Hypofractionation for prostate cancer: Is it the new standard of care?

Dr Nicholas van As
nicholas.vanas@rmh.nhs.uk
@nickva1

Lisbon: 26 January 2018
Disclosures

Research grants and honoraria from Accuray
Disclaimer

The views expressed in this presentation are those of the presenters and do not necessarily reflect the views or policies of Accuray Incorporated or its subsidiaries. No official endorsement by Accuray Incorporated or any of its subsidiaries of any vendor, products or services contained in this presentation is intended or should be inferred.
History of hypofractionation
St. Thomas Hospital; 1991 (UK)(1964-1984)

- Radical external beam radiotherapy for localised carcinoma of the prostate using a hypofractionation technique
- Retrospective 232 patients, clinically localized PCA.
- RT 36/6
- Conclusion: Comparable results to other series, early and late morbidity acceptable

Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis

- Retrospective. 705 men with T1-T4No PCA, 4F conformal RT
- dose 50/16 @ 3.13 Gy/fx.
- Conclusion: Similar tumor control and toxicity to standard 65-70 Gy

Why might hypofractionation work in localised prostate cancer?

FRACTIONATION AND PROTRACTION FOR RADIOTHERAPY OF PROSTATE CARCINOMA

Brenner DJ, Hall EJ.


Estimation of $\alpha/\beta$

Based on the $\alpha$ and $\beta$ estimates described above, the estimated value of $\alpha/\beta$ was 1.5 Gy
What’s the fraction sensitivity of prostate cancer?

1.8 Gy

1.4 Gy

1.55 Gy

3.7 Gy
4 RCT’s
Trial schema

Hormone treatment (3-6 months)

T1b-T3a N0 M0
Estimated risk of SV involvement ≤ 30%
PSA ≤ 30ng/ml

Randomise

74Gy / 37f (standard)
60Gy / 20f (hypofractionated)
57Gy / 19f (hypofractionated)

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>(N=3216)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Age (Median)</td>
<td>69</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>12</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>73</td>
</tr>
<tr>
<td>Low Risk</td>
<td>15</td>
</tr>
<tr>
<td>Pre-hormone PSA (ng/ml)</td>
<td>10</td>
</tr>
</tbody>
</table>
Time to biochemical failure/prostate cancer recurrence – primary analysis

Number at risk (events)

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

Non-inferiority to control:

HR$_{60/74} = 0.84$ 90% CI: 0.68 to 1.03

HR$_{57/74} = 1.20$ 90% CI: 0.99 to 1.46
Non-inferiority analysis (ITT)

<table>
<thead>
<tr>
<th>Biochemical failure or prostate cancer recurrence</th>
<th>74Gy/37f (n=1065)</th>
<th>60Gy/20f (n=1074)</th>
<th>57Gy/19f (n=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>138</td>
<td>119</td>
<td>164</td>
</tr>
<tr>
<td>KM 5 year proportion event-free estimate (95% CI)</td>
<td>88.3 (86.0, 90.2)</td>
<td>90.5 (88.4, 92.2)</td>
<td>85.8 (83.3, 87.9)</td>
</tr>
<tr>
<td>Hazard ratio (90% CI)</td>
<td><strong>0.83 (0.68, 1.02)</strong></td>
<td><strong>1.19 (0.99, 1.44)</strong></td>
<td></td>
</tr>
<tr>
<td>Pr(HR&lt;1.208)</td>
<td>p=0.003</td>
<td>p=0.91</td>
<td></td>
</tr>
<tr>
<td>Log rank p-value</td>
<td>p=0.14</td>
<td>p=0.13</td>
<td></td>
</tr>
<tr>
<td><strong>Absolute difference at 5 years (90% CI)</strong></td>
<td>1.86 (-0.26, 3.62)</td>
<td>-2.10 (-4.74, 0.16)</td>
<td></td>
</tr>
<tr>
<td>Absolute difference at 5 years (90% CI)</td>
<td></td>
<td>-3.84 (-6.52, -1.58)</td>
<td></td>
</tr>
</tbody>
</table>

74 v 60Gy  Non-inferior
74 v 57Gy  Inconclusive

HR<1 favours hypofractionation
Short-term side-effects – bowel and bladder
A randomized trial of a shorter radiation fractionation schedule for the treatment of localized prostate cancer

OCOG / TROG PROstate Fractionated Irradiation Trial

Charles Catton MD FRCPC
PRINCESS MARGARET CANCER CENTRE, TORONTO
on behalf of the PROFIT trial investigators
Intermediate risk prostate cancer

**Stratify:** Pre-randomization ADT* (yes/no)
Risk of seminal vesical involvement (≥15%, <15%)
Treatment center

60Gy in 20 fractions
5 days/week for 4 weeks
**Short** (n = 608)

78Gy in 39 fractions
5 days/week for 8 weeks
**Standard** (n = 598)

*Up to 90 days permitted pre-randomization; No post-randomization ADT
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short n=608</th>
<th>Standard n=598</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range)</strong></td>
<td>72 (48-87)</td>
<td>71 (50-88)</td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>5 to 10</td>
<td>50%</td>
<td>51%</td>
</tr>
<tr>
<td>10.1 to 20</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 + 3</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>3 + 4</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td>4 + 3</td>
<td>28%</td>
<td>27%</td>
</tr>
</tbody>
</table>
Results: BCF

Freedom from Biochemical - Clinical Failure

BCF-free Survival

HR_{Short} \mid \text{Standard} = 0.99

90\% CI, 0.83 to 1.19 < 1.32

p_{\text{non-inf}} = 0.0044

Adjusted for strata

N at risk:
- Short: 608, 585, 549, 524, 485, 341, 221, 123, 48, 8
- Standard: 598, 584, 558, 530, 490, 341, 219, 121, 56, 10
Comparison of CHHiP and PROFIT

- **Complementary studies CHHiP ADT : PROFIT no ADT**
- **Same experimental group: 60Gy 20f 4w**
- **Standard group CHHiP 74Gy : PROFIT 78Gy**

**RESULTS**

- **Efficacy results: CHHiP 74Gy non inf to 60 Gy PROFIT 78Gy non inf to 60Gy**
- **Same GU/GI acute toxicity profiles**
- **Same GU late toxicity profiles**
- **GI toxicity increased in PROFIT 78Gy group : isotoxic in CHHiP 74Gy group compared to 60Gy**
- **Failure rate (60Gy) in CHHiP 10% vs 21% PROFIT – similar to 13% benefit of ADT in EORTC 22991**
Should “moderate” hypofractionation be the new standard of care?
What about “profound” hypofractionation?
Can we go below 3 Gy/fraction?
Biologically effective dose of 36.25 Gy in 5 fractions

<table>
<thead>
<tr>
<th></th>
<th>BED if α/β ratio = 5</th>
<th>BED if α/β ratio = 4</th>
<th>BED if α/β ratio = 3</th>
<th>BED if α/β ratio = 2.7</th>
<th>BED if α/β ratio = 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 Gy in 39 fractions</td>
<td>109 Gy</td>
<td>117 Gy</td>
<td>130 Gy</td>
<td>135 Gy</td>
<td>182 Gy</td>
</tr>
<tr>
<td>36.25 Gy in 5 fractions</td>
<td>88 Gy</td>
<td>101 Gy</td>
<td>123 Gy</td>
<td>134 Gy</td>
<td>211 Gy (circled)</td>
</tr>
<tr>
<td>40 Gy in 5 fractions</td>
<td>104 Gy</td>
<td>120 Gy</td>
<td>147 Gy</td>
<td>158 Gy</td>
<td>253 Gy</td>
</tr>
</tbody>
</table>
Until 2013, state of the evidence base...

<table>
<thead>
<tr>
<th>Fractionation</th>
<th>Stage</th>
<th>PSA</th>
<th>Gleason</th>
<th>Low risk</th>
<th>Int risk</th>
<th>High risk</th>
<th>5 yr bRFS: low risk</th>
<th>5 yr bRFS: High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-36.35 Gy in 5 #</td>
<td>Low risk</td>
<td>&lt;10</td>
<td>3+3</td>
<td>None</td>
<td>93%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33.5 Gy in 5 #</td>
<td>T1c or T2a</td>
<td>10 or less</td>
<td>G1 6 or less</td>
<td>100%</td>
<td>48 month bRFS 90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.25 Gy in 5 #</td>
<td>T1c or T2a/b</td>
<td>&lt;10</td>
<td>3+4 or less</td>
<td>None</td>
<td>4-year bRFS 94%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 Gy-36.25 Gy in 5 #</td>
<td>92% T1c</td>
<td>Median 5.8</td>
<td>73% G16 23% G1 7</td>
<td>70%</td>
<td>1.3 % failed so far (17-30 month FU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38 Gy in 4 fraction</td>
<td>T1c-T3a</td>
<td>Median 7.5</td>
<td>Any</td>
<td></td>
<td>Median follow up 18.3 months 100% bRFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32-36 Gy in 4 #</td>
<td>T1c-T3</td>
<td>Median 15.8</td>
<td>4-9</td>
<td>5%</td>
<td>29%</td>
<td>100%</td>
<td>90.9%</td>
<td></td>
</tr>
<tr>
<td>45-50 Gy in 5 # (dose escalation cohorts)</td>
<td>T1c-T2b</td>
<td>Median 5.6</td>
<td>6-7 (36% Gleason 3+4)</td>
<td>40%</td>
<td>0%</td>
<td>Median follow up 12-30 months 100% bRFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.25-37.5 in 5 #</td>
<td></td>
<td></td>
<td>100%</td>
<td>0%</td>
<td>3 yr bRFS 97.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 Gy in 5 weekly #</td>
<td>T1-T2b</td>
<td>All &lt;10 Median 6</td>
<td>All Gleason 6</td>
<td>100%</td>
<td>0%</td>
<td>Median PSA at 6 months 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 Gy in 5 #</td>
<td>79% T2</td>
<td>Median 7.96</td>
<td>Median Gleason 6</td>
<td>14%</td>
<td>21%</td>
<td>41 month bRFS 86%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Two papers – Green Journal and Red Journal

**Green Journal**

*Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials.*


**Red Journal**

*Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials.*


Limitations

Not randomised

“phase II study”

Variable definitions of follow-up schedule (although no physician-reported toxicity outcomes in this paper)

Median follow-up 36 months
PSA outcomes

King et al, Rad Oncol, 2013
QOL in GU, GI and sexual domains over time

Bladder function

Bowel function

Sexual function

King et al, IJROBP, 2013
Bottom line

SBRT causes a QOL ‘dip’ in urinary and bowel domains at 3 months post-treatment.

QOL nearly back to baseline by 6 months.

Patients with poorer urinary and bowel QOL at baseline actually have an QOL better than baseline after 6/12.
The data from these two papers caused ASTRO to change their position on prostate SBRT.

“It is ASTRO’s opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.”
LDR

EBRT

Loblaw et al, Clin Oncol 2017
Rob Meier data – abstract only

309 patients, prospective, multicentre Phase II
40 Gy in 5 to CTV, 36.25 Gy in 5 to PTV
5 year PFS 97.1%

<table>
<thead>
<tr>
<th>Abstract 74; Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GU Toxicity</strong></td>
</tr>
<tr>
<td>Any time</td>
</tr>
<tr>
<td>&lt; 3 mos</td>
</tr>
<tr>
<td>&gt; 3 mos</td>
</tr>
<tr>
<td><strong>GI Toxicity</strong></td>
</tr>
<tr>
<td>Any time</td>
</tr>
<tr>
<td>&lt; 3 mos</td>
</tr>
<tr>
<td>&gt; 3 mos</td>
</tr>
</tbody>
</table>
The PACE trial

CI Dr Nick van As
Funded by Accuray

Low/Intermediate risk prostate cancer

Candidate for surgery?

Yes

Randomise

Prostatectomy

SBRT 36.25 Gy in 5 fractions

No

Randomise

SBRT 36.25 Gy in 5 fractions

EBRT 60 Gy in 20 fractions

PACE A
234 patients

PACE B
858 patients
Actual and target accrual – PACE A (08/01/2018)

PACE-A: Actual and target cumulative recruitment

- Actual recruitment
- Target recruitment (234 patients)
Actual and target accrual – PACE B (08/01/2018)

Recruitment stopped at 871 pts

PACE-B: Actual and target cumulative recruitment

- Red line: Actual recruitment
- Blue line: Target recruitment

Time line: Aug 12, Dec 12, Apr 13, Aug 13, Dec 13, Apr 14, Aug 14, Dec 14, Apr 15, Aug 15, Dec 15, Apr 16, Aug 16, Dec 16, Apr 17, Aug 17, Dec 17, Apr 18, Aug 18
Proposed PACE C trial

- Intermediate/high risk localised prostate cancer
- Non-surgical candidate
- Randomise

1-2 of
- Gleason 3+4>50% cores, Gleason 4+3 or Gleason 4+4
- T3aNo
- PSA 15-30
Should SABR be the new standard of care?
Where to next?
But,.... watch this sPACE

SABR
Thank you