Performance of very high-energy electron therapy delivered in conventional and FLASH conditions:

the case of Stereotactic treatments

PhD in Accelerator Physics

Candidate:
Dott. Daniele Carlotti

Thesis Advisor:
Prof. Alessio Sarti

Index

- Radiotherapy, FLASH effect & VHEE
- Clinical aspects in stereotactic pancreas treatments
- Flash effect Activation & critical aspect
- Lung lesions Non-Small-Cell-Lung Cancer (NSCLC)

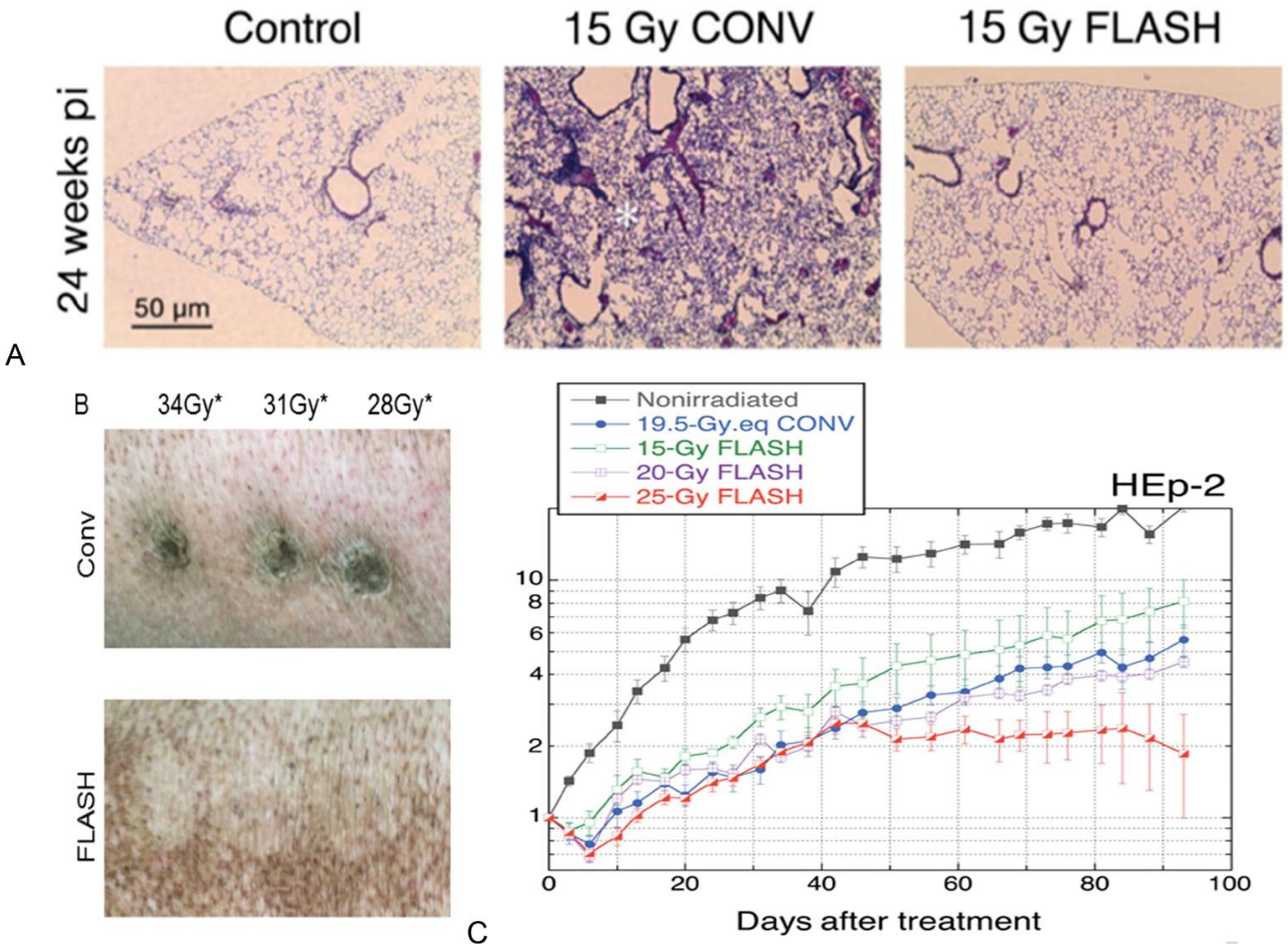
RADIOTHERAPY
FLASH EFFECT & VHEE

Conventional Radiotherapy

High-lines:

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

FLASH Effect



High-lines:

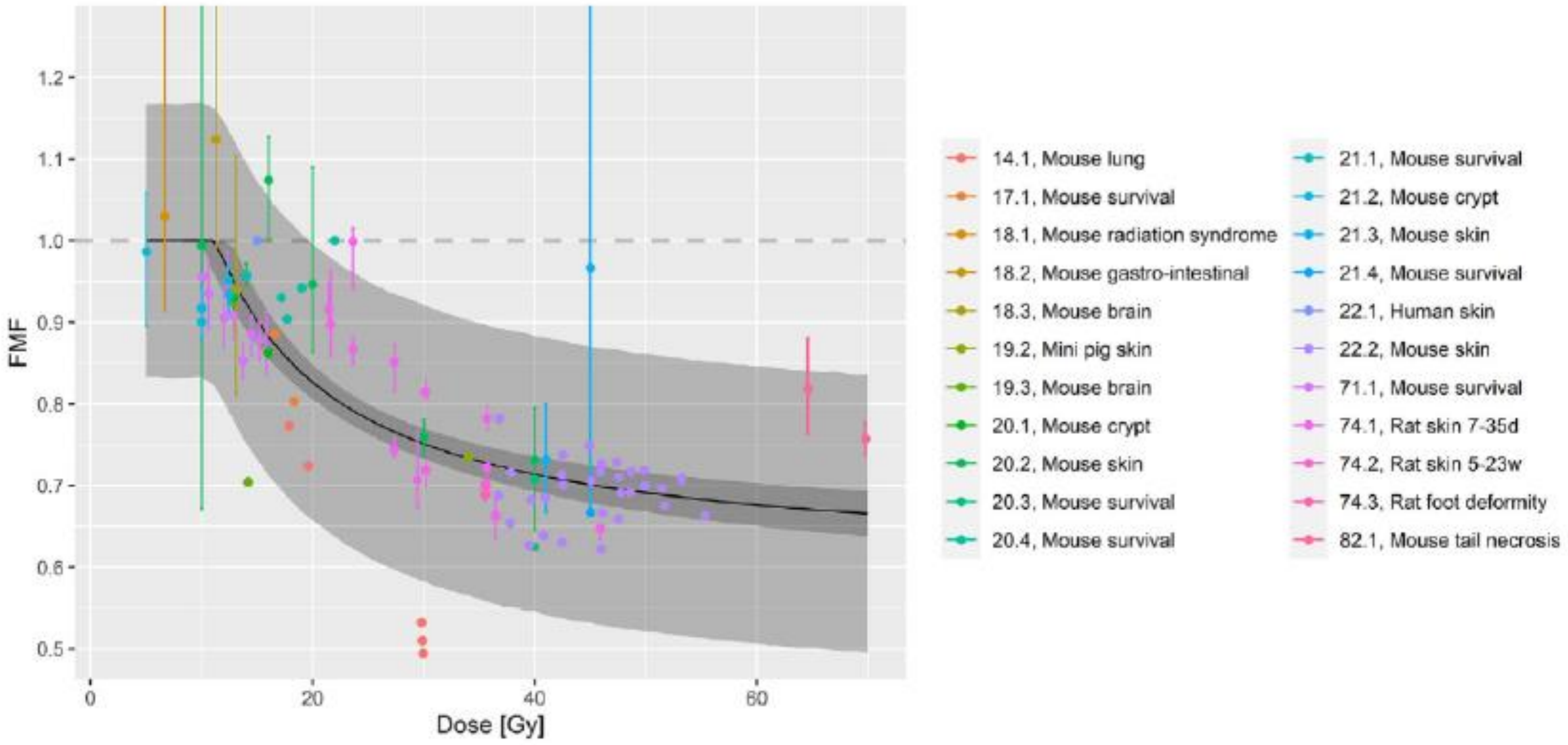
- Delivery high dose (> 4-6 Gy)
- Ultra High Dose Rate (> 40 Gy/s)

[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

FLASH-Modifying Factor:

$$\mathrm{FMF} = \frac{D_{CONV}}{D_{UHDR}}\Big|_{isoeffect}$$



[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 singlefraction dose: A quantitative analysis. Int J Radiat Oncol Biol Phys, 114(5):1032– 1044, 2022. ISSN 1879-355X.

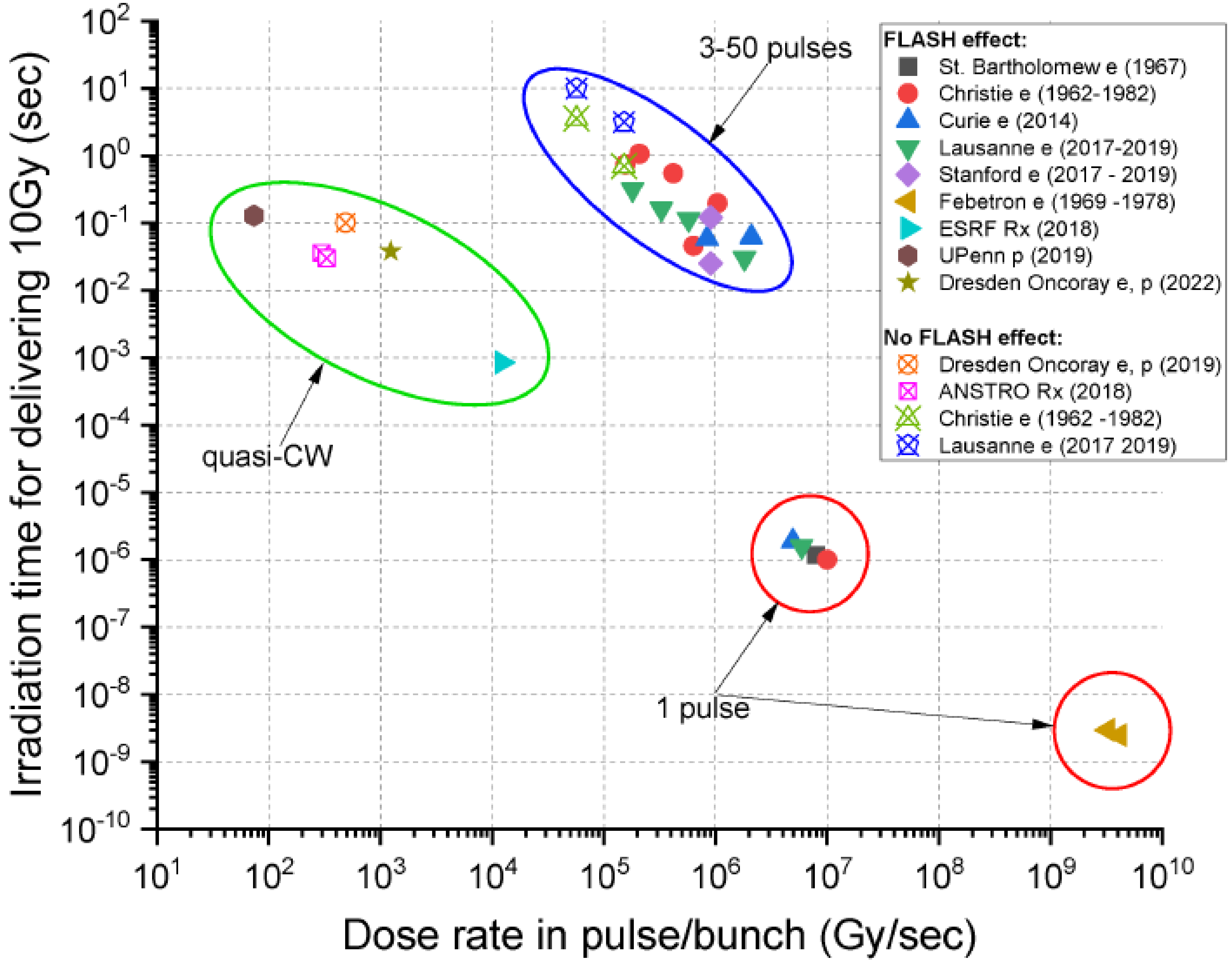
High-lines:

To meet these requirements:

- pathologies that are already being considered for hypo-fractionation (treatment delivered in less fractions, with a dose per fraction exceeding the standard 2Gy/fraction conventional approach)
- pathologies that have an outcome that is not yet satisfactory are particularly interesting.

Will focus on pancreatic and lung cancer

FLASH: the beam delivery



High-lines:

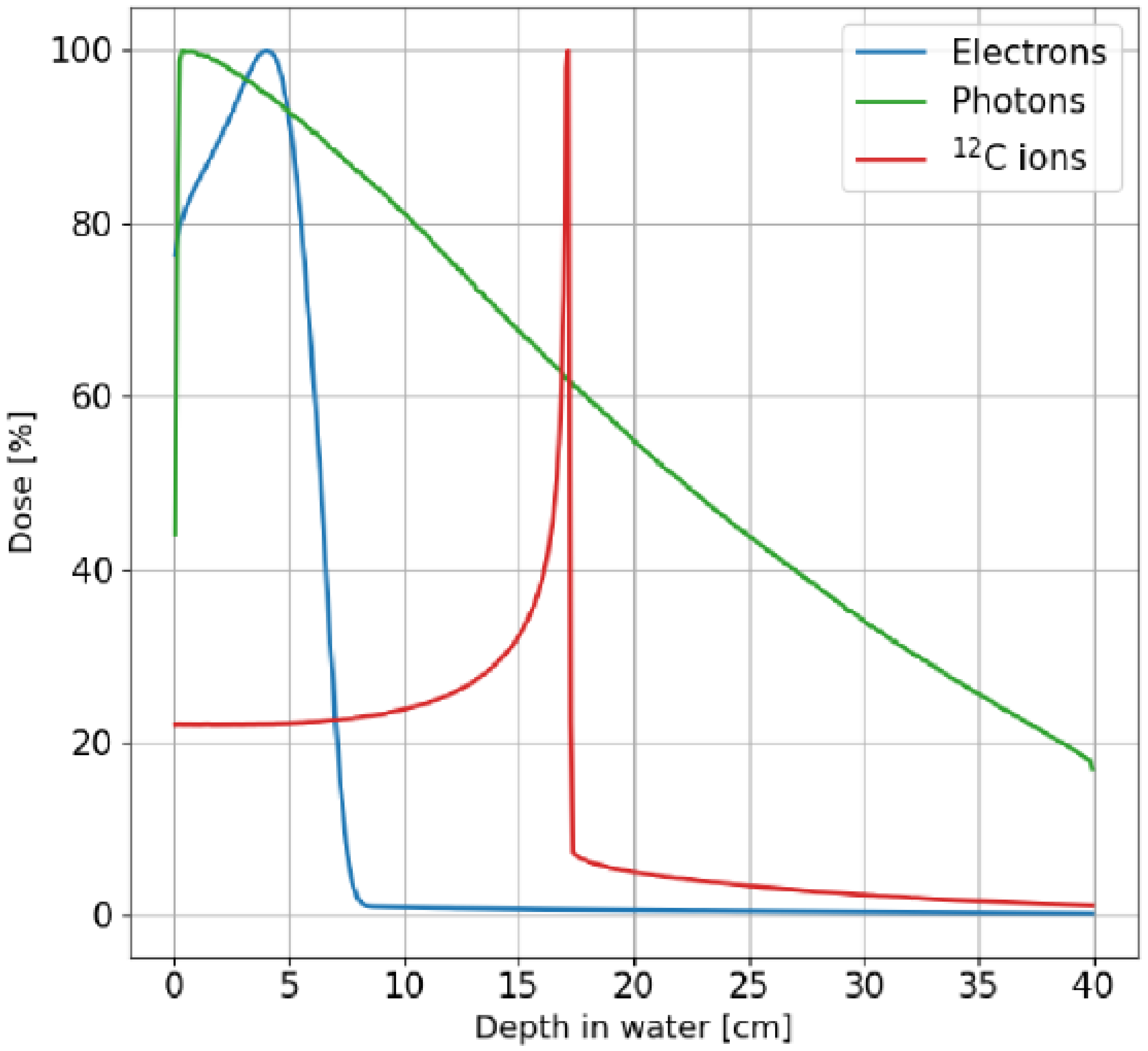
Going FLASH' is not just a matter of 'total absorbed dose'. One has also to deliver the dose within a given total time.

- Changing the beam energy with protons becomes really difficult (--> 3D range modulators are being explored)
- VHEE have the nice advantage that with a 'single energy' a complete field can be delivered!

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)



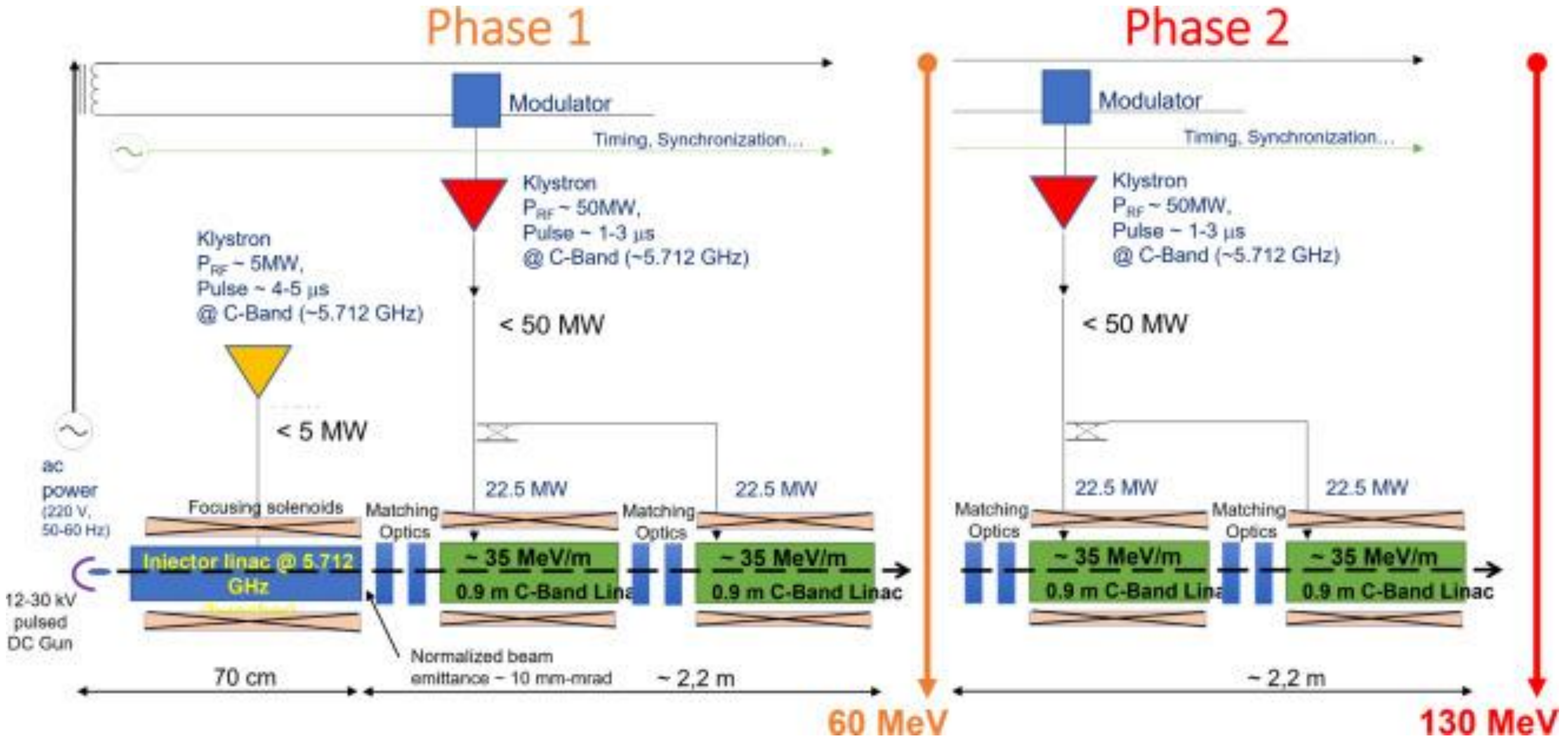
High-lines:

- Machine dimension
- Difference RBE effect
- Pencil beam scanning VS VMAT

Study VHEE as possible solution

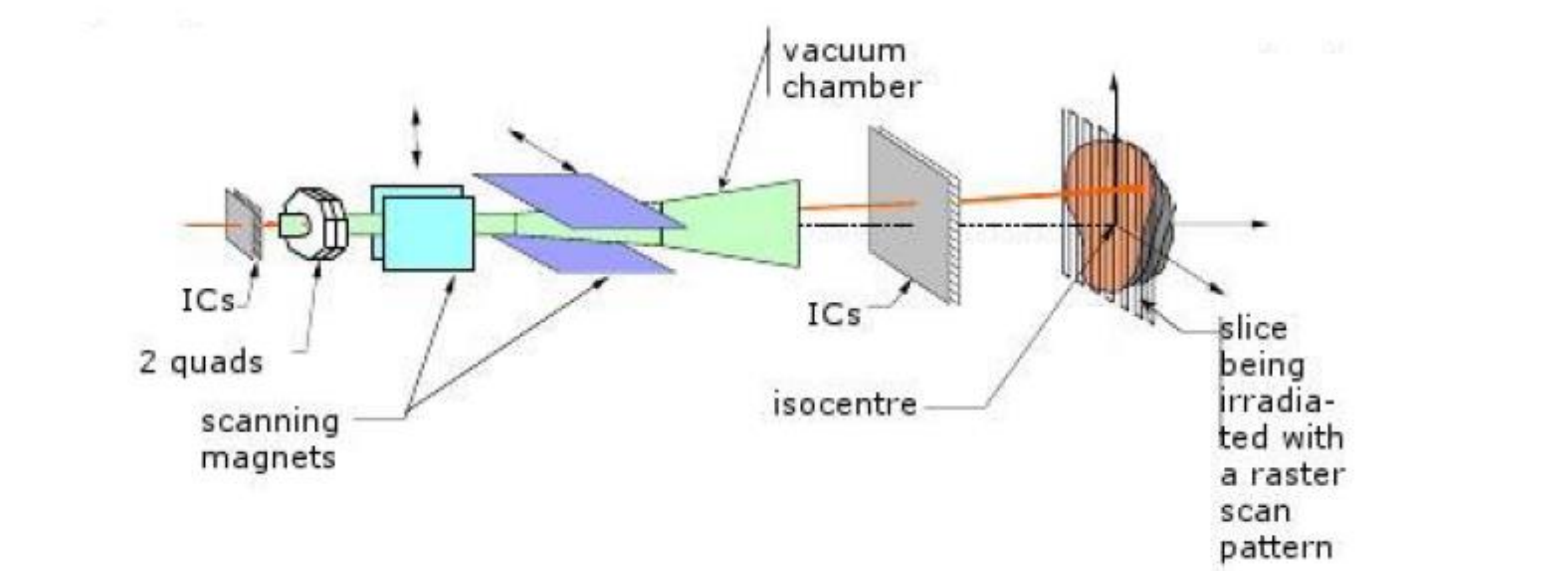
Prototipe VHEE Accelerator

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



High-lines:

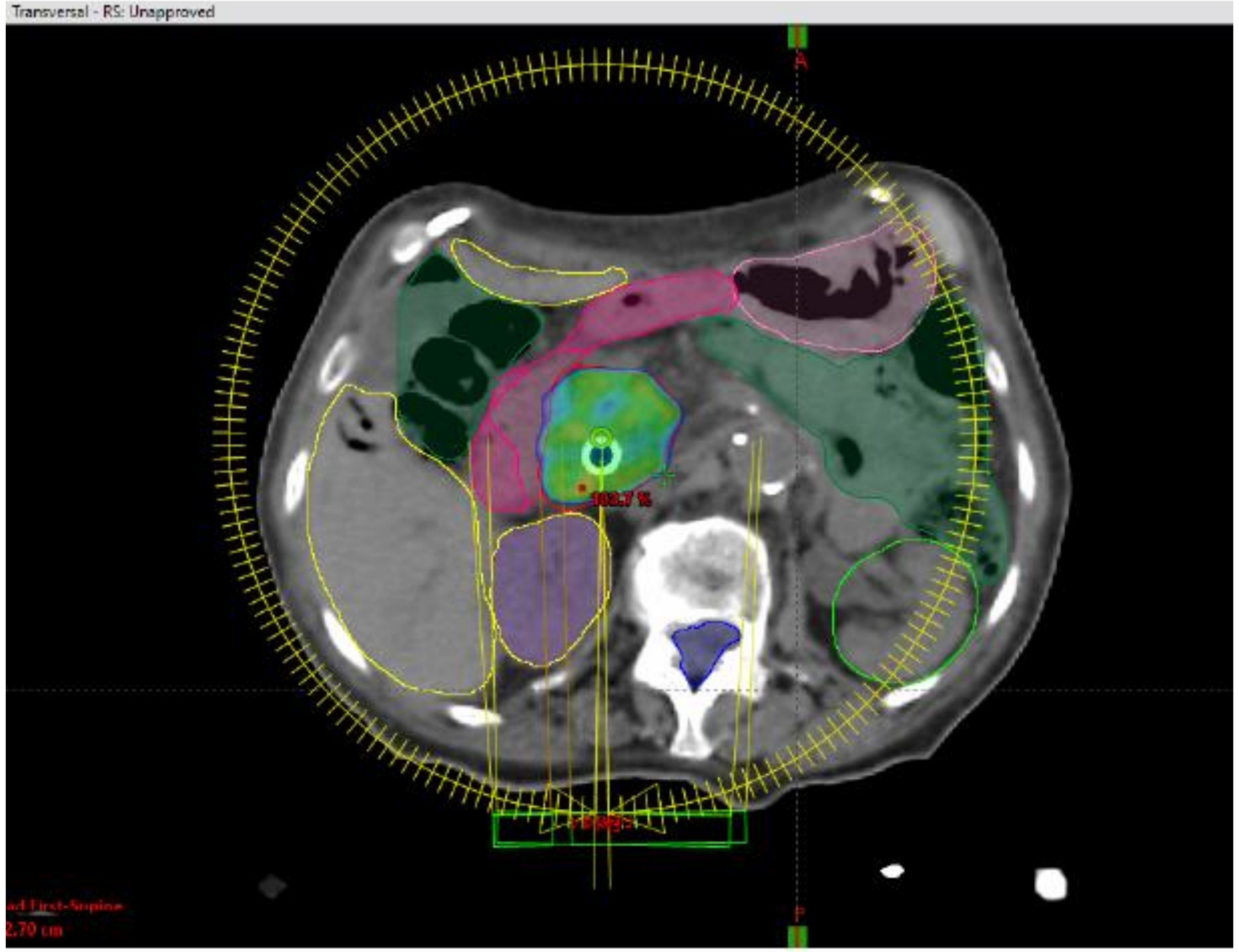
To move from superficial (4-12 MeV) to deep-seated (up to 130 MeV) tumors.. a 'new' compact accelerator is needed



[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.

CLINICAL ASPECTS IN STEREOTACTIC PANCREAS TREATMENTS

STEREOTACTIC PANCREAS - VMAT



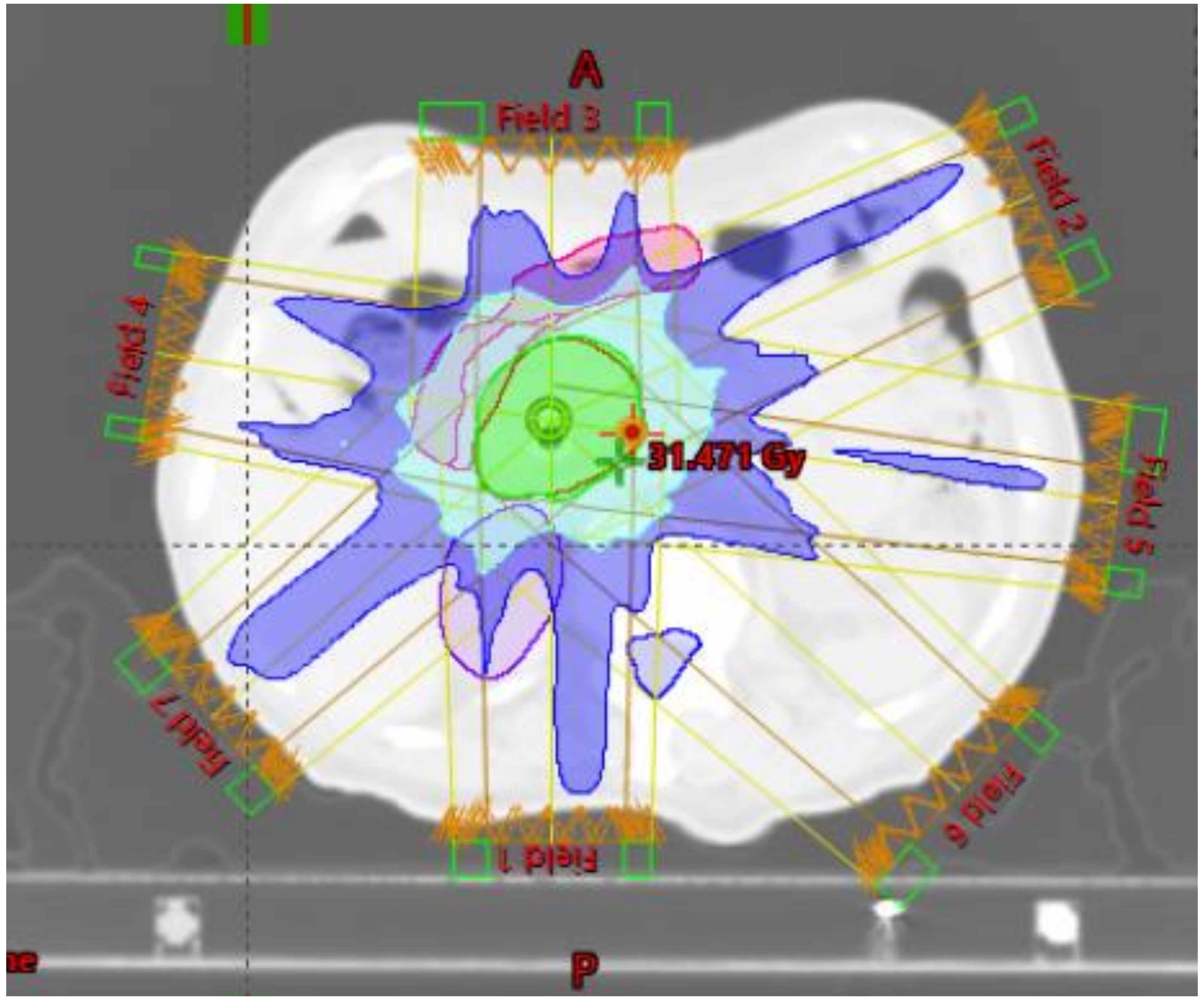
VMAT

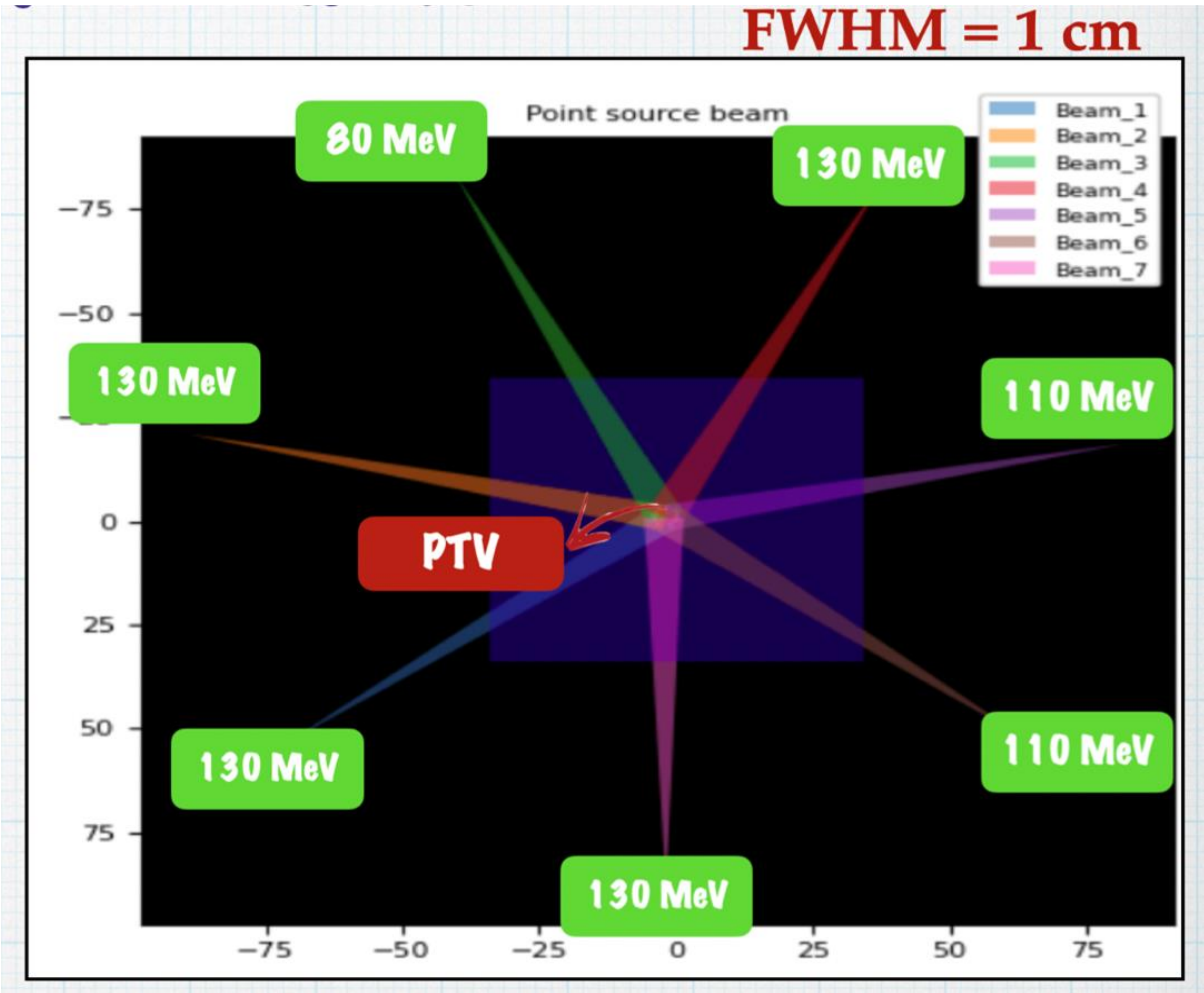
High-lines:

- PTV Prescription 6x5=30Gy
- Duodenum Constraints: 35 Gy
- Spinal cord Constraints: 18 Gy
- Kidneys Constraints: Mean Dose 10 Gy

Structure	Max Dose [Gy]	Mean Dose [Gy]
PTV	31.737	30.000
PTV_Low		
BODY	31.737	1.184
Cauda equina	1.191	0.291
Duodeno	30.851	14.828
Duodeno OUT		
Fegato	31.369	3.754
Intestino	29.444	4.109
IntestinoOUT		
Kidney R_cortex	23.995	6.557
Midollo spinale	5.689	1.660
NS_Ring 0		
NS_Ring 2cm		
Rene dx	23.942	6.879
Rene sx	6.900	3.152
Stomaco	12.452	4.177

PANCREAS IMRT-Like for VHEE planning





IMRT-LIKE

VHEE

SBRT PANCREAS – VHEE Optimizer

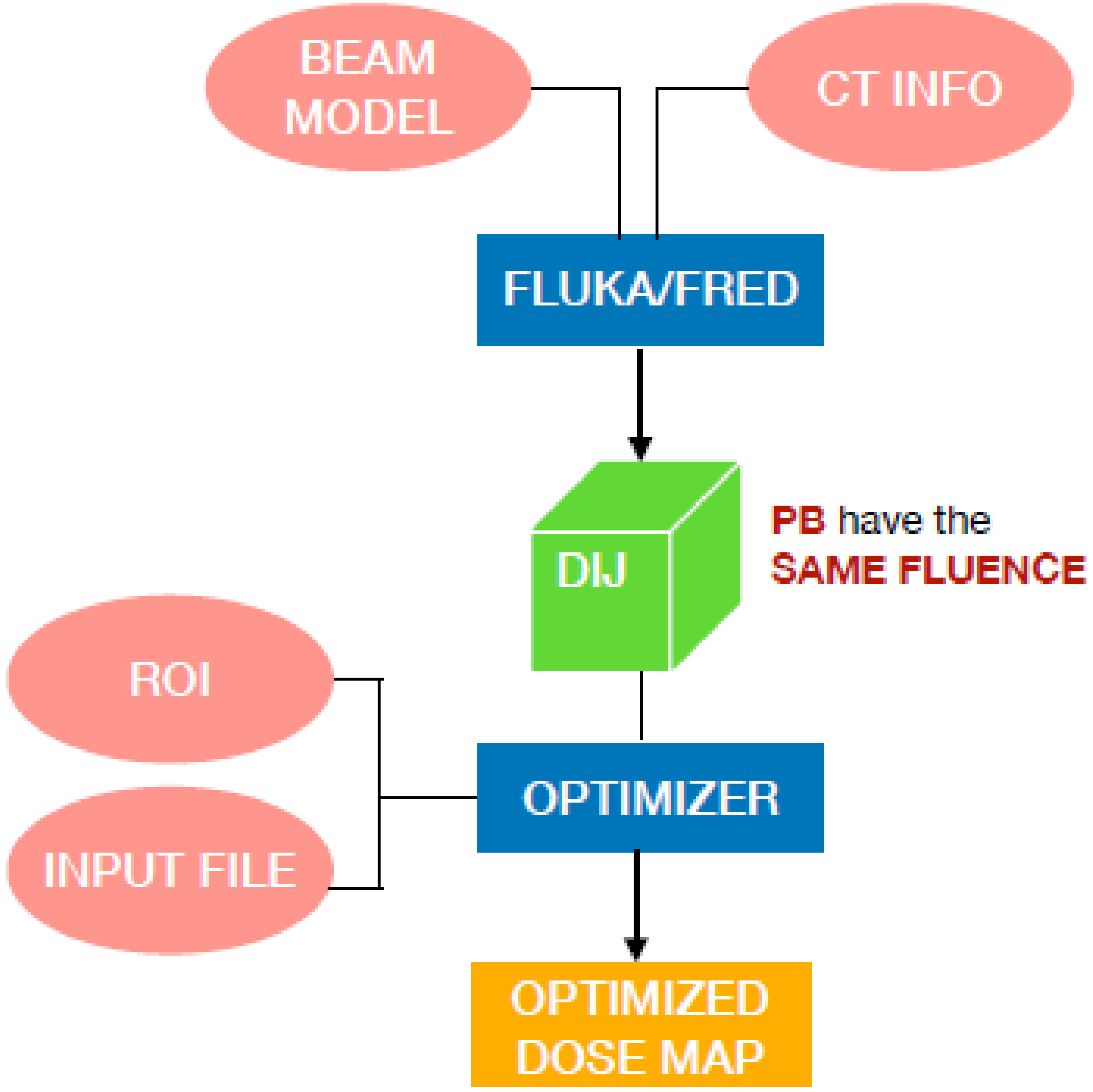
The algorithm we currently use for the optimization of a **treatment with VHEE** is based on the Proton Therapy algorithm (LOMAX) for pencil beam, rearranged for electrons.

The main **goal** of the Optimizer is to select the **number of particles** for each Pencil Beam that **minimize the Cost Function**:

Dose — Dose Goal — Plan factor — Voxel based

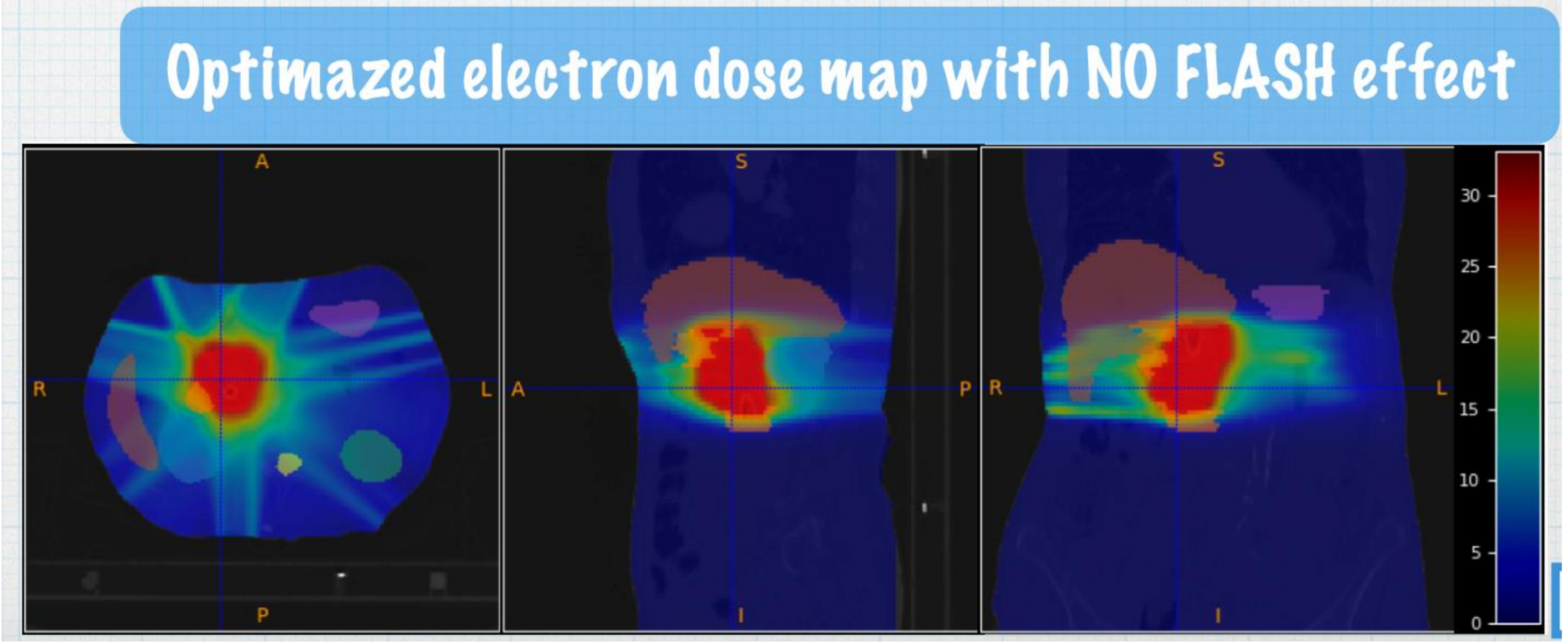
$$\chi^2 = \sum_{i \epsilon PTV} \omega_i \frac{(d_i - D_{PTV})^2}{d_i^2} + \sum_{i \epsilon OAR} \omega_i \frac{(d_i - D_{OAR})^2}{d_i^2} * g(d_i - D_{OAR})$$

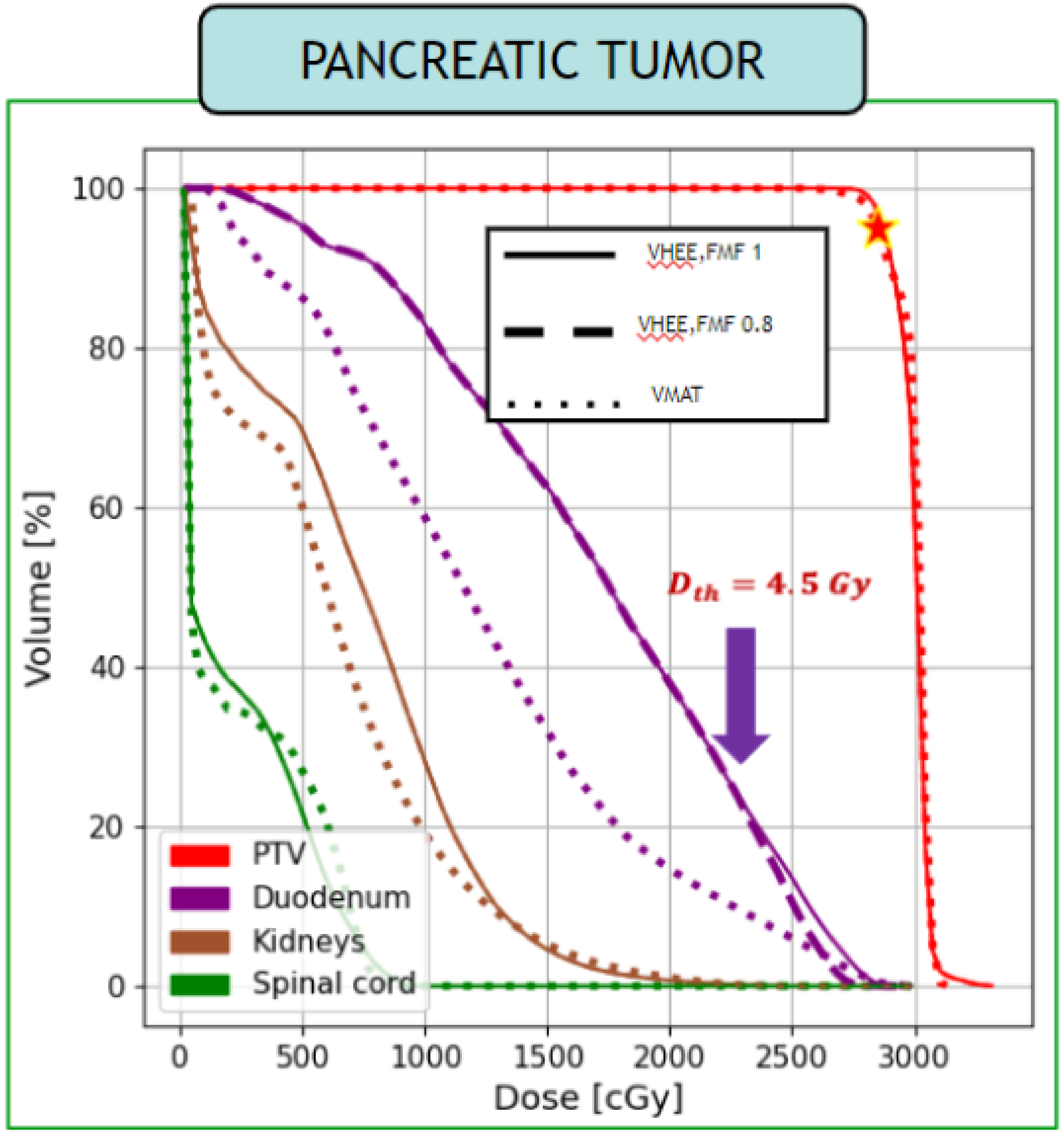
$$d_i = \sum_{j=1}^{N_j} N_j D_{ij}$$



[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.

DVH RESULTS PANCREAS

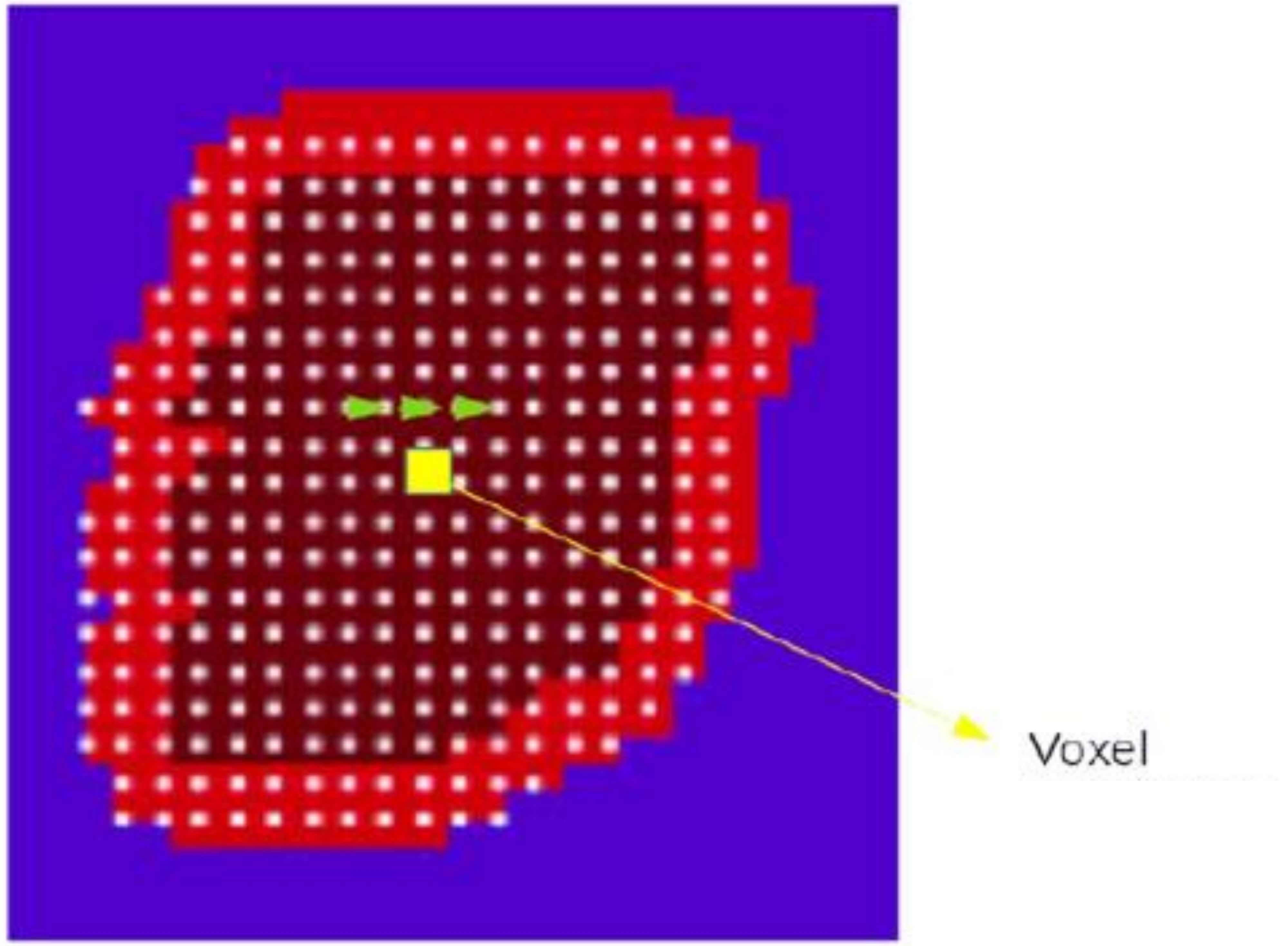




First TPS for VHEE, there are no commercial solutions to plan VHEE since clinical machines do not exist

FLASH EFFECT ACTIVATION
&
CRITICAL ASPECT

FLASH effect and dose rate



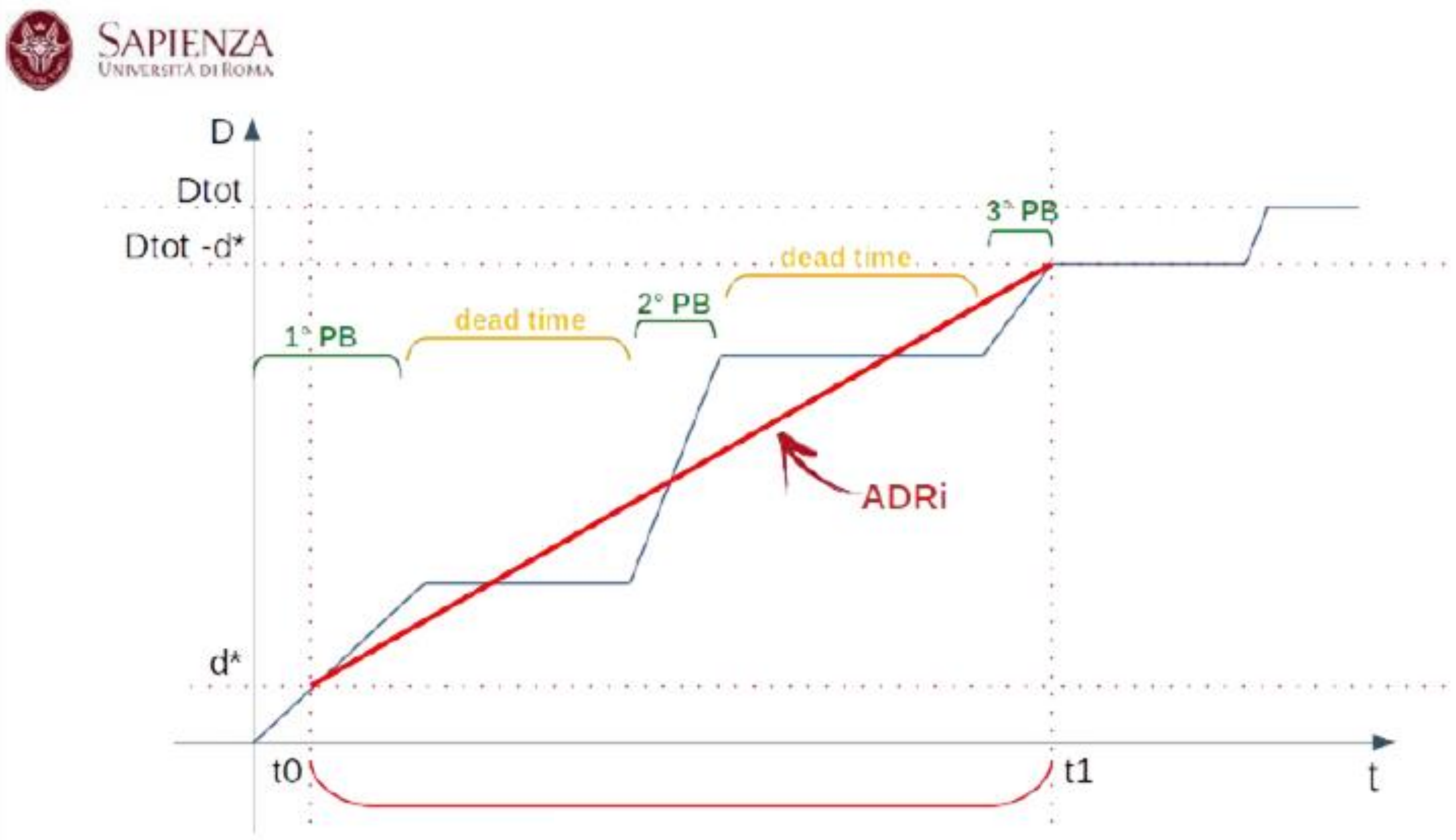
BEAM FIELD of VIEW

High-lines:

Radiobiology experiments the dose is pulsed in the time domain, with the entire field delivery happening simultaneously within one pulse. This mode of dose delivery has two characteristic dose rates:

- The first is the instantaneous dose rate, which is the dose per pulse divided by the pulse duration.
- The second is the average dose rate which is the total dose divided by the entire delivery duration.

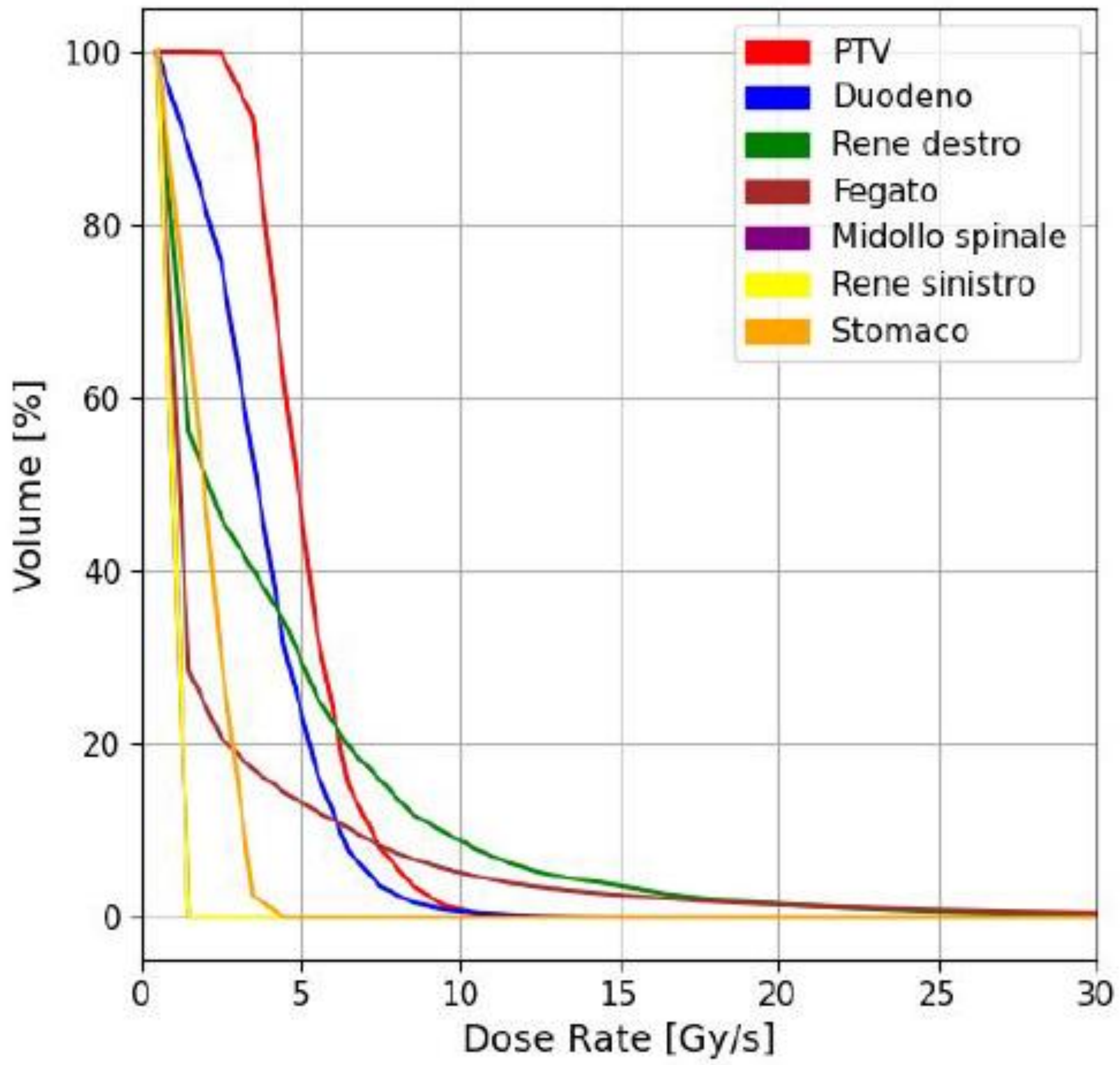
Average Dose Rate



- i-Voxel
- J- beams
- d_{tot} Total Voxel Dose
- T_i Irradiation time
- d* threshold value of effective irradiance

$$\mathrm{ADR_i} = \frac{\mathrm{d_{tot}} - 2\mathrm{d}*}{\mathrm{T_i}} \qquad \dot{D}_j^{ADR} = \frac{D_j - 2d^*}{T_j}$$

Average Dose Rate

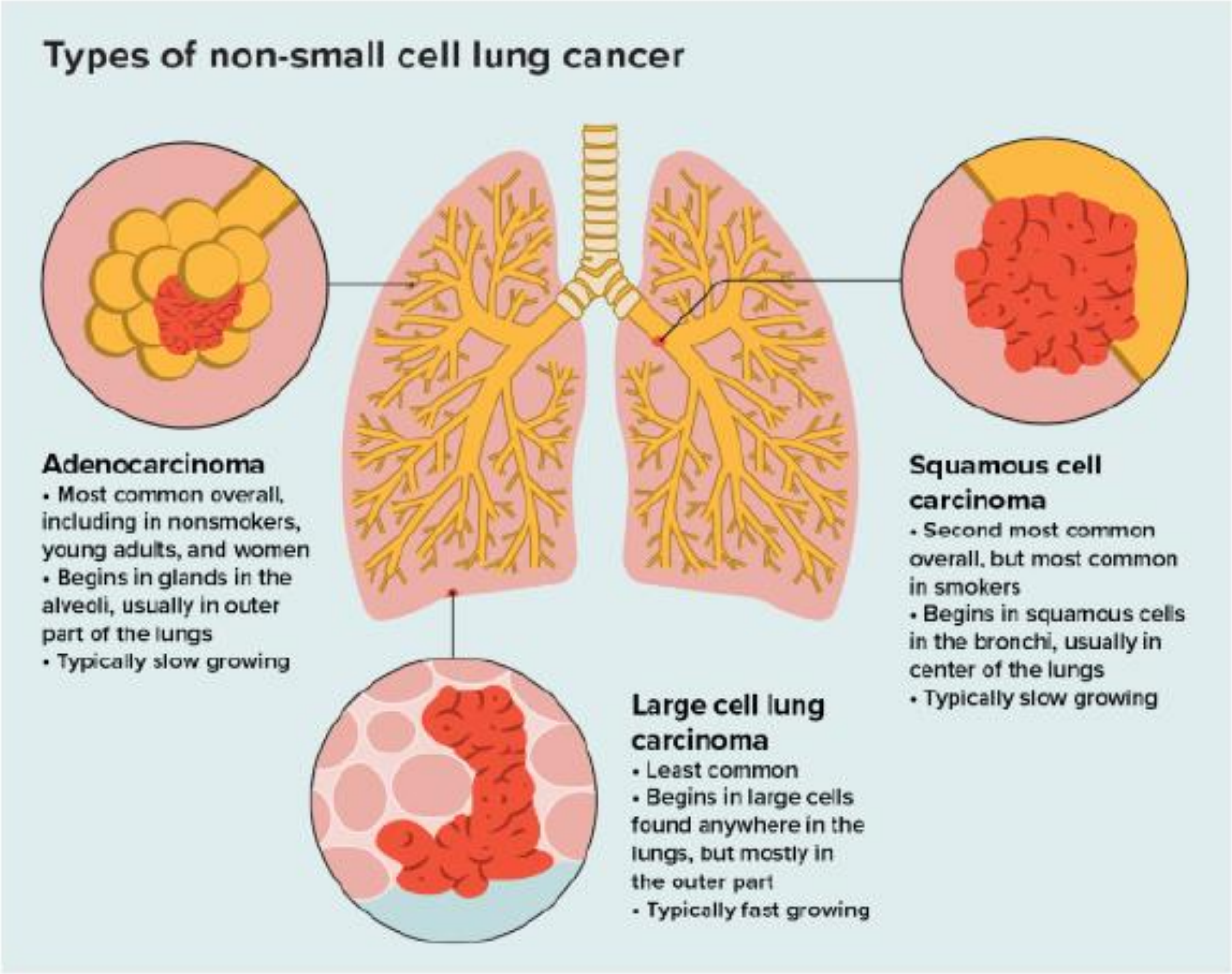


High-lines:

When analyzing the pancreas optimized plan, I have found that for a threshold dose of 4Gy none of the beams matches the delivery timing needed to activate the FLASH effect.

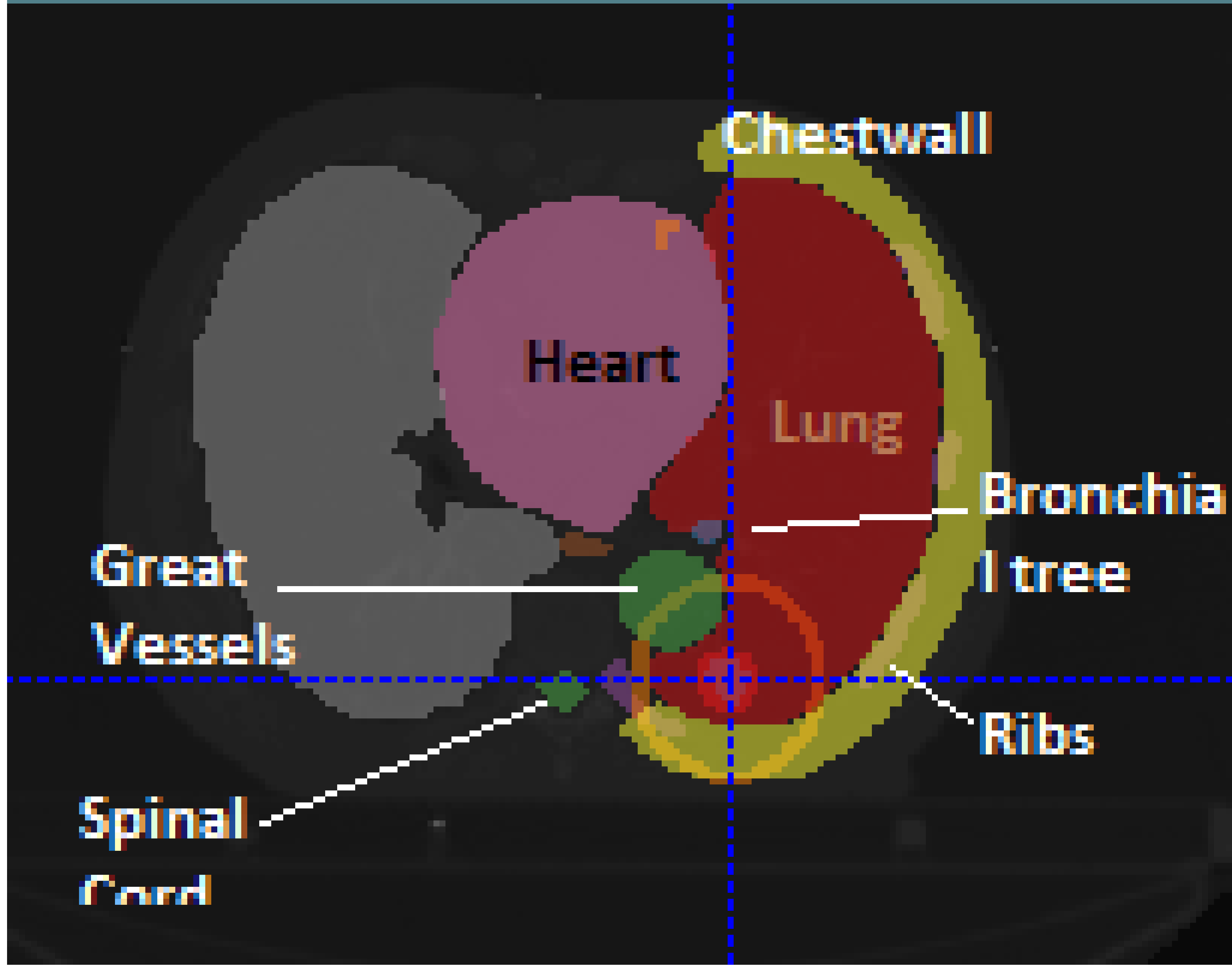
LUNG LESIONS
NON-SMALL-CELL-LUNG CANCER (NSCLC)

LUNG LESIONS NSCLC

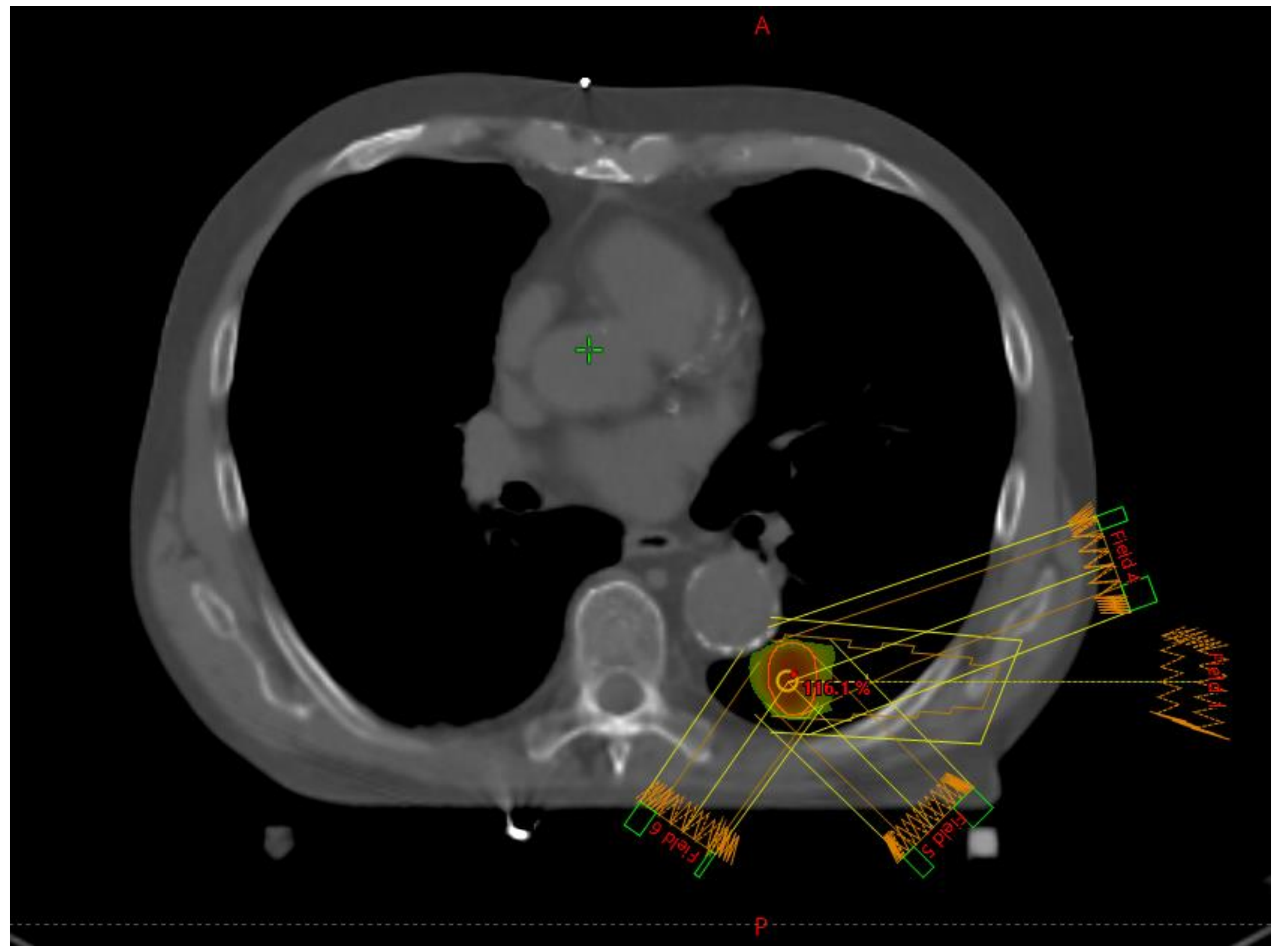


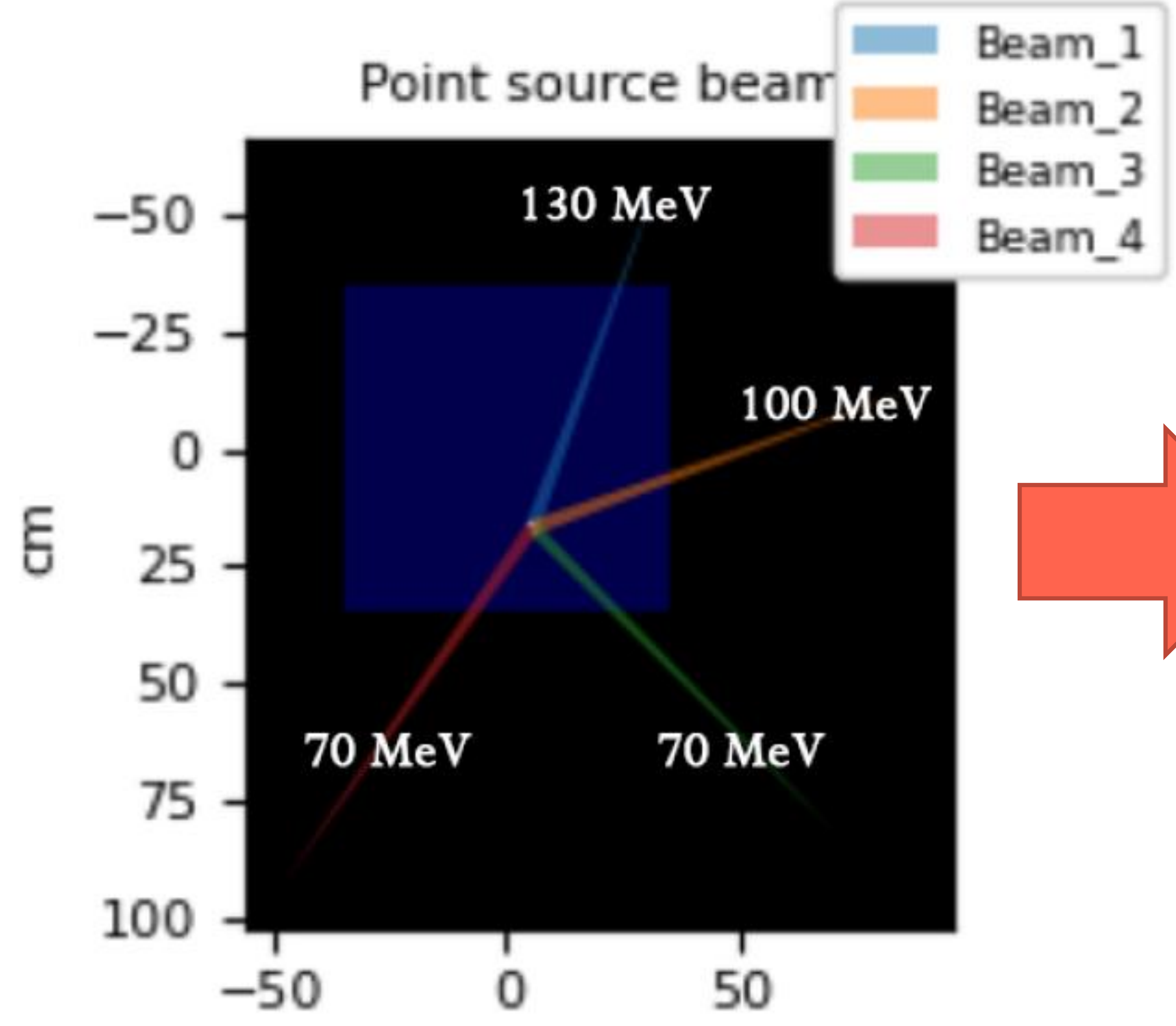
High-lines:

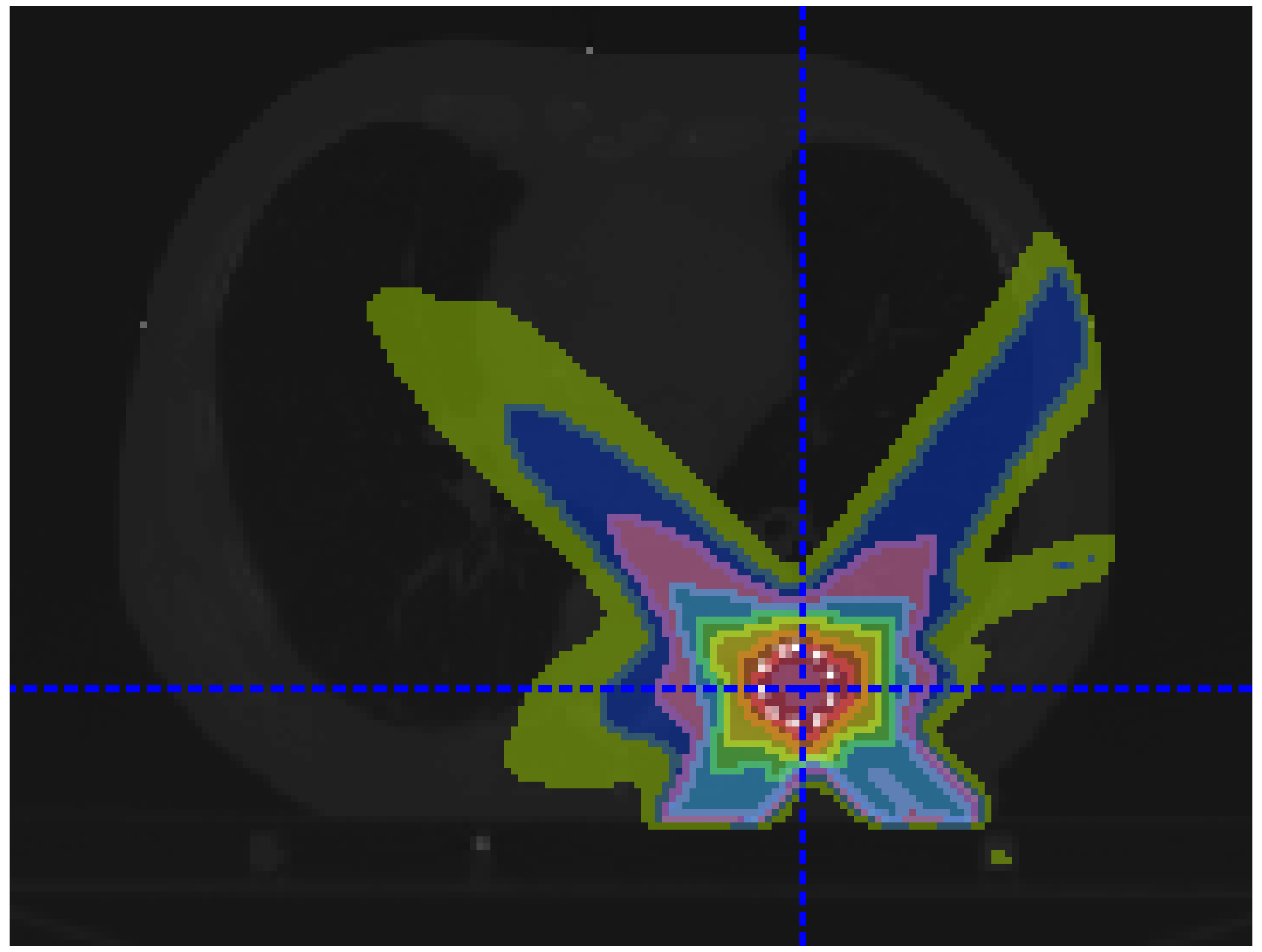
- PTV Prescription 12x4=48Gy
- Ribs Constraints: 43 Gy
- Spinal cord Constraints: 23 Gy



Lung IMRT-Like for VHEE planning



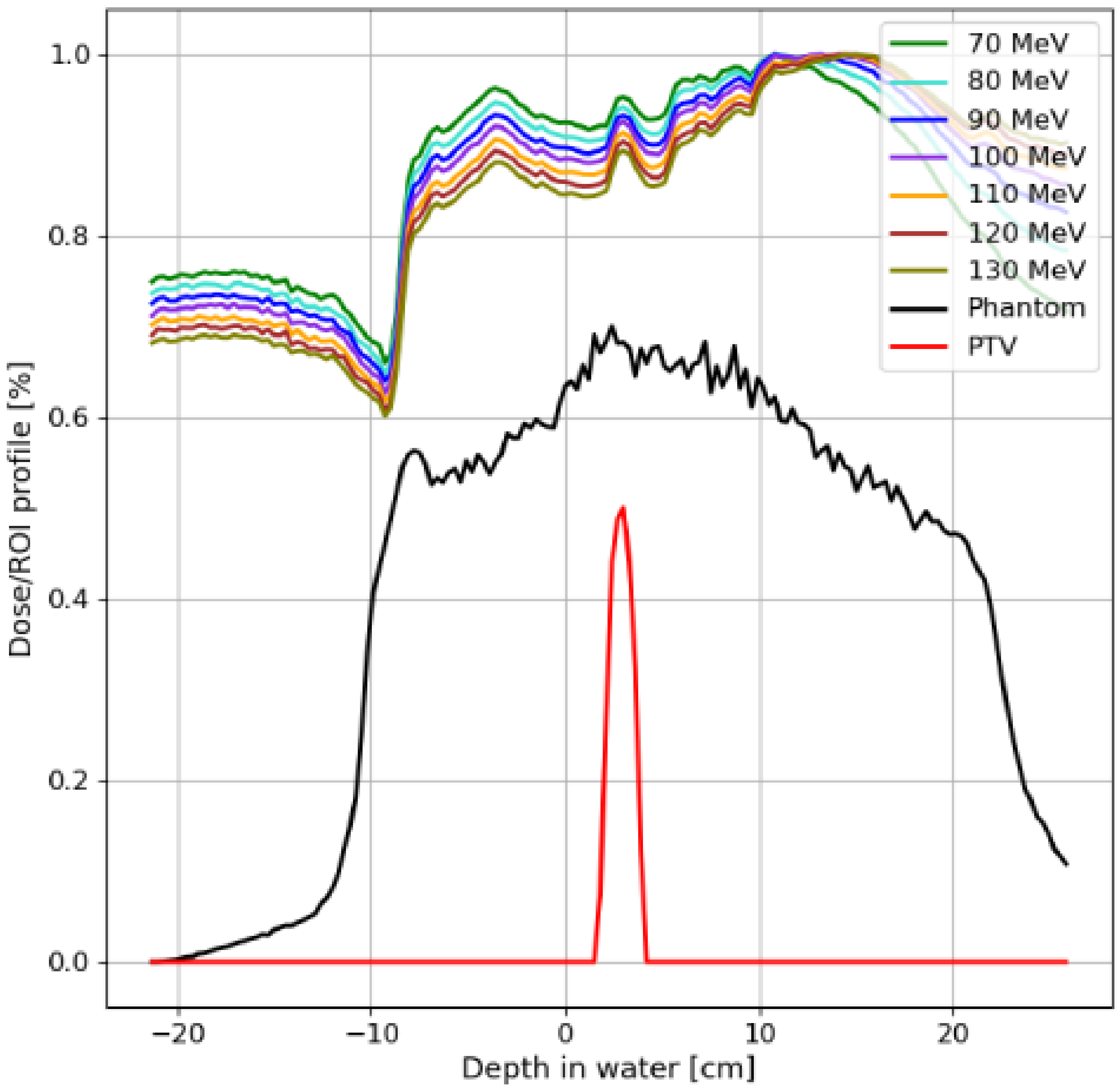


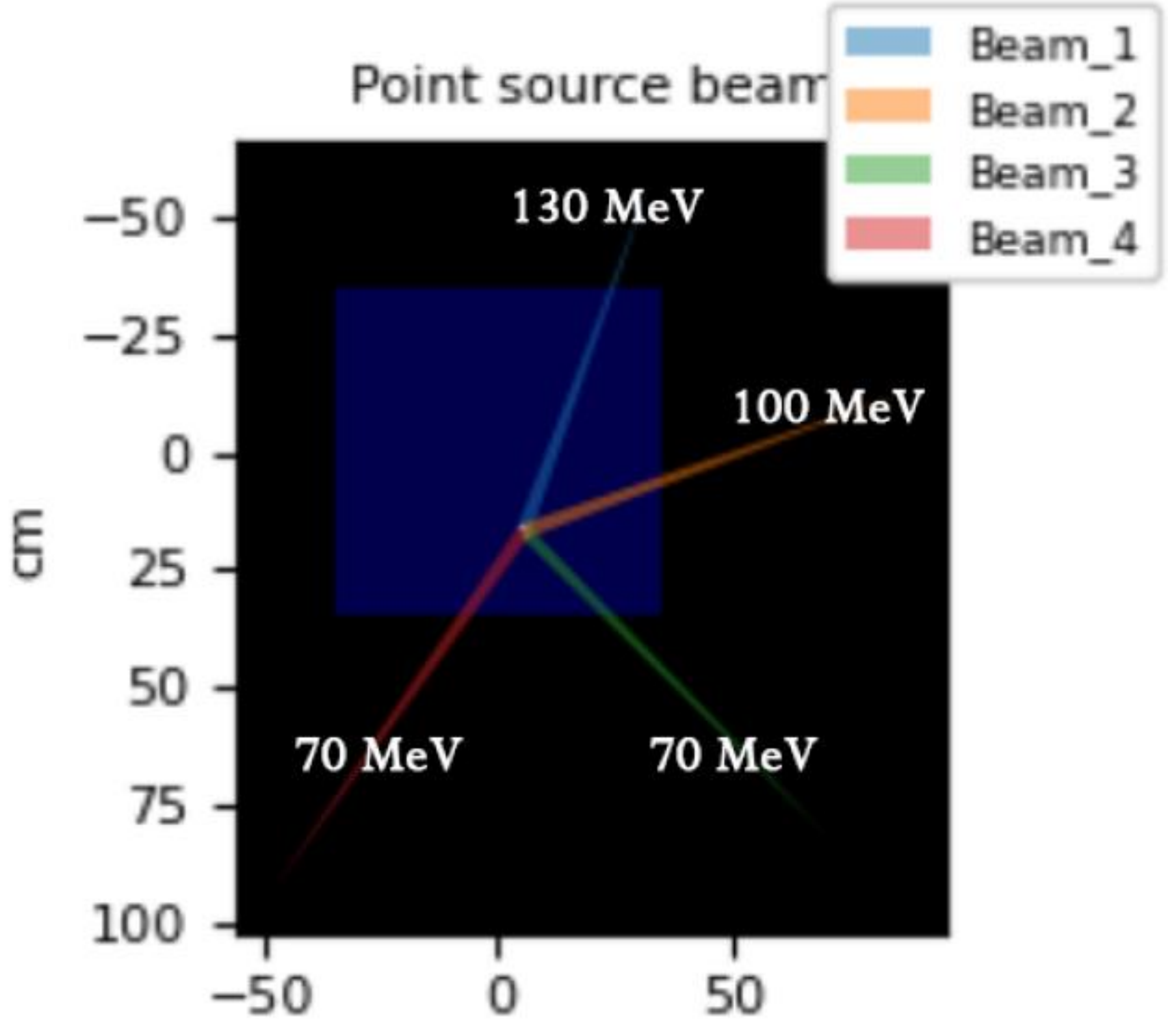


IMRT-LIKE

VHEE

Lung Cancer – Energy Beam

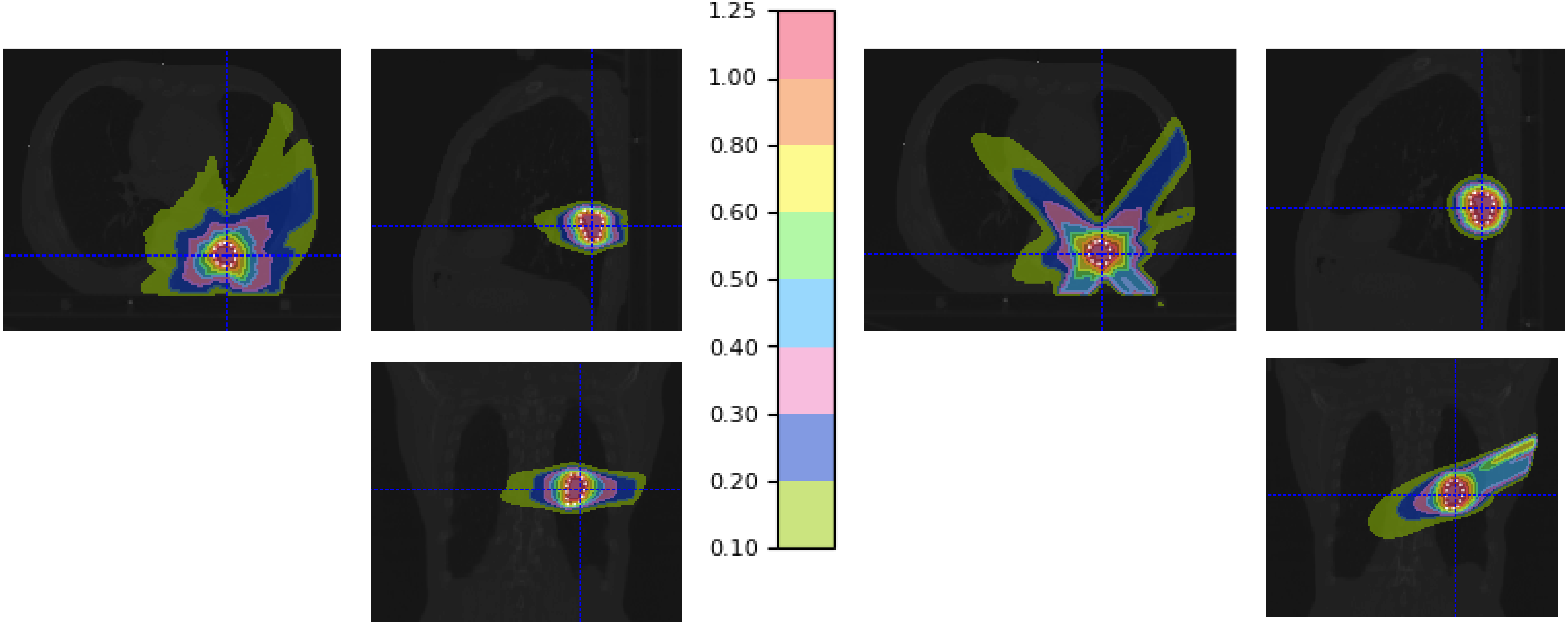




Lung Cancer – isodose distribution

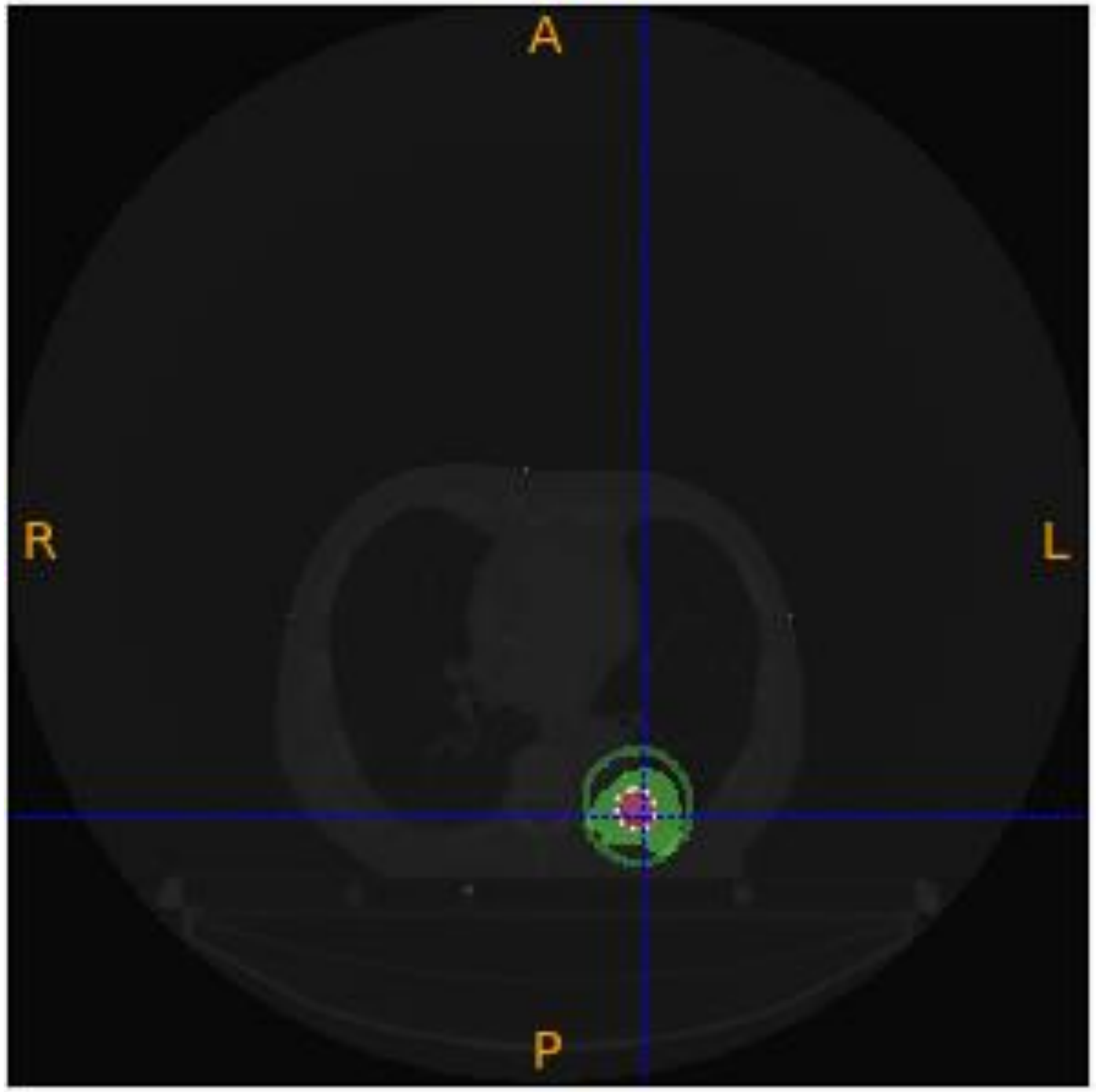
VMAT

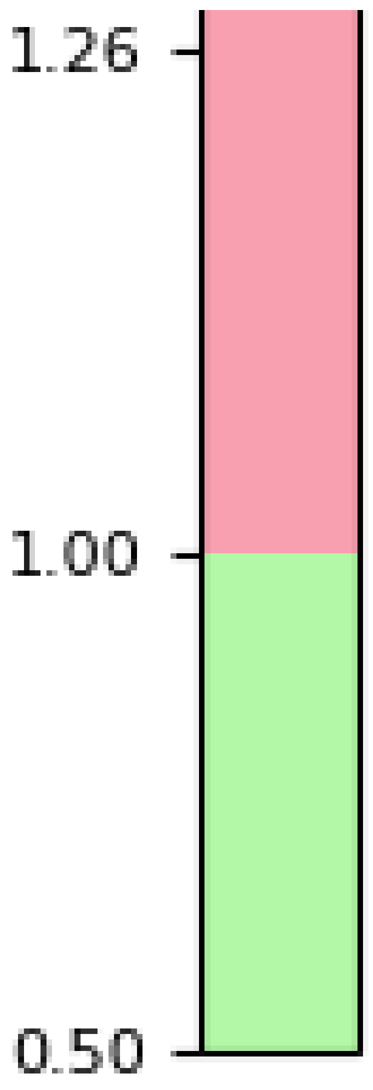
VHEE



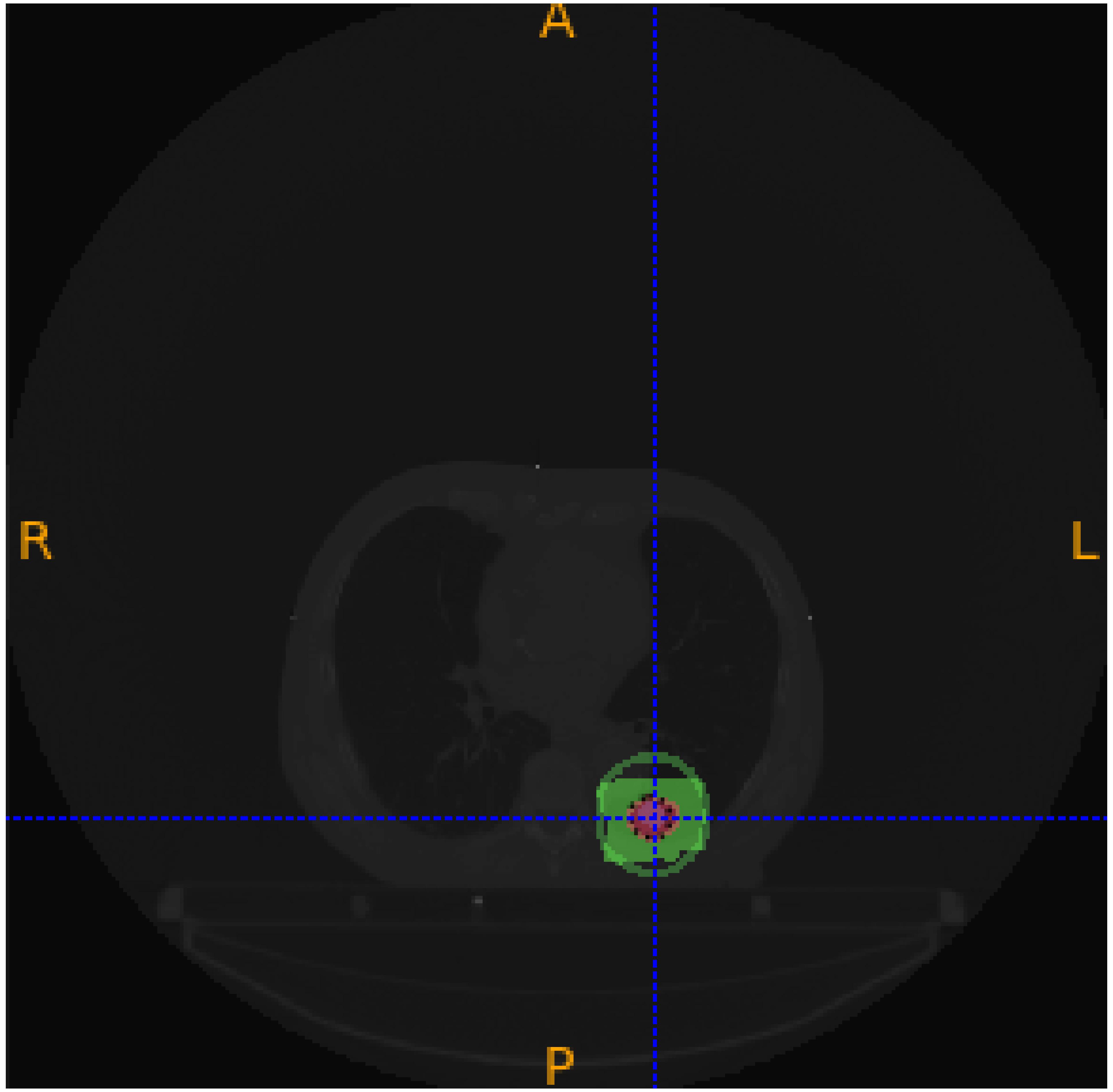
Lung Cancer

VMAT

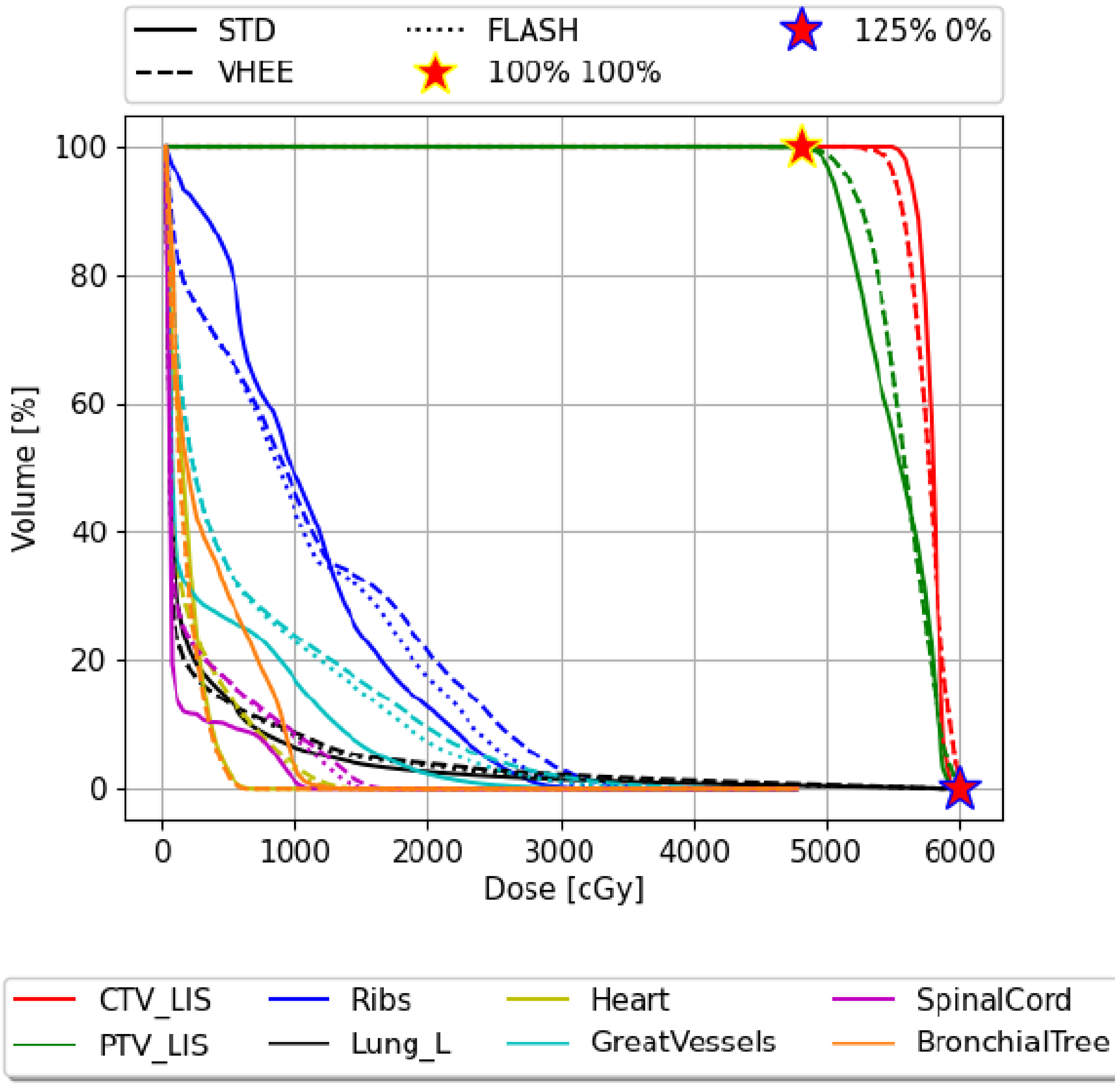




VHEE



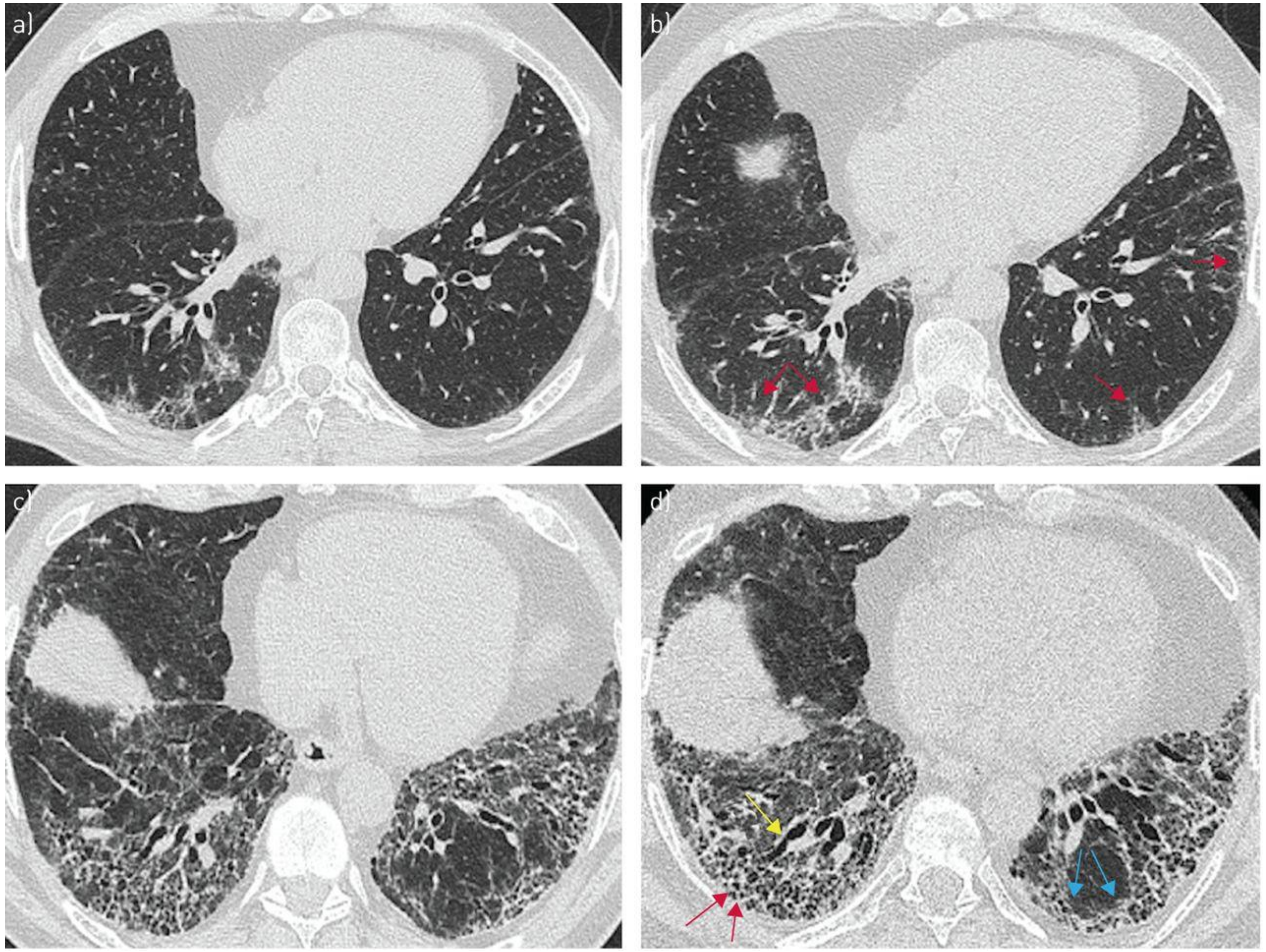
Lung Cancer DVH RESULTS



High-lines:

- PTV Prescription 12x4=48Gy
- Ribs Constraints: 43 Gy
- Spinal cord Constraints: 23 Gy

FLASH Fibrosis reduction



High-lines:

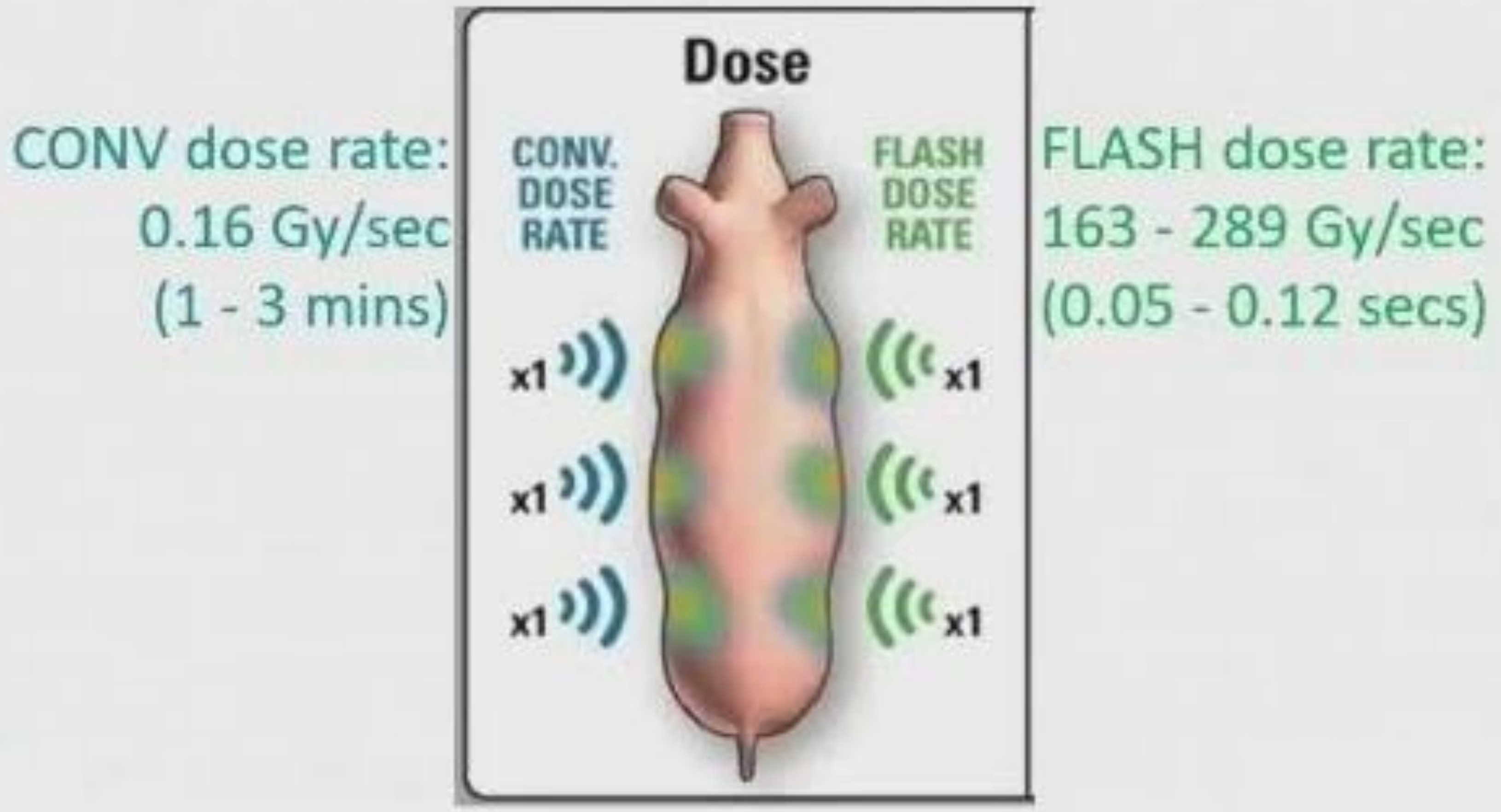
Pulmonary fibrosis is a late-stage injury that typically manifests in the time period from six to 24 months post irradiation

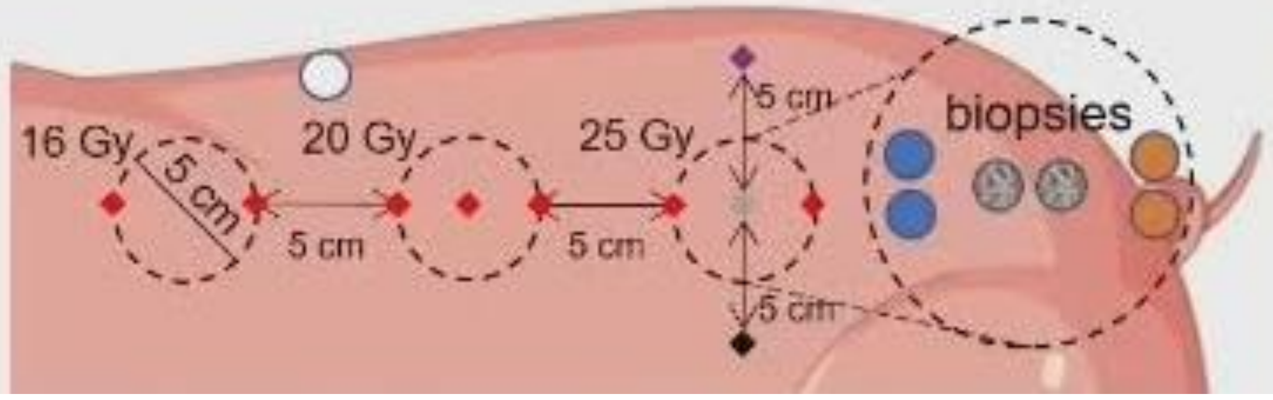
- While currently there is no good therapeutic intervention for fibrosis available

[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.

FLASH News

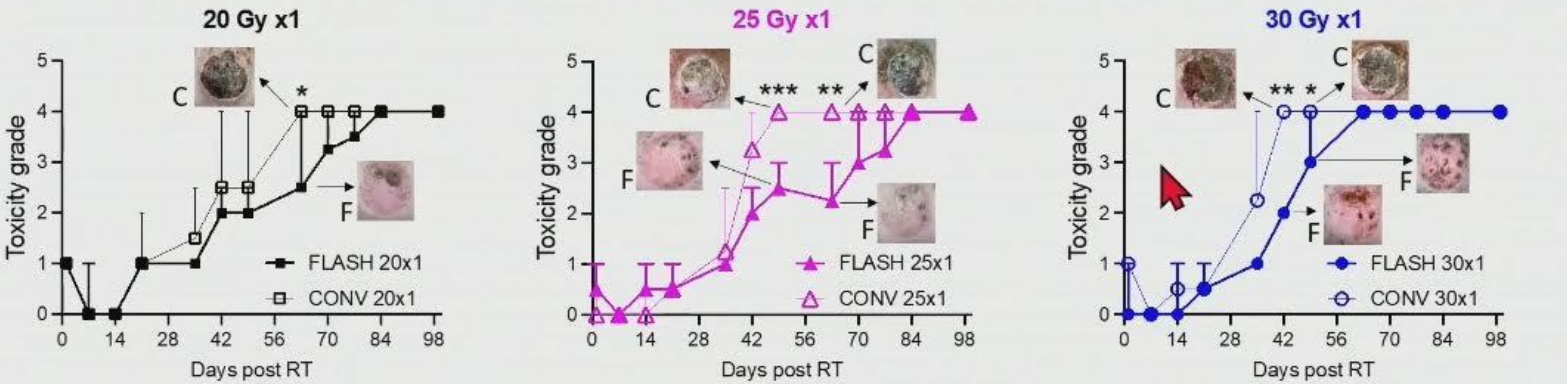
Materials & Methods





MD Anderson Cancer Center

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

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:

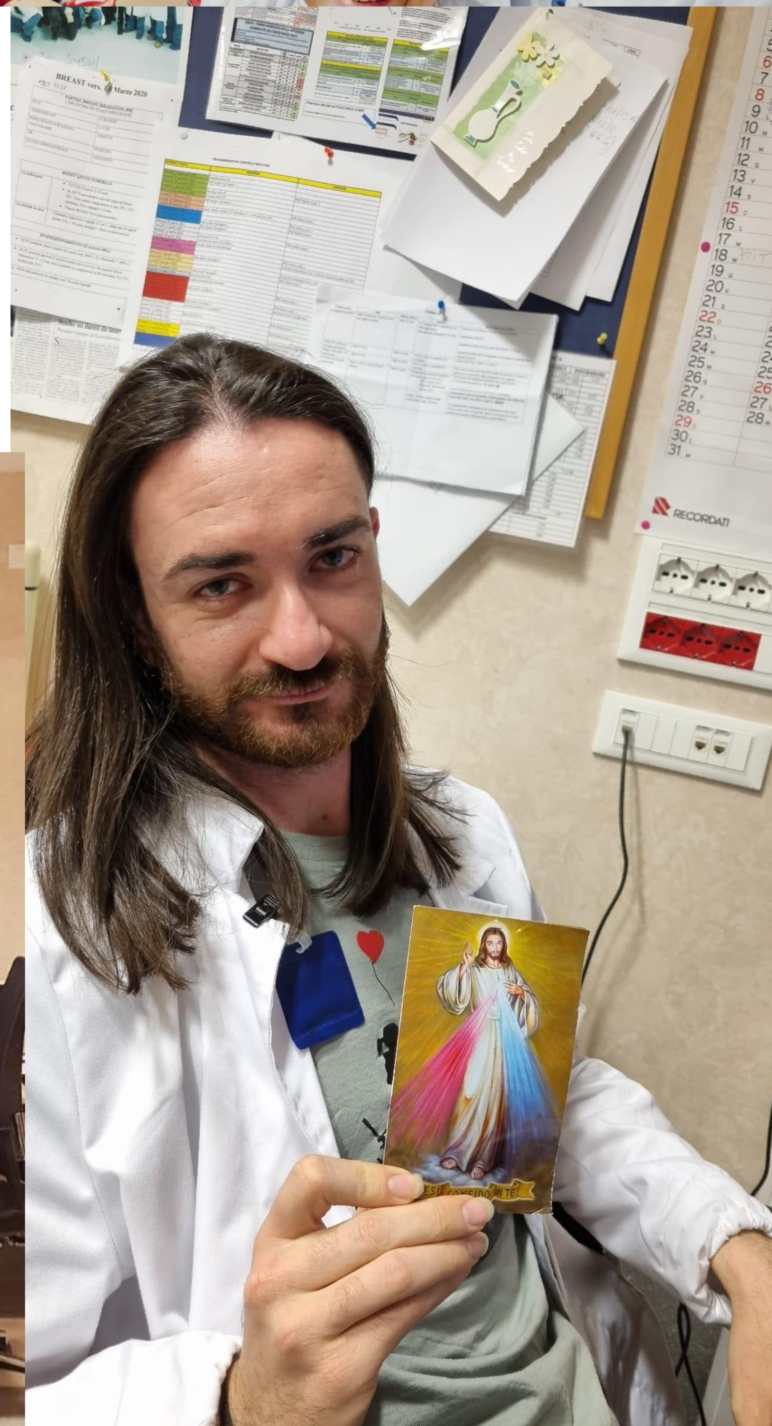
- FLASH effect is a complex phenomenon that is likely dependent on an optimal combination of various factor including dose, fractionation, field size and beam property.

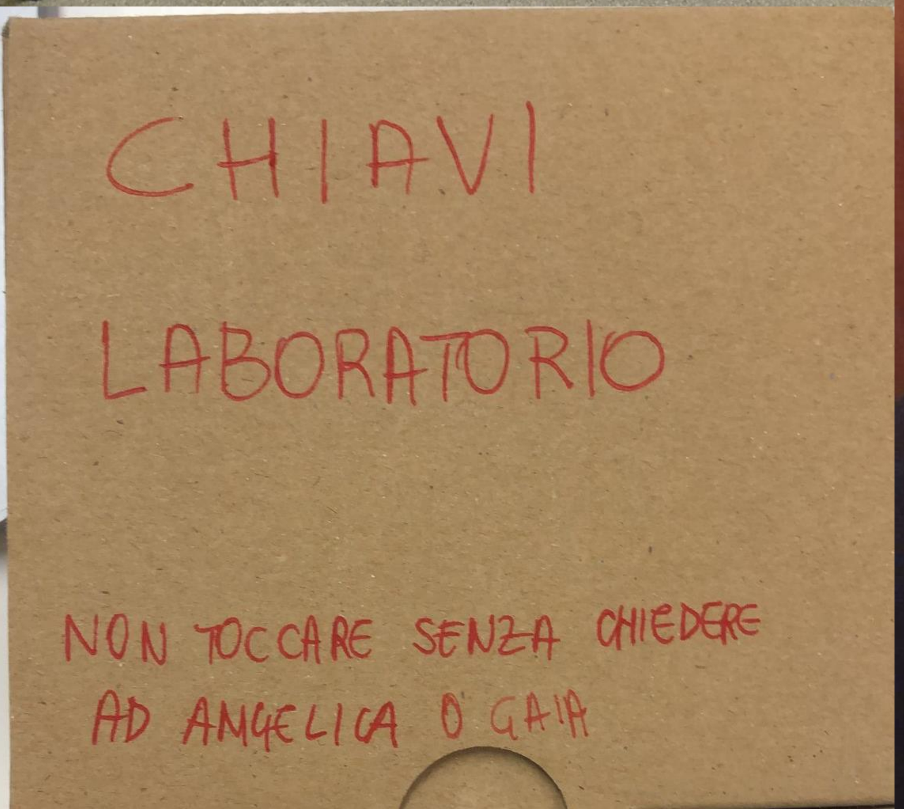
- In this kind of effect the rules of conventional radiotherapy will be overturned, and we need more radiobiology experiments to be able to apply the new FLASH methods so that prescriptions can be adapted to the new techniques.

- The results obtained in this thesis show that VHEEs could represent an early field of experimentation of the FLASH effect in the field of stereotactic treatments. In the lung case, the high prescription allows for greater safety in activating the FLASH effect, thus solving the single-field problem encountered in the pancreas case; consequently, treatments of early-stage NSCLCs could be one of the first field of application for FLASH with VHEE.

Acknowledge

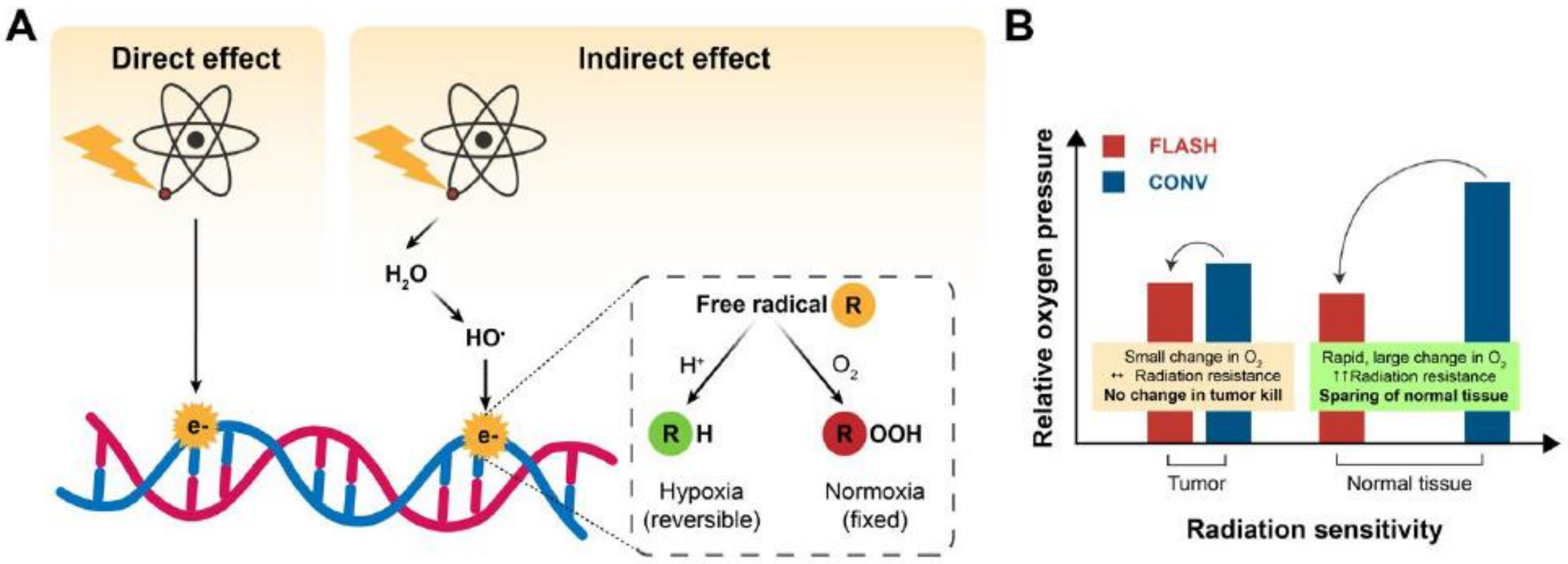
Thanks to Gaia Antonio Angelica Annalisa
Micol Giacomo Teresa e Valerio





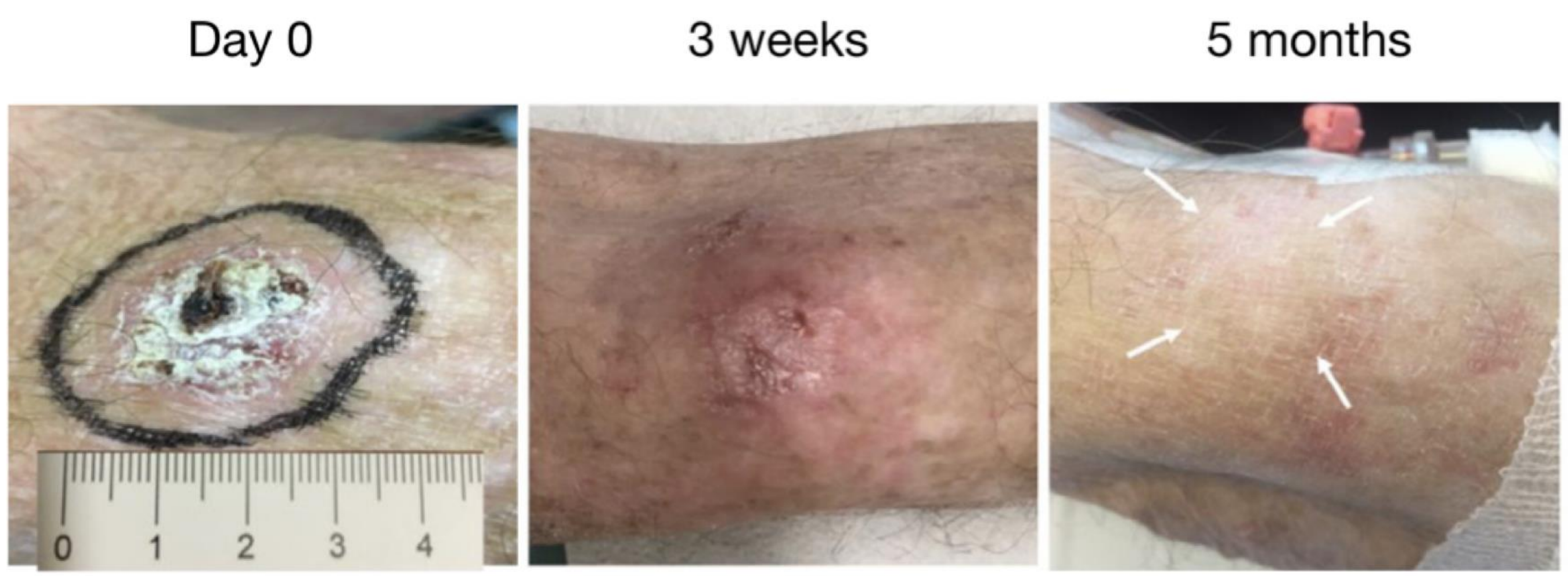
SPAN

FLASH Effect



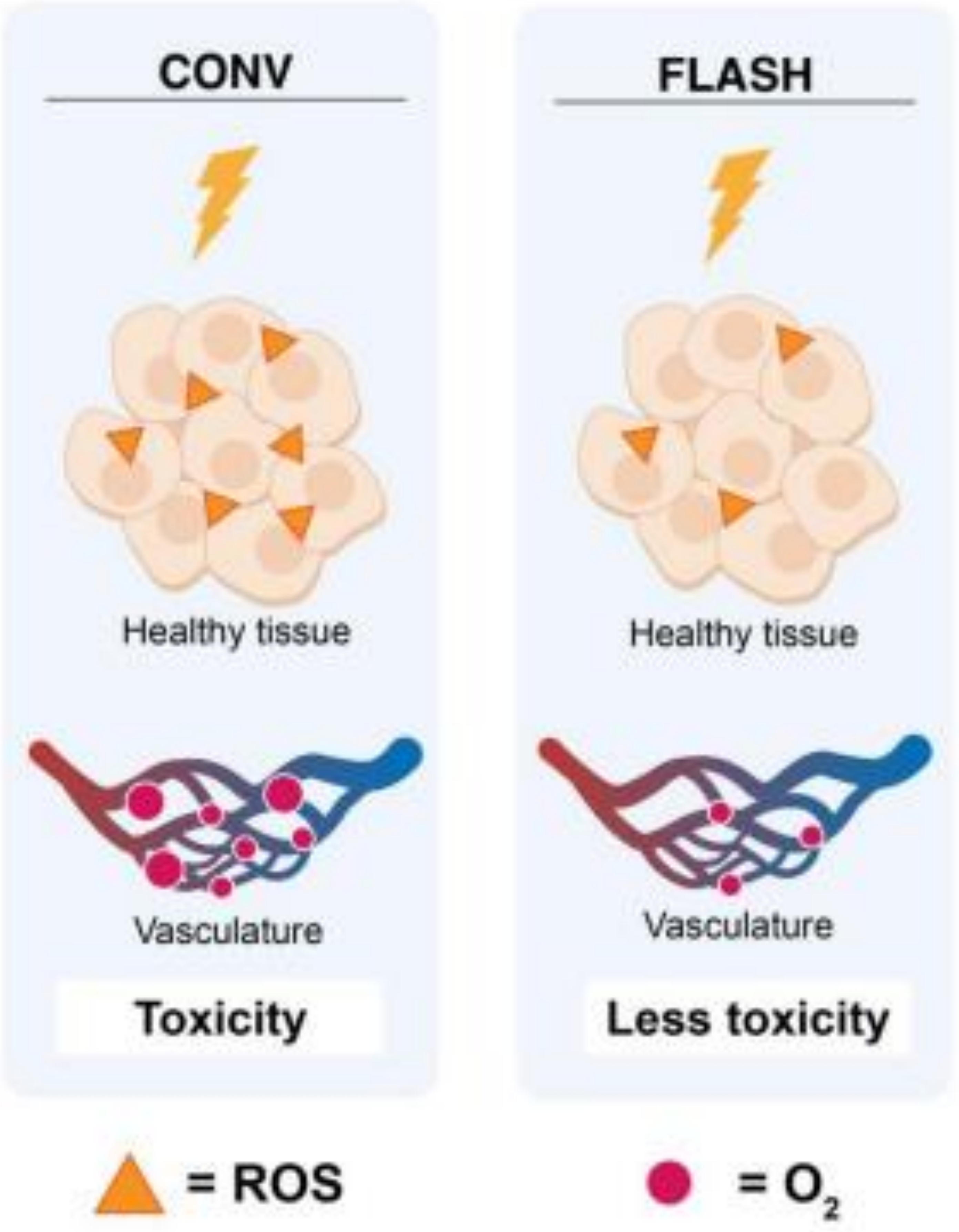
Highlines:

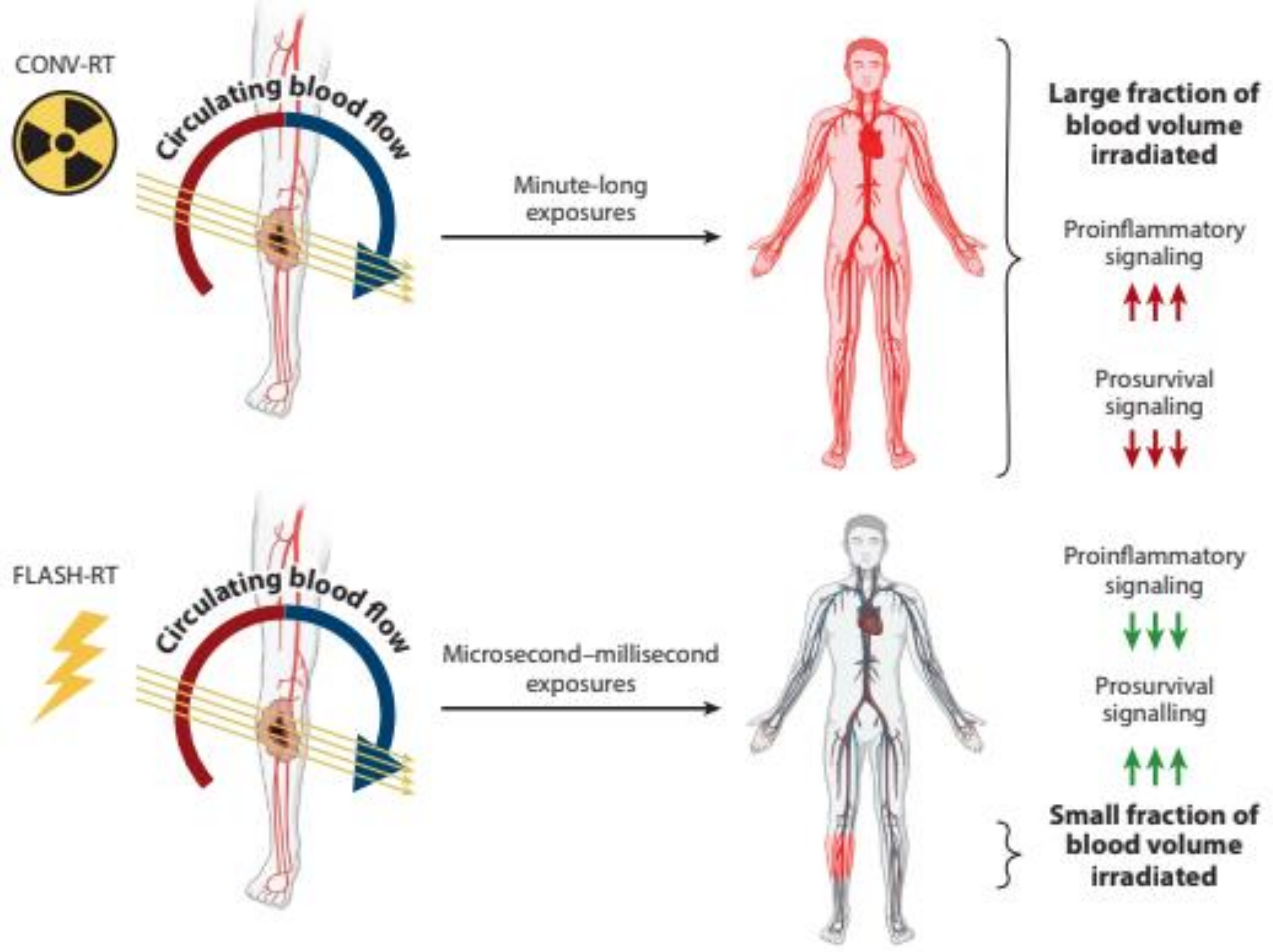
- deliver high doses (>4-6 Gy)
- very short period of time (<200 ms)



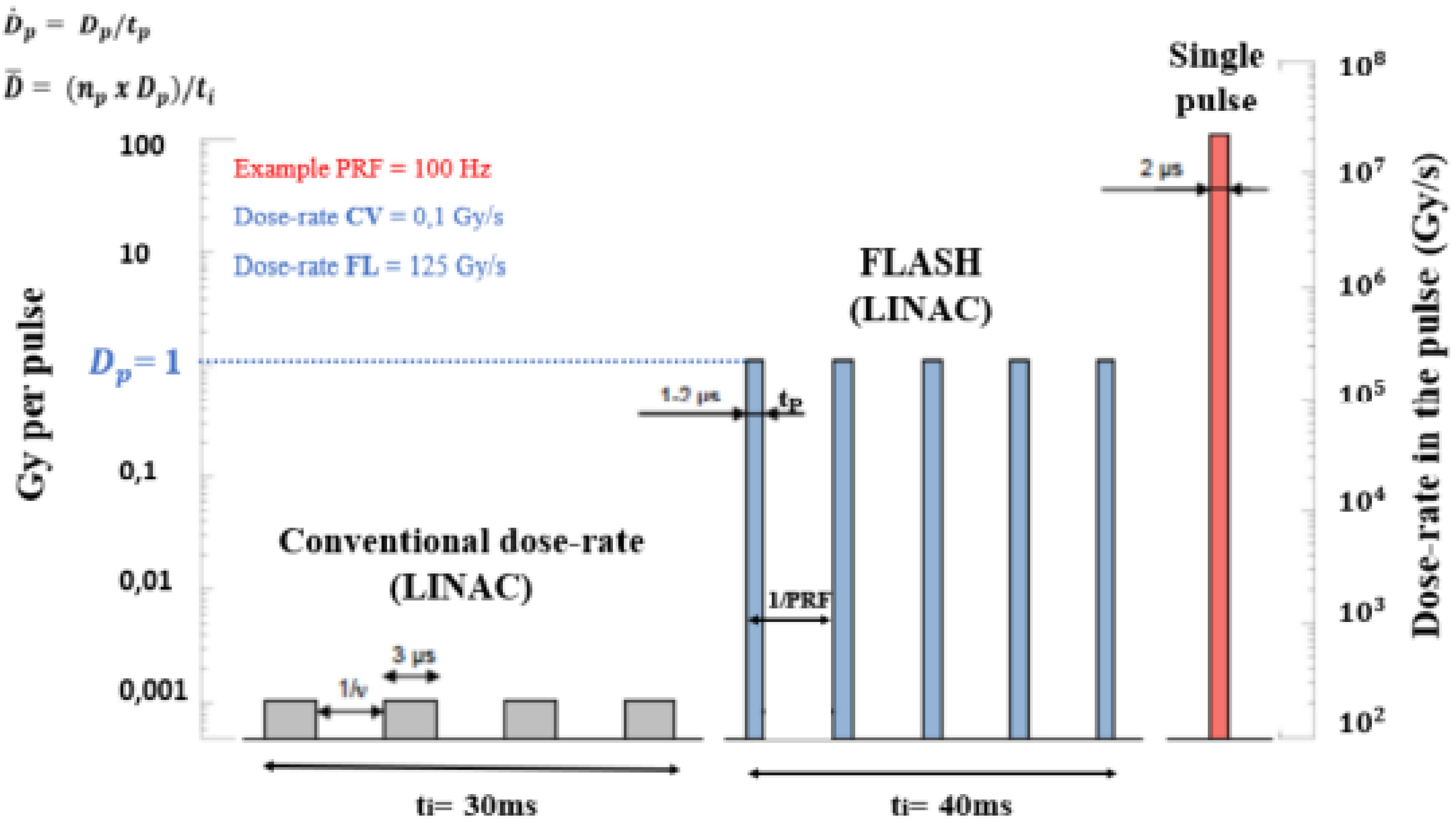
[5]. doi.org/10.1016/j.radonc.2021.12.045

FLASH Effect





Very High-Energy Electron (VHEE)



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)**

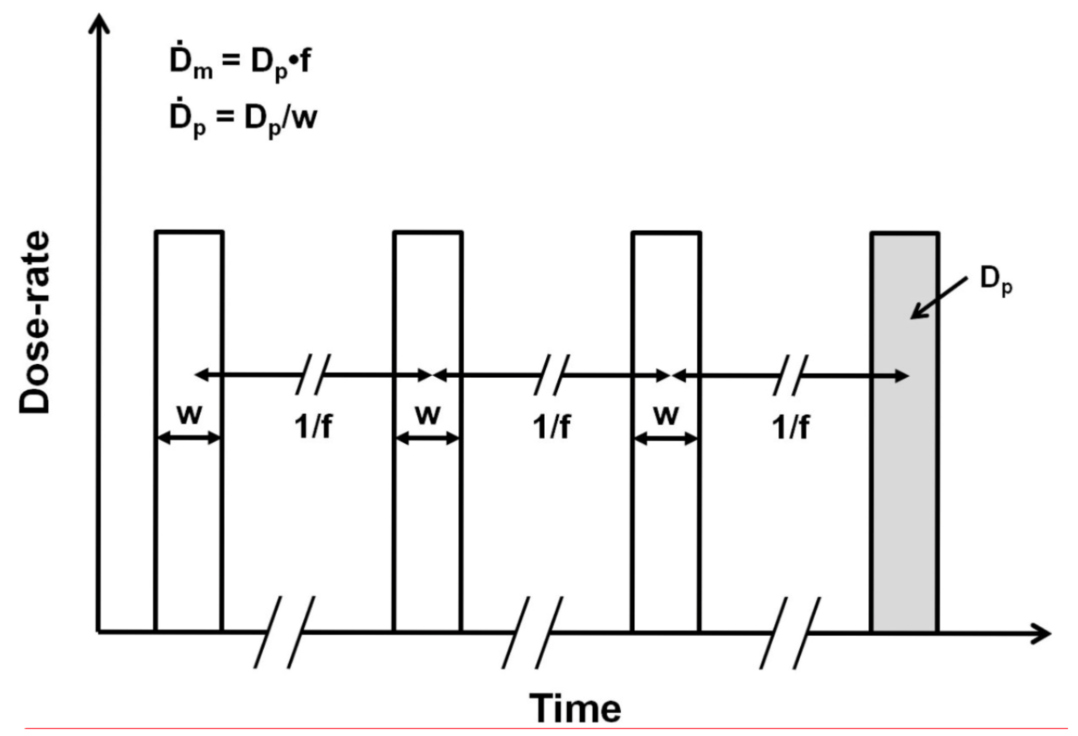
DADR - Dose Average Dose Rate

- 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

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

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

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

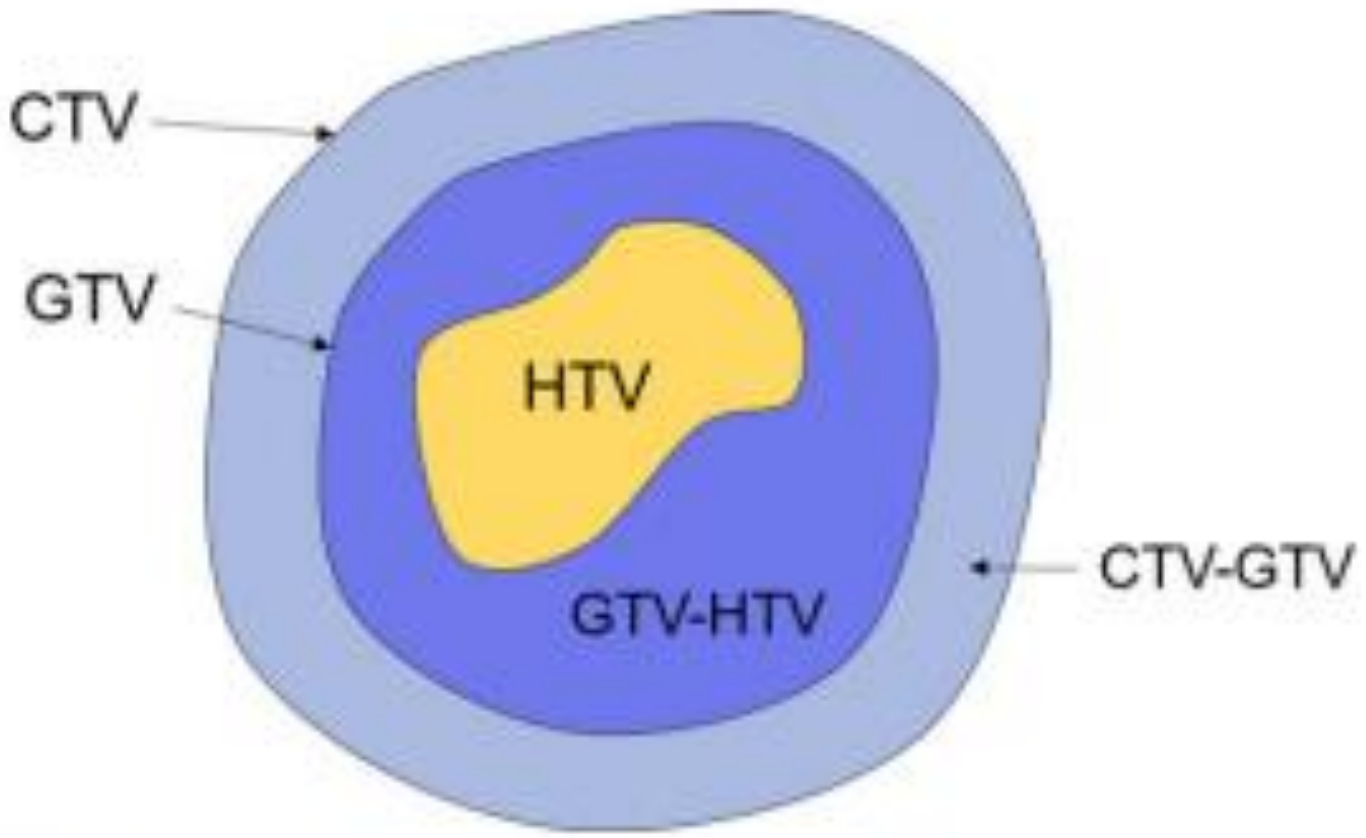
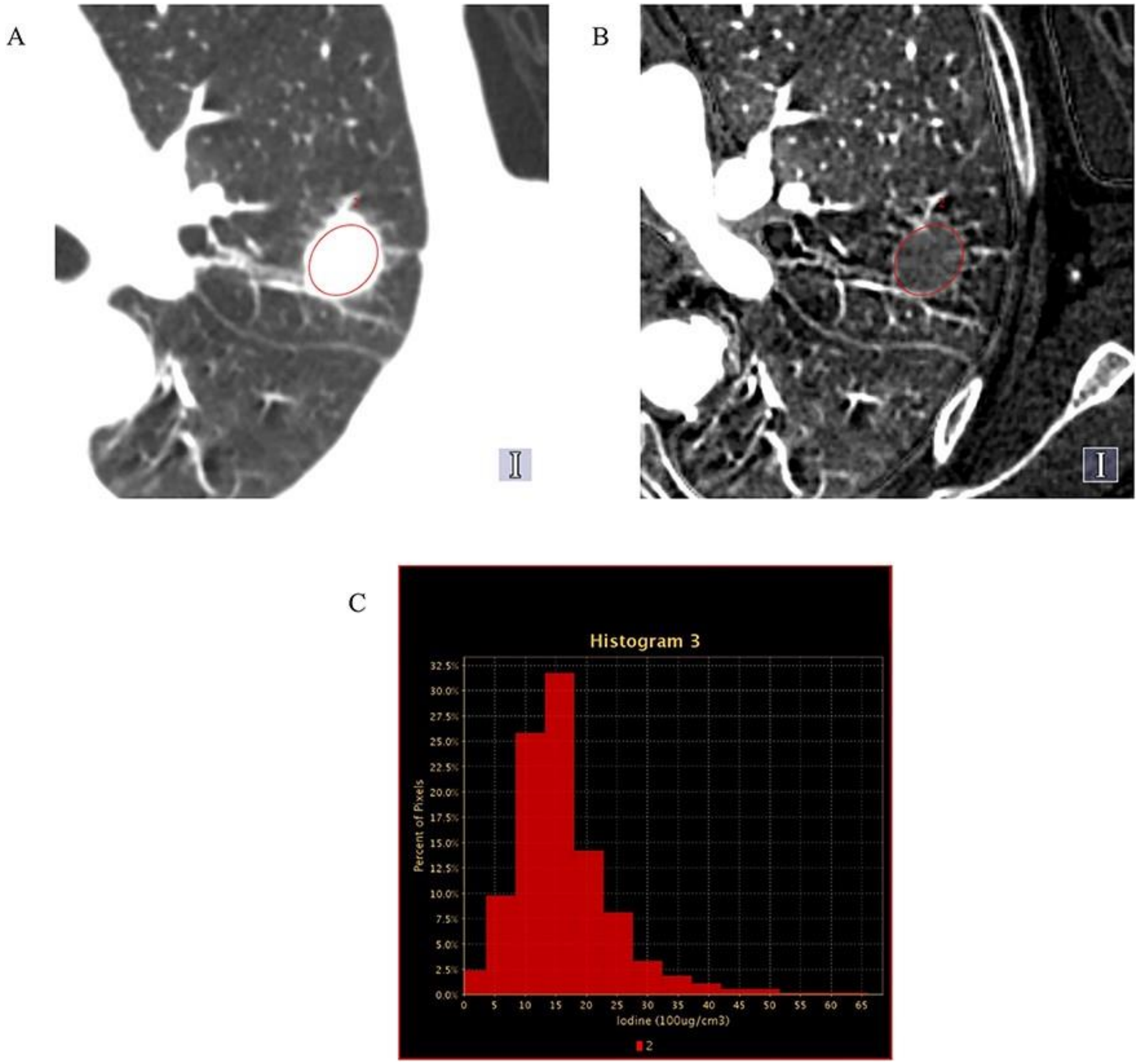


FIG. 1. Illustration of the target volumes considered for homogeneous dose prescription: clinical target volume (CTV), gross target volume (GTV), hypoxic target volume (HTV), the GTV not containing the HTV (GTV-HTV), and the CTV not containing the GTV (CTV-GTV). [Color figure can be viewed at wileyonlinelibrary.com]



J Radiat Res, Volume 62, Issue 3, May 2021, Pages 448–456,
https://doi.org/10.1093/jrr/rrab015

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

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

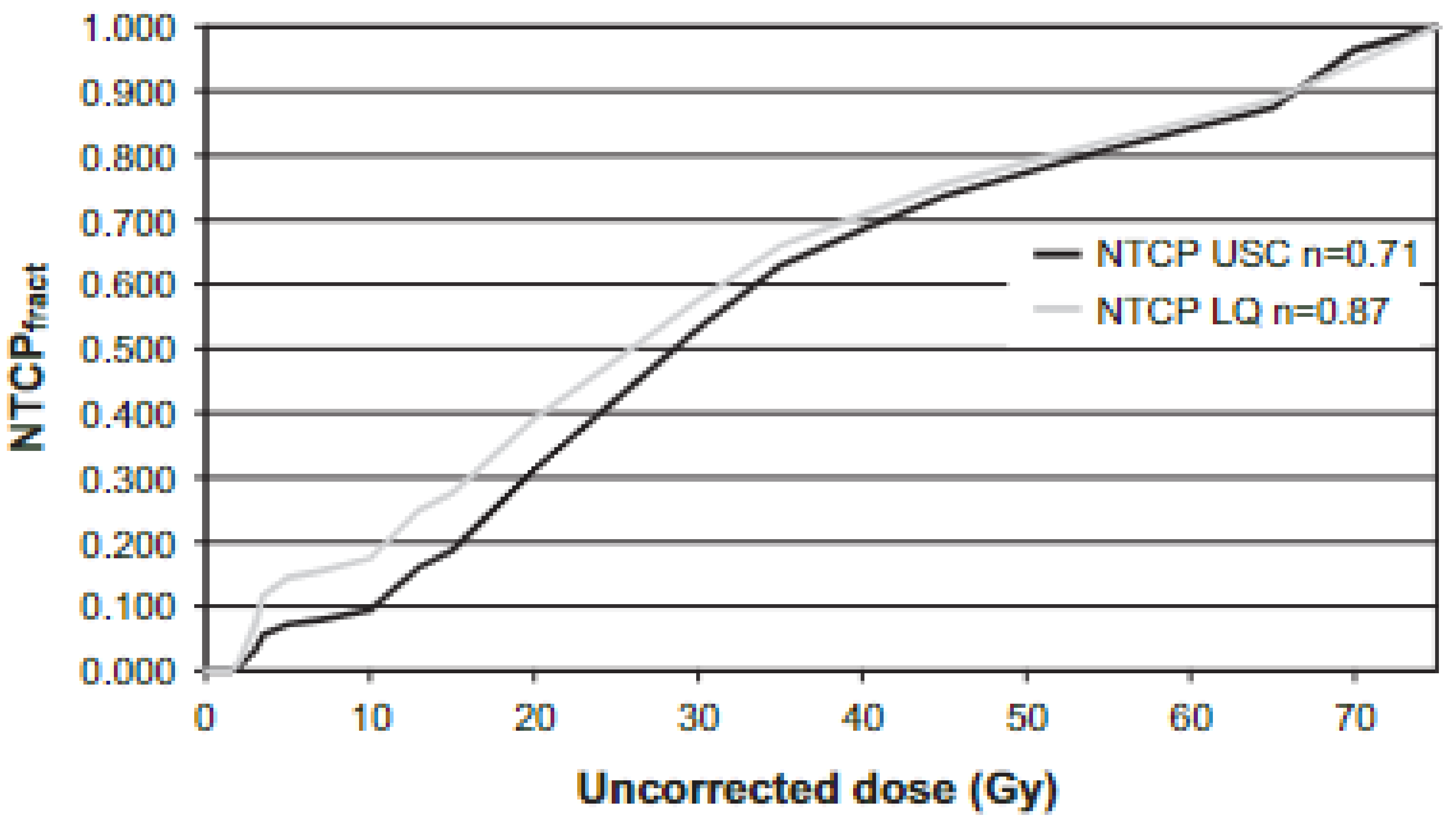


Figure 5. Fractional $NTCP_{fract}$ calculated with DVH-data corrected with USC and LQ (α/β =3) as a function of cut-off dose for a representative patient. The plot illustrates the cumulative contribution to the NTCP. With the USC correction the low doses have less impact on NTCP compared to what is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

https://doi.org/10.3109/0284186X.2010.543695