EMORY
PROTON THERAPY CENTER
WINSHIP CANCER INSTITUTE

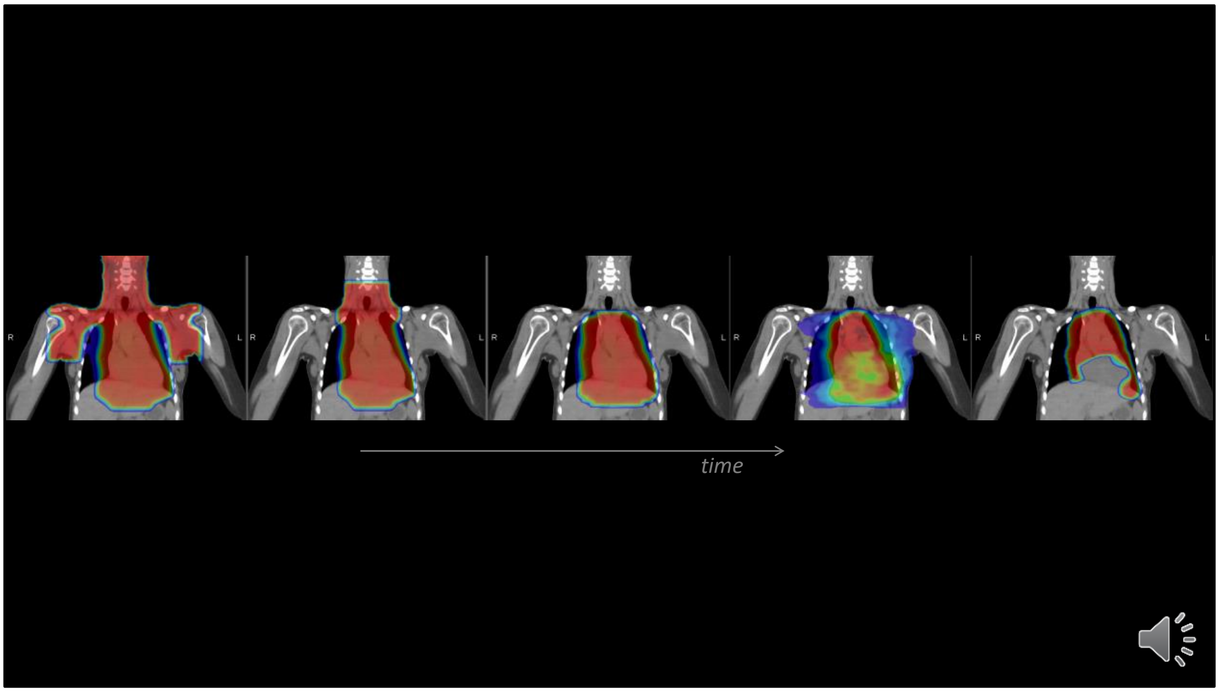
Most pediatric patients should be treated at proton therapy centers

Yes, because proton therapy is technically superior to photon therapy

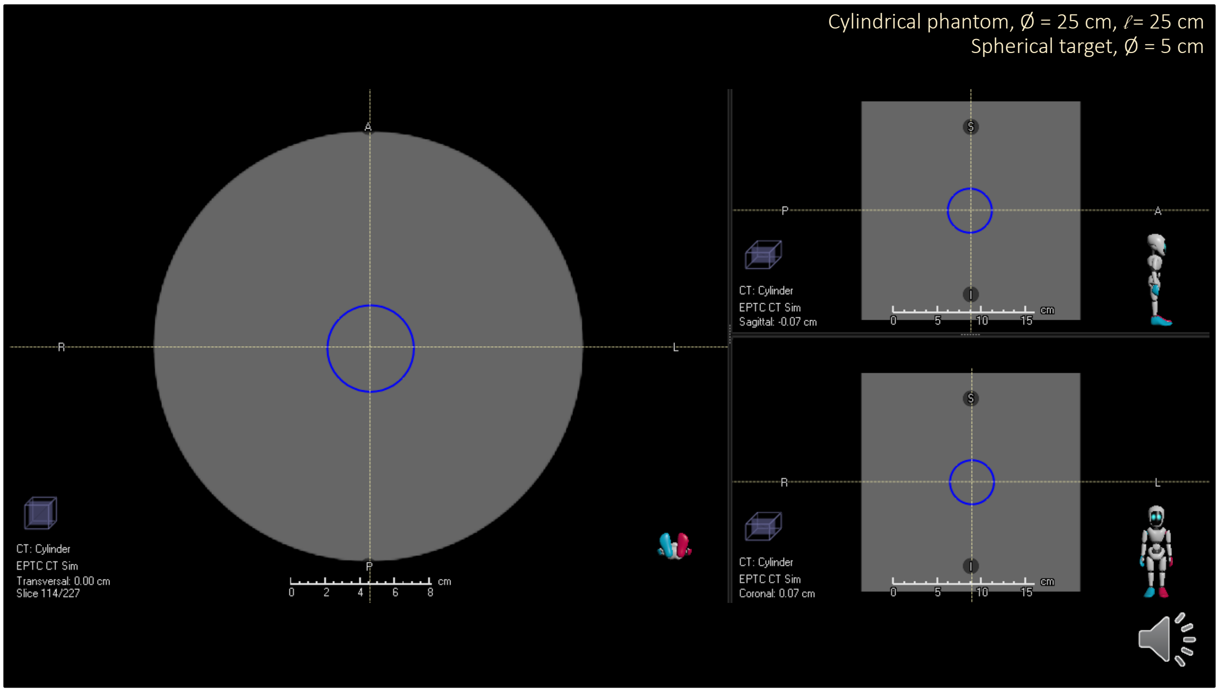
Stella Flampouri

July 2020

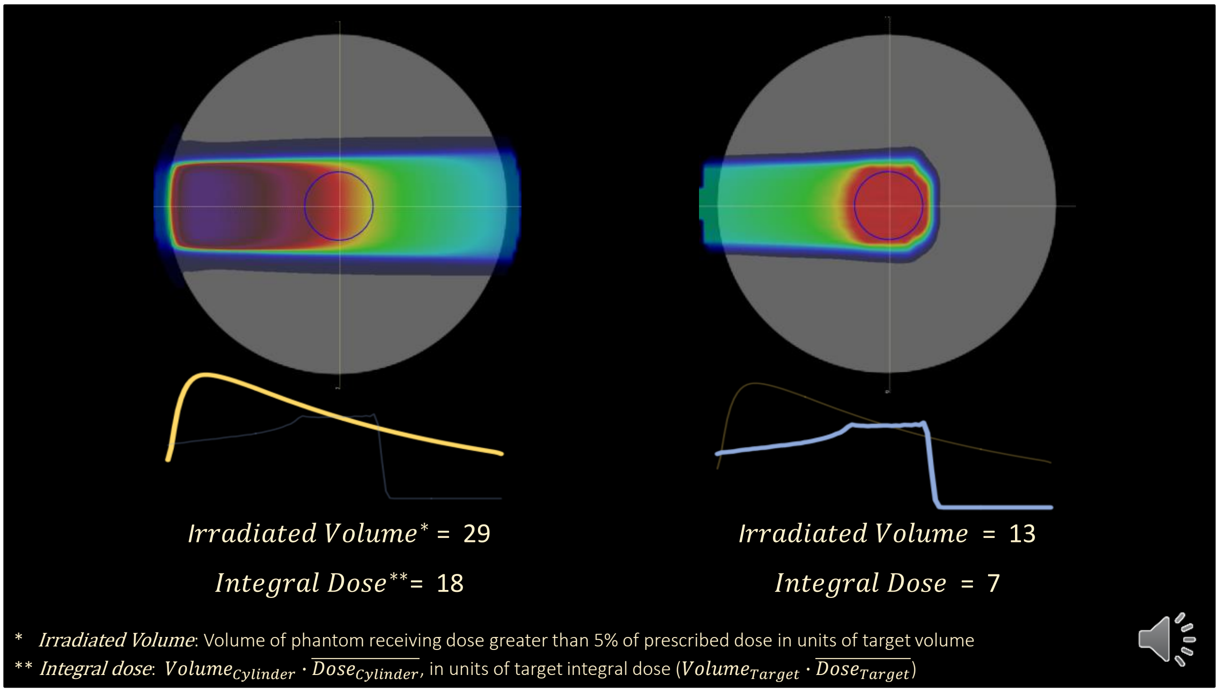
Protons are more suitable than photons for children in need of radiation treatment



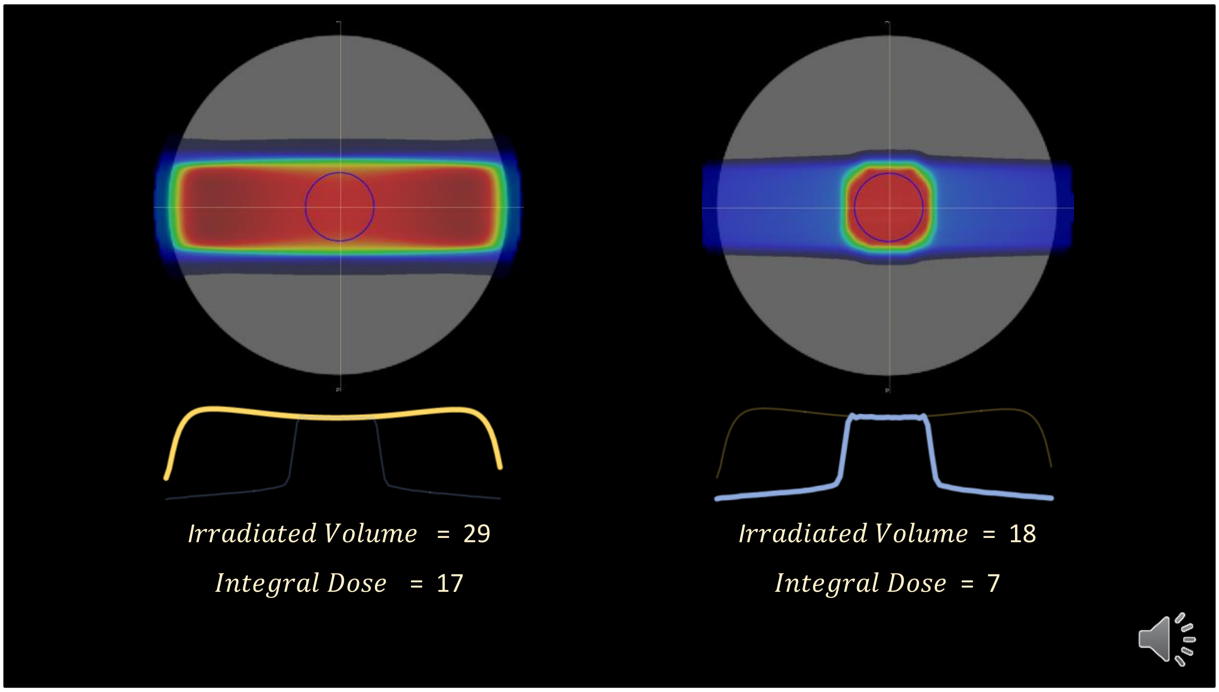
Progress in radiotherapy means less dose to non-target tissue.



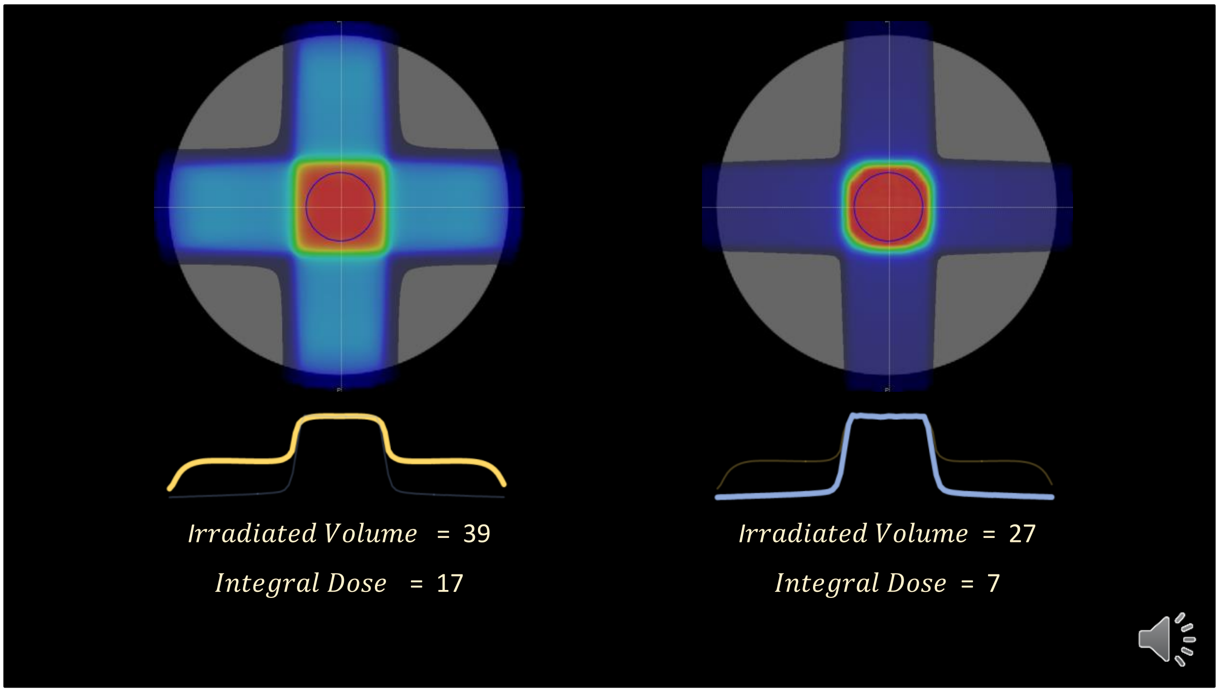
Proton are ‘technically’ better than photons because they treat the target while irradiating less of non-target tissue or to lower doses
Water phantom example



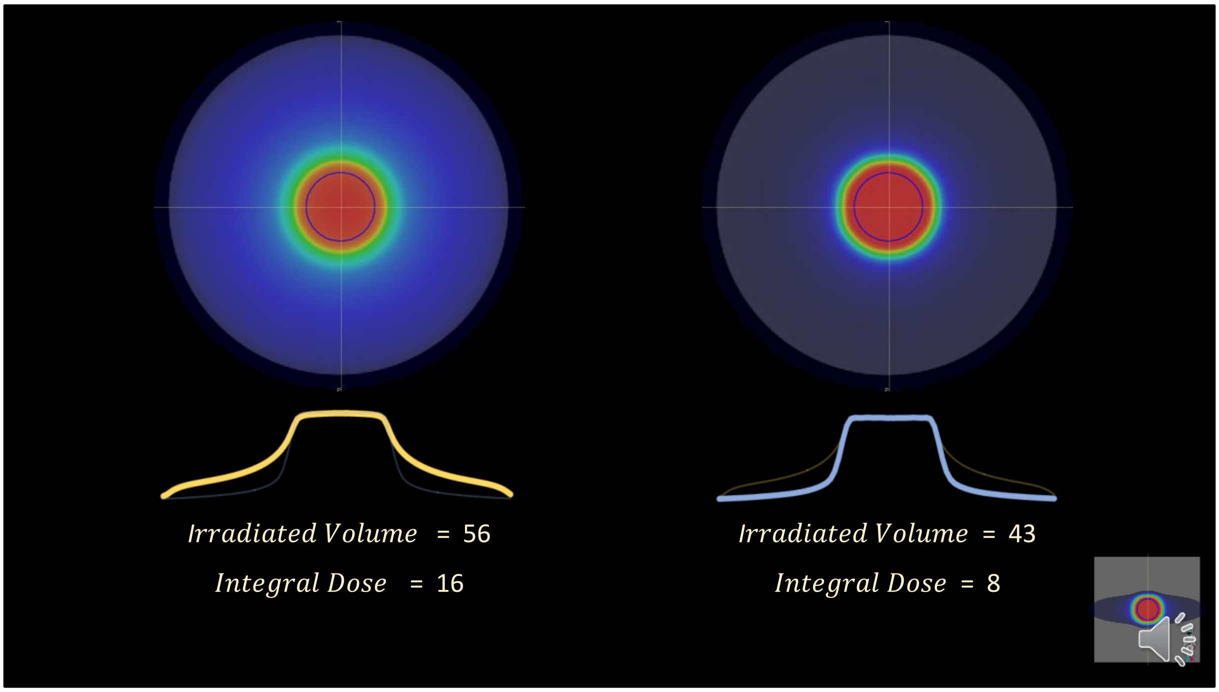
Single proton field treats target with homogenous dose while irradiating less volume and depositing less energy outside the target



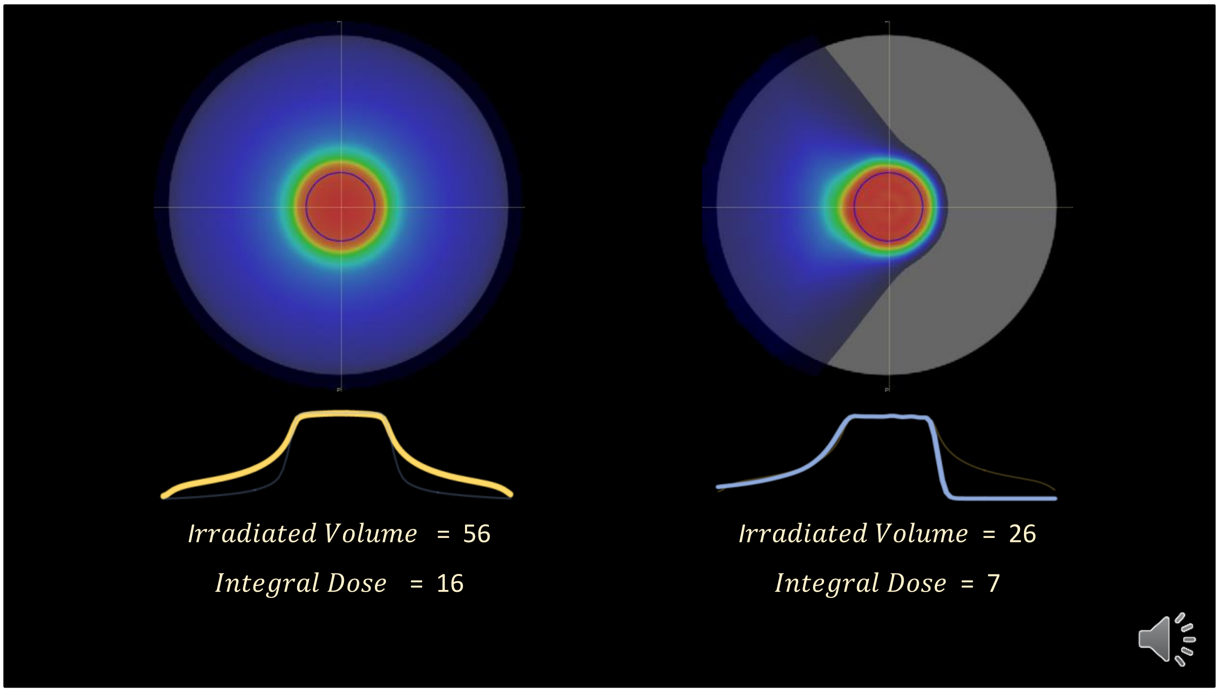
For 2 fields, photons treat the target almost as well as protons but do not spare non-target tissues



With 4 fields photons are improving



Photon state of the art treatments are delivered by arcs. Similar field arrangement with protons still deposits less dose outside the target.



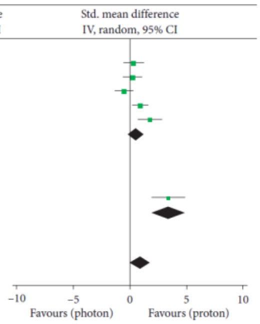
Accepting similar proximal non-target dose, protons can deliver the same target dose with partial arcs and spare completely tissues (full photon arc versus 130degree proton arc)

Proton versus Photon Radiotherapy for Pediatric Central Nervous System Malignancies: A Systematic Review and Meta-Analysis of Dosimetric Comparison Studies

Roberta Carbonara, Alessia Di Rito, [...], and Angela Sardaro

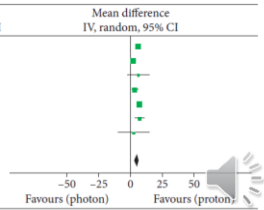
Homogeneity Index

Study or subgroup	Photon Mean	Photon SD	Photon Total	Proton Mean	Proton SD	Proton Total	Weight	Std. mean difference IV, random, 95% CI
1.1.1 IMRT/VMAT								
Boehling, 2012	0.25	0.06	10	0.23	0.06	10	17.2%	0.32 [−0.56, 1.20]
Correia, 2019	5	1.4	11	4.7	1	11	17.5%	0.24 [−0.60, 1.08]
Freund, 2015	0.07	0.05	13	0.12	0.12	13	17.8%	−0.53 [−1.31, 0.26]
Howell, 2012	1.05	0.009	18	1.04	0.012	18	18.4%	0.92 [0.23, 1.61]
Stoker, 2018	15.1	6.3	10	6.8	0.8	10	15.9%	1.77 [0.70, 2.84]
Subtotal (95% CI)			*62*			*62*	*86.8%*	*0.51 [−0.19, 1.21]*
Heterogeneity: $tau^2 = 0.45$; $chi^2 = 13.93$; $df = 4$ ($P = 0.008$); $I^2 = 71\%$								
Test for overall effect: $Z = 1.42$ ($P = 0.16$)								
1.1.2 3D-CRT								
Yoon, 2011	28.7	5.9	10	12.8	2.3	10	13.2%	3.40 [1.93, 4.87]
Subtotal (95% CI)			*10*			*10*	*13.2%*	*3.40 [1.93, 4.87]*
Heterogeneity: not applicable								
Test for overall effect: $Z = 4.54$ ($P < 0.00001$)								
Total (95% CI)			*72*			*72*	*100.0%*	*0.90 [0.02, 1.78]*
Heterogeneity: $tau^2 = 0.98$; $chi^2 = 28.43$; $df = 5$ ($P < 0.0001$); $I^2 = 82\%$								
Test for overall effect: $Z = 2.01$ ($P = 0.04$)								
Test for subgroup differences: $chi^2 = 12.16$; $df = 1$ ($P = 0.0005$); $I^2 = 91.8\%$								



Normal Brain D_{mean}

Study or subgroup	Photon Mean	Photon SD	Photon Total	Proton Mean	Proton SD	Proton Total	Weight	Mean difference IV, random, 95% CI
Correia, 2019	17.84	1.62	11	12	1.03	11	23.1%	5.84 [4.71, 6.97]
Boehling, 2012	7.6	2.7	10	5.6	1.8	10	19.0%	2.00 [−0.01, 4.01]
Takizawa, 2017 (1)	14.79	8.87	6	8.6	6.17	6	3.4%	6.19 [−2.46, 14.84]
Takizawa, 2017 (2)	18.33	2.26	6	14.88	1.89	6	17.3%	3.45 [1.09, 5.81]
MacDonald, 2008 (1)	12.5	0.5	2	5.5	0.5	2	23.7%	7.00 [6.02, 7.98]
Freund, 2015	17.5	5.6	13	10.3	4	13	11.6%	7.20 [3.46, 10.94]
Stoker, 2018	38.9	19.9	10	36.3	0.5	10	1.8%	2.60 [−9.74, 14.94]
Total (95% CI)			*58*			*58*	*100.0%*	*5.08 [3.36, 6.80]*
Heterogeneity: $tau^2 = 3.00$; $chi^2 = 24.10$; $df = 6$ ($P = 0.0005$); $I^2 = 75\%$								
Test for overall effect: $Z = 5.79$ ($P < 0.00001$)								



Superior proton distribution holds not only for the simple example but also patients. It is very difficult to find a dosimetric comparison study that photon dose is better.
This is a recent review of dosimetric comparisons between protons and photons for pediatric CNS. Protons better on everything but conformity

Radiation Oncology

Advantage of proton-radiotherapy for pediatric patients and adolescents with Hodgkin's disease

S. Lautenschlaeger[1*], G. Iancu[1], V. Flatten[1,2], K. Baumann[1,2], M. Thiemer[1], C. Dumke[1], K. Zink[1,2], H. Hauswald[1,3,7], D. Vordermark[4], C. Mauz-Körholz[5,6], R. Engenhart-Cabillic[1,7] and F. Eberle[1,7]

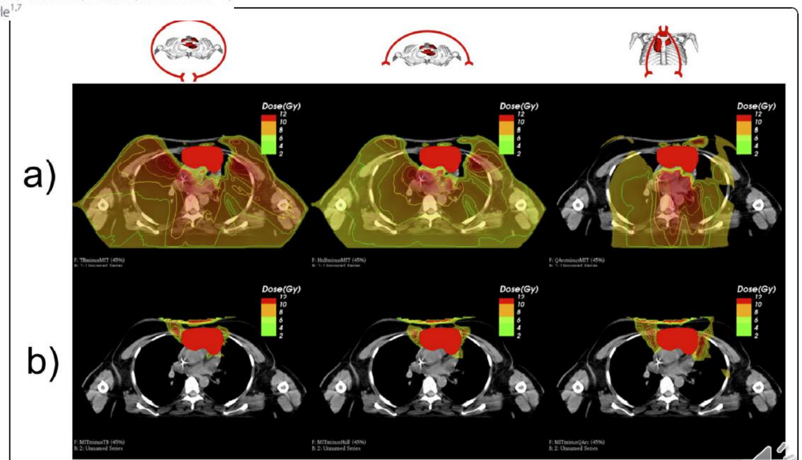


Fig. 6 **a** Areas in which the VMAT / IMRT plans will deliver more dose to organs at risk or the body compartment. **b** Areas in which the proton plan delivers more dose to organs at risk or the body compartment compared to the VMAT / IMRT plant

Pediatric HL dose comparison. State of the art plans for both modalities

Comparative Study > Radiother Oncol. 2019 Sep;138:158-165. doi: 10.1016/j.radonc.2019.06.025.
Epub 2019 Jul 11.

Evaluating the Benefit of PBS vs. VMAT Dose Distributions in Terms of Dosimetric Sparing and Robustness Against Inter-Fraction Anatomical Changes for Pediatric Abdominal Tumors

Filipa Guerreiro [1], Cornel Zachiu [2], Enrica Seravalli [3], Cássia O Ribeiro [4], Geert O Janssens [5], Mario Ries [6], Baudouin Denis de Senneville [7], John H Maduro [8], Charlotte L Brouwer [9], Erik W Korevaar [10], Antje C Knopf [11], Bas W Raaymakers [12]

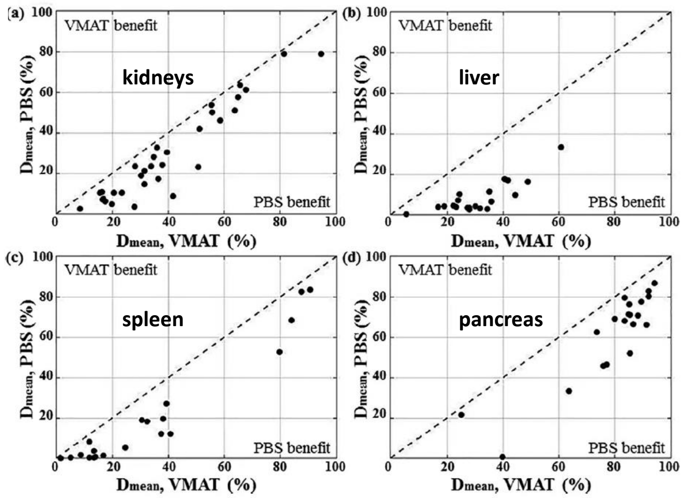
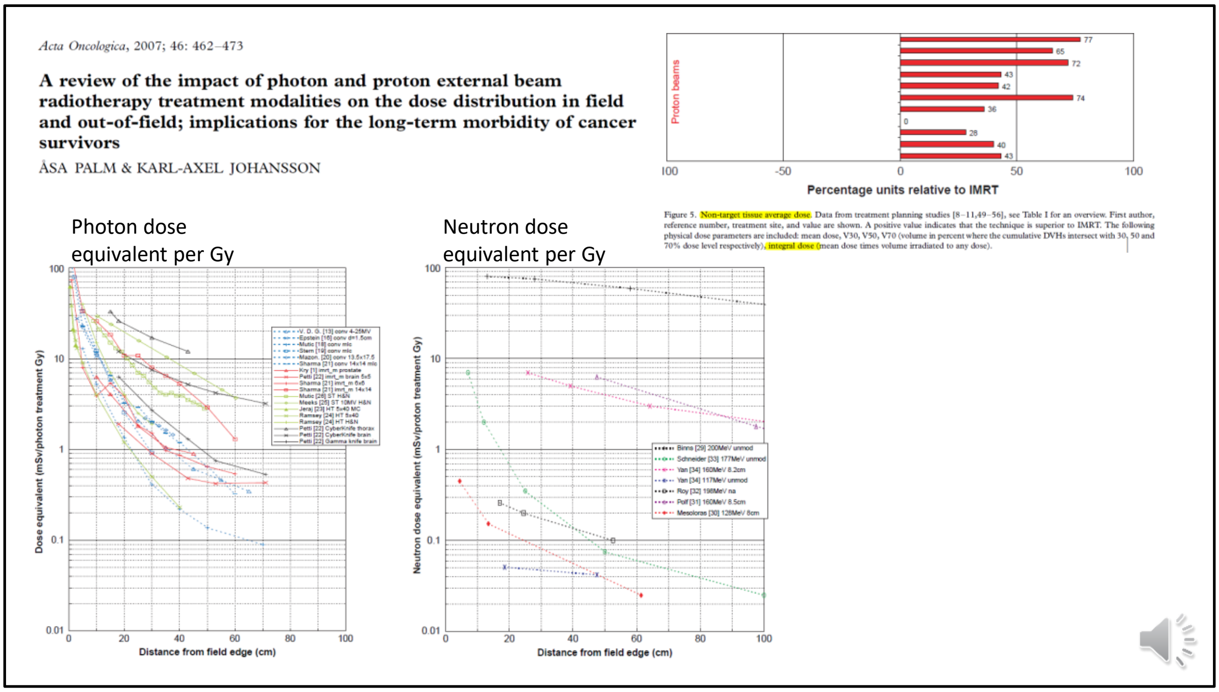
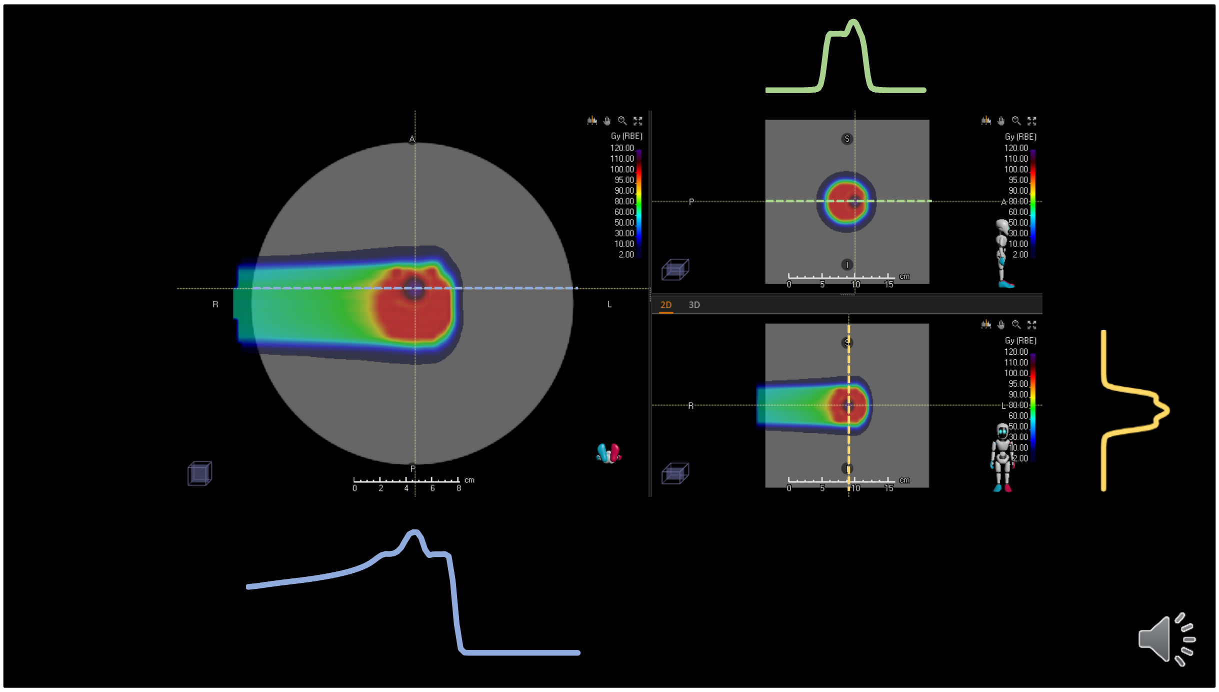


Fig. 2. D_{mean} delivered by VMAT and PBS to the OARs for the kidneys (a), liver (b), spleen (c) and pancreas (d).

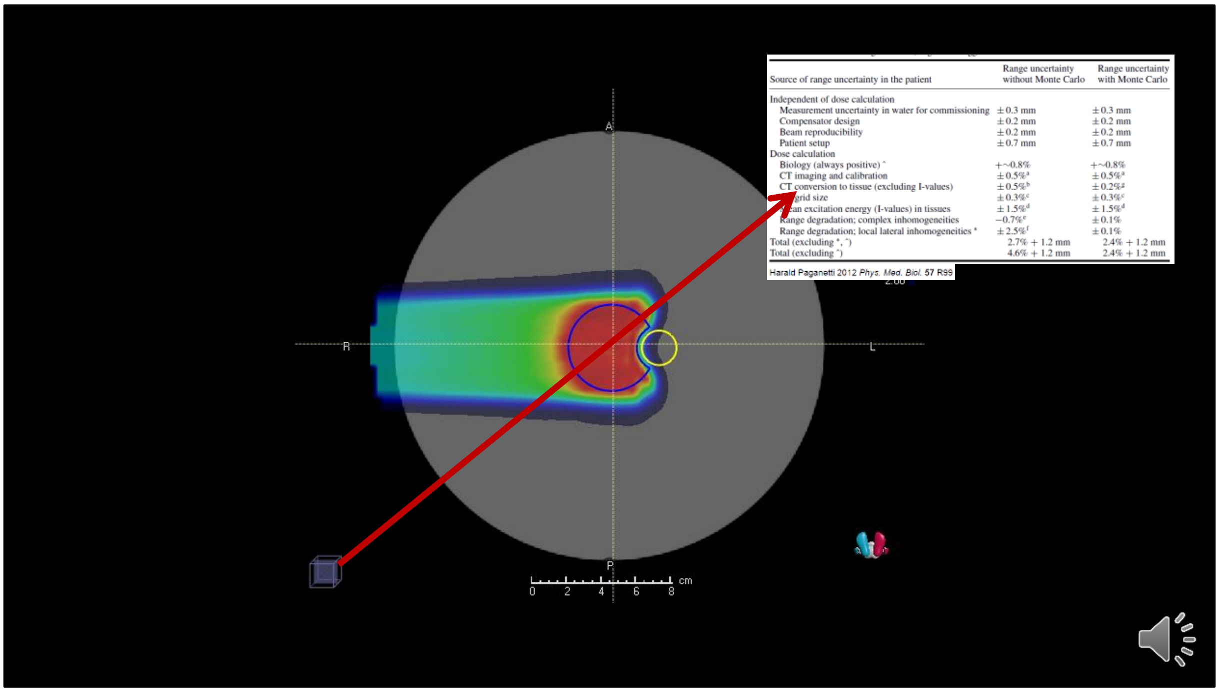
This dose comparison includes daily setup errors and their dosimetric effects



Not pediatric specific but this study includes integral dose and out of field dose.



Another inherent quality of protons is our ability to modulate them in depth, an additional dimension compared to photons



Source of range uncertainty in the patient	Range uncertainty without Monte Carlo	Range uncertainty with Monte Carlo
Independent of dose calculation		
Measurement uncertainty in water for commissioning	±0.3 mm	±0.3 mm
Compensator design	±0.2 mm	±0.2 mm
Beam reproducibility	±0.2 mm	±0.2 mm
Patient setup	±0.7 mm	±0.7 mm
Dose calculation		
Biology (always positive) ^	+~0.8%	+~0.8%
CT imaging and calibration	±0.5%[a]	±0.5%[a]
CT conversion to tissue (excluding I-values)	±0.5%[b]	±0.2%[g]
grid size	±0.3%[c]	±0.3%[c]
ean excitation energy (I-values) in tissues	±1.5%[d]	±1.5%[d]
Range degradation; complex inhomogeneities	−0.7%[e]	±0.1%
Range degradation; local lateral inhomogeneities *	±2.5%[f]	±0.1%
Total (excluding *, ^)	2.7% + 1.2 mm	2.4% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm	2.4% + 1.2 mm

There are uncertainties, but proton planning is more advanced than photon planning and takes care of them efficiently. 4D robust optimization is just an example.

ELSEVIER
Seminars in RADIATION ONCOLOGY

Robust Proton Treatment Planning: Physical and Biological Optimization

Jan Unkelbach, PhD,* and Harald Paganetti, PhD†

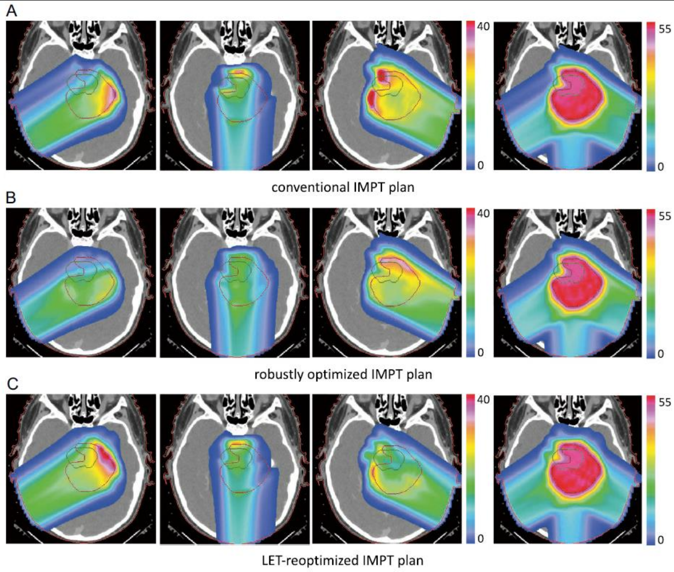
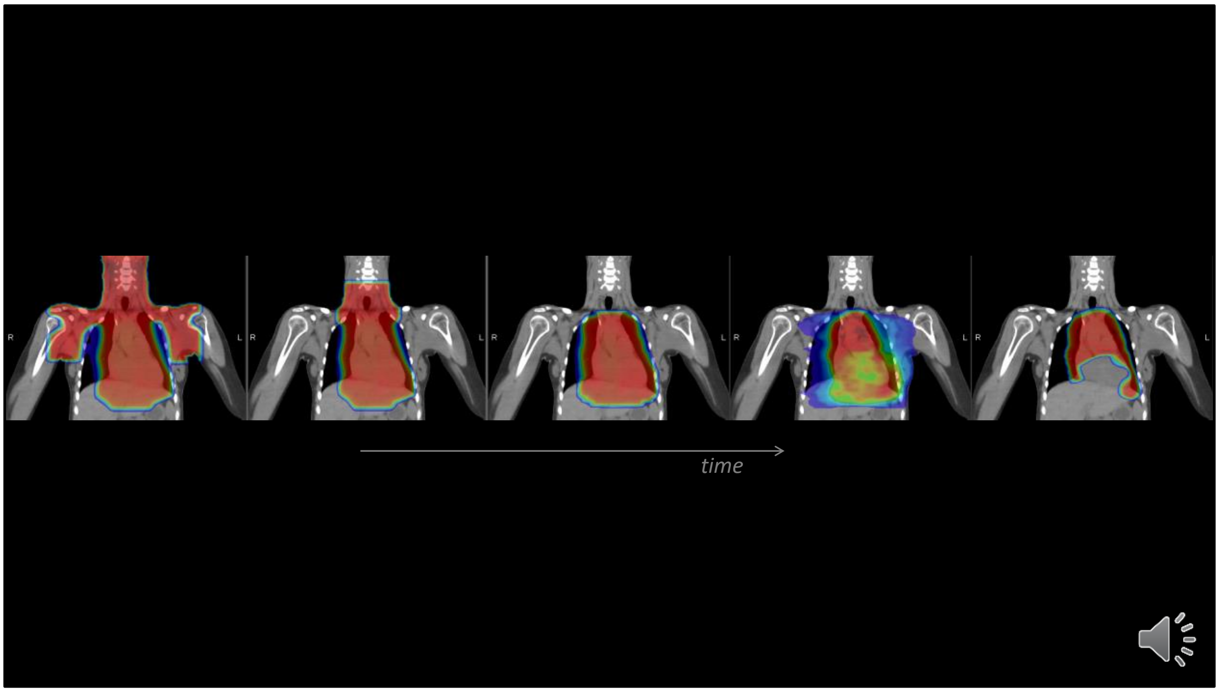


Figure 1 IMPT plans for an ependymoma patient in whom the target volume involves parts of the brainstem. The patient is treated with 3 posterior oblique beams. Pencil beams of approximately 3-5 mm sigma are assumed, corresponding to the latest generation of proton therapy machines. Shown is the dose distribution (right panel) and the dose contributions of the 3 beams. (A) conventional IMPT plan created based on a 2-mm CTV to PTV expansion. (B) Robustly optimized plan accounting for range uncertainty. (C) LET re-optimized plan obtained after minimizing LET × dose in the brainstem while constraining the dose distribution to remain close to the conventional plan.

From PTV optimization we moved to robust optimization and soon to LET-optimization.



Remember what progress in radiotherapy means!