LOCALIZED PROSTATE CANCER: ROLE OF RADIOTHERAPY

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and
Experimental Cancer Research
Overview:
Introduction
Dose escalation: evidence
Dose escalation: toxicity
Alternative fractionation
Conclusion
Introduction
Introduction

Ward et al, Clinical Genitourinary Cancer, 2013
Introduction
Introduction
Overview:

Introduction
Dose escalation: evidence
Dose escalation: toxicity
Alternative fractionation
Conclusion
<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (Gy)</th>
<th>N</th>
<th>Follow up</th>
<th>bRFS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zietman</td>
<td>70.2 GyE</td>
<td>197</td>
<td>8.9</td>
<td>61</td>
<td>0.0012</td>
</tr>
<tr>
<td></td>
<td>79.2 GyE</td>
<td>196</td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Peeters</td>
<td>68</td>
<td>331</td>
<td>8.9</td>
<td>54</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>333</td>
<td></td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Dearnaley</td>
<td>64</td>
<td>421</td>
<td>5.3</td>
<td>60</td>
<td>0.0007</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>422</td>
<td></td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Kuban</td>
<td>70</td>
<td>150</td>
<td>8.7</td>
<td>59</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>151</td>
<td></td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Beckendorf</td>
<td>70</td>
<td>153</td>
<td>5.1</td>
<td>68</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>153</td>
<td></td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>
Dose escalation: Evidence

Biochemical failure at 10 years

Hou et al, J Cancer Res Clin Oncol, 2014
### Prostate cancer specific mortality at 10 years

**Dose escalation: Evidence**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High dose Events</th>
<th>High dose Total</th>
<th>Conventional dose Events</th>
<th>Conventional dose Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creak A et al 2013</td>
<td>59</td>
<td>62</td>
<td>56</td>
<td>64</td>
<td>3.1%</td>
<td>2.81 [0.71, 11.13]</td>
<td></td>
</tr>
<tr>
<td>DUTCH 2013</td>
<td>287</td>
<td>331</td>
<td>289</td>
<td>333</td>
<td>44.1%</td>
<td>0.99 [0.63, 1.56]</td>
<td></td>
</tr>
<tr>
<td>MD Anderson 2011</td>
<td>149</td>
<td>151</td>
<td>142</td>
<td>150</td>
<td>2.2%</td>
<td>4.20 [0.88, 20.10]</td>
<td></td>
</tr>
<tr>
<td>MRC RT01 2014</td>
<td>375</td>
<td>422</td>
<td>377</td>
<td>421</td>
<td>48.4%</td>
<td>0.93 [0.60, 1.44]</td>
<td></td>
</tr>
<tr>
<td>PROG9509 2010</td>
<td>194</td>
<td>196</td>
<td>193</td>
<td>197</td>
<td>2.3%</td>
<td>2.01 [0.36, 11.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1162</td>
<td>1165</td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td>1.11 [0.83, 1.49]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1064 (High dose) vs 1057 (Conventional dose)

Heterogeneity: Chi² = 5.85, df = 4 (P = 0.21); I² = 32%

Test for overall effect: Z = 0.71 (P = 0.47)

Hou et al, J Cancer Res Clin Oncol, 2014
Overall survival

Hou et al, J Cancer Res Clin Oncol, 2014
**Dose escalation: Evidence**

7-years PSA relapse-free survival:

- **Low risk**: 98.8%
- **Intermediate risk**: 85.6%
- **High-risk**: 67.9%

Dose escalation: Evidence

7-years distant metastasis relapse-free survival:

*Low risk: 99.4%*

*Intermediate risk: 94.1%*

*High-risk: 82%*

Dose escalation: Evidence

No prostate cancer-related deaths were observed in the very-low or low-risk group

Overview:

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Dose escalation: toxicity
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Conclusion
Rectal toxicity

**Late grade ≥2 rectal toxicity:**
Conventional dose radiotherapy: 18.6%
High dose radiotherapy: 28%

Hou et al, J Cancer Res Clin Oncol, 2014
Rectal toxicity
Rectal toxicity

Quality of life

Men with excellent baseline domain score (100 points)

- Active surveillance
- External beam radiation
- Radical prostatectomy

Bowel Function Symptoms Domain Score, Unadjusted Mean (95% CI)

No. of patients
- Active surveillance: 259, 246, 234
- External beam radiation: 331, 319, 309
- Radical prostatectomy: 948, 896, 892

Barocas et al, Jama, 2017
## Urinary toxicity

**Late grade ≥2 urinary toxicity:**
- Conventional dose radiotherapy: 19.5%
- High dose radiotherapy: 22.6%

Hou et al, J Cancer Res Clin Oncol, 2014

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High dose</th>
<th>Conventional dose</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>DUTCH 2008</td>
<td>133</td>
<td>331</td>
<td>136</td>
</tr>
<tr>
<td>GETUG06 2011</td>
<td>27</td>
<td>153</td>
<td>15</td>
</tr>
<tr>
<td>MD Anderson 2008</td>
<td>20</td>
<td>151</td>
<td>12</td>
</tr>
<tr>
<td>MRC RT01 2007</td>
<td>46</td>
<td>422</td>
<td>32</td>
</tr>
<tr>
<td>PROG9509 2010</td>
<td>57</td>
<td>196</td>
<td>49</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1253</strong></td>
<td><strong>1254</strong></td>
<td><strong>100.0%</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>283</td>
<td>244</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 5.54, df = 4 (P = 0.24); I² = 28%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.06 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Urinary toxicity

<table>
<thead>
<tr>
<th>Whole bladder</th>
<th>RTOG</th>
<th>UTHSCSA</th>
<th>Univ Miami</th>
<th>MSKCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 Gy</td>
<td>15%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>75 Gy</td>
<td>25%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70 Gy</td>
<td>35%</td>
<td>25%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>65 Gy</td>
<td>50%</td>
<td>-</td>
<td>25%</td>
<td>-</td>
</tr>
<tr>
<td>60-50 Gy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>45 Gy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>53% (V47)</td>
</tr>
<tr>
<td>40 Gy</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>-</td>
</tr>
</tbody>
</table>

Swanson et al, Am J Clin Oncol, 2011
Urinary toxicity

Quality of life

Barocas et al, Jama, 2017
Erectile dysfunction

Magli et al, Strahlenther Onkol, 2012

N= 19
3D-CRT to 72-76 Gy
No ADT

$D_{mean\ penile\ bulb} < 50\ Gy$
Quality of life

Barocas et al, Jama, 2017
Overview:

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Phase III trials

Ritter et al, Cancer J, 2009
## Phase III trials

### Phase 3 trials of moderate hypofractionation in prostate cancer

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Sample size</th>
<th>Risk group</th>
<th>Regimens tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 0415</td>
<td>1067</td>
<td>Low</td>
<td>73.8 Gy (41x1.8 Gy) v 70 (28x2.5 Gy)</td>
</tr>
<tr>
<td>OCOG (Canada)</td>
<td>1204</td>
<td>Intermediate</td>
<td>78 (39x2 Gy) v 60 (20x3 Gy)</td>
</tr>
<tr>
<td>CHHIP (UK)</td>
<td>3216</td>
<td>Low/Intermediate/High</td>
<td>74 (37x2 Gy) v 57 (29x3 Gy) v 60 (20x3 Gy)</td>
</tr>
<tr>
<td>HYPRO (Dutch)</td>
<td>820</td>
<td>Int/High</td>
<td>78 (39x2 Gy) v 64.6 (19x3.4 Gy: 3 x/week)</td>
</tr>
</tbody>
</table>
# Evidence

## Phase 3 trials of moderate hypofractionation in prostate cancer

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Sample size</th>
<th>Risk group</th>
<th>Regimens tested</th>
</tr>
</thead>
</table>
| RTOG 0415        | Non inferiority trial  
Primary endpoint: disease free survival | Low                         | 73.8/1.8 Gy v 70/2.5 Gy                                                        |
| OCOG (Canada)    | Non inferiority trial  
Primary endpoint: biochemical-clinical failure | Intermediate                   | 78/2 Gy v 60/3 Gy                                                               |
| CHHIP (UK)       | To assess non-inferiority powered in biochemical or clinical failure-free survival 
Primary outcome time to biochemical or clinical failure 3-arm design | Low/Intermediate/High              | 74/2 Gy v 57/3 Gy v 60/3 Gy                                                     |
| HYPRO (Dutch)    | Primary endpoint: detection of 10% enhancement in 5-years relapse-free survival  
Additionaly: non-inferiority of hypofractionation in ≥grade 2 toxicity | Int/High                        | 78/2 Gy v 64.6/3.4 Gy (3 fractions/week)                                       |
Evidence: CHHiP

Acute Bowel toxicity
Evidence: CHHiP

**Acute Bladder toxicity**
Late Bowel toxicity

Evidence: CHHiP
**Evidence: CHHiP**

**Late Bladder toxicity**
# Extreme hypofractionation in prostate cancer

**Phase III trials**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Regimens tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO trial</td>
<td>78 Gy/39 F v</td>
</tr>
<tr>
<td></td>
<td>43.7 Gy/7 F</td>
</tr>
<tr>
<td>PACE trial</td>
<td>78 Gy/39 F v</td>
</tr>
<tr>
<td></td>
<td>36.25 Gy/5F</td>
</tr>
</tbody>
</table>
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Conclusion

External beam radiotherapy is an excellent treatment option for patients with localised prostate cancer

A dose of ≥ 74 Gy must be delivered

High dose radiotherapy improves:

1) PSA control for all risk groups

BUT NOT

1) PCSM at 10 years
2) OS at 10 years

Toxicity is acceptable after high dose external beam radiotherapy

There is evidence for use of hypofractionated radiotherapy