Analysis of Outcomes Using External Beam Radiotherapy Plus High Dose Rate Brachytherapy (4x7 Gy or 2x9 Gy) for Cervix Cancer in a Multi-institution Trial

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The IAEA is an independent intergovernmental science and technology organization within the United Nations family. Serves as the global focal point for nuclear cooperation worldwide.

**Objective:** To enhance capabilities in Member States to address needs related to the prevention, diagnosis and treatment of health problems through the development and application of nuclear and related techniques within a quality assurance framework.
Background

• 8 in 10 patients with locally advanced cervical cancer live in lower- or middle-income countries

• Radiation therapy is an essential component of management of cervical cancer

• Prospective, multicenter, international randomized trial to confirm the effectiveness of high-dose brachytherapy, or internal radiation therapy, for managing locally advanced cervical cancer
Trial Design

- Histologically confirmed cervix cancer
- FIGO stage IIB or IIIB
- Age over 18 years
- ECOG 0-2 or Karnofsky status ≥ 50
- No contraindications for chemotherapy
- Adequate bone marrow/renal function
- Electrolytes within normal limits
- Expected good compliance for FU
- Written informed consent

**Arm1:** [EBRT 2Gy x 23fx] + [HDR 7Gy x 4fx]
**Arm2:** [Arm 1] + [CDDP day 1 of each EBRT w]
**Arm3:** [EBRT 2Gy x 23fx] + [HDR 9Gy x 2fx]
**Arm4:** [Arm 3] + [CDDP day 1 of each EBRT w]

**EBRT (all arms):**
- 2D planning
- AP-PA or 4-field technique
- Prescription at midplane or isocenter

**HDR Brachytherapy:**
- 2D planning
- Arms 1 and 2: 7Gy at point A x 4fx
- Arms 3 and 4: 9Gy at point A x 2fx

**Chemotherapy (arms 2 and 4):**
- CDDP 40mg/m² up to maximum of 80mg
- Day 1 of each week during EBRT
Recruiting center
Administration
Data management

<table>
<thead>
<tr>
<th>CENTER</th>
<th>TOTAL CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumbai (India)</td>
<td>257</td>
</tr>
<tr>
<td>Lima (Perú)</td>
<td>147</td>
</tr>
<tr>
<td>Cape Town (South Africa)</td>
<td>76</td>
</tr>
<tr>
<td>Porto Alegre (Brazil)</td>
<td>53</td>
</tr>
<tr>
<td>Bahawalpur (Pakistan)</td>
<td>32</td>
</tr>
<tr>
<td>Rabat (Morocco)</td>
<td>19</td>
</tr>
<tr>
<td>FYRM (Skopje)</td>
<td>18</td>
</tr>
</tbody>
</table>
# Five-Year Results by Treatment Arm

<table>
<thead>
<tr>
<th>Study arm</th>
<th>OS %, (95% CI)</th>
<th>CSS %, (95% CI)</th>
<th>LRF %, (95% CI)</th>
<th>Grade ≥ 3 AE %, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm1 7Gy x 4 fx</td>
<td>62 (53-70)</td>
<td>70 (61-78)</td>
<td>19 (13-27)</td>
<td>16 (9-29)</td>
</tr>
<tr>
<td>Arm2 [Arm1] + CDDP</td>
<td>73 (64-80)</td>
<td>81 (72-87)</td>
<td>13 (8-21)</td>
<td>14 (8-24)</td>
</tr>
<tr>
<td>Arm3 9Gy x 2 fx</td>
<td>68 (59-76)</td>
<td>74 (65-81)</td>
<td>26 (19-34)</td>
<td>5 (2-10)</td>
</tr>
<tr>
<td>Arm4 [Arm3] + CDDP</td>
<td>65 (56-73)</td>
<td>71 (63-78)</td>
<td>29 (22-38)</td>
<td>8 (4-14)</td>
</tr>
<tr>
<td>Number of events</td>
<td>177 deaths</td>
<td>136 deaths</td>
<td>121 failures</td>
<td>44 with AE</td>
</tr>
<tr>
<td>2-tailed p-value log-rank 4-arms</td>
<td>0.18</td>
<td>0.17</td>
<td>0.004</td>
<td>0.56</td>
</tr>
<tr>
<td>2-tailed p-value log-rank 2-groups (†)</td>
<td>HDR = 0.6 Chemo = 0.2</td>
<td>HDR = 0.4 Chemo = 0.2</td>
<td>*HDR = 0.0008 **Chemo = 0.6</td>
<td>**HDR = 0.3 **Chemo = 0.5</td>
</tr>
</tbody>
</table>

OS: overall survival; CSS: cause specific survival; LRF: loco regional failure; AE: pelvic adverse effects gastrointestinal, genitourinary or gynaecological

(‡) HDR: [Arm1+Arm2] vs. [Arm3+Arm4]; Chemo: [Arm2+Arm4] vs. [Arm1+Arm3]

(†) Median follow-up 4y; maximum follow-up 7y

* 78 v 43 events ** 62 v 59 events

*HDR = 0.0008 **Chemo = 0.6

**HDR = 0.3 **Chemo = 0.5

25 v 19 events
LOCO-REGIONAL FAILURE

SITE of 181 FAILURES

Sub-group analysis (dose-effect)

<table>
<thead>
<tr>
<th></th>
<th>LRC (%)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm1+Arm2 (7Gy x 4fx)</td>
<td>88</td>
<td>84-92</td>
</tr>
<tr>
<td>Arm3+Arm4 (9Gy x 2fx)</td>
<td>77</td>
<td>72-82</td>
</tr>
<tr>
<td>p value</td>
<td>0.0008</td>
<td>0</td>
</tr>
</tbody>
</table>

LOCAL

Median time to LRF = 0.97 y (n = 121)

4-arm log-rank p=0.004
Chemo vs. no-chemo p=0.66
4HDR vs. 2 HDR p=0.0008

REGIONAL

Median time to DF = 1.65 y (n = 119)

4-arm log-rank p=0.31
Chemo vs. no-chemo p=0.068
4HDR vs. 2 HDR p=0.88

DISTANT

Median time to DF = 1.65 y (n = 119)

4-arm log-rank p=0.31
Chemo vs. no-chemo p=0.068
4HDR vs. 2 HDR p=0.88
Trial Results by Treatment Arm

**ALL CAUSE MORTALITY**

- Graph showing proportion with event over time from randomization (years) for different treatment arms: 4 hr, 2 hr, 4 hr + chemo, 2 hr + chemo.
- Intention-to-treat 4-arm log-rank p-value: 0.18.

**CAUSE-SPECIFIC MORTALITY**

- Graph showing proportion with event over time from randomization (years) for different treatment arms: 4 hr, 2 hr, 4 hr + chemo, 2 hr + chemo.
- Intention-to-treat 4-arm log-rank p-value: 0.17.
Conclusions

• A dose-effect relationship is implied by a 11% reduction in local failure (4x7 superior to 2x9 HDR).

• However, no statistical difference in overall survival or cause-specific survival.

• Also no statistical difference in grades 3-5 GI, GU and GYN chronic side-effects attributable to treatments occurring in the absence of relapse (local, nodal or distant).

• Not enough statistical power to detect significant effect of CDDP among arms.

• If resources are severely limited and 2x9 Gy is used, a small decrease in local control can be expected.