An Update on Radiation Therapy for Prostate Cancer

~ David C. Beyer, MD

Objectives

- Review significant new data
- Identify leading trends in PCa

2009 Issues for:
- Dose and Fractionation
- Post-operative radiation
- Role of hormones

XRT Dose Escalation (All Risk Groups)
Meta-analysis of Biochemical Failure

Vani, G. et al. IJROBP V74(5):1405-1418, 2009
XRT Dose Escalation (All Risk Groups)
Meta-analysis of PCa Specific Mortality

<table>
<thead>
<tr>
<th>Study code</th>
<th>Dose in Gy</th>
<th>NED</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeller et al</td>
<td>6.0</td>
<td>0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Fack</td>
<td>6.0</td>
<td>0.05</td>
<td>0.004</td>
</tr>
<tr>
<td>Mitlome</td>
<td>6.0</td>
<td>0.03</td>
<td>0.017</td>
</tr>
<tr>
<td>Zeilhofer</td>
<td>6.0</td>
<td>0.04</td>
<td>0.013</td>
</tr>
<tr>
<td>Nighting</td>
<td>6.0</td>
<td>0.03</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Regression Analysis
All Subgroups

Meta-regression Analysis
High-Risk Group

Meta-regression Analysis
Intermediate-Risk Group
### An Update on Radiation Therapy for Prostate Cancer

#### Meta-regression Analysis

**Low-Risk Group**

- **Dose in Gy**
  - PSA NED

#### Meta-regression Analysis Projection for 100% “Cure”

- **Low Risk**: 86.5 Gy
- **Intermediate Risk**: 90.4 Gy
- **High Risk**: 95.5 Gy

#### Improvements in Technology

- IMRT allows greater precision in radiation delivery
- Spare tissues adjacent to target
- IGRT allows greater accuracy in radiation delivery
- “Hit” the target with each fraction
- Taken together should yield better cure and lower toxicity

#### IMRT DOES Reduce Acute GI & GU Toxicity

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IMRT Reduces Late GI Toxicity

Fractionation = Daily Radiation

- Based on radiobiology principles
  - $\alpha/\beta$ ratio determines optimal daily dose
  - $\alpha/\beta$ ratio not precisely known for PCA nor for OAR
- Conventional wisdom
  - Prostate cancer $\alpha/\beta \sim 10$
  - For any biologically effective dose, daily fractions of 1.8-2.0 Gy/day reduces late complications
  - Steady increase from 33Fx to 45 Fx or more
  - 6 1/2 to 9+ weeks

Radiobiology for Prostate Cancer

- But what if $\alpha/\beta$ for prostate is < 3??
- Then fewer fractions of higher daily dose =
  - Better or same cancer control
  - Fewer complications
  - Greater convenience
  - Better patient acceptance
  - Lower cost

Hypofractionated Radiotherapy

70Gy = 250Gy x 28 Fx

Kupelian, PA. et al. IJROBP. Aug 2007. V68(5); pp 1424-1430

Hypofractionated Radiotherapy

Kaplon, PA. et al. IJROBP. Aug 2007. V68(5); pp 1621-1630
Hypofractionation in Prostate XRT

- Retrospective
- University of Wisconsin
- Patient choice (n=219)
  - 78 Gy / 2 Gy/day / 39 fractions / 55 elapsed days
  - 60 Gy / 3 Gy/day / 20 fractions / 33 elapsed days

Five-year Actuarial Rates of bNED

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Hypo (n=89)</th>
<th>Standard (n=130)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>96%</td>
<td>98%</td>
<td>0.64</td>
</tr>
<tr>
<td>Medium risk</td>
<td>84%</td>
<td>84%</td>
<td>0.75</td>
</tr>
<tr>
<td>High risk</td>
<td>85%</td>
<td>87%</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Late Complications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Rectal</th>
<th>Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypo</td>
<td>Standard</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Phase III Confirmatory Data

- Randomized trial
- National Cancer Institute, Italy
- 168 high risk patients
- 9 months TAB
  - 80 Gy / 40 Fx’s / 8 weeks
  - 62 Gy / 20 Fx’s / 5 weeks
Hypofractionation 3 Year Results

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypofractionated</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA nadir &lt;0.5</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>FBF</td>
<td>79%</td>
<td>87%</td>
</tr>
<tr>
<td>Late G2 GI toxicity</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>Late G2 GU toxicity</td>
<td>11%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Source: Arcangeli et al, IJROBP 75(3):S79, October 2009

Stereotactic Body Radiation Therapy (SBRT)

SBRT for Prostate Cancer

- Considered *Investigational* in 2009
  - ASTRO SBRT Task Force
  - Noridian (Medicare) payment policy
    - Varies by locale

SBRT Prostate

Early “Phase II” Results

- 44 patients with 3 year bNED 78%
  - Choi et al, IJROBP 69(3):s375 2007
- 40 patients with 4 year bNED 70%
- 10 patients with decreasing PSA at 4 months
  - Fuller et al, IJROBP 69(3):s358, 2007
- 22 patients with low toxicity (18 f/u> 1 month)
- 23 patients with 9% acute grade ≥2 toxicity
  - Pawlicki et al, IJROBP Front Rad Ther Onc, 40:395-406, 2007

- Highly precise, and tight conformality
- Ablative doses
- ≤ 5 Fractions
- Image guidance / tracking
- Increased dose rate
- 725cGy x 5
- 900cGy x 4
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~ David C. Beyer, MD

PSA Bounce following SBRT

% With Urinary QOL after SBRT

<table>
<thead>
<tr>
<th>QOL score (IPSS)</th>
<th>Baseline</th>
<th>3 months</th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>51%</td>
<td>37%</td>
<td>44%</td>
<td>92%</td>
</tr>
<tr>
<td>2-3</td>
<td>41%</td>
<td>58%</td>
<td>52%</td>
<td>8%</td>
</tr>
<tr>
<td>4-5</td>
<td>8%</td>
<td>-</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>5%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

% With Rectal QOL after SBRT

<table>
<thead>
<tr>
<th>QOL score (EPIC)</th>
<th>Baseline</th>
<th>3 months</th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>89%</td>
<td>37%</td>
<td>46%</td>
<td>45%</td>
</tr>
<tr>
<td>2-3</td>
<td>11%</td>
<td>48%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>16%</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Late Urinary & Rectal Toxicity on RTOG scale after SBRT

<table>
<thead>
<tr>
<th>RTOG grade</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary, late % (no. patients)</td>
<td>30%</td>
<td>41%</td>
<td>24%</td>
<td>5%</td>
<td>-</td>
</tr>
<tr>
<td>Rectal, late % (no. patients)</td>
<td>51%</td>
<td>33%</td>
<td>15%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Late Urinary & Rectal Toxicity on MDA dose escalation trial

<table>
<thead>
<tr>
<th>RTOG grade</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary, late toxicity % (no. patients)</td>
<td>76%</td>
<td>14%</td>
<td>7%</td>
<td>7%</td>
<td>-</td>
</tr>
<tr>
<td>Rectal, late toxicity % (no. patients)</td>
<td>47%</td>
<td>28%</td>
<td>19%</td>
<td>19%</td>
<td>-</td>
</tr>
</tbody>
</table>


Comparison of QD vs QOD for SBRT

<table>
<thead>
<tr>
<th></th>
<th>QD</th>
<th>QOD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU QOL 4-6</td>
<td>19%</td>
<td>5%</td>
<td>0.34</td>
</tr>
<tr>
<td>Rectal (6mos), Any score 4-5</td>
<td>38%</td>
<td>0%</td>
<td>0.0035</td>
</tr>
<tr>
<td>Rectal QOL 4-5</td>
<td>24%</td>
<td>0%</td>
<td>0.048</td>
</tr>
</tbody>
</table>


Phase I Dose Escalation SBRT

- Low to intermediate risk prostate cancer
- 5 fractions
- 2 weeks
- 45 Gy -- 47.5 Gy -- 50 Gy
- With 12 month follow-up
  - 100% PSA control
  - No dose limiting toxicity


Post-Operative Radiation Spectrum

- Immediate adjuvant
  - High risk
  - No gross residual / PSA
- Immediate salvage
  - Gross residual / PSA
- Late salvage
  - PSA failure
  - Documented recurrence
  - Hormone refractory

~ David C. Beyer, MD
Phase III Trials: Adjuvant RT after RRP

<table>
<thead>
<tr>
<th>Trial/RT</th>
<th>Chemotherapy</th>
<th>Ferumoxytol</th>
<th>Ferumoxytol + RT</th>
<th>Placebo + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>62</td>
<td>93</td>
<td>155</td>
<td>171</td>
</tr>
<tr>
<td>PSA &gt; 0.2</td>
<td>Median</td>
<td>1.7</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Overall</td>
<td>Median</td>
<td>1.2</td>
<td>4.1</td>
<td>4.5</td>
</tr>
<tr>
<td>OS</td>
<td>Median</td>
<td>10.9</td>
<td>12.8</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>P=0.023</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


SWOG 8794 Update
Metastasis-free Survival

Adjuvant Radiotherapy Metastasis-free Survival Post Operative PSA

PSA ≤ 0.2
PSA > 0.2

Adjuvant Radiotherapy Metastasis-free Survival

Overall Survival

SWOG 8794

P=0.023

**An Update on Radiation Therapy for Prostate Cancer**

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**Hormone Therapy for Prostate Cancer**

- **In general**
  - Improved outcomes with ADT
  - Long term better than short term
- **Possible mechanism?**
  - Eradicate subclinical microscopic disease
  - Synergy with XRT
    - Enhanced response to dose of XRT
  - Compensate for suboptimal local therapy
    - (65-70 Gy)

---

**10 Year Results “Bolla” Study**

- 415 patients treated EORTC 1987-1995
- XRT (pelvis + prostate) +/- 3 years
  - Goserelin (concomitant and adjuvant)
- Median F/U 9.1 years
### EORTC 10 Year

<table>
<thead>
<tr>
<th></th>
<th>RT Alone</th>
<th>RT+LTAD</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>39.8%</td>
<td>58.1%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Clinical PFS</td>
<td>22.7%</td>
<td>47.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Distant PFS</td>
<td>30.2%</td>
<td>51.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA PFS</td>
<td>17.6%</td>
<td>37.9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bolla et al. IJROBP 72(1):s30-31, 2008

<table>
<thead>
<tr>
<th></th>
<th>RT Alone</th>
<th>RT+LTAD</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC Mortality</td>
<td>31%</td>
<td>11.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>11.1%</td>
<td>8.2%</td>
<td>0.75</td>
</tr>
<tr>
<td>Pathologic Fracture</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Bolla et al. IJROBP 72(1):s30-31, 2008

### Impact of NHT on Mortality

- 1709 brachytherapy monotherapy patients
  - 786 NHT median 3.5 months
  - All Cause Mortality (ACM)

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHT</td>
<td>1.2</td>
</tr>
<tr>
<td>Age</td>
<td>1.1</td>
</tr>
<tr>
<td>Gleason ≥ 7</td>
<td>1.2</td>
</tr>
</tbody>
</table>


### Overall Survival by Hormone Status

- No Prior Hormone
- NeoAdjuvant Hormone

Beyer et al. IJROBP 61(5):1299-1305, 2005
Impact of Hormones and Comorbidity on All Cause Mortality Following Brachytherapy

Value of Hormones with Dose Escalated XRT

RTOG 0815

• Intermediate risk factors
  • Gleason 7
  • PSA 10-20
  • T2b-T2c
  • Stratify for number of risk factors
  • Exclude if all 3 and >50% cores involved

• Endpoints
  • Survival
  • PSA
  • HROQOL
  • QALY

RTOG 0815

• XRT 79.2 Gy
  • @ 1.8/day
  • 3D or IMRT

• XRT 45 Gy + LDR implant
  • 110 Gy 125I
  • 100 Gy 103Pd

• XRT 45 Gy + HDR implant
  • 10.5 Gy x 2 fractions
  • ≥ 6 hour interval

http://rtog.org/members/protocols/0815/0815.pdf