Delivering the FLASH: Technological Foundations and Clinical Horizons

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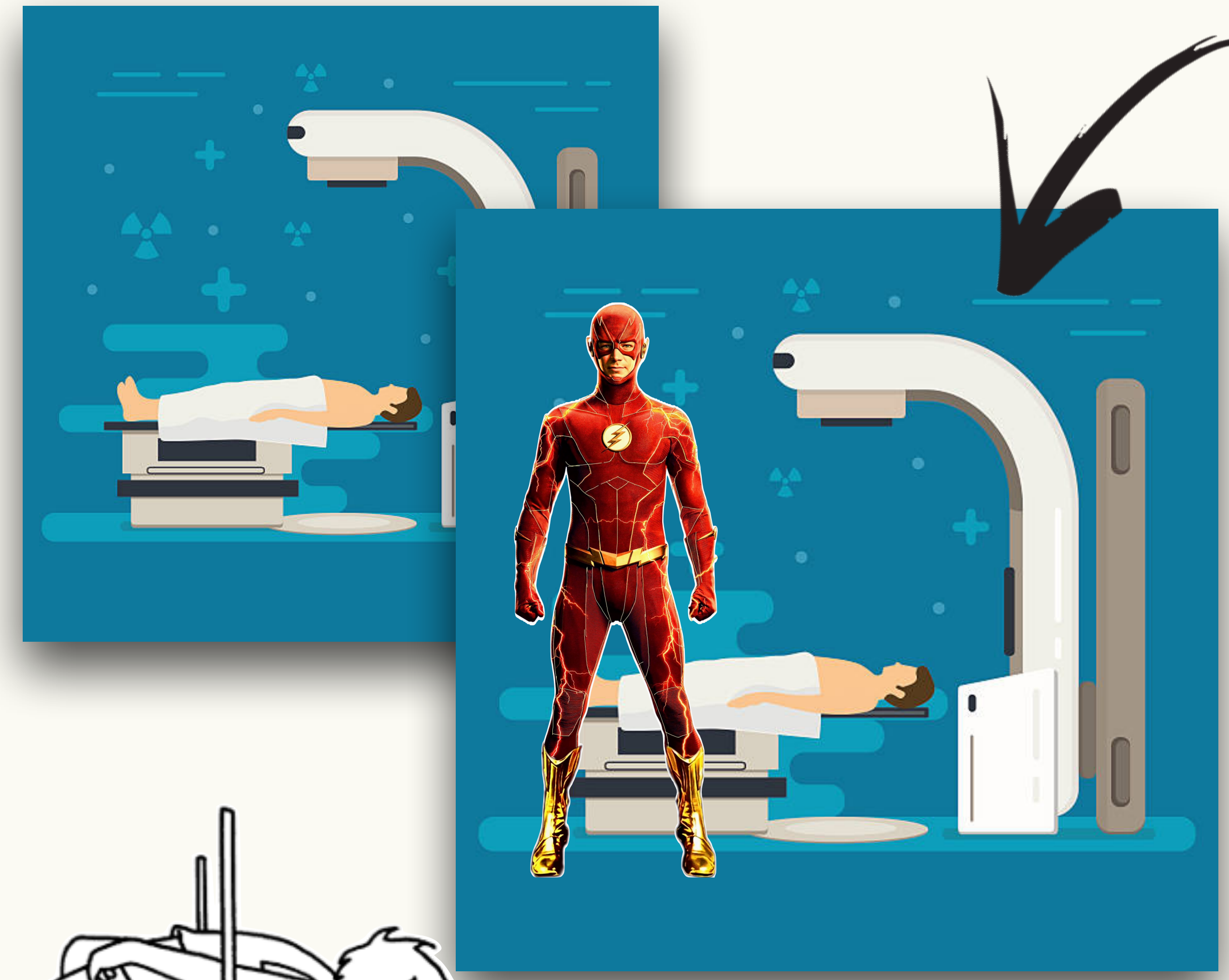

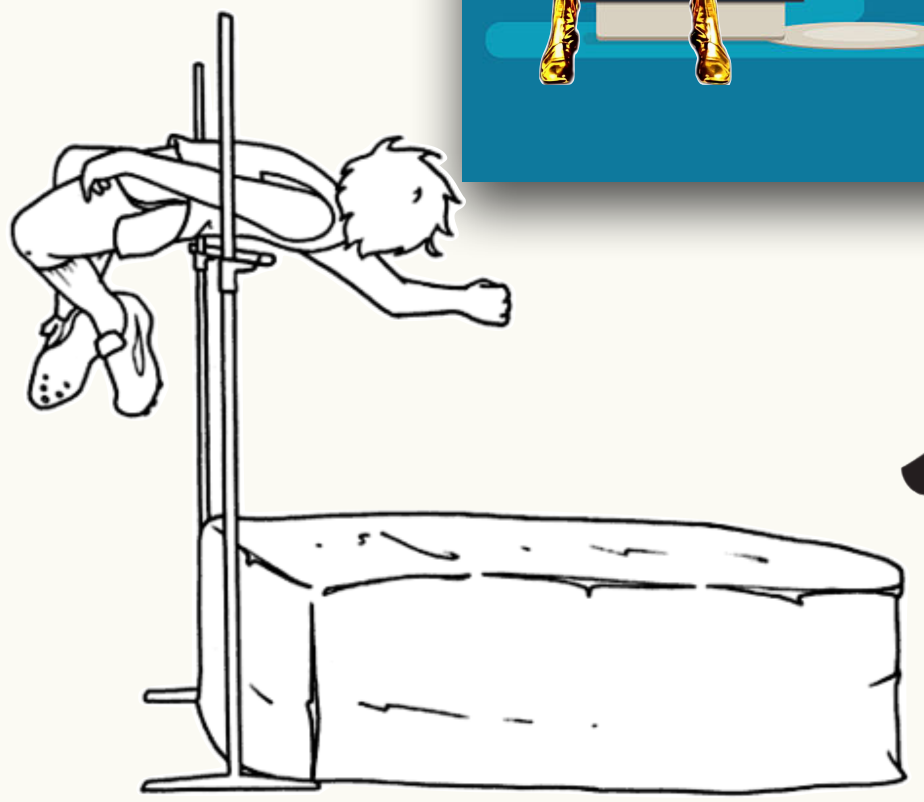

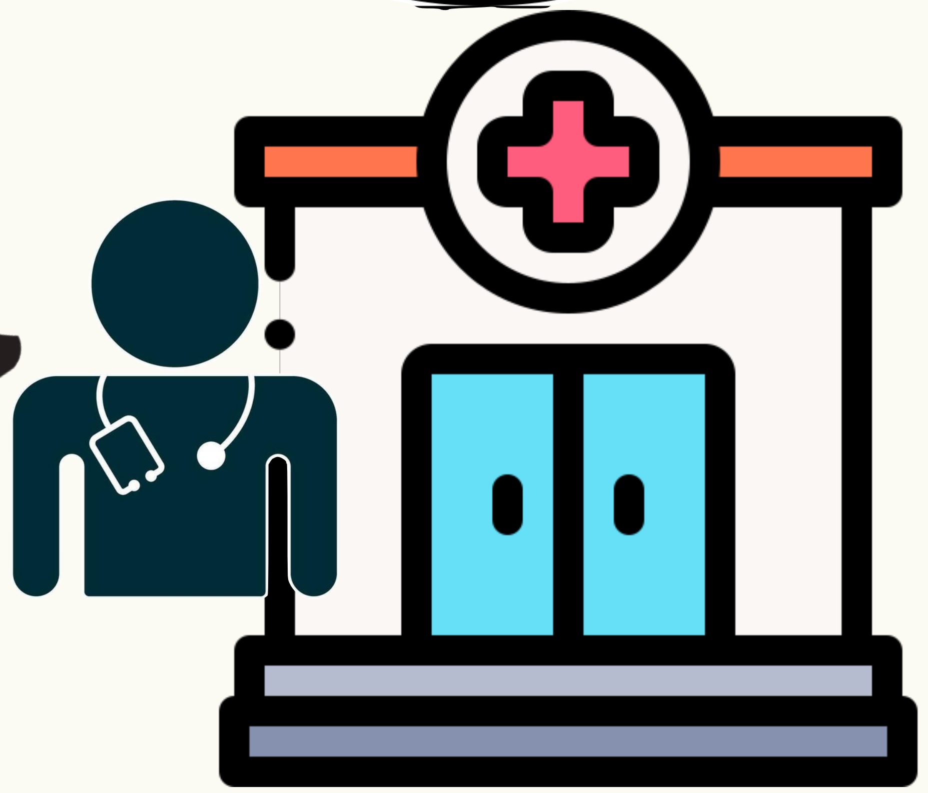

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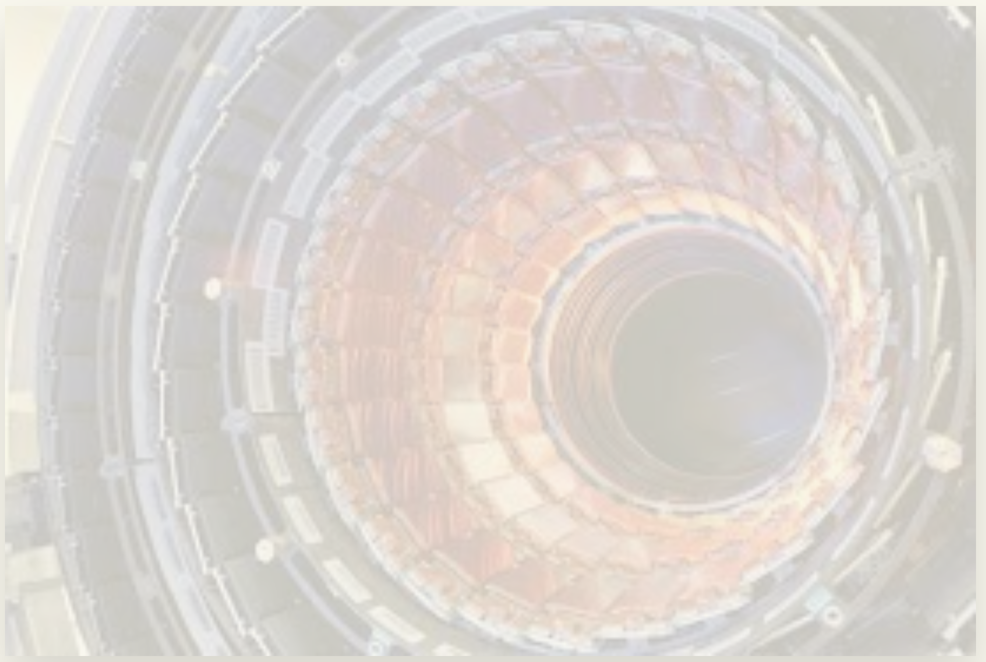
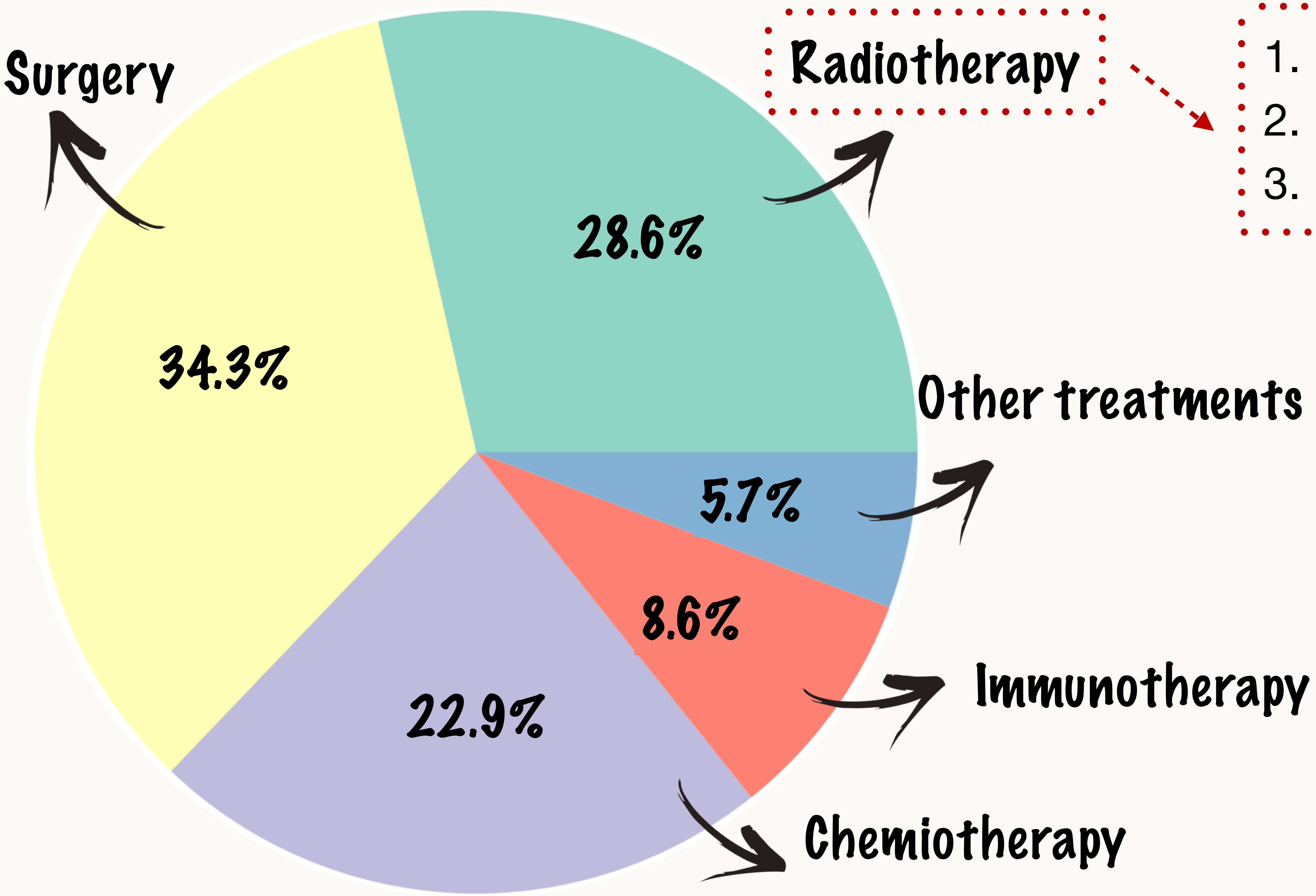
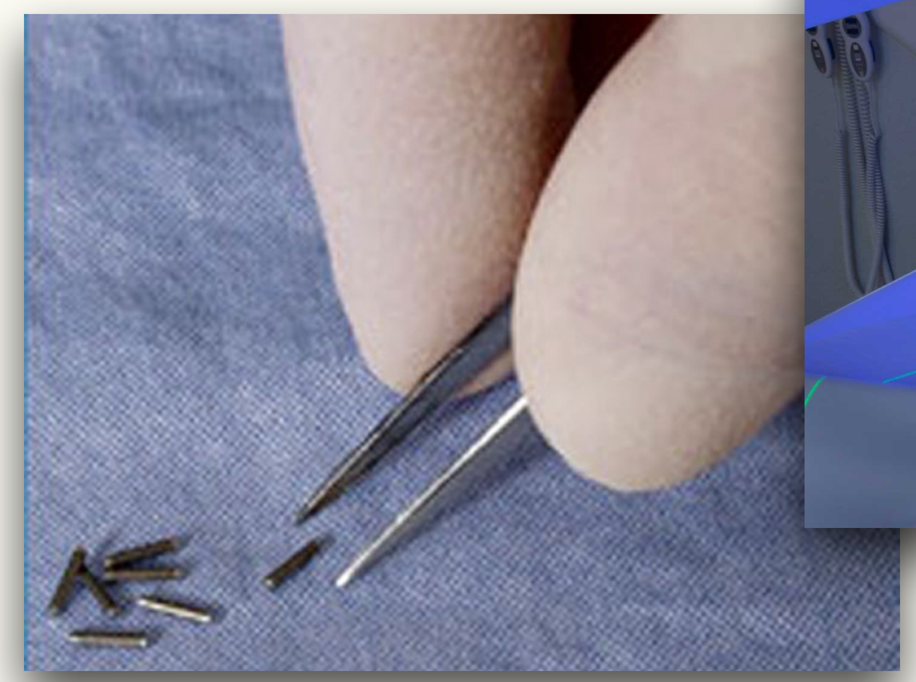


Radiation Therapy

Radiotherapy uses ionizing radiation to target and destroy malignant cells. The principle is based on **inducing DNA damage** in tumor cells, disrupting replication and leading to cell death.



1. External Beam Radiotherapy (EBRT) 70%;
2. Brachytherapy 20%;
3. Others 10%.

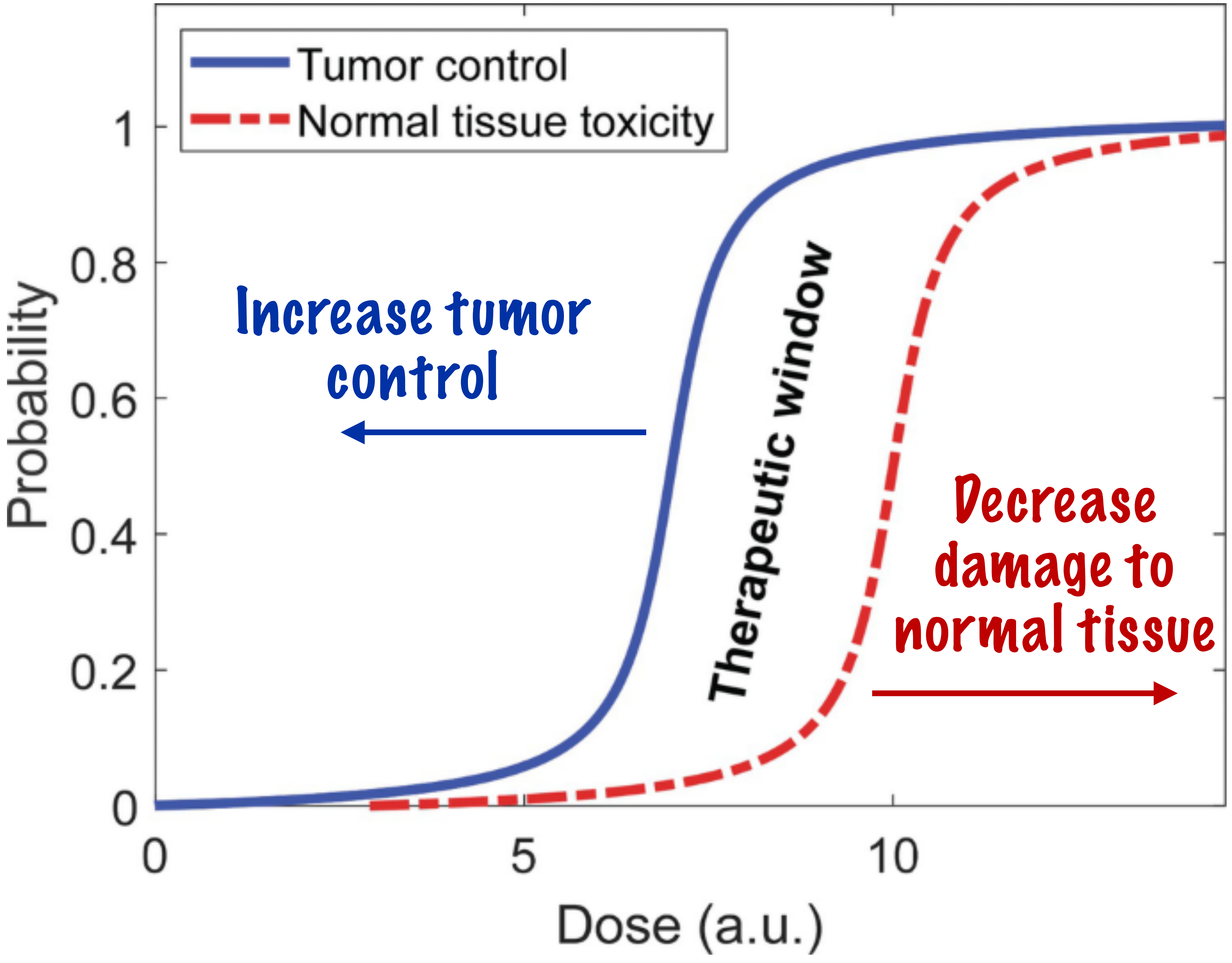


Main Parameter:

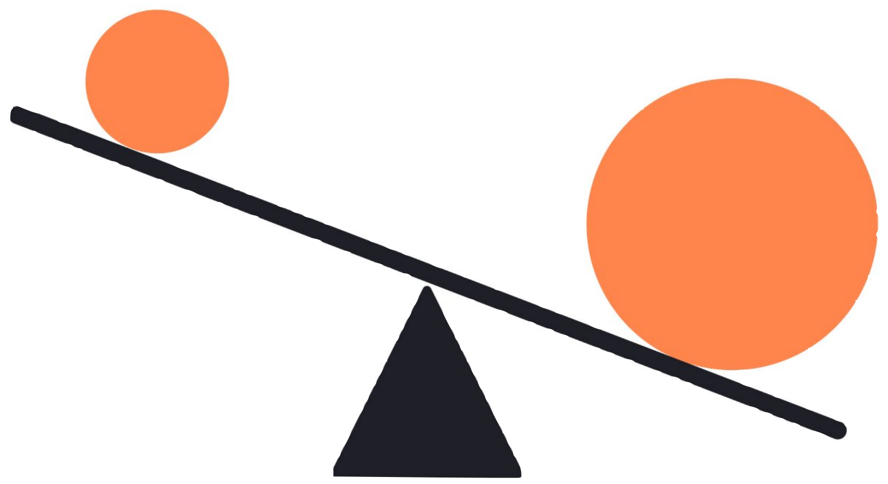
$$Dose = \frac{dE}{dm}[Gy]$$

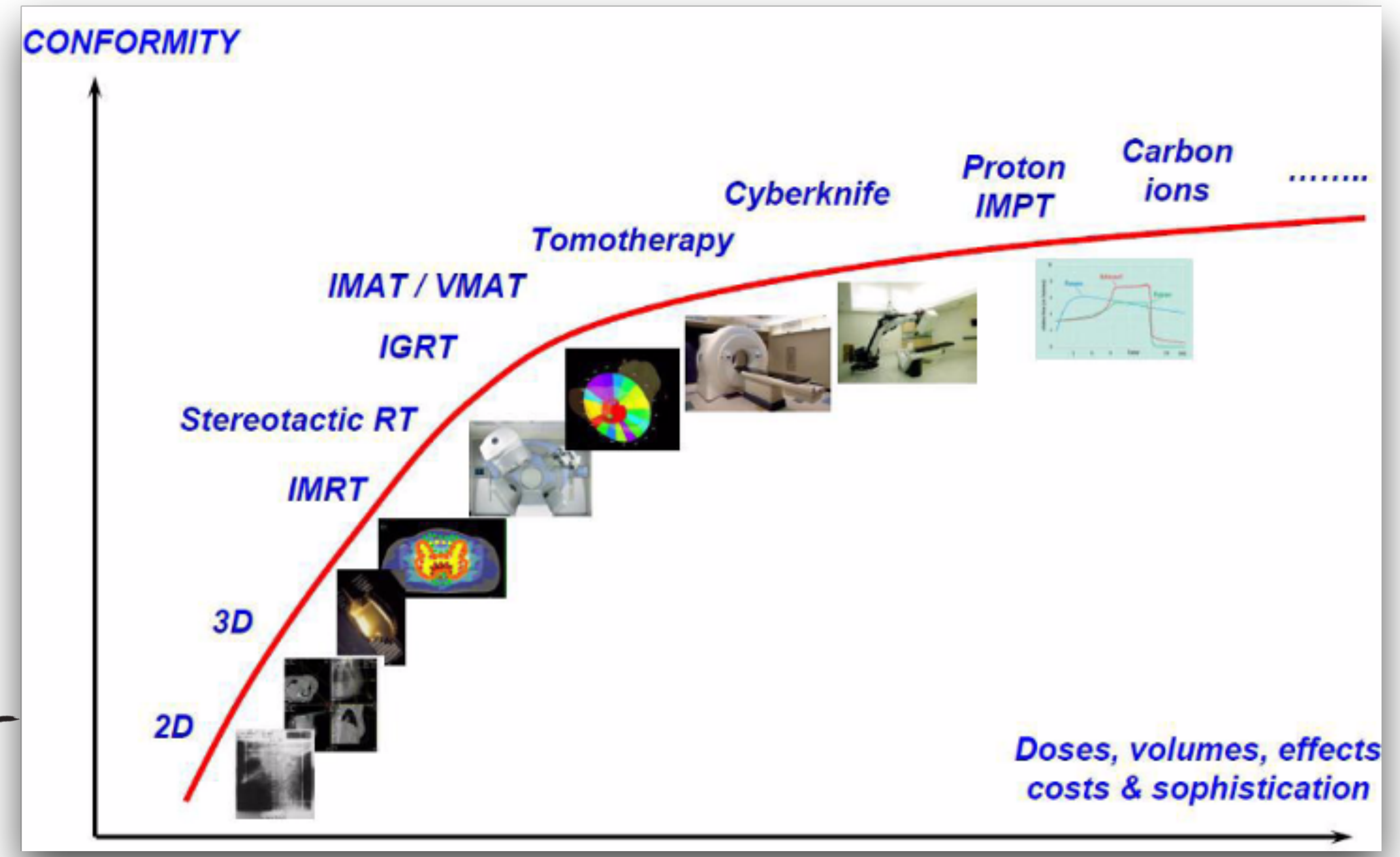
RT Conformality

The paradigm of modern radiotherapy is **CONFORMALITY**: to give as much as possible dose to the tumor region saving as much as possible the surrounding healthy tissues



Careful balance is needed to give enough dose to control the tumor growth without damaging healthy tissues.





Impressive improvement in the last 30 years, but state of the art techniques of radiotherapy (IGRT, IMRT and stereotactic radiotherapy) seems to approach a plateau.

Type of Radiation

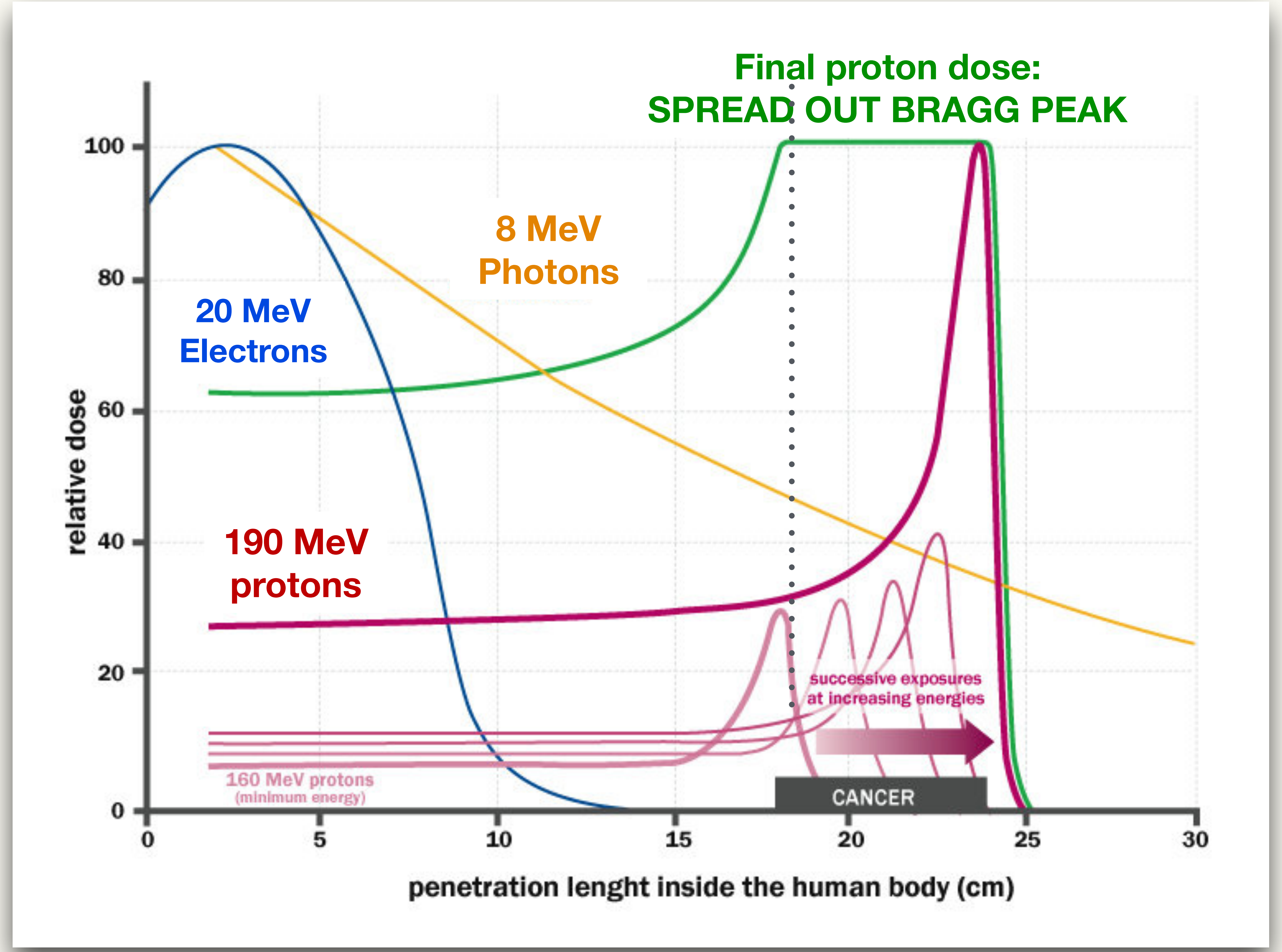
The players involved in the game are: **PARTICLES**. Depending on the type and location of the tumor, different techniques can be used, exploiting the characteristic dose release inside the patient.

Photon Therapy: deep tissue penetration, suitable for treating tumors located at various depths.

Low-Energy Electron Therapy: shallow penetration, ideal for treating surface or near-surface tumors.

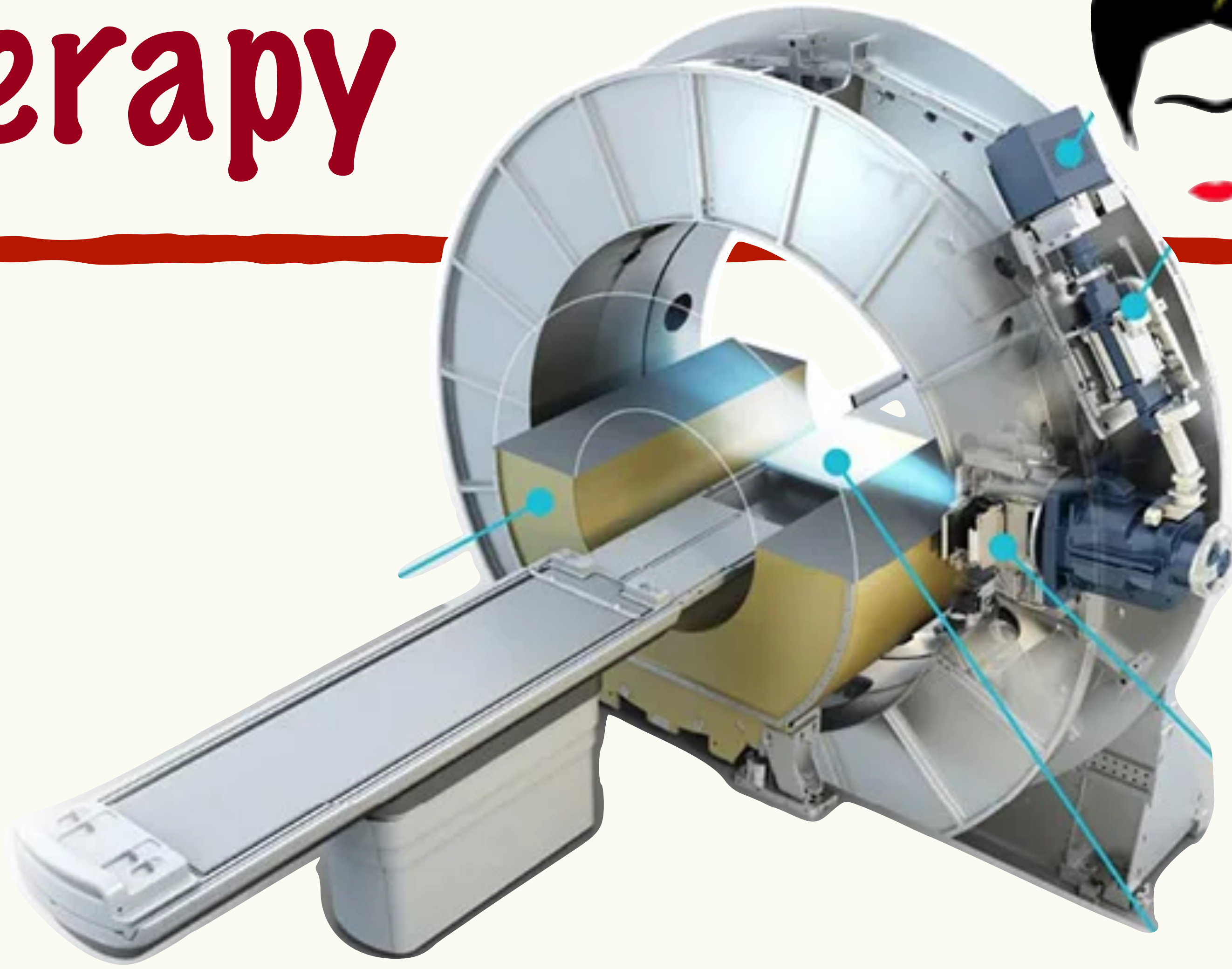
The quest for conformality fully exploited photon beams, and aims now to complex and (very) expensive beams like:

Particle Therapy (proton, Carbon Ions): intense localized energy deposition (Bragg peak), deep-seated tumors.



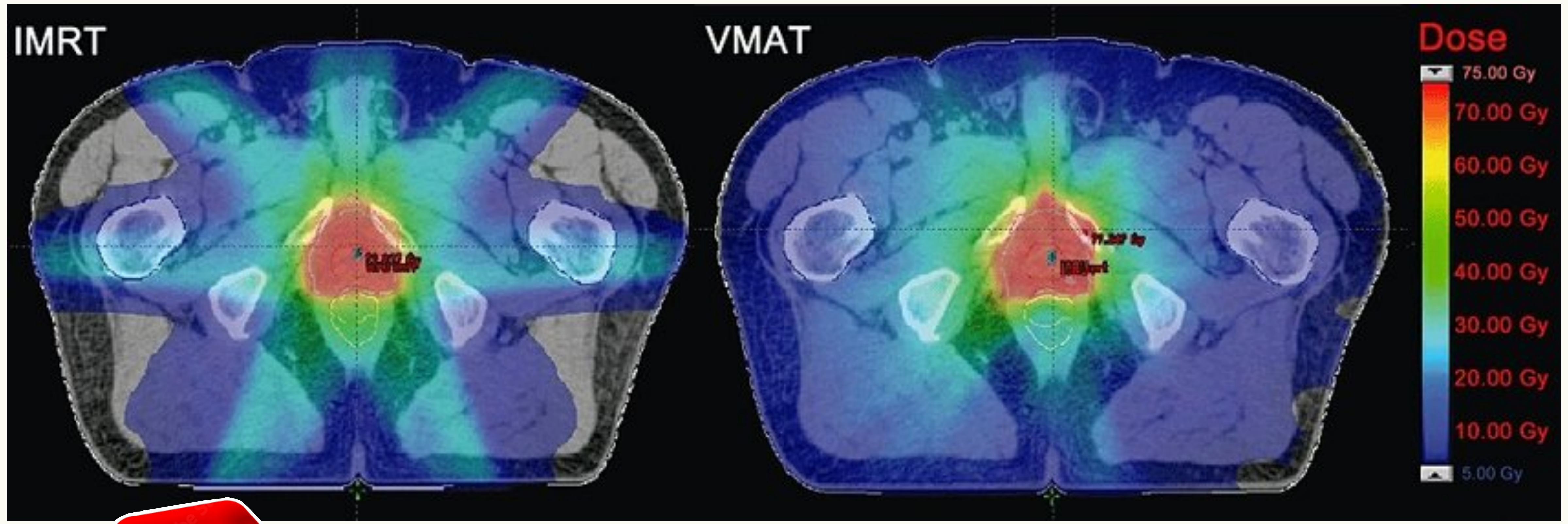
- 250 MeV proton from cyclotron;
- 350 MeV/nucleon carbon from synchrotron.

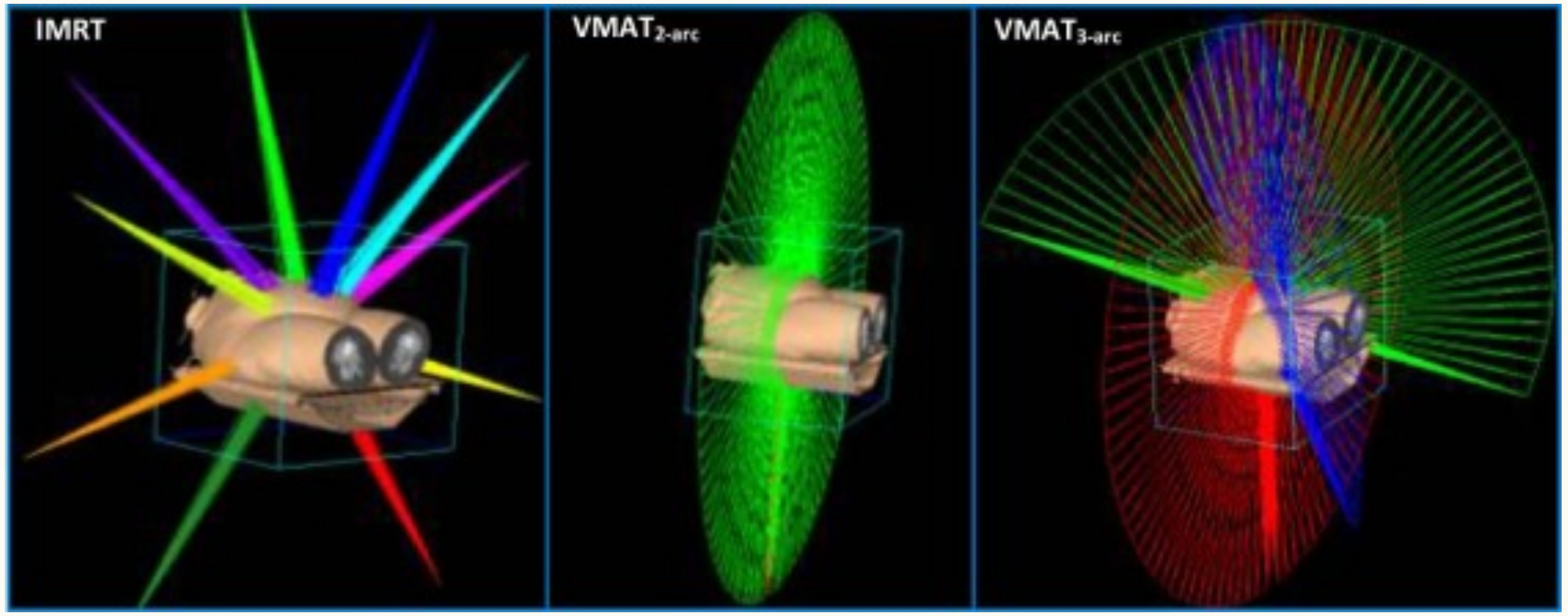
STANDARD Radiation Therapy



STATE OF THE ART:

- Multiple **6-8 MeV photon beams** from compact, light weight electron LINAC, with photon production on tungsten target;
- **Multiple field treatment** delivered in **multiple fractions** (up to 30). Up to 1-2 months;
- Each fraction delivers **~ Gy** to the tumor in **~ minute**;
- Very advanced IT technology, now also AI based.





MAIN LIMITATIONS:

- Radio resistant, bulky tumors;
- Diffuse tumors -> metastases.

FLASH effect: the discovery

Reduction of toxicity in healthy tissues, while keeping the same efficacy in cancer killing, if the dose rate is radically increased (~**100 Gy/s**, or even more) with respect to conventional treatments (~**0.01 Gy/s**).

Dose-Rate per pulse

$$\dot{D}_p = \frac{D_p}{t_p}$$

Pulse dose

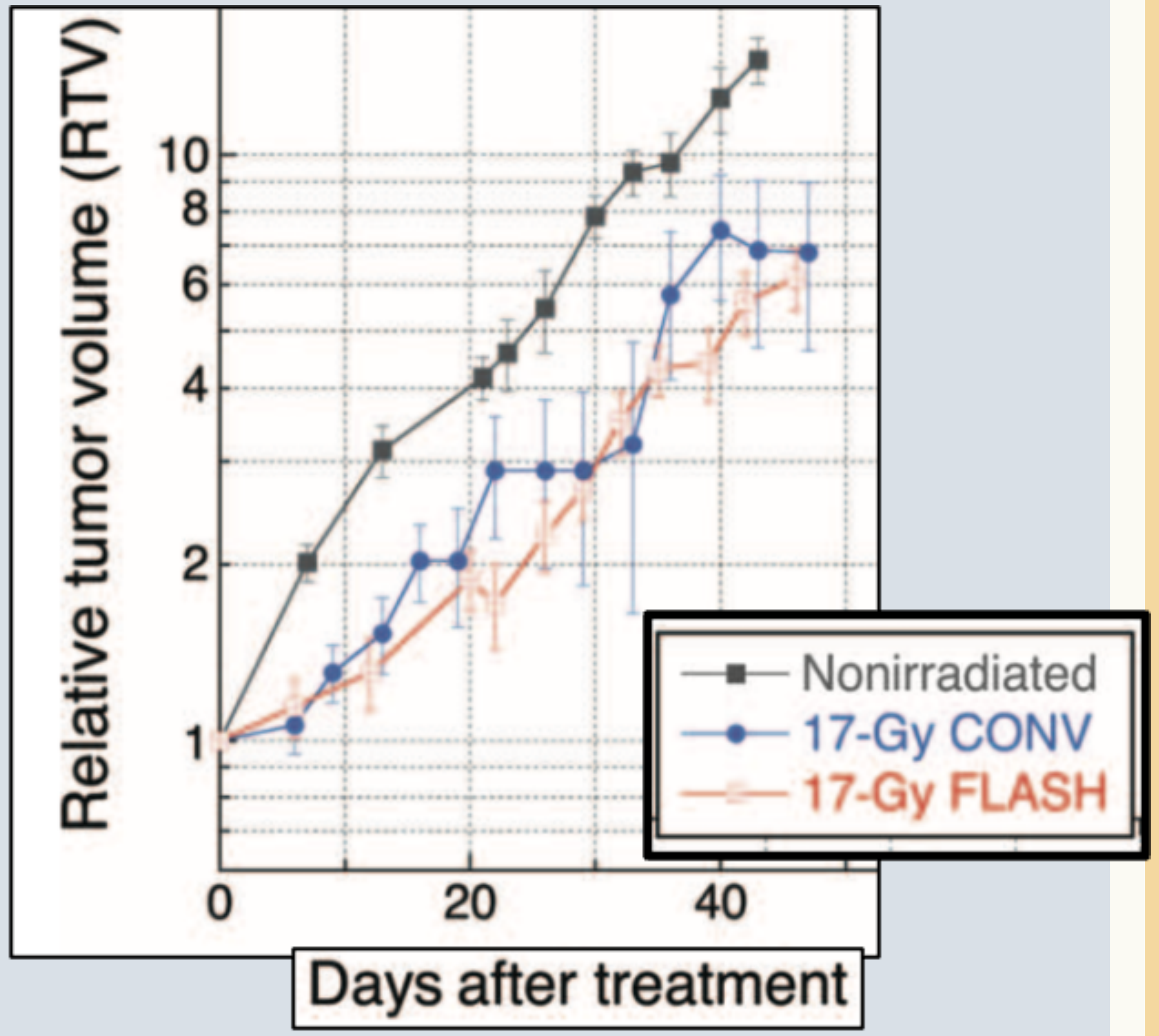
Pulse duration

Average Dose-Rate

$$\dot{D}_m = \frac{D_p}{t_r}$$

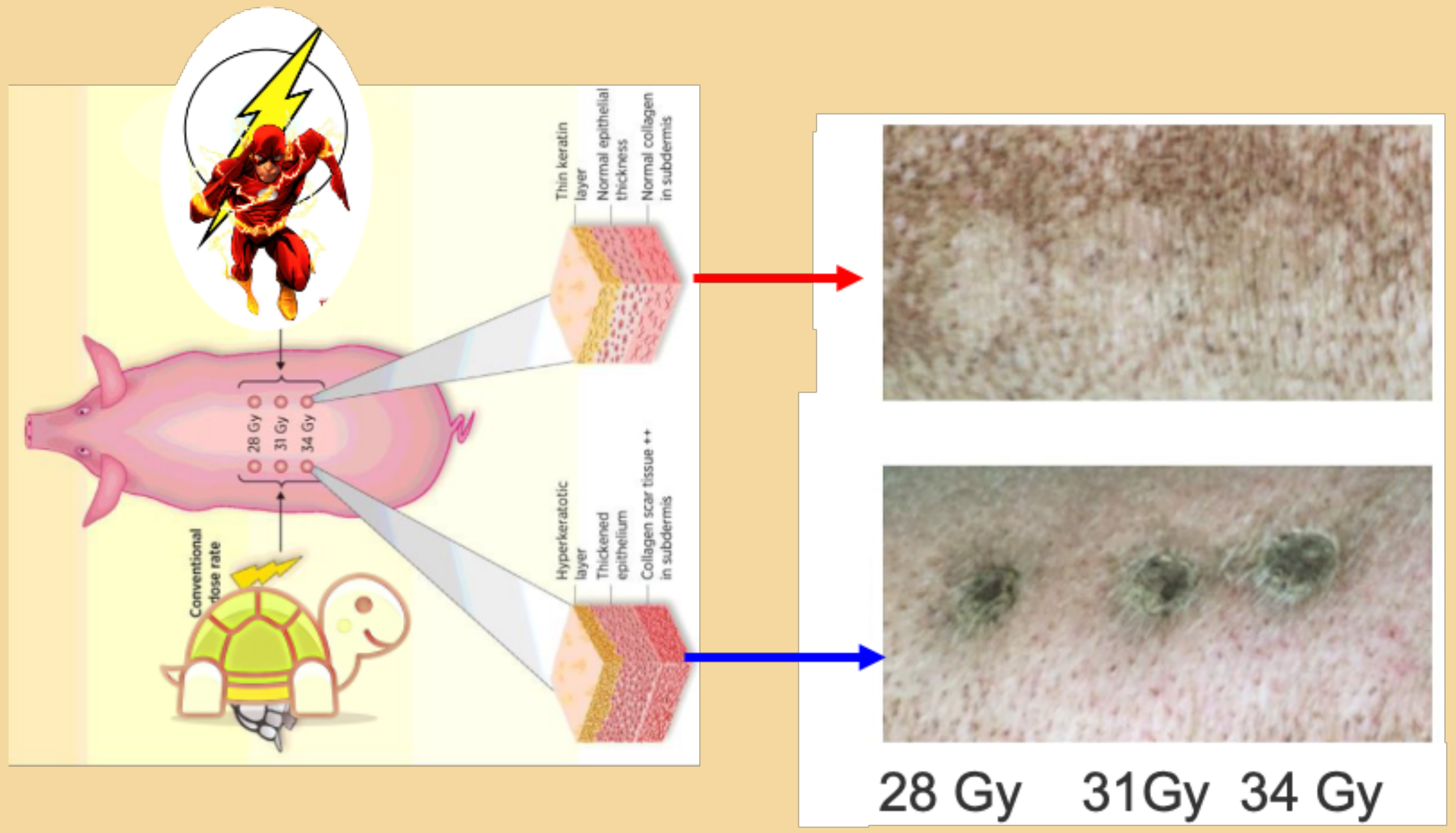
Time between pulses

Preservation of tumor control:

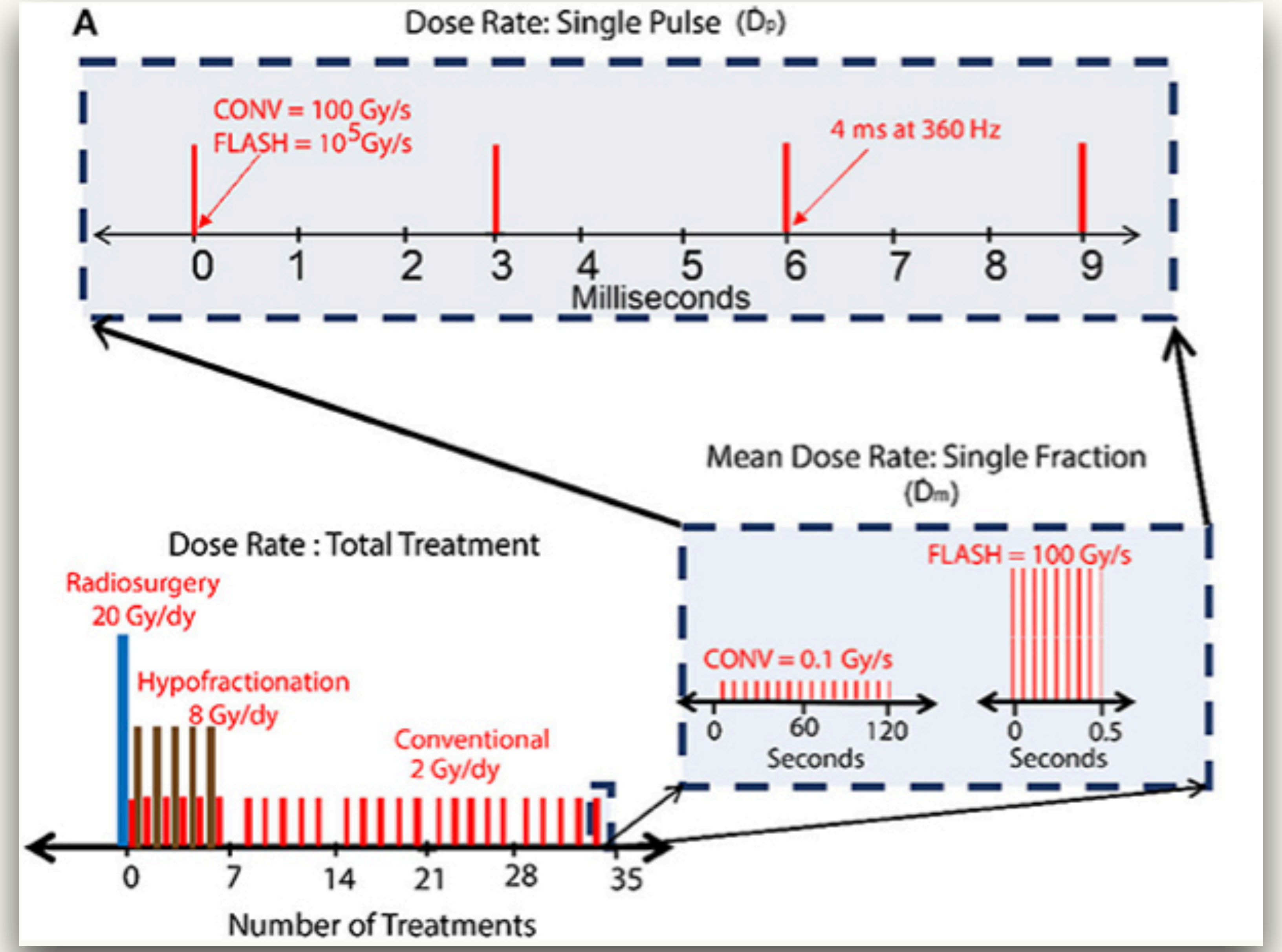


(V. Favaudon et al. 2014, Sci. Transl. Med.)

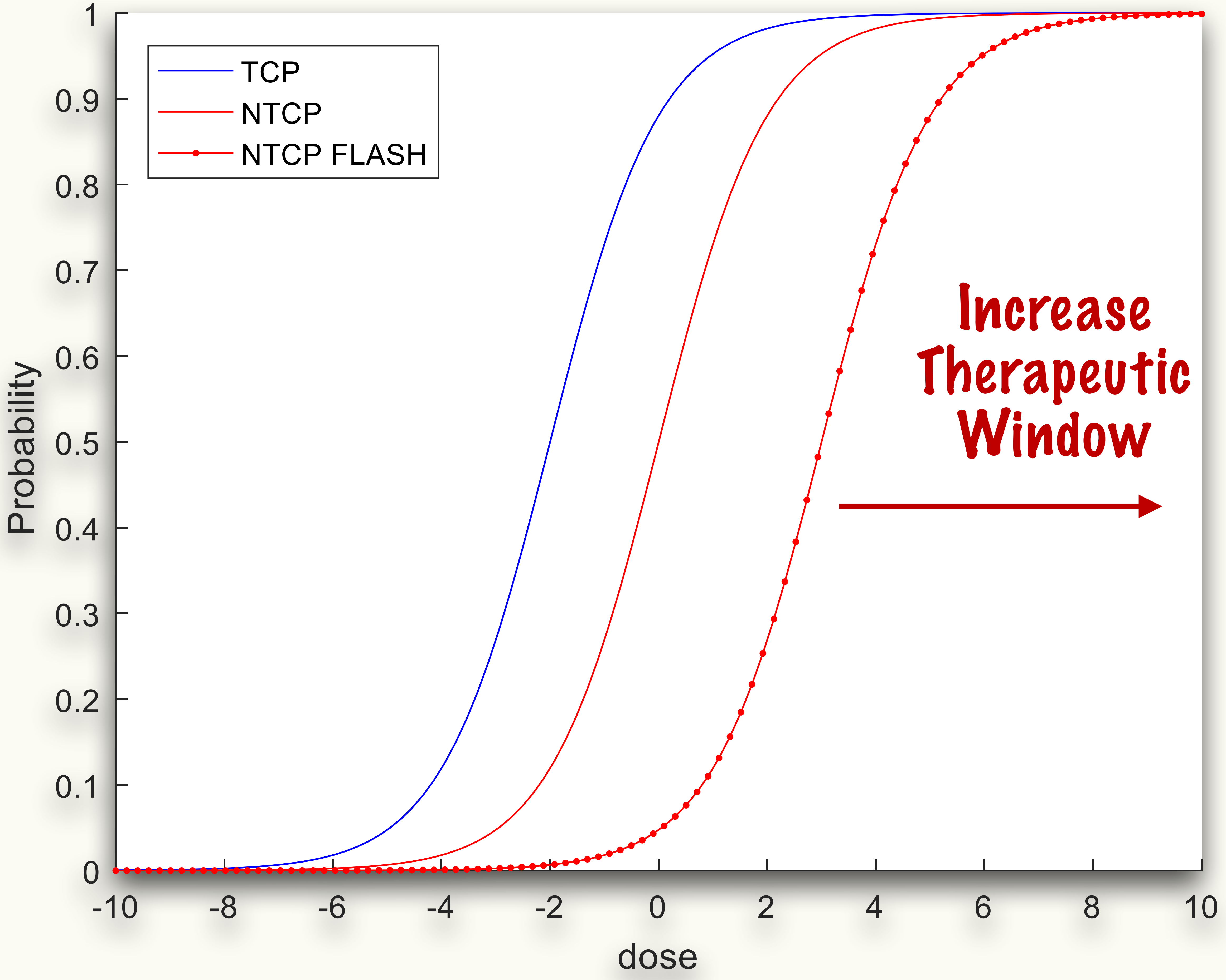
Decrease of the normal tissue response:



(Vozenin et al. 2019, Clin. Canc. Res.)



Decreased toxicity, same tumor control



TCP = Tumour Control Probability

NTCP = Normal Tissue Complication Probability

CONVENTIONAL RADIOTHERAPY:

Dose	Dose/rate	Irradiation time
~ 2 Gy/fraction	~ Gy/min	~ min

FLASH RADIOTHERAPY:

Dose	Dose/rate	Irradiation time
> 6 Gy/fraction	> 40 Gy/s	< 200 ms

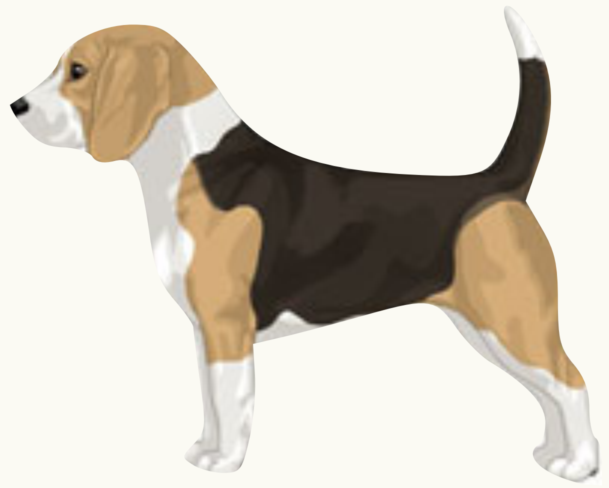
FLASH EFFECT: observations

D. Melanogaster

Hart et al. 2024

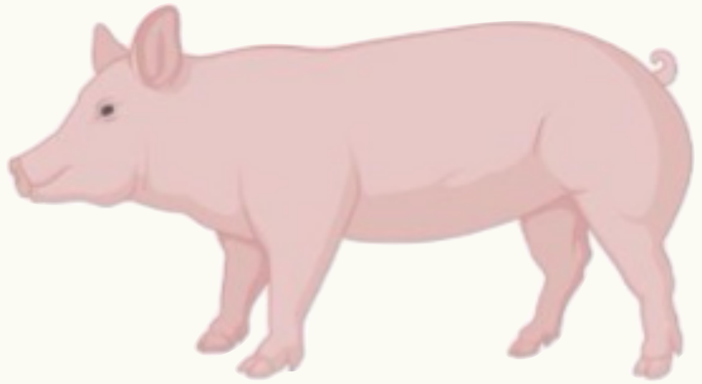
C. Elegans

Shoenauen et al. 2023



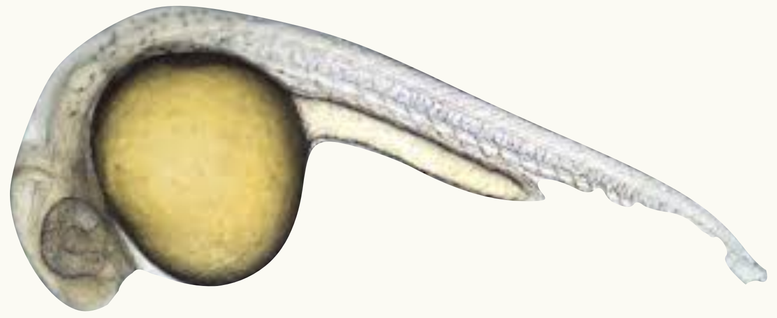
Canine skin

Konradsson et al. 2021
Velalopoulou et al. 2021
Gjaldbaek et al.2024



Mini pig skin

Vozenin et al. 2018
Rohrer Bley et al. 2022

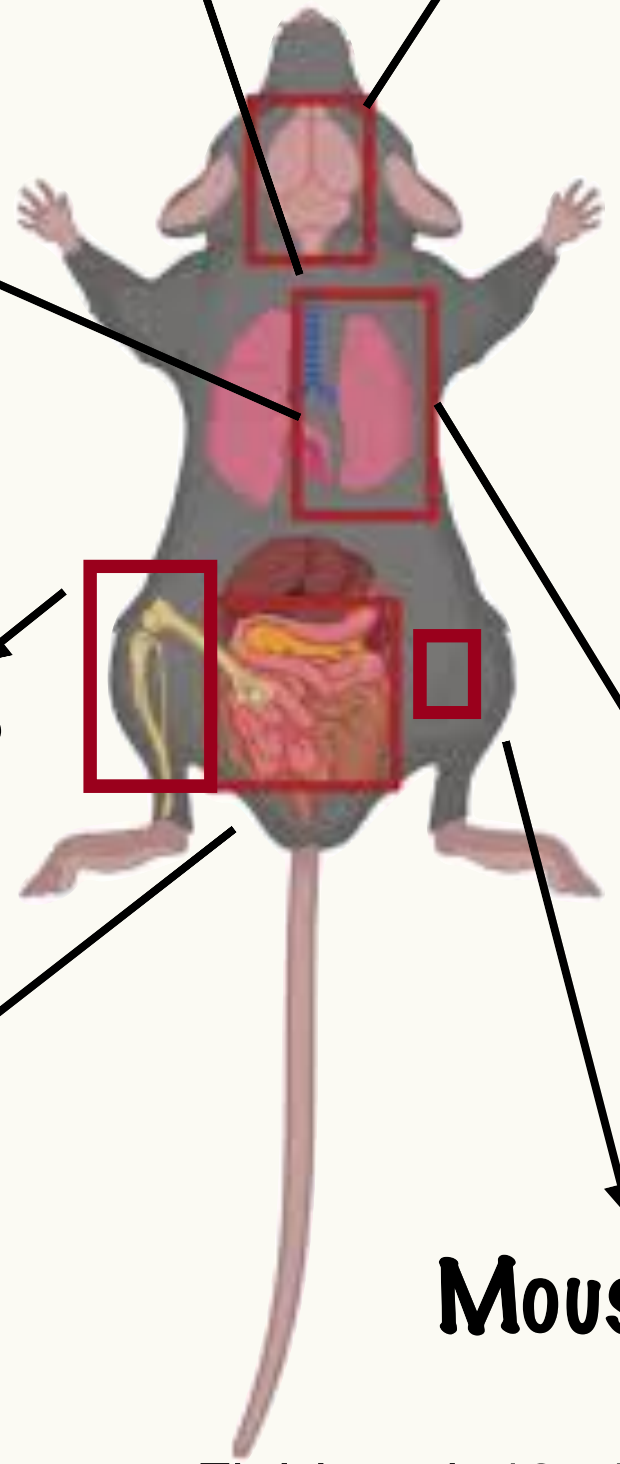


Zebrafish embryo

Montay-Gruel et al. 2019
Vozenin et al. 2019
Kacem et al. 2022
Beyreuther et al. 2019
Pawelke et al. 2021
Karsh et al. 2022
Saade et al. 2023
Horst et al. 2024

Feline skin

Vozenin et al. 2018
Rohrer Bley et al. 2022



Mouse esophagus

Ren et al. 2024

Mouse brain

Montay-Gruel et al. 2017
Montay-Gruel et al. 2019
Simmons at al. 2019
Montay-Gruel et al. 2020
Limoli et al. 2023
Simmons at al. 2019
Allen et al. 2020
Montay-Gruel et al. 2018
Alaghband et al. 2020
Dokic et al. 2022
Williams et al. 2022
Alaghband et al. 2023
Dickstein et al. 2024
Mertinez-Rovira et al. 2024

Mouse heart

Kim et al. 2024

Mouse hematopoiesis

Chabi et al. 2020

Mouse lung

Favaudon et al. 2014
Fouillade et al. 2020
Gao et al. 2022

Mouse gut

Levy et al. 2020
Kim et al. 2021
Ruan et al. 2021
Eggold et al. 2022
Velalopoulou et al. 2021
Gao et al. 2022
Moral et al. 2024
Vergidanis et al. 2024

Mouse skin, bone, muscle

Field et al. 1974
Inada et al. 1980
Hendry et al. 1982
Soto et al. 2020
Rudigkeit et al. 2024
Tinganelli et al. 2024
Velalopoulou et al. 2021

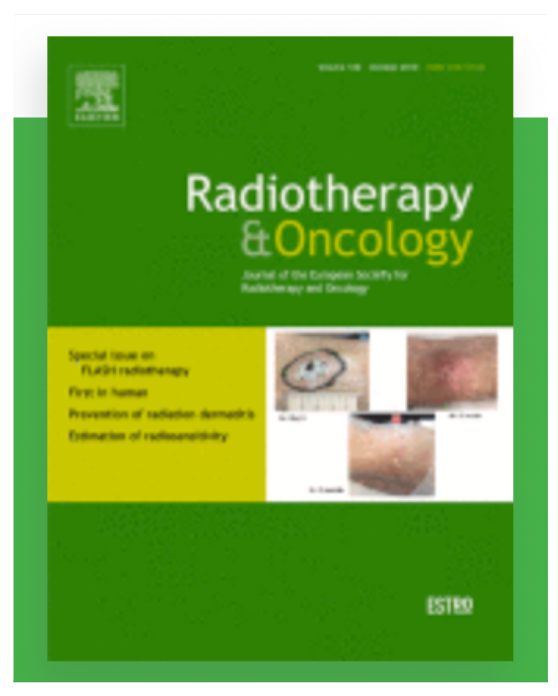
Cunningham et al. 2021
Sorensen et al. 2022
Tinganelli et al. 2022
Vergidanis et al. 2024
Demidova et al. 2024

FLASH EFFECT: humans trial

First in Human

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a b], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a b c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c 1], Marie-Catherine Vozenin [a b 1]



Temporal evolution of the treated lesion: (a) before treatment; the limits of the PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

Gjaldbaek et al.2024

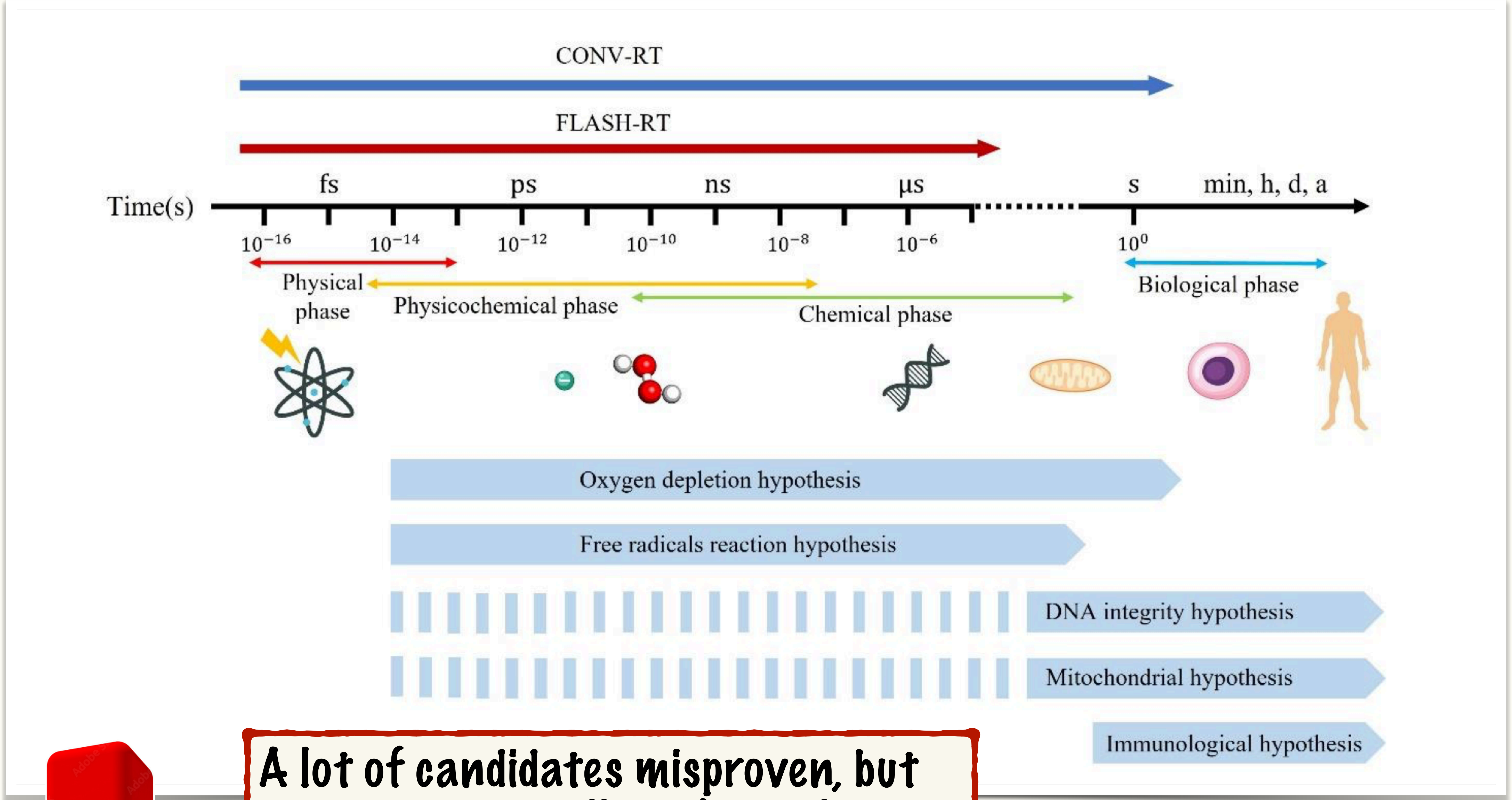
Study	Radiation
FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases in the Thorax (FAST-02)	Proton
Irradiation of Melanoma in a Pulse (IMPulse)	Electron
FLASH Radiotherapy for Skin Cancer (LANCE)	Electron
FLASH Radiotherapy for Non Melanoma Skin Cancer (ULISSE)	Electron

Horst et al. 2024

Velalopoulou et al. 2021

FLASH EFFECT: the mechanism

Radiation damage spans many orders of magnitude both on the space and time scale: the FLASH irradiation mixes them up tightely.



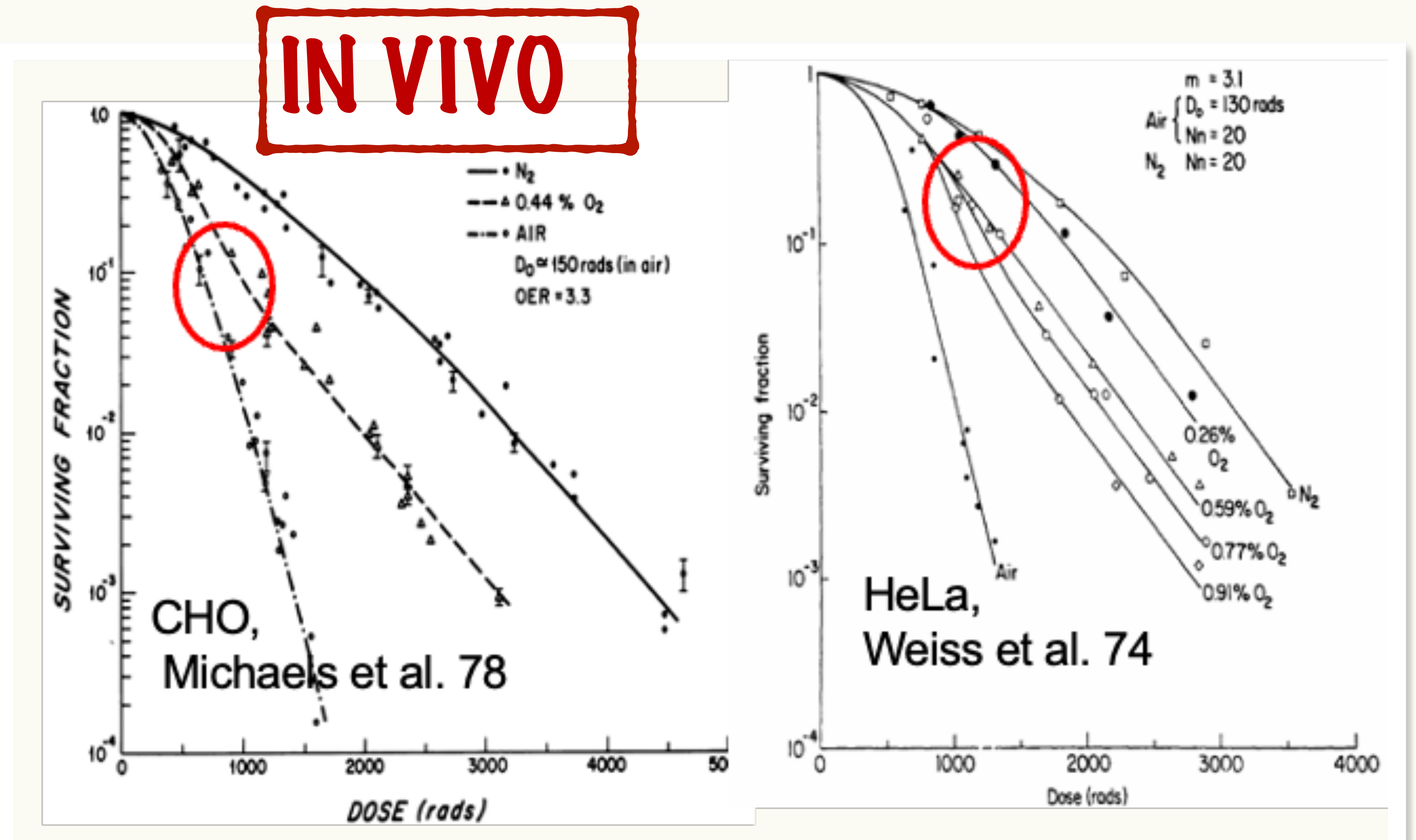
A lot of candidates misproven, but many options still on the table...

Without a mechanism the implementation is forced to go with a **phenomenological approaches**.

1. **Transient oxygen depletion :**
   UHDR consume local oxygen rapidly, creating temporary hypoxia.
2. **Differential ROS dynamics:**
   Rapid radiation delivery may alter the production and decay of reactive oxygen species.
3. **Immune modulation:**
   FLASH may preserve immune cell function better than conventional RT, enhancing anti-tumor immunity while sparing normal tissue inflammation.
4. **Reduced endothelial damage:**
   UHDR delivery may protect vascular structures in normal tissue preventing radiation-induced inflammation and late fibrosis.
5. **DNA repair kinetics:**
   FLASH might influence the timing or efficiency of DNA repair pathways differently in normal vs. tumor cells.

FLASH EFFECT: the role of Oxygen

Oxygen is well known to have a role since early FLASH experiments in the 60ies, confirmed in cell cultures, tail clamp exp., hyperbaric breathing etc.



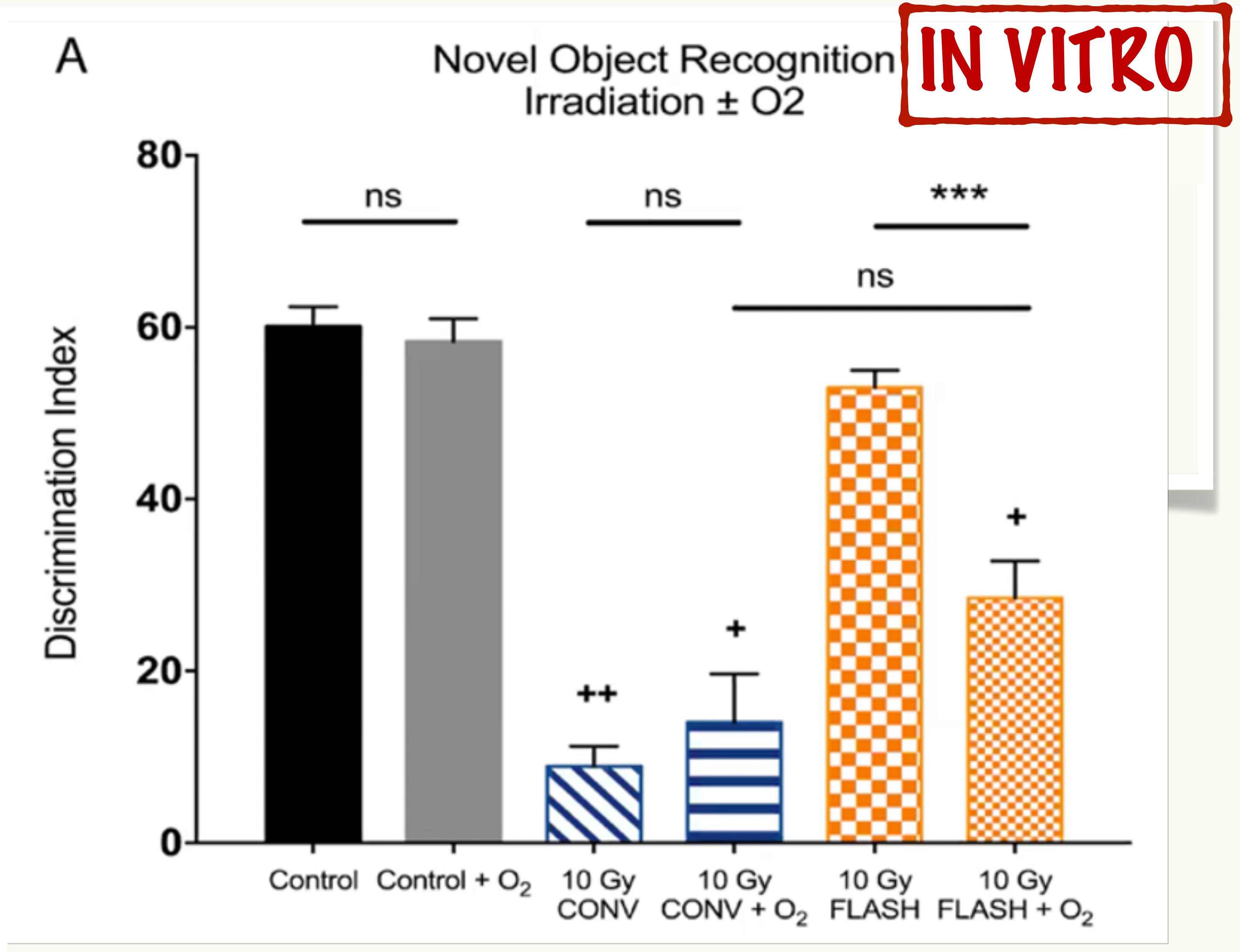
- **Oxygen is a radiosensitizer**: It enhances radiation-induced DNA damage by stabilizing DNA radicals.

- **At FLASH dose rates**, radiation deposits large amounts of energy in milliseconds, **rapidly consuming available oxygen** through water radiolysis and ROS formation.

- This results in **transient hypoxia**, which protects normal tissues by reducing the fixation of DNA damage.

Tumor tissues are often already hypoxic → less affected by further oxygen depletion.

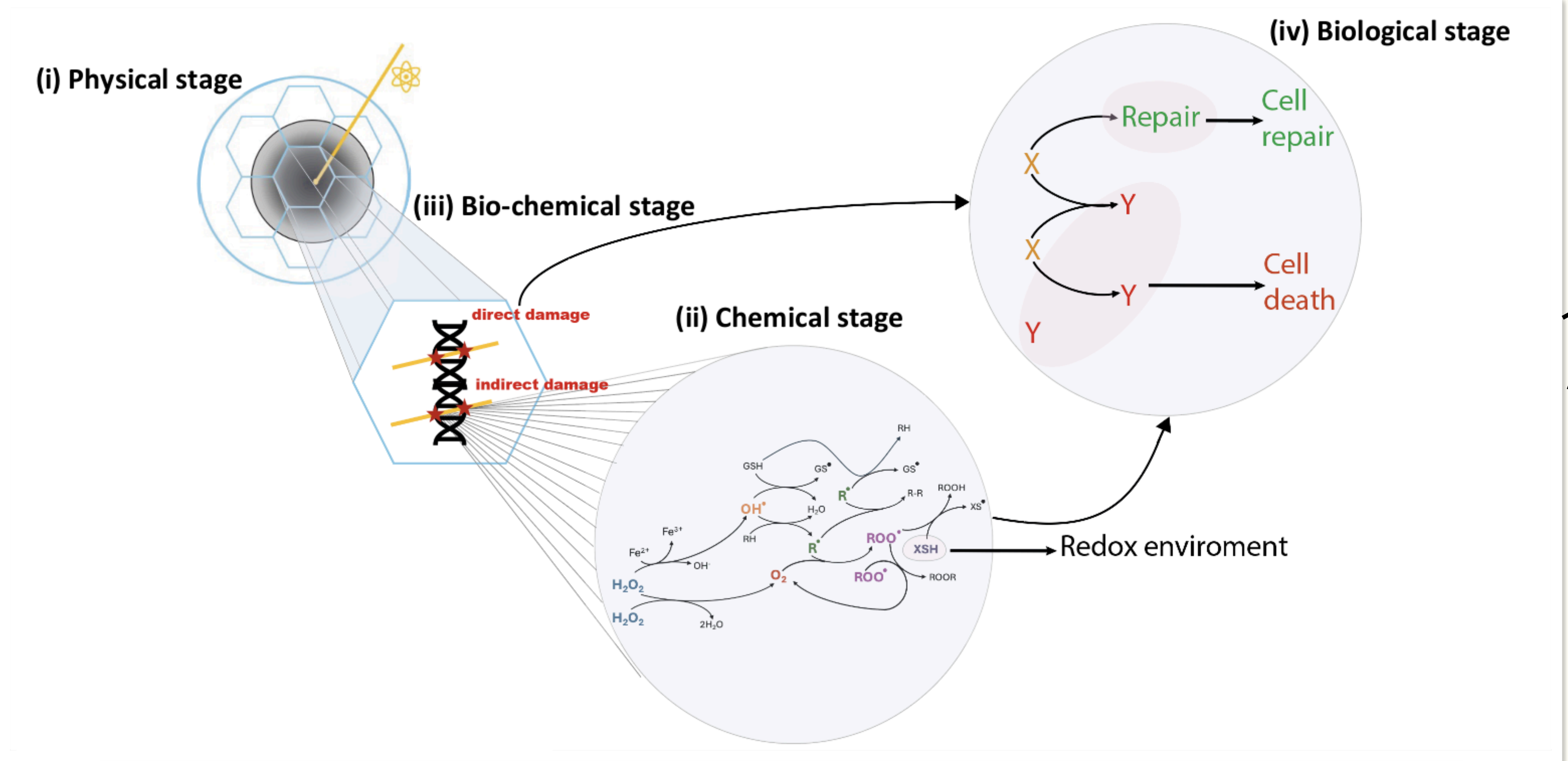
Normal tissues are well-oxygenated → more likely to benefit from protective hypoxia during FLASH.



Pierre Montay-Gruel, et al. PNAS (2019)

FLASH EFFECT: the MS-GSM2 model

The **Multi-Scale Generalized Survival Model 2 (MS-GSM2)** is a theoretical framework that aims to explain the FLASH effect by integrating biological responses at multiple scales—from molecular damage to tissue-level recovery.



Provides a quantitative model to predict survival curves under FLASH vs. conventional irradiation.

Helps distinguish between tumor and normal tissue responses based on their repair capacities and microenvironment.

FLASH EFFECT: the MS-GSM2 model

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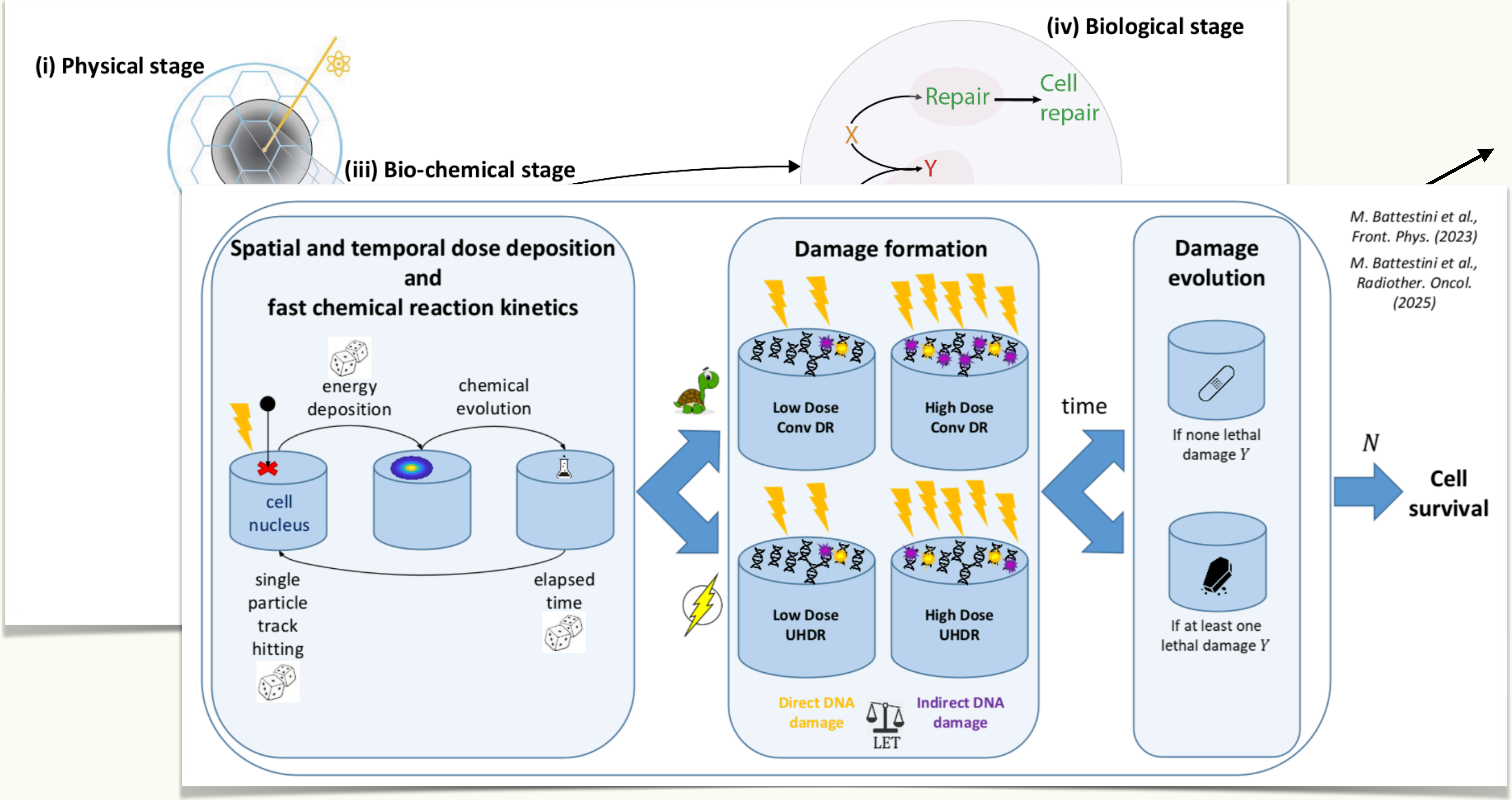


M. Battestini et al., Front. Phys. (2023)

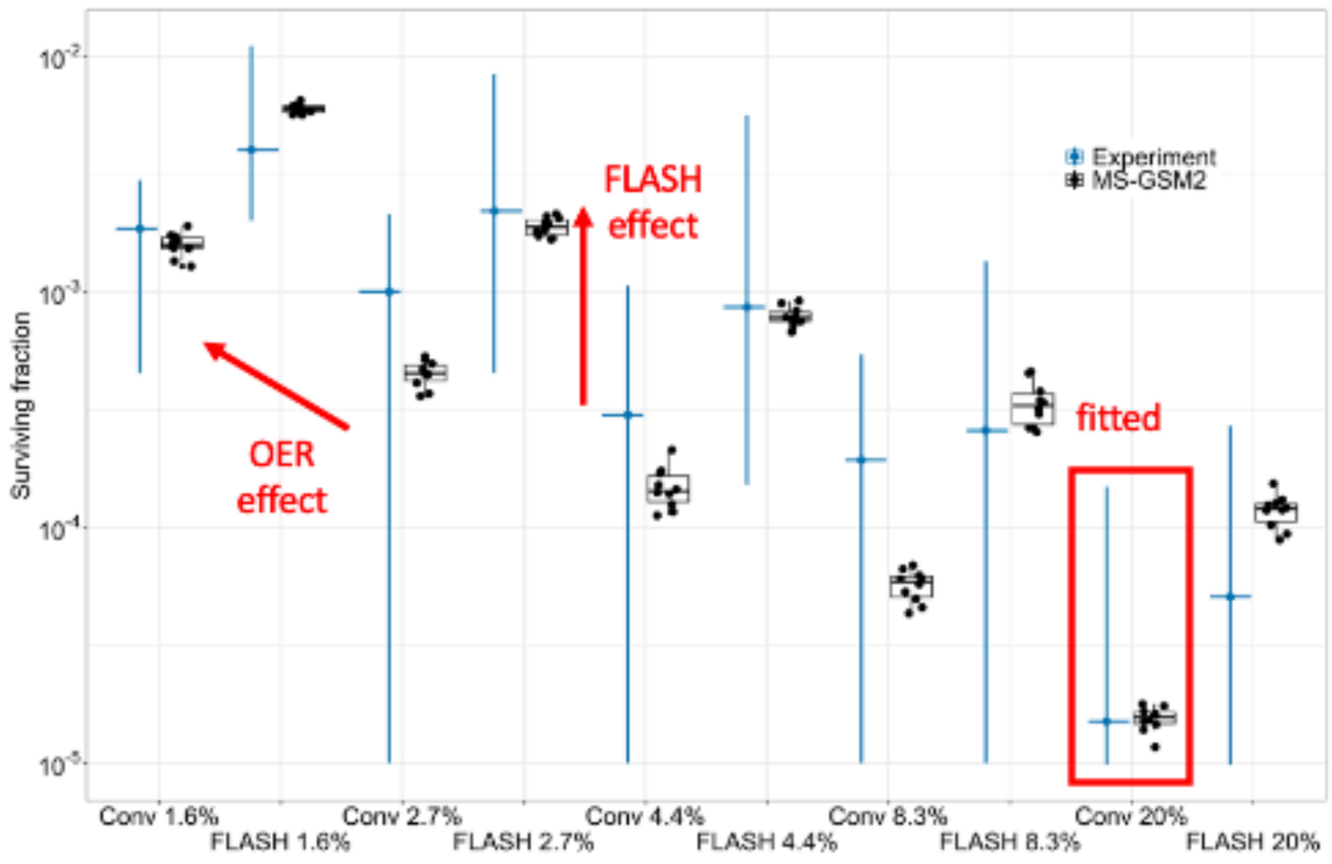
M. Battestini et al., Radiother. Oncol. (2025)

Provides a quantitative model to predict survival curves under FLASH vs. conventional irradiation.

Helps distinguish between tumor and normal tissue responses based on their repair capacities and microenvironment.

FLASH EFFECT: the MS-GSM2 model

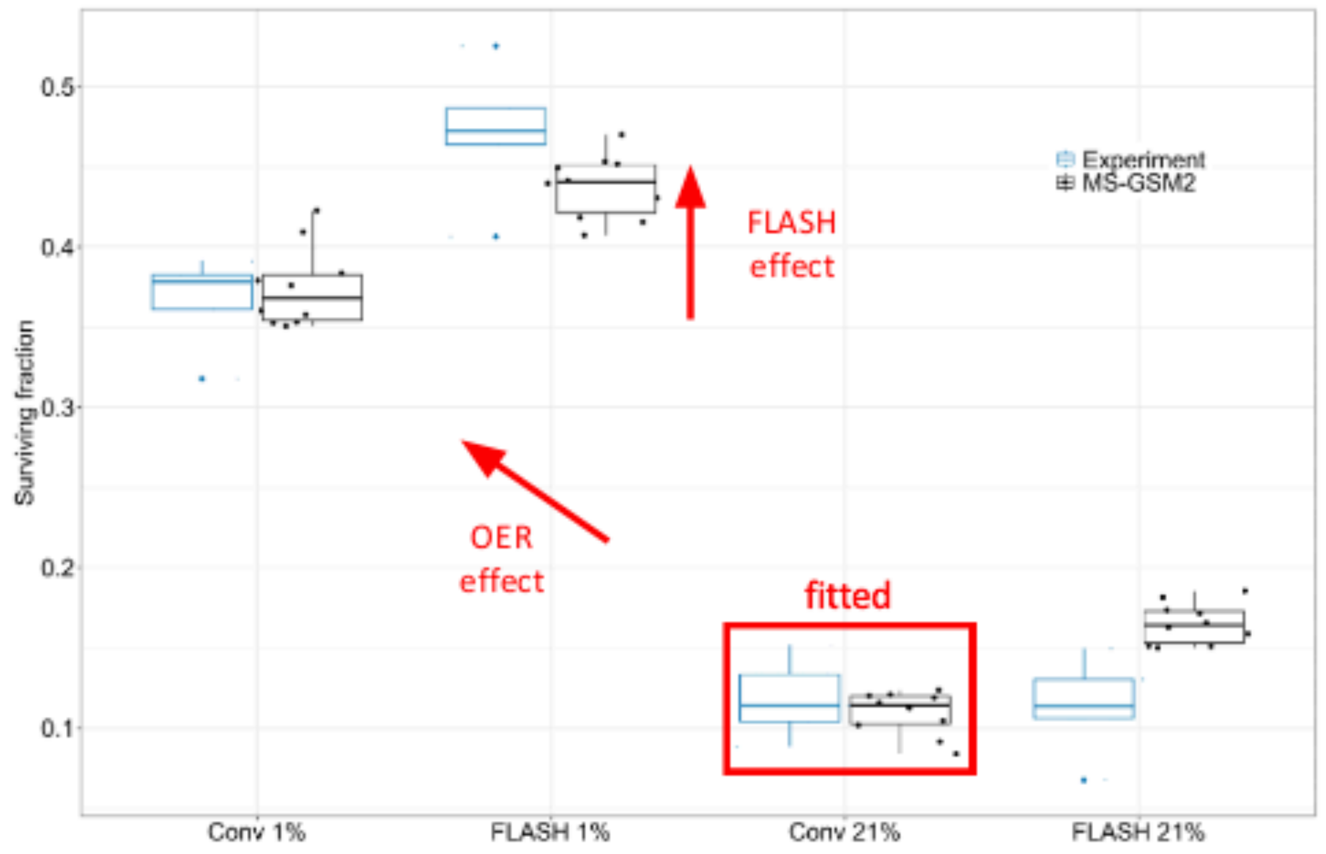
Electrons (10 MeV)



Exp: Adrian et al., Br. J. Radiol. (2020)

- DU145 cell line
- 18.0 Gy
- 14 Gy/min (Conv), 600 Gy/s (FLASH)

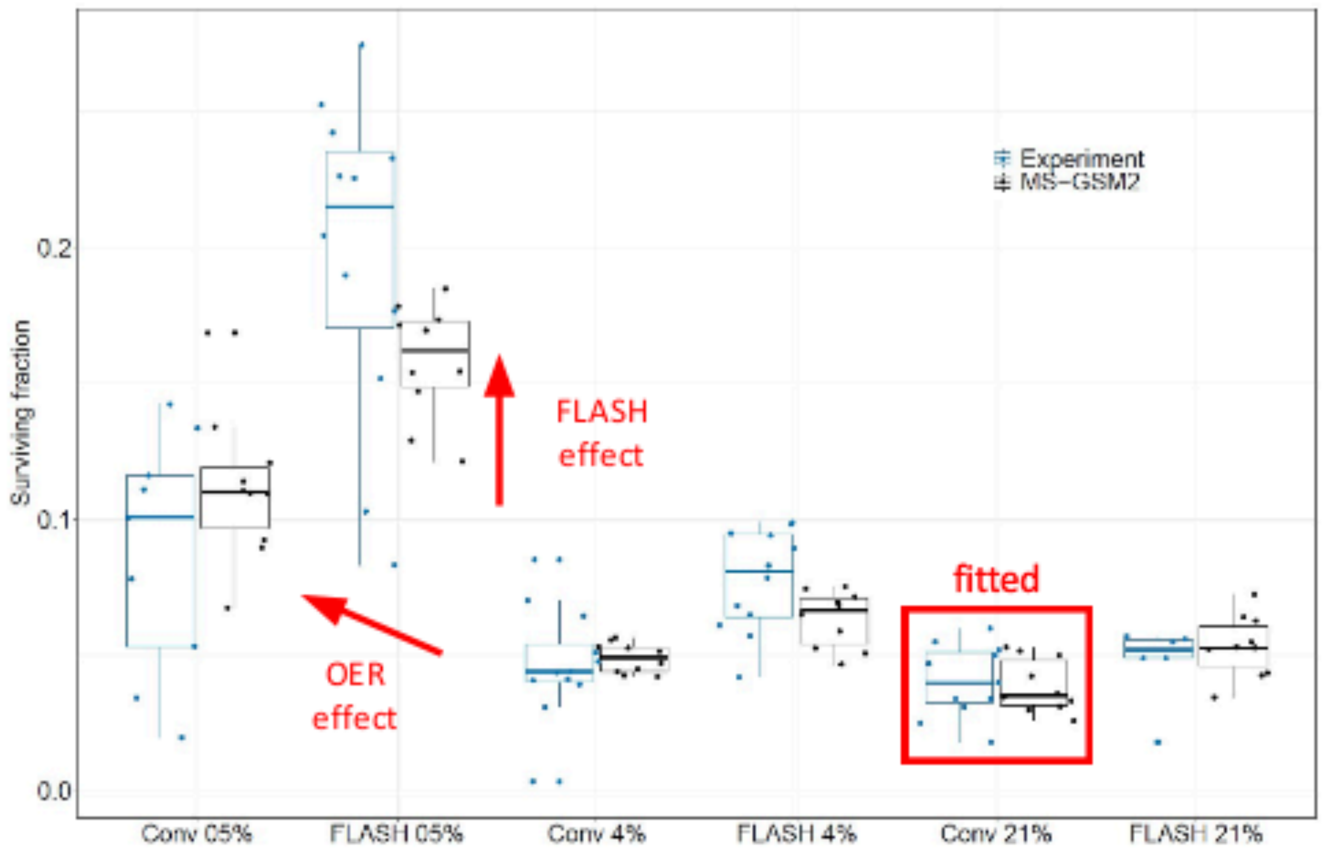
Helium ions (56 MeV/u)



Exp: Tessonnier et al., Int. J. Radiation Oncol. Biol. Phys. (2022)

- A549 cell line
- 8.0 Gy
- 0.1 Gy/s (Conv), 205 Gy/s (FLASH)

Carbon ions (280 MeV/u)



Exp: Tinganelli et al., Int. J. Radiation Oncol. Biol. Phys. (2022)

- CHO-K1 cell line
- 7.5 Gy
- 0.6 Gy/s (Conv), 70 Gy/s (FLASH)

M. Battestini et al., Radiother. Oncol. (2025)

MS-GSM2 simulations **match in vivo observations** of normal tissue sparing at dose rates >40 Gy/s.

Reproduces survival curves consistent with **mouse lung, brain, and gut** FLASH studies.

FLASH EFFECT: the Bohlen model

Sapienza Università di Roma — INFN

Biological dose — Physical dose

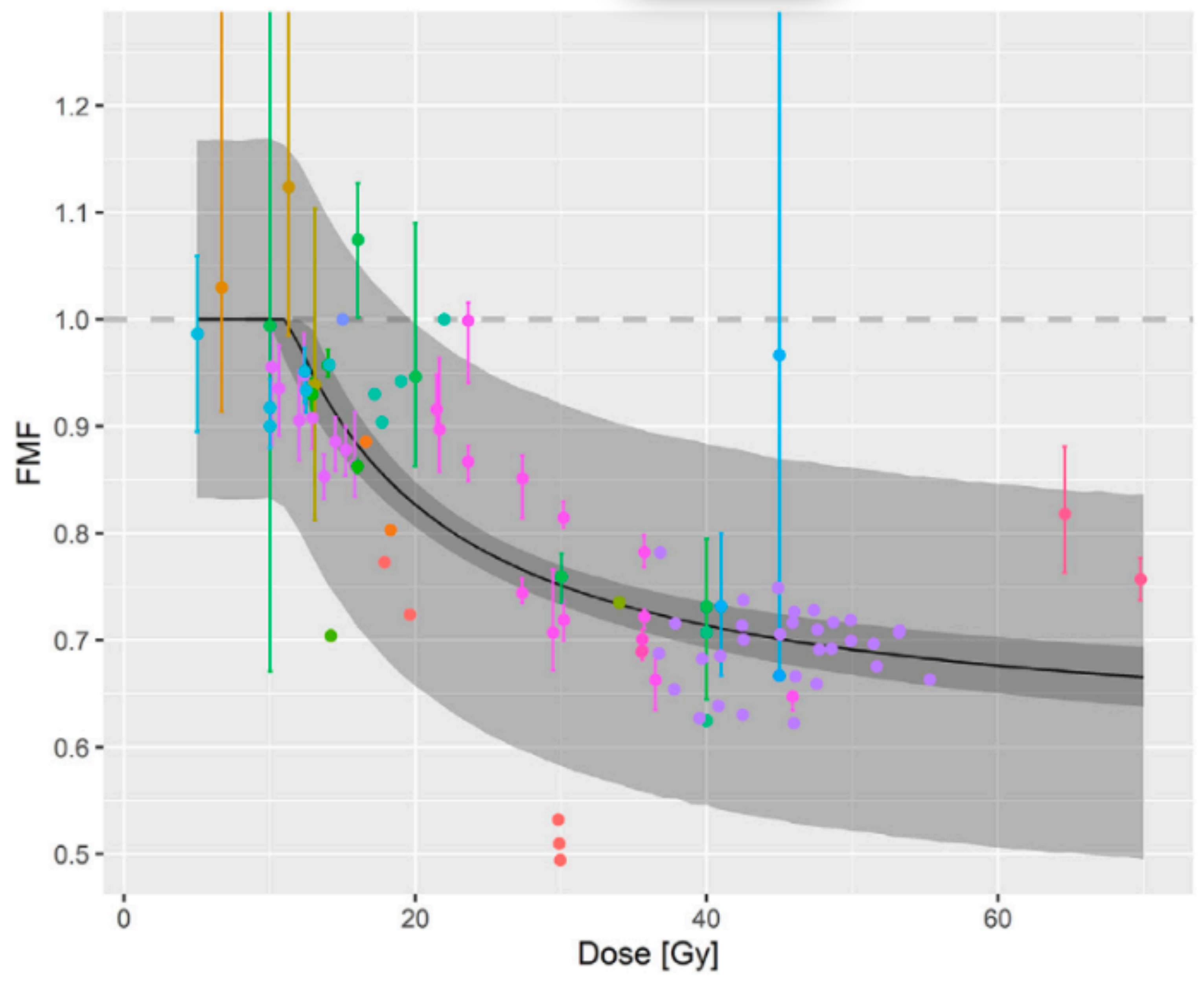
$$D_{FMF} = FMF \cdot D$$

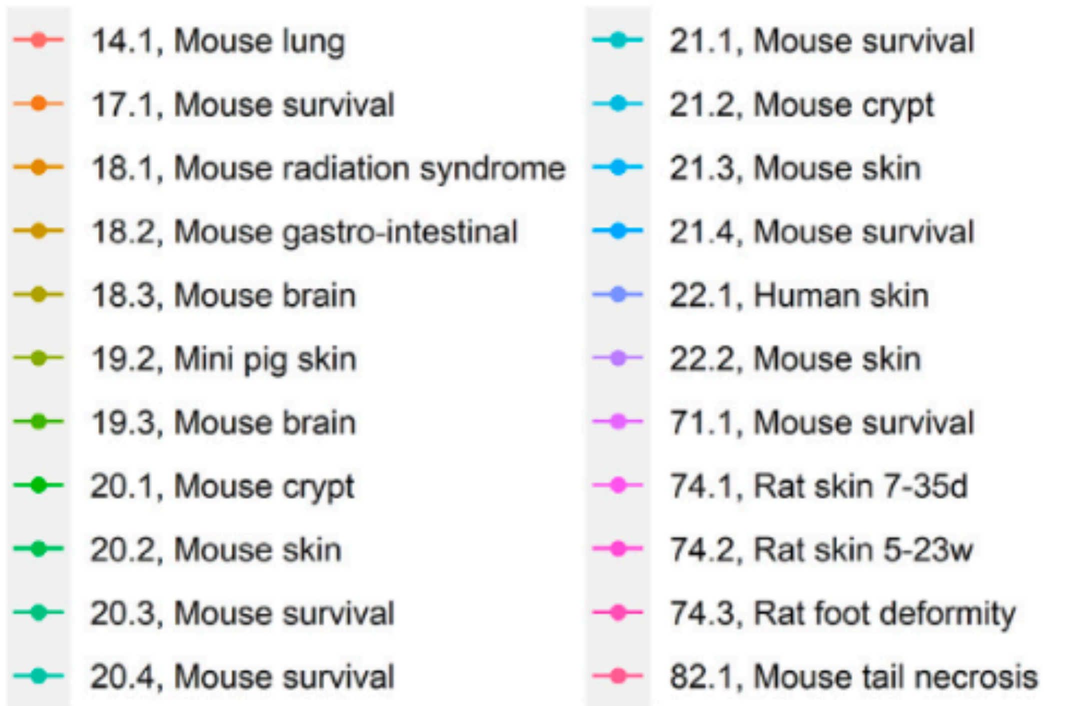
$$FMF = \begin{cases} 1 & \text{if } D \leq D_T \\ (1 - FMF^{min})\frac{D_T}{D} + FMF^{min} & \text{if } D > D_T \end{cases}$$

FMF → Reduction of radiation effect on healthy tissue.

CHUV Centre hospitalier universitaire vaudois

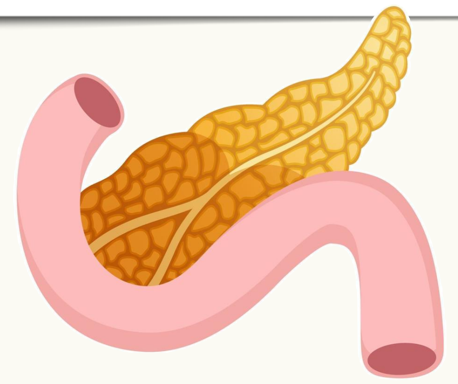
Taken from available data





Böhlen TT, Germond JF, Bourhis J, Vozenin MC, Ozsahin EM, Bochud F, Bailat C, Moeckli R. Normal Tissue Sparing by FLASH as a Function of Single-Fraction Dose: A Quantitative Analysis. Int J Radiat Oncol Biol Phys. 2022 Dec 1;114(5):1032-1044. doi: 10.1016/j.ijrobp.2022.05.038. Epub 2022 Jul 8. PMID: 35810988.

- FLASH effect seems to be triggered on normal tissues beyond quite high threshold (>6-8 Gy) → effective only on healthy tissue very close to the tumor.
- An hypothetical clinical treatment optimization must include the phenomenological FMF_{min} and the D_T parameters.



The threshold selects as target for FLASH treatment highly hypofractionated tumors (e.g. pancreas, lung etc)

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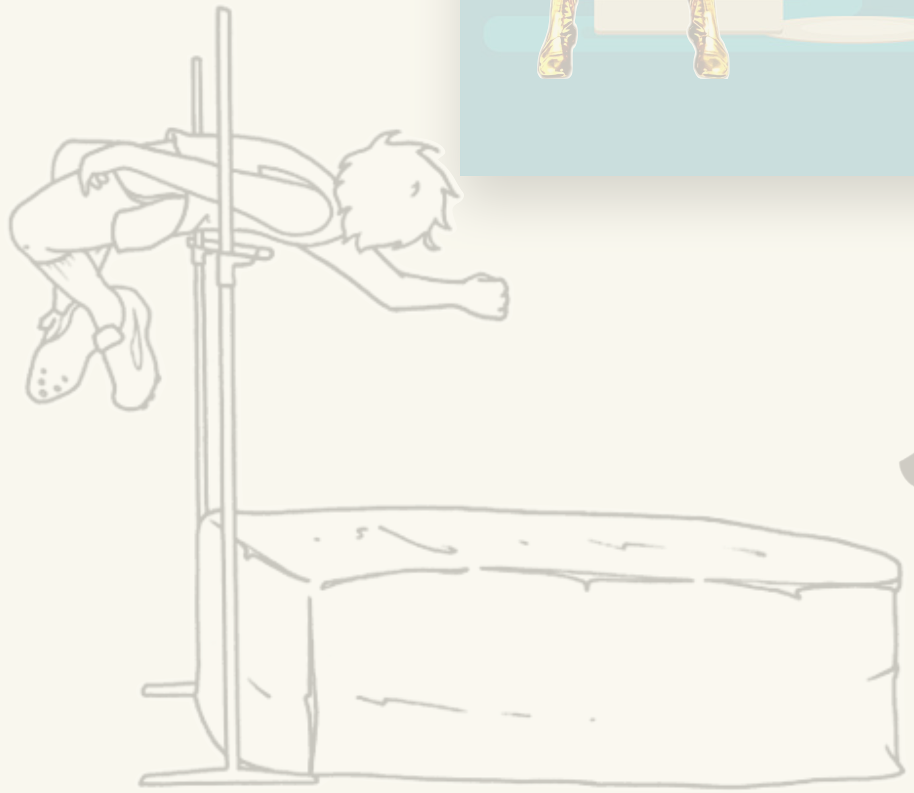
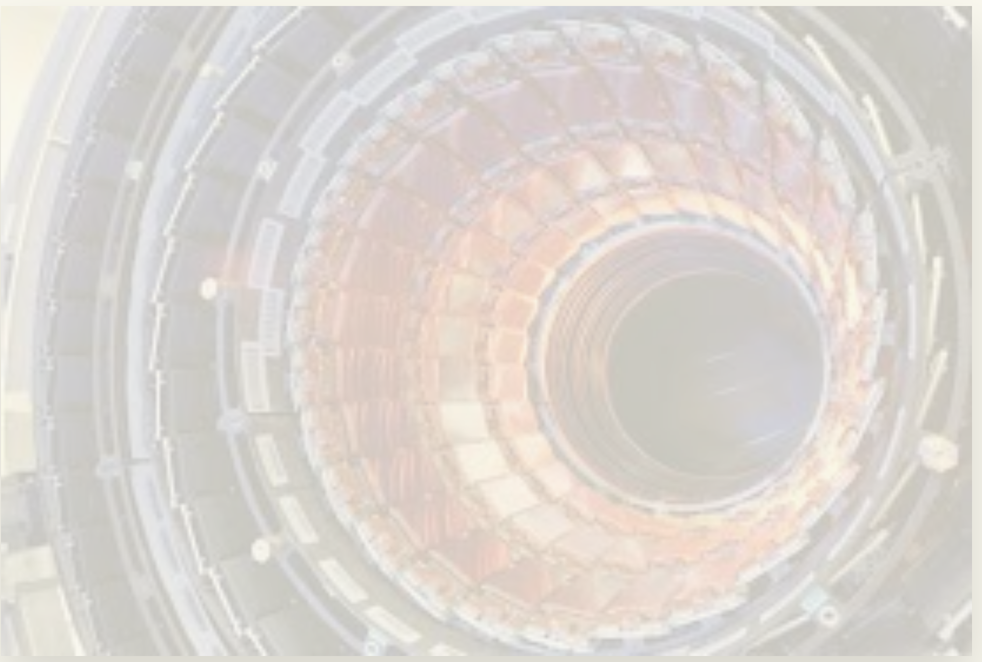
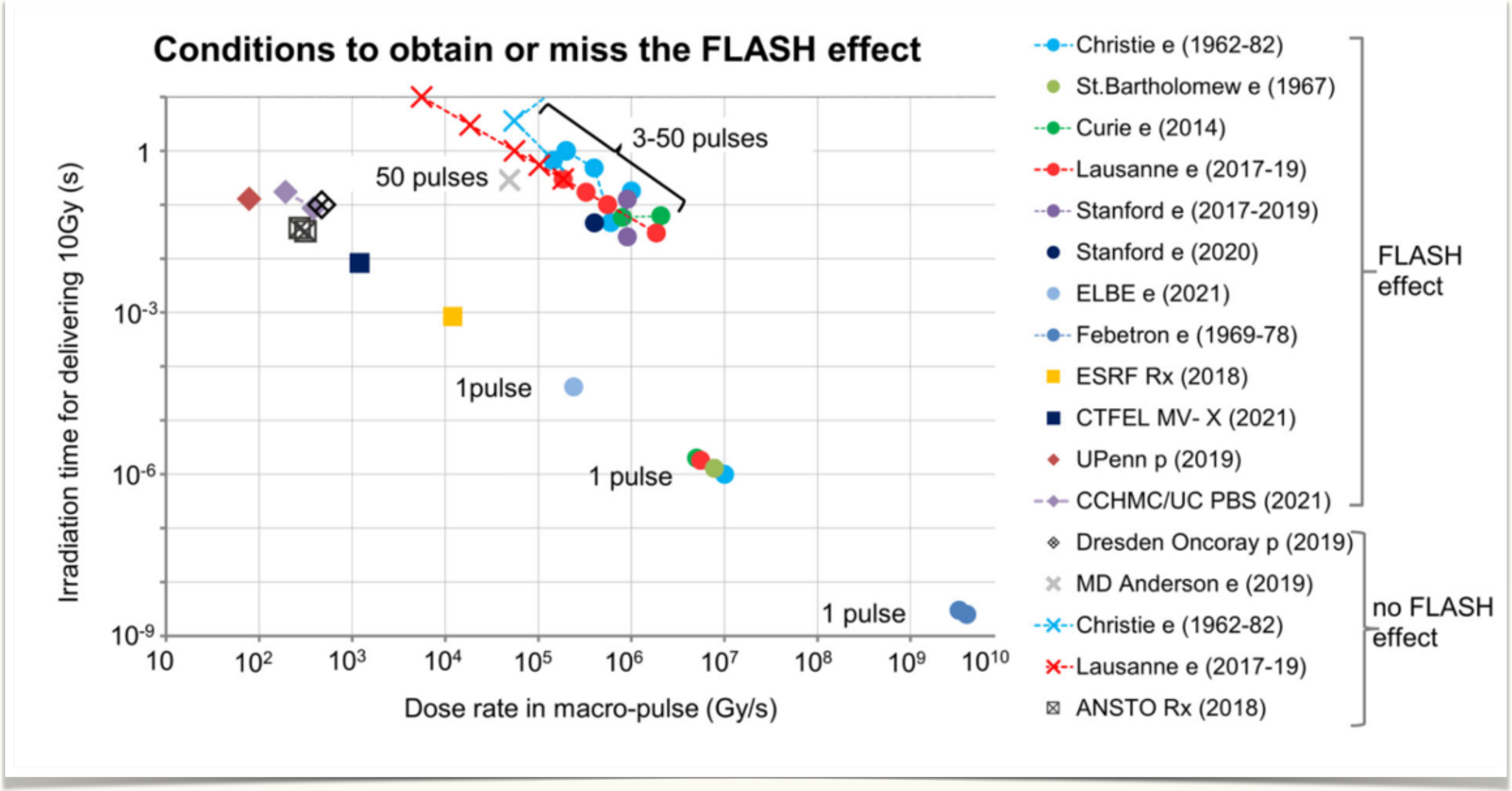




Delivery parameters

FLASH effect has been often correlated with (too) many parameters:

1. Mean Dose Rate [Gy/s];
2. Pulse Dose Rate [Gy/s] delivered in each pulse;
3. Pulse Dose [Gy];
4. Total Dose [Gy];
5. Pulse width [ms] of the single beam shot;
6. Total duration od the Dose administration;
7. Repetition Frequency of the pulses [Hz];
8. Number of pulses delivered.



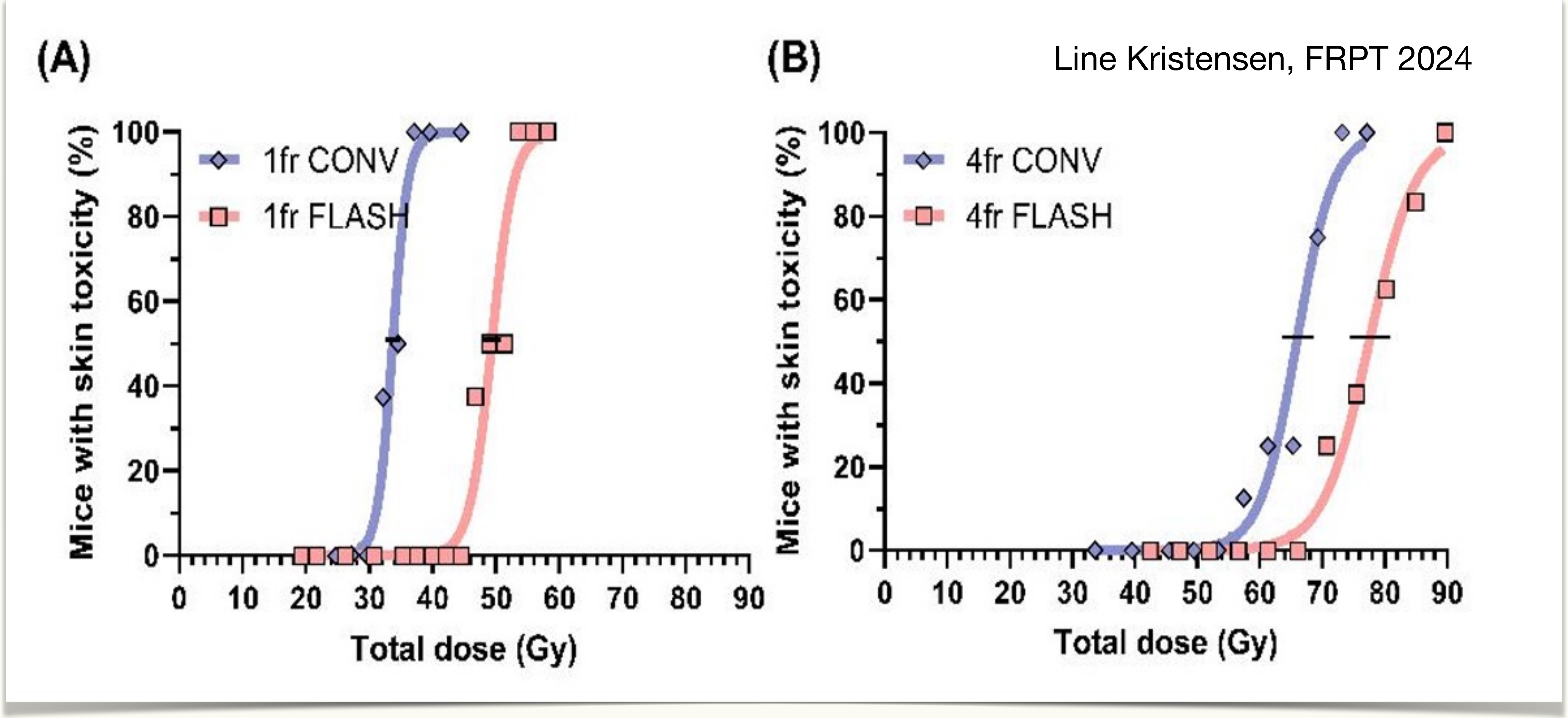
Consensus about the need for a minimal average dose rate around 50-100 Gy/s and minimal 5-6 Gy threshold dose.

FLASH EFFECT: the fractionation

During a real treatment the dose is given in many fraction: the FLASH effect is killed/modified/ unperturbed by the divided irradiation?

Research are actively on-going, the answer is likely to be dependent on tissues, fraction timing and so on.

- The dose-response curves for severe acute skin toxicity achieved a **46% FLASH protection ratio** (95% CI: 37-56%) for **a single fraction** (Figure A).
- For the **four-fractions study**, a **FLASH protection ratio of 18%** (95% CI: 9-27%) was achieved (Figure B).



Treatment Planning Systems must be able to take into account also this effect!!!

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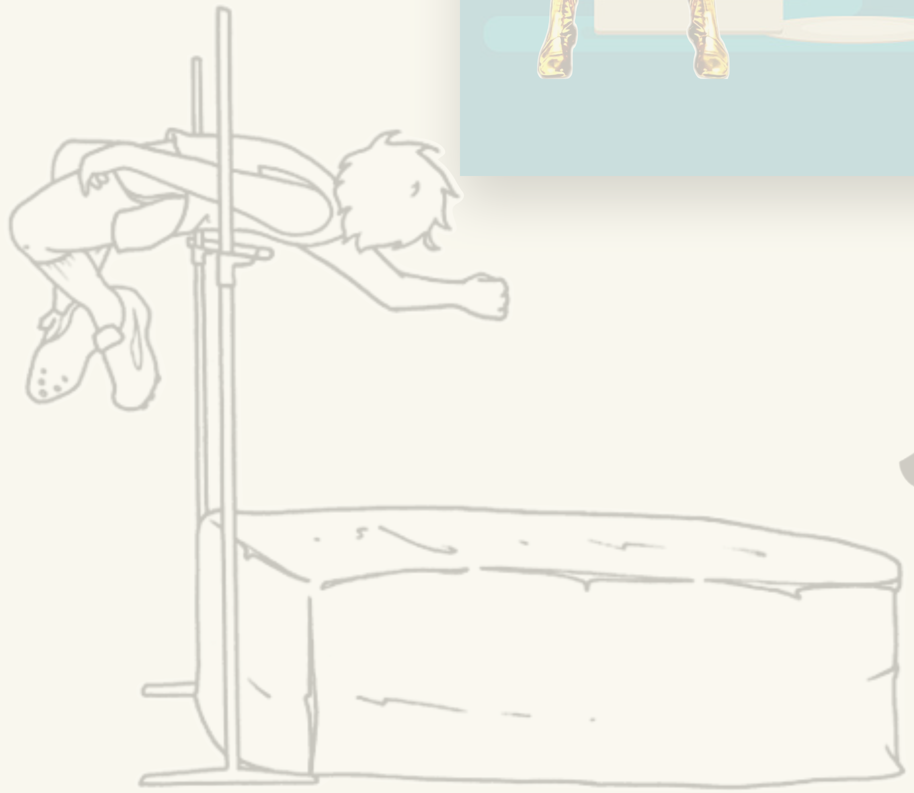
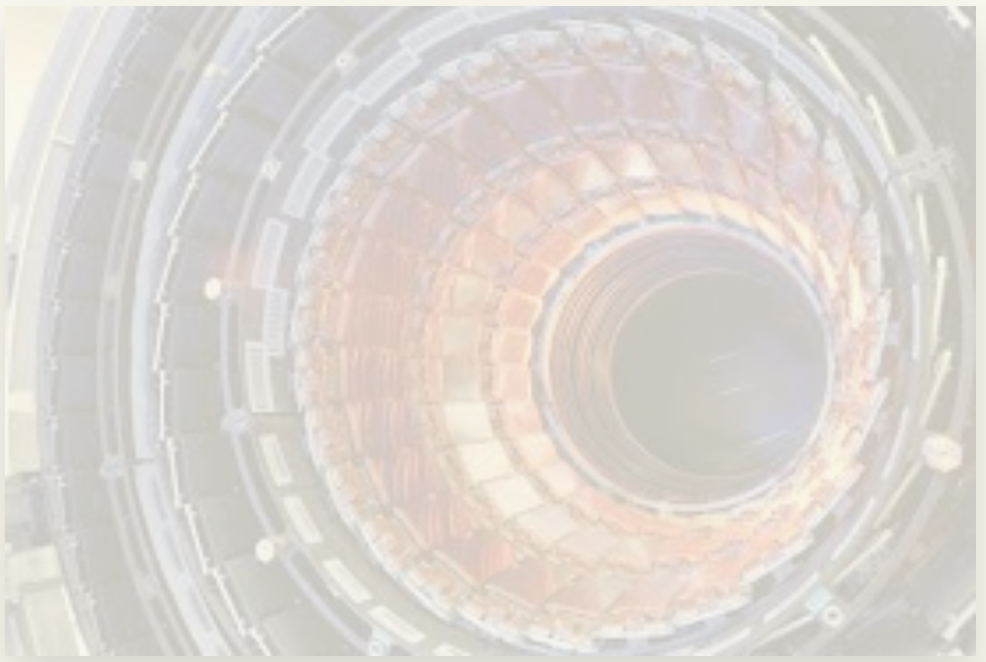




FLASH EFFECT: available beams

During last years the number and the types of available FLASH beams is greatly increased, and more are foreseen.

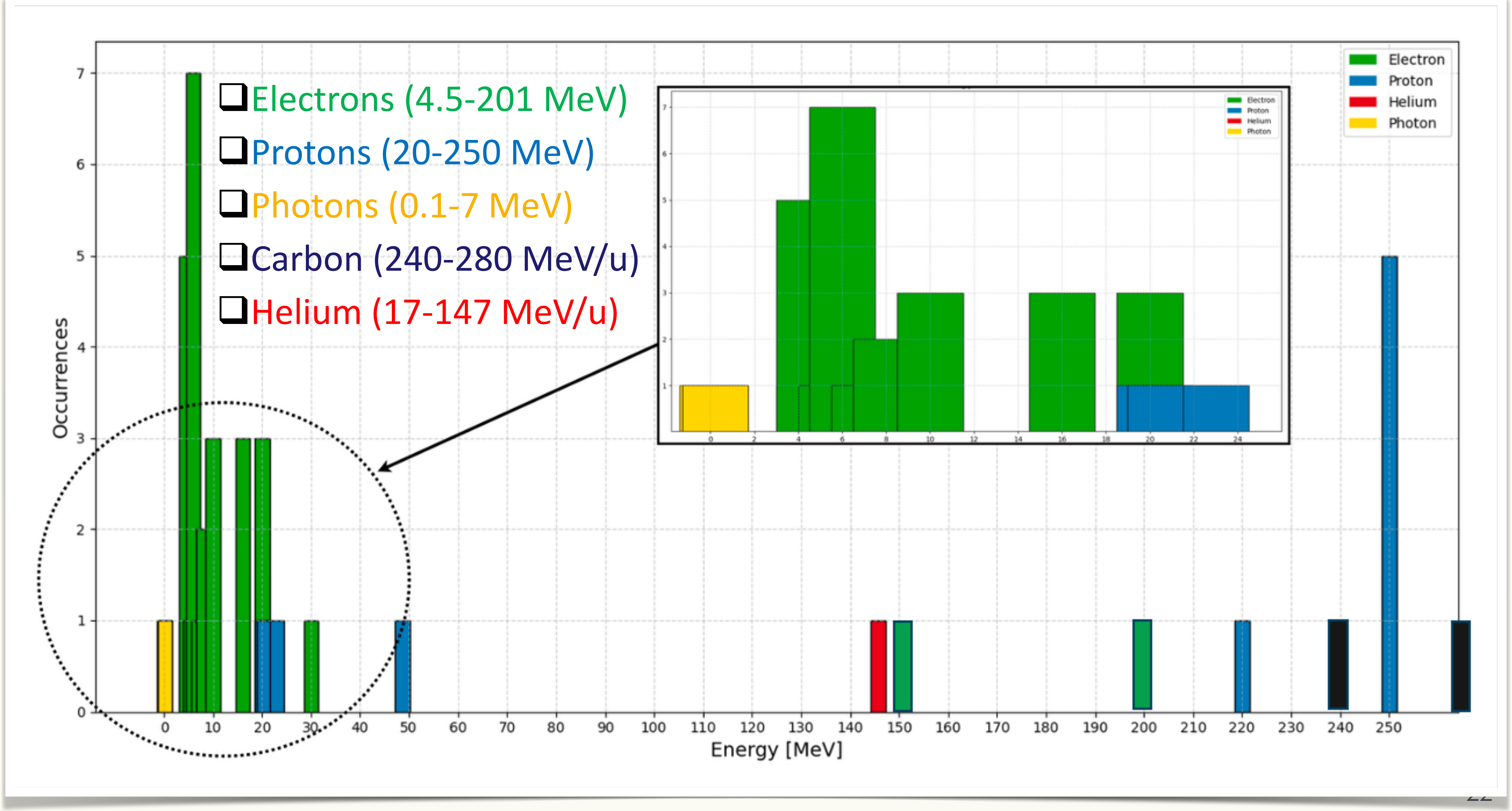
Three main families:

Commercially produced: beams specifically designed for preclinical research;

Home made modification to existing clinical beams: available both for preclinical and clinical research;

Laboratory beam, obtained from large experimental infrastructure. Usually only preclinical research is possible.

The FLASH effect has been reported on several beams, with different energies and completely different time structure.

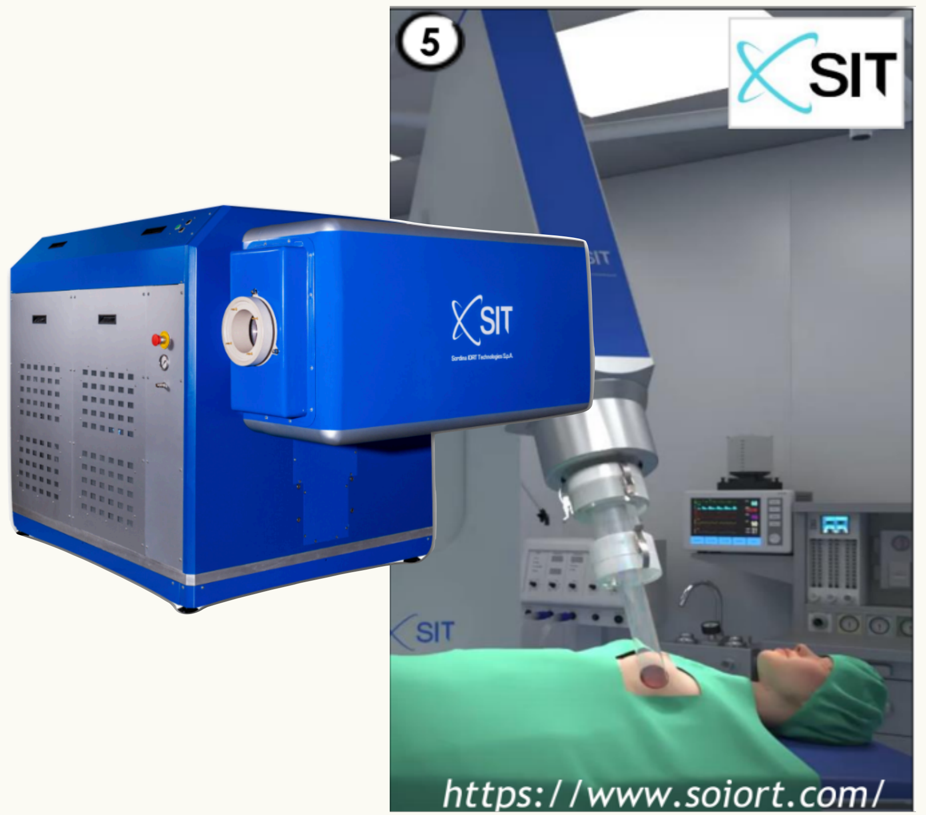


FLASH EFFECT: electron beams

The electron beam have been the first, and are still now the main source of flash effect results (now also in clinical trial!)

6-12 MeV

Commercially available beams designed mainly for preclinical research.

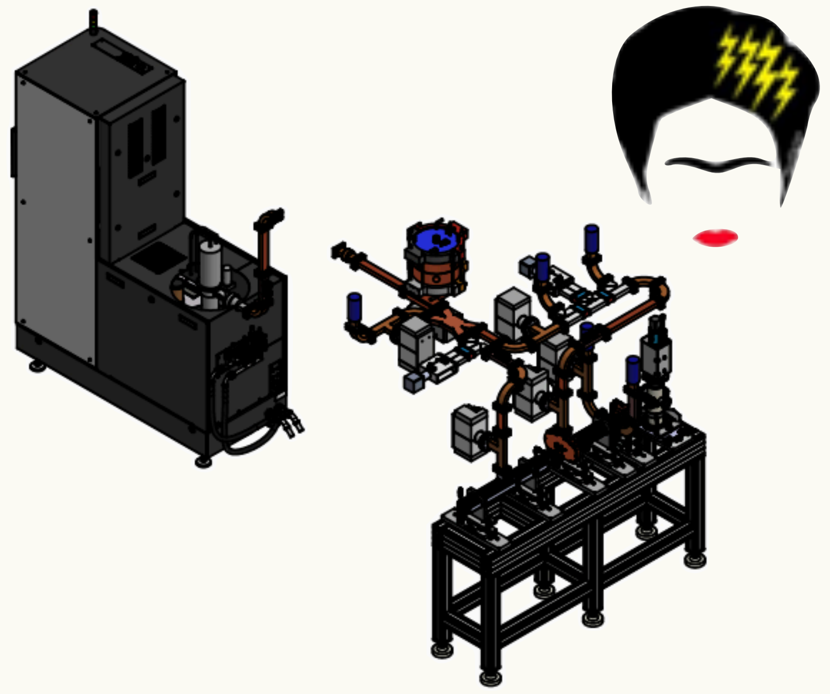


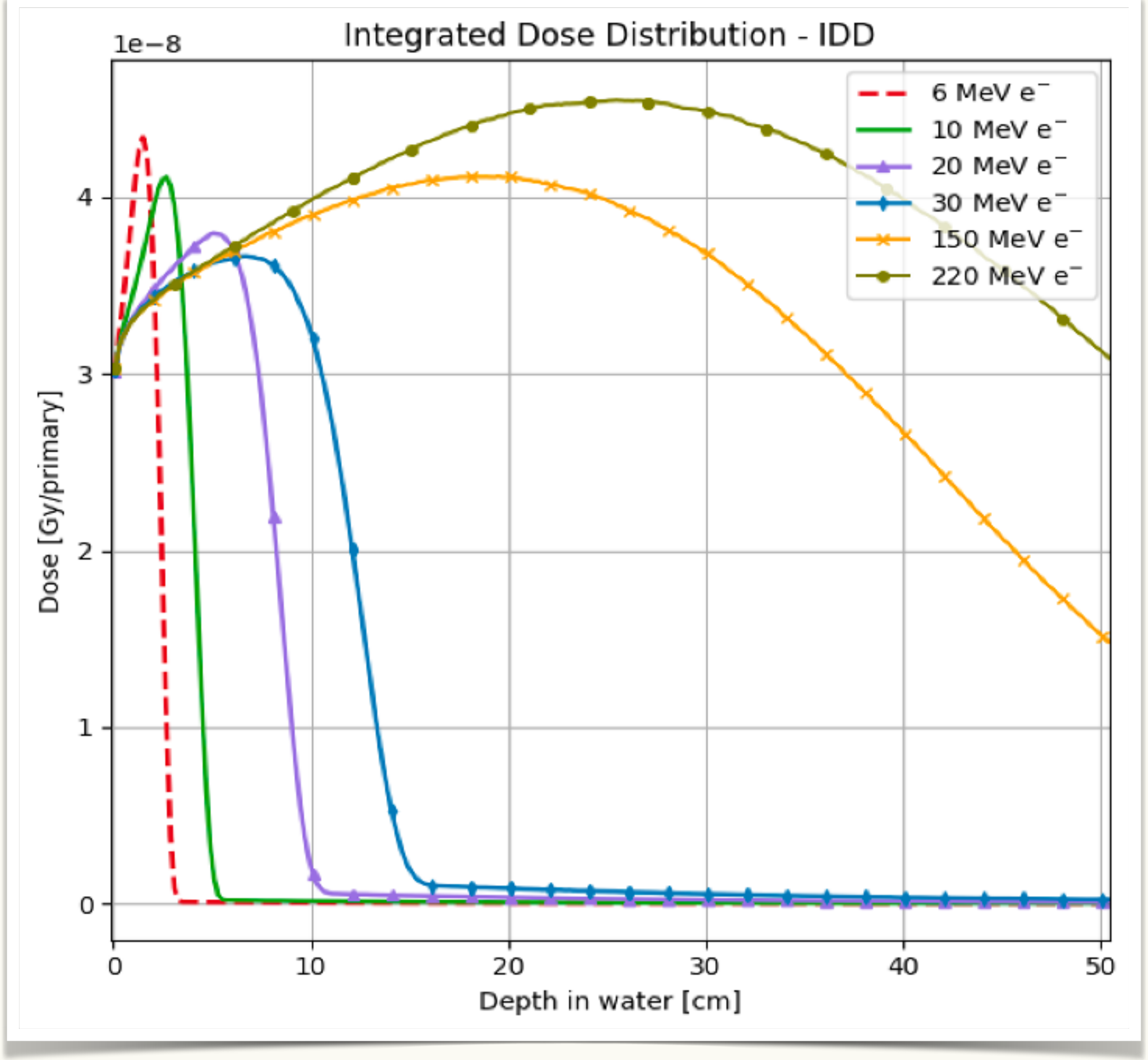
18-20 MeV

Beams obtained by custom modification of standard Xray LINAC.

10-220 MeV

Different energy beams available in research infrastructure outside clinical environments.





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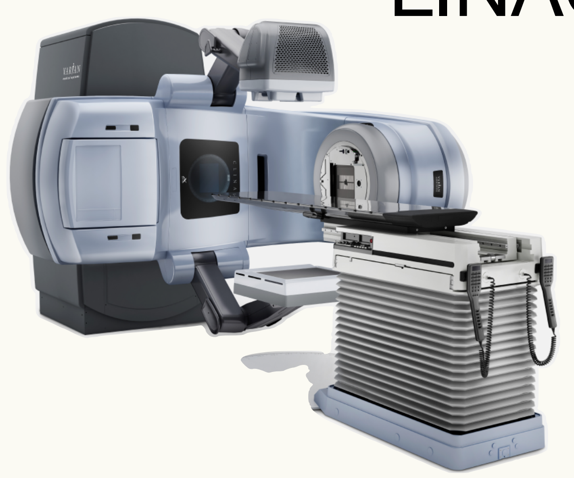
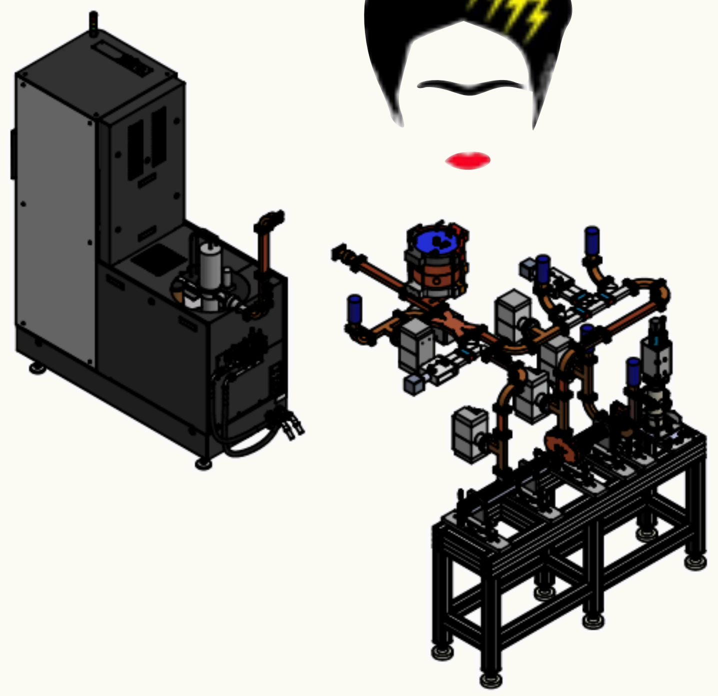
Beams obtained by custom modification of standard Xray LINAC.

10-220 MeV

Different energy beams available in research infrastructure outside clinical environments.





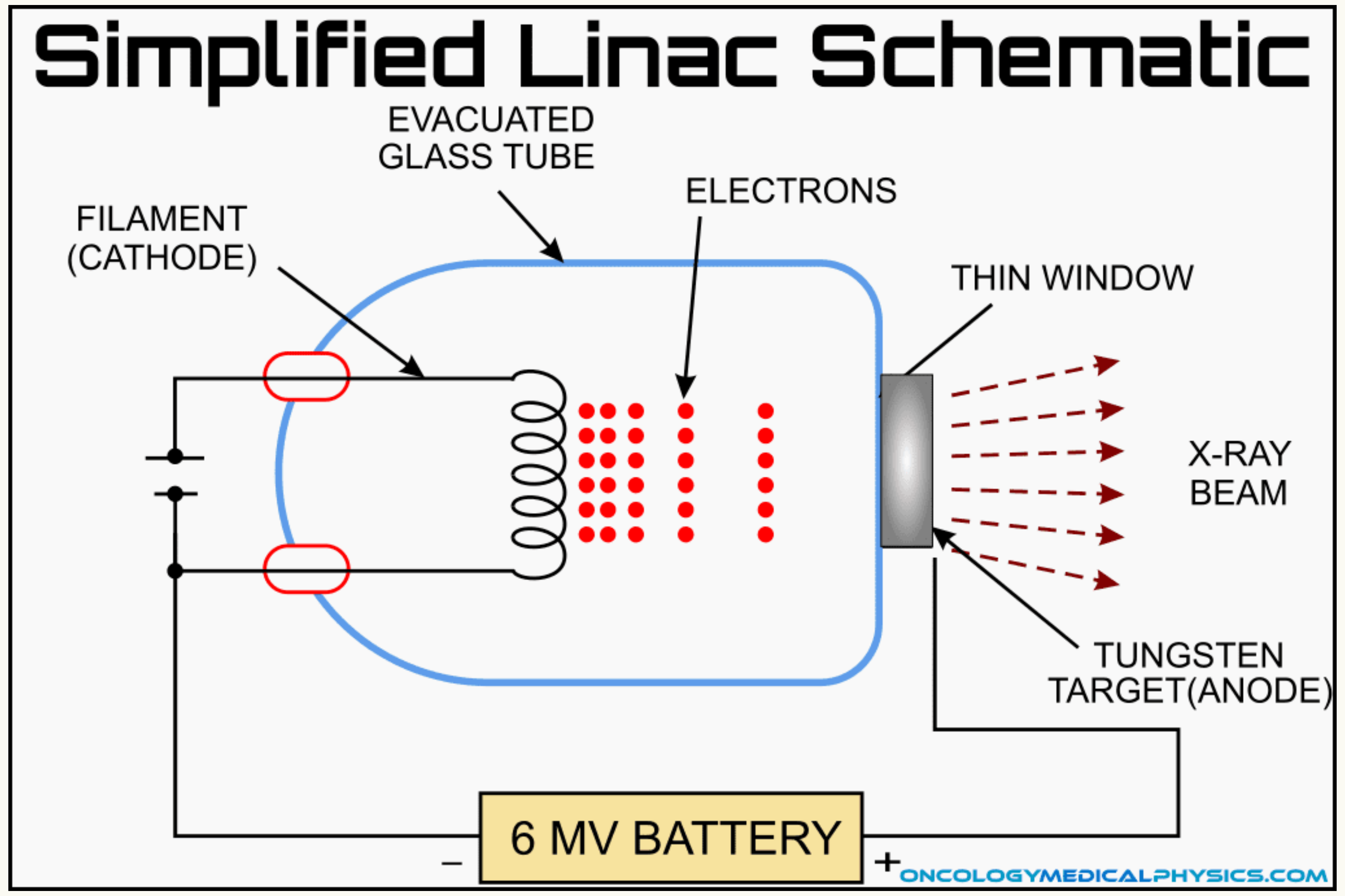
Accelerator	Pulse Dose Rate (Gy/s)	Pulse width	Pulse per second (Hz)	Energy (MeV)
Alcen Oriatron eRT6	10^2 - 10^7	0.5-4	5-200	6
ElectronFLASH SIT	0.5-1.0 10^6	0.5-4	1-240	5-12
IntraOp Mobetron	2-16 10^6	0.5-4	5-90	6-9
Elekta Precise	120	3.5	200	10
Varian Trilogy	4 10^5	5	108	16
Varian Clinac 21EX	8. 75 10^5	2	108	20
Varian Truebeam	1.4 10^4-8 10^6	0.34-3.4	300	6
Mitsubishi ML-15MII	3.7 10^3-1.6 10^4	3.4-4	20-80	8

New **Modified**

FLASH EFFECT: photon beams

The production of photon FLASH beam is very challenging with traditional production mechanism:

The photons are produced by the Bremsstrahlung of e⁻ LINAC beam (E 10-20 MeV) on a high Z target (W) with low efficiency



FLASH requires a dose 10^2-10^3 times higher than CONV-RT.
Needed an increase of the mean beam current from tens of μA to several mA.

1. Technical challenges in modulating beam intensity quickly enough;
2. Risks of melting the Bremsstrahlung target.

LINAC	Varian Clinic	Varian Clinic	Elekta SL25	Elekta SL25	KD Siemens	KD Siemens
Energy [MeV]	6	18	6	26	6	18
Photons per 1000 electrons	1.6	7.2	1.5	4.6	2.5	6.3

FLASH EFFECT: proton beams

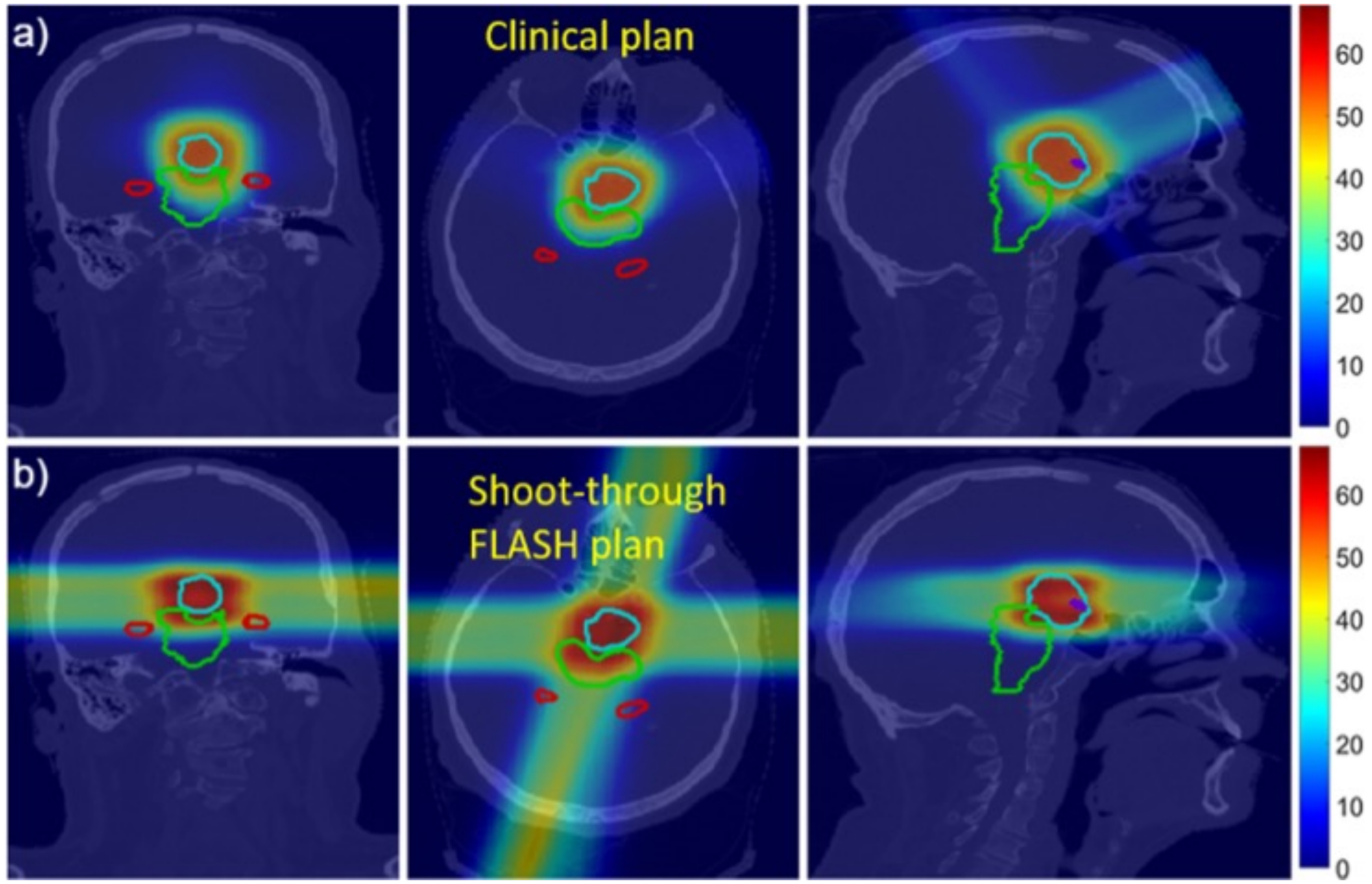
Clinical proton beams can achieve the FLASH threshold rate beyond ~ 50 Gy/s at the maximum energy of ~250 MeV.

The proton beams, due to their range, are the main candidates for a ready clinical translation of FLASH to deep seated tumor treatment

Take time and lower dose rate.

Unfortunately the FLASH rate can be usually achieved on a ~cm^2 beam spot. For clinical volume tumor you need:

1. Longitudinal: Insert range shifters to change energy (SOPB);
2. Transverse: Scanning magnetically the pencil beam.



The magnet scanning (~ms) can maintain FLASH effect but not the change of energy (~1 sec).

Loose proton conformality but FLASH effect can compensate high dose on OAR?

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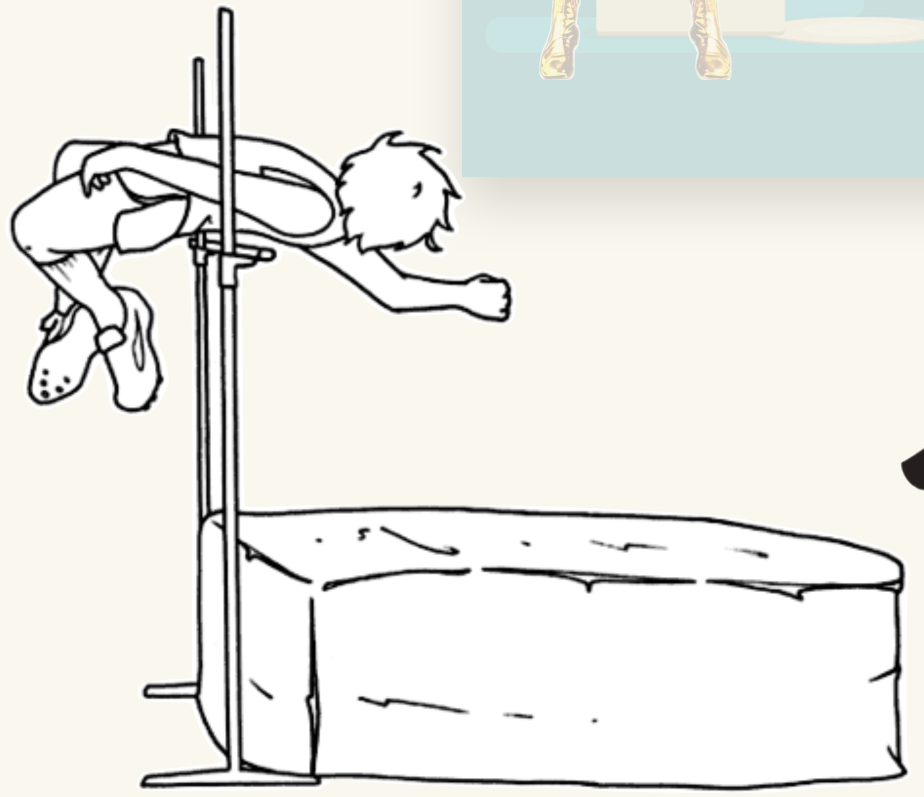
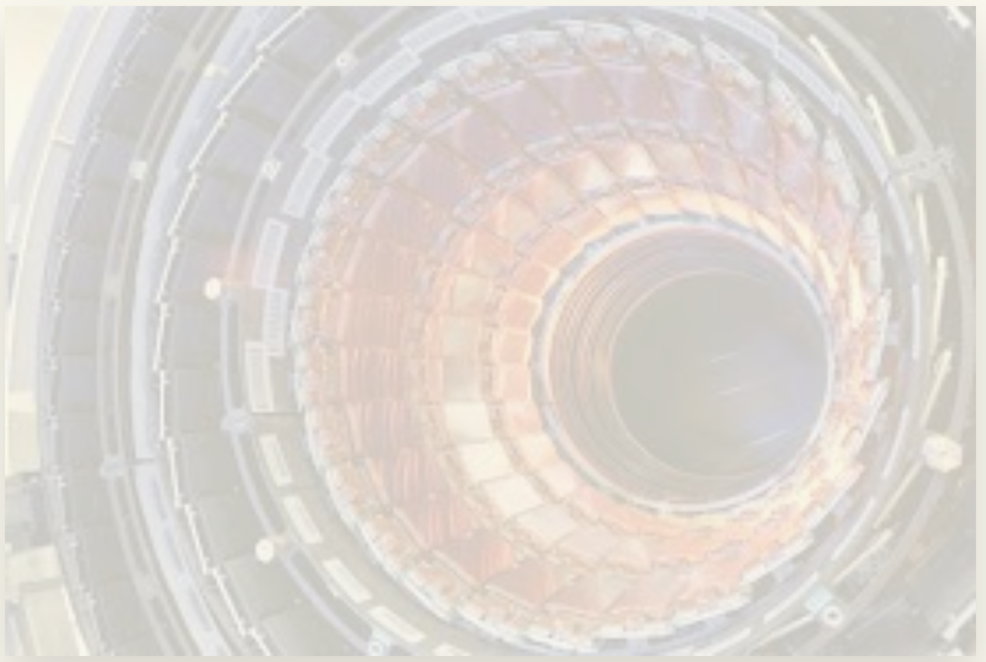


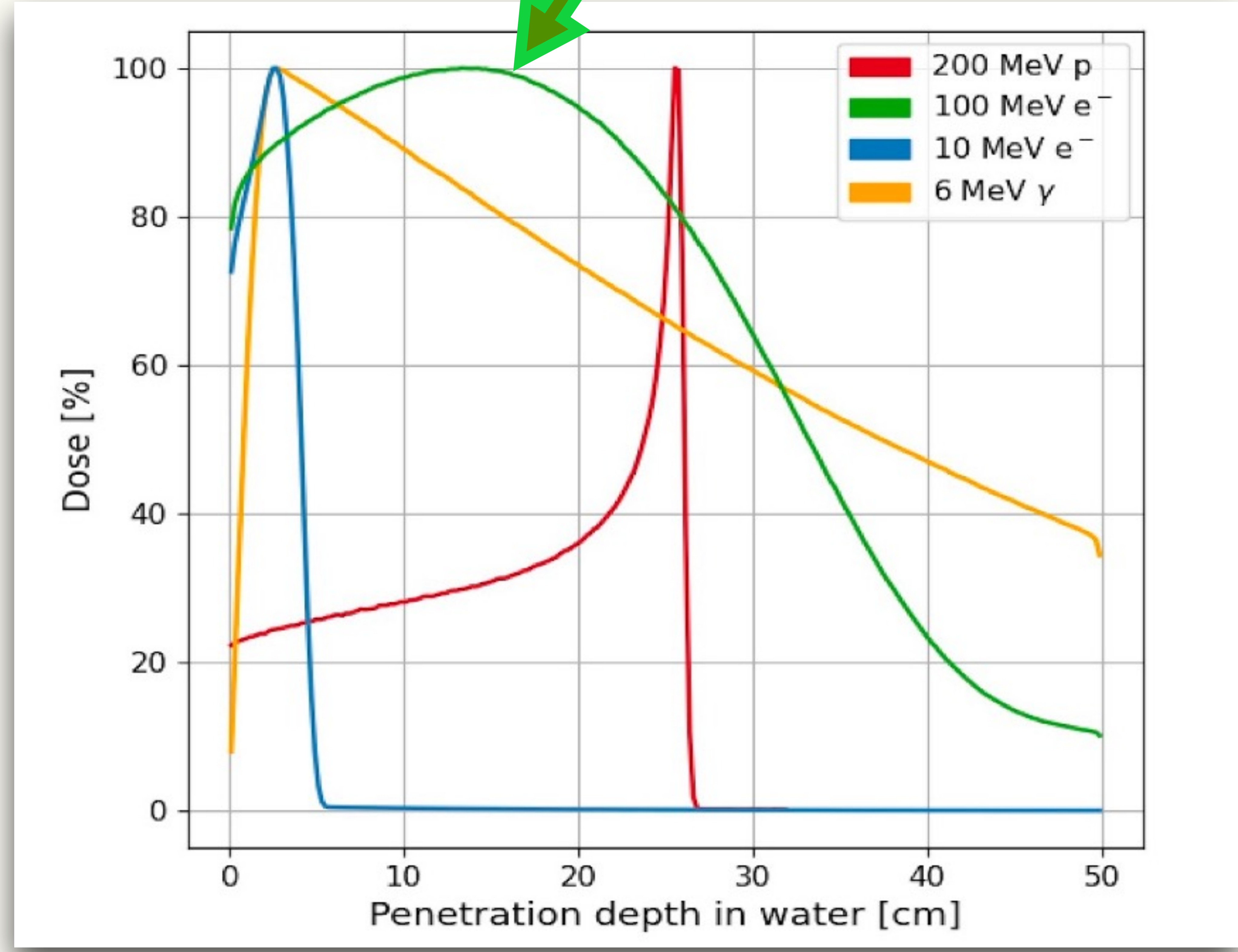


Very High Energy Electrons: why?

To treat deep seated tumors the electron energy must be larger than that one of the standard RT LINAC (20-15 MeV). At E>50 MeV e^- beams have typical features…

- ☑ Lateral extension (penumbra) is dominated by Multiple Scattering inside the patient and decreases with energy;
- ☑ Dose depth distribution with tail after the peak increasing with energy;
- ☑ Dose depth distribution with a broad peak shifting with beam energy

NATURAL SPREAD OUT BRAGG PEAK



Very High Energy Electrons: why?

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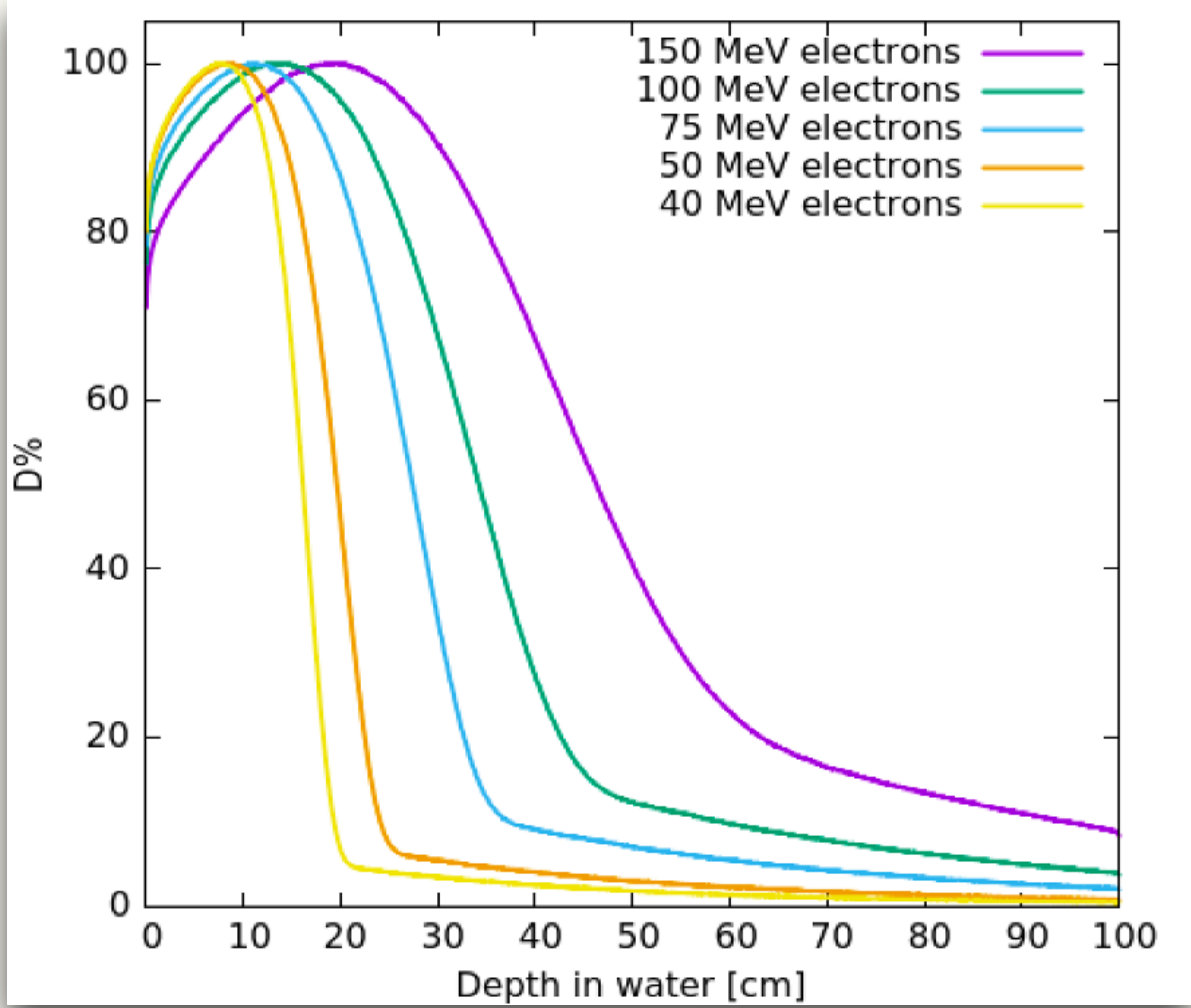
- Lateral extension (penumbra) is dominated by Multiple Scattering inside the patient and decreases with energy;
- Dose depth distribution with tail after the peak increasing with energy;
- Dose depth distribution with a broad peak shifting with beam energy

- If $E > 50MeV$: DDD covers a 10-15 cm deep tumor;
- If $E > 75MeV$: DDD covers quite well a 20 cm deep tumor.

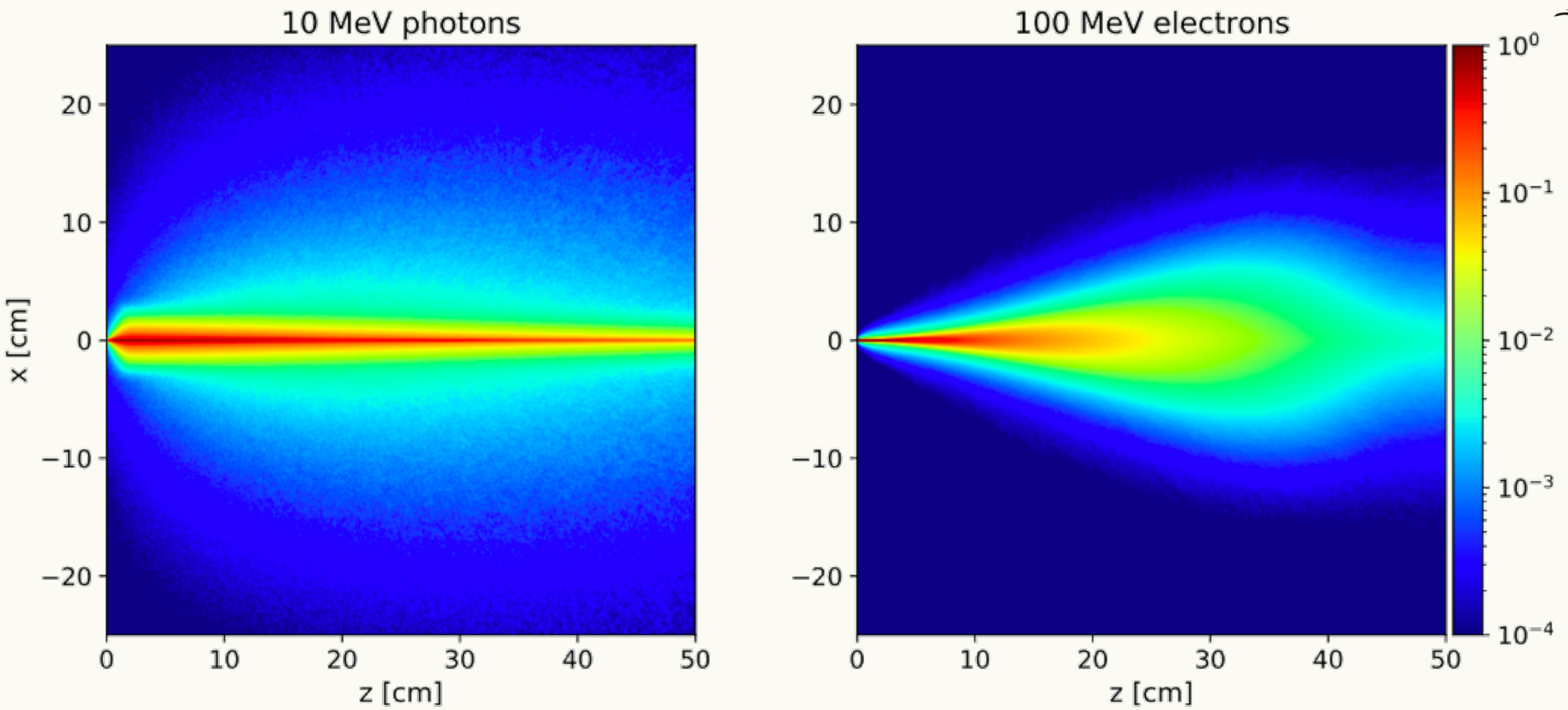


FLUKA 2020: pencil beam simulation in water

- The lower the energy, the smaller the tails beyond the tumor region;
- The DDD has much better behavior than photons in the entrance channel.

VHEE: Lateral Distribution

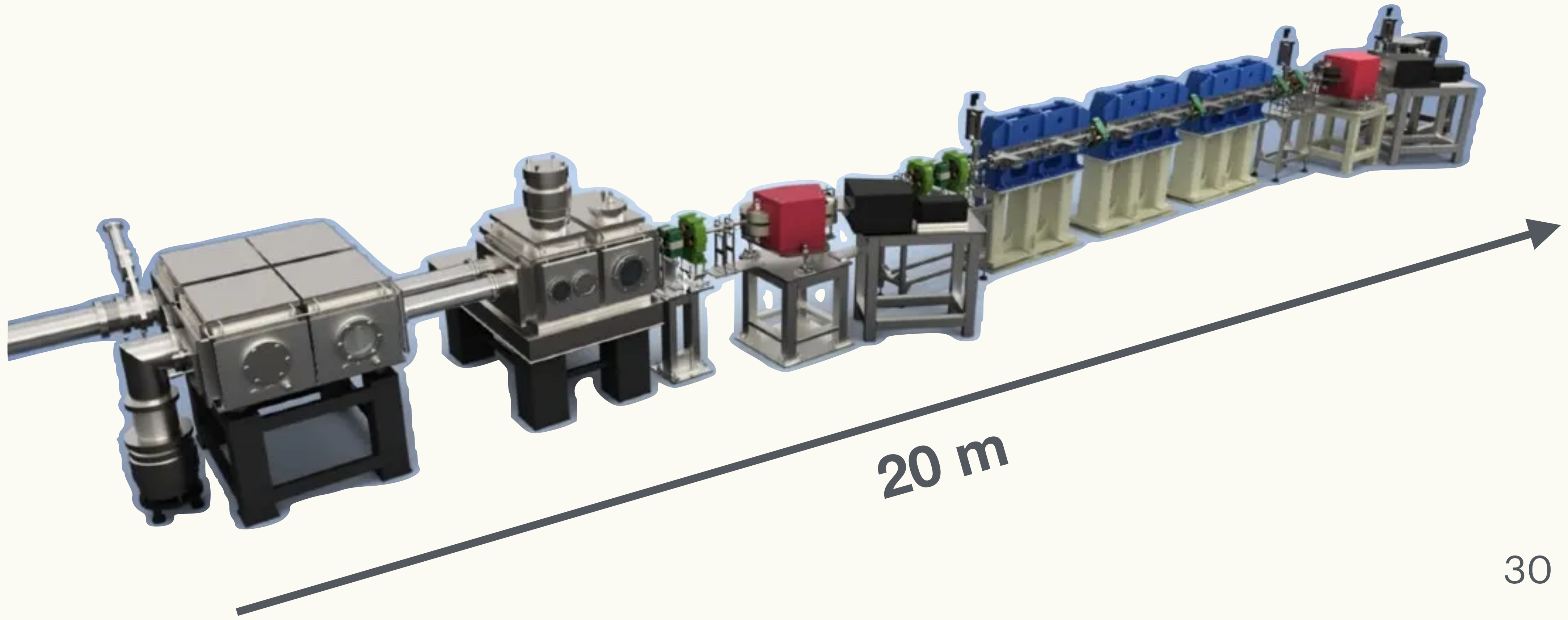
Multiple scattering spread out the dose in the path to the tumor. This effect gives the **main limitation** to the use of VHEE in clinical practice



Even if the electron beam is pencil like, it «explode» inside the patient in a rigid (but predictable: **SIMULATIONS**) behavior due to MS;

To overcome VHEE must be used (E>100 MeV): high cost, large and expensive machines

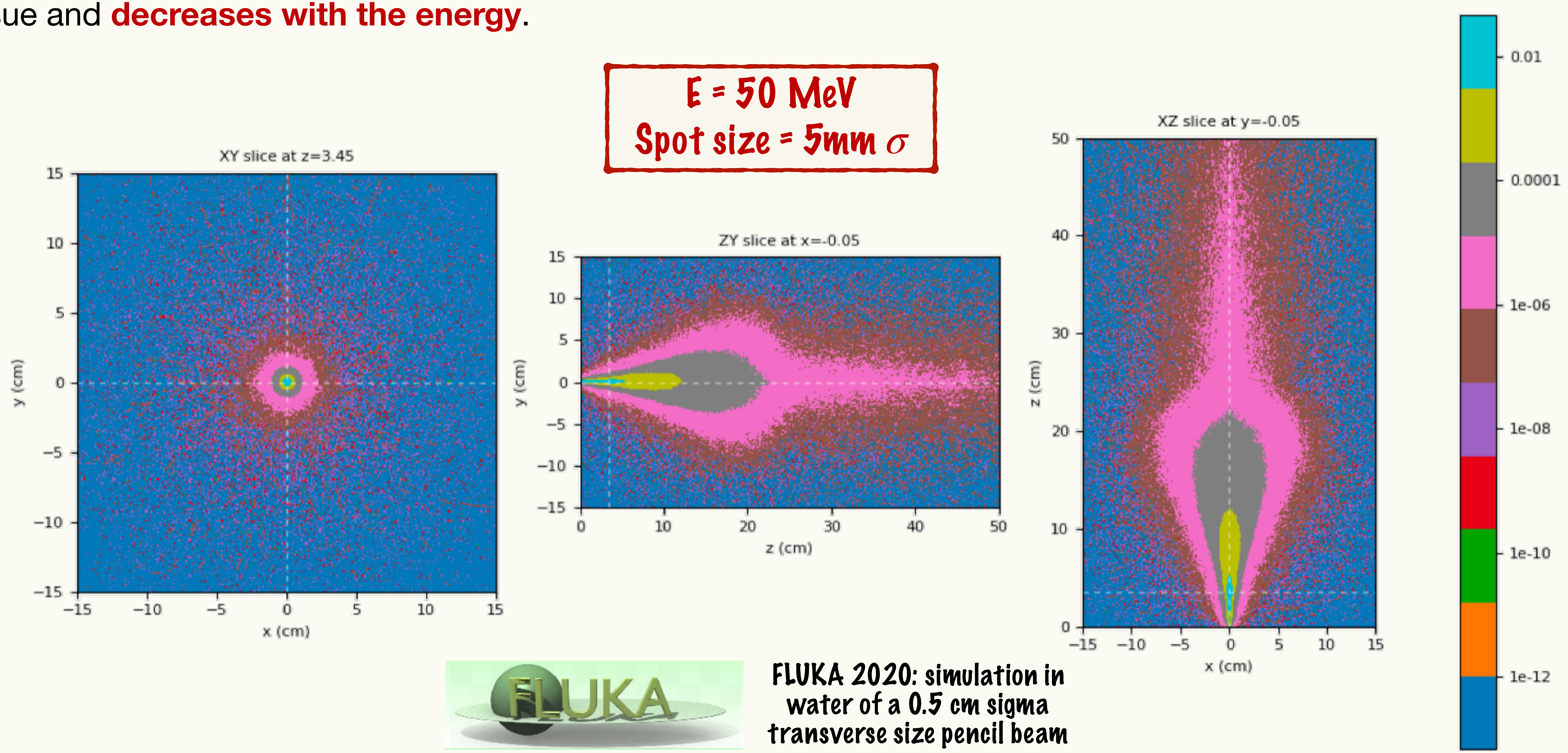
SPOILER!!!
if something reduces the "effective" dose seen by the healthy tissue…..



VHEE: 2D distributions

The electron beams with E>50 MeV has a 2-dimesional dose with a **penumbra that increases with the penetration** in tissue and **decreases with the energy**.

E = 50 MeV
Spot size = 5mm σ

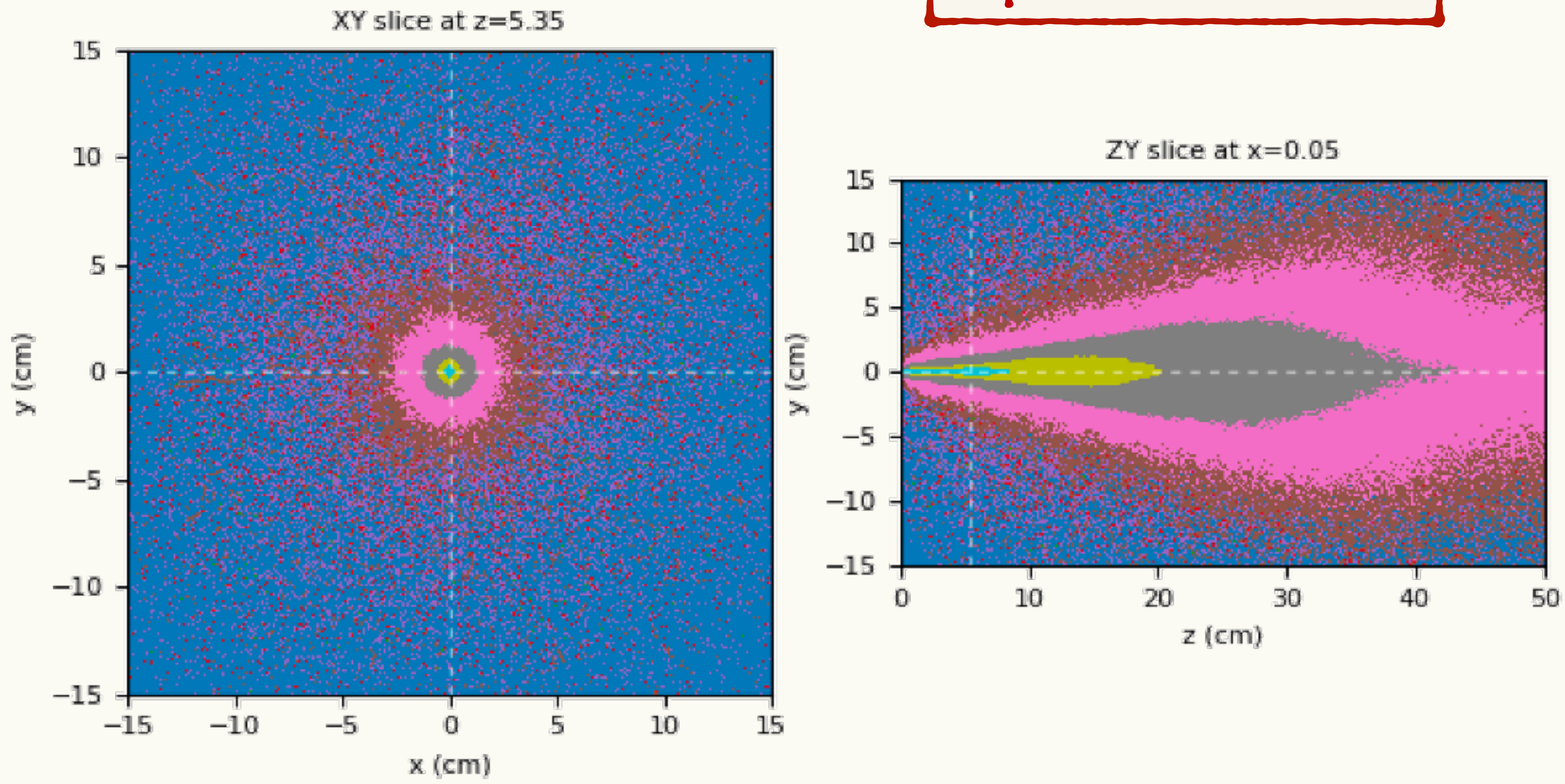


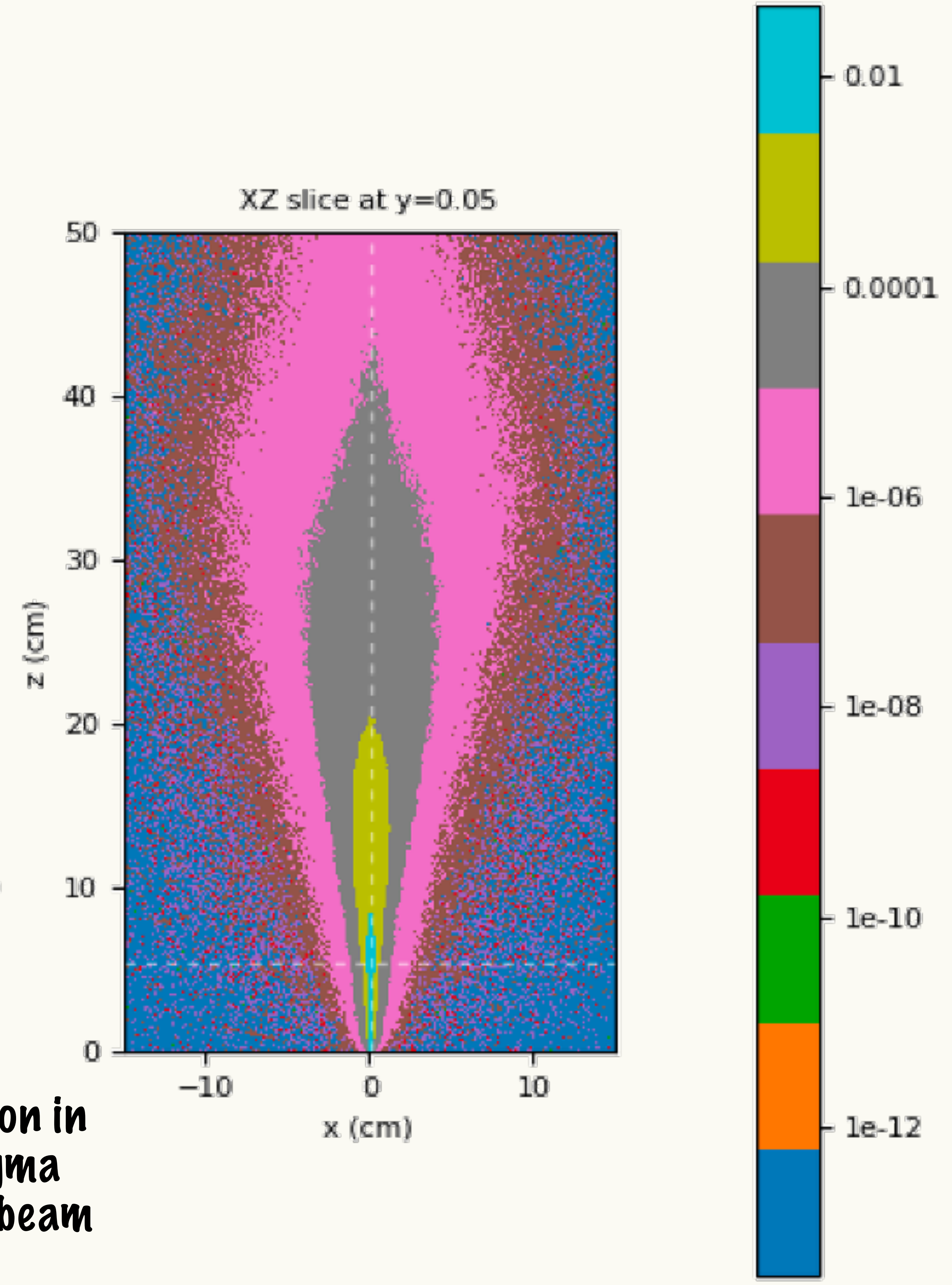
FLUKA 2020: simulation in water of a 0.5 cm sigma transverse size pencil beam

VHEE: 2D distributions

The electron beams with E>50 MeV has a 2-dimesional dose with a **penumbra that increases with the penetration** in tissue and **decreases with the energy**.

E = 100 MeV
Spot size = 5mm σ



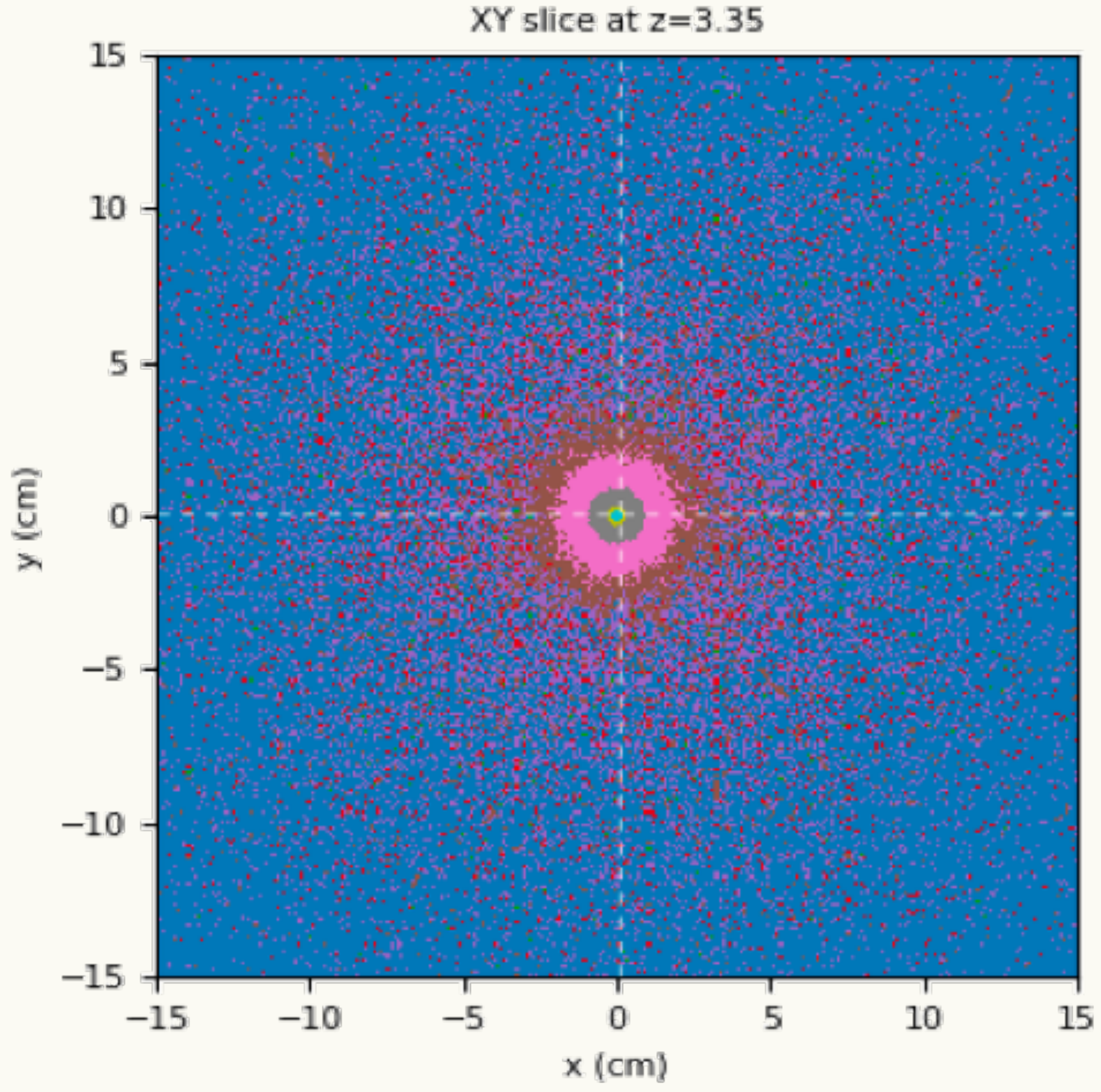


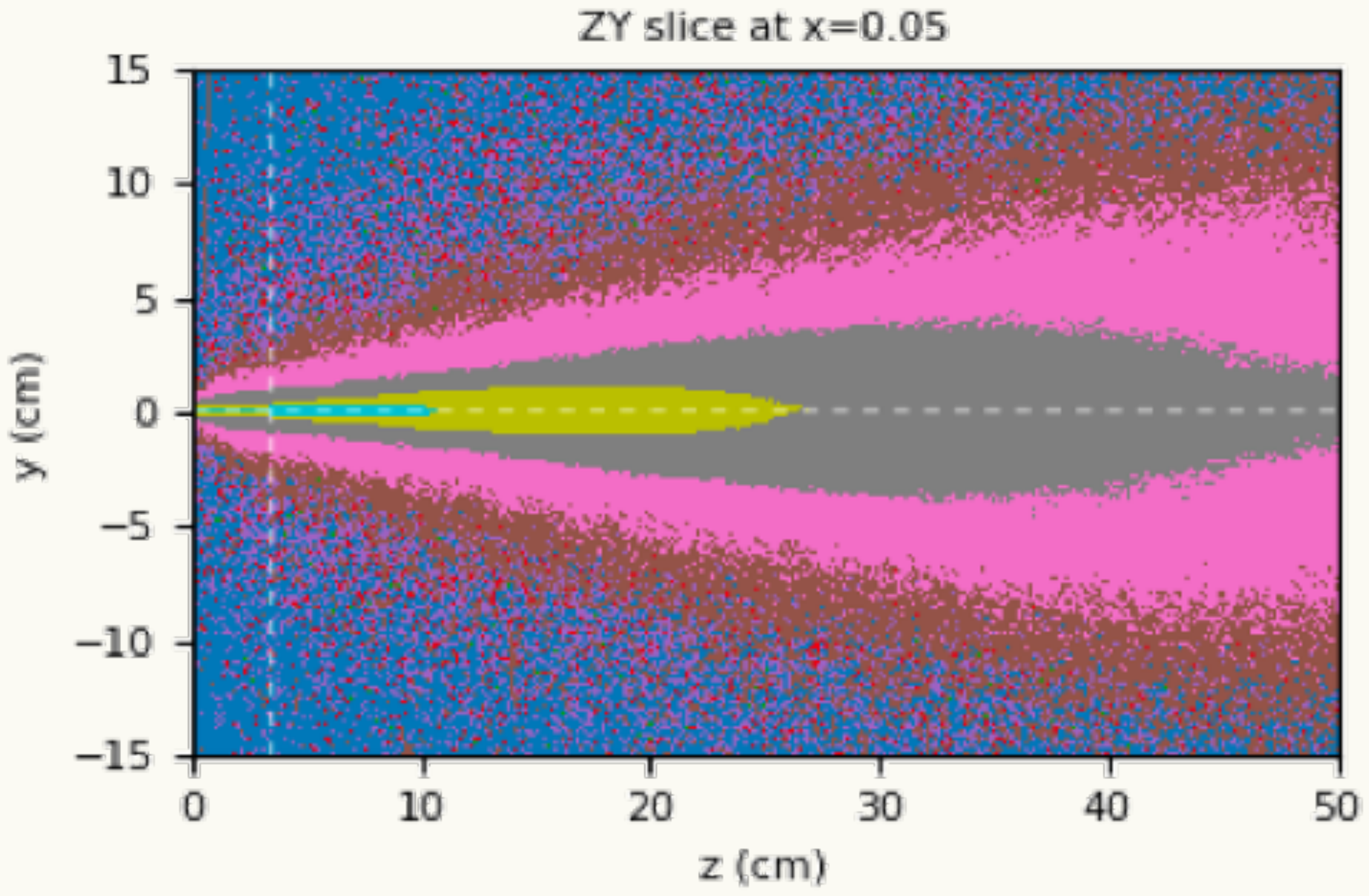
FLUKA 2020: simulation in water of a 0.5 cm sigma transverse size pencil beam

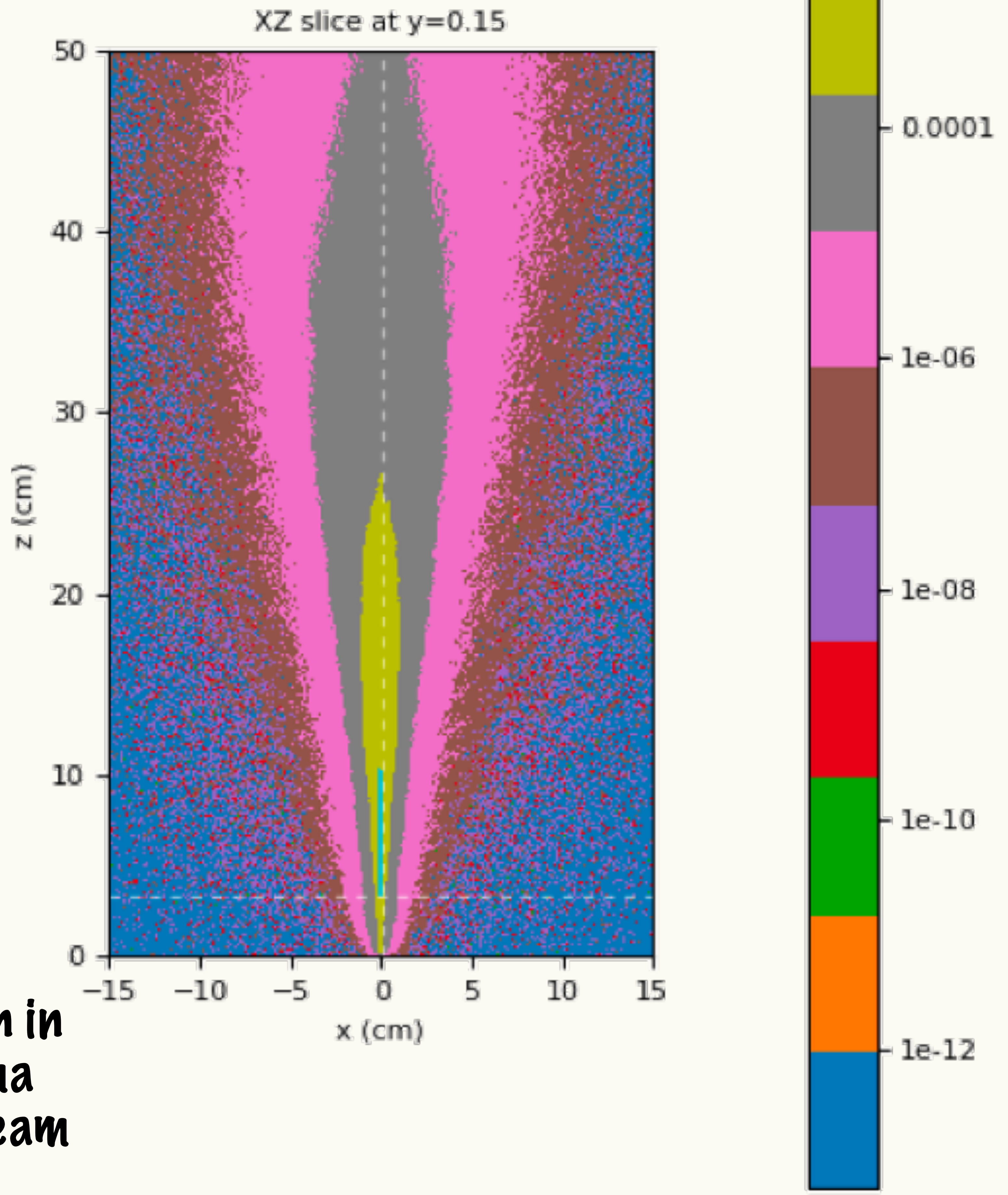
VHEE: 2D distributions

The electron beams with E>50 MeV has a 2-dimesional dose with a **penumbra that increases with the penetration** in tissue and **decreases with the energy**.

E = 150 MeV
Spot size = 5mm σ







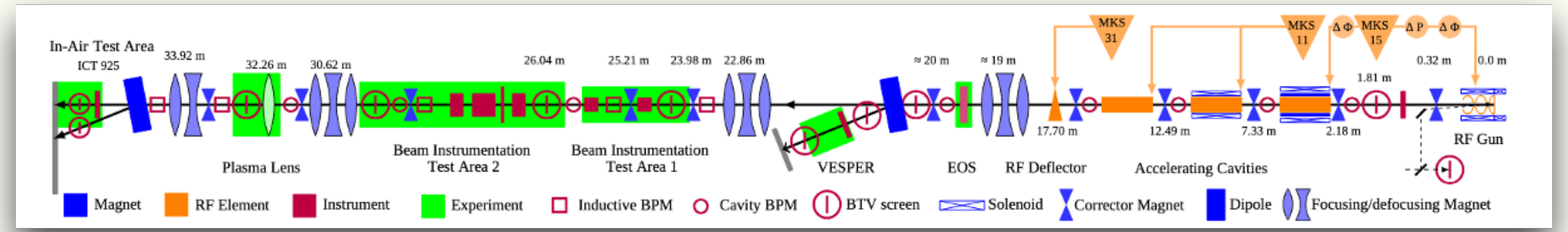
FLUKA 2020: simulation in water of a 0.5 cm sigma transverse size pencil beam

VHEE: what is already among us

Beam produced from high energy eLINAC whose technology is taking advantage from high energy particle tech (S,C,X band RF)

clear CERN Linear Electron Accelerator for Research

- FLASH effect on VHEE already observed at CLEAR@CERN, 201 MeV e⁻ beam;



- Available FLASH beams at PITZ@DESY (40 MeV), SINBAD@DESY, BTF@LNF (150MeV), ELBE@DRESDEN (30MeV), CLARA@Daresbury (50MeV);

UKRI Science and Technology Facilities Council | ASTeC

HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

DESY.

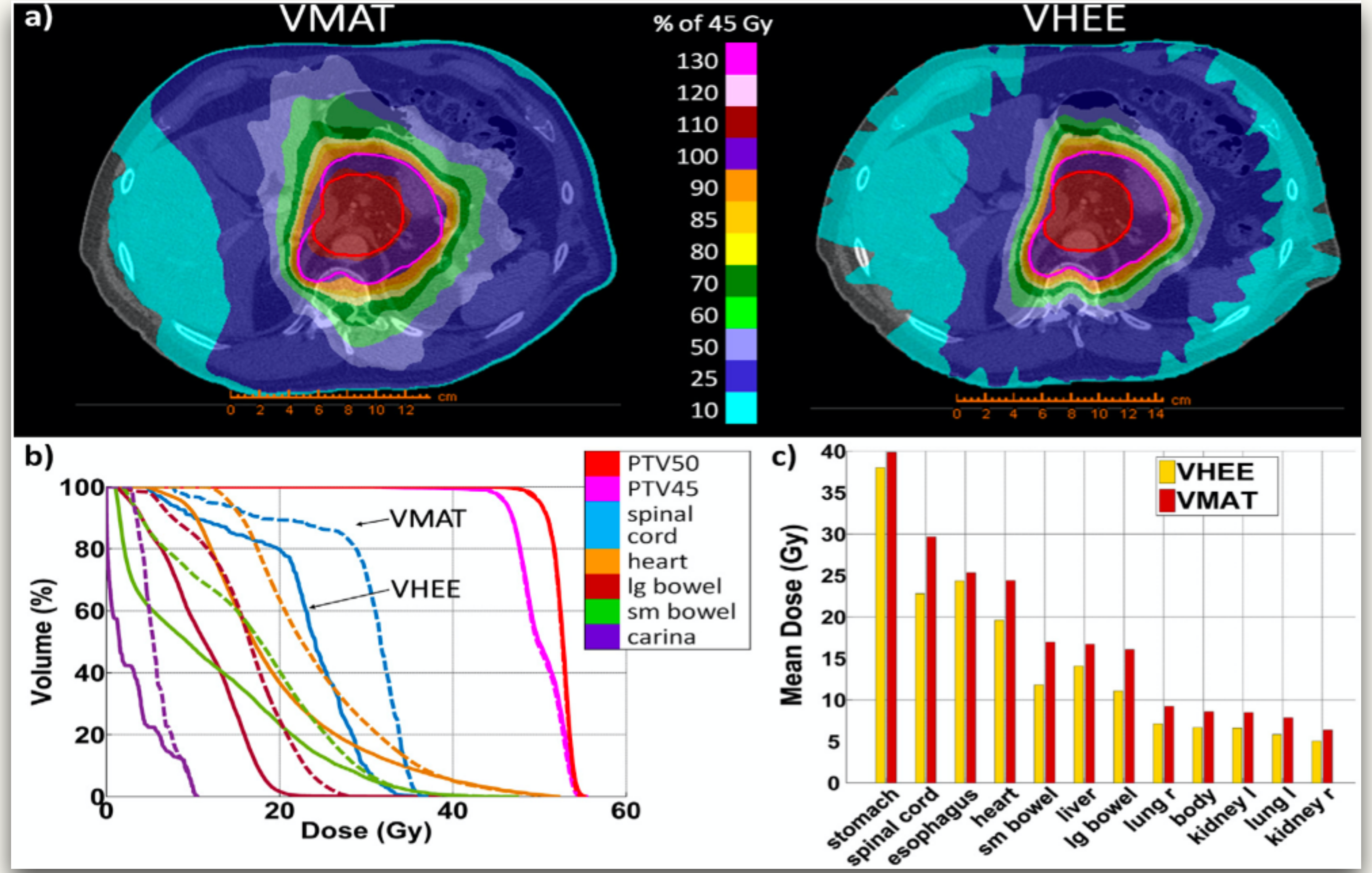
INFN LNF

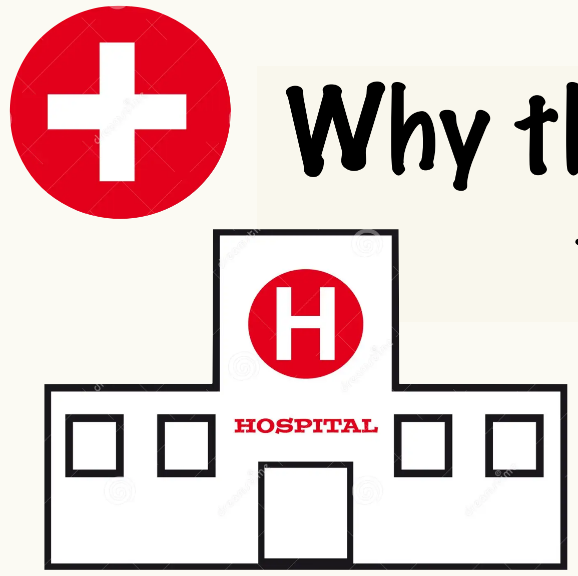
Large infrastructure, not clinical style, possibility to vary the parameters

Huge effort to reduce size and cost!

VHEE & RT in literature

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.





Why they have not yet reached the clinical stage?

Reported results are often based on simulated setup with:

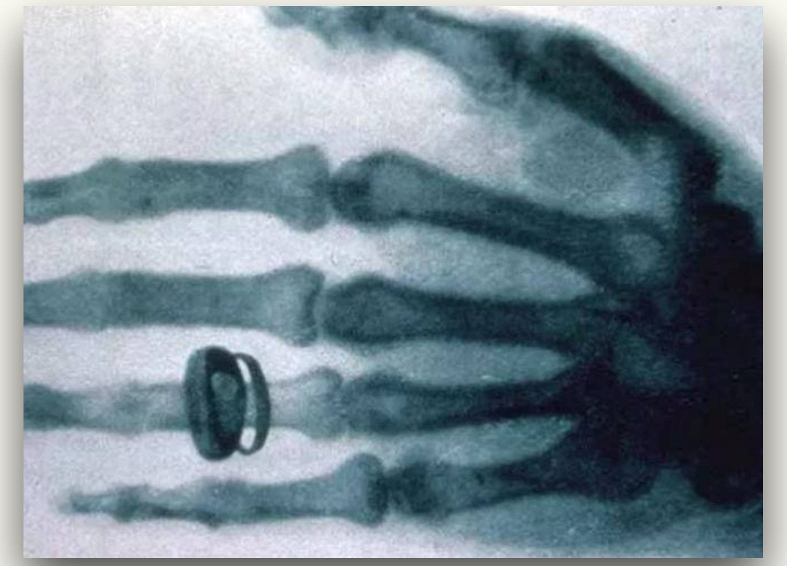
1. Many entrance fields (>10)
2. Beam energies ≥ 100 MeV (200 MeV typical) to minimize the beam penumbra

Too long for an hospital!

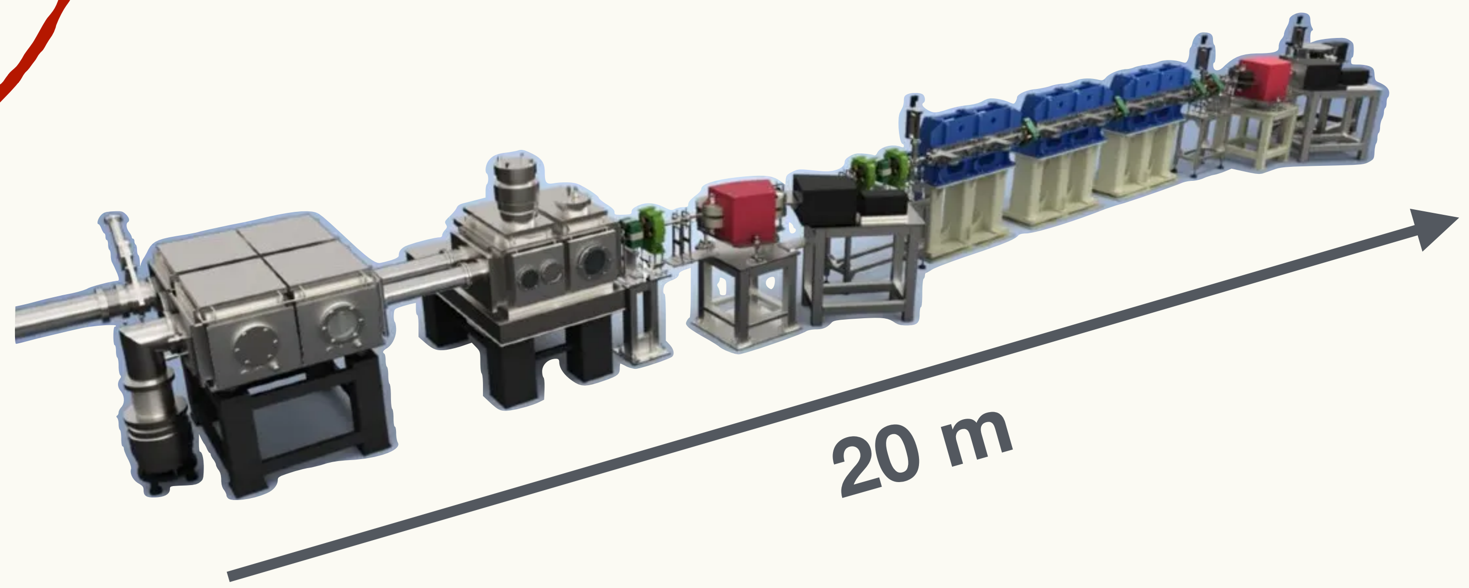
VHEE: the limitations

Why they have not yet reached the clinical stage?

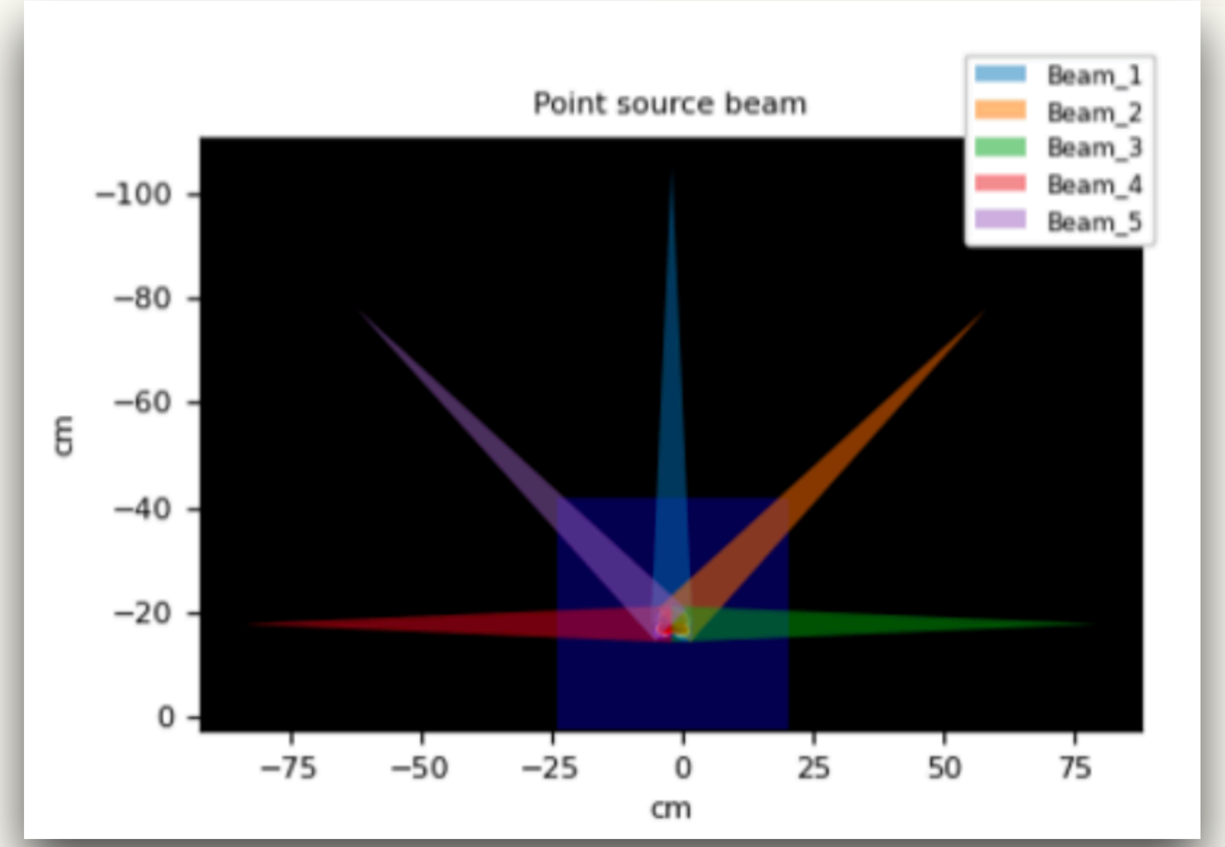
RADIOPROTECTION ISSUES

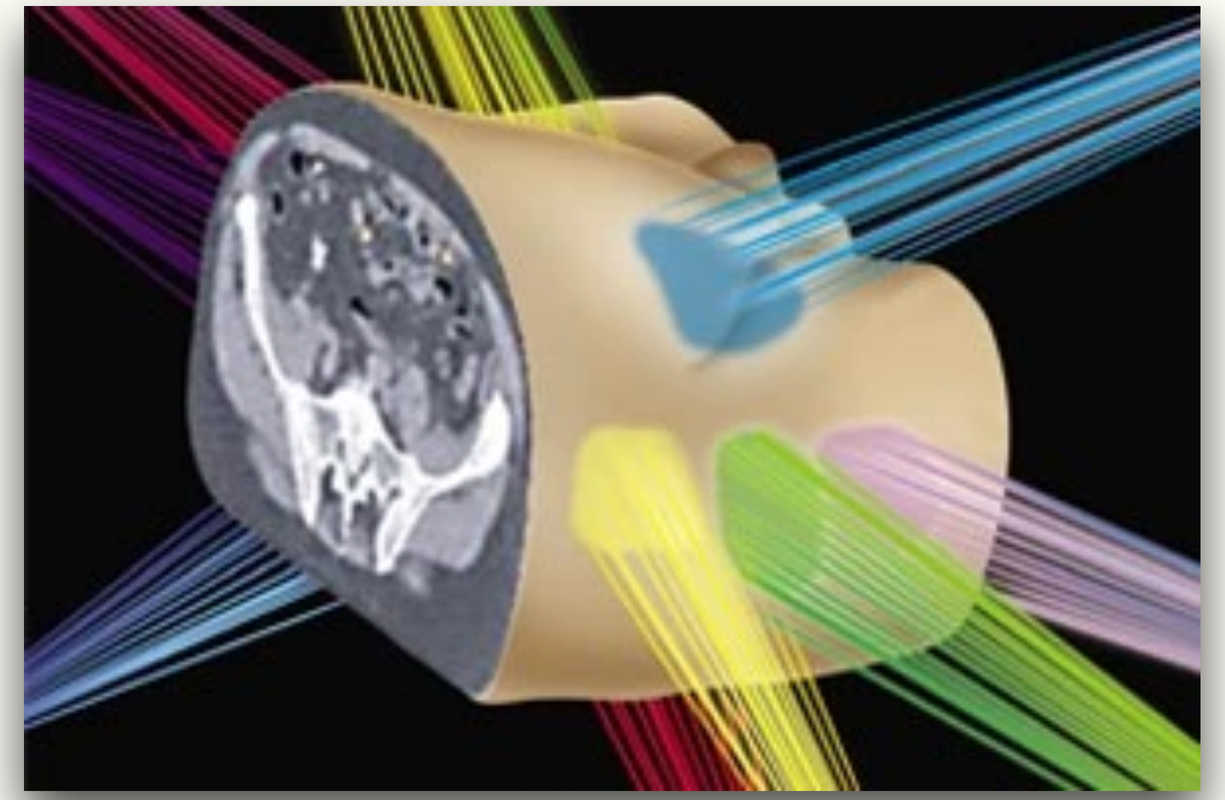


COST, COMPLEXITY AND SPACE



LARGE NUMBER OF FIELDS AND HIGH ENERGY





UNAVAILABILITY OF COMMERCIAL TREATMENT PLANNING SYSTEMS

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The SAFEST project

VHEE source based on a **C-band LINAC**, working at **5.712 GHz**, delivering a high intensity electron beam in FLASH regime.

It will **accelerate electrons up to 130 MeV**, maintaining a good transmission efficiency of the particles, necessary to transport the high peak current.

PRF	$100Hz$
Pulse duration	$< 3\mu s$
Charge per pulse	$600nC$
Dose rate per pulse	$> 10^7 Gy/s$
Average dose rate	$> 10^2 Gy/s$
Pulse current	$200mA$

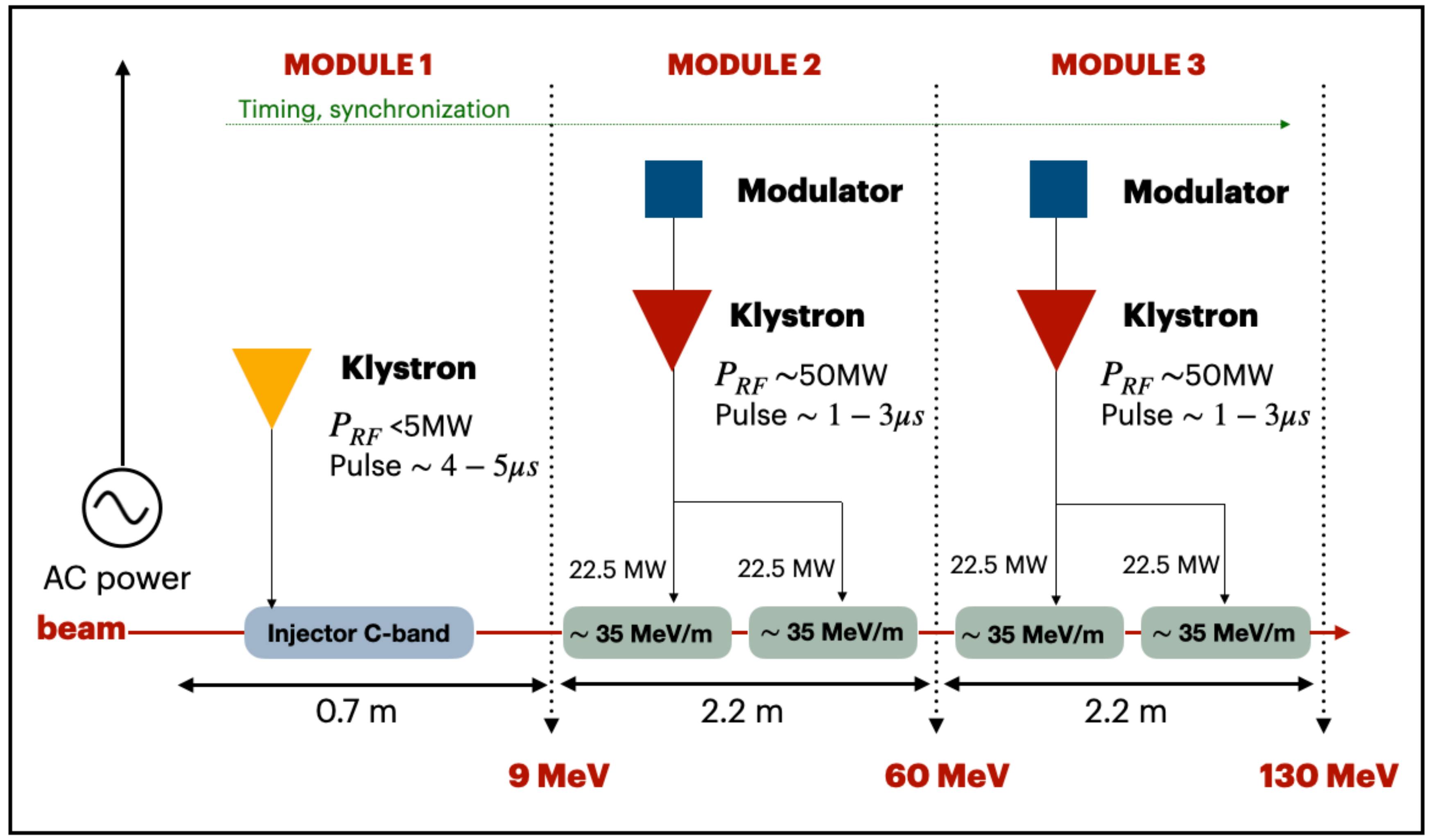
FRIDA

SAFEST project

SApienza **F**lash **E**lectron **S**ource for radio-**T**herapy

Composed by **three modules**, each dedicated to different electron energies (9, 60 and 130 MeV).

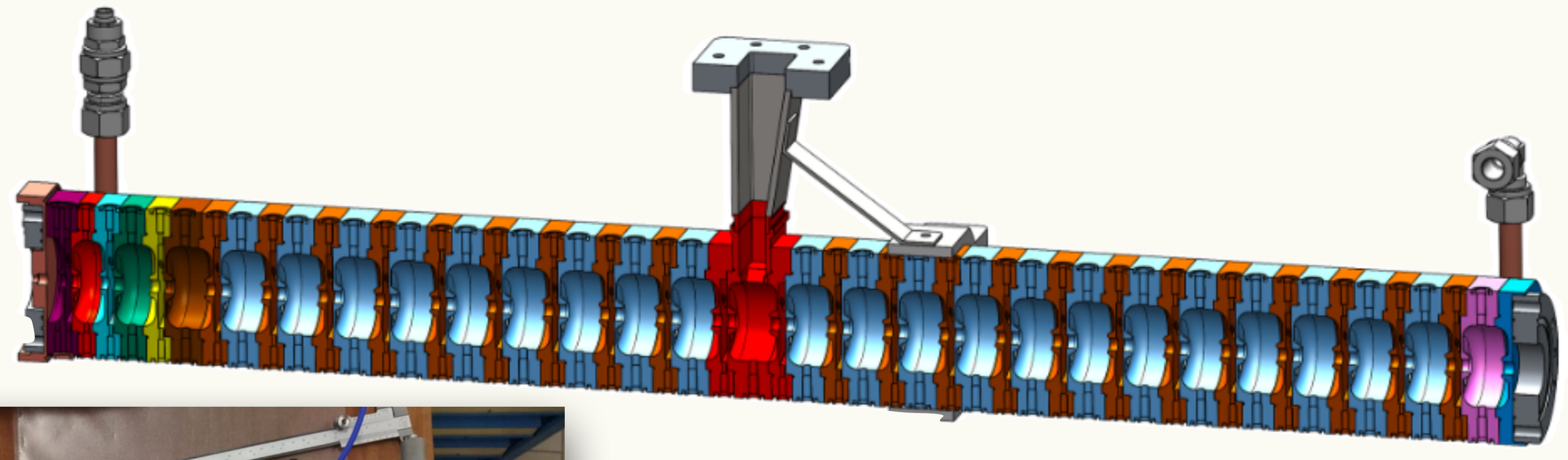
1. **SW injector:** accelerates a current from a pulsed DC gun to ~200 mA (energy of 9-12 MeV);
2. **Compact TW C-band:** high gradient accelerating structure (~ 50 MeV/m).

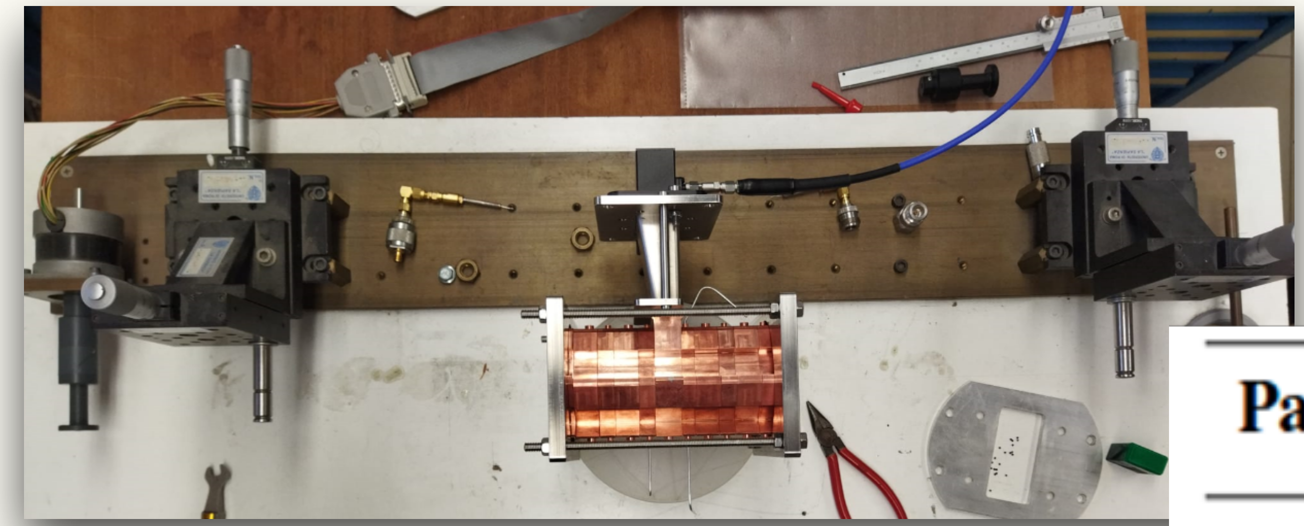


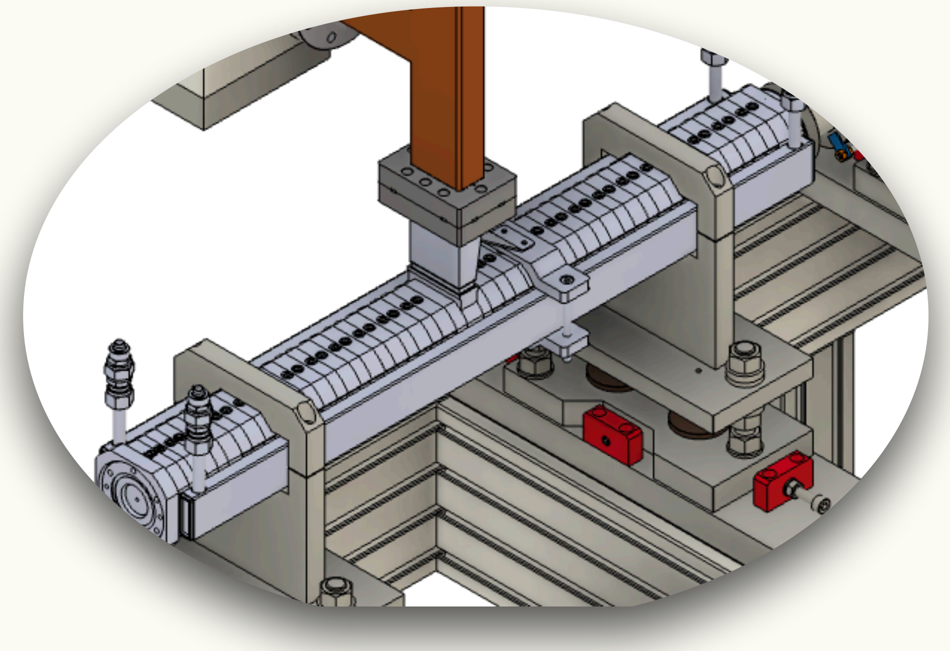
The accelerating structures

STANDING WAVE STRUCTURE

The C-band SW bi-periodic structure operates in a $\pi/2$ -mode. It alternates coupling cavities, with no electric field, and accelerating cavities in which the electric field is maximum.

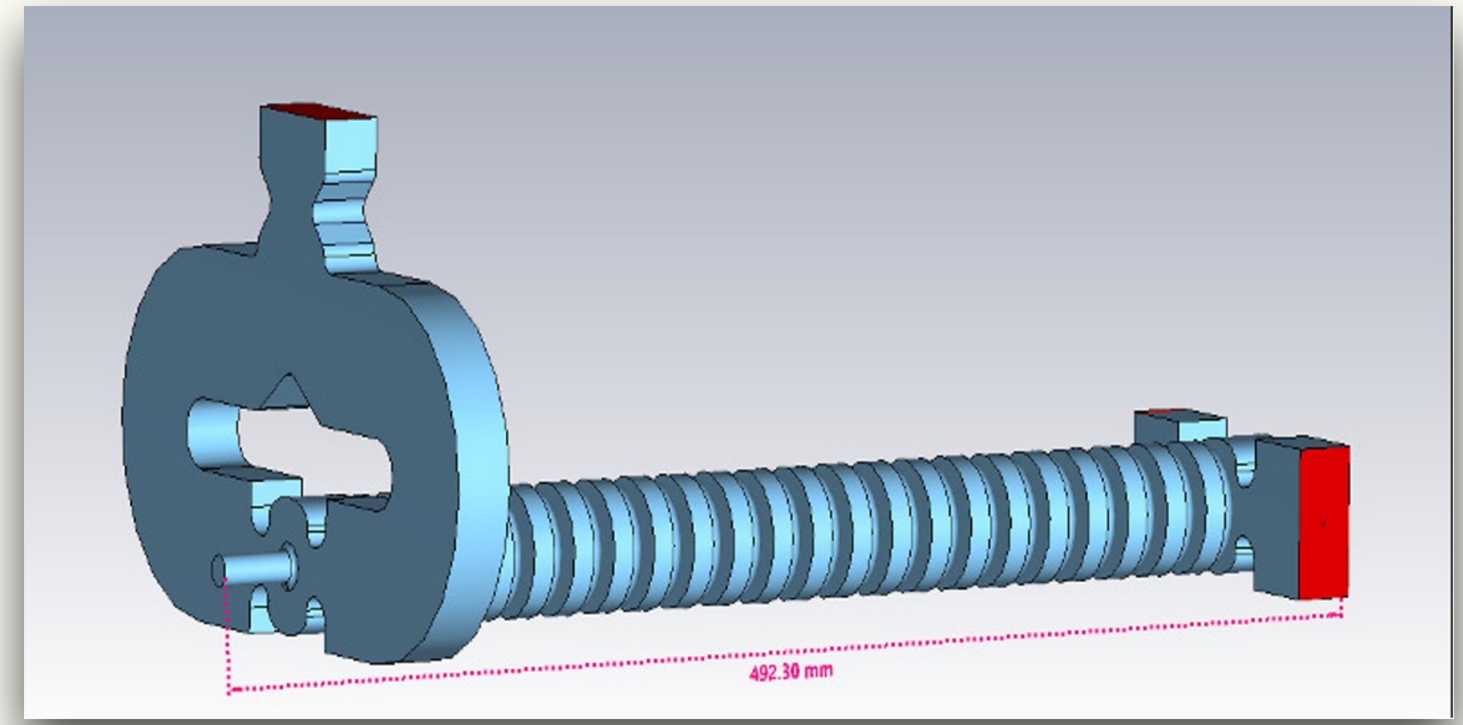






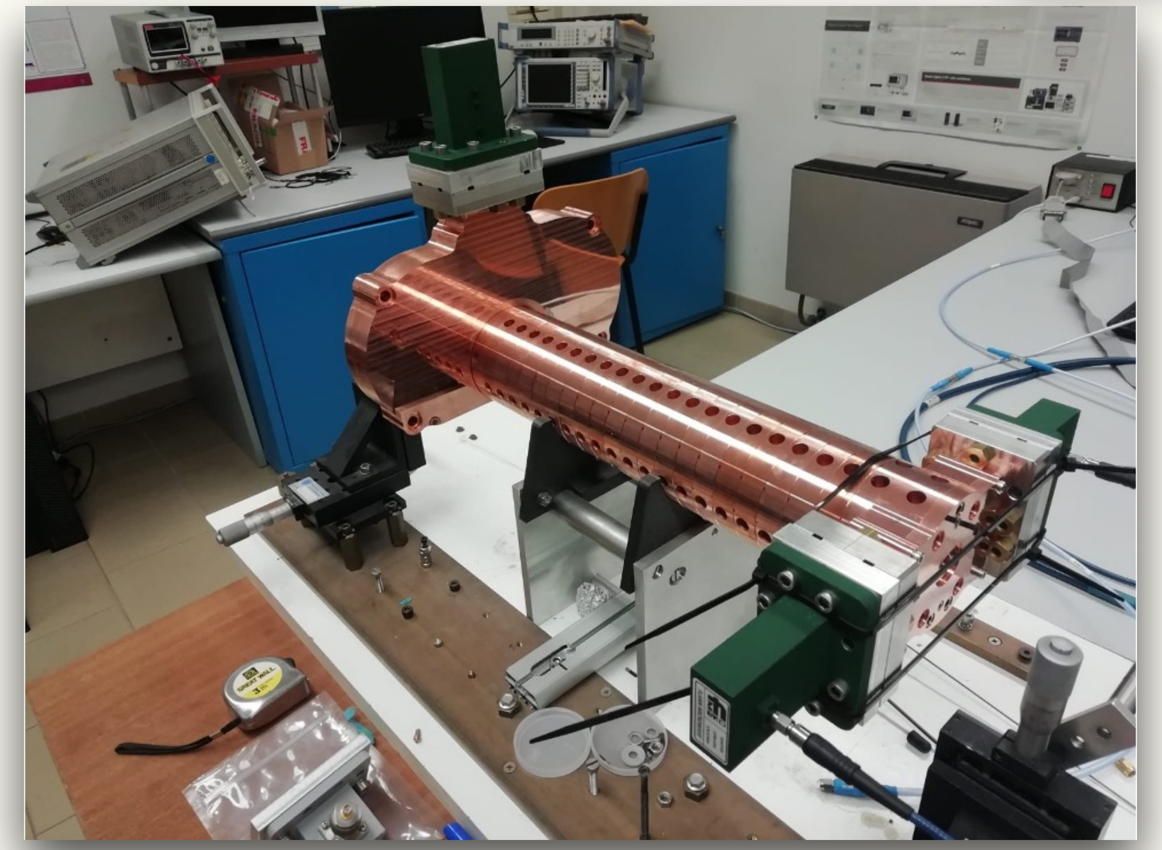
TRAVELING WAVE STRUCTURE

The traveling wave (TW) device is a C-band accelerating structure operating in a TM01-like mode with a $2\pi/3$ -phase advance per cell, optimizing the acceleration process's efficiency.



PARMELA SIMULATIONS!

Parameter	Value
Structure length L_{SW}	69 cm
Shunt Impedance R_{SW}	116 MΩ/m
Quality factor Q_{SW}	10178
Mode of operation	Bi-periodic $\pi/2$
N of accelerating cells N_{SW}	27
Coupling cells length	3 mm
Iris radius	3 mm
Filling time	0.220 μs
Coupling coefficient β_{SW}	1.58

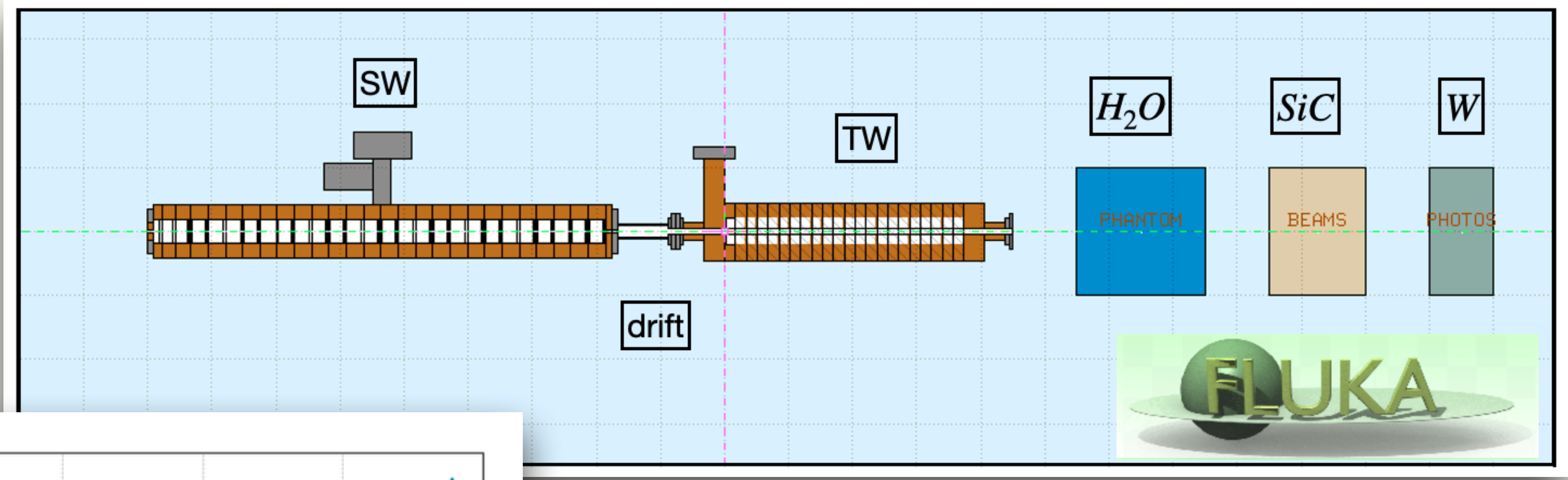


Parameter	Value
Structure length L_{TW}	43 cm
Number of cells	24
Shunt Impedance R_{TW}	107 MΩ/m
Quality factor Q_{TW}(cell)	10630
Type	Constant Impedance
Operation mode	$\frac{2}{3}\pi$
Iris radius	5 mm
Filling Time	0.143 μs
Group velocity v_g	0.01c*

(*) c = speed of light

Radioprotection studies

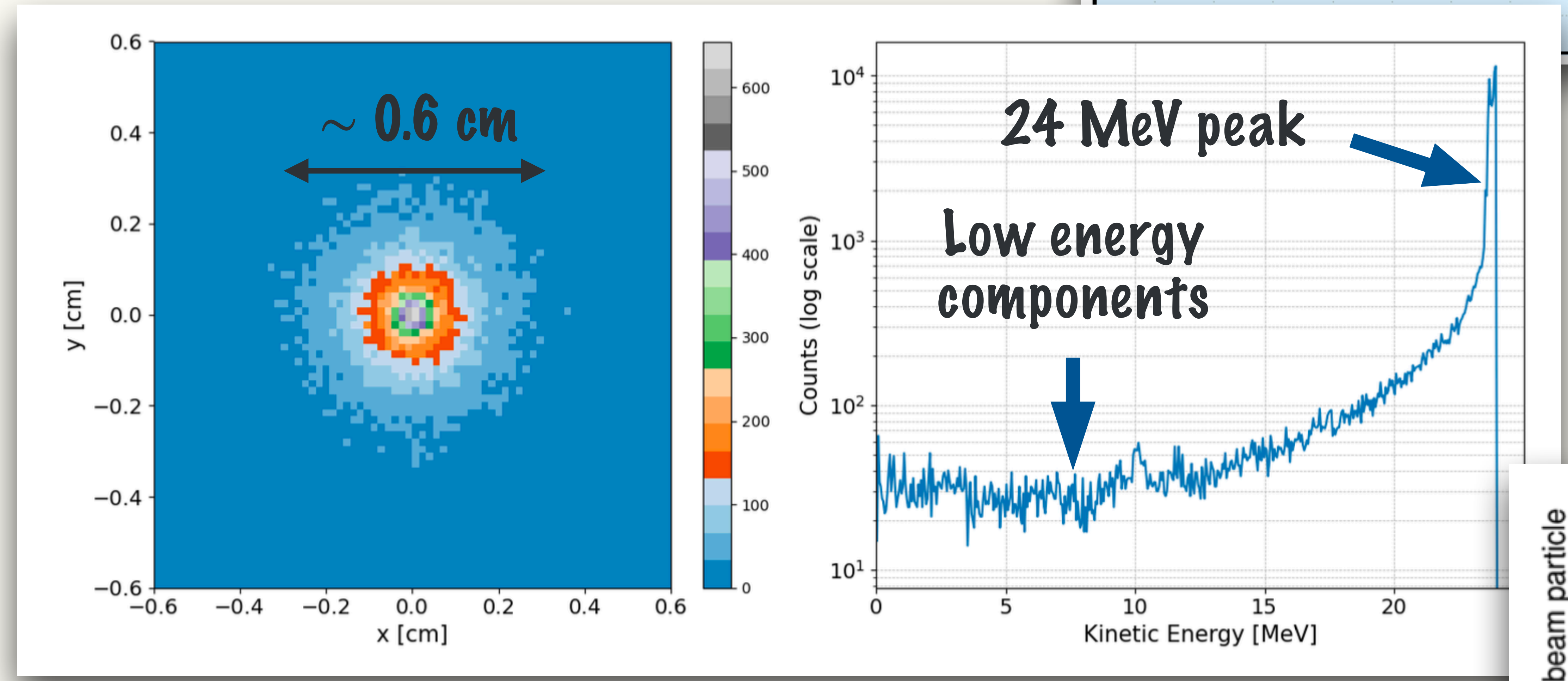
1 **Replicate the geometry and materials** of the prototype.



GOAL

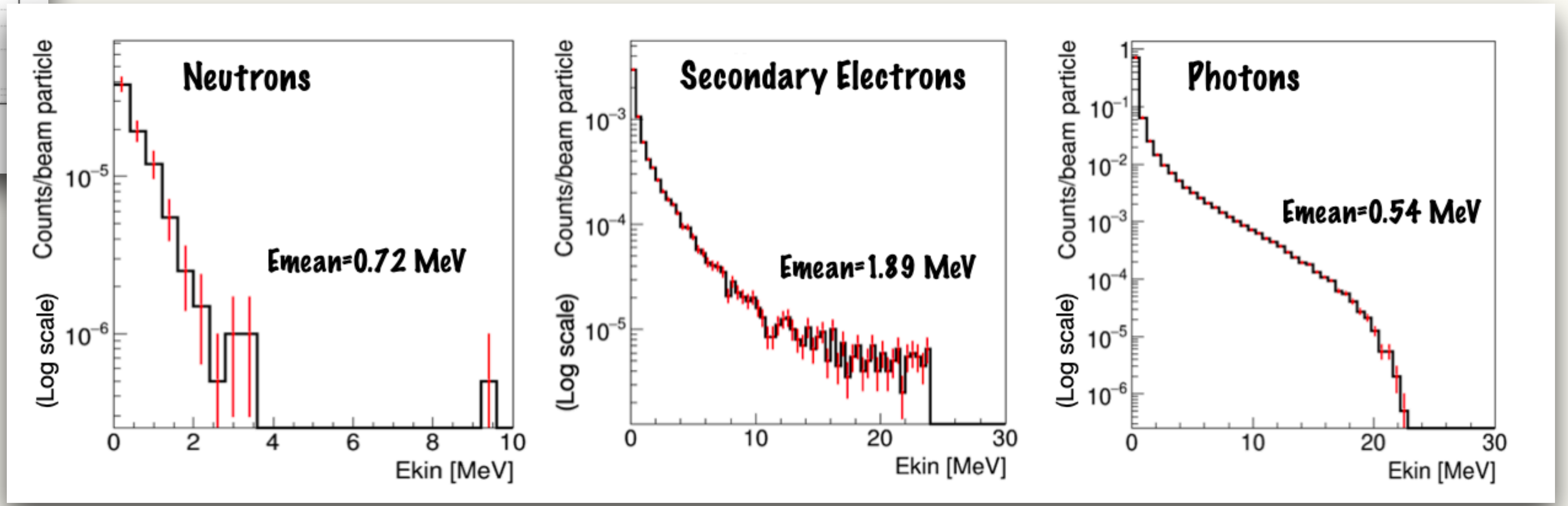
Evaluate the dispersed radiation to design the needed shielding.

Exiting particles: ~7.4 % of total



2 Study of **the position, direction, and energy** of particles exiting from the accelerator structure.

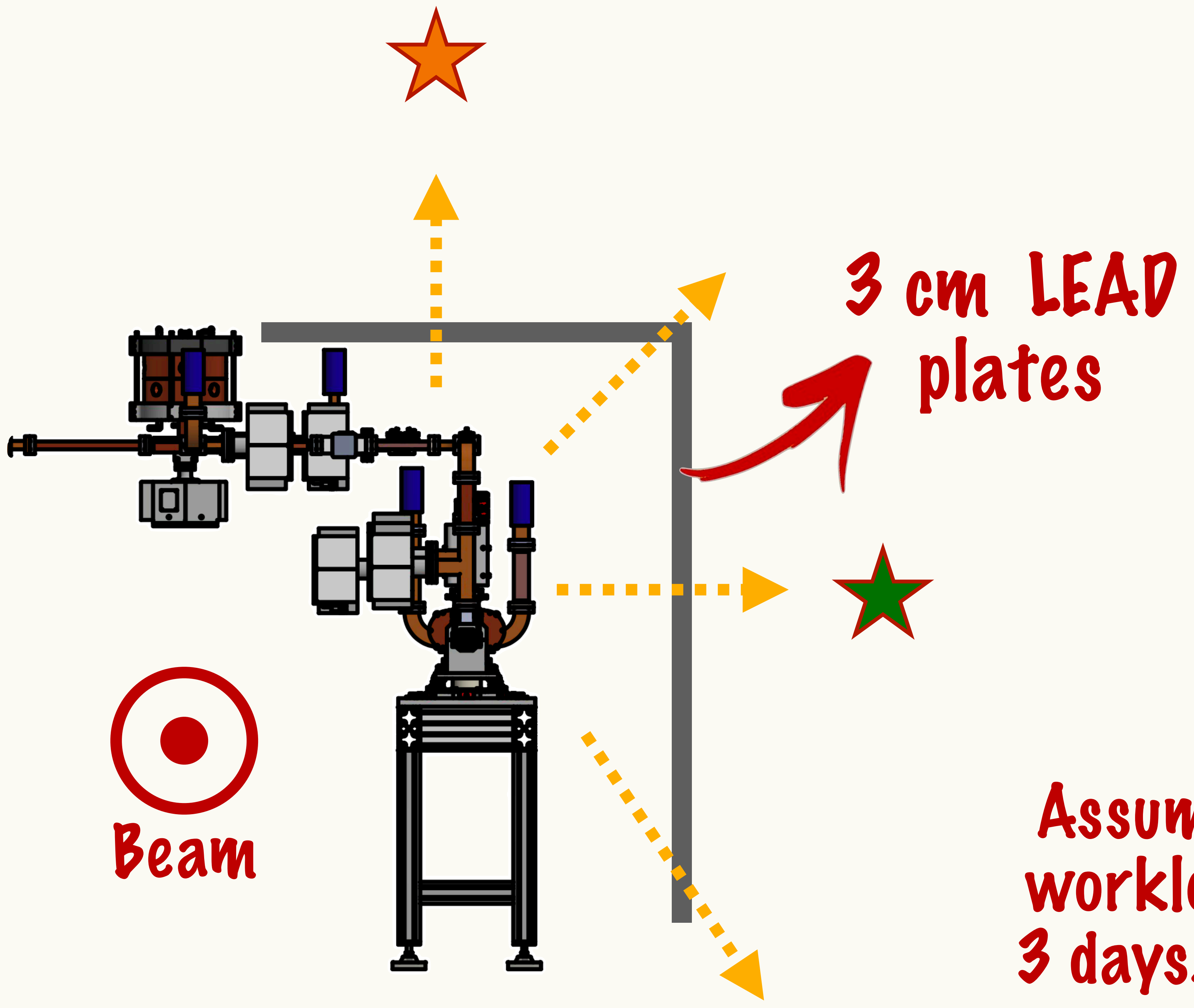
3 **Characterize the different types of radiation produced** by various interactions within the accelerator.



Statistics: 10^8 primaries

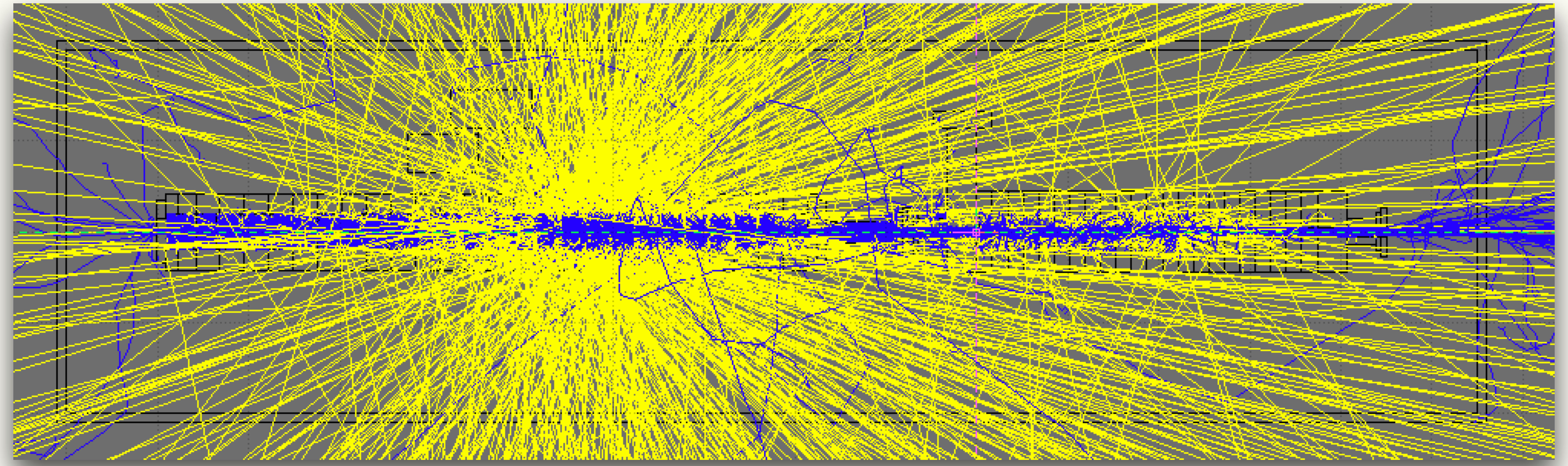
Radioprotection studies

The dose was evaluated at different positions and **radiation shielding barriers were calculated**.



	Laterally [Gy/prim] ★	Above [Gy/prim] ★
NO SHIELDING	$7.3 \cdot 10^{-18} \pm 3.3 \cdot 10^{-19}$	$3.9 \cdot 10^{-18} \pm 2.3 \cdot 10^{-19}$
3 cm SHIELDING	$5.9 \cdot 10^{-19} \pm 7.6 \cdot 10^{-20}$	$3.5 \cdot 10^{-19} \pm 4.6 \cdot 10^{-20}$

Assuming a workload of 3 days/week



FLUKA 2020: simulation of the electron beam passing through the accelerating structure

RESULTS:

Lead plates (3 cm of thickness) around the structure are enough to ensure safety of users and workers.

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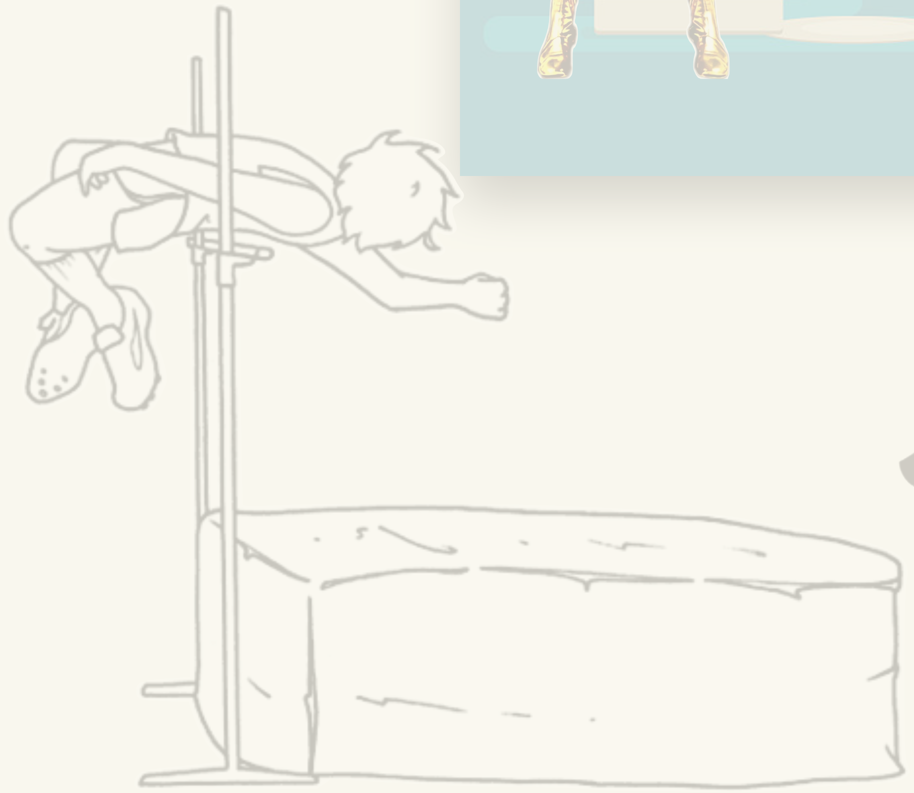
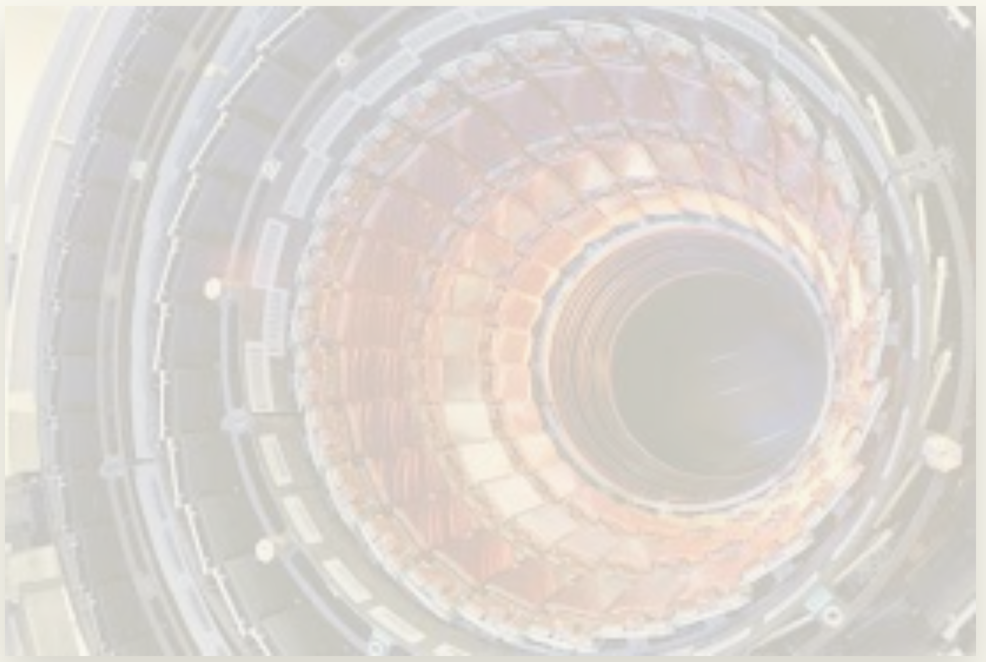
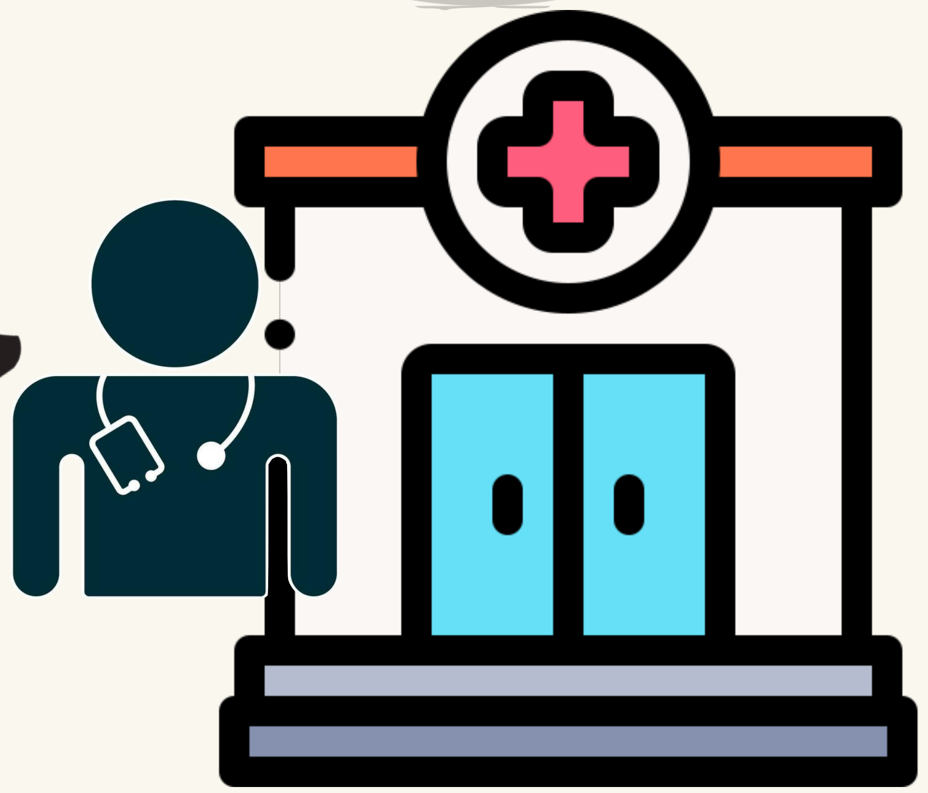
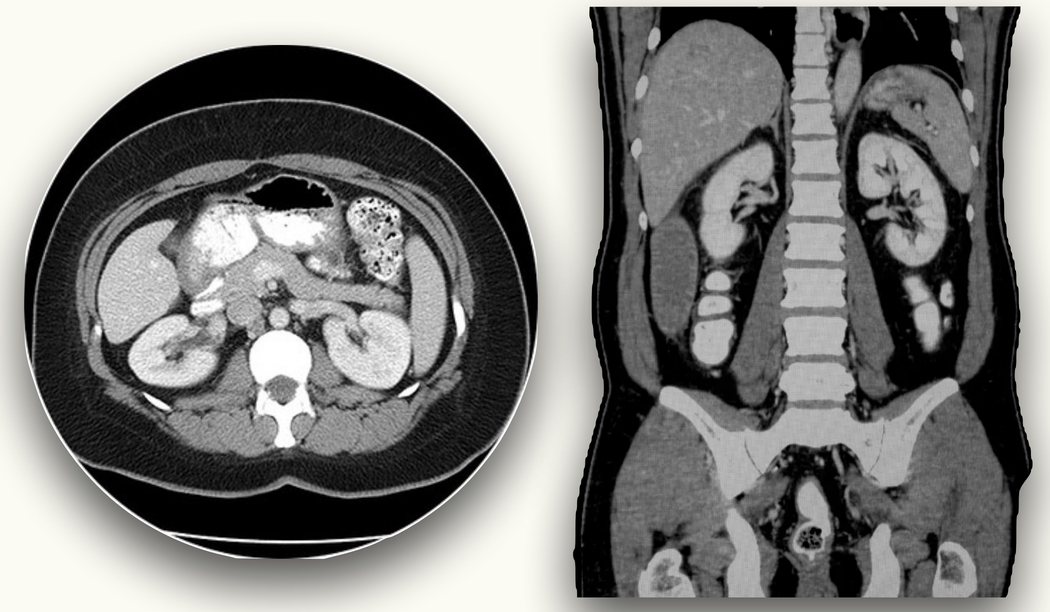







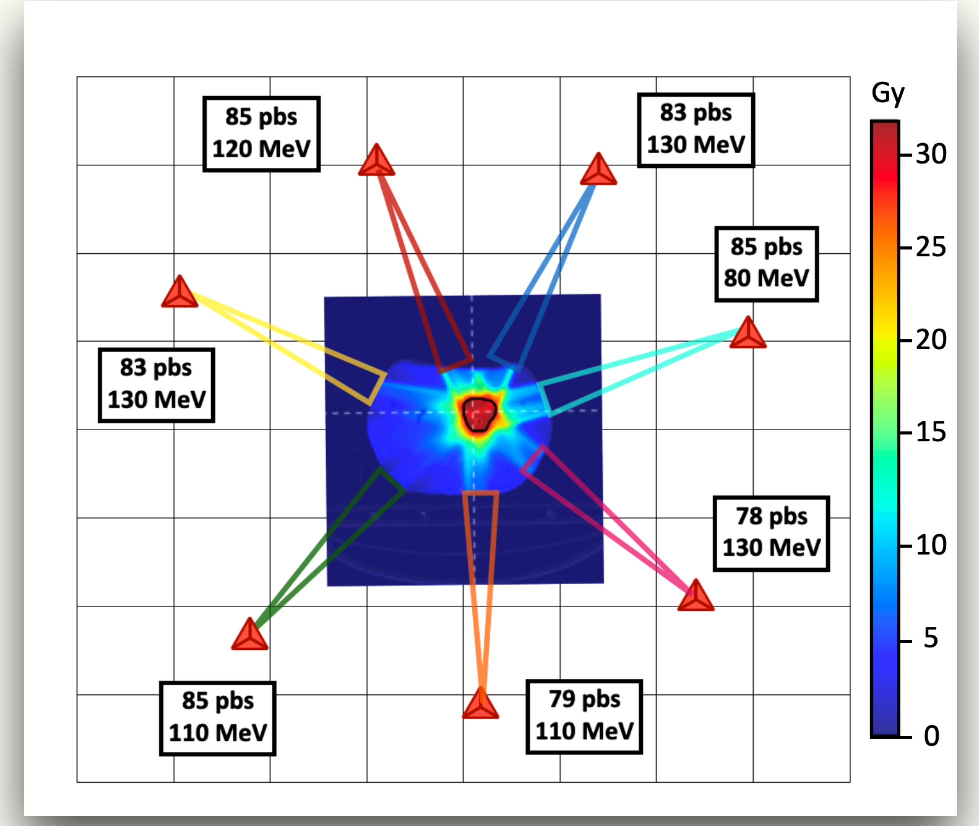
Treatment Planning System



PATIENT IMAGING

Patient		
Organ	Dosimetric constraint	Volume [cc]
PTV	$V_{95\%}$>95%,D_{max} ≤105[illegible]	[illegible]
Optic nerves	$D_1 \leq 54$ Gy(RBE)	0.95
Chiasm	$D_1 \leq 54$ Gy(RBE)	0.03
Posterior optical path	$D_1 \leq 54$ Gy(RBE)	[illegible]
Eyeballs	$D_1 \leq 40$ Gy(RBE)	8.14
Brainstem	$D_1 \leq 54$ Gy(RBE)	28.19
Carotid arteries	D_{max} ≤105%	1.15

DOSIMETRIC CONSTRAINTS



PHYSICAL MODEL

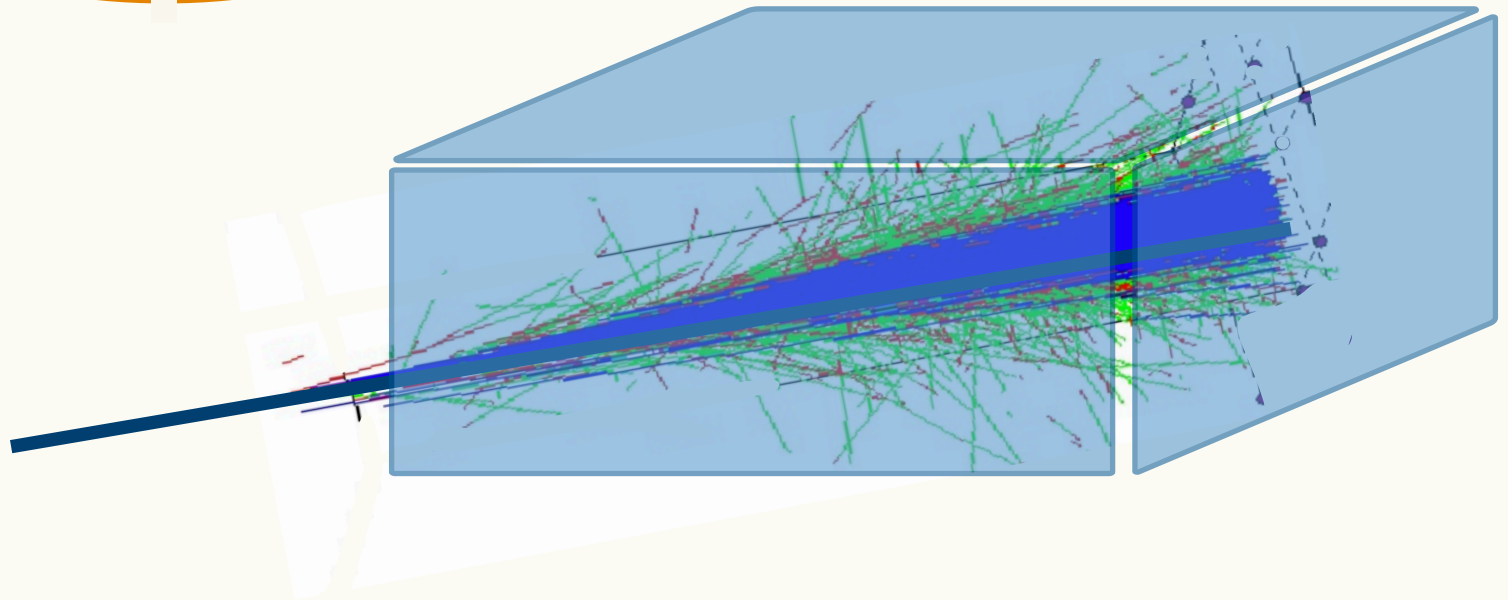
Inputs

TPS Optimization algorithm

Ouputs

ACCELERATOR PARAMETERS

1. Energy
2. Intensity
3. Direction



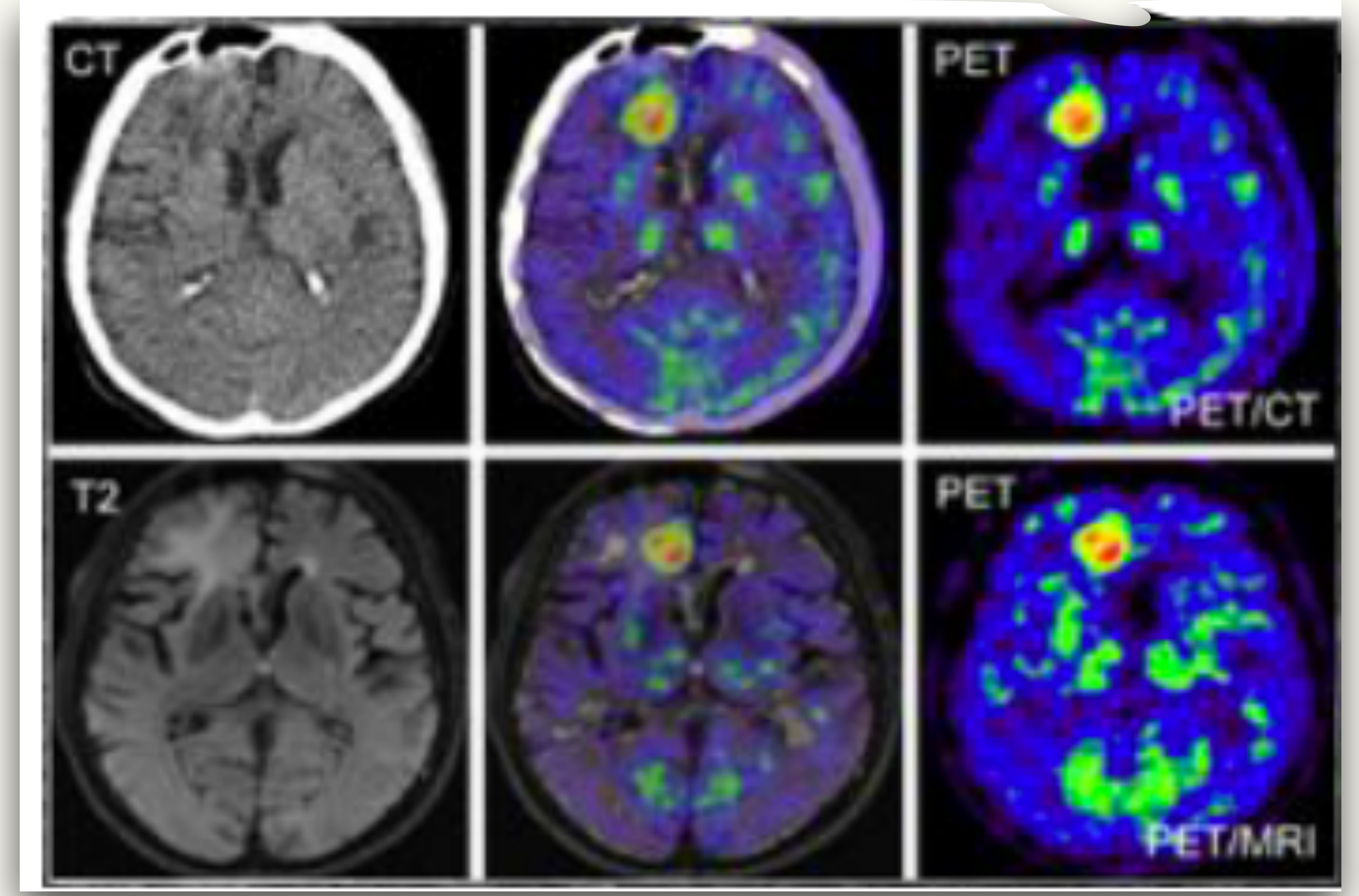
Treatment Planning System

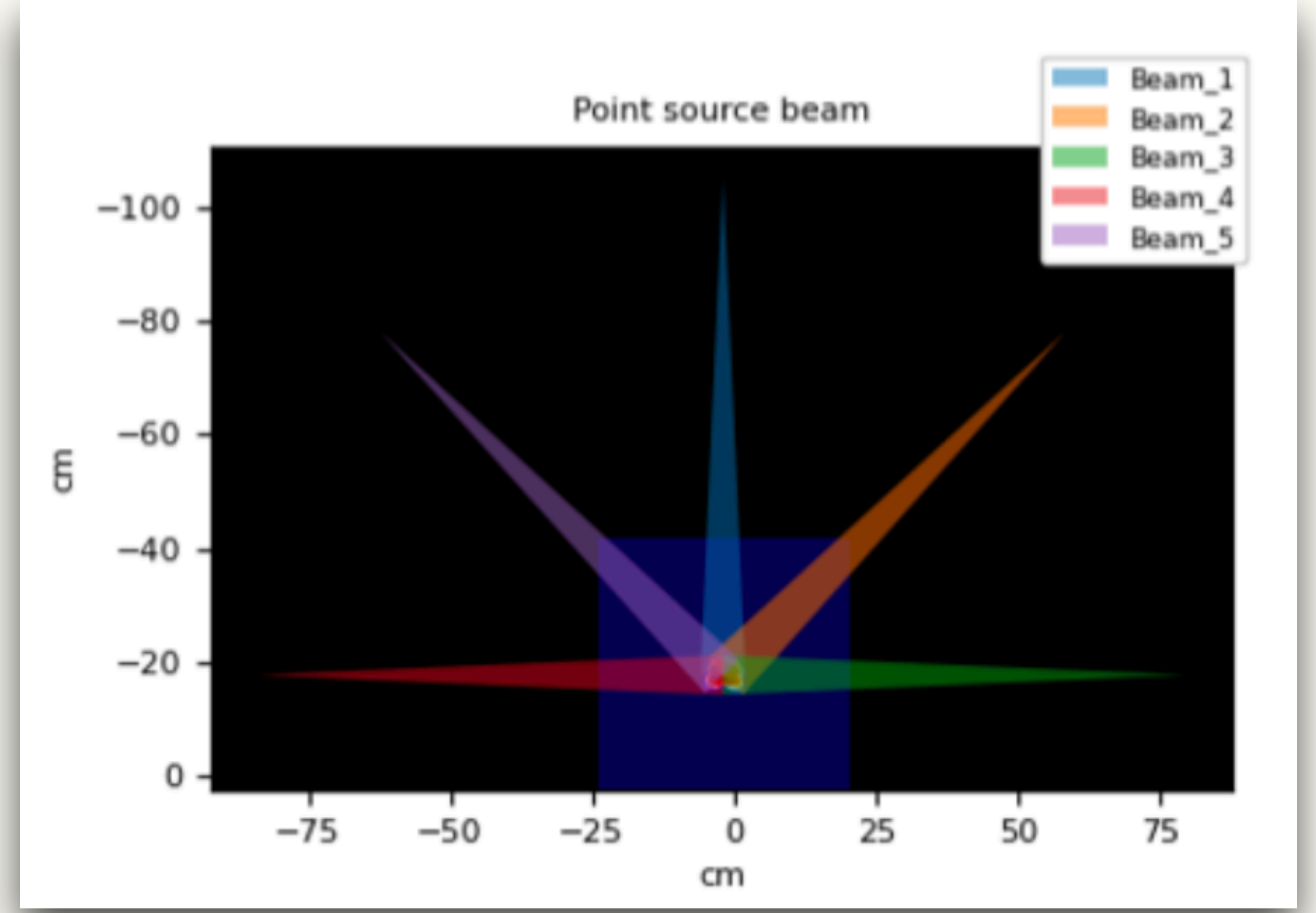
VHEE irradiation was simulated assuming the **compact C-band acceleration technology** which will be capable of delivering **multi-fields** with an **active scanning-like approach.**

CT IMAGES & FIELD DIRECTIONS

- **Planning CT**
- **Entry points**
- **Dosimetric constraints**
- **Prescribed dose**

Provided by the hospital where the patients were treated.





Organ	dosimetric constraints
Target volume	$V_{95\%} > 95\%$, never above 107%
Rectum	$V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, $V_{75} < 15\%$
Anus	$V_{30} < 50\%$
Bulbourethral Glands	$\bar{D} < 50$ Gy
Femurs	$\bar{D} < 52$ Gy, $V_{60} < 5\%$
Bladder	$\bar{D} < 65$ Gy, $V_{65} < 50\%$, $V_{70} < 35\%$, $V_{75} < 25\%$, $V_{80} < 15\%$

A TPS for VHEE does not yet exist, so we derive geometric, dosimetric, and energy information from standard radiotherapy

Treatment Planning System

VHEE irradiation was simulated assuming the **compact C-band acceleration technology** which will be capable of delivering **multi-fields** with an **active scanning-like approach.**

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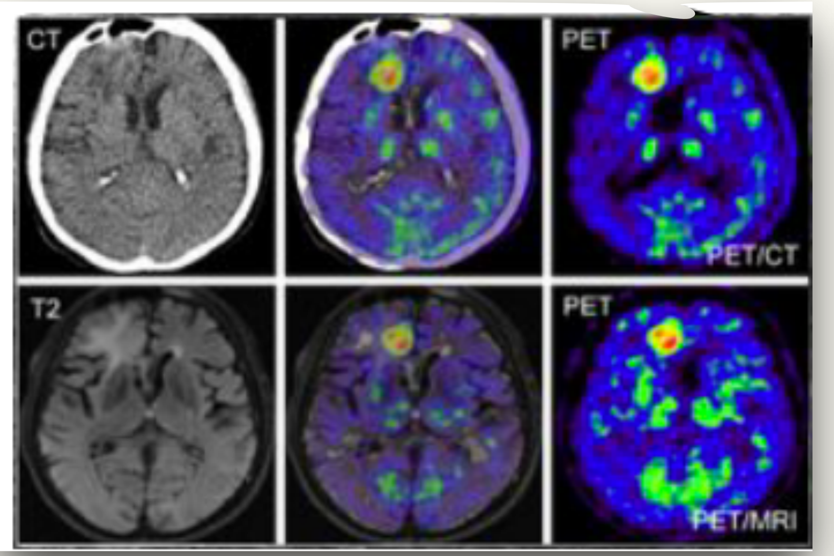

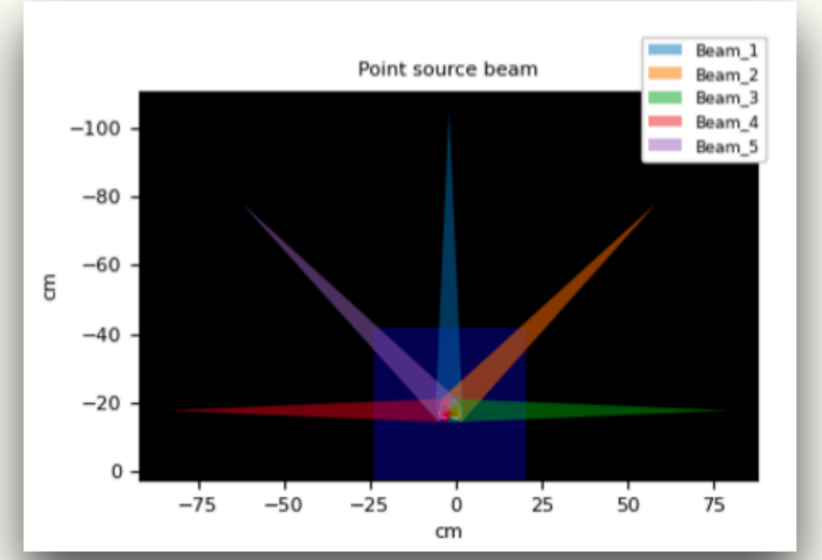

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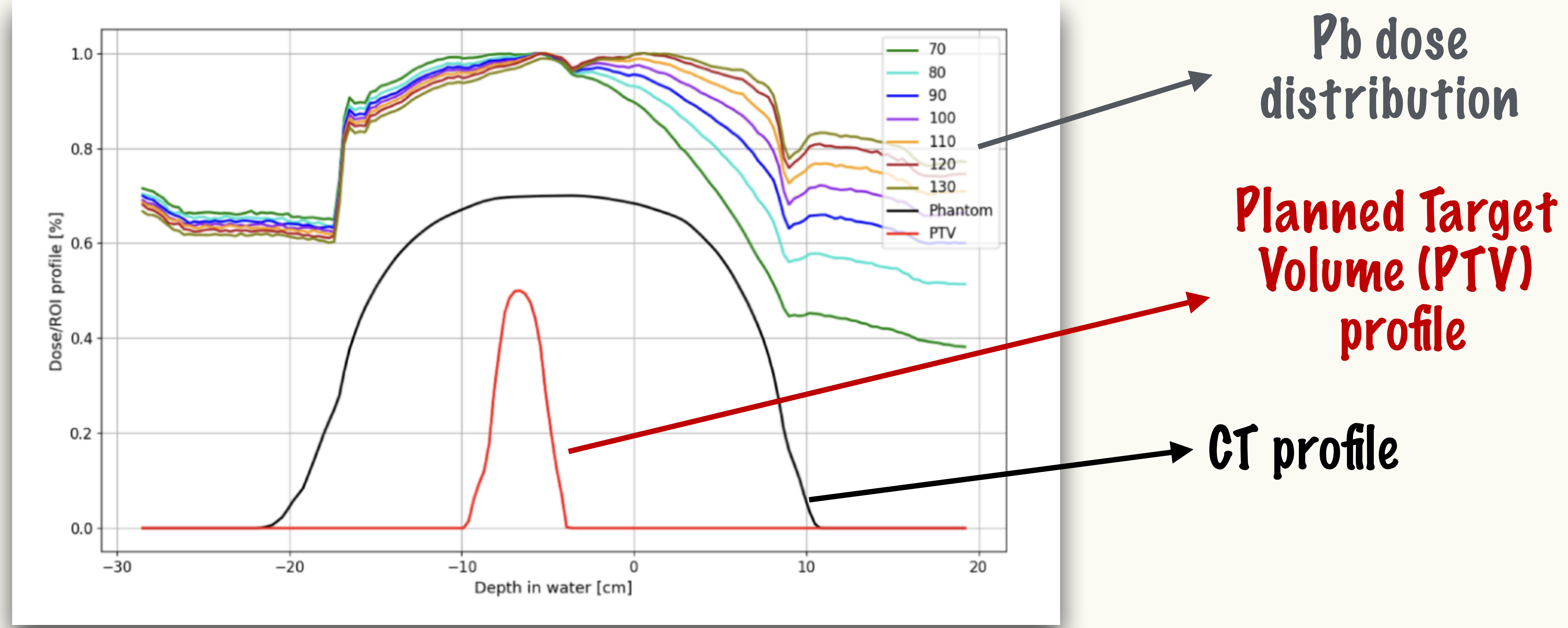
Bulbourethral Glands	$\bar{D}$ < 50 Gy
Femurs	$\bar{D}$ < 52 Gy, V_{60} <5%
Bladder	$\bar{D}$ < 65 Gy, V_{65} <50%, V_{70} <35%, V_{75} <25%, V_{80} <15%

ENERGY SELECTION

The **initial** beam energies (70-150 MeV) are chosen looking at the dose distributions obtained simulating **a single PB delivered at the center of the PTV**.



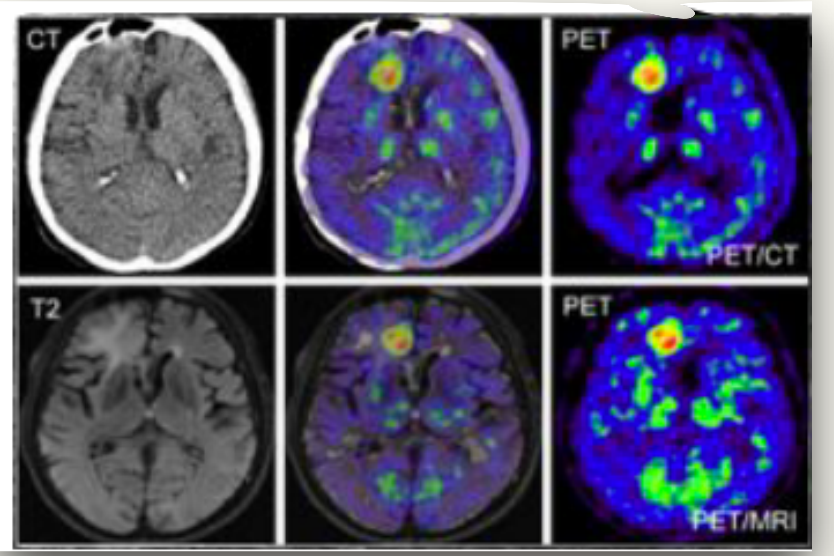
Treatment Planning System

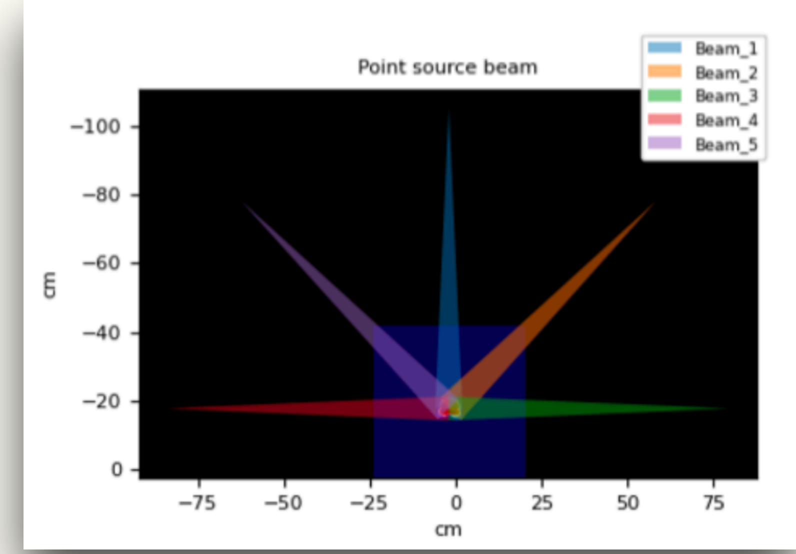
VHEE irradiation was simulated assuming the **compact C-band acceleration technology** which will be capable of delivering **multi-fields** with an **active scanning-like approach.**

CT IMAGES & FIELD DIRECTIONS

- **Planning CT**
- **Entry points**
- **Dosimetric constraints**
- **Prescribed dose**

Provided by the hospital.





Organ	dosimetric constraints
Target volume	$V_{95\%} > 95\%$, never above 107%
Rectum	$V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, $V_{75} < 15\%$
Anus	$V_{30} < 50\%$
Bulbourethral Glands	$\overline{D} < 50$ Gy
Femurs	$\overline{D} < 52$ Gy, $V_{60} < 5\%$
Bladder	$\overline{D} < 65$ Gy, $V_{65} < 50\%$, $V_{70} < 35\%$, $V_{75} < 25\%$, $V_{80} < 15\%$

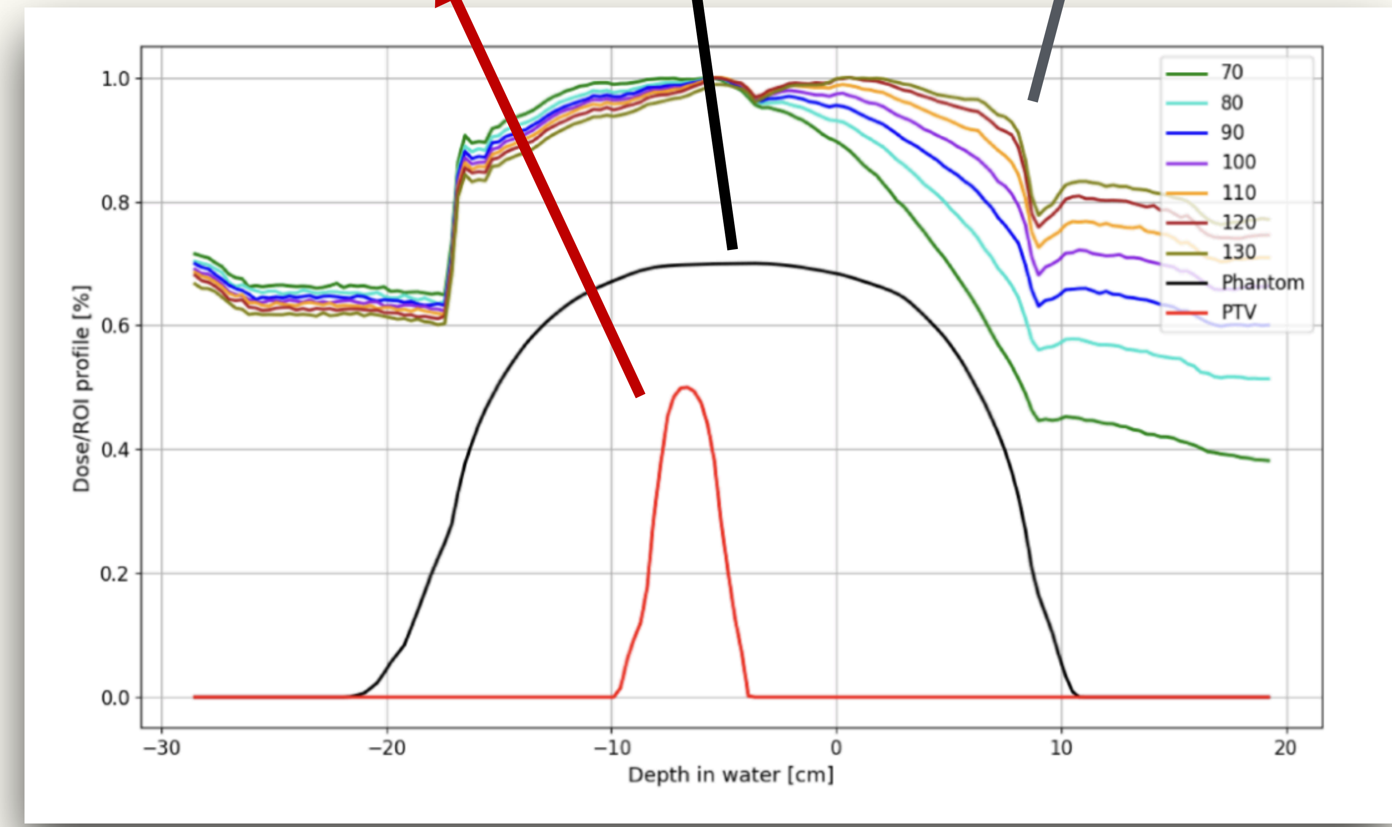
ENERGY SELECTION

The **initial** beam energies are chosen simulating **a single PB delivered at the center of the PTV**.

Pb dose distribution

CT profile

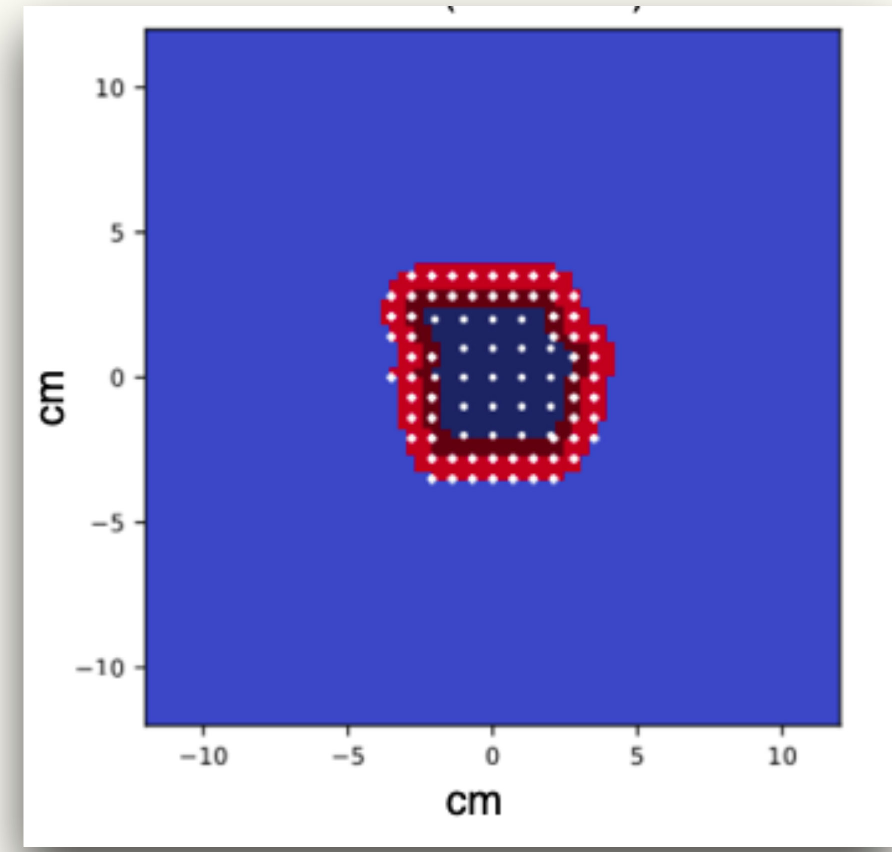
PTV profile



PENCIL BEAM CONFIGURATION

The **size of each PB** is defined using **active scanning delivery.**

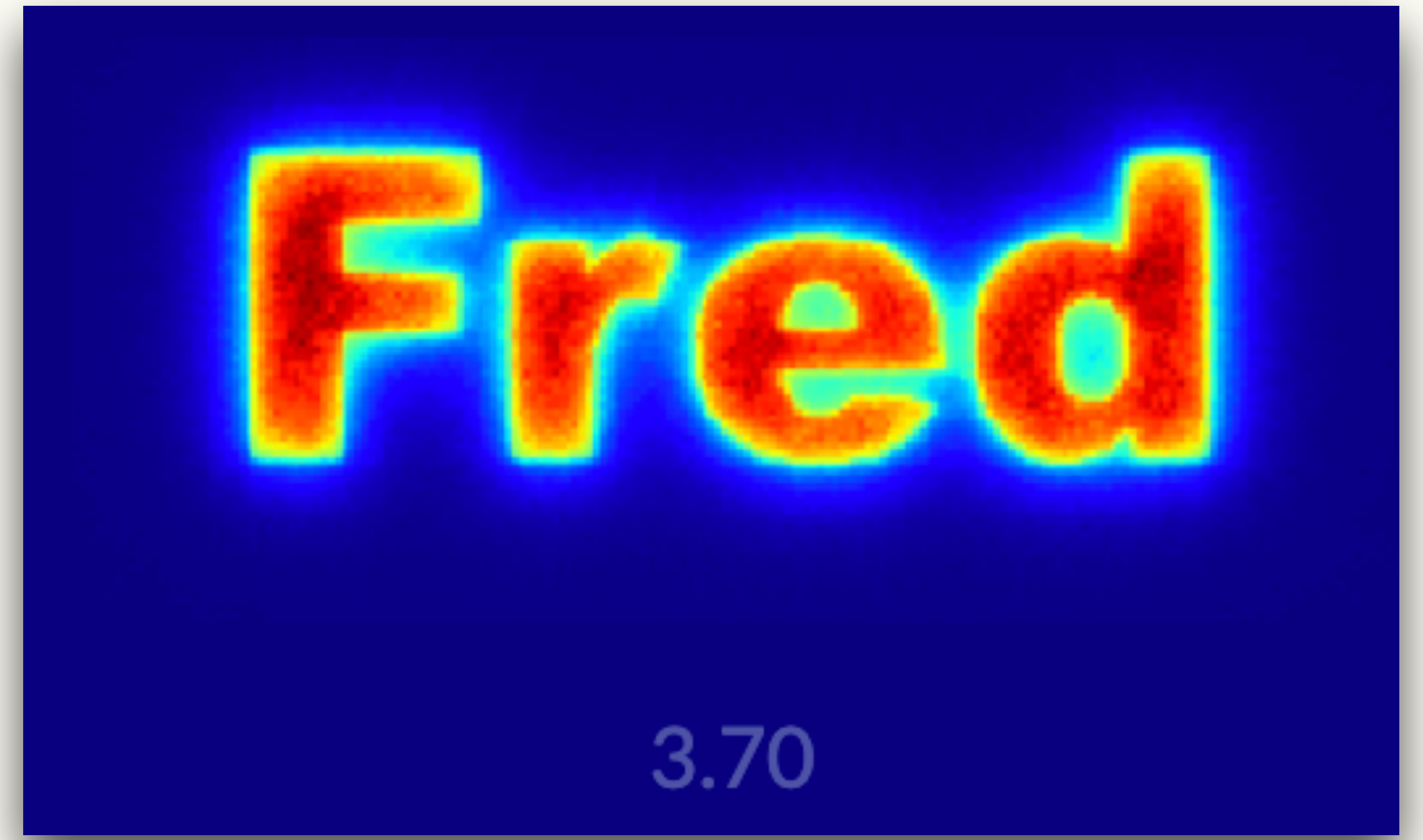
The spot spacing varies according to the irradiation geometry



To reduce the number of spots, and thus the computational time (**FLASH regime in mind!**)

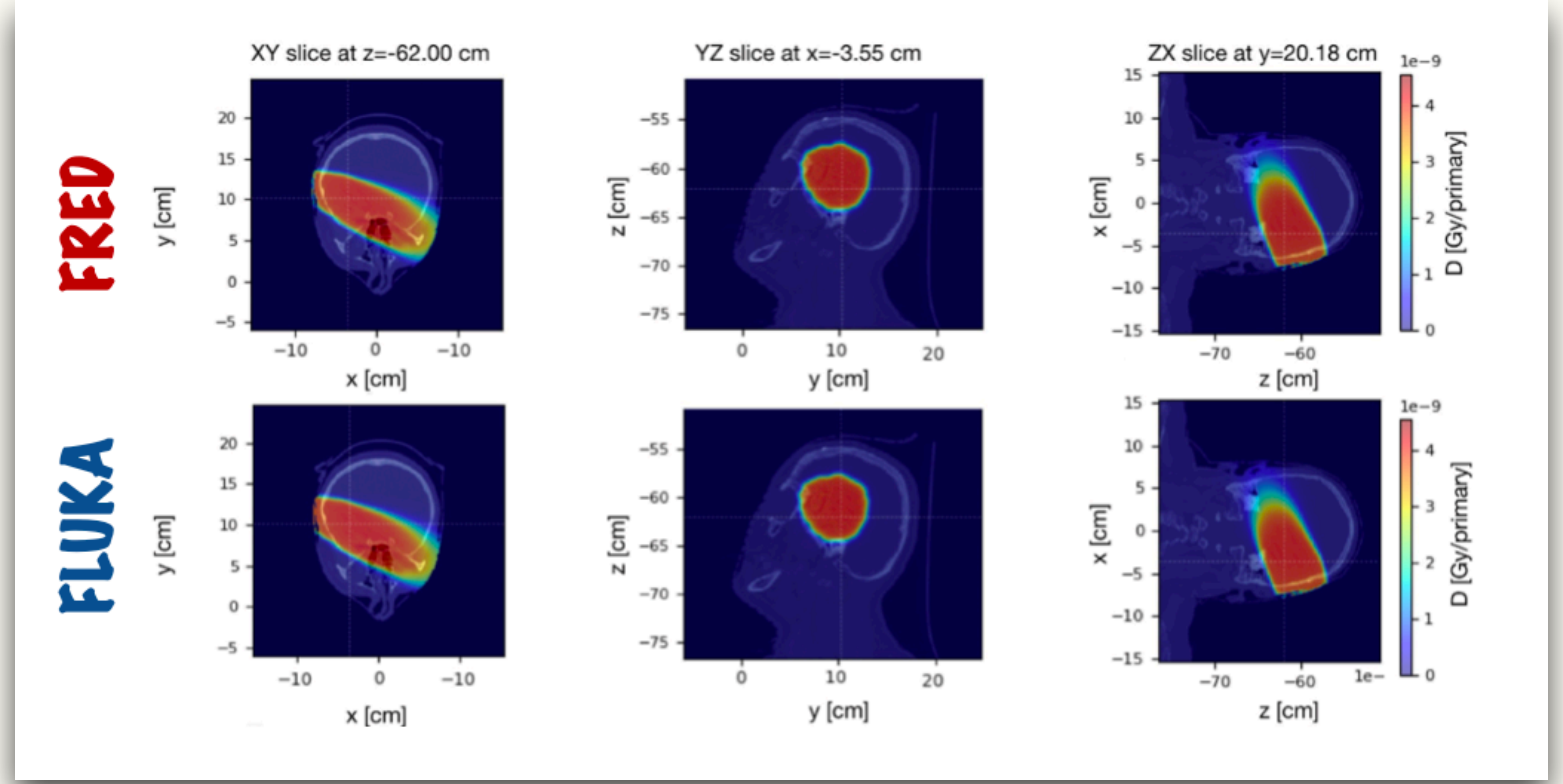
Dose evaluation: FRED

TPS softwares use an **analytical** dose evaluation approach, which may be **not so accurate**. Our solution is to use **FRED**.



The FRED MC has been developed to allow a **fast optimization of the TPS** in Particle Therapy, while keeping the dose release accuracy typical of a MC tool. Today **FRED protons is used** in various medical and research centers: MedAustron (Vienna), APSS (Trento), Maastro (Maastricht) and CNAO (Pavia) while **C ions and electromagnetic models for FRED are used for research purposes**.

Gamma-Index pass rate (2mm/2%) 97%



Developed to work on GPU

Reduces the simulation time **by a factor 1000** compared to standard MC

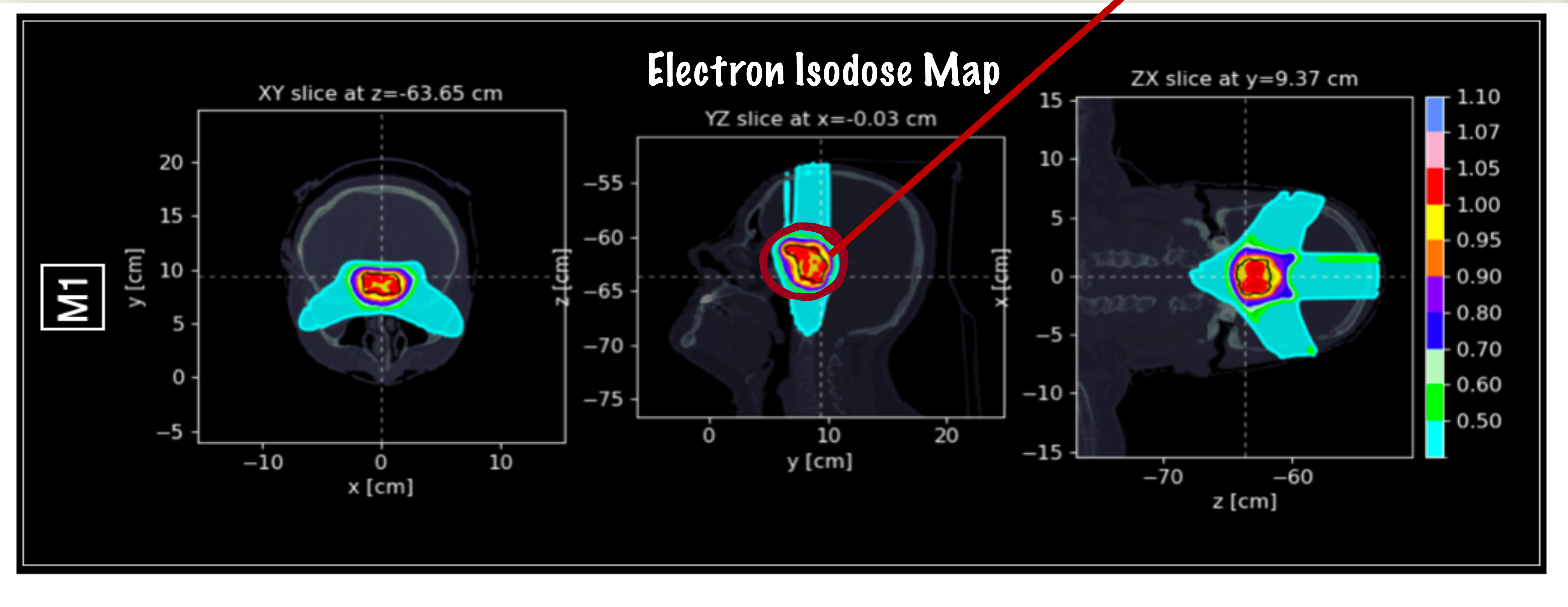
Feasability study on real patients

Validate VHEE treatment on DIFFICULT GEOMETRY due to the PTV position

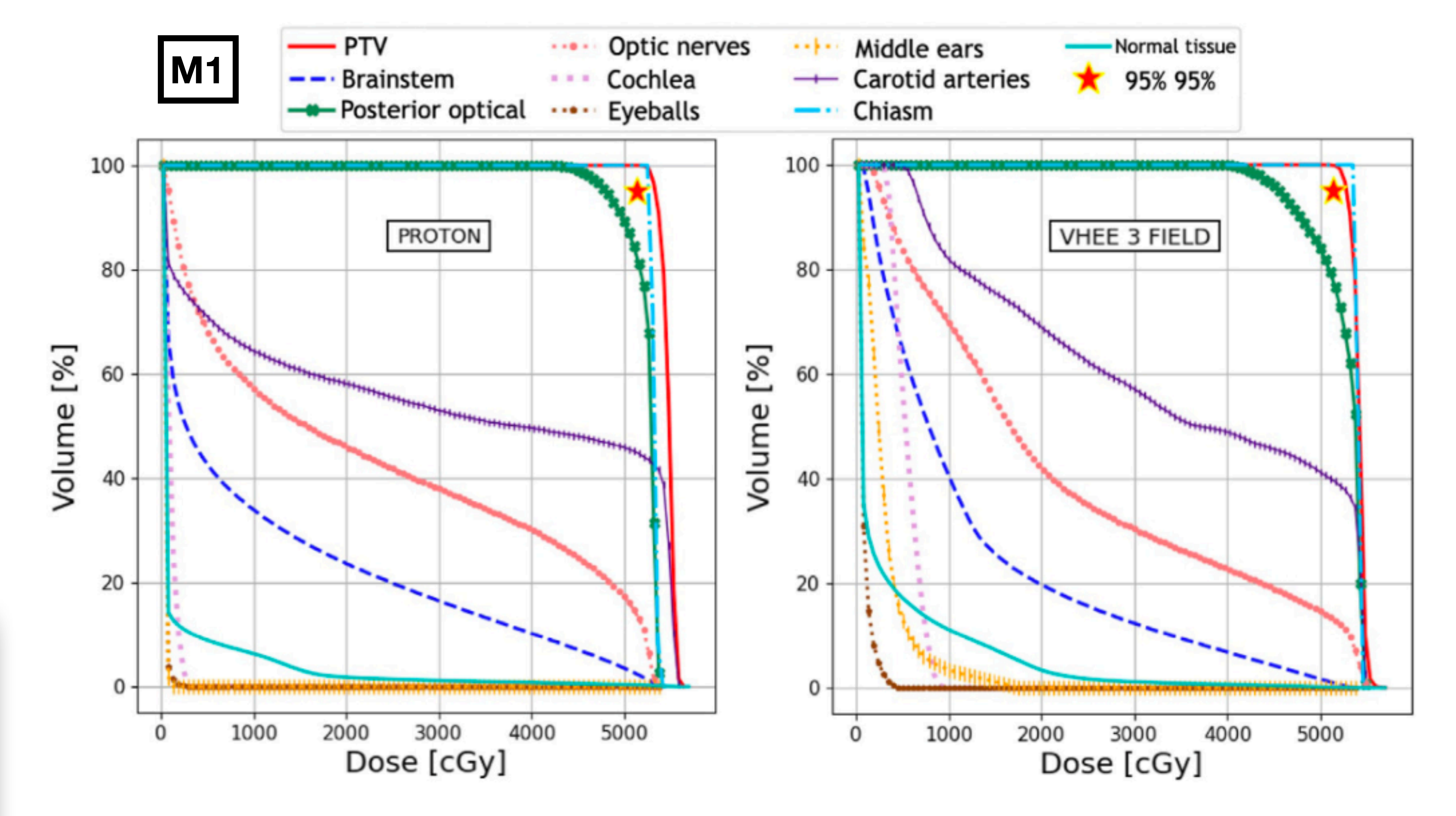
M1
- **Meningioma**: 3 fields, with a prescription to the **PTV of 54Gy(RBE)** in **27 fractions**.

C1
- **Chordoma**: 4 fields, with a prescription to the **PTV of 54Gy(RBE)** in **30 fractions**.

PTV



Dose Volume Histogram



Comparing PT delivered plan and VHEE simulated plan, the DVH show COMPETITIVE performance.

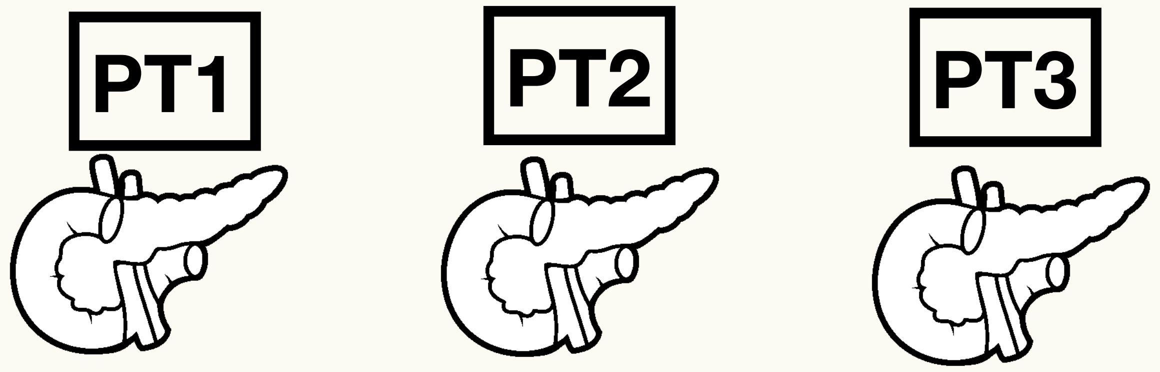
Similar results for C1, with even more complex geometry (in SPARE!)

Feasability study on real patients

For pancreatic tumors it is crucial to **minimize radiation-induced toxicity to the nearby duodenum.**

GOOD CANDIDATE FOR FLASH IRRADIATION!

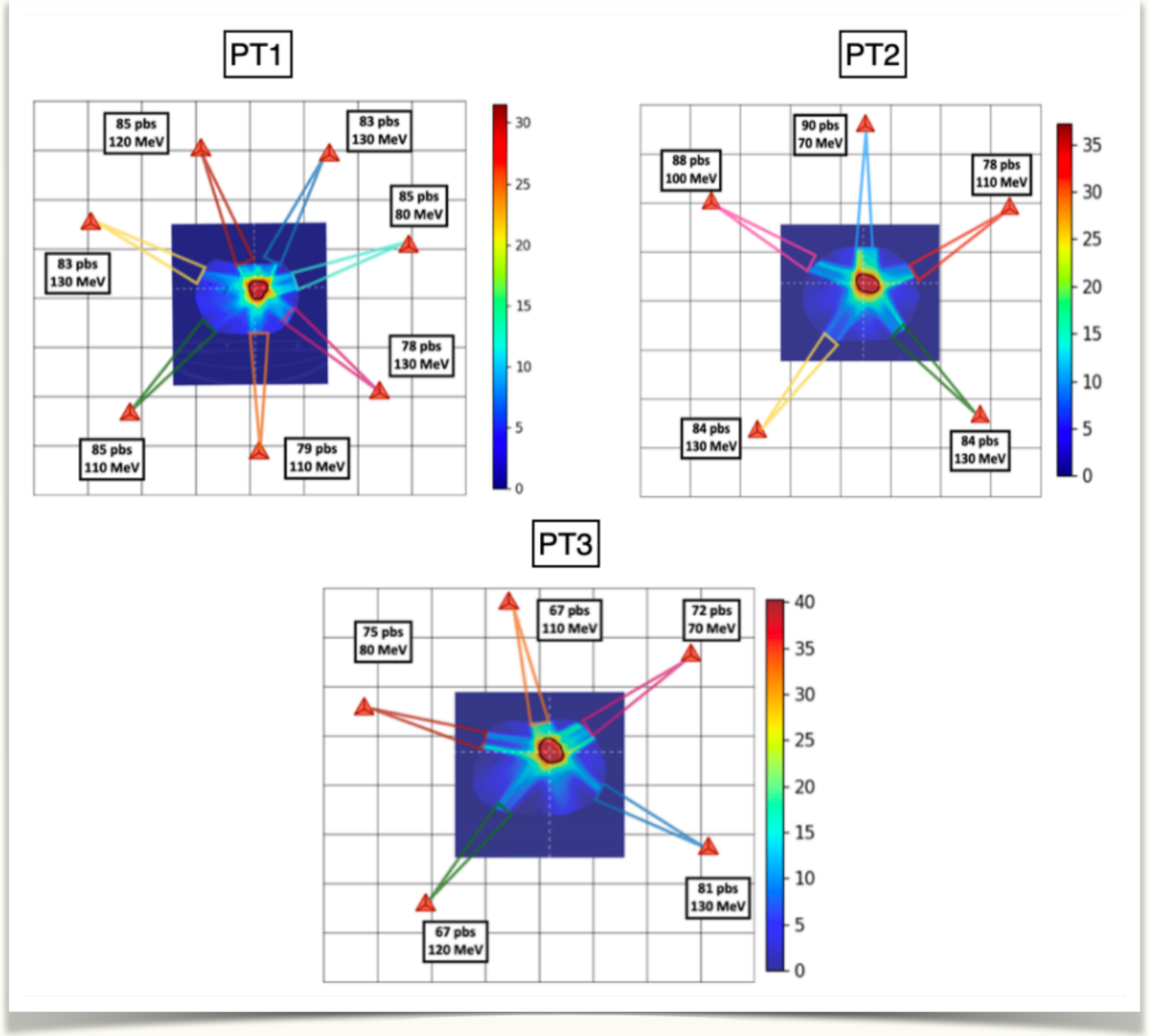
PRESCRIPTION



- **PT1**: seven fields were used, with a prescription to the **PTV of 30 Gy** in **5 fractions.**
- **PT2**: five fields were used, with a prescription to the **PTV of 32.5 Gy** in **5 fractions.**
- **PT3**: five fields were used, with a prescription to the **PTV of 30 Gy** in **5 fractions.**

FONDAZIONE
POLICLINICO UNIVERSITARIO
CAMPUS BIO-MEDICO

FIELD GEOMETRY



DOSIMETRIC CONSTRAINTS

ROI	Constraints	Volumes [cc] PT1	PT2	PT3
PTV	$V^{PT1}_{95\%}$ >95% $V^{PT1}_{105\%} < 5\%$ $V^{PT2,PT3}_{100\%} > 95\%$ $D^{PT2}_{max} \leq 40.95$ Gy $D^{PT3}_{max} \leq 37.8$ Gy	94.9	81.6	117.9
Duodenum	$V_{35Gy} < 0.1$ cc $V_{25Gy} < 10$ cc	93.5	94.4	101.6
Bowel	$V_{30Gy} < 1$ cc	1035.1	563	1511.4
Stomach	$V_{12Gy} < 50$ cc $V_{33Gy} < 0.1$ cc	173.2	168.6	287.1
Spinal cord	$V_{25.3Gy}$ <0.035 cc	60.3	111	109.2
Liver	$D_{mean} \leq 13$ Gy $V_{15Gy} < 700$ cc	892.5	1202.8	1504
Kidneys	$V^{P}_{10Gy} < 45\%$	256.6	250.3	940.7

Slightly different modalities for irradiation

Feasability study on real patients

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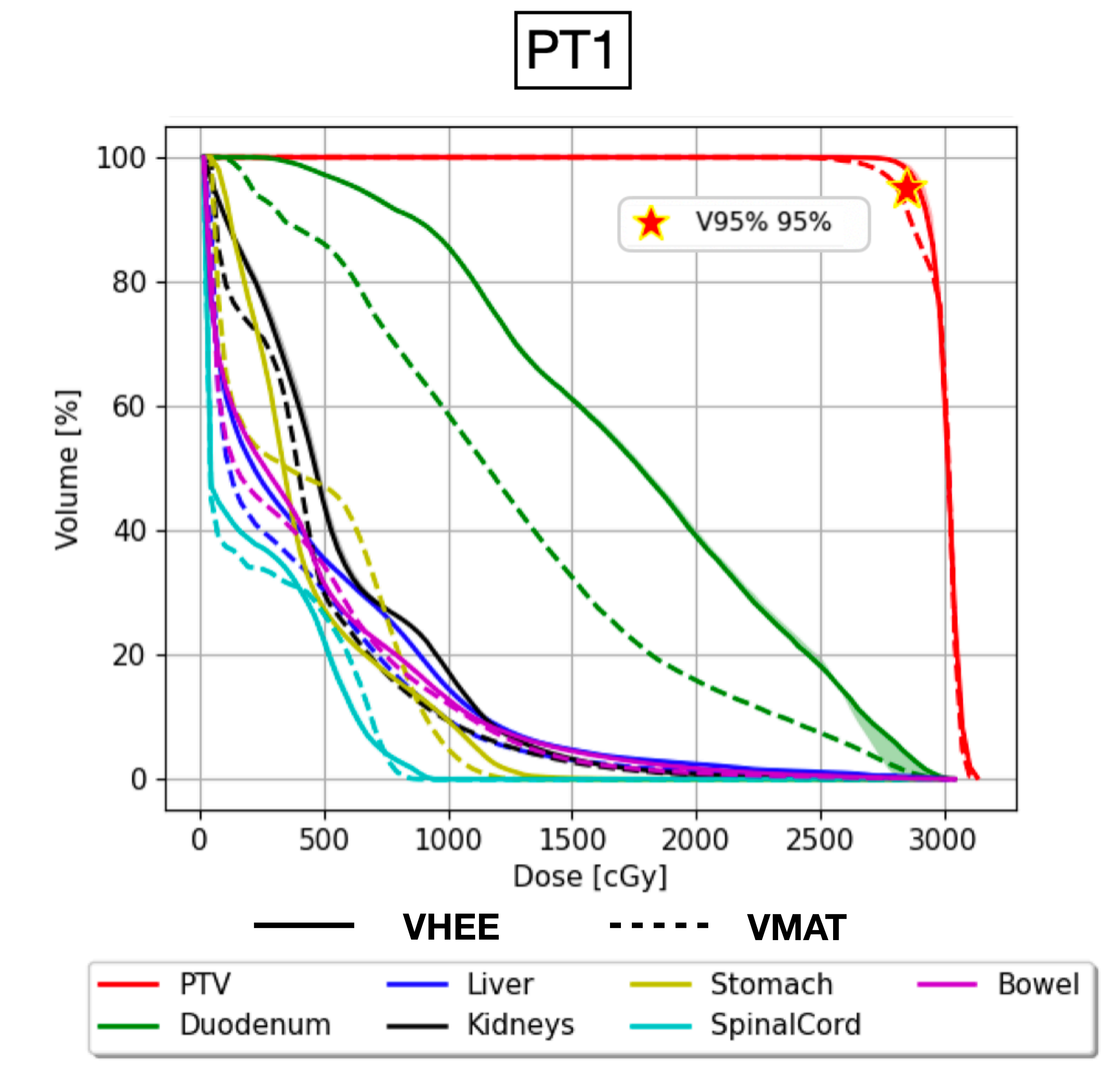
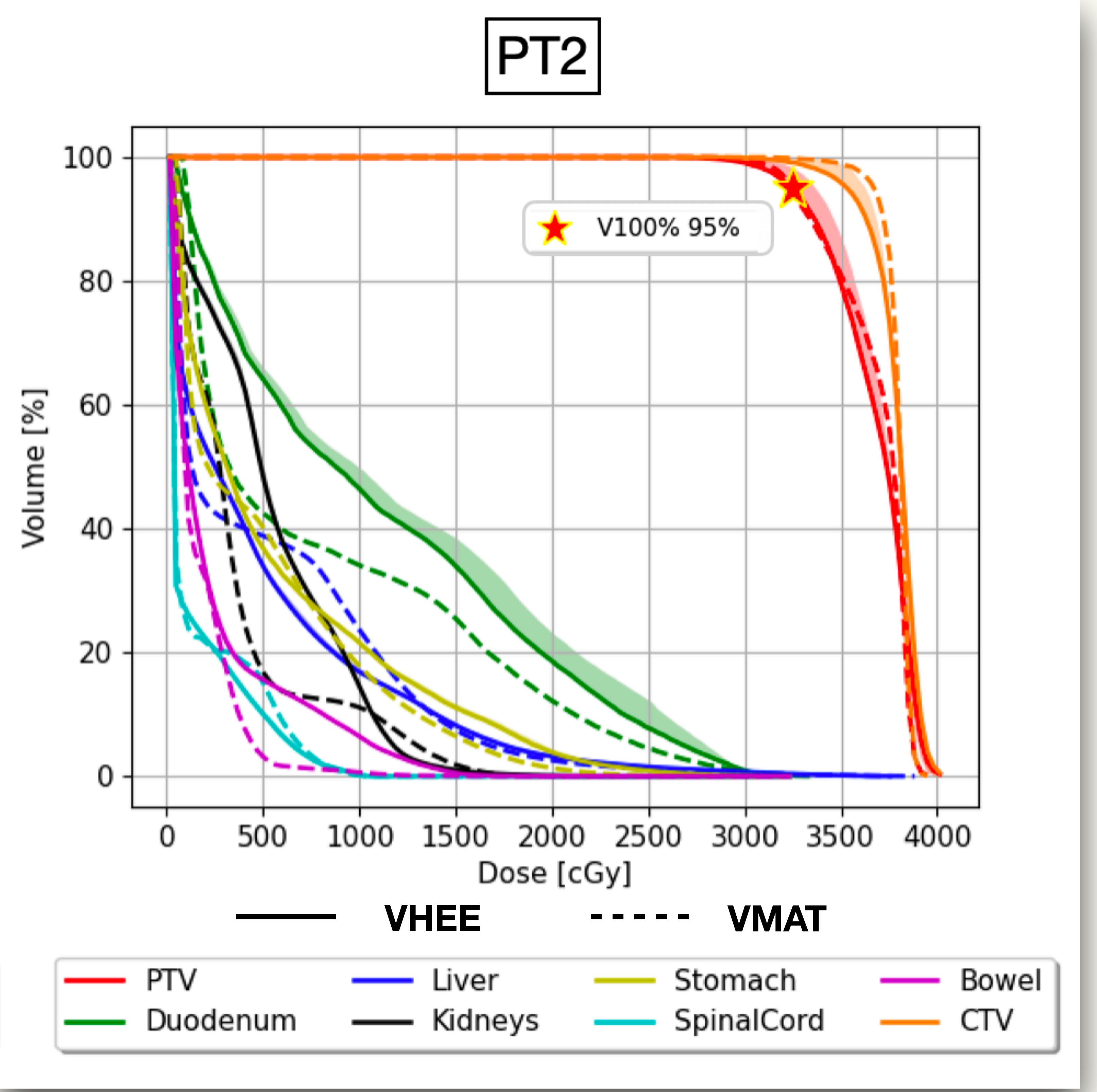
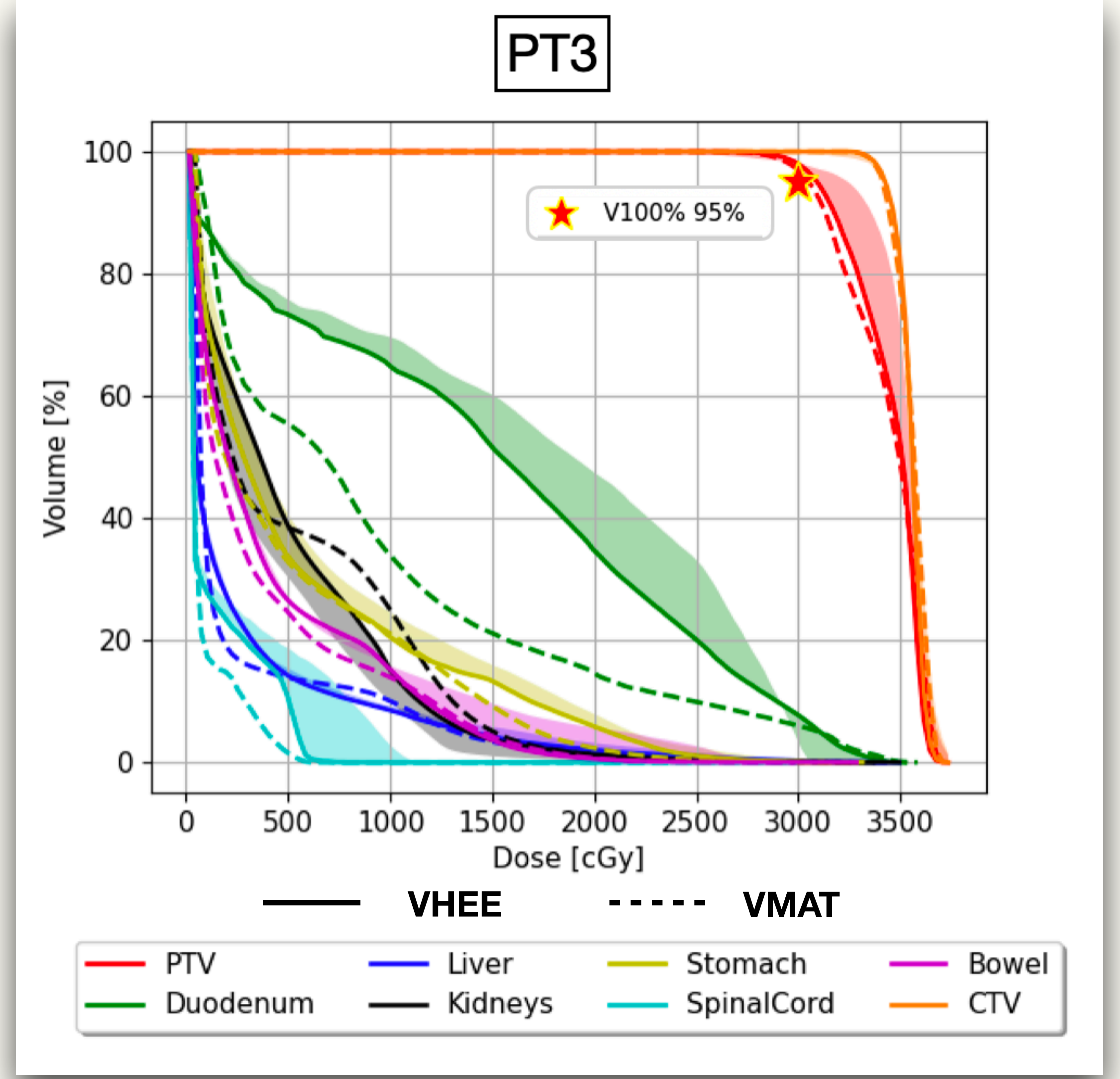
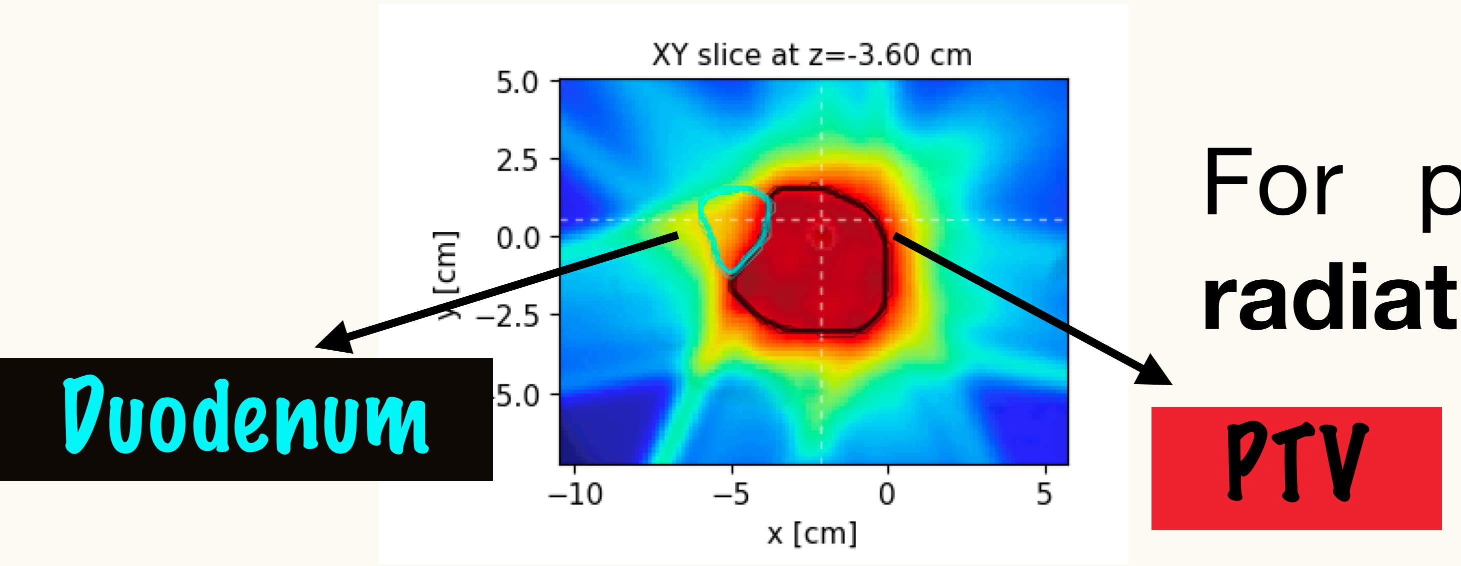






Feasability study on real patients



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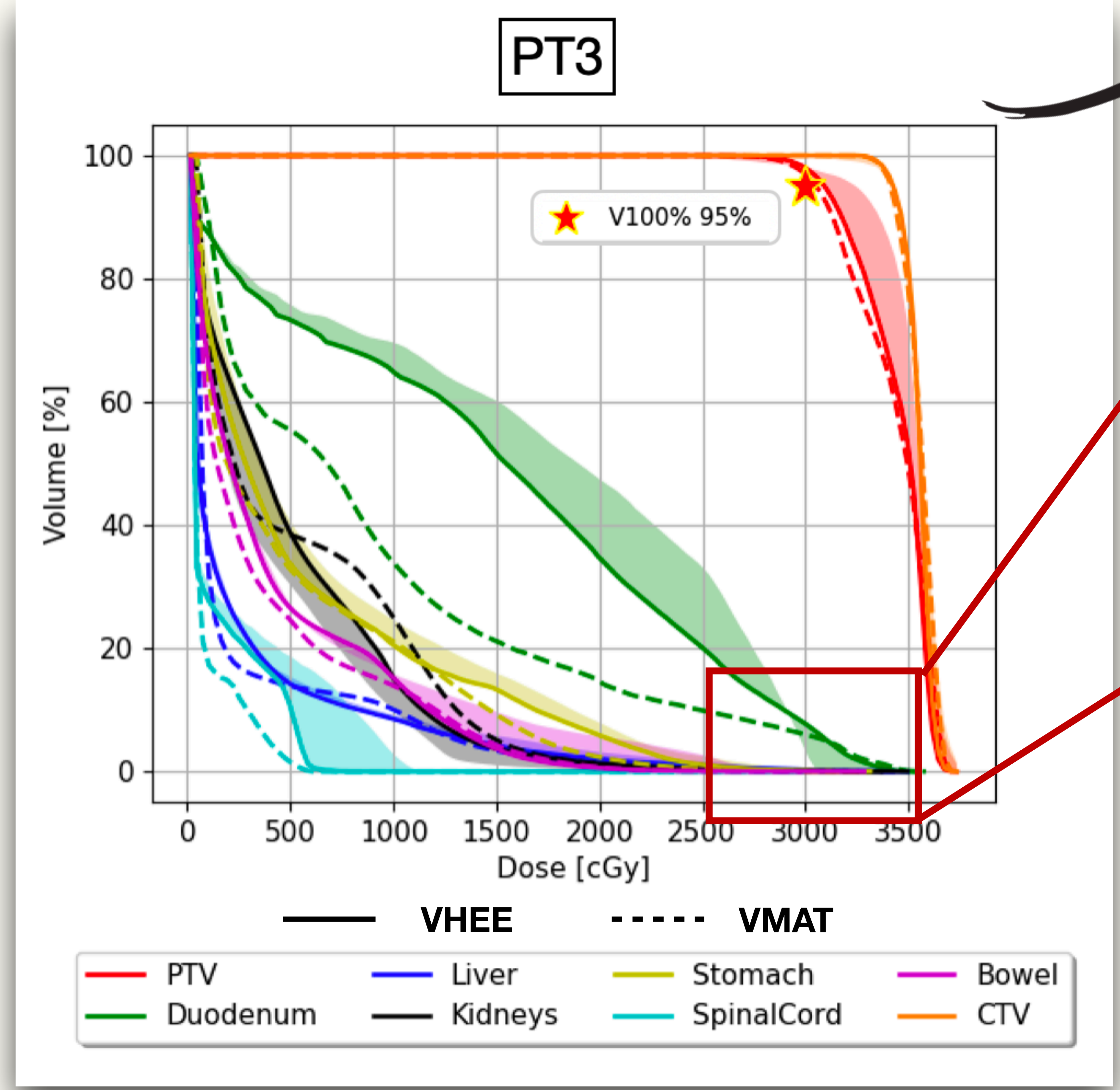

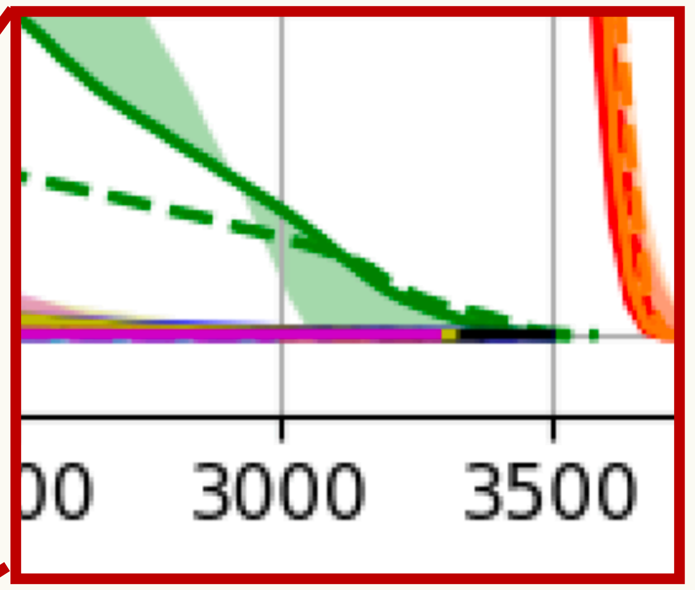

Transparent bands: potential improvement if the plan is delivered in UHDR conditions.

	VMAT	VHEE	VHEE-FLASH
PTV	99%	98.32%	98.32%
Duodenum	35.88 Gy	35.11 Gy	31.06 Gy
Stomach	31.04 Gy	33.28 Gy	29.97 Gy

- FMFmin = 0.6 to 1
- Dth value of 25 Gy.

The FLASH optimization results in an **increase in the average** dose delivered to the duodenum, while **reducing its maximum absorbed dose** by approximately 4 Gy. This allows to increase the PTV coverage!

Feasability study on real patients

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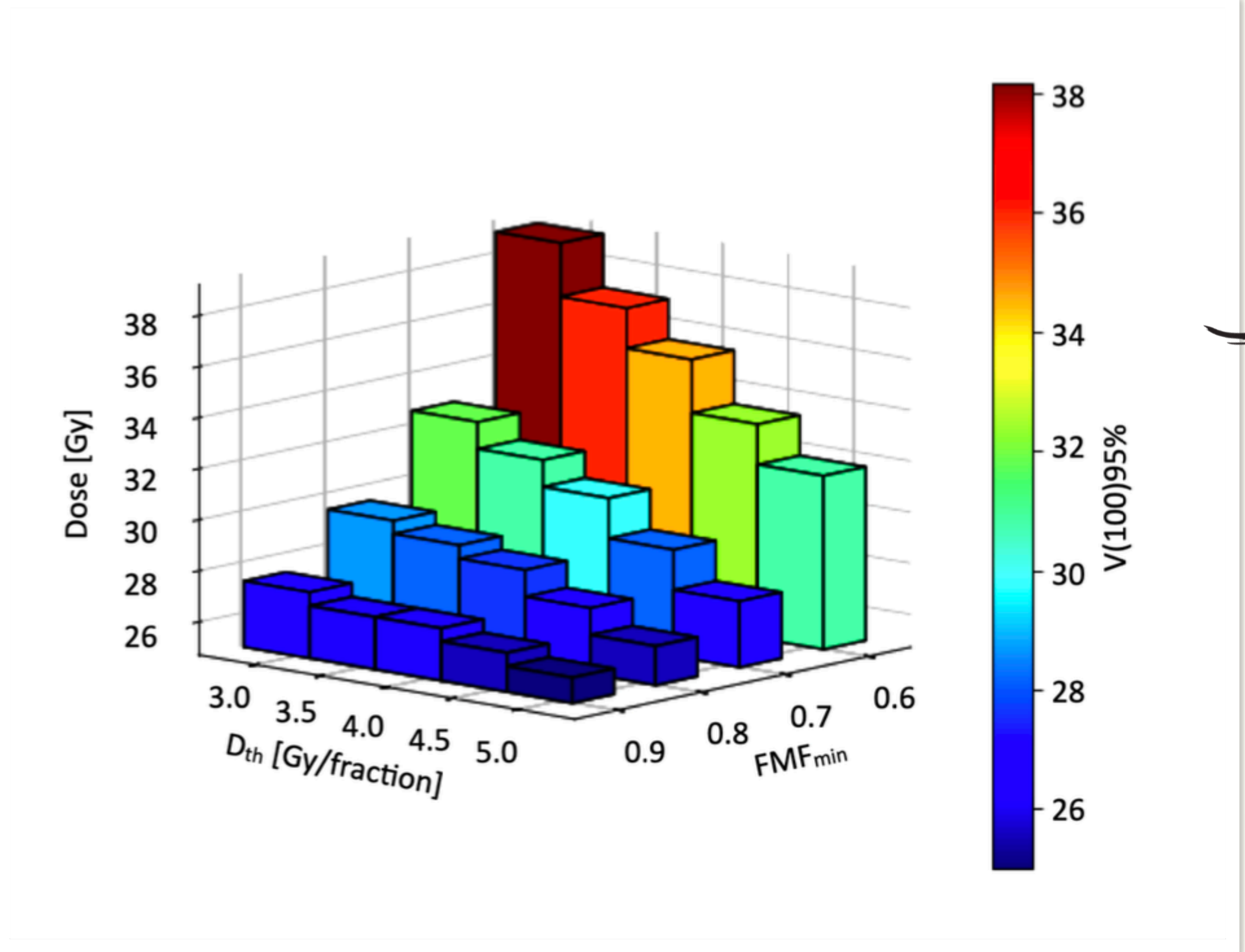

Correlation among FMF_{min} values D_{th} and the resultant increase of the 95% of the dose absorbed by the 100% of the PTV volume on the z-axis.

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$$D_{FMF} = FMF \cdot D$$

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

The FLASH optimization results in an increase in the average dose delivered to the duodenum, while reducing its maximum absorbed dose by approximately 4 Gy. This allows to increase the PTV coverage!

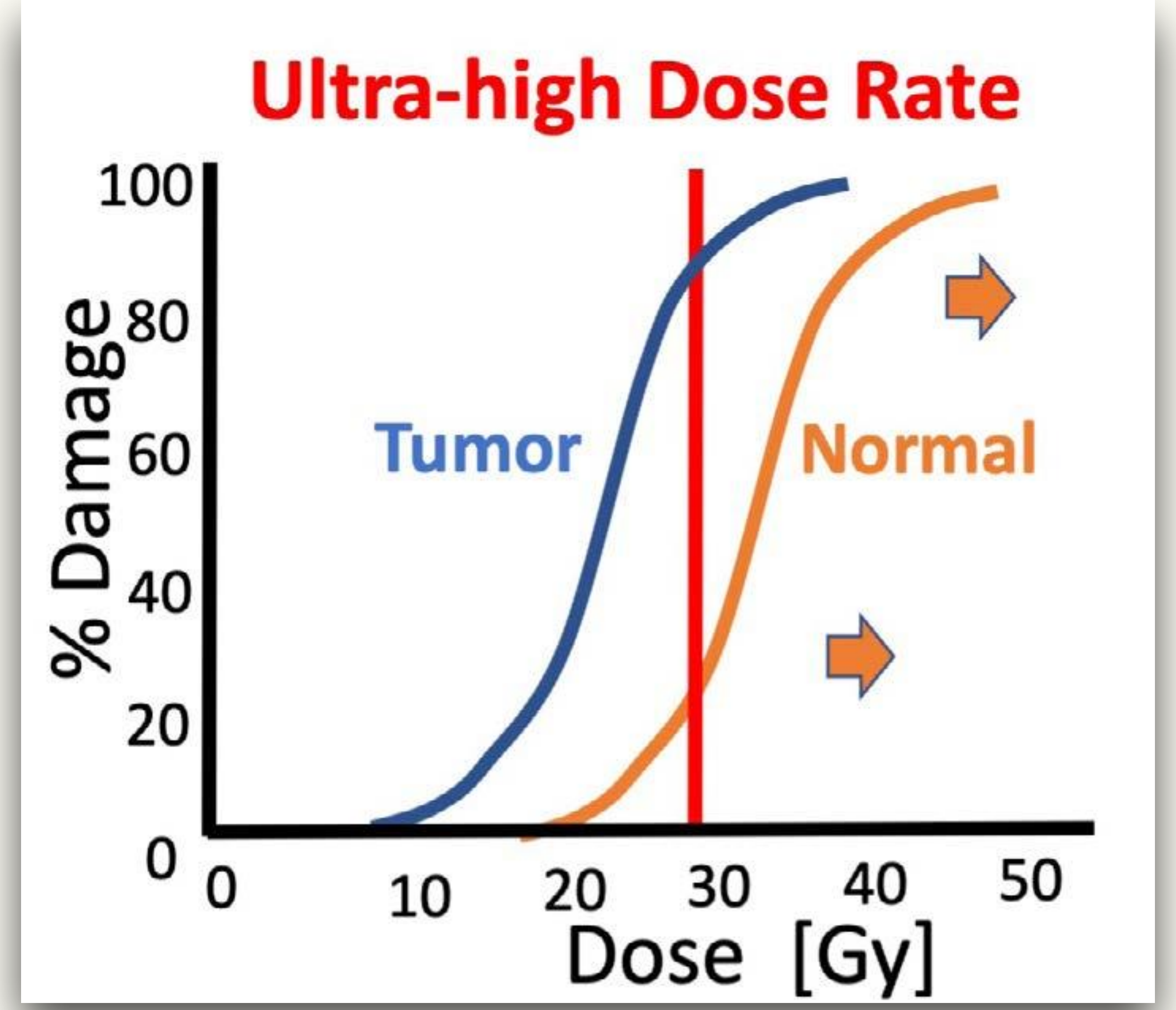
Take home message

* FLASH radiotherapy delivers ultra-high dose rates in a very short time, potentially reducing damage to healthy tissue compared to conventional radiotherapy.

* A wide variety of beams now allow FLASH-rate irradiation, enabling preclinical research at many facilities using different particles and energies.

* While the biological mechanisms behind the FLASH effect are still under investigation, feasibility studies are expanding, and dedicated research centers are rapidly emerging worldwide.

* Very High Energy Electrons (VHEE) represent a promising option for future FLASH treatments (but no dedicated clinical machines are currently available —> SAFEST!)



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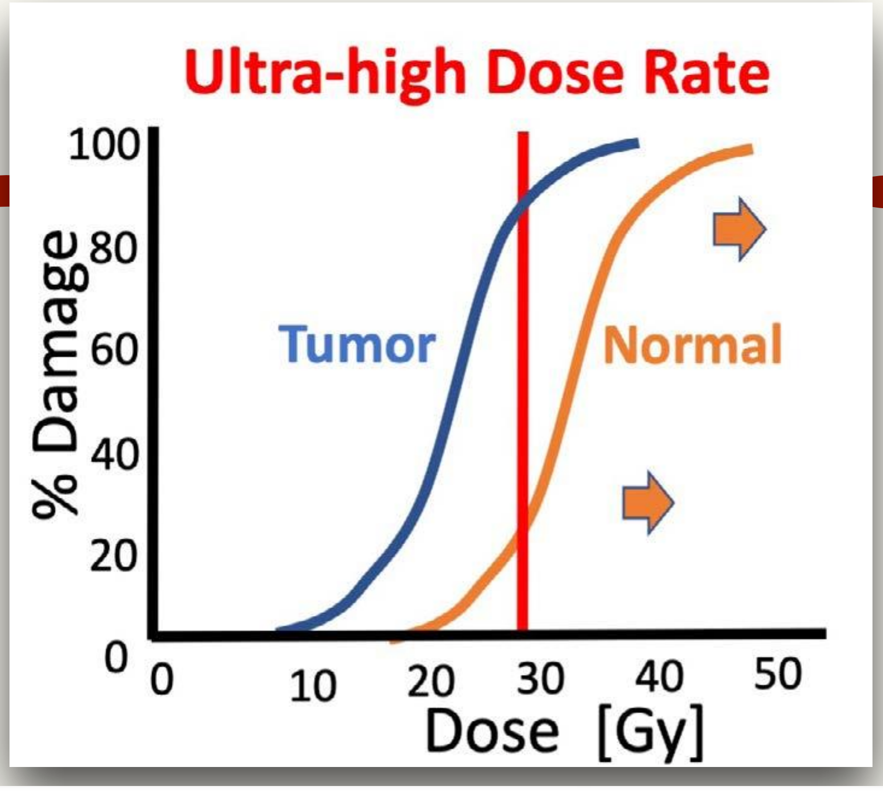

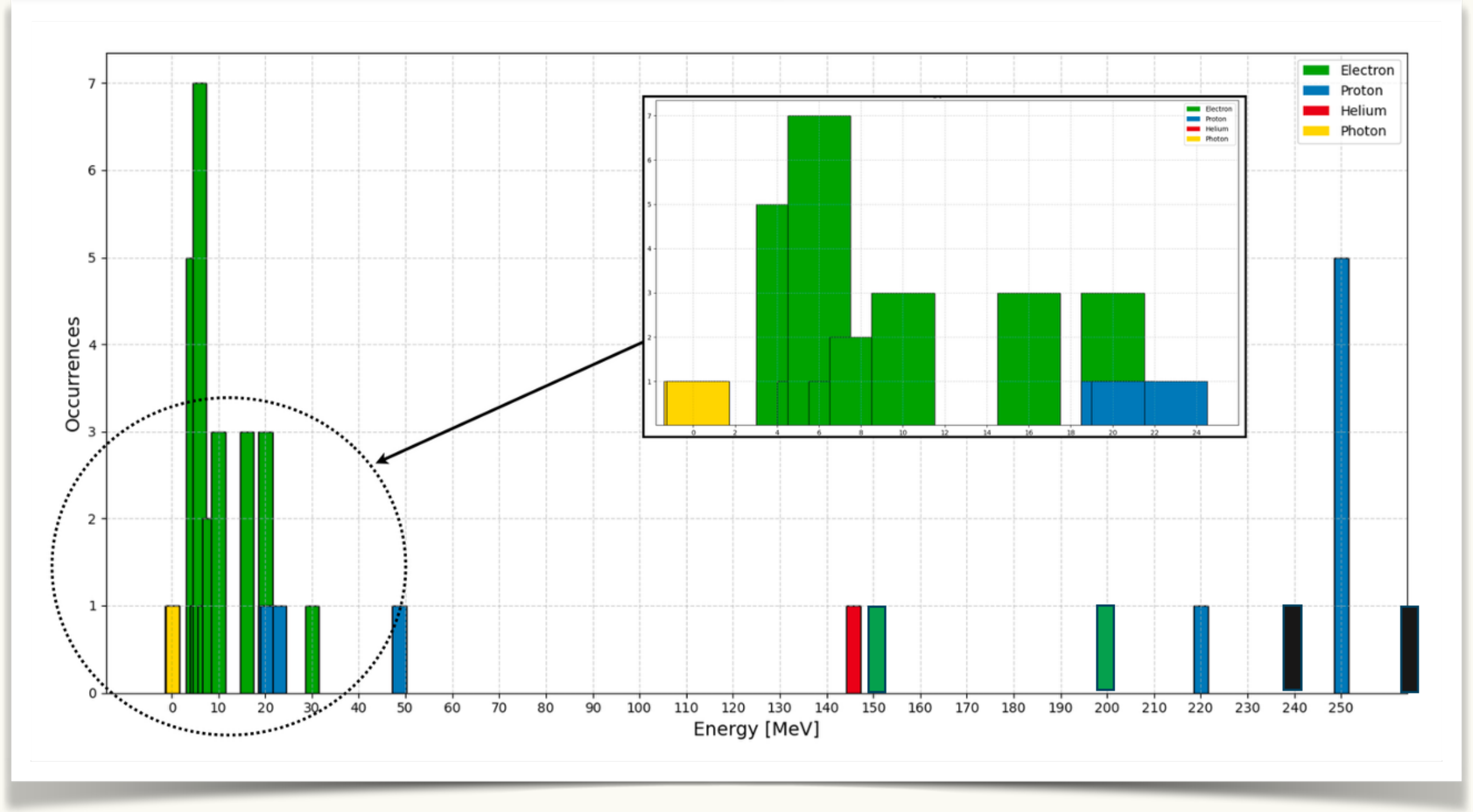

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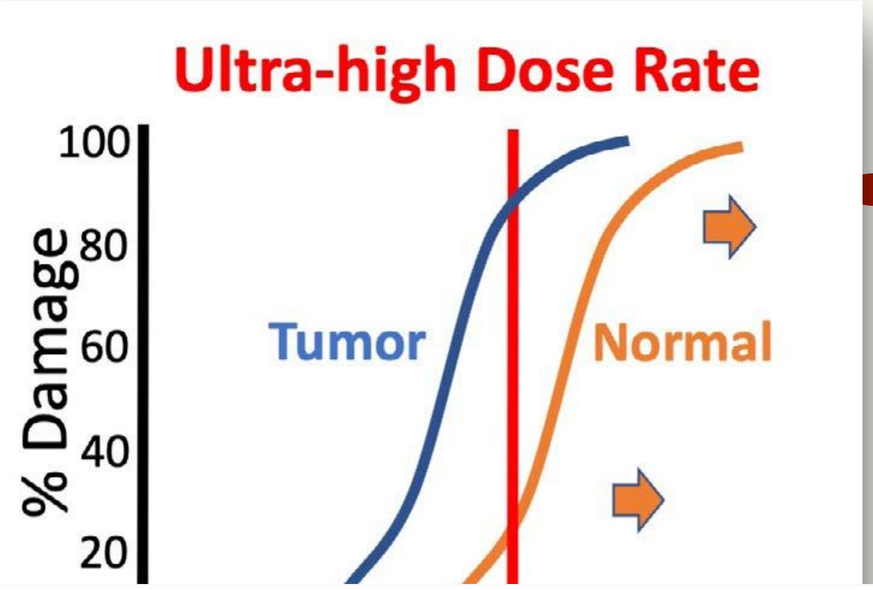

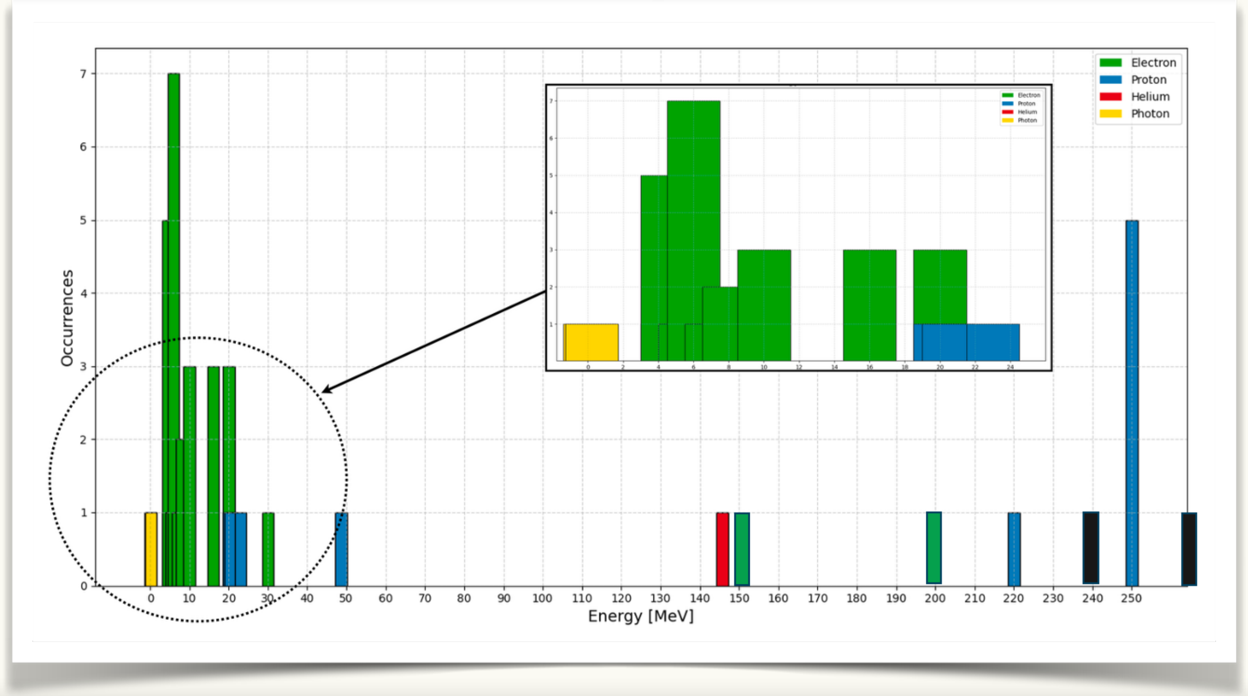

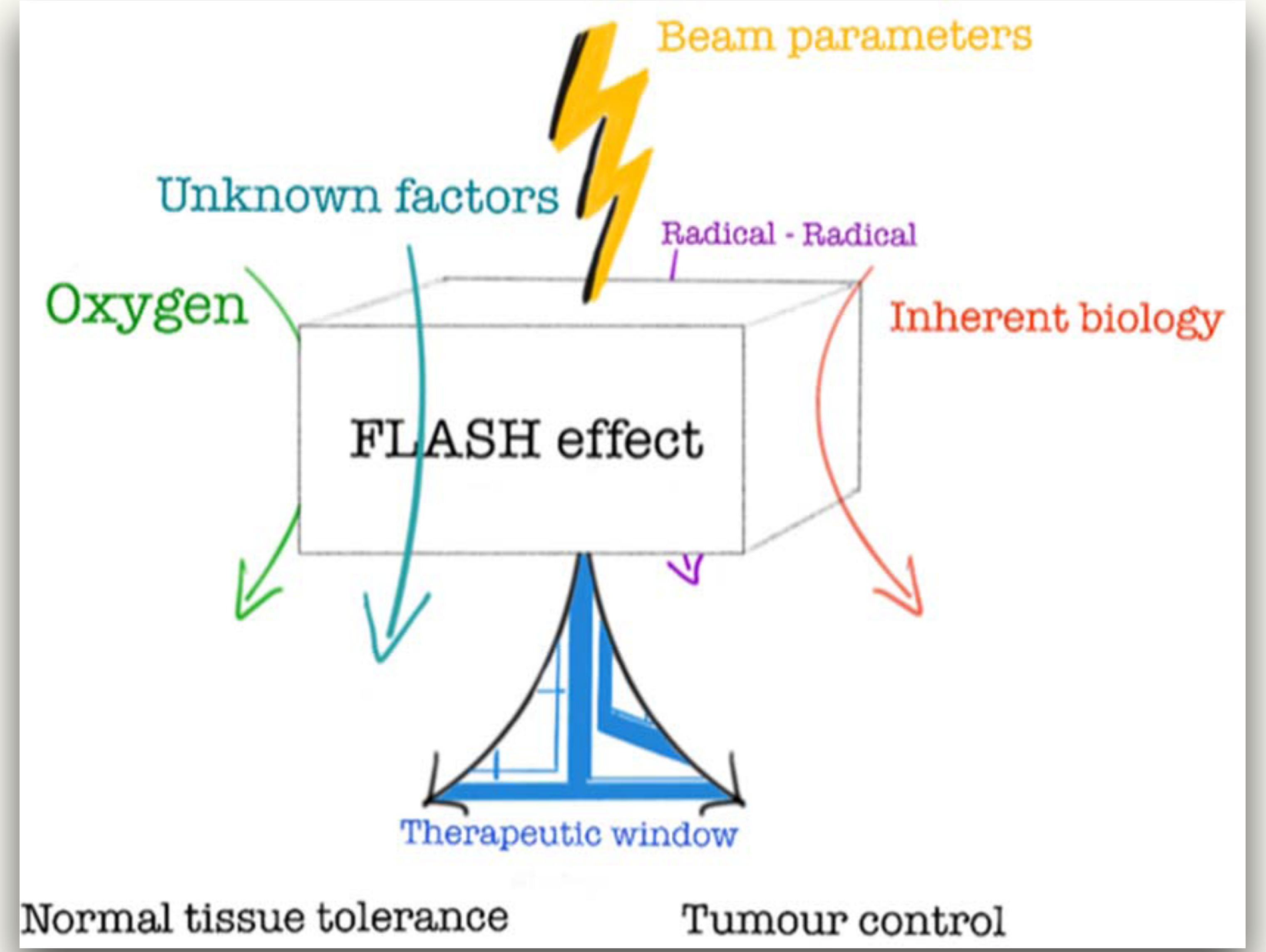

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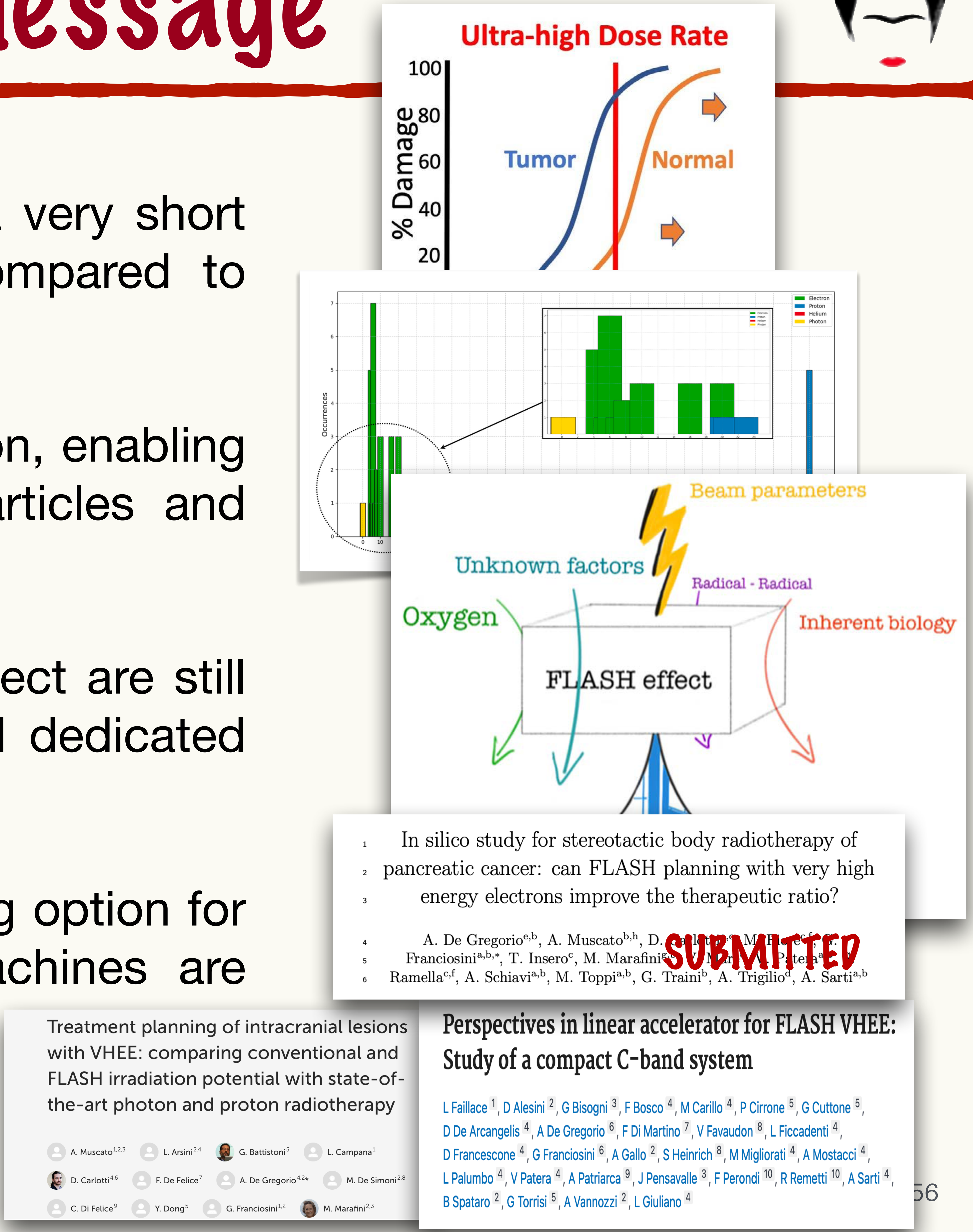


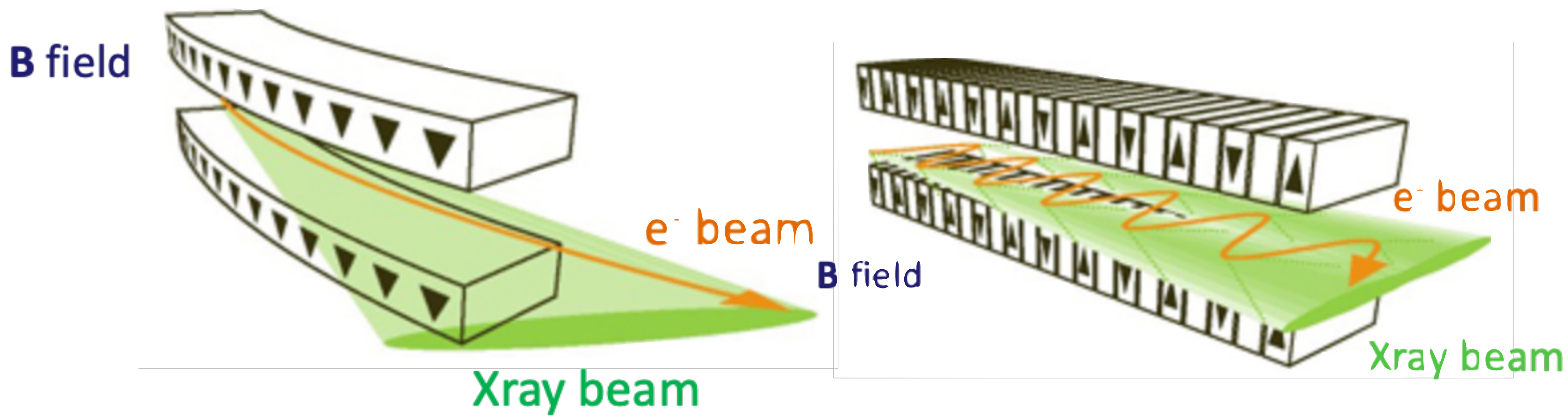
SPARE SLIDES

FLASH EFFECT: synchrotron X beams

These beams are obtained from synchrotron radiation source at high energy (>GeV) electron-synchrotron facility;

The X ray beam is emitted by the high energy charged beam in a magnetic field:

- From a dipole magnet that bends the beam trajectory;
- From a wiggler where the beams has multiple curves with enhanced Xray emission.



Large infrastructure are needed -> not suitable for clinical environment.

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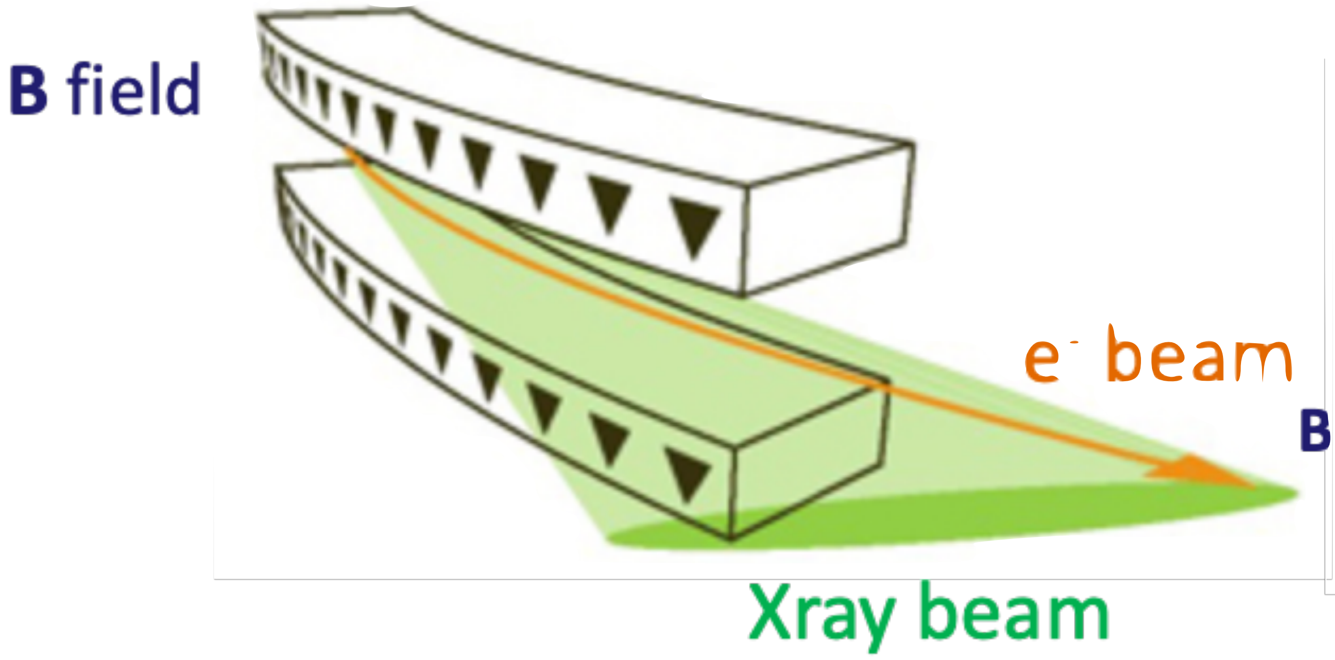

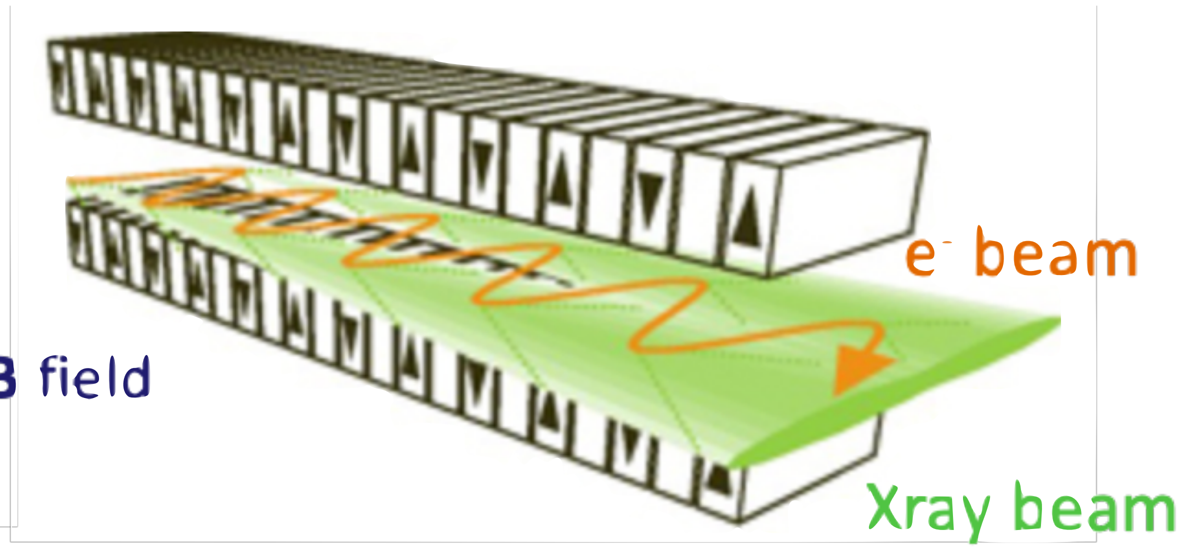

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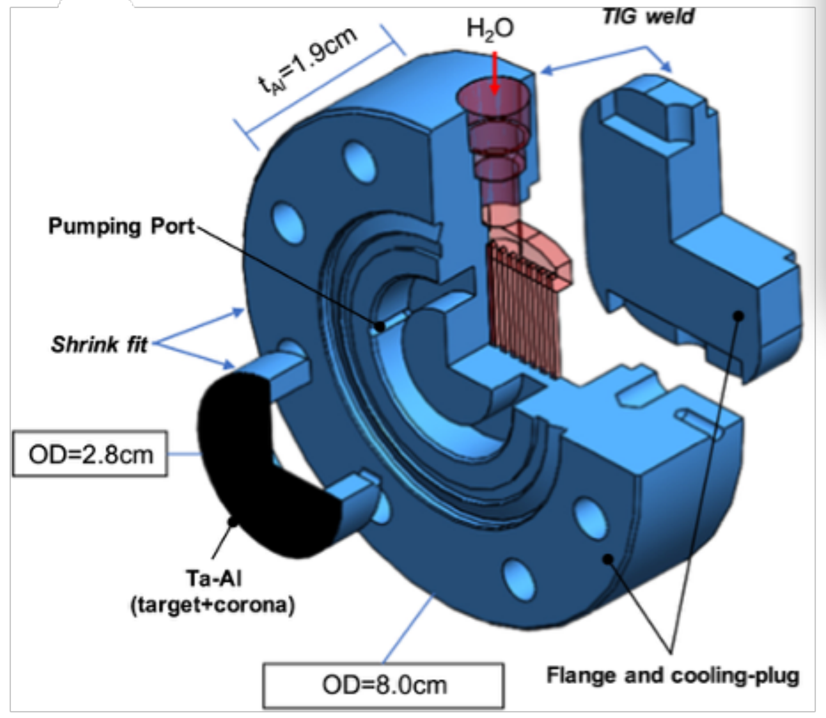
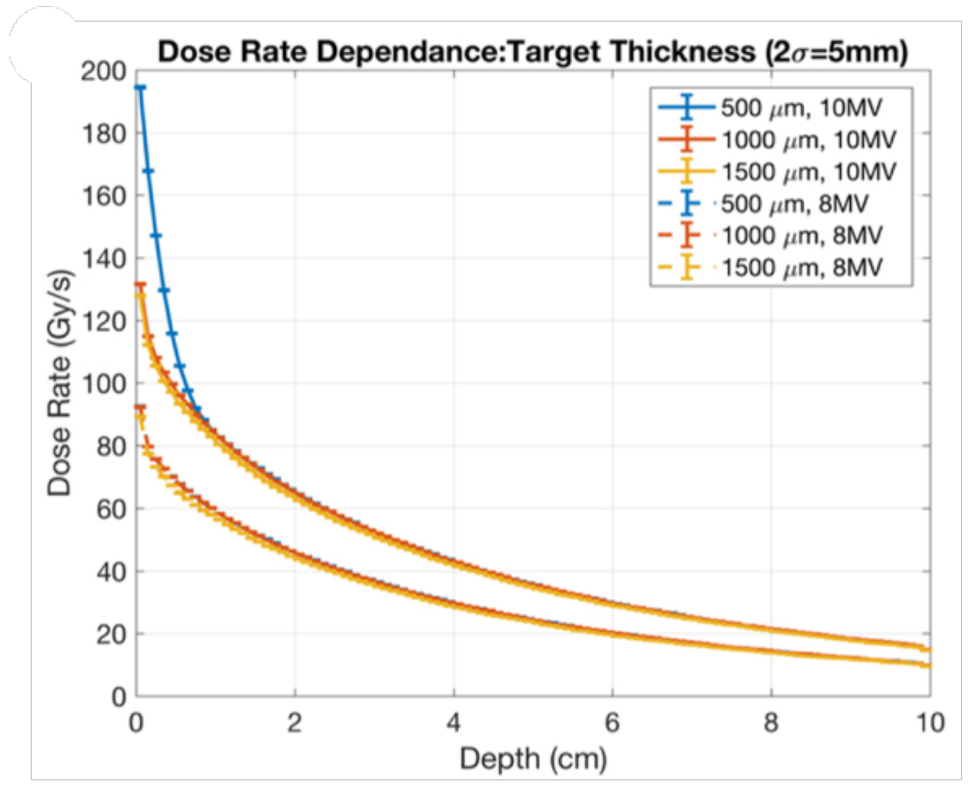
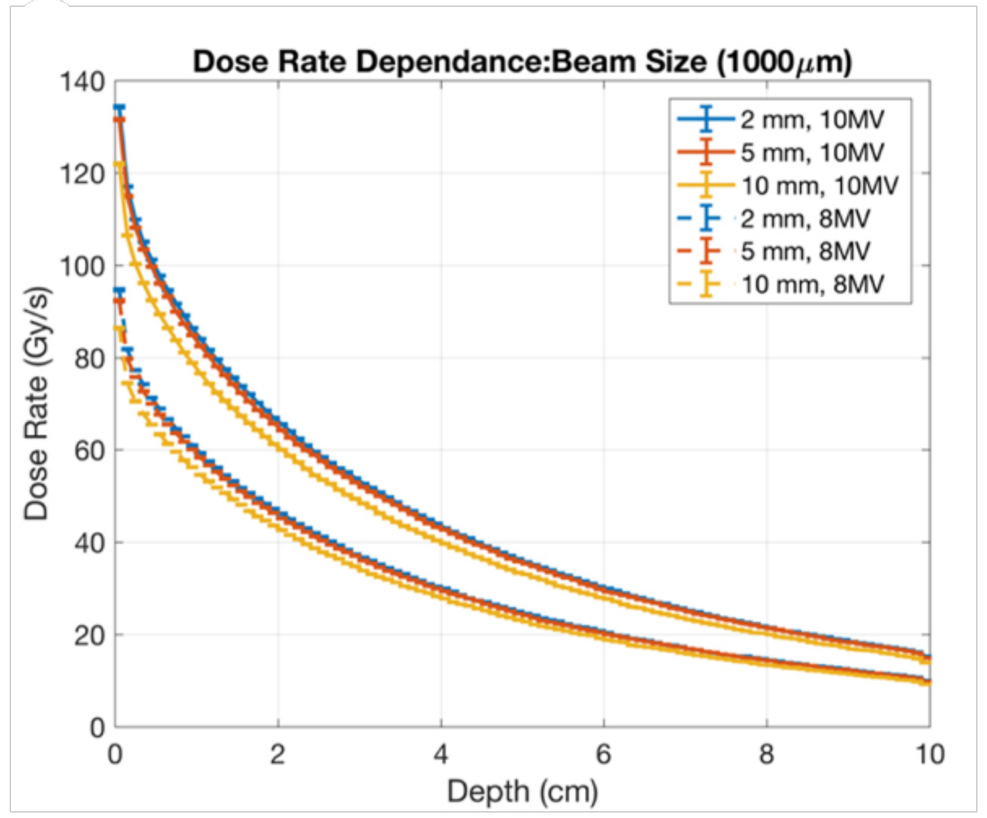
Ariel @ TRIUMF



- Optimization of target for Xray production produced ~5 MeV FLASH beam;
- FLASH capable tantalum target to be mounted on the 10 MeV eLINAC. MC optimization, including cooling and mechanical stress;
- FLASH dose up to ~ 10^2 Gy/s possible for several combination of target thickness and beam sizes.





Nolan Esplen *et al* 2022 *Phys. Med. Biol.* **67** 105003

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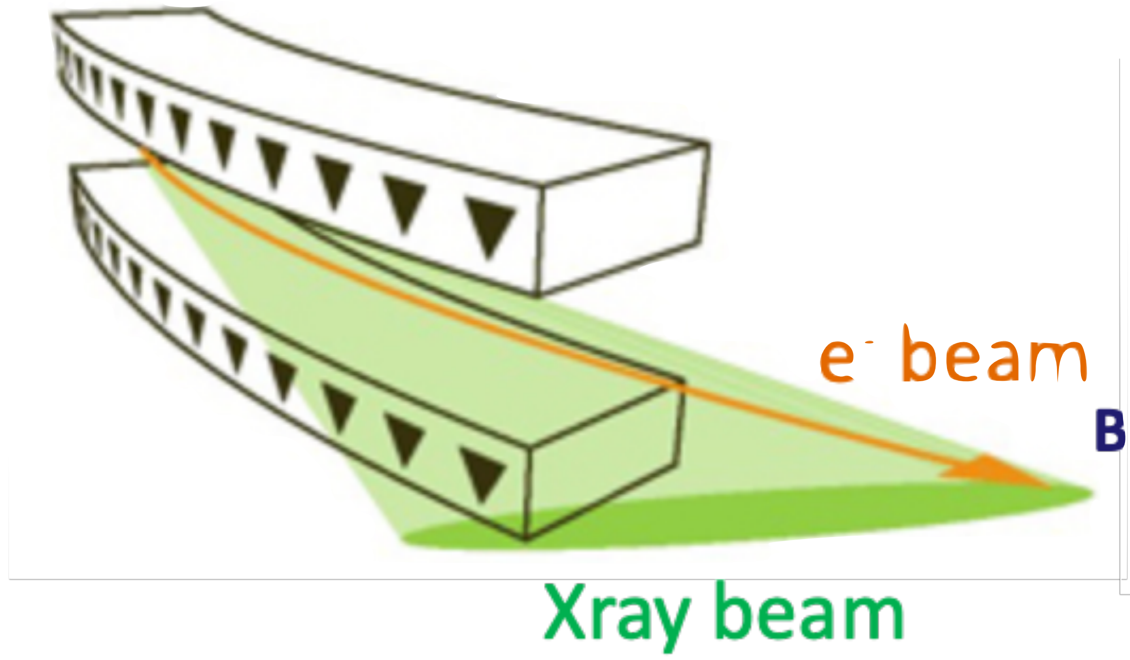
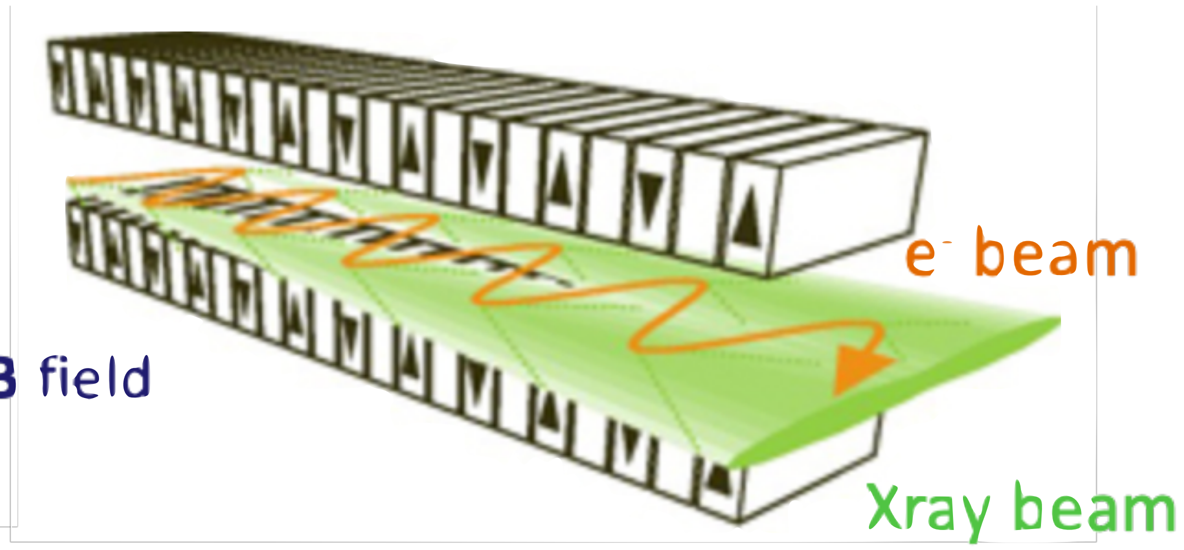


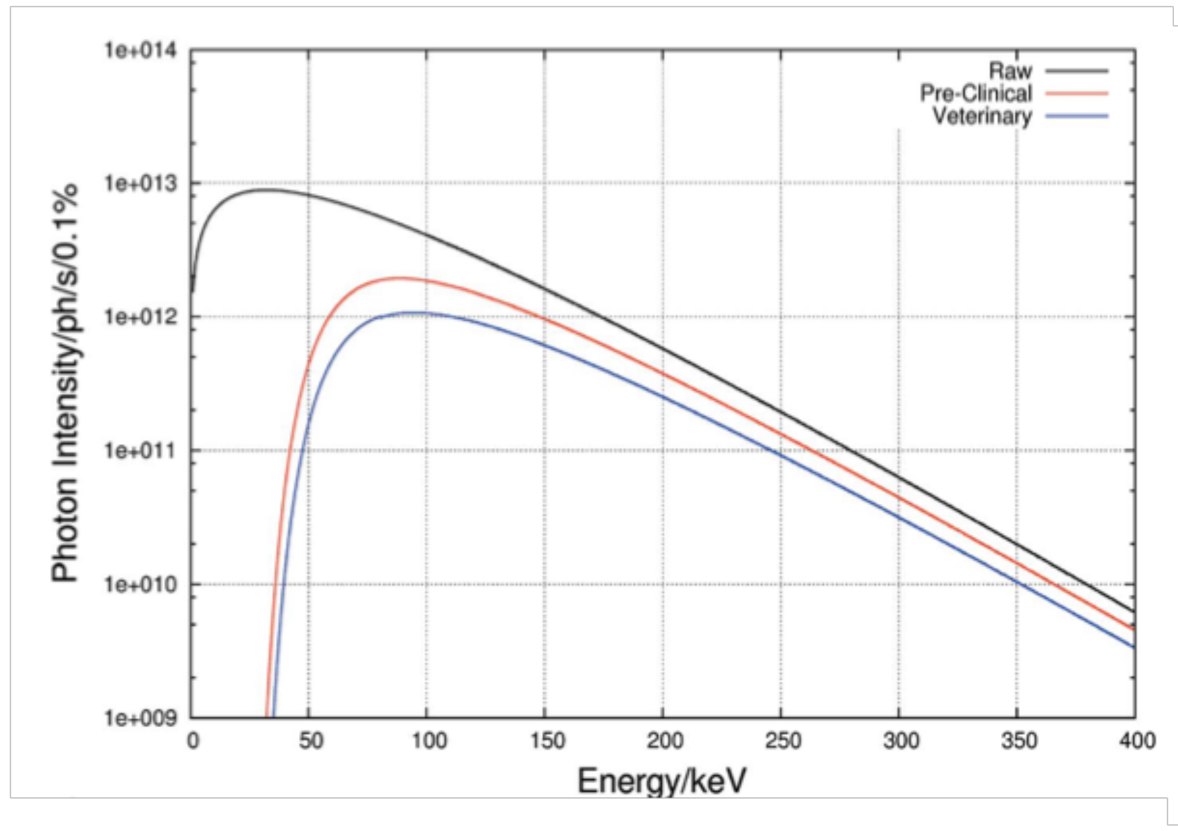


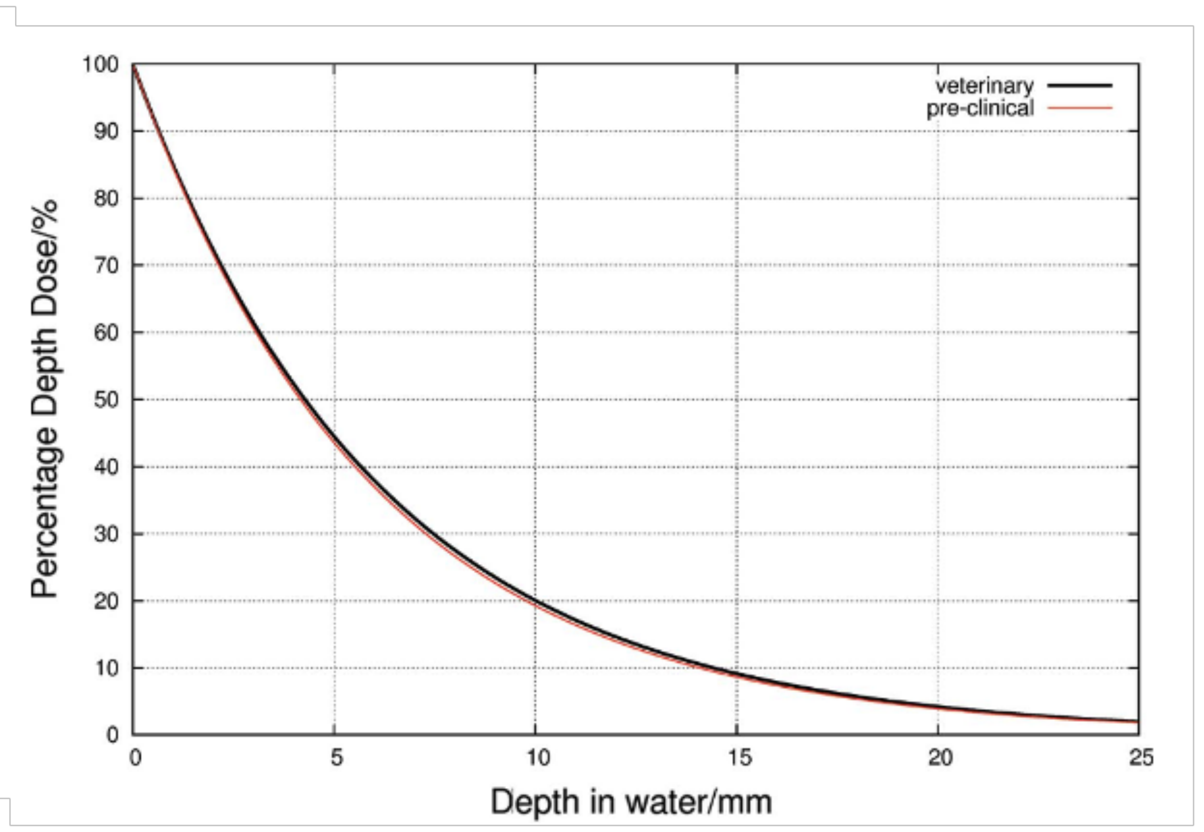
Large infrastructure are needed -> not suitable for clinical environment.

ESFR

The ID17 beamline is produced at the European Synchrotron Radiation Facility by wiggler B field ~ 1.6 T ;

- The intensity can be locally extremely high-> flash rate
- Max beam size: 150 x 10 mm^2 asymmetric due to the production mechanism;
- FLASH dose up to ~ 10^2 Gy/s possible for several combination of target thickness and beam sizes;
- Photons with E < 30 MeV removed with a mm filter (C, Al, Be, Cu).





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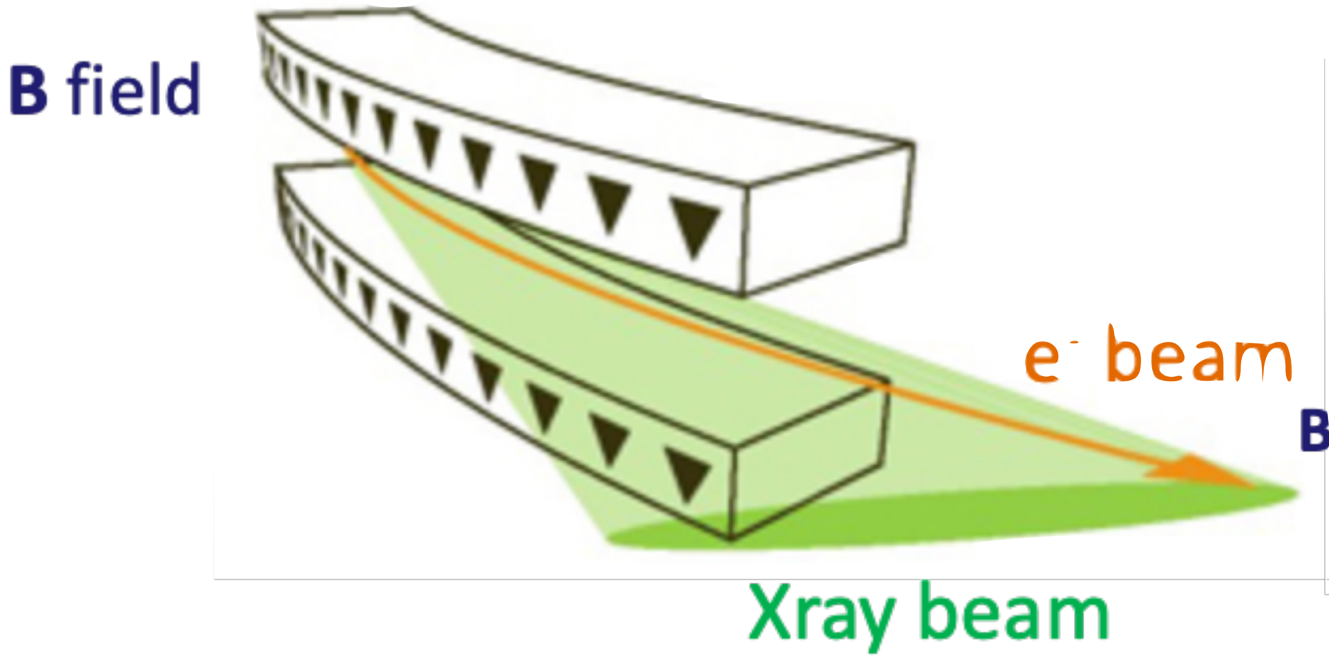

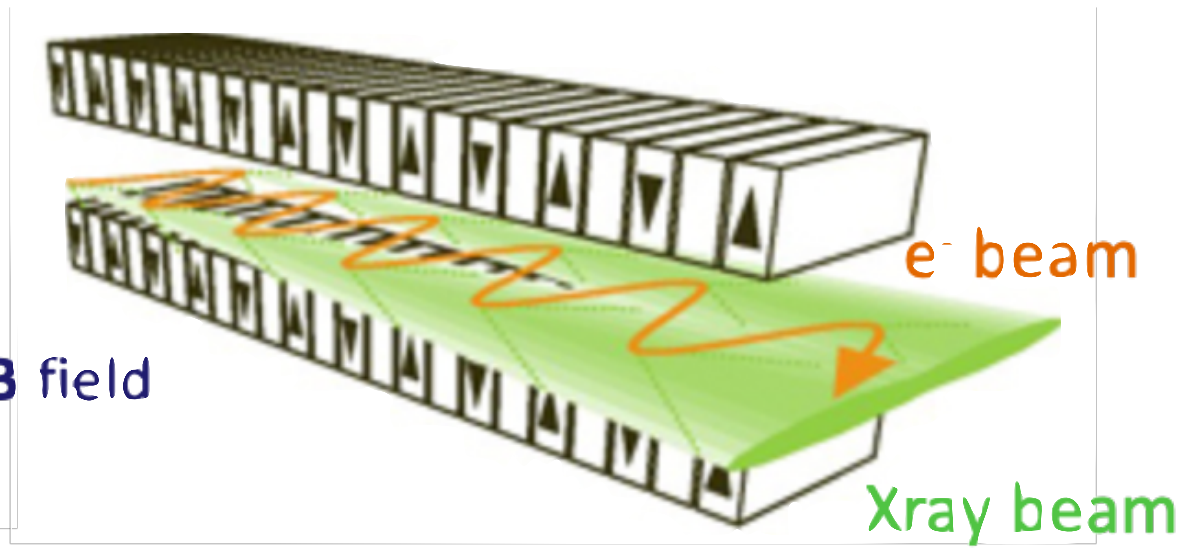

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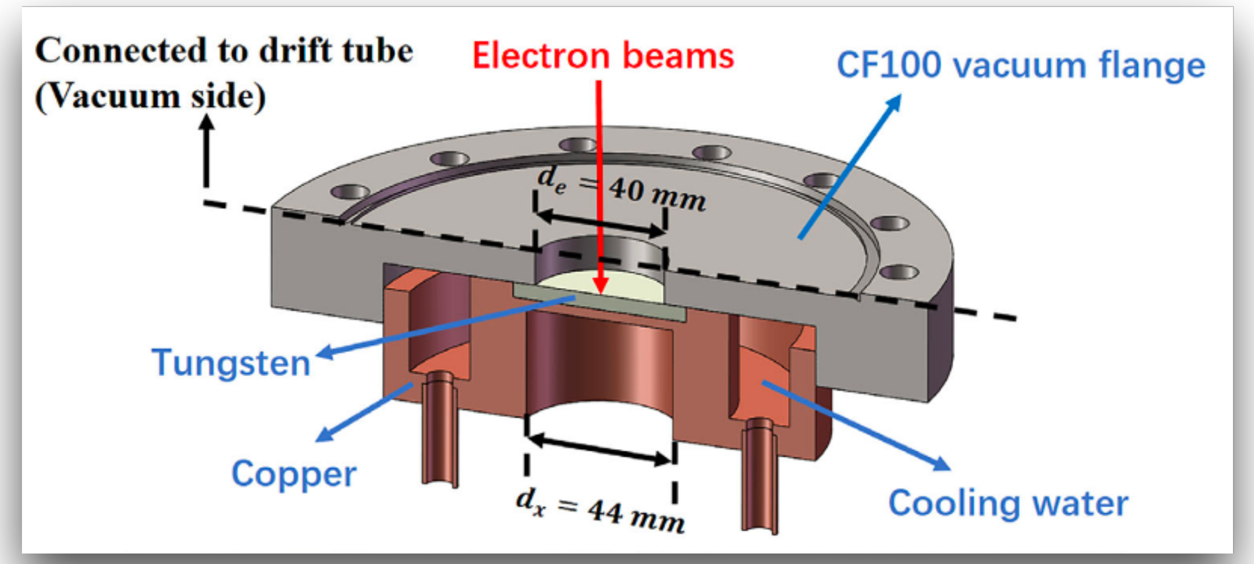
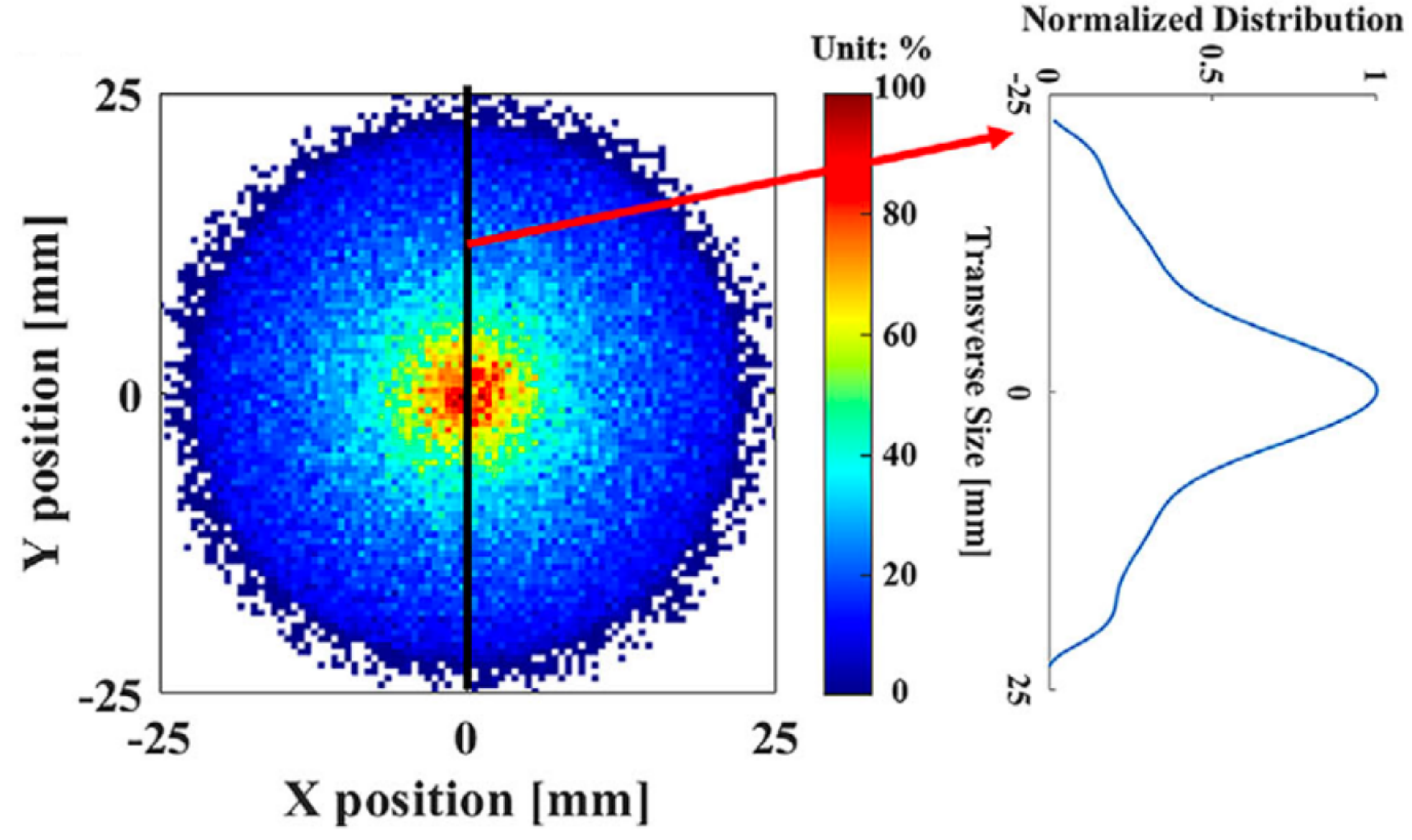
Tsinghua University



- Compact (1.65 m long) S-band backward-traveling-wave electron linac;
- Maximum mean dose rate of the room-temperature linac exceeded 80 Gy/s at an SSD of 50 cm and 45 Gy/s at an SSD of 67.9 cm;
- Target for UHDR X-rays optimized with Monte Carlo simulations using Geant4 and thermal finite element analysis simulations using ANSYS.



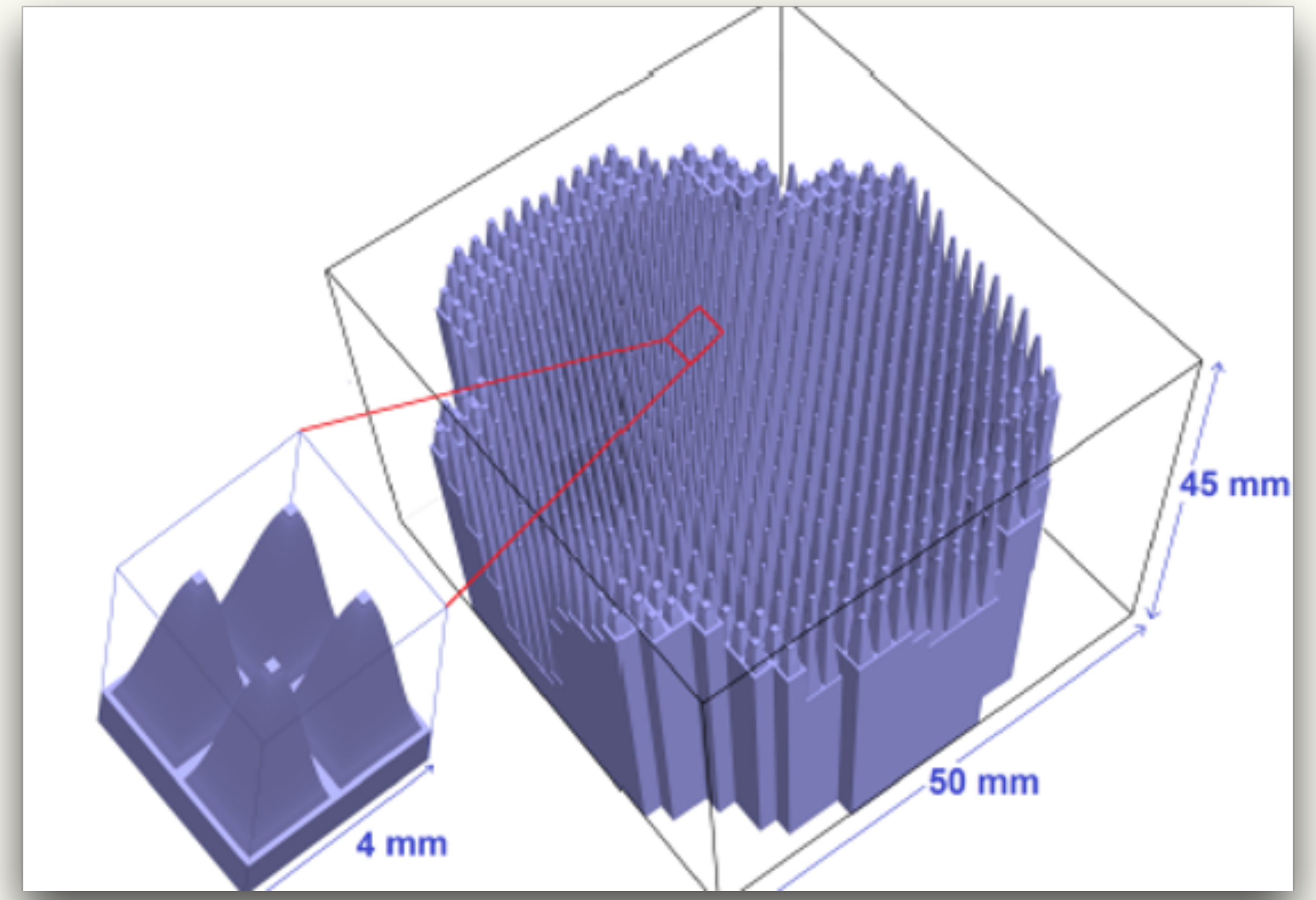
FLASH EFFECT: proton beams

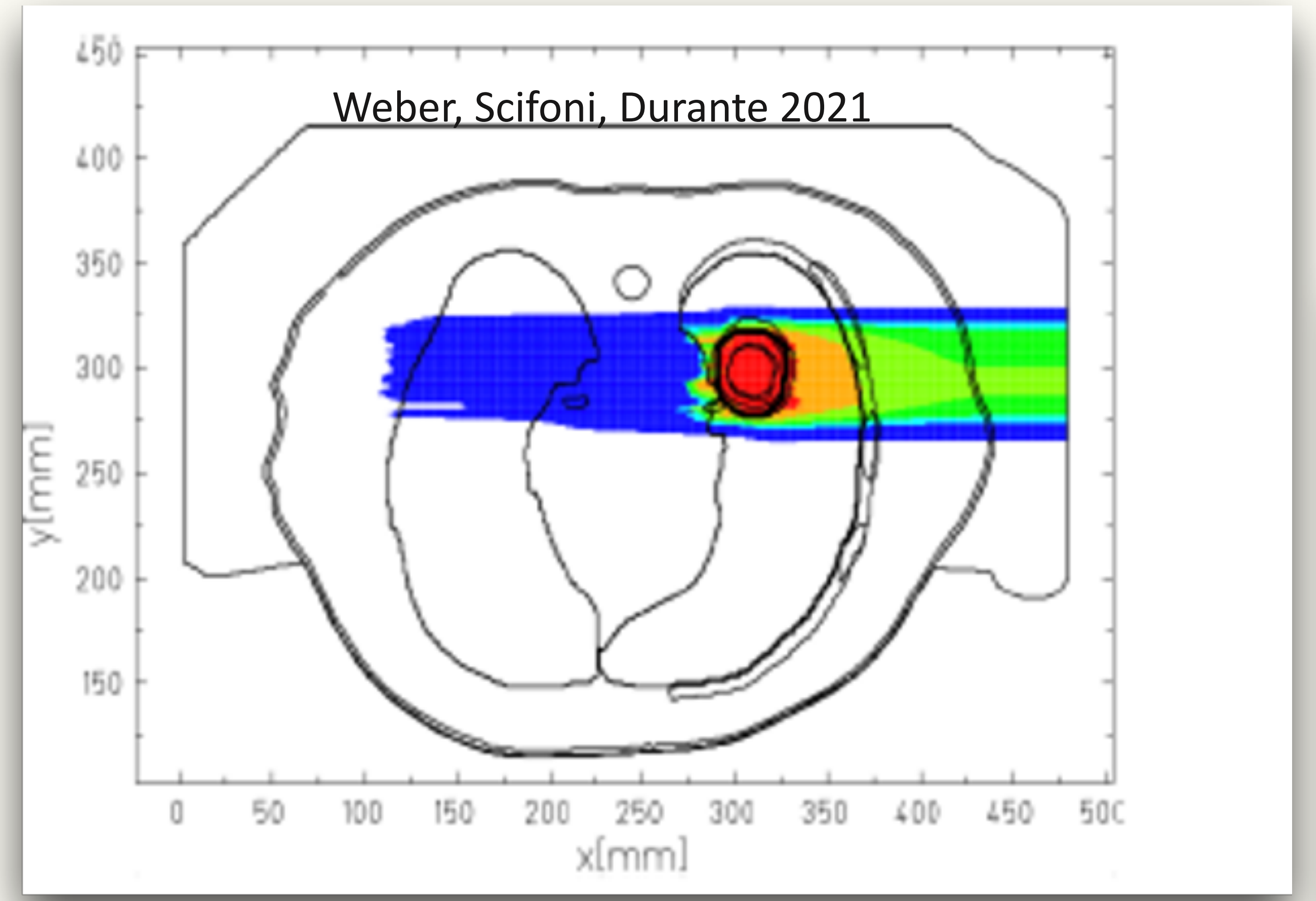
Forget about energy modulation and **use protons as photons** in the Plateau.

ALMOST ALL Preclinical studies, (and Clinical) used this option

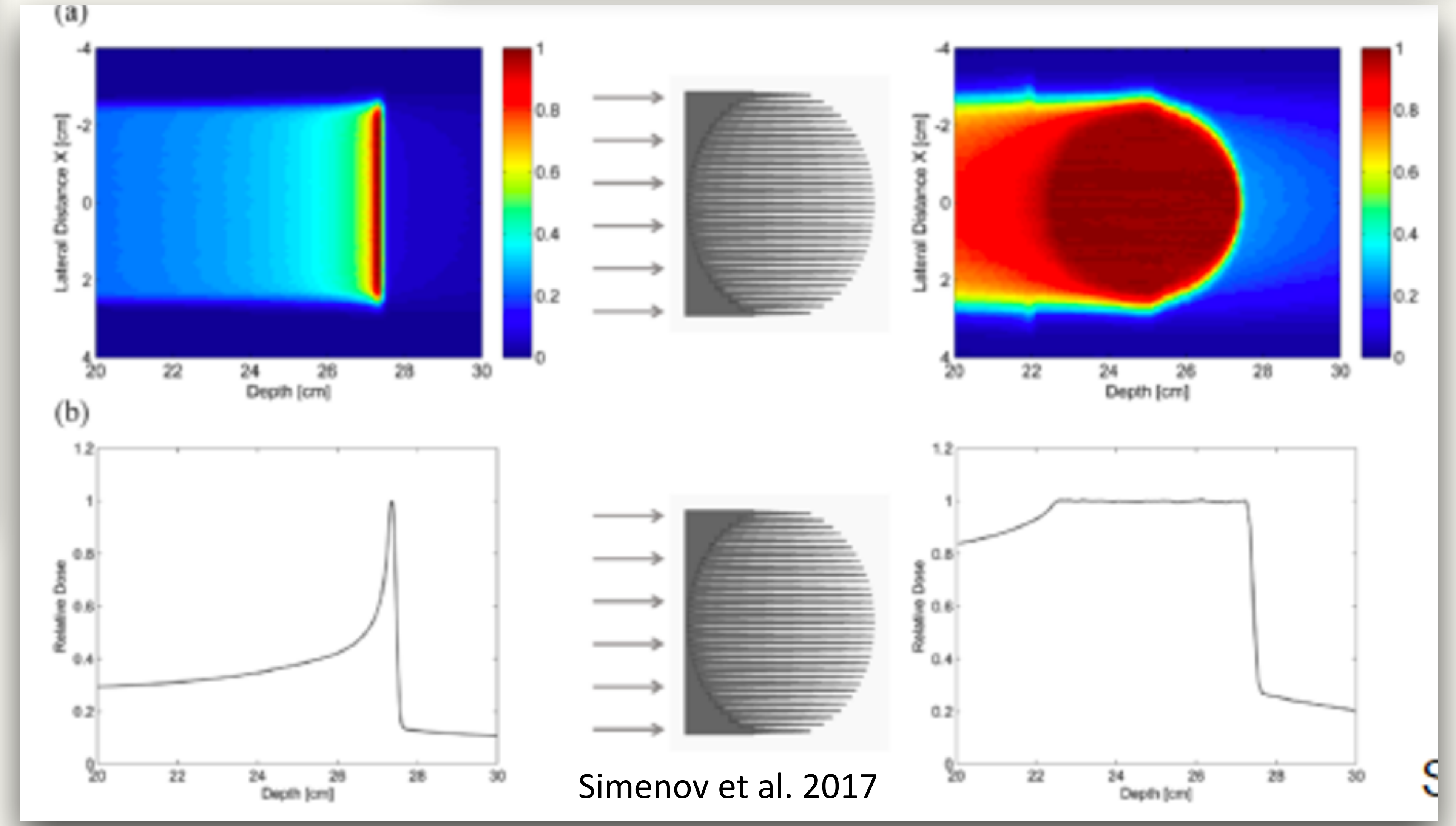
What about conformality?

- Range Shifter to move the BP inside the tumor;
- Patient specific ridge filter to conform to tumor volume.





Weber, Scifoni, Durante 2021

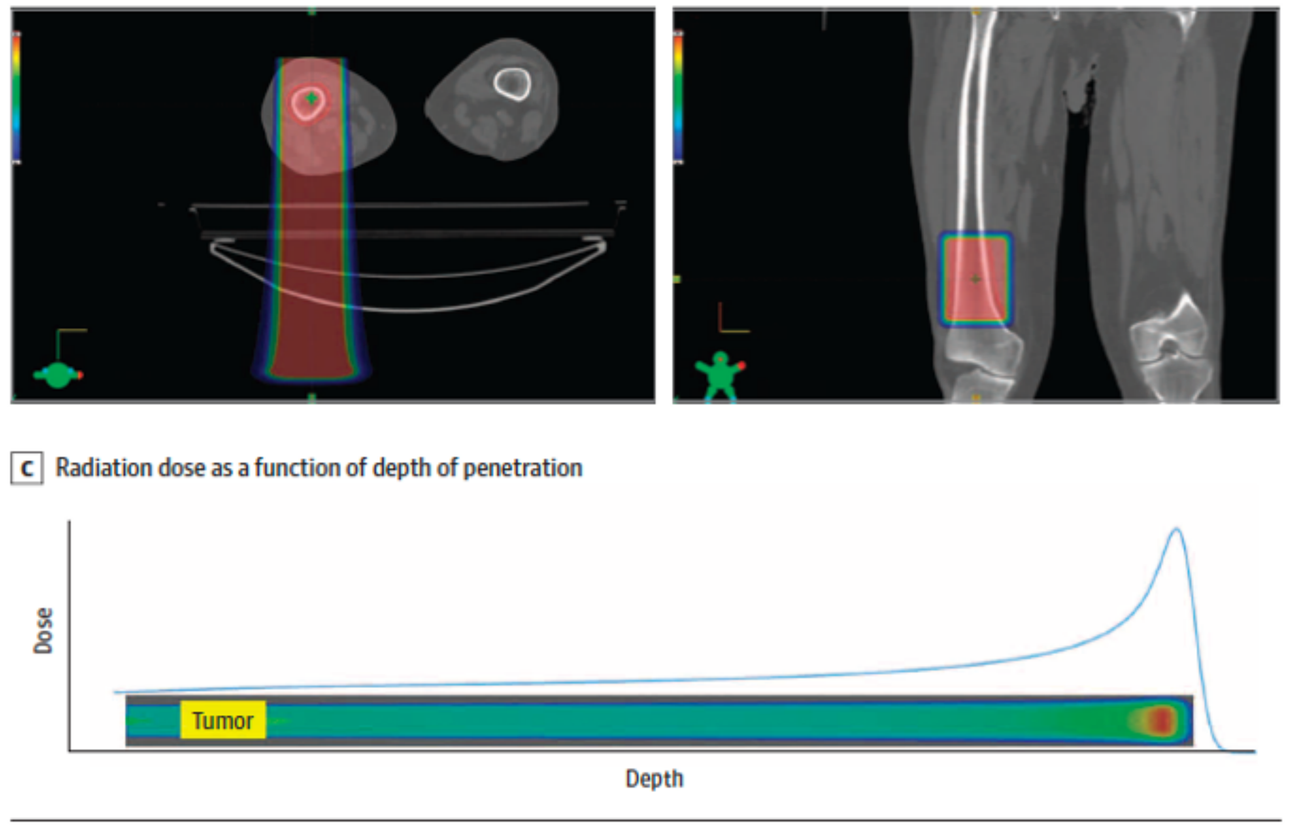


Simenov et al. 2017

JAMA Oncology | Original Investigation

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases

The FAST-01 Nonrandomized Trial



Dose rate was exceeding 400 Gy/s!

3D printed range modulators tested at the Dresden Proton Facility to produced flexible SOPB with a 225 MeV beam.

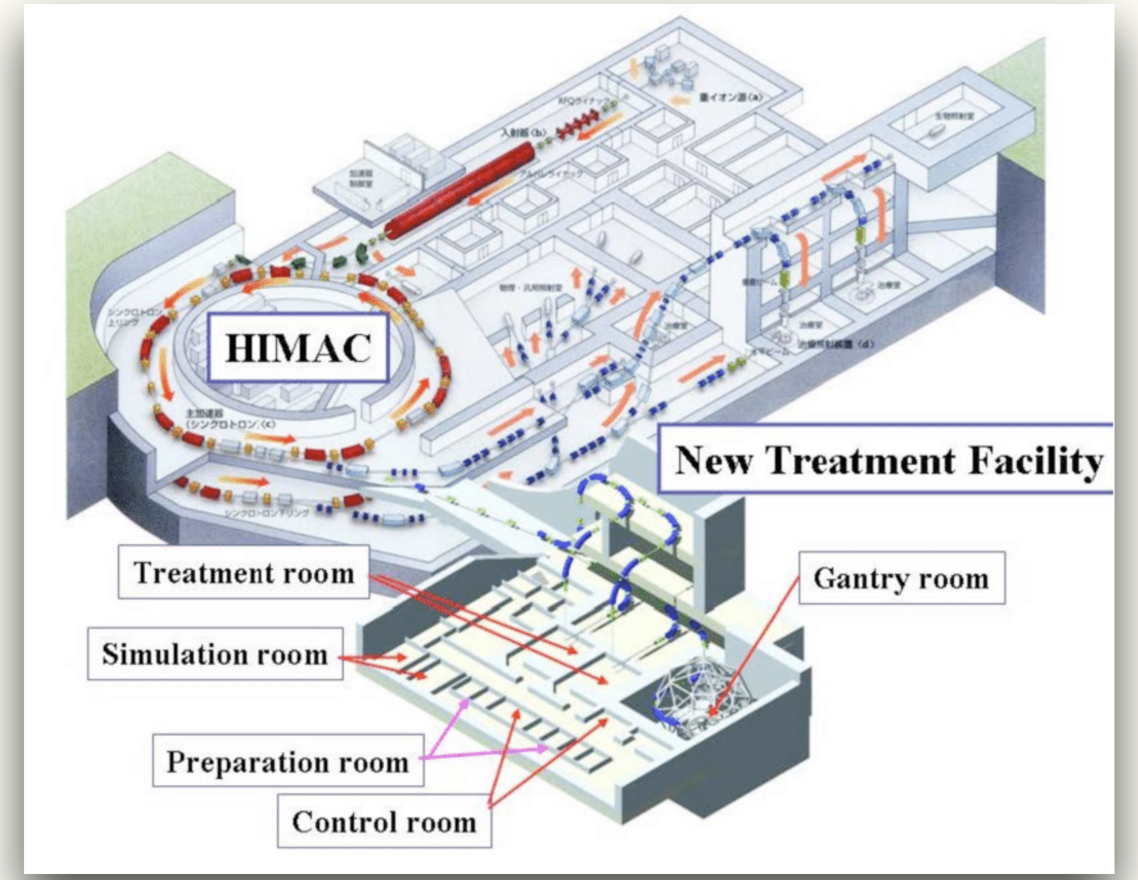
FLASH EFFECT: carbon beams

The FLASH delivery carbon beam ask for a **fast estraction** of the beam from the synchrotron ring.

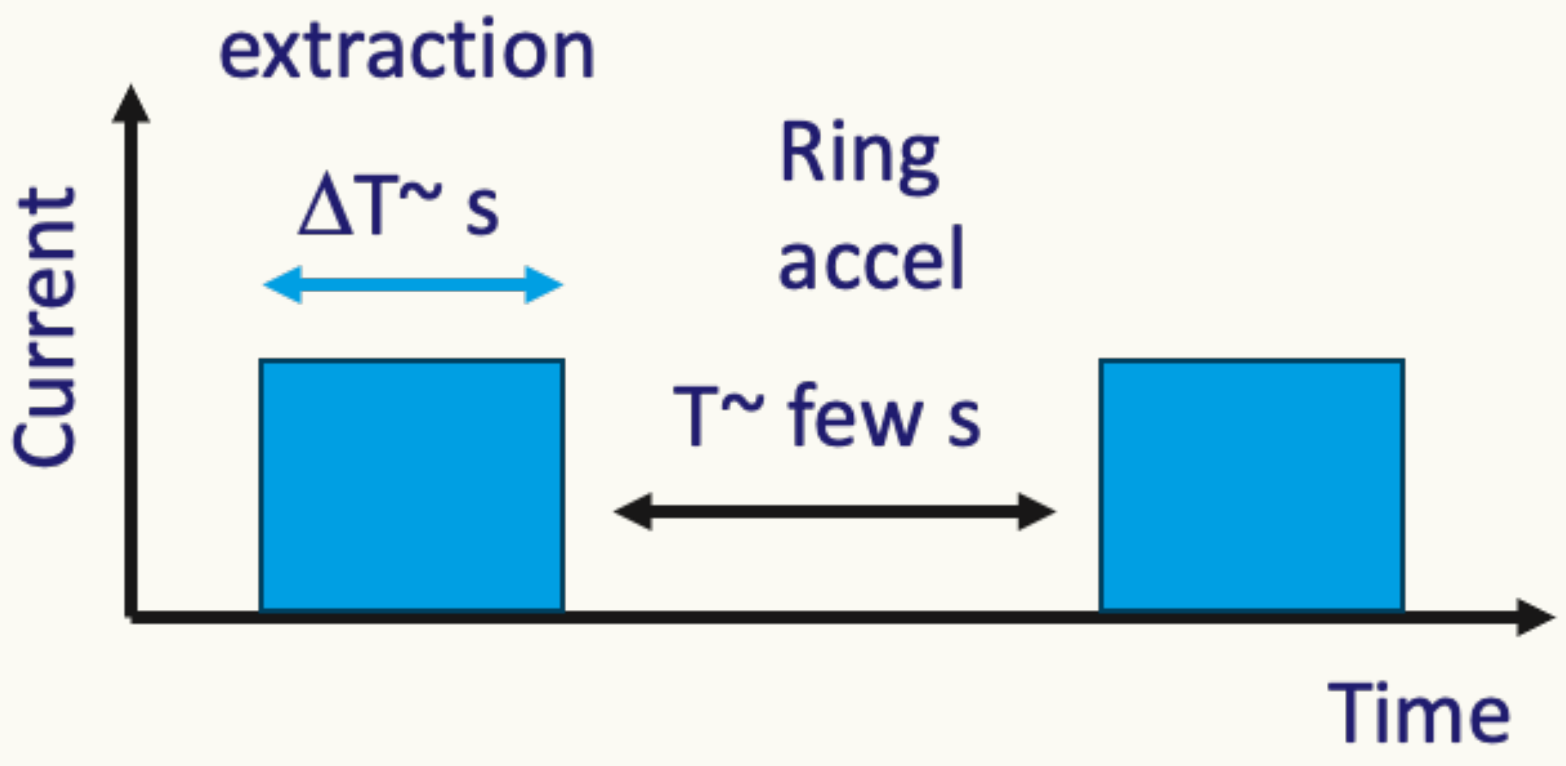
- First time of FLASH ^{12}C beam at HIT 2021 now available at GSI, HIMAC…

GSI

HIT Heidelberger Ionenstrahl-Therapiezentrum



- Standard spill time are seconds and must be reduced to ~ 100 ms:



- Also in synchrotron the energy change takes time (seconds, in general);
- PBS and range modulator to recover conformality are also needed

Only single energy used for FLASH

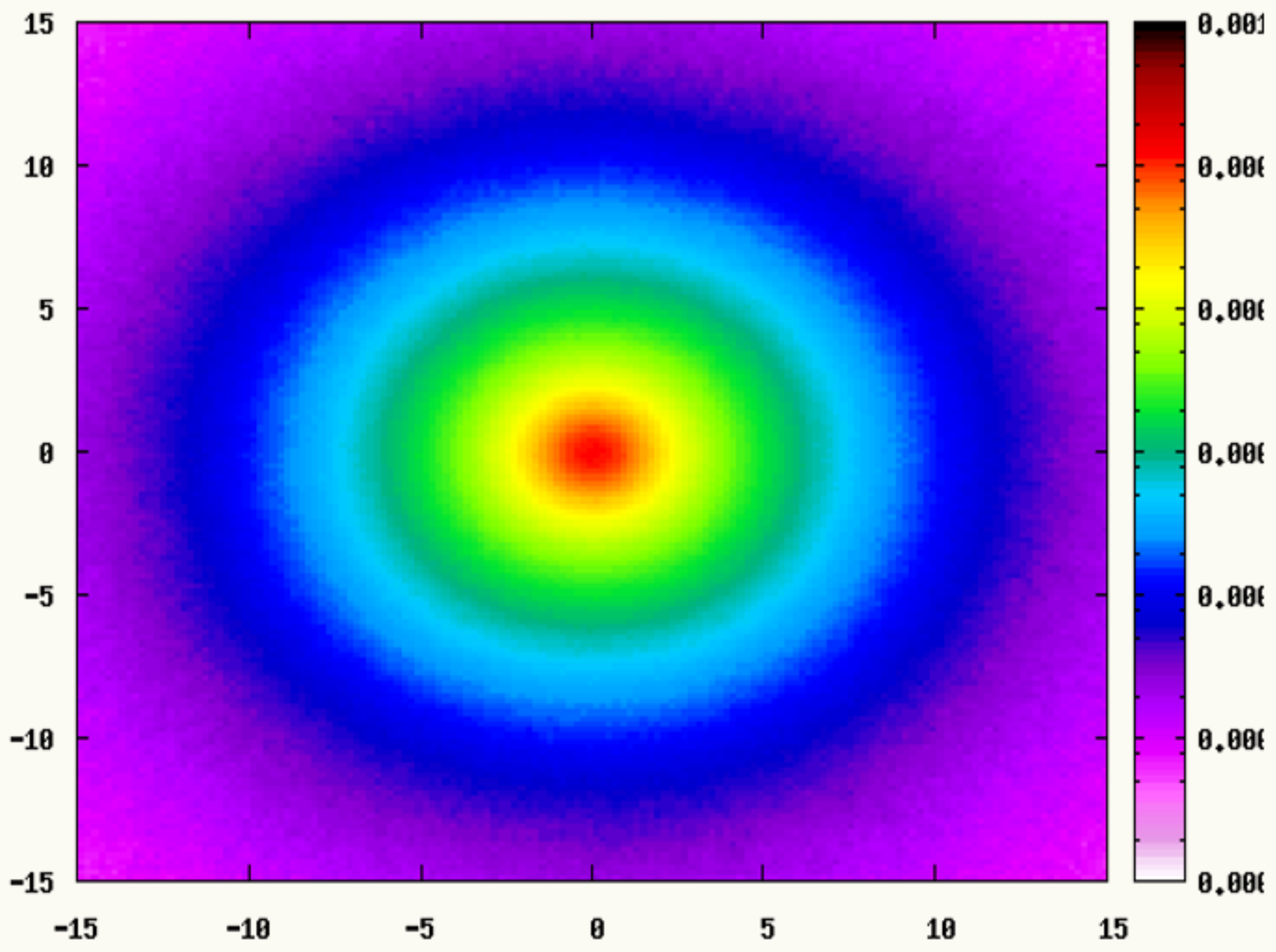
BTW Synchrotrons deliver also proton and (outside clinics) also electron!!

VHEE: additional benefit

The VHEE beam produces an **electromagnetic shower** with plenty of positrons, that slow down and annihilate providing a clear **PET back to back $\gamma\gamma$ signal**.

Possibility to exploit this signal to monitor ON-LINE the dose deposition!

75 MeV electrons log(Dose)



75 MeV electrons log(PET Activity)