LDR Monotherapy vs. HDR Monotherapy

Is it time for LDR to retire?

Gerard Morton
Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

Joseph Chin, R. Bryan Rumble, Marisa Kollmeier, Elisabeth Heath, Jason Efstatthiou, Tanya Dorff, Barry Berman, Andrew Feifer, Arthur Jacques,† and D. Andrew Loblaw

Recommendations
For patients with low-risk prostate cancer who require or choose active treatment, low-dose rate brachytherapy (LDR) alone, EBRT alone, and/or radical prostatectomy (RP) should be offered to eligible patients. For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy, brachytherapy boost (LDR or high-dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen $< 10$ ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL), LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and androgen-deprivation therapy, brachytherapy boost (LDR or HDR) should be offered to eligible patients. Iodine-125 and palladium-103 are each reasonable isotope options for patients receiving LDR brachytherapy; no recommendation can be made for or against using cesium-131 or HDR monotherapy. Patients should be encouraged to participate in clinical trials to test novel or targeted approaches to this disease.

Additional information is available at www.asco.org/Brachytherapy-guideline and www.asco.org/guidelineswiki.
LDR Seed Brachytherapy

First 2000 LDR patients from BCCA
Low and Intermediate Risk

LDR Implant

Morris et al, Brachytherapy 2014
LDR Seed Brachytherapy

LDR Implant

Fig. 1. PSA relapse-free survival for favorable-, intermediate-, and high-risk prostate cancer patients treated with brachytherapy ($p < 0.001$). PSA = prostate-specific antigen.

LDR Seed Brachytherapy

Fig. 1. PSA relapse-free survival for favorable-, intermediate-, and high-risk prostate cancer patients treated with brachytherapy ($p < 0.001$). PSA = prostate-specific antigen.

EBRT Challengers

Low Risk

Intermediate Risk

PROCARS Database
LDR Monotherapy

• The undefeated champion for low and favourable intermediate risk prostate cancer

• Has defeated all challengers
  – Nadir PSA values: typically < 0.05 ng/ml
  – bDFS: typically > 90%
LDR vs. HDR?
However – LDR seed implants have some disadvantages..

• Seeds displacement – so dose delivered may differ from that planned
• Cost of seeds
• Dose is delivered slowly
  – so may not be best for more rapidly growing cancers
  – so side-effects take months to resolve
HDR Monotherapy

- Consistent Dosimetry – no seed displacement
- Reusable source
- Rapid dose delivery
  - Repopulation not a problem
  - Rapid resolution of side effects
## HDR Monotherapy – the safe!

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Gy x f</th>
<th>Dose (Gy)</th>
<th>Median FU (yrs)</th>
<th>bDFS</th>
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<tr>
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<td>6 x 9</td>
<td>54</td>
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<td>81%</td>
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<td></td>
<td>6.5 x 7</td>
<td>45.5</td>
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<tr>
<td>Komiya</td>
<td>51</td>
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<tr>
<td>Hauswald</td>
<td>448</td>
<td>7-7.25 x 6</td>
<td>42-43.5</td>
<td>6.5</td>
<td>99%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>95%</td>
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<tr>
<td>Rogers</td>
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<td>39</td>
<td>2.7</td>
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<tr>
<td>Mark</td>
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<tr>
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<tr>
<td>Patel</td>
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<tr>
<td>Martinez</td>
<td>171</td>
<td>9.5 x 4</td>
<td>38</td>
<td>4.6</td>
<td>91%</td>
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</tbody>
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11
## Linear Quadratic Calculations

For alpha/beta = 1.5

<table>
<thead>
<tr>
<th>HDR Dose x Fractions</th>
<th>BED</th>
<th>Equivalent EBRT Dose</th>
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<tr>
<td>6 Gy x 9</td>
<td>270</td>
<td>116 Gy</td>
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<tr>
<td>7.5 Gy x 6</td>
<td>270</td>
<td>116 Gy</td>
</tr>
<tr>
<td>9.5 Gy x 4</td>
<td>278</td>
<td>120 Gy</td>
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<tr>
<td>11.5 Gy x 3</td>
<td>286</td>
<td>122 Gy</td>
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<td>13.5 Gy x 2</td>
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<td>116 Gy</td>
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<tr>
<td>19 Gy x 1</td>
<td>260</td>
<td>112 Gy</td>
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# HDR Monotherapy: the daring!

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Gy x f</th>
<th>Dose (Gy)</th>
<th>Median FU (yrs)</th>
<th>bDFS</th>
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<tbody>
<tr>
<td>Barkati</td>
<td>19</td>
<td>10 x 3</td>
<td>30</td>
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<td></td>
<td>19</td>
<td>10.5 x 3</td>
<td>31.5</td>
<td>3.3</td>
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</tr>
<tr>
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<td>19</td>
<td>11 x 3</td>
<td>33</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>22</td>
<td>11.5 x 3</td>
<td>34.5</td>
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<tr>
<td>Zamboglou</td>
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<td>5-7.7</td>
<td>95%</td>
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<tr>
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<td>226</td>
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<td>34.5</td>
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<tr>
<td>Kulkielka</td>
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<td>15 x 3</td>
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<td>4.7</td>
<td>97%</td>
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<tr>
<td>Jawad</td>
<td>319</td>
<td>9.5 x 4</td>
<td>38</td>
<td>5.5</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>12 x 2</td>
<td>24</td>
<td>3.5</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>13.5 x 2</td>
<td>27</td>
<td>2.9</td>
<td>100%</td>
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<tr>
<td>Hoskin</td>
<td>30</td>
<td>8.5 x 4</td>
<td>34</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>9 x 4</td>
<td>36</td>
<td>4.5</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>10.5 x 3</td>
<td>31.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>13 x 2</td>
<td>26</td>
<td>0.5</td>
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## HDR Monotherapy: the bold!

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Gy x f</th>
<th>Dose (Gy)</th>
<th>Median FU (yrs)</th>
<th>bDFS</th>
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<tbody>
<tr>
<td>Prada</td>
<td>60</td>
<td>19 x 1</td>
<td>19</td>
<td>6</td>
<td>66% (6 yrs)</td>
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<tr>
<td>Hoskin</td>
<td>115</td>
<td>13 X 2</td>
<td>26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>19 x 1</td>
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</tr>
<tr>
<td></td>
<td>26</td>
<td>20 x 1</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Krauss</td>
<td>63</td>
<td>19 x 1</td>
<td>19</td>
<td>2.9</td>
<td>93% (3 yrs)</td>
</tr>
</tbody>
</table>
Sunnybrook Randomized Trial

Ca Prostate
T1c/T2a, G6 or 7, PSA < 20
Volume < 60 cc
IPSS < 19
No ADT or TURP

19 Gy x 1
13.5 Gy x 2
1 week apart

randomization

Follow-up
CTCAE v4
EPIC
IPSS
Clinical PSA

170 patients accrued June 2013 to April 2015
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>19 Gy x 1 (n=87)</th>
<th>13.5 Gy x 2 (n=83)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Median Age (range)</strong></td>
<td>65 (46,80)</td>
<td>65 (49,80)</td>
<td>0.7364</td>
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<tr>
<td><strong>Stage</strong></td>
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<tr>
<td>T1c</td>
<td>67</td>
<td>63</td>
<td>0.8648</td>
</tr>
<tr>
<td>T2a</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Median PSA (range)</strong></td>
<td>6.4 (1.1,13.7)</td>
<td>6.3 (2.0,16.0)</td>
<td>0.9366</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
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<td></td>
</tr>
<tr>
<td>Gleason 6</td>
<td>28 (32%)</td>
<td>19 (23%)</td>
<td>0.2298</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>59 (68%)</td>
<td>64 (77%)</td>
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</tr>
<tr>
<td><strong>Risk Grouping</strong></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>23 (26%)</td>
<td>16 (19%)</td>
<td>0.5295</td>
</tr>
<tr>
<td>Intermediate</td>
<td>64 (74%)</td>
<td>67 (81%)</td>
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</table>

Median Follow-up 30 months
Treatment Details

• PTV = prostate +0-3 mm
• Median V100 = 97%
• Median V200 = 11%
• Median D90 = 110%
• Median urethra max = 120%
• Relative dosimetry same in both arms
Toxicity

- Minimal toxicity in either arm
- No GI toxicity
- Acute retention rate 2.4%
- 1 acute Grade 3 toxicity (haematuria)
- 1 late Grade 3 toxicity (stricture)
- Less urinary symptoms and less erectile dysfunction in single fraction arm within first year

Radiother Oncol 122: 87-92, 2017
Urinary Symptoms: HDR vs. LDR

MEDIAN IPSS OVER TIME

MONTHS SINCE IMPLANT

MEDIAN IPSS

HDR
LDR
Similar PSA response among
High-Tier Intermediate (n= 18)
Low-Tier Intermediate (n = 113)
Low Risk (n = 39)
bDFS by Risk Groups (all patients)

3-year bDFS:
Low Risk: 100%
Low-Intermediate: 96%
High Intermediate: 86%

Time since baseline (months)
PSA Response by treatment arm

More rapid PSA response in 2x fraction arm

Median PSA (95% CI) Value (ng/mL)

Baseline   Week    Month    Month    Month    Month   Month   Month    Month   Month
6               3              6 9            12           18           24            30           36

0
1
2
3
4
5
6
7
8
9
10

Median PSA (95% CI) Value (ng/mL)
19gy1f 27gy2f

1.35
0.48
1 biochemical failure in 2-fraction arm: distant mets
8 failures in 1-fraction arm: all with local recurrence

Disease-Free Survival by treatment arm

Biochemical disease-free survival probability

Time since baseline (months)

p-value = 0.0409
HDR Monotherapy Randomized Trial

• HDR Monotherapy in 1 or 2 fractions is really well tolerated
• Less urinary symptoms than LDR
• High local recurrence rate with single 19 Gy, almost always at site of initial disease
  – Potential for further dose escalation
Local Recurrence Analysis

Recurrence

- 19 Gy
- 22.8 Gy
- 28.5 Gy
Dose escalation to GTV with HDR

- T2
- Diffusion
- DCE

Dose escalation to GTV using MR/TRUS fusion
Dose escalation to GTV with HDR

Prostate: V100 96%, D90 109% (21 Gy), Mean dose 30 Gy
GTV: V100 100%, D90 163% (31 Gy), Mean Dose 47 Gy
Time for the old champ to retire?
PR.19
A Randomized Phase II Trial Evaluating High Dose Rate Brachytherapy and Low Dose Rate Brachytherapy as Monotherapy in Localized Prostate Cancer

Study Chairs: Eric Vigneault
            Gerard Morton

Eligibility criteria:
- Prostate carcinoma
- cT1- T2 and PSA < 20 and Gleason = 6
  Or
- cT1-T2 and PSA < 15 and Gleason = 7 (3+4) and ≤ 50% of positive cores

<table>
<thead>
<tr>
<th>R A N D O M I Z E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm 1:</strong></td>
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<tr>
<td>LDR brachytherapy with I-125 to a total dose of 144 Gy</td>
</tr>
<tr>
<td><strong>Arm 2:</strong></td>
</tr>
<tr>
<td>HDR brachytherapy: 19 Gy in 1 fraction with intraprostatic boost to GTV</td>
</tr>
</tbody>
</table>

N=232
Conclusions

• LDR Monotherapy
  – Delivers ablative dose to the prostate
  – Durable long term cancer control
  – Short to medium term urinary toxicity

• HDR Monotherapy
  – Well fractionated protocols likely have same efficacy as LDR
  – Less short to medium term urinary toxicity
  – Single fraction protocols attractive but unproven
  – GTV dose painting

• Await our randomized trial!