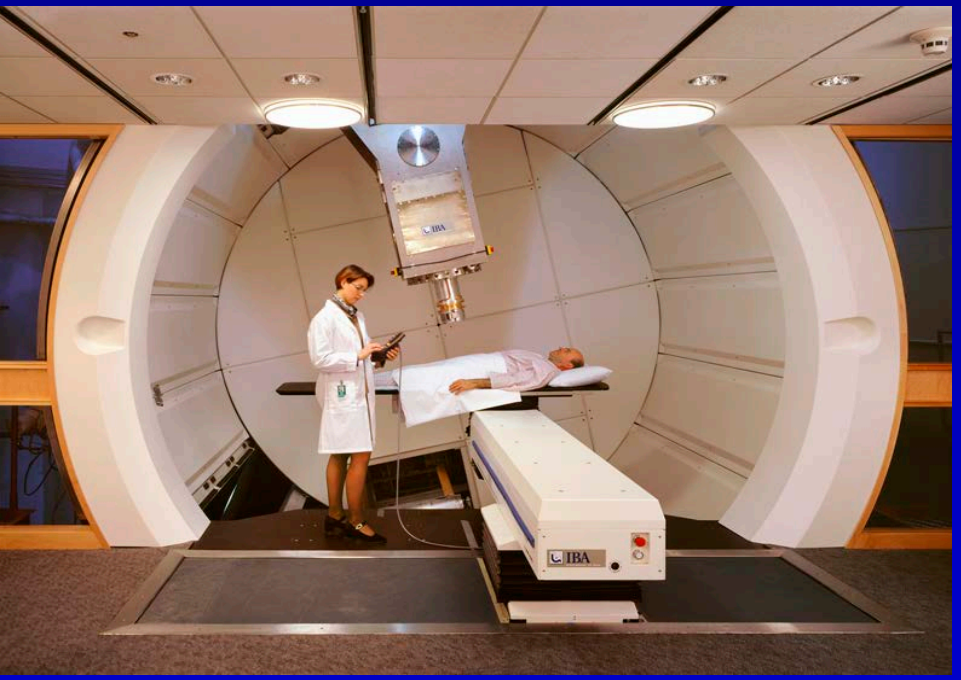
Proton Radiation Therapy: Current Status of Clinical Trials



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+ MGH/MDACC/Penn/RTOG and Other Colleagues!!!

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Disclosure

- **No conflicts of interest to disclose.**

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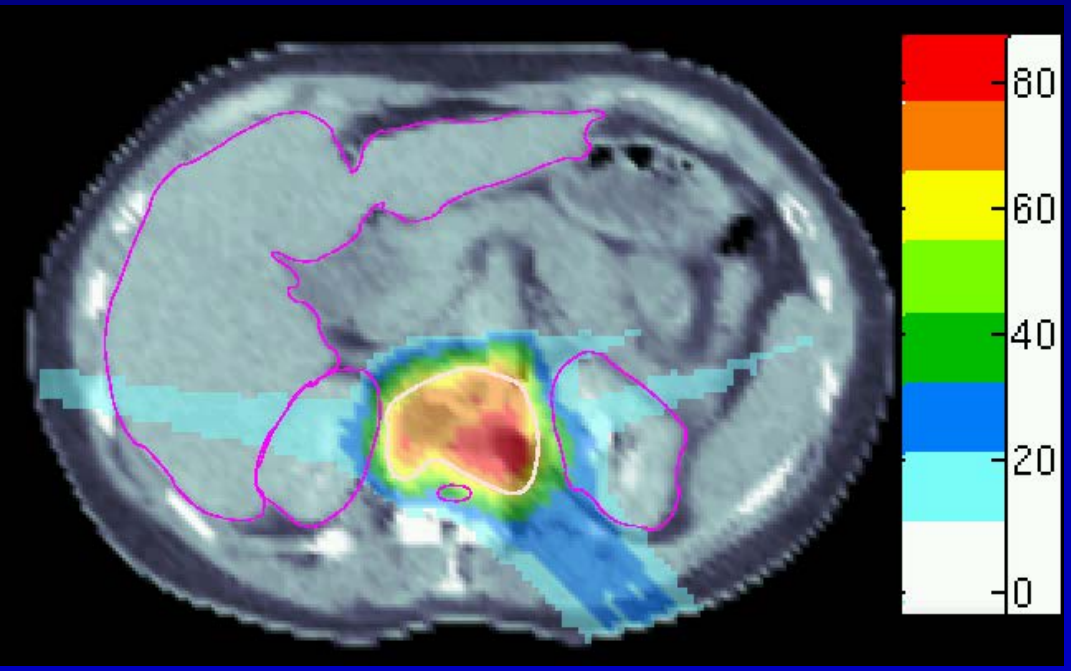
Protons: Clinical Advantage

- Potential clinical advantage for passively scattered protons vs. photons is physical (vs. biologic)
  - Absence of exit dose beyond the Bragg Peak yields a marked reduction in integral dose by up to ~60%
  - Improved dose distributions compared to 3D conformal photons
    - Permitted dose escalation with acceptable normal tissue side effects (i.e. skull base sarcomas, uveal melanomas, prostate)

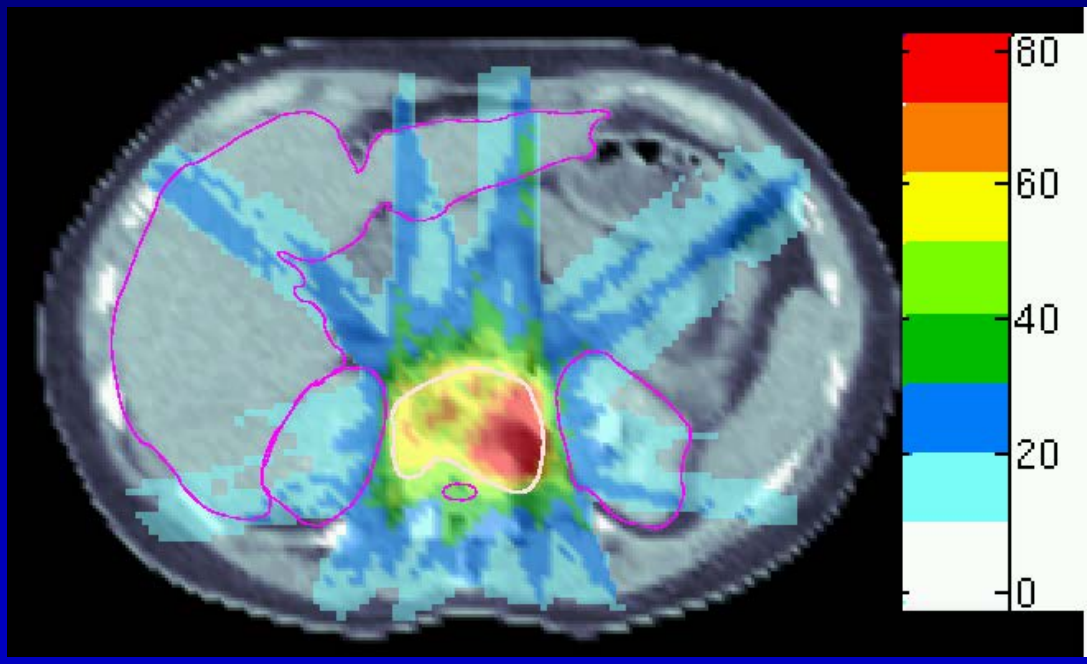
Protons: Potential Clinical Advantages

- Lower integral dose and absence of exit dose:
  - Lower normal tissue doses decrease toxicity
  - Improve Rx tolerance: Uninterrupted Rx
    - Allows integration with systemic chemotherapy
  - Reduce late effects (i.e. growth arrest in child)

L1 Angiosarcoma



3D Proton



IMRT

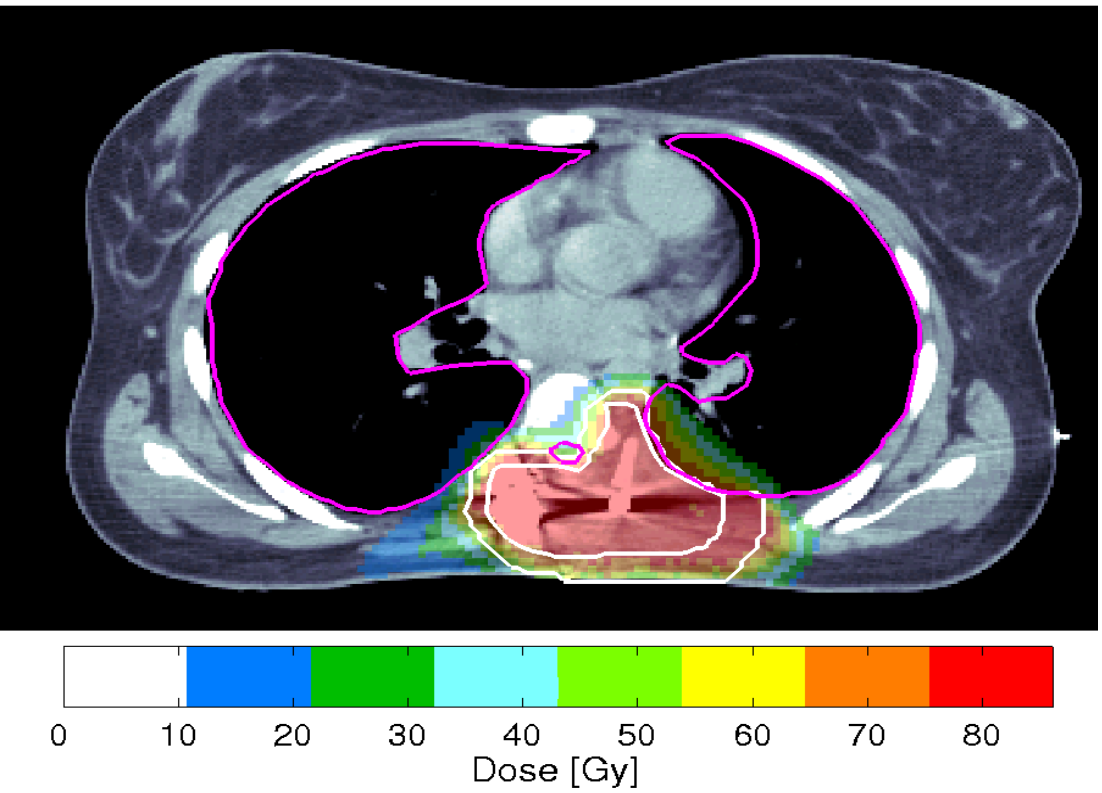
ASTRO 2003

Protons: Physical Dose Advantage

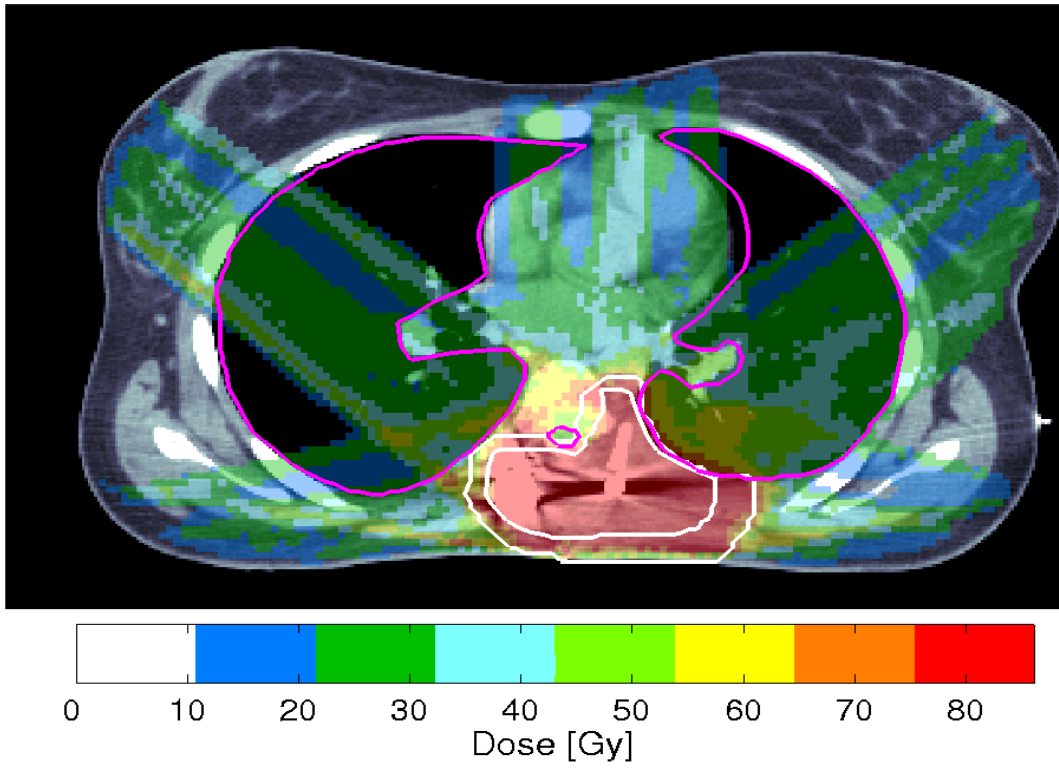
- Intensity modulated radiotherapy-IMRT
  - Target dose distribution ~ to 3D passively scattered protons, although IMRT may be more conformal in the high dose region
  - Integral dose is ALWAYS higher than protons
  - Although IMRT can spare selected normal tissues, this is at the cost of INCREASED DOSE TO OTHER NORMAL TISSUES
    - No advantage to patient to radiate normal tissue
    - Toxicity of low-moderate dose bath with IMRT?
- PROTON INTENSITY MODULATION!
  - Will match conformality of IMRT with lower integral dose
  - May allow some differential LET weighting in the tumor for higher RBE in the tumor (Giantsoudi et al.)

Paravertebral Epithelioid Sarcoma
Intensity Modulated Protons (IMPT) vs. Intensity Modulated Photons (IMRT) (7 field)

IMPT



IMXT



Evaluating the Clinical Role for Protons

- Clinical studies designed to document proton Rx clinical outcomes and where possible compare/contrast with best available photons
  - **Mass General Hospital/MD Anderson Proton Program Project Grant Clinical Trials**
  - **Mass General Federal Share Grant Clinical Trials**
    - **Other institutions invited to participate in these studies**
  - **NRG (i.e. RTOG) Proton Working Group**
    - Several studies allow protons (prostate, GBM, HCCa)
    - Comparative proton photon studies: Lung, GBM
  - Other Studies (Can access at clinicaltrials.gov)

Pediatrics

- Emerging consensus that the reduction in integral dose is likely to have the greatest impact in children
  - Protons allowed in Children's Oncology Group studies
- Phase II studies are the only ones that can be conducted from ethical perspective
- Eligible children should be considered for referral to appropriate center
- Increase # of proton centers with pediatric oncology and anesthesia expertise to manage these patients
  - Employ scanned beams to reduce neutron contamination associated with passive scattered beam delivery

Clinical/Technical Considerations for Use of Protons in Adult Patients

- Greatest gain for protons will be where there is the largest reduction in integral dose
  - Large tumors or large target volumes
  - Tumors large relative to the affected organ; i.e. eye
- Logically, this would also likely be for patients requiring higher doses→tumors with gross disease or positive margins not well treated with conventional photon doses

Protons: Clinical Advantage?

ADULT MALIGNANCIES

- Does superior proton dosimetry yield measurable clinical gain?
  - Clinical trial strategies to define any advantage
    - Which patients experience the greatest gain
  - Quantitate the magnitude of advantage
- Cost
  - IMPT cost estimated 2.4 x IMRT (Goitein, 2003)
    - Capital cost for facility→protons are 1800 x heavier than electrons
  - Is proton therapy cost effective?
    - Can costs of proton therapy be reduced**?**
      - Technical improvements and/or hypofractionation

Protons: Clinical Advantage?

ADULT MALIGNANCIES

- Randomized studies of protons vs. photons
  - Equipoise: Clinicians/patients aware of dose advantage may refuse randomization in phase III studies in some anatomic sites: i.e.: low grade brain tumors
  - Tissue heterogeneity (i.e. mucus in sinus), motion, changes in tumor/tissue density more critical to protons
    - Adaptive proton therapy strategies will be critical
  - Was it necessary to randomize patients between orthovoltage and megavoltage photons?

Proton Clinical Trials

- Issues to consider
  - Are randomized studies ethical and/or feasible?
    - Randomization to photons acceptable to patients/clinicians?
      - Perhaps---if equipoise--->
        - Lung cancer: longer proton range in lung reduces normal lung sparing compared to denser tissues
        - Prostate where IMRT may be more conformal in high dose region(near bladder, rectum) than 3D protons
        - ? Hepatocellular carcinoma– dose shaping near mucosal structures, differential impact of motion management on proton/photon OAR dose
      - No: Pediatric malignancies

Clinical Trials and Proton Therapy

- Can studies include a photon arm where centers without protons can participate to generate meaningful comparison data?
- Encouragement from NCI to do multi-institutional clinical studies to speed accrual and generalize results
  - Can comparable technologies be employed in different centers with confidence that proposed dose distributions can be reliably delivered?
    - Different beam qualities and different planning systems
  - Comparable levels of image guidance?
    - Proton centers just now adding volumetric imaging

Clinical Trials and Proton Therapy

- Why do we need controls?
  - Concerns that protons are not cost effective
    - Cost differential…if cost were the same, one could argue that a broader group of patients should be getting protons
  - Unanticipated late effects of protons
    - ? Neutrons generated with passively scattered protons
    - Long term data, even with passively scattered protons do not suggest this to date
      - Chung et al, Int J Radiat Oncol Biol Phys, 2013
    - Further marked reduction in beam line neutrons with scanned protons

Second Malignancies

- Chung et al (MGH-Harvard Cyclotron)
  - Matched retrospective cohort study of 1,450 HCL proton pts and photon cohort in SEER cancer registry.
  - Matched 558 HCL proton pts (1972-2001) with 558 SEER pts
  - 6.4% of proton patients (32 patients) developed a second malignancy, versus 12.8% of photon patients (203 patients)
  - Median f/u: 6.7 years (protons) and 6.0 years (photon)
  - The median age at time of Rx was 59
  - Proton NOT associated with↑ second malignancy risk
    - Hazard Ratio 0.52 (95% CI 0.32 -0.85), p< 0.009.

Int J Radiat Oncol Biol Phys 2013

Clinical Trials and Proton Therapy

- Many recent clinical studies to date have been developmental (i.e. new sites, scanning beam)
  - Important to note that proton technology is not yet mature
- MGH/MDACC Program Project Grant (2008-2014)
  - New sites, range uncertainty, motion management, IMPT
    - Stage II/III NSCLCa (Phase 2: Protons vs. Photons, 66-74 Gy)
    - Hepatocellular/Intrahepatic Cholangiocarcinoma: Phase 2 proton
    - Paranasal Sinus: Phase II: IMRT, 3D protons, IMPT arms
    - Skull base/spine sarcomas: IMPT robust plans→Phase II IMPT
  - Pediatric: Phase II: Medulloblastoma(CSI) Rhabdomyosarcoma

Clinical Trials and Proton Therapy

- Concern from skeptics that many proton clinical studies lack a control arm→ controlled studies
- RTOG 1308 Locally Advanced NSC Lung Ca (J. Bradley)
  - Phase IIIR Photon vs. Proton 60-70 Gy ChemoRT (activated)
- RTOG 1326 Glioblastoma(M. Mehta)
  - Phase IIIR 60 vs. 75 Gy (SIB); IMRT and Proton Cohorts
- MGH/Penn+Prostate: Phase IIIR IMRT vs. Protons 79.2 Gy
- MGH/MDACC PO1 (?2014-19): Phase IIR/? Phase III(NRG)
  - IMRT vs IMPT: Oropharynx (S. Frank), Nasopharynx (A. Chan), Low grade brain(D. Grosshans), Liver (T. Hong/C. Crane), Stage III NSCLCa with SIB (X. Liao)

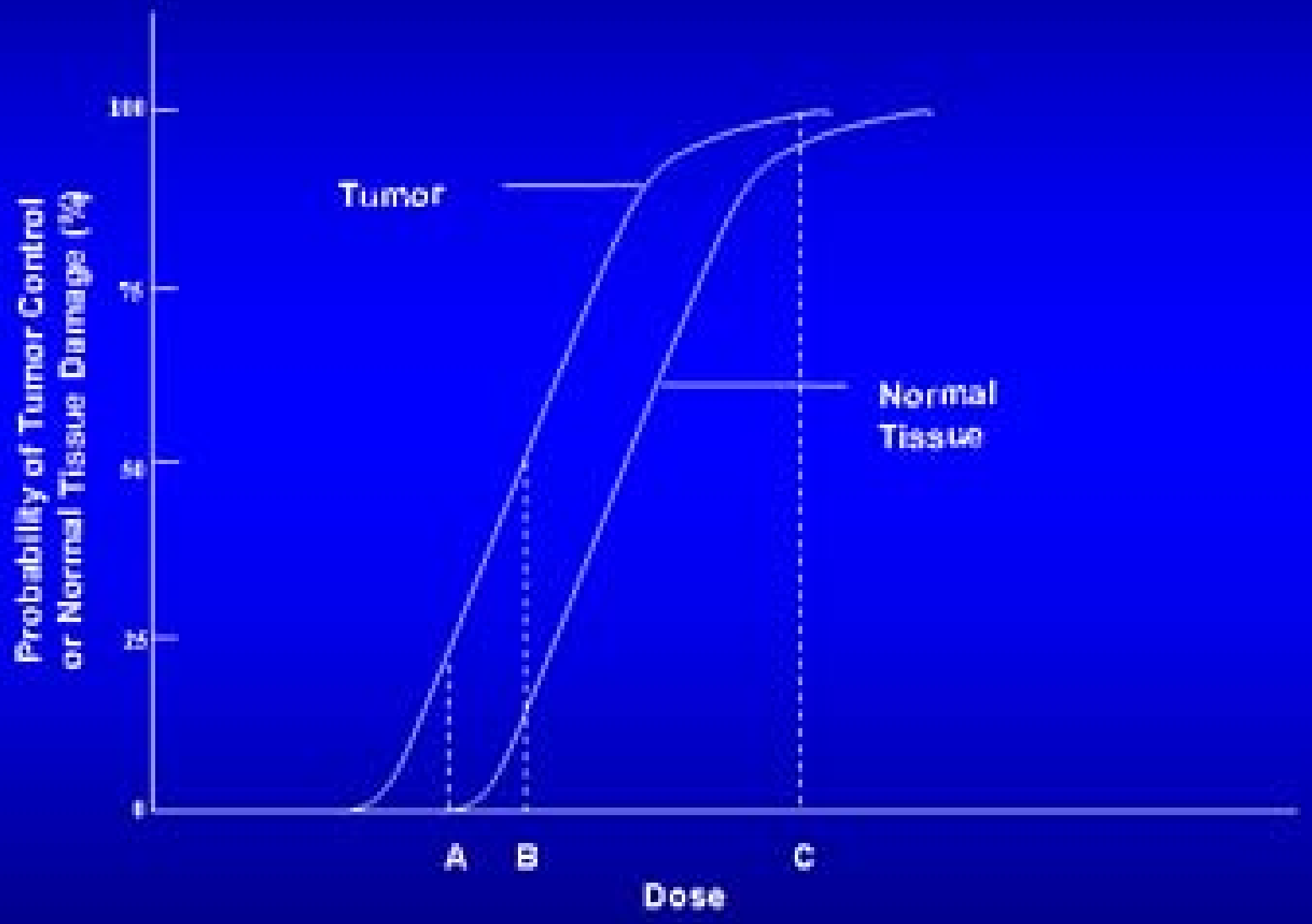
Clinical Trials and Proton Therapy

- What is the appropriate control arm?
  - ? Photons: Randomized versus registry studies
    - Parallel studies: Paranasal Sinus: IMRT, 3D protons, IMPT
  - Protons with altered fractionation
    - Hypofractionated where cost of protons comparable to photons
  - High LET/heavier charged particles (i.e. carbon)
    - Because of denser ionization, ↑ double strand breaks, target GTV only with C-12 to avoid OAR injury in surrounding CTV
    - Tumors where LC with low LET 20-80% dose range, otherwise, size of clinical trials becomes prohibitive
    - Spine sarcoma: Assume ↑10-year LC from 84% p+ to 94% C12
      - N = 175-185 per arm gives 84-86% power.
      - MGH: 7.25 years to accrue 50 pts to spine sarcoma trial

Clinical Trials and Proton Therapy

- Randomized Carbon Ion Studies (Heidelberg)
  - Skull base chordoma RCT
    - Carbon 45 GyRBE/15 fx CTV1 + 18 GyRBE/6 fx CTV2
    - Proton 50 GyRBE/25 fx CTV1 + 22 GyRBE/11 fx CTV2
  - Glioblastoma RCT: 50 GyRBE/25 fx chemoRT CTV1
    - Carbon 18 GyRBE/6 fx CTV2 boost
    - Proton 10 GyRBE/5 fx CTV2 boost
      - Would any difference be due to dose or LET?
  - Skull base chondrosarcoma RCT
    - Carbon 45 GyRBE/15 fx CTV1 + 15 GyRBE/5 fx CTV2
    - Proton 50 GyRBE/25 fx CTV1 + 20 GyRBE/11 fx CTV2
      - Local control with protons 94% at 10 years….how to power this study?

Steep Portion of Dose Response Curve from 20% to 80%

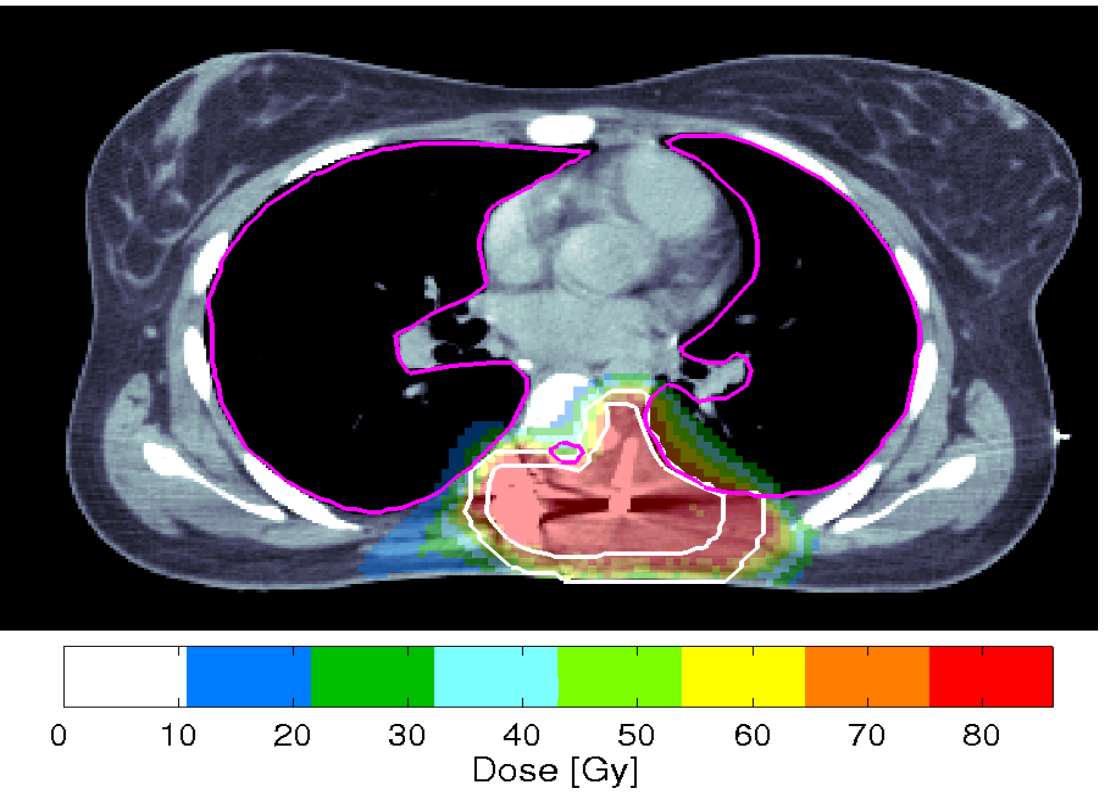


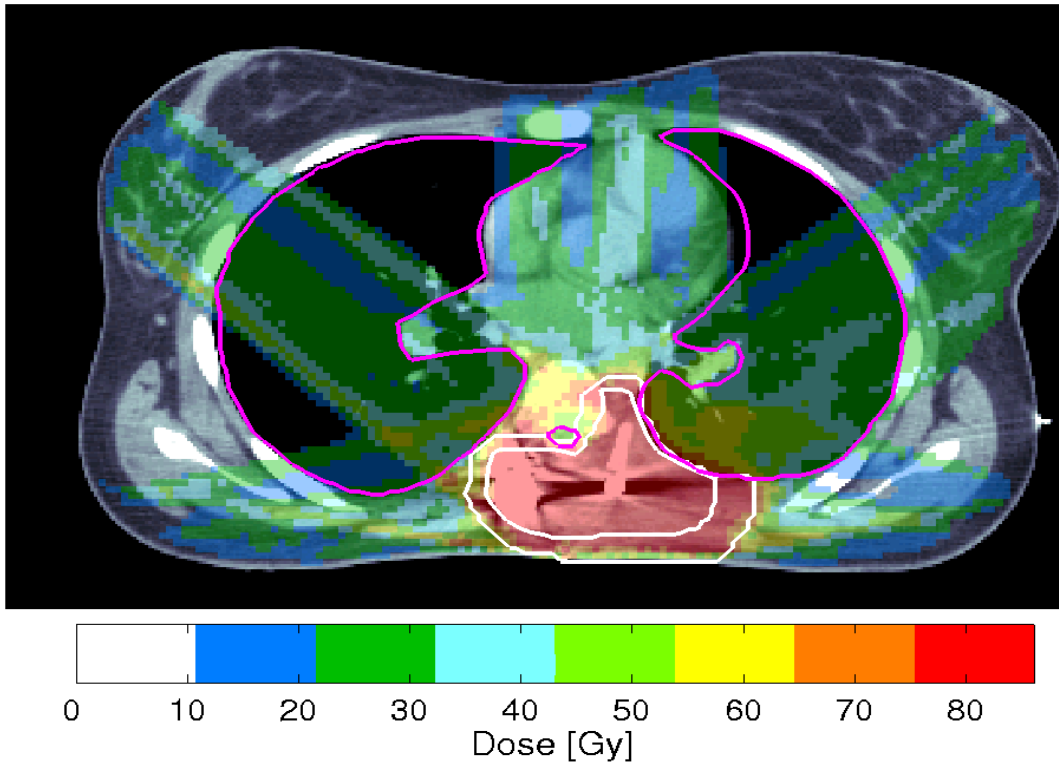
Randomized clinical trials large when LC in control arm >80%

When IMPT is clinically achievable, perhaps the research focus in some clinical sites should shift to making protons less expensive via improved efficiency and better technology, thus making more widely available to more patients!

IMPT

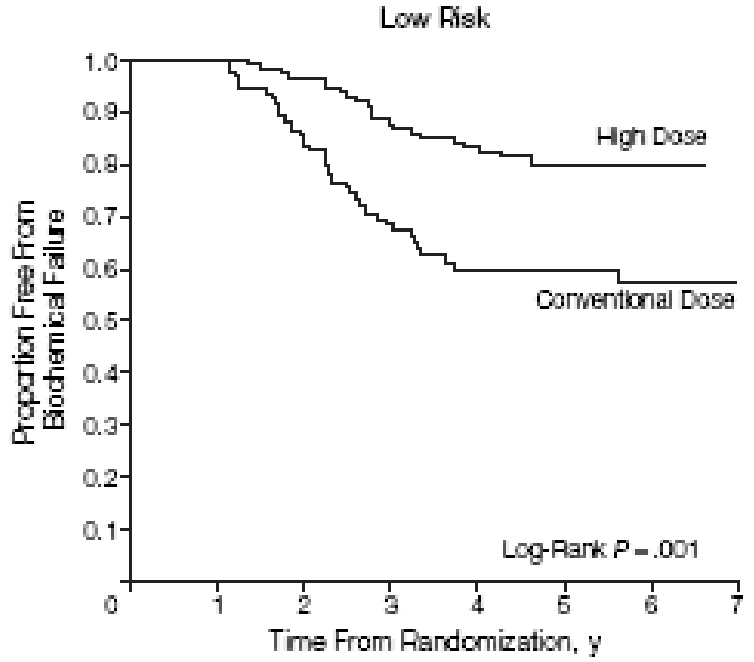
IMXT

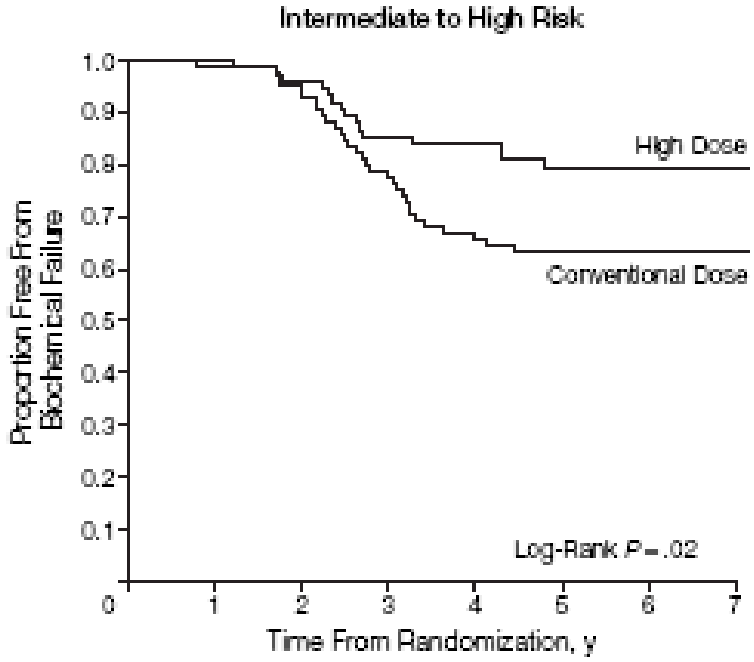




Dose Escalation for Prostate Cancer with Protons

Figure 3. Freedom From Biochemical Failure (ASTRO Definition) Following Either Conventional-Dose (70.2 GyE) or High-Dose (79.2 GyE) Conformal Radiation Therapy



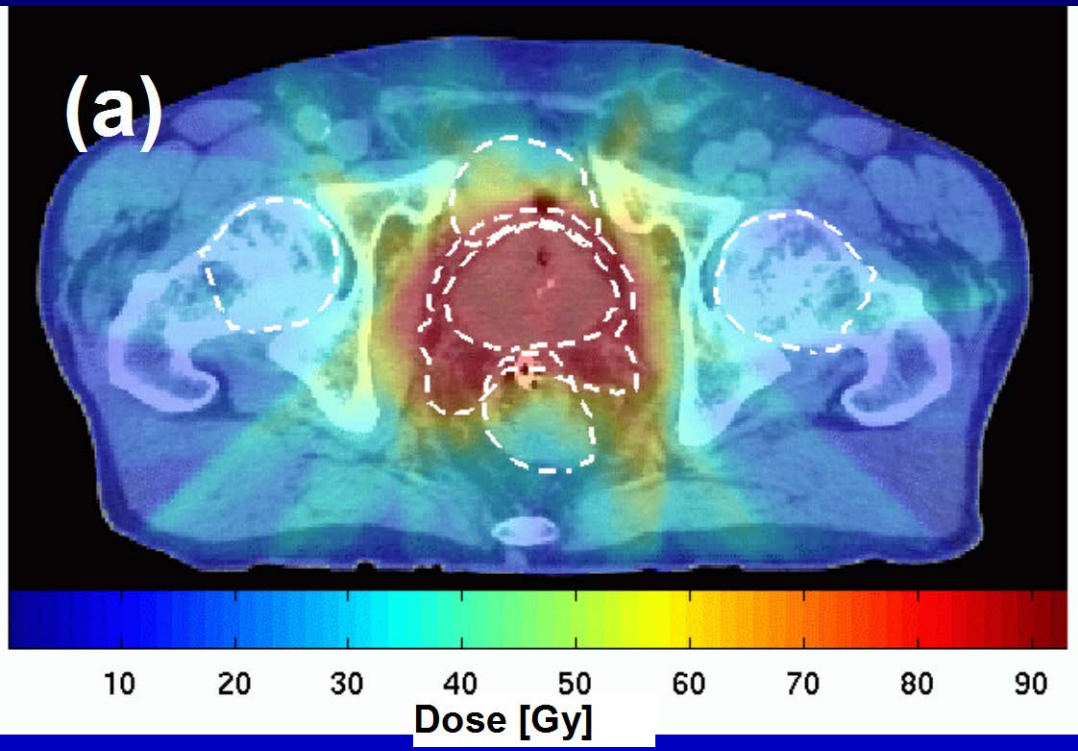


No. at Risk								
High Dose	111	111	92	74	64	38	14	4
Conventional Dose	116	116	111	99	89	56	24	12

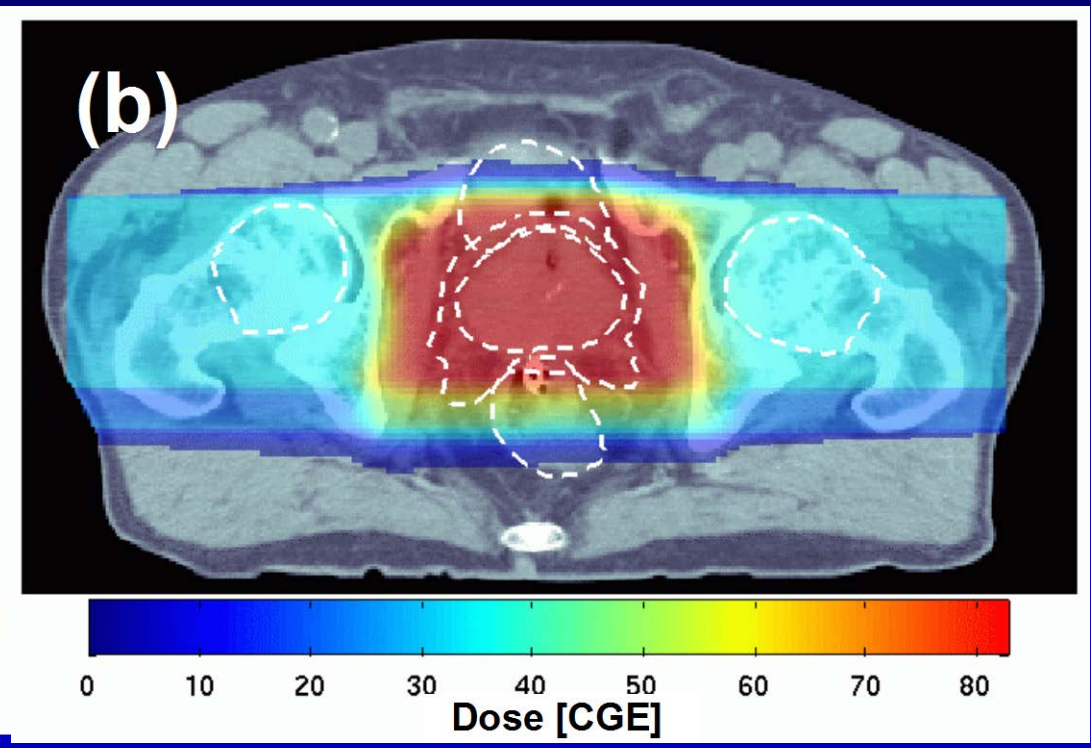
No. at Risk								
High Dose	86	85	79	65	54	38	17	6
Conventional Dose	76	75	70	61	57	40	19	8

Analysis of these early cases is by risk subgroup. Low-risk patients have prostate-specific antigen level <10 ng/mL, stage ≤T2a tumors, and Gleason scores ≤6. ASTRO indicates American Society for Therapeutic Radiology and Oncology; GyE, gray equivalents (see "Methods" section).

Prostate IMRT and Proton Treatment Plans



IMRT



3D Conformal Protons

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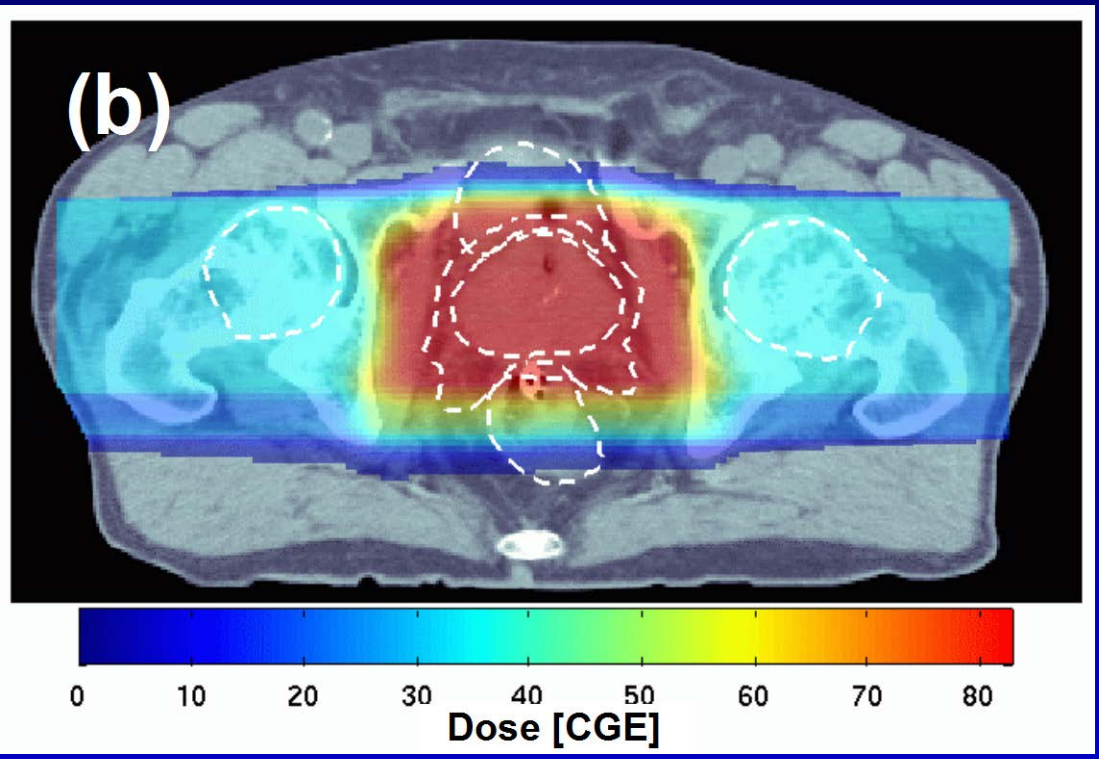
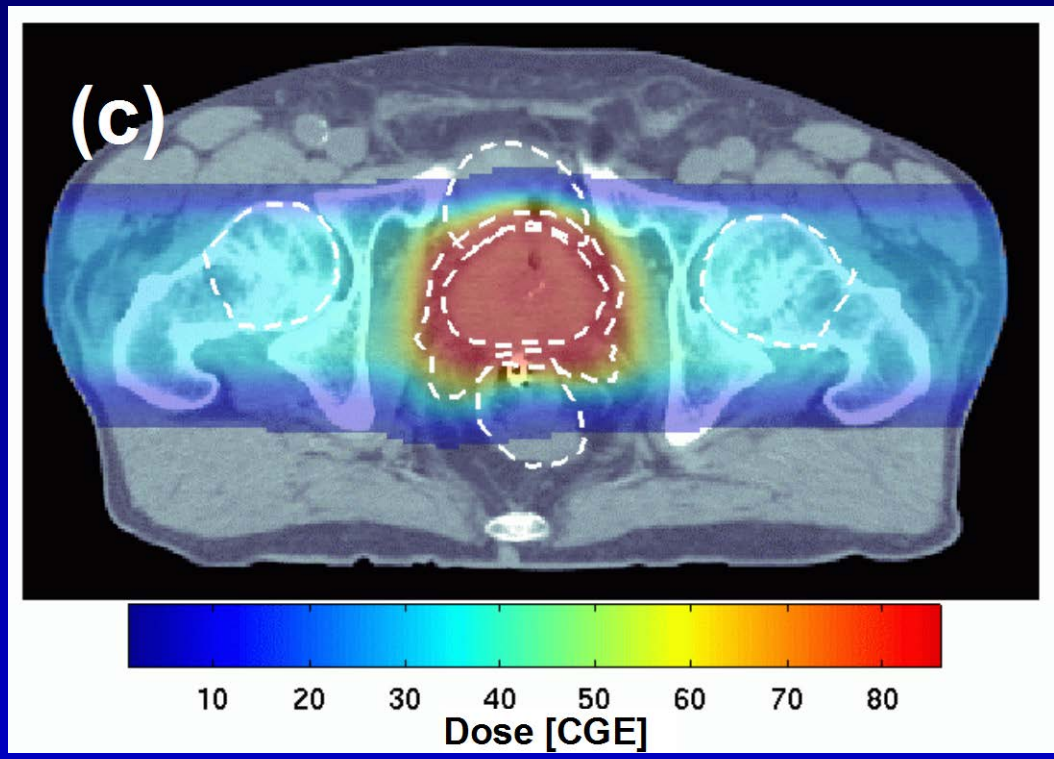
Trofimov et al, 2007

Prostate IMRT and Proton Treatment Plans



3D Conformal Protons



Intensity Modulated Protons**

Optimal IMPT will need to account for range uncertainty→
Rectal probe dosimeter

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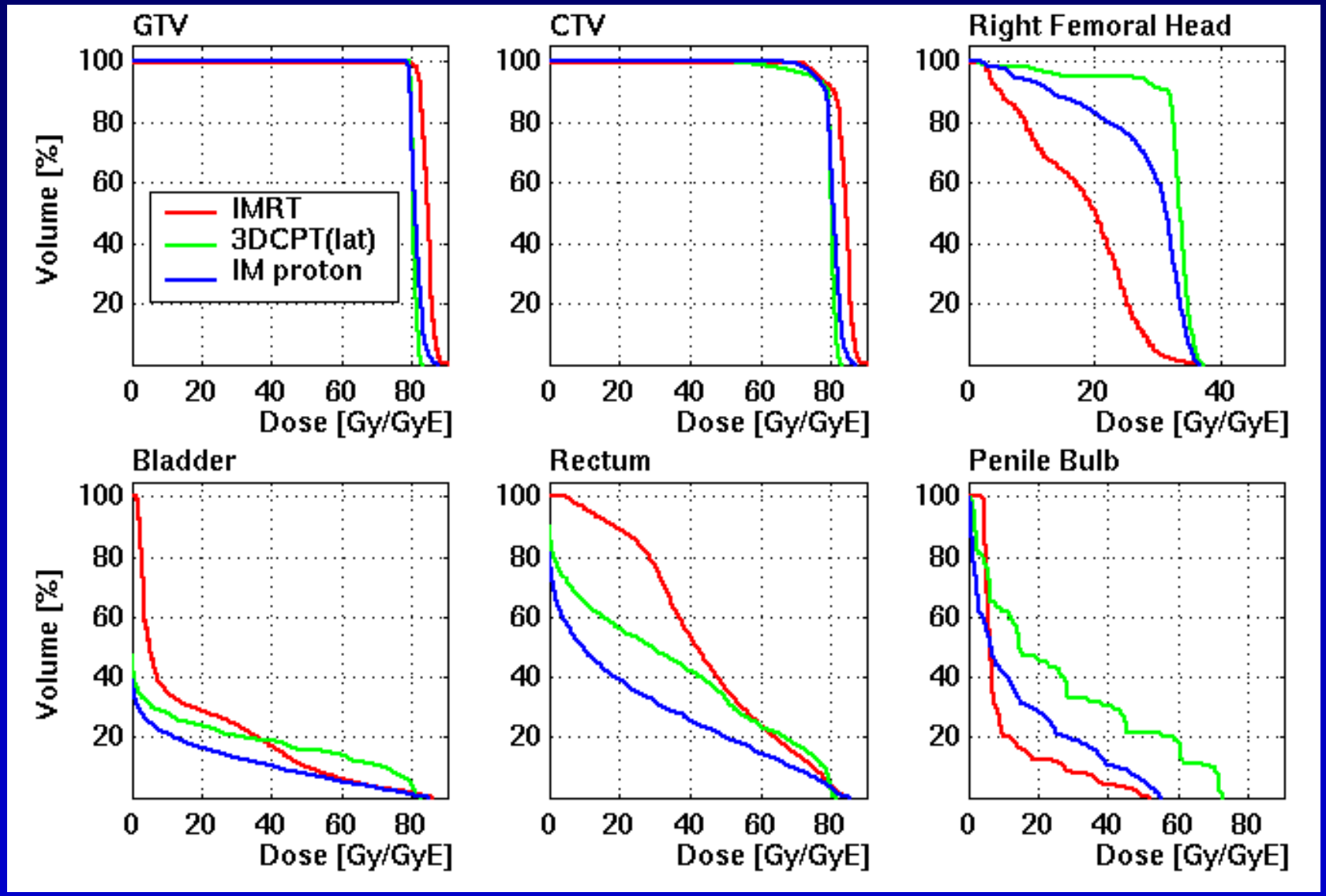
Prostate IMRT and Proton Treatment Plans



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Trofimov et al, 2007

Randomized Prostate Protocol

- Phase III Randomized Clinical Trial of Proton vs. IMRT for Low or Low-intermediate Risk Prostate Cancer (J. Efstathiou, J Bekelman PIs)
  - Mass General and University of Pennsylvania
  - Endpoints of efficacy and bowel/bladder/erectile toxicity
    - Will randomize 400 patients
      - May need to add patients for IMPT arm
    - Companion registry study of 350 patients

Protons: Cost

- **Reduction in cost differential between protons and photons should be a priority**
  - If protons/photons were = in cost, talk about need for randomized proton vs. photon studies would end
  - Less expensive facilities- ? Single room facilities
    - Alternatives to gantry→robotic positoner and fixed beam
  - Improved efficiency
  - Hypofractionation where appropriate
    - Early stage lung cancer, hepatocellular
  - Scanned beams reduce cost: ↓ aperture fabrication $
  - Combined photon/proton treatment

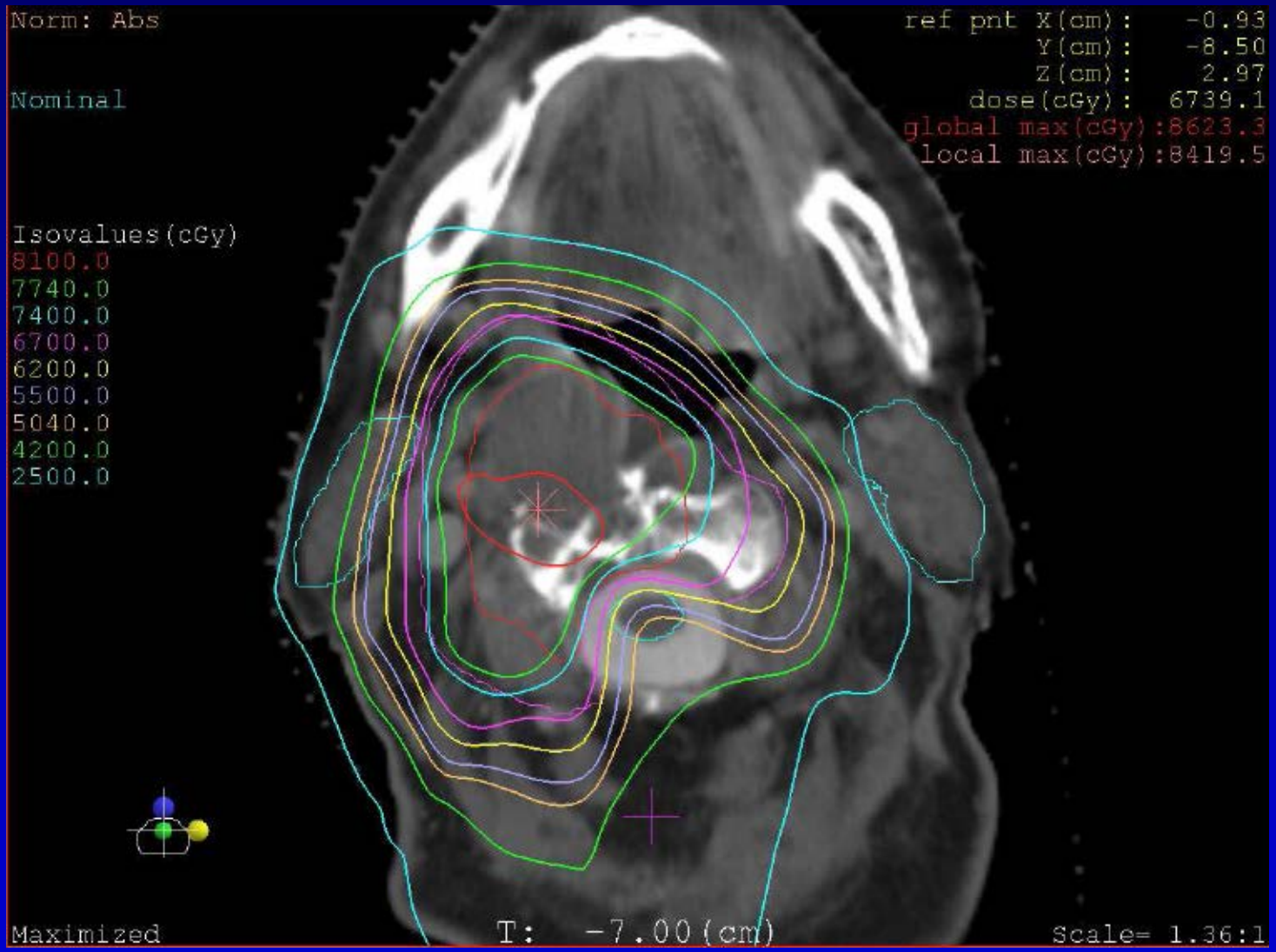
Combined IMRT and 3D Protons

C2 Chordoma

18 Gy IMRT
59.4 Gy Proton

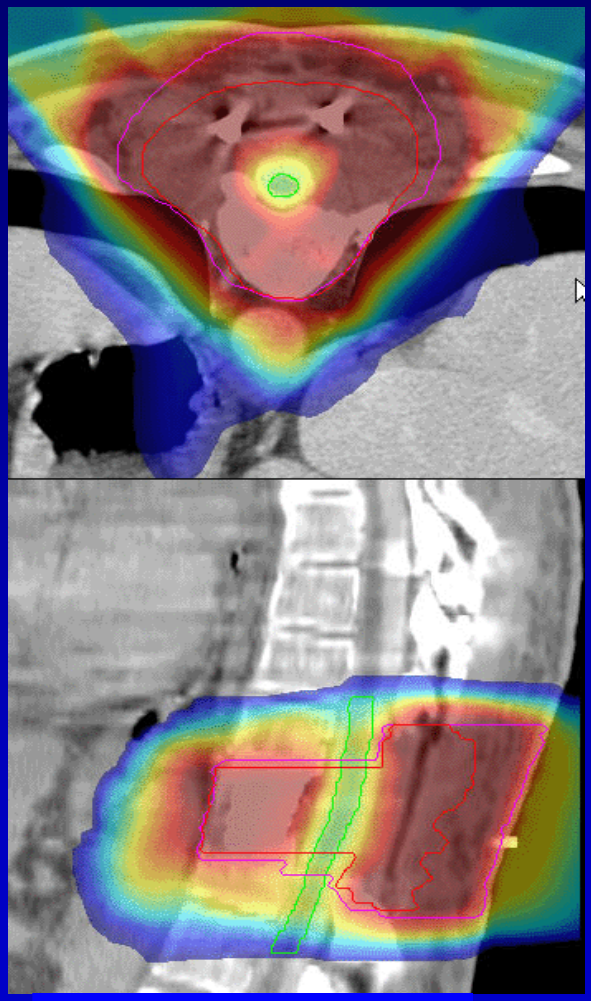
77.4 Gy

Note intrathecal contrast



Current Passively Scattered Proton Operations

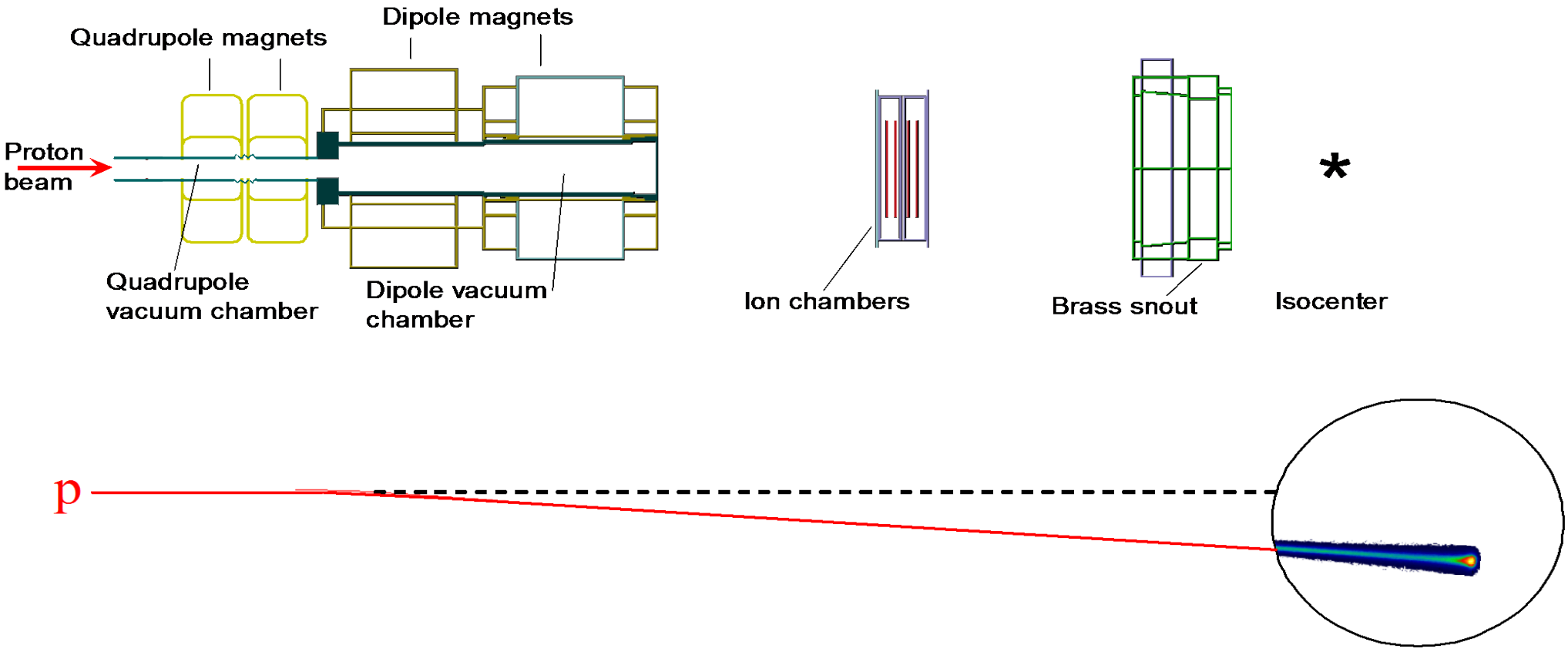
- Scattered field delivery can be challenging
- Especially for large(r) volumes
  - Apertures for 25, 18 cm snouts: heavy
  - Multi-isocenter setups very laborious
- Patching: only technique for “complex” shapes
  - Demanding technique for planning and delivery
  - Sole reliance on penumbral edge
  - Insufficient knowledge of distal edge
- Brass apertures are very expensive
  - FHBPTC produces ~5,000 apertures+range-compensators / year (~$500,000 / year)
  - MLC is not the solution (H. Kooy PhD)
  - Pencil Beam Scanning is the answer
    - Lower neutron dose



3 PA/PO Fields

Methods of Beam Scanning

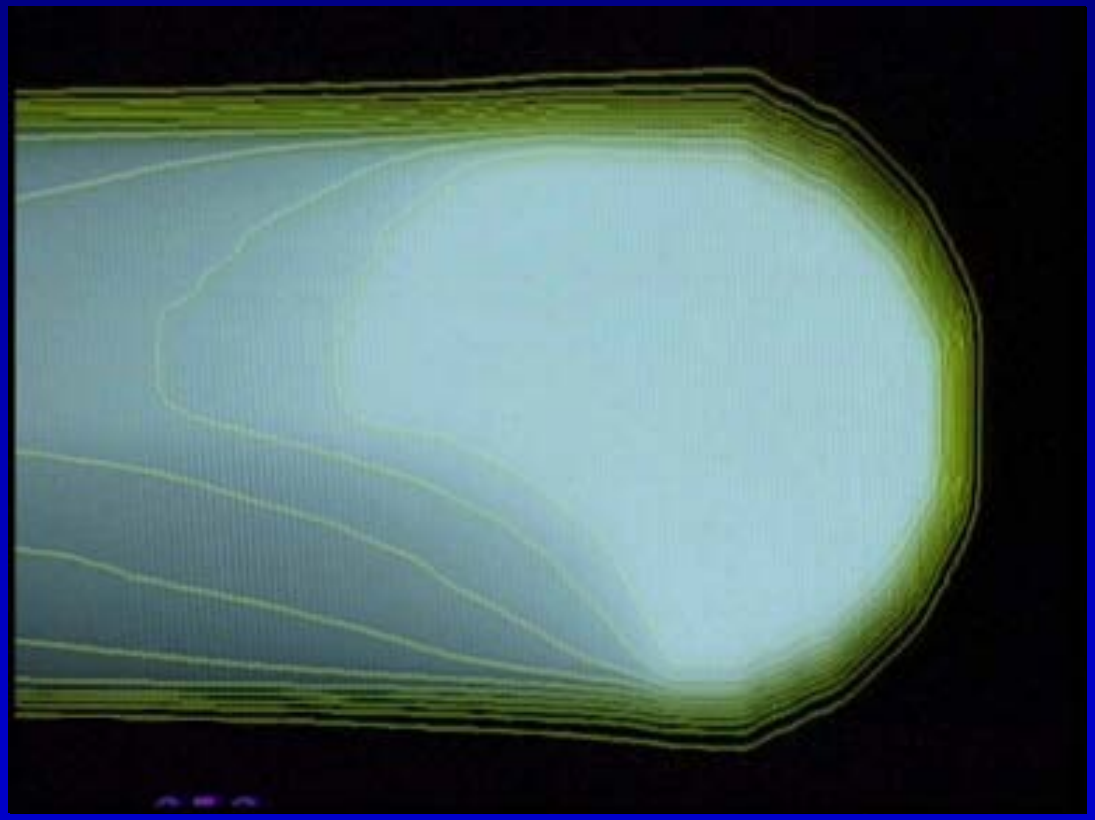
- Beam Scanning Hardware



Intensity Modulated Proton Therapy (IMPT)

Spot Scanning - Principle

The dynamic application of scanned
and modulated proton pencil beams

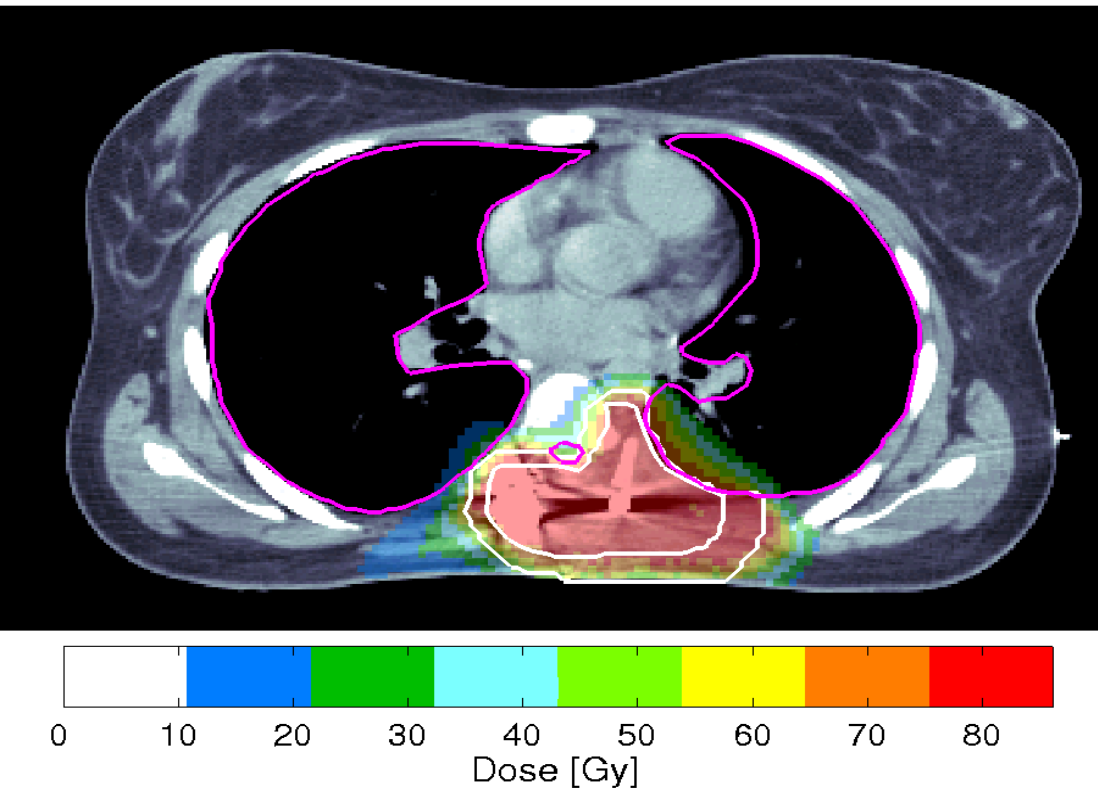


A full set, with a homogenous dose conformed distally ***and*** proximally

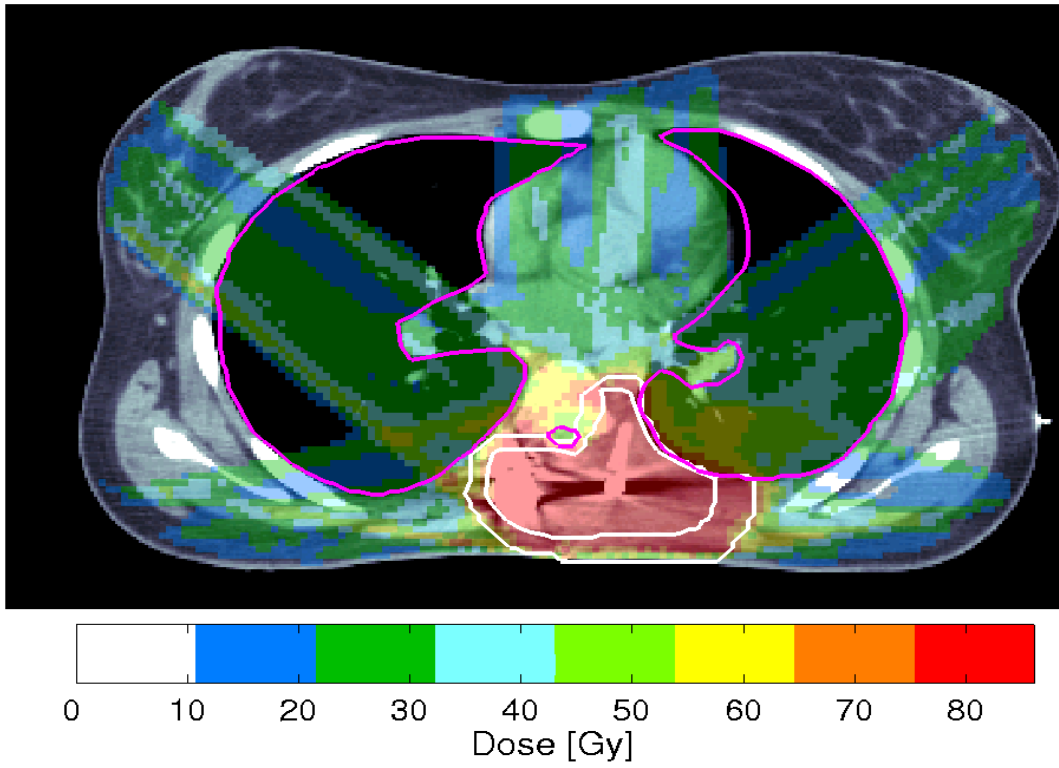
Images courtesy of Eros Pedroni

Paravertebral Epithelioid Sarcoma
Intensity Modulated Protons (IMPT) vs. Intensity Modulated Photons (IMRT) (7 field)

IMPT

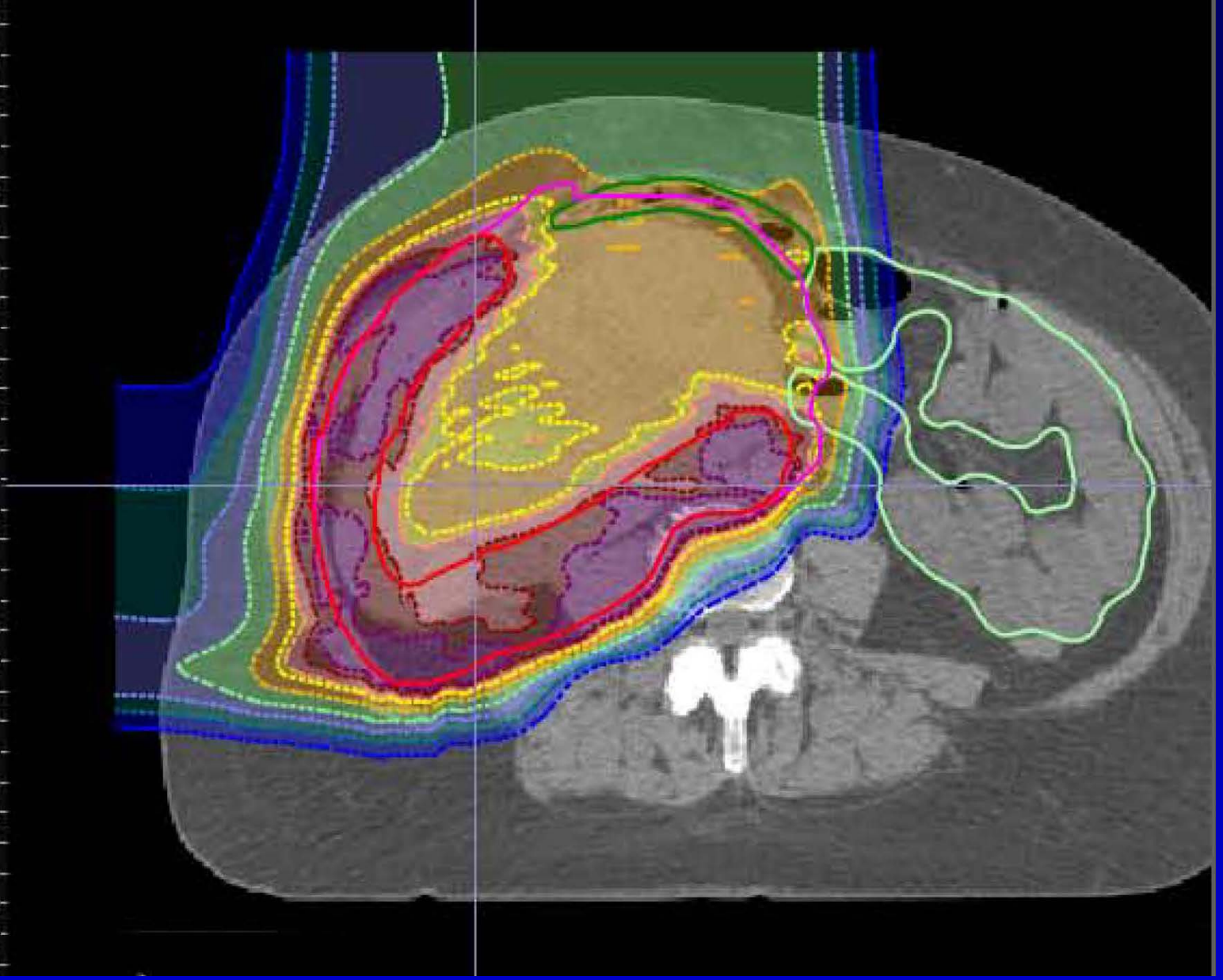


IMXT



Future Clinical Trials Proton Therapy

- MGH/MDACC PO1 (?2014-19) Pilot, Developmental
  - IMPT post-mastectomy Breast (cardiac sparing) [S. MacDonald]
  - IMPT Growth Plate Sparing Craniospinal [S. MacDonald]
  - IMPT/IMRT Phase I/II Preop Dose-Escalated, Dose Painted Retroperitoneal Sarcoma [T. DeLaney]
  - IMPT, Dose escalated, Meningioma/Atypical Meningioma (H. Shih)
  - IMPT, Phase I RBE/LET modulated, glioblastoma (D. Grosshans)

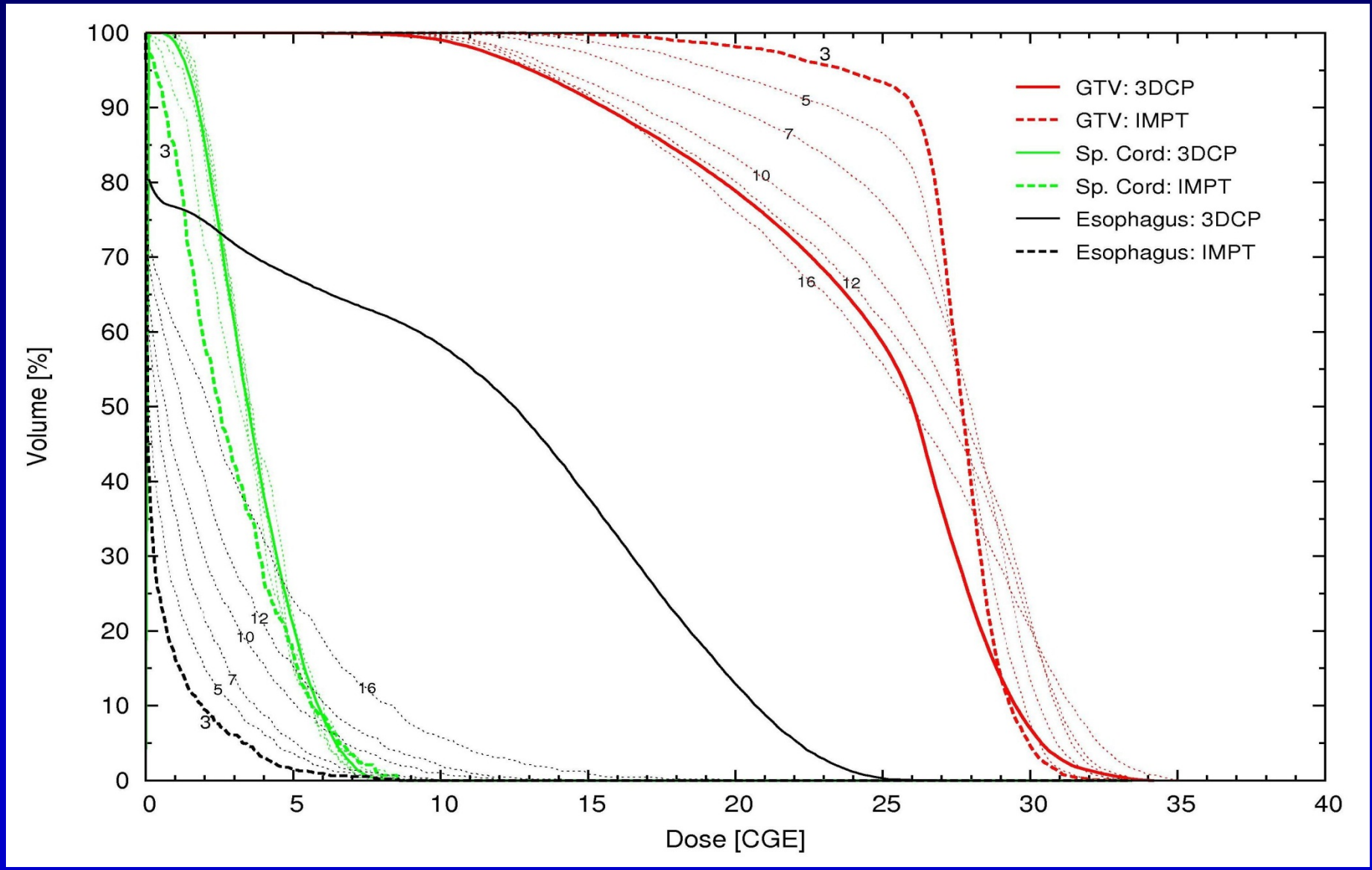


PREOP IMPT
PROTOCOL
PHASEI/II
CTV1 50.4 GyRBE
High Risk CTV2 SIB
60.2→61.6→63 GyRBE

58 yo female with Grade 2/3 retroperitoneal leiomyosarcoma- Pre-op IMPT

CTV 1: 50.4 Gy and CTV2 60.2 Gy/28 fx with IMPT

Spine Sarcoma: 3D passive proton plan (3DCP) vs. IMPT



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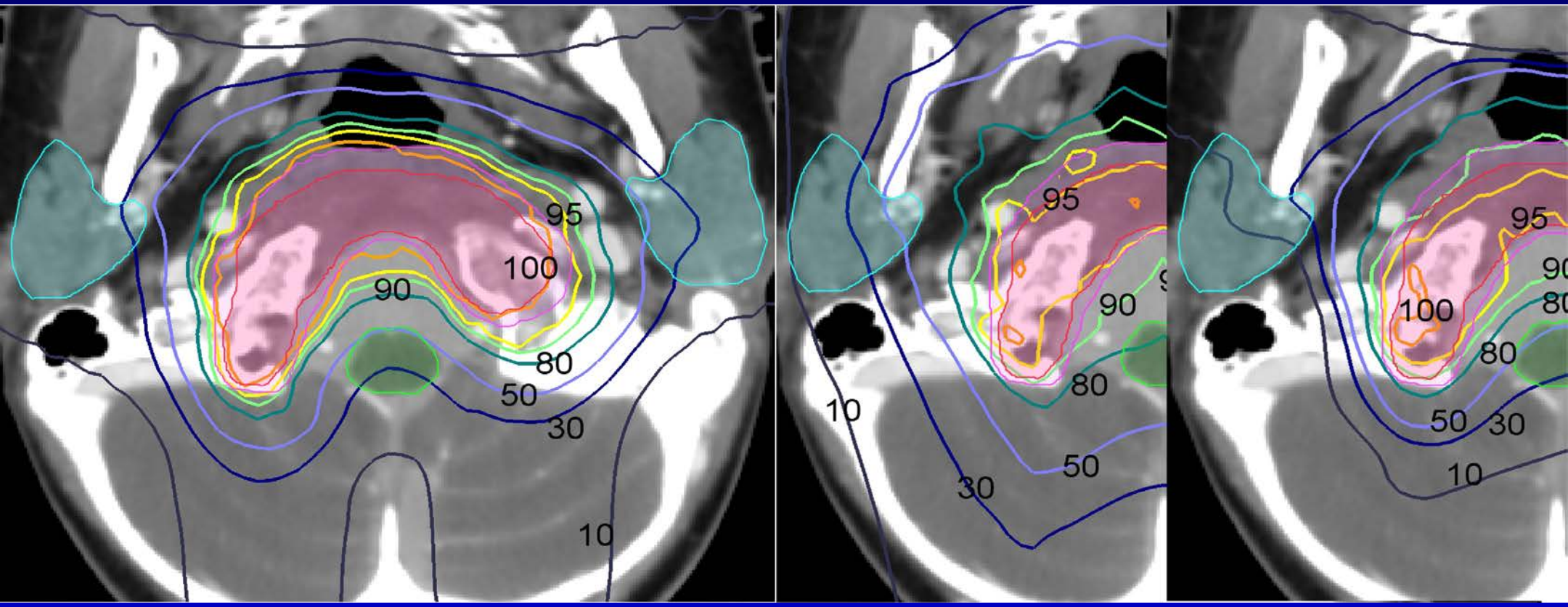
Courtesy of Sairos Safai, Ph.D.

Pencil Beam Scanning with Devices

- Apertures to improve penumbral edge
  - Expect, in fact, sharper, compared to SOBP
  - Quantify: Source effect
- Range-Compensators and Shifters
  - RC for reducing layers and distal edge control
  - Shifters for near-skin treatments
  - Quantify: Loss of primary protons and mean scatter angle

Clinical Effectiveness



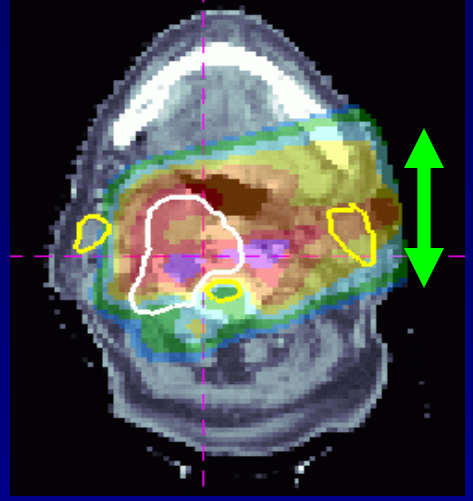
4 mm MGH 10-20 mm spot MGH + APERTURE

- The use of aperture produces dosimetry on par with the “best” PBS beam
- Thus, provides a path to move this complex patients to PBS with greatly improved planning efficiency afforded by Astroid planning engines.

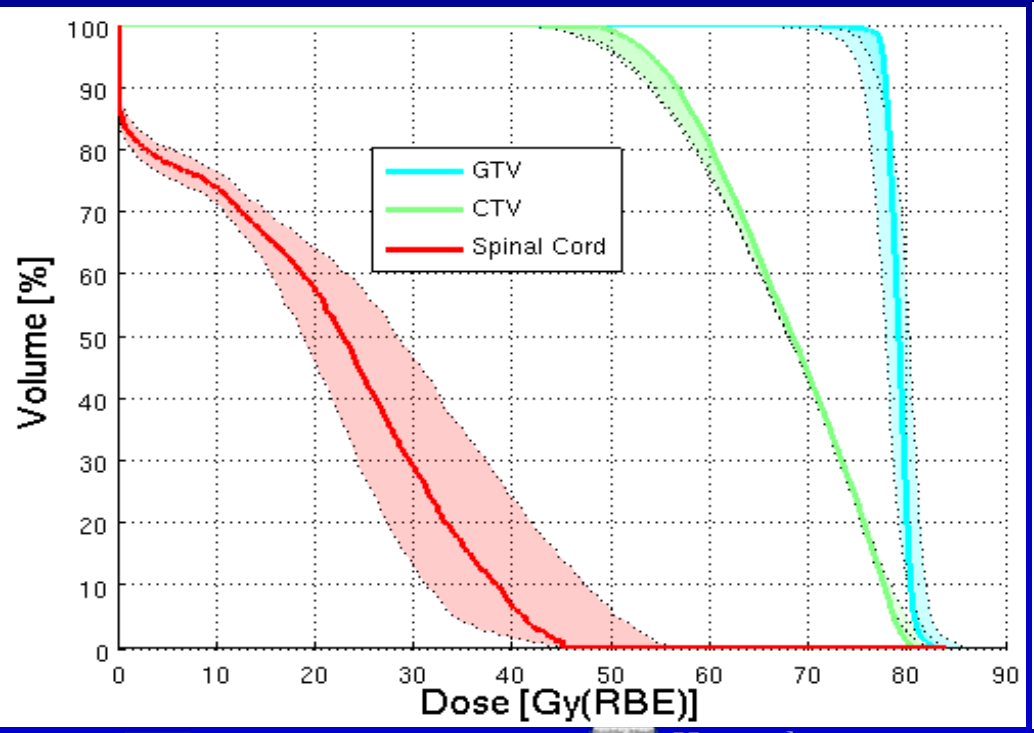
EVALUATION OF ROBUST IMPT OPTIMIZATION Trofimov et al

- Evaluate uncertainties in the dose distributions and realistic gain from intensity-modulated proton therapy delivered with beam scanning
  - Consider challenging clinical cases, where IMPT may potentially be advantageous
  - Use a robust optimization method to reduce the effect of anticipated delivery uncertainties on IMPT dose
  - Use beam parameters specific to the MGH scanning system

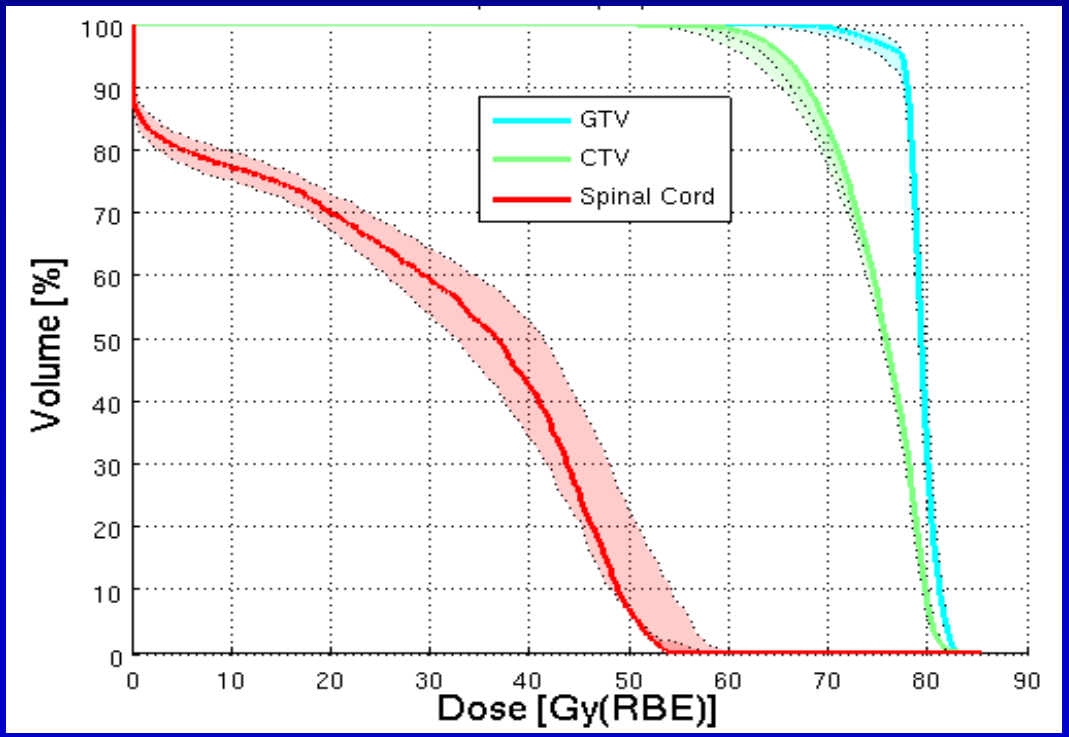
DVH variation due to set-up errors (± 3mm AP)



Standard IMPT



Probabilistic IMPT



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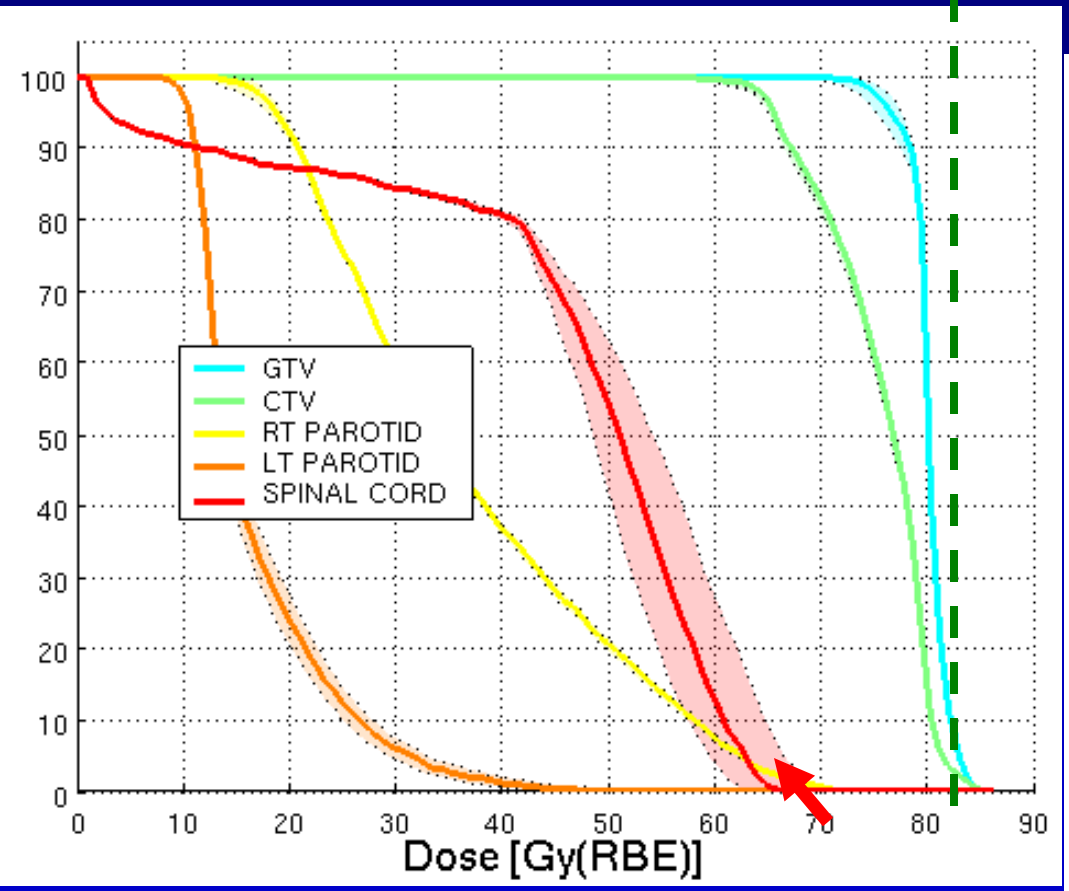
Trofimov et al

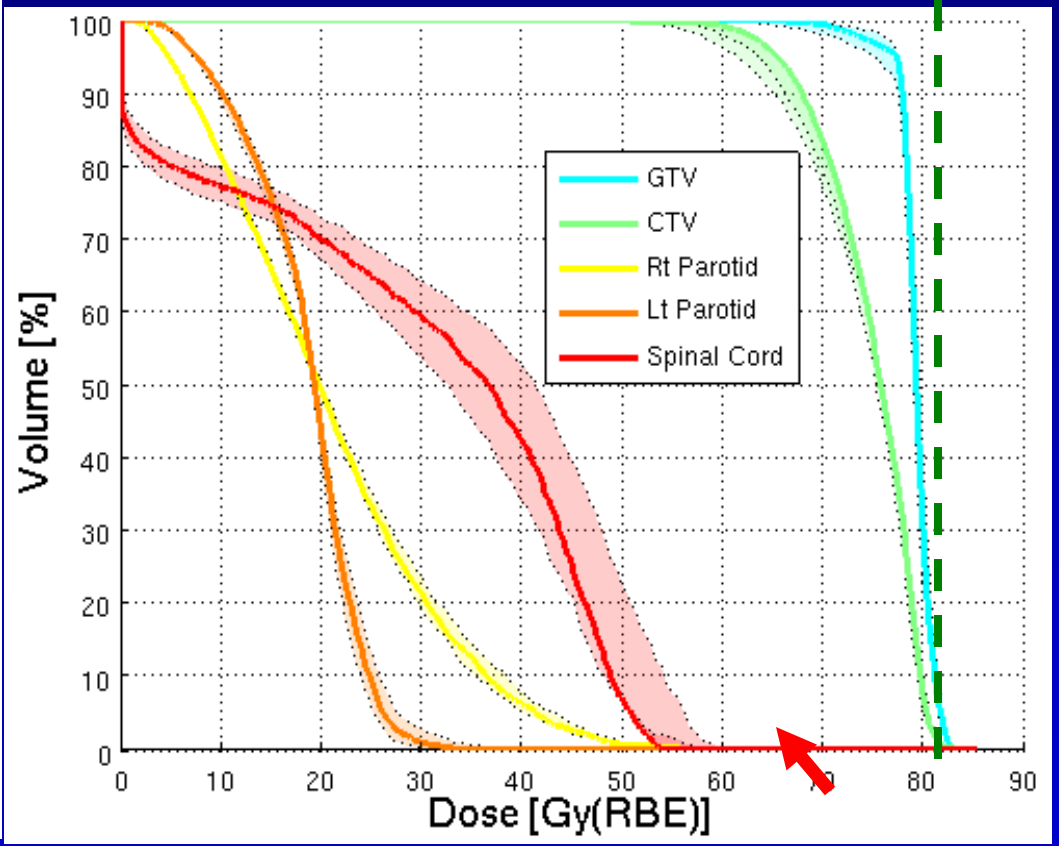
C2 chordoma: Rx = 77.4 Gy

DVH sensitivity to set-up errors (± 3mm AP)

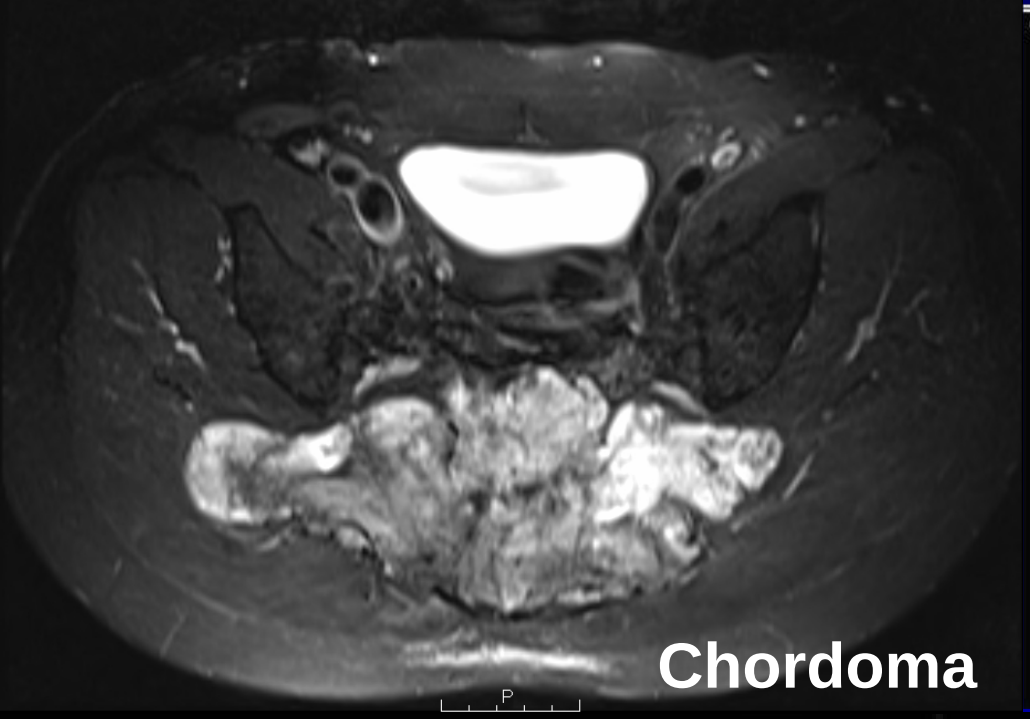
3D-conformal Passive

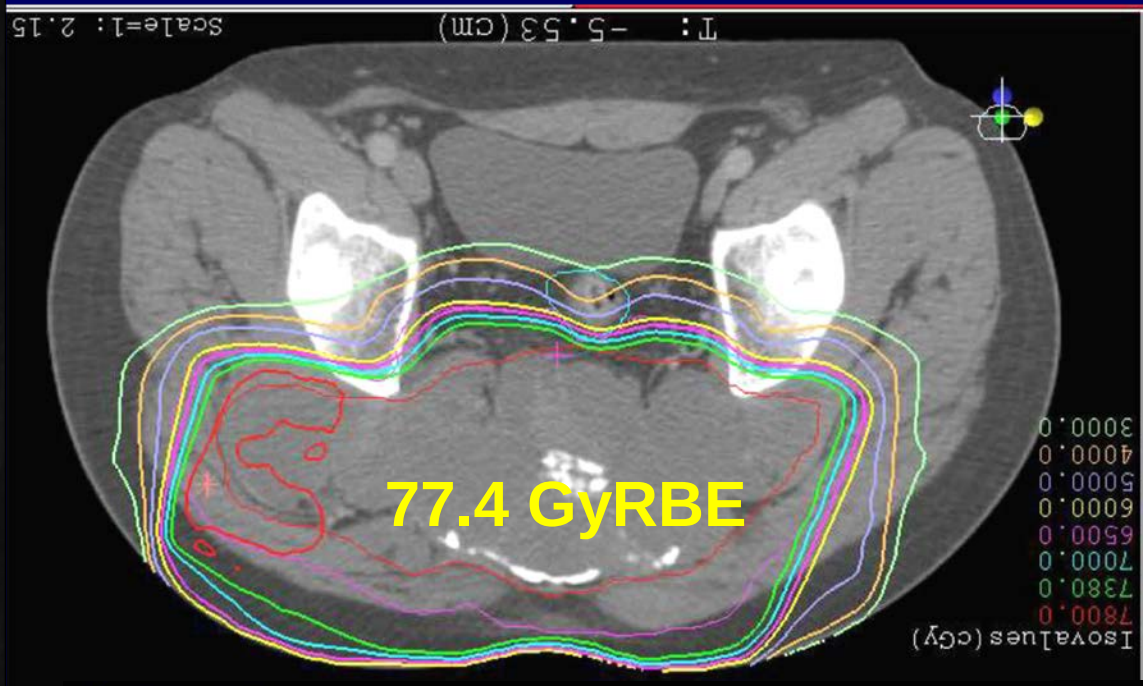


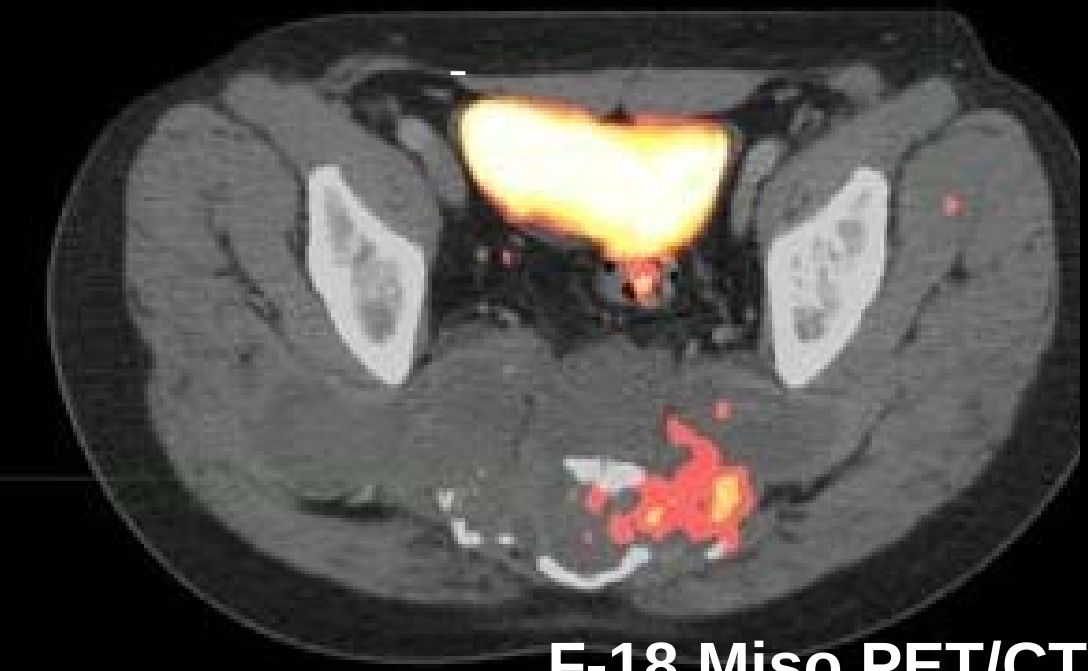
Probabilistic IMPT

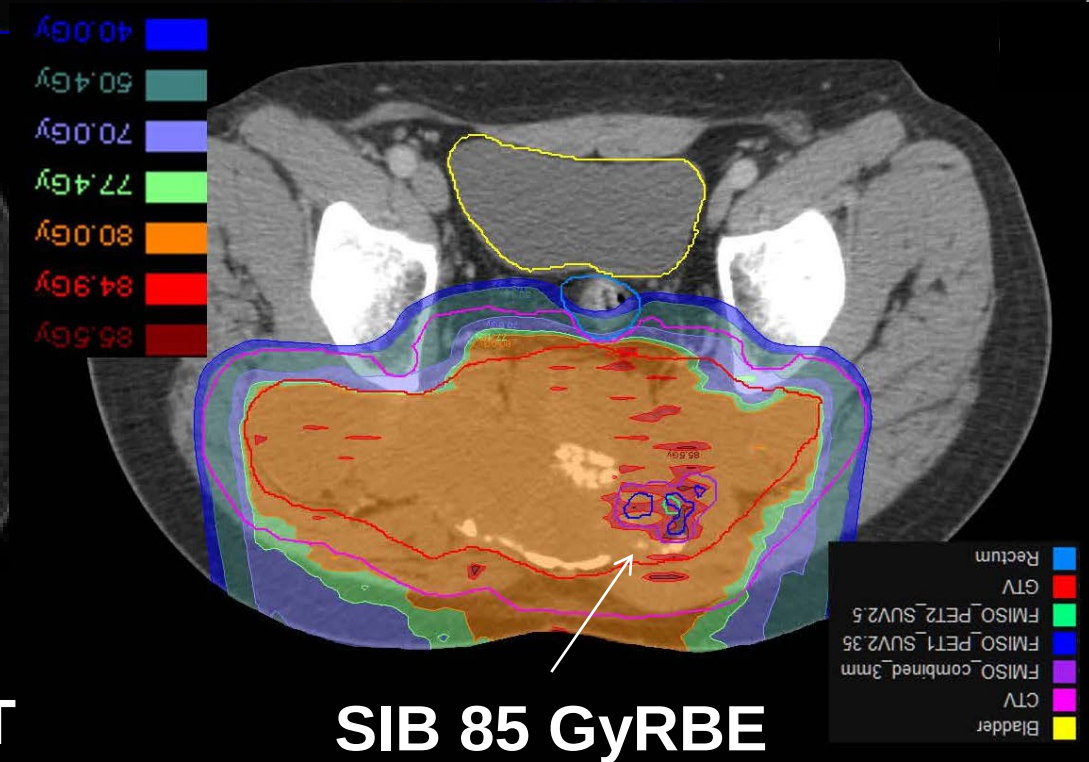


Trofimov et al


Chordoma


77.4 GyRBE


F-18 Miso PET/CT


40.0Gy
50.4Gy
70.0Gy
77.4Gy
80.0Gy
84.9Gy
85.5Gy
Bladder
CTV
FMISO_combined_3mm
FMISO_PET1_SUV2.35
FMISO_PET2_SUV2.5
GTV
Rectum
SIB 85 GyRBE