CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

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P.G.I.M.E.R., CHANDIGARH
Why is there a need for chemo-radiation in carcinoma cervix?
<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence</th>
<th>5 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
<td>5.0</td>
<td>85%</td>
</tr>
<tr>
<td>IIA</td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>IIB</td>
<td>25.0</td>
<td>65%</td>
</tr>
<tr>
<td>III</td>
<td>68.0</td>
<td>38%</td>
</tr>
<tr>
<td>IVA</td>
<td>2.0</td>
<td>00%</td>
</tr>
</tbody>
</table>

Mallinckrodt Institute of Radiology, 1959-89.
# Failure Rate Following Radical Radiation in Carcinoma Cervix

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pelvic Failure</th>
<th>Distant mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>IIA</td>
<td>17%</td>
<td>30%</td>
</tr>
<tr>
<td>IIB</td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td>III</td>
<td>42%</td>
<td>45%</td>
</tr>
<tr>
<td>IVA</td>
<td>74%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Mallinckrodt Institute of Radiology, 1959-89.
<table>
<thead>
<tr>
<th>Tumour Size</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 cm</td>
<td>95%</td>
</tr>
<tr>
<td>3-5 cm</td>
<td>75%</td>
</tr>
<tr>
<td>≥ 5 cm</td>
<td>65%</td>
</tr>
</tbody>
</table>

Perez, 1992
CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

1. Radiation therapy is treatment of choice for all stages of carcinoma cervix except those few stage-I and IIA where surgery is also equally effective.

2. The pelvic local control decreases with advancing stage.

3. Local control is also related to size of local growth at cervix.

4. The survival also decreases with the stage in spite of radical radiation therapy.
Therefore, there is need to use some additional modality of treatment with radiation to improve results of locally advanced carcinoma cervix.
METHODS TO IMPROVE RESULTS OF RADIOTHERAPY

1. Altered fractionations.
2. High LET radiation.
3. Electron affinic hypoxic cell sensitizers.
4. Hyperbaric oxygen.
5. Hyperthermia.
CHEMO-RADIATION IN CARCINOMA CERVIX

Need is:-

To improve local pelvic control of disease.
To control distant metastatic failures.
To improve survival rate, if above two can be achieved.

Sequence of chemo-radiation:-
Sequential
Neo-Adjuvant
Concurrent
Neo-adjuvant chemotherapy in carcinoma cervix
Concurrent chemoradiation in carcinoma cervix
CONCLUSIONS:-

1. 18 trials, having 2074 patients, have been published on neo-adjuvant CT.

2. No evidence of any benefit with neoadjuvant chemotherapy

3. Cycles > 14 days & less dose intensive are detrimental

4. Tumor cells may be less sensitive to chemotherapy & conventional radiotherapy due to changed tumor kinetics

5. Therefore, neo-adjuvant chemo-radiation has no role in the treatment of carcinoma cervix.
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1. Additive effects:
   - Increased killing of cells.

2. Synergistic effects:
   - Inhibition of repair of radiation induced damage.
   - Promoting the synchronization of cells into a radio-sensitive phase of the cell cycle.
   - Initiating proliferation in non-proliferating cells.
   - Reducing fraction of hypoxic cells.

3. Independent effect:
   - Chemotherapy may independently increase the rate of death of tumour cells.
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1996 – NIH Consensus Statement on Cervical Cancer

concluded that there was no evidence that any concomitant chemotherapy agent should be routinely combined with irradiation as standard clinical practice for women with locally advanced cervical cancer (FIGO stages IIB-IVA)
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1999 – NCI issued a rare clinical alert

Results were based on five phase III randomized trials.

“strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation in women who require radiation therapy for treatment of cervical cancer.”
## CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

<table>
<thead>
<tr>
<th>Study</th>
<th>FIGO Stage</th>
<th>Treatment Gr.</th>
<th>Control Gr.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulky stage IB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keys</td>
<td>Bulky IB</td>
<td>XRT+CP+Hyst</td>
<td>XRT+Hyst</td>
</tr>
<tr>
<td>GOG-123</td>
<td>-ve pelvic &amp; PA</td>
<td>OS - 83%</td>
<td>OS – 74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Suboptimal RT dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Trial for pre op regimen IB only</td>
<td></td>
</tr>
<tr>
<td><strong>Post-op. high risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peters</td>
<td>IA2-IIA</td>
<td>Hyst+lymad</td>
<td>Hyst+lymad</td>
</tr>
<tr>
<td>SWOG 8797</td>
<td>-ve PA</td>
<td>+XRT+CP+FU</td>
<td>+ XRT</td>
</tr>
<tr>
<td></td>
<td>+ pel,par,margin</td>
<td>OS – 80%</td>
<td>OS – 63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Post op RT, no brachy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Early stage</td>
<td></td>
</tr>
</tbody>
</table>
## CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

<table>
<thead>
<tr>
<th>Study</th>
<th>FIGO Stage</th>
<th>Treatment Gr.</th>
<th>Control Gr.</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Locally advanced - Radiotherapy + HU as a control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whitney</td>
<td>IIB-IVA</td>
<td>XRT+CP+FU</td>
<td>XRT+HU</td>
<td>1. Comparison of two CTRT regimens</td>
</tr>
<tr>
<td>GOG-85</td>
<td>-ve PA</td>
<td>OS – 55%</td>
<td>OS – 43%</td>
<td>2. No RT alone arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Protracted RT (median duration 63 days)</td>
</tr>
<tr>
<td>Rose</td>
<td>IIB-IVA</td>
<td>XRT+CP; XRT+CP+HU+FU; XRT+HU</td>
<td>PFS – 67% PFS – 64% PFS – 47%</td>
<td>1. No RT alone arm</td>
</tr>
<tr>
<td>GOG-120</td>
<td>-ve PA</td>
<td>PFS – 67%</td>
<td>PFS – 64%</td>
<td>2. Comparison of 3 CTRT regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Low total RT dose &amp; protracted treatment time</td>
</tr>
</tbody>
</table>
## Chemo-Radiotherapy in Carcinoma Cervix

<table>
<thead>
<tr>
<th>Study</th>
<th>FIGO Stage</th>
<th>Treatment Gr.</th>
<th>Control Gr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris</td>
<td>IIB-IVA -vePA</td>
<td>XRT+CP+FU</td>
<td>XRT-PA field</td>
</tr>
<tr>
<td>RTOG90-01</td>
<td>IA,B &gt;5cm</td>
<td>OS – 73%</td>
<td>OS – 58%</td>
</tr>
</tbody>
</table>

Locally advanced-Radiotherapy as a control

- +ve pelvic nodes
  1. RT optimal, 89Gy to pt A, 58 days
  2. Survival benefit in IB-IIB, not in adv stage
  3. control arm had PA field
CHEMO-RADIO THERAPY IN CARCINOMA CERVIX

NCIC Trial: 6th RCT
Median follow-up: 82 months

Stage IB2 and IIA (5 cm in diameter), IIB, IIIB, IIIA, and IVA
(< 5 cm if LN + ve)

<table>
<thead>
<tr>
<th>Randomization</th>
<th>CT+RT (CDDP)</th>
<th>RT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS 3 yrs</td>
<td>69%</td>
<td>66%</td>
</tr>
<tr>
<td>5 yrs</td>
<td>62%</td>
<td>58%</td>
</tr>
<tr>
<td>HR</td>
<td>1.13 (95% CI 0.77 to 1.67)</td>
<td>P=0.42</td>
</tr>
</tbody>
</table>

Conclusions:
The best results are certainly achieved by careful attention to RT details, including dose and overall delivery time, the use of ICBT whenever possible, and probably the addition of concurrent CDDP CRT

Approximately 53% of patients on the CRT regimen had decreases in their hemoglobin levels of 9 g/L or more.

Pearcey et al JCO 2002
CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

Reduction in the risk (1 - relative risk) of death from six chemo-radiation clinical trials in cervix cancer

- Collectively, the six trials continue to support improvement in local control, progression-free survival, and survival with concurrent cisplatin-based CRT.
- Although the NCIC study alone fails to demonstrate significant differences in progression-free and overall survival, all outcomes slightly favored cisplatin CRT.

CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

Cochrane Collaborative group
Meta-analysis – Green et all

19 (17+2)  4580  2001  \textit{Lancet} 358;781 (Sept. 2001)

Review strongly suggests that CH-RT improves
OS with absolute benefit of 12% (10%) &
PFS with absolute benefit of 16% (13%).
There was statistical heterogeneity for these outcomes.

Effect was greater in trials including a high proportion of Stage I&II patients.

Acute hematological & gastrointestinal toxicity was significantly greater in CH-RT group.

Late effects not well reported, hence impact on CH-RT on these effects could not be determined adequately.
CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

Meta-analysis – Lukka et all
Role of concurrent Cisplatin plus radiotherapy

9 trials (-1) 6 trials for locally advanced
2 trials for early stage.

RR of death=0.74; Advanced=0.78; Early=0.56

Absolute reduction in risk of death of 11%

Lukka et al, Clinical Oncology 14;203 (June 2002)
Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

From the Meta-Analysis Group, Medical Research Council Clinical Trials Unit, London, United Kingdom.

15 trials evaluated
3452 women
1138 deaths
CHEMO-RADIOThERAPY IN CARCINOMA CERVIX

- **13 trials with no adjuvant**
  - HR of 0.81 - Absolute survival benefit of 6% at 5 yrs (60-66%)

- **2 trials with CRT + adjuvant chemotherapy**
  - HR of 0.46 – Absolute survival benefit of 19% at 5 yrs (60-79%)
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

![Graph showing overall survival probability over time for different treatment groups.](image)
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

- Benefit of Chemo-RT
  - 5 yrs survival benefit of
    - 10% for Stage IB-IIA
    - 7% for Stage IIB
    - 3% for Stage III-IVA
OS at 5 yrs with any radical treatment – 56%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical RT</td>
<td>44%</td>
</tr>
<tr>
<td>Radical CRT</td>
<td>55%</td>
</tr>
<tr>
<td>Surg + post-op RT</td>
<td>71%</td>
</tr>
</tbody>
</table>

Radiotherapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>59%</td>
</tr>
<tr>
<td>IIB</td>
<td>44%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>24%</td>
</tr>
<tr>
<td>Gr 3-4 Toxicity</td>
<td>8%</td>
</tr>
</tbody>
</table>

Chemotherapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>65%</td>
</tr>
<tr>
<td>IIB</td>
<td>61%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>44%</td>
</tr>
<tr>
<td>Gr 3-4 Toxicity</td>
<td>10%</td>
</tr>
</tbody>
</table>
In the review 68% of all patients were of Stage I & II

Although an overall reduction in risk of death with CTRT was shown Gillian Thomas advised “caution in extrapolation of the results to advanced stages”

This analysis shows less benefit & more heterogeneity in studies with a high proportion of advanced stage disease than in those with a low proportion of such patients
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

- Large well conducted RCT has merit over a meta-analysis.

- Publication bias.

- Difference in stage, CT regimen & dose, RT treatment, protraction of treatment, hemoglobin levels etc.

- Investigations to assess PA nodes.
Conclusion

- Selected group of trial patients
- 70% had Stage I&II Disease
- PA Nodes negative
- Better results in early stage patients
- More early complications in CT-RT group
- Late effects??
CRITICAL REVIEW OF EVIDENCE

- Heterogenous patient data
- Suboptimal Radiotherapy Schedules Used
- Non-uniform use of CT drugs and Sequencing
- QOL issues: Unknown
- Cost effectiveness in India including developing countries? due to
  - Advance Disease at presentation
  - Poor nutritional status (anemia) & low compliance rates
  - Inadequate supportive therapy & financial constraints
- Sparse literature from developing countries
- Hence Concomitant chemo-radiation needs to be tested optimally in Indian setting
In India:

- Present in late stages.
- Compromised renal functions.
- Poor nutritional status.
- Poor patients, unable to afford costly investigations, chemotherapy & supportive care for reactions.
Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

AEEs: Arm A 71.9%, Arm B 23.9%
Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix:
A Phase III Randomized Trial (CRACx Study - NCT00193791)

Carcinoma Cervix Stage FIGO IIIB (SQ CA)
- 10% (35 to 45%) improvement in Overall Survival with CRT
- Two tailed test
- Power of detection: 80% (alpha error: 0.05)
- 10% lost to follow-up and Protocol violations

425 patients
Radical Radiotherapy (Ext RT+ICA)
50 Gy (MLB at 40) /5wks + LDR / HDR
LDR: 30Gy or HDR: 7Gy x 3#

425 patients
Concomitant chemotherapy
weekly Cisplatin (40 mg/m2 x 4 - 5 #) &
Radical Radiotherapy

Objectives:
- Overall Survival
- Disease free Survival
- Acute toxicities
- Late Toxicities

Initiated in August 2003
Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix (CRACx)

August 2003 to Dec. 2008 = 631 pts Randomized

**Accrual Details**

- Study Started: Aug. 2003
- Randomized till March 2010: 727 pts
- Audit of pts till Dec. 2008: 631 pts
- Planned Accrual Completion: Dec 2010

**Acute Toxicities**

<table>
<thead>
<tr>
<th></th>
<th>RT Alone 316 pts</th>
<th>CT + RT* 315 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Gr II</td>
<td>88 (28%)</td>
<td>102 (32%)</td>
</tr>
<tr>
<td></td>
<td>Gr III</td>
<td>44 (14%)</td>
</tr>
<tr>
<td>GU Gr II</td>
<td>19 (6%)</td>
<td>30 (10%)</td>
</tr>
<tr>
<td></td>
<td>Gr III</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Anemia Gr II</td>
<td>68 (21.5%)</td>
<td>110 (40%)</td>
</tr>
<tr>
<td></td>
<td>Gr III</td>
<td>11 (1.9%)</td>
</tr>
<tr>
<td>Neutropenia Gr II</td>
<td>02 (0.5%)</td>
<td>39 (12.8%)</td>
</tr>
<tr>
<td></td>
<td>Gr III</td>
<td>03 (1%)</td>
</tr>
<tr>
<td>Thrombocytopenia Gr II</td>
<td>-</td>
<td>23 (7.6%)</td>
</tr>
<tr>
<td></td>
<td>Gr III</td>
<td>07 (2.4%)</td>
</tr>
</tbody>
</table>

* 2 pts dyselectrolytemia and death
* 2 pts Gr IV Oto-toxicity (Irreversible)

**Concomitant Cisplatin CT Compliance**

<table>
<thead>
<tr>
<th>No of Cycles</th>
<th>No of pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 6#</td>
<td>217 (68.8%)</td>
</tr>
<tr>
<td>4#</td>
<td>45 (14.2%)</td>
</tr>
<tr>
<td>3#</td>
<td>18 (5.5%)</td>
</tr>
<tr>
<td>&lt;2#</td>
<td>33 (10.5%) (1pt had single kidney)</td>
</tr>
</tbody>
</table>
Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix (CRACx)

August 2003 to Dec. 2008 = 631 pts Randomized

Follow-up: Median: 36 months (mean: 39 range: 12 - 76)

<table>
<thead>
<tr>
<th></th>
<th>RT ALONE (316 pts)</th>
<th>CT + RT (315 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NED</td>
<td>187</td>
<td>205</td>
</tr>
<tr>
<td>Recurrences</td>
<td>129</td>
<td>110</td>
</tr>
<tr>
<td>Loco - regional Recurrence</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>LR - Distant</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Died due to Disease</td>
<td>126</td>
<td>105</td>
</tr>
<tr>
<td>Died due to Rx Complications</td>
<td>01 (Unknown)</td>
<td>02</td>
</tr>
<tr>
<td>Died of other causes / UK</td>
<td>12</td>
<td>08</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>Late sequelae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal Gr 2</td>
<td>10 (2%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>Rectal Gr 3</td>
<td>8 (1.5%)</td>
<td>4 (0.8%)</td>
</tr>
</tbody>
</table>

- Acute Haematological and GI toxicities: Higher with concomitant CRT
- Disease outcome and late Sequelae: Comparable so far
- Completion of accrual and final outcome analysis: Awaited
Conclusion

- Use CT-RT judiciously in Indian population:
  - 70% advanced stage
  - 12% hydronephrosis
  - Increased toxicity – prolong treatment
  - Aim for good quality radiotherapy planning & brachytherapy.
Thank you