Demands and Perspectives of Hadron Therapy

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Disclosures

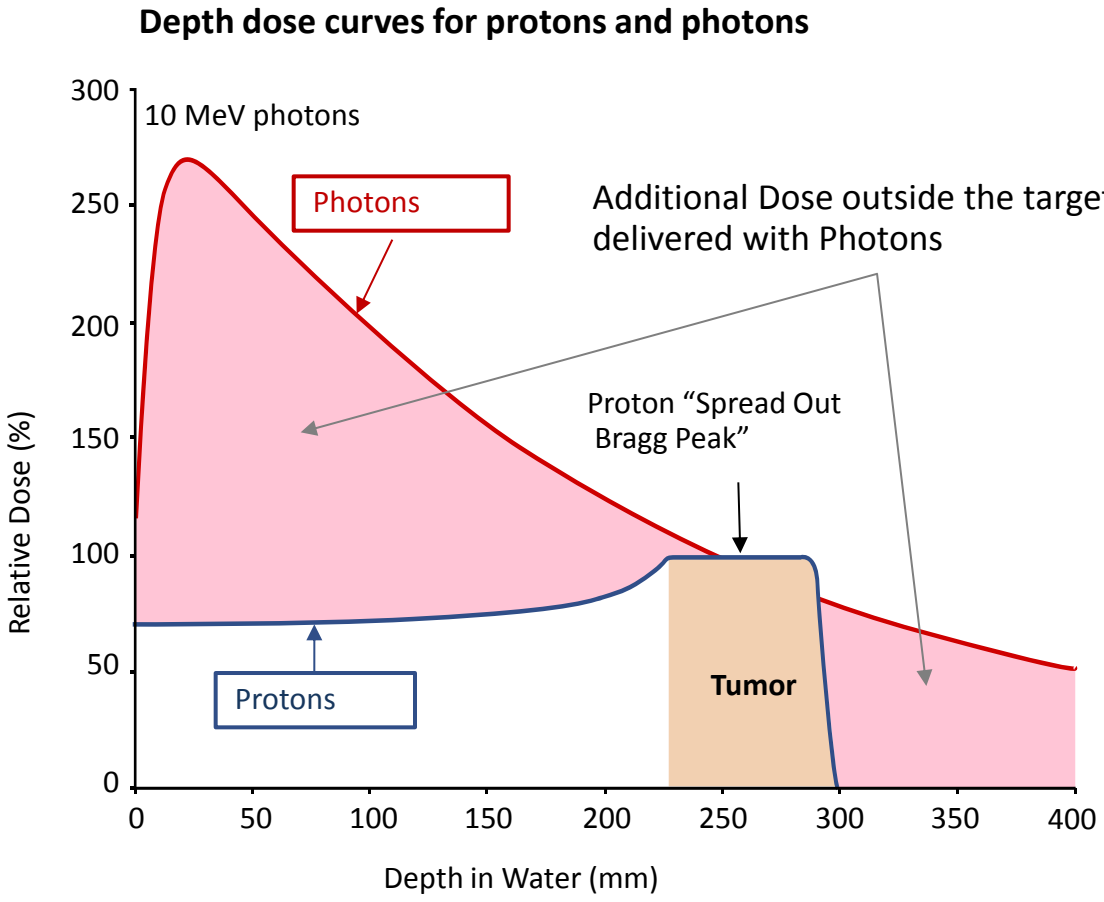
- Teva Pharmaceuticals: Advisory Panel
- Elekta: Consultant

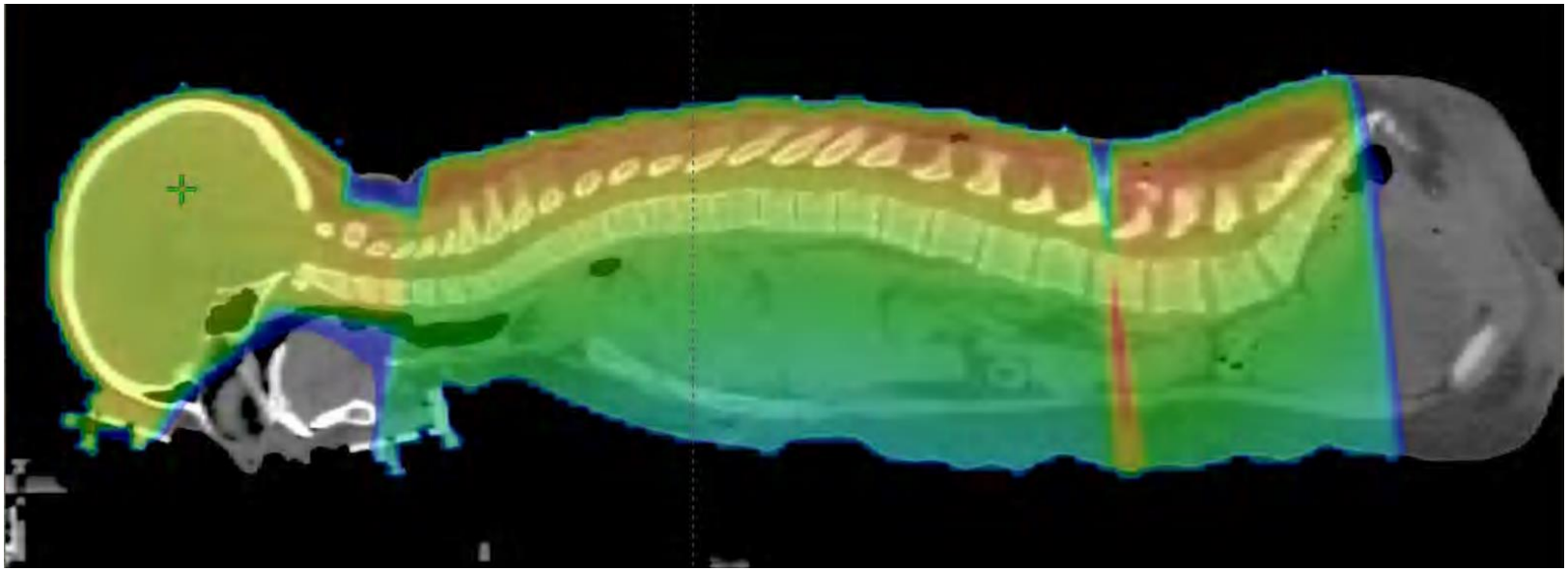
Outline

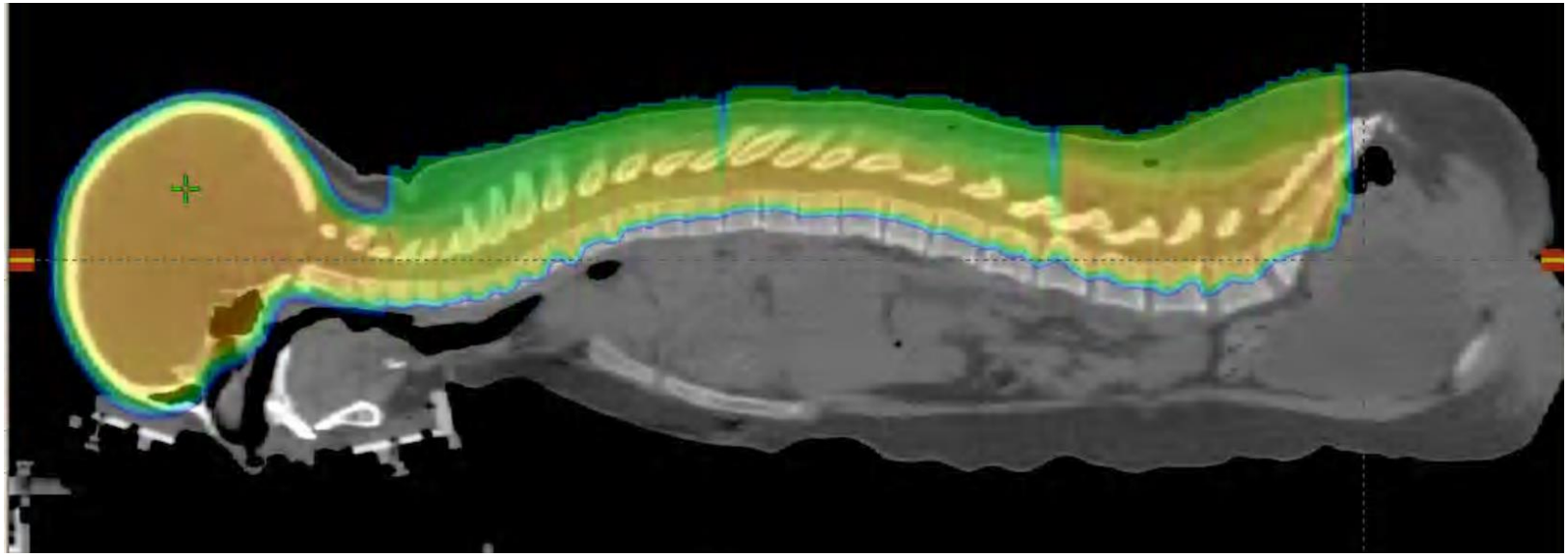
- Advantages of proton therapy
- Challenges to implementation
- Current evidence in support of proton therapy
- Implementation of prospective clinical trials
- The University of Pennsylvania Experience

The Physics of Protons

X-rays deliver a greater dose outside the target for the same dose within the target volume as protons







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Who are the patients being treated?

Estimated New Cases*

Males			Females		
Prostate	238,590	28%	Breast	232,340	29%
Lung & bronchus	118,080	14%	Lung & bronchus	110,110	14%
Colorectum	73,680	9%	Colorectum	69,140	9%
Urinary bladder	54,610	6%	Uterine corpus	49,560	6%
Melanoma of the skin	45,060	5%	Thyroid	45,310	6%
Kidney & renal pelvis	40,430	5%	Non-Hodgkin lymphoma	32,140	4%
Non-Hodgkin lymphoma	37,600	4%	Melanoma of the skin	31,630	4%
Oral cavity & pharynx	29,620	3%	Kidney & renal pelvis	24,720	3%
Leukemia	27,880	3%	Pancreas	22,480	3%
Pancreas	22,740	3%	Ovary	22,240	3%
All Sites	**854,790**	**100%**	**All Sites**	**805,500**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	87,260	28%	Lung & bronchus	72,220	26%
Prostate	29,720	10%	Breast	39,620	14%
Colorectum	26,300	9%	Colorectum	24,530	9%
Pancreas	19,480	6%	Pancreas	18,980	7%
Liver & intrahepatic bile duct	14,890	5%	Ovary	14,030	5%
Leukemia	13,660	4%	Leukemia	10,060	4%
Esophagus	12,220	4%	Non-Hodgkin lymphoma	8,430	3%
Urinary bladder	10,820	4%	Uterine corpus	8,190	3%
Non-Hodgkin lymphoma	10,590	3%	Liver & intrahepatic bile duct	6,780	2%
Kidney & renal pelvis	8,780	3%	Brain & other nervous system	6,150	2%
All Sites	**306,920**	**100%**	**All Sites**	**273,430**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2013.
*Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Siegel et al., CA CANCER J CLIN 2013

IMRT is well tolerated

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 4, pp. 1124–1129, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.11.044

ASTRO Online CME

CLINICAL INVESTIGATION Prostate

INCIDENCE OF LATE RECTAL AND URINARY TOXICITIES AFTER THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY AND INTENSITY-MODULATED RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

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- 1571 pts, 10 yr median f/u
- Incidence of grade 3 GI and GU toxicity: 1% and 3%

Is treatment required?

The NEW ENGLAND JOURNAL of MEDICINE

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Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D., William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D., Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D., Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D., Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., and Thomas Wheeler, M.D., for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group

731 men with localized prostate cancer, randomized to radical prostatectomy or observation

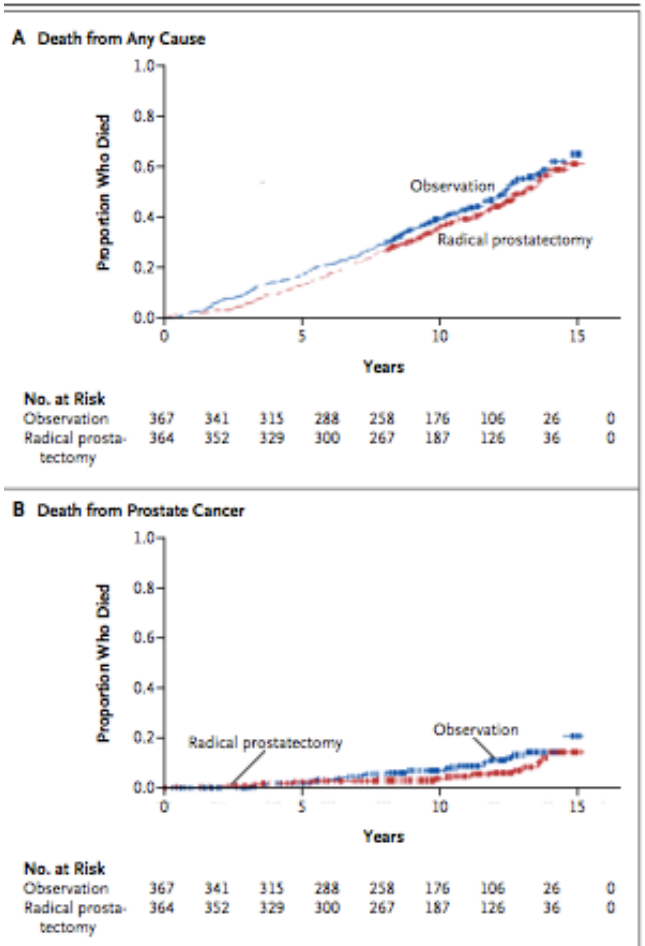

Figure 2. Kaplan–Meier Plots of Mortality.

By the end of the study, 354 men (48.4%) had died from any cause (Panel A). Death attributed to prostate cancer or treatment occurred in 52 men (7.1%) (Panel B). Data from the radical-prostatectomy group are shown in red, and data from the observation group in blue.

- Prostate cancer is a common diagnosis
- Treatment with IMRT is well tolerated
- Disease outcomes are excellent, with or without treatment

- Is this the disease site on which we seek to build the foundation for proton therapy?

What is the evidence comparing PBT to IMRT for localized prostate cancer?

Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

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Anne-Marie Meyer, PhD
Yang Wu, PhD
YunKyung Chang, PhD
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Jordan A. Holmes, BS
Bryce B. Reeve, PhD
Paul A. Godley, MD, PhD
William R. Carpenter, PhD
Ronald C. Chen, MD, MPH

Context There has been rapid adoption of newer radiation treatments such as intensity-modulated radiation therapy (IMRT) and proton therapy despite greater cost and limited demonstrated benefit compared with previous technologies.

Objective To determine the comparative morbidity and disease control of IMRT, proton therapy, and conformal radiation therapy for primary prostate cancer treatment.

Design, Setting, and Patients Population-based study using Surveillance, Epidemiology, and End Results–Medicare-linked data from 2000 through 2009 for patients with nonmetastatic prostate cancer.

Main Outcome Measures Rates of gastrointestinal and urinary morbidity, erectile dysfunction, hip fractures, and additional cancer therapy.

Results Use of IMRT vs conformal radiation therapy increased from 0.15% in 2000 to 95.9% in 2008. In propensity score–adjusted analyses (N=12 976), men who received IMRT vs conformal radiation therapy were less likely to receive a diagnosis of gastrointestinal morbidities (absolute risk, 13.4 vs 14.7 per 100 person-years; relative risk [RR], 0.91; 95% CI, 0.86-0.96) and hip fractures (absolute risk, 0.8 vs 1.0 per 100 person-years; RR, 0.78; 95% CI, 0.65-0.93) but more likely to receive a diagnosis of erectile dysfunction (absolute risk, 5.9 vs 5.3 per 100 person-years; RR, 1.12; 95% CI, 1.03-1.20). Intensity-modulated radiation therapy patients were less likely to receive additional cancer therapy (absolute risk, 2.5 vs 3.1 per 100 person-years; RR, 0.81; 95% CI, 0.73-0.89). In a propensity score–matched comparison between IMRT and proton therapy (n=1368), IMRT patients had a lower rate of gastrointestinal morbidity (absolute risk, 12.2 vs 17.8 per 100 person-years; RR, 0.66; 95% CI, 0.55-0.79). There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.

Conclusions Among patients with nonmetastatic prostate cancer, the use of IMRT compared with conformal radiation therapy was associated with less gastrointestinal morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy was associated with less gastrointestinal morbidity.

JAMA. 2012;307(15):1611-1620 www.jama.com

- Population-based study using SEER-Medicare data
- IMRT had lower risk of GI toxicity compared to PBT

Proton Versus Intensity-Modulated Radiotherapy for Prostate Cancer: Patterns of Care and Early Toxicity

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Manuscript received May 15, 2012; revised September 24, 2012; accepted September 25, 2012.

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Background Proton radiotherapy (PRT) is an emerging treatment for prostate cancer despite limited knowledge of clinical benefit or potential harms compared with other types of radiotherapy. We therefore compared patterns of PRT use, cost, and early toxicity among Medicare beneficiaries with prostate cancer with those of intensity-modulated radiotherapy (IMRT).

Methods We performed a retrospective study of all Medicare beneficiaries aged greater than or equal to 66 years who received PRT or IMRT for prostate cancer during 2008 and/or 2009. We used multivariable logistic regression to identify factors associated with receipt of PRT. To assess toxicity, each PRT patient was matched with two IMRT patients with similar clinical and sociodemographic characteristics. The main outcome measures were receipt of PRT or IMRT, Medicare reimbursement for each treatment, and early genitourinary, gastrointestinal, and other toxicity. All statistical tests were two-sided.

Results We identified 27,647 men; 553 (2%) received PRT and 27,094 (98%) received IMRT. Patients receiving PRT were younger, healthier, and from more affluent areas than patients receiving IMRT. Median Medicare reimbursement was $32,428 for PRT and $18,575 for IMRT. Although PRT was associated with a statistically significant reduction in genitourinary toxicity at 6 months compared with IMRT (5.9% vs 9.5%; odds ratio [OR] = 0.60, 95% confidence interval [CI] = 0.38 to 0.96, $P = .03$), at 12 months post-treatment there was no difference in genitourinary toxicity (18.8% vs 17.5%; OR = 1.08, 95% CI = 0.76 to 1.54, $P = .66$). There was no statistically significant difference in gastrointestinal or other toxicity at 6 months or 12 months post-treatment.

Conclusions Although PRT is substantially more costly than IMRT, there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment.

J Natl Cancer Inst

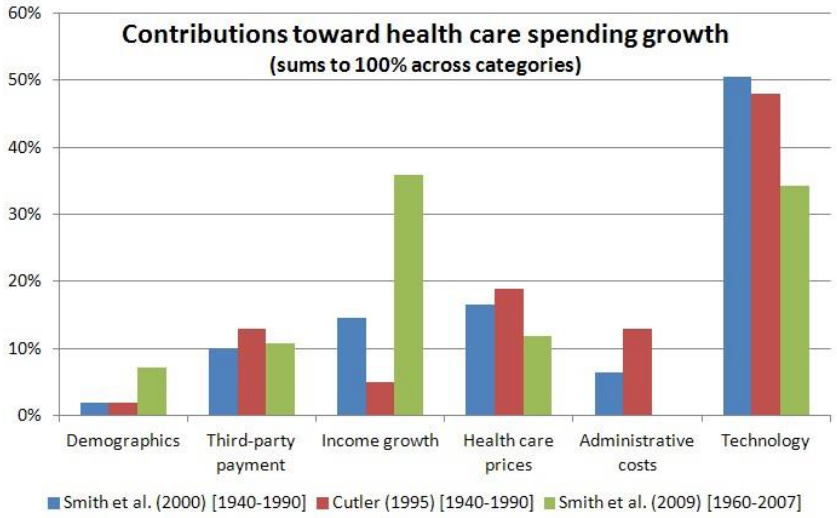
- Retrospective observational comparison of men > 65 receiving PBT (553) vs IMRT (27,094) using 2008-2009 Medicare claims data
- Reduced 6 mo GU complications (5.9 vs 9.5%) in favor of PBT, but no difference at 12 mo
- Median reimbursement
  - $32,428 (PBT) vs $18,575 (IMRT)

- Potential weaknesses from retrospective studies
  - Toxicity evaluated by billing codes
  - No dosimetric information or quality assurance of radiation delivery
- Not the most rigorous comparison of IMRT vs PBT

“Prostate-Cancer Therapy Comes Under Attack” Wall Street Journal Aug 28, 2013

- 3 major insurers have decided to stop covering PBT for early stage prostate cancer
  - Blue Shield of CA
  - Aetna
  - Cigna (review)
- Stopping coverage procedure without evidence of harm
  - Not in step with Medicare policy, which covers prostate PBT
  - Resisting proton beam coverage largely because of its price
  - Insurers face pressure from clinicians, health care organizations, and pts when they try to limit coverage

- Bias in U.S. in favor of covering new technology
  - Technology is one of the leading drivers of health care spending growth



Frakt, JAMA Forum, 2013

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Contents lists available at SciVerse ScienceDirect

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Systematic review

An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee

Aaron M. Allen [a,*], Todd Pawlicki [b], Lei Dong [c], Eugene Fourkal [d], Mark Buyyounouski [d], Keith Cengel [e], John Plastaras [e], Mary K. Bucci [c], Torunn I. Yock [f], Luisa Bonilla [a], Robert Price [d], Eleanor E. Harris [g], Andre A. Konski [h]

[a] *Davidoff Center, Tel Aviv University, Israel;* [b] *University of California, San Diego, La Jolla, USA;* [c] *M.D. Anderson Cancer Center, University of Texas, Houston, USA;* [d] *Fox Chase Cancer Center, Philadelphia, USA;* [e] *University of Pennsylvania, Philadelphia, USA;* [f] *Massachusetts General Hospital, Boston, USA;* [g] *H. Lee Moffit Cancer Center, Tampa, USA;* [h] *Wayne State University Medical Center, Detroit, USA*

- Not recommended
  - Lung
  - Head and Neck
  - Gastrointestinal
  - Pediatric non-CNS
- Not superior
  - Hepatocellular carcinoma
  - Prostate
- Superior, but more data needed
  - Pediatric CNS
- Protons > Photons
  - Large, ocular melanoma
  - Chordoma (control with protons ~80%)

- Awarding PBT higher reimbursements based on dosimetric advantages over photons is not enough
- Prospective, comparative clinical trials are needed

Proposed coverage options for PBT

- Ezekiel Emanuel
  - Professor and Chair of Medical Ethics and Health Policy, Perelman School of Medicine, University of Pennsylvania
  - Vice Provost, University of Pennsylvania

- New York Times Editorial:
  - Coverage with Evidence Generation
  - Dynamic Pricing:
    - Medicare would pay more for PBT, but only for diseases that are proven to be treated more effectively with PBT
    - If studies performed showing that PBT was superior, payment would go up
    - If no studies done, or evidence demonstrated no advantages, coverage would continue, but at lower reimbursement

- “Is a randomized trial of proton therapy vs IMRT worth the costs? A rough calculation of the incremental health-care expenditures associated with replacing IMRT with proton therapy for even just one-third of the nearly 28,000 Medicare beneficiaries who received treatment in 2008 and 2009 would be at least $100 million of excess spending. The costs of a randomized trial that would compare the two radiation modalities range from $5 to $15 million. For such a scientifically important question in radiotherapy CER, a randomized trial of proton therapy vs IMRT would appear to be a good investment for patients and clinicians.”
  - Bekelman and Hahn, JNCI 2012

Ideal target sites for proton therapy and clinical trials

- Suboptimal locoregional control with current treatment options (PBT to improve disease outcomes and survival)
  - Dose escalation
    - Lung
    - Pancreas
    - Esophagus
- Current treatment options yield high cure rates, but with significant toxicity (PBT to improve side effects and patient QOL)
  - Head and Neck

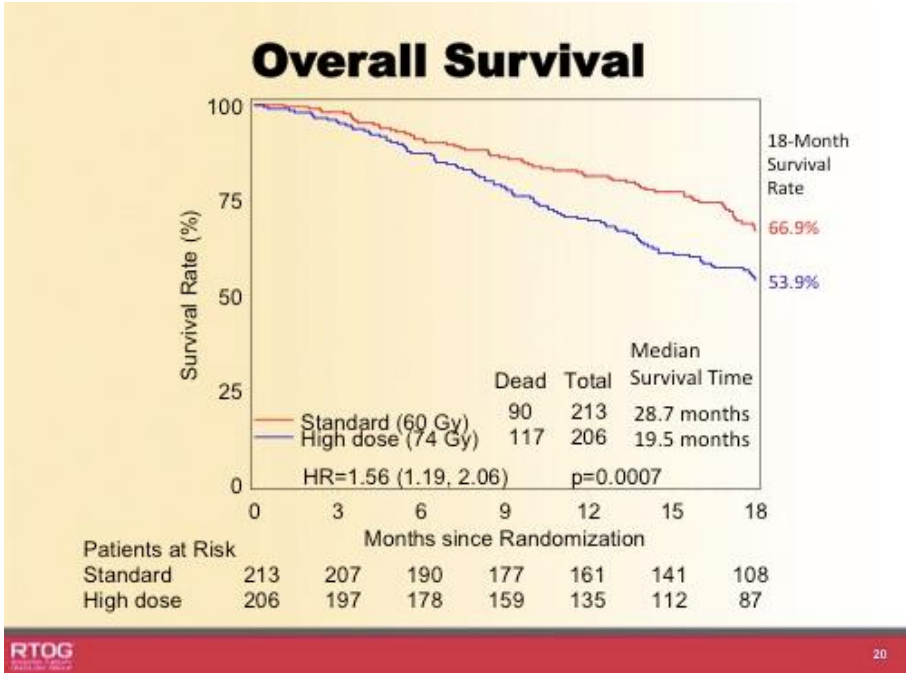
Lung

- Early stage
  - Excellent results with photon SBRT
  - LC 90%, minimal toxicity
  - Little room for improvement
- Advanced stage
  - Possible gains (pneumonitis, esophagitis, heart dose)
  - Challenge of organ motion
  - Lessons learned from RTOG 0617

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL +/- CETUXIMAB (IND #103444) IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

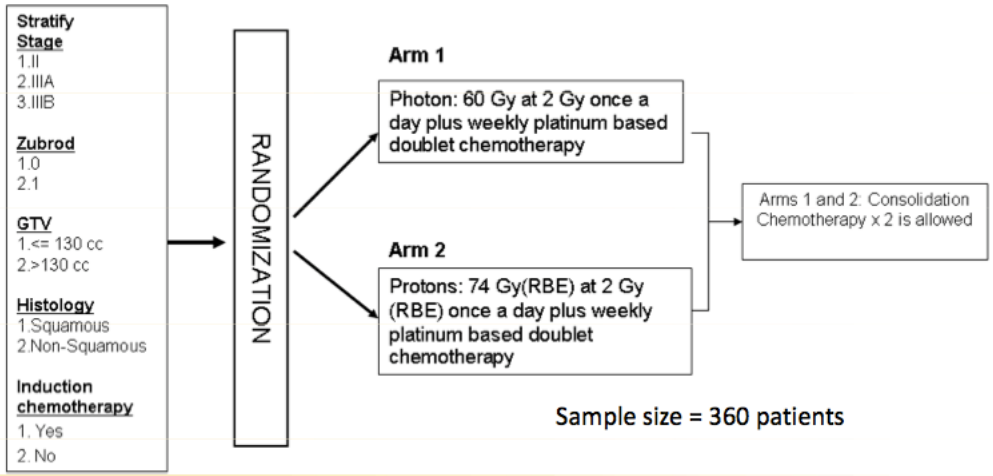


RTOG 0617: findings

- Pts receiving higher dose had a significant decline in QOL compared to standard dose
  - Captured only on patient-reported surveys, while MD-reported surveys showed no difference
- Correlation between worse QOL and diminished survival
- Those receiving IMRT had less decline in QOL compared to 3-D CRT
  - Importance of technology?
    - Can dose deposition to organs at risk impact QOL and survival?

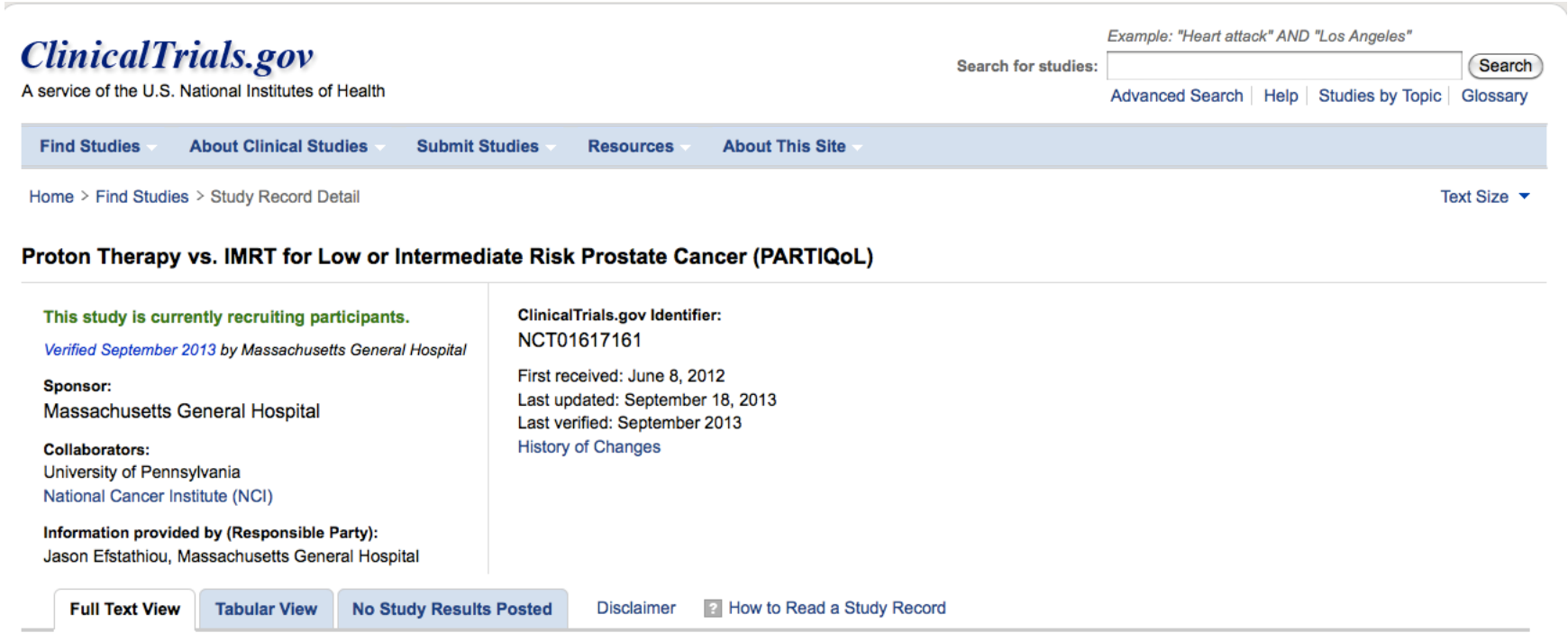
Protons vs IMRT Concept

Phase III Randomized Trial Comparing Overall Survival after Photon vs Proton Radiochemotherapy for Stage II-IIIB NSCLC



Prostate

- “Outcome is similar to IMRT, with no clear advantage from clinical data for either technique in disease control or prevention of late toxicity”



Primary outcome: bowel toxicity at 2 yrs

Secondary outcomes:

- Disease-specific QOL
- Cost effectiveness
- Correlation btwn RT dose and bowel, urinary and erectile function
- Identification and evaluation of biomarkers for response and cancer behavior
- Long-term survival

Head and Neck

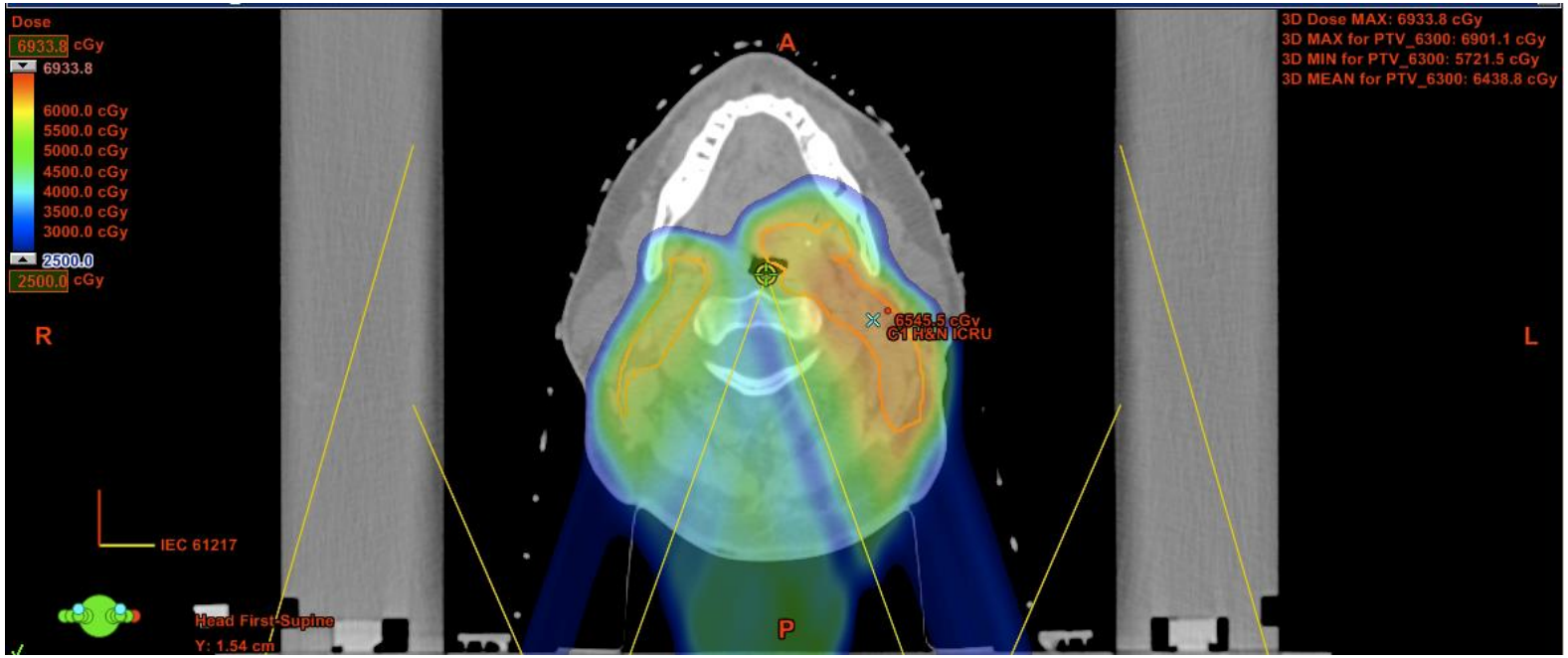
- Outcomes excellent
  - ~90% cure rate for locally-advanced, HPV+ oropharynx cancer (young pts)

- Toxicity significant
  - Operative site breakdown
  - Xerostomia
  - Dysgeusia
  - Dysphagia
  - Significant impact on head and neck specific and global QOL

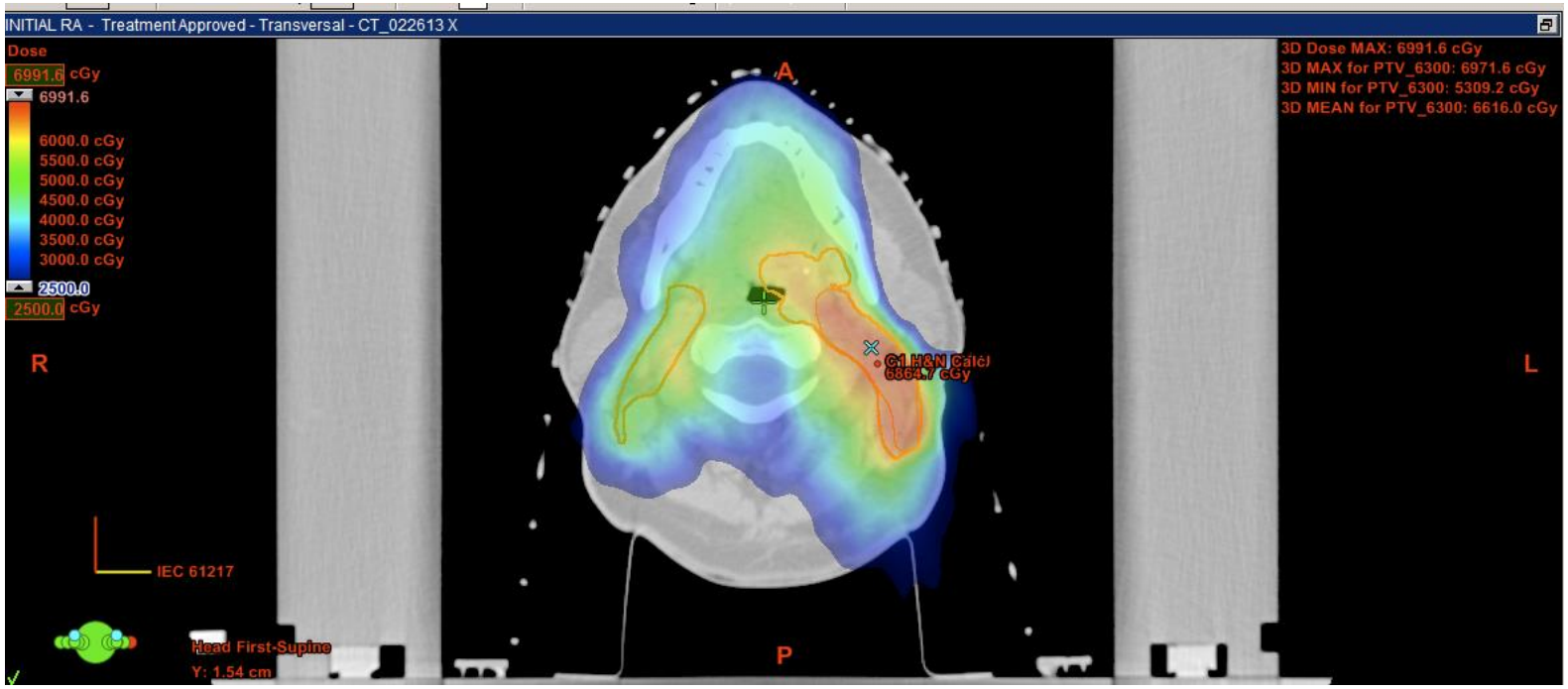
Head and Neck

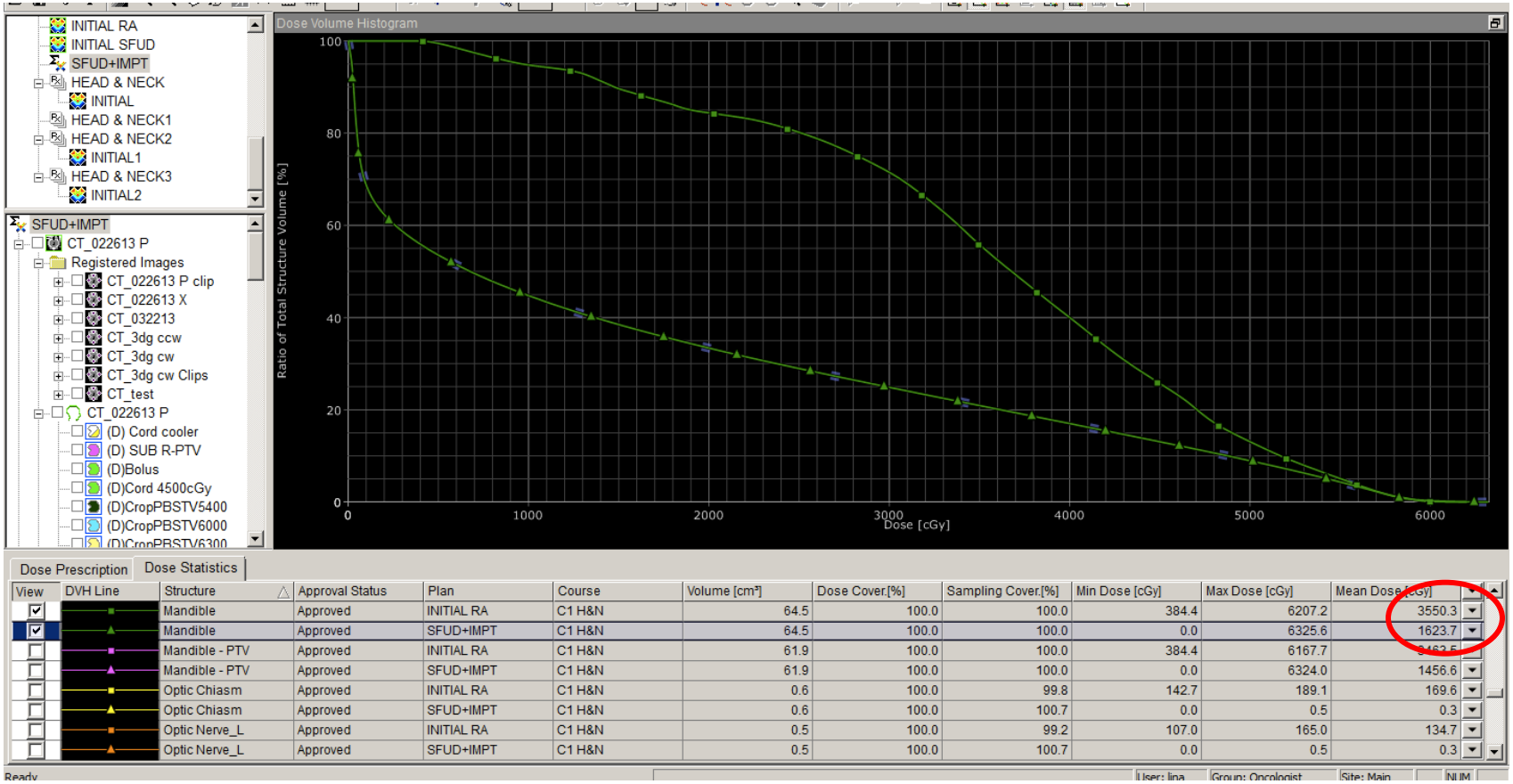
- UPenn Phase II study
  - TORS ➔ SND ➔ RT (+/- chemo)
    - Allows for IMRT or PBT (with PBS)
  - Stage III/IV OPC
    - HPV+
    - T1/T2
    - Negative margin
    - No PNI
- RT nodal regions only
- Omission of primary tumor bed
- Rationale
  - Improve toxicity profile, while maintaining high LC
    - Operative site breakdown
    - Mucositis
    - Dysphagia/Odynophagia
  - Prospective patient-reported QOL data collection

Proton therapy



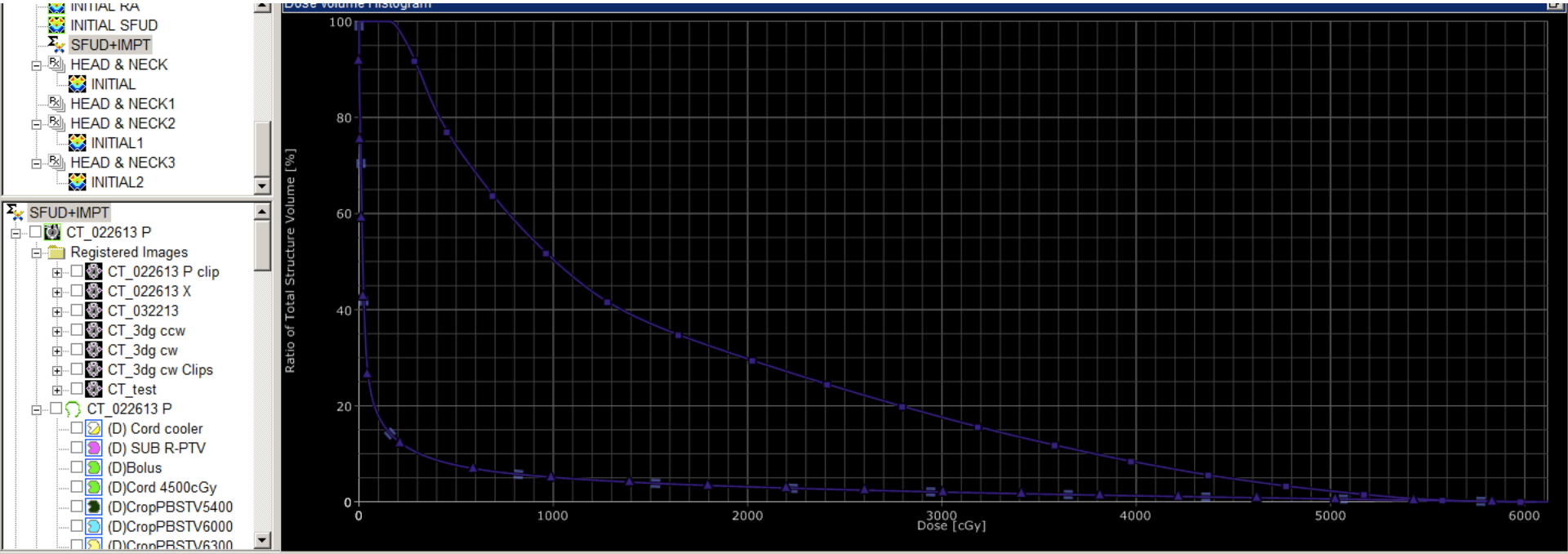
Rapid Arc IMRT





Dose Prescription | Dose Statistics

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		Mandible	Approved	INITIAL RA	C1 H&N	64.5	100.0	100.0	384.4	6207.2	3550.3
☑		Mandible	Approved	SFUD+IMPT	C1 H&N	64.5	100.0	100.0	0.0	6325.6	1623.7
☐		Mandible - PTV	Approved	INITIAL RA	C1 H&N	61.9	100.0	100.0	384.4	6167.7	[illegible]
☐		Mandible - PTV	Approved	SFUD+IMPT	C1 H&N	61.9	100.0	100.0	0.0	6324.0	1456.6
☐		Optic Chiasm	Approved	INITIAL RA	C1 H&N	0.6	100.0	99.8	142.7	189.1	169.6
☐		Optic Chiasm	Approved	SFUD+IMPT	C1 H&N	0.6	100.0	100.7	0.0	0.5	0.3
☐		Optic Nerve_L	Approved	INITIAL RA	C1 H&N	0.5	100.0	99.2	107.0	165.0	134.7
☐		Optic Nerve_L	Approved	SFUD+IMPT	C1 H&N	0.5	100.0	100.7	0.0	0.5	0.3



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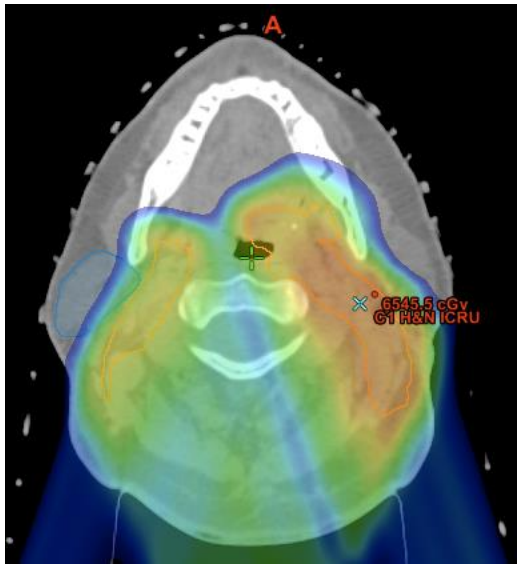
☑		Oral cavity	Approved	INITIAL RA	C1 H&N	374.7	100.0	100.0	157.0	6062.8	1564.4
☑		Oral cavity	Approved	SFUD+IMPT	C1 H&N	374.7	100.0	99.9	0.0	6117.4	202.8
☐		Oral cavity-PTV	Approved	INITIAL RA	C1 H&N	374.4	100.0	100.0	157.0	6062.8	1561.3
☐		Oral cavity-PTV	Approved	SFUD+IMPT	C1 H&N	374.4	100.0	99.9	0.0	6073.8	198.6
☐		PATIENT	Approved	INITIAL RA	C1 H&N	15299.1	100.0	100.1	0.6	6991.6	1131.8
☐		PATIENT	Approved	SFUD+IMPT	C1 H&N						
☐		PTV-composite	Approved	INITIAL RA	C1 H&N						
☐		PTV-composite	Approved	SFUD+IMPT	C1 H&N						

Ready | User: lina | Group: Oncologist | Site: Main | NUM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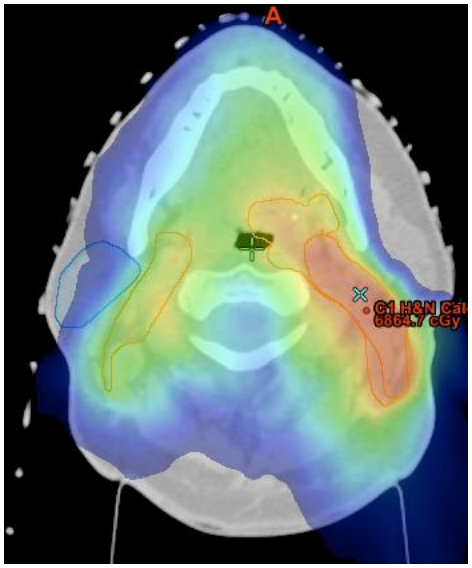
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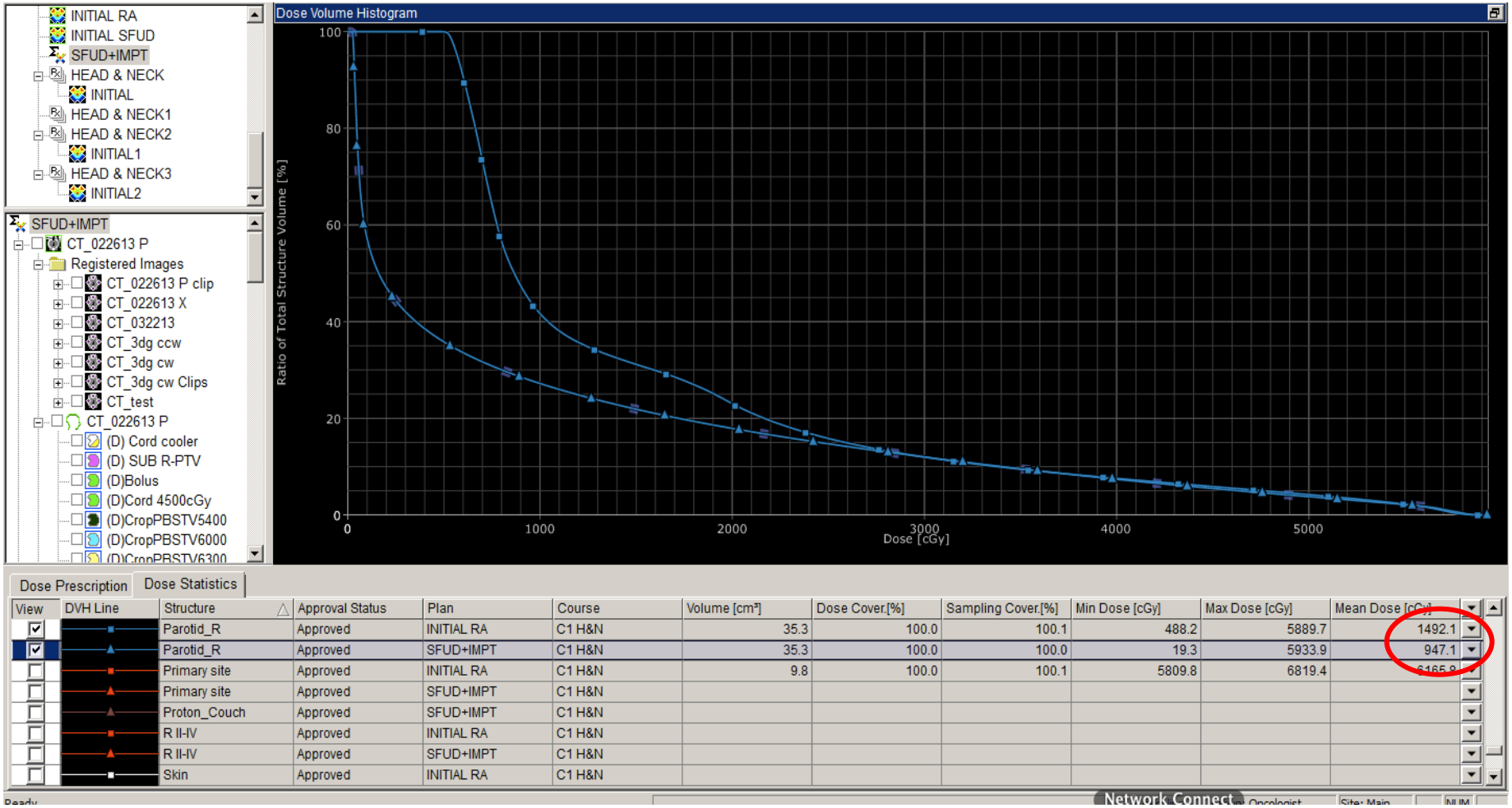

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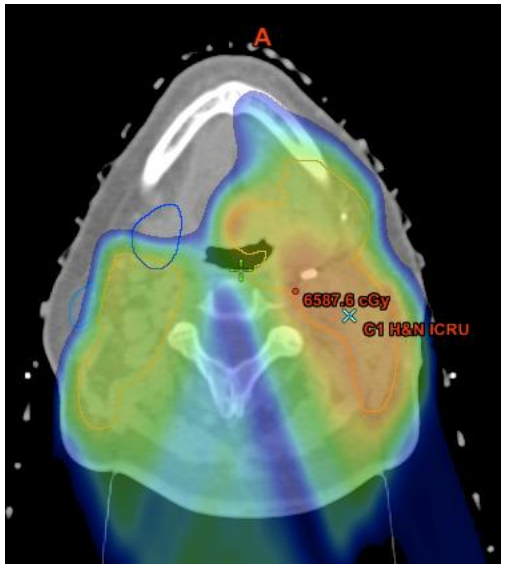
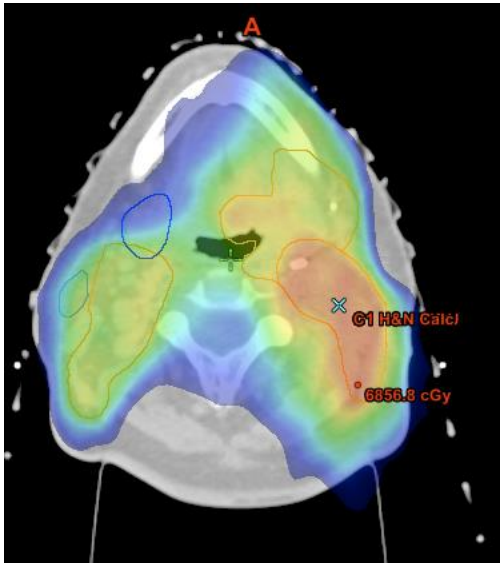
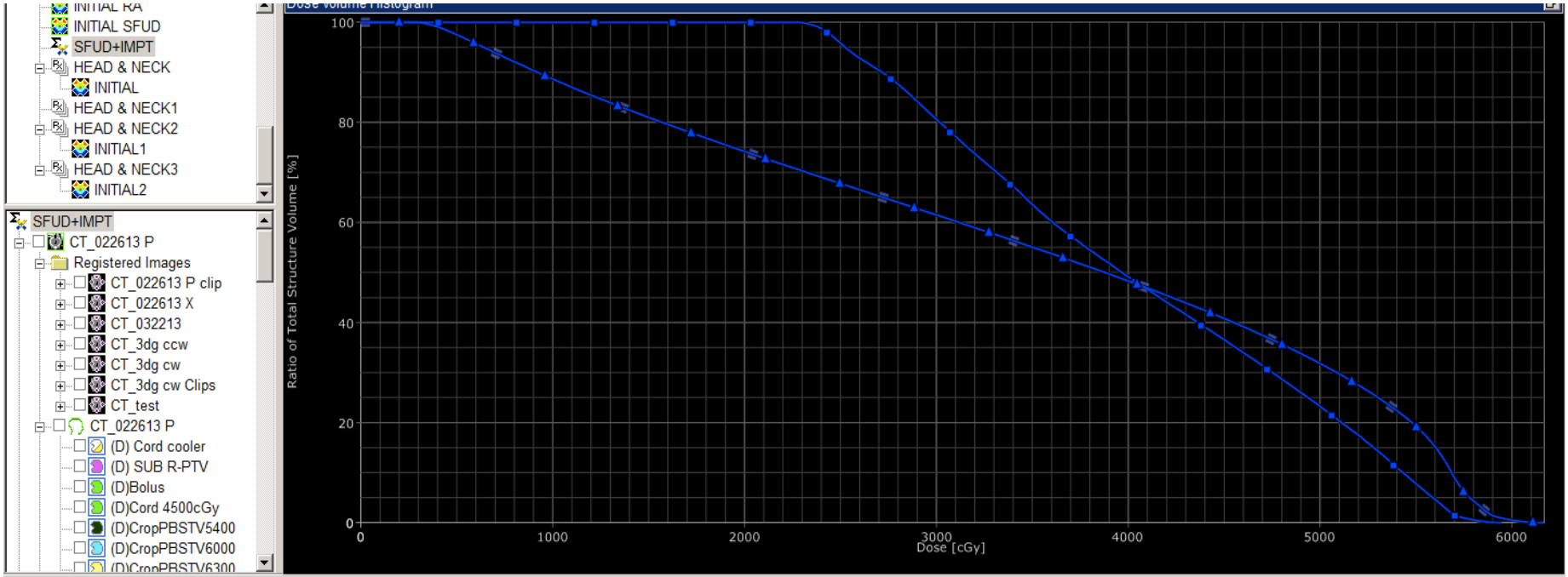
☑		Parotid_R	Approved	INITIAL RA	C1 H&N	35.3	100.0	100.1	488.2	5889.7	1492.1
☑		Parotid_R	Approved	SFUD+IMPT	C1 H&N	35.3	100.0	100.0	19.3	5933.9	947.1
☐		Primary site	Approved	INITIAL RA	C1 H&N	9.8	100.0	100.1	5809.8	6819.4	6165.8
☐		Primary site	Approved	SFUD+IMPT	C1 H&N						
☐		Proton_Couch	Approved	SFUD+IMPT	C1 H&N						
☐		R II-IV	Approved	INITIAL RA	C1 H&N						
☐		R II-IV	Approved	SFUD+IMPT	C1 H&N						
☐		Skin	Approved	INITIAL RA	C1 H&N						


A
6587.8 cGy
G1 H&N ICRU


A
G1 H&N Calc
6858.8 cGy



Dose Prescription | Dose Statistics

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		Submandibular_R	Approved	INITIAL RA	C1 H&N	11.1	100.0	100.0	2273.4	5947.0	4034.6
☑		Submandibular_R	Approved	SFUD+IMPT	C1 H&N	11.1	100.0	100.1	278.5	6169.1	3578.5
☐		Temp_Lobe_L	Approved	INITIAL RA	C1 H&N	51.3	100.0	100.0	103.7	463.1	[illegible]
☐		Temp_Lobe_L	Approved	SFUD+IMPT	C1 H&N	51.3	100.0	100.0	0.0	689.6	36.3
☐		Temp_Lobe_R	Approved	INITIAL RA	C1 H&N	48.4	100.0	100.0	84.3	287.7	155.9
☐		Temp_Lobe_R	Approved	SFUD+IMPT	C1 H&N	48.4	100.0	100.0	0.0	38.6	6.1
☐		cord+5mm	Approved	INITIAL RA	C1 H&N	95.8	100.0	99.9	38.6	4712.8	2148.5
☐		cord+5mm	Approved	SFUD+IMPT	C1 H&N	95.8	100.0	100.0	0.0	4903.6	2220.8

Outline

- Advantages of proton therapy
- Challenges to implementation
- Current evidence in support of proton therapy
- Implementation of prospective clinical trials
- The University of Pennsylvania Experience

Proton Prioritization System (PROPS)

Department of Radiation Oncology
Roberts Proton Therapy Center
University of Pennsylvania
PENN Medicine

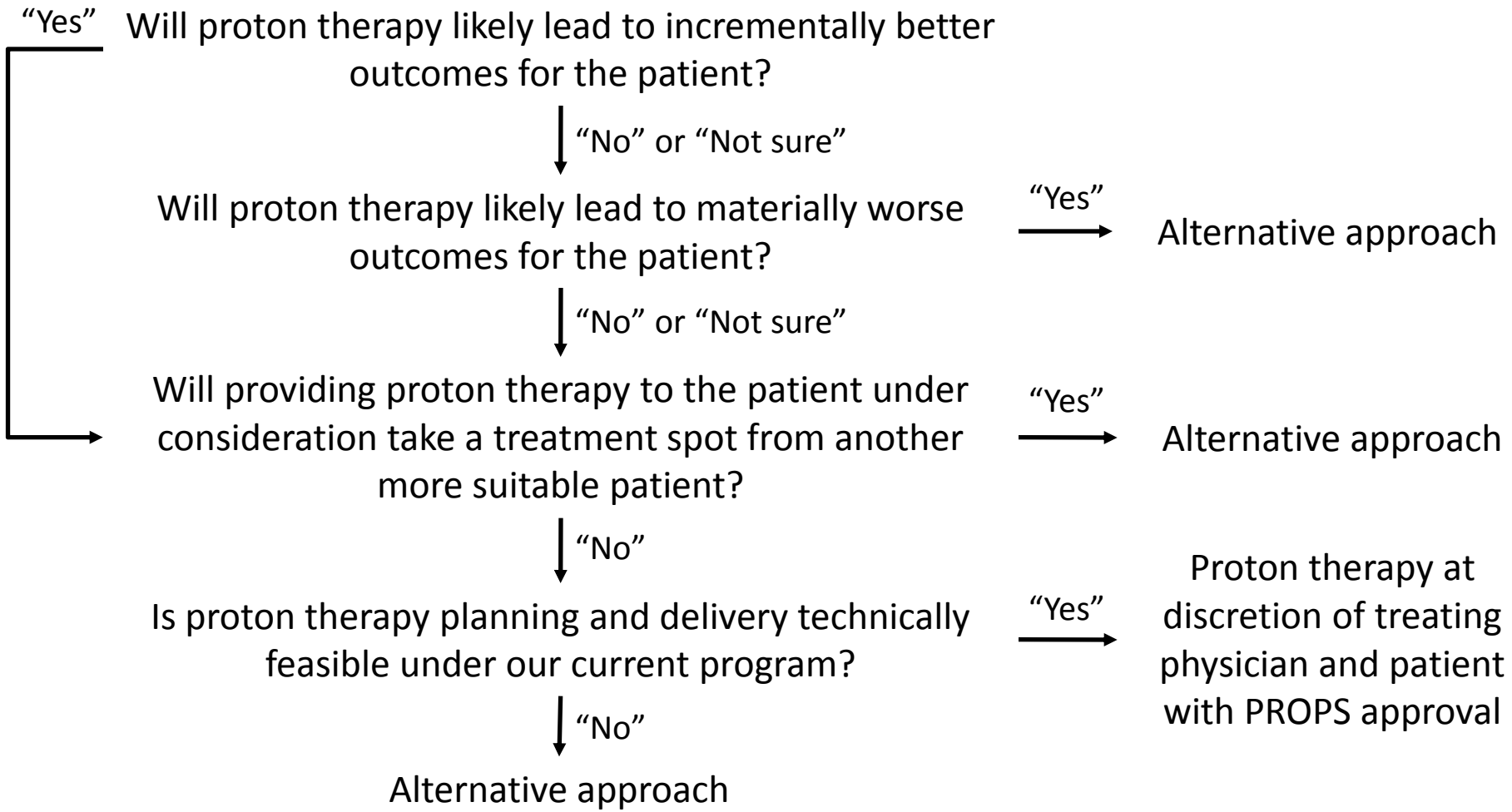
Principles of Proton Prioritization

- *Incremental Benefit*
- *Equity*
- *Transparency*
- *Age*
- *Contribution to Medical Knowledge*

PENN Proton Priority System (PROPS)

- **Diagnosis**: certain diagnoses given priority
- **Site**: skull base, orbit, spine, RP, retreatment
- **Stage**: local, regional, metastatic
- **Performance Status/Comorbidities**
- **Age**
- **Urgency**: gross disease with symptoms
- **Clinical trial**

Proton Therapy Consideration for Exceptional Cases



4 primary evidence generation goals

1) Conduct phase III randomized trials in prevalent disease sites where phase II evidence is available (prostate, lung, breast)
2) Conduct phase II trials of combined modality regimens with goal of adaptively transitioning to phase III randomized studies (head and neck)
3) Conduct phase II or cohort studies in low prevalence malignancies with long natural histories.
4) Conduct phase II trials in special situations (reirradiation)

Conclusions

- PBT has great promise as a tool to improve disease outcomes and/or mitigate RT toxicity
  - Toxicity and QOL can impact patient survival
- We need to identify ideal disease sites for which PBT may be most beneficial
- Prospective clinical trials needed
- We must take advantage of technological advances and apply them judiciously, or else risk loss of control and options for our patients