Clinical Protocols for HDR Prostate Brachytherapy

Dr Ann Henry
Consultant Clinical Oncologist
About Leeds

- Leeds Cancer Centre
  - University Public Hospital
  - Sole RT provider in region
  - Well established patient pathways and site specialised multi-disciplinary teams (MDTs)
  - EBRT to population of 3.2 million
  - 10 clinical linear accelerators with 6,500 new patients/yr
- Prostate Brachytherapy
  - Population of 6 million
  - Established I-125 program 1997 (Stranded seeds, Variseed TPS)
  - HDR introduced 2007 (Ir-192, Nucletron Oncenra prostate)
Outline

• Review published patient outcomes in terms of
  – PSA control and survival
  – Acute and late toxicity
• Look at clinical scenarios
  – HDR boost with EBRT
  – HDR monotherapy (including partial gland irradiation)
  – HDR salvage following previous RT
Why Brachytherapy?

- Multiple RCTs using EBRT demonstrate dose escalation of order of 10Gy improves PSA control by 10-15%
- Prostate brachytherapy allows dose escalation beyond that achievable by any form of external beam
- Brachytherapy allows greater conformity and sparing of surrounding tissues
- No issues with organ motion during treatment
- Higher efficacy, less toxicity, and probably less risk of second malignancy
EBRT vs. Brachytherapy
LOW RISK RESULTS

Weighted

% PSA Progression Free

EBRT

Surgery

Treatment Success

→ Years from Treatment ←

• Prostate Cancer Results Study Group
• Numbers within symbols refer to references

12/2/2015 Update of
BJU Int, 2012, Vol. 109(Supp. 1)

Prostate Cancer Center of Seattle
INTERMEDIATE RISK RESULTS

Weighted

% PSA Progression Free

Treatment Success

EBRT & Seeds

Brachy

EBRT

Surgery

Years from Treatment

EBRT & Seeds Study Group

Numbers within symbols refer to references

• Prostate Cancer Results Study Group

12/2/2015

Update of

BJU Int, 2012, Vol. 109(Supp 1)

Prostate Cancer Center of Seattle
HIGH RISK RESULTS
Weighted

12/2/2015 Update of
BJU Int, 2012, Vol. 109(Supp 1) Prostate Cancer Center of Seattle
### Level I (RCT) evidence: EBRT +/- BT boost

<table>
<thead>
<tr>
<th></th>
<th>Hoskin 2007 (UK)</th>
<th>Sathya 2005 (Canada)</th>
<th>Zapatero-Ortho 2010 (Spain)</th>
<th>Morris 2015 (ASCENDE-RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. patients</strong></td>
<td>218</td>
<td>104</td>
<td>30</td>
<td>400</td>
</tr>
<tr>
<td><strong>Mean age yrs</strong></td>
<td>68.9</td>
<td>65</td>
<td>68.57</td>
<td></td>
</tr>
<tr>
<td><strong>Technique</strong></td>
<td>HDR (8.5Gy×2)</td>
<td>PDR (35Gy over 48 hrs)</td>
<td>LDR (108Gy)</td>
<td>LDR (115Gy)</td>
</tr>
<tr>
<td><strong>Risk groups</strong></td>
<td>Low 4% Inter 42% High 54%</td>
<td>Inter 40% High 60%</td>
<td>Low/ Intermediate risk</td>
<td>Inter 31% High 69%</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>At 7.1 yrs 31% reduction in recurrence</td>
<td>Reduction in PSA and clinical failure</td>
<td>Similar toxicity no survival date</td>
<td>At 7 yrs 86% PSA control vs. 75% in 78Gy EBRT alone</td>
</tr>
<tr>
<td><strong>Criticism</strong></td>
<td>EBRT comparator only 55Gy/20</td>
<td>EBRT comparator only 66Gy/33</td>
<td>EBRT comparator 76Gy but abstract only</td>
<td>Higher late urinary toxicity with brachytherapy</td>
</tr>
</tbody>
</table>
Kaplan–Meier survival curves for patients free of biochemical and or clinical failure (top panel) and overall survival (bottom panel).

Solid line: external-beam radiotherapy plus high-dose-brachytherapy boost (EBRT + HDR-BTb).

Dashed line: external-beam radiotherapy alone (EBRT). Number of patients at risk is shown against each time interval.
Incidence of severe Grade 3 urinary (top) and bowel events (bottom) from 6 months to 8 years after radiotherapy.

Solid line: external-beam radiotherapy plus high-dose-brachytherapy boost (EBRT + HDR-BTb).

Dashed line: external-beam radiotherapy alone
ASCENDE trial 2015

Morris: abstract no. OC-0485: "LDR Brachytherapy is Superior to 78 Gy of EBRT for Unfavourable Risk Prostate Cancer: The Results of a Randomized Trial," Highest scoring 3rd ESTRO Forum abstracts session
## Variety of schedules!

<table>
<thead>
<tr>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of implants</td>
<td>1 - 4</td>
</tr>
<tr>
<td>No. of fractions per implant</td>
<td>1 - 4</td>
</tr>
<tr>
<td>HDR dose per fraction</td>
<td>5.5 – 15 Gy</td>
</tr>
<tr>
<td>HDR total dose</td>
<td>18 – 30 Gy</td>
</tr>
<tr>
<td>Schedule</td>
<td>HDR before EBRT&lt;br&gt; HDR after EBRT&lt;br&gt; HDR during EBRT</td>
</tr>
<tr>
<td>EBRT total dose</td>
<td>36 – 50 Gy</td>
</tr>
<tr>
<td>BED of HDR + EBRT</td>
<td>78 – 163 Gy</td>
</tr>
</tbody>
</table>
American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

Yoshiya Yamada¹,*, Leland Rogers², D. Jeffrey Demanes³, Gerard Morton⁴, Bradley R. Prestidge⁵, Jean Pouliot⁶, Gil’ad N. Cohen⁷, Marco Zaidaer⁷, Mihai Ghilezan⁸, I-Chow Hsu⁶

“Given the heterogeneity of prescription doses described in the literature, all reporting similar excellent outcomes in terms of toxicity and disease control, no particular dose fractionation schedule can be recommended.”
Morton et al
Sunnybrook Odette Cancer Centre
Single # HDR boost
15Gy HDR
Followed by 37.5Gy in 15#
N= 123
Intermediate risk patients
Median FU 45 months
Long term QoL: EPIC scores

![Graph showing EPIC scores over time for different domains such as Urinary, Bowel, Sexual, and Hormonal. The graph indicates significant changes over time with asterisks marking p<0.001 significance levels.]

* = p<0.001
Important dosimetry issues

• Acute urinary toxicity associated with prostate V200 (p .0141) and baseline IPSS (p.0125)
• Late urinary function and bother associated with dose to urethra (p.0168), threshold D10 =120%
• Erectile Dysfunction associated with larger volume of CTV

Advantages of HDR brachytherapy

- Provides extreme hypo-fractionation
- Short overall treatment time
- TRUS planned technique robust and less subject to operator error
- Can cover extra-prostatic and seminal vesicle disease
- Equipment often already available in departments
Brachytherapy: Current Status and Future Strategies — Can High Dose Rate Replace Low Dose Rate and External Beam Radiotherapy?

Clinical Oncology Volume 25, Issue 8 2013 474 - 482

http://dx.doi.org/10.1016/j.clon.2013.04.009
Better implant quality results in improved PSA control

Higher D90 and V100 associated with improved PSA in RCT

Quality improves outcomes

Patient selection for single # HDR boost

• Intermediate or high risk disease

• In patients where staging MRI suggests early rT3a macroscopic disease, the disease extension should be ≤ 3mm and if T3b just into base of seminal vesicles

• IPSS ≤ 15 and no TURP within 6 months

• Relative contra-indications include full anti-coagulation, unfit for GA, pelvic anatomical abnormalities and obesity

• Combined with EBRT 37.5Gy/15# to prostate and SV or whole pelvis XRT 46Gy in 23#, higher if pelvic IMRT available
Single # HDR Boost Planning

**GTV**: Prostate +/- seminal vesicles

**PTV**: GTV plus 3mm 3D expansion apart from posterior 0mm margin

At least 15Gy to the D90prostate

(15Gy normalised to the 100% isodose)

\[ V_{100\text{PTV}} > 95\% , \]
\[ V_{150\text{prostate}} < 45\% , \]
\[ V_{200\text{prostate}} < 15\% \]

Rectum: \( V_{15\text{Gy}} = 0 \), \( D_{2\text{cc}} < 11.8\text{Gy} \).

Urethra: \( D_{10\%} < 17.5\text{Gy} \), \( D_{0.1\text{cc}} < 17.5\text{Gy} \)
Clinical issues

- Time under GA can be longer than for seed brachytherapy
- Thromboembolic prophylaxis
  - compression stockings, leg position, intermittent calf compression intra-op, LMWT heparin
- Infection
  - Consider same anti-biotic prophylaxis as used for TRUS biopsies
  - Care with immuno-suppressed and catheter removals
- Bleeding
  - Frank haematuria usual post-procedure
- Sleep apnoea
  - High prevalence in these patients
  - Identify pre-operatively and may need more intensive post-op monitoring
Multi-parametric MRI identifies GTV

Example of Focal-GTV delineation:
(a) T2 weighted MRI
(b) ADC map from diffusion weighted MRI
(c) Ktrans map from dynamic contrast enhanced MRI
(d) F-GTV generated by combining suspicious areas from (a), (b) and (c).

Can you give additional dose to the F-GTV with the aim of improving local control?
Pilot study of mp MRI guided focal boost

F-GTV identified and contoured from mp MRI pre-HDR

Contours imported into Oncentra and fused using visual best fit with TRUS

Additional needles inserted into F-GTV (5mm spacing)

Allows escalation of dose in context of 15Gy (minimum peripheral dose) single HDR boost

Increased median D90 from 17.6 to 20.9Gy

Initially retrospective then treated prospectively

Mason et al Brachytherapy 2014;13(2):137-45
**Boost Randomisation**

**Eligible patient group:** Patients with node-negative localised prostate cancer and:
- NCCN high risk or locally advanced disease (T3-T4, dominant Gleason 4-5, PSA>20 ng/ml), OR
- NCCN intermediate risk (T2a-c, Gleason 7, PSA 10-20 ng/ml) with adverse features (MTL>5mm or ≥50% biopsy cores positive)

**At randomisation specify:**
- Risk group, hormone duration, boost volume on MRI (none, <50% or >50%)

**If there is, on staging MRI**
- No boost volume identified or boost volume >50% of prostate volume
  And
- Patient suitable for HDR brachytherapy and available

**Boost Randomisation**

**If boost volume on MRI >50% or no volume identified**

- A: Prostate IMRT
- B: Prostate & Pelvic IMRT
- C1: Prostate IMRT + HDR*
- D1: Prostate & pelvic IMRT + HDR *

**Stratification for risk group, hormone duration, boost volume on MRI, and type of boost**

***HDR:** If boost volume on MRI >50% or no volume → Whole gland HDR

**ICR The Institute of Cancer Research**
Sector boosting vs. F-GTV definition

- **Problems**: Observer variability in contouring, hormone effects, needles distorting gland
- Retrospective planning study in 15 patients treated with F-GTV boost
- **12 prostate sectors were defined**:  
  - three base, mid-gland and apex segments  
  - then dividing each of these into four sectors: right anterior, left anterior, right posterior and left posterior
- Comparison of median F-GTV D90  
  - in F-PTV boosted plans was 162%  
  - in the sector boosted plans was 149%  
  - An acceptable compromise

*Mason et al. RO in press*
Summary of HDR monotherapy outcomes

<table>
<thead>
<tr>
<th>Author, y (ref.)</th>
<th>No. of patients</th>
<th>Gy/fraction</th>
<th>Fractions (no. of implants)</th>
<th>Total</th>
<th>Median follow-up (y)</th>
<th>Biochemical control (risk group)</th>
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<tbody>
<tr>
<td>Yoshioka et al, 2011 (14)</td>
<td>111</td>
<td>6</td>
<td>9 (1 implant)</td>
<td>54 Gy</td>
<td>5.4</td>
<td>85% low-risk at 5 y</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93% intermediate-risk at 5 y</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79% high-risk at 5 y</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>95% intermediate-risk at 4 y</td>
</tr>
<tr>
<td>Hoskin et al, 2012 (15)</td>
<td>197</td>
<td>8.5-9</td>
<td>4 (1 implant)</td>
<td>34-36 Gy</td>
<td>4.5-5</td>
<td>87% high-risk at 4 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.5</td>
<td>3 (1 implant)</td>
<td>31.5 Gy</td>
<td>3</td>
<td>94% intermediate-risk at 5 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>2 (1 implant)</td>
<td>26 Gy</td>
<td>0.5</td>
<td>88% all</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>100% low-risk at 32 mo</td>
</tr>
<tr>
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<td>88% intermediate-risk at 32 mo</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>91% low- and intermediate-risk at 5 y (WBH series)</td>
</tr>
<tr>
<td>Rogers et al, 2012 (19)</td>
<td>284</td>
<td>6</td>
<td>6 (2 implants)</td>
<td>36 Gy</td>
<td>3</td>
<td>87% low- and intermediate-risk at 5 y (CET series)</td>
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<td>Mark et al, 2010 (13)</td>
<td>301</td>
<td>7.5</td>
<td>6 (2 implants)</td>
<td>45 Gy</td>
<td>8</td>
<td>97% low- and intermediate-risk at 5 y</td>
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<td>Prada et al, 2012 (20)</td>
<td>40</td>
<td>19</td>
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<td>Martinez et al, 2010 (12)</td>
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<td>6 (2 implants)</td>
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<td>4 (1 implant)</td>
<td>38 Gy</td>
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<td>Demanes et al, 2011 (17)</td>
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<td>9.5</td>
<td>4 (1 implant)</td>
<td>38 Gy</td>
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<td>Present study</td>
<td>718</td>
<td>9.5</td>
<td>4 (1 implant)</td>
<td>38 Gy</td>
<td>4.4</td>
<td>95% low-risk at 5 y</td>
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<tr>
<td></td>
<td></td>
<td>9.5</td>
<td>4 (2 implants)</td>
<td>38 Gy</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>11.5</td>
<td>3 (3 implants)</td>
<td>34.5 Gy</td>
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<td>93% intermediate-risk at 5 y</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>93% high-risk at 5 y</td>
</tr>
</tbody>
</table>
Summary of toxicity rates with HDR monotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Group A (n=141)</th>
<th>Group B (n=351)</th>
<th>Group C (n=225)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of occurrences (%)</td>
<td>No. of occurrences (%)</td>
<td>No. of occurrences (%)</td>
</tr>
<tr>
<td>Genitourinary Frequency/urgency</td>
<td></td>
<td>48 (34.0%)</td>
<td>105 (29.9%)</td>
<td>61 (27.1%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>13 (9.2%)</td>
<td>17 (4.8%)</td>
<td>17 (7.5%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (2.1%)</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Dysuria</td>
<td></td>
<td>9 (6.3%)</td>
<td>17 (4.8%)</td>
<td>18 (8.0%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1 (0.7%)</td>
<td>4 (1.1%)</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (0.7%)</td>
<td>2 (0.6%)</td>
<td>4 (1.7%)</td>
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<tr>
<td>Incontinence</td>
<td></td>
<td>7 (4.9%)</td>
<td>30 (8.6%)</td>
<td>26 (11.5%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>11 (7.8%)</td>
<td>18 (5.1%)</td>
<td>17 (7.5%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (0.7%)</td>
<td>1 (0.3%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Retention</td>
<td></td>
<td>22 (15.6%)</td>
<td>59 (16.8%)</td>
<td>26 (11.5%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>39 (26.3%)</td>
<td>19 (5.4%)</td>
<td>10 (4.4%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 (2.8%)</td>
<td>7 (2.0%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td></td>
<td>45 (31.9%)</td>
<td>85 (24.2%)</td>
<td>53 (23.5%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>30 (21.2%)</td>
<td>55 (15.7%)</td>
<td>41 (18.2%)</td>
</tr>
<tr>
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<td>2</td>
<td>17 (12.0%)</td>
<td>58 (16.5%)</td>
<td>43 (19.1%)</td>
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<tr>
<td>Gastrointestinal (rectum)</td>
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<tr>
<td>Pain</td>
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<td>2 (1.4%)</td>
<td>7 (2.0%)</td>
<td>6 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1 (0.7%)</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis/necrosis</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5 (3.5%)</td>
<td>3 (0.8%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>1 (0.7%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

Fractionation is a disadvantage for monotherapy, can it be delivered safely in a single fraction?
UK national protocol for HDR monotherapy

- PI Professor Peter Hoskin (Mount Vernon Hospital)
- Prospective data collection but not formal trial
- Uses 19Gy single # (lower rate of catheter requirement compared to 20Gy) [Hoskin et al RO 110 (2014):268-271].
- Supported by Spanish data in 40 patients using same dose
- For low, intermediate or high risk, N0 M0 and iPSA < 40, no previous TURP
- Hormones for intermediate and high risk
- We currently use in 2 patient groups:
  - Those with inflammatory bowel disease where EBRT contra-indicated and too high risk for I-125
  - Those with previous pelvic irradiation typically previous short or long course pelvic RT for rectal cancer
# Dose prescription

<table>
<thead>
<tr>
<th>Prescribed dose</th>
<th>BED</th>
<th>2Gy EQD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha\beta$ 1.5</td>
<td>$\alpha\beta$ 1.5</td>
</tr>
<tr>
<td>19Gy/1f</td>
<td>259.7</td>
<td>111.3</td>
</tr>
</tbody>
</table>

*D90 PTV ≥100% and V100 ≥95%*

**OAR tolerance doses**
- Rectum D2cc < 15Gy
- Rectum V100 nil
- Urethra D10 < 22Gy
- Urethra D30 < 20.8Gy
- Urethra V150 nil
HDR as salvage after previous radiation

• Fractionated protocol from Dr Kovacs, limited publications from single centres
• Biopsy proven recurrence after EBRT or I-125, negative staging
• 30Gy in 3 # over 21days if whole gland, single 19Gy if hemi-gland
• Objectives:
  • For partial volumes: $V_{100\text{prostate}} > 90\%$, $V_{150\text{prostate}} < 45\%$, $V_{200\text{prostate}} < 15\%$.
  • For a full retreat: $D_{90\text{prostate}} > 90\%$.
  • Rectum : $D_{1\text{cc}}< 75\%\text{Gy}$.
  • Urethra: $D_{10\%} < 75\% \text{ Gy}$. 
Partial gland irradiation
Conclusions

- HDR brachytherapy can safely deliver large doses per fraction in a short overall treatment time.
- A low $\alpha/\beta$ for prostate cancer means biological advantage without the image guidance issues of EBRT hypo-fractionation techniques.
- TRUS HDR technique is robust and dose delivered where planned.
- Established role as boost, emerging as monotherapy and salvage treatment.
Thank You
References

- **General**

- **HDR Boost**
  - Hoskin PJ. High dose rate brachytherapy boost treatment in radical radiotherapy for prostate cancer Radiotherapy and Oncology, 2000; 57: 285-288

- **HDR Monotherapy**
References II


- Salvage HDR