Meta-analysis
Cervical Cancer

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Key Metaanalysis

- Early Cervix Cancer
  - Postoperative Radiation Chemoradiation
  - Postoperative adjuvant CRT + chemotherapy
- Locally Advanced Cervix cancer
  - Paraaortic lymph node dissection for nodal staging
  - Concurrent chemoradiation
  - Neoadjuvant chemotherapy
  - Adjuvant chemotherapy
  - Dose Rate for brachytherapy
- Newer Radiation Techniques

Background

- Postoperative pelvic RT improves recurrence-free survival in node-negative patients with adverse prognostic factors (Sedlis, 1999, Rotman 2006 GOG 92)
- Chemo+RT (concurrent and adjuvant) improves PFS in patients with high-risk features on histopathology (Peeters JCO 2002, GOG 109)
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### Acute Sequelae Sx+PORT Phase III RCT (without brachy)

<table>
<thead>
<tr>
<th>RCT</th>
<th>Study Design</th>
<th>GI Gr II</th>
<th>GI Gr III-IV</th>
<th>GU Gr II</th>
<th>GU Gr III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landoni</td>
<td>Sx+RT vs RT</td>
<td>26% vs. 12% (p&lt;0.0004)</td>
<td>Not Categorized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotman</td>
<td>Sx vs Sx+RT</td>
<td>NR</td>
<td>0% vs 2%</td>
<td>NR</td>
<td>1.5% vs 3%</td>
</tr>
<tr>
<td>Keys</td>
<td>Sx vs Sx+RT</td>
<td>7% vs 58% (P&lt;0.001)</td>
<td>0.4% vs 8%</td>
<td>8% vs 30% (P&lt;0.001)</td>
<td>NIL</td>
</tr>
<tr>
<td>Peters</td>
<td>Sx+RT vs CT/RT+radiotherapy</td>
<td>48.2% vs. 46%</td>
<td>5% vs. 10%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>


### Postoperative Radiation

**Int Risk Patients: Recurrence Free Survival at 5 years**

- Surgery vs Surgery+RT
  - No difference in OS
  - Cochrane, 2014

### Postoperative CRT vs RT

**Disease Progression**

- No difference in survival endpoints
- Not possible to assess by stage or chemo type

**Death from any cause**

- N=401: 4 trials, 2 for survival endpoints
Chemoradia9on for Locally Advanced Cervical Cancer (IB2-IVA)

- Concurrent chemoradia9on
  - Lukka’s MA
  - Green’s MA
  - IPD Cochrane Metaanalysis
  - Others
- Neoadjuvant chemoradia9on
  - Cochrane
- Adjuvant chemotherapy
  - Only 1 trial
  - Outback awaited

Lukka’s metaanalysis (2001)

- 8 randomized trials.
- Only trials that asked questions of CRT vs RT (+/- hydroxyurea) were considered.
- 6 trials with LACC, others post op high risk patients
Patient Characters

Results: Lukka’s Metaanalysis

- 95% CI demonstrate benefit of CRT however 99% CI straddle unity.
- 25-52% patients with locally advanced stage.
- Largest cleanest trial by Pearcey was negative

Green’s Metaanalysis (Cochrane)

- Questions addressed
  - OAS
  - PFS
  - Local and Distant Control
  - Acute and Late Toxicity
- NCI Alert based on only 5 trials
- Lukka’s metaanalysis included 8 trials
- 4580 randomized patients 19 trials
- 62-78% patients available for analysis
Ø 70% patients had stage I and II Cervix Cancer
Ø Both Platinum and Non Platinum Regimens tested
Ø 4/19 included trials had sequential chemotherapy
Ø 3/19 trials did not have optimal RT dose delivery
Ø Median follow up < 3 years for 4/19 trials
Ø Median follow up not known in 7/19 trials

Green’s Metaanalysis

Approximately 12% survival benefit (5 year OS: 40% to 52%)

PFS (-11% to +28%) Overall 13% benefit

Impact of chemoradiation in advanced stage not clear

Results

• Effect of chemoradiation much higher when trials included> 70% early stage benefit
• 5 year DFS benefit essentially in Stage IB-IIB patients
• Caution against extrapolation of results to advanced stage disease
Treatment related Toxicity

<table>
<thead>
<tr>
<th>Site of toxicity</th>
<th>Number of trials</th>
<th>Treatment (events/total)</th>
<th>Control (events/total)</th>
<th>Risk ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic</td>
<td>17/19</td>
<td>76/1255</td>
<td>76/1274</td>
<td>0.99 (0.98-1.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16/19</td>
<td>11/1215</td>
<td>11/1223</td>
<td>1.07 (0.88-1.31)</td>
<td>0.00</td>
</tr>
<tr>
<td>Neurological</td>
<td>9/19</td>
<td>9/1176</td>
<td>9/1182</td>
<td>1.14 (0.58-2.31)</td>
<td>0.82</td>
</tr>
<tr>
<td>Other specified</td>
<td>1/19</td>
<td>1/1262</td>
<td>1/1274</td>
<td>5.80 (0.56-50.70)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Acute Toxicity reported by only 8/19 trials
Late toxicity reported only by 3/19 trials
Odd's ratio 1.5-8 times for GI and Hematological Toxicity

Green, Lancet 2001

IPD Metaanalysis

Demonstrated benefit of Platinum and Non-Platinum
Also in adjuvant setting on basis of 2 small adjuvant trials
Cochrane JCO 2008 2010

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**Metaanalysis on Chemoradiation in Cervical Cancer**

<table>
<thead>
<tr>
<th>Author</th>
<th>Trials/Pts</th>
<th>PFS</th>
<th>OAS</th>
<th>Early Stage Benefit</th>
<th>Stage Wise Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green, 2001</td>
<td>19 trials, 455 pts</td>
<td>16%</td>
<td>12%</td>
<td>68% pts</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Lukka, 2002</td>
<td>8 trials, NR</td>
<td>11%</td>
<td>28%</td>
<td>Greatest in postop high risk, lowest in advanced stage</td>
<td></td>
</tr>
<tr>
<td>Cochrane, 2005</td>
<td>24 trials</td>
<td>13%</td>
<td>15%</td>
<td>70%</td>
<td>Higher benefit in early stage</td>
</tr>
<tr>
<td>CACC-MAC, 2008</td>
<td>16 trials, 481 pts</td>
<td>DFS: 8%</td>
<td>6%</td>
<td>66%</td>
<td>3% OAS benefit for advanced stage</td>
</tr>
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<td>Cochrane, 2010</td>
<td>24 trials, 421 pts</td>
<td>13%</td>
<td>15%</td>
<td>70%</td>
<td>Higher benefit in early stage</td>
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<td>16 trials, 481 pts</td>
<td>DFS: 8%</td>
<td>6%</td>
<td>66%</td>
<td>5% benefit in IIIB, 7% in IIb, 10% in IB-IA</td>
</tr>
</tbody>
</table>

*= 19% benefit in trials using concurrent CTRT and adjuvant chemotherapy

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**Cisplatin Chemoradiotherapy vs Radiotherapy in FIGO Stage IIIb Squamous Cell Carcinoma of the Uterine Cervix**

A Randomized Clinical Trial

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No Patients with HIV Included
Meta-analysis Summary

- Results of large Phase III trial yet to be included.
- Benefit from CRT with OTT < 50 days (EMBRACE Data)
- Chemo dose intensity important (> 160-200 mg/m²)
- Strategies such as chemotherapy dose intensity and 9ming (weekly vs. three weekly need to be further invesgated)

Hyperthermia in LACC
Chemoradiation+Hyperthermia
Network Meta-analysis

- 217 abstracts
- 6 RCT HTRT/CT (n=215) vs RT/CT (n=212)
- Non significant survival advantage of HTRT over RT.
- HTRT vs RT (complete response 83% vs.46%)
- HTTR best therapeutic option for OS.
- Need for prospective randomized trial.

Cochrane Metaanalysis: Hyperthermia

Local Recurrence

Overall Survival

Toxicity: Hyperthermia (C) RT
Neoadjuvant chemotherapy for LACC

Neoadjuvant Chemotherapy for LACC

<table>
<thead>
<tr>
<th>Study in inclusion</th>
<th>Neoadjuvant</th>
<th>Surgery alone</th>
<th>Total (88% CI)</th>
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<tr>
<td>Neckors 1882</td>
<td>53/56</td>
<td>17/17</td>
<td>216 (95% CI)</td>
</tr>
<tr>
<td>Yang 2002</td>
<td>33/42</td>
<td>20/20</td>
<td>53 (85% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>1300</td>
<td>120</td>
<td>1420 (88% CI)</td>
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High Heterogeneity in Included Trials, Time between chemo and Dose

Neoadjuvant chemo+Sx vs RT alone

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High Heterogeneity in Included Trials, Time between chemo and Dose

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NACT-Sx(CRTT) vs. CRT

Up to 40% utilization of CRT in NACT-Sx group either due to cross over or adjuvant RT or salvage RT

Patients those who were crossed over did worse than patients who were considered for upfront CRT

Gupta S, et al. JCO 2018
Dose Rate in Cervical Brachytherapy

Pooled Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall survival (%)</th>
<th>Disease-free survival (%)</th>
<th>Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azadi et al.</td>
<td>Stage 1: 82</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Stage 2: 82</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Stage 3: 82</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Stage 4: 76</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Trikora et al.</td>
<td>Stage 1: 88</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Stage 2: 88</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Stage 3: 88</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Stage 4: 88</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Hameed et al.</td>
<td>Stage 1: 89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Stage 2: 89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td></td>
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<td>89</td>
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</tr>
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<td></td>
<td>Stage 4: 89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Gurtug et al.</td>
<td>Stage 1: 87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Stage 2: 87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Stage 3: 87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Stage 4: 87</td>
<td>87</td>
<td>87</td>
</tr>
</tbody>
</table>

* Non-randomisation scheme used.
* Combined trend for grade 3-5 late complications, adjusted for all stages.
* Survival; Kaplan-Meier.
* 4-year results.

Meta-analysis: 1265 patients, 4 RCTs

Toxicity Results

<table>
<thead>
<tr>
<th>Grade 1 or 2 normal complication</th>
<th>Number of studies</th>
<th>Total patients</th>
<th>Patients treated</th>
<th>OR</th>
<th>CI 95%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>365</td>
<td>17136</td>
<td>16997</td>
<td>0.9</td>
<td>0.63-1.34</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Grade 3 or 4 bladder complication

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Total patients</th>
<th>Patients treated</th>
<th>OR</th>
<th>CI 95%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>365</td>
<td>17136</td>
<td>0.98</td>
<td>0.64-1.53</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Grade 3 or 4 rectal complication

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Total patients</th>
<th>Patients treated</th>
<th>OR</th>
<th>CI 95%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>780</td>
<td>12342</td>
<td>1.15</td>
<td>0.98-1.32</td>
<td>0.36</td>
</tr>
</tbody>
</table>
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Hysterectomy aoeR CRT

- RCT by French Group
- No advantage of adjuvant hysterectomy aoeR CRT.

Meta-analysis: Dosimetric Impact of IMRT

13 articles: 222 IMRT treated and 233 3DCRT treated patients included

- Rectum: One Third reduction in volumes receiving >30 Gy; p=0.002
- Small Bowel: Reduction in V40 and V45 Small Bowel by 17%; p=0.04
- No difference in Bone Marrow Doses

Phase III Randomized Controlled Trials Postoperative Gynecological IMRT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary/ Patient Populatio n</th>
<th>Endpoints</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARCER Study (NCT01279135)</td>
<td>2011 Post Op Cervix</td>
<td>Primary Endpoint Late Grade ≥ II GI Toxicity (13 GI subscales of CTCAE)</td>
<td>N= 240</td>
</tr>
<tr>
<td>ACTREC, Tata Memorial Centre, India</td>
<td>2011 Post Op Cervix</td>
<td>Primary Endpoint Late Grade ≥ II GI Toxicity (13 GI subscales of CTCAE)</td>
<td>N= 240</td>
</tr>
<tr>
<td>TIME-C (NCT01672892)</td>
<td>2012 Postop Cervix Endometri um</td>
<td>Primary Endpoint Acute (Wk5) GI Toxicity (EPIC Bowel Domain 14 functional and bother scales)</td>
<td>N= 289</td>
</tr>
<tr>
<td>NRG/RTOG1203</td>
<td>2012 Postop Cervix Endometri um</td>
<td>Primary Endpoint Acute (Wk5) GI Toxicity (EPIC Bowel Domain 14 functional and bother scales)</td>
<td>N= 289</td>
</tr>
<tr>
<td>MD Anderson Cancer Centre, USA</td>
<td>2012 Postop Cervix Endometri um</td>
<td>Primary Endpoint Acute (Wk5) GI Toxicity (EPIC Bowel Domain 14 functional and bother scales)</td>
<td>N= 289</td>
</tr>
</tbody>
</table>

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Phase III RCT of Postoperative 3DCRT Vs. IG-IMRT for reducing Late Bowel Toxicity in Cervical Cancer (PARCER): Interim Analysis

Observed Difference: 25% vs 11.4% p=0.12
Presumed Difference: 18% vs 5%

Number at Risk (Number of Events)
3DCRT (n=56) 42 (1) 28 (3) 17 (2) 8 (2) 7 (3)
IMRT (n=61) 46 (1) 29 (2) 15 (2) 3 (2) 3 (0)

Chopra, S ASTRO

Summary

- Difference in week 5 EPIC scores in IMRT cohort in endometrial cancer patients (86% RT alone)
- 14% difference in late effects (p=ns) phase III trial from India
- Further data and pooling data for clinical endpoint awaited

P-value = 0.0476

IMRT Pelvic RT
4 Field Pelvic RT

Baseline Week 3 of RT Week 5 of RT 4-6 weeks post-RT
IMRT 128 113 111 102
4 Field 148 132 130 125

Week 3 of RT  Week 5 of RT