Role of Radiotherapy in Prostate Cancer

Recent advances

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Instructor, Duke-NUS Graduate Medical School, Singapore

ESMO Advanced Course on Prostate Cancer,
21-22 Sep 2018, Singapore
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Varian, AstraZeneca, Janssen

Advisory/Consultancy roles:
Varian
Outline

- RT in the management of localised PCa
  - Intermediate-risk vs High-risk vs M1 disease

- Advancement in RT techniques
  - Technological advances – SBRT; PSMA PET-fusion
  - Dose escalation and fractionation regimes
  - HDR brachytherapy – more than just dose escalation?
Options

- Active surveillance
- Surgery (Radical prostatectomy, RadP – open vs robotic)
Treatment of Prostate Cancer in 2018

Options

- Active surveillance
- Surgery (Radical prostatectomy, RadP – open vs robotic)
- Radiotherapy
  - Image guidance
  - Brachytherapy
  - Stereotactic body ablative radiotherapy
  - Proton beam therapy
- Radiotherapy + hormonal therapy (? novel anti-androgens)

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Treatment of Prostate Cancer in 2018

Low

- cT1-T2a
- PSA <10
- GS ≤6

Active surveillance

Intermediate

- cT2b-T2c
- PSA 10-20
- GS 7

Favourable RadP vs IGRT

High

- cT3-4
- PSA >20
- GS 8-10

Unfavourable IGRT + ADT

RadP +/- IGRT

IGRT + ADT

NCCN Zumsteg-Spratt criteria (Eur Urol, 2013)

Sub-stratification for IR-PCa

- ≥50% +ve biopsy cores
- Primary GG 4
- ≥2 NCCN IRF – cT2b,c; GS 7; PSA 10-20 ng/ml

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Radiotherapy of Prostate Cancer in 2018

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PSA <10
GS ≤6

Intermediate
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Active surveillance

Favourable RadP vs IGRT

Unfavourable IGRT + ADT

RadP +/- IGRT
IGRT + LTAD

IGRT (image-guided RT)
- SBRT – 36.25 Gy/5#
- Mod hypofract – 60 Gy (3 Gy/#)
- Conv fract – 74-78 Gy (2 Gy/#)

Brachy – LDR (seeds) vs HDR mono

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Radiotherapy of Prostate Cancer in 2018

**Low**
cT1-T2a  
PSA <10  
GS ≤6

**Intermediate**
cT2b-T2c  
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**High**
cT3-4  
PSA >20  
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- Active surveillance
- **Favourable** RadP vs IGRT
- **Unfavourable** IGRT + ADT
- RadP +/- IGRT  
IGRT + LTAD

- **IGRT (image-guided RT)**
  - SBRT – 36.25 Gy/5#
  - Mod hypofract – 60 Gy (3 Gy/#)
  - Conv fract – 74-78 Gy (2 Gy/#)
  - **Brachy** – LDR (seeds) vs HDR mono

- **IGRT (image-guided RT)**
  - SBRT – 37-40 Gy/5#
  - Conv fract – 74-78 Gy (2 Gy/#)  
  *over mod hypofract*
  - RT to Pelvis

- **Brachy** – HDR boost

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Radiotherapy of Prostate Cancer in 2018

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Favourable
RadP vs IGRT

Unfavourable
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RadP +/- IGRT

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IGRT + LTAD

IGRT (image-guided RT)
- SBRT – 37-40 Gy/5#
- Conv fract – 74-78 Gy (2 Gy/#) over mod hypofract
- RT to Pelvis???

Brachy – HDR boost

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Radiotherapy of Prostate Cancer in 2018

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**Active surveillance**

**Favourable**
- RadP vs IGRT

**Unfavourable**
- IGRT + ADT

**RadP +/- IGRT**

**IGRT (image-guided RT)**
- SBRT – 36.25 Gy/5#
- Mod hypofract – 60 Gy (3 Gy/#)
- Conv fract – 74-78 Gy (2 Gy/#)

**Brachy**
- LDR (seeds) vs HDR mono

**IGRT (image-guided RT)**
- SBRT – 37-40 Gy/5#
- Conv fract – 74-78 Gy (2 Gy/#) over mod hypofract
- RT to Pelvis???

**Brachy**
- HDR boost

**IGRT (image-guided RT)**
- SBRT – 37-40 Gy/5#
- Conv fract – 74-78 Gy (2 Gy/#) + 50-54 Gy to Pelvis

EAT

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
1st LEVEL 1 evidence comparing local tx in *localised prostate cancers*

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer


UK-wide clinical trial of 1,500 men, reported 2016

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
PROTECT cohort

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer


2664 Patients with localized disease were eligible

1643 Underwent randomization

545 Were assigned to active monitoring

553 Were assigned to radical prostatectomy

545 Were assigned to radical radiotherapy
### PROTECT cohort

**Majority favourable-risk patients**

<table>
<thead>
<tr>
<th></th>
<th>Active monitoring protocol (n=545)</th>
<th>Surgery (n=553)</th>
<th>Radiotherapy protocol (n=545)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PSA² in ng/ml (IQR³)</td>
<td>4.7 (3.7, 6.7)</td>
<td>4.9 (3.7, 6.7)</td>
<td>4.8 (3.7, 6.7)</td>
</tr>
<tr>
<td>PSA² 10+ ng/ml (%)</td>
<td>57 (10)</td>
<td>57 (10)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>421 (77)</td>
<td>422 (76)</td>
<td>423 (78)</td>
</tr>
<tr>
<td>7</td>
<td>111 (20)</td>
<td>120 (22)</td>
<td>108 (20)</td>
</tr>
<tr>
<td>8-10</td>
<td>13 (2)</td>
<td>10 (2)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>410 (75)</td>
<td>410 (74)</td>
<td>429 (79)</td>
</tr>
<tr>
<td>T2</td>
<td>135 (25)</td>
<td>143 (26)</td>
<td>116 (21)</td>
</tr>
</tbody>
</table>

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Outcomes: **low-risk and favourable intermediate-risk prostate cancers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active Monitoring (N = 545)</th>
<th>Surgery (N = 553)</th>
<th>Radiotherapy (N = 545)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate-cancer mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total person-yr in follow-up</td>
<td>5393</td>
<td>5422</td>
<td>5339</td>
</tr>
<tr>
<td>No. of deaths due to prostate cancer†</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Hamdry et al. on behalf of **PROTECT** investigators, NEJM, 2016
PROTECT: QOL post-RT

Incontinence

Leakage (Pads usage)

Erectile function

Sexual satisfaction

Donovan et al., NEJM, 2016

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NC prospective: QOL post-RT

North Carolina Prospective Observational cohort
N = 1225; 2011-2013

Chen, et al., JAMA 2017

Sexual Dysfunction

UK PROTECT

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NC prospective: QOL post-RT

Contemporary data
Consistent with PROTECT
Highlights need for such high quality data

Chen, et al., JAMA, 2017

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Propensity-matched analysis

- LDR brachytherapy; N = 165
- IGRT-EBRT; N = 394
- 50% Unfavourable IR-PCa
Radiotherapy of Prostate Cancer in 2018

Low
- cT1-T2a
- PSA <10
- GS ≤6

Intermediate
- cT2b-T2c
- PSA 10-20
- GS 7

High
- cT3-4
- PSA >20
- GS 8-10

What is the optimal dose??

Active surveillance

Favourable RadP vs IGRT

Unfavourable IGRT + ADT

RadP +/- IGRT

IGRT (image-guided RT)
- SBRT – 35.25 Gy/5#
- Mod hypofract – 60 Gy (3 Gy/#)
- Conv fract – 74-78 Gy (2 Gy/#) over mod hypofract
- RT to Pelvis??
- Brachy – LDR (seeds) vs HDR mono
- Brachy – HDR boost

SBRT – 37-40 Gy/5#
- Conv fract – 74-78 Gy (2 Gy/#) + 50-54 Gy to Pelvis
- Brachy – HDR boost

Brachy – HDR boost

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Defining the optimal dose in PCa

Biological Effective Dose

\[ BED = Total \ Dose \ (1 + \frac{dose \ per \ #}{\alpha/\beta}) \]

- Assumption: \( \alpha/\beta = 1.5 \ \text{Gy for tumour} \ \& \ 3.0 \ \text{Gy for normal tissue} \)

- **SBRT - 40 Gy/5#**
  - EQD2tumour = 108.6 Gy
  - EQD2normal = 88 Gy

- **Conv fract 74-78 Gy/37-39# vs Pelvic RT (54 Gy) + Brachy boost (21 Gy/3#)**
  - EQD2tumour = 101.9 Gy
  - EQD2normal = 93.8 Gy

- **Mod Hypofract - 60 Gy/20#**
  - EQD2tumour = 77 Gy
  - EQD2normal = 72 Gy
Contemporary moderate hypofractionation RCTs

N = 6339

CHHIP (UK)

RTOG 0415 (US)

PROFIT (Canada/EU)

HYPRO (Dutch)

N = 3216

N = 1115

N = 1206

N = 820

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Contemporary moderate hypofractionation RCTs

N = 6339

CHHIP (UK)  RTOG 0415 (US)

Caveat: >75% of patients are fav risk disease

What about unfav risk?
Dose escalation in the unfavourable risk group? 
Evidence for a dose response for PSA control

Zelefsky et al J Urol 2006
Dose escalation in the unfavourable risk group?

Evidence for a dose response for PSA control

Improved outcomes with dose escalation in localized prostate cancer treated with precision image-guided radiotherapy


Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Department of Radiation Oncology, University of Toronto; Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto; and Département de radio-oncologie, Centre hospitalier de l’Université de Montréal (CHUM), Montréal, Canada.

IR-PCa

HR-PCa

Overall

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Dose escalation in the unfavourable risk group?

Evidence for a dose response for PSA control

Improved outcomes with dose escalation in localized prostate cancer treated with precision image-guided radiotherapy

Hamid Raziei a, Fabio Y. Moraes a, Jure Murgic a, Melvin L.K. Chua a, Melanie Pintilie b, Peter Chung a, Cynthia Ménard a,c, Andrew Bayley a, Mary Gospodarowicz a, Padraig Warde a, Tim Craig a, Charles Catton a, Robert G. Bristow a, David A. Jaffray a, Alejandro Berlin a,*

a Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Department of Radiation Oncology, University of Toronto; b Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto; and c Département de radio-oncologie, Centre hospitalier de l’Université de Montréal (CHUM), Montréal, Canada

Gray’s test p=1.4e-06

Overall

IR-PCa

HR-PCa

Unfav IR-PCa

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Randomised trials of dose escalation with Conventional Hyperfractionation

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Risk group(s)</th>
<th>Freedom from Biochemical Failure (5-10 year)</th>
<th>Subgroup benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson</td>
<td>301</td>
<td>All</td>
<td>73% v 50%</td>
<td>PSA&gt;10 or High-risk</td>
</tr>
<tr>
<td>GETUG 06</td>
<td>306</td>
<td>Intermediate, High</td>
<td>77% v 68%</td>
<td>PSA&gt;15</td>
</tr>
<tr>
<td>PROG</td>
<td>393</td>
<td>All</td>
<td>83% v 68%</td>
<td>Low</td>
</tr>
<tr>
<td>Dutch</td>
<td>664</td>
<td>All</td>
<td>54% v 47%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>UK MRC RT01</td>
<td>843</td>
<td>All</td>
<td>55% v 43%</td>
<td>All</td>
</tr>
<tr>
<td>RTOG 0126</td>
<td>1499</td>
<td>Intermediate</td>
<td>70% v 55%</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>
Randomised trials of dose escalation with **Conventional Hyperfractionation**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Local control</th>
<th>Salvage AST</th>
<th>Distant metastases</th>
<th>Prostate cancer mortality</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>(8-year)</td>
</tr>
<tr>
<td>GETUG 06</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>(5-year)</td>
</tr>
<tr>
<td>PROG</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>(10-year)</td>
</tr>
<tr>
<td>Dutch</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>(7-year)</td>
</tr>
<tr>
<td>UK MRC RT01</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>(10-year)</td>
</tr>
<tr>
<td>RTOG 0126</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>(10-year)</td>
</tr>
</tbody>
</table>
**RTOG 0126:** *Largest DE study with 10 Gy dose response*

**Effect of Standard vs Dose-escalated Radiation Therapy for Patients With Intermediate-risk Prostate Cancer**

The NRG Oncology RTOG 0126 Randomized Clinical Trial

2018

**No overall survival**

**Improved PSA control of 10-15%**

**Table:**

<table>
<thead>
<tr>
<th>Toxic Effects</th>
<th>70.2 Gy</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>79.2 Gy</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>(n = 731)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n = 728)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>146 (20)</td>
<td>113 (15)</td>
<td>10 (1)</td>
<td>0</td>
<td>0</td>
<td>136 (19)</td>
<td>116 (16)</td>
<td>10 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>61 (8)</td>
<td>33 (5)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>50 (7)</td>
<td>50 (7)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Late</td>
<td>(n = 741)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n = 736)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>21 (3)</td>
<td>52 (7)</td>
<td>15 (3)</td>
<td>0</td>
<td>0</td>
<td>16 (3)</td>
<td>81 (11)</td>
<td>19 (3)</td>
<td>3 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>23 (3)</td>
<td>93 (13)</td>
<td>23 (3)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>26 (4)</td>
<td>119 (16)</td>
<td>34 (5)</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Limited DE: *Boost to DIL*

Prostate Stereotactic Ablative Radiation Therapy Using Volumetric Modulated Arc Therapy to Dominant Intraprostatic Lesions

Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial

<table>
<thead>
<tr>
<th>Plan set B: Boost to DILs, prostate alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCP: Prostate minus DIL (Gy)</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>DIL</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>

MRI DIL, DWI

2014

2018

GU

GI

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Radiotherapy treatment protocol

NCCS GU Radiation Oncology Program

**Low-risk**
- Active surveillance
- *Offer SBRT trial – PROSTAR*

**Intermediate-risk**
- Favourable – 60 Gy in 20# or PROSTAR
- Unfavourable – 74-78 Gy in 39# +/- 6-mo ADT (STAD)

**High-risk**
- 74-78 Gy in 39# + 3-y ADT (LTAD) +/- 1-2 y *combination Zytiga??*
- 46 Gy + HDR boost (15 Gy) + 1 to 3-y ADT (LTAD)
- *ASCENDE-RT*

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Early data with Prostate SBRT

N = 67
MFU = 2.7y
36.25Gy in 5 fractions over 1.5 weeks

King, et al, IJORBP, 2012
“Comparable” outcomes with DE-EBRT

N = 1100

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>35 Gy</th>
<th>36.25 Gy</th>
<th>38–40 Gy</th>
<th>ADT use</th>
<th>FL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>641 (58%)</td>
<td>254 (40%)</td>
<td>319 (50%)</td>
<td>68 (11%)</td>
<td>50 (8%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>334 (30%)</td>
<td>108 (32%)</td>
<td>188 (56%)</td>
<td>38 (11%)</td>
<td>49 (15%)</td>
</tr>
<tr>
<td>High</td>
<td>125 (11%)</td>
<td>23 (18%)</td>
<td>82 (66%)</td>
<td>20 (16%)</td>
<td>48 (38%)</td>
</tr>
<tr>
<td>Total</td>
<td>1100</td>
<td>385 (35%)</td>
<td>589 (54%)</td>
<td>126 (11%)</td>
<td>147 (14%)</td>
</tr>
</tbody>
</table>

5-year Kaplan-Meier PSA relapse-free survival rates as a function of risk group, use of ADT and dose.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>5-yr bRFS</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>95.2%</td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>84.1%</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>High Risk</td>
<td>81.2%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>ADT use</td>
<td>92.6%</td>
<td></td>
</tr>
<tr>
<td>No ADT</td>
<td>91.3%</td>
<td>p = 0.71</td>
</tr>
<tr>
<td>Dose 35 Gy</td>
<td>92.5%</td>
<td></td>
</tr>
<tr>
<td>Dose 36.25 Gy</td>
<td>90.7%</td>
<td>p = 0.08</td>
</tr>
<tr>
<td>Dose 38–40 Gy</td>
<td>95.8%</td>
<td>p = 0.83</td>
</tr>
</tbody>
</table>

*Reference group.
“Comparable” late toxicities with DE-EBRT

Figure 1: RTOG-graded late toxicity for patients treated with 35 or 36.25 Gy.

Table 3: Comparison of late urinary (GU) and rectal (GI) toxicity on the RTOG scale from the dose-escalation arm of randomized trials and intensity-modulated radiotherapy-based hypofractionated studies.

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Dose/no. fx and median FU</th>
<th>GI Gr. 2</th>
<th>GI Gr. 3</th>
<th>GI Gr. 4</th>
<th>GU Gr. 2</th>
<th>GU Gr. 3</th>
<th>GU Gr. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch†</td>
<td>333</td>
<td>78/39 and 4.2 yr</td>
<td>27%</td>
<td>5%</td>
<td>0%</td>
<td>26%</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>MDA‡</td>
<td>151</td>
<td>78/39 and 8.7 yr</td>
<td>19%</td>
<td>7%</td>
<td>0%</td>
<td>7%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>MGH§</td>
<td>196</td>
<td>79.2/44 and 8.9 yr</td>
<td>24%</td>
<td>1%</td>
<td>0%</td>
<td>27%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>RT01∥</td>
<td>422</td>
<td>74/37 and 5.2 yr</td>
<td>20%</td>
<td>6%</td>
<td>0%</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Kupelian‖</td>
<td>770</td>
<td>70/28 and 3.7 yr</td>
<td>3.1%</td>
<td>1.3%</td>
<td>0.1%</td>
<td>5.1%</td>
<td>0.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Martin※※</td>
<td>92</td>
<td>60/20 and 3.2 yr</td>
<td>4%</td>
<td>NR</td>
<td>0%</td>
<td>3%</td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td>Coote††</td>
<td>60</td>
<td>60/20 and 2 yr*</td>
<td>4%</td>
<td>NR</td>
<td>0%</td>
<td>4.2%</td>
<td>1.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Lock‡‡</td>
<td>66</td>
<td>63.2/20 and 3 yr</td>
<td>25%</td>
<td>3.1%</td>
<td>1.5%</td>
<td>14.1%</td>
<td>4.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>
PROSTAR (PROstate STereotactic Ablative Radiotherapy)
NCCS prospective phase II trial

- Single institution; Single-arm
- **NCCN Low-risk** or **single intermediate risk factor** (DRE T2b-c or Gleason 7 or PSA 10-20); organ-confined prostate adenocarcinoma, with no MRI evidence of ECE and SV invasion
- **36.25Gy in 5 fractions over 1.5 weeks (EOD) delivered using LINAC-based treatment system**
- No hormonal therapy
- **Primary end-point** - severe late GI and GU toxicities
- **Secondary end-points** – Patient-reported QOL, acute RT toxicities, biochemical relapse, prostate cancer specific mortality, overall survival
Clinical & Pathologic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Pts (%) N=51</th>
</tr>
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<tbody>
<tr>
<td>Age, Median (Yrs)</td>
<td>68 (Range: 52-79)</td>
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<tr>
<td>Chinese</td>
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Target accrual
N = 80
N = 62 (from 2014-Jul 2018)
### Clinical & Pathologic characteristics

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**Target accrual**

N = 80
N = 62 (from 2014-Jul 2018)
Precise targeting of *prostate & pelvis*

Contouring

MRI

CT

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Small overlap

Small overlap
Target contouring

Accurate delineation of normal organs

- Rectum
- Bladder
- Fem heads
- Urethra
- Penile bulb
PET staging in prostate cancer

PET-imaging (PSMA)

Types of Tracers
- PSMA (Overall)
- F-Choline (LN)
- Na-F (Bone)
- Fluciclovine (Overall; newest)
PET utility for RT planning in PCa

PET-fusion for target delineation

- Requires deformable registration due to different CT slice thickness

RT plan

- Image guidance and distance from bowel allows safe dose escalation

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Plan optimisation for PTV coverage against OAR doses
Precise targeting of prostate & pelvis

RT plan – Prostate + Pelvis

Dose constraints

<table>
<thead>
<tr>
<th>Target</th>
<th>Parameter</th>
<th>Required Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV</td>
<td>D95%Gy</td>
<td>$\geq 35.00$Gy</td>
</tr>
<tr>
<td>PTV Dmin</td>
<td>DminGy</td>
<td>$\geq 33.25$Gy</td>
</tr>
<tr>
<td>PTV Dmin (Major)</td>
<td>DminGy</td>
<td>$\geq 32.55$Gy</td>
</tr>
<tr>
<td>PTV</td>
<td>D1ccGy</td>
<td>$\leq 37.45$Gy</td>
</tr>
<tr>
<td>PTV</td>
<td>DmaxGy</td>
<td>$\leq 37.45$Gy</td>
</tr>
<tr>
<td>PTV Volume</td>
<td>V0Gy(cc)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Parameter</th>
<th>Required Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>D1ccGy</td>
<td>$\leq 36.75$Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>D3ccGy</td>
<td>$\leq 33.25$Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>D10%Gy</td>
<td>$\leq 31.50$Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>D20%Gy</td>
<td>$\leq 28.00$Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>D50%Gy</td>
<td>$\leq 17.50$Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>D1ccGy</td>
<td>$\leq 36.75$Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>D10%Gy</td>
<td>$\leq 31.50$Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>D50%Gy</td>
<td>$\leq 17.50$Gy</td>
</tr>
<tr>
<td>Femur L</td>
<td>DmaxGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Femur L</td>
<td>D10ccGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Femur R</td>
<td>DmaxGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Femur R</td>
<td>D10ccGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Femur Both</td>
<td>DmaxGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Femur Both</td>
<td>D10ccGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Urethra</td>
<td>DmaxGy</td>
<td>$\leq 37.45$Gy</td>
</tr>
<tr>
<td>Penile Bulb</td>
<td>DmaxGy</td>
<td>$\leq 35.00$Gy</td>
</tr>
<tr>
<td>Penile Bulb</td>
<td>D3ccGy</td>
<td>$\leq 19.25$Gy</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>DmaxGy</td>
<td>$\leq 30.00$Gy</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>D1ccGy</td>
<td>$\leq 27.50$Gy</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>DmaxGy</td>
<td>$\leq 30.00$Gy</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>D1ccGy</td>
<td>$\leq 27.50$Gy</td>
</tr>
<tr>
<td>Skin</td>
<td>DmaxGy</td>
<td>$\leq 29.05$Gy</td>
</tr>
</tbody>
</table>

- (L) Limitation of hotspot
- Ability to limit doses to rectum even if we RT the SVs
- (Top) SIB plan – 25 Gy to Pelvis; 35 Gy to Prostate
Post-SBRT *Late effects*

<table>
<thead>
<tr>
<th>Late GI Toxicities</th>
<th>Number of Patients (%) N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>30 (63.8%)</td>
</tr>
<tr>
<td>G1</td>
<td>16 (34.1%)</td>
</tr>
<tr>
<td>G2</td>
<td>1 (2.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late GU Toxicities</th>
<th>Number of Patients (%) N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>26 (27.6%)</td>
</tr>
<tr>
<td>G1</td>
<td>17 (69.8%)</td>
</tr>
<tr>
<td>G2</td>
<td>4 (8.4%)</td>
</tr>
</tbody>
</table>

GI – 1 case of bleed  
GU – 4 cases of urine frequency
Post-SBRT QOL change over time

Mean Score for each domain

GI
GU

Mean Score for each domain for Top 50th percentile

Sexual

Mean Score for each domain for Bottom 50th percentile

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Post-SBRT Sexual dissatisfaction

Mean Score for Sexual Subscale

Mean Score for Sexual Subscale for Top 50th percentile

Mean Score for Sexual Subscale for Bottom 50th percentile

Score

Score

Score

Baseline

12 months Post RT FU

24 months Post RT FU

Time after SBRT (months)

Time after SBRT (months)

Time after SBRT (months)

BOTHER

Function

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PROSTAR vs other SBRT studies

- 230 low-risk treated with Cyber-knife;
- 35Gy & 36.25Gy in 5 consecutive days;
- 10 yr DFS 93%;
- 10% G2-3 GU; 4% G2 GI;
- EPIC sexual score declined by 40%

Biochemical Disease Free Survival

- EPIC GU QOL
- EPIC GI QOL
- EPIC Sexual QOL

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
HDR brachytherapy boost as an effective dose intensification strategy

**ASCENDE-RT**

**Ph III trial**

(Morris et al., IJORBP, 2017)

---

### Control arm

- 46 Gy EBRT to Pelvis
- + 32 Gy to Prostate
- + 12-mo ADT

### Experimental arm

- 46 Gy EBRT to Pelvis
- + LDR 110 Gy to Prostate
- + 12-mo ADT

---

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HDR brachytherapy boost as an effective dose intensification strategy

Intermediate-risk

High-risk
Contemporary data with **HDR brachy boost**

**UK MVCC Ph III (Hoskin et al., 2012)**
- Int-high-risk Prostate Cancers
- 55 Gy/20# vs
- 37.5 Gy/15# + 8.5 Gy x 2 HDR

**Beaumont (Martinez et al., 2011)**
- Int-high-risk Prostate Cancers
- 46 Gy/23# to Pelvis ->
  - <8.5 Gy x 2 HDR vs >9 Gy x 2 HDR
SBRT boost to replace HDR Brachy boost?

Biological Effective Dose

\[ BED = \text{Total Dose}(1+ \text{dose per } \alpha/\beta) \]

- Assumption: \( \alpha/\beta = 1.5 \text{ Gy for tumour} \) & \( 3.0 \text{ Gy for normal tissue} \)

Pelvic RT + SBRT boost (19.5 Gy/3#)
- EQD2tumour = 98.6 Gy
- EQD2normal = 91.1 Gy

Pelvic RT (54 Gy) + Brachy boost (21 Gy/3#)
- EQD2tumour = 101.9 Gy
- EQD2normal = 93.8 Gy

Axial – 19.5 Gy colour wash
Sag – 19.5 Gy colour wash

*Courtesy of Ashley Ong

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Summary

- Contemporary techniques have resulted in optimal local control and favourable toxicity profiles in localised prostate cancer

- Dose escalation and fractionation require a risk-adapted approach

- Modern technologies from imaging to enhance target contouring; precision matching and dose escalation permit novel RT strategies in high-risk disease
Thank you!

Questions