Modern Dose Fractionation and Treatment Techniques for Definitive Prostate RT

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Disclosures

• Recently began offering and implanting SpaceOAR in my clinic
  - No financial obligations to or income received from Augmenix
Outline

• Screening
• ProtecT Trial
• RadBio of Prostate AdenoCA
• EBRT + brachytherapy boost
• Hypofractionated EBRT
• SBRT
• Immobilization and OAR sparing

Screening: Myth Busters

DRE  
PSA ?
PSA screening trials

<table>
<thead>
<tr>
<th></th>
<th>PLCO (&quot;US&quot;)</th>
<th>ERSPC (&quot;European&quot;)</th>
<th>Goteberg (&quot;Swedish&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Men</td>
<td>76,693</td>
<td>162,388</td>
<td>20,000</td>
</tr>
<tr>
<td>Age Range</td>
<td>55-74</td>
<td>55-69</td>
<td>50-64</td>
</tr>
<tr>
<td>Screening group</td>
<td>PSA q1yr x6, DRE qyr x4</td>
<td>PSA q4yr</td>
<td>invitation to PSA q2 yrs</td>
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<tr>
<td>Control group</td>
<td>'usual' care</td>
<td>no screening</td>
<td>no screening</td>
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<tr>
<td>Med flu (years)</td>
<td>13</td>
<td>13</td>
<td>14 yrs</td>
</tr>
<tr>
<td>Indication for biopsy</td>
<td>PSA&gt;4 or abnormal DRE</td>
<td>PSA&gt;3</td>
<td>PSA&gt;2.5-3.4 (dep on yr)</td>
</tr>
<tr>
<td>Intervention arm compliance</td>
<td>85% PSA, 86% DRE</td>
<td>82% screened Ionce Avg. 2.27 per subject</td>
<td>76% of invited had ≥1 PSA</td>
</tr>
<tr>
<td>PrCa detection (scr/cont)</td>
<td>11.1% vs 9.9%</td>
<td>9.6% vs 6.0%</td>
<td>12.7% vs 8.2%</td>
</tr>
<tr>
<td>PrCa deaths (scr/cont)</td>
<td>158 vs 145</td>
<td>299 vs 452</td>
<td>44 vs 78</td>
</tr>
<tr>
<td>RR of PrCa death</td>
<td>1.06 (0.87-1.36)</td>
<td>0.79 (0.69-0.91)</td>
<td>0.56 (0.39-0.82)</td>
</tr>
<tr>
<td>NNI (Invite)/NND (Diagnose)</td>
<td>na</td>
<td>781/27</td>
<td>293/12</td>
</tr>
<tr>
<td>Notes</td>
<td>44% prescreened in both arms</td>
<td>Low/Int risk: 84.8% (scr) vs 68.4% (cont)</td>
<td>Younger men, less prescreening</td>
</tr>
</tbody>
</table>

Andriole et al., JNCI 2012; Schroder et al., Lancet 2014; Hugosson et al., Lancet 2010

PSA Screening

- **USPSTF:**
  - Previously recommended against screening (2012)
  - New draft DOES NOT recommend against screening in men 55-69

- **AUA (2013)**
  - 40-54yo: No screening recommended unless higher risk (ex: family hx, AA)
  - 55-69 yo: Risk/Benefit discussion with “shared decision making” “based on a man’s values and preferences”
  - 70+ yo: No screening recommended, some in excellent health may benefit
ProtecT: RP vs RT vs AS

- 1999 – 2009 @ 337 UK PCP centers
  - Age: 50 – 69 years (median = 62)

- Eligibility:
  - Stage: cT1c (76%) - cT2 (23%)
  - Gleason: 6 (77%) - 7 (20%) - 8-10 (3%)
  - PSA: 3 – 20 (3.0 – 9.9 in 90%)
ProtecT: RP vs RT vs AS

- 1643 patients randomized:
  - AS: 545 pts (482)
  - RT: 545 pts (391)
  - RP: 553 pts (405)

- 58% low, 40% intermediate, 2% high risk patients

- Median f/u 10 years

- Primary outcome: **Prostate-cancer-related mortality**

- Secondary outcomes:
  - OS - DM - Clinical progression - Primary tx failure - QoL


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ProtecT: RP vs RT vs AS

- **AS:**
  - PSA Q3m x1yr → Q6-12m
  - All rises assessed, but > 50% increases in 1yr prompted formal review

- **RT:**
  - Neoadj & concurrent ADT for 3-6 months
  - 3DCRT: 74 Gy in 37 fractions
  - PSA rise of at least 2.0 above nadir prompted formal review

- **RP:**
  - Postoperative PSA Q3m x1yr → Q6m x 2yrs → Q1yr
  - Adjuvant RT discussed with +SM, ECE, or postop PSA >= 0.2
  - Tx failure = PSA of 0.2 or higher at 3 months postop

Results

• **AS:** 55% required intervention by Nov 2015
  - 49% RP  -  42% EBRT  -  8% brachy  -  1% HIFU

• **RT:** 14% had PSA rise >2 above nadir
  - 5% RP  -  25% ADT  -  2% HIFU

• **RP:**
  - 2% had PSA >0.2 between 31 to 183 days postop
  - 2% underwent adjuvant RT for pT3 or +SM (29/24% total)
  - 4 of 280 with PLND had pN+ disease

• **Prostate-cancer-related mortality:**
  - ~1% in all three arms with 10 yr median f/u (p=0.48)

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Numbers needed to treat

• **RT:**
  - 33 AS pts to avoid one DM
  - 9 AS pts to avoid one clinical progression

• **RP:**
  - 27 pts to avoid one DM
  - 9 AS pts to avoid one clinical progression

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Patient-reported survey outcomes

- **AS:**
  - Sexual and urinary function gradually declined

- **RT:**
  - Negative effect on sexual function was greatest at 6 months, but then recovered somewhat and remained stable
  - Minimal effect on urinary continence
  - Bowel function negatively impacted at 6 months, but recovered (except for increasing frequency of bloody stools)
  - Urinary voiding and nocturia worse than other groups at 6 months, but mostly recovered to similar at 12 months

- **RP:**
  - Greatest negative effect on sexual function and urinary incontinence
  - Some recovery seen, but remained SS lower than other tx groups
Active Surveillance

• Within 6 months, can get mpMRI, repeat bx, or do MRI-bx if <10 cores or other concerns (i.e. +MRI, low free PSA, PSADT, age, race, FamHx)
• PSA no more often then every 6 months
• DRE no more often than every 12 months
• Repeat biopsy if:
  - PSA rises
  - DRE changes
  - Suspicious MRI

Observation: < 10 yr life expectancy
- Preferred for low risk patients
- Option for intermediate risk patients

Active Surveillance – NCCN 2018

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

• Advantages of active surveillance:
  › About 2/3 of men eligible for active surveillance will avoid treatment
  › Avoidance of possible side effects of definitive therapy that may be unnecessary
  › Quality of life/normal activities potentially less affected
  › Risk of unnecessary treatment of small, indolent cancers reduced

• Disadvantages of active surveillance:
  › Chance of missed opportunity for cure although very low
  › About 1/3 of men will require treatment, although treatment delays do not seem to impact cure rate.
  › Periodic follow-up mpMRI and prostate biopsies may be necessary.

• Advantages of observation:
  › Avoidance of possible side effects of unnecessary definitive therapy and early initiation and/or continuous ADT

• Disadvantages of observation:
  › Risk of urinary retention or pathologic fracture without prior symptoms or concerning PSA level
When it’s time to treat...

- Why surgery?
  - Physically tolerable
  - Convenient
  - Low risk of GI toxicity
  - RT as salvage

- Why not?
  - “Open” urethra risks
  - Neurologic ED
  - Operative risks

- Why RT?
  - Medically inoperable/risky
  - Non-invasive
  - Continence
  - Vascular ED

- Why not?
  - “Narrowed” urethra risks
  - GI toxicity
  - Salvage difficult
  - Contraindicated

Standard RT options pre-2015-ish

- Dose-escalated EBRT: ~ 72-81 Gy @ 1.8-2 Gy/fxn
  - 7-9 weeks of daily RT

- Monotherapy Brachytherapy: LDR or HDR

- EBRT + LDR/HDR Brachy BOOST
<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose</th>
<th>Late ≥ grade 2 GI Toxicity</th>
<th>Late ≥ grade 2 GU Toxicity</th>
<th>p=0.013</th>
<th>p=ns</th>
<th>p=0.005</th>
<th>p=ns</th>
<th>p=0.04</th>
<th>p=0.6</th>
<th>p=0.005</th>
<th>p=0.14</th>
<th>p=0.0063</th>
<th>p=0.001</th>
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<tr>
<td>MD Anderson</td>
<td>70Gy</td>
<td>13%</td>
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<td>Kuban 2007</td>
<td>78Gy</td>
<td>26%</td>
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<td>PROG</td>
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<td>Zietman 2005</td>
<td>79.2GyE</td>
<td>17%</td>
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<td>Netherlands</td>
<td>68Gy</td>
<td>25%</td>
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<td>Al-Mamgani 2008</td>
<td>78Gy</td>
<td>35%</td>
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<tr>
<td>MRC</td>
<td>64Gy</td>
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<td>Dearnaley 2007</td>
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<td>RTOG</td>
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<td>16%</td>
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<tr>
<td>Michalski 2014</td>
<td>79.2Gy</td>
<td>22%</td>
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<table>
<thead>
<tr>
<th>Regimen for Definitive Therapy</th>
<th>NCCN Risk Group</th>
<th>Very-Low¹</th>
<th>Low¹</th>
<th>Favorable or good prognosis² Intermediate</th>
<th>Unfavorable, or poor prognosis², Intermediate</th>
<th>High and Very-High³</th>
<th>Node Positive</th>
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<tbody>
<tr>
<td>Beam Therapies</td>
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<tr>
<td>72 Gy to 80 Gy at 2 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ with 4-6 mo ADT</td>
<td>✓ with 2-3 y ADT</td>
<td>✓ with 2-3 y ADT</td>
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<td>75.6 Gy to 81.0 Gy at 1.8 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ with 4-6 mo ADT</td>
<td>✓ with 2-3 y ADT</td>
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<td>70.2 Gy at 2.7 Gy per fraction</td>
<td>✓</td>
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<td>✓</td>
<td>✓ with 4-6 mo ADT</td>
<td>✓ with 2-3 y ADT</td>
<td>✓ with 2-3 y ADT</td>
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<tr>
<td>70 Gy at 2.5 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ with 4-6 mo ADT</td>
<td>✓ with 2-3 y ADT</td>
<td>✓ with 2-3 y ADT</td>
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<tr>
<td>60 Gy at 3 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ with 4-6 mo ADT</td>
<td>✓ with 2-3 y ADT</td>
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<tr>
<td>51.6 Gy at 4.3 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ with 4-6 mo ADT</td>
<td>✓ with 2-3 y ADT</td>
<td>✓ with 2-3 y ADT</td>
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<tr>
<td>37 Gy at 7.4 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>40 Gy at 8 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>36.25 Gy at 7.25 Gy per fraction</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Brachytherapy Monotherapy</td>
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<tr>
<td>Iodine 125 implant at 145 Gy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Palladium 103 implant at 125 Gy</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Cesium implant at 115 Gy</td>
<td>✓</td>
<td>✓</td>
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<td></td>
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<tr>
<td>HDR 27 Gy at 13.5 Gy in 2 implants</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>HDR 38 Gy at 9.5 Gy BID in 2 implants</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Combined EBRT and Brachytherapy (EBRT 45–50.4 Gy at 1.8-2.0 Gy/ф, unless otherwise noted)</td>
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<tr>
<td>Iodine 125 implant at 110-115 Gy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
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<tr>
<td>Palladium 103 implant at 90-100 Gy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
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<tr>
<td>Cesium implant at 85 Gy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
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<tr>
<td>HDR 21.5 Gy at 10.75 Gy x 2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td></td>
</tr>
<tr>
<td>EBRT 37.5 Gy at 2.5 Gy + 12-15 Gy single HDR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td>± 4 mo ADT</td>
<td></td>
</tr>
</tbody>
</table>
RadBio: $\alpha/\beta$ ratio

- Historically:
  - Tumors = HIGH $\alpha/\beta$ ratios
  - Fractionation spares LOW $\alpha/\beta$ ratio cells & late effects

- Modern:
  - Prostate AdenoCA = LOW $\alpha/\beta$ ratio
  - Highly conformal treatments sparing OAR’s

A. Loblow, Univ or Toronto. ASTRO 2017.
RadBio: $\alpha/\beta$ ratio

- Historically:
  - Tumors = HIGH $\alpha/\beta$ ratios
  - Fractionation spares LOW $\alpha/\beta$ ratio cells & late effects

- Modern:
  - Prostate AdenoCA = LOW $\alpha/\beta$ ratio
  - Highly conformal treatments sparing OAR’s
Hypotheses on hypofractionation:

• Biologically more effective
• Slows rate of progression
• Makes prostate cancer cells less likely to metastasize

Brachytherapy

Grimm, et al. BJU 2012; Morris et al., IJROBP 2017; T Mitin, 2018 ASTRO Refresher
EBRT vs EBRT+HDR

Phase III clinical trials of EBRT vs. EBRT plus brachytherapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>N</th>
<th>Median followup</th>
<th>Risk groups</th>
<th>Outcomes</th>
<th>EBRT</th>
<th>Combo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sathya et al. (83)</td>
<td>2005</td>
<td>104</td>
<td>8.2 years</td>
<td>Low: 0% Intermediate: 40% High: 60%</td>
<td>5 yr bRFS: 39% Post-tx biopsy positive: 51%</td>
<td>71% SS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoskin et al. (40)</td>
<td>2012</td>
<td>218</td>
<td>7.1 years</td>
<td>Low: 5% Intermediate: 42% High: 53%</td>
<td>7-yr bRFS 48%</td>
<td>66% SS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCENDE-RT (59)</td>
<td>2015</td>
<td>398</td>
<td>6.5 years</td>
<td>Low: 0% Intermediate: 31% High: 69%</td>
<td>9-yr bRFS 58%</td>
<td>78% SS</td>
<td></td>
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</tr>
</tbody>
</table>

EBRT = external beam radiation therapy; bRFS = biochemical recurrence-free survival; SS = statistically significant.

Spratt et al., The ABS Task Group Report, Brachytherapy 2016

ASCENDE-RT

- EBRT vs combination EBRT+HDR
- ~400 pts with unfav-int or high risk disease
  - 1 year of ADT
  - Pelvic IMRT to 46 Gy (2 Gy/fxn) -->
    1) IMRT BOOST of 32 Gy (78 Gy total)
    2) I-125 LDR BOOST of 115 Gy
ASCENDE-RT

- EBRT+HDR BOOST increased rates of grade 3 GU toxicity:
  - 5 --> 19% (SS)

- No difference in GI toxicity
  - 4 --> 9% (NSS)
Prostate EBRT Hypofractionation

- Becoming the new standard of care for many cases

- Widely available technology advances allowing more conformality

- ~ 2.5 – 3.5 Gy per fraction

- 4 randomized trials showing equal efficacy w/o major toxicity
Prostate Cancer
Radiation Therapy Physician Worksheet
(As of 20 October 2016)

9. If brachytherapy is included in the treatment plan, then answer the following set of questions (#9):
   a. What type of brachytherapy will be utilized?
      - Low dose brachytherapy (seed implant)
      - High dose brachytherapy
   b. If HDR brachytherapy is selected, what is the number of applications? Applications:
   c. If HDR brachytherapy is selected, what is the number of fractions? Fractions:

10. a. For regimens that do not include brachytherapy or SBRT, is a moderately hypofractionated regimen (i.e. 20-28 fractions) being utilized? □ Yes □ No
   b. If #10 answer is No, why is a moderately hypofractionated regimen not being utilized?
      - The pelvic lymph nodes are not treated
      - Hypofractionated regimen is not a standard of care
      - There is insufficient evidence to support a hypofractionated regimen
      - Lack of comfort or experience in delivering a hypofractionated regimen

11. Note additional information in the space below.

Table 1: Overview of Clinical Trials Evaluating Moderate Hypofractionation in Localized Prostate Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N, Risk</th>
<th>RT Arms</th>
<th>Median Follow-up</th>
<th>Outcome</th>
<th>HR for Efficacy</th>
<th>Grade 2+ Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 0415¹</td>
<td>1,115 All low</td>
<td>73.8 Gy/41 fx 70 Gy/28 fx</td>
<td>5.8 years</td>
<td>Disease-free survival</td>
<td>0.85 (0.64–1.14)</td>
<td>Increased late grade 2/3 GI/GU toxicity</td>
</tr>
<tr>
<td>CHHiP²</td>
<td>3,163 Mainly intermediate</td>
<td>74 Gy/37 fx 60 Gy/20 fx (57 Gy/19 fx)</td>
<td>5.2 years</td>
<td>Prostate-specific antigen failure</td>
<td>0.84 (0.68–1.03) for 60 Gy vs 74 Gy (57 Gy inferior)</td>
<td>No difference</td>
</tr>
<tr>
<td>PROFIT³</td>
<td>1,206 Intermediate</td>
<td>78 Gy/39 fx 60 Gy/20 fx</td>
<td>6.0 years</td>
<td>Disease-free survival</td>
<td>0.99 (0.83–1.19)</td>
<td>No difference</td>
</tr>
<tr>
<td>HYPRO⁴</td>
<td>820 Intermediate and high</td>
<td>78 Gy/39 fx 64.6 Gy/19 fx (3 fx/wk)</td>
<td>5.0 years</td>
<td>Recurrence-free survival</td>
<td>0.86 (0.63–1.16)</td>
<td>Increased late grade 2+ GI/GU toxicity</td>
</tr>
</tbody>
</table>

fx = fraction; GI/GU = gastrointestinal/genitourinary; HR = hazard ratio; RT = radiotherapy.
<table>
<thead>
<tr>
<th>Regimen for Definitive Therapy</th>
<th>NCCN Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very-Low&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Beam Therapies</strong></td>
<td></td>
</tr>
<tr>
<td>72 Gy to 80 Gy at 2 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>76.6 Gy to 84 Gy at 2.8 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>70.2 Gy at 2.7 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>70 Gy at 2.5 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>60 Gy at 3 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>51.6 Gy at 4.3 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>37 Gy at 7.4 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>40 Gy at 8 Gy per fraction</td>
<td>✓</td>
</tr>
<tr>
<td>36.25 Gy at 7.25 Gy per fraction</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Brachytherapy Monotherapy**

- Iodine 125 implant at 145 Gy
- Palladium 103 implant at 125 Gy
- Cesium implant at 115 Gy
- HDR 27 Gy at 13.5 Gy in 2 implants
- HDR 38 Gy at 9.5 Gy BID in 2 implants

**Combined EBRT and Brachytherapy (EBRT 45–50.4 Gy at 1.8–2.0 Gy/frac, unless otherwise noted)**

- Iodine 125 implant at 110–115 Gy
- Palladium 103 implant at 90–100 Gy
- Cesium implant at 85 Gy
- HDR 21.5 Gy at 10.75 Gy x 2
- EBRT 37.5 Gy at 2.5 Gy + 12-15 Gy single HDR

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Normal organ limit</th>
<th>No more than 15% volume receives dose that exceeds</th>
<th>No more than 25% volume receives dose that exceeds</th>
<th>No more than 35% volume receives dose that exceeds</th>
<th>No more than 50% volume receives dose that exceeds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bladder constraint</td>
<td>80 Gy</td>
<td>75 Gy</td>
<td>70 Gy</td>
<td>65 Gy</td>
</tr>
<tr>
<td></td>
<td>Rectum constraint</td>
<td>75 Gy</td>
<td>70 Gy</td>
<td>65 Gy</td>
<td>60 Gy</td>
</tr>
<tr>
<td></td>
<td>Penile Bulb</td>
<td>Mean dose less than or equal to 52.5 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Arm 2 (Assumes alpha-beta for rectum bladder is 3)**

<table>
<thead>
<tr>
<th>Normal organ limit</th>
<th>No more than 15% volume receives dose that exceeds</th>
<th>No more than 25% volume receives dose that exceeds</th>
<th>No more than 35% volume receives dose that exceeds</th>
<th>No more than 50% volume receives dose that exceeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder constraint</td>
<td>79 Gy</td>
<td>74 Gy</td>
<td>69 Gy</td>
<td>64 Gy</td>
</tr>
<tr>
<td>Rectum constraint</td>
<td>74 Gy</td>
<td>69 Gy</td>
<td>64 Gy</td>
<td>59 Gy</td>
</tr>
<tr>
<td>Penile Bulb</td>
<td>Mean dose less than or equal to 51 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prostate SBRT

- Ultimate dose escalation and hypofractionation

- Caters to suspected **LOW** $\alpha/\beta$ ratio

- Gland immobilization and motion tracking

- Typically 5 fxn tx courses
Dose escalation trial: MSKCC (Zelefsky, et al.)

- Phase I
  - 6.5 Gy x 5 = 32.5 Gy
  - 7.0 Gy x 5 = 35.0 Gy
  - 7.5 Gy x 5 = 37.5 Gy
  - 8.0 Gy x 5 = 40.0 Gy

- Treatment delivery every other day
- PTV = prostate and SV with a 5mm circ margins and 3mm posteriorly
- Ferromagnetic beacons for intra-fraction motion tracking
Dose escalation trial: MSKCC

- Low and intermediate risk PCa
- KPS ≥80
- Prostate volume ≤60cc
- No ADT allowed
- IPSS ≤15

Exclusion:
- Prior TURP/stricture/prostatitis
- Radiographic evidence of T3-4 or N1

Dose escalation trial: MSKCC (Zelefsky, et al.)

- Late rectal bleeding:

<table>
<thead>
<tr>
<th>dose</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.5 Gy</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>35 Gy</td>
<td>3%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>37.5 Gy</td>
<td>3%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>40 Gy</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Dose escalation trial: MSKCC (Zelefsky, et al.)

**Acute Urinary Frequency (≤ 6 Months)**

**Late Urinary Frequency (> 6 Months)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>% PSA Failure (Nadir + 2 Definition)</th>
<th>% Positive Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.5 Gy</td>
<td>20% (6/30)</td>
<td>48% (10/21)</td>
</tr>
<tr>
<td>35 Gy</td>
<td>2.9% (1/35)</td>
<td>19% (5/26)</td>
</tr>
<tr>
<td>37.5 Gy</td>
<td>0% (0/36)</td>
<td>17% (4/24)</td>
</tr>
<tr>
<td>40 Gy</td>
<td>2.9% (1/35)</td>
<td>8% (2/25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Arm</th>
<th>Low Risk</th>
<th>Favorable Intermediate</th>
<th>Unfavorable Intermediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.5 Gy</td>
<td>27% (3/11)</td>
<td>40% (2/5)</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td>35 Gy</td>
<td>0% (0/6)</td>
<td>25% (2/8)</td>
<td>33% (3/9)</td>
</tr>
<tr>
<td>37.5 Gy</td>
<td>13% (1/8)</td>
<td>25% (3/12)</td>
<td>0% (0/4)</td>
</tr>
<tr>
<td>40 Gy</td>
<td>0% (0/7)</td>
<td>0% (0/13)</td>
<td>40% (2/5)</td>
</tr>
</tbody>
</table>
PROCARS: LDR vs SBRT vs EBRT

- Low-risk patients only
- ~5-6 yrs of f/u


PROCARS: LDR vs SBRT vs EBRT

Urinary toxicity

Sexual toxicity

Bowel toxicity

Ongoing Prostate SBRT Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>To Be Accured</th>
<th>Population</th>
<th>Endpoint</th>
<th>Dose Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAT</td>
<td>456</td>
<td>Low and Int Risk</td>
<td>PSA-RFS</td>
<td>36.25 Gy/5 fx vs 70.2 Gy/26 fx</td>
</tr>
<tr>
<td>NCT01794403</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPO-RT-PC ISRCTN5905321</td>
<td>1200</td>
<td>Intermediate Risk</td>
<td>PSA-RFS</td>
<td>42.7 Gy/7 fx vs 78 Gy/39 fx</td>
</tr>
<tr>
<td>NRG-GU005</td>
<td>606</td>
<td>Intermediate Risk</td>
<td>QOL</td>
<td>36.25 Gy/5 fx vs 70 Gy/28 fx</td>
</tr>
<tr>
<td>PACE B NCT01584258</td>
<td>858</td>
<td>Low and Int Risk</td>
<td>PSA RFS</td>
<td>36.25 Gy/5 fx vs 78 Gy/39 fx</td>
</tr>
</tbody>
</table>

Immobilization and OAR sparing techniques

- VacLoc
- Daily IGRT
- Bladder filling
- Rectal gas reduction
  - Gasex/Beano
  - Rectal tube
- Fiducial markers
  - Calypso
- Rectal Balloon
- Real-time IGRT
  - Clarity
- SpaceOAR Hydrogel
Intrafraction IGRT, tracking, and gating
Tumor Location Identification Imaging

mpMRI

PSMA PET
Gold Fiducial Markers

Rectal Balloons
SBRT - 45 Gy in 5 fractions
Max rectal dose: 46.2 vs 42.3 Gy (SS)
Rectal V45: 1.7 vs 0.3 cc (SS)
33% circumference: 35.1 vs 38 Gy (SS)

Conclusions

• Hypofractionation via EBRT +/- Brachytherapy is becoming a new standard in many cases

• SBRT dose ranging from 32.5 Gy-40 Gy in 5 fx were well tolerated without significant urinary or rectal toxicities.

• Important and impressive technology exists for inter/intrafraction prostate gland motion to improve targeting and OAR sparing

THANK YOU !!!