Overview of Radiotherapy for Clinically Localized Prostate Cancer

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Introduction: Topics to be covered

1. Recent Randomized Trials RP vs RT +/- ADT
2. ADT
   1. How Long
   2. Future directions?
3. Brachy vs IMRT dose escalated boost?
4. What to irradiate: WPRT vs PORT

*Not covered:
  - Early vs delayed RT post OP
  - Use of chemotherapy or secondary forms of ADT
  - Predictive markers (not ready for prime time?)
10-Year Outcomes after Monitoring, Surgery Radiotherapy for Localized Prostate Cancer
Hamdy et al. NEJM, 2016

METHODS “We compared active monitoring, radical prostatectomy, and external-beam radiotherapy for ... localized prostate cancer ... men 50 to 69 years of age ... 1643 agreed to undergo randomization ... ”

RESULTS “… Metastases developed in more men in the active-monitoring ... than in the surgery ... or radiotherapy ... (p=0.004) ... ”
Radical prostatectomy versus high-dose irradiation in Localized/locally Advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes


Figure 1. Cumulative probability of prostate-specific survival in RP, radical prostatectomy group compared to RT, radiotherapy group.
Purpose: … evaluated whether the duration of AST had an impact on the risk of PCSM in men with unfavorable-risk PC …

Patients and Methods: … 761 men with unfavorable-risk PC were treated in Australia, New Zealand, Ireland, or the USA in a randomized trial with RT and 3, 4, or 6 months of AST …

Results: … 6 vs 3 or 4 mos of AST was associated with a reduced risk of PCSM …

Conclusion: AST durations of no less than 6 mos should be considered when treating GS 7 PC with conventional dose RT.
Neoadjuvant Androgen Suppression Duration Trial Design (RTOG 9910, Pisansky et al. JCO 2014)

<table>
<thead>
<tr>
<th>Intermediate Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>T1b-4</td>
</tr>
<tr>
<td></td>
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<tr>
<td>T1b-c</td>
</tr>
</tbody>
</table>

Randomize

- 16 Weeks Androgen Suppression
- 8 Weeks Androgen Suppression + External RT
- 36 Weeks Androgen Suppression
- 28 Weeks Androgen Suppression
- 8 Weeks Androgen Suppression + External RT

*85% NCCN

www.rtog.org → Clinical Trials → 9910
Neoadjuvant Androgen Suppression Duration Trial Design (RTOG 9910, Pisansky et al. JCO 2014)

**Disease-Specific Survival**

- Year after randomization
  - Disease-specific survival (%)
  - **Events**
    - 8-week AS: 30
    - 28-week AS: 24
    - $P=0.45$
  - **HR** = 0.81 (0.48-1.39)

<table>
<thead>
<tr>
<th>Year after randomization</th>
<th>Patients at risk</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-week AS</td>
<td>752 725 690 677 639 609 5</td>
<td>30</td>
</tr>
<tr>
<td>28-week AS</td>
<td>737 718 686 664 642 610 5</td>
<td>24</td>
</tr>
</tbody>
</table>

**Overall Survival**

- Year after randomization
  - Overall survival (%)
  - **Events**
    - 8-week AS: 230
    - 28-week AS: 220
    - $P=0.62$
  - **HR** = 0.95 (0.79-1.15)

<table>
<thead>
<tr>
<th>Year after randomization</th>
<th>Patients at risk</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-week AS</td>
<td>752 729 703 689 652 621 5</td>
<td>230</td>
</tr>
<tr>
<td>28-week AS</td>
<td>737 722 701 681 657 625 5</td>
<td>220</td>
</tr>
</tbody>
</table>

**Median follow-up:**
- 8.7 yrs (0-12.4) all patients
- 9.3 yrs (0-12.4) for survivors

**Death due to prostate cancer:**
- 3% of all patients
- 12% of all deaths
- PI – site concordance = 86%

**Cause of Death – Other**
- Cardiovascular: 31% (not ↑ 28-week)
- Cancer – other: 28%
- Pulmonary: 12%
### Neoadjuvant Androgen Suppression Duration Adverse Events

<table>
<thead>
<tr>
<th>Grade ≥2 Adverse Event Incidence, %</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8-week AS → RT</td>
<td>28-week AS → RT</td>
</tr>
<tr>
<td>Endocrine (e.g. flushing)</td>
<td>27</td>
<td>46</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Overall</td>
<td>58</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual (e.g. erectile dys.)</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>31</td>
</tr>
</tbody>
</table>
### My Conclusions Are:

1. 4 mo. improves OS vs 0 for Int Risk (RTOG 9408, 8610?)
2. 3 a little worse (p=NS) than 6 or 8 mo. (TROG, Crook)
3. 4 ~ 8 or 28 (Armstrong, RTOG 9202) (why worse than 6?)
4. Therefore no evidence > 4 mo. required for Inter Risk Pts

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**Prostate Cancer Trials Using Short Term ADT + RT vs RT Alone or Long Term ADT**

<table>
<thead>
<tr>
<th>First Au, (Yr)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>T=28 months ADT for Intermediate Risk patients</td>
</tr>
</tbody>
</table>

*NHT=Neoadjuvant hormonal therapy; **months=mos. ***GS: Gleason Score*
High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study.  
Nabid et al. ASCO 2013

**Background:** ... Randomized ... to compare ... 36 vs. 18 mos of androgen blockade (AB) in high risk prostate ca. with ... RT ...  

**Methods:** ... randomized ... high risk prostate ca. (T3-4, PSA >20 ng/ml or Gleason score >7), to ... whole pelvis ... prostate 70 Gy and 36 (arm 1) vs. 18 mos (arm 2) of AB ...  
... OS was the primary end point.  

**Results:** ... 310 pts ... to arm 1 & 320 to arm 2 ... (med age 71 yrs, PSA 16 ng/ml, GS=8) ... fu of 77 mos, ... 78% died of causes other than prostate ca.  
5 yr OS & DSS rates were 92.1% vs. 86.8%, p=0.052 & 97.6% (95.9-99.4) vs. 96.4% (94.2-98.6), p=0.473 ... for arm 1 vs 2, respectively. There were no sign. Diff. in the rates of biochemical, regional or distant failure between arms.  

**Conclusions:** ... long term AB can be safely reduced from 36 to 18 mos without compromising outcomes.
High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study. Nabid et al. ASCO 2013

### Multivariate Cox regression for overall survival

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 vs 18 months</td>
<td>1.17 (0.84-1.62)</td>
<td>0.353</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.03-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA &gt;20</td>
<td>1.15 (0.77-1.71)</td>
<td>0.501</td>
</tr>
<tr>
<td>Gleason score &gt;7</td>
<td>1.48 (0.97-2.24)</td>
<td>0.067</td>
</tr>
<tr>
<td>T3-T4</td>
<td>1.06 (0.70-1.61)</td>
<td>0.772</td>
</tr>
<tr>
<td>Biochemical failure</td>
<td>1.33 (0.90-1.94)</td>
<td>0.148</td>
</tr>
</tbody>
</table>
High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study.
Nabid et al. ASCO 2013

Overall survival (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
</tr>
</thead>
<tbody>
<tr>
<td>36m Patients at risk</td>
<td>310</td>
<td>301</td>
<td>283</td>
<td>243</td>
<td>152</td>
<td>94</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>18m Patients at risk</td>
<td>320</td>
<td>306</td>
<td>290</td>
<td>212</td>
<td>143</td>
<td>83</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>HR: 1.15 (0.83-1.59), p=0.398</td>
<td></td>
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<td></td>
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</tbody>
</table>

BUT … Issues:
1. Underpowered
   a. OS at 5yrs p=0.05 36 >18 mo.
   b. known factors not sign. (e.g. GS, T-stage)
   c. Med age 70, 78% deaths non-prostate ca.
2. Def High Risk (e.g. PSA> 20 ng/ml)
3. Short follow-up (e.g. RTOG 8531)

92.1 (89.1-95.1) 86.8 (83.0-90.6)
P=0.052
63.6 (55.7-71.5)
Level One Evidence for benefit of Brachytherapy

Canadian ASCENDE-RT  *WJ Morris et al*

- 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)

Pelvic IMRT 4600/23

Prostate boost 3200/16

I^{125} Brachytherapy boost: 115 Gy
Results: Biochemical PFS all patients
Intent-to-treat analysis of the primary endpoint

<table>
<thead>
<tr>
<th>Kaplan-Meier (95% CI)</th>
<th>Randomization (N=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE-EBRT</td>
</tr>
<tr>
<td>5 yr</td>
<td>83.8</td>
</tr>
<tr>
<td></td>
<td>(+5.6)</td>
</tr>
<tr>
<td>7 yr</td>
<td>75.0</td>
</tr>
<tr>
<td></td>
<td>(+7.2)</td>
</tr>
<tr>
<td>9 yr</td>
<td>62.4</td>
</tr>
<tr>
<td></td>
<td>(+9.8)</td>
</tr>
</tbody>
</table>

Absolute difference
5y – 4.9%
7y – 11.2%
9y – 20.95%

p=0.004
Progression-Free Survival: RTOG 9413

Nonfailure Rate

Years since Randomization
0.0 0.2 0.4 0.6 0.8 1.0
0 1 2 3 4 5

NHT + WP RT
NHT + PO RT
WP RT + AHT
PO RT + AHT

P=.008

NHT=neoadjuvant hormonal therapy; AHT=adjuvant hormonal therapy, Roach, et al. JCO 2003
PFS per Protocol Definition (Includes death due to any cause)

(Update Lawton et al. IJROBP 2007)

% ALIVE WITHOUT DISEASE

Impact of Pelvic nodal treatment

Impact of Local Failure & Death from other causes

At Risk:

WP + NHT 196 109 10
PO + NHT 165 83 2
WP + AHT 172 87 6
PO + AHT 183 106 6
WPRT for Prostate Cancer: Important & Challenging

• Practical issues:
  – Small field vs Big Field?
  – Potential Morbidity
  – Cost (time and money)?

• Challenge – tough to prove:
  – 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
    • ... improved “salvage” treatments, delaying deaths
    • ... “study too small?”

Thus, RTOG 0924: n=2580 (@1400 pts)!
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

PURPOSE: ... long-term results ... (GETUG)-01 ... event-free survival (EFS) & overall survival (OS) ... & pelvic nodes irradiation.

PATIENTS AND METHODS: ... 446 patients with T1b-T3, N0pNx, M0 ... assigned to either pelvic nodes ... or prostate-only radiation ...

“upper limit defined as the level of the anterior portion of the junction of the junction between the first & second sacral vertebra.”

... 6-mo. Neoadjuvant/concomitant HT allowed for high-risk pts.

... a 4-field technique for the pelvic volume (46 Gy).

RESULTS: ... nonsignificant EFS was ... in the low-risk subgroup in favor of pelvic nodes radiation ... (77.2% vs 62.5%; P=.18).

CONCLUSION: Pelvic nodes irradiation did not statistically improve EFS or OS ... but may be beneficial in selected low & intermediate-risk ... treated with exclusive radiation therapy.
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

Event-free survival (EFS) according subset with risk of + lymph nodes <15%
“Whole Pelvic Field” (n=298)
RTOG 9413 Progression-Free Survival & Field Size: Protocol Definition

**Table 3a**

<table>
<thead>
<tr>
<th>Field Size Comparisons</th>
<th>Median FFS Time (yrs)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT vs. PORT (&lt;15 cm x 11 cm)</td>
<td>4.9 vs. 2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>WBRT vs. &quot;Mini&quot;-Pelvis (&lt;11 cm x 11 cm)</td>
<td>4.9 vs. 3.1</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
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 (%)</th>
<th>[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</td>
<td>[58, 78]</td>
<td>0.027</td>
</tr>
<tr>
<td>Hormones + RT Prostate Alone</td>
<td>56</td>
<td>125</td>
<td>46.6</td>
<td>[36, 58]</td>
<td></td>
</tr>
<tr>
<td>RT Whole Pelvis+Boost + Hormones</td>
<td>44</td>
<td>113</td>
<td>53.8</td>
<td>[42, 65]</td>
<td></td>
</tr>
<tr>
<td>RT Prostate Alone + Hormones</td>
<td>50</td>
<td>118</td>
<td>49.8</td>
<td>[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>Diff = 13%</th>
<th>Log-Rank</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO (n=145)</td>
<td>0.8497</td>
<td>0.1503</td>
<td>0.0358</td>
<td>16</td>
</tr>
<tr>
<td>WPRT (n=146)</td>
<td>0.9741</td>
<td>0.0259</td>
<td>0.0150</td>
<td>3</td>
</tr>
<tr>
<td>Diff = 13%</td>
<td>Log-Rank</td>
<td>8.7735</td>
<td>1</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

Max PSA < 100 ng/ml
## 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

| REGISTE R | REGISTE R | Arm 1: NADT + Prostate & SV vs Arm 2: NADT + Whole-Pelvic RT |
Overall Survival and Failure-free Survival in All Patients and According to Metastatic Status at Randomization (Intention-to-Treat Population).

Clinically Localized Prostate Cancer: Evidence Based Conclusions

1. RP prolongs OS vs “WW” in men < 65 yrs of age.
2. Primary ADT is more effective than observation.
3. No role for ADT with RP except in men with + nodes.
4. Post-op RT improve PSA control +/- improve survival.
5. Anti-androgens + PO EBRT > PO EBRT alone.
6. Hi-dose EBRT improves PSA control but not OS.
7. EBRT+ADT > EBRT for Intermed & High Risk pts.
8. LTADT for High & STADT (4 mo.) for int. risk pts.
9. ADT+EBRT > ADT for locally advanced disease.