Localized prostate cancer:

Role of radiotherapy

Valérie Fonteyne, MD, PhD
Lugano 2016

Faculty of Medicine and Health Sciences
Department of Radiation Oncology
and
Experimental Cancer Research
Overview:

1. Introduction
2. Dose escalation: why?
3. Dose escalation: evidence
4. Dose escalation: toxicity
5. Alternative fractionation
6. Conclusion
Introduction
Introduction

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

1. Introduction
2. Dose escalation: why?
3. Dose escalation: evidence
4. Dose escalation: toxicity
5. Alternative fractionation
6. Conclusion
### Dose escalation: Why?

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Local Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 yr</td>
</tr>
<tr>
<td>T1 Nx</td>
<td>583</td>
<td>3-6</td>
</tr>
<tr>
<td>T2 Nx</td>
<td>117</td>
<td>12-14</td>
</tr>
<tr>
<td>T3 Nx</td>
<td>2292</td>
<td>12-26</td>
</tr>
</tbody>
</table>

Pilepich IJROBP 1987  
Goffinet and Bagshawe EORTC 1990  
Zagars Cancer 1987  
Perez NCI Monograph 1988
# Dose escalation: Why?

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Treatment effect</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>≥81</td>
<td>26 (25)</td>
<td>53 (52)</td>
<td></td>
</tr>
<tr>
<td>75.6</td>
<td>38 (27)</td>
<td>66 (46)</td>
<td></td>
</tr>
<tr>
<td>70.2</td>
<td>26 (38)</td>
<td>36 (52)</td>
<td></td>
</tr>
<tr>
<td>&lt;70.2</td>
<td>17 (65)</td>
<td>6 (23)</td>
<td></td>
</tr>
</tbody>
</table>

**Biochemical control**

**Dose escalation: Why?**

**Biochemical control**

**Dose escalation: Why?**

**Fig. 1.** Negative vs positive biopsy p < 0.001 and positive vs treatment effect biopsy p < 0.001.

Dose escalation: Why?

10 Y DMFS for intermediate risk patients

Overview:

1. Introduction
2. Dose escalation: why?
3. Dose escalation: evidence
4. Dose escalation: toxicity
5. Alternative fractionation
6. Conclusion
## Dose escalation: Evidence

<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
# Dose escalation: Evidence

Prostate cancer specific mortality at 10 years

Hou et al, J Cancer Res Clin Oncol, 2014

<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>M-H, Fixed, 95% CI</th>
<th>Odds Ratio</th>
<th>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>
<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>
<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>
<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>
<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>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1162</strong></td>
<td></td>
<td><strong>1165</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.11 [0.83, 1.49]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1064</td>
<td></td>
<td>1057</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 5.85, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 0.71 (P = 0.47)
Dose escalation: Evidence

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:

1. Introduction
2. Dose escalation: why?
3. Dose escalation: evidence
4. Dose escalation: toxicity
5. Alternative fractionation
6. 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

Viani et al, Cancer, 2016
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
**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

Viani et al, Cancer, 2016
Erectile dysfunction

$D_{\text{mean \, penile bulb}} < 50 \text{ Gy}$

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

Magli et al, Strahlenther Onkol, 2012
Overview:

1. Introduction
2. Dose escalation: why?
3. Dose escalation: evidence
4. Dose escalation: toxicity
5. Alternative fractionation
6. Conclusion
Phase III trials

Ritter et al, Cancer J, 2009
The biologic rationale for applying hypofractionation to PCa is based on the theory that the slow proliferation of PCa cells leads to a biologic radiation response in PCa that differs from most other cancers. Traditional fractionation causes the accumulation of DNA damage, ultimately causing apoptosis, mitotic catastrophe, or senescence [1]. A slow proliferation rate results in a high reparation ability of radiation damage over time, such that standard fractionation given in small increments over a long time period may be suboptimal for PCa for which a high total dose is required for effective control [2]. For slowly proliferating cells, high doses per fraction may be more effective because immediate cell death is instigated due to the high number of DNA double-strand breaks caused by each fraction.

Radiobiology has developed a concept to explain how fraction size and total dose interact to compare differing treatment regimens, described as the $\alpha/\beta$. General radiobiology teaches that tumors with high $\alpha/\beta$ values are less able to repair injury between fractions than normal tissues with low $\alpha/\beta$ values, such that small fractions to high doses will allow preferential recovery of low $\alpha/\beta$ tissues while still killing cancer cells. Alternatively, if tumor cells have a lower $\alpha/\beta$ than nearby normal tissues, low-dose long treatment courses will require higher total doses than a few large fractions given over a short time. Thus hypofractionation using a few large fractions may result in the same tumor cell kill with lower total doses achieving comparable normal tissue toxicity. It is believed that PCa has a low $\alpha/\beta$ of approximately 1.5 Gy. Retrospective data from 11,330 patients with PCa treated with EBRT of varying fraction size supports this theory [3].
## Phase III trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimens</th>
<th>Treatment schedule</th>
<th>N</th>
<th>Treatment outcome</th>
</tr>
</thead>
</table>
| Lukka, 2005    | Hypofractionated versus conventional     | 52.5 / 2.63 Gy     | 936| **TCP:** 5Y clinical/biochemical failure: 59.95% (hypo) v 52.9% No difference in OS  
**NTCP:** similar late toxicity |
| Pollack, 2013  | Hypofractionated IMRT versus conventional IMRT | 70.2 / 2.7 Gy     | 303| **TCP:** 5Y clinical/biochemical failure: 23.3% (hypo) v 21.4%  
**NTCP:** small increase in GI toxicity for hypofractionation |
| Kuban, 2010    | Hypofractionated versus conventional     | 72 / 2.4 Gy        | 204| **TCP:** 5Y clinical/biochemical failure: 4% (hypo) v 8%  
**NTCP:** similar toxicity |

**No or non conclusive therapeutic gain**
## Phase III trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimens</th>
<th>Treatment schedule</th>
<th>N</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norkus, 2009</td>
<td>Hypofractionated 3D-CRT <em>versus</em> conventional 3D-CRT</td>
<td>57/3-4.5 Gy <em>versus</em> 74/2 Gy</td>
<td>91</td>
<td><strong>NTCP:</strong> acute grade 2 GU: 19.1% (hypo) v 47.7 (conventional); duration of acute GI toxicity shorter with hypofrac (3 v 6 weeks)</td>
</tr>
</tbody>
</table>
| Arcangeli, 2010| Hypofractionated *versus* conventional | 62/3.1 Gy *versus* 80/2 Gy          | 168 | **TCP:** 5 year freedom from biochemical failure: 85% (hypo) v 79%  
**NTCP:** more acute GI toxicity, no difference in late toxicity |
| Yeoh, 2010     | Hypofractionated 2D *versus* Conventional 2D | 55/2.75 Gy *versus* 64/2 Gy         | 217 | **TCP:** @ 90 months: biochemical relapse free survival: 53% (hypo) v 34%; no difference in OS  
**NTCP:** acute but not late GI toxicity worse for hypo |

**Presence of therapeutic gain**
## Phase III trials

### Non inferiority 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>73.8/1.8 Gy v 70/2.5 Gy</td>
</tr>
<tr>
<td>OCOG (Canada)</td>
<td>1204</td>
<td>Intermediate</td>
<td>78/2 Gy v 60/3 Gy</td>
</tr>
<tr>
<td>HYPRO (Dutch)</td>
<td>820</td>
<td>Int/High</td>
<td>78/2 Gy v 64.6/3.4 Gy (3 fractions/week)</td>
</tr>
<tr>
<td>CHHIP (UK)</td>
<td>3216</td>
<td>Low/Intermediate/High</td>
<td>74/2 Gy v 57/3 Gy v 60/3 Gy</td>
</tr>
</tbody>
</table>
RTOG 0415 trial

Lee et al, JCO, 2016
# Phase III trials

## RTOG 0415

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Conventional dose RT</th>
<th>Hypofractionated RT</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GI</strong></td>
<td>Grade 2: 56 (9%) Grade 3: 3 (1%)</td>
<td>Grade 2: 58 (10%) Grade 3: 3 (1%)</td>
<td>1.03 (0.73-1.46) 1.31 (0.29-5.81)</td>
<td>0.85 0.72</td>
</tr>
<tr>
<td><strong>Acute GU</strong></td>
<td>Grade 2: 132 (25%) Grade 3: 13 (2%)</td>
<td>Grade 2: 129 (24%) Grade 3: 18 (3%)</td>
<td>0.99 (0.82-1.21) 1.36 (0.67-2.74)</td>
<td>0.95 0.39</td>
</tr>
<tr>
<td><strong>Late GI</strong></td>
<td>Grade 2: 61 (11%) Grade 3: 14 (2%)</td>
<td>Grade 2: 99 (18%) Grade 3: 22 (4%)</td>
<td>1.59 (1.22-2.06) 1.55 (0.80-2.99)</td>
<td>0.005 0.19</td>
</tr>
<tr>
<td><strong>Late GU</strong></td>
<td>Grade 2: 109 (21%) Grade 3: 12 (2%)</td>
<td>Grade 2: 142 (26%) Grade 3: 19 (4%)</td>
<td>1.31 (1.07-1.61) 1.56 (0.76-3.18)</td>
<td>0.009 0.22</td>
</tr>
</tbody>
</table>
HYPRO trial

Incrocci et al, Lancet Oncol, 2016
HYPRO trial

Incrocci et al, Lancet Oncol, 2016
# CHHiP trial

![Graph showing the 5-year biochemical or clinical failure-free survival rates for different radiation doses.](graph.png)

## Number at risk (events)

<table>
<thead>
<tr>
<th>Radiation Level</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 Gy</td>
<td>1065 (4)</td>
<td>1037 (24)</td>
<td>991 (39)</td>
<td>926 (24)</td>
<td>795 (20)</td>
<td>495 (11)</td>
<td>284 (3)</td>
<td>167 (11*)</td>
</tr>
<tr>
<td>60 Gy</td>
<td>1074 (4)</td>
<td>1042 (15)</td>
<td>1011 (23)</td>
<td>965 (28)</td>
<td>816 (18)</td>
<td>533 (10)</td>
<td>280 (10)</td>
<td>176 (10*)</td>
</tr>
<tr>
<td>57 Gy</td>
<td>1077 (5)</td>
<td>1044 (30)</td>
<td>1004 (35)</td>
<td>944 (31)</td>
<td>798 (31)</td>
<td>492 (9)</td>
<td>262 (13)</td>
<td>151 (9*)</td>
</tr>
</tbody>
</table>

## Number censored

<table>
<thead>
<tr>
<th>Radiation Level</th>
<th>0</th>
<th>24</th>
<th>22</th>
<th>26</th>
<th>107</th>
<th>280</th>
<th>200</th>
<th>114</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 Gy</td>
<td>0</td>
<td>28</td>
<td>16</td>
<td>23</td>
<td>121</td>
<td>265</td>
<td>243</td>
<td>94</td>
</tr>
<tr>
<td>60 Gy</td>
<td>0</td>
<td>28</td>
<td>10</td>
<td>25</td>
<td>115</td>
<td>275</td>
<td>221</td>
<td>98</td>
</tr>
</tbody>
</table>

Dearnaley et al, Lancet Oncol, 2016
CHHiP trial

Dearmaley et al, Lancet Oncol, 2016
CHHiP trial

Acute Bowel toxicity

CHHiP trial

Acute Bladder toxicity

Late Bowel toxicity

CHHiP trial

CHHiP trial

Late Bladder toxicity

Dearnaley et al, Lancet Oncol, 2016
**Phase III trials**

**Extreme hypofractionation in prostate cancer**

<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>
Overview:

1. Introduction
2. Dose escalation: why?
3. Dose escalation: evidence
4. Dose escalation: toxicity
5. Alternative fractionation
5. Conclusion
Conclusion
Conclusion

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

A dose of $\geq 74$ 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