Projet Emblématique

Programme SESAME

Introduction: VHEE Grid-therapy on PRAE

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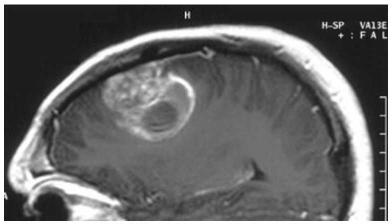
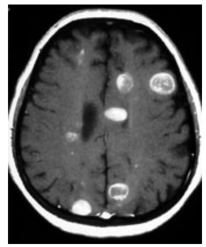
Limitations of radiotherapy

- ## Limitations of "conventional" radiotherapy

Radioresistant, bulky and diffuse cancers (glioblastomas)

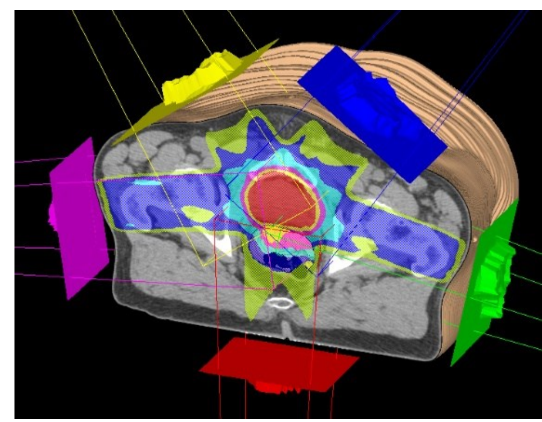


Non-localized tumors (metastases)



→Toxicity to healthy tissue limits the dose

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

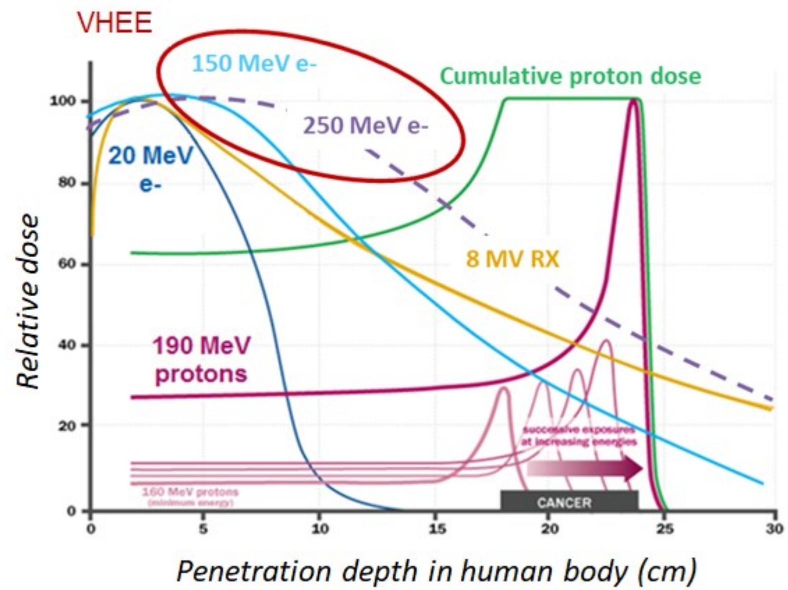


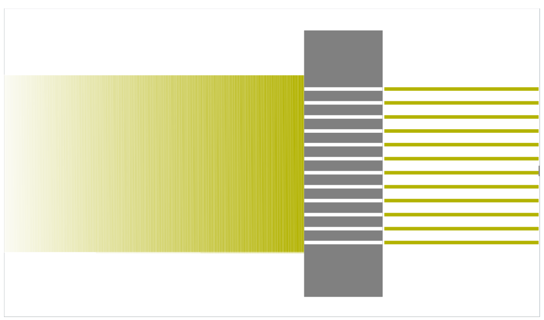
- ## Standard dose-delivery:

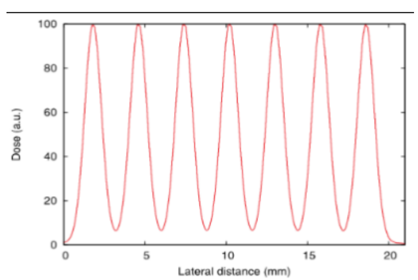
  - ✓ **Particles** *(95%)*: X-rays 6-25 MV (every tumors), electrons 3-18 MeV (surface tumors)
  - ✓ **Time fractionation**: 2Gy/session, 5 session/week
  - ✓ **Dose**: 40-70 Gy
  - ✓ **Dose rate**: 30-70 mGy/s
  - ✓ **Field sizes**: 2 - 40 cm^2

Limitations of radiotherapy

- How to improve the treatment:
  - ➢ Induce a more efficient tumoral irradiation:
    - ○ Particle/energy: hadrontherapy *(p, C-ion)*
    - ○ Targeted radiotherapy *(nanoparticles)*
  - ➢ Preserve the healthy tissues:
    - ○ Particle/energy (hadrontherapy, **VHEE**…)
    - ○ Dose delivery: **spatial fractionation of dose with small beams** (beam sizes < mm), "**FLASH**" (high dose rate > 40 Gy/s)







→ Play on physical parameters to induce a different biological effect

Advantages VHEE (50-250MeV) for radiotherapy

Agnese Lagzda

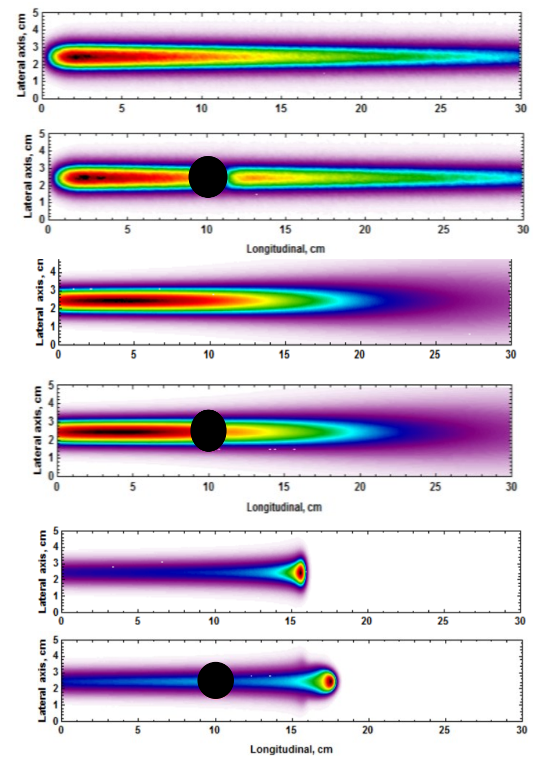
VHEE beams: advantages vs MV photons

- ✓ ***Dose profile***: deep-seated tumors with flatter profile than photons and reduced penumbrae
- ✓ ***Magnetic collimation***: pencil beam scanning
- ✓ ***Heterogeneities***: no electronic disequilibrium at interfaces
- ✓ **Clinical case comparisons*:*** *compared to VMAT (gold std in photon radiotherapy)* → Better protection of OAR *(prostate, pediatric, Lung, brain, H&N…)*

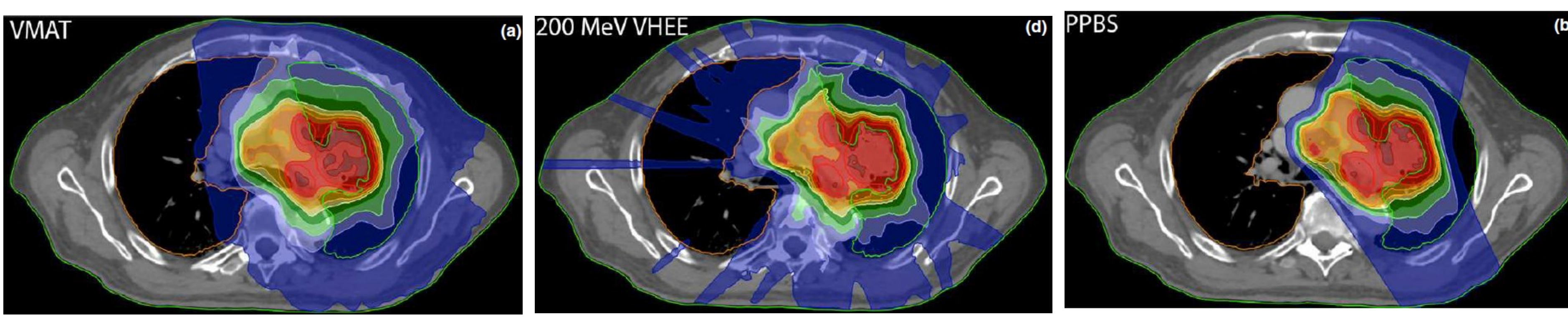
6 MV photons

200 MeV VHEE

150 MeV protons



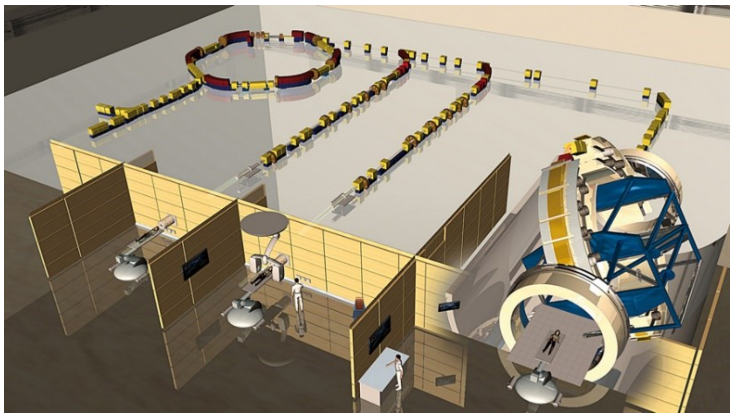
Lung tumor : comparison X-ray, VHEE, & protons *Schuler, 2017 (Stanford)*



Advantages VHEE (50-250MeV) for radiotherapy

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

50 m



Hadrontherapy center of Heidelberg
(~130 hadron centers in world, cost 50-100 M€)

VHEE
(~10 M€ ?)

Potential **cost-effective** approach

4 m

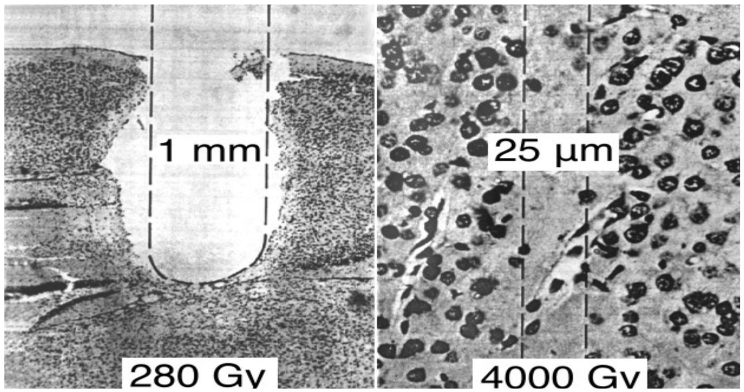
Standard medical accelerator
(~ 500 en France, ~1 M€)

VHEE beams: advantages vs protons

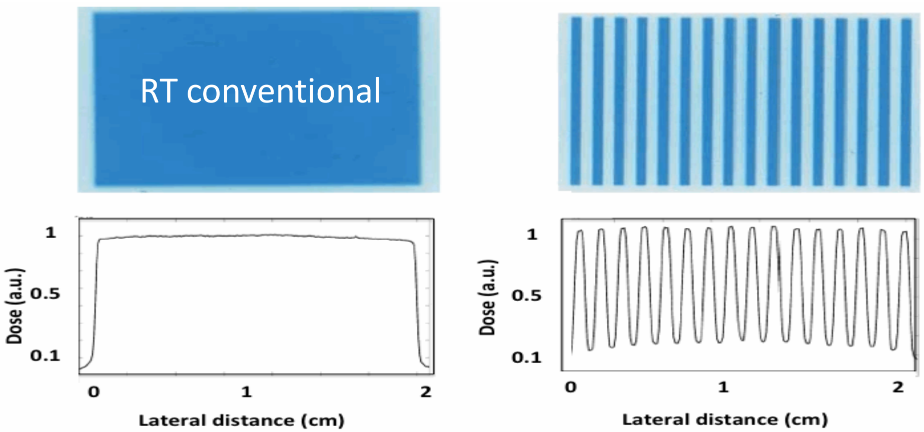
- ✓ Cost and ease of beam manipulation, more compact accelerators
- ✓ For our mini-beams applications: very small beam sizes (<1mm) and low penumbrae

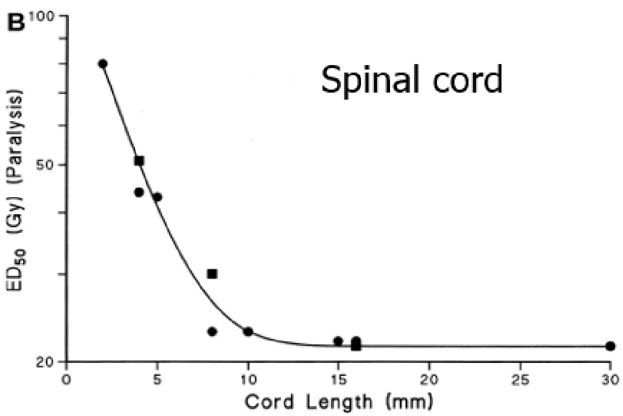
- Spatial Fractionation and dose-volume effect

Very small beam sizes (< 1 mm^2) + Spatial Fractionation of Dose

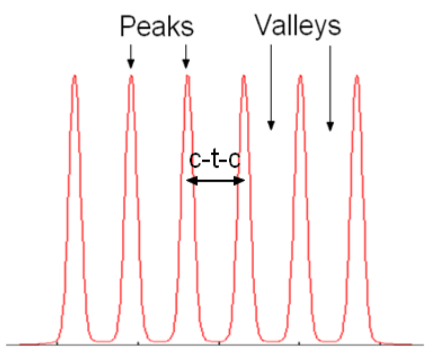


Zeman et al., Science (1959)





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



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

↗ 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.

Microbeam radiation therapy (25-100 µm beams) born at synchrotrons

Toward clinics using Mini-Beam Radiation Therapy (MBRT, <u>400-700 µm beams</u>)

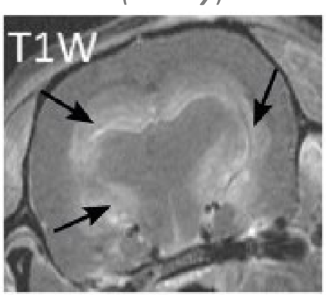
✓ **Experimental evidences with Photon MBRT:**

- Remarkable <u>increase of the rat brain dose tolerance</u> (up to **100 Gy/session**), against lethal dose at **20 Gy** in standard irradiation → Prezado *et al.* 2015, 2017
- Life span increase in <u>9L gliosarcoma-bearing rats</u>, interlaced MBRT (100 Gy) → Prezado *et al* 2012

✓ **Experimental evidences with Proton MBRT*:***

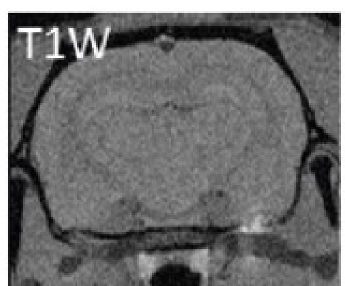
- Remarkable <u>tissue-sparing with pMBRT</u> irradiation → Prezado *et al.* 2017
- <u>Tumor regression</u> on RG2 glioma bearing rats with <u>fully fractionated pMBRT</u> → Prezado Estro2018

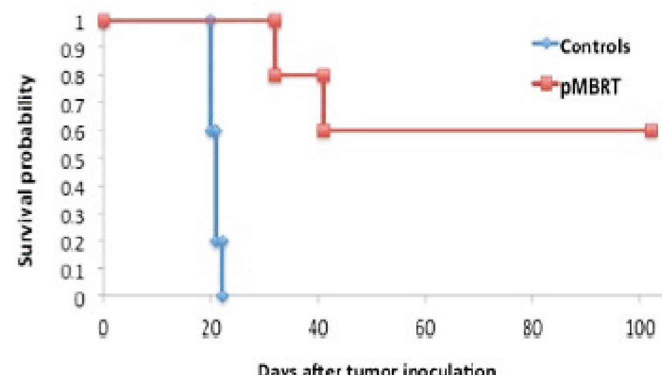
Standard protontherapy (~25Gy)



Proton MBRT (~25Gy)

Non-irradiated





Spatial Fractionation of Dose

Microbeam radiation therapy (25-100 µm beams) born at synchrotrons

Toward clinics usi… beams)

✓ **Experimenta…**

- Remarka…),
  against l… 7
- Life span…) → Prezado *et al* 2012

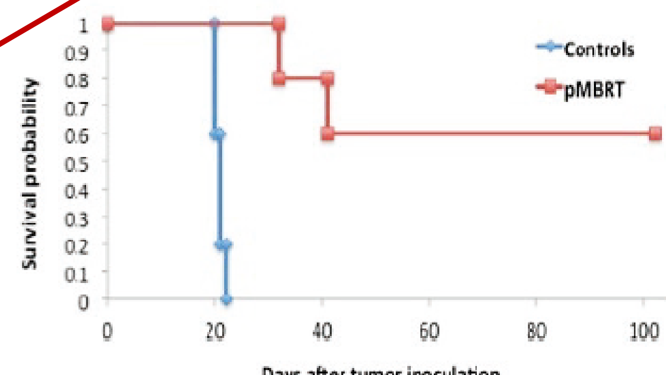
✓ **Experimenta…**

- Remarka…
- Tumor reg… BRT → Prezado *et al* 2018

What biological effects to explain the tissue sparing and differential response normal/tumor ?

- Repopulation of peak regions from valleys ?
- Effect on immature vasculature ?
- Hypoxia ?

Standard protontherapy (~25Gy) | *Proton MBRT (~25Gy)* | *Non-irradiated*



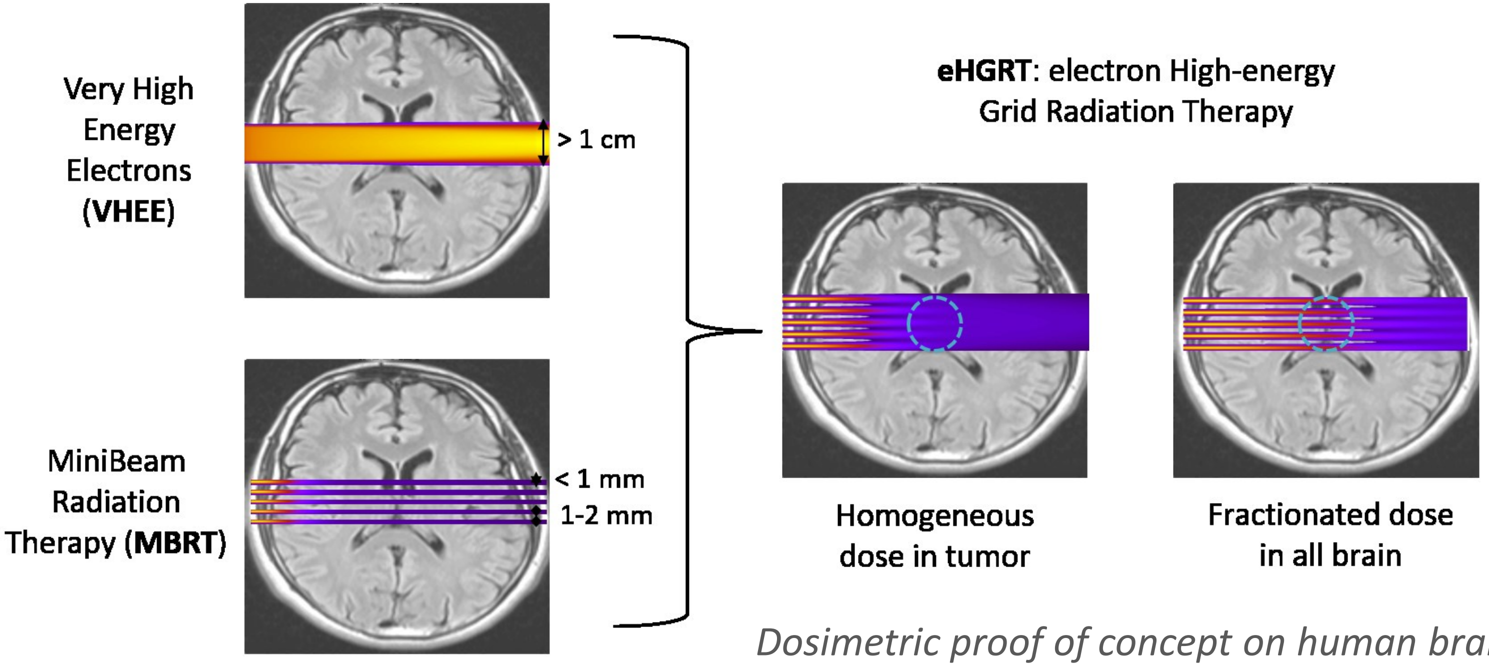
VHEE grid-therapy: implementation on PRAE

Main objective on PRAE: evaluate *<u>in vivo</u>* the therapeutic benefit of VHEE grid-therapy

Platform for Research and Applications with Electrons

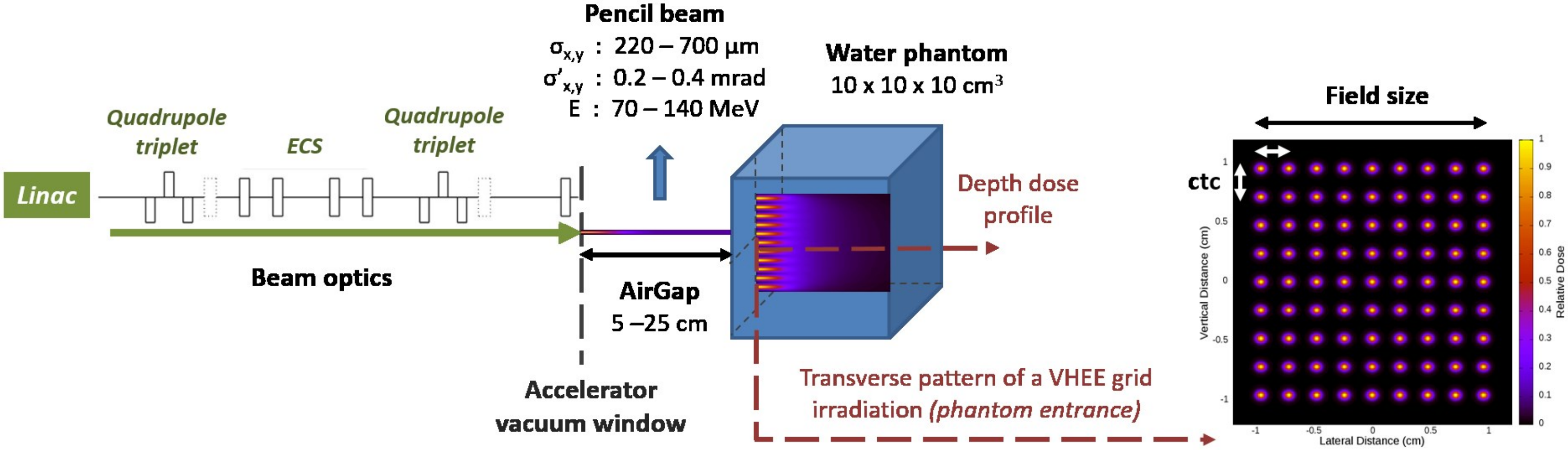
PRAE

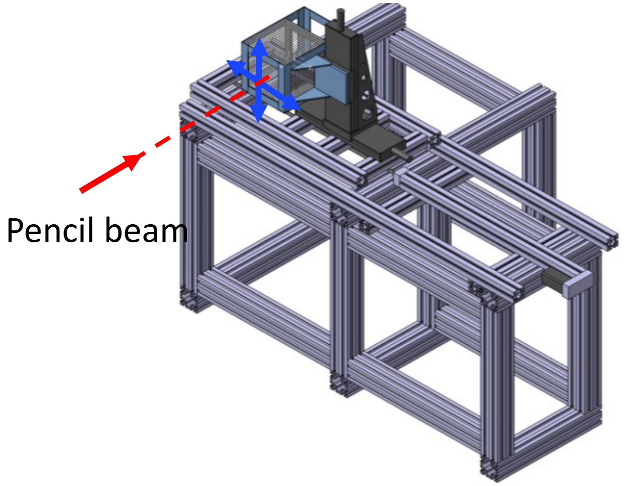
Use the advantages of VHEE beams with SFR approach *(skin and normal tissue sparing)*



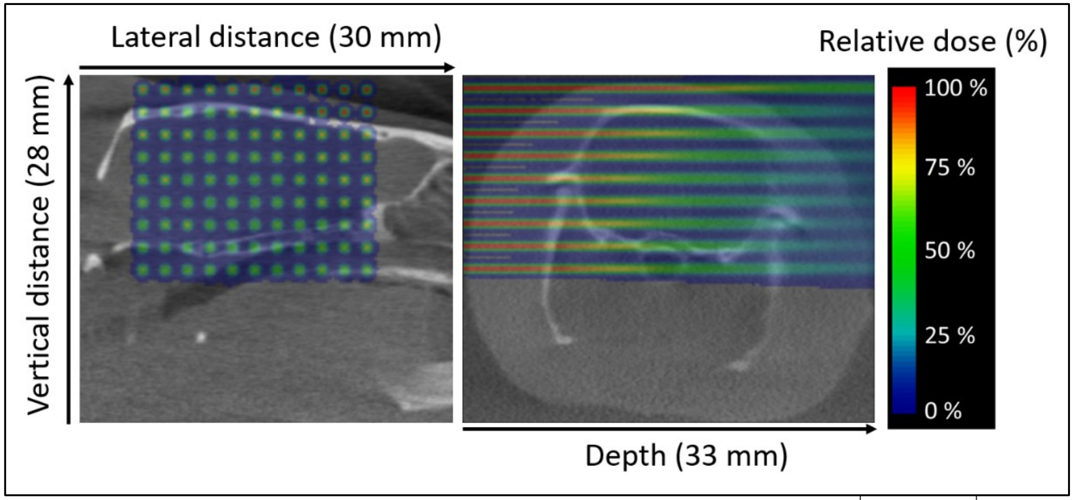
Dosimetric proof of concept on human brain
Martinez-Rovira & Prezado 2015

Beam-optics calculations for preclinical experiments :



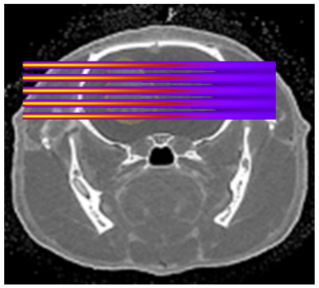


Calculation in rat head

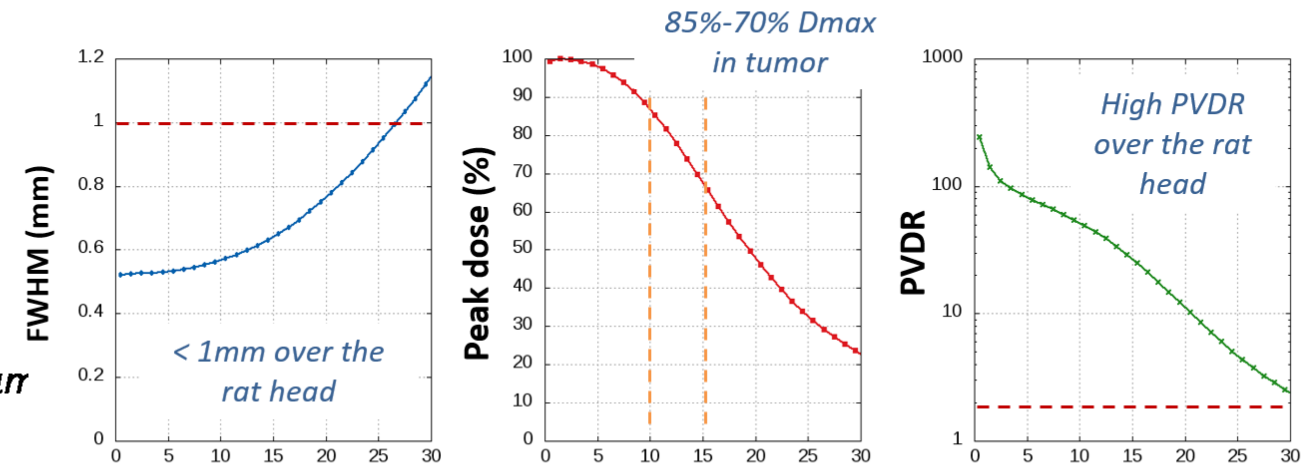


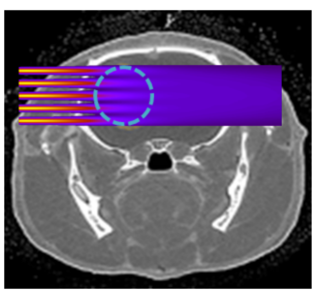
ESTRO 2018: Delorme R. et al. EP-2198
IPAC 2018: A. Faus-Golfe et al. MOPML051

Dosimetry optimization: VHEE grid calculation in a **rat head**

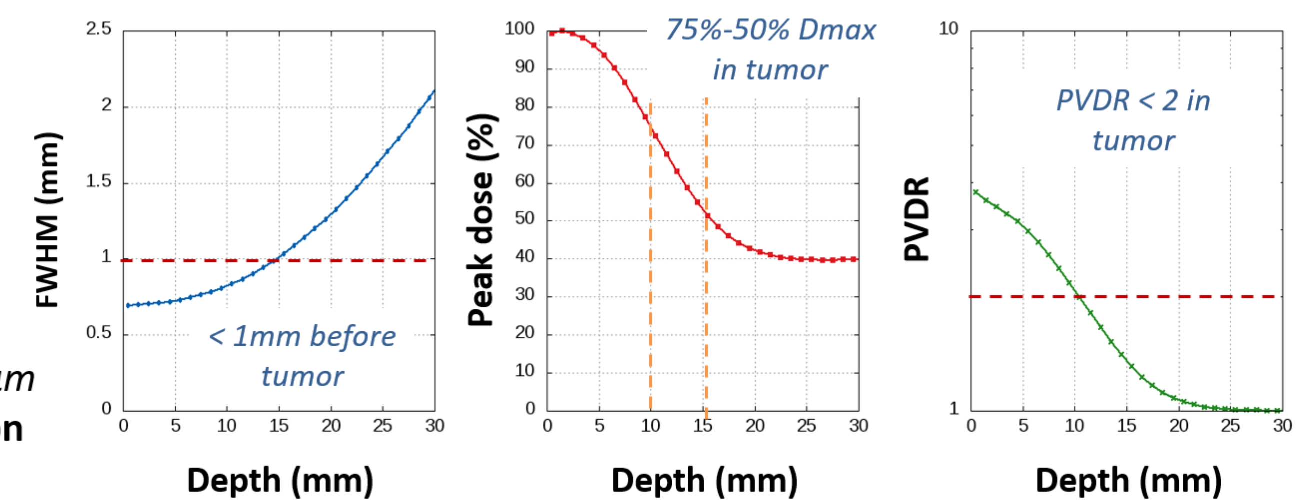


140MeV, σ 220μm, ctc 1800μm
Healthy tissue sparing optimization





70MeV, σ 220μm, ctc 1200μm
Tumor control optimization



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

VHEE grid-therapy: implementation on PRAE

What do we need to achieve the goal of preclinical experiments :

✓ **Reliable experimental dosimetry:**

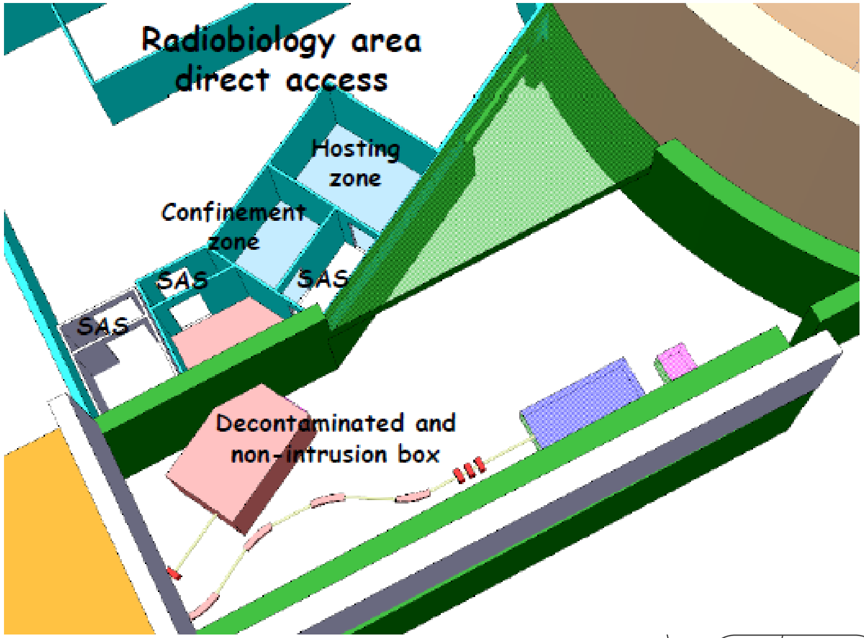
- No current standard for VHEE
- Very small beam sizes used: gafchromics, micro-diamond (?)
- Potential high dose rate / pulse: ion recombination factors, is it enough?

→ ***Anna Subiel:*** *VHEE dosimetry research program at NPL*

Andreas Schüller: *Radiation dosimetry of electron beams up to 50 MeV at MELAF*

✓ **Adapted infrastructure for animal and biological experimentation :**

→ ***Frédéric Pouzoulet:*** *Animal experimentation on radiation beamlines*



Conclusion and perspectives

- ✓ **Objectives**: go **towards the clinics** with SFR approaches + explore **VHEE therapy**.
- ✓ Need for **animal experimentation** to study the radiobiological processes
- ✓ Need for ***in vitro* standards** for VHEE.

- ✓ 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.**

- ✓ Other **radiobiology studies** on VHEE beams (on PRAE ?) :
  - High dose rates *(> 100 Gy/s)*: interesting for **FLASH therapy**

    → ***Vincent Favaudon****: Dose, dose-rate, beam-on time: what requisites for the "FLASH effect" ?*
  - Effect of **time-structure of pulsed beams** on cells

    → ***Emilie Bayart****: Effect of ultra-short laser-accelerated particle pulses pace on cells survival*

Thank you for your attention

Platform for Research and Applications with Electrons

The extended PRAE Collaboration:

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With the support of:

References:

1. Marchand D. et al. *A new platform for research and applications with electrons: the PRAE project*. EPJ Web Conf. 2017;138:1012. doi:10.1051/epjconf/201713801012.
2. Barsuk S, Borgo B, Douillet D, et al. *First Optics Design And Beam Performance Simulation Of Prae: Platform For Research And Applications With Electrons At Orsay*. In: IPAC 2017, Copenhagen, Denmark. ; 2017.