2020 Improving Health QUALITY. Increasing Global IMPACT.
JULY 12–16 VIRTUAL EASTERN TIME [GMT-4]
JOINT AAPM | COMP MEETING

Proton Flash-RT, the fastest way to the clinic?

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Options of technologies for clinical translation

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

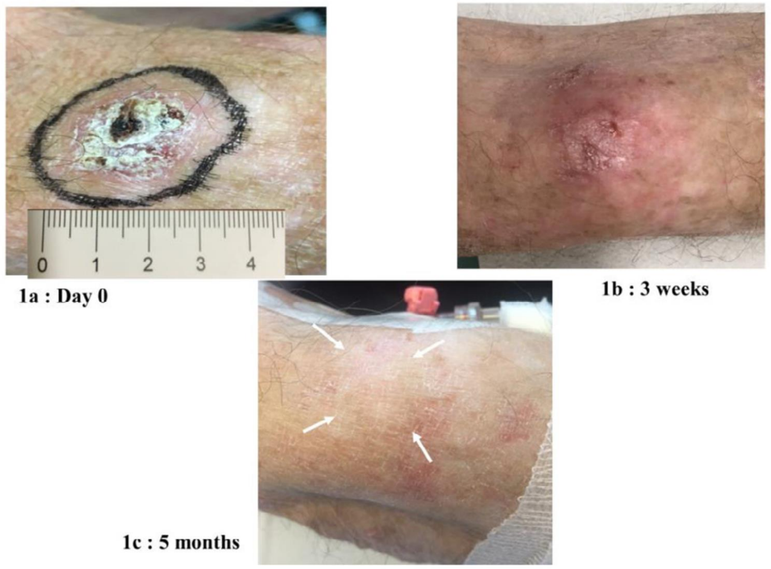
- ★ My personal opinions.

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

- ★ More details in the last talk

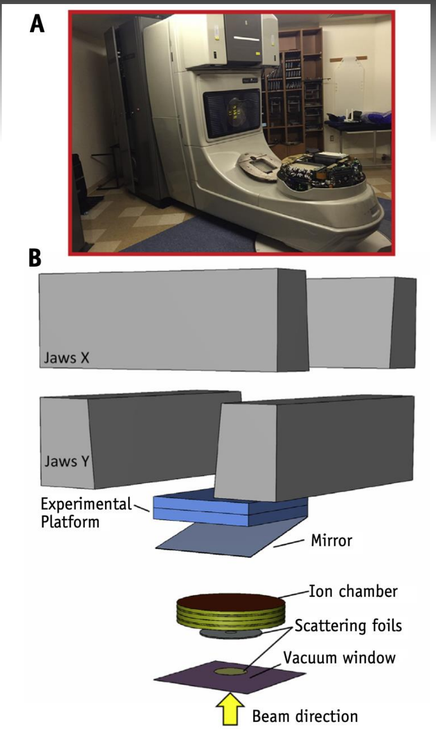


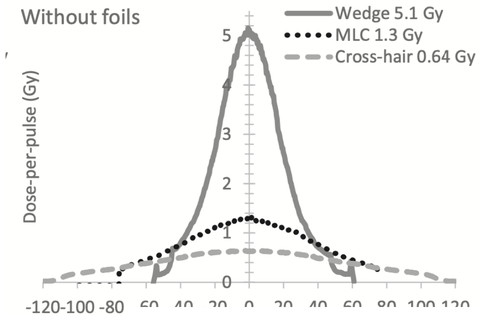
Bourhis, J., et al. (2019). Radiotherapy and Oncology,139, 18.

MV photons

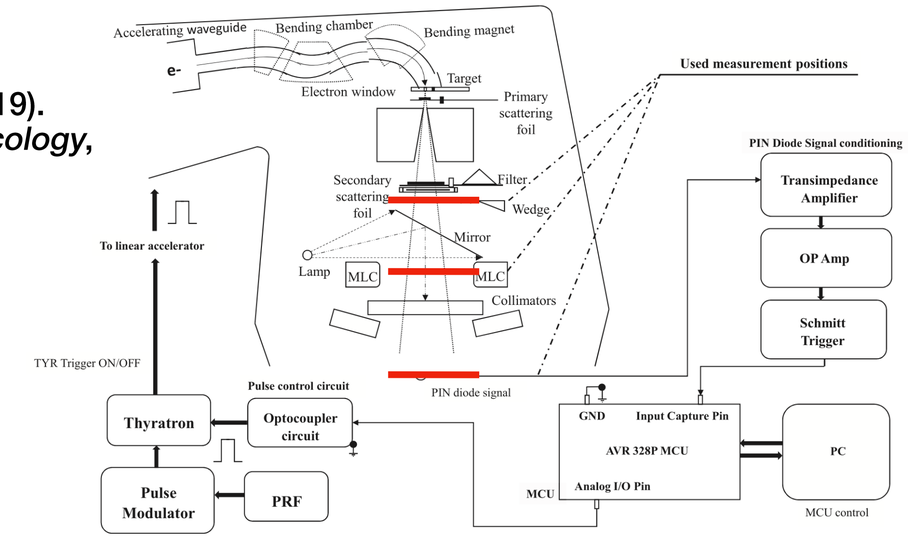
- ★ Linac based approaches
- ★ Used for small animals
- ★ Clinically usable Flash dose rates (up to 120 Gy/s in position 3)
- ★ Flatness good enough for preclinical studies

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





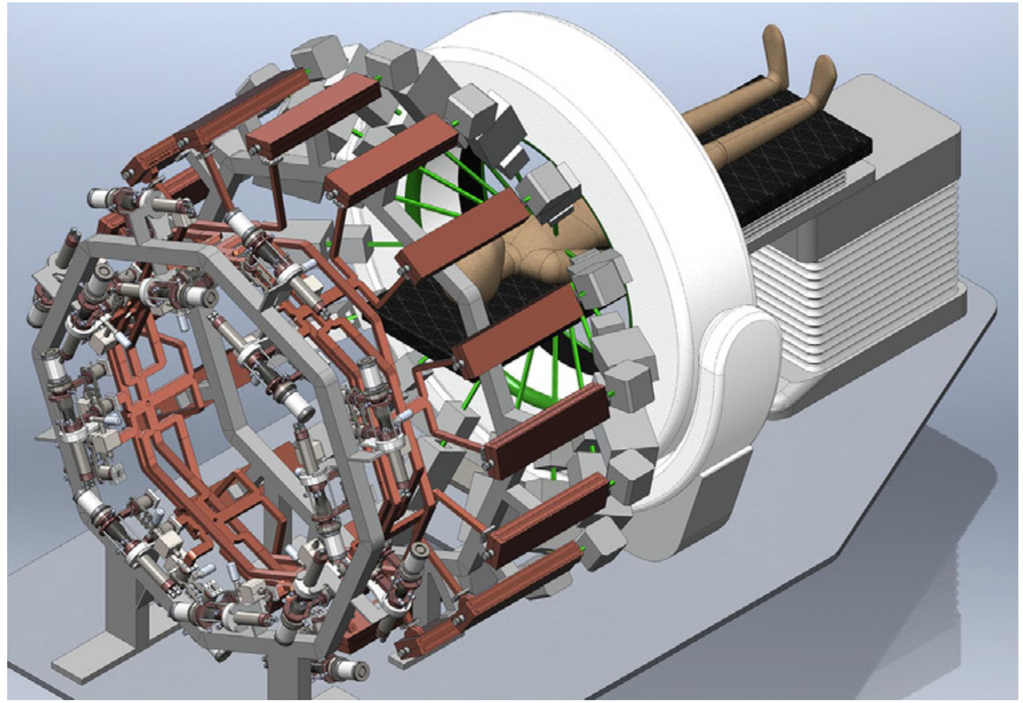
Lempart, M., et al. (2019). *Radiotherapy and Oncology*, *139*, 40–45.



- ★ Reversible to standard clinical operation

PHASER

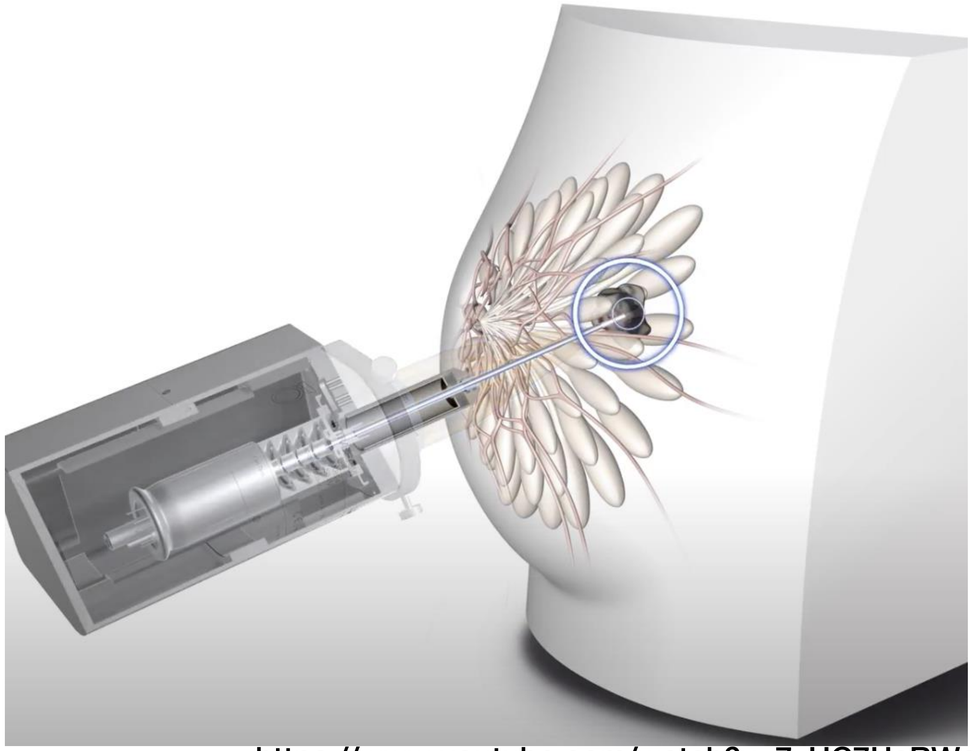
- ★ Originally designed to reduce motion effects and provide cost effective easily transportable RT module
- ★ No moving parts
- ★ Very high energy electrons (100-200 MeV)
- ★ Achieves Flash-like dose rates



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

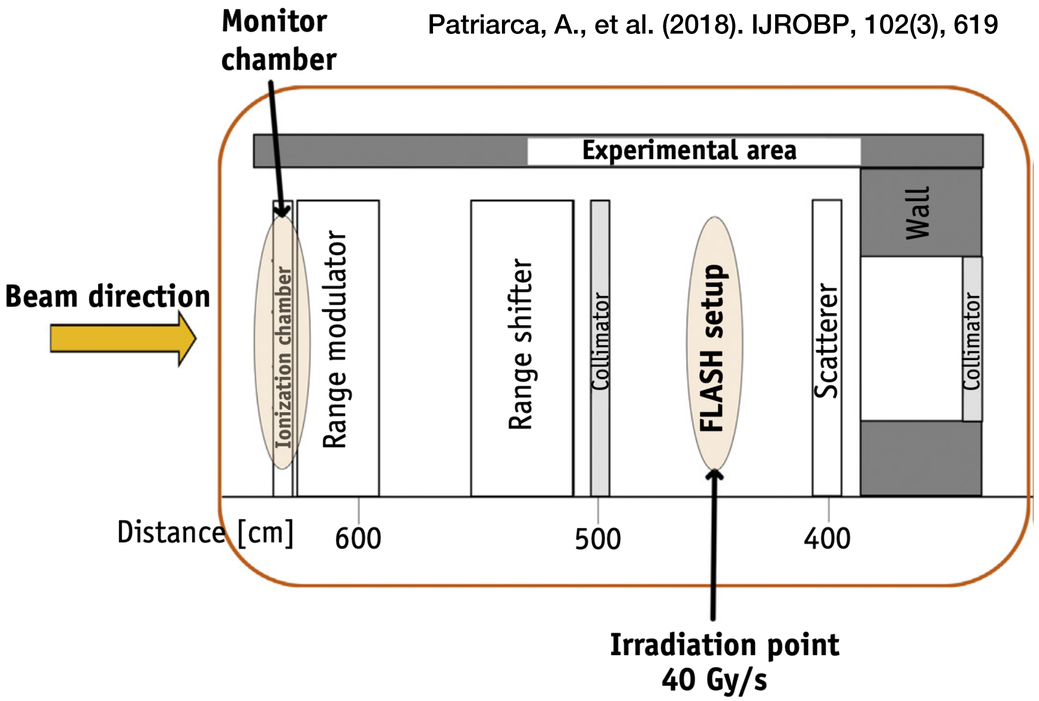


https://www.youtube.com/watch?v=7yUC7HaRWcI

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?



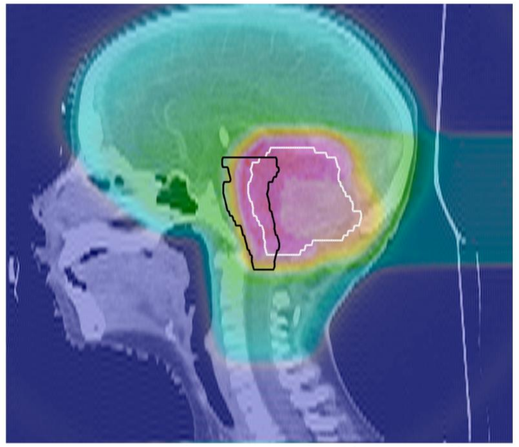
The case for protons - Distal Layer

- ★ 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

- ★ For double scattering delivery this would require single Modulator Wheel rotation
- ★ Pencil beam scanning would require single scan

Treatment Room at UMCG

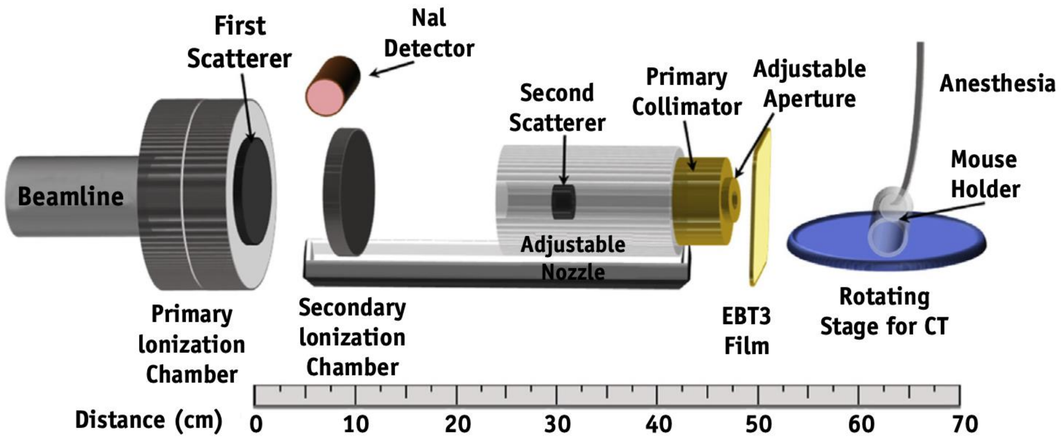
https://www.youtube.com/watch?v=T6m0hnHvZbU

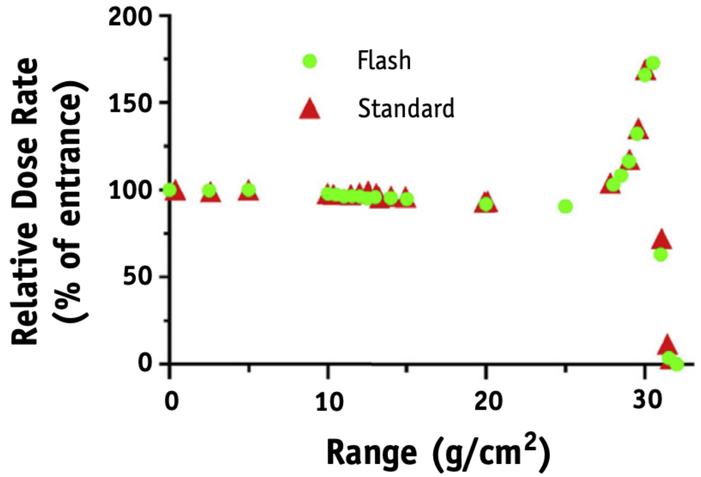


by Drosoula Giantsoudi

UPenn implementation

- ★ Double scattering system
- ★ Rigorous detector system
  - ★ Including prompt gamma detector
- ★ See next talk

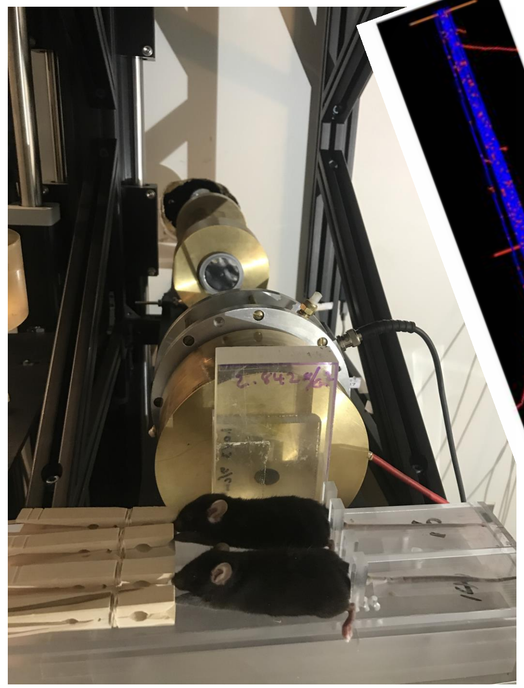


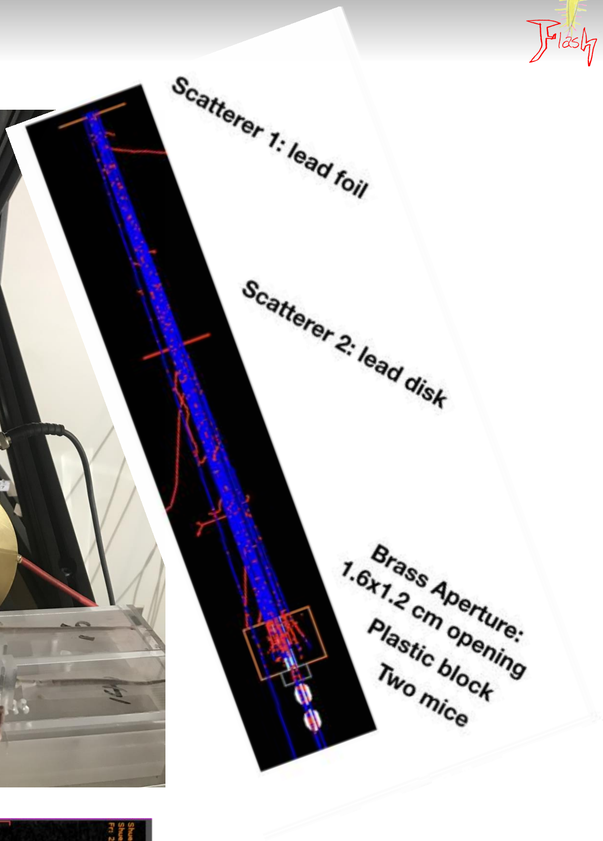


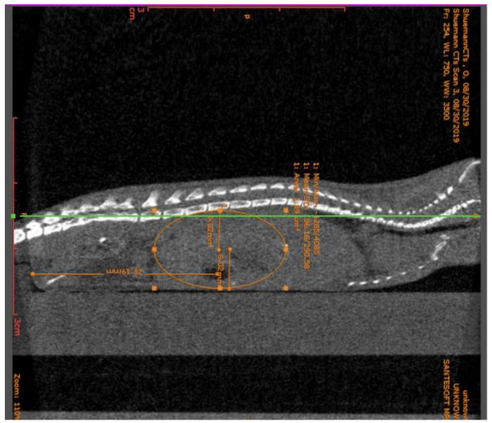
Diffenderfer, E. S., et al. (2020). IJROBP, 106(2), 440.

MGH implementation

- ★ Beamline design with Monte Carlo and analytical tools
- ★ Double scattering system
- ★ Similar to UPenn, longer throw
- ★ 1.6 cm x 1.2 cm field (90%)
- ★ Up to 2 mice in a row
  - ★ ~10-15% dose difference
- ★ MRI for setup relative to mouse holder
- ★ 2-4 cm plastic block to absorb aperture scattering

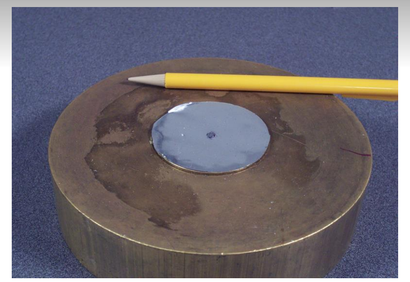


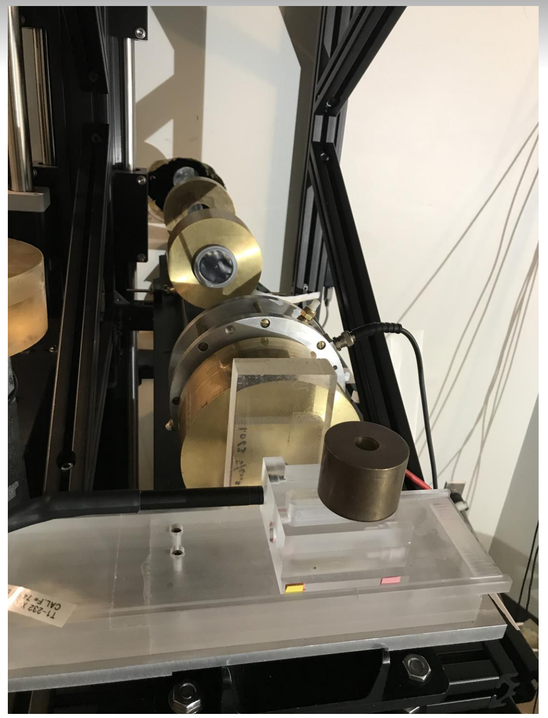


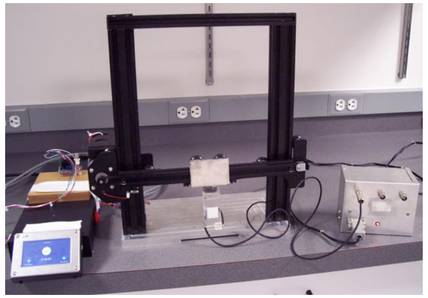


MGH dosimetry

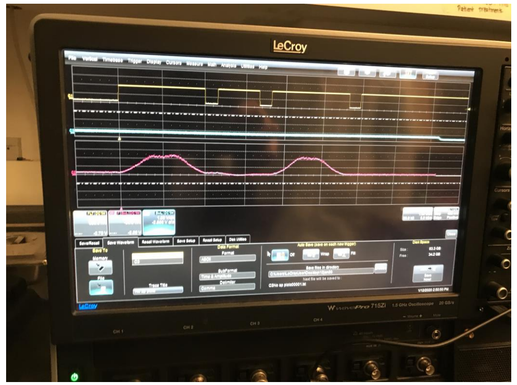
- ★ Combine
  - ★ Thin gap ion chamber
  - ★ Faraday cup
  - ★ Thimble chamber
  - ★ Diode
  - ★ Film
  - ★ New: biological dosimetry
- ★ Used 3D printer to measure dose profiles (non-Flash mode)
- ★ Monte Carlo for dose distributions

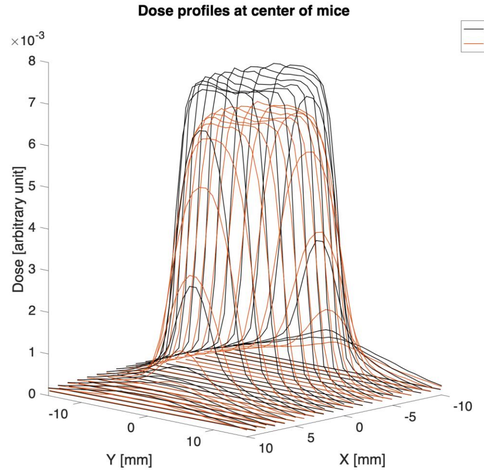






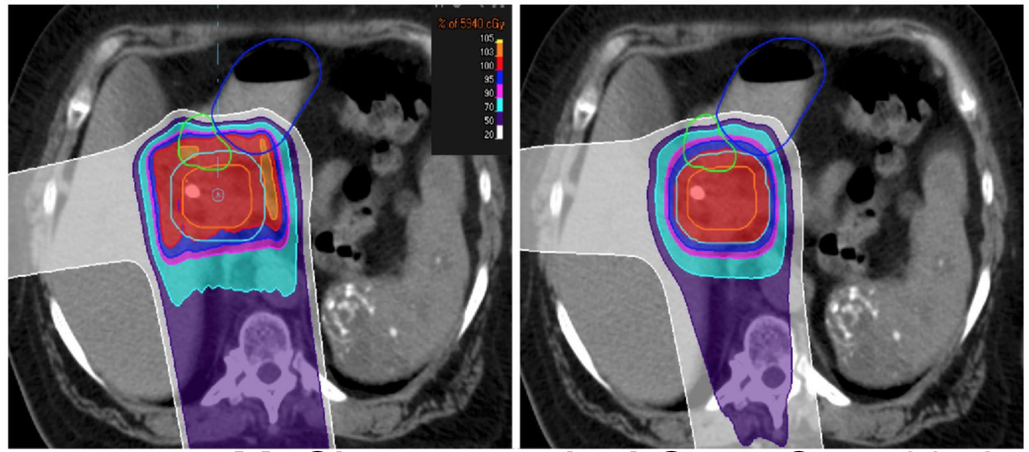
Ethan W. Cascio and B. Gottschalk, arXiv:1908.03763v1 (2019)





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

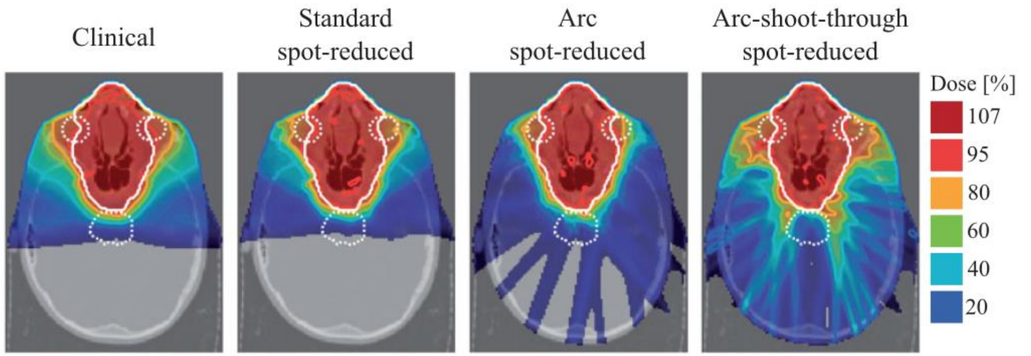
- Is it worth giving up the dose distribution achievable with scanning?

The case for protons - Scanning

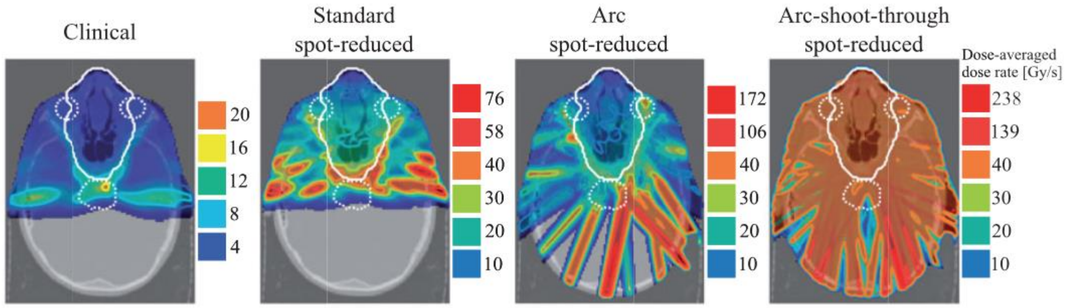
- ★ High dose rate in single pencils
- ★ Lateral scanning is fast
- ★ Depth scanning not as fast
- ★ No more rescanning (is it needed?)
- ★ May need highly reduced spot map
- ★ What about the penumbra of each pencil?

- ★ Is it better?

Dose



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



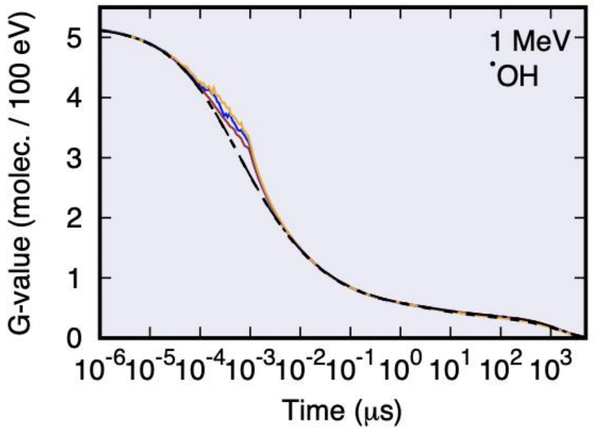
Dose Rate

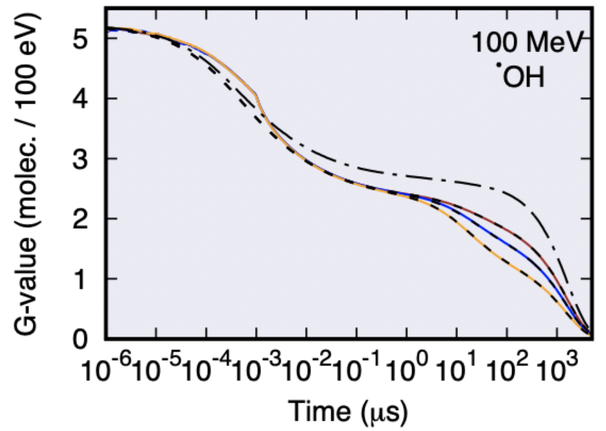
The Mechanism? Chemistry for protons / ions

- ★ Radiation induced ionizations (Radiolysis products) lead to chemical reactions
- ★ High-LET tracks produce denser clusters of chemical species that can recombine

→ Lower LET should cause higher Flash effects

- ★ Heavy ions can produce molecular oxygen at the Bragg peak
  - ★ Opposite to supposed Flash mechanism of Oxygen depletion.
  - ★ Potential to selectively turn “On” and “Off” the Flash effect in different regions? (Colangelo, Azzam, Radiat. Res. 2020)



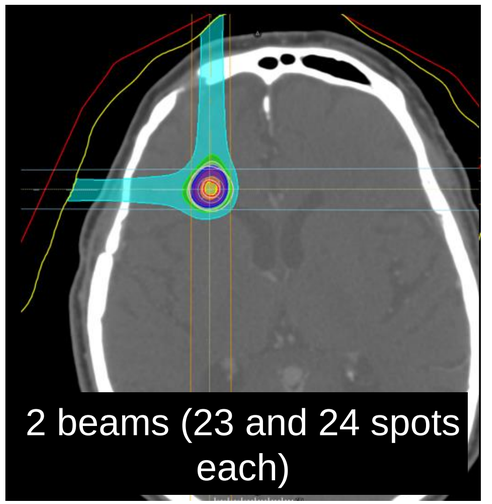


Ramos et al. Radiat. Res. (submitted)

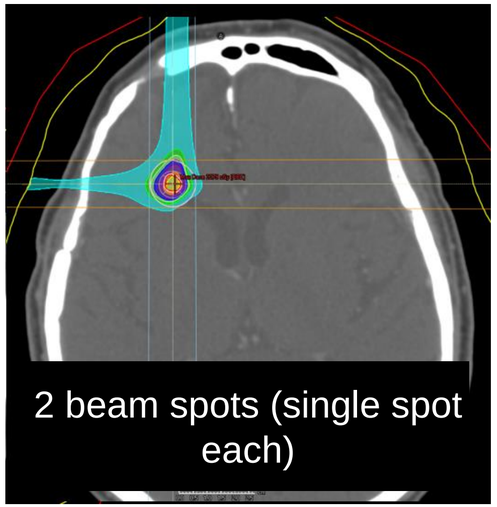
Optimal targets / first targets

- 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



2 beams (23 and 24 spots each)



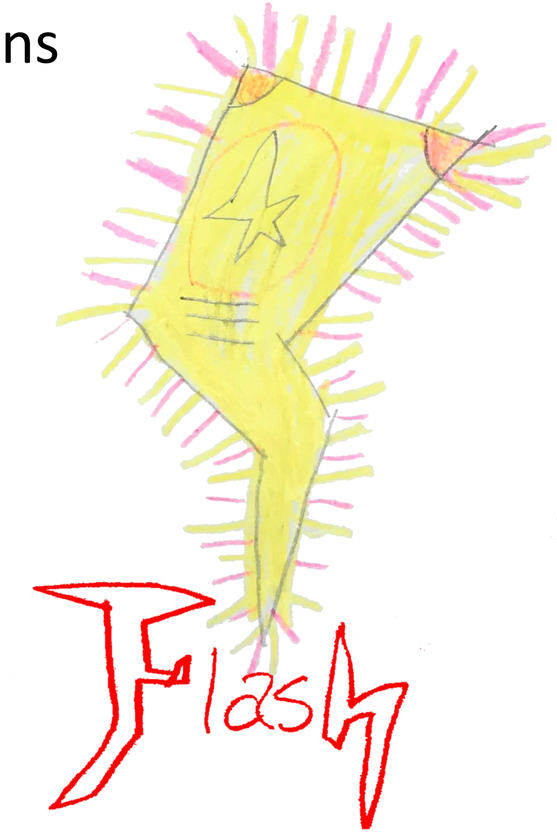
2 beam spots (single spot each)

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)?
- 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
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- Damon Runyon Foundation
- The Brain Tumour Charity

- And many more.