Chemo-Radiation in Advanced Stage Carcinoma Cervix

- Cochrane Review: Green et al, *The Lancet* 01
- Canadian Meta-analysis: Lukka et al, *Clin Oncol* 02

- Green Meta-analysis Update, *Cochrane Database Syst Rev*’05
- Lukka Meta-analysis, *Clin Oncol*’02
- Green Meta-analysis, *The Lancet*’01
- Pearcey, *Proc ASCO*’00 [abst]
- NCI Clinical Announcement’ 1999
- Tseng, Rose, Keys, Morris, Peters, Whitney
- Wong, *Gynecol Oncol*’89
## Critical Review of 5 trials

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>ARMS</th>
<th>RESULTS</th>
<th>COMMENTS</th>
<th>CRITICISMS</th>
</tr>
</thead>
</table>
| Whitney et al. 1999 (GOG-85) IIB-III B | RT+Cisplatin / 5FU Vs. RT+HU | OS-55%  Vs. 43% | Better PFS and OS than HU with manageable toxicity | 1. Comparison of two CTRT regimens  
2. No RT alone arm  
3. Sub optimal (81Gy to pt A)  
4. protracted RT (median duration 63 days) |
| Morris et al. 1999 (RTOG 9001) IB-IVA | RT+Cisplatin Vs. 5FU + RT | OS-73%  Vs. 58% | CT had a survival advantage with decrease in both LR and distant failure | 1. RT optimal, 89Gy to pt A, 58 days  
2. Survival benefit in IB-IIB, not in adv stage |
| Keys et al. 1999 (GOG-123) Bulky IB | RT+Cisplatin+ SX Vs. RT+ SX | OS-83%  Vs. 74% | Significant differences in PFS and OS favoring CTRT | 1. Suboptimal RT dose  
2. Trial for pre op regimen IB only |
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Peters et al. 2000</td>
<td>SX+RT+Cisplatin/ 5FU Vs. SX+RT</td>
<td>OS-80% Vs. 63%</td>
<td>Survival favored the chemoradiotherapy arm</td>
<td>1. Post op RT, no brachy</td>
</tr>
<tr>
<td>IIA2-IIA</td>
<td></td>
<td></td>
<td></td>
<td>2. Early stage</td>
</tr>
<tr>
<td>Rose et al. 1999</td>
<td>RT+Cisplatin Vs. RT+Cisplatin/ 5FU/HU Vs. RT+HU</td>
<td>PFS- 67% Vs. 64% Vs. 47%</td>
<td>Superiority of concomitant CTRT regimen with cis alone was less toxic than 3 drug regimen</td>
<td>1. No RT alone arm</td>
</tr>
<tr>
<td>(GOG 120) IIB-III-IV A</td>
<td></td>
<td></td>
<td></td>
<td>2. Comparison of 3 ctrl regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Low total RT dose &amp; protracted Rx time</td>
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</table>
CONCURRENT CHEMORADIATION FOR CERVICAL CANCER

in February 1999

“Five major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery”
Cochrane Collaborative Group (19 Trials)

Meta-analysis

Green JA et al Lancet 358;781 (Sept. 2001)

- 19 RCTs between 1981 and 2000: 4580 pts
- Increase in OAS by 12% & RFS by 16% (absolute benefit) (p=0.0001)
- Greater benefit in patients in stages IB2 and IIB
- Decrease in local and systemic recurrence (p=0.0001)

- Update in July 2005: 21 trials and 4921 pts
- Similar findings (absolute benefit: 10%)
- Test for Heterogeneity: Positive
- No data on late toxicities

Cisplatin based Concomitant Chemo-radiation

Significant improvement in Overall Survival
- Advanced Stages (Only 30% tumors)
- Bulky IB tumors (prior to surgery)
- High risk early disease (post-surgery)

Toxicities
Acute Grade 3/4 Hematological and G.I significantly higher : all short lived
2 deaths due to the toxicities
No significant late toxicities seen

Lukka et al, Clinical Oncology 14;203(June 2002)
Critical Review of Trials
Chemo-radiation in Carcinoma Cervix

- Heterogenous patient data
- Suboptimal Radiotherapy Schedules Used
- Non-uniform use of CT drugs and Sequencing
- QOL issues : Unknown
- Cost effectiveness ?
- Hence Concomitant chemo-radiation needs to be tested optimally in our setting
- Sparse literature form Developing Countries
Chemo-Radiation in Advanced Stage Carcinoma Cervix (FIGO IIIB): A Phase III Randomized Trial (CRACx Trial)

HSRC / HEC Project No: 114/2003

Clinicaltrials.gov ID : NCT00193791

Protocol ID : TMH/114/2003/CRACx TRIAL

TMC Cervix Working Group
**Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial): 2003**

**Carcinoma Cervix Stage FIGO IIIB**

- 425 patients
- Radical Radiotherapy Ext RT+ICA
  - 50 Gy (MLB at 40)/5wks + LDR/HDR
  - LDR: 30Gy or HDR: 7Gyx3#
- 425 patients
- Concomitant chemotherapy
  - weekly Cisplatin and Radiotherapy

- **Hypothesis**: Improvement in OAS by 10% (35% to 45%)
- **Power of detection**: 80% (alpha error: 0.05)
- **Intent to treat basis**
- **Accrual Period**: 5-6 years
- **Interim analysis**: Twice One at 50 % and another at 75 % event rates
**Aims & Objectives**

**Primary**

1. To compare the overall and disease free survivals
2. To compare acute toxicities
3. To evaluate single agent chemotherapy ‘Cisplatin’

**Secondary**

1. To compare distant metastasis rate.
2. To compare late toxicities in both groups.
Pre-treatment Evaluation

- Pelvic Examination / EUA (sos) / Gynae Joint Clinic
- Complete Blood Profile
- Serum Biochemistry (Liver+Renal functions+ Electrolytes)
- Chest X-Ray
- USG (A + P) / CT Scan (A+P) : Optional
- ECG
- Cystoscopy: if indicated.
**Inclusion Criteria**

- Squamous carcinoma
- Performance index WHO Grade 0 or 1
- Age < 65 years
- FIGO stage III B
- Normal ECG and Cardiovascular systems
- Normal hematological parameters.
- Normal renal & liver function test.

**Exclusion Criteria**

- Co-morbid conditions like medical renal disease.
- Medical or psychological condition that would preclude Rx.
- History of previous treatment.
- Patient unreliable for treatment completion & follow-up.
**Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)**

**Treatment Protocol**

- **External RT**: Whole Pelvis with AP/PA or four field box technique
- **Dose**: 50 Gy / 25 # / 5 Weeks (40 Gy open + 10 Gy with MLB)
- **Brachytherapy**:
  - **LDR**: 30 Gy X 1 # to pt A
  - **Or**
  - **HDR**: 7 Gy X 3 # to pt A

**Chemotherapy**

Patient randomised to CT+ RT
receive Inj. Cisplatin 40 mg/m2 wkly
Evaluation of Response & Toxicity

- **Response**: WHO Criteria

- **Toxicity Scoring**
  - Acute toxicities: CTC version 2.0
  - Late toxicities: RTOG / LENT-SOMA scoring criteria.

- **Follow Up**:
  
  Clinical examination, Assessment of tumor response, late complications & relevant investigations / Rx will be done accordingly
  
  - 1st follow-up: 6 - 10 weeks
  - Subsequently every 3 - 4 mths for the first 2 years.
  - 6 monthly thereafter
Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

ACCRUAL DETAILS

- Study Started: August 2003
- Pts randomised till Nov. 2008: 627 pts
- Audit of pts till Dec. 2007: 528 pts
- Planned Accrual Completion: Dec 2009
- Interim Analysis: Jan 2010
- Final Analysis: Dec 2011
Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

AUDIT

• Audit of pts till Dec. 2007 : 528 pts
• RT Alone : 255 pts
• CT + RT : 263 pts
• Randomization : Computerized (open label)
• Analysis : ITT
<table>
<thead>
<tr>
<th>No of Cycles</th>
<th>No of pts (263 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6#</td>
<td>03</td>
</tr>
<tr>
<td>4-5#</td>
<td>226 (4#: 43 pts)</td>
</tr>
<tr>
<td>3#</td>
<td>17</td>
</tr>
<tr>
<td>2#</td>
<td>7 (1pt had single kidney)</td>
</tr>
<tr>
<td>0-1#</td>
<td>10 (Incomplete Rx)</td>
</tr>
</tbody>
</table>
**Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)**

### RESPONSE RATES (6-10 weeks Post Rx)

<table>
<thead>
<tr>
<th></th>
<th>RT Alone 255 pts</th>
<th>CT + RT 263 pts</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>229</td>
<td>227</td>
</tr>
<tr>
<td>PR</td>
<td>08</td>
<td>14</td>
</tr>
<tr>
<td>Prog. Disease</td>
<td>05</td>
<td>06</td>
</tr>
<tr>
<td>Not assessed*</td>
<td>13</td>
<td>16</td>
</tr>
</tbody>
</table>

* 6-10 weeks Post Rx not completed
ACUTE TOXICITIES

<table>
<thead>
<tr>
<th></th>
<th>RT Alone 255 pts</th>
<th>CT + RT* 263 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr II</td>
<td>68</td>
<td>78</td>
</tr>
<tr>
<td>Gr III</td>
<td>12 (4.7%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td><strong>GU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr II</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>Gr III</td>
<td>10 (4%)</td>
<td>15 (5.7%)</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr II</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Gr III</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr II</td>
<td>24</td>
<td>101</td>
</tr>
<tr>
<td>Gr III</td>
<td>5 (2%)</td>
<td>15 (5.7%)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr II</td>
<td>06</td>
<td>39</td>
</tr>
<tr>
<td>Gr III</td>
<td>02 (0.7%)</td>
<td>09 (3.5%)</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr II</td>
<td>01</td>
<td>16</td>
</tr>
<tr>
<td>Gr III</td>
<td>02 (0.7%)</td>
<td>09 (3.5%)</td>
</tr>
</tbody>
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* 1 pt Dyselectrolytemia and death & 2 pt Gr IV Oto-toxicity (Irreversible)
**Chemo-Radiation in Advanced Carcinoma Cervix (FIGO IIIB) (CRACx Trial)**

*N= 486 pts: Follow-up: Median: 24 months (3 - 48 months)*

<table>
<thead>
<tr>
<th></th>
<th><strong>RT ALONE (255 pts)</strong></th>
<th><strong>CT + RT (263 pts)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrences</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>04</td>
<td>04</td>
</tr>
<tr>
<td>Loco-regional Recurrence</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>LR + Distant Recurrence</td>
<td>07</td>
<td>04</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Died due to Rx Complications</td>
<td>01 (Unknown)</td>
<td>01</td>
</tr>
<tr>
<td>Lost to follow-up (after 1- 2 FU)</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

* Acute Gr II/III Genitourinary/hematological toxicities higher in CT+ RT arm

* Grade II / III Proctitis seen in 7 pts in each arm so far

Ongoing
Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

AUDIT SUMMARY

- Acute Grade III GI and Hematological toxicities: Higher with CT+ RT
- Recurrence event rates comparable so far
- Late toxicities yet to evaluated
- Cost benefit analysis – most critical in our setting
- Completion of accrual and outcome analysis
- Report on 1st Interim Analysis: Jan 2010
Thank You