Is ASCENDE-RT still pertinent?
Is LDR-PB obsolete?

W. James Morris
BSc MSc MD FRCPC
Clinical Professor, Dept of Surgery UBC
Rad Onc. BCCA-Vancouver Centre
PI for Developmental Brachytherapy
Disclosures

• Creator and PI for ASCENDE-RT
  – funded by unrestricted educational grants to the BCCA from:
  – Oncura - a division GE Healthcare and the manufacturer
    RapidStrand® model 6711 125-Iodine
  – Sanofi-Aventis, Canada - the suppliers of buserelin acetate
    (Suprefact Depot®) and leuprolide acetate (Eligard®)

• Speaking/travel fees from Varian corporation promoting
  RapidArc IMRT technology: 2008-2009

• PI for BC Cancer Foundation-sponsored Pilot Study of Focal
  LDR Brachytherapy: 2013-present
ASCENDE-RT
Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy

A RANDOMIZED TRIAL COMPARING LOW-DOSE-RATE BRACHYTHERAPY BOOST TO DOSE-ESCALATED EXTERNAL BEAM BOOST FOR HIGH- AND INTERMEDIATE-RISK PROSTATE CANCER

W. James Morris, Scott Tyldesley, Sree Rodda, Ross Halperin, Howard Pai, Michael McKenzie, Graeme Duncan, Mira Keyes, Gerard Morton, Jeremy Hamm, Nevin Murray

BC Cancer Agency: Vancouver, Vancouver Island, Southern Interior, and Fraser Valley Centres
Sunnybrook Cancer Centre and Princess Margaret Hospital, Toronto, Ontario
ASCENDE-RT

• Very short version
• Short version
• A slightly deeper dive
ASCENDE-RT simplified schema

Stratified by NCCN intermediate- or high-risk

Randomised

DE-EBRT arm
12m ADT, 8m neo-adjuvant
46 Gy whole pelvis EBRT
32 Gy 3-DCRT boost

LDR-PB arm
12m ADT, 8m neo-adjuvant
46 Gy whole pelvis EBRT
LDR 115 Gy I^{125} boost

Follow up:
Clinical visits: q6 months to 5 y and annually afterwards
PSA and Testosterone: q6 months
ASCENDE-RT: Very short version

- 6.5 yrs median FU
- DE-EBRT - twice as likely to have biochemical relapse
  - Cox MVA HR = 2.04 (95% CI 1.25-3.33; p=0.004)
- No significant difference in overall survival
  - nor in metastasis free or prostate cancer specific survival
ASCENDE-RT: Very short version

• LDR-PB - twice as likely to have acute Grade 2+ GU toxicity
  – 32.5% vs 16.3% (Chi square p<0.001)
• LDR-PB >3 times higher cumulative incidence of late grade 3 GU toxicity
  – 18.6% versus 5.2% (Log rank p <0.001)
Is ASCENDE-RT pertinent?
Some will dismiss ASCEND-RT as no longer pertinent because:

1. LDR is obsolete – HDR has a better therapeutic ratio
2. IGRT + dose painting is iso-effective and easier to learn/apply consistently
3. SABR will make all other forms of XRT obsolete
4. Surgery +/− EBRT is at least as effective, and the harmful effects of XRT can be avoided in some patients

All four points are speculative at this juncture
Others will be tempted to dismiss ASCEND-RT as:

1. Underpowered
2. Uses an artificial endpoint (b-PFS)
3. The PSA threshold used (Phoenix or nadir + 2 ng/mL) prevents direct comparison with surgery
PSA endpoints are ideal

- PSA endpoints are objective, sensitive and reliable instruments
- Residual PSA is proportional to risk of relapse and therefore proportional to the biological dose delivered
- *And who says we can’t compare to surgery?*
ASCENDE-RT: the short version
Prognostic features: summary

no significant differences between arms

- Median age: 68 years
- NCCN High-risk: 69%
- Gleason sum ≥8: 40%
- iPSA >20 ng/mL: 19%
- cT3a: 29%
- Positive cores ≥ 50% 68%
Endpoints

• Primary:
  – Biochemical Progression Free Survival (b-PFS) (Phoenix = nadir + 2 ng/mL PSA threshold)

• Secondary:
  – Overall survival
  – The incidence and prevalence of treatment related adverse effects
  – Metastasis-free and prostate cancer specific survival
  – Erectile function
  – Quality of life
Accrual

- 398 accrued by 29 radiation oncologists working in 6 Canadian cancer centres
  - 93% from the four BCCA centres
- Open 11/2002 to 8/2003 (feasibility phase)
- Reopened 8/2004 until completion December 2011
  - Open ~81 months
Protocol violations

• 29 (7%) major protocol violations including
  – 14 cross-over events
    • 6 men assigned to DE-EBRT received LDR-PB
    • 8 men assigned to LDR-PB received DE-EBRT
  – 15 received neither of the two protocol regimens
    (7 assigned to DE-EBRT 8 assigned to LDR-PB)
Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint

![Graph showing biochemical PFS over time with numbers at risk and log rank P = 0.001 for DE-EBRT ARM compared to LDR-PB ARM]
Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint

Kaplan-Meier (95% CI)

<table>
<thead>
<tr>
<th>Randomization (N=398)</th>
<th>DE-EBRT (N=200)</th>
<th>LDR-PB (N=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b-PFS 5 yr</td>
<td>83.8 (±5.6)</td>
<td>88.7 (±4.8)</td>
</tr>
<tr>
<td>b-PFS 7 yr</td>
<td>75.0 (±7.2)</td>
<td>86.2 (±5.4)</td>
</tr>
<tr>
<td>b-PFS 9 yr</td>
<td>62.4 (±9.8)</td>
<td>83.3 (±6.6)</td>
</tr>
</tbody>
</table>
MVA analysis of biochemical failure:
(Backwards:Conditional Cox model, Intent-to-treat, N=398
Factors on UVA with $p< 0.3$ included)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomization arm</strong> (DE-EBRT vs LDR-PB)</td>
<td>2.04</td>
<td>1.25 – 3.33</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>PPC (unit = 1%)</strong></td>
<td>1.01</td>
<td>1.00 – 1.02</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Clinical T stage (T3a vs T1-T2)</strong></td>
<td>1.97</td>
<td>1.24 – 3.13</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Log iPSA (unit = 1 log)</strong></td>
<td>1.62</td>
<td>1.11 – 2.36</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Gleason Sum (8-10 vs ≤ 7)</strong></td>
<td>1.38</td>
<td>0.87 – 2.19</td>
<td>0.17</td>
</tr>
</tbody>
</table>
b-PFS
by treatment actually received, N=383

Kaplan-Meier (95% CI)

<table>
<thead>
<tr>
<th>Treatment received</th>
<th>DE-EBRT (N=195)</th>
<th>LDR-PB (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>84.9 (±5.6)</td>
<td>89.7 (±4.8)</td>
</tr>
<tr>
<td>7 yr</td>
<td>76.3 (±7.0)</td>
<td>88.0 (±5.2)</td>
</tr>
<tr>
<td>9 yr</td>
<td>65.0 (±9.6)</td>
<td>84.9 (±6.6)</td>
</tr>
</tbody>
</table>

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority
High-risk stratum, N=276 (intent to treat)

<table>
<thead>
<tr>
<th>Kaplan-Meier (95% CI)</th>
<th>Randomization (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE-EBRT (N=137)</td>
</tr>
<tr>
<td></td>
<td>LDR-PB (N=139)</td>
</tr>
<tr>
<td>b-PFS 5 yr</td>
<td>83.6 (±7.0)</td>
</tr>
<tr>
<td></td>
<td>85.6 (±6.4)</td>
</tr>
<tr>
<td>b-PFS 7 yr</td>
<td>71.9 (±9.4)</td>
</tr>
<tr>
<td></td>
<td>82.9 (±7.2)</td>
</tr>
<tr>
<td>b-PFS 9 yr</td>
<td>58.2 (±12.8)</td>
</tr>
<tr>
<td></td>
<td>78.0 (±9.6)</td>
</tr>
</tbody>
</table>

Log rank P = 0.05

DE-EBRT ARM

LDR-PB ARM
Intermediate-risk stratum, N=122 (intent to treat)

Log rank P <0.001

Kaplan-Meier (95% CI)

| b-PFS | 5 yr | 84.1 (±9.8) | 96% (±5) |
|       | 7 yr | 80.1 (±10.8) | 93.9 (±6.8) |
|       | 9 yr | 69.8 (±14.6) | 93.9 (±3.8) |

Randomization (N=122)

DE-EBRT (N=63) | LDR-PB (N=57)
Prevalence of Late GI toxicity
LENT-SOMA scale, (prospective, physician-graded)

Years after start of EPNI

<table>
<thead>
<tr>
<th>Grade</th>
<th>DE-EBRT</th>
<th>LDR-PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of Late GU toxicity
LENT-SOMA scale, (prospectively physician-graded)
Summarizing Late toxicity

• At 6 years, minimal or no toxicity (G0-1)
  – GI: 95% of patients in both arms
  – GU: 90% in DE-EBRT arm vs 80% in LDR-PB arm
Overall survival

• 68 deaths in total
• At 18 events, prostate cancer is the most common cause of death among trial patients (responsible for 26% of all deaths)
• There have also been 15 cardiovascular deaths
• And 26 from other cancers
  – 7 lung, 5 pancreas/bile duct, 3 TCC of bladder/ureter, 3 colon, 3 with primary unknown, and 1 each; stomach, oesophagus, meningioma, metastatic melanoma, and a head and neck primary).

• 9 additional deaths
  – including one man treated on the LDR-PB arm who died at T+8y from Fournier’s gangrene secondary to complications related recto-urethral fistula repair
Overall survival
Intent-to-treat analysis, N=398 (68 events)

Log rank P = 0.29
Kaplan-Meier (95% CI)

Randomization (N=398)

<table>
<thead>
<tr>
<th></th>
<th>DE-EBRT (N=200)</th>
<th>LDR-PB (N=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>88.7 (±4.8)</td>
<td>91.3 (±4.4)</td>
</tr>
<tr>
<td>7 yr</td>
<td>81.5 (±6.4)</td>
<td>85.7 (±5.8)</td>
</tr>
<tr>
<td>9 yr</td>
<td>73.6 (±8.4)</td>
<td>77.9 (±8.2)</td>
</tr>
</tbody>
</table>

Median survival not reached
K-M estimate = 13 years
OS by treatment received

Log rank p = 0.09

LDR-PB ARM
N = 188

DE-EBRT ARM
N = 195

Other N = 15

time since first LHRH injection (yrs)

proportion alive
MVA analysis of overall survival:
(Backwards:Conditional Cox model, Intent-to-treat, N=398

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization arm (LDR-PB vs DE-EBRT)</td>
<td>0.84</td>
<td>0.51 – 1.38</td>
<td>0.49</td>
</tr>
<tr>
<td>Disease status (relapse vs no relapse)</td>
<td>1.96</td>
<td>1.14 – 3.38</td>
<td>0.015</td>
</tr>
<tr>
<td>Age (unit = 1 year)</td>
<td>1.06</td>
<td>1.02 – 1.10</td>
<td>0.004</td>
</tr>
<tr>
<td>Log iPSA (unit = 1 log)</td>
<td>1.30</td>
<td>0.87 – 1.95</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Will OS advantage emerge with further FU?

- LDR-PB arm
- ↓ Biochemical relapse
- ↓ Overall mortality
ASCENDE-RT: a deeper dive
Residual PSA is proportional to risk of relapse and therefore proportional to the biological dose delivered.
Prostate-Specific Antigen at 4 to 5 Years After Low-Dose-Rate Prostate Brachytherapy Is a Strong Predictor of Disease-Free Survival

Andrea C. Lo, MD,*† W. James Morris, MD, FRCP,*,† Vincent Lapointe, BSc,‡ Jeremy Hamm, MSc,§ Mira Keyes, MD, FRCP,*,† Tom Pickles, MD, FRCP,*,† Michael McKenzie, MD, FRCP,*,† and Ingrid Spadinger, PhD†,‡

*Department of Radiation Oncology, British Columbia Cancer Agency Vancouver Centre, Vancouver, British Columbia, Canada; †Department of Surgery, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; ‡Department of Medical Physics, British Columbia Cancer Agency Vancouver Centre, Vancouver, British Columbia, Canada; and §Department of Population Oncology, British Columbia Cancer Agency Vancouver Centre, Vancouver, British Columbia, Canada

Received Jul 24, 2013, and in revised form Oct 3, 2013. Accepted for publication Oct 4, 2013.
Predictive capacity of the 48-month PSA value

- 48mPSA ≤0.2 ng/mL  
  10 yr K-M b-PFS = 98.5%

- 48mPSA 0.2 – 0.4 ng/mL  
  10 yr K-M b-PFS = 89.7%

- 48mPSA 0.4 – 1.0  
  10 yr K-M b-PFS = 70.9%

- If 48mPSA >1.0  
  10 yr K-M b-PFS = 0%

- No safe threshold – the lower the better
Residual PSA value (for non-relapsed patients)

DE-EBRT ARM
- Median = 0.22 ng/mL
- Mean = 0.32 (SD = 0.32)
- 9% are undetectable

LDR-PB ARM
- Median = 0.03 ng/mL
- Mean = 0.09 (SD = 0.20)
- 44% are undetectable

These differences are even larger if analysis is restricted to those with > median FU where 67% of the LDR-PB patients have undetectable PSA and the DE-EBRT median rises to 0.31 ng/mL
Unpublished data (courtesy of Andrew Loblaw)
What can be learned by using a **surgical** definition of biochemical recurrence: failure to maintain a PSA of ≤0.2?
All ASCENDE-RT patients analyzed by treatment received (N = 383) using two thresholds to define biochemical recurrence.

<table>
<thead>
<tr>
<th>Kaplan-Meier (95% CI)</th>
<th>By failure definition (N=383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>phoenix</td>
<td>&gt;0.2ng/mL</td>
</tr>
</tbody>
</table>

- **5 yr**: 87.2 (±3.6) vs. 66.8 (±5.0)
- **7 yr**: 81.9 (±4.4) vs. 61.5 (±5.6)
- **9 yr**: 74.4 (±6.2) vs. 57.6 (±6.2)
b-PFS using two definitions of biochemical relapse

DE-EBRT (N=195)

9-year K-M PFS = 32% using >0.2 ng/mL

log rank P value <0.001

LDR-PB (N=188)

9-year K-M PFS = 82% using >0.2 ng/mL

log rank P value = 0.32
These lines are parallel.
b-PFS using a >0.2 ng/mL threshold (by treatment received N= 383)

Kaplan-Meier (95% CI) By treatment received (N=383)

<table>
<thead>
<tr>
<th></th>
<th>DE-EBRT (N=195)</th>
<th>LDR-PB (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>46.5 (±7.6)</td>
<td>87.9 (±5.0)</td>
</tr>
<tr>
<td>7 yr</td>
<td>37.7 (±8.0)</td>
<td>86.0 (±5.6)</td>
</tr>
<tr>
<td>9 yr</td>
<td>31.5 (±8.8)</td>
<td>82.2 (±7.0)</td>
</tr>
</tbody>
</table>
Is surgery equivalent?

- After LDR-PB boost, the 10 year b-PFS is ~80% using the surgical threshold of >0.2 ng/mL.
- I’m unaware of any surgical results that come close – for example the 5 year rate* after surgery for Gleason 4+3 =7 is 65.1%.

*Pierorazio PM, Walsh PC, Partin AW, and Epstein JI. 2013 Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU International; 111(5):689–852
Are HDR and LDR iso-effective?
HDR vs LDR for unfavourable risk

ASCENDE-RT

Hoskins et al.

Biochemical relapse-free survival (%)

Time from randomization (months)

Proportion free of recurrence

Time since first LHRH injection (yrs)

P = 0.001

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority
Local control
Local control

- 35 of 76 PSA recurrence events (46%) were metastatic
  - 17 LDR
  - 18 DE-EBRT
  - Presumably distributed evenly by randomisation

- 30 of 35 (86%) had evidence of mets <2 years from biochemical failure
  - Median interval = 4 months
Local control

• 46 biochemical relapses were not associated with early metastatic relapse
• 80% of these (N = 37) were in the DE-EBRT arm
b-PFS in ASCENDE-RT participants in whom biochemical relapse was not accompanied by metastatic disease within two years (Phoenix)

Log rank p < 0.001

LDR-PB

DE-EBRT
b-PFS in ASCENDE-RT participants in whom biochemical relapse was not accompanied by metastatic disease within two years (>0.2 ng/mL)
b-PFS in ASCENDE-RT participants in whom biochemical relapse was not accompanied by metastatic disease within two years (>0.2 ng/mL).

*subset of men who received one of the two treatment regimens who did not have evidence of metastatic disease within 2 years of biochemical recurrence.
Renormalize on 100% at Time 0

proportion free of recurrence

Time since first LHRH injection (years)
Local control

• For DE-EBRT ~5% per year local recurrence rate
  – Constant from year 5-10
• For LDR-PB ~1% per year local recurrence rate
  – Constant from year 5-10
Why LDR-PB boost for high risk

• LDR-PB provides low residual PSA values leading to local recurrence rates of ~1%/year

• Using a > 0.2 ng/mL threshold results in the same b-PFS as Phoenix allowing comparison with surgery

• Increased GU toxicity in ASCENDE-RT may be related to BCCA dose planning and obsolete imaging technology
Why LDR-PB boost for high risk

- The purported equivalence or superiority of SABR, HDR and RP demand confirmation with long term multi-institutional studies, population-based outcomes analysis and/or randomised data
Acknowledgements

– Data cross-checking, statistical support and general advice
  • Dana Matuszewski
  • Vince Lapointe
  • Sree Rodda
  • Scott Tyldesley
  • Jeremy Hamm
  • Nevin Murray

– Top 5 accruing physicians (N=194)
  • Jim Morris
  • Howard Pai
  • Ross Halperin
  • Michael Mckenzie
  • Graeme Duncan

– Data management
  • Adam Kahnamelli
  • Devon Poznanski

– LDR planning algorithm
  • Ingrid Spadinger
Acknowledgements (continued)

– Eric Berthelet
– Mitchell Liu
– **Gerard Morton**
– Paul Blood
– Tom Pickles
– Charmaine Kim-sing
– Juanita Crook
– David Petrik
– **Mira Keyes**
– Anand Karvat
– David Kim
– Andrew Loblaw
– Winkle Kwan

– Alex Agranovich
– Mohamed Manji
– Milton Po
– Belinda Campbell
– Author Cheung
– Jennifer Goulart
– Caroline Holloway
– Paris-Ann Ingledew
– Amy Hayden
– Richard Shaffer