A small introduction about cancer, treatments and modeling

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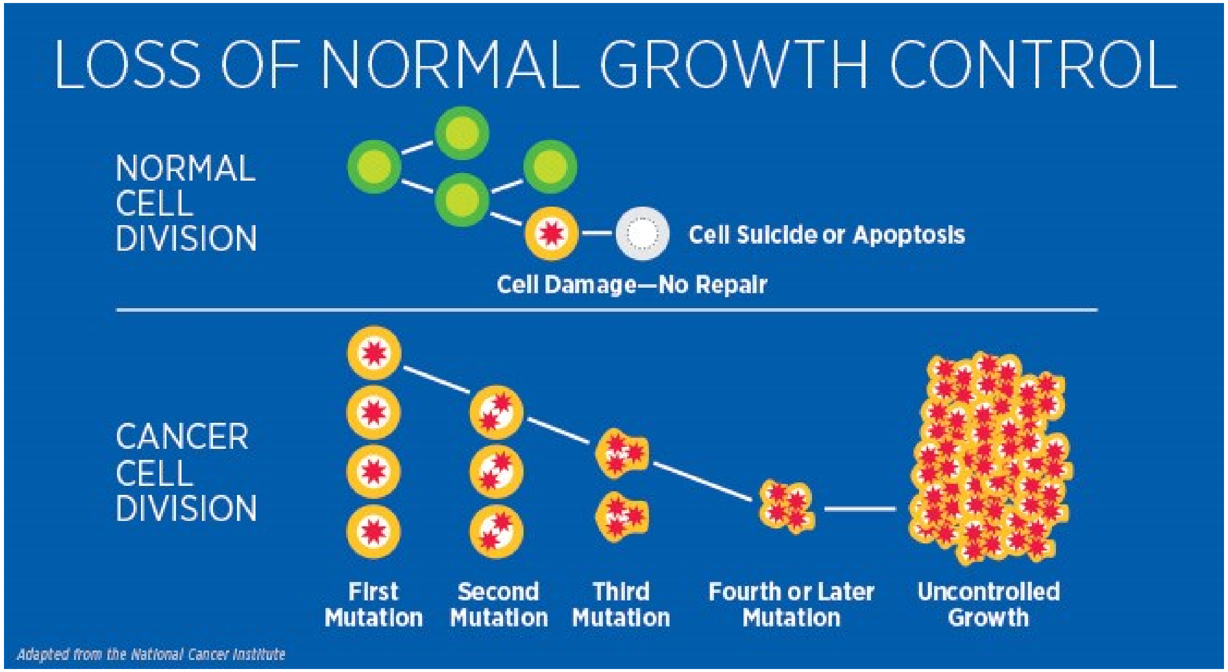
- Cancer:
  - ✓ ~360 000 new case /year in France, ~150 000 death.
  - ✓ What is a cancer?
    - Abnormal cell division → mutation



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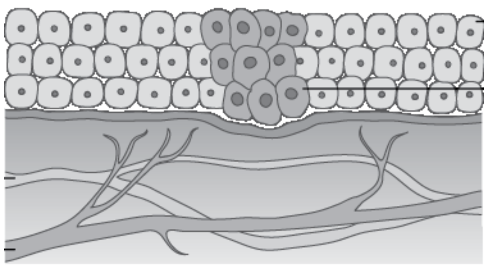
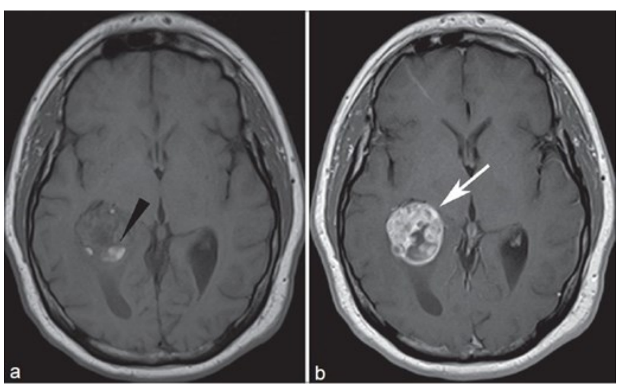
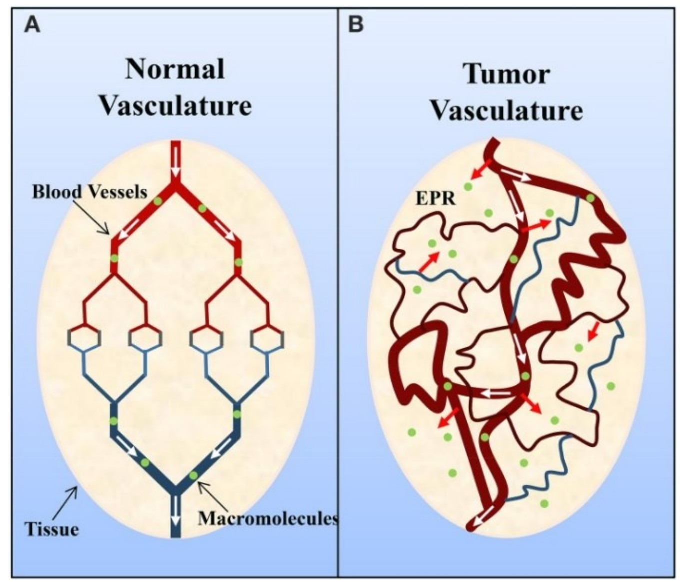
    - Growth of the tumor → angiogenesis to get oxygen, immature vasculature



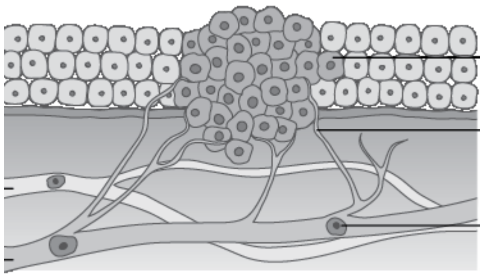


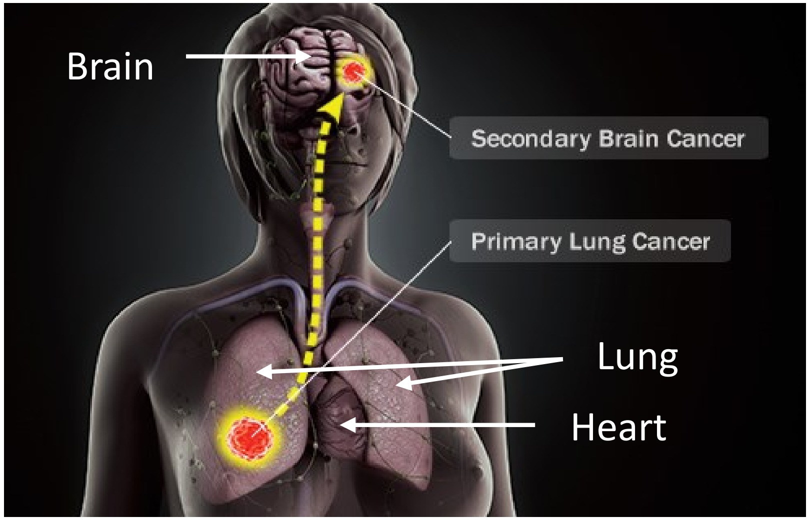
IRM image without agent

IRM image with Gd contrast agent



- **Cancer:**
  - ✓ ~360 000 new case /year in France, ~150 000 death.
  - ✓ What is a cancer?
    - Abnormal cell division → mutation
    - Growth of the tumor → angiogenesis to get oxygen, immature vasculature
    - Propagation of a tumor → extension to lymphatic and blood vessels = 2^{nd} cancer

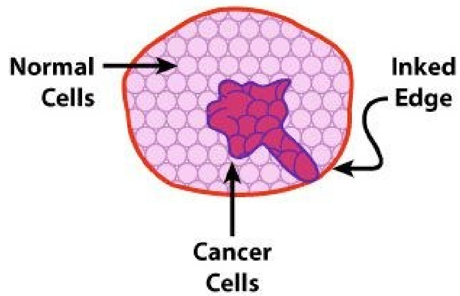




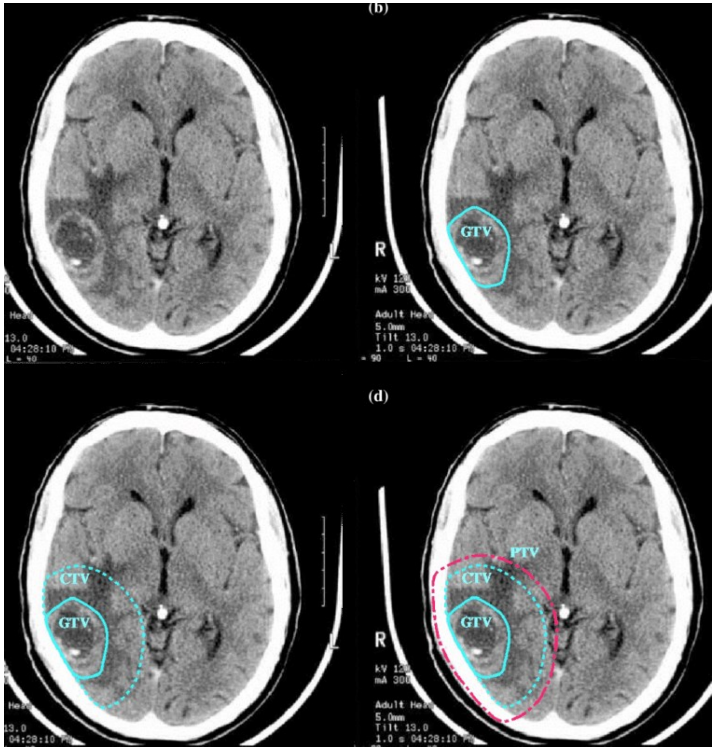
→Treatment challenge: kill/remove the tumor cells without damaging the organs at risk. Better to treat before 2^{ndary} propagation.

- Main treatments:
  - ✓ **Surgery**:
    - First indication (if feasible): trying to be as <u>conservative</u> as possible.
    - Adapted for <u>localized</u> cancer.
    - Problem of <u>tumor micro-extension</u>, borders unclear → What margins ??

The micro-tumoral extensions have to be considered in the resection margins



Important to well understand the tumor growth / invasion to define more reliable margins



→ ***Enzo Fabiani**: Modèles numériques et analytiques d'invasion cellulaire à 1D avec et sans interactions de contact*

- Main treatments:
  - ✓ **Surgery**
  - ✓ **Chemotherapy**:
    - <u>Specific</u> to a tumor type: targeted drugs… *But rarely perfect (toxicity ++)*
    - Adapted also for <u>non-localized</u> secondary cancers

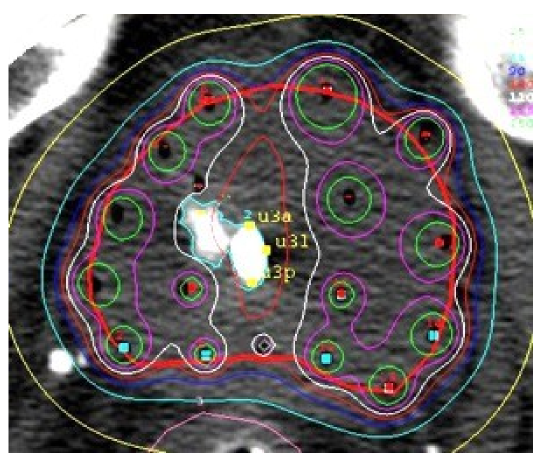
Cancer treatment

- Main treatments:
  - ✓ **Surgery**
  - ✓ **Chemotherapy**
  - ✓ **Radiotherapy (RT)**:
    - Used for half of the patients.
    - Adapted for localized cancers, and non-localized in the case of targeted therapies
    - Problems of toxicity to organs at risk (OAR)

Absorbed dose:

$$D = \frac{d\bar{\varepsilon}}{dm} \quad (Gy)$$

Internal targeted RT *(β,α…)*



Brachytherapy *(Ir, I,…)*

External RT *(RX, e-, p, C…)*

Cancer treatment

- Main treatments:
  - ✓ **Surgery**
  - ✓ **Chemotherapy**
  - ✓ **Radiotherapy (RT)**:
  - ✓ Immunotherapy
  - ✓ Hormonotherapy
  - ✓ …

Often combined (Surgery, Chemotherapy, Radiotherapy)

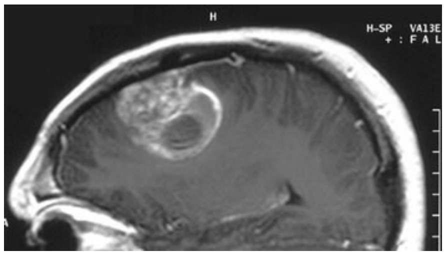
Radiotherapy developments

- Main research radiotherapy-related topics in our domains:
  - **Develop new strategies for RT treatment** to improve the therapeutic index:
    - New particles/energy
    - New dose delivery approaches
    - Combined radiotherapy
  - **Understand radiobiological mechanism**:
    - Experimental *in vitro/in vivo* measurements
    - Modelling physical, chemical and biological processes at nano/micro-scale
  - **Quality control for treatment and diagnostic**:
    - Detection systems for imaging
    - Online control of dose-delivery: detection developments
    - Improve dose calculation of treatment planning systems

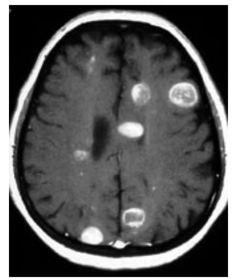
Limitations of radiotherapy

- Limitations of conventional radiotherapy

Radioresistant, bulky and diffuse cancers (glioblastomas)



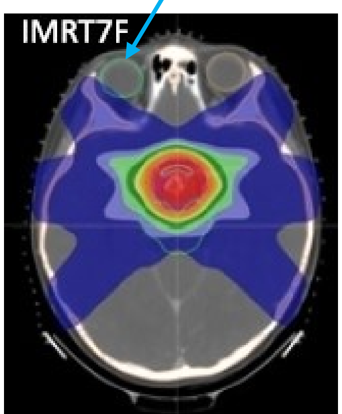
Non-localized tumors (metastases)

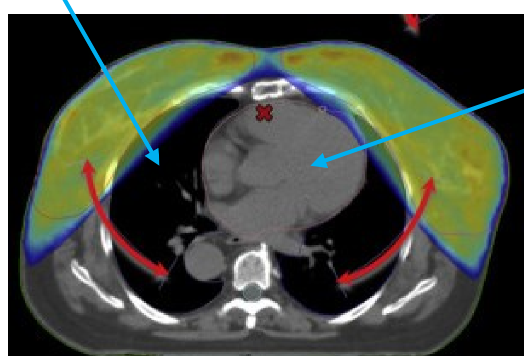


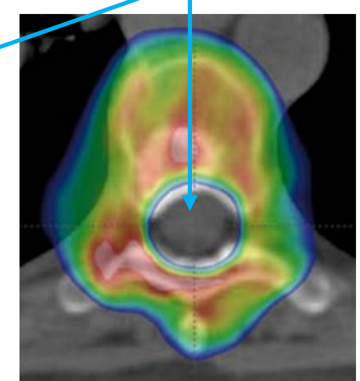
Clinical electron accelerator ***(X-rays ~6-25 MV)***

➢ Type of tumors : radioresistivity (hypoxic tumors), localized or widespread tumors

➢ Organs at risk : dose limitation to surrounding healthy tissues: spinal cord (<45 Gy), optic structures (< 54 Gy), lung (30% volume < 20Gy), kidney (< 15 Gy), heart, etc.)

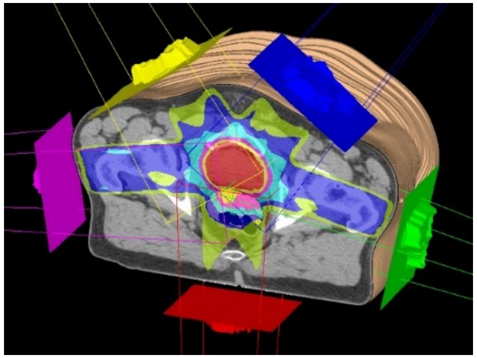






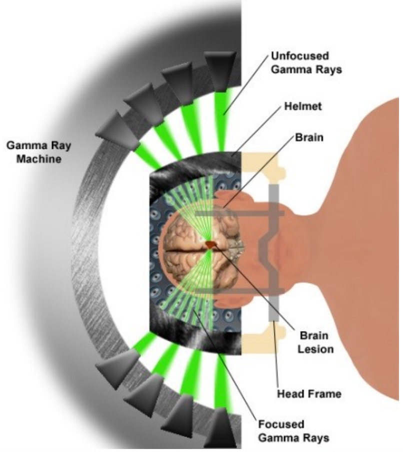
- Improve the ballistic: improved radiotherapy technologies (photons)

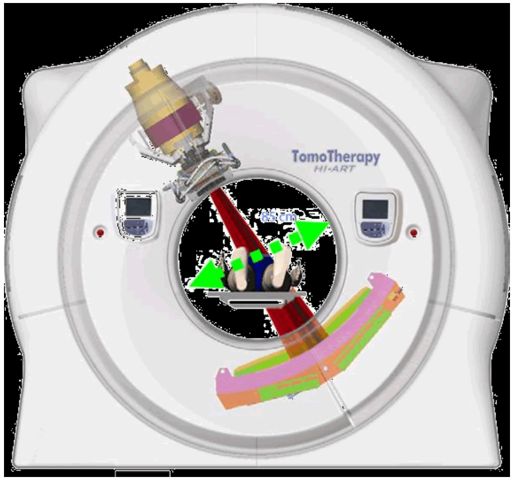
Standard clinical accelerator with embedded imaging systems



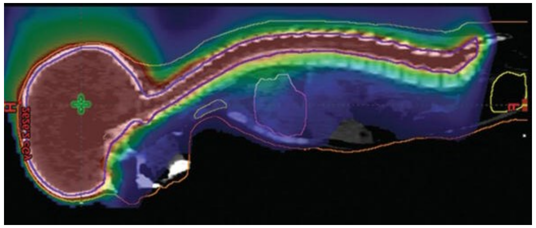
Dosimetry example (prostate) with intensity modulated irradiation (IMRT)

Gamma knife radiosurgery





Tomotherapy



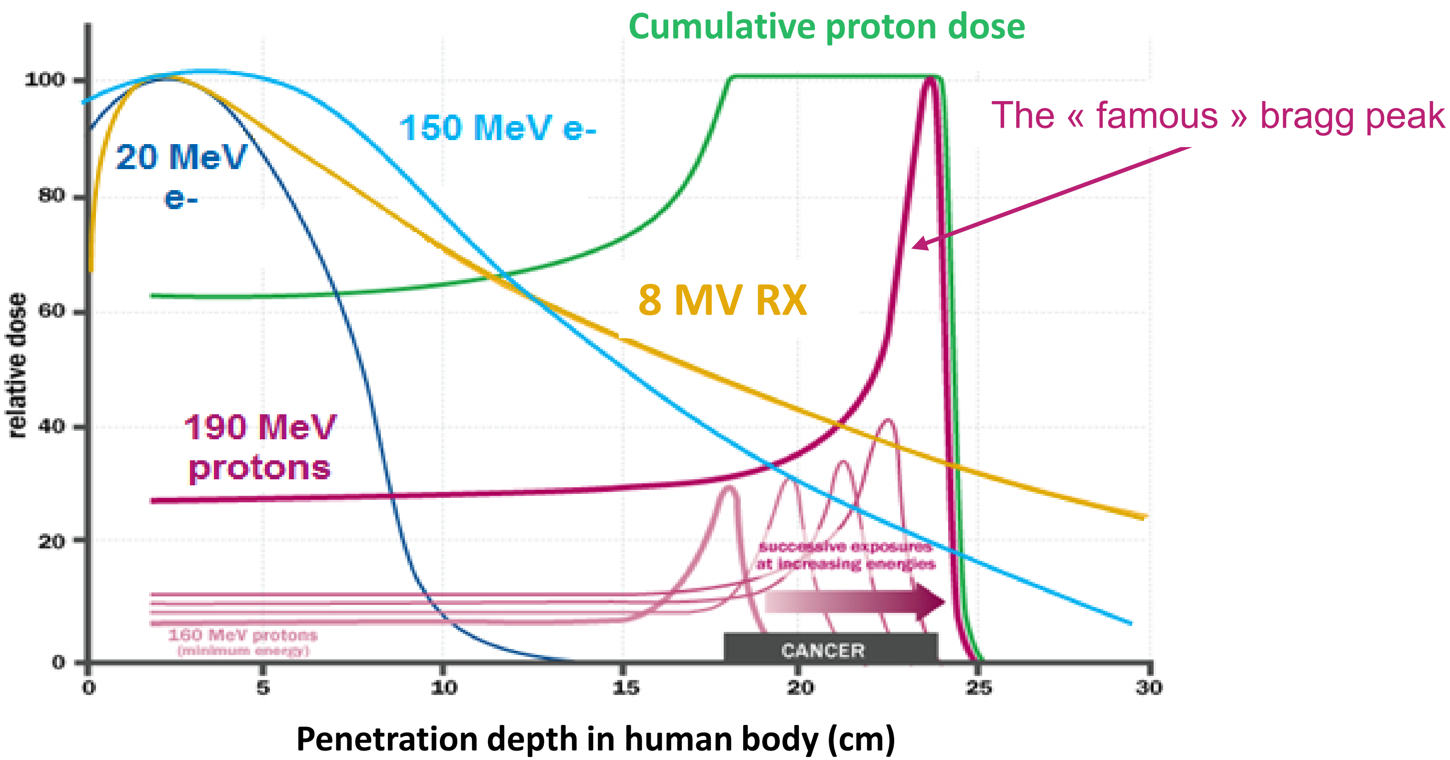
Dosimetry example of medulloblastoma

Cyber-knife

→ Objectives: large dose in tumor, low doses in healthy tissues

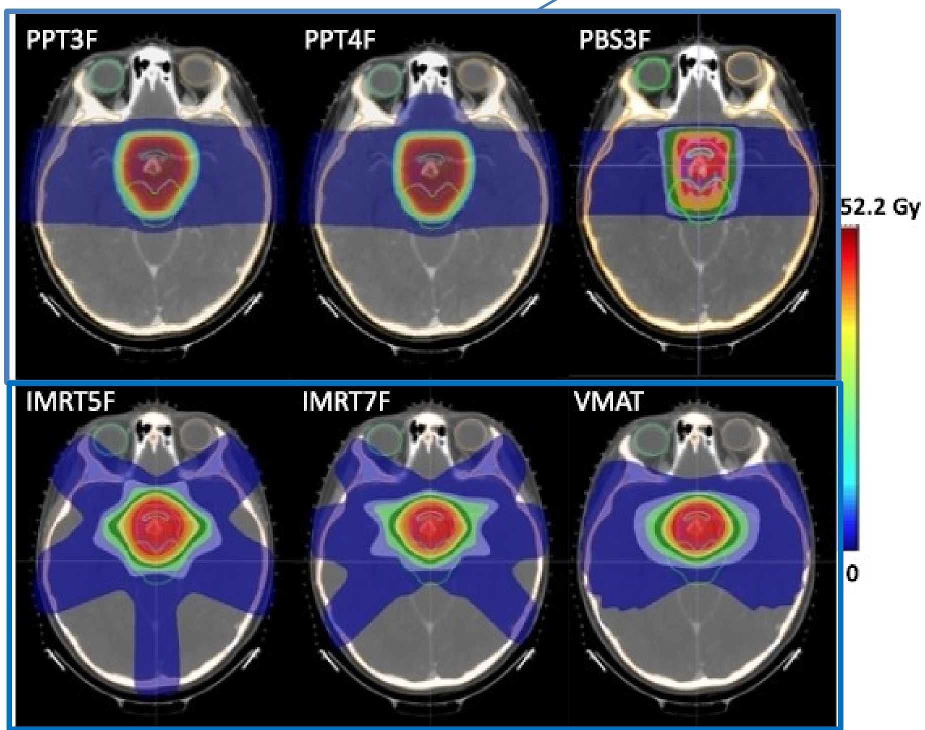
How to improve it ?

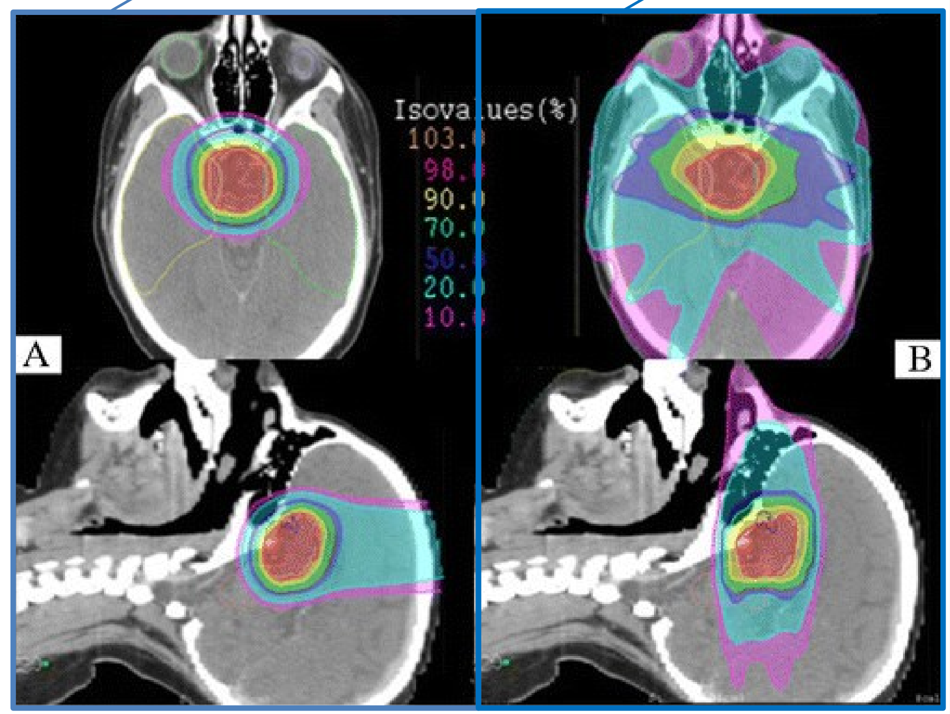
- Improve the ballistic: improved radiotherapy technologies (photons)
- Induce a more efficient tumoral irradiation: play on ballistic & radiobiology
  - Particle/energy: **hadrontherapy** (p, C-ion)



- Example of isodose comparisons between proton & photon irradiation

protons *protons* *photons*



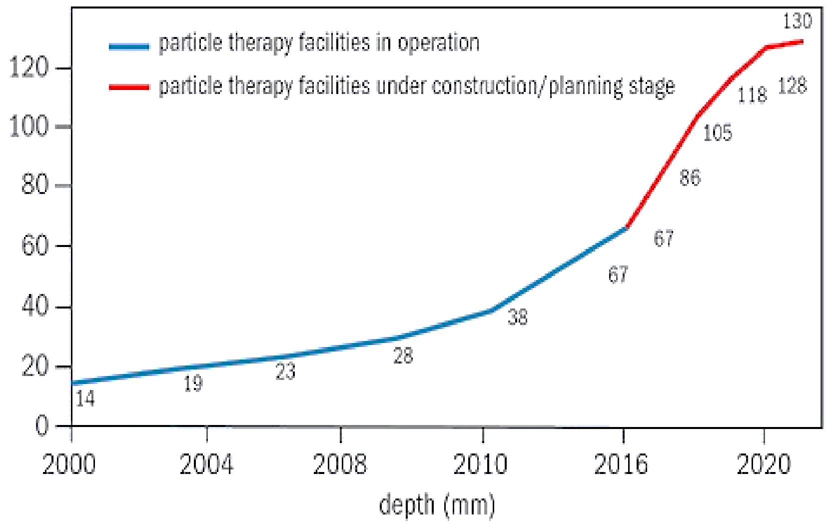


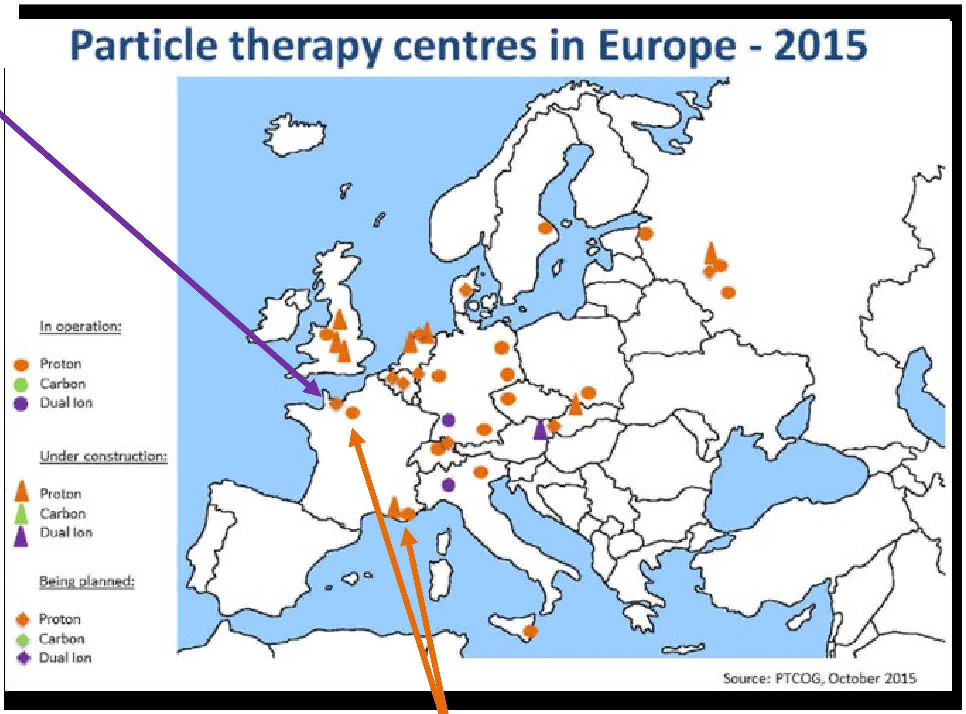
photons

→ Nice isodoses, normal tissue well avoided…

- **Hadrontherapy centers in Europe:**

Archade (Caen): protontherapy center
& futur carbon-ion therapy



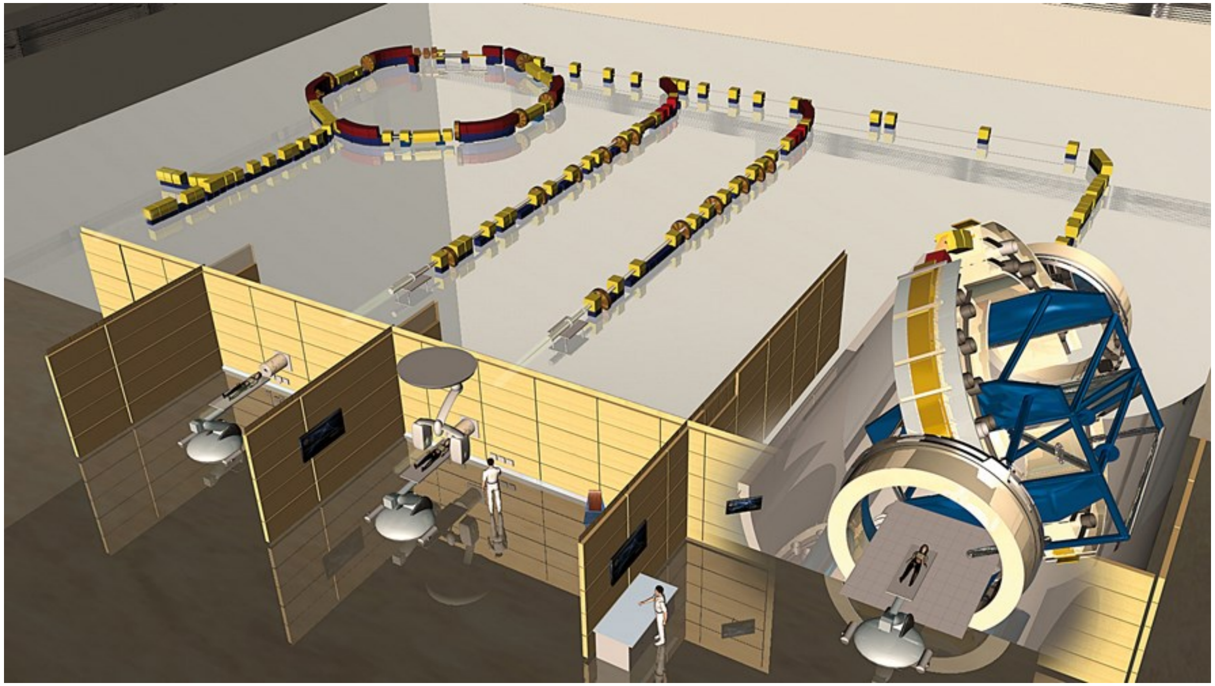


Orsay and Nice: protontherapy centers
(~600 patients/year)

Hadrontherapy

- 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€)

4 m

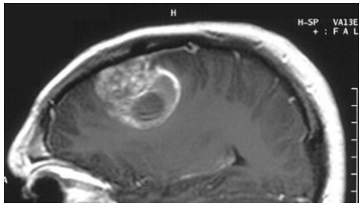
Standard medical accelerator
(~ 500 en France, ~1 M€)

→ … Few patients can benefit from it: priority to pediatric and some specific clinical cases.

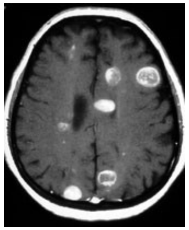
How to improve it ?

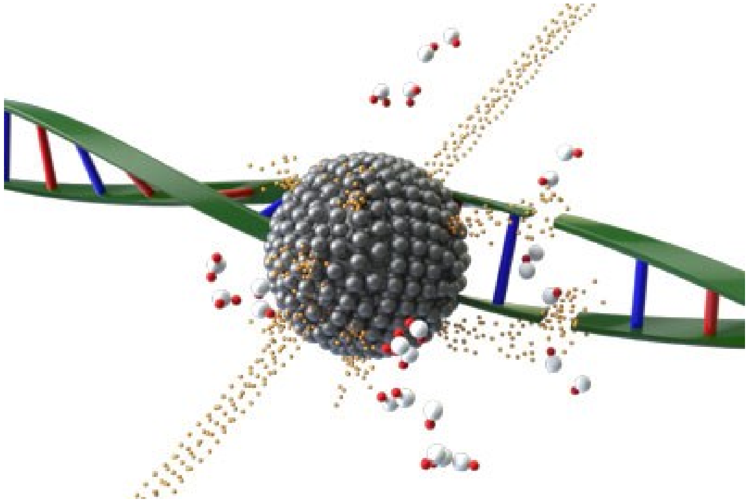
- Improve the ballistic: improved radiotherapy technologies (photons)
- Induce a more efficient tumoral irradiation: play on ballistic & radiobiology
  - ➢ Particle/energy: **hadrontherapy** (p, C-ion)
  - ➢ Targeted radiotherapy:

Radioresistant and diffuse cancers (glioblastomas)

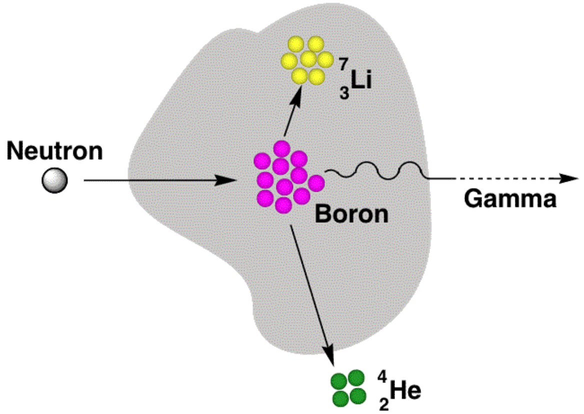


Non-localized tumors (metastases)





Nanoparticules



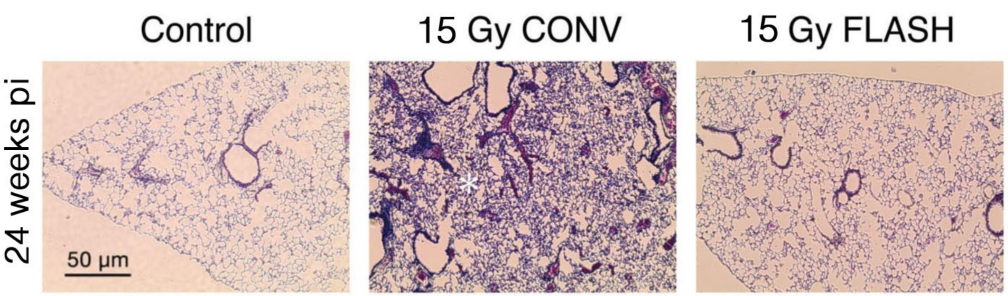
Boron Neutron Capture Therapy

How to improve it ?

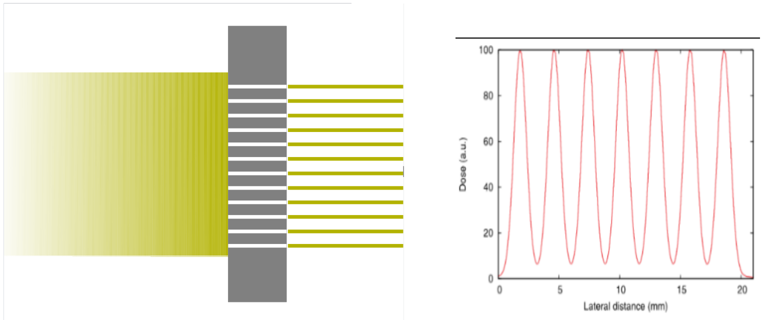
- Improve the ballistic: improved radiotherapy technologies (photons)
- Induce a more efficient tumoral irradiation: play on ballistic & radiobiology
- Preserve the healthy tissues: play on dose delivery & radiobiology
  - Particle/energy (hadrontherapy, VHEE…)
  - Dose delivery: Spatial fractionation of dose = very small beam sizes < mm

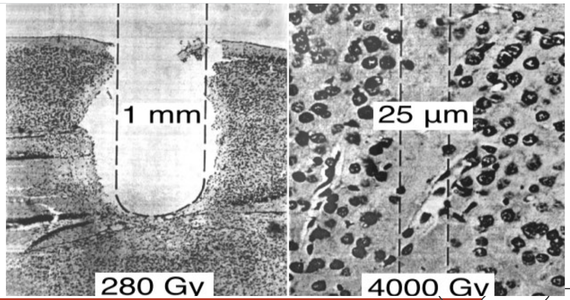
& FLASH = very high dose rate

Total dose delivered in < 100 ms



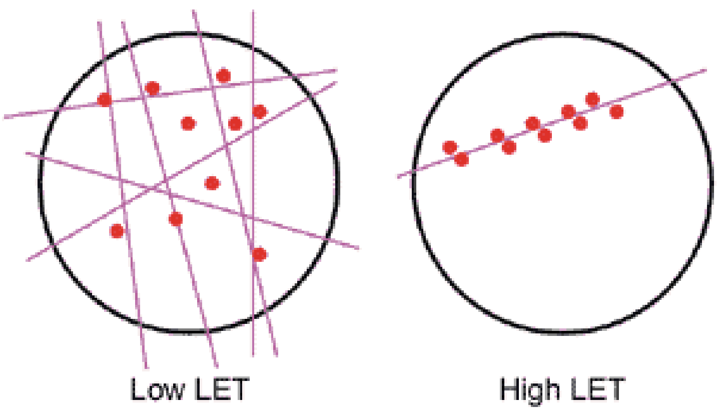
Total dose > 100 Gy
(max 20 Gy in CONV)

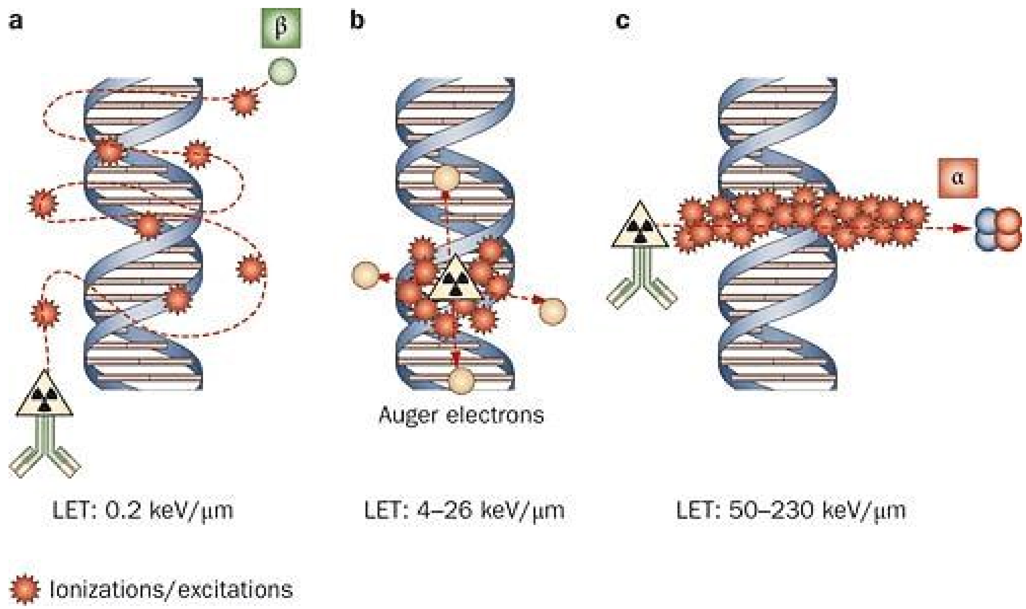




- Linear Energy Transfer (LET):
  - Energy transferred along a particle track per unit distance
  - LET related to the biological effect of radiation:

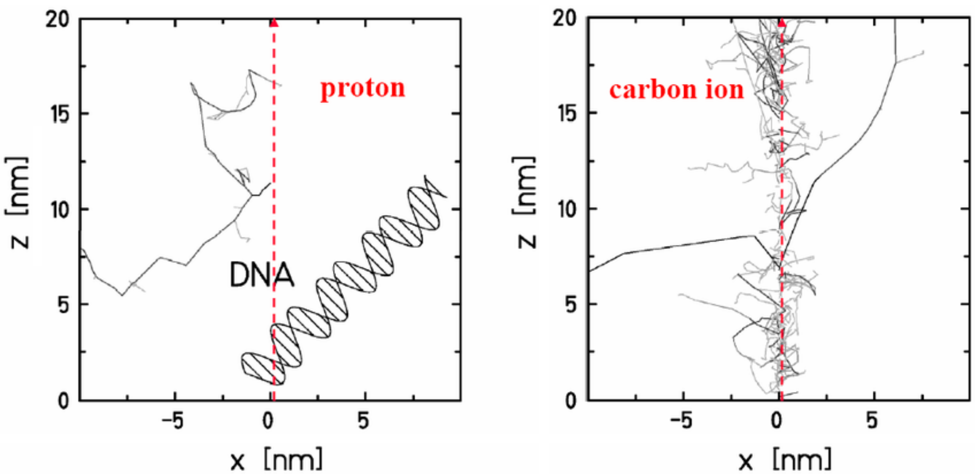
$$LET\left(\frac{keV}{\mu m}\right) = \frac{\Delta E}{\Delta D}$$



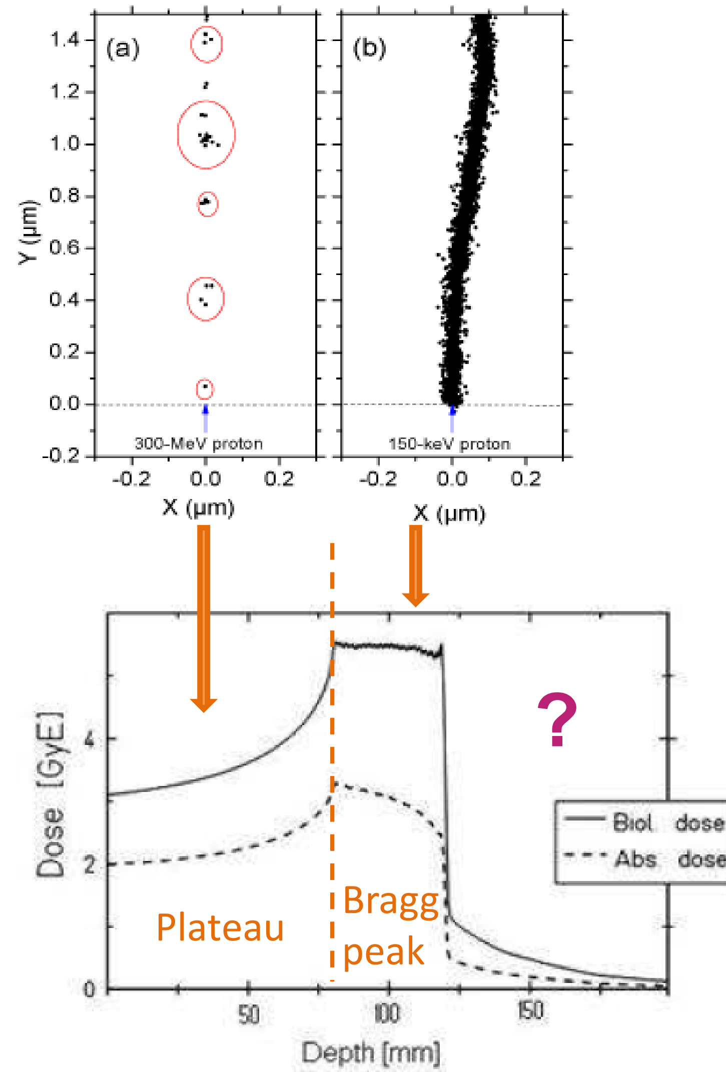


→ Equal macroscopical doses of high and low-LET radiation result in different biological effects

LET and track structures:



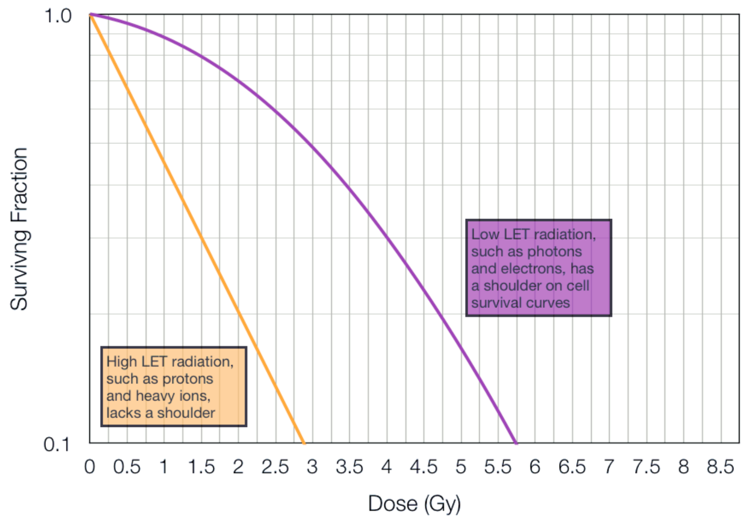
Ex: proton track in the plateau (a) or peak (b) region

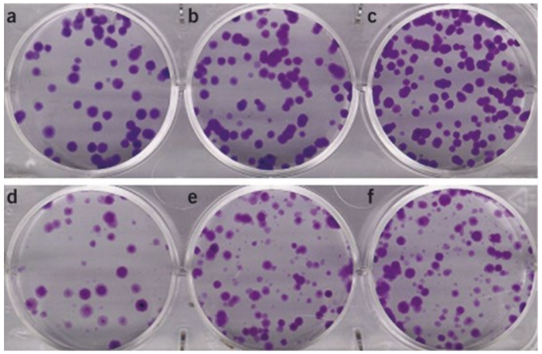


Relative Biological Effectiveness (RBE):

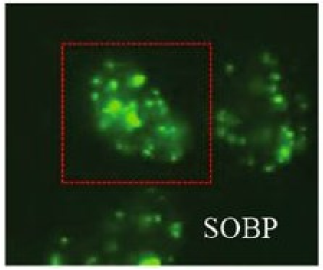
$$RBE_{Rad} = \frac{Dose(Gy)\ ^{60}Co\ \gamma}{Dose\ (Gy)\ Rad.\ for\ same\ biol. effect}$$

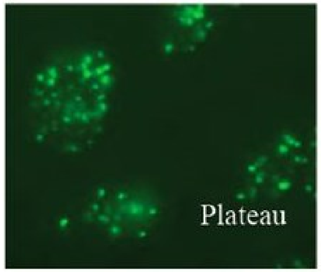
- Biological measurements to quantify the RBE *(in vitro)*:
  - **Survival cell** assays: clonogenic assays, cell viability, protein signal…





  - **DNA breaks**: γH2AX (double strand breaks), comet assay (simple and double breaks)…





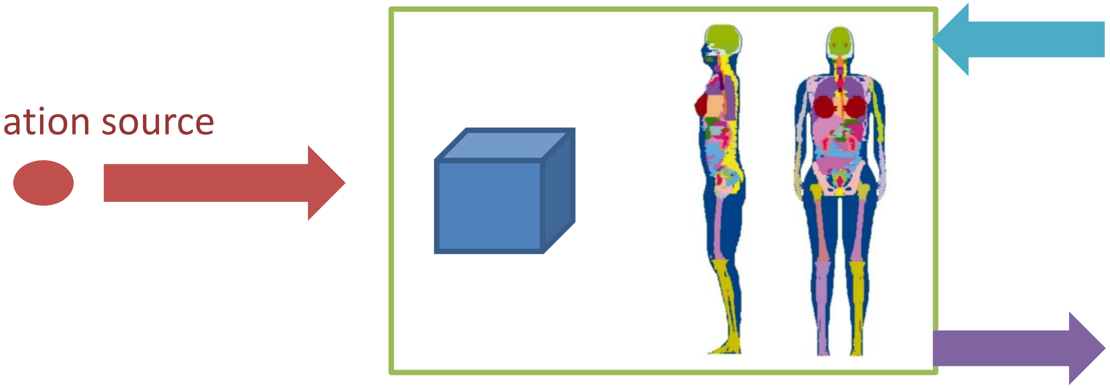
→ Dependant on cell line… Hard to get complete data base: let's try modelling!

Monte Carlo codes in Medical Physics

- Principle:

Geometry

Radiation source



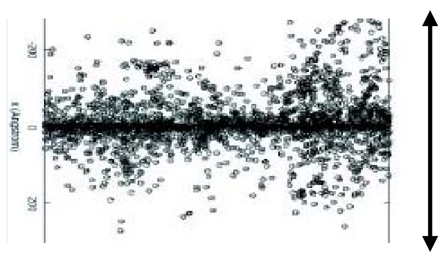
Input: physics (interaction cross sections, particle transport models, cuts…)

Transport of N primary particles with random selection of processes

Output: data of interest (depos. energy, angles, 2nd particles…)

- General purpose code:
  - Based on <u>macroscopic description of the particle transport</u>, using condensed-history methods: aims at being multi-purpose and relatively fast.
  - Ex: Geant4 (and declinations GATE, TOPAS…), FLUKA, MCNPX, EGS, PENELOPE …
  - Approximations and cuts in the low-energies → **non-adapted to nano level**

- « Track-structure » codes



~400 nm

Monte Carlo codes in Medical Physics

- « Track-structure » codes:
  - Description of **full particle histories step-by-step**, interaction after interaction.
  - Based on full calculation of differential cross section of charged particles in biological matter (water and DNA molecules…)
  - Intend to predict the radio-induced energy deposits at the nanometric level, and sometimes DNA damage induction and chemical stage.
  - Many very specific codes, among them:
    - **TILDA-V**: dedicated to proton transport in water and DNA

    *→ **Mario E. Alcocer-Avila**: Monte Carlo track structure simulation for radiation microdosimetry and targeted alpha therapy*

    - **Geant4-DNA**: extension of the Geant4 code that intend to add: all the physics process in biological materials, creation and transport of chemical radiolysis species, modelling the early biological damage

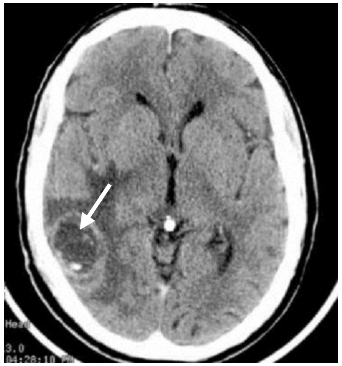
    *→ **E. Torfeh:** Micro dosimétrie des irradiations par microfaisceau d'ions en utilisant les méthodes Monte Carlo*

    - Very time-consuming, development of analytical models:

    *→ **E. Olivier:** Modelling of heavy ions transport in matter with entropic moments methods*

Workflow in radiotherapy treatment

Diagnostic

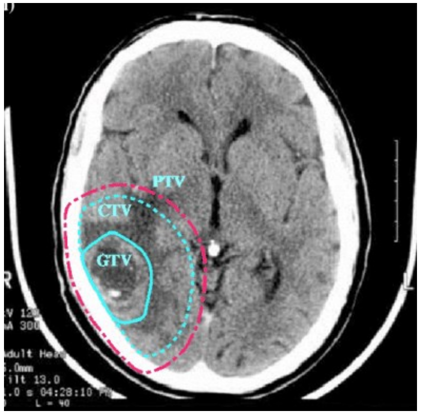


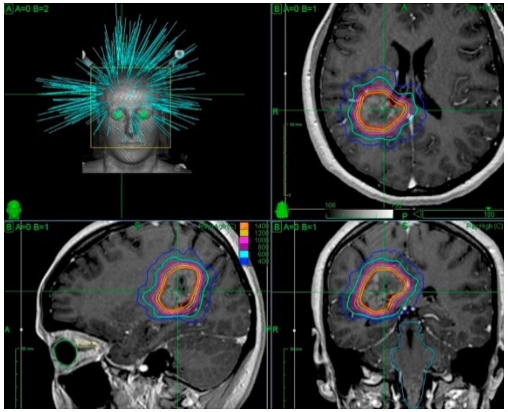
RT prescription

Treatment planification

Imaging: reference CT in treatment position + multimodal imaging (IRM, TEP…)

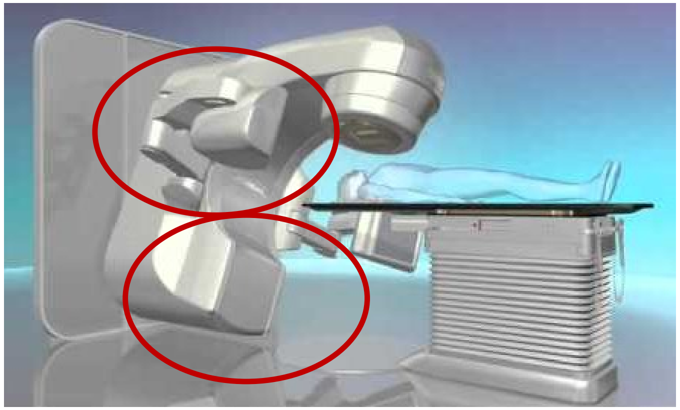
Treatment planning: delineation of tumor and OAR + dose calculation





Radiation therapy delivery

In multiple fractions



Patient QA

??

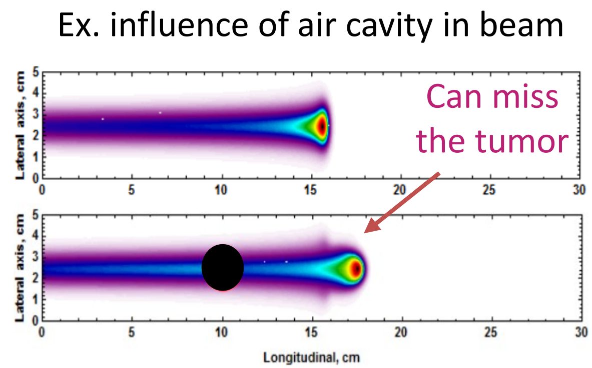
Embeded imaging system could be used for online verification

Long term Follow-up

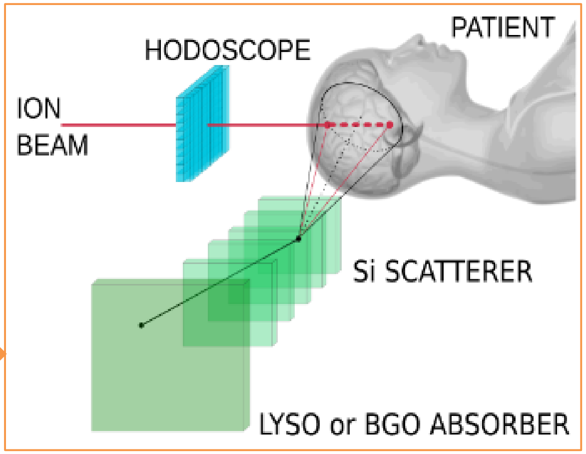
- Patient QA in hadrontherapy:
  - ➢ Challenge: no primary beam outgoing the patient.

    Range uncertainties in dose delivery unknown:
    a small error could have dramatic effect
    (patient/beam position error, patient loose weight…)

Ex. influence of air cavity in beam



  - ➢ Methods:
    - Use the β+ radioactive products: « inline » positron emission tomography
    - Detect the secondary particles:
      prompt gamma imaging camera



→ ***J. Livingstone:*** *Contrôle en ligne de l'hadronthérapie par rayonnements secondaires*

Questions?