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

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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 $\leq 6$
  - PSA $\leq 10$ 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

MEDLINE; n=1,995 → 476 articles

DARE/Cochrane; n=31 → 18 articles

EMBASE; n=1,817 → 261 articles

755 articles identified

Reference lists; n=11 → Excluded duplicates; n=381

385 unique articles identified

Excluded 226 studies (tx variants, study size, low-risk pts not ID’d, non-comparable outcomes)

Articles included in review: n=159*  
*Brachytherapy=136  
Proton beam=6  
IMRT=4  
Active surveillance=13
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 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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Author</th>
<th>Year</th>
<th>Sample Size</th>
<th>Failure Definition</th>
<th>Median Follow-Up</th>
<th>Timepoint (Years)</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachytherapy</td>
<td>Martin</td>
<td>2005</td>
<td>396 (80% LR)</td>
<td>Phoenix</td>
<td>60.4 mo</td>
<td>5</td>
<td>90.5%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2007</td>
<td>319</td>
<td>Phoenix</td>
<td>63 mo</td>
<td>5</td>
<td>96.0%</td>
</tr>
<tr>
<td></td>
<td>Stone</td>
<td>2007</td>
<td>2,188</td>
<td>Phoenix</td>
<td>42.5 mo</td>
<td>10</td>
<td>78.1%</td>
</tr>
<tr>
<td></td>
<td>Lawnon</td>
<td>2007</td>
<td>95</td>
<td>Phoenix</td>
<td>64 mo</td>
<td>5</td>
<td>98.9%</td>
</tr>
<tr>
<td></td>
<td>Crook</td>
<td>2007</td>
<td>292 (95% LR)</td>
<td>Phoenix</td>
<td>&gt;30 mo (min)</td>
<td>5</td>
<td>93.0%</td>
</tr>
<tr>
<td></td>
<td>Colberg</td>
<td>2007</td>
<td>249</td>
<td>Phoenix</td>
<td>44 mo (mean)</td>
<td>5</td>
<td>92.0%</td>
</tr>
<tr>
<td></td>
<td>Shah*</td>
<td>2006</td>
<td>28</td>
<td>Phoenix</td>
<td>63 mo</td>
<td>4</td>
<td>82.0%</td>
</tr>
<tr>
<td></td>
<td>Shah*</td>
<td>2006</td>
<td>81</td>
<td>Phoenix</td>
<td>63 mo</td>
<td>4</td>
<td>96.0%</td>
</tr>
<tr>
<td></td>
<td>Kuban</td>
<td>2006</td>
<td>2,693</td>
<td>Phoenix</td>
<td>63 mo</td>
<td>5</td>
<td>80.0%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2007</td>
<td>1,444</td>
<td>Phoenix</td>
<td>63 mo</td>
<td>8</td>
<td>74.0%</td>
</tr>
<tr>
<td></td>
<td>Ciezki</td>
<td>2006</td>
<td>162 (90% LR)</td>
<td>Phoenix</td>
<td>73 mo</td>
<td>5</td>
<td>96.0%</td>
</tr>
<tr>
<td></td>
<td>Potters</td>
<td>2005</td>
<td>481</td>
<td>Phoenix</td>
<td>82 mo</td>
<td>12</td>
<td>88.0%</td>
</tr>
<tr>
<td></td>
<td>Ellis</td>
<td>2007</td>
<td>239</td>
<td>Phoenix</td>
<td>47.2 mo</td>
<td>7</td>
<td>79.9%</td>
</tr>
<tr>
<td></td>
<td>Slater</td>
<td>2004</td>
<td>1255 (60% LR)</td>
<td>ASTRO</td>
<td>62 mo</td>
<td>3</td>
<td>81.0%</td>
</tr>
<tr>
<td></td>
<td>Slater</td>
<td>1999</td>
<td>315 (80% LR)</td>
<td>ASTRO</td>
<td>43 mo</td>
<td>1.5</td>
<td>95.0%</td>
</tr>
<tr>
<td></td>
<td>Slater</td>
<td>1998</td>
<td>643 (60% LR)</td>
<td>ASTRO</td>
<td>43 mo</td>
<td>1.5</td>
<td>92.0%</td>
</tr>
<tr>
<td></td>
<td>Rossi</td>
<td>2004</td>
<td>1038 (65% LR)</td>
<td>ASTRO</td>
<td>62 mo</td>
<td>3</td>
<td>85.0%</td>
</tr>
<tr>
<td></td>
<td>Rossi</td>
<td>1999</td>
<td>643 (55% LR)</td>
<td>ASTRO</td>
<td>43 mo</td>
<td>1.5</td>
<td>89.0%</td>
</tr>
<tr>
<td>Proton Beam</td>
<td>Slater</td>
<td>2004</td>
<td>1255 (60% LR)</td>
<td>ASTRO</td>
<td>62 mo</td>
<td>3</td>
<td>81.0%</td>
</tr>
<tr>
<td></td>
<td>Slater</td>
<td>1999</td>
<td>315 (80% LR)</td>
<td>ASTRO</td>
<td>43 mo</td>
<td>1.5</td>
<td>95.0%</td>
</tr>
<tr>
<td></td>
<td>Slater</td>
<td>1998</td>
<td>643 (60% LR)</td>
<td>ASTRO</td>
<td>43 mo</td>
<td>1.5</td>
<td>92.0%</td>
</tr>
<tr>
<td></td>
<td>Rossi</td>
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<td>1038 (65% LR)</td>
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<td>3</td>
<td>85.0%</td>
</tr>
<tr>
<td></td>
<td>Rossi</td>
<td>1999</td>
<td>643 (55% LR)</td>
<td>ASTRO</td>
<td>43 mo</td>
<td>1.5</td>
<td>89.0%</td>
</tr>
<tr>
<td>IMRT</td>
<td>Vora</td>
<td>2007</td>
<td>145</td>
<td>Phoenix</td>
<td>60 mo</td>
<td>5</td>
<td>91.5%</td>
</tr>
<tr>
<td></td>
<td>Eade</td>
<td>2008</td>
<td>216</td>
<td>Phoenix</td>
<td>43 mo</td>
<td>4</td>
<td>99.5%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2001</td>
<td>279</td>
<td>ASTRO</td>
<td>60 mo</td>
<td>3</td>
<td>95.0%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2006</td>
<td>203</td>
<td>Phoenix</td>
<td>84 mo</td>
<td>8</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

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.

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

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.

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

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.

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

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.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Author</th>
<th>Year</th>
<th>Sample Size</th>
<th>Median Follow-Up</th>
<th>Actuarial Timepoint</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachytherapy</td>
<td>Martin</td>
<td>2006</td>
<td>213 (69% LR)</td>
<td>63 mo</td>
<td>&gt;6 mo</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2007</td>
<td>367 (87% LR)</td>
<td>60 mo</td>
<td>&gt;12 mo</td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td>Lawton</td>
<td>2007</td>
<td>94</td>
<td>64 mo</td>
<td>2 yr</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td>Momma</td>
<td>2006</td>
<td>86 (65% LR)</td>
<td>28.9 mo med</td>
<td>3 yr</td>
<td>12.8%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>1999</td>
<td>145</td>
<td>24 mo</td>
<td>5 yr</td>
<td>11.0%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2000</td>
<td>248 (75% LR)</td>
<td>48 mo</td>
<td>5 yr</td>
<td>9.0%</td>
</tr>
<tr>
<td></td>
<td>Blasko</td>
<td>2000</td>
<td>403 (80% LR)</td>
<td>58 mo</td>
<td>UNK</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>Blank</td>
<td>2000</td>
<td>102 (42% LR)</td>
<td>60 mo</td>
<td>5 yr</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>Wallner*</td>
<td>2002</td>
<td>55</td>
<td>UNK</td>
<td>UNK</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>Wallner*</td>
<td>2002</td>
<td>55</td>
<td>UNK</td>
<td>UNK</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>Peschel</td>
<td>2004</td>
<td>87 (52% LR)</td>
<td>55.1 mo (mean)</td>
<td>5 yr</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Peschel</td>
<td>2004</td>
<td>155 (80% LR)</td>
<td>44 mo (mean)</td>
<td>5 yr</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>Vargas</td>
<td>2005</td>
<td>161 (92% LR)</td>
<td>40 mo</td>
<td>UNK</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>Ohashi</td>
<td>2007</td>
<td>227 (70% LR)</td>
<td>22 mo</td>
<td>UNK</td>
<td>4.8%</td>
</tr>
<tr>
<td></td>
<td>Gelblum</td>
<td>2000</td>
<td>685 (48% LR)</td>
<td>48 mo</td>
<td>4 yr</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td>Stone</td>
<td>1995</td>
<td>71 (85% LR)</td>
<td>24 mo (mean)</td>
<td>2 yr</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td>Koutrovelis</td>
<td>2000</td>
<td>301 (80% LR)</td>
<td>26 mo</td>
<td>UNK</td>
<td>1.0%</td>
</tr>
<tr>
<td>Proton Beam</td>
<td>Slater</td>
<td>1999</td>
<td>315 (80% LR)</td>
<td>43 mo</td>
<td>3 yr</td>
<td>26.0%</td>
</tr>
<tr>
<td></td>
<td>Slater</td>
<td>1998</td>
<td>643 (60% LR)</td>
<td>43 mo</td>
<td>3 yr</td>
<td>21.0%</td>
</tr>
<tr>
<td></td>
<td>Schulte</td>
<td>2000</td>
<td>870 (65% LR)</td>
<td>39 mo</td>
<td>3 yr</td>
<td>3.4%</td>
</tr>
<tr>
<td>IMRT</td>
<td>Fonteyne</td>
<td>2007</td>
<td>241</td>
<td>42 mo</td>
<td>3 yr</td>
<td>12.0%</td>
</tr>
<tr>
<td></td>
<td>Vora</td>
<td>2007</td>
<td>145 (80% LR)</td>
<td>48.1 mo</td>
<td>UNK</td>
<td>24.1%</td>
</tr>
<tr>
<td></td>
<td>Eade</td>
<td>2008</td>
<td>216</td>
<td>43 mo</td>
<td>3 yr</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Kirichenko</td>
<td>2006</td>
<td>489 (??% LR)</td>
<td>29.9 mo</td>
<td>3 yr</td>
<td>6.2%</td>
</tr>
<tr>
<td></td>
<td>Jani</td>
<td>2007</td>
<td>355 (50% LR)</td>
<td>UNK</td>
<td>UNK</td>
<td>6.0%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2002</td>
<td>772 (30% LR)</td>
<td>24 mo</td>
<td>3 yr</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Zelefsky</td>
<td>2006</td>
<td>561 (36% LR)</td>
<td>84 mo</td>
<td>8 yr</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

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)
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 \(< 6\), PSA\(< 10\), stage \(< T2a\)
  - 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
Prostate Cancer

Treatment

Proton Beam

IMRT

Brachytherapy

Recurrence

No Recurrence

Metastatic CaP

CaP Death

Non-CaP Death

Active Surveillance
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)