CLINICAL WORKSHOP

IMAGE-GUIDED HDR-BRACHYTHERAPY FOR PROSTATE CANCER

Klinikum Offenbach
April 27th 2014
Gleason's Pattern Scale

1. Small, even glands
2. More signet rings between glands
3. Distinguishable, large prostatic ducts
4. Irregular cell sizes, cells within ducts
5. Lack of cohesion, sheets of cells

Stage T1a
Absorption into the bladder

Stage T1b

Stage T1c

Stage T2
Cancer in back lobe
The crux of defining risk groups

Memorial Sloan Kettering criteria
VS
National Comprehensive Cancer Network criteria
VS
D’Amico criteria
The Intelligent Patient Guide to Prostate Cancer

Jerome P. Richie, MD
Richard J. Zeckhauser, PhD

1 Division of General Medicine, Brigham and Women's Hospital, Boston, Massachusetts
2 Department of Radiation Oncology, Harvard Medical School, Boston, Massachusetts
3 Department of Radiation Therapy, Beth Israel Deaconess Medical Center, Boston, Massachusetts
4 Division of Urology, Brigham and V A Hospital, Boston, Massachusetts
5 Harvard Kennedy School of Government, Cambridge, Massachusetts

A Woman's Guide to Prostate Cancer Treatment
Supporting the man in your life

Providing prostate cancer support and resources for women and families
American Cancer Society

Now in an all-new fourth edition

Demonstrate a strong association between preferences among patients with prostate cancer and the outcomes of treatment...
D´Amico et al. JAMA 1998

1872 patients with T1c-T2c (1989-1997)
Median follow-up 38 months
Figure 1.—Estimated prostate-specific antigen outcome for low-risk patients stratified by treatment.
RADICAL PROSTATECTOMY, EXTERNAL BEAM RADIOTHERAPY <72 Gy, EXTERNAL BEAM RADIOTHERAPY ≥72 Gy, PERMANENT SEED IMPLANTATION, OR COMBINED SEEDS/EXTERNAL BEAM RADIOTHERAPY FOR STAGE T1–T2 PROSTATE CANCER

Patrick A. Kupelian, M.D.,* Louis Potters, M.D.,† Deepak Khuntia, M.D.,‡ Jay P. Ciezki, M.D.,‡ Chandana A. Reddy, M.S.,‡ Alwyn M. Reuther, M.P.H.,‡ Thomas P. Carlson, M.D.,‡ and Eric A. Klein, M.D.‡

*Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, FL; †Department of Radiation Oncology, Memorial Sloan-Kettering at Mercy Medical Center, Rockville Centre, NY; ‡Department of Radiation Oncology and the Urological Institute, Cleveland Clinic Foundation, Cleveland, OH

Kupelian et al. IJROBP 2004

1866 patients with T1-T2 (1992 -1998)

Radical Prostatectomy
EBRT (<72 Gy vs ≥72 Gy)
Permanent BRT
Biochemical relapse free survival

Time (months)

RP

EBRT

PI

p=0.82

5yr

7 yr

RP  83%  79%

PI  82%  74%

EBRT  77%  77%
Zietman et al. JAMA 2005

393 patients with organ-confined disease (1996-1999) median follow-up 66 months

EBRT 70.2 Gy vs 79.2 Gy
Radiation Therapy for Prostate Cancer: The Role for Dose Escalation

MICHAEL J. SWARTZ, KRISTIN JANSON, THEODORE L. DEWESE, AND DANNY Y. SONG
Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

TOPIC PAPER

Alan Pollack · Alex Hanlon · Eric M. Horwitz
Steven Feigenberg · Robert G. Uzzo · Robert A. Price

Radiation therapy dose escalation for prostate cancer: a rationale for IMRT

Received: 7 July 2003 / Accepted: 7 July 2003 / Published online: 5 September 2003
© Springer-Verlag 2003

Abstract The response of prostate cancer to radiation was well-documented in the pre-PSA era. Large palpable tumors resolved within months of treatment with relatively modest radiation doses of 64–70 Gy. The use of PSA-based failure as an endpoint, however, has made it clear that cure rates were much lower than appreciated. While doses in this range are still widely used today, data from retrospective, sequential prospective, and randomized studies indicate that for patients with intermediate-to-high risk disease, doses above 70 Gy are associated with a significant reduction in biochemical failure. The use of 3D-conformal radiotherapy to escalate radiation dose has resulted in modest increases in rectal and bladder toxicity. The application of intensity modulated radiotherapy methods allows for greater sparing of the surrounding normal tissues and, hence, the potential to further escalate dose. The results of dose escalation, the ability of IMRT to reduce rectal and bladder exposure to high radiation doses and the use of new imaging methods to more accurately target the prostate are described.

Keywords Prostate cancer · Dose escalation · Intensity modulated radiotherapy

The concept of escalating radiotherapy dose to improve prostate cancer local control is as old as the technique itself. The best examples in the early pre-PSA (prostate-specific antigen) literature are from Hanks et al. [22, 23, 24] and Perez et al. [53]. Using conventional treatment techniques, a dose response was recognized in locally advanced patients, but it was at the expense of increased morbidity. For many years 70 Gy was considered the maximum dose that could be safely administered. Sometimes an extra 2-4 Gy was used in more advanced patients. Over the last decade there have been substantial advances in treatment delivery methods that have allowed for better targeting of the prostate and sparing of the bladder and rectum. These advances have given way to a new round of prospective dose escalation studies, which have in general confirmed that dose is a strong determinant of tumor control. These studies have also defined, for the first time, objective computer-based parameters for determining normal tissue complication risk. These findings will be reviewed.

Biochemical failure as an endpoint after radiotherapy

There continues to be debate about how best to define biochemical failure after external beam radiotherapy. The ASTRO consensus criteria of three consecutive rises with backdating to the midpoint in time between the PSA nadir and the first rise were devised to standardize this classification [9]. While there are concerns over backdating [28] (see Fig. 1), the ASTRO consensus definition is a robust correlate of distant metastasis and cause-specific death [56]. The correlation of a rising PSA with overall survival has been less obvious [34, 40, 56], probably because of the competing risk of death from intercurrent illness. Biochemical failure appears to be a valid endpoint in dose escalation studies, as opposed to using a strict nadir endpoint.
Dose Escalation with superior Conformality
LDR vs HDR ?
Permanent Implant vs. Temporary Implant
LDR BRT

- **Nuclide**
  - Energy
  - $T_{1/2}$
- Geometry
- Anatomy over time
- Accumulation over time
Seeds ($^{125}$I, $^{103}$Pd, $^{131}$Cs)

- Nuclide
  - Energy
  - $T_{1/2}$

<table>
<thead>
<tr>
<th>Nuklid</th>
<th>Energy (keV)</th>
<th>$T_{1/2}$ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{125}$I</td>
<td>28.0</td>
<td>59.49</td>
</tr>
<tr>
<td>$^{103}$Pd</td>
<td>21.0</td>
<td>16.991</td>
</tr>
<tr>
<td>$^{131}$Cs</td>
<td>30.4</td>
<td>9.689</td>
</tr>
</tbody>
</table>
Seeds ($^{125}$I, $^{103}$Pd, $^{131}$Cs)

- Geometry (Dose distribution)

“Cold”

“Hot”
Dose-Accumulation ~ Time

Anatomy ~ Time
(Prostate ~ Seeds)
LDR BRT

\[ D_{90} > 90\% \text{ Reference dose (145 Gy)} \]

Potters et al Urology 62 (6) 2003
Extraprostatic Extension

105 Prostatectomy spec.
Gleason 6.3 (3-9)
PSA 8.6 (0.3-98)

*Davis et al. Cancer 85(12) 1999
Extraprostatic Extension

Davis et al. Cancer 85(12) 1999
“… the brachytherapy equivalent of negative margins.”
LDR BRT

- **Indication**
  - Stage T1-T2a N0 M0
  - PSA < 10 ng/ml
  - Gleason-Score 2-6

Seeds 145 Gy
# Results of LDR BRT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient number $n$</th>
<th>P/I$^a$</th>
<th>Median follow-up (months)</th>
<th>% Recurrence-free survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasko et al. [11]</td>
<td>197</td>
<td>I</td>
<td>36</td>
<td>93 (5)</td>
</tr>
<tr>
<td>Blasko et al. [23]</td>
<td>230</td>
<td>P</td>
<td>41.5</td>
<td>83.5 (9)</td>
</tr>
<tr>
<td>Ragde et al. [24]</td>
<td>147</td>
<td>I</td>
<td>93</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Brachman et al. [25]</td>
<td>695</td>
<td>I/P</td>
<td>74</td>
<td>71% (5)</td>
</tr>
<tr>
<td>Grimm et al. [26]</td>
<td>125</td>
<td>I</td>
<td>78</td>
<td>85 (10)</td>
</tr>
<tr>
<td>Beyer et al. [27]</td>
<td>1266/73</td>
<td>I/P</td>
<td>49</td>
<td>76% (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65% (10a)</td>
</tr>
<tr>
<td>Potters et al. [28]</td>
<td>733</td>
<td>I/P</td>
<td>51</td>
<td>74 (7)</td>
</tr>
<tr>
<td>Kupelian et al. [29]</td>
<td>950</td>
<td>I/P</td>
<td>47</td>
<td>75 (7)</td>
</tr>
<tr>
<td>Sylvester et al. [30]</td>
<td>223</td>
<td>I/P</td>
<td>120</td>
<td>86% (15a)</td>
</tr>
<tr>
<td>Potters et al. [31]</td>
<td>1148</td>
<td>I/P</td>
<td>82</td>
<td>81 (12a)</td>
</tr>
<tr>
<td>Stone et al. [32]</td>
<td>279</td>
<td>I</td>
<td>72</td>
<td>78% (10a)</td>
</tr>
</tbody>
</table>

$^a P/I^{103}$ Paladium/$^{125}$ Jodine
Aspects in LDR BRT

- Radiation protection
- Evaluation of the Quality of Implant after 4 weeks possible (30 days CT)
- Influence of Edema on the implant Quality (Chen et al., 2000)
- Indication limited: Volume (TRUS-Volumetry)
- Seed-Migration (e.g. Thorax in 55% ø Seeds/Patient (Eshleman et al. 2004))
HDR BRT

Practical advantages

Physical advantages

Radiobiologic advantages
Practical advantages

Radioprotection
(No free Sources – No risk of Loss)

Cost-effective
(HDR-Source and Equipment)
Physical advantages

Anatomy-oriented Target definition
(AFTER Implantation, larger volumes)

Anatomy-oriented Dose Escalation
(Prostate √ Rectum, Urethra, Bladder)
Radiobiological advantages

Low $\alpha/\beta$ - value

Brenner et Hall, 1999: [EBRT vs I-125] $\alpha/\beta = 1.5$

Fowler et al, 2001: [EBRT vs I-125/Pd-103] $\alpha/\beta = 1.49$

Dose escalation through Hypofractionation
GEC/ESTRO recommendations

GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update

Peter J. Hoskin a,*,1, Alessandro Colombo b,1, Ann Henry c,1, Peter Niehoff d,1, Taran Paulsen Hellebust e,1, Frank-Andre Siebert f,1, Gyorgy Kovacs g,1

a Mount Vernon Cancer Centre, Northwood, UK; b Department of Radiotherapy, Manzoni Hospital, Lecco, Italy; c St. James Institute for Oncology, Leeds, UK; d Department of Radiotherapy, City Hospital Cologne, Germany; e DNR Norwegian Radium Hospital, Oslo, Norway; f Universitätsklinikum Schleswig-Holstein, Kiel; and g University Hospital Schleswig-Holstein Campus Lübeck, Germany

Inclusion criteria
- Stages T1b–T3b
- Any Gleason score
- Any PSA level

Exclusion criteria
- TURP within 3–6 months
- Maximum urinary flow rate (Qmax) <10 ml/s
- IPSS > 20
- Pubic arch interference
- Lithotomy position or anaesthesia not possible
- Rectal fistula
HDR BRT

• **Indication**
  – any T with N0 M0
  – any PSA
  – any Gleason-Score

  **Monotherapy**
  Low- and intermediate risk

  **Combined modality (as boost)**
  Unfavorable intermediate and high risk
HDR BRT

HDR-Brachytherapy as Boost

Microscopic regional disease

EBRT / moderate Dose

Macroscopic intraprostatic disease

BRT for Dose escalation
### IMRT vs. 3D-conformal RT + HDR-BRT

**Repair factor:** $\alpha/\beta = 2 \text{ Gy (1.2 Gy)}$

<table>
<thead>
<tr>
<th>IMRT -LINAC</th>
<th>Brachytherapy + LINAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$40 \times 2 \text{ Gy} = 80 \text{ Gy} \sim 160 \text{ Gy}$</td>
<td>$28 \times 1.8 \text{ Gy} = 50.4 \text{ Gy} \sim 95.8 \text{ Gy}$</td>
</tr>
<tr>
<td>$2 \times 9 \text{ Gy (BT)} = 18 \text{ Gy}$</td>
<td>$2 \times 9 \text{ Gy (BT)} = 18 \text{ Gy}$</td>
</tr>
<tr>
<td>$\sum \text{BED} 160 \text{ Gy (213)}$</td>
<td>$\sum \text{BED} 194.8 \text{ Gy (295)}$</td>
</tr>
</tbody>
</table>

**Biologic Effective Dose** = $f$ (Repair factor, fractional dose, number of fractions)
CTV 1 → Prostate capsule
CTV 2 → Peripheral zone
CTV 3 → Visible tumor
CTV-Criteria for HDR-Boost

CTV 1 → whole gland defined by capsule

CTV 2 → peripheral zone

CTV 3 → visible tumor = GTV
# Prostate target dose variations in temporary BT of localised prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>EBRT</th>
<th>#BT fx</th>
<th>Gy/ fx</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borghede et al. [9]</td>
<td>50</td>
<td>2</td>
<td>15</td>
<td>Tumor volume (CTV3)</td>
</tr>
<tr>
<td>Dinges et al. [20]</td>
<td>45</td>
<td>2</td>
<td>10</td>
<td>Prostate capsule (CTV1)</td>
</tr>
<tr>
<td>Kovács et al. [39]</td>
<td>40/50</td>
<td>2</td>
<td>15</td>
<td>Peripheral zone (CTV2)</td>
</tr>
<tr>
<td>Martinez et al. [49]</td>
<td>45</td>
<td>3</td>
<td>5.5–10.5</td>
<td>Prostate capsule (CTV1)</td>
</tr>
<tr>
<td>Mate et al. [53]</td>
<td>50.4</td>
<td>4</td>
<td>3–4</td>
<td>Prostate capsule (CTV1)</td>
</tr>
</tbody>
</table>
## HDR-BOOST to EBRT

### Protocols:

**1 Fraction / Implant:**
- Dinges: 2 implants (9 Gy / Implant) + 45 Gy EBRT
- Martinez: 2 implants (11.5 Gy / Implant) + 46 Gy EBRT
- Galalae: 2 implants (15 Gy / Implant) + 50 Gy EBRT
- Offenbach: 2 implants (10.5 Gy / Implant) + 45 Gy EBRT

**Multiple Fractions / Implant**
- Hsu: 1 implant (2 x 6 Gy / Implant) + 18 Gy EBRT
- Rodriguez: 2 implants (2 x 6 Gy / Implant) + 36 Gy EBRT
- Pellizzon: 2 implants (2 x 6 Gy / Implant) + 45 Gy EBRT
- Linares: 1 implant (4 x 5.5 Gy / Implant) + 45 Gy EBRT
DOSE ESCALATION IMPROVES CANCER-RELATED EVENTS AT 10 YEARS FOR INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER PATIENTS TREATED WITH HYPOFRACTIONATED HIGH-DOSE-RATE BOOST AND EXTERNAL BEAM RADIOThERAPy

- n = 417 Patienten
- median FU: 8.2 J
- PSA ≥ 10 or GL ≥ 7 or T2b
- Low dose (BED) < 268 Gy
  High dose (BED) > 268 Gy

EBRT = 46 Gy + BRT Boost
(a/β = 1.2)

Late Grade 3 genitourinary complications of 3.0 %
Late Grade 3 gastrointestinal complications <0.5%

[ Martinez et al. IJROBP 2011 ]
### Athens Consensus

Boost + EBRT 46 Gy at 2 Gy or 45 Gy at 1.8 Gy

**CTV 1 = CTV = PTV**

<table>
<thead>
<tr>
<th>Dose/Fx (Gy)</th>
<th># Fxs</th>
<th>Total D (Gy)</th>
<th>BED (a/b=1,5)</th>
<th>% Dose</th>
<th>EQD&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.5</td>
<td>2</td>
<td>19</td>
<td>247</td>
<td>57</td>
<td>106</td>
</tr>
<tr>
<td>10.5</td>
<td>2</td>
<td>21</td>
<td><strong>&gt;&gt; 160 Gy</strong></td>
<td>61</td>
<td><strong>118</strong></td>
</tr>
<tr>
<td>11.5</td>
<td>2</td>
<td>23</td>
<td>307</td>
<td>65</td>
<td>131</td>
</tr>
</tbody>
</table>
HDR-Boost to EBRT

“Evolution of Dose Constraints”


**HDR-Boost to EBRT**

### Prostate (PTV = CTV 1):
- $D_{90} \geq 100\%$
- $V_{100} \geq 90\%$
- $V_{150} \lessapprox 35\%$

### Urethra:
- $D_{10} \lessapprox 115\%$
- $D_{0.1cm^3} \lessapprox 120\%$

### Rectum & Bladder:
- $D_{10} \lessapprox 75\%$
- $D_{0.1cm^3} \lessapprox 80\%$
Offenbach protocol for High Risk HDR Boost to EBRT

- PTV = CTV 1 (in cT3: CTV 1+ 5.0 mm)
- BRT Boost: 2 x 10.5 Gy = 21.0 Gy upfront
- EBRT of Prostate+SV = 45.0 Gy after BRT
  - Androgen deprivation for 9 months
HDR Boost to EBRT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Total EBRT dose (Gy/fx)</th>
<th>Total HDR dose (Gy/fx)</th>
<th>Total BED/EQD2 (Gy)</th>
<th>Follow-up (y)</th>
<th>Biochemical control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galalae et al, 2002 [87]</td>
<td>144</td>
<td>40/20</td>
<td>18/2</td>
<td>219/94</td>
<td>median 8.2</td>
<td>74%/69% all risk groups at 5years/8 years</td>
</tr>
<tr>
<td>Pistas et al, 2010 [12]</td>
<td>114</td>
<td>60/20</td>
<td>9/1</td>
<td>203/87</td>
<td>mean 2.7</td>
<td>97.4% IR and HR at 4 years</td>
</tr>
<tr>
<td>Kotecha et al, 2013 [13]</td>
<td>229</td>
<td>45-50.4/25-28</td>
<td>16.5-22.5/3</td>
<td>171-226/74-97</td>
<td>median 5.1</td>
<td>95% LR at 7 years, 90% IR at 7 years, 57% HR at 7 years (81% HR with BED &gt; 190 Gy)</td>
</tr>
<tr>
<td>Martin et al, 2004 [99]</td>
<td>102</td>
<td>45/25</td>
<td>20-28/4</td>
<td>191-251/82-108</td>
<td>median 2.6</td>
<td>100% LR/IR at 3 years, 79% HR at 3 years</td>
</tr>
<tr>
<td>Prada et al, 2012 [14]</td>
<td>252</td>
<td>46/23</td>
<td>21-23/2</td>
<td>292-366/109-137</td>
<td>median 6.1</td>
<td>84%/78% HR at 5 years/10 years</td>
</tr>
<tr>
<td>Åström et al, 2005 [100]</td>
<td>214</td>
<td>50/25</td>
<td>20/2</td>
<td>269/116</td>
<td>median 4</td>
<td>82% all risk groups at 5 years</td>
</tr>
<tr>
<td>Martinez et al, 2002 [16]</td>
<td>207</td>
<td>46/23</td>
<td>16.5-23/2-3</td>
<td>184-306/79-131</td>
<td>mean 4.4</td>
<td>52% all risk groups for EQD2 &lt; 93 Gy and 87% all risk groups for EQD2 &gt; 93 Gy at 5 years</td>
</tr>
<tr>
<td>Noda et al., 2011 [102]</td>
<td>59</td>
<td>50/25</td>
<td>15-18/2</td>
<td>191-243/82-104</td>
<td>median 5.1</td>
<td>100% LR at 5 years, 92% IR at 5 years, 72% HR at 5 years</td>
</tr>
<tr>
<td>Hoskin et al, 2007 [88]</td>
<td>220</td>
<td>35.75/13</td>
<td>17/2</td>
<td>214/92</td>
<td>median 2.5</td>
<td>mean PSA-relapse free survival for all risk groups 4.3 years</td>
</tr>
</tbody>
</table>
HDR BRT

HDR-Monotherapy

Dose escalation in locally-confined disease
## HDR-Monotherapy

### International protocols

<table>
<thead>
<tr>
<th>Name</th>
<th>Implantations</th>
<th>Days</th>
<th>Dose 1</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez</td>
<td>1 Implantat</td>
<td>2</td>
<td>4x9.5 Gy</td>
<td>38.0 Gy</td>
</tr>
<tr>
<td>Yoshioka</td>
<td>1 Implantat</td>
<td>5</td>
<td>9x6.0 Gy</td>
<td>54.0 Gy</td>
</tr>
<tr>
<td>Corner</td>
<td>1 Implantat</td>
<td>2</td>
<td>3x10.5 Gy</td>
<td>31.5 Gy</td>
</tr>
<tr>
<td>Mark</td>
<td>2 Implantate</td>
<td>1</td>
<td>6x7.5 Gy</td>
<td>45.0 Gy</td>
</tr>
<tr>
<td>Offenbach</td>
<td>3 Implantate</td>
<td>1</td>
<td>3x11.5 Gy</td>
<td>34.5 Gy</td>
</tr>
</tbody>
</table>
LDR

90% Isodose

200% to urethra
100% to anterior rectum

HDR

3D-Dose painting of Margins

≤ 115% urethra
≤ 75% anterior rectum
## LDR vs HDR

<table>
<thead>
<tr>
<th></th>
<th>Seeds</th>
<th>HDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume Definition</strong></td>
<td>Pre/Peri-Implant</td>
<td>Post-Implant</td>
</tr>
<tr>
<td><strong>Dosimetry</strong></td>
<td>Pre/Peri-Implant</td>
<td>Post-Implant FLEXIBEL</td>
</tr>
<tr>
<td></td>
<td>FIX</td>
<td></td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td>Live</td>
<td>Afterloading</td>
</tr>
<tr>
<td><strong>Verification</strong></td>
<td>30 days-CT</td>
<td>Preloading</td>
</tr>
</tbody>
</table>
# LDR vs HDR

<table>
<thead>
<tr>
<th></th>
<th>Seeds</th>
<th>HDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA</strong></td>
<td>&lt; 15 ng/ml</td>
<td>Exclusion of Mets</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td>&lt; 7</td>
<td>Exclusion of Mets</td>
</tr>
<tr>
<td><strong>T-Stage</strong></td>
<td>T1-T2a</td>
<td>T1-T3</td>
</tr>
<tr>
<td><strong>Gland Volumen</strong></td>
<td>45-50 cc</td>
<td>~ 80 cc</td>
</tr>
</tbody>
</table>
Arguments pro HDR BRT

- Application of a high dose in very short time ensuring radiobiological dose escalation
  
  [ Martinez et al. IJROBP 2000 ]

- Intensity modulation with highest confority through Real Time Dosimetry + Inverse Planning
  
  [ Edmundson et al. IJROBP 1993 ]

- Compared to EBRT no interfraction or intrafraction movement
  
  [ Stromberg et al. IJROBP 1995 ]
  [ Martinez et al. IJROBP 2001 ]
  [ Deutsch et al. Brachytherapy 2010 ]

- Compared to LDR no influence of dose application by prostate deformation or seed migration
  
  [ Edmundson et al. IJROBP 1993 ]
  [ Martinez et al. IJROBP 2000 ]
Prostate Brachytherapy in Offenbach
- History -
Prostate–Brachytherapy since 1996

Transrectal HDR-BOOST to EBRT
Beginning of new era in 2001

Transperineal HDR-MONOTHERAPY
High-Dose-Rate Interstitial Brachytherapy as Monotherapy for Clinically Localized Prostate Cancer: Treatment Evolution and Mature Results

Nikolaos Zamboglou, MD, PhD,* Nikolaos Tselis, MD, PhD,* Dimos Baltas, PhD,† Thomas Buhleier, MD, PhD,* Thomas Martin, MD, PhD,‡ Natasa Milickovic, PhD,† Sokratis Papaioannou, MSc,† Hanns Ackermann, PhD,§ and Ulf W. Tunn, MD, PhD‖
2002-2009: 718 consecutive patients with localized prostate cancer

Transperineal Implantation under TRUS-guidance

2002-2004 (A): 1 Implant (4 x 9.5 Gy) CT-Plan (n=141)
2004-2008 (B): 2 Implants (2 x 9.5 Gy/Implant) TRUS-Plan (n=351)
2008-2009 (C): 3 Implants of 11.5 Gy TRUS-Plan (n=226)
2002-2004 (A): 1 Implant  (4 x 9.5 Gy)  
CT- Plan (n=141)

9.5 Gy → 6h → 9.5 Gy → 6h → 9.5 Gy → 6h → 9.5 Gy
2004-2008 (B): 2 Implants (2 x 9.5 Gy/Implant)  TRUS-Plan (n=351)

9.5 Gy → 6h → 9.5 Gy

after 14 days 2\textsuperscript{nd} implant

9.5 Gy → 6h → 9.5 Gy
2008-2009 (C): 3 Implants of 11.5 Gy

TRUS-Plan (n=226)

- 1x 11.5 Gy
- After 21 days 2\textsuperscript{nd} implant
- 1x 11.5 Gy
- After 21 days 3\textsuperscript{rd} implant
- 1x 11.5 Gy
### Protocol characteristics

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>PTV</th>
<th>BED (_{1.5/3.0})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (9.5 Gy x 4)</td>
<td>38.0 Gy</td>
<td>279/158 Gy</td>
</tr>
<tr>
<td>Group B (9.5 Gy x 4)</td>
<td>38.0 Gy</td>
<td>279/158 Gy</td>
</tr>
<tr>
<td>Group C (11.5 Gy x 3)</td>
<td>34.5 Gy</td>
<td>294/162 Gy</td>
</tr>
</tbody>
</table>

Potential doubling time of \(T_{\text{pot}} = 42 \text{ days}\) \(\text{ (Treatment completion within } 42 \text{ days)}\)
1 Implant (4 x 9.5 Gy)

BED 279 Gy_{1.5}

BED 346 Gy_{1.5}

BED 415 Gy_{1.5}

BED 554 Gy_{1.5}

D_{10} Rectum < 75 \% : BED 74 Gy_{10}
2 Implants (2 x 9.5 Gy/Implantat)

BED 279 Gy \(_{1.5}\)

BED 346 Gy \(_{1.5}\)

BED 415 Gy \(_{1.5}\)

BED 554 Gy \(_{1.5}\)

D_{10} Rectum < 75 \% : BED 74 Gy \(_{10}\)
3 Implants of 11.5 Gy

BED 294 Gy 1.5
BED 370 Gy 1.5
BED 445 Gy 1.5
BED 594 Gy 1.5

D_{10} Rectum < 75\% : BED 74 Gy 10
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 141)</th>
<th>Group B (n = 351)</th>
<th>Group C (n = 226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (months)</td>
<td>Median overall follow-up 52.8 months</td>
<td>91.9 (45.5-113.4)</td>
<td>59.3 (16.5-82.6)</td>
</tr>
<tr>
<td>Median Gland volume (cc)</td>
<td>40 (20-90)</td>
<td>39 (16-107)</td>
<td>36 (11-90)</td>
</tr>
<tr>
<td>Risk group (MSKCC)</td>
<td>Low: n= 103 (73.0%)</td>
<td>Intermediate: n= 23 (16.3%)</td>
<td>High: n= 15 (10.6%)</td>
</tr>
<tr>
<td></td>
<td>Low risk: n= 395 (55 %)</td>
<td>Intermediate: n= 177 (25 %)</td>
<td>High risk: n= 146 (20 %)</td>
</tr>
</tbody>
</table>
Evaluation

Survival estimates according to Kaplan-Maier method
Biochemical Control based on Nadir +2 (*Phoenix Criteria*)
Toxicity according CTC Version 3
Clinical Outcome (n=718)
Clinical Outcome (Risk Group)

Biochemical Control

Months

Low Risk (n=395)
Intermediate Risk (n=177)
High Risk (n=146)

(p=0.44)
Clinical Outcome (Treatment Group)

- Group A (n=141)
- Group B (n=351)
- Group C (n=226)

(p=0.08)
# Acute Toxicity (n=718)

<table>
<thead>
<tr>
<th></th>
<th>Group A (n= 141)</th>
<th>Group B (n= 351)</th>
<th>Group C (n= 226)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI Toxicity</td>
<td>GU Toxicity</td>
<td>GI Toxicity</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0.7 %</td>
<td>9.2 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0 %</td>
<td>15.6 %</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18.4%</td>
<td>46.8 %</td>
<td>15.7 %</td>
</tr>
</tbody>
</table>
### Late Toxicity (n=717)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Genitourinary</th>
<th>Grade</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Frequency/Urge: 9.2%</td>
<td>3</td>
<td>Pain: 0.7%</td>
</tr>
<tr>
<td>3</td>
<td>2.1%</td>
<td>4</td>
<td>Mucositis: 0.7%</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.8%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5%</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Genitourinary**
  - Frequency/Urge: 9.2% 2.1% 4.8% 0.5% 7.5%
  - Incontinence: 7.8% 0.7% 0.7% 5.1% 0.3% 7.5% 0.4% 0.4%
  - Retention: 6.3% 2.8% - 5.4% 2.0% 4.4% 0.8% -
  - Errect. dysfunction: 21.2% 12.0% - 15.7% 16.5% 18.2% 19.1% -

- **Gastrointestinal**
  - Pain: 0.7% 0.7% - 0.3% 0.3% -
  - Mucositis: 0.7% 3.5% - 0.8% 1.2% 0.4% 0.4% -

2 patients with endoscopically Grade 3 rectal necrosis: colostomy
3 patients with endoscopically grade 3 rectal mucositis: laser coagulation procedures

2 patients with incontinence indicating permanent urostomy
# Results of HDR Monotherapy

Literature results of high-dose-rate brachytherapy as monotherapy for localised prostate cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Gy/fx</th>
<th>Fractions (Implants)</th>
<th>Total</th>
<th>median f/u (y)</th>
<th>Biochemical control*</th>
<th>BED (Gy)</th>
<th>EQD2 (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoshioka et al., 2011 [80]</td>
<td>111</td>
<td>6.0 Gy</td>
<td>9 (1 Implant)</td>
<td>54 Gy</td>
<td>5.4</td>
<td>93% IR at 3 years, 85% HR at 3 years</td>
<td>270</td>
<td>116</td>
</tr>
<tr>
<td>Yoshioka et al., 2013 [65]</td>
<td>63</td>
<td>6.5 Gy</td>
<td>7 (1 Implant)</td>
<td>45.5 Gy</td>
<td>3.5</td>
<td>96% IR at 3 years, 90% HR at 3 years</td>
<td>243</td>
<td>104</td>
</tr>
<tr>
<td>Hoskin et al., 2012 [10]</td>
<td>197</td>
<td>8.5–9.0 Gy</td>
<td>4 (1 Implant)</td>
<td>34-36 Gy</td>
<td>4.5–5</td>
<td>95% IR at 4 years, 87% HR at 4 years</td>
<td>227-252</td>
<td>97-108</td>
</tr>
<tr>
<td>10.5 Gy</td>
<td></td>
<td>3 (1 Implant)</td>
<td>31.5 Gy</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.0 Gy</td>
<td></td>
<td>2 (1 Implant)</td>
<td>26 Gy</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rogers et al., 2012 [75]</td>
<td>284</td>
<td>6.5 Gy</td>
<td>6 (2 Implants)</td>
<td>39 Gy</td>
<td>3</td>
<td>94% IR at 5 years</td>
<td>208</td>
<td>89</td>
</tr>
<tr>
<td>Mark et al., 2010 [116]</td>
<td>301</td>
<td>7.5 Gy</td>
<td>6 (2 Implants)</td>
<td>45 Gy</td>
<td>8</td>
<td>88% all risk groups at 8 years</td>
<td>270</td>
<td>117</td>
</tr>
<tr>
<td>Prada et al., 2012 [123]</td>
<td>40</td>
<td>19.0 Gy</td>
<td>1 (1 Implant)</td>
<td>19 Gy</td>
<td>1.6</td>
<td>100% LR at 32 months, 88% IR at 32 months</td>
<td>260</td>
<td>111</td>
</tr>
<tr>
<td>Demanes et al., 2011 [9]</td>
<td>298</td>
<td>7.0 Gy</td>
<td>6 (2 Implants)</td>
<td>42 Gy</td>
<td>5.2</td>
<td>97% LR/IR at 5 years</td>
<td>238-279</td>
<td>102-119</td>
</tr>
<tr>
<td>9.5 Gy</td>
<td></td>
<td>4 (1 Implant)</td>
<td>38 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zamboglou et al., 2012 [8]</td>
<td>718</td>
<td>9.5 Gy</td>
<td>4 (1 Implant)</td>
<td>38 Gy</td>
<td>4.4</td>
<td>95% LR at 5 years, 93% IR at 5 years</td>
<td>279-299</td>
<td>119-128</td>
</tr>
<tr>
<td>9.5 Gy</td>
<td></td>
<td>4 (2 Implants)</td>
<td>38 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.5 Gy</td>
<td></td>
<td>3 (3 Implants)</td>
<td>34.5 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

Grimm et al. BJU 2012

52,087 analysed patients
Peer-reviewed journals from 2000-2011
Median follow-up of all studies \( \geq 60 \) months