2018 ASTRO Refresher Course: Prostate Cancer

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Oregon Health and Science University
Disclosures

• UpToDate
  • Chapter author, royalties

• Oregon Health and Science University
  • Practicing Radiation Oncologist, salary
Learning Objectives

• Review the most recent literature
• Learn how to incorporate clinical evidence into clinical practice
GLEASON GRADE GROUP DEFINITIONS

Gleason grade group 1: Gleason score ≤6
Only individual discrete well-formed glands

Gleason grade group 2: Gleason score 3+4=7
Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands

Gleason grade group 3: Gleason score 4+3=7
Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands

Gleason grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
• Only poorly-formed/fused/cribriform glands or
• Predominantly well-formed glands and lesser component lacking glands\(^1\) or
• Predominantly lacking glands and lesser component of well-formed glands\(^1\)

Gleason grade group 5: Gleason score 9-10
Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands\(^2\)
Outline

• Screening for Prostate cancer
• Low/intermediate risk Prostate cancer
  • Active surveillance vs treatment
  • Surgery vs EBRT
  • Brachytherapy vs EBRT
• Hypofractionated EBRT
• High risk Prostate cancer
  • Incorporation of brachytherapy boost
• ADT with EBRT

• Post-prostatectomy RT
  • Adjuvant vs salvage
• Lymph-node positive Prostate cancer
  • Role of pelvic RT
• Bone metastases from Prostate cancer
  • Radium-223 systemic therapy
• Prognostic biomarkers/PET imaging
• Contours and DVH parameters
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• Prognostic biomarkers/PET imaging

• Contours and DVH parameters
## Prostate Cancer Screening Trials

<table>
<thead>
<tr>
<th></th>
<th>PLCO (&quot;US&quot;)</th>
<th>ERSPC (&quot;European&quot;)</th>
<th>Goteberg (&quot;Swedish&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Men</td>
<td>76,693</td>
<td>162,388</td>
<td>20,000</td>
</tr>
<tr>
<td>Age Range</td>
<td>55-74</td>
<td>55-69</td>
<td>50-64</td>
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<tr>
<td>Screening group</td>
<td>PSA q1yr x6, DRE qyr x4</td>
<td>PSA q4yr</td>
<td>invitation to PSA q2 yrs</td>
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<tr>
<td>Control group</td>
<td>‘usual’ care</td>
<td>no screening</td>
<td>no screening</td>
</tr>
<tr>
<td>Med f/u (years)</td>
<td>13</td>
<td>13</td>
<td>14 yrs</td>
</tr>
<tr>
<td>Indication for biopsy</td>
<td>PSA&gt;4 or abnormal DRE</td>
<td>PSA&gt;3</td>
<td>PSA&gt;2.5-3.4 (dep on yr)</td>
</tr>
<tr>
<td>Intervention arm compliance</td>
<td>85% PSA, 86% DRE</td>
<td>82% screened ≥once, Avg. 2.27 per subject</td>
<td>76% of invited had ≥1 PSA</td>
</tr>
<tr>
<td>PrCa detection (scr/cont)</td>
<td>11.1% vs 9.9%</td>
<td>9.6% vs 6.0%</td>
<td>12.7% vs 8.2%</td>
</tr>
<tr>
<td>PrCa deaths (scr/cont)</td>
<td>158 vs 145</td>
<td>299 vs 462</td>
<td>44 vs 78</td>
</tr>
<tr>
<td>RR of PrCa death</td>
<td>1.09 (0.87-1.36)</td>
<td>0.79 (0.69-0.91)</td>
<td>0.56 (0.39-0.82)</td>
</tr>
<tr>
<td>NNI (Invite)/NND (Diagnose)</td>
<td>na</td>
<td>781/27</td>
<td>293/12</td>
</tr>
<tr>
<td>Notes</td>
<td>44% prescreened in both arms</td>
<td>Low/Int risk: 84.8% (scr) vs 68.4% (cont)</td>
<td>Younger men, less prescreening</td>
</tr>
<tr>
<td></td>
<td>Up to 52% of cont. arm screened</td>
<td>PPV 24.1%</td>
<td>lower PSA threshold</td>
</tr>
</tbody>
</table>

Andriole et al., JNCI 2012; Schroder et al., Lancet 2014; Hugosson et al., Lancet 2010
ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
Comparing to screening mammography

Based on randomized clinical trials, for women ages 40-49, NNI was estimated at 1904 (USPSTF, Intern Med 2009, 151:716-726)

Based on Cancer Intervention and Surveillance Modeling Network analysis:
- for women ages 40-49 NNS was estimated at 746,
- for women between 50-59 NNS was 351,
- for women ages 60-69 NNS was 233,
- for women ages 70-79 NNS was 377
PSA Screening Guidelines

• USPSTF (May 2012): recommends against PSA screening

• AUA (April 2013)
  • <40 yo: No screening recommended
  • 40-54 yo: No screening recommended unless higher risk (ex: family hx, AA)
  • 55-69 yo: Risk/Benefit discussion with patient and screening if patient is in agreement
    • “shared decision making” “based on a man’s values and preferences”
  • 70+ yo: No screening recommended, some men in excellent health may benefit
PSA Screening Guidelines

NCCN Guidelines Version 2.2017
Prostate Cancer Early Detection

**BASELINE EVALUATION**
- History and physical (H&P) including:
  - Family history
  - Medications
  - History of prostate disease and screening, including prior PSA and/or isoforms, exams, and biopsies
  - Race
  - Family or personal history of BRCA1/2 mutations

**RISK ASSESSMENT**
- Start risk and benefit discussion about offering prostate screening:
  - Baseline PSA
  - Strongly consider baseline digital rectal examination (DRE)

**EARLY DETECTION EVALUATION**

- **Age 45-75 y**
  - PSA <1 ng/mL, DRE normal (if done)
  - PSA 1-3 ng/mL, DRE normal (if done)
  - PSA >3 ng/mL or very suspicious DRE

- **Age >75 y, in select patients (category 2B)**
  - PSA <4 ng/mL, DRE normal (if done), and no other indications for biopsy
  - PSA ≥4 ng/mL or very suspicious DRE

- Repeat testing at 2–4 year intervals
- Repeat testing at 1–2 year intervals
- See Indications for Biopsy (PROSD-3)
- Repeat testing in select patients at 1–4 year intervals
- See Indications for Biopsy (PROSD-3)
Conclusion

• Conflicting evidence from randomized trials
• Conflicting national guidelines
• If one considers offering PSA screening, it should start with a thorough discussion of risks and benefits
ProtecT: The Trial of the Century
CAP/ProtecT

Age 50-69

550,000 men

Stratified: geography

Randomized by family practice (337)

Invited: 228,966
Attended: 100,444
Screened: 82,429

3 < PSA <20: 8566
Biopsy: 7414
Diagnosed: 2896
Localized, T1-T2: 2417

Case detection

Consented: 1643

Randomization

Surgery

553

EBRT + ADT

545

Active Monitoring

545

ProtecT

Turner, Br J Ca 2014
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ProtecT: Patients

- Criteria
  - 50-69 yo
  - PSA 3-20, median 4.6
  - cT1-T2N0M0, 76% T1c

- Initial workup
  - DRE
  - PSA
  - TRUS biopsy
  - MRI optional
  - Bone scan if PSA >10 or G>7

- Randomized by practice
- Stratified by
  - Age
  - Gleason
  - PSA

<table>
<thead>
<tr>
<th>Age at invitation (years)</th>
<th>Active monitoring (n=545)</th>
<th>Radiotherapy (n=545)</th>
<th>Radical prostatectomy (n=553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49-54</td>
<td>58 (11%)</td>
<td>62 (11%)</td>
<td>69 (12%)</td>
</tr>
<tr>
<td>55-59</td>
<td>140 (26%)</td>
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<td>137 (25%)</td>
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<td>60-64</td>
<td>184 (34%)</td>
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<td>172 (31%)</td>
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<td>65-69</td>
<td>163 (30%)</td>
<td>166 (30%)</td>
<td>175 (32%)</td>
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</tbody>
</table>

| Median age (range)       | 62 (50-69)                | 62 (49-69)*          | 62 (50-69)                    |
| PSA (µg/L)               |                           |                      |                               |
| 3.0-5.9                  | 373 (68%)                 | 373 (68%)            | 371 (67%)                     |
| 6.0-9.9                  | 116 (21%)                 | 121 (22%)            | 123 (22%)                     |
| ≥10.0                    | 56 (10%)                  | 51 (9%)              | 59 (11%)                      |

| Median PSA range; µg/L   | 4.6 (3.0-20.9)†           | 4.6 (3.0-18.8)       | 4.7 (3.0-18.4)               |
| Gleason score            |                           |                      |                               |
| 6                        | 421 (77%)                 | 423 (78%)            | 422 (76%)                     |
| 7                        | 111 (20%)                 | 108 (20%)            | 120 (22%)                     |
| 8-10                     | 13 (2%)                   | 14 (3%)              | 10 (2%)                       |
| Missing                  | 0                         | 0                    | 1 (<1%)                       |
| Clinical stage           |                           |                      |                               |
| T1c                      | 410 (75%)                 | 429 (79%)            | 410 (74%)                     |
| T2                       | 135 (25%)                 | 116 (21%)            | 143 (26%)                     |

Data are number (%) or median (range). *One person was aged 49 years when the primary care list was generated, but fitted the stated inclusion criteria as per protocol. †One patient from the feasibility study had a serum PSA concentration of 20.9 µg/L at the specialist nurse visit; the concentration fell to 17.6 µg/L on repeat measurement and he became eligible for recruitment.

Table 3: Participant and clinical characteristics at randomisation in the ProtecT trial

Lane, Lancet Oncol 2014
ProtecT: Treatments

- **Active monitoring**
  - PSA q3 mo x 1y, q6 mo thereafter
  - Rise of 50% in 12 mo: consider biopsy

- **RT**
  - 3D CRT
  - 74 Gy/37 fx
  - 3-6 mo neoadjuvant and concurrent ADT

- **Prostatectomy**
  - 82% open, 6% lap, 6% robot
  - 66% nerve-sparing
  - PLND if PSA ≥10, Gleason ≥7
  - 29% with ECE (upstaged to T3)

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<tr>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
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<td></td>
<td></td>
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Table 3: Participant and clinical characteristics at randomisation in the ProtecT trial

Lane, Lancet Oncol 2014
ProtecT: Outcomes

- Prostate-cancer-specific survival at 10 years:
  - 98.8% (AM)
  - 99.0% (Surgery)
  - 99.6% (EBRT+ADT)
# ProtecT: GS 6 vs 7

## Table 2. Deaths from Prostate Cancer, According to Subgroup.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Deaths Due to Prostate Cancer</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Monitoring (N=545)</td>
<td>Surgery (N=553)</td>
</tr>
<tr>
<td>Age at randomization</td>
<td>0.09</td>
<td></td>
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<tr>
<td>&lt;65 yr</td>
<td>1</td>
<td>3</td>
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<tr>
<td>≥65 yr</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PSA level at diagnosis</td>
<td>0.72</td>
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<tr>
<td>&lt;6 ng/ml</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>≥6 ng/ml</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Gleason score at diagnosis§</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥7</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Clinical stage at diagnosis¶</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>T2</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation†</th>
<th>Age at diagnosis</th>
<th>Gleason score at diagnosis</th>
<th>PSA at diagnosis</th>
<th>Biopsy cores with tumour</th>
<th>Stage at diagnosis</th>
</tr>
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<tbody>
<tr>
<td>AM</td>
<td>60-64</td>
<td>6</td>
<td>6-9.99</td>
<td>3</td>
<td>T2</td>
</tr>
<tr>
<td>AM</td>
<td>65-69</td>
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<td>1</td>
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<td>7</td>
<td>T1c</td>
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<tr>
<td>RP</td>
<td>55-59</td>
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<td>&lt;6</td>
<td>3</td>
<td>T1c</td>
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<tr>
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<td>60-64</td>
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<td>65-69</td>
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<td>&lt;6</td>
<td>4</td>
<td>T2</td>
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<tr>
<td>RT</td>
<td>55-59</td>
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<td>&lt;6</td>
<td>3</td>
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</tbody>
</table>
Other lessons from ProtecT:

• Conversion to treatment
  • 291/545 (53%) of AM underwent surgery or RT by 10y
    • AM often deferral, not avoidance, of treatment
    • 19% tx within 9 mo

• Primary treatment failure
  • RP: 4.6% (18) (PSA ≥0.2 at 3mo)
  • RT: 14% (55) (PSA ↑ ≥2+nadir)
Active surveillance: take-home message

• Does not jeopardize overall and prostate cancer-specific survival
• A shared-decision with patient:
  • Metastatic disease developed in 6.3 vs 3.0 per 1000 person-yr on AM vs RT
  • No difference in survival
  • Differences in quality of life
• Different approach in US:
  • Toronto experience (Klotz et al., JCO 2010):
    • Confirmatory biopsy at 6-12 months, then q 3-4 years until age 80
  • Johns Hopkins experience (Tosoian et al., JCO 2011):
    • Annual biopsies
  • NCCN guidelines (Version 1.2017): “A repeat prostate biopsy should be considered as often as annually to assess for disease progression, because PSA kinetics may not be as reliable as monitoring parameters to determine progression of disease. Biopsy is no longer indicated when life expectancy is < 10 years.”
### NCCN Guidelines Version 2.2017
Prostate Cancer

#### Table 2. Selected Active Surveillance Experiences in North America

<table>
<thead>
<tr>
<th>Center</th>
<th>Toronto (^{95,147,160})</th>
<th>Johns Hopkins (^{101,145,148,149})</th>
<th>UCSF (^{146})</th>
<th>UCSF (newer cohort) (^{532})</th>
<th>Canary PASS (^{163})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>993</td>
<td>1298</td>
<td>321</td>
<td>810</td>
<td>905</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>68</td>
<td>66</td>
<td>63</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>77</td>
<td>60</td>
<td>43</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Overall survival</td>
<td>80% (10-y)</td>
<td>93% (10-y)</td>
<td>98% (10-y)</td>
<td>98% (5-y)</td>
<td>-</td>
</tr>
<tr>
<td>Cancer-specific survival</td>
<td>98% (10-y)</td>
<td>99.9% (10-y)</td>
<td>100% (5-y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conversion to treatment</td>
<td>36.5% (10-y)</td>
<td>50% (10-y)</td>
<td>24% (3-y)</td>
<td>40% (5-y)</td>
<td>19% (28-mo)</td>
</tr>
</tbody>
</table>

#### Reason for treatment (% of entire cohort)

<table>
<thead>
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<th>Reason for treatment</th>
<th>Toronto</th>
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<th>UCSF</th>
<th>UCSF (newer cohort)</th>
<th>Canary PASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason grade change</td>
<td>9.5%</td>
<td>15.1%</td>
<td>38%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PSA increase</td>
<td>11.7%*</td>
<td>-</td>
<td>26%†</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Positive lymph node</td>
<td>-</td>
<td>0.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Personal choice</td>
<td>-1.6%</td>
<td>8%</td>
<td>8%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* PSA doubling time <3 years
† PSA velocity >0.75 ng/mL/year
ProtecT: QOL

Kiri Sandler (UCLA): Survey of expert GU radiation oncologists

I often recommend AS to patients with PCa

McClelland et al., Clinical Genitourinary Cancer, in press
Low/Intermediate PCa: Brachytherapy

Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

Peter Grimm¹, Ignace Billiet², David Bostwick³, Adam P. Dicker⁴, Steven Frank⁵, Jos Immerzeel⁶, Mira Keyes⁷, Patrick Kupelian⁸, W. Robert Lee⁹, Stefan Mačtens¹⁰, Jyoti Mayadev¹¹, Brian J. Moran¹², Gregory Merrick¹³, Jeremy Millar¹⁴, Mack Roach¹⁵, Richard Stock¹⁶, Katsuto Shinohara¹⁵, Mark Scholz¹⁷, Ed Weber¹⁸, Anthony Zietman¹⁹, Michael Zelefsky²⁰, Jason Wong²¹, Stacy Wentworth²², Robyn Vera²³ and Stephen Langley²⁴

BJU, 2012
Low/Intermediate PCa: Brachytherapy

- Surgery
- Brachy
- EBRT
- HDR
- Protons
- Robot
- HIFU
- EBRT+Seeds
- HDR
- Robot
- Seeds+ADT
- Protons
- Cryo

Maximum follow-up, years

% PSA Free Progression

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For a patient with Gleason 6 PCa who desires treatment, with no baseline urinary symptoms and a 40 cc gland, my first choice recommendation is:

- Brachy: 50.00%
- EBRT: 16.70%
- Either: 33.30%

McClelland et al., in submission
Conclusion

• Active surveillance is the default treatment modality for patients with low risk prostate cancer
• Potential for increased risk of metastatic disease progression should be discussed with patients
• Active surveillance may also be considered for patients with intermediate risk prostate cancer
• Brachytherapy may offer the most durable biochemical control for patients with low/intermediate risk disease
Updated Recommendations:

- For patients with low-risk prostate cancer who require or choose active treatment, LDR alone, EBRT alone, or RP should be offered to eligible patients.
- For low-intermediate risk prostate cancer (Gleason 7, PSA < 10 or Gleason 6, PSA 10-20), LDR brachy alone may be offered as monotherapy.
- I-125 and Pd-103 are each reasonable isotope options for patients receiving LDR brachytherapy.
- No recommendation can be made for or against Cs-131 or HDR monotherapy.
Outline

• Screening for Prostate cancer
• Low/intermediate risk Prostate cancer
  • Active surveillance vs treatment
  • Surgery vs EBRT
  • Brachytherapy vs EBRT
• Hypofractionated EBRT
• High risk Prostate cancer
  • Incorporation of brachytherapy boost
• ADT with EBRT

• Post-prostatectomy RT
  • Adjuvant vs salvage
• Lymph-node positive Prostate cancer
  • Role of pelvic RT
• Bone metastases from Prostate cancer
  • Radium-223 systemic therapy

• Prognostic biomarkers/PET imaging
• Contours and DVH parameters
EBRT: Conventional vs Hypofractionated

- RTOG 0415
- CHHiP (UK, Ireland, Switzerland, New Zealand)
- HYPRO (Dutch)
- PROFIT (Canada, Australia and France)
Hypofractionation: RTOG 0415

RTOG 0415

- 73.8 Gy (1.8 Gy x 41)
- 70 Gy (2.5 Gy x 28)

BED (GY)

α/β ratio

0 2 4 6 8 10 12

Favors HF

α/β for BED: 10

Favors CF

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RTOG 0415

- 1115 men, median age 67 years
- All low-risk:
  - T1b-T2c, Gleason 2-6, PSA <10
  - No ADT
- RT
  - Randomization: 73.8/41 (1.8) vs 70/28 (2.5)
  - All qd
  - 21% 3D, 79% IMRT
  - Fiducials required
  - No SVs or LN

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>≤ 59</td>
</tr>
<tr>
<td>60-69</td>
</tr>
<tr>
<td>≥ 70</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
</tr>
<tr>
<td>&lt; 4</td>
</tr>
<tr>
<td>4 to &lt; 10</td>
</tr>
<tr>
<td>Gleason score</td>
</tr>
<tr>
<td>2-4</td>
</tr>
<tr>
<td>5-6</td>
</tr>
<tr>
<td>T stage</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>Radiotherapy modality</td>
</tr>
<tr>
<td>3D-CRT</td>
</tr>
<tr>
<td>IMRT</td>
</tr>
</tbody>
</table>

Lee, JCO 2016
RTOG 0415: efficacy

• 5 yr DFS
  • CF: 85.3%
  • HF: 86.3%
    HR 0.85 (0.64-1.14) p(ni)<0.001

• Interpretation
  • HF is non-inferior to CF with respect to 5 yr DFS

• 5 yr biochemical recurrence
  • CF: 8.1%
  • HF: 6.3%
    HR 0.77 (0.51-1.17) p(ni)<0.001

• 5 yr OS
  • CF: 93.2%
  • HF: 92.5%
    HR 0.95 (0.64-1.41) p(ni)=0.008

Lee, JCO 2016
RTOG: toxicity

- Early (90d)
  - no difference
- Late
  - GI Gr 2: 1.59 (1.22-2.06) p=0.005
  - GU Gr 2: 1.31 (1.07-1.61) p=0.009
RTOG 0415: Toxicity

Results: EPIC PRO at 1 year

- Hormonal scores had no change from baseline in either arm.
- Sexual function had a large similar decline on both arms of about 15 points on the CF arm and 11 points on the HF arm but these changes were not significantly different.
- Urinary scores exhibited almost no decline from baseline in both arms: 0 points for CF and 2 points for HF and these changes were not significantly different between arms.
- Bowel scores exhibited a small decline from baseline in both arms: 0 points for CF and 2 points for HF and these changes were not significantly different between arms.
- As compared with CF, pts treated with HF had a statistically larger decline in bowel scores, however this change was not deemed clinically significant – meaning the patients could not tell the difference in bowel changes between the shorter HF arm and the longer CF arm.

Our findings are similar to studies of bowel and bladder function in men without cancer and me treated with even shorter courses of RT.
Hypofractionation: CHHiP

![Graph showing BED (Gy) vs. α/β ratio for different radiation doses.]

- 74 Gy (3 Gy x 23)
- 60 Gy (3 Gy x 20)
- 57 Gy (3 Gy x 19)

Favors HF: α/β for BED: 2.4
Favors CF
Hypofractionation: CHHiP

- 3216 men, 71 centers
  - UK, Ireland, Switzerland, New Zealand
  - Median 69 yo
  - T1b-T3aN0, PSA <30 (mean 11)
  - 13% low / 73% int / 12% high
- 96% ADT (median 24 wks)
- RT
  - Randomization: 74/37 (2), 60/20 (3), 57/19 (3)
  - No SVs or LN
  - All IMRT; 30% IGRT
  - Estimate PCa $\alpha/\beta$ 2.4 for 60/20 and 1.4 for 57/19

Dearmaley, Lancet Oncol 2016
CHHiP: efficacy

- 5 yr bRFS/cRFS
  - 74 Gy: 88.3% (86.0-90.2%)
  - 60 Gy: 90.6% (88.5-92.3%)
    vs 74: HR 0.84 (0.68-1.03), p=0.16
  - 57 Gy: 85.9% (83.4-88%)
    vs 74: HR 1.20 (0.99-1.46), p=0.11
- Interpretation (NI HR 1.208)
  - 60 Gy is non-inferior to 74
  - 57 Gy not non-inferior to 74
  - Not designed to compare 60 Gy vs 57 Gy
- OS: no differences
CHHiP: acute toxicity

- GI grade ≥ 2: 38% vs 25% (SS)
- GU grade ≥ 2: 49% vs 46% (NS)
- By week 18, there was no difference
- Earlier peak of acute toxicity
  - weeks 4-5 compared to weeks 7-8
CHHiP: late toxicity at 5 yrs

• GI grade ≥ 2: 12%
• GU grade ≥ 2: 10%
• Cumulative grade ≥ 3 toxicity < 4%
CHHiP: nuances

- 9% death within 5 years of starting ADT-RT:
  - 16% Pca-related
  - 35% related to 2nd malignancy
  - 44% non-cancer causes
  - 5% unknown

- Pre-specified subgroup analysis: age and biochemical control

- Improved biochemical control between 60/20 and 57/19
  - last fraction matters!

- 3 Gy fractions rarely used in UK until 2014-2015, now 20% of patients are treated with 60/20
Hypofractionation: PROFIT

PROFIT

Favors HF $\alpha/\beta$ for BED: 1.5 $\rightarrow$ Favors CF

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PROFIT: Trial and Efficacy

- 1206 men, 27 sites
  - Canada, Australia, France
- Intermediate risk
  - T1-T2, Gleason 6, PSA 10-20
  - T2b-c, Gleason 6, PSA <20
  - T1-2, Gleason 7, PSA <20
- ADT: not permitted with RT
- RT
  - Randomization: 78/39 (2) vs 60/20 (3)
  - Prostate +/- base of SV
  - IGRT required
  - Central plan review

Results:

Catton et al., JCO 35, 2017
PROFIT: Toxicity

### Table 3. Genitourinary Toxicity by Period, Treatment, and Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute* Toxicity (No. [%])</th>
<th>Late† Toxicity (No. [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short (n = 608)</td>
<td>Standard (n = 598)</td>
</tr>
<tr>
<td>None</td>
<td>150 (25)</td>
<td>143 (24)</td>
</tr>
<tr>
<td>1</td>
<td>273 (45)</td>
<td>272 (46)</td>
</tr>
<tr>
<td>2</td>
<td>161 (27)</td>
<td>159 (27)</td>
</tr>
<tr>
<td>3</td>
<td>24 (3.3)</td>
<td>24 (4.0)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 4. GI Toxicity by Period, Treatment, and Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute* Toxicity (No. [%])</th>
<th>Late† Toxicity (No. [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short (n = 608)</td>
<td>Standard (n = 598)</td>
</tr>
<tr>
<td>None</td>
<td>249 (41)</td>
<td>286 (48)</td>
</tr>
<tr>
<td>1</td>
<td>260 (43)</td>
<td>250 (42)</td>
</tr>
<tr>
<td>2</td>
<td>95 (16)</td>
<td>59 (10)</td>
</tr>
<tr>
<td>3</td>
<td>4 (0.7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Acute period = worst grade during the first 14 weeks.
†Late period = worst grade from 6 months onward.

P = 0.003

P = 0.006
Hypofractionation: HYPRO

HYPERSPHERIC

BED (Gy)

78 Gy (2 Gy x 39)

64.6 Gy (3.4 Gy x 19)

α/β ratio

Favors HF  α/β for BED: 5  Favors CF

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HYPRO: Trial

- 820 men, median age 70 years
- 7 centers in Netherlands
- T1b-T4N0, PSA <60
  - 0% low/26% int/74% high
- ADT 66%, median 32 mo
- RT
  - Randomization: 78/39 (2.0) qd vs 64.6/19 (3.4) tiw
  - Prostate; SV dose based on risk; no LN
  - 95% IMRT, 94% fiducials
HYPRO: efficacy

• 5 yr RFS
  • 64.6 Gy: 80.5% (75.7-84.4%)
  • 78 Gy: 77.1% (71.9-81.5%)
  • HR 0.86 (0.63-1.16), p=0.36

• Interpretation
  • HF not superior
  • Lower than CHHiP (88-90%), consistent with higher-risk disease

• OS no differences

Incrocci, Lancet Oncol 2016
HYPRO: toxicity
Meta-analysis

Datta, et al. IJROBP 2017
Kiri Sandler (UCLA): Survey of expert GU radiation oncologists

Default EBRT fractionation for Gleason 3+4 PCa

- Conventional: 54.80%
- Moderate hypo: 40.50%
- SBRT: 4.80%

McClelland et al., in submission
Prostate Cancer Radiation Therapy Physician Worksheet
(As of 20 October 2016)

9. If brachytherapy is included in the treatment plan, then answer the following set of questions (#9):

   a. What type of brachytherapy will be utilized?
      - [ ] Low dose brachytherapy (seed implant)
      - [ ] High dose brachytherapy

   b. If HDR brachytherapy is selected, what is the number of applications? Applications: ___

   c. If HDR brachytherapy is selected, what is the number of fractions? Fractions: ___

10. a. For regimens that do not include brachytherapy or SBRT, is a moderately hypofractionated regimen (i.e. 20-28 fractions) being utilized? □ Yes □ No

   b. If #10a answer is No, why is a moderately hypofractionated regimen not being utilized?
      - [ ] The pelvic lymph nodes are not treated
      - [ ] Hypofractionated regimen is not a standard of care
      - [ ] There is insufficient evidence to support a hypofractionated regimen
      - [ ] Lack of comfort or experience in delivering a hypofractionated regimen

11. Note: additional information in the space below.
Conclusion

• 4 randomized trials show no difference in treatment efficacy between conventional and hypofractionated RT to prostate at 5 years
• Three trials (60/20 or 70/28) showed no increased late toxicity at 5 years
  • No treatment of pelvic lymph nodes
  • Only one of three trials allowed treatment of SV base
• HYPRO had persistently higher treatment-related toxicity in hypofractionated arm with 3.4 Gy per fraction three times per week
  • SVs were treated based on risk of involvement
• Longer follow-up needed
• Many institutions consider moderate hypofractionation (60/20 or 70/28) as a new standard for EBRT to prostate gland
Outline

• Screening for Prostate cancer
• Low/intermediate risk Prostate cancer
  • Active surveillance vs treatment
  • Surgery vs EBRT
  • Brachytherapy vs EBRT
• Hypofractionated EBRT
• High risk Prostate cancer
  • Incorporation of brachytherapy boost
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• Post-prostatectomy RT
  • Adjuvant vs salvage
• Lymph-node positive Prostate cancer
  • Role of pelvic RT
• Bone metastases from Prostate cancer
  • Radium-223 systemic therapy
• Prognostic biomarkers/PET imaging
• Contours and DVH parameters
High Risk Prostate Cancer: Is EBRT enough?

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>N</th>
<th>Median followup</th>
<th>Risk groups</th>
<th>EBRT</th>
<th>Combo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sathy et al. (83)</td>
<td>2005</td>
<td>104</td>
<td>8.2 years</td>
<td>Low: 0%</td>
<td>5 yr bRFS:</td>
<td>39%</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intermediate: 40%</td>
<td></td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High: 60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-tx biopsy positive:</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hoskin et al. (40)</td>
<td>2012</td>
<td>218</td>
<td>7.1 years</td>
<td>Low: 5%</td>
<td>7-yr bRFS:</td>
<td>48%</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intermediate: 42%</td>
<td></td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High: 53%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ASCENDE-RT (59)</td>
<td>2015</td>
<td>398</td>
<td>6.5 years</td>
<td>Low: 0%</td>
<td>9-yr bRFS:</td>
<td>58%</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intermediate: 31%</td>
<td></td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High: 69%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EBRT = external beam radiation therapy; bRFS = biochemical recurrence-free survival; SS = statistically significant.

Spratt et al., The ABS Task Group Report, Brachytherapy 2016
ASCENDE-RT

- 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)

![Diagram]

Pelvic IMRT 4600/23

Prostate boost 3200/16

I^{125} Brachytherapy boost: 115 Gy

Courtesy of Dr. Crook
ASCENDE-RT: Results

Morris et al., IJROBP 2017, slides courtesy of Dr. Crook
ASCENDE-RT Results:

**PFS by NCCN Risk Group**

**Intermediate-risk stratum, N=122**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Kaplan-Meier (95% CI)</th>
<th>Randomization (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>84.1 (±9.8)</td>
<td>96% (±5)</td>
</tr>
<tr>
<td>7</td>
<td>80.1 (±10.8)</td>
<td>93.9 (±6.8)</td>
</tr>
<tr>
<td>9</td>
<td>69.8 (±14.6)</td>
<td>93.9 (±3.8)</td>
</tr>
</tbody>
</table>

Log rank P < 0.001

**PFS by NCCN Risk Group**

**High-risk stratum, N=276**

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Kaplan-Meier (95% CI)</th>
<th>Randomization (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>83.6 (±7.0)</td>
<td>85.6 (±6.4)</td>
</tr>
<tr>
<td>7</td>
<td>71.9 (±9.4)</td>
<td>82.9 (±7.2)</td>
</tr>
<tr>
<td>9</td>
<td>58.2 (±12.8)</td>
<td>78.0 (±9.6)</td>
</tr>
</tbody>
</table>

Log rank P = 0.05

9-year PSA Relapse Free Survival: 70% vs. 94% p<0.001

9-year PSA Relapse Free Survival 58% vs. 78%; p=0.05

Courtesy of Dr. Crook
ASCENDE-RT Results:

**b-PFS using a >0.2 ng/mL threshold**
(by treatment received N= 383)

**Kaplan-Meier (95% CI)**

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Treatment</th>
<th>% ADT use</th>
<th>8 yr</th>
<th>9 yr</th>
<th>10 yr</th>
<th>12 yr</th>
<th>16 yr</th>
<th>bRFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>148</td>
<td>Surgery + adjuvant RT</td>
<td>11</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2012</td>
<td>502</td>
<td>Surgery + adjuvant RT</td>
<td>10</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2007</td>
<td>122</td>
<td>Surgery + adjuvant RT</td>
<td>9</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.4</td>
</tr>
<tr>
<td>2014</td>
<td>159</td>
<td>Surgery</td>
<td>12</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2012</td>
<td>503</td>
<td>Surgery</td>
<td>10</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2007</td>
<td>122</td>
<td>Surgery</td>
<td>8</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.4</td>
</tr>
<tr>
<td>2015</td>
<td>1100</td>
<td>Surgery</td>
<td>1</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2014</td>
<td>1360</td>
<td>Surgery</td>
<td>43</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
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<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2012</td>
<td>1366</td>
<td>Surgery</td>
<td>30</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2012</td>
<td>378</td>
<td>Surgery</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2010</td>
<td>175</td>
<td>Surgery</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2008</td>
<td>236</td>
<td>Surgery</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2006</td>
<td>220</td>
<td>Surgery</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
<tr>
<td>2005</td>
<td>841</td>
<td>Surgery</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PSA ≤ 0.2</td>
</tr>
</tbody>
</table>

**Author**

| Wiegel et al. (73) | Bolla et al. (74) | Swanson et al. (75) | Wiegel et al. (73) | Bolla et al. (74) | Swanson et al. (75) | Abdollah et al. (76) | Ioniau et al. (55) | Briganti et al. (77) | Yamamoto et al. (78) | Loeb et al. (79) | Inman et al. (80) | Rusiang et al. (81) | Ward et al. (82) |

**bRFS definition**

PAS = 0.2

Spratt et al., The ABS Task Group Report, Brachytherapy 2016

Courtesy of Dr. Crook

**ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRSHR18**
ASCENDE-RT Toxicity:

• 398 pts accrued 2002-2011
• Implants by 16 radiation oncologists
• Prior to incorporation of MRI in QA
• Cumulative grade ≥ 3 GU toxicity:
  • 19% vs. 5% @ 5 years (p<0.001)
    • BUT @ 6 years persistent grade 3 GU toxicity is 6.3%
• Cumulative grade ≥ 3 GI toxicity:
  • 9% vs. 4% (NS)

Rodd et al., IJROBP 2017
ASCENDE-RT Toxicity:

Rodda et al., IJROBP 2017
Kiri Sandler (UCLA): Survey of expert GU radiation oncologists

First choice treatment for patients with high risk PCa, no baseline urinary symptoms and 40 cc gland

McClelland et al., Clinical Genitourinary Cancer, in press
High Risk Prostate Cancer: Brachy Boost

Fig. 1. Trend of radiation modality use in 2004–2012. E, external beam radiation therapy; B, brachytherapy; E + B, external beam radiation therapy + brachytherapy boost.

Orio et al., Brachytherapy 2016
Conclusion

• For high risk prostate cancer brachytherapy boost improves biochemical control based on 3 randomized clinical trials
• There is an increased cumulative grade ≥ 3 GU toxicity
• Brachytherapy requires technical skills and expertise, that is declining in the United States
Updated Recommendations:

- For patients with intermediate-risk prostate cancer choosing EBRT with or without ADT, brachy boost (LDR or HDR) should be offered to eligible patients.
- For patients with high-risk prostate cancer receiving EBRT and ADT, brachy boost (LDR or HDR) should be offered to eligible patients.
Outline

- Screening for Prostate cancer
- Low/intermediate risk Prostate cancer
  - Active surveillance vs treatment
  - Surgery vs EBRT
  - Brachytherapy vs EBRT
- Hypofractionated EBRT
- High risk Prostate cancer
  - Incorporation of brachytherapy boost
- ADT with EBRT

- Post-prostatectomy RT
  - Adjuvant vs salvage
- Lymph-node positive Prostate cancer
  - Role of pelvic RT
- Bone metastases from Prostate cancer
  - Radium-223 systemic therapy
- Prognostic biomarkers/PET imaging
- Contours and DVH parameters
ADT with EBRT

• Low Risk: EBRT alone*
• Intermediate Risk: EBRT +/- 4-6 months of ADT
• High Risk: EBRT + 24 months of ADT

*If discussing comparable outcomes between surgery and EBRT in ProtecT trial, may have to incorporate 3-6 months of ADT.
ADT with EBRT

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*If discussing comparable outcomes between surgery and EBRT in ProtecT trial, may have to incorporate 3-6 months of ADT.
### ADT in intermediate risk PCa

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Patients at intermediate risk (n)</th>
<th>Median follow-up (years)</th>
<th>Androgen deprivation therapy comparison arms</th>
<th>Radiotherapy dose (Gy)*</th>
<th>Primary endpoint</th>
<th>Reported outcomes with short-term androgen deprivation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones (2011)</td>
<td>1979</td>
<td>1068†</td>
<td>9.1</td>
<td>0 vs 4 months</td>
<td>63.3</td>
<td>Overall survival</td>
<td>Increased overall survival and biochemical progression-free survival, reduced prostate cancer-specific mortality and distant metastasis</td>
</tr>
<tr>
<td>D'Amico (2008)</td>
<td>206</td>
<td>153†</td>
<td>7.6</td>
<td>0 vs 6 months</td>
<td>70.35</td>
<td>Biochemical progression-free survival</td>
<td>Prolonged overall survival and decreased prostate cancer-specific mortality</td>
</tr>
<tr>
<td>Denham (2011)</td>
<td>818</td>
<td>130†</td>
<td>10.6</td>
<td>0 vs 3 vs 6 months</td>
<td>62.7</td>
<td>Prostate cancer-specific mortality and local control†</td>
<td>Augmented overall survival and diminished prostate cancer-specific mortality§</td>
</tr>
<tr>
<td>Roach (2008)</td>
<td>456</td>
<td>Not reported†</td>
<td>11.9–13.2</td>
<td>0 vs 4 months</td>
<td>61.8–66.5</td>
<td>Local control</td>
<td>Reductions in prostate cancer-specific mortality and distant metastasis, increases in biochemical progression-free survival and disease-free survival, but no improvements in overall survival or local control</td>
</tr>
<tr>
<td>Laverdière (2004)</td>
<td>161</td>
<td>Not reported</td>
<td>5</td>
<td>0 vs 3 vs 10 months</td>
<td>64</td>
<td>Biochemical progression-free survival</td>
<td>Prolonged biochemical progression-free survival</td>
</tr>
<tr>
<td>Dubray (2011)</td>
<td>366</td>
<td>366</td>
<td>3.1</td>
<td>0 vs 4 months</td>
<td>80</td>
<td>Freedom from failure**</td>
<td>Increased biochemical progression-free survival, non-significant rise in freedom from failure (p=0.09)</td>
</tr>
</tbody>
</table>
ADT in intermediate risk PCa

Castle et al., IJROBP 2012
## ADT in intermediate risk PCa

### PSA relapse-free survival

<table>
<thead>
<tr>
<th></th>
<th>aHR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADT</strong></td>
<td>0.516</td>
<td>0.360-0.739</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>1.0</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>3 + 4</td>
<td>2.092</td>
<td>1.231-3.553</td>
<td>0.006</td>
</tr>
<tr>
<td>4 + 3</td>
<td>3.993</td>
<td>2.250-7.086</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Stage (T2b or higher vs T2a or less)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.406</td>
<td>0.947-2.088</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>1.572</td>
<td>1.090-2.268</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Pretreatment PSA (≥10 vs &lt;10 ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.071</td>
<td>1.451-2.955</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>% Positive cores (≥50% vs &lt;50%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.986</td>
<td>0.963-1.009</td>
<td>0.220</td>
</tr>
<tr>
<td><strong>Age (continuous)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Zumsteg et al., IJROBP 2012

![Graph showing cause-specific incidence rates](image-url)
# ADT in intermediate risk PCa

<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 ^14</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 (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 and Zelefsky, JCO 2012
ADT in intermediate risk PCa

Dong et al., Can J Urol 2017
ADT in intermediate risk PCa

• GETUG 14 Abstract (Dubray et al) at ASCO 2016:
  • 80 Gy +/- 4 months of ADT

• Median followup of 84 months (range, 3-132)

• Biochemical relapse-free survival: 76% vs 84% at 5 years (p=0.02)
ADT in intermediate risk PCa

- **RTOG 9910:**
  - 70.2 Gy
  - 4 vs 9 months of ADT

- 85% with intermediate risk

- No difference in outcomes

Pisansky et al., JCO 2014
ADT in intermediate PCa

- NCDB analysis:
  - Favorable intermediate
  - RT 75.6 Gy+ or with brachy boost
  - 2004-2007: 18,598 patients
  - Use of ADT decreased from 44% in 2004 to 40% in 2007
  - ADT not associated with improved survival

Figure 1. Propensity score-weighted overall survival. ADT indicates androgen-deprivation therapy; RT, radiotherapy.

Falchook et al., Cancer 2016
ADT with EBRT

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Post-prostatectomy EBRT: adjuvant or salvage?

- Pooled analysis with propensity score matching:
  - 10 academic US centers
  - 1566 consecutive patients
  - 1987 – 2013
  - Median followup after RT: 5 years
1. Persistently elevated PSA after surgery = ESRT
2. Sensitivity analysis revealed that decreased risk of BF associated with ART lost SS when more than 56% in the ART cohort were assumed to have been cured by surgery alone

Hwang et al., JAMA Onc Published online 1/25/2018
Post-prostatectomy EBRT: adjuvant or salvage?

- **SWOG 8794 (Thompson et al., J Urol 2009)**
  - No restriction on PSA level at enrollment
    - Relationship between pre-RT PSA level and risk of metastases development:
      - \( \leq 0.2 \text{ ng/ml} \) vs \( 0.2 \) to \( \leq 1.0 \text{ ng/ml} \)
    - Local recurrence: 22% in observation vs 8% in adjuvant RT

- **EORTC 22911 (Bolla et al., Lancet 2012)**
  - Undetectable PSA defined as \( \leq 0.4 \text{ ng/ml} \)
  - Salvage pelvic RT administered to 54% of patients on observation arm with biochemical progression

- **ARO 96/02 (Wiegel et al., JCO 2009)**
  - Only PSA < \( 0.1 \text{ ng/ml} \)
  - Salvage RT strongly recommended in observation arm as soon as PSA became detectable, no information provided on the rate of salvage RT
Post-prostatectomy EBRT: adjuvant or salvage?

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Inclusion criteria</th>
<th>Dose (Gy)</th>
<th>Follow-up median (years)</th>
<th>10-year BPFS ART vs. NFT</th>
<th>10-year OS ART vs. NFT</th>
<th>10-year toxicity rate (%) ART vs. NFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson et al. (5)</td>
<td>425</td>
<td>pT3 cN0/pN0 R0/R1</td>
<td>60–64</td>
<td>12.7</td>
<td>52 vs. 26% p &lt; 0.001</td>
<td>74 vs. 66% p = 0.023</td>
<td>GI, G3 = 3.3 vs. 0 GU, G3 17.8 vs. 9.5</td>
</tr>
<tr>
<td>Bolla et al. (4)</td>
<td>1005</td>
<td>pT2–3 pN0 R0/R1</td>
<td>60</td>
<td>10.6</td>
<td>60 vs. 41% p &lt; 0.0001</td>
<td>77 vs. 81% p = 0.2</td>
<td>GU &gt; G2 = 21.3 vs. 13.5 (p = 0.003) GI &gt; G2 = 2.5 vs. 1.9 (p = 0.47)</td>
</tr>
<tr>
<td>Wiegel et al. (6)</td>
<td>388 (307)</td>
<td>pT3 pN0 R0/R1 PSA 0</td>
<td>60</td>
<td>9.3</td>
<td>56 vs. 35% p &lt; 0.0001</td>
<td>84 vs. 86% p = 0.59</td>
<td>ART: GU, G3 = 1 patient, G2 = 2 patients GI, G2 = 2 patients</td>
</tr>
</tbody>
</table>

BPFS, Biochemical progression-free survival; OS, overall survival; ART, adjuvant radiation therapy; NFT, no further therapy; GU, genitourinary; GI, gastro-intestinal; G, grade.
Margin Status for Adjuvant RT

- ARO 96/02 (Wiegel, European Urology 2014)
- EORTC 22911 (Van der Kwast, JCO 2007)

### Table

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Radiotherapy Total</th>
<th>Control Total</th>
<th>PFS, hazard ratio Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neg.</td>
<td>48</td>
<td>61</td>
<td>0.80 [0.45 – 1.43]</td>
</tr>
<tr>
<td>pos.</td>
<td>100</td>
<td>97</td>
<td>0.39 [0.27 – 0.57]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>148</td>
<td>158</td>
<td>0.49 [0.35 – 0.67]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.10$, df = 1 ($p = 0.04$); $I^2 = 76\%$
Test for overall effect: $Z = 4.41$ ($p < 0.0001$)

### Figure

- SM- 25 95 21 90 1.1 11.2
- SM+ 16 98 51 110 -20.3 16.5
- Total 41 193 72 200 -19.2 27.7

Heterogeneity $\chi^2 = 11.78$, $P < .001$
**Salvage RT: outcomes**

**TABLE 2 | Selected series of salvage radiotherapy for PSA relapse after radical prostatectomy.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Comparison</th>
<th>PSA pre-RT (ng/ml)</th>
<th>ADT (%)</th>
<th>Median follow-up (months)</th>
<th>BPFS (%)</th>
<th>Important prognostic factors</th>
<th>RT technique/dose (Gy)</th>
<th>Grade 3 toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfister</td>
<td>737</td>
<td>Early salvage</td>
<td>&lt;0.5</td>
<td>8.7</td>
<td>51</td>
<td>71</td>
<td>PSA pre RT &lt;0.2</td>
<td>2D/3D/MRT</td>
<td>0.6–1.3</td>
</tr>
<tr>
<td>Tock</td>
<td>160</td>
<td>SRT with PSA &gt;0.2–22</td>
<td>Median 0.7</td>
<td>12</td>
<td>72</td>
<td>89</td>
<td>PSA &gt;8</td>
<td>2D/3D/66.5</td>
<td>2D/3T/60–70 NR</td>
</tr>
<tr>
<td>Swanson</td>
<td>92</td>
<td>ART (n = 36) with postoperative PSA &lt;0.4 vs. SRT (n = 56)</td>
<td>Median 1.5</td>
<td>0</td>
<td>146.4</td>
<td>35 vs. 25</td>
<td>PSA &gt;0.5</td>
<td>2D/3T/66.5</td>
<td>NR</td>
</tr>
<tr>
<td>Tsubul</td>
<td>440</td>
<td>ART &lt;12 months from surgery (n = 211) SRT &gt;12 months from surgery (n = 238)</td>
<td>&lt;2</td>
<td>0</td>
<td>94</td>
<td>75 vs. 66</td>
<td>GS &gt;8 Use of SRT</td>
<td>2D/3D/64</td>
<td>NR</td>
</tr>
<tr>
<td>Fossati</td>
<td>965</td>
<td>Early salvage</td>
<td>&lt;0.5</td>
<td>0</td>
<td>57</td>
<td>82</td>
<td>PSA &gt;0.2, &gt;pT3, GS &gt;7, PSA &gt;1</td>
<td>2D/3D/66.6</td>
<td>NR</td>
</tr>
<tr>
<td>Cremer</td>
<td>197</td>
<td>SRT (&gt;6 months after RP)</td>
<td>45.7% with PSA &lt;10 and 53.8% with PSA &gt;10</td>
<td>0</td>
<td>40</td>
<td>59</td>
<td>GS &gt;7, ECE, PSA &gt;1ng/ml</td>
<td>3D/66</td>
<td>GU = 6, Gl = 0.6</td>
</tr>
<tr>
<td>Jenezczek-Fossa</td>
<td>431</td>
<td>ART &lt;6 months after RP (n = 258) SRT &gt;6 months after RT (n = 173)</td>
<td>ART 0–4 SRT 0.1–13.7</td>
<td>100</td>
<td>32</td>
<td>81 vs. 60.5</td>
<td>PSA &gt;0.2, GS &gt;6, Age &lt;65</td>
<td>70</td>
<td>Gl = 0.7, GU = 1.0</td>
</tr>
<tr>
<td>Riganti</td>
<td>300</td>
<td>PSA &lt;0.3 vs. PSA &gt;0.3 to &lt;0.5</td>
<td>58</td>
<td>0</td>
<td>40.6</td>
<td>81.8</td>
<td>stage, GS, and positive SM pT3b, positive SM, pre-SRT PSA doubling time</td>
<td>3D/66.2</td>
<td>NR</td>
</tr>
<tr>
<td>Siegmatt</td>
<td>301</td>
<td>SRT (median time to RT 23 months)</td>
<td>0.28</td>
<td>0</td>
<td>30</td>
<td>78 vs. 61% for a PSA ≤ or &gt;0.28 ng/ml</td>
<td>PSA doubling time</td>
<td>3D/68.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Stephens</td>
<td>1540</td>
<td>Nomogram for disease progression after SRT</td>
<td>&lt;0.5 to ≥0.5</td>
<td>0</td>
<td>53</td>
<td>PSA &lt;0.5 = 48, PSA &gt;0.51–1.00 = 40, PSA 1.01–1.50 = 28, PSA &gt;1.50 = 18</td>
<td>GS, PSA doubling time, SM, ADT</td>
<td>64.8</td>
<td>NR</td>
</tr>
</tbody>
</table>

Herrera and Berthold, Frontiers in Oncology 2016

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
Salvage Radiation Therapy

Our salvage radiation therapy nomogram predicts whether a recurrence of prostate cancer after radical prostatectomy can be treated successfully with salvage radiation therapy (external-beam radiation given after the prostate cancer returns). It calculates the probability that the cancer will be controlled and PSA level undetectable six years after salvage therapy. You can use this nomogram for applicable results if your post-radical prostatectomy serum PSA level was at first undetectable (less than 0.05 ng/mL) and then rose steadily, indicating a recurrence.

Enter Your Information

All fields are required unless noted optional

Important: If your PSA level never decreased to an undetectable level following radical prostatectomy, the results of this nomogram will not apply to you.

Stephenson et al., JCO 2007
The role of ADT with Salvage RT

• GETUG-AFU (Carrie et al., Lancet 2016)
  • 66 Gy in 33 fractions +/- 6 months of ADT (goserelin)
  • PFS at 5 years: 80% vs 62% (HR 0.5, p< 0.0001)
  • No difference in overall survival

• RTOG 9601 (Shipley et al., NEJM 2017):
  • 64.8 Gy in 36 fractions +/- 2 years of ADT (bicalutamide, 150 mg daily)
  • OS at 12 years: 76.3% vs 71.3% (HR 0.77, p=0.04)
  • No benefit for ADT in PSA < 0.7 ng/mL on post-hoc subgroup analysis

<table>
<thead>
<tr>
<th>PSA level at trial entry</th>
<th>Number</th>
<th>Survival</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.7 ng/ml</td>
<td>405 (53.3)</td>
<td>76.8</td>
<td>80.7</td>
<td>1.13 (0.77–1.65)</td>
</tr>
<tr>
<td>0.7–1.5 ng/ml</td>
<td>237 (31.2)</td>
<td>77.0</td>
<td>67.5</td>
<td>0.61 (0.39–0.95)</td>
</tr>
<tr>
<td>&gt;1.5 ng/l/ml</td>
<td>118 (15.5)</td>
<td>73.5</td>
<td>48.9</td>
<td>0.45 (0.25–0.81)</td>
</tr>
</tbody>
</table>
Salvage RT Dose

- SAKK 09/10 randomized trial
  - 64 in 2 vs 70 in 2
  - No difference in acute toxicity:
    - Grade 2 GU 13% vs 16.6%
    - Grade 3 GU 0.6% vs 1.7%
    - Grade 2 GI 16% vs 15.4%
    - Grade 3 GI 0.6% vs 2.3%

Ghadjar et al., JCO 2015
Radicals

Eligible patient post-prostatectomy

- **RT timing RANDOMISATION**
  - Early RT
  - Deferred RT (RT for PSA failure)

Patient for post-operative RT (either early or deferred RT)

- **Hormone duration RANDOMISATION**
  - Radiotherapy Alone
  - Radiotherapy + 6 months hormone therapy
  - Radiotherapy + 2 years hormone therapy
As a general rule, for patients with high risk features after radical prostatectomy, I recommend:

- 54.80% recommend adjuvant RT
- 45.20% recommend early salvage RT

McClelland et al., in submission
Conclusion

• All patients with high risk features after RP (+margin, pT3, persistently elevated PSA) should be seen by radiation oncologists for consultation to discuss the merits of adjuvant RT vs careful monitoring with early salvage RT in case of biochemical recurrence:
  • 30% of patients with high risk features will not experience biochemical progression if observed
  • OS was improved only when adjuvant RT was compared to no further RT even in case of disease progression
  • Early salvage RT has excellent outcomes
  • The role of ADT with EARLY salvage RT is unclear, although could be justified by RTOG 9601
Outline

• Screening for Prostate cancer
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• ADT with EBRT

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• Bone metastases from Prostate cancer
  • Radium-223 systemic therapy
• Prognostic biomarkers/PET imaging
• Contours and DVH parameters
Pelvis: RTOG 9413

Lawton et al., IJROBP 2007

% ALIVE WITHOUT DISEASE

WP RT  p-value=0.93  PORT

0 1 2 3 4 5 6 7 8 9 10

0 10 20 30 40 50 60 70 80 90 100

Lawton et al., IJROBP 2007

ASTRO Annual Refresher Course  •  Fort Lauderdale Marriott Harbor Beach Resort & Spa  •  March 2-4, 2018  •  #REFRESHER18
## Pelvis: RTOG 9413

Table 2. Progression-free survival of eligible and analyzable cases by radiotherapy (RT) field size, per protocol definition

<table>
<thead>
<tr>
<th>Time (y)</th>
<th>Whole-pelvis</th>
<th>Mini-pelvis</th>
<th>Prostate-only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% alive, NED</td>
<td>No. at risk</td>
<td>% alive, NED</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>309</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>89.0 (84.9, 92.0)</td>
<td>274</td>
<td>88.2 (82.3, 92.2)</td>
</tr>
<tr>
<td>2</td>
<td>74.3 (69.0, 78.8)</td>
<td>227</td>
<td>66.1 (58.5, 72.7)</td>
</tr>
<tr>
<td>3</td>
<td>63.1 (57.5, 68.3)</td>
<td>189</td>
<td>58.3 (50.4, 65.3)</td>
</tr>
<tr>
<td>4</td>
<td>57.4 (51.6, 62.7)</td>
<td>167</td>
<td>47.8 (40.1, 55.2)</td>
</tr>
<tr>
<td>5</td>
<td>50.7 (44.9, 56.2)</td>
<td>142</td>
<td>41.5 (33.9, 48.9)</td>
</tr>
<tr>
<td>6</td>
<td>45.1 (39.3, 50.7)</td>
<td>109</td>
<td>35.1 (27.8, 42.6)</td>
</tr>
<tr>
<td>7</td>
<td>40.1 (34.3, 45.8)</td>
<td>78</td>
<td>30.9 (23.6, 38.4)</td>
</tr>
</tbody>
</table>

Failure/total: 189/309
Median PFS time: 5.2 years
Log-rank p-value: 0.0243

Roach et al., IJROBP 2006
Laparoscopic Sentinel Lymph Node Dissection in patients selected for EBRT based on cN0

- 99Tc-nanocolloid injected into peripheral zone each quadrant of prostate gland transrectally w/ US guidance
- Positive SLNs found in 42% of patients with clinically N0 PCa referred for EBRT

<table>
<thead>
<tr>
<th>Gleason Sum</th>
<th>Overall (N=224)</th>
<th>pN0 (N=133)</th>
<th>pN1 (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>22</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>93</td>
<td>58</td>
<td>35</td>
</tr>
<tr>
<td>8-10</td>
<td>106</td>
<td>57</td>
<td>49</td>
</tr>
</tbody>
</table>

Grivas et al., IJROBP 2017
### Patterns of Recurrence after EBRT to Prostate

**Table 2.** Estimated 8-year cumulative incidence of FRS in given anatomical location in patient with prostate cancer at NCCN low, intermediate and high risk treated with dose escalated EBRT, and those of 474 patients with CDR who had given anatomical location as FRS

<table>
<thead>
<tr>
<th>FRS</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8-Yr Incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Any (95% CI):*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>3.5 (1.8—5.2)</td>
<td>9.8 (7.9—11.8)</td>
<td>14.6 (12.0—17.2)</td>
<td>9.9 (8.6—11.2)</td>
</tr>
<tr>
<td>PLNs</td>
<td>0</td>
<td>2.7 (1.7—3.8)</td>
<td>8.3 (6.3—10.5)</td>
<td>3.9 (3.1—4.8)</td>
</tr>
<tr>
<td>Abdominal lymph nodes</td>
<td>0.5 (0—1.2)</td>
<td>1.2 (0.1—1.9)</td>
<td>2.9 (1.6—4.2)</td>
<td>1.6 (1.1—2.2)</td>
</tr>
<tr>
<td>Thoracic lymph nodes</td>
<td>0</td>
<td>0.7 (0.2—1.1)</td>
<td>0.3 (0.0—0.8)</td>
<td>0.4 (0.1—0.7)</td>
</tr>
<tr>
<td>Bone</td>
<td>0.9 (0.1—1.7)</td>
<td>3.9 (2.6—5.2)</td>
<td>14.2 (11.7—16.8)</td>
<td>6.5 (5.4—7.9)</td>
</tr>
<tr>
<td>Viscera</td>
<td>0</td>
<td>0.1 (0—0.4)</td>
<td>1.0 (0.3—1.7)</td>
<td>0.4 (0.1—0.6)</td>
</tr>
<tr>
<td>% Isolated (95% CI):*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>3.5 (1.8—5.2)</td>
<td>8.5 (6.7—10.3)</td>
<td>12.2 (9.8—14.7)</td>
<td>8.5 (7.3—9.8)</td>
</tr>
<tr>
<td>PLNs</td>
<td>0</td>
<td>1.0 (0.3—1.7)</td>
<td>3.3 (1.9—4.6)</td>
<td>1.5 (1.0—2.1)</td>
</tr>
<tr>
<td>Abdominal lymph nodes</td>
<td>0.2 (0—0.5)</td>
<td>0.1 (0—0.3)</td>
<td>0.6 (0—1.2)</td>
<td>0.4 (0—0.6)</td>
</tr>
<tr>
<td>Thoracic lymph nodes</td>
<td>0</td>
<td>0.1 (0—0.3)</td>
<td>0</td>
<td>0.05 (0—0.14)</td>
</tr>
<tr>
<td>Bone</td>
<td>0.9 (0.1—1.7)</td>
<td>2.3 (1.3—3.3)</td>
<td>9.8 (7.6—11.9)</td>
<td>4.3 (3.5—5.2)</td>
</tr>
<tr>
<td>Viscera</td>
<td>0</td>
<td>0</td>
<td>0.7 (0.08—1.3)</td>
<td>0.2 (0.02—0.4)</td>
</tr>
</tbody>
</table>

Zumsteg et al., Journal of Urology, 2015
Kiri Sandler (UCLA), unpublished: Survey of expert GU radiation oncologists

For localized high risk PCa, I treat pelvic lymph nodes:

- Rarely: 31.00%
- Often: 69.00%
LN-positive PCa

- 703 consecutive patients treated with RP, PLND and adjuvant treatments between 1988 and 2003 at two large academic institutions
- All underwent CT and bone scan prior to surgery
- 171 received ADT and RT
- 532 received ADT alone
- Matched analysis for effect of RT on CSS and OS (1 RT:4 no RT)
- Mean follow up 8.4 years

Briganti et al., European Urology 2011

- HR 2.5, p=0.004
- HR 2.3, p<0.001
LN-positive PCa

Survival analyses cohort and propensity score matching flow chart

- Patients who were treated with ADT alone (n = 388) or ADT+RT (n = 595) and diagnosed between 2004 and 2006.

Estimated Propensity Score Model
The probability of being treated with ADT+RT was estimated using multivariable logistic regression with all variables listed in Table 2 for the cohort of 983 patients.

Propensity Score Matching
Patients treated with ADT alone were matched to patients treated with ADT+RT who had the closest propensity score (1:1 match) by a greedy 5 to 1 digit matching algorithm. Patients treated with ADT alone who did not have a match to a patient treated with ADT+RT were excluded.

Matched Sample
The final matched sample consisted of 318 patients treated with ADT alone and 318 patients treated with ADT+RT.

B
After propensity score matching

Surviving fraction

Time, mo

Log-rank p < .001

Lin et al., JNCI 2015
LN-positive PCa

| Prostate Cancer   | 1. ADT for 6 mo for maximum decrease in size of lymphatic involvement.  
|                   | 2. Restaging scans.  
|                   | 3. If no evidence of metastatic disease: IMRT to prostate, seminal vesicles, and pelvic lymph nodes, with concurrent ADT (with boost RT to known involved lymph nodes, based on bowel constraints).  
|                   | 4. Adjuvant ADT (for a total duration of ADT of 2 to 3 yr).  
| cN+ (any T, N1, M0) | 1. ADT for 6 mo to allow for maximal postoperative healing.  
|                   | 2. Restaging scans.  
|                   | 3. If no evidence of metastatic disease: IMRT to prostate bed and pelvic lymph nodes, with concurrent ADT.  
|                   | 4. Adjuvant ADT (for a total duration of ADT of 2 to 3 yr).  
| pN+ (after RP and PLND) |  

Mitin et al., Oncology 2013
LN-positive PCa

NCCN Guidelines Version 1.2017
Prostate Cancer

Regional:
Any T, N1, M0

EBRT^i + ADT^m (2–3 y; category 1)
or
ADT^m
Conclusion

• The role of prophylactic RT to pelvic lymph nodes is controversial
  • RTOG 9413: no difference in primary outcome between WP and RO
  • Future studies with advanced imaging (PSMA or C-11 PET) and/or SLNB may select appropriate patients for prophylactic RT to pelvic lymph nodes
• Patients with pN+ PCa have an excellent prognosis
  • Strong association with adjuvant RT administration
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• Prognostic biomarkers/PET imaging
• Contours and DVH parameters
Bone metastases: Radium-223

- Short-range high-energy alpha-emitting particle
- Targets osteoblastic bone metastases by acting as a calcium mimetic

Perez et al. Principles and Practice of Radiation Oncology, 5th ed. 2007
## Table 2: Endpoints in the ALSYMPCA Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Ra-223 + Best Standard of Care</th>
<th>Placebo + Best Standard of Care</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (interim analysis)</td>
<td>14 mo</td>
<td>11.2 mo</td>
<td>0.70 (0.55–0.88)</td>
<td>P = .002</td>
</tr>
<tr>
<td>Overall survival (updated analysis)</td>
<td>14.9 mo</td>
<td>11.3 mo</td>
<td>0.70 (0.58–0.53)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Median time to first symptomatic skeletal event</td>
<td>15.6 mo</td>
<td>9.8 mo</td>
<td>0.66 (0.52–0.83)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Median time to increase in total alkaline phosphatase</td>
<td>7.4 mo</td>
<td>3.8 mo</td>
<td>0.17 (0.13–0.22)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Median time to increase in PSA</td>
<td>3.6 mo</td>
<td>3.4 mo</td>
<td>0.64 (0.54–0.77)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Patients with ≥ 30% reduction in total alkaline phosphatase</td>
<td>47%</td>
<td>3%</td>
<td>—</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Patients with normalization of total alkaline phosphatase</td>
<td>34%</td>
<td>1%</td>
<td>—</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

Data are from Parker C et al; N Engl J Med. 2013.[7]

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

Lewis et al., Oncology 2015
Bone metastases: Radium-223

- Bone pain
- Diarrhea
- Nausea
- Vomiting
- Constipation
- Anemia (2%)
- Neutropenia
- Thrombocytopenia

<table>
<thead>
<tr>
<th>Timing</th>
<th>Lab Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>ANC ≥ 1.5 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Platelets ≥ 100 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Hgb ≥ 10 g/dL</td>
</tr>
<tr>
<td>Subsequent</td>
<td>ANC ≥ 1 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Platelets ≥ 50 x 10^9/L</td>
</tr>
</tbody>
</table>
Outline

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<table>
<thead>
<tr>
<th>Test</th>
<th>Platform</th>
<th>Populations studied</th>
<th>Outcome Reported (Test independently predicts)</th>
<th>References</th>
<th>Molecular Diagnostic Services Program (MoDX) Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decipher</td>
<td>Whole-transcriptome 1.4 M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue</td>
<td>Post radical prostatectomy (RP), adverse pathology/high-risk features</td>
<td>Metastasis Prostate cancer-specific mortality, Metastasis Biochemical failure</td>
<td>112-2018</td>
<td>Cover post-RP for 1) pT12 with positive margins; 2) any pT3 disease, 3) rising PSA (above nadir)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>IHC</td>
<td>Biopsy, intermediate- to high-risk treated with EBRT</td>
<td>Metastasis</td>
<td>115-2018</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Oncotype DX Prostate</td>
<td>Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls</td>
<td>Biopsy, low- to intermediate-risk treated with RP</td>
<td>Non-organ-confined pT3 or Gleason grade 4 disease on RP</td>
<td>111-2018</td>
<td>Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy</td>
</tr>
<tr>
<td>ProLaris</td>
<td>Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls</td>
<td>Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)</td>
<td>Prostate cancer-specific mortality</td>
<td>114-2018</td>
<td>Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy</td>
</tr>
<tr>
<td>ProMark</td>
<td>Multiplex immunofluorescent staining of 6 proteins</td>
<td>Biopsy, Gleason grade 3+3 or 3+4</td>
<td>Non-organ-confined pT3 or Gleason pattern 4 disease on RP</td>
<td>116</td>
<td>Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy</td>
</tr>
<tr>
<td>PTEN</td>
<td>Fluorescent in situ hybridization or IHC</td>
<td>Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)</td>
<td>Prostate cancer-specific mortality</td>
<td>115-2018</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
**Prognostic Biomarkers**

Prognostic Biomarkers Used for Localised Prostate Cancer Management: A Systematic Review

Pierre-Jean Lamy\textsuperscript{a,\textordmasculine}, Yves Allory\textsuperscript{b}, Anne-Sophie Gauchez\textsuperscript{c}, Bernard Asselain\textsuperscript{d}, Philippe Beuzeboc\textsuperscript{e}, Patricia de Cremoux\textsuperscript{f}, Jacqueline Fontugne\textsuperscript{g}, Agnès Georges\textsuperscript{h}, Christophe Hennequin\textsuperscript{i}, Jacqueline Lehmann-Che\textsuperscript{j}, Christophe Massard\textsuperscript{i}, Ingrid Millet\textsuperscript{i}, Thibaut Murez\textsuperscript{k}, Marie-Hélène Schlageter\textsuperscript{l}, Olivier Rouvière\textsuperscript{m}, Diana Kassab-Chahmi\textsuperscript{n}, François Rozet\textsuperscript{o}, Jean-Luc Descotes\textsuperscript{p}, Xavier Rébillard\textsuperscript{q}

Eur Urol Focus, 2017 (epub)

**Conclusions:** Blood biomarkers (PHI and 4Kscore) have the highest LOE for the prediction of more aggressive prostate cancer and could help clinicians to manage patients with localised prostate cancer. The other biomarkers show a potential prognostic value; however, they should be evaluated in additional studies to confirm their clinical validity.
Prognostic Biomarkers

• NCCN Guidelines Version 2.2017
  • Developed with extensive industry support, guidance and involvement
  • Marketed under the less rigorous FDA regulatory pathway for biomakers
  • Full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done

• “A bad tumor marker is as bad as a bad drug.” (Dr. Hayes)

• The NCCN panel believes that men with clinically localized disease may consider the use of tumor-based molecular assays at this time.
PET imaging

Detection rate as a function of Prostate Specific Antigen (PSA)

Percentage of Patients with Positive PET/CT scans

- <1.0
- 1.0-2.0
- >2.0

PSA (ng/mL)

Evans et al., PRO 2018
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