Radiotherapeutic Management of Clinically Localized Prostate Cancer

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Outline

• Management of low and intermediate risk disease with dose escalated IMRT and IGRT
• Role of brachytherapy for low and intermediate risk disease
• Toxicity outcomes after EBRT and brachytherapy
• Using Level I evidence to determine how to use ADT wisely in the management of intermediate and high risk disease
• Role of adjuvant and salvage radiotherapy after prostatectomy
• Extreme hypo-fractionation- outcomes and toxicity
• Proton Therapy-what is the evidence?
Disclosures

• Consultant for Bebig Brachytherapy products (honorarium)
• Editor in Chief Brachytherapy (honorarium)
Treatment Interventions for Low Risk Disease

- Active Surveillance- especially for very low risk disease
- Radical Prostatectomy, Robot-Assisted Prostatectomy
- Conventional fractionated IMRT/IGRT
- Proton Therapy
- Low Dose Rate Brachytherapy
- HDR Monotherapy
- SBRT (ultra-hypofractionated IGRT)
EBRT for Early Stage Disease
<table>
<thead>
<tr>
<th>Series</th>
<th>#</th>
<th>Randomization</th>
<th>PRFS</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC (2002, 2008)</td>
<td>301</td>
<td>78 Gy vs 70 Gy</td>
<td>73% vs 50% (10-yr)</td>
<td>Intermediate Risk (PSA&gt;10)</td>
</tr>
<tr>
<td>MGH/LLMC (2006, 2010)</td>
<td>393</td>
<td>79.2 Gy vs 70.2 Gy (protons)</td>
<td>83% vs 68% (10-yr)</td>
<td>Low and Int Risk</td>
</tr>
<tr>
<td>Peeters (2006)</td>
<td>669</td>
<td>78 Gy vs 68 Gy</td>
<td>64% vs 54%</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>Dearnelay (2007)</td>
<td>843</td>
<td>74 Gy vs 64 Gy (with ADT)</td>
<td>71% vs 60%</td>
<td>All risk groups</td>
</tr>
<tr>
<td>GETUG (2011)</td>
<td>306</td>
<td>80 Gy vs 70 Gy</td>
<td>72% vs 61%</td>
<td></td>
</tr>
</tbody>
</table>
Dose Escalation Advantage for Favorable Risk Disease
Zietman et al JCO 2010

Favorable Risk

Intermediate Risk
Improved Targeting of Radiotherapy with IMRT
(Zelefsky et al J Urol 2006)
Outcome of 1002 Patients Treated with 86.4 Gy IMRT (Spratt et al IJROBP 2012)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk*</td>
<td>97.70</td>
<td>93.40</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>89.10</td>
<td>75.50</td>
</tr>
<tr>
<td>High risk</td>
<td>76.10</td>
<td>65.80</td>
</tr>
</tbody>
</table>
Dose Constraints Used for 86.4 Gy

<table>
<thead>
<tr>
<th>Structures</th>
<th>Constraint</th>
<th>To</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal Wall</td>
<td>53% of total volume</td>
<td>$V_{47}$</td>
</tr>
<tr>
<td></td>
<td>30% of total volume</td>
<td>$V_{75.6}$</td>
</tr>
<tr>
<td></td>
<td>97% - 99%</td>
<td>Max Point Dose</td>
</tr>
<tr>
<td>Bladder Wall</td>
<td>53% of total volume</td>
<td>$V_{47}$</td>
</tr>
<tr>
<td></td>
<td>105% - 107%</td>
<td>Max Point Dose</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>60Gy</td>
<td>Max Point Dose</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>50Gy</td>
<td>Max Point Dose</td>
</tr>
</tbody>
</table>
Comparison of Toxicity Outcomes Between IGRT and IMRT (Zelefsky et al IJROBP- 2012)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-IGRT (N=190) 2006-2008</th>
<th>IGRT (N=186) 2008-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Dose</td>
<td>86.4 Gy</td>
<td>86.4 Gy</td>
</tr>
<tr>
<td>CTV-PTV Margins</td>
<td>1 cm except at prostate rectal interface where 6 mm margin used</td>
<td>1 cm except at prostate rectal interface where 6 mm margin used</td>
</tr>
<tr>
<td>Use of Androgen Deprivation Therapy</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>Median IPSS Score</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>
Actuarial Late Grade 2 or Higher Urinary Toxicity

(Zelefsky et al Int J Radiat Oncol Biol Phys- 2012)

\[ P = 0.024 \]
External Beam Radiotherapy 2014 for Low and Intermediate Risk

- High dose IMRT ($\geq 78\ \text{Gy}$) recommended even for low risk disease.

- Target volume should include prostate (+ seminal vesicles) and not pelvis.

- Routine use of IGRT with fiducial marker placement where margins can be tighter (at MSKCC a 6 mm circumferential margin is used).

- Increasing interest in hypo-fractionated regimens.
# Dose-escalation Toxicity

## Randomized Trials

<table>
<thead>
<tr>
<th>Institution</th>
<th>Dose (Gy)</th>
<th>5-year Outcome</th>
<th>Grade 3 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC RT01 (1998-2002)</td>
<td>74 vs. 64</td>
<td>NED 60% vs 71% (SS)</td>
<td>GI 6% vs 10% (SS) GU 2% vs 4% (NS)</td>
</tr>
<tr>
<td>Dutch CKVO96-10 (1997-2003)</td>
<td>78 vs. 68</td>
<td>NED 54% vs 64% (SS)</td>
<td>GI 4% vs 5% (NS) GU 12% vs 13% (NS)</td>
</tr>
<tr>
<td>PROG 95-09 (1996-1999)</td>
<td>79.2 vs. 70.2</td>
<td>NED 79% vs 91% (SS)</td>
<td>GI 1% vs 1% (NS) GU 1% vs 2% (NS)</td>
</tr>
<tr>
<td>MD Anderson (1993-1998)</td>
<td>78 vs. 70</td>
<td>FFP 75% vs 78% (SS)</td>
<td>GI 1% vs 7% (SS) GU 5% vs 4% (NS)</td>
</tr>
</tbody>
</table>
Toxicity after High Dose IMRT - MSKCC

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU ≥2</td>
<td>16.0</td>
<td>26.7</td>
</tr>
</tbody>
</table>

10-year Crude Toxicity Grade 3

GU 2.2%

Spratt et al 2012 - MSKCC
Role of the Bladder Trigone in Micturition

• Trigone contracts during bladder filling which helps keep the ureteral orifices open and the bladder neck shut.

• When micturition occurs, trigone musculature relaxes and urine is funneled into the urethra.

• RT may affect urothelial smooth muscle or vasculature or possibly negatively impact on nerve activation changes especially in the region of the trigone.
Delineate the Bladder Neck to Constrain the Dose to this Region

• Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for treatment planning.
  Hathout L, Folkert MR, Kollmeier MA, Yamada Y, Cohen GN, Zelefsky MJ.

• Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer.
Contouring the bladder trigone
Right UVJ

Left UVJ

Trigone
Impact of Dose to the Bladder Trigone on Long-Term Urinary Function after High Dose IMRT
( Ghadjar, Zelefsky and Spratt IJROBP 2014)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% confidence interval) ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS sum baseline: &gt;7</td>
<td>0.39 (0.20–0.79) (.009)</td>
</tr>
<tr>
<td>Trigone maximal dose: &gt;90.9 Gy</td>
<td>2.70 (1.35–5.32) (.005)</td>
</tr>
</tbody>
</table>
Overall Toxicity Outcomes after Dose Escalation EBRT

• **Gastrointestinal**
  – Grade 2 proctitis 3-4%
  – Grade 3 ulceration 1%

• **Genitourinary**
  – Grade 2 urethritis/urgency: 15-20%
  – Grade 3: 2-3%

• **Sexual Dysfunction**
  – Permanent loss of erections: 30-40%
  – Ejaculatory Dysfunction- nearly all patients
Brachytherapy for Low and Intermediate Risk Disease
Prostate Cancer Brachytherapy 2016

• Careful selection of patients to reduce the morbidity of therapy.
  – Prostate size of 50 grams or less
  – IPSS < 18
  – Post-void residual of 100 cc or less
  – No evidence of ECE on imaging

• Improved accuracy of seed delivery with enhancements in image guidance and sophisticated intraoperative planning systems has resulted in excellent long-term outcomes.

• Use of combined treatment of brachytherapy with external beam radiotherapy to provide dose escalation for intermediate and high risk patients.
Brachytherapy for Low Risk Disease

- 10 year biochemical tumor control outcomes of > 90%.

- Results achieved with permanent interstitial I-125 or Pd-103 or HDR monotherapy.

- Optimal tumor control outcomes seen with proper application of dose
  - $D_{90} > 140 \text{ Gy}$ (for I-125) to the prostate associated with improved long-term tumor control outcomes
PSA-Relapse Free Survival
Favorable Risk Patients
(Zelefsky et al Urology 2011)

BRT vs EBRT: 95% versus 89% at 7 years

Median PSA Nadir (ng/ml): 0.1 BRT; 0.6 EBRT
# Contemporary Series Reporting Proctitis Rates after Prostate Brachytherapy

<table>
<thead>
<tr>
<th>Series</th>
<th># pts</th>
<th>Median F/U</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phan 2008</td>
<td>263</td>
<td>5.5 yrs</td>
<td>3.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Zelefsky 2010</td>
<td>448</td>
<td>6.5 yrs</td>
<td>5.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Shiraishi 2011</td>
<td>458</td>
<td>4 yrs</td>
<td>9.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Keyes 2012</td>
<td>1006</td>
<td>5 yrs</td>
<td>7.3%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
# Late Urinary Toxicity after Prostate Brachytherapy

<table>
<thead>
<tr>
<th>Series</th>
<th># pts</th>
<th>Median F/U</th>
<th>% G-2</th>
<th>% G-3</th>
<th>% G-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson (2009)</td>
<td>351</td>
<td>5.7 yrs</td>
<td>6.5%</td>
<td>1.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Keyes (2009)</td>
<td>712</td>
<td>5 yrs</td>
<td>24%</td>
<td>6%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Zelefsky (2010)</td>
<td>448</td>
<td>6.5 yrs</td>
<td>15.6%</td>
<td>2.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Zilli (2011)</td>
<td>250</td>
<td>3 yrs</td>
<td>22%</td>
<td>1%</td>
<td>-----</td>
</tr>
</tbody>
</table>
Sexual Function after Radiotherapy

- Approximately 30-50% of patients develop ED after RT.
- Almost all patients will develop significant reduction in the ejaculate.
- Based on prospective QOL studies, patients who receive BRT may achieve better erectile preservation but this may be related to selection bias.
- Sildenafil citrate associated with a 60-70% improvement in EF function.
- Results of randomized trial comparing prophylactic sildenafil versus placebo given to reduce ED after RT indicate especially after 1-2 years improvements of function noted (Zelefsky et al. J Urol in press).
Combined Brachytherapy and IMRT as an Effective Means of Dose Escalation
Comparison of Combined Brachy and IMRT vs IMRT Alone
PSA-Relapse Free Survival

Probability of Biochemical Control

Time (years)

\[ P = 0.00005 \]

- 92.0%
- 81.4%

PSA-Relapse Free Survival
Comparison of Combined Brachy and IMRT vs IMRT Alone

Distant Metastasis-Free Survival

Probability of Distant Metastasis-Free Survival

Time (years)

97.2%

93.0%

P = 0.044
Comparison of LDR Brachytherapy vs IMRT @ 81 Gy for Low Risk Patients

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Brachytherapy</th>
<th>IMRT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI Late Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>5.1%</td>
<td>1.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1.1%</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>GU Late Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>15.6%</td>
<td>4.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2.2%</td>
<td>1.4%</td>
<td>0.62</td>
</tr>
</tbody>
</table>
ADT and Radiotherapy
Challenges in 2016 with ADT and Radiotherapy

• For which patients or risk group is appropriate?
• Is ADT necessary when dose-escalated radiotherapy is used? Is it necessary when brachytherapy is used?
• What is the optimal duration ADT for various risk groups?
• How do we more effectively address the burdensome side effects of ADT?
Randomized Trials of Short Term ADT with Intermediate Risk Prostate CA

• RTOG 94-08 (Jones NEJM 2011)
  – 10 yr OS: 62% vs 57%, p = 0.03
  – Benefit driven by intermediate risk patients

• DFCI Trial (D’Amico JAMA 2008)
  – 8 yr OS: 74% vs 61%, p=0.01
  – ~75% of patients were intermediate risk risk
PSA RFS Outcomes: ADT for Intermediate Risk Disease with Dose Escalated EBRT >75.6 Gy

**MSKCC Experience**

No ADT: 10 yr PSA-RFS = 67.5%
ADT: 10 yr PSA-RFS = 80.0%

*P = 0.003*
Impact of Short Course ADT on DMFS Prostate Cancer Death for Intermediate Risk Patients (Zumsteg et al IJROBP 2012)

DMFS

Cause-Specific Survival

$P = .011$

$P = .032$
**MSKCC Treatment Algorithm for Intermediate Risk Prostate Cancer**

<table>
<thead>
<tr>
<th>Favourable intermediate-risk prostate cancer*</th>
<th>Unfavourable intermediate-risk prostate cancer†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>One intermediate risk factor</td>
<td>Several intermediate risk factors$^{37}$</td>
</tr>
<tr>
<td>Gleason score of 3+4=7 or less</td>
<td>Gleason score of 4+3=7$^{34}$</td>
</tr>
<tr>
<td>&lt;50% positive biopsy cores</td>
<td>≥50% positive biopsy cores$^{11}$</td>
</tr>
<tr>
<td><strong>Recommended radiation options</strong></td>
<td></td>
</tr>
<tr>
<td>Dose-escalated external beam radiotherapy alone</td>
<td>Dose-escalated external beam radiotherapy and short-term androgen deprivation therapy</td>
</tr>
<tr>
<td>Brachytherapy alone in select cases (eg. ≤3 positive cores, none with &gt;50% involvement)</td>
<td>Combined brachytherapy and external beam radiotherapy with or without short-term androgen deprivation therapy</td>
</tr>
</tbody>
</table>

*All these criteria are required. †Any of these criteria can be met.

Table 5: Memorial Sloan-Kettering Cancer Center treatment algorithm for definitive radiotherapy in patients with intermediate-risk prostate cancer

Zumsteg & Zelefsky, Lancet Oncology 2012
RTOG 0815

- RCT of NCCN intermediate risk prostate cancer receiving “dose escalated RT” +/- 6 months CAB
  - Excludes patients with all 3 intermediate RF’s (T2b-c, GS = 7, and PSA 10-20) and ≥ 50% positive cores
  - Planned accrual: 1520 patients

- Dose escalated RT per physician choice:
  - EBRT alone (79.2Gy/44fx to PTV)
  - Combination EBRT + brachy (either LDR or HDR)
    - EBRT: 45Gy/25fx to prostate/SV
    - LDR: I-125 (110Gy) or Pd-103 (100Gy)
    - HDR: 21Gy/2fx
Optimizing the Use of Androgen Deprivation Therapy for High Risk Disease

• Based on randomized trials, ADT combined with RT is standard of care throughout the world for the management of high risk disease.

• It is our practice to utilize several months of neo-adjuvant and concurrent ADT.

• Longer courses of adjuvant ADT associated with survival benefits for high risk patients.

• All such patients should be on supplemental Vitamin D and calcium and recommended to have a baseline bone density examination.
What is the optimal duration of ADT for high risk patients when combined with RT?
# Phase III Trials of ADT and Conventional Dose RT

<table>
<thead>
<tr>
<th>Study</th>
<th># of Patients</th>
<th>Patient Mix</th>
<th>Duration of ADT</th>
<th>RT Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 92-02</td>
<td>1554</td>
<td>T2c-T4</td>
<td>4 Months NAD +/- 2 Yrs LHRH</td>
<td>65-70 Gy</td>
<td>Improved OS in Gleason 8-10</td>
</tr>
<tr>
<td>EORTC 22961</td>
<td>970</td>
<td>T1c-T2, N1; T2c-T4N0-1</td>
<td>6 Months NAD +/- 3yrs LHRH</td>
<td>70 Gy</td>
<td>ADT 6 months with inferior survival compared to 3 yrs</td>
</tr>
<tr>
<td>Nabid et al NCT 00223171</td>
<td>630</td>
<td>T3-4 PSA &lt;20</td>
<td>36 vs 18 months adjuvant LHRH</td>
<td>70 Gy</td>
<td>No differences</td>
</tr>
</tbody>
</table>
EORTC 22961

- 970 patients with locally advanced prostate cancer randomized to
  - 70 Gy EBRT + 6 months
  - 70 Gy EBRT + 3 Years
- HT given concomitant and adjuvant
- HT delivered via LHRH mono-therapy
- Goal of study to demonstrate non-inferiority of short-term ADT compared to long-term
  - Non-inferior survival defined as HR 1.35 for ST-ADT vs LT-ADT
Overall survival

HR(SADT/LADT): 1.43
(96.4% CI: 1.04-1.98)

P-Value: 0.6543 (H1: SADT non inferior)
P-value: 0.0191 (H1: LADT superior)
## Retrospective Studies of ADT and HD-RT

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>Pt Mix</th>
<th>Duration ADT</th>
<th>RT Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelefsky et al</td>
<td>1980</td>
<td>T1-T3</td>
<td>3-6 months LH-RH</td>
<td>64-86.4 Gy</td>
<td>6 mo ADT improves DFS, &amp; DMFS</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>741</td>
<td>NCCN Criteria</td>
<td>295 ADT 2yrs</td>
<td>70 Gy</td>
<td>Positive effect on OS</td>
</tr>
<tr>
<td>Zapatero et al</td>
<td>306</td>
<td>NCCN Criteria</td>
<td>231 pts 28 months</td>
<td>78 Gy</td>
<td>ADT for 28 months improves OS</td>
</tr>
<tr>
<td>Feng et al</td>
<td>234</td>
<td>NCCN Criteria</td>
<td>No ADT-48; STAD&lt;1 yr 84; LTAD&gt;1 YR 102</td>
<td>77 Gy</td>
<td>Long-term ADT improves OS</td>
</tr>
<tr>
<td>Tendulkar et al</td>
<td>585</td>
<td>NCCN Criteria</td>
<td>95% 6 Months</td>
<td>78 Gy</td>
<td>No benefit</td>
</tr>
</tbody>
</table>
Shorter courses of treatment demonstrated a 21% reduction in the risk of mortality (HR 0.79, 95% CI 0.69-0.90, $P = 0.0003$), longer treatment durations provided benefits of an even greater magnitude (HR 0.61, 95% CI 0.47-0.81, $P = 0.0005$)
High Risk Prostate Cancer Treated with Pelvic Radiotherapy and 36 versus 18 months of ADT: Phase III Trial (GU ASCO 2013)

- 630 patients with Gleason > 7 and or PSA > 20 or T3-T4 randomized to 18 months of ADT versus 36 months
- 1 month anti-androgen, and LH-RH started 4 months before conformal RT
- Median follow up 77 months
- Prescription dose of RT: 70 Gy
- 10 year survival was 64% for the 36 month arm and 63% for the 18 month arm (p=0.42)
- 10 year DFS was 87% in both arms
498 assessed for eligibility

- 121 refused to participate
  - 15 did not have pretreatment data

362 registered

- 7 did not meet inclusion criteria
  - 3 had inadequate disease stage
  - 1 histopathological finding
  - 1 synchronous malignancy
  - 2 neoadjuvant hormonal treatment for more than 3 months

355 randomised

178 allocated to STAD
- 170 received allocated intervention
  - 8 did not receive allocated intervention
    - 2 investigator decision
    - 2 patient decision
    - 4 major deviation

- 5 lost to follow-up

178 analysed

177 allocated to LTAD
- 169 received allocated intervention
  - 8 did not receive allocated intervention
    - 4 patient decision
    - 2 major deviation
    - 2 intolerance

- 3 lost to follow-up

177 analysed
RCT: High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR – Zapatero et al):

- Improvements in outcomes for:
  - PSA-RFS
  - DMFS
  - OS
Effects of duration of androgen deprivation stratified by risk group. STAD=short-term androgen deprivation. LTAD=long-term androgen deprivation.

<table>
<thead>
<tr>
<th></th>
<th>Number of events</th>
<th>5-year rate (%, 95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>STAD</td>
<td>LTAD</td>
<td>STAD</td>
</tr>
<tr>
<td><strong>Biochemical disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>189</td>
<td>23</td>
<td>13</td>
<td>76 (71-80)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>166</td>
<td>14</td>
<td>8</td>
<td>88 (84-91)</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>189</td>
<td>17</td>
<td>5</td>
<td>82 (77-86)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>166</td>
<td>10</td>
<td>6</td>
<td>91 (88-95)</td>
</tr>
<tr>
<td><strong>Metastasis-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>189</td>
<td>20</td>
<td>9</td>
<td>79 (74-83)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>166</td>
<td>13</td>
<td>6</td>
<td>89 (85-93)</td>
</tr>
</tbody>
</table>
Potential Important Ingredients to Improve Outcome with Radiotherapy for High Risk Disease

• Need to deliver escalated radiation dose levels
• Deliver and adequate duration of adjuvant androgen deprivation therapy
• Need to include regional nodes within the treatment portal
• To consider exploring in study settings the use of novel second generation anti-androgens or systemic therapy in conjunction with local therapy
RTOG 0521
High Risk Patients (n=600)

2 mo neoad ADT
+72-76 Gy 3D-CRT/IMRT
+ 2 Yrs LH-RH

neoad ADT+72-76 Gy IMRT
+ 2 Yrs LH-RH
6 cycles docetaxel+prednisone
Beginning 28 days post RT
RTOG 1115 – TAK 700
(Steroid 17alpha-monooxygenase)

MedOnc PI: Michaelson, D.
RadOnc PI: Hamstra, D.

High Risk Prostate Cancer

Arm 1: LHRH x 2 yrs + high dose RT*
Arm 2: LHRH + TAK700 x 2 yrs + high dose RT*

Primary Endpoint: Overall Survival

*N = 900

*EBRT 79.2 or LDR or HDR boost allowed
ENZARAD

**Hypothesis:** Earlier use of potent AR antagonist with standard ADT and radiation will increase the number of patients cured of prostate cancer and increase overall survival

**Study chairs:** Scott Williams, Paul Nguyen and Christopher Sweeney

Enzalutamide 160mg daily for 24 months
+ LHRHA for 24 months
+ EBRT 78 Gy in 39# starting after 16 weeks

Endpoints
- Overall survival (primary)
- Cause specific survival
- PSA progression free survival
- Clinical progression free survival
- Health related quality of life
- Adverse events
- Incremental cost-effectiveness

Conventional NSAA for 6 months
+ LHRHA for 24 months
+ EBRT 78 Gy in 39# starting after 16 weeks

**800 participants**
- 2 years accrual + 5.5 years minimum additional follow-up
- 80% power to detect 33% reduction in the hazard of death from any cause, assuming an OS rate at 5 years of 76% in the control group

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid*
AbiRT: Study Design

- Phase II single arm open-label study
- Target enrollment of 37 patients
- Protocol will be open at Duke Cancer Institute and MD Anderson Cancer Center
- Six months of ADT and abiraterone acetate and once daily prednisone concurrent with definitive RT to the prostate and seminal vesicles.
  - RT will start week 9 of Abiraterone acetate/prednisone

*Unfavorable =
- GS 7 PSA < 20 ng/ml T1-2b
- GS 8-10 PSA ≤ 20 ng/ml T1
- GS ≤ 6 PSA 10.1-40 ng/ml T1
- cT3 GS < 7 PSA ≤10 ng/ml

Unfavorable* Localized Prostate Cancer

Enroll

Abiraterone acetate 1000mg PO daily x 6 mo
Prednisone 5mg PO daily x 6 mo
LHRH-Agonist x 6 mo

RT x 2 mo 75-80 Gy

1° Endpoint: Undetectable PSA @ 1yr
MSKCC High Risk Phase II Study
Comparing 2 Second Generation Anti-Androgens with SBRT (N=66)

- RT: hypo=fractionated RT starting 3 months after initiation of ADT: 5 Gy x 5 to Pelvis and 8 Gy x 5 to Prostate
- Arm 1: Abiraterone and Leuprolide x 6 months
- Arm 2: Abiraterone, ARN-509, and Leuprolide x 6 months with hypofractionated RT starting 3 months after initiation of ADT: 5 Gy x 5 to Pelvis and 8 Gy x 5 to prostate
- ENDPOINTS: PSA Relapse Free Survival @ 3 years
  2 year biopsy outcomes
ADT Guidelines

• There is no role for ADT in low risk patients except for downsizing the prostate prior to EBRT or Brachytherapy

• Intermediate Risk patients who receive conventional EBRT should receive 6 months of ADT based on Level 1 evidence from 2 randomized trials.

• The role of ADT in brachytherapy patients or those receiving dose intensification IMRT is currently being tested prospectively.

• For high risk patients long course ADT for 18 months is reasonable

• Novel targeted and biologic agents are being tested in conjunction with radiotherapy to further improve outcomes in this cohort.
55 year old sexually active male with T3 Prostate Cancer

- PSA 18.2 ng/ml
- Rectal exam consistent with ECE on the right
- MRI demonstrates 60 gram gland with right sided ECE and SVI
- Biopsy reveals Gleason 8-9 disease in 12 of 16 cores with core involvement ranging from 30-90%
How would you manage this patient?

- Surgery
- EBRT + ADT for 6 months
- EBRT + ADT for 18 months
- EBRT + ADT for 28 months
- Brachytherapy + EBRT with hormones
- Brachytherapy + EBRT without hormones
Adjuvant and Salvage Radiotherapy after Surgery Failure
Randomized Trials of Adjuvant RT to Prostate Bed After RRP

<table>
<thead>
<tr>
<th>Trial</th>
<th>#</th>
<th>Arms</th>
<th>PSA Adj RT</th>
<th>PSA Control Surg alone</th>
<th>P value</th>
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<tbody>
<tr>
<td>EORTC</td>
<td>1005</td>
<td>60 Gy to bed vs observation</td>
<td>74%</td>
<td>53%</td>
<td>&lt;0.001</td>
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<tr>
<td>SWOG</td>
<td>425</td>
<td>60 -64 Gy vs observation</td>
<td>64%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARO</td>
<td>385</td>
<td>60 Gy vs observation</td>
<td>81%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
SWOG 8794: Phase III Study for T3NO Adjuvant Post-Prostatectomy RT

Overall Survival

10-Year Estimate
74% 66%

Number at risk
RT 214 179 143 32
## Salvage RT after RP

<table>
<thead>
<tr>
<th>Series</th>
<th># patients</th>
<th>RT dose</th>
<th>f/u-months</th>
<th>%BNED</th>
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<tbody>
<tr>
<td>Caddeau</td>
<td>57</td>
<td>64 Gy</td>
<td>40</td>
<td>20%</td>
</tr>
<tr>
<td>Anscher</td>
<td>89</td>
<td>66 Gy</td>
<td>48</td>
<td>53%</td>
</tr>
<tr>
<td>Do</td>
<td>60</td>
<td>64.8 Gy</td>
<td>36</td>
<td>55%</td>
</tr>
<tr>
<td>Nudell</td>
<td>69</td>
<td>68 Gy</td>
<td>35</td>
<td>53%</td>
</tr>
<tr>
<td>Forman</td>
<td>47</td>
<td>66 Gy</td>
<td>36</td>
<td>64%</td>
</tr>
<tr>
<td>Pisansky</td>
<td>166</td>
<td>64 Gy</td>
<td>52</td>
<td>46%</td>
</tr>
<tr>
<td>Schild</td>
<td>46</td>
<td>64 Gy</td>
<td>37</td>
<td>50%</td>
</tr>
<tr>
<td>Valicenti</td>
<td>34</td>
<td>64.8 Gy</td>
<td>32</td>
<td>59%</td>
</tr>
<tr>
<td>Vicini</td>
<td>23</td>
<td>61.2 Gy</td>
<td>46</td>
<td>58%</td>
</tr>
<tr>
<td>Zelefsky</td>
<td>28</td>
<td>64.8 Gy</td>
<td>24</td>
<td>53%</td>
</tr>
</tbody>
</table>
Adjuvant or Salvage Radiotherapy?
# 5 Year PSA Relapse Free Survival Outcomes

## Adjuvant Versus Salvage Radiotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th># Adj/# Salv</th>
<th>PRFS-Adjuvant</th>
<th>PRFS-Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catton-01</td>
<td>54 / 59</td>
<td>81%</td>
<td>30%</td>
</tr>
<tr>
<td>Morris-97</td>
<td>40 / 48</td>
<td>81%</td>
<td>47%</td>
</tr>
<tr>
<td>Valicenti-98</td>
<td>15 / 18</td>
<td>86%</td>
<td>38%</td>
</tr>
<tr>
<td>Kalapuraki-02</td>
<td>35 / 41</td>
<td>86%</td>
<td>57%</td>
</tr>
<tr>
<td>Vicini-99</td>
<td>38 / 23</td>
<td>67%</td>
<td>16%</td>
</tr>
<tr>
<td>Pacholke-04</td>
<td>107 / 56</td>
<td>80%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Controversies in Adjuvant & Salvage Radiotherapy After Prostatectomy

• What is the role of hormone therapy in conjunction with radiotherapy?
• Should the prostate bed only be treated or the pelvis as well?
• Should patients get immediate adjuvant RT for a positive margin? Or can one simply watch the patient and treat if the PSA becomes detectable?
Early Salvage Versus Adjuvant RT

• 4 Ongoing Trials evaluating this issue and in 3 of these trials the benefit of short course ADT is studied
  – RADICALS
  – GETUG-17
  – RAVES
  – EORTC 22043
RADICALS Trial
(Radiotherapy and Androgen Deprivation in Combination with Local Surgery)

- PSA <0.2 but detectable but some risk factor such as pT3, positive margin, Gleason>6
- These patients will be randomized between immediate radiotherapy and early salvage radiotherapy
RADICALS Trial
(Radiotherapy and Androgen Deprivation in Combination with Local Surgery)

RADICALS - RT timing randomisation: Immediate RT vs salvage RT post-operatively

Post-operative uncertainty about the need for immediate RT

RT timing RANDOMISATION

Immediate RT
Salvage RT Policy (RT for PSA failure)

RADICALS - hormone duration randomisation: Use of hormones with post-operative RT

Patient for post-operative RT (either immediate or salvage RT)

Hormone duration RANDOMISATION

Radiotherapy Alone
Radiotherapy + 6 months hormone therapy
Radiotherapy + 2 years hormone therapy
Other Area of Controversy Related to SRT after RP

• Use of ADT and its duration?

• Should the nodes be covered?
RTOG 9601
(Closed 3/03 - 840 patients)

pT2/pT3 and or + margins with rising PSA 0.2-4.0

prostatic fossa RT 64.8 Gy

Bicalutamide 150 mg X 2 years

Placebo x 2 yrs
EORTC 22043

pT3 and or + margins

NODE NEGATIVE

Prostate Bed RT + ADT

Prostate Bed Alone
RTOG 0534

pT2/pT3 and or + margins with rising PSA 0.2-4.0

prostatic fossa RT 64.8 Gy

4-6 mo ADT + whole pelvic RT

prostatic fossa RT 64.8 Gy + 4-6 months ADT
Issues Re Treatment of the Nodes

- Tremendous variability of the number of nodes and the extent of node dissections among urologists.

- Higher risk higher grade patients who have suboptimal node dissections should be considered for nodal irradiation.

- Positive node on imaging may require higher radiation doses or in select cases lymph node dissections.
Treatment of the Pelvic Lymph Nodes in the Salvage Setting

• RTOG 0534 will inform us in the future role of including nodes during salvage therapy. In the meantime………..

• We consider incorporation of the pelvic nodes to 45 Gy if:
  – high grade disease is present especially in the setting of negative margins
  – Inadequate lymph node dissection
  – Positive pelvic node dissection
Improving Outcomes for Salvage RT: Optimizing the Selection of Patients

- Better selection of patients who have residual disease confined to the prostate bed or pelvic nodes only.

  - **Pathology Clues**
    - Positive margins
    - Established ECE

  - **PSA Clues**
    - Delayed detectability > 2 yrs from RP
    - PSA doubling time > 6-12 months
Improving Outcomes of Salvage Radiotherapy

• Refer patients early- once a rising PSA trend is noted
• Especially with those patients who have + SM, the threshold for initiating salvage RT should be low even if PSA level is low (i.e. < 0.2 ng/ml)
• Will use ADT for 6 months with RT for:
  – High grade Gleason 8-10 disease
  – Node positive patients especially with extra-nodal extension
  – Positive imaging or positive biopsy at the prostate fossa
  – Immediate detectable PSA
Phase II LH-RH Agonist and Abiraterone in PSA Relapsed Patients after Surgery

- Center: Lyon France
- Planned Accrual: 43 patients
- Endpoint: 3 year PRFS
- Eligibility: undetectable PSA after surgery that had risen to ≥0.2-2 ng/ml
- Planned treatment: Salvage RT and LH-RH + abiraterone for 6 months
Case Presentation

• 46 year old presents after robotic surgery with pT3a, Gleason 4+3
• Established ECE
• Negative margins
• 2 nodes sampled and were negative
• Post-op PSA undetectable
• 8 months after surgery PSA becomes detectable and 6 months later rises from 0.06 to 0.12 ng/ml
• Patient’s urinary incontinence is still improving.
Clinical Questions

• Would you obtain any staging work-up such as a bone scan? MRI?
• Do you start salvage RT now?
• Do you utilize ADT? And if so what duration of ADT will you recommend?
• Will you treat the prostate bed alone or the pelvis?
Extreme Hypofractionation for Clinically Localized Disease
Popularity of Ultra-Hypofractionation for Prostate Cancer Therapy

- **Convenience** of 5 treatments over 1.5 weeks instead of 50 treatments in 10 weeks.

- **Accuracy** with targeting the prostate during the actual treatment.

- Tighter margins meaning less inclusion of normal tissues and less toxicity.

- Higher dose per fraction with higher BED potentially leading to increased tumor control.
Ongoing Phase I Dose Escalation Study at MSKCC

- Ultra-hypofractionated IGRT Phase I dose escalation study
  - 650 cGy x 5- accrual completed
  - 700 cGy x 5- accrual completed
  - 750 cGy x 5- accrual completed
  - 800 cGy x 5- accrual completed

- Primary endpoint is toxicity
- Secondary endpoints included PSA tumor control and 2-year biopsy outcomes
<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>Dose/Fx</th>
<th>Fx</th>
<th>Total Dose</th>
<th>Median F/u (mo)</th>
<th>PSA Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia Mason (2010)</td>
<td>40</td>
<td>6.7</td>
<td>5</td>
<td>33.5 Gy</td>
<td>41</td>
<td>90%</td>
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<tr>
<td>Stanford (2009)</td>
<td>41</td>
<td>7.25</td>
<td>5</td>
<td>36.25 Gy</td>
<td>33</td>
<td>100%</td>
</tr>
<tr>
<td>Naples (2009)</td>
<td>112</td>
<td>7-7.25</td>
<td>5</td>
<td>35-36 Gy</td>
<td>24</td>
<td>99%</td>
</tr>
<tr>
<td>Winthrop (2010)</td>
<td>304</td>
<td>7-7.25</td>
<td>5</td>
<td>35-36 Gy</td>
<td>30</td>
<td>99%</td>
</tr>
<tr>
<td>Boike (2011)</td>
<td>45</td>
<td>9-10 Gy</td>
<td>5</td>
<td>45-50 Gy</td>
<td>30</td>
<td>100%</td>
</tr>
<tr>
<td>Georgetown (2013)</td>
<td>100</td>
<td>7-7.25</td>
<td>5</td>
<td>35-36 Gy</td>
<td>27</td>
<td>99%</td>
</tr>
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</table>
## Ultra-Hypofractionated RT - Toxicity Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose/</th>
<th>Median F/u (mo)</th>
<th>Late GI Toxicity</th>
<th>Late GU Toxicity</th>
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</thead>
<tbody>
<tr>
<td>King et al 2009</td>
<td>36.25Gy</td>
<td>33</td>
<td>48% G1-G2</td>
<td>65% G1-G2; 5% G3</td>
</tr>
<tr>
<td>Katz et al 2014</td>
<td>35 Gy</td>
<td>72</td>
<td>9% G1/G2</td>
<td>9% G1/G2 0.5%- G3</td>
</tr>
<tr>
<td>Bolzicco et al 2010</td>
<td>35 Gy</td>
<td>20</td>
<td>2.2% G-2</td>
<td>9% G1/G2 2.2%- G3</td>
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<tr>
<td>Freeman et al (2010)</td>
<td>36.25 Gy</td>
<td>60</td>
<td>15.5% G1-G2</td>
<td>32% G1/G2 2.5%- G3</td>
</tr>
<tr>
<td>King et al 2012</td>
<td>36.25 Gy</td>
<td>32</td>
<td>16% G1-G2</td>
<td>28% G1/G2 3.5%- G3</td>
</tr>
</tbody>
</table>
SBRT for Low and Intermediate Risk Prostate Cancer
(Katz and Kang- Front Onc 2014)

- 477 (67% Low Risk and 33% Intermediate Risk)
- 11% patients treated with concurrent ADT x 6 months
- 33% received 35 Gy/5 fractions and 67% treated to 36.25 / 5 fractions
- Median follow up up 72 months
SBRT for Low and Intermediate Risk Prostate Cancer (Katz and Kang- Front Onc 2014)

- PSA-RFS Low Risk: 95.6%
- PSA-RFS Intermediate Risk 89.6%
- Median time to PSA nadir : 48 months
- No Grade 3-4 GI Toxicity
- 1.7% Grade 3 GU Toxicity
Ultra-hypofractionated SBRT for Prostate Cancer

• So far comparable biochemical control outcomes at 5-6 years with high dose IMRT
• Similar toxicity outcomes but longer follow up required.
• Preliminary results also indicate excellent tolerance especially when using tight margins and intra-fraction motion tracking.
• While not experimental at this time, patients should be aware of the shorter follow-up and the need for prospective studies carefully assessing outcomes.
Swedish Phase III

Int Risk

78 Gy/2

42.7 Gy/6.1

n=592

ISRCTN45905321 (Wid
Proton Phase III

Low Risk

RA ND OM I Z E

Randomize

n=192

2:1

79.2 Gy/1.8 Gy

38 Gy/7.6 Gy

NCT01230866 (Varg
PACE Trial(s)

Low, Int, Risk

Surgical Cohort

Non-Surgical Cohort

Robotic RP vs SBRT

IMRT vs SBRT

n=1716

NCT01584
Proton Therapy for Prostate Cancer
PROG 9509

Prostate boost with protons - LLUMC
Protons and Prostate Cancer

- Between 2006-2009 there has been a doubling of prostate cancer patients treated with proton therapy.
- Increase in usage speculated to be related to the allure of new technology and high reimbursement per course of treatment.
- No evidence in the literature of superior tumor control outcomes with protons compared to photons for treatment of prostate cancer.
- University of Penn and MGH and other conducting randomized trial of IMRT vs proton for clinically localized disease.
Comparison of Outcomes and Toxicity Between Proton Therapy and IMRT (Sheets et al JAMA 2012)

- Population-based study using SEER-Medicare Linked data of treatments from 2000-2009
- Salient Findings:
  - IMRT patients had lower rates of GI toxicity (absolute risk: 12.2 vs 17.8 per 100 person-years; RR-0.66)
  - No significant differences in rates of other morbidities
  - Comparable tumor control outcomes as reflected by need to receive additional cancer therapies
Comparison of Need for Additional Cancer Therapies Between Patients Treated Initially with Proton Therapy Vs IMRT

JAMA 2012

![Graph showing the probability of additional treatment over months after radiation therapy for intensity-modulated radiation therapy (IMRT) and proton therapy. The graph indicates that the probability of additional treatment is higher for IMRT compared to proton therapy. The log-rank test shows a P-value of 0.41, indicating no significant difference between the two treatments.](image_url)
5-Year Outcome of Proton Therapy from Single Institution
(Mendenhall et al Int J Radiat Oncol Biol Phys 2014)

- 211 patients (89 low risk, 82 intermediate risk and 40 high-risk)
- 78-82 CGE
- High risk patients treated with docetaxel and ADT
- Median follow-up: 5.2 years
- 5-year PSA outcomes were: 99% for low risk, 99% for intermediate risk and 76% for high risk.
- The 5-year incidence of grade 3 rectal and urinary toxicities were 1% and 5.4%, respectively.
Phase III Randomized Trial of Protons vs IMRT for Low and Intermediate Risk Cancer for QoL

- Multicenter trial-lead at MGH and U of Penn
- Sample size: 400 patients
- RT Dose 79.2 Gy
- Primary Endpoint: Bowel function at 24 months
- Secondary Endpoints: Urinary and Erectile Function at 24 months
Protons for Prostate Cancer

- No evidence to date for superior tumor control rates with protons compared with high-dose photons for low or intermediate risk prostate cancer.

- Grade 2 rectal bleeding rates appear to be somewhat higher with protons compared to photons
  - IMPT may possibly reduce this risk further
  - The use of a rectal spacer may further reduce the risk

- A randomized trial comparing protons to photons for early stages of disease is underway with and endpoint of QOL but not outcomes.
Proton Phase III

Low Risk

Randomize

n=192
2:1

79.2 Gy/1.8 Gy

38 Gy/7.6 Gy

NCT01230866 (Varg)
Future of Protons for Prostate Cancer

• Proton beam therapy will need to be further developed
• Intensity modulated proton beam therapy associated with greater conformality may translate into reduced side effects and ability to deliver higher doses or hypo-fractionated regimens
• Longer follow-up to assess whether proton beam therapy is associated with lower secondary cancer risk incidence