Flash Proton Therapy - Potentials and Pitfalls

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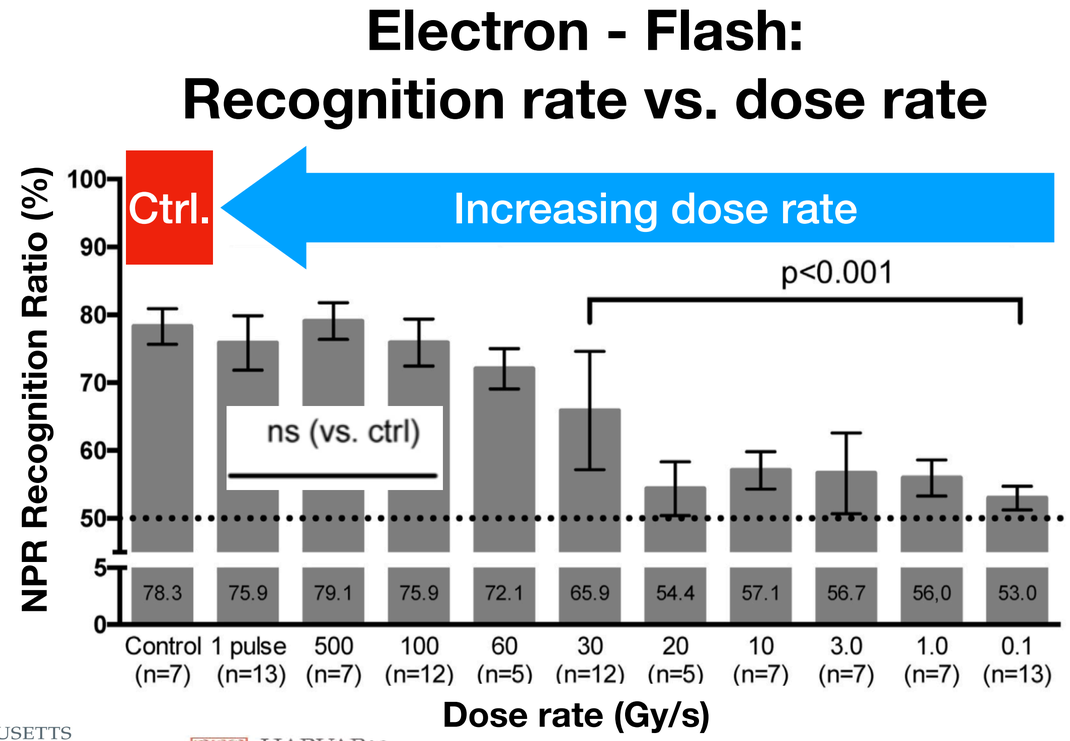
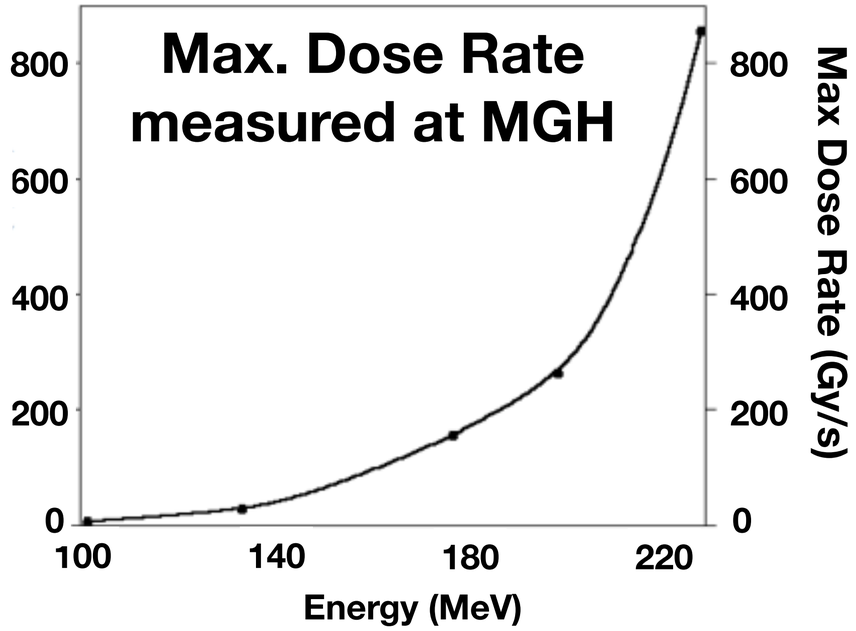
Background

- ★ Extremely high dose-rate (EDR/Flash) irradiations have been shown to reduce radiation damage of normal, healthy tissue in mice, but **NOT in tumors**.
- ★ Flash > 40 Gy/s
- ★ Flash proton therapy can use already existing treatment systems
- ➡ Flash proton therapy has the potential to fundamentally change radiation therapy





A lot more since then.

OPEN

Ultra high dose rate (35 Gy/sec) radiation does not spare the normal tissue in cardiac and splenic models of lymphopenia and gastrointestinal syndrome

Bhanu Prasad Venkatesulu[1,6], Amrish Sharma[1,6], Julia
Ramaswamy Sadagopan[3], Jessica Symons[1,4], Shiny
Ramesh Tailor[3], Steven H. Lin[1,2,4*] & Sunil Krishnan[1,2,4

Recent reports have shown that very high dose rate radiatio
tends to spare the normal tissues while retaining the therap
series of experiments to assess if ultra-high dose rate of 35 C

Radiotherapy and

Contents lists a

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journal homepage:

Original Article

PHASER: A platform for clinical translat

Peter G. Maxim[a,**], Sami G. Tantawi[b,**], Billy W.

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Institute, Stanford University School of Medicine, United States

ARTICLE INFO

Article history:

ABSTRACT

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Contents lists

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journal homepage

Original Article

Dosimetric and preparation procedures for irradiating biological models with pulsed electron beam at ultra-high dose-rate

Patrik Gonçalves Jorge[a,c,d], Maud Jaccard[a], Kristoffer Petersson[a,c,d], Maude Gondré[a], Maria Teresa Durán[a], Laurent Desorgher[a], Jean-François Germond[a], Philippe Liger[b], Marie-Catherine Vozenin[c,d], Jean Bourhis[c,d], François Bochud[a], Raphaël Moeckli[a,1], Claude Bailat[a,*,1]

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ARTICLE INFO

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International Journal of Radiation Oncology biology • physics

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Physics Contribution

Bringing FLASH to the Clinic: Treatment Planning Considerations for Ultrahigh Dose-Rate Proton Beams

Radiotherapy and Oncology xxx (xxxx) xxx

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journal homepage: www.thegreenjournal.com

Original Article

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J. St-Aubin[a], Ryan T. Flynn[a],

n and Imaging Program, Holden Comprehensive Cancer Center, United States

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Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis[a,b,*], Wendy Jeanneret Sozzi[a], Patrik Gonçalves Jorge[a,b,c], Olivier Gaide[d], Claude Bailat[c], Fréderic Duclos[a], David Patin[a], Mahmut Ozsahin[a], François Bochud[c], Jean-François Germond[c], Raphaël Moeckli[c,1], Marie-Catherine Vozenin[a,b,1]

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journal homepage: www.thegreenjournal.com

Original Article

Feasibility of proton FLASH effect tested by zebrafish embryo irradiation

Elke Beyreuther[a,b,*], Michael Brand[c], Stefan Hans[c], Katalin Hideghéty[d], Leonhard Karsch[b,e], Elisabeth Leßmann[a], Michael Schürer[f], Emília Rita Szabó[d], Jörg Pawelke[b,e]

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hole mouse brain
oss and
neuroinflammation

Danielle A. Simmons[a,#], Frederick M. Lartey[b,c,#], Emil Schüler[b], Marjan Rafat[b,d], Gregory King[b], Anna Kim[b], Ryan Ko[b], Sarah Semaan[a], Selena Gonzalez[a], Melissa Jenkins[b], Pooja Pradhan[b], Zion Shih[b], Jinghui Wang[b], Rie von Eyben[b], Edward E. Graves[b,e], Peter G. Maxim[b,f,*], Frank M. Longo[a,*], Billy W. Loo Jr.[b,e,*]

[a] Department of Neurology and Neurological Sciences, ; [b] Department of Radiation Oncology, Stanford University School of Medicine; [c] The Jackson Laboratory, Sacramento; [d] Department of Chemical and Biomolecular Engineering, Vanderbilt University, Nashville; [e] Stanford Cancer Institute, Stanford University School of Medicine; and [f] Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, United States

J. Schuemann, LLU, 2020

Options of technologies for clinical translation

- ★ Electrons
- ★ MV photons
- ★ Protons
- ★ Ions
- ★ Intra-operative (electrons or kV photons)

- ★ My personal opinions.

Electrons

- ★ ‘Original’ Flash irradiator
- ★ Highly flexible dose rate
- ★ Single pulse control
- ★ Multiple in vivo experiments
- ★ Already performed clinical ‘test’

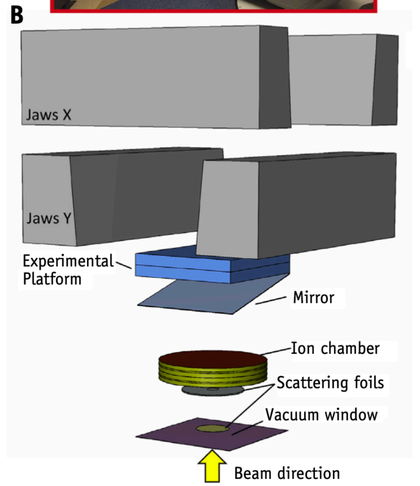
- ★ Caveats:
  - ★ Low energy / low penetration depth
  - ★ Specialized research machine

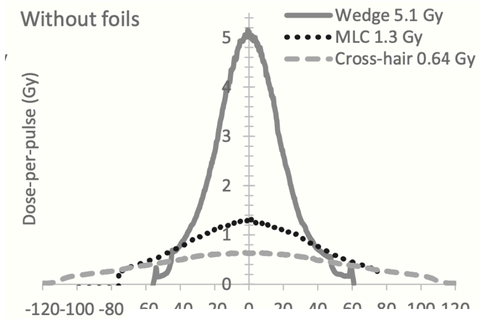
Bourhis, J., et al. (2019). Radiotherapy and Oncology,139, 18.

MV photons

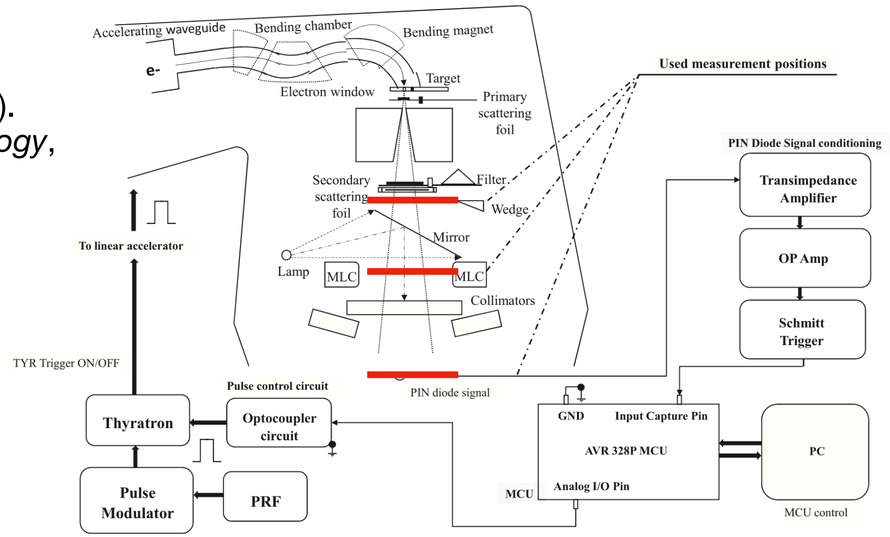
- ★ Linac based approaches
- ★ Used for small animals
- ★ Clinically usable Flash dose rates (up to 120 Gy/s in position 3)
- ★ Flatness good enough for preclinical studies

Schüler, E., et al. (2017). IJROBP, 97(1), 195–203.





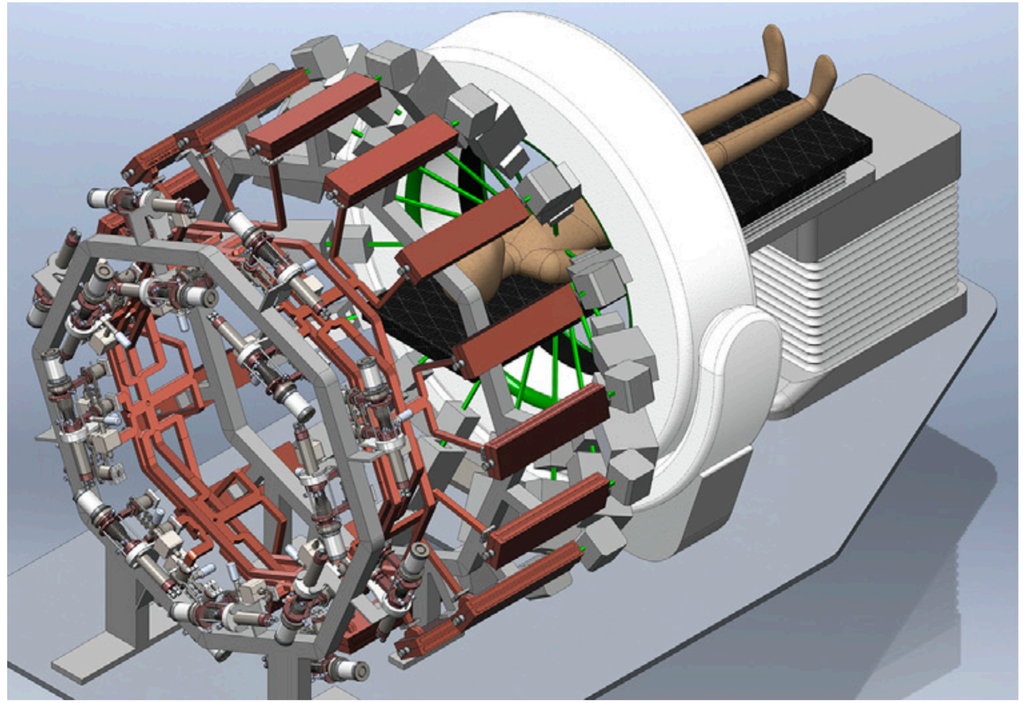
Lempart, M., et al. (2019). *Radiotherapy and Oncology*, *139*, 40–45.



★ Reversible to standard clinical operation

PHASER

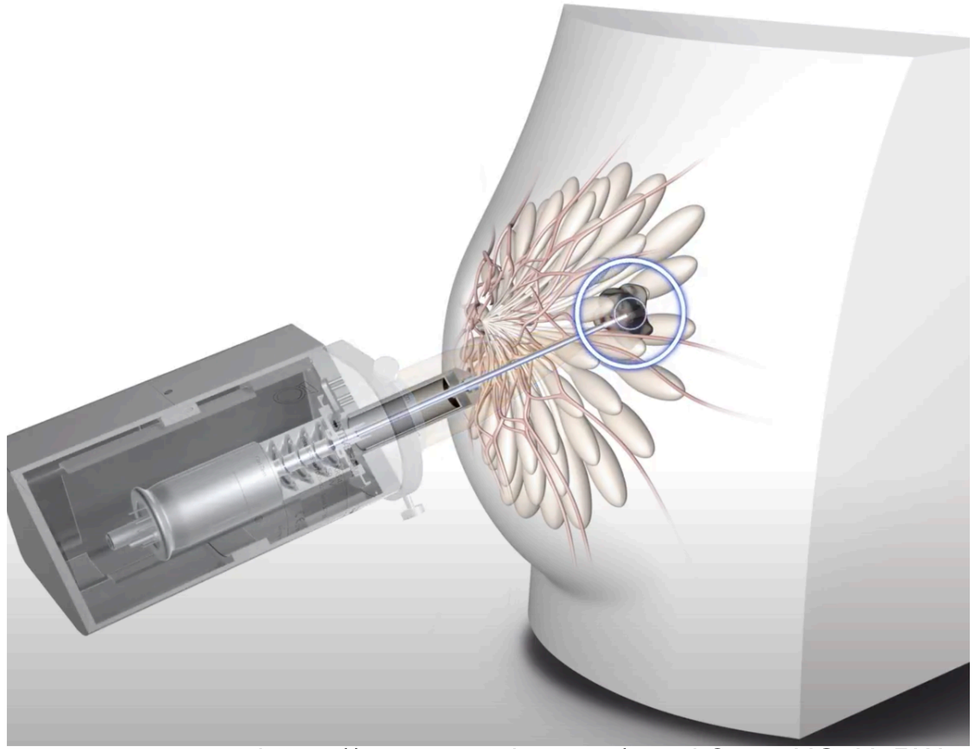
- ★ Originally designed to reduce motion effects and provide cost effective easily transportable RT module
- ★ No moving parts
- ★ Initially Photons
- ★ Later: very high energy electrons (100-200 MeV)
- ★ Achieves Flash-like dose rates



Maxim, P. G., Tantawi, S. G., & Loo, B. W. (2019). Radiotherapy and Oncology, 139, 28–33.

Intra-Op

- ★ Often not thought of
- ★ Short distance from accelerator
- ★ High dose rates often ‘readily’ available
  - ★ Potentially limited to shorter applicators
- ★ IORT provides limited applications



https://www.youtube.com/watch?v=7yUC7HaRWcI

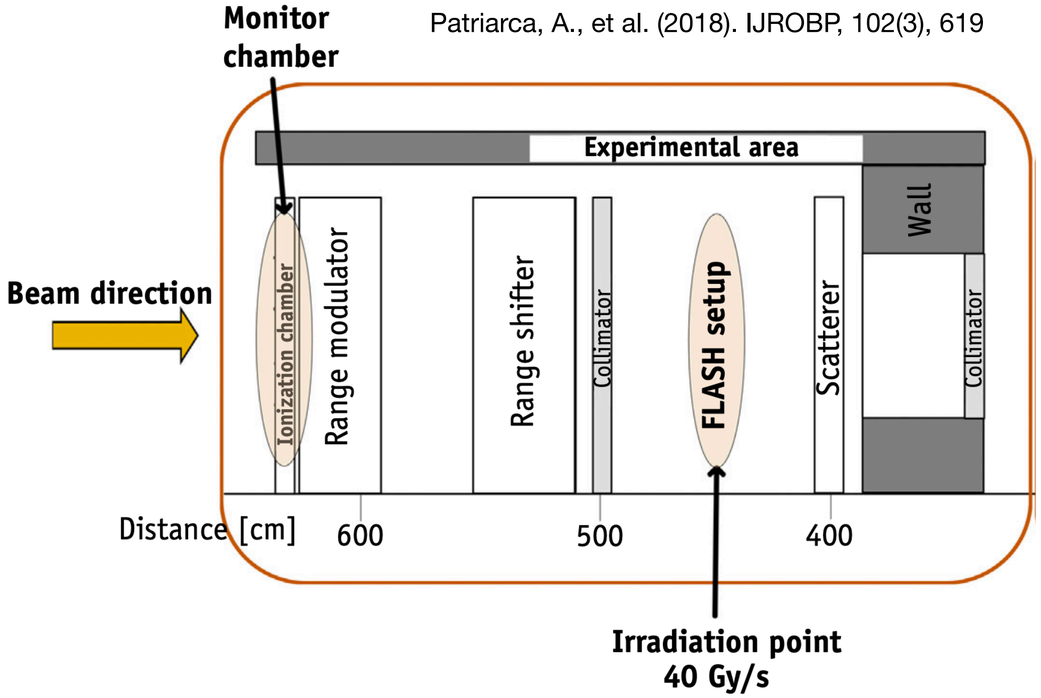
Protons and heavy ions

★ Several small animal systems designed (protons)

★ No heavy ion Flash machine yet

★ Bragg peak vs. Shoot through?

- ★ For small animals both is OK
- ★ Flash is normal tissue effect, Bragg peak in tumor.
- ★ For patients:
  Is it worth giving up the Bragg peak for the Flash effect?



Patriarca, A., et al. (2018). IJROBP, 102(3), 619

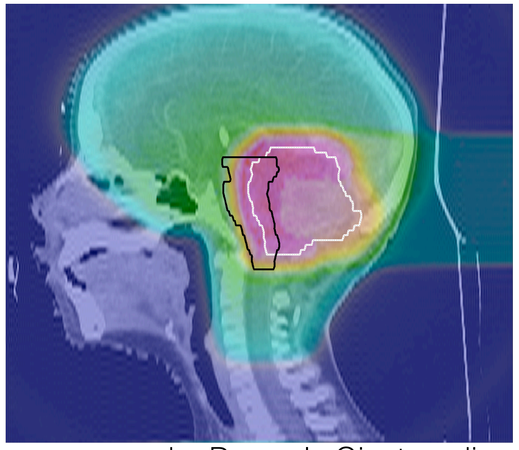
The case for protons - Distal Layer

- ★ Proton therapy typically delivers treatments layer by layer
- ★ Starting with the distal layer

- ★ Distal layer is always in healthy tissue
- ★ Sometimes in OARs
- ★ High RBE → potentially highest biological dose!
- ★ Potentially high impact of Flash

Treatment Room at UMCG

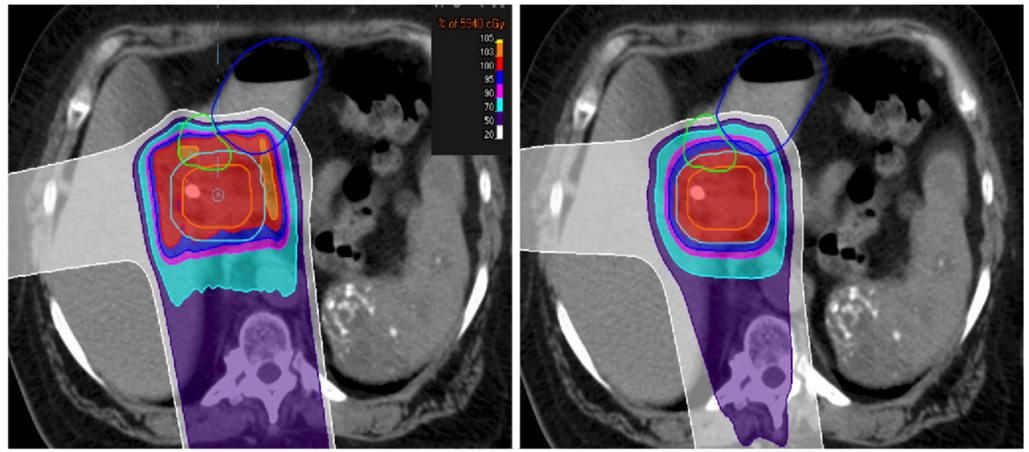
https://www.youtube.com/watch?v=T6m0hnHvZbU



by Drosoula Giantsoudi

The case for protons - Scattering

- ★ ‘Instant’ distal layer
- ★ Usually repainted multiple times (RMW rotation)
- ★ Dose rate in proximal layers likely not Flash
- ★ Dose rate depends on
  - ★ Field size
  - ★ Accelerator current
- ★ Good for small fields



M. Chuong et al., J Gast. Onc. 2018

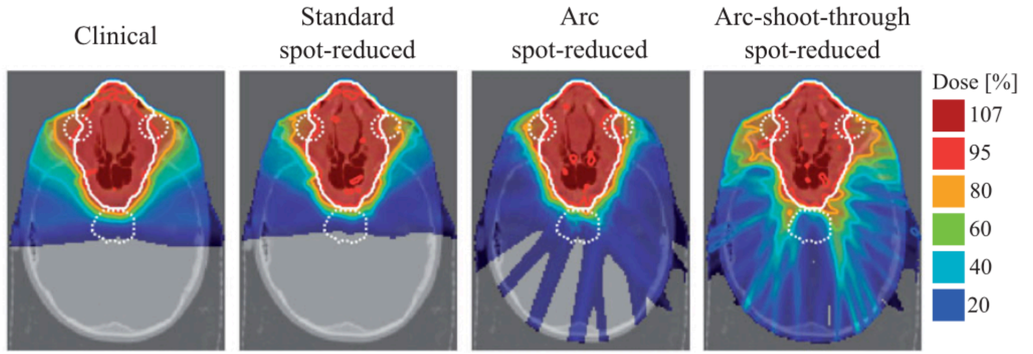
- ★ Is it worth giving up the dose distribution achievable with scanning?

The case for protons - Scanning

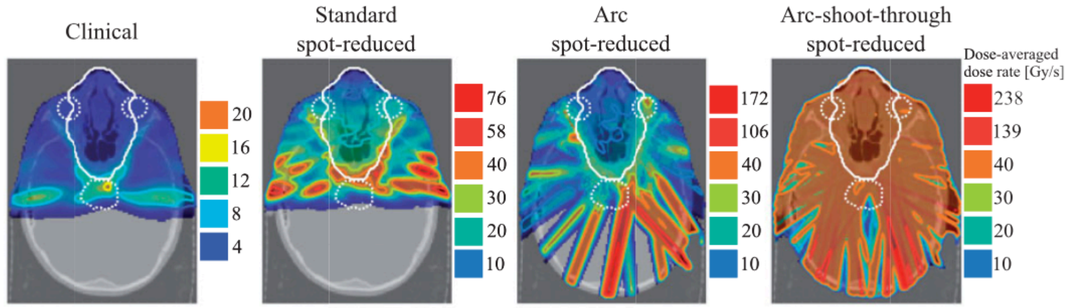
- ★ High dose rate in single pencils
- ★ Lateral scanning is fast
- ★ Depth scanning not as fast
- ★ What about the penumbra of each pencil?
- ★ No more rescanning (is it needed?)
- ★ May need highly reduced spot map

- ★ Is it better?

Dose



S. van de Waters et al., Acta Oncol. 2019

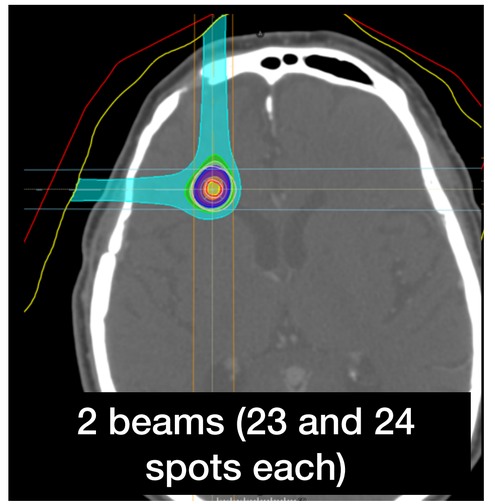


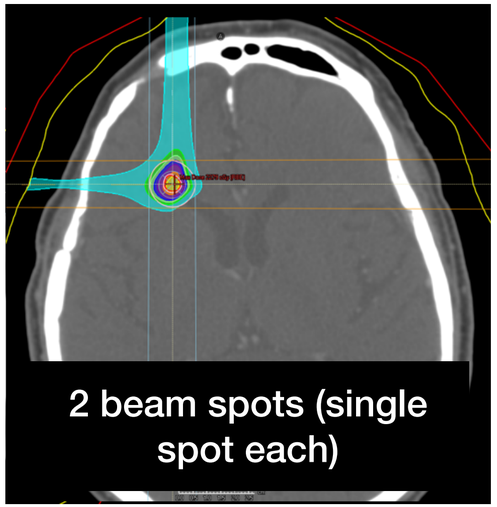
Dose Rate

Optimal targets / first targets

- ★ Radiosurgery (already high dose and dose rate)
- ★ Sites **with** current hypofractioantion (e.g. liver, lung, brain)
  - ★ how will it impact of number of fields
- ★ Will Flash lead to hypofractionation for sites **without** current hypofractionation?
- ★ Sites where NTCP is currently limiting our ability to escalate dose
- ★ Moving targets (requires imaging)
- ★ Intra-operative radiation (e.g. pancreas)

Courtesy J. Daartz



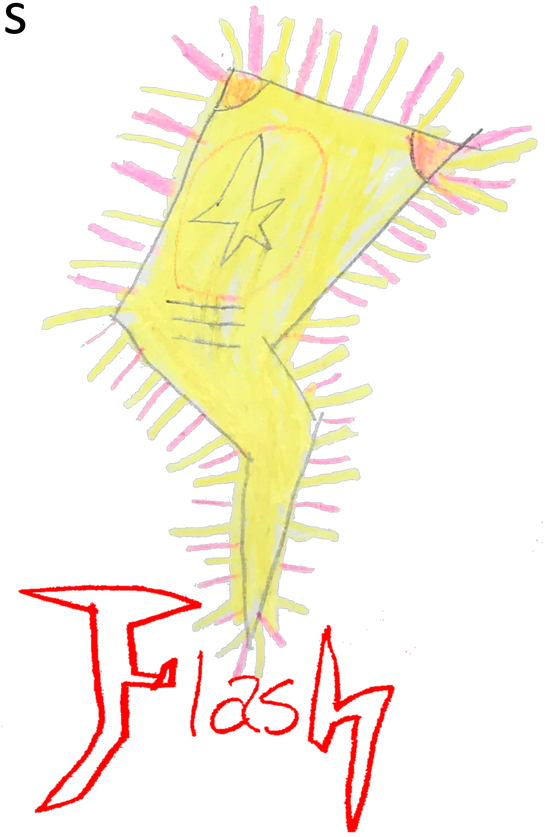


Research questions to be answered in future studies

- ★ What is the underlying mechanism(s)?
  - ★ Single or multiple involved mechanisms (de-oxygenation, lymphocytes, inflammation, …)
- ★ How robust is the effect?
- ★ What are the timing constraints?
  - ★ Intra fraction time limitations
  - ★ Inter fraction time and number limitations
- ★ Are there a field size effects?
- ★ What happens at the field edges (high dose, high but not Flash dose rate)?
- ★ Hypofractionation-Flash vs. fractionated treatments (the 4 Rs)
- ★ How does the Flash Effect interact with other treatments/drugs?

Concluding remarks

- ★ Many groups are working on answering the outstanding questions
- ★ There is a large potential for Flash
- ★ But also many pitfalls
- ★ Predestined for small tumors?
  - ★ Flash vs. SBRT
- ★ Large tumors:
  - ★ Technical challenges
  - ★ Gaps in understanding of the mechanism
- ★ Translation into the clinic should not be rushed



- ★ Potential Benefit of single treatment, even if Flash is only as good as fractionation

Acknowledgements

- ★ MGH Physics group
- ★ MGH Radiation Biology group
- ★ Steele Lab
- ★ TOPAS and TOPAS-nBio collaborations
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- ★ Funding agencies:
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- ★ Damon Runyon Foundation
- ★ The Brain Tumour Charity

- ★ And many more.