FLASH Radiotherapy with hIgh
Dose-rate particle beAms

VHEE for the treatment of deep seated tumors: an update

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Trento 29/03/2023

VHEE potential

After having verified the potential of FLASH and conventional irradiation of prostate cancer, we have carried out a detailed study of intra-cranial lesions comparing the VHEE results with state-of-the-art irradiations performed with p and IMRT.

We chose a case of **meningioma** and **chordoma** to study the potential of VHEEs for those treatments in which adequate tumor coverage is complex to achieve because of the extreme proximity of PTV to OARs. In addition, intracranial lesions are a good example to the test the potential of conventional and FLASH irradiation in order to obtain additional sparing to the OARs that are currently limiting the dose prescription to the PTV.

published

Deep Seated Tumour Treatments With Electrons of High Energy Delivered at FLASH Rates: The Example of Prostate Cancer

Alessio Sarti[1,2], Patrizia De Maria[3], Giuseppe Battistoni[4], Micol De Simoni[2,5], Cinzia Di Felice[6], Yunsheng Dong[4], Marta Fischetti[1,2], Gaia Franciosini[2,5], Michela Marafini[2,7], Francesco Marampon[8], Ilaria Mattei[4], Riccardo Mirabelli[2,5], Silvia Muraro[4], Massimiliano Pacilio[6], Luigi Palumbo[1,2], Loredana Rocca[1], Damiana Rubeca[1], Angelo Schiavi[1,2], Adalberto Sciubba[1,9], Vincenzo Tombolini[8], Marco Toppi[1,9], Giacomo Traini[2], Antonio Trigilio[2,5] and Vincenzo Patera[1,2]*

submitted

frontiers

Treatment planning of intra-cranial lesions with VHEE: comparing conventional and FLASH irradiations potential with state-of-the-art RT and PT.

A. Muscato[9], G. Battistoni[8], L. Campana[9], D. Carlotti[2,11], F. De Felice[7], A. De Gregorio[2,3,*], M. De Simoni[12,3], C. Di Felice[7], Y. Dong[8], G. Franciosini[1,3], M. Marafini[5,3], I. Mattei[8], R. Mirabelli[1,3], S. Muraro[8], M. Pacilio[7], L. Palumbo[1,3], V. Patera[1,3], A. Schiavi[1,3], A. Sciubba[1,4], M. Schwarz[10], S. Sorbino[9], V. Tombolini[6], M. Toppi[1,3], G. Traini[3], A. Trigilio[2,3] and A. Sarti[1,3]

Intracranial lesions: C1&M1

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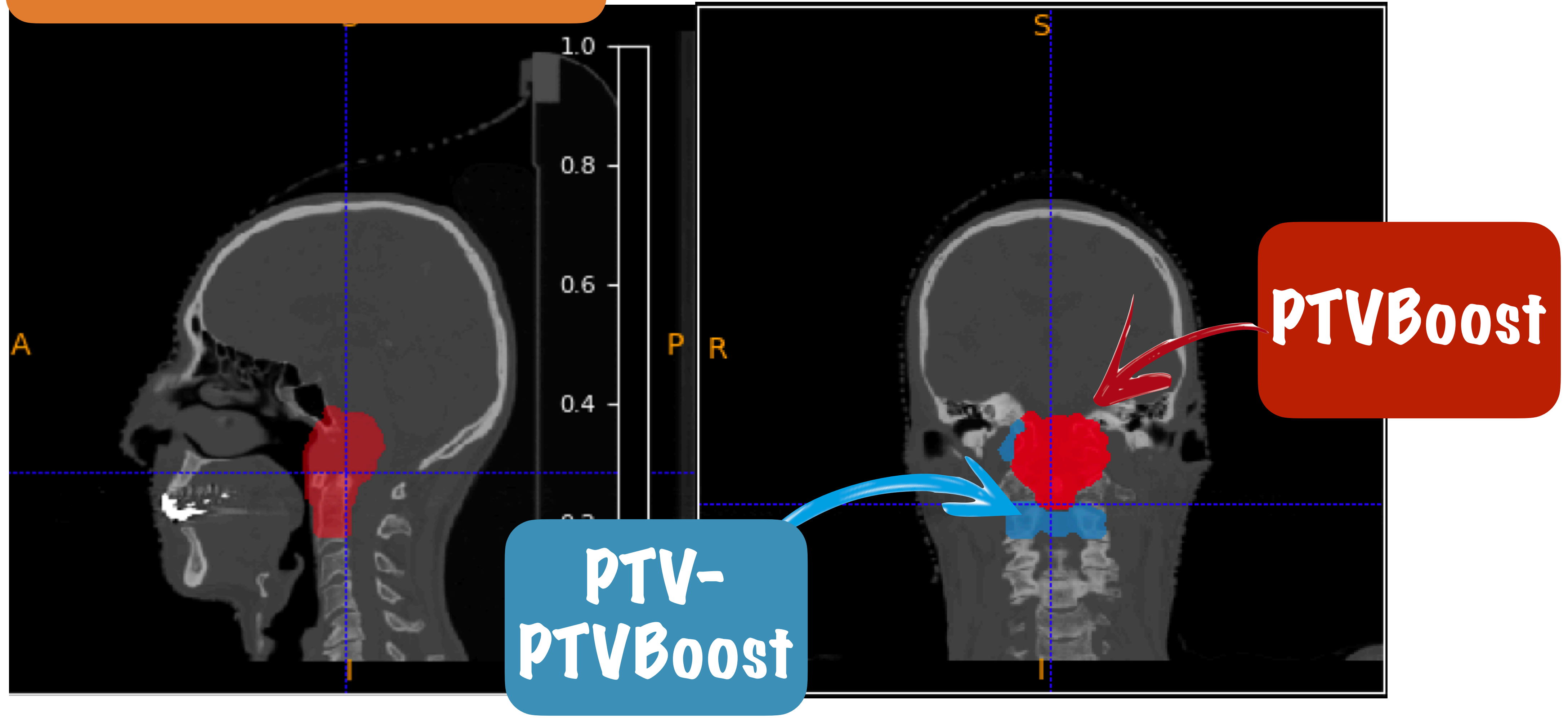
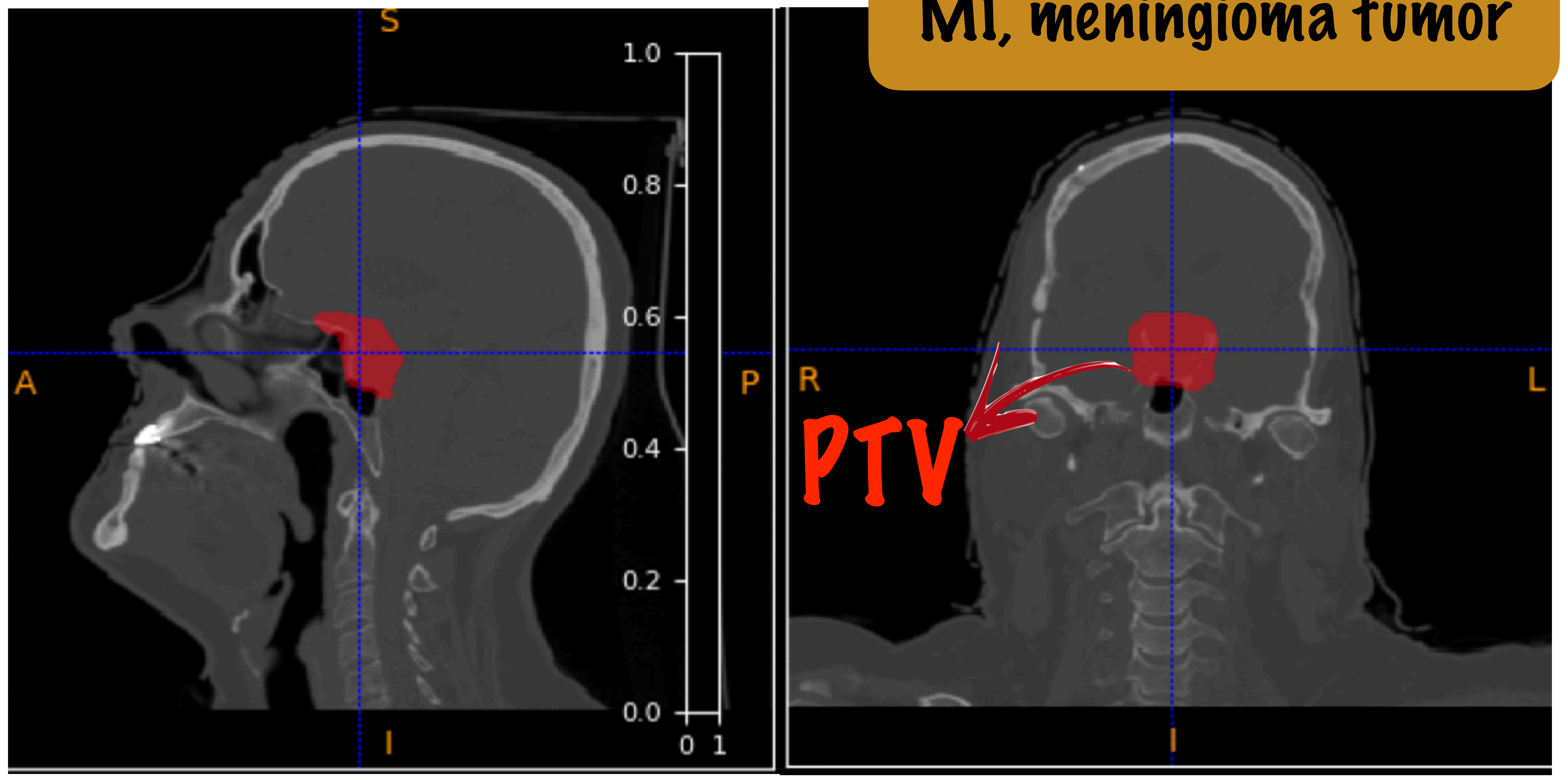
C1, chordoma tumor



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

Patient M1	dosimetric constraints
Target volume	$V_{95\%} > 95\%$, $D_{max} \leq 105\%$
Optic nerves	$D_1 \leq 54$ Gy(RBE)
Chiasm	$D_1 \leq 54$ Gy(RBE)
Posterior optical pathways	$D_1 \leq 54$ Gy(RBE)
Eyeballs	$D_1 \leq 40$ Gy(RBE)
Brainstem	$D_1 \leq 54$ Gy(RBE)
Cochlea	$D_{mean} \leq 35$ Gy(RBE)
Carotid arteries	$D_{max} \leq 105\%$

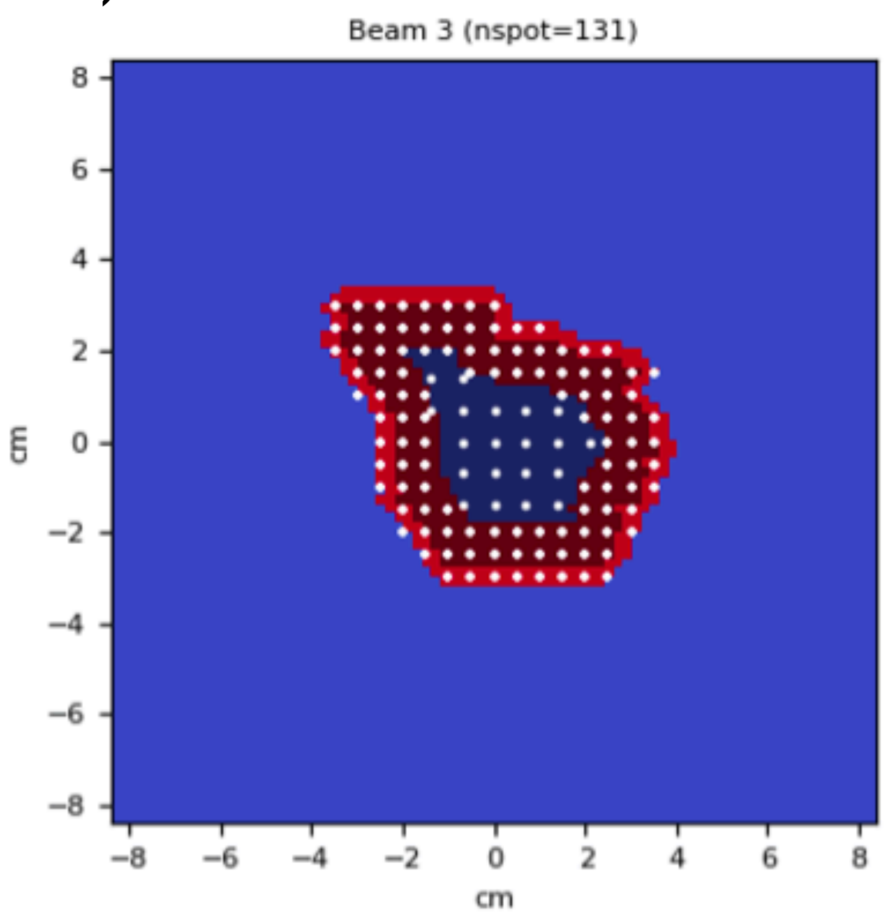
M1, meningioma tumor

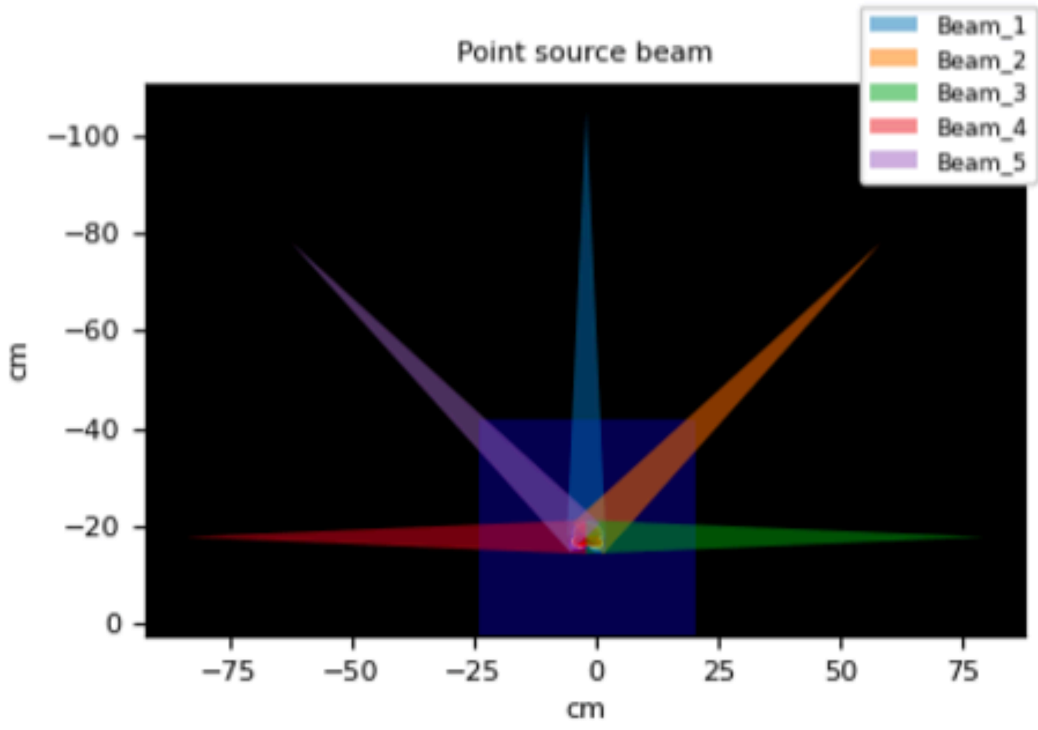


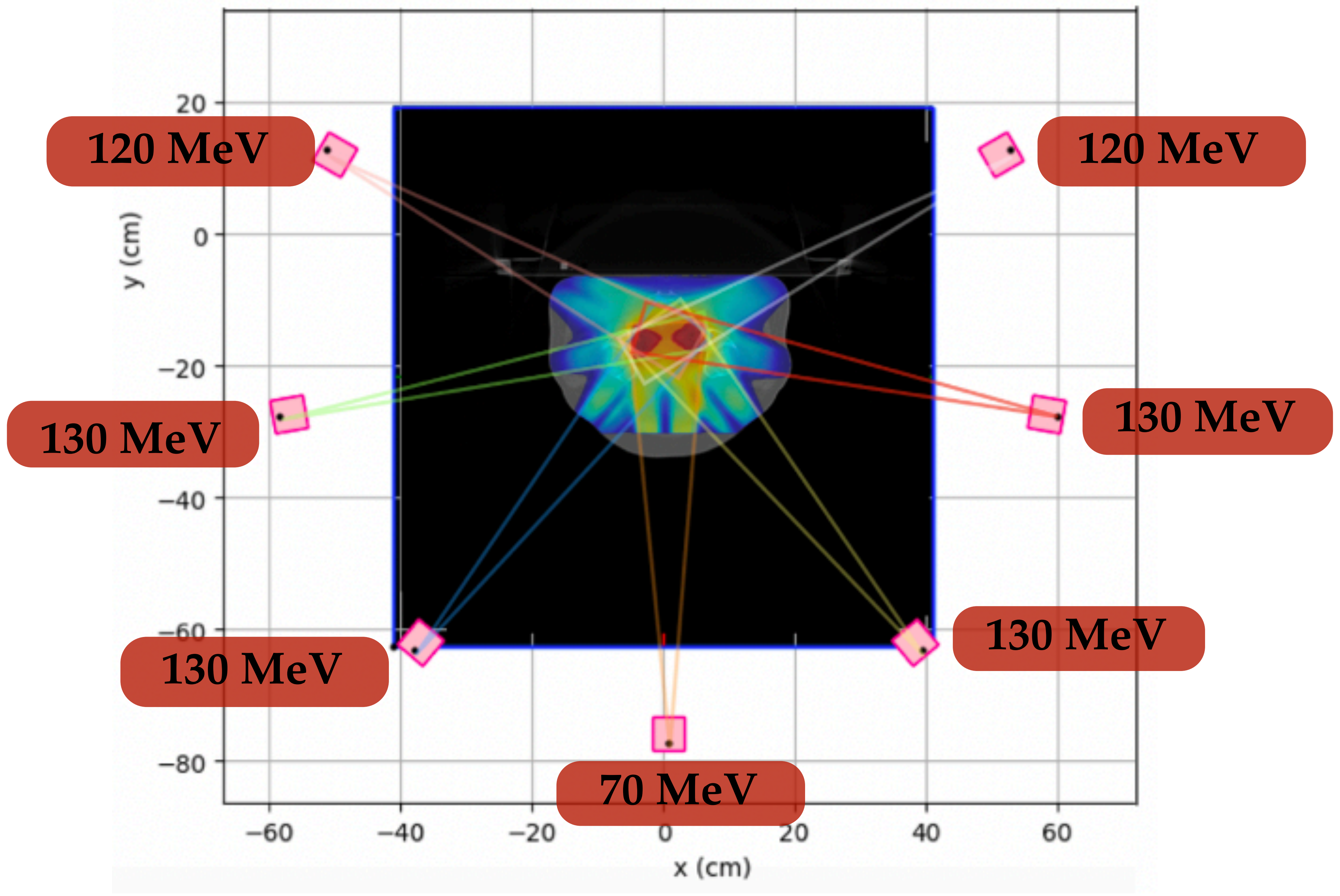
VHEE treatment plan

The very same approach already pursued in the planning of prostate cancer has been implemented and the input information came from APSS (proton plans) and Policlinico Umberto I (IMRT plans):

1. The **same equidistant fields** have been used for IMRT/proton and VHEE planning ;
2. VHEE beams have **transverse size of few mm** and a **negligible divergence**;
3. The electron pencil beam (PB) paints each irradiation field like in **active PB scanning techniques**;
4. The energy of each electron fields was chosen so to have the **maximum of dose release in the tumor center**;







With these assumption we performed a **FLUKA MC simulation**

OUTPUT

Dose map in Gy/primary units

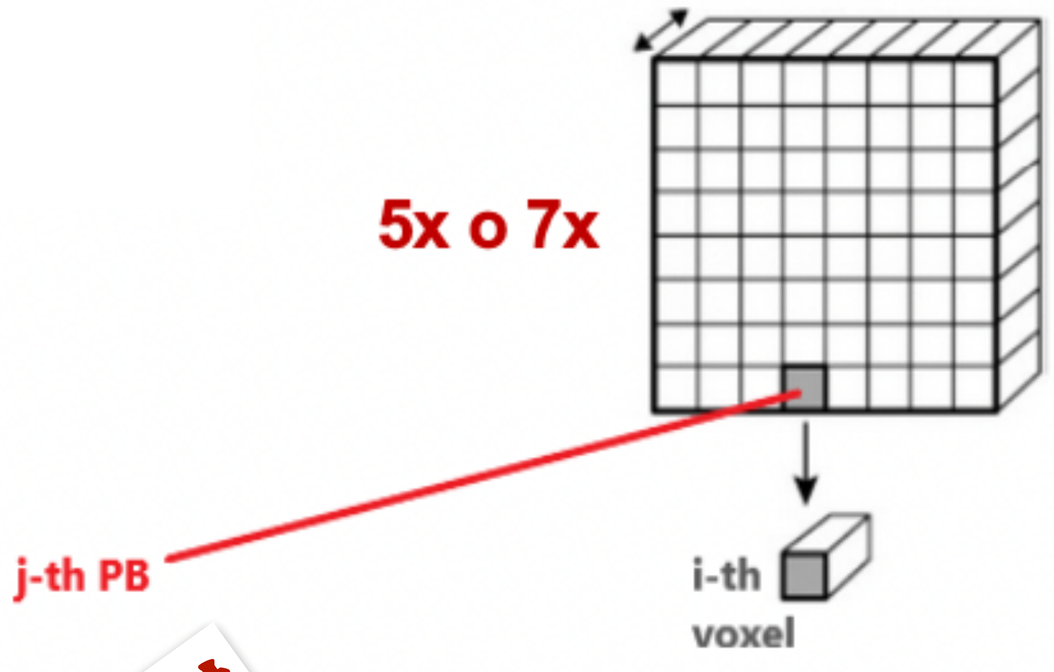
Treatment optimization

By optimizing the fluence of individual PBs, the optimizer searches for the global minimum of the following cost function:

Dose — Dose Goal — Plan factor — Voxel based

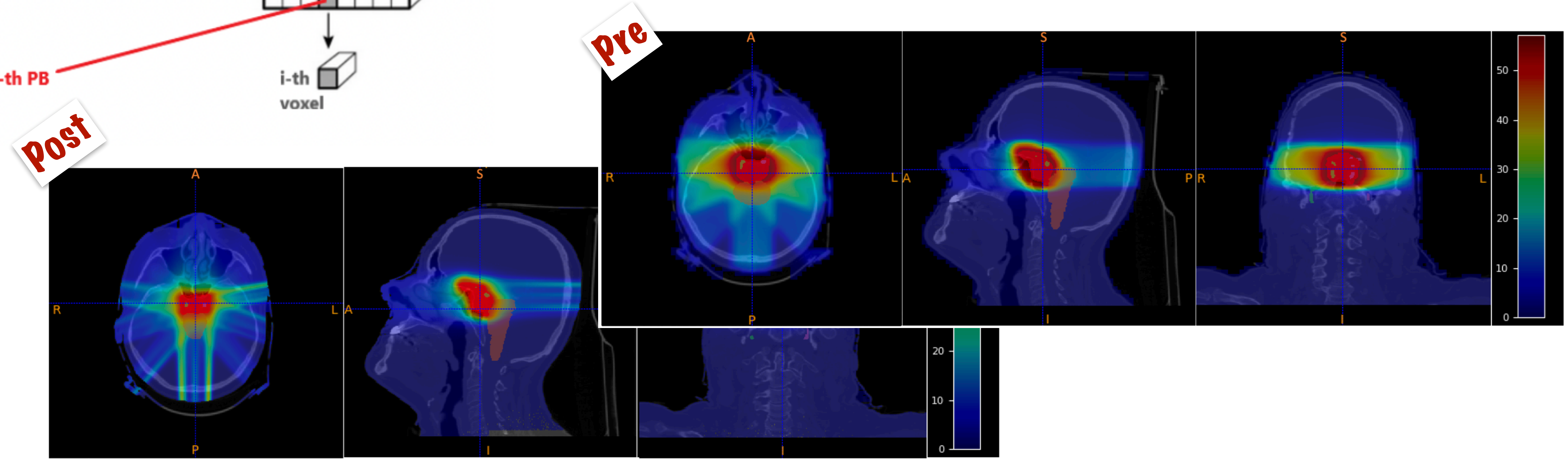
$$\chi^2 = \sum_{i \epsilon PTV} \omega_i \frac{(d_i - D_{PTV})^2}{d_i^2} + \sum_{i \epsilon OAR} \omega_i \frac{(d_i - D_{OAR})^2}{d_i^2} * g(d_i - D_{OAR})$$

- d_i, dose of i-th voxel
- w_i, weight of i-th voxel
- D_{PTV}, prescribed dose to PTV
- D_{OAR}, maximum allowable organ dose
- threshold of voxel in NoT
- red reduction voxel of NoT



Multiple PBs contribute to dose release in the i-th voxel:

$$d_i = \sum_{j=1}^{N_j} N_j D_{ij}$$



Treatment evaluation

Dose constraints for the PTV and the main OARs

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

The treatment plan is evaluated by analyzing the resulting **DVH** (Dose-Volume Histograms) and by verifying that the plan satisfies the **Dose-Volume constraints**.

Vxx < YY%: YY% of the referred organ or region must absorb less than XX Gy. D is the mean dose absorbed by a given organ

The DVH represents the 3D information of the **absorbed dose** (Gy or %) as a function of the **volume** (%) of the studied organs.

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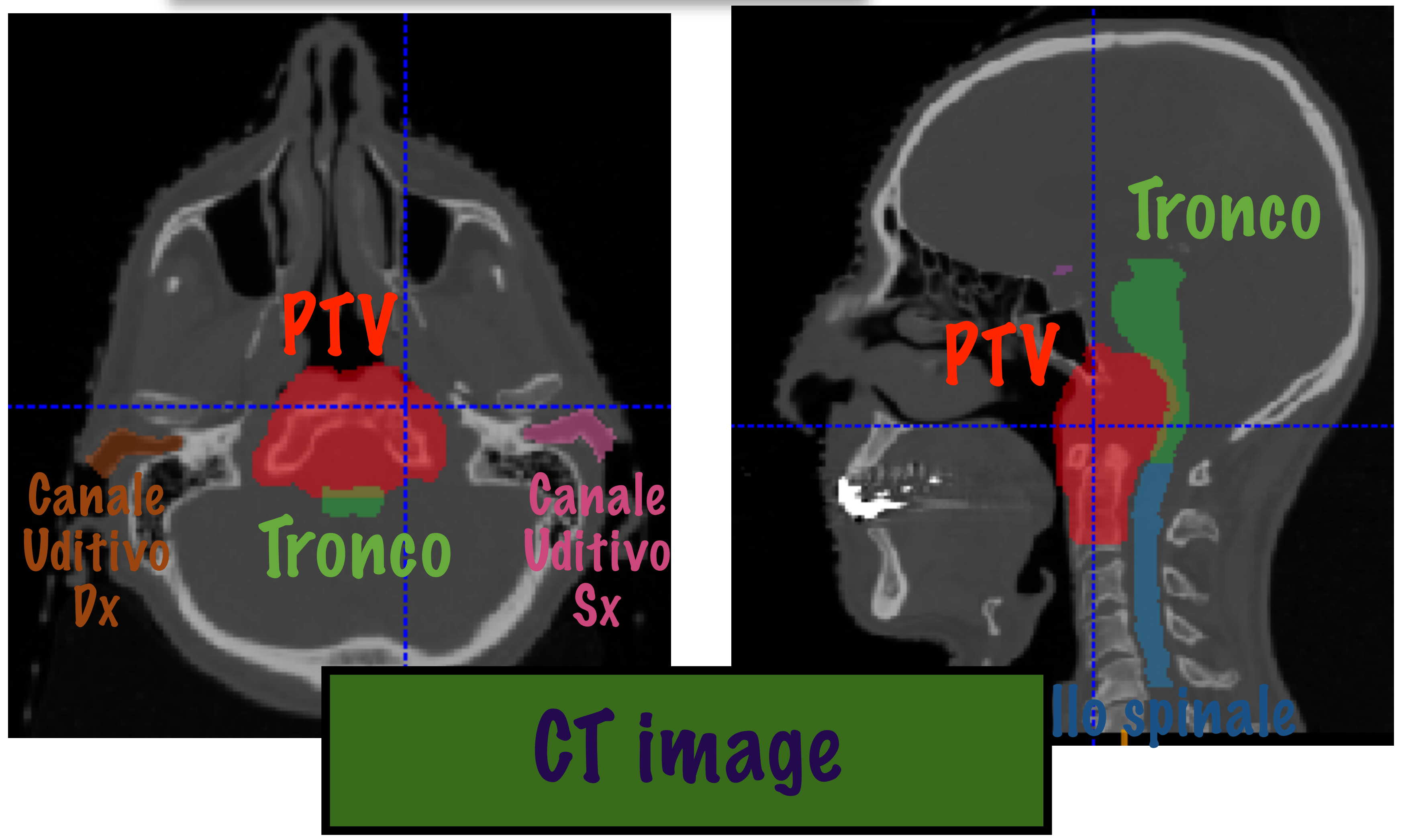
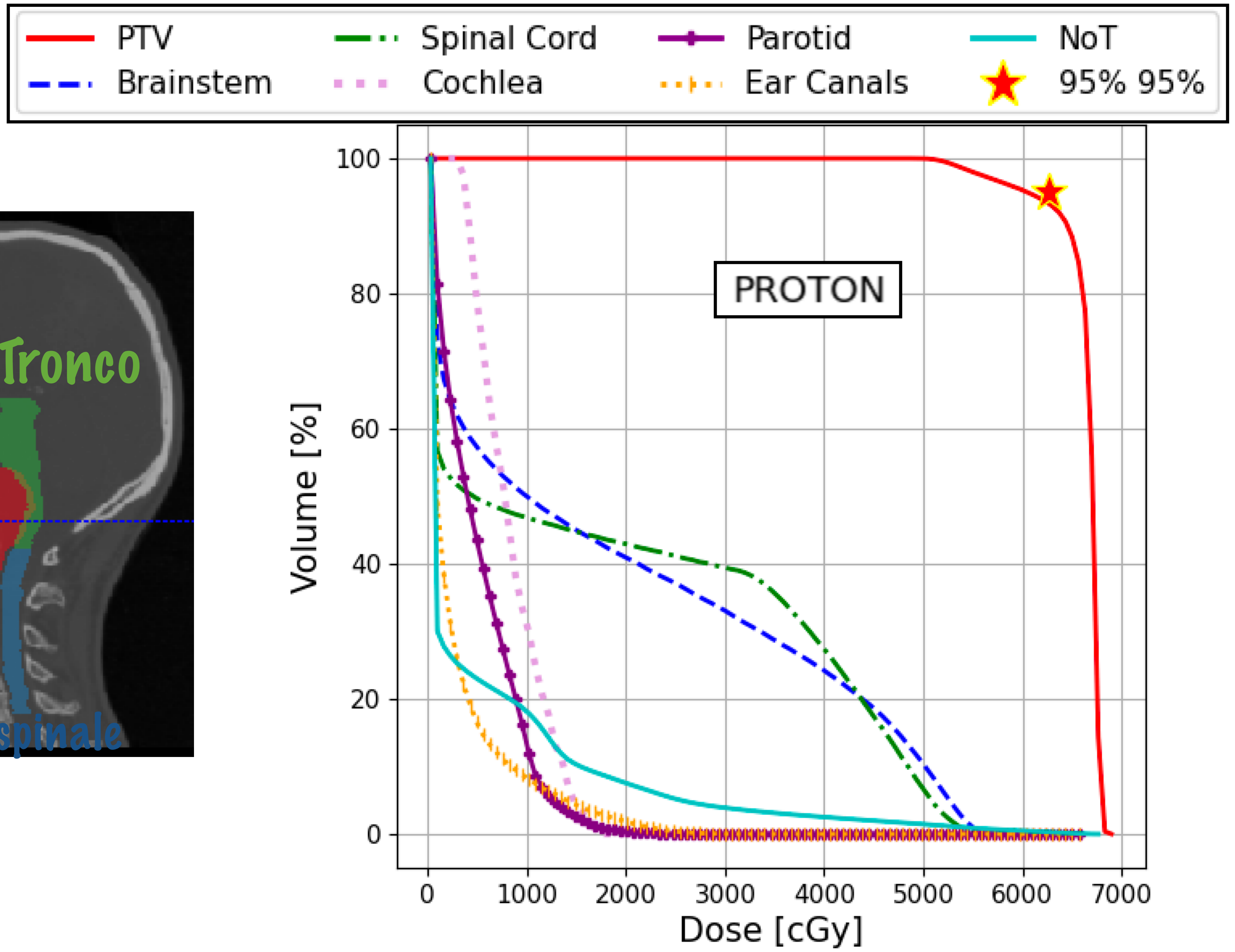
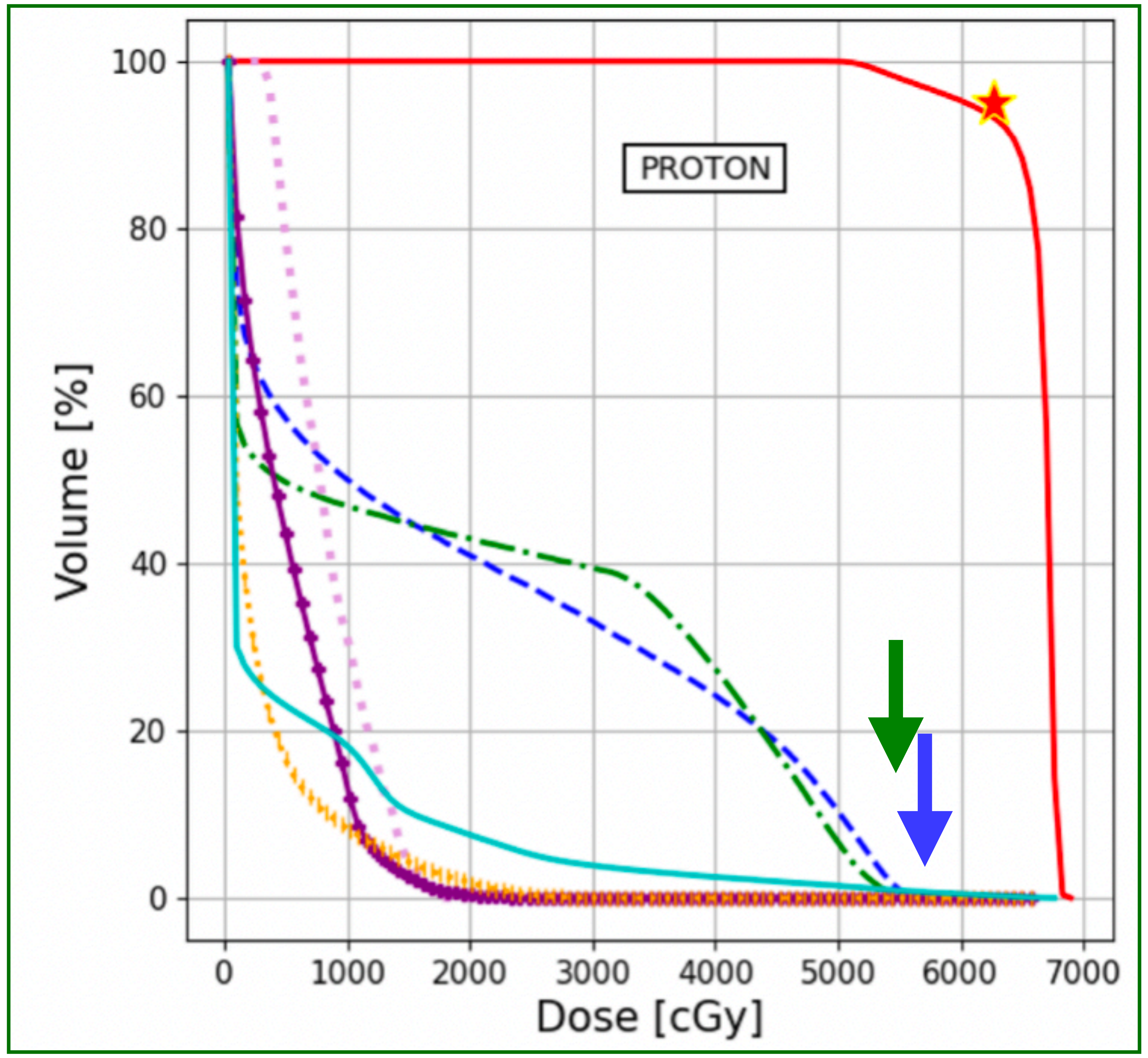




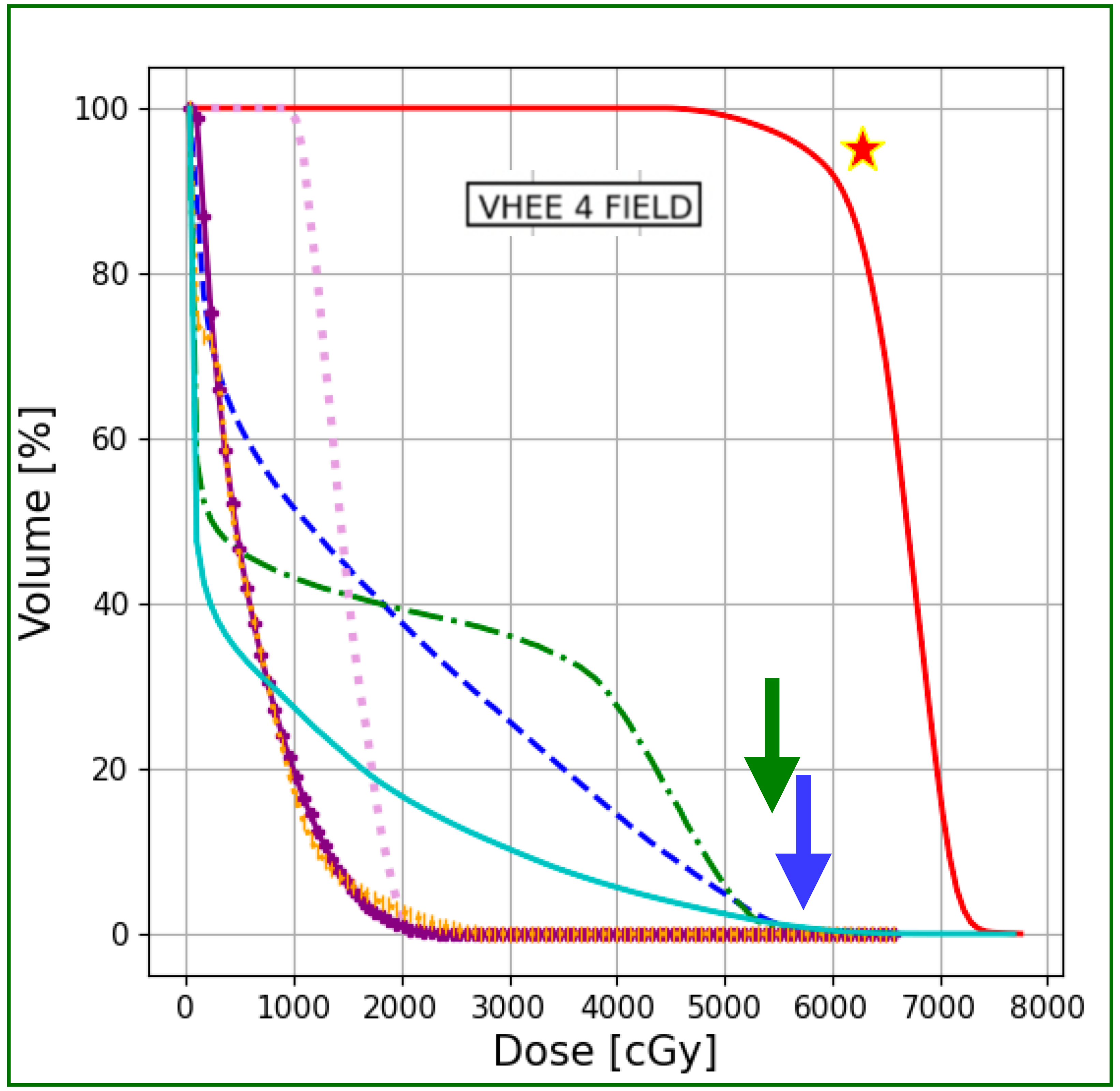
C1: p vs VHEE 4 field

DVH (**D**ose-**V**olume **H**istograms) for the Proton, photons and VHEE treatment.

PTV | Spinal Cord | Parotid | NoT
Brainstem | Cochlea | Ear Canals | 95% 95%

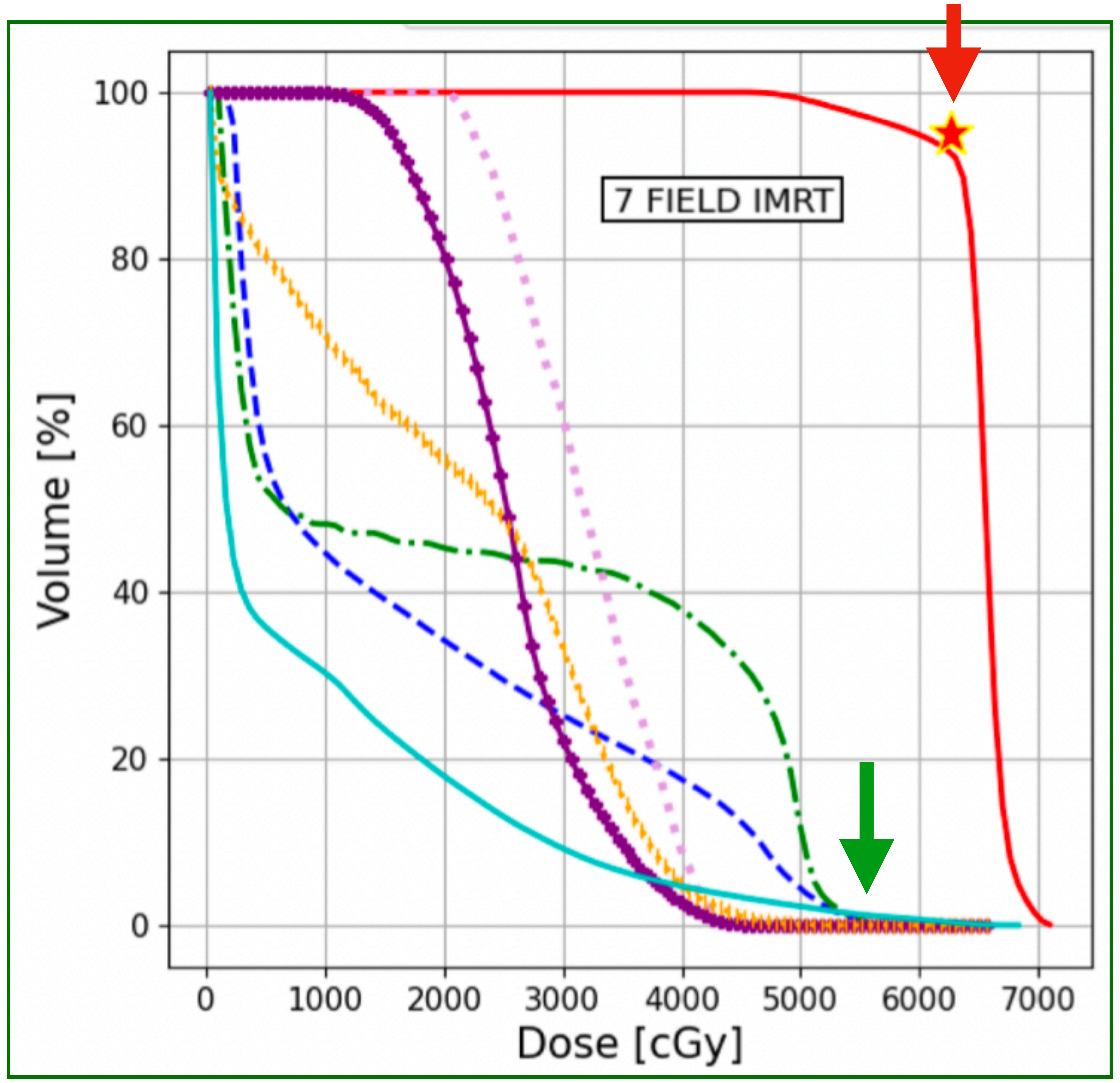


C1	Constraints	Protons	VHEE 4 field
PTV Boost	$V_{95\%}$ $V_{105\%}$	93.57 % 0 %	85.52 % 28.32 %
Brainstem	D_1	54.64 Gy	55.04 Gy
Spinal cord	D_1	53.39 Gy	53.54 Gy
Parothids	D_{mean}	4.74 Gy	5.73 Gy
Ear canals	D_{mean}	2.63 Gy	5.40 Gy
Cochlea	D_{mean}	7.98 Gy	14.32 Gy

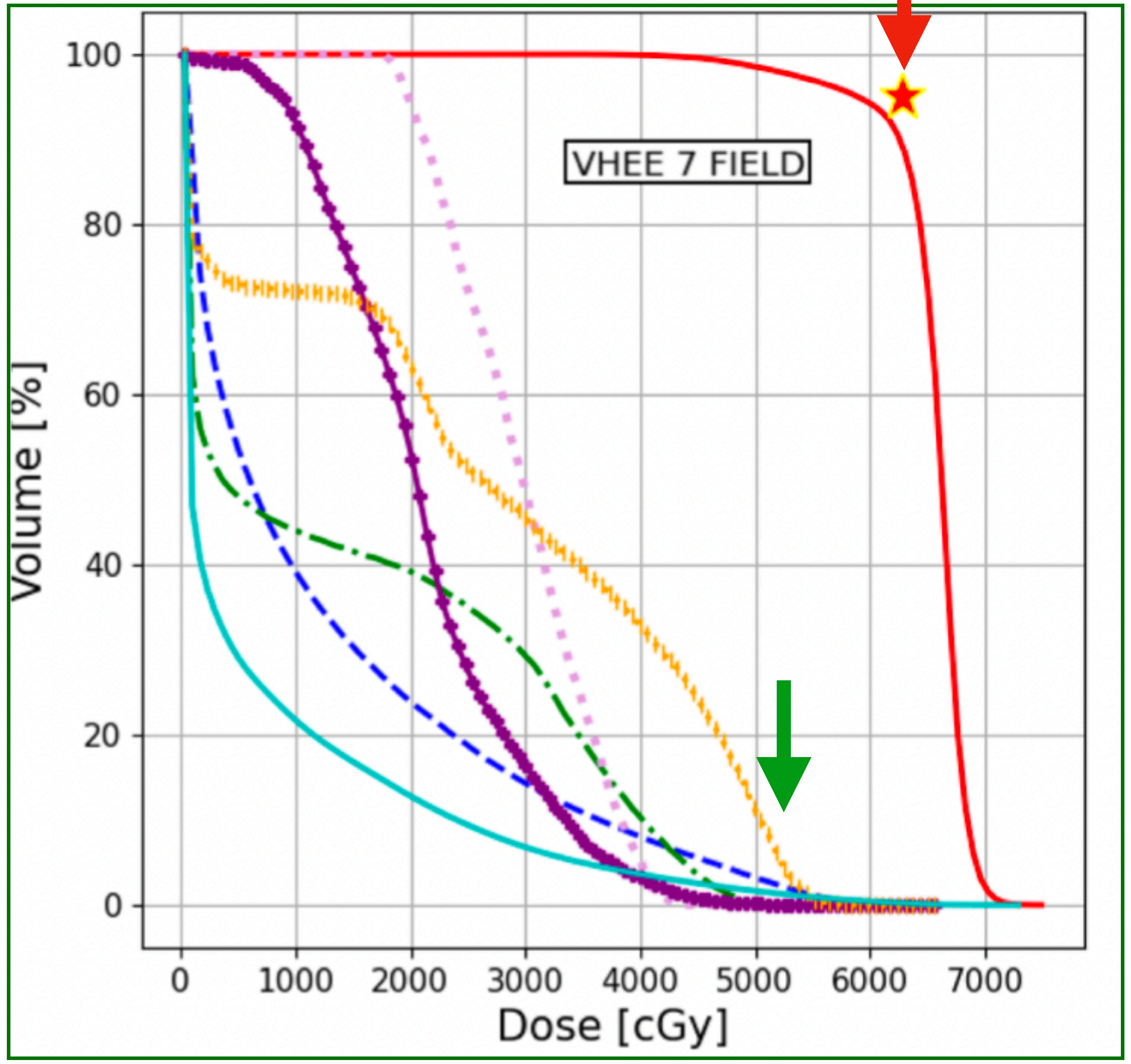


C1: IMRT vs VHEE 7 field

DVH (**D**ose-**V**olume **H**istograms) for the Proton, photons and VHEE treatment.

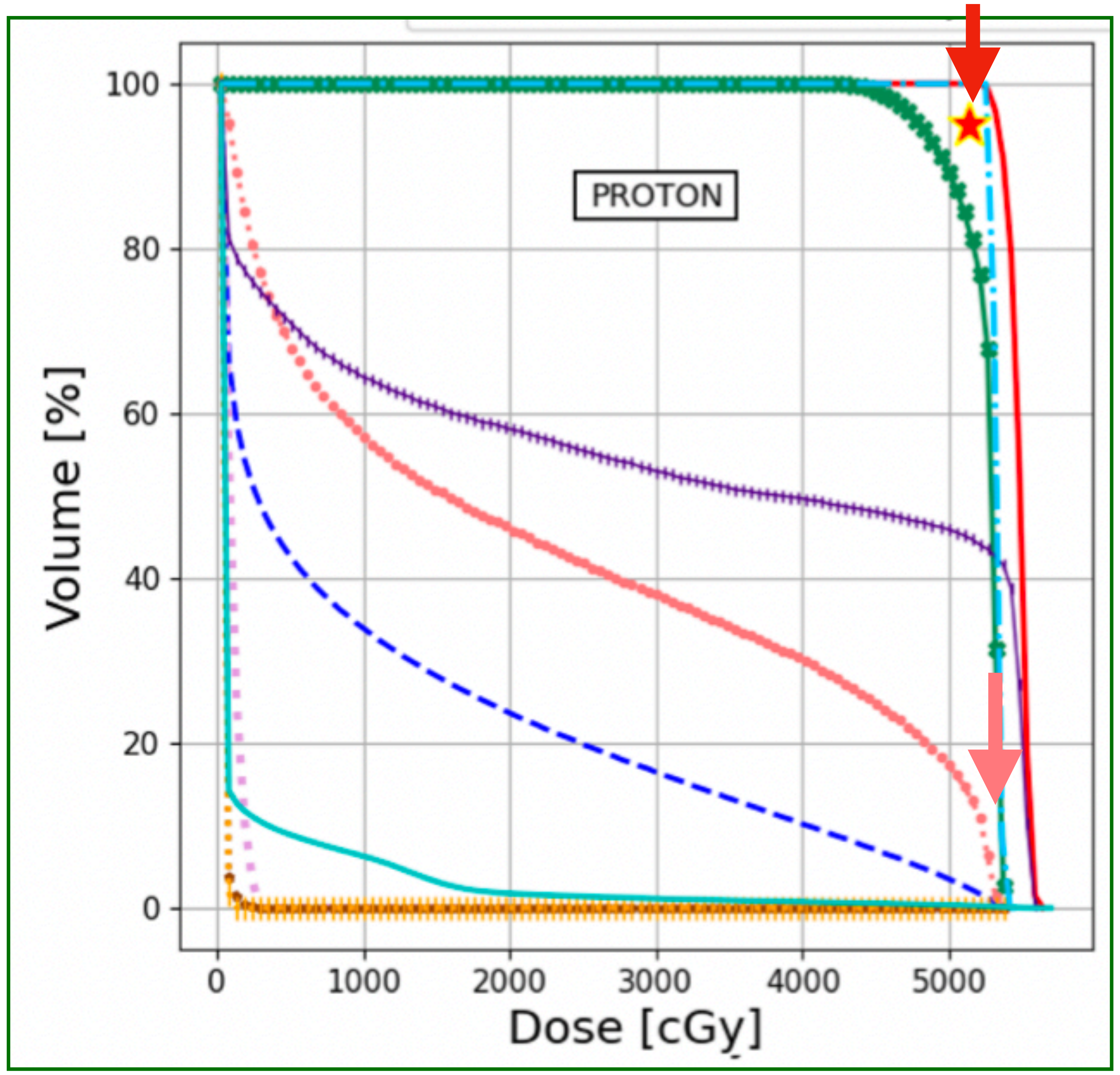


C1	Constraints	Photons	VHEE 7 field
PTV Boost	$V_{95\%}$ $V_{105\%}$	92.96 % 3.05 %	90.61 % 6.12 %
Brainstem	D_1	53.79 Gy	55.15 Gy
Spinal cord	D_1	54.04 Gy	47.77 Gy
Parothids	D_{mean}	25.29 Gy	20.82 Gy
Ear canals	D_{mean}	20.63 Gy	25.94 Gy
Cochlea	D_{mean}	31.54 Gy	29.39 Gy

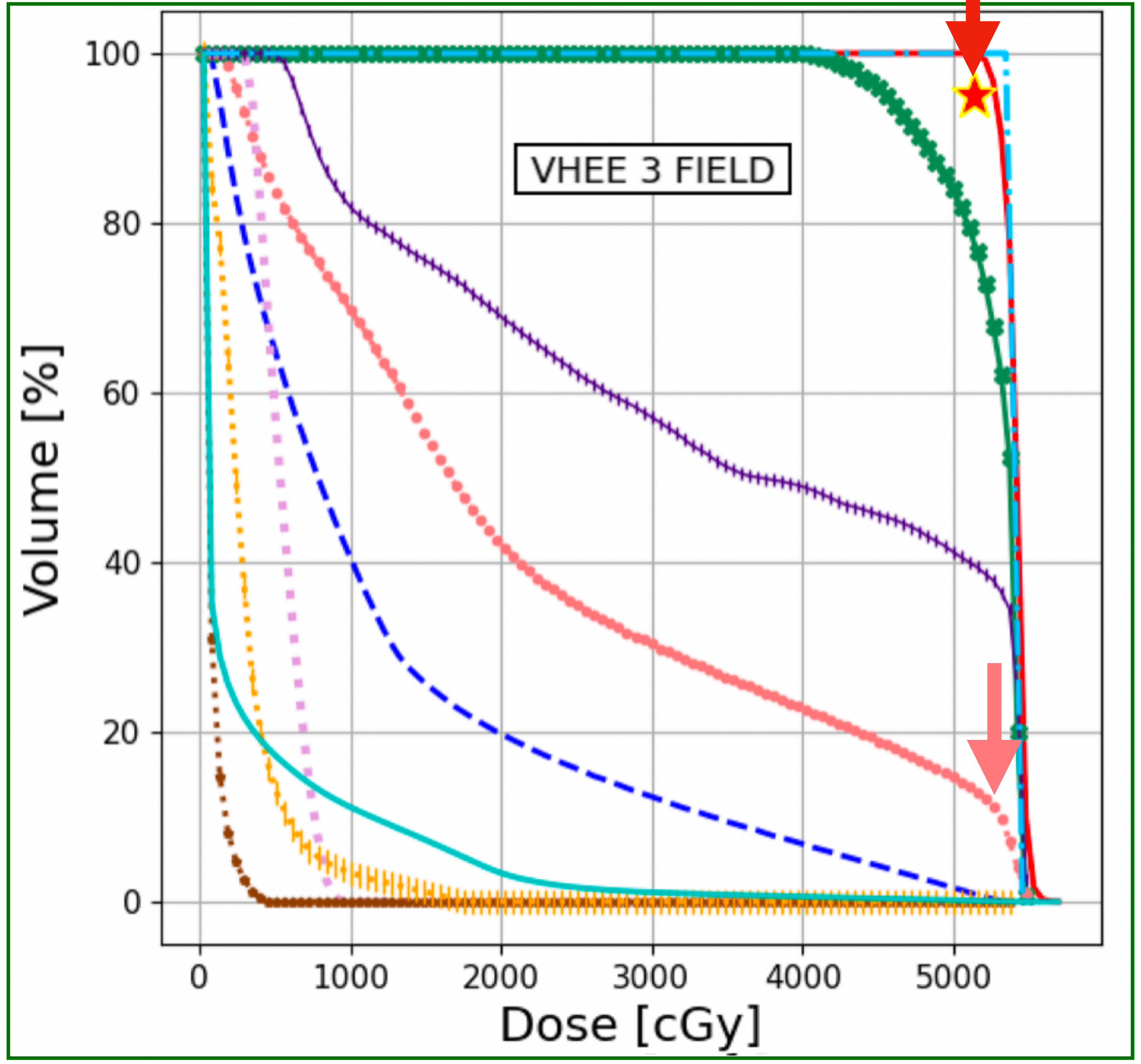


M1: p vs VHEE 3 field

DVH (**D**ose-**V**olume **H**istograms) for the Proton, photons and VHEE treatment.

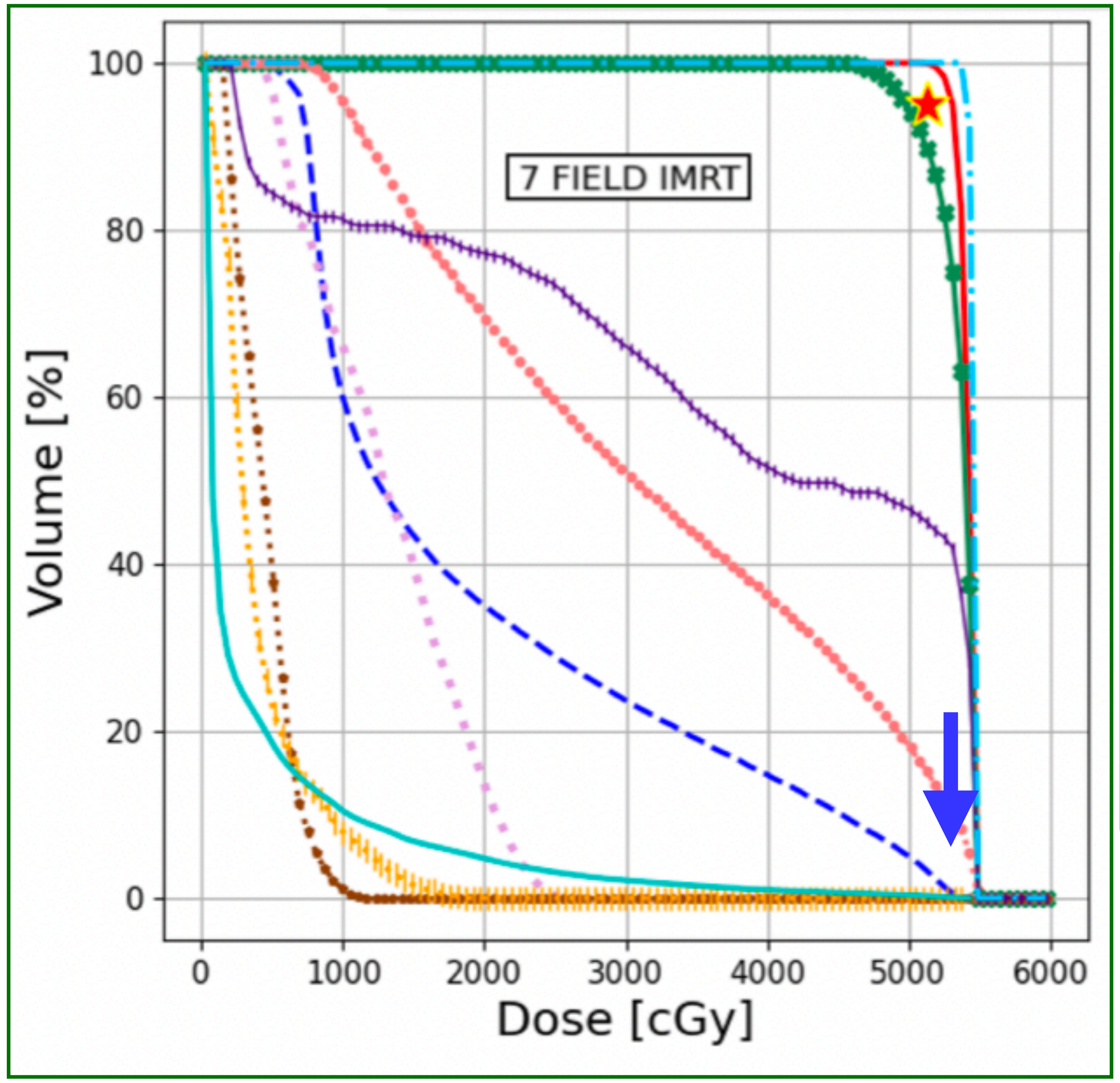


M1	Parameter	Protons	VHEE 3 field
PTV	$V_{95\%}$ $V_{105\%}$	100 % 0.01 %	98.97 % 0.05 %
Optic nerves	D_1	52.98 Gy	54 Gy
Chiasm	D_1	53.52 Gy	53.68 Gy
Posterior optical path.	D_1	53.58 Gy	53.94 Gy
Eyeballs	D_1	1.25 Gy	3.30 Gy
Brainstem	D_1	52.59 Gy	50.40 Gy
Carotid arteries	$V_{105\%}$	0.03 %	2.54 %

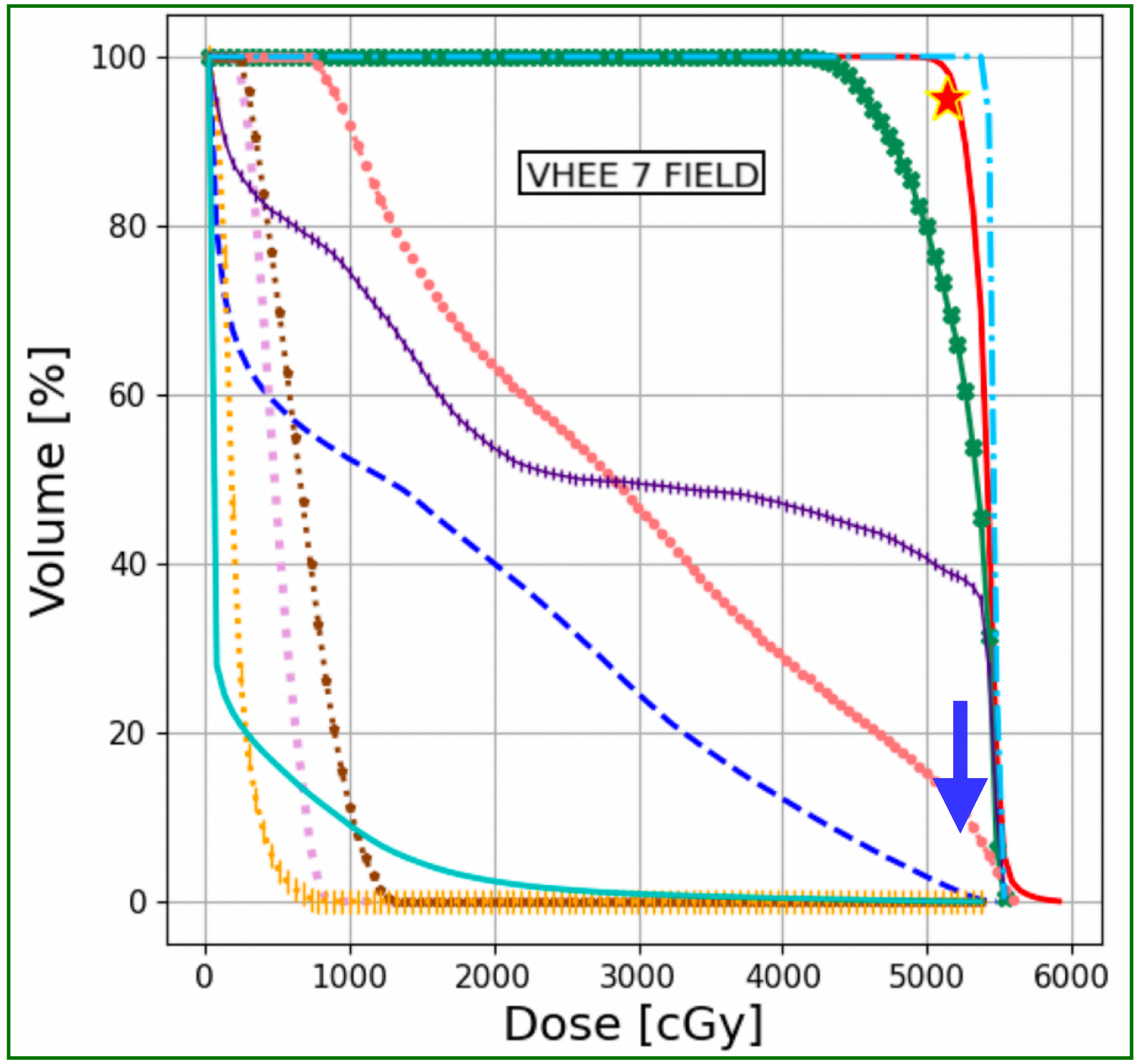


M1: IMRT vs VHEE 7 field

DVH (**D**ose-**V**olume **H**istograms) for the Proton, photons and VHEE treatment.



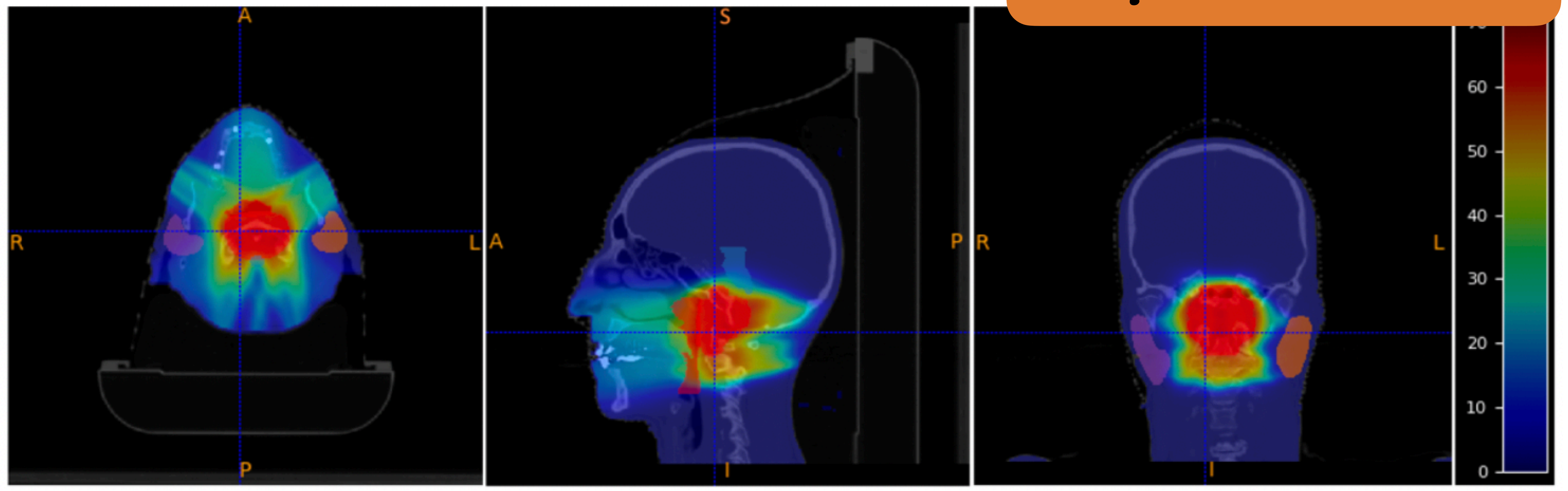
M1	Parameter	Photons	VHEE 7 field
PTV	$V_{95\%}$ $V_{105\%}$	99.30 % 0.009 %	97.00 % 1.27 %
Optic nerves	D_1	53.76 Gy	54 Gy
Chiasm	D_1	54 Gy	53.71 Gy
Posterior optical path.	D_1	53.82 Gy	53.67 Gy
Eyeballs	D_1	10.52 Gy	11.82 Gy
Brainstem	D_1	51.99 Gy	51.02 Gy
Carotid arteries	$V_{105\%}$	9.11 %	1.16 %



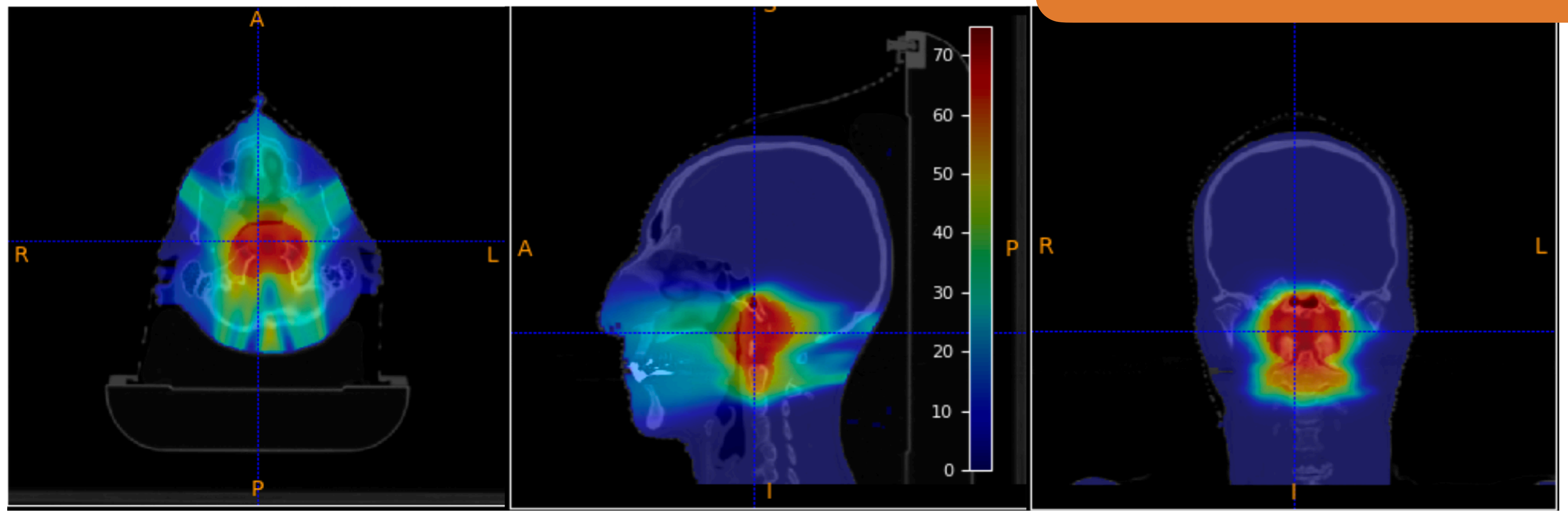
FLASH effect potential

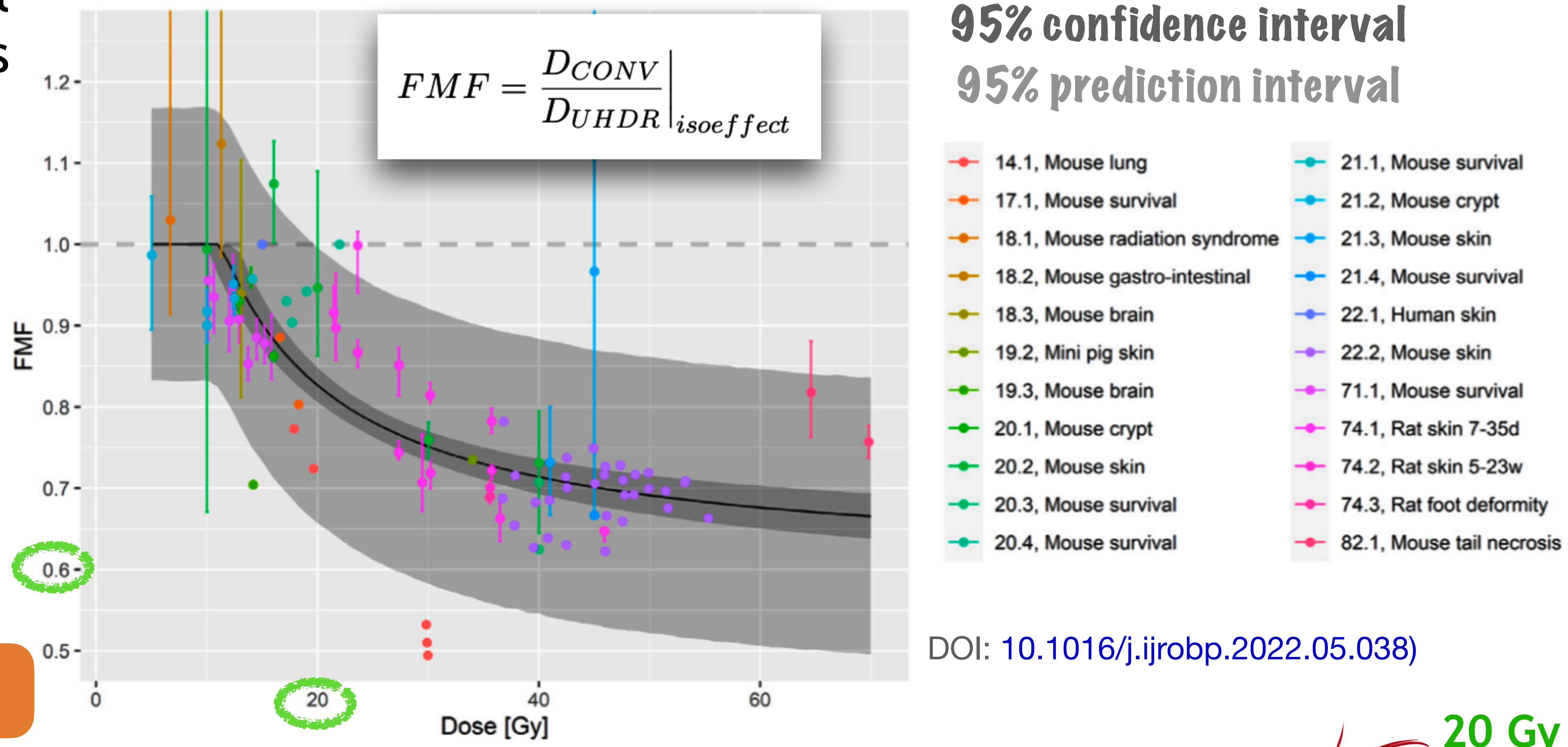
From the optimized dose maps, we evaluated the potential of the FLASH effect by applying FMF, the result obtained was used to rescale the optimized dose.

Optimized dose



FMF^{min} 0.8



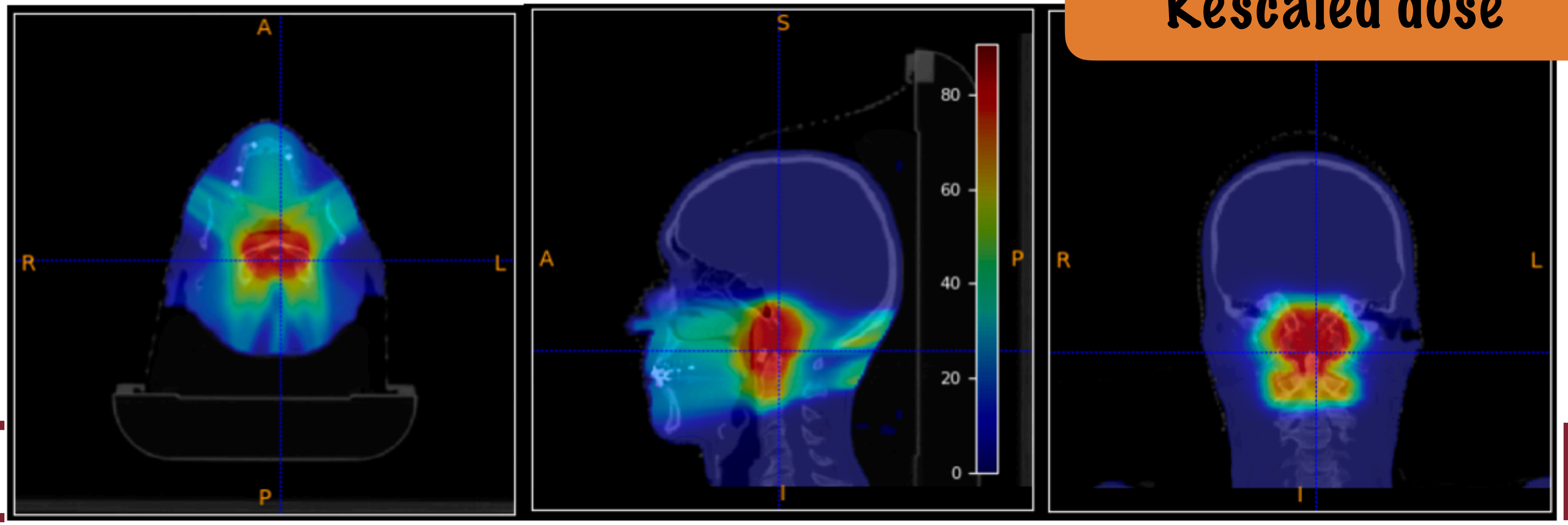


DOI: 10.1016/j.ijrobp.2022.05.038)

20 Gy

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

Rescaled dose

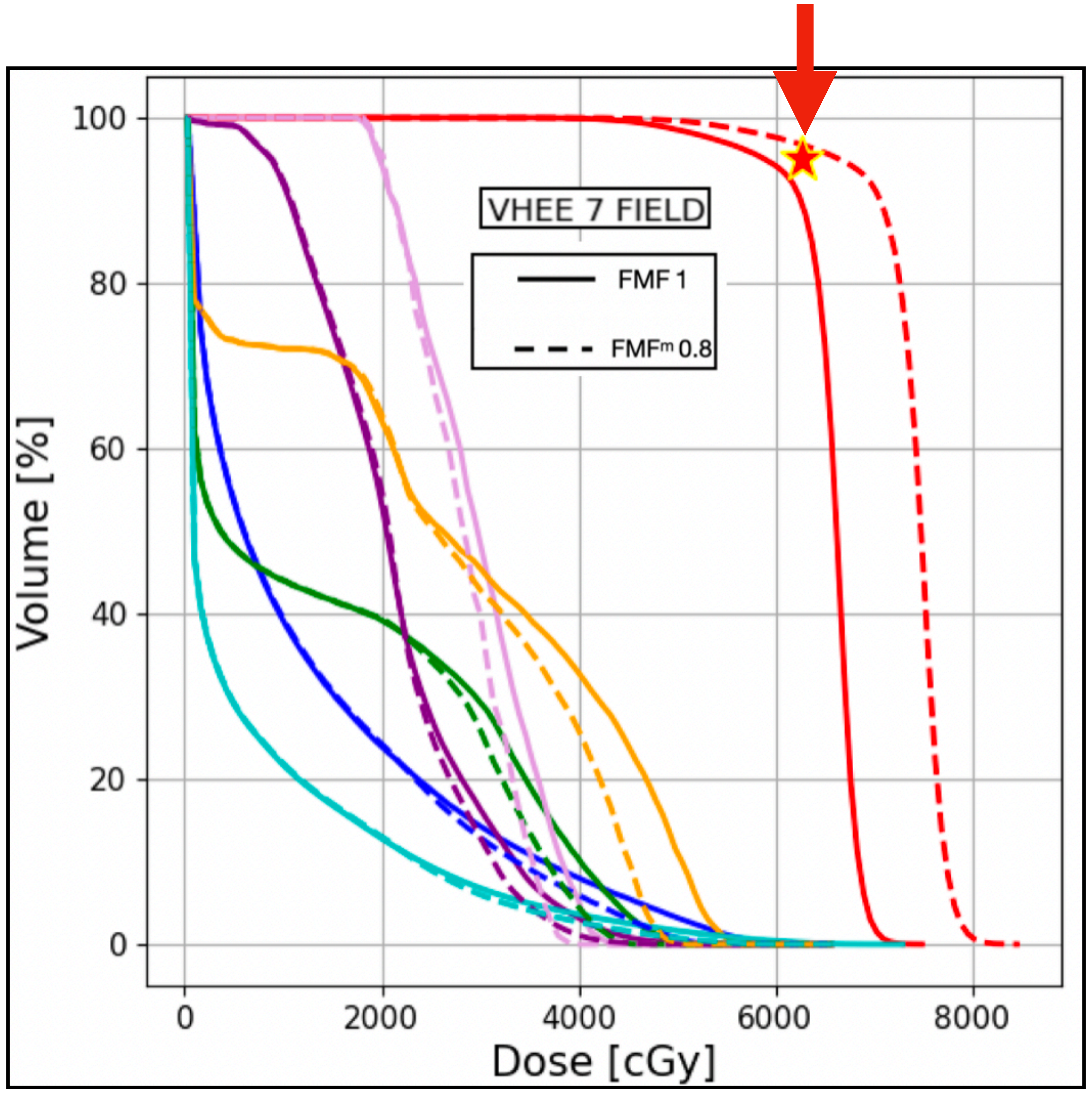


FLASH effect potential: C1 case

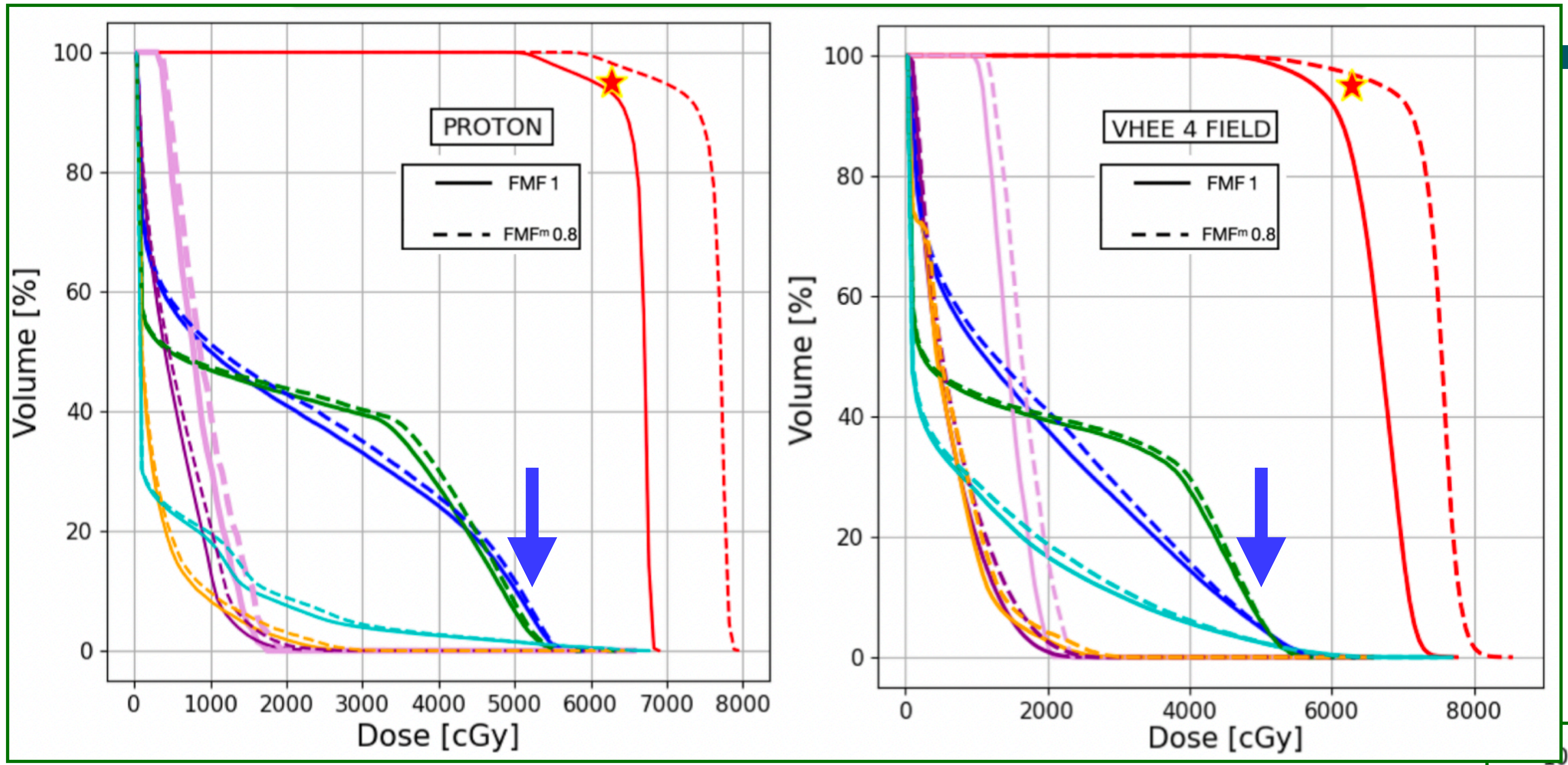
For C1 case, without FLASH effect, we observed a not achieving satisfactory tumor coverage. So we studied with the FLASH effect how it is possible to **increase the dose delivered to the PTV**, **while preserving dosimetric constraints on OARs.**

PTV · Brainstem · Spinal cord · Cochlea · Parothid glands · Middle ears · Normal tissue · ★ 95% 95%

C1	Constraints	VHEE 7F (FLASH)	VHEE 7 field (no FLASH)
PTV Boost	$V_{95\%}$ $V_{105\%}$	96.43 % 93.08 %	90.61 % 6.12 %
Brainstem	D_1 Gy(FMF)	54.37	55.15 Gy
Spinal cord	D_1 Gy(FMF)	47.70	47.77 Gy
Parothid	D_{mean} Gy(FMF)	22.67	20.82 Gy
Ear canal	D_{mean} Gy(FMF)	26.69	25.94 Gy
Cochlea	D_{mean} Gy(FMF)	31.07	29.39 Gy



FLASH effect potential: C1 case

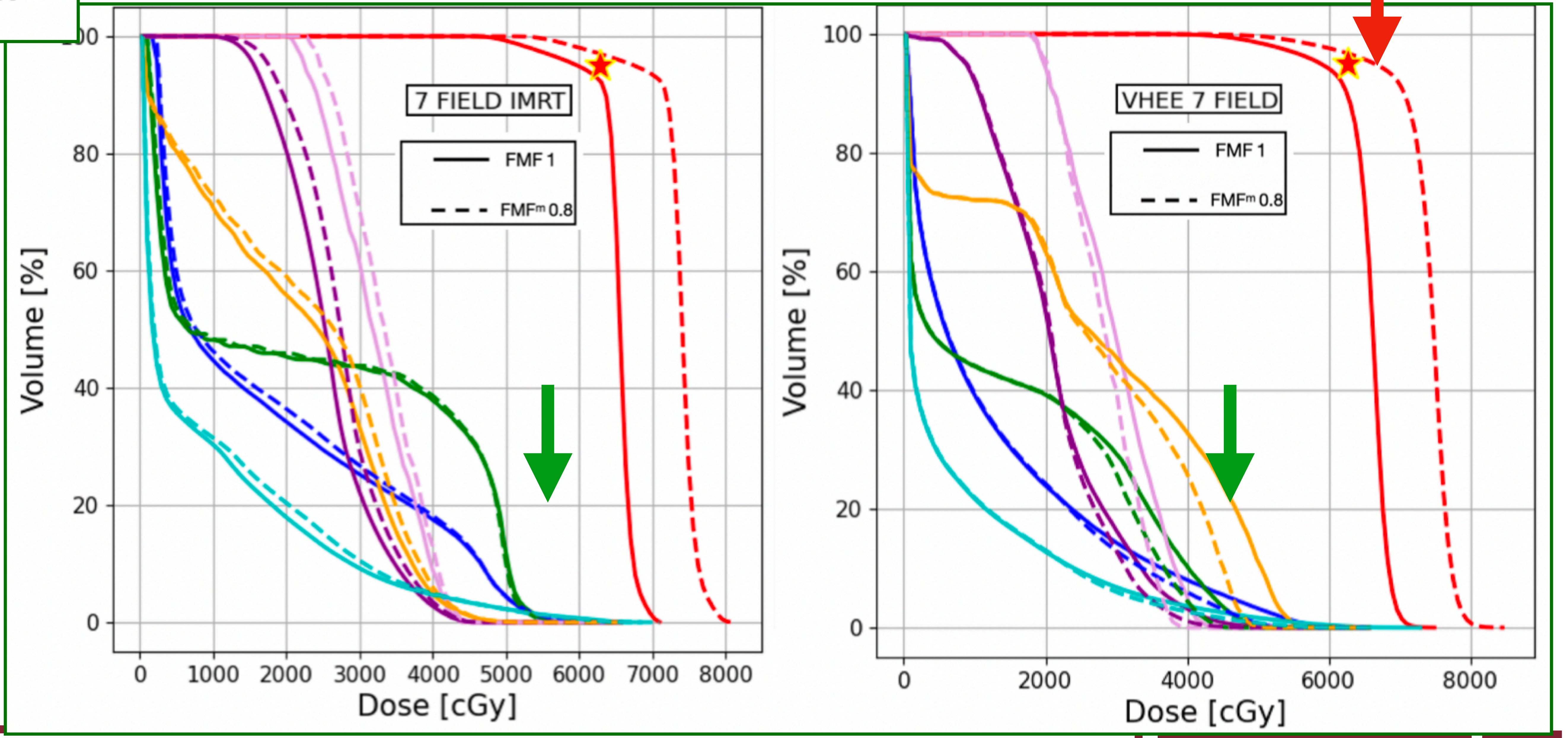


FLASH

C1	Constraints	PROTON	IMRT	VHEE 4F	VHEE 7F
PTV Boost	$V_{95\%}$ $V_{105\%}$	97.71 % 95.27 %	96.65 % 92.84 %	96.58 % 91.04 %	96.43 % 93.08 %
Brainstem	D_1 Gy(FMF)	54.85	54.79	54.76	54.37
Spinal cord	D_1 Gy(FMF)	53.69	53.41	53.39	47.70

no FLASH

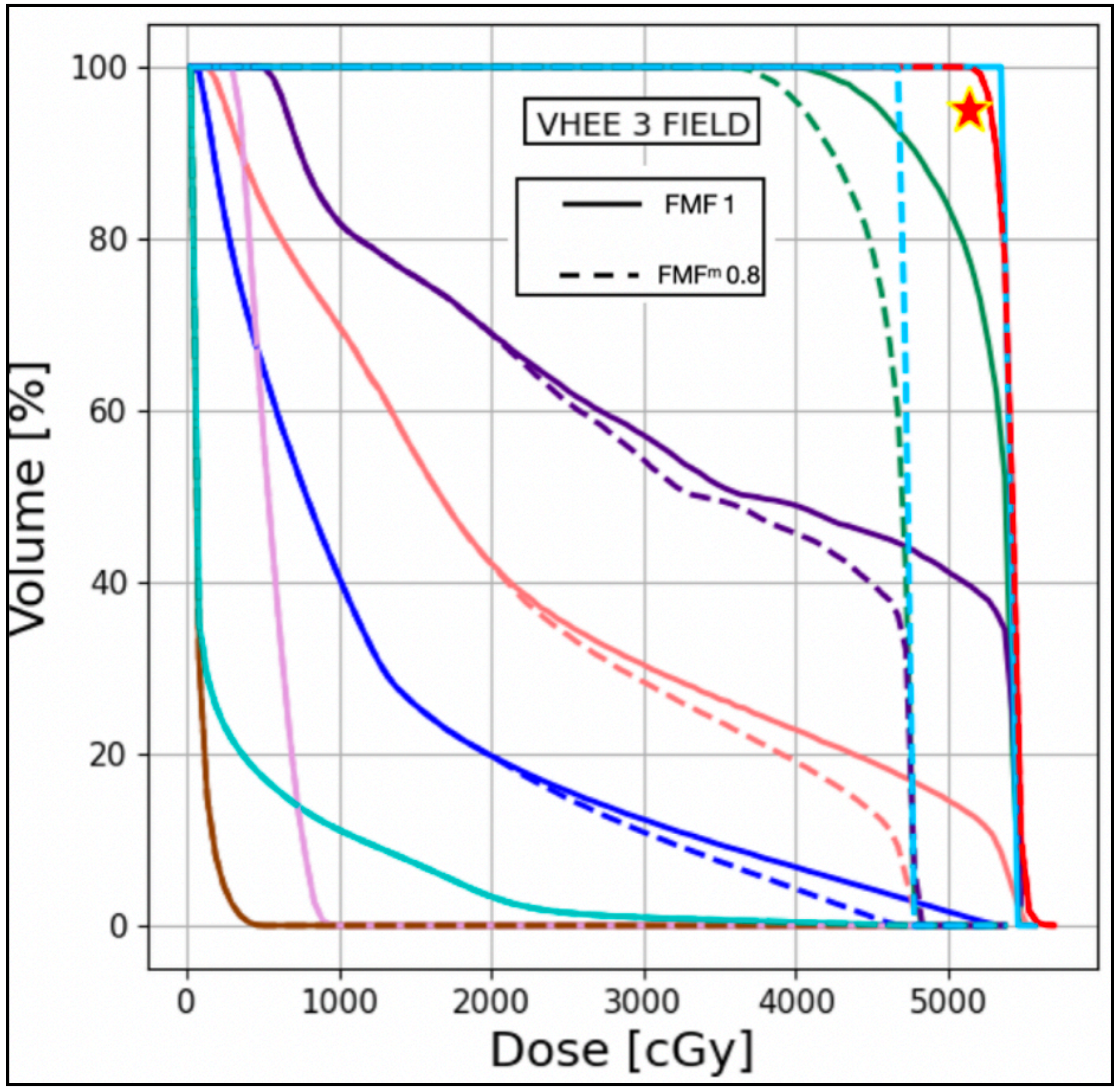
C1	Constraints	Protons	Photons	VHEE 4 field	VHEE 7 field
PTV Boost	$V_{95\%}$ $V_{105\%}$	93.57 % 0 %	92.96 % 3.05 %	85.52 % 28.32 %	90.61 % 6.12 %
Brainstem	D_1	54.64 Gy	53.79 Gy	55.04 Gy	55.15 Gy
Spinal cord	D_1	53.39 Gy	54.04 Gy	53.54 Gy	47.77 Gy



FLASH effect potential: M1 case

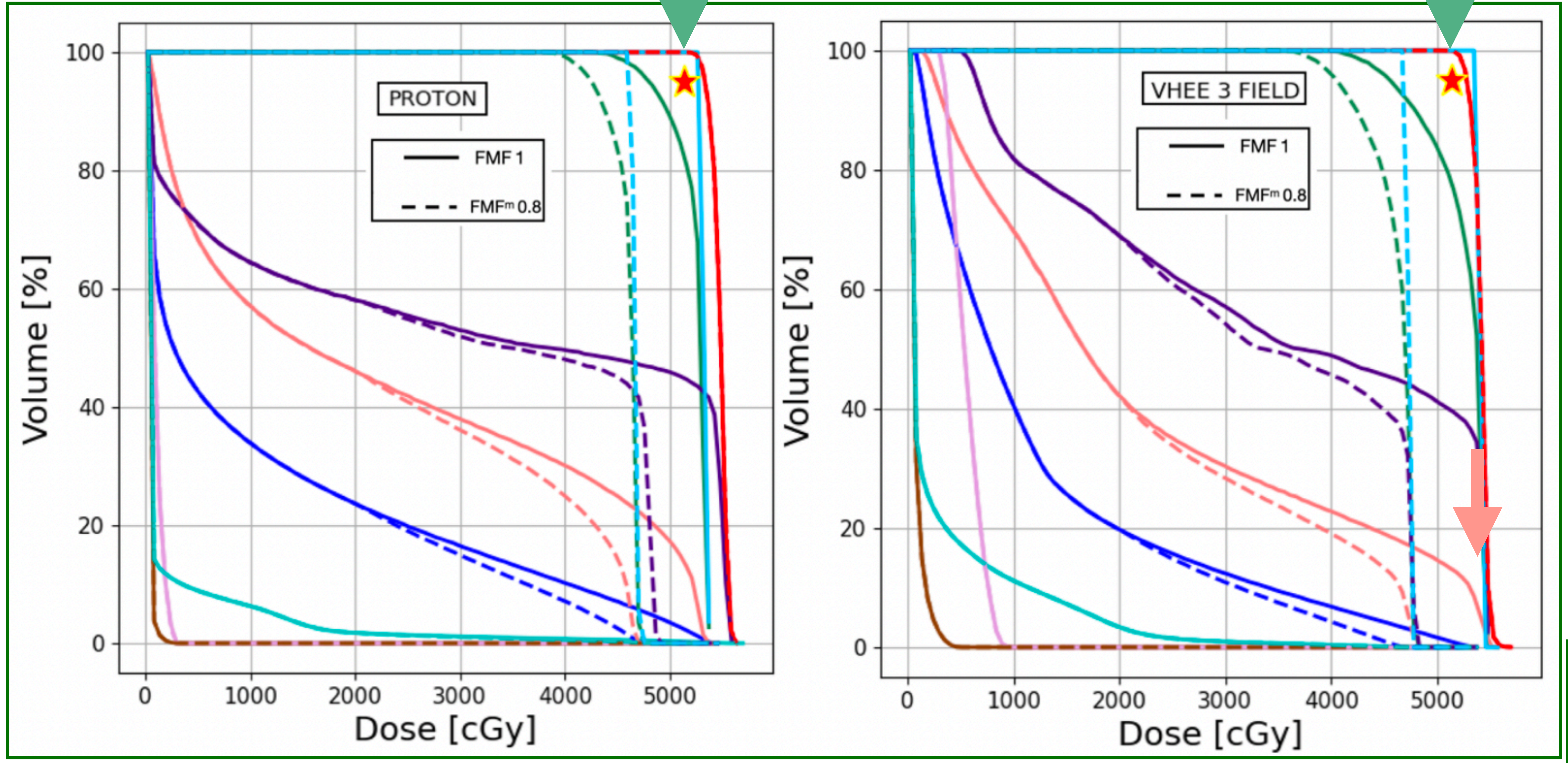
In that case, as the PTV coverage is already satisfactory without FLASH effect the latter would produce **an additional reduction of the dose absorbed to OARs** so resulting in additional OAR sparing.

M1	Constraints	VHEE 3F (FLASH)	VHEE 3 field (no FLASH)
PTV	$V_{95\%}$ $V_{105\%}$	98.97 % 0.05 %	98.97 % 0.05 %
Optic nerves	D_1 Gy(FMF)	47.64	54 Gy
Chiasm	D_1 Gy(FMF)	47.38	53.68 Gy
Posterior optical path.	D_1 Gy(FMF)	47.59	53.94 Gy



FLASH effect potential: M1 case

PTV | Optic nerves | Carotid arteries | Chiasm
Brainstem | Cochlea | Normal tissue | ★ 95% 95%
Posterior optical | Eyeballs

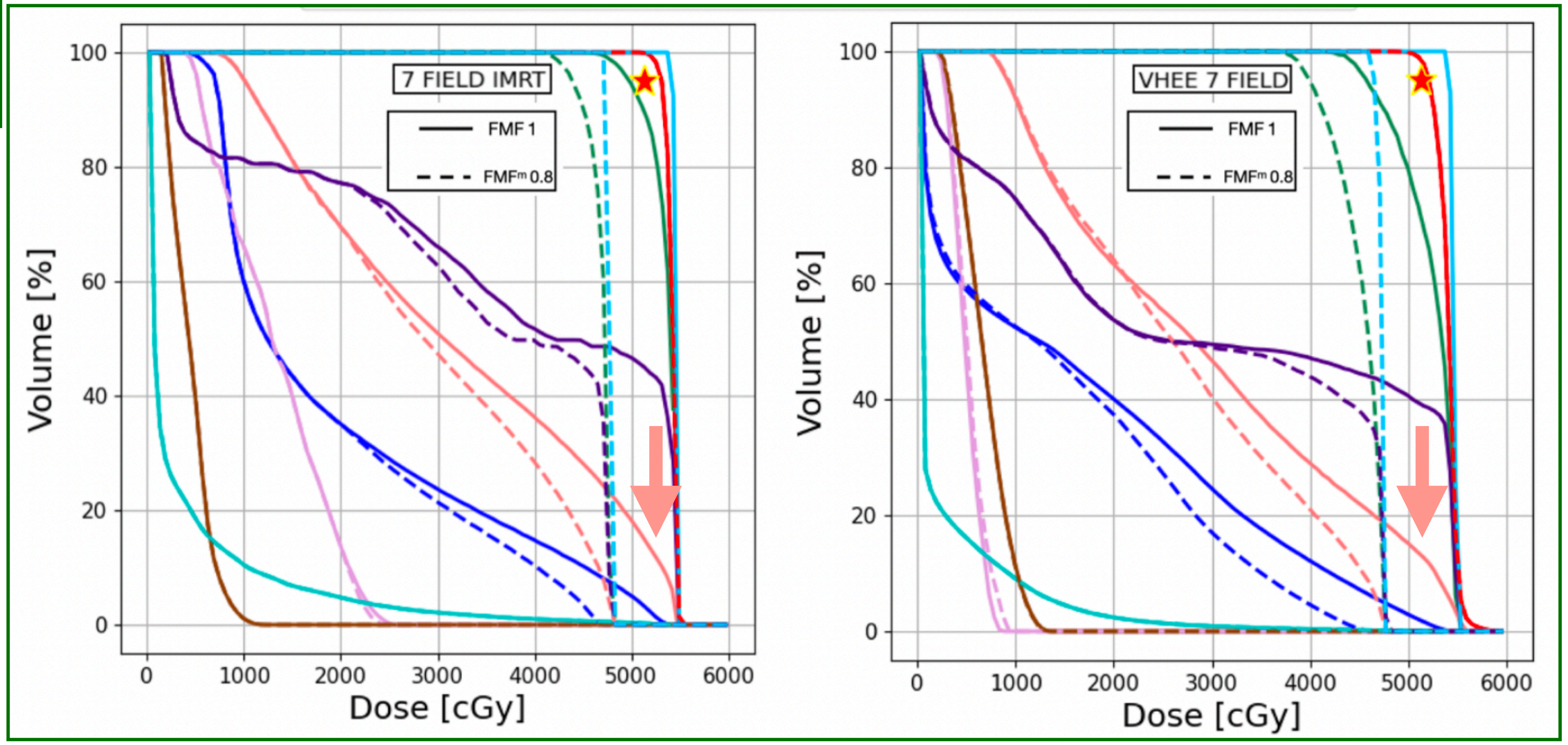


FLASH

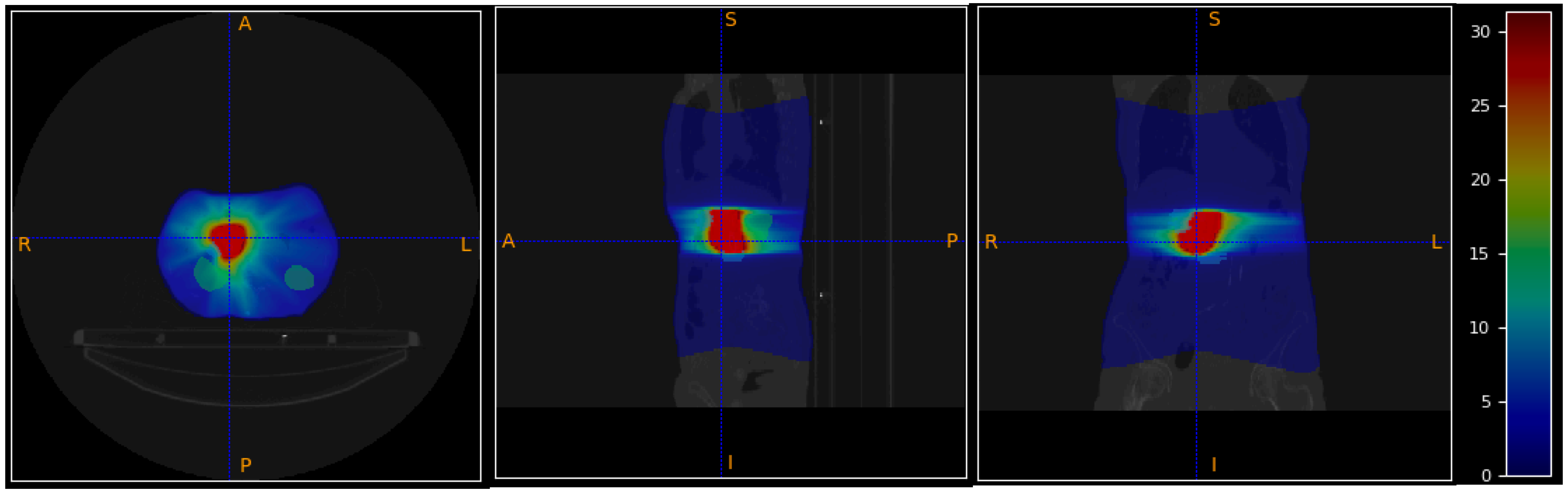
M1	Constraints	PROTON	IMRT	VHEE 3F	VHEE 7F
PTV	$V_{95\%}$ $V_{105\%}$	100 % 0.01 %	99.30 % 0.009 %	98.97 % 0.05 %	97.00 % 1.27 %
Optic nerves	D_1 Gy(FMF)	46.39	47.51	47.64	47.29
Chiasm	D_1 Gy(FMF)	47.47	46.81	47.38	47.36
Posterior optical path.	D_1 Gy(FMF)	46.86	47.47	47.59	47.26

no FLASH

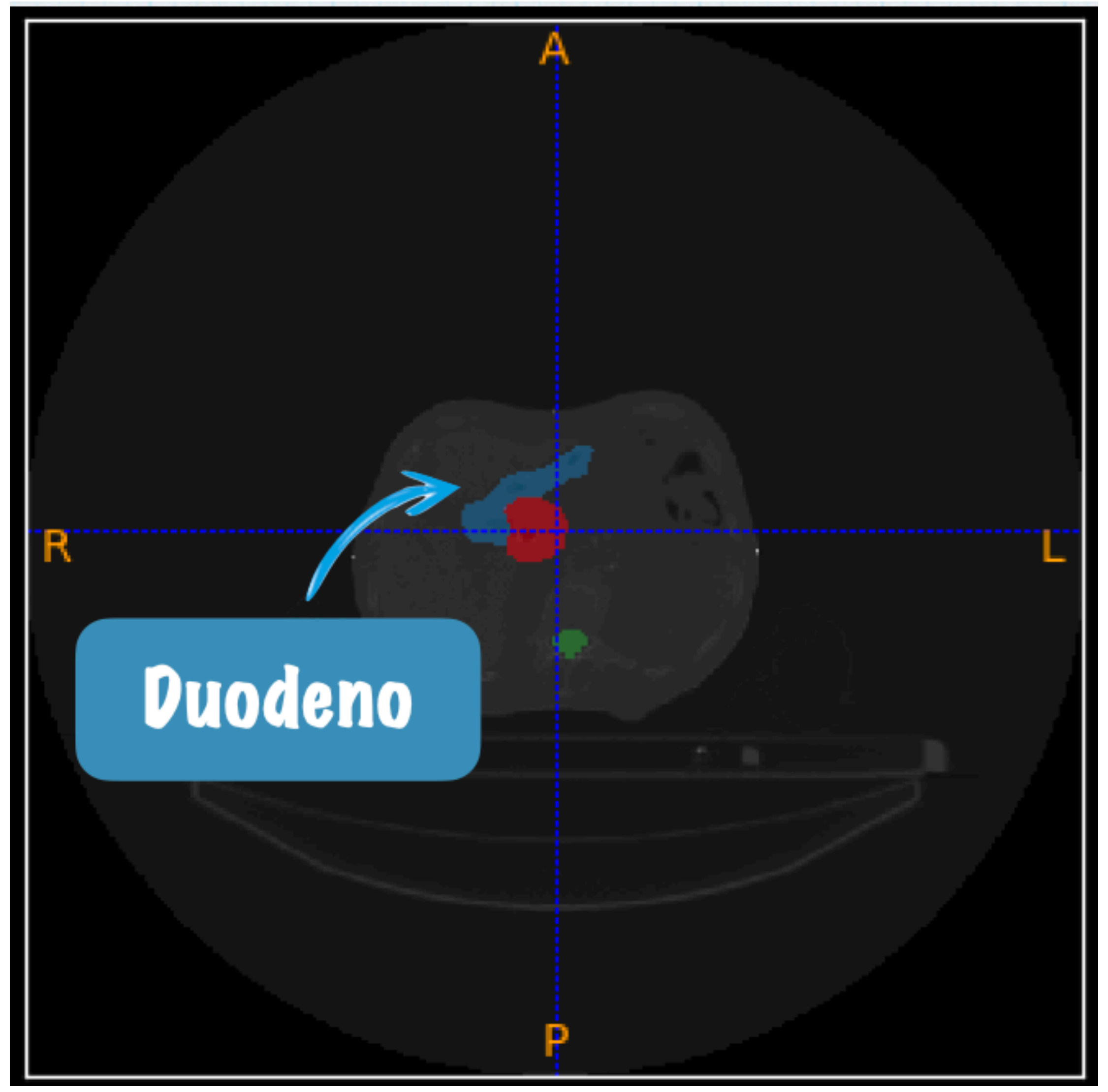
M1	Parameter	Protons	Photons	VHEE 3 field	VHEE 7 field
PTV	$V_{95\%}$ $V_{105\%}$	100 % 0.01 %	99.30 % 0.009 %	98.97 % 0.05 %	97.00 % 1.27 %
Optic nerves	D_1	52.98 Gy	53.76 Gy	54 Gy	54 Gy
Chiasm	D_1	53.52 Gy	54 Gy	53.68 Gy	53.71 Gy
Posterior optical path.	D_1	53.58 Gy	53.82 Gy	53.94 Gy	53.67 Gy



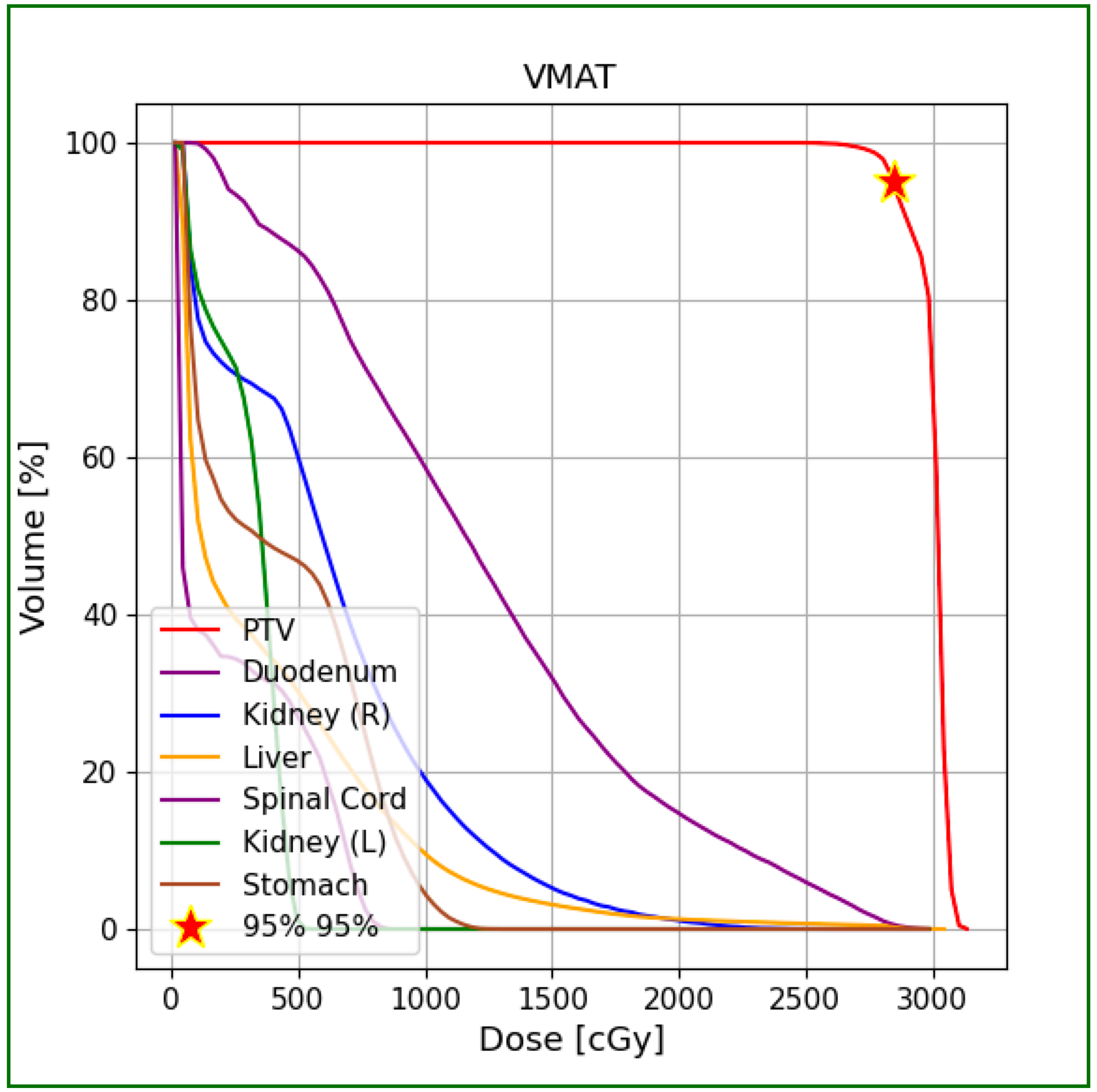
Pancreas case



Organ	Dosimetric constraints
PTV	$V_{95\%}$>95% never above 107%
Kidney	D_{mean}<10 Gy
Stomach	D_{max}<45 Gy
Duodenum	D_{max}<35 Gy
Spinal Cord	D_{max}<18 Gy
Liver	D_{mean}<15 Gy



Patient with pancreas tumor, was treated with **hypo-fractionated** treatment of **30 Gy in 5 fractions** using VMAT.



Pancreas case

Organ	Photons	VHEE 7 field
PTV	$V_{95\%}$ 99.13% $V_{105\%}$ 83.35%	$V_{95\%}$ 98.01% $V_{105\%}$ 71.26%
Kidney (R)	D_{mean} 5.88 Gy	D_{mean} 7.08 Gy
Stomach	D_{mean} 13.65 Gy	D_{mean} 18.99 Gy
Duodenum	D_{max} 29.98 Gy	D_{max} 29.50 Gy
Liver	D_{mean} 3.77 Gy	D_{mean} 4.08 Gy
Spinal cord	D_{max} 9.42 Gy	D_{max} 9.09 Gy

DVH (**D**ose-**V**olume **H**istograms) for the photons, VHEE treatment and with FLASH effect.

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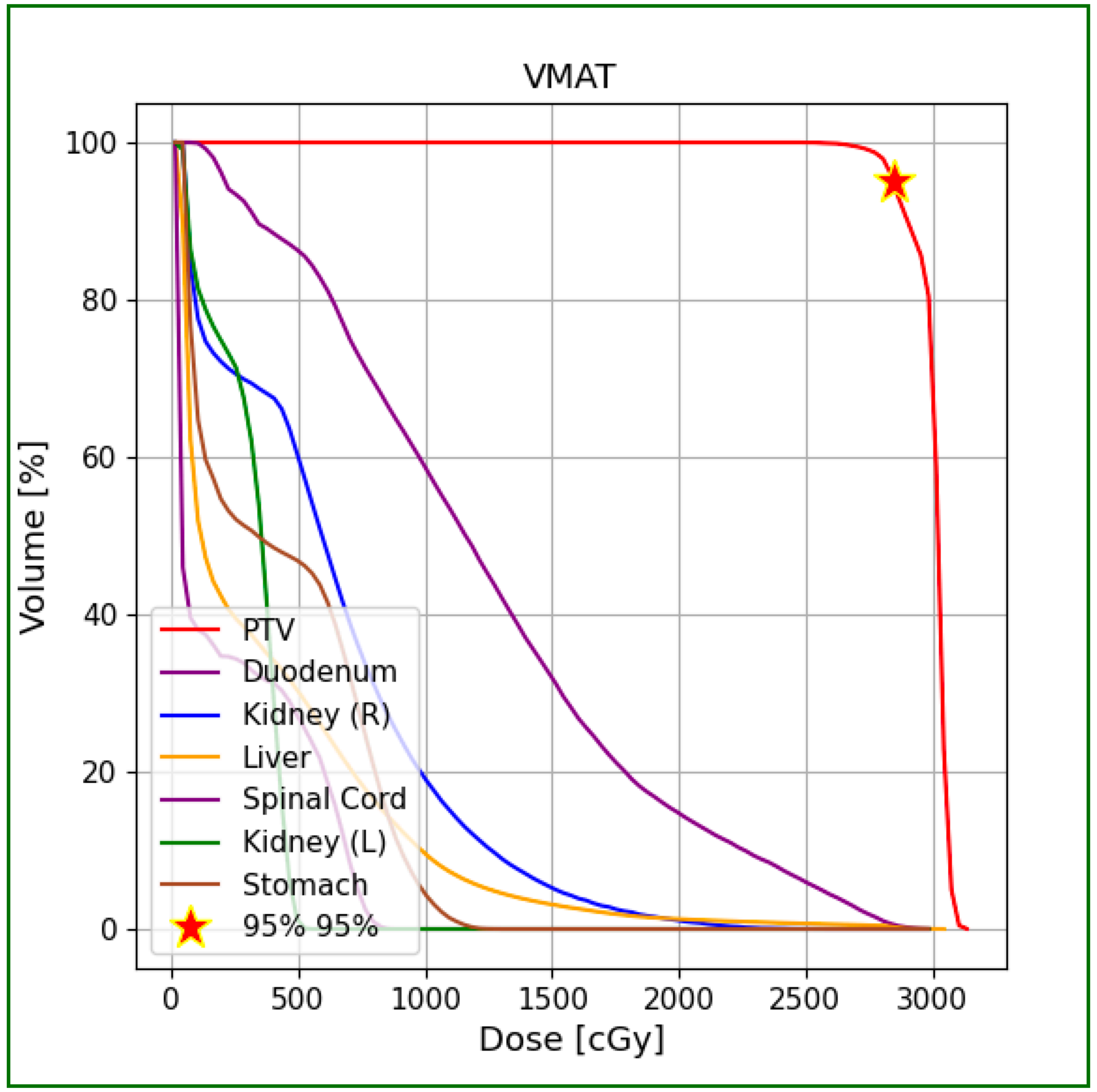
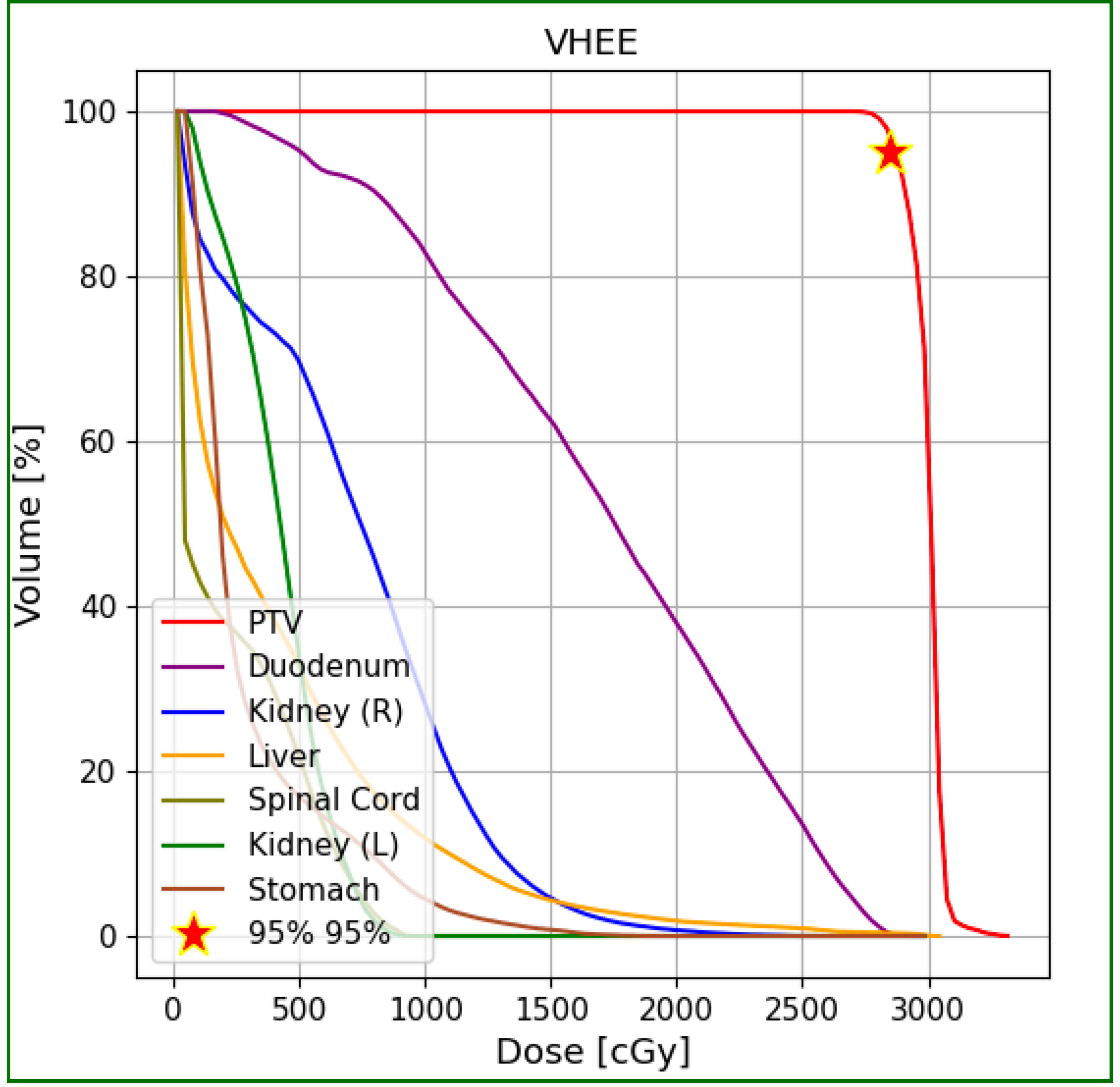
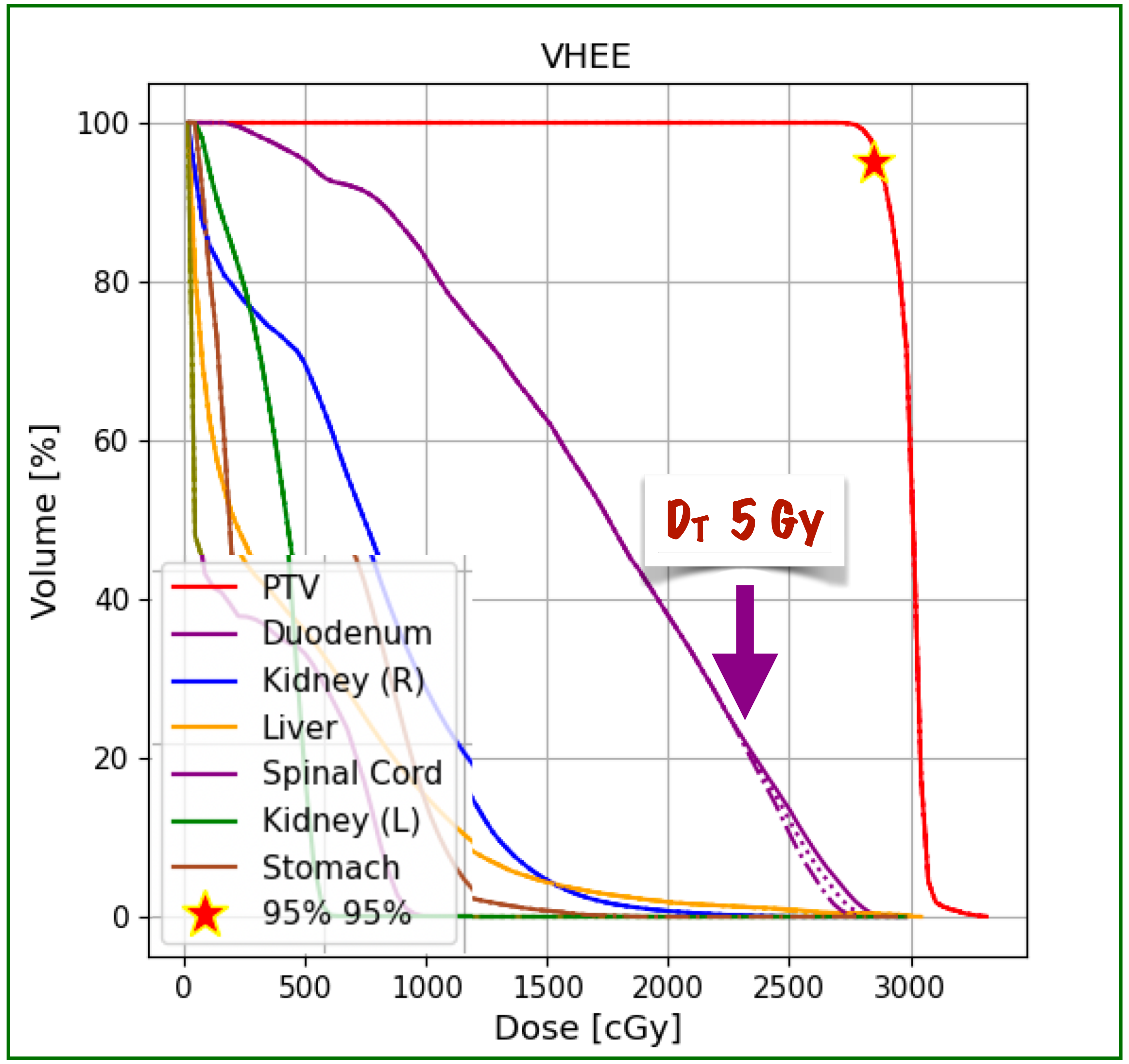






FLASH Radiotherapy with hIgh
Dose-rate particle beAms

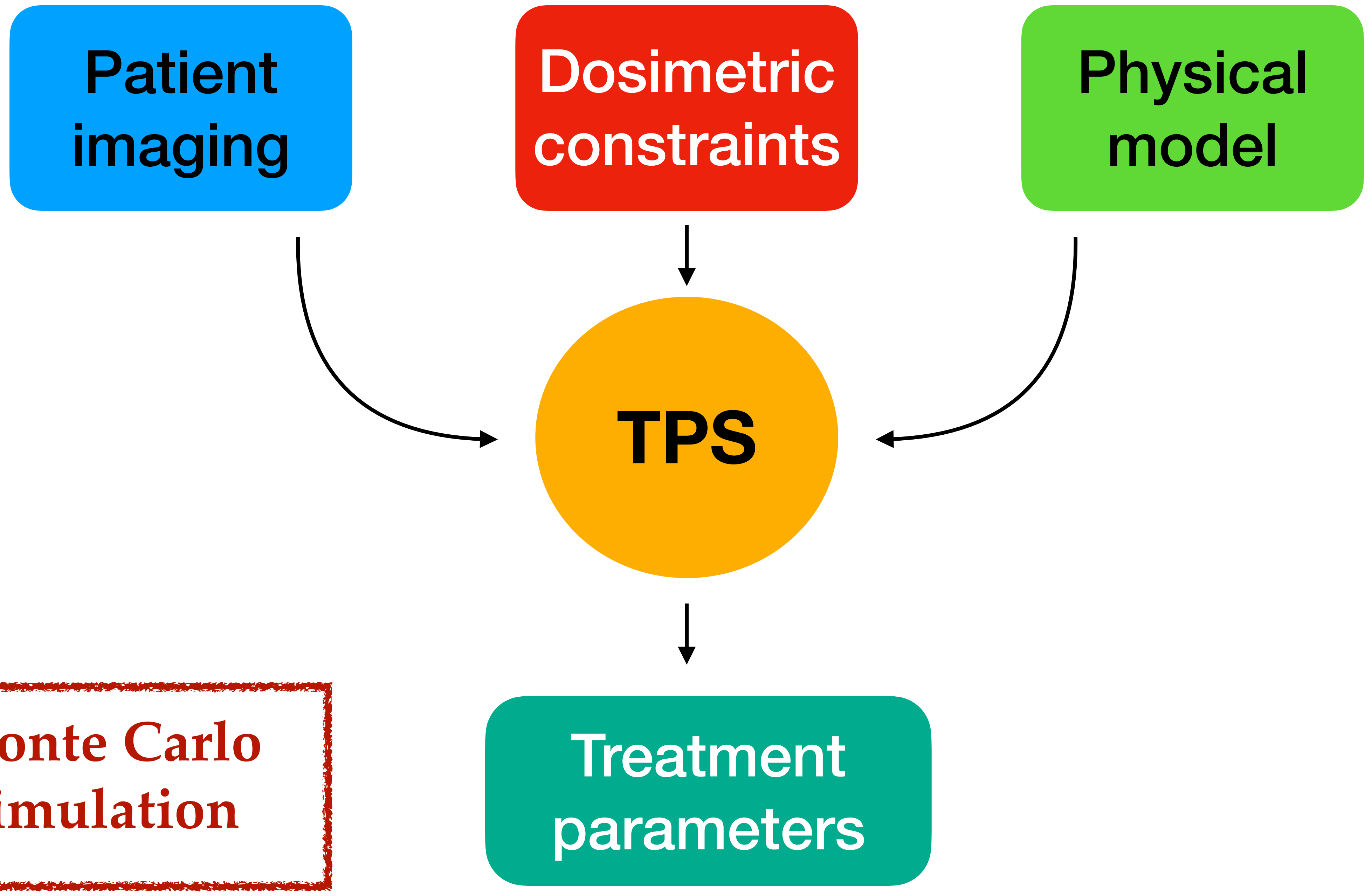
Update TPS for VHEE-FLASH algorithm

Thanks to Angelica De Gregorio!

TPS FOR VHEE

- In order to investigate the potential of VHEE based radiotherapy, a VHEE Treatment Planning System (TPS) is needed.

TPS are software that, by combining the physical models of the particles at the energies of interest with the accelerator parameters, allow to **optimize the dose distribution in the patient** with the intent to **maximize tumour control and minimize normal tissue complications.**

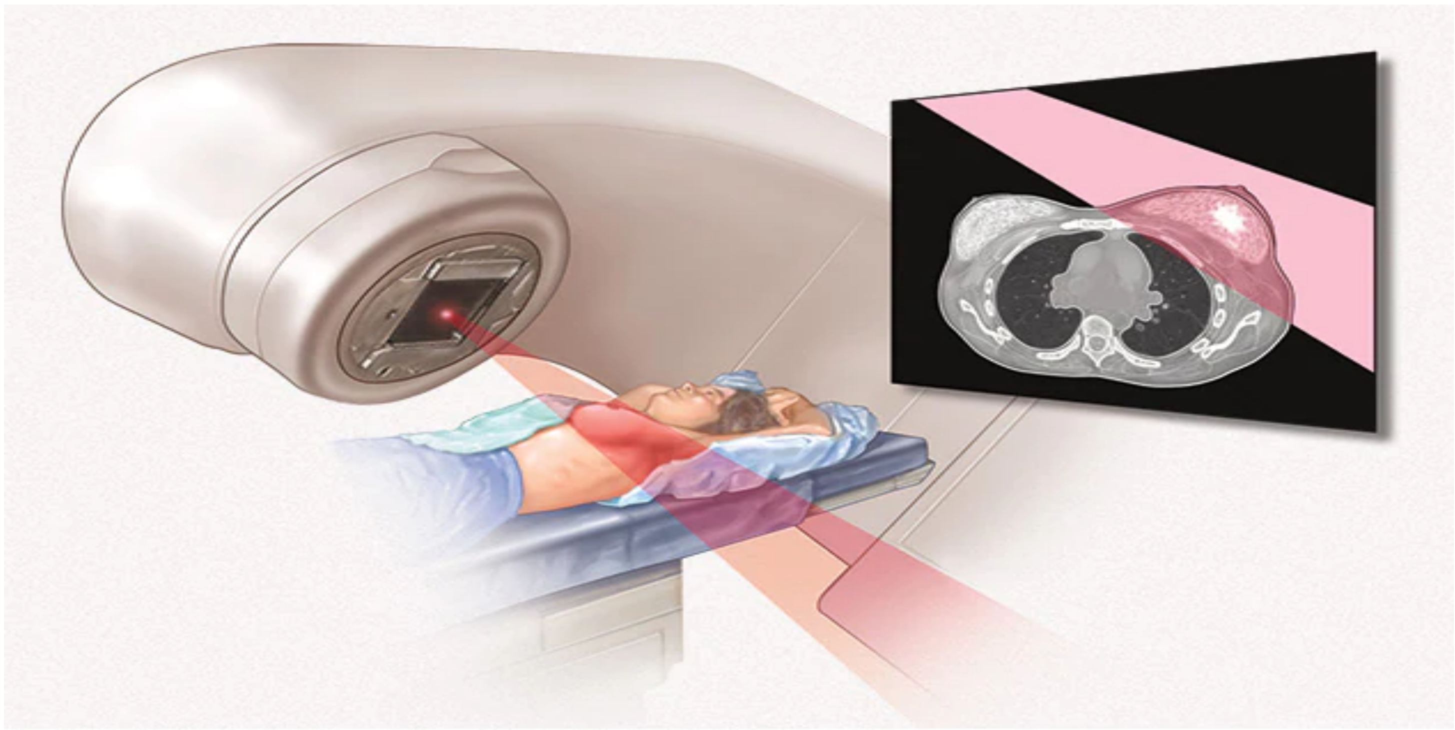


! The execution time must be minimized in order to be compatible with the clinical needs.

! The accuracy of the dose distribution calculation should be maximized. → **Monte Carlo simulation**

- The **features** that we would like to implement in a **VHEE/FLASH TPS** are:

1. Optimize **field direction**; ✗ **Not done yet**
2. Field **Energy** and **Pencil Beam flux** optimization **simultaneously**; ✓



Optimization process: Cost Function

The main **goal** of the Optimizer is to select:

1. The **Energy** of each field;
2. The **number of particles** of each PB.

Simultaneously

In order to **maximize tumor coverage e minimize the dose delivered to the OARs** and the normal tissue, the algorithm explore different set of energies and fluences.

↓

Calculate the cost function for a given configuration.

↓

Minimize the cost function using minimization methods.

Minimizing the so called **Cost Function**:

A Cost Function is used to measure how wrong the model is in finding a relation between the input (the planned dose for the tumor and the organs) and output (the absorbed dose according to the simulation).

Dose absorbed by the voxel — Planned dose — Plan factor — Voxel based

$$\chi^2 = \sum_{i \epsilon PTV} \omega_i \frac{(d_i - D_{PTV})^2}{d_i^2} + \sum_{i \epsilon OAR} \omega_i \frac{(d_i - D_{OAR})^2}{d_i^2} * g(d_i - D_{OAR})$$

$$d_i = \sum_{j=1}^{N_j} N_j D_{ij}$$

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	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%

The minimization methods used in the software are:

1. **Simulated Annealing (SA);**
2. **Quantum Annealing (QA).**

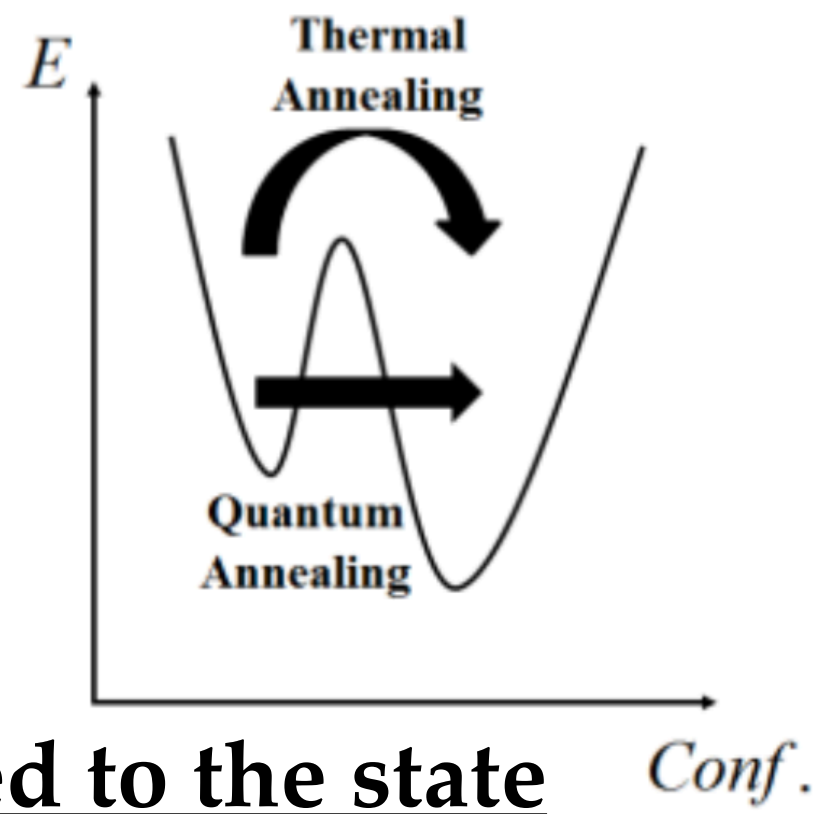
Able to get **out of local minima**

Optimization process: Minimization methods

- The minimization algorithm, **randomly varying the PB fluence and the beam energy**, defines specific configurations called "**grain**".
- At each iteration, **the change induced in the cost function is evaluated:** if the cost is less than value obtained in the previous iteration then the grain is accepted and the state stored.

Flux/Energy randomly changed → iteration ++ → Compute the Cost function

- $\Delta C < 0$ → Accepted!
- $\Delta C > 0$ → Rejected… but not always!



- The probability with which a grain is accepted or rejected is:

$$P = e^{-R(T)}$$

Dimensionless factor

$$R = \frac{\Delta C}{C} \times \frac{a}{w_{COST} \times T}$$

Simulated Annealing (SA)

Cost parameter

$$R = \sqrt{\frac{\Delta C}{C} \times \frac{1}{w_{COST}}} \times \frac{a}{T}$$

Quantum Annealing (QA)

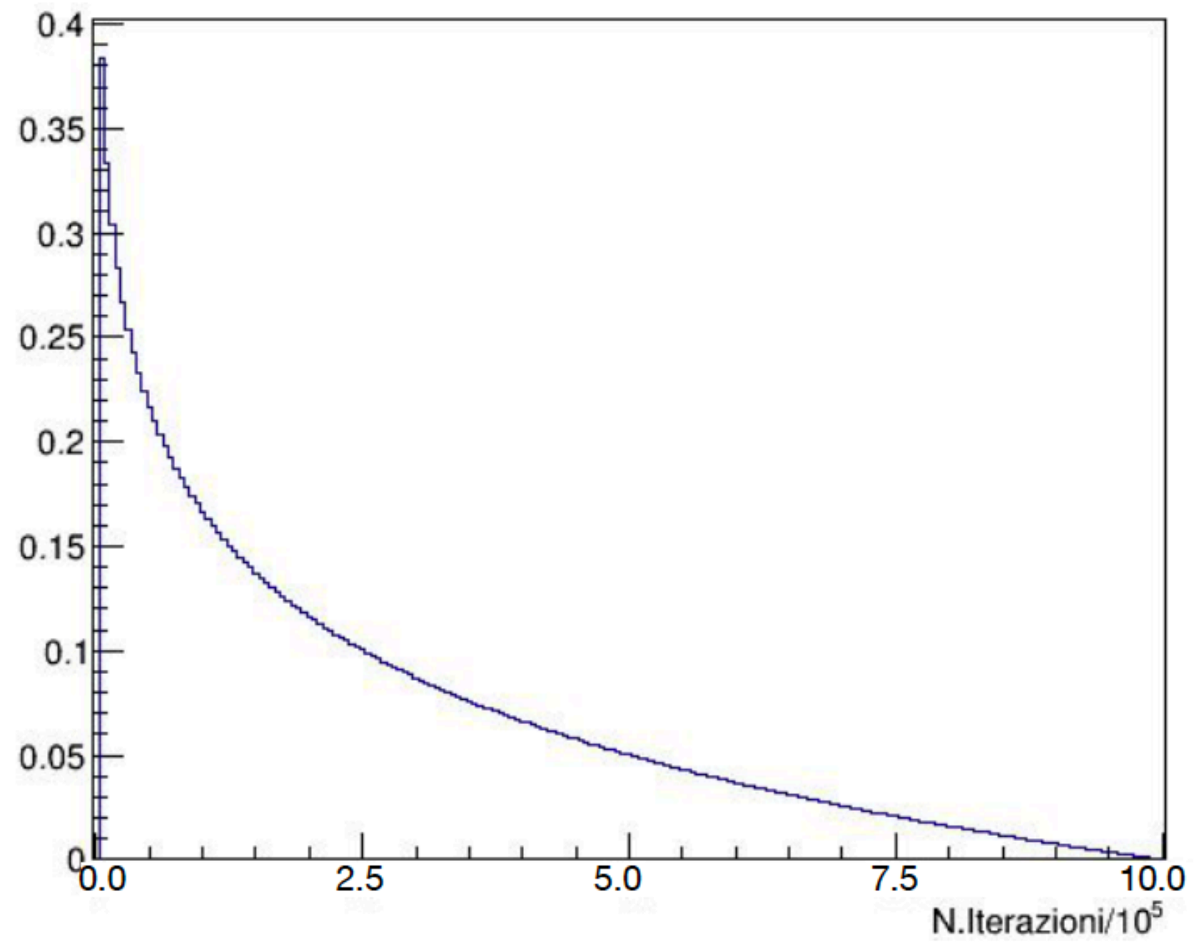
Temperature parameter related to the state

$$T = 1 - \left(\frac{log(iteration)}{log(MAXiteration)}\right)^{T}$$

START
T=1

Iteration ++

STOP
T=0

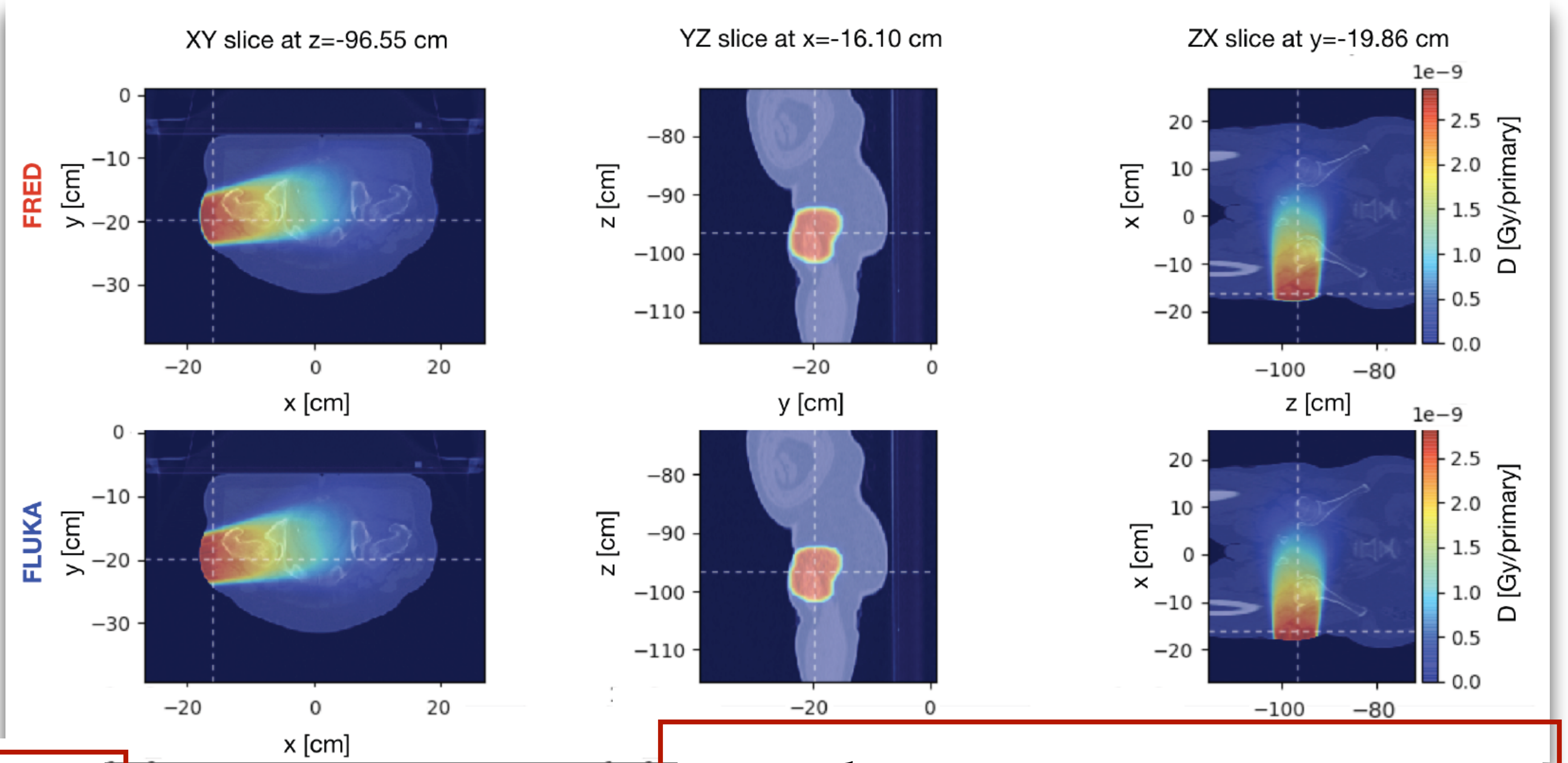


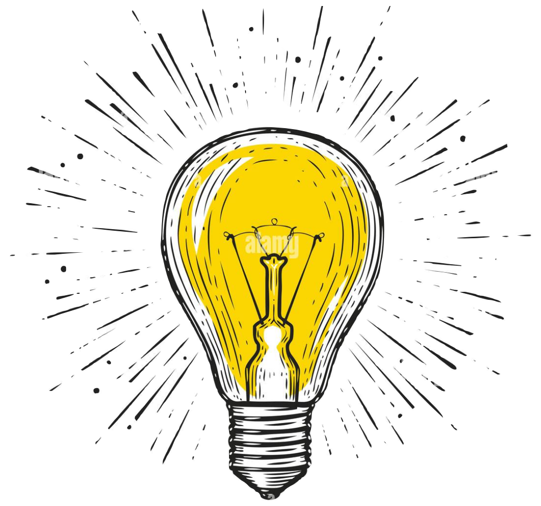
Monte Carlo software: FRED

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 starting from the Dij matrix given as output by a MC simulation. Our solution is to use **FRED**.

Dose evaluation with 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 such as MedAustron (Vienna), APSS (Trento), Maastro (Maastricht) and CNAO (Pavia) while carbon ions and electromagnetic models for FRED are under optimization.





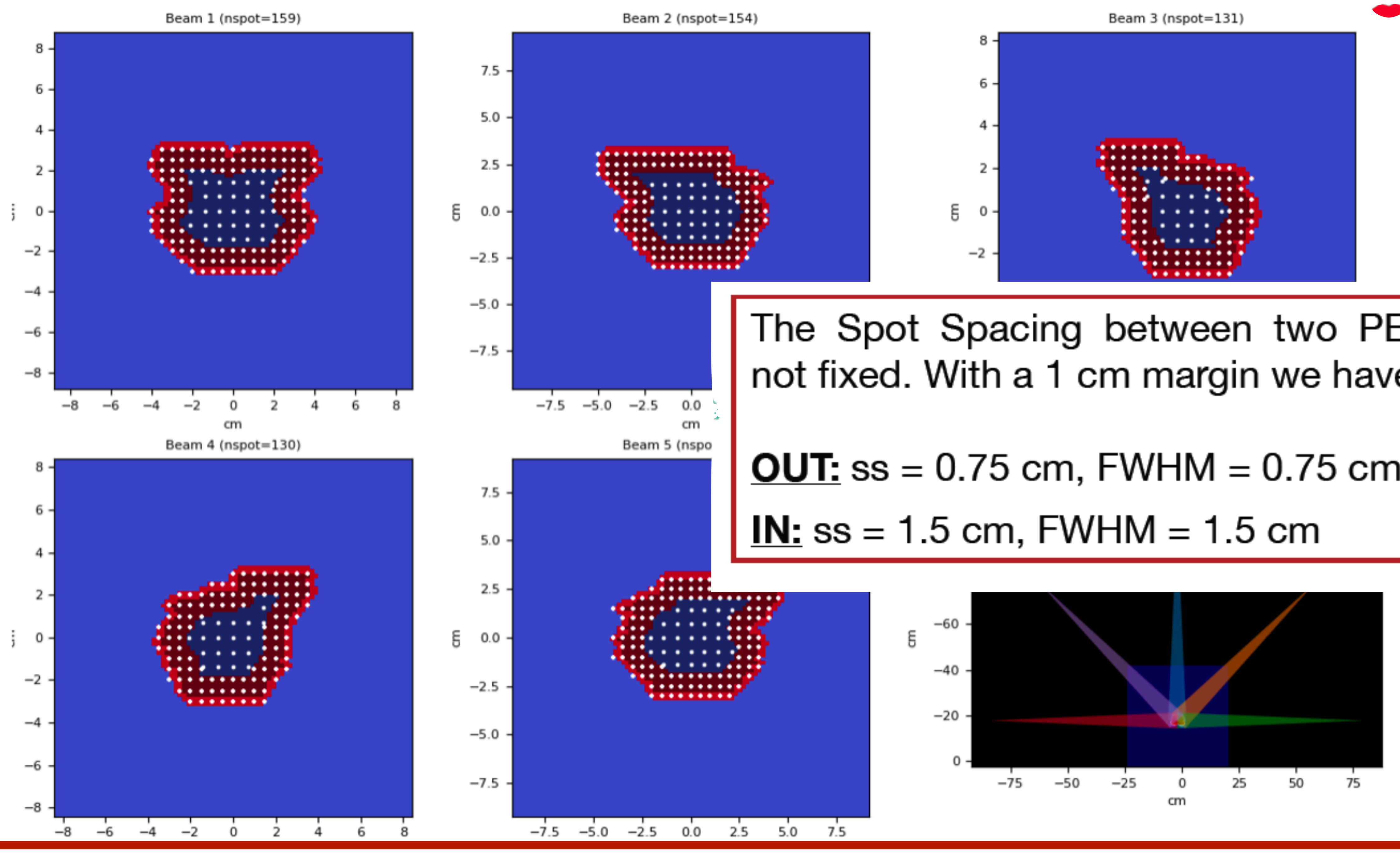
Our TPS software is capable to **optimize energies** and **fluences simultaneously** using **Dij matrix from FRED** at energies step of 10 MeV.

FRED has been developed to work on **GPU** (Graphic Process Unit) and it **reduces the simulation time** by a factor 1000 for proton treatments

Some results: Prostate Cancer

Real IMRT prostate treatment at Policlinico Umberto I hospital, Rome

- Patient with intermediate-risk prostate cancer, was treated with conventionally fractionated IMRT of **78 Gy** in **39 fractions**;
- Using FRED we have simulated the treatment, planned using 5 fields with energies that go from **70 MeV to 130 MeV** (step of 10 MeV).



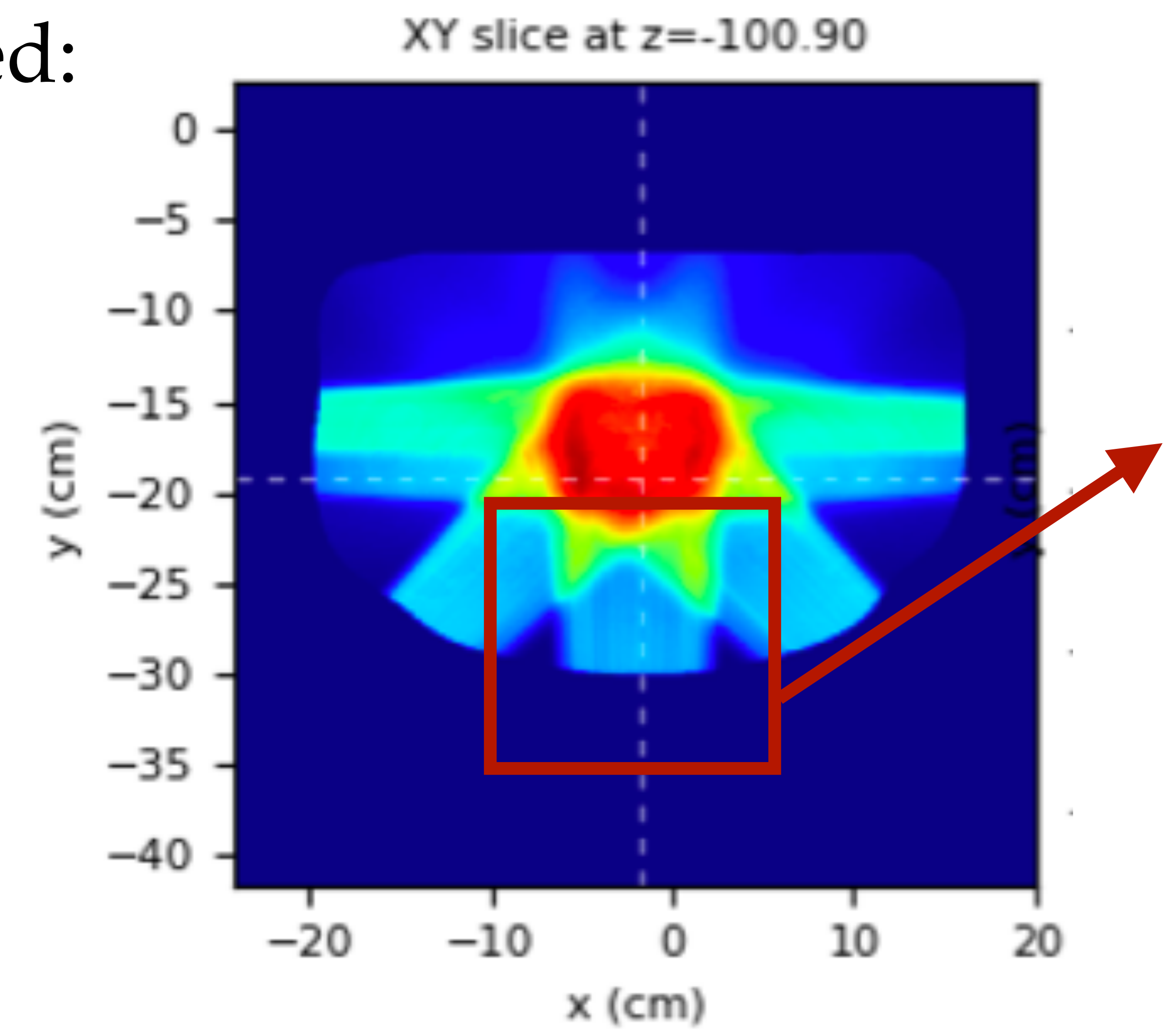
The Spot Spacing between two PB is not fixed. With a 1 cm margin we have:

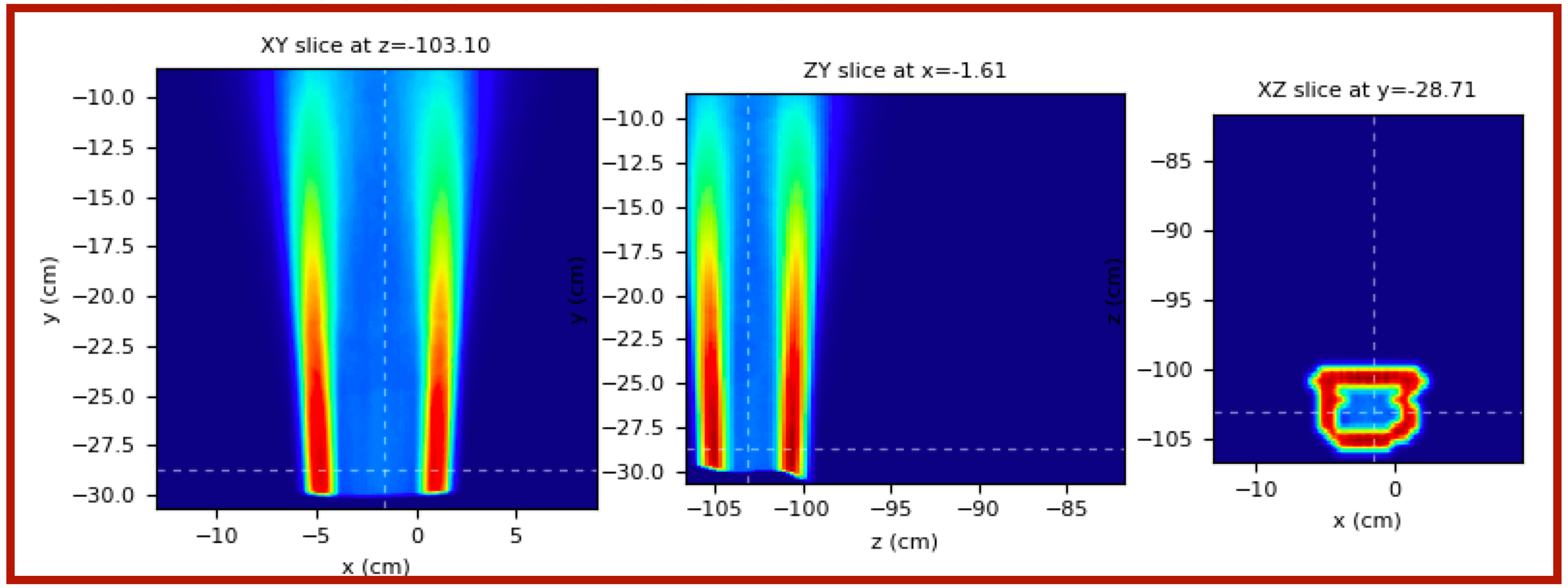
OUT: ss = 0.75 cm, FWHM = 0.75 cm

IN: ss = 1.5 cm, FWHM = 1.5 cm

- With this choice of SS we obtained:

Field	# PB
1	70
2	70
3	57
4	58
5	68





Some results: Prostate Cancer

- The first goal was to achieve **at least the result we have obtained with the standard approach** (already published, in which only the number of particle of each PB was optimized) but optimizing the energies of the fields and the PB fluences simultaneously.
- Choosing a proper set of weight for each ROI, we are able to achieve a **better sparing of the Organs at risk** with respect to the standard optimization.

- The energies of the 5 fields chosen by the TPS are:

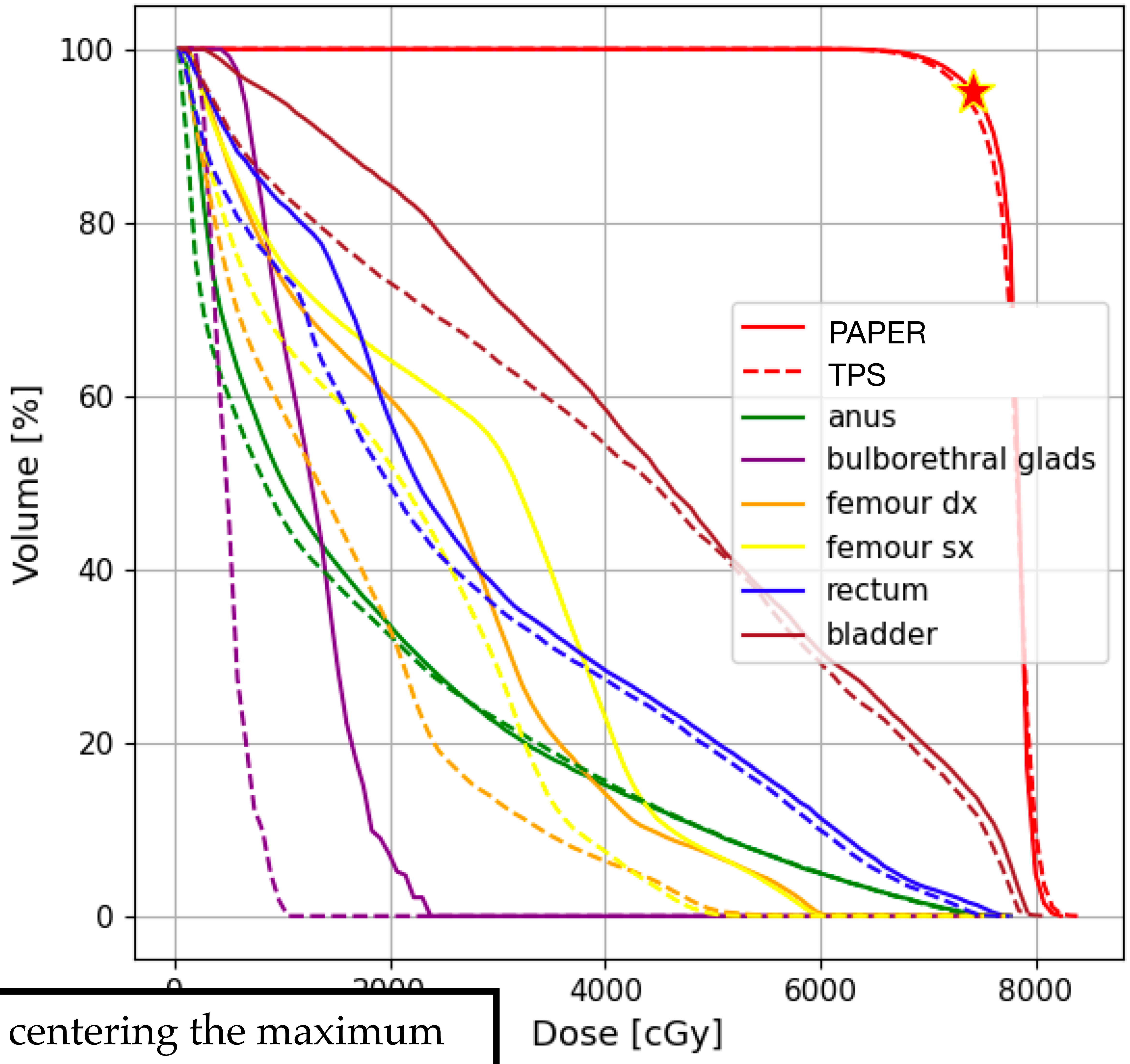
NEW TPS

Field	E [MeV]
1	120
2	110
3	130
4	130
5	90

OLD (fixed Energies)

Field	E [MeV]
1	70
2	120
3	130
4	130
5	120

The energies were chosen centering the maximum dose release on the isocenter of the PTV.



Conclusions

This preliminary study suggests that **VHEE** could be exploited in the treatments of deep sated tumor with performances that are **comparable** with the ones achieved in conventional RT or PT. In this context, the **FLASH** effect has a nice potential for improving the treatments efficacy;

The initial studies have been carried out **without optimizing** the **number** of used **fields**, their **energy** or they **direction**: the promising results obtained are then 'conservative' in that respect;

Next steps

Thanks for your attention!!

Develop and implement different clinical treatments with VHEE, like **VMAT**.

Current studies are exploring the potential for different pathologies that are suited for **hypo-fractionated regime** (lung and pancreas pathologies).

A further step will be to optimize the algorithm in order to reduce the execution time and make it compatible to the clinical need.

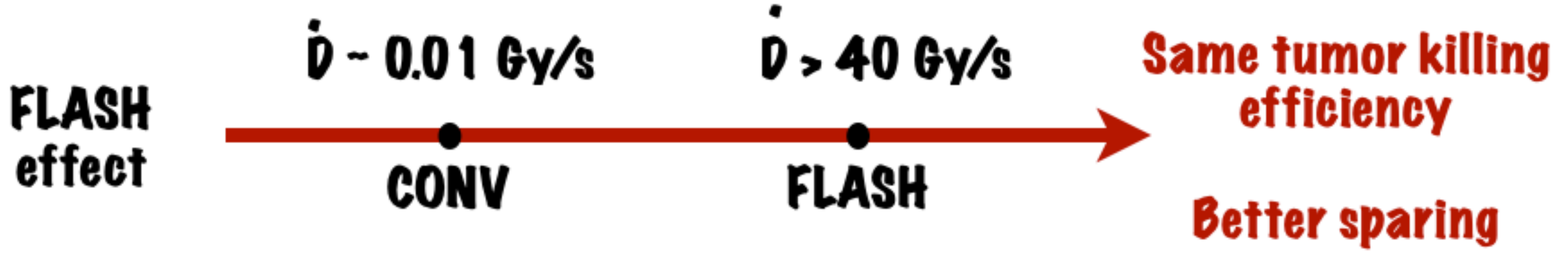
Even if the FLASH effect is already modelled using the Flash Modifying Factor (**FMF**) to account for the reduced normal tissue damage, a proper **evaluation voxel based of the Dose Rate** will be introduced as a constraint to be respected;

The study of the beam delivery is becoming more and more important.. different approaches to the PTV coverage (single large field or active scanning) **have a large impact on the dose rate.**

FLASH effect

In conventional radiotherapy, the dose is absorbed by the tissues at relatively low rate (~0.01 Gy/s)

Recent studies showed that the use of high dose rates (> 10 Gy/s) induces FLASH effect:



We decided to compare the performances of a realistic VHEE treatment, with and without the FLASH effect, with standard photon and proton RT. I focused my study on intra-cranial lesions.

External Beams Radiotherapy (EBRT)

Radiotherapy with External Beams (**EBRT**) is used to treat almost 50% of solid tumors. Beam of **photons** (6-15 MeV), **protons** (150-250 MeV) and **electrons** (4-20 MeV) can be used to treat different pathologies, exploiting the specific absorbed dose distribution of each projectile

PHOTONS (6-15 MV)

Suited for the treatment of **deep-seated tumor** (> 10 cm)

Release dose to healthy tissues

PROTONS

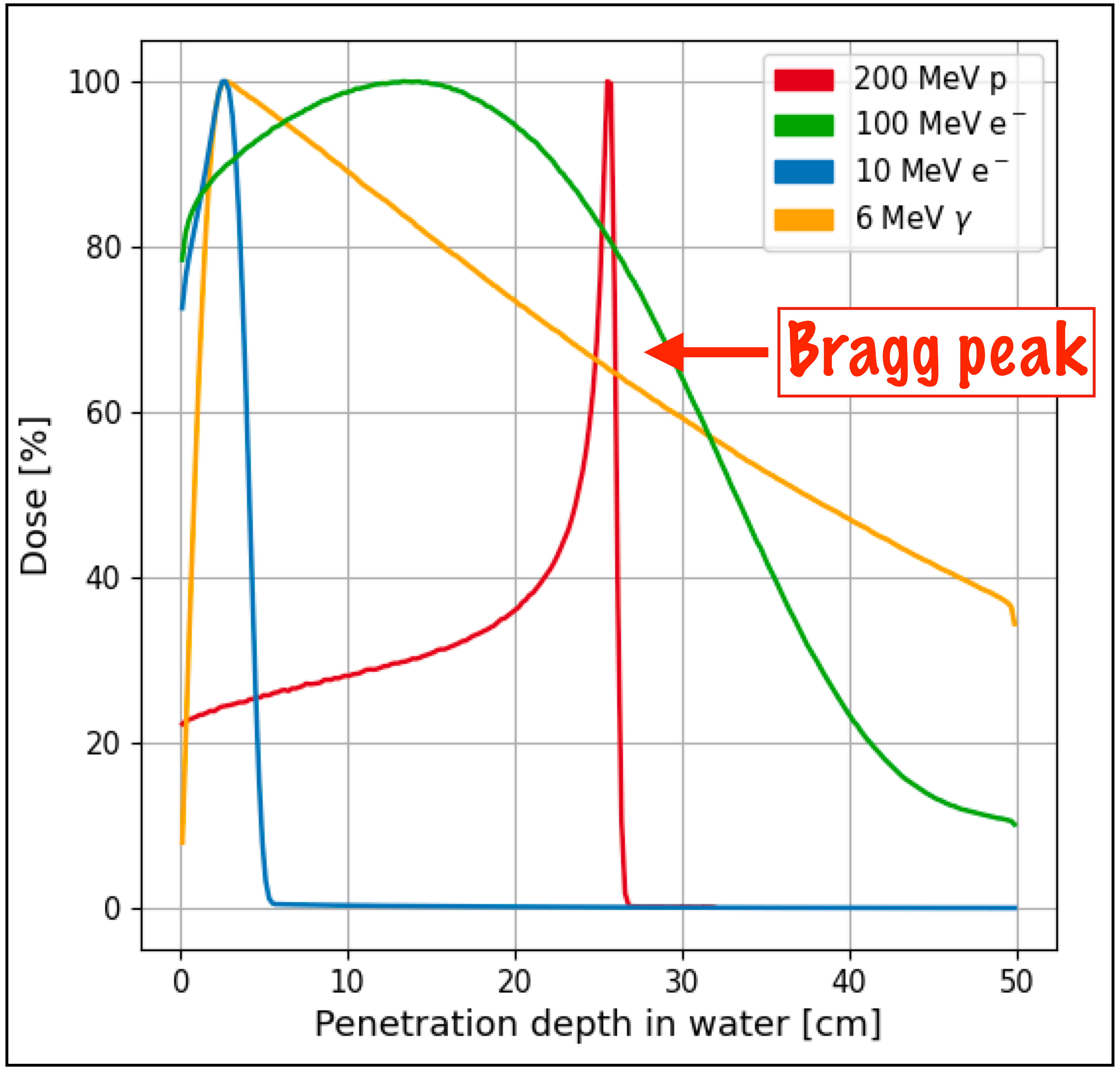
Better protection of healthy tissue

Complex and expensive accelerating equipment

ELECTRONS (4-25 MeV)

Used for the treatment of **superficial tumor**

Energy not adapt for the treatment of **deep-seated tumor**

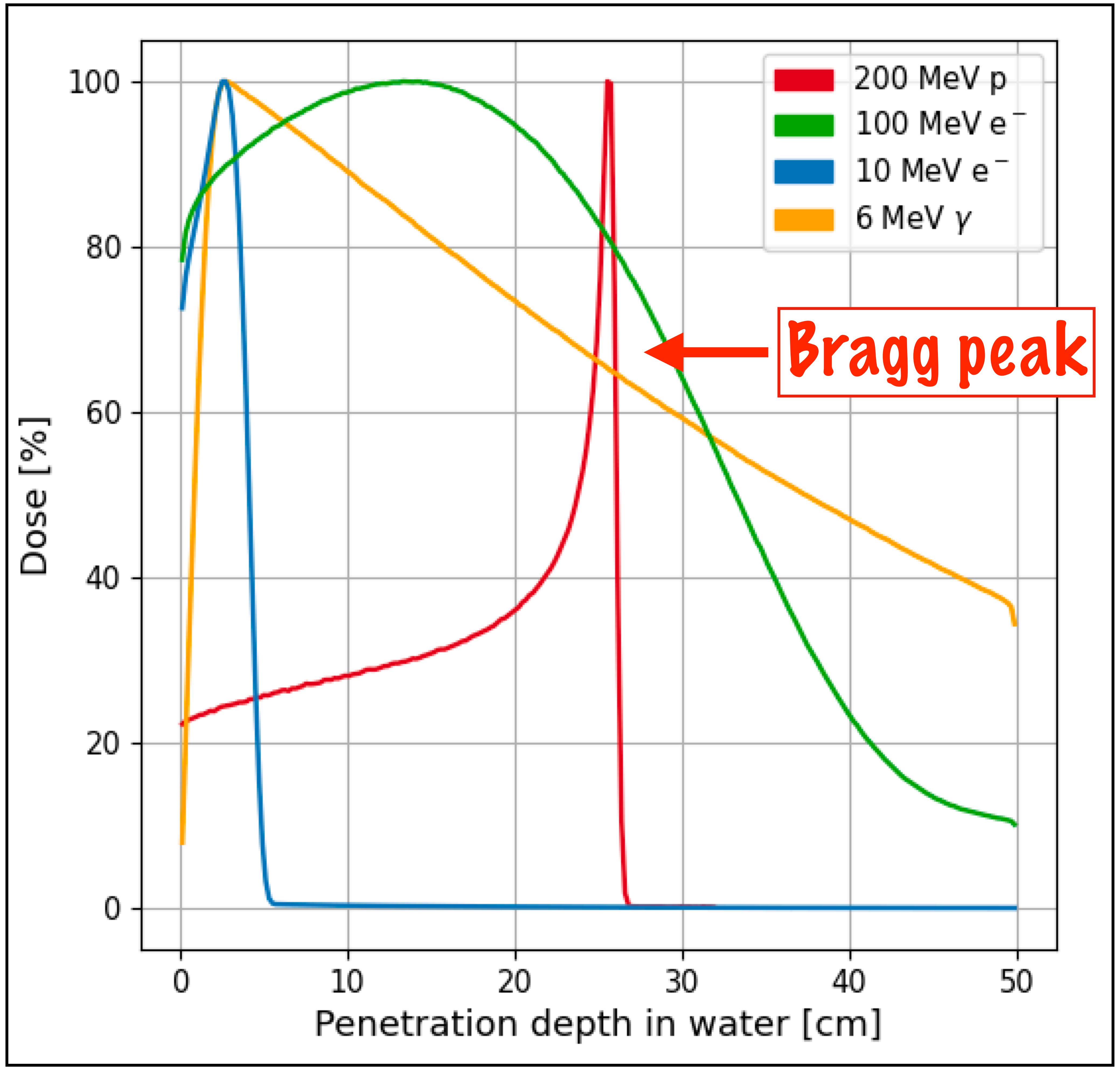


Very High Energy Electrons (VHEE)

ELECTRONS WITH E > 70 MeV have been considered already in the past as an alternative to protons and RT due to their better, with respect to conventional RT, longitudinal sparing of OARs (charged -> BP) and reduced impact of range uncertainties (broader BP).

So far, treatments using e- have shown performances (comparable with RT or p) only at the cost of having high energies (> 100 MeV) and number of fields (>13).

Due to cost, complexity and space encumbrance (**long accelerating system**) VHEE have not yet reached the clinical stage.



Today these issues can be addressed thanks to

C-band and X-band technology

2.9 GHz	5.7 GHz	12.0 GHz
S-band	C-band	X-band
G ~ 20 MeV/m	G ~ 50 MeV/m	G ~ 100 MeV/m

FLASH EFFECT

Dose rate radically increased from ~ 0.01 Gy/s to 100 Gy/s