New approaches in radiation therapy: high-energy electrons and spatial fractionation

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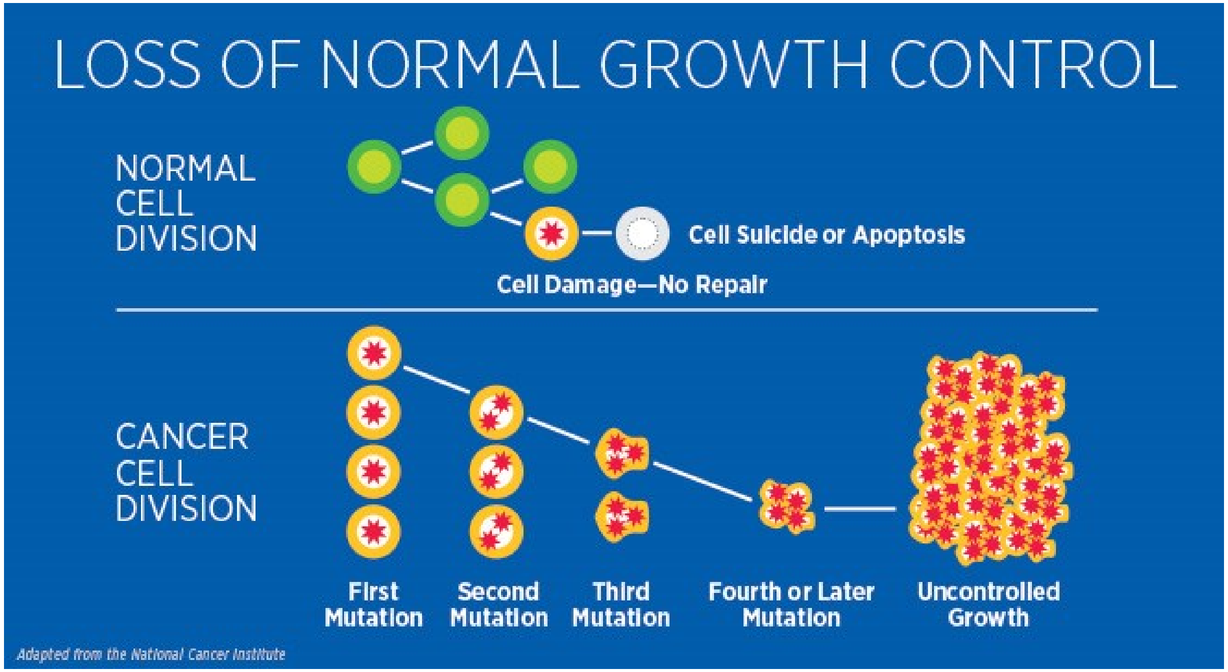
Cancer treatment

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



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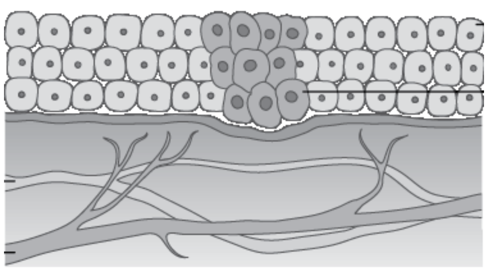

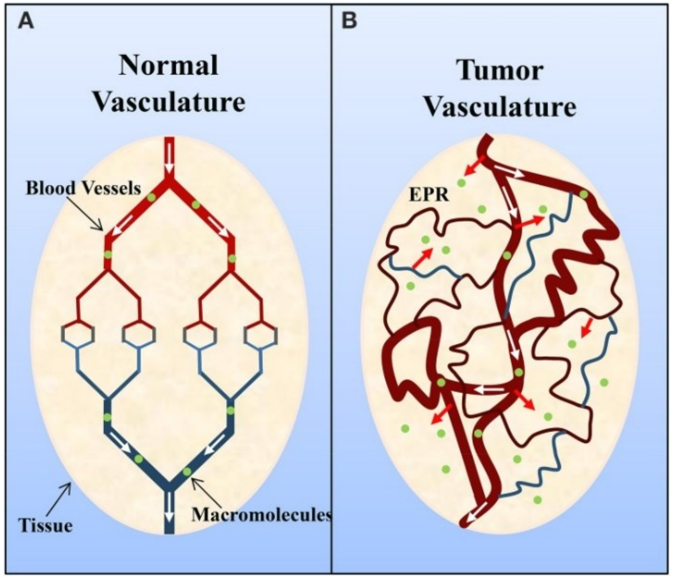

Cancer

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  - ✓ What is a cancer?
    - Abnormal cell division → mutation
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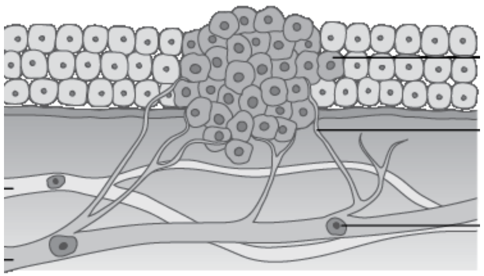
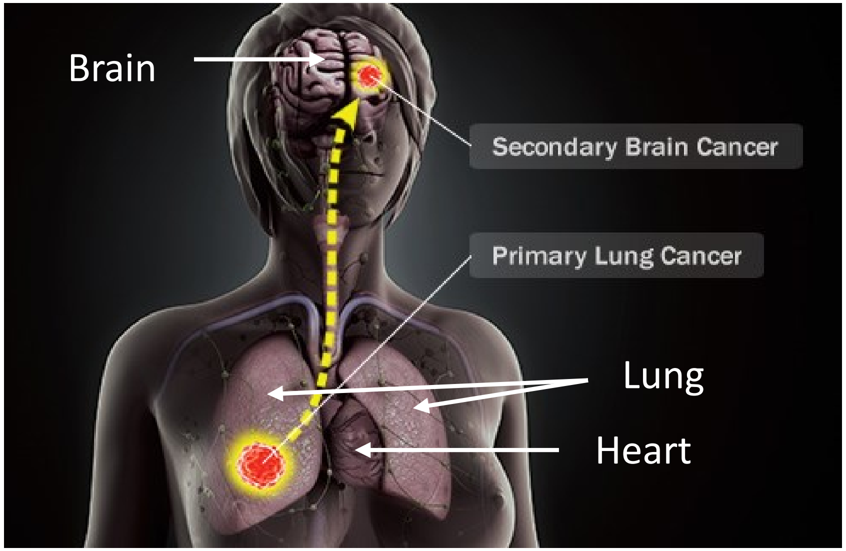
    - Propagation of a tumor → extension to lymphatic and blood vessels = 2nd cancer





→Treatment challenge: kill the tumor cells without damaging the organs at risk.

- Cancer treatment:
  - ✓ Main treatments:
    - Surgery
    - Chemotherapy
    - Radiotherapy *(half of patients)*
    - Immunotherapy
    - Hormonotherapy…

Often combined (Surgery, Chemotherapy, Radiotherapy)

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    - Surgery
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    - Radiotherapy *(half of patients)*
    - Immunotherapy
    - Hormonotherapy…

  Often combined (Surgery, Chemotherapy, Radiotherapy)

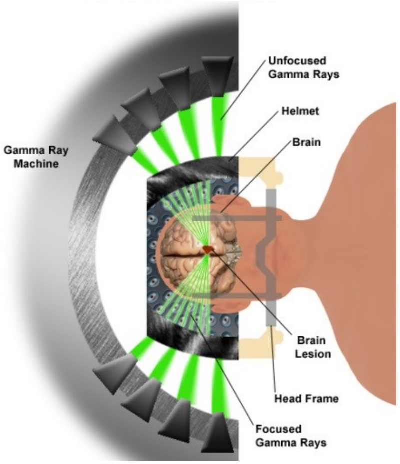
- "Conventional" radiotherapy *(~95%)*
  - ✓ **Particles**: X-rays 6-25 MV (every tumors), electrons 3-18 MeV (surface tumors)
  - ✓ **Machines**: clinical electron accelerators, with multileaf collimator and embedded imaging systems
  - ✓ **Time fractionation**: 2Gy/session, 5 session/week
  - ✓ **Dose**: 40-70 Gy
  - ✓ **Dose rate**: 30-70 mGy/s
  - ✓ **Field sizes**: 2 - 40 cm^2

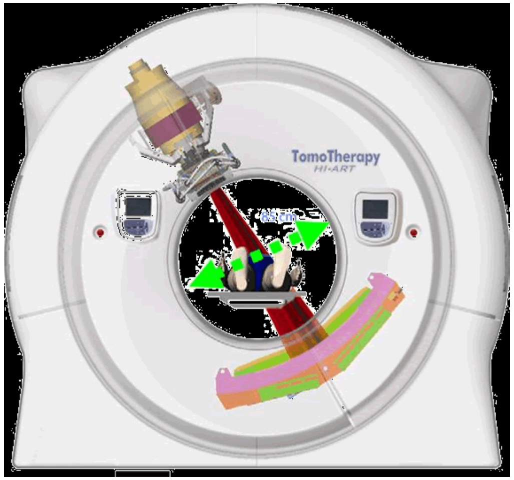
- Examples of current radiotherapy techniques (photons):

Standard clinical accelerator with embedded imaging systems

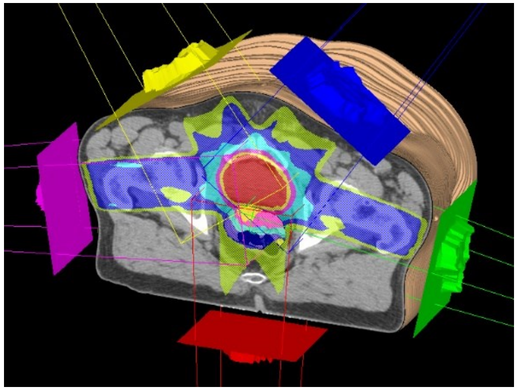
Cyber-knife

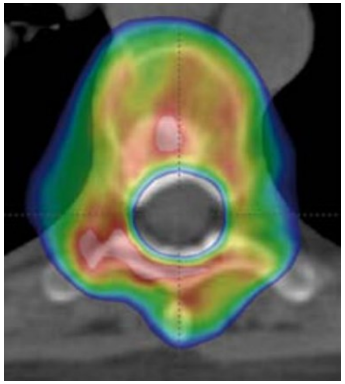
Gamma knife radiosurgery





Tomotherapy



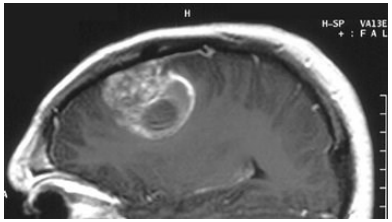


→ Objectives: large dose in tumor, low doses in healthy tissues

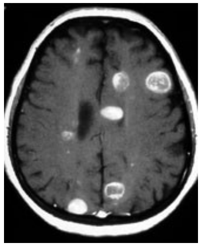
Limitations of radiotherapy

- Limitations of conventional radiotherapy

Radioresistant, bulky and diffuse cancers (glioblastomas)



Non-localized tumors (metastases)



→Toxicity to healthy tissue limits the dose

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

- Limitations of conventional radiotherapy

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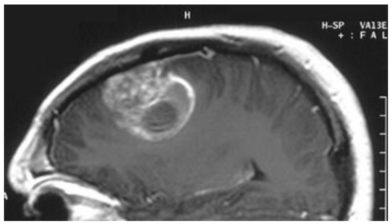

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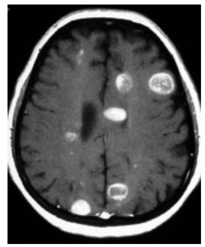
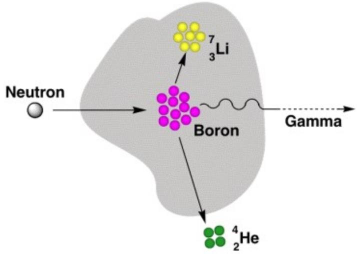


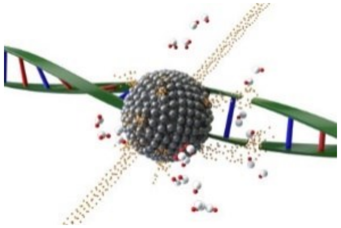
Clinical electron accelerator (X-rays ~6-25 MV)

→Toxicity to healthy tissue limits the dose

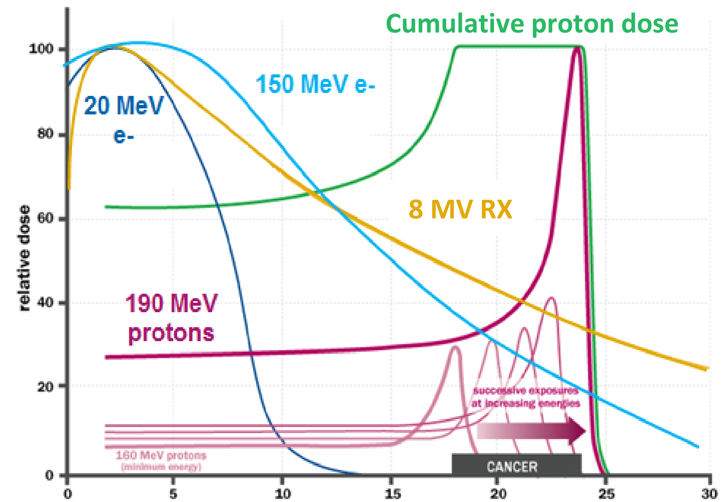
- How to improve the treatment?
  - Induce a more efficient tumoral irradiation:
    - Particle/energy: hadrontherapy (p, C-ion)
    - Targeted radiotherapy



Boron Neutron Capture Therapy



Nanoparticules



Penetration depth in human body (cm)

Limitations of radiotherapy

- ## Limitations of conventional radiotherapy

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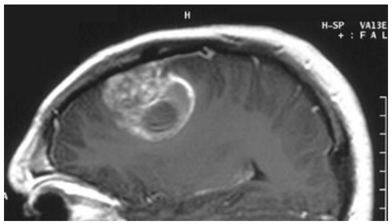

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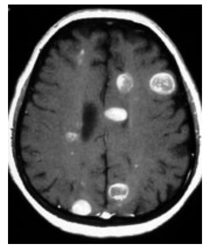
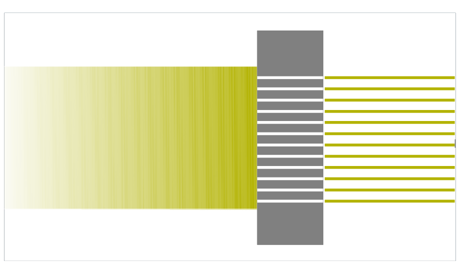
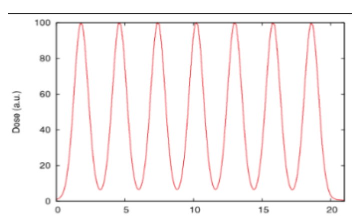


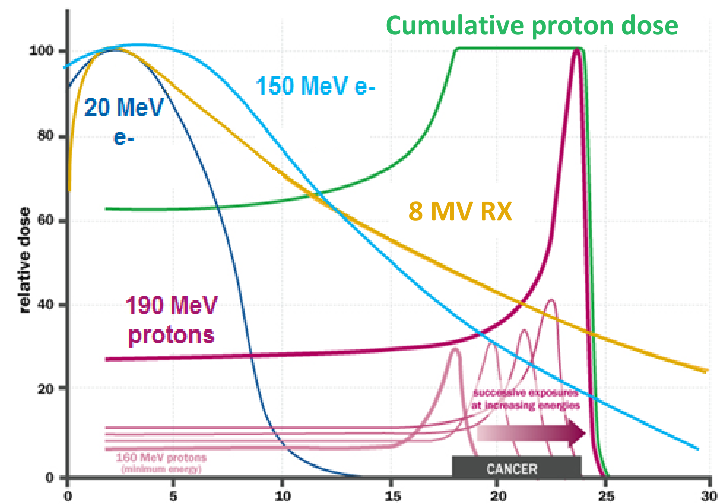
Clinical electron accelerator (X-rays ~6-25 MV)

→Toxicity to healthy tissue limits the dose

- ## How to improve the treatment?
  - Induce a more efficient tumoral irradiation
  - Preserve the healthy tissues:
    - Particle/energy (hadrontherapy, VHEE…)
    - Dose delivery: spatial fractionation of dose (beam sizes < mm), FLASH (high dose rate)

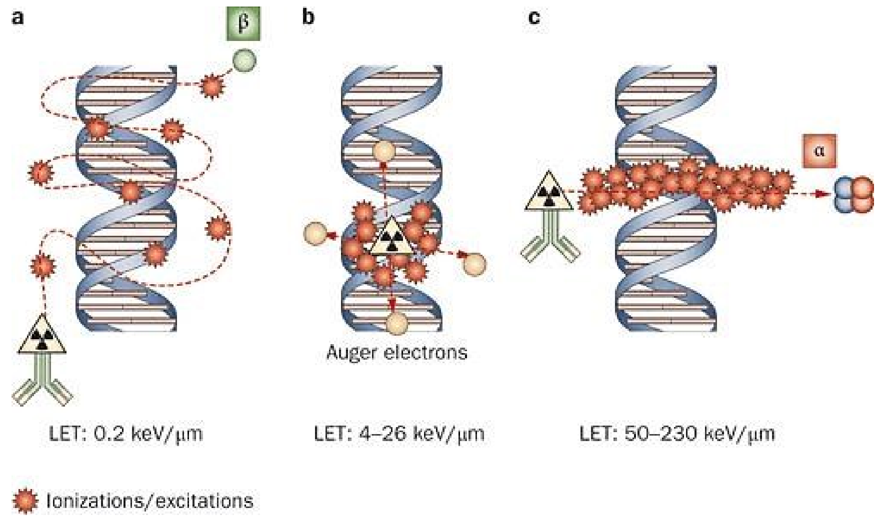




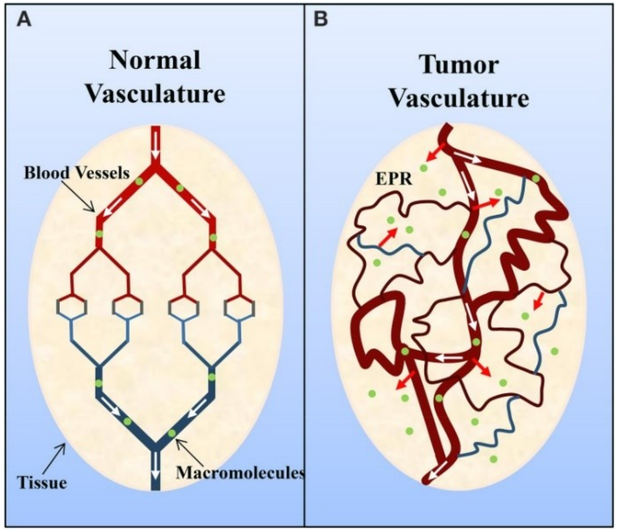


Penetration depth in human body (cm)

- Biological dose vs Physical dose
  - Molecular scale:
    - LET: ionization density
    - Repair mechanism
    - Radical production…
  - Tissue/Cell scale:
    - Cell regulation
    - Vasculature…

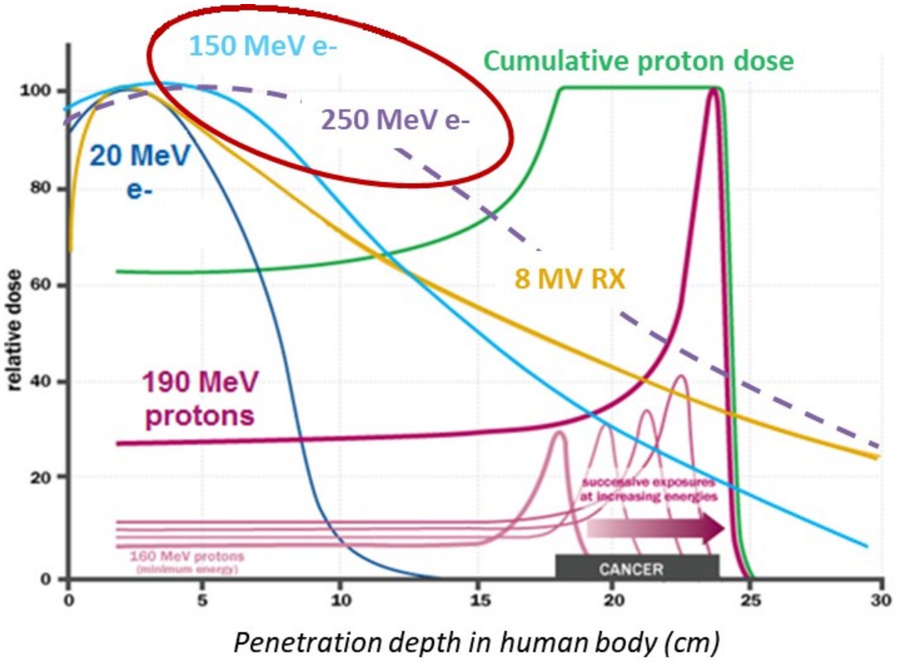


→The same physical dose will not induce the same biological response



VHEE beams: advantages vs MV photons

- ✓ ***Depth dose profile***: deep-seated tumors with flatter profile than photons
- ✓ ***Lateral scattering***: reduced, low penumbrae
- ✓ ***Magnetic collimation***: pencil beam scanning
- ✓ ***Heterogeneities***: no electronic disequilibrium at interfaces



Advantages VHEE (50-250MeV) for radiotherapy

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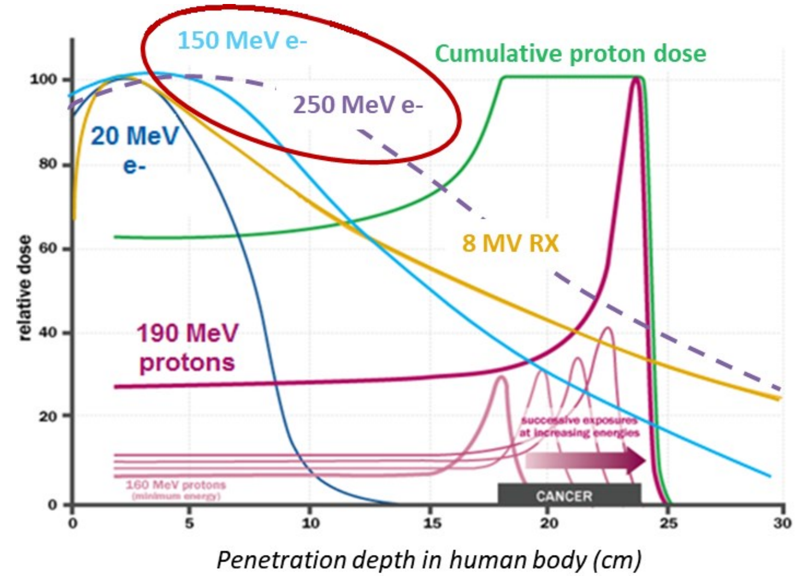
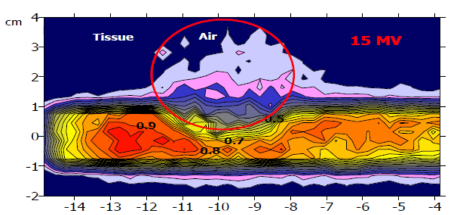
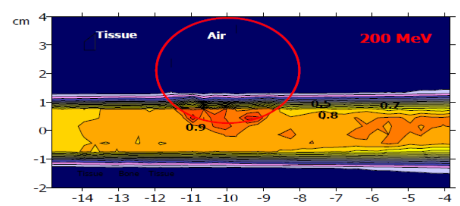


Heterogeneities

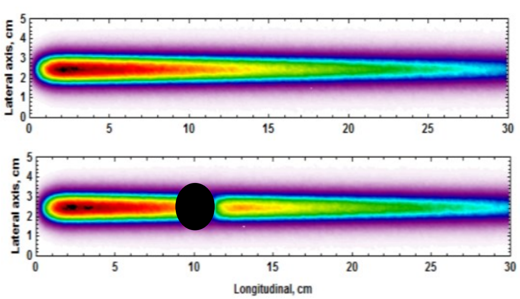




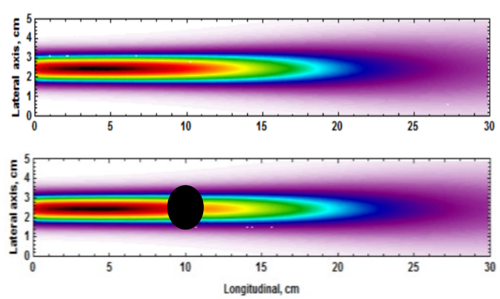
Papiez, DesRosiers et al. 2002

Agnese Lagzda

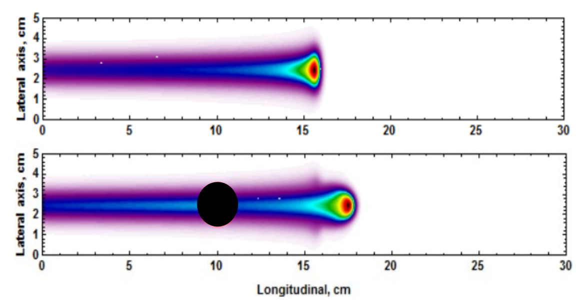
6 MV photons



200 MeV VHEE



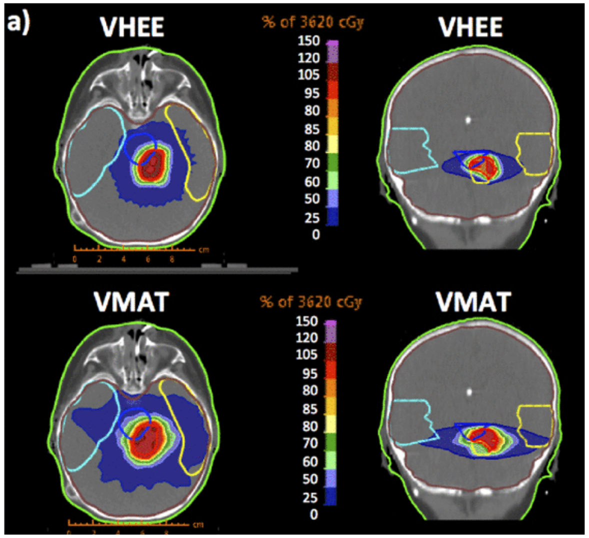
150 MeV protons



Advantages VHEE (50-250MeV) for radiotherapy

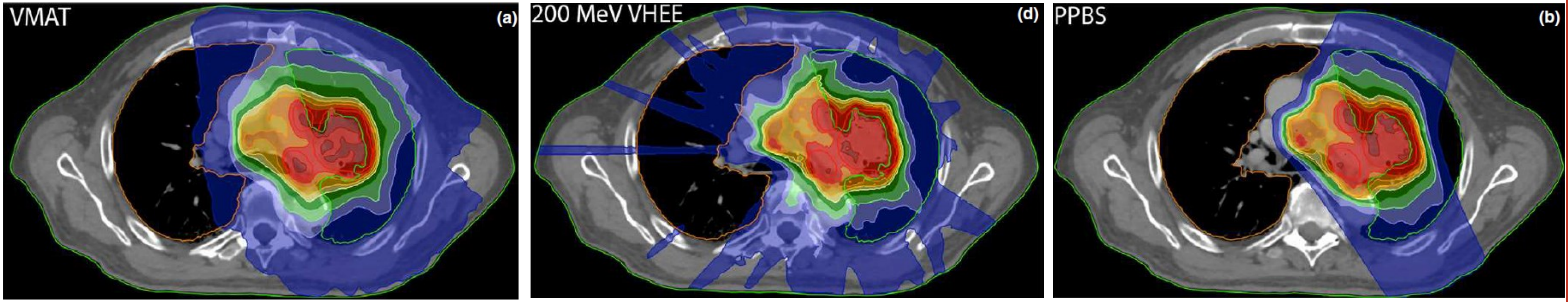
State of the Art:

- ✓ **Proof of concept** (dosimetry): *DesRosiers et al. 2000*
- ✓ **Clinical case comparisons*:***
  compared to VMAT (gold std in photon radiotherapy)
  → Better protection of OAR
  (prostate, pediatric, Lung, brain, H&N…)
- ✓ **Might be advantagous** vs **protons** for Head & Neck



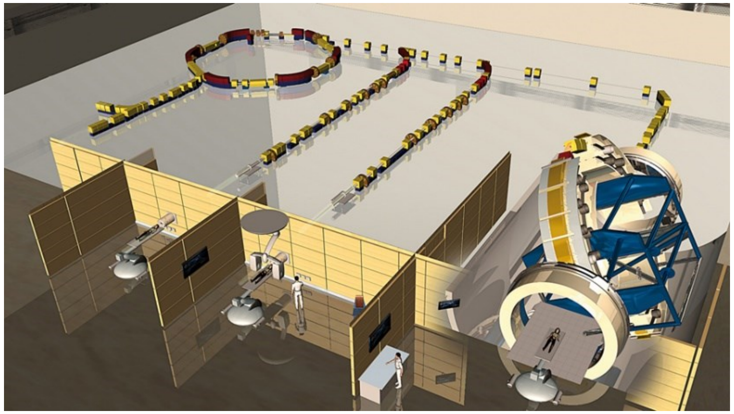
Brain tumour dose maps for 100 MeV VHEE and 6 MV volumetric modulated arc photon therapy (VMAT) *Bazalova-Carter, 2015 (Stanford)*

Lung tumor : comparison X-ray, VHEE, & protons *Schuler, 2017 (Stanford)*



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€ ?)

4 m

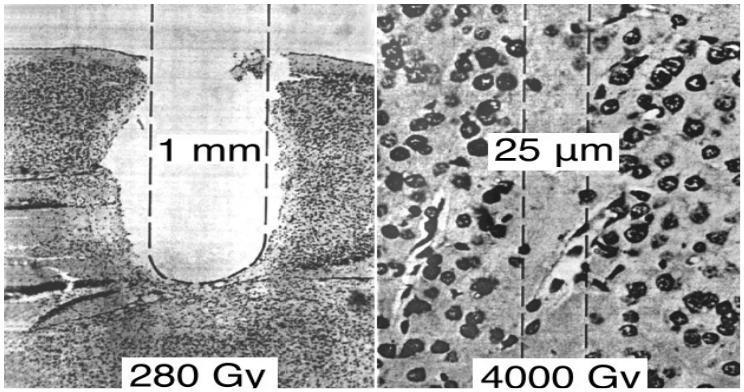
Standard medical accelerator
(~ 500 en France, ~1 M€)

VHEE beams: advantages vs protons

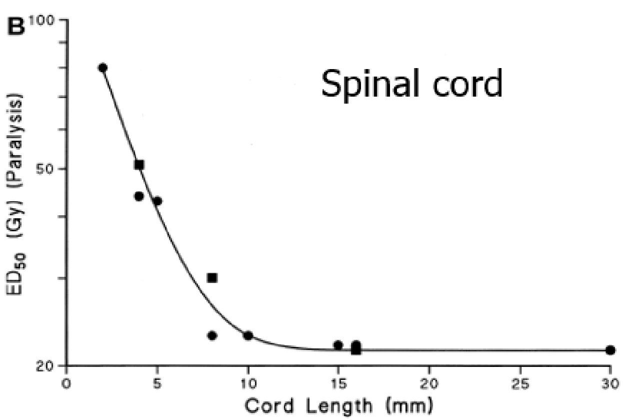
- ✓ Cost and ease of beam manipulation, more compact accelerators
- ✓ For our mini-beams applications: very small beam sizes (<1mm) and low penumbrae

- Spatial Fractionation and minibeam therapy

Very small beam sizes (< 1 mm²)



Zeman et al., Science (1959)

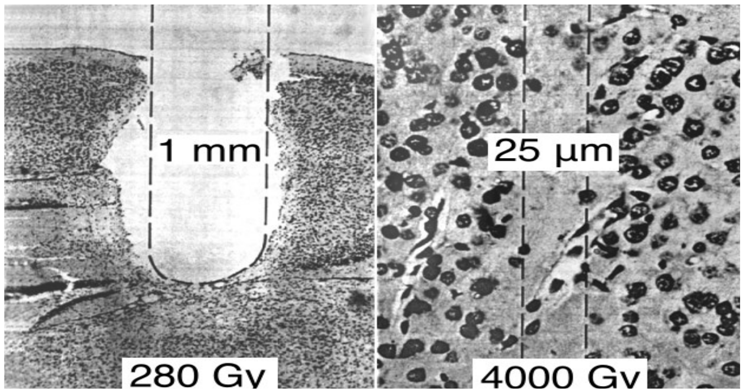


Hopewell et al., Radioth. Oncol. (2000)

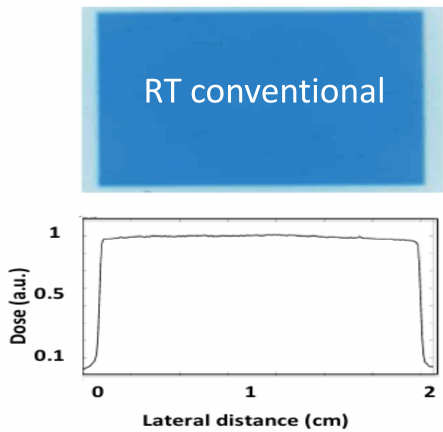
→ Dose-volume effect = the smaller the beam size, the higher the tolerance dose in healthy tissues.

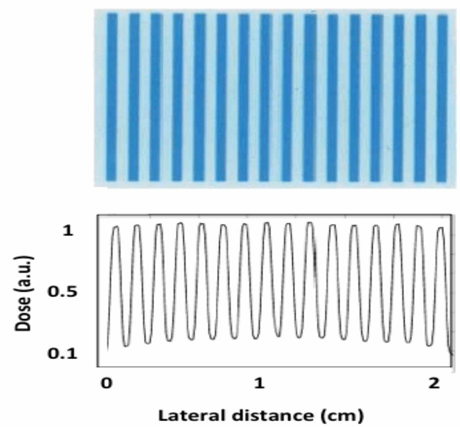
- Spatial Fractionation and minibeam therapy

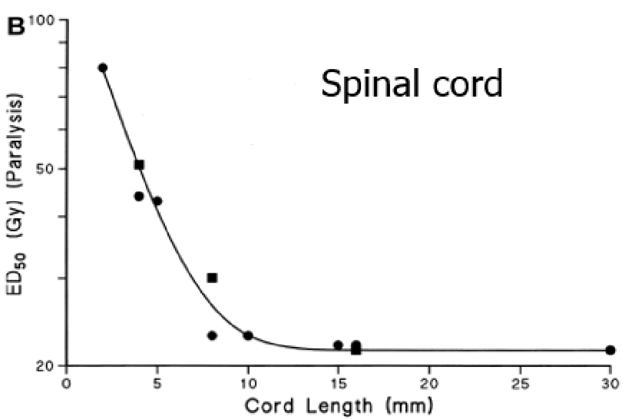
Very small beam sizes (< 1 mm²) + Spatial Fractionation of Dose



Zeman et al., Science (1959)







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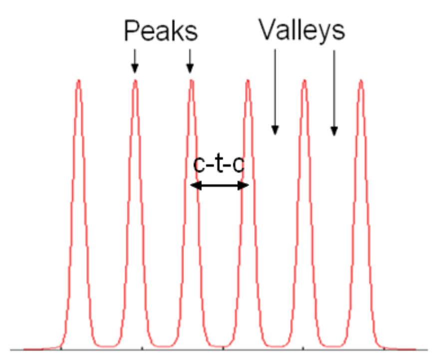


$$PVDR = \frac{D_{\text{peak}}}{D_{\text{valley}}}$$

↗ PVDR = ↗ tolerance normal tissues

↘ D_{valley} to garanty tissue preservation

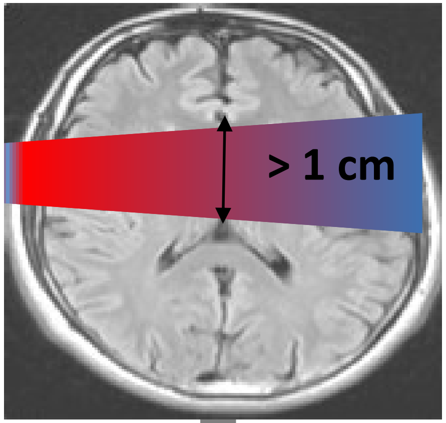
→ Dose-volume effect = the smaller the beam size, the higher the tolerance dose in healthy tissues.

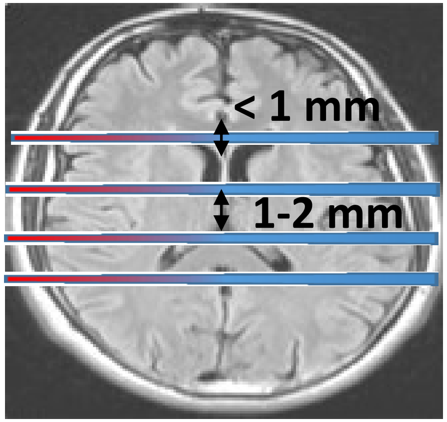
Standard Radiotherapy	Fractionated Radiotherapy *x-rays minibeam radiation therapy*

Large beam sizes
(> 1 cm^2)

+

Homogeneous Dose





Small beam sizes separated by region of low doses

+

Heterogeneous Dose

Lethal dose in rat > 20 Gy

Biological Mechanism not well known

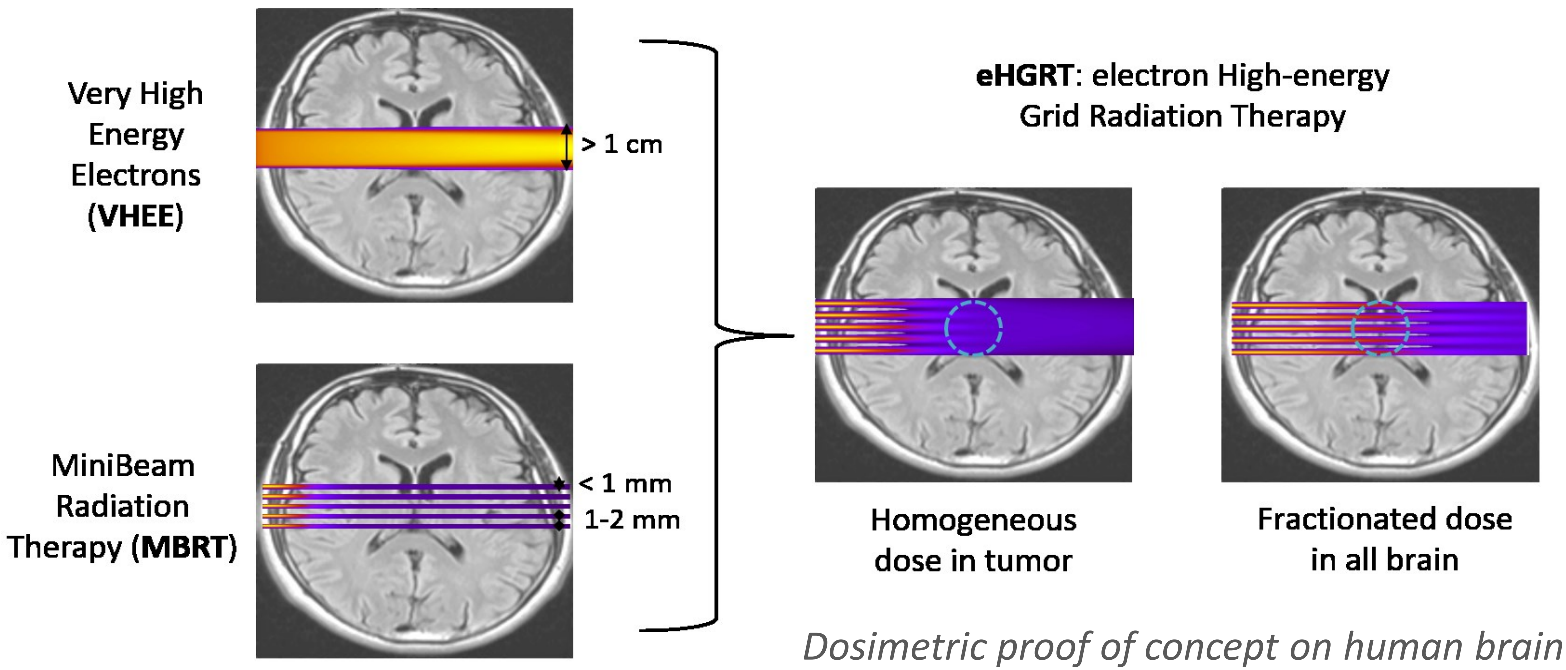
(cell migration, hypoxia, immature vasculature…)

Remarkable increase of the brain dose tolerance (up to 100 Gy/session)
Prezado et al. 2015 and increase in tumor control (to be published)

VHEE grid-therapy: implementation on PRAE

Objectives NARA (IMNC): combine advantages of VHEE beams with spatial fractionation

Grid therapy with beams < 1 cm



Dosimetric proof of concept on human brain
Martinez-Rovira & Prezado 2015

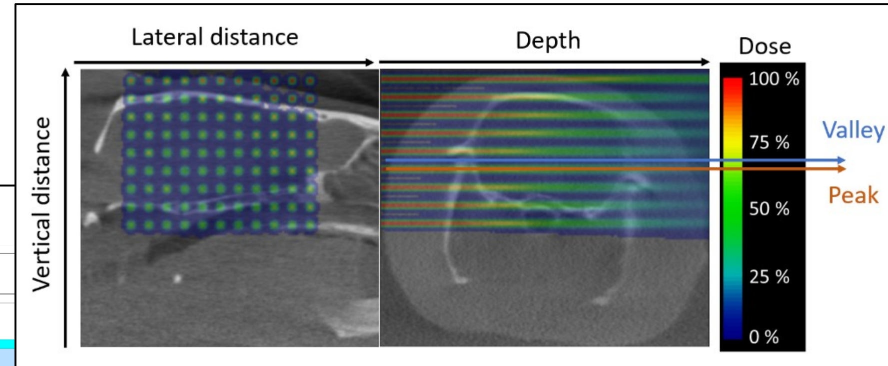
Platform for Research and Applications with Electrons

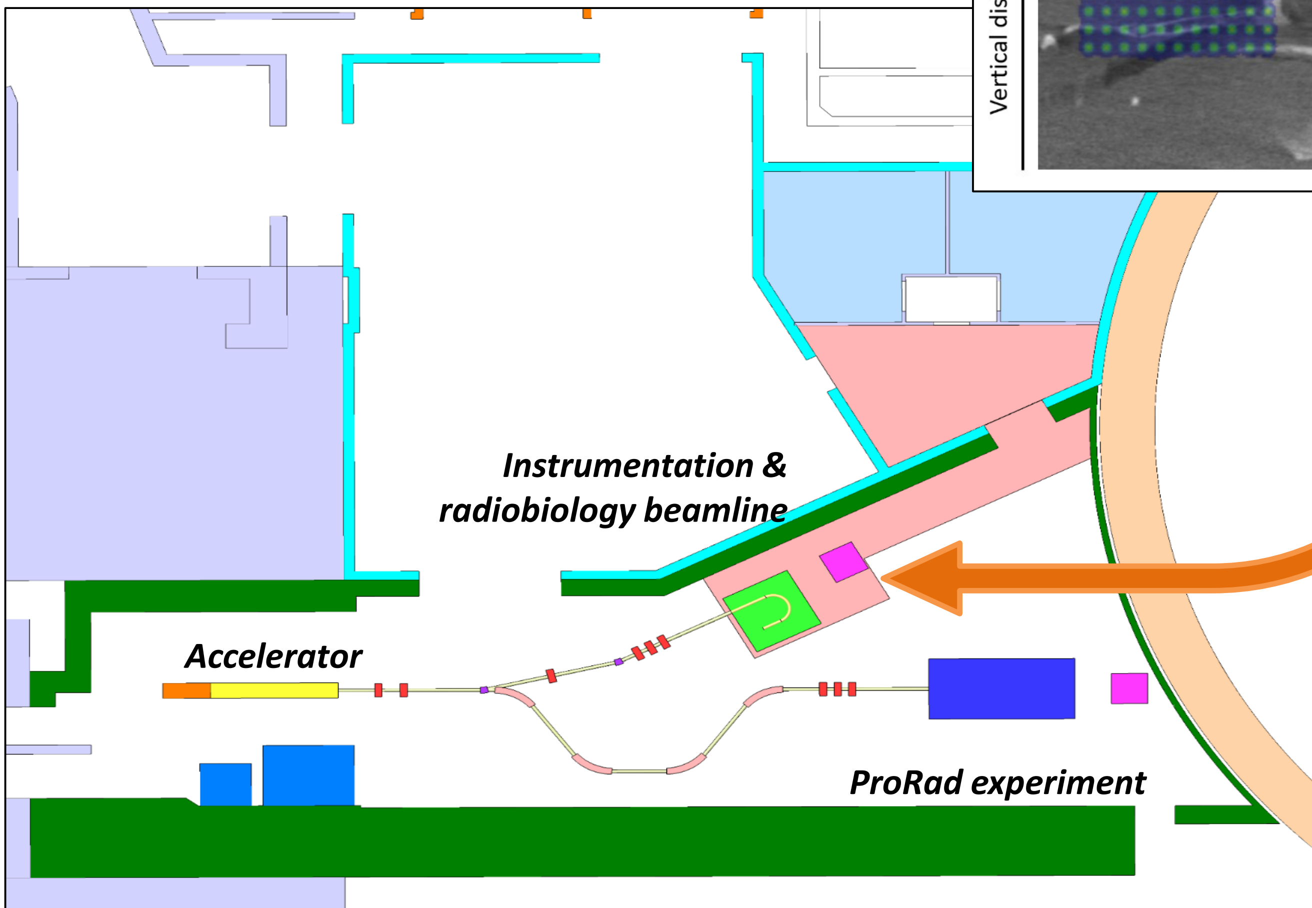
→ **On PRAE**: perform all numerical and experimental dosimetric validation up to the *in vivo* proof of concept

PRAE: "Platform" for Research and Applications with Electrons

High energy and high-performance electron beam in Orsay

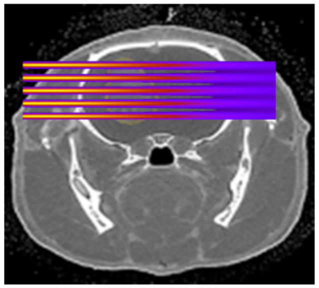
- phase I : 70 MeV → *2022*
- phase II : 140 MeV





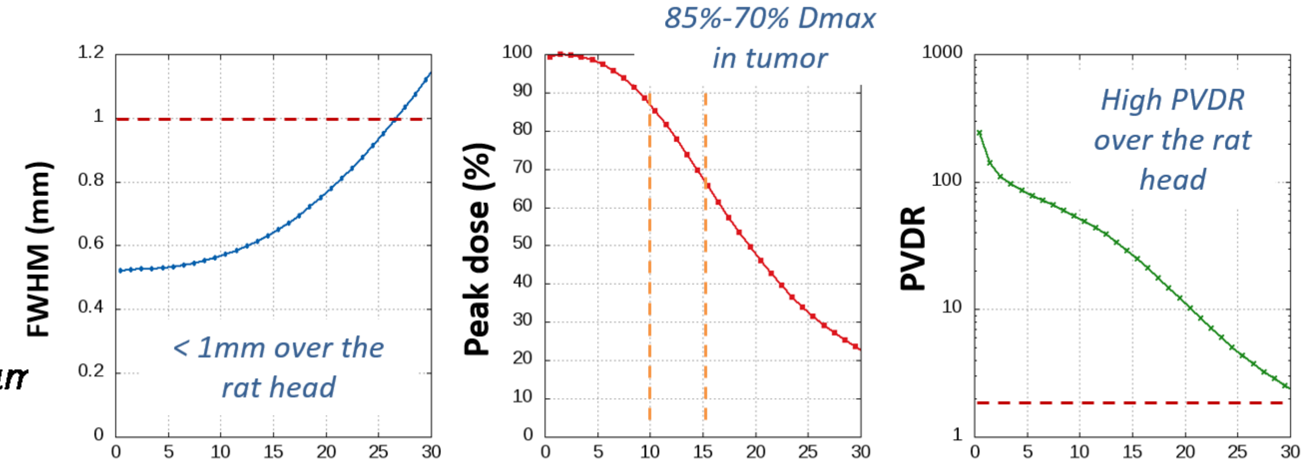
→ Perform the first in vivo exp. to evaluate the therapeutic benefit of VHEE grid-therapy

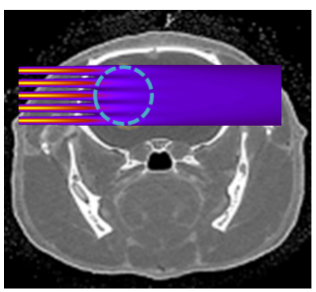
First dosimetry optimization: electron energy, beam size, beam divergence , air gap



140MeV, σ 220µm, ctc 1800µm

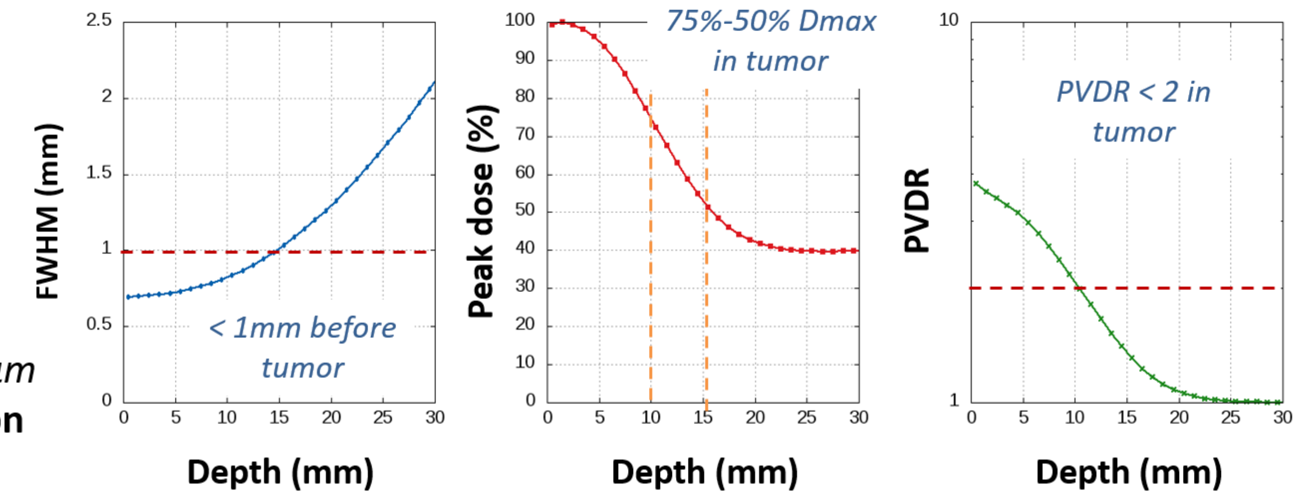
Healthy tissue sparing optimization





70MeV, σ 220µm, ctc 1200µm

Tumor control optimization



Delorme R. et al. EP-2198. Radiother Oncol. 2018;127:S1214-S1215.

Conclusion and perspectives on biological applications

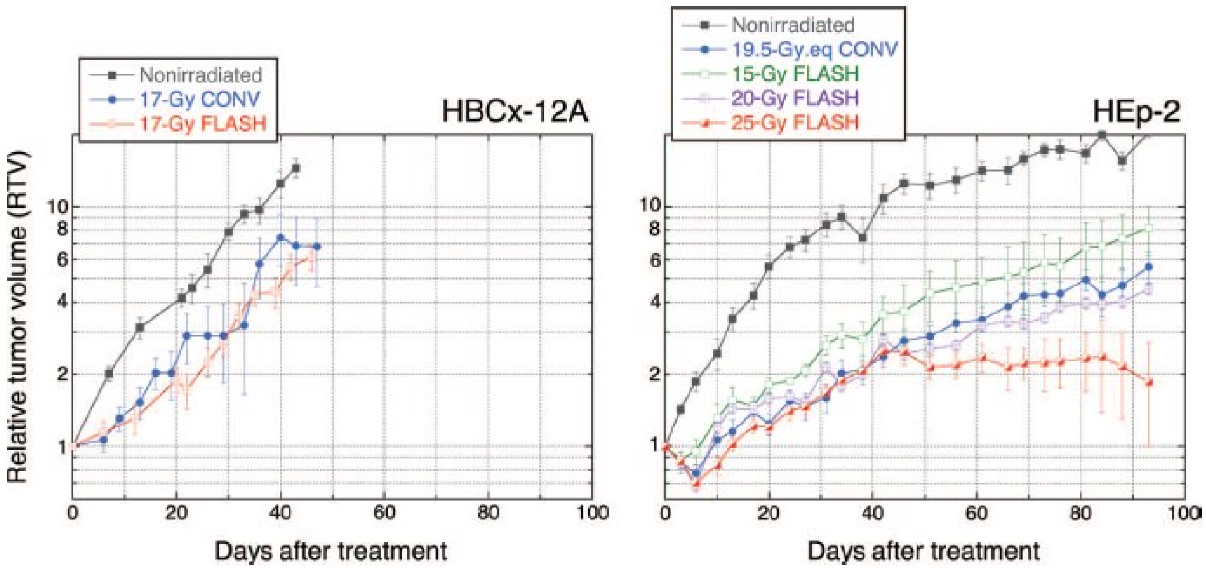
- Objectives: go **towards the clinics** with SFR approaches and explore VHEE therapy.
- Beam characteristics on PRAE for biological applications**:**

Platform for Research and Applications with Electrons
PRAE

-	Small beam-size:	150 µm < σ < 10 mm
-	Energies:	70 – 140 MeV
-	Small divergence:	0.1 – 0.4 mrad
-	Dose rate:	0.035 Gy/s – 40 kGy/s *

→ In vivo experiments would be a PRAE specificity compared to other VHEE facilities

- High dose rates *(> 100 Gy/s)*: interesting for **FLASH therapy**:



Very promising approach:

- Lung fibrosis: **15 Gy** in CONV **(0.03Gy/s)**
- No fibrosis in FLASH **(40 Gy/s)** up to **20 Gy.**
- Same tumor control for CONV & FLASH.
  →**Differential effect** in tumor / normal tissues

Thank you for your attention

delorme@imnc.in2p3.fr

Merci!

The PRAE Collaboration:

Platform for Research and Applications with Electrons

Imagerie et Modélisation en Neurobiologie et Cancérologie

Institut de Physique Nucléaire

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