Management of Early Stage Prostate Cancer

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Early Stage Disease: Favorable and Intermediate Risk Disease

- Role of dose escalation for favorable risk disease.

- Comparison of tumor control outcomes and toxicity profiles between IMRT and BRT.

- Enhanced technologies or treatment delivery for EBRT: IGRT, Protons, SBRT

- Management of Intermediate risk disease
  - Role of androgen deprivation therapy
  - Use of combined modality therapy (BRT+EBRT)

- Selection criteria for optimal radiotherapeutic management
Treatment Options

- Active Surveillance
- EBRT
- Brachytherapy as monotherapy
- Combined BRT with EBRT
- Surgery
- Focal therapy
- Cryotherapy
- HIFU (high intensity focused ultrasound therapy)
- Photodynamic therapy
Early Stage Disease- Case for Active Surveillance

• Increasing number of patients with low risk disease are considered for AS.

• Ideal candidates would include
  – Gleason 6 in < 50% of cores
  – PSA < 10 (and especially < 4)
  – T1c

• Patients should undergo MRI to document presence of dominant disease

• Consider second biopsy prior to pursing AS
Role of Dose Escalation for Early Stage Disease
## Randomized Trials of Dose Escalation with EBRT

<table>
<thead>
<tr>
<th>Series</th>
<th>Randomization</th>
<th>Outcome</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollack (2002)</td>
<td>78 Gy vs 70 Gy</td>
<td>70% vs 45%</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>Zietman (2006)</td>
<td>79.2 Gy vs 70.2 Gy (protons)</td>
<td>80% vs 60%</td>
<td>Low and Int Risk</td>
</tr>
<tr>
<td>Peeters (2006)</td>
<td>78 Gy vs 68 Gy</td>
<td>64% vs 54%</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>Dearnelay (2007)</td>
<td>74 Gy vs 64 Gy (with ADT)</td>
<td>85% vs 79%</td>
<td>All risk groups</td>
</tr>
</tbody>
</table>
Dose Escalation Advantage for Favorable Risk Disease
Zietman et al JCO 2010

Favorable Risk

Intermediate Risk
10-Year PSA Relapse-Free Survival
Low Risk Group: $\geq 75.6$ Gy vs $< 75.6$ Gy

Zelefsky et al Eur Urol 2011

P=0.04

84% vs 71%

PSA Relapse Free Survival

Month
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><em>Rectal Wall</em></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><em>Bladder Wall</em></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><em>Large Bowel</em></td>
<td>60Gy</td>
<td>Max Point Dose</td>
</tr>
<tr>
<td><em>Small Bowel</em></td>
<td>50Gy</td>
<td>Max Point Dose</td>
</tr>
</tbody>
</table>
Dose Delivered to PTV for 86.4 Gy

- Mean PTV 87.4 Gy
- D Max 95.1 Gy
- D95 82.5 Gy
- D90 86.1 Gy
- D75 88.3 Gy
- D50 89.2 Gy
- D05 91.4 Gy
Technological Enhancements for Treatment

A Moving Target
Technological Enhancements for External Beam Radiotherapy

• High dose IMRT (\(\geq 78\) Gy) is more routinely administered in the US even for low risk disease.

• Routine use of IGRT with fiducial marker placement to monitor and correct for inter-fraction motion and intra-fraction motion

• With the availability of IGRT, ultra-hypofractionation of treatment or SBRT is more commonly used
In 2008 gold fiducials routinely placed for all definitive prostate cancer IMRT.
During this time our PTV margins were maintained as 1 cm except at the prostate-rectal interface where a 6 mm margin used.
In late 2010 PTV margins reduced to 6mm circumferentially
Further margin reductions to 5 mm around the PTV and 3 mm posteriorly used for hypofractionated IGRT such as SRS and supplemental IMRT after brachytherapy
### 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


$P=0.024$
### Multivariable Analysis for Predictors of Late Urinary Toxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>%95 Confidence (+/-)</th>
<th>Standard Error</th>
<th>P value</th>
<th>Hazard Exponent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of Hormones</td>
<td>0.064</td>
<td>0.562</td>
<td>0.287</td>
<td>0.822</td>
<td>1.067</td>
</tr>
<tr>
<td>Non-IGRT vs IGRT</td>
<td>0.700</td>
<td>0.603</td>
<td>0.308</td>
<td>0.023</td>
<td>2.015</td>
</tr>
<tr>
<td>Age&gt;65</td>
<td>0.138</td>
<td>0.636</td>
<td>0.325</td>
<td>0.670</td>
<td>1.148</td>
</tr>
<tr>
<td>Baseline IPSS &gt;15</td>
<td>0.642</td>
<td>0.609</td>
<td>0.311</td>
<td>0.04</td>
<td>1.901</td>
</tr>
</tbody>
</table>
PSA Relapse-Free Survival According to Risk Group

Low Risk

Intermediate Risk

High Risk

$p = 0.592$

$P=0.439$

$p = 0.05$

## Dose-escalation

### 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%</td>
<td>GI 6% vs 10% (SS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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%</td>
<td>GI 4% vs 5% (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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%</td>
<td>GI 1% vs 1% (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GU 5% vs 4% (NS)</td>
</tr>
</tbody>
</table>
Urinary Toxicity after High Dose IMRT-

<table>
<thead>
<tr>
<th>Toxicity Grade ≥2</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>4.4</td>
<td>6.9</td>
</tr>
<tr>
<td>GU</td>
<td>16.0</td>
<td>26.7</td>
</tr>
</tbody>
</table>

10-year Crude Toxicity Grade 3

<table>
<thead>
<tr>
<th></th>
<th>GI</th>
<th>GU</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7%</td>
<td>2.2%</td>
<td></td>
</tr>
</tbody>
</table>

Grade 2+ GU Toxicity
Grade 2+ GI Toxicity

Spratt et al 2012- MSKCC
Late Grade 2 GI Toxicity Development
Median Follow-Up 8 years
(Zelefsky et al J Urol 2006)

13%
2%
p = 0.00018
81 Gy
0.05
0.1
0.15
0.2
0
12 24 36 48 60 72 84 96 108 120 132 144 156 168
Months
Probability
IMRT (n=170)
3DCRT (n=67)
Long Term Toxicity of IMRT (81-86.4 Gy)

- Grade 2 Urinary (frequency/urgency)- 15%-20%
- Grade 3 Urinary (urethral stricture)- 2%
- Grade 2 rectal (bleeding/proctitis): 2%
- Grade 3 rectal (ulceration/significant bleeding): <1%

- Erectile Dysfunction: 30-40% @ 5 years
  - Dry ejaculate in 90% of patients

MSKCC Data 2013
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
Brachytherapy for Low Risk Disease

- 5-10 year biochemical tumor control outcomes of ≥ 90%
- Results achieved with permanent interstitial I-125 or Pd-103 or HDR monotherapy
- With the exception of pre-tx volume reduction for prostate sizes > 50-60 grams, no need for combining with ADT.
- Reduced urinary toxicities (acute and late) observed among patients with IPS scores < 17
- Optimal tumor control outcomes seen with proper application of dose
  - D90 > 140 Gy to the prostate associated with improved long-term tumor control outcomes
Intra-operative Planning LDR Brachytherapy
PSA Relapse-Free Survival
(Zelefsky et al - Brachytherapy 2011)
Demonstration of Dose Response from Day 0 Dosimetry
(Zelefsky et al Brachytherapy 2011)

P = 0.005
<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>
## 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>
Technological Enhancements for Treatment

A Moving Target
Intraoperative Corrections of Inadequately Treated Regions
Intraoperative CT for Acquisition of Deposited Seed Coordinates To Use for True Real Time Planning
Focal Correction of Cold Spot with Intraoperative Real Time CT Guidance
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 comparison of additional treatment needs between Proton therapy and Intensity-modulated radiation therapy over time. The graph indicates that the need for additional treatments is similar for both therapies, with a log-rank P value of .41.]
Bragg peak serves as advantage to reduced exit dose potentially leading to reduced normal tissue exposure and theoretically lower risk of secondary cancers.

Bragg peak of a single energy is too to treat a tumor so different energies must be used to broaden the peak increasing the entrance dose.

Uncertainty as to how far protons will travel, so the high dose region is typically extended several mm beyond the target.

Protons susceptible to respiratory motion, rectal and bladder filling changes which can allow the high dose region to spill into the normal tissue regions increasing toxicity.

IMRT may conform the high dose region more effectively than traditional modes of proton therapy.
Ultra-Hypofractionated SBRT for Prostate Cancer

- Taking advantage of the theoretical radio-biologic advantage of higher dose per fraction
- IGRT will assure enhanced accuracy and reduce toxicity which is especially could be a concern with higher dose per fraction.

- **Will SBRT behave clinically like BRT or EBRT?**
Ultra-Hypofractionation for Prostate Cancer Therapy

- 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
- Higher dose in shorter period of time thought to cause greater biological damage inside the tumor
# Ultra-Hypofractionated RT
## Tumor Control 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>
</tr>
<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>
</tbody>
</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>
</tr>
</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 2010</td>
<td>35 Gy</td>
<td>30</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>
</tr>
<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>

Adapted from Seisen et al 2013
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 initiated
  - 800 cGy x 5
  - 850 cGy x 5

- Primary endpoint is toxicity

- Secondary endpoints included PSA tumor control and 2-year biopsy outcomes

- Eligibility includes IPSS < 17, Favorable/Intermediate Risk, no prior ADT
Planning constraints – Converted from 8640 planning protocols.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RW max</td>
<td>3832 cGy</td>
</tr>
<tr>
<td>D53 Rw</td>
<td>2400 cGy</td>
</tr>
<tr>
<td>RW NTCP</td>
<td>12.5 (Average NTCP of 8640cGy patient)</td>
</tr>
<tr>
<td>Urethra max</td>
<td>4011 cGy</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>4100 cGy</td>
</tr>
<tr>
<td>D53 BW</td>
<td>2400 cGy</td>
</tr>
<tr>
<td>BOWEL S/L</td>
<td>2516 / 2899 cGy</td>
</tr>
</tbody>
</table>

1. Margins 3 mm at prostate rectal interface and 5 mm circumferentially
2. Patient simulated with catheter so urethra can be well delineated
3. Real time Tracking employed for each of the 5 fractions
PTV D95 = 3700
Ultra-Hypofractionated SBRT for Prostate Cancer

• Taking advantage of the theoretical radio-biologic advantage of higher dose per fraction

• IGRT will assure enhanced accuracy and reduce toxicity which is especially could be a concern with higher dose per fraction.

• *Will SBRT behave clinically like BRT or EBRT?*
SBRT- Personal Perspectives

• SBRT will likely replace conventional EBRT for low and intermediate risk disease
• SBRT will more likely behave like BRT (HDR monotherapy) compared to EBRT.
• Dose painting with image guidance may further enhance outcomes with larger volume of disease
Management of Intermediate Risk Disease
Intermediate Risk Prostate Cancer

- NCCN Intermediate Risk Factors
  - Clinical stage T2b-c
  - Gleason score 7
  - PSA 10-20

- Multiple intermediate risk factors may be classified as high risk disease

- Optimum therapy is controversial
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
Can Dose Escalation Replace Short Term ADT?

• Low Doses Used in Both Trials
  – RTOG 94-08: ~63 Gy to 95% isodose line
  – DFCI Trial: 70.4 Gy to 95% isodose line

• Dose Escalation Trials

• Evidence that Short Term ADT + RT interacts locally
  – Negative Results of RCT’s w/ ADT + Surgery
  – RTOG 94-08 post-treatment biopsy data

• Is ADT necessary in the dose escalation era?
Why is ADT Beneficial w/ Dose Escalated EBRT?

- Post-treatment Biopsy Data
  - 33% positive after ≥ 81 Gy (MSKCC data)
- Molecularly targeted radiosensitization
- Improved target coverage
- Micrometastasis sterilization?
Adverse Sequelae of ADT

• Adverse Quality of Life Sequelae
  – Hot flashes, fatigue, sexual dysfunction, decreased libido, depression

• Adverse Medical Sequelae
  – Weight gain, muscle loss, diabetes
  – Anemia
  – Osteoporosis
  – Increased cardiovascular morbidity and mortality is controversial
PSA RFS for Intermediate Risk
\[ \geq 81 \text{ Gy} \text{ versus} < 81 \text{ Gy} \]
(Zelefsky et al Eur Urol 2011)

76%
57%
P < .0001
PSA –RFS for Intermediate Risk Treated with and *Without* ADT

P<0.001

Hormones

No Hormones

>=81 Gy

P<0.001
Impact of Short Course ADT on DMFS for Intermediate Risk Patients
(Zumsteg et al- IJROBP 2013)

P = .011
Impact of Short Course ADT on Prostate Cancer Related Deaths for Intermediate Risk
(Zumsteg et al- IJROBP 2013)

P = .032
### Prostate Cancer Specific Mortality: Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>UVA</th>
<th>MVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>ADT</td>
<td>0.380</td>
<td>0.157-0.921</td>
</tr>
<tr>
<td>Gleason (6 or less and 3+4 vs 4+3)</td>
<td>3.500</td>
<td>1.590-7.700</td>
</tr>
<tr>
<td>Stage (T2b+ vs ≤T2a)</td>
<td>1.500</td>
<td>0.671-3.370</td>
</tr>
<tr>
<td>Pretreatment PSA (≥ 10 vs &lt; 10)</td>
<td>0.726</td>
<td>0.312-1.690</td>
</tr>
<tr>
<td>% positive cores (≥ 50% vs &lt; 50%)</td>
<td>4.030</td>
<td>1.790-9.090</td>
</tr>
<tr>
<td>Dose (86.4 Gy vs 81.0 Gy)</td>
<td>1.380</td>
<td>0.617-3.070</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>1.000</td>
<td>0.944-1.058</td>
</tr>
</tbody>
</table>
Unfavorable Risk Factors: Gleason 7 (4+3) and ≥ 50% positive biopsy cores

Favorable: 10 yr PSA-RFS = 83.0%
Unfavorable: 10 yr PSA-RFS = 67.6%  P < 0.001
Unfavorable Risk Factors: Gleason 7 (4+3) and ≥ 50% positive biopsy cores

Favorable: 10 yr DM: 5.0%
Unfavorable: 10 yr DM: 12.4%  
P < 0.001
Unfavorable Risk Factors: Gleason 7 (4+3) and ≥ 50% positive biopsy cores

Favorable: 10 yr PCSM: 2.9%
Unfavorable: 10 yr PCSM: 5.0%  \( P < 0.001 \)
### Is there a Benefit adding ADT with Brachytherapy?

<table>
<thead>
<tr>
<th>Series</th>
<th>#</th>
<th># IR</th>
<th>% with ADT</th>
<th>Treatment</th>
<th>Outcome Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ash 2005</td>
<td>667</td>
<td>238</td>
<td>52%</td>
<td>LDR</td>
<td>None for IR</td>
</tr>
<tr>
<td>Stock 2010</td>
<td>432</td>
<td>432</td>
<td>81%</td>
<td>LDR+EB</td>
<td>No</td>
</tr>
<tr>
<td>Martinez 2005</td>
<td>934</td>
<td>NR</td>
<td>44%</td>
<td>HDR+EB</td>
<td>None for PSA, DM or OS</td>
</tr>
<tr>
<td>Merrick 2006</td>
<td>938</td>
<td>425</td>
<td>41%</td>
<td>LDR or LDR+EB</td>
<td>None for PSA, DM or OS for IR</td>
</tr>
<tr>
<td>Beyer 2005</td>
<td>2378</td>
<td>787</td>
<td>20%</td>
<td>LDR or LDR+EB</td>
<td>None for PCSM, reduced OS</td>
</tr>
<tr>
<td>Zelefsky 2011</td>
<td>1466</td>
<td>563</td>
<td>31%</td>
<td>LDR or LDR+EB or HDR+EB</td>
<td>No for PRFS</td>
</tr>
<tr>
<td>Krauss 2011</td>
<td>575</td>
<td>417</td>
<td>47%</td>
<td>LDR or LDR+EB or HDR+EB</td>
<td>Benefit for monotherapy, none for combined</td>
</tr>
</tbody>
</table>
Modes of Dose Escalation

- IMRT High Dose
- LDR+ IMRT
- HDR+ IMRT
- HDR Monotherapy
Intermediate Risk

\[ p < 0.001 \]

Deutch, Zelefsky et al Brachytherapy 2011

![Graph showing comparison between HDR and IMRT with significant difference marked as P < 0.001](image)
### Table 5: Memorial Sloan-Kettering Cancer Center treatment algorithm for definitive radiotherapy in patients with intermediate-risk prostate cancer

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Favourable intermediate-risk prostate cancer*</th>
<th>Unfavourable intermediate-risk prostate cancer†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One intermediate risk factor</td>
<td>Several intermediate risk factors</td>
</tr>
<tr>
<td></td>
<td>Gleason score of 3+4=7 or less</td>
<td>Gleason score of 4+3=7</td>
</tr>
<tr>
<td></td>
<td>&lt;50% positive biopsy cores</td>
<td>≥50% positive biopsy cores</td>
</tr>
<tr>
<td>Recommended radiation options</td>
<td>Dose-escalated external beam radiotherapy alone</td>
<td>Dose-escalated external beam radiotherapy and short-term androgen deprivation therapy</td>
</tr>
<tr>
<td></td>
<td>Brachytherapy alone in select cases (e.g., ≤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.