Prostate Cancer Proton Therapy

Past, Present, and Future Perspectives

Continuing Medical Education

Perelman School of Medicine
University of Pennsylvania

FRIDAY,
NOVEMBER 13, 2015
8:00 AM – 4:30 PM

The Inn at Penn
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The University of Pennsylvania PRESENTS

PROSTATE CANCER EVIDENCE ACADEMY

CME/CNE-Certified Course

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Adjunct, University of Pennsylvania

Disclosures

- **None**

Myths

- Proton therapy is new.
- There is no evidence demonstrating a benefit to proton therapy for prostate cancer.
- Proton therapy is better than photon therapy and has no side effects.

Opinionator

Exclusive Online Commentary From The Times

OPINIONATOR | January 2, 2012, 10:18 pm | 272 Comments

It Costs More, but Is It Worth More?

By EZEKIEL J. EMANUEL and STEVEN D. PEARSON

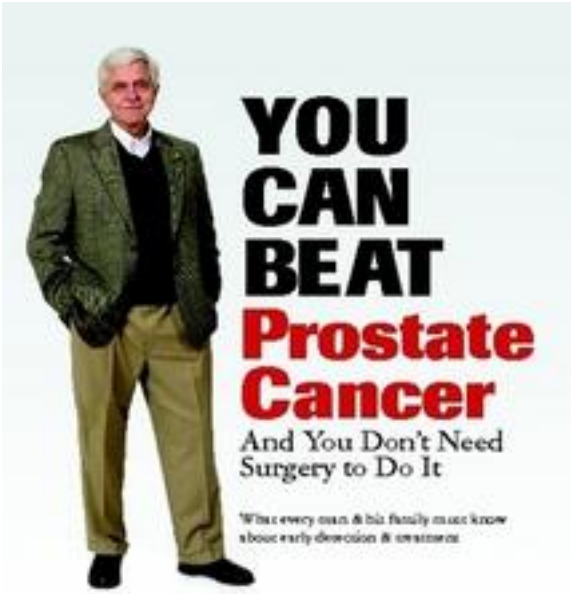
Ezekiel J. Emanuel on health policy and other topics.

TAGS:

BUDGETS, CANCER, MEDICARE, PROTON BEAM THERAPY

If you want to know what is wrong with American health care today, exhibit A might be the two new proton beam treatment facilities the Mayo Clinic has begun building, one in Minnesota, the other in Arizona, at a cost of more than $180 million dollars each. They are part of a medical arms race for proton beam machines, which could cost taxpayers billions of dollars for a treatment that, in many cases, appears to be no better than cheaper alternatives.

Proton beam therapy is a kind of radiation used to treat cancers. The particles are made of atomic nuclei rather than the usual X-rays, and theoretically can be focused more precisely on cancerous tissue, minimizing the danger to healthy tissue surrounding it. But the machines are tremendously expensive, requiring a particle accelerator encased in a football-field-size building with concrete walls. As a result, Medicare will pay around $50,000 for proton beam therapy for a patient with prostate cancer, roughly twice as much as it would if the patient received another type of radiation.



Proton Therapy for Prostate Cancer

- **Outline:**
  - Historical Perspective
  - Mechanism/Rationale
  - Clinical Evidence
  - Technical Considerations and Advances
  - Future Directions

Historical Perspective

- **Proton therapy has been used in cancer management for over 50 years.**
- **Post WWII study of nuclear technology and potential applications**
- **1946 – Dr. Robert Wilson at Harvard published on "The Radiological Use of Protons"**
  - Recognizing the unique pattern of dose deposition
- **1954 – first experiments at physics research centers:**
  - Lawrence Berkley National Laboratory
  - Gustav Werner Institute in Uppsala, Sweden (1957)
  - these facilities typically offered relatively low-energy protons delivered through a fixed beam, so clinical applications were limited.
- **1961 – Harvard Cyclotron Laboratory began a 40 year collaboration with MGH treating over 9000 patients through 2002 treatment transferred to MGH campus**

Historical Perspective

- **1990 – Loma Linda University Medical Center opened the first hospital based facility**
  - Higher energy protons, allowing the treatment of deep-seated tumors, such as the prostate
  - Marked the transition of proton therapy from physics labs to mainstream practice
- **2002 – MGH followed suit and established hospital based facility**
- **2010 – Roberts Proton Therapy Center at Penn began treatment**
- **2015 – Currently ~16 operational proton centers in US and 40 abroad.**
  - US centers expected to double in the next 3 years
  - Need for high-level evidence:
    - Physicians, policy makers, and the public are seeking clear and definitive data to support its use

US Proton Centers

Operating centers:

1) Hampton University Proton Therapy Institute, Hampton, Virginia
2) Mayo Clinic Proton Beam Therapy Program, Rochester, Minnesota
3) Ackerman Cancer Center; Jacksonville, Florida
4) Willis-Knighton Health System, Shreveport, Louisiana
5) Scripps Proton Therapy Center, San Diego, California
6) SCCA Proton Therapy, A ProCure Center in Seattle, Washington
7) MD Anderson Cancer Center's Proton Center, Houston
8) James M. Slater, M.D. Proton Treatment and Research Center at Loma Linda University Medical Center
9) S. Lee Kling Proton Therapy Center at the Siteman Cancer Center, St. Louis, Missouri
10) The University of Florida Health Proton Therapy Institute
11) ProCure Proton Therapy Center, Oklahoma City
12) The Roberts Proton Therapy Center at University of PA Health System
13) ProCure Proton Therapy Center in partnership with Princeton Radiation Oncology Group and CentraState Healthcare System, Somerset, N.J
14) Northwestern Medicine Chicago Proton Center, Chicago Area, Illinois
15) The Provision Center for Proton Therapy, Knoxville, Tennessee
16) Francis H. Burr Proton Center at Mass. General Hospital

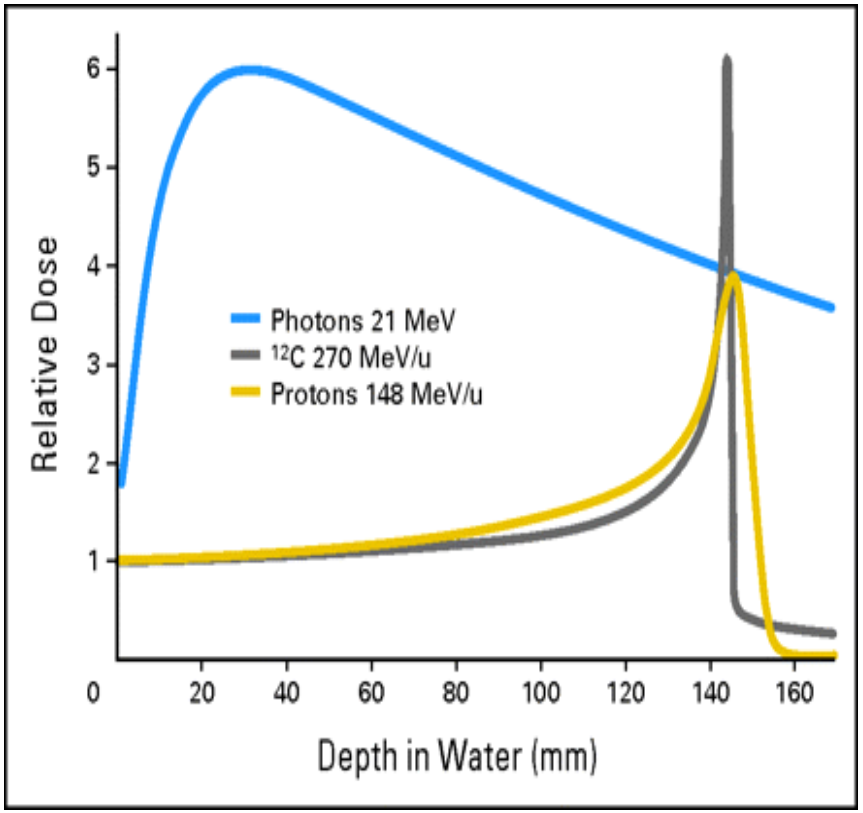
Centers under construction:

1) Cincinnati Children's Proton Therapy Center, Liberty Township, Ohio
2) Dallas Proton Treatment Center, Dallas, Texas
3) Emory Proton Therapy Center, Atlanta, Georgia
4) Maryland Proton Treatment Center, Baltimore, Maryland
5) Mayo Clinic Proton Beam Therapy Program, Phoenix, Arizona
6) The McLaren Proton Therapy Center, Flint, Michigan
7) Miami Cancer Institute at Baptist Health South Florida
8) University Hospitals Seidman Cancer Center, Case Medical Center
9) Texas Center for Proton Therapy, Irving, Texas
10) UF Health Cancer Center at Orlando Health

http://www.proton-therapy.org/map.htm

Mechanism and Rationale

- **Unlike X-rays, protons:**
  - are subatomic particles that have mass
  - do not travel an infinite distance
  - Stop in tissue at a distance proportional to their acceleration.
  - are 1,800 times as heavy as electrons, the primary subatomic particles with which they collide.
  - lose relatively little energy along the beam path until the end of their range
    - at which point they lose the majority of their energy
    - producing a characteristic sharp peak in radiation energy deposition known as **the Bragg peak**.



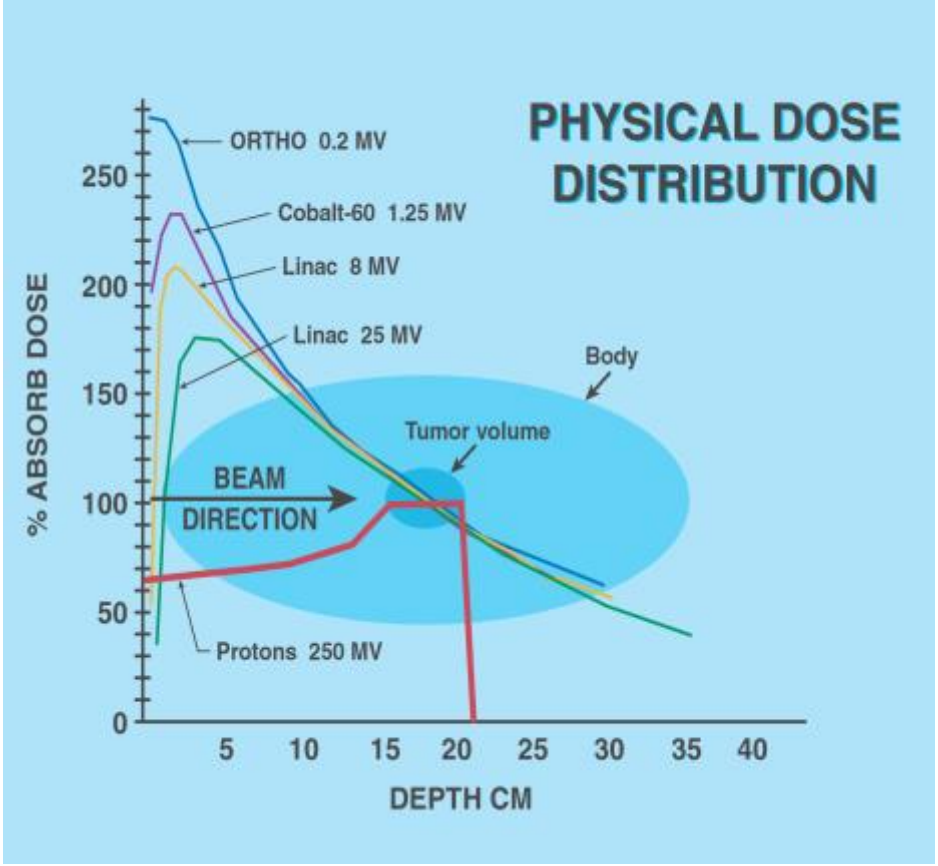
Mechanism and Rationale

- **Because the width of the Bragg peak is only 4 to 7 mm, clinically, a spread-out Bragg peak (SOBP) is used, to cover the full thickness of a particular target with a uniform dose.**

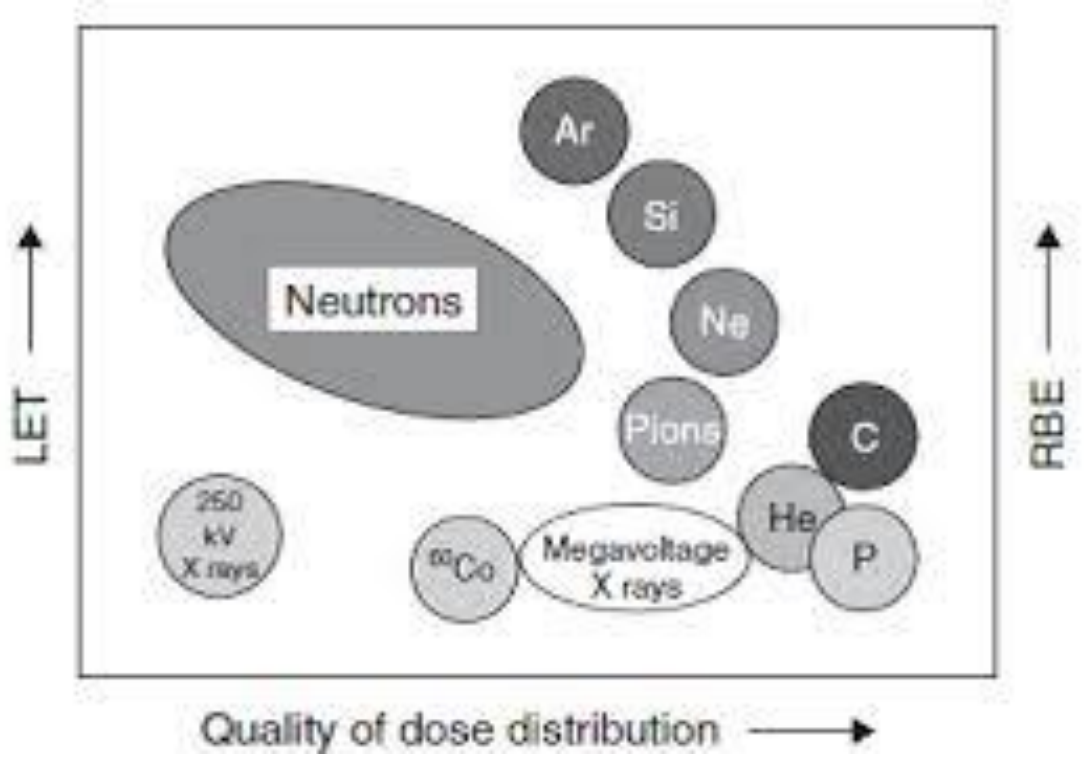
- **Thus, a typical proton beam disperses:**
  1) a low constant dose of radiation along the entrance path of the beam
  2) a high uniform dose throughout the range of the SOBP
  3) no exit dose, eliminating much of the integral dose inherent in X-ray therapy.

- **In contrast to photons, the majority of radiation energy from a proton beam is actually deposited in the target.**

- **<u>Theoretical advantage for proton therapy is its dose distribution.</u>**

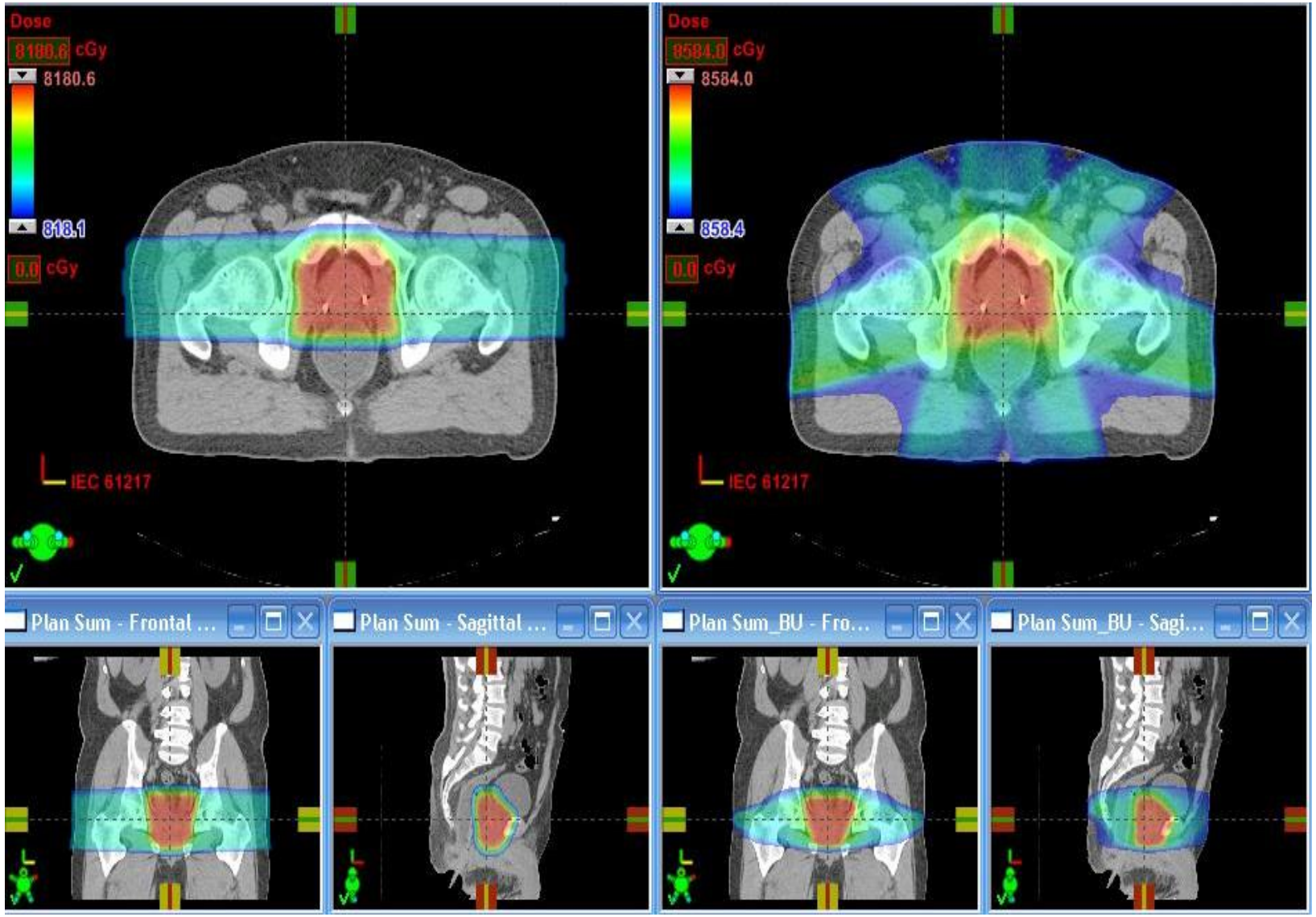


Mechanism and Rationale

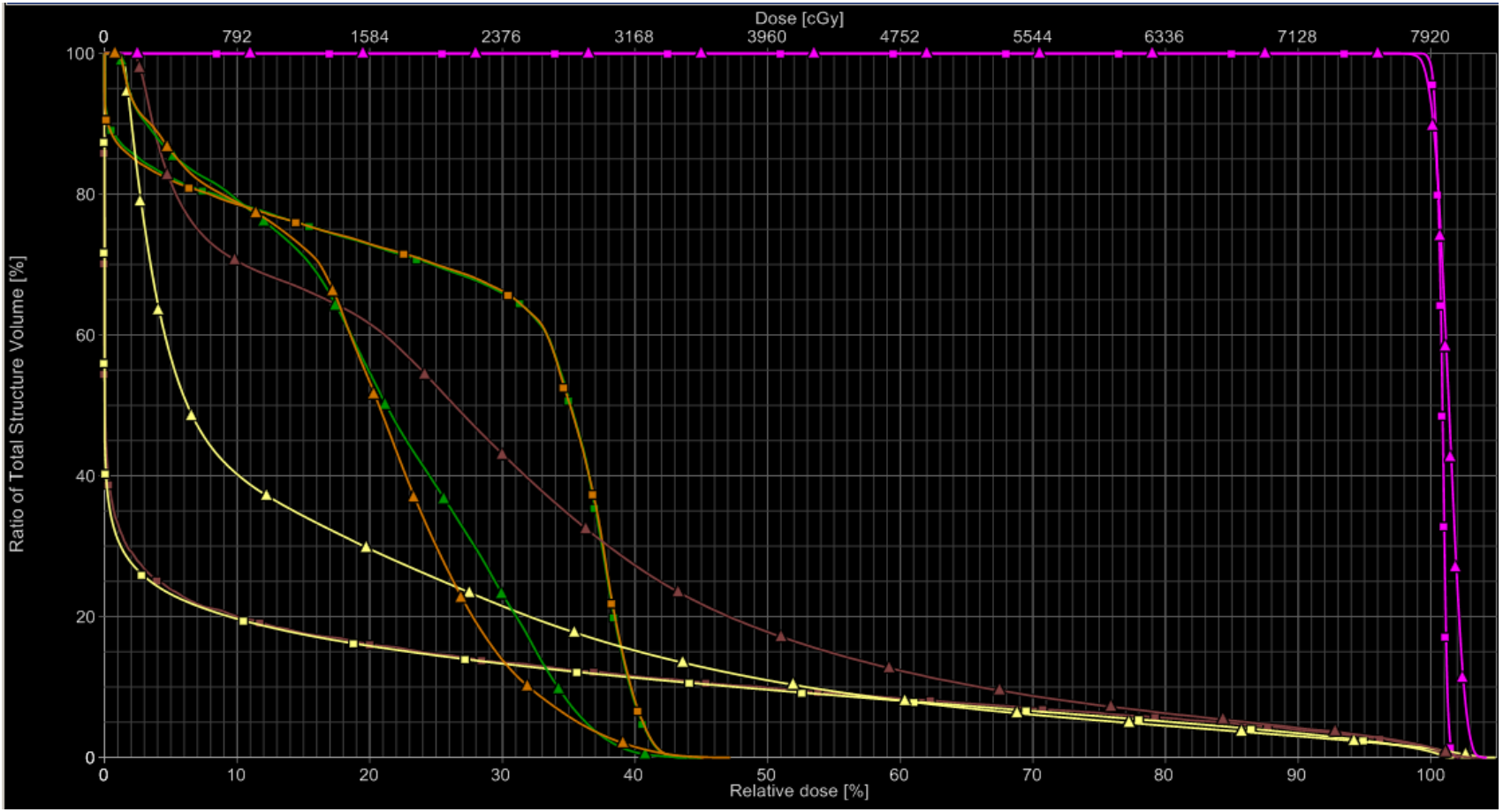


- Protons are generally not considered to be high linear energy transfer (LET) particles (despite having a slightly higher LET than x-rays).
- High-LET radiation deposits more dose along its path than low LET radiation
  - more damaging to hypoxic cells, less cell cycle dependent, and less DNA damage repair.
  - heavier charged particles, such as carbon and helium have this radiobiologic advantage

Clinical evidence – dosimetric advantages



Clinical evidence – dosimetric advantages



Dose-volume histogram comparing prostate cancer IMRT (triangle) and PT (squares) treated to 79.2 Gy (RBE).

Note the comparable target coverage (magenta lines) and reduction in low-intermediate dose regions to the adjacent rectum (brown) and bladder (yellow) – with the proton plan, which is lost in the high dose region.

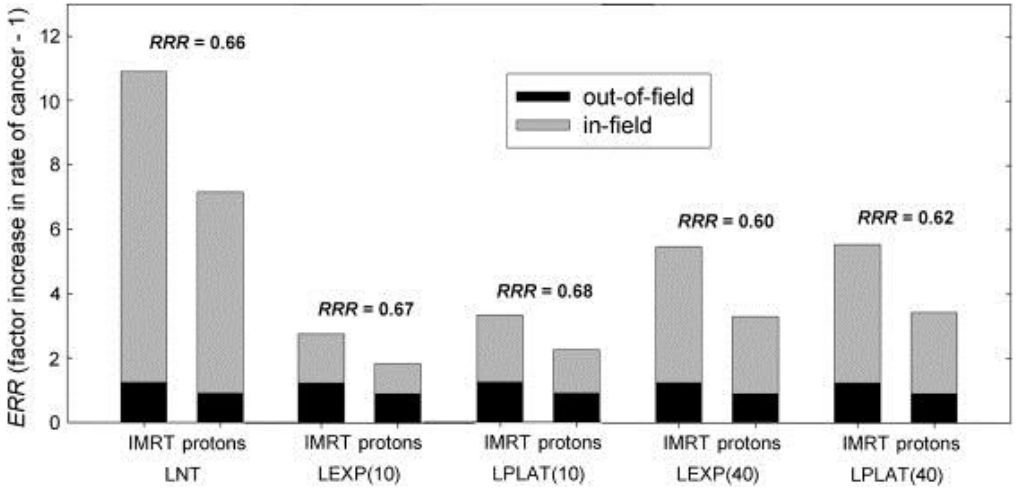
Deville C. Chapter 46. Proton Beam Therapy. In: Mydlo JH, Godec CJ (eds.) *Prostate Cancer: Science and Clinical Practice*, 2nd ed. Elsevier Press, 2015.

Clinical evidence – dosimetric advantages

- **An in-silico study from MD Anderson evaluated the risk of secondary malignancies (SMN) with IMRT compared to proton therapy in 3 patients with early-stage prostate cancer**

- **Proton therapy reduced the excessive relative risk (ERR) by 26%-39% for all models.**

- **This reduction in SMN risk may be particularly relevant in younger patients with prostate cancer.**



Fontenot J, et al. Red Journal 2009

History of Proton Therapy in Prostate Cancer

- **Initial studies in prostate cancer:**
  - used a 160-MeV proton beam from the Harvard cyclotron
  - applied as a conformal perineal boost after initial MV photon therapy.

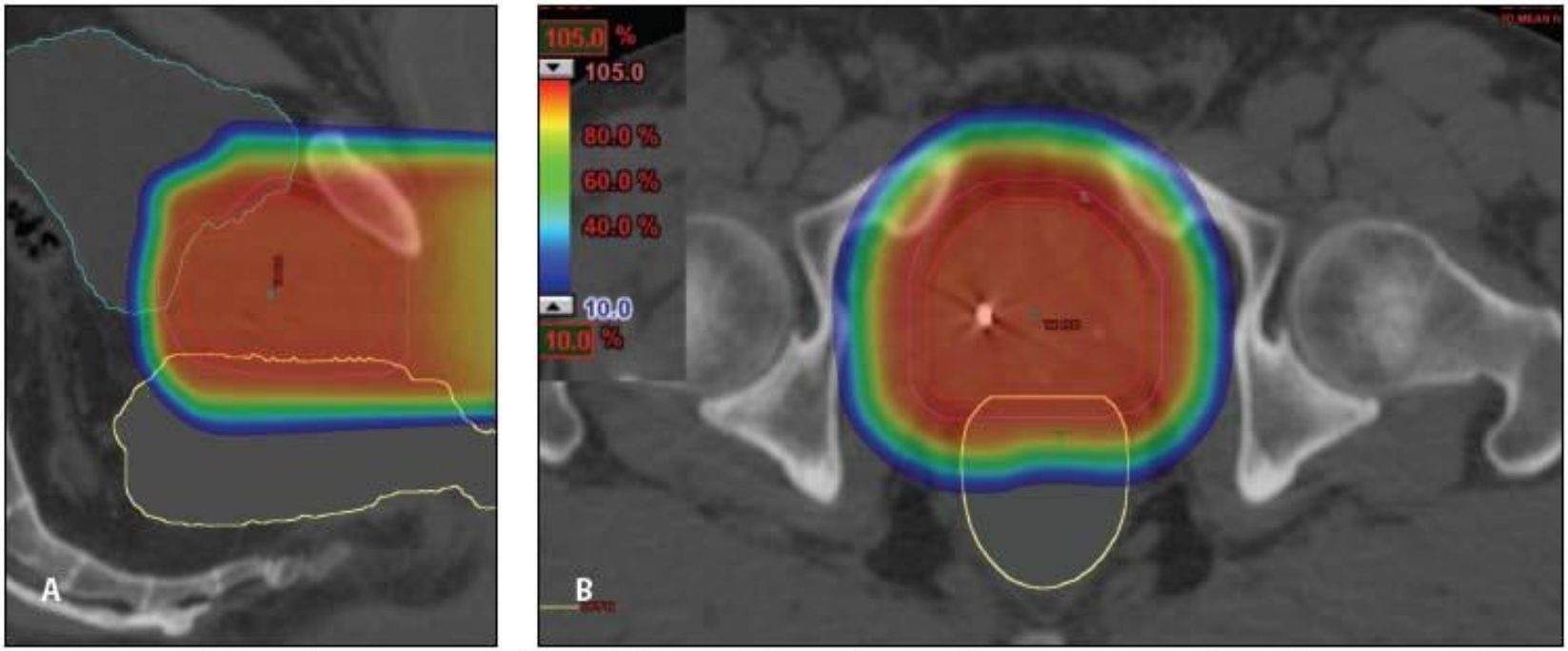


Figure 3: Sagittal (A) and Transverse (B) colorwash of a typical perineal proton boost with target and normal structures outlined as follows: prostate (red), planned target volume (pink), rectum (yellow), bladder (blue). Courtesy of Debbie Louis, CMD.

Hoppe B, et al. Oncology 2011

History of Proton Therapy in Prostate Cancer

- **Harvard conducted the first phase III proton therapy study randomly assigning patients with stage T3-4 prostate cancer to:**
  - 67.2 Gy photon therapy (n = 99)

  vs.
  - 75.6 CGE (50.4 Gy photon therapy + 25.2 CGE proton boost; n = 103)

  - 5 yr median f/u
    - ↑ local control (LC) in high-dose arm for poorly differentiated prostate cancer (Gleason score ≥ 7) (5-year LC, 94% vs. 64%; *P*=.0014).
    - trend toward improved LC in high-dose arm for entire cohort a (5-year LC, 92% vs. 80%; *P*=.089).
    - no significant differences in OS or DSS.

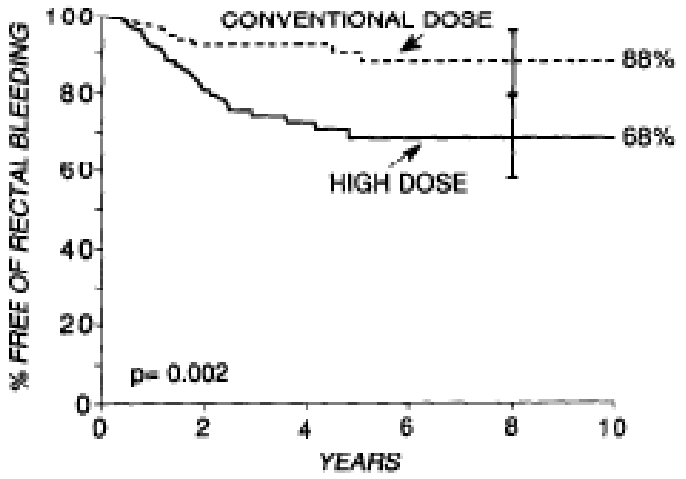
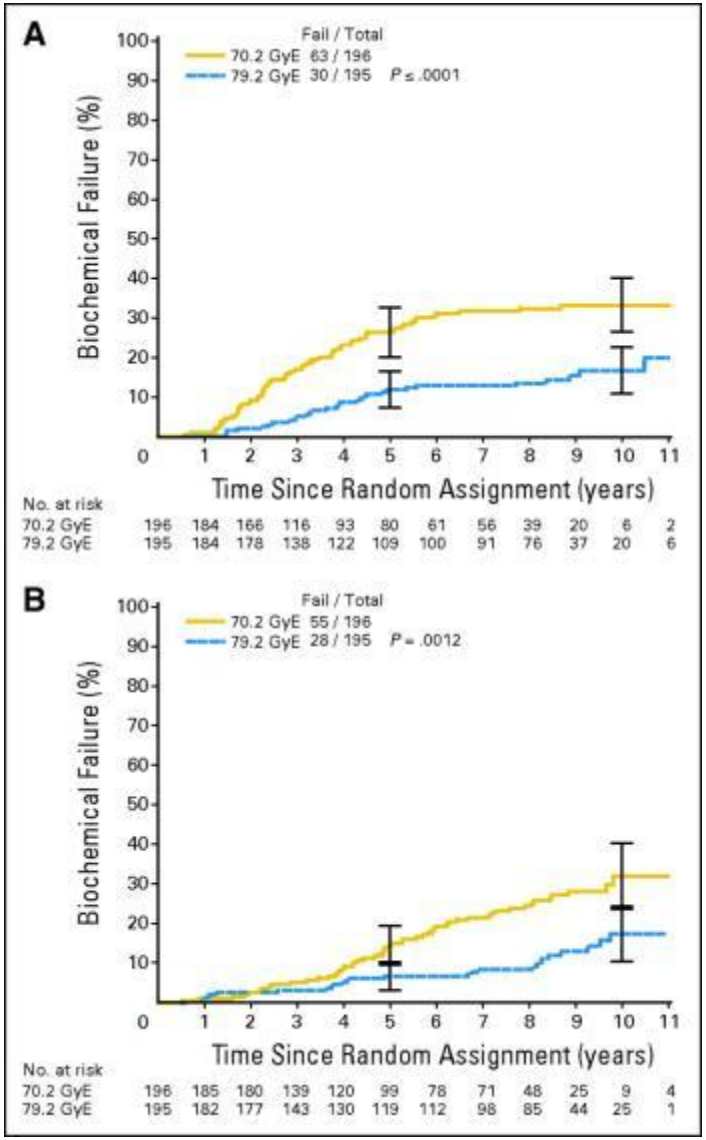


Fig. 1. Kaplan–Meier estimates of freedom from rectal bleeding for 189 patients completing a Phase III trial of high dose irradiation boosting with conformal protons (93 patients, 75.6 CGE) compared with conventional dose irradiation using photons alone (96 patients, 67.2 Gy). The *p*-value is computed by the log–rank test. The 95% confidence limits are shown.

Shipley WU, et al. Red Journal 1995

History of Proton Therapy in Prostate Cancer

- **Dose escalation: Proton Radiation Oncology Group trial 95-09**
- 1996-1999, randomized 393 men with T1b-2b prostate cancer and PSA<15 to either
  - low-dose (70.2 Gy/CGE)
  - high-dose (79.2 Gy/CGE)
- Proton “boost” with either 19.8 CGE or 28.8 CGE
- via opposed lateral 250-mV beams at Loma Linda or single perineal 160-mV proton beam at MGH, followed by 50.4 Gy with 3DCRT.
- **Importantly, dose-escalation reduced biochemical failure with still overall low rates of grade>3 GU (2%) and GI (1%) toxicity.**



Zietman A L et al. JCO 2010

History of Proton Therapy in Prostate Cancer

- ***Proton therapy as solo treatment***

- **Loma Linda reported retrospectively on:**
  - 1,255 prostate cancer patients treated to total doses of 74-75 CGE from 1991-1997
    - protons alone (n = 524)
    - proton boost (n = 731)
  - median follow-up, 62 mo (1-132 mo)
  - 5-year bochemical failure free survival was 75%
    - Long-term survival outcomes were comparable with those reported for other modalities
  - late grade 3+ GU or GI toxicities was < 1%

Slater JD, et al, Red Journal 2004

Clinical evidence

Table 1 Review of the Literature on Proton Therapy for Prostate Cancer

Author	Number of Patients	Inclusion Criteria	Protons Alone or As a Boost	Dose	Median Follow-up	BFFS	Acute GU & GI				Late GU & GI				Toxicity Report
							GI 2	GI 3	GU 2	GU 3	GI 2	GI 3	GU 2	GU 3	
Shipley et al[22]	103	T3–4, N0–2	-	50.4 Gy/25.3 CGE	61 mo	*5-year, 92%	-	0%	-	0%	27%[a]	3%	-	12%	RTOG
	99		-	50.4 Gy/16.8 Gy		*5-year, 80%	-	0%	-	0%	9%[a]	-	-	8%	
Zietman et al[28]	195	Low, intermediate risk	Proton boost	50.4 Gy/28.8 CGE	107 mo	10-year, 83.3%	63%	1%	60%	2%	24%	1%	27%	2%	RTOG
	197	Low, intermediate risk		50.4 Gy/19.8 CGE		10-year, 67.6%	44%	1%	51%	3%	13%	0%	22%	2%	
Slater et al[25]	1255	Low, intermediate, high risk	Both	74–75 CGE	63 mo	8-year, 73%	-	<1%	-	< 1%	-	-	-	-	RTOG
	731		Proton boost	45 Gy/30 CGE		-	-	-	-	-	-	-	-	-	
	524		Protons alone	74 CGE		-	-	-	-	-	-	-	-	-	
Nihei et al[30]	151	G <8, P <20	Protons alone	74 CGE	43 mo	3-year, 94%	1%	0%	12%	0%	4%	0%	8%	0%	CTCAE v 2.0
Mayahara et al[29]	287	All stages	Protons alone	74 CGE	N/A	N/A	0%	0%	39%	1%	-	-	-	-	CTCAE v 2.0
Mendenhall et al[6]	89	Low risk	Protons alone	78 CGE	Min 24 mo	2-year, 100%	-	-	-	-	4%	< 0.5%	24%	2%	CTCAE v 3.0
	82	Intermediate risk		78-82 CGE		2-year, 98%	-	-	-	-	-	-	-	-	
	40	High risk		78 CGE + docetaxel		2-year, 95%	-	-	-	-	-	-	-	-	

- Over the last decade, more proton centers have been built in the USA and abroad
- increased clinical experience in prostate cancer
- confirming the overall efficacy
- reporting low toxicity rates

Hoppe B, et al. Oncology 2011

Guidelines and Recommendations

Radiotherapy and Oncology 103 (2012) 8–11

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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

- Data through 2009 was reviewed for proton therapy.
- Insufficient evidence:
  - Lung cancer, head and neck cancer, GI malignancies, and pediatric non-CNS malignancies.
- <u>Sufficient evidence of benefit, but not superiority:</u>
  - Hepatocellular carcinoma and **<u>prostate cancer</u>**

Clinical Outcomes (CER)

- Attempts have been made to utilize comparative effectiveness research (CER) and population based data to compare outcomes in proton therapy vs. IMRT.
- Medicare-SEER analysis of 684 men treated with proton therapy 2002-2007 vs. matched IMRT cohort
  - IMRT associated with less GI “morbidity”
    - absolute risk, 12.2 vs 17.8 per 100 person-years; RR, 0.66; 95% CI, 0.55-0.79
  - No significant differences in other toxicities
  - No difference in additional cancer therapy

Sheets NC, et al, JAMA 2012

- Medicare analysis of 421 men treated with proton therapy 2008-2009 vs. matched IMRT cohort
  - Less GU “toxicity” at 6 mo for protons, disappeared by 1 yr
  - No other significant differences
  - Proton associated Medicare reimbursement costs were 75% higher: $32,428 PRT vs. $18,575 IMRT

Yu JB, et al, JNCI 2013

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

JAMA. 2012;307(15):1611-1620. doi:10.1001/jama.2012.460

Table 6. Outcomes for IMRT vs Proton Therapy With Propensity Score Matching and Instrumental Variable Analyses

	Propensity Score Matched[a]							Instrumental Variable Analysis						
	IMRT (n = 684)			Proton (n = 684)				IMRT (n = 8144)[b]			Proton (n = 1978)[b]			
Outcome per 100 Person-Years	Total Events	100 Person-Years	Rate	Total Events	100 Person-Years	Rate	IMRT vs PT, Rate Ratio (95% CI)	Total Events	100 Person-Years	Rate	Total Events	100 Person-Years	Rate	IMRT vs PT, Rate Ratio (95% CI)
Gastrointestinal events														
Procedures (including colonoscopy)	302	17	17.7	347	16.2	21.4	0.82 (0.70-0.97)	3074	169	18.2	883	41	21.6	0.60 (0.46-0.78)
Diagnoses	235	19	12.2	301	16.9	17.8	0.66 (0.55-0.79)	2620	182	14.4	714	45	16.0	0.66 (0.49-0.88)
Urinary nonincontinence events														
Procedures[c]	44	25	1.8	42	25.8	1.6	1.06 (0.69-1.63)	466	233	2.0	113	62	1.8	1.71 (0.87-3.36)
Diagnoses	161	22	7.5	144	22.9	6.3	1.25 (0.99-1.58)	1864	198	9.4	454	53	8.6	1.10 (0.78-1.58)
Urinary incontinence events														
Procedures	161	21	7.6	173	22.1	7.8	0.97 (0.77-1.20)	2029	194	10.5	511	51	10.0	1.06 (0.76-1.50)
Diagnoses[c]	75	24	3.1	82	24.8	3.3	0.96 (0.70-1.32)	816	226	3.6	200	59	3.4	1.03 (0.63-1.71)
Erectile dysfunction events														
Procedures[c]	21	25	0.8	36	26.2	1.4	0.61 (0.35-1.06)	206	239	0.9	70	63	1.1	0.58 (0.24-1.41)
Diagnoses	145	22	6.6	164	22.2	7.4	0.89 (0.70-1.12)	1454	208	7.0	436	53	8.3	0.78 (0.54-1.13)
Hip fracture[d]	21	26	0.8	18	26.6	0.7		192	239	0.8	40	63	0.6	1.42 (0.50-4.02)
Additional cancer therapy	58	26	2.2	52	27.5	1.9	1.26 (0.86-1.84)	588	252	2.3	124	67	1.9	1.60 (0.85-3.00)

Abbreviation: IMRT, intensity-modulated radiation therapy.
[a] Rates shown are adjusted for the variables presented in Tables 4 and 5, using propensity scores implemented by matching.
[b] Rates for IMRT and proton were adjusted with a 2-stage least-squares instrumental variable approach in which Radiation Therapy Oncology Group affiliation predicts proton use: this predicted value was subsequently used as exposure in an adjusted outcome model to estimate the effect of IMRT vs proton on the outcome.
[c] Because of zero cell counts, Surveillance, Epidemiology, and End Results region was not included in propensity score–matched models.
[d] Because of the small number of events and zero cell counts in some covariates in the propensity score–matched model, rate ratio could not be calculated.

Clinical Outcomes (CER)

- **Limitations:**
  - Demographically homogenous cohort (93% White, 80% Californian)
  - Loma Linda reported on nearly twice as many patients with lower rates of serious GI toxicity (<1% acutely; 1% in 5-year follow-up) than the 17.8 events per 100 person-years.
  - GI morbidity based on diagnoses/procedure codes, including screening colonoscopy.
    - Proton patients may be more likely to undergo screening procedures
  - Factors known to affect toxicity:
    - Dose
    - field size
    - image guidance
    - target margins
  - 3DCRT-proton boost included

Deville C, et al, JAMA 2012, In Reply

Table 5. Baseline Clinical Characteristics for the IMRT vs Proton Therapy Comparison

Characteristics	No. (%)					
	Before Propensity Matching			After Propensity Matching		
	IMRT (n = 9437)	Proton (n = 685)	*P* Value	IMRT (n = 684)	Proton (n = 684)	*P* Value
Concurrent androgen deprivation therapy	5293 (56.1)	212 (31.0)	<.001	200 (29.2)	212 (31.0)	.48
Tumor grade						
Well/moderately differentiated	4528 (48.0)	413 (60.3)	<.001	426 (62.3)	412 (60.2)	.74
Poorly differentiated	4786 (50.7)	268 (39.1)		254 (37.1)	268 (39.2)	
Unknown/not assessed	123 (1.3)	4 (0.6)		4 (0.6)	4 (0.6)	
Clinical stage						
T1	4989 (52.9)	348 (50.8)	.57	346 (50.6)	347 (50.7)	.81
T2	4131 (43.8)	314 (45.8)		319 (46.6)	314 (45.9)	
T3/T4	317 (3.4)	23 (3.4)		19 (2.8)	23 (3.4)	
Baseline comorbidities						
Diabetes	2563 (27.4)	130 (19.0)	<.001	119 (17.4)	130 (19.0)	.44
Anticoagulation, arrhythmia, or valvular disease	2384 (25.3)	144 (21.0)	.01	176 (25.7)	144 (21.1)	.04
Gastrointestinal diagnosis/procedure	1905 (20.2)	148 (21.6)	.37	123 (18.0)	148 (21.6)	.09
Urinary nonincontinence diagnosis/procedure	2084 (22.1)	104 (15.2)	<.001	111 (16.2)	104 (15.2)	.60
Urinary incontinence diagnosis/procedure	2233 (23.7)	109 (15.9)	<.001	119 (17.4)	109 (15.9)	.47
Erectile dysfunction diagnosis/procedure	901 (9.5)	83 (12.1)	.03	72 (10.5)	83 (12.1)	.35
Hip fracture	31 (0.3)	0	.27	1 (0.2)	0	>.99

Abbreviation: IMRT, intensity-modulated radiation therapy.

Clinical Outcomes (CER)

Table 2. Odds ratios (ORs) for receipt of proton radiotherapy*

	Unadjusted			Adjusted		
Characterisitics	**OR**	**95% CI**	***P*†**	**OR**	**95% CI**	***P*†**
Patient characteristics						
Age, y			<.001			<.001
66–69	1.00 (referent)	—		1.00 (referent)	—	
70–74	0.63	0.51 to 0.77		0.66	0.53 to 0.80	
75–79	0.43	0.34 to 0.54		0.45	0.35 to 0.57	
80–84	0.28	0.19 to 0.42		0.33	0.22 to 0.48	
85–94	0.12	0.04 to 0.39		0.15	0.05 to 0.46	
Race			<.001			<.001
White	1.00 (referent)	—		1.00 (referent)	—	
Black	0.22	0.12 to 0.38		0.22	0.13 to 0.39	
Other	0.61	0.38 to 0.97		0.64	0.40 to 1.10	
Year of treatment			.43			
2008	1.00 (referent)	—				
2009	1.07	0.90 to 1.28				
Residence in metro county			.048			.42
Yes	1.00 (referent)	—		1.00 (referent)	—	
No	0.78	0.61 to 0.998		0.90	0.68 to 1.17	
Median household income			<.001			<.001
Q1 (≤$31,848)	1.00 (referent)	—		1.00 (referent)	—	
Q2 ($31,849–$38,040)	1.66	1.20 to 2.29		1.38	0.995 to 1.91	
Q3 ($38,044–$45,494)	1.65	1.19 to 2.28		1.32	0.94 to 1.86	
Q4 ($45,495–$57,284)	1.62	1.16 to 2.26		1.18	0.83 to 1.69	
Q5 (>$57,294)	2.20	1.59 to 3.07		1.55	1.09 to 2.22	
Unknown	2.85	1.92 to 4.22		2.42	1.60 to 3.66	
Distance to nearest proton center, miles			<.001			.002
<75	1.00 (referent)	—		1.00 (referent)	—	
75–500	0.54	0.36 to 0.82		0.61	0.40 to 0.92	
>500	1.59	0.92 to 2.74		1.14	0.64 to 2.05	
Unknown	0.48	0.06 to 3.73		0.21	0.03 to 1.77	
Clinical characteristics						
Comorbidity			<.001			<.001
0 conditions	1.00 (referent)	—		1.00 (referent)	—	
1–2 conditions	0.47	0.38 to 0.58		0.52	0.43 to 0.64	
≥3 conditions	0.28	0.16 to 0.47		0.34	0.20 to 0.57	
Receipt of androgen deprivation therapy			<.001			<.001
No	1.00 (referent)	—		1.00 (referent)	—	
Yes	0.33	0.27 to 0.41		0.38	0.31 to 0.47	
Flu shot (9 months prior to start of radiation)			<.001			<.001
No	1.00 (referent)	—		1.00 (referent)	—	
Yes	0.63	0.51 to 0.77		0.63	0.52 to 0.78	
Visit to primary care physician (9 months prior to start of radiation)			.43			
No	1.00 (referent)	—				
Yes	0.80	0.46 to 1.39				
Health system characteristics						
State certificate of need for radiation facility			<.001			<.001
No	1.00 (referent)	—		1.00 (referent)	—	
Yes	0.41	0.31 to 0.56		0.53	0.39 to 0.71	
Discharges for ambulatory care sensitive conditions per 1000 Medicare enrollees	0.98	0.97 to 0.99	<.001	0.99	0.98 to 1.01	.41
Acute care hospital beds per 1000 residents	0.52	0.39 to 0.69	<.001	0.79	0.53 to 1.17	.23
Primary care providers per 100,000 residents	0.99	0.98 to 1.004	.17			
Radiation oncologists per 100,000 residents	0.84	0.50 to 1.42	.52			

* All odds ratios restricted to patients with known hospital referral region and metro status. CI = confidence interval; — = no 95% CI for referent values.

† Wald *P* value. All *P* values are two-sided.

Chronic Condition Warehouse includes comprehensive Medicare claims for all enrollees nationwide with prostate cancer. In contrast with prior studies they were able to include 6 treatment facilities rather than a single center.

Yu JB, et al, JNCI 2013

Clinical evidence – Penn IMRT vs. PBT

Table 1. Baseline Variables of All Patients and Patients Included in the Matching Study

Variable		All Patients Identified: IMRT (n = 213) #	%	PBT (n = 181) #	%	P	Patients Included in the Matching Study: IMRT (n = 94) #	%	PBT (n = 94) #	%	P
Risk Group**	Low	52	24.4	139	76.8	<0.001	52	55.3	52	55.3	1.00
	Intermediate	74	34.7	35	19.3		35	37.2	35	37.2	
	High	87	40.8	7	3.9		7	7.4	7	7.4	
Prior GI disorders*	No	196	92.0	159	87.8	0.17	80	85.1	83	88.3	0.52
	Yes	17	8.0	22	12.2		14	14.9	11	11.7	
Prior GU disorders*	No	154	72.3	157	86.7	<0.001	73	77.7	79	84.0	0.27
	Yes	59	27.7	24	13.3		21	22.3	15	16.0	
Age* (yrs)	40 – 49	1	0.5	3	1.7	0.001	0	0	0	0	0.38
	50 – 59	42	19.7	48	26.5		18	19.1	25	26.6	
	60 – 69	87	40.8	94	51.9		44	46.8	47	50.0	
	70 – 79	71	33.3	33	18.2		29	30.9	20	21.3	
	≥ 80	12	5.6	3	1.7		3	3.2	2	2.1	
Androgen deprivation therapy	No	91	42.9	164	90.6	<0.001	66	71.0	79	84.0	0.03
	Yes	121	57.1	17	9.4		27	29.0	15	16.0	
Hypertension	No	78	36.6	101	55.8	<0.001	31	33.0	51	54.3	0.003
	Yes	135	63.4	80	44.2		63	67.0	43	45.7	
Hemorrhoids	No	196	92.0	154	85.1	0.03	85	90.4	81	86.2	0.36
	Yes	17	8.0	27	14.9		9	9.6	13	13.8	
Diabetes mellitus	No	161	75.6	163	90.1	<0.001	72	76.6	81	86.2	0.09
	Yes	52	24.4	18	9.9		22	23.4	13	13.8	
ECOG PS	0	195	92.0	174	96.1	0.16	87	92.6	91	96.8	0.19
	1	15	7.1	7	3.9		7	7.4	3	3.2	
	2	2	0.9	0	0		0	0	0	0	
Pre-radiation GI toxicity grade	0	194	91.5	165	91.2	0.38	88	93.6	86	91.5	0.36
	1	18	8.5	14	7.7		6	6.4	6	6.4	
	2	0	0	2	1.1		0	0	2	2.1	
Pre-radiation GU toxicity grade	0	115	54.2	99	54.7	0.28	63	67.0	53	56.4	0.004
	1	90	42.5	69	38.1		31	33.0	31	33.0	
	2	7	3.3	12	6.6		0	0	10	10.6	
	3	0	0	1	0.6		0	0	0	0	
IPSS, Int'l Prostate Symptom Score	n	201		181		0.56	91		94		0.99
	Mean ± SD	7.7 ± 6.5		7.3 ± 6.2			6.9 ± 6.0		6.9 ± 5.8		
	Range	0 – 34		0 – 25			0 – 31		0 – 23		
BSS, Bowel Symptom Score	n	108		139		0.05	54		76		0.003
	Mean ± SD	94.8 ± 7.5		92.9 ± 7.9			96.6 ± 5.4		92.7 ± 9.3		

Original Article

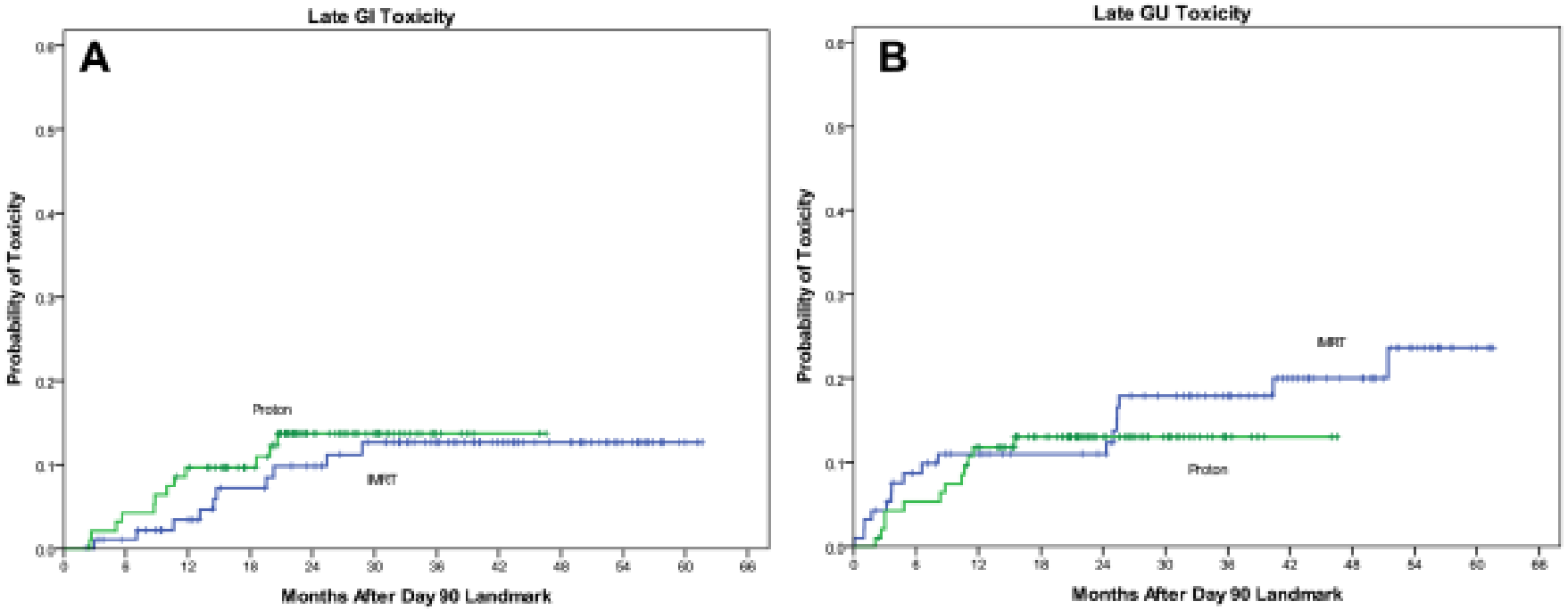
A Case-Matched Study of Toxicity Outcomes After Proton Therapy and Intensity-Modulated Radiation Therapy for Prostate Cancer

Penny Fang, MD[1]; Rosemarie Mick, MS[2]; Curtiland Deville, MD[1]; Stefan Both, PhD[1]; Justin E. Bekelman, MD[1]; John P. Christodouleas, MD, MPH[1]; Thomas J. Guzzo, MD, MPH[3]; Zelig Tochner, MD[1]; Stephen M. Hahn, MD[1]; and Neha Vapiwala, MD[1]

- N=394 contemporaneously treated (2010-2012), non-randomized proton therapy vs. IMRT cohorts using a case-matched analysis

A case-matched study of toxicity outcomes after proton therapy and intensity-modulated radiation therapy for prostate cancer

on multivariable analysis including direct adjustment for confounders and independent predictors, there were no significant differences in the risk of acute or late grade ≥2 GI or GU toxicities



(A) Late GI toxicity. IMRT versus PBT treatment comparison adjusted HR = 1.24, *P* = 0.62.
(B) Late GU toxicity. IMRT versus PBT treatment comparison adjusted HR = 0.56, *P* = 0.22.

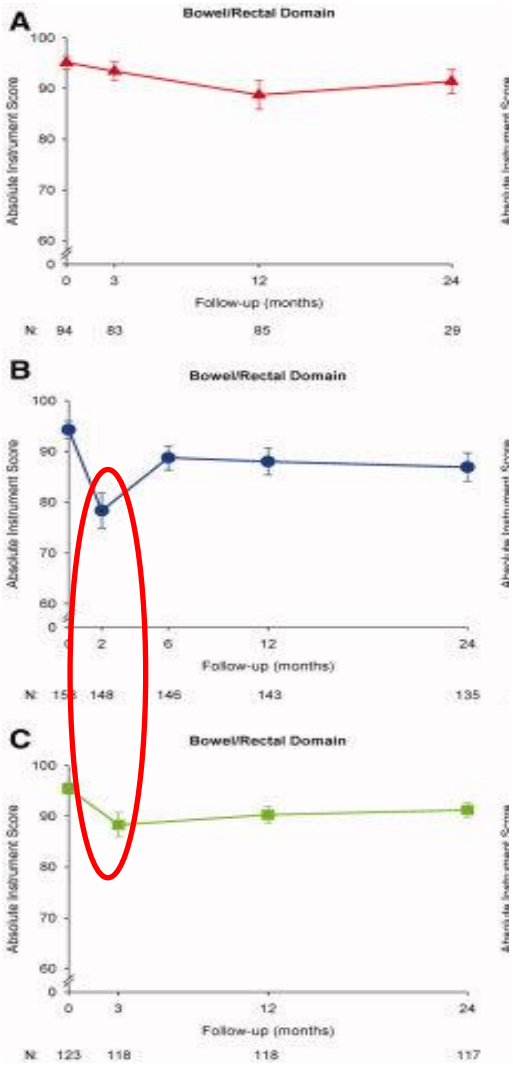
Cancer
Volume 121, Issue 7, pages 1118-1127, 25 NOV 2014 DOI: 10.1002/cncr.29148
http://onlinelibrary.wiley.com/doi/10.1002/cncr.29148/full#cncr29148-fig-0001

Clinical evidence – Patient Reported Outcomes

PBT
N=95

IMRT
N=153

3DCRT
N=123



Regarding GI outcomes:

1) At 2-3 mo, patients who received 3DCRT and IMRT reported a clinically meaningful **decrement in bowel QOL**, but not the proton cohort.

2) At 12-24 mo, all 3 cohorts reported clinically meaningful decrements in bowel QOL.

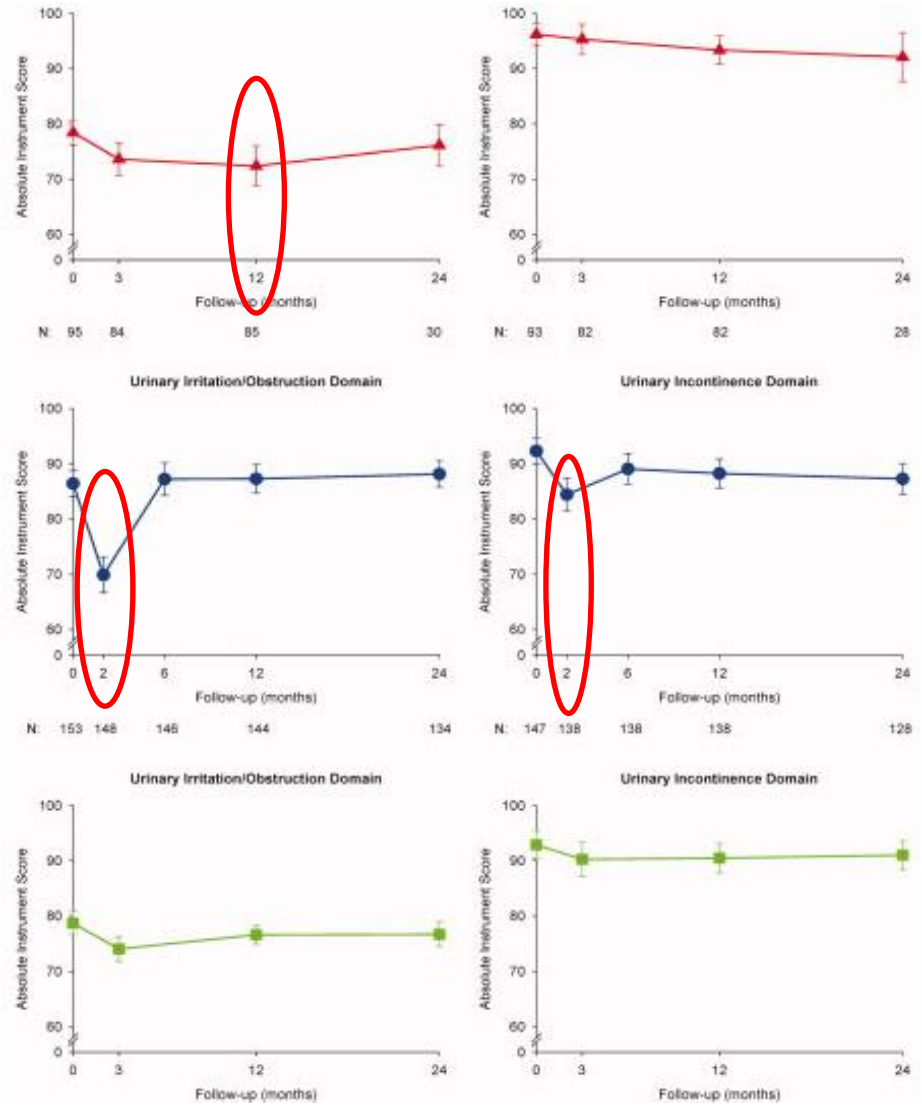
Gray PJ, et al. Cancer 2013

Clinical evidence – Patient Reported Outcomes

PBT
N=95

IMRT
N=153

3DCRT
N=123



GU:

1) At 2-3 mo, IMRT only reported clinically meaningful decrements in urinary irritation/obstruction and incontinence

2) At 12 mo, PBT cohort only reported clinically meaningful decrement in urinary irritation/obstruction.

3) At 24 mo, none of the 3 cohorts reported clinically meaningful changes in urinary QOL.

Gray PJ, et al. Cancer 2013

Comparative Effectiveness Summary

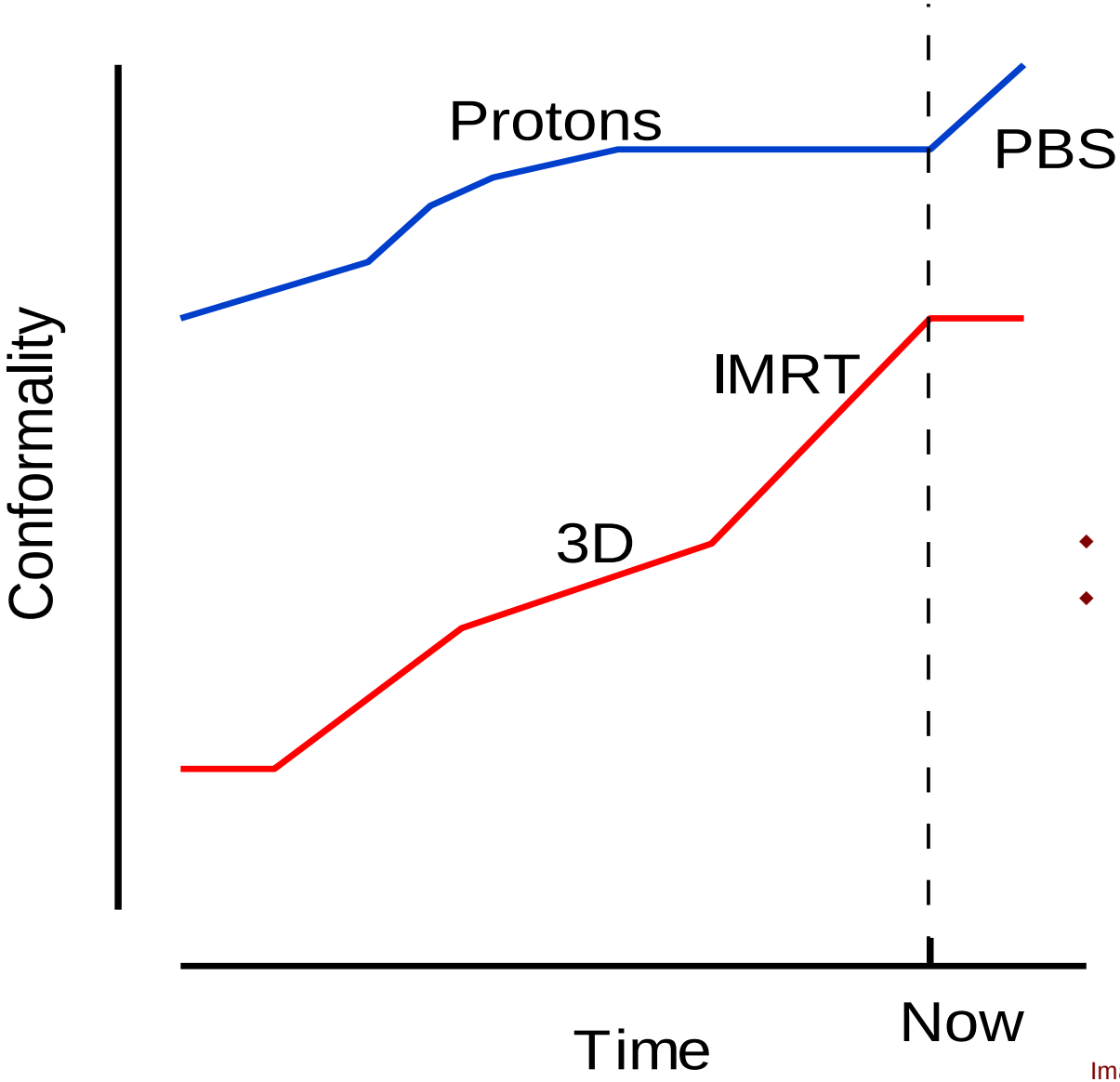
Comparative Effectiveness								Toxicity			
								Acute		Late	
	Modality	Time period	N (matched)	Inclusion	Dose IGRT	Follow-up mo	Toxicity measures	GI	GU	GI	GU
Sheets, JAMA 2012	IMRT	2002-2007	684	All PCa, excluding brachy, post-op	unknown	46 (0.4-88)	SEER-Medicare claims based (Dx and CPT codes) rates of GI, GU, ED, hip fractures, additional cancer tx (9mo post-RT) reported per 100 person years	N/A (excluded within 1 yr of RT)		17.7 (procedures)	7.6 (urinary incontinence procedures)
	PT		684			50 (0.3-90)				**21.4**	7.8
Yu, JNCI	IMRT	2008-2009	842	PCa ≥66-94 yo	unknown	6 mo 12 mo (N reduced at 12 mo)	Chronic Condition Warehouse Medicare claims based, 6 and 12 mo. GU (infection, upper urinary tract dysfunction, urethral stricture/ obstruction, incontinence, ED); GI (fistula, rectal repair, stenosis, bowel resection, other); and other toxicity (local musculoskeletal damage, red blood cell transfusion, systemic derangements, infection, nerve injury, and fractures).	N/A		3.6% 6mo 10.2% 12mo	**9.5%** 6mo 17.5% 12 mo
	PT		421							2.9% 6mo 9.9% 12mo	5.9% 6mo 18.8% 12mo
MGH, Cancer 2013	IMRT	2003-2006	153	PROSTQA 9 academic hospitals Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment	75.6-79.2 Gy 5-10 mm (with 5-mm to 7-mm rectal)	2-3 mo 12mo 24 mo	patient-reported outcomes data collected prospectively using validated instruments that assessed bowel and urinary quality of life (QOL). IMRT → EPIC PT → PCSI Differences in mean QOL scores were defined as those exceeding half the standard deviation of the baseline mean value	**Yes**	**Yes**	Yes 12mo Yes 24 mo	No 12mo No 24 mo
	PT	2004-2008	95	Low, int, and high risk	74.0-82.0 Gy 5mm PTV			No	No	Yes 12mo Yes 24 mo	**Yes 12mo** No 24 mo
Florida, Cancer 2014	IMRT	2003-2006	206	PROSTQA	75.6-79.4	6 mo 12 mo 24 mo	EPIC QOL. 5 domains, including urinary incontinence (UI) (4 questions), urinary irritative/obstructive (UO) (4 questions), bowel function (BS) (6 questions), sexual function (SS) (6 questions), and hormonal function (HF) (5 questions);			**Bowel at 6mo**	
	PT	2006-2010	1243	Low, int, and high risk	76-82 Gy						
Penn, Cancer 2015	IMRT	2010-2012	94	Low, int, and high risk	79.2/1.8 Gy Fiducials, daily kV	47 (5-65	CTCAE 3.0 gr≥2 (gr3)	13.8% (0)	28.7% (0)	10.8% (2.1)	18.3% (0)
	PT (PS and PBS)		94			29 (5-50)		4.3% (0)	21.3% (0)	12.8% (0)	12.8% (2.1)

Clinical evidence – Randomized controlled trial

Proton Therapy vs. IMRT for Low or Low-Intermediate Risk Prostate Cancer (PARTIQoL)

- **Currently recruiting (open 7/2012)**
- **Sponsor: Massachusetts General Hospital**
- **Collaborators:**
  - University of Pennsylvania
  - National Cancer Institute (NCI)
  - MD Anderson
- **ClinicalTrials.gov Identifier: NCT01617161**
- **Anticipated enrollment: 461**
- **Primary Outcome Measure:**
  - Compare the reduction in mean Expanded Prostate Cancer Index Composite (EPIC) **bowel scores at 24 mo**
- **Secondary Outcome Measures at 2yrs:**
  - Disease Specific Quality of Life as measured by patient-reported outcomes, perceptions of care and adverse events
  - Cost Effectiveness of PBT vs. IMRT under current conditions and model future cost-effectiveness for alternative treatment delivery and cost scenarios
  - Radiation Dose and Bowel, Urinary and Erectile Function - Develop predictive models to examine DVH associations
  - Identification and Evaluation Biomarkers of PCa Behavior (CTCs)
  - Disease-specific and overall survival
  - Development of late effects such as second cancers

Technical Considerations and Advances



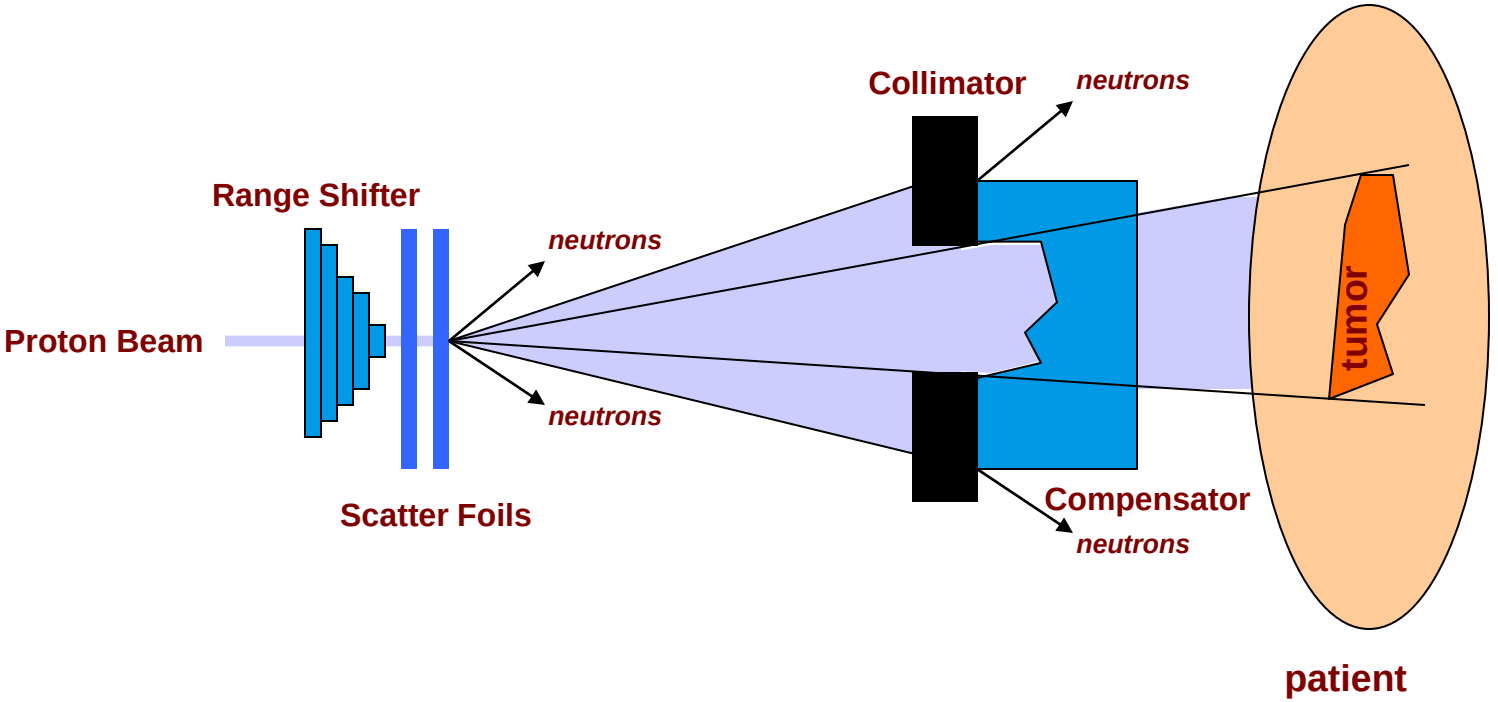
- IMRT is a mature technology
- Proton therapy is an immature technology
  - IMPT is still being developed

Image courtesy of Hanne Kooy, PhD, at Harvard, and Stefan Both, PhD, at MSKCC

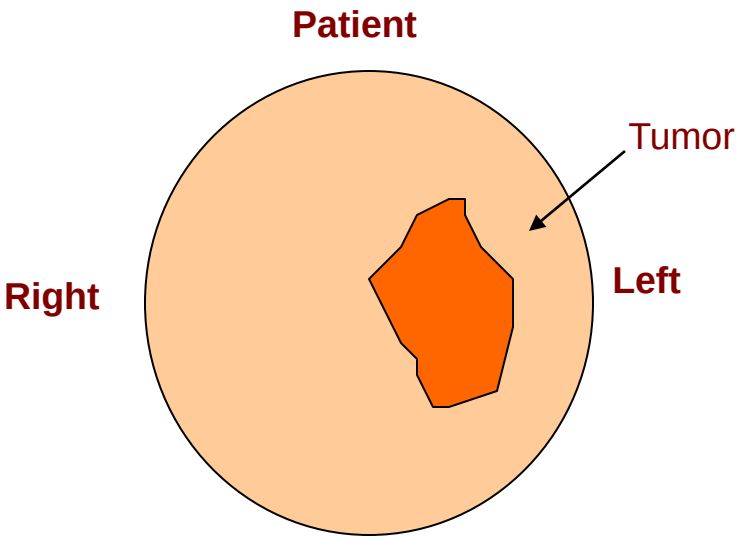
Technical Considerations and Advances

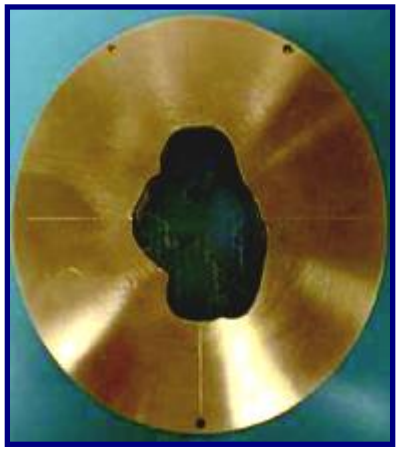
There are two approaches to form a desired dose distribution.

Historically what has been done:
1) Passive Scattering and modulation

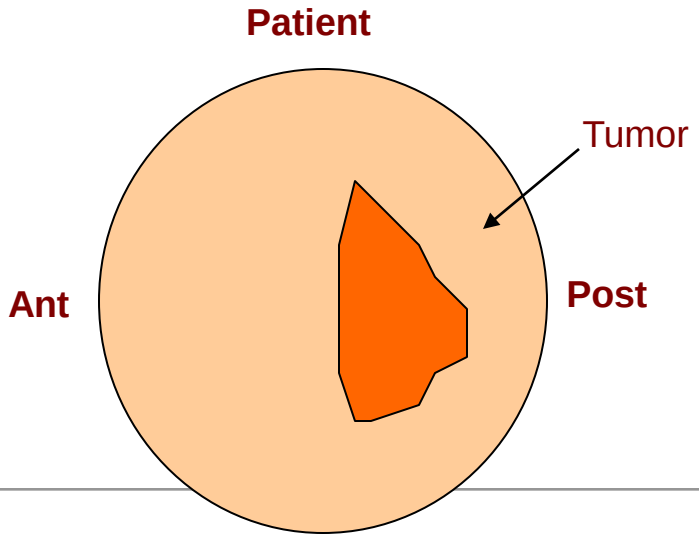


Technical Considerations and Advances





Aperture



Compensator

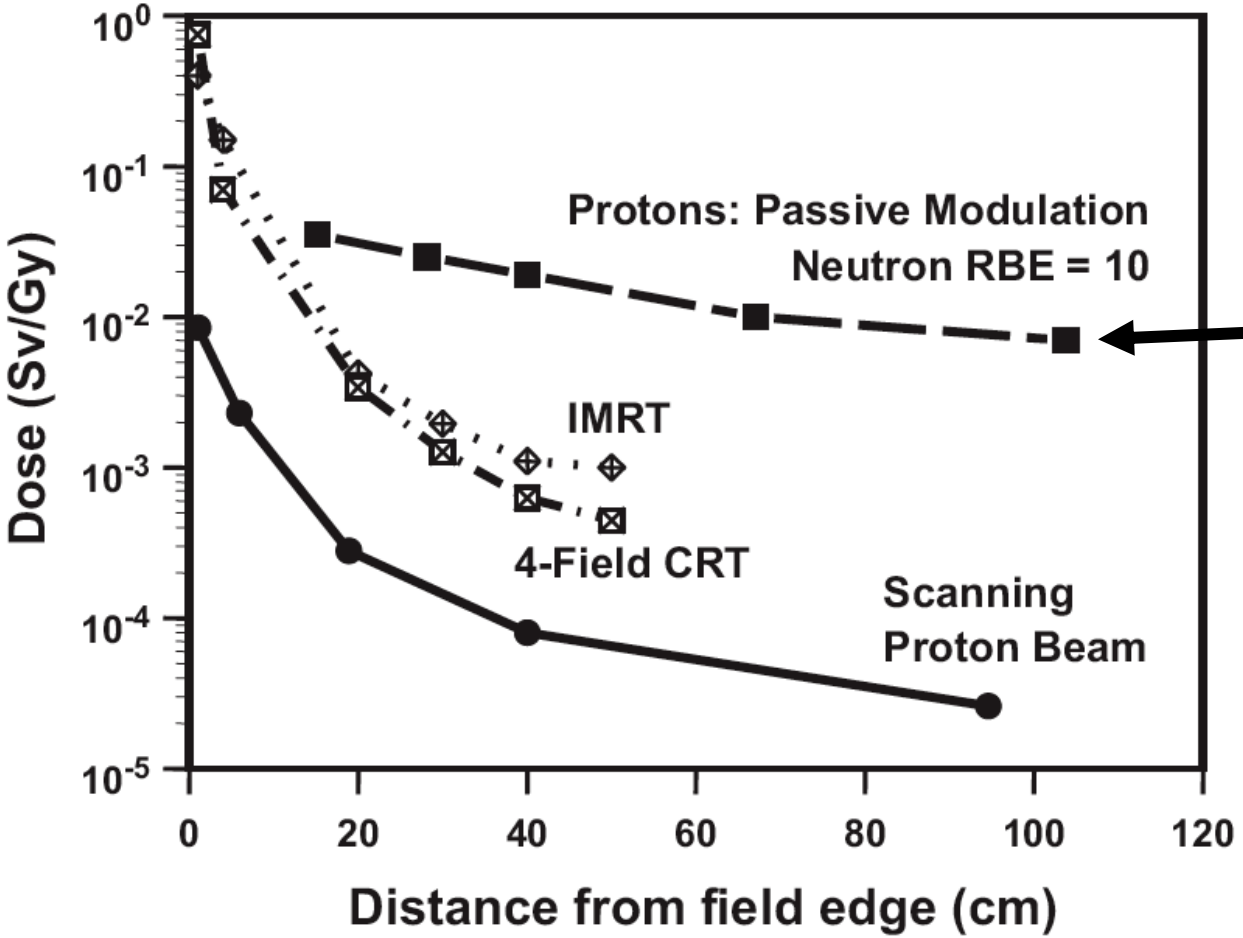
Technical Considerations and Advances

Caveats with scattered beam:

- More cumbersome project:
  - Apertures and compensators must be machined and QA'ed for each field.
  - Neutrons are produced by the scatterers and apertures.

Technical Considerations and Advances

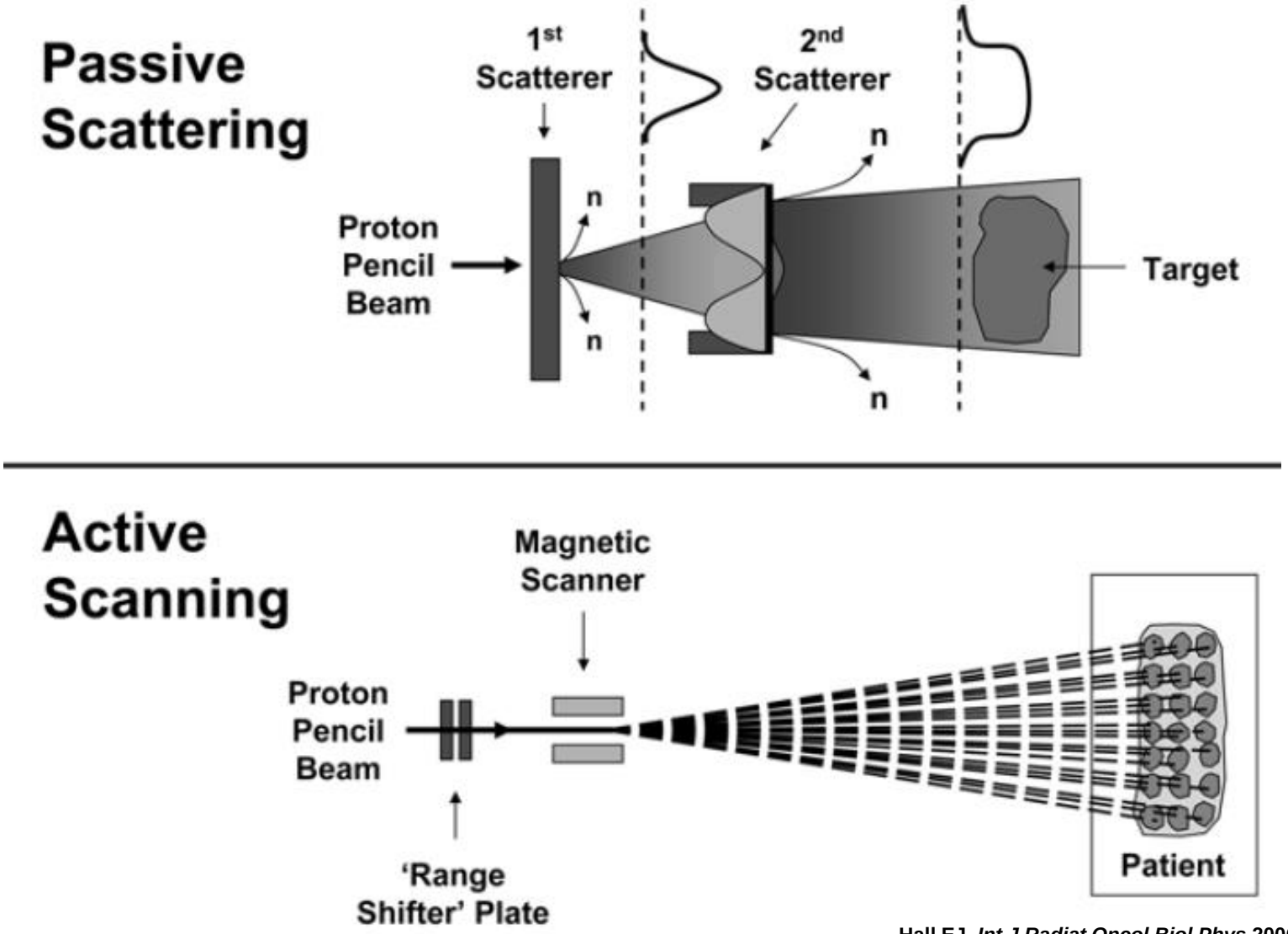
Neutron Contamination



Measurements on old Harvard cyclotron: extra "preabsorber" in head, was poorly tuned. Measurements recently done at Loma Linda are closer to IMRT curve.

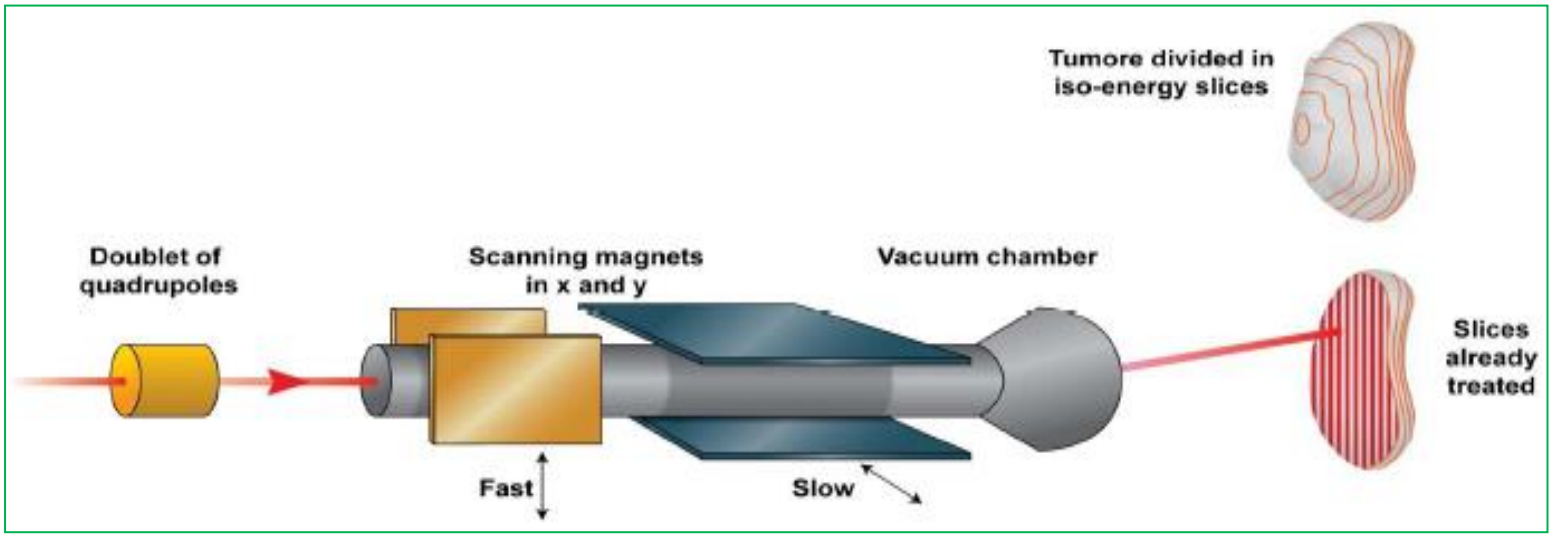
Hall EJ. Int J Radiat Oncol Biol Phys 2006;65(1):1-7

Technical Considerations and Advances



Hall EJ. *Int J Radiat Oncol Biol Phys* 2006;65(1):1-7

Pencil Beam Scanning

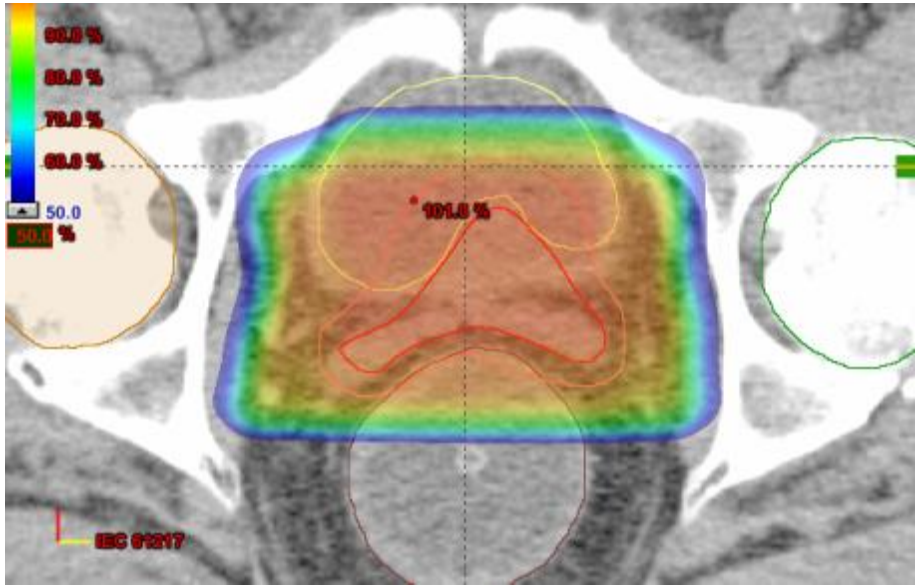


- Pencil Beam is scanned both laterally and in depth by changing its energy (Pedroni et al).
- Dose distribution is determined by weighting the pencil beam at each position within the field.
  - A target is divided into many layers
  - Each layer is divided into many spots
  - Spots are scanned one by one; layers by layers.
- Benefits:
  - Fully electronic and no mechanical parts
  - Homogenous dose conformed distally and proximally
- More recent and growing experience in the US

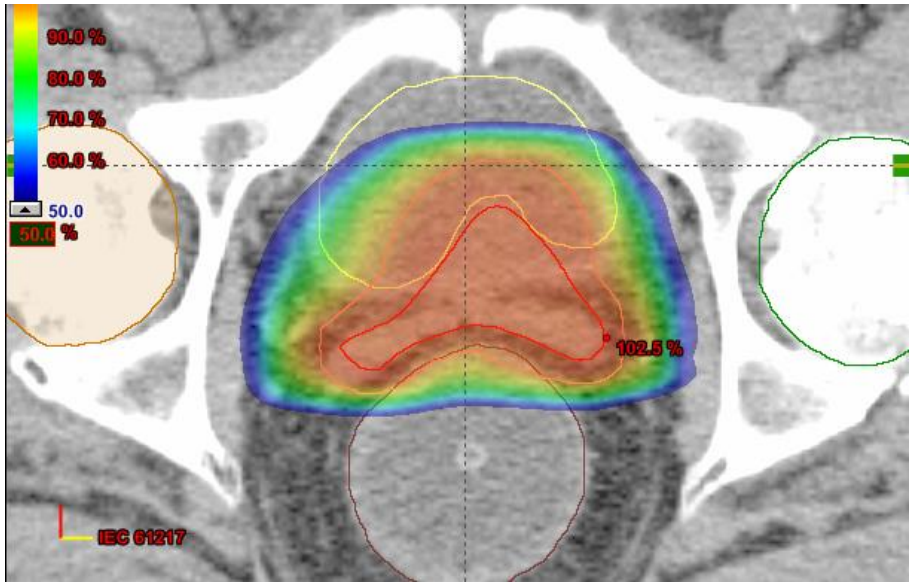
Technical Considerations and Advances

- **PBS improves normal tissue sparing, particularly when the SVs "droop" around the rectum or with a prominent median lobe**

Passive Scattering



PBS



Kirk M, et al. Practical Radiation Oncology 2015

Clinical evidence – Scattering vs Scanning

- MD Anderson Cancer Center reported:
  - 226 men receiving passively scattered (PS) and 65 spot scanning (SS) proton therapy
  - minimum 2 yr f/u on a prospective non randomized quality of life (QOL) protocol

  - Results:
    - statistically significant changes in sexual, urinary, and bowel EPIC summary scores.
    - Only bowel summary, function, and bother resulted in clinically meaningful decrements beyond treatment completion and through 24-month follow-up
    - Cumulative grade ≥ 2 GU and GI toxicity at 24 months were 13.4% and 9.6%, respectively, with only 1 grade 3 gastrointestinal toxicity (PS group) and no other grade ≥ 3 or greater GI or GU toxicity.
    - Argon plasma coagulation application was infrequent and not significantly different between groups: PS 4.4% vs. SS 1.5%.

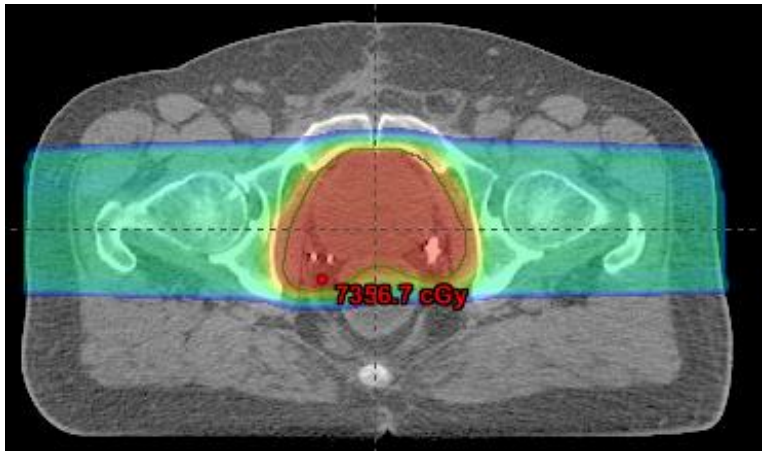
  - No statistically significant differences were appreciated between PS and SS regarding toxicity or QOL.

Pugh TJ, et al. Red Journal 2013

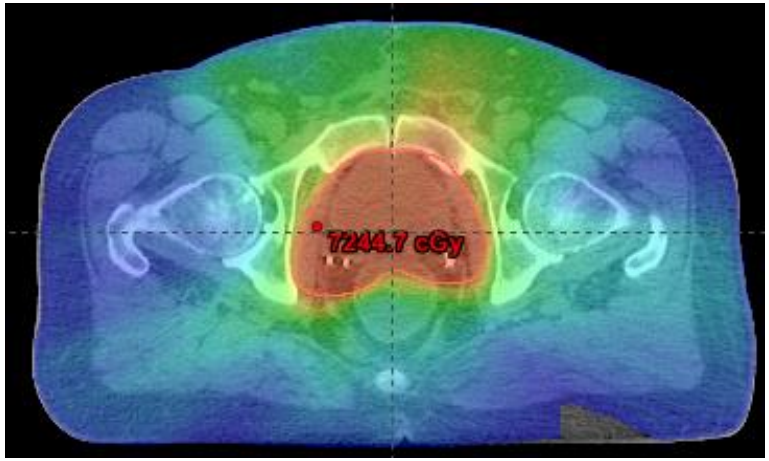
Future Directions – Post-op PT

Post-prostatectomy radiation

PBS



Rapid Arc

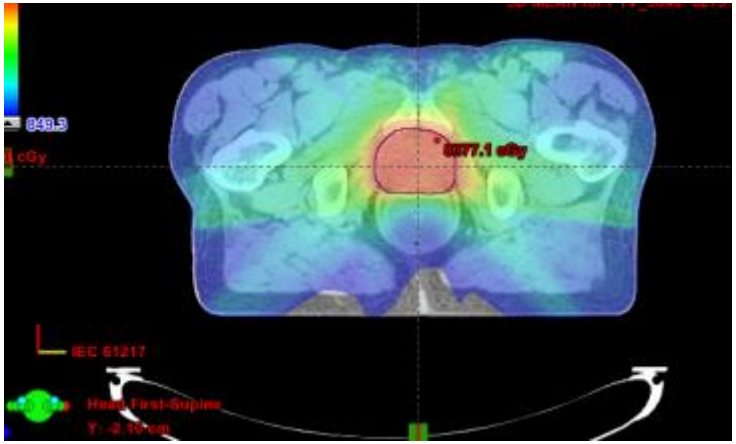


DVH Comparison Rapid Arc (☐) vs. PBS(Δ)

Deville C, et al. PTCOG 2014

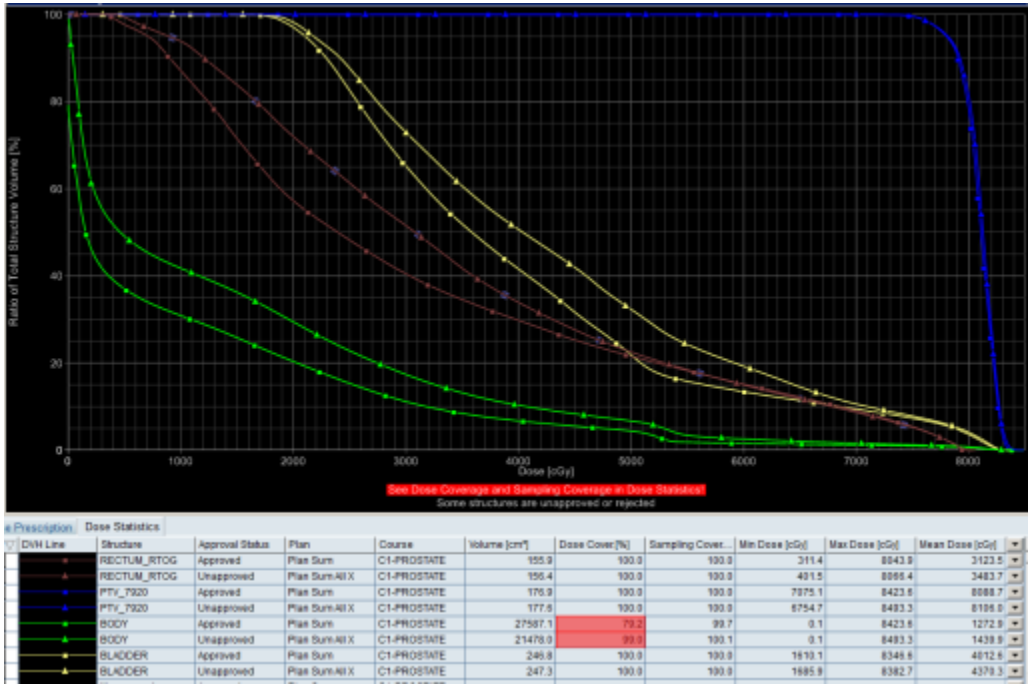
Clinical indication – pelvic nodal irradiation

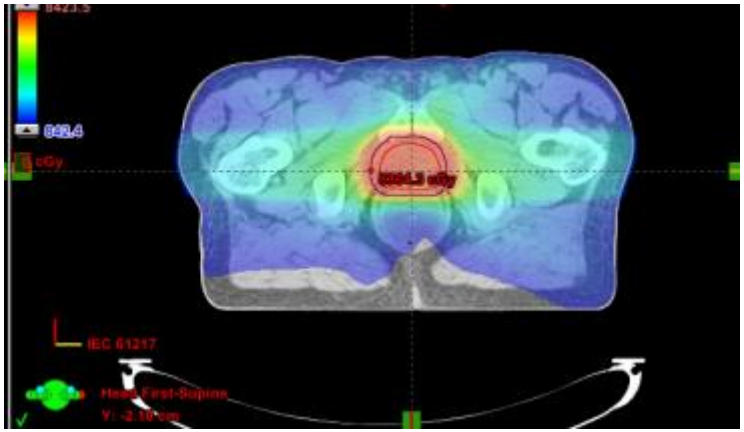
- **Proton therapy can be used as the prostate/SV boost for high risk prostate cancer after an initial course of whole pelvis irradiation with IMRT**



All IMRT

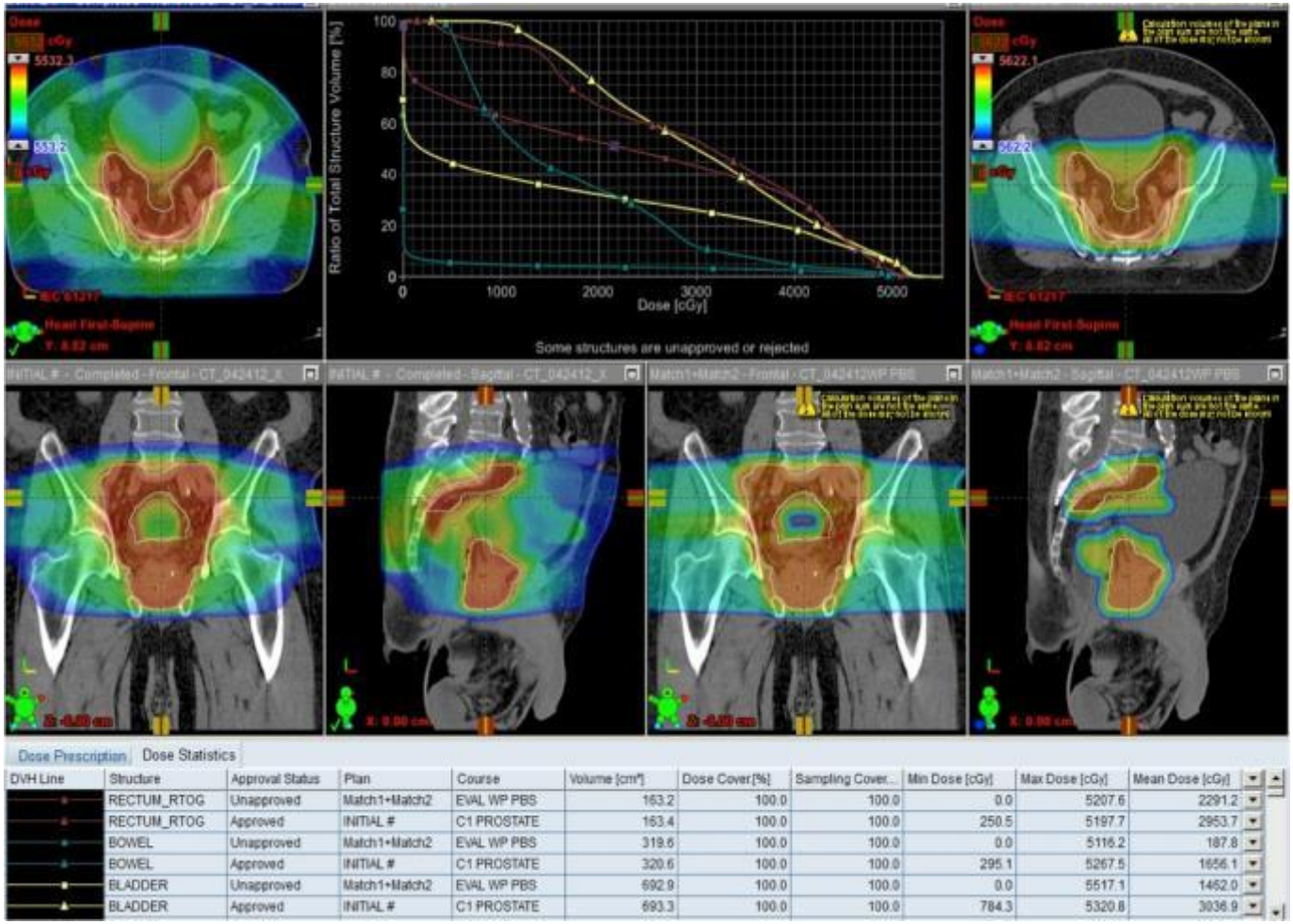
DVH Comparison All IMRT (☐) vs. IMRT + Proton (Δ)





Whole pelvis IMRT + proton boost

Future Directions – WP PT



DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover...	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	RECTUM_RTOG	Unapproved	Match1+Match2	EVAL WP PBS	163.2	100.0	100.0	0.0	5207.6	2291.2
	RECTUM_RTOG	Approved	INITIAL #	C1 PROSTATE	163.4	100.0	100.0	250.5	5197.7	2953.7
	BOWEL	Unapproved	Match1+Match2	EVAL WP PBS	319.6	100.0	100.0	0.0	5116.2	187.8
	BOWEL	Approved	INITIAL #	C1 PROSTATE	320.6	100.0	100.0	295.1	5267.5	1656.1
	BLADDER	Unapproved	Match1+Match2	EVAL WP PBS	692.9	100.0	100.0	0.0	5517.1	1462.0
	BLADDER	Approved	INITIAL #	C1 PROSTATE	693.3	100.0	100.0	784.3	5320.8	3036.9

- **Pelvic Nodal Irradiation (Whole Pelvis) Proton Therapy for High Risk Prostate Cancer Patients**
- **Potential to spare dose to the bladder, rectum, and bowel in the low and intermediate ranges compared to IMRT.**

Kirk M, Deville C, et al. PTCOG 2013

Summary

- The theoretical advantage for proton therapy is its physical properties and resultant dose distribution, i.e. Bragg Peak
  - generally results in reduced low and intermediate doses to non-target tissues.
- Proton therapy is an established and effective therapy for prostate cancer
- The fundamental question remains: is there a measurable, clinical meaningful benefit that justifies the current increase cost?
- Proton therapy for prostate cancer continues to evolve and has yet to achieve its full potential (vs. IMRT)
  - New delivery techniques, such as pencil beam scanning, will allow further advancement and refinement across expanding indications, such as post-prostatectomy and pelvic nodal irradiation in high risk prostate cancer.
- Rationale and deliberate study is needed to establish the relative clinical benefits/detriments and appropriate indications

Guidelines and Recommendations

Choosing Wisely®
An initiative of the ABIM Foundation

American Society for Radiation Oncology
ASTRO
TARGETING CANCER CARE

Five Things Physicians and Patients Should Question

1 Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules.

- Whole breast radiotherapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5–6 weeks, often followed by 1–2 weeks of boost therapy.
- Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (approximately 4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.

2 Don't initiate management of low-risk prostate cancer without discussing active surveillance.

- Patients with prostate cancer have a number of reasonable management options. These include surgery and radiation, as well as conservative monitoring without therapy in appropriate patients.
- Shared decision-making between the patient and the physician can lead to better alignment of patient goals with treatment and more efficient care delivery.
- ASTRO has published patient-directed written decision aids concerning prostate cancer and numerous other types of cancer. These types of instruments can give patients confidence about their choices, improving compliance with therapy.

3 Don't routinely use extended fractionation schemes (>10 fractions) for palliation of bone metastases.

- Studies suggest equivalent pain relief following 30 Gy in 10 fractions, 20 Gy in 5 fractions, or a single 8 Gy fraction.
- A single treatment is more convenient but may be associated with a slightly higher rate of retreatment to the same site.
- Strong consideration should be given to a single 8 Gy fraction for patients with a limited prognosis or with transportation difficulties.

4 Don't routinely recommend proton beam therapy for prostate cancer outside of a prospective clinical trial or registry.

- There is no clear evidence that proton beam therapy for prostate cancer offers any clinical advantage over other forms of definitive radiation therapy. Clinical trials are necessary to establish a possible advantage of this expensive therapy.

5 Don't routinely use intensity modulated radiotherapy (IMRT) to deliver whole breast radiotherapy as part of breast conservation therapy.

- Clinical trials have suggested lower rates of skin toxicity after using modern 3-D conformal techniques relative to older methods of 2-D planning.
- In these trials, the term "IMRT" has generally been applied to describe methods that are more accurately defined as field-in-field 3-D conformal radiotherapy.
- While IMRT may be of benefit in select cases where the anatomy is unusual, its routine use has not been demonstrated to provide significant clinical advantage.

ASTRO 2013

Guidelines and Recommendations

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Prostate Cancer

- 2015 – “The NCCN panel believes there is **no clinical evidence** supporting a **benefit or decrement** to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy **can be considered a reasonable alternative to X-ray based regimens** at clinics with appropriate technology, physics, and clinical expertise.”

- 2013 – “Proton therapy is not recommended for routine use at this time, since clinical trials have not yet yielded data that demonstrates superiority to, or equivalence of, proton beam and conventional external beam for treatment of prostate cancer.”

- 2009 – no mention

Thank You and Questions

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