Performance of very high-energy electron therapy delivered in conventional and FLASH conditions:
the case of Stereotactic treatments

PhD in Accelerator Physics

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Thesis Advisor:
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come fai.. **SBAI**

RADIOTHERAPY, FLASH EFFECT & VHEE

Conventional Radiotherapy

Conventional Radioterapy:

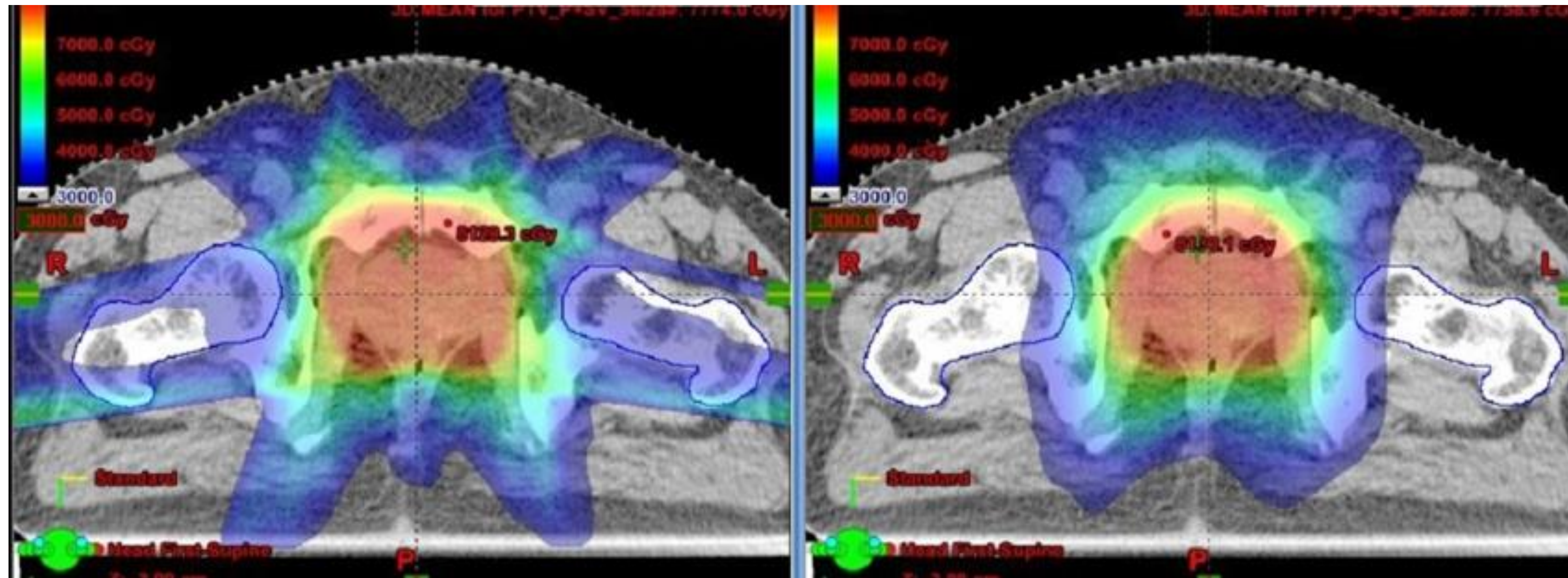⊙ Absorbed dose (2 Gy x Fraction)
⊙ Conventional Dose Rate (0.08 Gy/s)

Radiotherapy is a localised, non-invasive, painless therapy, mostly carried out on an outpatient basis, capable of inducing necrosis or the death of tumour cells through the use of high-energy radiation called ionising radiation.
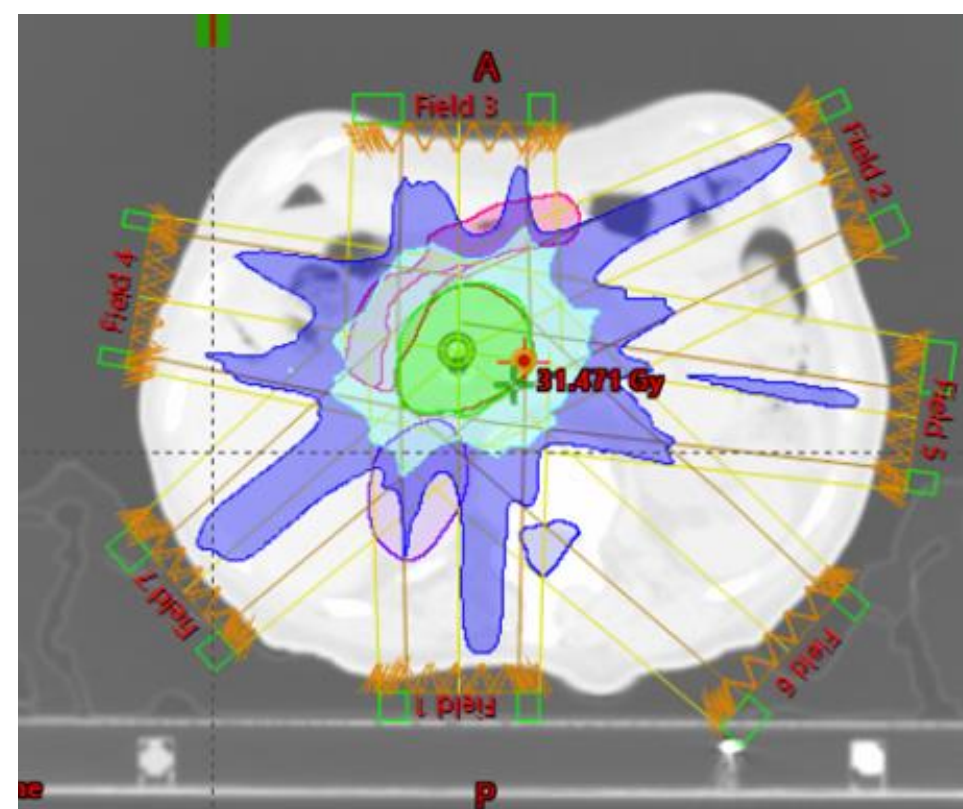
It is estimated that about **60 per cent of cancer patients undergo at least one course of radiotherapy during their care pathway.**
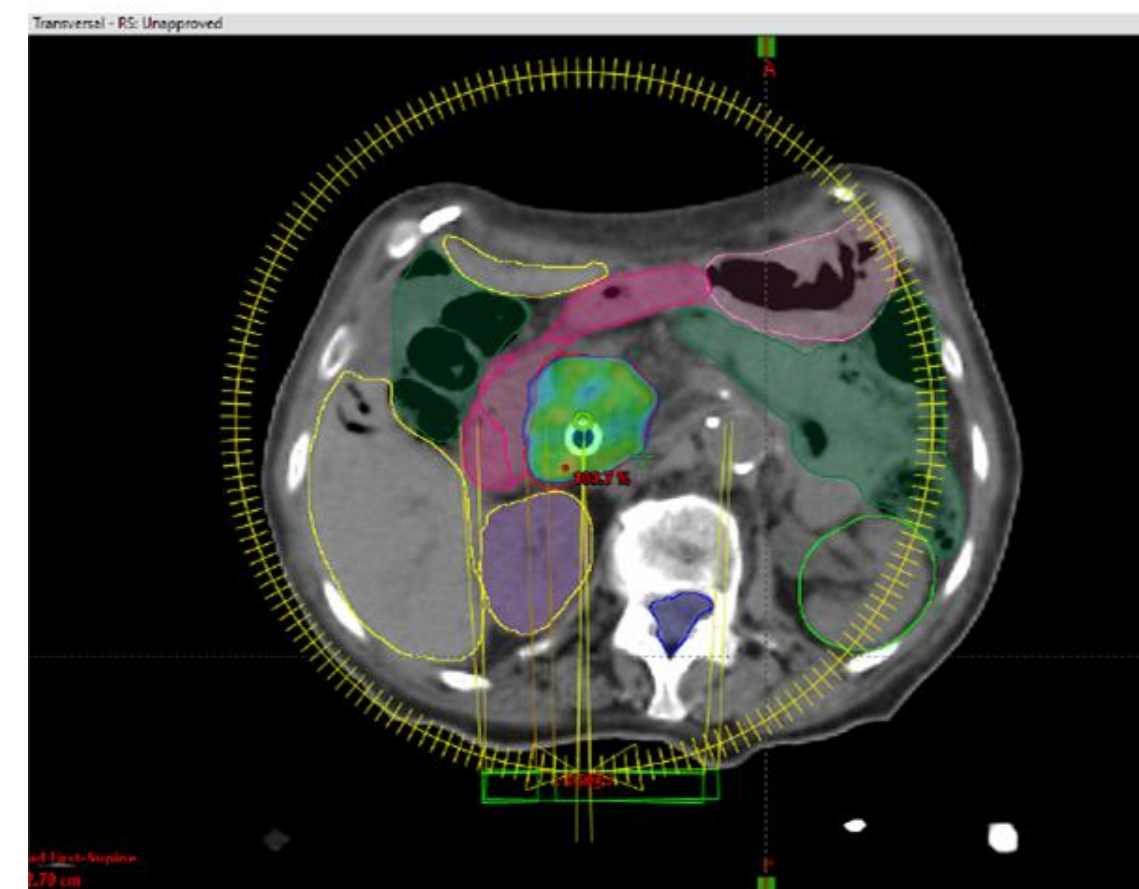
Photon radiotherapy is the gold standard in the clinic

Irradiation techniques: IMRT and VMAT

Intensity-modulated radiation therapy (IMRT)

Volumetric Modulated Arc Therapy (VMAT)

Conventional Radiotherapy:

- Absorbed dose (2 Gy x Fraction)
- Conventional Dose Rate (0.08 Gy/s)

Intensity-modulated radiation therapy (**IMRT**) allows for the radiation dose to conform more precisely to the three-dimensional (3-D) shape of the tumor by modulating or controlling the intensity of the radiation beam in multiple small volumes

Volumetric modulated arc therapy (**VMAT**) is a form of radiation therapy used to treat cancer. During treatment, a machine rotates around the patient body, sending multiple energy beams of varying strengths to kill cancer cells and destroy tumors.

FLASH Effect in radiotherapy

FLASH Effect activation:

- High absorbed dose per each fraction (> 3 Gy)
- Ultra High Dose Rate (> 40 Gy/s)
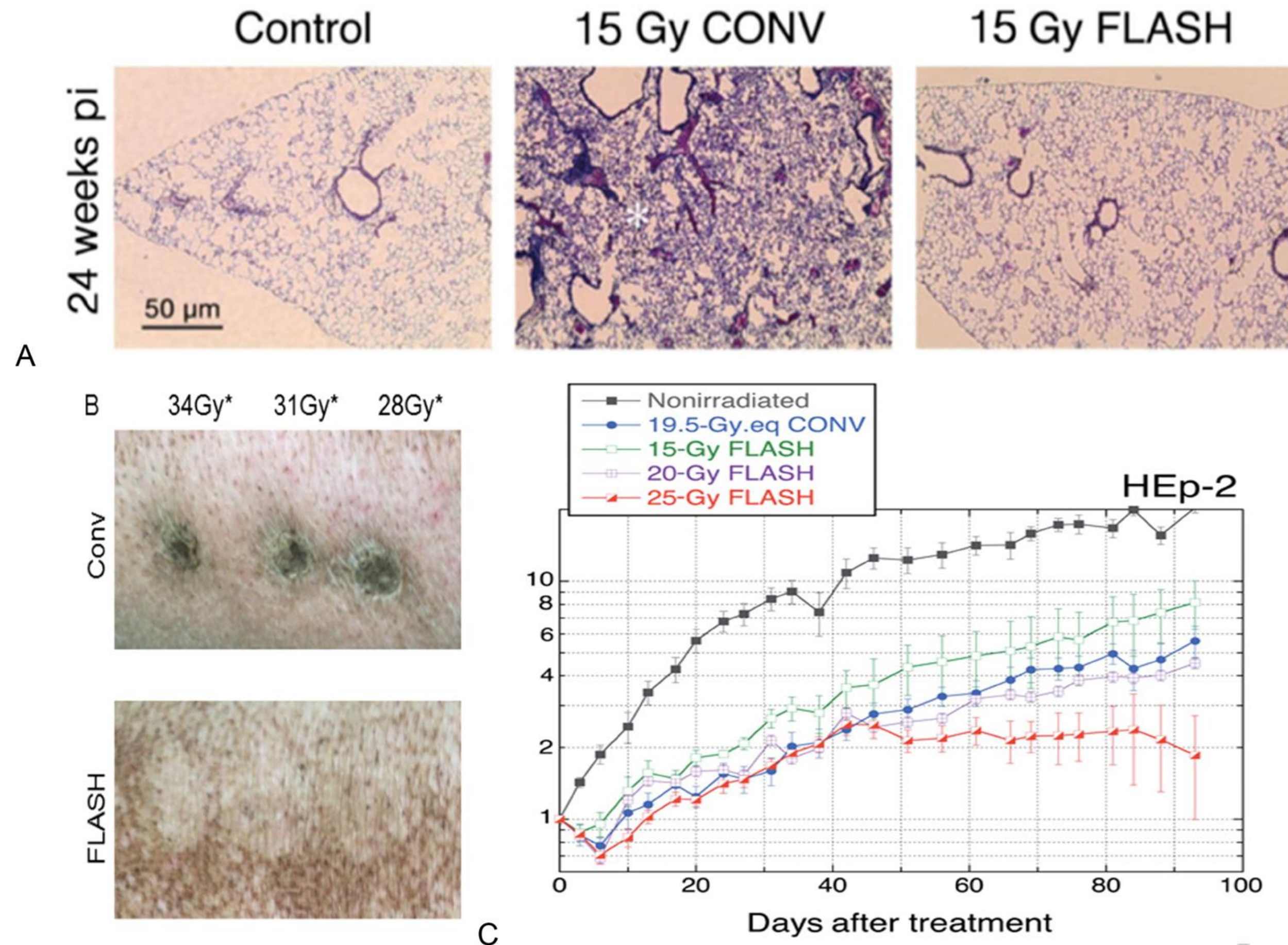
FLASH radiotherapy is a technique involving the delivery of **ultra-high dose rate** radiation to the target. FLASH-RT has been shown to reduce radiation-induced toxicity in healthy tissues without compromising the anti-cancer effects of treatment compared to conventional radiation therapy.

[1] V. Favaudon, L. Caplier, V. Monceau, F. Pouzoulet, M. Sayarath, C. Fouillade, M. F. Poupon, I. Brito, P. Hupé, J. Bourhis, J. Hall, J. J. Fontaine, and M. C. Vozenin. Ultrahigh dose-rate flash irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med, 6(245):245ra93, 2014.
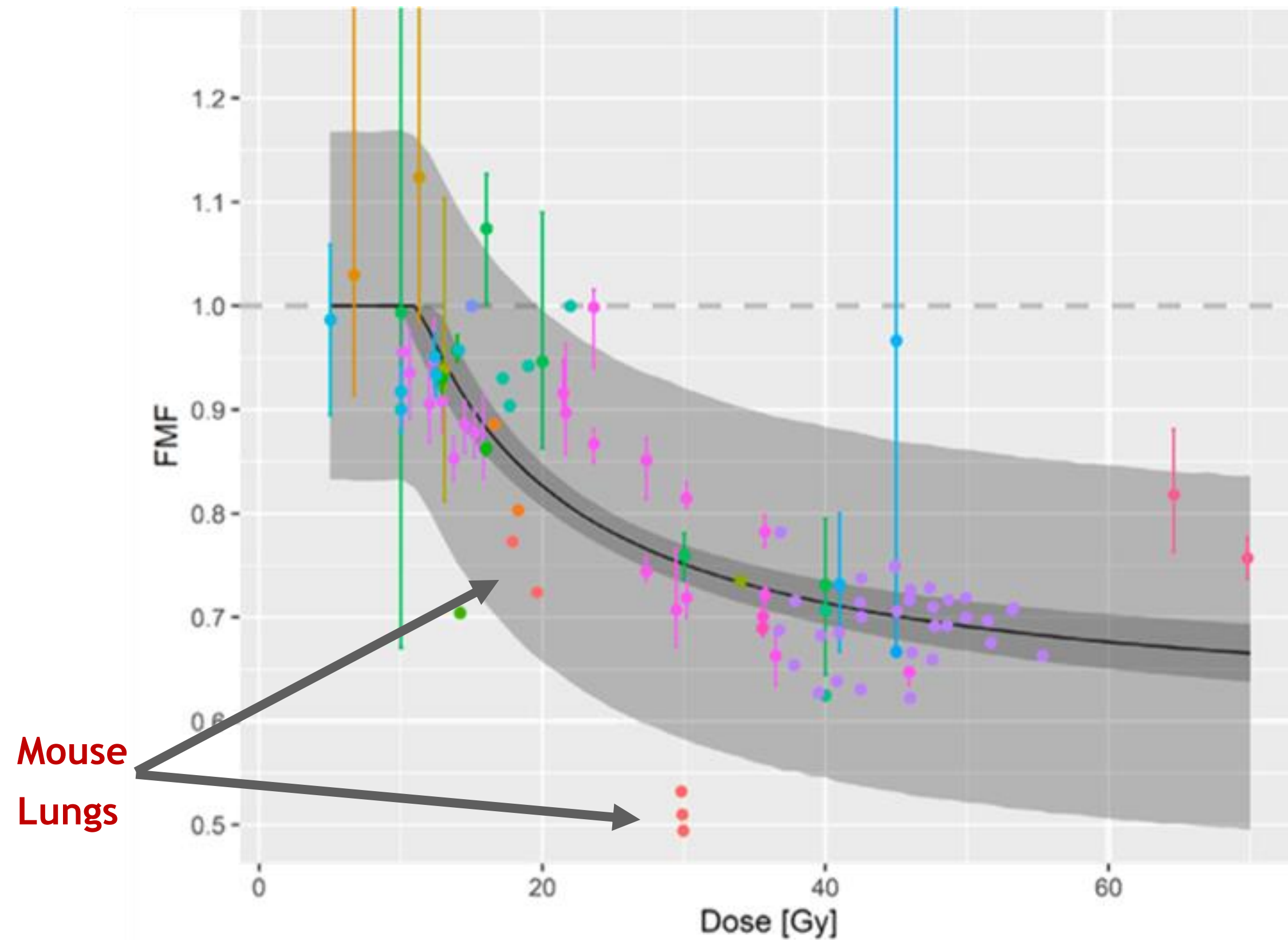[2] J. Bourhis, W. J. Sozzi, P. G. Jorge, O. Gaide, C. Bailat, F. Duclos, D. Patin, M. Ozsahin, F. Bochud, J. F. Germond, R. Moeckli, and M. C. Vozenin. Treatment of a first patient with flash-radiotherapy. Radiother Oncol, 139:18–22, 2019. ISSN 1879-0887. doi: 10.1016/j.radonc.2019.06.019.

FLASH Effect model

All the parameters (FMF$_{min}$, DT) can be tissue specific and must be extracted from fit to the data. Currently the error bars are really huge: radiobiological data are badly needed

Mouse
Lungs

With this parametrization we can define, referring to the same effect on the tissue:

$$FMF_{min} = \frac{D_{conv}}{D_{UHDR}}$$

So our FMF$_{min}$ factor is related to the maximal the sparing that happens for doses >> D$_T$ and at Ultra High Dose Rate.

With this definition, and with a bit of mathematics, we can generally describe the FMF as a function of any dose D

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

[3] T. T. Böhlen, J. F. Germond, J. Bourhis, M. C. Vozenin, E. M. Ozsahin, F. Bochud, C. Bailat, and R. Moeckli. Normal tissue sparing by flash as a function of single fraction dose: A quantitative analysis. Int J Radiat Oncol Biol Phys, 114(5):1032– 1044, 2022. ISSN 1879-355X.

FLASH: the beam delivery

Montay-Gruel, P. et al, Clin. Cancer Res. 2021,
DOI: 10.1158/1078-0432.CCR-20-0894

FLASH effect:
- St. Bartholomew e (1967)
- Christie e (1962-1982)
- Curie e (2014)
- Lausanne e (2017-2019)
- Stanford e (2017 - 2019)
- Febetron e (1969 -1978)
- ESRF Rx (2018)
- UPenn p (2019)
- Dresden Oncoray e, p (2022)

No FLASH effect:
- Dresden Oncoray e, p (2019)
- ANSTRO Rx (2018)
- Christie e (1962 -1982)
- Lausanne e (2017 2019)

Axis labels: Irradiation time for delivering 10Gy (sec) vs Dose rate in pulse/bunch (Gy/sec)

Going FLASH' is not just a matter of 'total absorbed dose'. One has also to deliver the dose within a given total time.
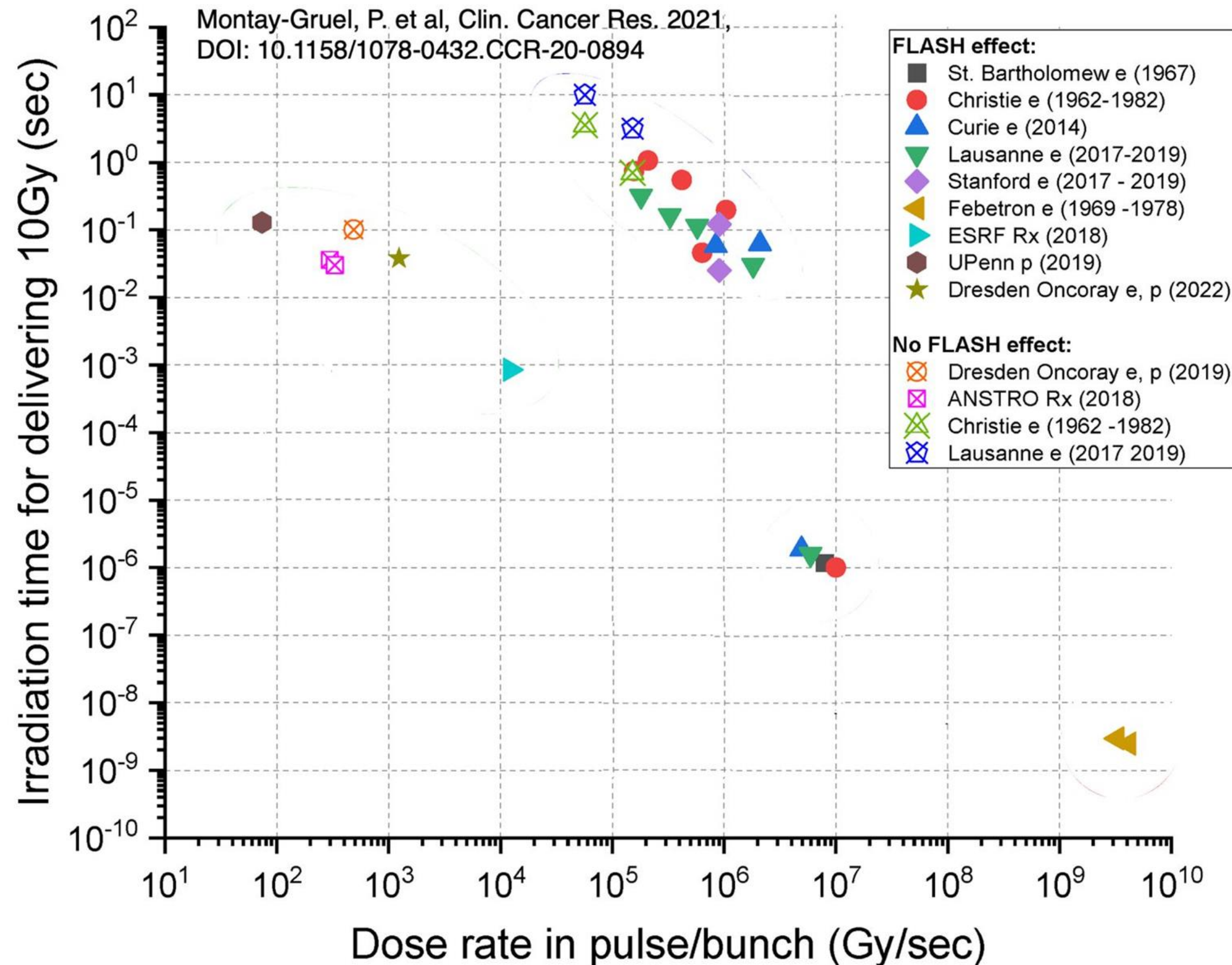
⊙ Changing the beam energy with protons becomes really difficult

⊙ VHEE have the nice advantage that with a 'single energy' a complete field can be delivered!

The points marked with an **x** in the graph are related to experiments not observing a significant FLASH effect

Need to explore the 'active scanning' solution

[4] Montay-Gruel P, Acharya MM, Jorge PG, et al. Hypofractionated FLASH-RT as an effective treatment against glioblastoma that reduces neurocognitive side effects in mice. Clin Cancer Res. 2021;27(3):775-784.

Very High-Energy Electron (VHEE)

⊙ VHEE are suitable for FLASH delivery
⊙ Machine dimension
⊙ Electron energies never tested in the clinic
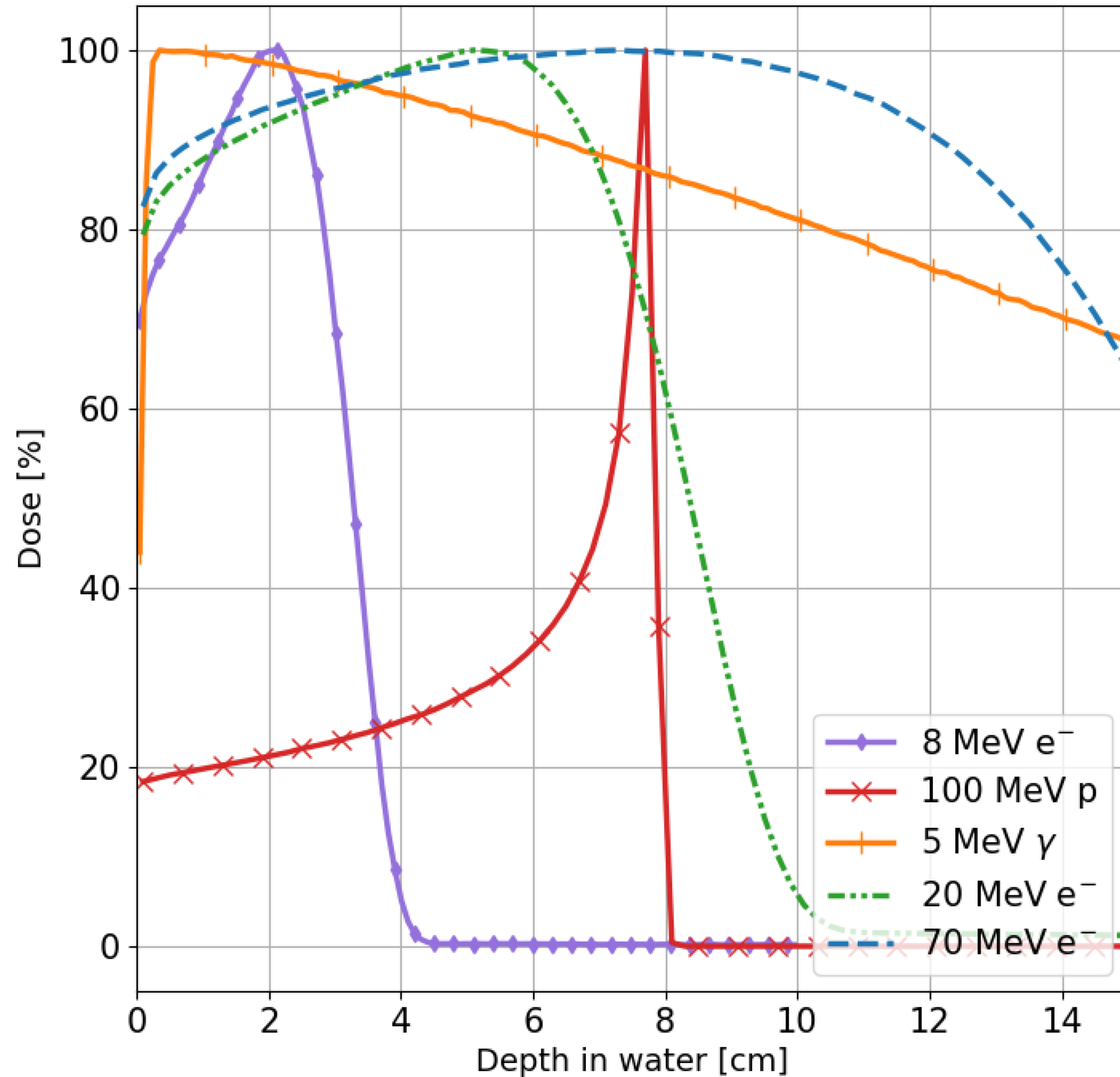
The commercial availability of C-band accelerators makes it possible to build compact machines,
if clinical applicability is demonstrated VHEE may have a new chance over protons in the treatment of tumours precisely because the FLASH effect with electrons is facilitated.
But it must be proved that with these energies and with this type of Pencil beam it is possible to have a quality comparable to VMAT.
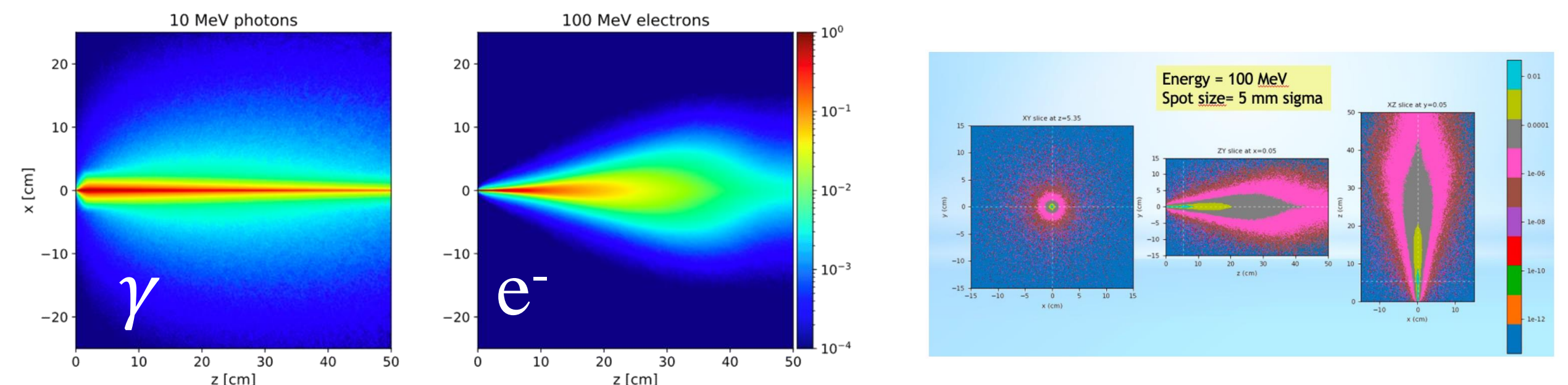
Prototype VHEE Accelerator

A possible implementation
being explored in Sapienza

- **C-band linac (f=5,712 GHz)**
- **Standing wave structure (SW)**
- **$\pi/2$ mode**
- **Bi-periodic geometry**

High-lines:

To move from superficial (4-12 MeV) to deep-seated (up to 130 MeV) tumors.. a 'new' compact accelerator is needed
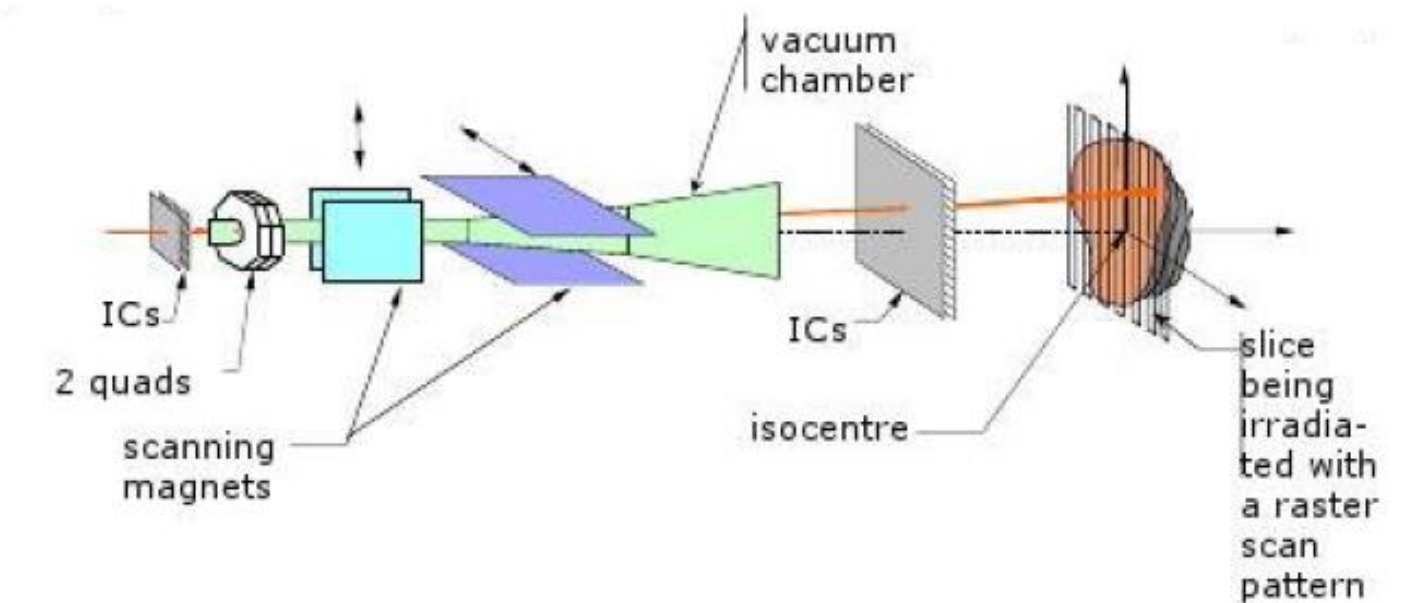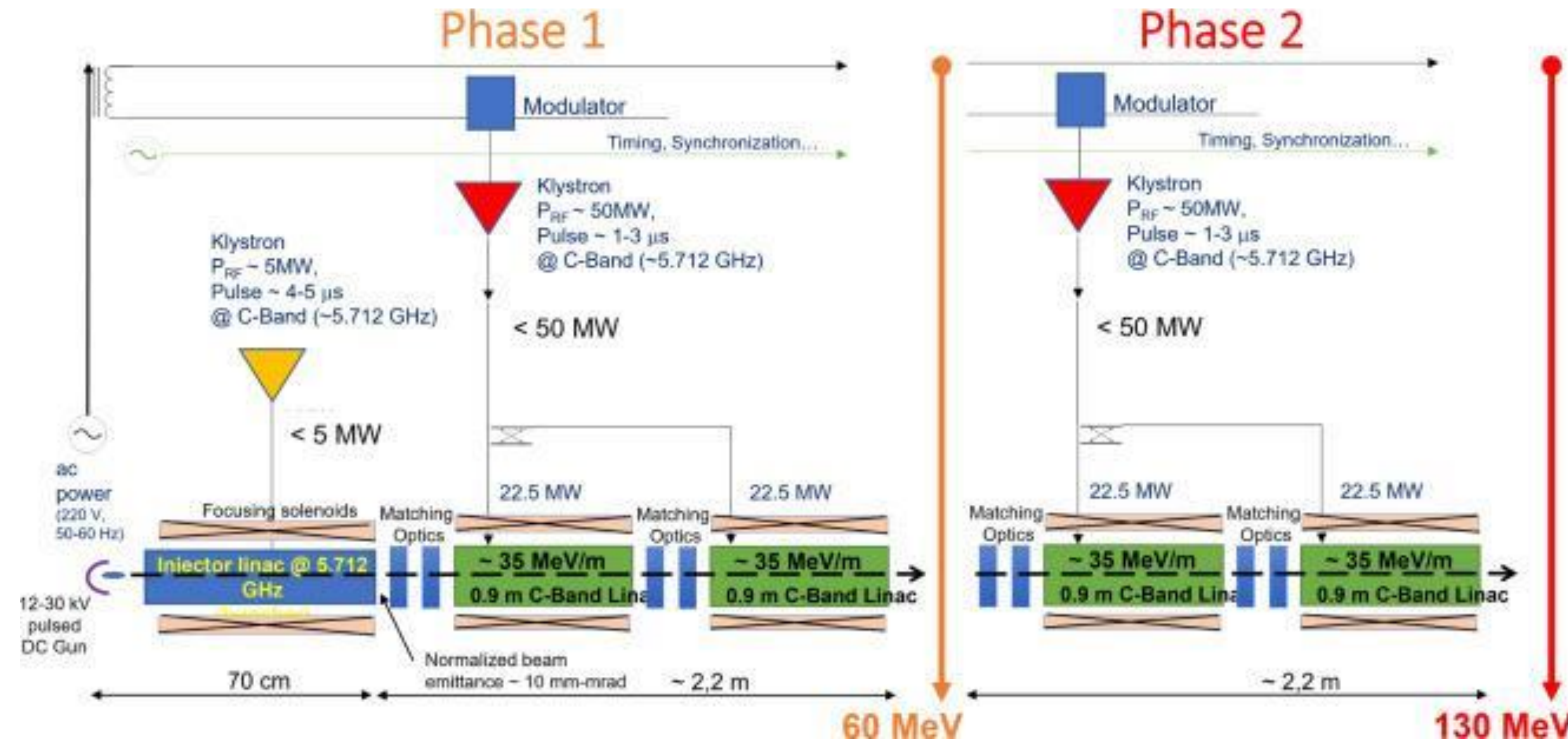
[5] L. Giuliano, D. Alesini, M. Behtouei, F. Bosco, M. Carillo, G. Cuttone, D. De Arcangelis, L. Faillace, V. Favaudon, L. Ficcadenti, S. Heinrich, M. Migliorati, A. Mostacci, L. Palumbo, A. Patriarca, B. Spataro, and G. Torrisi. Preliminary Studies of a Compact VHEE Linear Accelerator System for FLASH Radiotherapy. In Proc. IPAC'21, number 12 in International Particle Accelerator Conference, pages 1229– 1232. JACoW Publishing, Geneva, Switzerland, 08 2021.

Building a treatment plan

constructing a treatment plan is a process involving several competencies: as it is necessary to find the best way to treat the patient while keeping the risk of irradiation of healthy organs acceptable. Dose prescription will also be of paramount importance as the **FLASH technique prefers high dose prescriptions per single fraction**.

- ⊙ I used the infrastructure in the SBAI department

- ⊙ I spent about six months constructing each treatment plan for each patient.

Choose the direction of the field and energy so that they spare healthy organs and intercept the tumour
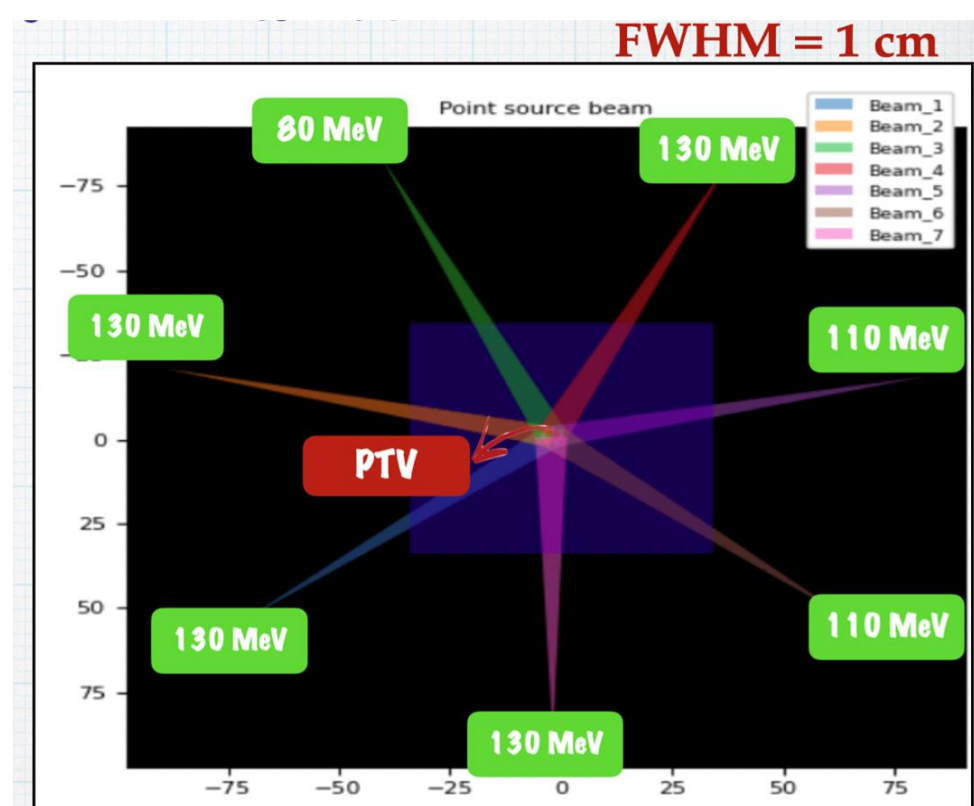
Distribute the pencil beams for each field so that they cover the entire surface of the tumour
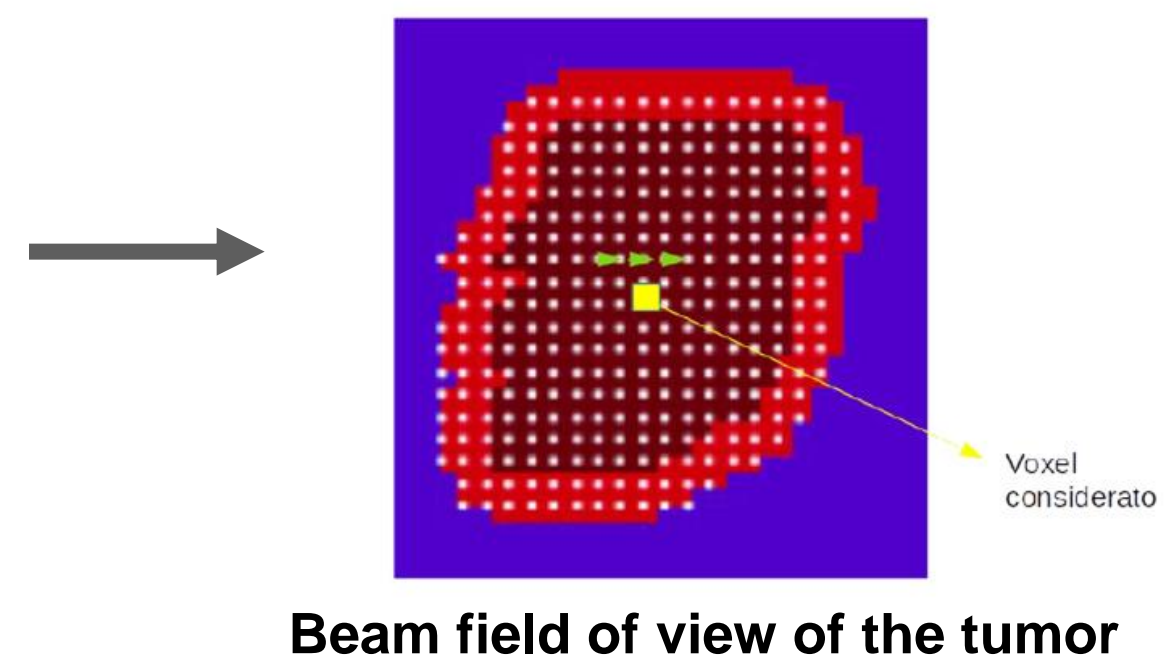
Simulate the dose per pencil beam with 10^5 events per pencil beam taking into account the particle path on the Patient's CT scan and optimise the fluence of each pencil beam
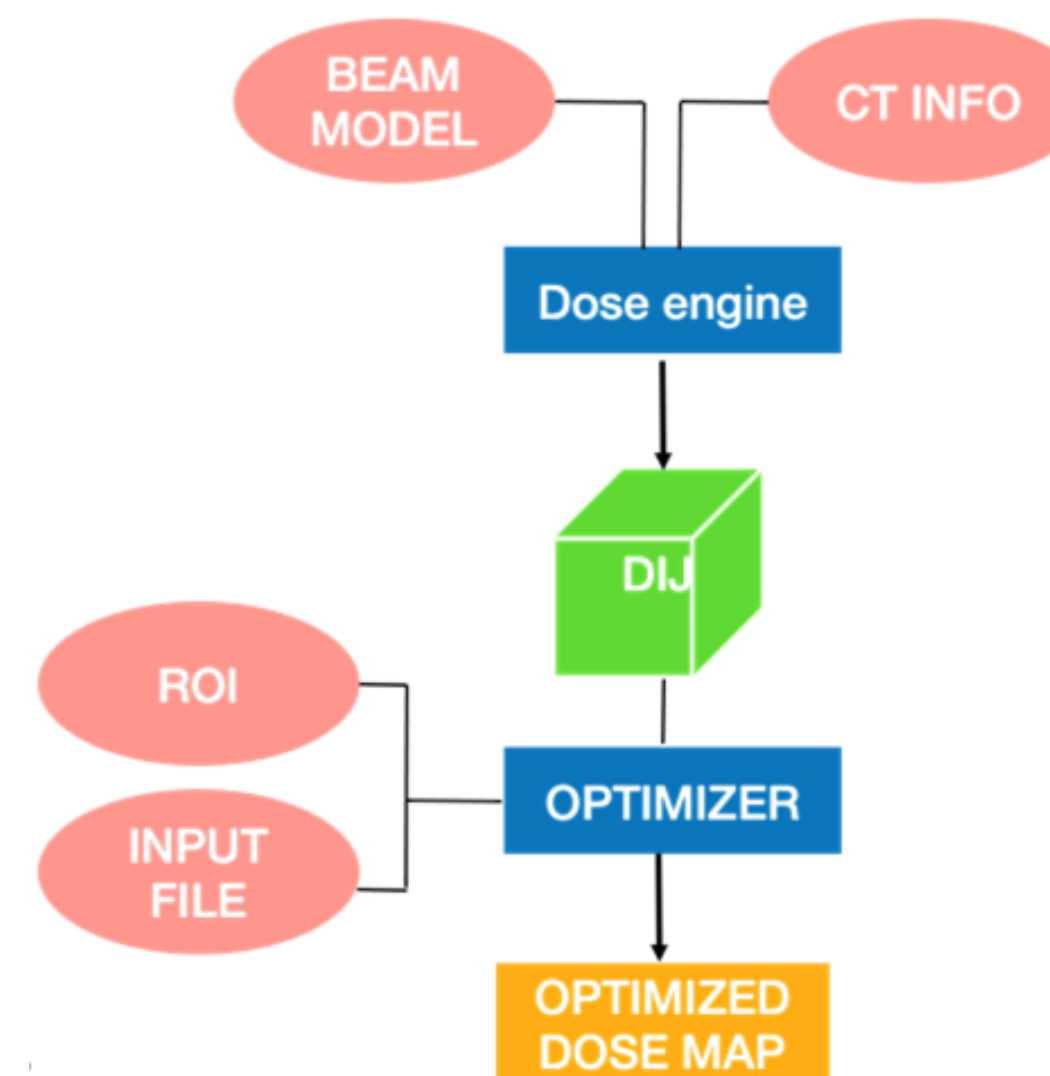
Evaluate the results obtained using the Dose-Volume Histogram estimating the dose absorbed by each organ

Beam field of view of the tumor


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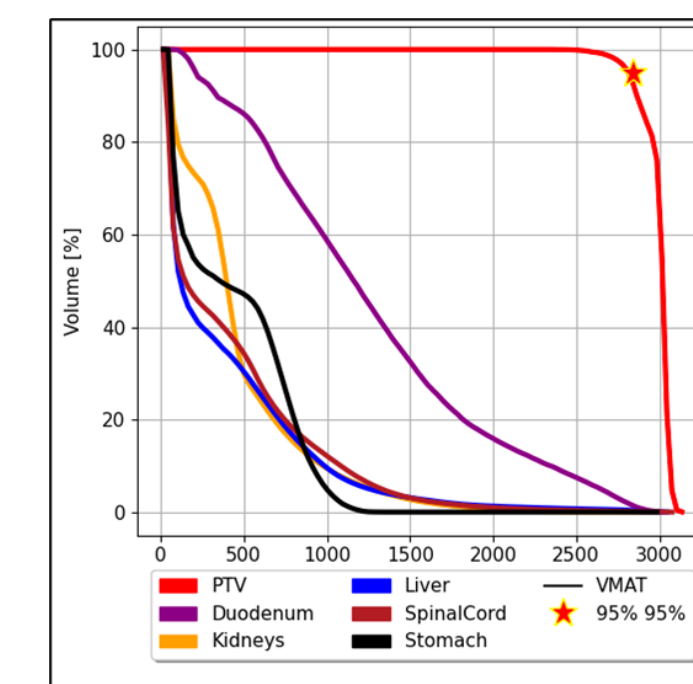
Treament Planning System

We consider a basic, "general" Treatment Planning System working on a multi-spots, multi-field delivery system. The different description of the beam model (flat beam, pencil beam, etc etc) adapts the TPS to the different beam. The algorithm we currently use for the optimization of a treatment with VHEE is based on the Proton Therapy algorithm (LOMAX) for pencil beam, rearranged for electrons.

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

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

D_{PTV} = dose target
D_{OAR} = dose threshold OAR
d_i = dose of the voxel
ω_i = relative weight of the voxel
N_j = pencil beam intensity
$g(x)$ = theta function
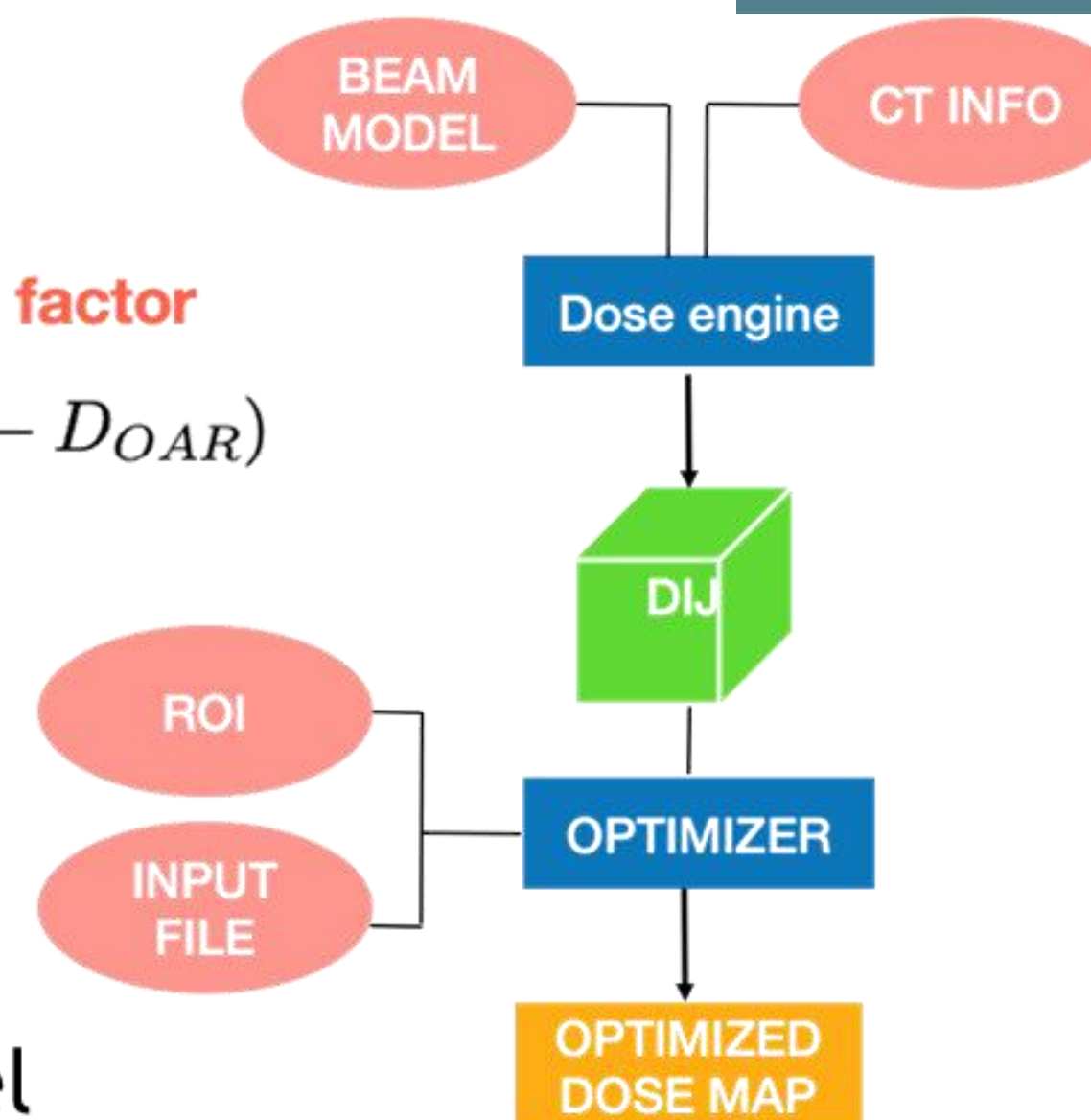
[6] A. Mairani, T. T. Böhlen, A. Schiavi, T. Tessonnier, S. Molinelli, S. Brons, G. Battistoni, K. Parodi, and V. Patera. A monte carlo-based treatment planning tool for proton therapy. Phys Med Biol, 58(8):2471–90, 2013. ISSN 1361-6560. doi: 10.1088/0031-9155/58/8/2471.

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FIRST CASE STUDY STEREOTACTIC PANCREAS
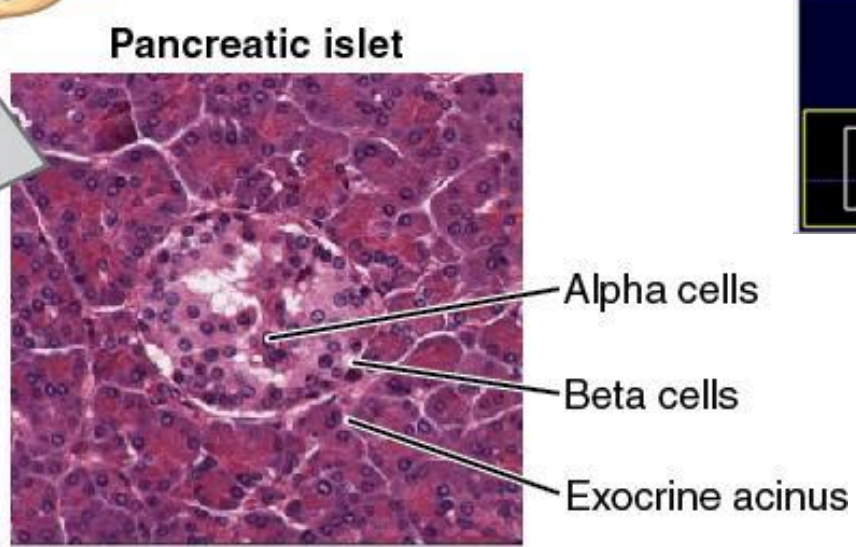
STEREOTACTIC PANCREAS PATOLOGY

Pancreas is a difficult tumour to treat, dose prescribed in current treatment plans is not sufficient because being a very aggressive disease it would require high prescriptions but constraints on the duodenum limit the prescription.
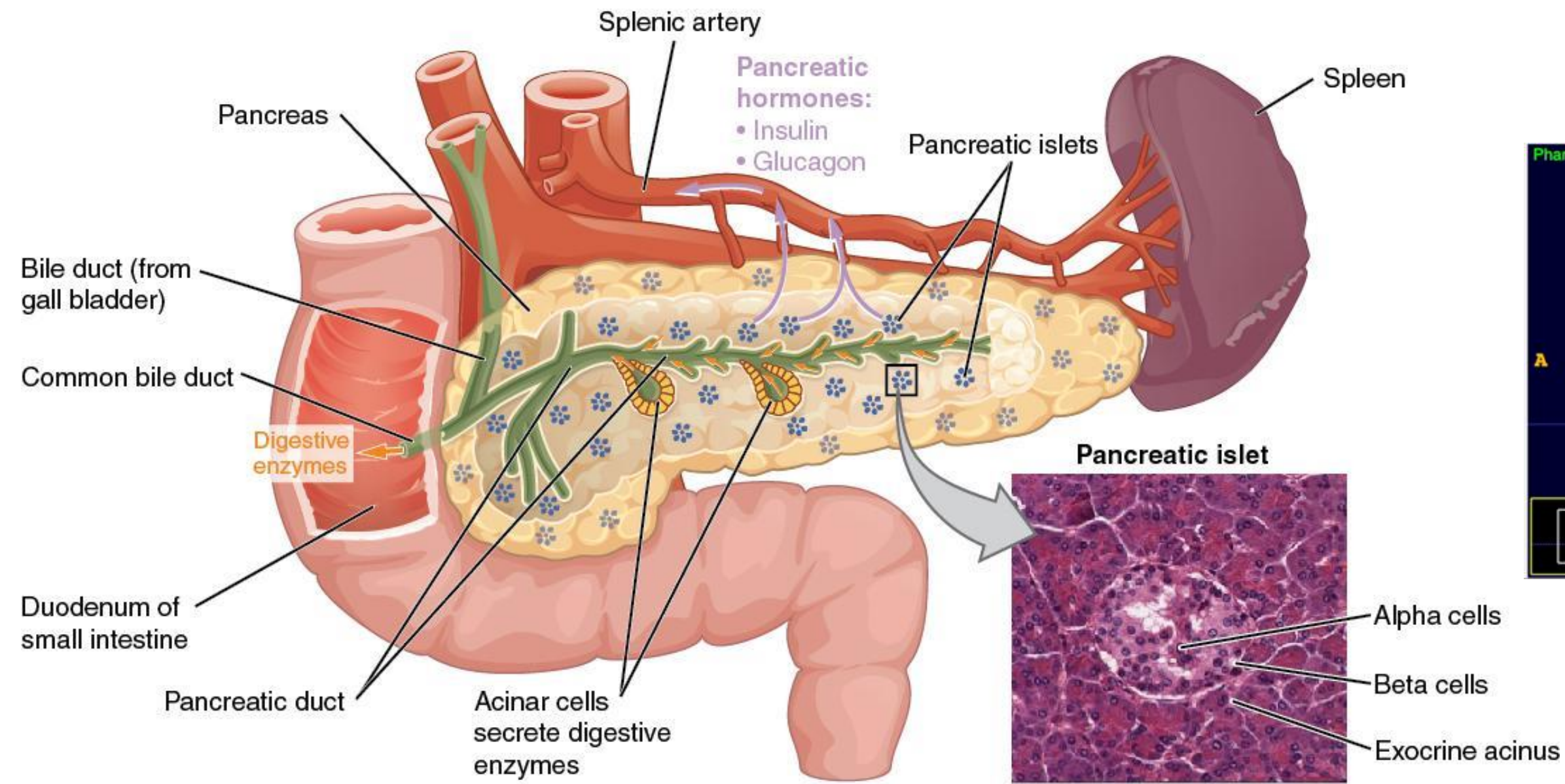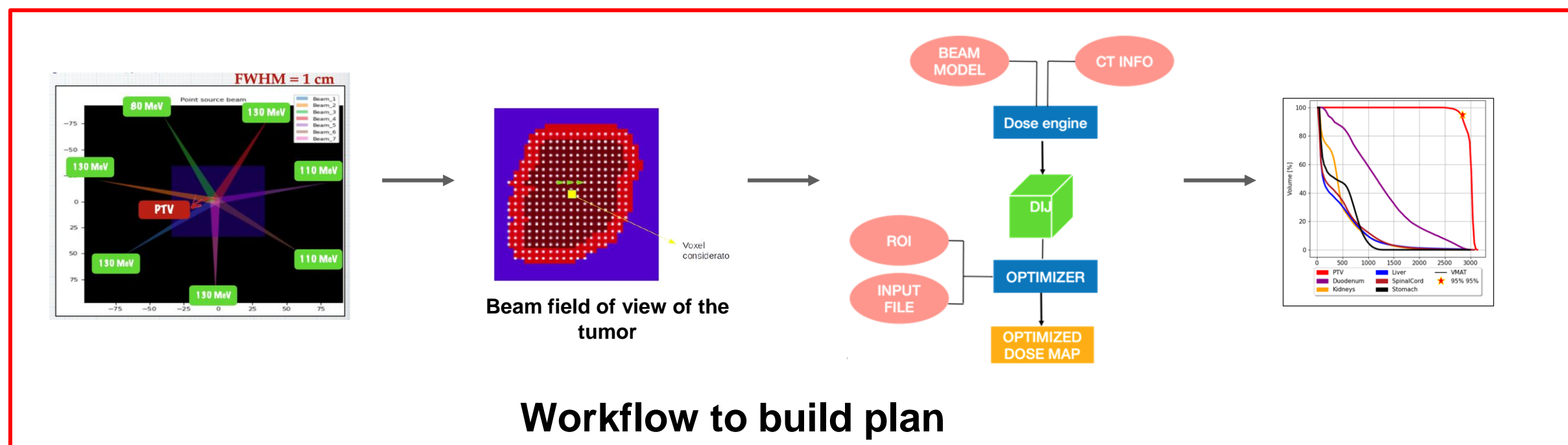
High-lines:

- Tumor Prescription 6 Gy x 5 fr =30Gy
- Duodenum Constraints: Dmax 35 Gy
- Spinal cord Constraints: Dmax 35 Gy
- Kidneys Constraints: Mean Dose 10 Gy

Anatomy

Pancreatic islet

Patient 1 pancreas

Red: pancreas

Violet: duodenum

The geometry of the patient limits the possibility of treatment with external beam radiotherapy because the duodenum is anatomically attached to the pancreas.

In order to evaluate the doses absorbed by each organ, we use international guidelines as a reference to quantify the probability of occurrence of toxicity to an organ as a function of the dose absorbed by it. There are therefore reference **constraints** for each specific organ.

Dose distribution VHEE PANCREAS

Workflow to build plan

High-lines:

- ◉ Tumor Prescription 6 Gy x 5 fr =30Gy
- ◉ Duodenum Constraints: Dmax 35 Gy
- ◉ Spinal cord Constraints: Dmax 35 Gy
- ◉ Kidneys Constraints: Mean Dose 10 Gy
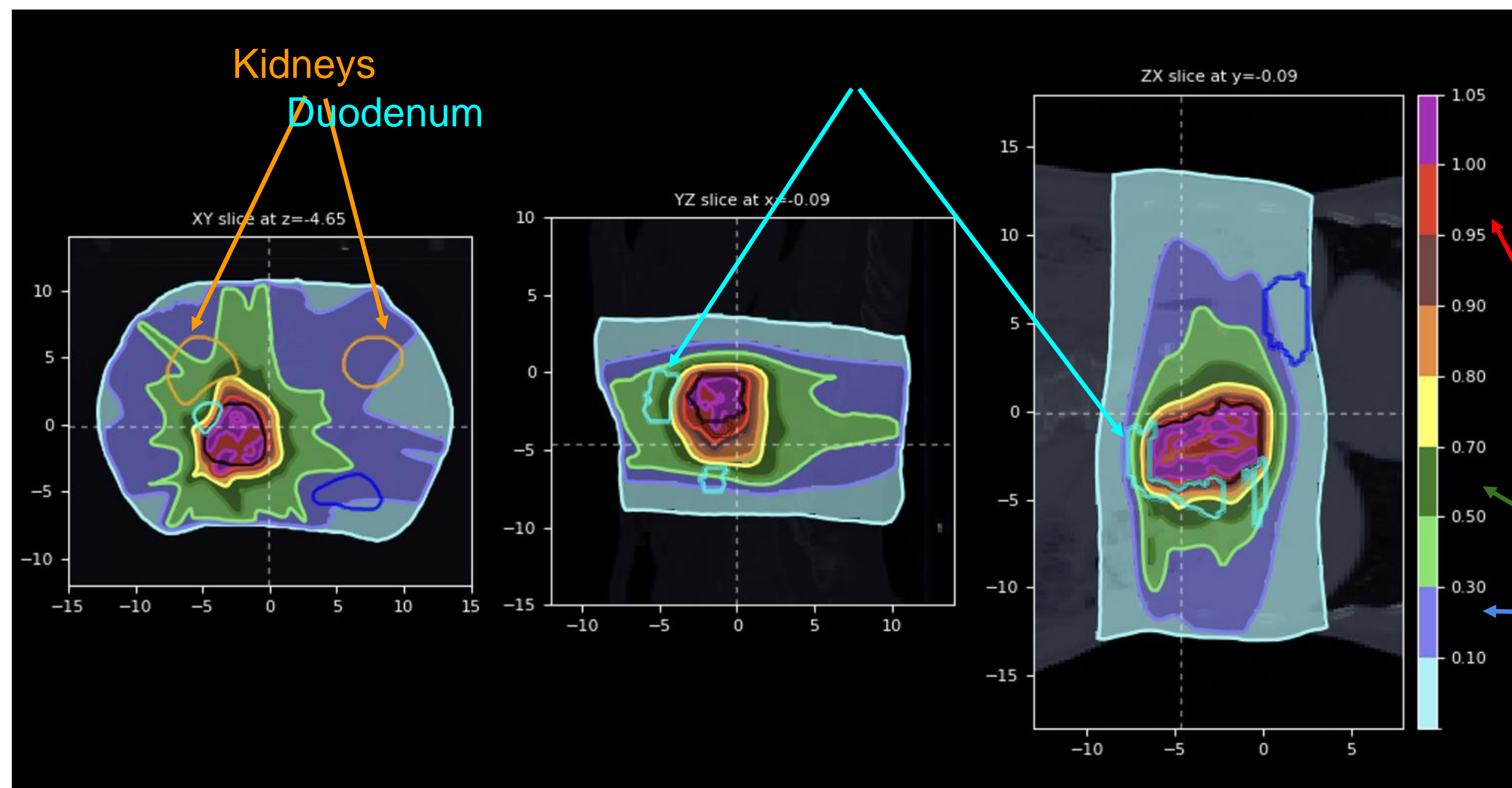
Dose distributions on the patient were simulated and optimized in order to assess tumor coverage and preservation of healthy organs.
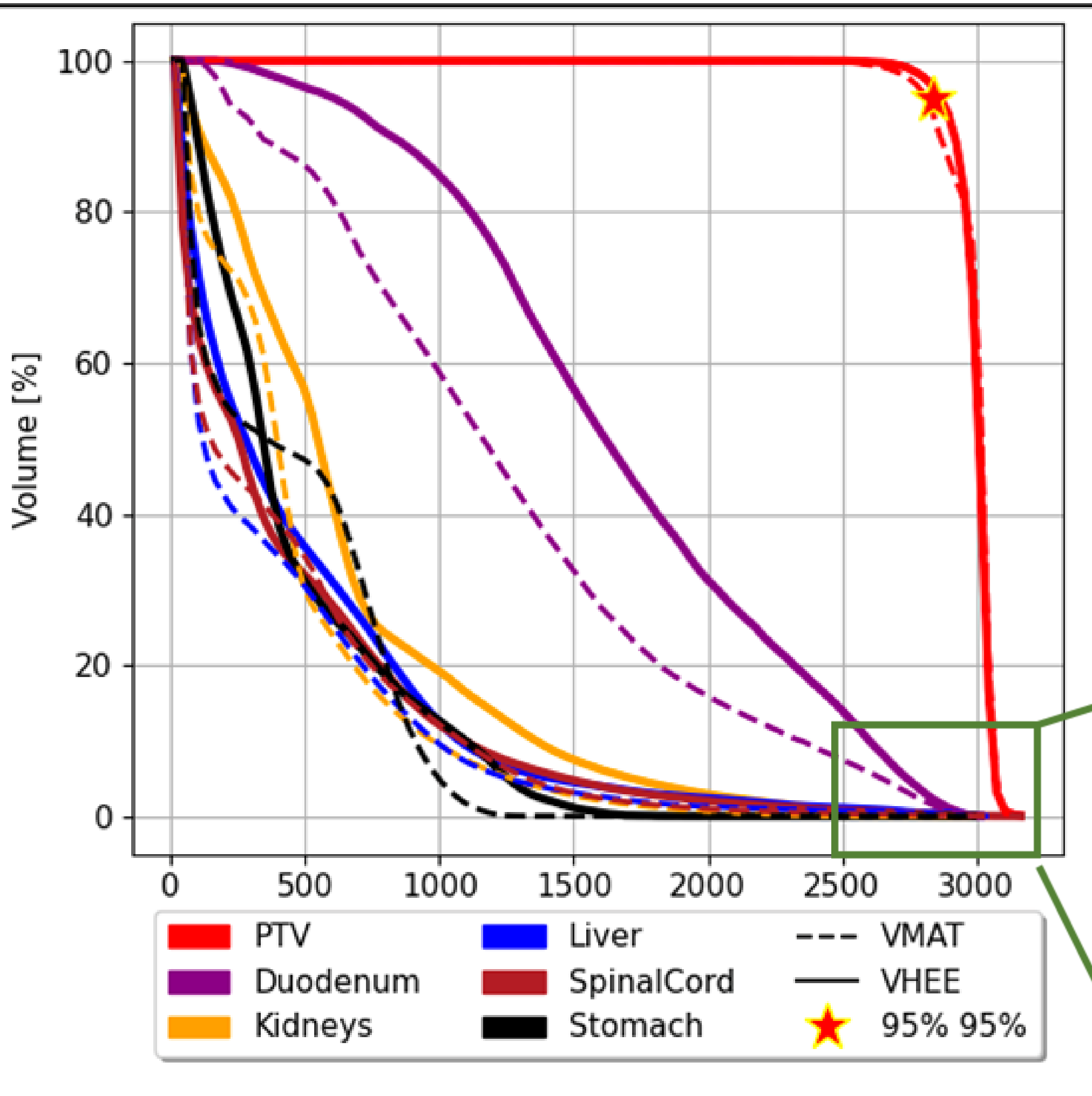
The isodose is the line connecting the points on a subject's body where the absorbed dose of radiation has the same value, i.e., isoline of absorbed dose.

The graph shows isodose curves expressed as a **percentage of the prescription dose.**

in red 28.5 Gy   in dark green 15 Gy
in blu 3Gy

A dose-volume histogram (**DVH**) is a histogram relating radiation dose to tissue volume in radiation therapy planning. DVHs are most commonly used as a plan evaluation tool and to compare doses from different plans or to structures.
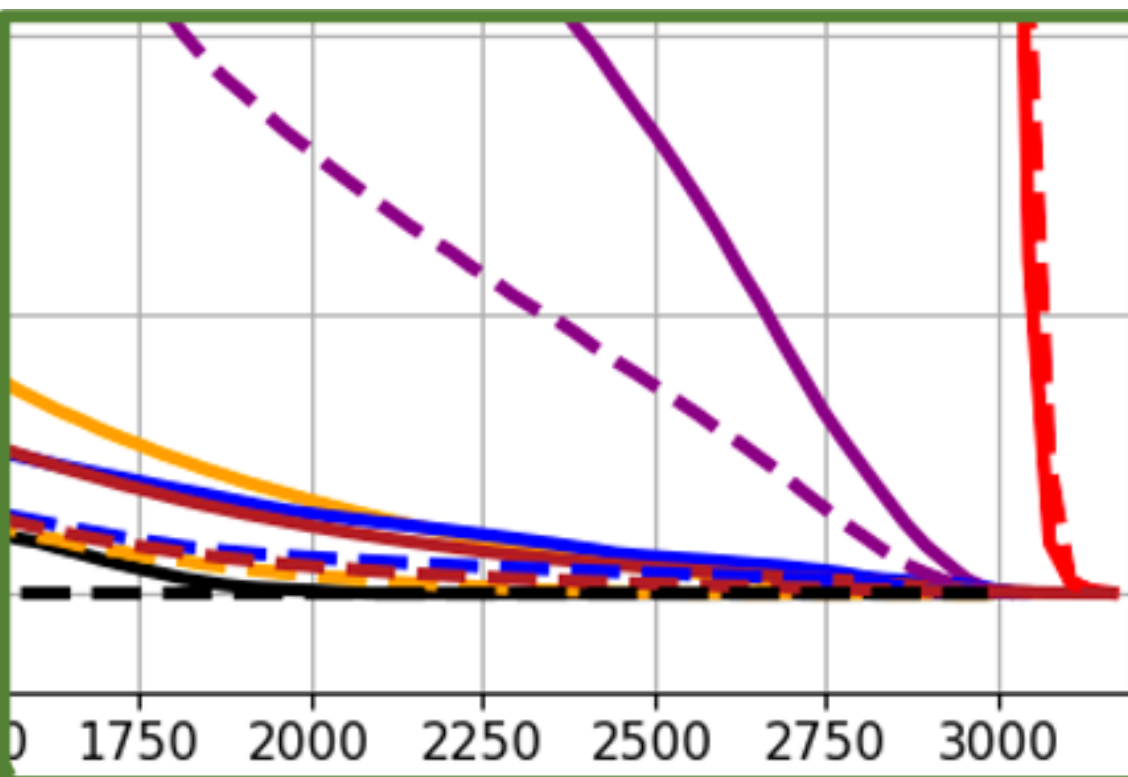
Organ	Constraint	VMAT	VHEE
Tumor (PTV)	V95%>95%	97%	98.4%
	D_{max} < 107%	0.04%	0.01%
Duodenum	D_{max} < 33 Gy (optimal)	30.3 Gy	30.2 Gy
	V25(Gy) < 6%	7.4 %	16.4 %
Stomach	D_{max} < 33 Gy (optimal)	13.4 Gy	20.7 Gy
		0%	0%
	V25(Gy) < 6%	0.4%	9.8%
	V12(Gy)< 31%		
Spinal Cord	D_{max} < 35 Gy (mandatory)	8.6 Gy	9.6 Gy
Kidneys	D_{mean}<10 Gy	4.5 Gy	6.7 Gy
Liver	D_{mean}<13 Gy	3.6 Gy	5.0 Gy
	V10(Gy)< 70%	9.4 %	15.4 %
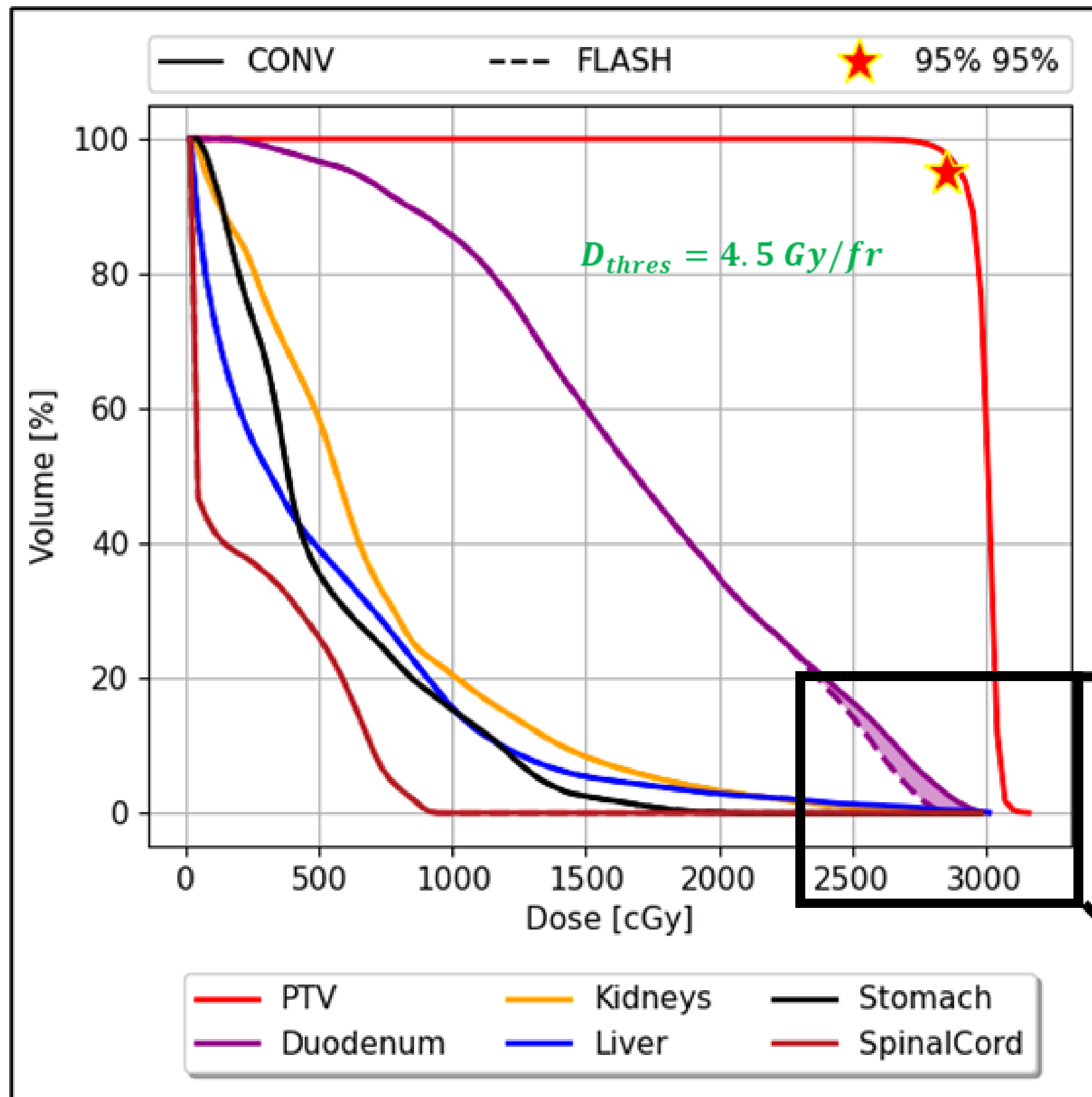
D_{th} = 4.5 Gy/fraction FMF_{min} = 0.8

The threshold on 5 fractions adds up to 22.5 Gy

The FLASH effect mitigate exactly the critical high dose region of duodenum
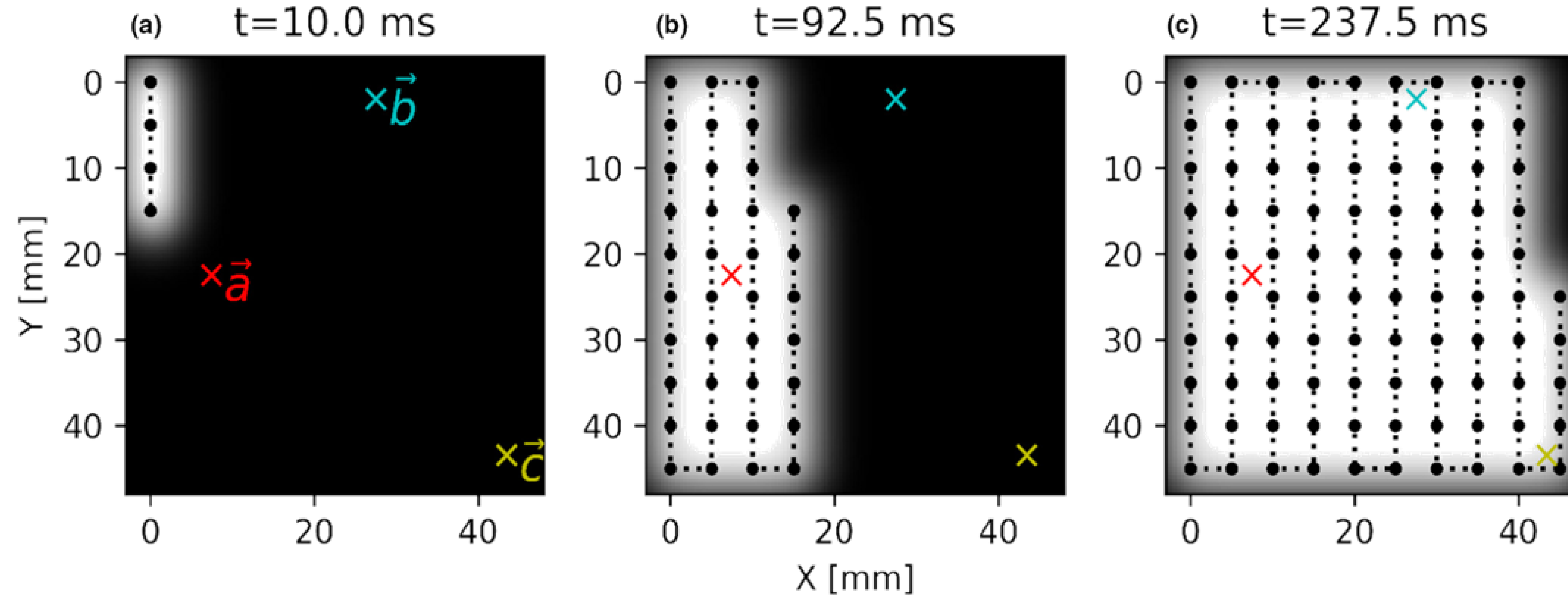
Due to the threshold, no effect can be seen elsewhere
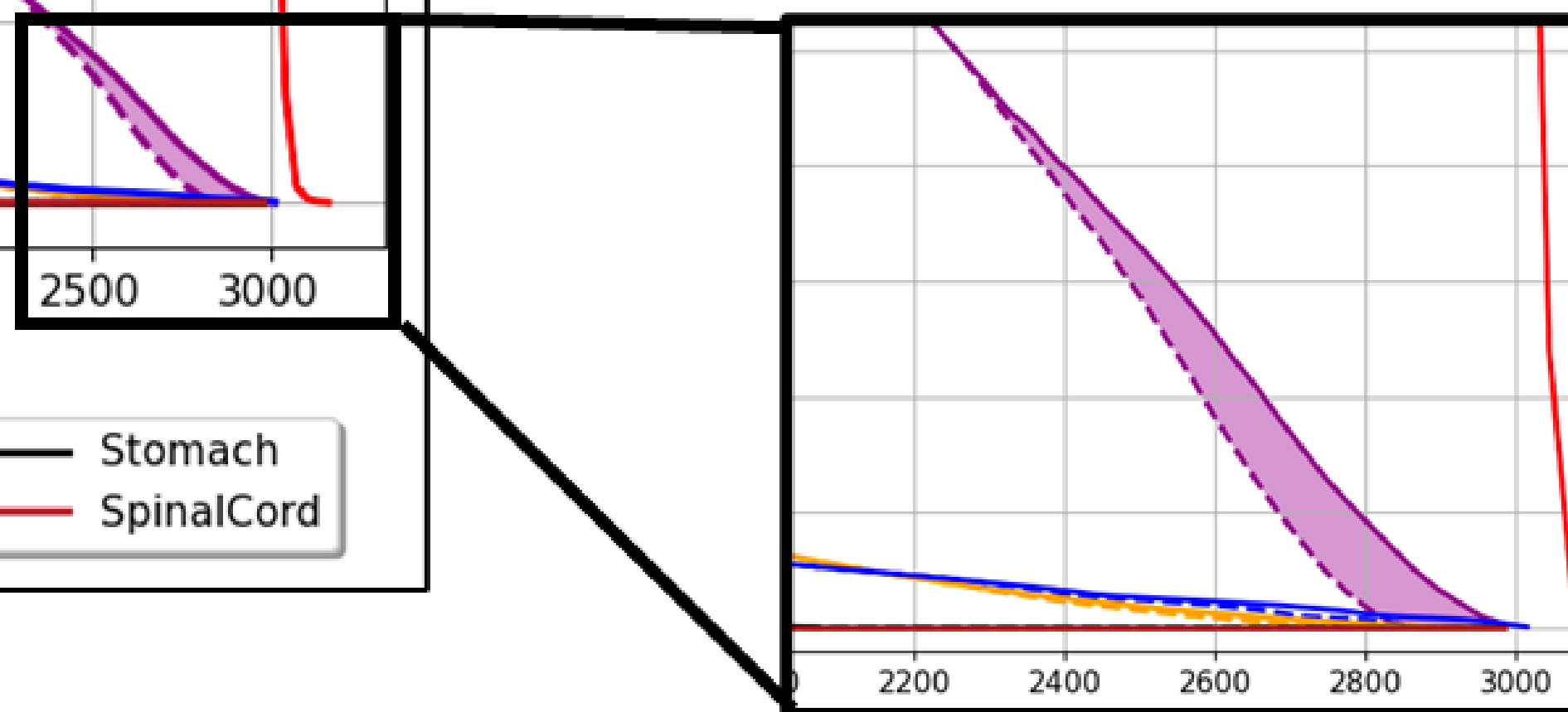
Duodenum
VHEE: $D_{max} = 30.07\ Gy$
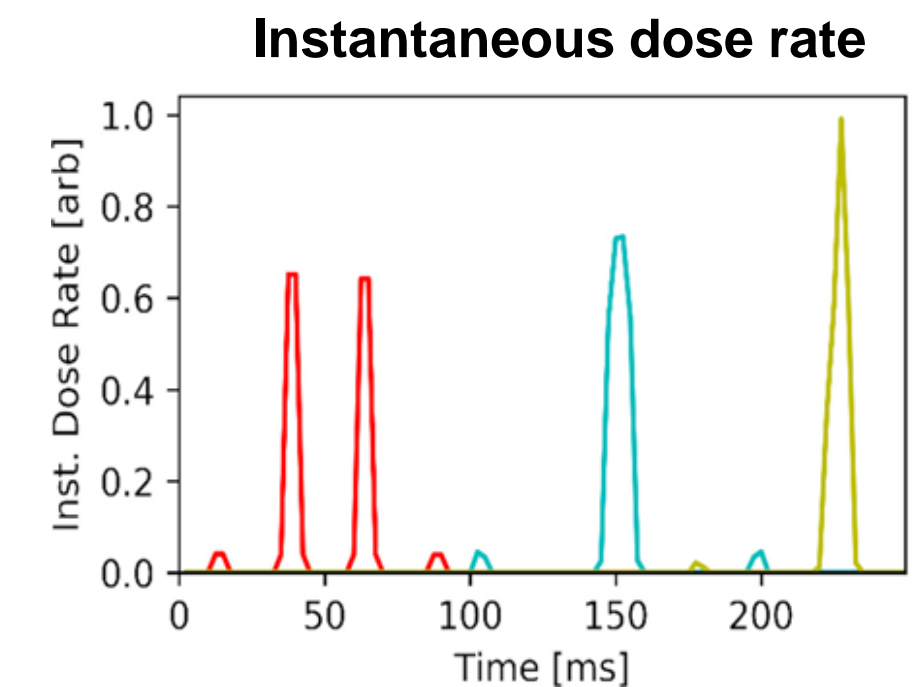FLASH: $D_{max} = 28.65\ Gy$

DOSE RATE STUDY
FOR FLASH APPLICATION

Dose rate for FLASH effect

As example we take a proton therapy spot scanning as use case.

(a) t=10.0 ms (b) t=92.5 ms (c) t=237.5 ms

The time for a voxel to accumulate the max dose is a fraction of the total time of irradiation.

The dose rate depends on the **scanning pattern** and the **relative position** between the spots.

Instantaneous dose rate

Average Dose Rate

The ADR consider the bulk of the dose release (from the very near PBs) to evaluate a "robust"dose rate
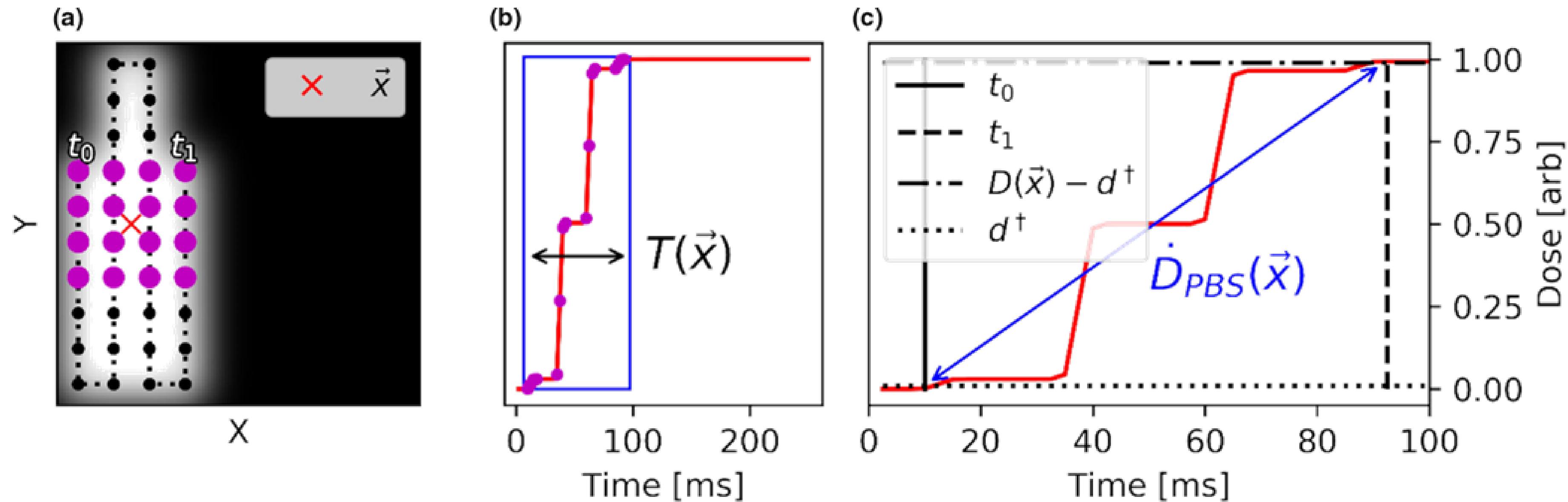
$$\dot{D}_j^{ADR} = \frac{D_j - 2d^*}{T_j}$$

$$d_j(t_0) = d^* \qquad d_j(t_1) = D_j - d^*$$

$$T_j = t_1 - t_0$$

d* preset dose-threshold that determines the effective irradiation time

Average Dose Rate For Pancreas

Highlines:

Although hypofractionation makes treatment of the pancreas very attractive for FLASH, beam delivery is still challenging because it is complicated to achieve an Average Dose Rate that is greater than 40 Gy/s.

But the beam delivery challenge is still open…
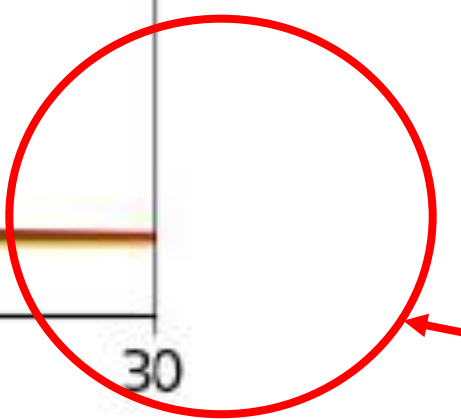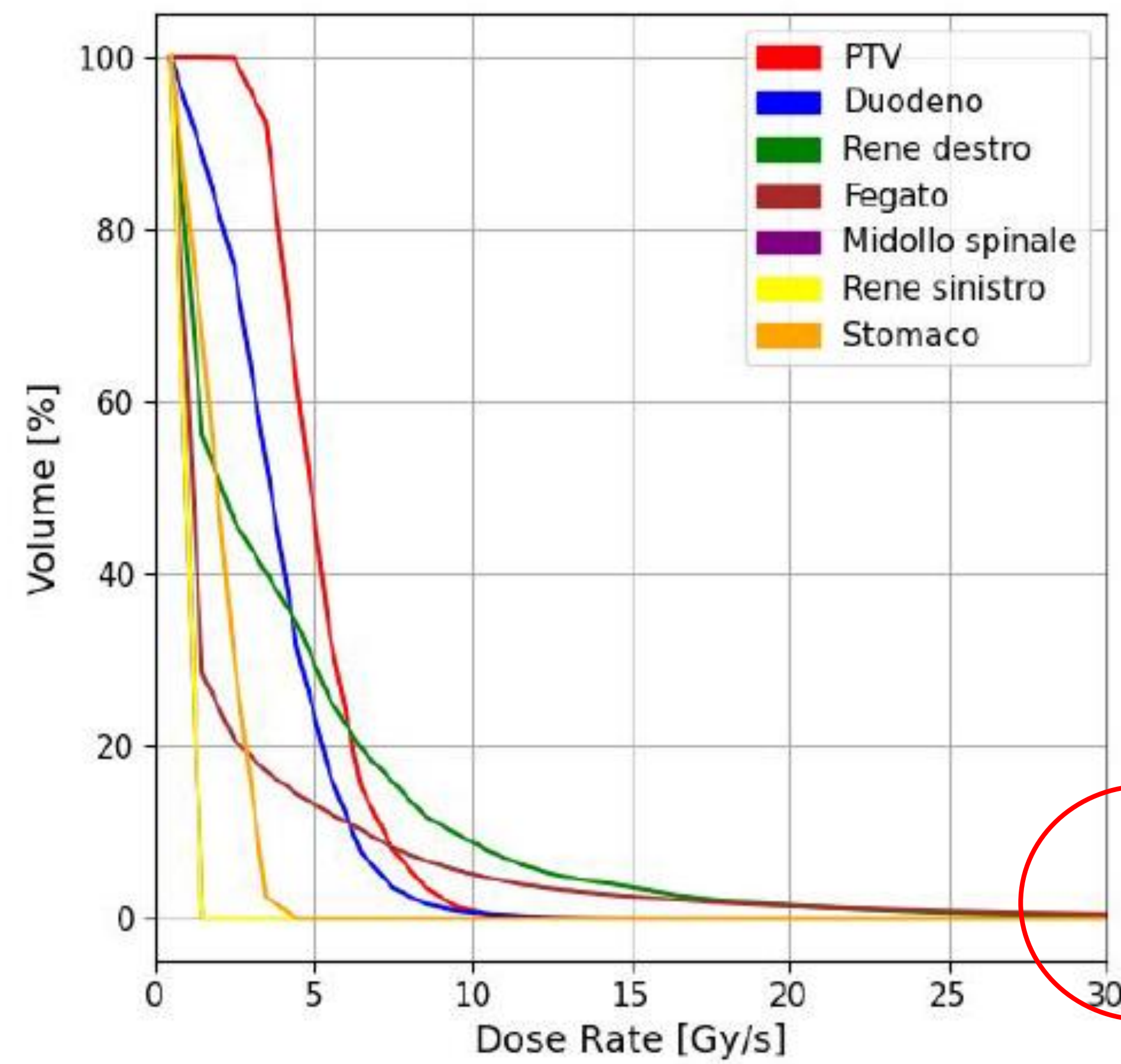
no healthy tissue achieves 40 Gy/s

Clinical difficulties

If we use 7 treatment fields in order to ensure healthy organs are spared, from the dose rate study, it is more difficult to apply the FLASH effect because given the large tumor volume and the dose per fraction limited by the prescription of 6 Gy, pencil beams do not simultaneously guarantee exceeding the 3Gy threshold and the dose rate of 40 Gy/s per single field

High-lines:

- Tumor Prescription 6 Gy x 5 fr =30Gy
- High absorbed dose per each fraction (> 3 Gy)
- Ultra High Dose Rate (> 40 Gy/s)

Tumor Prescription 6 Gy x 5 fr = 30Gy
6 Gy / 7 Fields ~ 0.86 Gy per field
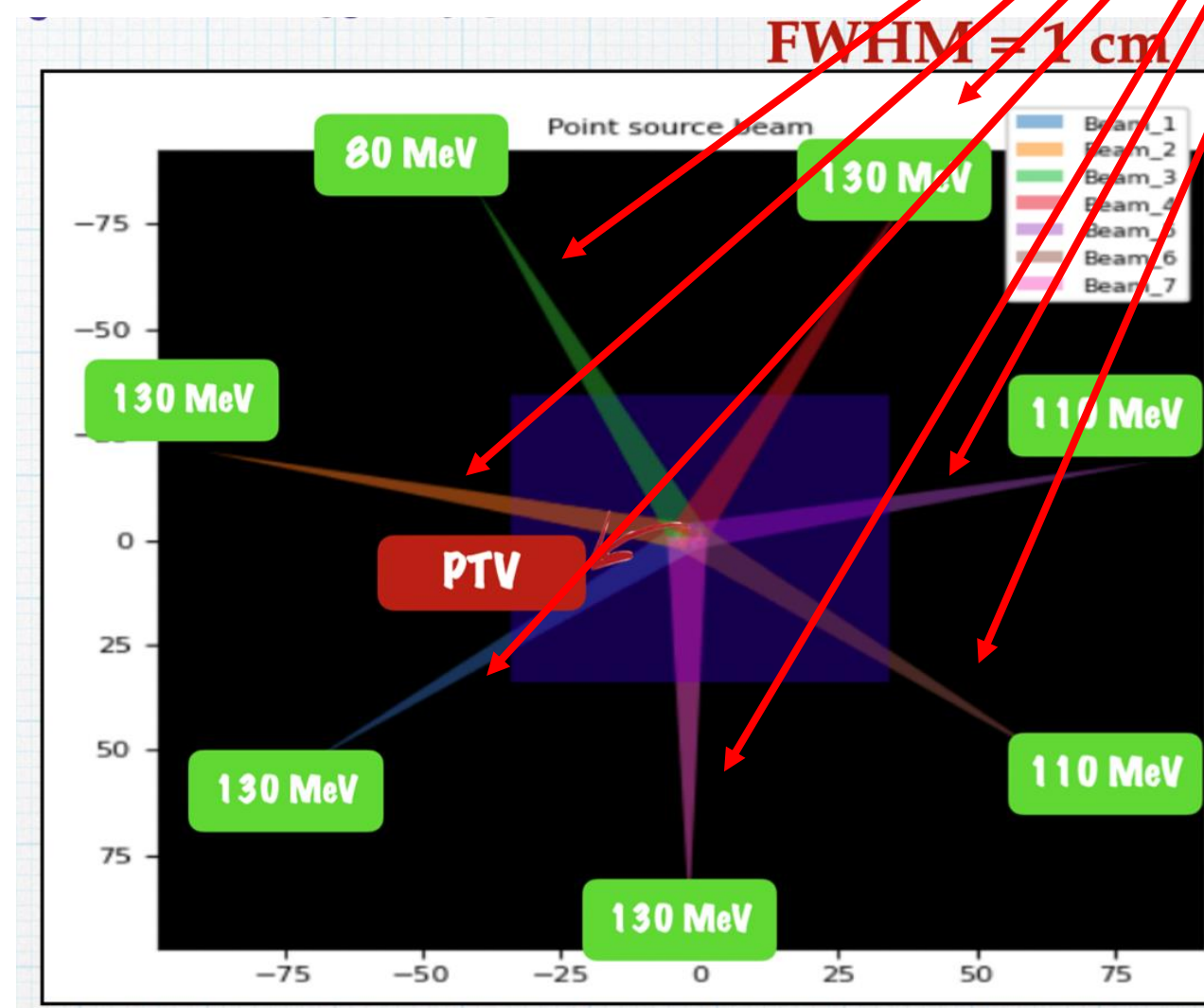
we need, in order to put ourselves in a safer state than FLASH activation, a pathology that offers:
- a higher dose per fraction,
- a relatively small tumor volume,
- and a number of treatment fields that is concordant with at least the 3 Gy per single field
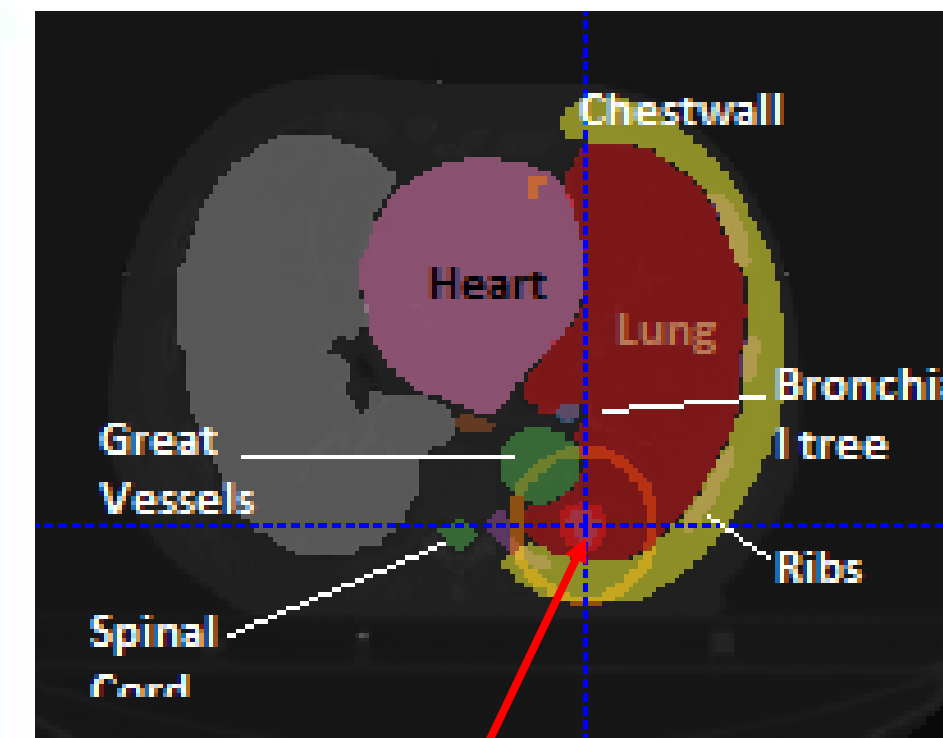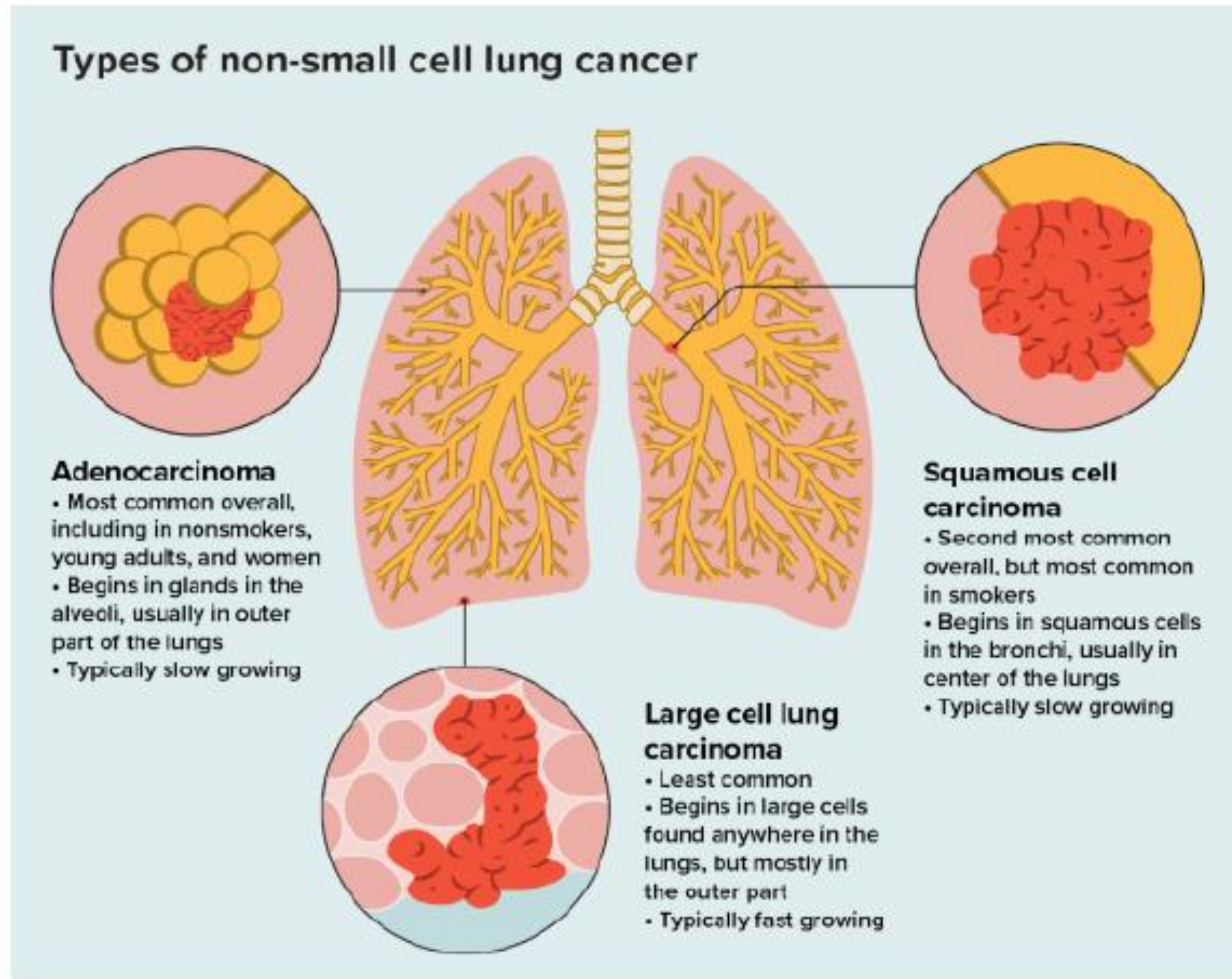
That's why we went to the second case study: the lung

SECOND CASE STUDY
LUNG LESIONS
NON-SMALL-CELL-LUNG CANCER (NSCLC)

LUNG LESIONS NSCLC

Types of non-small cell lung cancer

Adenocarcinoma
- Most common overall, including in nonsmokers, young adults, and women
- Begins in glands in the alveoli, usually in outer part of the lungs
- Typically slow growing

Squamous cell carcinoma
- Second most common overall, but most common in smokers
- Begins in squamous cells in the bronchi, usually in center of the lungs
- Typically slow growing

Large cell lung carcinoma
- Least common
- Begins in large cells found anywhere in the lungs, but mostly in the outer part
- Typically fast growing

High-lines:

◉ Tumor Prescription 12Gy x 4 fr =48Gy
◉ Ribs Constraints: Dmax 43 Gy
◉ Spinal cord Constraints: Dmax 23 Gy

Patient 1 lung tumor

Lung cancer is another very difficult disease because if taken at an advanced stage it is difficult to treat, our specific case are tumors taken at an **early stage** and in fact the treatment **volume does not exceed 5 cm^3**.

This will allow us to be able to guarantee a safeguarded FLASH activation in a better way, moreover, the case was **studied with 4 treatment fields** precisely with a view to being FLASH on each individual field.
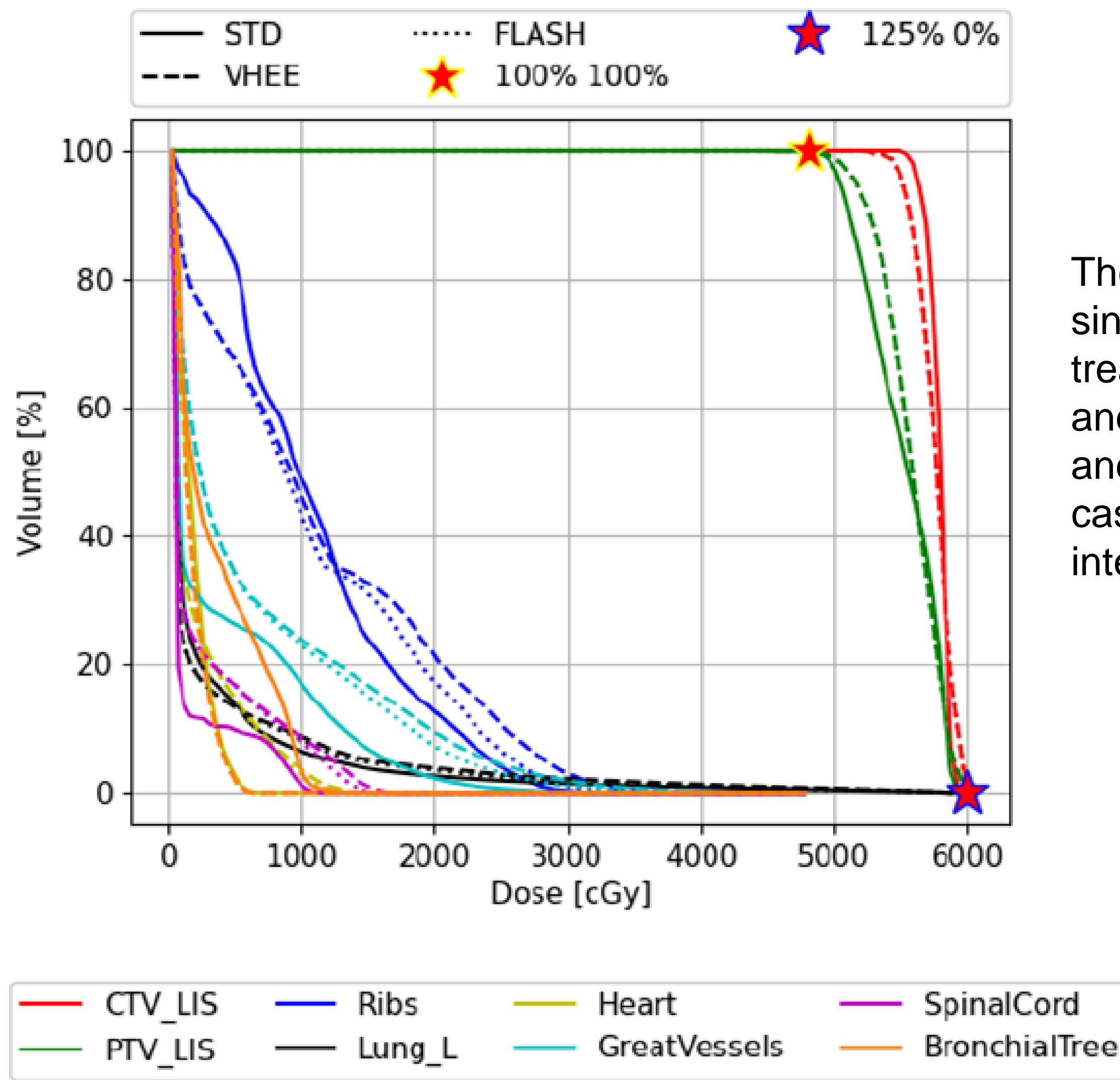
Lung VHEE isodose

Workflow to build plan

- Tumor Prescription 12Gy x 4 fr =48Gy
- Ribs Constraints: Dmax 43 Gy
- Spinal cord Constraints: Dmax 23 Gy

	48 Gy
	38.4 Gy
	28.8 Gy
	24 Gy
	19.2 Gy
	14.4 Gy
	9.6 Gy
	4.8 Gy
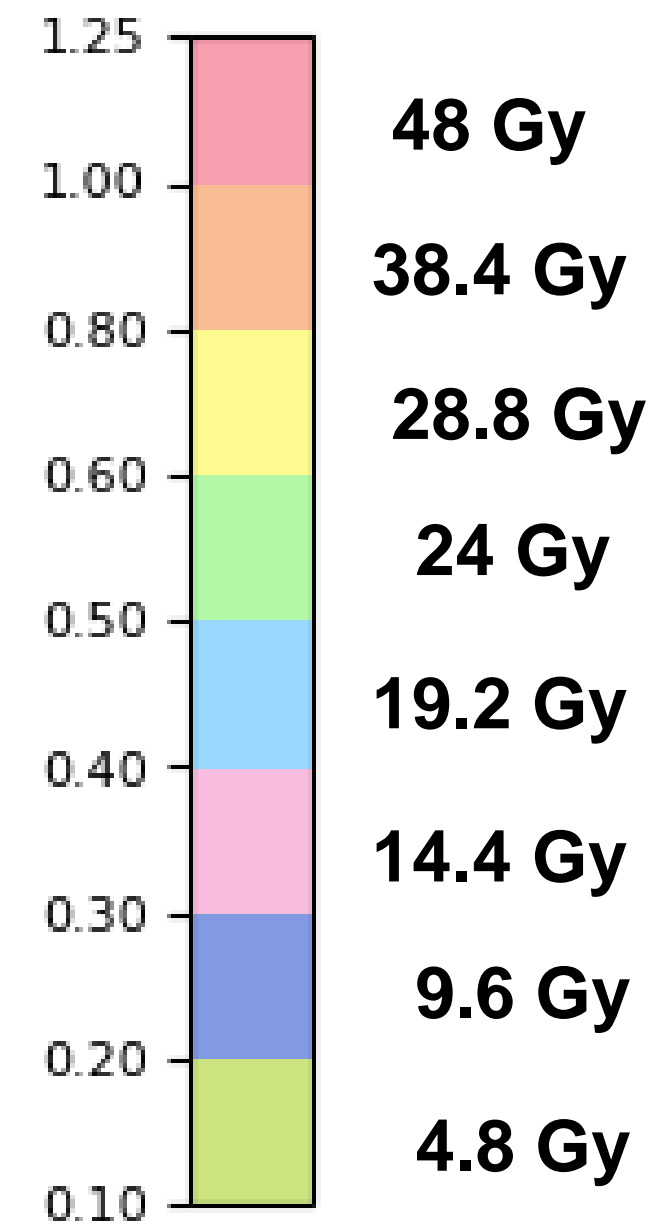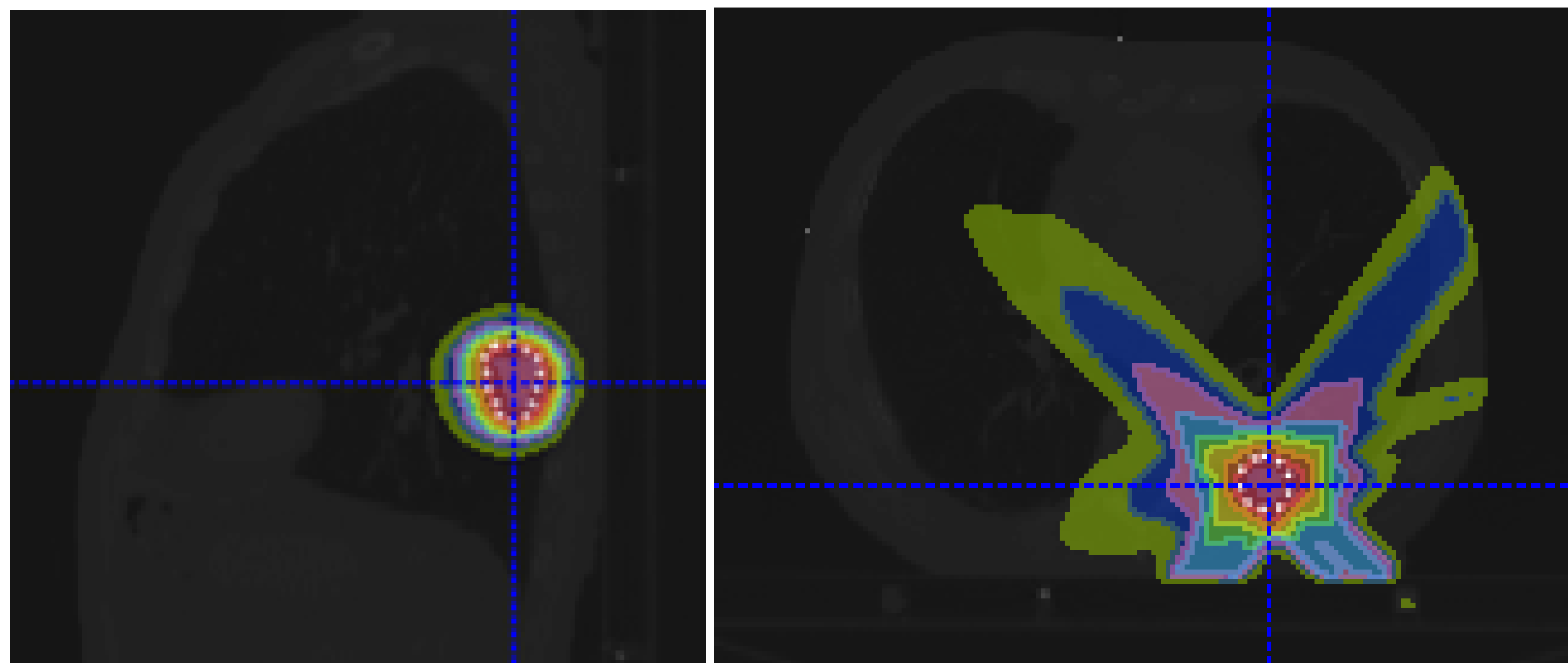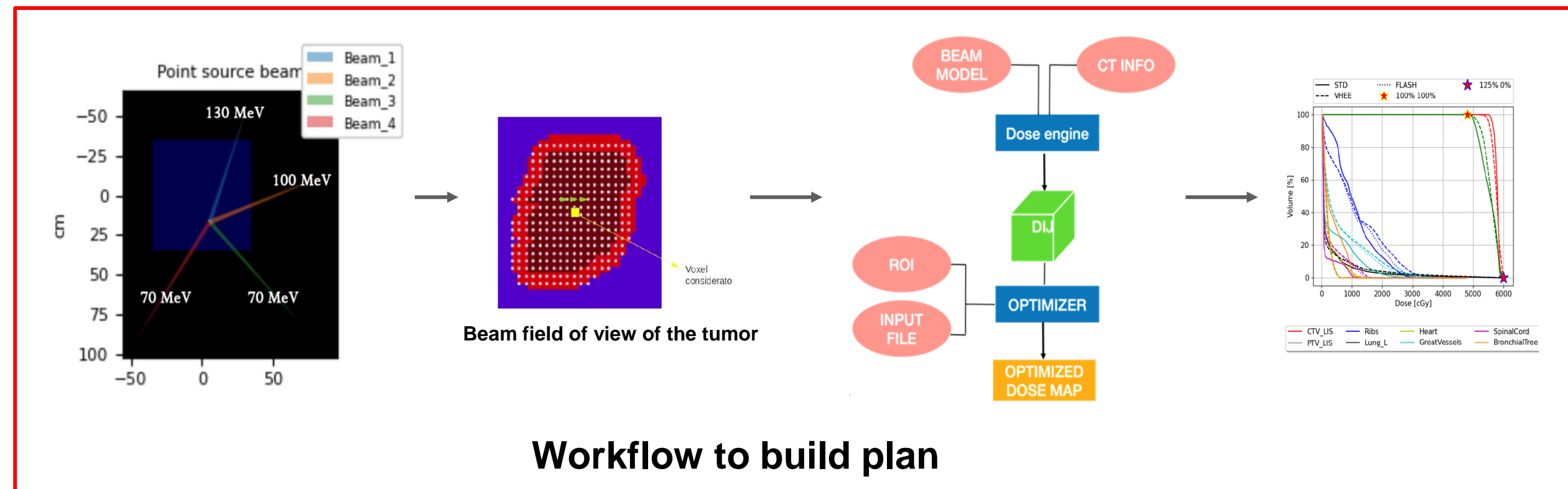
The plan was built and optimized so that the 50% prescription isodose was all contained within a maximum area of 2 cm from the tumor. Respecting constraints and trying to give less dose to the lungs and also the directions of the beams avoid the spinal cord.

The DVH shows that the dose per single organ compared in the 3 treatment cases (VMAT, VHEE and VHEE FLASH) is comparable and thus that all 3 plans for this case are approvable because international constraints are met.

Organ	Constraint	VMAT	VHEE	VHEE FLASH FMF 0.8
Tumor (PTV)	V100%>95% D_{max} < 125%	99.87% 0.002%	99.79% 0.2%	99.19% 0.2%
Bronchial Tree	D_{max} < 30 Gy (mandatory)	14.1 Gy	6.2 Gy	6.01 Gy
Ribs	D_{max} < 40 Gy (optimal)	32.2 Gy	41.2 Gy	37.6 Gy
Spinal Cord	D_{max} < 23 Gy (mandatory)	11.3 Gy	16.6 Gy	15.5 Gy
Heart	D_{max}<26 Gy (mandatory)	6.7 Gy	14.6 Gy	13.5 Gy
Lungs - tumor	V20(Gy)< 15% (mandatory)	1.12%	1.7%	1.5%

Although the 3 treatment plans are all acceptable as dose to healthy organs and as dose coverage of the tumor, the dose distribution does not provide direct access to the advantages that FLASH may imply in this type of treatment
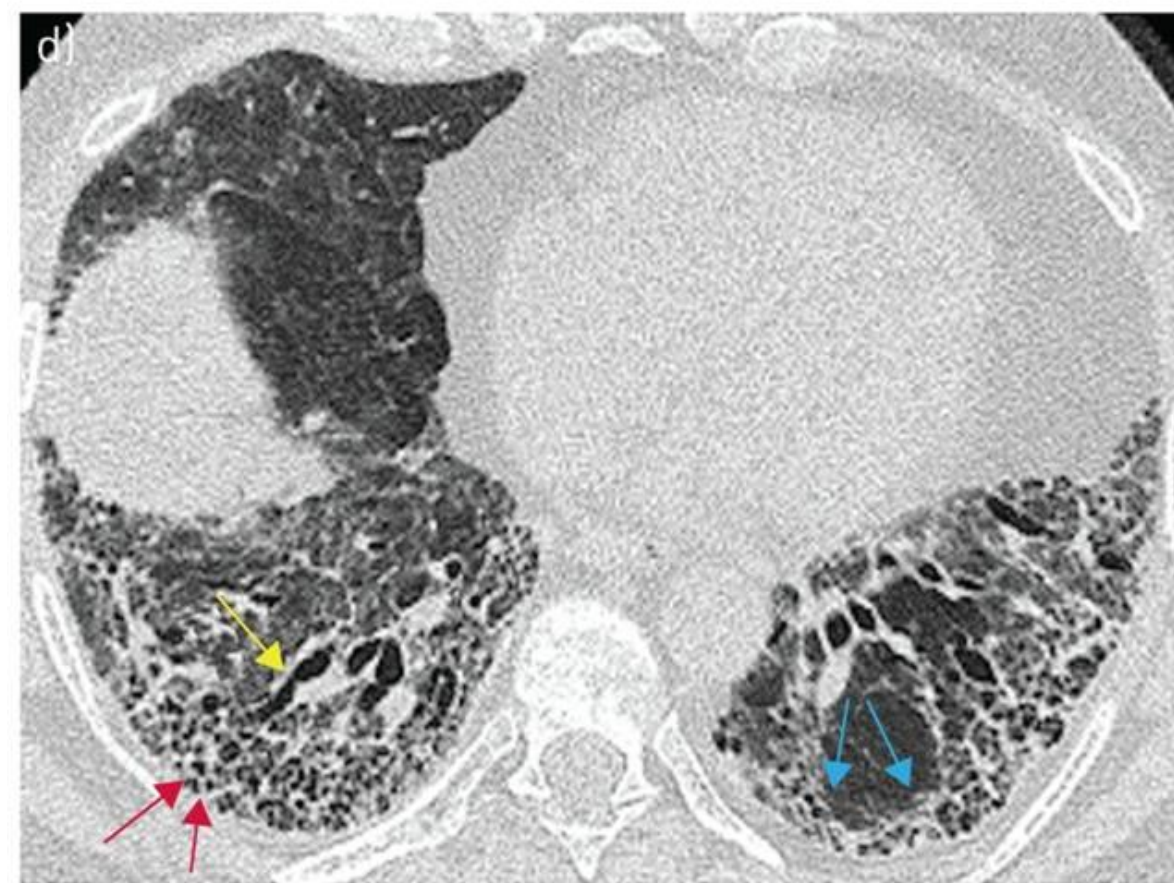
- ⊙ **To evaluate the possible FLASH benefit, dose calculation is not sufficient, one needs the prediction of biological damage in various scenarios.**

- ⊙ **Biological damage in the case of the lung are fibrosis and pneumonia, so I studied these effects according to the dose and the fractionation used.**

FROM DOSE TO BIOLOGICAL DAMAGE

Linear quadratic radiobiological model

The linear quadratic model (LQ) was developed as a mechanistic model to describe the radiobiological effects of cell killing and sublethal repair. The LQ describes the probability of DNA double-strand breaks (DSBs), considered to be the lethal radiation-induced damage. This probability is governed by a linear component representing the single-track damage that causes a DSB, while the quadratic component arises from two separate actions on DNA that lead to DSBs.
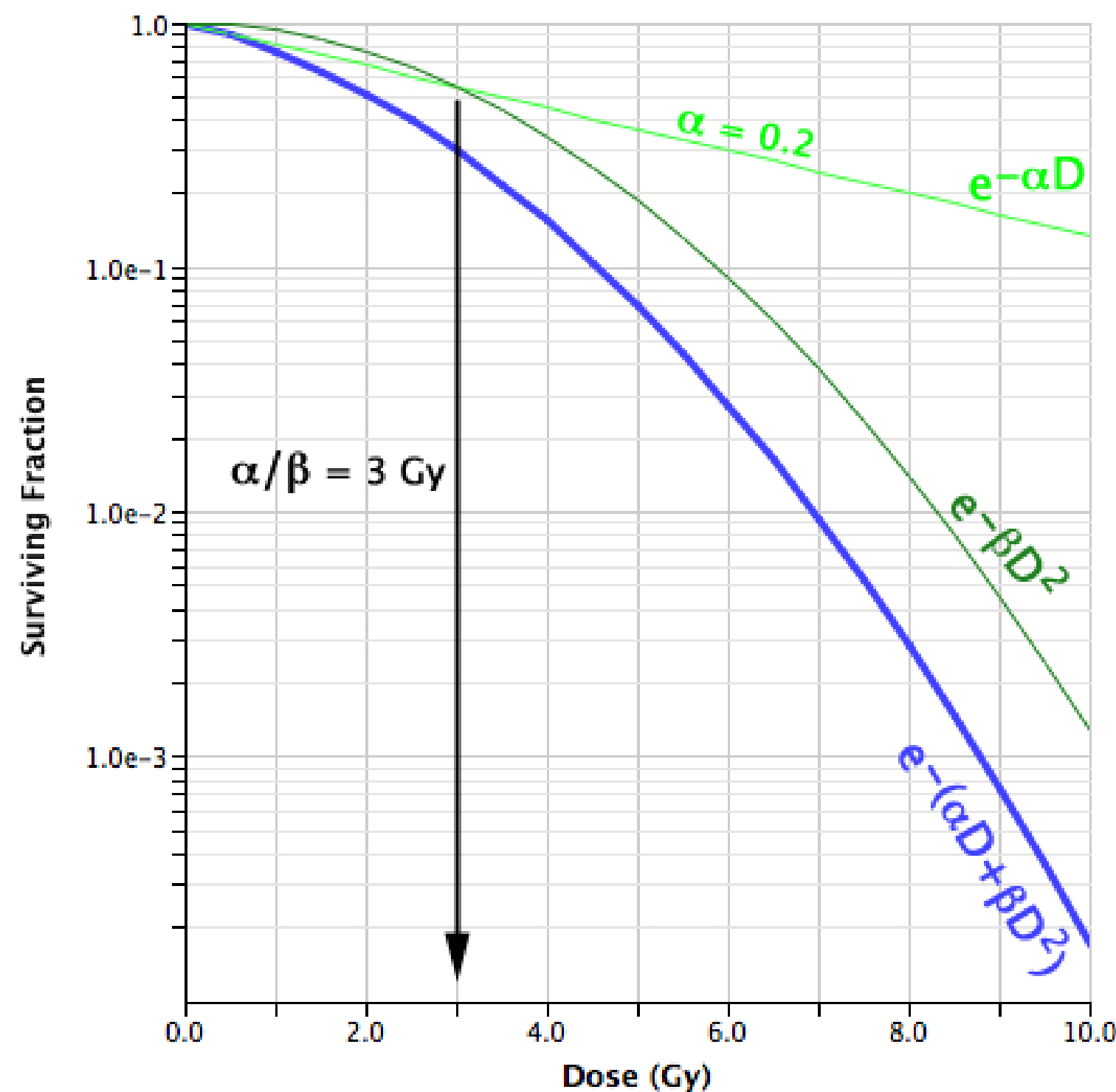
$$S_{LQ} = \left(e^{-(\alpha d_1 + \beta d_1^2)} \right)^{n_1}$$

S = Cell survival fraction
d_1 = dose per fraction
n_1 = number of fractions
α =linear component representing the single-track damage
β =DSB by breaking both strands of DNA in a single event

From this equation it follows that n_1 fractions given with d_1 Gy per fraction is converted to a second fractionation scheme with n_2 fractions given with d_2 Gy per fraction by:

$$n_2 d_2 = n_1 d_1 \frac{1 + \frac{d_1}{\alpha/\beta}}{1 + \frac{d_2}{\alpha/\beta}}$$

we can then correlate biological effects at different fractionations and for different doses

Total equieffective dose in 2 Gy

With the this formula, it was then possible to correct the dose absorbed by the lungs in order to equate the biological damage received as if it had been received in 2 Gy fractions (EQD2). It was necessary to transform the dose because then we could compare each portion of the lung.

$$n_2 d_2 = n_1 d_1 \frac{1 + \frac{d_1}{\alpha/\beta}}{1 + \frac{d_2}{\alpha/\beta}}$$

DVH differential is the frequency distribution within the volume of interest (In our case, the lungs).
In the DVH the corrected dose in EQD2 is shown.

Flash effect evidence in blu curve
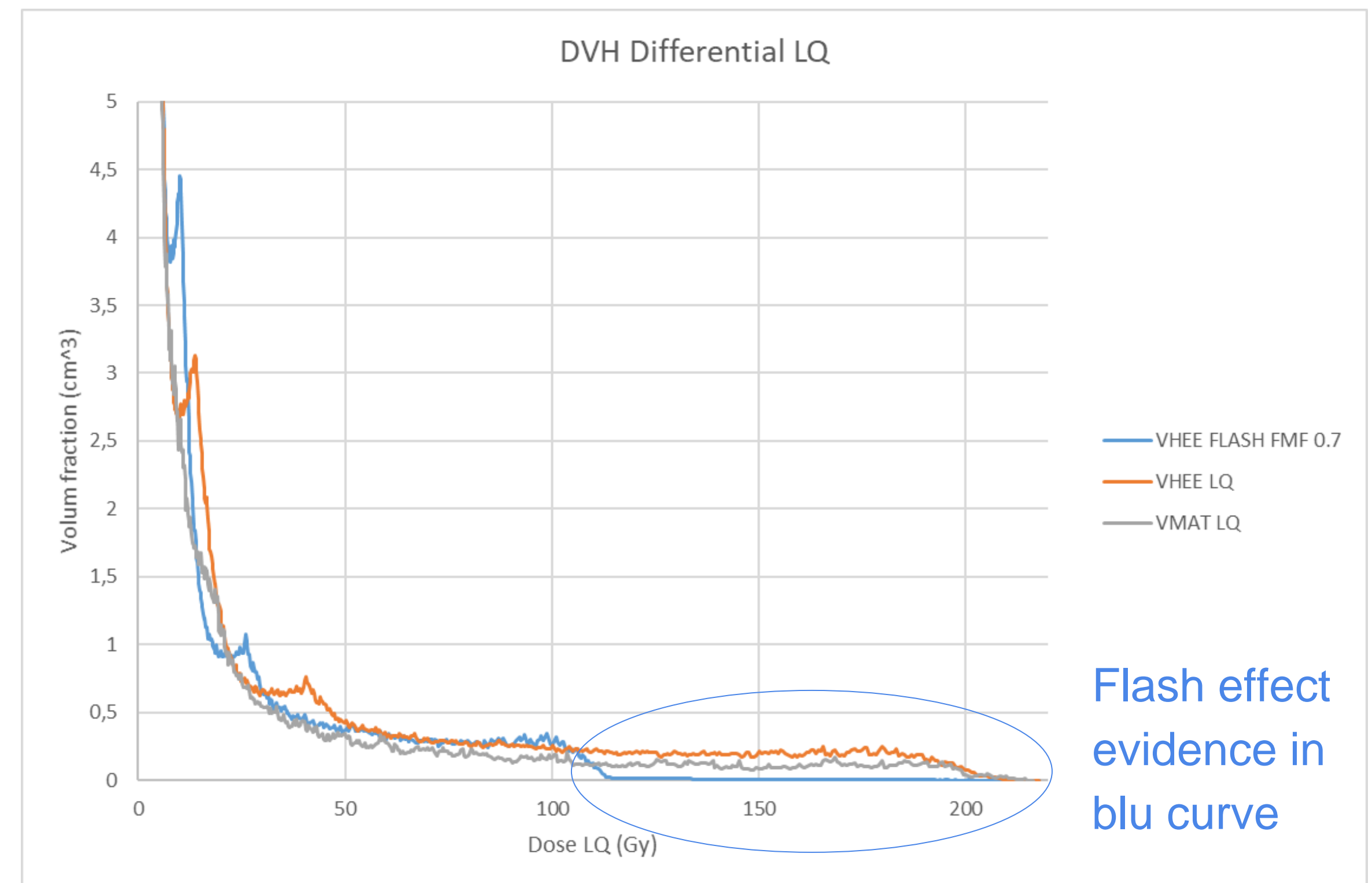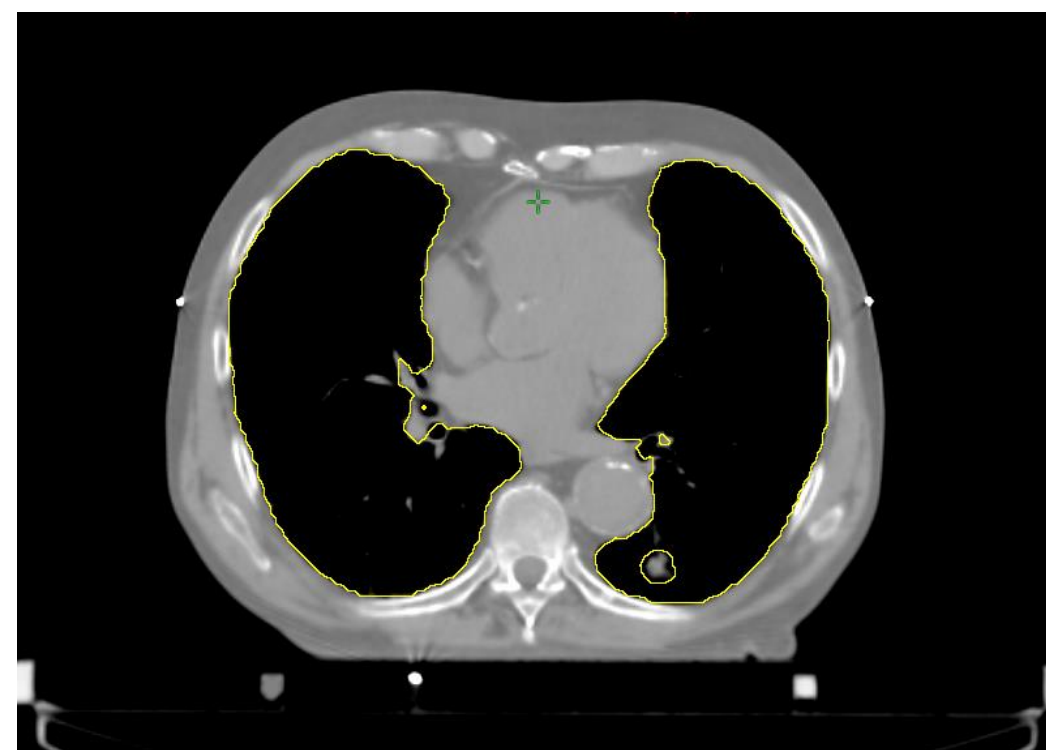
Normal tissue complication probability (NTCP)

The Lyman-Kutcher-Burman (LKB) [120] models in particular, is the most well-known and traditionally accepted method for predicting toxicity after EBRT. That model basically relies on dose volume histograms (DVHs) to account for dose distribution inside the OARs under consideration, and implicitly treat them as homogeneous in their response to radiation.

Were Equivalent Uniform Dose (EUD) is defined as the absorbed dose that, if homogeneously delivered to a tissue, causes the same expected number of clonogens to survive as the actual non-homogeneous absorbed dose distribution does.

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_t^{-\infty} e^{\frac{-x^2}{2}} \, dx$$

$$t = \frac{EUD - TD_{50}}{m * TD_{50}}$$

$$EUD = \left(\sum_i D_{i,corr}^{\frac{1}{n}} \frac{V_i}{V_{tot}} \right)^n$$

Radiobiological parameters

m = curve steepness
TD50 = the dose for which the probability of a selected response is 50%
n = a volume dependence parameter

Comes from a Swedish phase II study

[8] B. M. Wennberg, P. Baumann, G. Gagliardi, J. Nyman, N. Drugge, M. Hoyer, A. Traberg, K. Nilsson, E. Morhed, L. Ekberg, L. Wittgren, J. Lund, N. Levin, C. Sederholm, R. Lewensohn, and I. Lax. Ntcp modelling of lung toxicity after sbrt comparing the universal survival curve and the linear quadratic model for fractionation correction. Acta Oncol, 50(4):518–27, 2011. ISSN 1651-226X. doi: 10.3109/0284186X.2010.543695

Results

To summarise the results, it can be seen from the table that VHEEs have a probability of radiation pneumonitis around 10% coherent with the international study. With an equivalent uniform dose reflecting the results of 14.4 Gy for VHEE, 10.6 Gy for VMAT and 4.6 Gy for VHEE with FLASH.

With this modeling, FLASH could overcome VMAT.
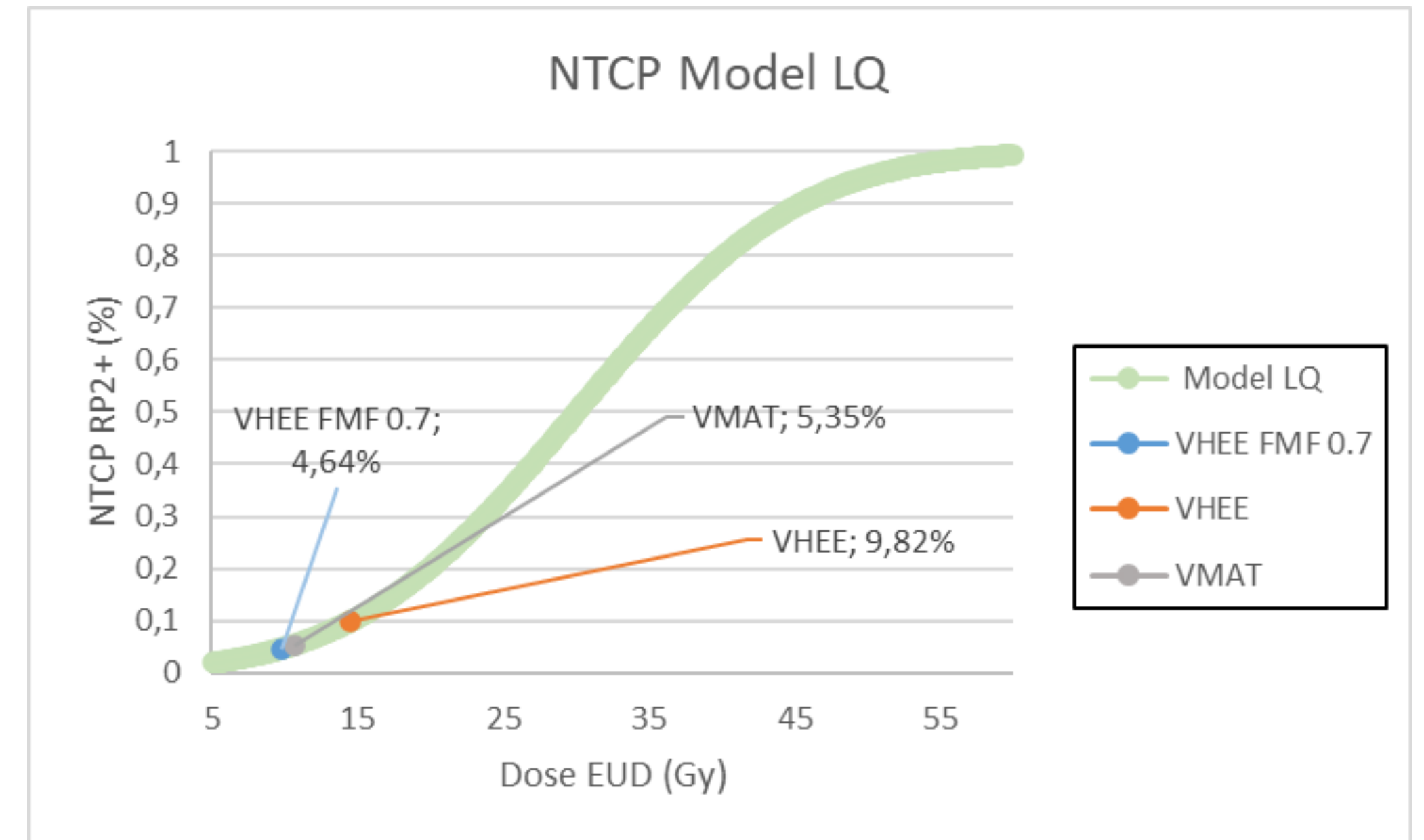
VHEE FMF 0.7   **VMAT**

~4.6% < **~5.3%**

Lungs-CTV	EUD	NTCP
VHEE FLASH FMF 0.7	9,8	4,6%
VHEE	14,4	9,8%
VMAT	10,6	5,3%

FLASH Dose
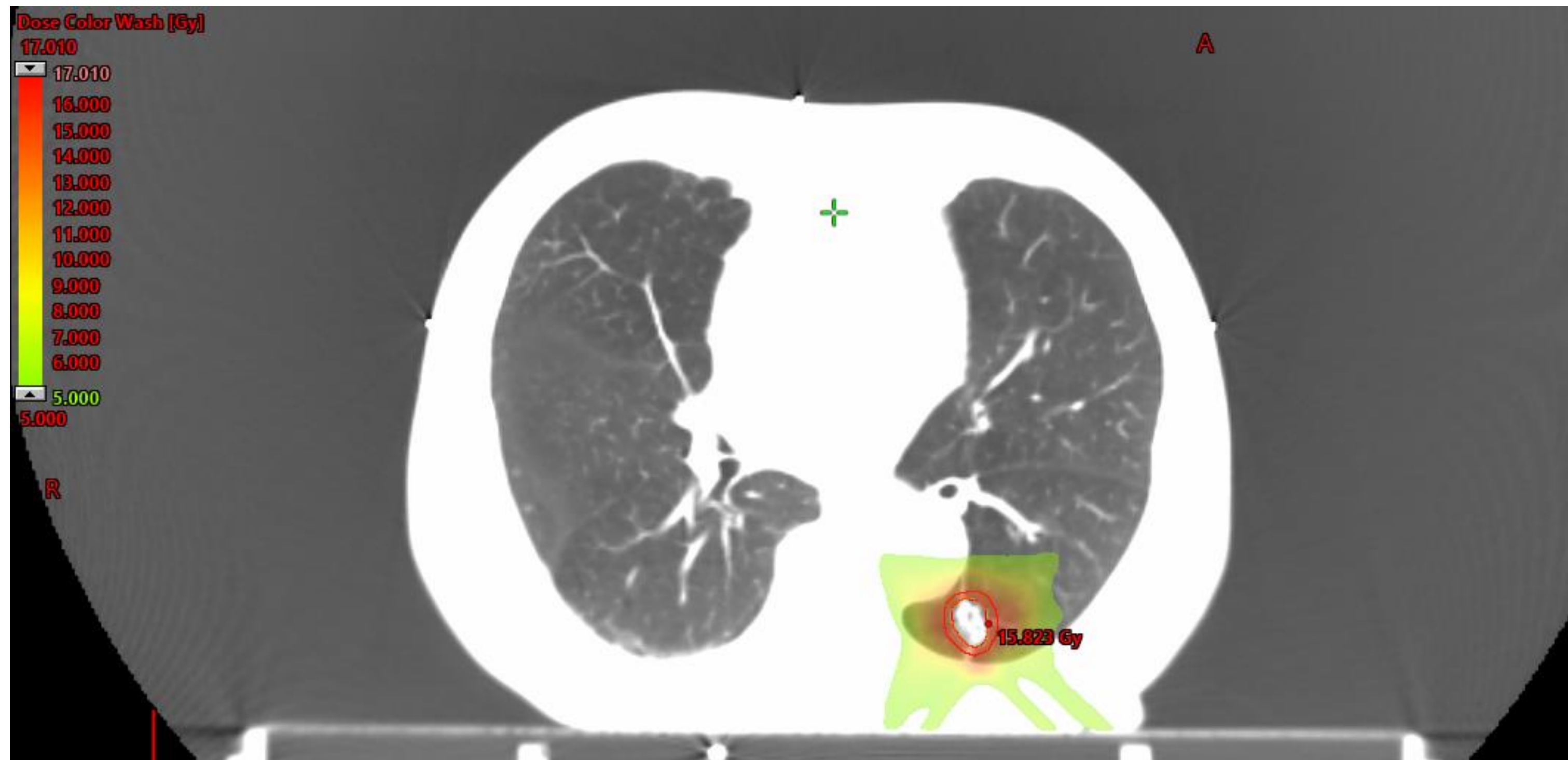
FLASH benefit = Dose VHEE - Dose VHEE FLASH FMF 0.7

From radiobiological models is clear that the contribution of FLASH in stereotactic treatments has an effect especially on high doses, and the results obtained, with current knowledge, could allow better sparing of organs at risk than VMAT.

The FLASH dose image on the left was obtained by subtracting the VHEE dose map from the VHEE FLASH dose map in order to highlight the healthy tissue preservation applied by FLASH modeling.

Conclusions

The evaluation of FLASH VHEE potential in the treatment of selected pathologies, plays a fundamental role in shaping the future accelerating, delivery, monitoring technologies that will have to be implemented. The conclusion are:

- I studied the issue of how to clinically trigger the flash effect for the treatment of deep-seated tumours: after studying the pancreas, I identified the lung as the best candidate.

- For the first time, starting from zero, I planned a VHEE treatment of the lungs, achieving results comparable to conventional radiotherapy.

- In the case of the lung, I made use of recent experimental data in the FLASH field to see how much would be the gain in terms of pneumonia in the VHEE field.

- Treatments of early-stage NSCLCs could be one of the first field of application for FLASH with VHEE.

- An article is in preparation

Acknowledge
Thanks to Gaia Antonio Angelica Annalisa Micol Giacomo Teresa e Valerio
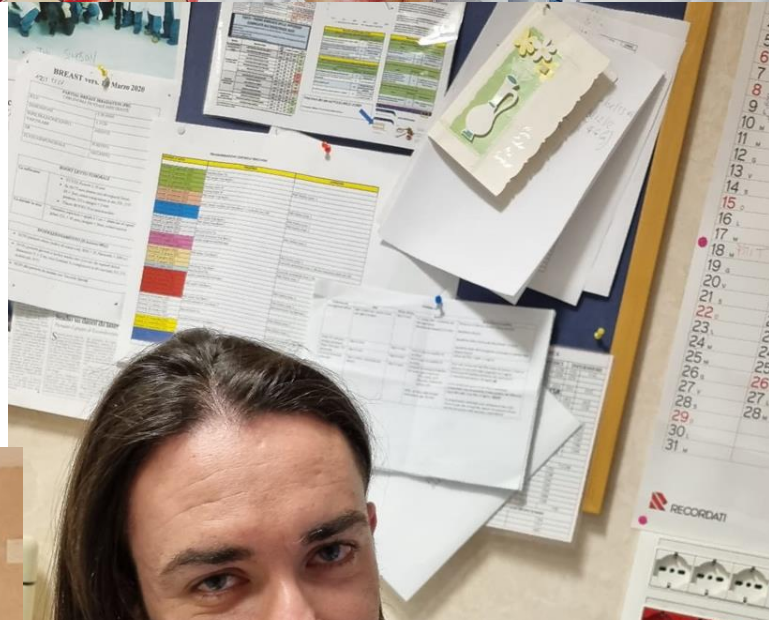
SPAN

FLASH Fibrosis reduction

High-lines:

Pulmonary fibrosis is a late-stage injury that typically manifests in the time period from six to 24 months post irradiation

⊙ While currently there is no good therapeutic intervention for fibrosis available
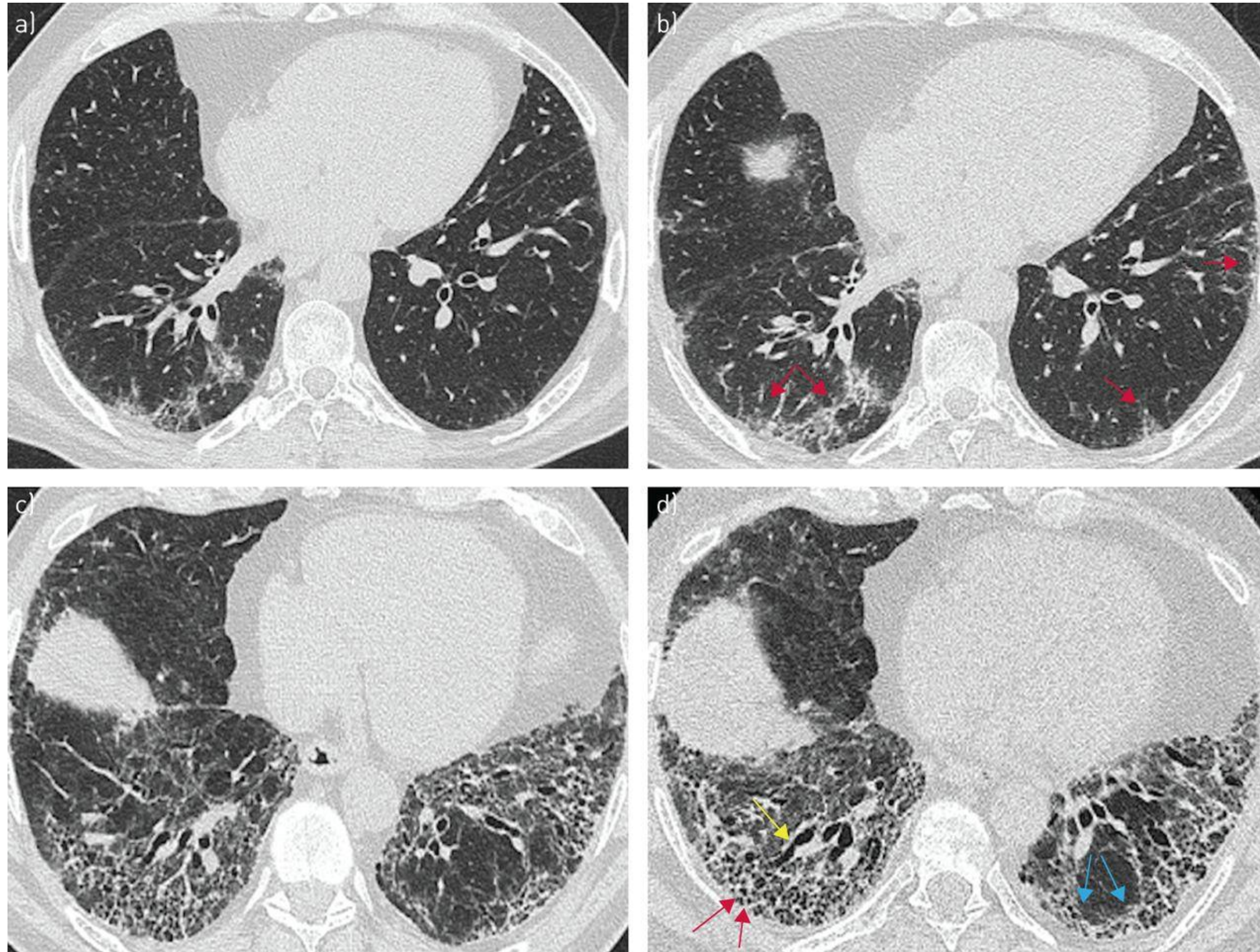
[7] M. D. Wright, P. Romanelli, A. Bravin, G. Le Duc, E. Brauer-Krisch, H. Requardt, S. Bartzsch, R. Hlushchuk, J. A. Laissue, and V. Djonov. Non-conventional ultra-high dose rate (flash) microbeam radiotherapy provides superior normal tissue sparing in rat lung compared to non-conventional ultra-high dose rate (flash) radiotherapy. Cureus, 13(11):e19317, 2021. ISSN 2168-8184.
[8] V. Favaudon, L. Caplier, V. Monceau, F. Pouzoulet, M. Sayarath, C. Fouillade, M. F. Poupon, I. Brito, P. Hupé, J. Bourhis, J. Hall, J. J. Fontaine, and M. C. Vozenin. Ultrahigh dose-rate flash irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med, 6(245):245ra93, 2014. ISSN 1946-6242. doi: 10.1126/scitranslmed.3008973.

DVH Differential data

DVH Differential

$$EUD = \left(\sum_i D_{i,corr}^{\frac{1}{n}} \frac{V_i}{V_{tot}} \right)^{n}$$

⊙ We will considered lung-CTV OAR

⊙ The main information came from the DHV differential i.e. the dose absorbed from each voxel

⊙ The biologically effective dose and equivalent dose in 2Gy calculators are based on the Linear Quadratic Model. The doses are calculated to allow conversion and comparability of different fractionation schemes.

⊙ The uniform equivalent dose (EUD) is the absorbed dose which, when administered homogeneously, produces the same average number of surviving clonogens as a non-homogeneous irradiation.
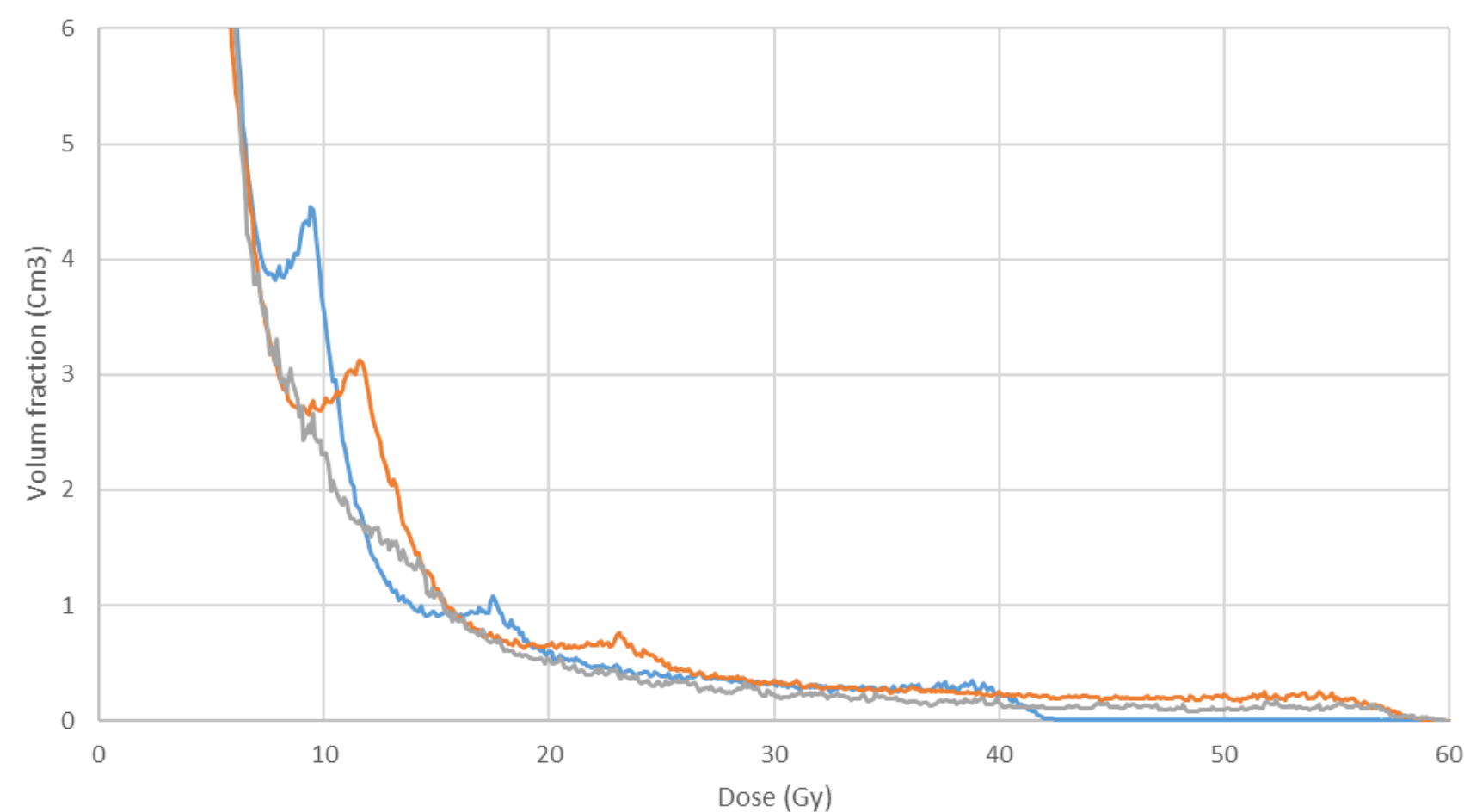
FLASH News

Materials & Methods

CONV dose rate: 0.16 Gy/sec (1 - 3 mins)
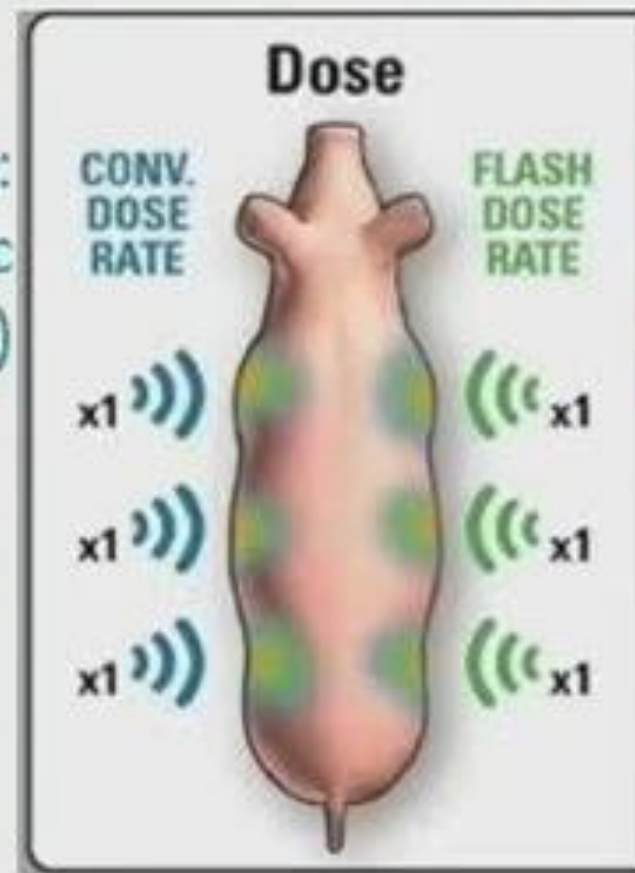
FLASH dose rate: 163 - 289 Gy/sec (0.05 - 0.12 secs)

Preliminary clinical assessments of biopsied targets suggested CONV-RT induced worse subacute cutaneous toxicity than FLASH-RT
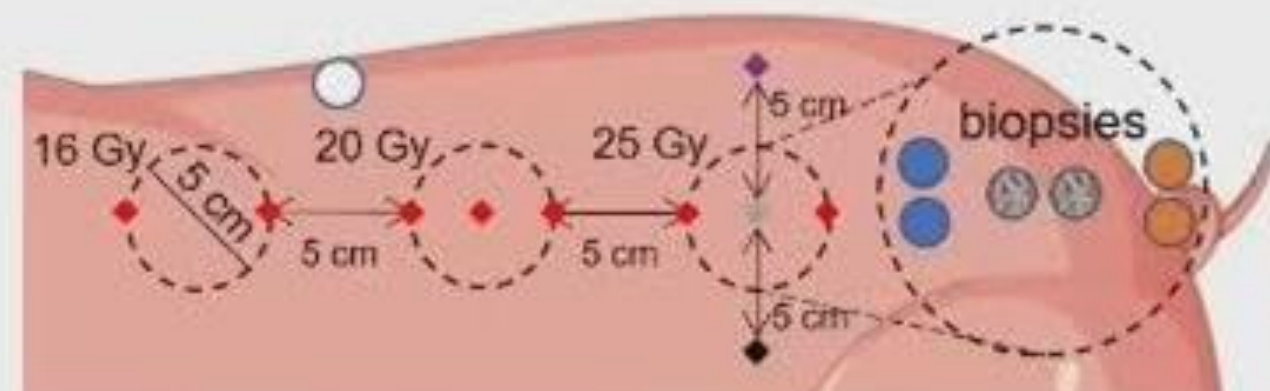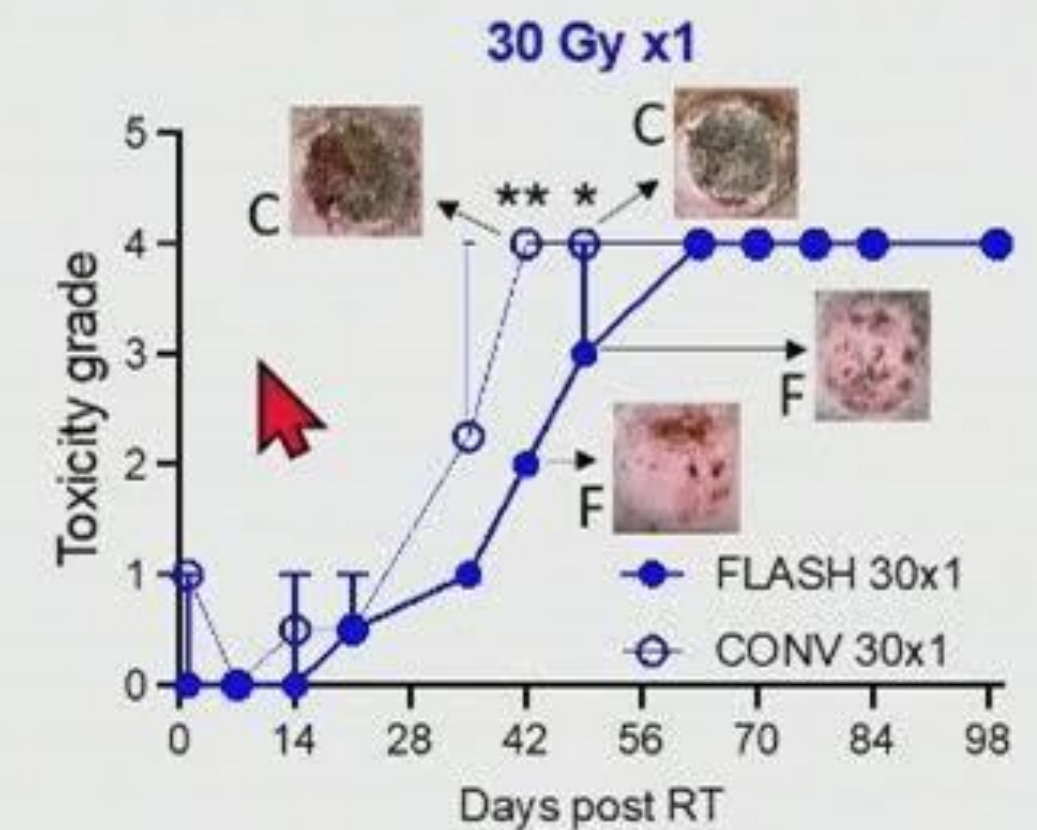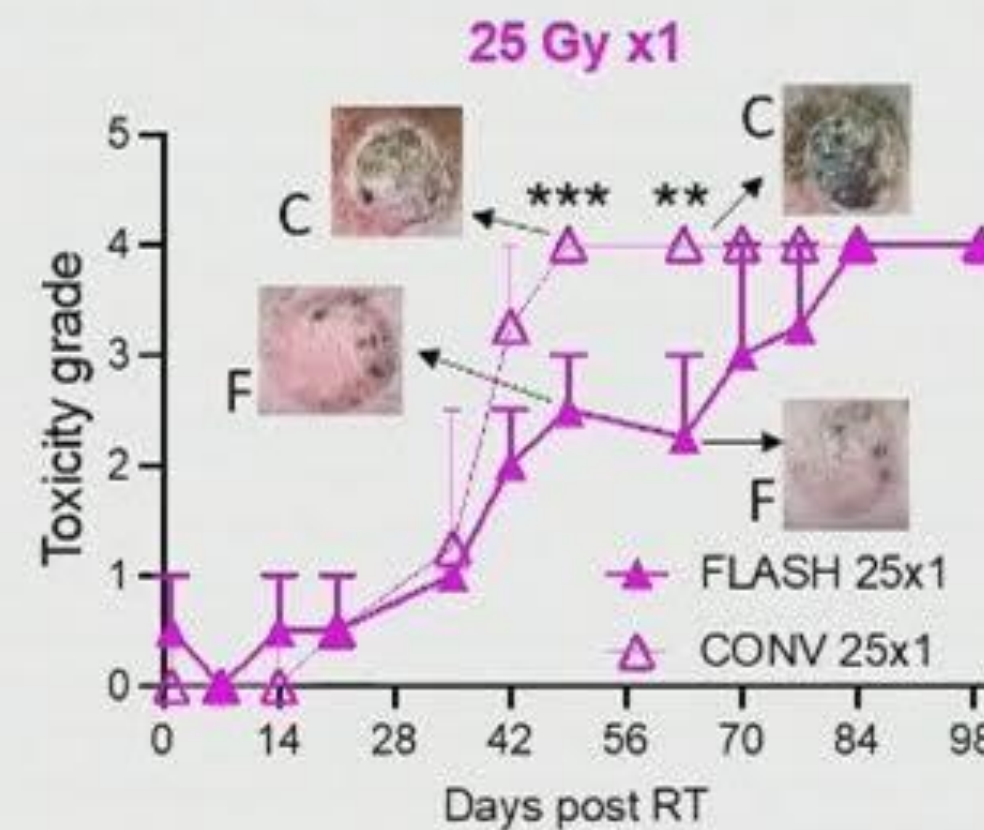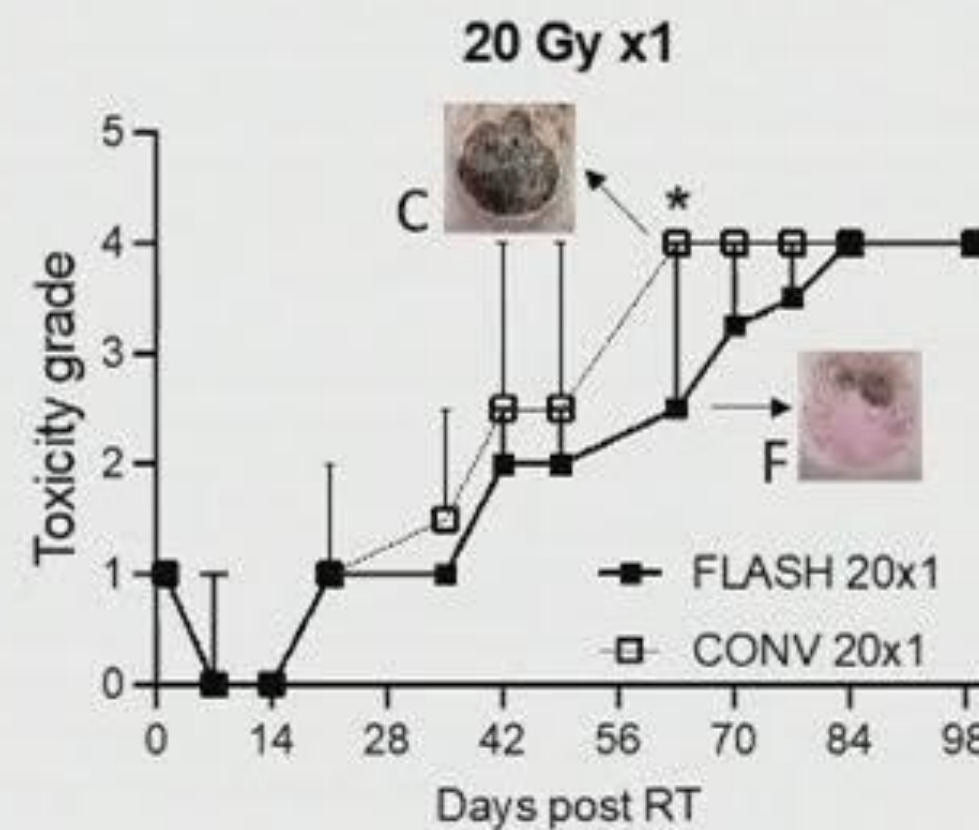
Modified RTOG Radiation Dermatitis Scale — Unpublished data (no photographs)

Grade 0	Grade 1	Grade 1.5	Grade 2	Grade 2.5	Grade 3	Grade 4
No change over baseline	Follicular, faint or dull erythema	Dry desquamation	Tender or bright erythema	Patchy moist desquamation	Confluent moist desquamation	Ulceration, hemorrhage, necrosis

Dose correction

Linear Quadratic
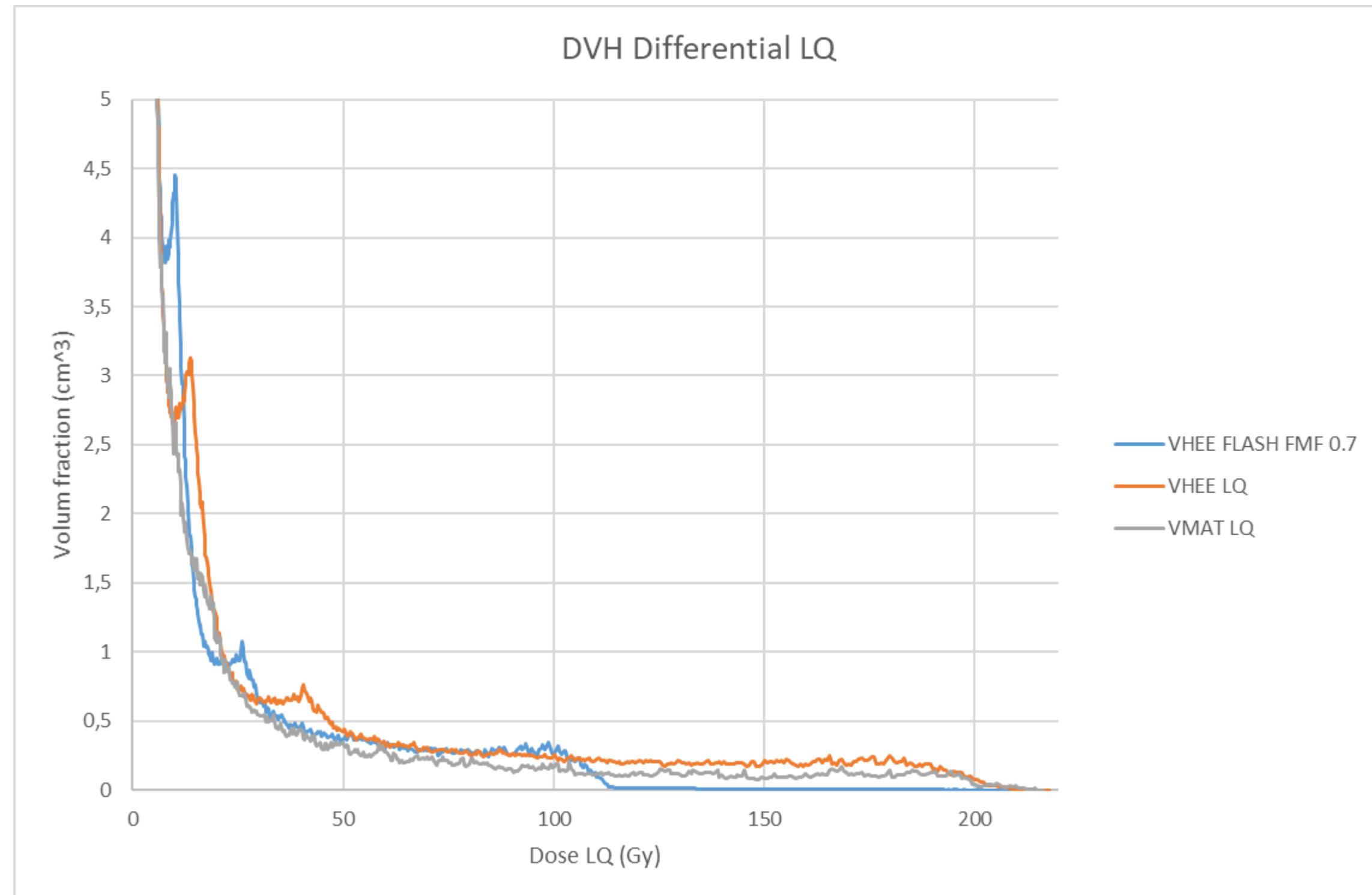
Retrospective court
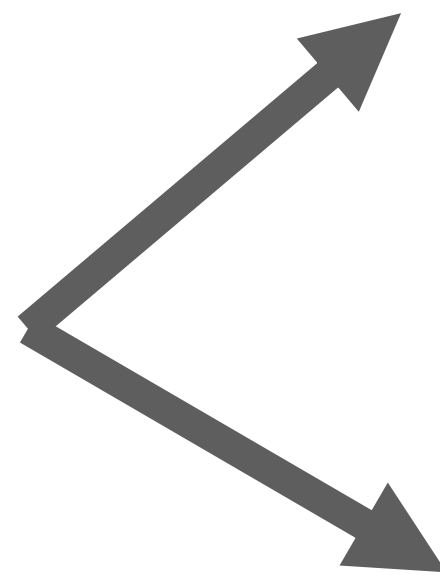
Universal Survival Curve

a/b	n	m	TD50	a	n barra	D0
3	0,71	0,4	30	0,206	10	1

Linear Quadratic

a/b	n	m	TD50
3	0,87	0,4	30

Lung Cancer – isodose distribution

VMAT
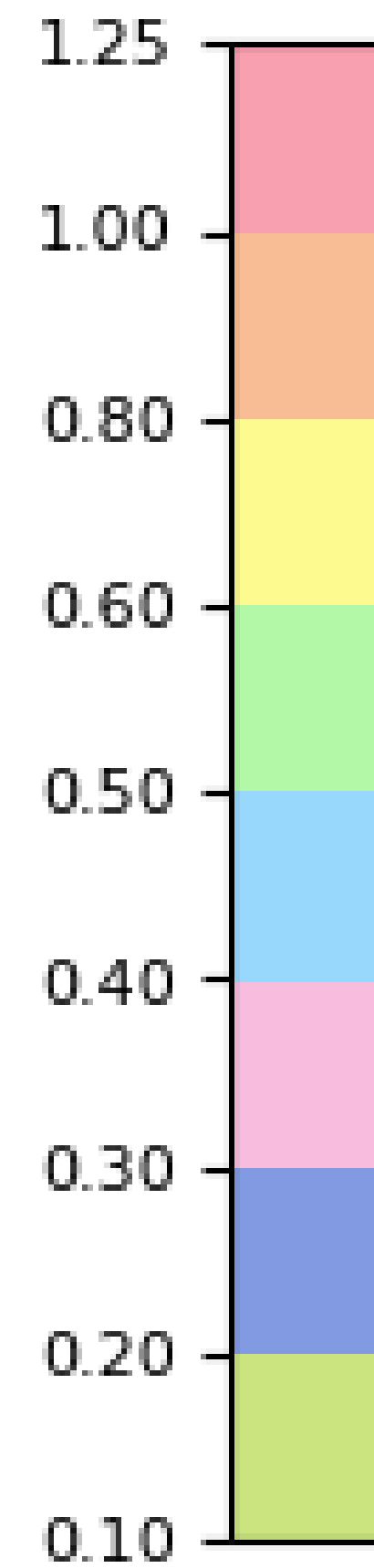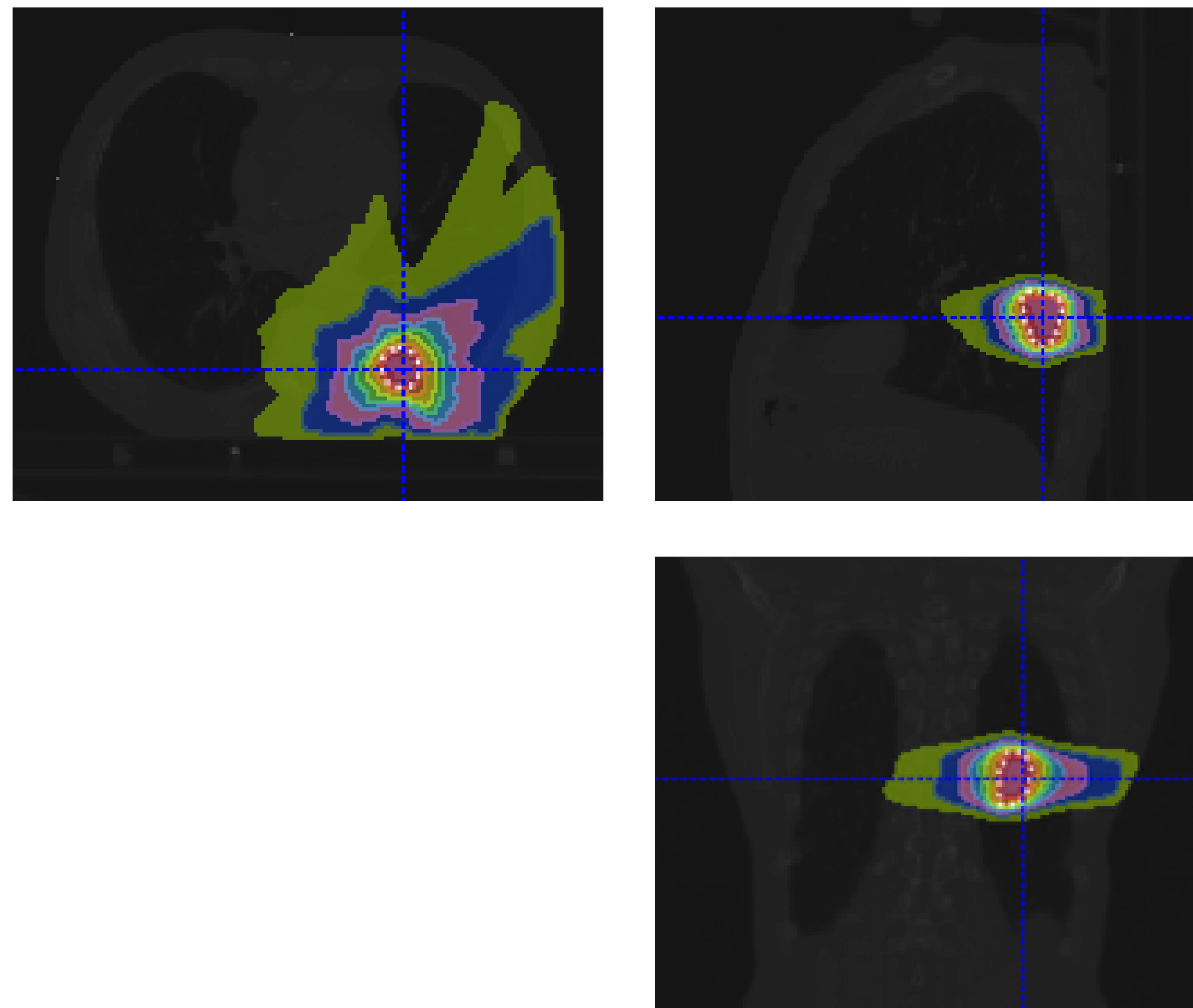
VHEE

Average Dose Rate

- ⊙ i-Voxel
- ⊙ J- beams
- ⊙ d_{tot} Total Voxel Dose
- ⊙ T_i Irradiation time
- ⊙ d* threshold value of effective irradiance
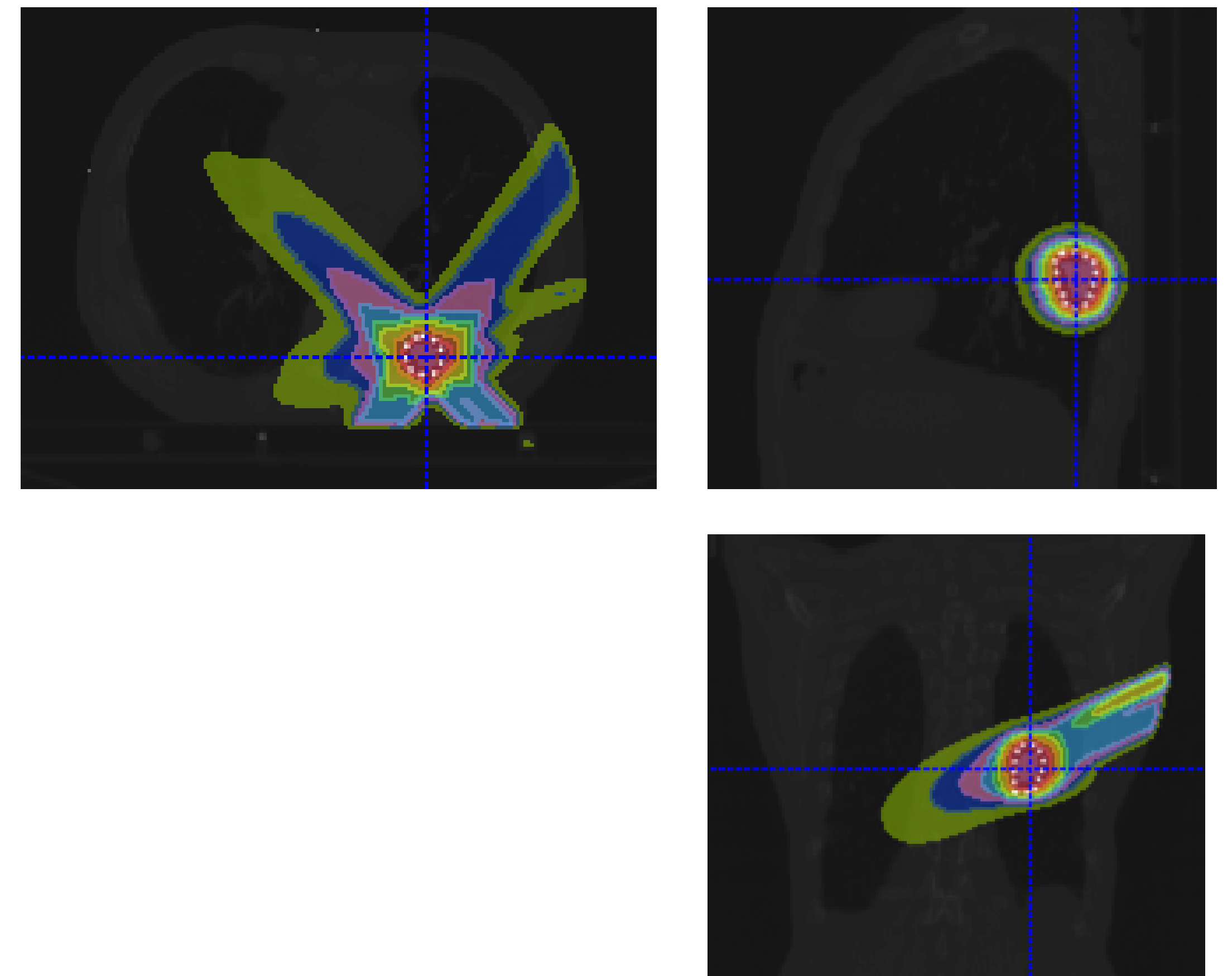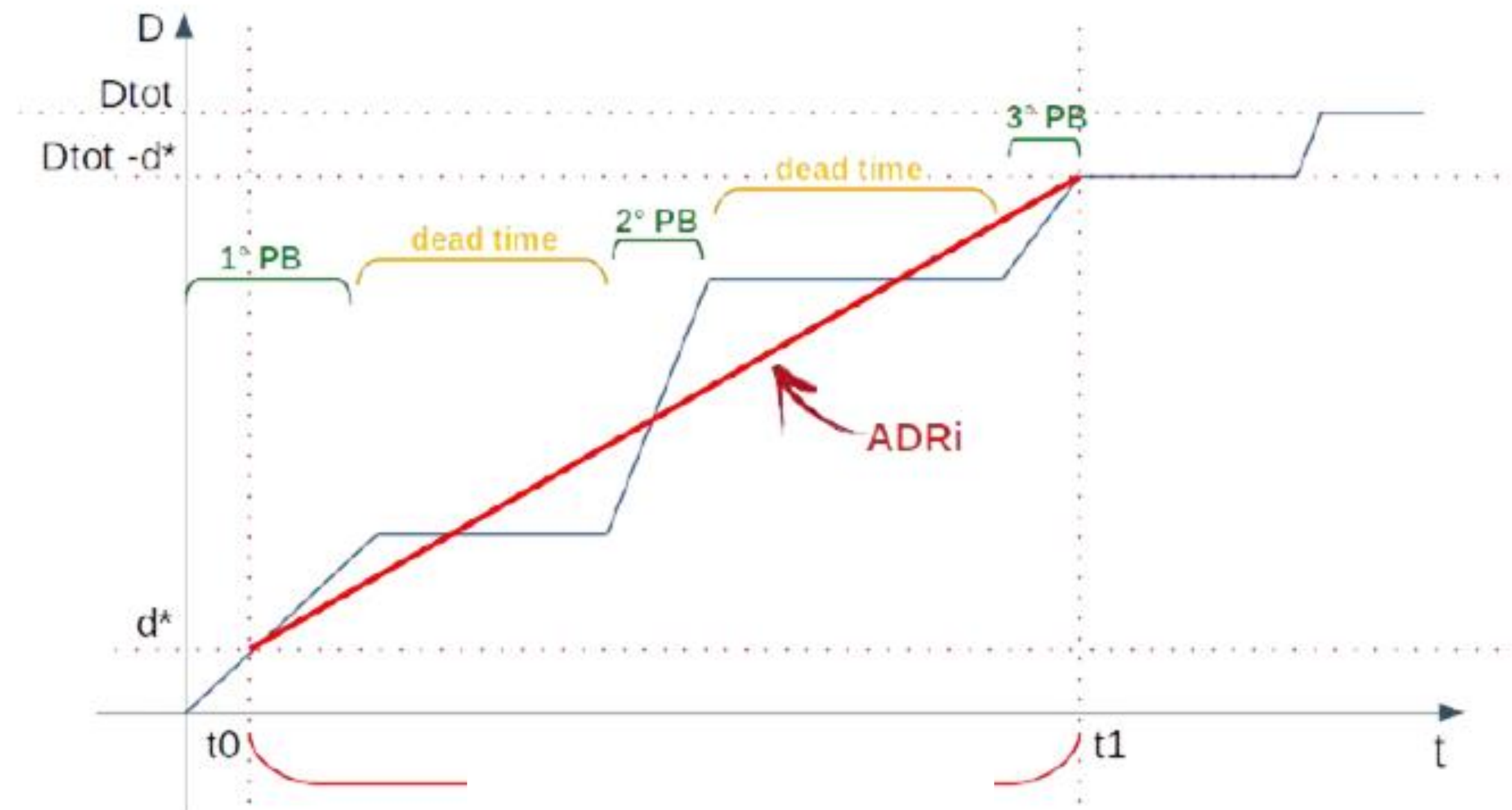
$$\text{ADR}_i = \frac{d_{tot} - 2d*}{T_i} \qquad \dot{D}_j^{ADR} = \frac{D_j - 2d*}{T_j}$$
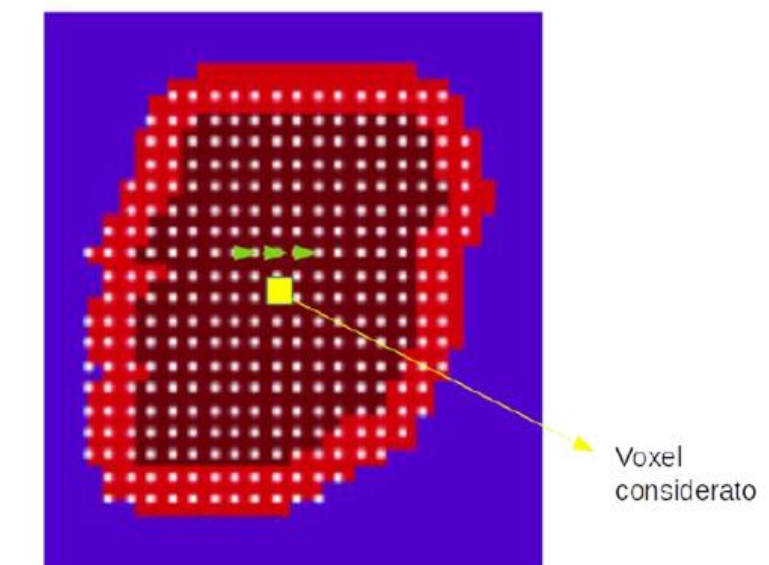
Beam field of view of the tumor

Dose correction

Linear Quadratic
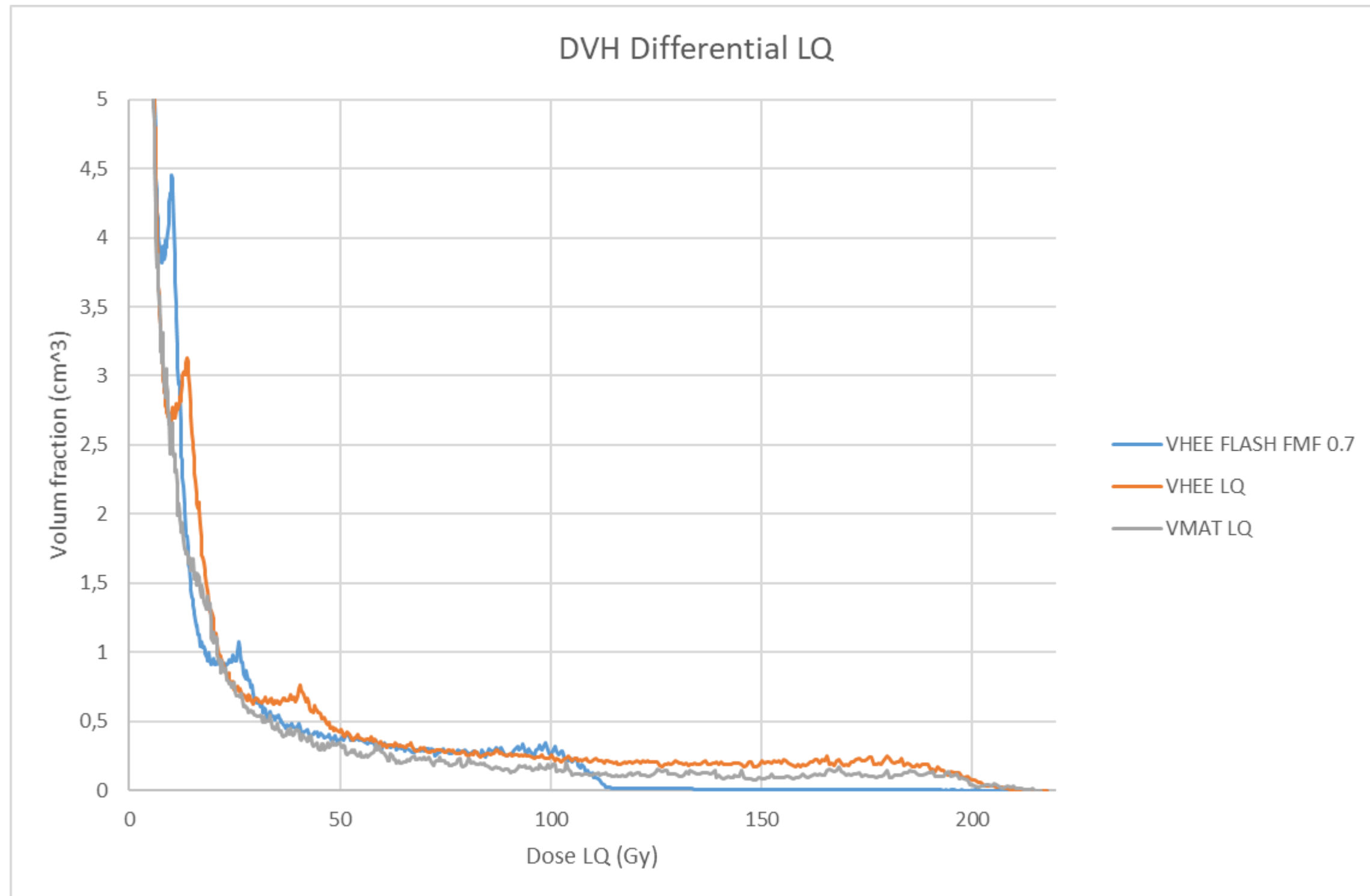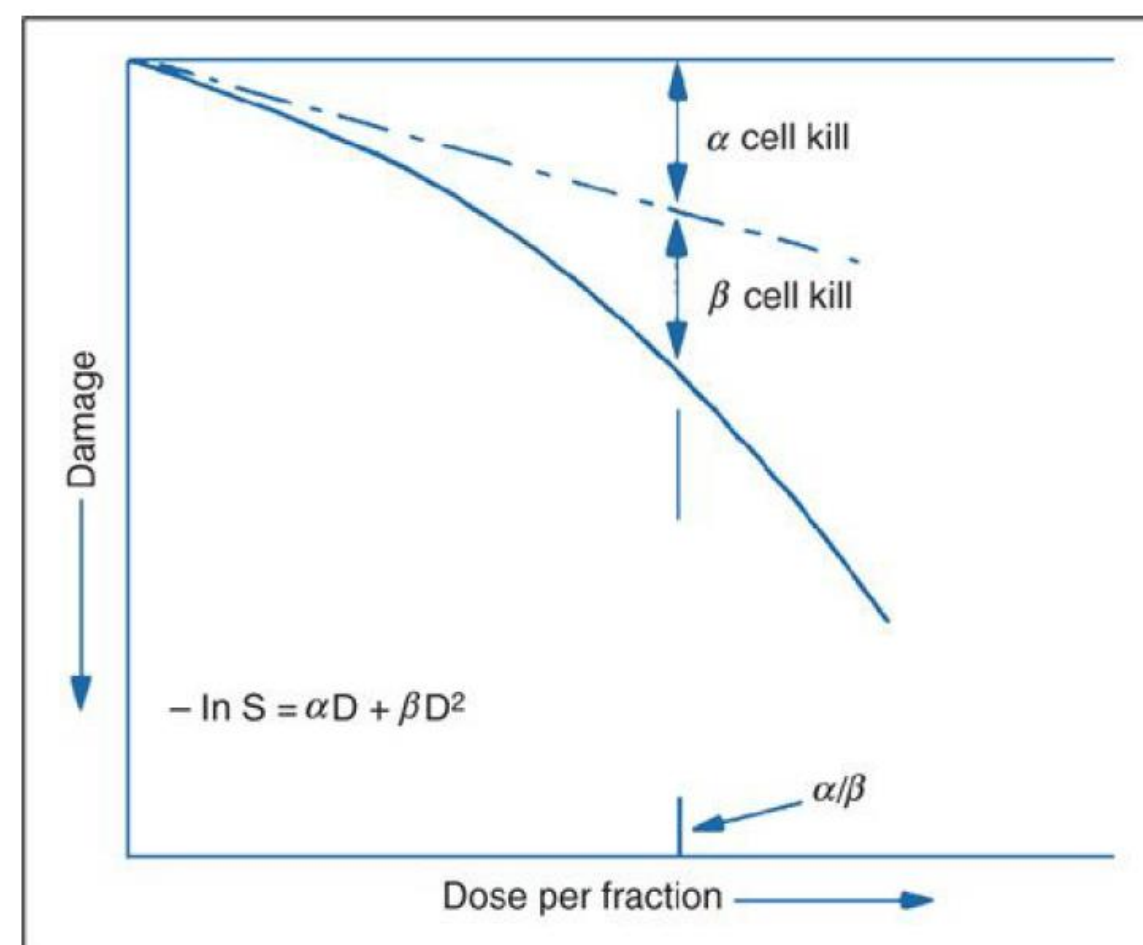
Universal Survival Curve
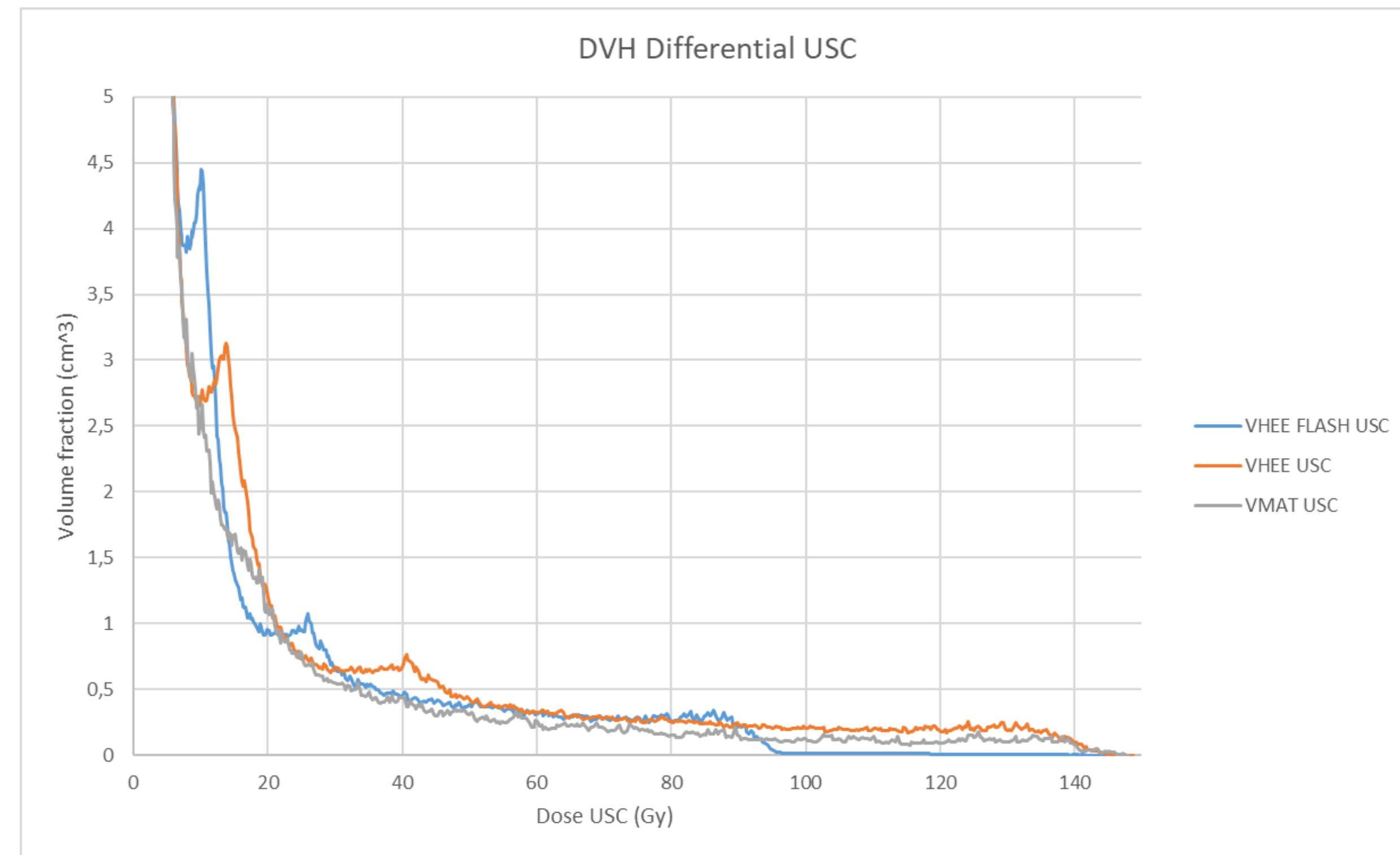
Lung Cancer – Energy Beam
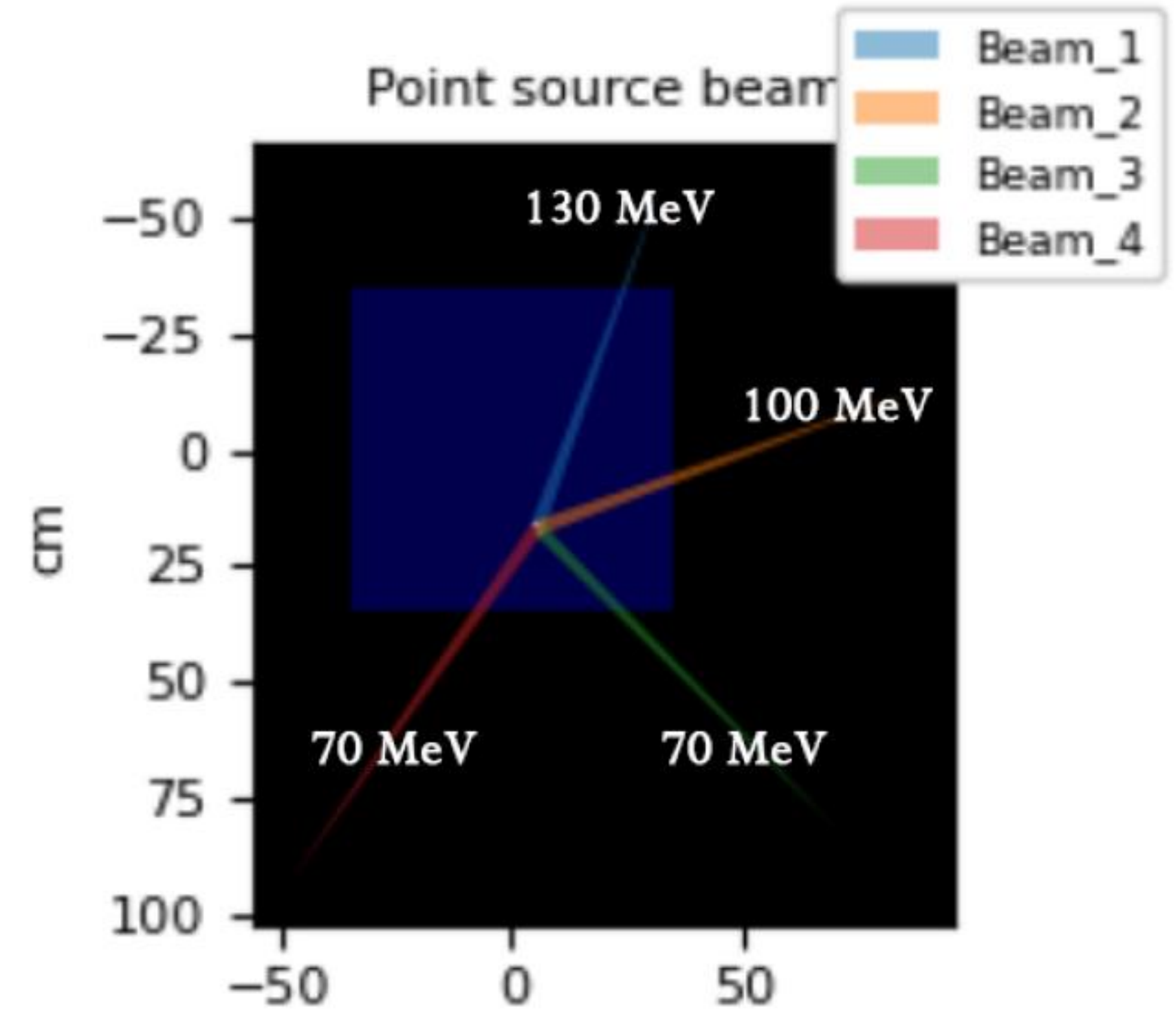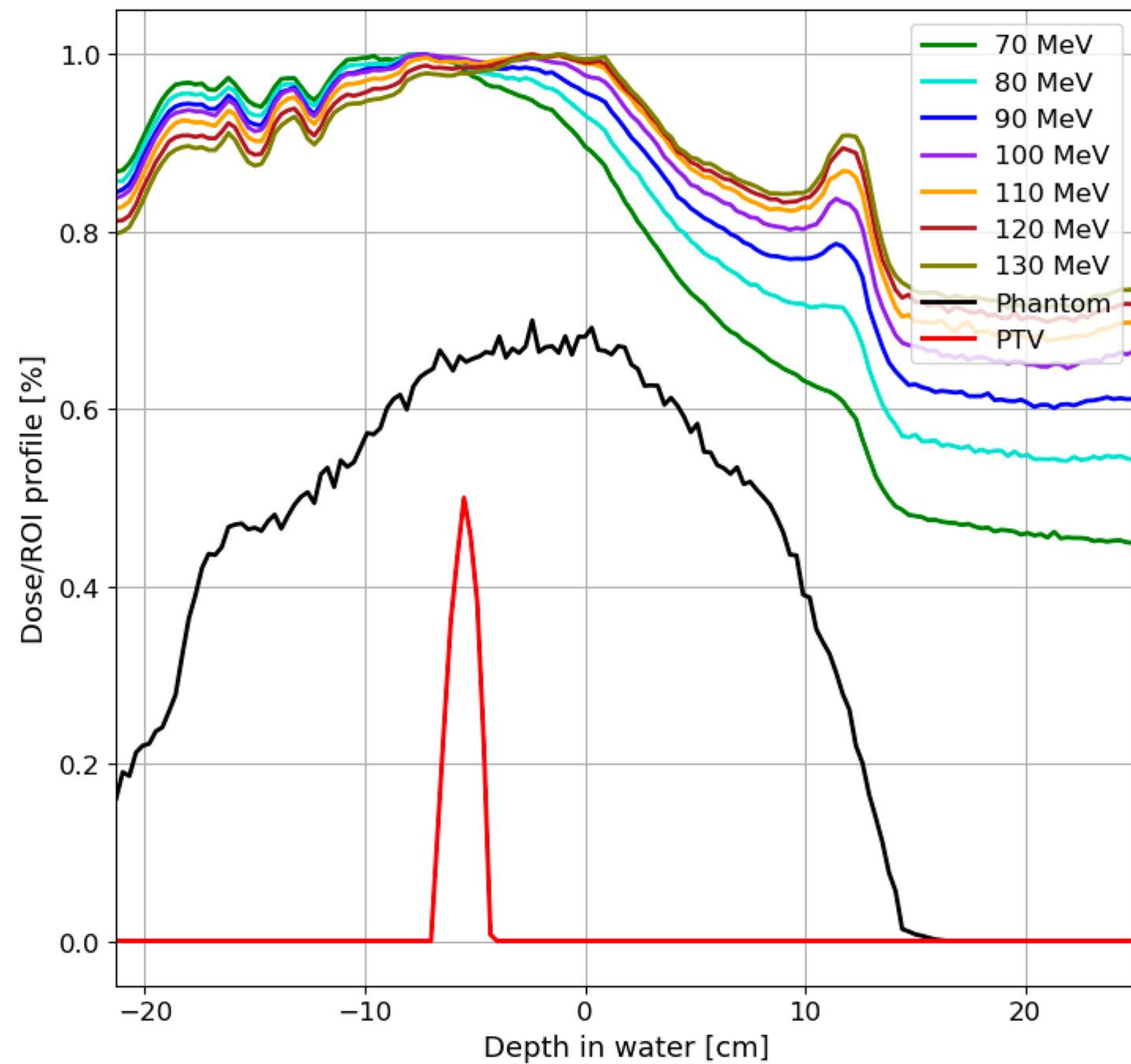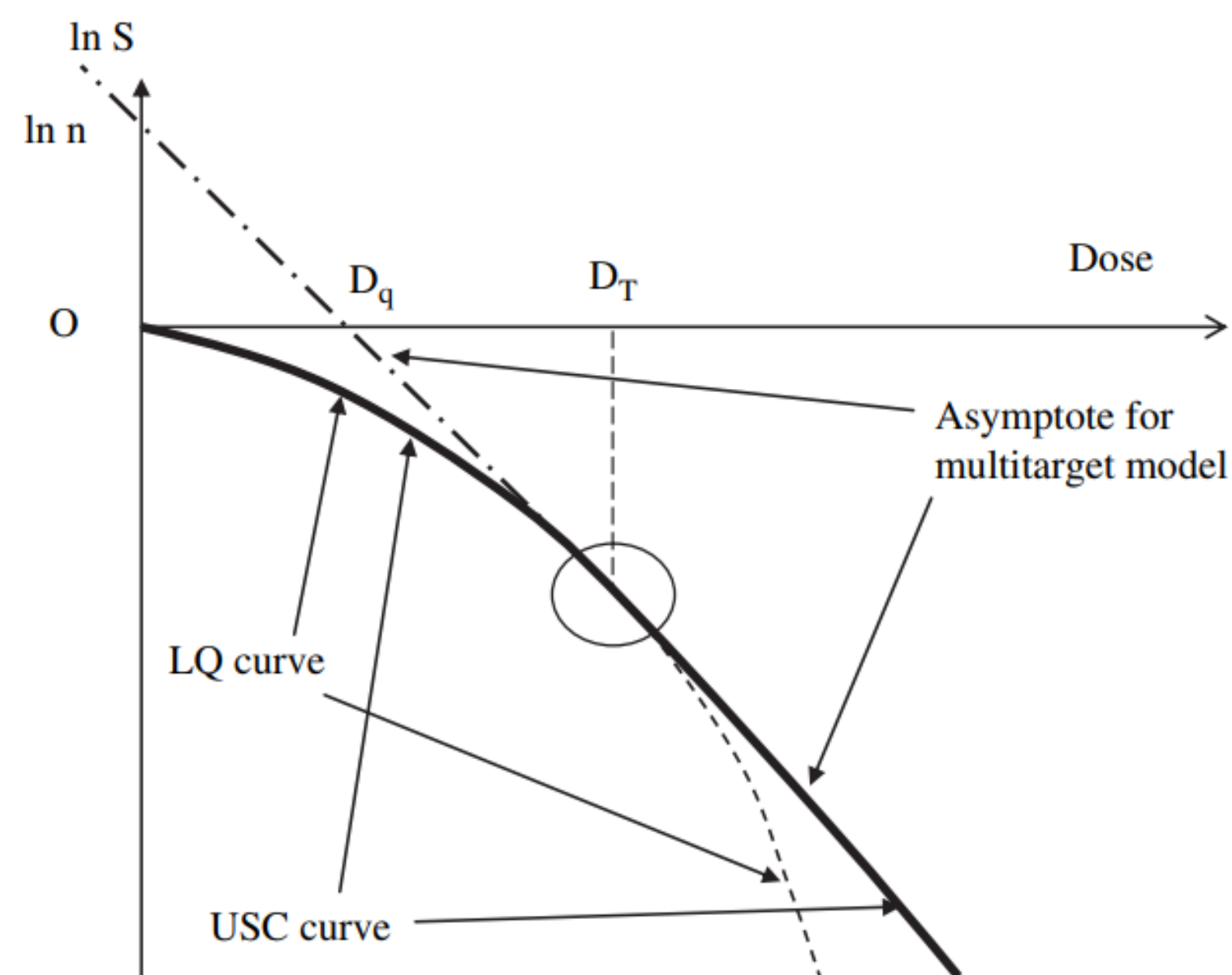
Radiobiological model

Linear Quadratic

$$S_{LQ} = \left(e^{-(\alpha d_1 + \beta d_1^2)} \right)^{n_1}$$

Universal Survival Curve

hybridizing two classical radiobiological models: the LQ model in the low-dose range and the Single Hit Multi-Target (SHMT) model in the high-dose range


$$S_{SHMT} = \left(1 - \left(1 - e^{(-d_2/D_0)} \right)^{\bar{n}} \right)^{n_2}$$

Radiobiological Parameters

The radiobiological models used are based on 3 parameters:

- ⊙ "TD50" which denotes the dose for 50% complication probability.

- ⊙ "m" which is inversely proportional to the slope at the steepest part of the response curve.

- ⊙ "n" parameter controls the volume effect. If it is small, (e.g., ≈ 0.1 for late rectal bleeding). Serial complications are most affected by the hottest portion of the DVH.
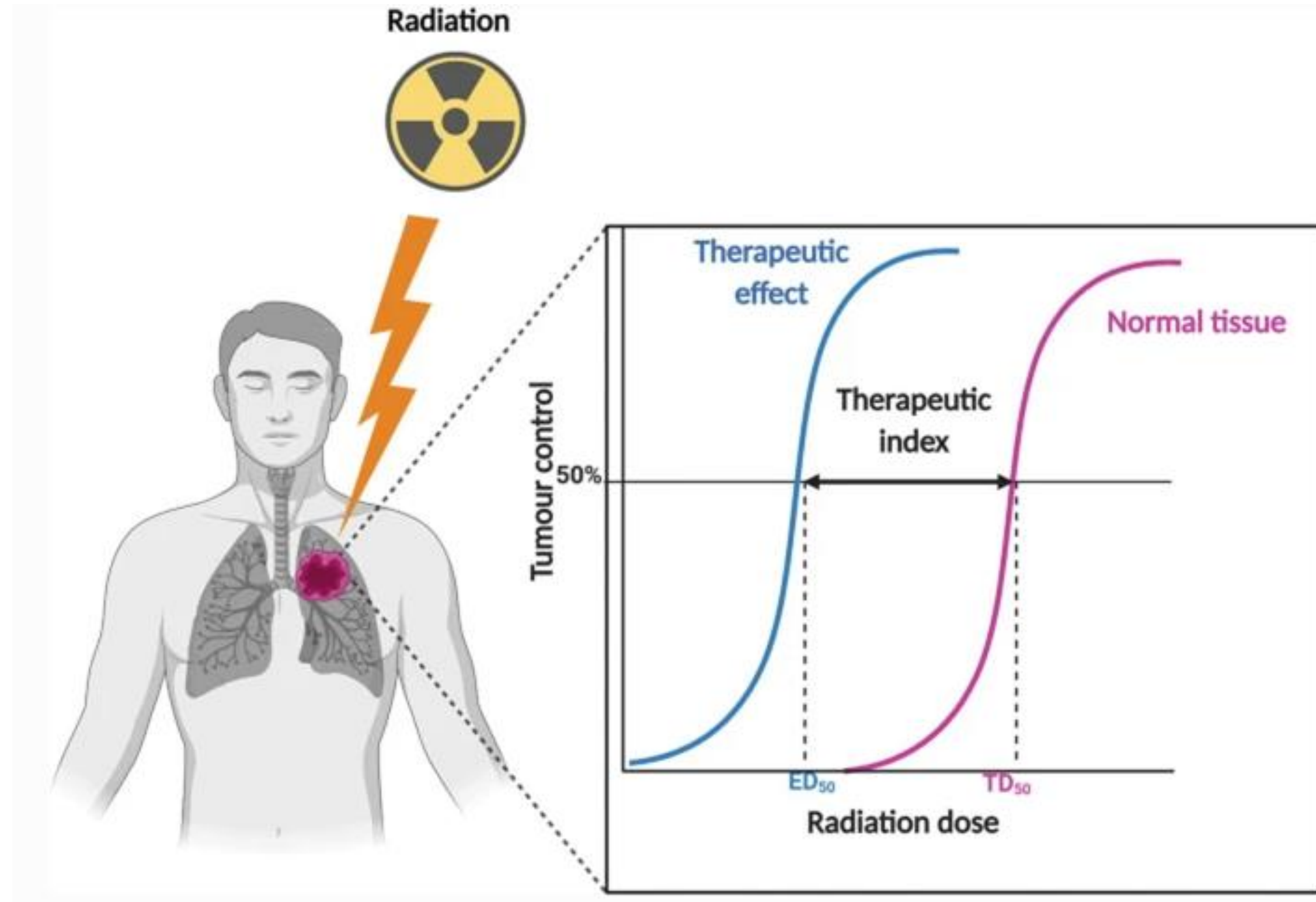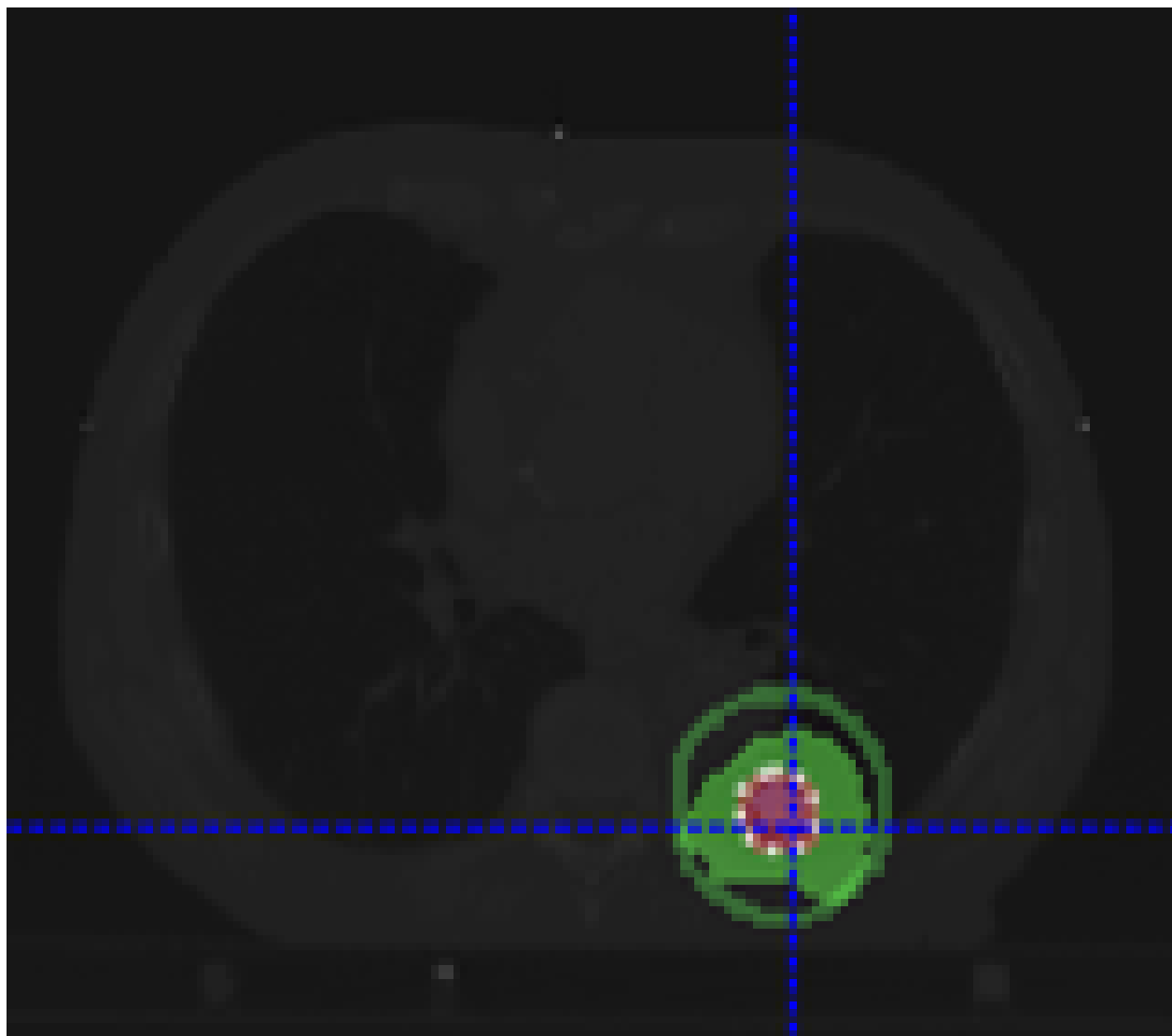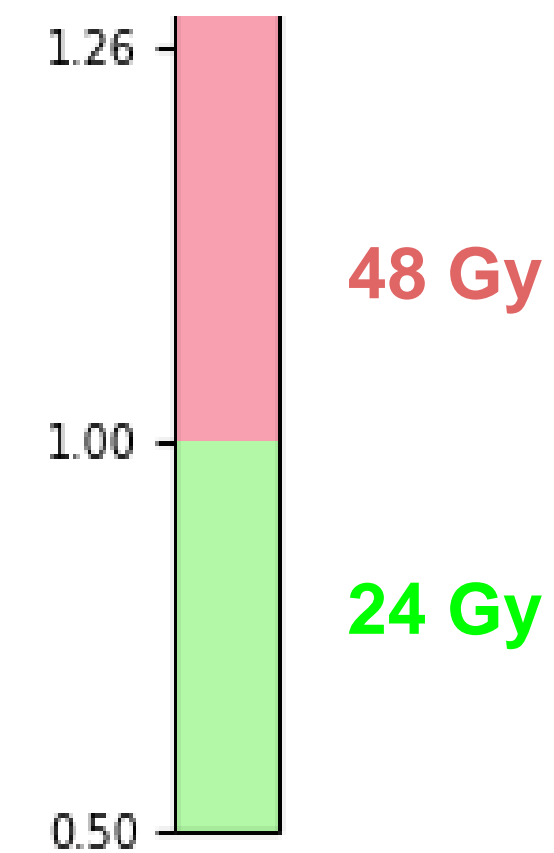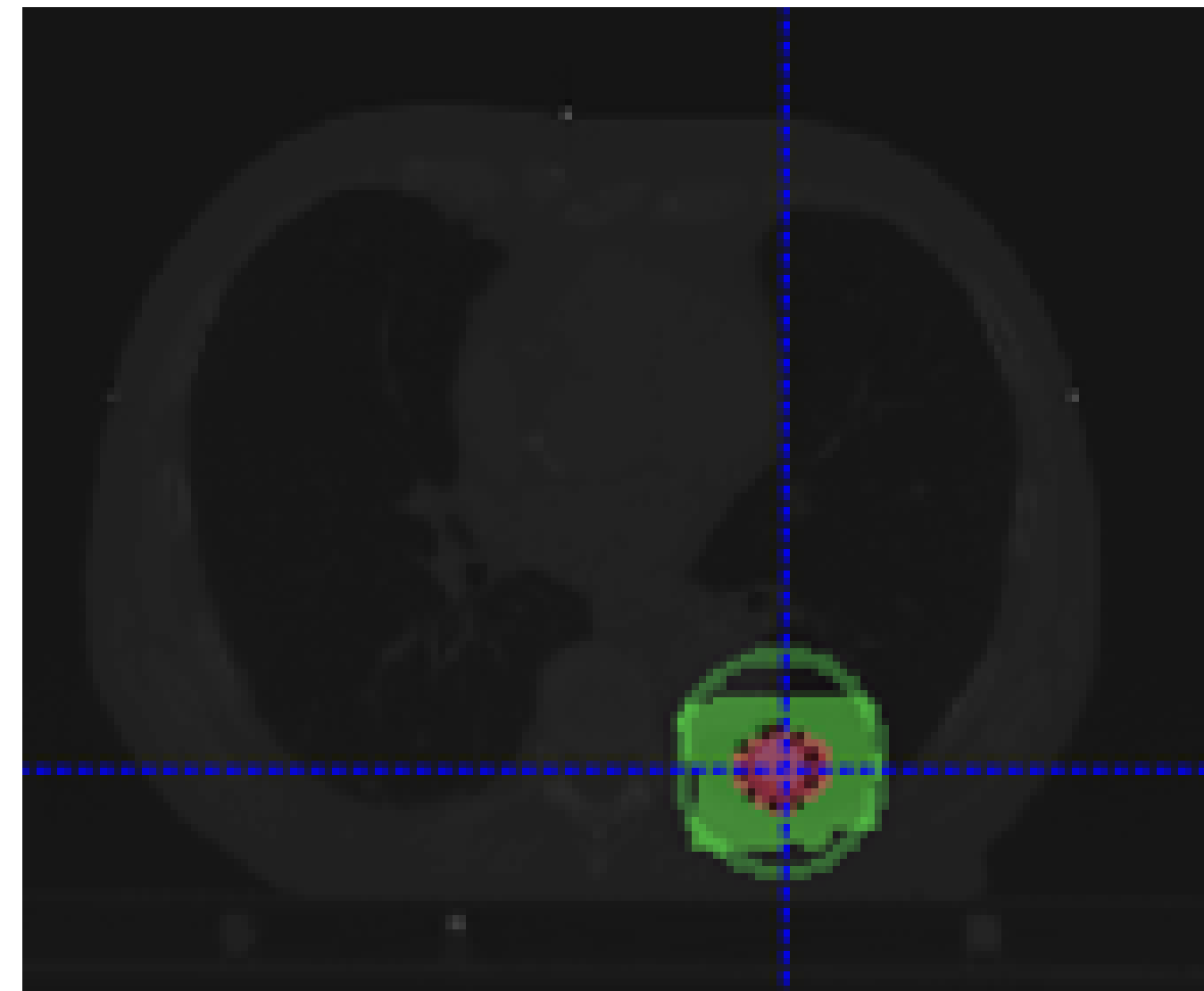
Lung Cancer

VMAT   VHEE

1.26

48 Gy

1.00

24 Gy
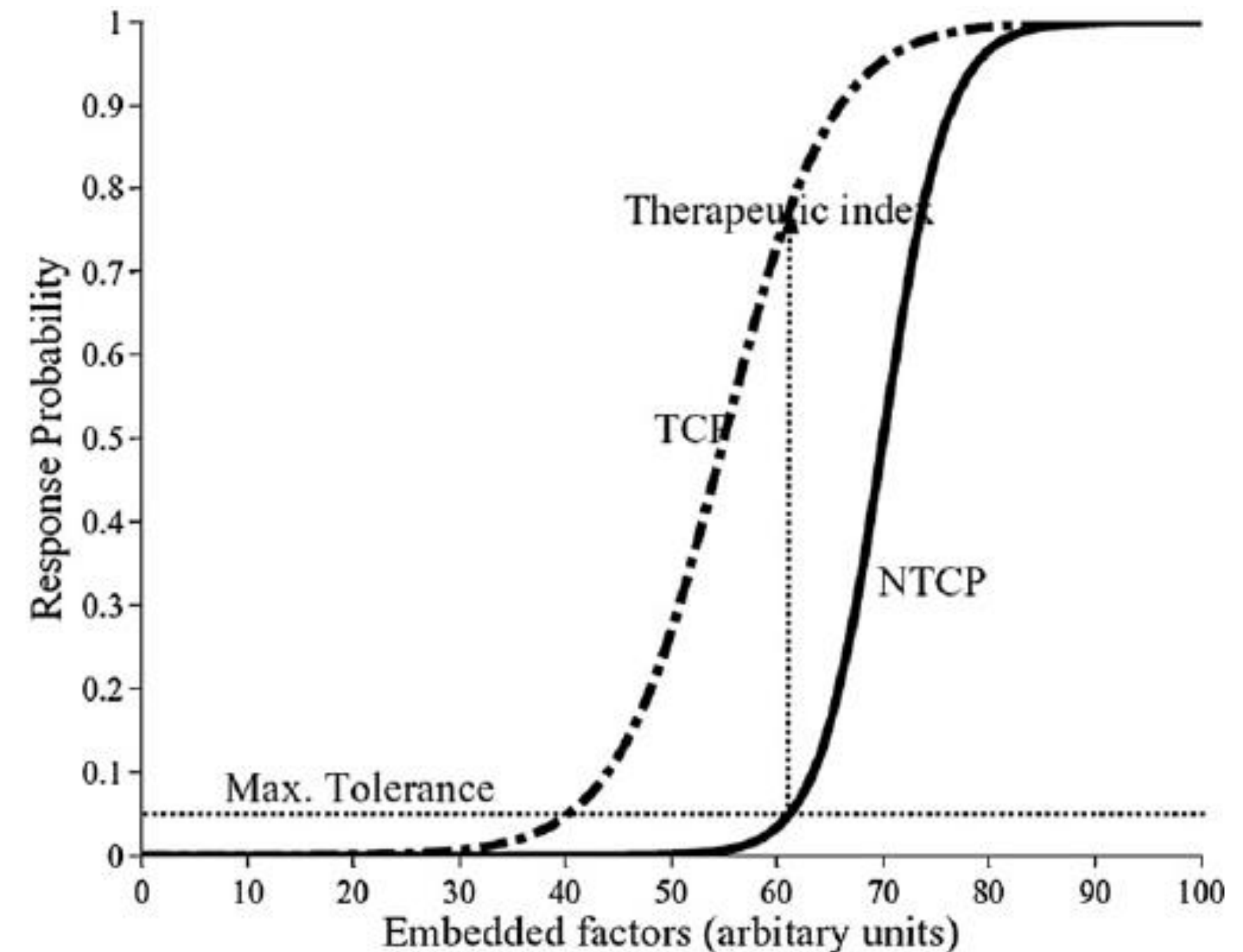
0.50

Normal tissue complication probability NTCP

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \qquad (9)$$

where

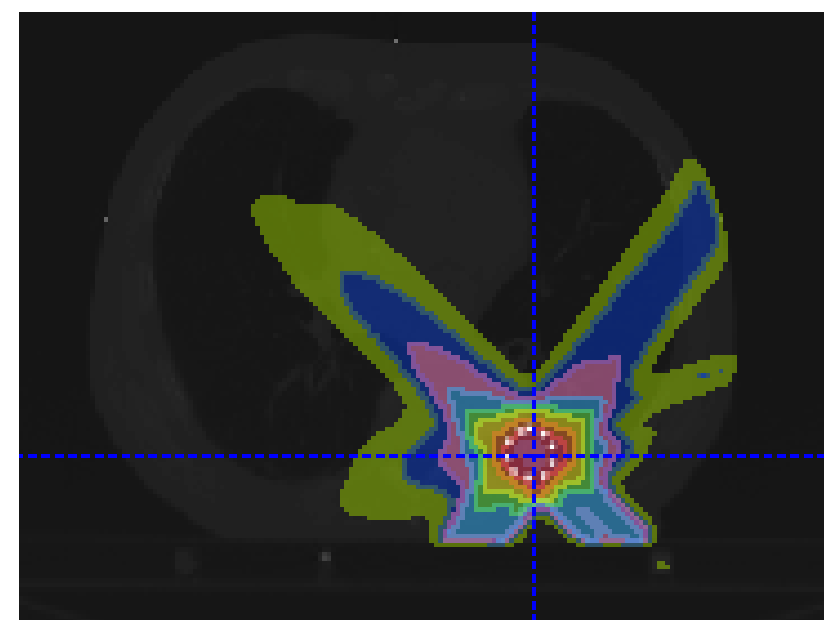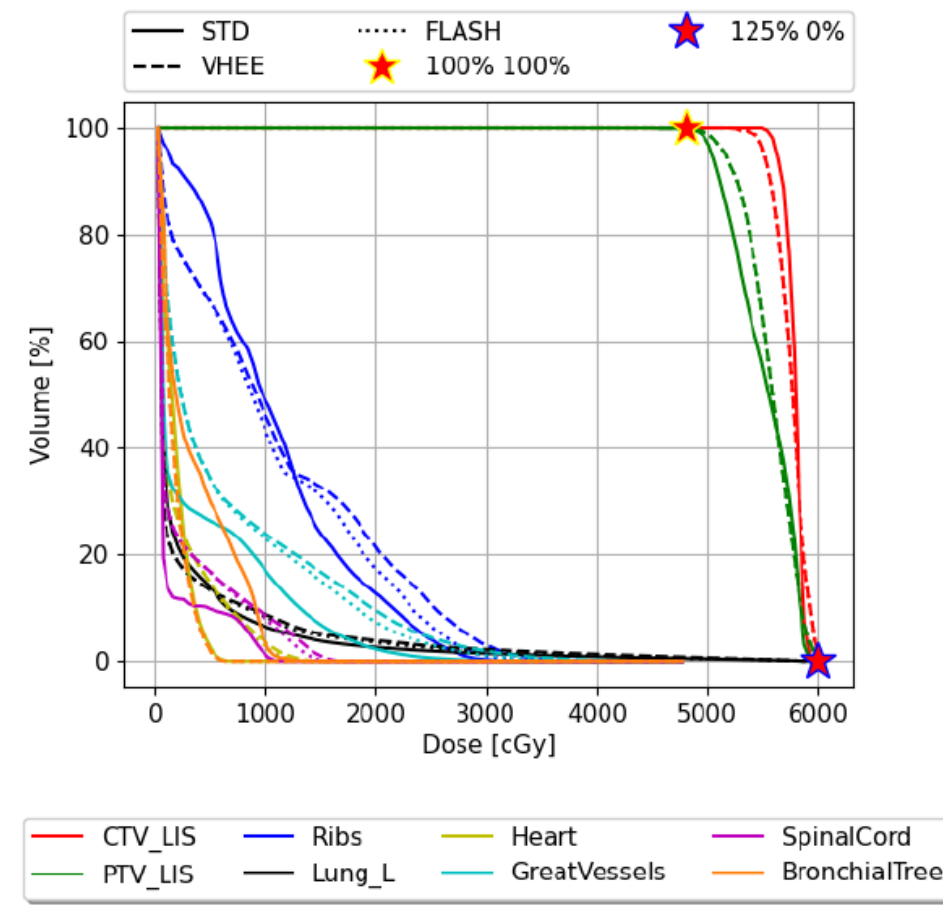$$t = \frac{EUD - D_{50}}{m \cdot D_{50}} \qquad (10)$$

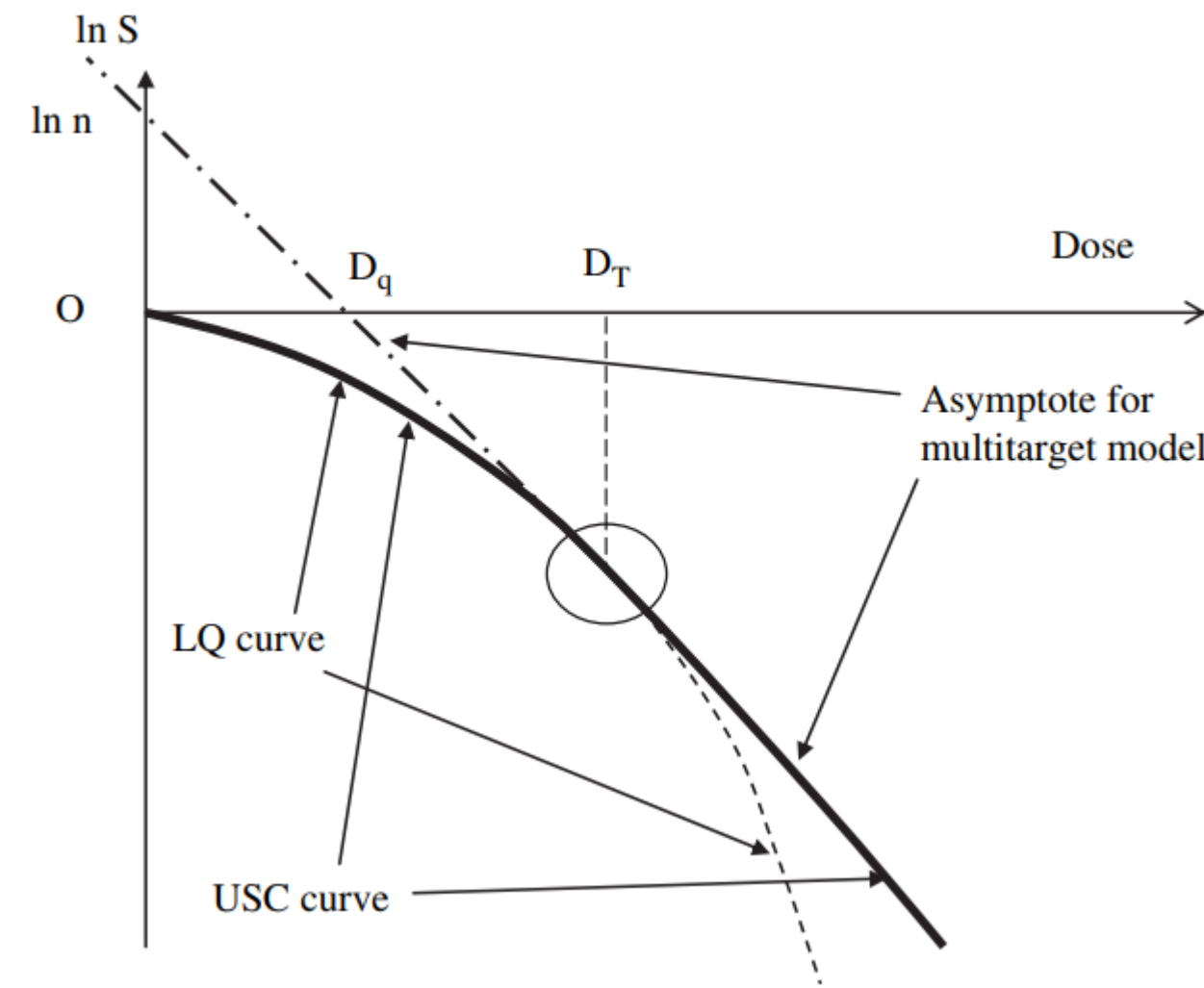and the equivalent uniform dose (EUD) was defined by

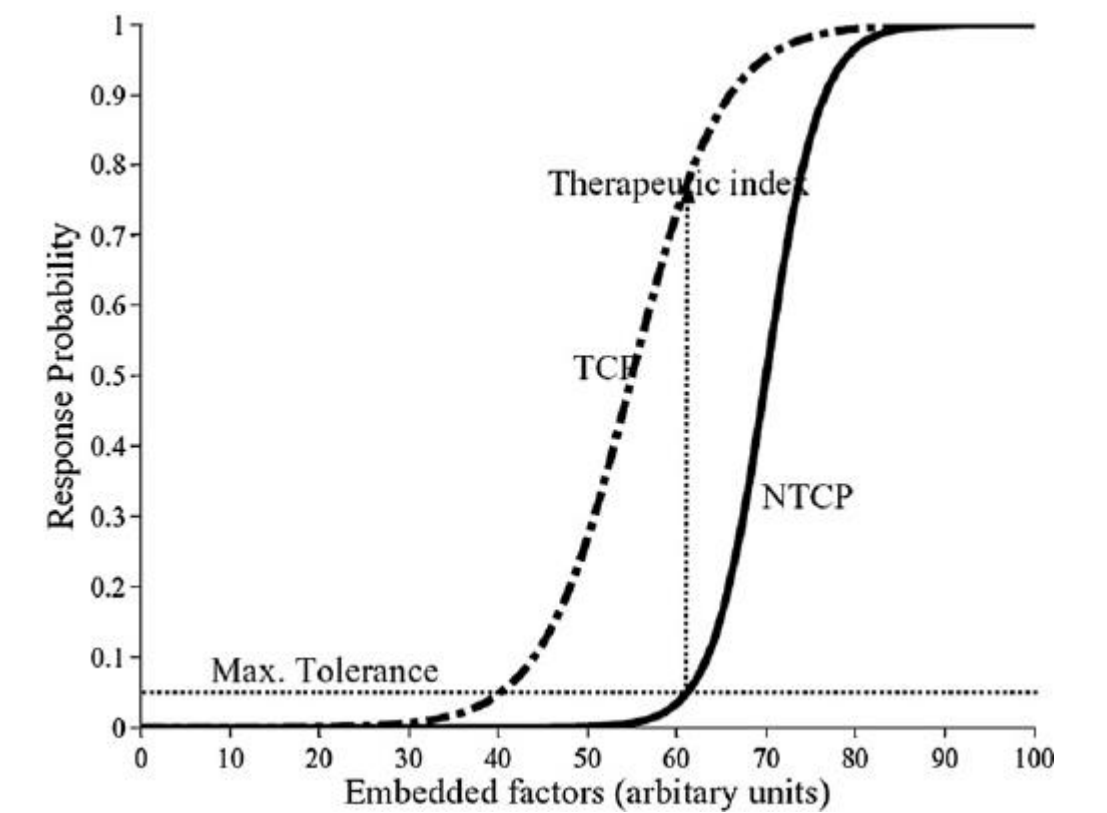$$EUD = \left(\sum_i D_{i,corr}^{\frac{1}{n}} \frac{V_i}{V_{tot}} \right)^n \qquad (11)$$

Dosimetric application in Radiobiological model

Dosimetric Information

Radiobiological model for cell survive LQ/USC

To predict the probability of radiation pneumonitis NTCP

Results

Universal Survival Curve

Lungs-CTV	dose fraction	number of fraction	EUD	NTCP
VHEE FLASH FMF 0.7	12	4	11,1	5,82%
VHEE	12	4	16,0	12,20%
VMAT	12	4	12,2	6,94%

Linear Quadratic

Lungs-CTV	dose fraction	number of fraction	EUD	NTCP
VHEE FLASH FMF 0.7	12	4	9,8	4,64%
VHEE	12	4	14,4	9,82%
VMAT	12	4	10,6	5,35%

VHEE
~11%

VHEE FMF 0.7
~5.2%

VMAT
~6.1%

NTCP Model USC

VHEE FMF 0.7; 5,8%

VMAT; 6,9%

VHEE; 12,2%

- Model USC
- VHEE FMF 0.7
- VHEE
- VMAT

NTCP RP2+ (%)

Dose EUD (Gy)

NTCP Model LQ

VHEE FMF 0.7; 4,64%

VMAT; 5,35%

VHEE; 9,82%

- Model LQ
- VHEE FMF 0.7
- VHEE
- VMAT

NTCP RP2+ (%)

Dose EUD (Gy)

FLASH Effect

A — Direct effect / Indirect effect
H_2O → $HO^·$
Free radical R
H^+ → R H Hypoxia (reversible)
O_2 → R OOH Normoxia (fixed)

B — Relative oxygen pressure vs Radiation sensitivity
FLASH / CONV
Tumor: Small change in O_2 — Radiation resistance — No change in tumor kill
Normal tissue: Rapid, large change in O_2 — ↑↑ Radiation resistance — Sparing of normal tissue

Day 0   3 weeks   5 months

Highlines:

⊙ deliver high doses (>4-6 Gy)
⊙ very short period of time (<200 ms)

FLASH Effect
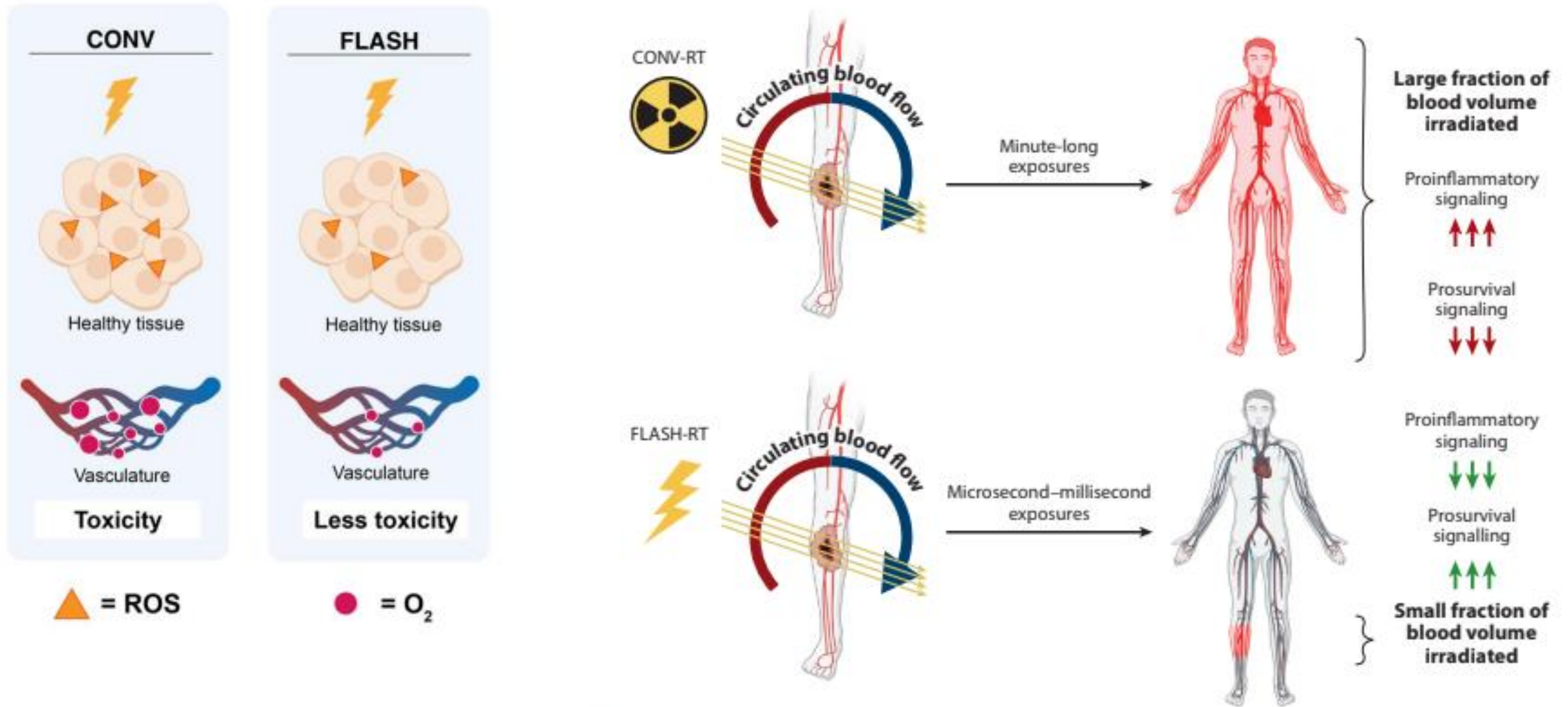
Highlights:

⊙ 70-130 MeV
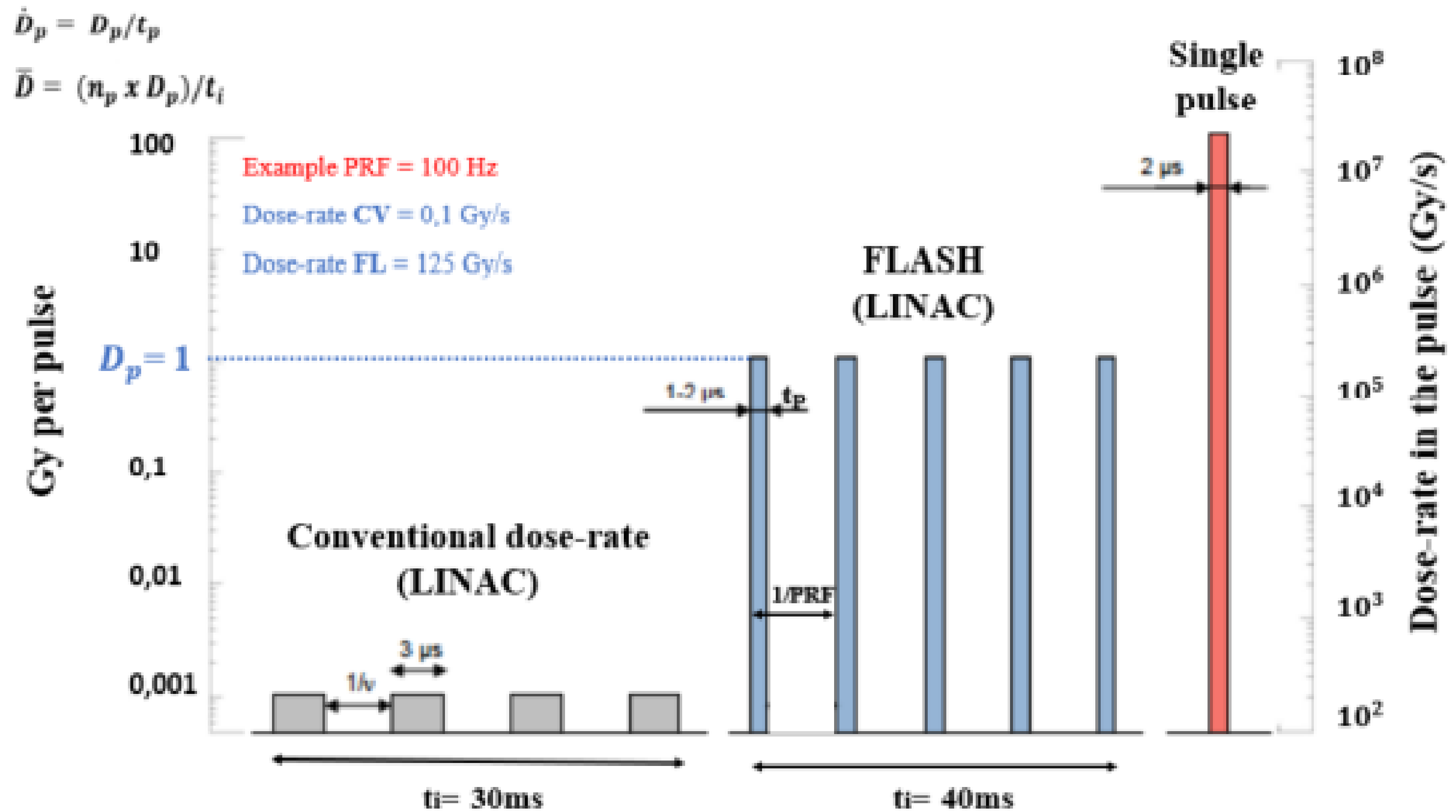
HUMAN Trials need more data

- FAST-01 completed proton FLASH RT for sintomatic bone mets (Univ. Cinn): 8Gy x 1 (Mascia et al, JAMA Onc, 2022)

- FAST-02 ongoing proton FLASH RT for thoracic bone mets (Univ. Cinn): 8Gy x 1, up 7,3 x 30 cm

- IMPulse ongoing electron FLASH RT for skin metastases from melanoma (CHUV): 2Gy increments from 22-34 Gy x1, <=5,5cm

- LANCE ongoing electron FLASH RT and CONV RT for localized cutaneous SCC e BCC (CHUV): 22Gy x1 if <2cm, 5Gy x6 if >2cm but <= 4cm

- SURFACE planned face I Study on Ultra-hight dose rate Radioterapy For Any Cutaneus or subcutanEous tumor to assess safety & efficacy of electron FLASH RT (MD Anderson)

DADR - Dose Average Dose Rate

- ⊙ i-Voxel

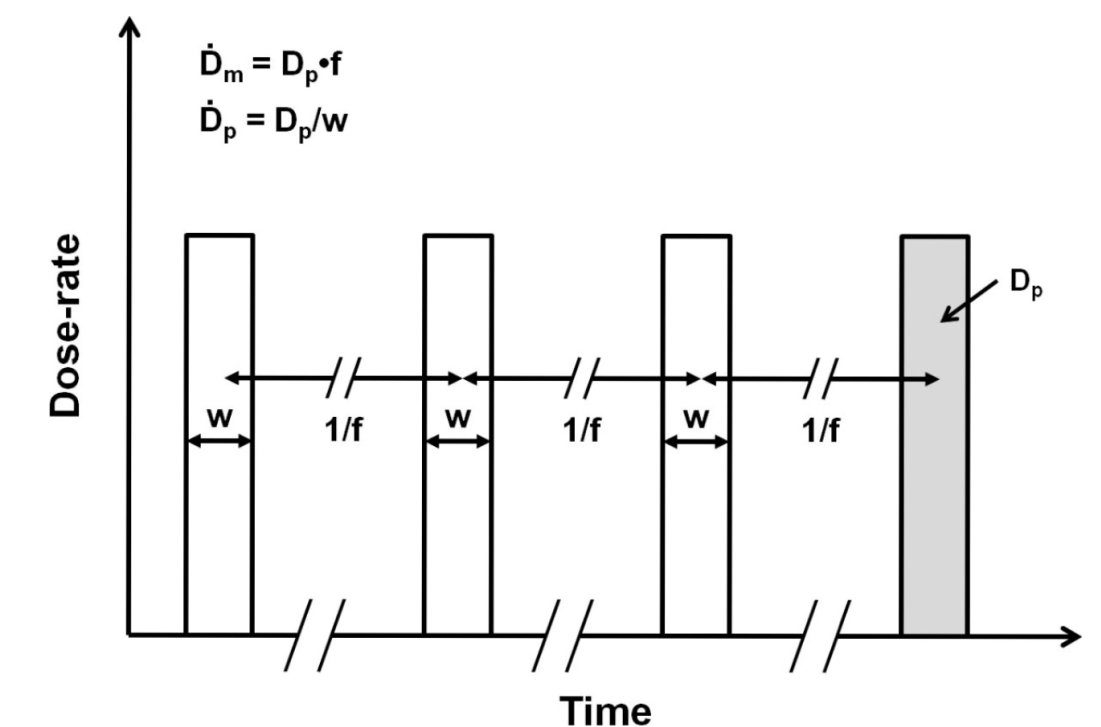- ⊙ J- beams

- ⊙ d_{tot} Total Voxel Dose

- ⊙ d_{ij} Dose of the j-th pencil beam at i-th voxel

- ⊙ $\dot{D}_{ij}$ Dose Rate of the j-th pencil beam at i-th voxel

$$DADR_i = \sum_{j=1}^{N} \frac{d_{ij}}{d_{tot}} \dot{D}_{ij}$$

Accelerator hypothesis

- $I_p = 200$ mA
- $w = 1 \, \mu s$
- $F = 1$ kHz
- $I_m \sim 10^{15} e^-/s$

SPECIAL ISSUE PAPER | 🔓 Free Access

Treatment planning for Flash radiotherapy: General aspects and applications to proton beams

Marco Schwarz ✉, Erik Traneus, Sairos Safai, Anna Kolano, Steven van de Water

First published: 25 February 2022 | https://doi.org/10.1002/mp.15579 | Citations: 2

Index

- Radiotherapy, FLASH effect & VHEE

- Clinical aspects in stereotactic pancreas treatments

- FLASH effect: activation & critical aspects

- Lung lesions: the case of Non-Small-Cell-Lung Cancer (NSCLC)

PERSONALIZED PRESCRIPTION

Research Article

Impact of SBRT fractionation in hypoxia dose painting — Accounting for heterogeneous and dynamic tumor oxygenation

Emely Kjellsson Lindblom, Ana Ureba, Alexandru Dasu, Peter Wersäll, Aniek J. G. Even, Wouter van Elmpt, Philippe Lambin, Iuliana Toma-Dasu
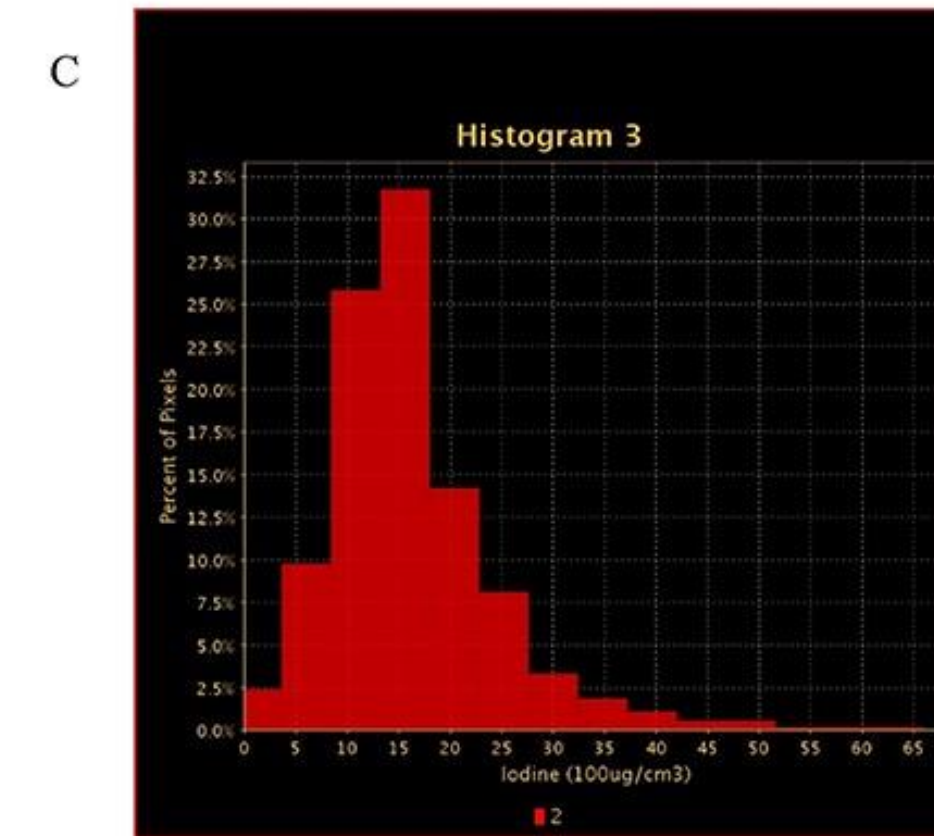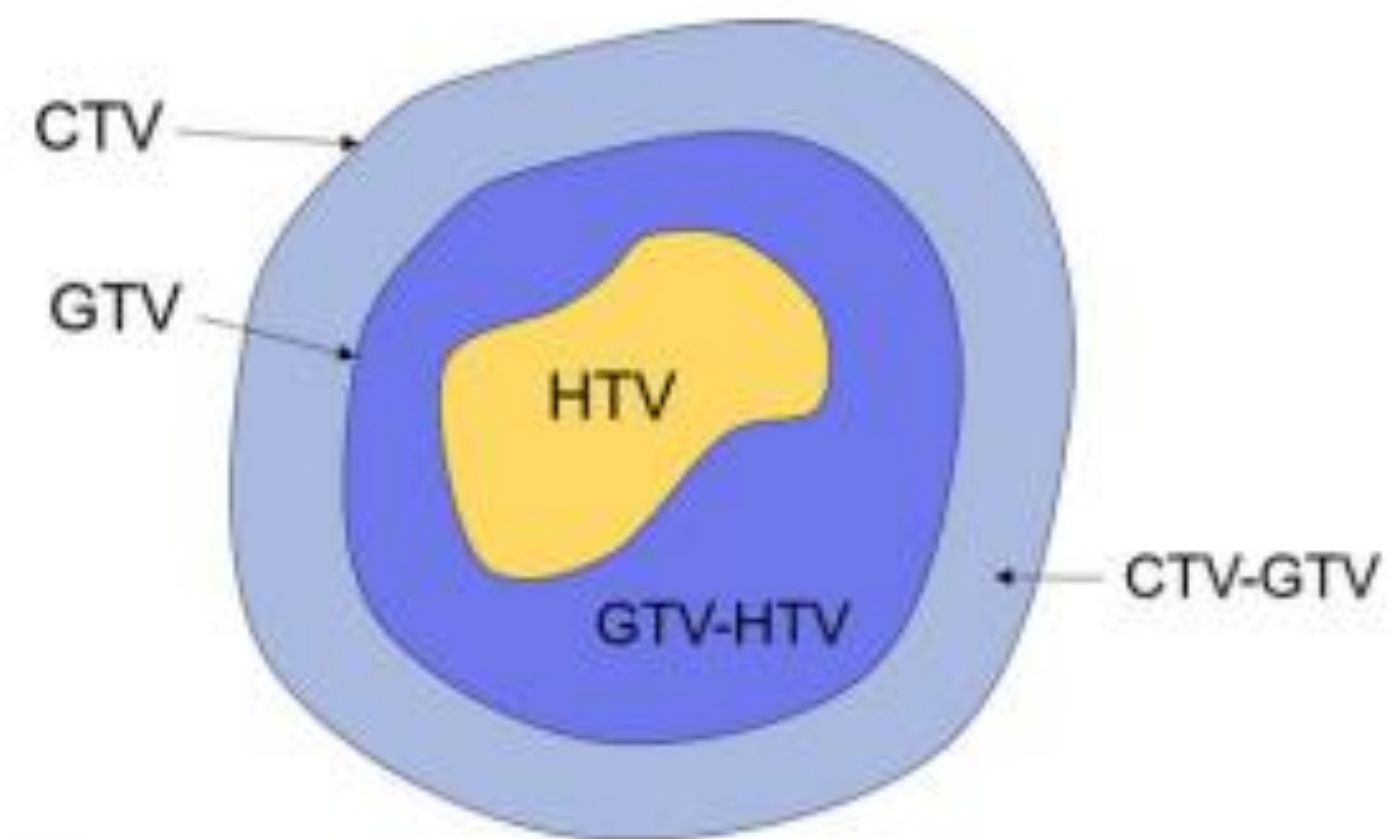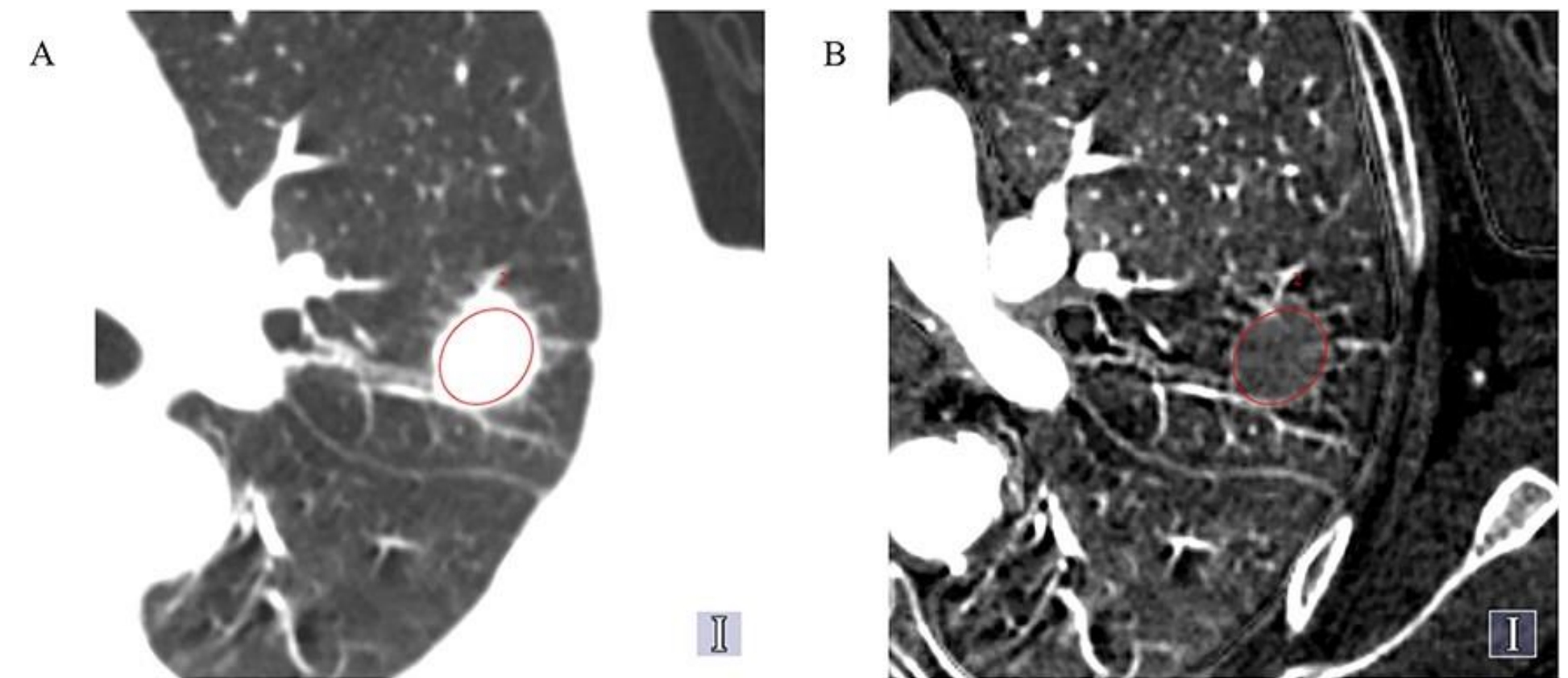

Fig. 1. Illustration of the target volumes considered for homogeneous dose prescription: clinical target volume (CTV), gross target volume (GTV), hypoxic target volume (HTV), the GTV not containing the HTV (GTV-HTV), and the CTV not containing the GTV (CTV-GTV). [Color figure can be viewed at wileyonlinelibrary.com]

NTCP Lyman Kutcher Burman (LKB) model

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \qquad (9)$$

where

$$t = \frac{EUD - D_{50}}{m \cdot D_{50}} \qquad (10)$$

and the equivalent uniform dose (EUD) was defined by

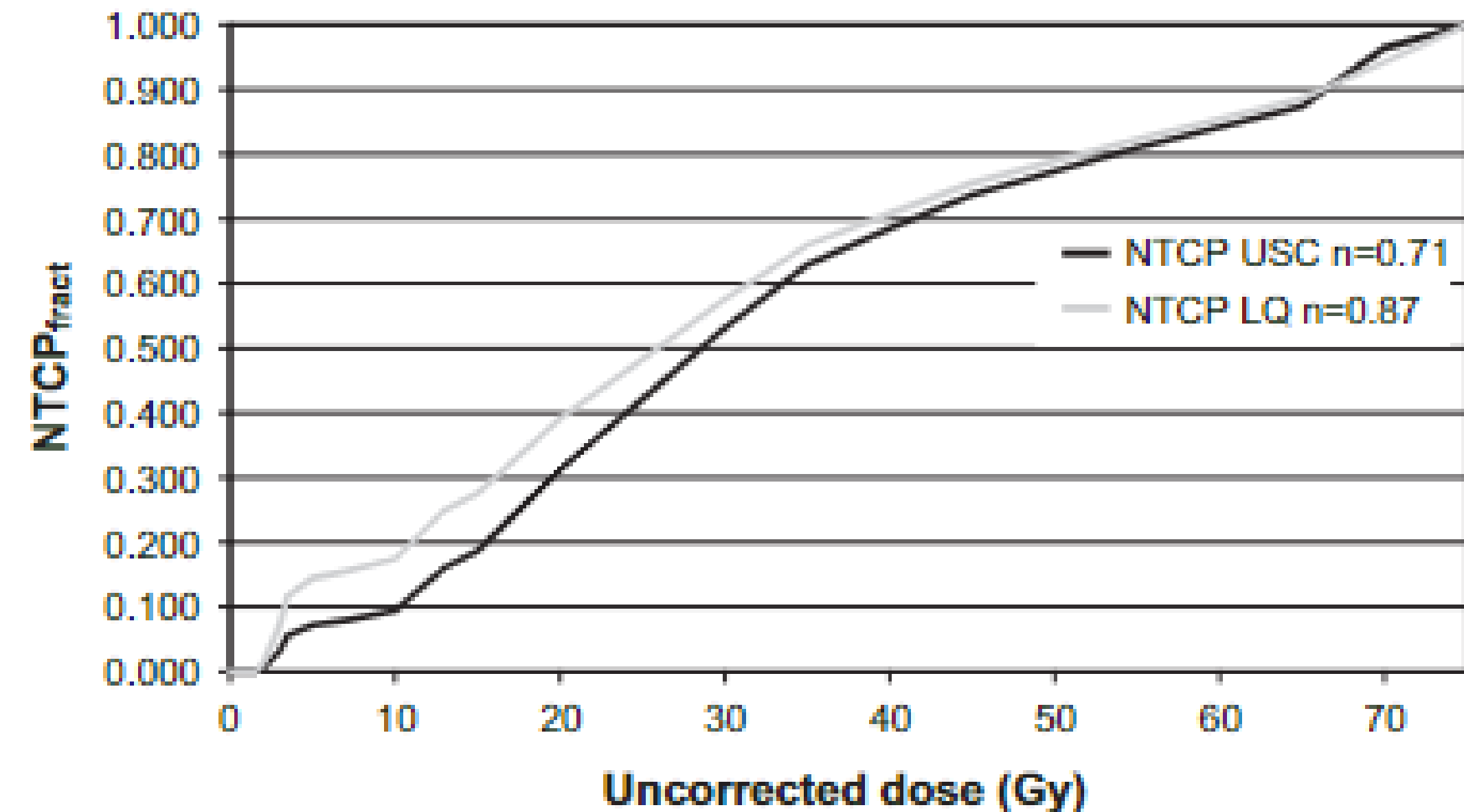$$EUD = \left(\sum_{i} D_{i,corr}^{\frac{1}{n}} \frac{V_i}{V_{tot}} \right)^{n} \qquad (11)$$

Figure 5. Fractional NTCP$_{fract}$ calculated with DVH-data corrected with USC and LQ (α/β =3) as a function of cut-off dose for a representative patient. The plot illustrates the cumulative contribution to the NTCP. With the USC correction the low doses have less impact on NTCP compared to what is seen with the LQ correction.

Daniele Carlotti