Definitive Radiation + /- ADT for Locally Advanced Prostate Cancer: What is the Optimal Treatment?

APCCC
Friday March 10th, 2017
ST GALLEN, SWITZERLAND
**Purpose:** ... We analyzed the available literature, to determine whether reliable conclusions could be made concerning the effectiveness of RP vs RT +/- ADT, assuming current Tx standards.

**Results:** ... 14 studies identified (one without CSS).
Median RS=12 (< or = “low” & > “high”)
Studies with RS ≤12 10-yr OS & CSS Diff. 17% & 6%, respectively.
... RS >12 10-yr OS & CSS, Diff, 5.5% & ~1%, respectively.

**Conclusions** ... The most reliable studies suggest that the differences in 10 year CSS between RP and RT ... < or = 1%.
Acta Oncologica, 2015; 54:875-881

ORIGINAL ARTICLE

Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes. Lennermas et al.

RP vs HDR+EBRT + 6 mo. ADT in PC pts in Sweden 1996-2001…

M & M: T1b-T3a, N0, M0 and PSA<50 ng/ml …

RESULTS: … survival rate ~ 76%. Only eight pts (9%) died of PC.

CONCLUSION: … RP and … HDR + EBRT appeared to be comparable …

Figure 1. Cumulative probability of prostate-specific survival in RP, radical prostatectomy group compared to RT, radiotherapy group.
**Level One Evidence for benefit of Brachytherapy**

**Canadian ASCENDE-RT**  
*WJ Morris et al IJROBP 2016*

- Phase 3: 78 Gy vs. 46 Gy + LDR Brachytherapy
- n=398: follow up 5-11 years
- High risk and high tier intermediate risk
- 1 year ADT (8 month neoadj + 4 month concurrent/adjuvant)

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**Diagram**

- Pelvic IMRT 4600/23
- Prostate boost 3200/16
- $^{125}$I Brachytherapy boost: 115 Gy

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*ASCENDE RT Trial published IJROBP 2016 slide Courtesy of Juanita Crook MD*
Results: Biochemical PFS all patients

Intent-to-treat analysis of the primary endpoint

<table>
<thead>
<tr>
<th>Time (yrs)</th>
<th>DE-EBRT 5 yr</th>
<th>DE-EBRT 7 yr</th>
<th>DE-EBRT 9 yr</th>
<th>LDR-PB 5 yr</th>
<th>LDR-PB 7 yr</th>
<th>LDR-PB 9 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>83.8 (±5.6)</td>
<td>75.0 (±7.2)</td>
<td>62.4 (±9.8)</td>
<td>88.7 (±4.8)</td>
<td>86.2 (±5.4)</td>
<td>83.3 (±6.6)</td>
</tr>
<tr>
<td>7</td>
<td></td>
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<td>9</td>
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Absolute diff.
5y – 4.9%
7y – 11.2%
9y – 20.95%

p=0.004

ASCENDE RT Trial published IJROBP 2016 slide Courtesy of Juanita Crook MD
B-PFS using nadir + 2 vs. PSA > 0.2 ng/ml

DE-EBRT (n=195)

9-year K-M PFS = 32% using >0.2 ng/mL

LDR-PB (n=188)

9-year K-M PFS = 82% using >0.2 ng/mL

log rank P value <0.001

log rank P value = 0.32

ASCENDE RT Trial published IJROBP 2016 slide Courtesy of Juanita Crook MD
Status of WPRT for Prostate Cancer

• Why Important?:
  - Small field vs Big Field?
    – PORT (e.g. CHHiP Trial) thru SBRT or HDR monotherapy
  - Potential Morbidity
  - Cost (time & money)?
  - Opportunity to improve outcomes!

• Why So Challenging?:
  - e.g. 1200 pts with 1/3rd (33%) having + nodes
    • ... then study really based on n=400 pts
    • ... if disease beyond pelvis in 25% down to n=300 pts
    • ... and local failures 1/3rd to n=200 pts
    • ... competing causes of death (e.g. 50%) n=100
    • ... “optimal size of trial to answer questions of WPRT?”

RTOG 0924: n=2580 “big enough?”
Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Update of the Long-Term Survival Results of the GETUG-01 Randomized Study
Pommier et al. IJROBP 96, 2016

“Negative Trial” but with issues:
1. Small (n=446)
2. Lower risk
3. Smaller fields
4. Variable ADT

Maybe when small fields are used only lower risk patients benefit?

Event-free survival (EFS) subset with risk of + nodes <15%
Patterns of Lymph Node Positivity on $^{11}$C-acetate PET Imaging in Correlation to the RTOG Pelvic Radiation Field for Prostate Cancer.
McClinton et al. ASTRO 2015

<table>
<thead>
<tr>
<th>Node Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aortic</td>
<td>31 (36.9)</td>
</tr>
<tr>
<td>Common iliac</td>
<td>20 (23.9)</td>
</tr>
<tr>
<td>External iliac</td>
<td>15 (17.8)</td>
</tr>
<tr>
<td>Cloquet node</td>
<td>15 (17.8)</td>
</tr>
<tr>
<td>Pre-sacral</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>
The Template of the Primary Lymphatic Landing Sites of the Prostate Should be Revisited: Results of a Multimodality Mapping Study. Mattei … Studer. EAU 53:118-125, 2008
**RTOG 9413 (UPDATED, 4-3-2016)**

**Progression-Free Survival Multivariate Analysis (Phoenix)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stratified variables</th>
<th>Variable categories</th>
<th>HR*</th>
<th>95% CI</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (Phoenix)</td>
<td>Treatment</td>
<td>NHT+WPRT</td>
<td>RL</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NHT+PORT</td>
<td>1.21</td>
<td>(1.02,1.43)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WPRT+AHT</td>
<td>1.21</td>
<td>(1.02,1.43)</td>
<td>0.025</td>
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<tr>
<td></td>
<td></td>
<td>PORT+AHT</td>
<td>0.93</td>
<td>(0.78,1.10)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gleason</td>
<td>2-6</td>
<td>RL</td>
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<td>7-10</td>
<td>1.27</td>
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<td></td>
<td></td>
<td>PSA</td>
<td>≤ 30</td>
<td>RL</td>
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<td></td>
<td></td>
<td>&gt; 30</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-Stage</td>
<td>T1c,T2a</td>
<td>RL</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1b,T2b</td>
<td>0.96</td>
<td>(0.76,1.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2c-T4</td>
<td>1.05</td>
<td>(0.90,1.21)</td>
</tr>
</tbody>
</table>

*HR: hazard ratio, a risk ratio of 1 indicates no difference between subgroups.
† p-value is from Chi-square test using the Cox proportional hazards model

*(Roach et al. unpublished data, 2017)*
## Basis of study design for RTOG 0924?

**Table 12.6.** 4-Yr PFS: Intermediate Risk (PSA <30 and GS 7-10 excluding Clinical Stages T2c-T4, or GS=6 with PSA <30, Gleason 2-6, and Clinical Stages T2c-T4, or PSA ≥30 and GS 2-6)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Failures</th>
<th>N</th>
<th>4-Yr Rate (%) [95% C.I.]</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones + RT Whole Pelvis+Boost</td>
<td>35</td>
<td>125</td>
<td>68.1 [58, 78]</td>
<td>0.027</td>
</tr>
<tr>
<td>Hormones + RT Prostate Alone</td>
<td>56</td>
<td>125</td>
<td>46.6 [36, 58]</td>
<td></td>
</tr>
<tr>
<td>RT Whole Pelvis+Boost + Hormones</td>
<td>44</td>
<td>113</td>
<td>53.8 [42, 65]</td>
<td></td>
</tr>
<tr>
<td>RT Prostate Alone + Hormones</td>
<td>50</td>
<td>118</td>
<td>49.8 [39, 61]</td>
<td></td>
</tr>
</tbody>
</table>

P-value from log-rank test for comparing the survival curves.

RTOG 9413* Subset middle stratification risk + nodes > 15% by Roach equation: (1) PSA <50 ng/ml & GS 7-10, T1c-T2b, or (2) GS=2-6 with Clinical Stages T2c-T4 or > 50% biopsies + & PSA <50 ng/ml, or (3) GS=2-6, PSA > 20 ng/ml and T1c-T2b

<table>
<thead>
<tr>
<th>Group</th>
<th>10 yr CSS</th>
<th>Log-Rank</th>
<th>Diff = 13%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO (n=145)</td>
<td>0.8497</td>
<td>0.1503</td>
<td>0.0358</td>
</tr>
<tr>
<td>WPRT (n=146)</td>
<td>0.9741</td>
<td>0.0259</td>
<td>0.0150</td>
</tr>
<tr>
<td>Diff = 13%</td>
<td>Log-Rank</td>
<td>8.7735</td>
<td>1</td>
</tr>
</tbody>
</table>

Max PSA < 100 ng/ml
Table 3a
Progression-Free Survival by Median Field Size per Protocol

<table>
<thead>
<tr>
<th>Field-Size Comparisons</th>
<th>Median PFS</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPRT vs. PORT (&lt;10cm x 11 cm)</td>
<td>4.9 vs. 2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>WPRT vs. &quot;Mini&quot;-Pelvis (&lt; 11cm x 11cm)</td>
<td>4.9 vs. 3.4</td>
<td>0.015</td>
</tr>
<tr>
<td>&quot;Mini&quot;-Pelvis vs. PORT</td>
<td>3.4 vs. 2.6</td>
<td>0.7697</td>
</tr>
</tbody>
</table>

*Pair-Wise Log-Rank test

Roach et al. IJROBP 66:647-653, 2006
### Treatment Schema

1. **Risk Group:**
   - "Favorable" High or "Unfavorable" Intermediate Risk:
     1. GS=7-10 and T1c-T2b and PSA < 50 ng/ml or
     2. GS=6, T2c-T4 or > 50% biopsies + & PSA <50 or
     3. GS=6, PSA > 20 ng/ml and T1c-T2b

2. **Type of RT Boost:**
   - IMRT vs Brachytherapy (HDR + PPI)

3. **Duration of Androgen Deprivation Therapy**
   - Short Term vs Long Term ADT

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<table>
<thead>
<tr>
<th>Arm 1: NADT + Prostate &amp; SV</th>
<th>vs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 2: NADT + Whole-Pelvic RT</td>
<td></td>
</tr>
</tbody>
</table>
Cumulative Accrual for RTOG 0924 - Data as of 10/31/2016

With the avg accrual of 38.3/mo. the last 6 mos completion date: June 2019

Projected Accrual

Observed Accrual

Cumulative Number of Patients Randomized
**Major Take Home Message: RT+/-ADT**

1. More high level evidence supporting RT+ADT for unfavorable prostate ca. (e.g. > 65 yrs) than for RP

2. Better PSA control rates with higher doses (particularly with brachytherapy e.g. ACENDE RT)

3. Progression Free Survival higher with NHT & WPRT than NHT and PORT (RTOG 9413)

4. RTOG (NRG) 0924 (n=2580) should allow the impact of prophylactic WPRT to be determined