Local Therapy for Prostate Cancer: Surgery and Radiotherapy

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The Naef Basile Cancer Institute
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OUTLINE

- Risk classification and patient selection
- Surgical techniques and outcome
- Common side effects of radical prostatectomy
- Role of adjunct androgen deprivation
- Indications for adjuvant radiation therapy
- Definitive radiation therapy: Dose escalation
- IMRT versus 3D CRT
- Optimal use of Androgen Ablation with RT
- Dose escalation and Androgen Ablation
- Hypofractionation schedules
Risk Groups

NCCN definition

Low risk: T1-T2a; PSA < 10; Gl 2-6

High risk: T3-T4
PSA > 20
Gl 8-10

Intermediate risk: All others
Risk Groups

NCCN definition

Low risk: T1-T2a; PSA < 10; G1 2-6

High risk: T3-T4; PSA > 20; G1 8-10

Intermediate risk: All others
Patient Selection

AUA Panel recommendations

- Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy and radical prostatectomy are appropriate monotherapy treatment options for low- and intermediate-risk patients...

- **Patients should be informed** of the benefits and harms of each intervention...

- **Patient preferences** and health conditions related to urinary, sexual, and bowel function should be considered in decision making ...

*J Urology; 1995; 2007; 2011, 2017*
Patient Selection

The PROTECT Trial

- 1999-2009; 1643 men with PSA detected prostate cancer (T1/T2)
- Randomized: Active monitoring (n = 545)
  - Surgery (n = 553)
  - Radiotherapy (n = 545)
- Median follow-up: 10 years
- Primary endpoint: Prostate cancer mortality

Hamdy FC, NEJM 2016
Patient Selection

The PROTECT Trial

Freedom from disease progression

Prostate cancer mortality

Hamdy FC, NEJM 2016
Surgical Techniques

- Open Retropubic Prostatectomy (ORP)
- Laparoscopic Retropubic Prostatectomy (LRP)
- Robot-Assisted Radical Prostatectomy (RARP)
### Surgical Techniques

<table>
<thead>
<tr>
<th></th>
<th>Open n=739</th>
<th>Robotic n=7598</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
<td>7.7%</td>
<td>2.4%</td>
<td>0.30 (0.25–0.35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intraoperative complication</td>
<td>1%</td>
<td>0.4%</td>
<td>0.44 (0.29–0.66)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postoperative complication</td>
<td>11.1%</td>
<td>9.3%</td>
<td>0.82 (0.73–0.91)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Length of stay &gt; 2 days</td>
<td>39.6%</td>
<td>14.5%</td>
<td>0.26 (0.24–0.28)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Trinh QD et al European urology 2012

**Nationwide Inpatient Sample database; 10/2008-12/2009**
## Surgical Techniques

Multinational, Multi-institutional Study; 22,393 patients
USA; Europe; Australia
Cox regression with propensity scores matching

<table>
<thead>
<tr>
<th>Surgical Techniques</th>
<th>Open n=9778</th>
<th>Laparoscopic n=4918</th>
<th>Robotic n=7697</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive margins</td>
<td>22.8%</td>
<td>16.3%</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive margins</th>
<th>Laparoscopic vs Open</th>
<th>Robotic vs Open</th>
<th>Robotic vs laparoscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>0.76 (0.69–0.84)</td>
<td>0.76 (0.69-0.83)</td>
<td>0.99 (0.89–1.11)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.88</td>
</tr>
</tbody>
</table>

Sooriakumaran P et al European urology 2014
## Surgical Techniques

### Randomized trial

2010-2014: RRPx 151 pts; Robotic RPx 157

<table>
<thead>
<tr>
<th></th>
<th>Open n = 151</th>
<th>Robotic n = 157</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery duration (min)</td>
<td>234</td>
<td>202</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intraoperative adverse event</td>
<td>12%</td>
<td>3%</td>
<td>0.02</td>
</tr>
<tr>
<td>blood loss (mL)</td>
<td>1338</td>
<td>443</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>3.27</td>
<td>1.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>9%</td>
<td>4%</td>
<td>0.05</td>
</tr>
<tr>
<td>LN yield</td>
<td>3.26</td>
<td>6.50</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive margins</td>
<td>10%</td>
<td>15%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Yaxley JW et al (Brisbane) Lancet 2016
Impotence

- 40-70% (extremely variable)
- Age, Baseline sexual function, and type of surgery (nerve-sparing versus non-nerve-sparing)
- Treatable by oral phosphodiesterase-5 inhibitors (Sildenafil)
- May improve over time (up to 2 years)
Surgery: common side effects

Urinary incontinence

• Results from urinary sphincter damage
• Low incidence with experienced surgical teams
• 10-15% patients report 1-2 episodes of urinary leakage/day after 1 year
• Less than 1% have complete incontinence
<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethral strictures</td>
<td>8-10%</td>
</tr>
<tr>
<td>Perioperative morbidity</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td>(age, comorbidity)</td>
</tr>
<tr>
<td>Perioperative mortality</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Surgery vs radiation vs controls

The PROTECT Trial

Incontinence Score

Sexual Quality of Life

Bowel Habits

Donovan JL, NEJM 2016
Surgery: Role of Adjunctive Androgen Deprivation

No impact for neoadjuvant ADT

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**Table 5. PSA-free survival**

<table>
<thead>
<tr>
<th>References</th>
<th>No. Pts.</th>
<th>Stage</th>
<th>Followup Mos.</th>
<th>% Neoadjuvant Hormonal Therapy</th>
<th>% No Neoadjuvant Hormonal Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witjes et al²⁰</td>
<td>173</td>
<td>CT2</td>
<td>48</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>320</td>
<td>CT2–3</td>
<td>48</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>Soloway et al²¹</td>
<td>256</td>
<td>CT2b</td>
<td>24</td>
<td>79</td>
<td>78.4</td>
</tr>
<tr>
<td>Aus et al²²</td>
<td>122</td>
<td>cT1b–3a</td>
<td>38</td>
<td>65.5</td>
<td>59.4</td>
</tr>
<tr>
<td>Goldenberg et al²³</td>
<td>162</td>
<td>A2–B2</td>
<td>24</td>
<td>72</td>
<td>80.0</td>
</tr>
<tr>
<td>Fair et al²⁴</td>
<td>194</td>
<td>cT1–2</td>
<td>29</td>
<td>84</td>
<td>89</td>
</tr>
</tbody>
</table>

Scolieri MJ et al J of Urology 2000
Surgery: Role of Adjunctive Radiation Therapy

- PSA relapse is defined as $>0.2 \text{ ng/ml}$
- Patients with pT3a (+ve margin); pT3b (Seminal vesicle involvement) have 50-75% risk of biochemical relapse
- Risk of relapse depend on:
  - Risk category (Low vs Intermediate vs High)
  - Gleason’s primary score
  - Number of positive margins
SWOG 8794, EORTC 22911:
- extracapsular tumor extension
- positive margins
- seminal vesicle invasion

ARO 96-02:
- Same;
+ undetectable PSA after surgery

Immediate RT vs. observation and salvage therapy
SWOG 8794

Overall survival

DM free survival

Thompson et al, J Urol 2009
EORTC 22911

biochemical Disease free survival

Overall survival

Bolla et al, Lancet 2012
German trial: ARO 96-02

- 1997-2004; 307 patients; pT3 pN0
- Postop PSA undetectable (< 0.1)
- Random: RT 60 Gy vs. Wait and see

Weigel Th et al JCO, 2009
Adjuvant RT

Number of patients to be treated to prevent:

1 Biochemical failure 3 pts
1 Distant Mets 12 pts
1 death 9 pts

Van der Kwast and Bolla, JCO, 2007
Thompson et al. J Urology, 2009
Is Concurrent Androgen Deprivation Therapy Needed? (The GETUG -16 Trial)

742 patients; postop RT (Pelvis 46 Gy; prostatic bed 66 Gy)
Randomized to adjuvant LHRH agonist or RT alone

Progression free survival

Overall survival

RT/ADT

RT alone

P < 0.001

Carrie Ch et al; Lancet Oncol 2016
RTOG 96-01 Trial (Salvage)

761 Post-RP patients with pT3 or pT2p (+ve margins), N0 with elevated PSA levels from 0.2 to 4.0 ng/ml

Randomized to:
- RT (64.8 Gy) + Bicalutamide 150 mg x 2yrs
- RT (64.8 Gy) + Placebo

Median follow up: 12.6 years

Shipley WU et al; ASCO 2015; ASCO GU 2016
# RTOG 96-01 Trial

<table>
<thead>
<tr>
<th></th>
<th>RT+Bica</th>
<th>RT alone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td>82%</td>
<td>78%</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>BRFS</strong></td>
<td>40%</td>
<td>30%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td>14%</td>
<td>23%</td>
<td>0.001</td>
</tr>
<tr>
<td>GU G3-4</td>
<td>7%</td>
<td>6.7%</td>
<td>NS</td>
</tr>
<tr>
<td>GI G3-4</td>
<td>2.7%</td>
<td>1.6%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Gynecomastia</strong></td>
<td>70%</td>
<td>11%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Shipley WU et al; ASCO 2015; ASCO GU 2016
SURGERY: Conclusions

- Radical prostatectomy is an adequate treatment for early and intermediate stage disease.
- Robotic and laparoscopic techniques are better than open techniques with regard to operative morbidity.
- Complications are mainly impotence and mild incontinence.
- Adjunctive ADT is not proven in surgical studies.
- Adjuvant radiation is necessary for positive margins, extracapsular and/or seminal vesical involvement.
OUTLINE

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- Definitive radiation therapy: Dose escalation
- IMRT versus 3D CRT
- Optimal use of Androgen Ablation with RT
- Dose escalation and Androgen Ablation
- Hypofractionation schedules (4-6wks)
High RT doses are better : Dose Escalation

Zaorsky NG. et al Radiother Onc 2015
IMRT vs. 3D (SEER Analysis 2000-2009)

Conformal radiation therapy

Intensity-modulated radiation therapy

Log-rank $P < .001$

Months After Radiation Therapy

Probability of Additional Treatment

Sheets NC. et al JAMA 2012
IMRT vs. 3D (RTOG 0126; Intermediate Risk; No ADT)

Total patients enrolled:
\[ n = 1532 \]

- 79.2 Gy in 44 fractions (IMRT or 3D)
- 70.2 Gy in 39 fractions (IMRT or 3D)

RTOG 0126
(Acute toxicity; Grade ≥2 and ≥3)

RTOG 0126
(Late GI toxicity; Grade ≥ 2 and ≥ 3)

GI Grade 2+

P = 0.0389

3D IMRT

GI Grade 3+

P = 0.09

3D IMRT

No difference in late GU toxicity

RTOG 0126
(Parameters of Late GI toxicity)

V75 Gy

P = 0.0014

> 10%

< 10%

V70 Gy

P = 0.0037

> 15%

< 15%

**RTOG 0126**  
(Patients Reported Outcomes)

**79.2 Gy IMRT vs 3D**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 mo</th>
<th>1 yr</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Urinary Function</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Change in Bowel Habits</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Bruner DW et al. Cancer 2015
IMRT VS. 3D: Conclusions

- Grades 2+ of both GU/GI **ACUTE** toxicity are better with IMRT.
- Grades 2+ of **LATE** GI toxicity are better with IMRT.
- GU acute and **LATE** effects are similar.
- Patient reported outcomes (PROs) are not different.
- Dose volume constraints are more important than the technique itself.
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• Optimal use of Androgen Ablation with RT
• Dose escalation and Androgen Ablation
• Hypofractionation schedules (4-6wks)
Many randomized trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
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<tbody>
<tr>
<td>RTOG 85-31</td>
<td>977 pts</td>
</tr>
<tr>
<td>RTOG 86-10</td>
<td>471 pts</td>
</tr>
<tr>
<td>EORTC 22863</td>
<td>415 pts</td>
</tr>
<tr>
<td>EORTC 22961</td>
<td>970 pts</td>
</tr>
<tr>
<td>RTOG 9202</td>
<td>1559 pts</td>
</tr>
<tr>
<td>RTOG 9413</td>
<td>1323 pts</td>
</tr>
<tr>
<td>DFCI 95096</td>
<td>206 pts</td>
</tr>
<tr>
<td>TROG 96.01</td>
<td>802 pts</td>
</tr>
<tr>
<td>EORTC 22991</td>
<td>819 pts</td>
</tr>
<tr>
<td>ICORG 97-01</td>
<td>261 pts</td>
</tr>
<tr>
<td>RTOG 99-10</td>
<td>1489 pts</td>
</tr>
</tbody>
</table>
RT + ADT vs RT: Metanalysis

Biochemical failure

Local control

Distant control

Overall survival

Bria E. et al. Cancer 2009
## Low/intermediate risk: RTOG 94-08

Overall survival; Median F-up: 8.5 yrs

<table>
<thead>
<tr>
<th>Risk category</th>
<th>n</th>
<th>RT+ AA</th>
<th>RT alone</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T1-T2a; ≤ GI 6; PSA &lt;10)</td>
<td>685</td>
<td>76%</td>
<td>73%</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Intermediate risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T2b; GI 7; PSA 10-20)</td>
<td>1,068</td>
<td>72%</td>
<td>66%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Jones C. et al. NEJM 2011
RTOG 94-08

Low Risk

Intermediate Risk

Jones C. et al. NEJM 2011
OPTIMAL SEQUENCE, TIMING, AND DURATION OF ABLATION
SEQUENCE OF AA-RT: Preclinical data

SEQUENCE OF AA-RT: CLINICAL TRIAL

RTOG 94-13

1323 pts.; PSA<100
Stratified by T-stage, PSA, GL score

Neo/Conc + WP XRT vs.
Neo/Conc + PO XRT vs.
WP XRT + Adj AA vs.
PO XRT + Adj AA

Median F-up 6 yrs

RTOG 94-13

TIMING: WHEN TO START RT?

RTOG 9910

1449 pts; T1b-4 Gleason 2-10, PSA 10-100

Neo AA 8 weeks → RT vs.
Neo AA 28 weeks → RT
Median F-up 9.4 yrs

RTOG 9910

Biochemical failure

Disease Free Survival

TIMING: WHEN TO START RT?

MDACC study

TIMING: WHEN TO START RT?

MSKCC study


PSA < 0.3

PSA > 0.3

$P < 0.001$
DURATION OF ABLATION

Important question
Potential complications of AA (osteoporosis)
Quality of life issues (potency, hot flashes, fatigue)
Impact on healthcare cost
RTOG 92-02

1554 pts.; T2c-T4; PSA < 150
CAB (4 mo.) + XRT vs.
CAB (4 mo.) + XRT → LHRH A for 2 years
Closed in April 1995

1554 pts.; T2c-T4; PSA < 150
CAB (4 mo.) + XRT vs.
CAB (4 mo.) + XRT → LHRH A for 2 years
Closed in April 1995

<table>
<thead>
<tr>
<th></th>
<th>ST</th>
<th>LT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>12%</td>
<td>22%</td>
<td>0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>23</td>
<td>12</td>
<td>0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>54%</td>
<td>52%</td>
<td>0.36</td>
</tr>
<tr>
<td>OS (GS 8-10)</td>
<td>32%</td>
<td>45%</td>
<td>0.006</td>
</tr>
<tr>
<td>GI complic &gt; Gr 2</td>
<td>1.2%</td>
<td>2.6%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

EORTC TRIAL: 36 VS 6 MONTHS

970 patients T2C-T4, any N; Any T+N1/N2; 9% had N+ve
RT + 6 months vs RT + 36 months ADT
Stratification by T-stage; GS, bPSA; Median f-up 5.2 yrs

Bolla M et al NEJM 2009
CANADIAN TRIAL: 36 VS 18 MONTHS

- 630 patients were randomized to 36 vs 18 months; median follow-up of 78 months
- Overall and cancer-specific survival not significantly different (p=0.366 and 0.819 respectively)
- 5- and 10-year overall survival rates were not significantly different
- There were no significant differences in the rates of biochemical, regional, or distant failure between arms

Nabid A et al. ASCO 2013
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• Hypofractionation schedules (4-6wks)
Dose escalation ± short term ablation

GETUG 14 (EU-20503/NCT00104741)

Intermediate risk

Dubray B et al. ASCO 2011, 2016
### Dose escalation ± short term ablation

Median follow up: 84 months

<table>
<thead>
<tr>
<th></th>
<th>AA+RT</th>
<th>RT alone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>bRF S</td>
<td>90</td>
<td>79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>b/cRFS</td>
<td>84</td>
<td>76</td>
<td>0.02</td>
</tr>
<tr>
<td>GU (G3-4)</td>
<td>5</td>
<td>7</td>
<td>0.44</td>
</tr>
<tr>
<td>GI (G3-4)</td>
<td>5</td>
<td>4</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Closed with 377 pts due to poor accrual

Dubray B et al. ASCO 2016
Dose escalation ± short term ablation

Canadian Trial

December 2000 to September 2010
600 patients with Intermediate Risk PC; median f-up: 7.2 yrs
Randomized: ST-AA x 6 months + RT 70 Gy
ST-AA x 6 months + RT 76 Gy
RT 76 Gy

Nabid A et al. ASCO GU 2015
Dose escalation ± short term ablation

Canadian Trial

December 2000 to September 2010
600 patients with Int Risk PC; median f-up: 7.2 yrs
Randomized:
- ST-AA x 6 months + RT 70 Gy
- ST-AA x 6 months + RT 76 Gy
- RT 76 Gy

<table>
<thead>
<tr>
<th></th>
<th>AA +76</th>
<th>AA +70</th>
<th>76</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF</td>
<td>8</td>
<td>12.5</td>
<td>21.5</td>
<td>.001</td>
</tr>
<tr>
<td>DFS (10 yrs)</td>
<td>90</td>
<td>77</td>
<td>64</td>
<td>.001</td>
</tr>
<tr>
<td>OS (10 yrs)</td>
<td>70</td>
<td>64</td>
<td>78</td>
<td>NS</td>
</tr>
</tbody>
</table>

Nabid A et al. ASCO GU 2015
Short term ablation ± Dose escalation

EORTC Trial 22991

December 2001 to September 2008
819 patients with Int Risk PC (75%); High Risk (25%);
Median f-up: 7.2 years
Randomized:  
- ST-AA x 6 m + RT 70 Gy  vs 70 Gy
- ST-AA x 6 m + RT 74 Gy  vs 74 Gy
- ST-AA x 6 m + RT 78 Gy  vs 78 Gy

Bolla M et al J Clin Onc 2016
EORTC Trial 22991

Short term ablation ± Dose escalation

<table>
<thead>
<tr>
<th>RT Dose</th>
<th>RT/AS</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 Gy</td>
<td>40%</td>
<td>66%</td>
</tr>
<tr>
<td>74 Gy</td>
<td>25%</td>
<td>43%</td>
</tr>
<tr>
<td>78 Gy</td>
<td>26%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Dose escalation ± short term ablation

RTOG 0815

A Phase III Prospective Randomized Trial of Dose-Escalated Radiotherapy 79.2 Gy with or without Short-Term Androgen Deprivation Therapy for Patients with Intermediate-Risk Prostate Cancer

Opened 2008
Target accrual 1520 patients
Accrued to date 1527 patients
ADT and RT: Conclusion

- Low risk pts do not require concurrent ADT
- Intermediate risk pts benefit from a short course of ADT
- High risk pts benefit from longer ADT (1.5-3 yrs)
- Aim to start RT when PSA < 0.3 ng/ml
- Dose escalation seems to maintain effectiveness on BFFS with short term androgen ablation
- Both risk groups (intermediate and high) seem to benefit (EORTC 2291)
OUTLINE

- Risk classification and patient selection
- Surgical techniques and outcome
- Common side effects of RP
- Role of adjunct androgen deprivation
- Indications for adjuvant radiation therapy
- Definitive radiation therapy: Dose escalation
- IMRT versus 3D CRT
- Optimal use of Androgen Ablation with RT
- Dose escalation and Androgen Ablation
- Hypofractionation schedules (4-6wks)
If the hypothesis that $\alpha/\beta$ ratio for prostate cancer is low (near 1)

- Then a radiation therapy schedule that employs less frequent and larger fractions, termed hypofractionation, may be more effective.
- Moderate Hypofractionation (2.5-3 Gy)
- Extreme hypofractionation (> 5 Gy)
### Moderate Hypofractionation: Early trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>F-up</th>
<th>RT</th>
<th>Regimen</th>
<th>Outcome</th>
<th>Late Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario ‘05</td>
<td>936</td>
<td>5.7 yrs</td>
<td>3D</td>
<td>52.5 (2.62) vs 66 Gy</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Italy ‘10</td>
<td>168</td>
<td>5.8 yrs</td>
<td>3D</td>
<td>62 (3.1) vs 80 Gy</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Australia ‘11</td>
<td>217</td>
<td>7.5 yrs</td>
<td>3D</td>
<td>55 (2.75) vs 64 Gy</td>
<td>P &lt; 0.05 (HF)</td>
<td>GU better (HF)</td>
</tr>
<tr>
<td>Fox Chase ‘13</td>
<td>303</td>
<td>5.7 yrs</td>
<td>IMRT</td>
<td>70.2 (2.7) vs 76 Gy</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MDACC ‘14</td>
<td>204</td>
<td>4.6 yrs</td>
<td>IMRT</td>
<td>72 (2.4) vs 75.6 Gy</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
The RTOG 0415: Phase III non-inferiority trial

- Randomized, non-inferiority phase 3 trial
- 1115 patients; 2006-2009
- T1–T2CN0M0 prostate cancer, PSA ≤ 10 ng/mL, Gl Score ≤ 6
- Randomized:
  73.4 Gy in 41 fractions (1.8 Gy) vs
  70 Gy in 28 fractions (2.5 Gy);
- Low risk: 100%; No ADT
- Median F-up: 5.8 years

Lee RW et al, ASTRO 2015
The RTOG 0415: Phase III non-inferiority trial

Both IMRT (79%) and 3D (21%) techniques were allowed.

<table>
<thead>
<tr>
<th>Study arm</th>
<th>n</th>
<th>7 year BF</th>
<th>Gr 3+ late bowel</th>
<th>Gr 3+ late GU</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.4 Gy</td>
<td>542</td>
<td>12%</td>
<td>2.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>70 Gy</td>
<td>550</td>
<td>8%</td>
<td>4.1% (p = .002)</td>
<td>3.5% (p = .06)</td>
</tr>
</tbody>
</table>

No difference in Acute GI and GU reactions.

73.4 Gy vs 70 Gy: NS (Non–Inferior) for Efficacy, but with slightly higher late Toxicity.

Lee RW et al, ASTRO 2015, ASCO GU 2016; JCO 2016
The HYPRO study: Phase III non-inferiority trial

- Randomized, non-inferiority phase 3 trial
- 820 patients; 7 Dutch centers; 2007-2010
- T1b–T4N0M0 prostate cancer, PSA \( \leq 60 \text{ ng/mL} \)
- Randomized:
  - 78 Gy in 39 fractions (2 Gy) vs
  - 64.6 Gy in 19 fractions (3.4 Gy); 3 fractions per week

- Intermediate risk: 27%; High Risk: 73%; ADT: 66%
- Median F-up: 5 years

Aluwini, SP et al, Lancet Oncol 2015
The HYPRO study: Phase III non-inferiority trial

<table>
<thead>
<tr>
<th>Study arm</th>
<th>n</th>
<th>5 year BFFS</th>
<th>Gr 2+ bowel (120 days)</th>
<th>Gr 2+ late GU (120 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 Gy (2 Gy)</td>
<td>390</td>
<td>77%</td>
<td>31.2%</td>
<td>57.8%</td>
</tr>
<tr>
<td>64.6 Gy (3.4/T.I.W)</td>
<td>402</td>
<td>80%</td>
<td>42%</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

Toxicity: 78 Gy vs 64.6 Gy: 0.0015 (Non Non-Inferior) for grade 2+ GI toxicity at 120 days. *Lancet Oncol 2015*

Efficacy: 78 Gy vs 64.6 Gy: p=0.36 (No difference). *Lancet Onc 2016*

Aluwini, SP et al, Lancet Oncol 2015
Moderate Hypofractionation: the CHHIP trial

- Randomized, non-inferiority phase 3 trial
- 3216 patients; 71 UK centers; 2002-2011
- T1b–T3aN0M0 prostate cancer, PSA \leq 30 \text{ ng/mL},
- Randomized:
  - 74 Gy in 37 fractions (2 Gy) vs
  - 60 Gy in 20 fractions (3 Gy) vs
  - 57 Gy in 19 fractions (3.1 Gy)

- Low Risk: 15%; Intermediate: 73%; High Risk: 12%; ADT: 97%
- Median F-up : 5.2 years

Dearnaley DP et Al. ASCO GU 2016, Lancet Onc 2016
Moderate Hypofractionation: CHHIP trial

<table>
<thead>
<tr>
<th>Study arm</th>
<th>n</th>
<th>5 yr BFFS</th>
<th>Gr 2+ late bowel</th>
<th>Gr 2+ late GU</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 Gy (2Gy)</td>
<td>1065</td>
<td><strong>88.3%</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>60 Gy (3 Gy)</td>
<td>1074</td>
<td><strong>90.6%</strong></td>
<td>2.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>57 Gy (3 Gy)</td>
<td>1077</td>
<td><strong>85.9%</strong></td>
<td>1.8%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

74 Gy vs 60 Gy: NS (Non-Inferior)
57 Gy vs 60 Gy: p = 0.003 (Inferior)
→ 60 Gy in 20 fractions and 4 weeks is a good alternative to CF

Dearnaley DP et Al. ASCO GU 2016; Lancet Onc 2016
Moderate Hypofractionation: CHHIP trial

biochemical Disease free survival

Overall survival

Dearaley DP et Al. ASCO GU 2016; Lancet Onc 2016
Chhip trial: QOL patient reported outcome

2100 patients consented to this QOL study

Wilkins A et Al. Lancet Oncol 2015
Hypofractionation: conclusions

- Equivalent effectiveness (non-inferior)
- Equivalent side effects (HYPRO; RTOG !)
- Shorter and more convenient (CHHiP: 4 weeks)
- Slow to gain acceptance (?!)

Note: this document is a snapshot of a slide presentation and may contain additional context or information not visible in the image.
What I could not discuss today!

- Brachytherapy (alone or in combination with RT)
- Elective radiation to the pelvis
- Treatment of positive pelvic lymphnodes
- LHRH agonist alone or complete blockade
- Extreme hypofractionation (5 fractions)
Thank You