

Particle accelerators for cancer therapy: overview and recent trends

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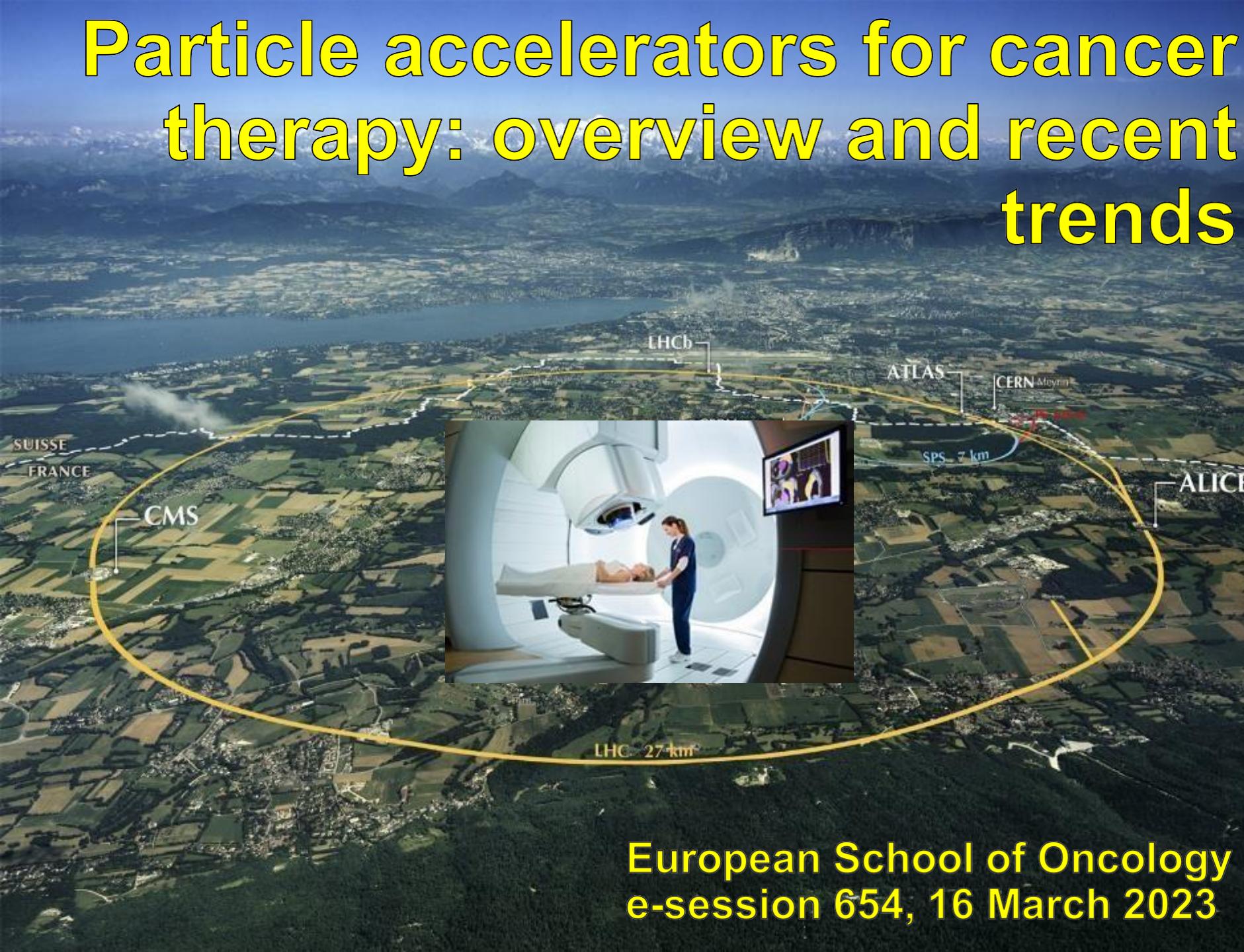
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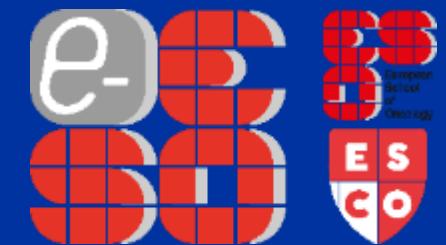
Particle accelerators for cancer therapy: overview and recent trends



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CERN, ATS/DO
Accelerator and
Technology Projects
and Studies



European School of Oncology
e-session 654, 16 March 2023



Particle accelerators for society

Particle accelerators are the largest scientific instruments ever invented by humanity.



They can break the atom, create new particles, recreate the conditions at the beginning of the universe...

The 27-km long Large Hadron Collider at CERN, Geneva, 100-m underground between Switzerland and France, is the largest particle accelerator ever built.



Over 35'000 particle accelerators are in operation worldwide. But only ~1% are used for fundamental research.

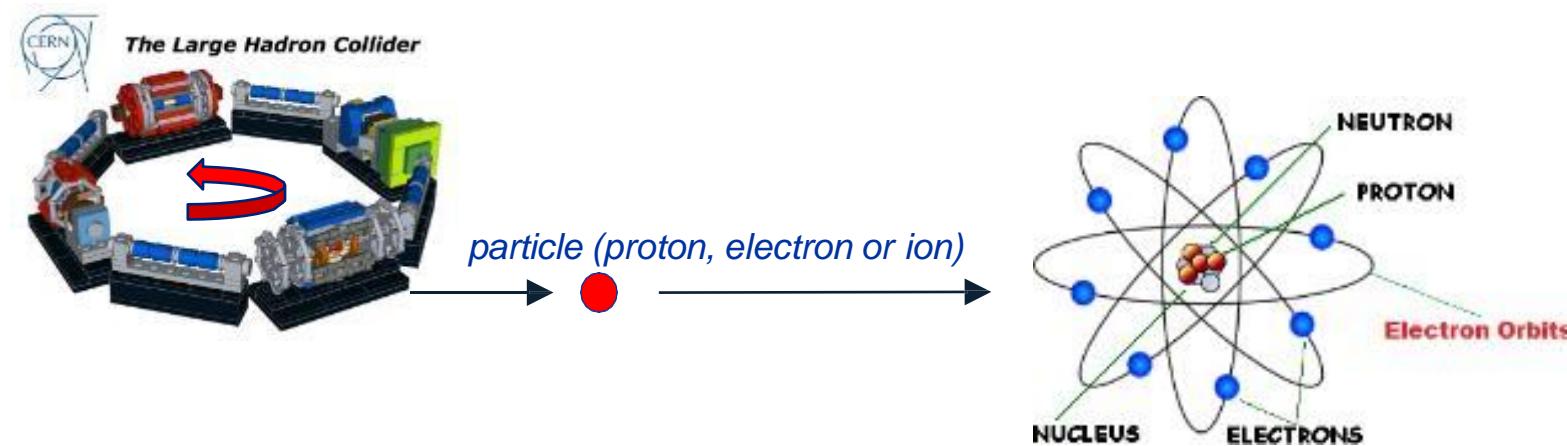
Medicine is the largest user of particle accelerators with more than 1/3 of all operating units!

Accelerators: our key to enter the subatomic world

Particle accelerators are our door to access the subatomic dimension... to study and exploit the atom and its components



When we extract particles from an atom (*protons, electrons, charged nuclei=ions*) and we accelerate them we concentrate **enormous amounts of energy in tiny volumes**



Where will this energy go?

An accelerated subatomic particle sent towards an atom will:

1. Deliver some **energy to the electrons**.
2. Deliver some **energy to the nucleus**

Electrons will come out of the atom (ionization) and nuclei can produce **radiation**

Accelerators can precisely deliver energy

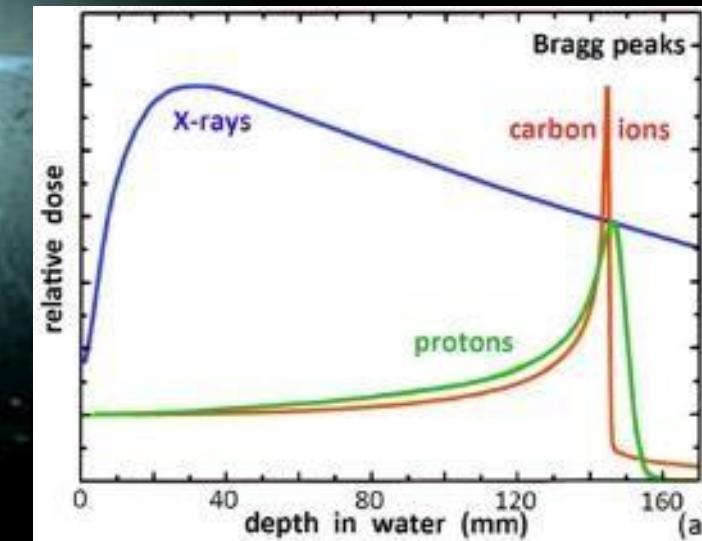
A «beam» of accelerated particles is like a small “knife” penetrating into the matter

- it produces breakings of chemical bounds, up to DNA breaking and cell killing.
- it can extract beams of secondary particles (X-rays or neutrons).

Energy is delivered to a precisely defined area (order of mm) that can be well inside matter or tissues (Bragg peak).

Particles can penetrate in depth (different from lasers!).

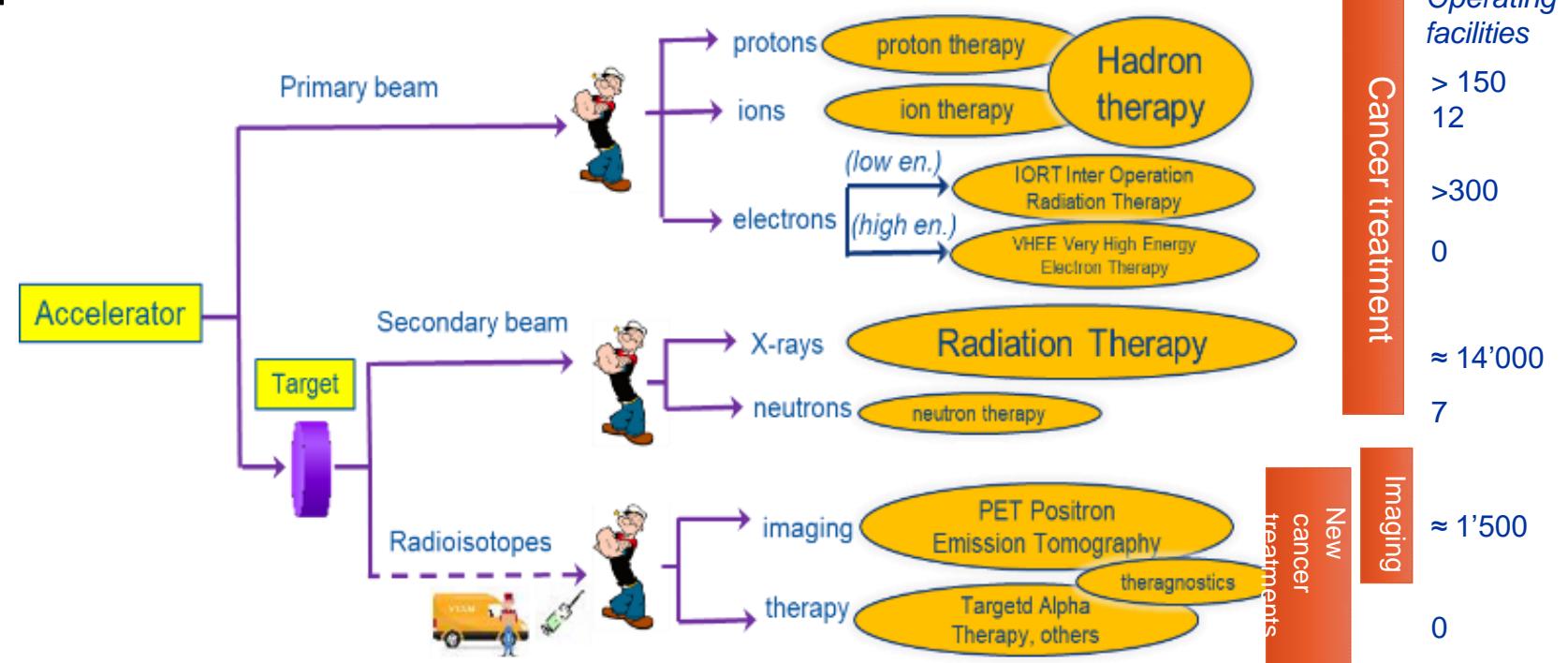
Particle beams are used in medical and industrial applications, e.g. cure cancer, kill bacteria, treat materials, dope semiconductors,...



But note: particle beams propagate **only in high vacuum**, they can travel in air only for very short distances !

Particle accelerators: a formidable tool for medicine

- Particles beams can break chemical bonds destroying **cells**, can generate **X-rays**, or can create unstable nuclei that produce **radiation** detectable from outside.
- The energy deposited by a proton or ion beam has a well-defined peak (**Bragg peak**) inside the body: can destroy the cancer cells with minimum damage to other tissues.
- Accelerators are the way to realise the old dream of a **bloodless surgery and imaging**: penetrate into the human body to **treat diseases** and to **observe internal organs** without using surgical tools.



≈ 16'000 particle accelerators operating for medicine worldwide, in cancer therapy and imaging

The most successful particle accelerator



Electron Linac (linear accelerator) for **radiotherapy** (X-ray treatment of cancer)

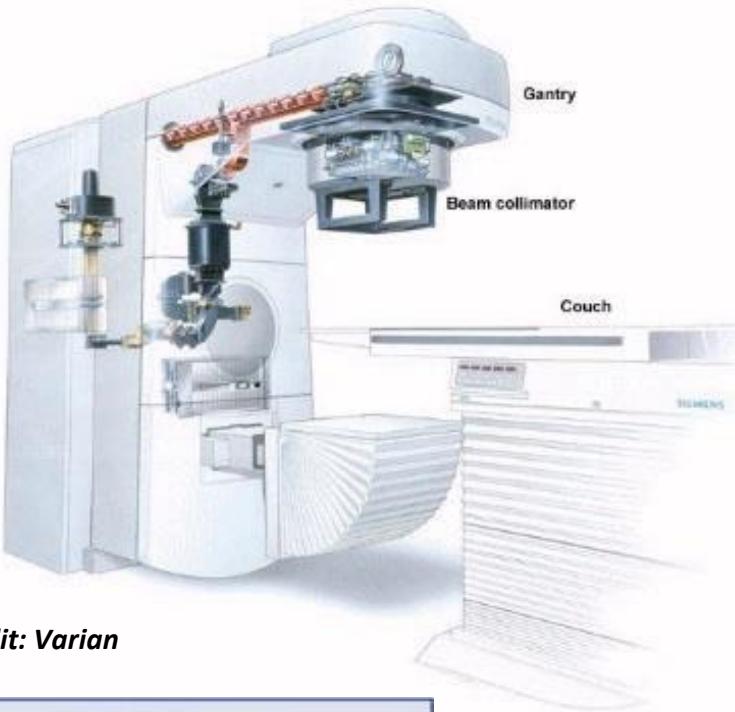
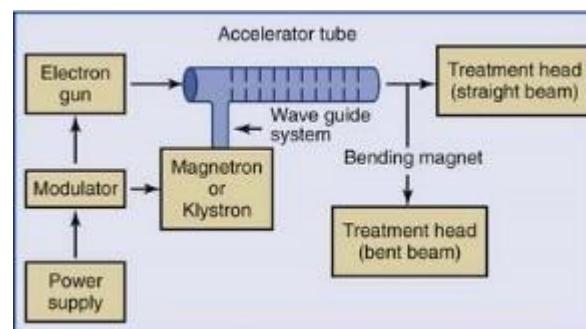


Image credit: Varian

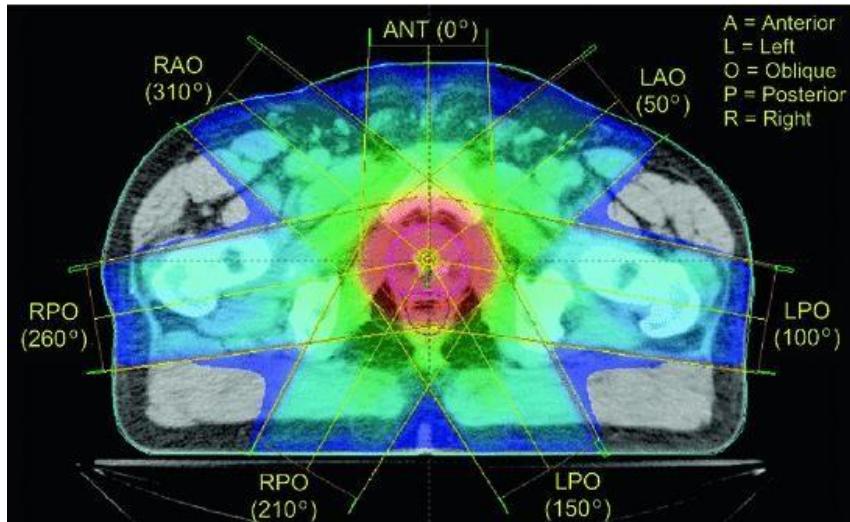


The radiotherapy linac accelerates electrons that are converted to X-rays on a metal block 5 – 25 MeV e-beam on Tungsten target

>14,000 in operation worldwide!

Modern radiotherapy

X-rays are used to treat cancer since last century. The introduction of the electron linac has made a huge development possible, and new developments are now further extending the reach of this treatment.



Combined imaging and therapy

Modern imaging techniques (CT computed tomography, MRI magnetic resonance imaging, PET positron emission tomography) allow an excellent 3D (and 4D, including time) modelling of the region to be treated.

The next challenge is to combine imaging and treatment in the same device.

Accurate delivery of X-rays to tumours

To spare surrounding tissues and organs, computer-controlled treatment methods enable precise volumes of radiation dose to be delivered. The radiation is delivered from several directions and transversally defined by multi-leaf collimators (MLCs).



Image credit: Varian

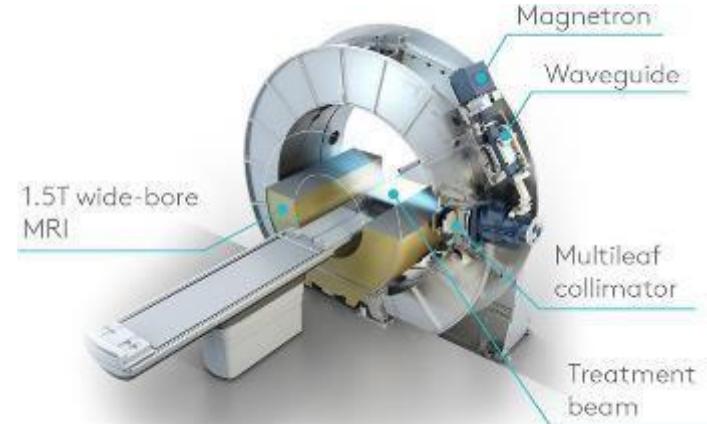


Image credit: Elekta

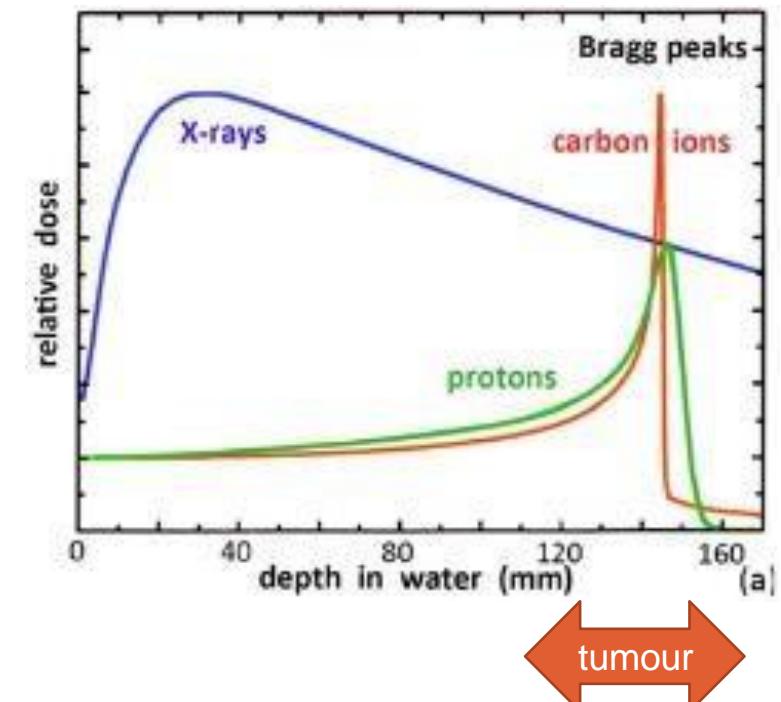
Treating cancer directly with particle beams

- **Goal:** treat the >10% “not curable” cancers, usually large, deep seated, radioresistant.
- **Particle Therapy** (protons or ions).
- **Challenge:** Deposit enough dose on the cancer, sparing the surrounding tissues.

In clinic, particle therapy has already shown benefits in treatment of:

- **paediatric** oncological malignancies
- **brain and head and neck** region tumours
- other localizations in **vicinity of critical vital organs**
- **radioresistant** tumours as gliomas and sarcomas (heavy ions).

Hadron Therapy (or Particle Therapy) using protons or ions allows concentrating the radiation dose on the tumour, thanks to the «Bragg peak». More **expensive** than X-ray therapy, is rapidly growing thanks to new compact industry-made proton accelerators.



Clinical perspective: Indications for particle therapy

Group I

Based on established clinical data:

- ocular tumors (also intra-ocular melanomas)
- skull base tumors (chordoma, chondrosarcoma)
- primary or metastatic cancer in spine
- hepatocellular tumors
- primary and benign paediatric tumors (both radical and palliative)
- patients with genetic syndromes (*decrease integral dose/irradiated volume*)
- malignant and benign primary CNS tumors
- tumors in sinuses
- non-metastatic retroperitoneal sarcoma
- re-irradiation

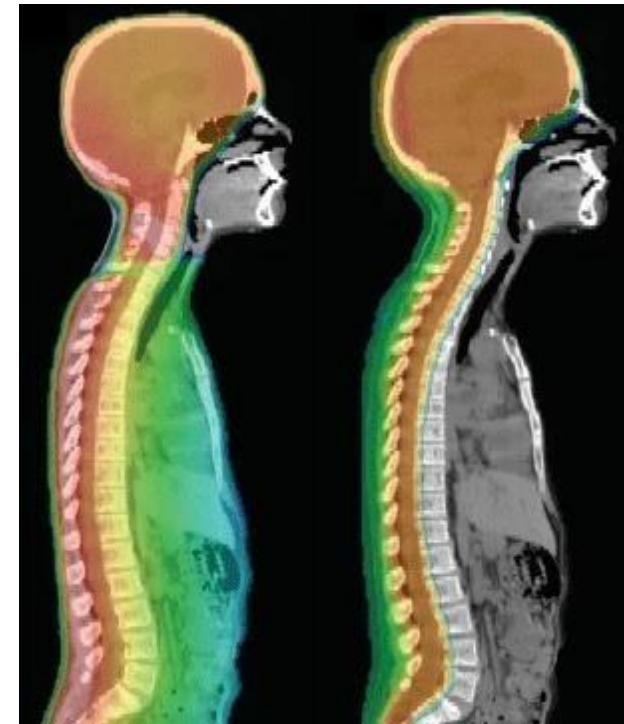
Source: ASTRO Model Policy on Proton Beam Therapy

Group II

Clinical data and effectiveness comparisons still to be based in ongoing clinical trials

- head&neck tumors
- thorax: non-metastatic primary lung cancer, esophageal tumors and mediastinal lymphoma
- abdomen: non-metastatic primary pancreatic cancer, gallbladder and adrenal gland cancers
- pelvis: rectal and anal cancers, urinary bladder and cervical tumors
- non-metastatic prostate cancer
- breast cancer

10

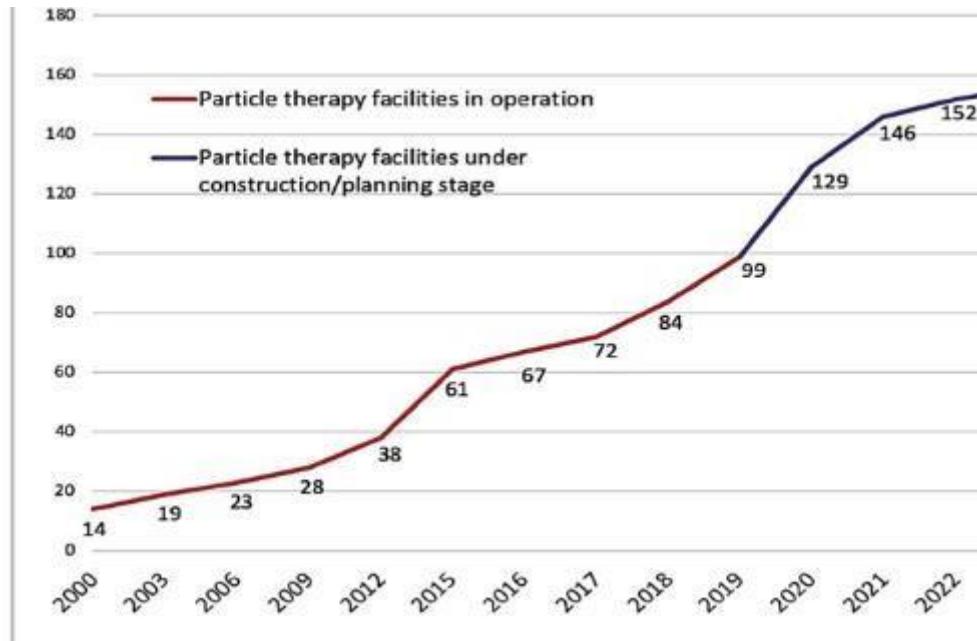


Source: Rowe LS, Krauze AV, Ning H, Camphausen KA, Kaushal A. Optimizing the Benefit of CNS Radiation Therapy in the Pediatric Population—PART 2: Novel Methods of Radiation Delivery. *Oncology* (Williston Park). 2017 Mar 15;31(3):224-6, 228.

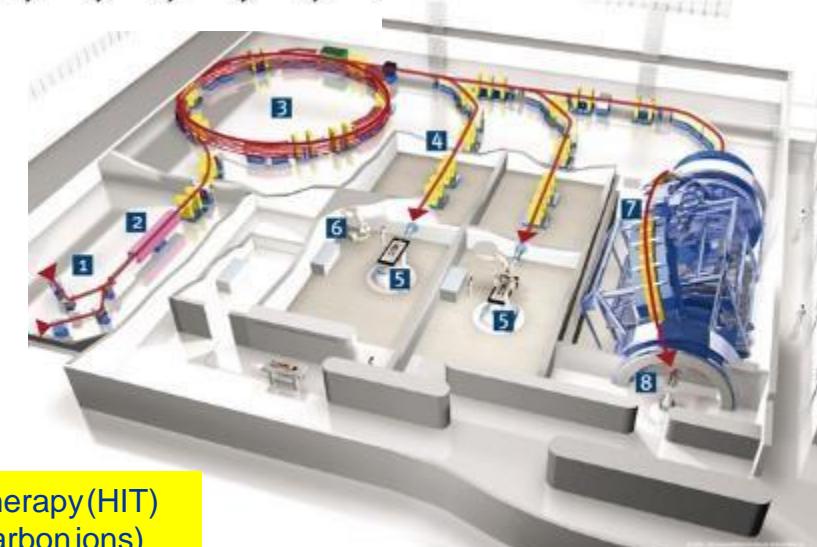
Acknowledgements: K. Palskis, RTU/CERN

The rise of particle therapy

- Proposed 1946, first **experimental treatment** Berkeley 1954.
- First **hospital-based** proton treatment facility in 1993 (Loma Linda, US).
- First treatment facility with **carbon ions** in 1994 (HIMAC, Japan).
- Treatment in Europe at **physics facilities** from end of '90s.
- First dedicated European facility for **proton-carbon ions** in 2009 (HIT).
- From 2006, **commercial proton therapy** accelerators (mostly cyclotrons) come to market.
- In 2022, 5 **competing vendors** for protons, 1 for carbon ions. A total of 152 centres worldwide.

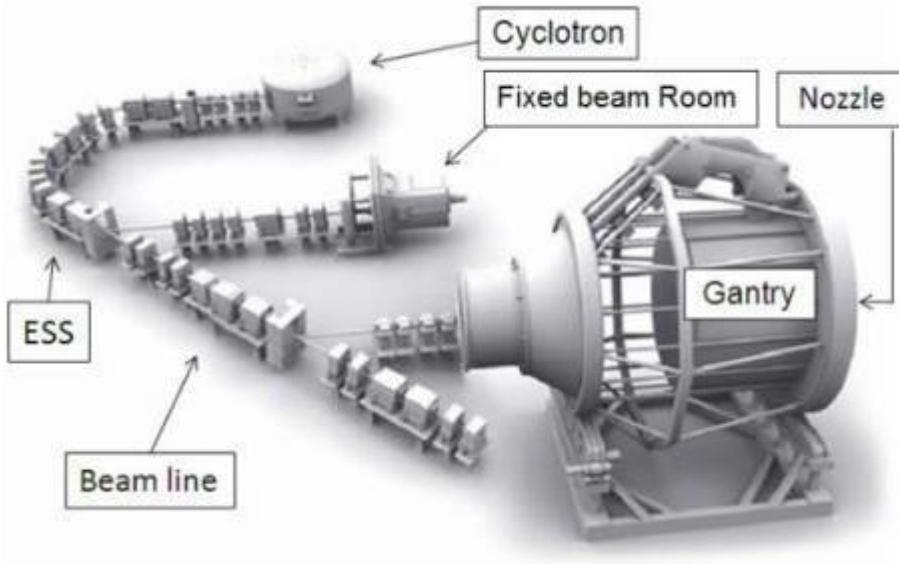


Source: ptcog.com



The Heidelberg Ion Therapy(HIT) facility (protons and carbon ions)

Proton therapy accelerators: cyclotrons

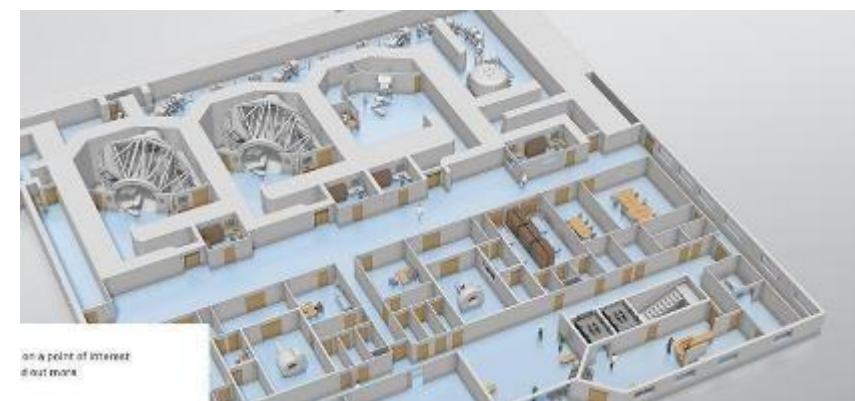


*ProteusOne and
ProteusPlus turn-
key proton
therapy solutions
from IBA
(Belgium)*

At present, the cyclotron is the best accelerator to provide proton therapy reliably and at low cost (4 vendors on the market).

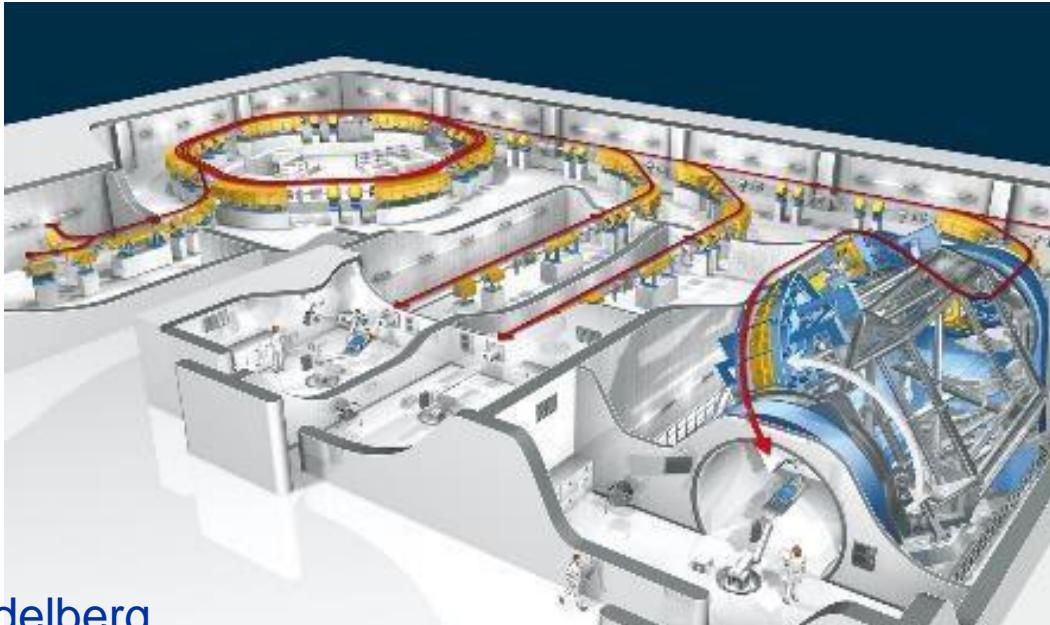
Critical issues with cyclotrons:

1. Energy modulation (required to adjust the depth and scan the tumour) is obtained with slow sliding plates that become rapidly radioactive → need large shielding.
2. Very effective for protons, become complex and expensive for heavier particles.

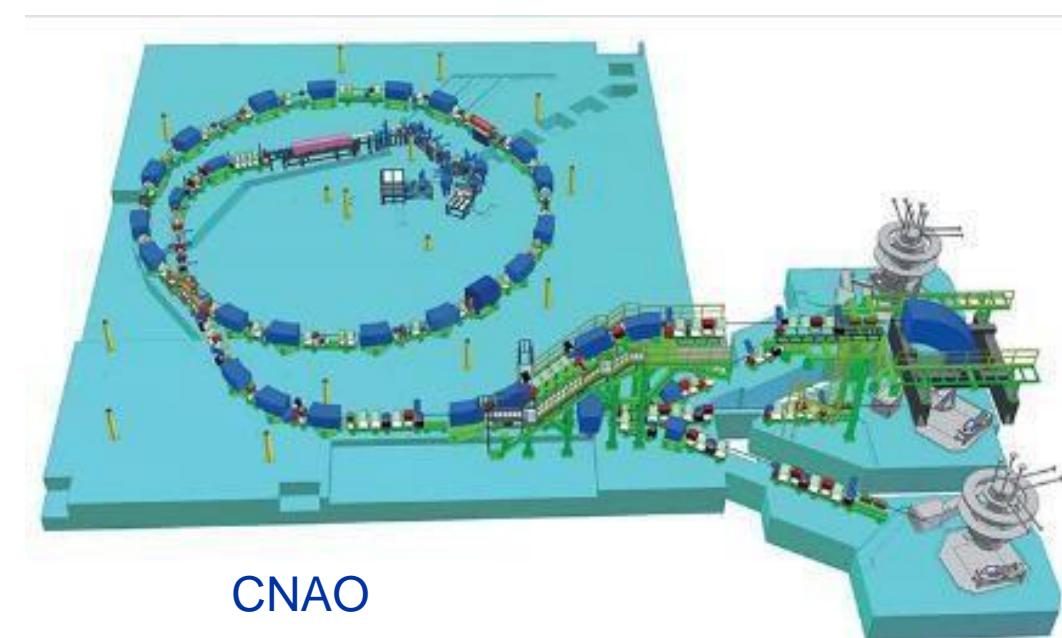


Synchrotrons for proton and ion therapy

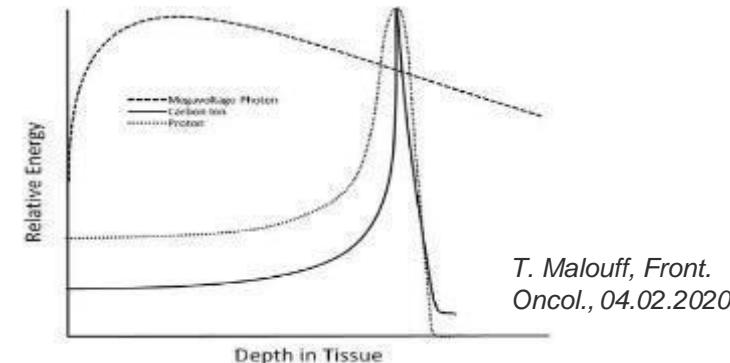
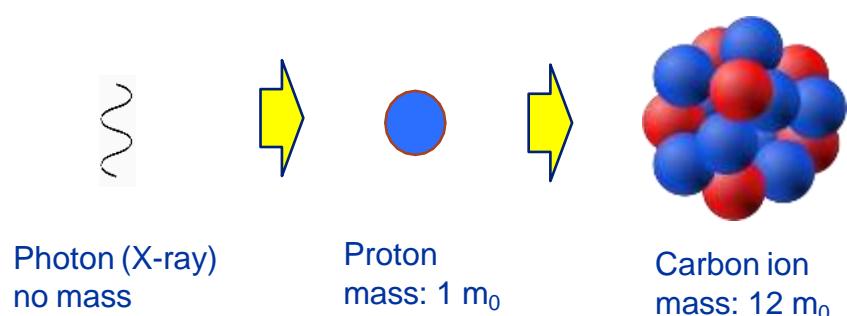
- The Loma Linda Medical Centre in US (only protons) and the ion therapy centres in Japan have paved the way for the use of synchrotrons for combined proton and ion (carbon) therapy).
- 2 pioneering initiatives in Europe (ion therapy at GSI and the Proton-Ion Medical Machine Study PIMMS at CERN) have established the basis for the construction of 4 proton-ion therapy centres: Heidelberg and Marburg Ion Therapy (HIT and MIT) based on the GSI design, Centro Nazionale di Terapia Oncologica (CNAO) and Med-AUSTRON based on the PIMMS design.



HIT Heidelberg

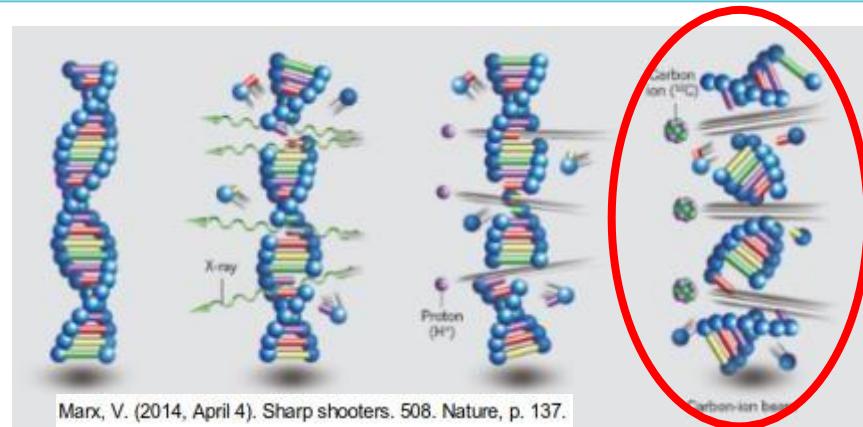


Ion therapy: from photons to protons to ions



Advantages of cancer therapy with ions heavier than protons:

- **Higher energy deposition** and ionisation per length generates non-reparable **double-strand DNA breakings**.
- Energy deposition more precise, with lower straggling and scattering
- Effective on **hypoxic radioresistant tumours**.
- Opportunities from **combination with immunotherapy** to treat diffused cancers and metastasis.



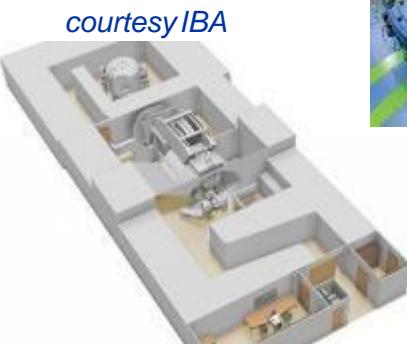
- Only carbon ions licensed for treatment (for historical and practical reasons)
- First patient treatments with carbon ions only in 1994: ion therapy is still in its infancy !

Comparing accelerator designs

Ions deliver more energy to the tissues but **need more energy to enter the body** → factor 2.8 in accelerator diameter going from protons to carbon



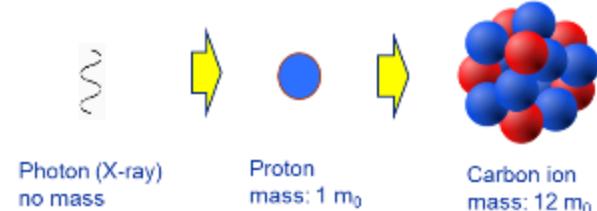
Linac, X-rays
~50 m²
~few M€



Cyclotron, protons
~500 m²
~few 10 M€

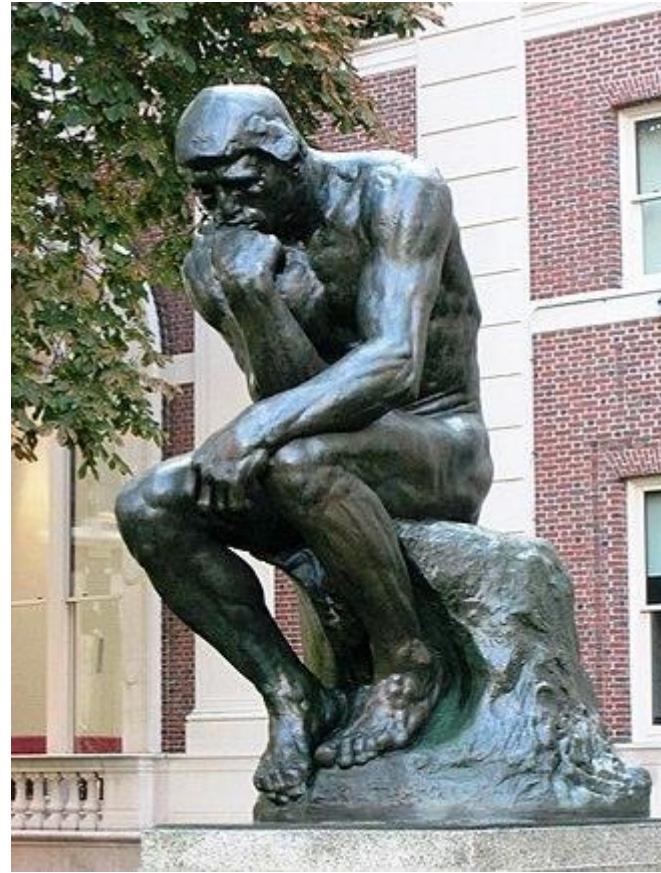


Synchrotron, heavy ions
~5,000 m²
~200 M€



In general, the heavier the particle the higher the energy that we need to enter the body, and the larger the accelerator required to produce the beam!

New trends in particle therapy of cancer



A. Rodin, *Le penseur*
(Wikimedia)

New trends 1: FLASH irradiation

- Treating tumours delivering radiation in short pulses at ultra-high dose rates appears to reduce toxicity to healthy tissue while maintaining tumour control.
- Dose delivered in **fractions of a second instead of several minutes.**
- First observed in the 70's, rediscovered in 2014 (Favaudon and Vozenin), 1st treatments 2014-18, 1st clinical trial in 2020.

The hottest topic in radiation therapy!

Several theories to explain the experimental data, all somehow related to Oxygen depletion and time to restore Oxygen in cells.

Does not work with photons (X-rays) at standard parameters

Being tested worldwide with electrons and protons.

To be tested with carbon ions.

Challenges:

- Dosimetry
- Deep tumours, large volumes

Illustration of the Flash-RT effect in pig : A major decrease of radiation side effects



First human patient – skin cancer treated with 10 MeV-range electrons

Accelerators for FLASH therapy

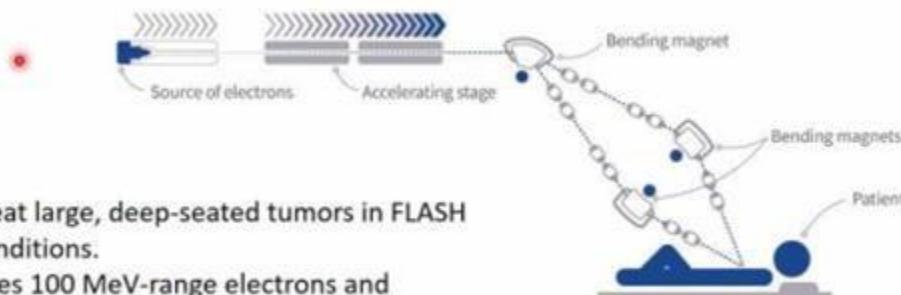
Three collaborations ongoing for the construction of the first accelerator for treating deep seated tumours with **FLASH electron beams** (100 MeV):

- CERN-CHUV-THERYQ using high-frequency technology from particle physics
- Curie Institute-THALES using conventional technology
- Rome University-INFN-(company) using intermediate frequency technology

Clinical trials with **proton FLASH** ongoing



CLIC technology for a FLASH facility being designed in collaboration with CHUV



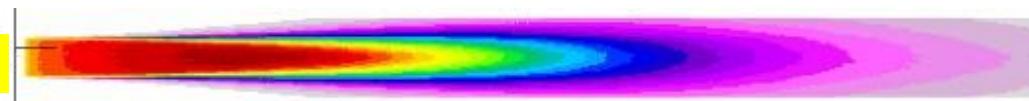
Treat large, deep-seated tumors in FLASH conditions.

Uses 100 MeV-range electrons and optimized dose delivery.

Compact to fit on a typical hospital campus.

Courtesy W. Wuensch, CERN

Dose distribution for high-energy electron beam

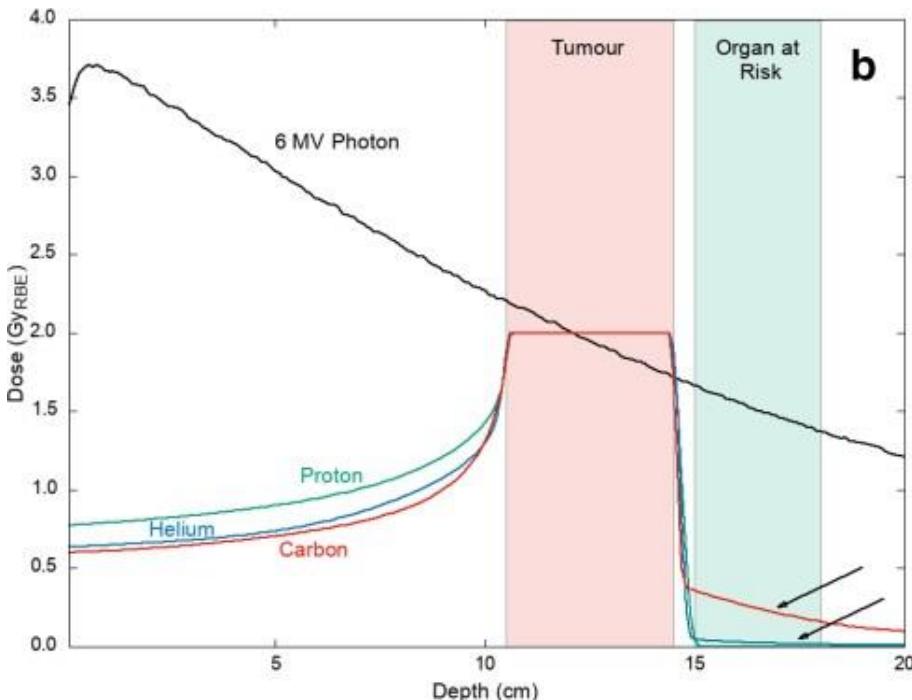


Balloon debate at FLASH conference 2022:

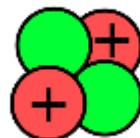
Photon, electrons or protons, what has the best long-term potential for FLASH for clinical application?

- 1st vote: 37% protons, 33% electrons, 30% photons.
- 2nd vote: 53% electrons, 47% protons.

New tends 2: helium beams for cancer



Spread-out Bragg peak for proton, helium, carbon compared to X-rays
(K. Kirkby et al., Heavy Charged Particle Beam Therapy and related new radiotherapy technologies, <https://doi.org/10.1259/bjr.20200247>)



- Helium ions (2 protons, 2 neutrons): treatment tried in Berkeley in the 70's then stopped.
- Recent years have seen a surge of interest for He in the European ion centres, **first patient treated in September 2021 at HIT Heidelberg.**
- **Clinical trials** starting, will be soon licensed for treatment.
- An accelerator designed for **helium treatment** can easily produce **protons for standard treatment**, and be used for **research with helium and heavier ions.**

Advantages:

- reduced lateral **scattering** w.r.t. protons, better conformality.
- lower **fragmentations** than carbon, lower dose after tumour.
- lower **neutron dose** than protons or carbon, less risks in paediatric patients,
- could treat **some radioresistant** tumours at lower cost than carbon.
- might be better suited for **FLASH** than other ions.

Phys. Med. Biol. 67 (2022) L57R02

<https://doi.org/10.1088/1361-6560/ac65d3>

Physics in Medicine & Biology

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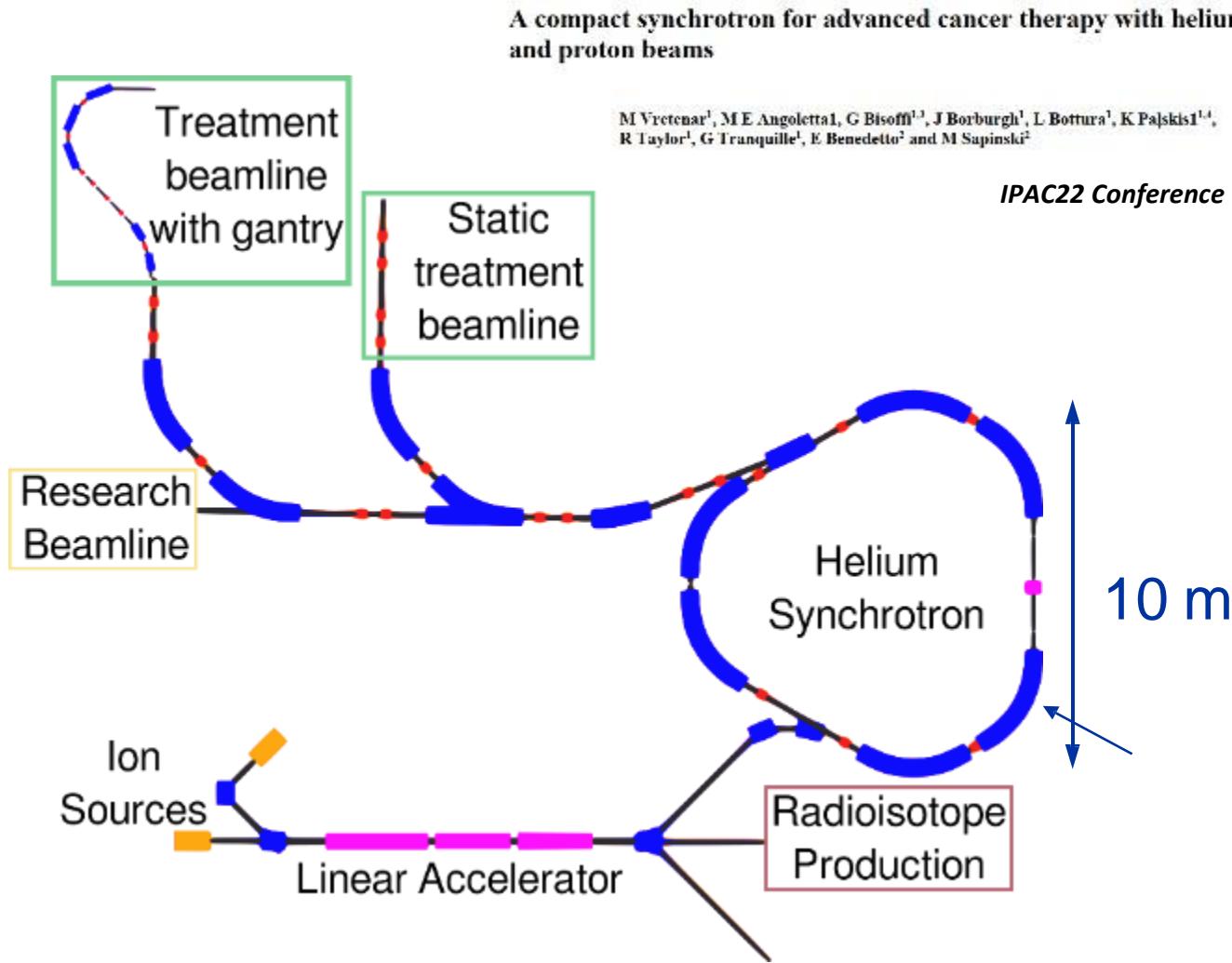
TOPICAL REVIEW

Roadmap: helium ion therapy

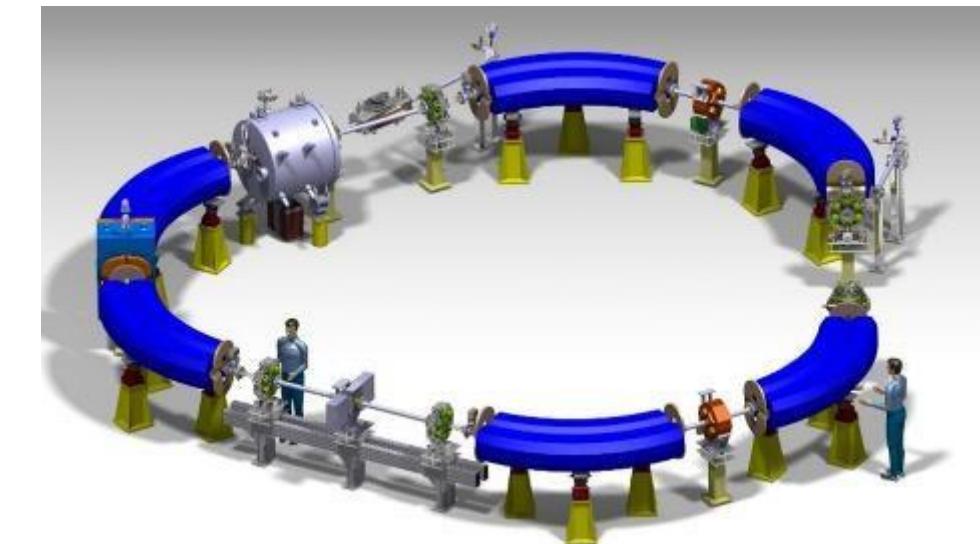
Andrea Mairani^{1,2,3,4}, Stewart Mein^{1,2,4,5}, Eleanor Blakely⁶, Jürgen Debuss^{1,3,4,5,7}, Marco Durante^{1,2,1}, Alfredo Ferrari¹, Hermann Fuchs^{2,3,10}, Dietmar Georg^{5,10}, David R Grosshans¹¹, Fada Guan^{1,12,13}, Thomas Haberer¹, Semsi Harrabi^{1,14,15}, Felix Horst¹, Taku Imanawa^{1,16,17}, Christian P Kurger^{1,18,19}, Radhe Mohan¹, Harald Paganetti^{1,2,13}, Katia Parodi^{1,20}, Paola Sala¹⁷, Christoph Schuy¹, Thomas Tessonnier¹, Uwe Titt¹¹ and Ulrich Weber¹

Recently published (August 2022)
helium ion therapy Roadmap

Layout of a facility for treatment and research with helium and proton beams

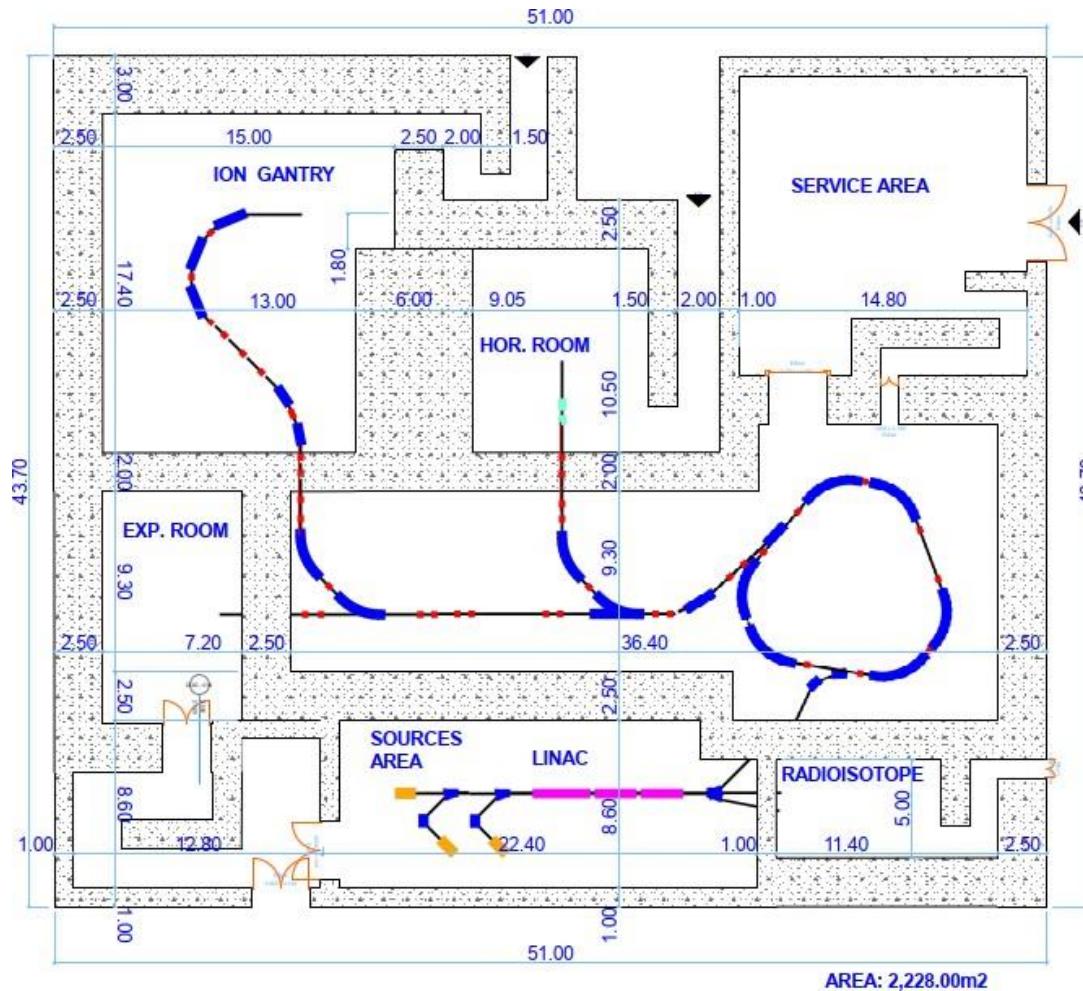


- Two beamlines for treatment, one for research.
- Rotating superconducting gantry.
- Injector with parallel radioisotope production
- Surface $\sim 2,000 \text{ m}^2$



Small triangle-shaped synchrotron with FLASH extraction capability

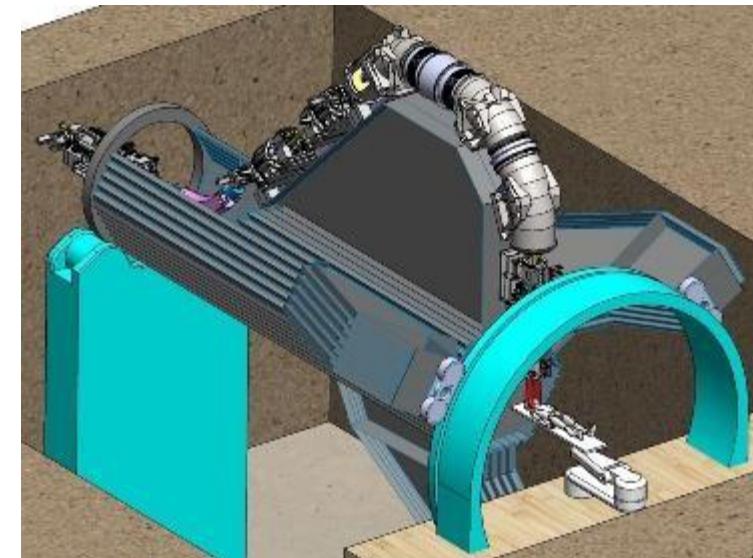
The Advanced Particle Therapy Centre for the Baltic States



Proposed for construction
as a a cooperation of
Baltic States (Estonia,
Latvia, Lithuania).



Draft concept-paper
Advanced Particle Therapy Center for the Baltic States



Courtesy L. Piacentini, RTU/CERN

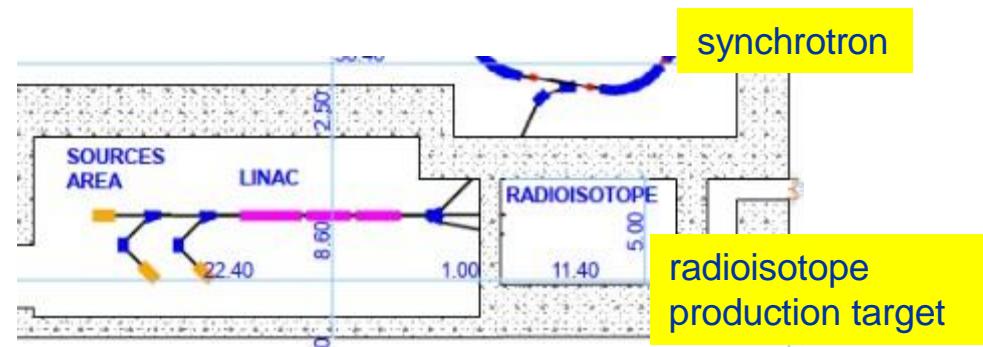
The rotating
superconducting gantry
under development
within the EU project
HITRIPplus.

Linear accelerator for radioisotope production

Coupling particle therapy with nuclear medicine

The linear injector of a helium therapy synchrotron can be used to produce radioisotopes for imaging and therapy, in parallel to operation for therapy.

Linear accelerators are more efficient and less demanding than conventional cyclotrons for operation with helium ions.



Example: Targeted Alpha Therapy with Astatine 211

Alpha particles = Helium ions (2 protons, 2 neutrons) are the most dangerous radiation, short range and high toxicity!

The linear injector produces alpha-emitting therapeutic isotopes like ^{211}At that are attached to antibodies and injected to the patient. The targeting vector accumulates the isotopes in the cancerous tissues where they selectively deliver their dose.

Advanced experimentation, promising for solid or diffused cancers (leukaemia).

| Radioisotope | Usage |
|-----------------|---------------------------|
| Scandium-43, 44 | Diagnostic – PET |
| Cobalt-57 | Diagnostic – SPECT |
| Copper-64 | Theranostic (β^-) |
| Copper-67 | Theranostic (β^-) |
| Indium-111 | Diagnostic – SPECT |
| Tin-117m | Theranostic (β^-) |
| Samarium-153 | Theranostic (β^-) |
| Rhenium-186 | Theranostic (β^-) |
| Astatine-211 | Therapeutic (α) |

Courtesy K. Palskis, RTU/CERN

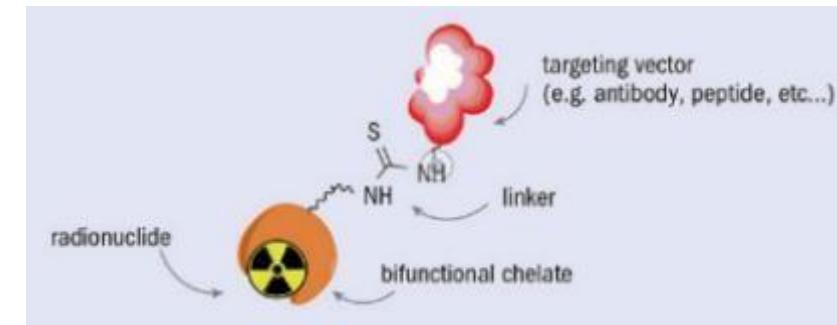
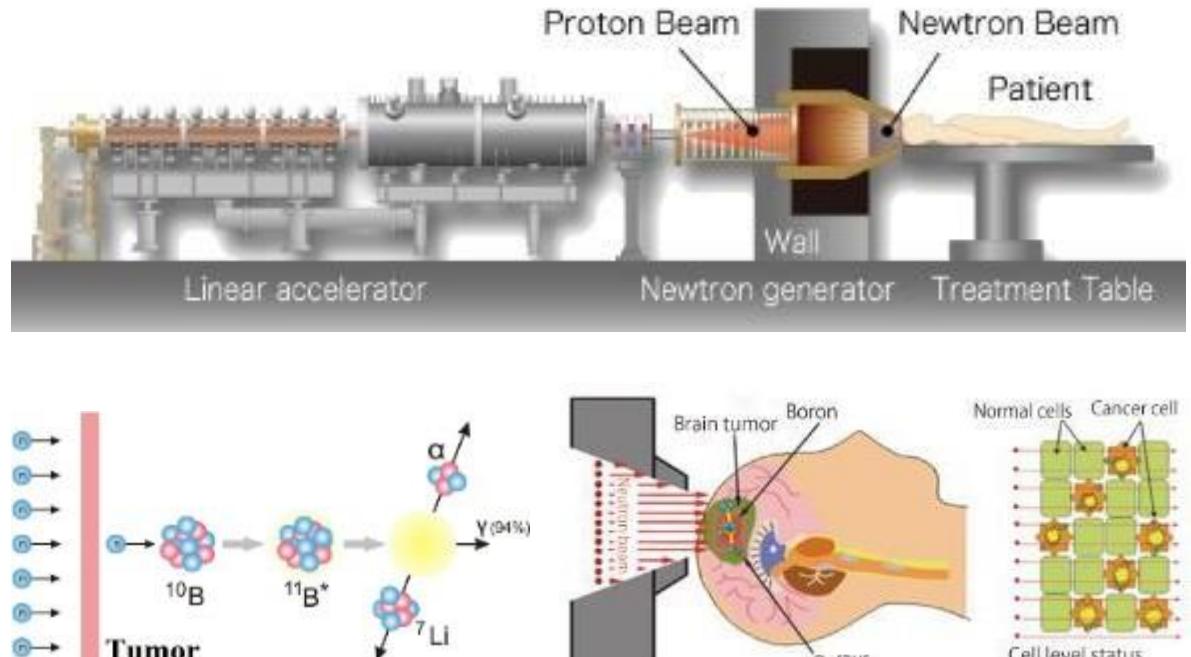


Image credit: Caterina F Ramogida, CERN Courier

Boron Neutron Capture Therapy (BNCT)

Boron Neutron Capture Therapy

- Alternative way for targeted delivery of strong doses of alpha-particles to brain tumours (e.g. glioblastoma) and others (e.g. malignant melanoma).
- A boron-containing drug (^{10}B) designed to localise in cancerous cells is injected into the patient.
- A beam of low-energy neutrons is directed at the cancerous sites where it activates the boron, that decays producing alpha particles only in the region targeted by the particle beam.
- Neutron production requires intense proton beams.



- In use in Japan (7 centres), clinical trials ongoing
- In Europe, one centre in construction in Finland and **two centres in design/construction in Italy**: at the Italian particle therapy centre CNAO in Pavia, and at the Caserta Hospital

Looking into the future

Radiation Therapy, Proton Therapy, Ion therapy, FLASH, Targeted Alpha Therapy, Immunotherapy, ...

What is going to be the future landscape of our tools to fight cancer ?

A few key concepts:

- Medicine is becoming the **technology driver of XXIst century**. The development of sophisticated medical tools in particular to fight cancer is generating a fantastic progress in all technologies. This progress is going to continue (think of the progress in the last 50 years).
- The techniques that we are studying are becoming **complementary**, with different cost and range of applications. The most likely scenario is that they will coexist, providing oncologists with a range of instruments to fight different types of cancer (personalized medicine).
- The **therapeutic impact systems**, controlled by **artificial intelligence** and **quantum mechanics** can act at the **atomic and molecular level**. **Therapy and diagnostics** are going to be more and more integrated, in the device or via “theragnostic” approaches.

Thank you for your attention!



Particle accelerators will be crucial actors in this technological evolution – what is advanced medicine today will be standard clinical practice tomorrow!

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