SAPIENZA UNIVERSITÀ DI ROMA | INFN | FRIDA

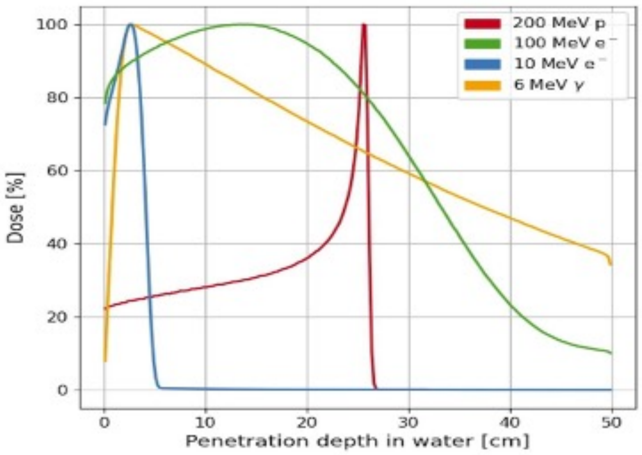
# SAFEST project

Roma, 30/01/2024

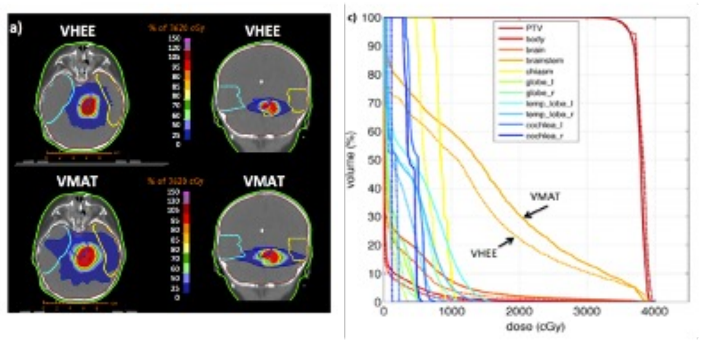
# VHEE and FLASH: dreams vs reality

VHEE has lately received an impressive boost

- Low energy electrons seem a perfect schoolyard for the first clinical application of FLASH
- Very fast developments in the field of
  - Electron LINAC
  - passive/magnetic Beam delivery
  - Treatment Planning System




[1]Bazalova-Carter, *et al* (2015),. Med. Phys.,




Few e⁻ facilities already in operation as test bench for FLASH radiobiology (CLEAR, PITZ, CPFR,..)

Expectation in (near?) future from LASER PLASMA acceleration

# VHEE: highway, escape room or labirynth?

- The path to transform the VHEE option in a solid RT choice in clinical practice could be long

- There are some crucial joints that can take this technique to very different clinical setup and workflow

**Energy**
- energy range: 70 to 250 MeV

**Beam**
- Flat vs pencil vs focusing vs ….

**TPS**
- Multi vs single field, fixed vs variable energy

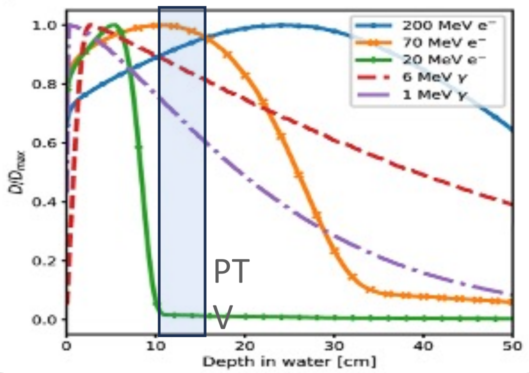
**Dose delivery**
- Couch + multiple beam lines, couch + magnetic gantry, chair + single line

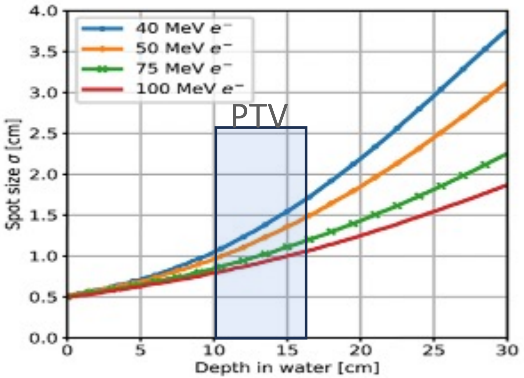
# Ariadne string for VHEE FLASH

Any VHEE  solution can be evaluated only after the full exercise, starting from machine features to the specific patient lesion, all to be plugged in a Treatment Planning System.

Typical example could also be:

- the reduced MS penumbra versus the longer longitudinal dose tail of high energy electron
- Impact of magnetically focused VHEE pencil beams




# The SAFEST “baseline” VHEE machine

A possible/ambitious philosophy is to aim to a VHEE machine that

1) Could fit a photon RT standard bunker

1) Would have a cost closer to a photon RT unit than to a proton machine

1) Specifically designed for the clinic operation: based on reliable and known technology

Radioprotection can be a issue → is not trivial to obtain the RP permission for VHEE in an hospital!

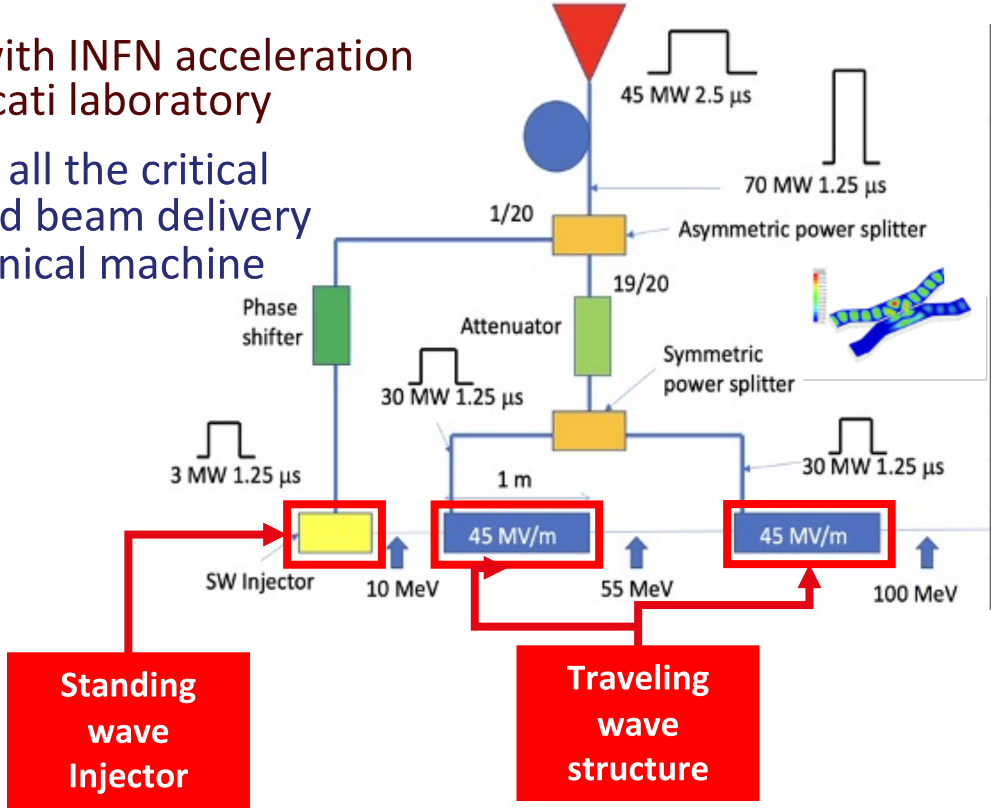

The SAFEST (SApienza Flash Electron Source for radio-Therapy) option:

- ❑ C-band electron LINAC @ 70-130 MeV energy
- ❑ 5-6 meters of encumbrance
- ❑ Active scanning PBS by steering dipoles
- ❑ Beam pulse of few μs providing controlled dose of few Gy
- ❑ 0.1-1 kHz repetition frequency
- ❑ Focus/defocus with quadrupoles

# SAFEST PROJECT general layout

Collaboration with INFN acceleration division of Frascati laboratory

Mission: to test all the critical components and beam delivery options for a clinical machine



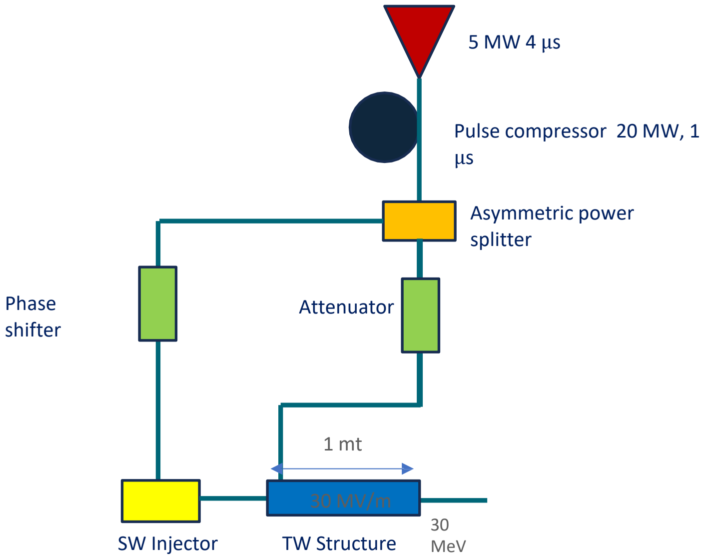

| | |
|---|---|
| Frequency | 5.712 GHz |
| **Target Beam Energy** | **65 - 130 MeV** |
| **RF Repetition rate** | 100 Hz – 1kHz |
| **C-band average accelerating gradient** | 45 MV/m |
| **RF pulse duration** | 1.2 – 2.5 μs |
| **In pulse dose rate** | > 10^6 Gy/s |
| **Average dose rate** | > 100 Gy/s |
| **Dose per pulse** | >> 1 Gy |

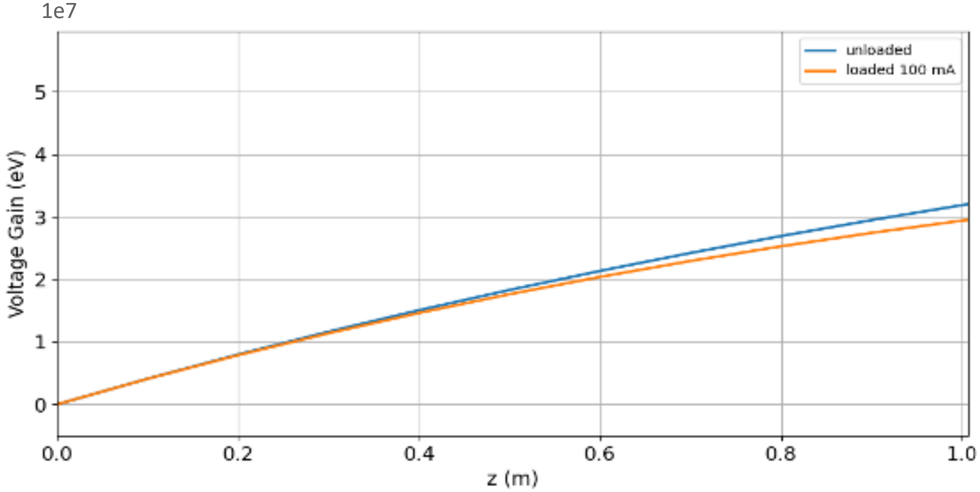
Funded by EU Recovery Plan & INFN

Operational mid 2025

# First step@Sapienza

**Machine for pre-clinical studies of FLASH was funded with budget of 1.6 ME**




**Energy gain for 1 m travelling wave structure unloaded and loaded with 100 mA**

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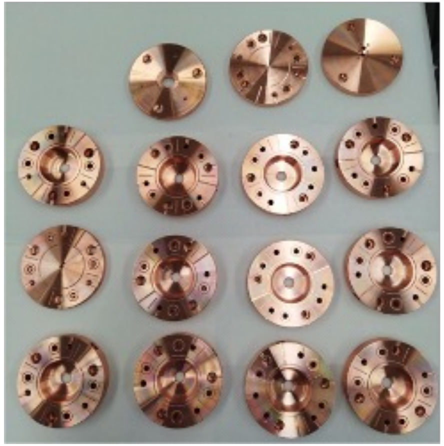
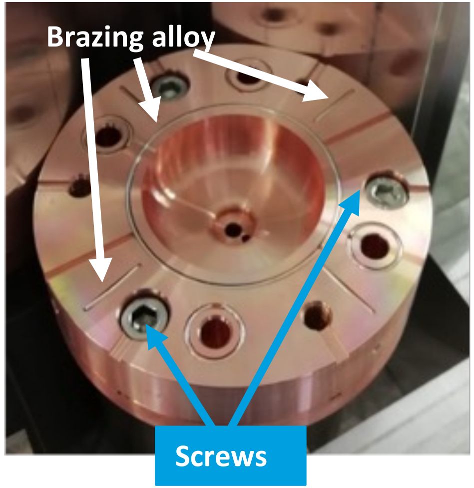
INFN Istituto Nazionale di Fisica Nucleare
HEAL ITALIA
Finanziato dall'Unione europea NextGenerationEU
MUR
Italiadomani

# Prototyping phase

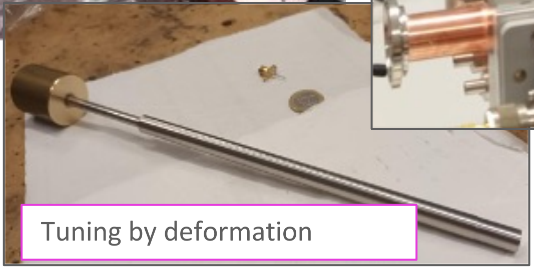
1. **Pre-prototypes** on 5-cells **without couplers** to test the brazing procedure, vacuum sealing and the **in-house** mechanical design.
2. **Prototype of 12 cells** with couplers has been **brazed** @INFN LNF –FRASCATI oven to perform low-power RF tests.

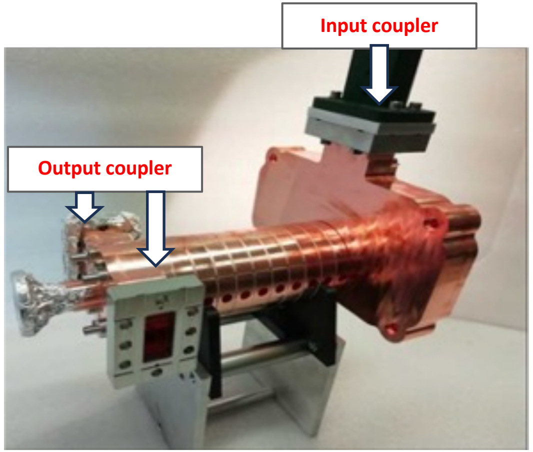


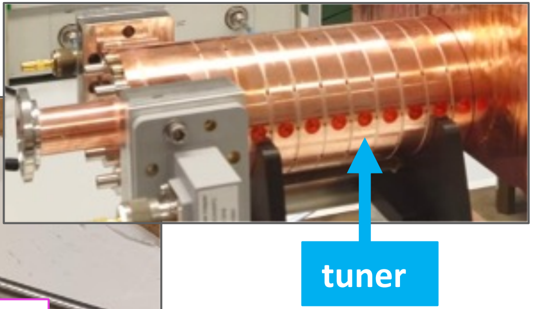
**In house** building of the accelerating cavities




Screws: **prevent external clamping** and ensure alignment and easier assembly




Main contributors: D. Alesini, **R. Di Raddo**, L. Faillace, L. Giuliano, **M. Magi**, M. Migliorati

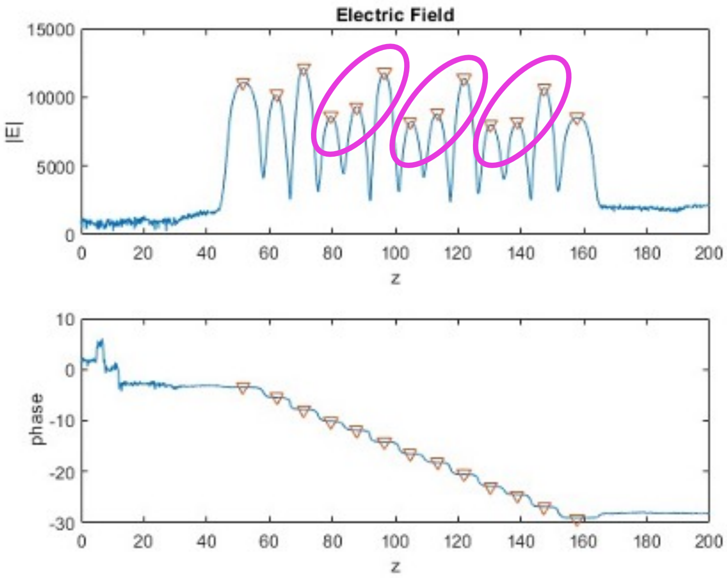
# BeadPull measurements @ first tuning session

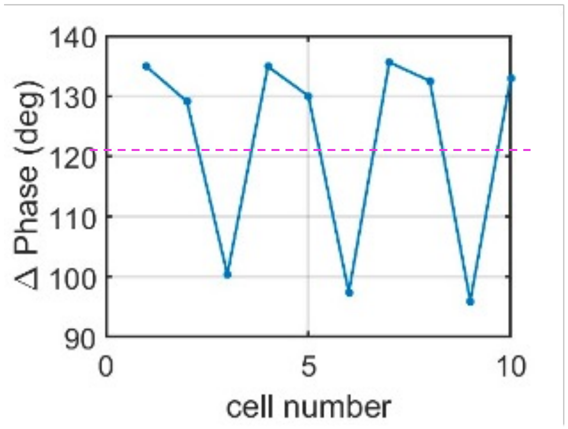
The structure after mechanical processing is **untuned:**

Accelerating cells are not resonant exactly at the working frequency of 5.712 GHz : the electric **field is unflat**

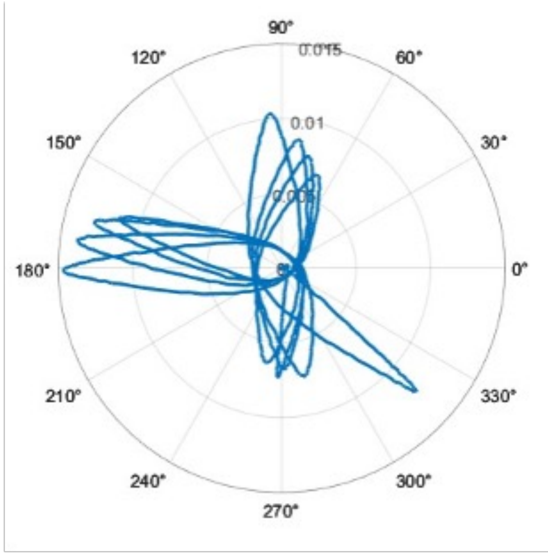
The phase shift of the electric field in the adjacent cell is not of 120 degree: **the petals are not superimposed** in the RF phase diagram

The electric field presents a **stationary pattern**: couplers need to be tuned




The average phase advance is 122,38°

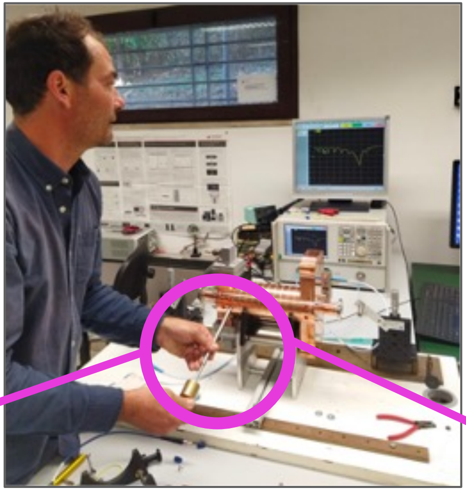


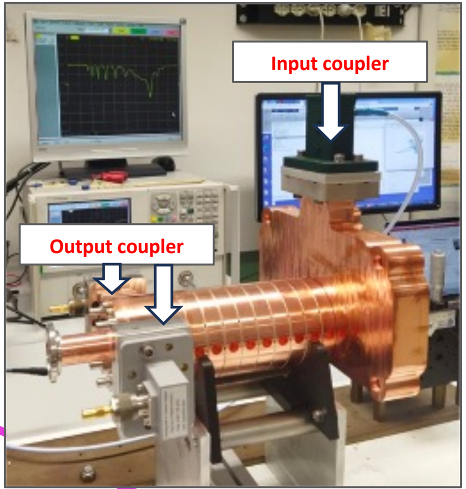

Others contribution: F. Cardelli, D. Alesini, L.Faillace, **L.Ficcadenti A. Most**

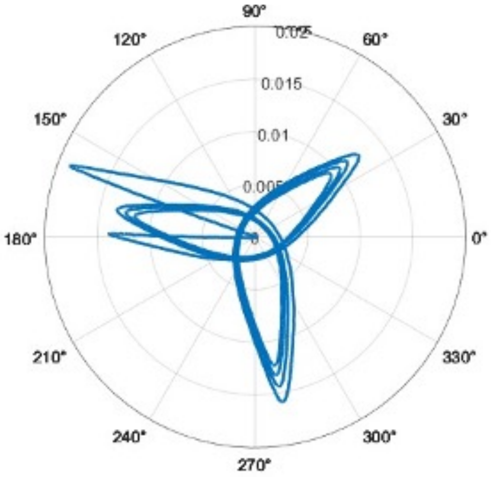
# Tuning process

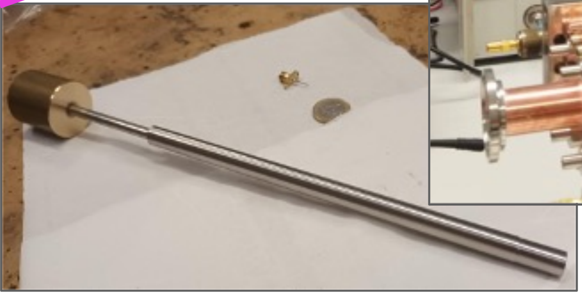
- After tuning the structure presents a average phase advance is 120,38° , the petals are superimposed in the RF phase
- The electric field is sufficiently flat

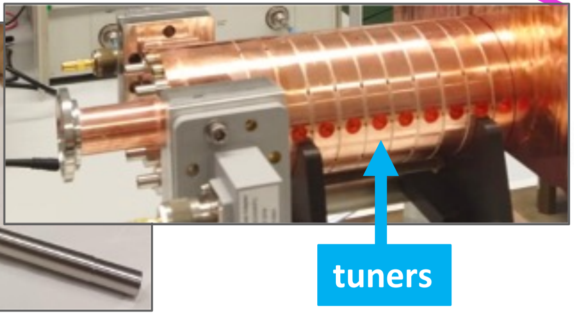
Tuning by deformation

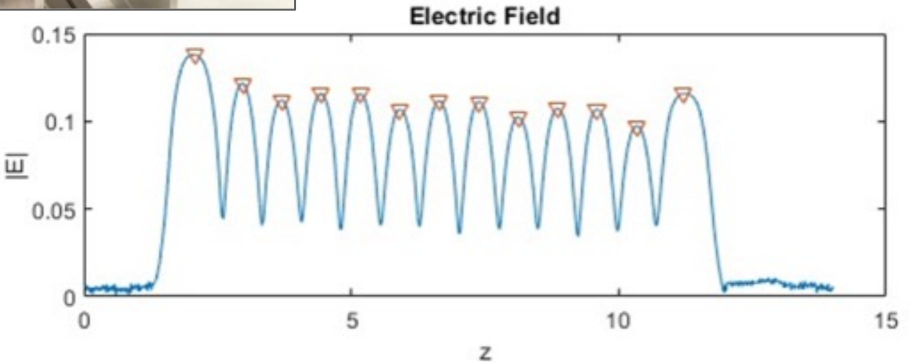




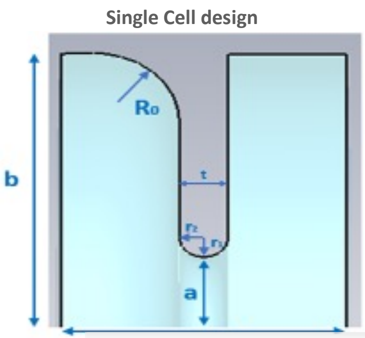





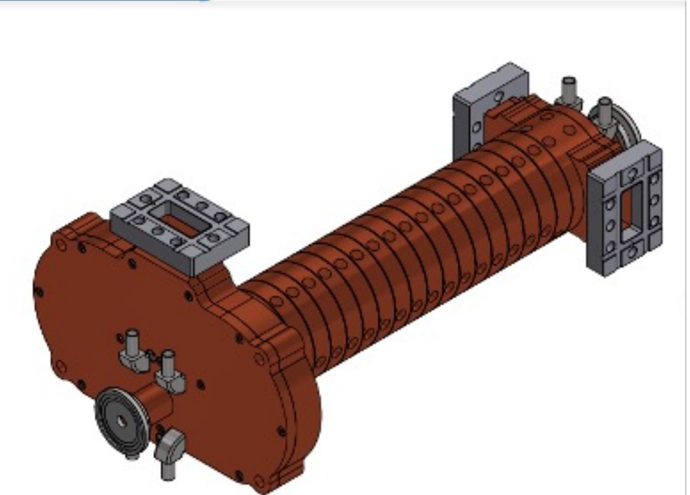

Others contribution: F. Cardelli, D. Alesini,L.Faillace, L.Ficcadenti A.

# New 50 cm prototype: the Joint lab Frascati



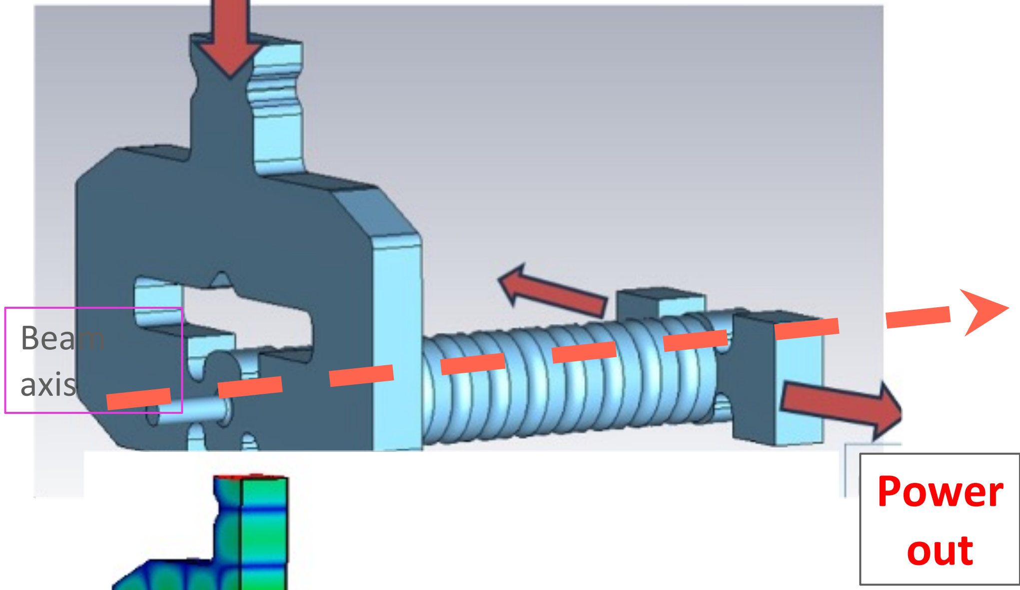

Asymmetric cell to facilitate in-house mechanical processing.

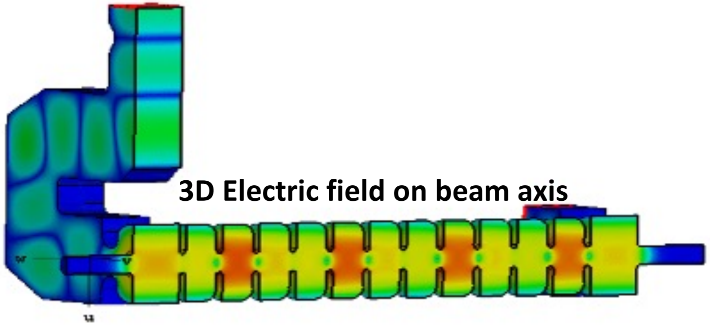
| a | b | d | R0 | t | $r_1/r_2$ |
|---|---|---|---|---|---|
| 5 | 21.03 | 17.5 | 6 | 3 | 1.25 |



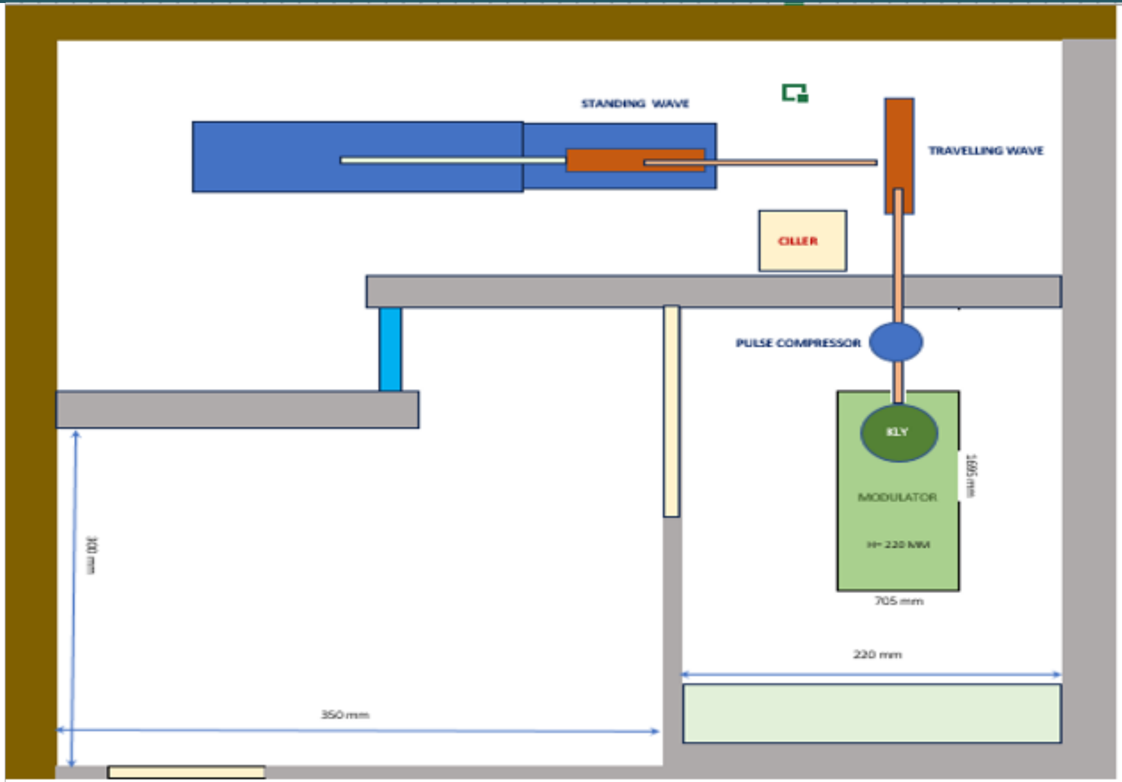
Mechanical design courtesy of M.Magi

Dual-feed *different* input and output RF power couplers



# The bunker @Sapienza




- The first inspection for the start of the works was carried out at the beginning of January
- The RUP for works and purchases has been appointed

# VHEE LINAC: magnetic scanning system

The LINAC provides a pencil beam with few mm FWHM. A PBS design can scale down the system of a PT center, due to reduced VHEE magnetic rigidity

| | |
|---|---|
| **Effective cross-section** | 79.5 $mm^2$ |
| **Length** | **123.04 m** |
| **Ampereturns NI per coil** | **17'603.5 A** |
| **Inductance** | **4.4 mH** |
| **Max. current ramp** | **121256 A/s** |
| **Current density** | 7.38 $A/mm^2$ |
| **Power** | **42.6 kW (max 335 kW)** |

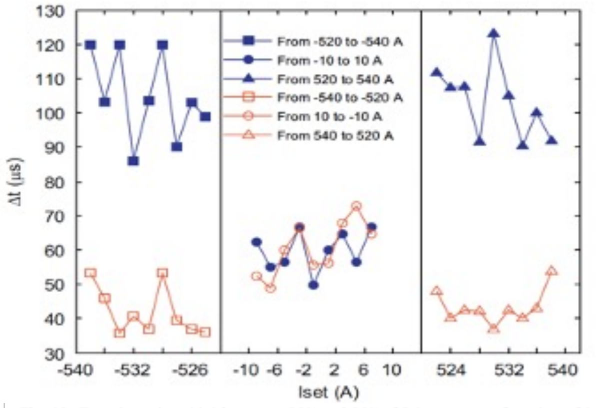



**Fig. 10.** Transient time (Δt) between 20% and 80% of 2 A steps as a function of $I_{set}$ for increasing and decreasing currents.

S. Giordanengo et al., NIM A 613 (2010) 317–322

- Beam sweep must be shorter than the inverse of the repetition frequency of the LINAC (1kHz max) to keep the FLASH dose rate
- Can be safely used the same scanning system used in the CNAO center (Pavia, Italy), stands a repetition frequency of up to 5 kHz

# Optimization in VHEE TPS

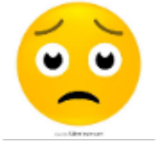
Main issues must be handled to optimize VHEE irradiation modalities, from machine design to patient DVH :

Flexible TPS, including with very different beam delivery options and machine features, not available for VHEE→ we develop developed a TPS for VHEE FLASH with

- multi fields, multi energies optimization, both in active scanning or flat beam option
- steepest descent and/or annealing optimization algorithms

No medical prescription available for: fields numbers, entrance ports, beam energy for VHEE dose release

- As baseline approach we decided to stick to existing photon IMRT prescription



# MC dose evaluation in VHEE TPS

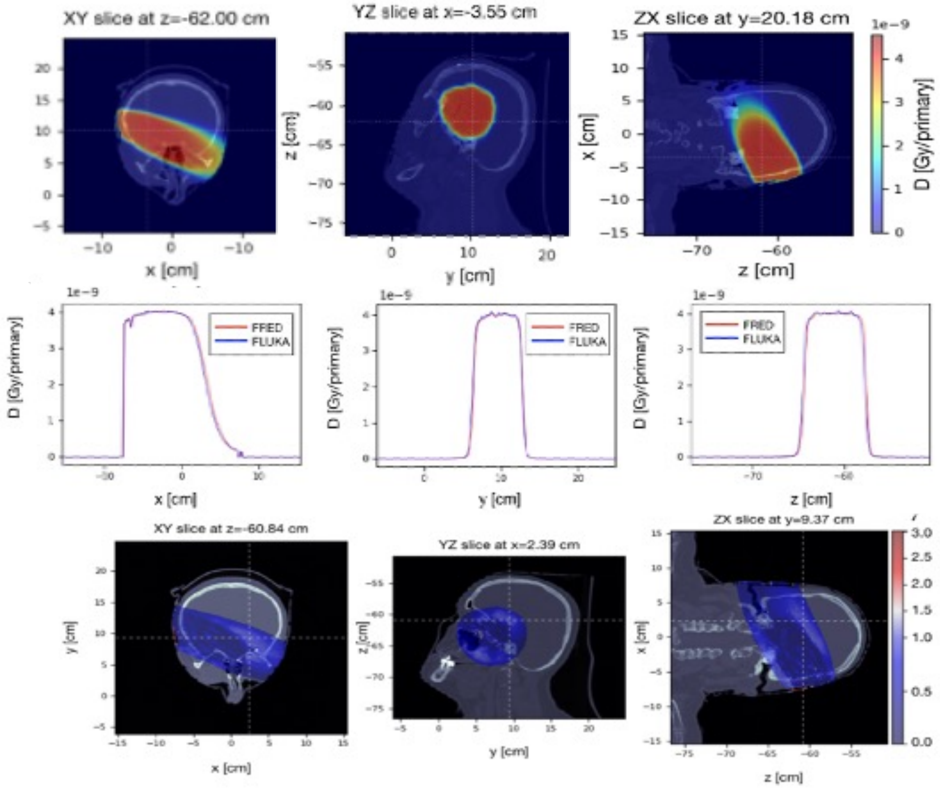
A key ingredient of TPS is an accurate dose evaluation software able to easily:

- handle patient inhomogeneities
- implement different beam models

MC is a viable solution, and several very robust and reliable MC software are available for electrons.

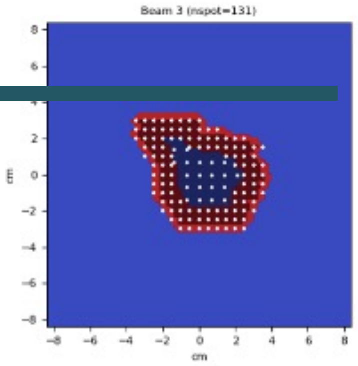
We used the FRED code (running on GPU), to avoid the long computing time, with γ-index based cross check with FLUKA

FRED-FLUKA dose distribution comparison:
2mm/3% global gamma-index pass rate 99.40%,

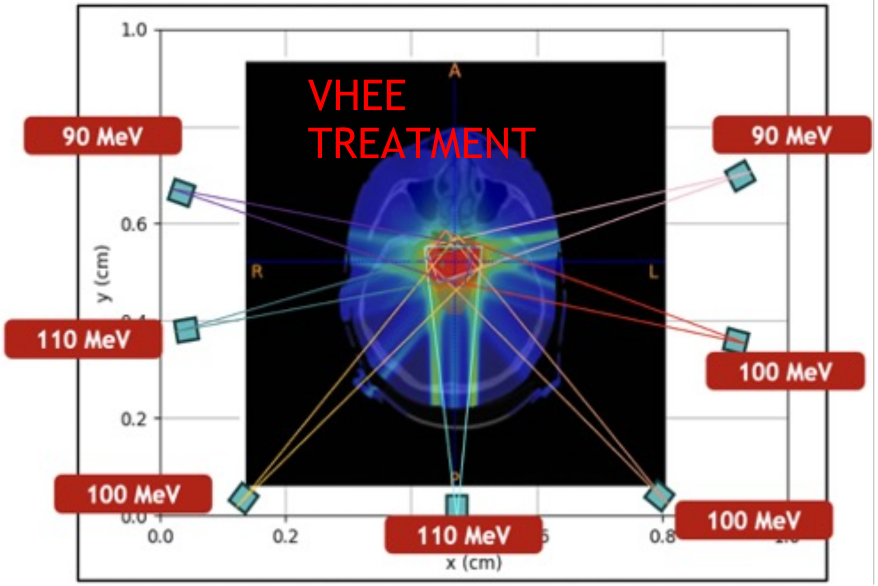



G Franciosini *et al* 2023 *Phys. Med. Biol.* **68** 044001

# Head & Neck: VHEE, proton & photons




We successfully compared in the past such a VHEE option with a photon IMRT/VMAT on real treatments of prostatic cancer*.
The Head & Neck lesion is a further step: severe benchmark to test the conformality on a district with a lot of close OARs



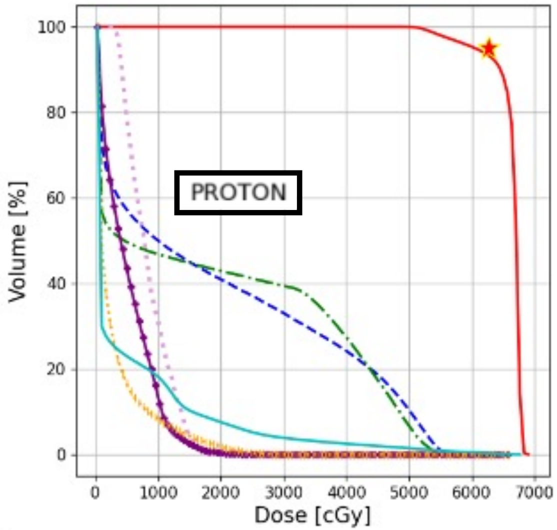

To produce the VHEE treatment plan:

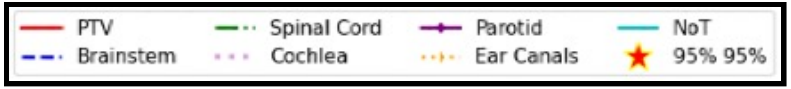
- the same entrance fields have been used for real IMRT/proton and VHEE planning
- Active Beam Scanning: 7(3) fields with 8 mm spot spacing: ~80 pb/field→ 80-800 ms irradiation time/field
- The energy of each electron fields was chosen so to have the maximum dose release in the tumor center

*Front Oncol . 2021 Dec 23:11:777852. doi:10.3389/fonc.2021.777852.

# Proton, IMRT & VHEE (no FLASH)

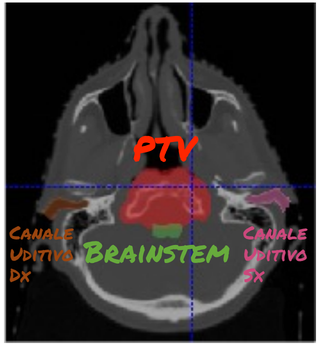
The delivered Proton plan (APSS, Trento) and VHEE plans are compared looking at the **D**ose-**V**olume **H**istograms and fulfillments of the **Dose constraints**. To compare with photon also an IMRT plan has been produced

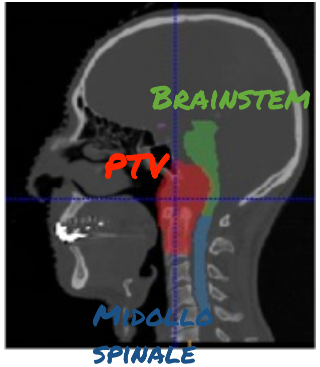



The DVH represents the 3D information of the **ABSORBED DOSE** (Gy or %) as a function of the **VOLUME** (%) of the studied organs.

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento



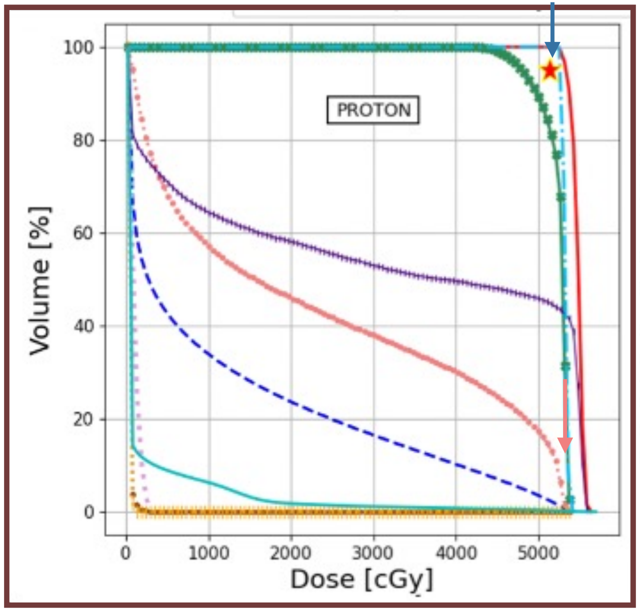




| Patient C1 | dosimetric constraints |
|---|---|
| PTV and PTV Boost | $V_{95\%}$ >95%, never above 107% |
| Brainsteam | $D_1 \leq 55$ GyRBE |
| Spinal cord | $D_1 \leq 54$ GyRBE |
| Parothids | $D_{mean} \leq 26$ GyRBE |
| Ear canals | $D_{mean} \leq 30$ GyRBE |
| Cochlea | $D_{mean} \leq 35$ GyRBE |

Dose constraints for the PTV and the main OARs

# Meningioma DVH: proton vs VHEE 3 field

The constraints are fulfilled also by VHEE with no FLASH effect




| M1 | Parameter | Protons | VHEE 3 field |
|---|---|---|---|
| PTV | $V_{95\%}$<br>$V_{105\%}$ | 100 %<br>0.01 % | 98.97 %<br>0.05 % |
| Optic nerves | $D_1$ | 52.98 Gy | 54 Gy |
| Chiasm | $D_1$ | 53.52 Gy | 53.68 Gy |
| Posterior optical path. | $D_1$ | 53.58 Gy | 53.94 Gy |
| Eyeballs | $D_1$ | 1.25 Gy | 3.30 Gy |
| Brainstem | $D_1$ | 52.59 Gy | 50.40 Gy |
| Carotid arteries | $V_{105\%}$ | 0.03 % | 2.54 % |

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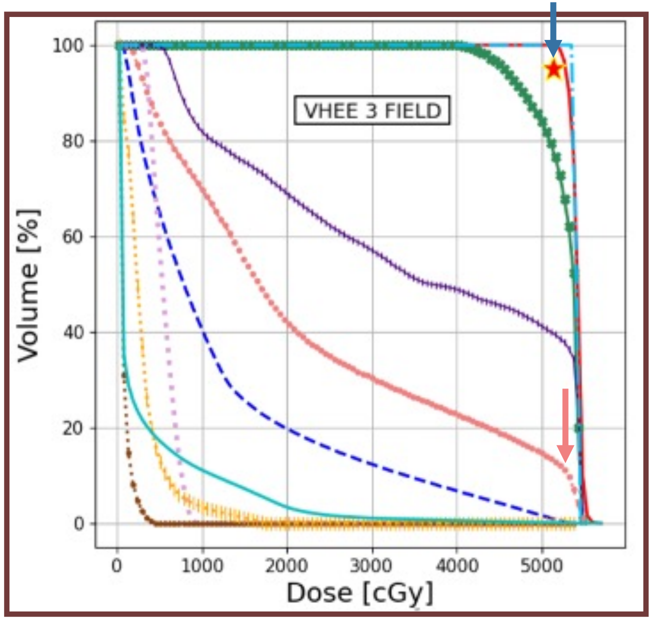
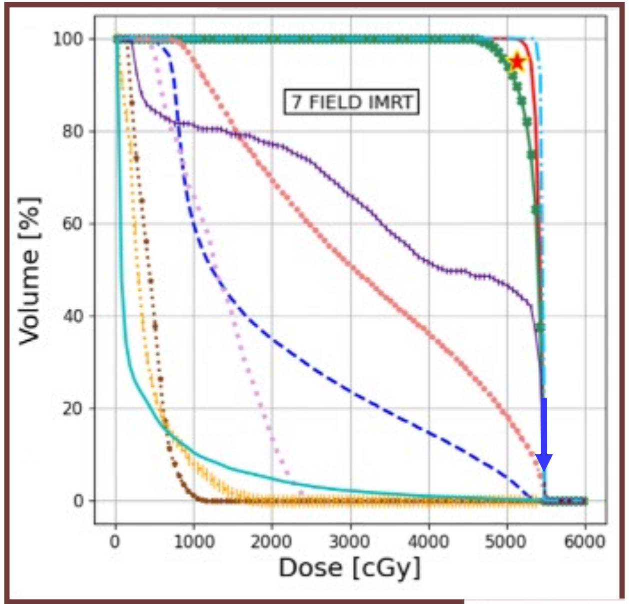



PTV
Brainstem
Posterior optical
Optic nerves
Cochlea
Eyeballs
Middle ears
Carotid arteries
Chiasm
Normal tissue
95% 95%

# Meningioma DVH: IMRT vs VHEE 7 field

The VHEE with no FLASH effect are more than competitive with respect to photon IMRT plan!




| M1 | Parameter | Photons | VHEE 7 field |
|---|---|---|---|
| PTV | $V_{95\%}$<br>$V_{105\%}$ | 99.30 %<br>0.009 % | 97.00 %<br>1.27 % |
| Optic nerves | $D_1$ | 53.76 Gy | 54 Gy |
| Chiasm | $D_1$ | 54 Gy | 53.71 Gy |
| Posterior optical path. | $D_1$ | 53.82 Gy | 53.67 Gy |
| Eyeballs | $D_1$ | 10.52 Gy | 11.82 Gy |
| Brainstem | $D_1$ | 51.99 Gy | 51.02 Gy |
| Carotid arteries | $V_{105\%}$ | 9.11 % | 1.16 % |

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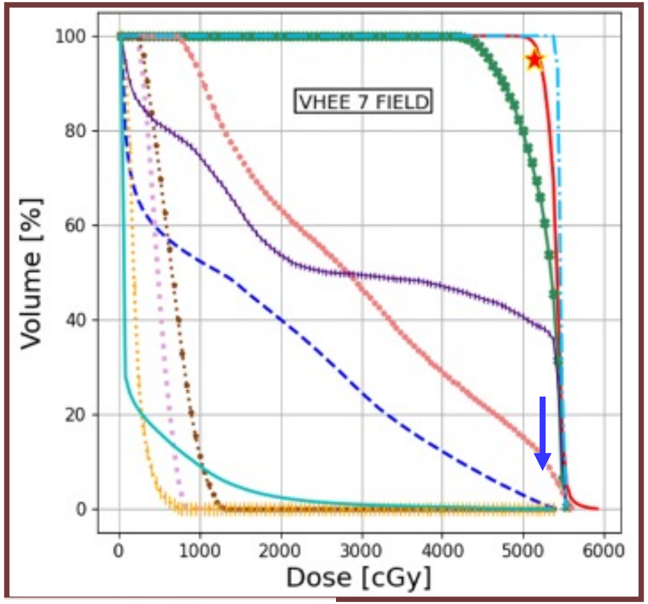
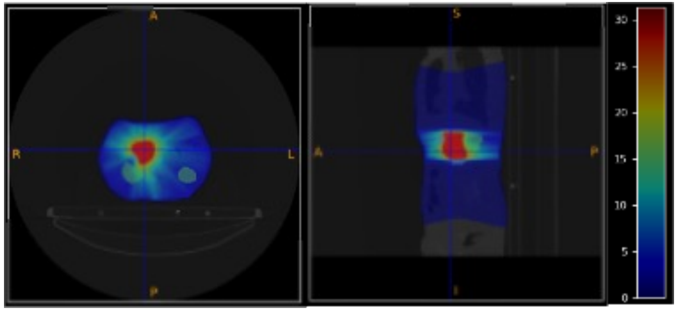



# The pancreas case and the duodenum




Hypo-fractionated:
5 fractions x 6 Gy (30 Gy), golden case for FLASH !!

UCBM
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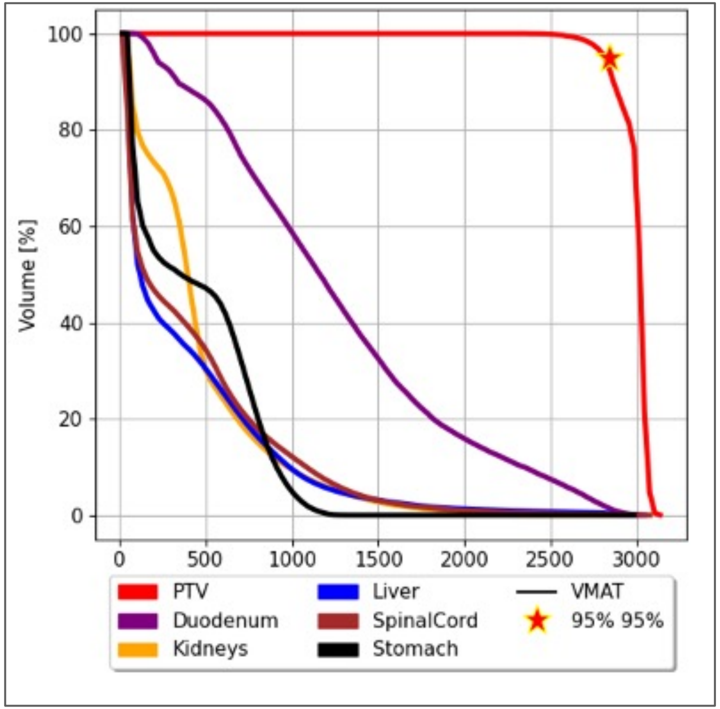
| Organ | Constraint |
|---|---|
| **PTV** | V95%>95%<br>$D_{max}$ < 107% |
| **Duodenum** | $D_{max}$ < 33 Gy (optimal)<br>V25(Gy) < 6% |
| **Stomach** | $D_{max}$ < 33 Gy (optimal)<br>V25(Gy) < 6%<br>V12(Gy)< 31% |
| **Spinal Cord** | $D_{max}$ < 35 Gy (mandatory) |
| **Kidneys** | $D_{mean}$<10 Gy |
| **Liver** | $D_{mean}$<13 Gy<br>V10(Gy)< 70% |

To consider a FLASH VHEE planning, we chose some cases of pancreas cancer, due to its hypo-fractioning

- The main difficulty of this plan is to treat the PTV, while sparing the duodenum that is very, very close to the tumor. Critical $D_{max}$ to the organ
- The FLASH sparing effect could be really a breakthrough in this specific lesion

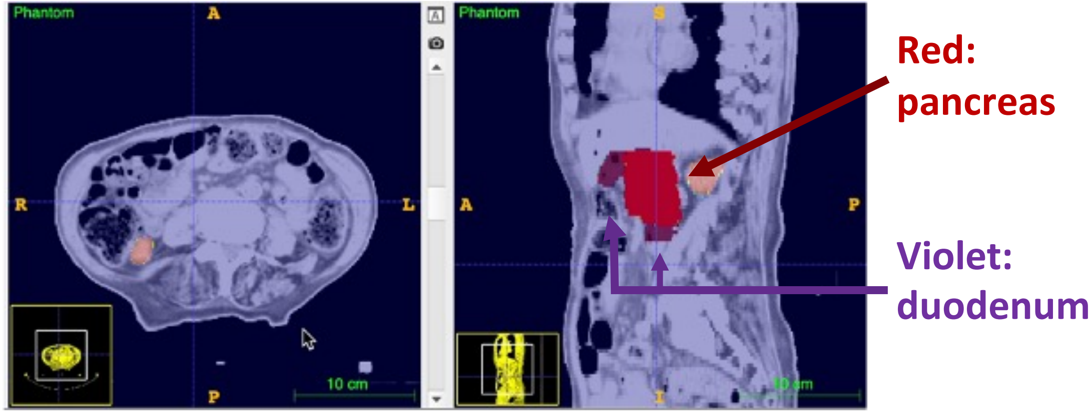
# VMAT vs VHEE 7 fields no FLASH

Patient 1




Red: pancreas

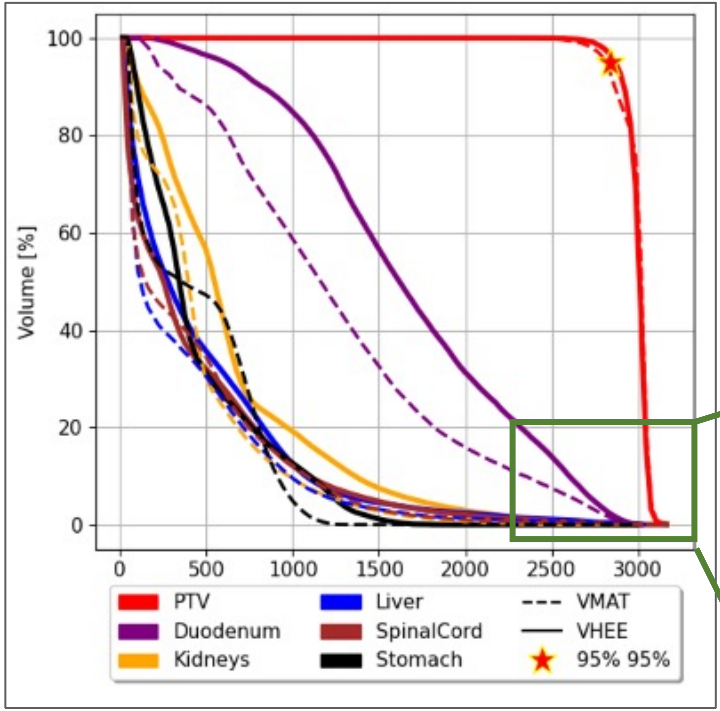
Violet: duodenum




The cases in study have been treated with 5 fractions x 6 Gy (30 Gy total) using VMAT at Campus Biomedico University Hospital of Rome

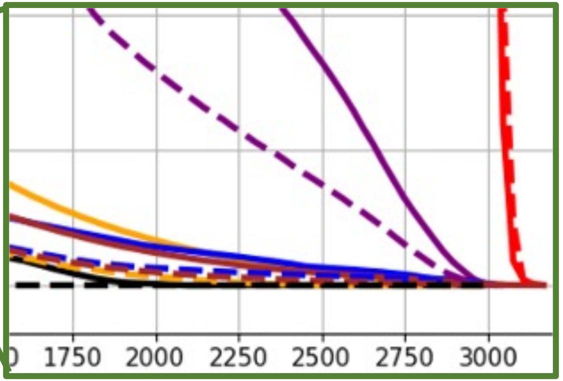
# VMAT vs VHEE 7 fields no FLASH

Patient 1

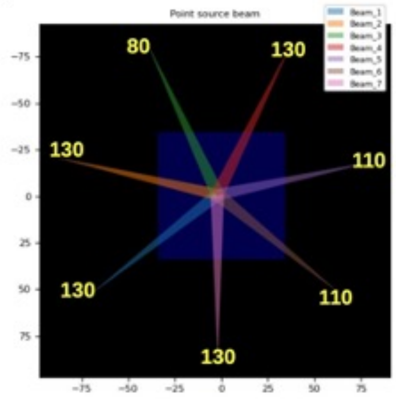



To plan the case in study we used the 7 fields geometry that would have been used for a photon IMRT plan

- The PBS managed ~ 80 pb per field
- Beam energy range 80-130 MeV
- No FLASH effect introduced

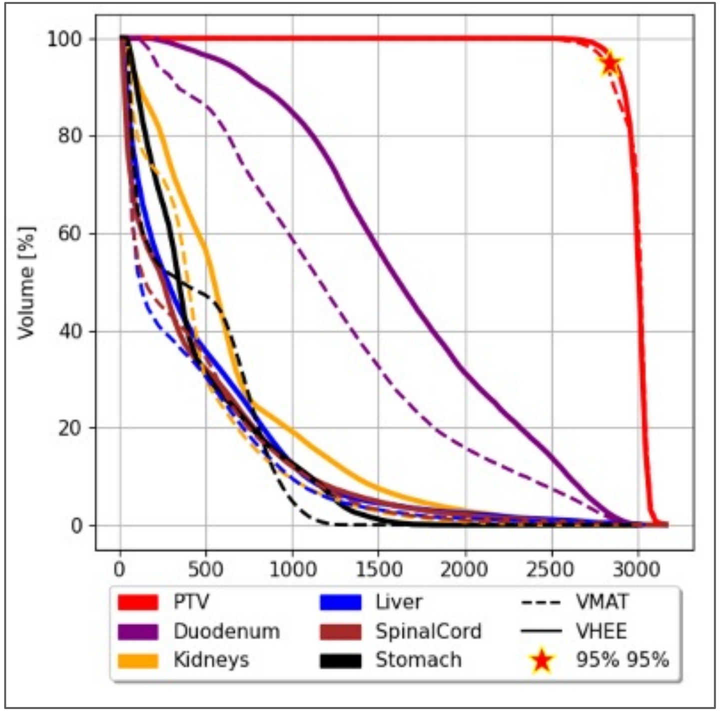



Couch material taken into account in MC



# VMAT vs VHEE 7 fields no FLASH

The VHEE, no FLASH plan is competitive but…. What about FLASH ?




Patient 1

| Organ | Constraint | VMAT | VHEE |
|---|---|---|---|
| **PTV** | **V95%>95%**<br>**$D_{max}$ < 107%** | 97.03%<br>0.04% | 98.35%<br>0.01% |
| **Duodenum** | **$D_{max}$ < 33 Gy**<br>**(optimal)**<br>**V25(Gy) < 6%** | 30.28 Gy<br>7.38 % | 30.19 Gy<br>16.4 % |
| **Stomach** | **$D_{max}$ < 33 Gy**<br>**(optimal)**<br>**V25(Gy) < 6%**<br>**V12(Gy)< 31%** | 13.43 Gy<br>0%<br>0.44% | 20.67 Gy<br>0%<br>9.79% |
| **Spinal Cord** | **$D_{max}$ < 35 Gy**<br>**(mandatory)** | 8.55 Gy | 9.56 Gy |
| **Kidneys** | **$D_{mean}$<10 Gy** | 4.45 Gy | 6.66 Gy |
| **Liver** | **$D_{mean}$<13 Gy**<br>**V10(Gy)< 70%** | 3.60 Gy<br>9.41% | 5.01 Gy<br>15.36% |

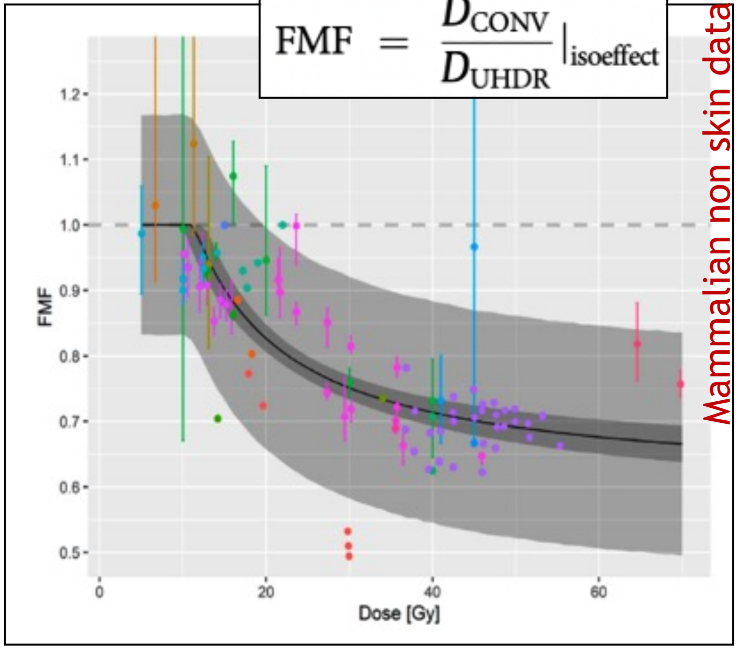
# The FLASH effect in the optimization

- The TPS is able to compute at each optimization iteration all the different possible dose rate (ADR,DADR, ..) of all voxels but..
- The typical field irradiation time for a 1 KHz LINAC is less than 100 ms -> any dose rate metric is substantially in flash regime in all the voxels!

In the TPS, the optimization models the FLASH effect according to [3] via the $FMF_{min}$ and the $D_{thr}$ parameters

$$FMF = \begin{cases} 1 & \text{for } D \leq D_{Th} \\ (1 - FMF^{min})\frac{D_{Th}}{D} + FMF^{min} & \text{for } D > D_{Th} \end{cases}$$

[3] **Bohlen** TT, et al. *International Journal of Radiation Oncology*Biology*Physics* 114 (2022) 1032–1044.

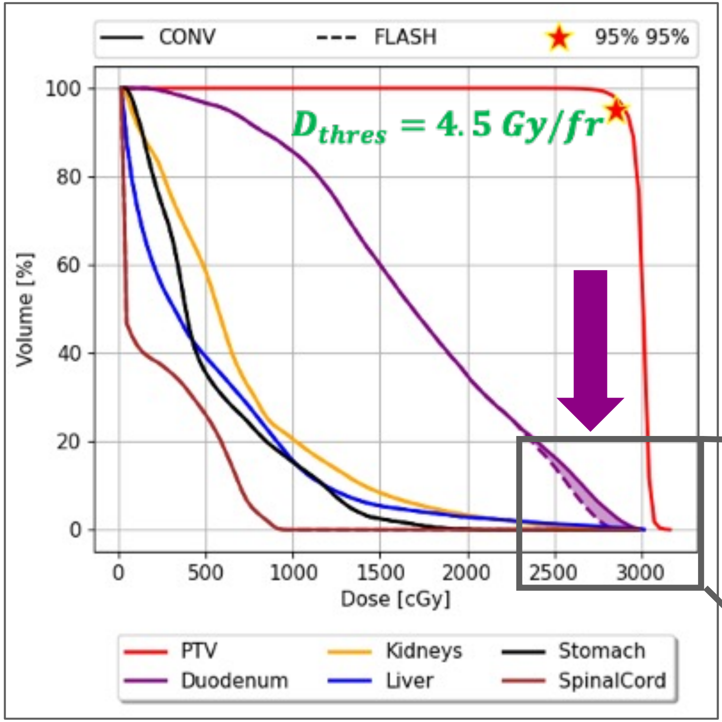



$$FMF = \frac{D_{CONV}}{D_{UHDR}}\Big|_{isoeffect}$$

Mammalian non skin data

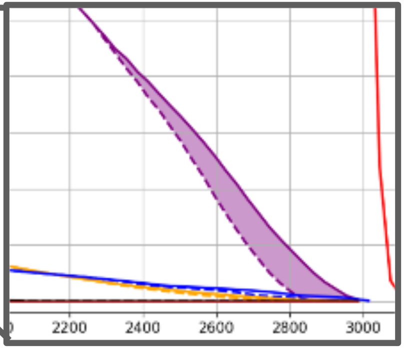
# Here comes the FLASH effect

Forced to make an assumption on FLASH parameters (conservative?)




$D_{th}$ = 4.5 Gy/fraction $FMF_{min}$ = 0.8

- The threshold on 5 fraction adds up to 22.5 Gy
- The FLASH effect mitigate exactly the critical high dose region of duodenum
- Due to the threshold, no effect can be seen elsewhere



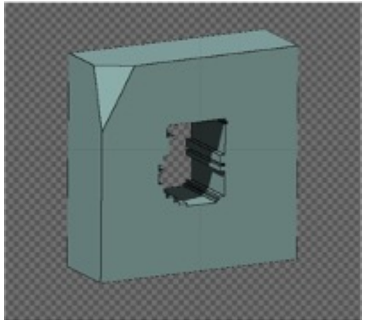
**Duodenum**

VHEE: $D_{max} = 30.07\ Gy$

FLASH: $D_{max} = 28.65\ \ Gy$

# Can we get rid of conformality ?

What about a unique flat beam per field?
- could be easier to achieve the FLASH regime
- transverse size of each field could be safely shaped by a multileaf collimators in tungsten

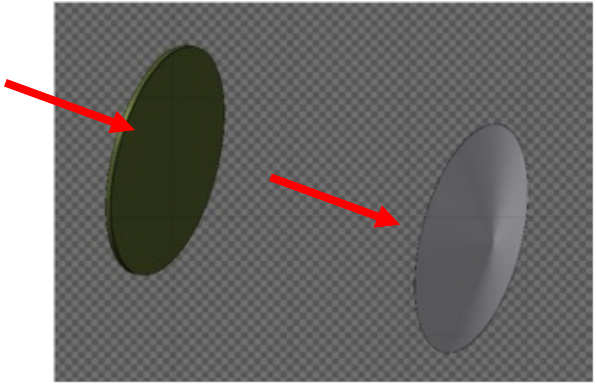


Several approach to produce large field uniform beam

a) Passive scattering (foils, piramid, occluding sphere)
- Cheap and stable, reduce the beam intensity and affect the energy spectrum of the beam

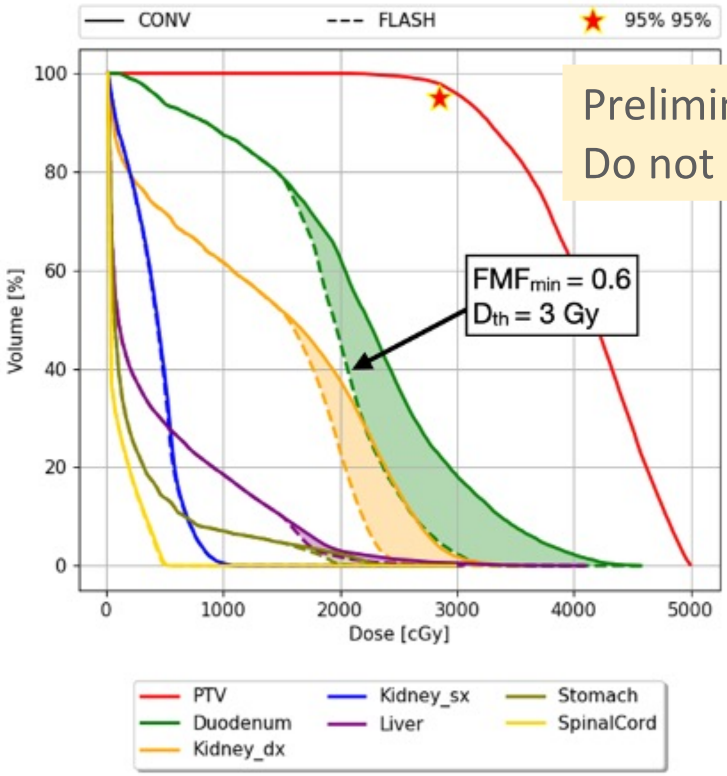
b) Sets of defocusing magnetic quadrupoles
- longer beam line and must be managed (as dipoles..)

c) Pencil beams (!) suitably spaced
- Best uniformity, need PBS



# Pancreas flat beams treatment@120 MeV

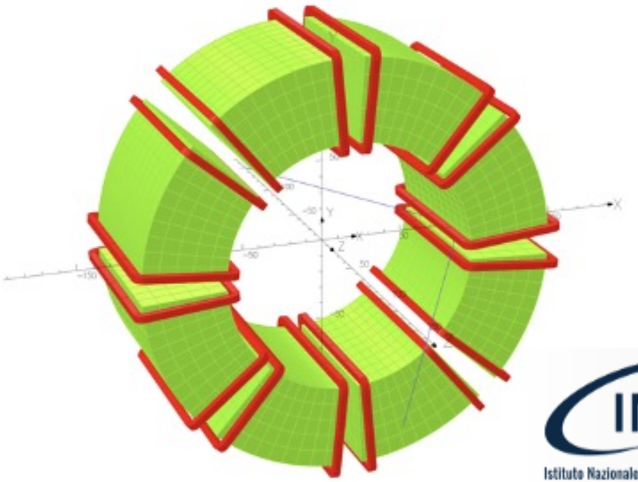
- We planned a FLASH treatment of PZ1 using “perfect” (non scattered) flat beam.
- We adopted the same IMRT entrance ports for the 7 flat fields and then optimized their fluences and energies
- The FLASH parameters were varied from NO FLASH condition up to with $D_{th}$ = 3 Gy Gy/fraction and $FMF_{min}$ = 0.6
- The results suggest that on this lesion and at this low energy the flexibility to have different intensities for different pencil beam needs to be kept (aka IMRT for photons..)




Preliminary
Do not share

# What’s still pending & missing? (I)

- No clear technical solution yet to take several fields (flat or PBS) to the patient:
  a) Static magnetic gantry aka Gatoroid: in development at CERN, Manchester, LNF. Heavy, expensive but extremely elegant and appealing
  b) Multiple lines (CLEAR, PHASER). Solution that asks for larger space and/or complexity
  c) Single line, patient on rotating chair. Option cheap and compliant with a standard RT bunker, but needs a change in the clinical practice (seated imaging?)



INFN LNF Istituto Nazionale di Fisica Nucleare

| | |
|---|---|
| **Deflection angle** | 90° (test) |
| **Effective length** | **1 m** |
| **Torus outer radius** | **1.5 m** |
| **Number of directions** | **8** |
| **Number of coils** | **16 (test)** |
| **Ampereturns NI per coil** | **45’863.9 A** |
| **Effective field** | **0.524 T** |
| **Air aperture** | **0.11 m** |

# What’s still pending & missing? (IV)

Up to now, there is no commercially available TPS for VHEE. The obtained results were achieved using a custom tool developed by our group.

Today, one of the leading companies in hospital software development, RaySearch, is actively working on the first commercial TPS for VHEE.

In collaboration with the **CHUV Lausanne University Hospital**, which is employing RaySearch tool for research purposes, we are testing our results

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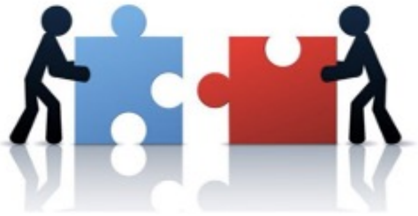
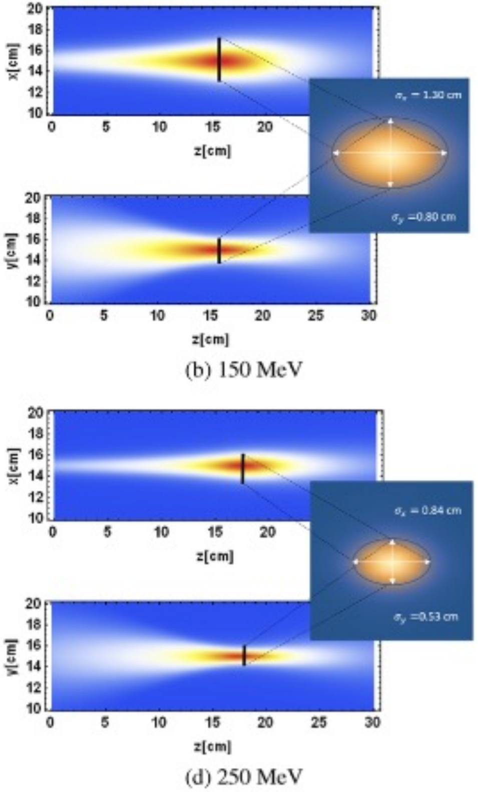


CHUV

# What’s still pending & missing? (II)

There are other delivery options that could be explored like focused beams, also if at energy below 150 MeV the focusing effect is hampered…




A close collaboration has recently begun between **Sapienza** (SBAI Department and Policlinico Umberto I hospital) and **MD Anderson Cancer Center** on this item!! We will perform a feasibility study on the use of focused beams for the treatment of deep-seated tumors.

Whitmore L, Mackay RI, van Herk M, Jones JK, Jones RM.. Sci Rep. 2021 Jul 7;11(1):14013.

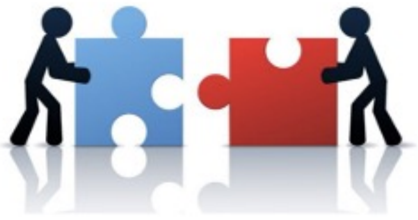
# What's still pending & missing? (III)

The real piece of information missing should/will come from radiobiological experiment:

- The FLASH effect will survive fractions??
- The FLASH effect can (even partially) survive multi fields irradiation?
- Which is the maximum time delay between two fields irradiation to maintain the FLASH sparing to a significant level?

SAFEST, in collaboration with CPFR, will start in 2024 a clinical trial on dermatologic FLASH treatment.

The next FRPT conference will be held in Rome (4-7th of December 2024)



Thanks!!!

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