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Photon vs. Proton SBRT Clinical Debate: Protons as a Standard of Care

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NEW YORK PROTON CENTER

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Dr. Higgins Established That Protons Have Better Survival Than Photons for Conventional Fractionation…

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Clinical Investigation

National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer

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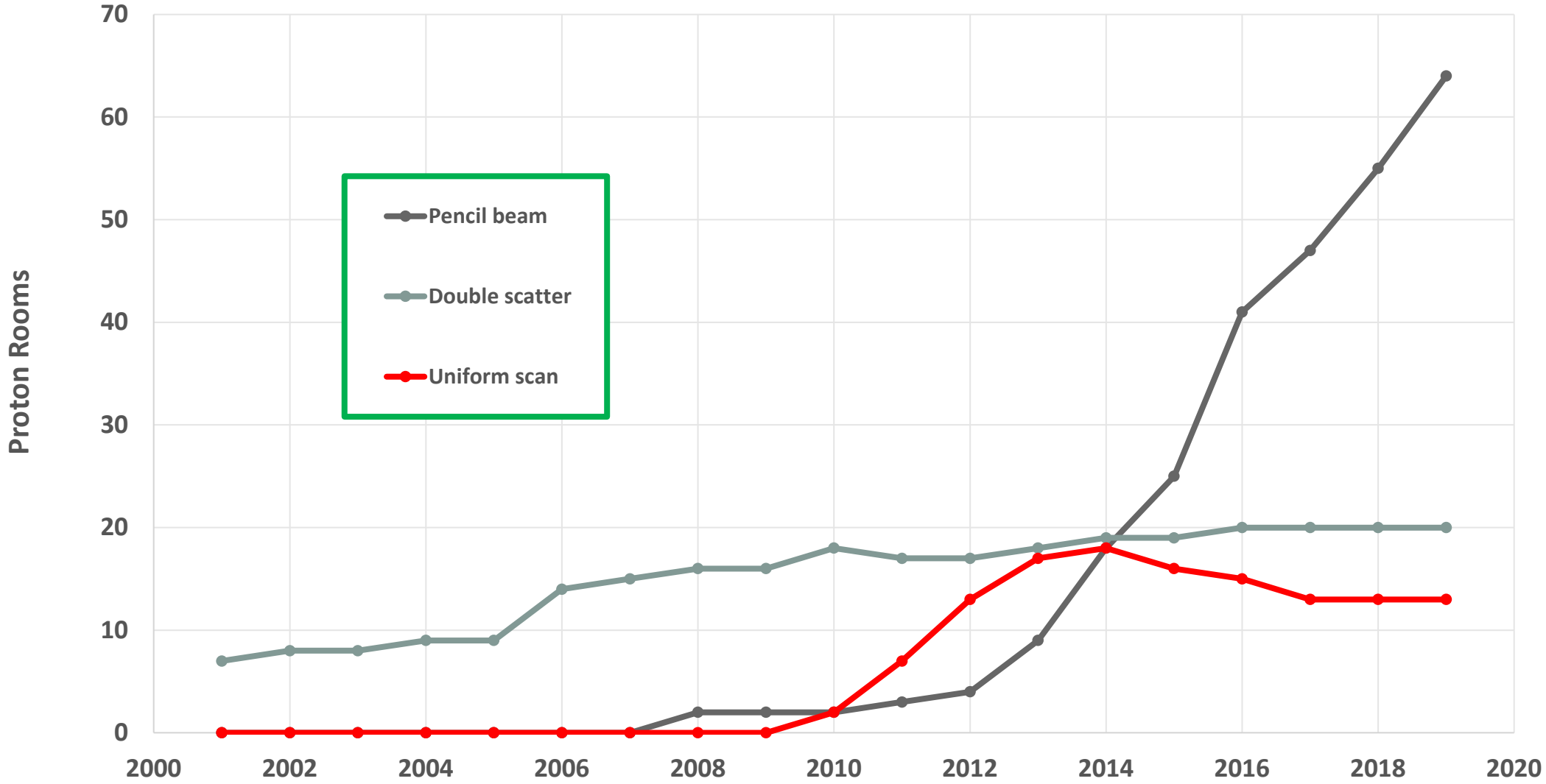
What about for SBRT?

Increasing Use of PBS (and CBCT) Enables Proton SBRT



2020 NAPT Annual Member Survey

Technology Advances of Protons

- While advances in treatment delivery, adaptive planning, and IGRT have also improved photon therapy, technology advances have disproportionately helped protons
  - Pre-CBCT proton era (now CBCT routine)
  - Poor understanding of beam optimization and robustness (now models to determine the most robust beams, ability to calculate plan robustness and modify plans accordingly)
  - Pre-repainting proton era (now clinically implemented)
  - Adaptive planning for disproportionately favors protons over IMRT dosimetrically
  - Double/passively scattering being replaced with PBS/IMPT
    - Dosimetric benefit
    - Dose rate benefit, table times with proton SBRT equivalent to photon SBRT

Rationale for Proton Therapy for SBRT

- Reduce dose to normal tissues, which can reduce treatment toxicities
- May be particularly beneficial for:
  - Tumors immediately adjacent to critical structures, especially those in which dose constraints to OARs with photon SBRT are approached/exceeded
  - Recurrent tumors after prior RT
  - Large tumors
  - Dose escalation of SBRT, especially for radio-resistant tumors/metastases
  - More safely allowing for combining SBRT with chemotherapy or immunotherapy for oligometastatic or oligoprogressive disease
- Best evidence to date for lung cancer, liver tumors, benign brain lesions
- Increasing evidence for prostate cancer, spinal metastases, pancreatic cancer, renal carcinomas, brain metastases, head and neck recurrences

Added Benefits Specifically of Proton SBRT

- Increased patient convenience (and safety) for short-course proton treatments
  - Large proportion of patients traveling great distances to receive proton therapy
  - Particularly important during the COVID-19 pandemic
- More safely allows for dose escalation relative to photons that can increase biologically effective dose, allowing increased tumor control/survival
- Potential increased differential tumor kill with protons (higher LET and RBE) relative to photons
- Potential enhanced immune effective relative to photons, with decreased lymphopenia and increased immune stimulation

- New York Proton Center: 8.6% of all treatment courses are SBRT (lung, liver are #1, #2)

PROTON SBRT
FOR LUNG CANCER

Hypofractionated Photon Data in LA-NSCLC

- Increasing data of hypofractionated RT (typically 4 Gy x 15) for LA-NSCLC when not delivered with chemo
  - UT Southwestern, MDACC, Jiangsu Cancer Hospital China
- Generally too toxic to deliver hypofractionated photon RT with chemotherapy
  - CALGB 31102 (Alliance) 22 patient trial of 60 Gy in 27 → 24 → 22 → 20 fractions with carbo/paclitaxel
    - Grade 5 toxicity in 3/21 patients (hemoptysis, pneumonitis)
    - MTD 60 Gy in 2.5 Gy/fx
    - Urbanic JJ, et al. *Int J Radiat Oncol Biol Phys*. 2018;101(1):177-185.
  - 92 patient series from Poland of 55.8 Gy in 21 fractions (2.8 Gy/fx) with cisplatin/vinorelbine
    - 14% grade ≥3 acute esophageal toxicity, grade 5 toxicity in 7/92 patients
      - 2 deaths within 3 months of RT (fatal hemoptysis, esophageal toxicity), 5 additional deaths within 12 months of RT (lung abscess, fatal hemoptysis)
    - Glinski K, et al. *Radiother Oncol*. 2020 Jul;148:174-180.

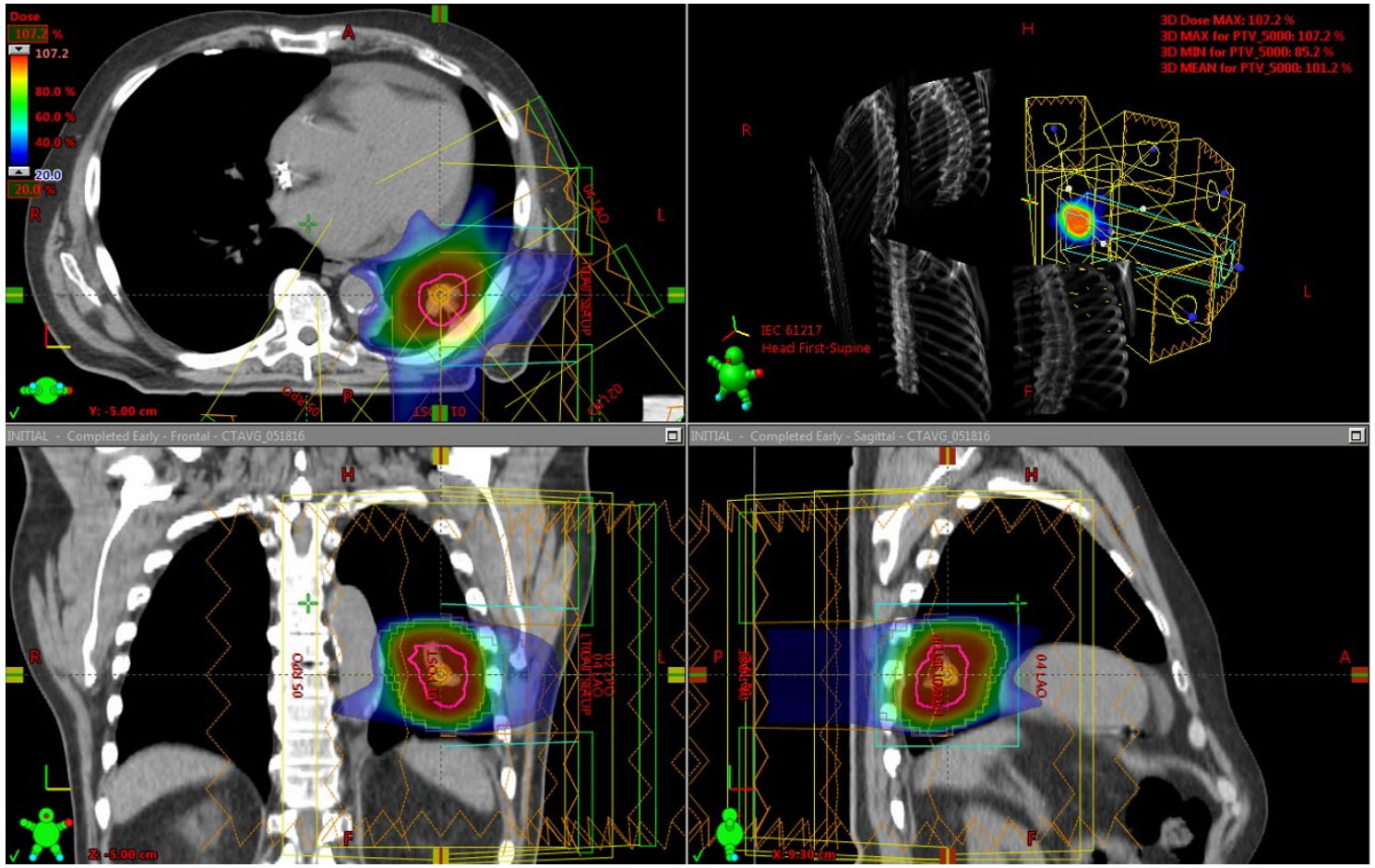
Hypofractionation with Proton Therapy

- Proton Collaborative Group LUN005: Multi-center Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III NSCLC
  - Phase I: Proton RT with concurrent chemotherapy to 60 CGE in 24 (2.5 CGE) → 20 (3.0 CGE) → 17 (3.53 CGE) → 15 (4 CGE) fractions [find maximum tolerated dose]
  - Phase II: expansion cohort treated with MTD [primary endpoint: 1-yr OS]
- 18 patients enrolled to phase I, 2 SAEs (both in the 3.53 CGE arm and both from chemo unrelated to RT)
- 28 patients analyzed for phase II (22/28 stage III, only 3/28 adjuvant durva)
  - No acute grade ≥3 esophagitis, 14% acute or later grade ≥ 3 pulmonary toxicity
  - 1- and 3-year OS rates were 89% and 49%
  - 1- and 3-year PFS rates were 58% and 32%

Hoppe BS, Simone CB 2nd, et al. *IJROBP*. 2020;107(3):455-461. Hoppe BS, Simone CB 2nd, et al. *IJROBP.* 2022; in press.

My First Proton SBRT Patient – Reirradiation, Cardiac Device

- Male in 70s with left lower lobe stage I NSCLC s/p photon SBRT (12.5 Gy x 4)
- Myocardial infarction ~10 months following SBRT
- Isolated local recurrence <18 months after SBRT
- Proton SBRT reirradiation (10 Gy x 5) to avoid heart dose
- NED ~7 ¾ years later



ROCOCO Stage I Multinational Study

- 25 pts with stage I NSCLC prescribed to 60 Gy in 8 fractions
  - Esophagus: proton SBRT achieved an 8-fold reduction in mean dose relative to RapidArc, 9-fold reduction relative to CyberKnife, 11-fold reduction relative to IMRT
  - Heart: proton SBRT associated with 2-fold reduction in dose relative to RapidArc, 3-fold reduction relative to CyberKnife and IMRT
  - Cord: proton SBRT associated with 9-fold reduction in max dose relative to CyberKnife, 13-fold reduction relative to IMRT, 17-fold reduction relative to RapidArc
  - Lung: modest numeric improvements in mean lung dose relative to other modalities

  - Above based on double scattered proton, benefits would be even greater with PBS

Wink KC, Simone CB 2nd, et al. *Radiother Oncol*. 2018;128(1):139-146.

Proton Therapy for Stage I NSCLC

- Prospective study of 80 patients with stage I NSCLC who were medically inoperable or refused surgery treated with protons (n=57) or carbon-ions (n=23) most commonly to 60 CGE in 10 fractions
  - 3-year overall survival 75%, cause-specific survival 86%
  - Grade 2 pneumonitis in 11%, grade 3 pneumonitis in 2%
- Phase II prospective study of 111 patients with stage I NSCLC who were medically inoperable or refused surgery treated in 10 fractions to escalated doses of 51 CGE, 60 CGE, 70 CGE
  - 4-yr overall survival increased with increasing dose level (18% vs. 32% vs. 51%, p=0.006)
  - No clinical radiation pneumonitis requiring steroid therapy

Iwata H, et al. *Cancer*. 2010;116(10):2476-85.

Busch DA, et al. *Int J Radiat Oncol Biol Phys*. 2013;86(5):964-8.

Proton Therapy for Stage I NSCLC

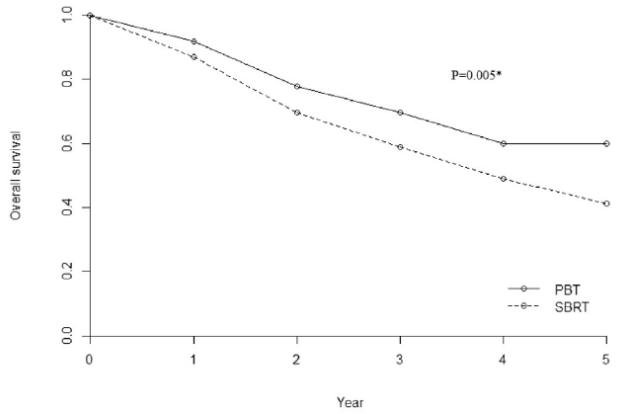
- Retrospective study of 74 pts with 80 stage I NSCLCs
  - 72.6/3.3 Gy [RBE] (central) or 66/5.5-6.6 Gy [RBE] (peripheral)
  - 5-yr OS 65.8%, PFS 52.5%
  - Toxicity
    - Acute: 2.5% grade 2 (1 skin, 1 esophagitis), 1.3% grade 3 (pneumonitis)
    - Late: 2.5% grade 3 (1 skin ulcer, 1 pulm), 13.8% grade 4 (11 rib fracture)
- Prospective study of 56 patients with stage I NSCLC
  - 66/6.6 Gy (peripheral) or 80/3.2 Gy (central)
  - 3-yr OS 81.3%, LC 96.0%
  - Late toxicity: 13.4% grade 2, 1.5% grade 3

Kanemoto A, et al. *Clin Lung Cancer*. 2014;15(2):e7-12

Makita C, et al. *Acta Oncol*. 2015;54(3):307-14.

Proton Therapy for Stage I NSCLC

- Meta-analysis comparing hypo-fractionated particle beam therapy (PBT) to photon SBRT for early stage (cT1-T3 N0 M0) NSCLC
  - 72 SBRT studies, 9 hypo-fractionated PBT studies
    - PBT patients had large median tumors (2.92 cm vs. 2.41cm, p=0.02) and were less likely to have T1 disease (57% vs. 71%, p=0.05)
  - PBT had improved overall survival (5 yr OS 60% vs. 41.3%, p=0.005) and progression-free survival (57.2% vs. 37.7%, p=0.01) on univariate analysis



  - 3-year local control (LC) improved for PBT (p=0.03) on multivariate analysis
  - Overall incidence of Grade 3-5 toxicities lower with PBT (4.8% vs. 6.9%, p=0.05)
    - Grade ≥3 pneumonitis: 0.9% vs. 3.4% (p=0.001)

Chi A, et al. *Radiother Oncol*. 2017;123(3):346-354.

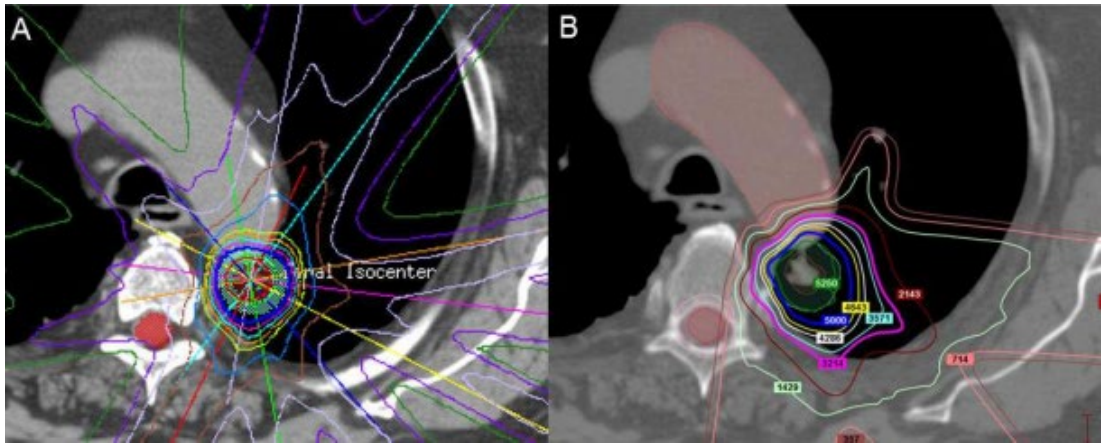
MGH True SBRT Experience

- MGH retrospective experience of proton SBRT for 15 patients with 20 Stage I NSCLC
  - Most had interstitial lung disease, multiple primary tumors, or had prior thoracic RT thought not to be safe candidates for photon SBRT
  - Median total dose of 45 Gy [RBE] (42-50 Gy) in 14 Gy fx (10-16 Gy)
  - 2-year LC 100%, regional control 78%, distant control 86%, OS 64%
  - Toxicities
    - Only grade 3-5 toxicity was a single pt with grade 3 pneumonitis
    - 1 pt each with grade 2 chest wall pain, dermatitis, fatigue

Westover KD, et al. *J Thorac Oncol*. 2012;7(6):1021-1025.

Randomized Phase II Trial

- MDACC randomized trial of photon SBRT vs. proton SBPT for high-risk (centrally located or <5 cm-T3 or isolated lung parenchymal recurrences) medically inoperable early-stage NSCLC to 50 Gy(RBE) in 4 fx
  - SBPT given with passive scattering and IGRT with KVs (SBRT arm used CBCT)
  - Closed early due to poor accrual (insurance coverage, lack of volumetric imaging for SBPT)
  - 21 patients were enrolled, 19 evaluable (9 SBRT, 10 SBPT)
- Outcomes at a median follow-up of 32 months
  - Median OS: 28 months SBRT vs. not reached SBPT
  - 3-yr OS 27.8% vs. 90%
  - 3-yr LC 87.5% vs. 90.0%
  - 3-yr regional control 47.6% vs. 90%
  - Proton toxicities: 1 pt with grade 3 skin fibrosis (only 3 fields)



Nantavithya C, et al. *IJROBP*. 2018;101(3):558-563.

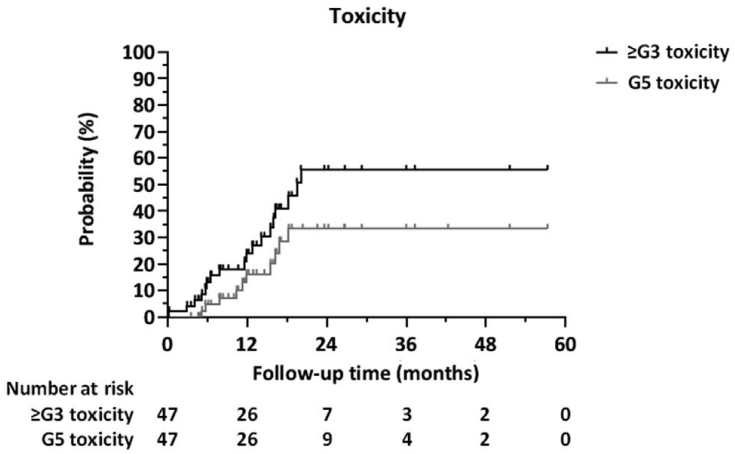
Toxicity with Photon SBRT for Central Tumors

- Proton SBRT can benefit nearly all patients dosimetrically
  - *Biggest benefits for centrally located tumors, larger tumors, dose escalation, reirradiation, poor lung function/interstitial lung disease*
- Indiana U Phase II Study of SBRT for Medically Inoperable Early-Stage Lung Cancer
  - 70 patient treated to 3 x 20 Gy (T1) or 22 Gy (T2)
  - 2-year freedom from toxicity only 54% for central tumors, 6 deaths attributable to therapy (4 in patients with perihilar/central tumors)
- Wash U: Prospective Phase I/II Trial of SBRT for Central Early-Stage NSCLC
  - 74 patients treated in 5 fraction regimens (9-12 Gy x 5)
  - Nearly 50% with grade ≥3 late toxicity (27% grade 3, 12% grade 4, 4% grade 5) [median follow-up only 17 months]
- RTOG 0813 - Seamless Phase I/II Study of SBRT for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients
  - 120 patients treated in 5 fraction regimens (10-12 Gy x 5)
  - 7.25% developed DLT at the MTD, 12.1% in highest 2 dose arms developed grade ≥3 toxicity within the first yr of SBRT
  - 6 of 92 evaluable pts (7%) with grade 5 toxicities

Timmerman R, et al. *J Clin Oncol*. 2006;24:4833-9. Roach MC, et al. *J Thorac Oncol*. 2018;13(11):1727-1732. Bezjak A, et al. *J Clin Oncol*. 2019;37(15):1316-1325.

Photons are Even Worse for ULTRA-Central Lesions

- Hypofractionation for ULTRA-central tumors
  - 47 pts treated to 5 Gy x 12 (BED10 = 90 Gy) to ultracentral tumors (PTV overlapping trachea or main bronchi)
  - Grade ≥3 toxicity in 38%
  - 21% with possible (n=2) or likely (n=8) treatment-related death (5.2-18.2 months after RT)
    - Fatal pulmonary hemorrhage in 15% of all pts



- **Protons can more safely treat central and ultra-central tumors by having all dose stop before circumferential treatment of esophagus, proximal airway**

Tekatli H, et al. *J Thorac Oncol*. 2016;11(7):1081-9.

Limitations of Photon SBRT for Large Tumors

- 92 pts from 12 centers treated with SBRT for cN0 NSCLC ≥5.0 cm
  - Median tumor size 5.4 cm (range 5.0-7.5 cm)
  - Median dose/fractionation 50 Gy in 5 fx

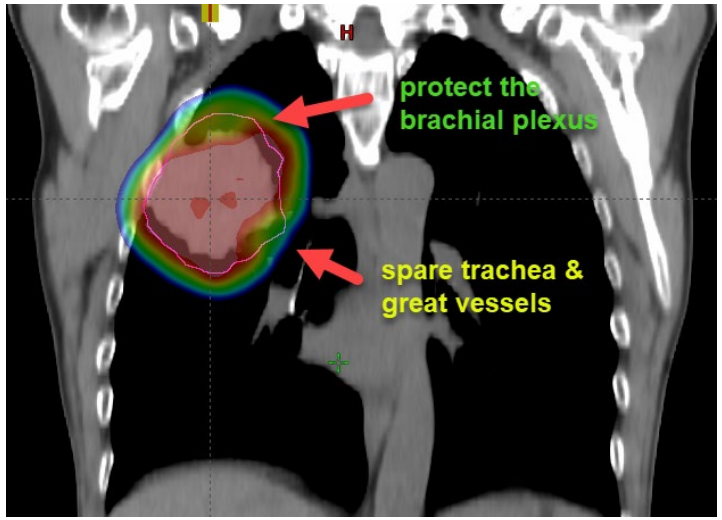
	1 Year	2 Year
Local Control	95.5%	73.2%
Disease-free Survival	72.1%	53.5%
Disease-specific Survival	95.5%	78.6%
Overall Survival	76.2%	46.4%

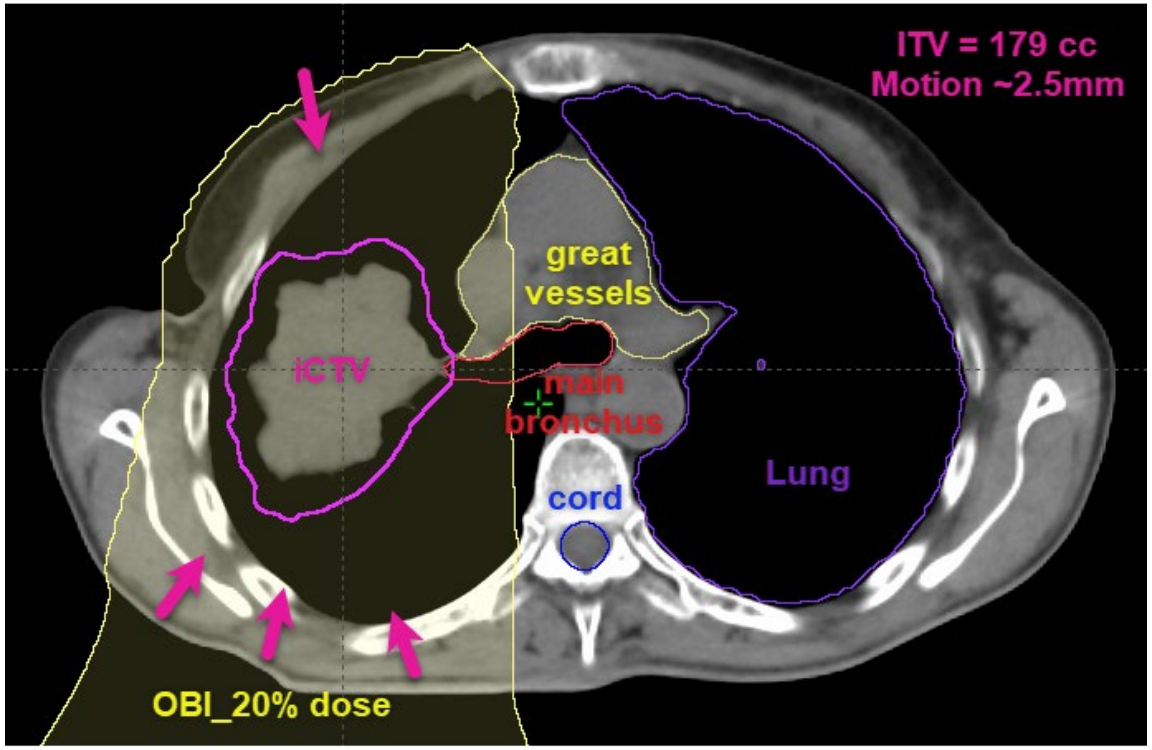
- Pattern of failure: distant (33%), local (26%), elsewhere in the lung (23%)
- 43% of patients receiving QOD fractionation had high grade toxicities
- NCBD Analysis: chemotherapy with SBRT improves survival for tumors ≥5 cm

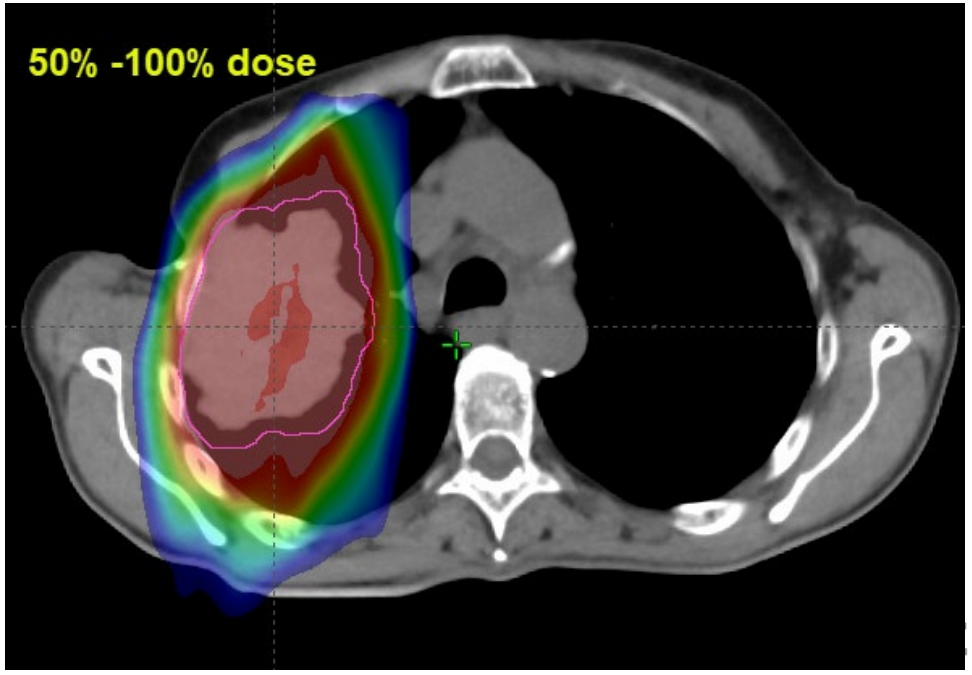
Verma V, Simone CB 2nd, et. *Cancer*. 2017;123(4):688-698 Verma V, Simone CB 2nd, et. *IJROBP*. 2017;97(1):146-154. Verma V, Simone CB 2nd, et. *IJROBP*. 2017;97(1):146-154.

Protons Better Allow Dose Escalation for SBRT

- 7.3 cm cT4N0M0 NSCLC, medically inoperable, refused chemo
- Prior RT on right breast 2015
- Planned with SFO of 4 beams, RO on iCTV with 5mm/3.5% margins, daily kV and CBCT for IGRT
- Prescription 12 Gy x 5 = 60 Gy

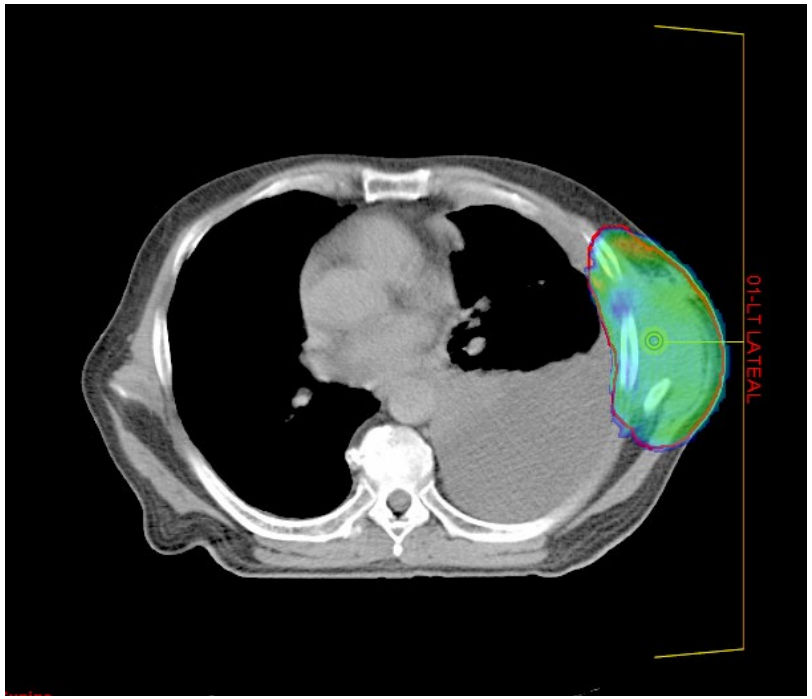




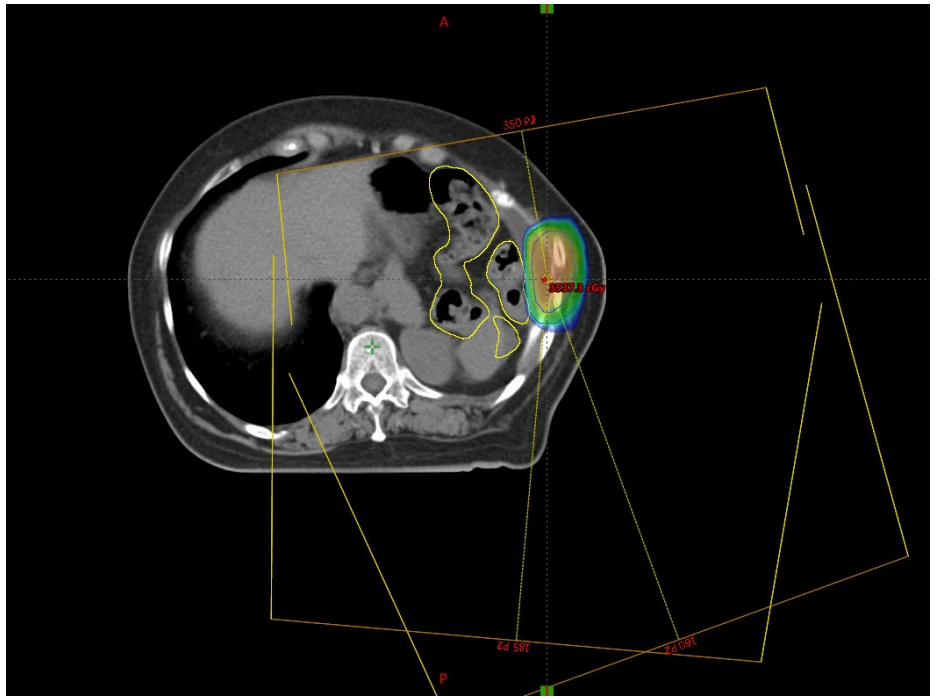


Mesothelioma Proton SBRT as Salvage

After Whole Pleural IMRT



After Extended Pleurectomy/Decortication

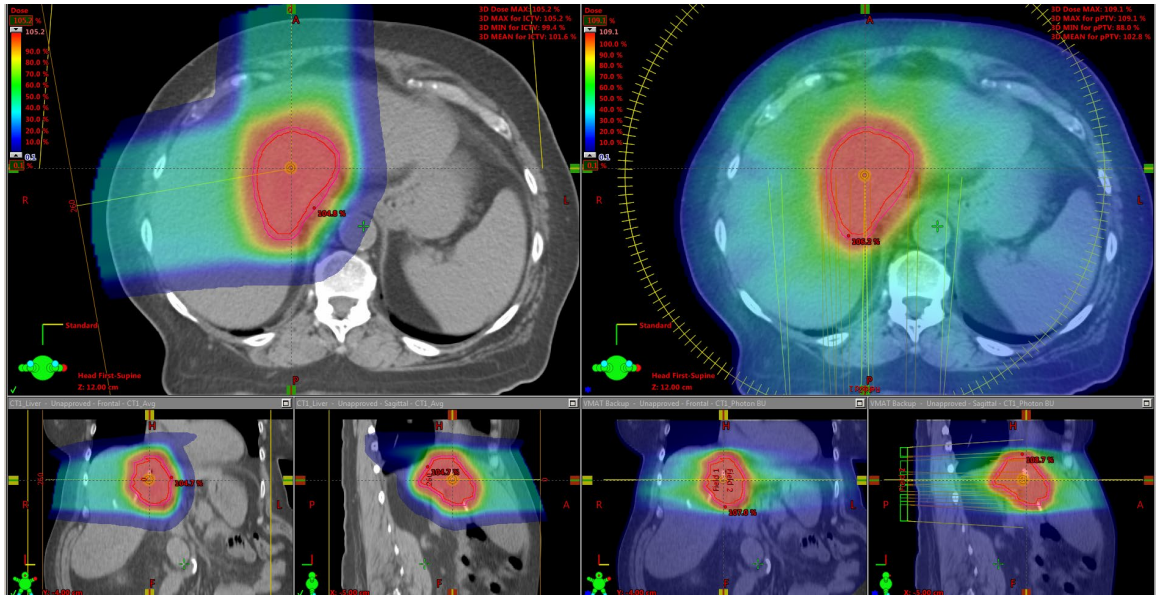


PBS allows for increase conformality, OAR reductions,
and dose escalation via dose painting

PROTON SBRT
FOR LIVER CANCERS

Hepatocellular Carcinoma

- HCC and many liver metastases (ie colorectal) have narrow therapeutic window
  - Normal liver highly radiosensitive, higher RT doses improves tumor control
- Proton therapy can better spare liver and surrounding bowel/stomach/kidney, allow for safer liver ablation
  - Liver sparing magnified for larger tumors and for tumors in dome/left medial/central locations
- Proton therapy can more consistently meet SBRT constraints (versus hypofractionation)

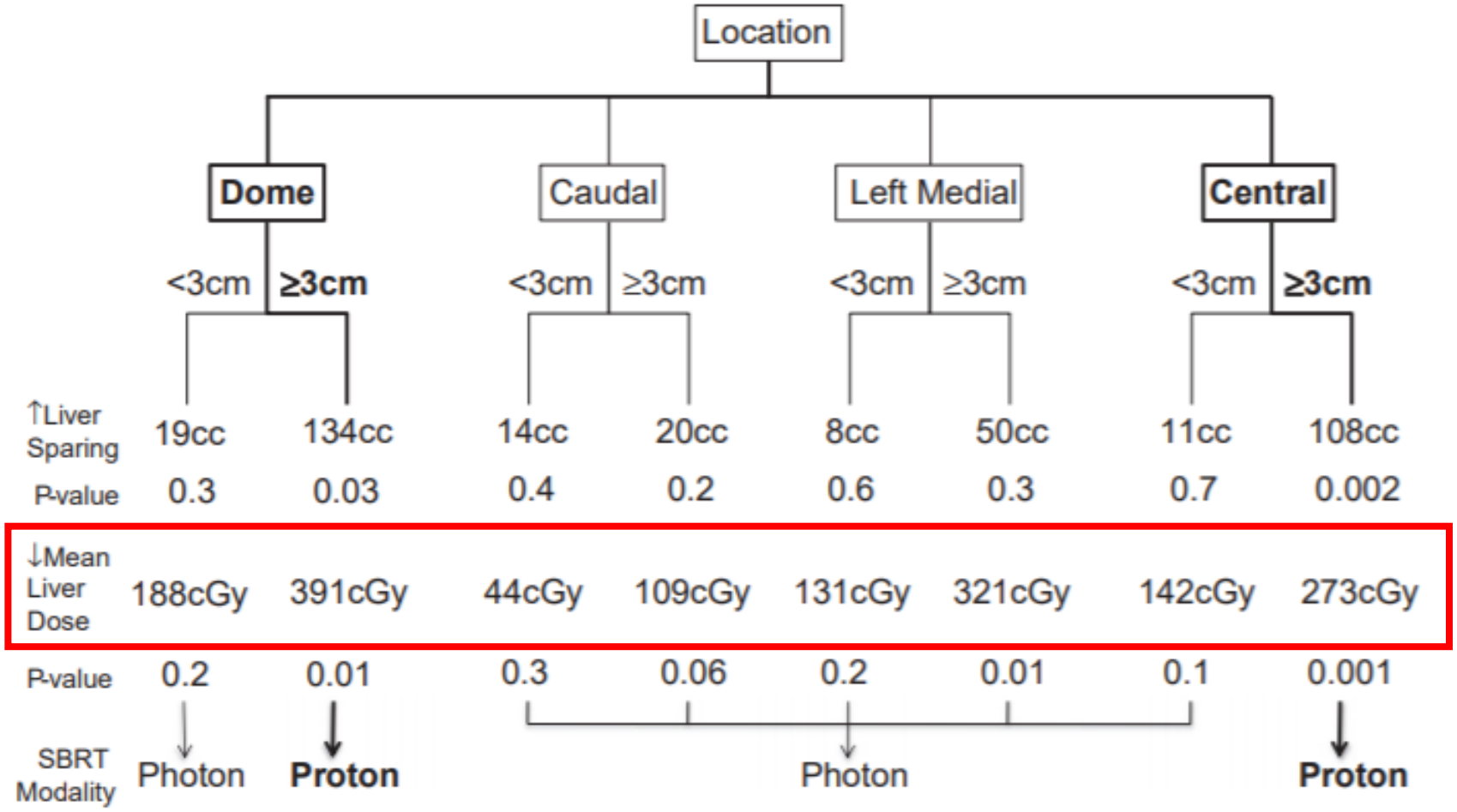


Hypofractionated Proton Therapy for Liver: Long-term Outcomes

- 129 pts from 2002-2009 treated for hepatocellular carcinoma
  - 66.0-77.0 GyE in 10-35 fractions
  - Barcelona Clinic Liver Cancer (BCLC) staging classifications
- 5-yr LC: 94% (stage 0/A), 87% (stage B), 75% (stage C)
- 5-yr PFS 28% (0/A), 23% (B), 9% (C)
- 5-yr OS 69% (0/A), 66% (B), 25% (C)
- No grade ≥3 adverse effects

Fukuda K, et al. *Cancer Sci*. 2017;108(1):53-60.

Liver Determinants for Proton vs. Photon SBRT



Ganhdi SJ, et al. *Prac Rad Onc*. 2015;5(4):209-18.

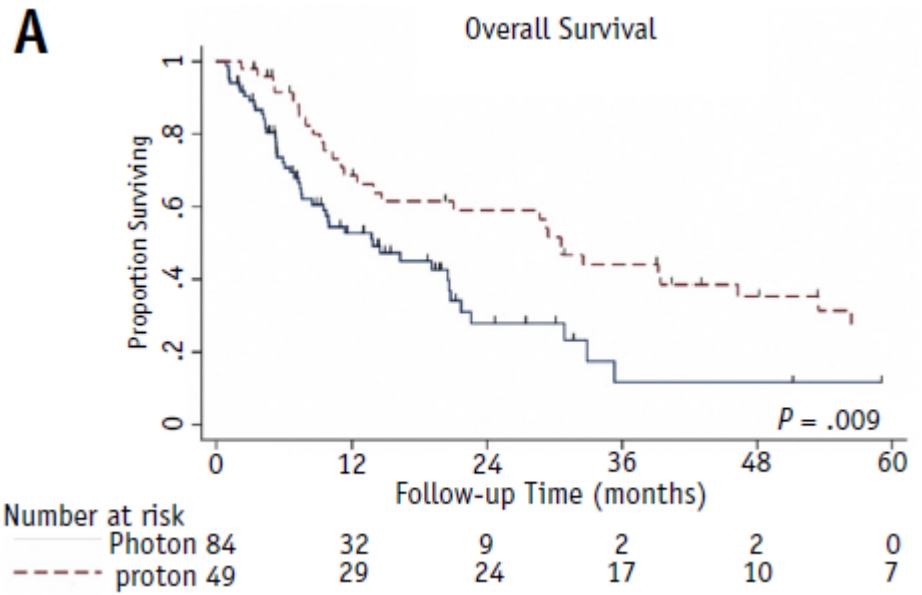
Phase II Liver Proton SBRT

- Phase II trial of risk-adapted proton SBRT for 89 patients with limited extrahepatic disease, ≥800 mL of uninvolved liver, no cirrhosis or Child-Pugh A, 1-4 liver metastases from solid tumors
- 30-50 GyE in 5 fx based on the effective volume of liver irradiated (median 40 GyE)
- No grade ≥3 toxicity
- Median survival time 18.1 months
- LC 1-yr 71.9% and 3-yr 61.2%
- Tumors (≥6 cm) LC 1-yr 73.9%

Hong TS, et al. *J Natl Cancer Inst*. 2017;109(9).

Hepatocellular Proton vs. Photon Comparison

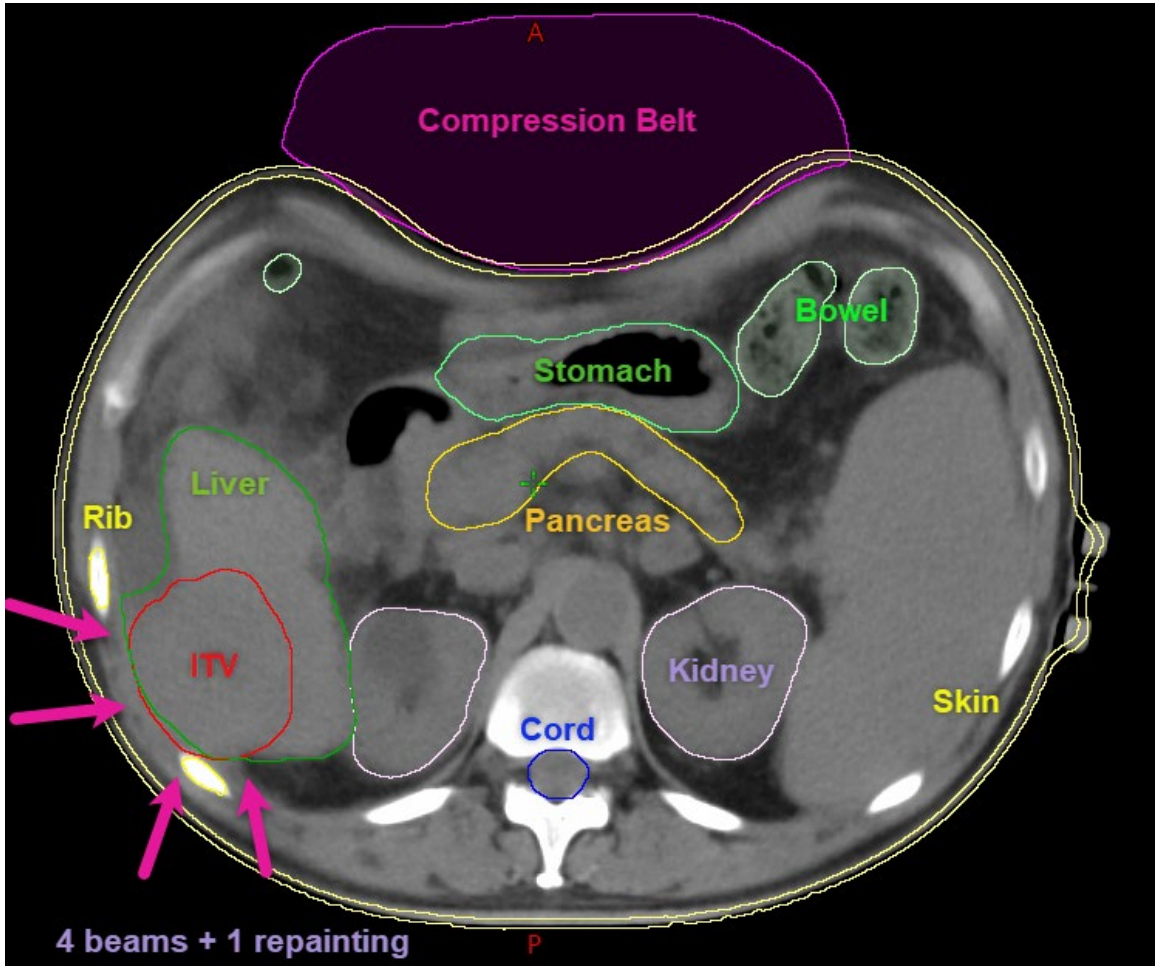
- 133 patients with nonmetastatic, unresectable HCC treated at MGH from 2008-2017 treated with ablative protons (n=49) or photons (n=84)
- No different in local or locoregional failure
- Proton radiation therapy was associated with improved OS (HR 0.47, p=0.008)
- Median OS for protons vs. photons: 31 months vs. 14 months
- 24-month OS: 59.1% and 28.6%
- Proton radiation therapy was also associated with decreased risk of radiation-induced liver disease (OR 0.26, p=0.03)



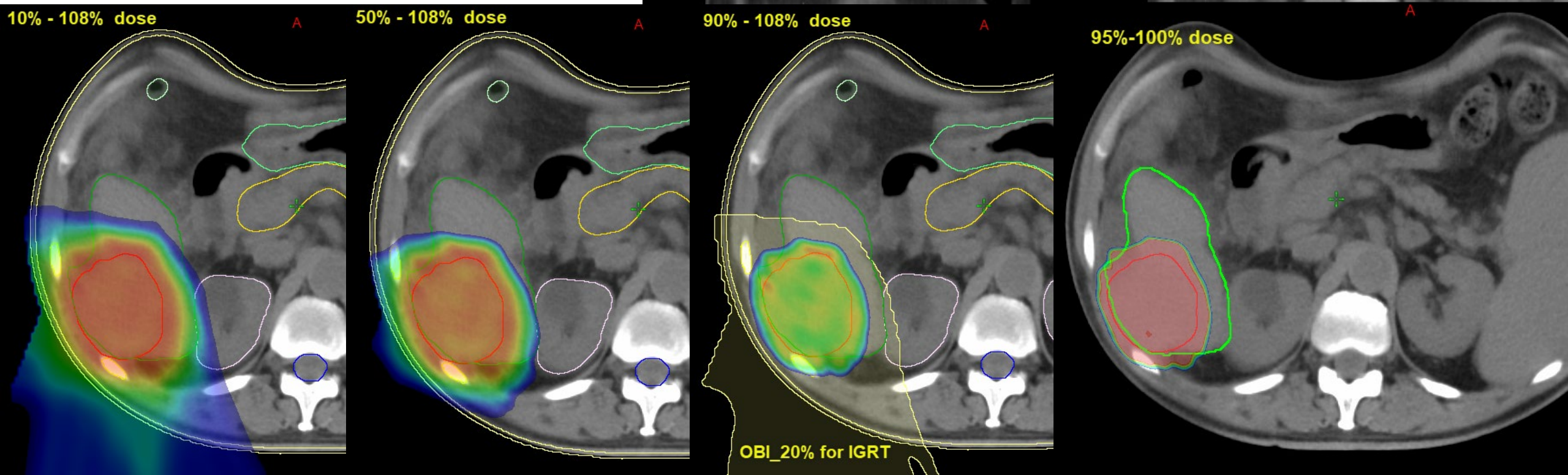
Sanford NN, et al. *IJROBP*. 2019;105(1):64-72.

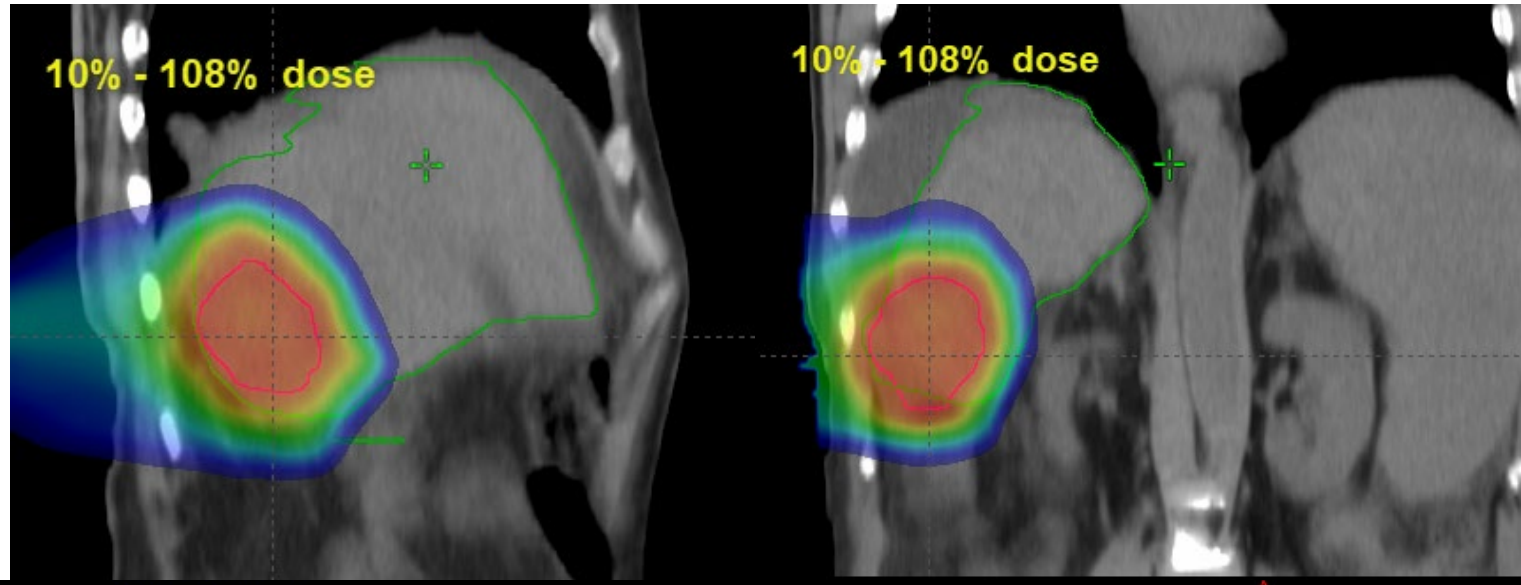
Liver Hepatocellular Carcinoma Proton SBRT

- 67 y/o M with T4N0M0 HCC
- Prior RT liver PTV (photon) overlapped with ITV, significant prior right kidney dose
- 4DCT with abdominal compression belt
- ITV = 166 cc
- Motion amplitude 7.8 mm in sup-inf and AP-PA
- Prescription 8 Gy x 5 = 40 Gy (RBE)
- SFO 4 beams with one volumetric repainting
- kV and daily CBCT for IGRT



Liver HCC Proton SBRT: 3D Dose





FUTURE THINKING OF PROTON SBRT AND CONCLUSIONS

Adding Biology to the Physical Advantages of Protons: Beyond Toxicity Reductions

- Why there might be a survival advantage with protons over photons for lung and liver cancers
  - Reduction of toxicity
    - Treatment-related deaths from pneumonitis, major cardiac events, liver failure, failure to thrive
  - More safely allows for dose escalation that, when delivered safely, may improve local control and thus overall survival
  - Immune: decreased lymphopenia and increase immune stimulation (S1914, PACIFIC 4)
  - Increased LET/RBE
    - Overcome tumor resistance, hypoxia

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RBE and Particle Therapy Biology

Tumor Cells Surviving Exposure to Proton or Photon Radiation Share a Common Immunogenic Modulation Signature, Rendering Them More Sensitive to T Cell–Mediated Killing

Sofia R. Gameiro, PhD,* Anthony S. Malamas, PhD,*
Michael B. Bernstein, MD,† Kwong Y. Tsang, PhD,*
April Vassantachart, BS,† Narayan Sahoo, PhD,† Ramesh Tailor, PhD,†
Rajesh Pidikiti, PhD,† Chandan P. Guha, MBBS, BS, PhD,‡
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James W. Hodge, PhD, MBA*

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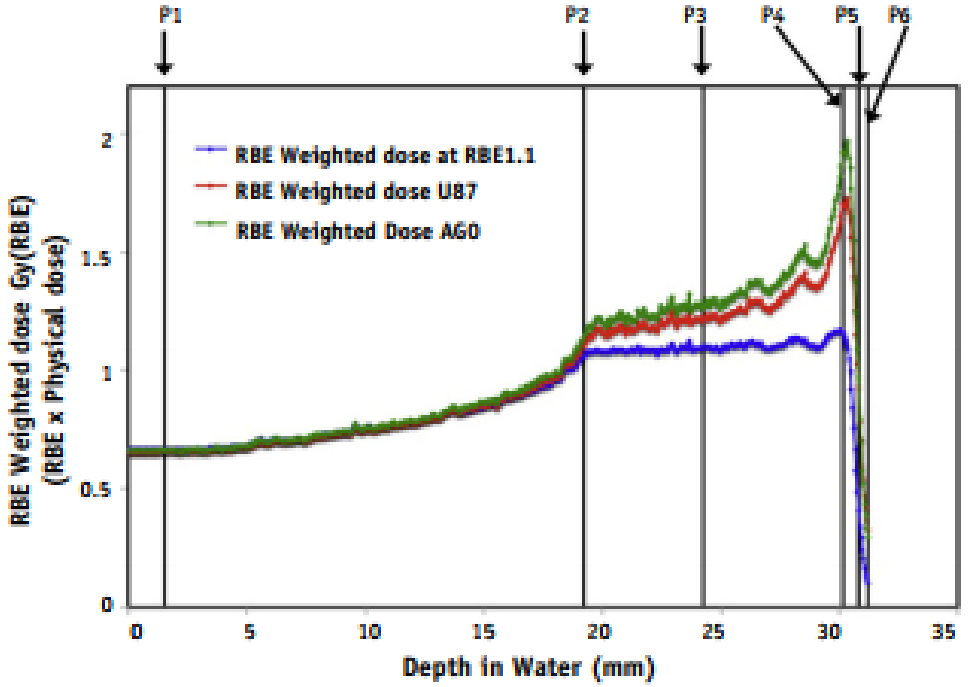
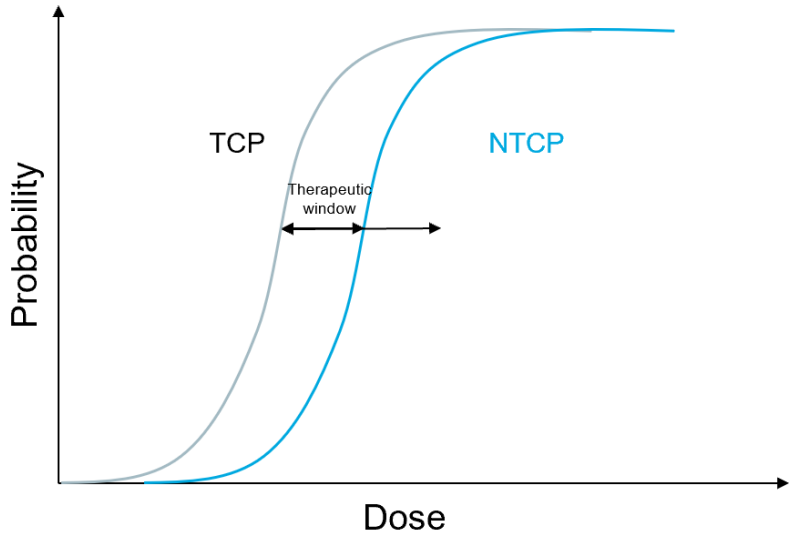


Chaudhary P, et al. *Int J Radiat Oncol Biol Phys*. 2014;90(1):27-35.

Proton FLASH

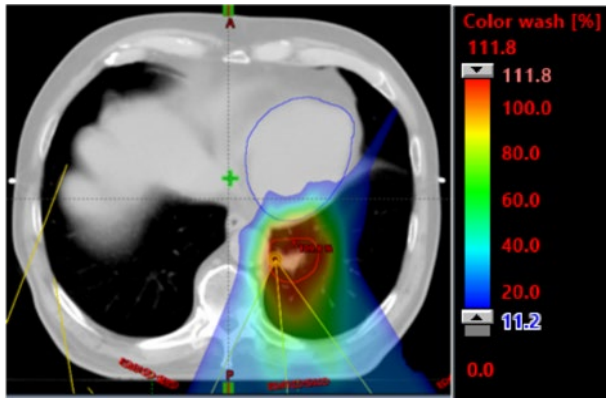
- Linear accelerators - 0.06-0.4 Gy/sec
- Proton accelerators - 1.67 Gy/sec
- Ultra-high dose rate to achieve a FLASH effect - 40-120 Gy/sec



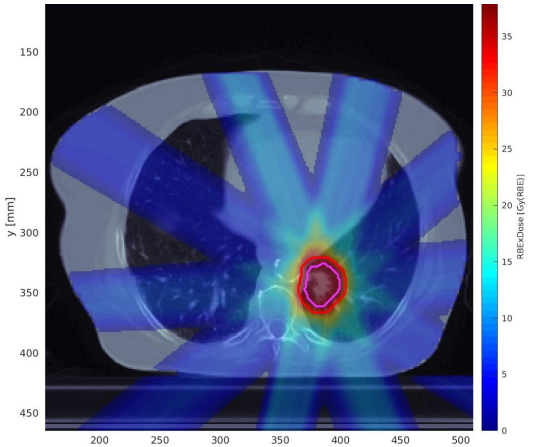
- FLASH has potential to widen the therapeutic window:
  - Improve Normal Tissue Complication Probability (NTCP) while maintaining Tumor Control Probability (TCP)
  - Allow for dose escalation and improved TCP without increasing NTCP
- Proton FLASH
  - Proton accelerators (cyclotrons, synchrotrons) are better suited to deliver FLASH without significant machine manipulation and can (unlike linear accelerators) treat in both FLASH and standard modes
  - Can treat deeper tumors, allows for larger field sizes, can be more conformal in dose distribution relatively to electron FLASH
  - Potential biological advantage with protons having a higher linear energy transfer
  - Can combine the biological OAR sparing of the FLASH effect with the physical OAR sparing of proton therapy when treating with Bragg peak beams

Ultracentral Lung and Liver: Bragg Peak FLASH

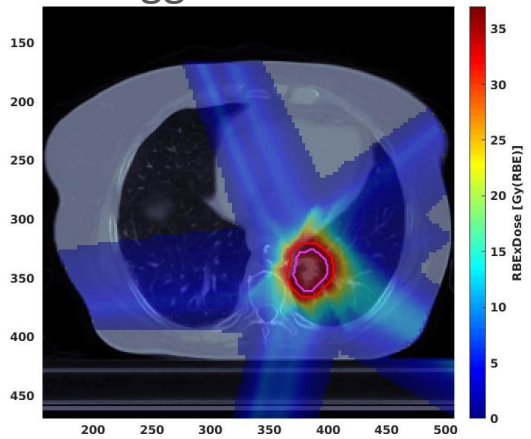
Conventional IMPT

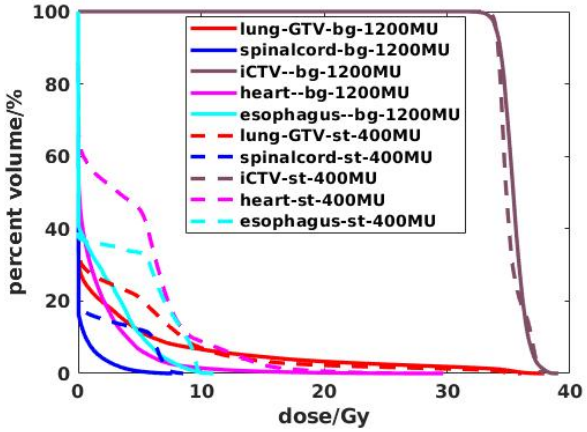


Transmission FLASH

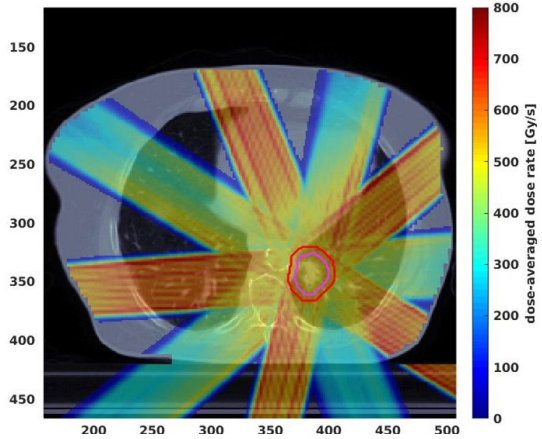


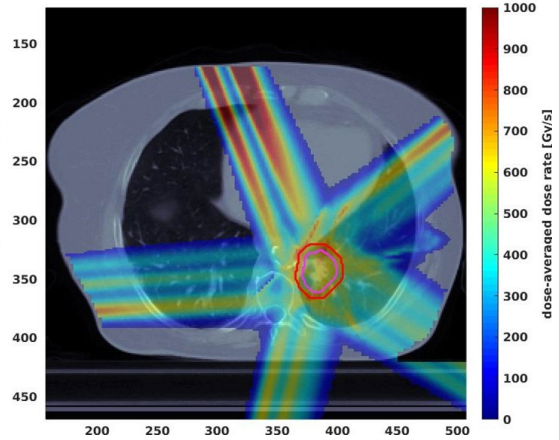
Bragg Peak FLASH

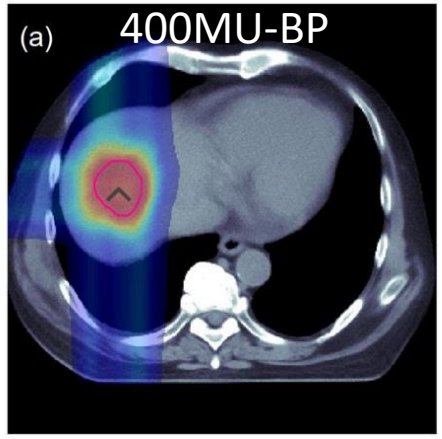


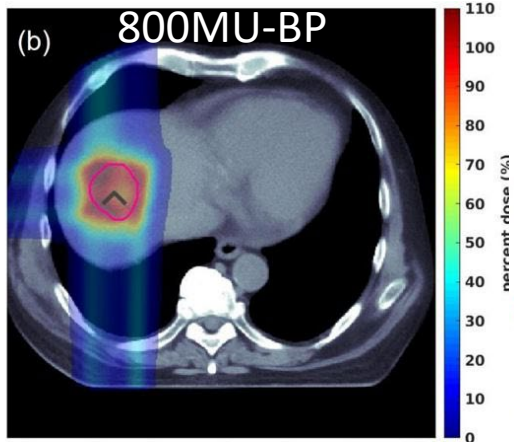


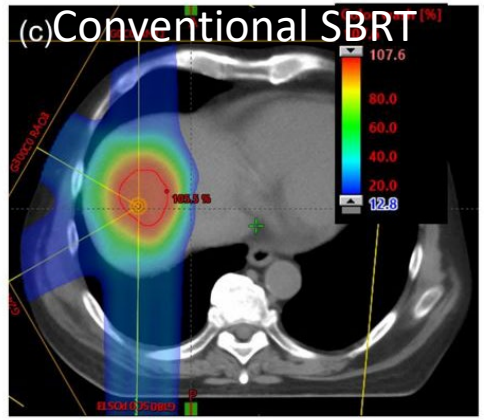
V40Gy/s dose rate coverage:V40Gy/s as the volume ratio received dose rate ≥ 40 Gy/s to assess FLASH dose rate











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Conclusions

- Proton SBRT is increasingly being used for lung and liver cancers
  - Can reduce normal tissue doses that may lead to fewer toxicities
  - Can treat lesions potentially not safely ablatable with photon therapy
  - May more safely allow for dose escalation
  - May allow for retreatment of recurrent tumors
- PBS offers even greater dosimetric benefits over scattered proton therapy
  - Pre-treatment CBCT capability is essential
- Proton SBRT has emerged as a standard of care and being featured in GI003 (liver) and LU008 (lung)