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Comparative Effectiveness of Proton Irradiation Treatment

Clinical and Policy Context
Systematic Review
Review of VHA Experiences
9/10/15

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Audience Poll Question #1

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- **What is your primary role in VA?**
  - student, trainee, or fellow
  - clinician
  - researcher
  - manager or policy-maker
  - Other

Audience Poll Question #2

- **What is your role in cancer care?**
  - Radiation oncology
  - Medical oncology
  - Surgery
  - Nursing
  - Nonclinical or none

Audience Poll Question #3

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- **What do you know about radiation therapy?**
  - Nothing
  - I know it kills cancer cells
  - I understand the different types
  - I work in radiation therapy

Audience Poll Question #4

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- **What type of cancer is of particular interest to you?**
  - Prostate
  - Lung
  - Head and neck
  - Gastrointestinal cancer
  - All or other

Audience Poll Question #5

- **What is your view on protons in prostate/lung cancers?**
  - Data is sufficient; adopt it
  - Need more research
  - We should stick with current methods
  - Not sure

Proton Therapy Overview

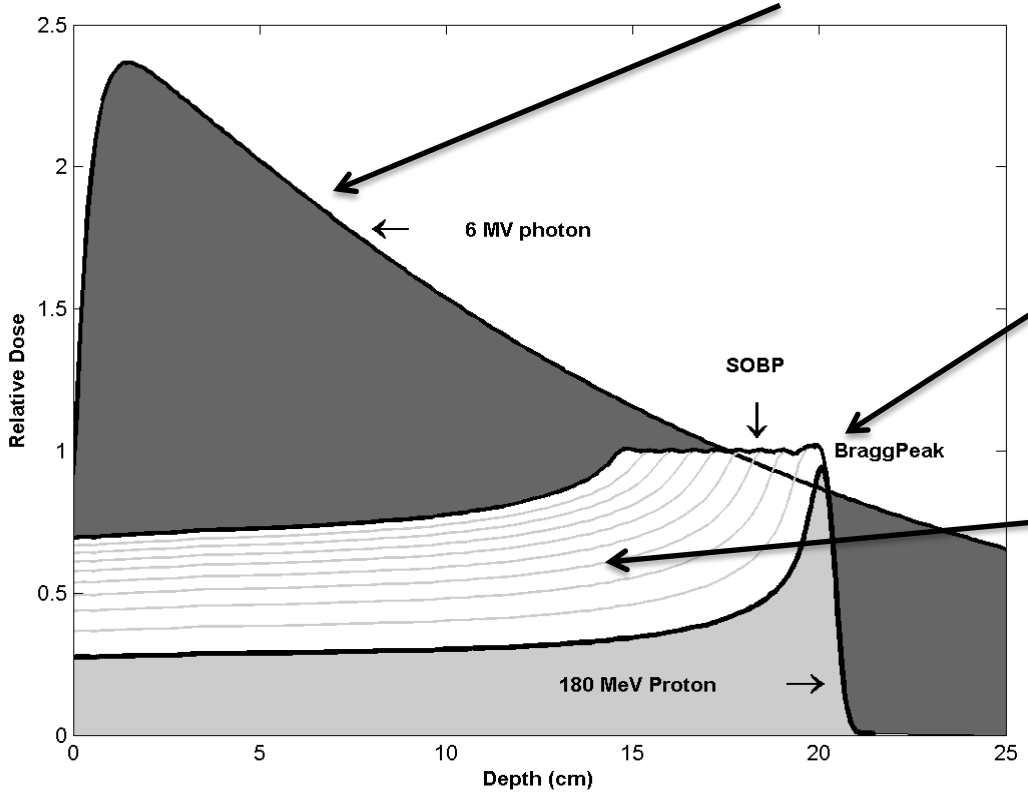
Michael Hagan, M.D., Ph.D.

Director, VHA National Radiation Oncology Program

9/9/2015

Depth Dose Comparison of Photon and Proton Beams

Photons beam intensity decreases steadily



Protons slow until recombining with an electron to stop quickly.

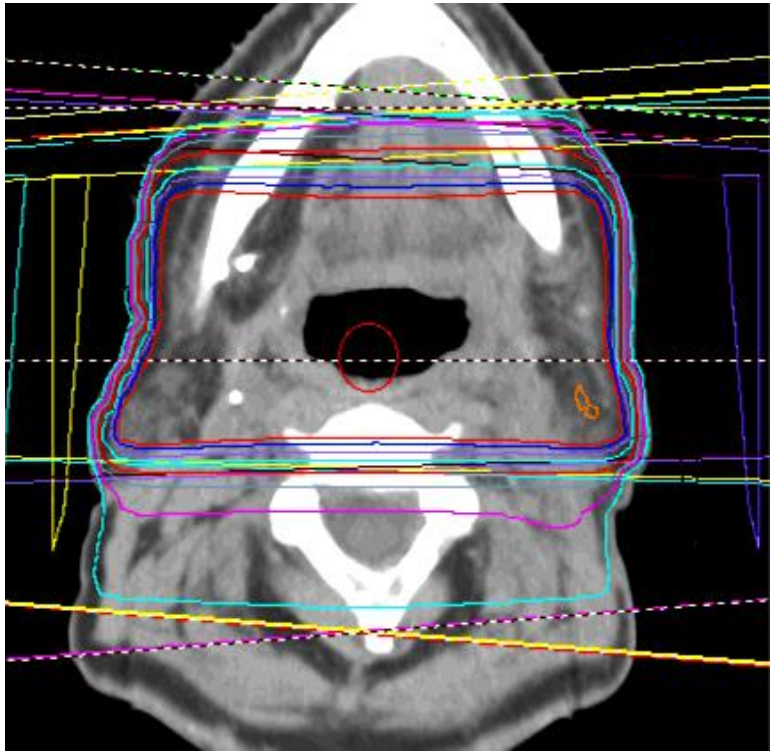
Adjusting the proton energy alters the depth at which recombination occurs.

Summing proton beams creates A spread-out Bragg peak (SOPB)

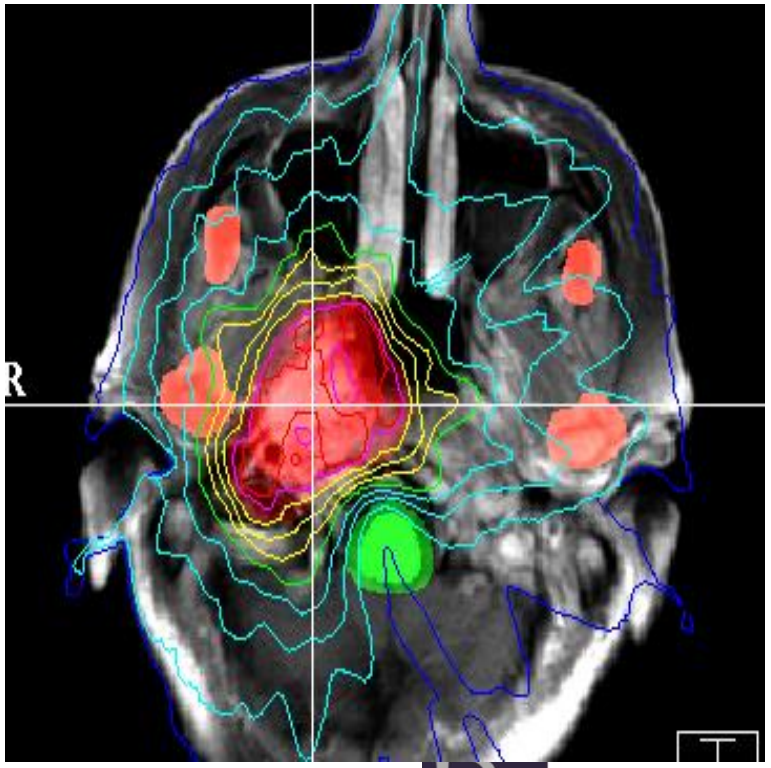
J Johansson PhD Thesis 2006

Comparison of Conventional vs IMRT Treatment

Bilateral Opposed Fields
Uniform Dosing



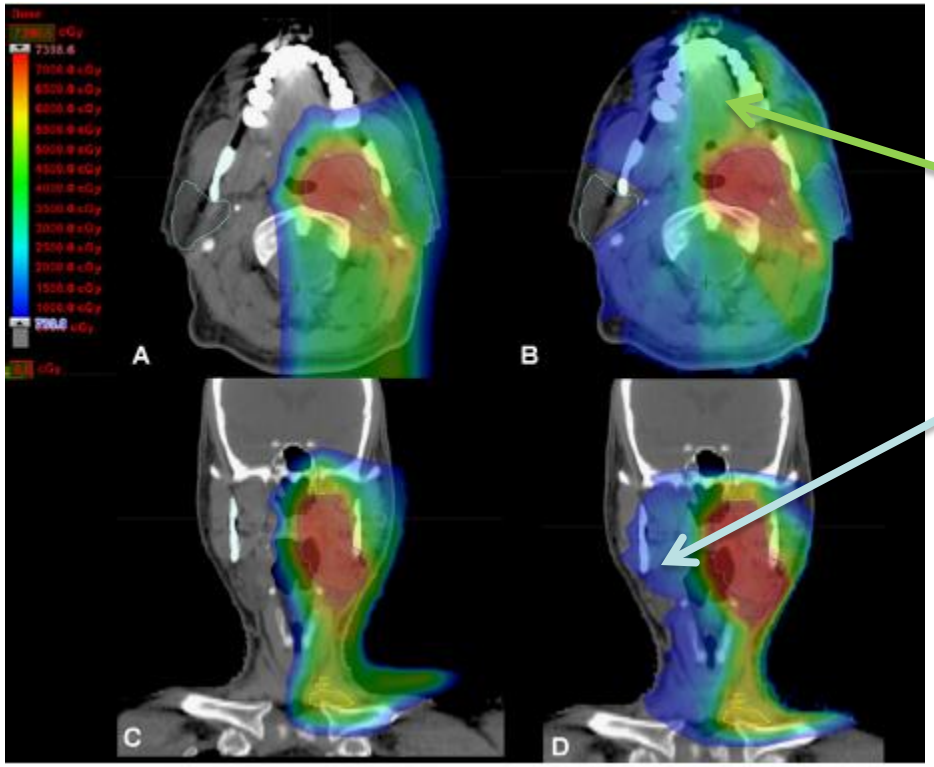
IMRT
Targeted Dosing



Comparison of Proton vs IMRT Treatment

Scanning Proton Beam **IMRT photon** irradiation

Rx: 7400cGy Tumor dose



Regions of excess irradiation

Oral cavity:

Green region 55% (>4000cGy)

Contralateral Neck:

Blue region 20% (1500 cGy)

Kandula, et al.,Medical Dosimetry38(2013)390–394

Non-VA Community Radiation Treatment Costs

Costs

per treatment	per case (CAP)	
• $224	$8K	Conventional Irradiation
• $400	$14K	Intensity Modulated RT
• $940-$3200	$40-60K	Proton Therapy (varies by state)

VHA Utilization of Proton Therapy

FY14: 10 VAMCs; 21 pts

FY15: 17 VAMCs; 29 pts

Cost abuse for CAP by community providers

$629K Baltimore VAMC single case

$124K Richmond VAMC single case

Audience Poll Question #6

- **How familiar are you with the Evidence-based Synthesis Program and their methodology?**
  - Not at all
  - Somewhat
  - Very

Evidence Review Team

Research Team

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- Kallie Waldrip, MS
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Operational Partners

- Michael Hagan, MD, PhD, National Director, VA Radiation Oncology Program, VHA
- Michael Kelley, MD, National Program Director for Oncology/SCS/PCS

ESP Program Information

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- **Funding:** Quality Enhancement Research Initiative (QUERI)
- **Sites:** Four VA medical centers with systematic review expertise, Portland, West LAL, Durham, Minneapolis, and Coordinating Center
- **Products:** Evidence synthesis reports on health care topics important to VA leaders, managers and policy makers for quality improvement.
- **Purpose:** Inform VA clinical policy, develop clinical practice guidelines, future research, performance measures, and drug formulary decisions.
- **Topics:** Identified by HSR&D Planning and Oversight Committee; may be nominated using form on ESP website: http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm

Disclosure

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Key Questions

- **KQ1:** What is the effectiveness of proton beam irradiation compared to conventional X-ray-based external beam modalities?
- **KQ2:** What is the effectiveness of proton beam irradiation compared to state-of-the-art therapies?
- **KQ3:** In patients with local recurrences after irradiation, what is the effectiveness of proton beam irradiation compared to conventional X-ray-based external beam modalities and state-of-the-art therapies?
- **KQ4:** What are the short- and long-term harms of proton beam irradiation compared to conventional X-ray-based external beam modalities and state-of-the-art therapies?
- **KQ4A:** What are the harms of proton beam irradiation compared to photon-based therapies in treating mobile targets that may move during treatment

Inclusion Criteria

- **Population:** Adults with any cancer type, *except* ocular
- **Intervention:** Proton therapy
- **Comparator:** Intensity Modulated Radiation Therapy (IMRT), brachytherapy, Stereotactic Ablative Body Radiation Therapy (SBRT), 3-dimensional conformal radiation therapy (3D-CRT)
- **Effectiveness Outcomes:** Survival (overall, progression-free), local tumor control, ability to deliver planned chemotherapy regimen, ability to deliver planned radiation regimen, quality of life, functional capacity
- **Harms:** Acute and late toxicity acute, late, secondary malignancies
- **Timing:** No restrictions
- **Setting:** No restrictions

Methods

Searching

- MEDLINE®, Cochrane Central Register of Controlled Trials through December 2014
- Requests to proton therapy centers and manufacturers, ClinicalTrials.gov

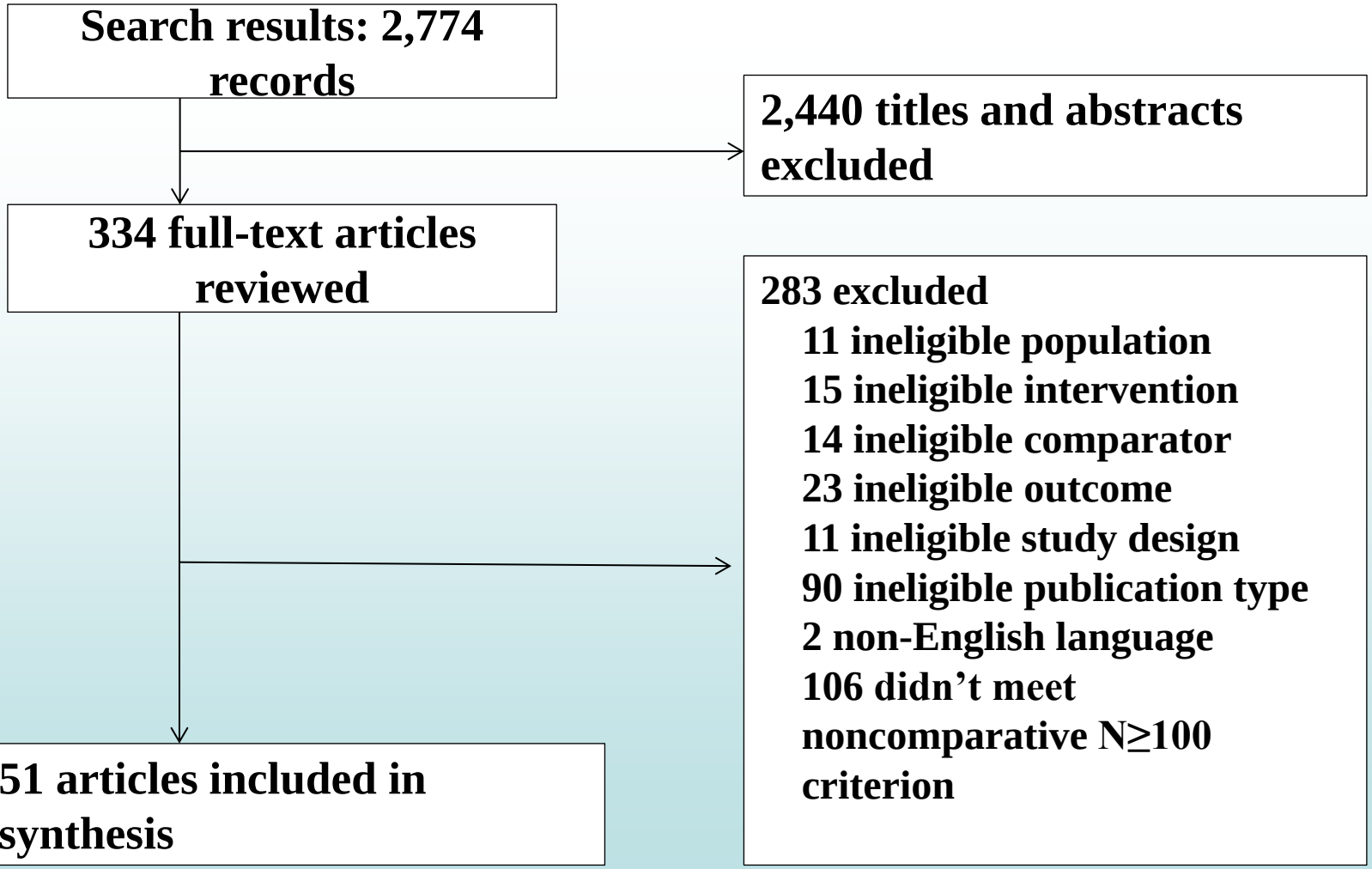
Assessment of internal validity of individual studies

- Used prespecified criteria to assign quality score of good, fair or poor based on how well studies minimized selection, performance, detection and attrition bias

Grading strength of body of evidence:

- Used prespecified criteria to rate as high, moderate, low, or insufficient based on methodologic limitations, directness, precision, and consistency.

Literature Flow



Characteristics of comparative studies

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Cancer	#	Comparators			
		IMRT	3D-CRT	CP	Other*
Breast	1		1		
CNS	3	1		2	
Esophageal	2	1	1		
Medulloblastoma	1			1	
Head/Neck	1	1			
Liver	1			1	
Lung	2	1	1		
Meningioma	2			2	
Prostate	10	6	2	3	1
Various	1				1

Abbreviations: IMRT=Intensity Modulated Radiation Therapy, 3D-CRT= 3-dimensional conformal radiation therapy; CP=conventional photon; CNS=central nervous system; *Brachytherapy for prostate, various for various cancers

Strength of evidence: Low to insufficient overall

- Many cancer types with single small study

- Main methodological limitations:
  - Photon-based groups had poorer prognostic profiles without accounting for the important differences
  - Historical control groups for the photon-based comparator groups
  - Lacked data on radiation dose and field size
  - Flawed methods for measuring toxicity

Findings in 6 primary tumor types supported by low-strength evidence*

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- **Key Question 1. What is the effectiveness of proton beam irradiation compared to conventional x-ray-based external beam modalities?**
- **Key Question 2. What is the effectiveness of proton beam irradiation compared to state-of-the-art therapies?**
- **Key Question 4. What are the short- and long-term harms of proton beam irradiation compared to conventional x-ray-based external beam modalities and state-of-the-art therapies?**

**Excludes unacceptably flawed evidence for giant cell tumors, head and neck cancer, and meningiomas.*

Breast Cancer: Accelerated partial breast irradiation, single-field

	Results (Low Strength of Evidence)	Studies
↑	None	One fair-quality prospective study (N=98) Comparator: 3-dimensional conformal radiation (3D-CRT)
=	7-year self-reported cosmetic outcomes and local failure rate	
↓	Increased skin toxicity: Proton beam=54-90% versus 3D-CRT=15-28%	

Esophageal Cancer

	Results (Low Strength of Evidence)	Studies
↑	30-day post-op pulmonary complications: OR: 9.13 (95% CI, 1.83-45.42) for trimodal 3D-CRT vs proton beam	Two fair- quality prospective studies (N=519) Comparators: Intensity Modulated Radiation Therapy (IMRT), 3-dimensional conformal radiation therapy (3D-CRT)
=	Post-op pulmonary complications: OR: 2.23; 95% CI: 0.86-5.75 for trimodal IMRT vs proton beam Gastrointestinal complications: OR: 1.02; 95% CI: 0.47-2.25) for IMRT vs proton beam; OR: 2.31; 95% CI: 0.69-7.74 for trimodal 3D-CRT vs proton beam	
↓	Acute Pneumonitis: proton beam=33% vs IMRT/3D-CRT=5%, P=.04	

Trimodal therapy=neoadjuvant chemoradiation, then surgical resection

Medulloblastoma

	Results (Low Strength of Evidence)	Studies
↑	1-month medical management of esophagitis: proton=5% vs photon=57%, P<.001; > 5% weight loss: proton=16% vs photon=64%, P=.004; Grade ≥ 2 nausea/vomiting: proton=26% vs photon=71%, P=.004	One fair-quality prospective study (N=40) Comparator: Conventional photon
=	2-year overall and progression-free survival, proportion of patients with treatment breaks, and locoregional failure	
↓	None	

Non-Small Cell Lung Cancer: 74% stages III-IV

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	Results (Low Strength of Evidence)	Studies
↑	6-month severe esophagitis (grade ≥ 3): Proton=6% vs IMRT=28%, P<.0001	One fair-quality prospective study (N=652) Comparators: Intensity Modulated Radiation Therapy (IMRT), 3-dimensional conformal radiation therapy (3D-CRT)
=	6-month severe esophagitis (grade ≥ 3): Proton=6% vs 3D-CRT=8%, P=.42	
↓	None	

Prostate Cancer: Proton Therapy vs Intensity Modulated Radiation Therapy (IMRT)

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	Results (Low Strength of Evidence)	Studies
↑	Genitourinary (GU) toxicity at 0-6 months: Proton=5.9% vs IMRT=9.5%; OR (Proton vs IMRT): 0.60; 95% CI: 0.38-0.96 (N=1263)	6 fair-poor quality retro-spective studies
=	2-year quality of life (N=1695), 12-24 month gastrointestinal (GI) or GU toxicity vs IMRT (N=1130)	
↓	4-5 year toxicity (N=6350) • Any GI toxicity, # per 1,000 patient years: proton=20.1 vs IMRT=8.3; HR (proton vs IMRT): 3.32 (95% CI: 2.12-5.20) • Patients with GI procedures: IMRT=18% vs proton=21%; RR (IMRT vs proton): 0.82 (0.70-0.97) • Patients with GI Diagnoses: IMRT=12% vs proton=18%; RR (IMRT vs proton): 0.66 (95% CI: 0.55-0.79)	

Prostate Cancer: Proton therapy vs 3-dimensional conformal radiation therapy (3D-CRT)

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	Results (Low Strength of Evidence)	Studies
↑	None	2 fair-poor quality retrospective studies (N=19281)
=	Urinary incontinence, # per 100 patient years: proton=3.3 vs 3D-CRT=3.7 Erectile dysfunction, # per 100 patient years: proton=7.4 vs 3D-CRT=5.3	
↓	Increased 1-year gastrointestinal toxicity: aHR (PBT vs 3D-CRT): 2.13 (95% CI: 1.45-3.13)	

Prostate Cancer: Proton+photon therapy vs brachytherapy

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	Results (Low Strength of Evidence)	Studies
↑	None	1 fair-quality retrospective cohort (N=282)
=	8-year overall survival and freedom from distant metastasis vs brachytherapy	
↓	None	

Prostate Cancer: proton+photon vs photon alone

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	Results (Low Strength of Evidence)	Studies
↑	None	3 fair RCT; 2 poor quality observational (N=567)
=	8-year survival, quality of life, urethral stricture, gross hematuria (proton+photon vs photon alone)	
↓	8-year rectal bleeding: 32% (proton+photon) vs 12% (photon alone); P=.002	

Spinal Cord Glioma

	Results (Low Strength of Evidence)	Studies
↑	None	One poor-quality retrospective study vs Intensity Modulated Radiation Therapy (IMRT), (N=32)
=	None	
↓	5-year survival: aHR (IMRT vs proton): 55.82; 95% CI: 1.34-2316.8	

Key Question 3. Insufficient evidence in patients with local recurrences

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	Results (Insufficient Evidence)	Studies
↑	None	2 poor-quality studies: (1) recurrent malignant brain tumor vs stereotactive radiotherapy (SRT) or conventional photons (N=26) (2) recurrent liver cancer vs conventional photons (N=8)
=	Similar recurrence and survival for recurrent malignant brain tumor; similar survival for recurrent liver cancer	
↓	None	

Key Question 4A. Insufficient evidence on effects of tumor motion variability

- **Clinical outcomes:** No studies

- **Unclear how differences in dosimetric outcomes translate to clinical outcomes:** Lower doses to normal structure with four-dimensional computed tomography imaging vs other multiphase, free-breathing, or three-dimensional computed tomography imaging

Summary

- **Key Questions 1, 2, &4: Low-strength findings**
  - Advantages: ↓ toxicity ≤ 6 months for esophageal, medulloblastoma, NSCLC, and prostate cancer
  - Disadvantages: ↑ acute toxicity for breast and esophageal cancer, ↑ late GI toxicity for prostate cancer, ↓ survival for spinal cord glioma
- **Key Question 3:** Studies on secondary malignancies and in patients with local recurrences too flawed to draw conclusions.
- **Key Question 4A:** No studies evaluated impact of tumor motion variability on clinical outcomes

Limitations

- Potential for publication bias
- Insufficient reporting of most outcomes of greatest interest
- Limited applicability

Audience Poll Question #7

- **What is your view on proton in prostate/lung cancers?**
  - Data is sufficient; adopt it
  - More research needed
  - We should stick with current methods
  - Not sure

Conclusions

- Insufficient data to draw conclusions about overall net health benefit of proton therapy until data becomes available on a complete set of outcomes

- Still no evidence of important long-term advantages for proton therapy for any common tumors, but have demonstrated some important disadvantages

Acknowledgments

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Questions?

If you have further questions, feel free to contact:

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The full report is available on the ESP intranet:

http://vaww.hsrd.research.va.gov/publications/esp/reports.cfm