Management of Prostate Cancer

A Risk-Based Approach

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Learning Objectives

• To understand the evidence supporting the management options for men presenting with low or favorable intermediate risk PC

• To understand the evidence supporting the management options for men presenting with unfavorable intermediate risk PC

• To understand the evidence supporting the management options for men presenting with high risk PC
RT and Short Course ADT

- **RTOG 9408** – Mostly Low and Int Risk
  - RT (66.6 Gy) ± 4 mos ADT
    - Median follow up: 9.1 years
  - Overall Survival improved (p = 0.03; 5% by 10 yrs)
    - Driven by intermediate risk (Gleason 7)
      - No survival benefit in low risk
        - HR 1.07 (0.83-1.39)

- **TROG 9601, DFCI 95096** – Int and High Risk
  - RT (66, 70 Gy) +/- 6 mos ADT
    - Overall Survival Improved (p ≤ 0.01; 13% by 10 yrs)
Duration of short course ADT in Intermediate-risk

- RT0G 9910
  - 4 vs 9 mos of ADT and 70.2 Gy
    - 84% intermediate and 16% high-risk
  - Median f/u: 9.4yrs

- PC specific survival
  - 0.81 (0.48 to 1.39]; P = 0.45
    - 8 year point estimate PC specific survival
      - 96 vs 95% in the 9 vs 4 mo arms
70 Gy or 70 Gy + 6 mos ADT
10 yr PCSM, median f/u: 14.5 yrs
Median Age: 72
High 15%
Unfav Int 8%
Fav Int 0%
AHR: 1.64 [95% CI: 0.76 to 3.53]; p = 0.21
Unfavorable Intermediate Risk

AHR: 0.34 [0.13 to 0.91]; p = 0.03
19/136 or 14% had Gleason score 8 or 9 at RP
Duration of short course ADT in Intermediate-risk

- Favorable Int risk may not need ADT
  - RTOG 9910
    - If proportion with fav int risk was large, then unlikely to observe a survival difference

- Unfavorable Int risk may need > 4 mos ADT
  - HT with RT dose escalation trials
    - RTOG 0815 (79.2 Gy + 6 vs 0 mos ADT)
    - Dart 01/05 (78 Gy + 4 vs 28 mos ADT)
      - Post randomization analyses important
  - Role of 3T mpMRI to identify occult GI 8 to 10
# RT Dose Escalation Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>median age in yrs</th>
<th>Risk group</th>
<th>f/u yrs</th>
<th>PFS</th>
<th>DM</th>
<th>Late Gr 2+ toxicity</th>
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</thead>
<tbody>
<tr>
<td>MDACC 78 vs 70 ISO</td>
<td>301</td>
<td>69</td>
<td>20% low 45% int 35% high</td>
<td>9.0</td>
<td>p = 0.004</td>
<td>p = 0.06</td>
<td>GI 26 vs 13% 0.01</td>
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<td>GU 13 vs 8% NS</td>
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<tr>
<td>MDACC 75.6 vs 67 PTV</td>
<td>75.6</td>
<td>69</td>
<td>20% low 45% int 35% high</td>
<td>9.0</td>
<td>p = 0.004</td>
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<tr>
<td>ACR 9509 79.2 vs 70.2</td>
<td>393</td>
<td>67</td>
<td>58% low 37% int 5% high</td>
<td>8.9</td>
<td>&lt; 0.001</td>
<td>NA</td>
<td>GI 17 vs 8% 0.005</td>
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<td>GU 20 vs 18% NS</td>
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<tr>
<td>RTOG 0126 79.2 vs 70.2</td>
<td>1499</td>
<td>71</td>
<td>100% int</td>
<td>7.0</td>
<td>&lt; 0.001</td>
<td>0.03 (8% to 5% at 10 yrs)</td>
<td>GI 22 vs 15% 0.006</td>
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<td>GU 16 vs 10% 0.001</td>
</tr>
</tbody>
</table>
Low and Intermediate risk Prostate Cancer

• **Low Risk and Favorable Int Risk**
  – Dose escalated EBRT (I), brachy, RP
    • No role for ADT (II)
      – Consider Surveillance especially if life expectancy limited

• **Unfavorable Int Risk**
  • Conventional dose EBRT and 4 to 6 mos ADT (I)
    – Post randomization analyses RTOG 0815, DART 01/05
      » Define whether 6 or > 4 mos ADT adds to high dose RT
      » High dose RT alone may be insufficient (II)
Locally Advanced Prostate Ca

• Life long ADT ± RT
  – Hazard Ratio for overall survival
    • SPCG-7 (N = 875, CAB x 3 mos then AA)
      – 0.68 [0.52 to 0.89], p = 0.004 at median f/u 7.6 yrs
    • Intergroup (N = 1205, LHRH/orch)
      – 0.70 [0.57 to 0.85], p < 0.001 at median f/u 8.0 yrs

• RT ± 3 years of ADT
  • EORTC (N = 412, CAB x 1 mo then LHRH)
    – 0.51 [0.37 to 0.73], p < 0.001 at median follow up 5.5 yrs
36 months of ADT is a std of care for men with high-risk PC treated with RT.

To establish a shorter duration of ADT with efficacy that is “not inferior” requires a non-inferiority trial.

Requires a clinical decision on upper limit of the increased risk of death one would accept to say the lower duration of ADT is not inferior.
36 vs 6 month ADT EORTC study

- Non-inferiority trial
  - Upper bound of 95% CI for HR selected = 1.35
    - Means accept at most a 1.35 increased risk of death with 95% confidence in men receiving 6 mos as compared to 36 mos of ADT
  
- Enrolled 970; Result: 1.42 [upper bound: 1.79]

- Rejected Non-Inferiority
36 vs 18 month ADT Canadian Study

- Designed as a Superiority but requires non-inferiority trial

  - Enrolled 630; Result 1.15 [0.83 to 1.59] – when 147 deaths had been observed
  - Requires 275 deaths to assess non-inferiority with a 1.35 upper limit

- Follow up is ongoing to ascertain the upper bound on the 95% CI for death
## ADT Duration Considerations

<table>
<thead>
<tr>
<th>Durations of ADT in mos</th>
<th>Number Median f/u</th>
<th>HR [95% CI]</th>
<th>OS difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 vs 0</td>
<td>415 9.1 yrs</td>
<td>1.67 [1.25, 2.22]</td>
<td>18.3% at 10 yrs</td>
</tr>
<tr>
<td>36 vs 6</td>
<td>970 6.4 yrs</td>
<td>1.42 [1.09, 1.85]</td>
<td>3.8% at 5 yrs</td>
</tr>
<tr>
<td>36 vs 18</td>
<td>690 6.4 yrs</td>
<td>1.15 [0.85, 1.59]</td>
<td>0.4% at 10 yrs</td>
</tr>
</tbody>
</table>

For high-risk PC Rx utilizing 70 Gy RT
36, too much; 6, too little
but 18 months of ADT may be just right
### RESULTS

<table>
<thead>
<tr>
<th>Trial/Median RT dose</th>
<th>Years</th>
<th>Eligible (Median PSA)</th>
<th>N\text{study}</th>
<th>Median f/u in years</th>
<th>bDFS</th>
<th>MFS</th>
<th>CSS</th>
<th>Overall Survival (OS)</th>
<th>Late Grade 3+ RT related toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DART 01/05 78 Gy (76-82)</td>
<td>2006 to 2010</td>
<td>T1b-3 PSA &lt; 100 (11) ~50/50 split Int/high risk</td>
<td>355 (N_{\text{PC}}) (N_{\text{ALL}}) 5</td>
<td>38</td>
<td>5.3</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>RTOG 9202 70 Gy</td>
<td>1992 to 1995</td>
<td>T2c-4 PSA &lt; 150 (20) 100% High risk</td>
<td>1514 (N_{\text{PC}}) (N_{\text{ALL}}) 87</td>
<td>227</td>
<td>5.8</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>
**SUMMARY OF RCT DATA**

<table>
<thead>
<tr>
<th>ADT (mos)</th>
<th>N</th>
<th>Med f/u (y)</th>
<th>% Gleason 8 to 10</th>
<th>Overall Survival Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 vs 6</td>
<td>970</td>
<td>6.4</td>
<td>19</td>
<td>Yes</td>
</tr>
<tr>
<td>28 vs 4\textsubscript{DART}</td>
<td>375</td>
<td>5.3</td>
<td>25*</td>
<td>Yes</td>
</tr>
<tr>
<td>28 vs 4\textsubscript{RTOG}</td>
<td>1521</td>
<td>11.3</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>18 vs 6</td>
<td>1071</td>
<td>7.4</td>
<td>35</td>
<td>No</td>
</tr>
<tr>
<td>36 vs 18</td>
<td>690</td>
<td>6.4</td>
<td>60</td>
<td>No</td>
</tr>
</tbody>
</table>

*Less likely Grade 5

Gleason grade 5 may be less sensitive to conventional ADT
**DFCI:** Gleason score 8 or less

AHR: 0.30 [95% CI: 0.09 to 0.96]; p = 0.04

**TROG:** Gleason score 8 or less

AHR: 0.46 [95%: 0.28 to 0.75]; p = 0.002
Comparison of the distribution of PC prognostic factors among men with Gleason Gr 5

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>TROG 9601 (N = 38)</th>
<th>DFCI 95096 (N = 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PSA (IQR)</td>
<td>20.3</td>
<td>9.3</td>
<td>0.02</td>
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<tr>
<td>AJCC</td>
<td></td>
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<tr>
<td>T3,4</td>
<td>58%</td>
<td>0%</td>
<td>&lt; 0.001</td>
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<tr>
<td>T2</td>
<td>42%</td>
<td>73%</td>
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</tr>
<tr>
<td>T1</td>
<td>0%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Gleason 7 with 3º Gr 5</td>
<td>0%</td>
<td>14%</td>
<td>0.06</td>
</tr>
<tr>
<td>Gleason 9</td>
<td>92%</td>
<td>82%</td>
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<tr>
<td>Gleason 10</td>
<td>8%</td>
<td>4%</td>
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</table>
DFCI: Grade 5 present

AHR: 0.10 [95% CI: 0.002 to 6.07]; p = 0.27

TROG: Grade 5 Present

AHR: 0.51 [95% CI: 0.16 to 1.65]; p = 0.26
New Directions

• Disable the prostate cancer cells ability to synthesize testosterone
  – Abiraterone

• Inhibits translocation after binding of T to the cytoplasmic AR and inhibits nuclear activation
  – Enzalutamide
Newly diagnosed M1 PC
Overall Survival

HR = 0.61 (0.47-0.80) p = 0.0003

Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months

Docetaxel
High Risk PC

• Duration of conventional ADT (I)
  • 28 to 36 mos and possibly 18 mos
  • The benefit of long-term conventional ADT may decrease as the burden of grade 5 PC at biopsy increases (II)

➢ Future Rx of Grade 5 PC may include
  ➢ Docetaxel, Enzalutamide
What is the management based on level 1 evidence?

72, healthy T3b, GI 4+4, 11/12 cores +, PSA 25

1. Brachytherapy
2. High dose RT to 79.2 Gy
3. RT and ADT for 4 months
4. Active Surveillance
5. RT and ADT for at least 18 months
MENTORSHIP

• What makes a “Good” Doctor?
  – Expertise +
    • Core Values
      – Respectful, Listener, Kind, Compassionate, Loving, Integrity

• Shares these values with
  – Patients and their loved ones
  – Family and friends
  – Colleagues and staff
  – Residents, fellows, and medical students

• “Good” doctoring takes place inside and outside of the hospital
Of all this... What Lasts?

- The Love shared by
  - Teaching and mentoring
  - Working with the Team

From Anthony, please remember this

Along "Your Way"...

Share what Lasts with one another