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The State of the Art: Proton Therapy

2022 Chordoma Community Conference

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Disclosures

- Varian Medical Systems. Consultant, research funding
- BrainLab. Consultant
- University of Wollongong. Consultant Professor

Separation Surgery + SBRT

Laufer et al. J Neurosurgery Spine 2013; 18(3) 207-214

- N = 186 "Separation surgery"
- 40 = Single fraction SRS (2400cGy)
- 37 = High dose hypofrationated SRS (3 fractions)
- 109 = low dose hypofractionated (5 fractions)
- 144 = radioresistant
- **Prior RT N = 91**
- **Histology = NS**
- **High dose significantly higher LC (900cGyx3) vs low dose (600cGyx5) (p=0.04)**
- ***RT failures did no worse than RT naïve patients after separation surgery and high dose SBRT in MVA***

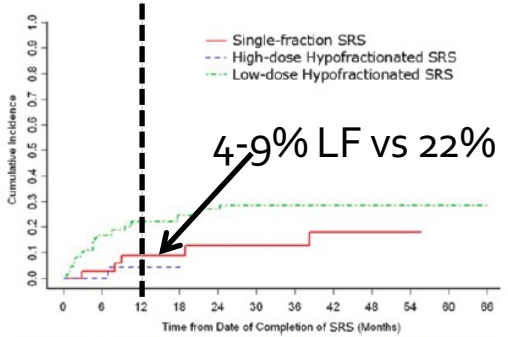

FIG. 2. The cumulative incidence of local progression by postoperative adjuvant SRS fractionation regimen.

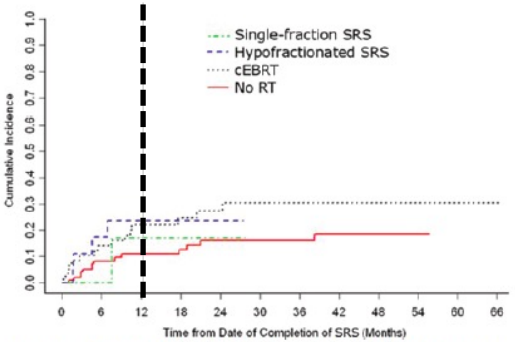

FIG. 3. The cumulative incidence of local progression by preoperative RT fractionation regimen.

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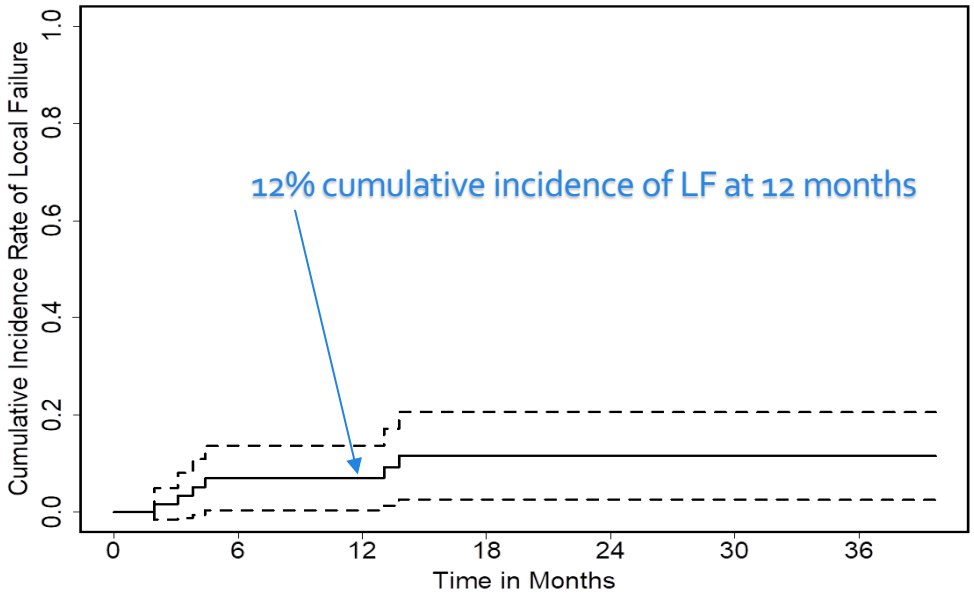
40Gy/5 Salvage SBRT

(Moore et al ASTRO 2022)

- Retrospective analysis of 63 consecutive patients salvaged with 800cGyx5 after prior SBRT for spine metastases.
- Median FU 11.9 months (1.8-39.6 months)
- 5 patients with late toxicity
  - G1 = 2
  - G2= 1
  - G3= 2 (1 subacute pneumonitis)
- Fracture risk
  - 3 patients post salvage kypho (4.8%)
  - 7 patients post salvage surgery (11.3%)



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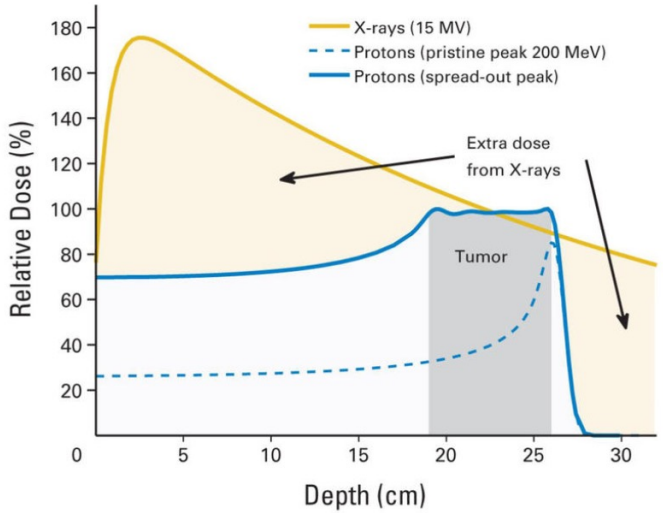
Reirradiation: Where Are We?

- Reirradiation – The most widely accepted indication for spine SBRT
  - Ablative nature of SBRT overcomes radioresistant clones (Laufer et al)
  - SBRT limits dose exposure to previously irradiated normal tissue resulting in acceptable toxicity
  - SBRT can be effective in salvage of SBRT failures (Moore)
- ***Is there a role for proton based salvage spine SBRT?***



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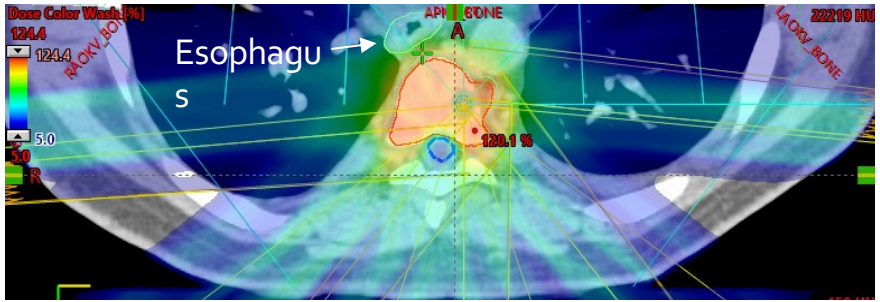
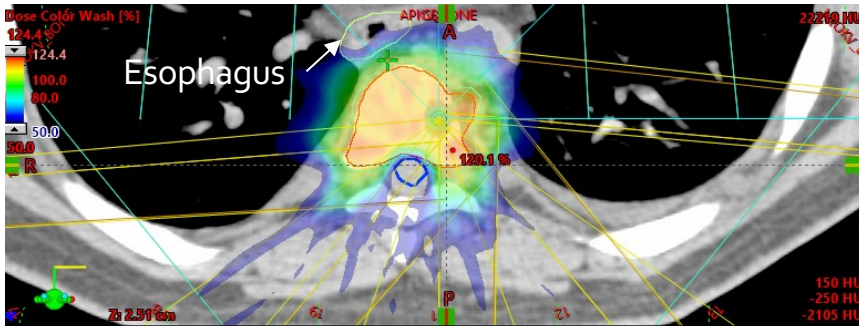
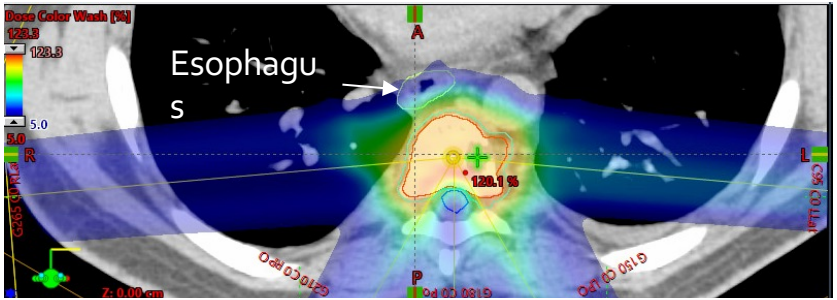
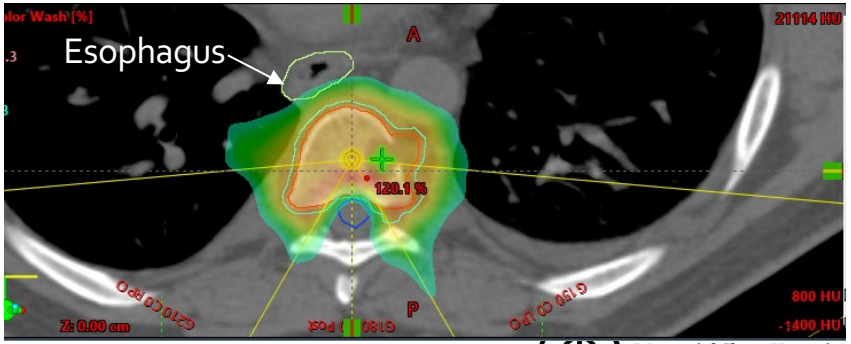
Photons





Protons





Courtesy Jessie Liang PhD

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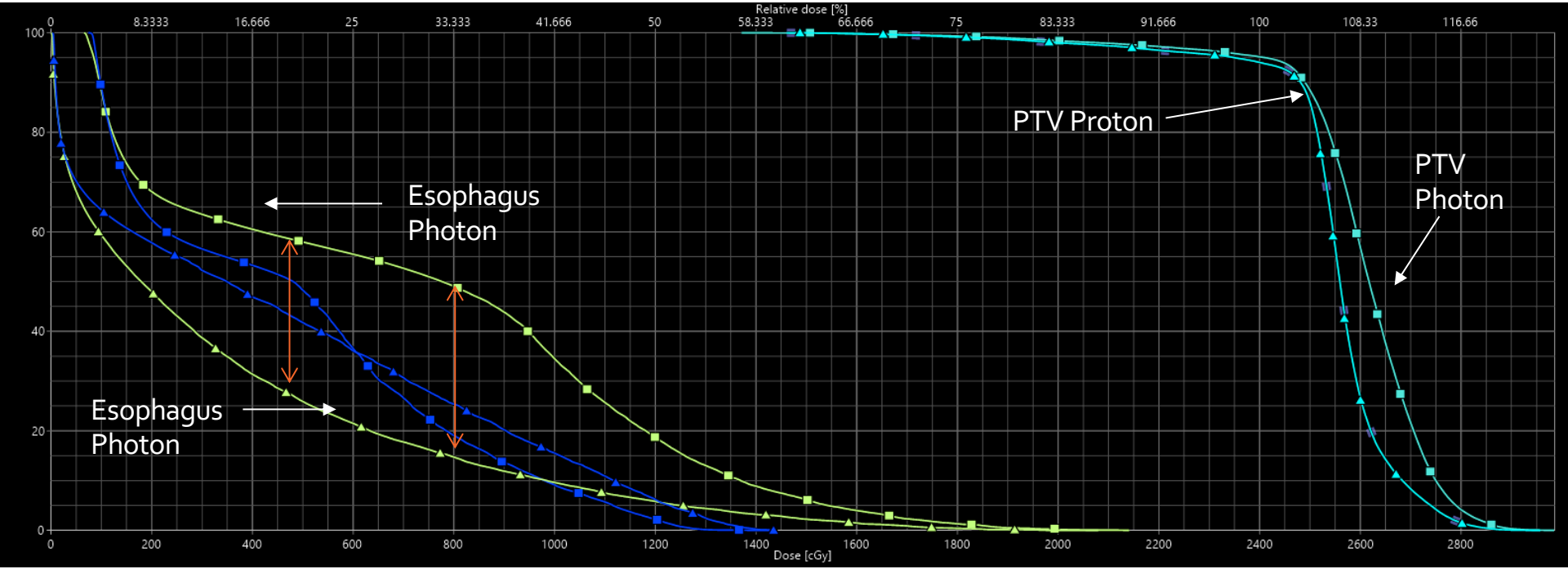
Proton vs Photon: Esophagus and Spinal Cord



Courtesy Jessie Liang PhD

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Proton vs Photon SRS: 24 Gy x 1 to T7

	Photon (cGY)	Proton (cGy)
PTV Dmin	1371.9	1463.0
PTV Dmax	2986.0	2958.5
Cord Dmax	1431.7	1441.8
Cord Dave	472.2	452.1
Cord Dmin	77.3	3.5
Esophagus Dmin	66.2	1.4
Esophagus Dave	705.4	345.2
Esophagus Dmax	2142.3	2082.0

“Flash” Radiotherapy

- Ultra high dose rate radiotherapy: RT delivered 400x (>40Gy/s) faster than conventional radiotherapy (5Gy/min).
  - Normal Tissue Sparing
    - Lung fibrosis
      - 17Gy FLASH = minimal fibrosis vs 17Gy Conventional Dose Rate RT
      - 30Gy FLASH = 17Gy CDR Fibrosis rate
    - Brain (juvenile mice WBRT)
      - FLASH 8Gyx 1 = control group (No RT) vs CDR 8Gy (significant determent)

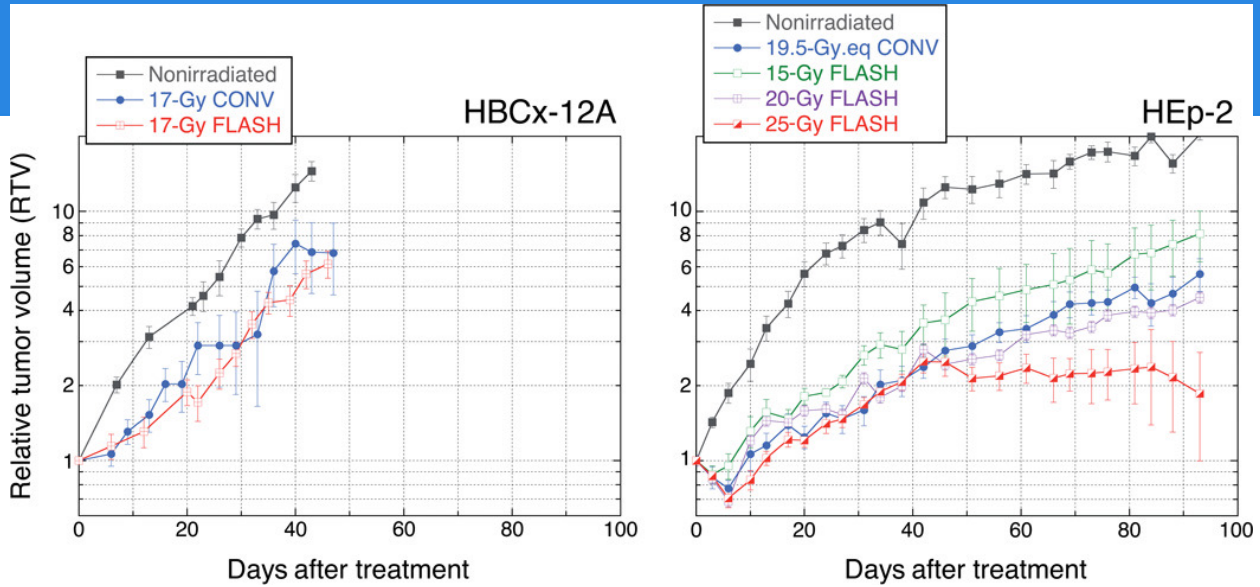
Model (Site of Irradiation)	Assay/Endpoint	Dose (Gy)	Dose Rate (Gy/s)	Radiation Source
Mice (WBI) [1]	Memory tests, neurogenesis	10	>100	Electron
Mice (WBI) [1]	Neurocognitive tests, mature/immature neurons, growth hormone levels	8	4.4×10^6	Electron
Mice (WBI) [1]	Neurocognitive tests, dendritic spine density, microglial activation, inflammation	30	200/300	Electron
Mice (WBI) [1]	Neurocognitive tests, neuroinflammation, neuronal morphology	10	>100	Electron
Mice (WBI) [1]	Neurocognitive tests, hippocampal cell division, astrogliosis	10	37	X-ray
Mice (thorax)	Survival, dermatitis, breathing function, lung pathology	15/17.5/20	40	Proton
Mice (thorax)	Lung fibrosis, skin dermatitis, survival	15/17.5/20	40	Proton
Mice (thorax)	Lung fibrosis, TGF-β signaling, apoptosis	17	40–60	Electron
Mice (thorax)	Cellular proliferation, pro-inflammatory gene expression, DNA damage (53BP1/γH2AX foci), senescence	17	40–60	Electron
Mice (abdomen)	Survival	10–22	70–210	Electron
Mice (abdomen)	Survival, stool production, crypt cell regeneration, apoptosis, DNA damage	12–16	216	Electron

Hughes JR, Parsons JL. FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. *Int J Mol Sci.* 2020;21(18):6492. Published 2020 Sep 5. doi:10.3390/ijms21186492

FLASH: Tumor Control

Model	Assay/Endpoint	Dose (Gy)	Dose Rate (Gy/s)	Radiation Source
Mice, HBCx-12A, and Hep-2 human xenografts (local)	Tumor growth	17–25	60	Electron
Mice, orthotopic engrafted lung carcinoma luciferase+ TC-1 cells (thorax)	Tumor growth	15–28	60	Electron
Mice, ID8 syngeneic ovarian cancer (thorax)	Tumor number/weight	14	216	Electron
Mice, orthotopic engrafted Lewis lung carcinoma (thorax)	Tumor size	18	40	Proton
Mice, pancreatic MH641905 flank tumor	Tumor growth	12/15	78	Proton
Cat, nasal planum SCC (local)	Tumor growth	25–41	130–390	Electron
Human, CD30+ T-cell cutaneous lymphoma	Tumor response	15	167	Electron

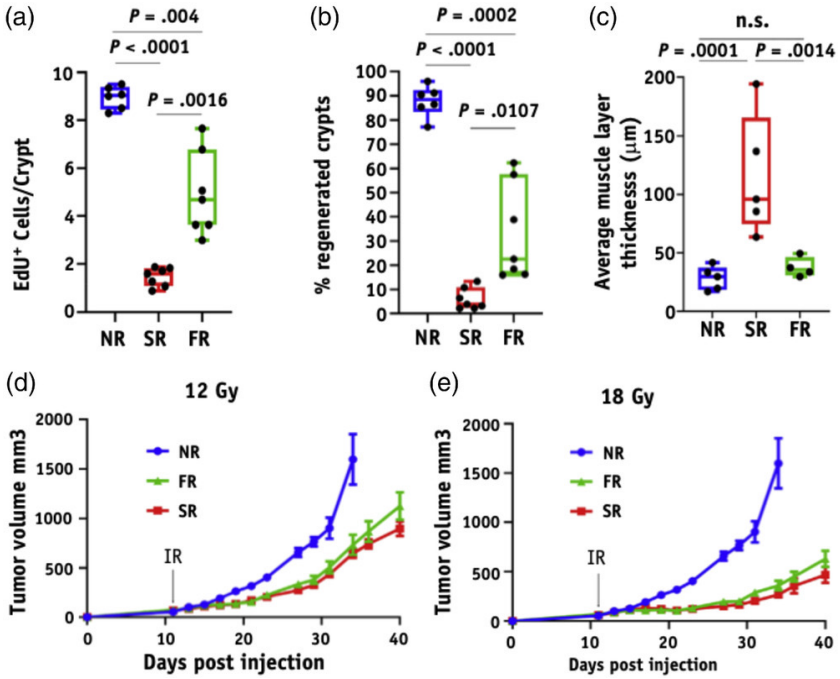
FLASH



- **No difference in tumor control vs CDR RT**
- Normal tissue sparing = opportunity for dose escalation
  - 15Gy CDR = 20% LC in implanted lung tumor vs 70% with 28Gy FLASH
  - CDR lungs significant fibrosis, minimal with FLASH

F, Sayarath M, Fouillade C, Poupon MF, Brito I, Hupé P, Bourhis J, Hall J, Fontaine JJ, Vozenin MC. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med. 2014 Jul 16;6(245):245ra93. doi: 10.1126/scitranslmed.3008973.

Standard Rate RT (0.9 Gy/s) and FLASH (78Gy/s) Mouse Model



Flash: spares proliferating crypt cells (a) , greater regeneration of crypt cells (b) with significant less fibrosis 8 weeks post RT (c)

Flash: no impact on probability of tumor control at 12Gyx1 (d) or 18Gy x 1 (e) compared to standard rate RT

Medical Physics, Volume: 49, Issue: 3, Pages: 2039-2054, First published: 13 October 2021, DOI: (10.1002/mp.15276)

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Role of Proton SRS/SBRT in Spine Tumors

- Advantages of Protons: Sparing Normal Tissue
  - Dosimetric
    - Sparing the esophagus
    - Pneumonitis risk
    - Bowel toxicity
  - Biologic
    - FLASH reduce toxicity by 50% equivalent dose.
- Ideal platform for reirradiation SBRT
  - Technical considerations/challenges:
    - Managing uncertainties
      - Patient related factors
      - Beam related factors
      - Surgical hardware
    - Treatment planning
- ***Reirradiation-a critical need***
  - ***Potential for proton SBRT cannot be understated***

FLASH: Technical Considerations/Challenges

- Ultra accurate patient set up
- Beam delivery
  - Developing tools for FLASH QA
  - Passive scatter vs scanning
  - Scanning + ridge filter for range modulation

- Treatment planning systems need to be adapted to provide FLASH compatible conditions
  - Increasing beam intensity
  - Reducing beam spots
  - Optimal number of fields

The Future of Spine SBRT: Proton FLASH

- Dosimetric and biologic advantages for normal tissue.
  - Esophagus
  - Spinal Cord
  - Bowel
  - Large volumes

- Normal tissue sparing will allow for tumor dose escalation and biologic effective dose escalation