Erectile Dysfunction (ED) after Radiotherapy (RT) for Prostate Cancer

William M. Mendenhall, MD
# Meta-Analysis of Probability of Maintaining Erectile Function after Treatment of Localized Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient no.</th>
<th>1-yr post treatment</th>
<th>Patient no.</th>
<th>2-yrs post treatment</th>
<th>Age adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT Alone</td>
<td>172</td>
<td>76%</td>
<td>No data</td>
<td>No data</td>
<td>80%</td>
</tr>
<tr>
<td>BT + EBRT</td>
<td>58</td>
<td>60%</td>
<td>58</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>EBRT</td>
<td>1343</td>
<td>55%</td>
<td>731</td>
<td>52%</td>
<td>68%</td>
</tr>
<tr>
<td>RP-Nerve Sparing</td>
<td>485</td>
<td>34%</td>
<td>128</td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>RP-Standard</td>
<td>3019</td>
<td>25%</td>
<td>2673</td>
<td>25%</td>
<td>16%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>264</td>
<td>13%</td>
<td>198</td>
<td>15%</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Abbreviations:** BT, brachytherapy; EBRT, external beam radiotherapy; RP, radical prostatectomy

Probability of Developing Erectile Dysfunction Due to RT Probably Plateaus after 2 to 3 Years
Etiology of Post-RT ED

- Conflicting data suggest that RT may damage the internal pudendal artery, posterior neurovascular bundles, and/or penile bulb
- Precise etiology remains unclear

Etiology of Post-RT ED

- Scatter radiation to testicles may cause decreased testosterone in patients treated with photon external beam RT (EBRT)
- Proton RT to prostate alone or prostate and proximal seminal vesicles does not result in decreased testosterone


• 207 patients with median pre-RT testosterone of 367.7 ng/dl
• Low or intermediate prostate cancer
• No androgen deprivation
• No testosterone supplements
• 70 to 72.5 Gy at 2.5 Gy/Fx
• Prostate or prostate and 2 cm proximal seminal vesicles
• 2008 to 2011

Post-Proton RT Testosterone Levels

- None of these changes were statistically significant

<table>
<thead>
<tr>
<th>Interval</th>
<th>Patient no.</th>
<th>Median post-RT change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion</td>
<td>207</td>
<td>-3.0 ng/dl</td>
</tr>
<tr>
<td>6 months</td>
<td>165</td>
<td>-6.0 ng/dl</td>
</tr>
<tr>
<td>12 months</td>
<td>116</td>
<td>+5.0 ng/dl</td>
</tr>
</tbody>
</table>

Prevention of Post-RT ED

- Daily Tadalafil (Cialis) on Sildenafil (Viagra)
- Limit RT to moderate and high risk volumes based on nomograms – i.e. MSKCC, Partin Tables
- Limit addition and duration of ADT
- Testosterone supplementation for low and intermediate risk patients after RT

Abbreviation: ADT, androgen deprivation therapy
RTOG 0831

- 242 patients between 2009 and 2012
- Intact erectile function
- EBRT, 63%; brachytherapy (BT), 37%
- Randomized to 24 weeks of Cialis 5 mg per day or placebo
- Erectile function (EF) was assessed prior to RT, at weeks 2 and 4, and between weeks 20 and 24
- Primary outcome was EF between weeks 28 and 30 after initiation of RT; secondary endpoints included EF at 1 year
- Assessed with International Index of Erectile Function

There was no significant improvement in EF at 28 to 30 weeks or at 1 year between daily Cialis and placebo.

MSKCC-Mt. Sinai Trial

- 202 patients with localized prostate cancer
- RT with EBRT (21%), BT (44%), or EBRT and BT (35%)
- ADT (10%)
- 2:1 randomization to Viagra 50 mg/day or placebo beginning 3 days prior to RT and continuing for 6 months
- EF was assessed with IIEF at 3, 6, 9, 12, 18, and 24 months after RT

**MSKCC-Mt. Sinai Trial**  
**12-month Outcomes**

- Better likelihood of mild or no ED with Viagra (73% vs 50%; p=.024)
- Better overall satisfaction with Viagra (p=.027)
- Better IIEF scores with Viagra (p=.043)

• EF (p=.172) and IIEF (p=.09) were no different
• Overall satisfaction was higher with Viagra (p=.033)
• Functional erection without meds was 81.6% in the Viagra arm (having been off Viagra for 18 months) and 56.0% in the placebo arm (p=.045)

NCCN Risk Groups

- Low – $T_{1C}$ to $T_{2A}$, PSA $\leq 10$, GS $\leq 6$
- Intermediate – $T_{2B}$ to $T_{2C}$ or PSA 10.1 to 19.9 or GS 7
- High - $\geq T_{3A}$ or PSA $\geq 20$ or GS $\geq 8$

GS, Gleason score
Limiting RT Volumes

- CT simulation fused with MR
  - MR better identifies apex and base
  - CT overestimates size of prostate
- Low risk – prostate with 4 to 6 mm margins
- Intermediate risk – prostate and 2 cm proximal SV
- High risk
  - Risk of positive nodes <15% - prostate and proximal SV
  - Risk of positive nodes ≥15% - prostate, proximal seminal vesicles, and pelvic nodes

CT, computed tomography; MR, magnetic resonance; SV, seminal vesicles
Elective Pelvic Node Irradiation (ENI)

• ENI reduces risk of pelvic node recurrence
• ENI probably does not improve survival
• Consider ENI when risk of positive nodes ≥15% based on Partin tables and MSKCC nomogram

Proton RT – Intermediate Risk
UFHPTI

• 536 patients between 2006 and 2010
• 98% received 78 to 82 Gy at 2 Gy/Fx
• Treatment planning CT fused with MR
• Protons alone to prostate and proximal 2 cm of seminal vesicles with 4 to 6 mm margins
• 9.7% received ADT
• Median follow-up – 4.9 years
• Treatment planning CT fused with MR

• $T_2$ – 34%
• PSA 10.1 to 19.9 – 26%
• GS – 4+3 – 27%
• >2 intermediate risk factors – 22%

### Proton RT – Intermediate Risk UFHPTI

<table>
<thead>
<tr>
<th>5-year outcomes</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>bPFS</em></td>
<td>95.4%</td>
</tr>
<tr>
<td><em>DMFS</em></td>
<td>98.9%</td>
</tr>
<tr>
<td><em>CSS</em></td>
<td>99.6%</td>
</tr>
<tr>
<td><em>OS</em></td>
<td>95.3%</td>
</tr>
</tbody>
</table>

*Abbreviations: bPFS, biochemical progression; DMFS, distant metastasis-free survival; CSS, cause-specific survival; OS, overall survival*

- MVA – ≥ intermediate risk factors associated with increased risk of biochemical failure
- ADT did not improve 5-year *bPFS*

Abbreviations: MVA, multivariate analysis
Proton RT – High Risk UFHPTI

- 245 patients between 2006 and 2010
- 94% received ≥78 Gy
- Protons alone to prostate and proximal seminal vesicles (83%) or combined with IMRT to pelvic nodes (17%)
- ADT was recommended to all and received by 67% (59% for 6 months; 8% for ≥18 months)
- Concomitant weekly docetaxel – 26%

Abbreviation: IMRT, intensity-modulated radiotherapy
Proton RT – High Risk
UFHPTI

<table>
<thead>
<tr>
<th>T-stage</th>
<th>( T_{1C} )</th>
<th>49%</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{2A}-T_{2B} )</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>( T_{2C} )</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>( T_3 )</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>6-7</th>
<th>16%</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>9-10</td>
<td>31%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSA</th>
<th>&lt;10</th>
<th>59%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

Docetaxel was not associated with improved outcomes

Pelvic node RT did not result in improved bPFS (64% with ENI; 76% without ENT; p=.09)

Erectile Function after Proton RT
UFHPTI

- 255 men ≤60 years
- Low risk – 143 patients
- Intermediate risk – 106 patients
- High risk – 6 patients
- No ADT
- Potency = erection firm enough for sexual intercourse
- Baseline and follow-up with Expanded Prostate Index Composite (EPIC)
- Median follow-up – 5 years

Ho et al. 2015.
Erectile Function after Proton RT
UFHPTI

- 5-year bPFS, 98.6%
- 5-year overall survival, 99.2%
- 5-year CSS, 100%
- 3 patients who failed (1 high risk, 2 intermediate risk) were alive at 5 years.

Ho et al. 2015.
Erectile Function after Proton RT UFHPTI

• Median sexual function score declined from 84 at baseline to 69 after 2 years and then stabilized
• Potency declined from 90% at baseline to 71% at 2 years and stabilized at 66%
• MVA – EPIC sexual summary score was the only factor associated with potency (p.0002)
• 5 year potency rates were:

<table>
<thead>
<tr>
<th>Baseline score</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>88%</td>
</tr>
<tr>
<td>99-68</td>
<td>61%</td>
</tr>
<tr>
<td>&lt;68</td>
<td>40%</td>
</tr>
</tbody>
</table>

Ho et al. 2015.
Erectile Dysfunction after RT
Testosterone Supplementation

• If a low or intermediate risk patient is biochemically disease free after RT with a testosterone level of 500, would you initiate treatment (ADT) to lower it?
• If not, then why would you not place a similar patient with a testosterone of 150 on a testosterone supplement?
Erectile Dysfunction after RT
Testosterone Supplementation

- Androgel Daily
- Depotestosterone IM every 1 to 2 weeks
Erectile Dysfunction after RT
UFHPTI

- 23 patients s/p proton RT (2006-2012) and biochemically disease free
- Low risk – 9 patients
- Intermediate risk – 12 patients
- High risk – 2 patients
- Low serum testosterone with symptomatic hypogonadism
- Median follow-up, 38 months; median follow-up after testosterone supplementation, 14 months

Erectile Dysfunction after RT UFHPTI

- After 1 to 6 months on testosterone supplements, median serum testosterone level increased from 238 to 497
- No patient experienced biochemical failure
- Median PSA did not rise
- Median EPIC sexual summary, sexual function, and sexual bother scores all increased
- Potency rates increased from 50% to 68% after 7 months
- No cardiac complications

Erectile Dysfunction after RT

- Probability of ED after RT is about 25 to 30%
- Mechanism is unclear
- Baseline EPIC sexual summary score is most predictive post-RT potency
- Unclear whether significant decrease in RT volume reduces risk of ED (but it results in decreased risk of other complications)
- Unclear whether erectile aids (i.e., Cialis; Viagra) reduces risk of ED
- Testosterone supplementation is probably safe and improves potency for low-intermediate risk patients with low testosterone levels
Erectile Dysfunction after RT

Like many things in life –
“Use it or lose it!”