Treatment planning for FLASH (with protons)

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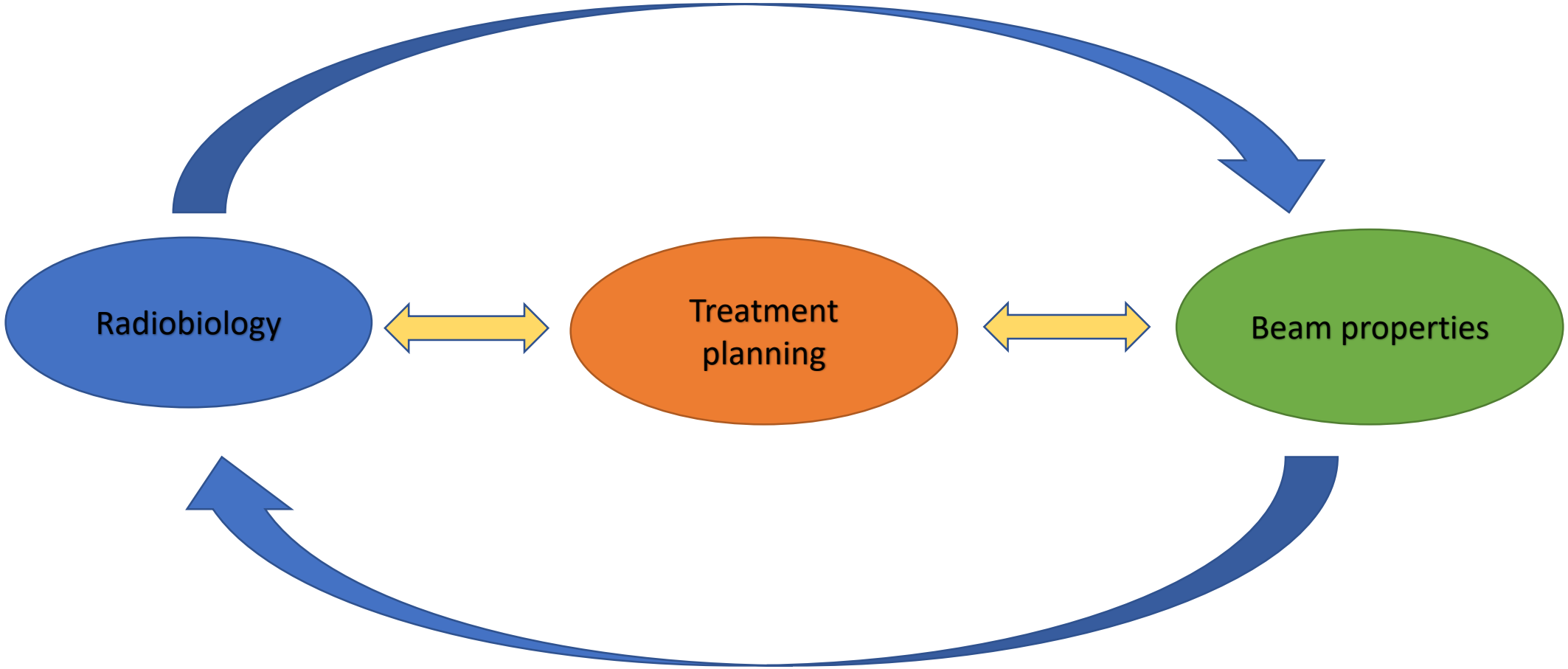
Still plenty of questions about FLASH

Among the most important:

-What are the key biological mechanisms behind FLASH?

-Can we use existing radiotherapy devices or do we need new equipment?

-Is there a sufficient overlap between the conditions needed for FLASH to happen and current clinical protocols in RT?

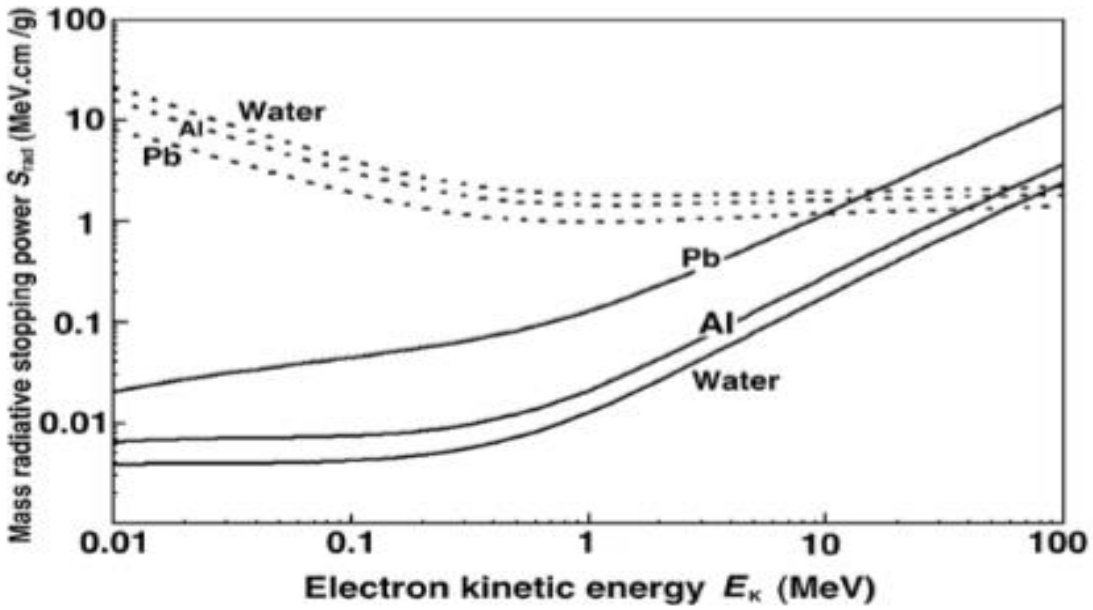


Treatment planning enters the picture as soon as *what we would like to do* based on radiobiology does not coincide with *what we can do* because of external constraints (physics, technology, patient anatomy, etc.)

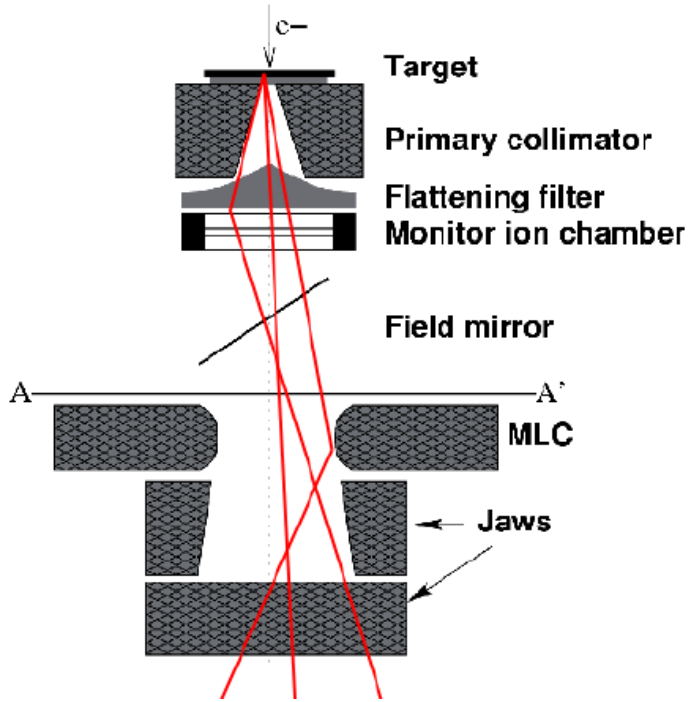
Why nobody talks about FLASH with X-Rays?

Max dose rate with current FFF linacs:

Roughly 20Gy/min
(*roughly* two orders of magnitude lower)



Mass radiative stopping power = solid line
Mass collision stopping power = dotted line



FLASH not even attempted with X-Rays with current equipment
(which is used to treat the vast majority of RT patients)

What about 6-20 MeV electrons then?

Good news

1a : Day 0

1b : 3 weeks

1c : 5 months

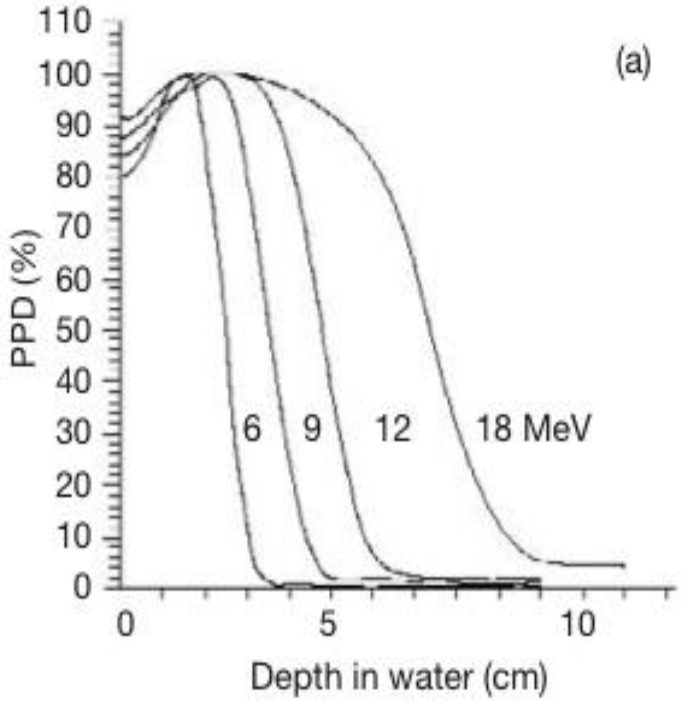
5.6 MeV electrons
15Gy in 90ms (!)

Bourhis
R&O 2020

No (complex) treatment planning needed

Less good news

Lower energy electrons are not well suited for deep seated lesions



Challenges and opportunities of current proton therapy systems *vis à vis* FLASH

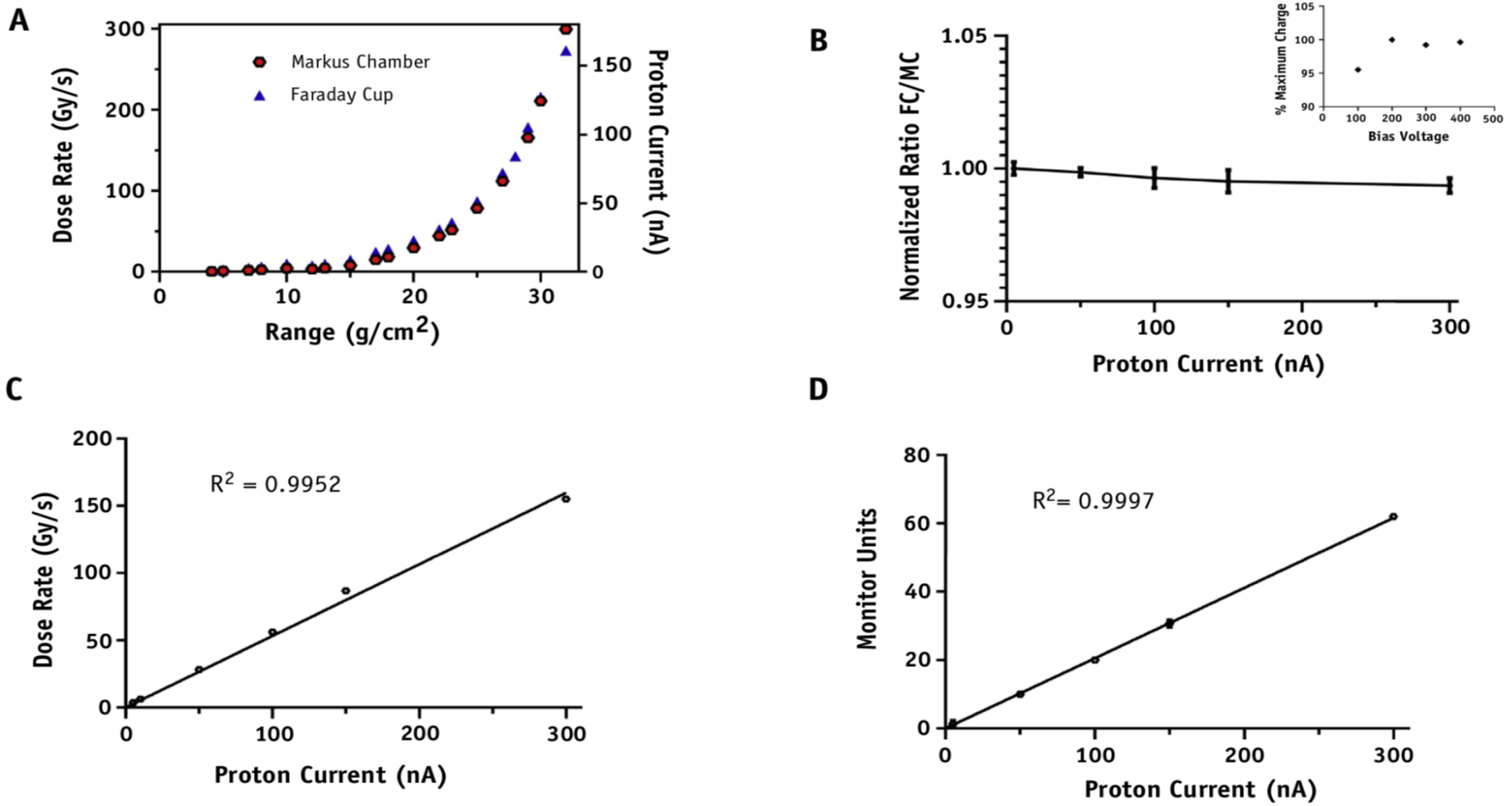
$$\dot{D} = \frac{i_p}{A}\frac{S}{\rho}\quad \frac{\mathrm{Gy}}{\mathrm{s}}$$

i_p= beam current in nA **at isocenter**
A= transversal area in cm^2
S/ρ= Mass Stopping Power in $MeV*cm^2/g$

With values representative of current practice
(e.g. i_p=2nA, A=25 cm^2 and S/ρ=5 $MeV*cm^2/g$)
Doserate=0.4 Gy/s

So the question becomes:
Can we increase i_p by roughly 2 orders of magnitude?

First order answer: yes we can!

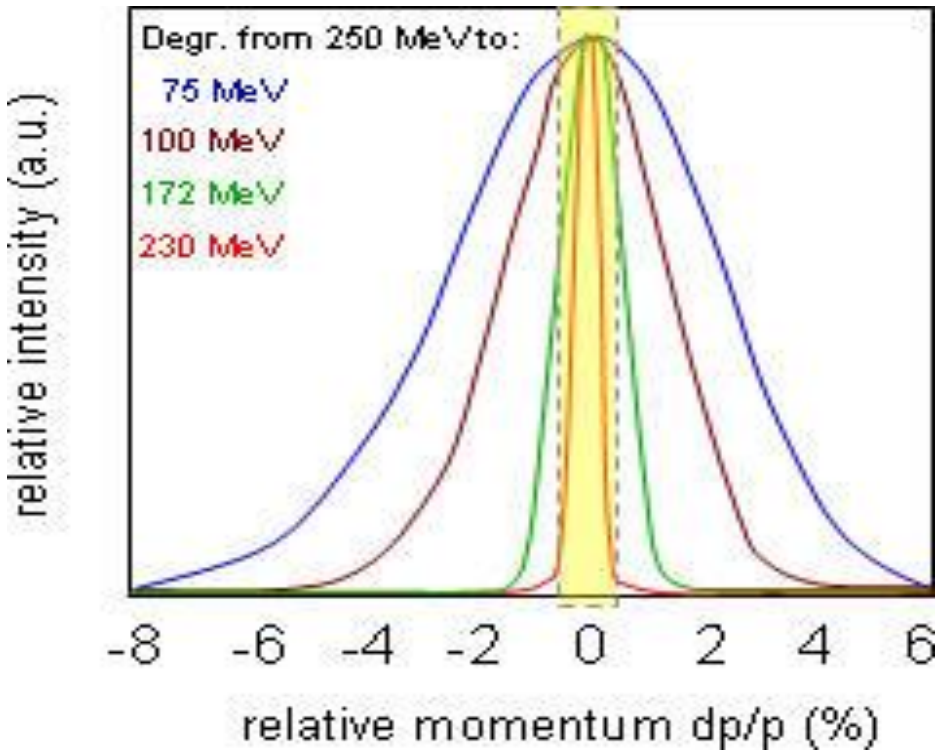


Diffenderfer 2020

But then…

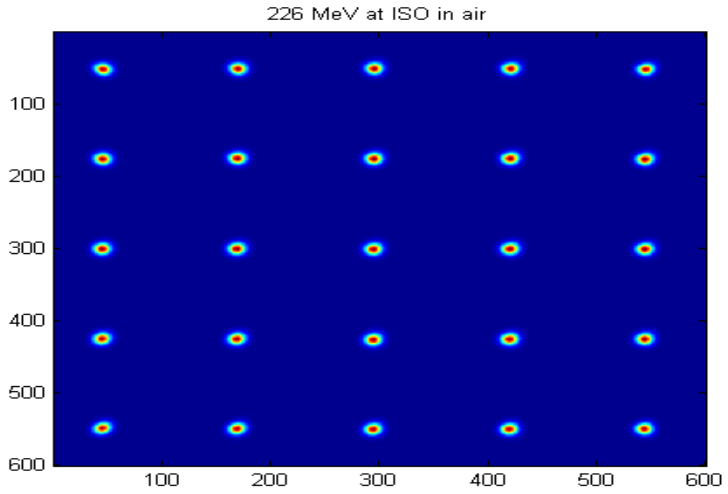
We can only use the highest energies

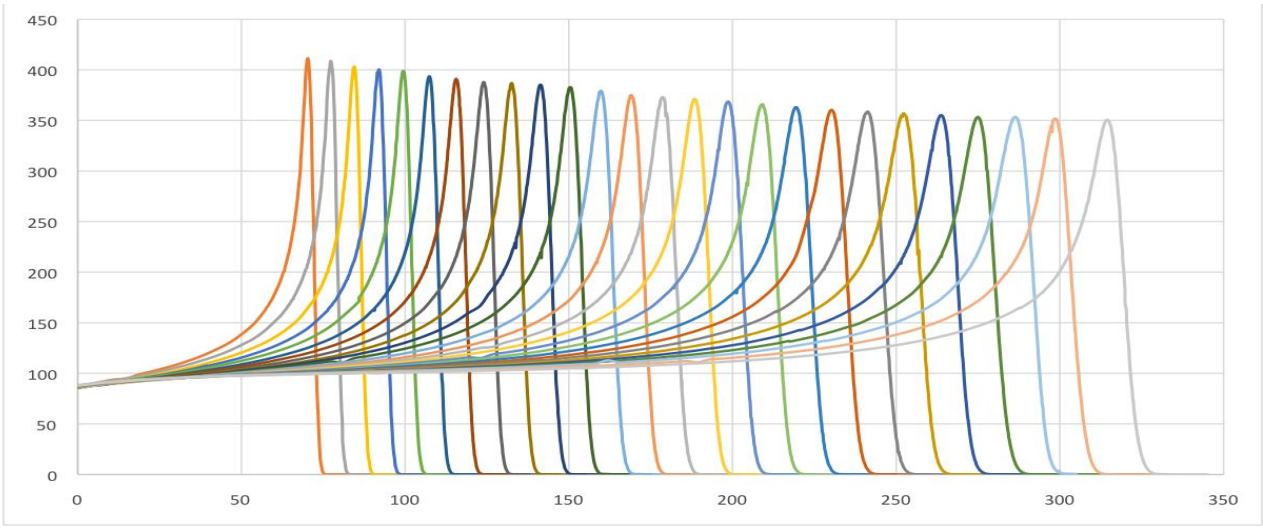
The lower the energy the higher the losses in the energy selection system



Schippers 2012

.. and we better use a single energy



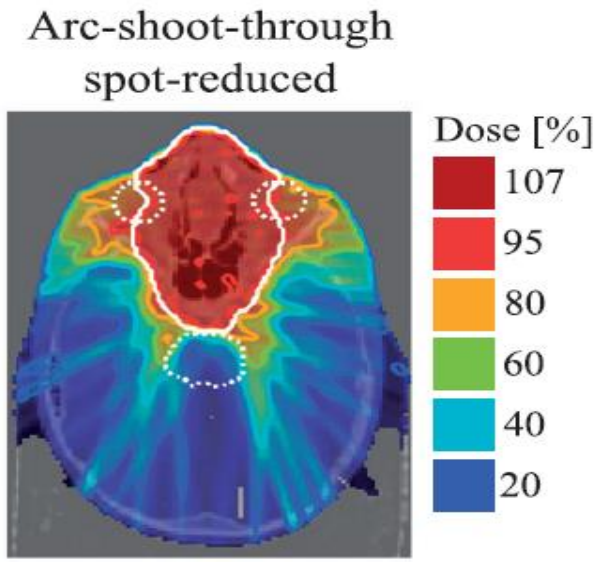


dead time between spots in the same energy layer: ≅ms

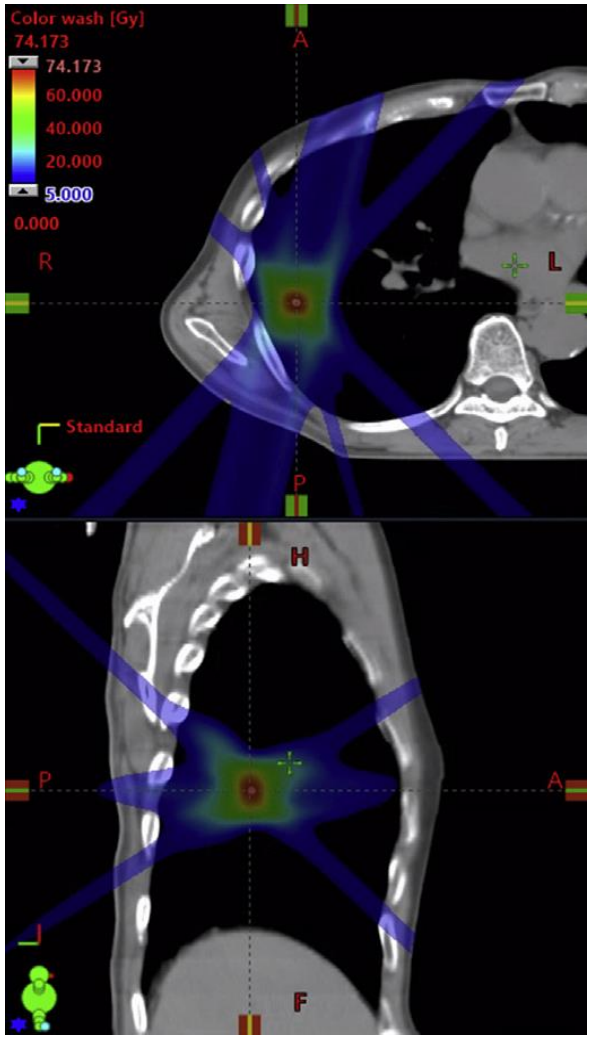
dead time between neighboring energy layers
In most PT centers: 0.5-2s

FLASH is incompatible with most of what we are currently doing in protontherapy

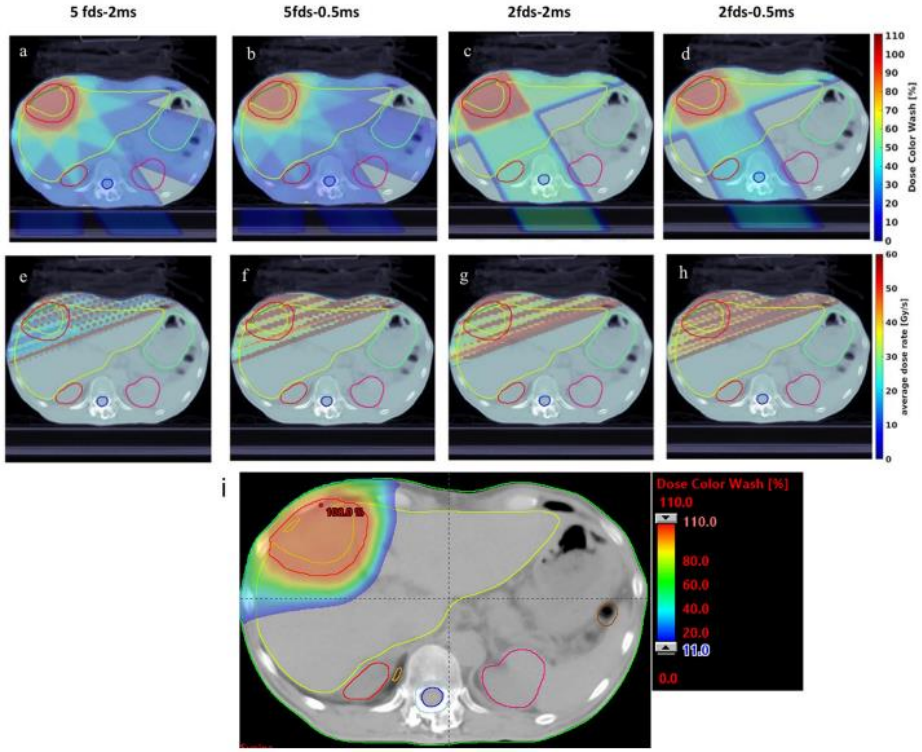
A way out /1 : proton “shoot through” beams



Van de Water Acta 2019

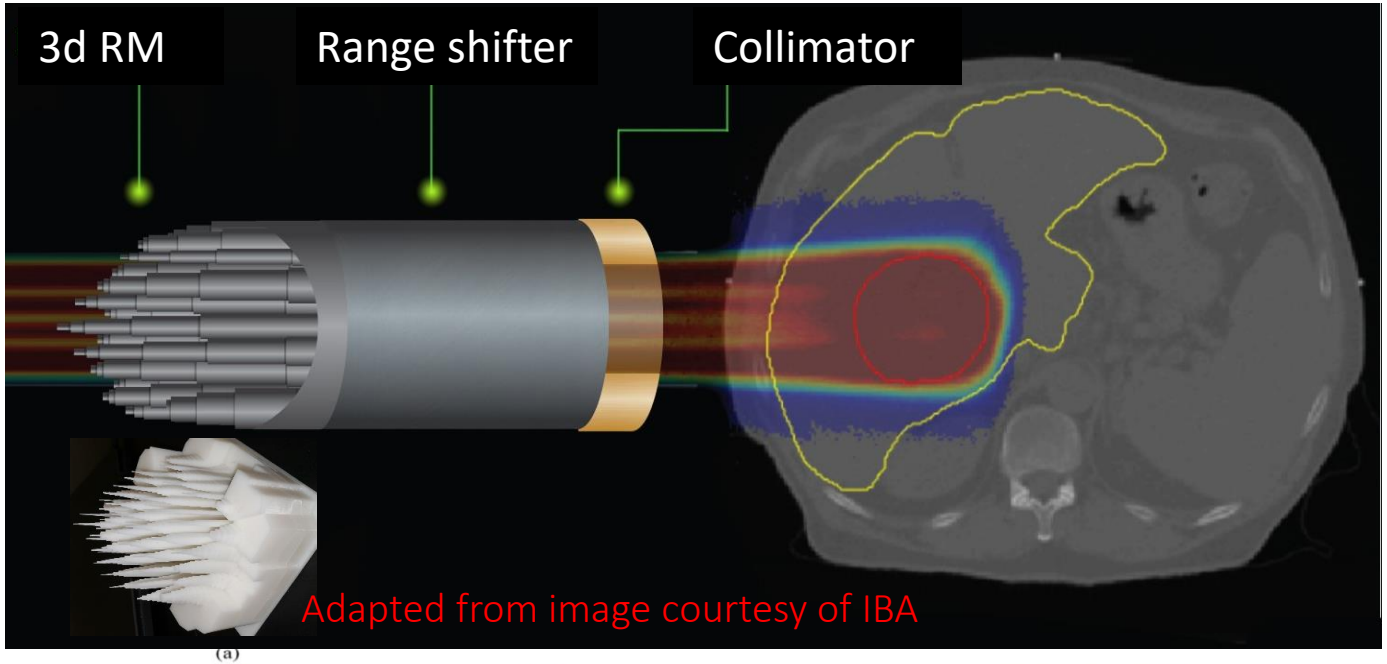


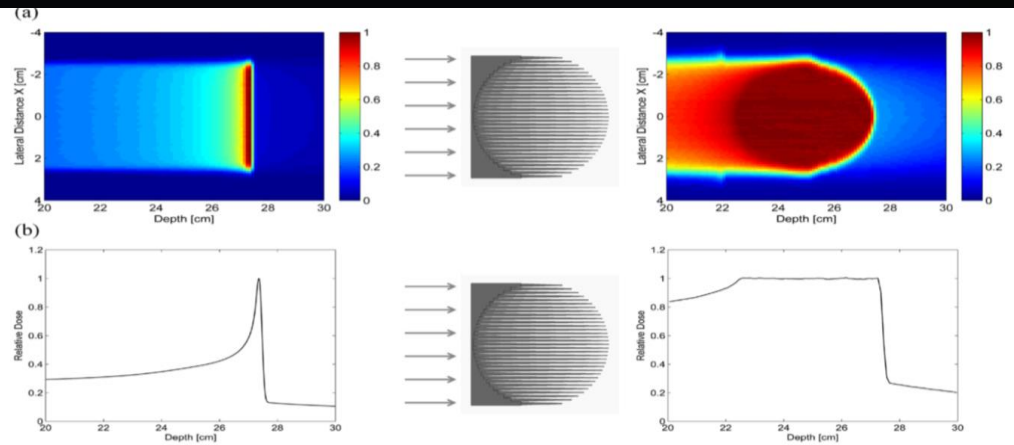
Van Marlen IJROBP 2020



Wei Frontiers 2022

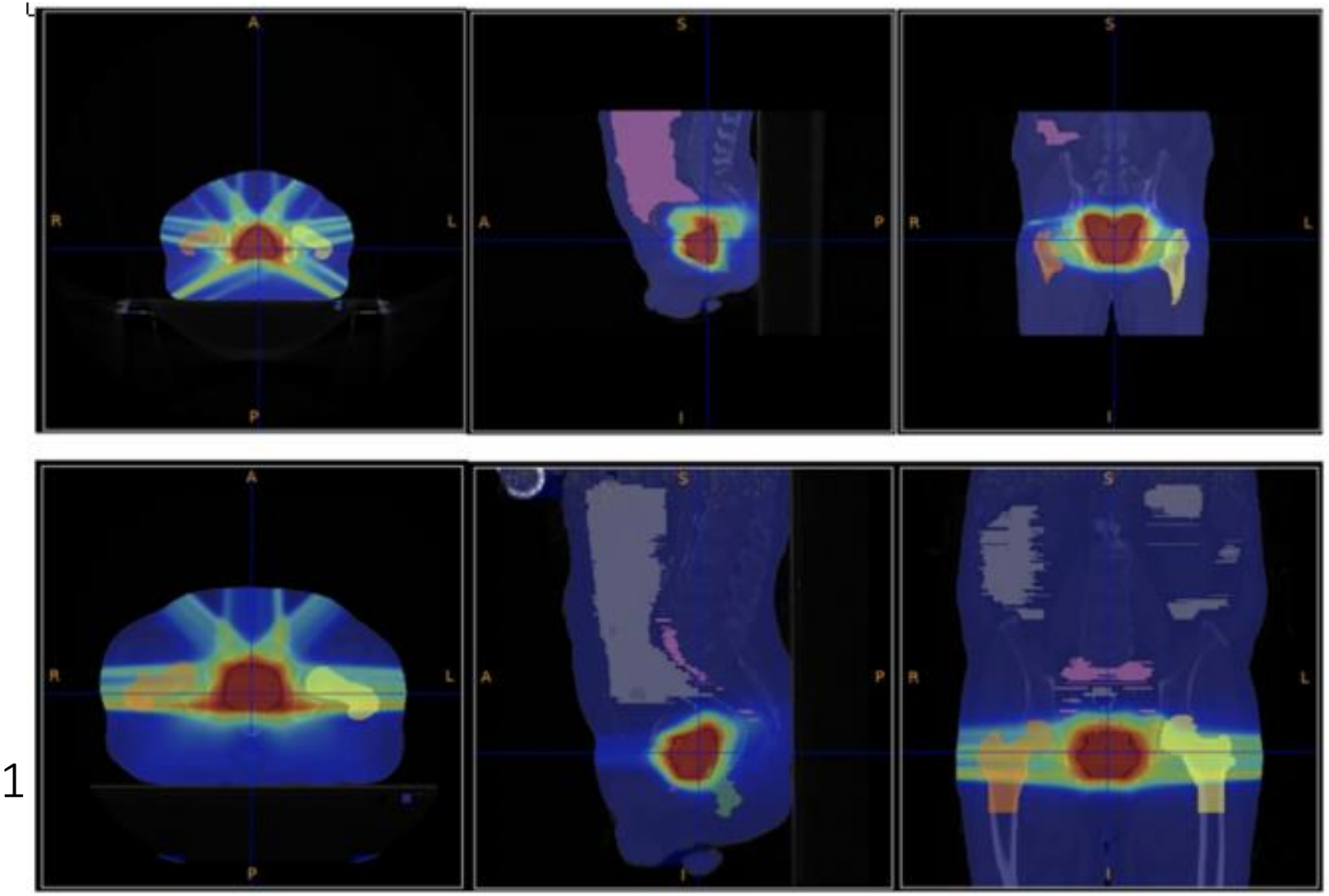
A way out /2 : single energy protons + 3D range modulator + range shifter + apertures





Simeonov 2017

A way out /3 : forget about protons. VHEE is the new cool

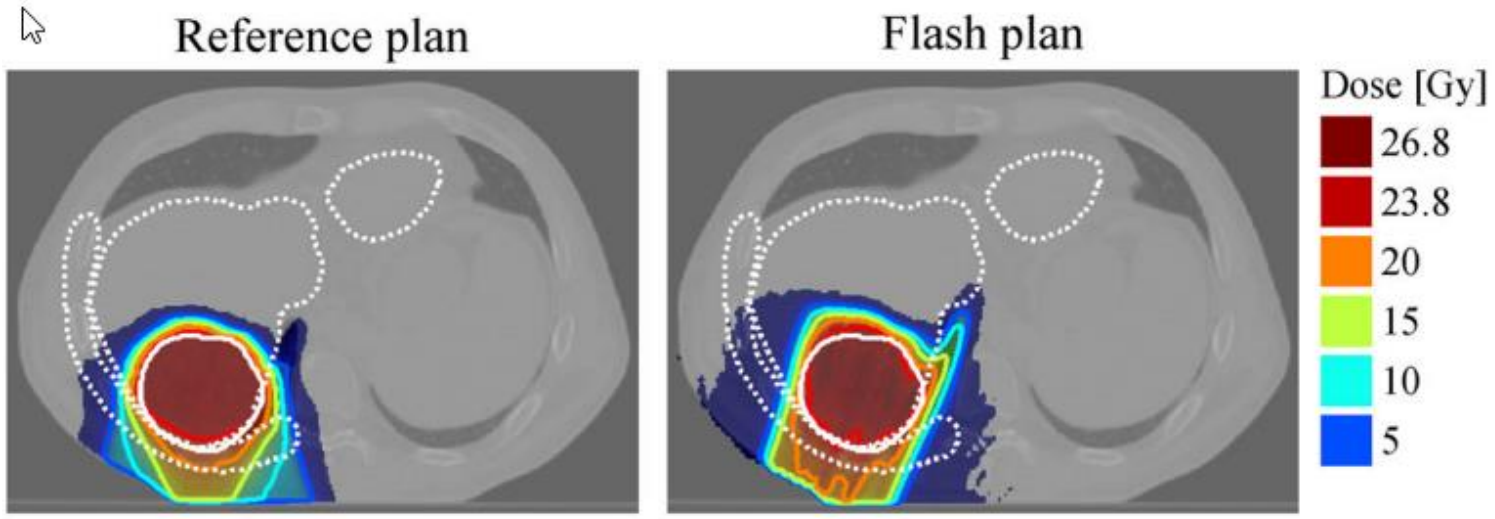


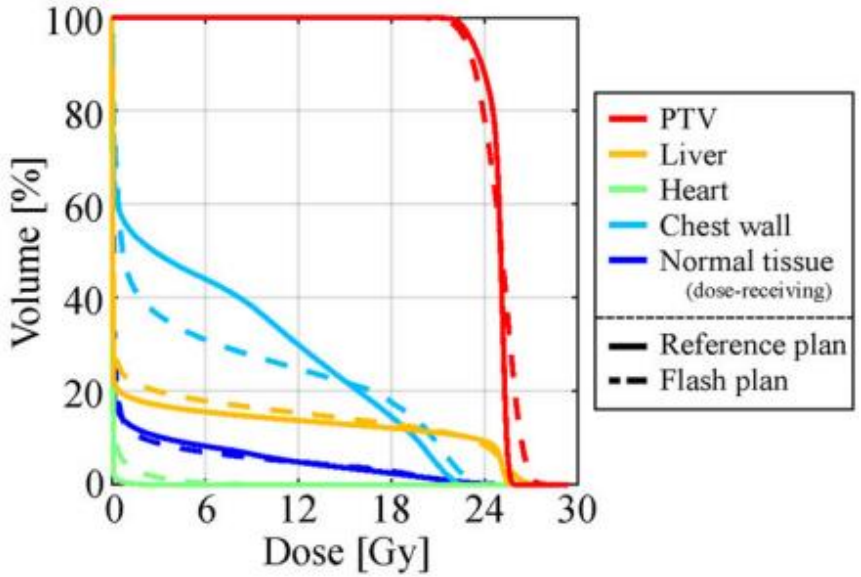
Sarti 2021

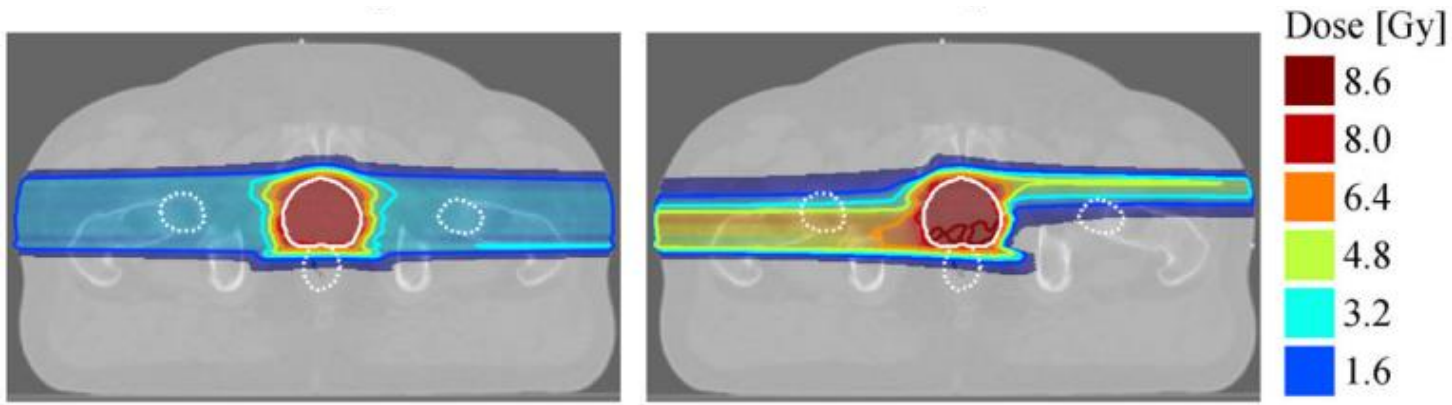
Even if this were the end of the story,
Quite some work is needed, as 2 of the three “ways out” can not be planned with current TPSs

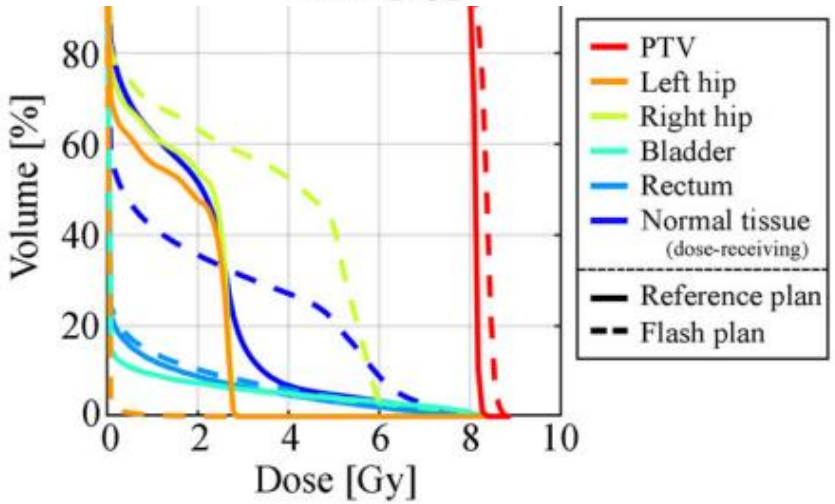
But this is not the end of the story.
Once we have hypothesized new planning&delivery techniques, we need **more** treatment planning to address additional questions:

Are new dose distributions competitive vs the current standard?









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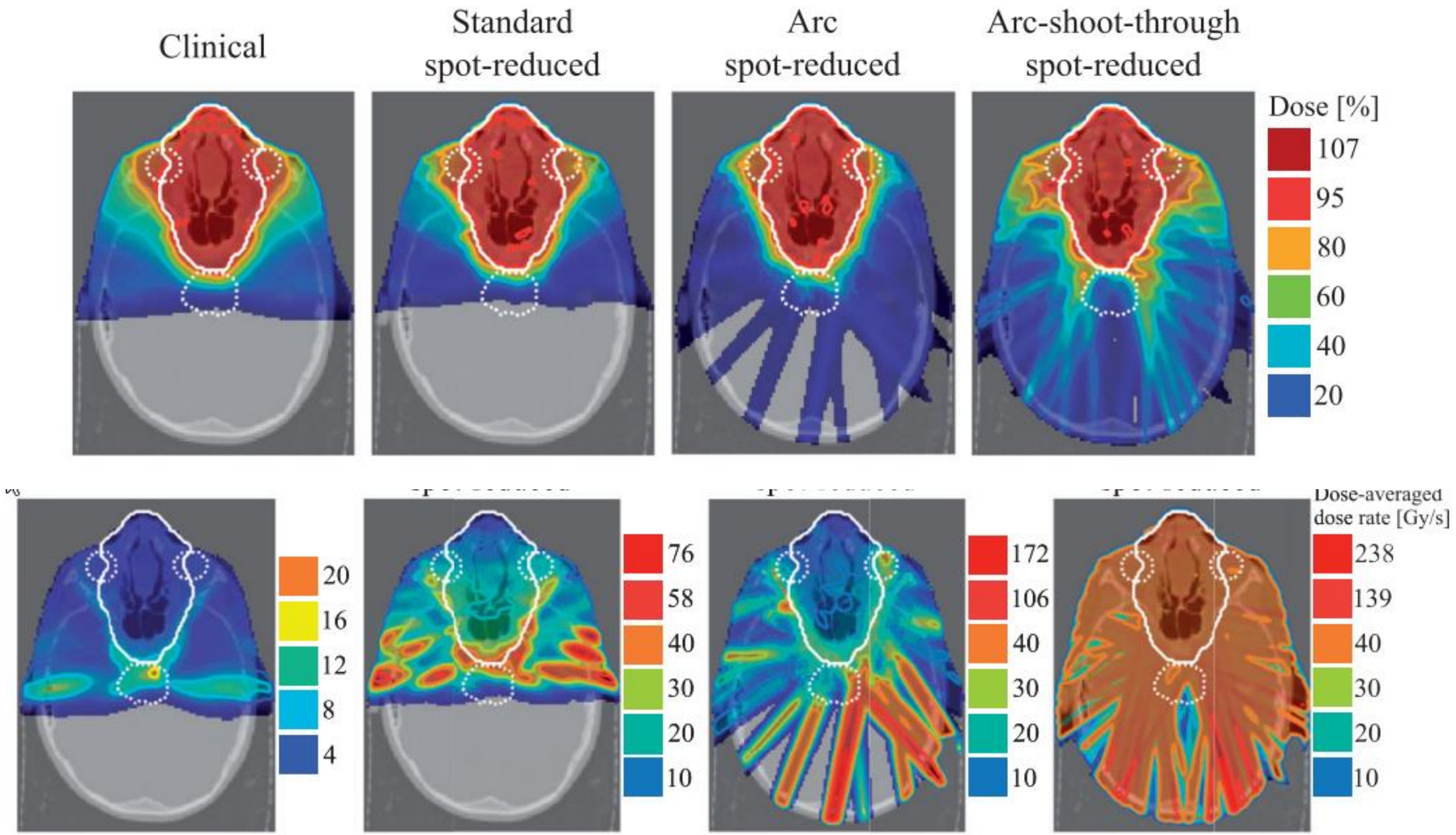
Better dose rate but worse dose distribution: what is the right compromise?



Van de Water 2019

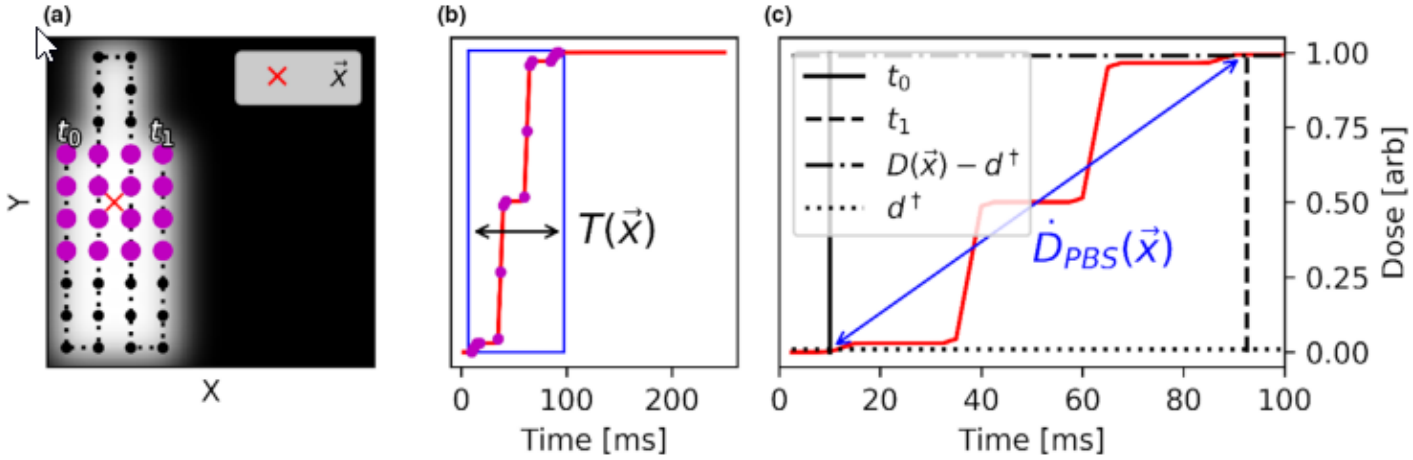
And can we agree on a definition of dose rate?

$$DADR_i = \sum_{j=1}^{n} \frac{(d_{ij}w_j)(d_{ij}BI_j)}{\sum_{j=1}^{n} d_{ij}w_j},$$

Van de Water 2019

$$\dot{D}_{\mathrm{PBS}}\left(\vec{x}\right) = \frac{D\left(\vec{x}\right) - 2d^{\dagger}}{T\left(\vec{x}\right)}$$

Folkerts 2021

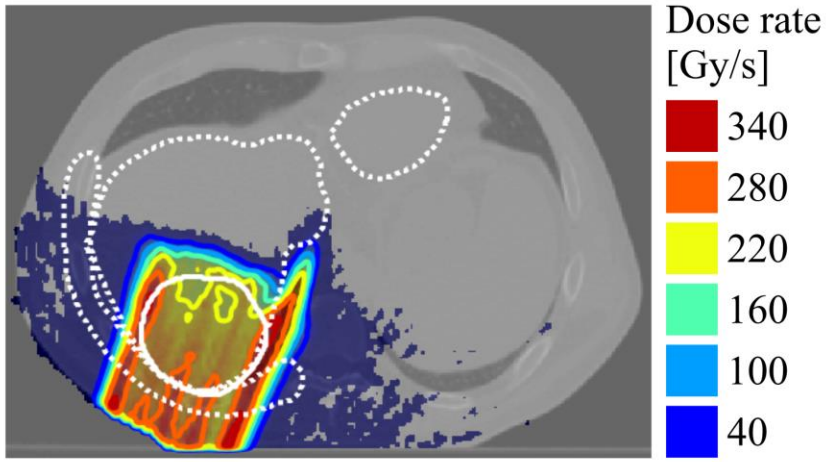


Ultimately, the definition of FLASH dose rate will come from radiobiology, not technology.
We are not there yet, so treatment planning should provide tools to explore different hypotheses.

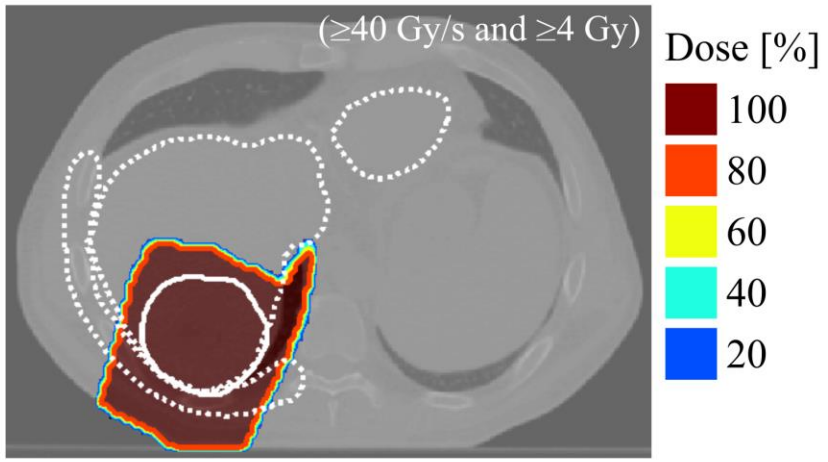
Impact of dose rate definition on the FLASH effect.

Dose-averaged dose rate

Dose rate



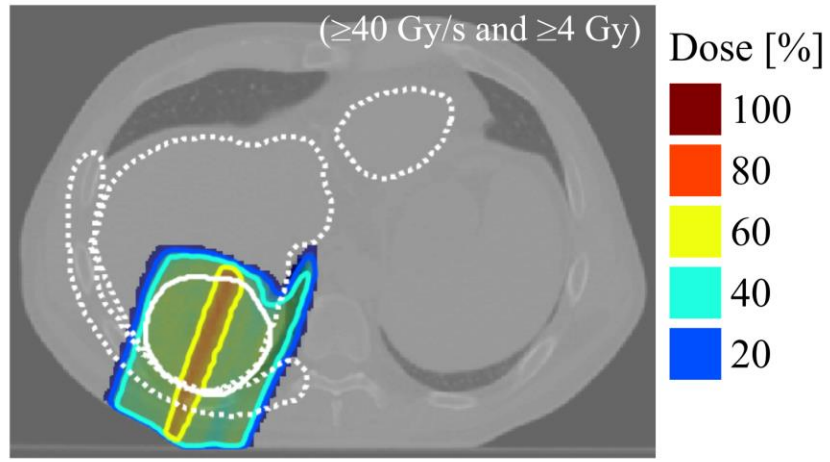
Dose @ Flash thresholds

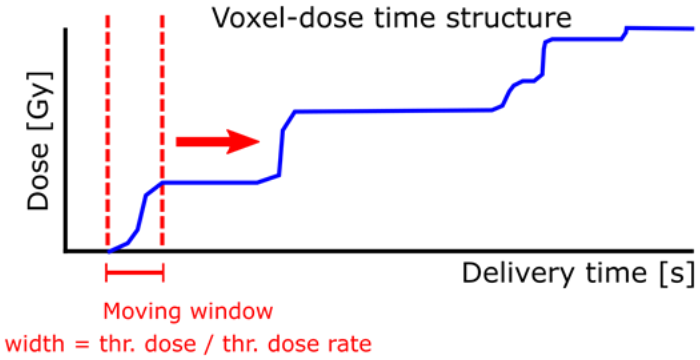


$$DADR_i = \sum_{j=1}^{n} \frac{(d_{ij}w_j)(d_{ij}Bl_j)}{\sum_{j=1}^{n} d_{ij}w_j},$$

Sliding window

Dose @ Flash thresholds





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What machine parameters should we assume in calculating the dose rate? What matter the most?

	Cyclotron	Linac
Max energy (MeV)	230	230
Frequency (Hz)	7.20E+07	200
Pulse length (ns)	0.8	3000
Energy switching time (ms)	100	5
Scanning speed (m/s)	10	10
Dead time between spots (ms)	1	1
Beam current at iso at 230 MeV (I_{230}) (nA)	**200 / 800**	25 / 50
Beam current per pulse at 230 MeV (nA)	3472 / 13 889	41 667 / 83 333
Protons/pulse @I_{230} (Mp)	0.0173 / 0.0694	**800 / 1600**
Beam current at 70 MeV and 150 MeV (nA)	1% and 10% of I_{230}	same as I_{230}

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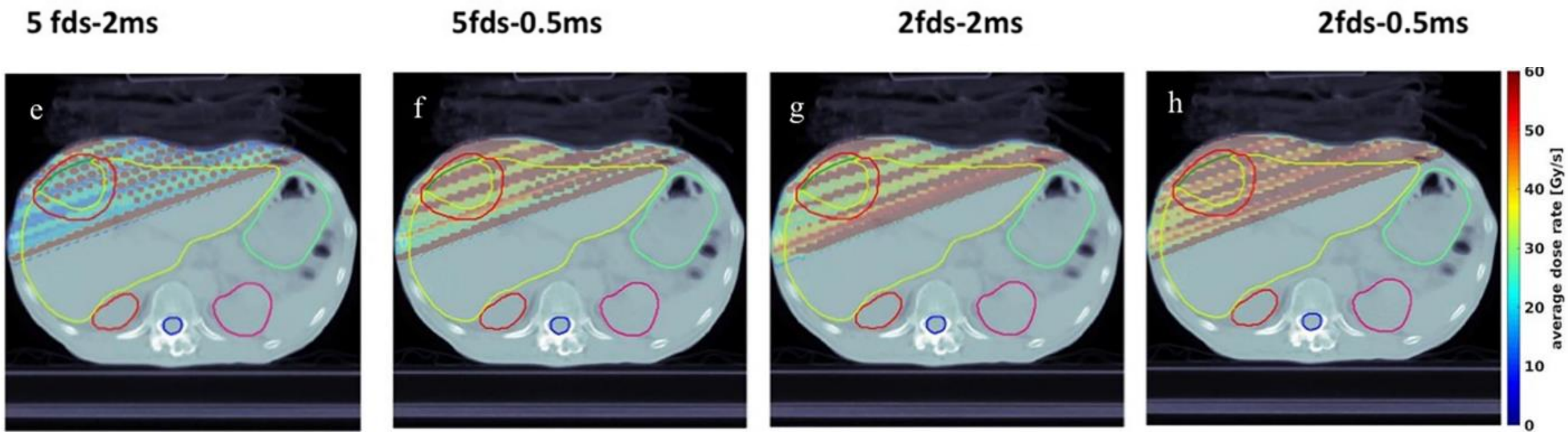
Impact of minimum spot duration



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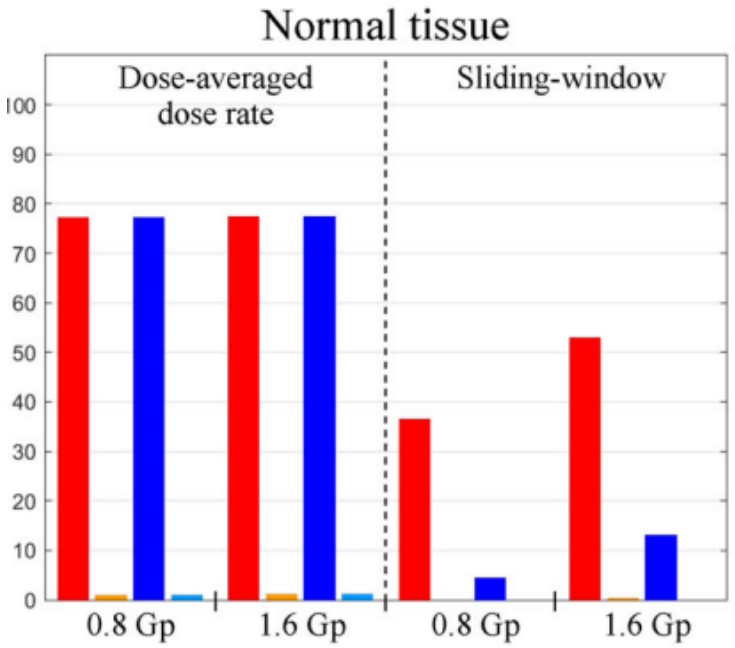
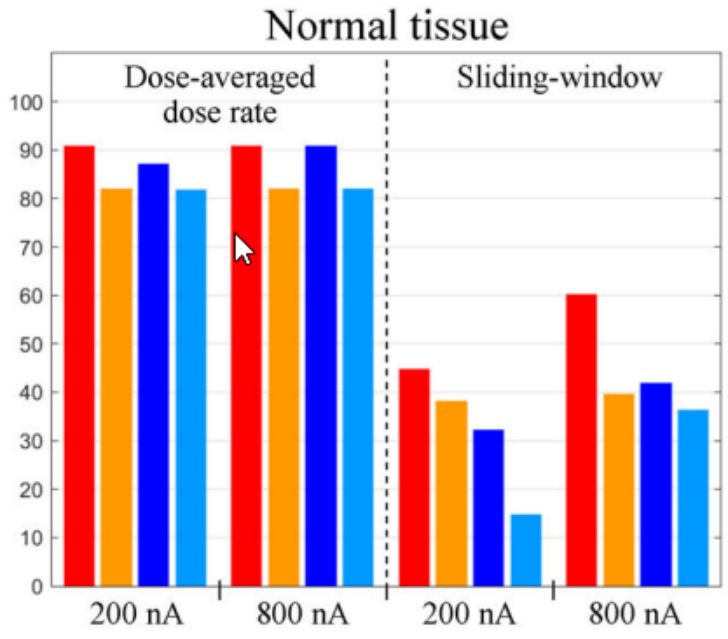
Also in this study the highest dose rates were associated with the worst dose distribution and viceversa

Last but absolutely not least: impact of the dose threshold

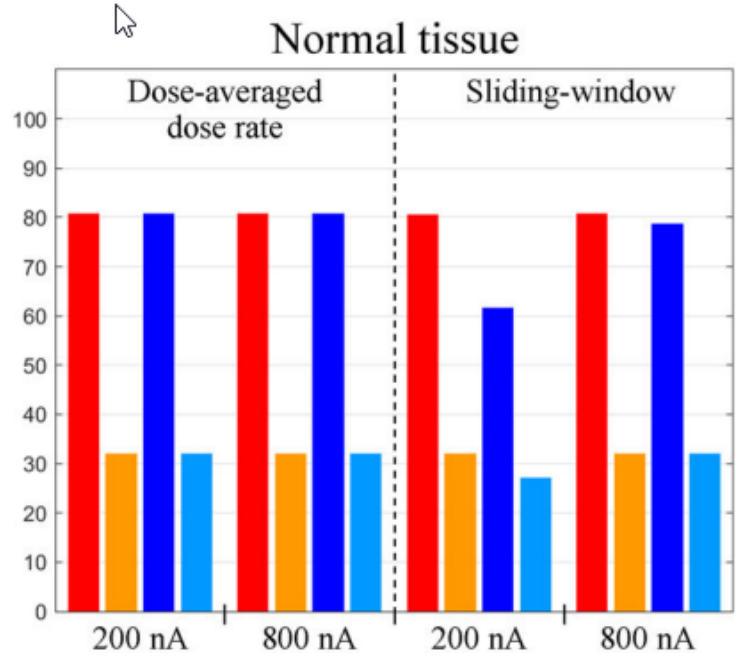
Prostate

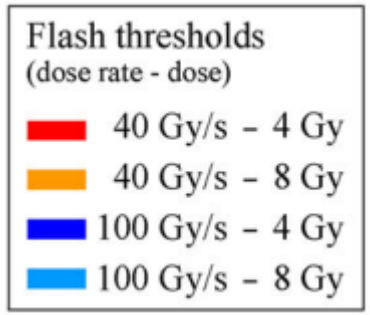


Liver



Lung





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Brief summary of the dimensions to explore so far

The particle type and planning technique matter
The dose rate definition matters
The beam delivery parameters matter
The dose threshold matters

And we haven't even touched questions such as:
How big/small is the FLASH effect?
Is it really on/off in dose and dose rate?
What is its volume effect, if any?

FLASH&treatment planning going forward