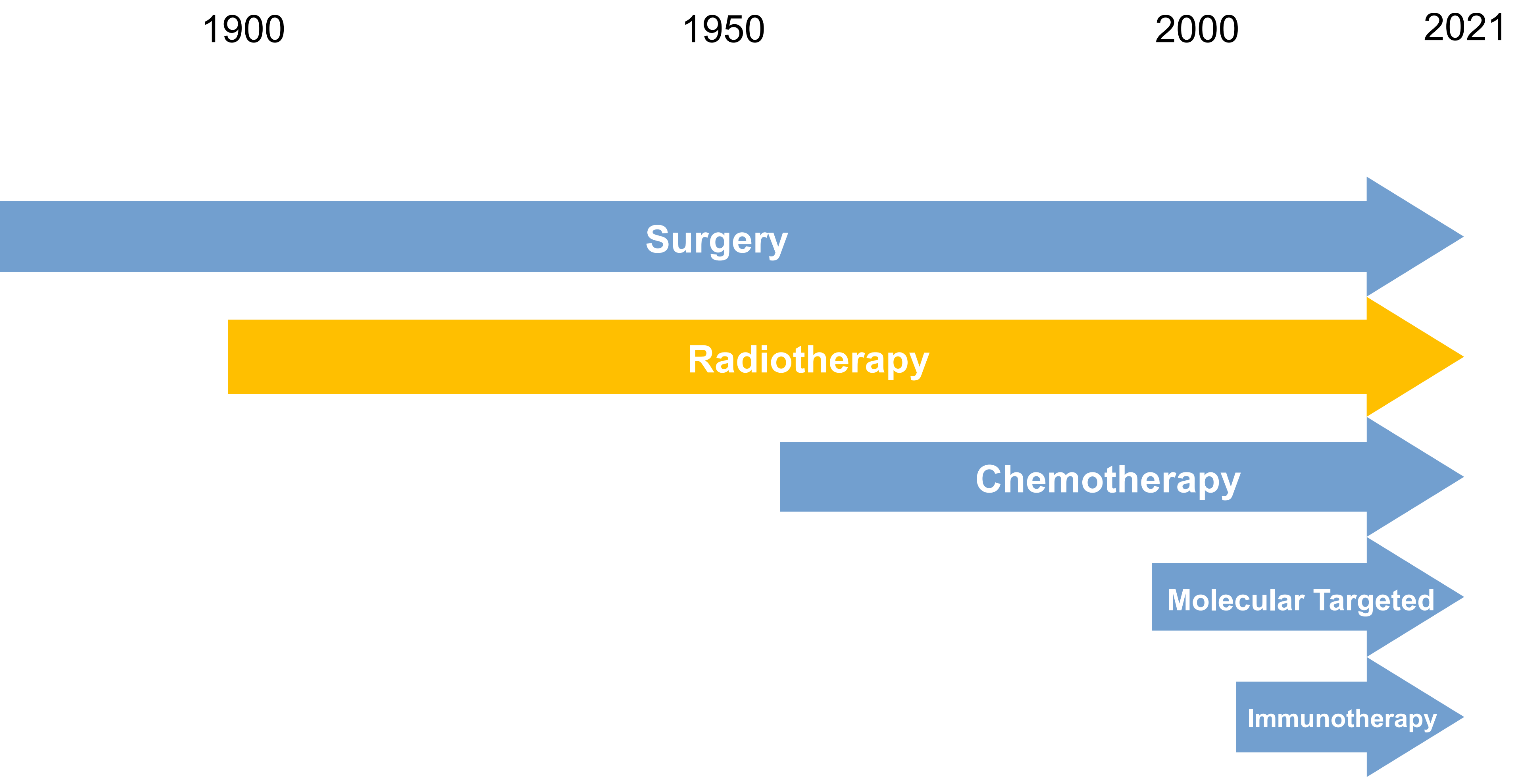
Combining anatomic and functional imaging



David Townsend, UK Physicist

Manjit Dosanjh, 09.08.2023

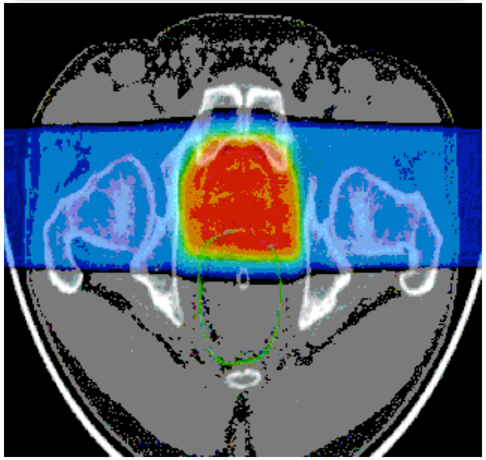
How do we treat cancer?



Treatment options

Surgery

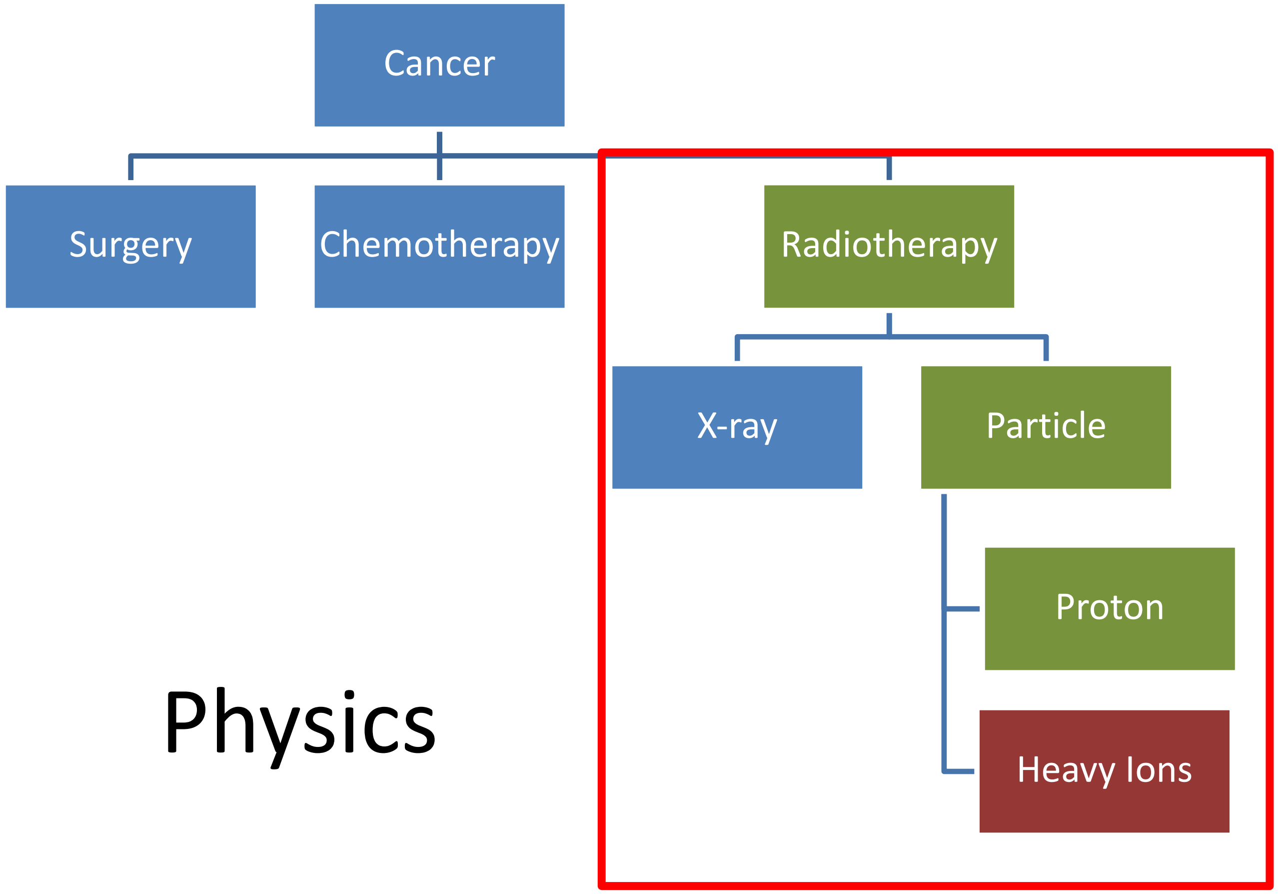
Radiotherapy



Chemotherapy (+ others)

AIM:
Survival, Quality of life

Cancer treatment options



Radiotherapy in 21st Century

3 "Cs" of Radiation

Cure (about 50% cancer cases are cured)

Conservative (non-invasive, fewer side effects)

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

(J.P.Gérard)

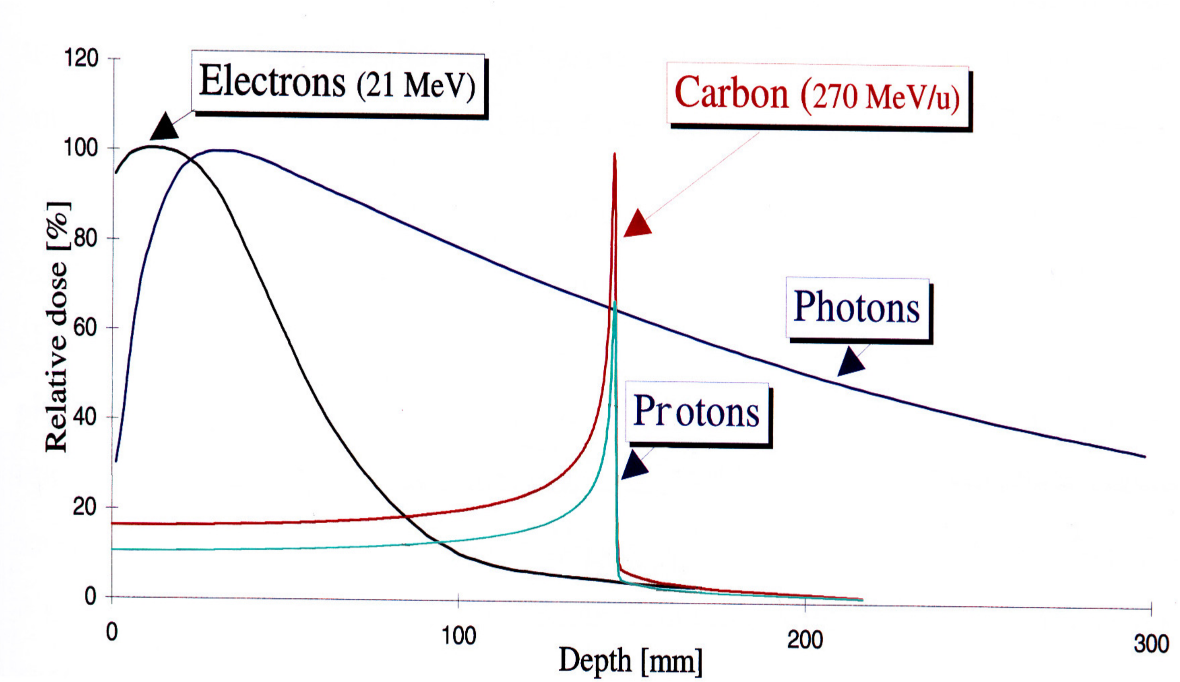
- About 50% patients are treated with RT
- No substitute for RT in the near future
- No of patients is increasing

Aims of Radiotherapy:

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

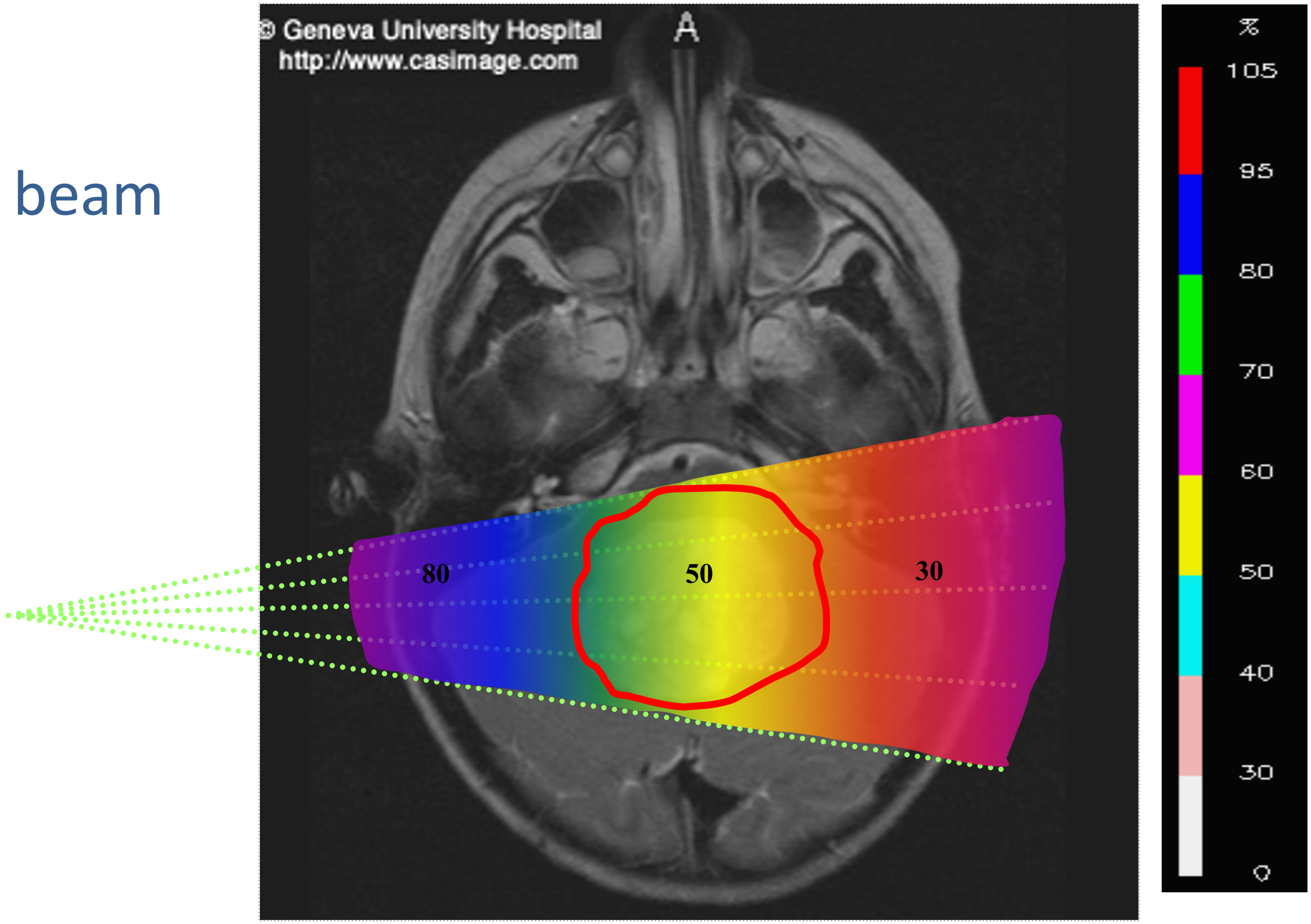
Current radiotherapy methods:

- 5-25 MV photons
- 5 - 25 MeV electrons
- 50 - 400 MeV/u hadrons



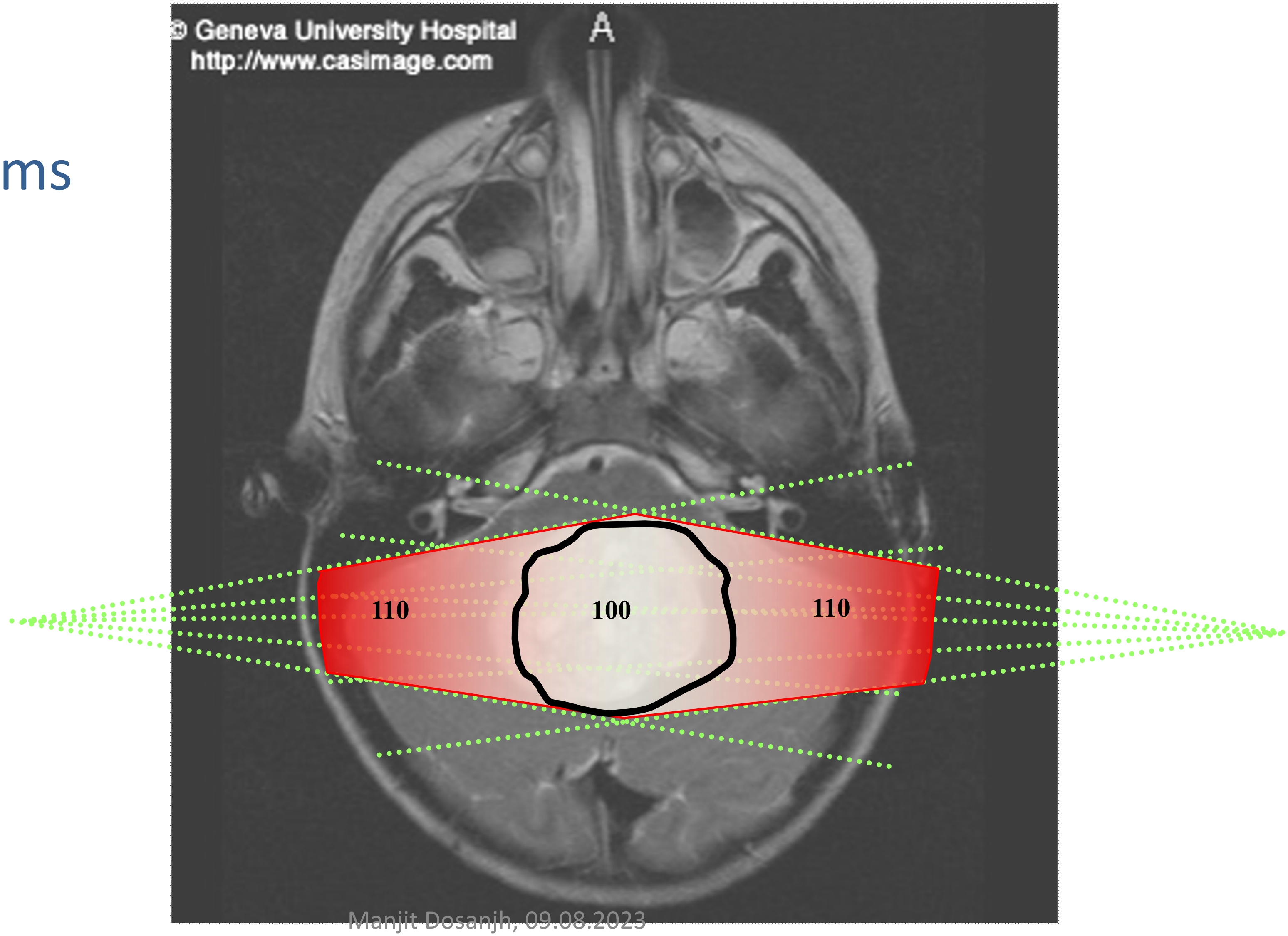
Classical Radiotherapy with X-rays

single beam

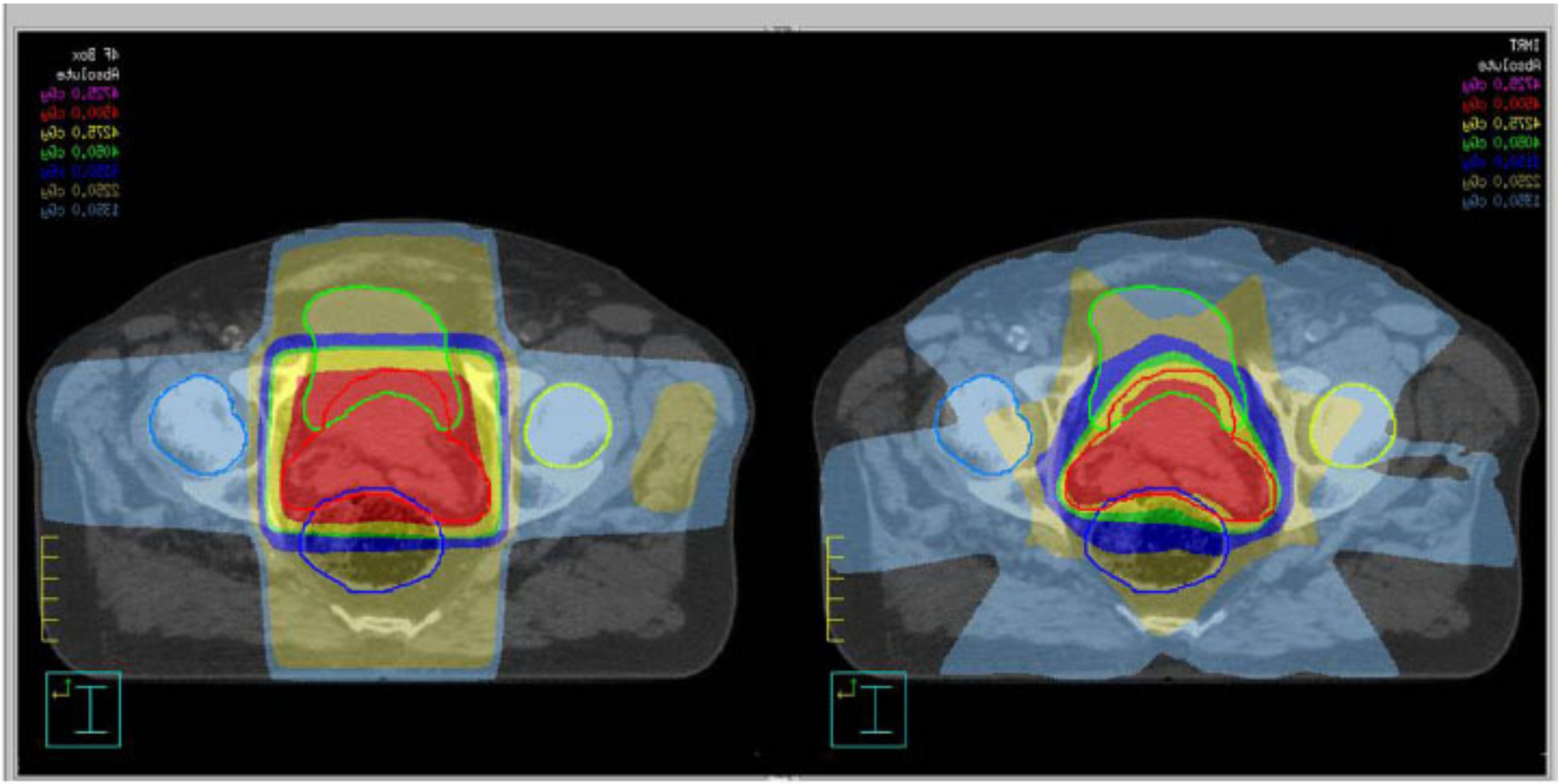


Radiotherapy with X-rays

two beams



Improved Delivery

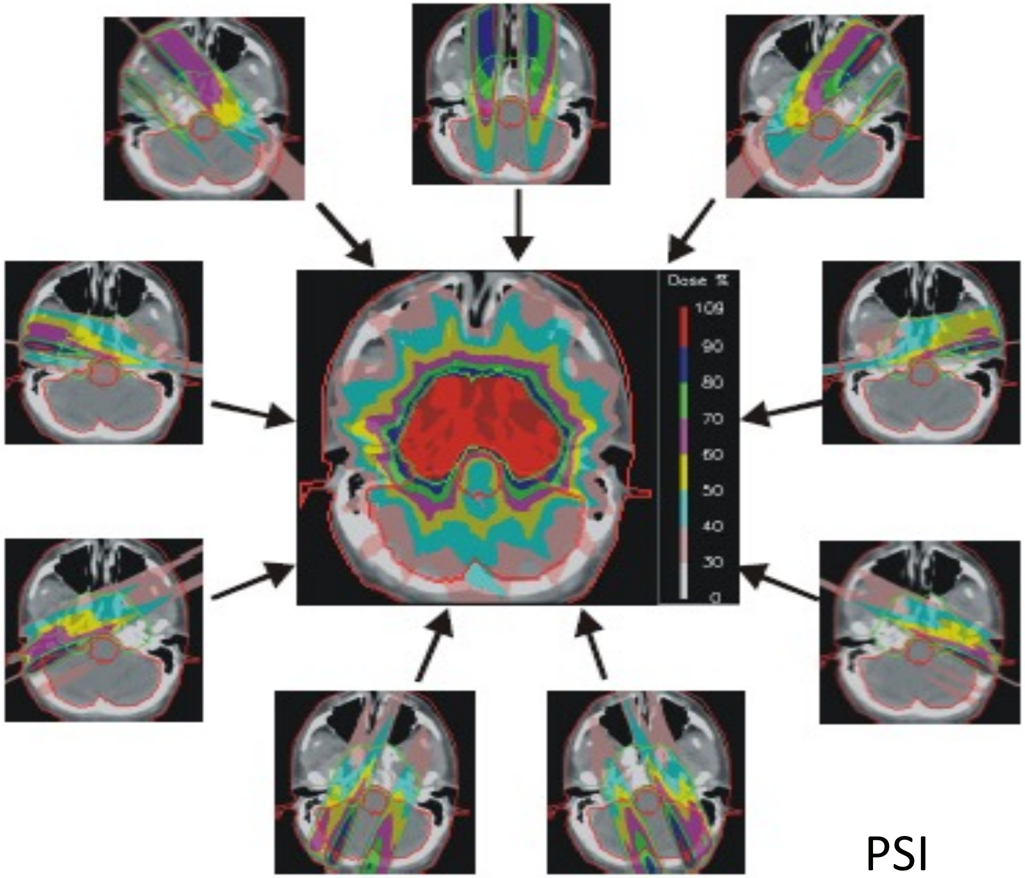


1990s: 4 constant intensity fields

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:

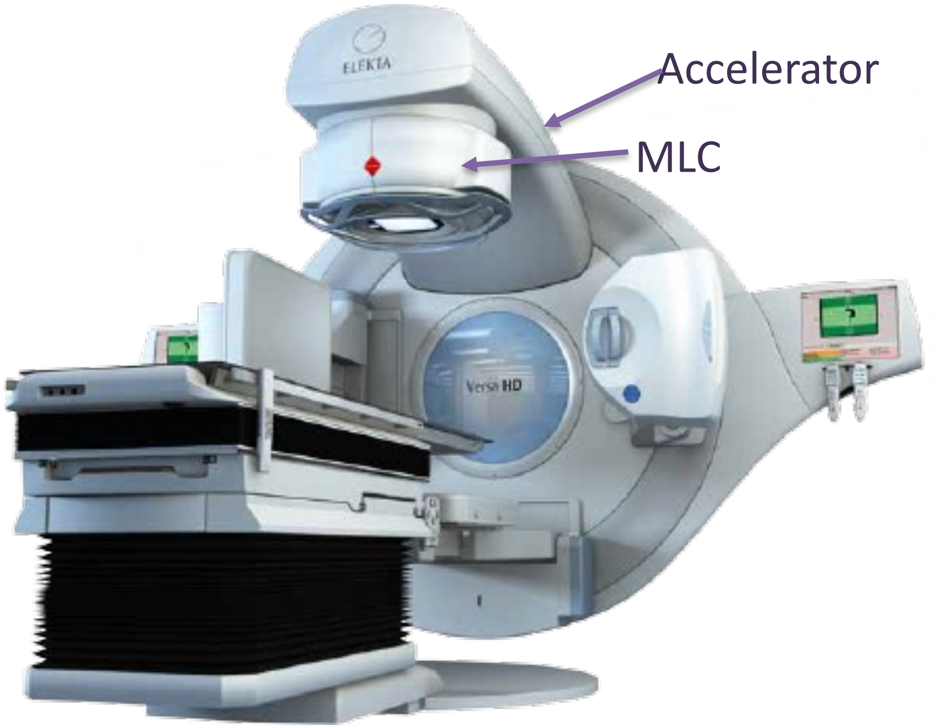
90% of the tumours are <u>radiosensitive</u>

Ugo Amaldi, TERA

The most widely available accelerator

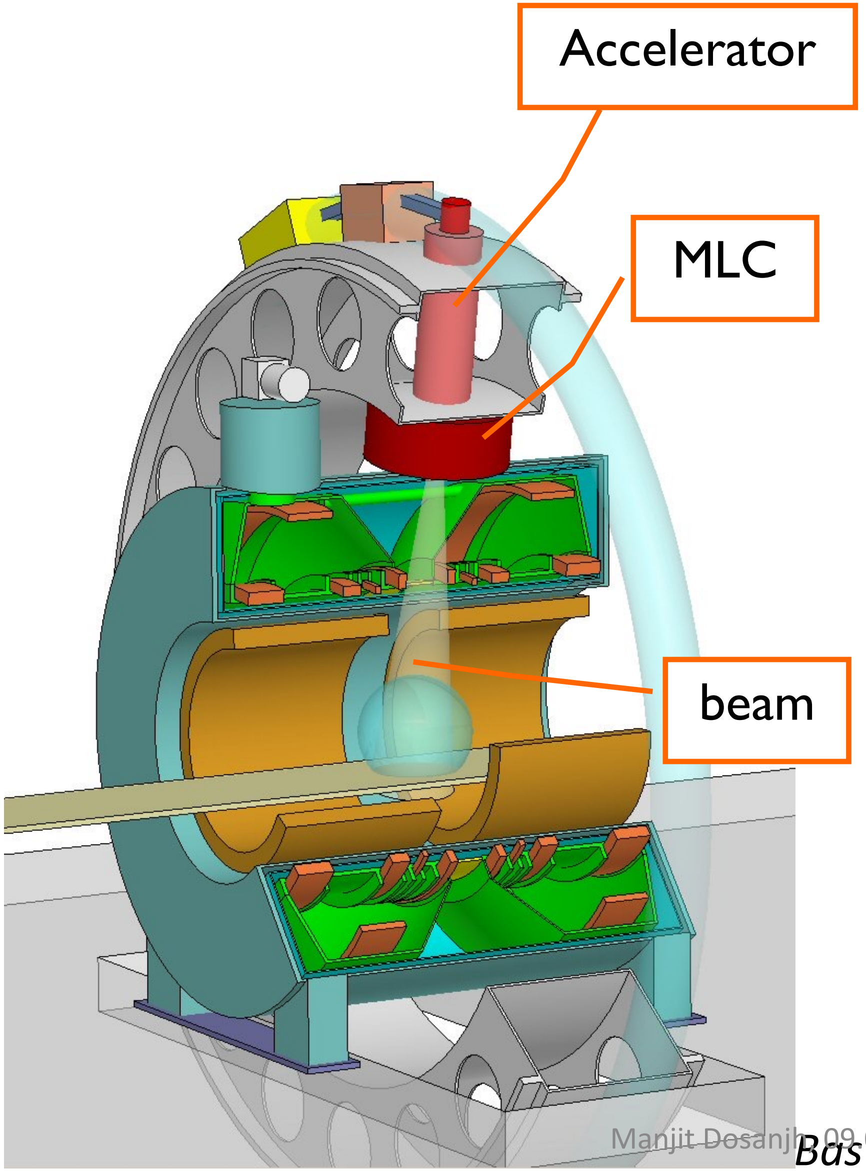
Electron Linac (linear accelerator) for radiation therapy treatment of cancer)

More than 15,000 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

Utrecht solution: Integrating a Philips MRI scanner with a Elekta radiotherapy accelerator

1.5T 70 cm bore Philips Ingenia

Lagendijk and Bakker, MRI guided radiotherapy - A MRI based linear accelerator
Radiotherapy and Oncology Volume 56, Supplement 1, September 2000, 220

Advances in Radiation Therapy

In the past two decades due to:

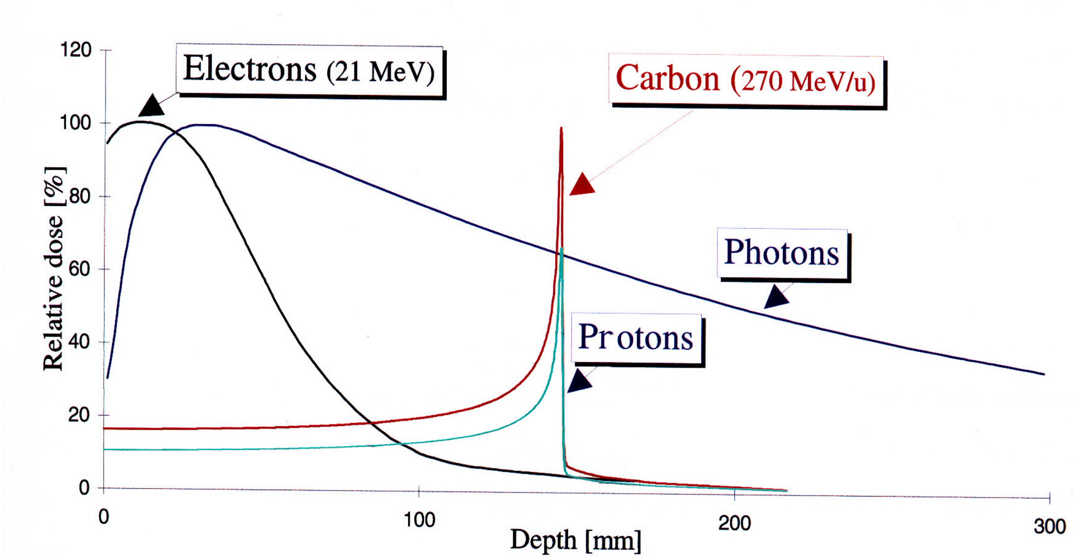
- improvements in imaging modalities, multimodality
- technology, powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
  - MRI-guided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

Hadron Therapy

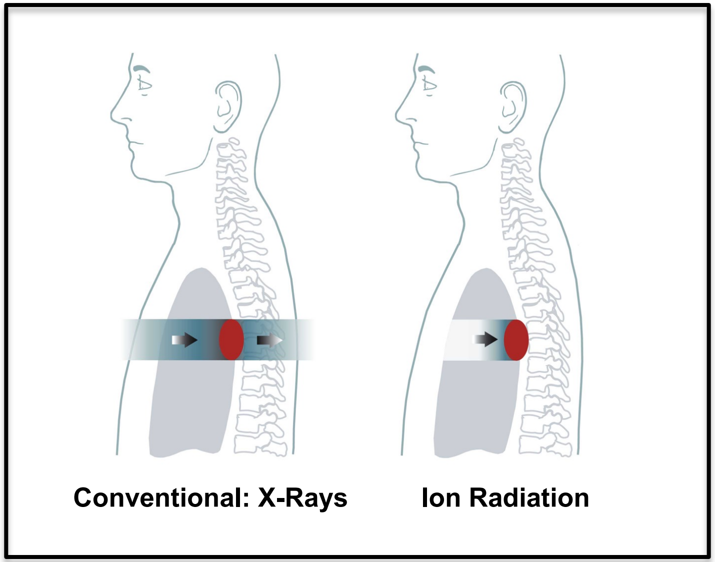
In 1946 Robert Wilson:

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

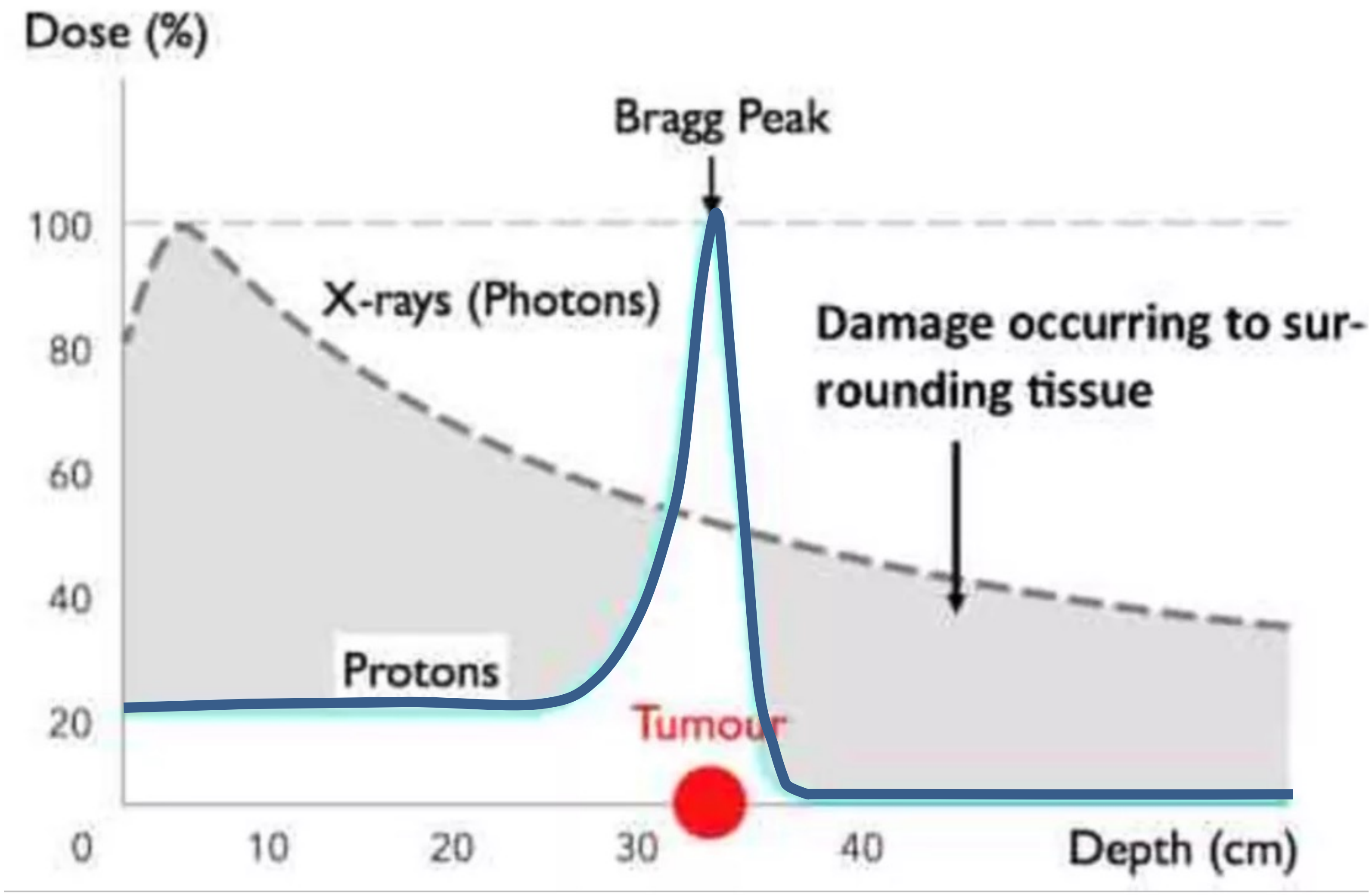
Robert Wilson
Fermi Lab



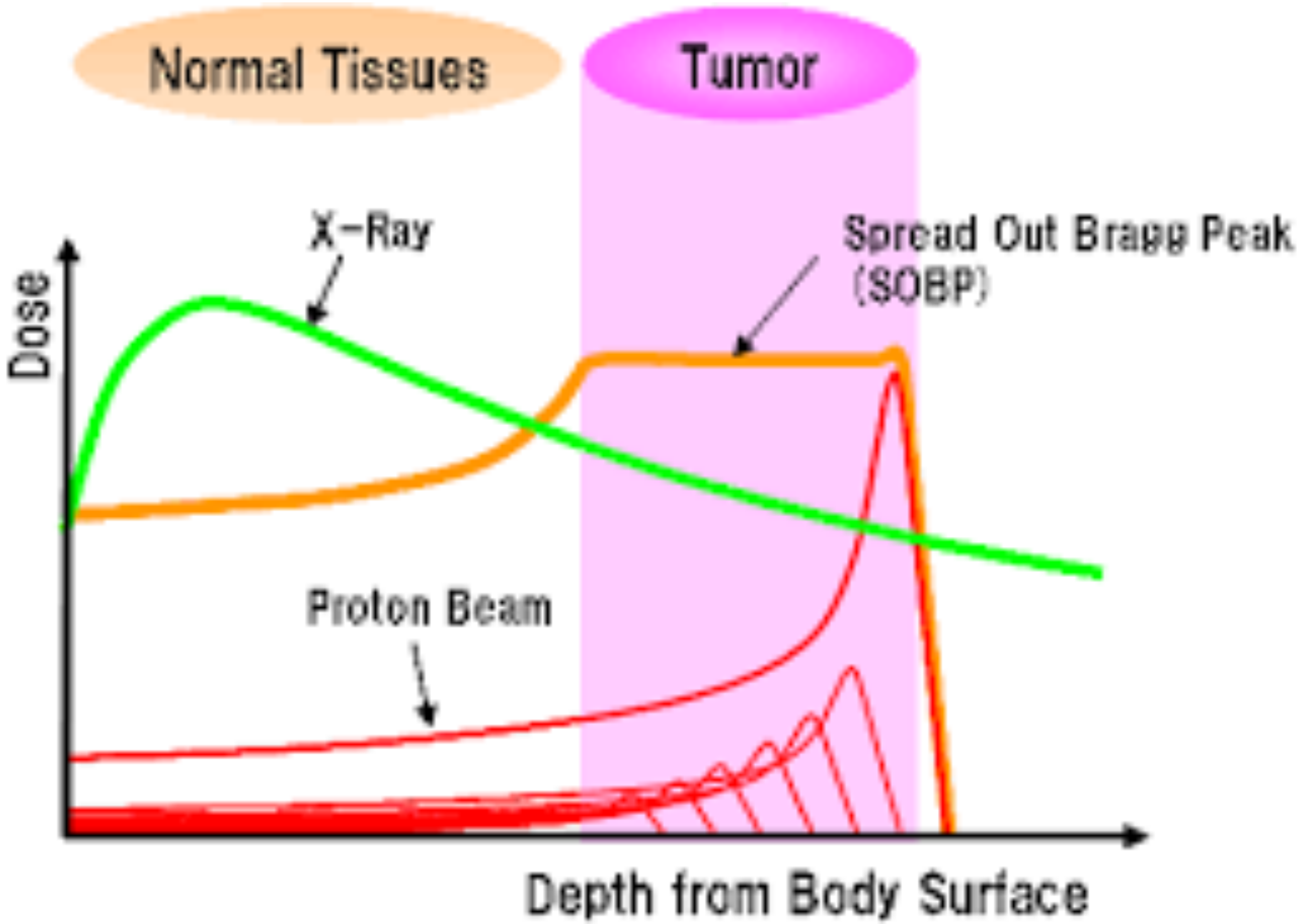
Depth in the body (mm)



Photons vs. protons



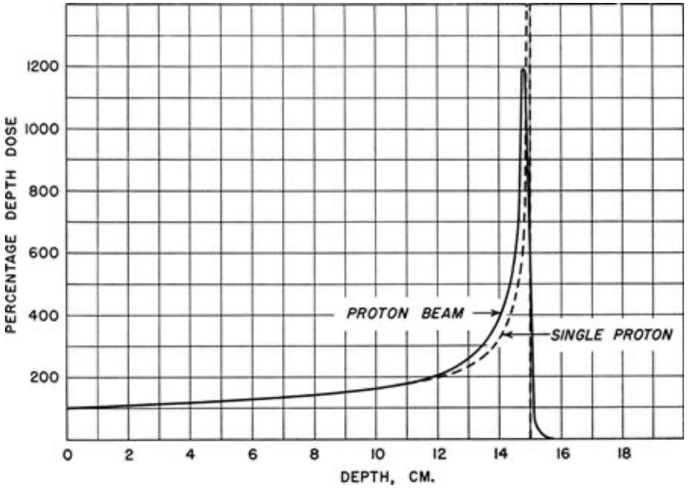
Spread Out Bragg-peak targeting the **tumour**



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

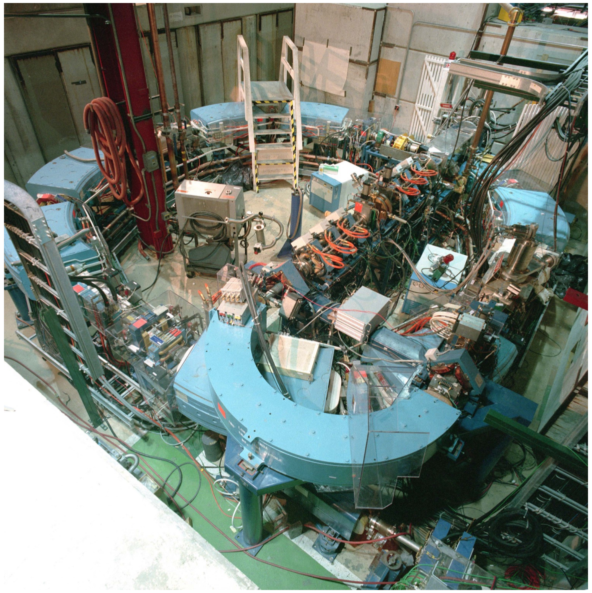
Sept 1954 – Berkeley
Treats first patient

Importance of collaboration……….

1993- Loma Linda USA (proton)

1994 – HIMAC/NIRS Japan (carbon)

1997 – GSI Germany (carbon)



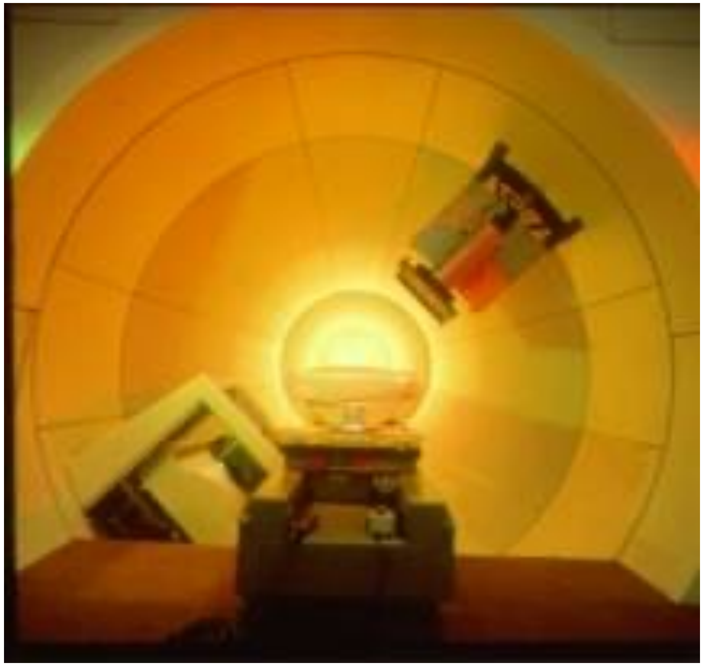
First dedicated clinical facility

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)

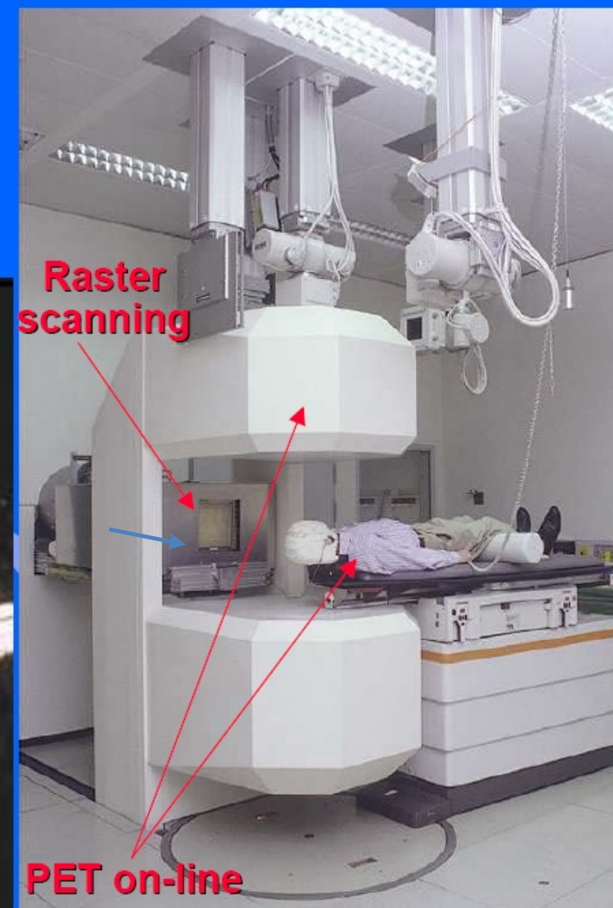
G. Kraft

J. Debus

G. Kraft

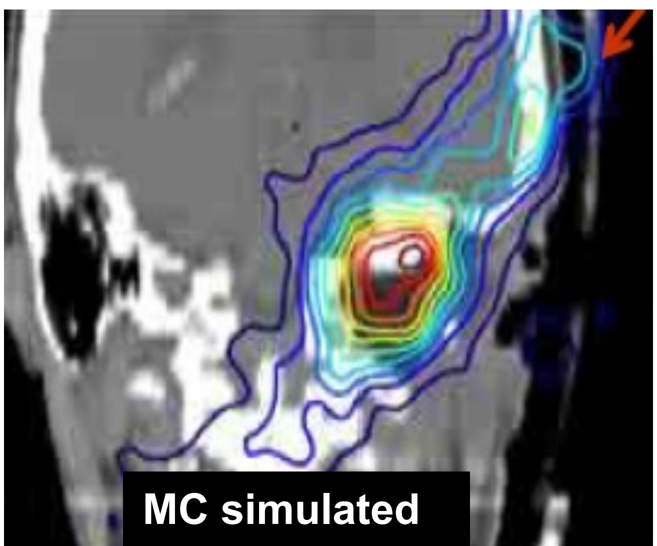
450 patients treated with carbon ions

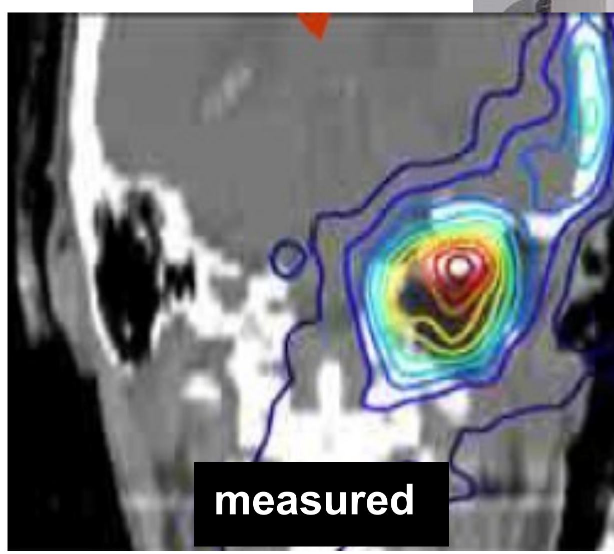
J. Debus (Heidelberg Univ.)



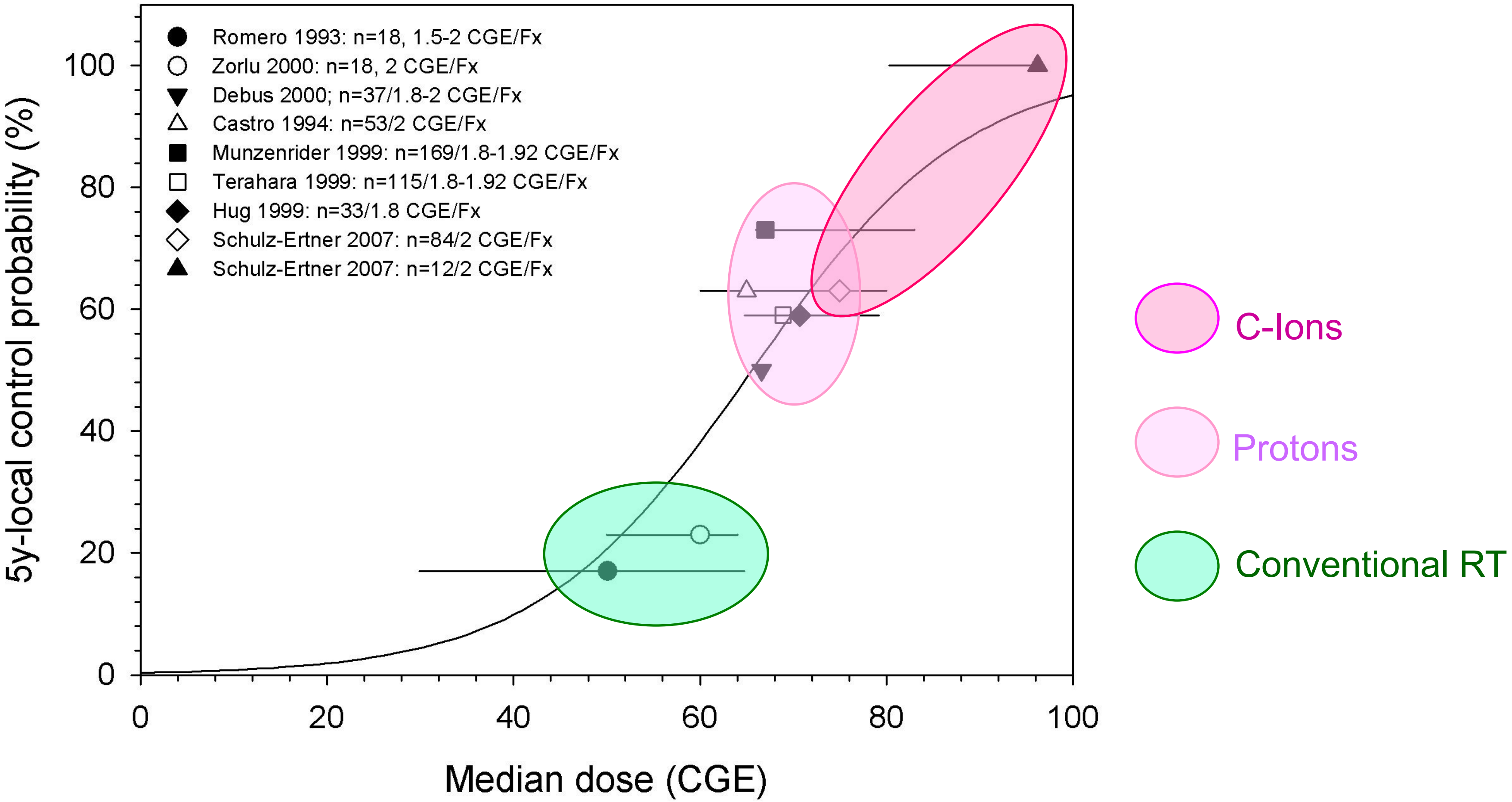
Real-time monitoring

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



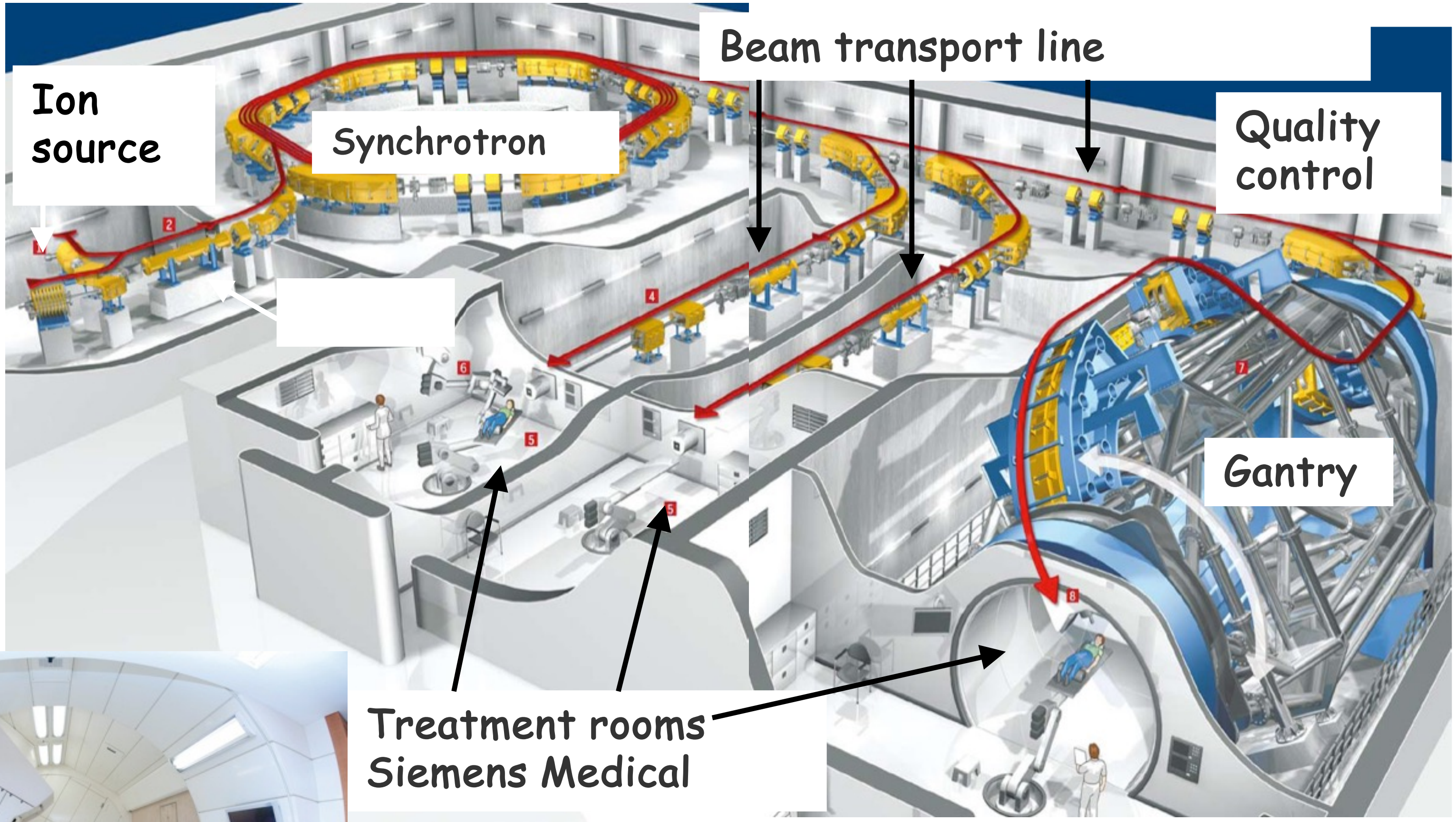


Tumour Control Rate: Chordomas



Schulz-Ertner, IJROBP 2007

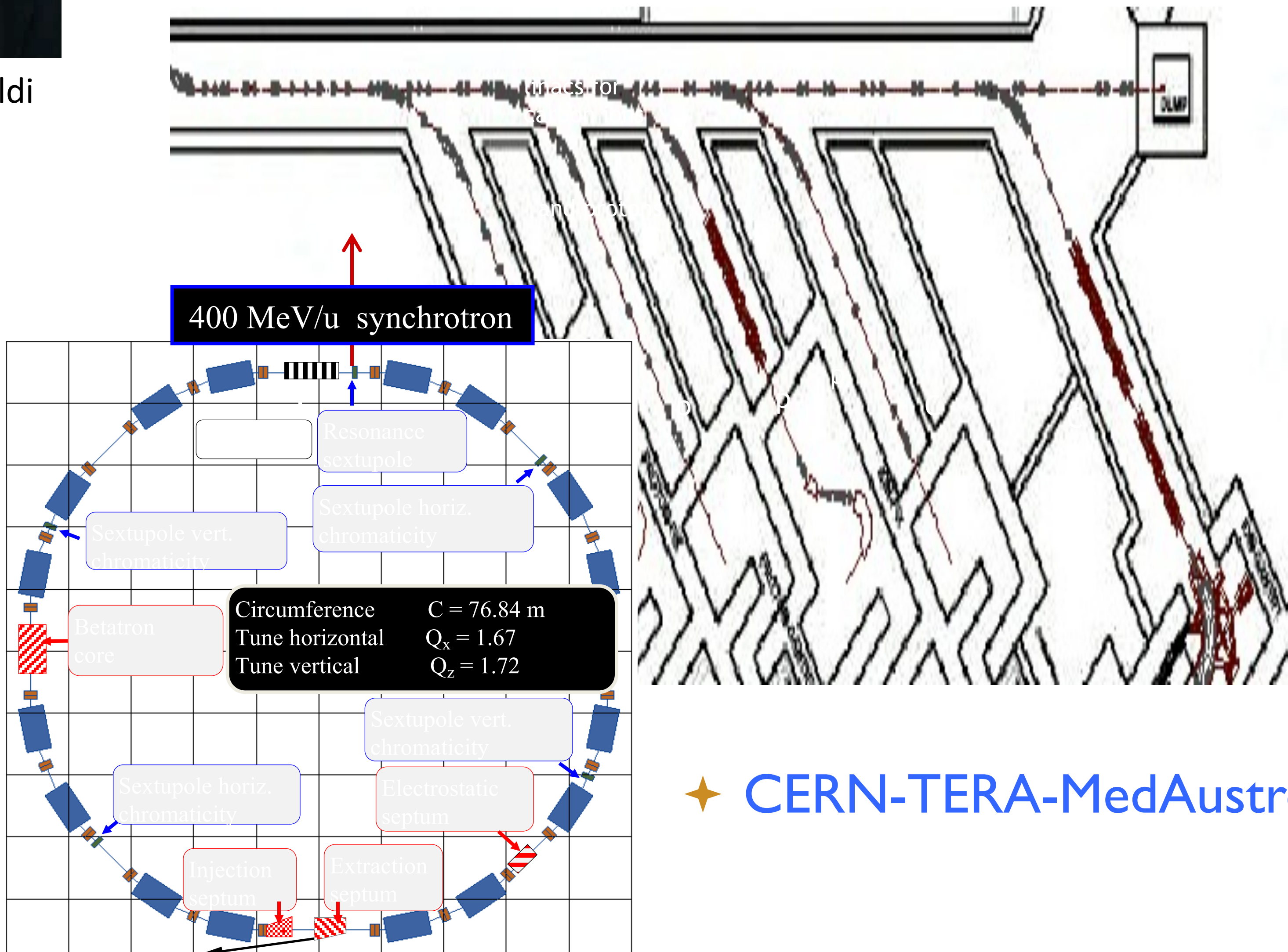
HIT - Heidelberg



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

PIMMS at CERN (1996-2000)

Ugo Amaldi
TERA

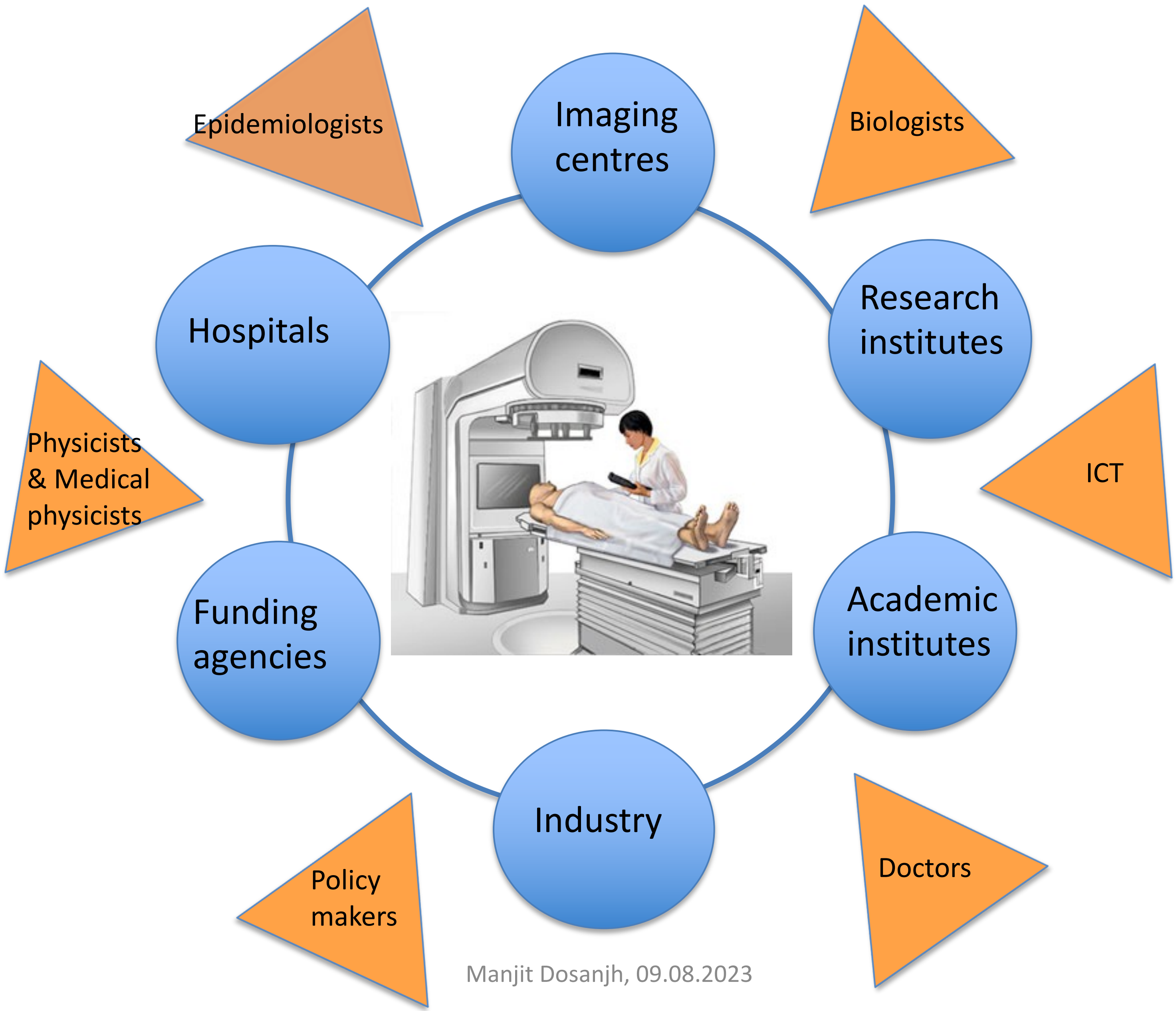


✦ CERN-TERA-MedAustron

The beginnings of ENLIGHT

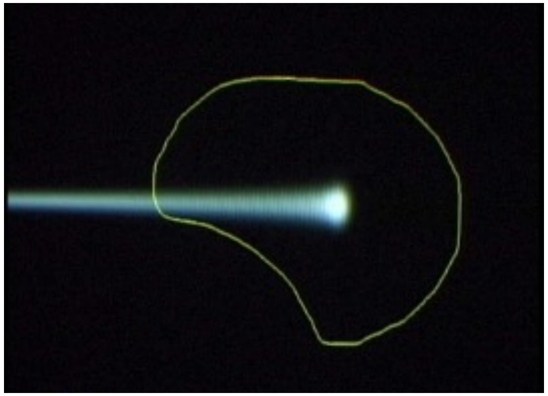
- The idea germinated in 2001 after ESTRO- Med-AUSTRON meeting
- In October 2001 the proposal for a Thematic Network was submitted to EC
- ENLIGHT was launched In February 2002 at CERN
- Funded: 1 million Euros in 2002

ENLIGHT: Importing physics collaboration spirit



ENLIGHT was established to ………

- Create common multidisciplinary platform
- Cancer treatment
- Identify challenges
- Share knowledge
- Share best practices
- Harmonise data
- Provide training, education
- Innovate to improve
- Lobbying for funding



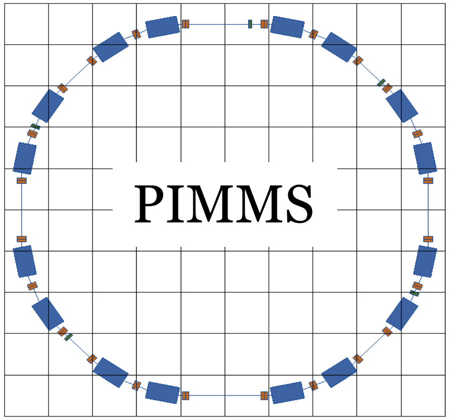
Leveraging Physics collaboration philosophy into a multidisciplinary medical environment

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

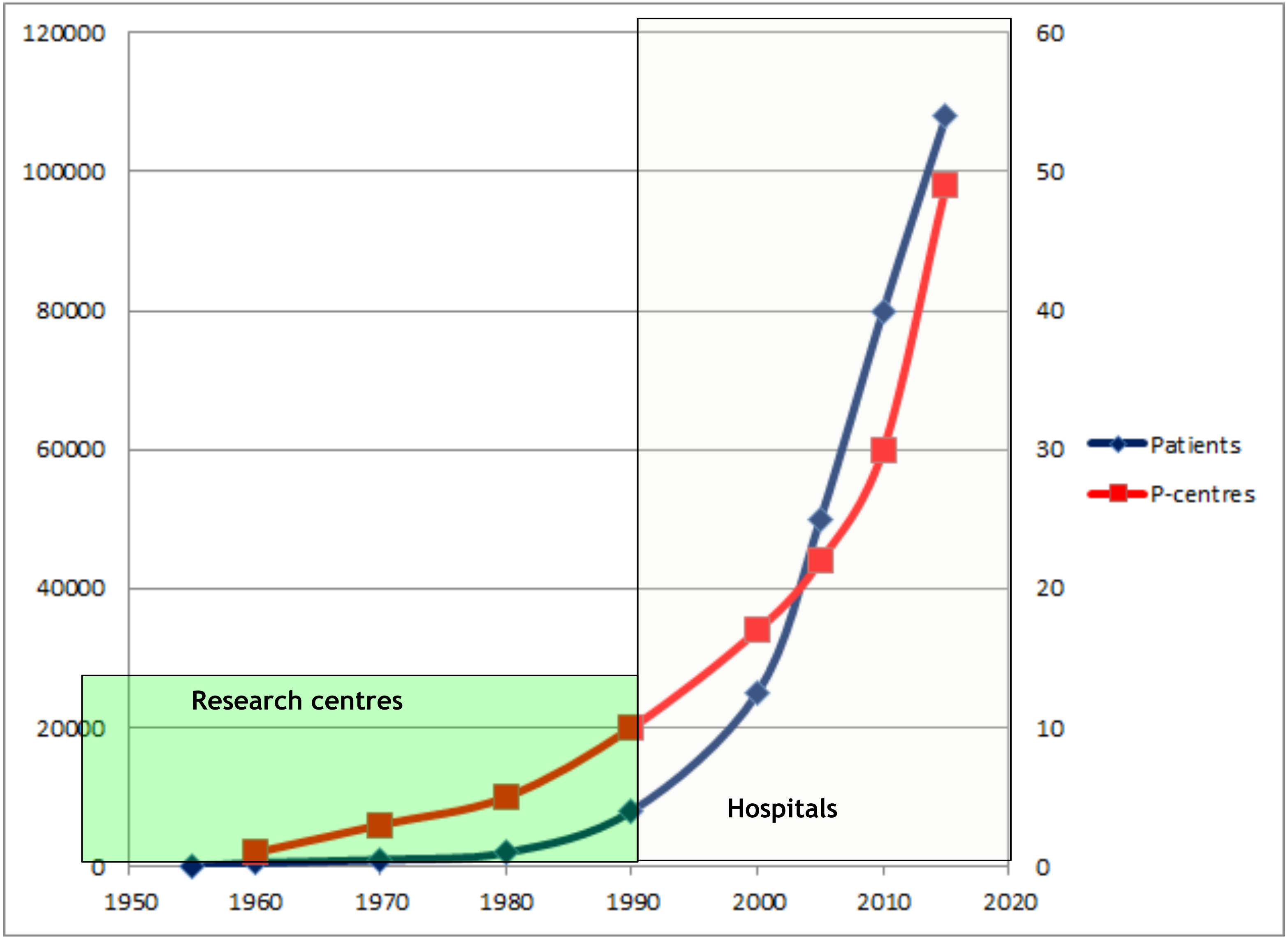
Treatment started in 2016

TERA celebrated 30 years on 16 September 2022

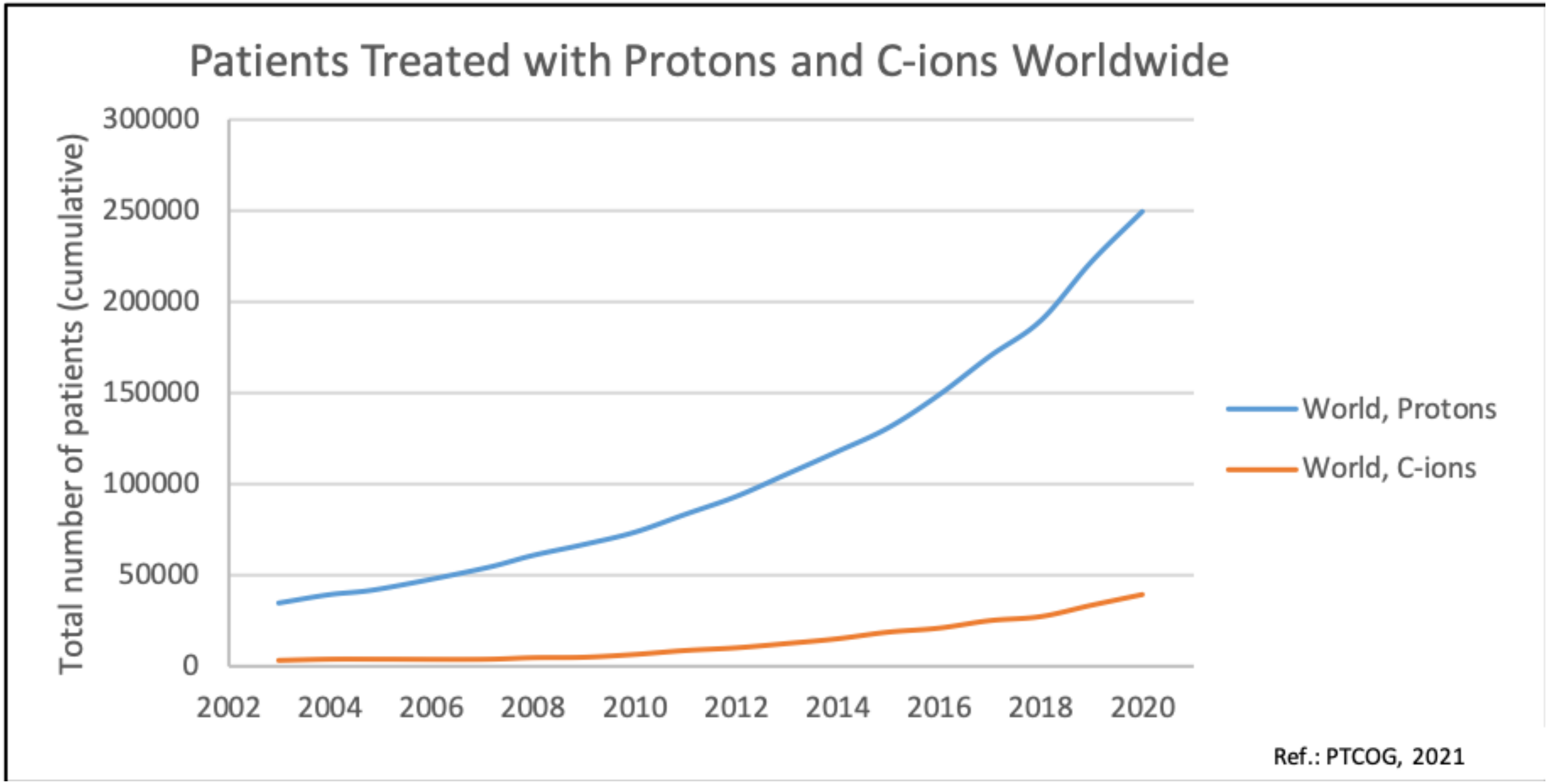
CNAO: Pavia, Italy

Started treating patients in 2011

[Data from www.ptcog.ch]



Patient Numbers

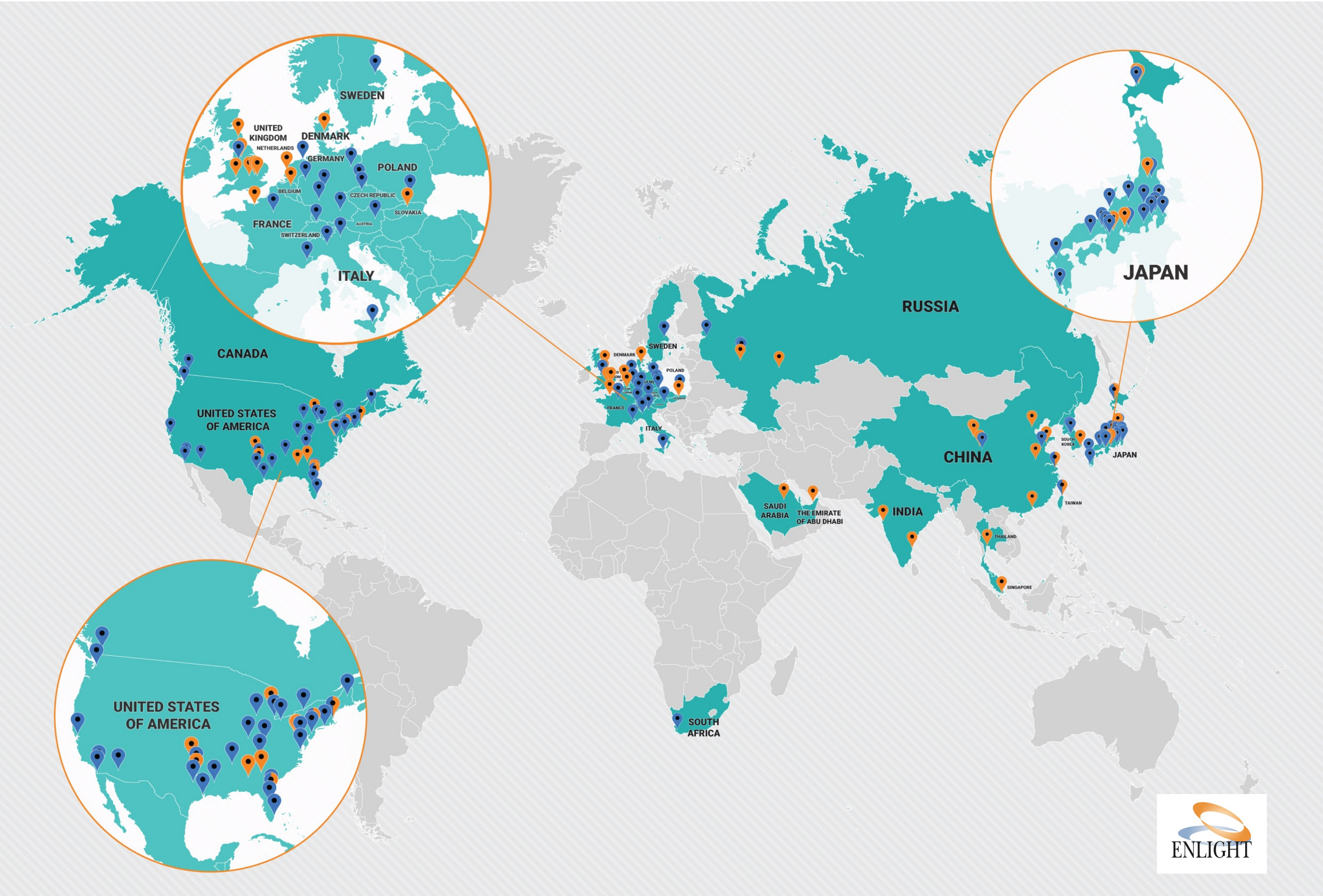


Particle Facilities Facilities in Europe in 2020

Manjit Dosanjh, 09.08.2023

Hadron Facilities in Europe: Baltics and SEE project

Manjit Dosanjh, 09.08.2023

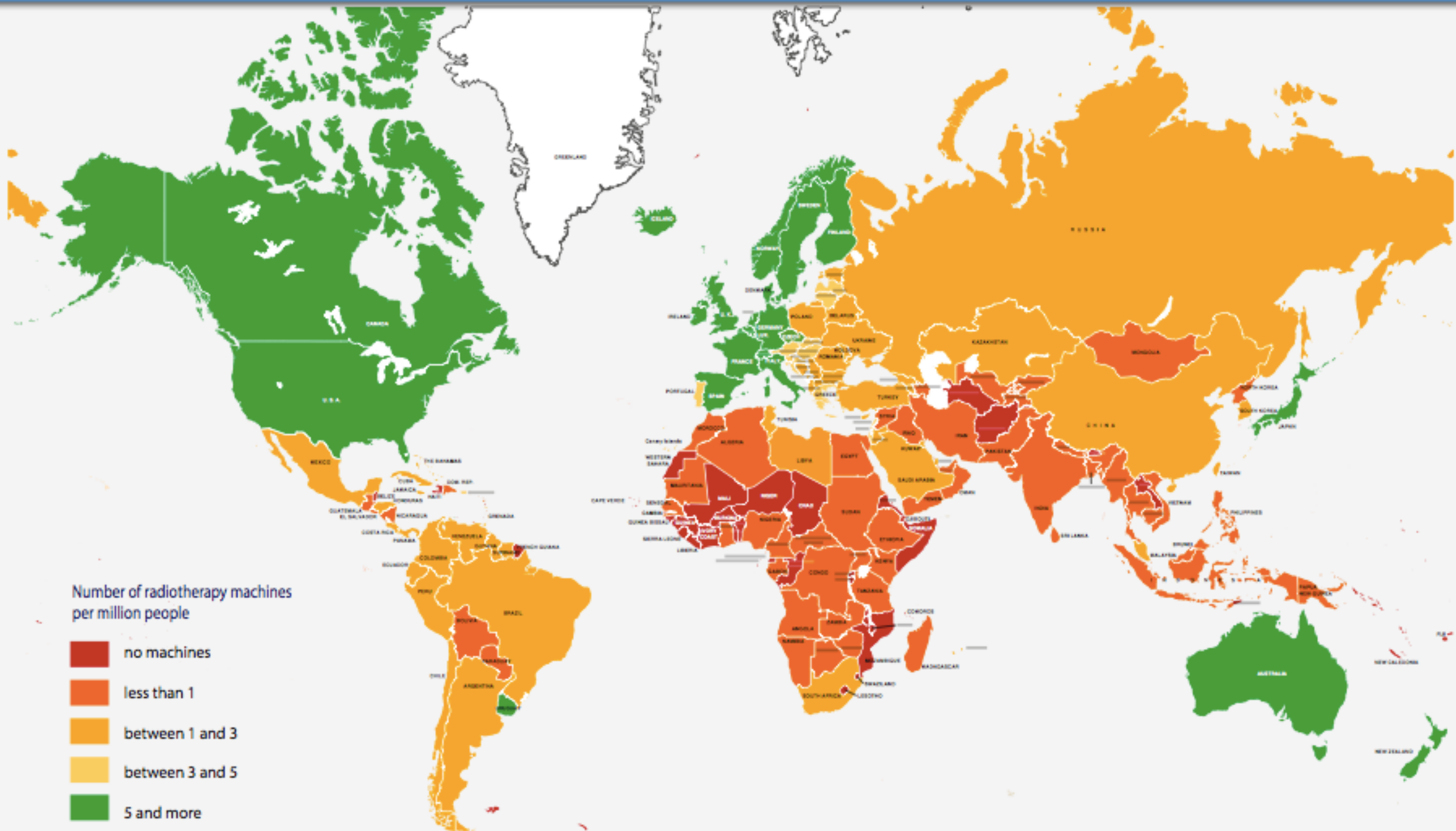

SWEDEN
UNITED KINGDOM
DENMARK
NETHERLANDS
GERMANY
POLAND
BELGIUM
CZECH REPUBLIC
SLOVAKIA
FRANCE
AUSTRIA
SWITZERLAND
ITALY
JAPAN
RUSSIA
CANADA
UNITED STATES OF AMERICA
CHINA
SOUTH KOREA
TAIWAN
SAUDI ARABIA
THE EMIRATE OF ABU DHABI
INDIA
THAILAND
SINGAPORE
SOUTH AFRICA
ENLIGHT
FUNCTIONAL CENTERS
UNDER CONSTRUCTION

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

Availability of **RADIATION THERAPY**

Number of Radiotherapy Machines per Million People 2012



Source: *DIRAC (Directory of Radiotherapy Centres), 2012 / IAEA*

For more information: *http://www-naweb.iaea.org/nahu/dirac/*
dirac@iaea.org

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

CERN

UNIVERSITY OF OXFORD

FLASH therapy – a growing clinical interest

NATURE May 23, 1959 Vol. 183

Modification of the Oxygen Effect when Bacteria are given Large Pulses of Radiation

D. L. Dewey
J. W. Boag

Research Unit in Radiobiology,
British Empire Cancer Campaign,
Mount Vernon Hospital,
Northwood.

> Sci Transl Med. 2014 Jul 16;6(245):245ra93. doi: 10.1126/scitranslmed.3008973.

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

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

Affiliations + expand

PMID: 25031268 DOI: 10.1126/scitranslmed.3008973

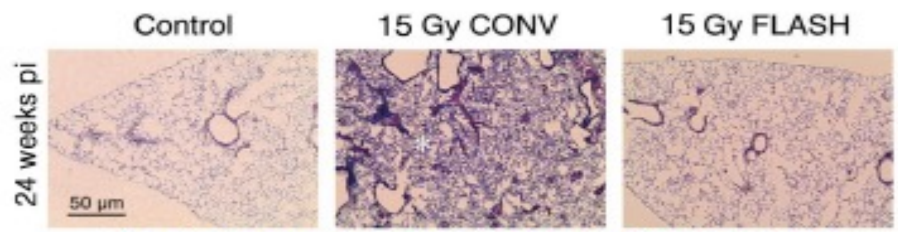
In vitro studies suggested that sub-millisecond pulses of radiation elicit less genomic instability than continuous, protracted irradiation at the same total dose. To determine the potential of ultrahigh dose-rate irradiation in radiotherapy, we investigated lung fibrogenesis in C57BL/6J mice exposed either to short pulses (≤ 500 ms) of radiation delivered at ultrahigh dose rate (≥ 40 Gy/s, FLASH) or to conventional dose-rate irradiation (≤ 0.03 Gy/s, CONV) in single doses. The growth of human HBCx-12A and HEp-2 tumor xenografts in nude mice and syngeneic TC-1 Luc(+) orthotopic lung tumors in C57BL/6J mice was monitored under similar radiation conditions. CONV (15 Gy) triggered lung fibrosis associated with activation of the TGF-β (transforming growth factor-β) cascade, whereas no complications developed after doses of FLASH below 20 Gy for more than 36 weeks after irradiation. FLASH irradiation also spared normal smooth muscle and epithelial cells from acute radiation-induced apoptosis, which could be reinduced by administration of systemic TNF-α (tumor necrosis factor-α) before irradiation. In contrast, FLASH was as efficient as CONV in the repression of tumor growth. Together, these results suggest that FLASH radiotherapy might allow complete eradication of lung tumors and reduce the occurrence and severity of early and late complications affecting normal tissue.

Glimpse of FLASH THERAPY - 2014

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

Sci Transl Med 6: 245ra93, 2014

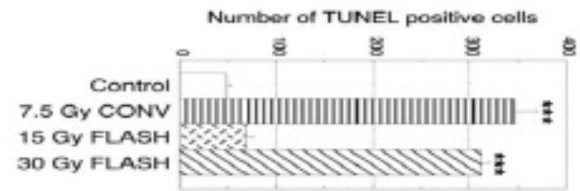
- **FLASH spared normal lung tissue** at doses known to induce fibrosis in mice exposed to conventional dose-rate irradiation (CONV).



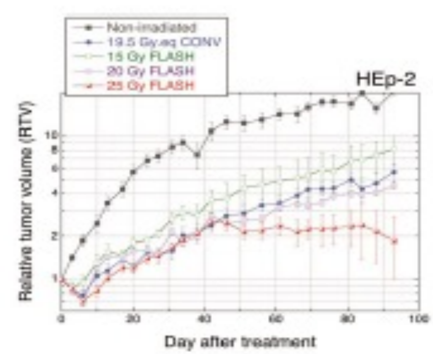
Visualisation of collagen invasion (Masson trichrome staining)

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.



institut Curie

FLASH THERAPY

What are the underlaying mechanisms in FLASH effect?

The role of the oxygen of emerges

Playing with the oxygen tension = modify ROS production

1 – Make mice breathe 95% of oxygen (before and during IR)

2 – Increase oxygen tension in the brain

3 – Deliver FLASH or conventional dose-rate irradiation

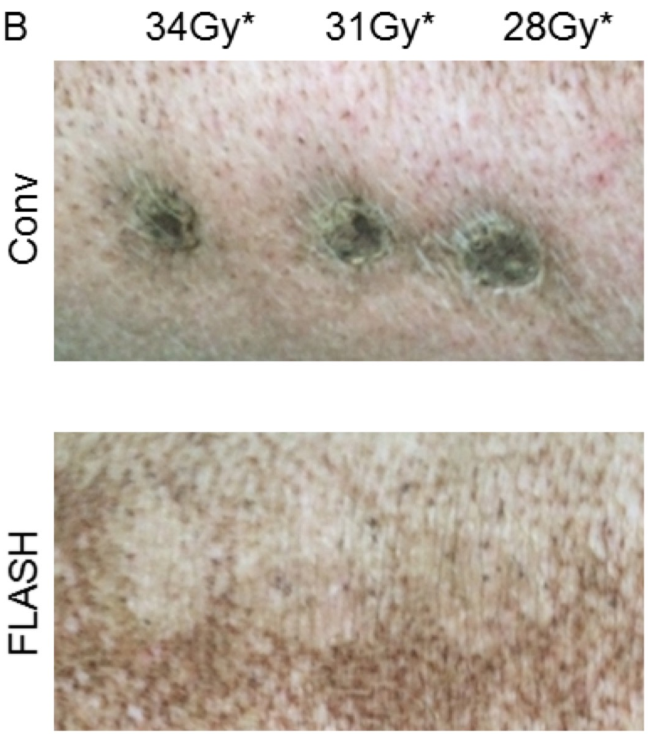
4 – Evaluate memory

Increase in O2 tension reverses the FLASH effect

Less ROS produced by FLASH-RT ?

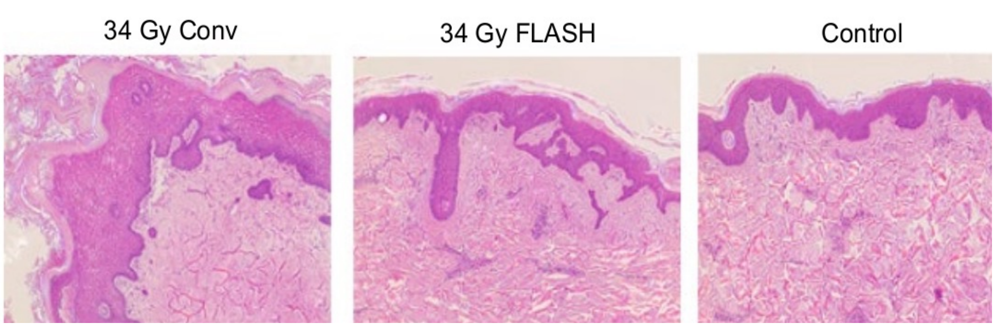
Montay-Gruel et al (in revision)

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

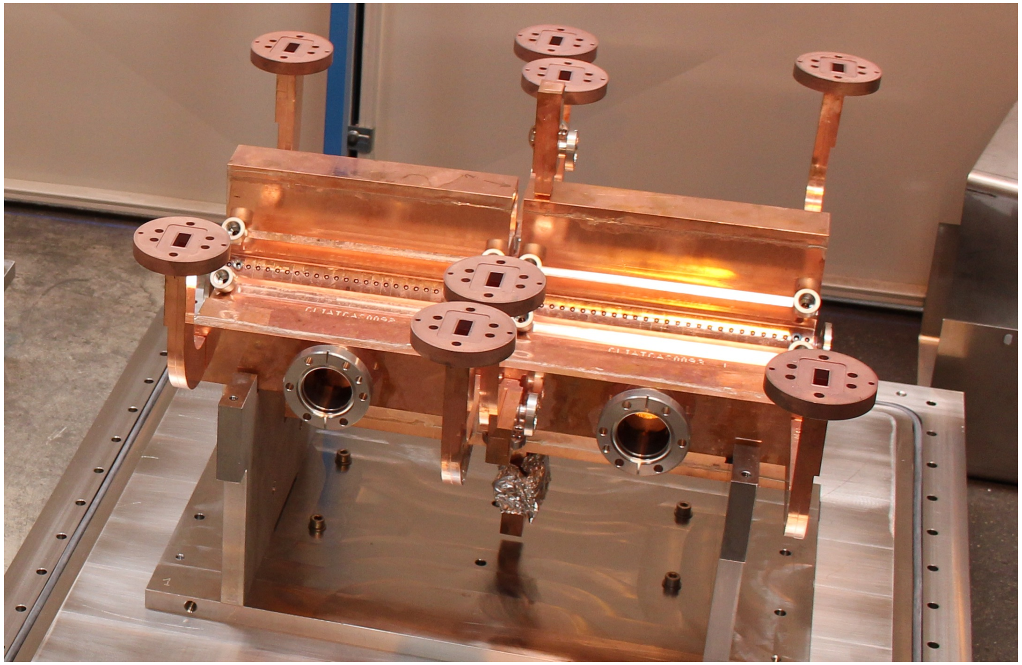
FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases). The clinical trial involves the investigational use of Varian’s ProBeam particle accelerator modified to enable radiation therapy delivery at ultra-high dose rates (dose delivered in less than 1 second) and is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

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

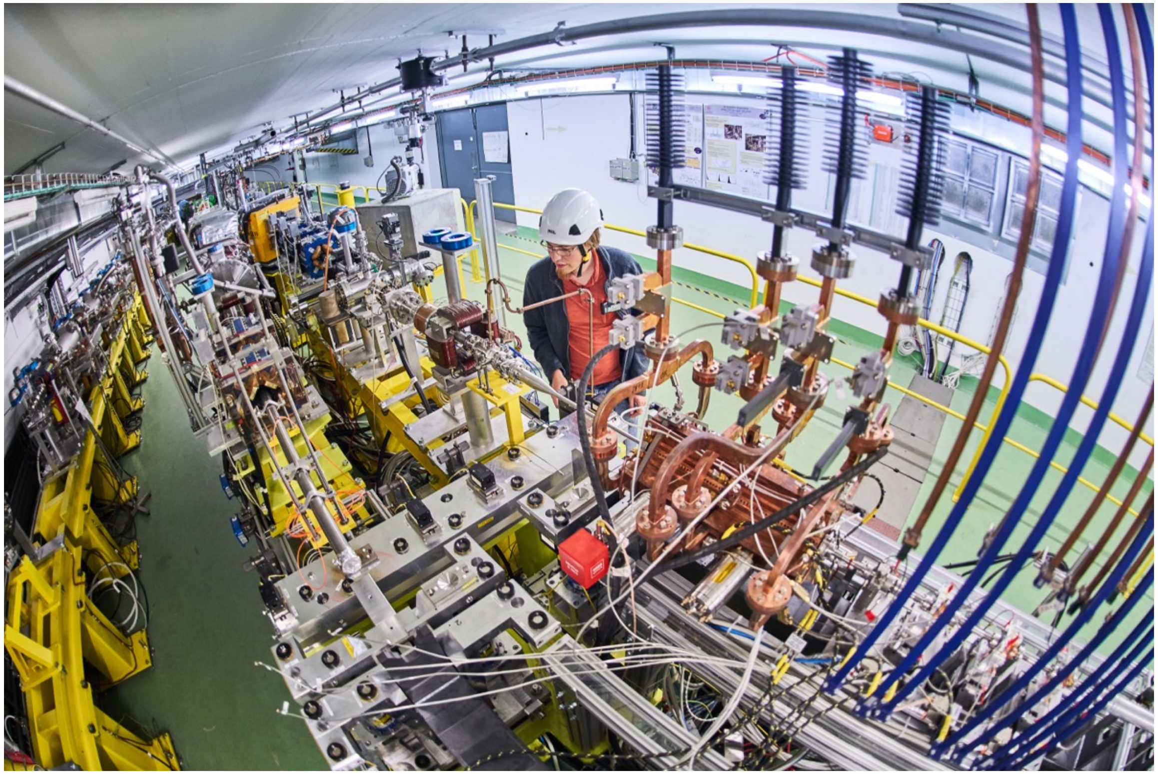


CLIC RF X-band cavity prototype (12 Ghz, 100 MV/m)

Compact Linear Collider

The CERN Linear Electron Accelerator for Research (CLEAR)

- CLEAR is a versatile 200 MeV electron linac + a 20m experimental beamline, operated at CERN as a multi-purpose user facility.



Roberto Corsini (CERN)

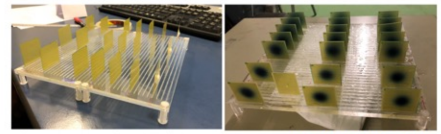
VHEE activities in CLEAR

Calibration of operational medical dosimeters – nonlinear effects with high-dose short pulses

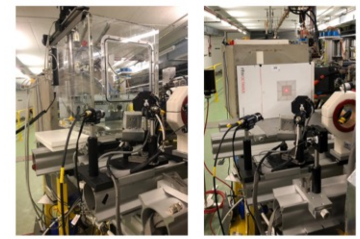
Verification of FLASH effect using biological dosimeters

Experimental verification of dose deposition profiles in water phantoms

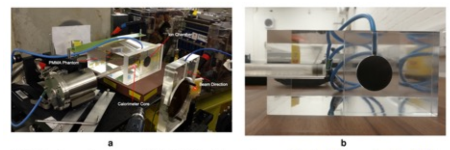
Demonstration of "Bragg-like peak" deposition with focused beams



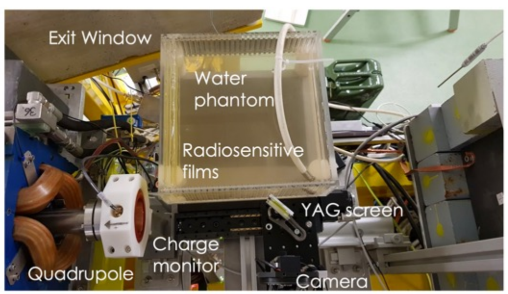
Films set-up for profile depth dose, CHUV Lausanne
(M.C. Vozenin, C. Bailat, R. Moeckli et al.)



Advance Markus chambers and SRS Array, Oldenburg University and PTW
(B. Poppe, D. Poppinga et al.)



Calorimeter and ROOS chamber, Nat. Phys. Lab. UK
(A. Subiel et al.)



de
chester

A. Lagdza, R. Jones et al., Influence of heterogeneous media on Very High Energy Electron (VHEE) dose penetration and a Monte Carlo-based comparison with existing radiotherapy modalities, Nuclear Inst. and Meth. in Physics Research, B, 482 (2020) 70-81.

M. McManus, A. Subiel et al., The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams, Nature Scientific Reports (2020) 10-9089.

Small, K.L., Henthorn, et al., Evaluating very high energy electron RBE from nanodosimetric pBR322 plasmid DNA damage, Nature Sci. Rep. 11, 3341 (2021).

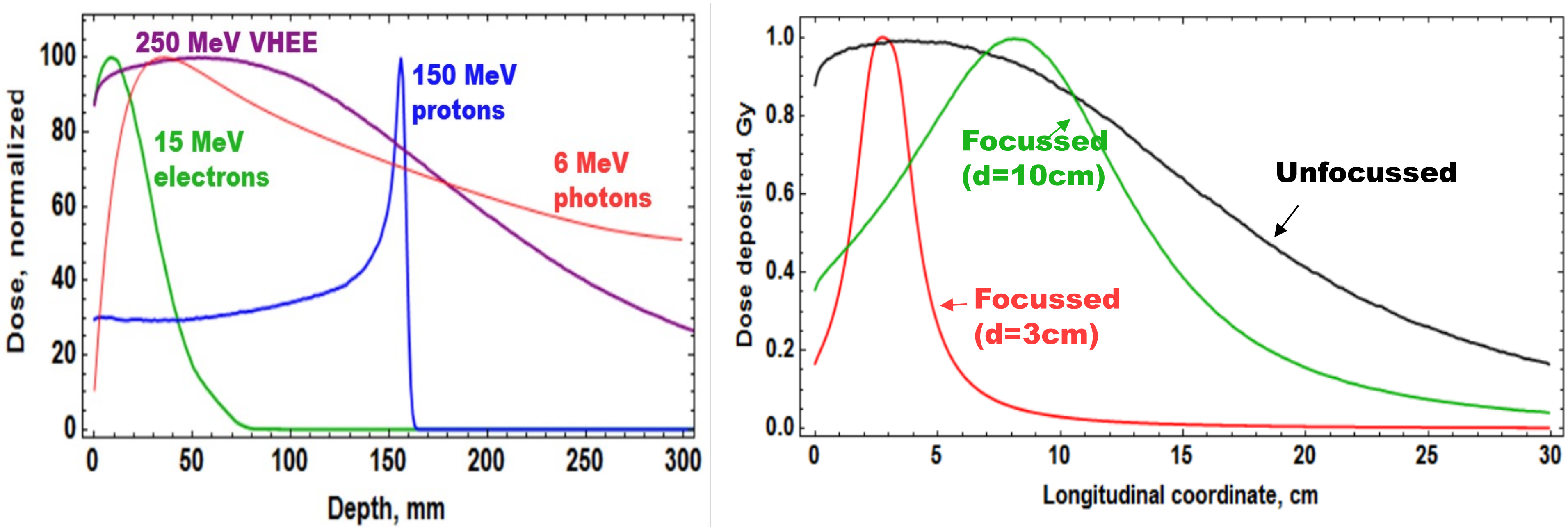
D. Poppinga et al., VHEE beam dosimetry at CERN Linear Electron Accelerator for Research under ultra-high dose rate conditions, 2021 Biomed. Phys. Eng. Express 7 015012.

Kokurewicz, K., Brunetti, E., Curcio, A. et al. An experimental study of focused very high energy electron beams for radiotherapy, Nature Commun. Phys. 4, 33 (2021).

Roberto Corsini (CERN)

VHEE

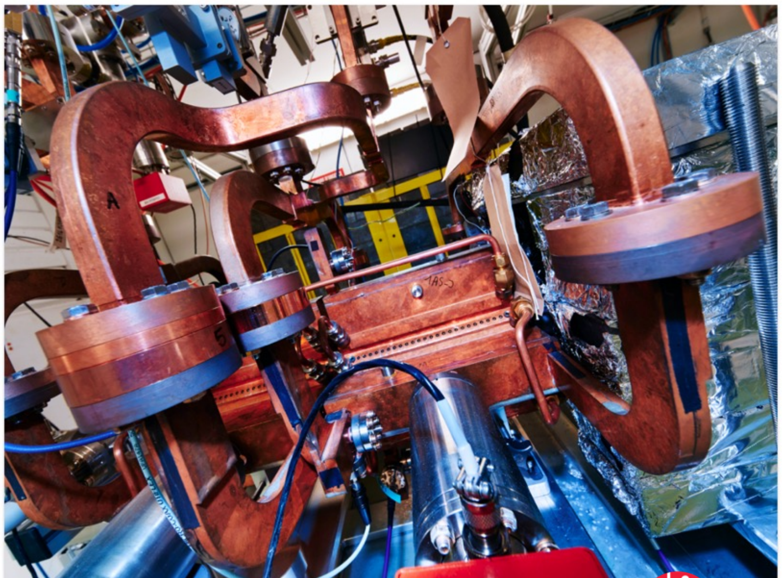
- Their ballistic and dosimetric properties can surpass those of photons, which are currently the most commonly used in RT.
- Their position compared to protons need to be evaluated, but they can be produced at a reduced cost.



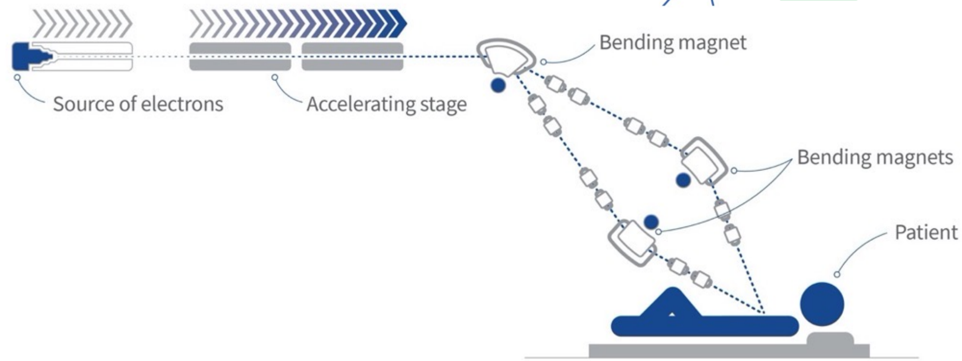
Depth Dose curve for various particle beams in water (beam widths r=0.5 cm)

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.

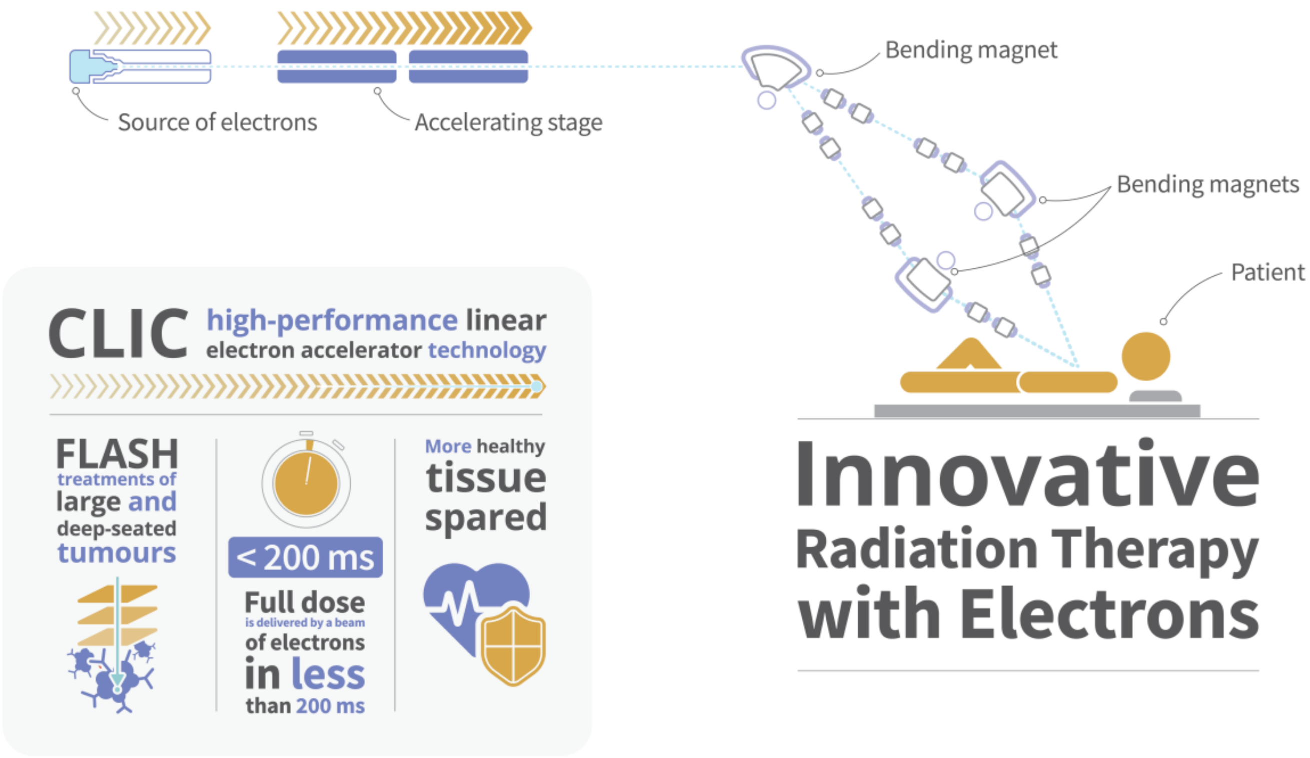
The design of this facility is the result of an intense dialogue between groups at CHUV and CERN.

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

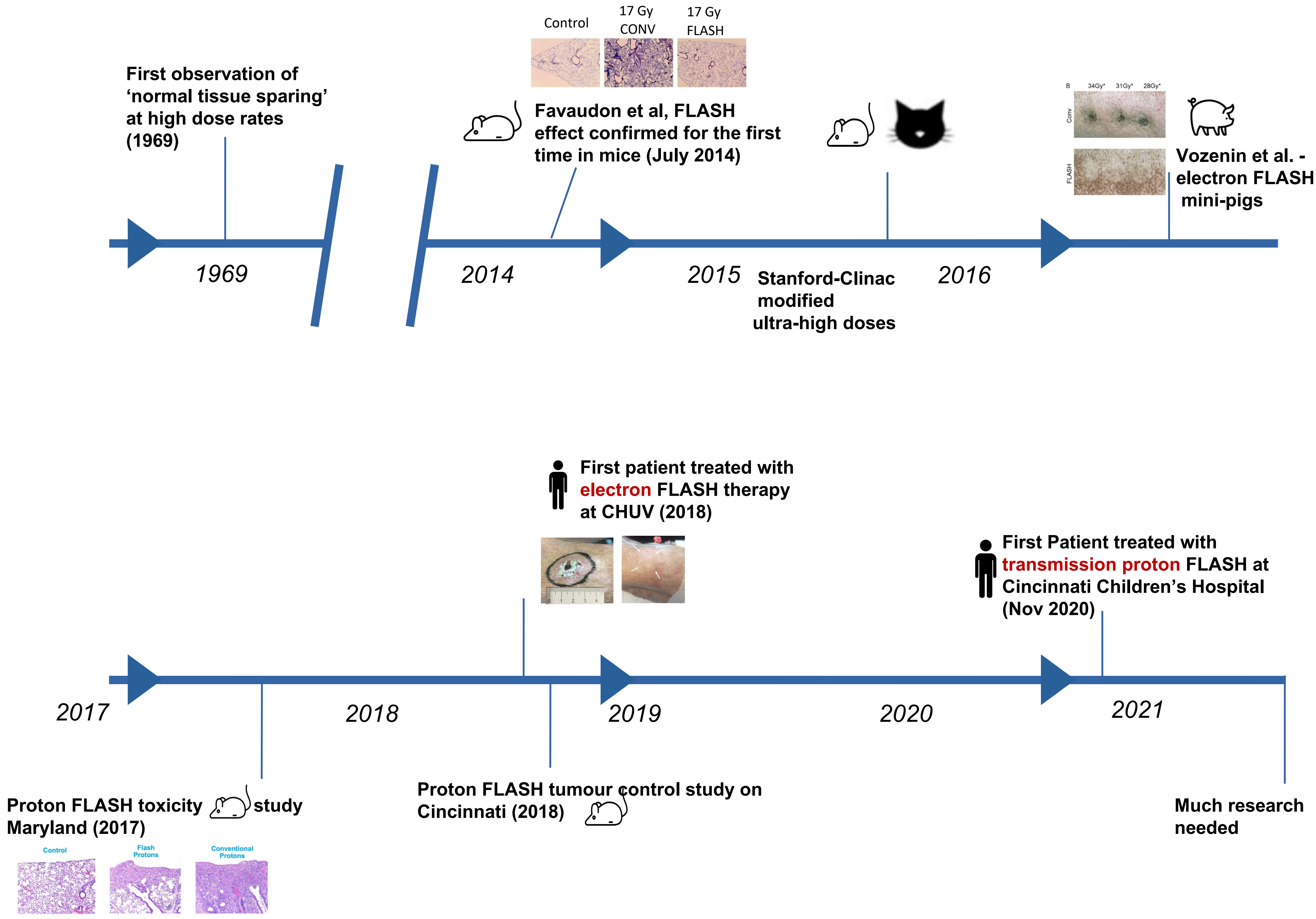
Walter Wuensch (CERN)

CERN, CHUV and THERYQ join forces for a first VHEE Facility

(Nov 2022)



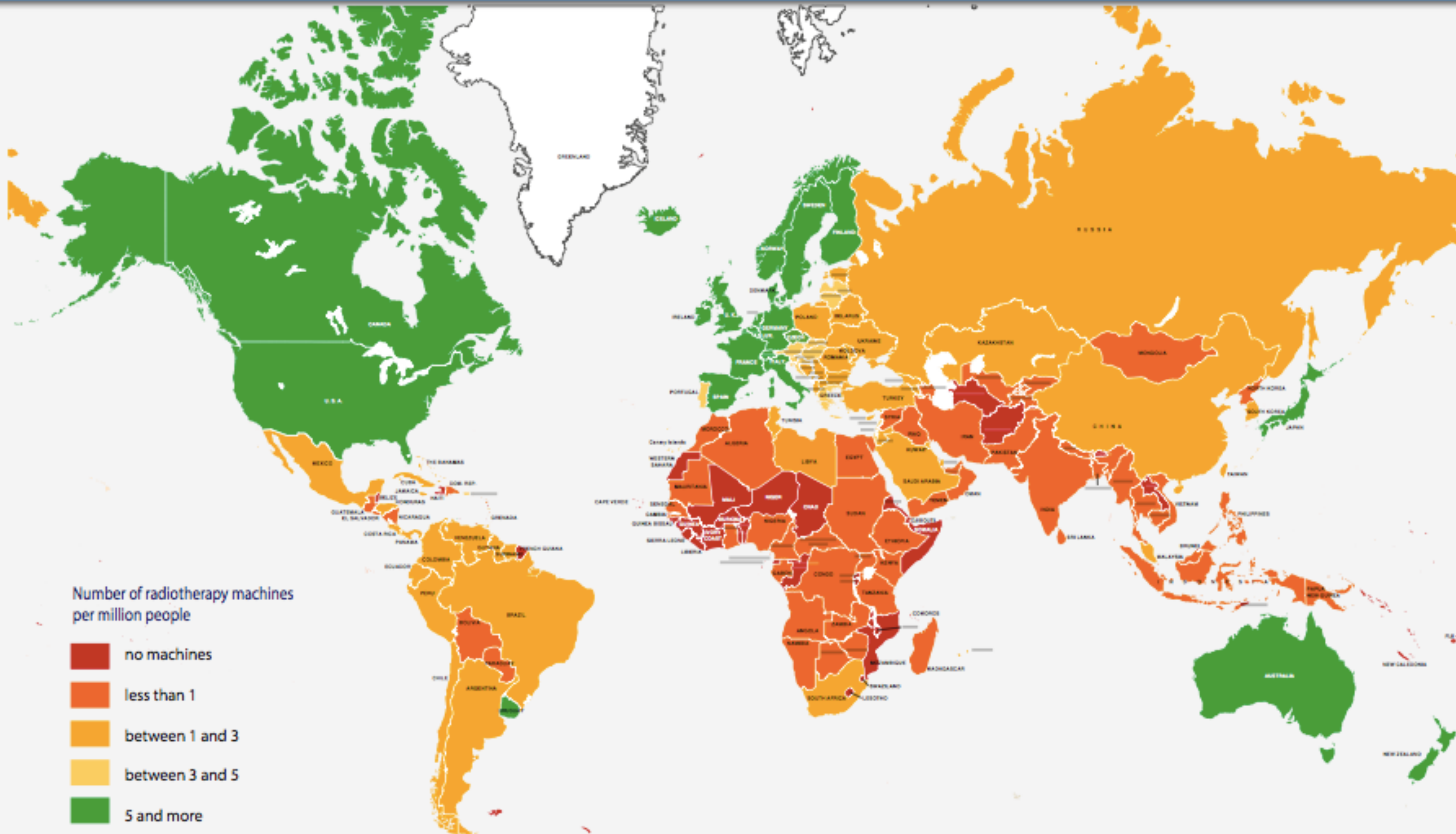
It will produce very high-energy electron (VHEE) beams of 100 to 200 MeV in less than 100-200ms, based on CLIC (Compact Linear Collider) technology, allowing all types of cancers up to a depth of 20 cm to be treated using the FLASH technique.


First observation of ‘normal tissue sparing’ at high dose rates (1969)
1969
Control
17 Gy CONV
17 Gy FLASH
Favaudon et al, FLASH effect confirmed for the first time in mice (July 2014)
2014
2015
Stanford-Clinac modified ultra-high doses
2016
34Gy*
31Gy*
28Gy*
Conv
FLASH
Vozenin et al. - electron FLASH mini-pigs
First patient treated with electron FLASH therapy at CHUV (2018)
First Patient treated with transmission proton FLASH at Cincinnati Children’s Hospital (Nov 2020)
2017
2018
2019
2020
2021
Proton FLASH toxicity study Maryland (2017)
Control
Flash Protons
Conventional Protons
Proton FLASH tumour control study on Cincinnati (2018)
Much research needed

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

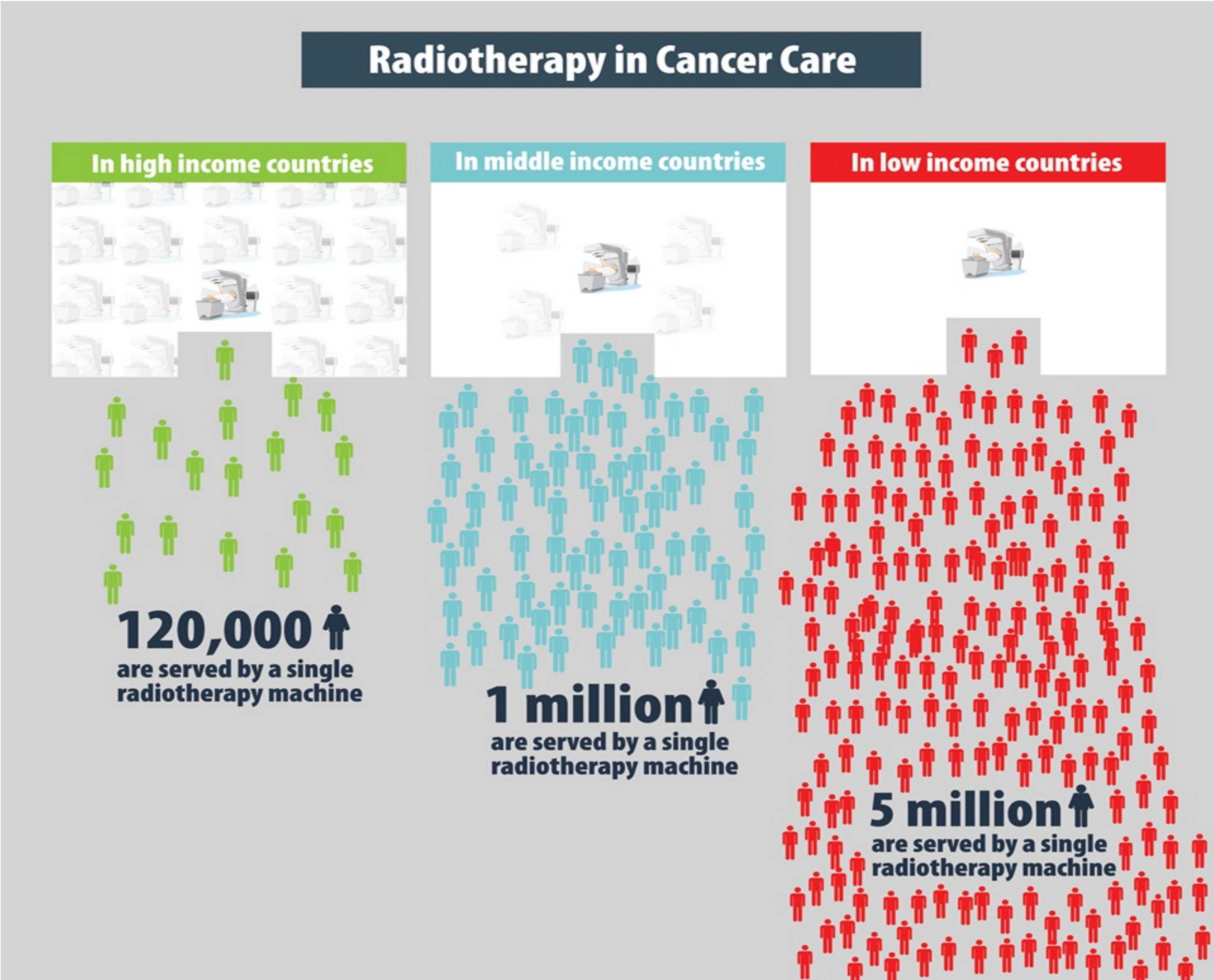
Availability of **RADIATION THERAPY**

Number of Radiotherapy Machines per Million People 2012



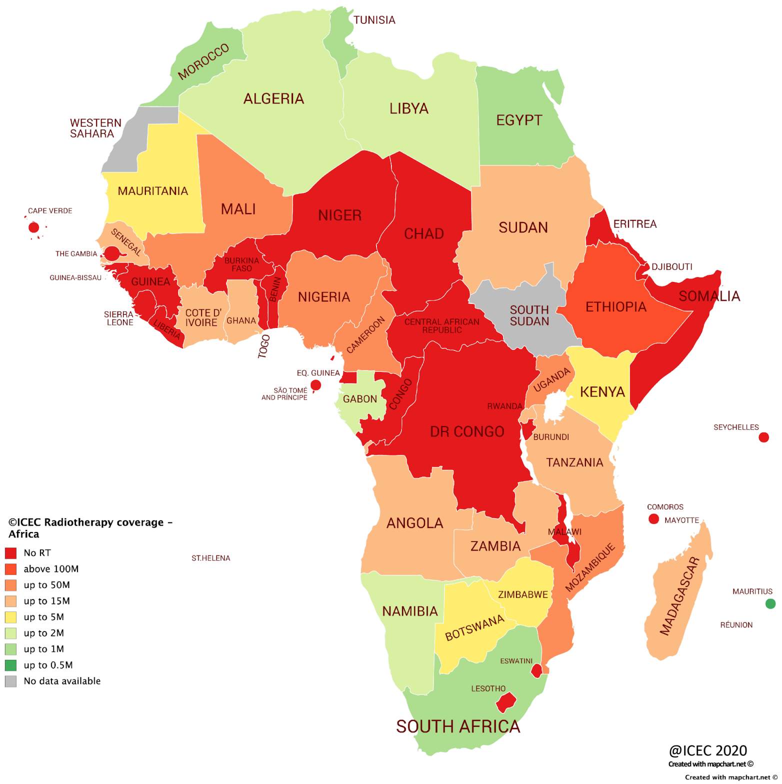
For more information: *http://www-naweb.iaea.org/nahu/dirac/*
dirac@iaea.org

Source: *DIRAC (Directory of Radiotherapy Centres), 2012 / IAEA*


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

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

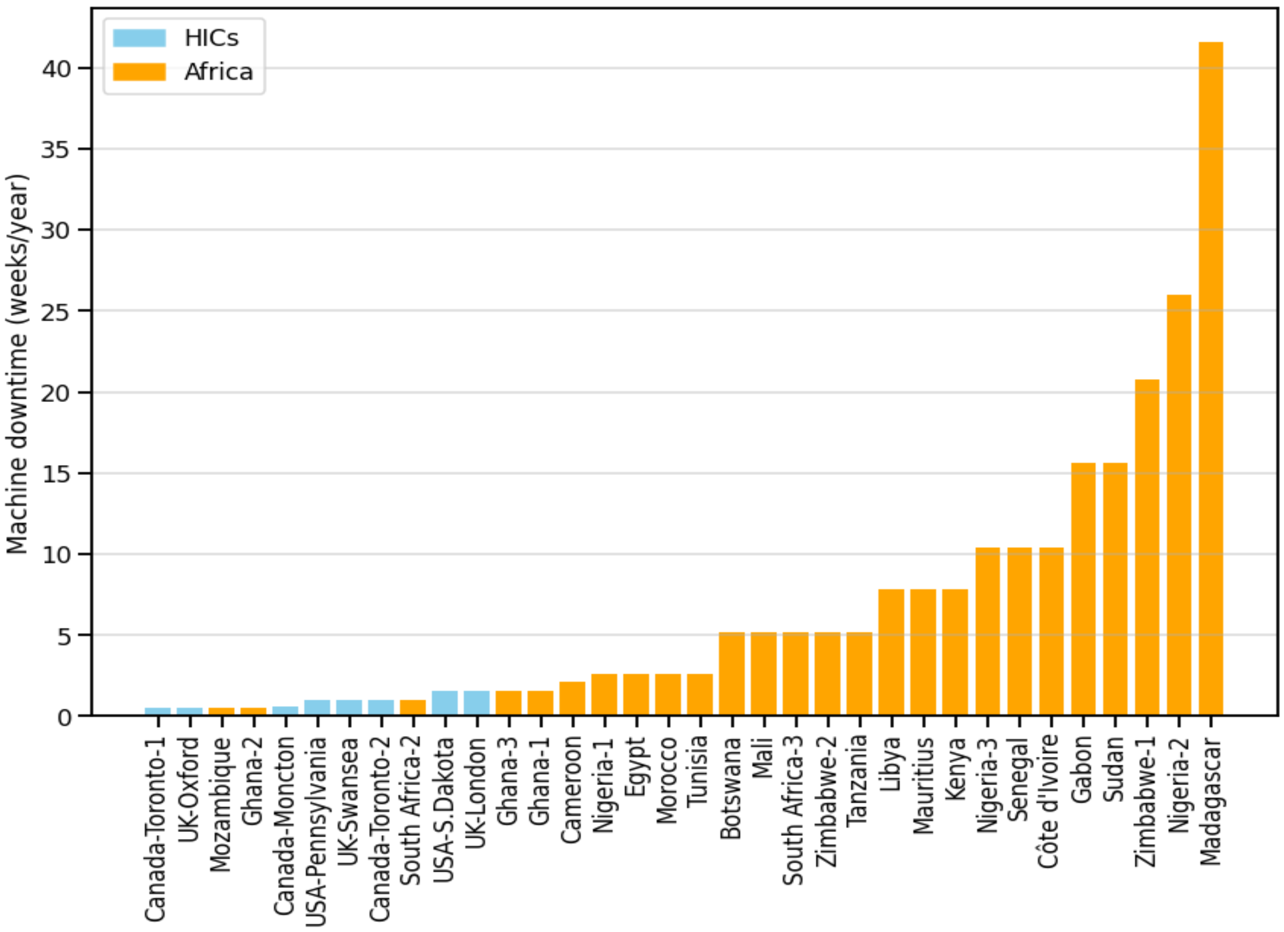


Map showing the number of people per functioning machine in countries in Africa

LINAC Needs Assessment and Challenges

- There are ~15,000 LINACs globally; approximately 400 in all of Africa
- There is a **current need for around 4000 LINACs** in Africa alone
- Estimated need for more than 10,000 LINACs in LMICS by 2035
- LINAC machines offer state of the art treatment but:
  - Cost more
  - More complex and
  - Labour intensive to operate and maintain
  - Need trained personnel experts which are lacking
- Current technology not designed for LMIC environments- infrastructure power, water, humidity challenges, etc.
- Need affordable LINACs and lower operating costs for RT is a global priority
- Risks associated with Cobalt-60 need a cost-effective alternative

Downtime in weeks comparison African and HICs



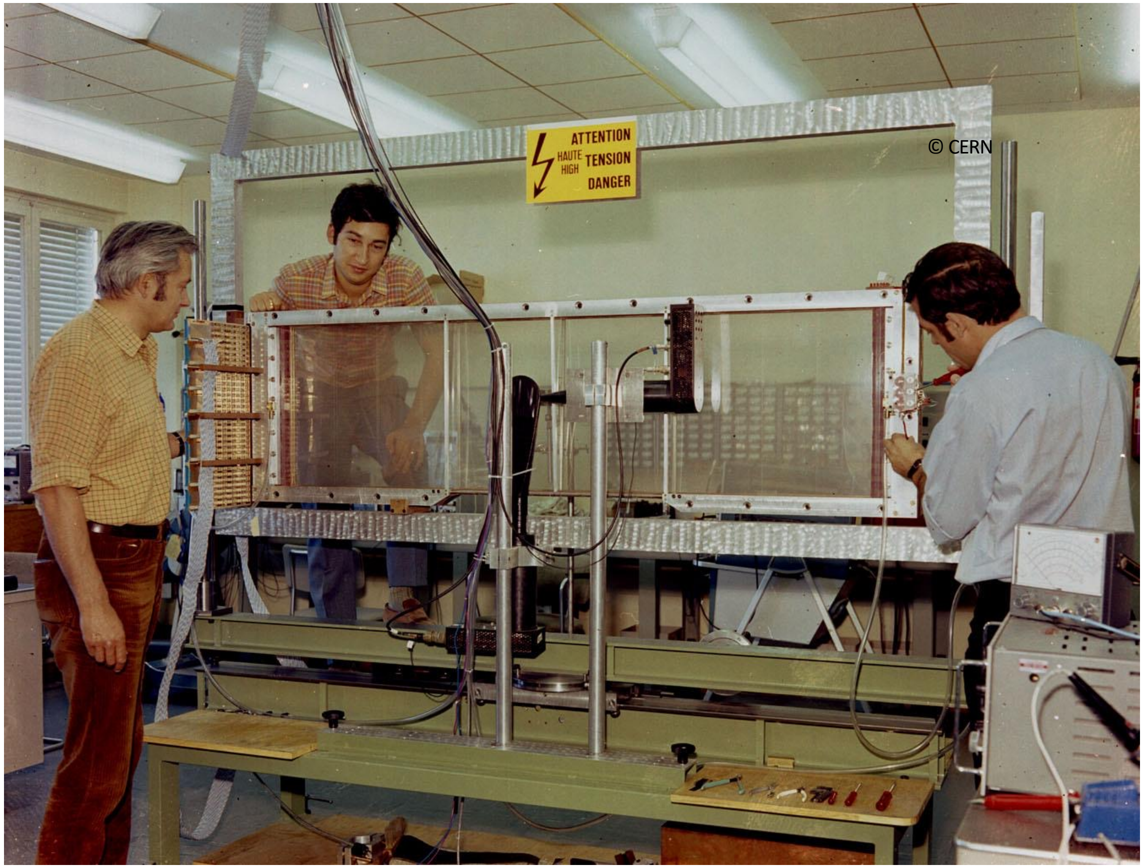
Looking for solutions for building affordable RT

- **Define the problem**
- **Gather information** from African hospitals/facilities regarding challenges experienced in providing radiotherapy in Africa compare these to data from **HIC**.
- **Identify** the challenges from 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
- Create **conceptual design report** for the radiotherapy system to enable technical design and prototyping in next phase

CERN

UNIVERSITY OF OXFORD

cern.ch/virtual-hadron-therapy-centre



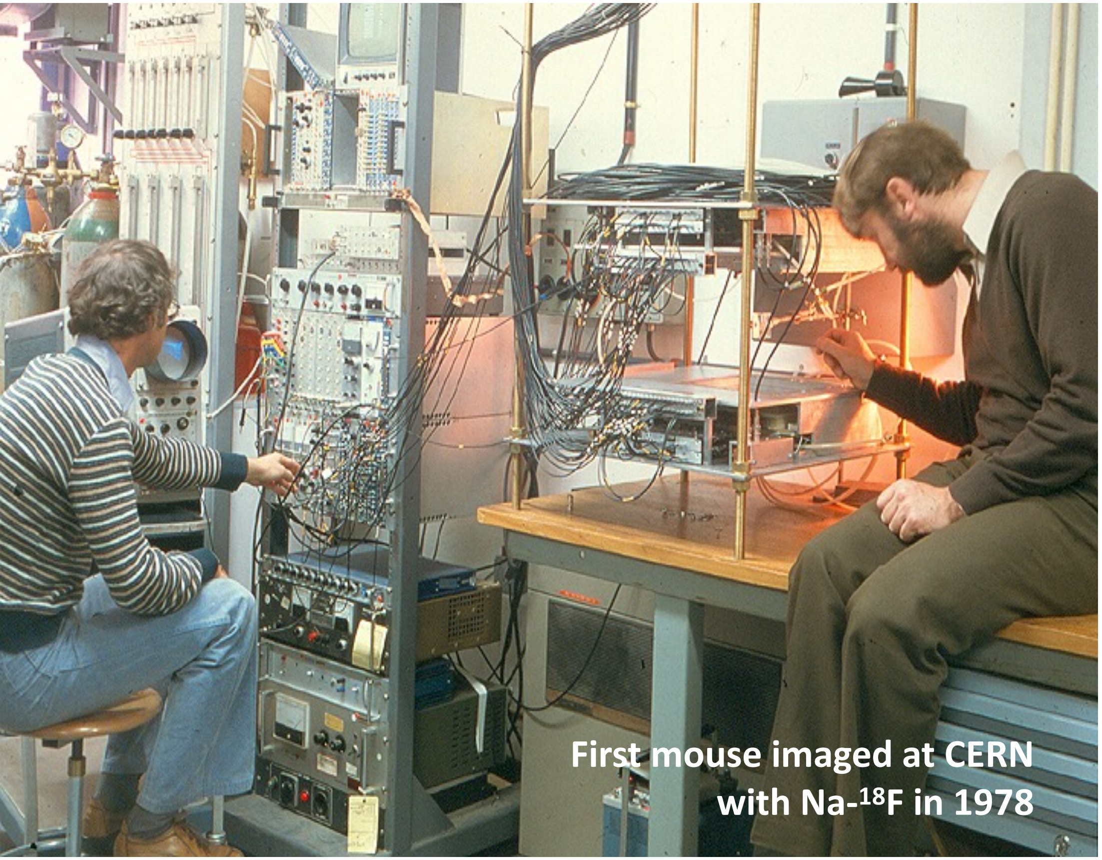
Radioprotection 2005 DOI: 10.1051/radiopro:2005010
Vol. 40, n° 2, pages 245 à 255

Produit nouveau

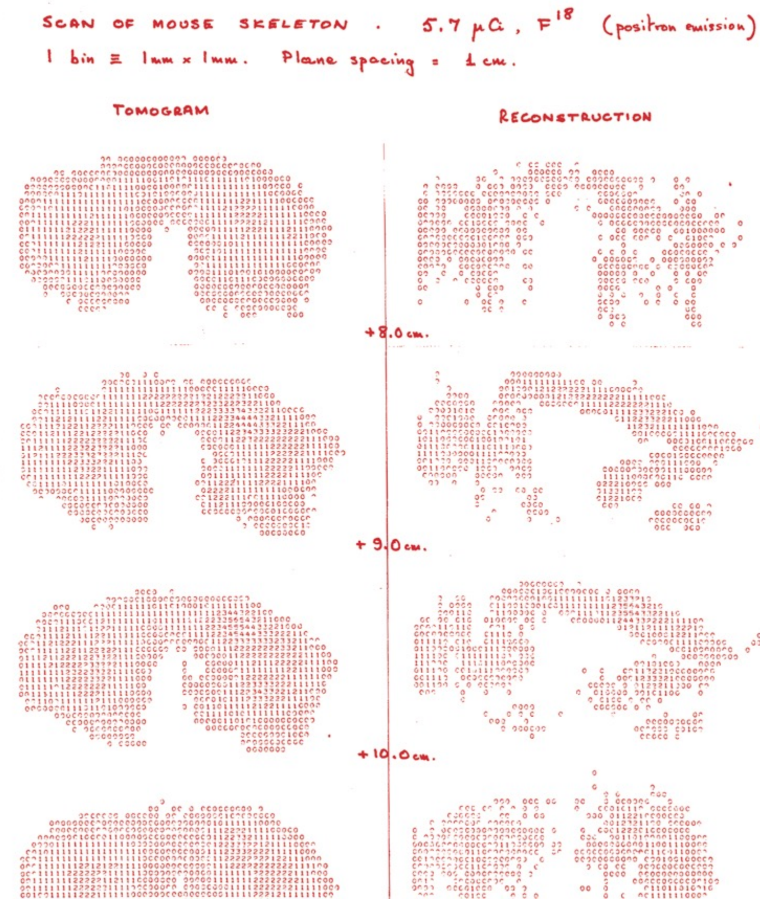
Une nouvelle imagerie ostéo-articulaire basse dose en position debout : le système EOS

J. DUBOUSSET[1], G. CHARPAK[2], I. DORION[2], W. SKALLI[3], F. LAVASTE[3], J. DEGUISE[4], G. KALIFA[5], S. FEREY[5]

Georges Charpak, Fabio Sauli and Jean-Claude Santiard working on a multiwire chamber in 1970



David Townsend and Alan Jeavons



Radiotherapy and Oncology 128 (2018) 76–82

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ENLIGHT

ENLIGHT: European network for Light ion hadron therapy

Manjit Dosanjh [a,*], Ugo Amaldi [b], Ramona Mayer [c], Richard Poetter [d], on behalf of the ENLIGHT Network

[a] *CERN, Geneva, Switzerland;* [b] *TERA Foundation, Novara, Italy;* [c] *Former Medical Director of MedAustron, Wiener Neustadt; and* [d] *Department of Radiotherapy, Medical University of Vienna, Austria*

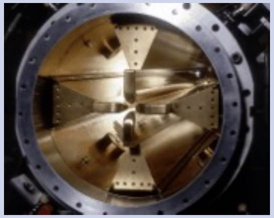
ENLIGHT was established to co-ordinate European efforts in using ion beams for radiation therapy and to catalyse collaboration and co-operation among the different disciplines involved. ENLIGHT had its inaugural meeting in February 2002 at CERN and was funded by the European Commission for its first 3 years.

While the ENLIGHT network itself flourishes without direct dedicated funding since 2006, the R&D and training activities under the umbrella of ENLIGHT have been funded primarily through European Commission (EC) projects.

http://cern.ch/enlight

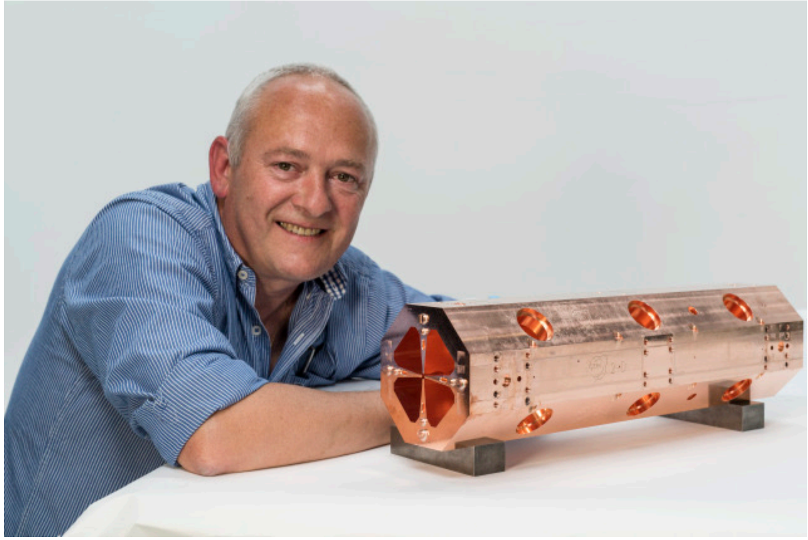
2012: Manjit Dosanjh, ENLIGHT co-ordinator, and members of the ENLIGHT network at the ENLIGHT 10th anniversary meeting

Protons: the LINAC way

1990 RFQ2 200 MHz 0.5 MeV /m Weight :1200kg/m Ext. diametre : ~45 cm	2007 LINAC4 RFQ 352 MHz 1MeV/m Weight : 400kg/m Ext. diametre : 29 cm	2014 HF RFQ 750MHz 2.5MeV/m Weight : 100 kg/m Ext. diametre : 13 cm
		

Compact High-Frequency Radio Frequency Quadrupole (RFQ)

M. Vretenar, A. Dallocchio, V. A. Dimov, M. Garlasché, A. Grudiev, A. M. Lombardi, S. Mathot, E. Montesinos, M. Timmins, "A Compact High-Frequency RFQ for Medical Applications", in Proc. LINAC2014, Geneva, Switzerland, September 2014

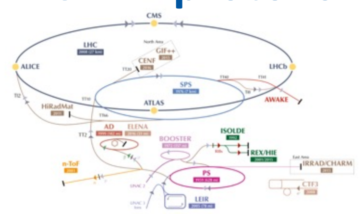


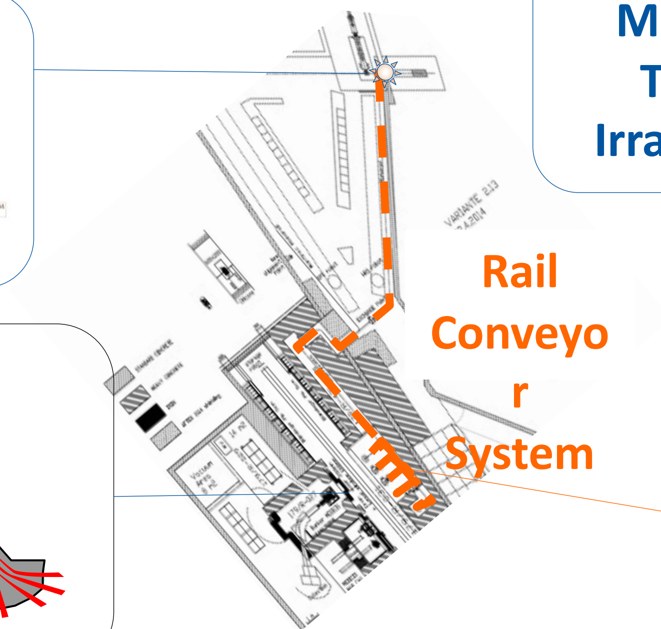
Licensed to AVO-ADAM

CERN-MEDICIS

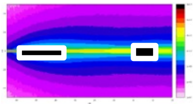
Non-conventional isotopes collected by mass separation for new medical applications

CERN protons



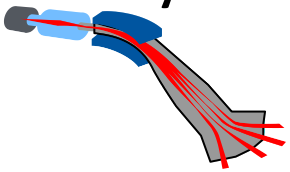


MEDICIS Target Irradiation



Rail Conveyor System

MEDICIS Laboratory



Thierry Stora (CERN)

Crystal Clear Collaboration – CERN RD18 Experiment

Initiated in 1990 by P. Lecoq, approved in 1991 by CERN for R&D for future LHC detectors

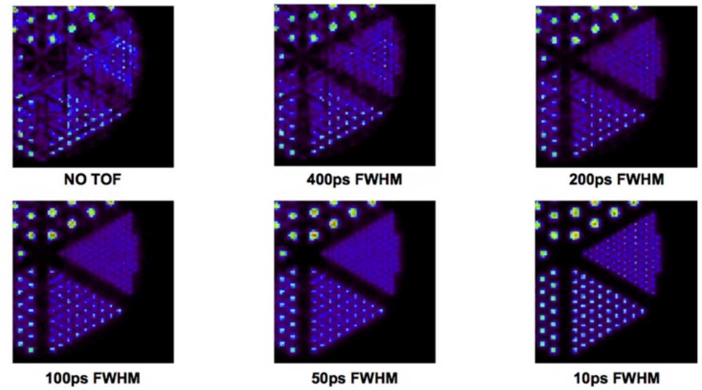
R&D on inorganic scintillators for HEP, medical imaging, industry

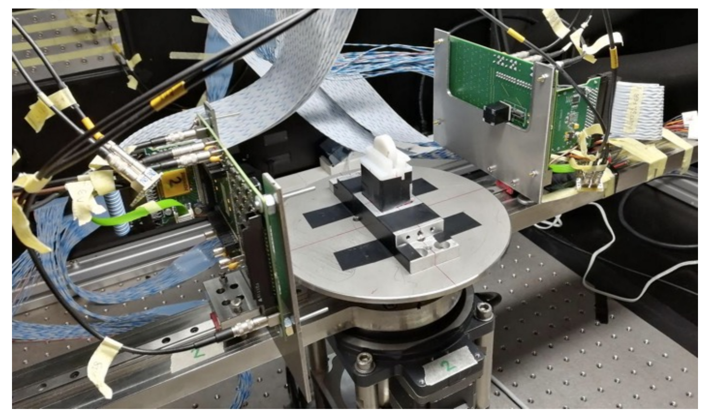
A CERN group very active in Positron Emission Tomography (PET), now focusing on:

Flexible testing facility to test “any” PET detector configuration

Scintillating heterostructures

pushing the limit of TOF-PET resolution



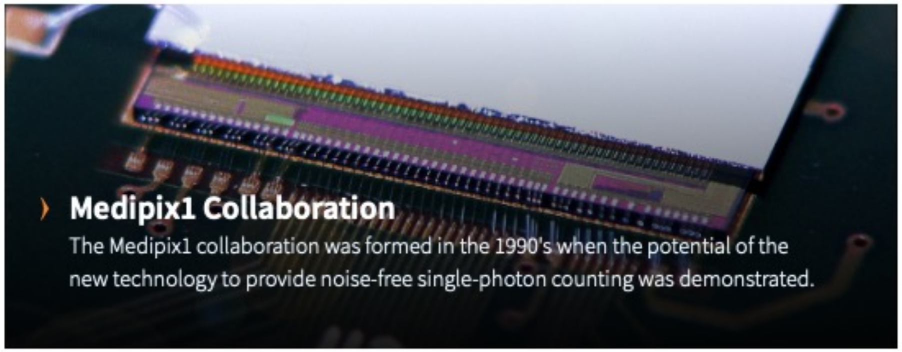


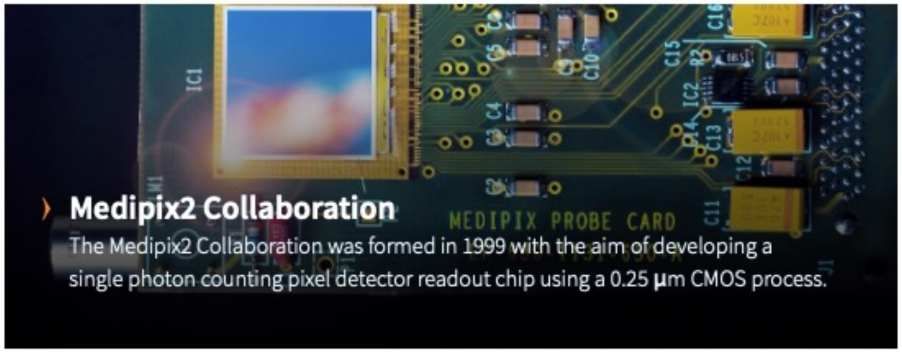
Development of a versatile PET scanner prototype, Polesel et al, IEEE MIC 2019 (Manchester), poster M-13-168

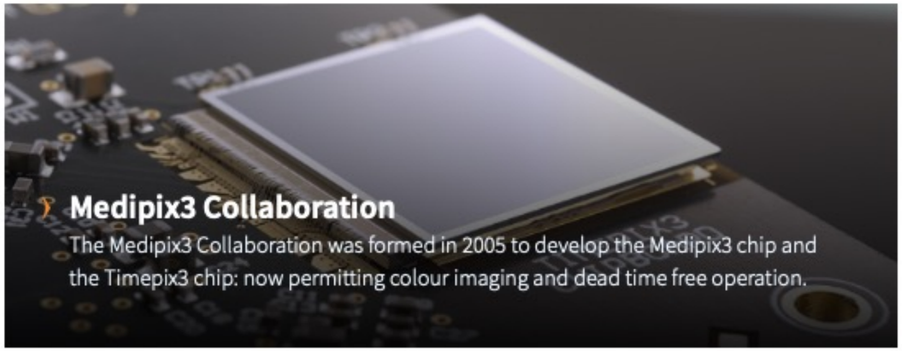
Etiennette Auffray (CERN)

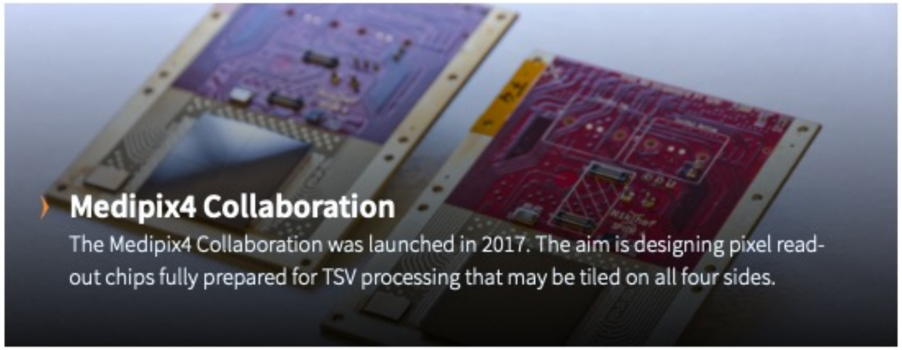
Medipix

A family of pixel detector read-out chips for particle imaging and detection developed by the Medipix Collaborations



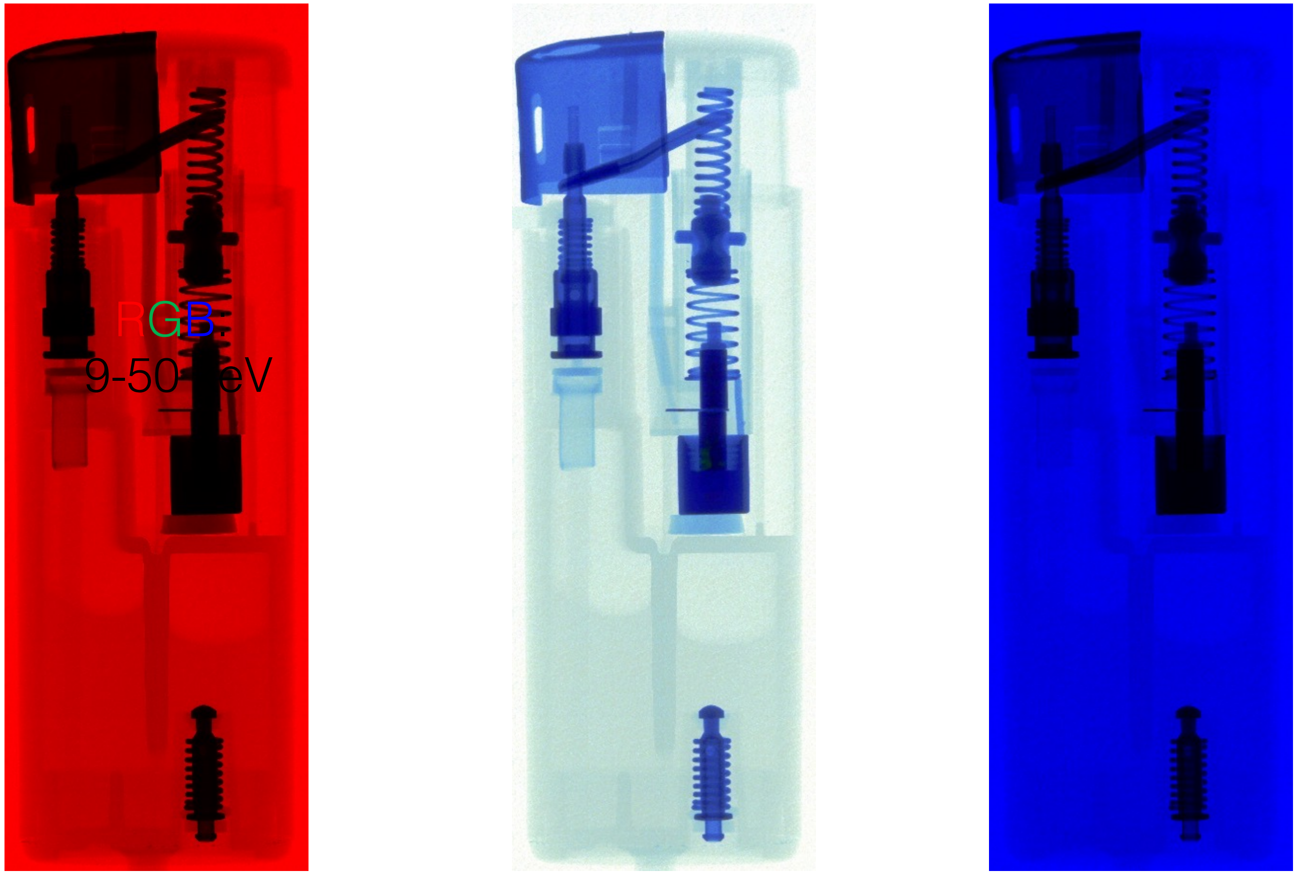






Michael Campbell (CERN)

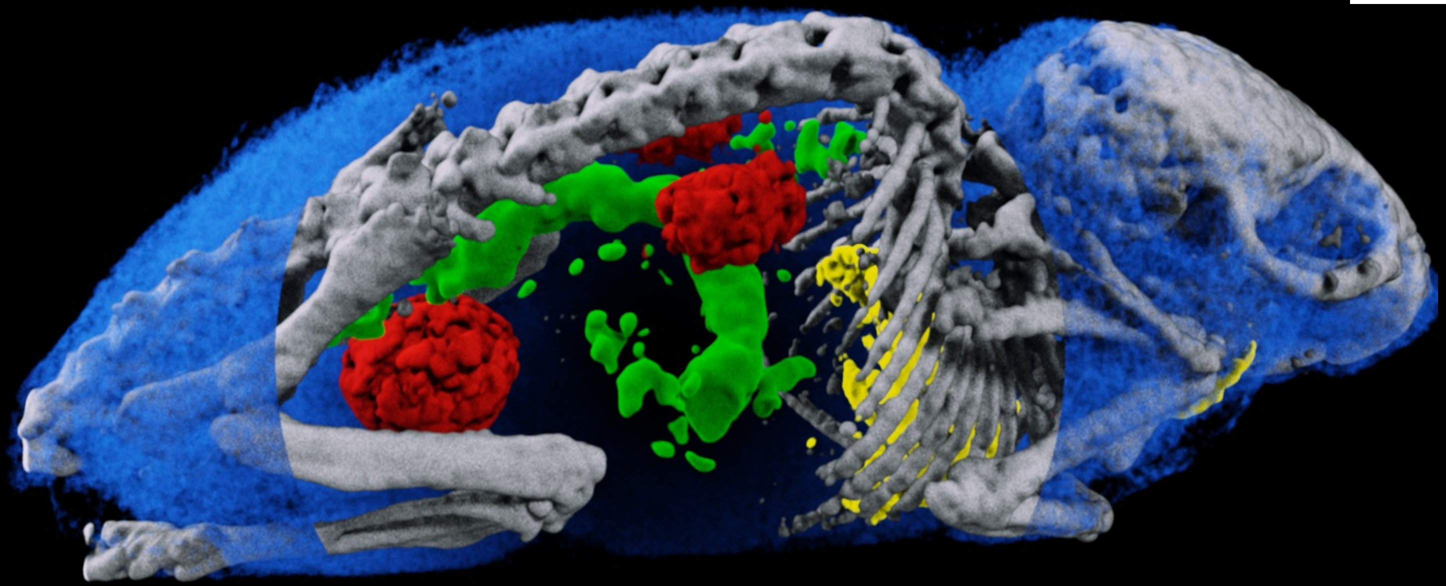
Colour x-ray of a lighter



S. Procz et al.

Spectroscopic information permits material separation

mars

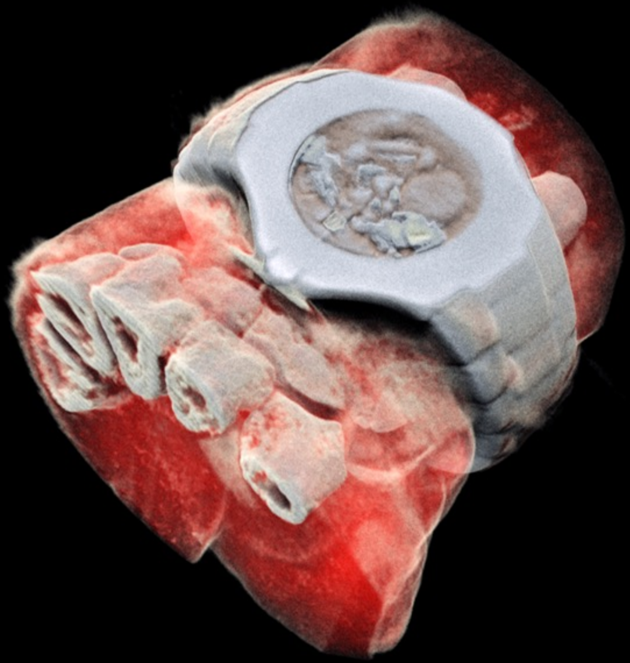


The water has been partly cut away to reveal the bone, gold, gadolinium and iodine

Images presented and the European Congress of Radiology, Vienna, March 2017.

A. Butler, University of Canterbury

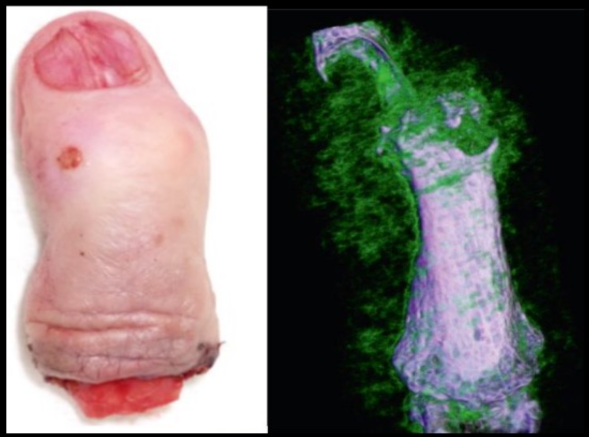
Fast forward to 2018



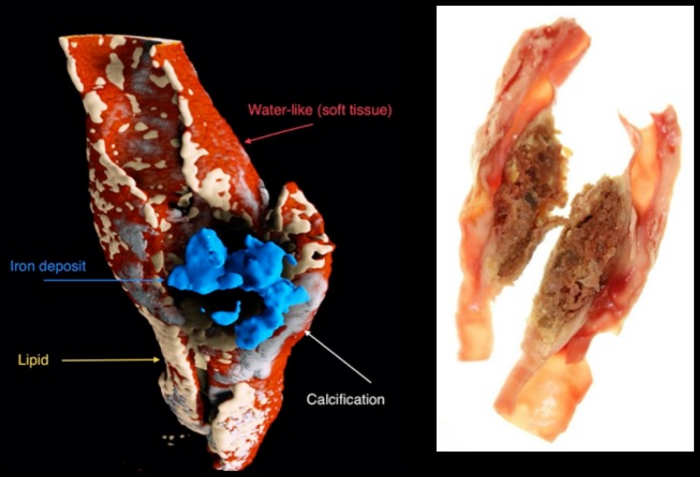
First 3D colour X-ray of a human using the Medipix3 technology developed at CERN

Molecular versus MARS

MARS - intrinsic information



Gout crystal characterisation
(Collab with CHUV)



Carotid plaque with quantitative measurements of fat, water, calcium, and iron

MARS SPCCT Imaging technology is in concept development for human use. It is not a product and is not cleared or approved by the US FDA or any other regulator for commercial availability outside of New Zealand

mars

Slide courtesy of Anthony Butler, University of Canterbury
Presented at 6th Workshop on Medical Applications of Spectroscopic X-ray Detectors, 29 Aug 2022, CERN

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

Articles

1. Dosanjh, M.K., From Particle Physics to Medical Applications, IOP Publishing, e-book, http://iopscience.iop.org/book/978-0-7503-1444-2/chapter/bk978-0-7503-1444-2ch1
2. https://cerncourier.com/a/the-changing-landscape-of-cancer-therapy/
3. Pistenmaa, D., Coleman, C.N., and Dosanjh, M.K.; Developing medical linacs for challenging regions: http://cerncourier.com/cws/article/cern/67710 (2017)
4. Dosanjh, M.K., Amaldi, U., Mayer, R. and Poetter, R.; ENLIGHT: European Network for Light Ion Hadron Therapy. DOI: 10.1016/j.radonc.2018.03.014

   https://www.sciencedirect.com/science/article/pii/S0167814018301464
5. Ugo Amaldi, et al . South East European International Institute for Sustainable Technologies (SEEIIST) Front. Phys., January 2021 | https://doi.org/10.3389/fphy.2020.567466
6. Angal-Kalinin D, Burt G and Dosanjh M. *Linacs to narrow radiation therapy gap,* CERN Courier, December 2021 https://cerncourier.com/a/linacs-to-narrow-radiotherapy-gap/
7. Manjit Dosanjh, Collaboration, the force that makes the impossible possible. Advances in Radiation Oncology 7(6):100966 DOI: 10.1016/j.adro.2022.100966

Many thanks to:

- U. Amaldi, CERN &TERA
- E. Blakely, LBNL, USA
- M Durante, GSI, Germany
- HIT, CNAO, MedAustro, PSI and ENLIGHT colleagues
- MARS BioImaging Ltd

Useful links

- *cern.ch/crystalclear*
- *cern.ch/enlight*
- *cern.ch/virtual-hadron-therapy-centre*
- *http://cds.cern.ch/record/1611721*
- *cern.ch/knowledgetransfer*
- *cern.ch/medipix*
- *cern.ch/twiki/bin/view/AXIALPET*
- *cern.ch/medaustron*
- *cern.ch/fluka/heart/rh.html*
- *www.fluka.org/fluka.php*
- *cern.ch/wwwasd/geant*
- *cern.ch/wwwasd/geant/tutorial/tutstart.html*
- www-pub.iaea.org/MTCD/Publications/PDF/TCS-42_web.pdf