Development of a VHEE accelerator in Sapienza for the treatment of deep seated tumors: planning and radioprotection challenges of a FLASH compact machine

Ph.D. in Accelerator Physics, XXXVII cycle

Department of Physics

Sapienza, University of Rome

Thesis Advisor: Prof. Alessio Sarti

Thesis Co-advisor: Prof. Vincenzo Patera

Candidate: Angelica De Gregorio

Radiation Therapy

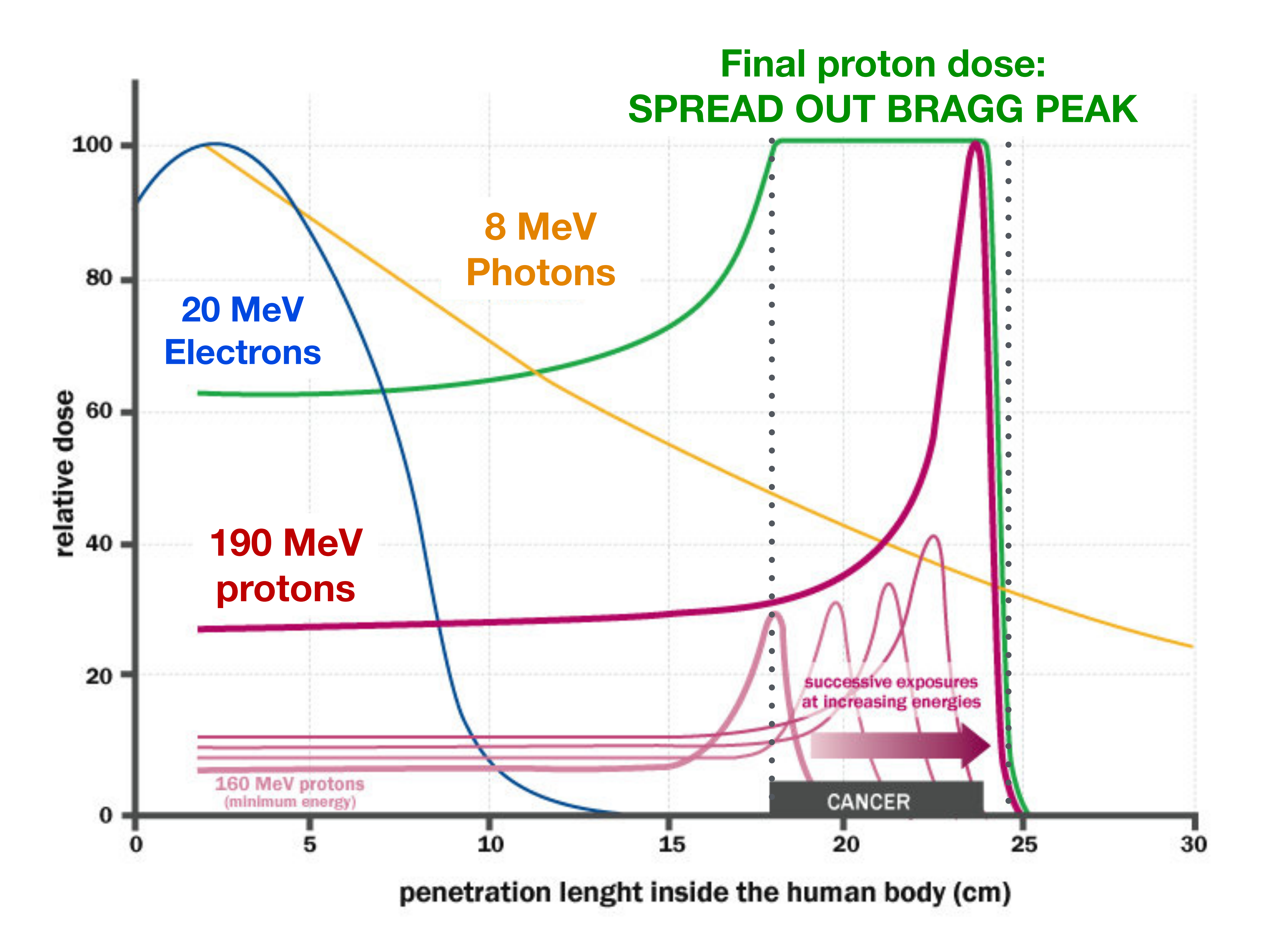
Radiotherapy uses ionizing radiation to target and destroy malignant cells. The principle is based on **inducing DNA damage** in tumor cells, disrupting replication and leading to cell death.

External Beam Radiotherapy (EBRT)

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.

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



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

SAPIENZA
UNIVERSITÀ DI ROMA

Radiation Therapy

NATURAL SPREAD OUT BRAGG PEAK

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.

External Beam Radiotherapy (EBRT)

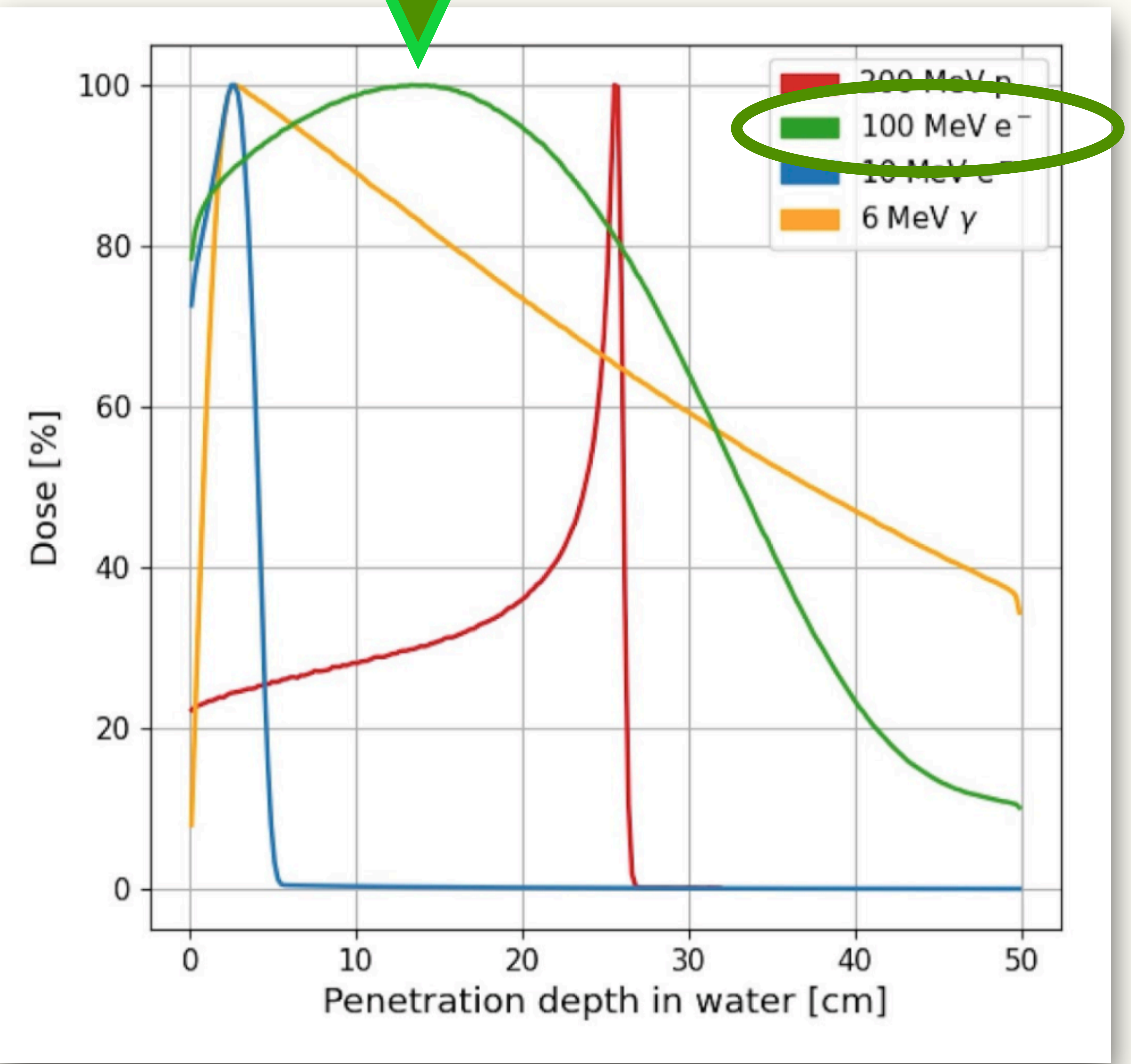
Photon Therapy: deep tissue penetration, suitable for treating tumors located at various depths.

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

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

+

Very High Energy Electrons (VHEE, 50-250 MeV): better longitudinal sparing of Organs at Risks (OARs), reduced impact on the range uncertainties.



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

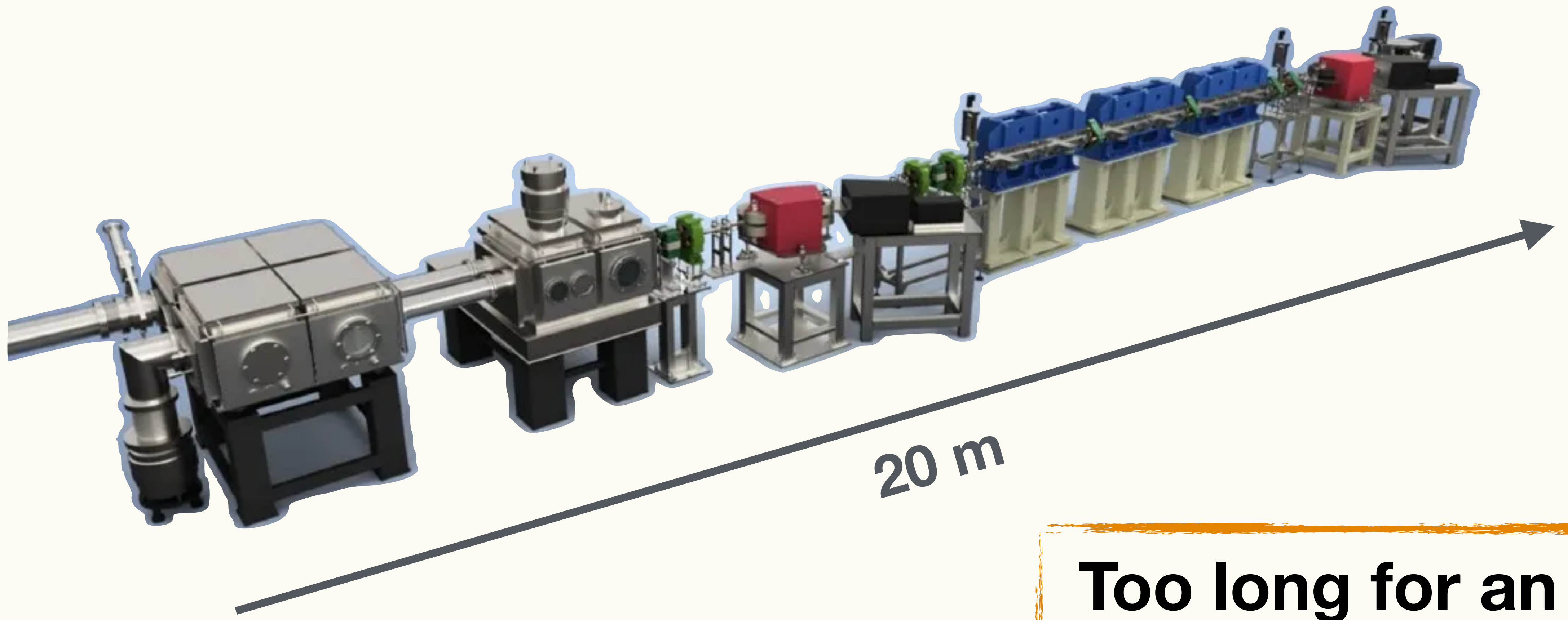
Very High Energy Electrons

SAPIENZA UNIVERSITÀ DI ROMA

PAST

Due to cost, complexity and space VHEE have not yet reached the clinical stage.

- YES — High penetration capability.
- NO — High energy and multi field.

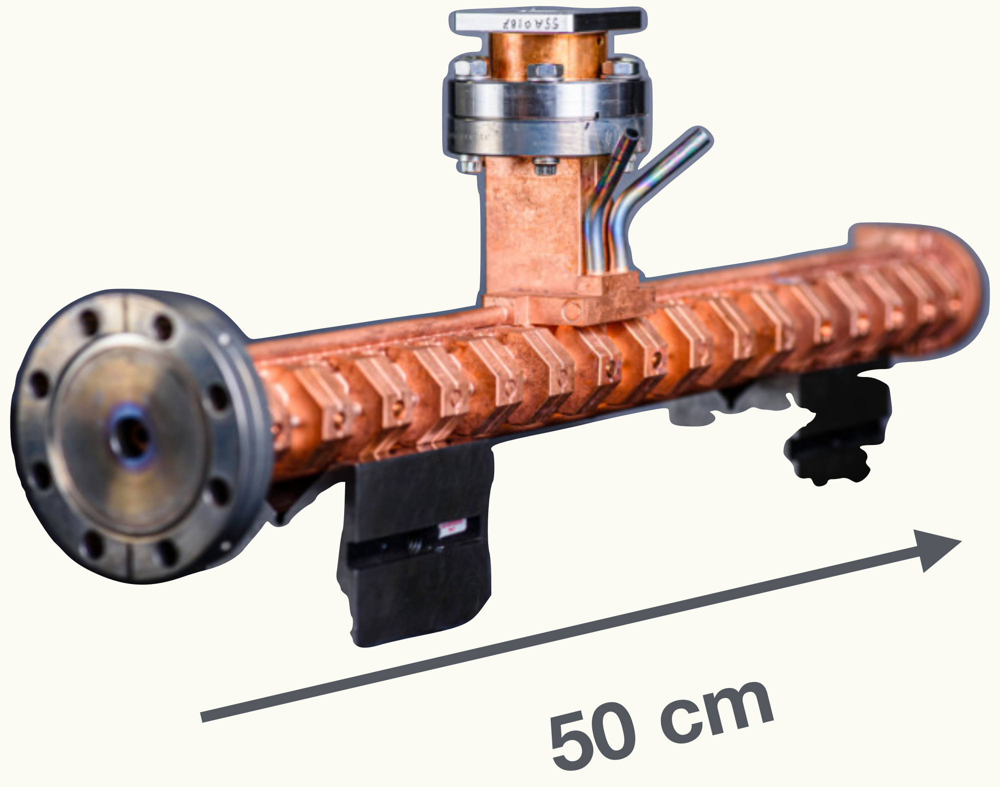


Too long for an hospital!

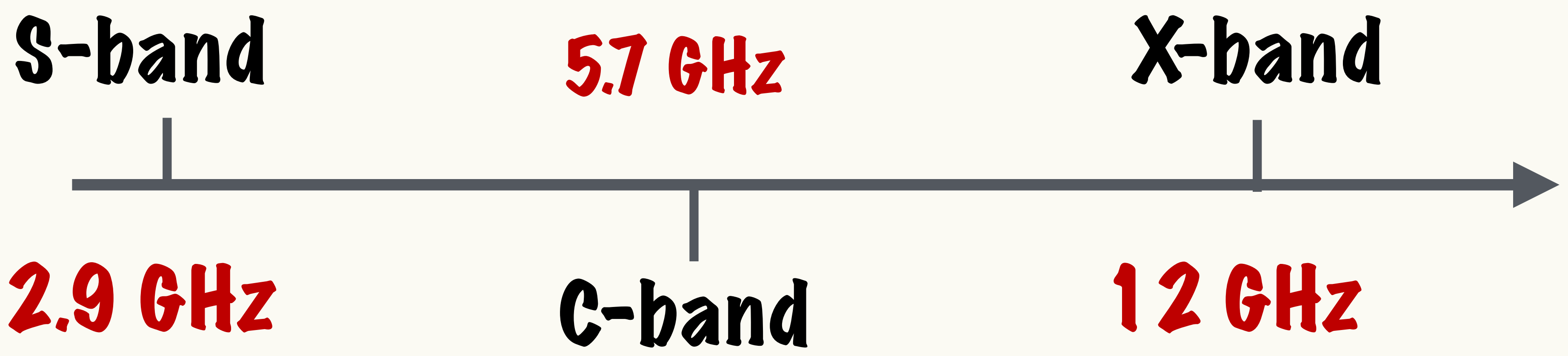
PRESENT

C and X-band accelerators with **higher gradient capabilities.**

- YES — Compact designs.
- YES — Precision in dose delivery.
- YES — Reduced treatment time.



Fit in an hospital room!



FLASH effect 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**).

Pulse dose

Dose-Rate per pulse

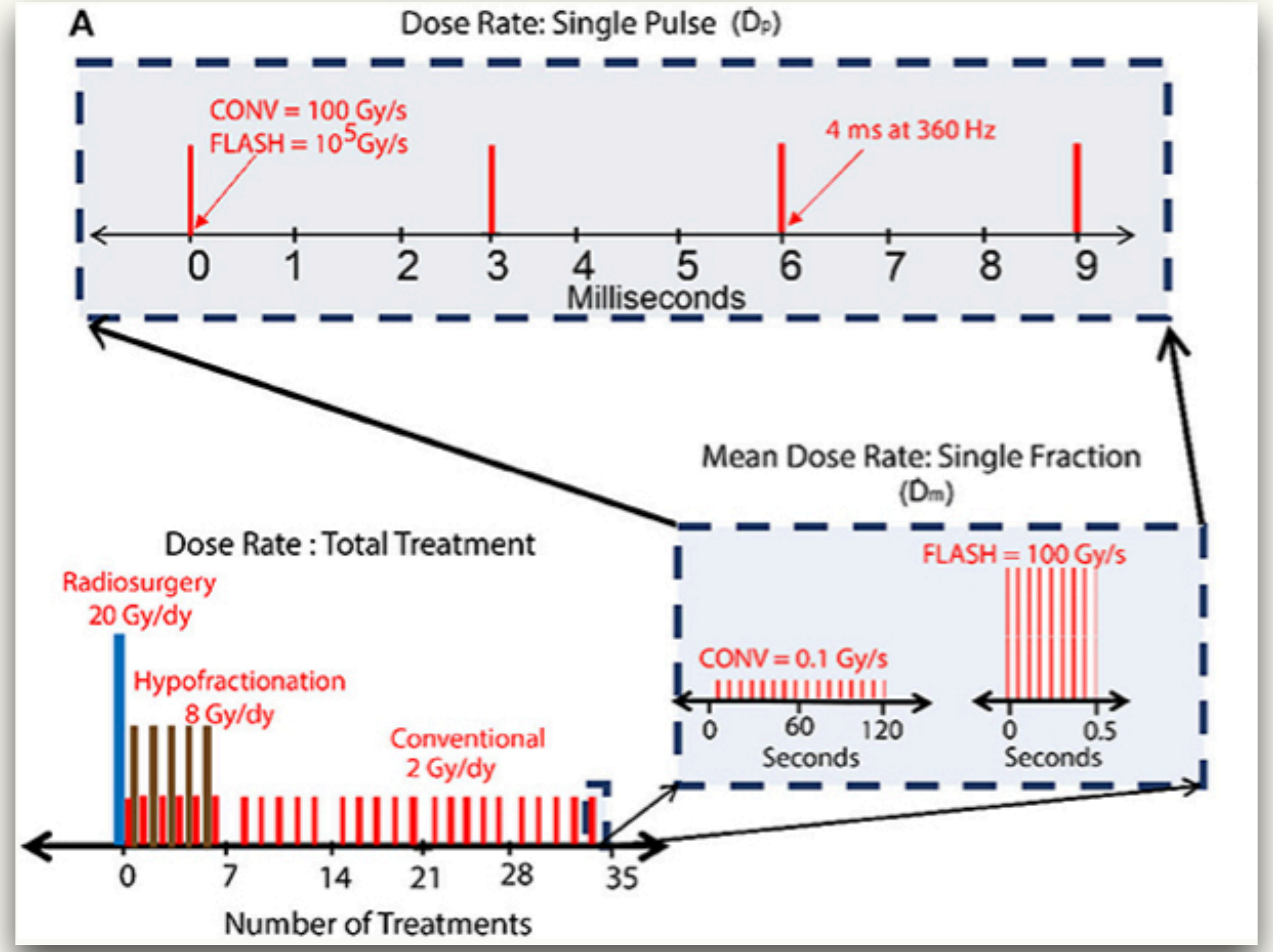
$$\dot{D}_p = \frac{D_p}{t_p}$$

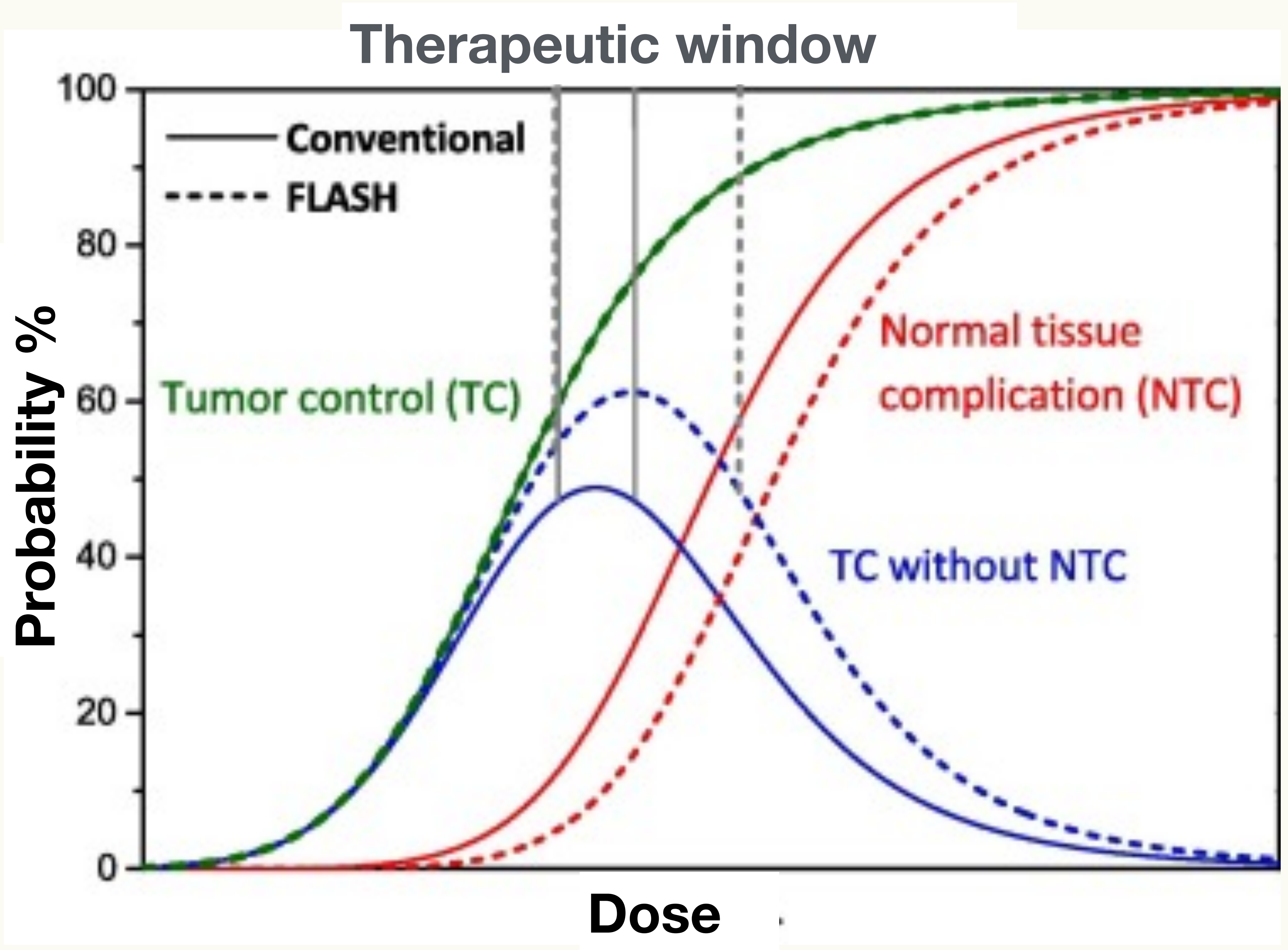
Pulse duration

Average Dose-Rate

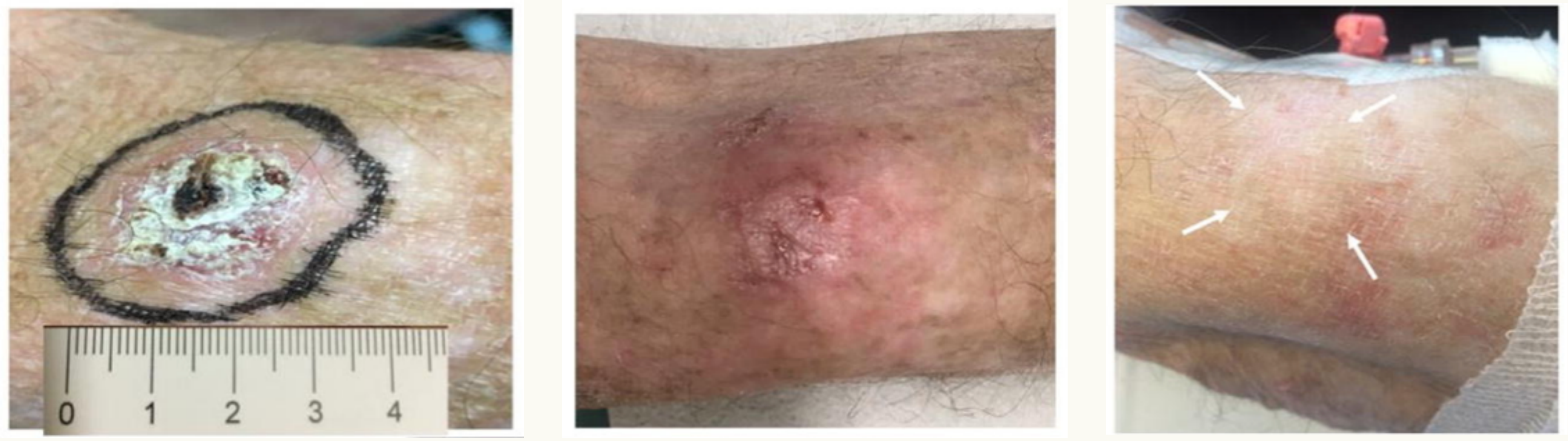
$$\dot{D}_m = \frac{D_p}{t_r}$$

Time between pulses





PATIENT 0



Day 0 | 3 weeks | 5 months

Bourhis J, Sozzi WJ, Jorge PG, Gaide O, Bailat C, Duclos F, Patin D, Ozsahin M, Bochud F, Germond JF, Moeckli R, Vozenin MC. Treatment of a first patient with FLASH-radiotherapy. Radiother Oncol. 2019 Oct;139:18-22. doi: 10.1016/j.radonc.2019.06.019. Epub 2019 Jul 11. PMID: 31303340.

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

FRIDA

INFN

SAPIENZA UNIVERSITÀ DI ROMA

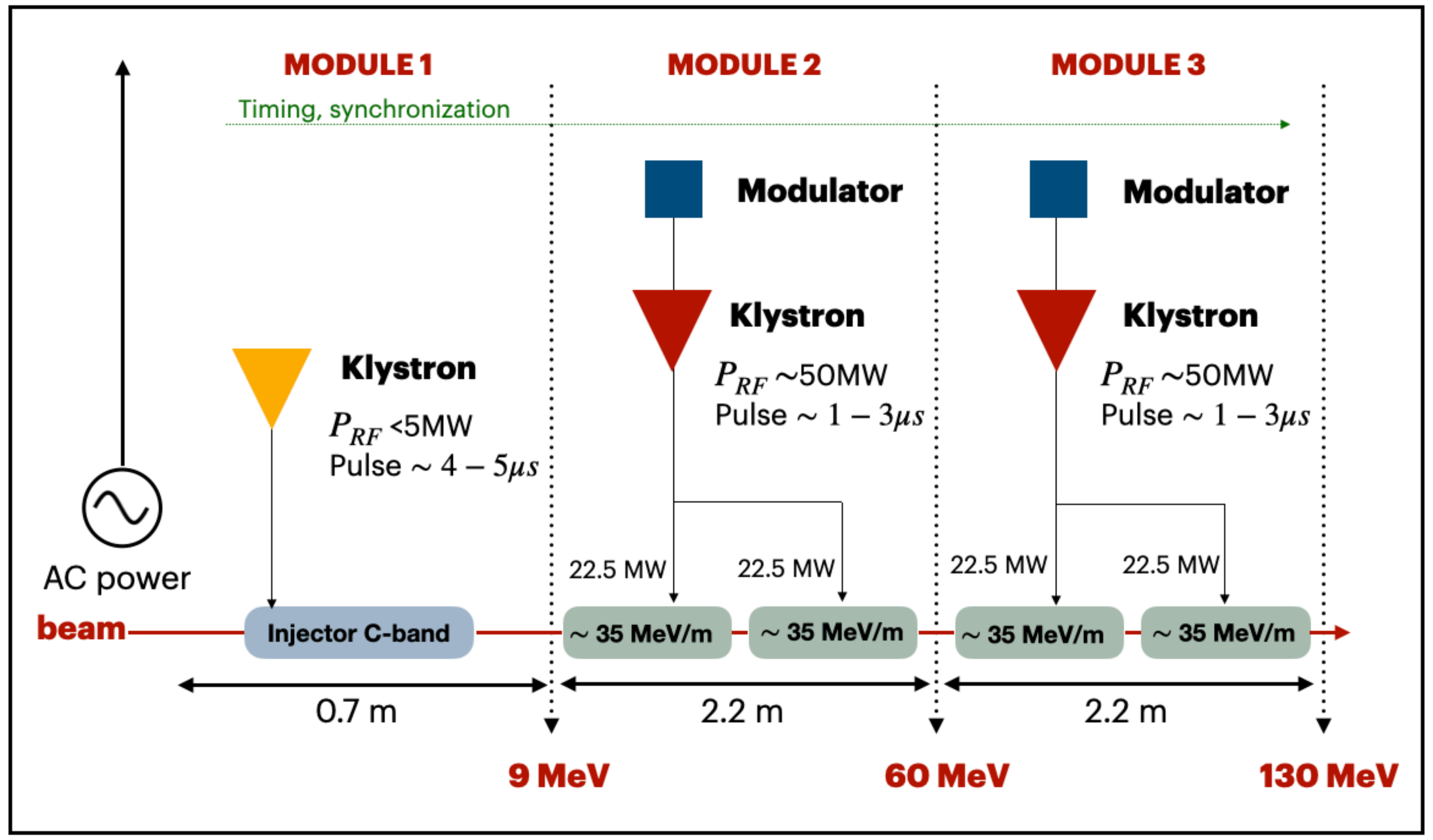
SIT

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).



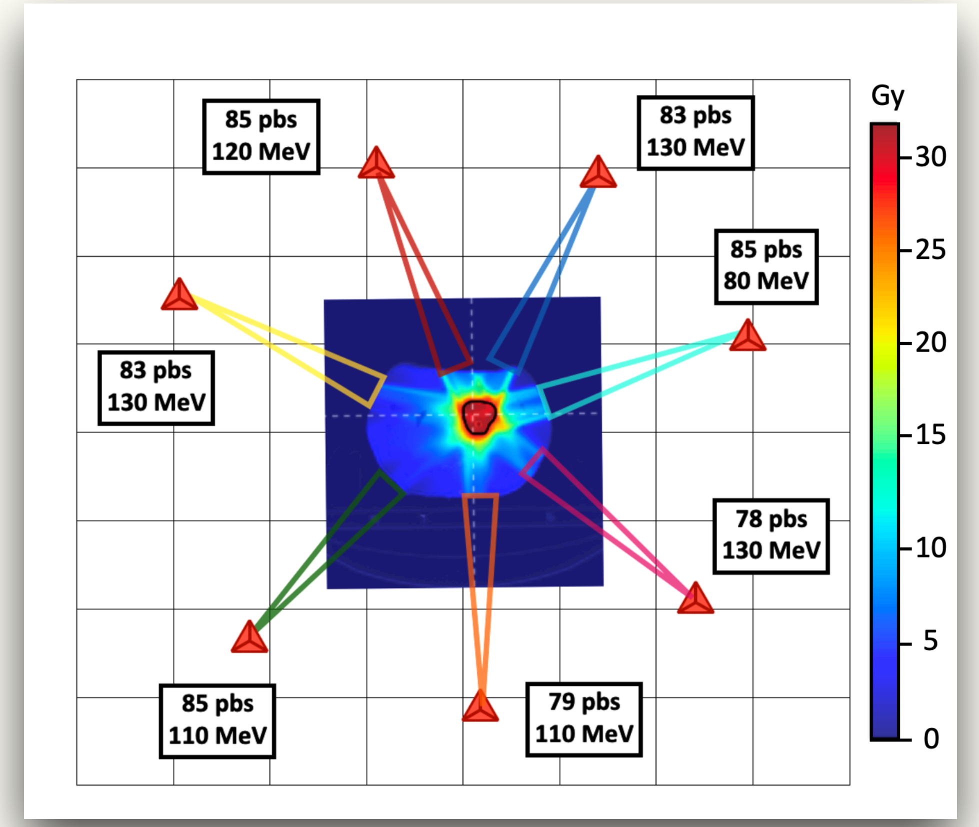
Treatment Planning System

To finalize the machine design and to investigate the potential of VHEE, a **VHEE Treatment Planning System (TPS)** is needed.

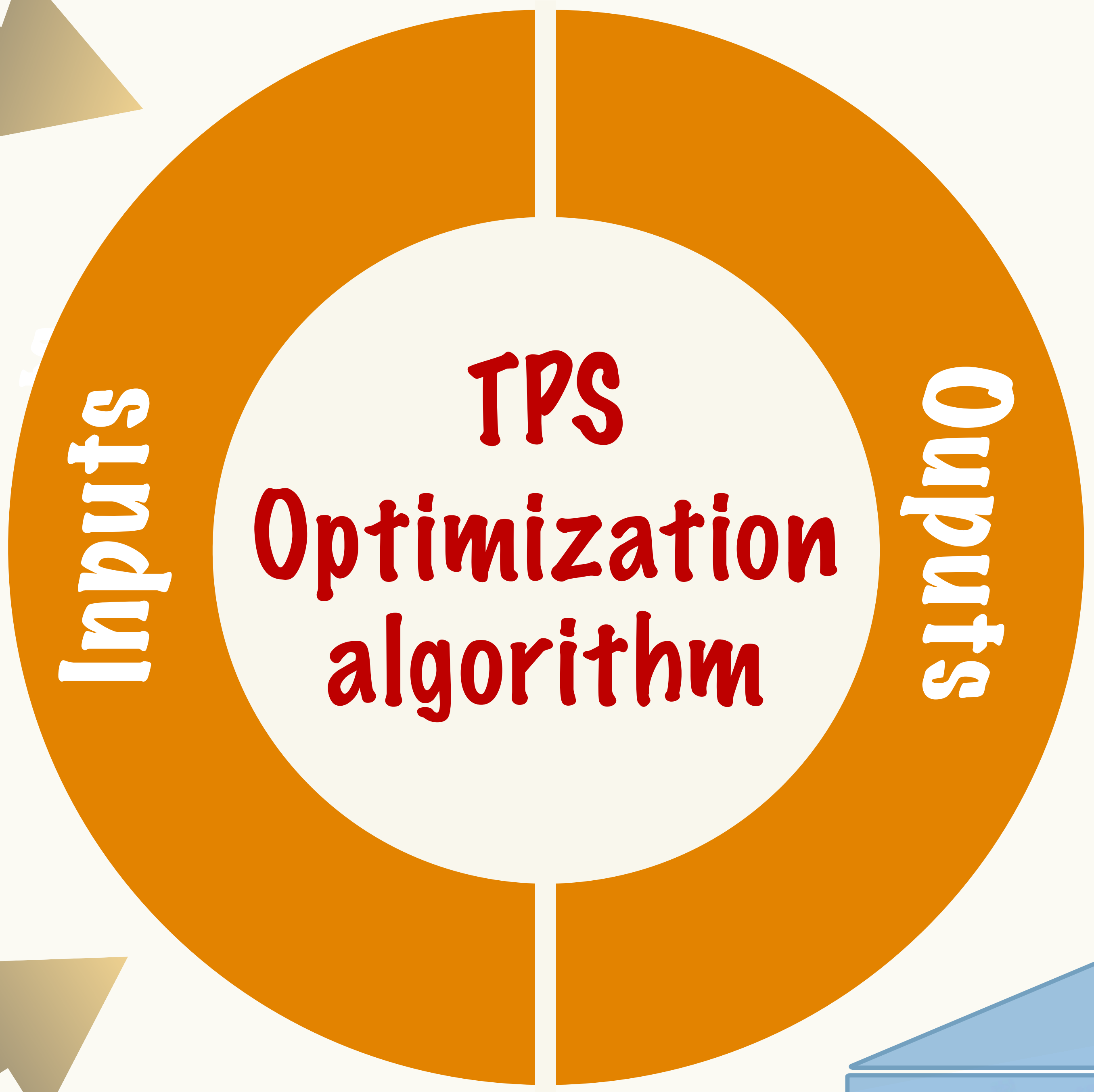
PATIENT IMAGING

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

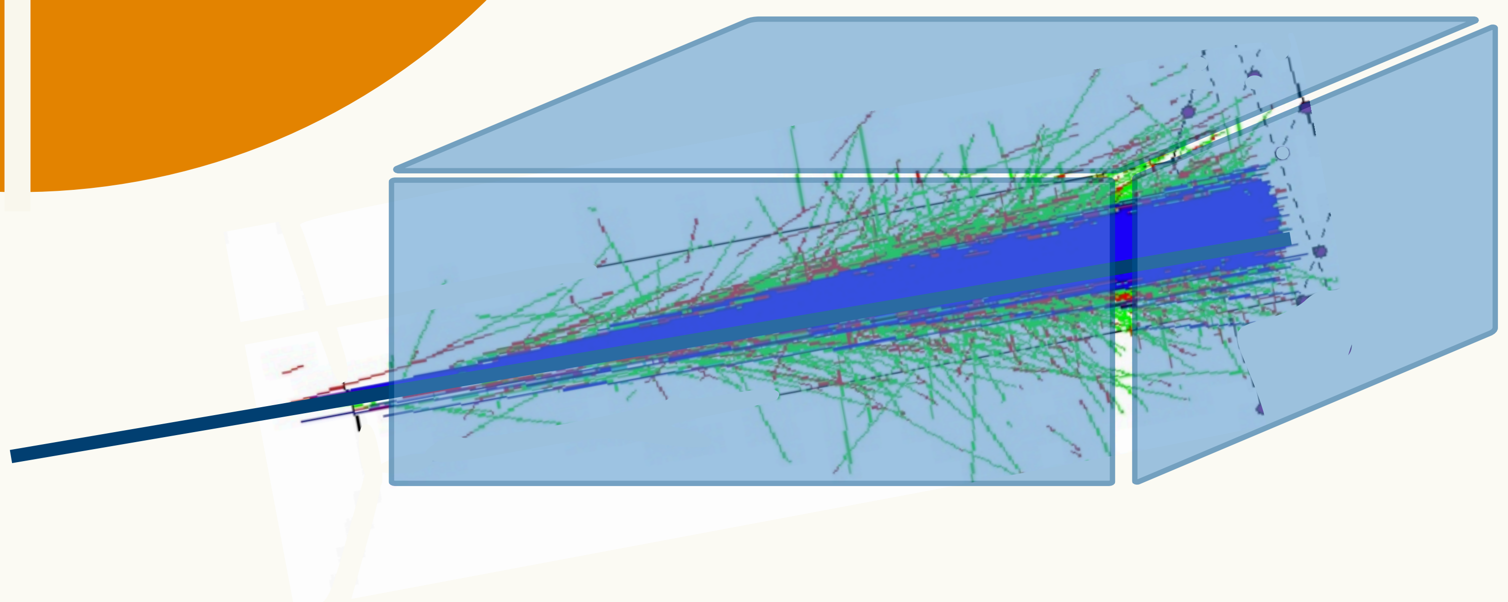
DOSIMETRIC CONSTRAINTS



PHYSICAL MODEL



ACCELERATOR PARAMETERS



1. Energy
2. Intensity
3. Direction

My thesis work

The availability of a dedicated facility would allow bridging the gaps in the current knowledge and characterization of the VHEE based radiotherapy, both including or not the FLASH effect.

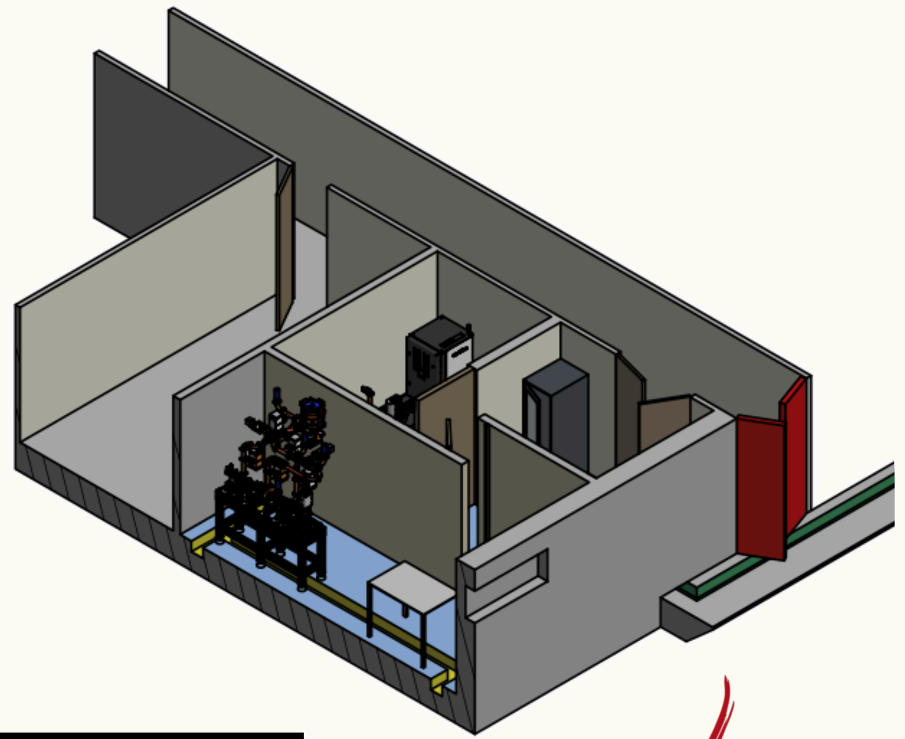
The aim of my **Ph.D. thesis work** was twofold: based on the VHEE LINAC designed within the SAFEST project, I focused on...

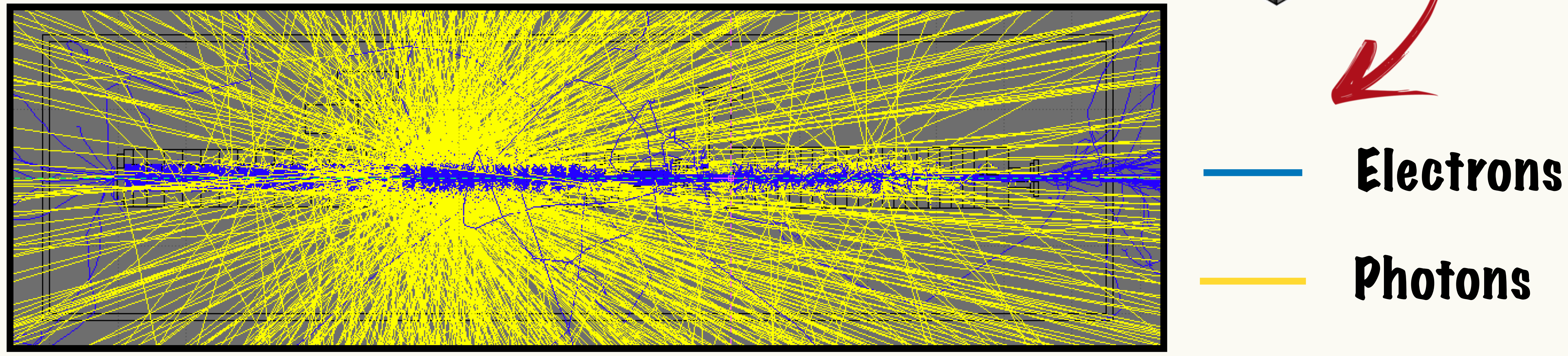
1

RADIOPROTECTION STUDIES FOR SAFEST LINAC

GOAL:

Evaluate the dispersed radiation to **design the needed shielding.**



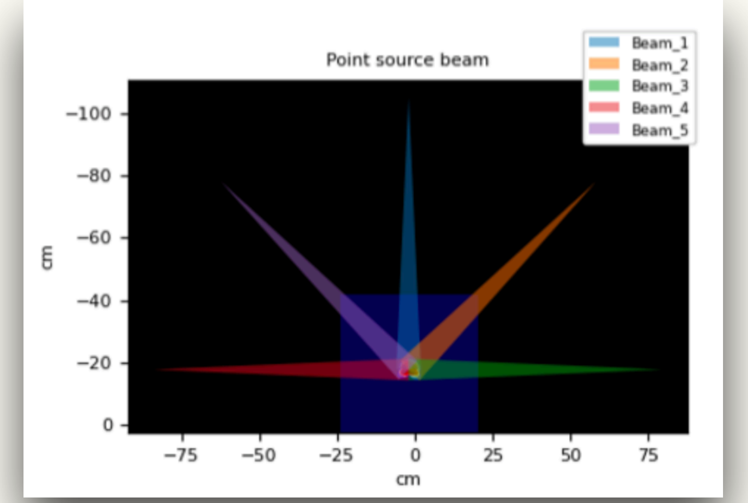


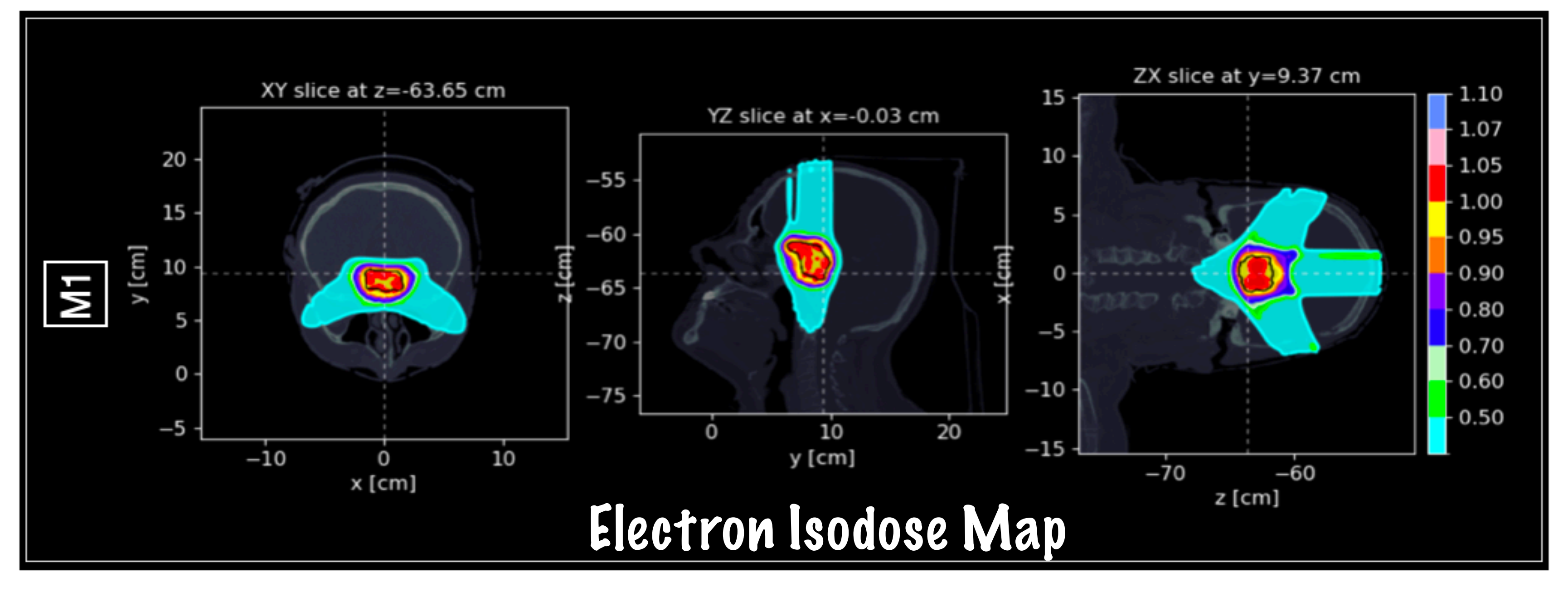
2

DEVELOPMENT OF A DEDICATED VHEE TPS

GOAL:

Compare the VHEE simulated plans with state-of-the-art conventional photon or PT treatments + **FLASH effect** exploration





SAPIENZA
UNIVERSITÀ DI ROMA

Radioprotection studies

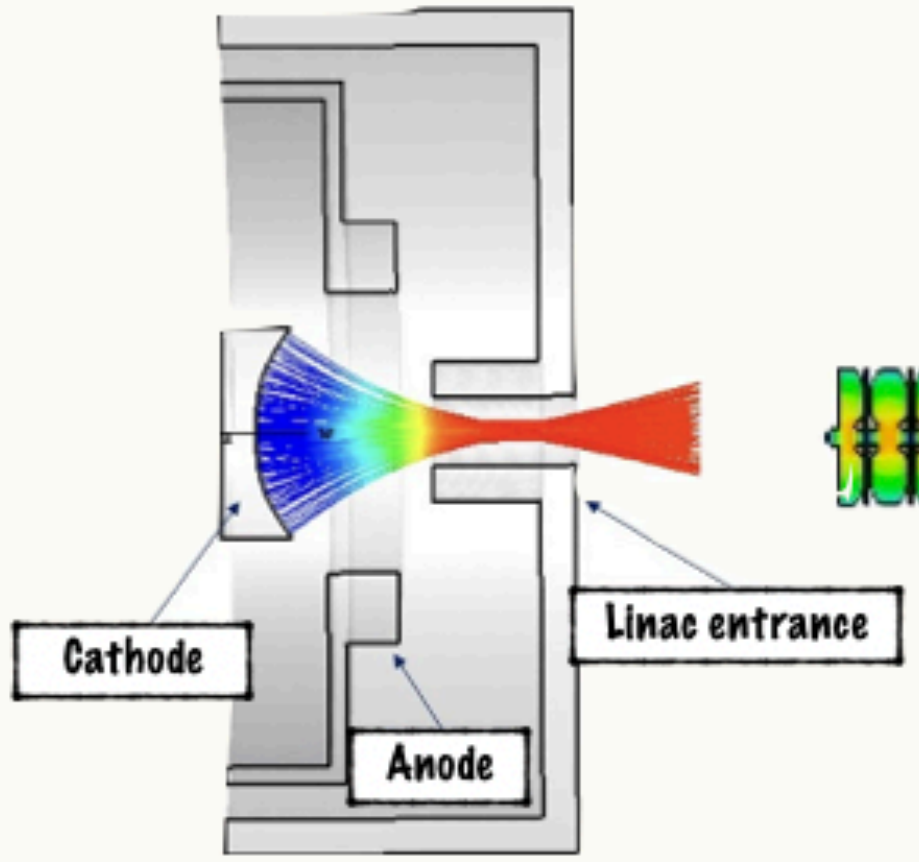
PROTOTYPE GEOMETRY | SIMULATION PROCESS | SHIELDING DESIGN

The **prototype** under construction in the SAFEST project is a **scaled-down version** of the proposed VHEE LINAC, designed to accelerate electron beams up to **24 MeV**.

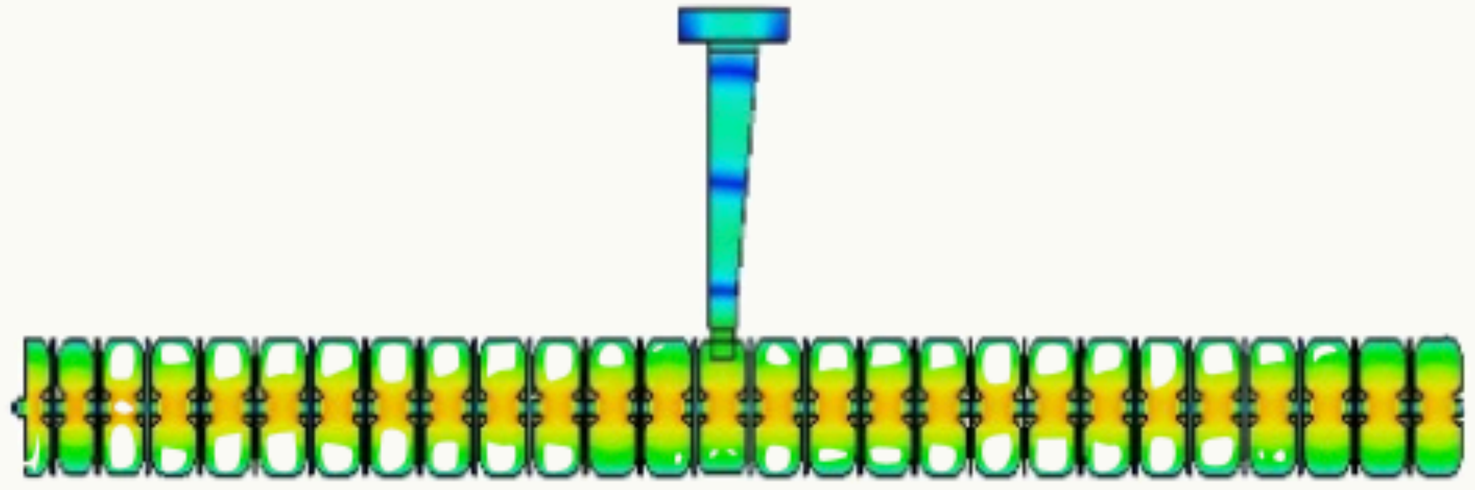
→ **Validate and test all components**

→ **Radiobiological experiments with 24 MeV beams**

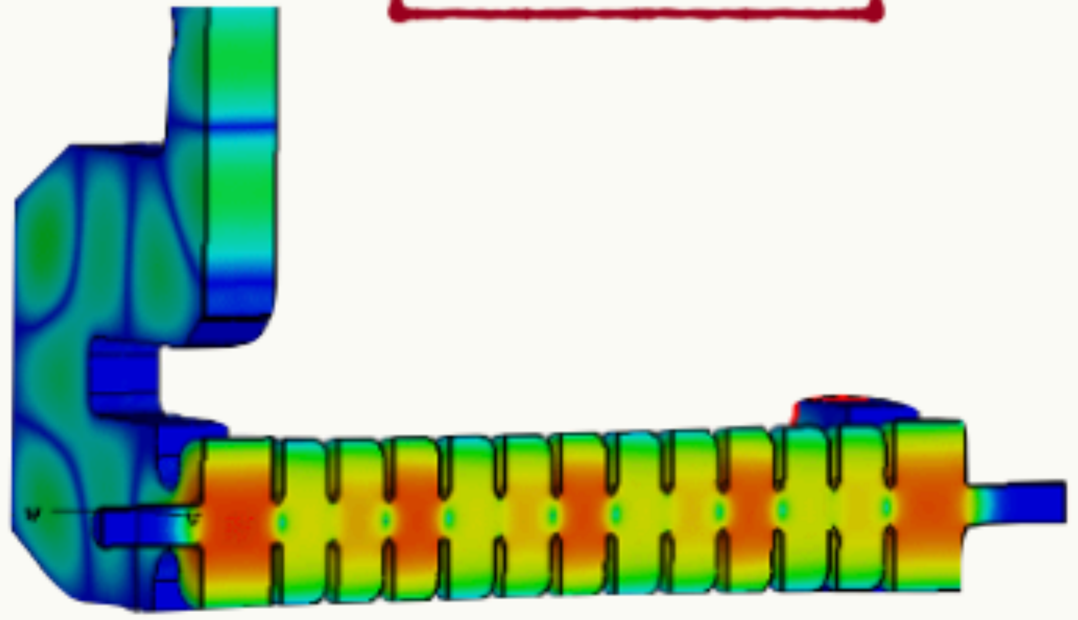
Source

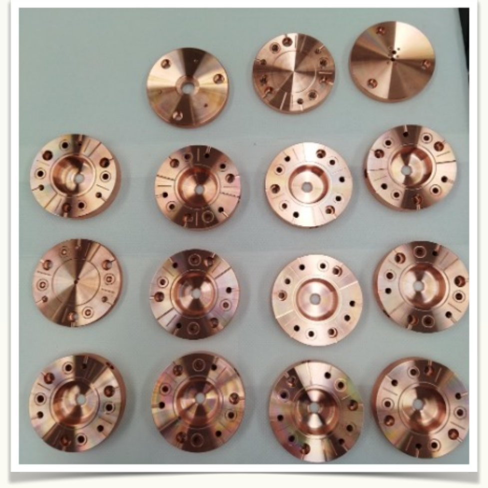


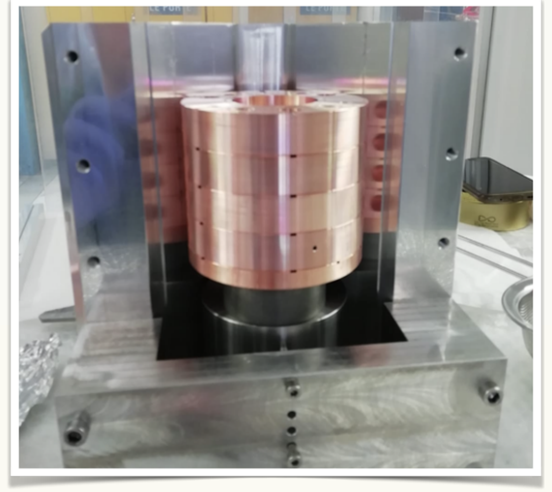
SW cavity

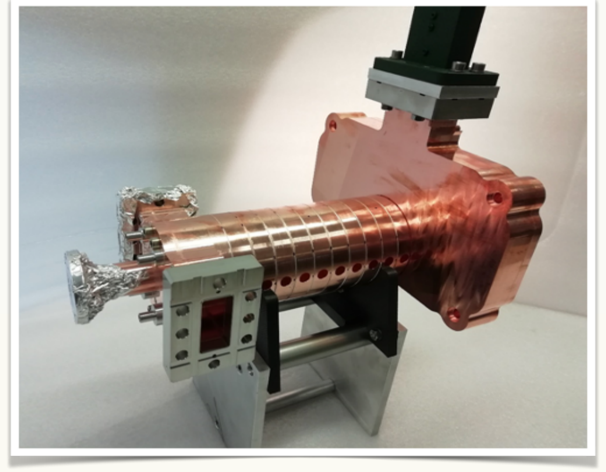


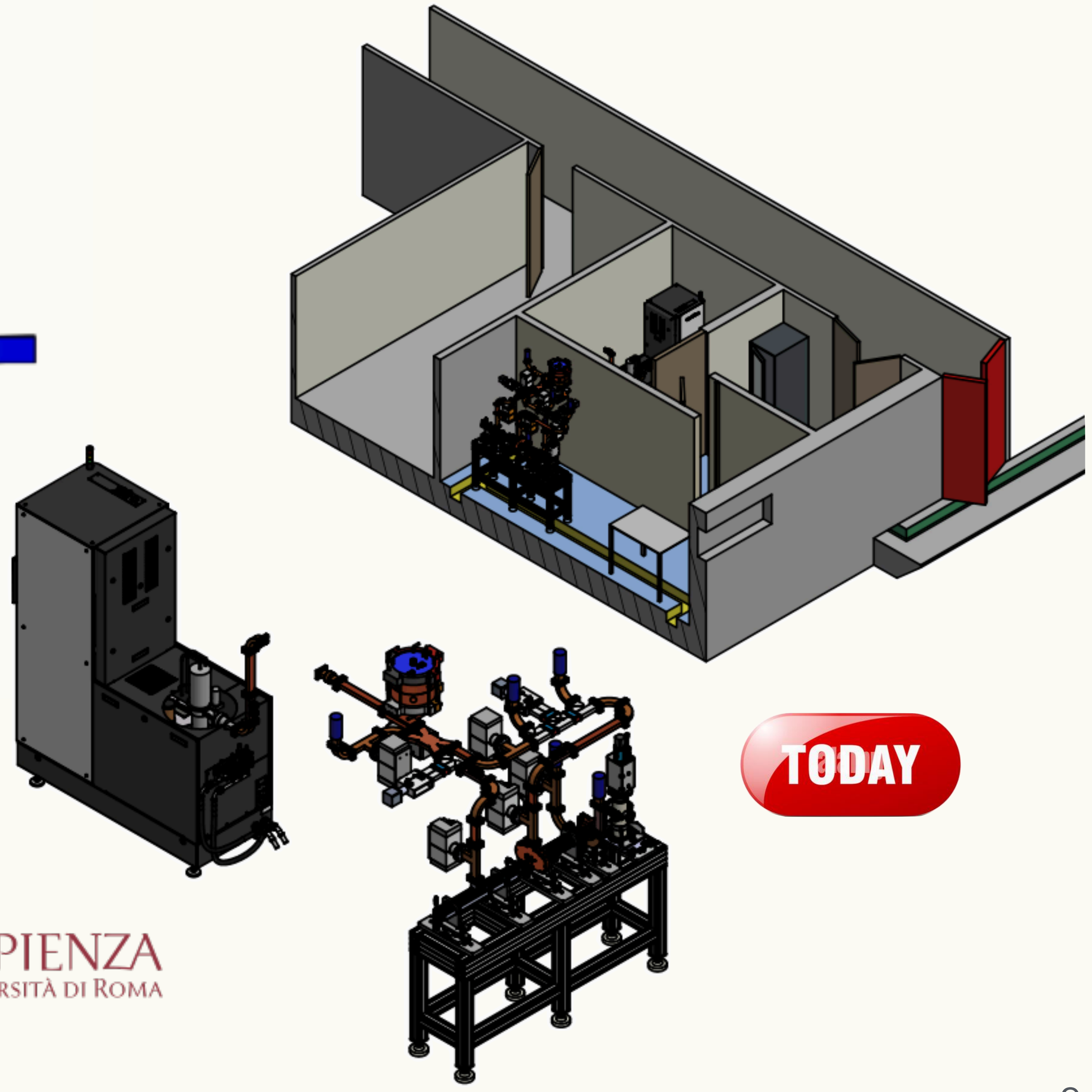
TW cavity











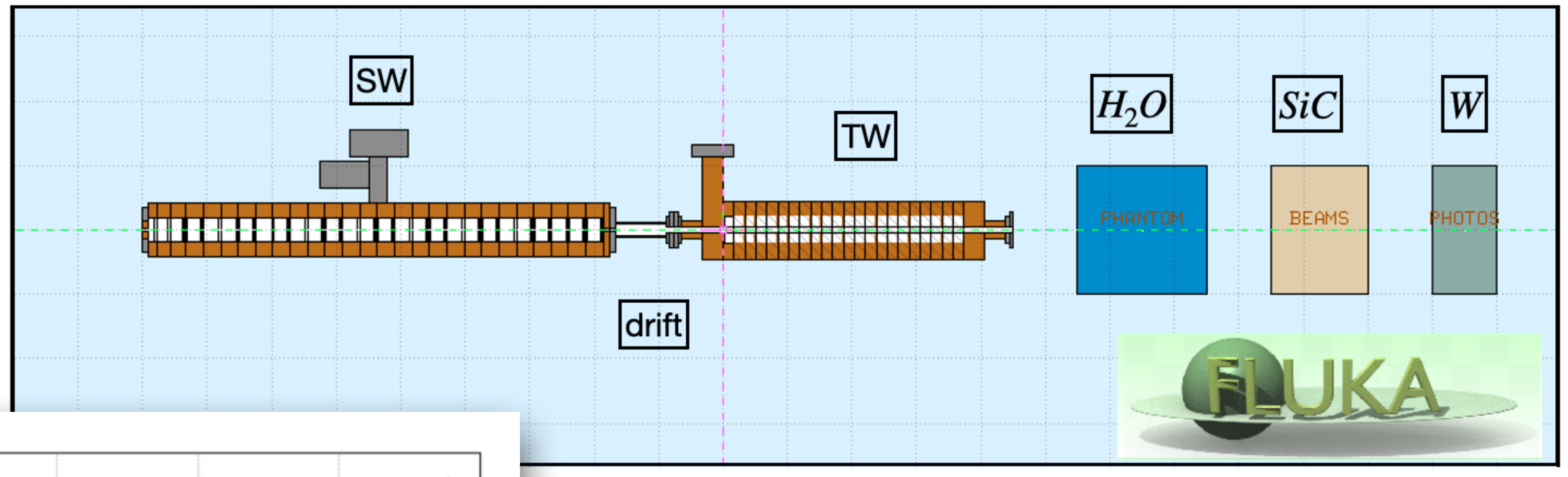
BUILT, TESTED AND INSTALLED IN HOUSE AT SBAI DEPARTMENT

SAPIENZA
UNIVERSITÀ DI ROMA

Radioprotection studies

PROTOTYPE GEOMETRY | **SIMULATION PROCESS** | SHIELDING DESIGN

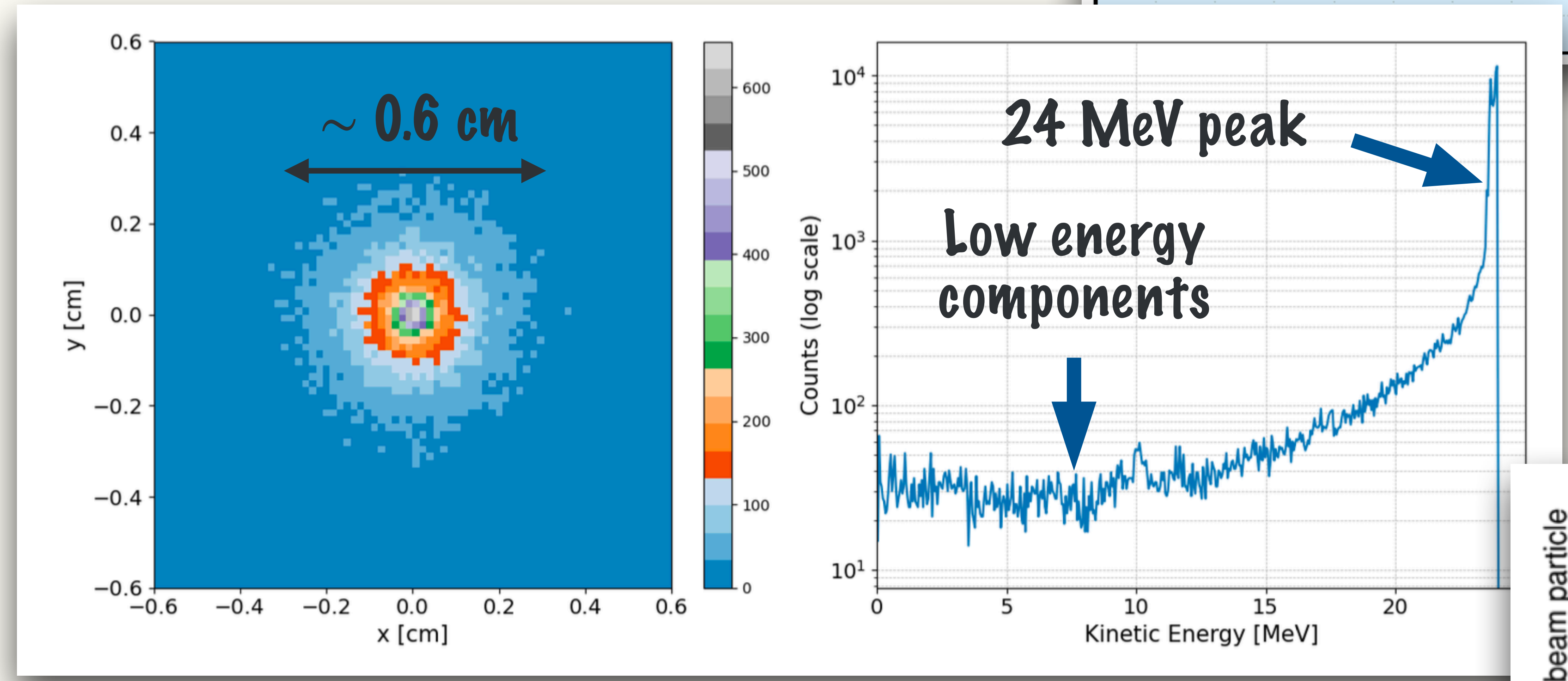
1 **Replicate the geometry and materials** of the prototype.



GOAL

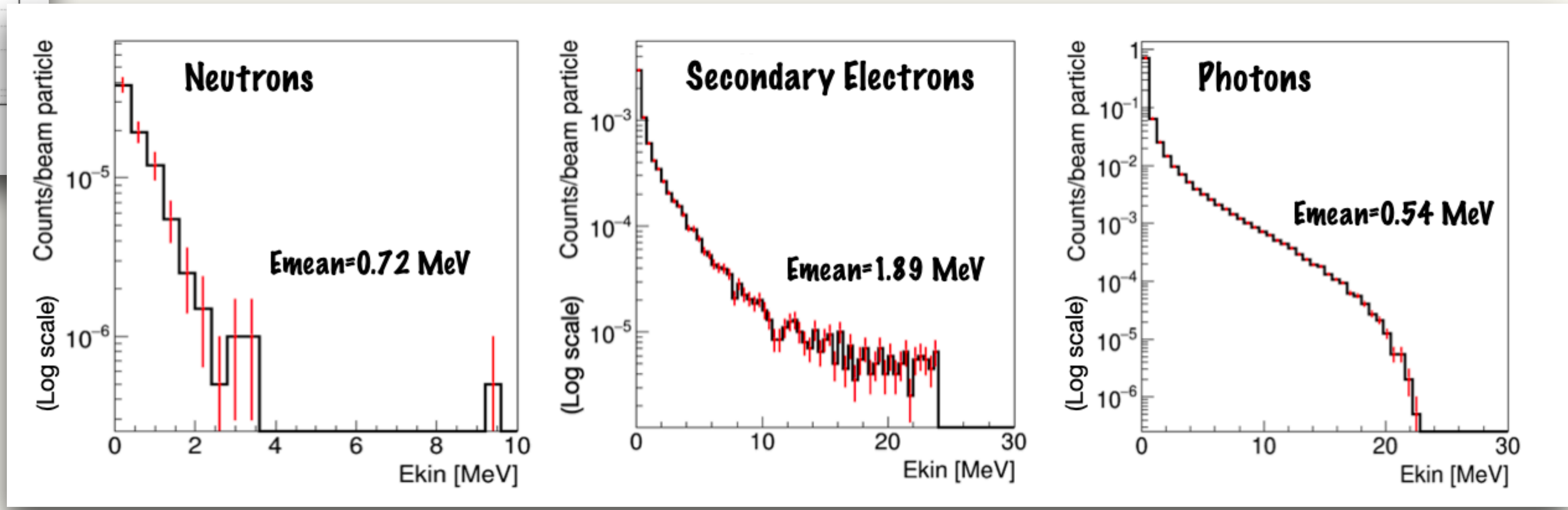
Evaluate the dispersed radiation to design the needed shielding.

Exiting particles: ~7.4 % of total



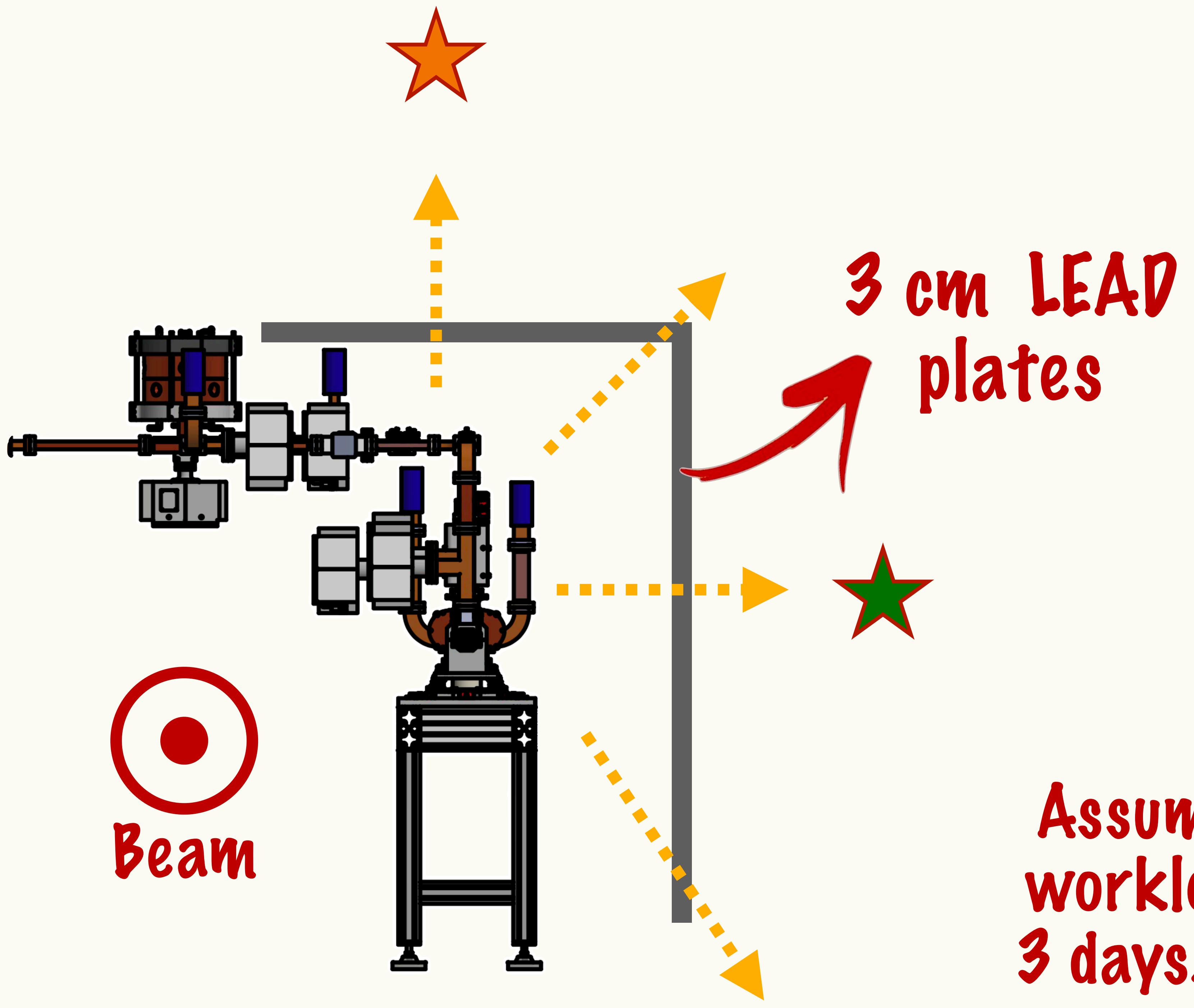
2 Study of **the position, direction, and energy** of particles exiting from the accelerator structure.

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



Statistics: 10^8 primaries

Radioprotection studies

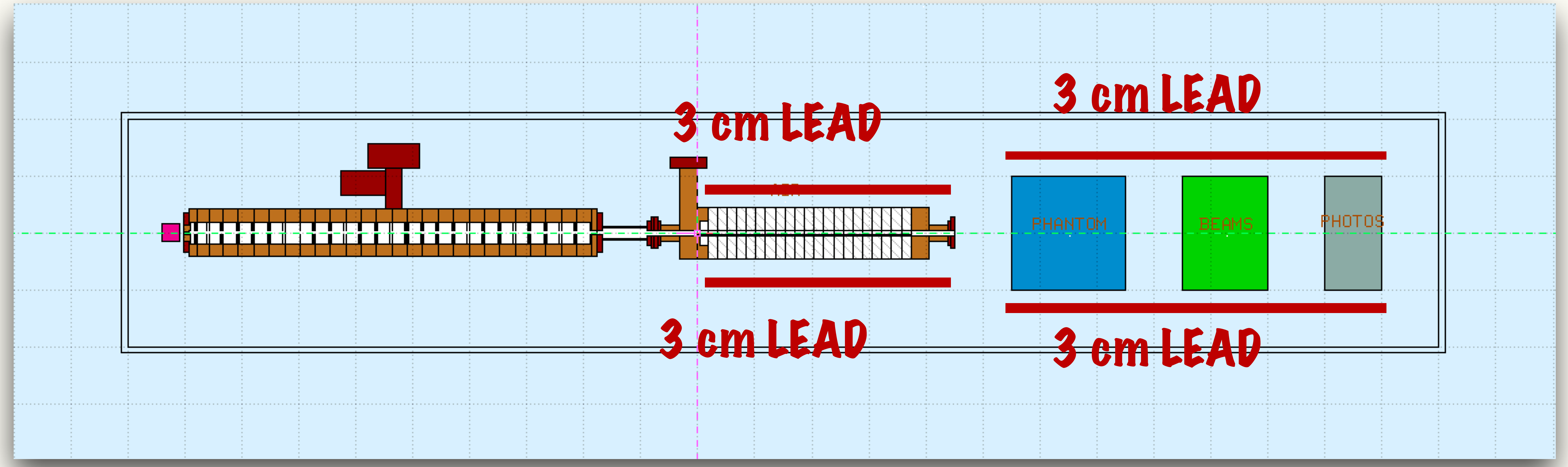


The dose was evaluated at different positions and **radiation shielding barriers were calculated**.

	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

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



SAPIENZA
UNIVERSITÀ DI ROMA

TPS for VHEE FLASH

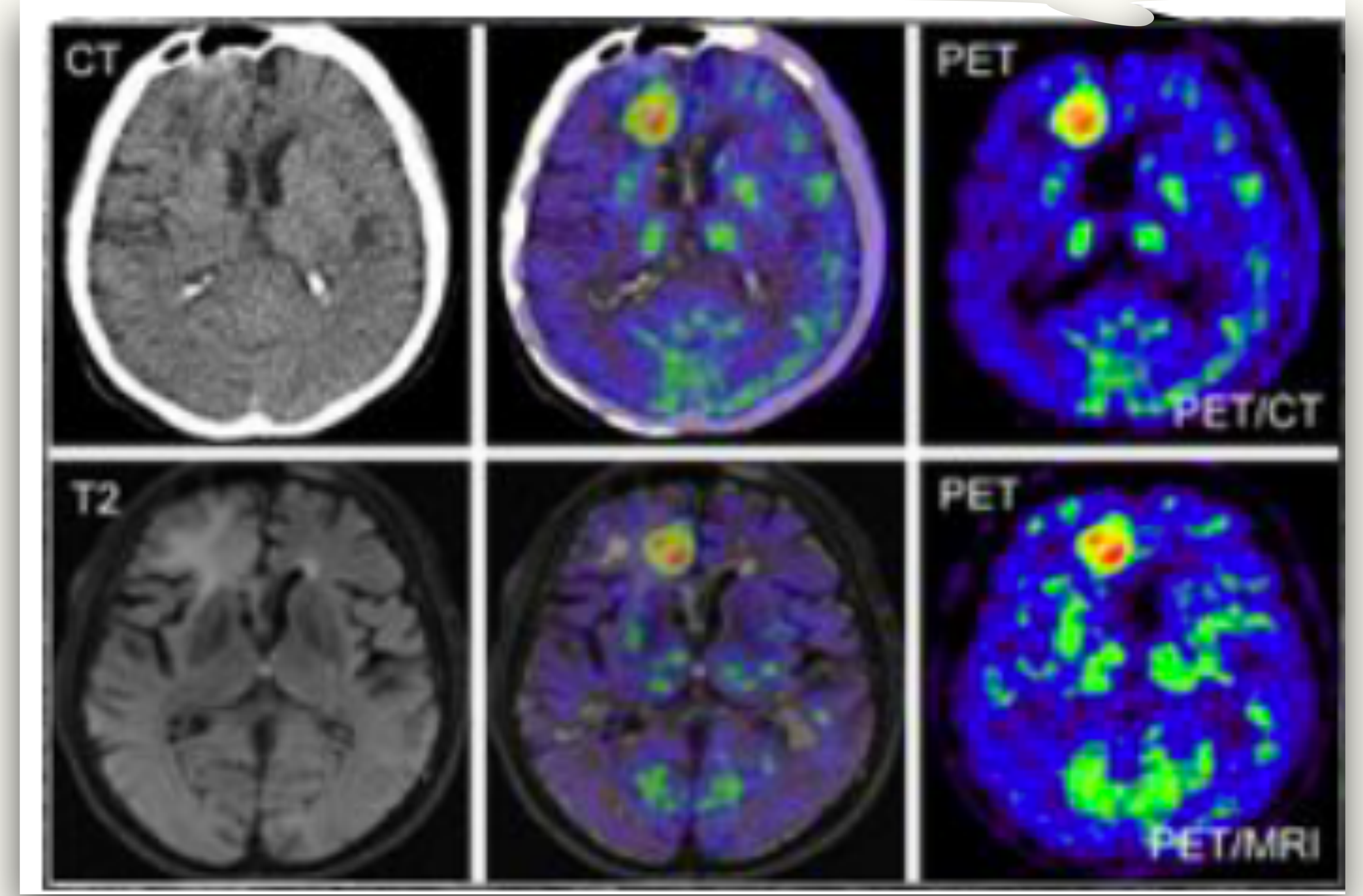
INPUT MODEL | DOSE EVALUATION | OPTIMIZATION | RESULTS

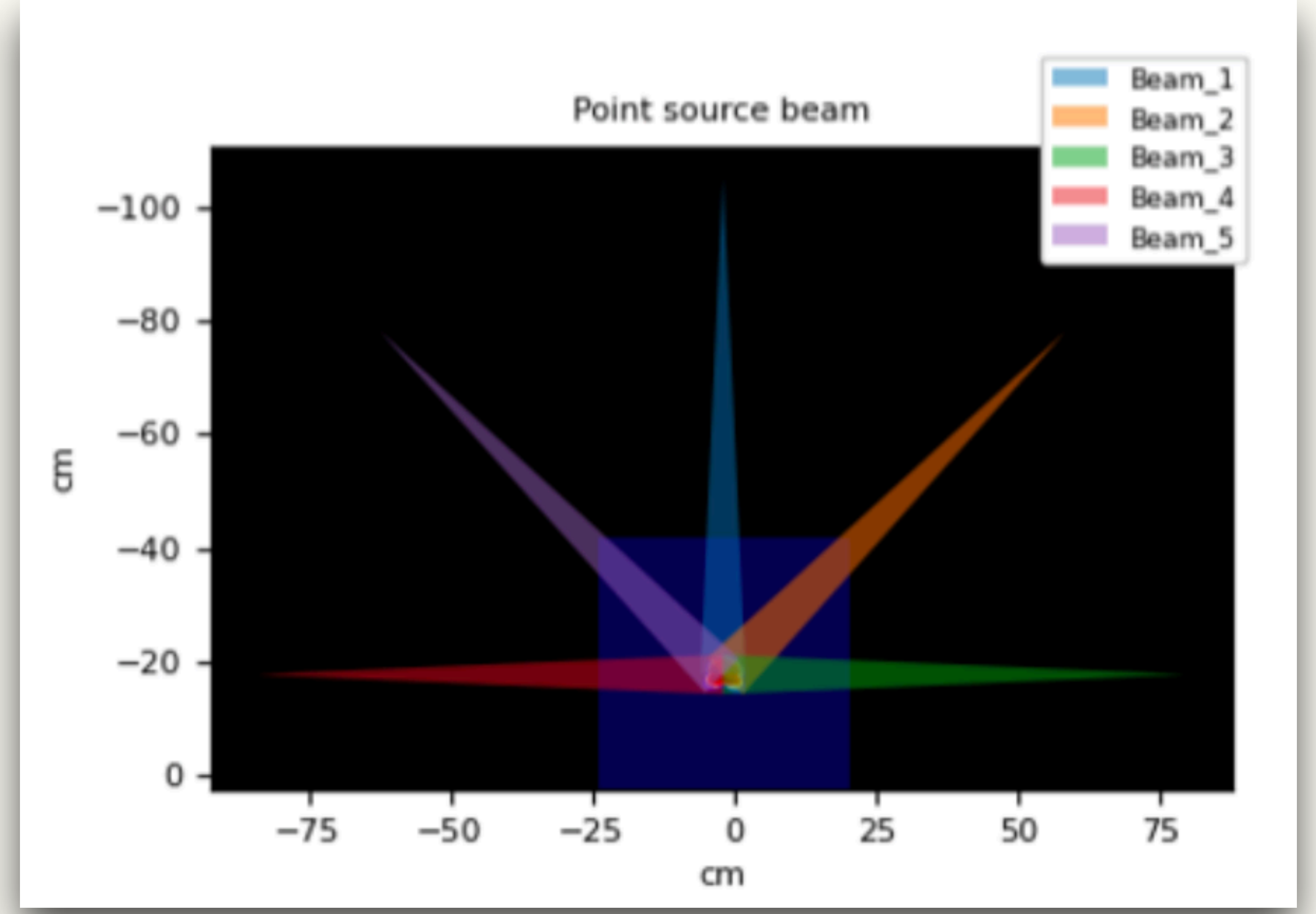
VHEE irradiation was simulated assuming the **compact C-band acceleration technology** which will be capable of delivering **multi-fields** with an **active scanning-like approach.**

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

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

TPS for VHEE FLASH

SAPIENZA UNIVERSITÀ DI ROMA

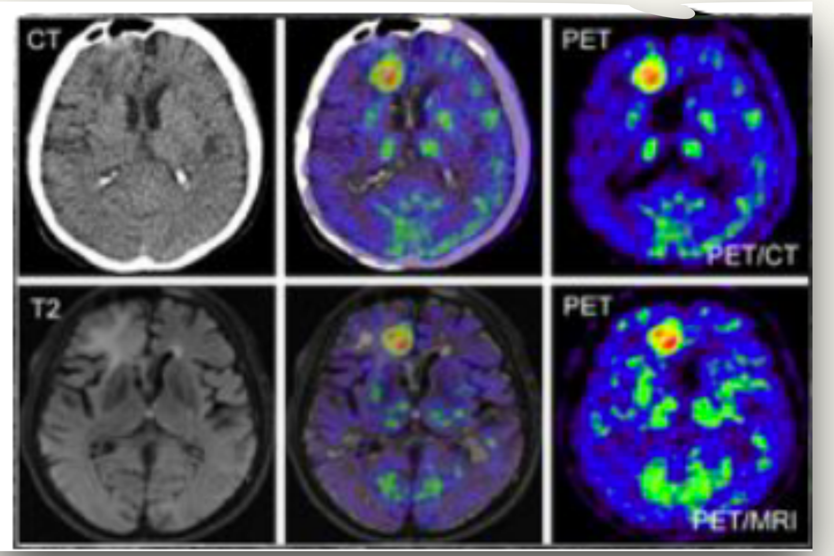
INPUT MODEL | DOSE EVALUATION | OPTIMIZATION | RESULTS

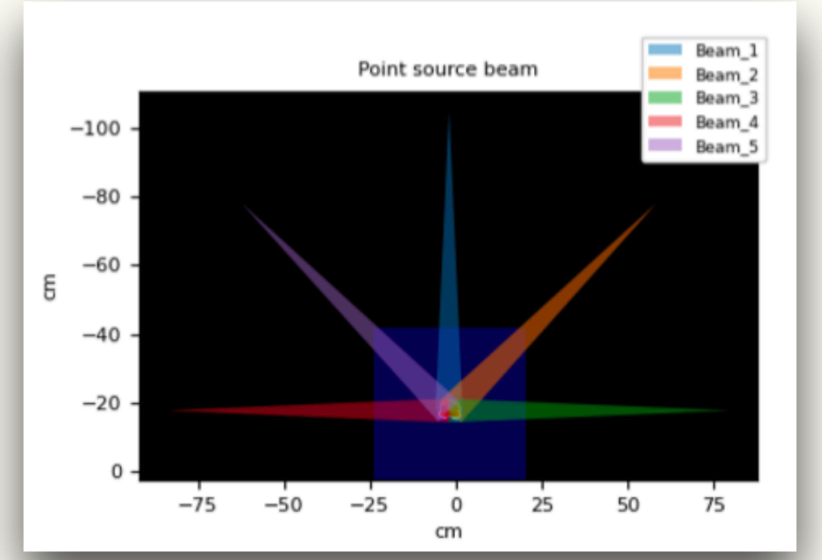
VHEE irradiation was simulated assuming the **compact C-band acceleration technology** which will be capable of delivering **multi-fields** with an **active scanning-like approach.**

CT IMAGES & FIELD DIRECTIONS

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

Provided by the hospital.

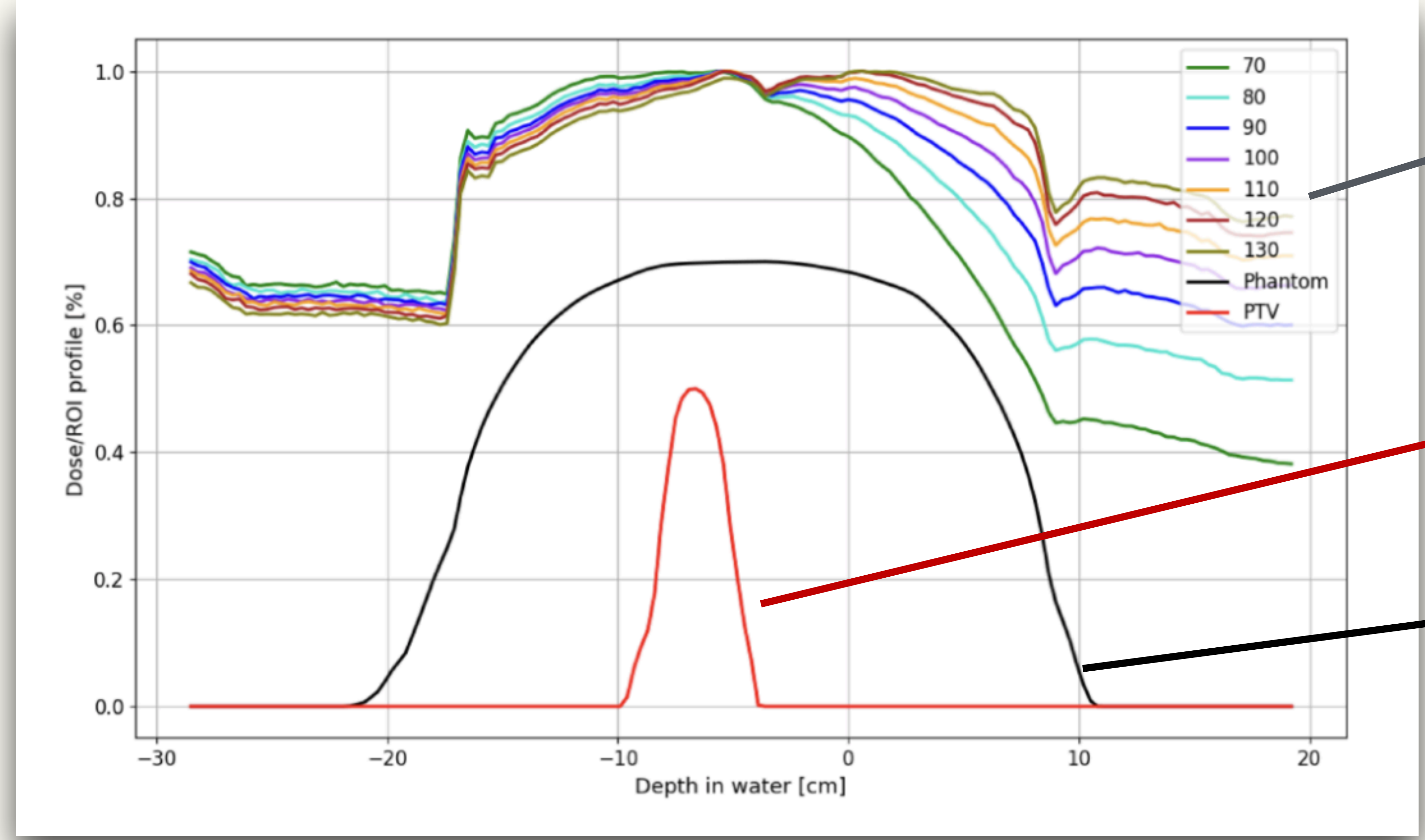




Organ	dosimetric constraints
Target volume	$V_{95\%} > 95\%$, never above 107%
Rectum	$V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, $V_{75} < 15\%$
Anus	$V_{30} < 50\%$
Bulbourethral Glands	$\bar{D} < 50$ Gy
Femurs	$\bar{D} < 52$ Gy, $V_{60} < 5\%$
Bladder	$\bar{D} < 65$ Gy, $V_{65}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

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**.



Pb dose distribution

Planned Target Volume (PTV) profile

CT profile

TPS for VHEE FLASH

SAPIENZA UNIVERSITÀ DI ROMA

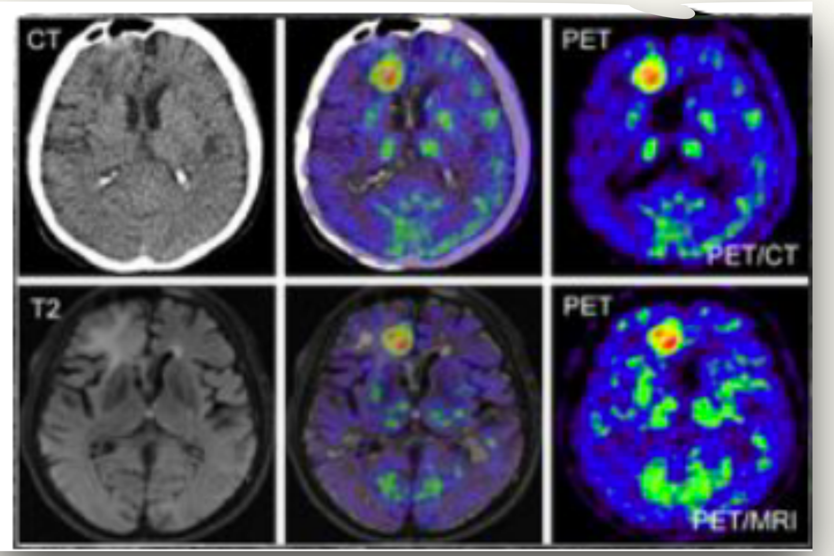
INPUT MODEL DOSE EVALUATION OPTIMIZATION RESULTS

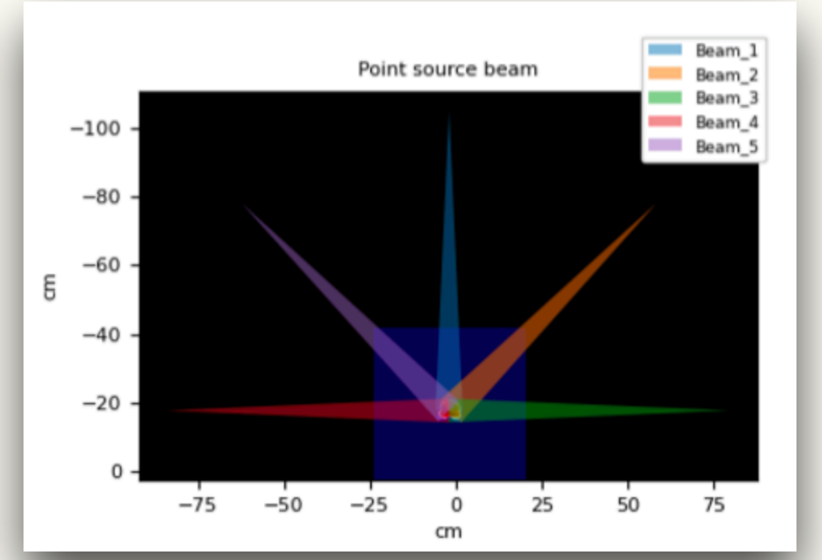
VHEE irradiation was simulated assuming the **compact C-band acceleration technology** which will be capable of delivering **multi-fields** with an **active scanning-like approach.**

CT IMAGES & FIELD DIRECTIONS

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

Provided by the hospital.

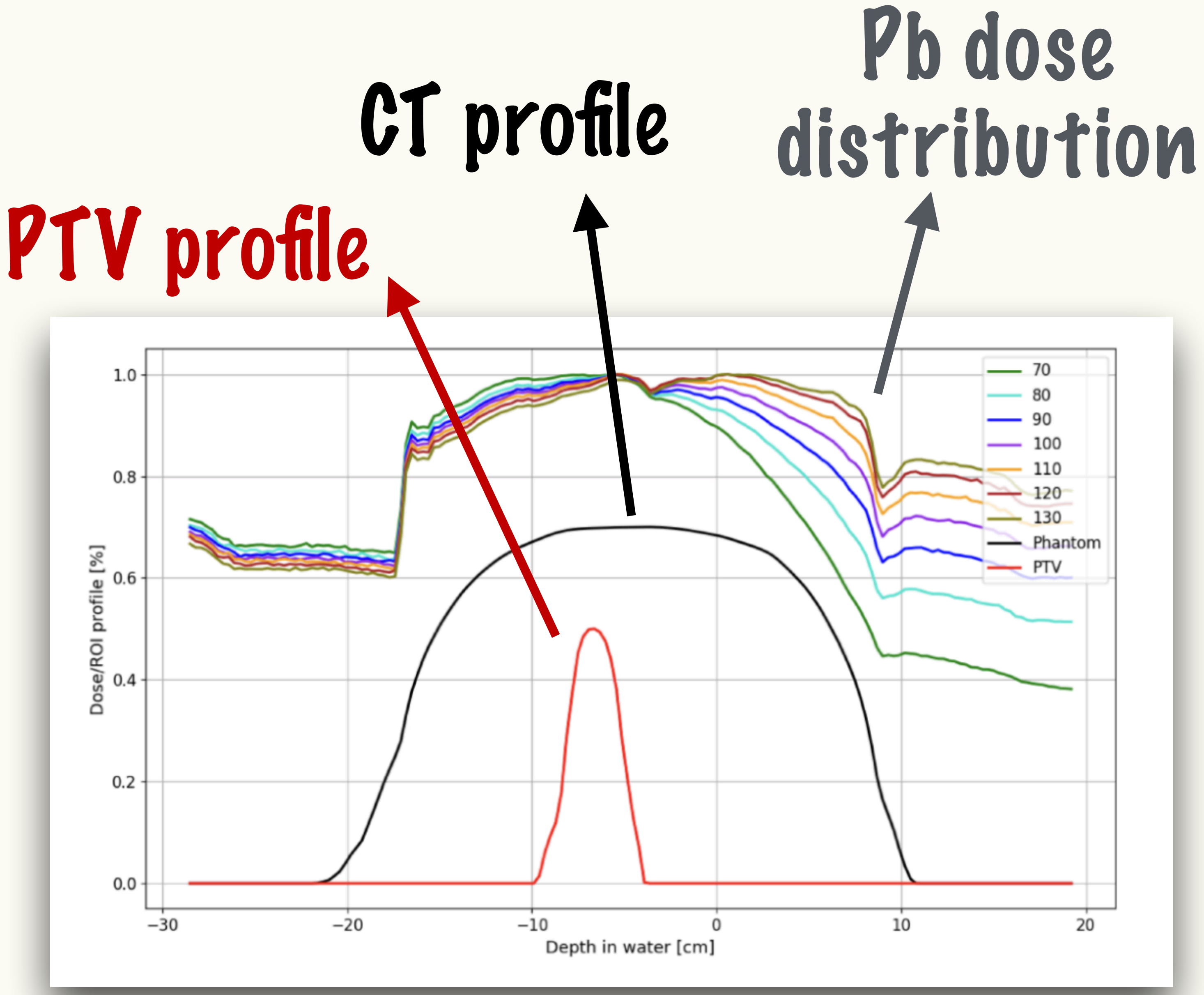




Organ	dosimetric constraints
Target volume	$V_{95\%}$ >95%, never above 107%
Rectum	V_{50} <50%, V_{60} <35%, V_{65} <25%, V_{70} <20%, V_{75} <15%
Anus	V_{30} <50%
Bulbourethral Glands	$\bar{D}$ < 50 Gy
Femurs	$\bar{D}$ < 52 Gy, V_{60} <5%
Bladder	$\bar{D}$ < 65 Gy, V_{65} <50%, V_{70} <35%, V_{75}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

ENERGY SELECTION

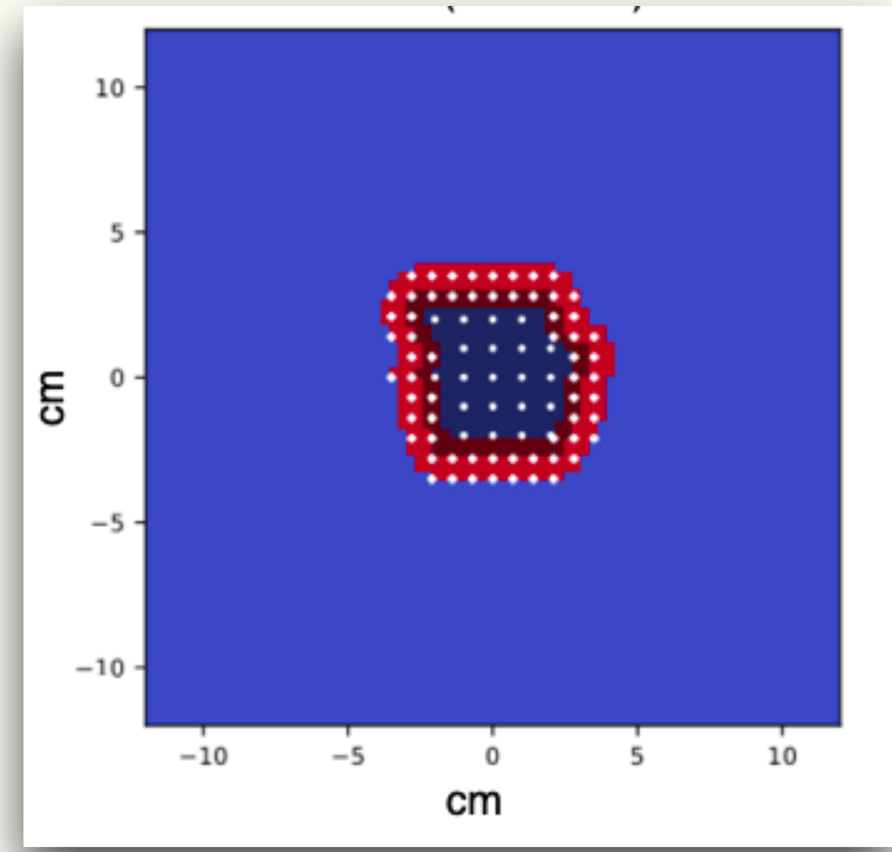
The **initial** beam energies are chosen simulating **a single PB delivered at the center of the PTV**.



PENCIL BEAM CONFIGURATION

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

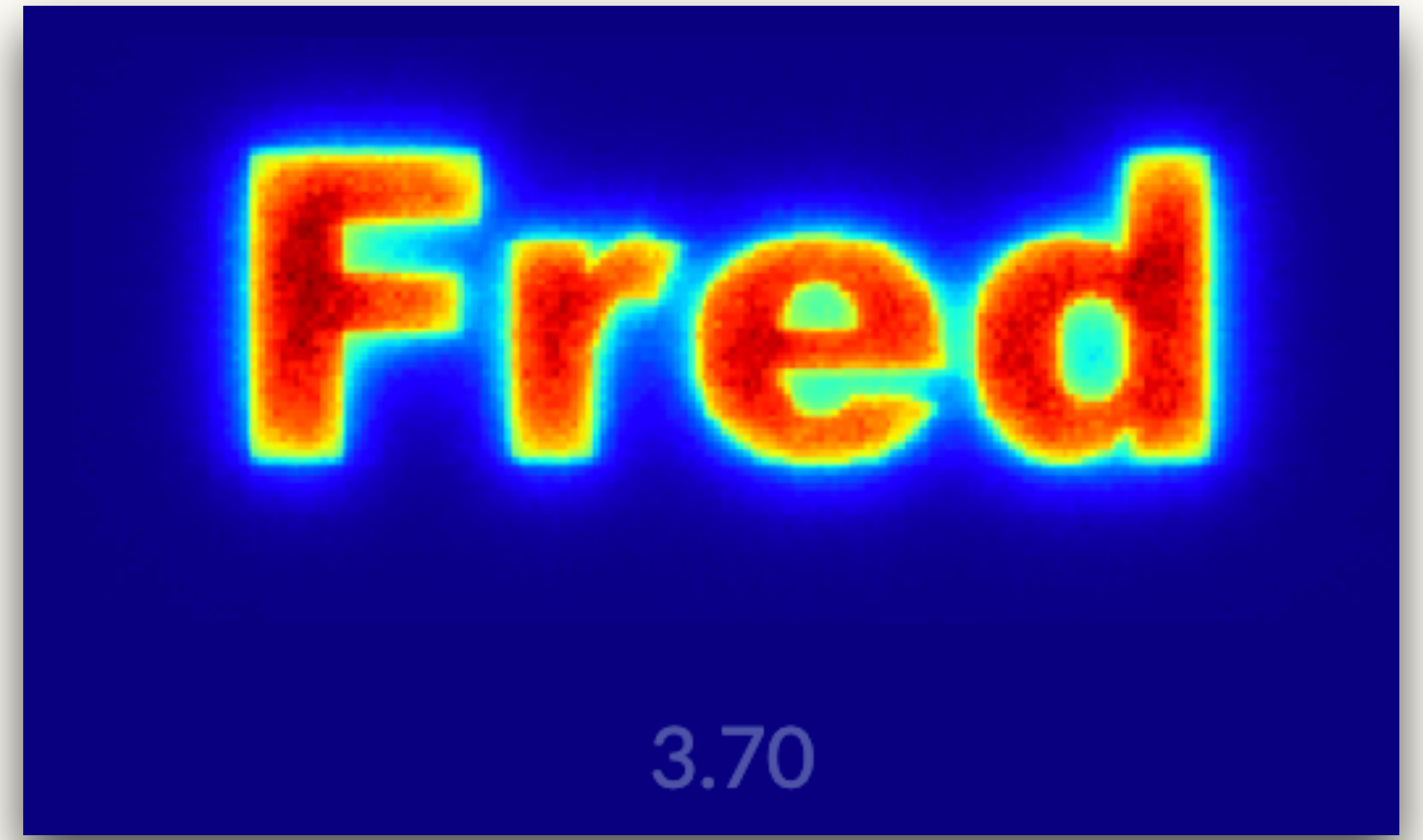
The spot spacing varies according to the irradiation geometry



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

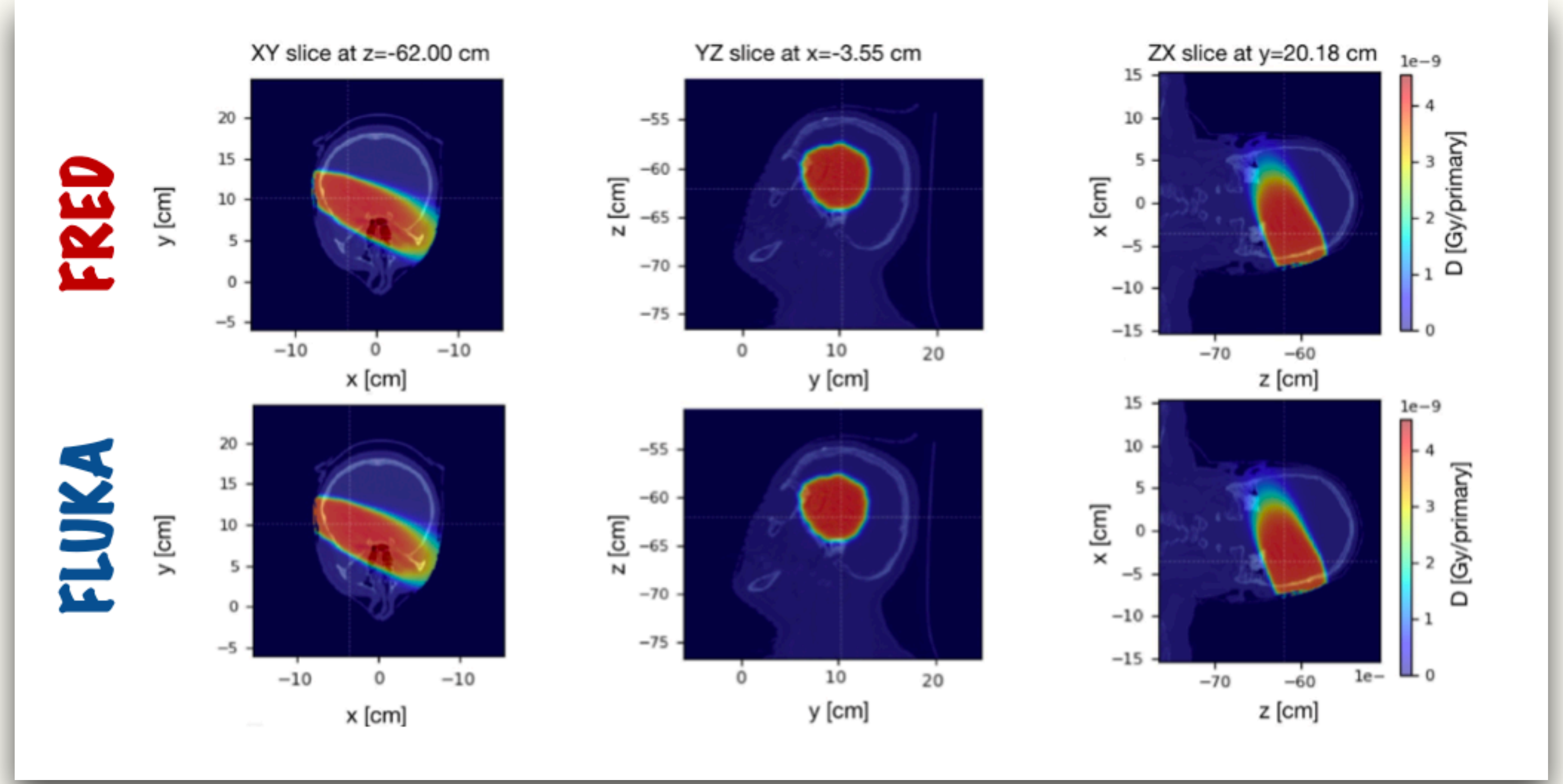
TPS for VHEE FLASH

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

TPS for VHEE FLASH

GOAL:

Select the **Energy of each field** and the **Intensity of each PB** of the treatment plan.

1. Explore different set of parameters to maximize tumor coverage and minimize the dose to the normal tissue;

2. Calculate the **COST FUNCTION** for a given configuration:

Dose absorbed by the voxel — Planned dose

$$\chi^2 = \sum_{i \epsilon PTV} \frac{(d_i - D_{PTV})^2}{D^2_{PTV}} + \sum_{i \epsilon OAR^j} \eta_i \frac{(d_i - D_{OAR^j})^2}{D^2_{OAR^j}} \cdot \theta(d_i - D_{OAR^j})$$

Voxel based — Heaviside function

3. Minimize the given cost function.

2 MINIMIZATION METHODS

SAPIENZA
UNIVERSITÀ DI ROMA

TPS for VHEE FLASH

INPUT MODEL | DOSE EVALUATION | **OPTIMIZATION** | RESULTS

GOAL:

Select the **Energy of each field** and the **Intensity of each PB** of the treatment plan.

1. Explore different set of parameters to maximize tumor coverage and minimize the dose to the normal tissue;

2. Calculate the **COST FUNCTION** for a given configuration:

Dose absorbed by the voxel — Planned dose

$$\chi^2 = \sum_{i \epsilon PTV} \frac{(d_i - D_{PTV})^2}{D^2_{PTV}} + \sum_{i \epsilon OAR^j} \eta_i \frac{(d_i - D_{OAR^j})^2}{D^2_{OAR^j}} \cdot \theta(d_i - D_{OAR^j})$$

Voxel based — Heaviside function

3. Minimize the given cost function.

2 MINIMIZATION METHODS

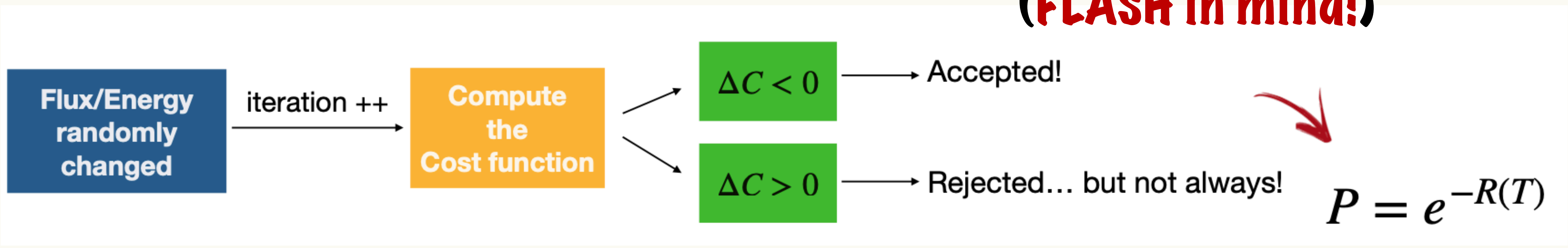
TO OPTIMIZE THE INTENSITIES OF PBs

The Lomax algorithm (**a conjugate gradient approach**) that effectively minimizes the cost function for **fixed beam energy** by adjusting pencil beam intensities, calculating the Hessian derivatives.

TO OPTIMIZE THE INTENSITIES OF PBs AND THE FIELD ENERGY

Simulated Annealing (**probabilistic optimization techniques**) is used for finding global minima in **high-dimensional spaces**, avoiding local minima where gradient-based methods may struggle.

Allows volumetric optimization (FLASH in mind!)

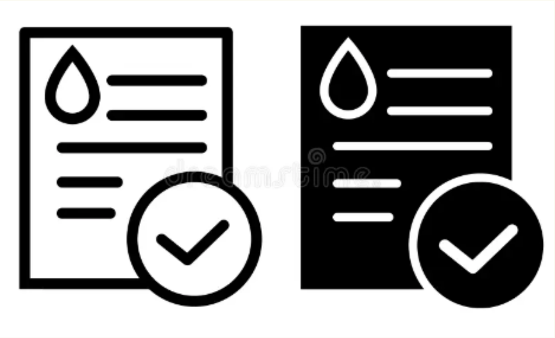


SAPIENZA UNIVERSITÀ DI ROMA

TPS for VHEE FLASH

GOAL:

Select the **Energy of each field** and the **Intensity of each PB** of the treatment plan.



RESULT:

OPTIMIZED DOSE MAP + list of ACCELERATOR PARAMETERS

1. Explore different set of parameters to maximize tumor coverage and minimize the dose to the normal tissue;

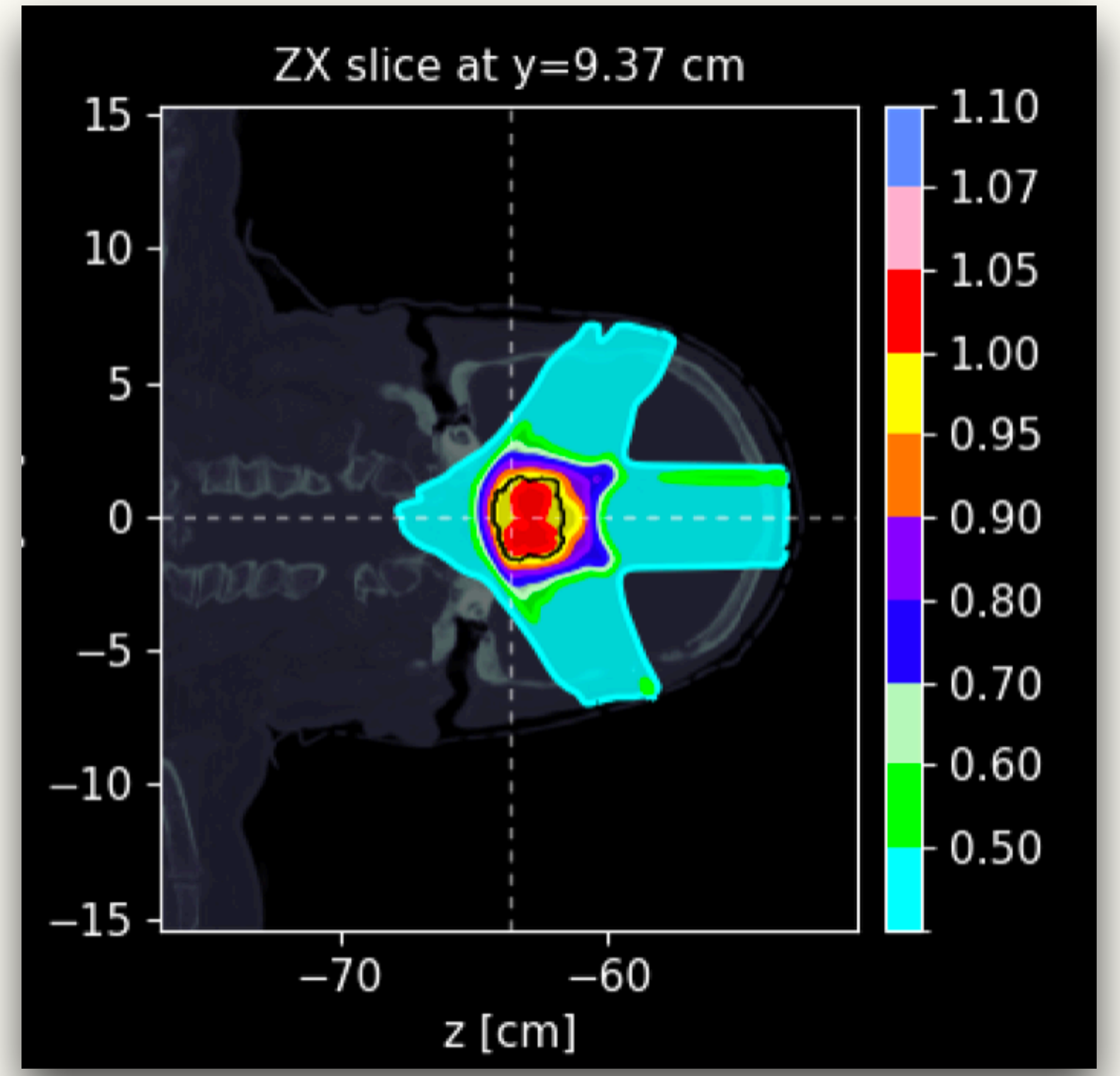
2. Calculate the **COST FUNCTION** for a given configuration:

Dose absorbed by the voxel — Planned dose

$$\chi^2 = \sum_{i \epsilon PTV} \frac{(d_i - D_{PTV})^2}{D^2_{PTV}} + \sum_{i \epsilon OAR^j} \eta_i \frac{(d_i - D_{OAR^j})^2}{D^2_{OAR^j}} \cdot \theta(d_i - D_{OAR^j})$$

Voxel based — Heaviside function

3. Minimize the given cost function. **2 MINIMIZATION METHODS**




```
 5
0  130  70
1  110  70
2  130  57
3  130  58
4  110  68
0  0    513    21706    33617
0  1    306    25686    38791
0  2    828    19949    34031
0  3    0    25812    40644
0  4    0    32028    47888
0  5    0    24089    42379
0  6    442    21539    35315
0  7    125    26100    41419
0  8    216    19958    36403
0  9    0    4442    8616
0  10    769    8685    11262
0  11    319    10349    13475
0  12    396    11077    14876
0  13    0    8816    13270
0  14    0    6885    11186
0  15    0    5045    9192
```

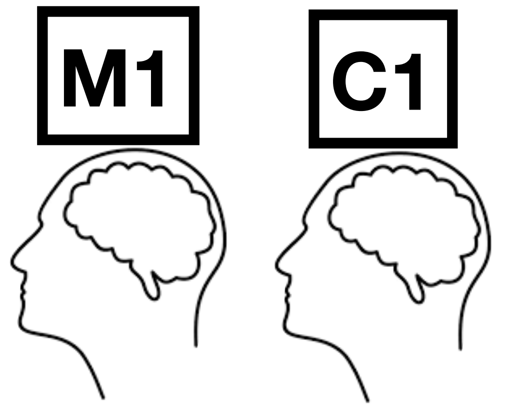
TPS for VHEE FLASH

INPUT MODEL | DOSE EVALUATION | OPTIMIZATION | **RESULTS**

GOAL:

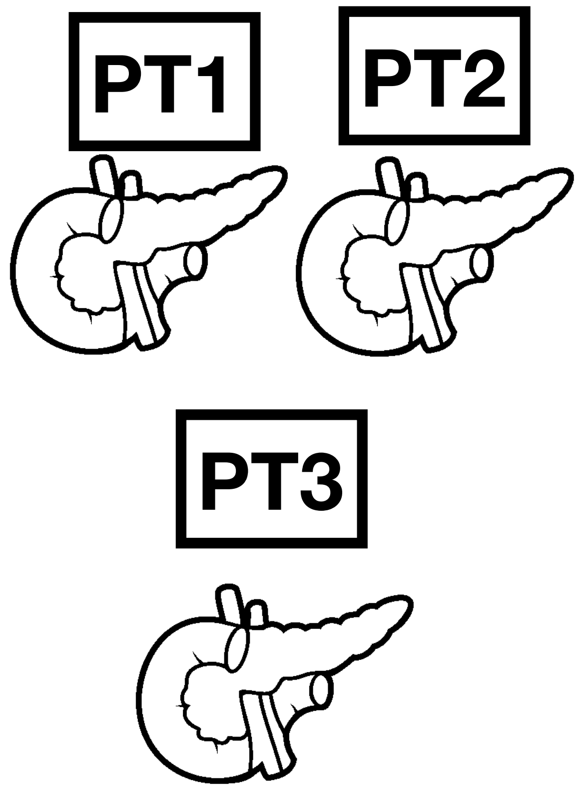
Compare the VHEE simulated plans with state-of-the-art conventional photon or PT treatments + **FLASH effect** exploration

STUDY OF INTRACRANIAL LESIONS



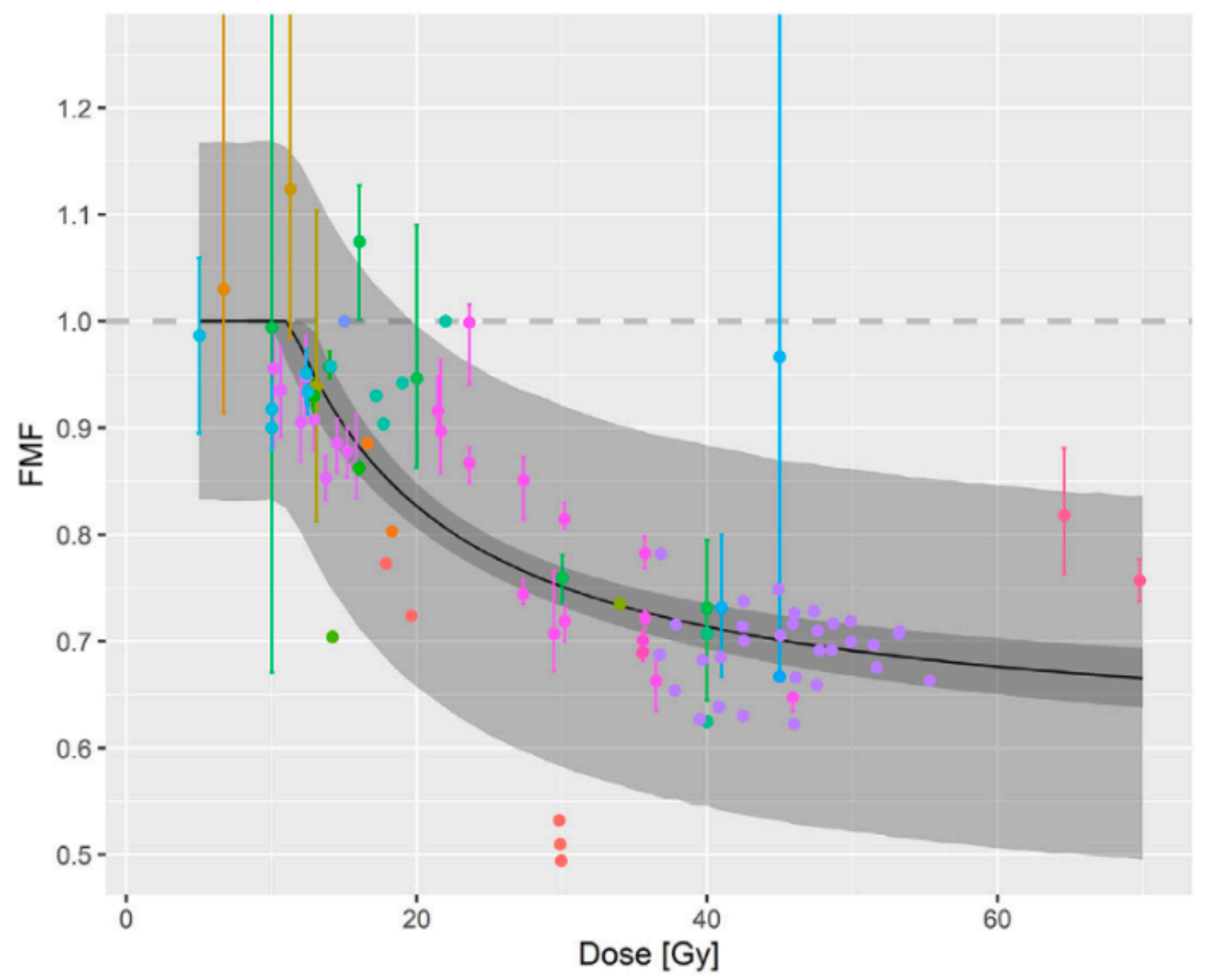
2 patients with intracranial lesion treated with **PT** at the Azienda Provinciale per i Servizi Sanitari (APSS) centre in Trento.

STUDY OF PANCREATIC TUMORS



3 patients with pancreatic tumor treated with **VMAT** treatments at the Fondazione Policlinico Universitario Campus Bio-Medico in Rome.

FLASH effect PARAMETRIZATION



Taken from available data

- 14.1, Mouse lung
- 17.1, Mouse survival
- 18.1, Mouse radiation syndrome
- 18.2, Mouse gastro-intestinal
- 18.3, Mouse brain
- 19.2, Mini pig skin
- 19.3, Mouse brain
- 20.1, Mouse crypt
- 20.2, Mouse skin
- 20.3, Mouse survival
- 20.4, Mouse survival
- 21.1, Mouse survival
- 21.2, Mouse crypt
- 21.3, Mouse skin
- 21.4, Mouse survival
- 22.1, Human skin
- 22.2, Mouse skin
- 71.1, Mouse survival
- 74.1, Rat skin 7-35d
- 74.2, Rat skin 5-23w
- 74.3, Rat foot deformity
- 82.1, Mouse tail necrosis

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.

The biological dose was optimized following the model:

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

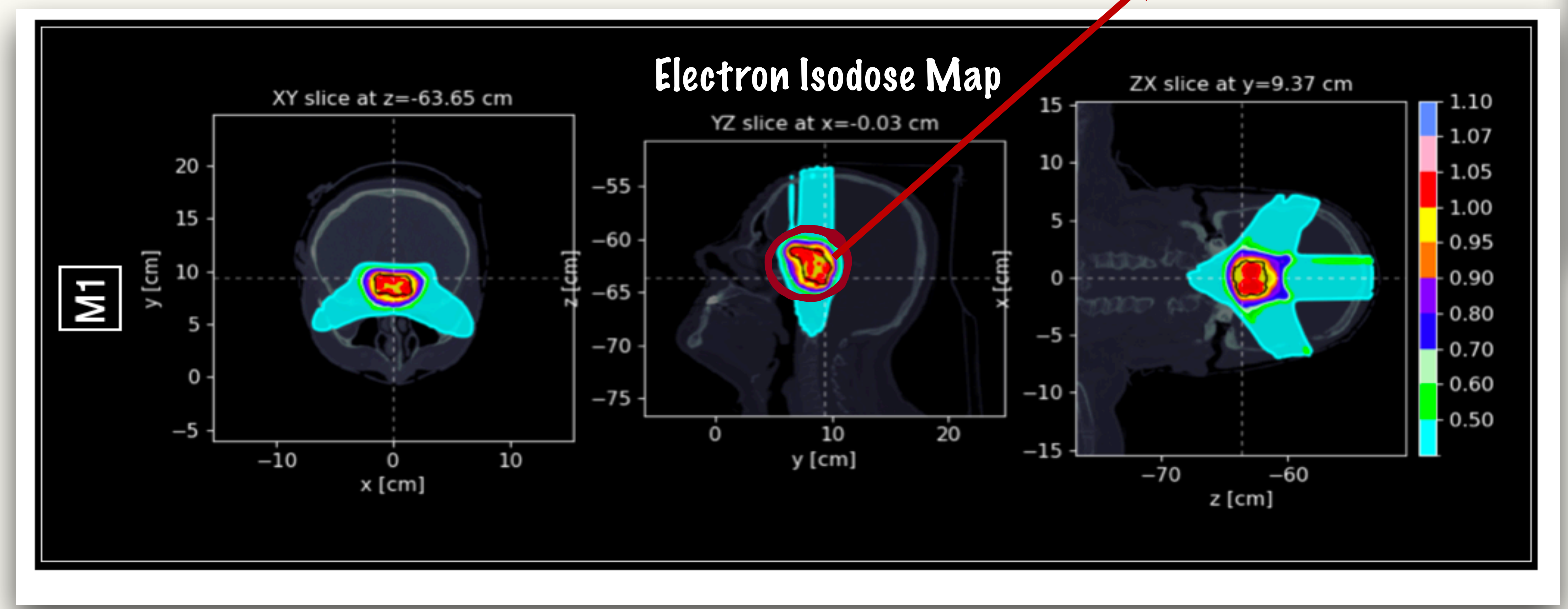
$$FMF = \begin{cases} 1 & \text{if } D \leq D_T \\ (1 - FMF^{min})\frac{D_T}{D} + FMF^{min} & \text{if } D > D_T \end{cases}$$

TPS for VHEE FLASH

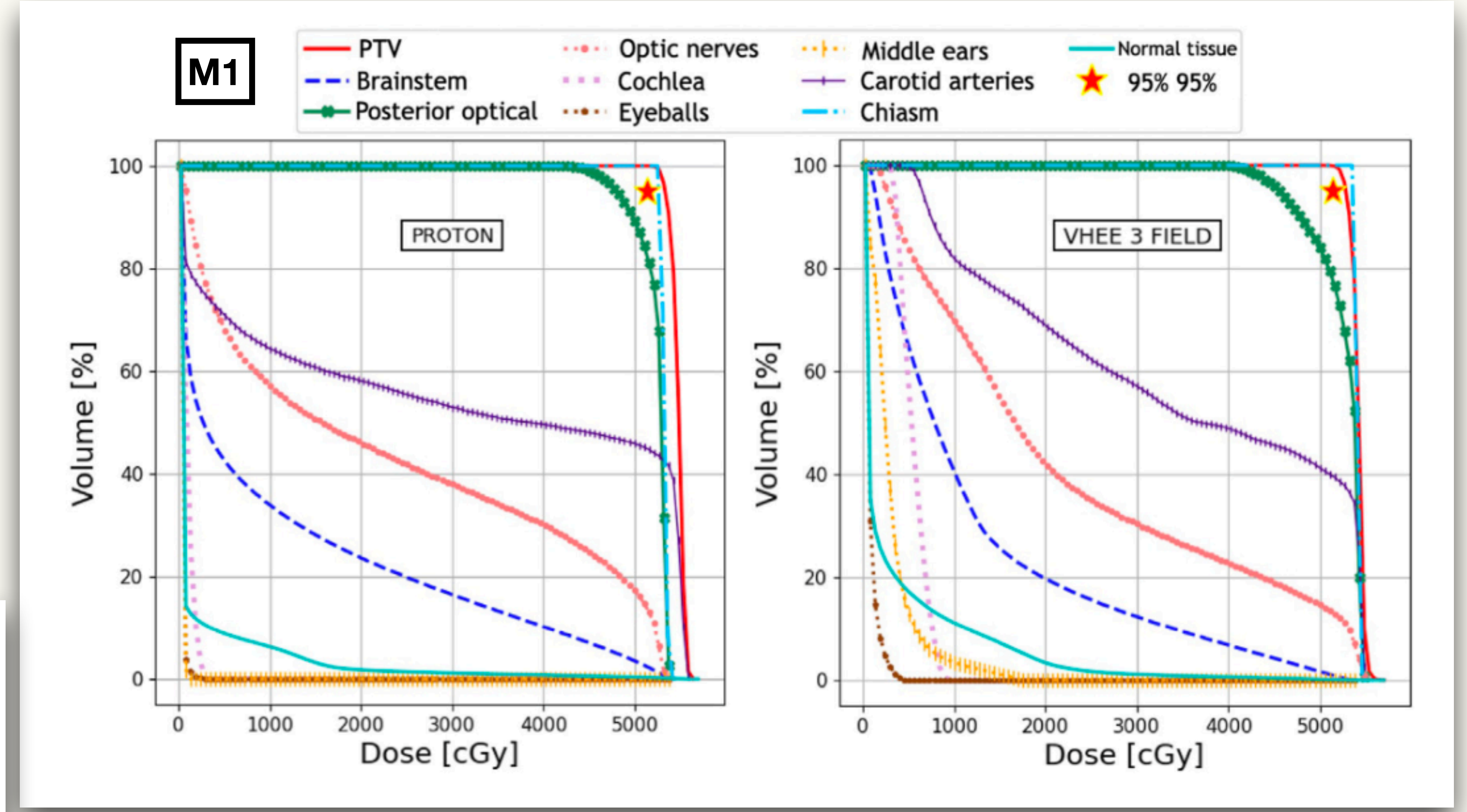
Validate VHEE treatment on DIFFICULT GEOMETRY due to the PTV position

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**.



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!)

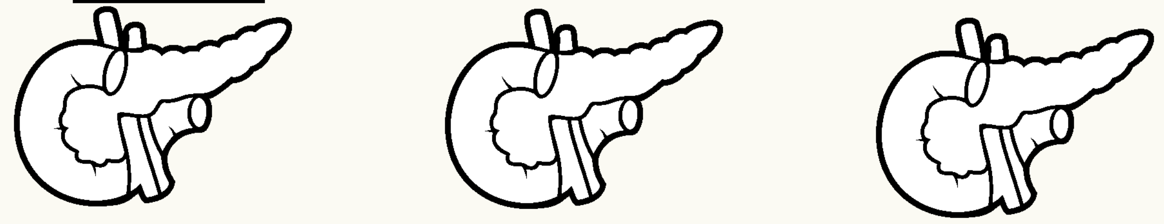
TPS for VHEE FLASH

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

GOOD CANDIDATE FOR FLASH IRRADIATION!

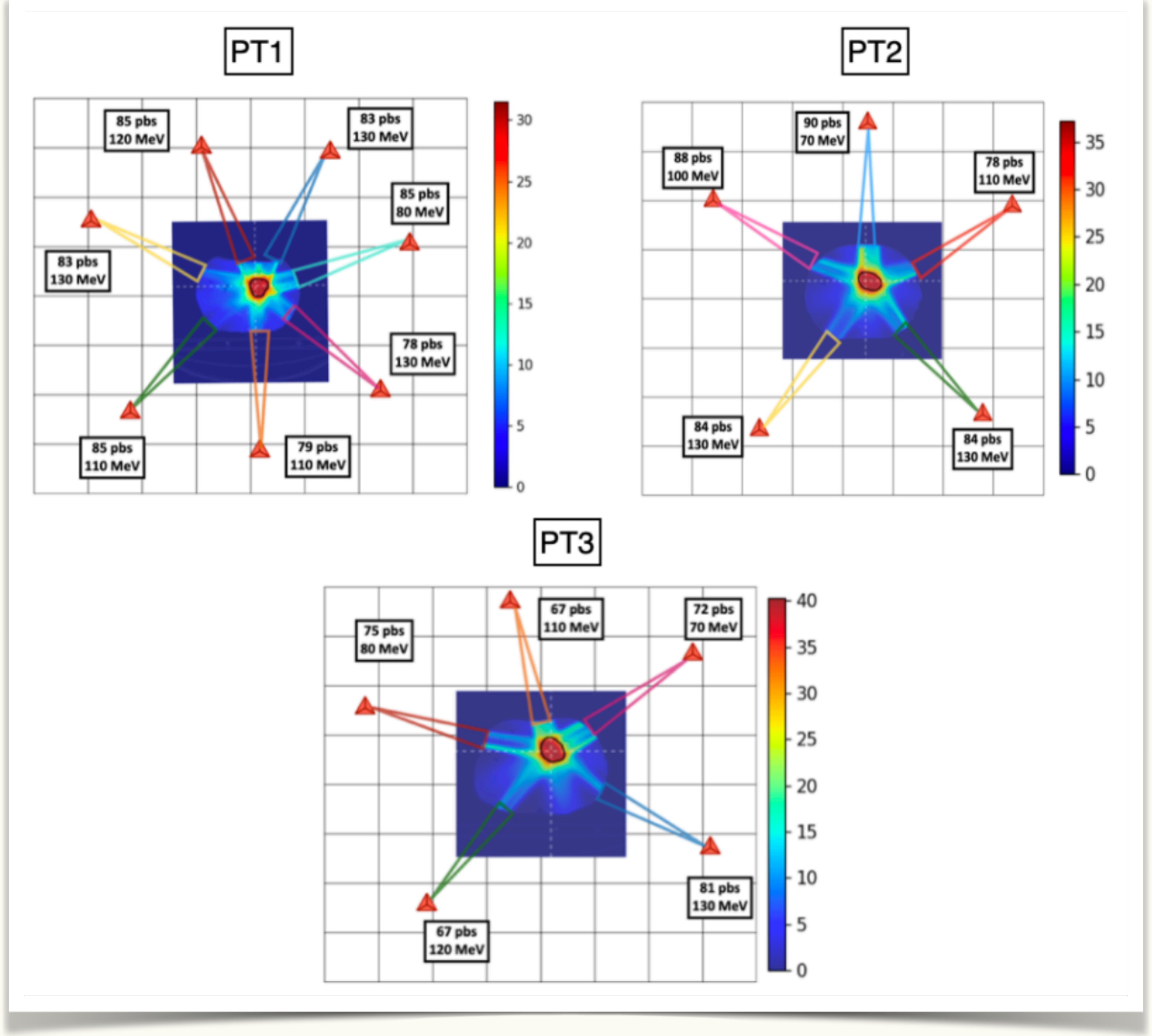
PRESCRIPTION

PT1 **PT2** **PT3**



- **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.**

FIELD GEOMETRY



DOSIMETRIC CONSTRAINTS

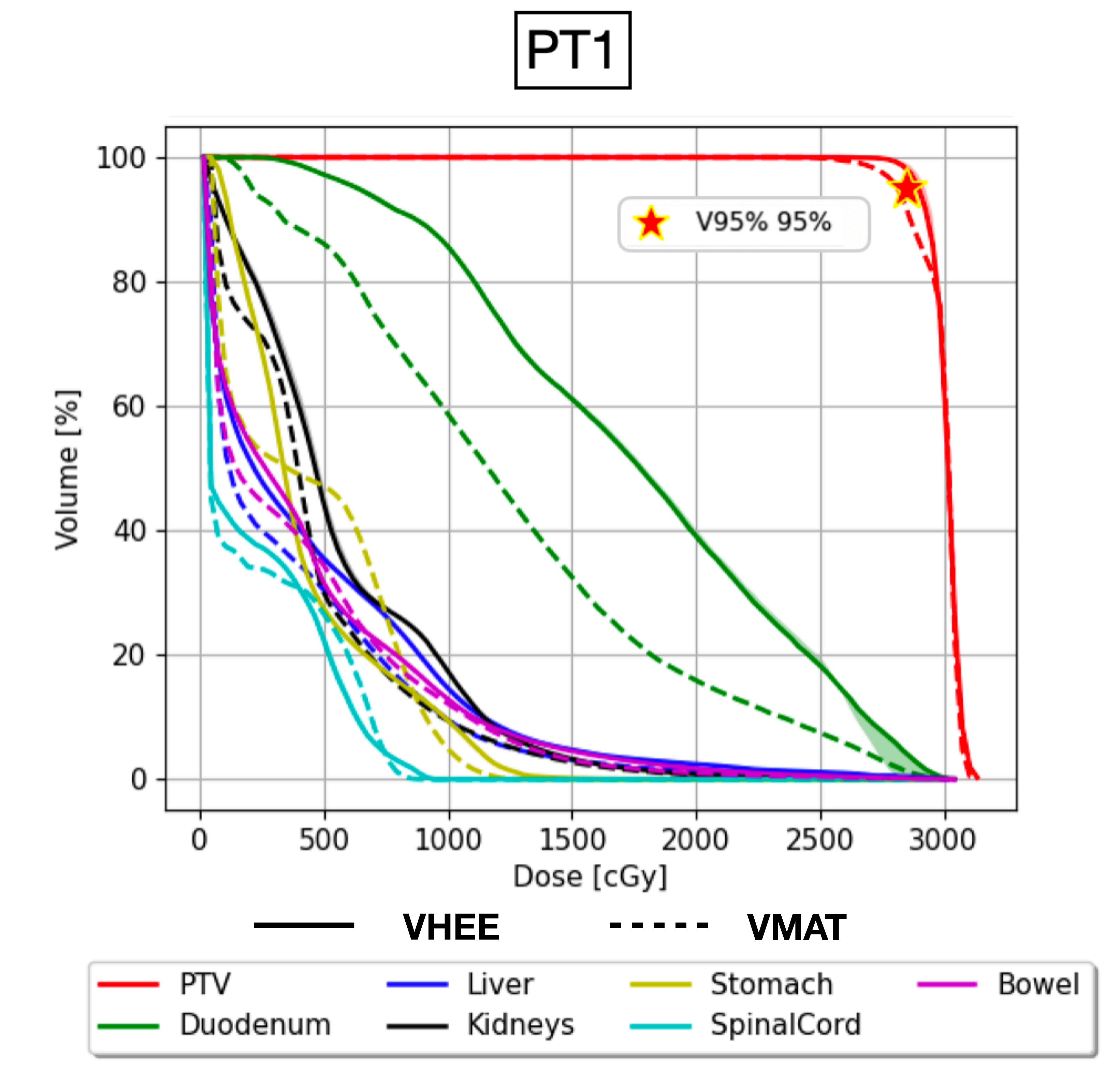
ROI	Constraints	Volumes [cc] PT1	PT2	PT3
PTV	$V^{PT1}_{95\%} > 95\%$ $V^{PT1}_{105\%} < 5\%$ $V^{PT2,PT3}_{100\%} > 95\%$ $D^{PT2}_{max} \leq 40.95$ Gy $D^{PT3}_{max} \leq 37.8$ Gy	94.9	81.6	117.9
Duodenum	$V_{35Gy} < 0.1$ cc $V_{25Gy} < 10$ cc	93.5	94.4	101.6
Bowel	$V_{30Gy} < 1$ cc	1035.1	563	1511.4
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

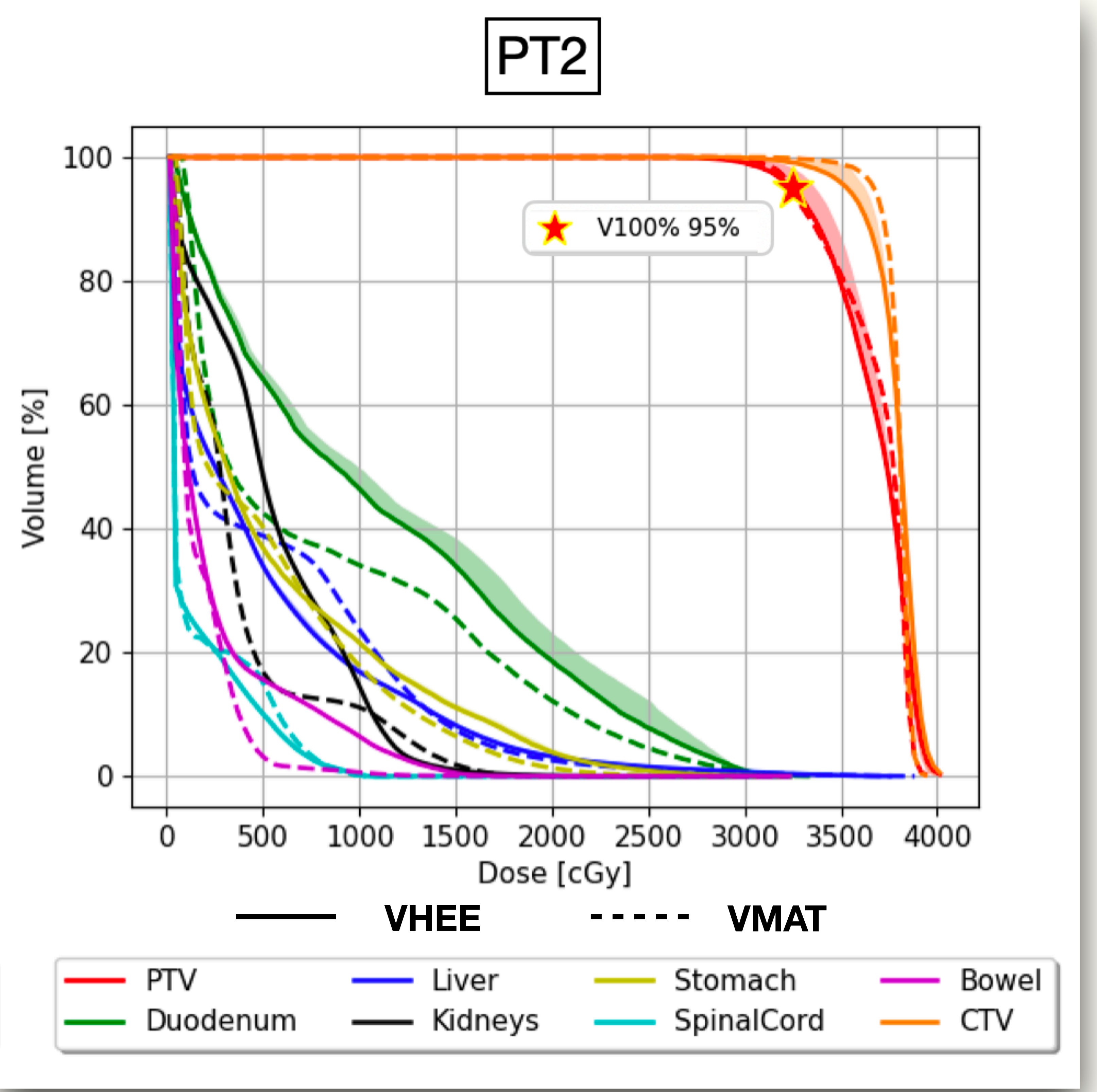
Slightly different modalities for irradiation

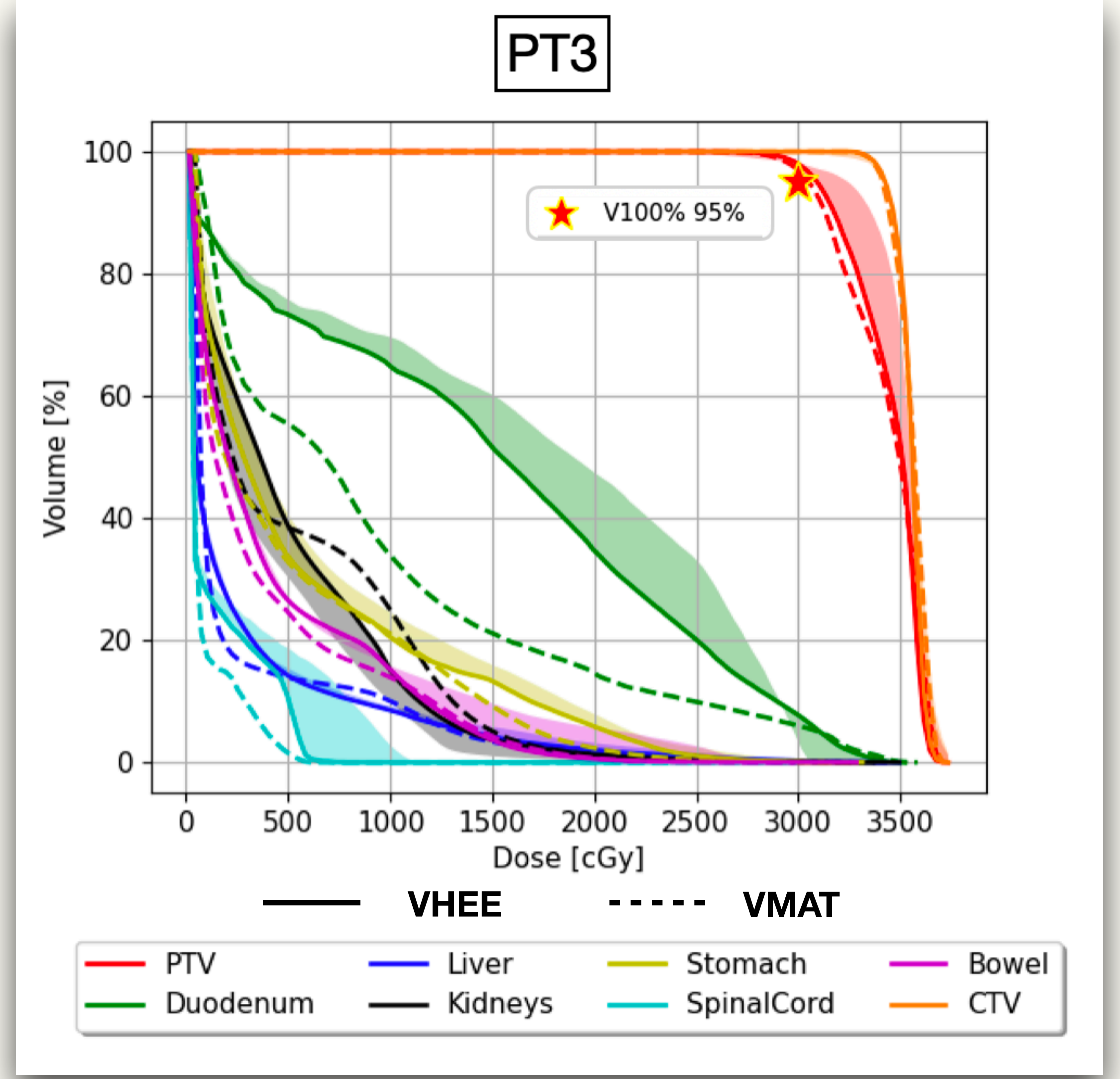
TPS for VHEE FLASH

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

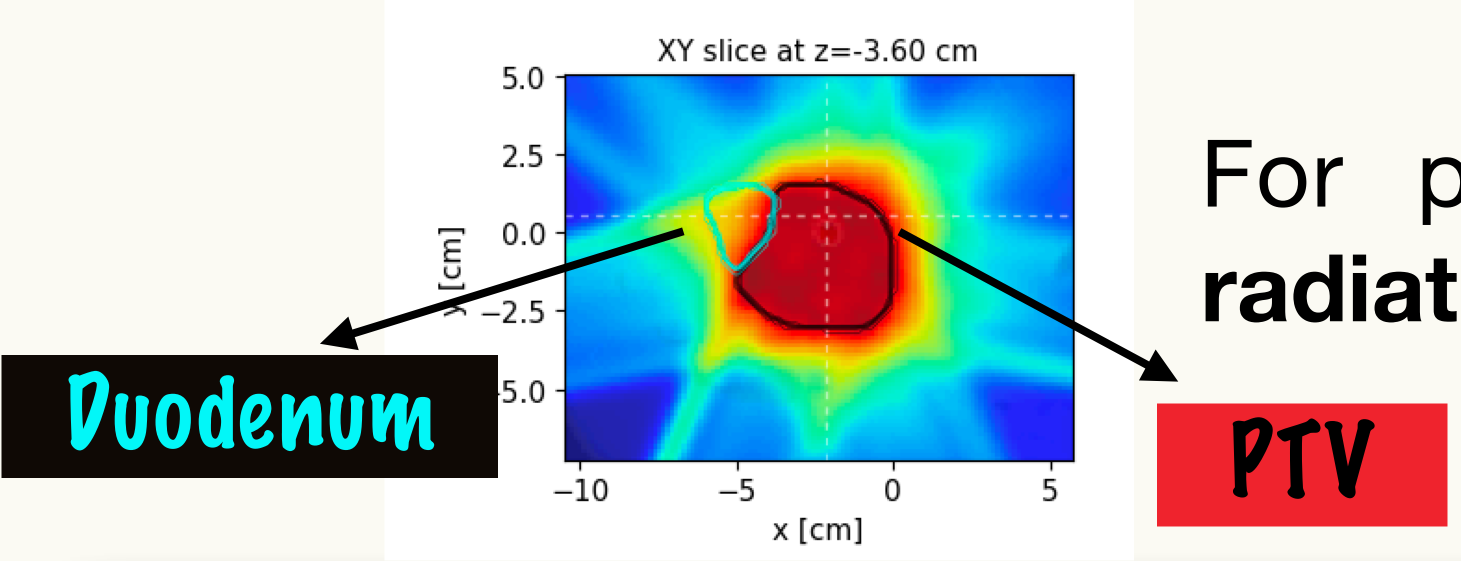
GOOD CANDIDATE FOR FLASH IRRADIATION!







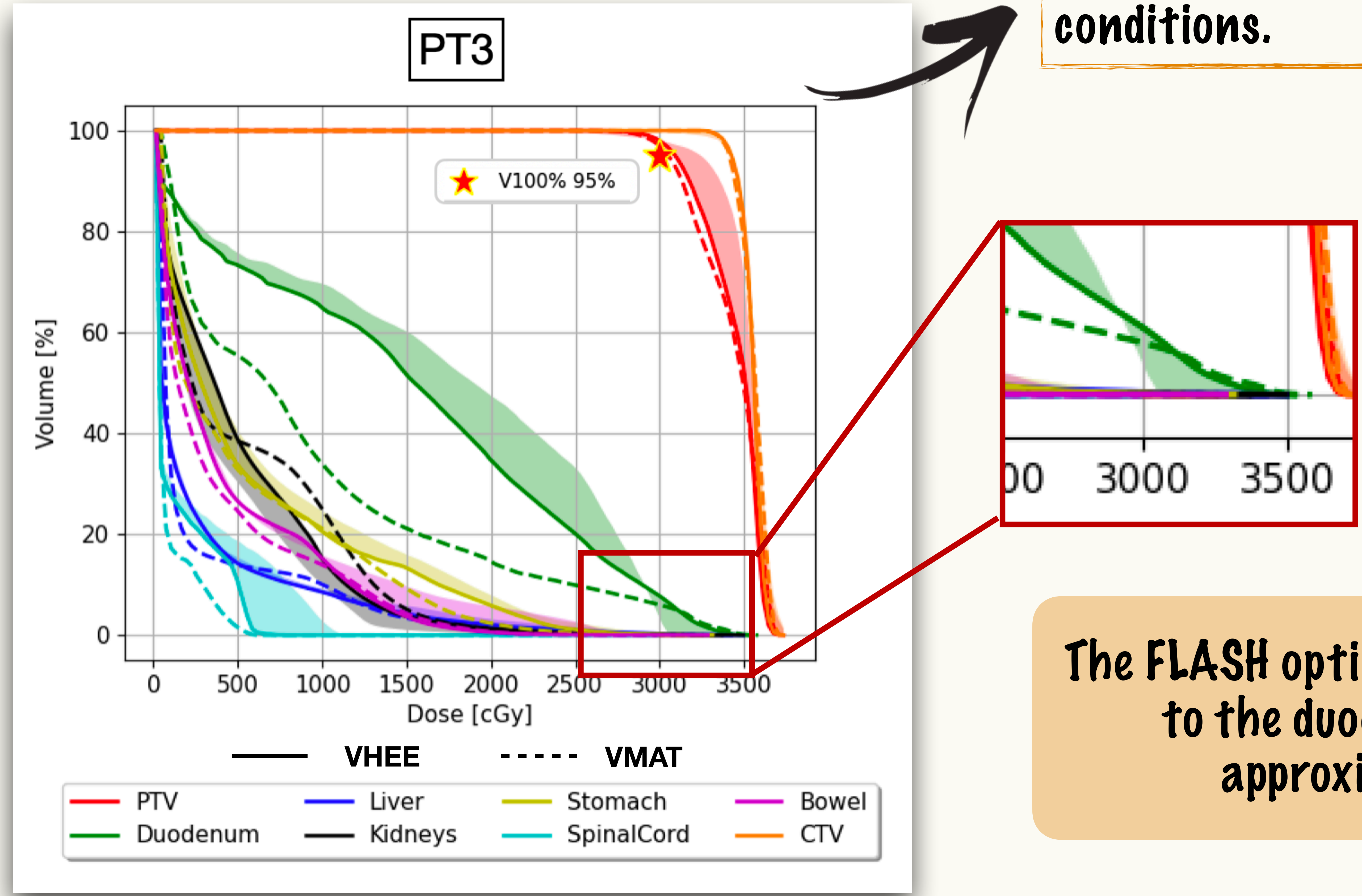
TPS for VHEE FLASH



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

GOOD CANDIDATE FOR FLASH IRRADIATION!

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

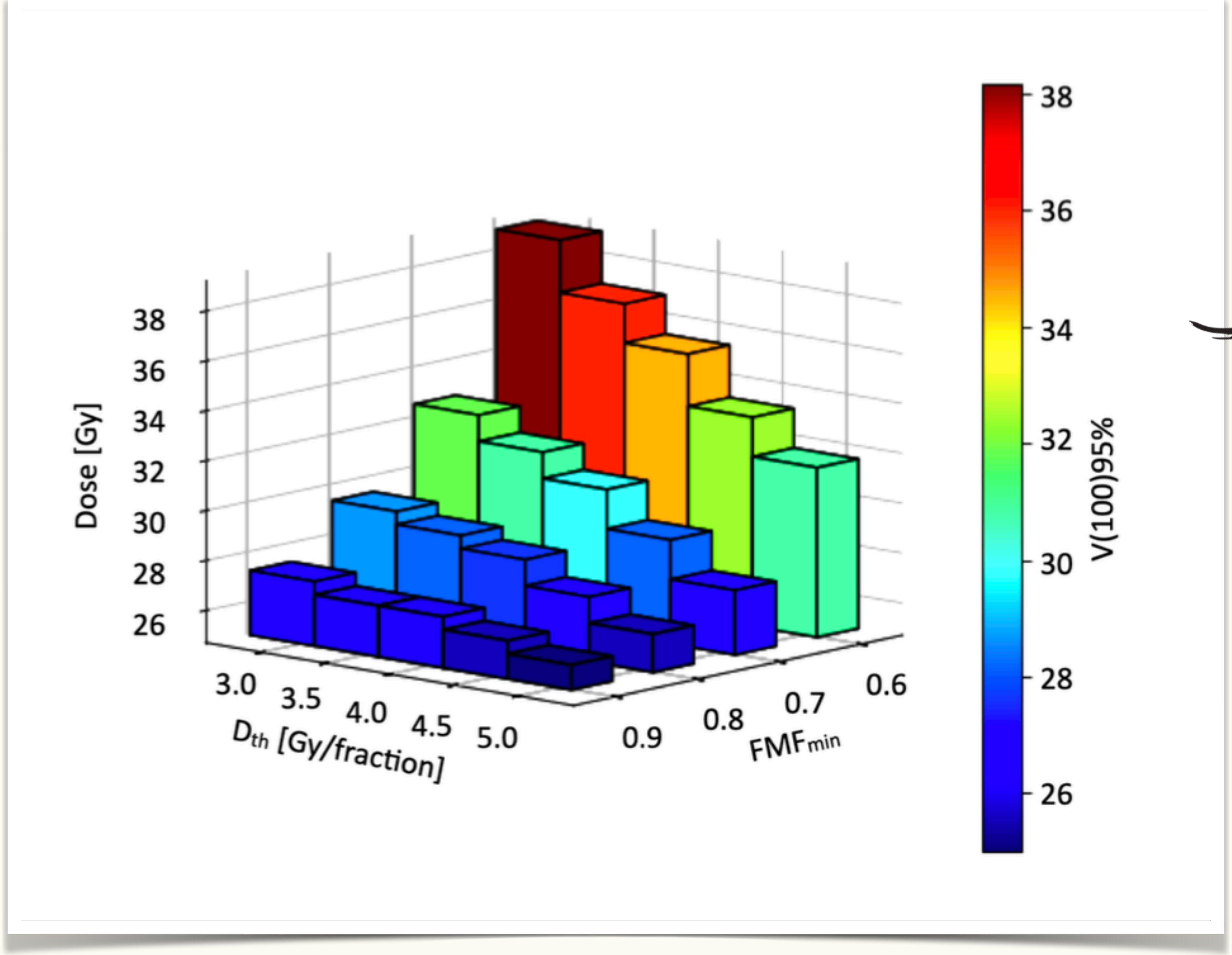
- FMFmin = 0.6 to 1
- Dth value of 25 Gy.

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!

TPS for VHEE FLASH

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

GOOD CANDIDATE FOR FLASH IRRADIATION!



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.

	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.

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

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

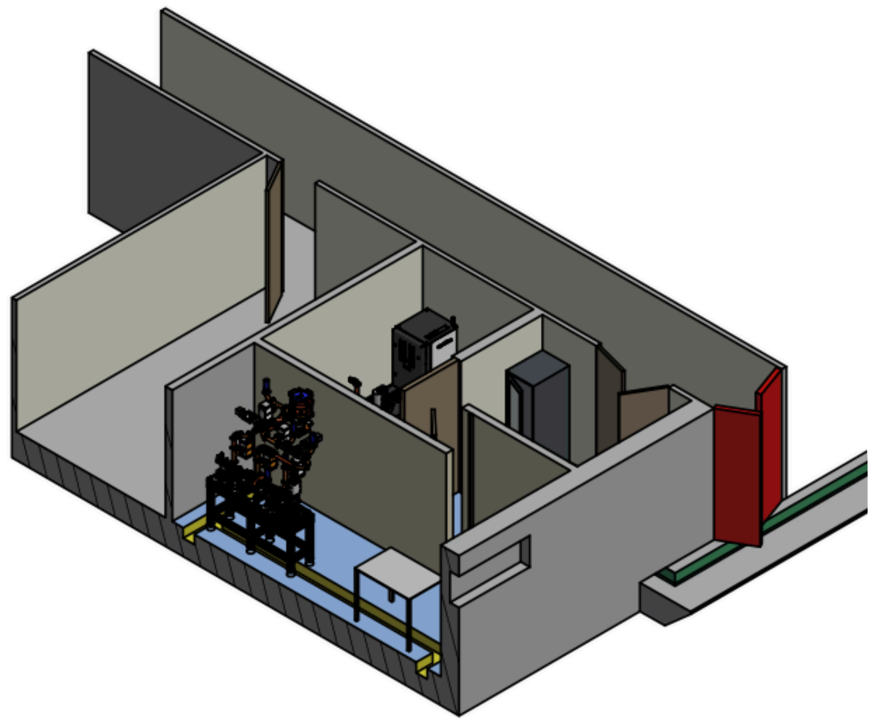
The FLASH optimization results in an **increase in the average** dose delivered to the duodenum, while **reducing its maximum absorbed dose** by approximately 4 Gy. This allows to increase the PTV coverage!

Conclusions and future steps

SAPIENZA UNIVERSITÀ DI ROMA

1 RADIOPROTECTION STUDIES FOR SAFEST LINAC

GOAL:
Evaluate the dispersed radiation to **design the needed shielding**.



HOW:

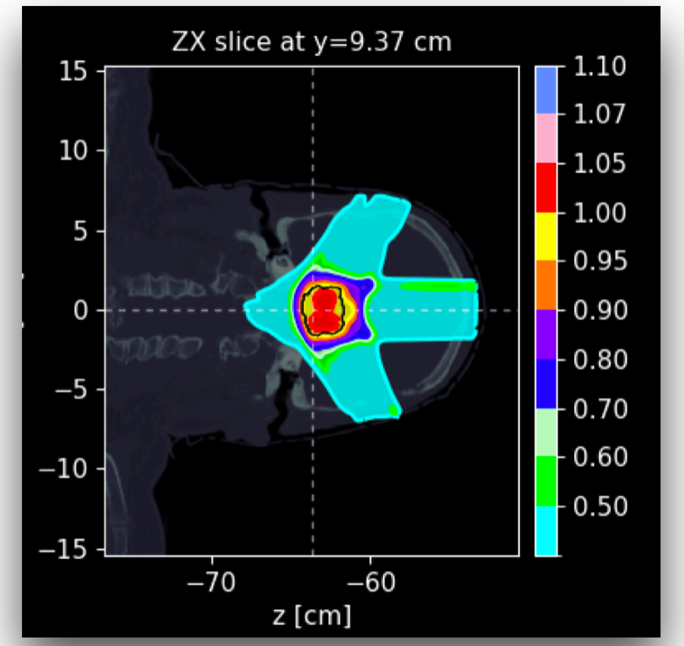
I performed the physics simulations to study the interaction between primary beam and accelerator.

RESULTS:

I studied and **defined the shielding parameters** to make the machine being designed for SAFEST **compatible with the university environment**, for which no radioprotection protocols currently exist.

2 DEVELOPMENT OF A DEDICATED VHEE TPS

GOAL:
Compare the VHEE simulated plans with state-of-the-art conventional photon or PT treatments + **FLASH effect** exploration



HOW:

I developed a TPS for VHEE and tested it on intracranial lesions and pancreatic cancer.

RESULTS:

Compared to state-of-the-art radiotherapy techniques **VHEE showed comparable performance**, even without UHDR delivery. Assuming plausible conditions to trigger the FLASH effect , the results suggest it is **possible to escalate the PTV dose without increasing OAR damage**.

THANK YOU!

Treatment planning of intracranial lesions with VHEE: comparing conventional and FLASH irradiation potential with state-of-the-art photon and proton radiotherapy

PUBLISHED

A. Muscato[1,2,3] L. Arsini[2,4] G. Battistoni ... D. Carlotti[4,6] F. De Felice[7] A. De Gregorio[4,2*] M. De Simoni[2,8] C. Di Felice[9] Y. Dong[5] G. Franciosini[1,2] M. Marafini[2,3]

In silico study for stereotactic body radiotherapy of pancreatic cancer: can FLASH planning with very high energy electrons improve the therapeutic ratio?

SUBMITTED

A. De Gregorio[e,b], A. Muscato[b,h], D. Carlotti ... Franciosini[a,b,*], T. Insero[c], M. Marafini[g,b], V. Marè[c], V. Patera[a,b], S. Ramella[c,f], A. Schiavi[a,b], M. Toppi[a,b], G. Traini[b], A. Trigilio[d], A. Sarti[a,b]

Perspectives in linear accelerator for FLASH VHEE: Study of a compact C-band system

PUBLISHED

L Faillace[1], D Alesini[2], G Bisogni[3], F Bosco[4], M Carillo[4], P Cirrone[5], G Cuttone[5], D De Arcangelis[4], A De Gregorio[6], F Di Martino[7], V Favaudon[8], L Ficcadenti[4], D Francescone[4], G Franciosini[6], A Gallo[2], S Heinrich[8], M Migliorati[4], A Mostacci[4], L Palumbo[4], V Patera[4], A Patriarca[9], J Pensavalle[3], F Perondi[10], R Remetti[10], A Sarti[4], B Spataro[2], G Torrisi[5], A Vannozzi[2], L Giuliano[4]

Publications

- A. De Gregorio et al., Measurements of the ^{16}O cross section on a C target with the FOOT apparatus. Nuovo Cimento della Societa Italiana di Fisica C; 2022, DOI: 10.1393/ncc/i2022-22194-4
- M. De Simoni et al., A Data-Driven Fragmentation Model for Carbon Therapy GPU-Accelerated Monte-Carlo Dose Recalculation. Frontiers in Oncology; 2022, DOI:10.3389/fonc.2022.780784
- M. Moglioni et al., In-vivo range verification analysis with in-beam PET data for patients treated with proton therapy at CNAO. Frontiers in Oncology; 2022, DOI:10.3389/fonc.2022.929949
- A. Trigilio et al., The FlashDC project: Development of a beam monitor for FLASH radiotherapy. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2022, DOI: 10.1016/j.nima.2022.167334
- M. Toppi et al., Elemental fragmentation cross sections for a 16 O beam of 400 MeV/nucleon kinetic energy interacting with a graphite target using the FOOT ΔE-TOF detectors. Frontiers in Physics, section Medical Physics and Imaging, 2022, DOI: https://doi.org/10.3389/fphy.2022.979229
- A.C. Kraan et al., Calibration and performance assessment of the TOF-Wall detector of the FOOT experiment. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2023, DOI: 10.1016/j.nima.2022.167615
- L. Galli et al., The fragmentation trigger of the FOOT experiment. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2023, DOI: https://doi.org/10.1016/j.nima.2022.167757
- A. Alexadrov et al., Characterization of 150 μm thick silicon microstrip prototype for the FOOT experiment. Journal of Instrumentation; 2022, DOI: 10.1088/1748-0221/17/12/P12012
- L. Faillace et al., Perspectives in linear accelerator for FLASH VHEE: Study of a compact C-band system. Physica Medica; 2022, DOI: 10.1016/j.ejmp.2022.10.018
- D. Rocco et al., TOPS fast timing plastic scintillators: Time and light output performances. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2023, DOI: 10.1016/j.nima.2023.168277
- G. Franciosini et al., GPU-accelerated Monte Carlo simulation of electron and photon interactions for radiotherapy applications. Physics in Medicine and Biology; 2023, DOI: 10.1088/1361-6560/aca1f2
- L. Giuliano et al., Proposal of a VHEE Linac for FLASH radiotherapy. Physics in Medicine and Biology; 2023, DOI: 10.1088/1742-6596/2420/1/012087
- A. Muscato et al., Treatment planning of intracranial lesions with VHEE: comparing conventional and FLASH irradiation potential with state-of-the-art photon and proton radiotherapy. Frontiers in Physics; 2023, DOI: 10.3389/fphy.2023.1185598
- Y. Dong et al., The FLUKA Monte Carlo simulation of the magnetic spectrometer of the FOOT experiment. Computer Physics Communications; 2025
- A. C. Kraan et al., In-beam PET treatment monitoring of carbon therapy patients: Results of a clinical trial at CNAO. Physica Medica; 2024
- G. Franciosini et al., IOeRT conventional and FLASH treatment planning system implementation exploiting fast GPU Monte Carlo: The case of breast cancer. Physica Medica; 2024
- A. Trigilio et al., Test beam results of a fluorescence-based monitor for ultra-high dose rates. Journal of Instrumentation; 2024
- G. Franciosini et al., Preliminary study on the correlation between accelerated current and dose in water for an electron-based LINAC. Frontiers in Physics; 2024
- G. Galati et al., Charge identification of fragments produced in ^{16}O beam interactions at 200 MeV/n and 400 MeV/n on C and C_2H_4 targets. Frontiers in Physics; 2023

SPARE SLIDES

SAPIENZA UNIVERSITÀ DI ROMA

Radiation Therapy

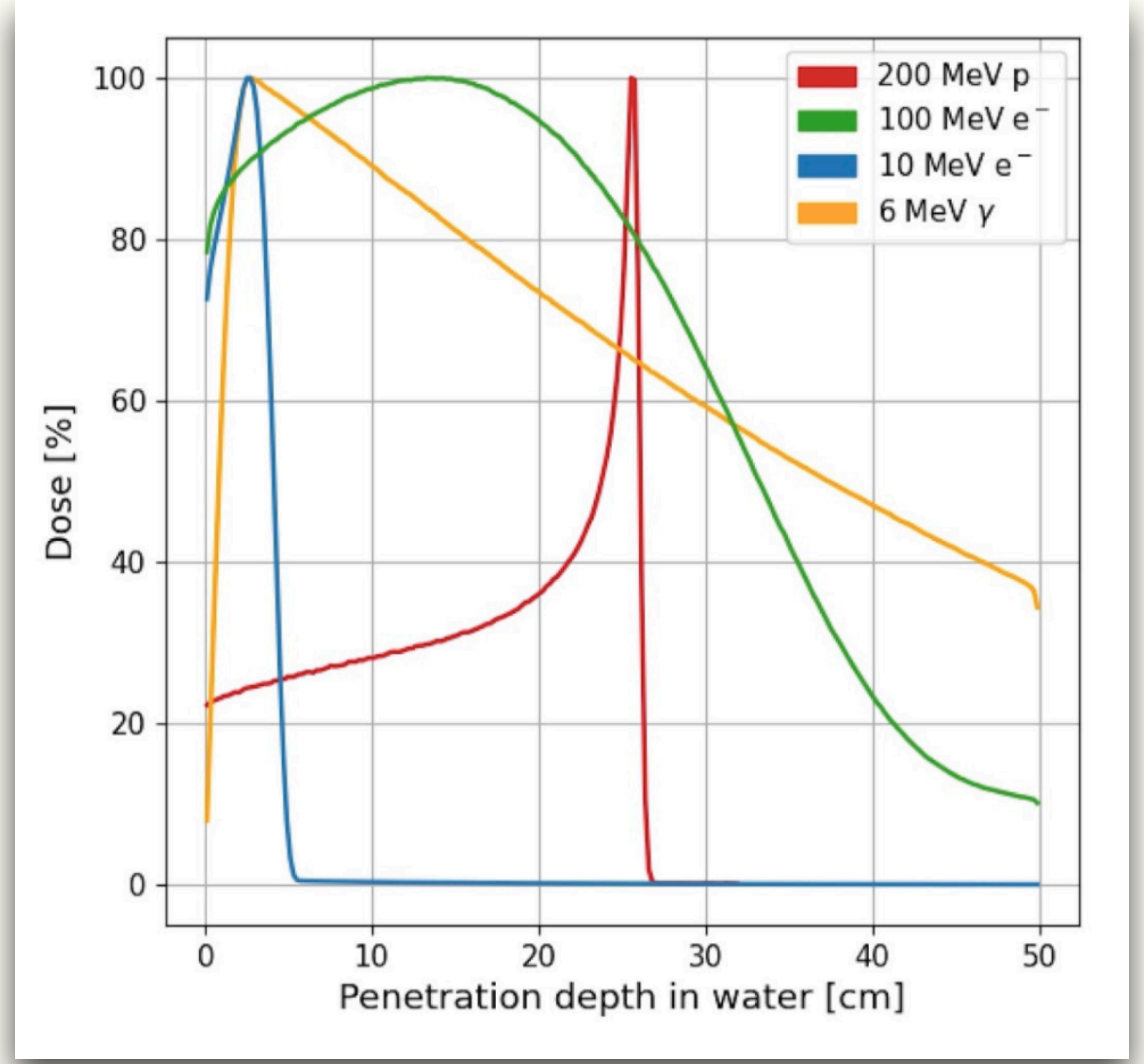
Radiotherapy uses ionizing radiation to target and destroy malignant cells. The principle is based on **inducing DNA damage** in tumor cells, disrupting replication and leading to cell death.

External Beam Radiotherapy (EBRT)

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.

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



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

My thesis work

The availability of a dedicated facility would allow bridging the gaps in the current knowledge and characterization of the VHEE based radiotherapy, both including or not the FLASH effect.

The aim of my **Ph.D. thesis work** was twofold: based on the VHEE LINAC designed within the SAFEST project, I focused on...

1

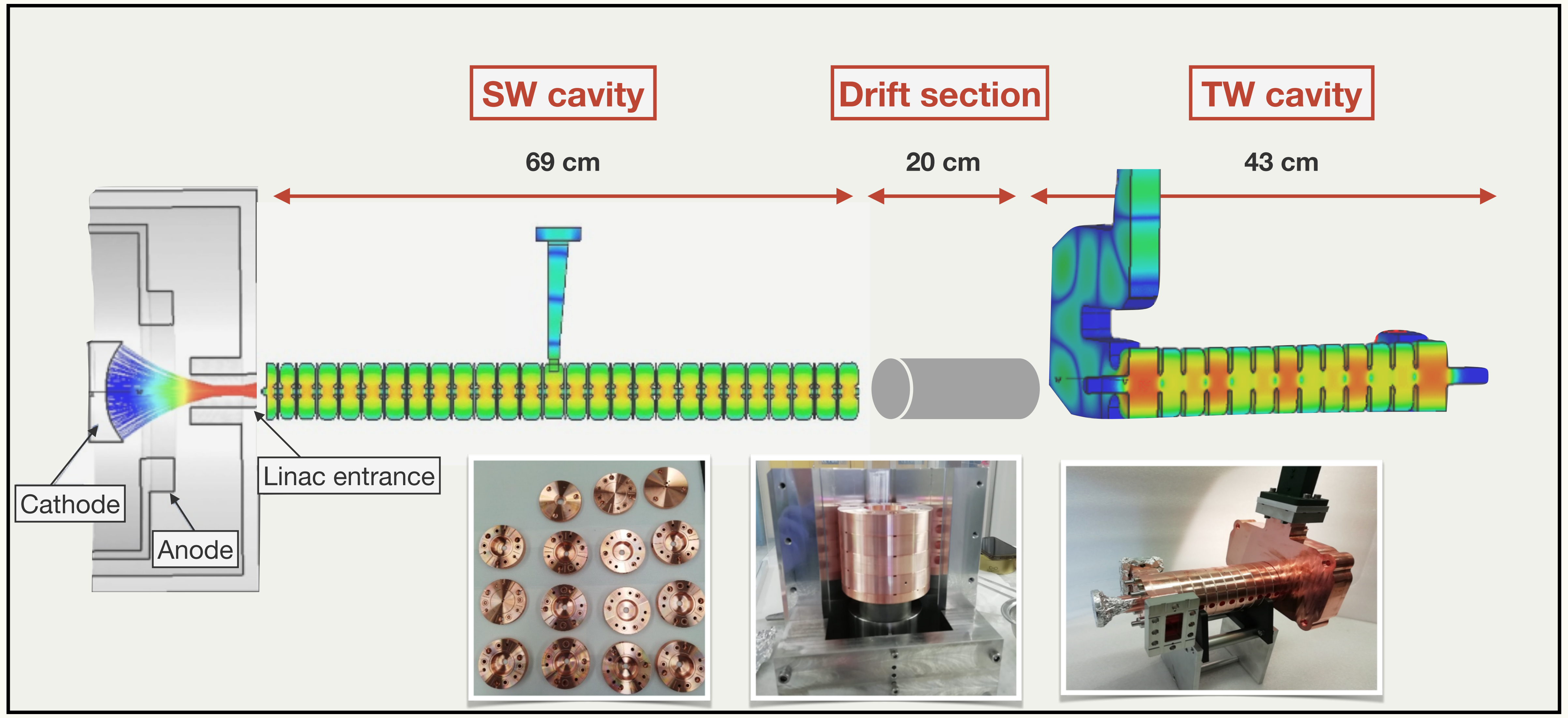
1. Geometry implementation and **Physics Simulations** with the Monte Carlo tool FLUKA;
2. Analysis of simulation results and **assessment of the dispersed radiation** in the LINAC's surrounding environment;
3. **Design and validation of the shielding** required for current protocols.

2

1. Implementation of **Monte Carlo dose evaluation** (using a fast MC) in place of analytical calculations;
2. Adoption of **Annealing algorithms** as minimization methods;
3. Development of an **optimization algorithm using the FLASH model** existing in the literature;
4. **Testing and validation** across various types of tumors.

Radioprotection studies

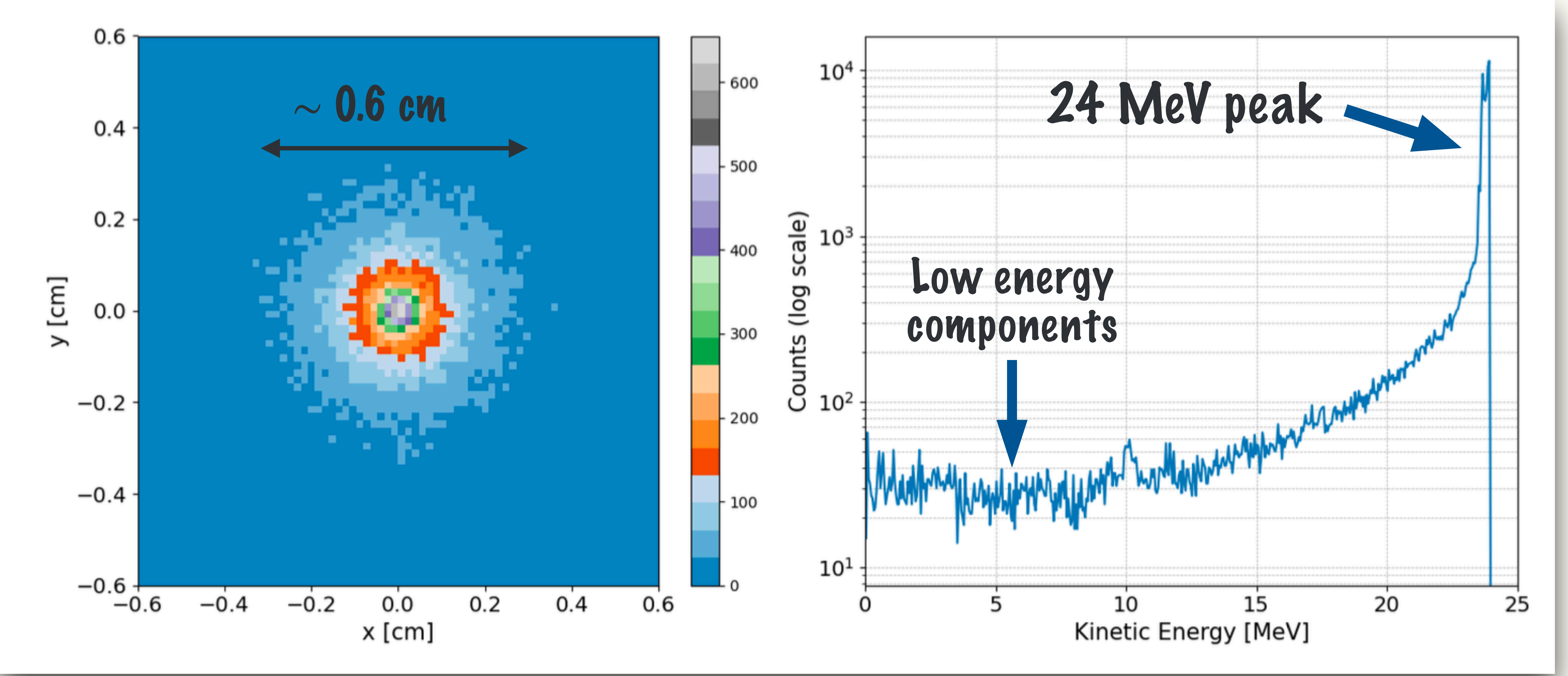
The **prototype** currently under construction as part of the SAFEST project is a **scaled-down version** of the proposed VHEE LINAC, designed to accelerate electron beams up to **24 MeV.**



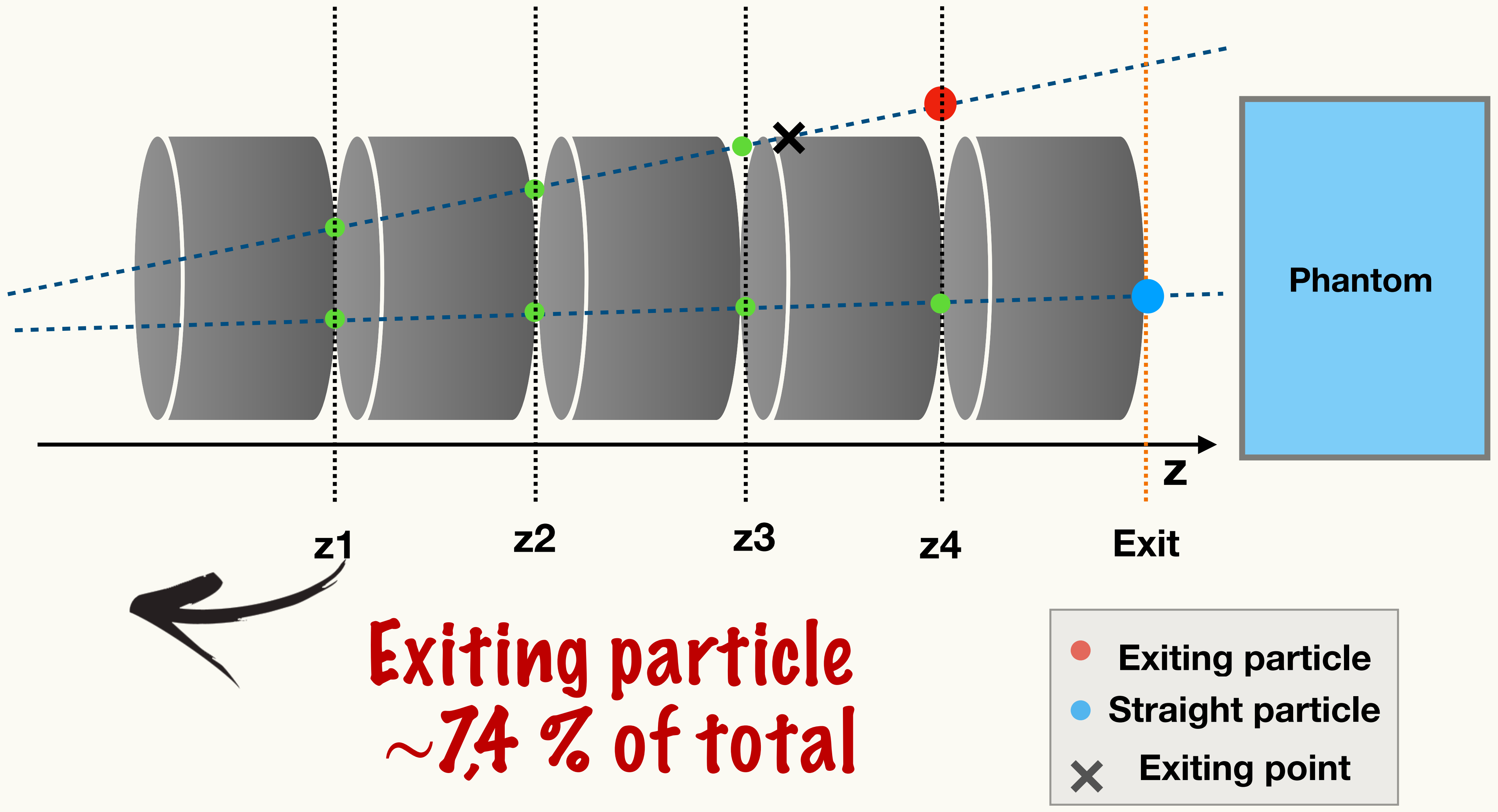
	SW section	TW section
Shunt Impedance	103 MOhm/m	107 MOhm/m
Quality Factor	10178	10127
Energy	10 MeV	24 MeV
Pulse current	100 mA	100 mA

Radioprotection studies

The **prototype** currently under construction as part of the SAFEST project is a **scaled-down version** of the proposed VHEE LINAC, designed to accelerate electron beams up to **24 MeV.**

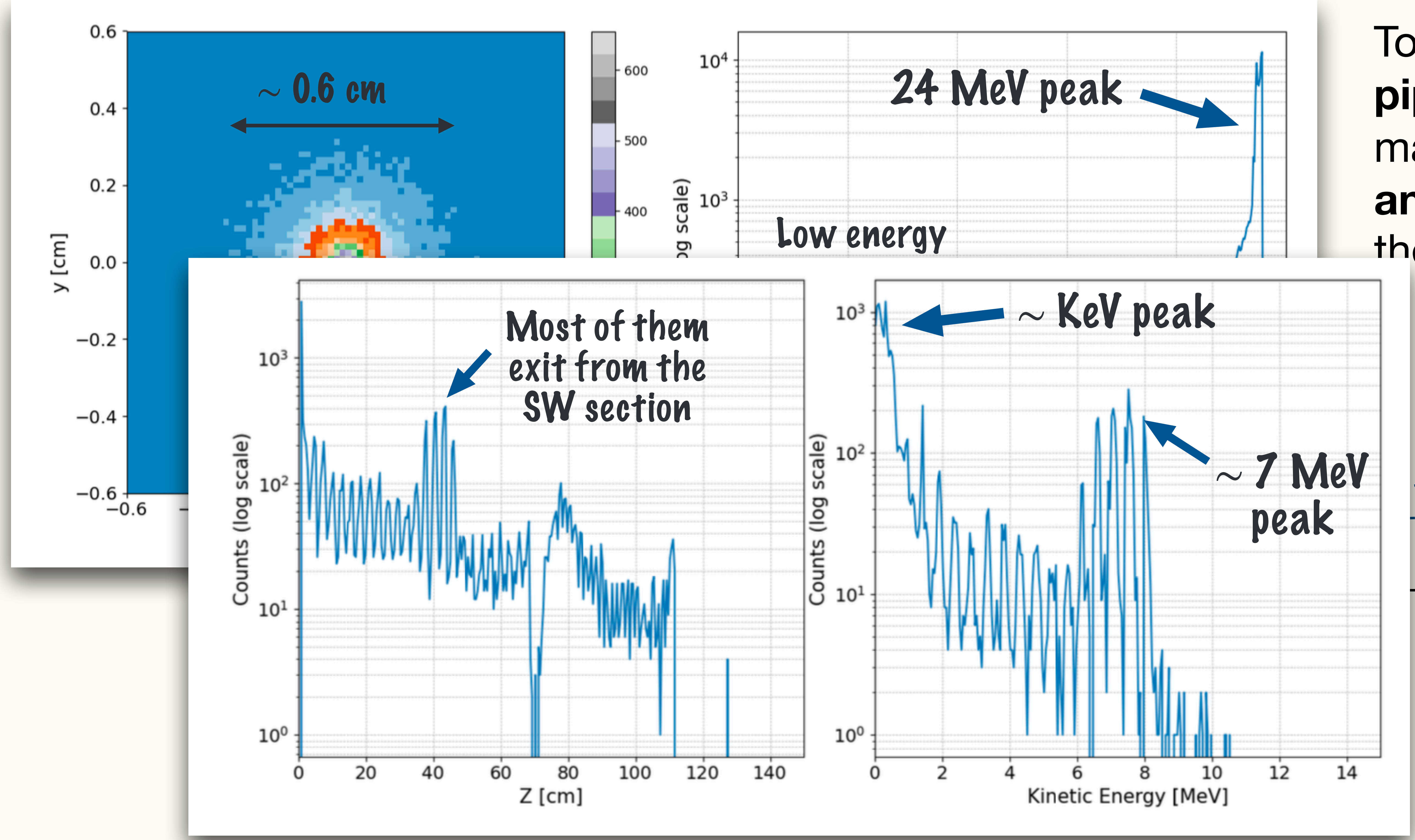


To **identify the electrons exiting the beam pipe** which interact with the external accelerator material (copper), I conducted a **geometrical analysis** in order to save the exit positions from the iris of the accelerator:

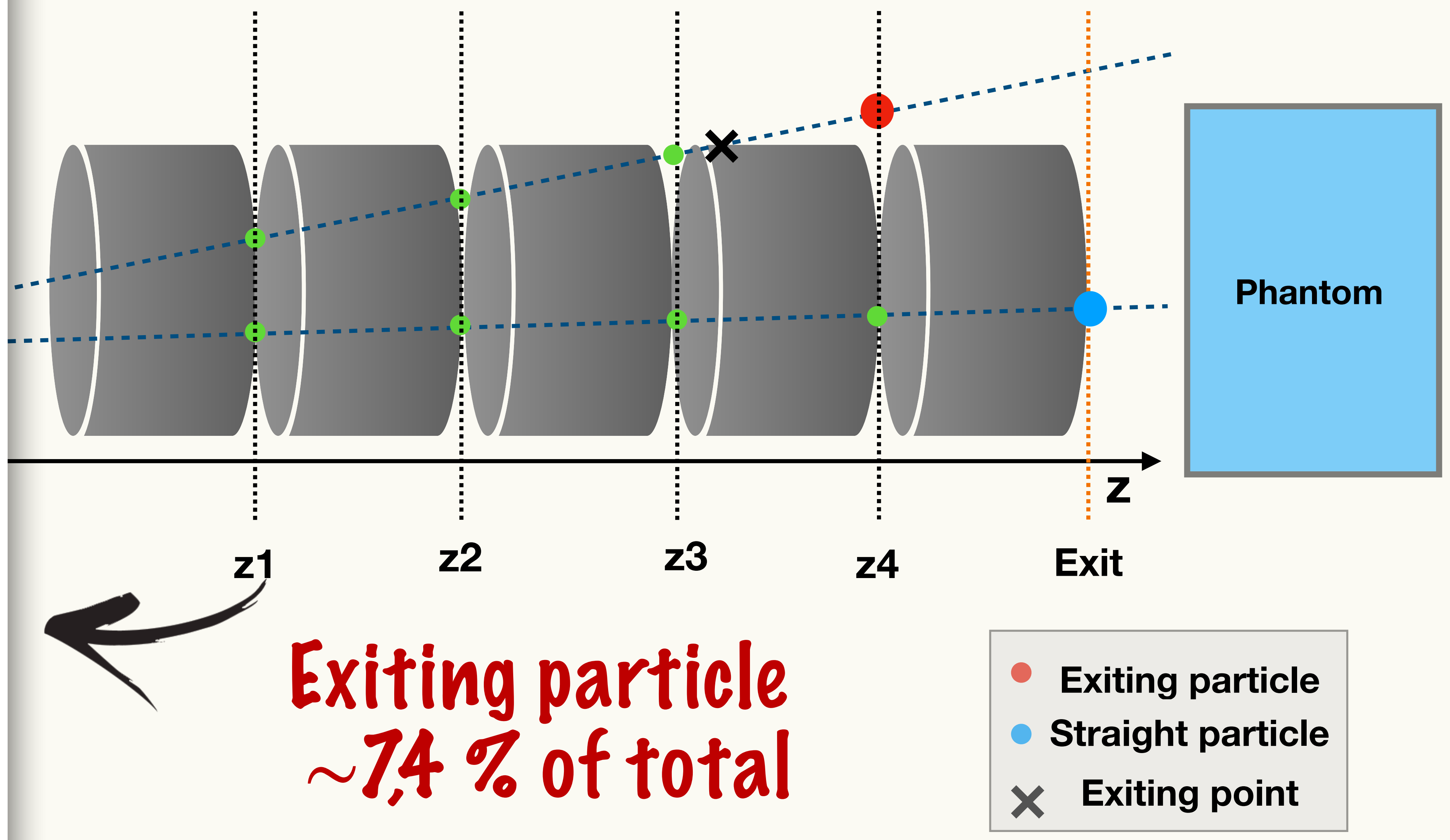


Radioprotection studies

The **prototype** currently under construction as part of the SAFEST project is a **scaled-down version** of the proposed VHEE LINAC, designed to accelerate electron beams up to **24 MeV.**



To **identify the electrons exiting the beam pipe** which interact with the external accelerator material (copper), I conducted a **geometrical analysis** in order to save the exit positions from the iris of the accelerator:



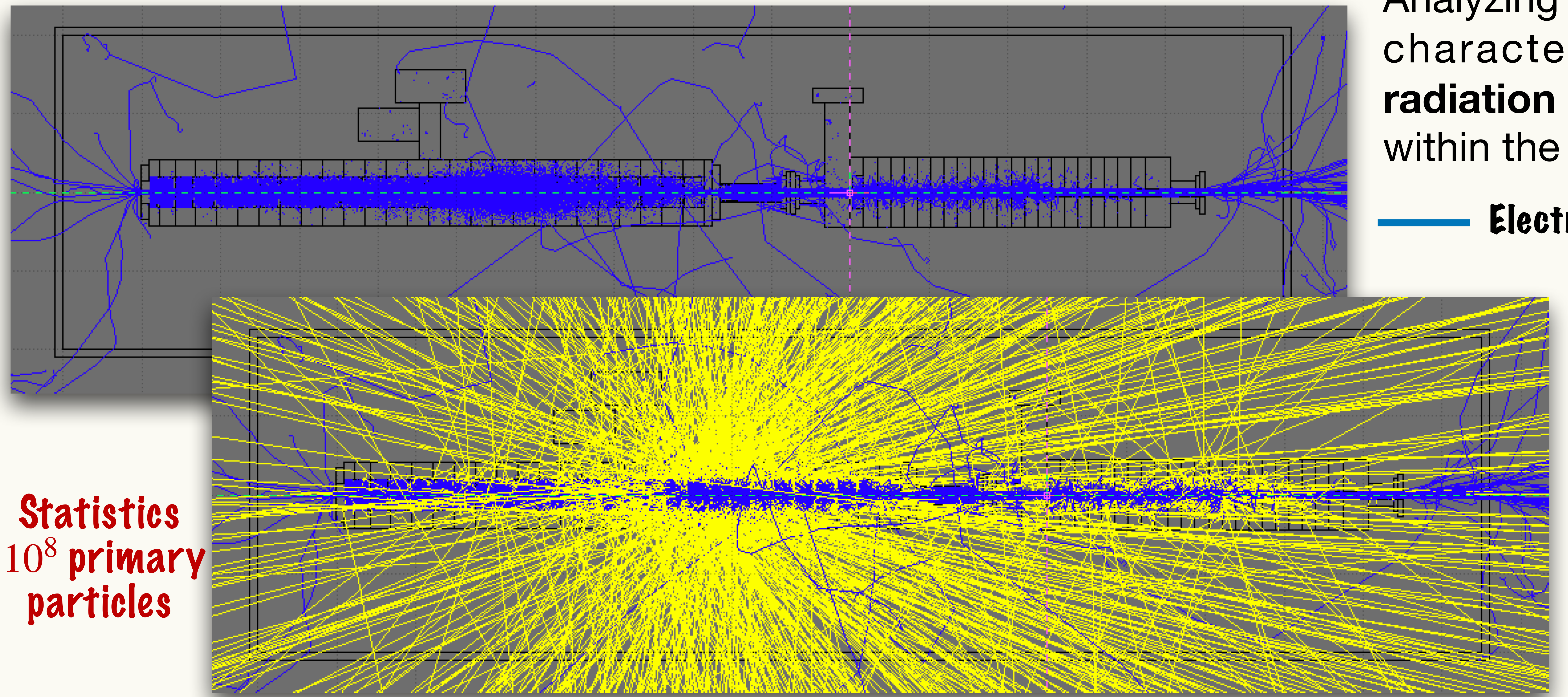
SAPIENZA
UNIVERSITÀ DI ROMA

Radioprotection studies

After identifying the coordinates at which the electrons exited the accelerator, both for the straight and scattered electrons, **further simulations were conducted using FLUKA** to model the **radiation transport** and **secondary particle production**.

Analyzing the FLUKA output allowed me to characterize the **different types of radiation produced** by various interactions within the accelerator.

Electrons — Photons — Neutrons

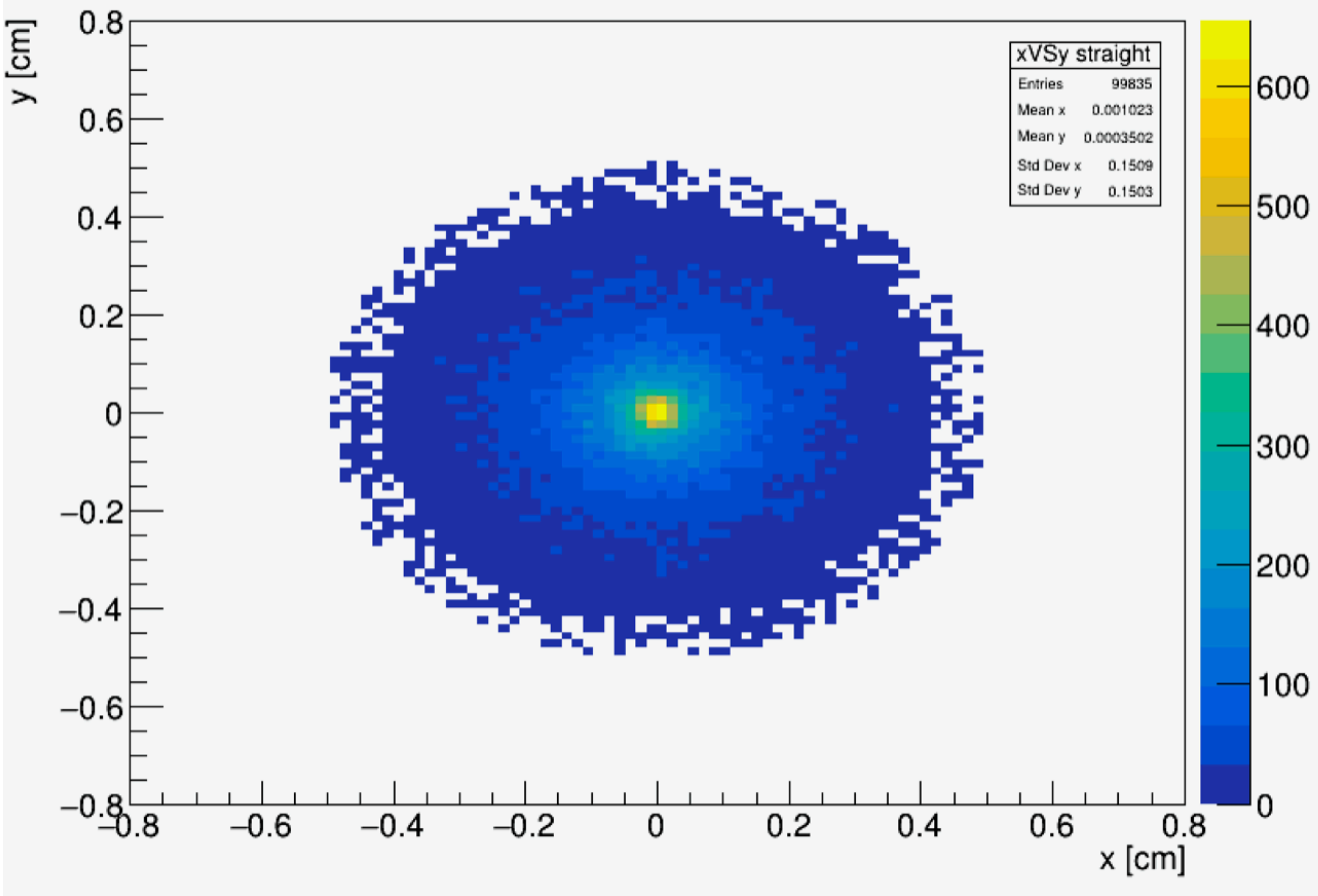


Statistics
10^8 primary particles

GOAL?

Evaluate the dispersed radiation to **design the needed shielding.**

Input file: from Parmela to FLUKA



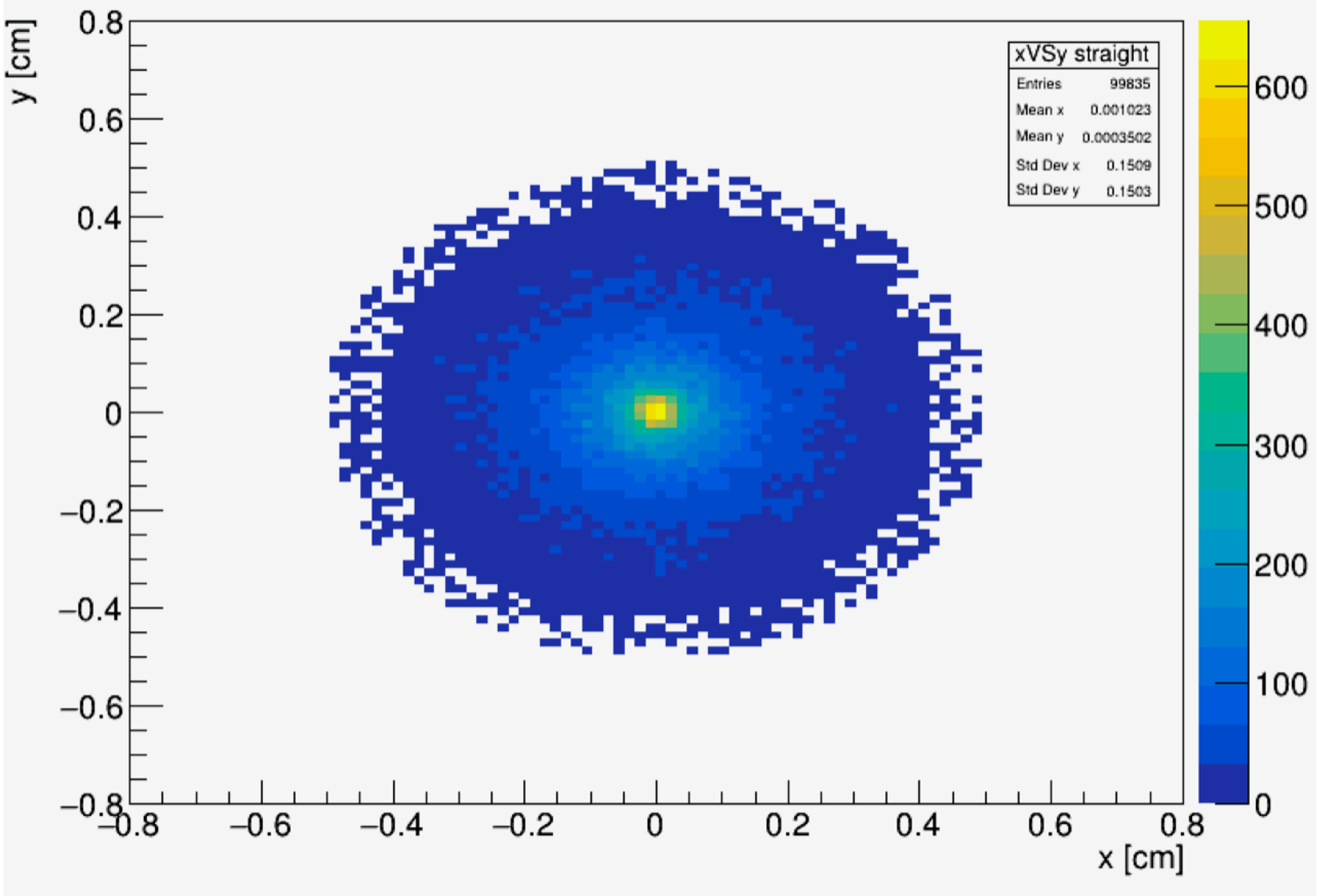
Distribution (x,y) of all particles read from the output file of Parmela.

- The beam dynamic has been evaluated by means of simulations performed with the PARMELA software, which provides the **spatial and energy information of all beam particles subjected to the accelerating electromagnetic fields of the structure**.

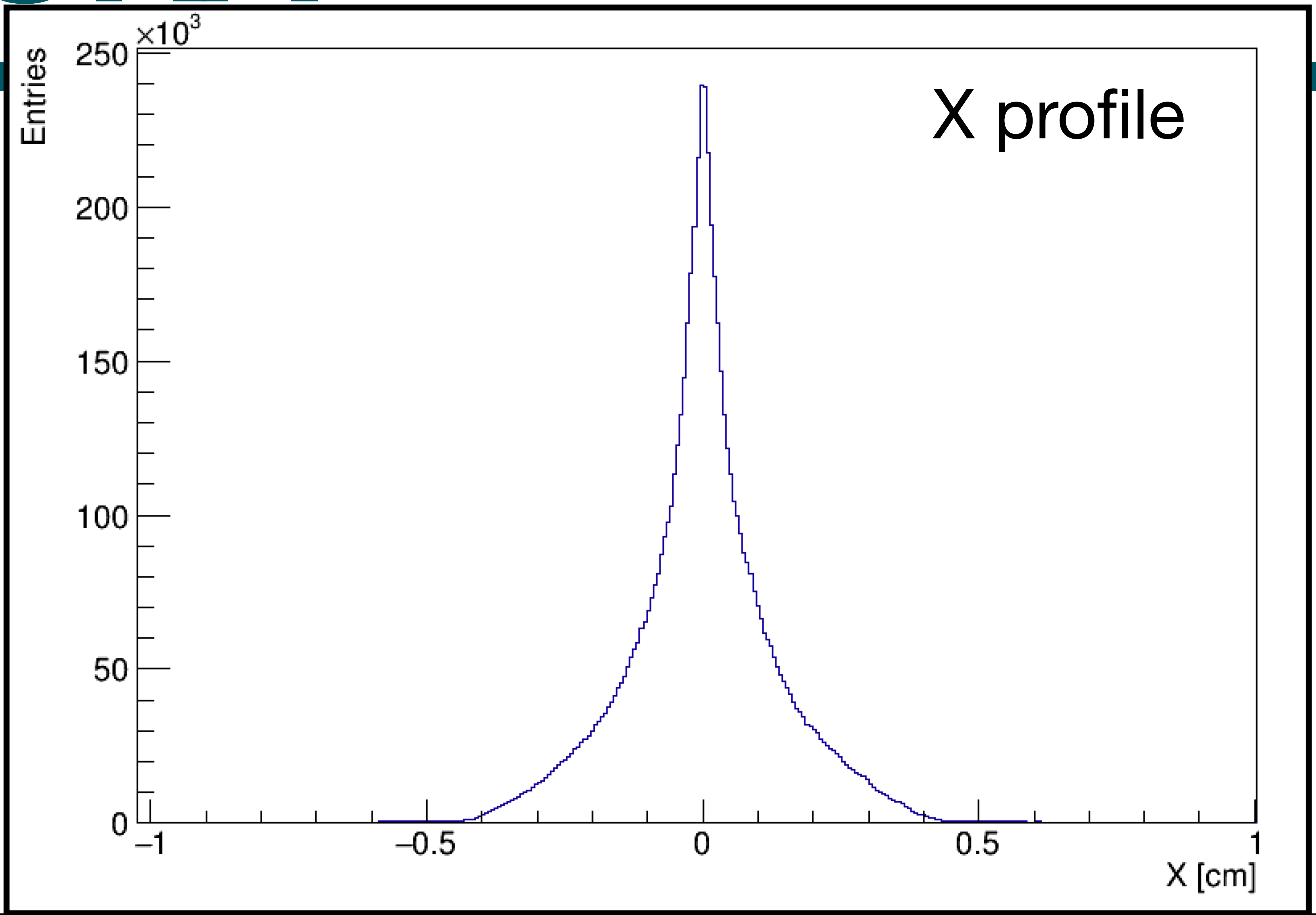
↓

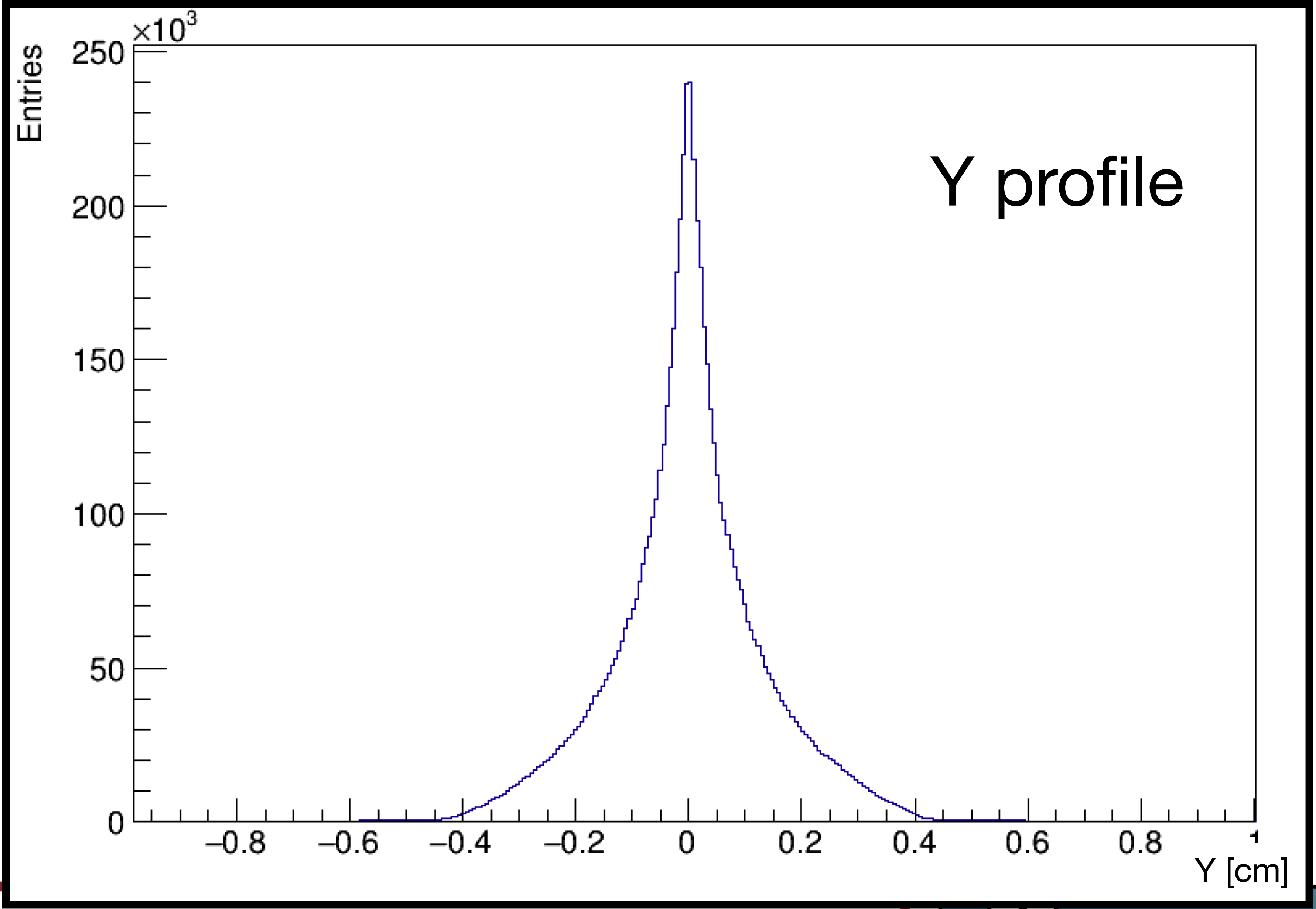
The beam interactions with the accelerator passive materials has been simulated with FLUKA using as input the beam kinematic information provided by PARMELA.

Input file: from Parmela to FLUKA



Distribution (x,y) of all particles read from the output file of Parmela.





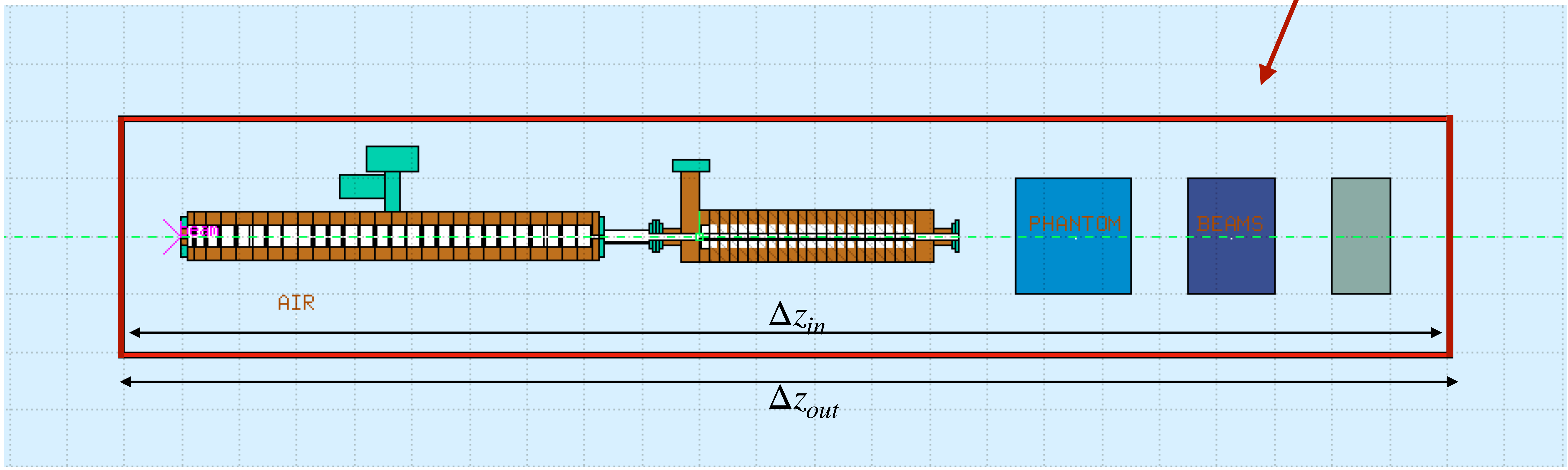
FLUKA number of primaries

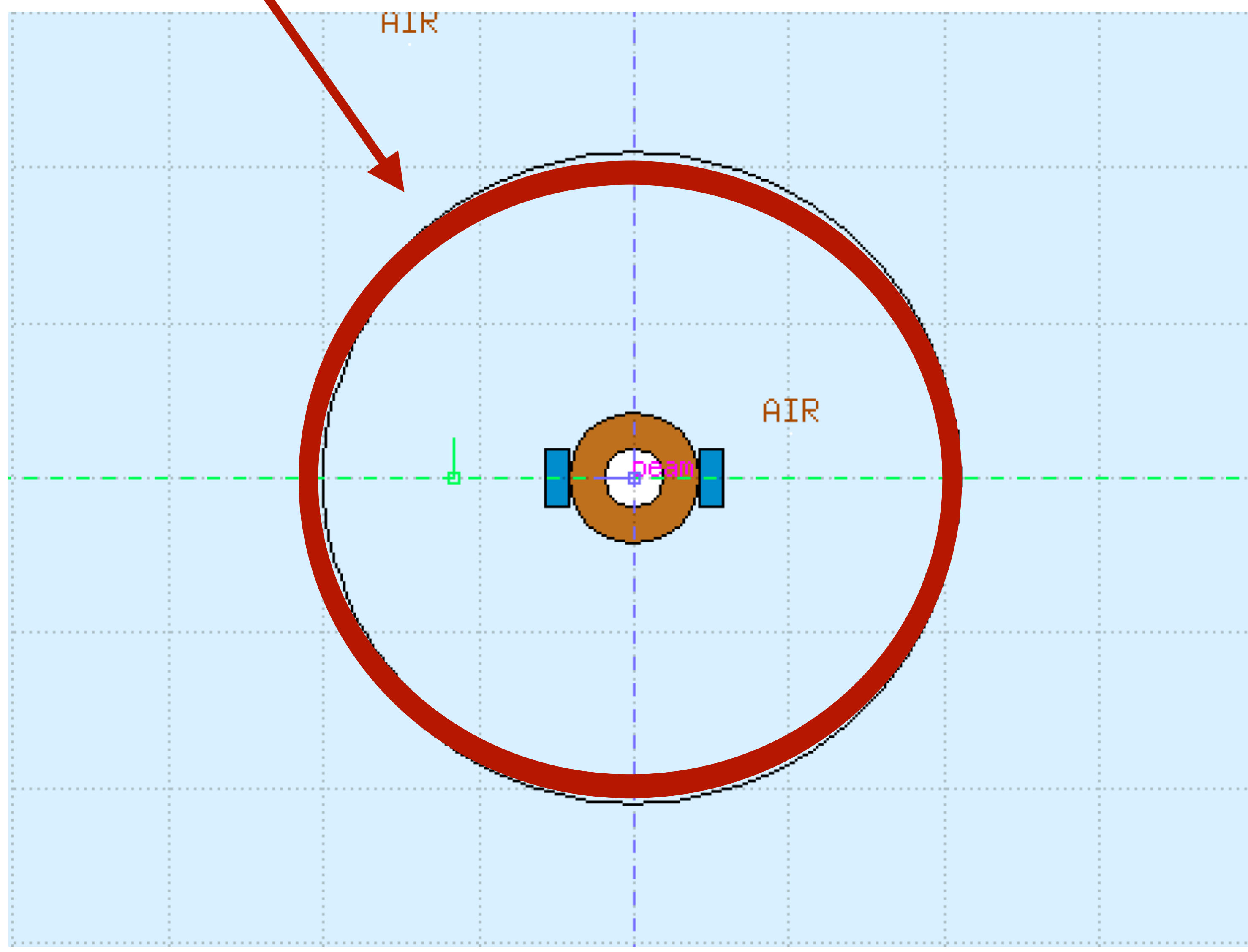
- The number of particles traced forward, crossing the accelerator, from the beam dynamics studies, is 114625. This statistic is too low to be used as input for the FLUKA simulations. Therefore, what has been done is to **increase the multiplicity in the azimuthal angle** ϕ of each outgoing primary particle.

 # particles before = 114625

 # particles after = 1146250

- The evaluation of the dispersed flux was performed in a **cylindrical region surrounding the accelerator**. Here, the scoring of the following quantities was carried out.

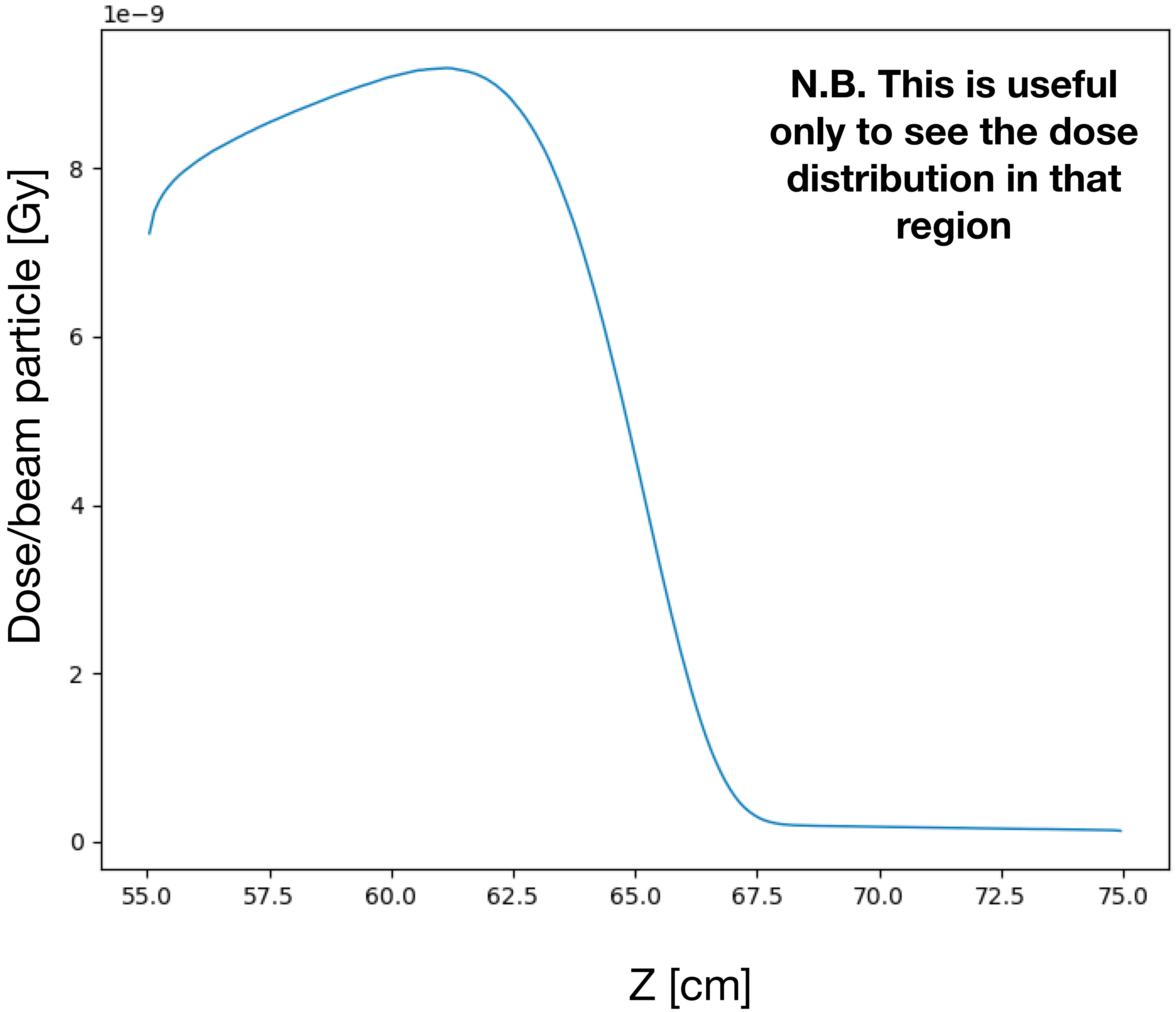




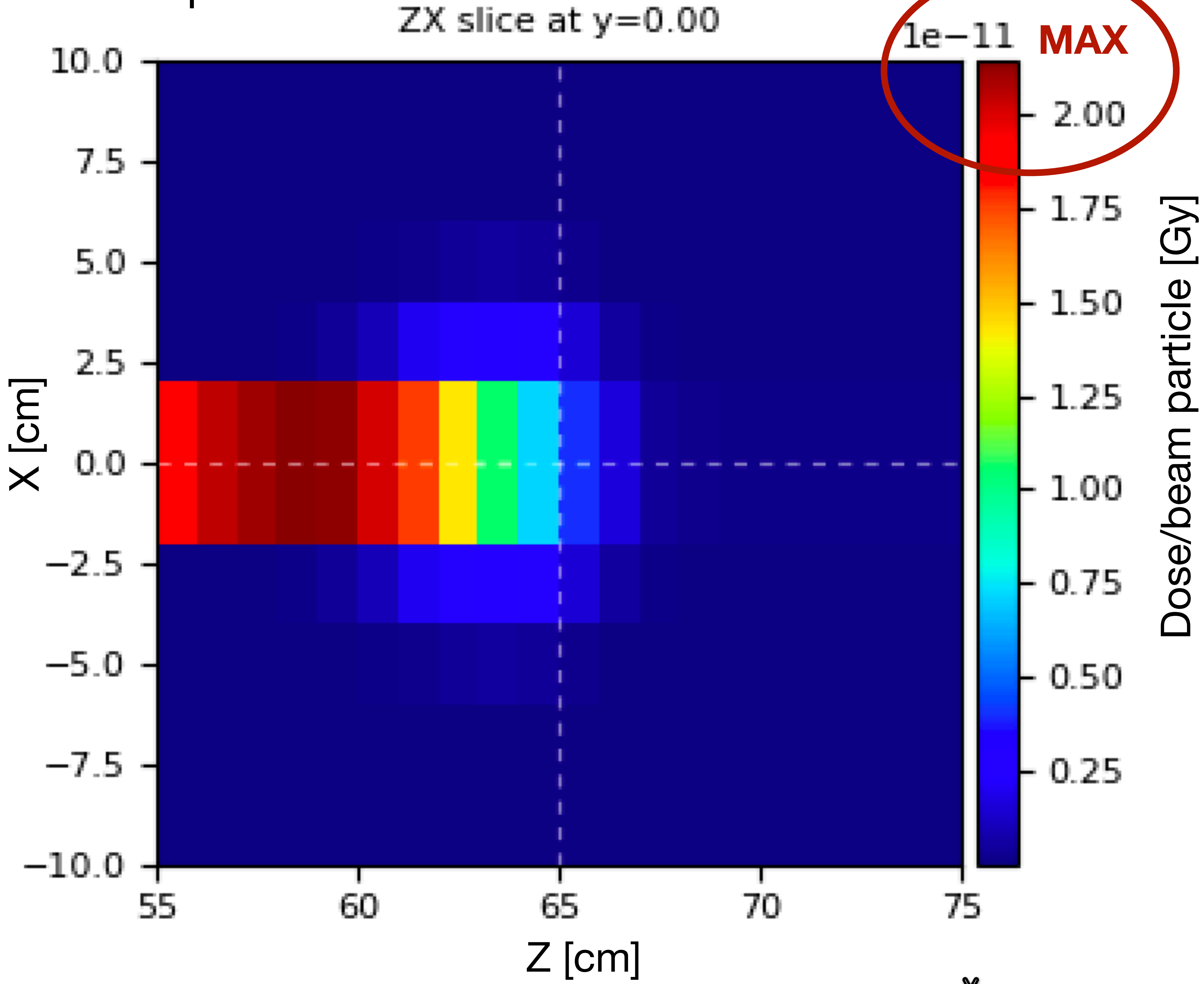
- Scoring cylinder dimensions: $R_{in} = 20cm$ $R_{out} = 21cm$ $\Delta z_{in} = 230cm$ $\Delta z_{out} = 232cm$

Dose calculated inside the Phantom

- This is the **INTEGRATED dose profile along the beam axes**, per particle beam inside the water phantom.

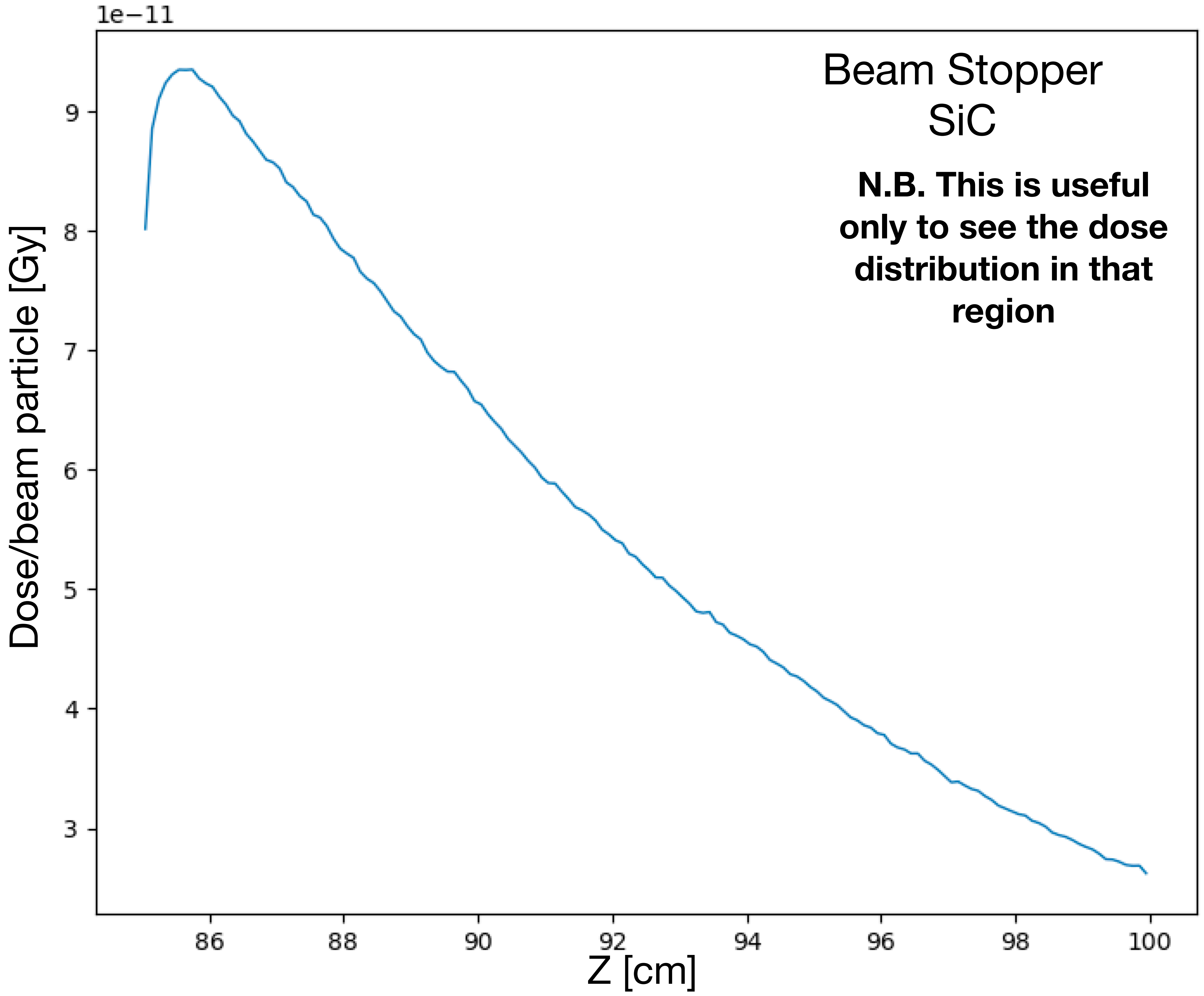


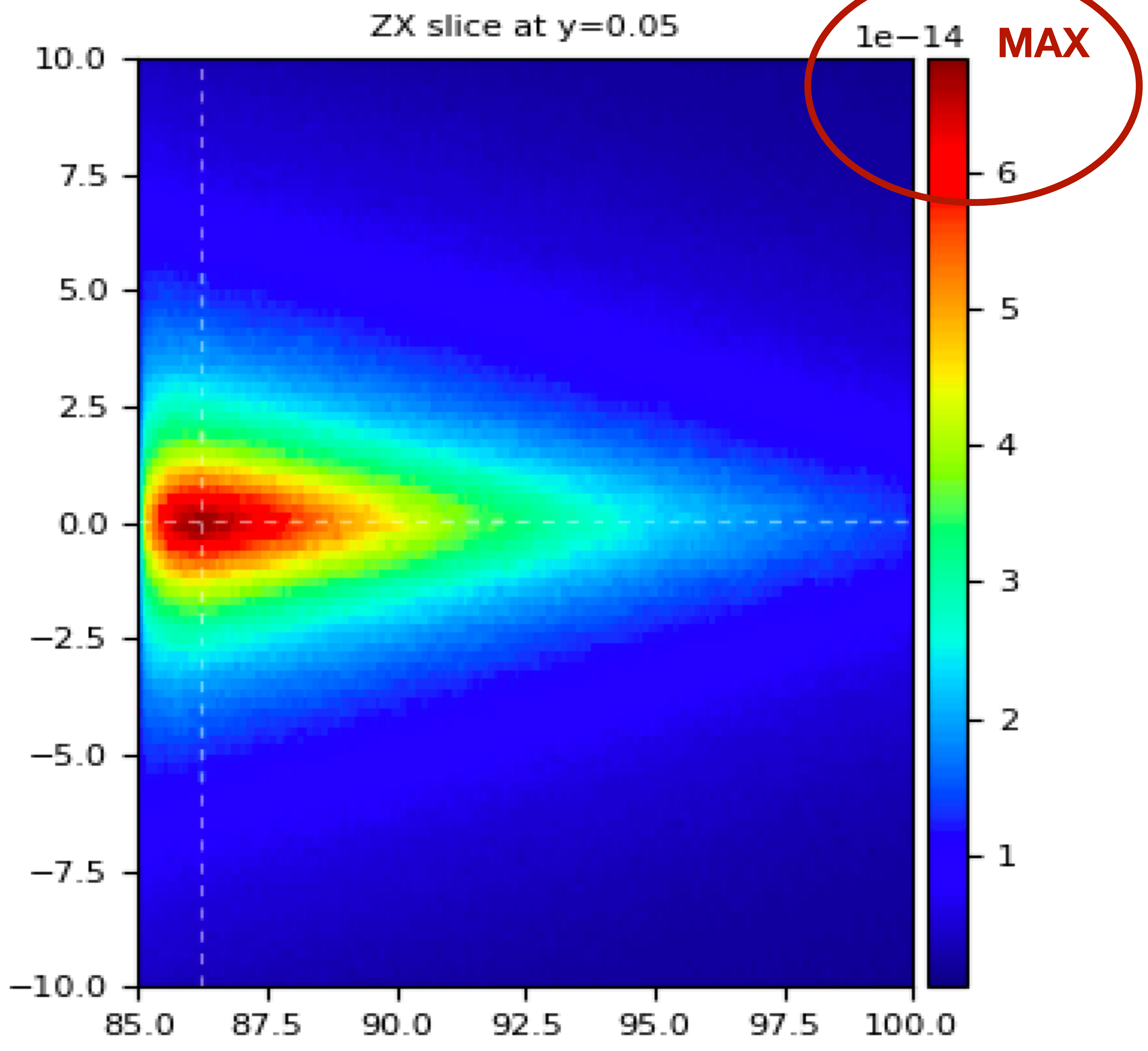
- This is the **DOSE MAP** per particle beam inside the water phantom.



Dose in Beam Stopper

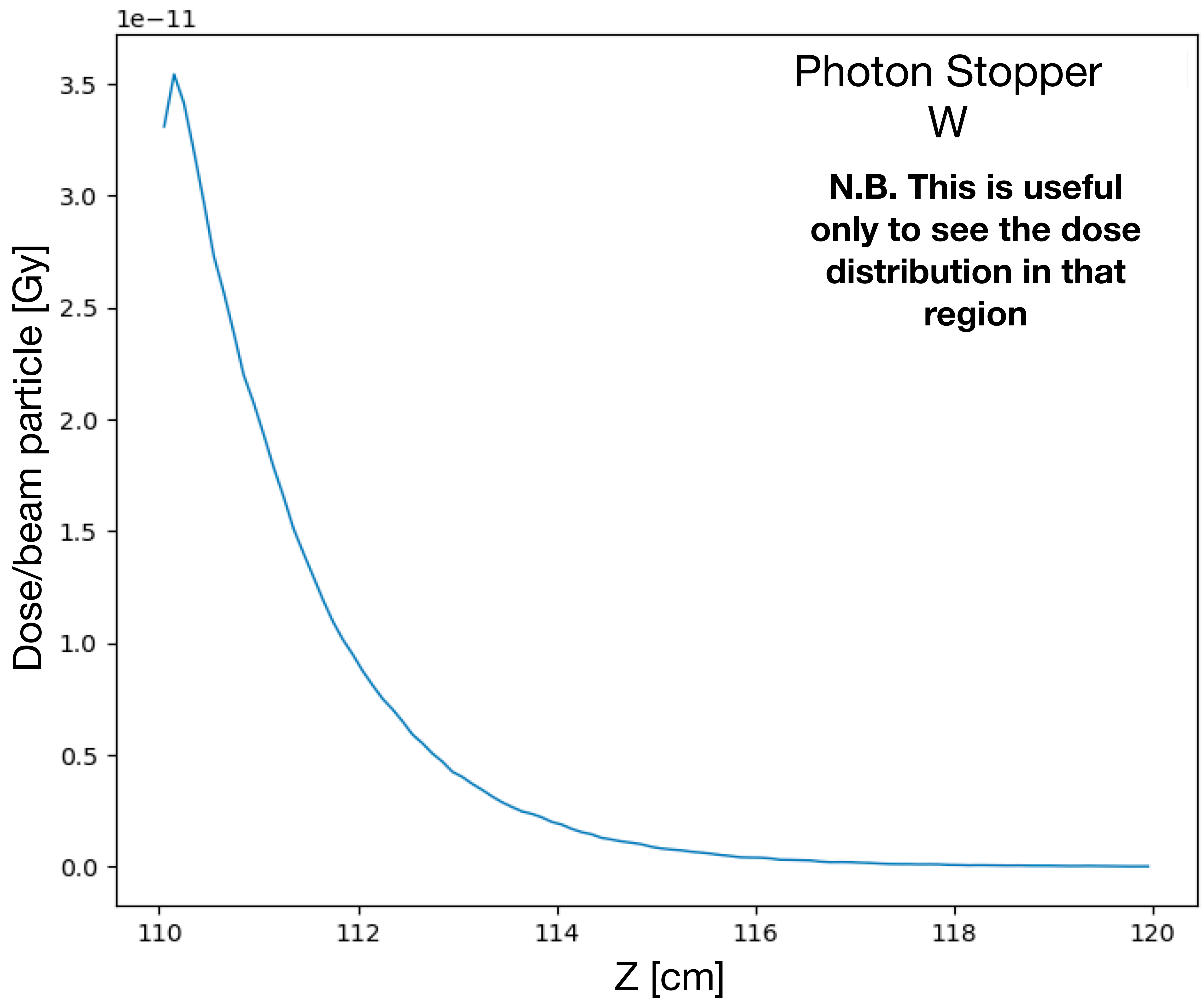
- **Integrated dose along the beam axes** (z) per particle beam inside the SiC beam stopper and W photon stopper.

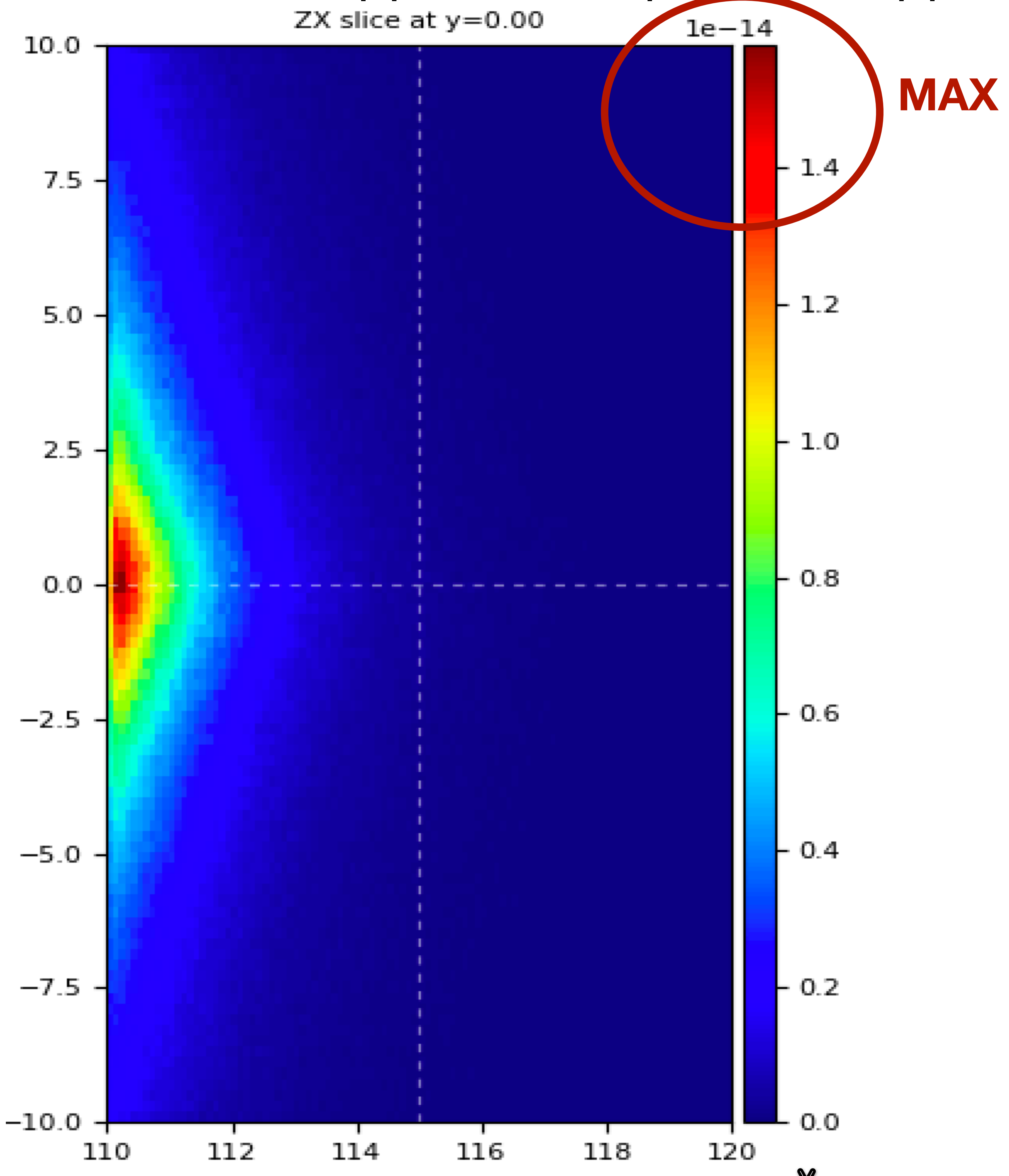




Dose in Photon Stopper

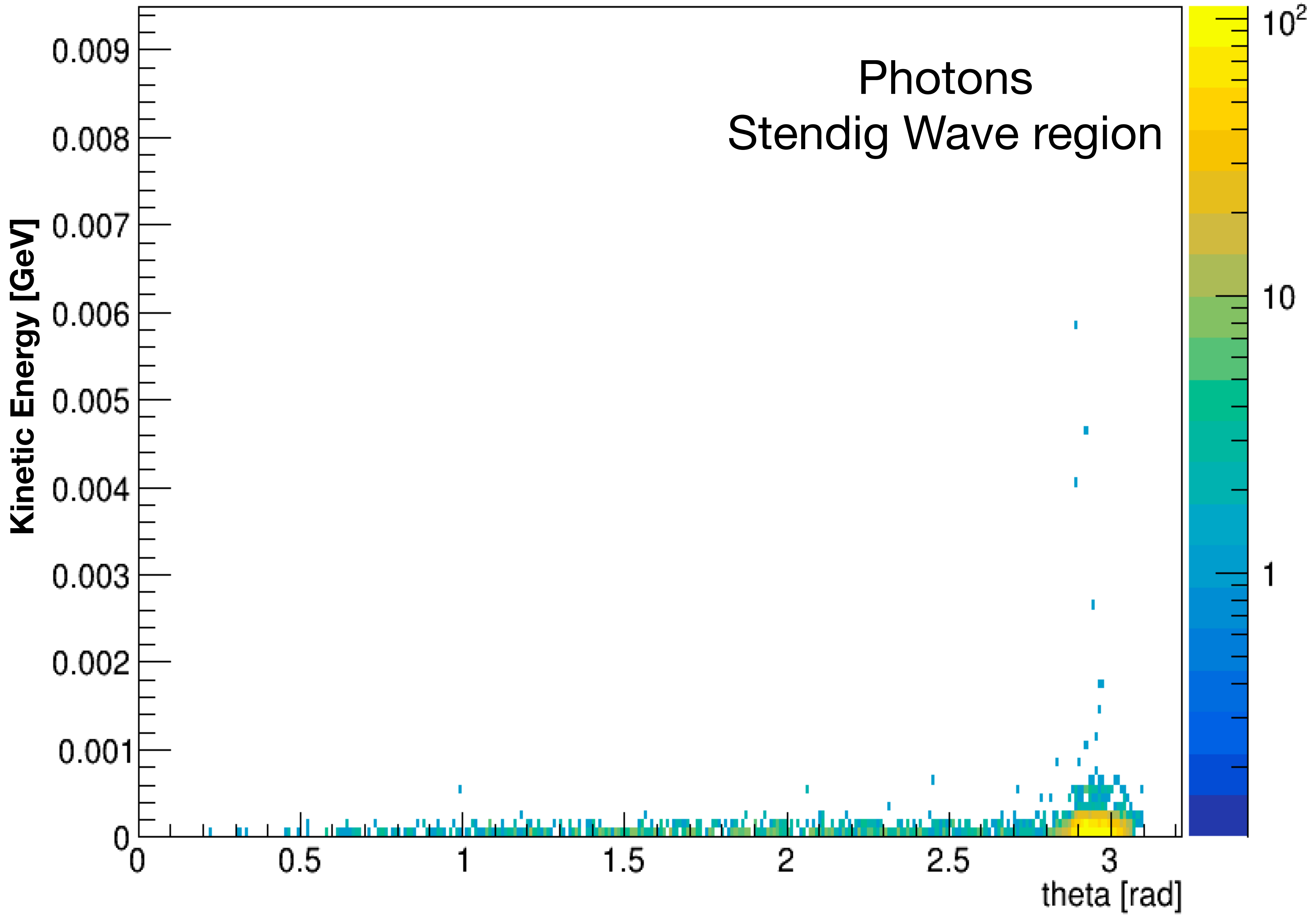
- **Integrated dose along the beam axes** (z) per particle beam inside the SiC beam stopper and W photon stopper.

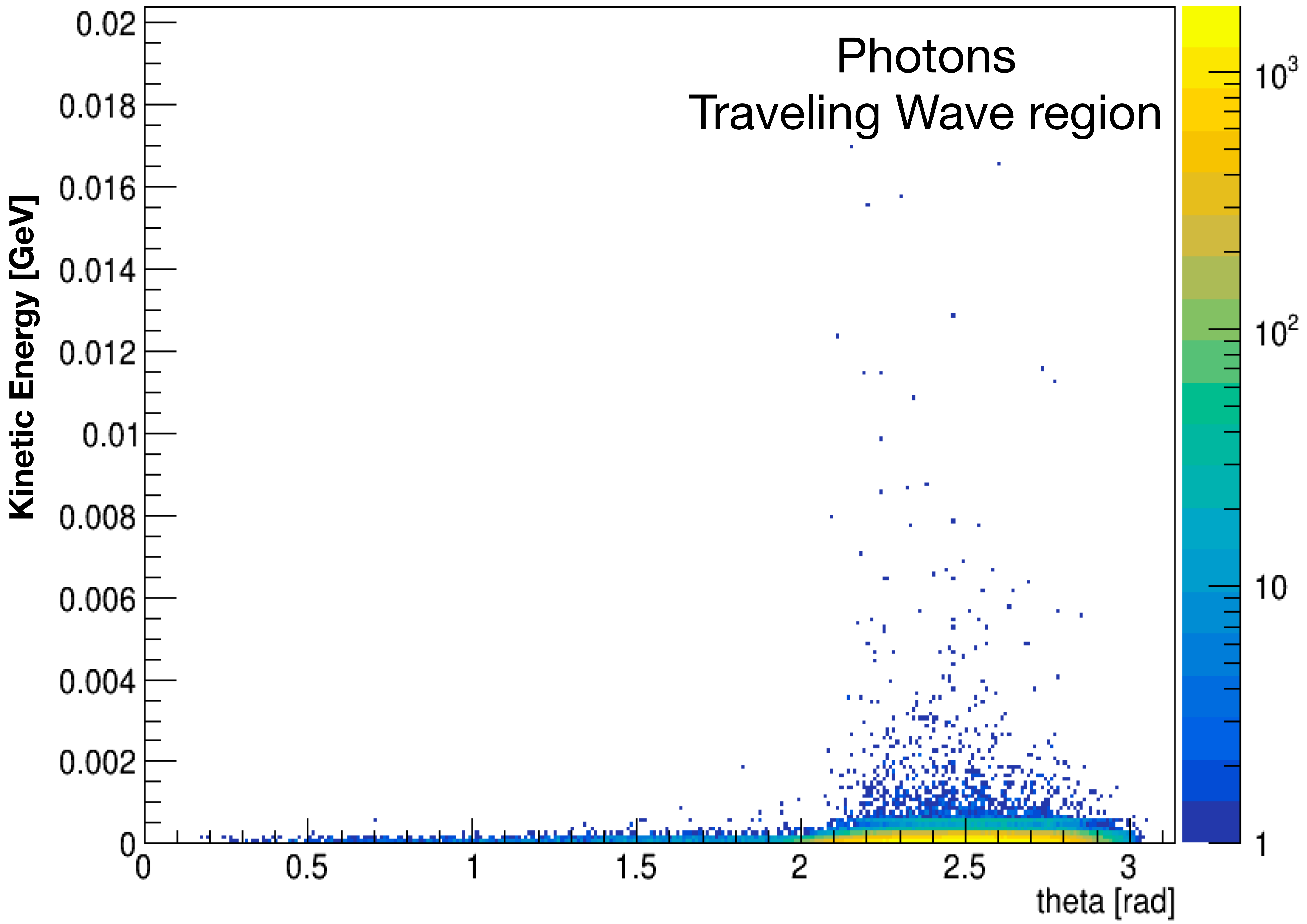




Dose evaluation for Radioprotection protocols

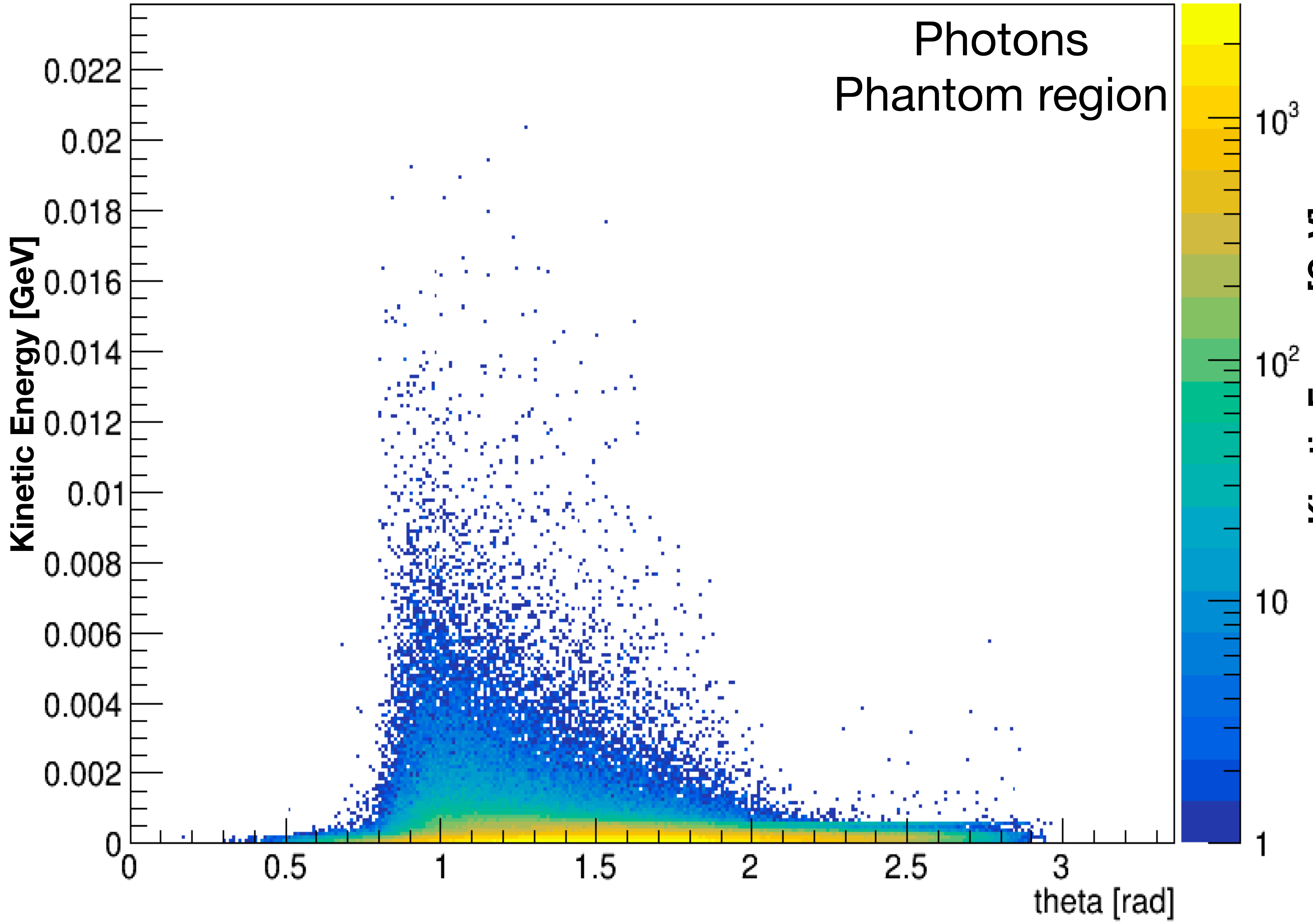
- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated along the entire accelerator.

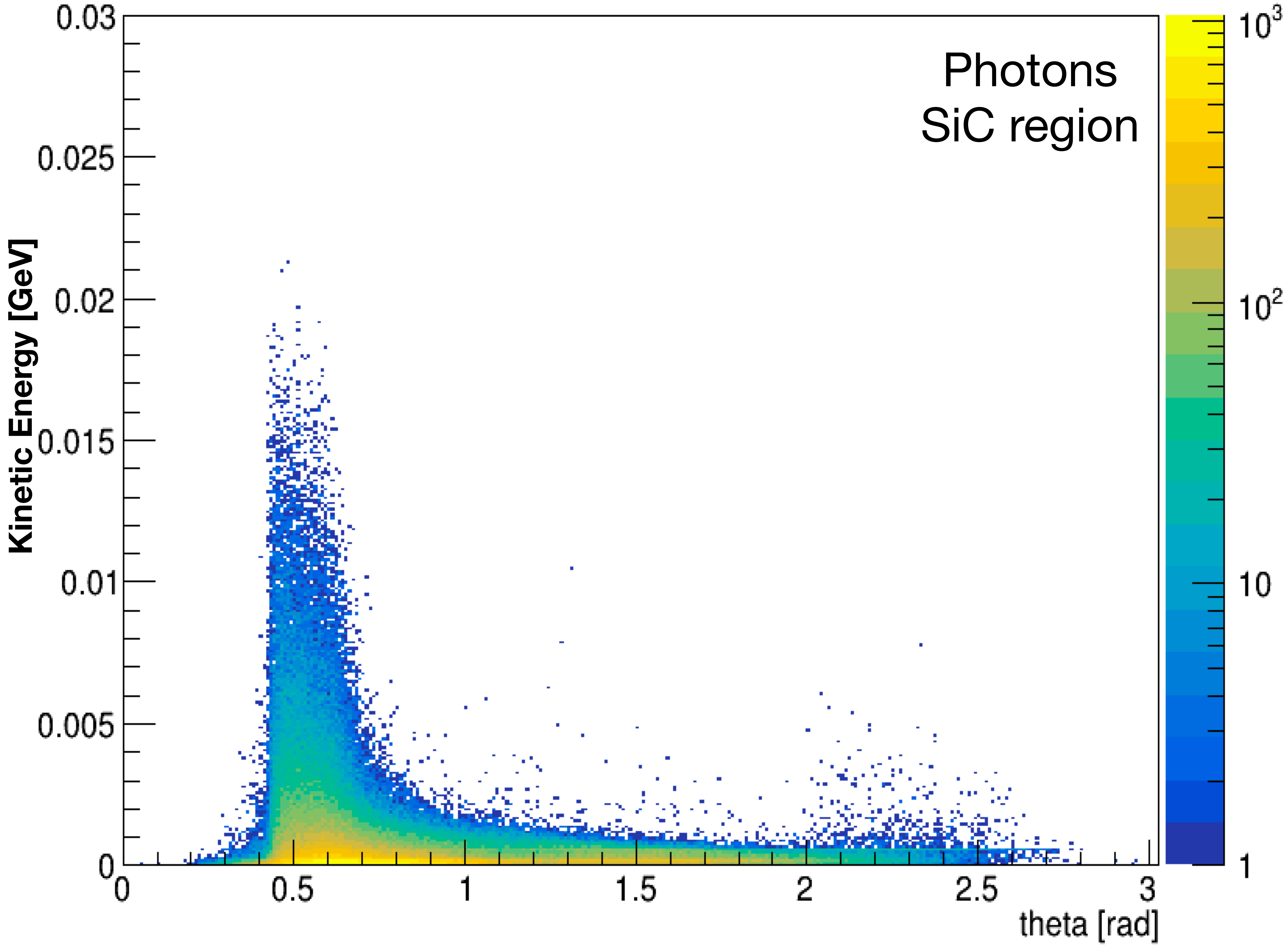




Dose evaluation for Radioprotection protocols

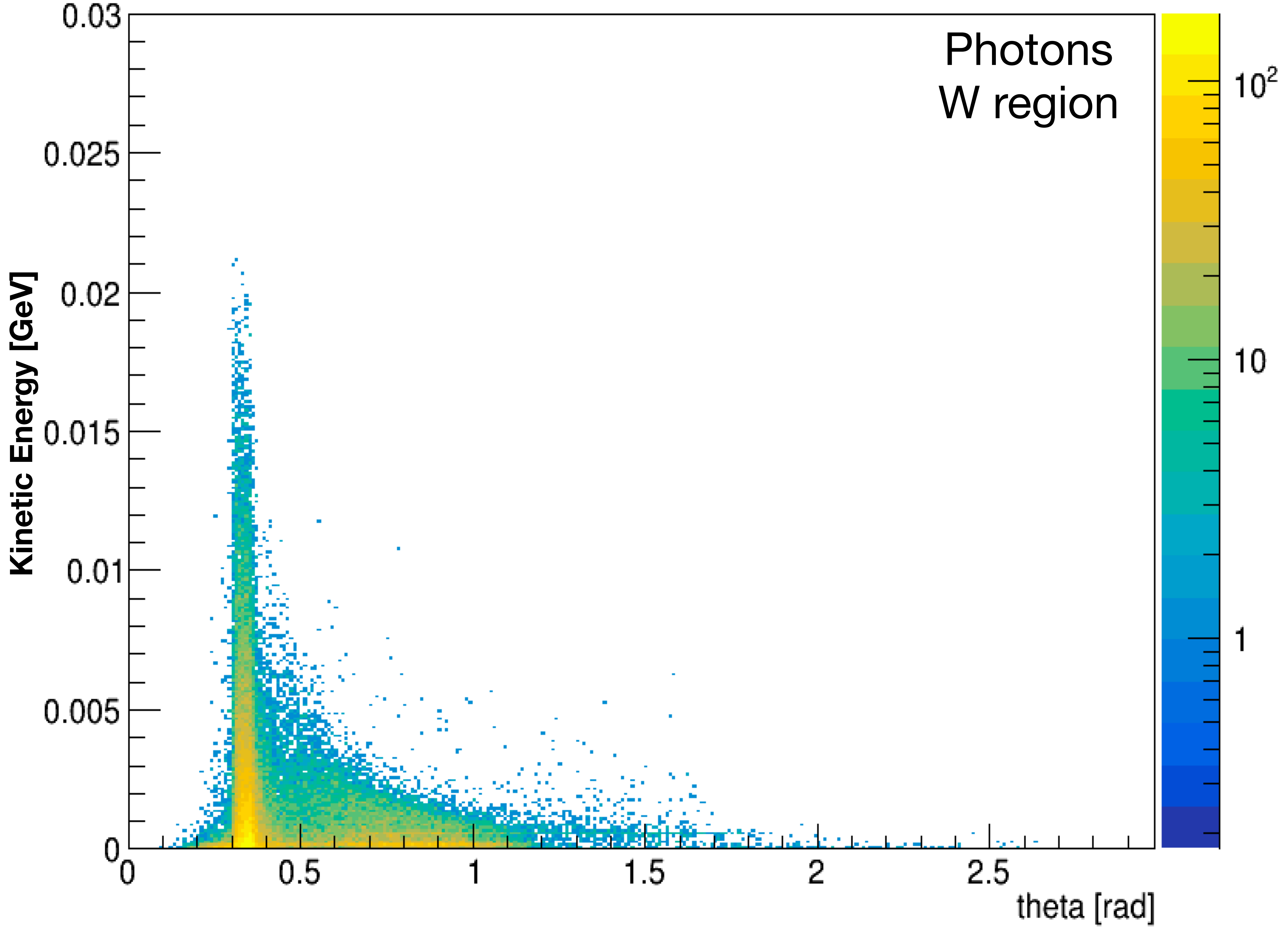
- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated along the entire accelerator.

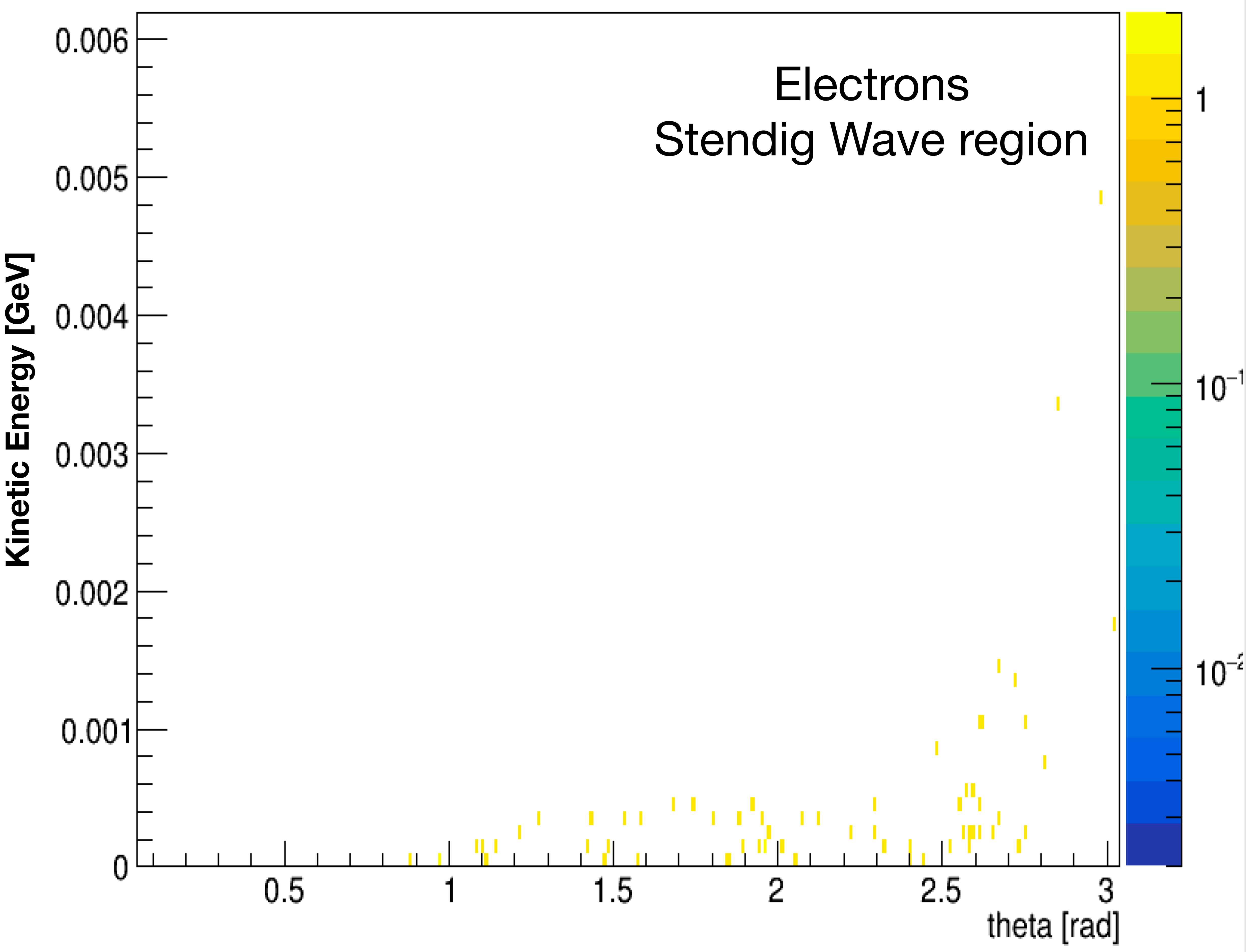




Dose evaluation for Radioprotection protocols

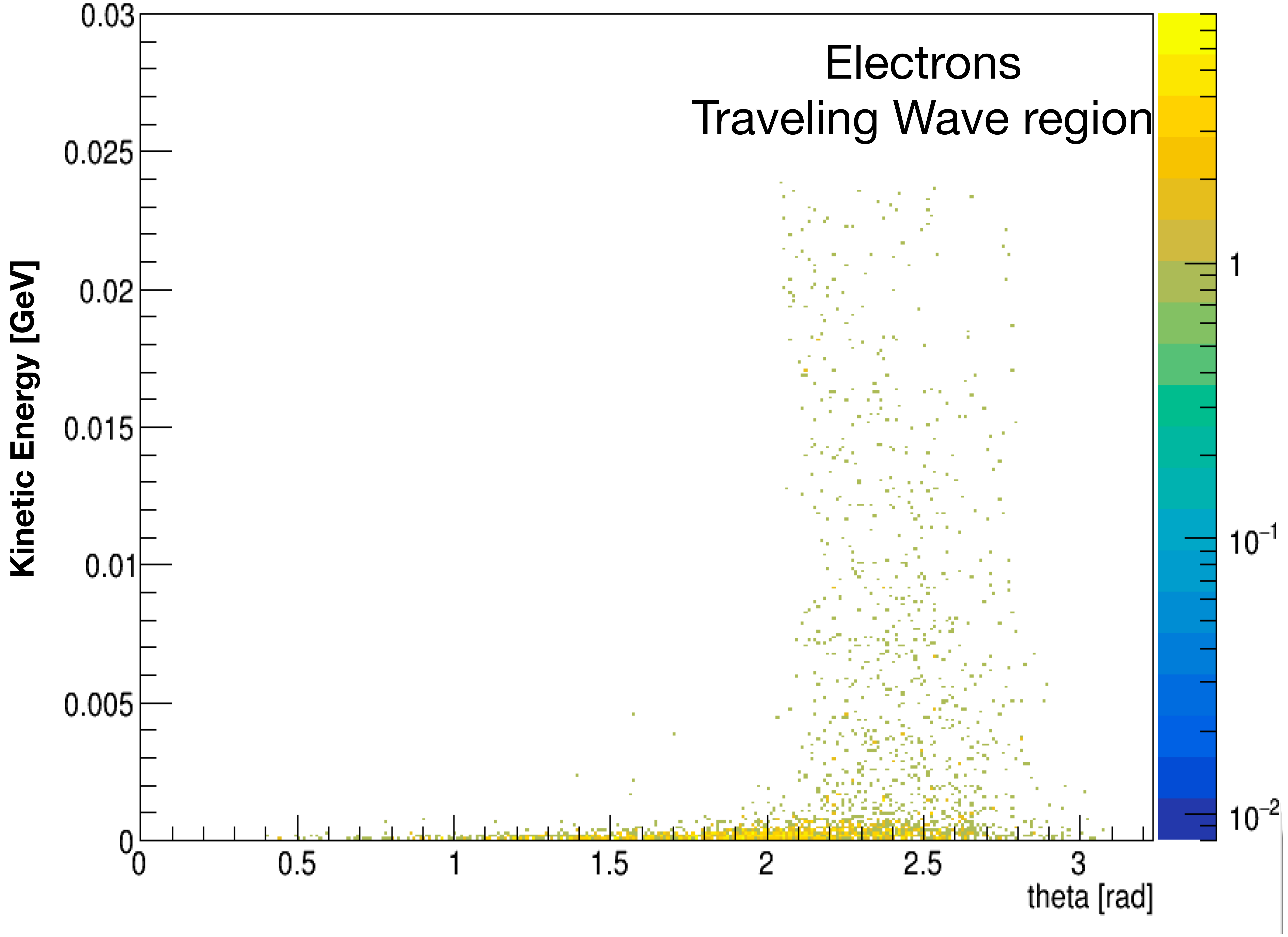
- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated along the entire accelerator.

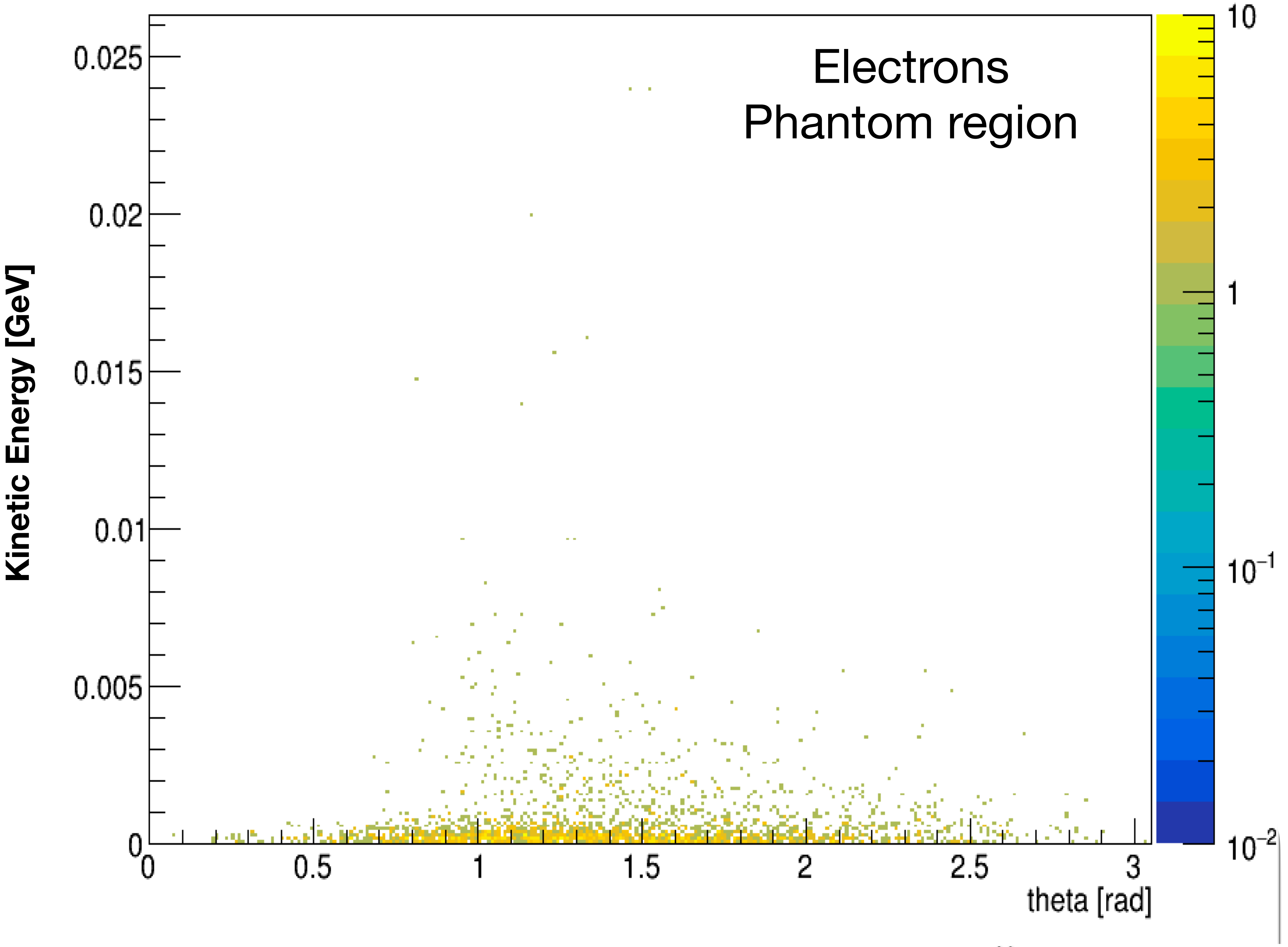




Dose evaluation for Radioprotection protocols

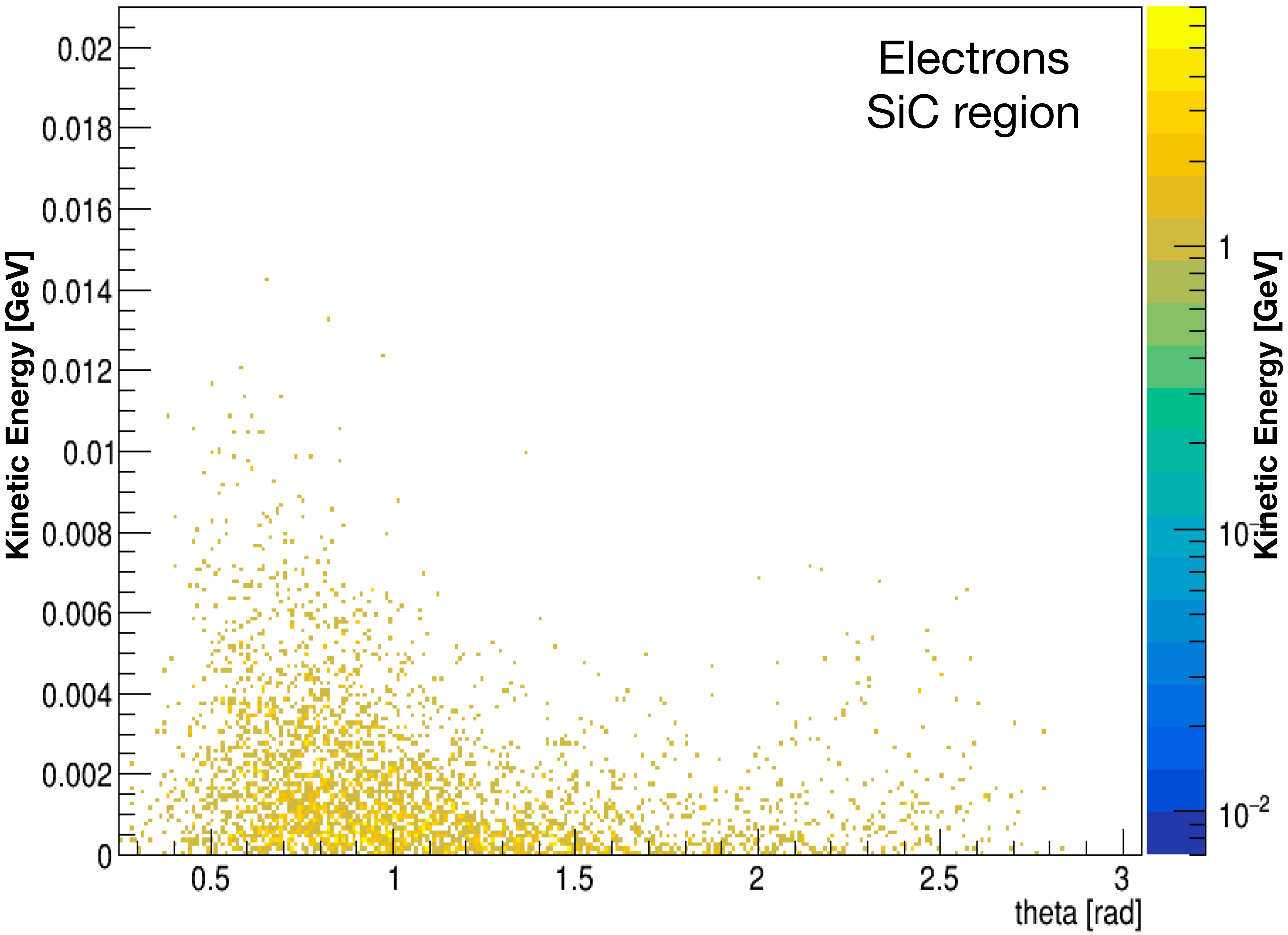
- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated along the entire accelerator.

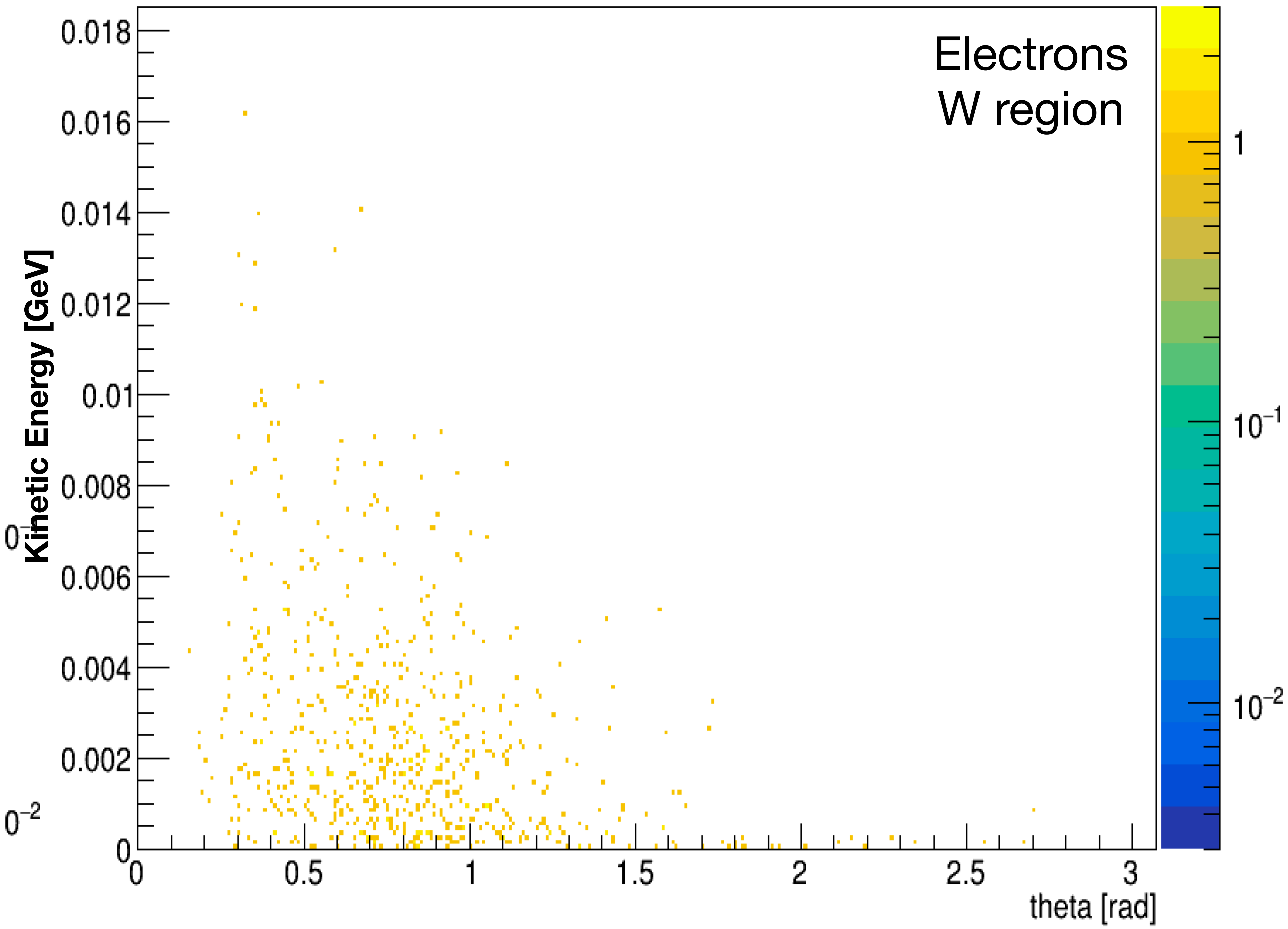




Dose evaluation for Radioprotection protocols

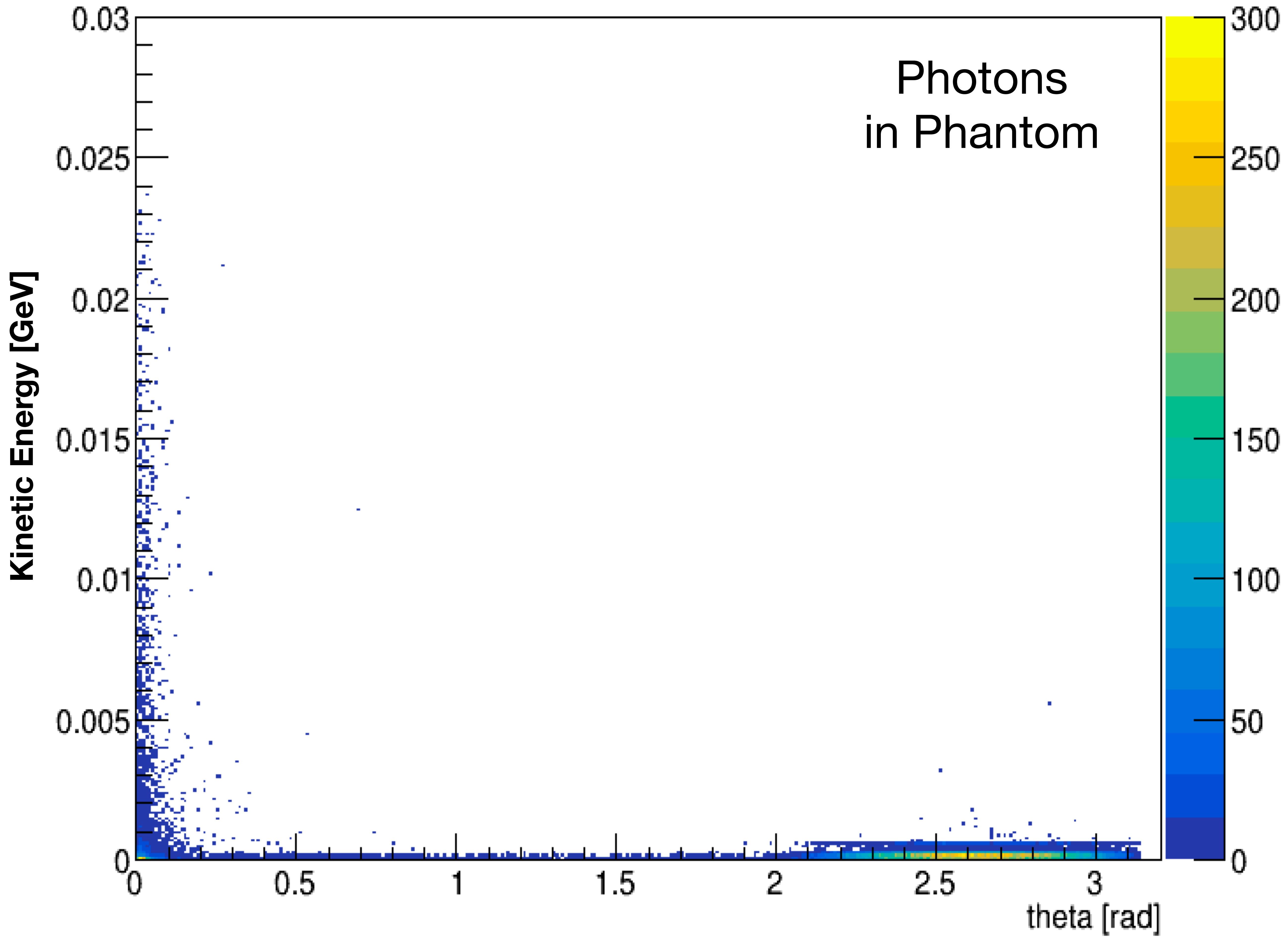
- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated along the entire accelerator.

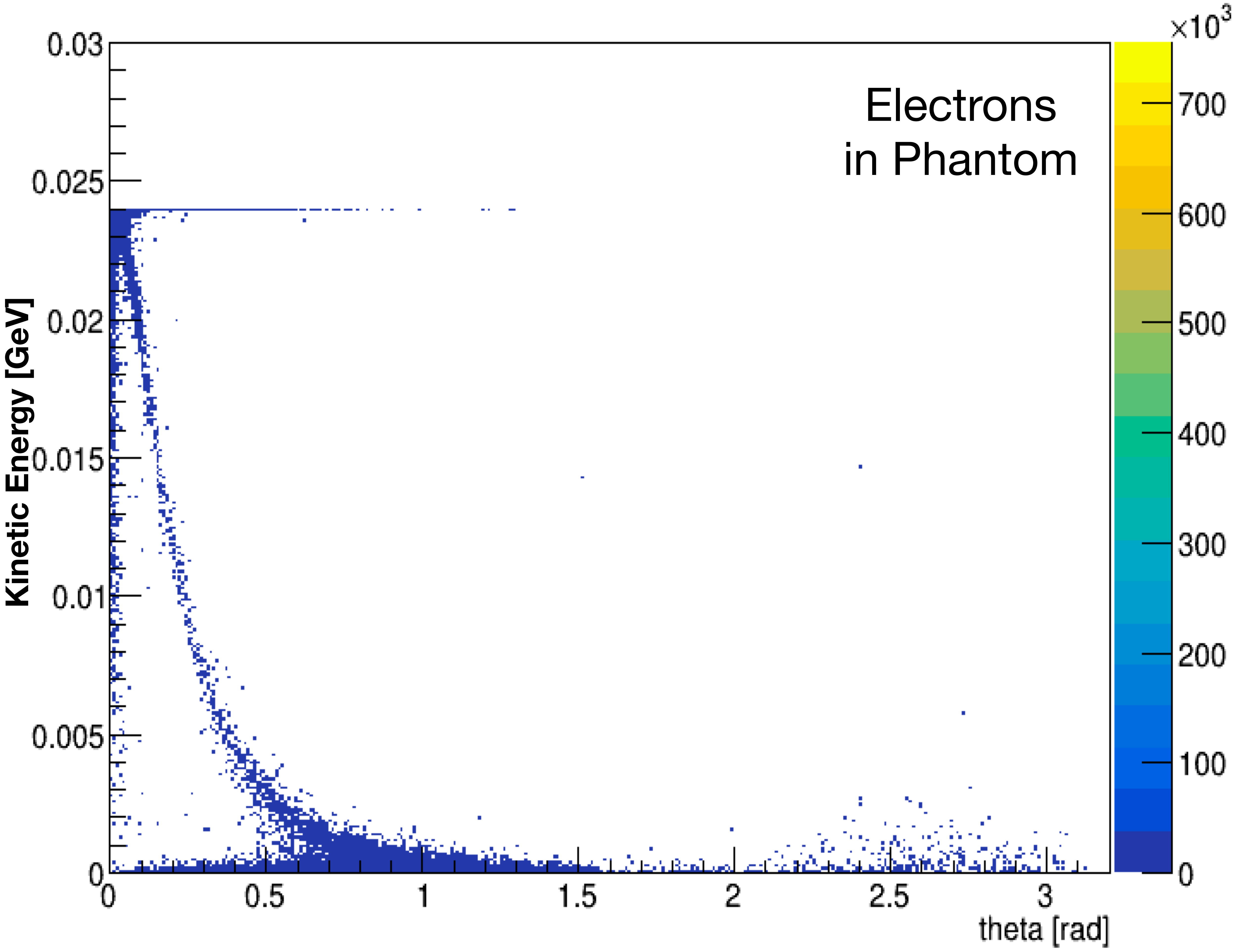




Dose evaluation for Radioprotection protocols

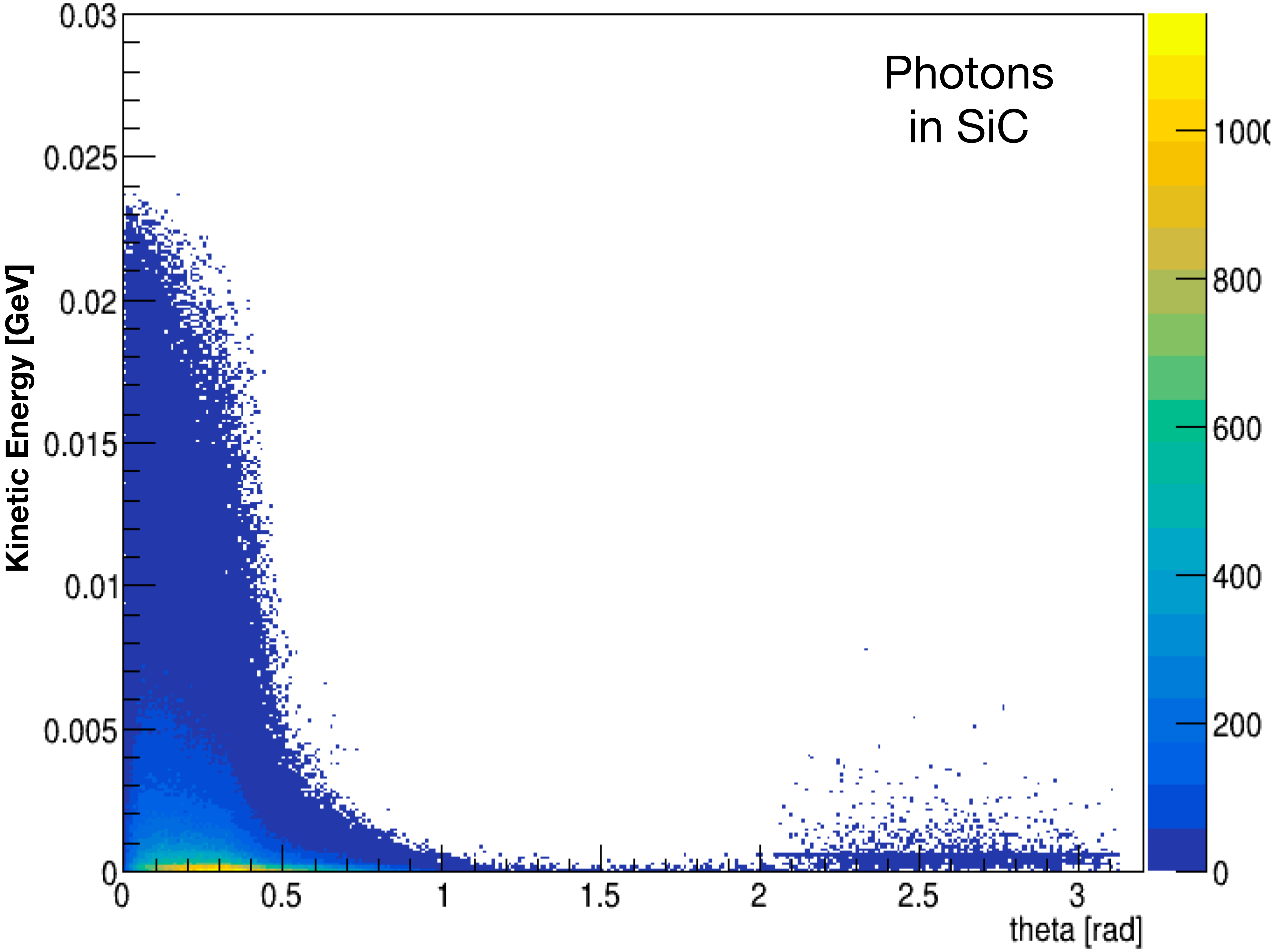
- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated in the three different regions after the accelerator.

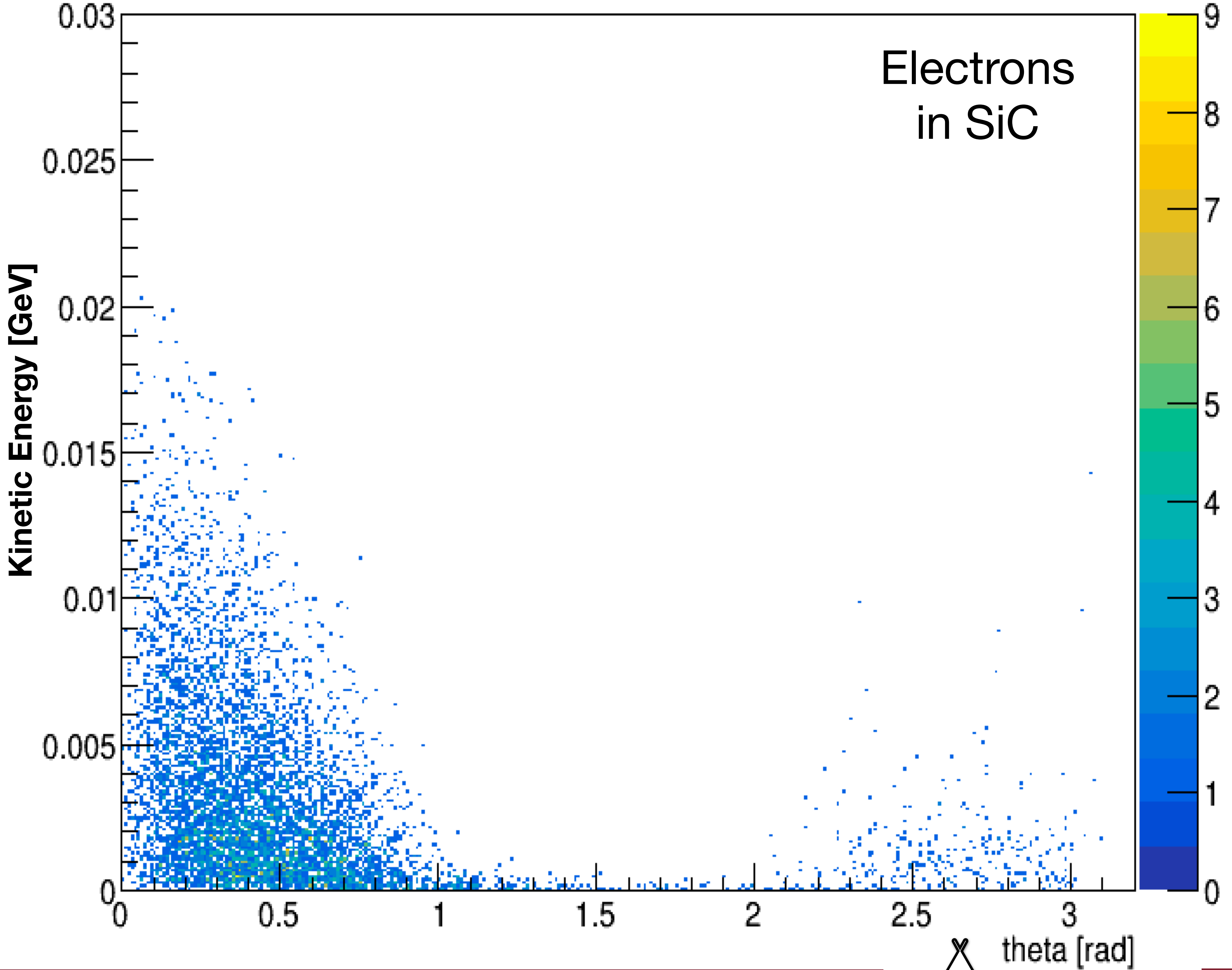




Dose evaluation for Radioprotection protocols

- To understand which region of space is affected by scattered radiation flux, the crossing angles relative to the axis of the photon and electron beam were evaluated in the three different regions after the accelerator.

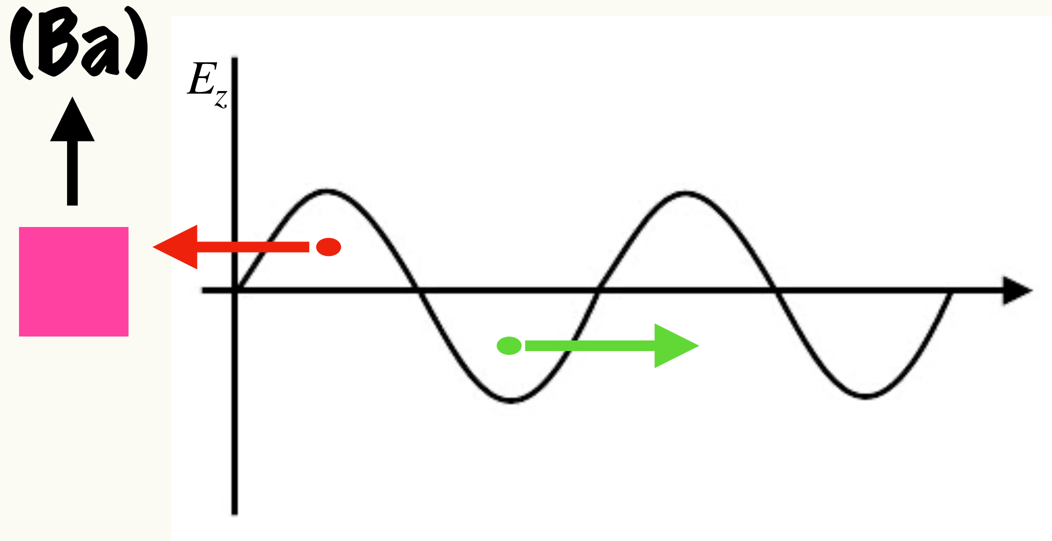




SAPIENZA
UNIVERSITÀ DI ROMA

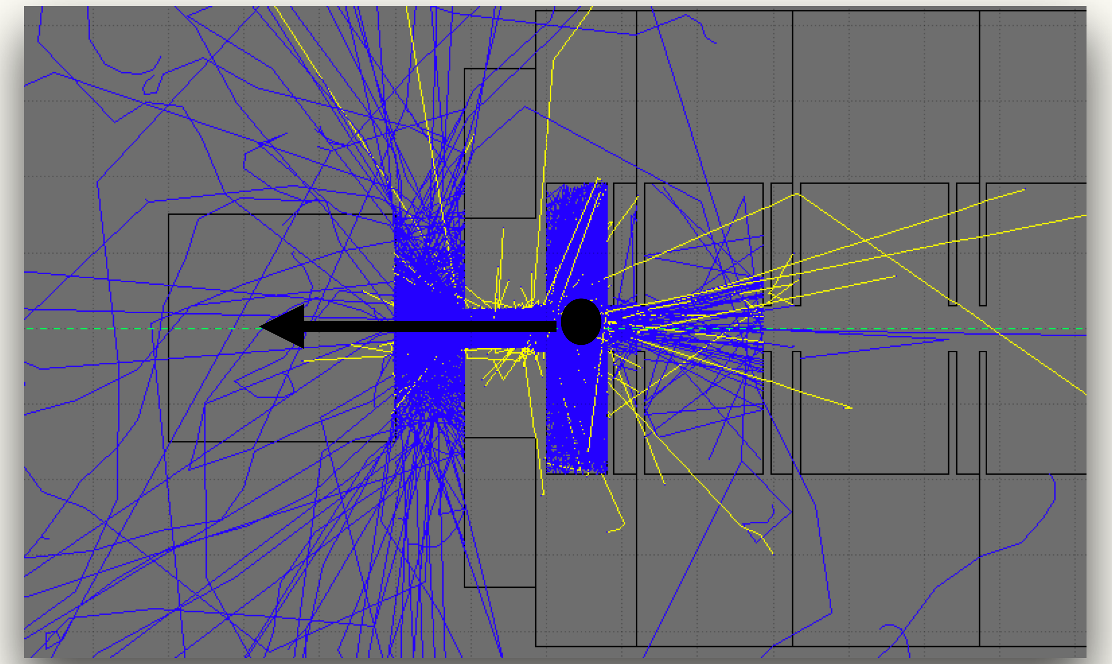
Radioprotection studies

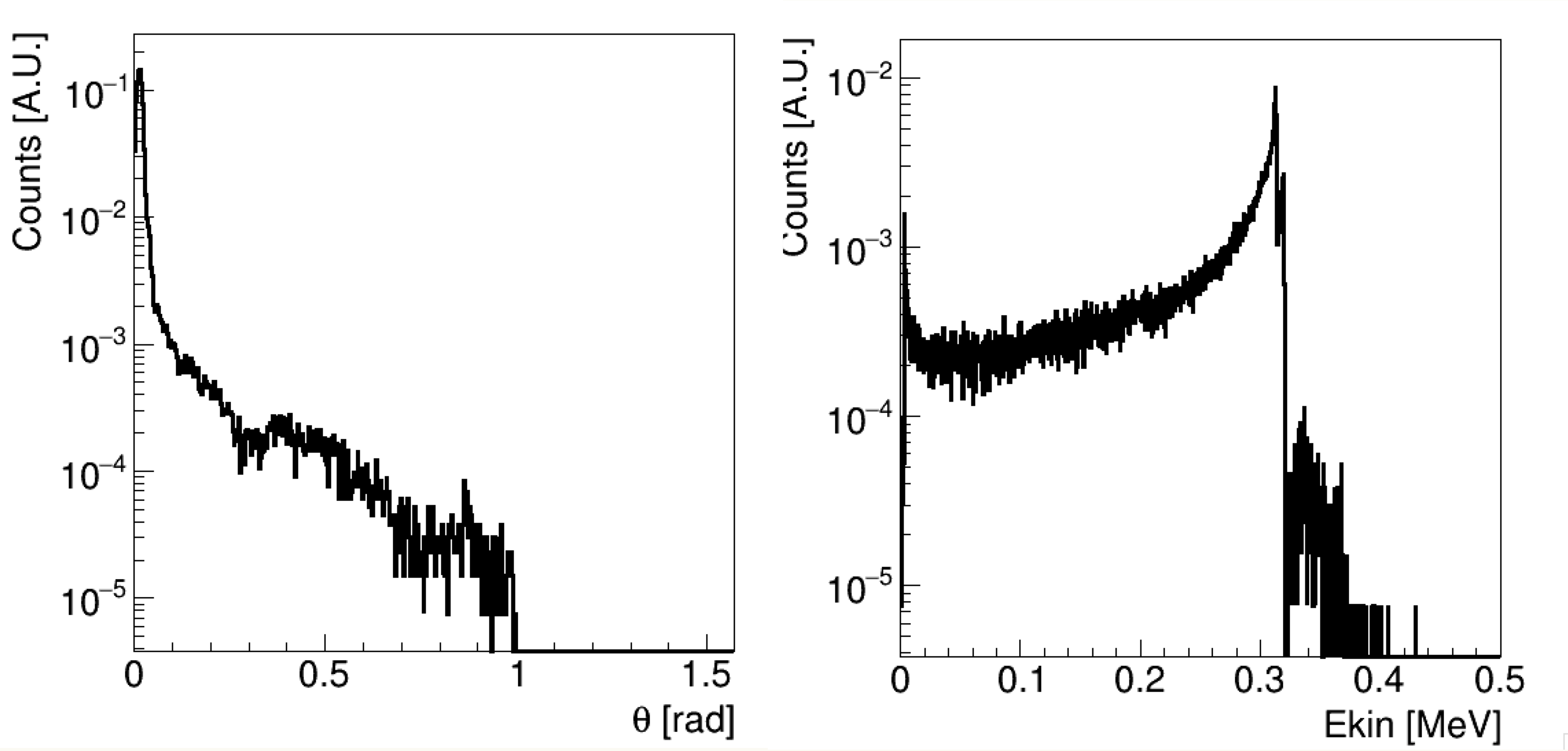
Cathode (Ba)



Backscattered primaries evaluation

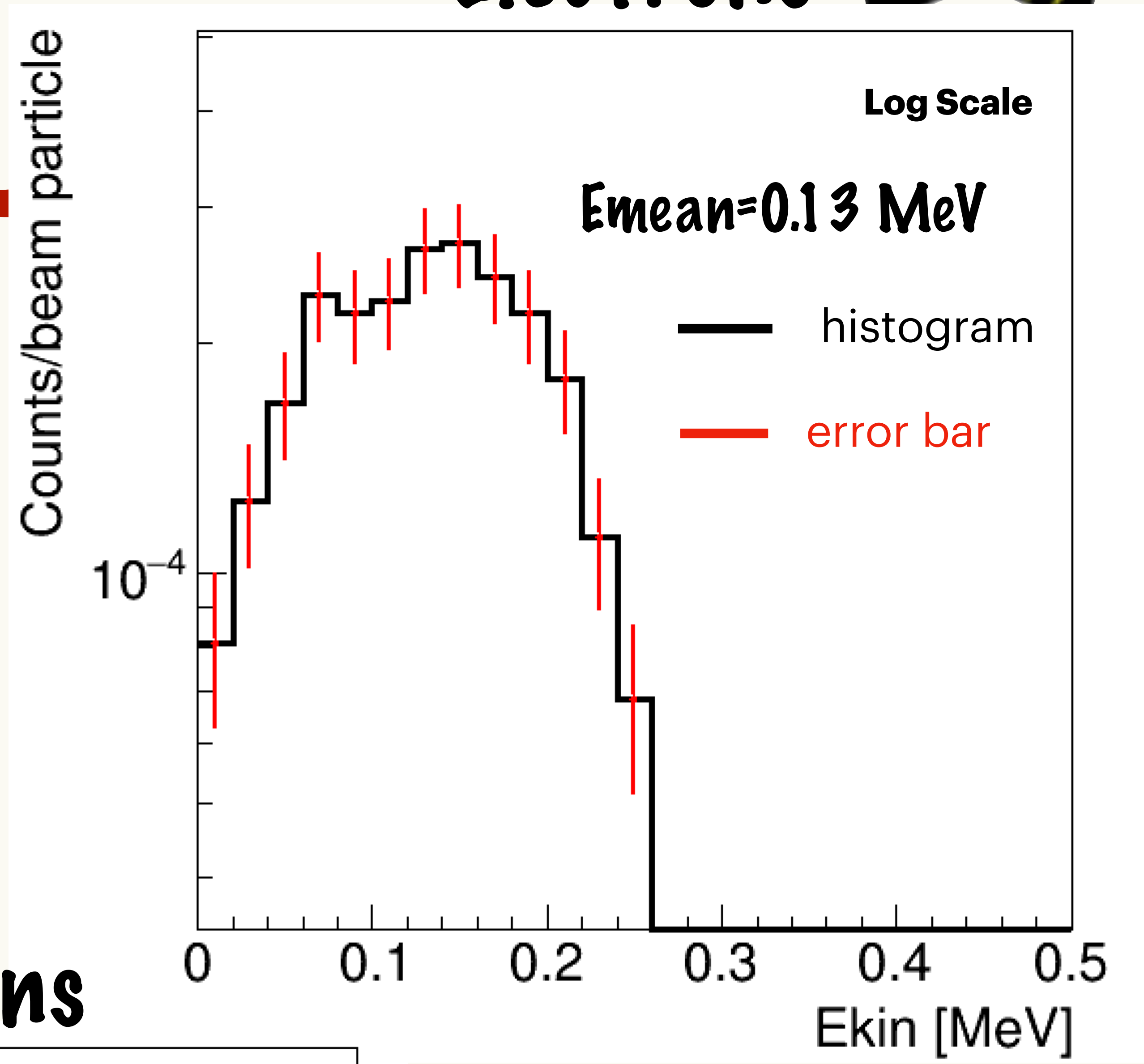
Inside the SW structure, approximately **half of the particles** within the first cell will experience a decelerating electric field and are **transported backward towards the cathode**.



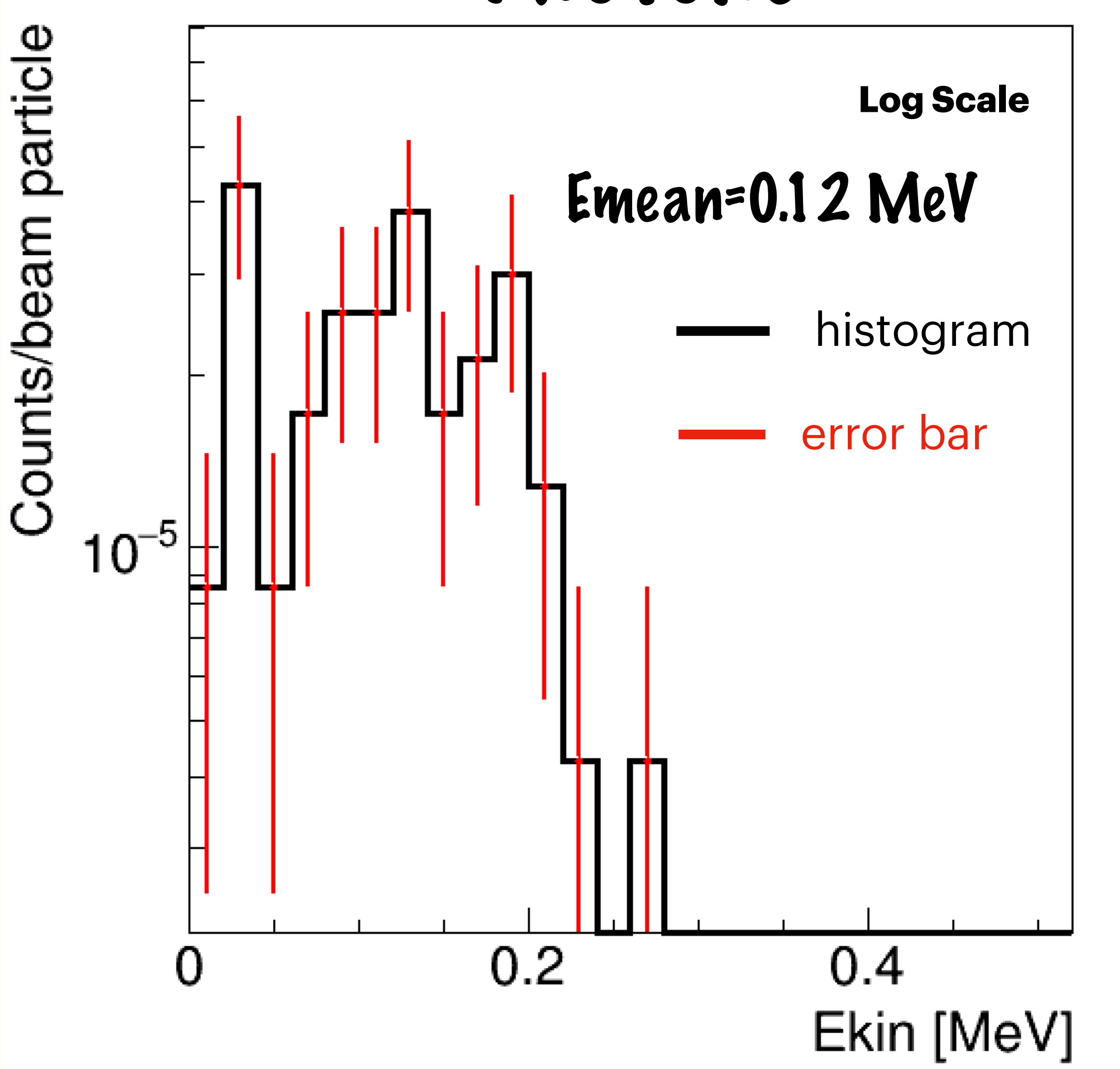


They travel in the **opposite direction** to the accelerated beam and that their **energy distribution** is, at most, that of the particles accelerated forward from the second cavity onwards.

Electrons



Photons



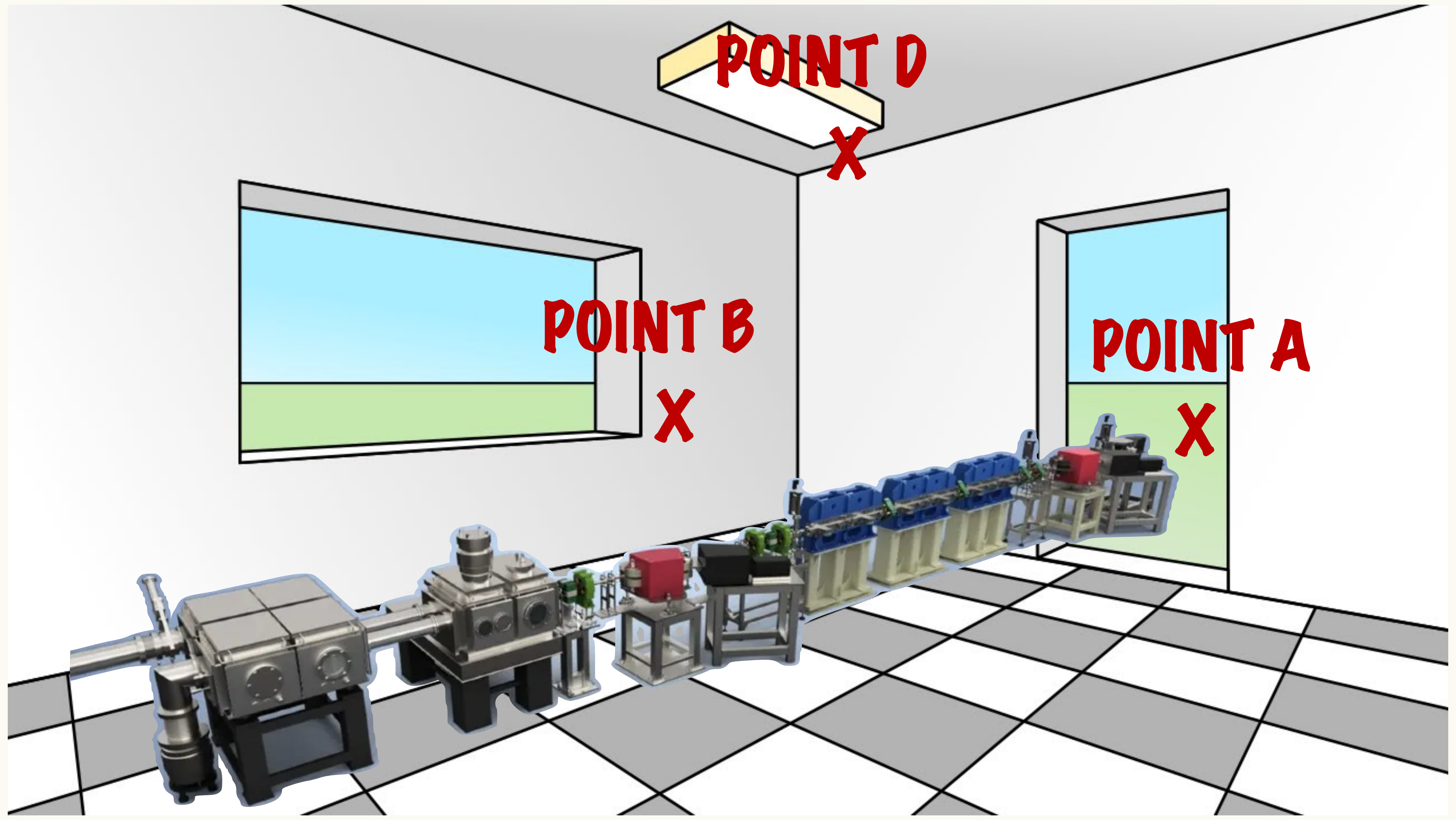
The majority are **absorbed by the materials composing the accelerator** (copper and steel) and by the cathode (barium).

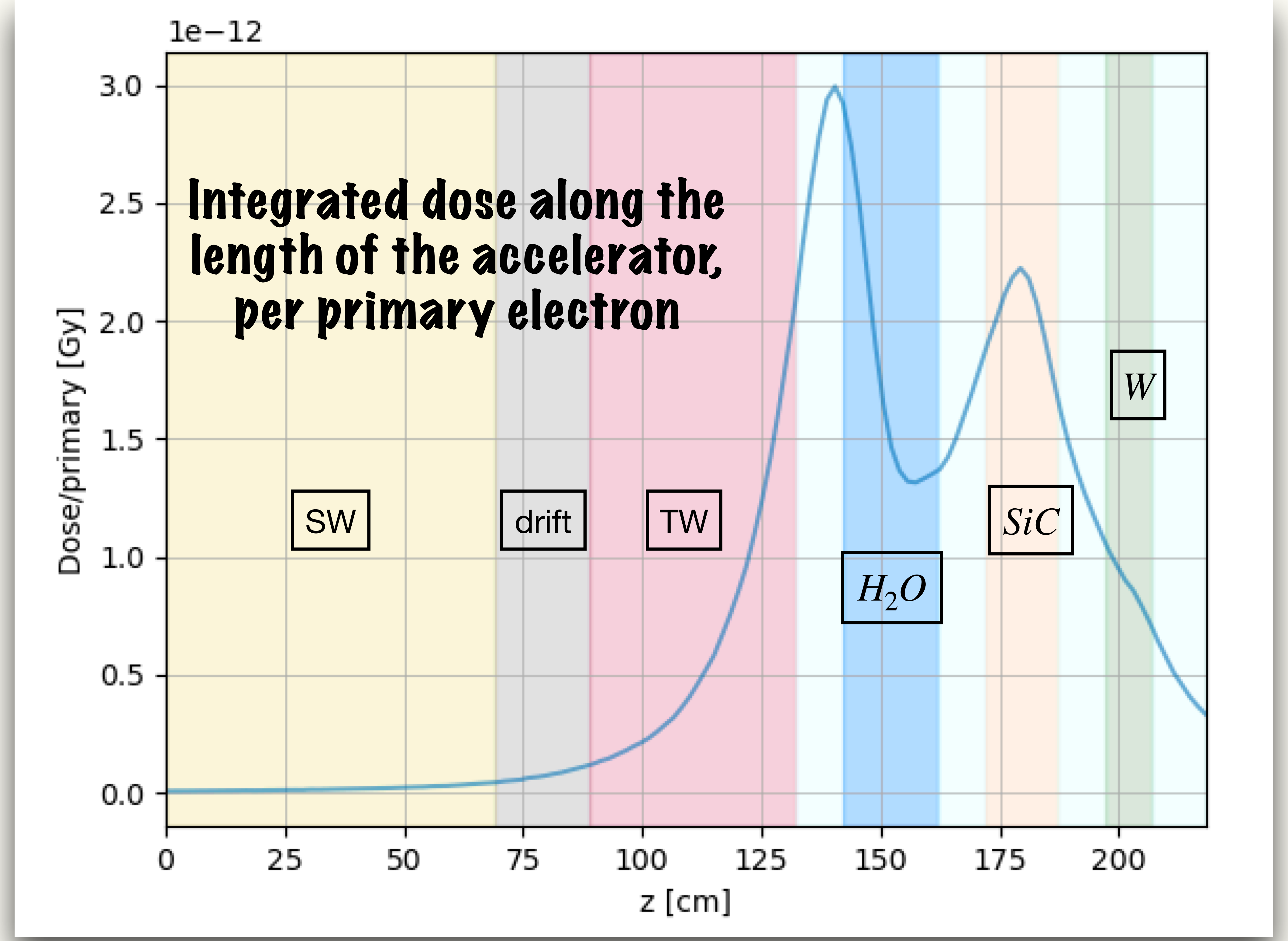
Radioprotection studies

The simulation results provided insights into the **dose delivered to the surrounding air** by the particles exiting the accelerator, as well as the dose **deposited** by the focused primary beam in the region **beyond the exit window.**

The dose was then evaluated at **4 key positions**:

- A : 180 cm from W block
- B & C: laterally 170 cm from the beam axis;
- D: 230 cm above the beam axis.





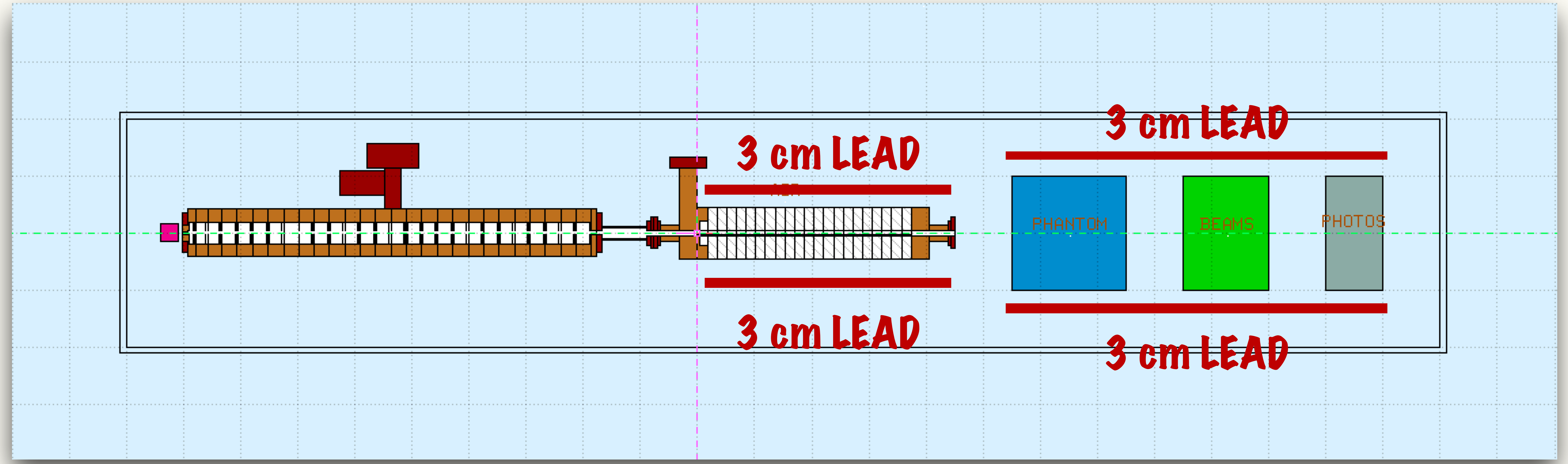
POINT A	POINT B	POINT C	POINT D
$9.73 \cdot 10^{-18} Gy/p$	$7.28 \cdot 10^{-18} Gy/p$	$7.82 \cdot 10^{-18} Gy/p$	$3.86 \cdot 10^{-18} Gy/p$

Radioprotection studies

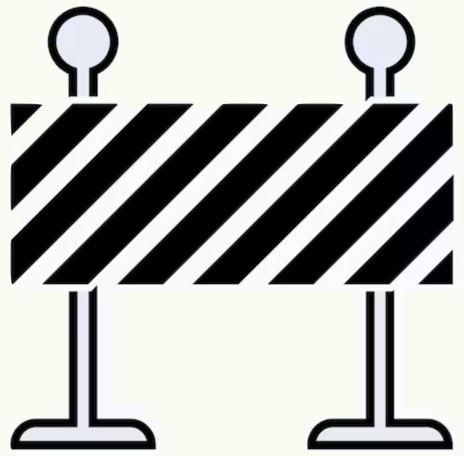
Based on these values, assuming a **workload of 3 days per week** with a number of pulses appropriate for the machine's use, **radiation shielding barriers were calculated** to reduce these values and comply with the legal limits.

$$B = \frac{P}{T}\frac{d^2}{WUT}$$

- P: Shielding design goal
- d^2: Distance from the source
- T: Occupancy factor
- W: Workload
- U: Use factor
- T: Occupancy factor



The resulting barriers were determined to be **3 cm of lead around the final section** of the LINAC.



	POINT A	POINT B	POINT C	POINT D
NO SHIELDING	$9.73 \cdot 10^{-18} Gy/p$	$7.28 \cdot 10^{-18} Gy/p$	$7.82 \cdot 10^{-18} Gy/p$	$3.86 \cdot 10^{-18} Gy/p$
3 cm SHIELDING	$3.75 \cdot 10^{-18} Gy/p$	$5.99 \cdot 10^{-19} Gy/p$	$8.49 \cdot 10^{-19} Gy/p$	$3.48 \cdot 10^{-19} Gy/p$

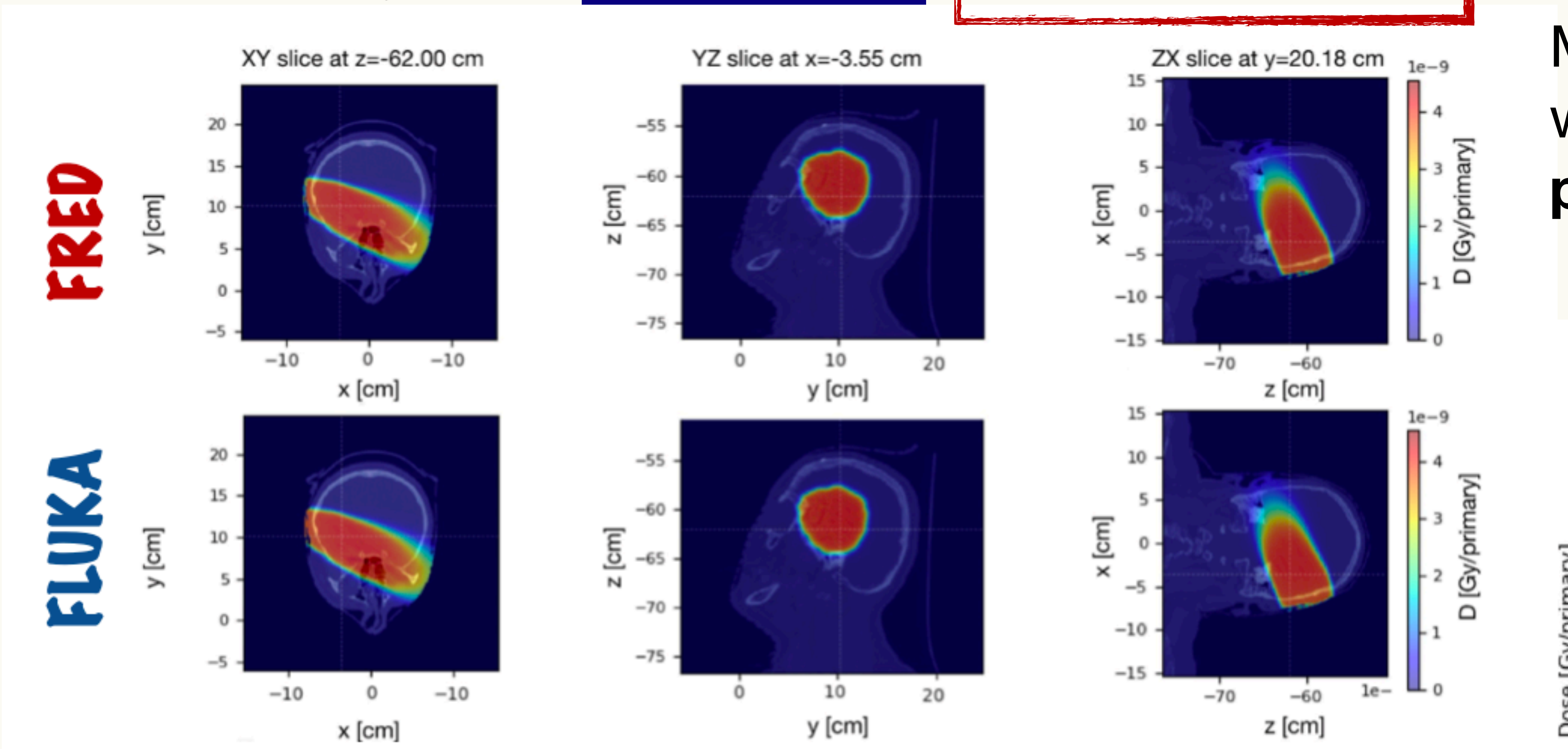
CRITICAL POINT

FRED dose engine

SAPIENZA UNIVERSITÀ DI ROMA

The majority of the TPS softwares use an **analytical** dose evaluation approach, which may be **not so accurate**. However the computational cost of the problem didn't allow so far to make a more precise calculation. Our solution is to use **FRED**.

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

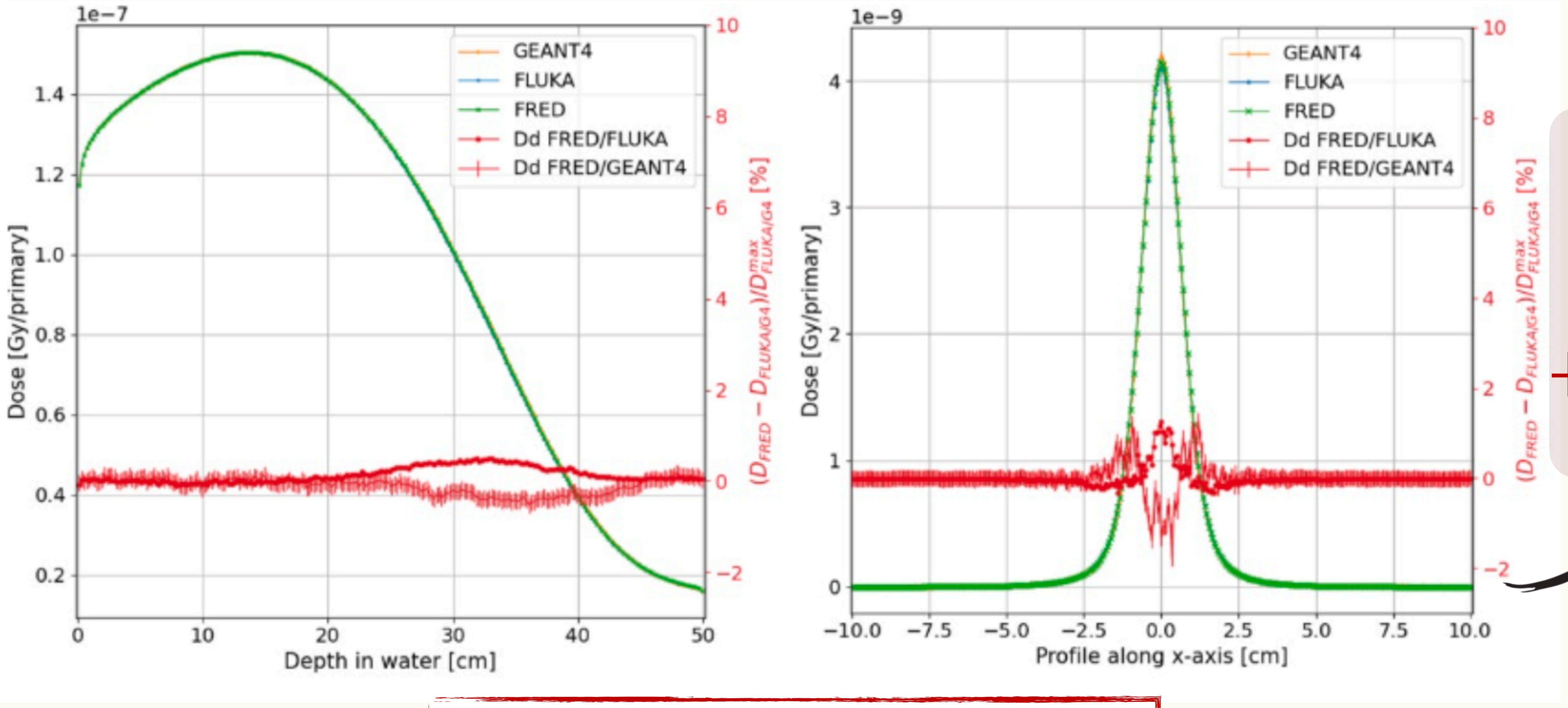


Developed to work on GPU

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

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**.

100 MeV Electron beam



Longitudinal and lateral dose profiles

Dose difference:

- • • • • FRED vS FLUKA
- ++++++ FRED vS GEANT4

TPS for FLASH

M1

Meningioma: three fields were used, with a prescription to the **PTV of 54Gy(RBE)** in **27 fractions**.

Patient M1		
Organ	**Dosimetric constraint**	**Volume [cc]**
PTV	$V_{95\%}$>95%,D_{max} ≤105%	20.71
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)	0.45
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

C1

Chordoma: four fields were used, with a prescription to the **PTV of 54Gy(RBE)** in **30 fractions**.

Patient C1		
Organ	**Dosimetric constraint**	**Volume [cc]**
PTV	$V_{95\%}$>95%,D_{max} ≤107%	99.15
PTV boost	$V_{95\%}$>95%,D_{max} ≤107%	71.94
Brainstem	$D_1 \leq 55$ Gy(RBE)	27.09
Spinal cord	$D_1 \leq 54$ Gy(RBE)	8.25
Parotid glands	$D_{mean} \leq 26$ Gy(RBE)	26.26
Middle ears	$D_{mean} \leq 30$ Gy(RBE)	3.80
Cochlea	$D_{mean} \leq 35$ Gy(RBE)	0.35

The clinical proton plans delivered to the patients were sent to the Medical Physics Unit of Policlinico Umberto I in Rome to carry out the **IMRT treatment planning**, together with the dose prescriptions, the details about the OARs constraints, and the CT imaging data.

TPS for FLASH

M1

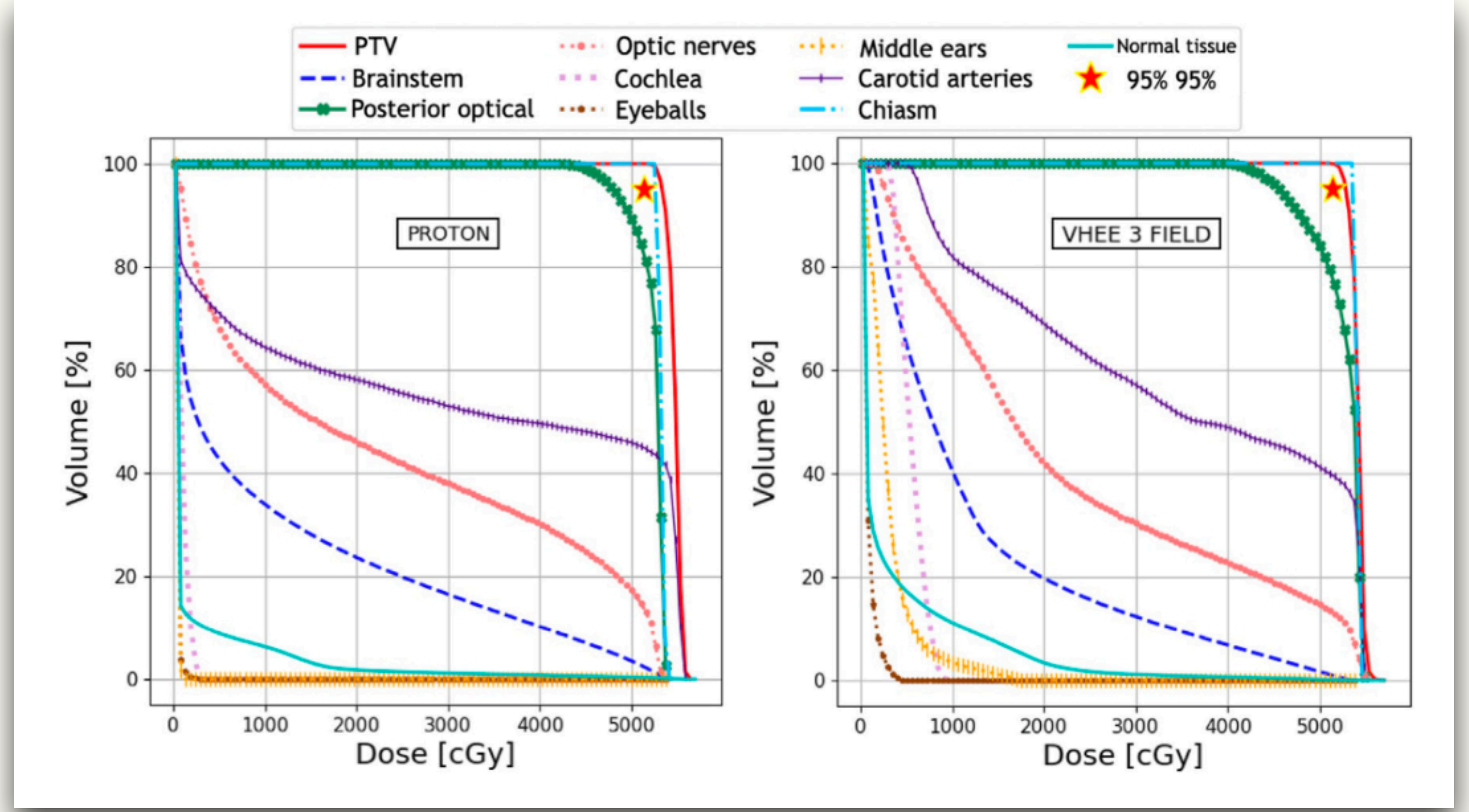
Meningioma: three fields were used, with a prescription to the **PTV of 54Gy(RBE)** in **27 fractions**.

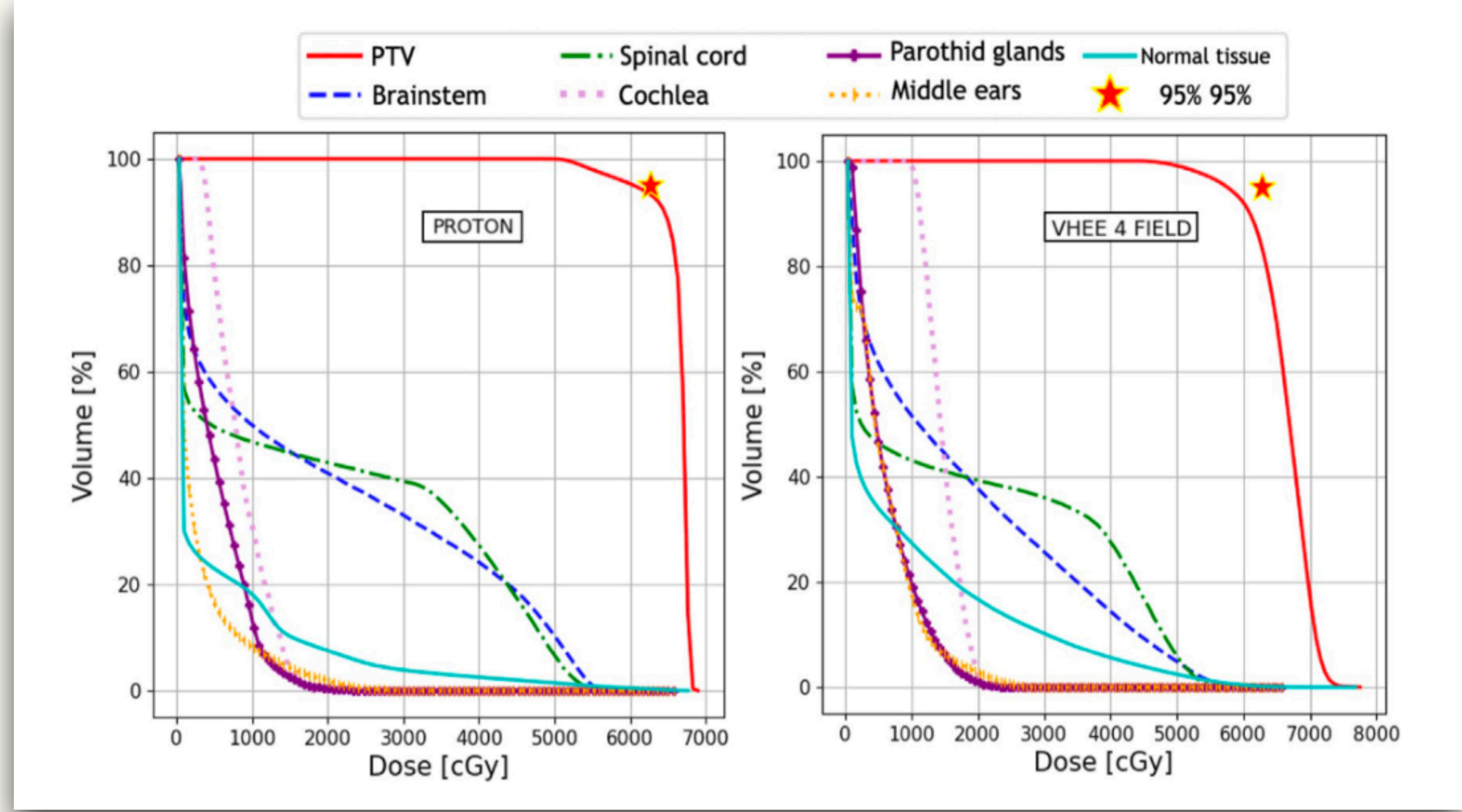
- **1st configuration:** 3 fields [110, 110, 100] MeV;
- **2nd configuration:** 7 fields [90, 100, 100, 110, 100, 100, 90] MeV;

C1

Chordoma: four fields were used, with a prescription to the **PTV of 54Gy(RBE)** in **30 fractions**.

- **1st configuration:** 4 fields [120, 90, 90, 120] MeV;
- **2nd configuration:** 7 fields [120, 80, 60, 60, 60, 60, 90] MeV;



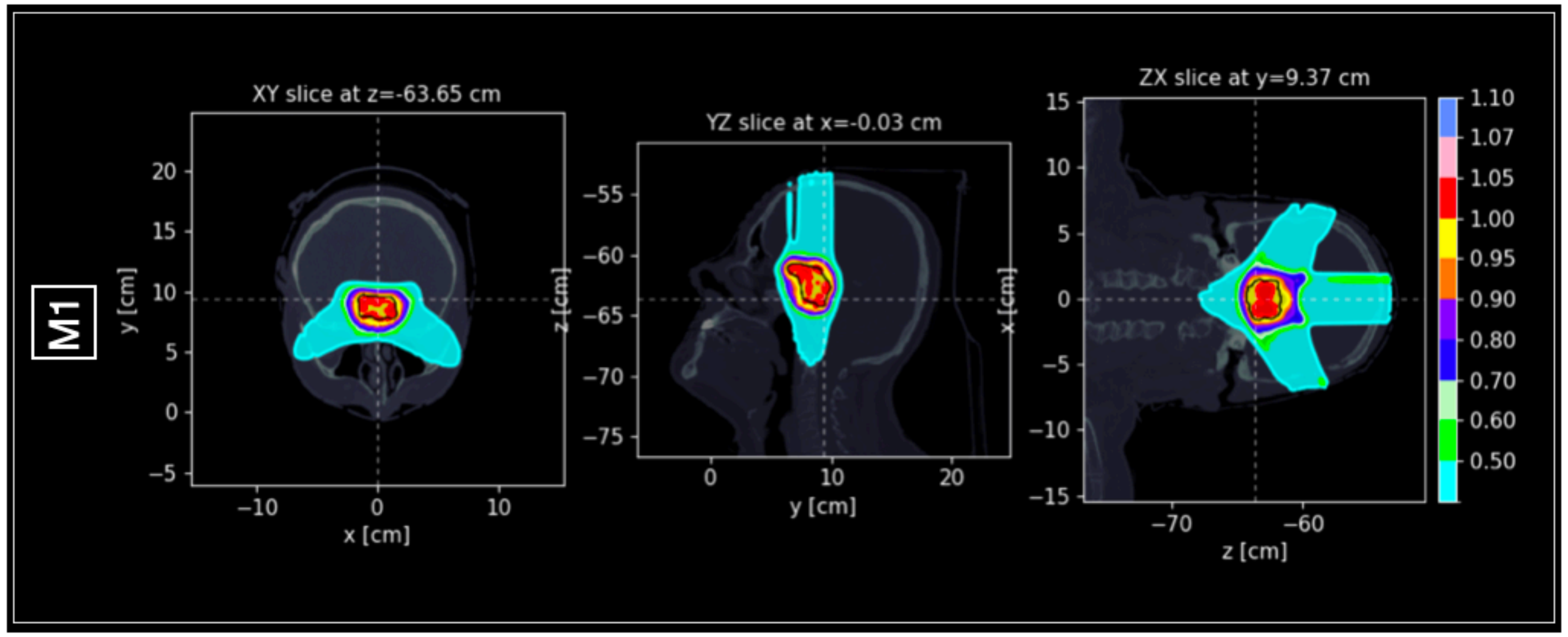


TPS for FLASH

M1

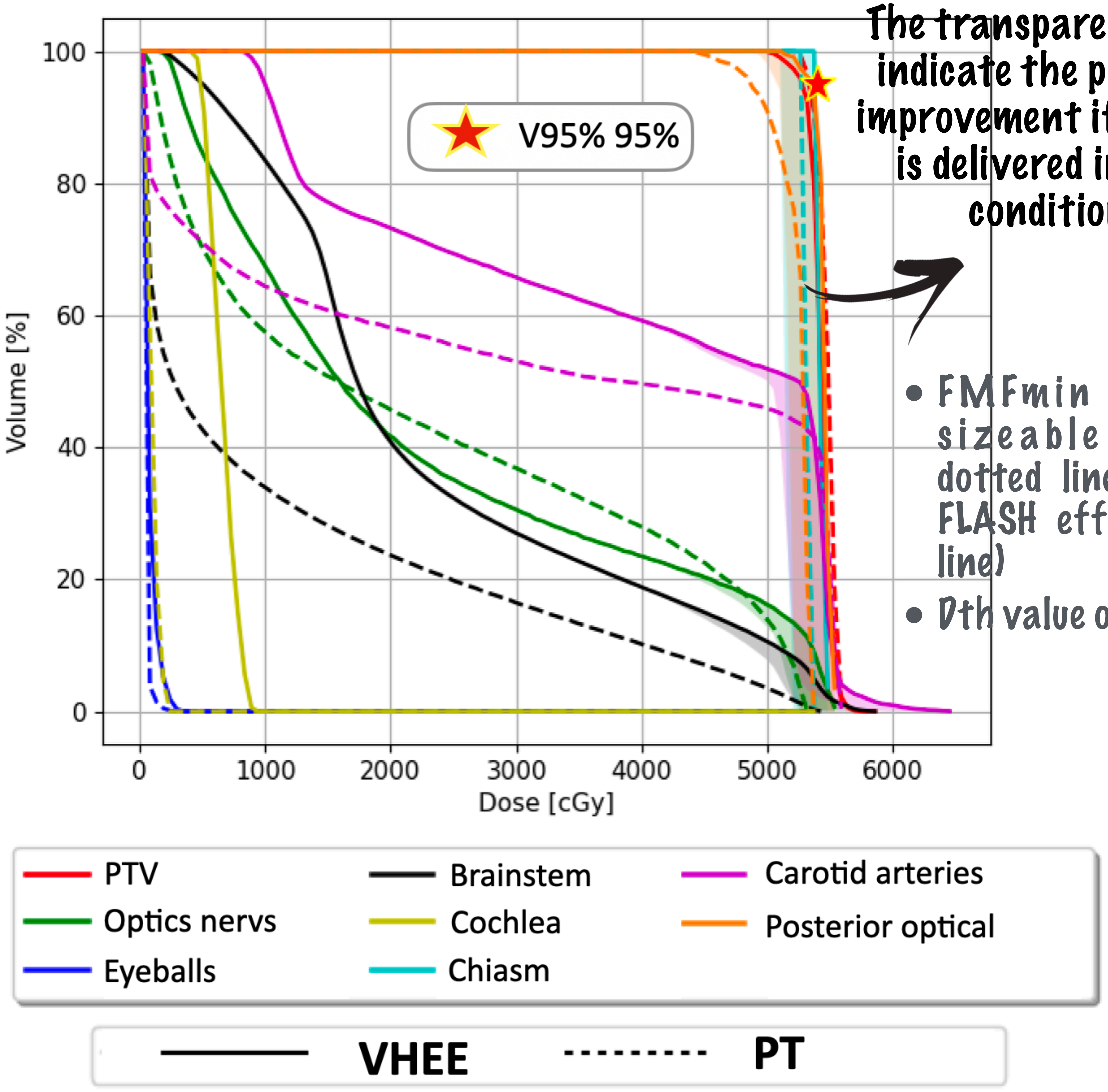
Meningioma: three fields were used, with a prescription to the **PTV of 54Gy(RBE)** in **27 fractions**.

- **1st configuration:** 3 fields [110, 110, 100] MeV;
- **2nd configuration:** 7 fields [90, 100, 100, 110, 100, 100, 90] MeV;



Isodose maps are graphical representations that show curves connecting points in space where the dose is constant, in this way it is possible to display the contours of regions where the dose reaches a predefined value.

FLASH OPTIMIZATION



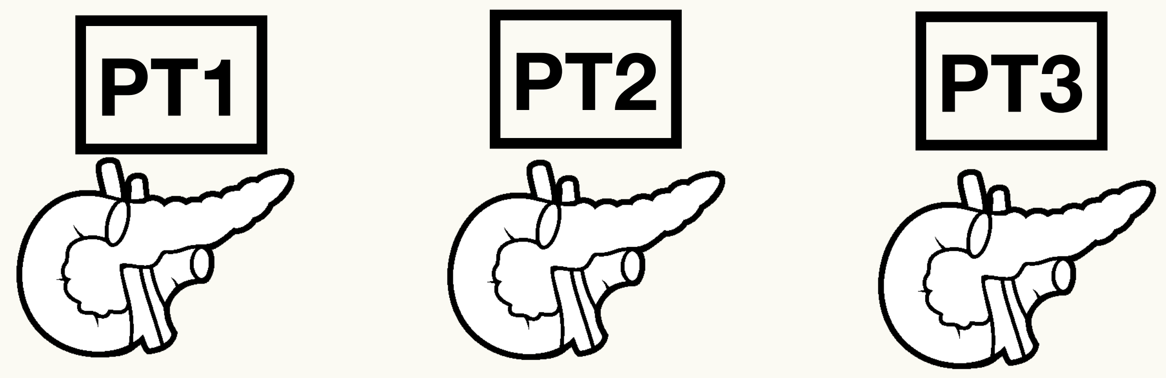
The transparent bands indicate the potential improvement if the plan is delivered in UHDR conditions.

- FMFmin = 0.8 (a sizeable sparing, dotted line) to 1 (no FLASH effect in solid line)
- Dth value of 40 Gy.

TPS for FLASH

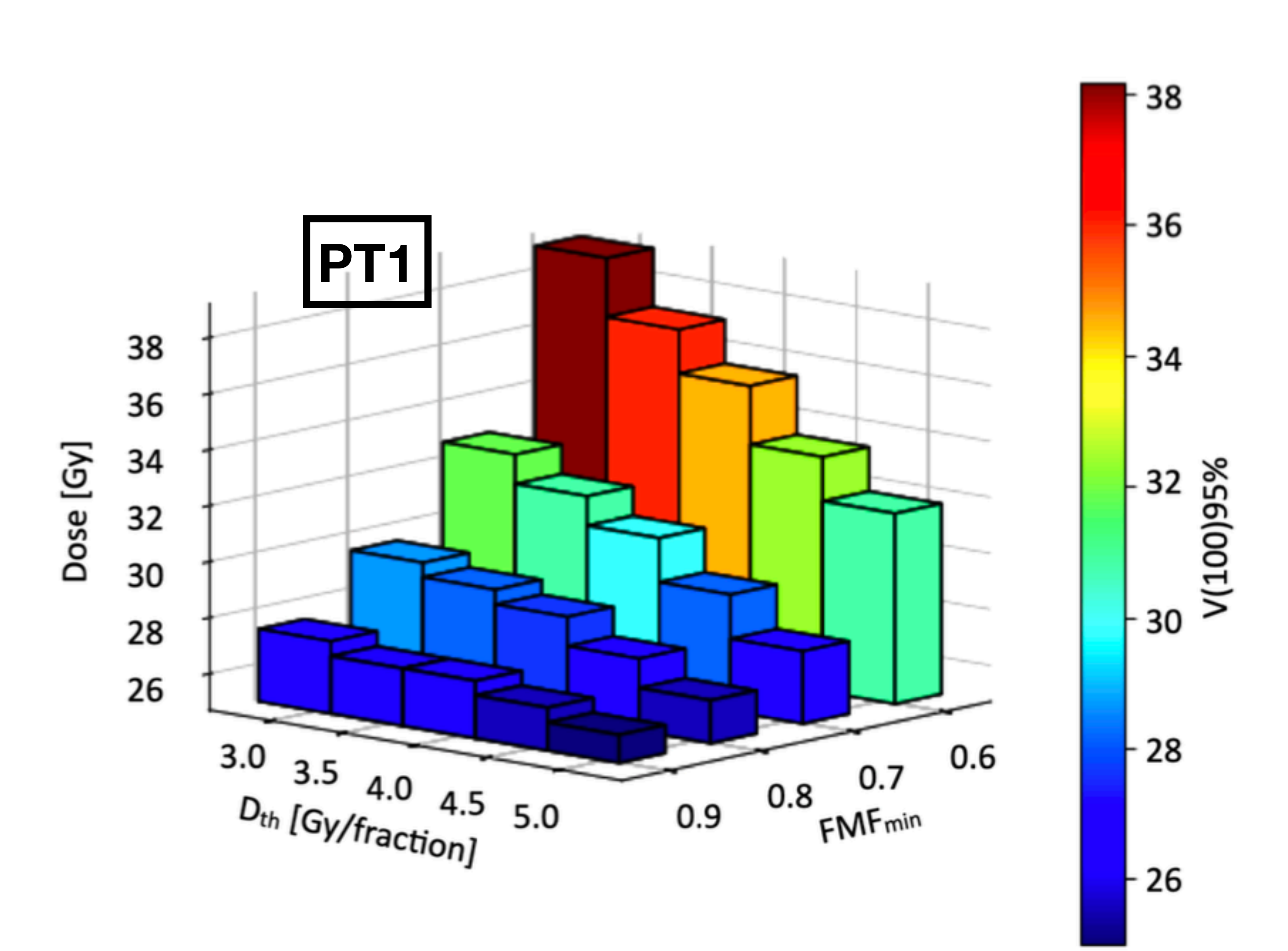
The TPS is crucial for pancreatic tumors as it enables precise dose delivery to the tumor while **minimizing radiation-induced toxicity to the nearby duodenum**. This approach enhances treatment efficacy by targeting the tumor effectively and reducing harmful side effects.

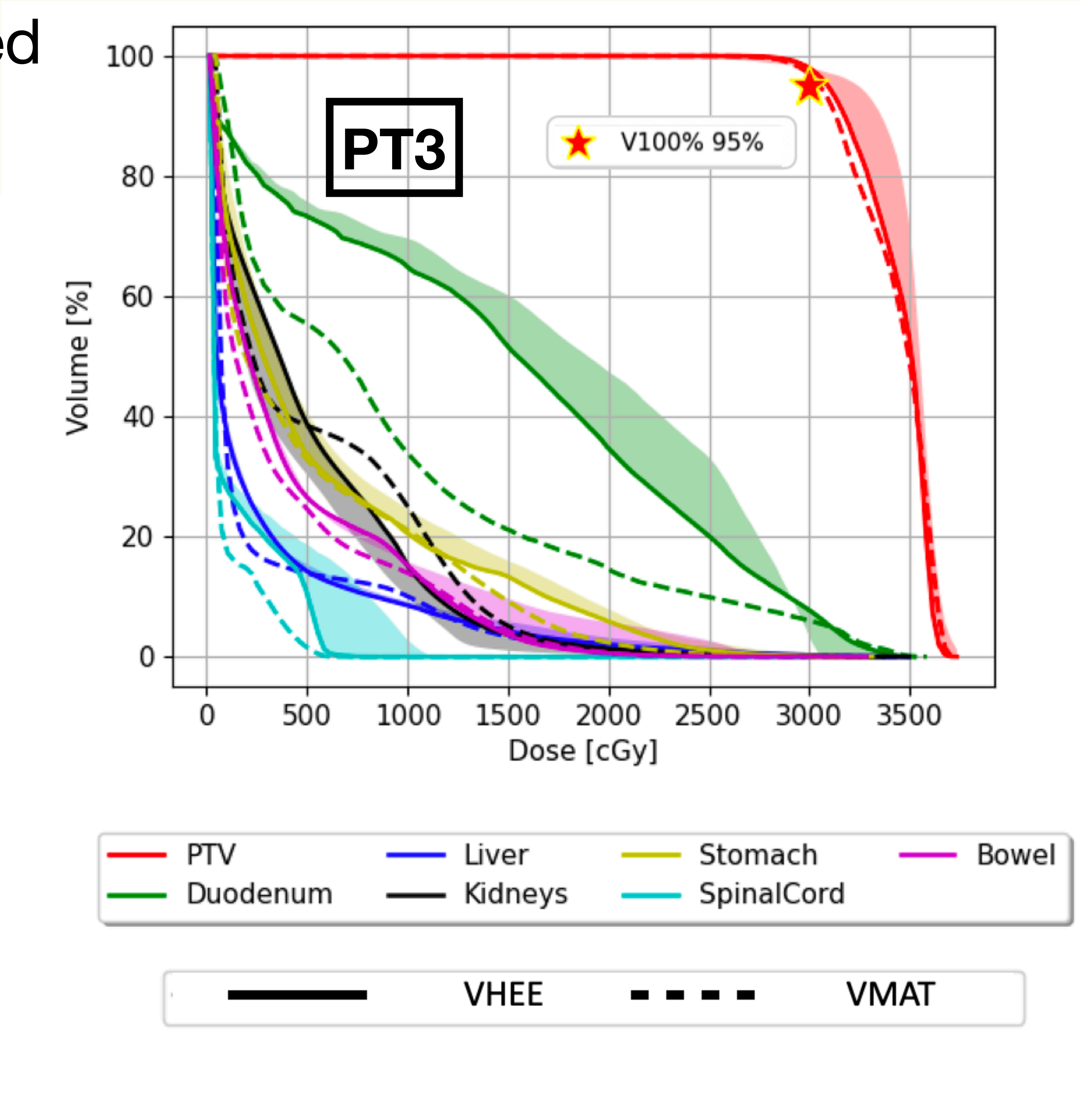
BEST CANDIDATE FOR FLASH IRRADIATION!



- **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**.

- 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.





Conclusions and future steps

1. **Radioprotection Studies for the LINAC:** being constructed as part of the SAFEST project. I conducted an analysis of simulation results on interactions between the primary beam and accelerator materials to determine the shielding thickness required to reduce dose levels in the surrounding environment.

2. **Development of a TPS for VHEE in FLASH Mode:** I developed software capable of optimizing, through various methods, the dose absorbed by the tumor and surrounding healthy organs to output the accelerator's setting parameters for treatment. Several feasibility studies were conducted on patient data provided by various hospitals.

Suitability of VHEE for both intracranial lesions and pancreatic cancer treatment. When compared to state of the art conventional radiotherapy, e.g. PT and VMAT plans, **VHEE show a comparable performance** even without reaching the UHDR regimen required to trigger the FLASH effect. Under a few plausible assumptions on the conditions required to trigger the FLASH effect, the results demonstrated that it should be possible to escalate the dose at the PTV without worsening the OARs injury.

Treatment planning of intracranial lesions with VHEE: comparing conventional and FLASH irradiation potential with state-of-the-art photon and proton radiotherapy

A. Muscato[1,2,3] L. Arsini[2,4] G. Battistoni
D. Carlotti[4,6] F. De Felice[7] A. De Gregorio[4,2*] M. De Simoni[2,8]
C. Di Felice[9] Y. Dong[5] G. Franciosini[1,2] M. Marafini[2,3]

PUBLISHED

In silico study for stereotactic body radiotherapy of pancreatic cancer: can FLASH planning with very high energy electrons improve the therapeutic ratio?

A. De Gregorio[e,b], A. Muscato[b,h], D. Carlotti, M. Fiore[c,f], G. Franciosini[a,b,*], T. Insero[c], M. Marafini[g,b], V. Marè[c], V. Patera[a,b], S. Ramella[c,f], A. Schiavi[a,b], M. Toppi[a,b], G. Traini[b], A. Trigilio[d], A. Sarti[a,b]

SUBMITTED

Perspectives in linear accelerator for FLASH VHEE: Study of a compact C-band system

PUBLISHED

L Faillace [1], D Alesini [2], G Bisogni [3], F Bosco [4], M Carillo [4], P Cirrone [5], G Cuttone [5], D De Arcangelis [4], A De Gregorio [6], F Di Martino [7], V Favaudon [8], L Ficcadenti [4], D Francescone [4], G Franciosini [6], A Gallo [2], S Heinrich [8], M Migliorati [4], A Mostacci [4], L Palumbo [4], V Patera [4], A Patriarca [9], J Pensavalle [3], F Perondi [10], R Remetti [10], A Sarti [4], B Spataro [2], G Torrisi [5], A Vannozzi [2], L Giuliano [4]