High Dose Rate Brachytherapy in Cervix Cancer

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Radiotherapy of Cervix Cancer

- **External Beam Radiation Therapy**
  - 40 – 50 Gy

- **Brachytherapy**
  - LDR
  - HDR
Variations in Treatment Regimens

- **Low Dose Rate**
  - 1 or 2 applications
  - 20 to 40 Gy/fraction

- **High Dose Rate**
  - More than 50 treatment regimens*
  - 1 to 16 fractions
  - 3 to 17 Gy/fraction

*Orton et al. IJROBP 1991
Why Fractionate?

Low Dose Rate

- Allow tumor regression
- Better pelvic geometry

High Dose Rate

- Radiobiology (toxicity)
- Allow tumor regression
- Better pelvic geometry
- Financial stimulus
Pioneers in HDRB for Cervix Cancer

- O’Connel, Joslin et al. Cardiff 1965: 4 x 10 Gy
- Arai et al. Japan 1968: various fractionation
- Akine et al. Japan 1972: 4 x 5 Gy
- Shigematsu et al. Japan 1973: 3 x 10 Gy
- Inoue et al. Japan 1978: 3-6 x 7.5 Gy
- Chen et al. Taiwan 1980: 3 x 7.7-8.5 Gy
- Roman et al. Montreal 1984: 3 x 8 Gy
- Choi et al. Hong Kong 1984: 3 x 7-8 Gy
- Patel et al. Chandigarh 1986: 2-4 x 9-9.5 Gy
“With remote control applicators, thousands of rads are given in a few minutes. The predominance of single hit events, which has the biologic advantage of continuous low dose rate irradiation, is lost and extrapolation from past experience is impossible”.
Converting LDR to HDR

- **Liversage - Br J Radiol 1969**
  \[ N = \mu T / 2 \left\{ 1 - [1 - \exp(-\mu T)] / \mu T \right\} \]
  \[ N = \# \text{ fractions}; \ T = \text{time}; \ \mu = \text{recovery constant} \]

- **Dale - Br J Radiol 1990**
  \[ \text{BED}_\text{tum} = Nd \times \left[ 1 + d / (\alpha / \beta)_\text{tum} \right] \]
  \[ \text{BED}_\text{late} = fNd \times \left[ 1 + fd / (\alpha / \beta)_\text{late} \right] \]
  \[ f = \text{known fraction of the true tumor dose} \]

\[ \text{BED}_\text{tum} = \text{RT} \times \left[ 1 + 2R / \left\{ \mu_\text{tum} (\alpha / \beta)_\text{tum} \right\} \right] \]
\[ \text{BED}_\text{late} = fRT \times \left[ 1 + 2R / \left\{ \mu_\text{late} (\alpha / \beta)_\text{late} \right\} \right] \]
\[ R = \text{dose rate} \]
Fractionation in HDR

- Dale 1985 - HDR equivalent to LDR if 17 fractions of 3.5 Gy given
- Orton 1992 - 6 to 12 fractions will do it
- Brenner and Hall - 5 to 12 fractions for early effects
McGill Experience

- First Selectron in N. America
- First treatment in 1984
- Micro Selectron installed in 1988
- Implant always done under spinal anesthesia
- “Home made” planning system

Roman, Souhami et al: IJROBP 1991
Souhami et al: Gynecol Oncol 2005
# Patient Characteristics

- **282 patients (1984 - 1997)**
- **Median age: 62 years (25 - 95)**
- **Stage:**
  - IB: 22 patients, 8%
  - IIA: 49 patients, 17.5%
  - IIB: 116 patients, 41%
  - IIIA: 7 patients, 2.5%
  - IIIB: 77 patients, 27%
Technical Parameters

- **EBRT**
  - Median Dose: 46 Gy (40 - 54.6 Gy)

- **HDRB**
  - Median Dose: 24 Gy (6.8 - 31.8 Gy)
  - Median nºfxs: 3 (1 - 3)
Results

- Median follow-up: 50.1 months
- Median follow-up patients at risk: 86.6 months
Overall survival

Overall Survival

- 57% at 5 years
- 52% at 10 years
- 47% at 15 years

Survival vs. Time (y)
Survival by Stage

Survival by Stage

Survival

Time (y)

IB
IIA
IIB
IIIA
IIIB
IVA

p < 0.0001

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## Overall Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 years (%)</th>
<th>10 years (%)</th>
<th>15 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>57</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>IIA</td>
<td>72</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>IIB</td>
<td>65</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>IIIA</td>
<td>51</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>IIIB</td>
<td>42</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Overall</td>
<td>57</td>
<td>52</td>
<td>47</td>
</tr>
</tbody>
</table>

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Patterns of Failure

- Local only: 43 patients (15%)
- Distant only: 33 patients (12%)
- Local & distant: 25 patients (9%)
Local Failure by Stage

Time (y)

Failure

- fail IB
- fail IIA
- fail IIB
- fail IIIA
- fail IIIB
- fail IVA

p < 0.0001
McGill Experience

Local Failure by Treatment Duration

- Rx duration > 47d
- Rx duration < 47d

IIB

$p = 0.046$
# Cervix Cancer

## Duration of RT vs Local Control

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>Pelvic Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fyles</td>
<td>830</td>
<td>↓ 1% day/30 days</td>
</tr>
<tr>
<td>Lanciano</td>
<td>837</td>
<td>↓ 0.85% day/55 days</td>
</tr>
<tr>
<td>Petereit</td>
<td>209</td>
<td>↓ 0.7% day/55 days</td>
</tr>
<tr>
<td>Perez</td>
<td>1224</td>
<td>↓ 0.85% day/49 days</td>
</tr>
<tr>
<td>Girinsky</td>
<td>386</td>
<td>↓ 1.1% day/52 days</td>
</tr>
</tbody>
</table>
The adverse effect of increasing treatment time on pelvic control probability in cervical cancer by Shang-Wen Chen\textsuperscript{a,b,c} and Sheng-Jen Lin\textsuperscript{a,b,c,*}

Abstract

Background and purpose: The potential adverse effect of increasing treatment time on pelvic control probability in cervical cancer has been extensively studied for many low-dose rate (LDR) and high-dose rate (HDR) studies, with an estimated overall treatment time of 70 days. This study aimed to evaluate the treatment time schedule for fractionated high-dose rate intracavitary brachytherapy (HDR-ICB) and to compare the overall treatment time for low-dose rate studies. Since the treatment time can be adjusted based on patient condition. This report aims to evaluate the adverse effect of treatment prolongation specifically for cervical cancer treated with HDR-ICB.

Material and methods: From September 1992 to December 1997, 257 patients diagnosed with uterine cervical cancer (35 Ib, 26 IIa, 122 IIb, 10 IIIa, 57 IIIb, 7 IVa), who underwent external radiotherapy combined with between two and four courses of HDR-ICB, and a minimum...
Late Toxicity

<table>
<thead>
<tr>
<th></th>
<th>GI</th>
<th>GU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>15.3%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>6.3%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

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Complication Probability vs BED

Clark, Souhami et al IJROBP 1997

McGill University
### HDRB: Regimens
#### Stages IIB-IIIB

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>Year</th>
<th>Median FU (mos)</th>
<th>EBRT (Gy)</th>
<th>HDR #fxs/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosalaei</td>
<td>190</td>
<td>75-95</td>
<td>60</td>
<td>50</td>
<td>3/10</td>
</tr>
<tr>
<td>Souhami</td>
<td>193</td>
<td>84-97</td>
<td>86</td>
<td>45</td>
<td>3/8</td>
</tr>
<tr>
<td>Lorvidhaya</td>
<td>1577</td>
<td>85-91</td>
<td>96</td>
<td>46-50</td>
<td>4-6/6-7.5</td>
</tr>
<tr>
<td>Han</td>
<td>58</td>
<td>87-92</td>
<td>39.6</td>
<td>8-12/3.86</td>
<td></td>
</tr>
<tr>
<td>Ferrigno</td>
<td>138</td>
<td>92-96</td>
<td>38</td>
<td>45</td>
<td>4/6</td>
</tr>
<tr>
<td>Pötter</td>
<td>138</td>
<td>93-97</td>
<td>34</td>
<td>50</td>
<td>3-4/7</td>
</tr>
<tr>
<td>Patel</td>
<td>85</td>
<td>96-00</td>
<td>36</td>
<td>46</td>
<td>2/9</td>
</tr>
</tbody>
</table>

Int J Gyn Cancer 2006; Gynecol Oncol 2005; IJROBP 2000; Gynecol Oncol 1996; IJROBP 2001; Cancer Radioth 2000; IJROBP 2005
### HDRB: Regimens
**Stages IIB-IIIB**

<table>
<thead>
<tr>
<th>Author</th>
<th>Local Control</th>
<th>Rectal Toxicity (≥ Grade III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosalaei</td>
<td>IIB = 96%; IIIB = 87%</td>
<td>11%</td>
</tr>
<tr>
<td>Souhami</td>
<td>IIB = 80%; IIIB = 61%</td>
<td>6%</td>
</tr>
<tr>
<td>Lordidhaya</td>
<td>IIB = 80%; IIIB = 61%</td>
<td>10%</td>
</tr>
<tr>
<td>Han</td>
<td>80% (overall)</td>
<td>3.5%</td>
</tr>
<tr>
<td>Ferrigno</td>
<td>62% (overall)</td>
<td>3%</td>
</tr>
<tr>
<td>Pötter</td>
<td>IIB = 87%; IIIB = 69%</td>
<td>6%</td>
</tr>
<tr>
<td>Patel</td>
<td>IIB = 80%; IIIB = 67%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Int J Gyn Cancer 2006; Gynecol Oncol 2005; IJROBP 2000; Gynecol Oncol 1996; IJROBP 2001; Cancer Radioth 2000; IJROBP 2005
Making it really complicated

Han et al: Gynecol Oncol 1995
GOG: 45 Gy + 5fxs/6 Gy
Potter: 45 Gy + 4fxs/7 Gy
Souhami: 45 Gy + 3fxs/8 Gy
Lorvidhaya: 50 Gy + 4fxs/6 Gy

Patel: 45 Gy + 2fxs/9 Gy
Ferrigno: 45 Gy + 4fxs/6 Gy
Mosalaei: 50 Gy + 3fxs/10 Gy
Stage III B: Pelvic Control and Survival vs Point A Gy10

Peterit, Pearcey IJROBP 1999
All Complications vs Point A Gy3

Complications vs Point A

Pt A

r=-0.04

Complication Probability

BED (Gy3)

Petereit, Pearcey IJROBP 1999
Randomized Trials

1- Lertsanguansinchai et al IJROBP 2004
2- Hareyama et al Cancer 2002
3- Patel et al IJROBP 1994
Dr. S.K. Shrivastava

High Dose Rate (HDR)
&
Low Dose Rate (LDR)

Brachytherapy in Carcinoma Cervix
A Randomized Controlled Study

Trial supported by IAEA - CRP N°E33016

An Interim Analysis

Presented at ASTRO 2006
INCLUSION CRITERIA

- Carcinoma Cervix FIGO Stage I, II & III
- Histologically confirmed squamous carcinoma
- WHO Performance Index 0 and 1
- Age below 65 years
- Vaginal space adequate for intracavitary application
- Normal Hematological and Renal parameters
Ca. Cervix LDR Vs HDR
PROTOCOL

FIGO Stage I & II
Randomized

External RT
40 Gy / 20#/ 5 Wks
(MLB after 20 Gy)
+ ICA - LDR
30 Gy x 2# to point A

External RT
40 Gy / 20#/ 5 Wks
(MLB after 20 Gy)
+ ICA - HDR
7 Gy x 5# to point A

| Wk 1 | ♦ ♦ ♦ ♦ ♦ ♦ |
| Wk 2 | ♦ ♦ ♦ ♦ ♦ ♦ |
| Wk3  | ♦ ♦ ♦ ♦ ♦ ♠  |
| Wk4  | ♦ ♦ ♦ ♦ ♦ ♦   |
| Wk5  | ♦ ♦ ♦ ♦ ♠      |

| Wk 1 | ♦ ♦ ♦ ♦ ♦ ♦ ♦ |
| Wk 2 | ♦ ♦ ♦ ♦ ♦ ♦ ♠  |
| Wk3  | ♦ ♦ ♦ ♦ ♦ ♠     |
| Wk4  | ♦ ♦ ♦ ♦ ♠       |
| Wk5  | ♦ ♦ ♦ ♠         |
| Wk6  | ♠              |
Ca. Cervix LDR Vs HDR
PROTOCOL
FIGO Stage IIIb
Randomized

External RT
50 Gy / 25#/ 6 Wks
(MLB after 40 Gy)
+ ICA- LDR
30 Gy x 1# to point A

External RT
50 Gy / 25#/ 6 Wks
(MLB after 40 Gy)
+ ICA - HDR
7 Gy x 3# to point A

Wk 1 ◆◆◆◆◆◆◆
Wk 2 ◆◆◆◆◆◆◆
Wk3 ◆◆◆◆◆◆◆
Wk4 ◆◆◆◆◆◆◆
Wk5 ◆◆◆◆◆◆◆
Wk6 ◆

Wk 1 ◆◆◆◆◆◆◆
Wk 2 ◆◆◆◆◆◆◆
Wk3 ◆◆◆◆◆◆◆
Wk4 ◆◆◆◆◆◆◆
Wk5 ◆◆◆◆◆◆◆
Wk6 ◆◆◆
Ca. Cervix LDR Vs HDR

- **Patients Randomized**: 830
- **Patients suitable for Analysis**: 800

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>LDR</th>
<th>HDR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>200</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>III</td>
<td>200</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>400</td>
<td>400</td>
<td>800</td>
</tr>
</tbody>
</table>
## TREATMENT RESPONSE
(6 - 10 weeks post RT)

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>LDR (n=400)</th>
<th>HDR (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGO Stage I &amp; II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>142 (71%)</td>
<td>152 (76%)</td>
</tr>
<tr>
<td>PR</td>
<td>54 (27%)</td>
<td>44 (22%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>FIGO Stage III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>156 (78%)</td>
<td>170 (85%)</td>
</tr>
<tr>
<td>PR</td>
<td>36 (18%)</td>
<td>24 (12%)</td>
</tr>
<tr>
<td>PD</td>
<td>8 (4%)</td>
<td>6 (3%)</td>
</tr>
</tbody>
</table>
## DISEASE STATUS AT LAST FOLLOW-UP

*Follow-up: Median: 21 months (6-109)*

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>DFS_STATUS</th>
<th>LDR</th>
<th>HDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>NED</td>
<td>164 (82%)</td>
<td>166 (83%)</td>
</tr>
<tr>
<td></td>
<td>Local Recc</td>
<td>12 (06%)</td>
<td>12 (06%)</td>
</tr>
<tr>
<td></td>
<td>LR Recc</td>
<td>16 (08%)</td>
<td>06 (03%)</td>
</tr>
<tr>
<td></td>
<td>LR + Dist.Mets</td>
<td>08 (04%)</td>
<td>16 (08%)</td>
</tr>
<tr>
<td>III</td>
<td>NED</td>
<td>146 (73%)</td>
<td>150 (75%)</td>
</tr>
<tr>
<td></td>
<td>Local Recc</td>
<td>28 (14%)</td>
<td>26 (13%)</td>
</tr>
<tr>
<td></td>
<td>LR Recc</td>
<td>12 (06%)</td>
<td>08 (04%)</td>
</tr>
<tr>
<td></td>
<td>LR + Dist.Mets</td>
<td>14 (07%)</td>
<td>16 (08%)</td>
</tr>
</tbody>
</table>
Ca. Cervix LDR Vs HDR
STAGE I & II

Disease free survival

Overall survival

No difference in DFS and OAS

p = 0.33

p = 0.99
Ca. Cervix LDR Vs HDR
STAGE IIIB

DISEASE FREE SURVIVAL

OVERALL SURVIVAL

% Survival

0.0 0.2 0.4 0.6 0.8 1.0 1.2

HD LDR

p = 0.33  
p = 0.99

MONTHS

No difference in DFS and OAS
<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>LDR</th>
<th>HDR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>Rectal</td>
<td>05 (2.5%)</td>
<td>02 (1%)</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>06 (03%)</td>
<td>02 (01%)</td>
</tr>
<tr>
<td>III</td>
<td>Rectal</td>
<td>04 (2%)</td>
<td>05 (2.5%)</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>02 (01%)</td>
<td>04 (02%)</td>
</tr>
</tbody>
</table>
Authors’ conclusions
This review showed no significant differences between HDR- and LDR-ICBT when considering OS, DSS, RFS, local control rate, recurrence, metastasis and treatment related complications for women with cervical carcinoma. Due to some potential advantages of HDR-ICBT (rigid immobilization, outpatient treatment, patient convenience, accuracy of source and applicator positioning, individualized treatment) we recommend the use of HDR-ICBT for all clinical stages of cervix cancer.
What is the optimal HDRB fractionation?
Randomized Trial: 3 vs 5 Gy fractions
Nam, Ahn: J Korean Med Sci 2004

Korean study: only 56 pts studied

EBRT 45 Gy
HDRB: 3 Gy (3 times/week) X 10 vs 5 Gy (twice/week) X 5

Late toxicity: 24% (group A) vs 9% (Group B)
It must be emphasized that the dose recommendations are intended to serve only as a guide; it should be noted that these schedules have not been thoroughly tested.

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# HDR Cervix: UK

## Table 1. Ranges of results for all data given as external beam or HDR alone or combined treatment

<table>
<thead>
<tr>
<th></th>
<th>Cervix cancer post-hysterectomy</th>
<th>Cervix cancer (small volume) intact uterus</th>
<th>Cervix cancer (large volume) intact uterus</th>
<th>Corpus uterus cancer post-hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External beam dose per fraction</strong></td>
<td>1.8–2.5 Gy</td>
<td>1.78–2.25 Gy</td>
<td>1.78–2.25 Gy</td>
<td>1.8–2.5 Gy</td>
</tr>
<tr>
<td><strong>Brachytherapy total dose</strong></td>
<td>6–18 Gy in 1–4 fractions (prescribed at 0.5 cm from surface of applicator)</td>
<td>7.5–42 Gy in 1–6 fractions (prescribed at point A)</td>
<td>7.5–16 Gy in 1–2 fractions (prescribed at point A)</td>
<td>6–24 Gy in 1–4 fractions (prescribed at 0.5 cm from surface of applicator)</td>
</tr>
<tr>
<td><strong>Brachytherapy dose per fraction</strong></td>
<td>4–6 Gy</td>
<td>5.5–8.5 Gy</td>
<td>6–8 Gy</td>
<td>4–7 Gy</td>
</tr>
<tr>
<td><strong>Overall dose</strong></td>
<td>42.5–63 Gy</td>
<td>30–74 Gy</td>
<td>57.5–66 Gy</td>
<td>22–63 Gy</td>
</tr>
<tr>
<td><strong>Biological effective dose Gy$_3$</strong></td>
<td>90–124 (mean 103)</td>
<td>93–149 (mean 123)</td>
<td>110–137 (mean 124)</td>
<td>90–124 (mean 104)</td>
</tr>
<tr>
<td><strong>Biological effective dose Gy$_{10}$</strong></td>
<td>63–81 (mean 70)</td>
<td>61–96 (mean 79)</td>
<td>73–84 (mean 81)</td>
<td>63–81 (mean 70)</td>
</tr>
</tbody>
</table>

Jones et al: Br J Radiol 1999

McGill
### HDR: Australian Protocols

**Table 3.** High-dose-rate brachytherapy for the radical treatment of cervix cancer

<table>
<thead>
<tr>
<th>Centre</th>
<th>Total dose (Gy)</th>
<th>Fraction size (Gy)</th>
<th>Number of fractions per week</th>
<th>Accepted rectal dose, as % of total dose</th>
<th>Dose of external beam/fraction size</th>
<th>Prescription point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canberra</td>
<td>15.5–18</td>
<td>5.5–6</td>
<td>1–2</td>
<td>75</td>
<td>50.4/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>Royal North Shore</td>
<td>18</td>
<td>6</td>
<td>1</td>
<td>66</td>
<td>50.4/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>Repatriation</td>
<td>21</td>
<td>3–3.5</td>
<td>6 (2 per day)</td>
<td>70</td>
<td>45–50.4/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>Prince of Wales</td>
<td>Use low-dose-rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Queensland Radium Institute</td>
<td>Use low-dose-rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peter MacCallum Cancer Institute (mainly use low-dose-rate)</td>
<td>30</td>
<td>5</td>
<td>2–3</td>
<td>55 Gy</td>
<td>40–50/2</td>
<td>Point A</td>
</tr>
<tr>
<td>Alfred</td>
<td>Use pulse-dose-rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Prince Alfred</td>
<td>17–18</td>
<td>6–8.5</td>
<td>1</td>
<td>70</td>
<td>50.4/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>Liverpool</td>
<td>17–18</td>
<td>6–8.5</td>
<td>1</td>
<td>70</td>
<td>50.4/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>Launceston</td>
<td>33</td>
<td>5.5</td>
<td>1</td>
<td>70–80</td>
<td>45/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>Royal Adelaide</td>
<td>18</td>
<td>6</td>
<td>1</td>
<td></td>
<td>50.4/1.8</td>
<td>Point A</td>
</tr>
<tr>
<td>North Queensland Oncology</td>
<td>20–30</td>
<td>4–6</td>
<td>1</td>
<td>75</td>
<td>60/1.7</td>
<td>Central shield</td>
</tr>
</tbody>
</table>

MacLeod et al Austral Radiol 2001
IAEA Study - E33026
Treatment Scheme

Stage IIB-IIIB

RANDOMIZE

→ EBRT + HDRB 7 Gy/4 fxs plus CDDP weekly
→ EBRT + HDRB 7 Gy/4 fxs - no CDDP
→ EBRT + HDRB 9 Gy/2 fxs plus CDDP weekly
→ EBRT + HDRB 9 Gy/2 fxs - no CDDP

EBRT = 46 Gy/23 fxs
CDDP = 40 mg/m²
IAEA Study E33026
Rationale

- Common disease in developing countries. Locally advanced disease is norm and curative therapy is radiation-based
- No prior RCT comparing HDRB fractionations. Results with fewer fractions stimulating
- 2-fraction HDR with no-chemo would spare resources and may reduce toxicities
- Chemotherapy has yielded mixed results from RCTs. No study has compared different HDRB fractionations with chemo for any interaction effect
IAEA Study - E33026
Eligibility

- Biopsy-confirmed cervix cancer Stages IIB and IIIB
  - Biopsy can be up to 120 d prior to date of randomization
- Age > 18.0 yr and KPS > 40
  - Life expectancy (>6m) with good general condition and no contraindications (medical, psychiatric, oncological)
- Not pregnant, breast-feeding, HIV+, etc.
- Imaging (CT recommended, optional other tests)
- Investigations done < 31 d prior to date of randomization:
  - Appropriate bone marrow reserve
  - Normal renal function
  - Other blood tests (electrolytes; Calcium; LFTs)
  - Para-aortic nodes “benign”, no bilateral hydronephrosis
- Written consent and likely compliant to follow-up
Objectives

- Confirm there is no interaction between HDR fractionation and chemotherapy for survival and toxicity
- Determine efficacy and toxicity of 4x vs. 2x HDRB
  - That 4x is not clinically superior to 2x
- Determine benefit and toxicity of chemo vs. no chemo
  - Improves local control and survival without significant increase in high-grade toxicity
- Directly compare 2xHDRB no-chemo with 4xHDRB + chemo
IAEA Study - E33026

Objectives

- Detect patterns of molecular markers and determine one or more that predict for treatment success
- Determine whether E6 and E7 viral protein expressions predict for treatment resistance
- Compare staff documentation and patient self-reporting of toxicities in a subset of patients
First patient accrued in September 2005
Last patient accrued in May 2010
Expect first outcomes analysis in 2012-2013
HDRB - Recent Developments

- Potter et al. pioneered the integration of 3D imaging with 3D treatment planning using MRI.
- The Gyn GEC-ESTRO Working Group developed concepts and terms for 3D imaging and planning.

McGill
GEC-ESTRO Working Group Definitions

- GTV
  - GTV - defined by imaging plus visible and palpable disease
  - GTV_D - at time of diagnosis
  - GTV_{B1}, GTV_{B2}, GTV_{B3}… - at brachytherapy

McGill
GEC-ESTRO Working Group Definitions

- CTV - based on tumor load
- High Risk CTV - major risk for local recurrence. Includes the GTV at time of brachytherapy and the entire cervix
- Intermediate Risk CTV - major risk of recurrence (HR CTV) plus a margin (0.5 - 1.5 cm)
- Low Risk CTV - potential microscopic spread

McGill
Target volume based on cancer cell density

Haie-Meder, Potter et al. Radioth Oncol 2005
Organs at Risk - defined by MR
- Rectum
- Bladder
- ICRU points to be documented
- DVH of bladder and rectum
- To report minimum dose by maximally irradiated contiguous of organ at:
  - $1 \text{ cm}^3$, $2 \text{ cm}^3$ and $5 \text{ cm}^3$
HDRB in Cervix Cancer
Lessons Learned

- More convenient for staff and patient
  - Outpatient
  - Short administration time
- Outcomes similar to LDRB
- Cost-effective
- Fewer fractions equally effective and safe
Conclusions

- Optimal fractionation regimen not established
- Small number of fractions (<5) is well tolerated without apparent tumor control compromise
- Results comparable to HDRB using larger number of fractions
- Results comparable to LDR

McGill
Conclusions

- ICRU rectal point dose should be kept below 125 Gy
- Treatment duration should be kept short
- 3D imaging and planning replacing classical standard prescription at Point A