Innovative radiotherapies: therapeutic strategies and physical issues

Rachel DELORME (LPSC, Grenoble)

rachel.delorme@lpsc.in2p3.fr

Contributors:

Anne-Marie FRELIN (Ganil, Caen)

Thanks to Charlotte ROBERT (IGR, Villejuif) and Denis Dauvergne (LPSC) for sharing some slides

GDR Groupement de recherche MI2B Outils et méthodes nucléaires pour la lutte contre le cancer

Presentation outline

➢ Introduction to radiation therapy and fundamental notions

- **Introduction to cancer treatment**
- **Use of ionizing radiation** : physical interactions and Radiobiological aspects on living matter

➢ Therapeutic strategies to improve cancer treatments

- **Differential effect**: find the good balance between tumor control and tissue preservation
- **X-ray radiation therapy** : technological evolution improving the dose conformation to the tumor
- **Use of different particles**: **Hadrontherapy** (protons, carbon ions…), high energy electrons (**VHEE**), neutrons…
- **Play on dose delivery**: temporal fractionation of the dose, very-high dose-rate radiation (**FLASH** therapy), spatial fractionation of the dose (**Grid, MBRT, MRT**)
- **Combined radiotherapies** (with molecular vector): **radionuclide therapy** (alpha targeted therapy), **BNCT**, **nanoparticle-enhanced** radiotherapy…

➢ Conclusions

Presentation outline

- Introduction to radiation therapy and fundamental notions
  - **Introduction to cancer treatment**
  - **Use of ionizing radiation** : physical interactions and Radiobiological aspects on living matter

- Therapeutic strategies to improve cancer treatments
  - **Differential effect**: find the good balance between tumor control and tissue preservation
  - **X-ray radiation therapy** : technological evolution improving the dose conformation to the tumor
  - **Use of different particles**: **Hadrontherapy** (protons, carbon ions…), high energy electrons (**VHEE**), neutrons…
  - **Play on dose delivery**: temporal fractionation of the dose, very-high dose-rate radiation (**FLASH** therapy), spatial fractionation of the dose (**Grid, MBRT, MRT**)
  - **Combined radiotherapies** (with molecular vector): **radionuclide therapy** (alpha targeted therapy), **BNCT**, **nanoparticle-enhanced** radiotherapy…

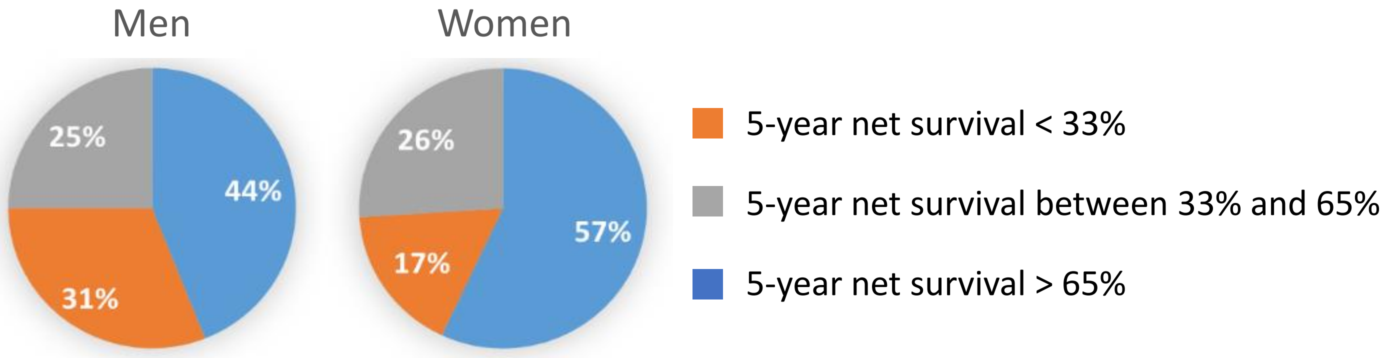
- Conclusions

Cancer figures for France

- Population aging → First cause of death in France
  157 400 deaths in 2018 (over ~430 000 new cases per year, https://www.e-cancer.fr/)

- Significant progress in prevention, early diagnosis and treatment:
  Mortality rate: **-18%** between 2005 and 2018

- Heterogeneity between different locations and cancer types:



Lung: about 10% of incidences
5-year net survival = 17%
Brain: about 1.4% of incidences
5-year net survival = 20%

Prostate: 25% of incidences (♂)
5-year net survival = 94%
Breast: 36% of incidences (♀)
5-year net survival = 88%

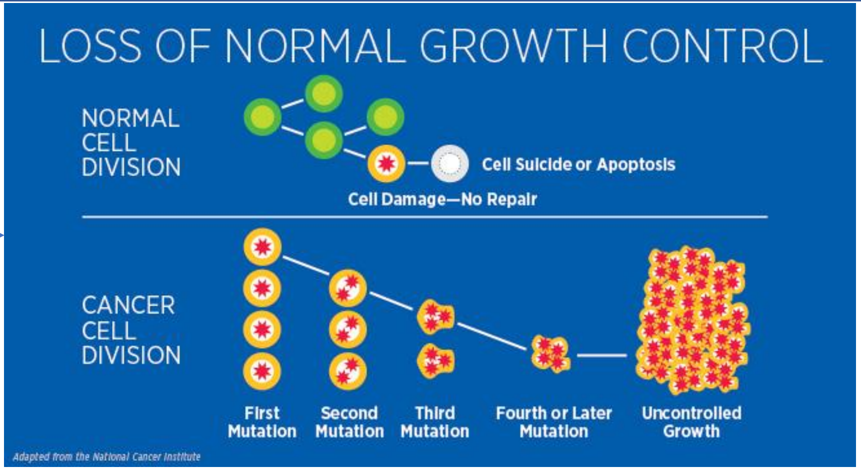
Importance of current and new treatments

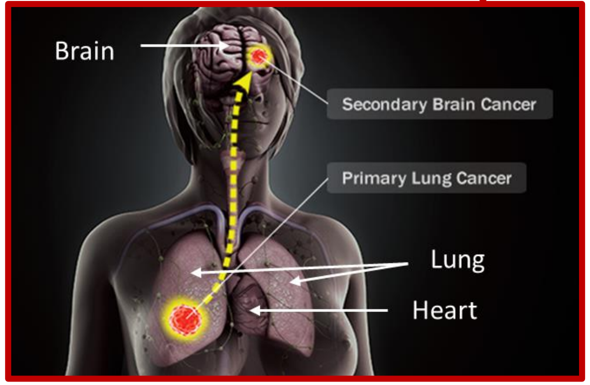
- Efficiency ++
- Toxicity -
  living well after cancer

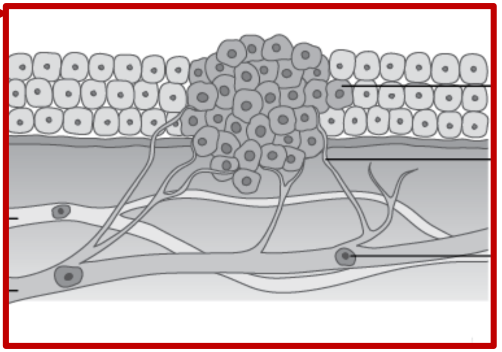
It cannot exist only one universal cancer treatment

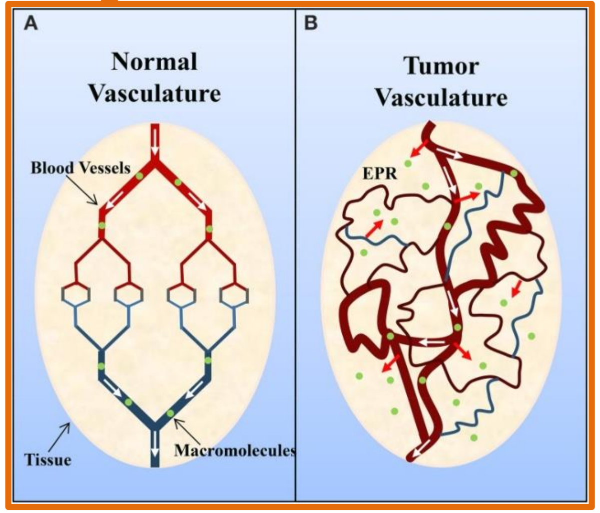
What is a cancer ?(very roughly)

- What is a cancer ?
  - ✓ ~430 000 new case /year in France, ~150 000 death.
  - **Abnormal cell division** → mutation
  - **Growth of the tumor** → angiogenesis to get oxygen, immature vasculature
  - **Propagation of a tumor** → extension to lymphatic nodes or blood vessels = metastasis



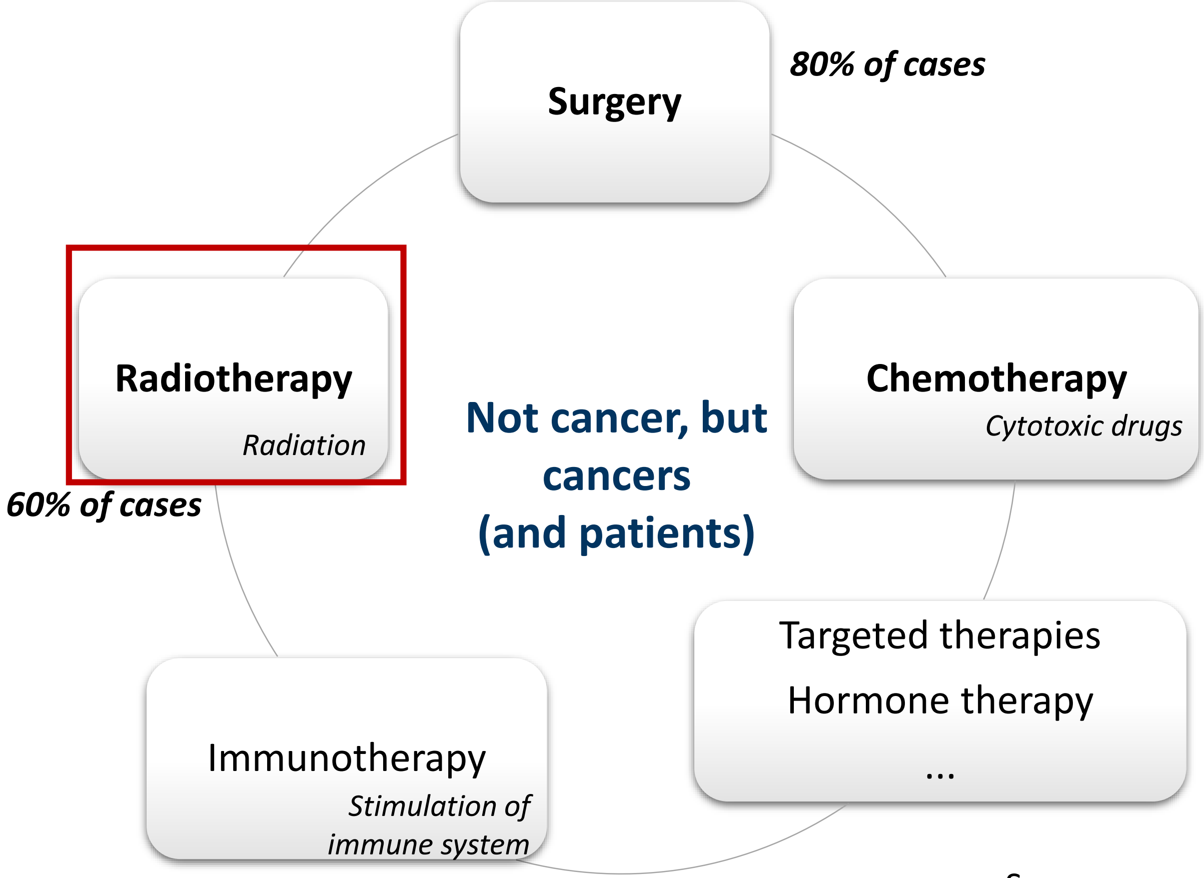






→ Different treatment strategies to kill « only » cancer cells

Different treatment modalities used alone or in combination



Multidisciplinary therapeutic teams

Surgeons
Pharmacists
Biologists
Physicists
...

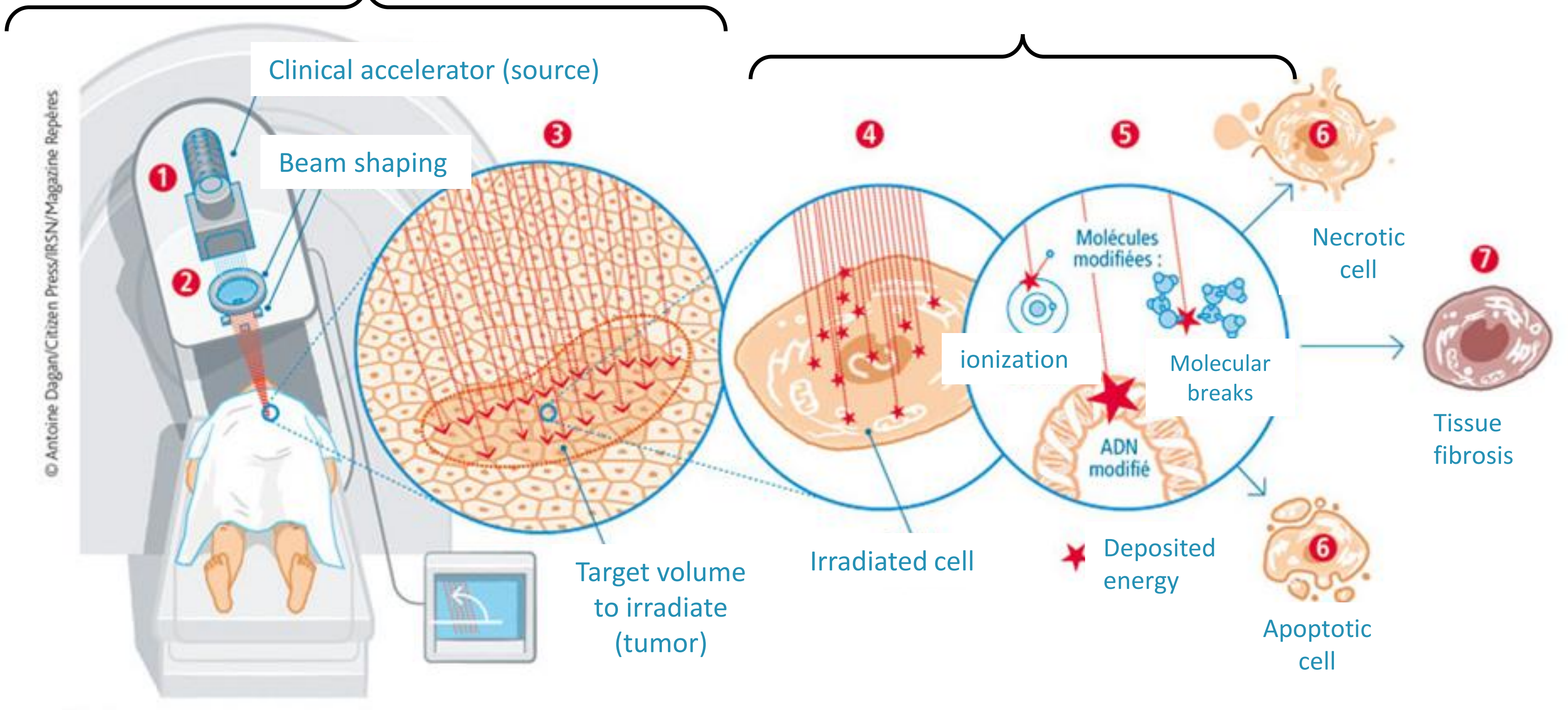
<u>They must take this into account:</u>

- **Biological analysis:** anatomopathology, molecular and genetic analyses → characteristics of a tumor
- **Cancer extension** (clinical, anatomical and functional imaging)
- **Stage** (T: Tumor, N: Nodes, M: Metastasis. Tumors classified from I to IV. I: small tumor (localized), II: large tumor (localized), III: tumor with lymph node involvement (locally advanced), IV: tumor with distant metastases (advanced).
- **Proximity to organs at risk**
- **Patient's age** and general condition

Use of ionizing radiation: (external) radiotherapy (RT) principle

Tumor irradiation with a radiation beam (X-ray, electrons, protons…)

Energy deposition by radiation in tissues
→ Alterations to molecules, DNA, cells and eventually tissues



Radiotherapy challenge:

Guaranty treatment efficacy while limiting side effects

① Interaction of radiation with the environment
② Biological effects of radiation

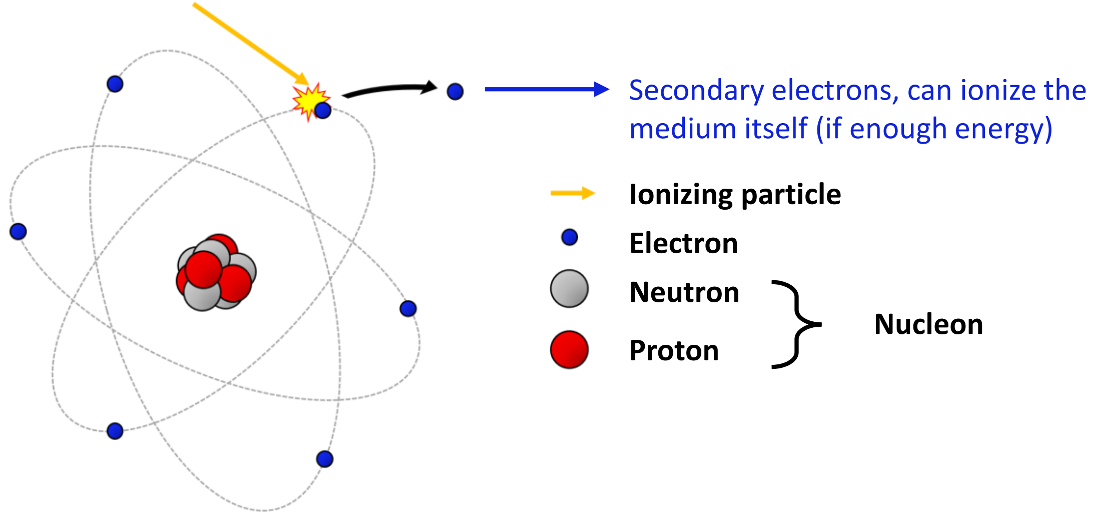
③ Tumor dose conformation improvements
④ Achieving a differentiated "biological" effect

Use of ionizing radiation

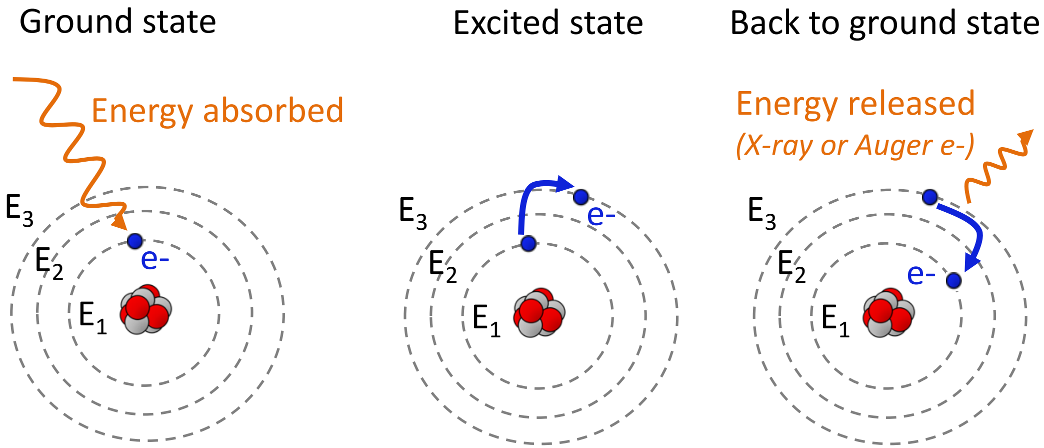
Physical interaction of radiation with the environment

Interaction of radiation with the environment: physical interactions and indexes

- **Ionizing radiations**: by definition, ionizing particles have enough energy to excite or detach electrons from the atoms of the molecules of the medium



Ionization



Excitation

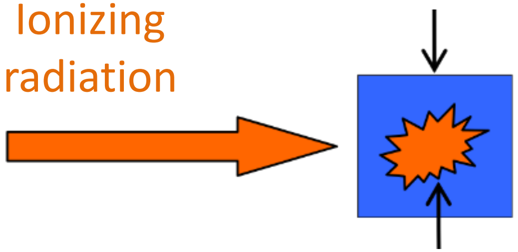
- Here, the environment is the patient: composed of > 70% of water.

Use of ionizing radiation

Interaction of radiation with the environment: physical interactions and indexes

➢ Physical indexes to quantify deposited energy in matter:

- **Dose** in Gray *(Gy)*



$$D(Gy) = \frac{dE(J)}{dm(kg)}$$

Dose is a mean quantity at « macroscopic » scale

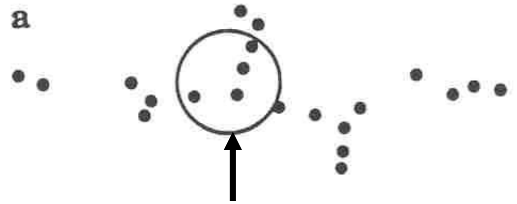
Energy → J (SI)

The **electronvolt** value is defined as the kinetic energy acquired by an electron accelerated by a potential difference of one volt: 1 eV = (1 *e*) × (1 V) :

1 eV = 1.602 × 10^{-19} J
1 **MeV** = 10^6 eV

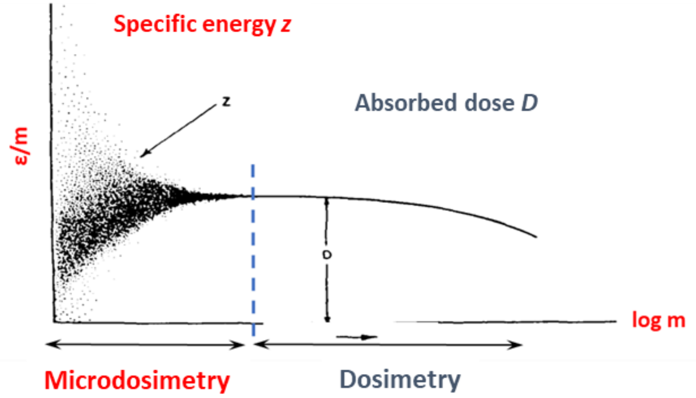
In aqueous media, the **minimum energy required to ionize water is 12.6 eV**.

Ionizing radiation is a **stochastic process**



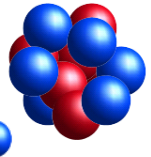
***Biological target: µm** (cell) to **nm** (DNA)*

Specific energy *Z* (Gy) = microscopic equivalent of dose

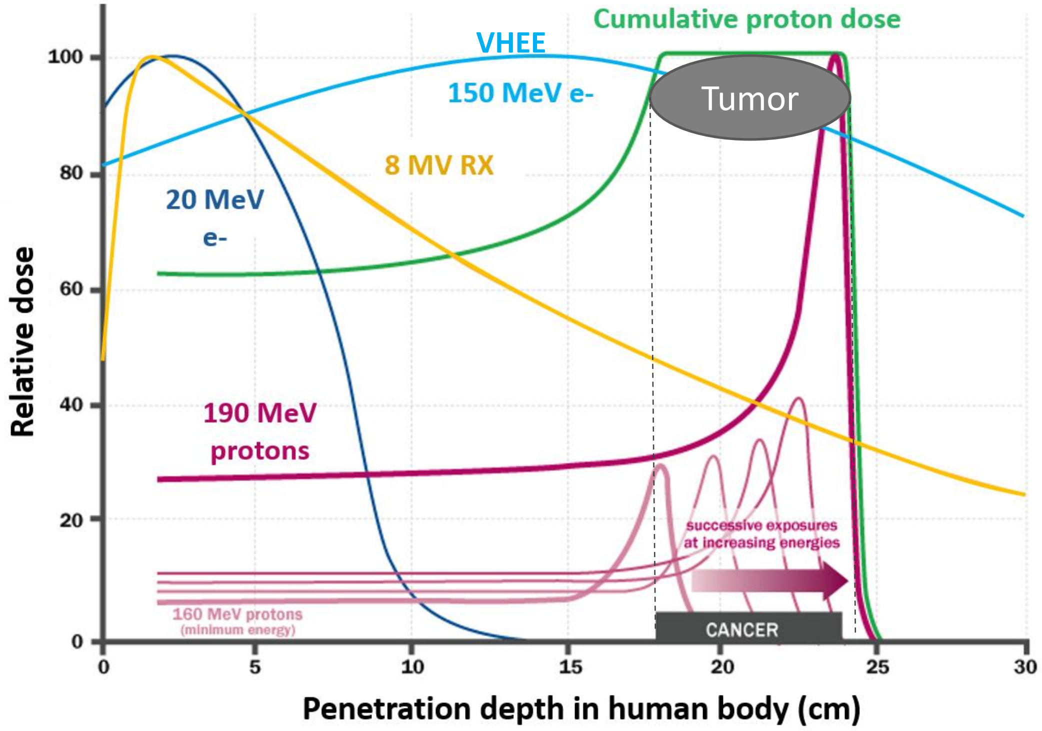


Interaction of radiation with the environment

➢ Types of particles used in RT

- Uncharged particles :
  - **Photons** (**X-rays**, γ) ~1 MeV
    vast majority of treatments (> 95%)
  - **Neutrons** epithermal (< 10keV)
- Charged particles
  - **Clinical Electrons** (or β) < 20 MeV
  - **Very-high energy electrons** (VHEE), ~70-300 MeV
  - **Protons**  < 200 MeV
  - **Carbon ions**  < 4800 MeV *(400 MeV/n)*
  - **α particles**  ~5 - 9 MeV

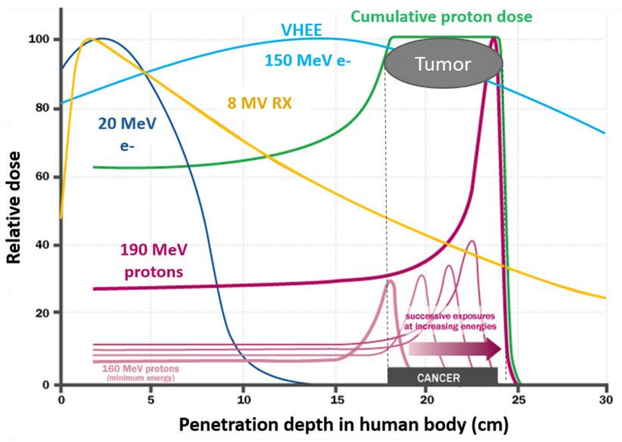
Typical depth-dose profiles
for beams delivering a dose to the tumor *(~30 – 70 Gy)*



Interaction of radiation with the environment

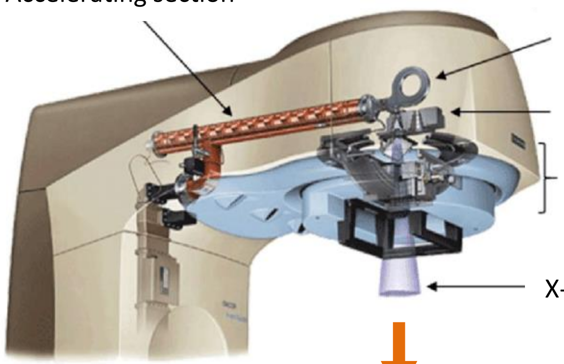
➢ Types of particles used in RT

- Uncharged particles :
  - **Photons (X-rays, γ)** ~1 MeV
    vast majority of treatments (> 95%)
  - **Neutrons**
- Charged particles
  - **Clinical Electrons**

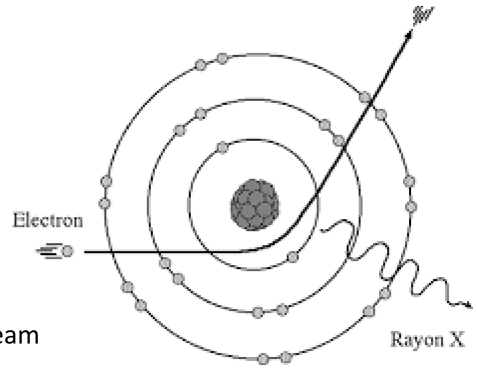


Electrons can also directly be used for surface tumor/ganglion irradiation
(ionize matter by coulomb scattering)

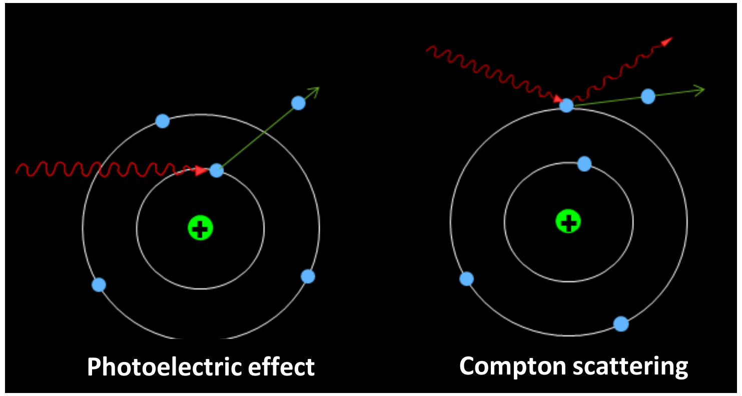
Linear electron accelerator (LINAC)



Bremsstrahlung radiation



Interacting with the patient



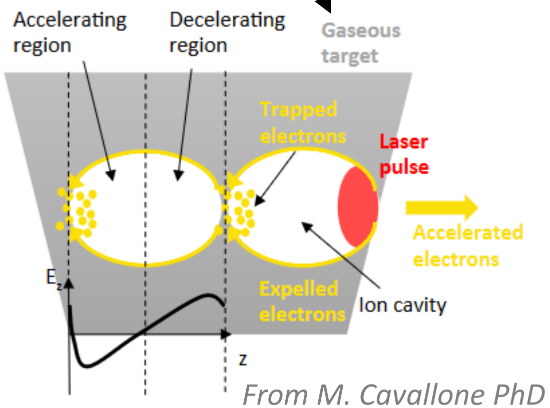
Interactions with the electron cortege (**ionization/excitation**) → lead to secondary electron emission

Use of ionizing radiation

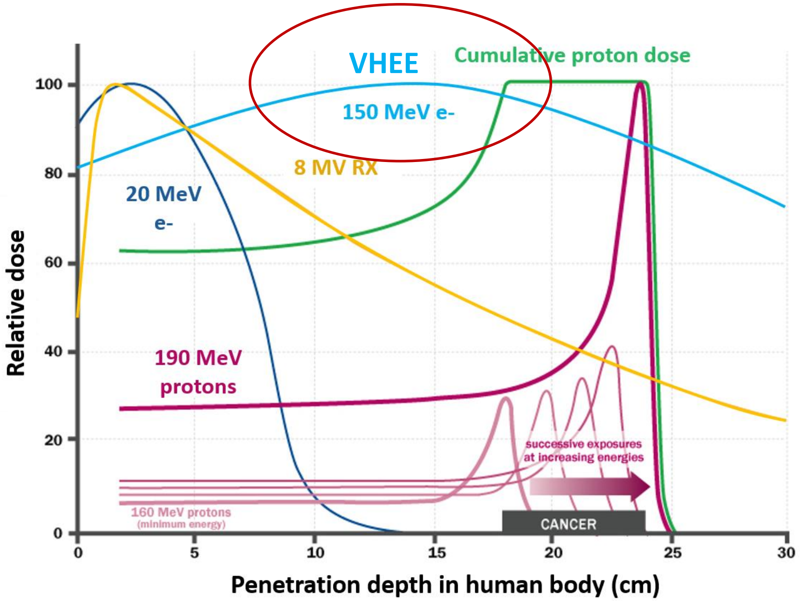
Interaction of radiation with the environment

- Types of particles used in RT
  - Uncharged particles :
    - **Photons** (**X-rays**, γ)
      vast majority of treatments (> 95%)
    - **Neutrons**
  - Charged particles
    - **Clinical Electrons**
    - **Very-high energy electrons** (VHEE), ~70-300 MeV
      - Depth dose profile suited for deep-seated tumors
      - Magnetic collimation: pencil beam scanning and possible MBRT
      - Less sensitive to tissue heterogeneities (↘errors on treatment plans)
      - Ultra-high dose rate irradiation (FLASH)

Production in **high-gradient** (~100 MV/m) **RF accelerators** (ex. CLEAR, CERN) or with **wake-field Laser-Plasma** (~GV/m)



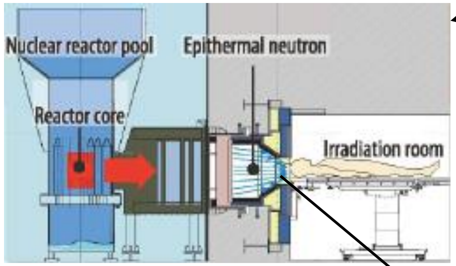
From M. Cavallone PhD thesis

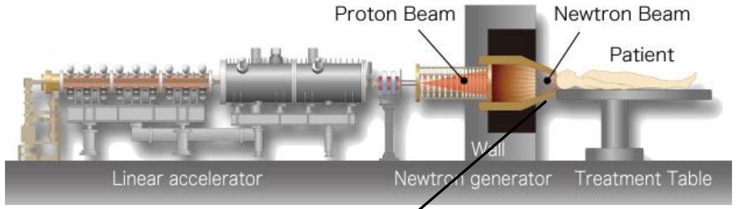


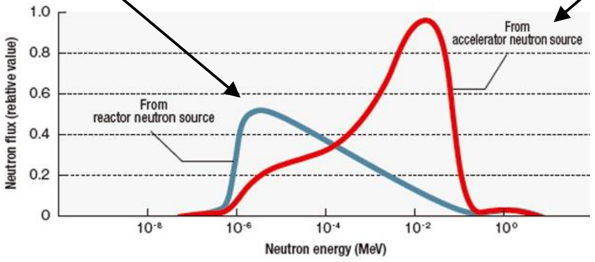
Interact through Ionizations/Excitations + Nuclear interactions (neutron production)

Interaction of radiation with the environment

Produced in **reactors** or **accelerators** :







Neutron energy spectra as a function of the source

➢ Types of particles used in RT

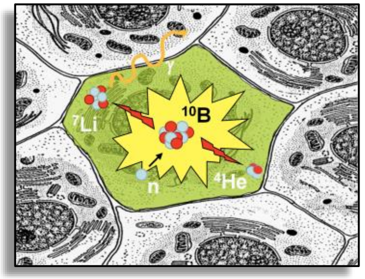
- Uncharged particles :
  - **Neutrons**

epithermal (< 10keV)
in the case of Boron Neutron Capture Therapy (**BNCT**)

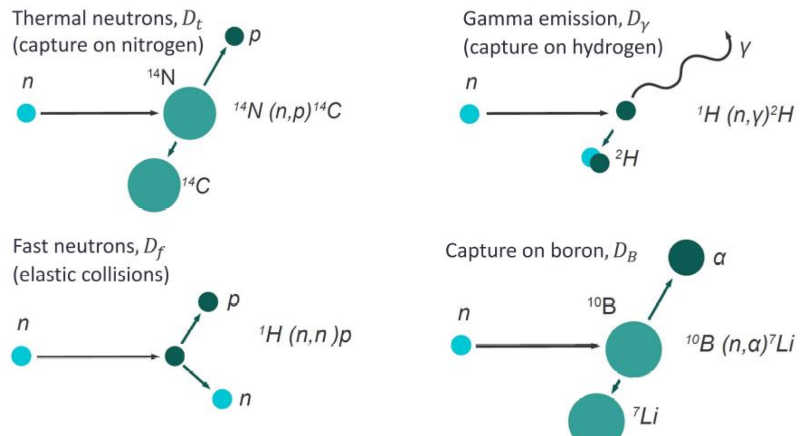
$^{10}B + n_{th} \rightarrow [11B]^*$

- 6 % → $^{4}He + ^{7}Li$ (2,79 MeV)
- 94 % → $^{4}He + ^{7}Li$ (2,31 MeV) + γ 0,48 MeV

Natural (20%), enriched boron isotope, delivered in cancerous cells (BPA or BSH)



Can interact in **many different processes**, the main of interest in BNCT:



From M. Pedrosa PhD thesis

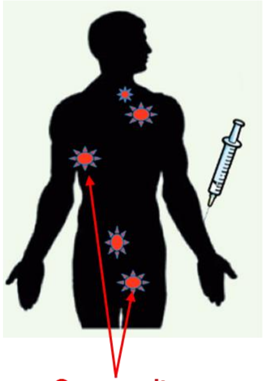
Use of ionizing radiation

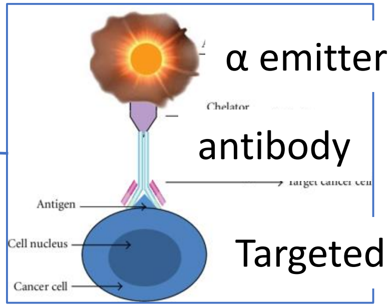
Interaction of radiation with the environment

➢ Types of particles used in RT

- Uncharged particles :
  - **Photons** (**X-rays**, γ)
  - **Neutrons**
- Charged particles
  - **Clinical Electrons**
  - **VHEE**
  - **Protons**
  - **Carbon ions**
  - α **particles** (He ions) ~5 - 9 MeV

Interact through Ionizations/Excitations





Of interest in **Targeted alpha therapy (TAT)** – internal RT

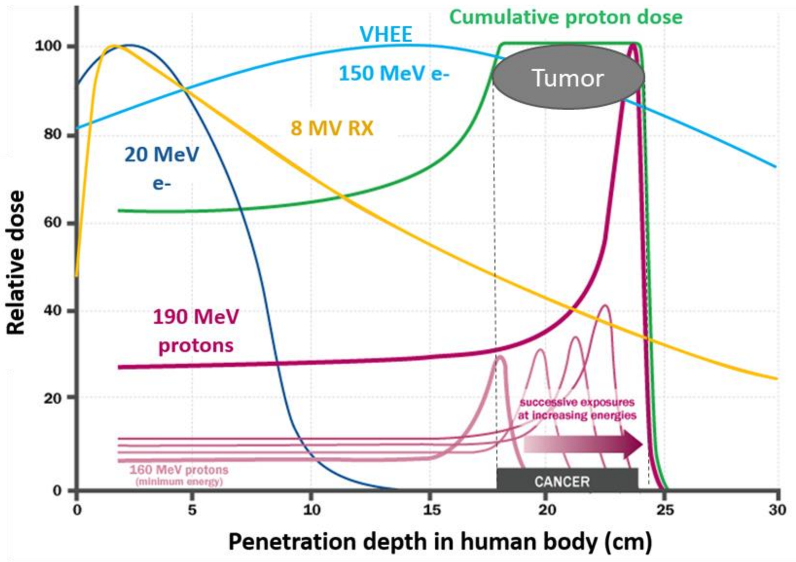
- Come from **alpha decay** of heavy unstable isotopes:

^{223}Ra, ^{225}Ac, $^{212/213}$Bi, ^{211}At, ^{212}Pb…

- **short range: 40 – 100 µm**
- **Production modes of radionuclides**:
  - **Compact generators:** i.e. radioactive system with a long-live parent which decays in short-live daughters
  - **Cyclotrons**
  - **Nuclear reactors**

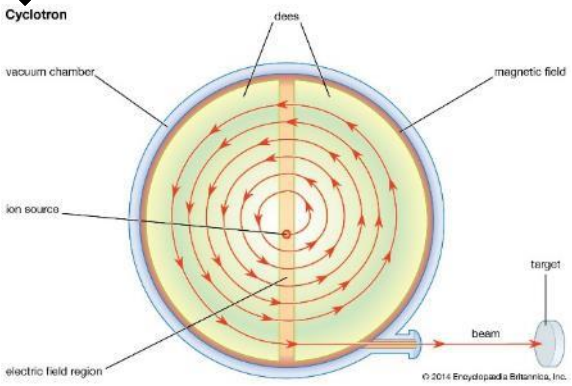
Use of ionizing radiation

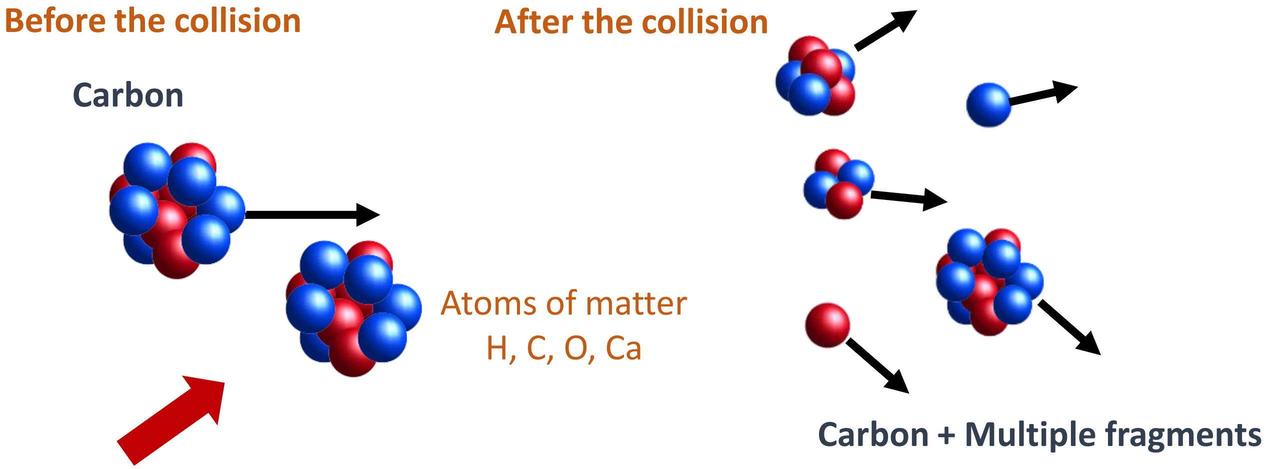
Interaction of radiation with the environment

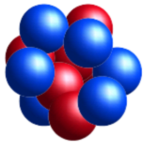


Heavy charged particles – of interest in **hadrontherapy**

Production in synchrotron, **cyclotron** or synchro-cyclotrons





- Charged particles
  - **Protons** 
  - **Carbon ions** 
  - **α particles**

< 200 MeV

< 4800 MeV

Interact through Ionizations/Excitations + Nuclear interactions

Use of ionizing radiation

Interaction of radiation with the environment: physical interactions and indexes

➢ Physical indexes to quantify deposited energy in matter:

- **Linear energy transfer (LET)** in keV/µm

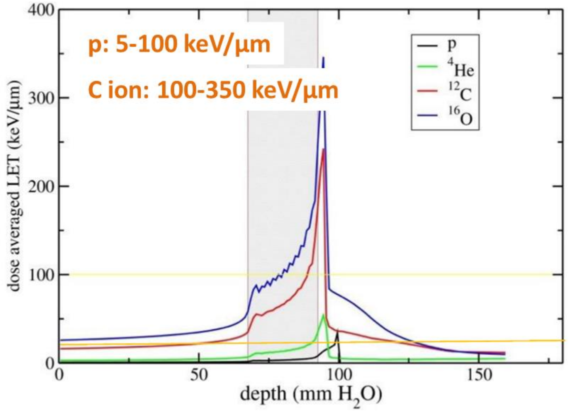
$$L_\Delta\ (KeV.\mu m^{-1}) = \frac{dE_\Delta}{dl}$$

Another macroscopic quantity to characterize the « quality of a radiation »
≈ ionization density *(equivalent to electronic stopping power for ions)*

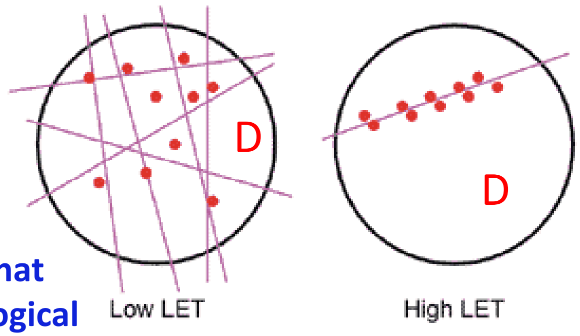
dE$_\Delta$ *the average energy lost by charged particles due to electronic interactions while traveling a distance* ***dl***

- The LET depends on the ionizing particle type and energy

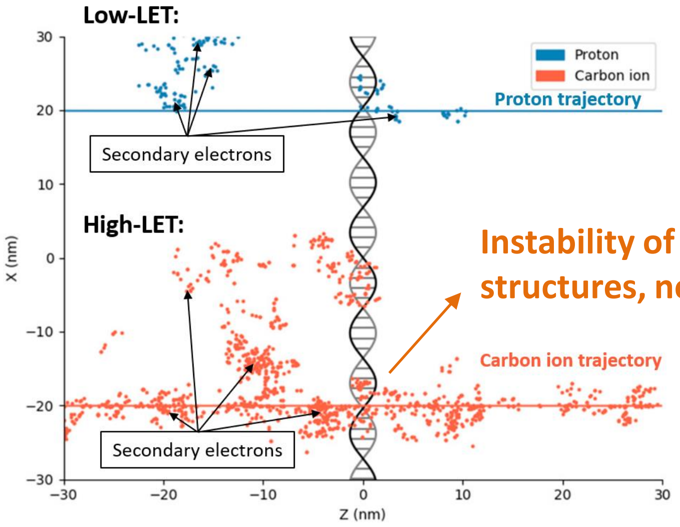
LET changes with depth



Characterize what happen at biological target scales



At microscale



~**5 keV/µm**
(10 MeV proton)

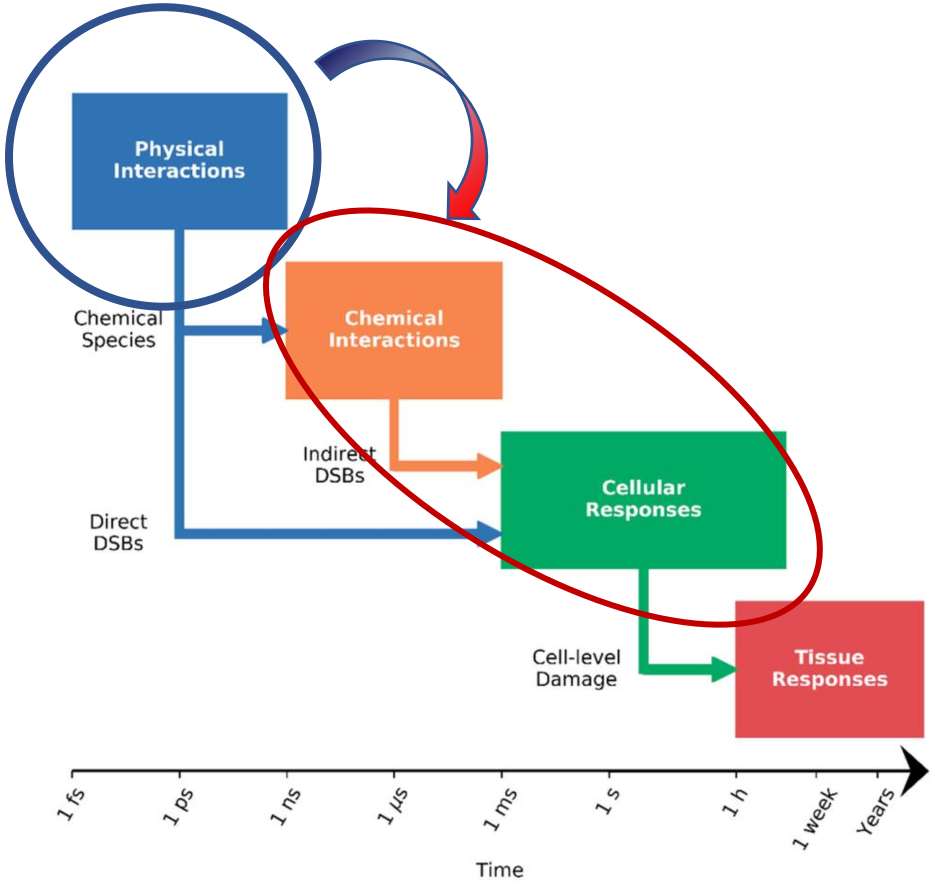
Instability of molecular structures, no longer functional

~**100 keV/µm**
(200 MeV C ion)

At nanoscale *(ex. of DNA scale)*

➔ A same dose D will not lead to the same biological effect

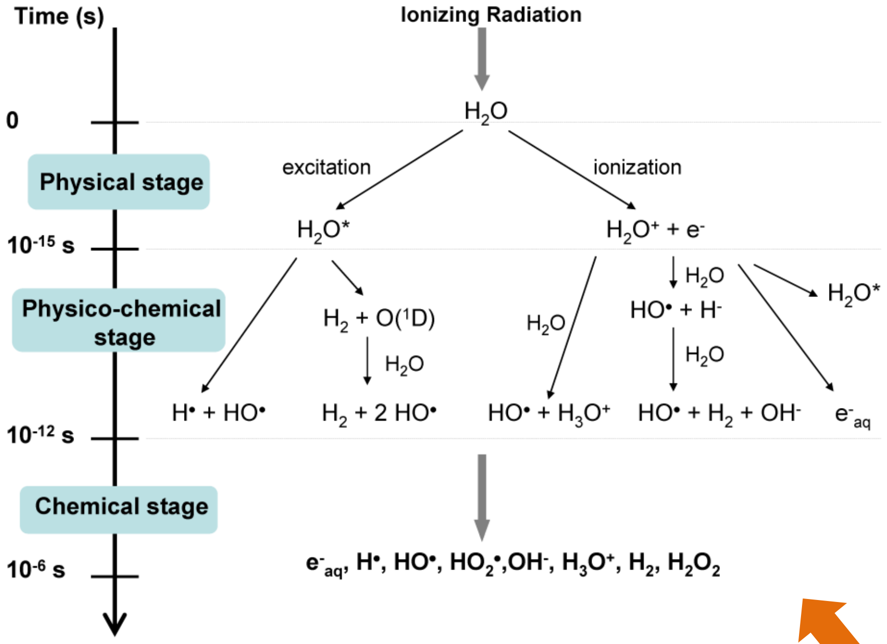
Use of ionizing radiation



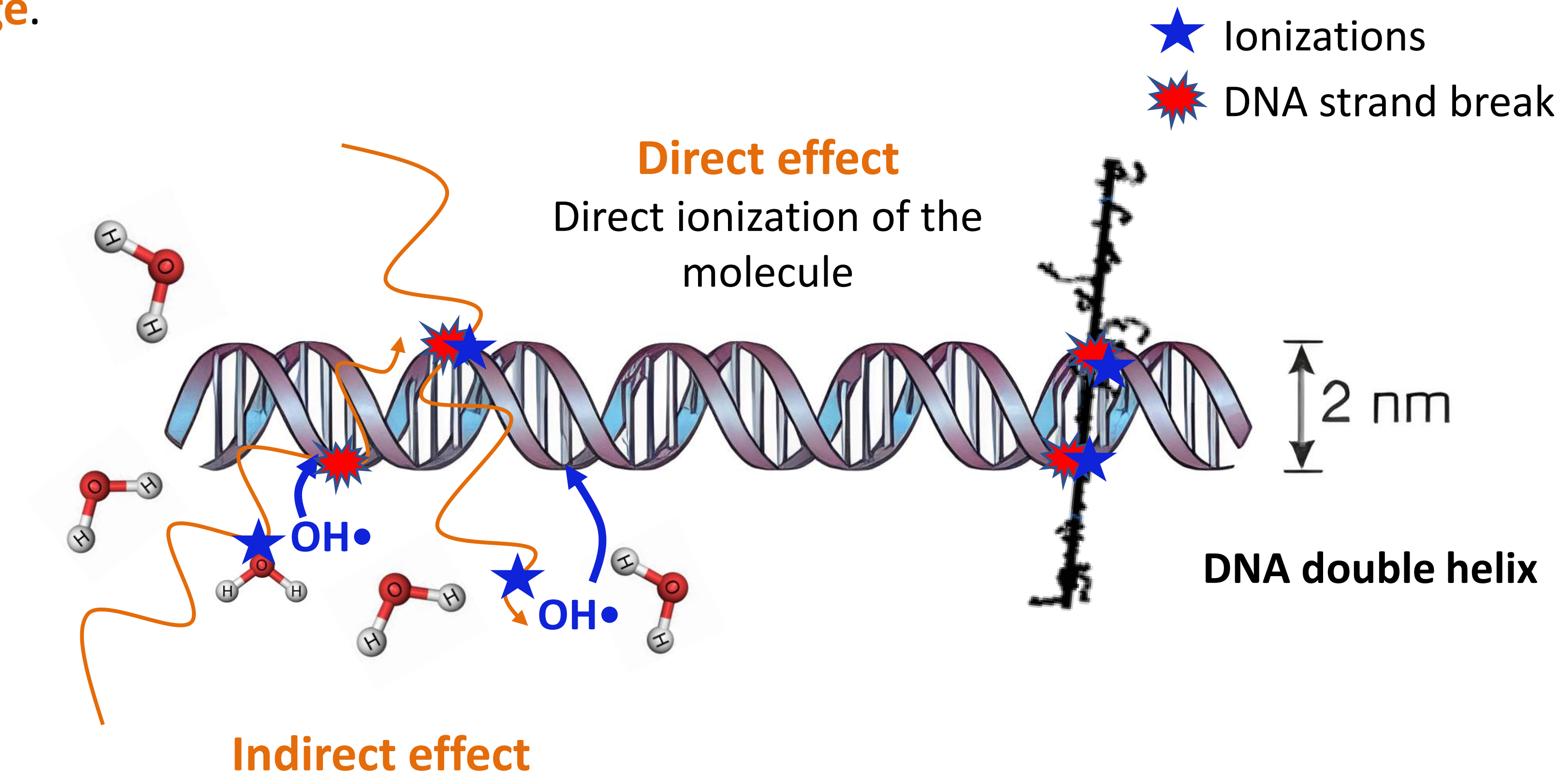
From physical interactions to biological effects

Biological effects - Direct and indirect damage

- **Direct vs indirect effect**: Body mainly composed of water → **most ionizations will occur in water molecules**. **Example on DNA damage**.



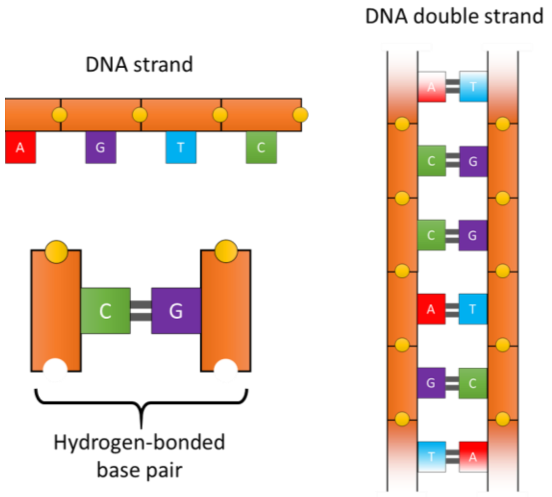
Water radiolysis process leading to reactive free radical productions



Water radiolysis: creation of reactive chemical species (OH•, H_2O_2, e^-_{aq}…) that will interact with organic molecules

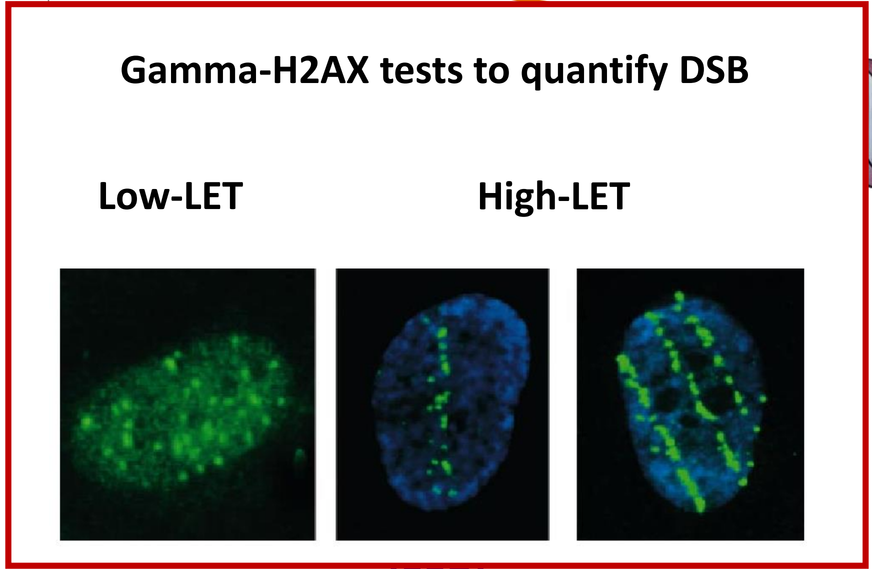
Biological effects – damage at molecular scale

- **DNA damage**:



DNA structure

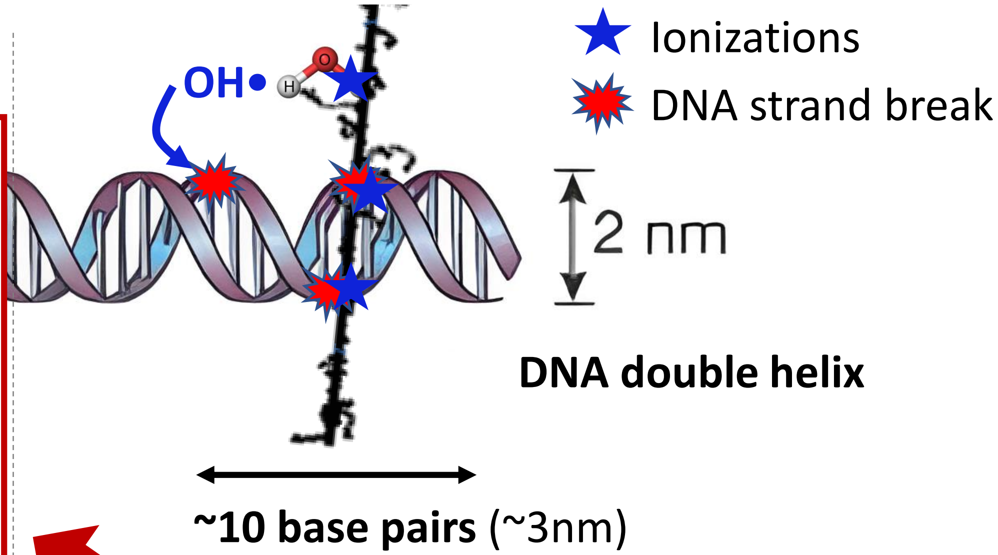
Low-LET particle



(SSB)

More easily reparable

High-LET particle



DNA Double Strand Break (DSB)

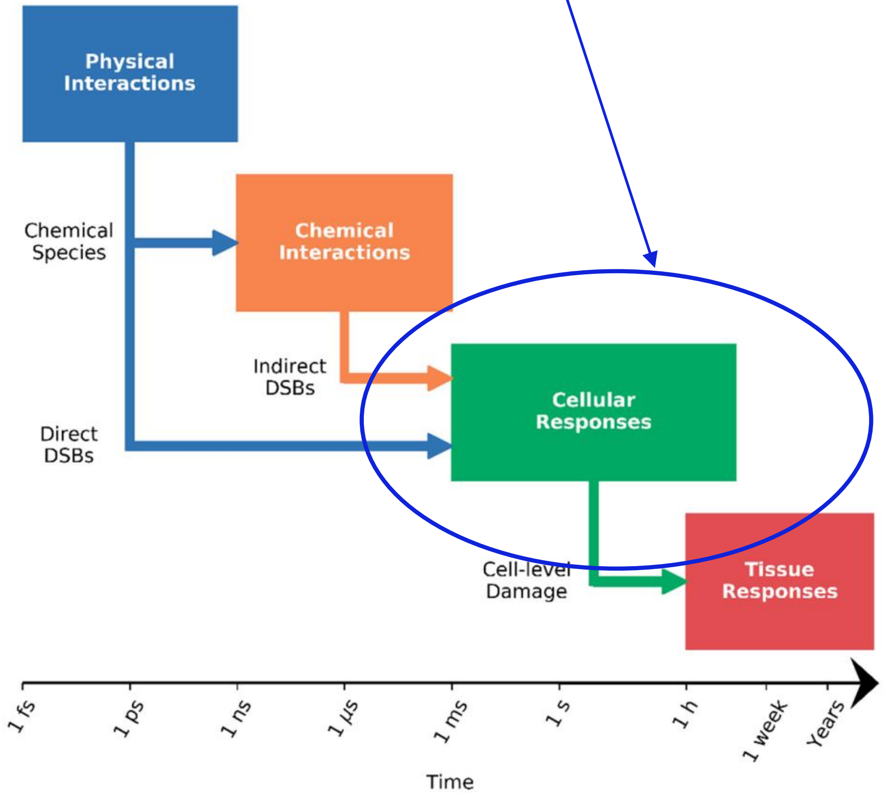
Harder to repair ➔ cell death or mutation

The more breaks within 10 base pairs, the more complex the damage

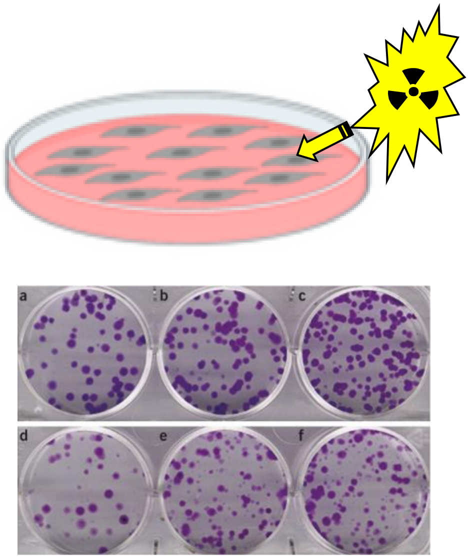
The higher the LET, the higher the production of complex lethal damage

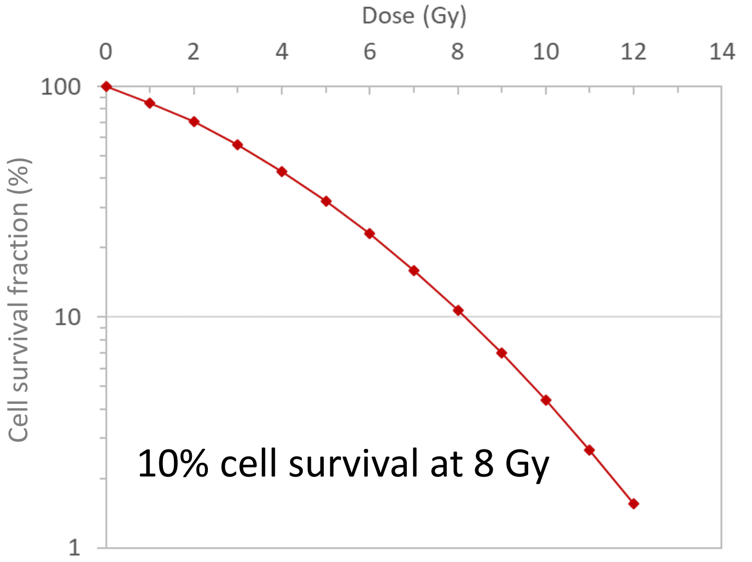
Biological effects – quantification at cell scale

- **Cell survival:** To compare irradiation protocols and RT approaches, we can use **clonogenic cell survival** which quantify biological effects at cell level *(elementary constituent of living matter)*



Curve linking **dose** to **cell survival**





« Macroscopic" description using **mathematical models**

Biological effects – quantification at cell scale

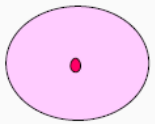
- **Cell survival**: Relationship between **DOSE** delivered and **CELL SURVIVAL**: **Linear Quadratic Model**

$$S(D) = e^{-(\alpha D + \beta D^2)}$$

Radiobiological parameters:
α (Gy^{-1})
β (Gy^{-2})

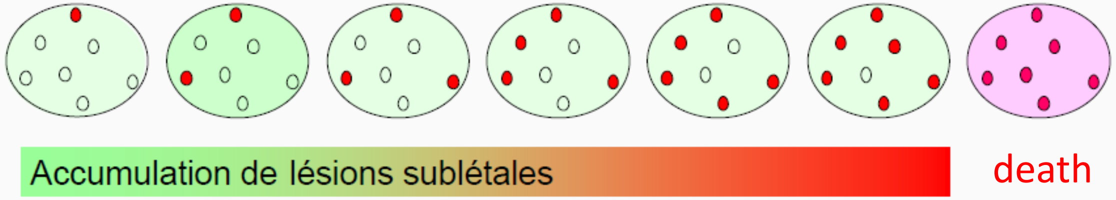
Total damage

1 immediately lethal component (e.g. double-strand breaks)



« Linear » component $S = e^{-\alpha D}$

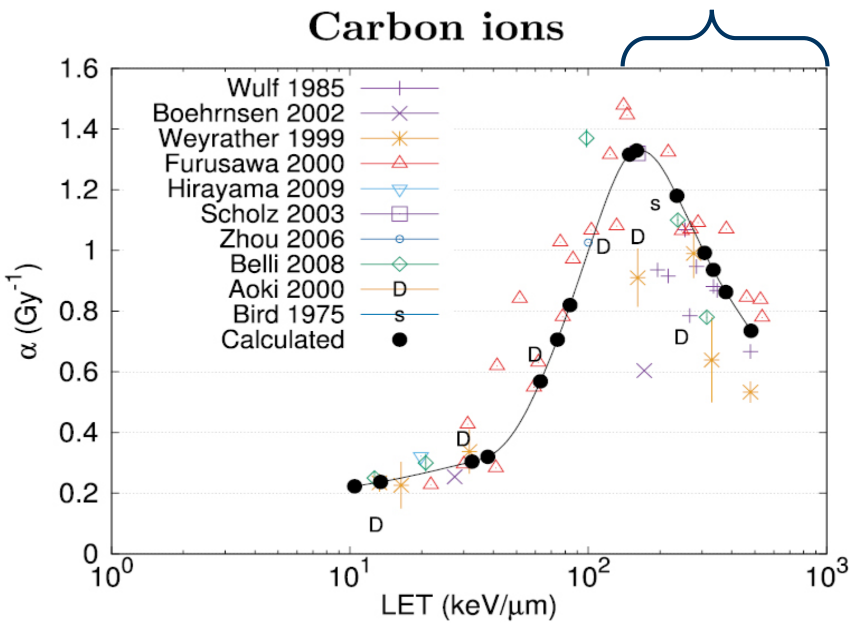
accumulation of sublethal lesions (e.g. single-strand breaks)



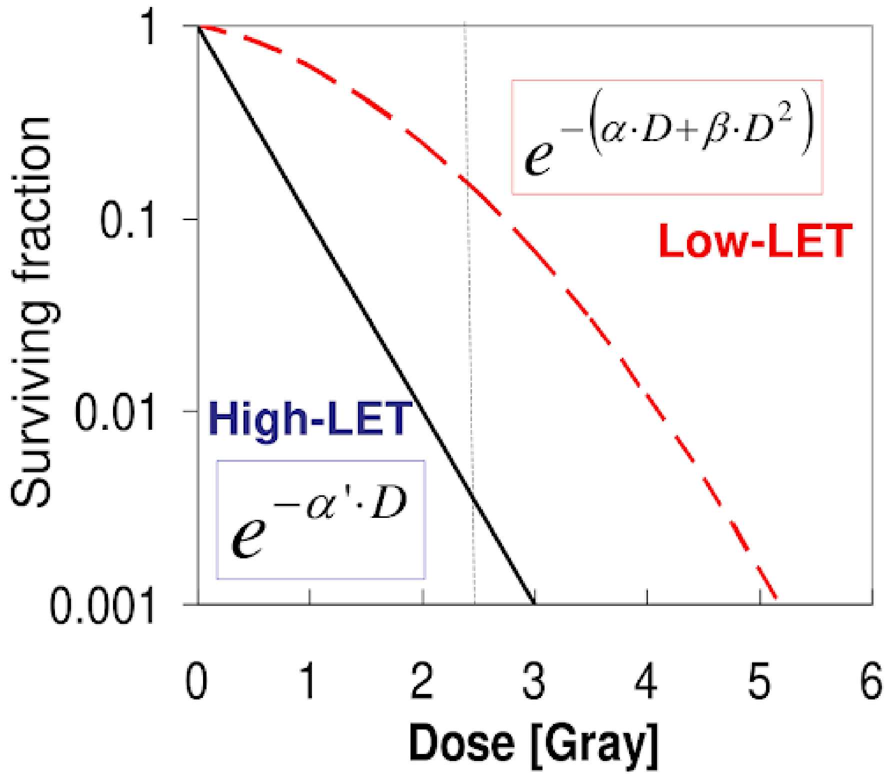
« Quadratic » component $S = e^{-\beta D^2}$

Biological effects – quantification at cell scale

- **Cell survival:** LET dependence:
  - **High-LET** induce **more direct lethal damage**.
  - **α parameter dependency with LET:** saturation effect above ~160 keV/µm, due to an **overkill effect**



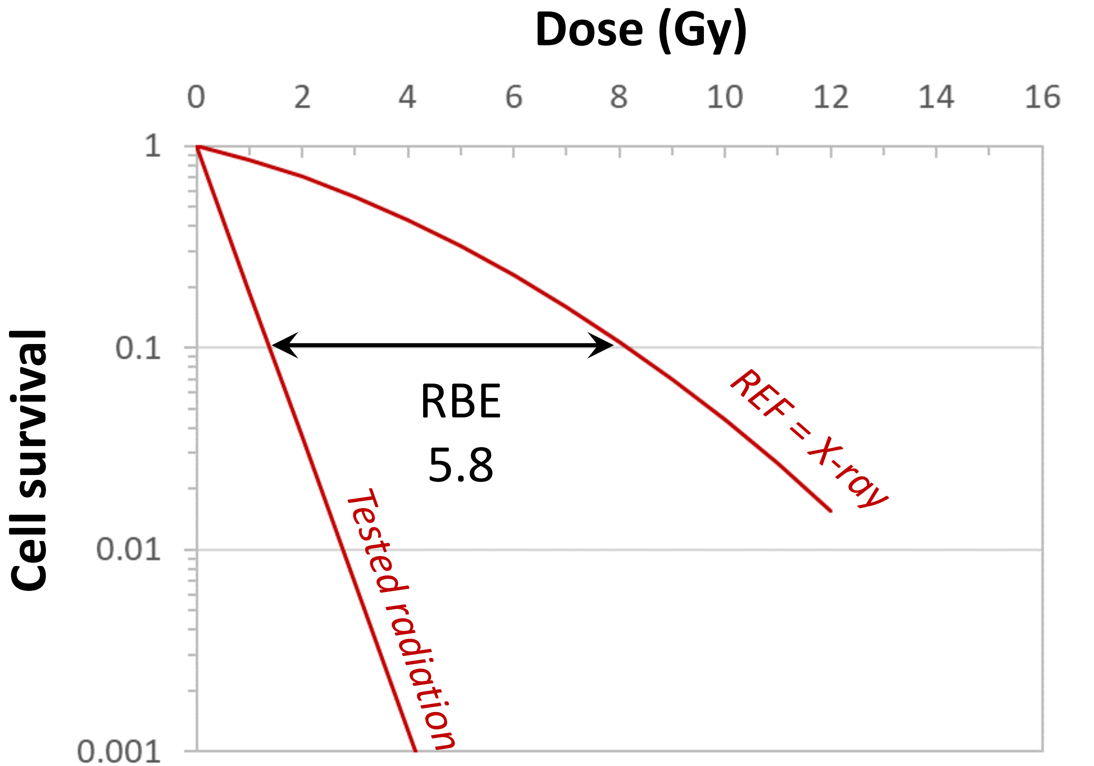
α radiobiological coefficient as a function of LET, for carbon ions irradiating V79 cells (From Cunha et al. 2017)



Biological effects – quantification at cell scale

- **Relative Biological Effectiveness (RBE):**
  - Used to compare different radiation types.

$$RBE = \frac{D_{ref}|_{10\%}}{D_r|_{10\%}}$$



proton: RBE ~1.1
C ion: RBE ~3

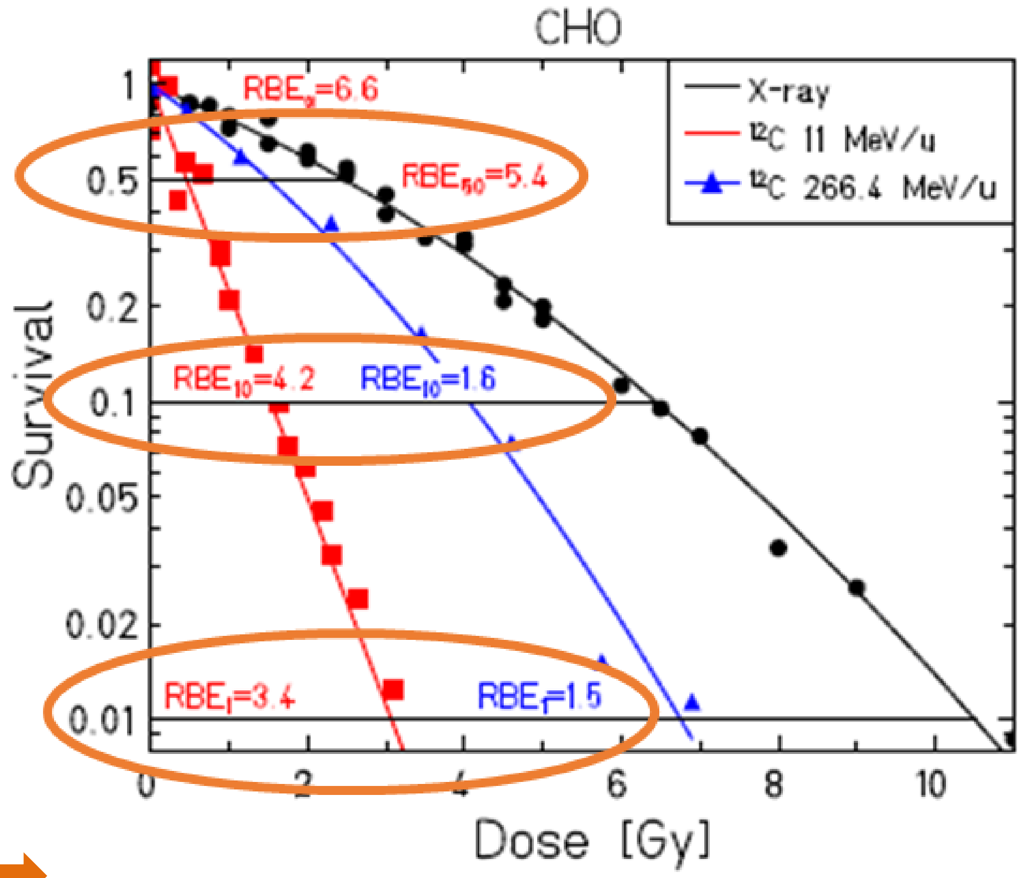
Biological effects – quantification at cell scale

➢ Relative Biological Effectiveness (RBE):

- Used to compare different radiation types.

$$RBE = \frac{D_{ref}|_{10\%}}{D_r|_{10\%}}$$

- **RBE depend on many parameters:**
  - Particle type, energy and **LET**
  - Dose-rate $\dot{D}$ of the irradiation
  - **Biological system** (cell type), **oxygenation** (OER)…
  - **Biological effect considered** (e.g. % survival)



M. Krämer, NIM-B. Vol.267 I.6 (2009)

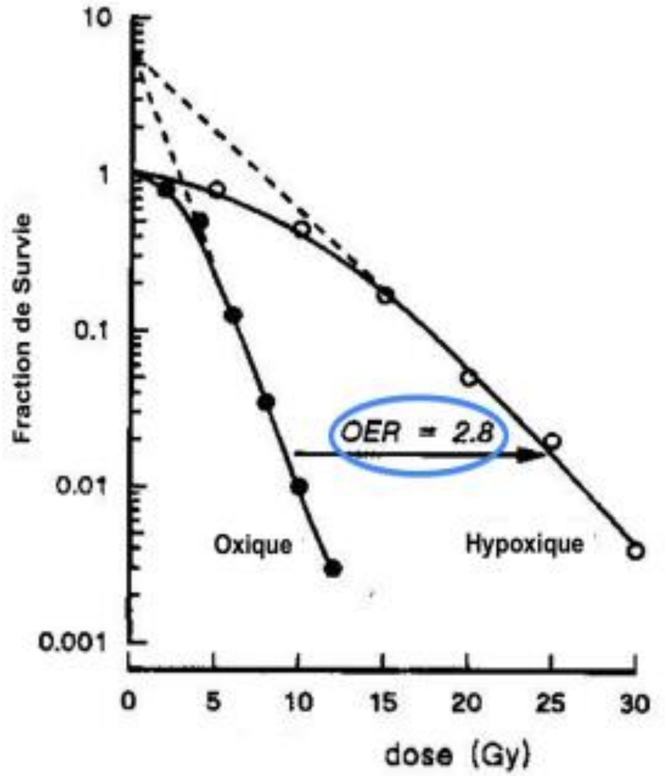
Use of ionizing radiation

Biological effects – quantification at cell scale

➢ **Cell survival**: effect of cell/tissue **oxygenation**:

- The oxygen **O_2** plays an important role in **indirect effects**:
  - It increases the efficiency of water radiolysis
  - It can react with free radicals to generate peroxyl radicals ROO•, increasing toxicity.

➔ Need more dose to destroy **hypoxic cells (= radioresistance)**



$$OER = \frac{D_{hypoxic}|_{x\%}}{D_{normoxic}|_{x\%}}$$

OER = Oxygen Enhanced Ratio

Limitation to treat hypoxic tumor in normoxic healthy tissue!

Biological effects – quantification at cell scale

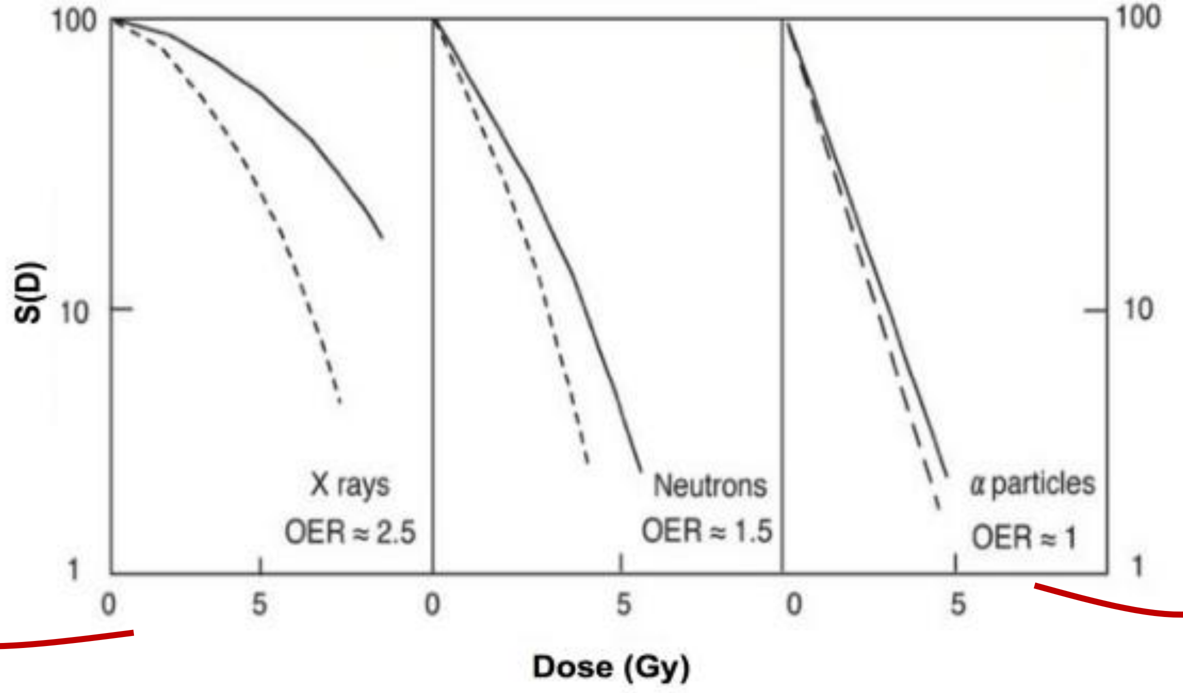
- **Cell survival:** effect of cell/tissue **oxygenation**: high-LET decreases the oxygen effect

Low LET (RX)

Indirect effects ++
(free radicals)

Sensitive to
oxygen level

Radiation resistance ++



High LET (α, C)

Direct effects ++
(double-strand breaks)

Less sensitive to
oxygen level

Radiation resistance --

Use of ionizing radiation

Things to remember

- Radiotherapy uses **ionizing radiation** to destroy cancer cells.
- **Molecular damage** can be **direct** or **indirect** (formation of free radicals that will cause damage).
- **X-rays** (the vast majority of treatments) have a low ionization density (LET) → **dominant "sub-lethal" damage** (repairs +)
- **"Heavy" charged particles** have a high ionization density (high-LET) → **more complex/lethal damage (DSB)** & less **sensitivity** to $\mathbf{O_2}$

The strategy of preferentially irradiating the tumour and preserving healthy tissue has not yet been addressed.
→ **Obtaining a differential effect**

Presentation outline

- **Introduction to radiation therapy and fundamental notions**
  - **Introduction to cancer treatment**
  - **Use of ionizing radiation** : physical interactions and Radiobiological aspects on living matter

- **Therapeutic strategies to improve cancer treatments**
  - **Differential effect**: find the good balance between tumor control and tissue preservation
  - **X-ray radiation therapy** : technological evolution improving the dose conformation to the tumor
  - **Use of different particles**: **Hadrontherapy** (protons, carbon ions…), high energy electrons (**VHEE**), neutrons…
  - **Play on dose delivery**: temporal fractionation of the dose, very-high dose-rate radiation (**FLASH** therapy), spatial fractionation of the dose (**Grid, MBRT, MRT**)
  - **Combined radiotherapies** (with molecular vector): **radionuclide therapy** (alpha targeted therapy), **BNCT**, **nanoparticle-enhanced** radiotherapy…

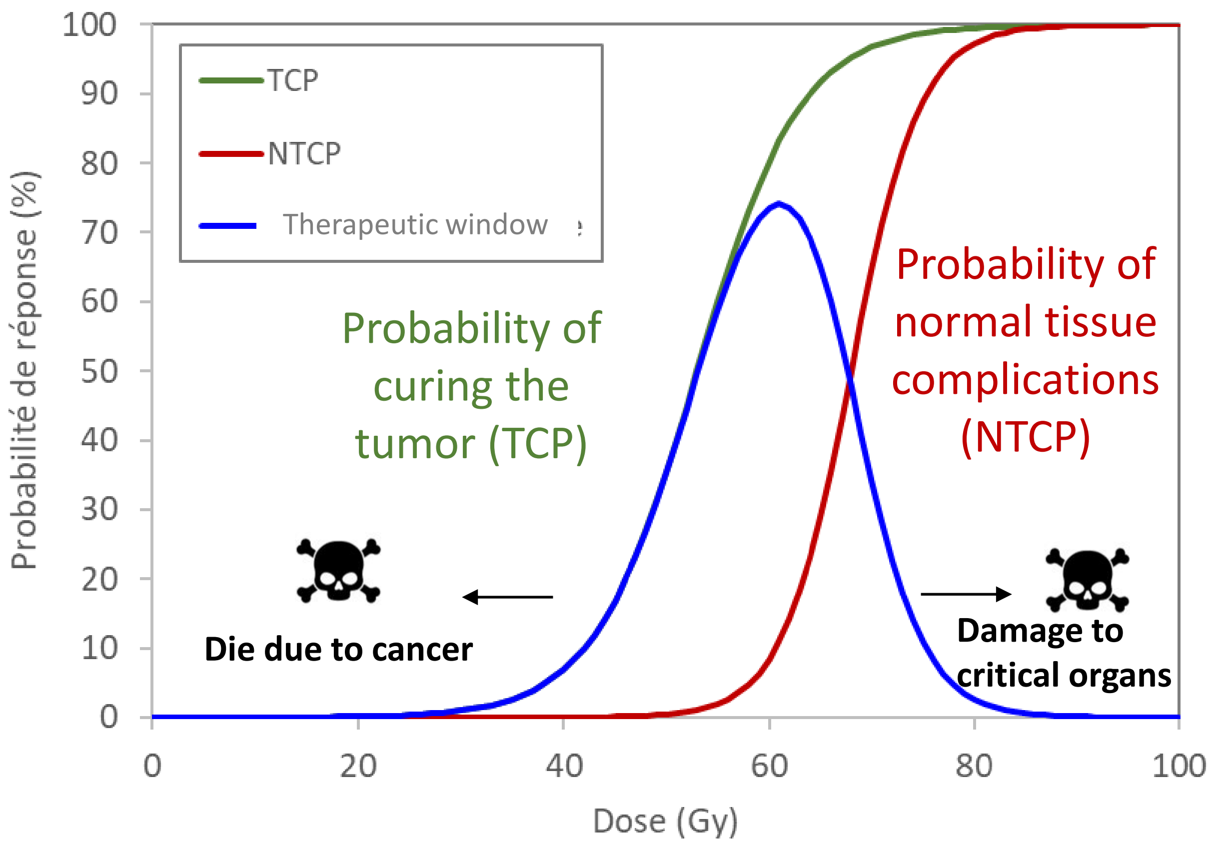
- Conclusions

Therapeutic strategies

Differential effect, therapeutic window

Treatment efficacy vs. toxicity

TCP/NTCP models



Tumor (treatment target)

- Early effect

Organs at risk:

- Early effects
- Late effects

Two conflicting objectives → Modeling these objectives

1. Eliminating cancer cells
   Tumor Control Probability (TCP)
2. Preserving healthy cells
   Normal Tissue Complication Probability (NTCP)

Maximizing the therapeutic **window**

➜ **Developing new therapeutic strategies**

Therapeutic strategies

Enhancing the differential effect between tumor cells and healthy cells

- **Major strategies:**
  - **Anatomical radiation restriction**:
    Conformation of dose to tumor volume
  - **Radiation choice:**
    X-rays, protons, α, ions…
  - Dose **time** and **spatial fractionation**:
    play on dose delivery mode
  - **Pharmacomodulation / combined therapies:**
    Radiosensitizers, molecular targeting

Technological advances

Differentiated biological effects

Therapeutic strategies

Enhancing the differential effect between tumor cells and healthy cells

➢ **Major strategies:**

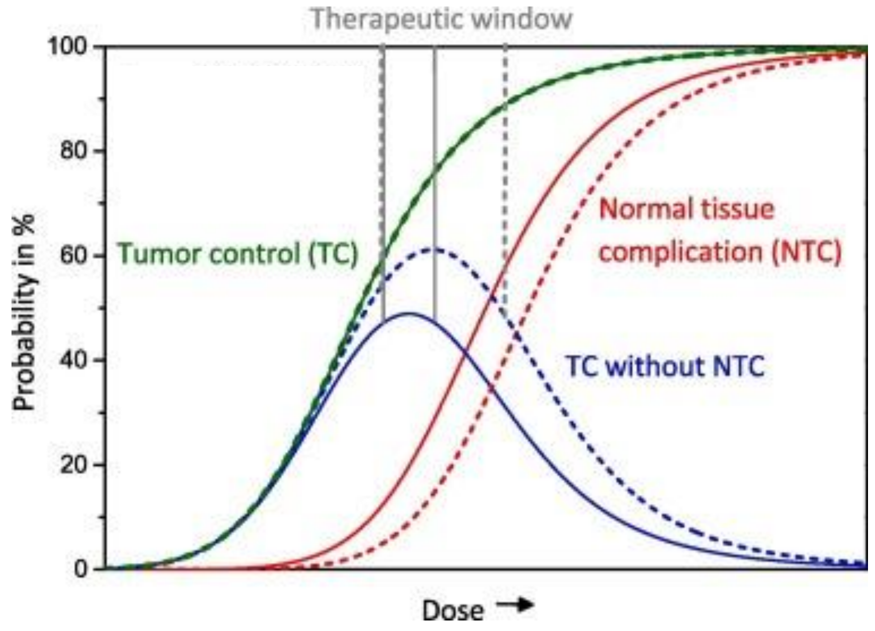
- **Anatomical radiation restriction**:
  Conformation of dose to tumor volume

- **Radiation choice:**
  X-rays, protons, α, ions…

- Dose **time** and **spatial fractionation**:
  play on dose delivery mode

- **Pharmacomodulation / combined therapies:**
  radiosensitizers, molecular targeting

Technological advances



Therapeutic strategies

Technological advances in X-ray radiation therapy

History of X-ray RT and « technological » evolution

LPSC GRENOBLE | MODANE

- Global view of the technological evolutions improving the dose conformation to the tumor: i.e Maximizing the dose delivery to the tumor vs. <u>minimizing the irradiation of normal/healthy tissues</u>

Beam delivery

kV voltage

- 1895 – Discovery of X Rays
- 1913 – Invention of the **heated cathode tube** → enables EBRT
- 1925 – **50 kV** accelerator → Superficial tumors
- 1948 – Telecobalt therapy → Skin barrier tolerance

MV voltage

- 1953 – **MV Linear accelerators**
- 1965 – Multi-leaf collimator
- 1990 – **IMRT** *(intensity modulated RT)*
- 2000's – **VMAT** *(volumetric modulated RT)*

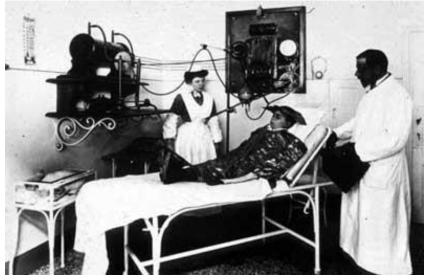
Gold standard X-ray irradiation protocols (IMRT, VMAT)

Imaging + computing

- 1972 – CT Scan
- 1980 – 3D TPS
- 1996 – PET Scan

Facilities

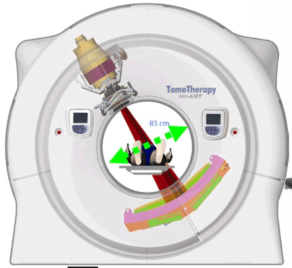
X-ray (Roentgen hand) and radioactivity discoveries



kV irradiator (enables external beam therapy, but skin toxicity)

^{60}Co therapy (~1.25 MeV gammas)

MV electron LINAC



Tomotherapy (helical irradiation, like CT)

Cyber-knife (stereotaxic irradiation)

History of X-ray RT and « technological » evolution

- Global view of the technological evolutions improving the dose conformation to the tumor:
  i.e Maximizing the dose delivery to the tumor vs. <u>minimizing the irradiation of normal/healthy tissues</u>

Beam delivery

kV voltage

- 1895 — Discovery of X Rays
- 1913 — Invention of the **heated cathode tube** → enables EBRT
- 1925 — **50 kV** accelerator → Superficial tumors
- 1948 — Telecobalt therapy → Skin barrier tolerance

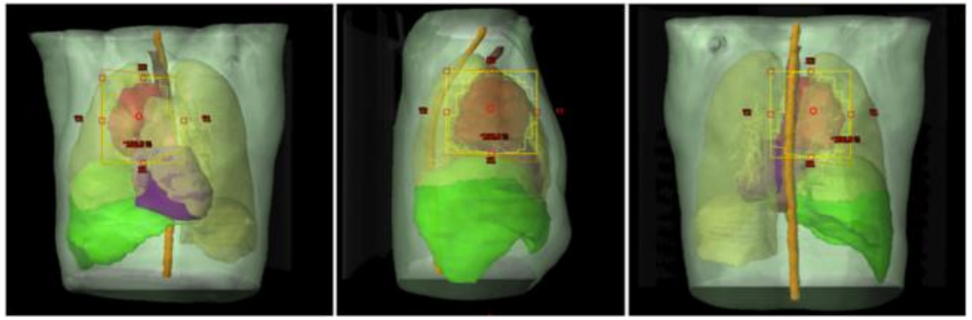
MV voltage

- 1953 — **MV Linear accelerators**
- 1965 — Multi-leaf collimator
- 1972 — CT Scan
- 1980
- 1990 — PET Scan
- 1996 — **IMRT** *(intensity modulated RT)*
- 2000's — **VMAT** *(volumetric modulated RT)*

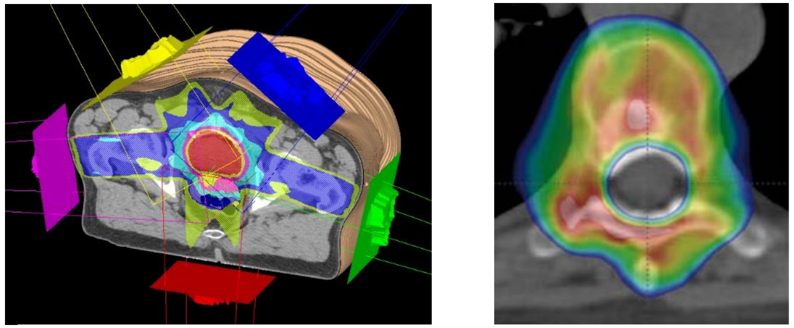
Gold standard X-ray irradiation protocols (IMRT, VMAT)

Imaging + computing
(dose calculation and planning)

From rudimentary 2D imaging and dose calculation to **very complex irradiation scheme** and dose plans:



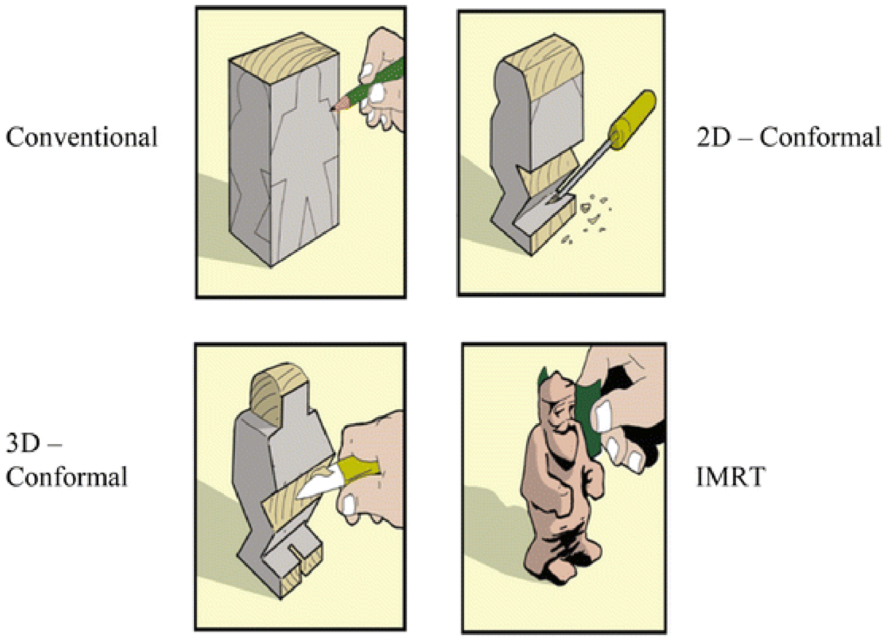
3D images with organs segmentations for treatment planification



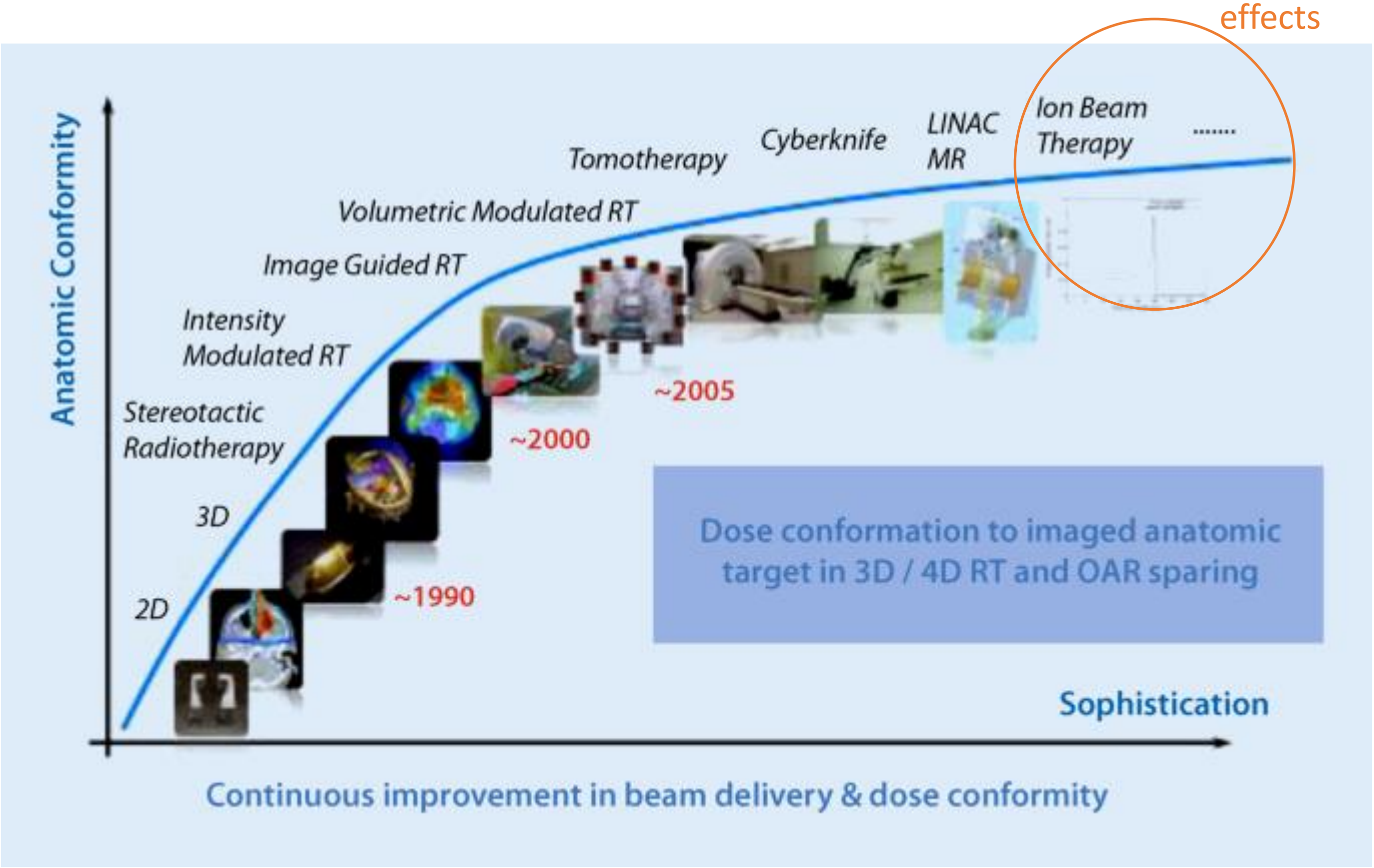
Very complex multiple-incident beam irradiation with dose modulation to allow even concave isodoses

History of X-ray RT and « technological » evolution

- Global view of the technological evolutions improving the dose conformation to the tumor: i.e Maximizing the dose delivery to the tumor vs. minimizing the irradiation of normal/healthy tissues



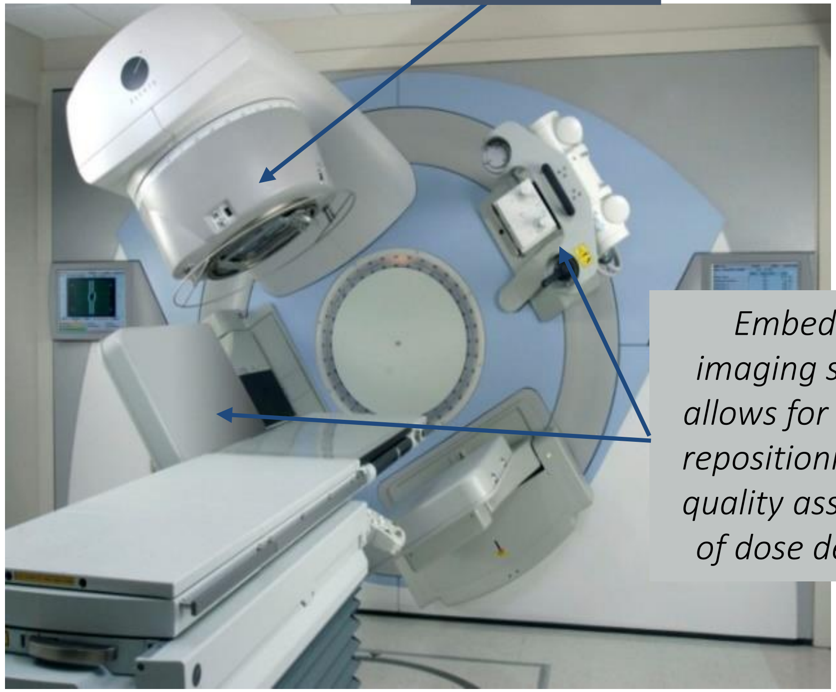
Innovative RT strategies inducing differential biological effects



Current main-used external radiotherapy

- "Conventional" radiotherapy (> 95%)
  - **Particles**: X-rays 6-25 MV (every tumors), electrons 3-18 MeV (surface tumors)
  - **Machines**: very compact clinical electron accelerators with multileaf collimators, dose delivery modulation and embedded imaging systems
  - **Time fractionation**: 2 Gy/session, 5 session/week
  - **Total dose delivered**: 40-70 Gy
  - **Dose rate**: 30-70 mGy/s
  - **Field sizes**: 2 - 40 cm²

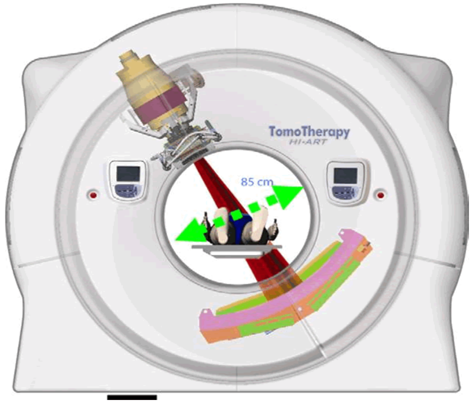
Multileaf collimator allowing optimized dose conformity



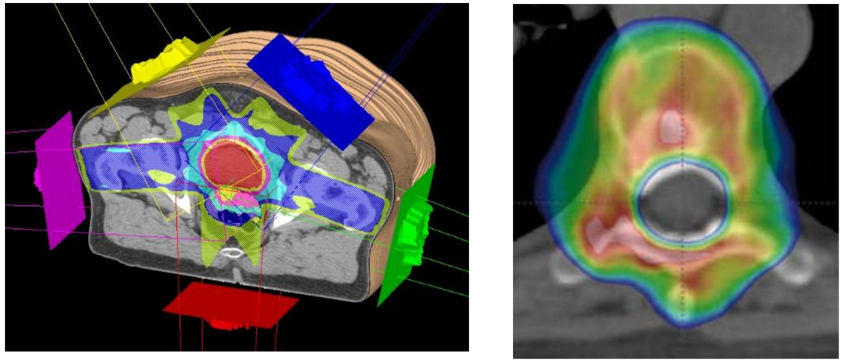
Embedded imaging system allows for precise repositioning and quality assurance of dose delivery

4 m

Standard clinical accelerator (~600 in France)



Tomotherapy

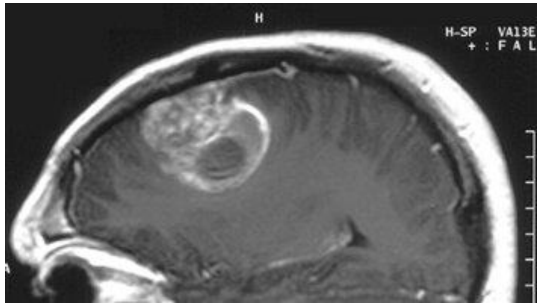


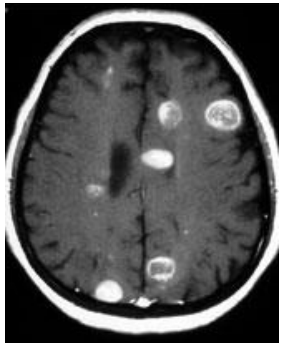
Very performant Iintensity and volumetric-modulated irradiation, sparing OAR

→ Already works well on most indications, "innovative therapies" need to keep these achievements in terms of dose conformation and dose delivery quality assurance.

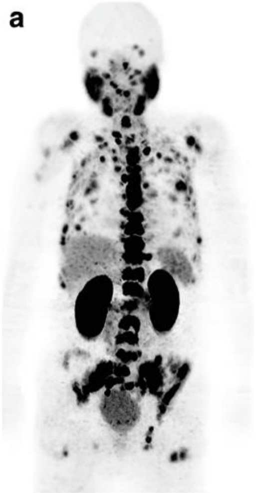
Limitations of « conventional » radiotherapy

- **The toxicity to healthy tissue** still limits the dose delivered and the curative use of RT:
  - In particular for very **radioresistant**, **bulky** and **diffuse** cancers *(e.g. glioblastoma…)*, and for **non-localized tumors** *(multiple metastasis)*





a



- How to improve the treatment?
  - Induce a more efficient tumoral irradiation
    - **High-RBE particles**: hadrontherapy (p, α, ^{12}C, ions)
    - **Targeted radiotherapy** (using molecular targeting or sensitizers)**+ high-RBE**: BNCT, nanoparticles, radionuclide therapy…
  - Preserve the healthy tissues:
    - Improve more ballistics with different particle/energy: hadrontherapy, VHEE
    - **Dose delivery mode**: spatial fractionation of dose (beam size < mm), "FLASH" irradiation (ultra-high dose-rate)

→ Play on physical parameters to induce a different biological effect

Presentation outline

- **Introduction to radiation therapy and fundamental notions**
  - **Introduction to cancer treatment**
  - **Use of ionizing radiation** : physical interactions and Radiobiological aspects on living matter

- **Therapeutic strategies to improve cancer treatments and physical issues**
  - **Differential effect**: find the good balance between tumor control and tissue preservation
  - **X-ray radiation therapy** : technological evolution improving the dose conformation to the tumor
  - **Use of different particles**: **Hadrontherapy** (protons, carbon ions…), high energy electrons (**VHEE**), neutrons…
  - **Play on dose delivery**: temporal fractionation of the dose, very-high dose-rate radiation (**FLASH** therapy), spatial fractionation of the dose (**Grid, MBRT, MRT**)
  - **Combined radiotherapies** (with molecular vector): **radionuclide therapy** (alpha targeted therapy), **BNCT**, **nanoparticle-enhanced** radiotherapy…

- Conclusions

Treatment efficacy vs. toxicity

Enhancing the differential effect between tumor cells and healthy cells

➢ **Major strategies:**

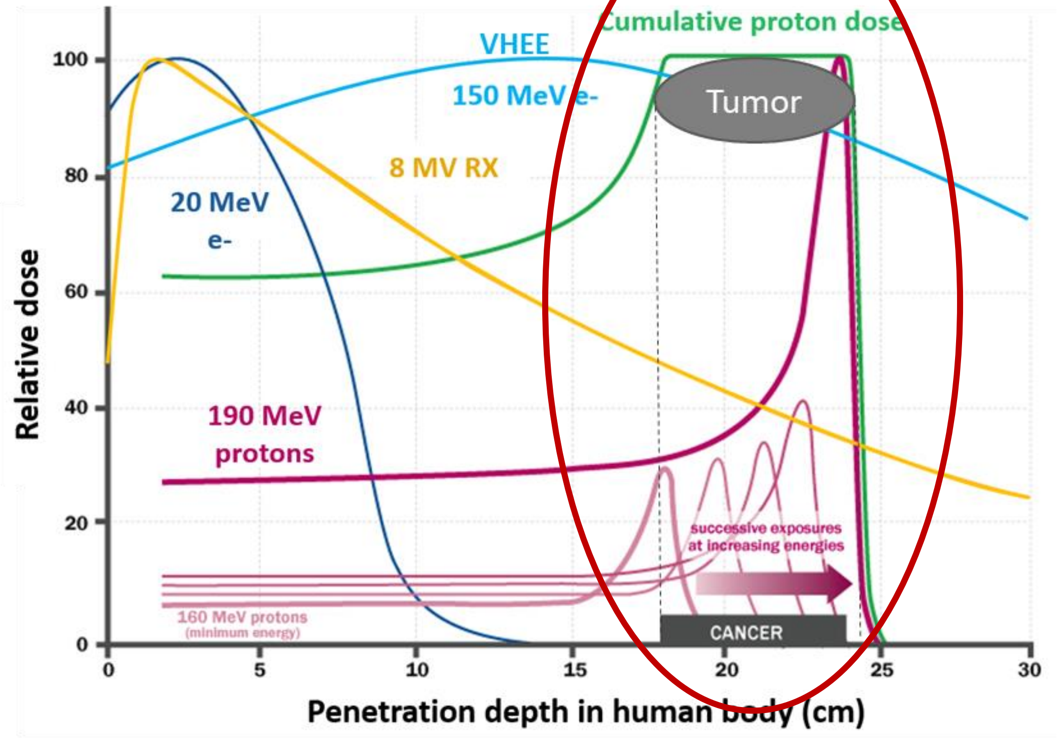
- **Anatomical radiation restriction**: Conformation of dose to tumor volume
- **Radiation choice:** protons, α, ions…
- Dose **time** and **spatial fractionation**: play on dose delivery mode
- **Pharmacomodulation / combined therapies:** radiosensitizers, molecular targeting

Technological advances

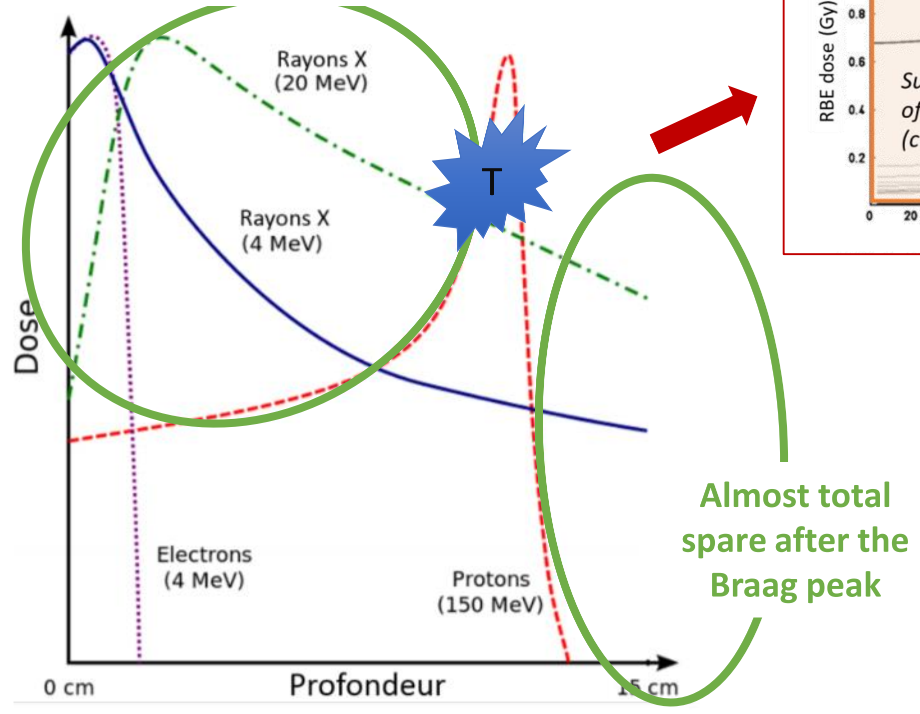
Differentiated biological effects

Hadrontherapy

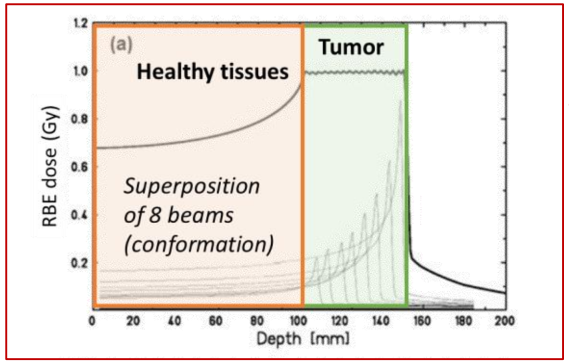
Protons, He, Carbon or heavier ions



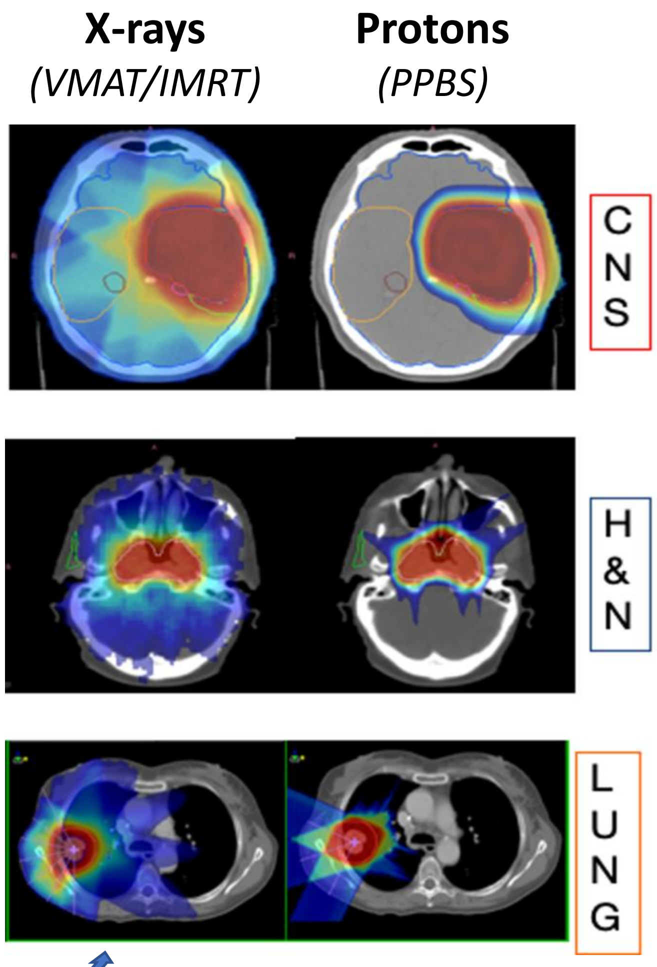
*Ballistic advantage of **protons** over photons*



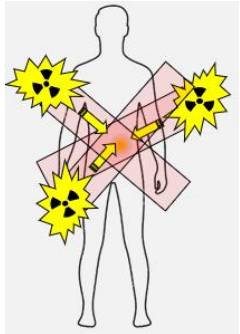
Source: Robin Fabbro thesis

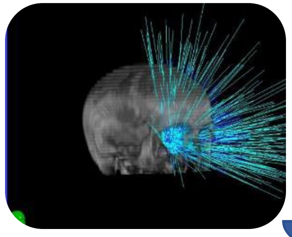


Beam energy modulation to reach the tumor depth and full coverage



Protons needs less beam incidences than X-rays to reach dose conformity *= less irradiated normal tissues*





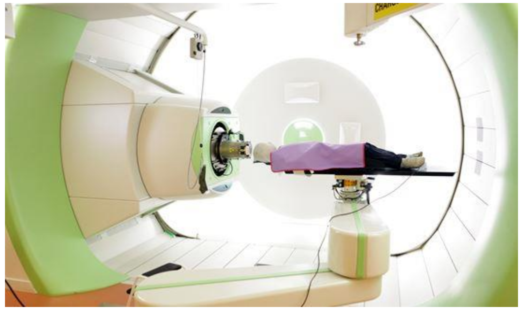
➡ Take advantage of the spatially limited energy deposit before tumor and max at the end of the range (Braag peak).

From Durante et al. 2019, Applied nuclear physics at the new high-energy particle accelerator facilities.

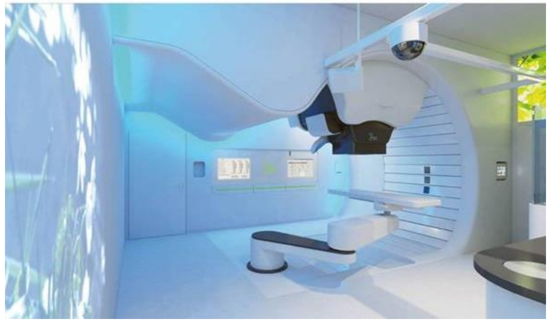
In clinics

- **Protontherapy in France:**
  - Vey interesting but **cost** (~40 M€ vs ~1M€ X-rays) and **size** (needs dedicated building) limits access
  - “only” **3 protontherapy centers** in France:

CPO (Orsay, since 1991)



CAL (Nice, since 1991)



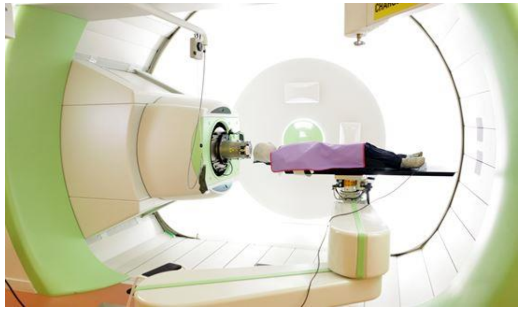
Archade (Caen, since 2018)

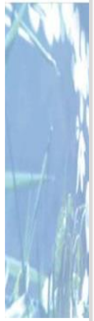
  - **~1% of RT indications**: mainly ophtalmogical, intracranial and pediatric treatments

Protontherapy: Radiation choice strategy

In clinics

- **Protontherapy in France:**
  - Vey interesting but **cost** (~40 M€ vs ~1M€ X-rays) and **size** (needs dedicated building) limits access
  - "only" **3 protontherapy centers** in France:
    CPO (Orsay, since 1991) C





  - **~1% of RT indications**: mainly ophtalmo

- **Protontherapy progression worldwile:**
  - Turnkey industrial solutions
  - Significant development

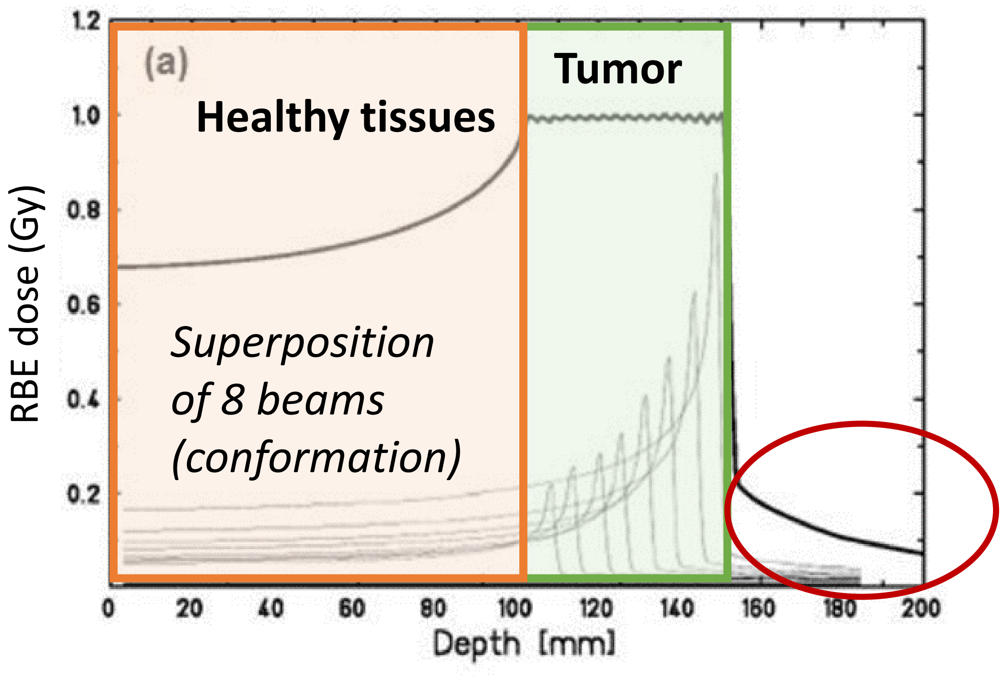
Hadrontherapy: Radiation choice strategy (C or heavier ions)

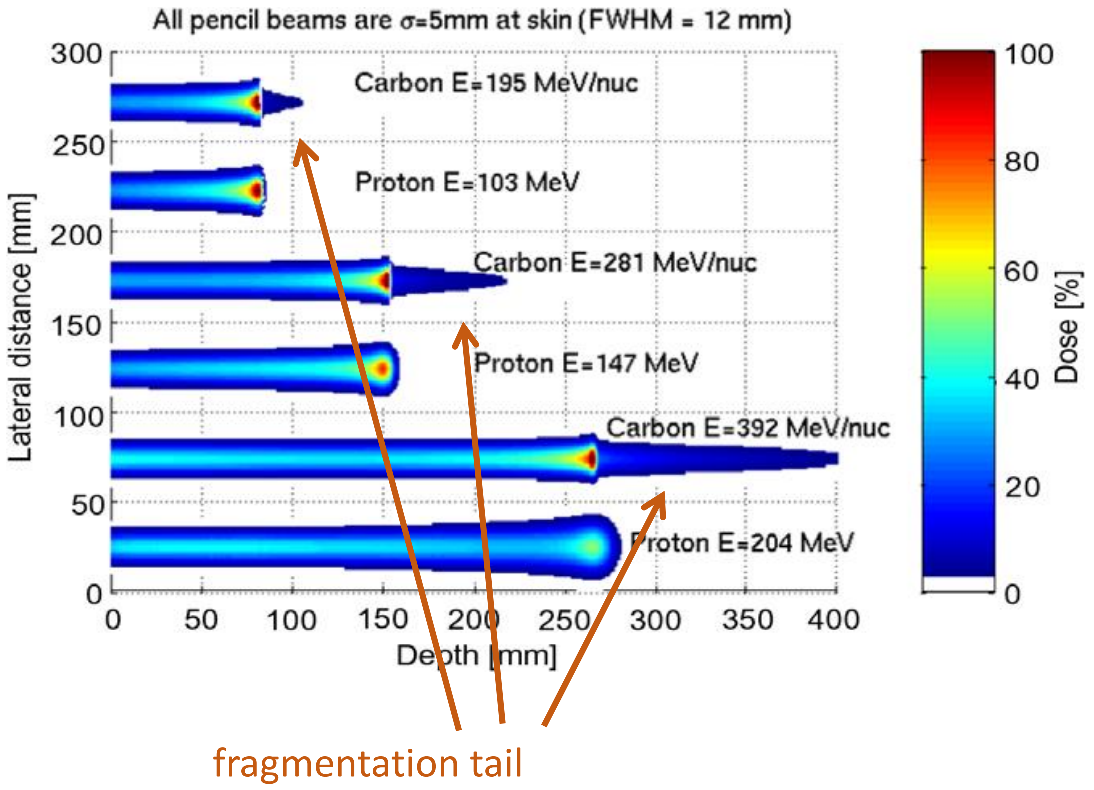
Enhancing the differential effect between tumor cells and healthy cells

Carbon ion therapy (or heavier ions)

- **Ballistic advantage** over photons
- **Differentiated RBE** in tumor vs healthy cells

Depth dose profile

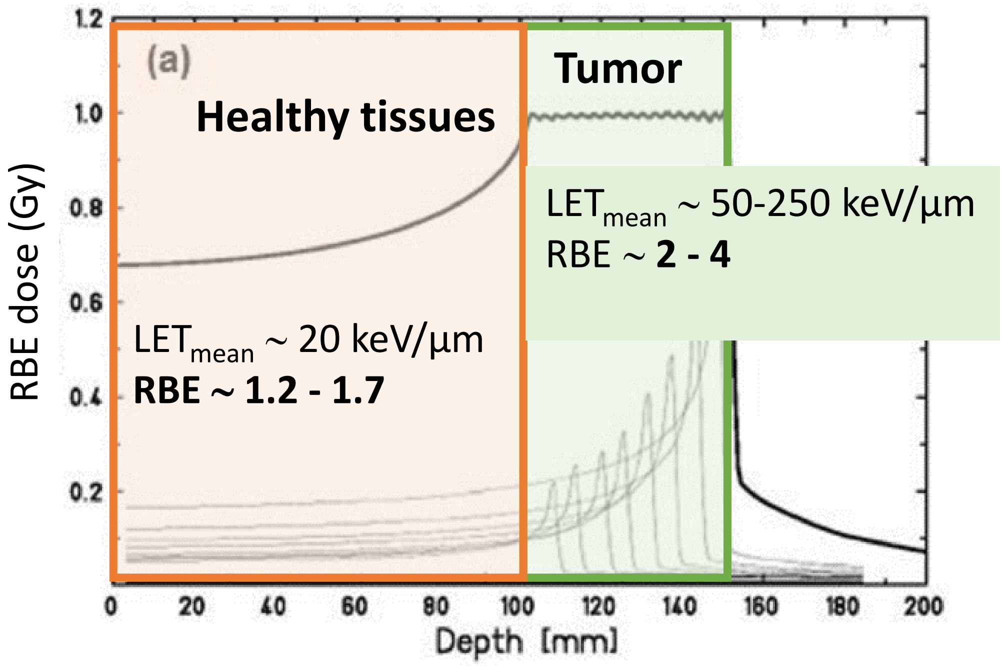




Enhancing the differential effect between tumor cells and healthy cells

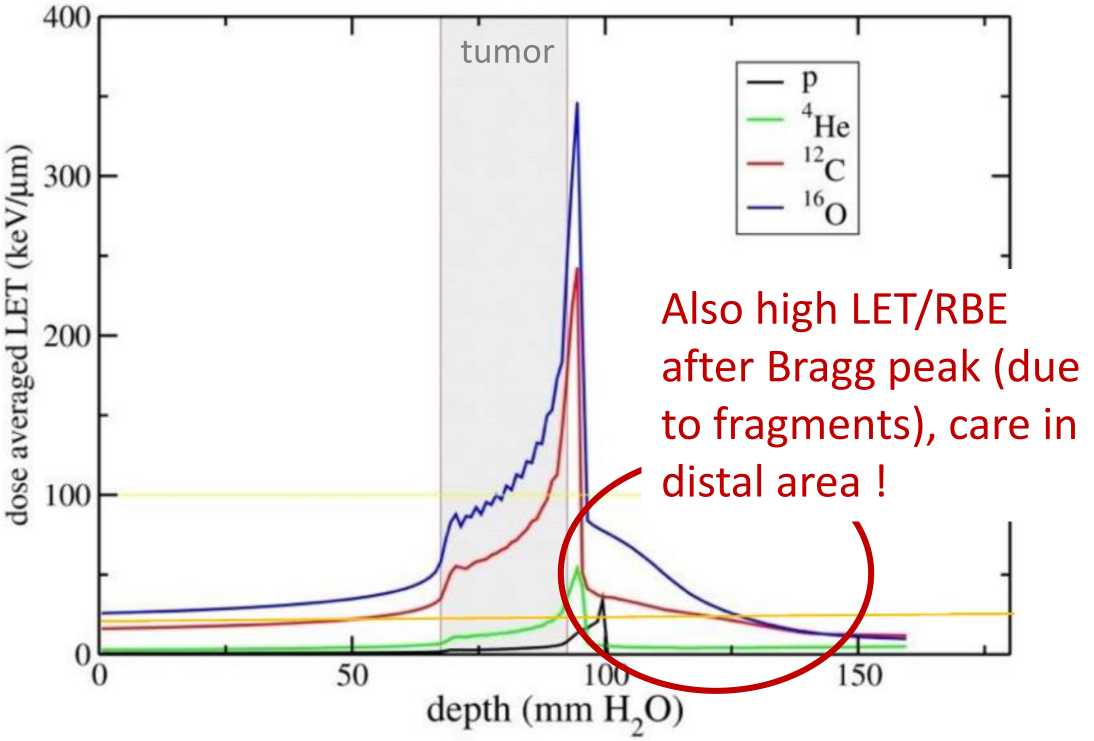
Carbon ion therapy (or heavier ions)

- **Ballistic advantage** over photons
- **Differentiated RBE** in tumor vs healthy cells



Complications ↗ **Tumor control ↗ ↗**

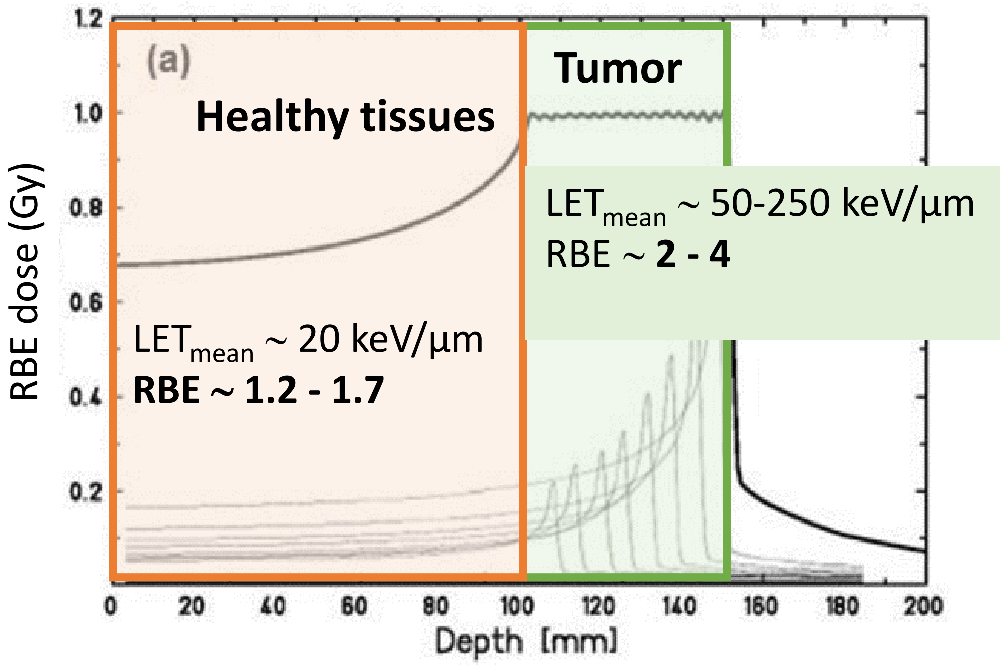
LET changes with depth



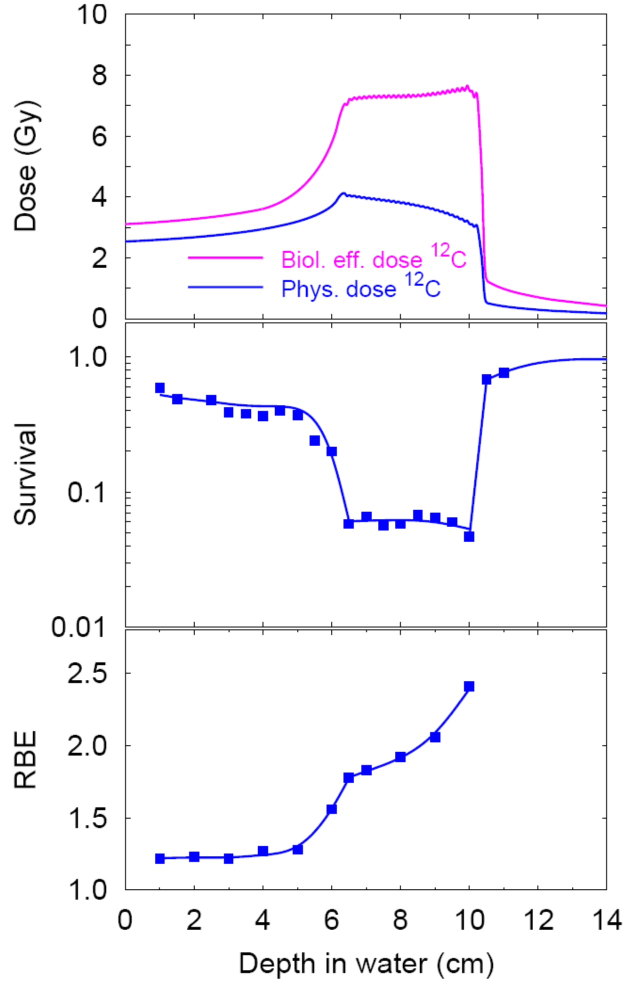
Enhancing the differential effect between tumor cells and healthy cells

Carbon ion therapy (or heavier ions)

- **Ballistic advantage** over photons
- **Differentiated RBE** in tumor vs healthy cells



Complications ↗   Tumor control ↗ ↗



From Sommerer F. PhD thesis (2007)

In the treatment planing systems, need to consider the RBE variation with depth of ion beams ➔ developments of biophysical models !

Treatment efficacy vs. Toxicity: Hadrontherapy

Therapeutic window

Hadrontherapy (proton or C ion beams)

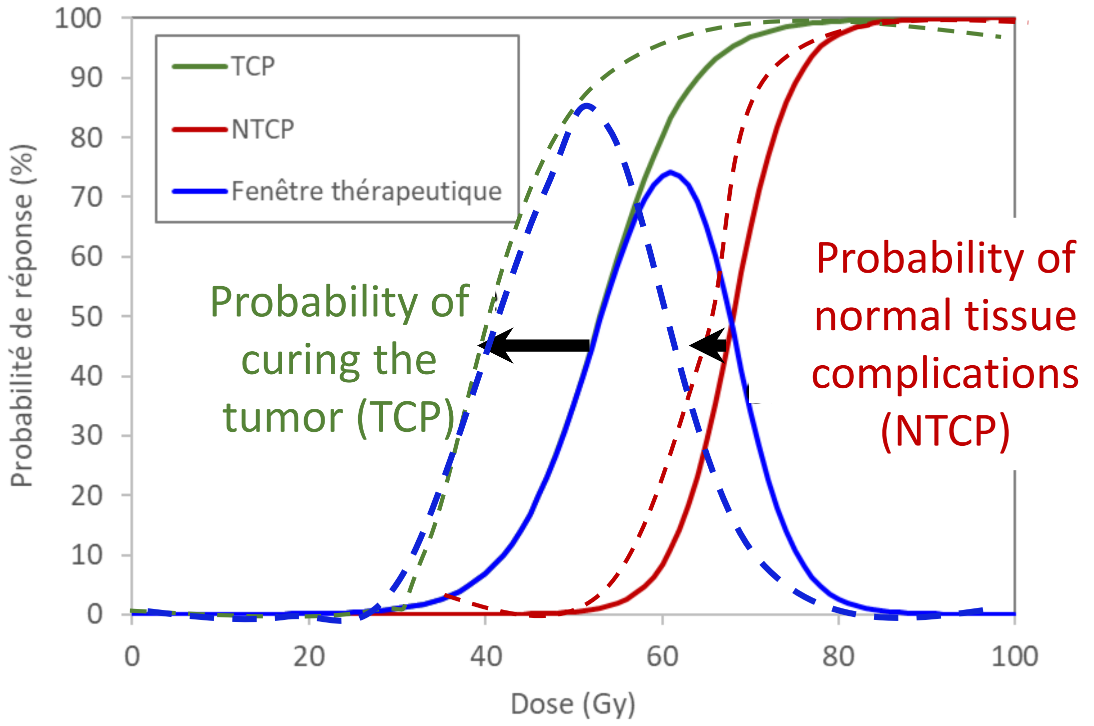
- **Ballistic advantage** over photons
- **Differentiated RBE** in tumor vs healthy cells

Toxicity increased in all tissues, but more in the tumor region.

➔ **L**ess dose would be needed for a same tumor control (↗TCP)

➔ Tissue toxicity compensed by the excellent dose conformation of ion beams

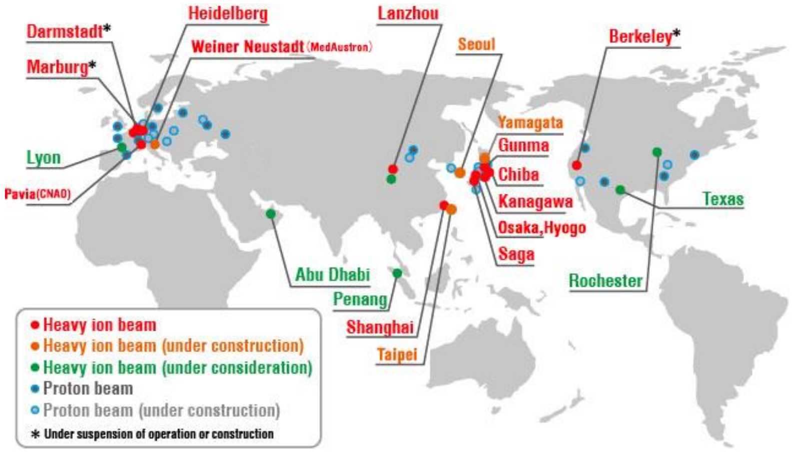
↗ therapeutic window



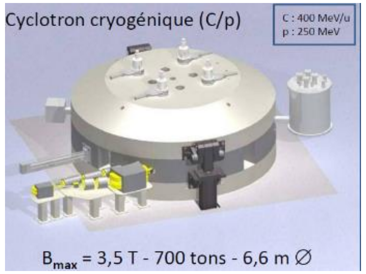
Hadrontherapy: carbon ion therapy

Worldwide development of hadrontherapy in clinics and research

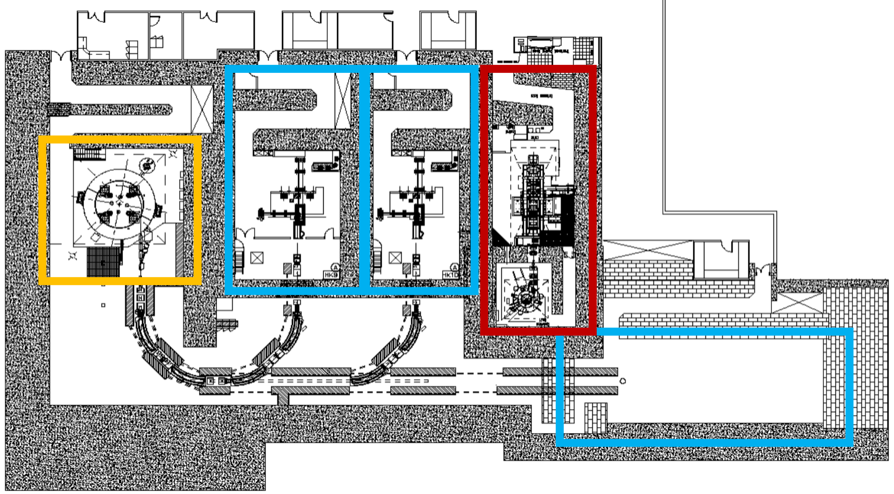
- **Caron-ion therapy:**
  - **Very high cost** (but like many new treatments)
  - **New commercial solutions**:
    example of **C400 IBA system** : compact, potentially lower construction/installation costs
  - **Ex. of Archade Caen hadrontherapy center**:

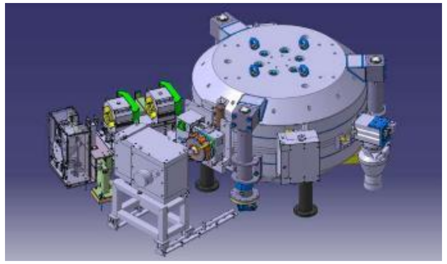


Supraconducting Cyclotron C400
^{12}C at 400 MeV/u
Protons at 250 MeV
All light nuclei with A/Z=2



Research in carbon-therapy





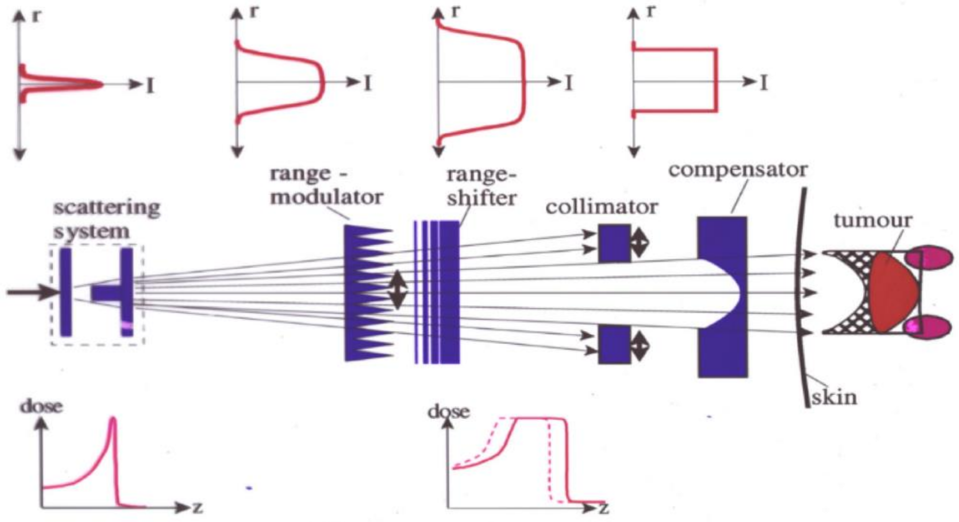
Protontherapy treatments
- Proteus One (S2C2)
- Protons at 250 MeV

- **Main indications**: Hypofractionation (Lungs, liver...), Radiation-resistant tumors (Sarcoma, adenocarcinoma...)

Hadrontherapy

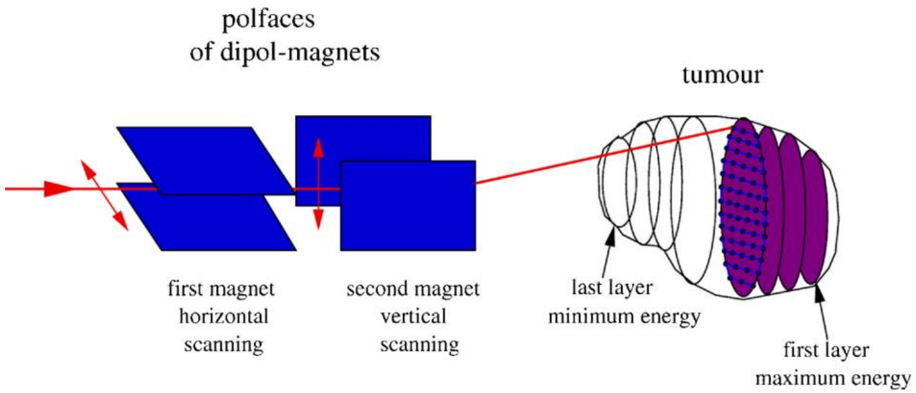
Physical issues and some examples of research developments

Hadrontherapy: passive vs pencil beam scanning



Passive beam delivery

- Whole PTV irradiated at once
- Fast delivery (no beam parameter change)
- Personalized compensator
- Secondary radiation production in passive elements (neutron dose)



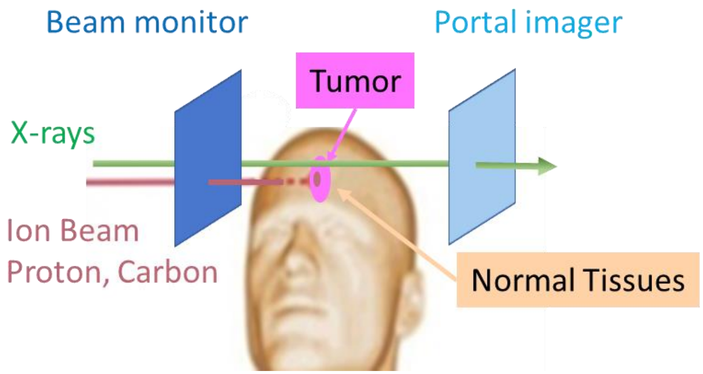
Active beam delivery: Pencil Beam Scanning

- Energy layers (energy variation at accelerator exit)
- No passive element in the nozzle
- The PTV is painted spot-by-spot

O. Jäkel et al, Z Med Phys 2022

Hadrontherapy: current challenges

Physical and radiobiological issues in hadrontherapy

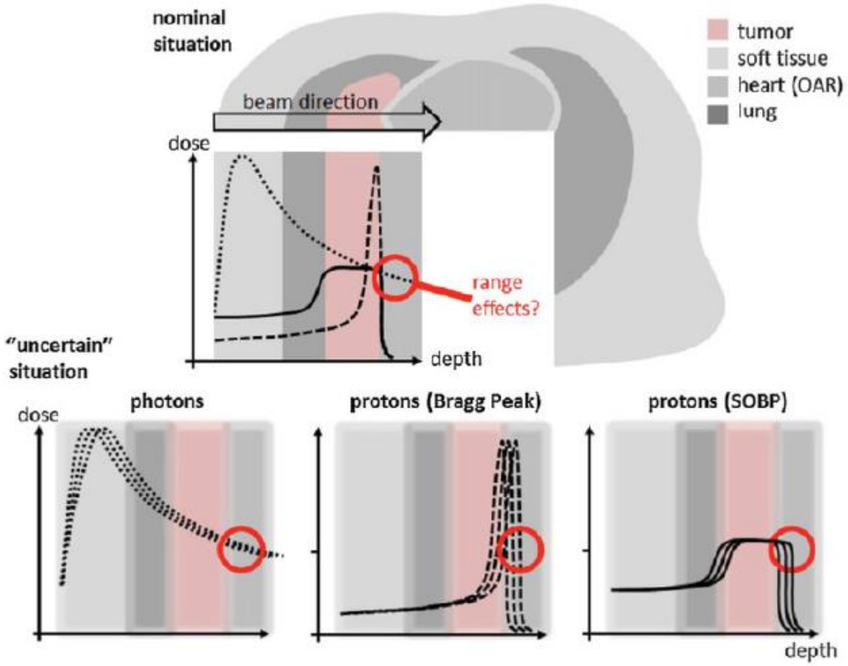


- **Instrumentation and online quality control of ion beams:**
  - **Beam monitoring systems**
  - **« Online » dose delivery control and ion range verification**: prompt gamma imaging, online PET…
  - **Dosimeter developments and LET measurements** (microdetectors)
- **Numerical tools, dose and RBE planification sytems:**
  - **Fragmentation of ions**: mixed particles, uncertainties in cross sections and computation tools → measurements and implementation in TPS
  - **Multiscale modeling and biophysical models**: consideration of LET/RBE in TPS
- **Radiobiology of ions:**
  - Need for hadronic research platforms to understand biological mechanism, "hadronbiology"
- **Protocol optimization to enhance therapeutic index:** clinical data analysis (PMRT project) and opening for new treatment indications

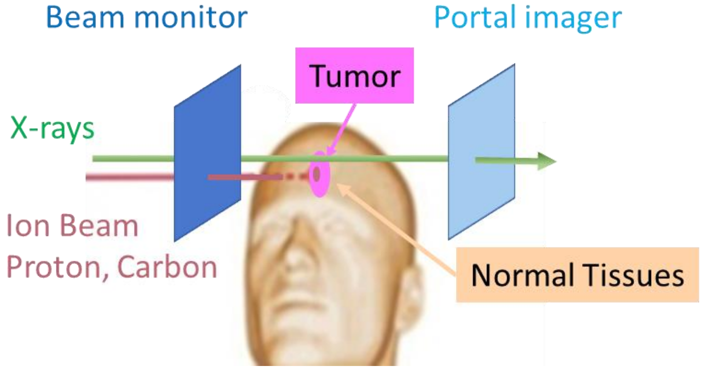
Physical and radiobiological issues in hadrontherapy

➢ Instrumentation and online quality control of ion beams:

- **Beam monitoring systems**
- **« Online » dose delivery control and ion range verification**: prompt gamma imaging, online PET…



A.C. Knopf et al. Phys. Med. Biol. 2013

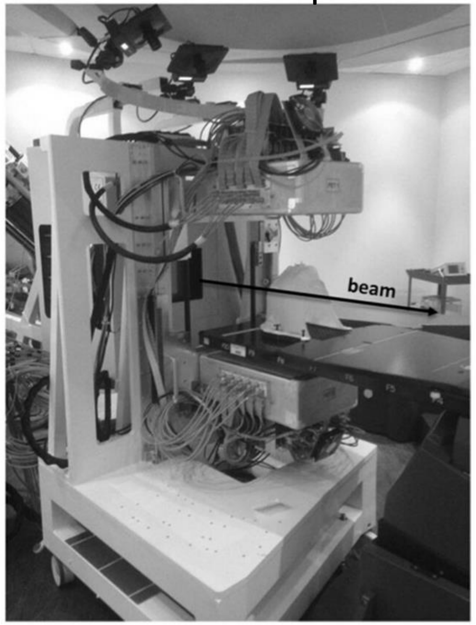


- **Ions are more sensitive than photons to tissue heterogeneities.**
- **Primary ions stop in the patient! advantage for dose optimization, but disadvantage for dose delivery control**

➔ **adapted instrumentation using secondary particle detection**

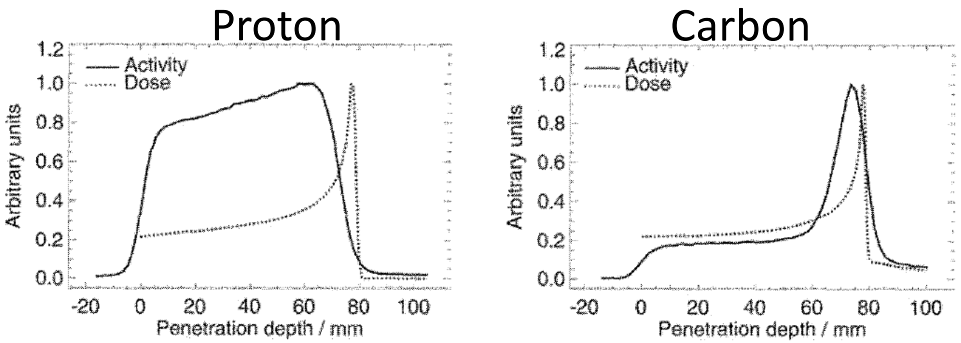
Use of positron emission tomography (PET) systems

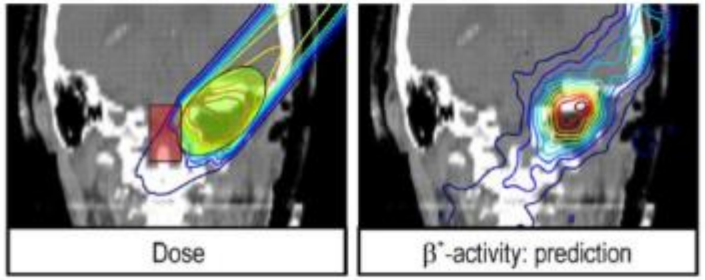
INSIDE (CNAO)
Ferrero Scient Rep 2018



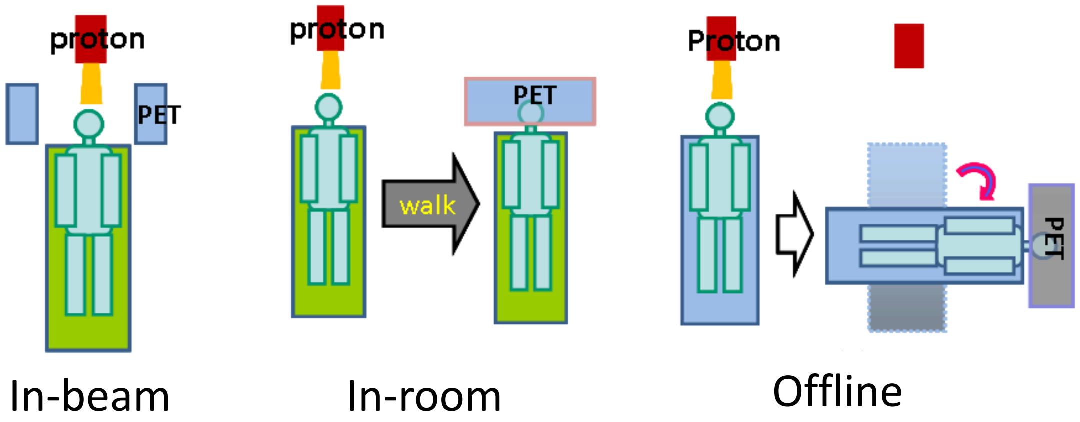
➤ **Image of the auto-activation of β+ emitters due to ion beam nuclear interactions :** only method used clinically (off-line)

- **Main isotopes of interest : ^{11}C** *($T_{1/2}$~20min)* and **^{15}O** *($T_{1/2}$~2min)*





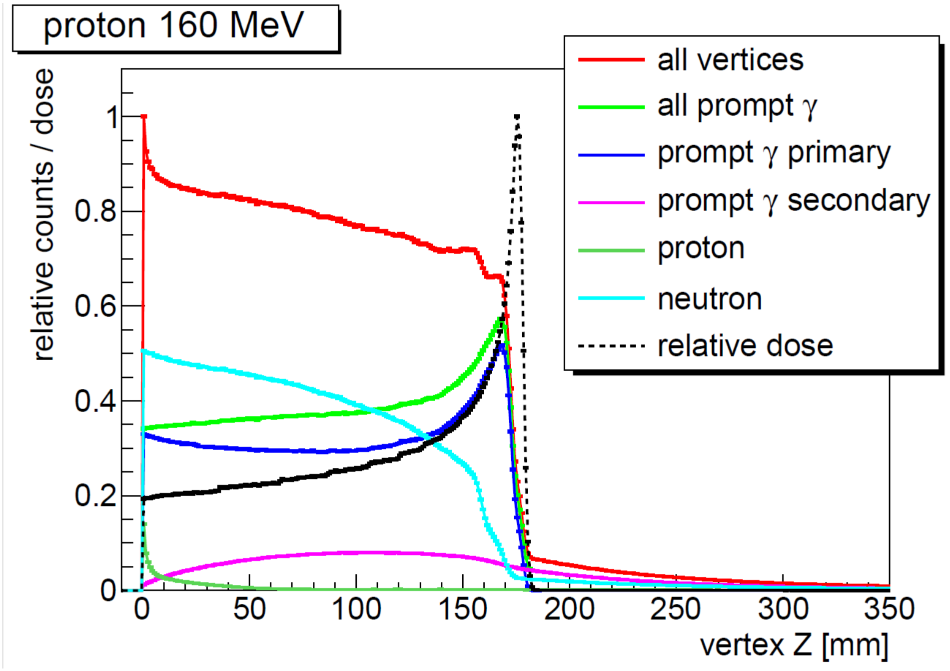
Proton and carbon induced activity profiles
(Enghardt JRO 2004)



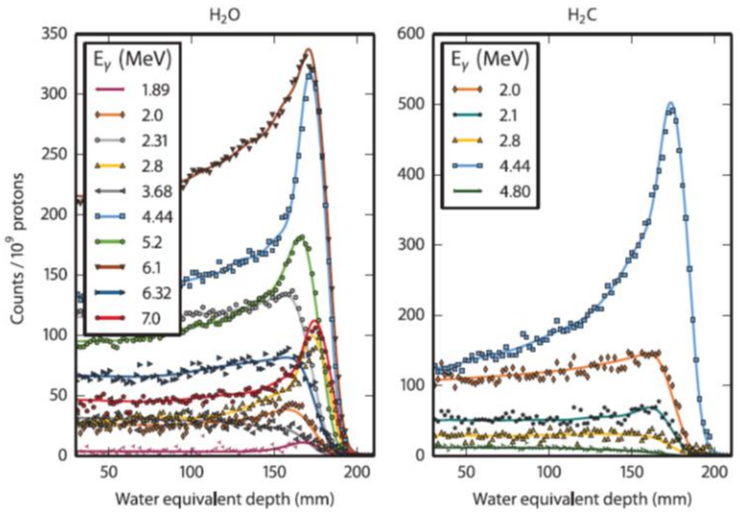
- Measurement challenges/limits
  - Integral measurements (short lifetimes)
  - Statistics issue
  - Washout issue (especially when used off-line)

Use of prompt gamma emission

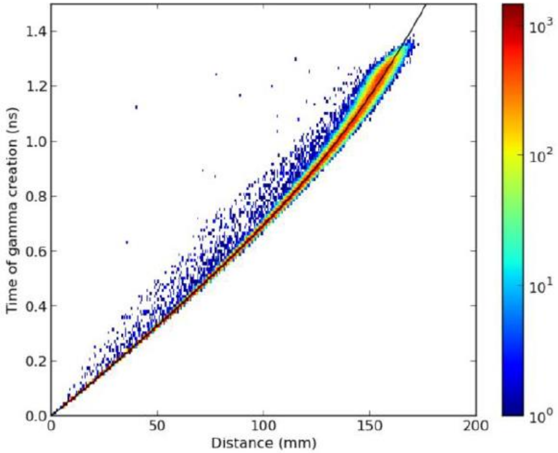
- **Image of the spontaneous (prompt) gamma (PG) emission produced by ion beams due to nuclear interaction:**
  - Emission profile correlated to beam range



Krimmer et al, NIMA 2018



PG Energy correlation
Verburg et al, PMB 2014

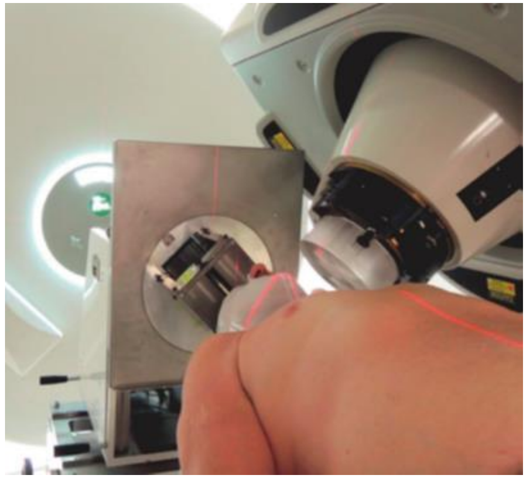


PG Timing correlation
Livingstone et al, PMB 2020

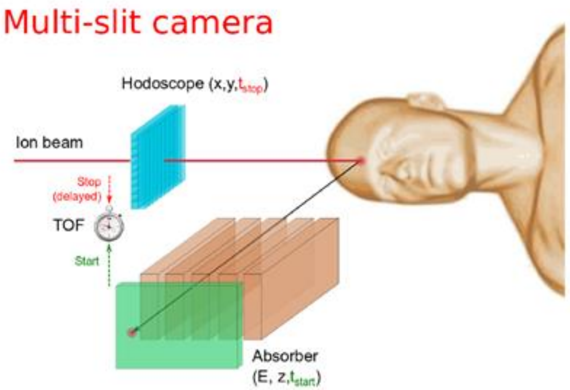
Use of prompt gamma emission

Several project developments at IN2P3.

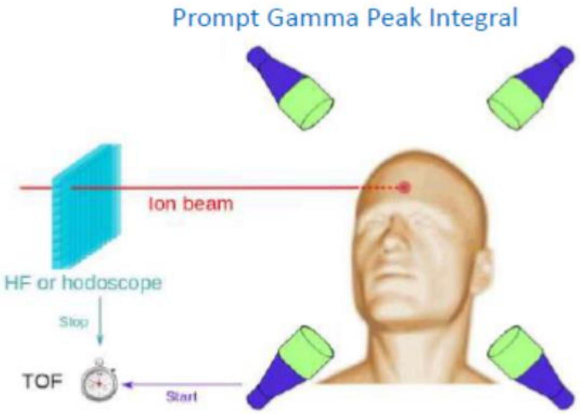
➢ Range verification devices:



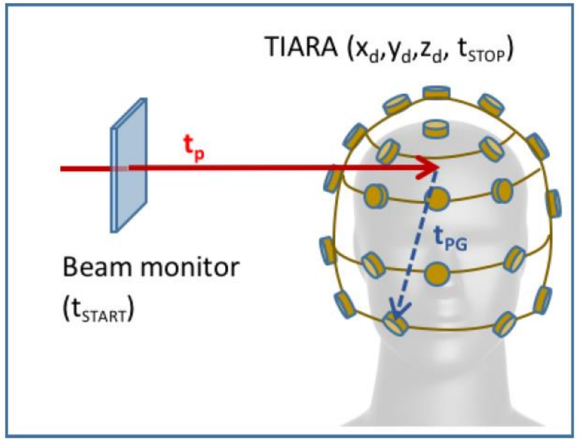
Knife-edge slit camera (IBA, Xie et al 2017) Tested in clinics



1D Imaging device with Time of Flight



Integral measurements



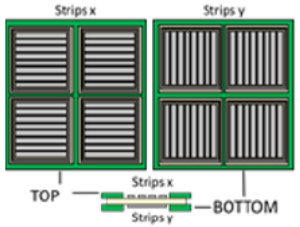
PG Timing Imaging

- Measurement challenges
  - Background (neutrons, scattered…), high instantaneous count rate
  - Statistics (# of PG per pencil beam), highly challenging with carbon ions
  - Accelerator time structure (pulsed vs continous beams)

Use of prompt gamma emission

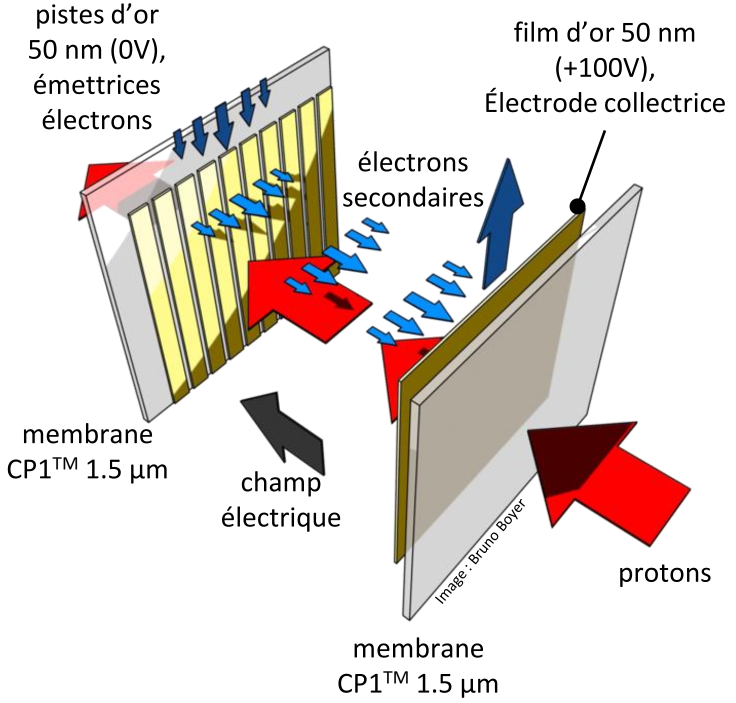
➢ **Beam monitoring devices (hodoscopes):**

- Requirements:
  - Thin enough to not alter the treatment
  - Fast measurement for Time of flight measurements (TOF)
  - Spatial information to reconstruct the vertex of interaction
  - Adapted to accelerator time structure



4 sCVD (4,5x4,5 mm² chacun)

PEPITES



Example of scintillating fiber hodoscope or stripped Diamond monitors developped for time tagging of PG imaging systems

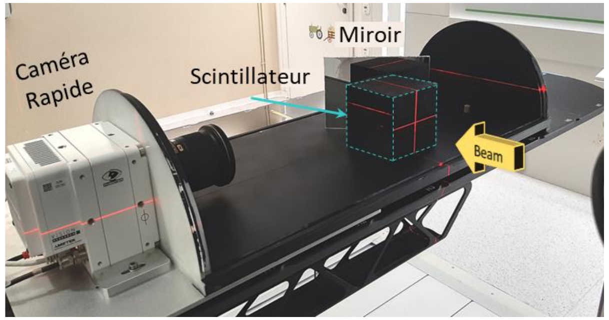
Ultra-thin (< 10µm) stripped monitor, adapted also for high-dose rate measurements (installed on ARRONAX)

Hadrontherapy: current challenges

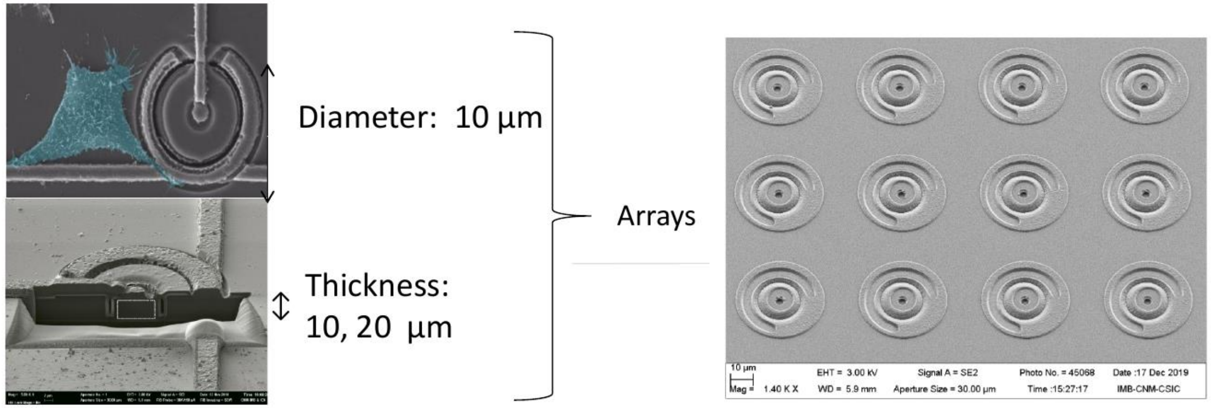
Physical and radiobiological issues in hadrontherapy

➢ Instrumentation and online quality control of ion beams:

- **Beam monitoring systems**
- **« Online » dose delivery control and ion range verification**: prompt gamma imaging, online PET…
- **Dosimeter developments and LET measurements** (microdetectors)

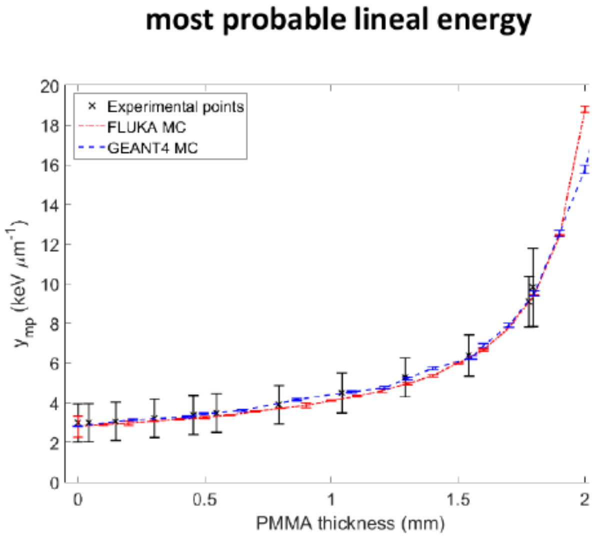


Example of 3D scintillating dosimeter for PBS quality control (from A.M. Frelin)



C. Guardiola, Applied Physics Letters 107, 023505 (2015)

Examples of 3D silicon microdosimeters capable of measuring directly the LET (or lineal energy y) of the ion beam (Guardiola et al.)



Hadrontherapy: current challenges

Physical and radiobiological issues in hadrontherapy

➢ Numerical tools, dose and RBE planification sytems:

- **Fragmentation of ions**: uncertainties in cross sections and computation tools → measurements and implementation in TPS
- **Multiscale modeling and biophysical models**: consideration of LET/RBE in TPS

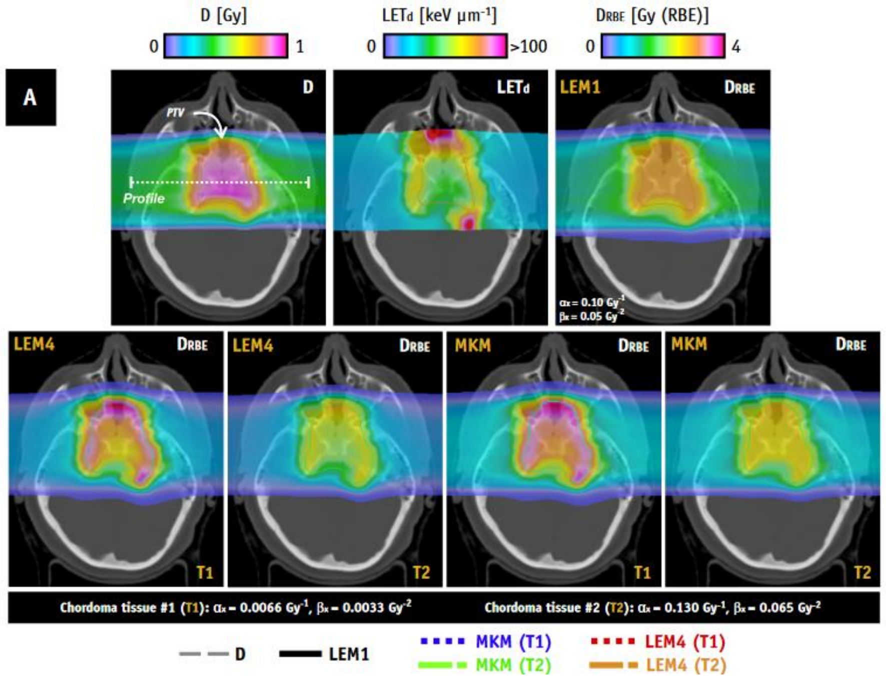
➢ Requirements for treatment planing:

- Need for **correct representation of dose contributors** in Monte Carlo modeling tools (or TPS) (**including fragments**)
- Good representation of **ions and fragment RBE**

Cf. presentation of Mario Alcocer

→ Can use **Biophysical models** like LEM, MKM or **NanOx** to quantify the RBE-weigthed dose.

- Based on dose deposit considerations at micro or nanoscales
- Sensitives to cell type and alpha/beta parameters of a tissue



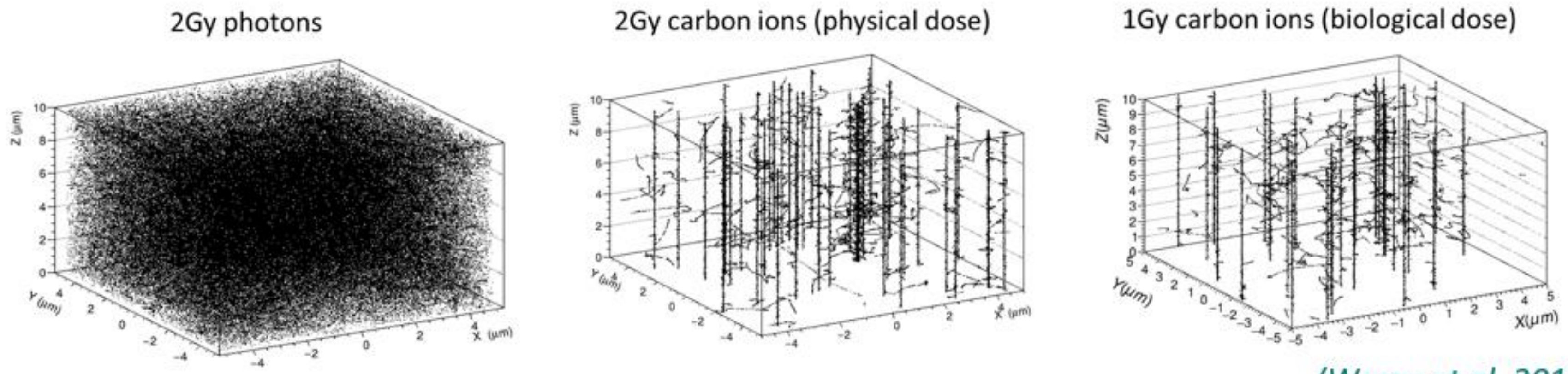
From Mein et al., 2020

Hadrontherapy: current challenges

Physical and radiobiological issues in hadrontherapy

➢ Radiobiology of ions:

- Need for **hadronic research platforms** to **understand biological mechanism**, “hadronbiology”



(Wozny et al. 2019)

- **Several research French plateforms already available**: GANIL (Caen), Precy (Strasbourg), Arronax (Nantes), Aifira (Bordeaux), maybe soon in ALTO (Orsay ;-)… and others in europe.

➢ **Protocol optimization to enhance therapeutic index:** clinical data analysis (PMRT project) and opening for new treatment indications

Time and spatial dose fractionation

Dose delivery mode

Treatment efficacy vs. toxicity

Enhancing the differential effect between tumor cells and healthy cells

- **Major strategies:**
  - **Anatomical radiation restriction**:
    Conformation of dose to tumor volume
  - **Radiation choice:**
    X-rays, protons, α, ions…
  - Dose **time** and **spatial fractionation**:
    play on dose delivery mode
  - **Pharmacomodulation / combined therapies:**
    radiosensitizers, molecular targeting

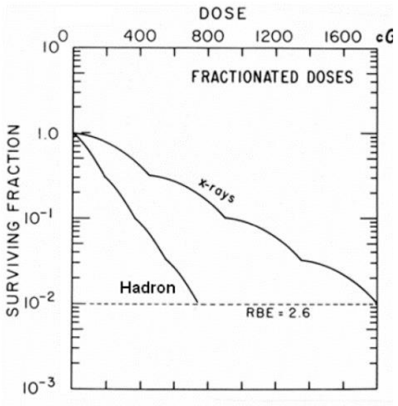
Technological advances

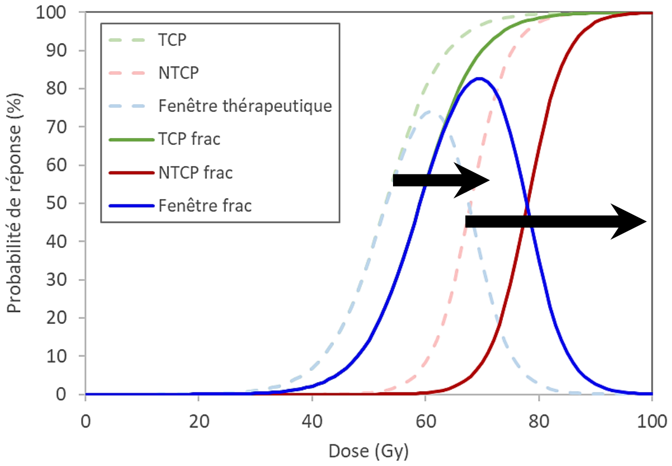
Differentiated biological effects

Dose time and spatial fractionation

Play on dose-delivery mode to decrease normal tissue complications

- **Dose fractionation (in several sessions) used clinically to increase the differential effect between normal tissue recovering vs tumor cells**
    - This uses « standard » **dose-rates (of ~2 Gy/min)** and as **homogeneous as possible irradiations** over the tumor





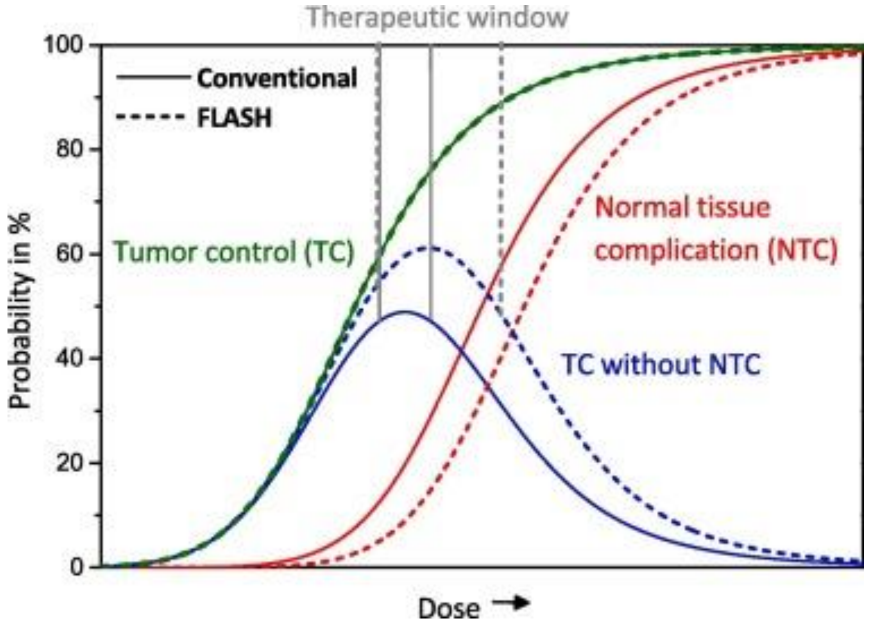
Other « extreme » dose-delivery methods can lead to increased differential response between healthy and tumoral tissues.

- **Use of ultra-high dose rates: FLASH**

- **Use of very heterogeneous and ultra-thin beams: microbeam, minibeam or Grid therapy**

FLASH therapy

Ultra-high dose rate irradiations:
principle and challenges

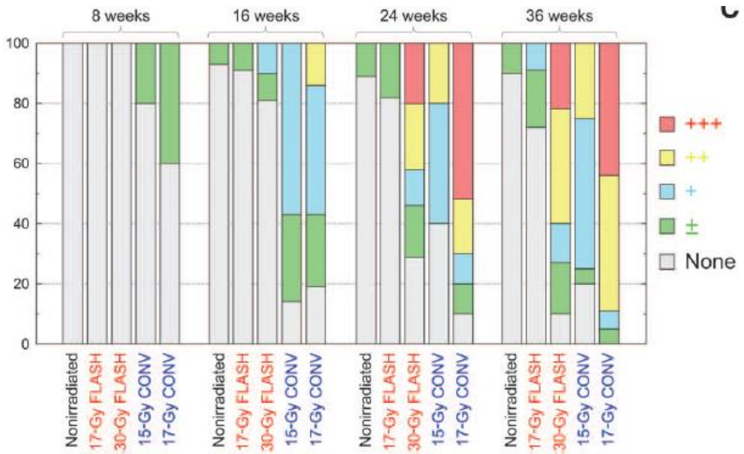


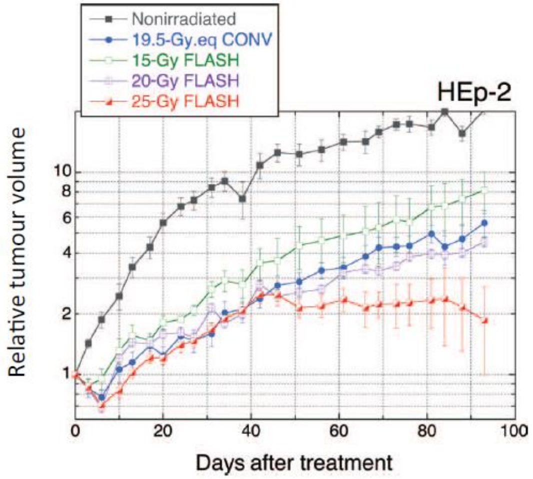
NTPC →

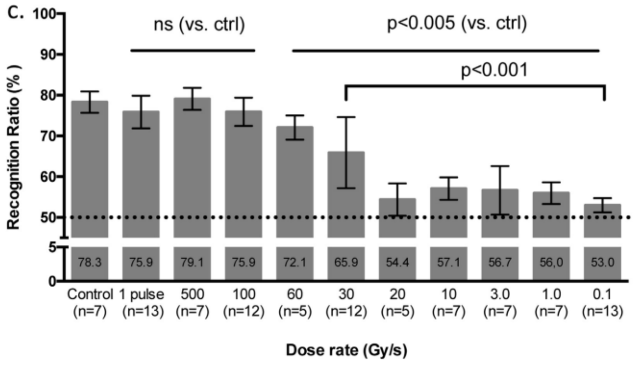
FLASH therapy: discovery

➢Ultra-high dose rates (> 40-100 Gy/s) protect normal tissues with same tumor control:

- Pioneer work of Favaudon *et al.* 2014: observed **lower normal tissue toxicity** (lung fibrosis) using **high-dose rate e-beam (> 40 Gy/s,** E~6 MeV**)** with **similar tumor control** to conv. (~0.03 Gy/s)







Memory sparing in mice after whole brain irradiation for dose rates > 100 Gy.s^{-1} (Montay-Gruel et al. 2017)

First demonstration of lung fibrosis reduction (twice more dose) on mice treated with FLASH compared to CONV irradiation, with comparable tumor response *(Favaudon et al. 2014)*.

- FLASH-effect confirmed with **e-/photon beams** in several *in vivo* experiments. Recently demonstrated with **scattered and PBS proton beam** *(Diffenderfer et al. 2019)*.
- **First patient treated** in Lausanne *(Bourhis et al. 2019)*.
- Several clinical trials started (on electron beam UHDR facilities, < 10 MeV)

FLASH therapy:

➢A picture of articles showing (or not) a FLASH effect in different beams *(M.C. Vozenin, 2022)*

THE FLASH EFFECT is a biological effect

Normal tissue sparing

FLASH-RT does not induce Normal tissue toxicity When CONV-RT does

Electron
Chabi et al. IJROBP2020
Montay-Gruel et al. Rad Res, 2020
Allen et al. Rad Res, 2020
Alaghban et al. Cancers, 2020
Bourhis J et al. Radiother Oncol. 2019.
Jorge PG et al. Radiother Oncol. 2019 Oct.
Montay-Gruel P et al. Proc Natl Acad Sci U S A. 2019.
Vozenin et al. Clin Can Res, 2019.
Montay-Gruel P et al. Radiother&Oncol., 2017.
Jaccard M et al. Med Phys, 2018.
Favaudon V et al. Sci Transl Med. 2014.

X-ray-synchrotron
Montay-Gruel P et al. Radiother Oncol. 2018.

Electron
Ruan et al, IJROBP, 2021
Beyreuther et al., Radiother Oncol, 2021
Levy et al, Sc Rep, 2020
Soto et al. Rad Res, 2020.
Fouillade C et al. CCR, 2019.
Simmons et al. Radiother Oncol. 2019.
Loo B et al. IJROBP, 2017, abst.
Hendry et al. Rad Res, 1982.

Proton
Kim et al, Cancers, 2021 (BI)
Evans et al, IJPT, 2021
Cunningham et al., Cancers, 2021 (PBS)
Zhang et al. Rad Res, 2020.
Diffenderfer et al. IJROBP, 2020.
Girdhani et al. Can Res, 2019, abst.

X -ray synchrotron
Smyth et al. Sci Rep, 2018.
Proton
Beyreuther et al. Radiother Oncol. 2019.
Electron
Venkatesulu at al. Sc Rep, 2019.

And FLASH-RT is equally able to eradicate tumors compared to CONV-RT

Electron
Chabi et al. IJROBP, 2020.
Montay-Gruel P et al. CCR, 2020.
Bourhis J et al. Radiother Oncol. 2019.
Jorge PG et al. Radiother Oncol. 2019.
Favaudon V et al. Sci Transl Med. 2014.

Electron
Kim et al. IJROBP, 2020
Levy et al, Sc Rep, 2020

Proton
Kim et al, Cancers, 2021 (BI)
Velalopoulou et al, Can Res, 2021
Cunningham et al., Cancers, 2021
Diffenderfer et al. IJROBP, 2020.
Girdhani et al. Can Res, 2019, abst.

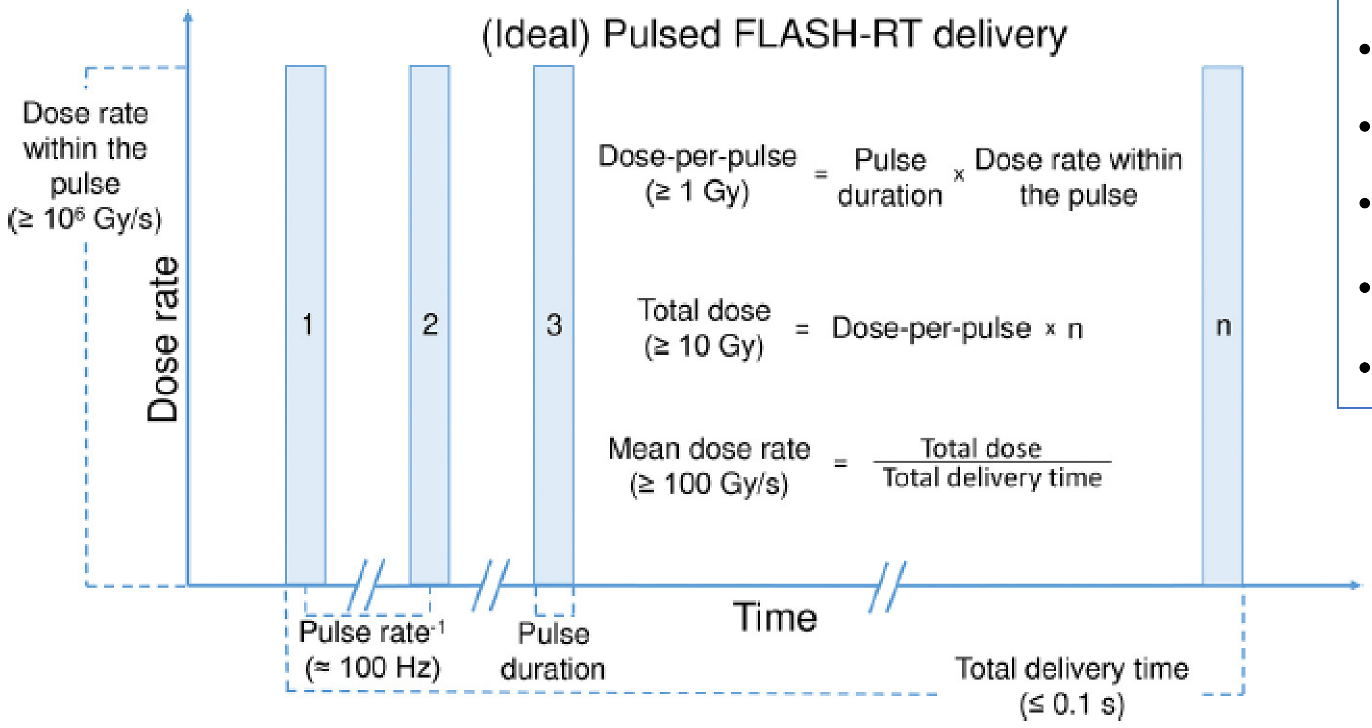
High and fast enthousiasm with FLASH therapy…
Sometimes forgeting the basic rules of protection in RT

➔ Some negative results in veterinary trials on cats (Vozenin et al.) or dogs (*Børresen B. et al., Front Onc 2023)* were animals developed osteoradionecrosis.

➢*« FLASH » is a very interesting « magical » effect, but we don't understand why it works…*

FLASH therapy: What is needed to trigger a "Flash" effect ?

➢Important physical irradiation parameters



From Wilson et al. (2020), Frontiers in Oncology, volume 9:1563.
https://doi.org/10.3389/fonc.2019.01563

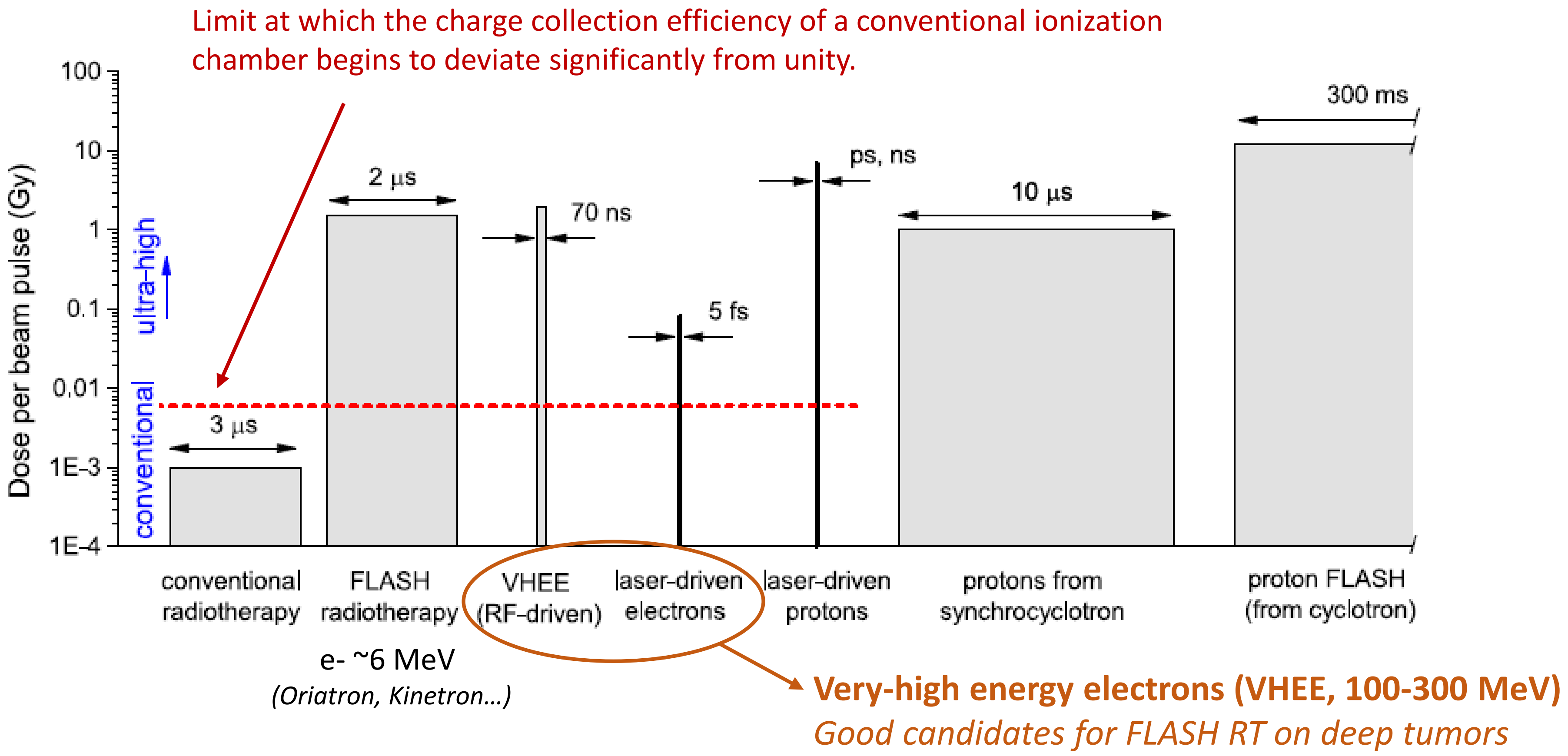
	FLASH	CONV
• **Mean dose rate ($\dot{D}$)**	≥ 100 Gy/s	~ 0,03 Gy/s
• **Total irradiation time (t)**	≤ 100 ms	> min
• **Dose per pulse (DPP)**	≥ 1 Gy	~ 1 mGy
• **Pulse dose rate ($\dot{D}_p$)**	≥ 10^6 Gy/s	≥ 10^3 Gy/s
• **Pulse duration** (t_p)	?	~1 µs

With which beams:

- **Electrons** *(4-20 MeV)* : >20 preclinical articles
- **Protons** : ~6 articles précliniques
- **RX** *(synchrotron)* : 1 article
- *At least 3 negative FLASH results published (e-, RX & p)*

FLASH therapy: accelerators and dosimetry

➢Time structure characteristics of UHDR facilities and dosimetric issues:



From Schuller et al. (2020), Physica Medica 80 (2020) 134–150.
https://doi.org/10.1016/j.ejmp.2020.09.020

FLASH Therapy: dosimetric challenges

➢ Issue in absolute dose measurements in UHDR:

- **No active dosimeter adapted to such dose-rates**
- Gold standard = ion chamber, parallel for electrons. D'après **l'IAEA 398 :**

$$D_{W,Q} = M \cdot \boldsymbol{k_s} \cdot k_{pol} \cdot k_{TP} \cdot k_{Q,Q_0} \cdot N_{D,w,Q_0}$$

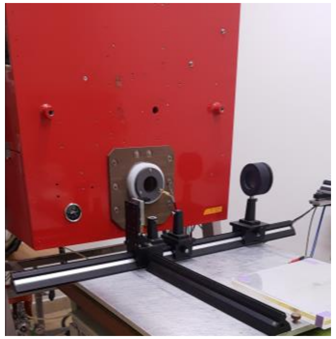
- $\boldsymbol{k_s}$: correction factor for charge recombination in the air cavity

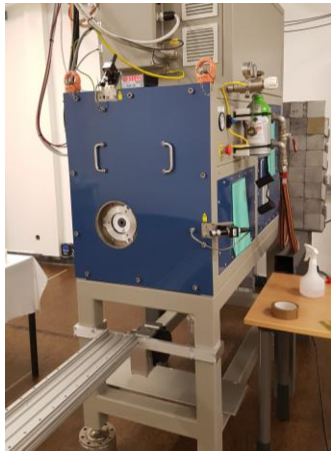
Calculation with the Two Voltage Analysis: **non adapted for DPP > 20 mGy**.

- New methods for $\boldsymbol{k_s}$ determinations.

Some commercial solutions arriving: FLASHKnife (TheryQ)

→ **Use of references: calorimeters** *(McManus et al. 2020)* or **passive dosimeters** *(radiochromic films, thermoluminescent diodes, Alanine)* *(Petersson 2017, Cavallone 2022)* known to be independent of dose-rate *(Jaccard et al. 2017, Jorge et al. 2019)*



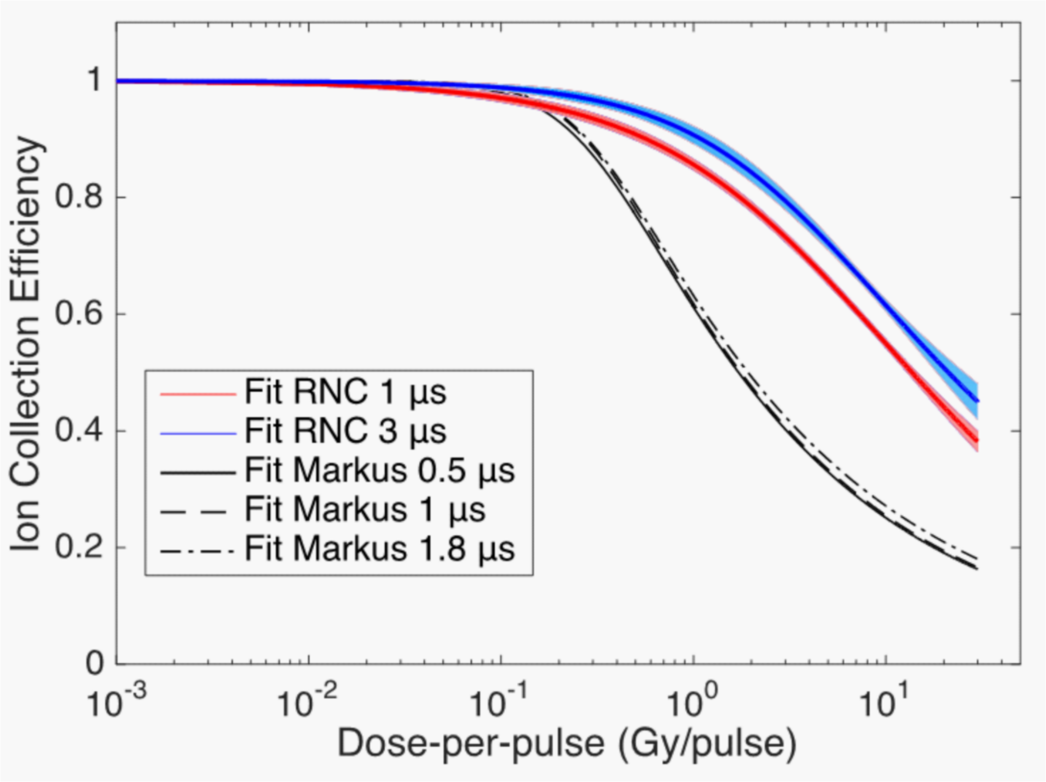


Exemples of FLASH electron research accelerators : Kinetron (Orsay), Oriatron (Lausanne)

FLASH Therapy: dosimetric challenges

➢ Determination of the ion collection efficiency of Razor NanoChamber (RNC) of IBA

- Fit from a logistic model proposed by *Petersson et al. 2017* for the Advanced Markus Chamber (PTW) :



Cavallone et al., Med Phys. 2022 ;49:4731–4742.
https://doi.org/10.1002/mp.15675

$$ICE\,(DPP) = \left(1 + \left(\frac{DPP}{\gamma}\right)^{\alpha}\right)^{\beta}$$

Results ICE:

DPP	RNC	Markus*
0,1 Gy	> 95%	95%
1 Gy	>85%	60%
10 Gy	>55%	25%

** Issu de Petersson et al. 2017, résultats similaires obtenus par Mc Manus pour la ROOS chamber.*

RNC gives better results, but still large uncertainties (~6%) and saturation after ~200 mGy/pulse → for preclinical exp.
➔ **Need for new dosimetry developments**

FLASH Therapy: dosimetric challenges

New dosimeter developments, for clinical use:

- **With the european project UHDpulse** *(metrology labs)* **:** examples of developments

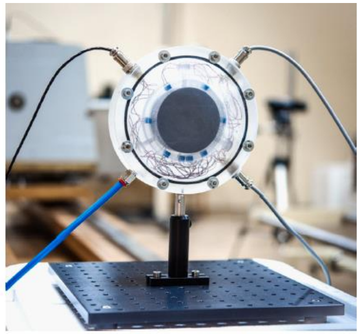


Fig. 9. GUM's portable graphite calorimeter to be tested for use as a primary standard for UHPDR electron beams.

Fig. 12. A prototype of the Graphite Probe Calorimeter without its waterproof housing, next to a Sun Nuclear SNC 600c Farmer chamber for scale. The cylindrical graphite core (not visible) has a length of 10 mm and a diameter of 6.1 mm.

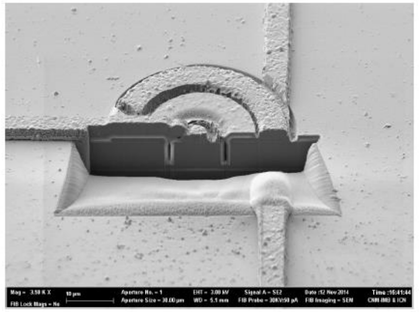


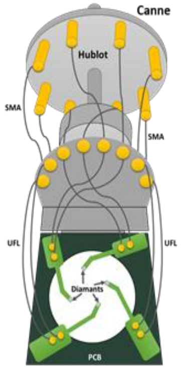
Fig. 13. SEM image of the section of a Si-microdosimeter. The central electrode is surrounded by a 3D trench electrode that delimits the active volume.

Commercial solutions (PTW)

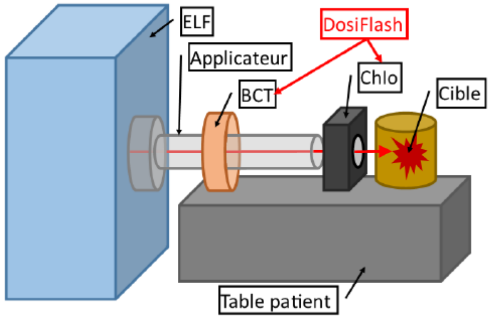
flashDiamond Detector T60025

Issu de Schuller et al. (2020), Physica Medica 80 (2020) 134–150. https://doi.org/10.1016/j.ejmp.2020.09.020

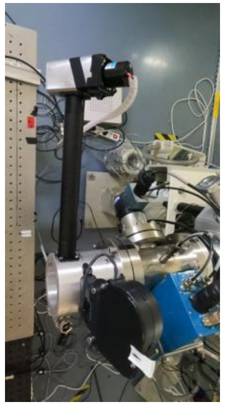
- Other french lab development for dose monitoring of UHDR beams, to equip FLASH ion beam plateforms: ex of **Diamond detector (arronax)** **Ultra-thin chamber** (gap < 200 µm) or **air fluorescence detector (arronax)**

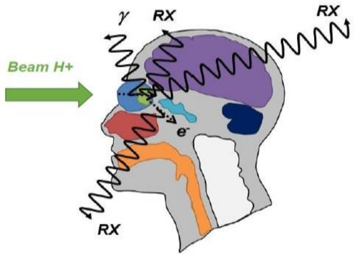


Up to 100 kGy/s with 65 MeV protons. Courtesy ML Gallin-Martel



Instantaneous dose rate up to 1 MGy/s. Fontbonne





Courtesy of A. Guertin

FLASH therapy: challenges and open questions

➢ Summary of physical and radiobiological challenges/ Open questions:

- **Development of UHDR stable facilities** (with deep beam penetration)

- **Limits of physical parameter's impact on FLASH biology**: pulse duration/intensity, mean or instantaneous dose-rate, beam size:
  - Can we have a FLASH effect in single pencil beams (or micro-beams) or occurs only in a large enough volume ?

- **Chemical and biological mechanisms of FLASH-effect** ? **Is it observable *in vitro* ?**
  - Some clues on the **role of oxygen** and **chemistry reactions** at µs scale, maybe role of **Fe ion** explaining a possible differential cancer/normal effect… ➔ but no clear conclusion, we don't know why it work.
  - **See review for mecanism hypothesis**: Shiraishi, Y., Matsuya, Y., & Fukunaga, H. (2024). Possible mechanisms and simulation modeling of FLASH radiotherapy. Radiological Physics and Technology, 17(1), 11-23.

  ➔ **Need for research radiobiology platforms AND dose monitoring of radiobiology experiments.**

- **Calculation**: Integrate in TPS "predictors" of FLASH effects

- **Adapted experimental dosimetry solutions** for UHDR needed (without charge recombination)

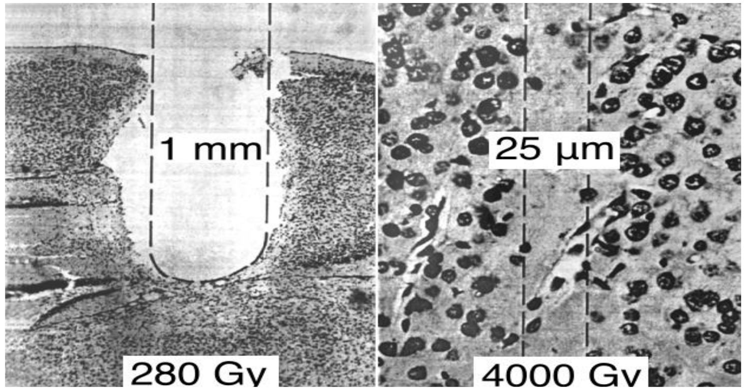
Spatial Fractionation

Grid therapy, minibeam (MBRT), microbeam (MRT)

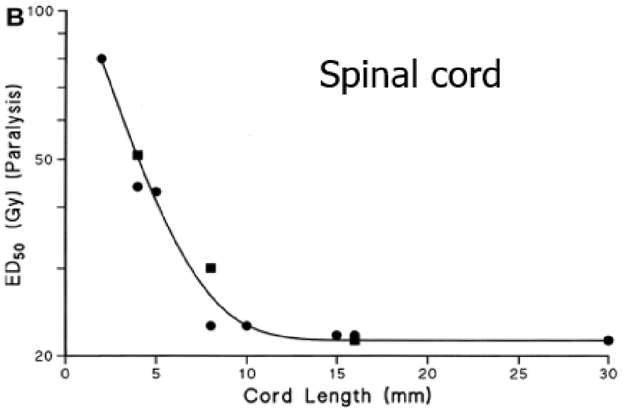
New delivery mode: Spatially fractionated RT (SFRT)

➢Principle:

- Combines **submillimetric beam sizes** with **spatial fractionation of the dose**

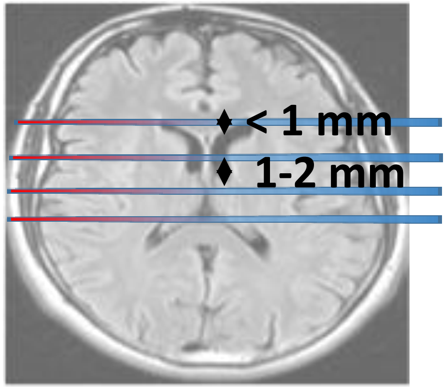


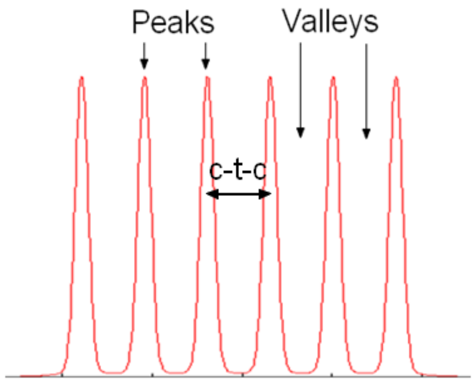
Dose-Volume effect (Zeman et al. 1959)



Hopewell et al., Radioth. Oncol. (2000)

+

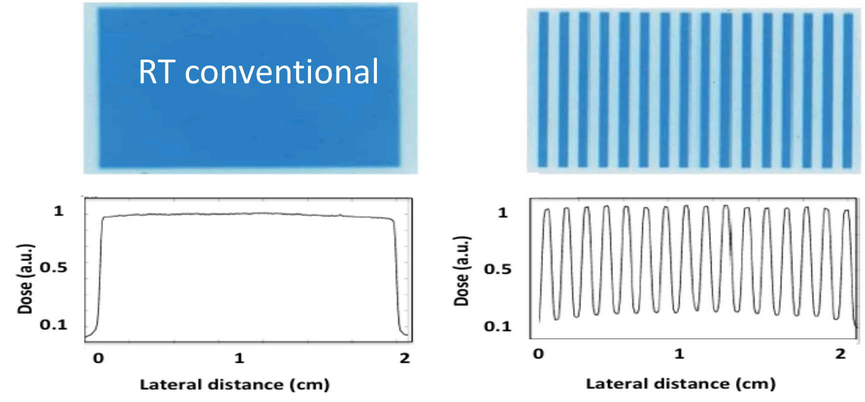




Heterogeneous dose profiles

→ Dose-volume effect = the smaller the beam size, the higher the tolerance dose in healthy tissues.

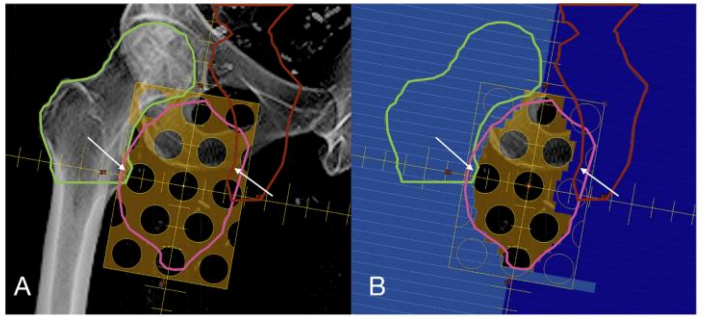
- Beam < 200 µm (**MRT, synchrotron**) ;
  400-700 µm (**MBRT**, accessible clinical facilities)
  ~0.5-1 cm in Grid (or Latice) therapy used clinically
- Remarkable **increase of the dose tolerance** in normal tissues: **dose tolerance (up to 100 Gy/session) in the brain** *(Prezado et al. 2015), while lethal dose in rat in homogeneous field = 20 Gy*
- Equivalent **tumor control** efficiency



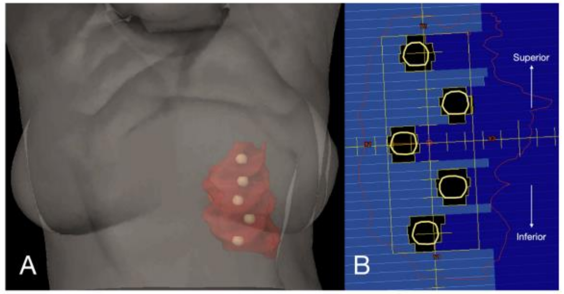
SFRT: in clinics

➢SFRT in clinics: GRID or LATTICE RT (beam size ~1cm):

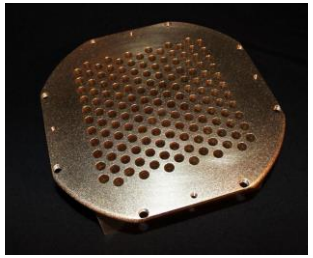
- **Used in clinical routine to treat large (> 8cm) or radioresistant tumors, re-irradiations or as immunostimulation**
  → reduce acute skin and subcutaneous tissue toxicity
  - **GRID =** 1 static field delivered with block collimators
  - **LATTICE:** 3D way of delivering GRID and can decrease the dose in peripheral tissues compared to 2D GRID
  - Doses of 10 to 20 Gy are delivered in single fraction, with good tolerance (mostly used palliative)



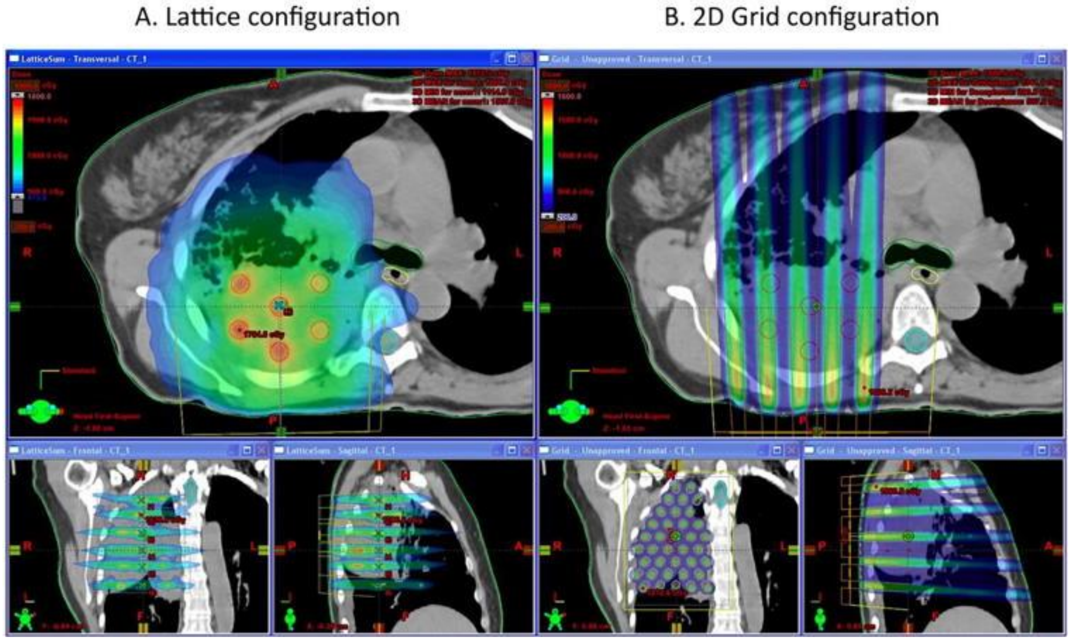
Divergent holes of 1.4cm diameter at isocenter



Grams M.P. et al., Physica Medica 2023 – clinical trial over 240 patients, Mayo clinic



Ex. of clinical GRID block commercially available from decimal, LLC,

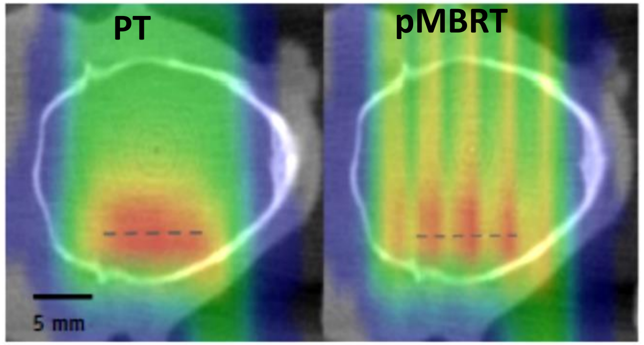


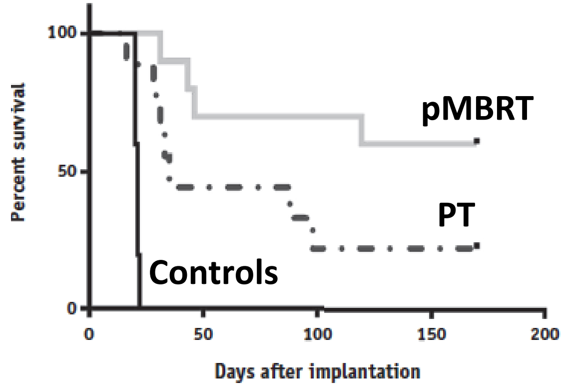
Lattice vs GRID in same lung case (Photo Credit Dr. Xiaodong Wu) – (Lattice is a 3D way of delivering GRID and can decrease the dose in peripheral tissues compared to 2D GRID). From Yan et al. 2020.

New delivery mode: Spatially fractionated RT

➢ Proton minibeams vs protontherapy: towards clinics?

- **Remarkable normal-tissue tolerance**, brain **tumor-control** similar or better PT *(Prezado et al. 2017,18,19, ERC)*
- Systematic characterization of parameters of influence:
  - Temporal fractionation, multiple beam incidence
  - Full or partial fractionation
  - Mechanism in normal & cancer cell/tissue/microenvironnement
- Adaptation of dose-calculation and protocols **for clinics**





➢ Synchrotron X-ray microbeam irradiation:

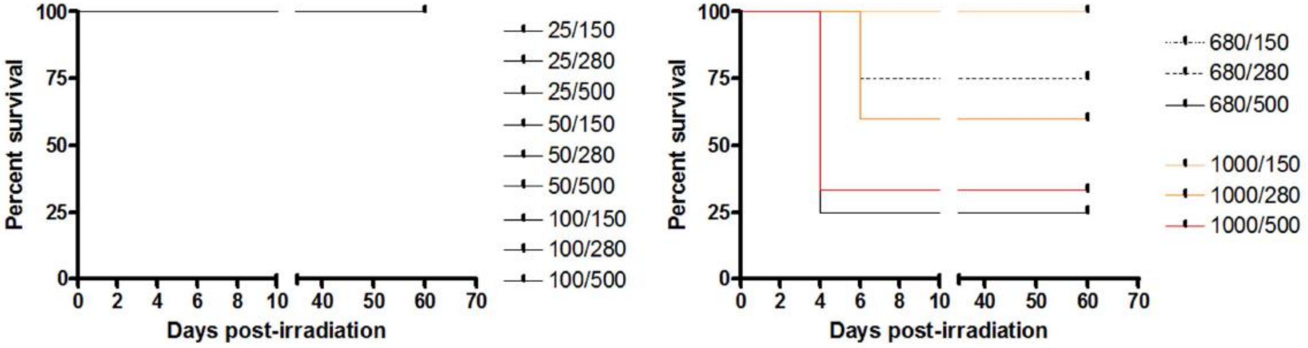
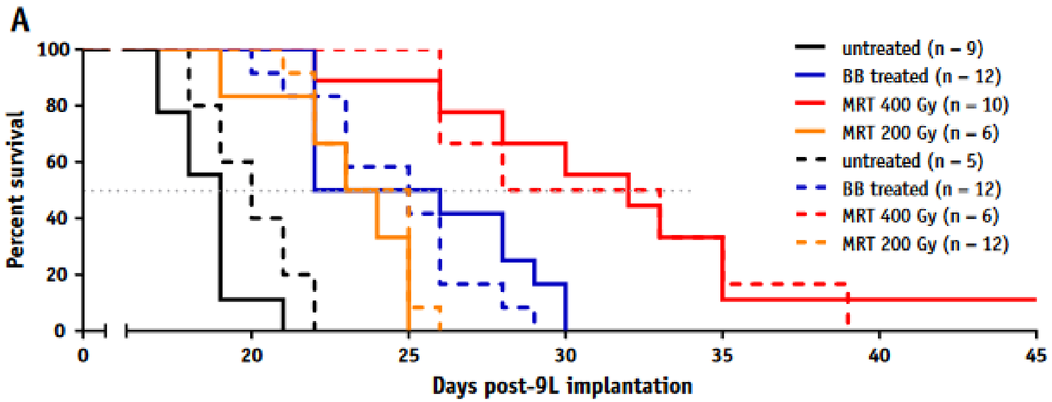


Figure 2. Survival curves of normal rats as a function of the configurations for irradiation. The first number in the legend denotes the width (µm) of the beamlets, the second, the dose (Gy), for instance: 25 µm/150 Gy. All surviving rats were culled at day 60 after exposure.
doi:10.1371/journal.pone.0088244.g002

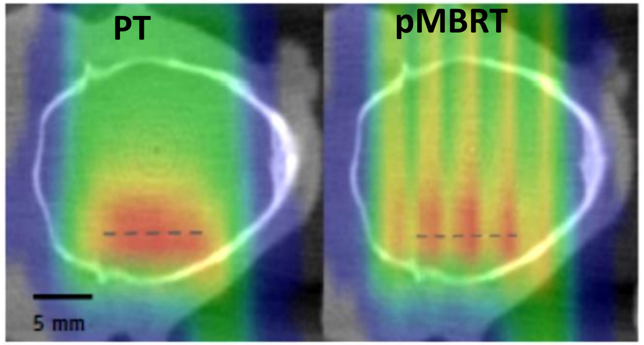
Serduc et al. Red Journal, (2014)

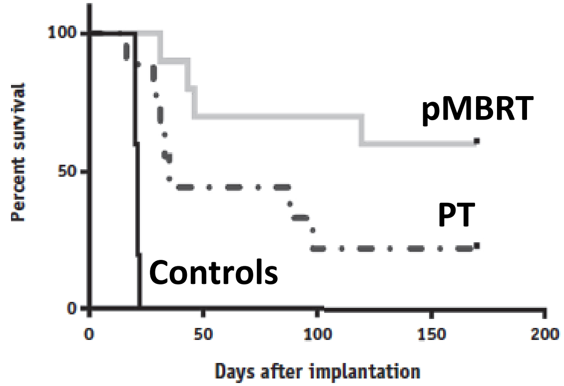


Bouchet et al. Red Journal, (2016)

New delivery mode: Spatially fractionated RT

GRENOBLE | MODANE





➢Proton minibeams vs protontherapy: towards clinics?

- **Remarkable normal-tissue tolerance**, brain **tumor-control** similar or better PT *(Prezado et al. 2017,18,19, ERC)*
- Systematic characterization of parameters of influence:
  - Temporal fractionation, multiple beam incidence
  - Full or partial fractionation
  - Mechanism in normal & cancer cell/tissue/microenvironnement
- Adaptation of dose-calculation and protocols **for clinics**

➢Synchrotron X

Very promising veterinary trials under way on dogs… unfortunately ESRF close this research topic for now, due to machine upgrade… Search for other sources (Australian synchrotron, or other compact-sources)

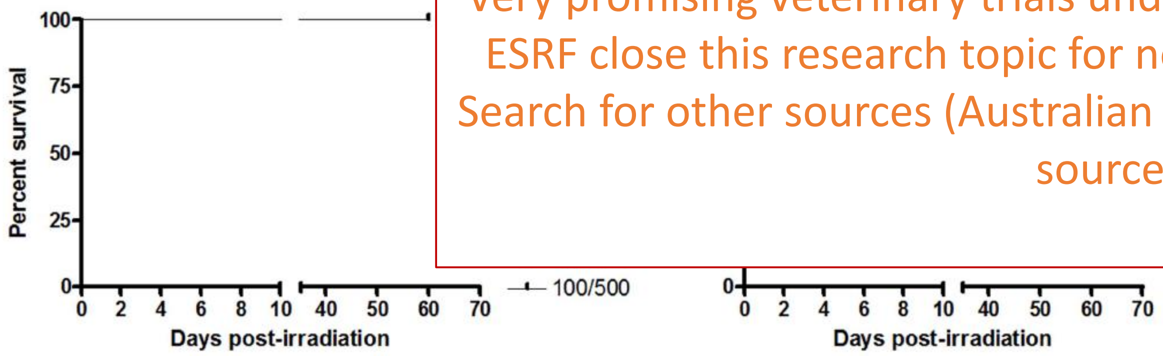
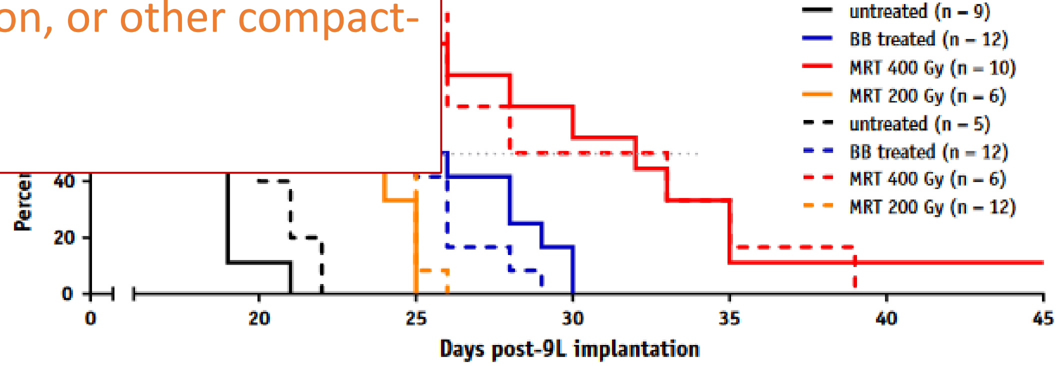


Figure 2. Survival curves of normal rats as a function of the configurations for irradiation. The first number in the legend denotes the width (µm) of the beamlets, the second, the dose (Gy), for instance: 25 µm/150 Gy. All surviving rats were culled at day 60 after exposure.
doi:10.1371/journal.pone.0088244.g002

Serduc et al. Red Journal, (2014)

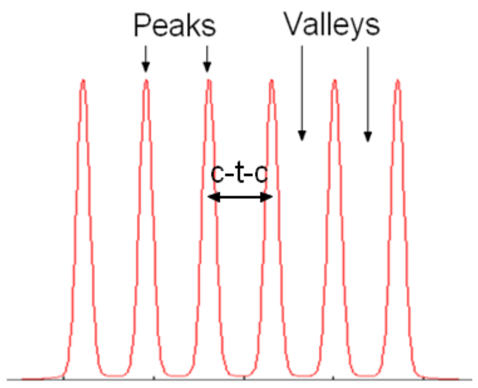


Bouchet et al. Red Journal, (2016)

New delivery mode: Spatially fractionated RT

➢ Challenges/developments of SFRT:

- Explore the *terra incognita* of influence parameters
  - Very **particular metrics that needs to be correlated** to « equivalent » uniform dose responses.
  - Need for **systematic evaluation of tissue/tumor response according to irradiation parameters** (ctc, beam size, PVDR…)
    ➔ **More radiobiological studies.**
  - **Which valley, peak or average dose to use for « homogeneous » irradiation comparison ?**



Heterogeneous dose profiles

- Biological processes induced in normal and cancerous cells/tissues ?
  - **Not well known**: hypothesis of cell migration, hypoxia, immature vasculature…

- Reliable numerical and experimental dosimetry protocols for very small beams and potential high-dose rates! (synchrotron beam)

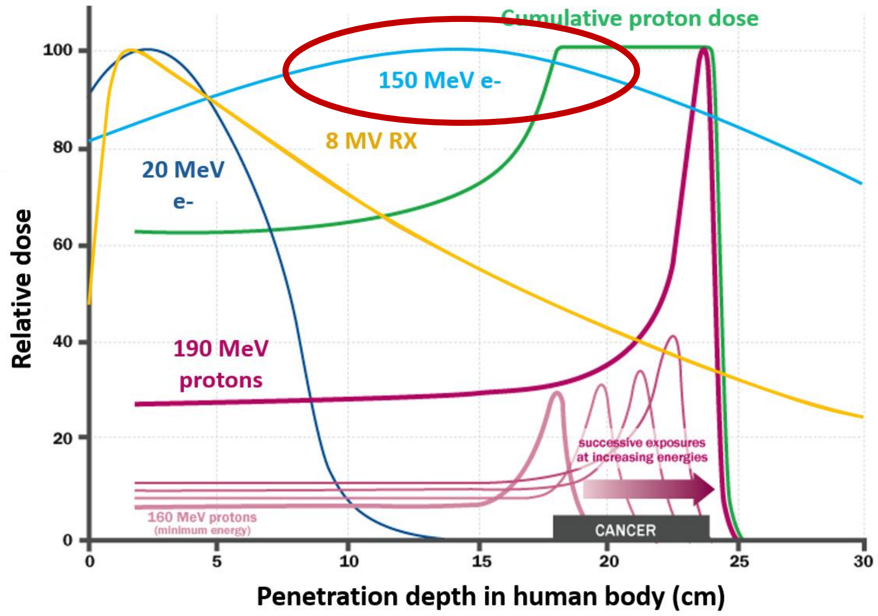
- Need for compact source developments for clinical development.

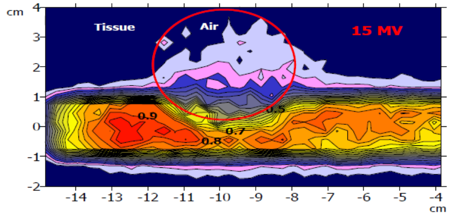
VHEE therapy

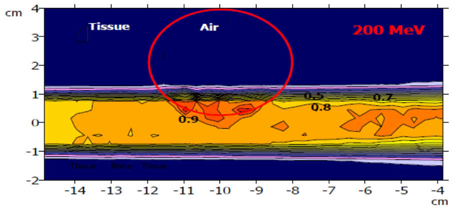
And their combination with new spatial and temporal dose-delivery approaches

Different particles: VHEE (50-250 MeV)

- Advantages vs MV photons
  - Flatter depth dose profile: deep tumors
  - **Relative insensitivity to heterogeneities**
  - Magnetic collimation



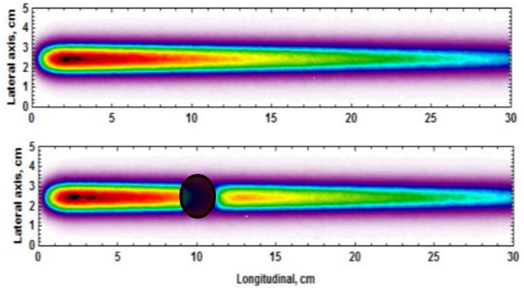




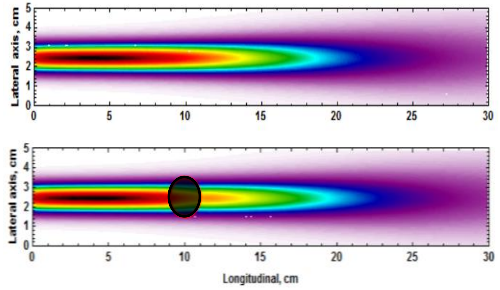
Papiez, DesRosiers et al. 2002

Agnese Lagzda

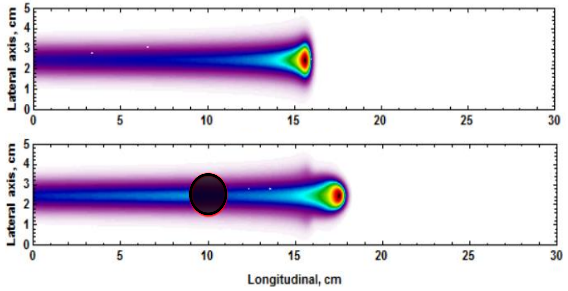
6 MV photons



200 MeV VHEE

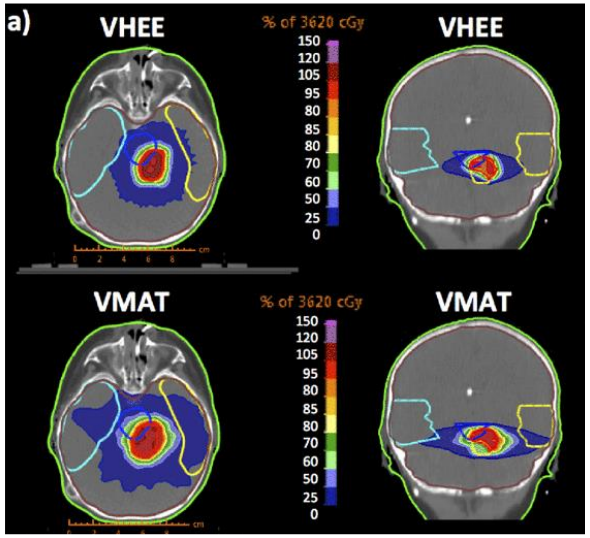


150 MeV protons

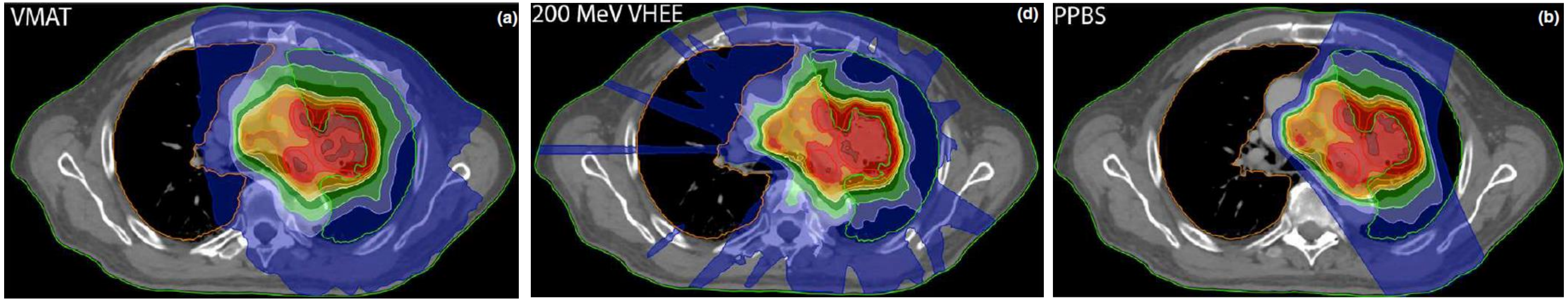


Different particles: VHEE (50-250 MeV)

- Advantages vs MV photons
  - ✓ **Clinical case comparisons*:***
    compared to VMAT (gold std in photon radiotherapy)
    → Better protection of Organs at Risk (OAR)
    (prostate, pediatric, Lung, brain, H&N…)
  - ✓ **Might be advantageous** vs **protons** for Head & Neck



Brain tumour dose maps for 100 MeV VHEE and 6 MV volumetric modulated arc photon therapy (VMAT) *Bazalova-Carter, 2015 (Stanford)*

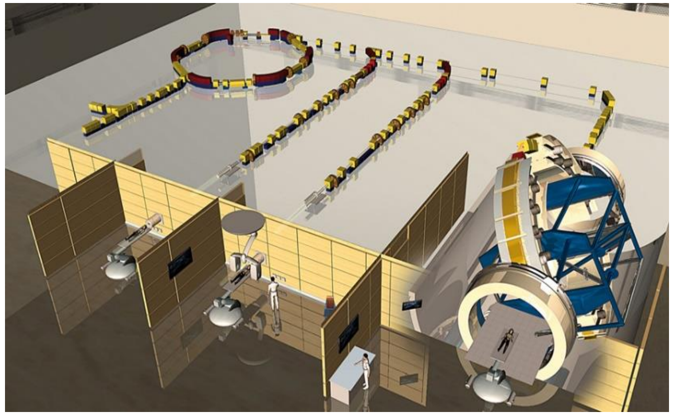


Clinical case VHEE compared to VMAT → Better protection of OAR (prostate, Lung, brain, H&N…) Schuler et al. 2017

Different particles: VHEE (50-250 MeV)

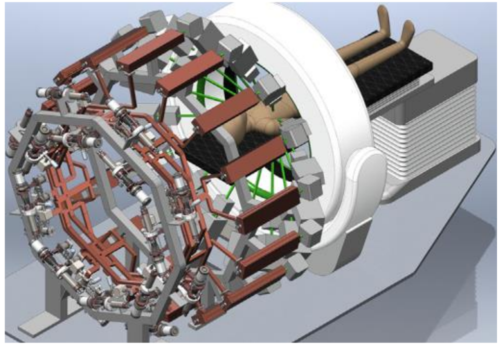
- **Impact of the cost and size of the facilities on the number of treated patients**

50 m



Hadrontherapy center of Heidelberg
(~ten C-ion and ~50 p centers in world, cost 50-100 M€)

VHEE
(~10 M€ ?)



PHASER prototype
(Maxim et al. 2019)

Quid laser-plasma VHEE beams ?

4 m

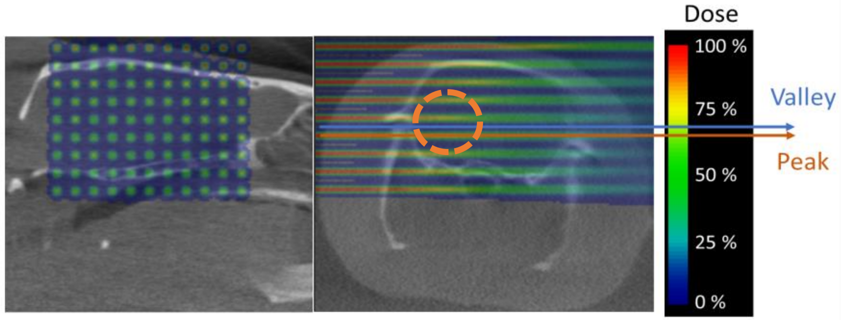
Standard medical accelerator
(~ 600 in France, ~1 M€)

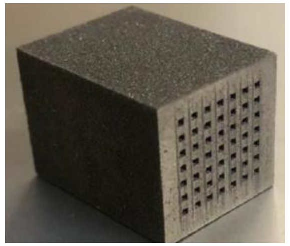
- **VHEE beams:**
  - ✓ Cost and ease of beam manipulation, more compact accelerators (than protons).
  - ✓ For **mini-beams applications**: very small beam sizes (<1mm) and low penumbrae
  - ✓ **FLASH** dose rate accessible in deep tumors

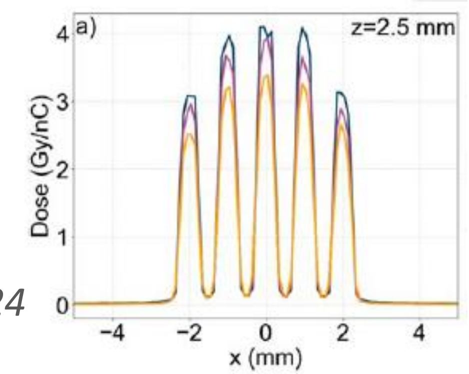
VHEE for grid therapy

- Potential interest in Grid or MBRT therapy with magnetic or lead collimation:

Dose distribution in a rat head (~3 cm) with VHEE grid-therapy (Delorme et al. 2018)

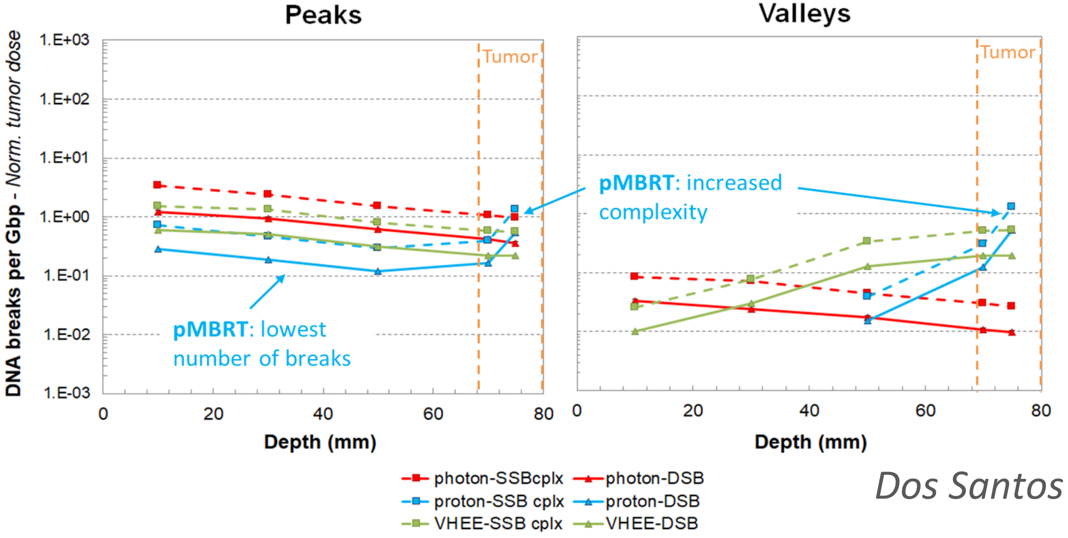


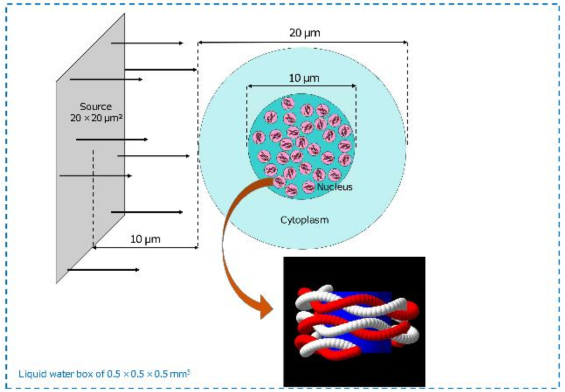




Clement & Bazalova 2024

- intermediate tunable solution between spatial fractionation in normal tissue and homogeneous dose in tumor to favor control of the disease





Dos Santos & Delorme et al., Med. Phys. 2020

Different particles: VHEE (50-250 MeV)

GRENOBLE | MODANE

Current challenges:

- Development of **compact and reliable facilities**: **High-gradient RF cavities** vs **Laser-plasma technologies** ?
  - Need for beam spectra and pointing stability to reach RT quality control requirements

- **Radiobiology of VHEE and pulsed-regime to test with MBRT or FLASH delivery mode**:
  ➔ need for VHEE research platforms

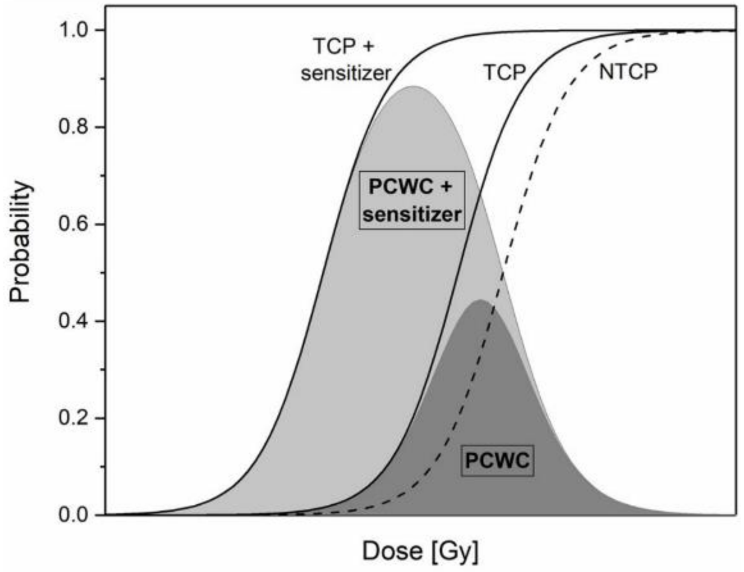
- **Reliable VHEE dosimetry protocols** : potential ultra-short pulses, high-dose rates mean and within the pulses

Targeted RT using short-range particles

Boron Neutron Capture Therapy (BNCT)

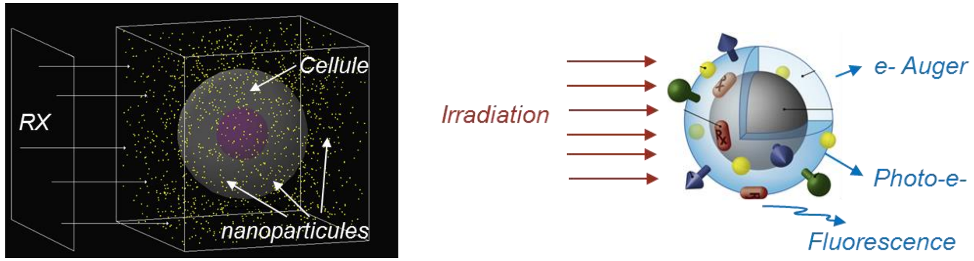
And alpha targeted therapy

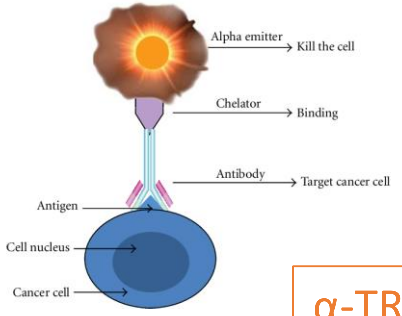
Metallic nanoparticles



Targeted therapy using short-range particles

- Combined (or targeted) RT= combine cell targeting with molecular vector with local irradiation
  - Photoactivation of high-Z nanoparticles (NP): Au, Gd, Pt…



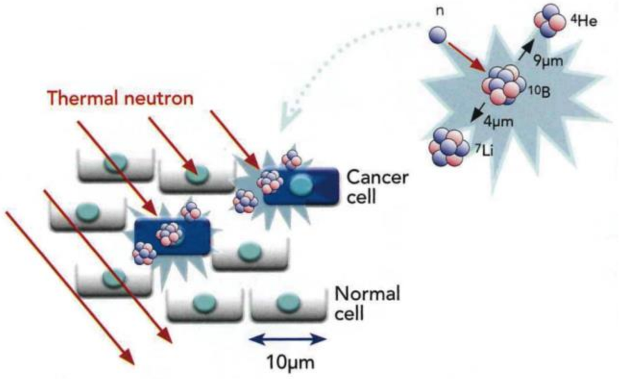


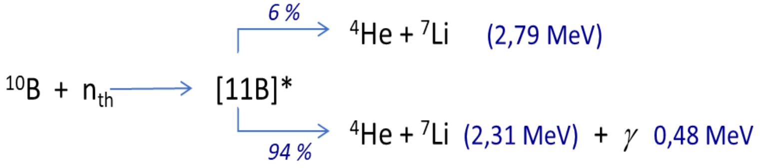
Molecular vector
Antibody + radionuclide

Injection of vectors = metabolic targeting of cancer cells

α-TRT

  - Radiothérapie interne vectorisée alpha (RIV-α)
  - Neutron Boron capture Therapy (BNCT): $^{10}B(n,^{7}Li)\alpha$





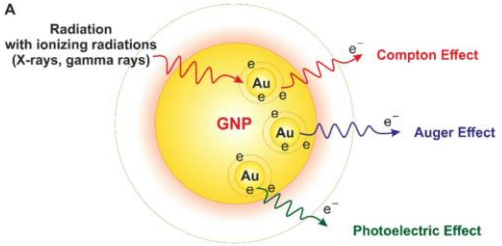
BNCT

	α-TRT	BNCT	NP
Radionuclide/particle	^{223}Ra, ^{225}Ac, $^{212/213}$Bi, ^{211}At…	^{10}B/^{11*}B	e- (PE, Auger)
Energies α (et ^{7}Li) or e-	5-9 MeV	0.8-1.7 MeV	0-100 keV
Range α (and ^{7}Li) or e-	40 –100 µm *(few cells)*	5 –9 µm *(<cell)*	0-100 µm
LET *(keV/µm)*	60 – 100	≥ 200	0.5-20

Targeted therapies: nanoparticles (NP)

➢ Metallic / Oxide NP can enhance radiosensitization of RT:

- **First showed by Hainfeld *et al.*** in 2004: GNP + RX
- **Confirmed in numerous studies** with different NP/beams
- **2 clinical trials** in France: AGuIX® (Gd), NBTXR3® (Hf oxide)



Borran et al., 2018. Rad. Phys. Chem.

Clinical Trial > Radiother Oncol. 2021 Jul:160:159-165. doi: 10.1016/j.radonc.2021.04.021. Epub 2021 May 5.

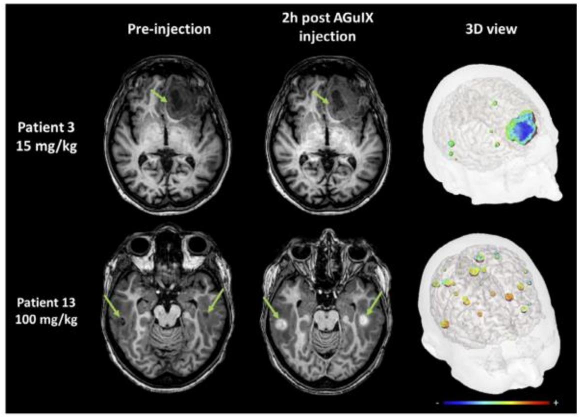
Theranostic AGuIX nanoparticles as radiosensitizer: A phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial)

Camille Verry [1], Sandrine Dufort [2], Julie Villa [3], Marylaure Gavard [4], Carole Iriart [3], Sylvie Grand [5], Julie Charles [6], Benoit Chovelon [7], Jean-Luc Cracowski [8], Jean-Louis Quesada [8], Christophe Mendoza [8], Lucie Sancey [9], Audrey Lehmann [10], Florence Jover [3], Jean-Yves Giraud [3], François Lux [9], Yannick Crémillieux [11], Stephen McMahon [12], Petrus J Pauwels [13], Daniel Cagney [14], Ross Berbeco [14], Ayal Aizer [14], Eric Deutsch [15], Markus Loeffler [2], Géraldine Le Duc [2], Olivier Tillement [9], Jacques Balosso [3]

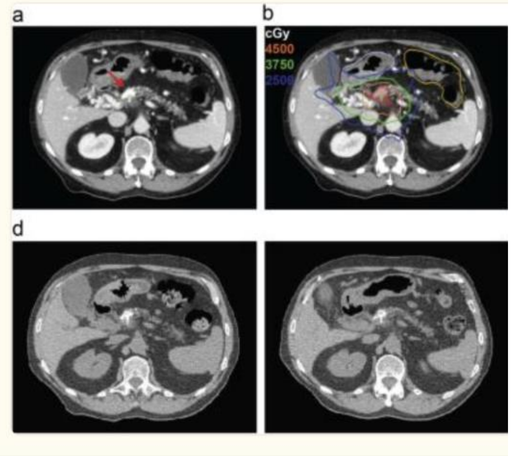
Affiliations + expand

PMID: 33961915 DOI: 10.1016/j.radonc.2021.04.021

Free article



Verry C. et al., R&O, 2021



Bagley F.B. et al., Clin Transl Radiat Oncol, 2021

Pancreatic adenocarcinoma

Clinical Trial > Lancet Oncol. 2019 Aug;20(8):1148-1159. doi: 10.1016/S1470-2045(19)30326-2. Epub 2019 Jul 8.

NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial

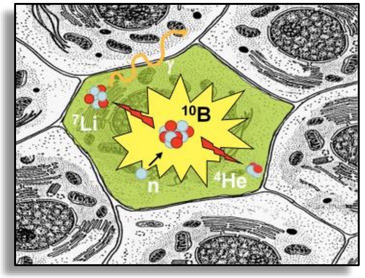
Sylvie Bonvalot [1], Piotr L Rutkowski [2], Juliette Thariat [3], Sébastien Carrère [4], Anne Ducassou [5], Marie-Pierre Sunyach [6], Peter Agoston [7], Angela Hong [8], Augustin Mervoyer [9], Marco Rastrelli [10], Victor Moreno [11], Rubi K Li [12], Béatrice Tiangco [13], Antonio Casado Herraez [14], Alessandro Gronchi [15], László Mangel [16], Teresa Sy-Ortin [17], Peter Hohenberger [18], Thierry de Baère [19], Axel Le Cesne [20], Sylvie Helfre [21], Esma Saada-Bouzid [22], Aneta Borkowska [23], Rodica Anghel [24], Ann Co [25], Michael Gebhart [26], Guy Kantor [27], Angel Montero [28], Herbert H Loong [29], Ramona Vergés [30], Lore Lapeire [31], Sorin Dema [32], Gabriel Kacso [33], Lyn Austen [34], Laurence Moureau-Zabotto [35], Vincent Servois [36], Eva Wardelmann [37], Philippe Terrier [38], Alexander J Lazar [39], Judith V M G Bovée [40], Cécile Le Péchoux [41], Zsusanna Papai [42]

➢ High complexity to optimize NP-based treatments

- **Radiosensitization is cell-line and NP-type dependent**: need for standardization
- **Treatment efficacy may depend on tumor targeting and cell-uptake**
- **Macroscopic dose-enhancement** cannot explain alone observed biological effects

Targeted therapies: boron-enhanced therapies

➢ Boron Neutron Capture Therapy (BNCT): $^{10}B(n,^{7}Li)\alpha$

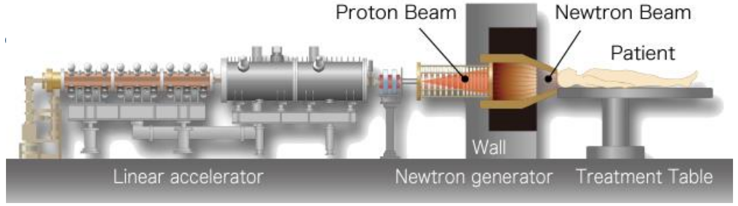


Natural (20%) or enriched boron isotope, delivered in cancerous cells (BPA or BSH)

$^{10}B + n_{th} \rightarrow [11B]^*$

- *6 %* → $^{4}He + ^{7}Li$ (2,79 MeV)
- *94 %* → $^{4}He + ^{7}Li$ (2,31 MeV) + γ 0,48 MeV

- BNCT efficacy relies on local emission of high-LET ions: destruction limited to the cell
- Several clinical trials in nuclear reactors *(Barth et al. 2012)*: promising results for **GBM**
- Recent increase of interest with **the development of accelerator-based NCT**
- New clinical trials started worldwhile in Finland and Asia ➔ **already passed in clinical routine for recurrent H&N cancers in Japan**



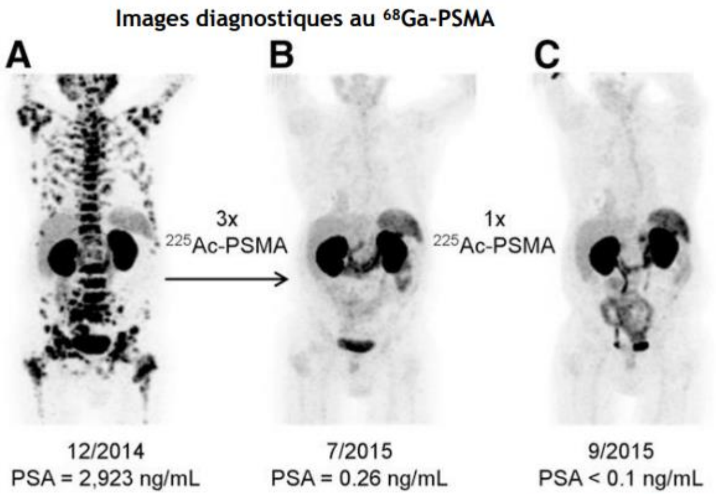
➢ Challenges/developments:

- Improve selectivity of boron-carriers
- Access to in-hospital epithemal neutron-beams
- Modeling: nanometric precision and biophysical models needed + reaction cross sections

➢ Targeted alpha therapy (TAT):

- Recent interest after spectacular response of metastatic protate cancers.

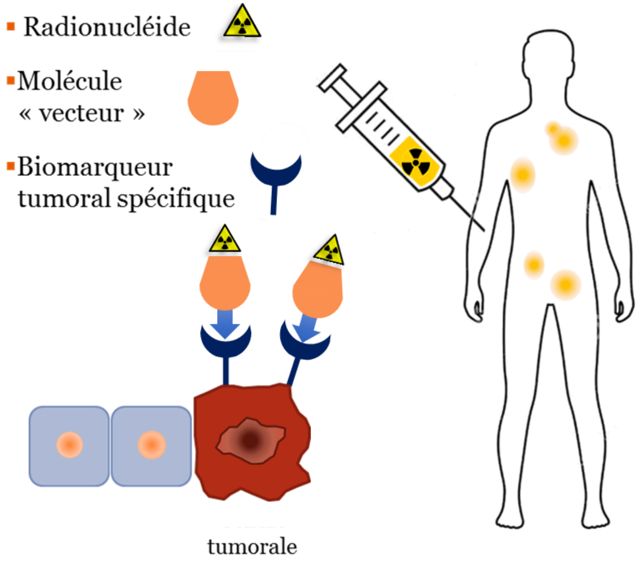
Radiothérapie Interne Vectorisée à l'^{225}Ac-PSMA (Prostate-specific membrane antigen)



Kratochwil, J Nucl Med, 2016

Interest ++

Development of new treatments / vectors / indications

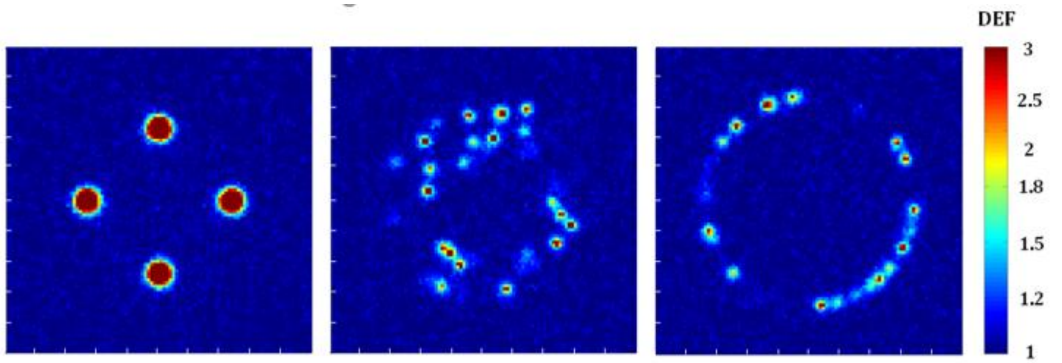


- TAT already used clinically for Bone metastasis with Ra-223 (Xofigo)
- Nowadays almost 30 clinical trials involving various isotopes (^{211}At, ^{225}Ac, ^{212}Pb…) and vectors

Treats tumors (metastases) that have spread throughout the body
⇨ Need for new isotopes / radiopharmaceuticals

Targeted therapy: dosimetric issues

- Common difficulties in dose calculations and biological response prediction:
  - **« Local »** (cell scale) of **low-range particles of potential high-LET** (Auger e-, α, ions)
  - **Heterogeneity ++ of energy deposition at nano / micro scale**



*Exemple of heterogeneous dose deposition at cellular scale according to **intracellular location of Gd-NP** (Delorme et al. (2017), Medical Physics 44 (11):5949-5960. https://doi.org/10.1002/mp.12570)*

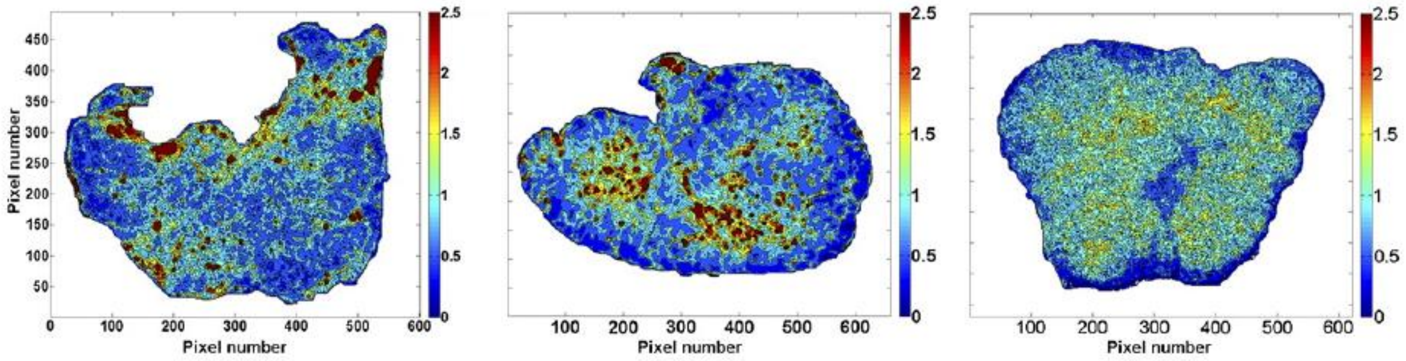
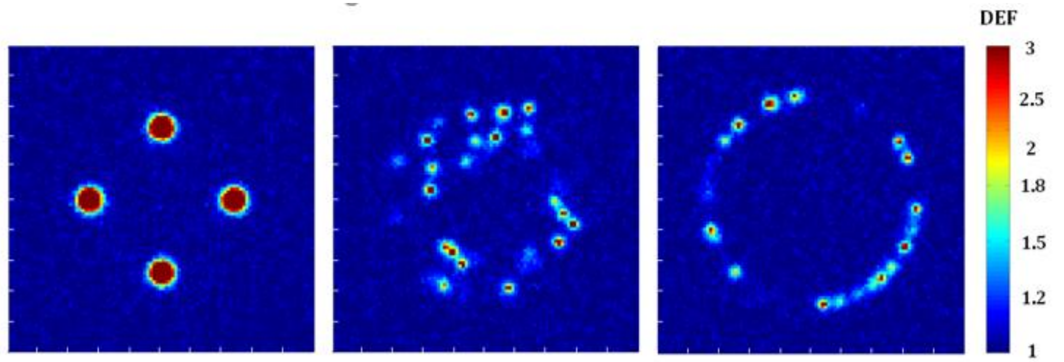


Figure 1.28: Activity distributions of xenografted OVCAR-3 tumors taken 7 minutes (left), 7 hours (center) and 21 hours (right) post irradiation, obtained via the α-camera method. One hundred pixels correspond to 1 mm (from [Bäck and Jacobsson, 2010]).

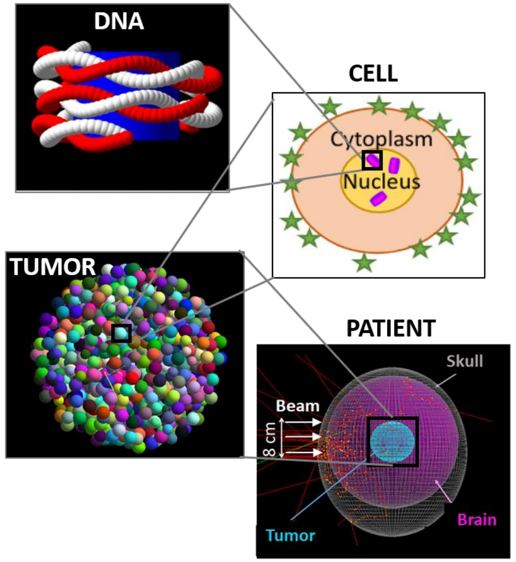
Targeted therapy: dosimetric issues

- Common difficulties in dose calculations and biological response prediction:
  - **« Local »** (cell scale) of **low-range particles of potential high-LET** (Auger e-, α, ions)
  - **Heterogeneity ++ of energy deposition at nano / micro scale**
  - **Question of the relevant sensitive target at cell scale** to consider biological damage

DNA, Cell nucleus, Cytoplasm, Membrane…? How?



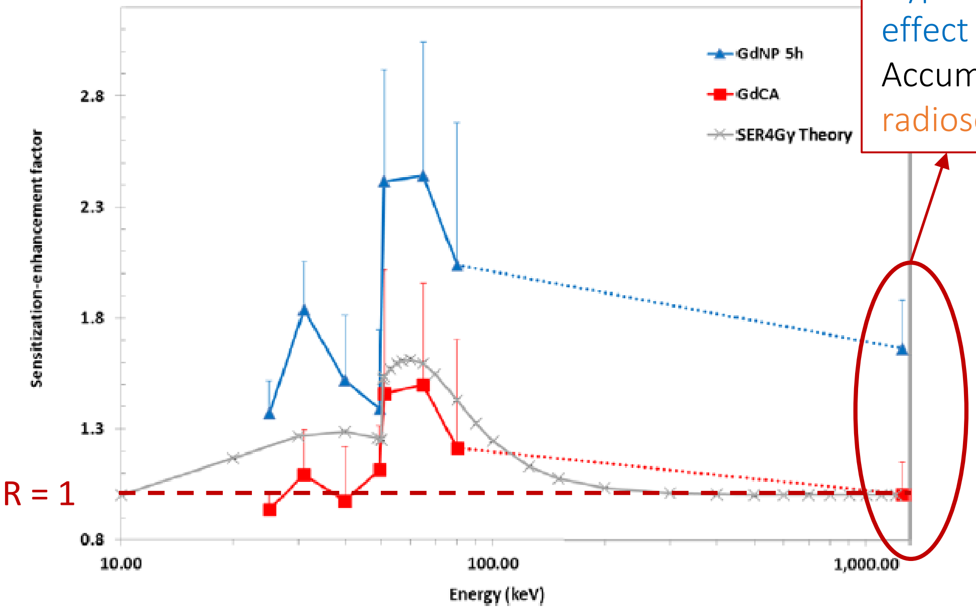
*Exemple of heterogeneous dose deposition at cellular scale according to **intracellular location of Gd-NP** (Delorme et al. (2017), Medical Physics 44 (11):5949-5960. https://doi.org/10.1002/mp.12570)*



- **Lack of precise biological/clinical data of such heterogeneities**:
  → But we can simulate it to quantify the impact of such « unknown » heterogeneous distributions.
  Multiscale modeling tools.

Targeted therapy: dosimetric issues: Nanoparticles

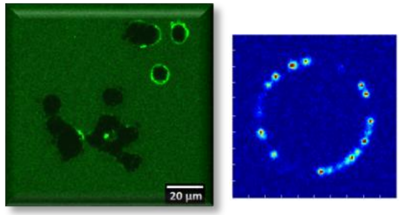
- Improving dosimetry: from macroscopic dose to biolgogical effects
  - **Ex. of NP radiotherapy**: we can quantify a Dose enhancement factor **(DEF)** linked to the increase of photoelectric cross section of X-rays on high-Z elements *(Gd, Au, Hf…)*
    → **But observed NP biological effects much higher than DEF** *(in vitro & in vivo)*

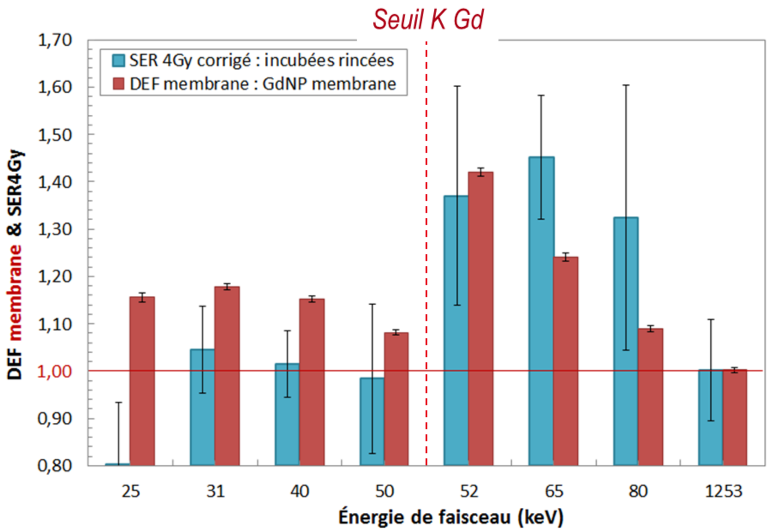


Hypothesis of increased biological effect after NP incubation: Accumulation in a more radiosensitivecell phase (G2/M)

Membrane is potentially a more relevant critical target to explain the physical part of the radiosensitivity

Cell scale simulation





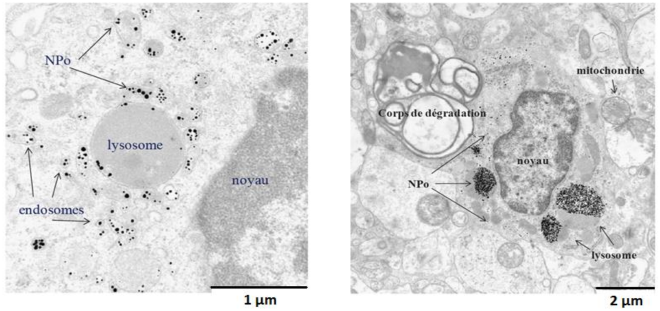
Comparaison of SER (Sentitization enhancement ratio) of incubated cells with GdNP (blue), or with a Gd contrast agent (red) with the calculated macroscopic DEF, Taupin et al. (2015), Phys. Med. Biol. 60, 4449–4464. https://doi.org/10.1088/0031-9155/60/11/4449

Simulation nano/micro-dosimetric: comparaison of membrane DEF to SER normalised at ^{60}Co energy. Delorme et al. (2017), Med. Phys. 44 (11):5949-5960. https://doi.org/10.1002/mp.12570

Targeted therapy: dosimetric issues: Nanoparticles

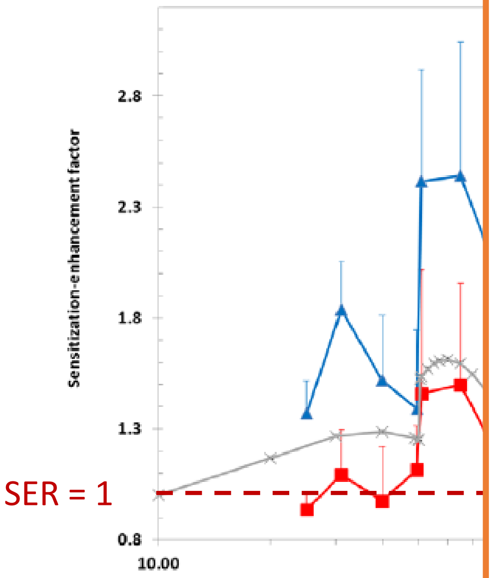
- Improving dosimetry: from macroscopic dose to biolgogical effects
  - **Ex. of NP radiotherapy**: we can quantify a Dose enhancement factor **(DEF)** linked to the increase of photoelectri
    → **But obse**

Our experiment case, other NP intracell location maybe more probable e.g. cytoplasm, lysosomes, extra-cellular media… → different cell targets

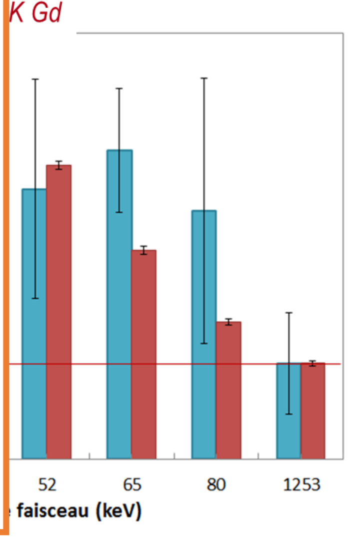


High energy of ^{60}Co the less favorable in a cross section point of view, **better results can be expected with FFF beams** (higher contrib of low-energy X-ray spectrum) *(A. Detappe et al. (2016), Scientific reports, 6:34040, https://doi.org/10.1038/srep34040)*

more relevant critical target of the radiosensitivity



Comparaison of SER (Sentitization enhancement ratio) of incubated cells with GdNP (blue), or with a Gd contrast agent (red) with the calculated macroscopic DEF, Taupin et al. (2015), Phys. Med. Biol. 60, 4449–4464. https://doi.org/10.1088/0031-9155/60/11/4449



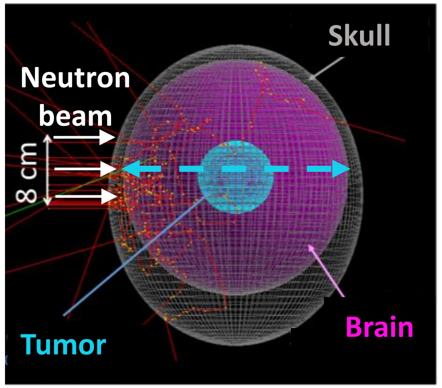
Simulation nano/micro-dosimetric: comparaison of membrane DEF to SER normalised at ^{60}Co energy. Delorme et al. (2017), Med. Phys. 44 (11):5949-5960. https://doi.org/10.1002/mp.12570

PICTURE project – biophysical modeling for TAT/BNCT

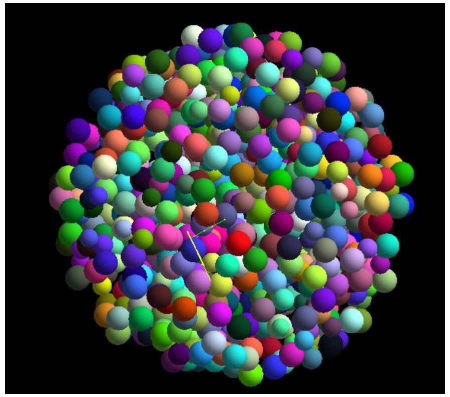
➢ Material & methods

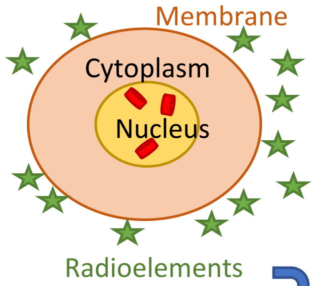
- Coupling **numerical multiscale simulations** *(Geant4, CPOP)* and the **NanOx biophysical model**
- Perform **dedicated radiobiology experiments** to constraint NanOx parameters for low-energy ions and different cell sentitive targets.

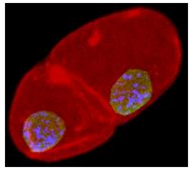
Macroscopical MC modeling of treatment case conditions
(Geant4, ex. BNCT brain tumor)



Microtumor and micro-scale MC modeling
Consider tissue and cell radionuclide/boron distribution heterogeneity, cell morphology… (CPOP/Geant4)



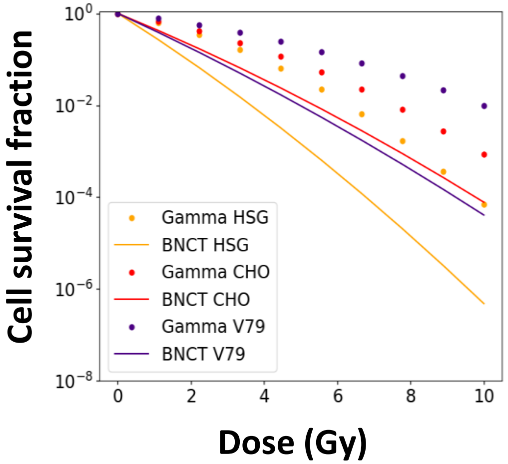




Integration of reaslistic cellular models from microscopy imaging

NanOx model :
(physical & chemical nano/microscale modeling ➔ cell survival)

Cell survival, TCP & RBE predictions
(ex: BNCT treatment condition for 3 cell lines)



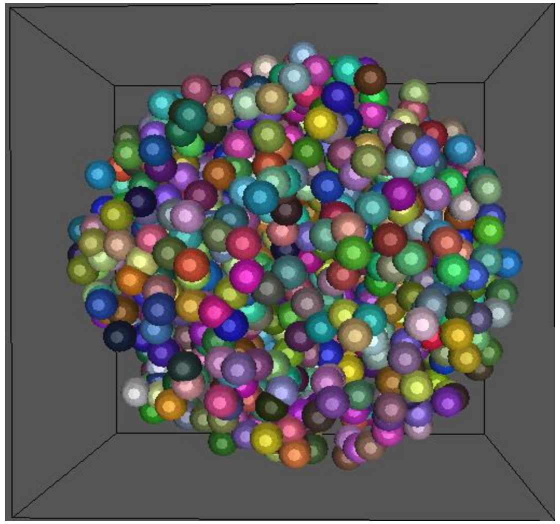
Main objectives:
- *adapt to low-energy ions* √
- *add extra-nuclear sensitive volume* ×
- *Parametrize from biological data* ×

Impact of intracellular radionuclide distribution in TAT

- **Objective: quantify the error in predictions when source microdistribution is unkown.**
- Influence parameters :
  - **Spheroid compaction** : 25 - 75 %*
  - **Radionuclide** used (~ α energy) : ^{210}Po, ^{211}At , ^{213}Bi
  - **Spheroid radius** : 30 - 95 µm
  - **3 cell lines** : HSG, V79 and CHO-K1

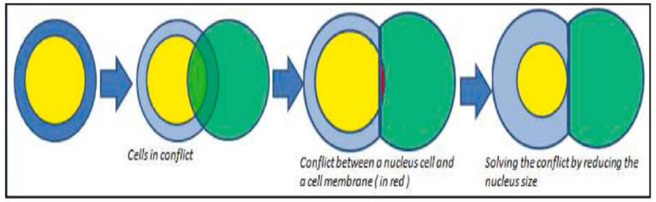
*default conditions

Work of V. Levrague (PhD, LPSC)



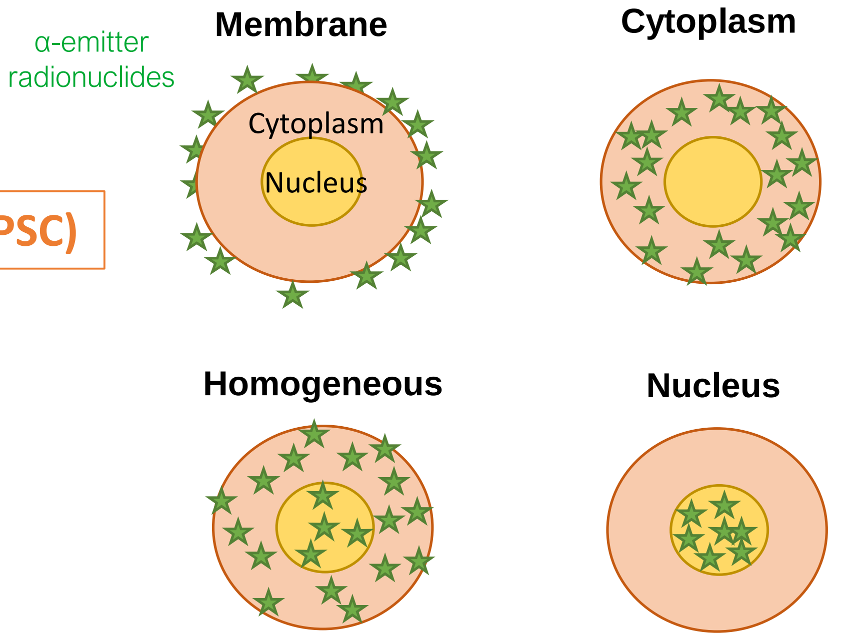
95 µm radius Spheroid generated by CPOP

CPOP code and python analysis adapted for TAT: available on GitHub (GitHub - lpc-umr6533/cpop) and soon in an official Geant4 example



Maigne et al. 2021: allow high compaction and more realistic spheroid geometries

Different distributions studied :



***Same number of alpha particles (42 α /cell)** for each distribution: we used the activity experimentally determined by **Chouin et al. 2012** in murine treatment of injected 400kBq of ^{211}At*

Impact on biological quantities: TCP

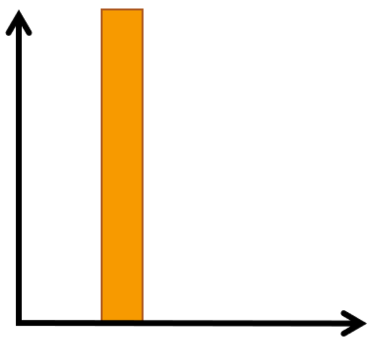
i = each cell of the spheroid

- Tumor Control Probability (TCP)
  - Computed from NanOx cell surviving fraction S as:

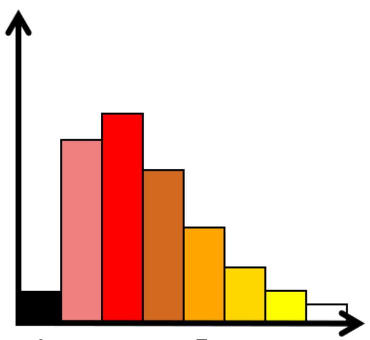
$$TCP = \prod_{i=1}^{n} (1 - S_i)$$

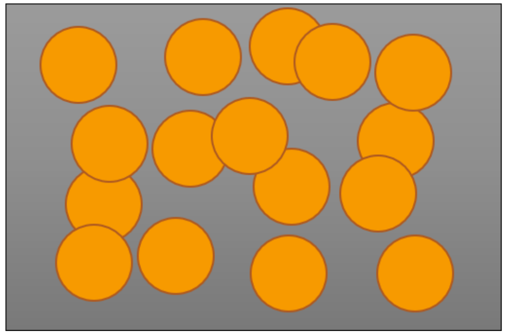
Example with **HSG** cell line: TCP as a function of activity per cell (APC)

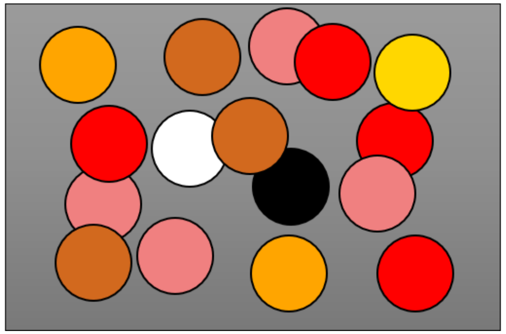
Uniform distribution

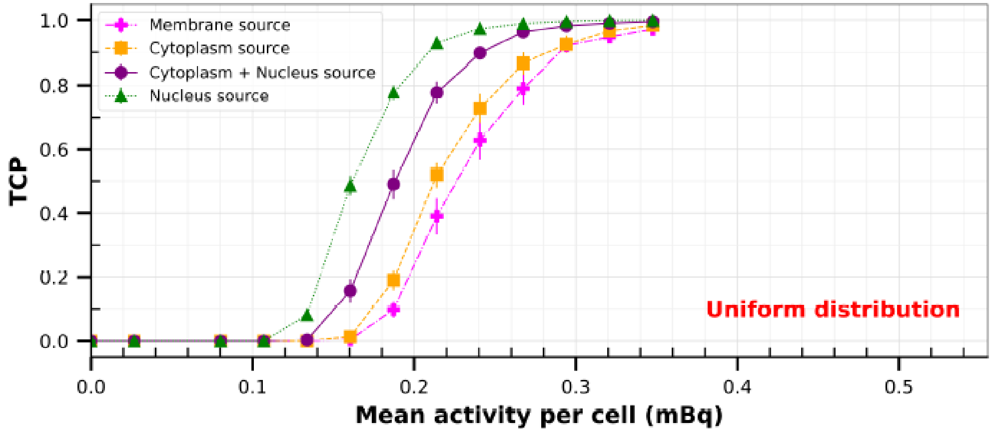


Lognormal distribution

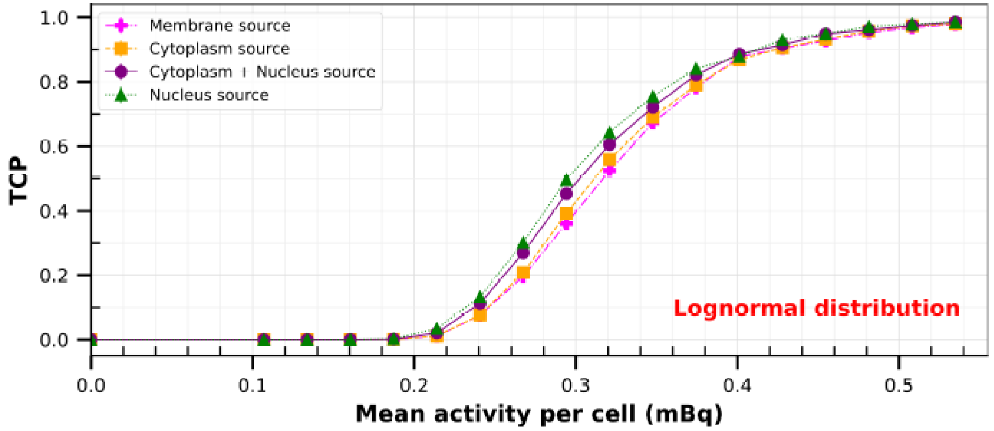








(A)



Work of V. Levrague (PhD, LPSC), article to come…

Conclusions

- Several strategies to increase differential effect in RT:
  - Playing on particle type/energy
  - Playing on dose-delivery mode
  - Combining radiosensitizer or using a molecular targeting

- Several avenues for physics developments (modeling, instrumentation) and radiobiological studies to understand mecanisms and optimize treatments

➔ Need for multidisciplinary field of research with biologist, chemists and physicists!

Thank you for your attention

rachel.delorme@lpsc.in2p3.fr