Optimal fractionation in HDR brachytherapy

Gerard Morton
Objectives

- Choose a dose and fractionation to use for HDR boost
- Interpret recent clinical trial results to select dose and fractionation for HDR monotherapy
- Assess ongoing clinical trials of monotherapy
American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

Yoshiya Yamada¹,* , Leland Rogers², D. Jeffrey Demanes³, Gerard Morton⁴, Bradley R. Prestidge⁵, Jean Poulit⁶, Gil’ad N. Cohen⁷, Marco Zaider⁷, 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.”
## Equivalent dose at 2 Gy/fraction

<table>
<thead>
<tr>
<th>Radiation Schedule</th>
<th>$\alpha/\beta=2$</th>
<th>$\alpha/\beta=3$</th>
<th>$\alpha/\beta=10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Gy x 2 HDR + 45 Gy/25f</td>
<td>102</td>
<td>95</td>
<td>77</td>
</tr>
<tr>
<td>15 Gy x 1 HDR + 37.5 Gy/15f</td>
<td>106</td>
<td>95</td>
<td>62</td>
</tr>
</tbody>
</table>
Sunnybrook HDR Boost Protocols

Intermediate Risk Patients

Single 15 Gy + 37.5 Gy/15 fractions (median FU 6.2 yrs)

10 Gy x 2 + 45 Gy/25 fractions (median FU 8.3 yrs)

Log-rank test: $p = 0.9953$
Single 15 Gy HDR Boost + 37.5 Gy/15 f EBRT

Findings

• Nadir PSA: 0.05 ng/ml
• Positive biopsy rate at 2 years < 1%
• 5-year bDFS: >97%
• Late Grade 3 toxicity 3%

Morton, Radiother Oncol 2011
Helou et al, Radiother Oncol 2015
D’Alimonte et al, Brachytherapy 2015
Shahid et al, Clin Oncol 2017
# HDR Monotherapy Dose Fractionations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Fraction</th>
<th>Dose</th>
<th>Fraction</th>
<th>Dose</th>
<th>Fraction</th>
<th>Dose</th>
<th>Fraction</th>
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</thead>
<tbody>
<tr>
<td>6 Gy</td>
<td>9</td>
<td>6 Gy</td>
<td>8</td>
<td>7 Gy</td>
<td>6</td>
<td>7.25 Gy</td>
<td>6</td>
</tr>
<tr>
<td>6.5 Gy</td>
<td>6</td>
<td>6 Gy</td>
<td>6</td>
<td>6 Gy</td>
<td>6</td>
<td>6 Gy</td>
<td>6</td>
</tr>
<tr>
<td>7 Gy</td>
<td>4</td>
<td>9 Gy</td>
<td>4</td>
<td>9.5 Gy</td>
<td>4</td>
<td>9.5 Gy</td>
<td>4</td>
</tr>
<tr>
<td>10 Gy</td>
<td>3</td>
<td>10.5 Gy</td>
<td>3</td>
<td>11.5 Gy</td>
<td>3</td>
<td>13 Gy</td>
<td>2</td>
</tr>
<tr>
<td>13.5 Gy</td>
<td>2</td>
<td>19 Gy</td>
<td>1</td>
<td>20.5 Gy</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# HDR Monotherapy – 4 and more fractions

<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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR IR HR</td>
<td></td>
</tr>
<tr>
<td>Yoshioka</td>
<td>190</td>
<td>6 x 8</td>
<td>48</td>
<td>7.6</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 x 9</td>
<td>54</td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.5 x 7</td>
<td>45.5</td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>Rogers</td>
<td>284</td>
<td>6.5 x 6</td>
<td>39</td>
<td>2.7</td>
<td>94%</td>
</tr>
<tr>
<td>Mark</td>
<td>301</td>
<td>7.5 x 6</td>
<td>45</td>
<td>8</td>
<td>88%</td>
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<tr>
<td>Demanes</td>
<td>157</td>
<td>7 x 6</td>
<td>42</td>
<td>5.2</td>
<td>97%</td>
</tr>
<tr>
<td>Patel</td>
<td>190</td>
<td>7.25 x 6</td>
<td>43.5</td>
<td>6.2</td>
<td>90%</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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<tr>
<td>Zamboglou</td>
<td>492</td>
<td>9.5 x 4</td>
<td>38</td>
<td>5-7.7</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93%</td>
</tr>
</tbody>
</table>
## HDR Monotherapy: 2-3 fractions

<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>
<th>LR</th>
<th>IR</th>
<th>HR</th>
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<tbody>
<tr>
<td>Barkati</td>
<td>19</td>
<td>10 x 3</td>
<td>30</td>
<td>3.3</td>
<td>85%</td>
<td></td>
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<tr>
<td></td>
<td>19</td>
<td>10.5 x 3</td>
<td>31.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>11 x 3</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>11.5 x 3</td>
<td>34.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strouthos</td>
<td>450</td>
<td>11.5 x 3</td>
<td>34.5</td>
<td>4.7</td>
<td>96%</td>
<td>96%</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>Kulkielka</td>
<td>77</td>
<td>15 x 3</td>
<td>45</td>
<td>4.7</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jawad</td>
<td>319</td>
<td>9.5 x 4</td>
<td>38</td>
<td>5.5</td>
<td>98%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>12 x 2</td>
<td>24</td>
<td>3.5</td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>13.5 x 2</td>
<td>27</td>
<td>2.9</td>
<td>100%</td>
<td></td>
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<tr>
<td>Hoskin</td>
<td>55</td>
<td>8.5-9 x 4</td>
<td>34-36</td>
<td>5</td>
<td>99%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>10.5 x 3</td>
<td>31.5</td>
<td>9</td>
<td>91%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>13 x 2</td>
<td>26</td>
<td>5.25</td>
<td>93%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HDR Monotherapy by Risk Group

11.5 Gy x 3

Low Risk (n=198)
Intermediate Risk (n=135)
High Risk (n=117)

Patients at risk
- low risk: 198, 197, 185, 145, 112, 85, 63, 22
- intermediate risk: 135, 134, 119, 102, 88, 68, 51, 19
- high risk: 117, 115, 107, 80, 58, 48, 33, 17

Streuthos, Radiother Oncol 2018
**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>
</tr>
</thead>
<tbody>
<tr>
<td>6 Gy x 9</td>
<td>270</td>
<td>116 Gy</td>
</tr>
<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>
</tr>
<tr>
<td>11.5 Gy x 3</td>
<td>286</td>
<td>122 Gy</td>
</tr>
<tr>
<td>13.5 Gy x 2</td>
<td>270</td>
<td>116 Gy</td>
</tr>
<tr>
<td>19 Gy x 1</td>
<td>260</td>
<td>112 Gy</td>
</tr>
</tbody>
</table>

BED = nd \(1 + \frac{d}{\alpha/\beta}\)
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>
</tr>
</thead>
<tbody>
<tr>
<td>6 Gy x 9</td>
<td>270</td>
<td>116 Gy</td>
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<tr>
<td>11.5 Gy x 3</td>
<td>286</td>
<td>122 Gy</td>
</tr>
<tr>
<td>13.5 Gy x 2</td>
<td>270</td>
<td>116 Gy</td>
</tr>
<tr>
<td>19 Gy x 1</td>
<td>260</td>
<td>112 Gy</td>
</tr>
</tbody>
</table>

\[ \text{BED} = nd \left(1 + \frac{d}{\alpha/\beta}\right) + C + D \]

C = Caution
D = Doubt
Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer

Peter Hoskin, Ana Rojas *, Peter Ostler, Robert Hughes, Roberto Alonzi, Gerry Lowe

19 Gy (n=23)
20 Gy (n=26)
Median FU 49 mos
Interm/High Risk: 28/21
74% had ADT

4 yr bDFS: 94%
High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results

Pedro J. Prada a,*, Juan Cardenal a, Ana García Blanco a, Javier Anchuelo a, María Ferri a, Gema Fernández c, Elisabeth Arrojo c, Andrés Vázquez b, Maite Pacheco b, José Fernández d

19 Gy x 1
N=60
Low/Interm: 44/16
1/3 had ADT
Median FU 6 yrs

66% bDFS

Radiother Oncol 2016
Five-Year Outcomes of a Single-Institution Prospective Trial of 19-Gy Single-Fraction High-Dose-Rate Brachytherapy for Low- and Intermediate-Risk Prostate Cancer


68 patients med FU 3.9 yrs 5 yr bDFS: 77%

Int J Radiat Oncol Biol Phys 2019
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

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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (range)</strong></td>
<td>65 (46,80)</td>
<td>65 (49,80)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>T2a</td>
<td>20</td>
<td>20</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>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason 6</td>
<td>28 (32%)</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>59 (68%)</td>
<td>64 (77%)</td>
</tr>
<tr>
<td><strong>Risk Grouping</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>21 (24%)</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Fav Intermediate</td>
<td>40 (46%)</td>
<td>46 (56%)</td>
</tr>
<tr>
<td>Unfav Intermediate</td>
<td>26 (30%)</td>
<td>25 (30%)</td>
</tr>
</tbody>
</table>

Median Follow-up 51 months
## Dosimetry Data

<table>
<thead>
<tr>
<th></th>
<th>19 Gy x 1</th>
<th>13.5 Gy x 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>#1</td>
<td>#2</td>
</tr>
<tr>
<td>Mean PTV cc</td>
<td>46.9 (14.2)</td>
<td>44.6 (11.4)</td>
<td>51 (13.8)</td>
</tr>
<tr>
<td>Mean V100</td>
<td>97.2 (1.7)</td>
<td>96.9 (1.5)</td>
<td>97.3 (1.2)</td>
</tr>
<tr>
<td>Mean V150</td>
<td>36.0 (4.8)</td>
<td>34.5 (5.3)</td>
<td>35.6 (6.1)</td>
</tr>
<tr>
<td>Mean V200</td>
<td>11.4 (3.3)</td>
<td>11.4 (3.9)</td>
<td>11.2 (3.3)</td>
</tr>
<tr>
<td>D 90 %</td>
<td>110.6 (3.1)</td>
<td>109.6 (2.9)</td>
<td>110.0 (2.5)</td>
</tr>
<tr>
<td>Urethra D max %</td>
<td>122.9 (2.6)</td>
<td>122.4 (8.3)</td>
<td>121.1 (7.1)</td>
</tr>
<tr>
<td>Urethra D10 %</td>
<td>116.4 (1.1)</td>
<td>116.2 (1.2)</td>
<td>116.2 (1.1)</td>
</tr>
<tr>
<td>Rectal D max %</td>
<td>84.5 (9.9)</td>
<td>81.0 (10.6)</td>
<td>81.6 (13.1)</td>
</tr>
<tr>
<td>Rectal V 80 (cc)</td>
<td>0.17 (0.2)</td>
<td>0.11 (0.18)</td>
<td>0.08 (0.16)</td>
</tr>
</tbody>
</table>
Acute Toxicity

- Minimal acute toxicity in either arm
- Acute retention rate 2%
- 1 acute Grade 3 toxicity (haematuria)

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

MEDIAN IPSS OVER TIME

MONTHS SINCE IMPLANT

MEDIAN IPSS

0 2 4 6 8 10 12 14 16 18

0 6 12 18 24 30

HDR  LDR

Radiation Oncology
UNIVERSITY OF TORONTO
Sunnybrook
HEALTH SCIENCES CENTRE
PSA Response by treatment arm

More rapid PSA response in 2x fraction arm
Nadir PSA > twice as high

Median PSA (95% CI) Value (ng/mL)
19gy1f 27gy2f
Baseline   W6     M3      M6    M9   M12    M18   M24   M30   M36 M42   M48   M54   M60

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

0.75 0.21
Conclusions from Sunnybrook Trial

• 13.5 Gy x 2 is the clear winner
• Treatment with either 1 or 2 fractions is very well tolerated
• Toxicity from single fraction slightly less in first 12 months but slightly worse beyond 3 years

• 13.5 Gy x 2 is highly effective, looks similar to LDR
• 19 Gy x 1 has unacceptable local failure rate, usually at site of initial disease
So what should we do?

- Stick to 2 fractions
- Increase single fraction dose to whole gland
- Use dose painting to increase dose to dominant lesion
- Something else
Higher Whole Gland Dose

High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results

Pedro J. Prada1,6, María Ferri1, Juan Cardenal1, Ana García Blanco1, Javier Anchuelo1, Iván Díaz de Cerio1, Andrés Vázquez2, Maite Pacheco2, Ignacio Raba2, Samuel Ruiz2

63% Gleason 6
37% Gleason 7
68% PSA < 10
43% ADT

bDFS
Low Risk: 82%
Int Risk: 79%

G6: 87%
G7: 62%

N=60
Median FU 51 mos
Higher Whole Gland Dose?

Prostate

High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results

Pedro J. Prada¹,², María Ferri¹, Juan Cardenal¹, Ana García Blanco¹, Javier Anchuelo¹, Iván Díaz de Cerio¹, Andrés Vázquez², Maite Pacheco², Ignacio Raba², Samuel Ruiz²

<table>
<thead>
<tr>
<th>Variable</th>
<th>V₀ (%)</th>
<th>V₁₅ (%)</th>
<th>V₂₀ (%)</th>
<th>D₀ (%)</th>
<th>V₁₀₀ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>97</td>
<td>17</td>
<td>4</td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>Median</td>
<td>98</td>
<td>18</td>
<td>5</td>
<td>22</td>
<td>92</td>
</tr>
<tr>
<td>Minimum</td>
<td>96</td>
<td>11</td>
<td>2</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td>Maximum</td>
<td>100</td>
<td>23</td>
<td>7</td>
<td>22</td>
<td>96</td>
</tr>
</tbody>
</table>

Sunnybrook Dosimetry (19Gy)

D₀ (Gy)

Mean 21
Median 21.1
Minimum 18.9
Maximum 22.2
Increasing Dose to Dominant Lesion

- Failure occurs at site of initial bulk disease
- Can we improve results by dose escalating to site of dominant disease?
Dosimetry of Local Failures with 19 Gy Whole Gland

Average Dose-Volume histogram for recurrent nodule and prostate

\[ D_{90_{nodule}} = 22.5 \text{ Gy (118\%)} \]

Mendez, Morton. Brachytherapy 2018
Monotherapy: HDR 19 Gy with Focal Boost

Dose escalation to GTV using MR/TRUS fusion
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  
Senior Investigator (SI): Wendy Parulekar  
Senior Biostatistician: Keyue Ding  
Study Coordinator (SC): Kate Whelan

Activated: Nov 2016  
Accrual to March 2019: 100/232
### PR.19 Schema

#### 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>Randomize</th>
<th>Arm 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDR brachytherapy with I-125 to a total dose of 144 Gy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomize</th>
<th>Arm 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDR brachytherapy: 19 Gy in 1 fraction with intraprostatic boost to GTV</td>
<td></td>
</tr>
</tbody>
</table>
PR.19 Treatment Arms

Arm 1: LDR 144 Gy

Arm 2: HDR 19 Gy + GTV boost to 28.5 Gy
Single Fraction with GTV Boosting

- 65 yr old with PSA 7.85
- Gleason 3+4 in 3/12 cores at right apex, 25% p4
- MRI: PIRAD 4 right apex

HDR 19 Gy + GTV Boost

Prostate V100: 97.6%
Prostate D90: 20.9 Gy

GTV D90: 30.5 Gy
Mean GTV: 45.3 Gy
PSA Profile

HDR
Feb
2016

7.85
3.8
3.1

5.8
4.8
5.2

10.6

01-Dec-15
01-Mar-16
01-Jun-16
01-Sep-16
01-Dec-16
01-Mar-17
01-Jun-17
01-Sep-17
01-Dec-17
01-Mar-18

PSMA PET

Persistent disease right apex
PSA Profile

HDR Feb 2016

PSMA PET

Biopsy:
G4+3 right apex 3/3 cores, 90% pattern 4
Systematic bx negative
PSA Profile

HDR Feb 2016

HDR 13.5 Gy x 2

#1

#2
PSA Profile

HDR Feb 2016

HDR 13.5 Gy x 2

HDR DCE HDR

7.85
3.38
3.1
5.8
4.8
5.2
10.6
7.14
2.81
1.8
1.2

01-Dec-15 01-Mar-16 01-Jun-16 01-Sep-16 01-Dec-16 01-Mar-17 01-Jun-17 01-Sep-17 01-Dec-17 01-Mar-18 01-Jun-18 01-Sep-18 01-Dec-18 01-Mar-19
Conclusions

• HDR Monotherapy in 2 or more fractions works really well
  – 13.5 Gy x 2, 11.5 Gy x 3, 9.5 Gy x 4
• 19 Gy x 1 may be associated with more late urinary symptoms and has unacceptably high local failure rate
• Not yet sure if single fraction with dose escalation to nodule will result in better outcome