To Treat or Not to Treat Pelvic Lymph Nodes in Unfavorable Clinically Localized Prostate Cancer

Mack Roach III MD
Professor Radiation Oncology & Urology
Chair Department of Radiation Oncology
University of California San Francisco
NCI-Designated Comprehensive Cancer Center

The Debate!
Is there a Role of Whole Pelvic Radiotherapy?

- It makes biologic sense.
  - Prostate is a radiosensitive tumor
  - Populations of patients can be defined who are at risk

- What policy does the preponderance of Radiotherapy evidence support?

- There is supportive:
  - Surgical Data
  - Retrospective data

Extended Pelvic Lymphadenectomy in Patients Undergoing Radical Prostatectomy: High Incidence of Lymph Node Metastasis

103 consecutive Pt's (Med PSA=15.9) undergoing extending node dissection 9 selective fields:

1. External Iliac bilateral
2. Internal Iliac bilateral
3. Obturator bilateral
4. Common Iliac bilateral
5. Presacral

Concluded:
1. + Nodes 26%
2. 42% outside of std node dissection

Table 3 Selected Papers Highlighting More Sensitive Methods for Detecting Pelvic Lymph Node Involvement in patients with N0 by Standard Pathological Evaluations

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shariat</td>
<td>Archival lymph nodes tissues evaluated in 199 men with pT3N0 disease using the detection of human glandular kallikrein 2 (hK2) mRNA in men with histopathologically normal pelvic lymph nodes, removed at radical prostatectomy.</td>
<td>Twenty percent of had positive results, and on multivariable analysis models, the RT-PCR/hK2 result was associated with prostate cancer progression, development of distant metastases, and prostate cancer-specific survival.</td>
</tr>
<tr>
<td>Pagliarulo</td>
<td>274 patients with pT3 prostate cancer treated by radical prostatectomy and bilateral lymph node dissection. 180 were staged N0, while 94 were N+. LN's from the 180 patients were evaluated for occult metastasis by immunochemistry. Recurrence and overall survival were compared among patients with occult tumor cells (OTN+), with patients whose LN remain negative (OLN-), and with the 94 N+ patients. Occult tumor cells were found in 24 of 180 N0 patients (13.3%). OLN+ was associated with increased recurrence and decreased survival compared with OLN- patients. Outcome for pts with OLN+ disease was similar to that for pts with N+ disease. Immunohistochemistry can detect tumors not recognized at initial histology.</td>
<td></td>
</tr>
<tr>
<td>Ferrari</td>
<td>Quantitative measures of PSA mRNA copies in N0-PLN, defined by PSA-N, and a threshold PSA-N 100 or more versus PSA-N less than 100 copies, were assessed by continuous and categorical multivariate analysis to be independent.</td>
<td>4 yr biochemical recurrence-free survival of pts with PSA-N &gt; 100 vs &lt;100 was 55% &amp; 77% P = &lt;0.05. PSA-N Identifies occult mets in N0-PLN. PSA-N &gt; 100 an independent molecular marker identifying patients with occult micrometastasis.</td>
</tr>
<tr>
<td>Miyake (2007)</td>
<td>Pathology exams detected tumor cells in 29 lymph nodes from 11 patients, compared to 143 with micrometastasis using real-time reverse transcriptase-PCR in 32 pN0 patients. In multivariate analysis only micrometastasis independently associated with PSA recurrences.</td>
<td>Approximately 30% of clinically localized prostate cancers shed cancer cells to the pelvic lymph nodes, and this fact may explain some of the biochemical recurrences occurring after radical prostatectomy.</td>
</tr>
<tr>
<td></td>
<td>True incidence of lymph node involvement 13.3 to 30% higher than estimated based on N0 path status.</td>
<td></td>
</tr>
</tbody>
</table>
Node Negative Pts? Relevant to RTOG 9413?

Modified from Shariat et al. JCO 2003

Cancer Specific Mortality (%) vs. Months from Surgery

Positive RT-PCR-hK2
Negative RT-PCR-hK2
Equivocal RT-PCR-hK2

P < 0.001

RTOG 9413 Scheme: Impact of the Timing of HT on PFS?

<table>
<thead>
<tr>
<th></th>
<th>First Month</th>
<th>Second Month</th>
<th>Third Month</th>
<th>Fourth Month</th>
<th>Fifth Month</th>
<th>Sixth Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms 1</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Arms 2</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Arms 3</td>
<td>EBRT</td>
<td>EBRT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
</tr>
<tr>
<td>Arms 4</td>
<td>EBRT</td>
<td>EBRT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
</tr>
</tbody>
</table>

HT=hormonal therapy

Impact of the Timing of HT on PFS?

Arms 1 and 2

Arms 3 and 4

First Month
Second Month
Third Month
Fourth Month
Fifth Month
Sixth Month

HT=Hormonal therapy

Progression-Free Survival: RTOG 9413

Nonfailure Rate vs. Years since Randomization

P=0.008

NHT=neoadjuvant hormonal therapy
AHT=adjuvant hormonal therapy
Roach, et al.
Progression-Free Survival: Protocol Definition

Table 3a Progression-Free Survival by Median Field-Size per Protocol

<table>
<thead>
<tr>
<th>Field-Size Comparisons</th>
<th>Median PFS (yrs)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Pelvis vs. Prostate Only</td>
<td>4.9 vs. 2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Whole Pelvis vs. Mini-Pelvis</td>
<td>4.9 vs. 3.4</td>
<td>0.015</td>
</tr>
<tr>
<td>Mini-Pelvis vs. Prostate Only</td>
<td>3.4 vs. 2.6</td>
<td>0.7697</td>
</tr>
</tbody>
</table>

*Pair-Wise Log-Rank test
I There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Preliminary Results of GETUG -01
Pommier et al. JCO 25:5366-73, 2007

<table>
<thead>
<tr>
<th>“WPRT”</th>
<th>“PORT”</th>
</tr>
</thead>
<tbody>
<tr>
<td>225</td>
<td>221</td>
</tr>
</tbody>
</table>

Risk >15%
4 to 8 mo. ADT
ASTRO Def.
“upper limit defined as the level of the anterior portion of the junction of the junction between the first & second sacral vertebra.”

Role of Prostate Dose Escalation in Patients with Greater Than 15% Risk of Pelvic Lymph Nodes Involvement
Jacob … Pollack IJROBP 61:695-701, 2005

- 420 Pts with Risk +LN > 15%
- Compared WPRT vs PPRT vs PO
- RT Dose, Short term Androgen Deprivation (STAD) ….
- Conclusions:
  - STAD (NHT) not associated with FFBF
  - Radiation Dose was most important
- **FLAWED STUDY DESIGN & LOGIC!**

- Retrospective Study vs Prospective Trial
- Only 67 pts received NHT vs >600 pts
  - NHT Required (throw out this study!)
- ASTRO definition vs Protocol definition
  - Recovery of Testosterone (throw out the study)
- Median PSA=11 ng/ml vs 23 ng/ml
- Fu 43 mo. versus 60 mo.
- WPRT vs PPRT vs PO?
  - field sizes too small & too large?

“Prostate Only Field” (n=48)
“Partial Pelvic Field” (n=74)

Max field size 10 x 10 cm
Median Dose 46 Gy
“Partial Pelvic Field” (n=74)  
Median Dose 46 Gy

“Whole Pelvic Field” (n=298)  
Median Dose 45 Gy

“Whole Pelvic Field” (n=298)  
Median Dose 45 Gy

“Whole Pelvic Field” (n=298)  
Median Dose 45 Gy
1. Higher dose to testes – False see per protocol DVH data
2. Big field favored over small field – False arm 3 (WP) vs 4 (PO)
3. Sequence favors Neoadj ADT & WPRT – False Taussky et al
4. Lower Testosterone recovery impacts PSA failure – False Roach et al. '10

RTOG 0924

<table>
<thead>
<tr>
<th>Treatment Schema</th>
<th>1. Risk Group:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Favorable” High or “Unfavorable” Intermediate Risk:</td>
</tr>
<tr>
<td></td>
<td>1. GS=7-10 and T1c-T2b and PSA &lt; 50 ng/ml or</td>
</tr>
<tr>
<td></td>
<td>2. GS=6, T2c-T4 or &gt; 50% biopsies + &amp; PSA &lt;50 or</td>
</tr>
<tr>
<td></td>
<td>3. GS=6, PSA &gt; 20 ng/ml and T1c-T2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Type of RT Boost:</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMRT vs Brachytherapy (HDR + PPI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Duration of Androgen Deprivation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Term vs Long Term ADT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>10 yr CSS</th>
<th>Diff</th>
<th>Log Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO (n=145)</td>
<td>0.3497</td>
<td>0.1503</td>
<td>0.0358</td>
</tr>
<tr>
<td>WPRT (n=46)</td>
<td>0.9741</td>
<td>0.0259</td>
<td>0.0150</td>
</tr>
</tbody>
</table>

Max PSA < 100 ng/ml

Truth and Wisdom

“The wise boldly pick up a truth as soon as they hear it …”
– Zen Master XUEDOU