Tony Lomax :: Head of Medical Physics :: Paul Scherrer Institute
Department of Physics :: ETH-Zurich

Special techniques II: Proton therapy

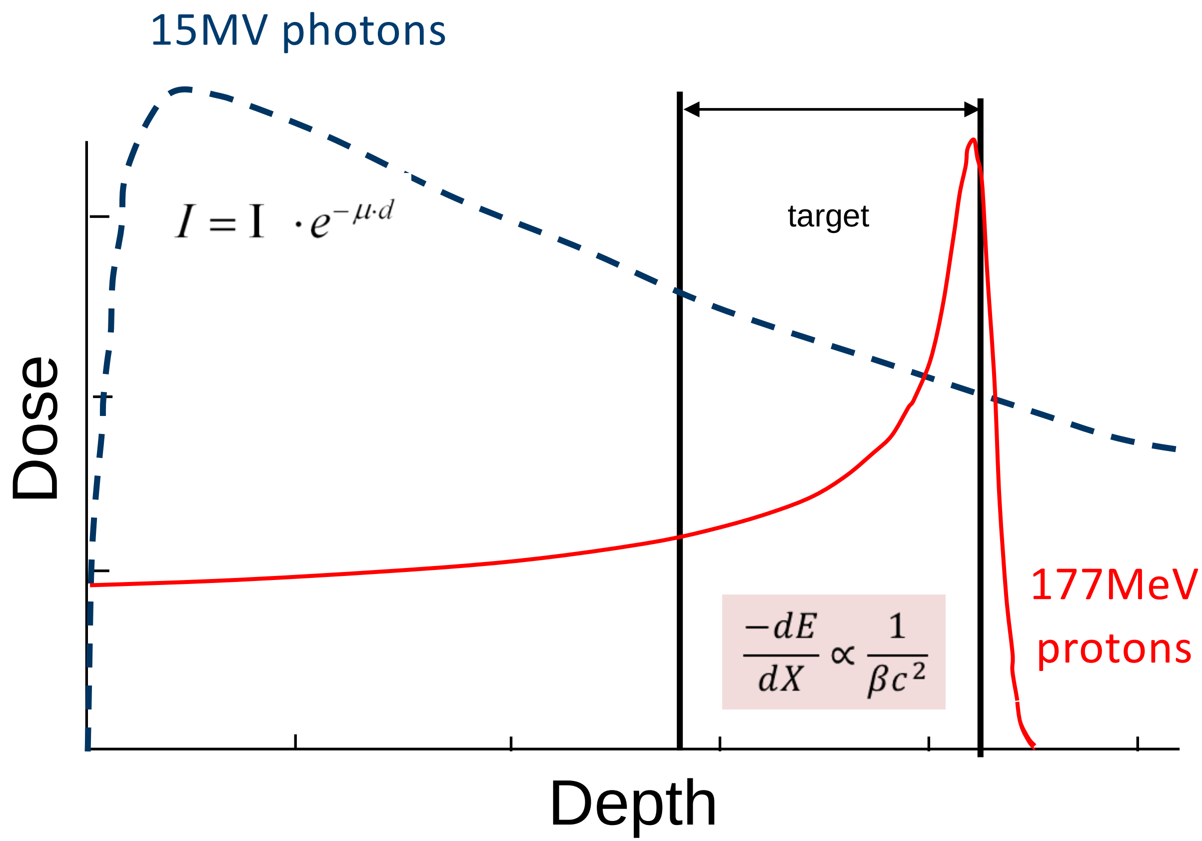
FMH physics training 2024

Overview

1. The principles of proton therapy
2. The challenges of proton therapy
3. The potential of proton therapy

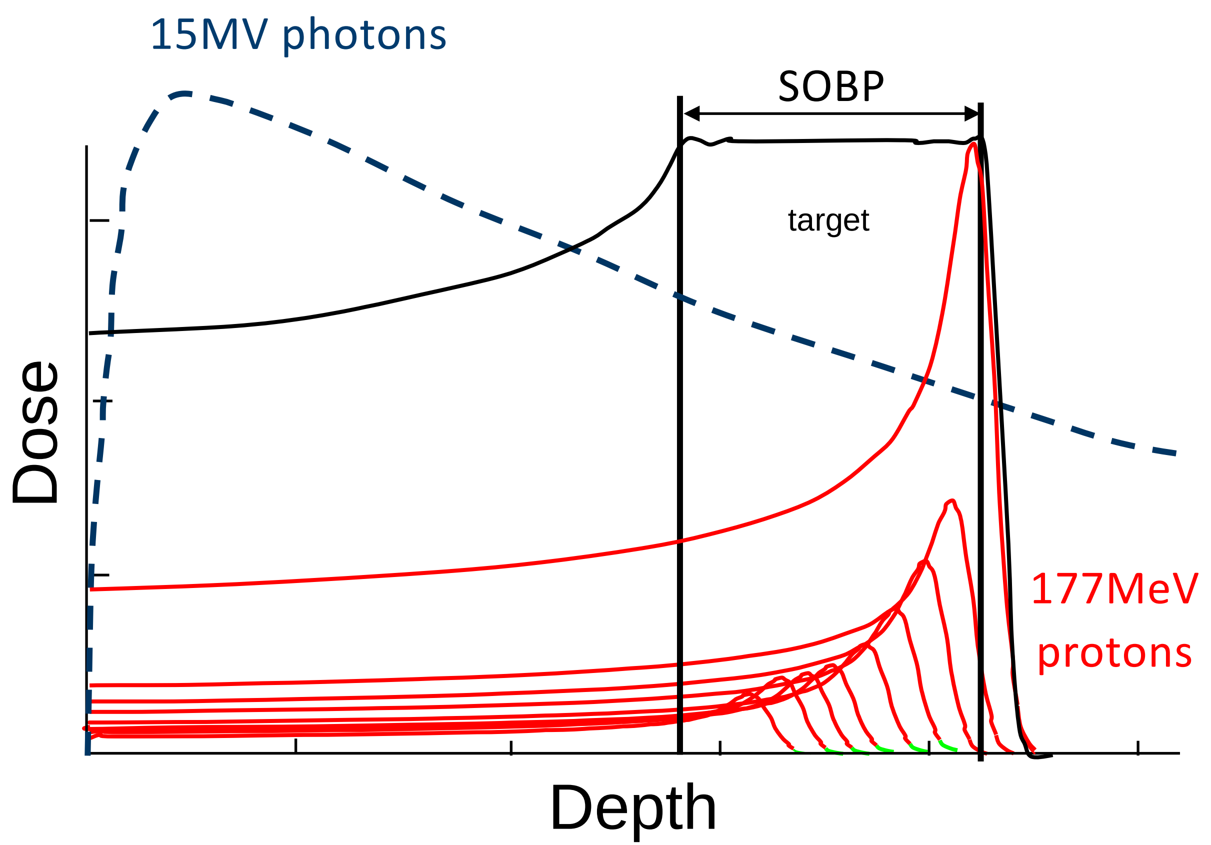
Interactions of protons

The proton depth-dose curve



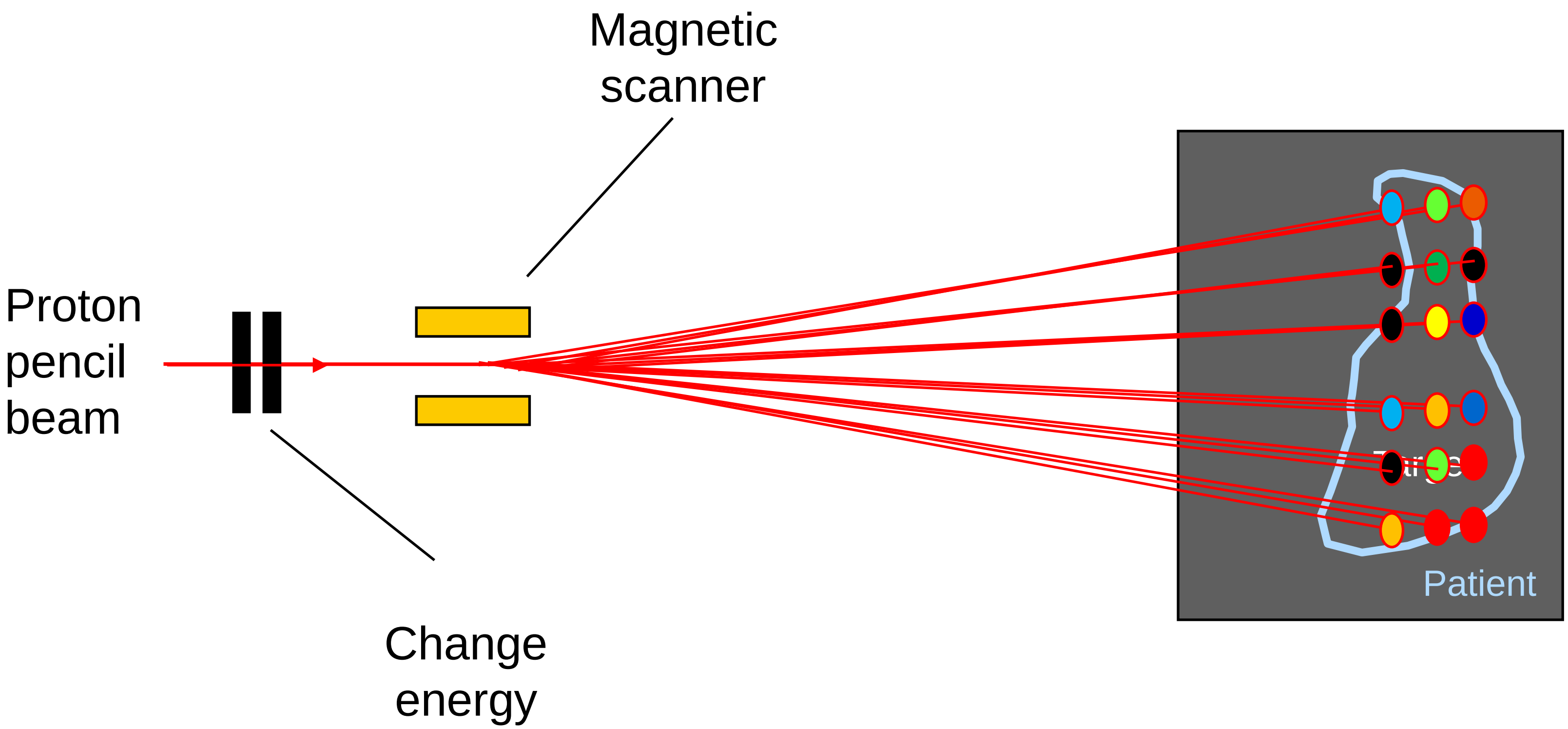
The principles of proton therapy

Modulating protons in depth.



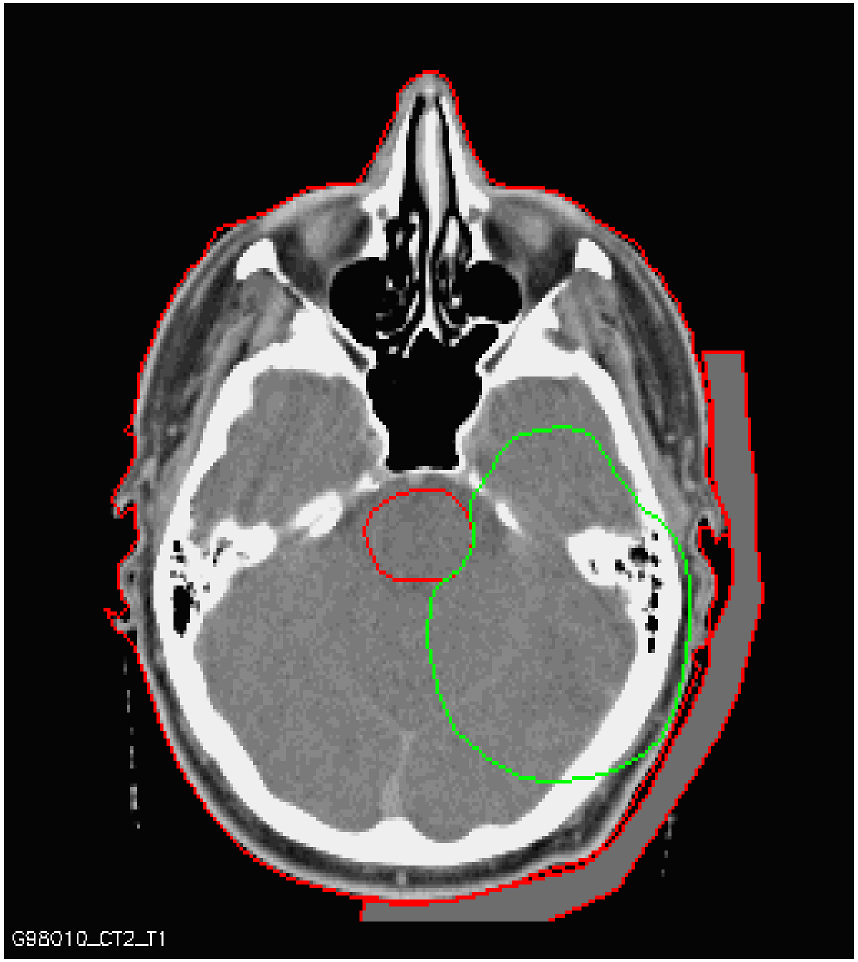
The principles of proton therapy

Pencil Beam Scanning (PBS).

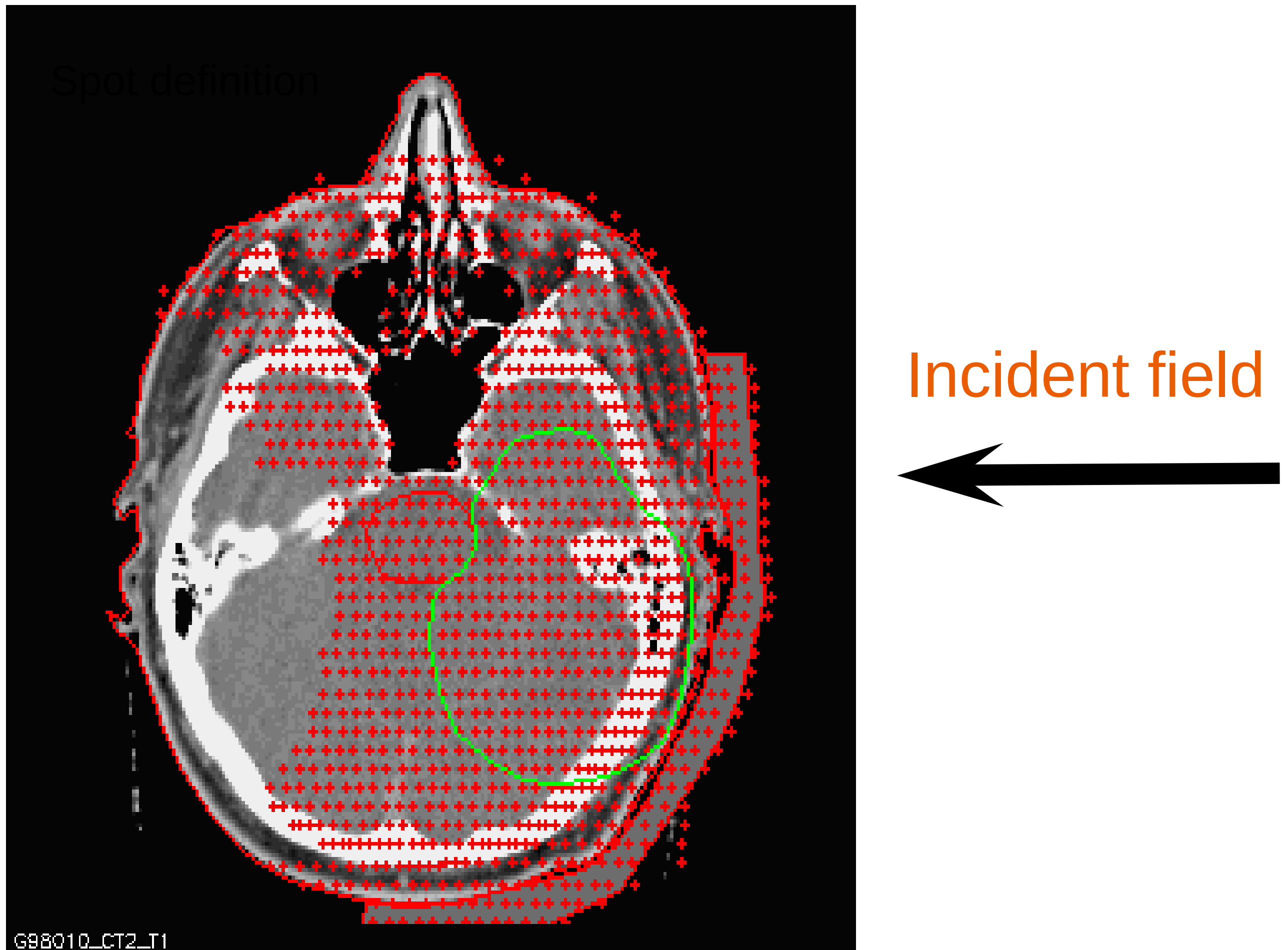


Pedroni et al 1995, Med. Phys. 22:37-53.

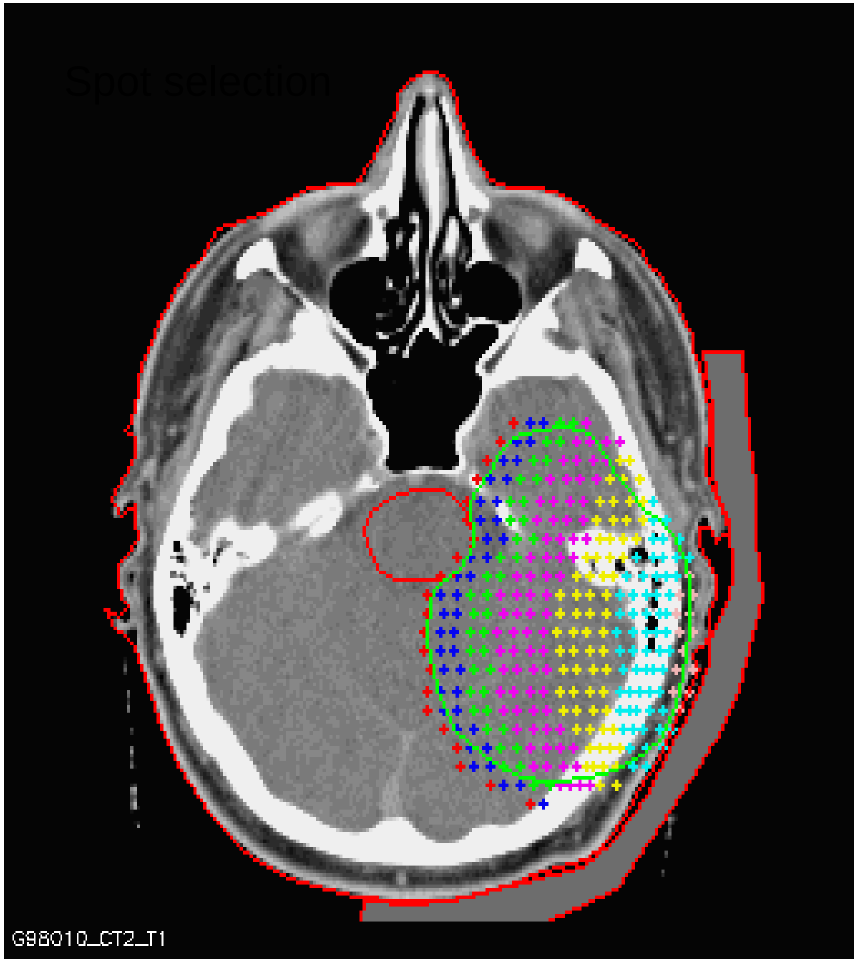
Treatment planning for protons



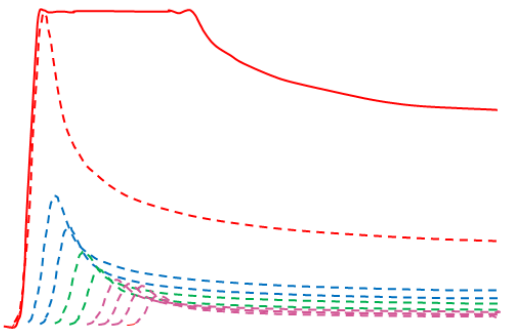
Treatment planning for protons



Treatment planning for protons

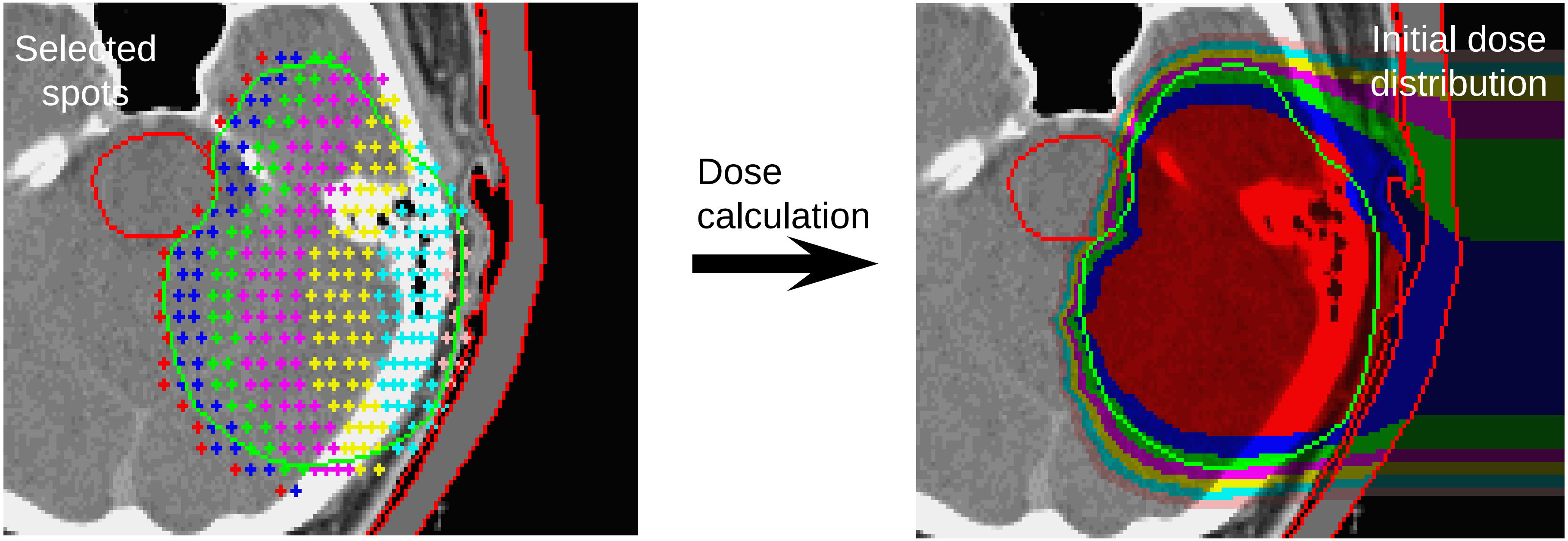


Incident field

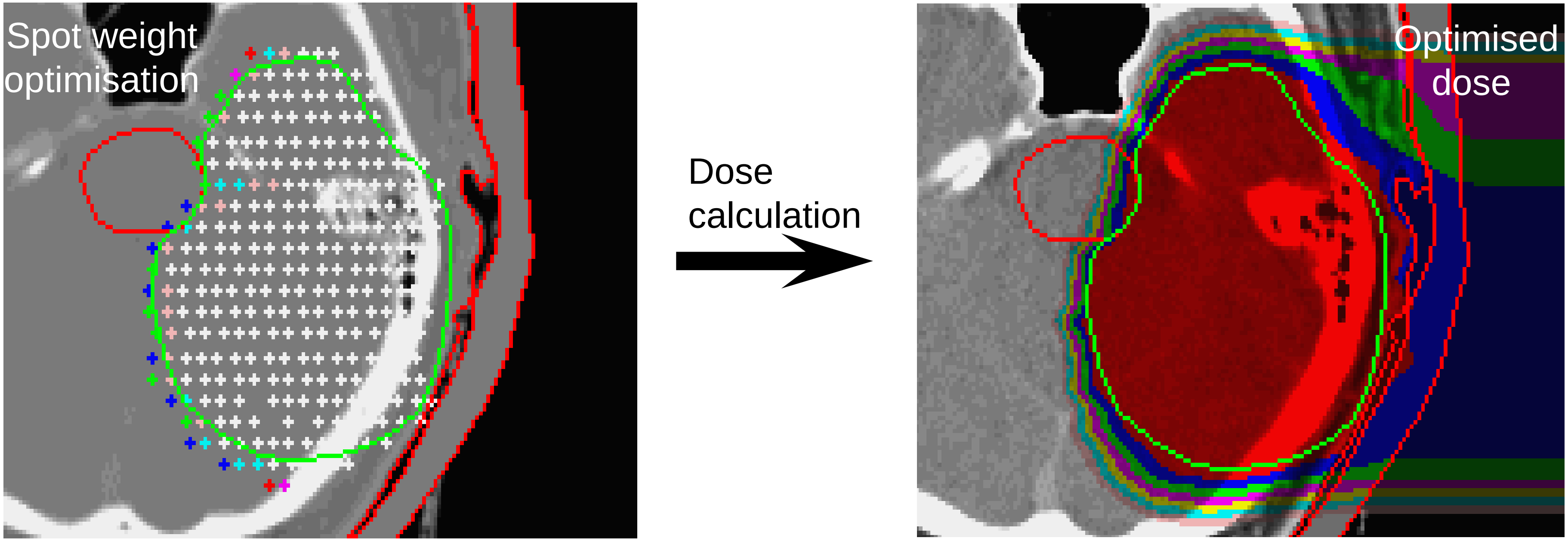


The principles of proton therapy

Treatment planning for protons

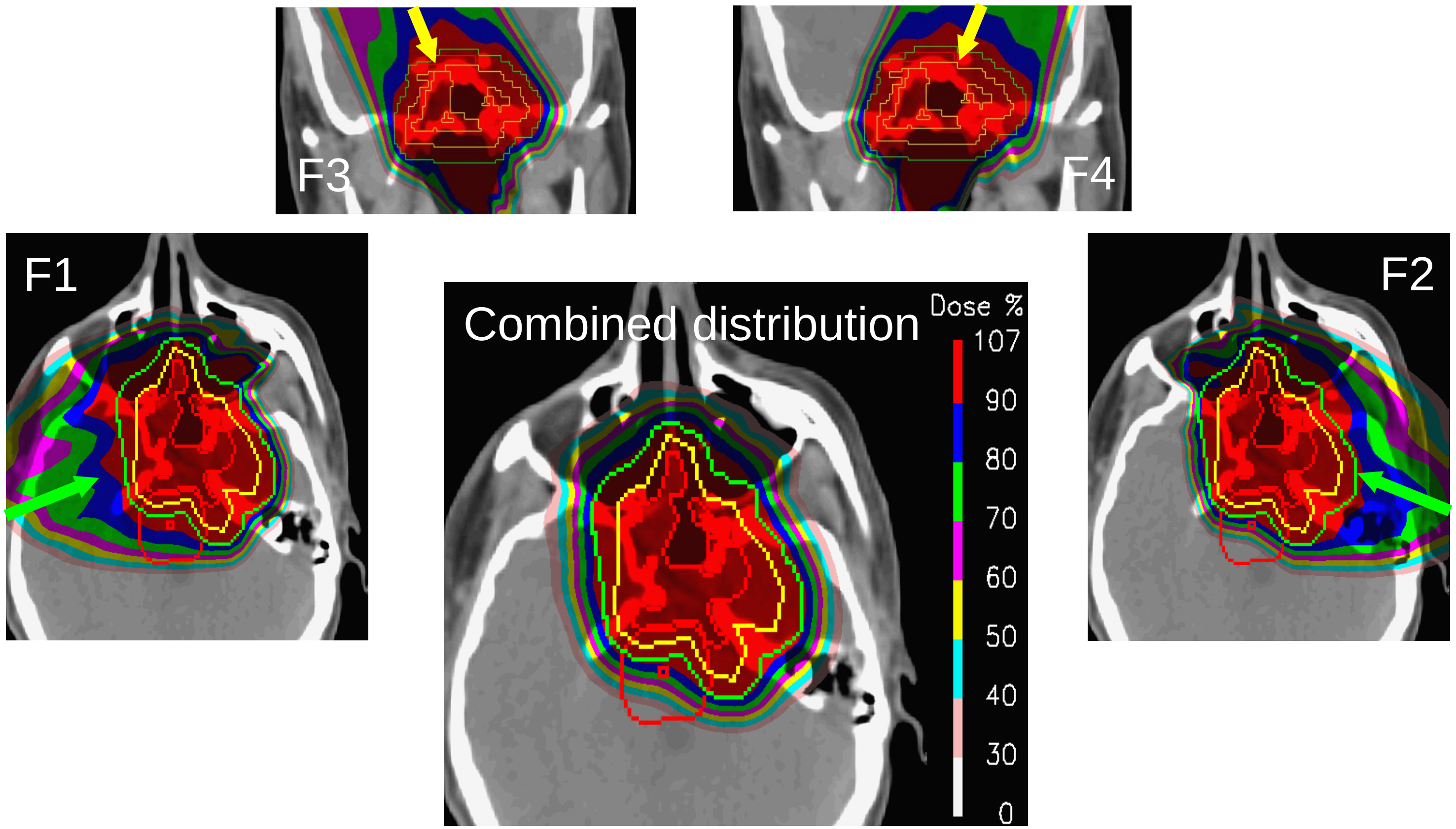


Treatment planning for protons



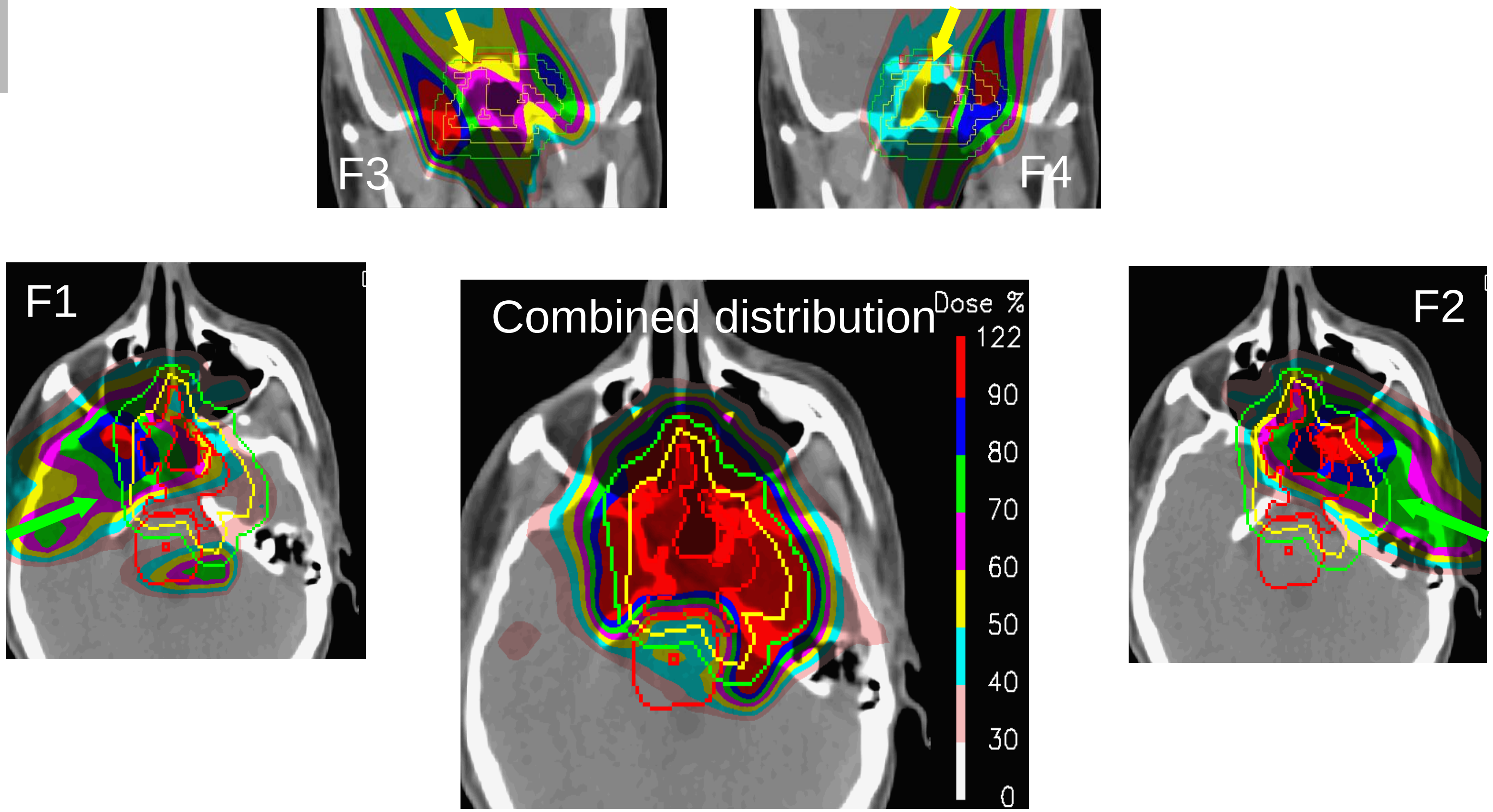
The principles of proton therapy

A multi-field plan (SFO/SFUD).



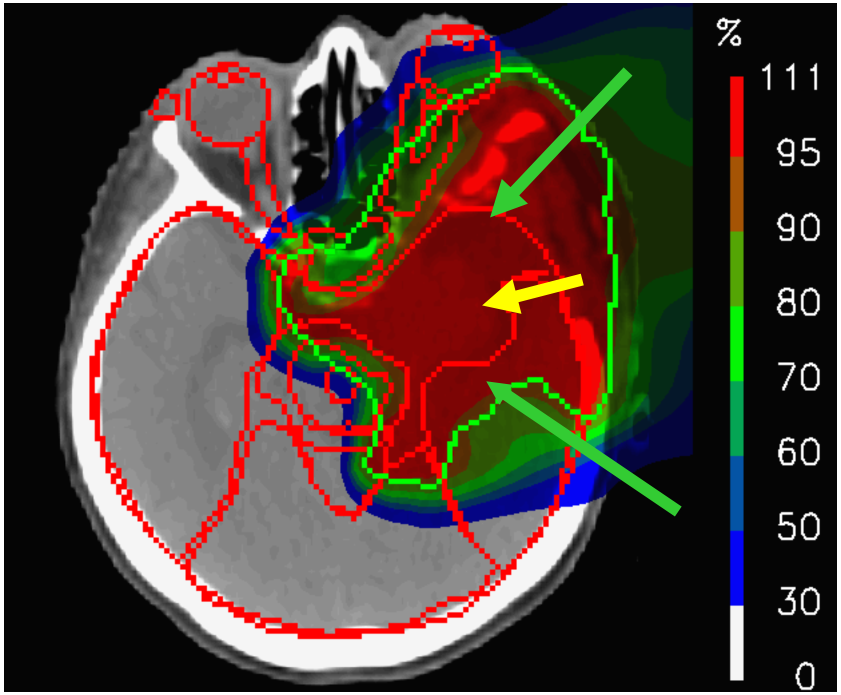
Note, each individual field is (more or less) homogenous across the target volume

An multi-field plan (MFO/IMPT)

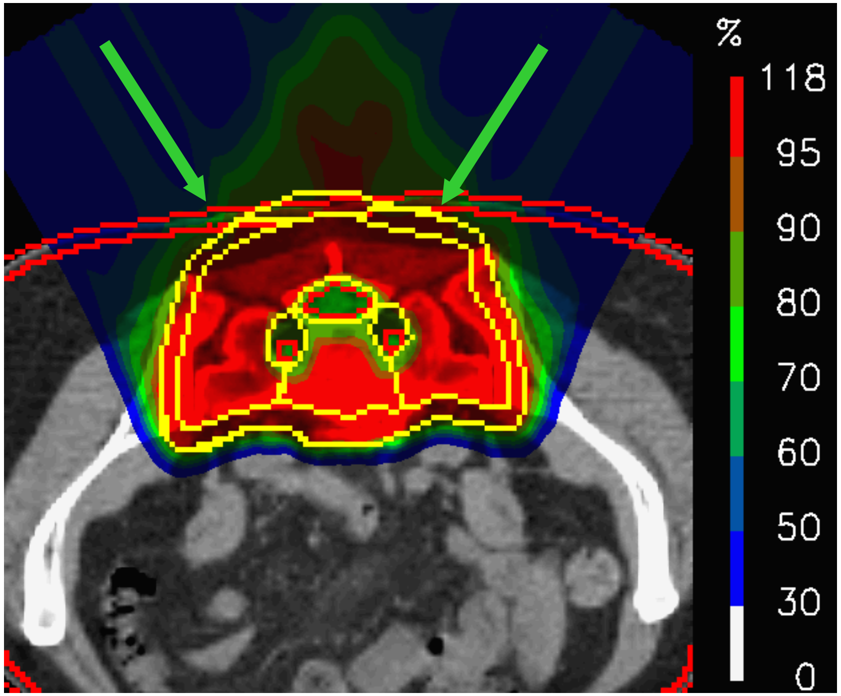


Note, each individual field is highly in-homogenous (in dose) across the target volume (c.f. SFUD plans)

Example clinical IMPT plans delivered at PSI



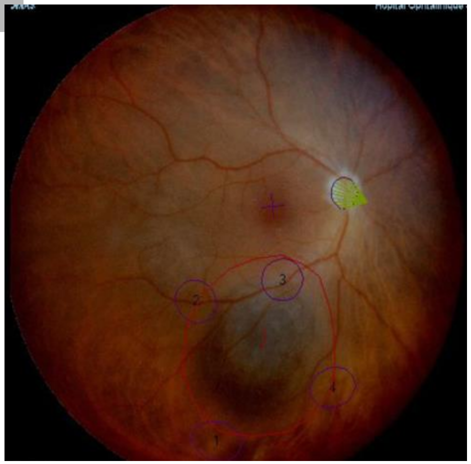
Meningioma (3 fields)



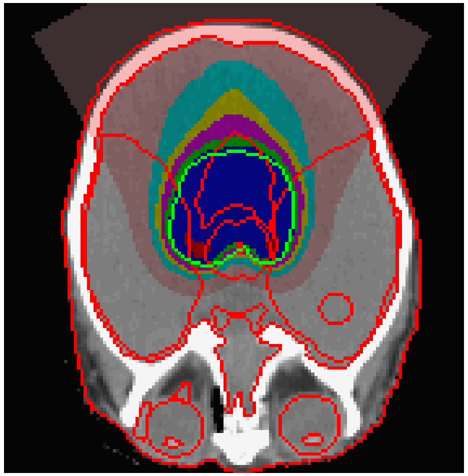
Sacral Chordoma (2 fields)

The power of the proton (1).

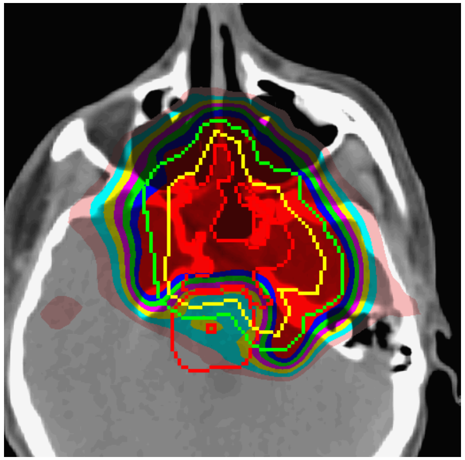
Clinical results from PSI



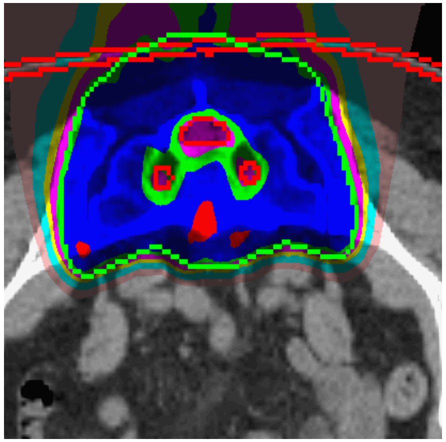
Uveal melanomas
>8000 Patients
5y Local control: 98%



Ependymomas
50 Patients
5y Local control: 78%



Skull base tumours
222 Patients
7y Local control: 80%



Sacral chordomas
36 Patients
5y Local control: 66%

Overview

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2. The challenges of proton therapy
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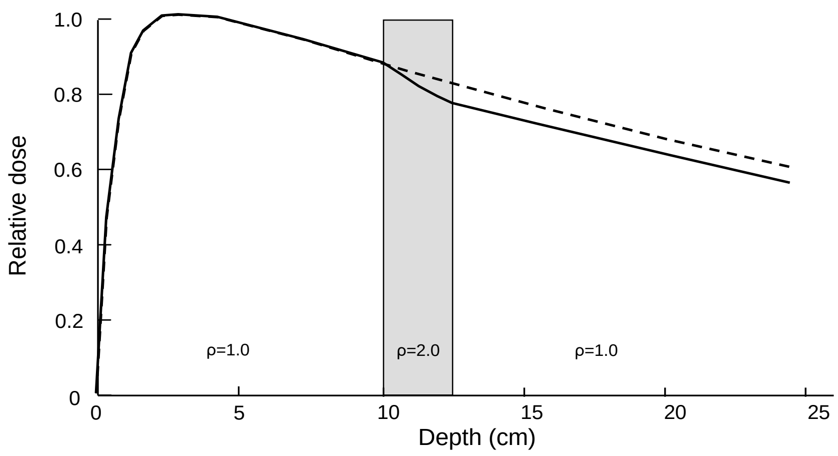
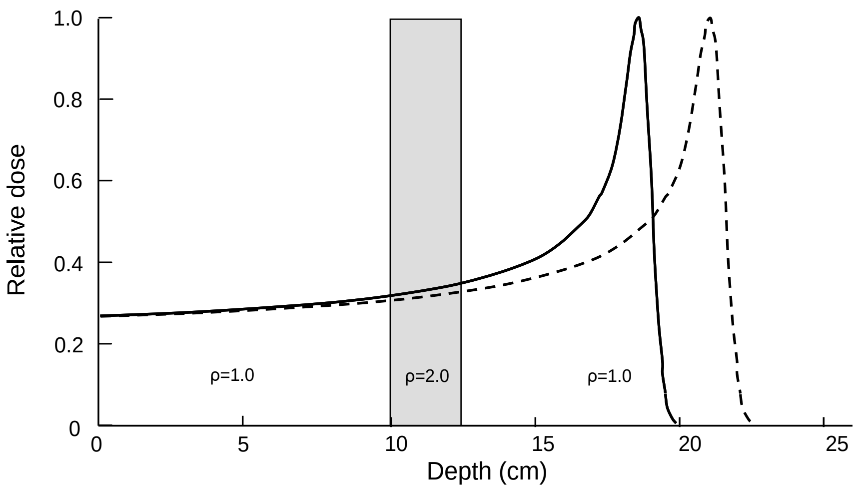
Range uncertainty

The effect of (unplanned) density heterogeneities on photons and protons

Photons…



… and protons.

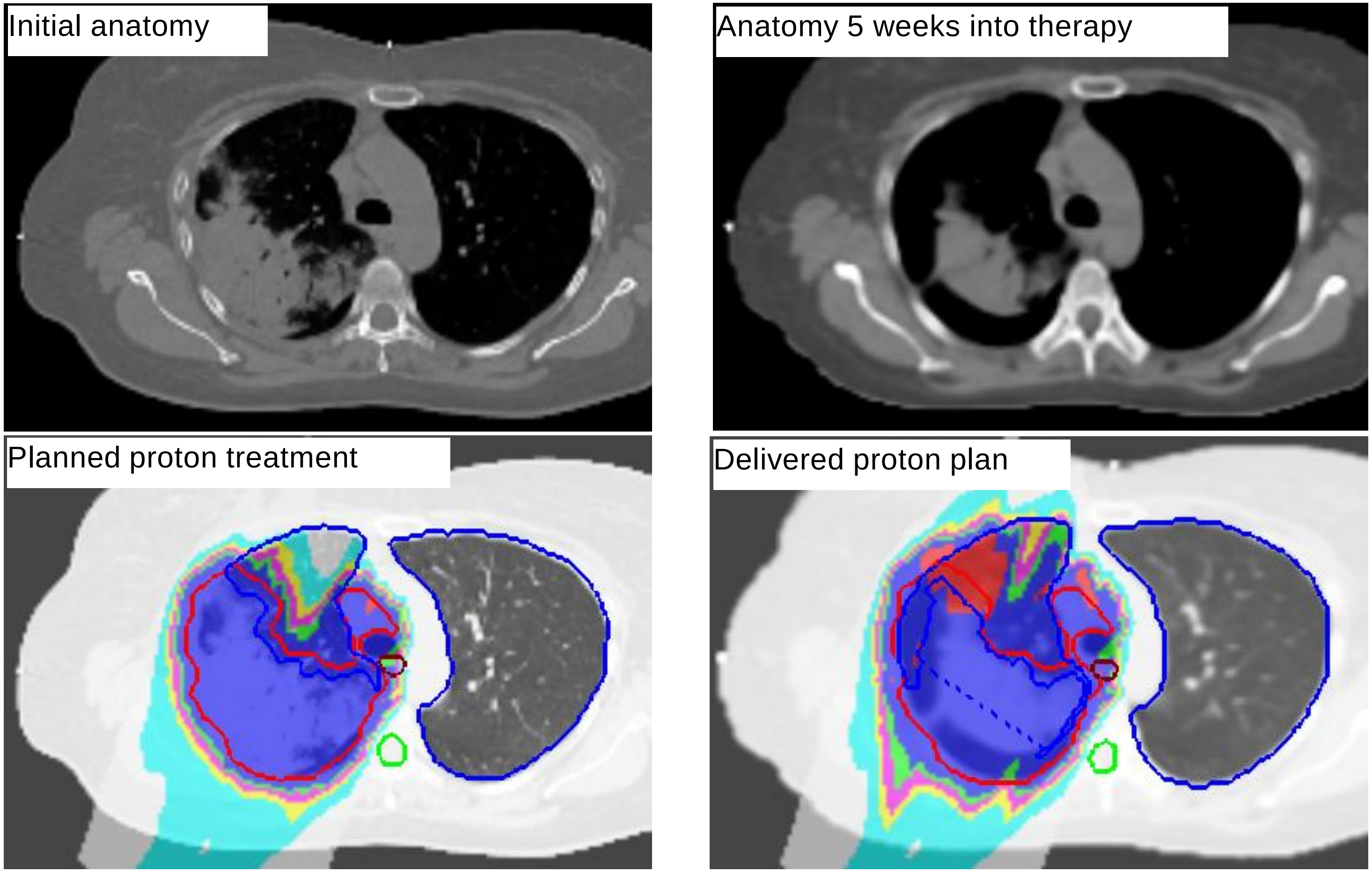


The advantage of protons is that they stop ☺

The disadvantage of protons is that we don’t always know where… ☹

Range uncertainty

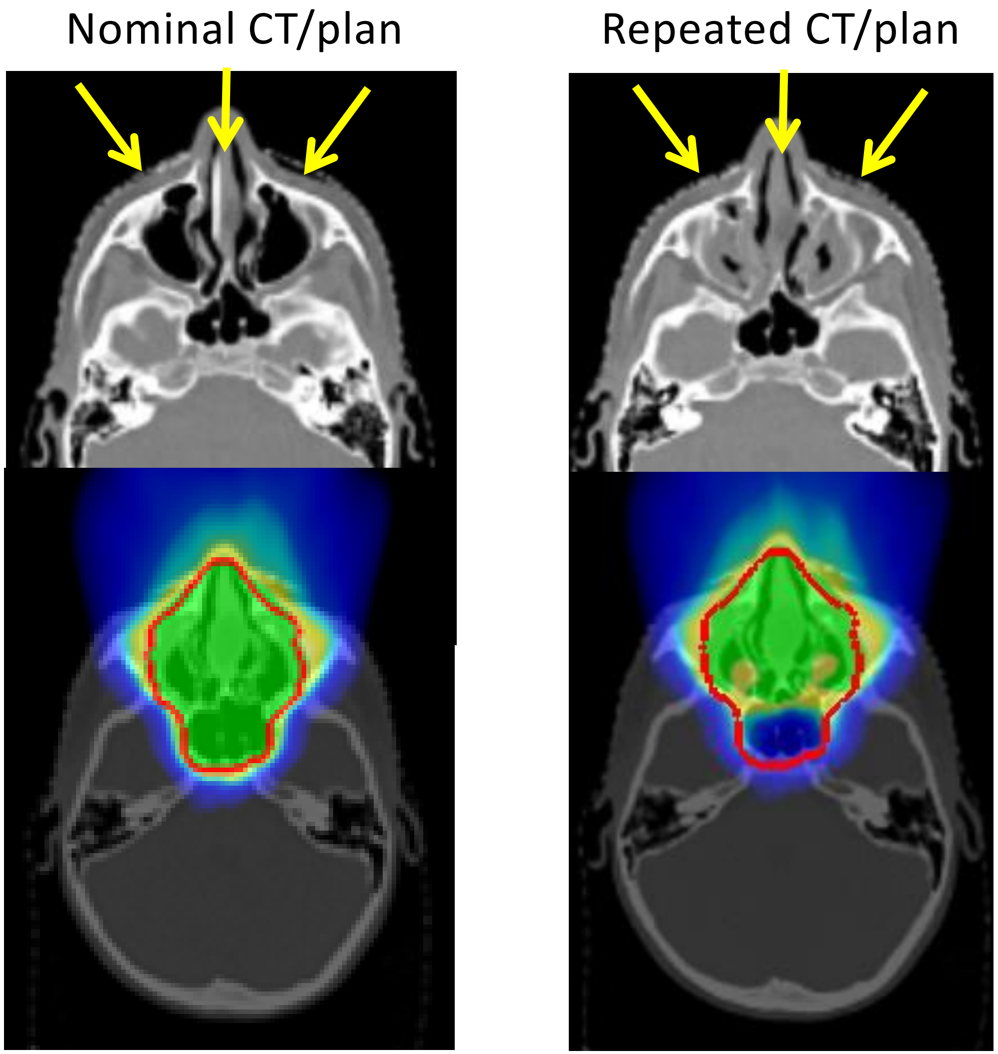
E.g. the effect of anatomical changes (1)



Michael Matter, Lena Nenoff and Francesca Albertini (SNF)

Range uncertainty

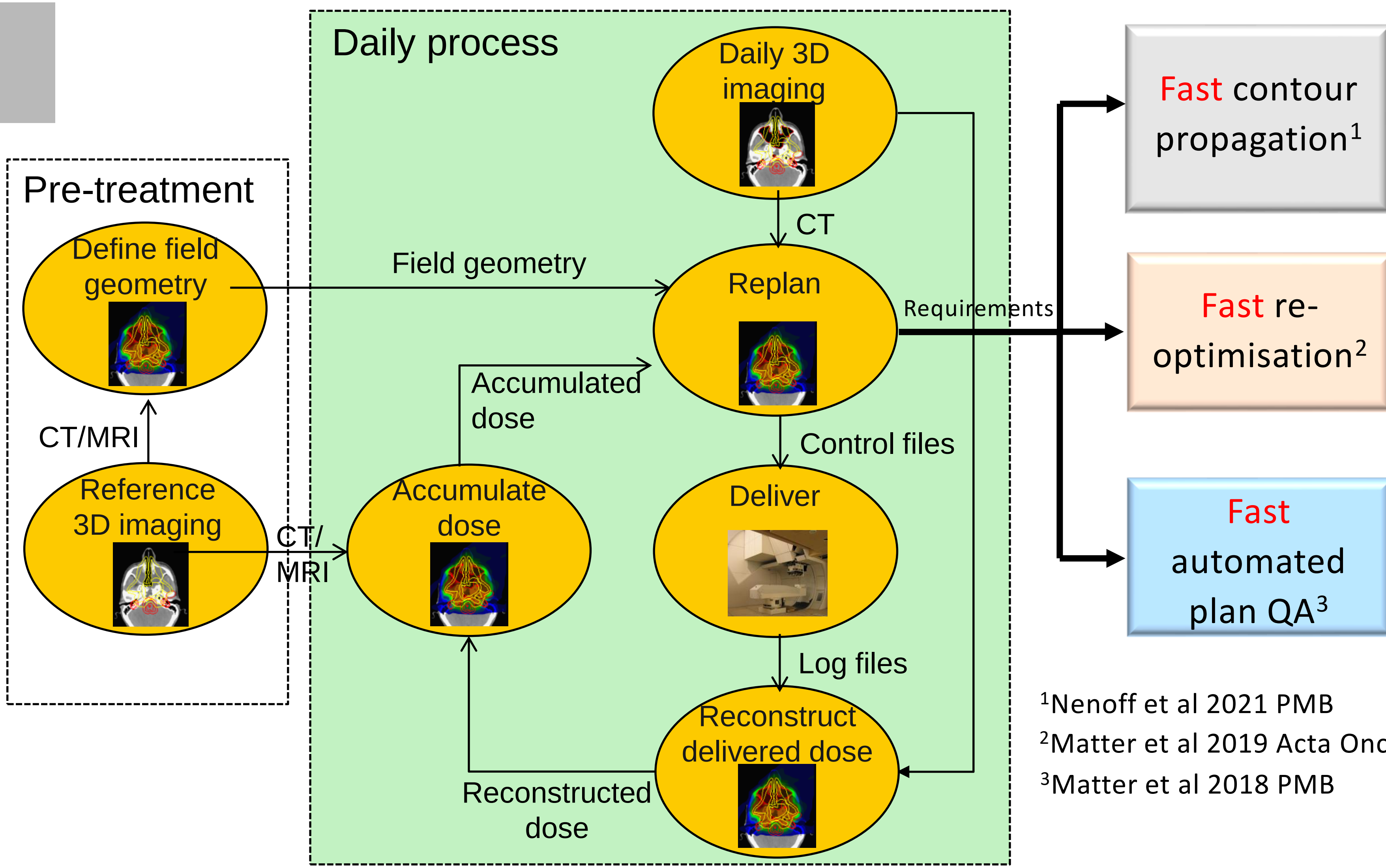
E.g. the effect of anatomical changes (2)



Nenoff et al 2019, Acta Oncologica

Range uncertainty

Towards Daily Adaptive Proton Therapy (DAPT)

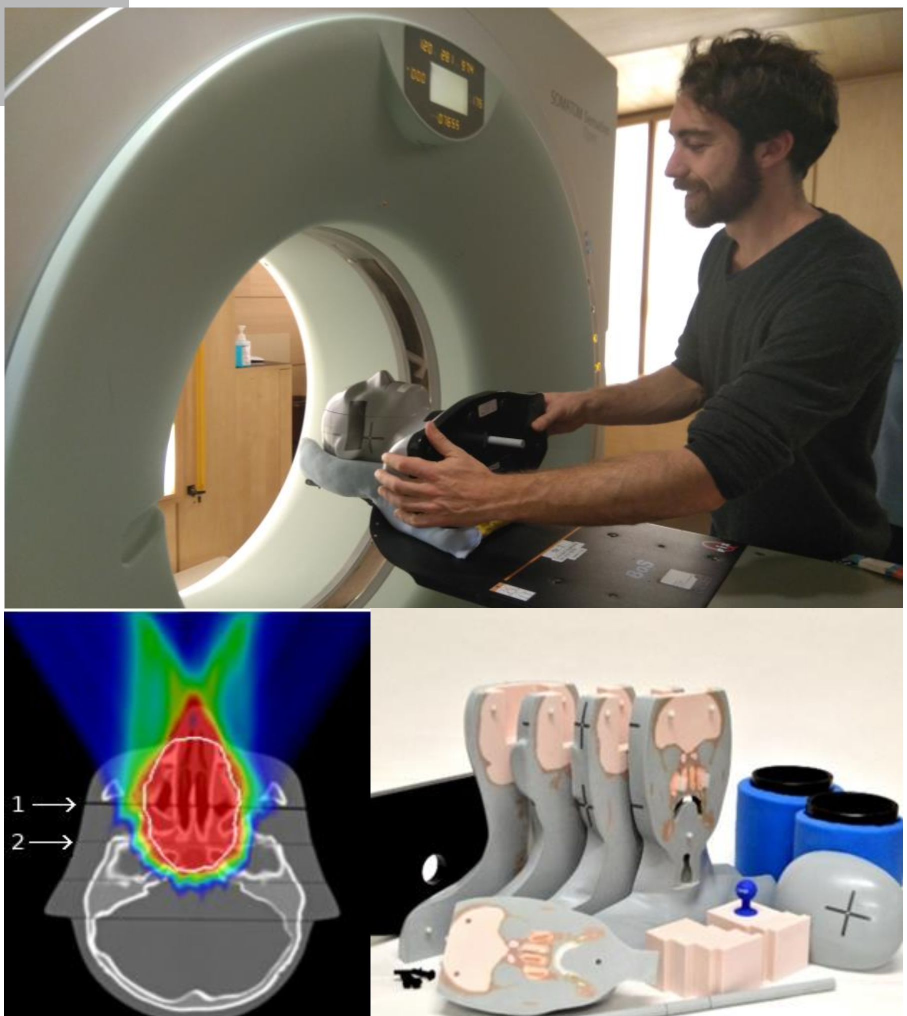


[1]Nenoff et al 2021 PMB
[2]Matter et al 2019 Acta Oncol
[3]Matter et al 2018 PMB

Albertini et al 2019 BJR

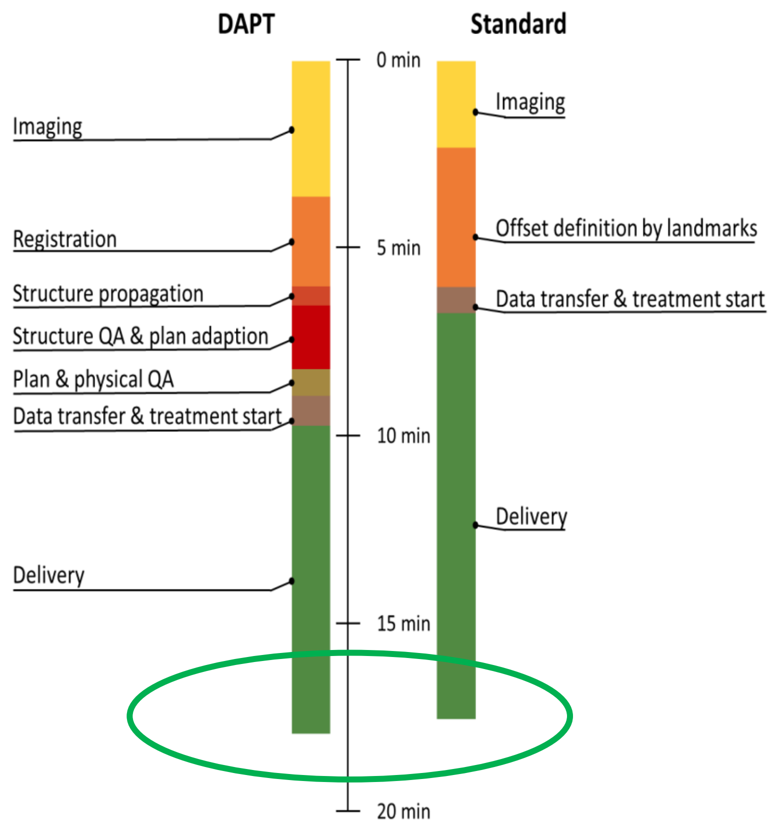
Range uncertainty

Daily Adaptive Proton Therapy (commissioning)



Nenoff et al 2021 PMB

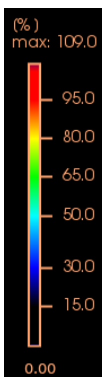
Timings of conventional and full DAPT deliveries

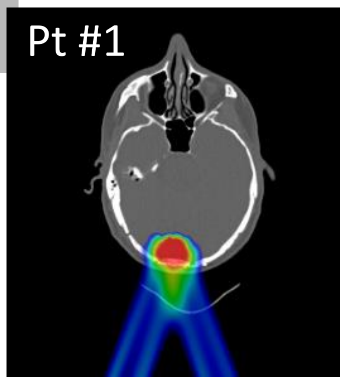


Almost the same time for a DAPT and conventional fraction (<20mins)

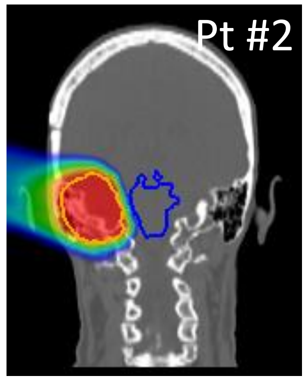
Range uncertainty

Daily Adaptive Proton Therapy (clinical)

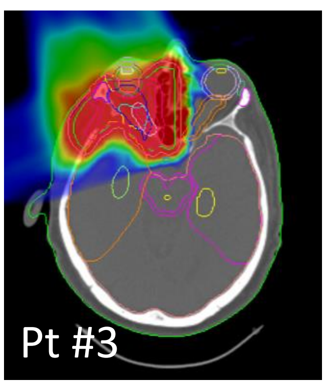




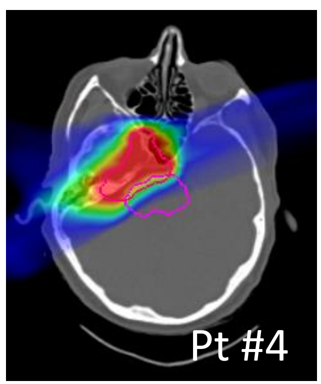
Hemangiopericytoma



Chondrosarcoma



Ewing sarcoma



Meningioma

Delivery times

		Average duration [range] (min)
	Set-up and CT acquisition	2:50 [2:30-3:10]
Online adaptive steps	Registration	3:10 [2:10-4:50]
	Initial integrity checks	1:10 [0:50-1:40]
	Daily structure approval	2:30 [1:10-3:50]
	Daily Plan clinical evaluation & approval	2:20 [1:10-3:40]
	Plan QA (incl. check of secondary dose)	0:50 [0:30-1:00]
	Delivery	9:00 [7:00-11:10]
	Total	22:20 [17:30-25:50]

Online steps:
6:50 mins

DAPT fraction times:
22:20 (17:30-25:50) mins

Andreas Smolders, Eva Choulilitsa, Kasia Czerska, Francesca Albertini

Size and costs

Photon and proton gantries

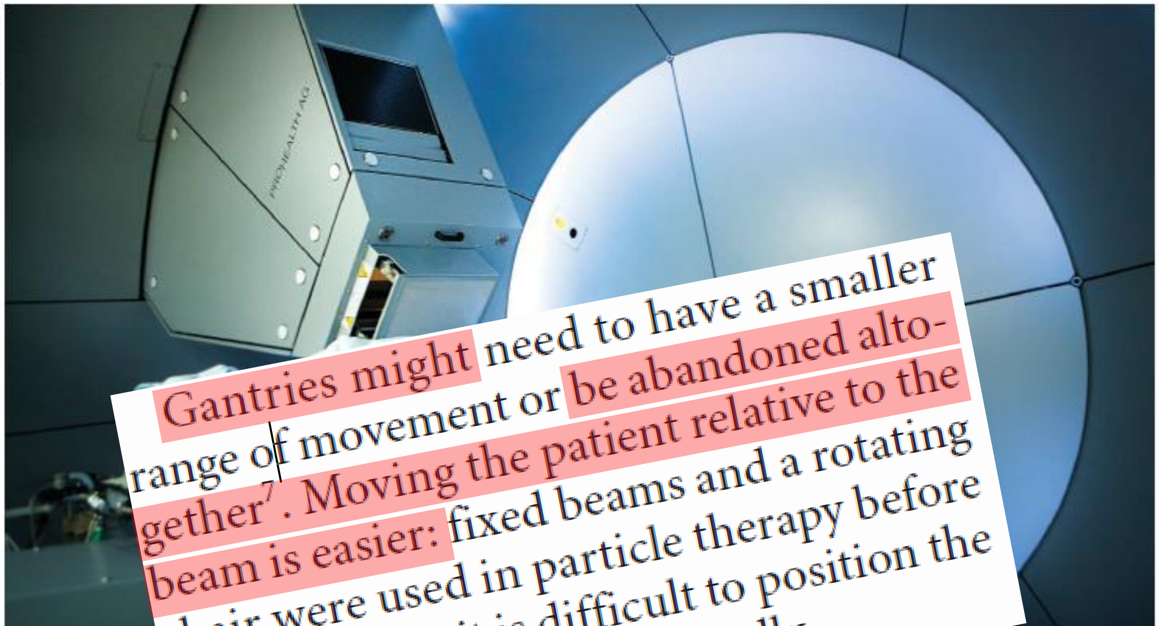
Photon LINAC - Ø~2m

Proton gantry - Ø~10m

Size and costs

The return of gantry-less systems?

BSIP/UIG/GETTY



Gantries might need to have a smaller range of movement or be abandoned altogether[7]. Moving the patient relative to the beam is easier: fixed beams and a rotating chair were used in particle therapy before the 1990s. But it is difficult to position the patient accurately and repeatedly.

A proton-therapy ma

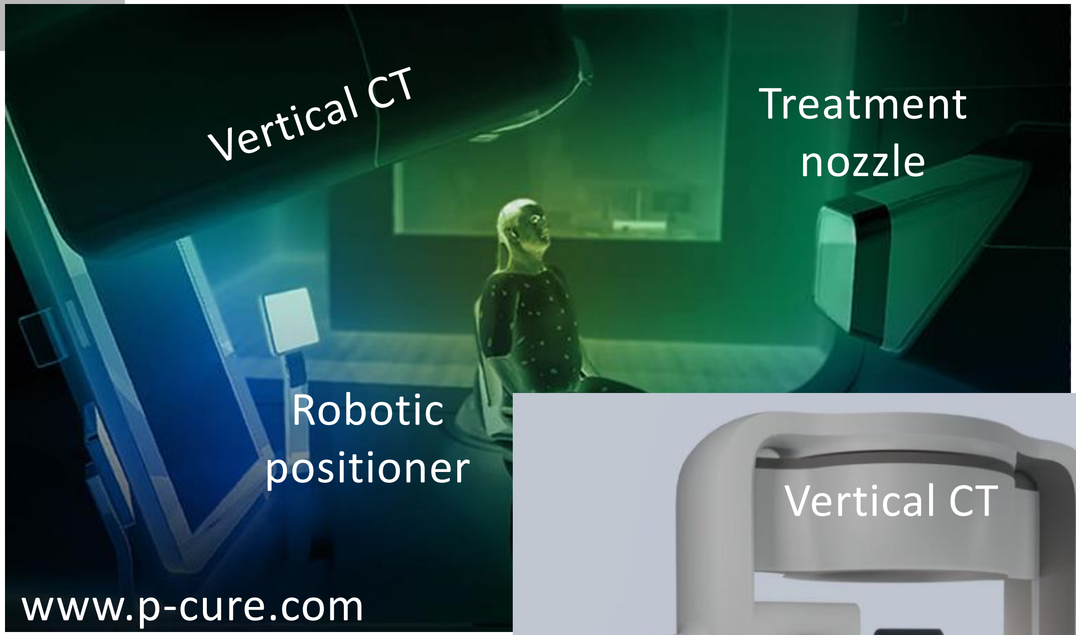
ways to make proton therapy affordable

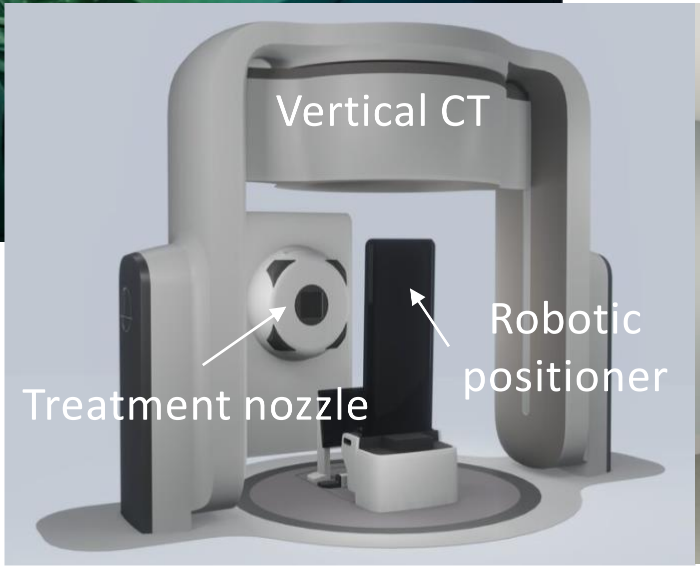
Shrink accelerators, sharpen beams and broaden health-care coverage so more people can get this type of radiation treatment, argue **Thomas R. Bortfeld** and **Jay S. Loeffler**.

28 SEPTEMBER 2017 | VOL 549 | NATURE | 451

Size and costs

The return of gantry-less systems?





Overview

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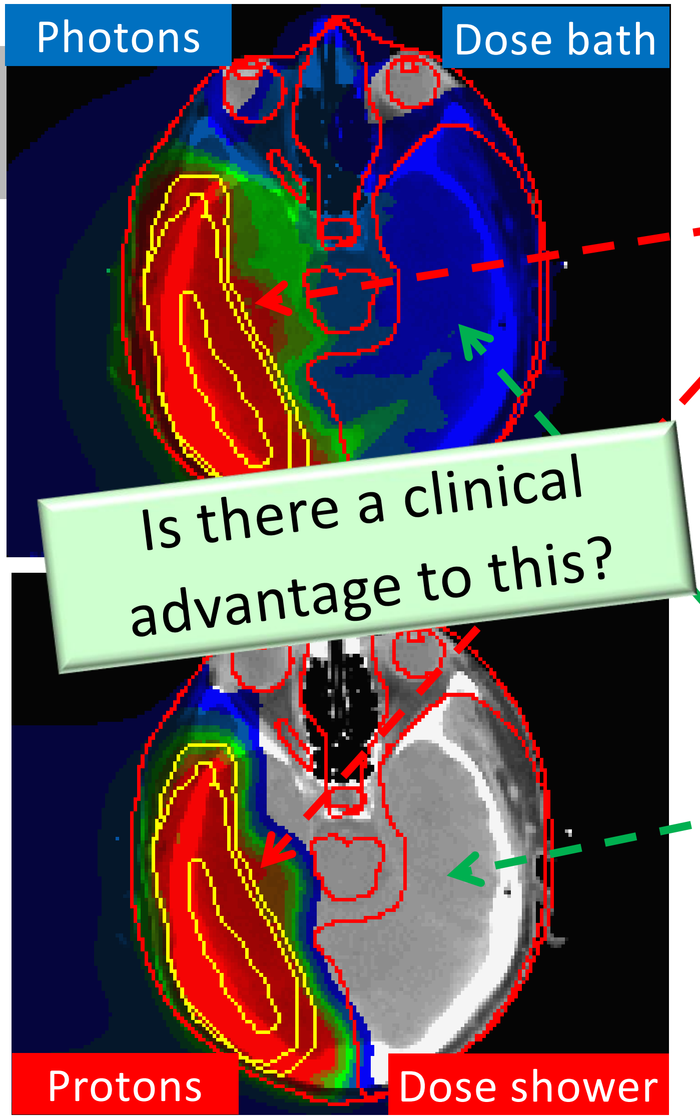
The potential of proton therapy

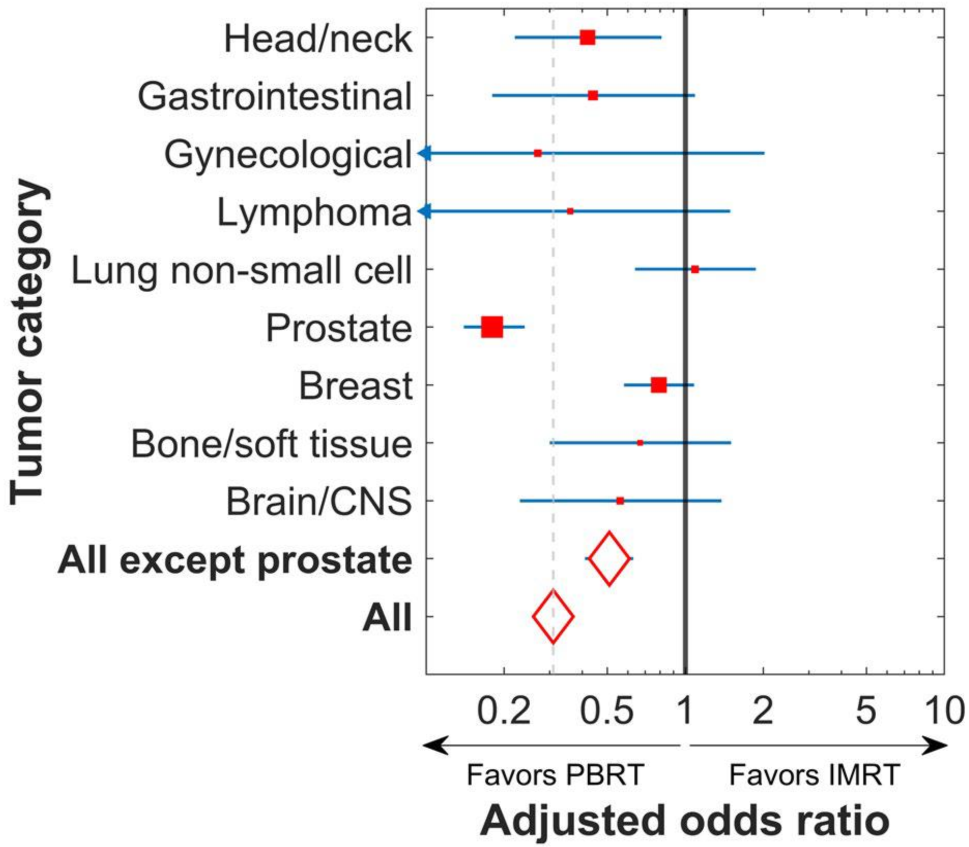


- The advantage of protons is NOT in high dose conformation
- Their advantage is mainly in reducing the mid-to-low dose levels in comparison to photons

1. Reduced secondary cancer risk

A retrospective study from Stanford*

- *>450000 RT patients identified from National Database (US)*
- *9 tumour types, 35% 3DCRT, 65% IMRT, 1.3% Protons*
- *Median F/U 5.1 Yrs*



Incidence per 100 patient-years

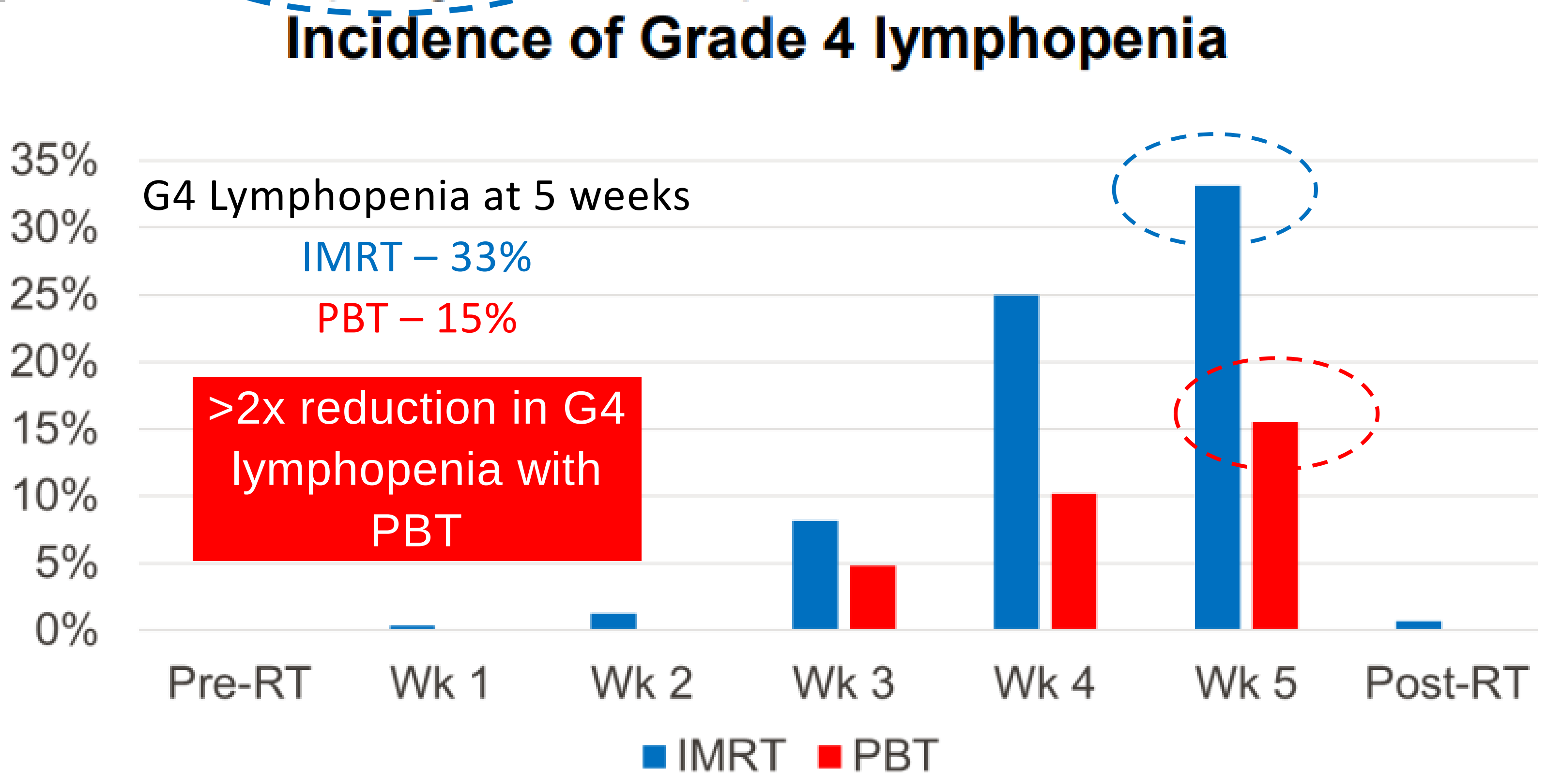
- Protons 0.44
- IMRT 1.55
- Hazard ratio 0.31!

*Xiang et al. Cancer. 2020 126:3560-3568.

2. Reduced impairment of immune system

Reduced treatment induced lymphopenia

504 esophageal cancer patients treated with CRT

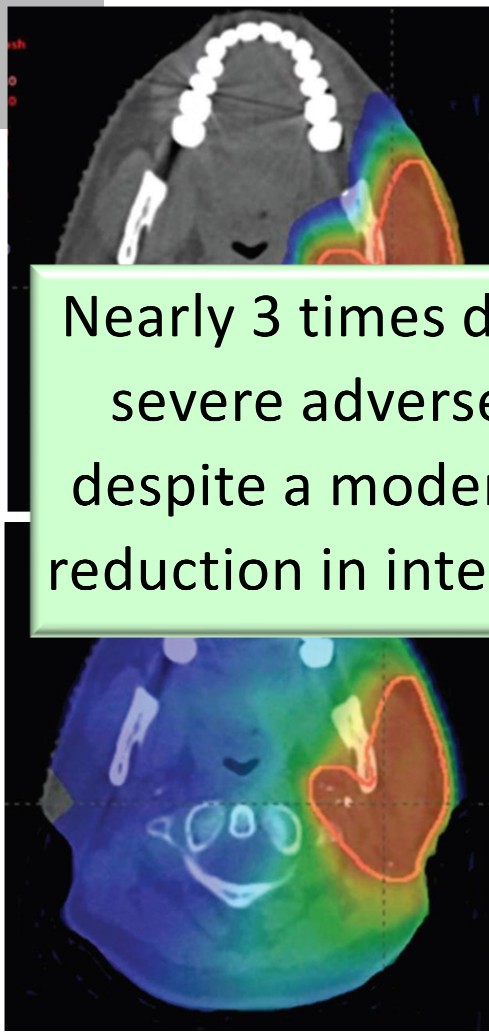


Shiraishi et al Radiother Oncol 2017

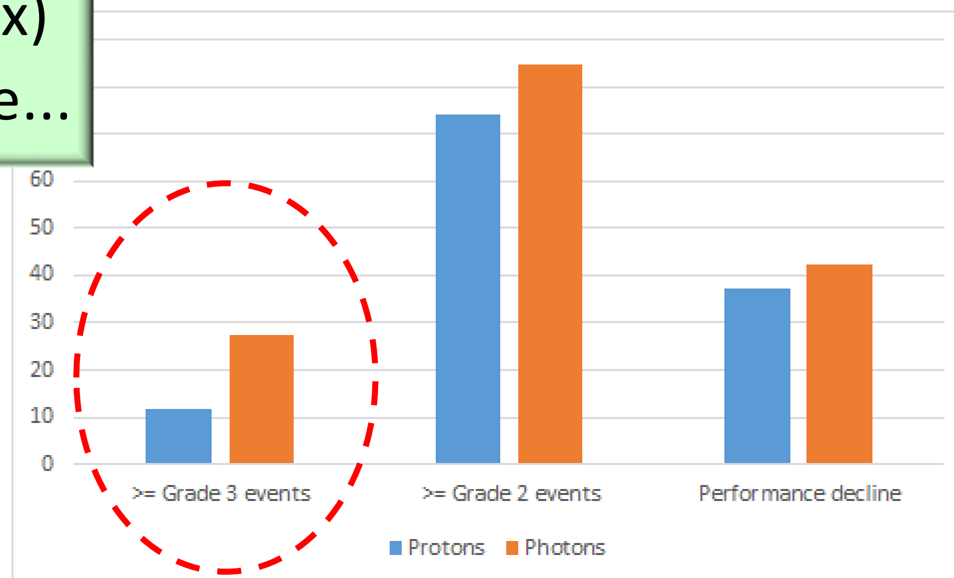
3. Improved tolerance to treatments

A retrospective study from the University of Pennsylvania

- *Comparison of 391 proton and 1092 photon patients treated with concurrent chemotherapy*
- *Endpoint – number of unplanned hospitalizations due to adverse events*
- patients include those also treated with a tion of protons and photons.
- tegral dose ratio protons/photons **~0.7**



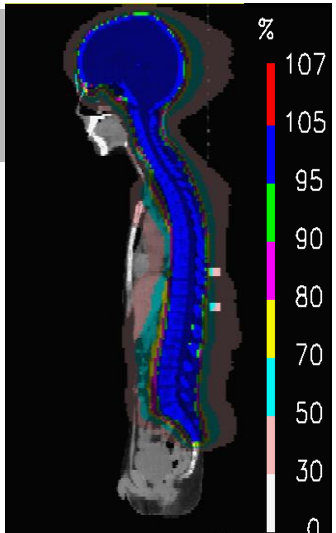
Nearly 3 times decrease in severe adverse events, despite a moderate (1.3x) reduction in integral dose...

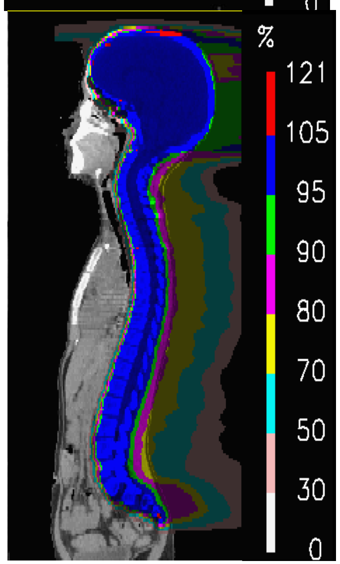


Baumann et al 2020 JAMA Oncol. 6:237-246

4. Reduced toxicities (1)

A comparative study from MGH/Emory





- *Comparison of CSI patient cohorts treated with protons (MGH) and photons (Emory)*
- Median age: PRT 6.2 and XRT 8.3 years ($p<0.01$).
- Co CSI dose, tot
- Me p<0.01)

1.5-6 times reduction of *frequent* (>19% incidence) radiation induced side effects

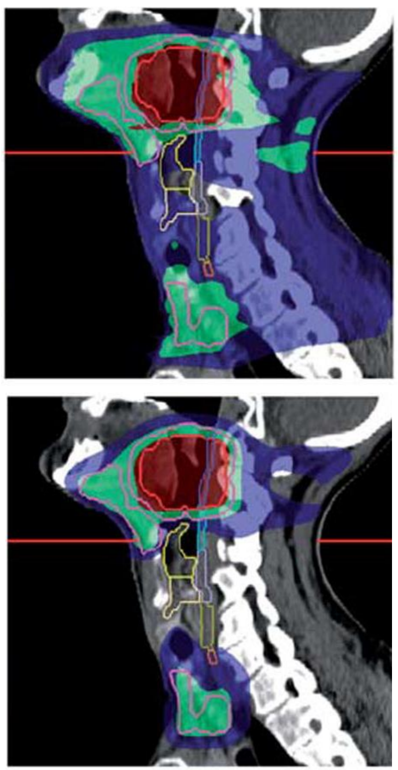
Outcome	Modality	Events	Reduction	P-value
Hypothyroidism	Protons	23%	**2.8**	<0.001
	X-rays	65%		
Sex hormone deficiency	Protons	3%	**6.3**	0.025
	X-rays	19%		
Endocrine replacement therapy	Protons	55%	**1.4**	0.030
	X-rays	78%		

Eaton et al Neuro. Oncol. 2016 18: 881-7

4. Reduced toxicities (2)

A comprehensive toxicity analysis for Nasopharynx

- University of Groningen, model based patient selection
  - 141 Nasopharynx patients (42 IMRT, 99 PT)



Total Toxicity Burden (grade 2+ and grade 3+)

Toxicity endpoints	Photons (n=42)												
	T0	W1	W2	W3	W4	W5	W6	W7	W12	M6	M12	M18	M24
Dysphagia Gr2+	16%	17%	31%	60%	70%	91%	97%	97%	77%	29%	16%	16%	17%
Dysgeusia Gr2+	7%	8%	8%	42%	73%	92%	92%	100%	46%	13%	17%	14%	32%
Mucosal reactions Gr2+	0%	0%	0%	28%	59%	79%	83%	88%	34%	3%	19%	12%	21%
Dry mouth Gr2+	0%	3%	8%	8%	53%	71%	75%	74%	49%	56%	48%	39%	48%
Dysphagia Gr3+	8%	11%	25%	34%	55%	71%	81%	79%	71%	9%	0%	0%	0%
Tube feeding	5%	6%	17%	31%	46%	62%	69%	77%	69%	3%	0%	0%	0%
Salivary duct inflammation Gr2+	0%	0%	13%	23%	43%	59%	70%	79%	30%	12%	10%	7%	10%
Dermatitis Gr2+	0%	0%	0%	0%	8%	17%	42%	58%	0%				
Sore mouth Gr2+	5%	0%	6%	11%	18%	24%	24%	38%	6%	0%	0%	0%	0%
Mucosal reactions Gr3+	0%	0%	0%	3%	3%	27%	39%	39%	3%	0%	0%	0%	0%
Sore throat Gr2+	3%	0%	0%	7%	11%	14%	13%	18%	13%	0%	0%	0%	0%
Laryngeal voice Gr2+	2%	3%	8%	10%	14%	3%	11%						
Aspiration Gr2+	0%	0%	0%	7%	8%	8%	17%						
Dry mouth Gr3+	0%	0%	0%	5%	5%	6%	8%						
Laryngeal edema Gr2+	0%												

Acute toxicity (W1–W12) | Late toxicity (M6–M24)

1.3 late toxicities per patient

Figure courtesy of Hans Langendijk

4. Reduced toxicities (2)

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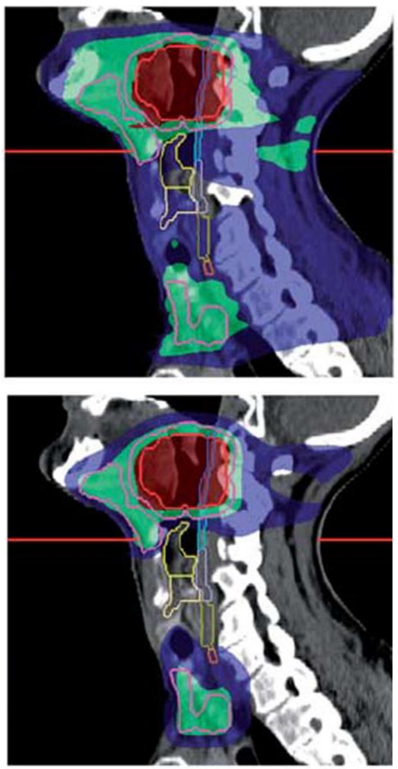


Total Toxicity Burden (grade 2+ and grade 3+)

Photons (n=42)

Toxicity endpoints	T0	W1	W2	W3	W4	W5	W6	W7	W12	M6	M12	M18	M24
Dysphagia Gr2+	16%	17%	31%	60%	70%	91%	97%	97%	77%	29%	16%	16%	17%
Dysgeusia Gr2+	7%	8%	8%	42%	73%	92%	92%	100%	46%	13%	17%	14%	32%
Mucosal reactions Gr2+	0%	0%	0%	28%	59%	79%	83%	88%	34%	3%	19%	12%	21%
Dry mouth Gr2+	0%	3%	8%	8%	53%	71%	75%	74%	49%	56%	48%	39%	48%
Dysphagia Gr3+	8%	11%	25%	34%	55%	71%	81%	79%	71%	9%	0%	0%	0%
Tube feeding	5%	6%	17%	31%	46%	62%	69%	77%	69%	3%	0%	0%	0%
Salivary duct inflammation Gr2+	0%	0%	13%	23%	43%	59%	70%	79%	30%	12%	10%	7%	10%
Dermatitis Gr2+	0%	0%	0%	0%	8%	17%	42%	58%	0%				
Sore mouth Gr2+	5%	0%	6%	11%	18%	24%	24%	38%	6%	0%	0%	0%	0%
Mucosal reactions Gr3+	0%	0%	0%	3%	3%	27%	39%	39%	3%	0%	0%	0%	0%
Sore throat Gr2+	3%	0%	0%	7%	11%	14%	13%	18%	13%	0%	0%	0%	0%
Laryngeal voice Gr2+	2%	3%	8%	10%	14%	3%	11%	18%	29%	2%	0%	0%	0%
Aspiration Gr2+	0%	0%	0%	7%	8%	8%	17%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dry mouth Gr3+	0%	0%	0%	5%	5%	6%	8%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Laryngeal edema Gr2+	0%								[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Protons (n=99)

Toxicity endpoints	T0	W1	W2	W3	W4	W5	W6	W7	W12	M6	M12	M18	M24
Dysphagia Gr2+	7%	6%	7%	19%	28%	40%	51%	68%	19%	5%	0%	0%	0%
Dysgeusia Gr2+	7%	7%	12%	19%	36%	44%	47%	50%	17%	0%	0%	0%	0%
Mucosal reactions Gr2+	0%	0%	0%	7%	17%	33%	58%	75%	0%	5%	11%	10%	7%
Dry mouth Gr2+	2%	0%	0%	0%	3%	7%	11%	14%	15%	12%	13%	10%	13%
Dysphagia Gr3+	3%	3%	5%	10%	14%	26%	35%	45%	9%	2%	0%	0%	0%
Tube feeding	2%	2%	4%	5%	12%	19%	28%	34%	8%	2%	0%	0%	0%
Salivary duct inflammation Gr2+	2%	2%	0%	2%	5%	9%	18%	16%	9%	5%	7%	5%	6%
Dermatitis Gr2+	0%	0%	0%	0%	9%	28%	63%	84%	0%				
Sore mouth Gr2+	2%	2%	2%	6%	6%	12%	12%	14%	2%	0%	0%	0%	0%
Mucosal reactions Gr3+	0%	0%	0%	0%	2%	5%	14%	32%	0%	0%	0%	0%	0%
Sore throat Gr2+	0%	0%	0%	3%	5%	9%	12%	18%	0%	0%	0%	0%	0%
Laryngeal voice Gr2+	0%	0%	5%	10%	7%	0%	2%	0%	4%	0%	0%	0%	0%
Aspiration Gr2+	0%	0%	0%	[illegible]	0%	[illegible]	13%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dry mouth Gr3+	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Laryngeal edema Gr2+	[illegible]												

Acute toxicity (T0–W12) | Late toxicity (M6–M24)

1.3 late toxicities per patient

4.3x reduction

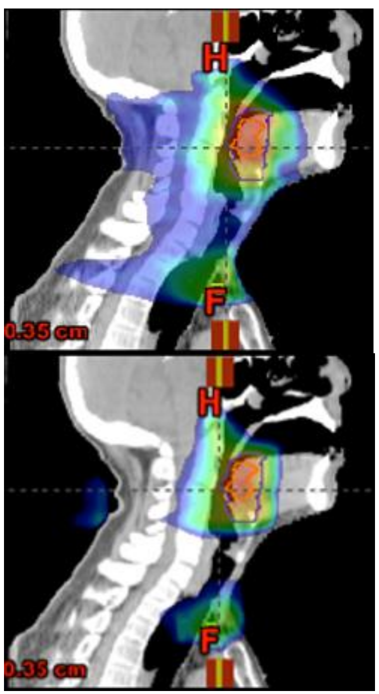
0.3 late toxicities per patient

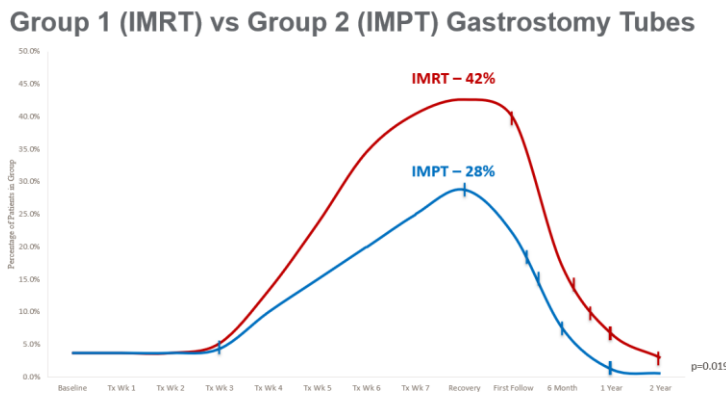
Figure courtesy of Hans Langendijk

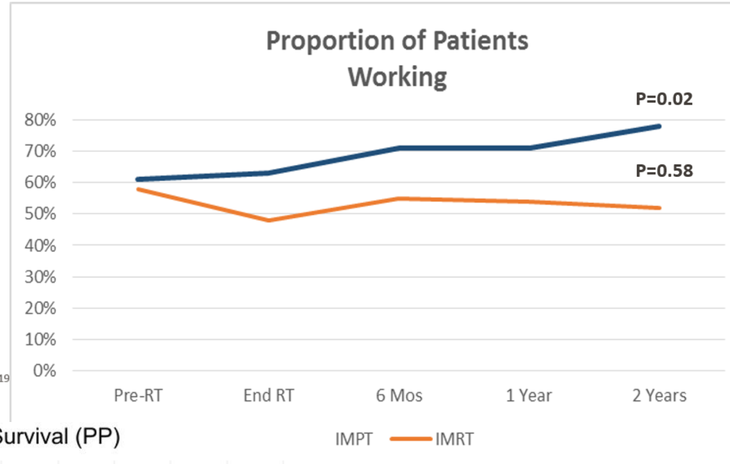
5. Increased survival?

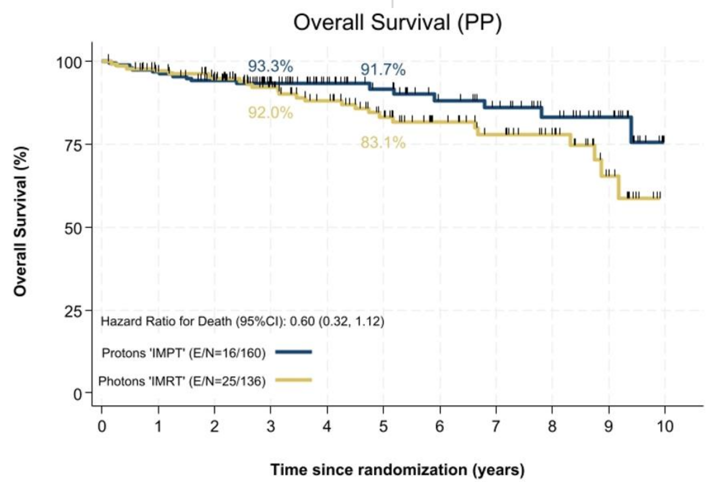
The recent phase 3 clinical trial from MD Anderson

- MD Anderson Phase III clinical trial
- 296 Oropharyngeal cancer treatments (136 IMRT, 160 PBS PT)









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Summary

- The proton Bragg peak can substantially reduce mid-to-low doses delivered to normal tissues…
- … but makes proton therapy more sensitive to anatomical changes and motion
- Nevertheless, studies indicate that reduced normal tissue could result in substantial reductions in secondary tumour incidence (factor 2-3)…
- … and also to improved tolerance to radio-chemo therapy regimes
- In addition, substantial reductions in late normal tissue side effects are also being observed.
- Costs however remain high, making patient selection an important topic

Proton therapy in Switzerland

Any questions?