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

May 28, 2008

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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

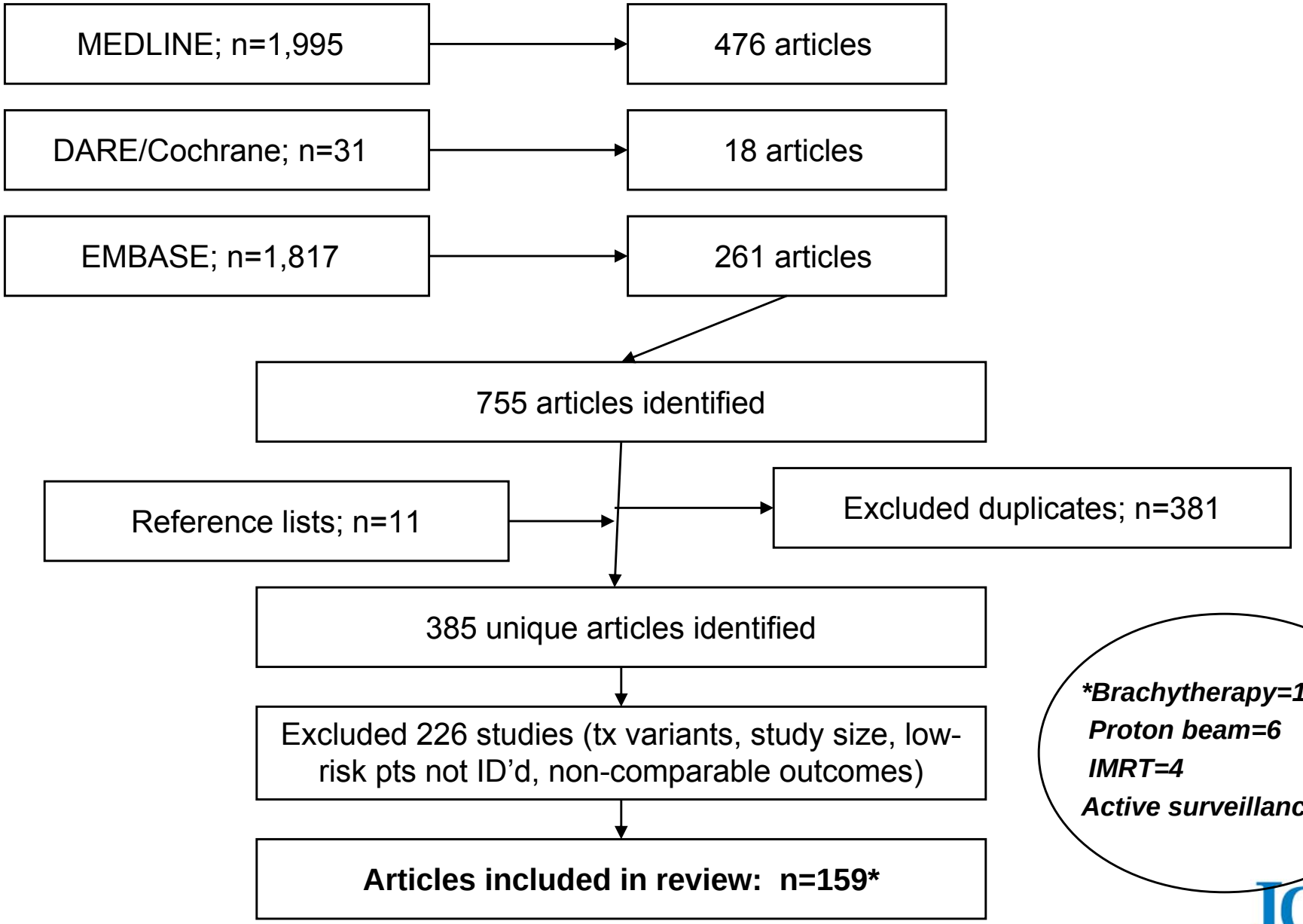
Outcomes Assessed

- 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

Literature Search Results



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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

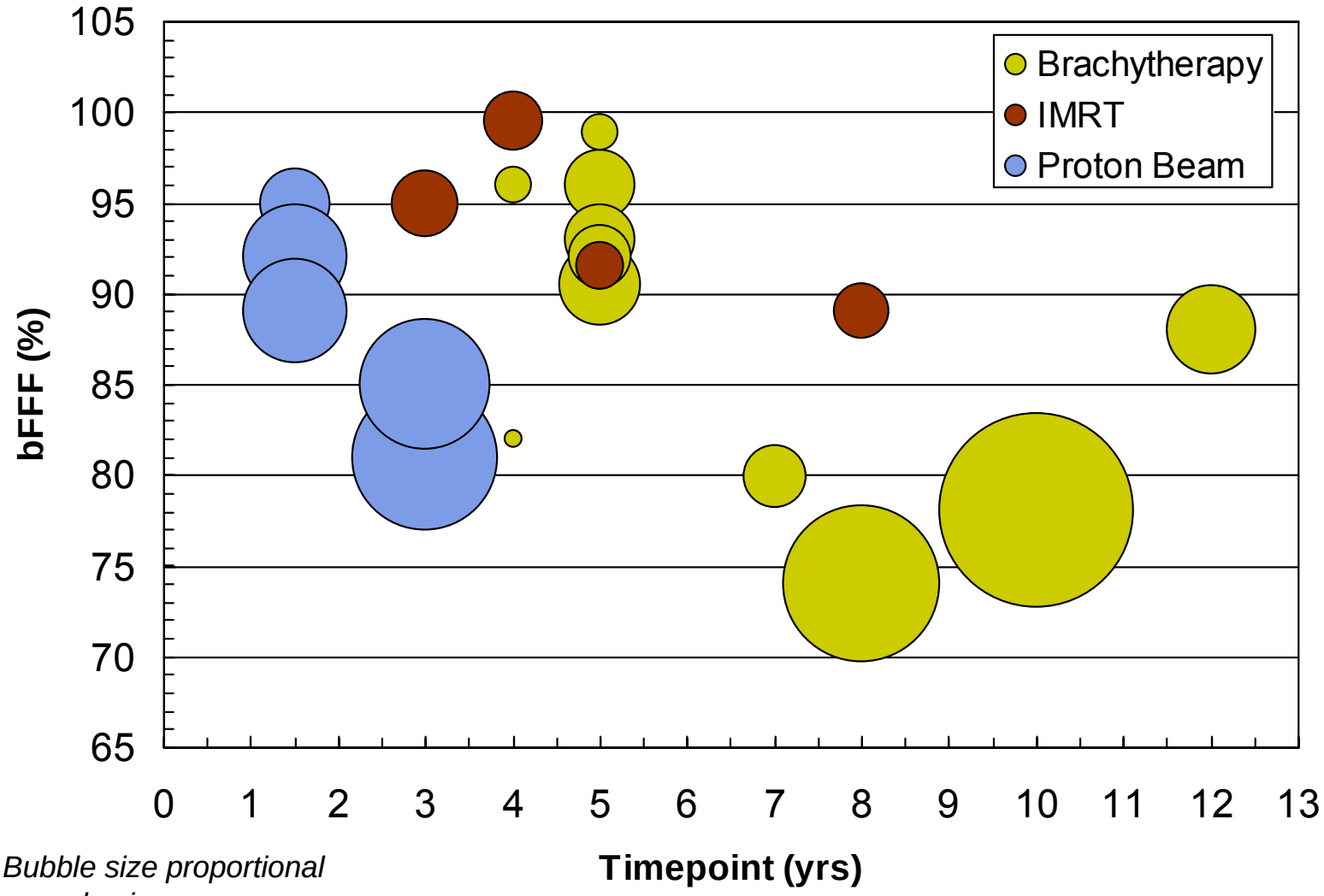
Systematic Review Findings

- 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

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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 hormonotherapy)
  - 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%
	Zelefsky	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%
	Zelefsky	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	81.0%
	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%
	Zelefsky	2001	279	ASTRO	60 mo	3	95.0%
	Zelefsky	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%
	Zelefsky	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%
	Zelefsky	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%
	Zelefsky	1999	145	24 mo	5 yr	37.9%
	Zelefsky	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%
	Zelefsky	2002	772 (30% LR)	24 mo	3 yr	15.0%
	Zelefsky	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%
	Zelefsky	2007	367 (87% LR)	60 mo	< 1 yr	3.8%
	Lawton	2007	94	64 mo	6 mo	9.6%
	Zelefsky	1999	145	24 mo	3 mo	0.0%
	Zelefsky	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%
	Zelefsky	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%
	Zelefsky	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%
	Zelefsky	1999	145	24 mo	5 yr	11.0%
	Zelefsky	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	26.0%
	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%
	Zelefsky	2002	772 (30% LR)	24 mo	3 yr	4.0%
	Zelefsky	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)

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Economic Model of Multiple Radiation Therapy Treatments for Low-Risk Prostate Cancer: Overview

June 4, 2008

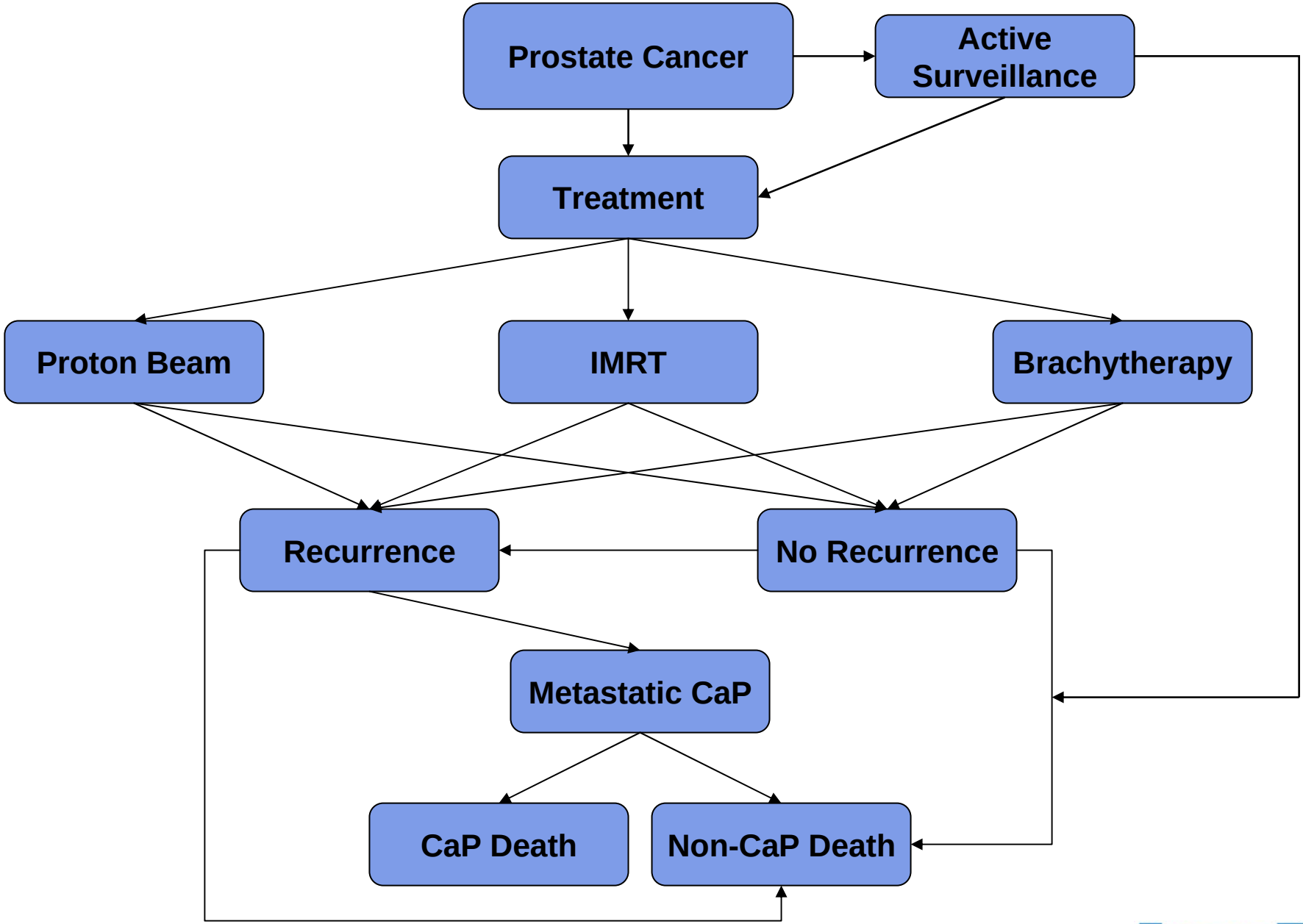
Julia Hayes, M.D.
Pamela McMahon, Ph.D.

ICER Model: Overview

- Markov cohort model
- One year cycle length
- Patient population
  - Low-risk disease (D'Amico criteria)
    - Gleason $\leq$6, PSA<10, stage $\leq$T2a
  - Base case: 65 year old man
    - Limited analyses will be conducted for 55 year old man, varying selected age-specific risks

ICER Model: Overview

- Multiple treatment strategies evaluated
  - Initial treatment at diagnosis
    - Brachytherapy
    - Proton beam therapy
    - IMRT (common referent standard)
  - Active surveillance
    - Treated upon clinical progression
    - Treated based on patient decision without progression



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ICER Model: Overview

- Health states will reflect presence or absence of treatment-related complications
  - Short- and long-term complications of all 3 treatments
  - Acute urinary retention with brachytherapy
- Utilities will be assigned to each health state
- Major cost categories will include:
  - Treatment-related (incl. management of complications)
  - Treatment-unrelated (e.g., annual medical costs, costs of terminal care)

ICER Model: Overview

- Primary Outcomes
  - Life Expectancy
    - Overall mortality, prostate cancer-specific mortality
  - Quality adjusted life expectancy
  - Cost-effectiveness ($/QALY)
- Secondary Outcomes
  - Biochemical freedom from failure
  - Cost per complication averted

Model Assumptions: Disease Course

- No men die of prostate cancer within 3 years of diagnosis
- All men who recur after definitive therapy will recur biochemically (BCR)
- Probability of progressing from BCR to metastatic disease same for all low-risk patients regardless of treatment
- Men die of prostate cancer only after the development of metastatic disease
- The probability of progressing from metastatic disease to death is the same regardless of treatment

Model Assumptions: Disease Course

- Active surveillance (AS)
  - Progression on AS is defined as
    - Increase in Gleason score or
    - Rapid PSA rise
  - No patients progress to metastatic disease while on AS
  - Patients who progress are treated with IMRT plus 6 months of androgen deprivation therapy (ADT)
  - 3 additional strategies for non-progressing patients who choose to be treated (1 each for brachytherapy, proton beam therapy, and IMRT respectively)
  - Patients who choose to be treated have same disease outcomes as those treated at diagnosis

Model Assumptions: Complications of Treatment/Disease

- All complications will be treated
- The occurrence of any complication is independent of the occurrence of a second complication

Model Assumptions: Complications of Treatment

- Long-term treatment complications
  - Erectile dysfunction (ED)
  - Genitourinary (e.g., incontinence)
  - Gastrointestinal (e.g., proctitis)
  - Occur at least 90 days after treatment
  - All long-term complications will have occurred by 24 months after treatment
  - All patients treated with 6 months ADT/IMRT will have ED during the year of treatment

Model Assumptions: Complications of Treatment

- Short-term complications
  - Genitourinary
  - Gastrointestinal
  - Acute urinary retention (for brachytherapy only)
    - All occur within 90 days of treatment
- Secondary malignancy after radiation (any tx):
  - Patients will receive associated disutility

Model Assumptions: Complications of Disease

- Active surveillance (AS)
  - ED
  - Incontinence
  - Occur beginning two years after placement on AS

ICER Model: Utilities

- Utility for each health state remains constant for life, with 2 exceptions:
  - Short-term complication utilities will be applied to first year only and will be adjusted to be proportionate to 3-month duration
  - ED from ADT therapy assumed to persist for year in which treatment given only
- Disutility for secondary malignancy will differ between brachytherapy and other forms of radiation
  - Will be subject to sensitivity analyses as well

Categories of Cost

- Annual medical care costs (unrelated)
- Terminal care costs
  - Prostate cancer vs. other cause
- Direct medical costs
  - Outpatient surveillance
  - Outpatient treatments
  - Patient out of pocket costs
- Patient time costs (e.g., time-in-therapy)

Direct Medical Costs

- Outpatient surveillance
  - Active surveillance
  - Post-treatment surveillance
- Outpatient treatments
  - Initial treatments
  - Management of treatment-related complications
- Patient copayments, coinsurance, and deductibles

Base Case

- Perspective = “payer plus”
  - Costs from CMS, RedBook + patient time + out-of-pocket
  - Sensitivity analyses will focus on payer-only perspective
- Time horizon = lifetime
- Discounting = 3% annually
- Constant 2007 US $
  - CPI adjusted, +/-medical care component
- For each CPT:
  - RVU*annual units*national conversion factor

Omitted Costs

- Caregiver time
- Costs incurred by all patients prior to entering model
  - Diagnosis, staging of prostate cancer
- Non-health care resource use costs
  - Add a constant to each year of life; little variation in survival across treatments
- Amortization costs (e.g., for proton-beam facility)