# Particle physics techniques for cancer therapy: new frontiers in treatment planning and monitoring in Charged Particle Therapy

Giacomo Traini

giacomo.traini@roma1.infn.it

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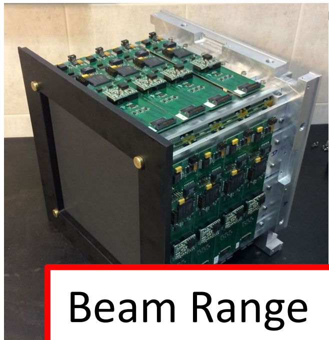
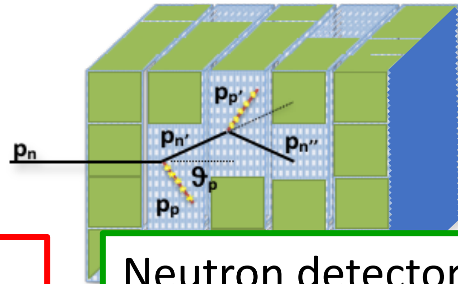
Applied Radiation Physics Group

INFN
Istituto Nazionale di Fisica Nucleare

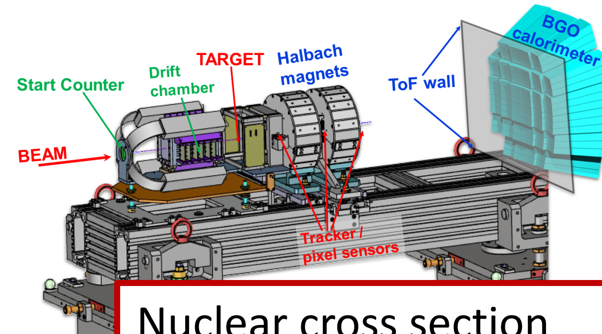
# Applied Radiation Physic Group (ARPG)



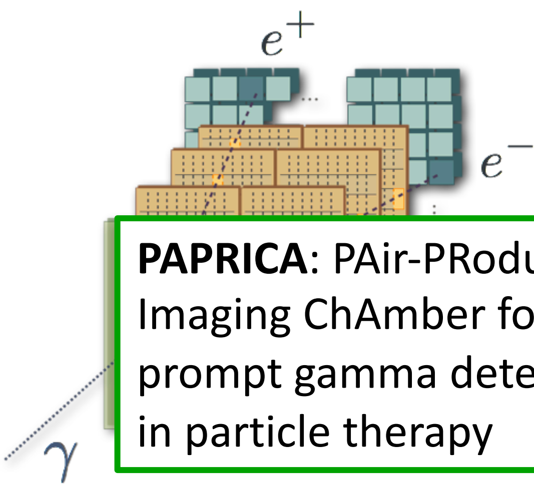
Beam Range monitoring in Carbon therapy: **INSIDE** (INnovative SolutIon for Dosimetry in HadronthErapy)



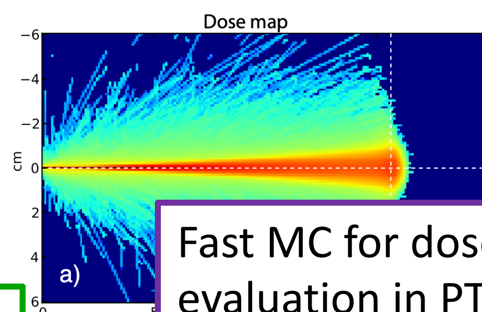

Neutron detector for PT: **MONDO** (MONitor for Dose in hadrOntherapy)



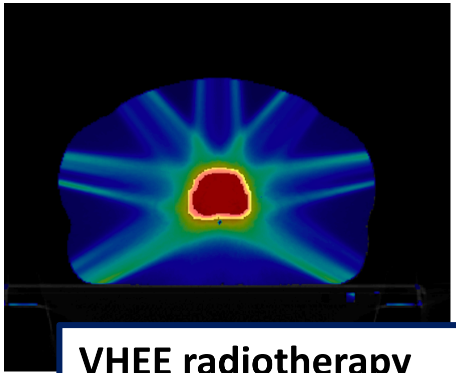

Nuclear cross section measurement for PT and Radioprtotection in space: **FOOT**




**PAPRICA**: PAir-PRoduction Imaging ChAmber for prompt gamma detection in particle therapy




Fast MC for dose evaluation in PT: **FRED** (Fast paRticle thErapy Dose evaluator )

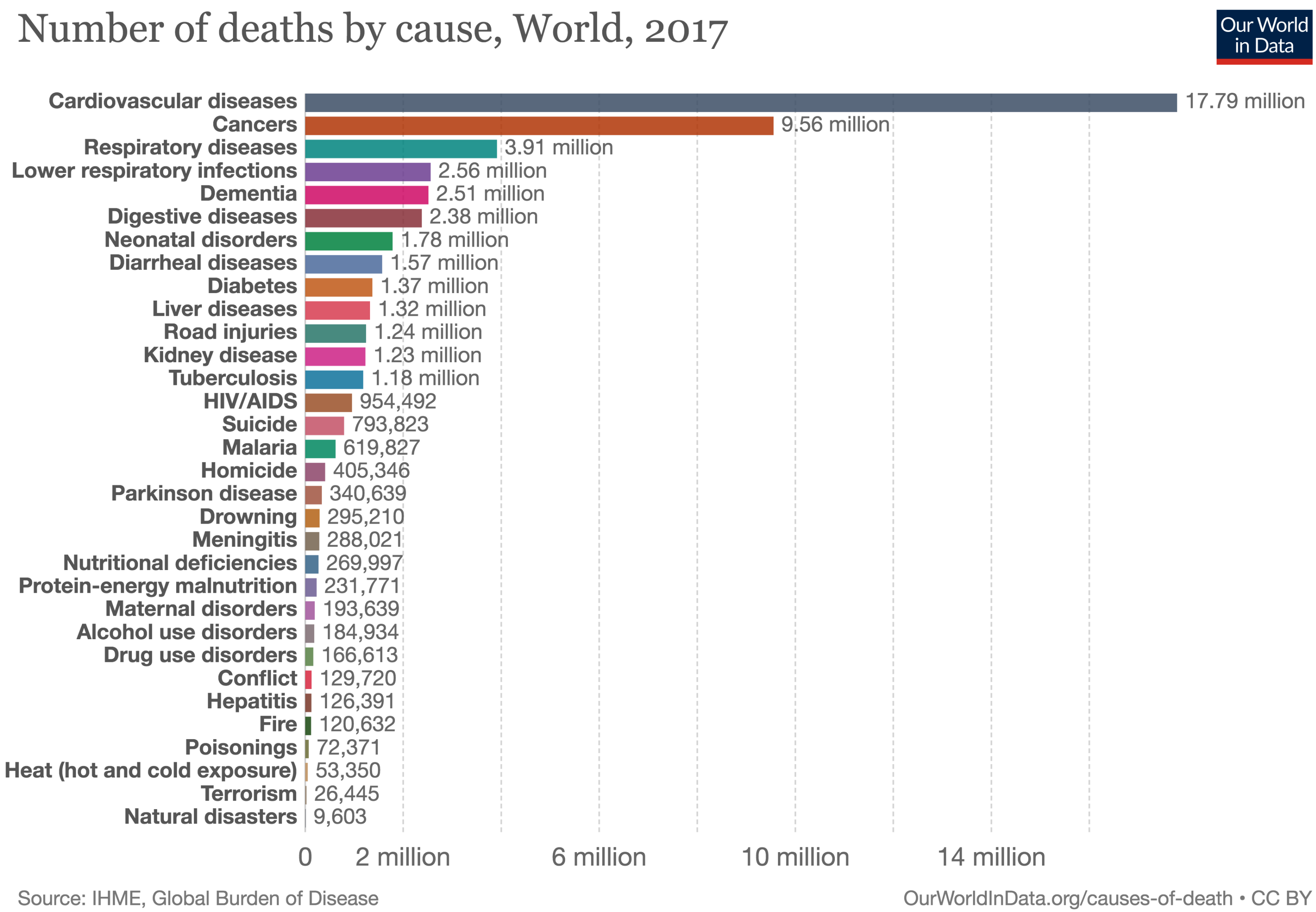


**VHEE radiotherapy**



http://arpg-serv.ing2.uniroma1.it/

# Cancer impact in world



# Cancer treatment

Cancer therapy needs always a multimodal approach in which radiotherapy plays a fundamental role (>50% of cases)

## Chemical

**Goal**: stopping or slowing the growth of cancer cells using drugs (chemotherapy, immunotherapy)

## Surgery

**Goal**: mechanical removal of the tumor mass (open surgery, laparoscopic)

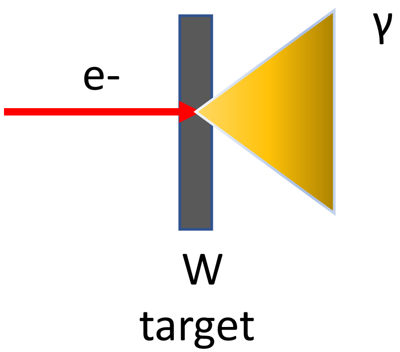
## Radiotherapy

**Goal**: kill cancerous cells by damaging the DNA chemical bounds using radiations

# Standard modern radiotherapy

- The energy needed to destroy the DNA bounds is carried on by **X-rays** beams

- Production principle:




$\langle E_\gamma \rangle \sim$ 5-8 MeV

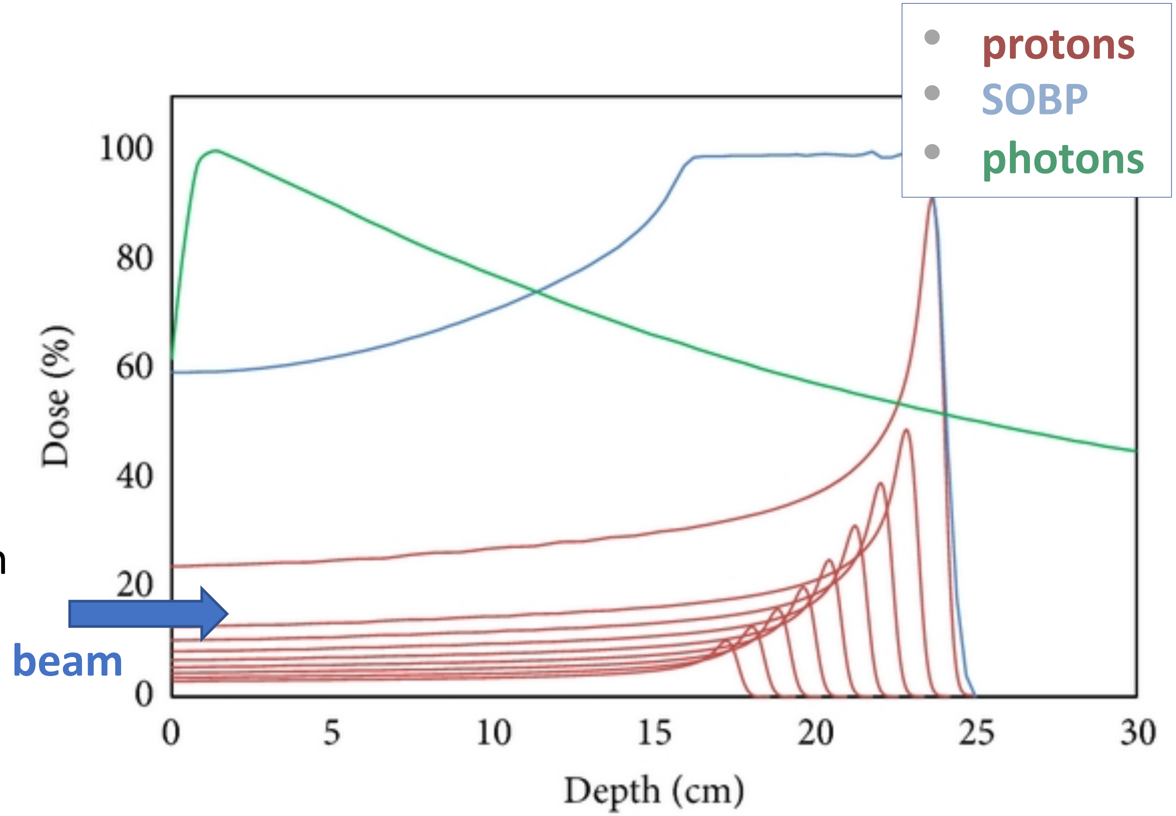
↕

$\lambda_{water} \sim$ 30 cm


- More than 50 years of R&D made photon RT a very optimized, compact, effective technology (**IMRT**, **radio surgery**, etc )

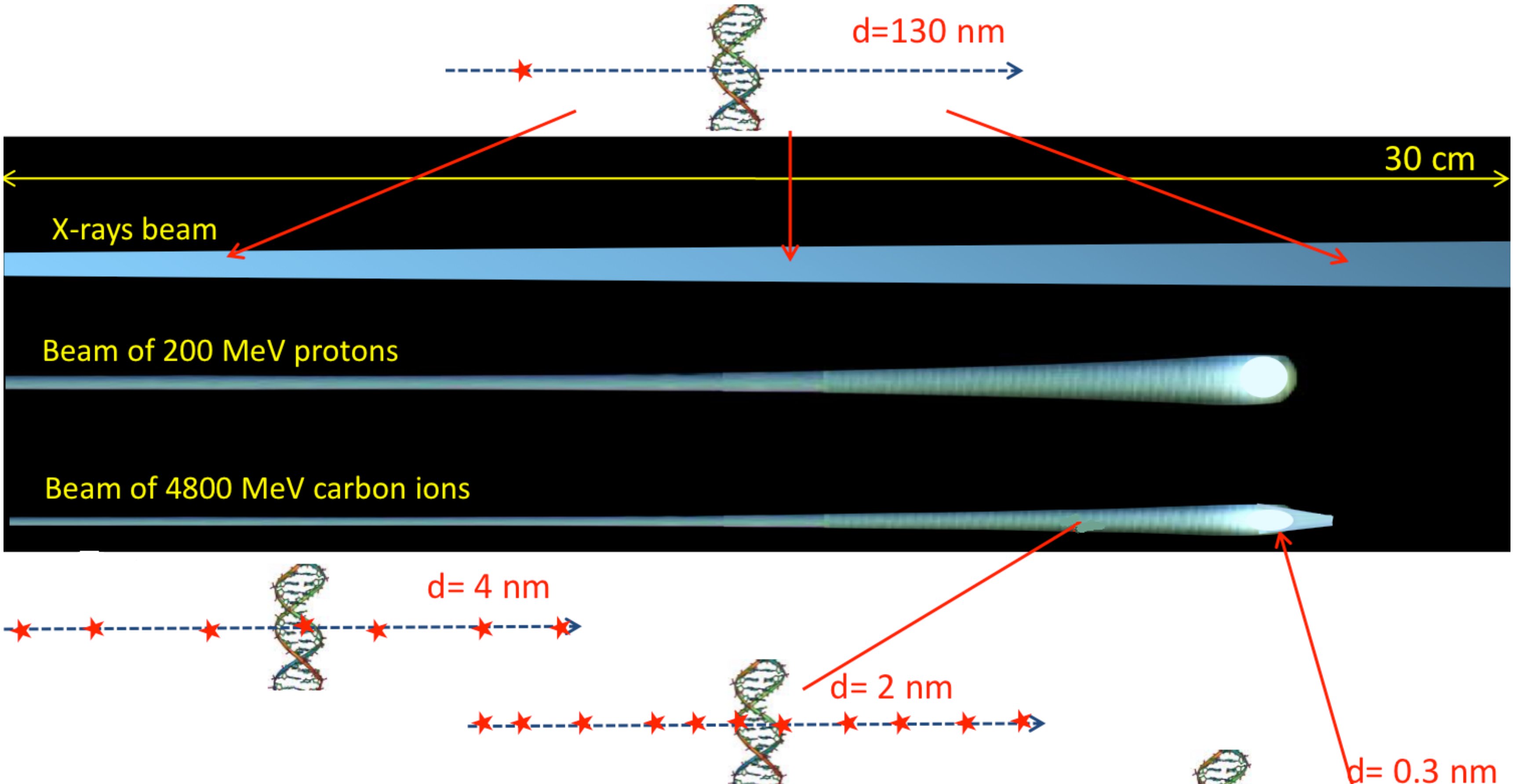
# Particle therapy

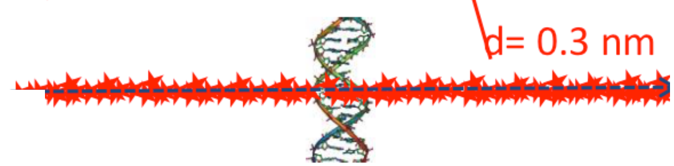
- The **Particle Therapy** (PT) Proposed for the first time in 1946 (R. Wilson) but has mainly spread in the last decades thanks to the development of accelerators
- Better efficacy wrt photons in covering the tumor volume due to the peaked dose-depth profile (**Bragg Peak**)
- **Modulating the beam energy** and deflecting the beam a uniform dose can be delivered to the whole tumor volume (**Spread-out Bragg Peak**)




- **p (50-250 MeV)** or **$^{12}$C ions (100-400 MeV/u)** are currently used in PT

# Different bullet, different effects

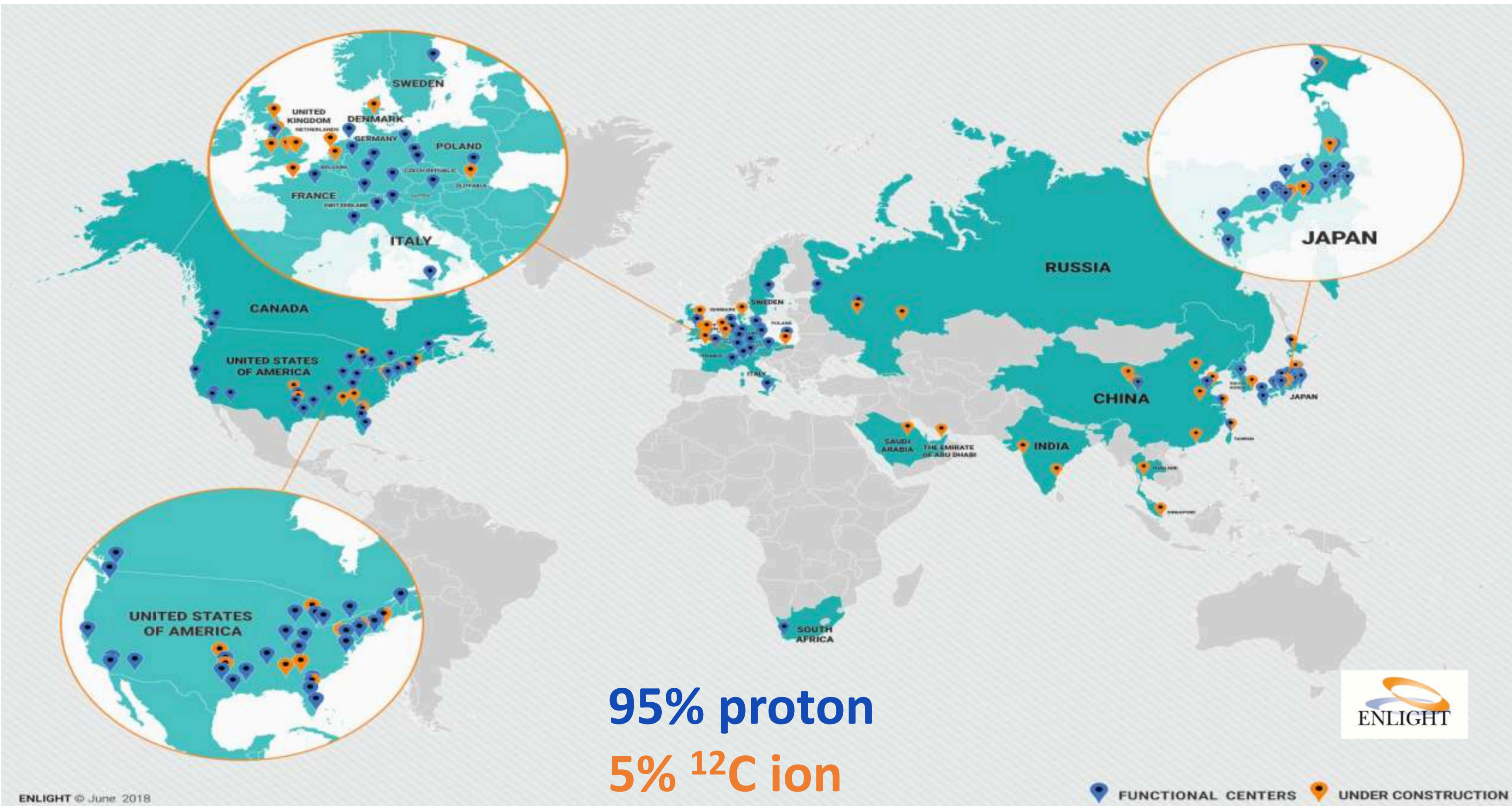


The **heavier ions are much better at killing the tumor cells** with respect to the X rays (and p) for a given ➔high Radiobiological Effectiveness (RBE)

# Particle therapy in the world

- 95 facilities currently in clinical operation in the world (25 in Europe, 3 in Italy → **CNAO, APSS Trento, LNS** ) , ~40 under construction




**95% proton**

**5% $^{12}$C ion**

# PT planning

3D information (CT, MRI)

Tumor localisation inside the body, **density map**

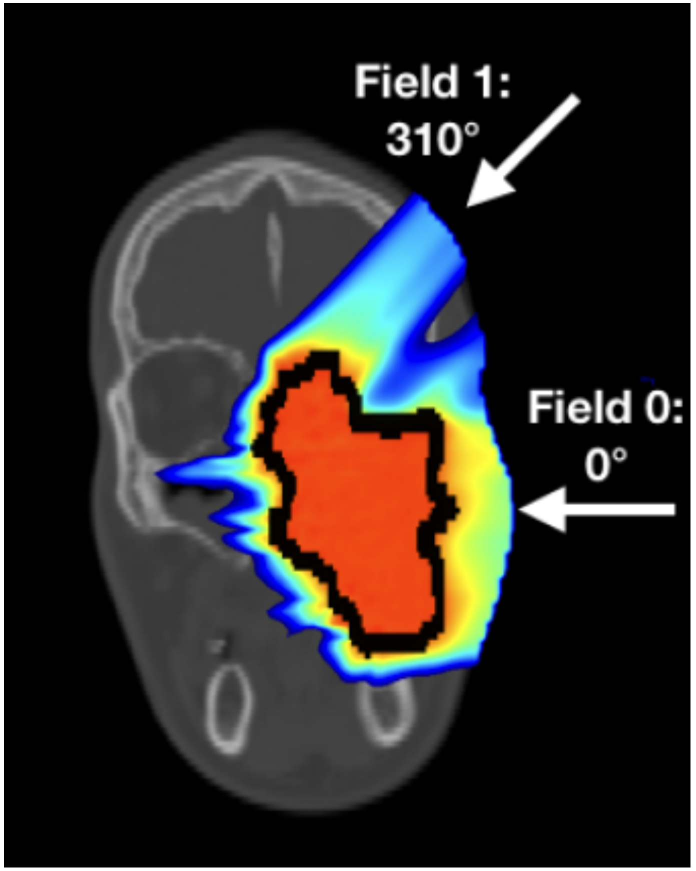
Density to de/dx conversion

Uwe Schneider *et al* 1996 *Phys. Med. Biol.* **41** 111.

Treatment planning

Beams characteristics (E, θ, N)

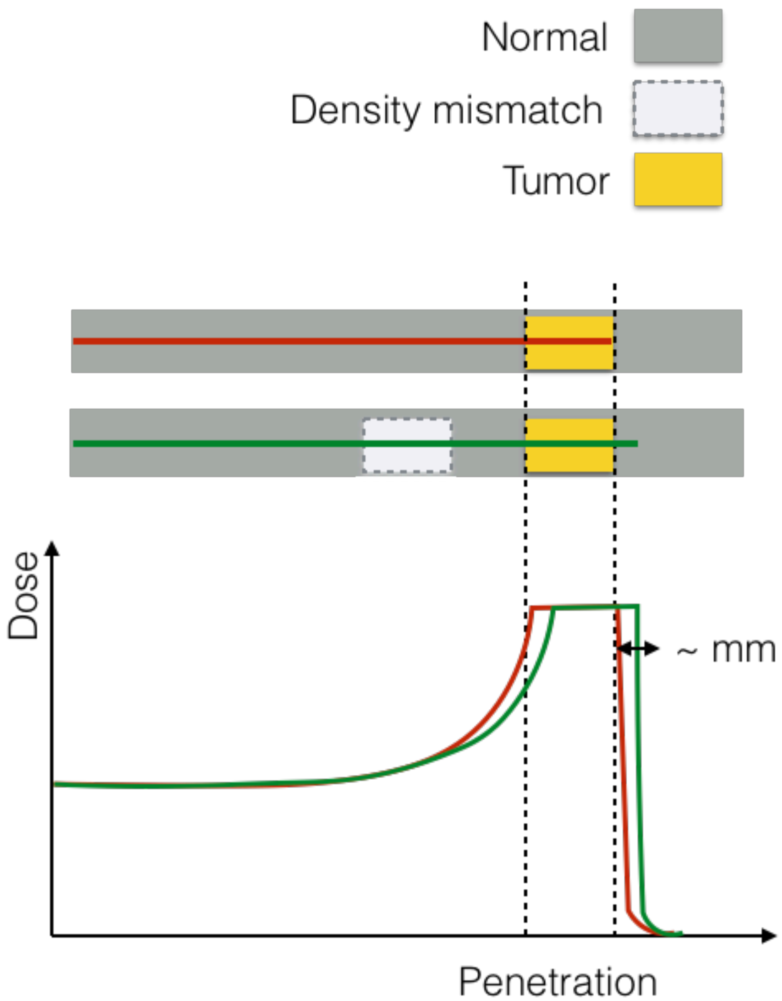
Dose delivery




The total dose is delivered within few weeks **(~15-30 fractions)**, each one lasting **few minutes**

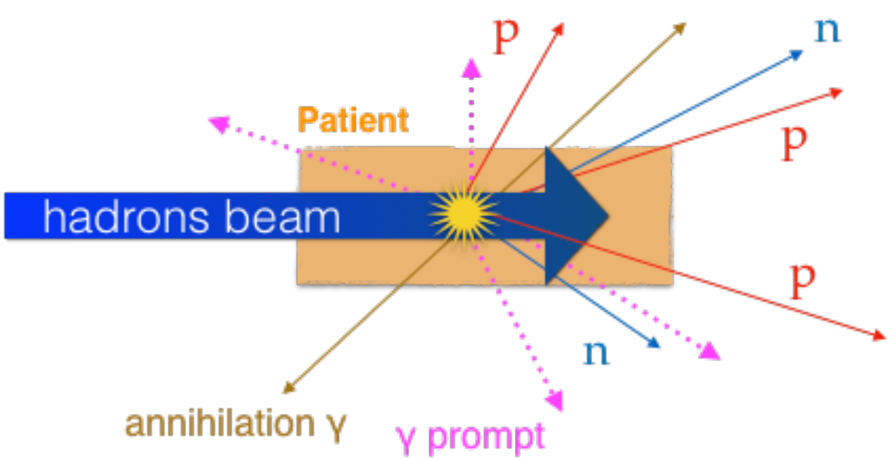
# Range uncertainties

- <u>PT is extremely sensible to range variations</u> wrt what predicted at planning stage
- Possible causes: patient mispositioning, uncertainties on the CT Hounsfield number conversion, **anatomical density variation**
- Planning rationale: **avoid tumor under-dosage** by using **safety margins** (3.5% range + 3 mm)
- **<u>At present, a monitoring system is missing in clinical routine</u>**



# Secondary particles

A range monitor must rely on **secondary particles produced in nuclear interactions** and coming out from the patient, giving a feedback during the treatment (possibly online)

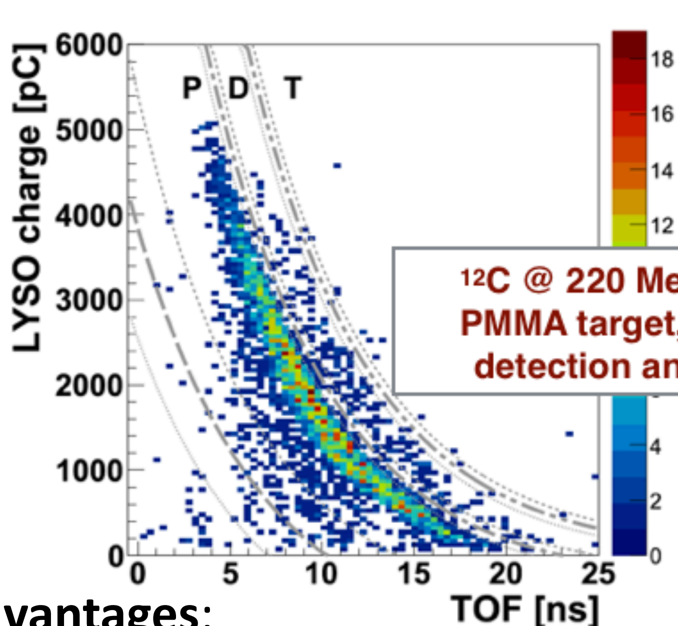


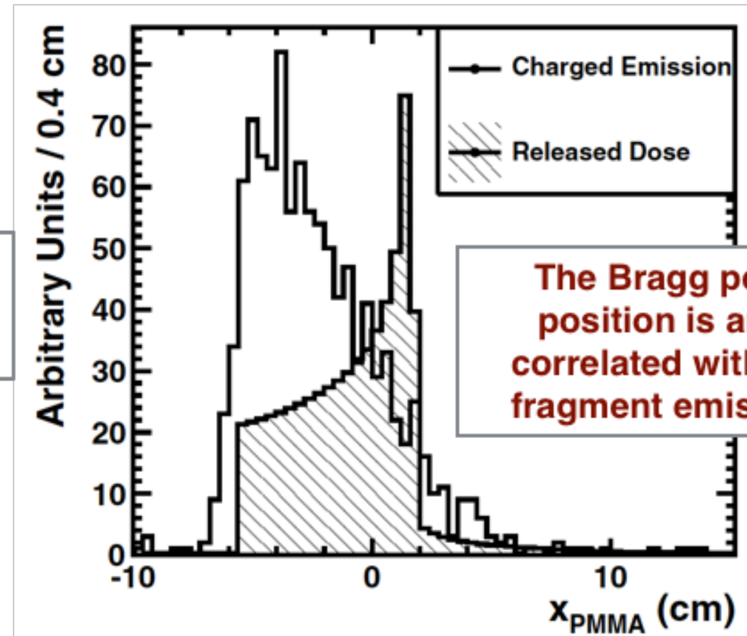

- **Annihilation photons** due to β+ emitters produced by beam interactions (PET-like signal)
- **Prompt-γ** generated in de-exitation pf nuclei (1-10 MeV) ( PAPRICA)
- **Charged fragments (FOOT)**

- Secondaries production is correlated ( spatial correlation, but not only…) to the therapeutic beam range
- Ingredients: **deep knowledge of the underlying physics processes**, **detector development with environment-driven design criteria** , **not trivial analysis for range assessment**

# Exploiting fragments @ large angle

A **significant emission of secondary charged fragments** occurs when using **Z>1** ions also @ large angles with respect to the beam direction)!




**Advantages**:

Easy to detect (high detection efficiency, small background)

Easy reconstruction of the production vertex with tracking devices

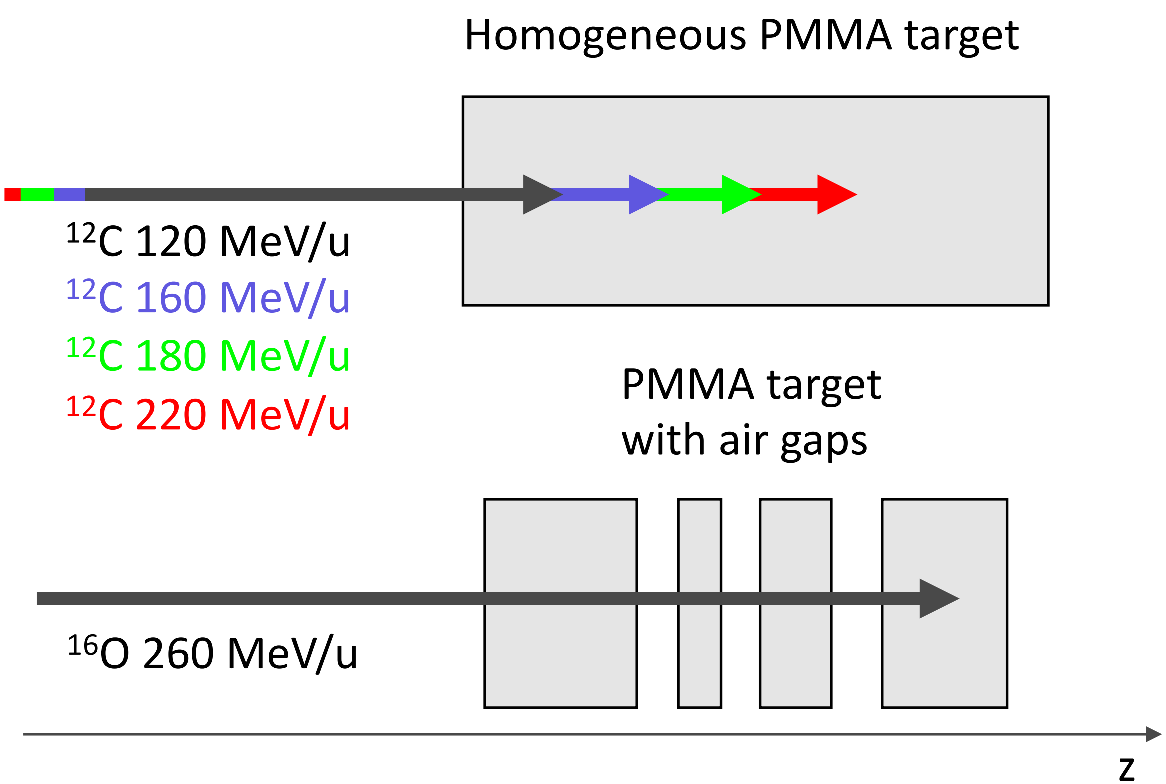
**Drawbacks**:

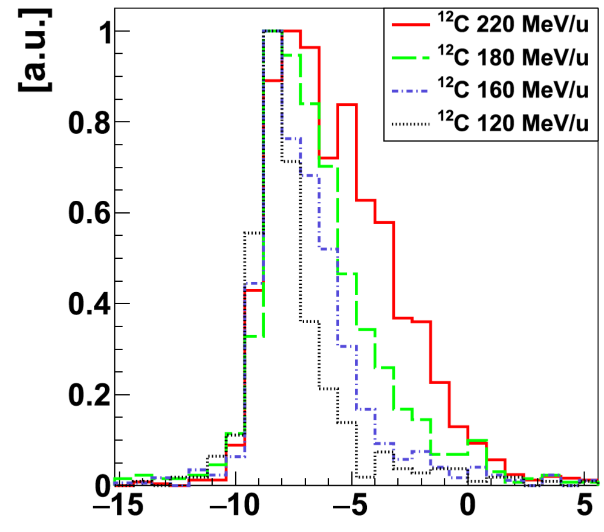
Patient-dependent fragment absorption —> non trivial correlation with the Bragg peak

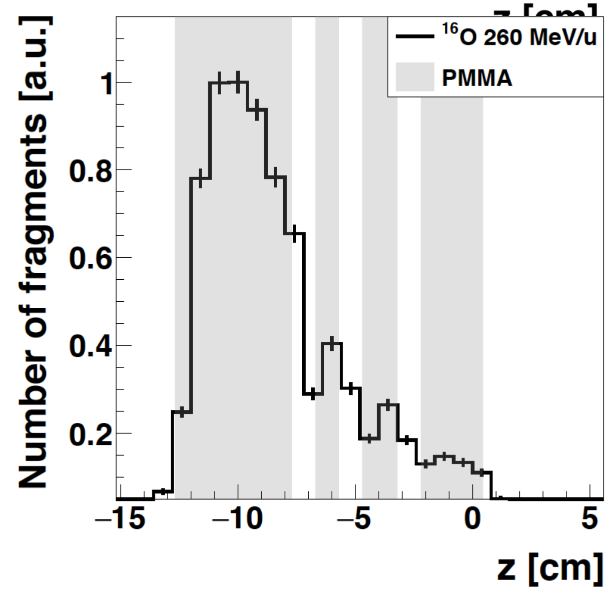
Resolution limited by the multiple scattering

# Proof of concept

The emission shape is sensitive to density variations!



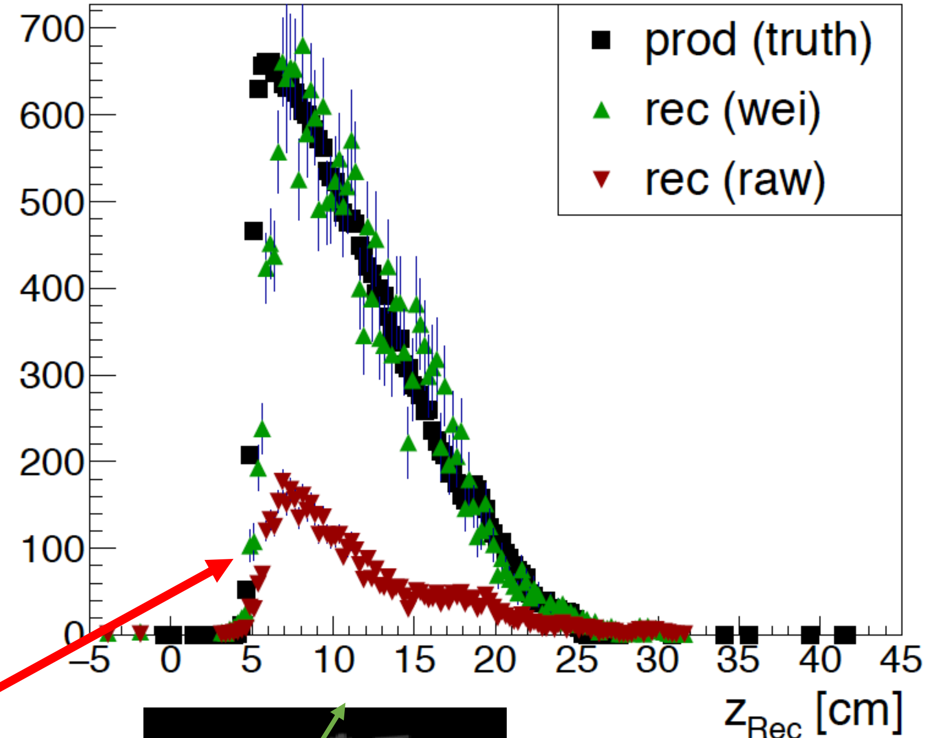



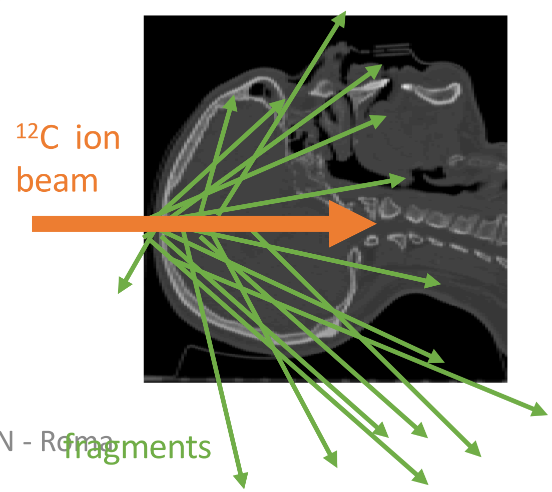




Rucinski A. et al, https://doi.org/10.1016/j.ejmp.2019.06.001

# The range monitoring challenge

- Ideal outcome: evaluate the range for each **pencil beam PB (which defines a beam energy and direction)**
- A PT treatment can be constituted by > $10^3$- $10^4$ number of PB depending on the tumor volume/location
- Limitations : **multiple scattering**, **collected statistics**, **not trivial correlation with the Bragg peak ( <u>unfolding is needed</u>)**

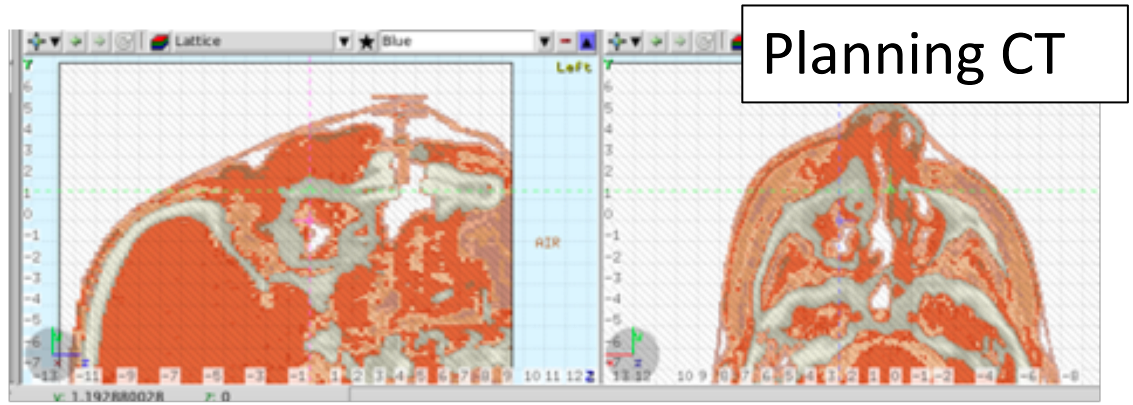


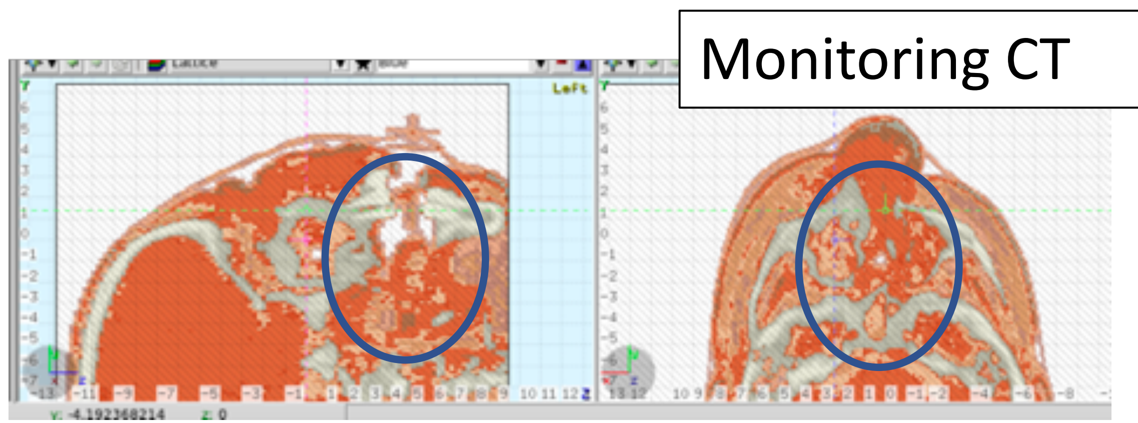

Fragments cross different length of different materials

# Inter-fractional monitoring

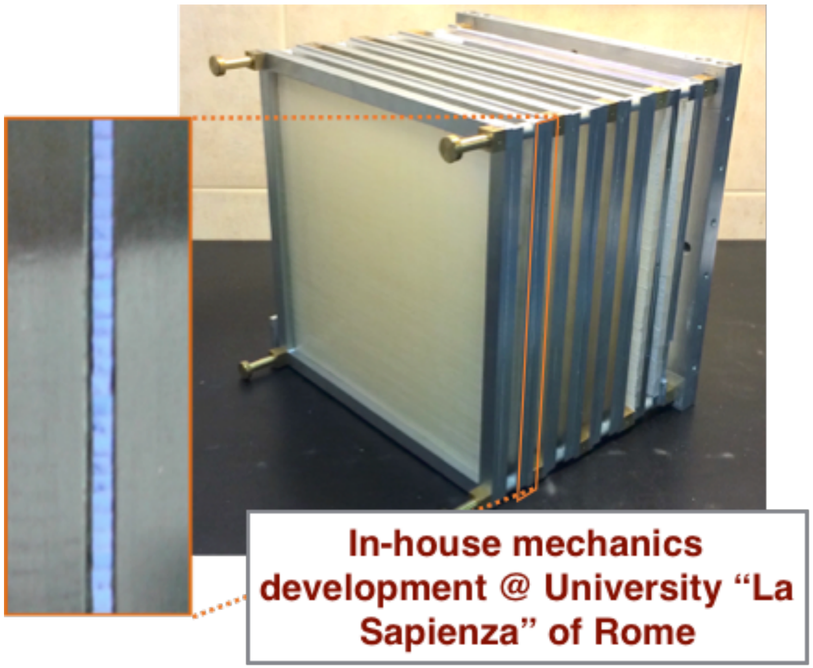
- **Goal**: spotting morpholocial changes **comparing the reconstructed emission map of the secondary charged particles in different fractions of the treatment.**




- In clinical practice a replanning CT is performed only when evident external morphological variations are expected, to avoid additional dose to the patient.

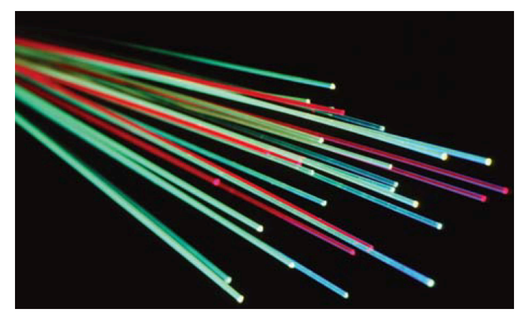


# The Dose Profiler



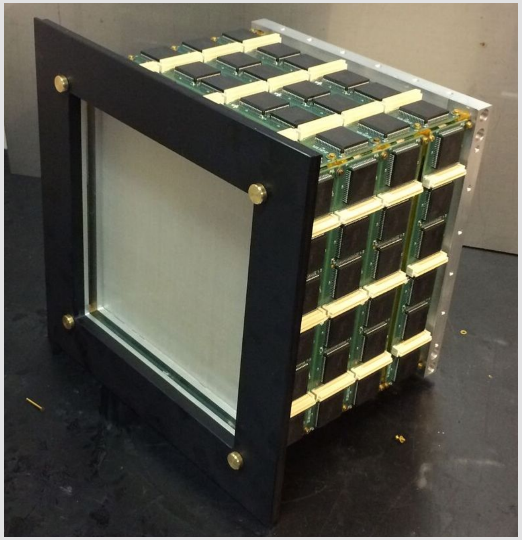

- 8 planes each one composed of 2 orthogonally oriented layers of **plastic scintillating fibres** (squared **500 µm**, double cladding) are used to track the incoming particles
- **Custom read-out system** based on ASIC and FPGAs
- Interface with the Dose Delivery system of CNAO

| Fiber | Color | Peak, nm | Time, ns | m* | per MeV** |
|---|---|---|---|---|---|
| BCF-12 | Blue | 435 | 3.2 | 2.7 | ~8000 |

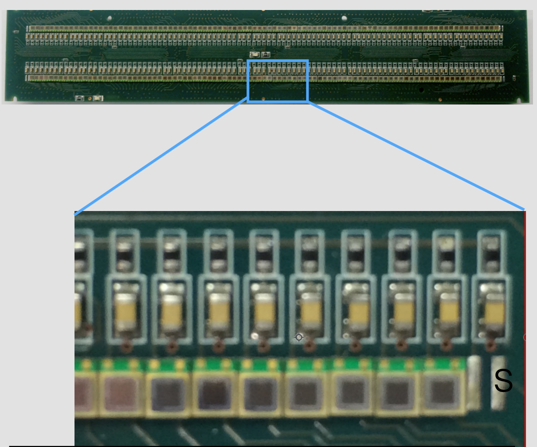


Design criteria: **compactness**, **easy of maintenance**, **high detection efficiency** and **DAQ rate capability** (up to 100kHz)

# Read-out system



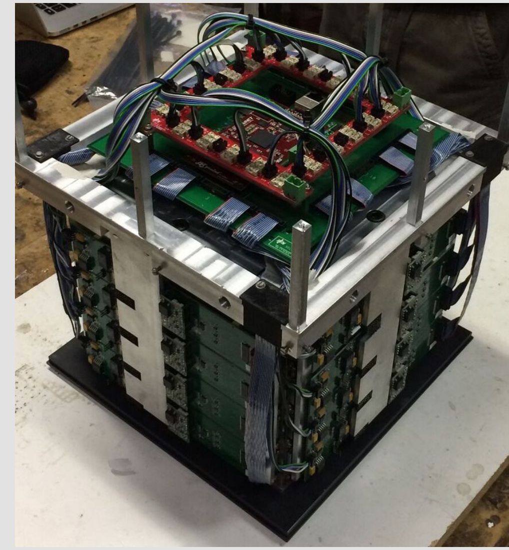
**SiPM boards**



Hamamatsu SiPM 1 mm$^2$

**FPGAs boards**

- 3072 channels
- 16 FPGA used for ASIC configuration and readout

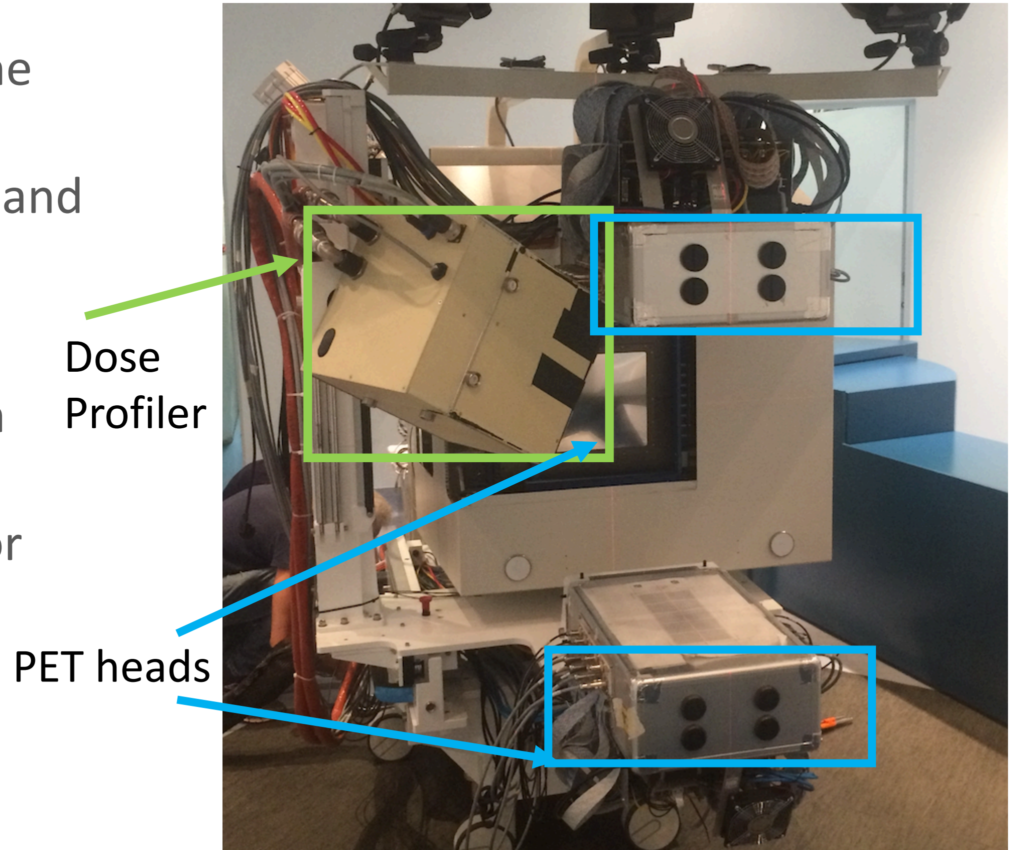


**Concentrator board**

- Data collection and event building
- Trigger (sustainable rate > 100KHz)
- Data transfer via ethernet link (TCP/IP)
- Dose Delivery system interface

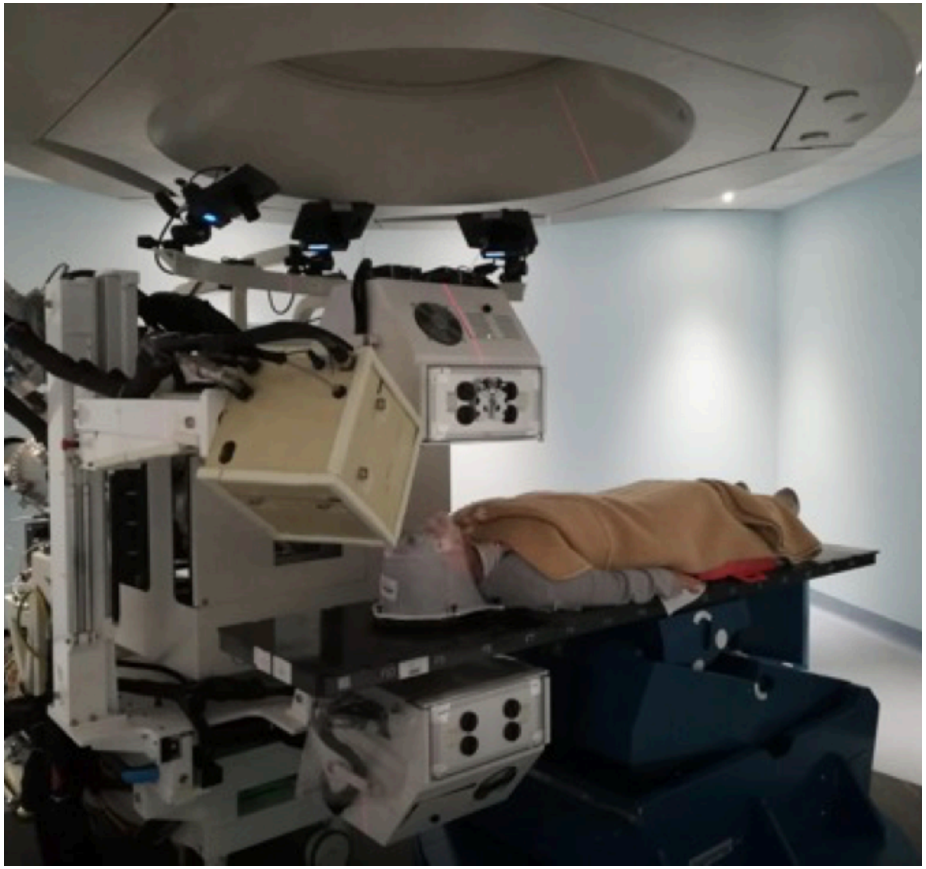
# The INSIDE project

- Inside pioneered since 2013 the **bi-modal approach** with synergistic combination of PET and charged fragment detection.
- In beam PET exploits the β+ emitters activated by the beam inside the patient ($^{11}C$, $^{10}C$, $^{14}O$, $^{15}O$, $^{13}N$...). It's more suitable for proton treatment monitoring
- Charged fragments emission significanlty occurs only in $^{12}C$ treatment.



# Clinical trial @ CNAO

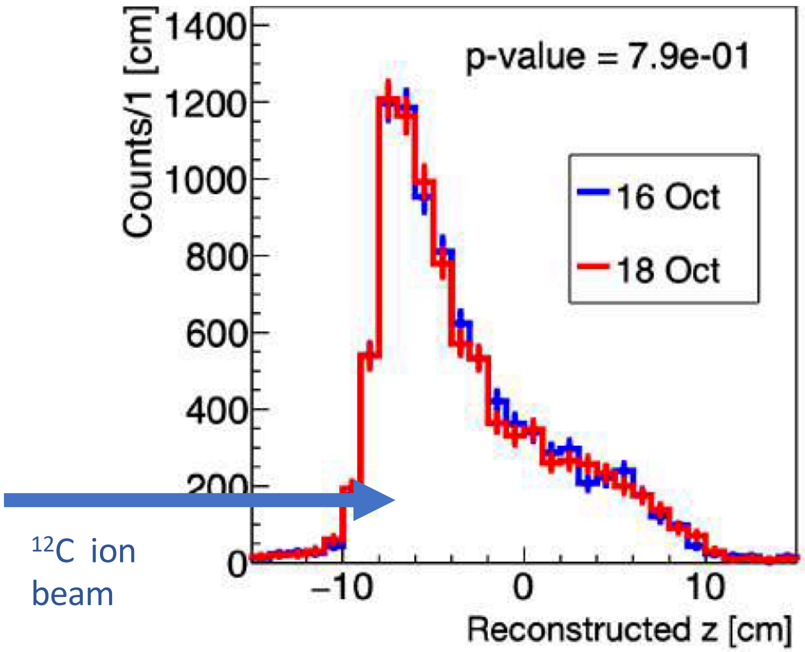
- A **clinical trial @ CNAO** started in july 2019 to **evaluate the detector sensitivity to range variation and morphological changes** inside the patient in the context on the INSIDE project
- Four selected pathologies have been identified: meningioma and nasopharynx cancer treated with proton beams, **Adenoid Cystic Carcinoma (ACC)** and **clival chordoma treated** with carbon ion beams
- The system can be used with minimum impact in the treatment time workflow in the clinical routine



# Monitoring strategy

The fragment production yield correlated with the tissue density crossed by the beam, then the inter-fractional morphological changes can be identified **comparing the reconstructed emission position distribution of the fragments** collected during each treatment session

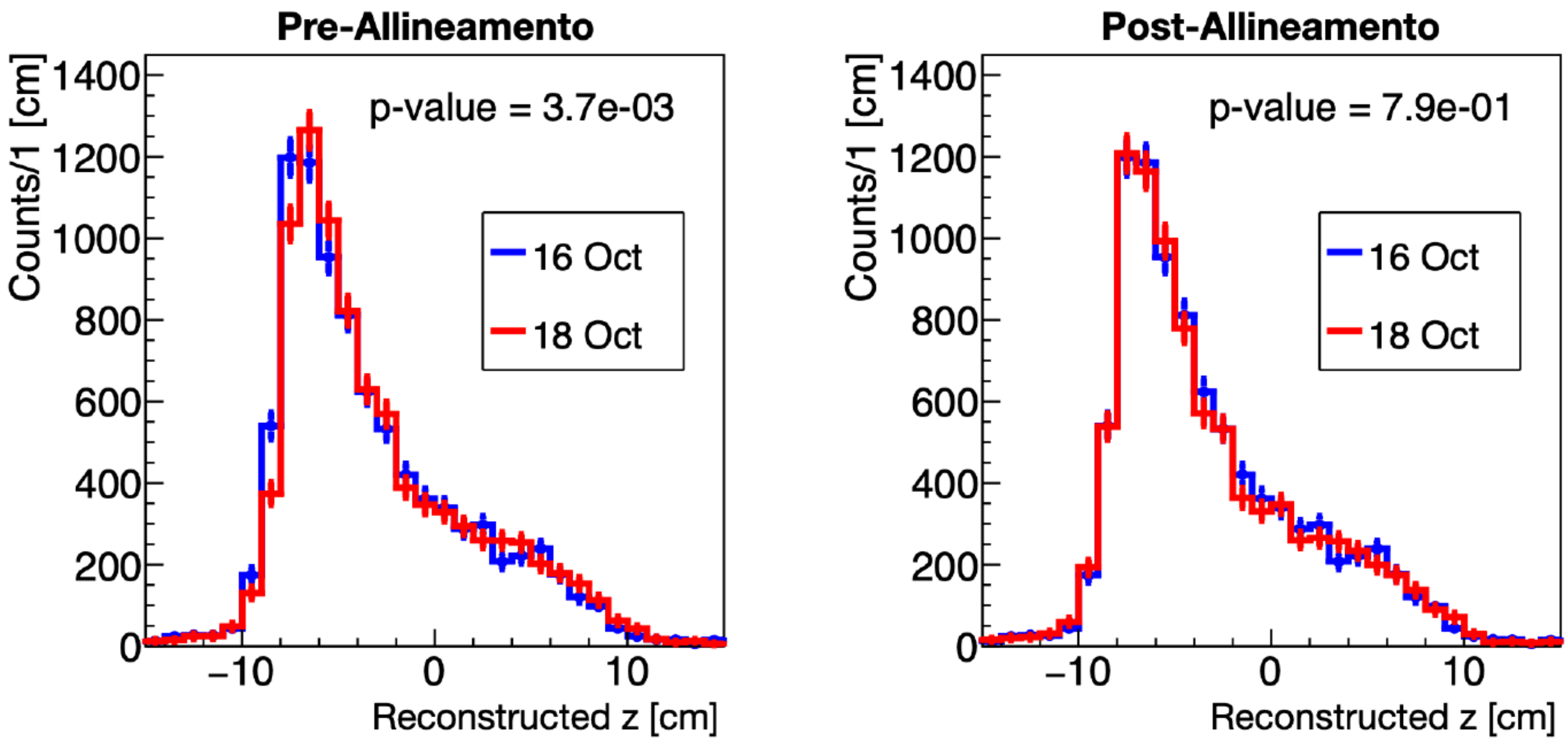
- The 1D emission spatial distribution along the beam axis (z in the reference frame) is built for each pencil beam (PB) delivered in the treatment
- A statistical comparison between spectra of single PB would be too sensible to fluctuations (~**50 tracks per PB**). **PBs belonging from the same target volume of 1cm x 1cm x 0.6 cm have been summed up in order to create Super Pencil Beams (SPB).**



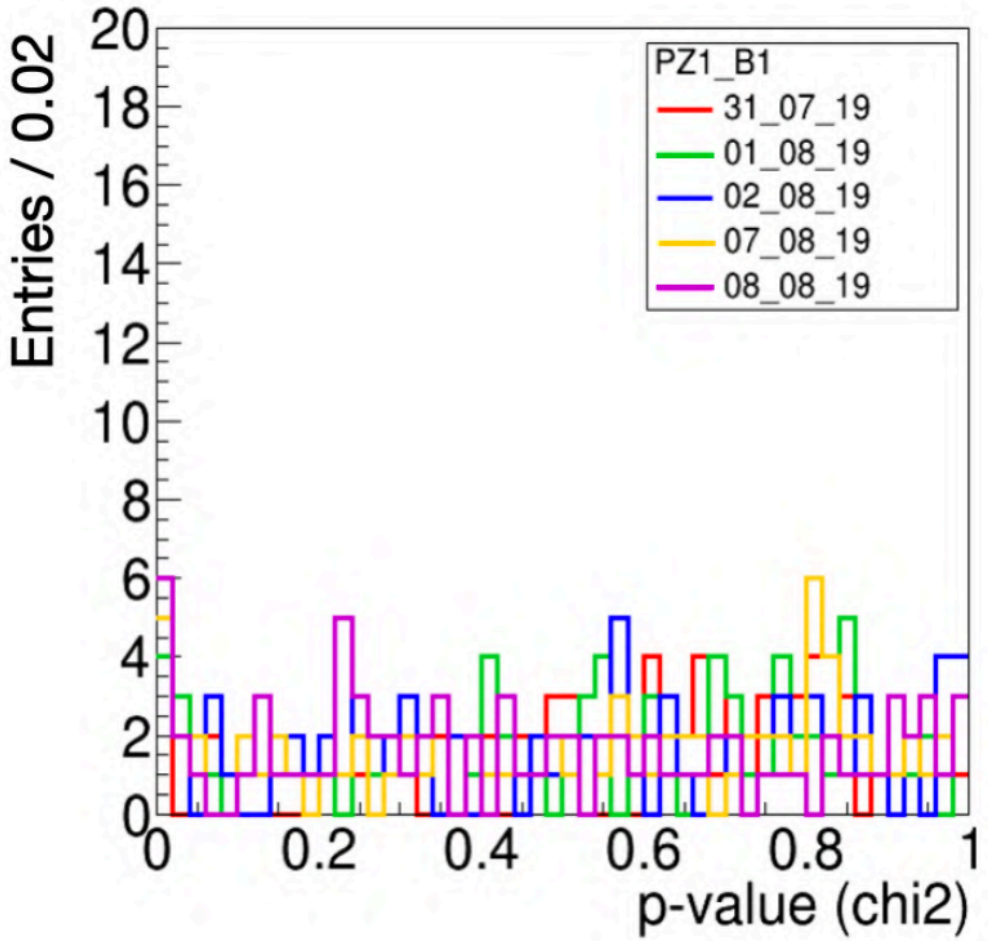
# Systematic effects

- **Fluctuation of the therapeutic beam intensity between the treatment fractions**. Due to the detector dead time ( ~5 μs ), this lead to a systematc effect in the number of reconstructed tracks that has to be corrected a posteriori

- **Dose Profiler or Patient inter-fraction misalignment**. The INSIDE cart is hooked to the beam nozzle with a precision of ~ 1 mm.



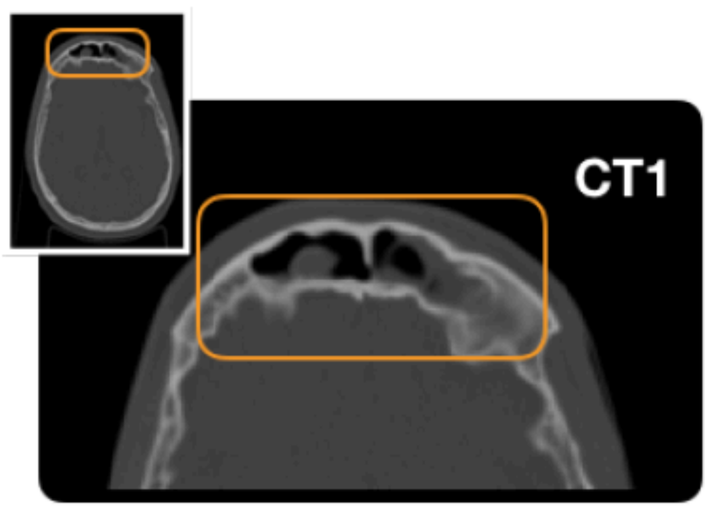
# Results (I)

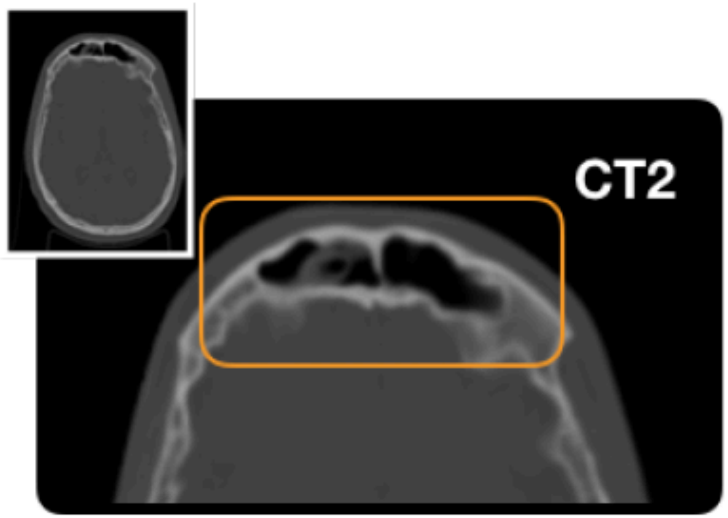



- **1st scenario: patient for which no morphological changes are expected** (pathology: Adenoid Cystic Carcinoma)
- The observed p-value distribution per SPB is ~ flat, which is **compatible with a no morphological variation hypothesis**

# Results (II)

- **2nd scenario**: patient that showed in the re-evaluation CT the **emptying of the frontal sinuses**.

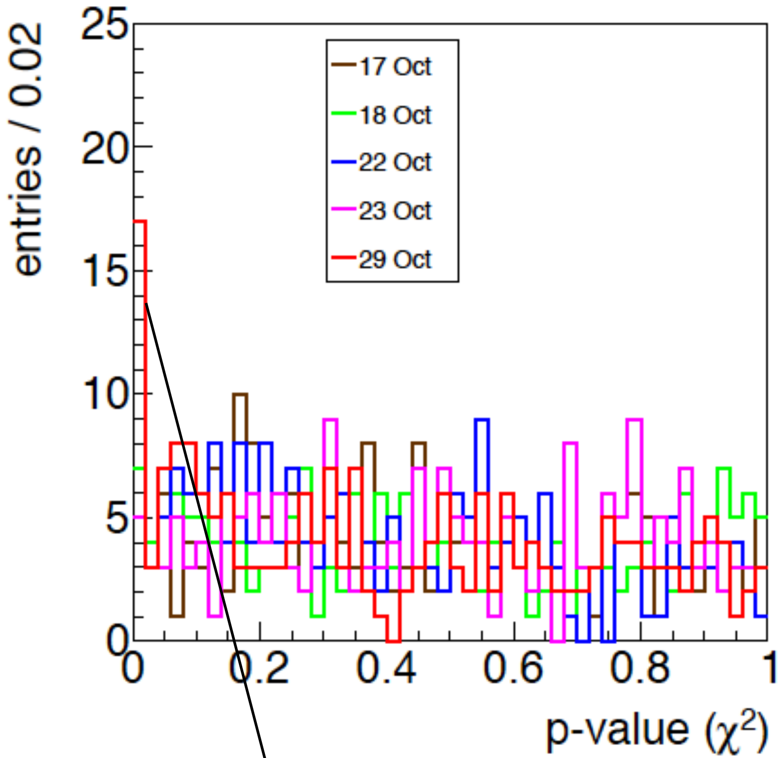


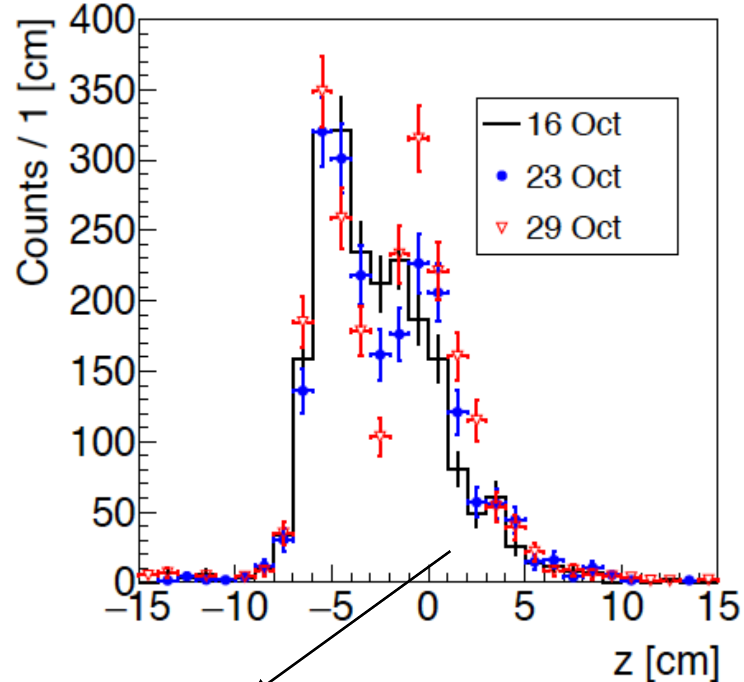

Fischetti M et al, *Sci Rep* **10,** 20735 (2020). https://doi.org/10.1038/s41598-020-77843-z

# Results (III)

- **2nd scenario**: patient that showed in the re-evaluation CT the **emptying of the frontal sinuses**.

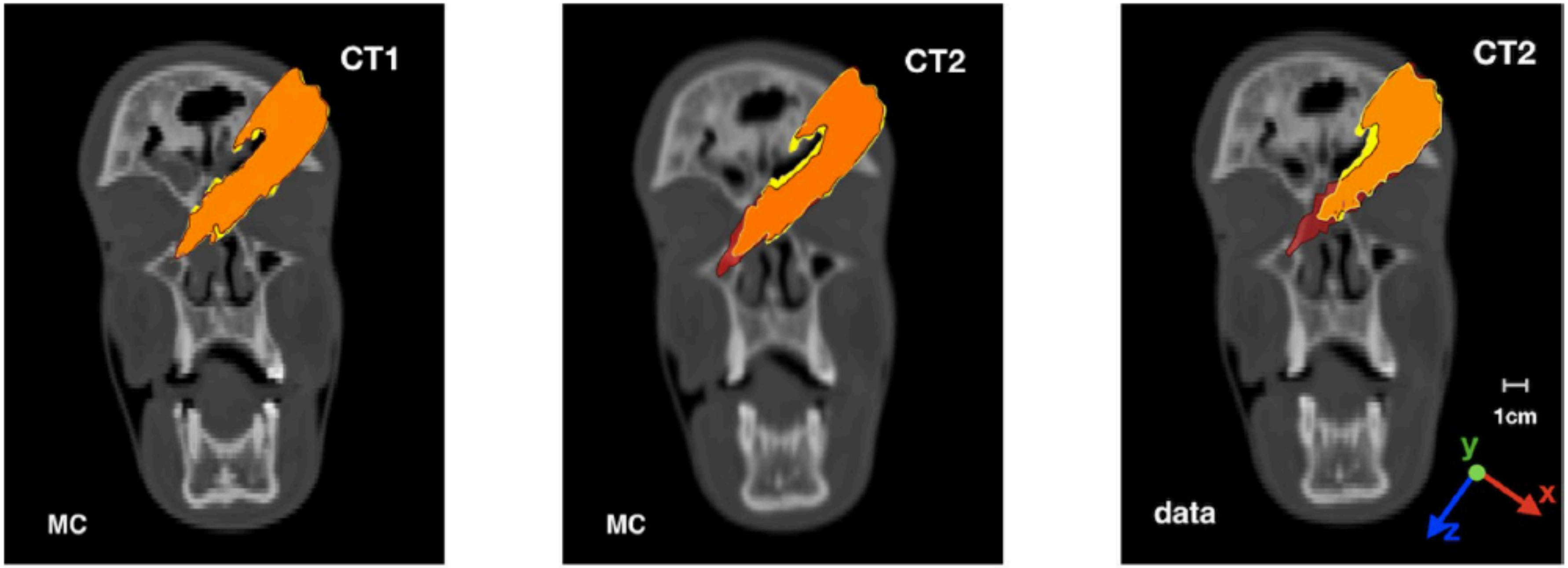



Excess of SBP with p-value<2%




Reconstructed fragment emission profiles for a single SPB measured in three different fractions. A **gradual shape change** can be observed

# Range monitoring potential




- Fragment emission map measured in the first treatment fraction (16 October)
- Fragment emission map measured in the last treatment fraction (29 October)
- Overlap between the twos

# The next future

- The 2nd part of the trial has been delayed due to the COVID (possible restart in may-june?)

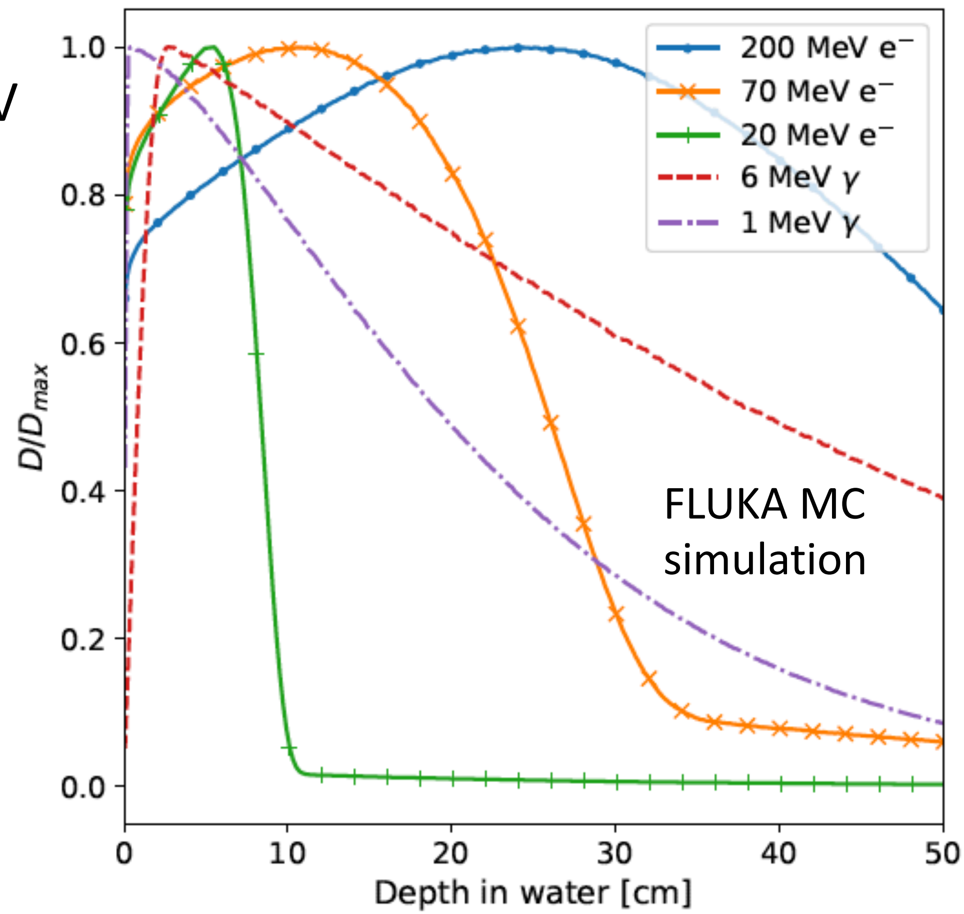
- We need a larger patient sample to assess the ultimate sensitivity of the technique in the early spotting of significant morphological changes and to carefully evaluate the **impact of the tumor positioning, size and treatment strategy** on the achievable sensitivity

- Develop a more refined comparison strategy using a **3D processing approach** in order to provide a more precise spatial information

- The data collected during the trial will be also used to evaluate the **range variations detection potential (unfolding)**

# What about high energy electrons?

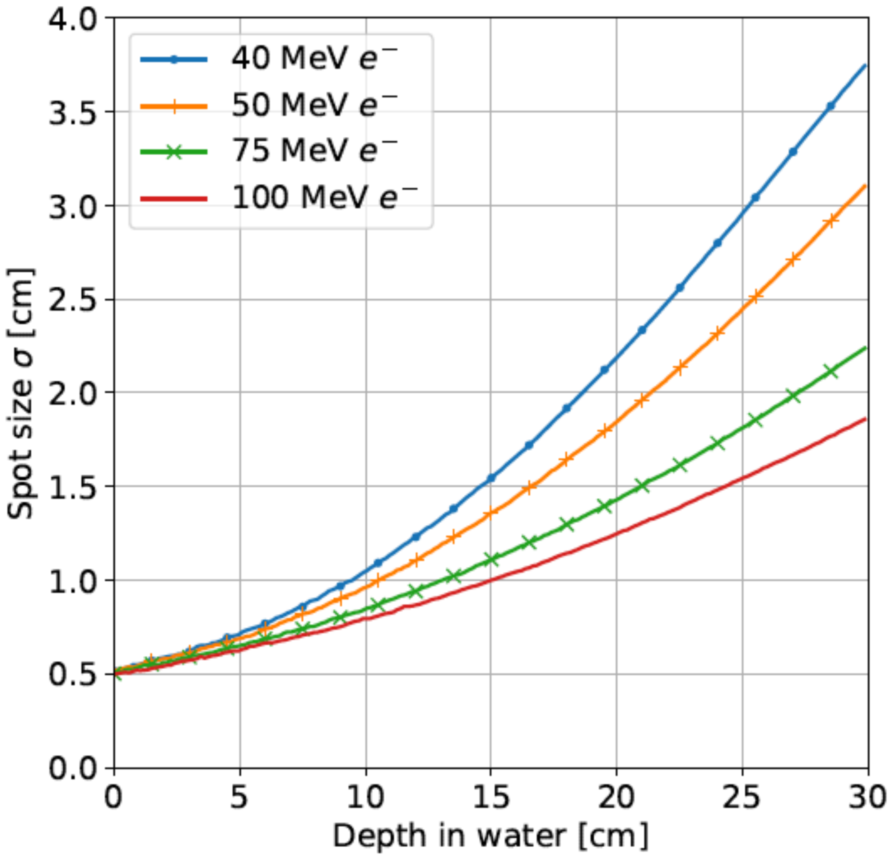
- The dose-depth relation of electron beams with E>50 MeV has a behaviour that is in between the photons and the protons
- It shows **peak slowly moves downstream with the beam energy**
- The **tails largely increase with beam energy**



# What about high energy electrons?

- The weak point of the electron dose release is the lateral distribution. **Multiple scattering** spread out trasversally the dose in the path to the tumor inside the patient.

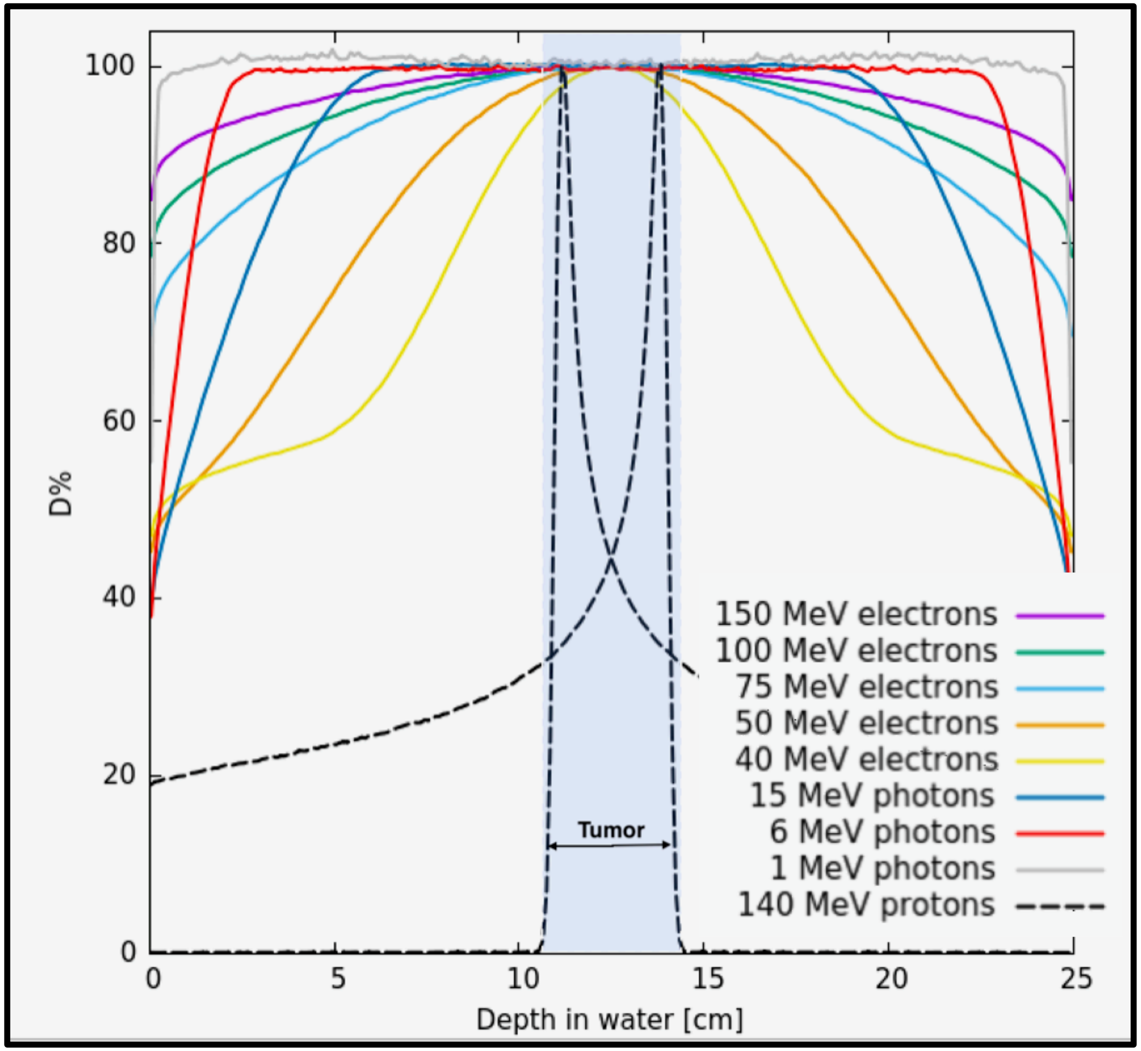
- To overcome this problem (**very high energy electrons VHEE)** must be used (E>100 MeV)



# Opposite fields

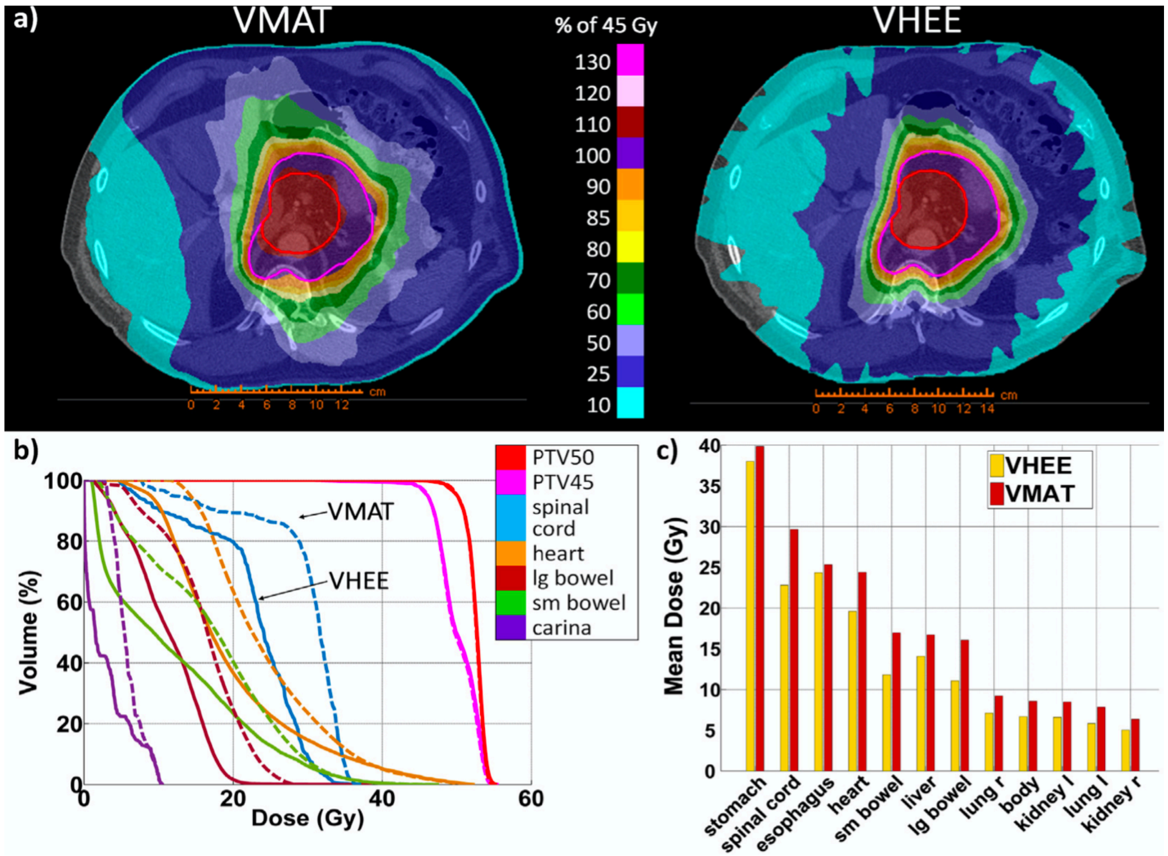
The dose distribution of two opposite VHEE electron fields can have as good conformality as 10-15 MeV collimated photons

Interesting enough: the 50 MeV electrons can cover a tumor 10-15 cm deep!!!!



# VHEE in radiotherapy (I)

In the last years few research groups studied the possibility to use VHEE electron beam with 100 MeV < E < 250MeV in RT. Some papers reported a superiority VHEE RT vs standard VMAT in the treatment of some tumors.




Reported results are often based on simulated setup with many entrance fields (>10) with beam energies ≥ 100 MeV (200 MeV typical) to minimize the beam penumbra



Palma, B. *et al*. *Radiother Oncol* **119**, 154–158, (2016)

# VHEE in radiotherapy (II)

**Why the VHEE technology has not spread out in hospitals in spite of the reported results, obtained using simulation?**

- Main motivation: cost, complexity and the space needed, up to now, by a 100-200 MeV electron beam. All these items grow more then linearly wrt beam energy

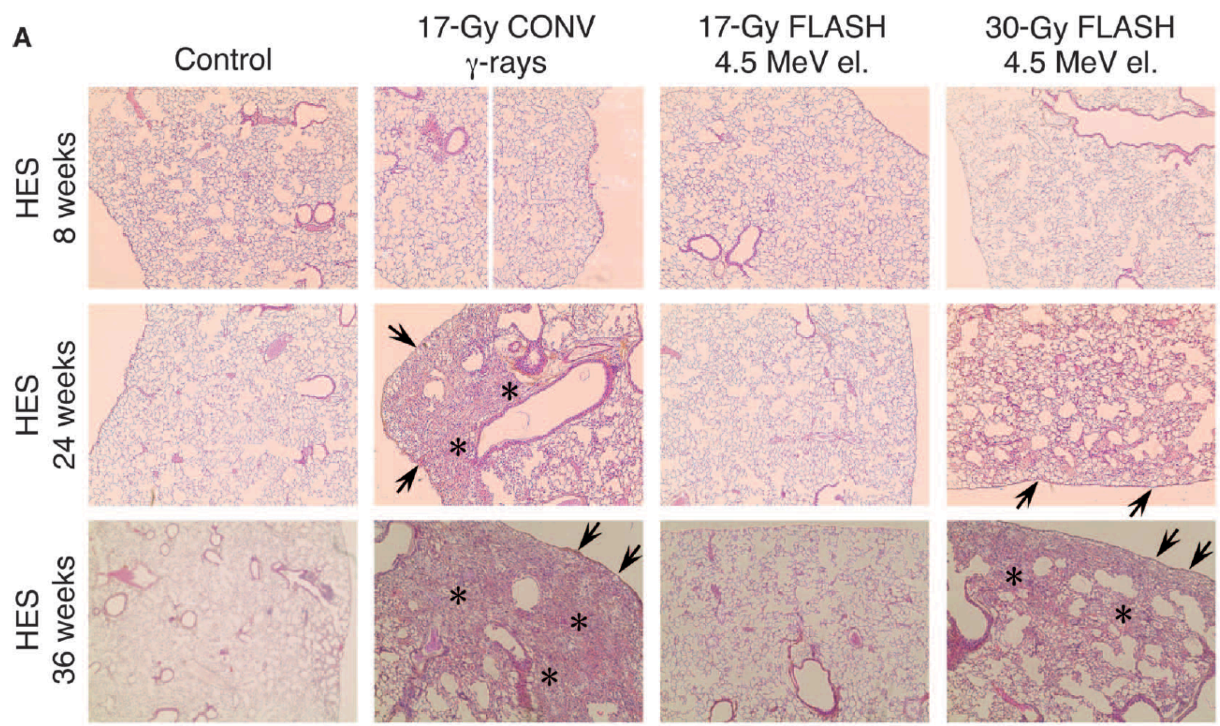
- Radioprotection issues (at least in Italy, but it's similar all over the Europe) for electron beams with E>25 MeV

- Some/all simulated results are obtained with a very ideal, complex setup with a lot of fields and high energy.

- Unavailability of commercial TPS (no machine available) to compare standard RT treatment with VHEE

# A new ingredient: the flash effect

- When the dose is delivered with high intensity (>10 Gy/s) it seems that the biological damage on normal tissues is reduced




Vincent Favaudon et al. https://doi.org/10.1126/scitranslmed.3008973

| γ 0.660 MeV | Electrons 4.5 MeV |
|---|---|
| 0.03 Gy/s | 60 Gy/s |

- FLASH irradiation protects lungs cells from radiation-induced fibrosis and it is as efficient as CONV irradiation in the repression of tumor growth

# VHEE and flash therapy

- **The flash effect found with 10 MeV electrons will be present also with 100 MeV electrons?**
- **The feature of a realistic external RT treatment with electrons ( pencil beam scanning, multiple fields) will keep the FLASH effect**?

**The answer is currently missing**! However…

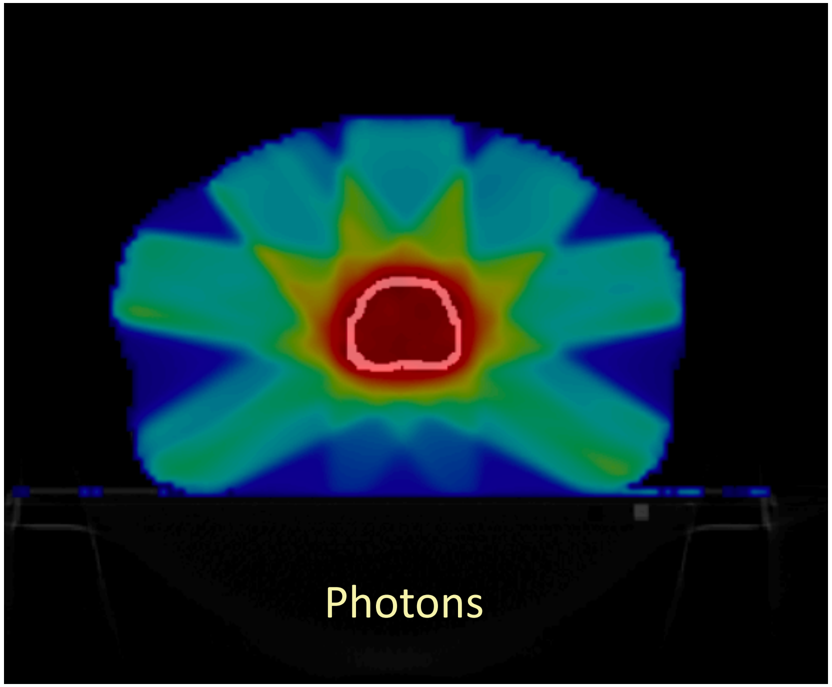
- From accelerators technology point of view an high energy electron FLASH accelerator compliant to clinical condition (intensity, space, weight) could be more easily achievable wrt photons/protons/carbons beam

- The FLASH effect could mitigate the effect of the wide lateral distribution of the dose release of such an energetic electrons

# A first feasibility study

We started our exercise in collaboration with UOD Fisica Medica and UOC Radioterapia Policlinico Umberto I Roma. **Goal**: make an VHEE plan for a prostate tumor. The ingredients are:

- Prostate treatment: IMRT (ONCO) on Pinnacle TPS with 7 fields, 39x2Gy
- FLUKA 2020 MC to evaluate the dose release of each PB of electrons
- A Treatment Planning Software adapted from FRED software developed for PT (A Schiavi *et al* 2017 *Phys. Med. Biol.* **62** 7482)

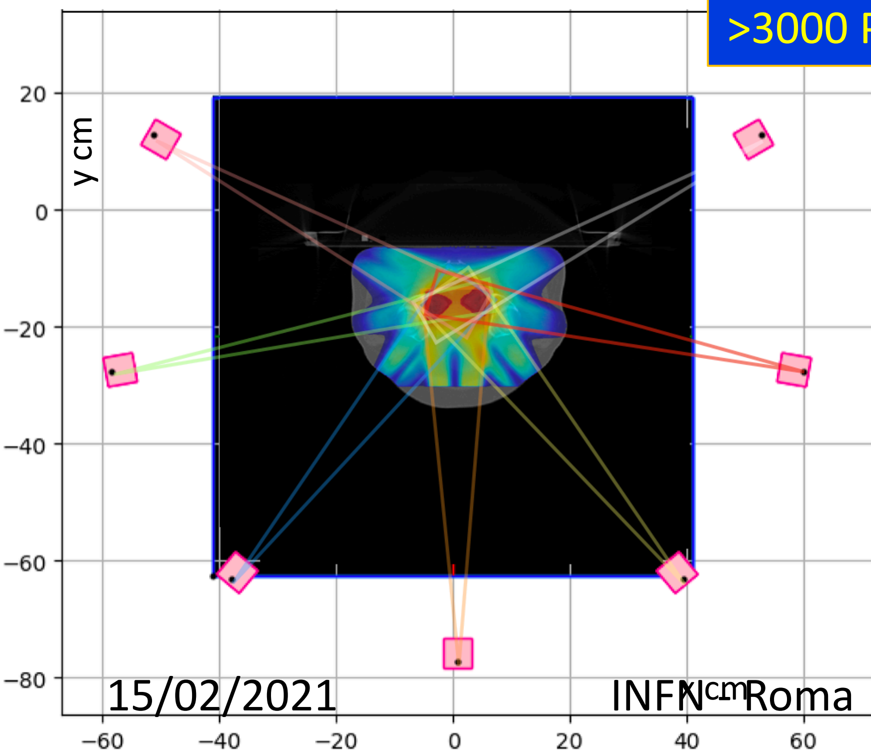


# Starting FLASH VHEE exercise

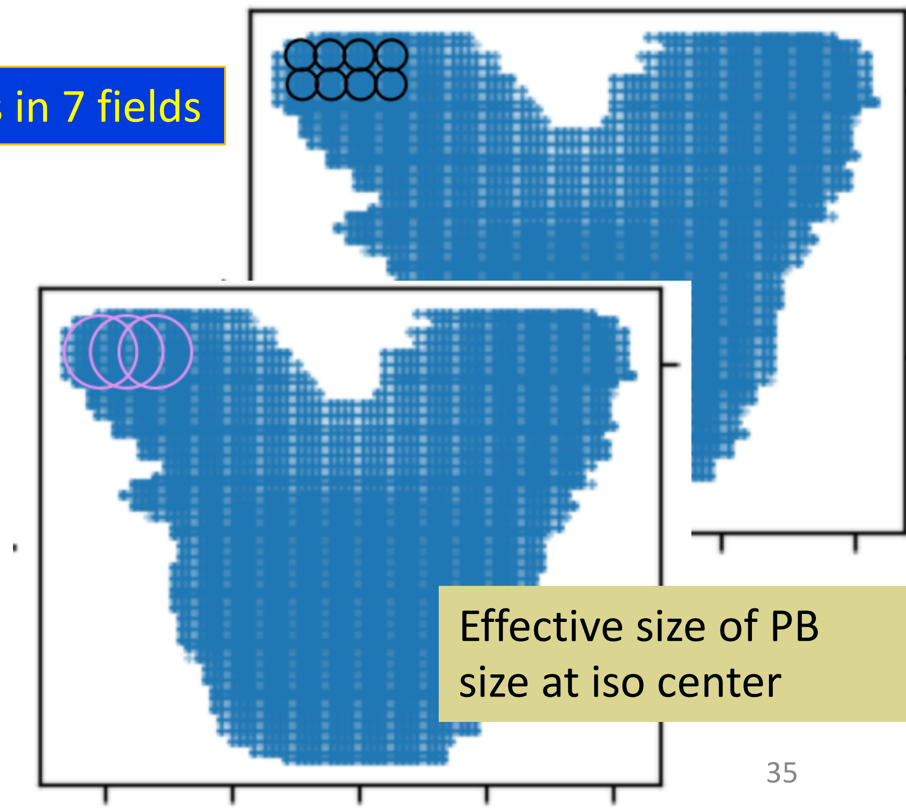
We assumed as beam model a pencil beam with ~0.5 cm FWHM, with no angular divergence. We used the same 7 fields of the photon planning.

Inside the same field the pencil beam has possibility to do scanning. The PB axis projection is spaced 0.5 cm on transverse plane at the isocenter, but the PB FWHM is of the order of 1.5 cm due to MS

>3000 PBs in 7 fields




Projection of starting PB size at nozzle



Effective size of PB size at iso center

# Flash modelling and planning

- Very basic modelling of the flash effect: constant Dose Modulating Factor

$$\mathrm{DMF} = \frac{D_{\mathrm{conv}}}{D_{\mathrm{flash}}}$$

| DMF | |
|---|---|
| 1.0 | No flash effect |
| 0.8 | Observed in abdomen organ irradiation |
| 0.6 | Observed in skin irradiation |

- The optimisation is done with respect to the **fluence** of each PB, with the aim to match the PTV and OARs dose constraints derived from the medical prescriptions

- The cost function the first one is used to constrain the absorbed dose inside the PTV to the goal value for each fraction (2 Gy, in our case) while the other term is related to the OARs and it is activated whenever a threshold in the OAR voxels is surpassed

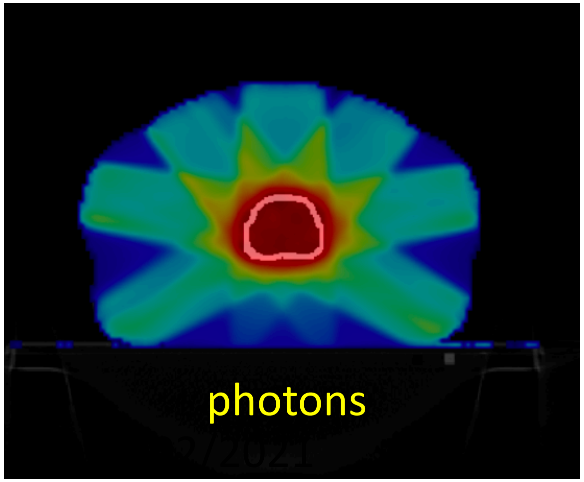
# Photons vs VHEE: a first clue

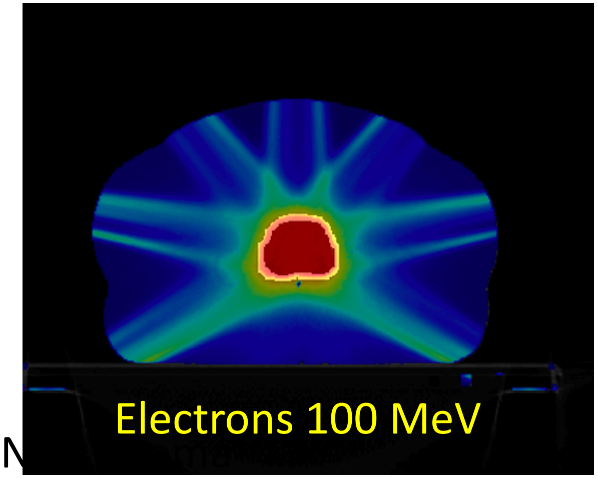
CAVEAT: As first approach to this exercise we used the same cost function and OARs treatment of a PT optimization: comparing an extremely well tuned software (Pinnacle) with a brand new skeleton of a VHEE TPS. Needed MC stats tuning, dose matrix smoothing tailoring , boundary voxels treatment, etc etc

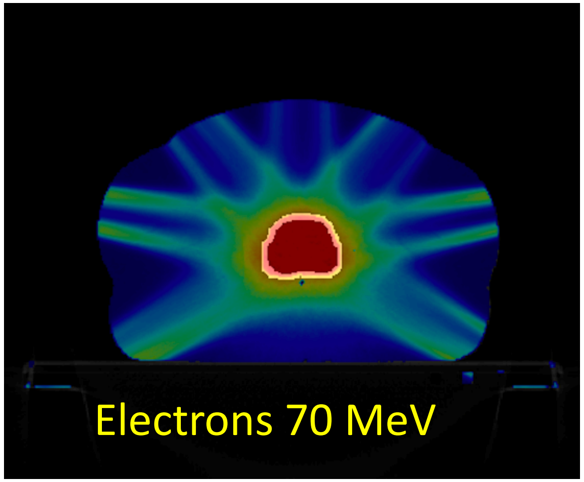
submitted to SciRep

In spite of that the results are interesting because:

- ✓ Are the worst case scenario for VHEE
- ✓ Provide a clear indication about the effect of FLASH
- ✓ Even in this unfair competition the VHEE behave very well



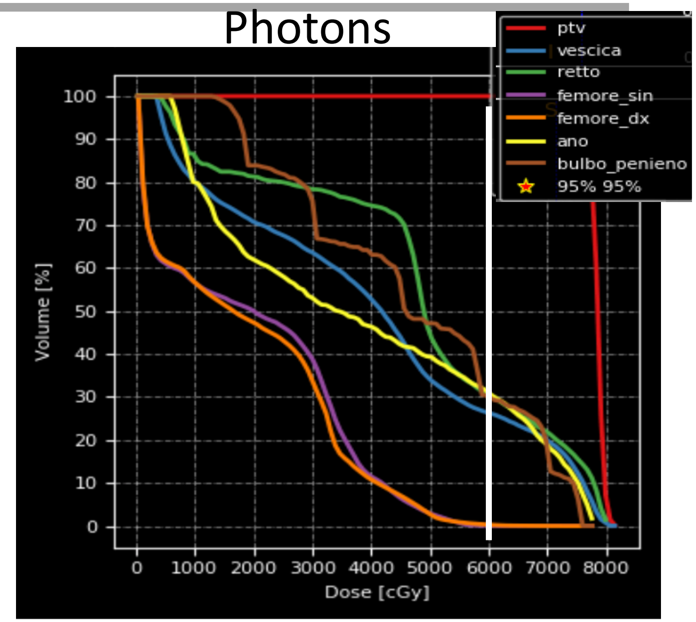
# DVH first results @ 100 MeV

DMF=1: slightly worse than photons on PTV, but better on OARs

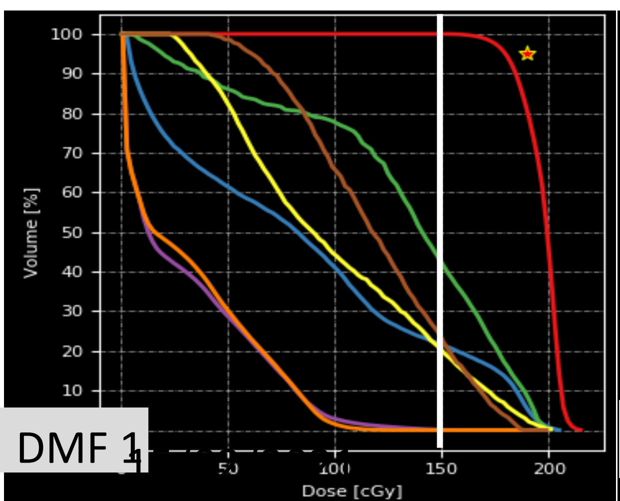
DMF=0.8: electrons coverage of the PTV is optimal, better than photons on OARs

DMF = 0.6 much better than photons both on PTV and OARs

Photons

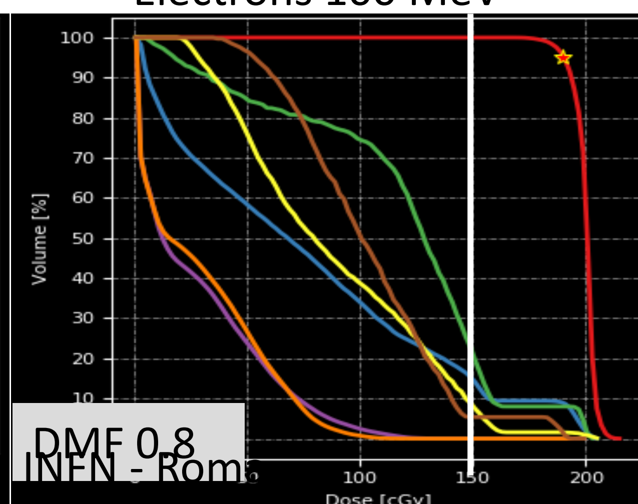



Electrons 100 MeV



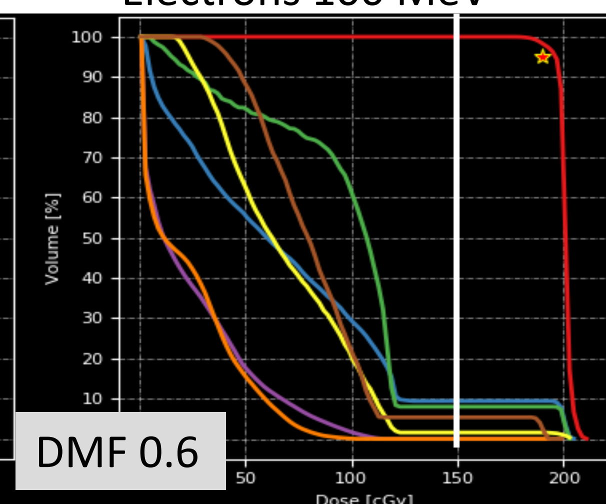

DMF 1

Electrons 100 MeV




DMF 0.8

Electrons 100 MeV



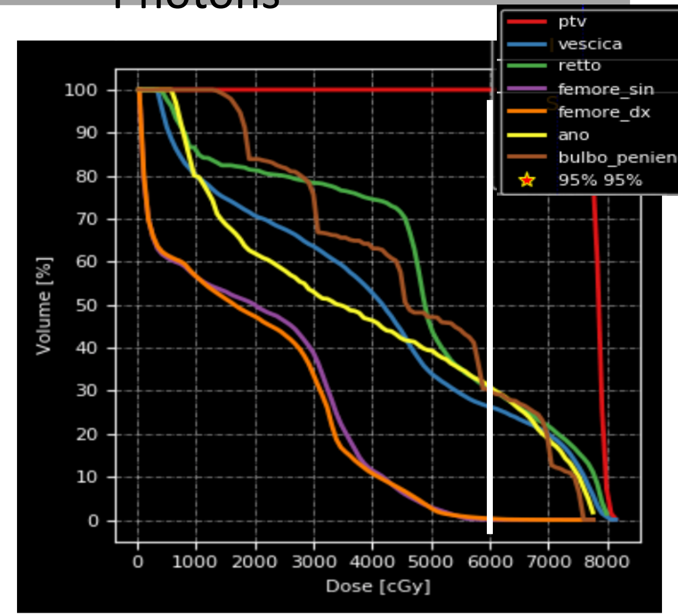

DMF 0.6

# DVH first results @ 70 MeV

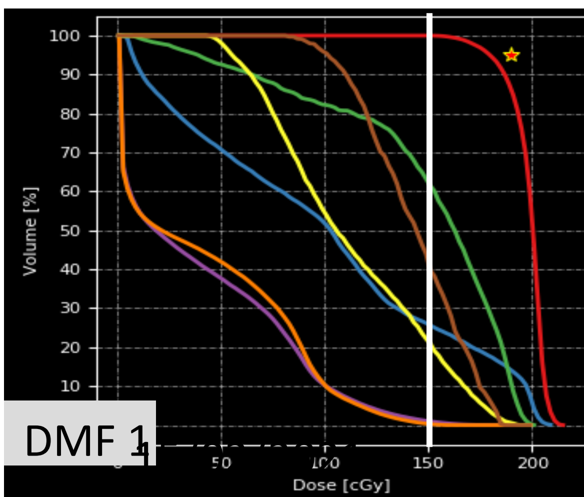
The results for 70 MeV electrons are almost equivalent of that one of 100 MeV. In particular better than photons with DMF 0.8!

This is a nice suggestion: a 70 MeV energy can be enough with mild FLASH effect for prostate!

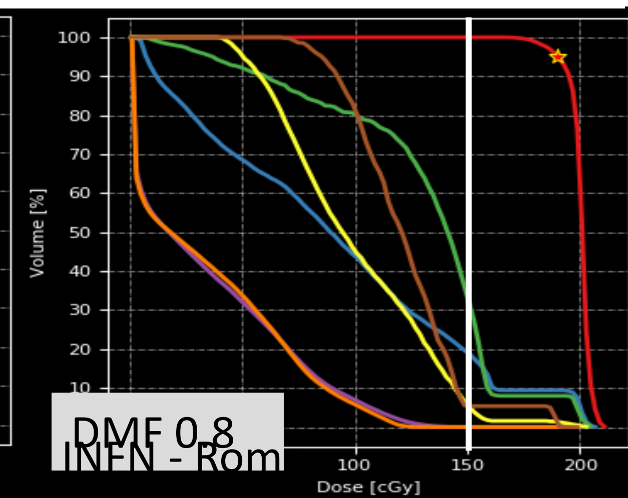
Photons



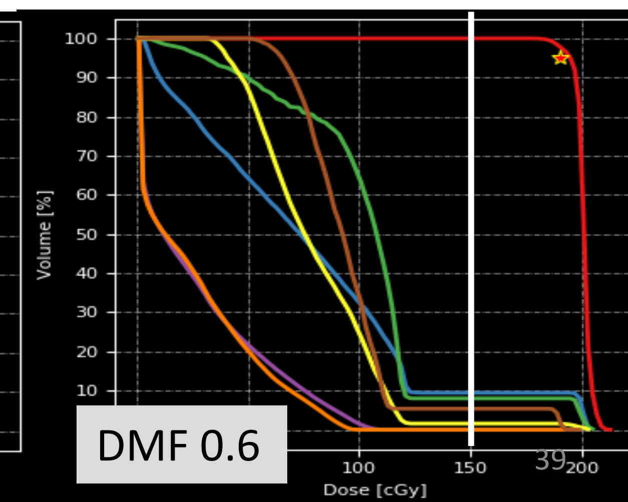

Electrons 70 MeV




Electrons 70 MeV




Electrons 70 MeV



# Conclusions

- **The FLASH effect, MUST YET BE confirmed** for VHEE in external RT conditions, in particular for active scanning, multi field use.
- A deep tumor as prostate seems VERY well treated. Perfect possible matching with head & neck tumors (working on it), with possible dose escalation for radioresistant tumor
- R&D activity is needed  to design (and building) of MEE, HEE, VHEE (whatever definition you prefer!) linac compliant to hospital condition
- The technique is newborn… plenty of space for optimization and improvements