

Online ARPG Meeting

Flash therapy with medium/ high energy electron beams

G. Franciosini on behalf of the SBAI group

Rome, 4/02/2021

External photon Beam Radiotherapy in Prostate cancer

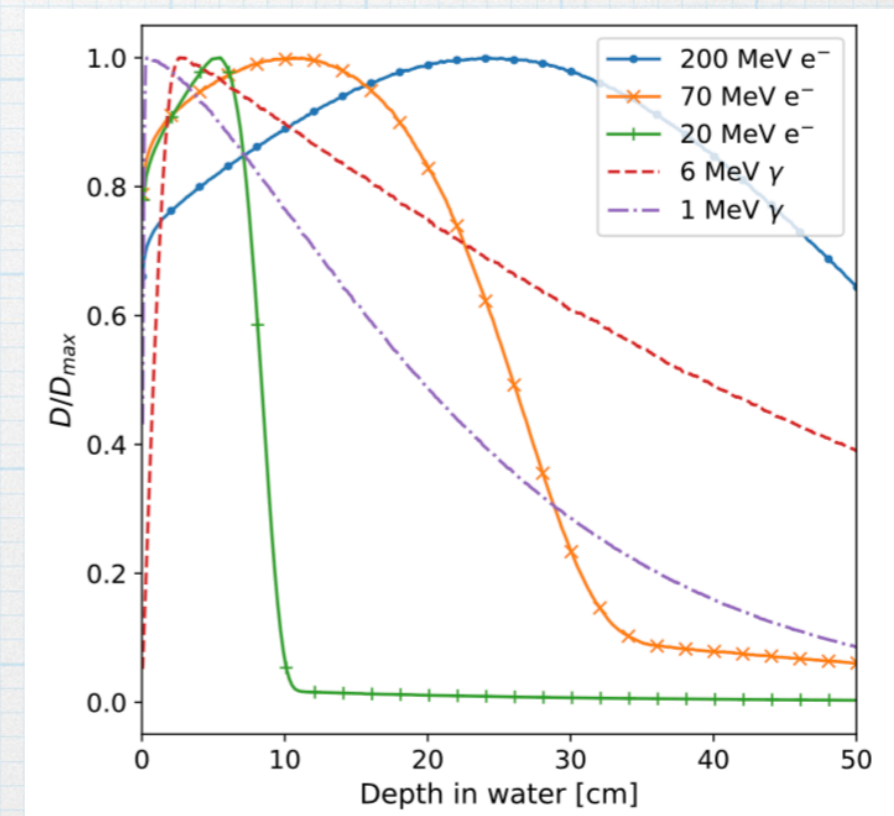
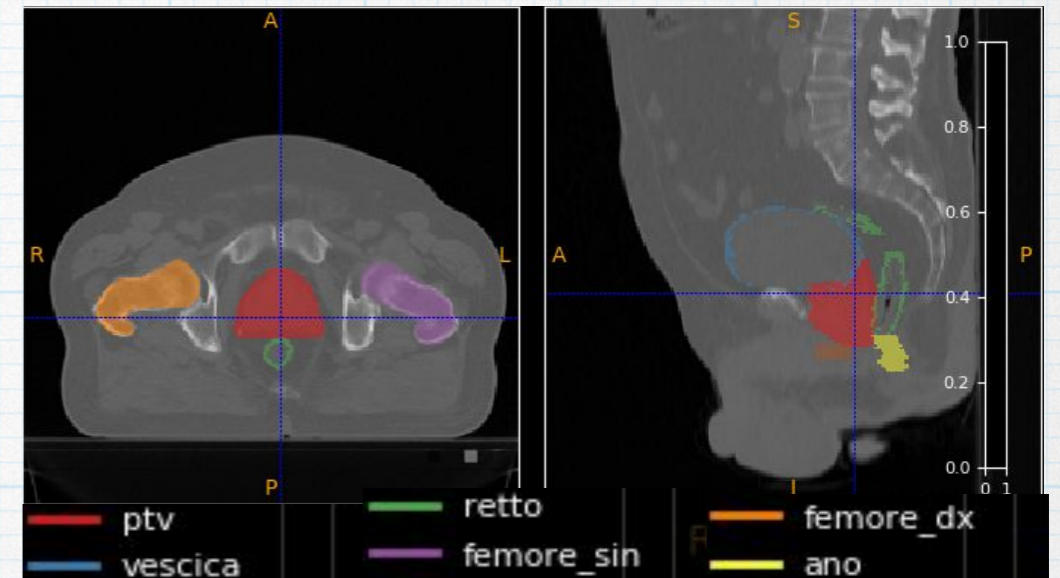
Prostate cancer is mostly treated with external beam radiotherapy (**EBRT**), an established technique that uses high energy photons (4-25 MV) to stop or slow the tumor growth.

One of the possible technical implementation of such treatment is the Intensity Modulated Radiation Therapy (**IMRT**):

- 3D radiotherapy based on the acquisition of CT images;
- beams with modulating intensity;
- multiple treatment sessions (38 up to 40 fractions of 180-200 cGy each).

The treatment consists of the following steps:

- definition of the **PTV** (Planned Treatment Volume);
- definition of the **OARs** (Organs at Risk);
- Optimization.



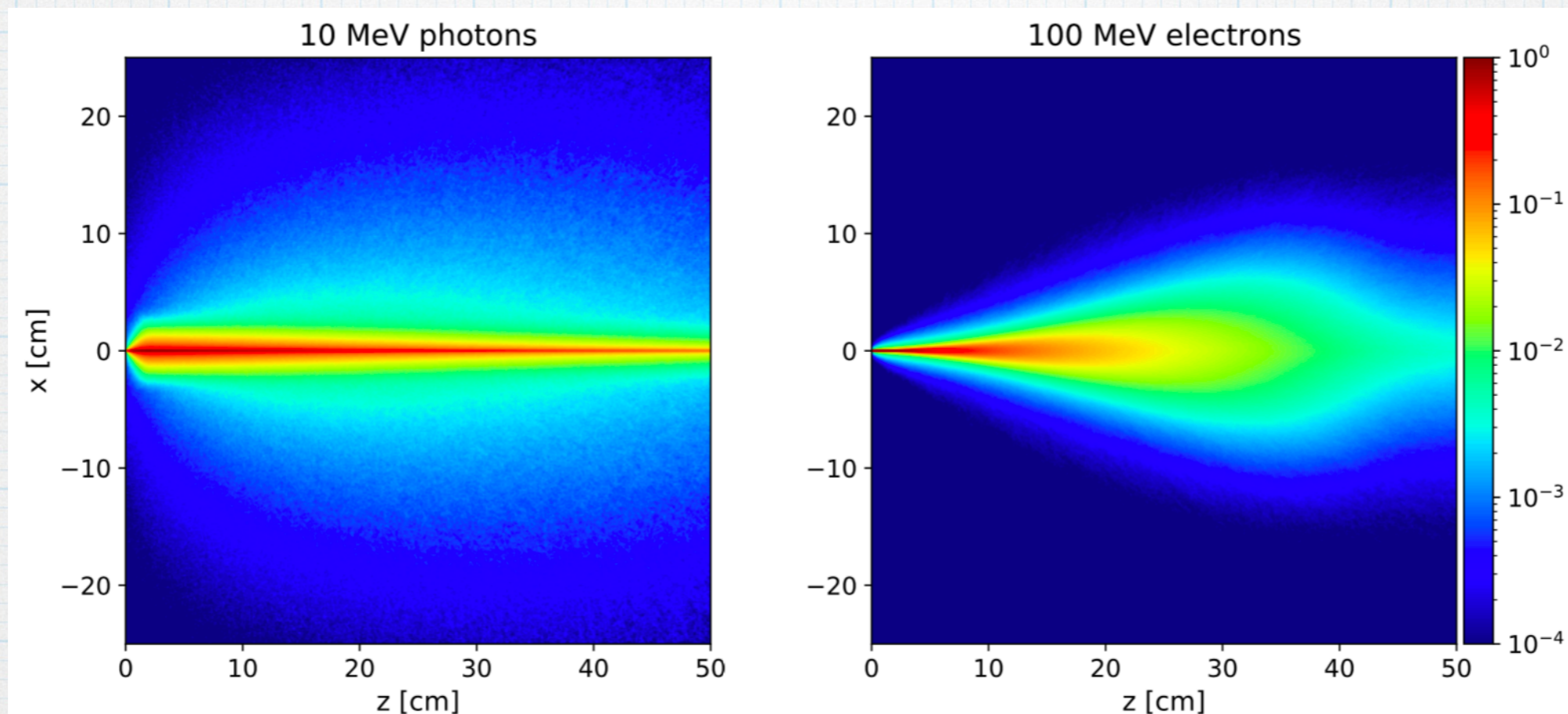
Main Limitation: dose peaks few mm after entering the patient body and decreases exponentially irradiating the healthy tissues



**Charged Particles:
Very High Electrons
Beam**

Photons vs Very High Energy Electrons (VHEE)

VHEE beams have enough energy to reach **deep seated tumours** but Multiple Scattering interactions, the photons and positrons produced along the path make the obtained irradiation intrinsically **less selective**.



Comparing VHEE treatments with photon standard RT ones, the conformity of the absorbed dose distribution is comparable with latter only at the expense of using a large number of electron fields (order of tens) and a beam energy > 100 MeV.

Expensive and technologically challenging for a clinical center with respect to IMRT

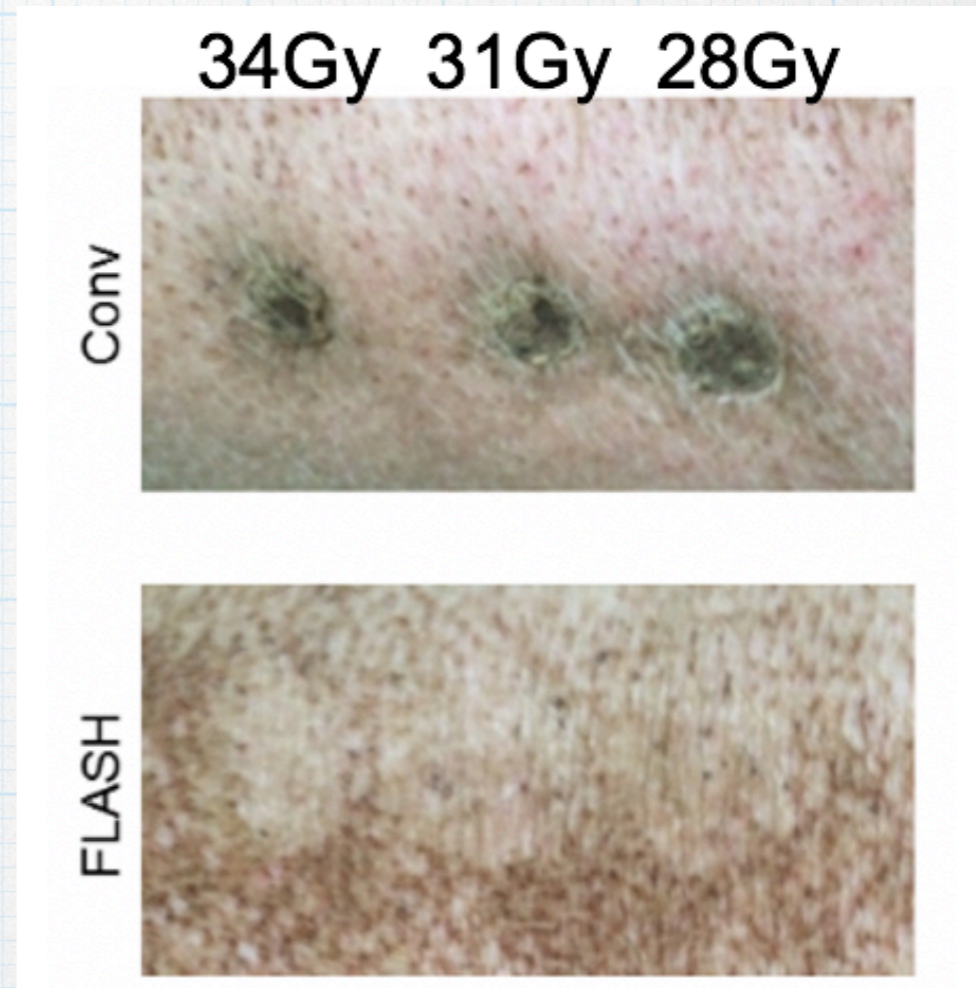
**FLASH
EFFECT**

Flash Effect

Several pre-clinical studies recently claimed that the toxicity in healthy tissues related to tumour treatments can be significantly reduced (from 80% down to 60%), while keeping the same efficacy in cancer killing, if the dose rate is radically increased (~ 10 Gy/s, or even more) with respect to conventional treatments (~ 0.01 Gy/s).



1. Tumor response, analogous to the one obtained with conventional RT
2. Reduced radiation-induced toxicities in the healthy tissues



The mechanism responsible for reduced tissue toxicity following FLASH radiotherapy is yet to be clarified

Flash Effect + VHEE

In our work we have investigated the treatment of prostate cancer using VHEE beams with energy limited to the 70 - 130 MeV energy range while taking into account the FLASH effect.

What we have done:

- We used a real prostate IMRT treatment to benchmark the FLASH VHEE performance;
- We performed a full MC simulation (**FLUKA**);
- The FLASH effect is modeled introducing a Dose Modifying Factor (**DMF**) to account for the reduced damage due to the FLASH effect in human healthy tissues;
- Finally, we compared the results of our FLASH VHEE model with the real case of a prostate cancer treatment with the reference IMRT case, showing the potential of the FLASH electron RT.

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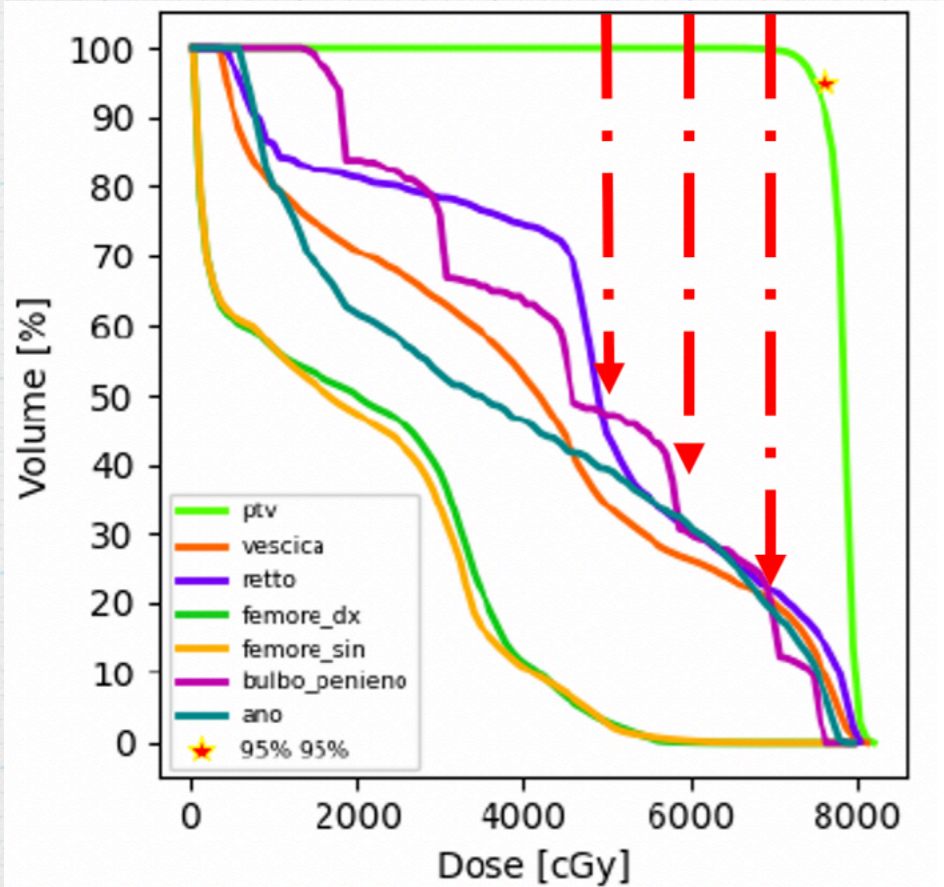
The DMF is defined as the ratio of the dose under reference conditions (D_{conv}) to that under the modified conditions (D_{flash}) needed to produce the same level of effect in the tissues under evaluation:

$$DMF = \frac{D_{conv}}{D_{FLASH}}$$

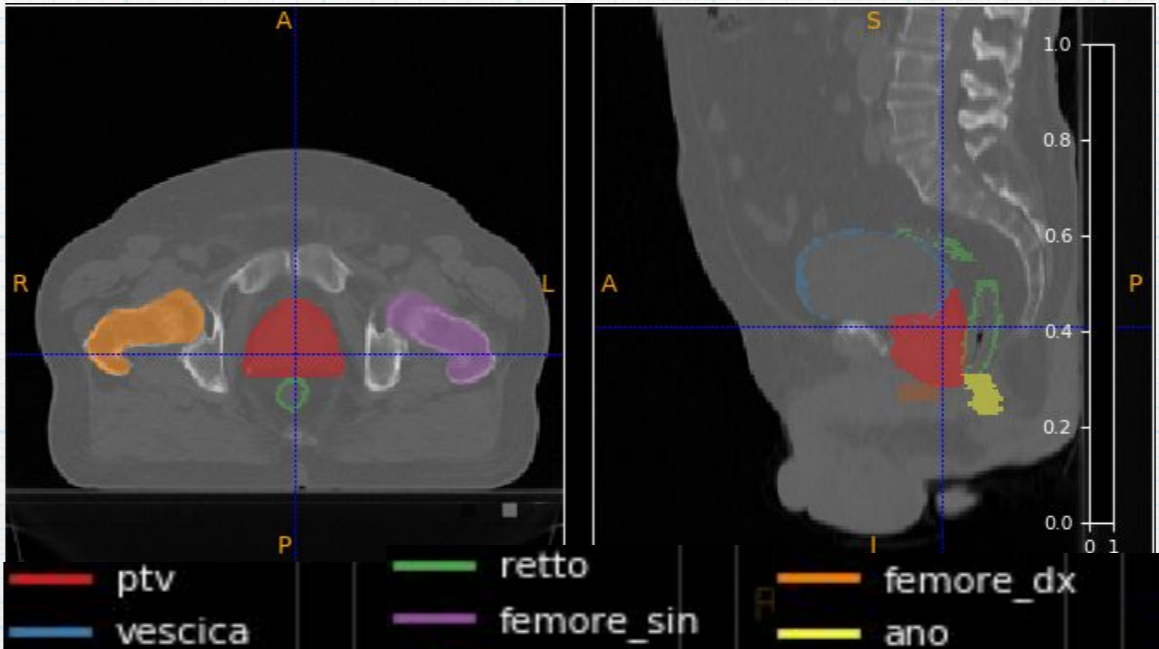
We have
implemented
**DMF=1,0.8
and 0.6**

Prostate tumor treated with IMRT

The tumour (PTV) coverage and the dose absorbed by the OARs have been compared, carrying out a quantitative analysis using the Dose Volume Histograms (**DVH**), with the results obtained in a real IMRT case (7 fields, 6 MV photons, 78 Gy in 39 fractions), (Policlinico Umberto I)



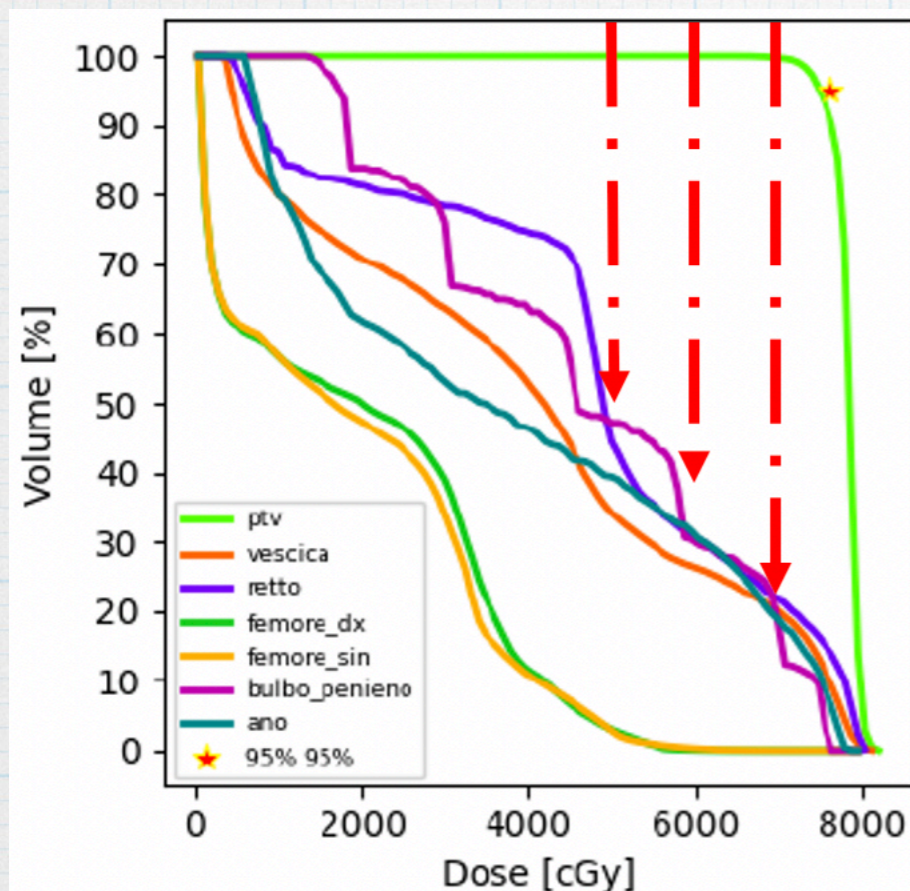
Organ	dosimetric constraints
Target volume	78 Gy on at least 95%, $V_{95\%} > 95\%$, $V_{105\%} < 95\%$, never above 107%
Rectum	$V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, $V_{75} < 15\%$
Anus	$V_{30} < 50\%$
Bulbourethral Glands	$\bar{D} < 50$ Gy
Femurs	$\bar{D} < 52$ Gy, $V_{60} < 5\%$
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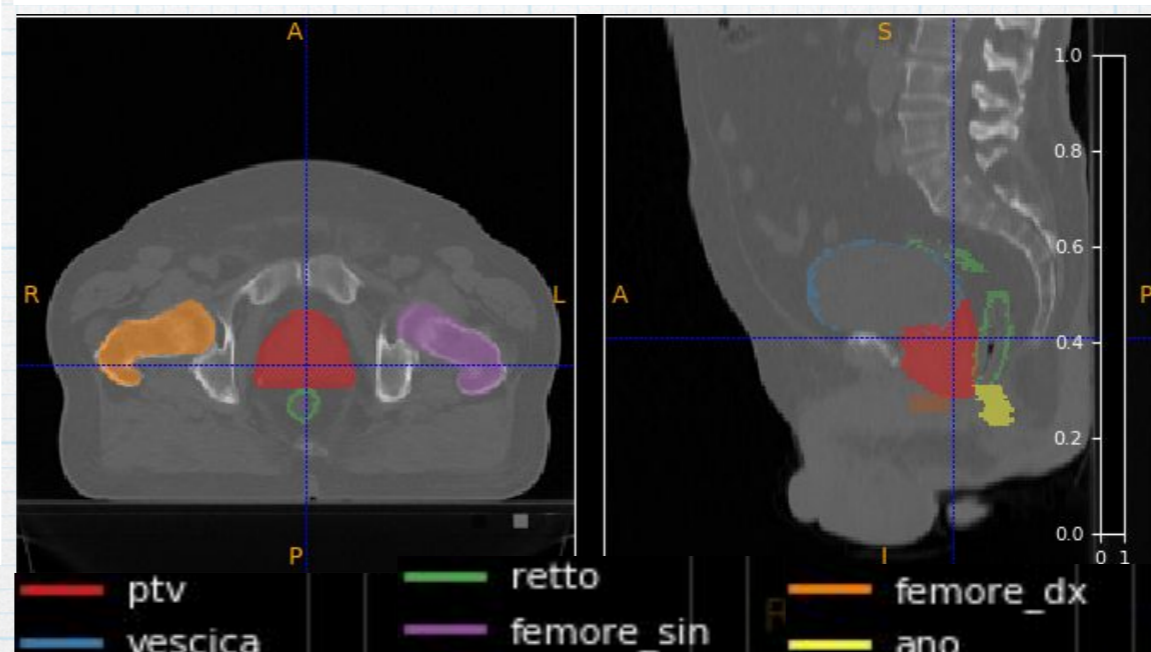
$V_{XX} < YY\%$: YY% of the referred organ or region must absorb less than XX Gy.

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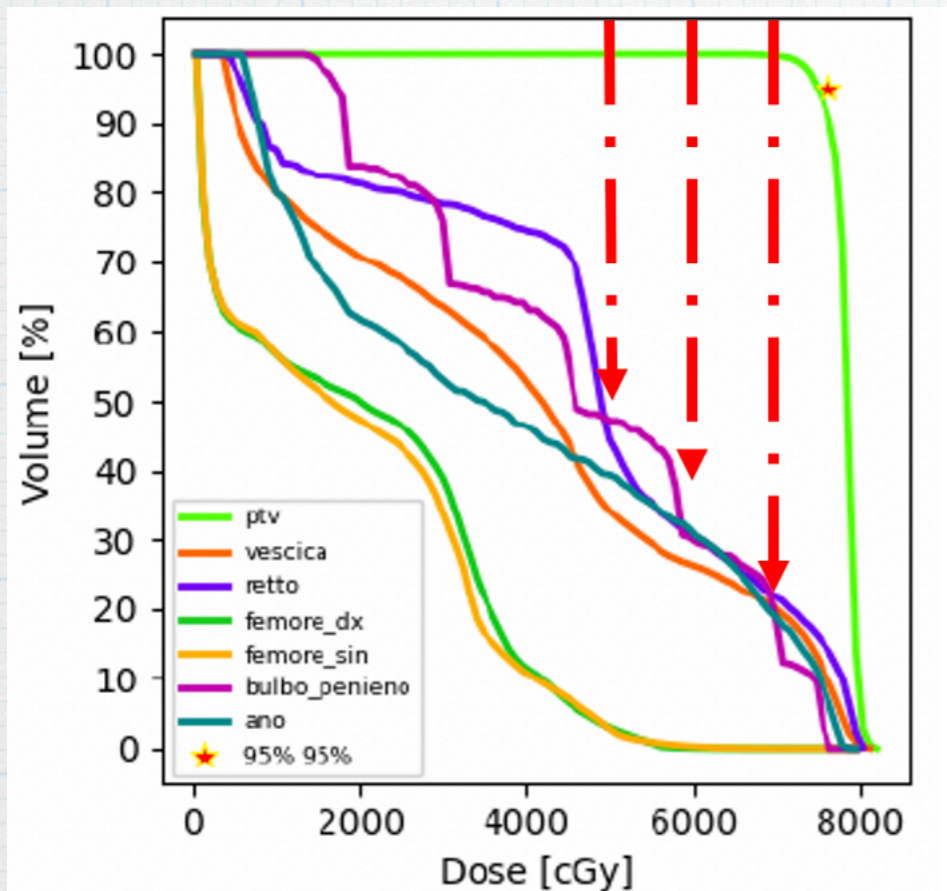
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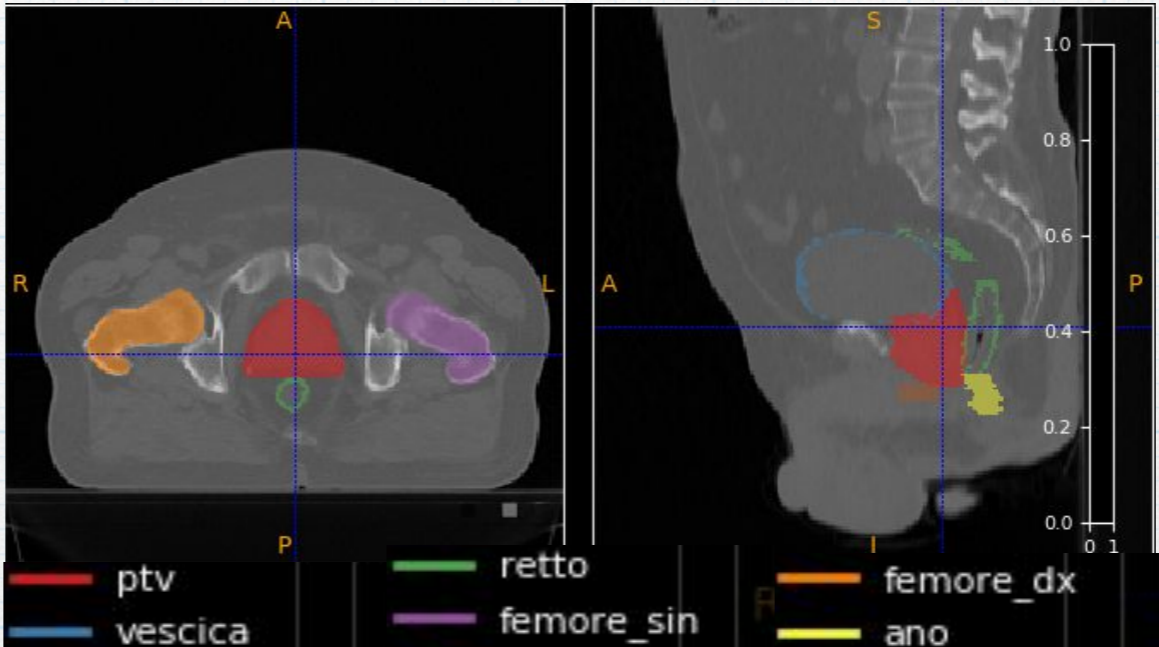
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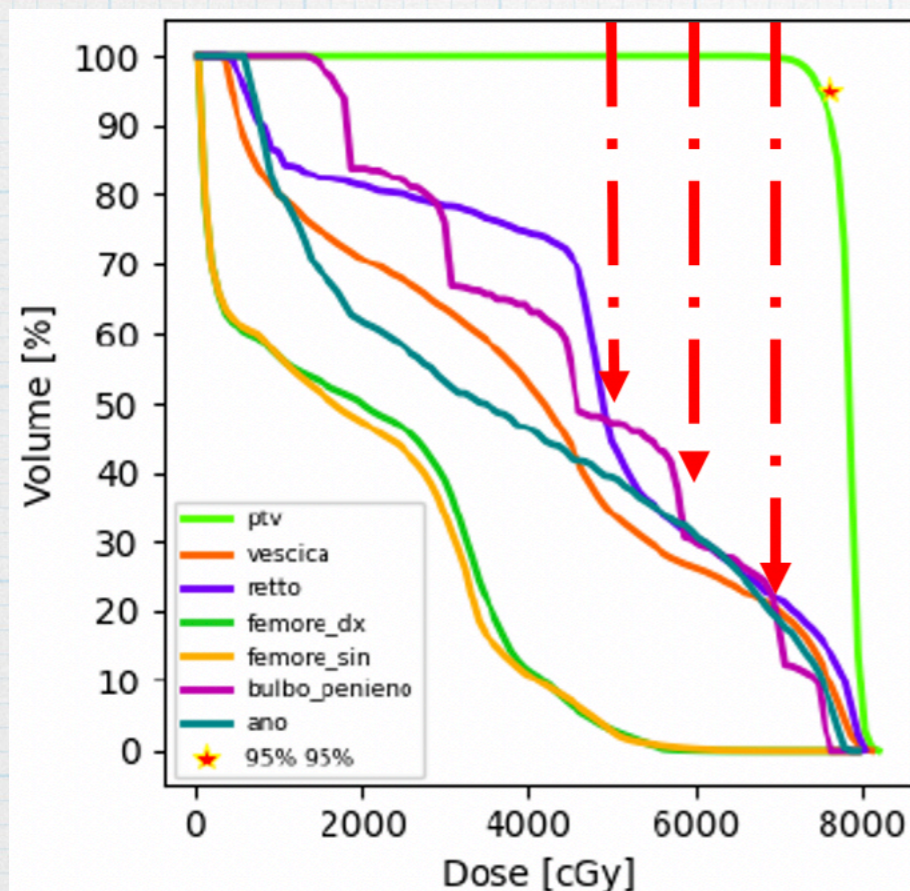
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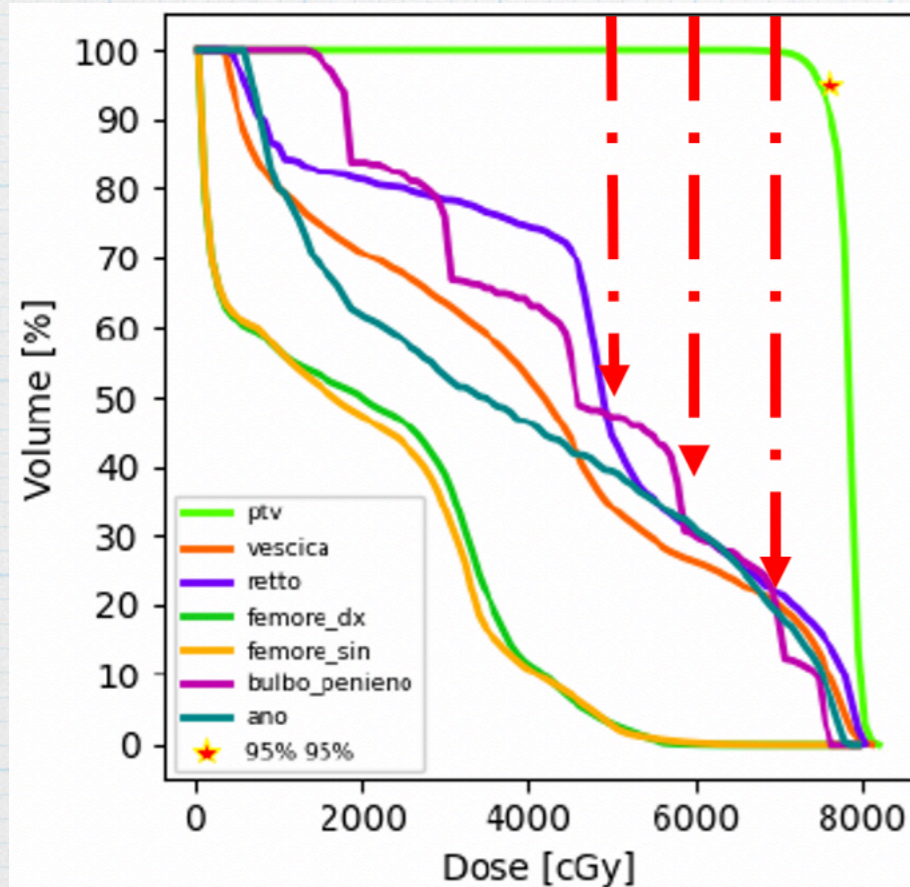
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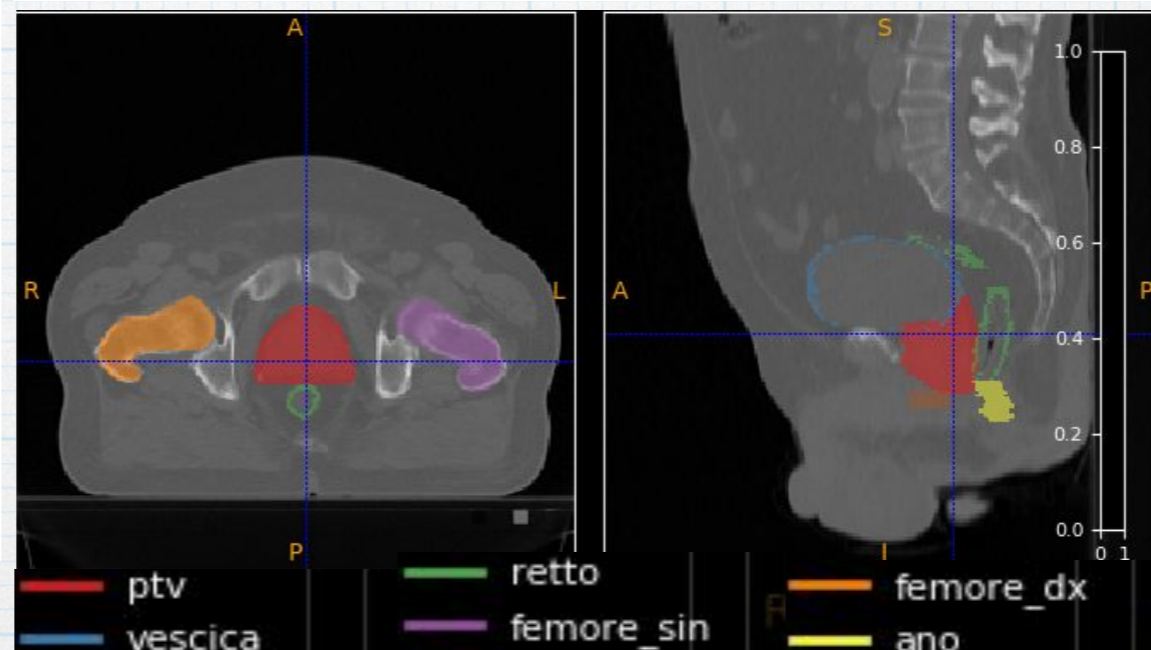
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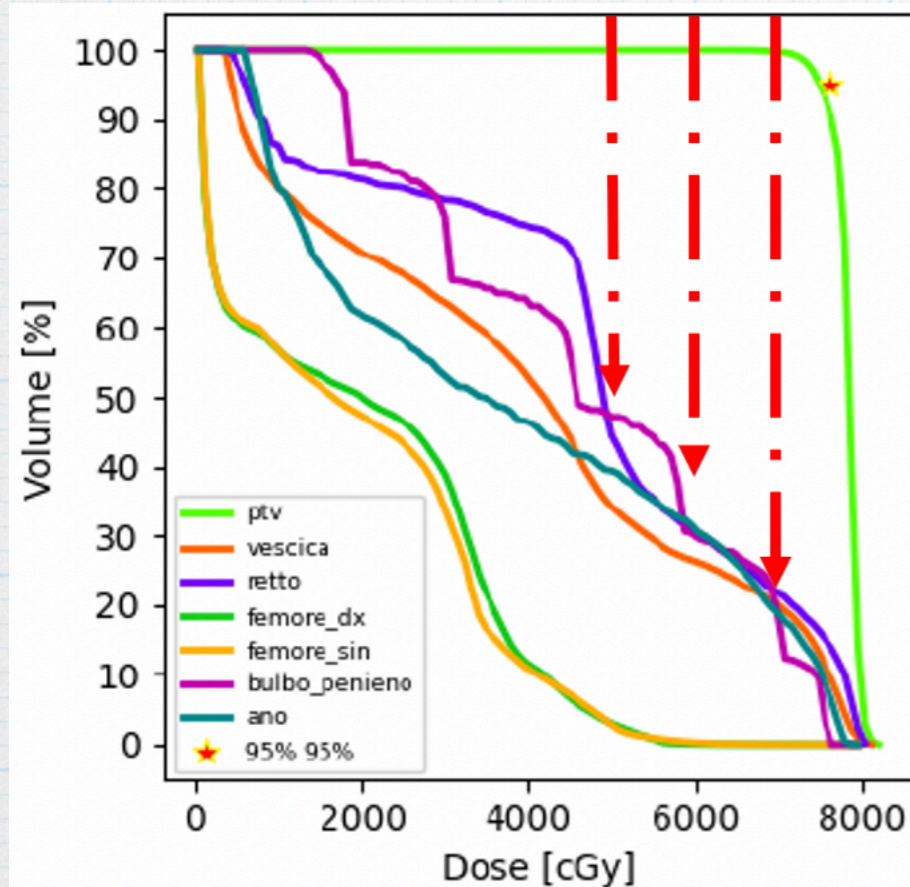
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Our assumptions

- The clinical accelerating system, able to produce a high energy electron beam, high accelerating gradients (~ 50 MeV/m) would be needed, C-band technology could provide the solution
- The VHEE beams at the nozzle exit window have transverse size ($O \sim \text{mm}$) and divergence ($O \sim \text{mrad}$)

Fluka Simulation

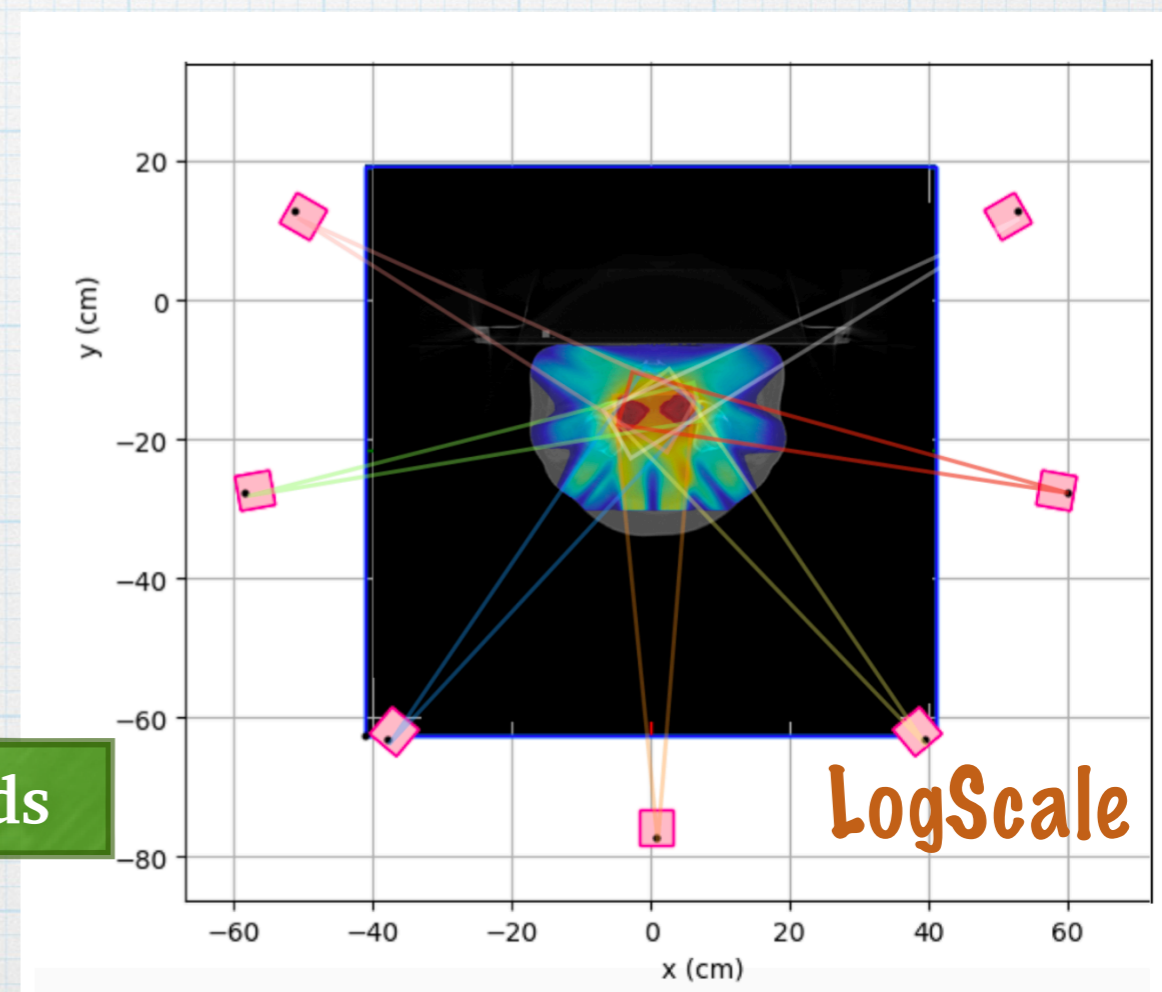
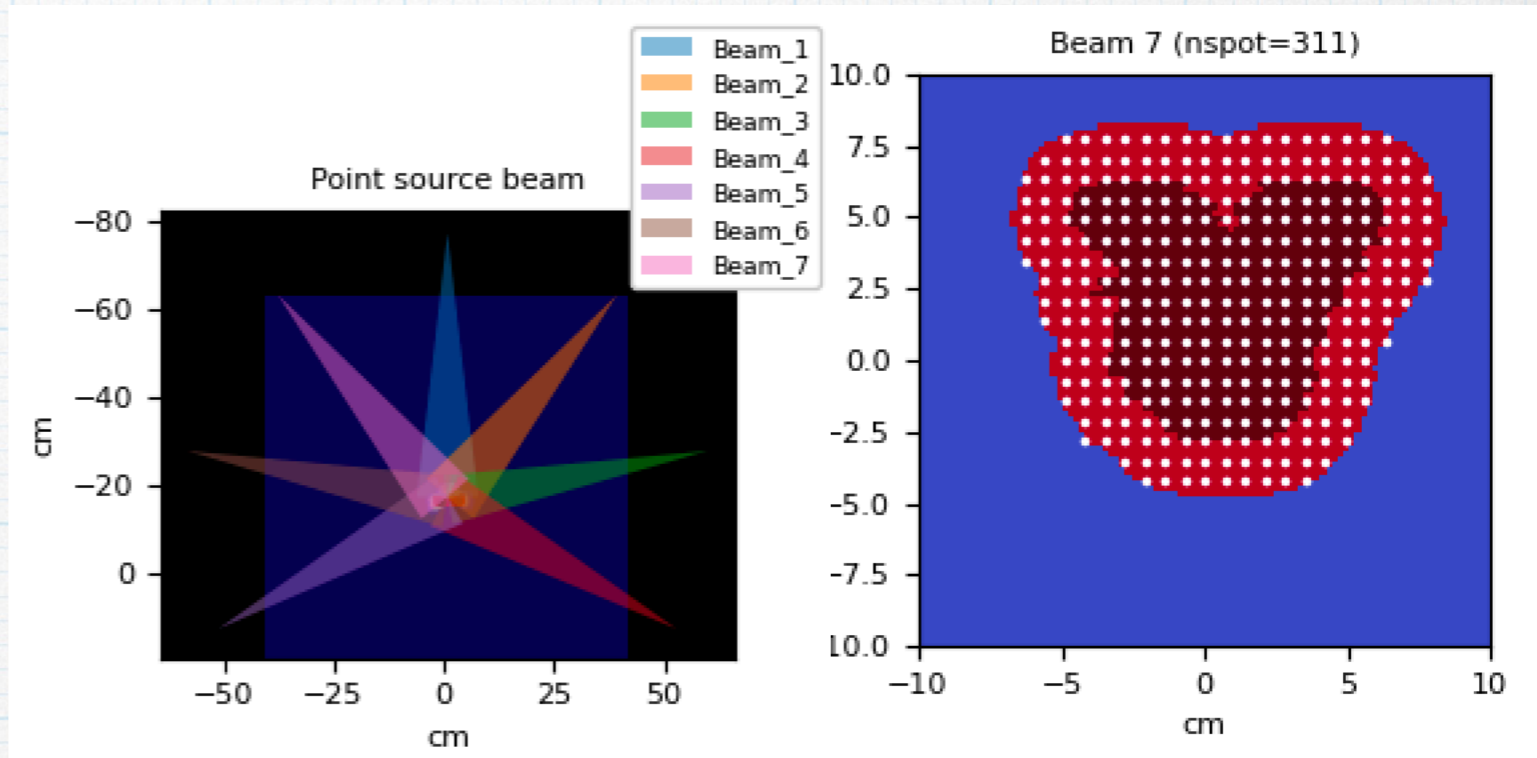
Taking into account the CT images, the beam properties and the 7 fields positions we have built the electrons treatment plan:

Inside the same field the dose is released using an active **scanning approach**.

FLUKA INPUT FILE

- * 7 electron beams;
- * Electron beams properties: $E = 70, 100$ and 130 MeV, Gaussian profile with $\text{FWHM} = 0.5$ cm;
- * Field positions are exactly the same of IMRT ones.

~ 3900 PBs in 7 fields

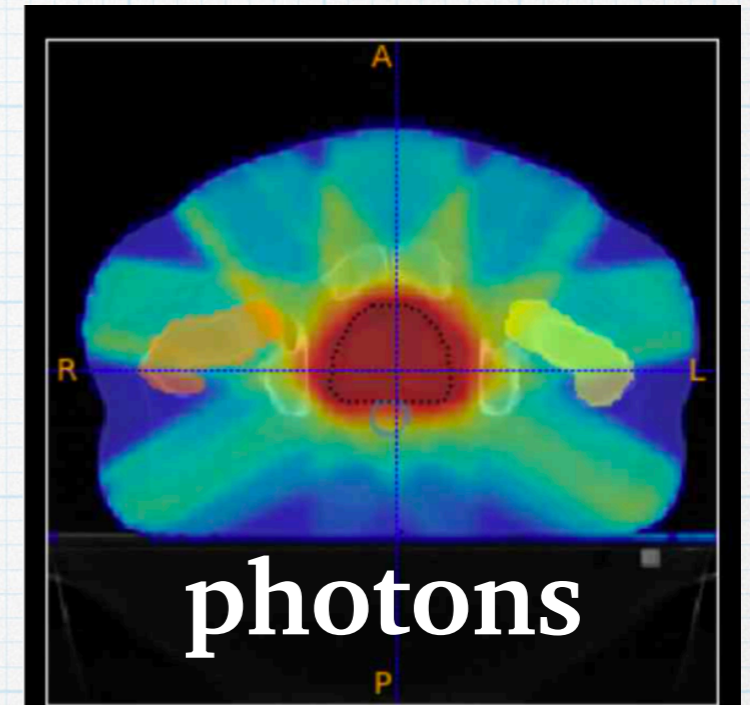


Map Dose optimization

Once the absorbed dose maps have been obtained for each PB in the treatment plan, the fluence of each PB is optimised to ensure the required PTV coverage while sparing the OARs.



The output of the optimisation process is the absorbed dose map used to compute the DVHs and compare with the standard IMRT treatments optimised using the Pinnacle RTP software.

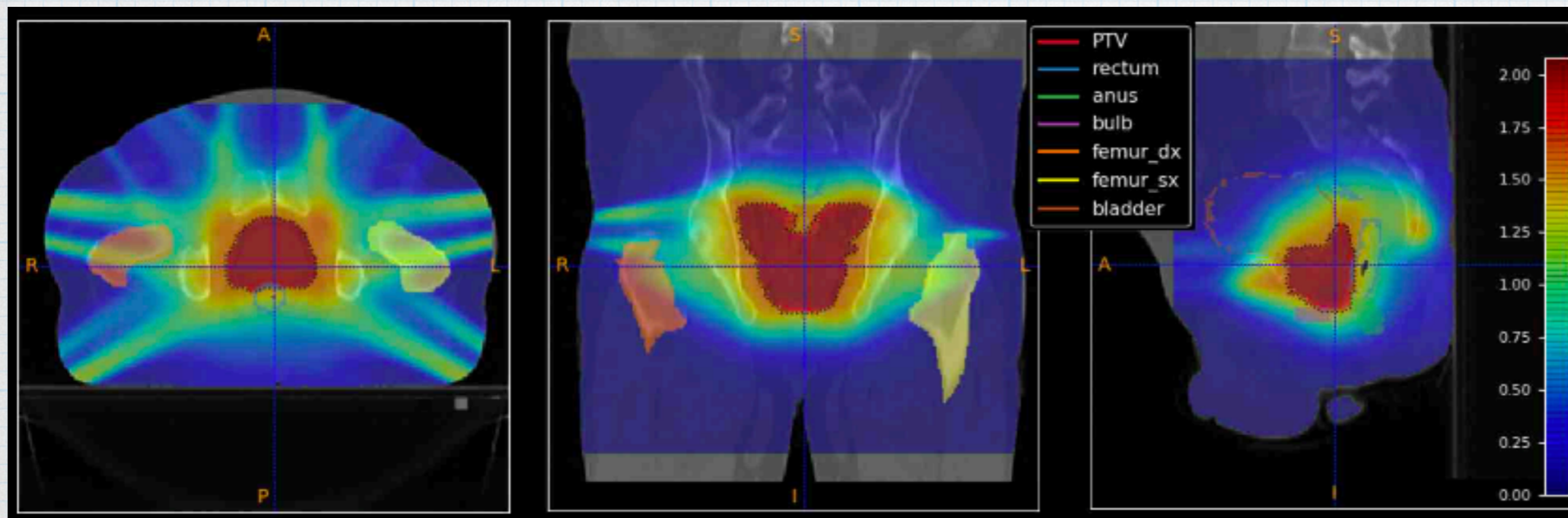
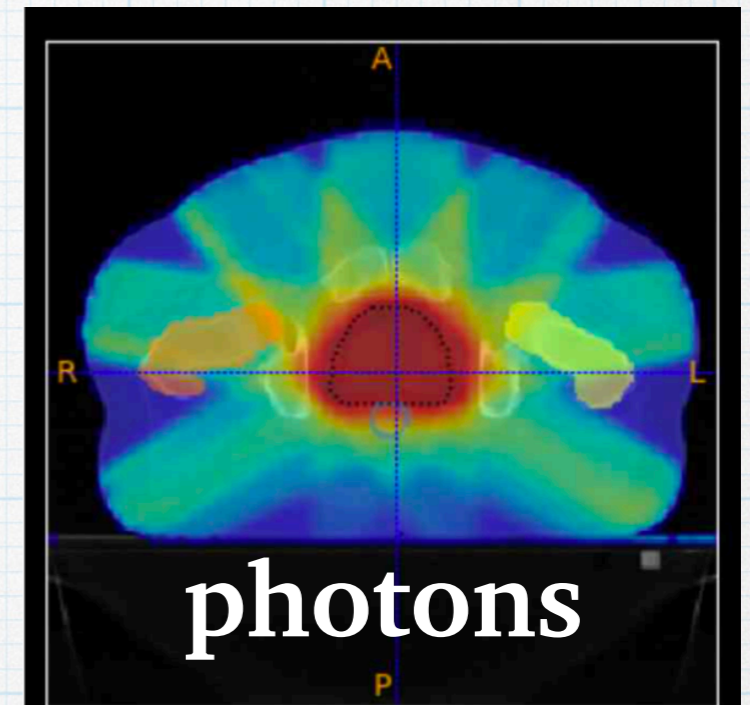


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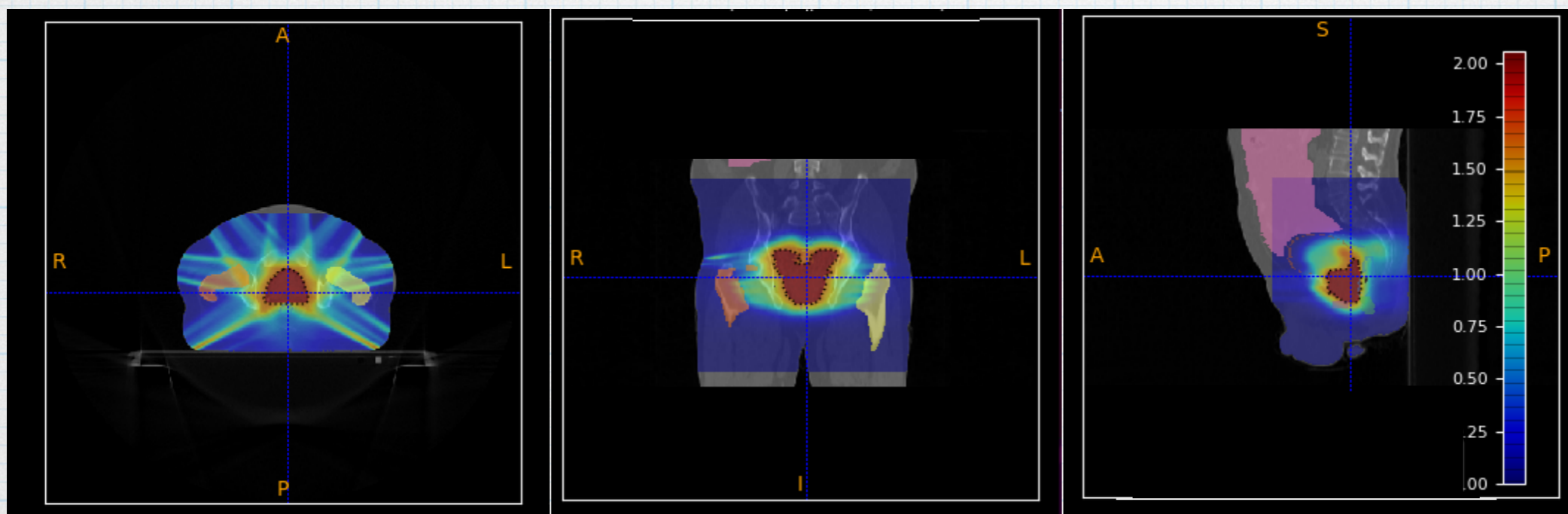
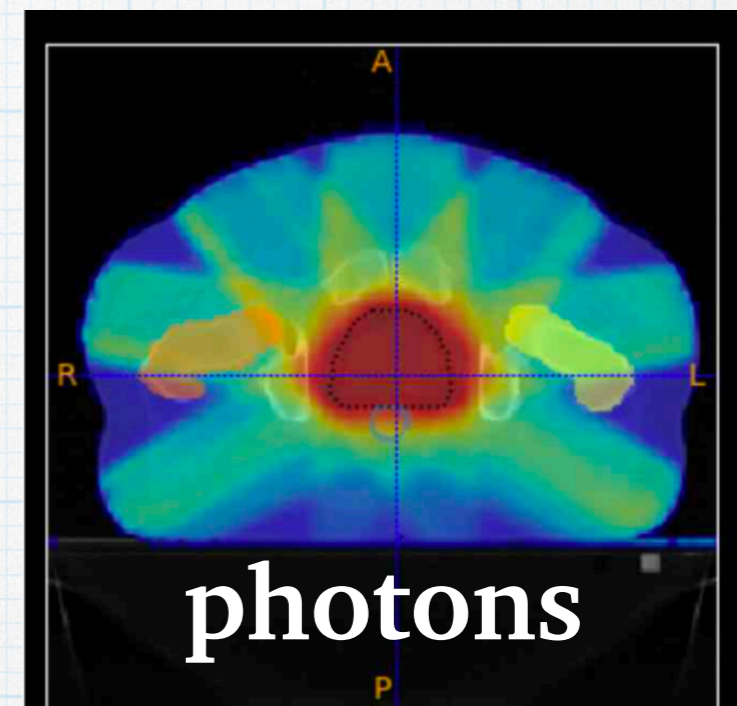
70 MeV

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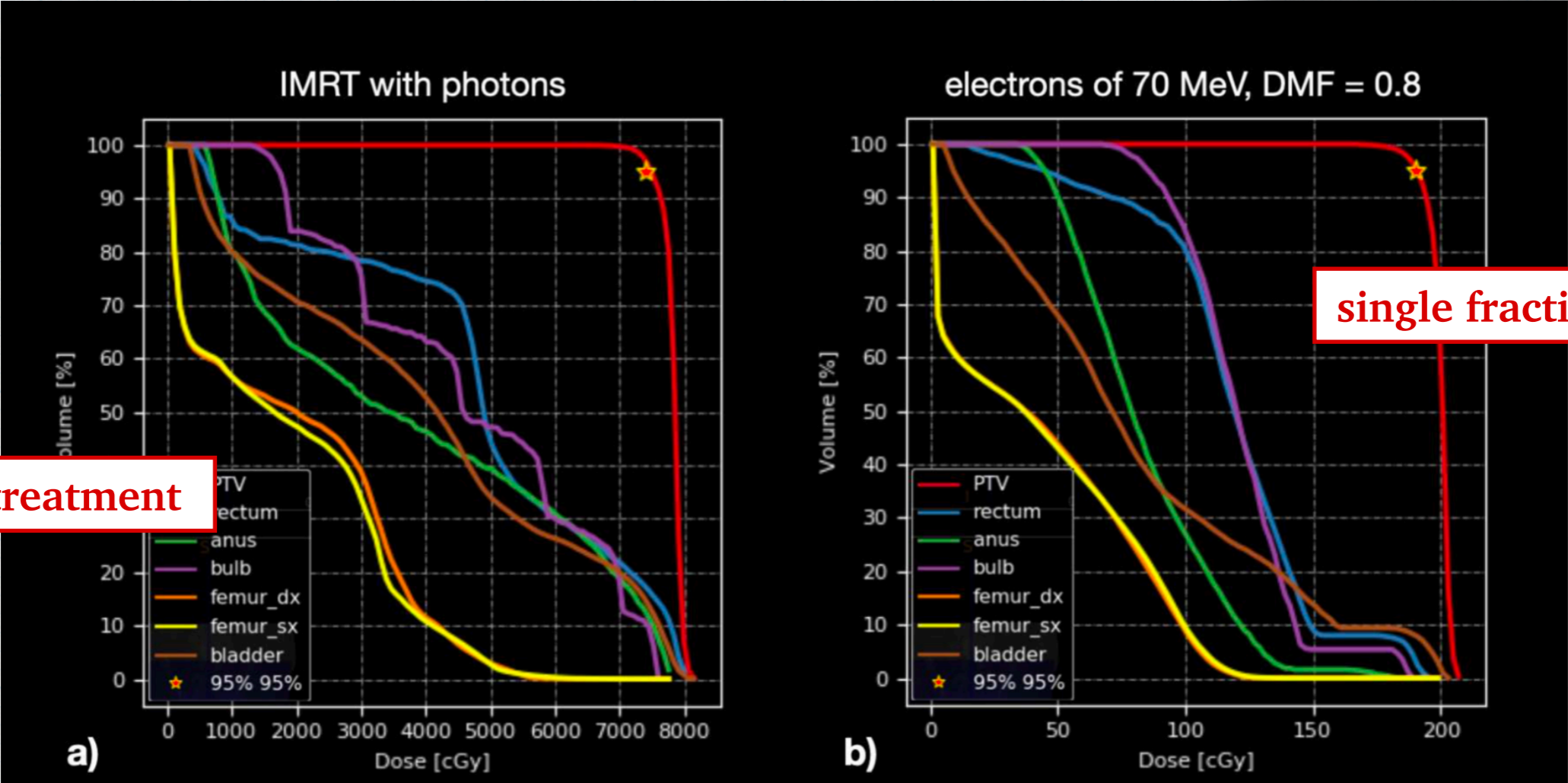


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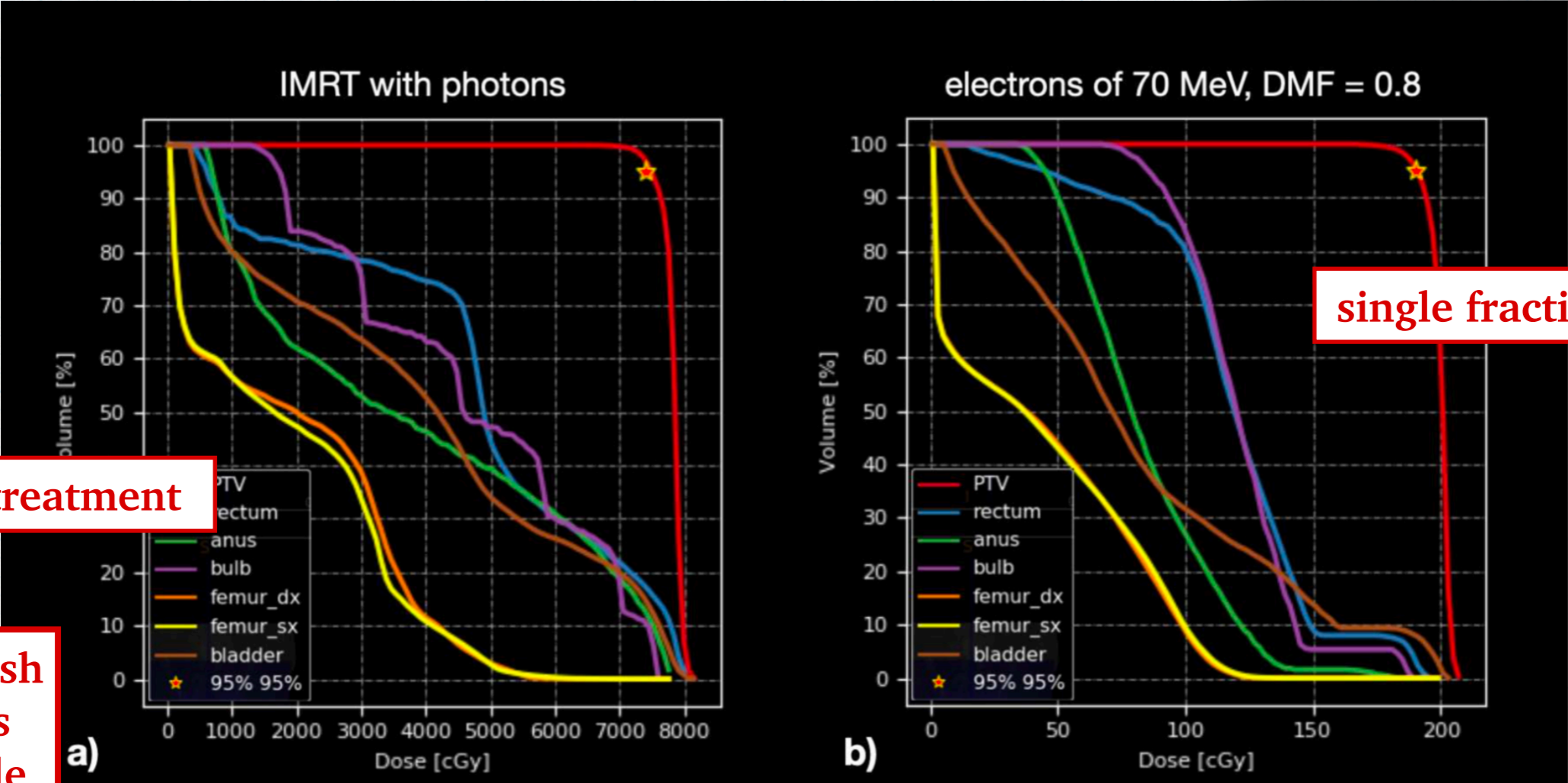
130 MeV

Results: 70 MeV electrons DVH



E = 70 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	$V_{95\%}$ 92 % $V_{105\%}$ 0.3 %	$V_{95\%}$ 96.5 % $V_{105\%}$ 0.4 %	$V_{95\%}$ 99.9 % $V_{105\%}$ - %
Rectum	V_{75} 0.3 % V_{50} 71%	V_{75} 1 % V_{50} 36 %	V_{75} 8 % V_{50} 8 %
Anus	V_{30} 92%	V_{30} 53%	V_{30} 49%
Bulbourethral Glands	\bar{D} 51 Gy	\bar{D} 47 Gy	\bar{D} 47 Gy
Femurs	\bar{D} 18 Gy	\bar{D} 16 Gy	\bar{D} 14 Gy
Bladder	\bar{D} 35 Gy V_{70} 13% V_{65} 18%	\bar{D} 32 Gy V_{70} 9% V_{65} 9%	\bar{D} 37 Gy V_{70} 9% V_{65} 9%

Results: 70 MeV electrons DVH



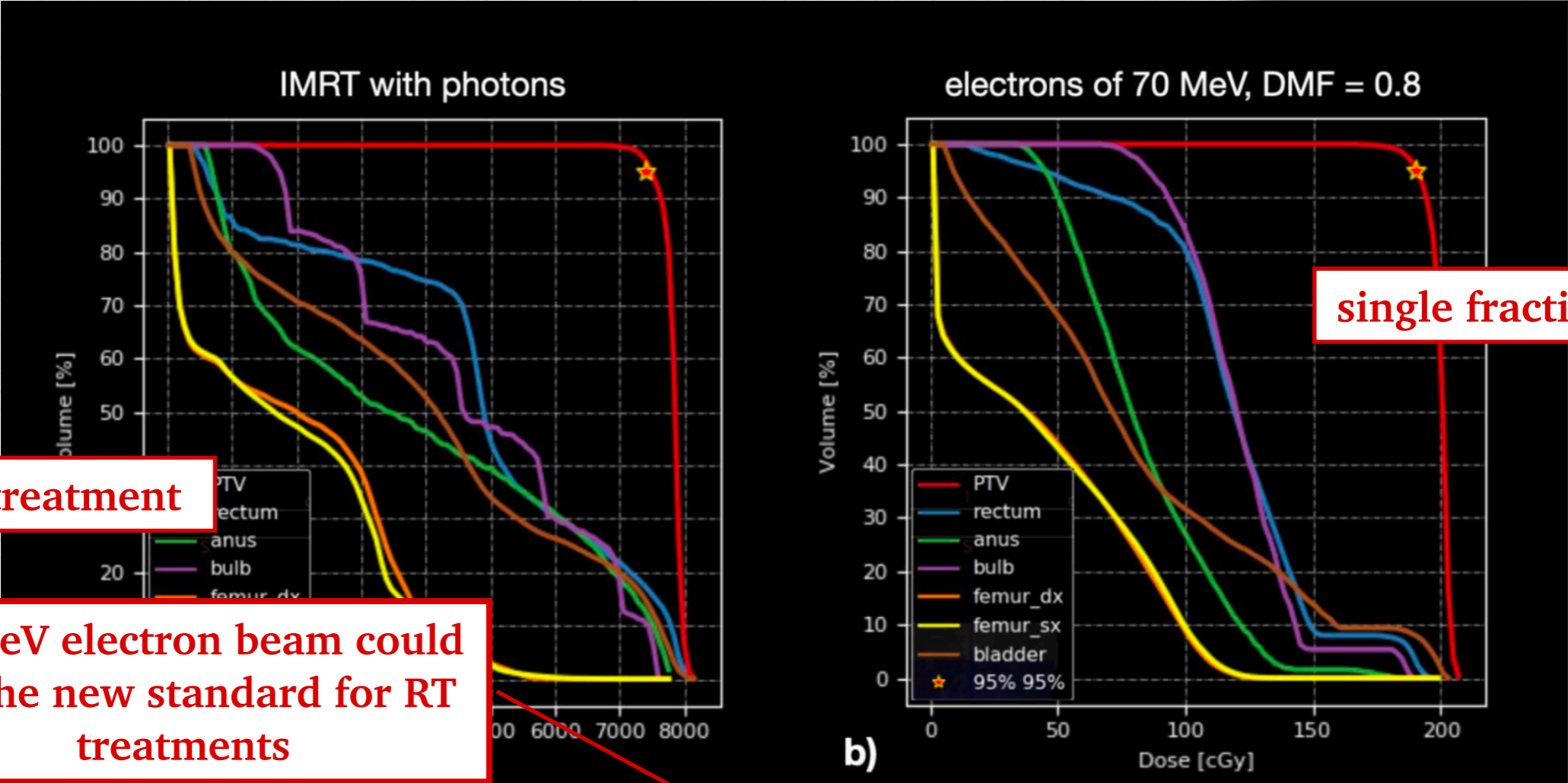
single fraction

All treatment

With no Flash effect, it is not possible to ensure the PTV full coverage.

E = 70 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	V _{95%} 92 % V _{105%} 0.3 %	V _{95%} 96.5 % V _{105%} 0.4 %	V _{95%} 99.9 % V _{105%} - %
Rectum	V ₇₅ 0.3 % V ₅₀ 71%	V ₇₅ 1 % V ₅₀ 36 %	V ₇₅ 8 % V ₅₀ 8 %
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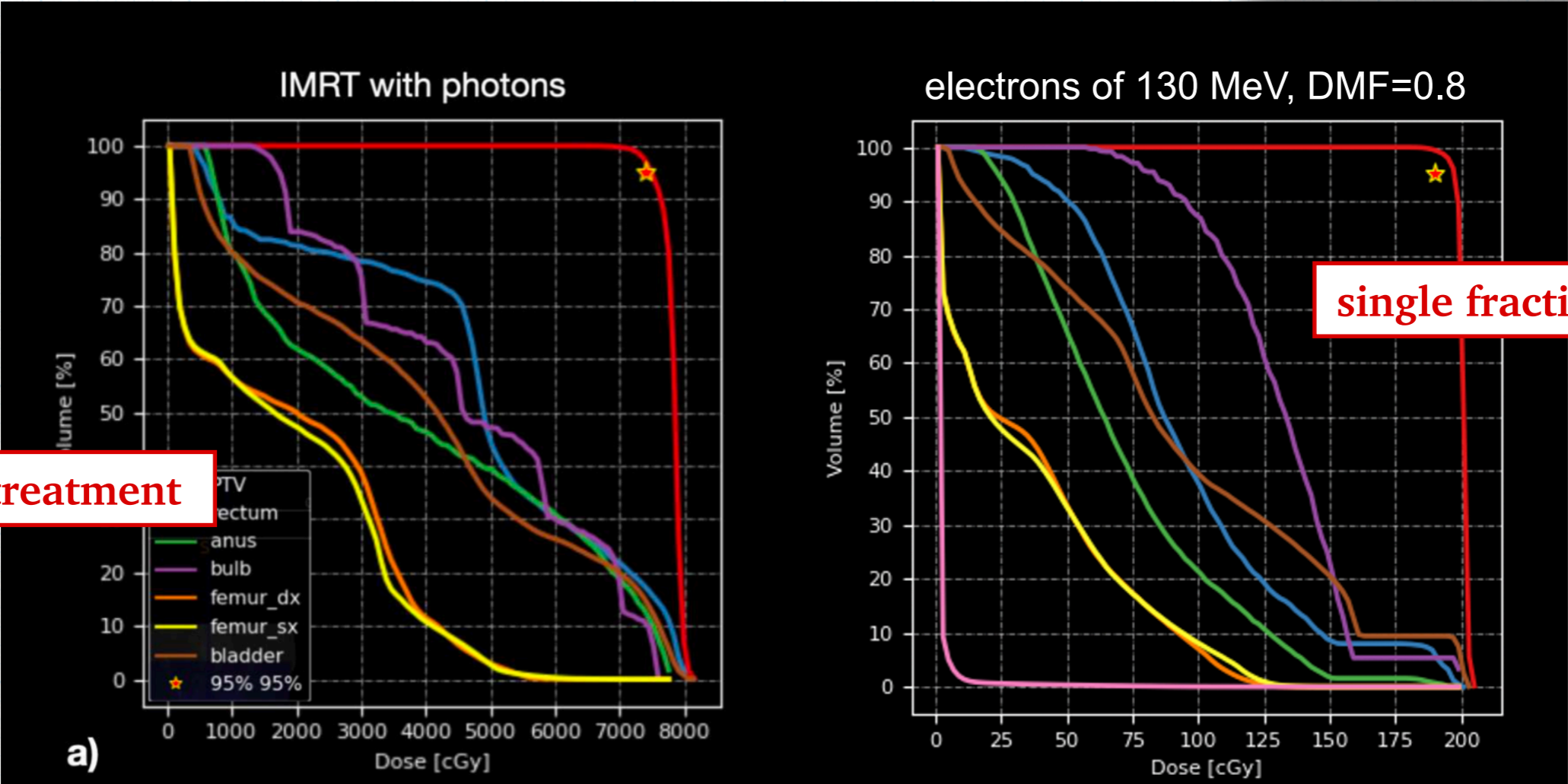
All treatment

70 MeV electron beam could set the new standard for RT treatments

E = 70 MeV	DMF 1	DMF 0.8	DMF 0.6
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there is still a significant dose absorbed by the anus, at higher energies both the OARs sparing and the PTV coverage is ensured.

Results: 130 MeV electrons DVH



E = 130 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	$V_{95\%}$ 95 % $V_{105\%}$ -	$V_{95\%}$ 99.6 % $V_{105\%}$ 0.15 %	$V_{95\%}$ 99.9 % $V_{105\%}$ 0.74 %
Rectum	V_{75} 1% V_{50} 27 %	V_{75} 4 % V_{50} 17 %	V_{75} 8 % V_{50} 8 %
Anus	V_{30} 36%	V_{30} 37%	V_{30} 39%
Bulbourethral Glands	\bar{D} 47 Gy \bar{D} 14 Gy	\bar{D} 50 Gy \bar{D} 14 Gy	\bar{D} 47 Gy \bar{D} 14 Gy
	Gy V_{70} 17% V_{65} 20%	\bar{D} 36 Gy V_{70} 19% V_{65} 10%	\bar{D} 33 Gy V_{70} 10% V_{65} 10%

130 MeV electrons treatment seems, also with DMF=1, better than the IMRT one

Conclusions:

Without the FLASH effect the energy needed to deliver treatments that are of comparable efficacy with respect to IMRT or VMAT must be of the order of or greater than 100 MeV. However, if the FLASH effect is taken into account, lower energies can be exploited opening a completely new landscape for the clinical implementation of VHEE treatments.

E = 130 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	V _{95%} 95 % V _{105%} -	V _{95%} 99.6 % V _{105%} 0.15 %	V _{95%} 99.9 % V _{105%} 0.74 %
Rectum	V ₇₅ 1% V ₅₀ 27 %	V ₇₅ 4 % V ₅₀ 17 %	V ₇₅ 8 % V ₅₀ 8 %
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Bulbourethral Glands	\bar{D} 47 Gy	\bar{D} 50 Gy	\bar{D} 47 Gy
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Rectum	V ₇₅ 0.3% V ₅₀ 35 %	V ₇₅ 4 % V ₅₀ 21 %	V ₇₅ 8 % V ₅₀ 8 %
Anus	V ₃₀ 58%	V ₃₀ 55%	V ₃₀ 50%
Bulbourethral Glands	\bar{D} 57 Gy	\bar{D} 55 Gy	\bar{D} 47 Gy
Femurs	\bar{D} 18 Gy	\bar{D} 17 Gy	\bar{D} 15 Gy
Bladder	\bar{D} 43 Gy V ₇₀ 20% V ₆₅ 23%	\bar{D} 41 Gy V ₇₀ 9% V ₆₅ 9%	\bar{D} 35 Gy V ₇₀ 9% V ₆₅ 9%
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The values shown in red are the ones that do not satisfy the requirements

The results demonstrate that FLASH therapy with VHEE beams of 70-130 MeV could represent a valid alternative to standard RT allowing a better sparing of the healthy tissues surrounding the tumour, in the framework of an affordable technological development.

Conclusions:

Without the FLASH effect the energy needed to deliver treatments that are of comparable efficacy with respect to IMRT or VMAT must be of the order of or greater than 100 MeV. However, if the FLASH effect is taken into account, lower energies can be exploited opening a completely new landscape for the clinical implementation of VHEE treatments.

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Target volume	V _{95%} 97 % V _{105%} - %	V _{95%} 99.6 % V _{105%} 0.1 %	V _{95%} 99.9 % V _{105%} 0.9 %
Rectum	V ₇₅ 0.3% V ₅₀ 35 %	V ₇₅ 4 % V ₅₀ 21 %	V ₇₅ 8 % V ₅₀ 8 %
Anus	V ₃₀ 58%	V ₃₀ 55%	V ₃₀ 50%
Bulbourethral Glands	\bar{D} 57 Gy	\bar{D} 55 Gy	\bar{D} 47 Gy
Femurs	\bar{D} 18 Gy	\bar{D} 17 Gy	\bar{D} 15 Gy
Bladder	\bar{D} 43 Gy V ₇₀ 20% V ₆₅ 23%	\bar{D} 41 Gy V ₇₀ 9% V ₆₅ 9%	\bar{D} 35 Gy V ₇₀ 9% V ₆₅ 9%
E = 70 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	V _{95%} 92 % V _{105%} 0.3 %	V _{95%} 96.5 % V _{105%} 0.4 %	V _{95%} 99.9 % V _{105%} - %
Rectum	V ₇₅ 0.3 % V ₅₀ 71%	V ₇₅ 1 % V ₅₀ 36 %	V ₇₅ 8 % V ₅₀ 8 %
Anus	V ₃₀ 92%	V ₃₀ 53%	V ₃₀ 49%
Bulbourethral Glands	\bar{D} 51 Gy	\bar{D} 47 Gy	\bar{D} 47 Gy
Femurs	\bar{D} 18 Gy	\bar{D} 16 Gy	\bar{D} 14 Gy
Bladder	\bar{D} 35 Gy V ₇₀ 13% V ₆₅ 18%	\bar{D} 32 Gy V ₇₀ 9% V ₆₅ 9%	\bar{D} 37 Gy V ₇₀ 9% V ₆₅ 9%

The approach that we have implemented is highly “conservative”: an irradiation geometry different from the IMRT one should be implemented as also the possibility to have different energies in the same treatment...

WE CAN DO BETTER

The results demonstrate that FLASH therapy with VHEE beams of 70-130 MeV could represent a valid alternative to standard RT allowing a better sparing of the healthy tissues surrounding the tumour, in the framework of an affordable technological development.

Feasibility study of a prostate cancer FLASH therapy treatment with electrons of high energy

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We are working on other projects....

1. We are porting the FRED-EM code to GPU (G. Franciosini, G. Traini, A. Trigilio);
2. We are collaborating with S.I.T. for low energy FLASH IORT (G. Franciosini, M. Palma);
3. We are investigating other possible tumors that has to be treated with flash therapy: other prostates and H&N (D. Rubeca, P. De Maria);
4. We are starting a new collaboration with S.I.T. and Israeli research group to expand our studies concern the FLASH therapy imagining also comparison with protons (TIFPA)