



**Systematic Review of Brachytherapy &
Proton Beam Therapy for Low-Risk
Prostate Cancer: Preliminary Findings**

May 28, 2008

**Dan Ollendorf, MPH, ARM
Chief Review Officer**

Systematic Review Objectives

- To compare the potential clinical benefits of brachytherapy and proton beam therapy relative to standard radiation therapy (IMRT) among low-risk prostate cancer patients
 - Biochemical recurrence
 - Disease-specific and overall survival
- To compare the potential harms of such therapies
 - Gastrointestinal
 - Genitourinary
 - Sexual

Review Scope

- Patients with low-risk disease (D'Amico criteria):
 - Stage T1-T2a
 - Gleason score ≤ 6
 - PSA ≤ 10 ng/mL
- Treatments of interest:
 - Low-dose-rate brachytherapy (with I^{125} or Pd^{103} isotopes)
 - Proton beam therapy
 - IMRT (referent standard)
 - Active surveillance (to support economic modeling)

Major Exclusions

- Treatment variants:
 - High-dose-rate brachytherapy, LDR brachytherapy with adjuvant external beam radiation (where feasible)
 - Proton “boost” therapy
- Study types:
 - Without identifiable low-risk subgroup or preponderance of low-risk participants
 - Sample size <50, or outcomes reported in <50 patients
 - Non-English language

Outcomes Assessed

- Survival:
 - Overall
 - Disease-specific
- Freedom from biochemical recurrence
 - ASTRO-Phoenix definition (increase of 2+ ng/mL from nadir) or ASTRO 1997 (3 consecutive PSA rises from nadir)
 - Latter only included if study parameters support comparison to Phoenix:
 - Date of call 2+ years short of median follow-up (or available from K-M curves)
 - No backdating

Outcomes Assessed

- Morbidity:
 - Acute (≤ 90 days) and chronic/late
 - Genitourinary:
 - Acute urinary retention (brachytherapy only)
 - Incontinence (if recorded separately)
 - All GU (RTOG 2+)
 - Gastrointestinal (All GI, RTOG 2+)
 - Impotence/erectile dysfunction

Evidence Quality

- 6 reports from 2 RCTs:
 - Pd-103 vs. I-125 isotopes in permanent brachytherapy
 - Active surveillance vs. watchful waiting
- 1 report from non-randomized controlled study:
 - Brachytherapy vs. 3D-CRT
- 40 reports from cohort/case-control studies
- Remaining studies all uncontrolled case series

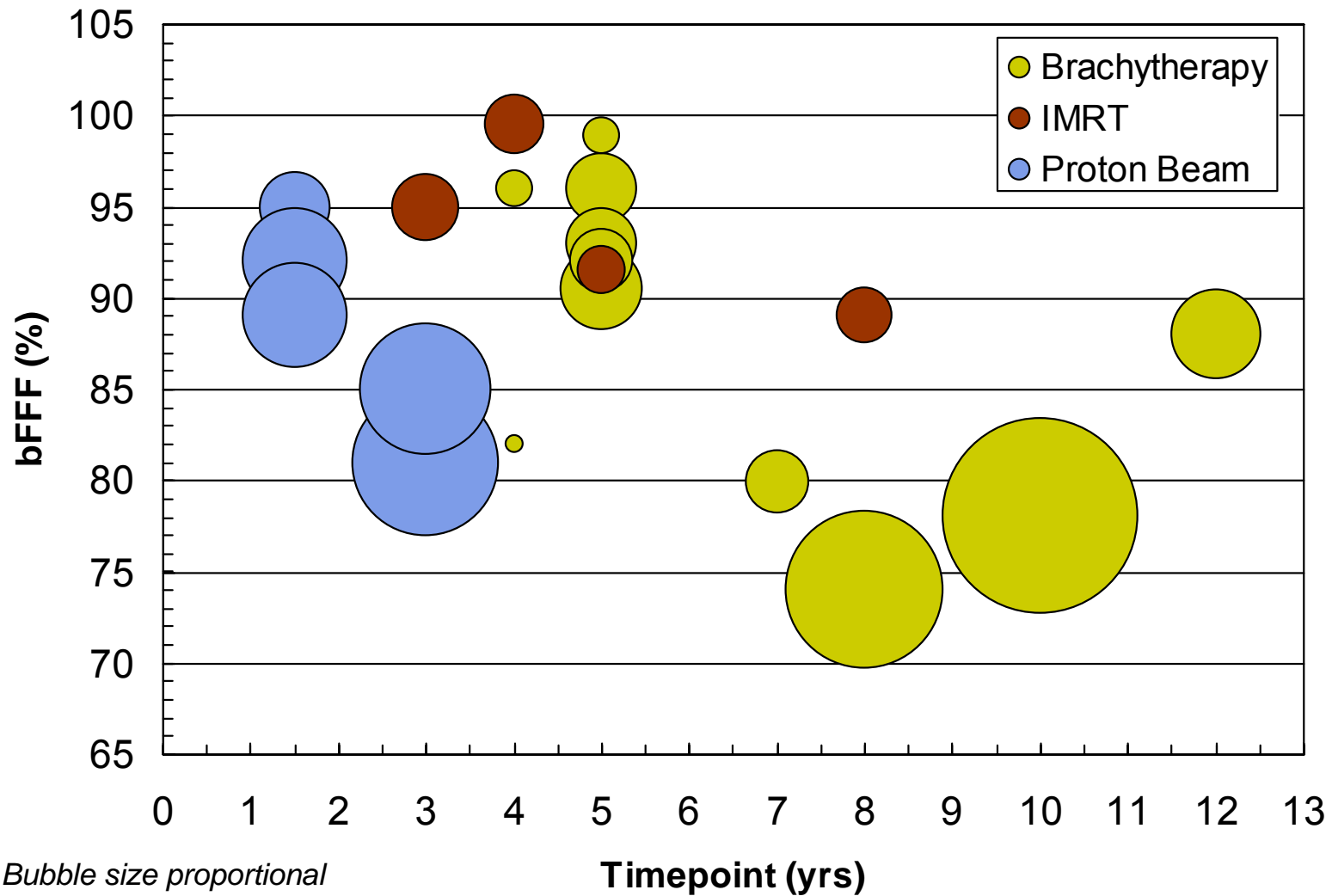
Systematic Review Findings

- Overall Survival
 - Not reported in proton or IMRT studies
 - Rates range from 60-98.6% at 3-10 years in 16 brachytherapy studies
 - Differential rate also reported by age (Tward 2006): 92.1% vs. 62.9% at 10 years for men <60 and 60+ years respectively
- Disease-Specific Survival
 - Also not reported in proton or IMRT studies
 - Rates range from 93-99% at 5-12 years in 6 brachytherapy studies:
 - Age-stratified rates in Tward study: 99.5% vs. 94.7%

Systematic Review Findings

- Biochemical Recurrence (K-M or Actuarial)
 - Proton beam: 5 included case series, all based on Loma Linda experience
 - IMRT: 4 single- or multi-institution case series (focus on higher dose delivery)
 - Brachytherapy: 12 included recent single- or multi-institution case series
- Significant ***differences*** in study design (e.g., timepoint, definition, sample size); significant ***overlap*** in findings

Biochemical Freedom from Failure



NOTE: Bubble size proportional to study sample size

Biochemical Freedom from Failure

- bFFF measures complicated by study heterogeneity:
 - Variable biochemical failure definitions
 - Definition of low-risk populations
 - Detail in reporting of adjuvant treatment received (e.g., external beam, adjuvant hormone therapy)
 - Population demographics

Harms

- Genitourinary
 - Incontinence only reported separately in brachytherapy studies (n=15)
 - Pooled rates similar regardless of whether RTOG grading used (1.6% vs. 1.8% respectively)
 - Acute urinary retention reported in 8 brachytherapy studies:
 - Rates similar (pooled: 13.3%; range: 12.1%-17.0%) across studies, with exception of 2 Israeli studies (1.7%-3.3%, excluded from pooled rate above)
 - Design/population issues in excluded studies?

All GU

- Acute Symptoms
 - Proton beam: 3 studies, no acute rates reported
 - IMRT: 4 studies, n=1,241, pooled rate 27.7% (range: 6.9%-49.0%)
 - Brachytherapy: 9 studies, n=1,859, pooled rate 39.1% (range: 9.7%-64.8%)

All GU

- Late Symptoms
 - Proton beam: 3 studies, n=1,828, pooled rate 5.4% (range: 5.0%-5.7%)
 - Additional study (Slater 2004) excluded because RTOG 3+ threshold employed
 - IMRT: 5 studies, n=2,183, pooled rate 13.3% (range: 3.5%-28.3%)
 - Brachytherapy: 11 studies, n=1,936, pooled rate 14.6% (range: 0.0%-40.3%)

All GI

- Acute Symptoms
 - Proton beam: 4 studies, no acute rates reported
 - IMRT: 4 studies, n=1,241, pooled rate 11.0% (range: 2.3%-50.3%)
 - Brachytherapy: 7 studies, n=1,177, pooled rate 3.3% (range: 0.9%-9.6%)

All GI

- Late Symptoms
 - Proton beam: 3 studies, n=1,828, pooled rate 13.5% (range: 3.4%-26.0%)
 - IMRT: 7 studies, n=2,779, pooled rate 5.8% (range: 1.6%-24.1%)
 - Brachytherapy: 16 studies, n=3,455, pooled rate 5.0% (range: 0.0%-12.8%)

ED/Impotence

- Limited (IMRT: 48%-49%) or no (proton beam) reporting for certain treatments
- Reported in 15 brachytherapy studies; baseline potency known in 7
 - Pooled results:
 - Overall (n=9901): 17.2% (range: 5.3%-45.0%)
 - Known prior potency (n=1389): 33.8% (range: 14.3%-43.0%)
- Best guess from AS literature suggests 17% incremental increase in ED during surveillance

Summary

- Little data on overall mortality; significant overlap in bFFF findings, complicated by study heterogeneity
- Heterogeneity also noted for evaluation of harms, but differences observed by treatment:
 - Brachytherapy appears to impart a higher risk of acute and late GU symptoms relative to proton beam:
 - Comparable rate of late GU effects relative to IMRT
 - Proton beam/IMRT associated with a higher risk of acute GI symptoms relative to brachytherapy
 - Protons appear to impart higher risk of late GI effects vs. brachytherapy or IMRT
- Little to no data on ED for comparative purposes

Key Questions/Next Steps

- Given heterogeneity issues with measures of bFFF, what cautions would you recommend in our reporting?
- Is the entire body of evidence on brachytherapy appropriate to include, or are there appropriate limits to impose?
- Focus of attention for modeling currently on long-term morbidity:
 - Are there short-term effects of particular interest, and for which treatments?
- Should we consider a net increase in ED relative to AS (e.g., 15-20%) for all treatments of interest?

Appendix: Evidence Tables

Table 1. Biochemical freedom from failure for patients with low-risk prostate cancer, by treatment type and biochemical failure definition

Therapy	Author	Year	Sample Size	Failure Definition	Median Follow-Up	Timepoint (Years)	Rate (%)
Brachytherapy	Martin	2005	396 (80% LR)	Phoenix	60.4 mo	5	90.5%
	Zelevsky	2007	319	Phoenix	63 mo	5	96.0%
	Stone	2007	2,188	Phoenix	42.5 mo	10	78.1%
	Lawton	2007	95	Phoenix	64 mo	5	98.9%
	Crook	2007	292 (95% LR)	Phoenix	>30 mo (min)	5	93.0%
	Colberg	2007	249	Phoenix	44 mo (mean)	5	92.0%
	Shah*	2006	28	Phoenix	63 mo	4	82.0%
	Shah*	2006	81	Phoenix	63 mo	4	96.0%
	Kuban	2006	2,693	Phoenix	63 mo	5	80.0%
	Zelevsky	2007	1,444	Phoenix	63 mo	8	74.0%
	Ciezki	2006	162 (90% LR)	Phoenix	73 mo	5	96.0%
	Potters	2005	481	Phoenix	82 mo	12	88.0%
	Ellis	2007	239	Phoenix	47.2 mo	7	79.9%
	Proton Beam	Slater	2004	1255 (60% LR)	ASTRO	62 mo	3
Slater		1999	315 (80% LR)	ASTRO	43 mo	1.5	95.0%
Slater		1998	643 (60% LR)	ASTRO	43 mo	1.5	92.0%
Rossi		2004	1038 (65% LR)	ASTRO	62 mo	3	85.0%
Rossi		1999	643 (55% LR)	ASTRO	43 mo	1.5	89.0%
IMRT	Vora	2007	145	Phoenix	60 mo	5	91.5%
	Eade	2008	216	Phoenix	43 mo	4	99.5%
	Zelevsky	2001	279	ASTRO	60 mo	3	95.0%
	Zelevsky	2006	203	Phoenix	84 mo	8	89.0%

LR: Low-risk; 100% of sample size unless otherwise noted

*Results in Shah study stratified by pre-operative and intra-operative planning groups

Table 2. Rate of acute genitourinary toxicity (RTOG grade ≥ 2), by treatment type.

Therapy	Author	Year	Sample Size	Median Follow-Up	Acute Timepoint	Rate (%)
Brachytherapy	Martin	2006	213 (69% LR)	63 mo	<1 yr	42.5%
	Lawton	2007	94	64 mo	6 mo	50.0%
	Block	2006	114	48.9 mo	3 mo	9.6%
	Morita	2004	95 (31% LR)	UNK	UNK	16.8%
	Zelevsky	2000	248 (75% LR)	48 mo	4 mo	57.3%
	Wallner*	2002	55	UNK	3 mo	27.0%
	Wallner*	2002	55	UNK	3 mo	26.0%
	Wallner	1996	92 (97% LR)	36 mo	w/in 1-2 wks	46.0%
	Kang	2001	139 (65% LR)	11 mo	UNK	64.7%
	Gelblum	1999	600 (70% LR)	37 mo	3 mo	43.2%
Proton Beam	Not Reported					
IMRT	Vora	2007	145 (80% LR)	48.1 mo	UNK	49.0%
	Eade	2008	216	43 mo	3 mo	6.9%
	Jani	2007	108 (50% LR)	UNK	UNK	37.0%
	Zelevsky	2002	772 (30% LR)	24 mo	3 mo	28.2%

LR: Low-risk; 100% of sample size unless otherwise noted

UNK: Unknown

*Results in Wallner 2002 study stratified by randomized treatment groups defined by isotope (I-125, Pd-103)

Table 3. Rate of late genitourinary toxicity (RTOG grade ≥ 2), by treatment type.

Therapy	Author	Year	Sample Size	Median Follow-Up	Actuarial Timepoint	Rate (%)
Brachytherapy	Martin	2006	213 (69% LR)	63 mo	12 mo	23.0%
	Lawton	2007	94	64 mo	2 yr	22.6%
	Momma	2006	86 (65% LR)	28.9 mo	3 yr	30.2%
	Block	2006	114	48.9 mo	12 mo	0.0%
	Zelevsky	1999	145	24 mo	5 yr	37.9%
	Zelevsky	2000	248 (75% LR)	48 mo	5 yr	40.3%
	Blank	2000	102 (42% LR)	60 mo	5 yr	5.9%
	Wallner	1996	92 (97% LR)	36 mo	12 mo	14.0%
	Peschel	2004	87 (52% LR)	55.1 mo (mean)	UNK	11.0%
	Peschel	2004	155 (80% LR)	44 mo (mean)	UNK	2.0%
	Gelblum	1999	600 (70% LR)	37 mo	3 yr	0.0%
Proton Beam	Slater	1999	315 (80% LR)	43 mo	3 yr	5.0%
	Slater	1998	643 (60% LR)	43 mo	3 yr	5.7%
	Schulte	2000	870 (65% LR)	39 mo	3 yr	5.4%
IMRT	Vora	2007	145 (80% LR)	48.1 mo	UNK	28.3%
	Eade	2008	216	43 mo	3 yr	3.5%
	Kirichenko	2006	489 (??% LR)	29.9 mo	3 yr	8.4%
	Zelevsky	2002	772 (30% LR)	24 mo	3 yr	15.0%
	Zelevsky	2006	561 (36% LR)	84 mo	8 yr	15.0%

LR: Low-risk; 100% of sample size unless otherwise noted

UNK: Unknown

Table 4. Rate of acute gastrointestinal toxicity (RTOG grade ≥ 2), by treatment type.

Therapy	Author	Year	Sample Size	Median Follow-Up	Acute Timepoint	Rate (%)
Brachytherapy	Martin	2006	213 (69% LR)	63 mo	<6 mo	0.9%
	Zelevsky	2007	367 (87% LR)	60 mo	< 1 yr	3.8%
	Lawton	2007	94	64 mo	6 mo	9.6%
	Zelevsky	1999	145	24 mo	3 mo	0.0%
	Zelevsky	2000	248 (75% LR)	48 mo	4 mo	5.6%
	Wallner*	2002	55	UNK	3 mo	0.0%
	Wallner*	2002	55	UNK	3 mo	0.0%
Proton Beam	Not Reported					
IMRT	Vora	2007	145 (80% LR)	48.1 mo	UNK	50.3%
	Eade	2008	216	43 mo	<3 mo	2.3%
	Jani	2007	108 (50% LR)	UNK	UNK	21.3%
	Zelevsky	2002	772 (30% LR)	24 mo	3 mo	4.5%

LR: Low-risk; 100% of sample size unless otherwise noted

UNK: Unknown

*Results in Wallner 2002 study stratified by randomized treatment groups defined by isotope (I-125, Pd-103)

Table 5. Rate of late gastrointestinal toxicity (RTOG grade ≥ 2), by treatment type.

Therapy	Author	Year	Sample Size	Median Follow-Up	Actuarial Timepoint	Rate (%)
Brachytherapy	Martin	2006	213 (69% LR)	63 mo	>6 mo	0.0%
	Zelevsky	2007	367 (87% LR)	60 mo	>12 mo	8.7%
	Lawton	2007	94	64 mo	2 yr	5.3%
	Momma	2006	86 (65% LR)	28.9 mo med	3 yr	12.8%
	Zelevsky	1999	145	24 mo	5 yr	11.0%
	Zelevsky	2000	248 (75% LR)	48 mo	5 yr	9.0%
	Blasko	2000	403 (80% LR)	58 mo	UNK	2.0%
	Blank	2000	102 (42% LR)	60 mo	5 yr	3.9%
	Wallner*	2002	55	UNK	UNK	1.0%
	Wallner*	2002	55	UNK	UNK	1.0%
	Peschel	2004	87 (52% LR)	55.1 mo (mean)	5 yr	4.0%
	Peschel	2004	155 (80% LR)	44 mo (mean)	5 yr	2.0%
	Vargas	2005	161 (92% LR)	40 mo	UNK	0.6%
	Ohashi	2007	227 (70% LR)	22 mo	UNK	4.8%
	Gelblum	2000	685 (48% LR)	48 mo	4 yr	6.9%
	Stone	1995	71 (85% LR)	24 mo (mean)	2 yr	4.2%
	Koutrovelis	2000	301 (80% LR)	26 mo	UNK	1.0%
	Proton Beam	Slater	1999	315 (80% LR)	43 mo	3 yr
Slater		1998	643 (60% LR)	43 mo	3 yr	21.0%
Schulte		2000	870 (65% LR)	39 mo	3 yr	3.4%
IMRT	Fonteyne	2007	241	42 mo	3 yr	12.0%
	Vora	2007	145 (80% LR)	48.1 mo	UNK	24.1%
	Eade	2008	216	43 mo	3 yr	2.4%
	Kirichenko	2006	489 (??% LR)	29.9 mo	3 yr	6.2%
	Jani	2007	355 (50% LR)	UNK	UNK	6.0%
	Zelevsky	2002	772 (30% LR)	24 mo	3 yr	4.0%
	Zelevsky	2006	561 (36% LR)	84 mo	8 yr	1.6%

LR: Low-risk; 100% of sample size unless otherwise noted

UNK: Unknown

*Results in Wallner 2002 study stratified by randomized treatment groups defined by isotope (I-125, Pd-103)