Adjuvant therapy for Early Stage Endometrial Cancer

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Founding Member
ENGOT (European Network of Gynaecological Oncology Trials Groups)

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Board of Directors
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I have no disclosures!
“In all affairs it’s a healthy thing now and then to hang a question mark on the things you have long taken for granted.”

Bertrand Russell
author, mathematician, & philosopher (1872 – 1970), Nobel Prize Laureate
Theoretical reasons to remove lymph nodes

• To identify extent of disease spread, risk of recurrence, prognosis?

• LNE as a therapeutic intervention?

• To direct post-operative treatment?
Adjuvant EBRT / Brachytherapy

Adjuvant EBRT + Chemotherapy

Adjuvant Chemotherapy

Conclusions
### Cochrane Meta-analysis of 8 clinical trials (n = 3628)

#### Overall Survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>Total Weight</th>
<th>IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT vs no additional treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG 99 (1)</td>
<td>0.04</td>
<td>0.38</td>
<td>128</td>
<td>132</td>
<td>8.4%</td>
<td>1.04 [0.49, 2.19]</td>
</tr>
<tr>
<td>PORTEC-1</td>
<td>0.2</td>
<td>0.2</td>
<td>354</td>
<td>360</td>
<td>30.4%</td>
<td>1.22 [0.83, 1.81]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>482</td>
<td>492</td>
<td>38.8%</td>
<td></td>
<td></td>
<td>1.18 [0.83, 1.67]</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau² = 0.00;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 0.14,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>df = 1 (P = .71);</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I² = 0%</td>
<td></td>
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</tr>
</tbody>
</table>

Test for overall effect: Z = 0.93 (P = .35)

#### Locoregional Control

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Total Weight</th>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GOG 99</td>
<td>-1.77</td>
<td>0.63</td>
<td>190</td>
<td>202</td>
<td>9.3%</td>
<td>0.17 [0.05, 0.59]</td>
</tr>
<tr>
<td>PORTEC-1</td>
<td>-1.12</td>
<td>0.34</td>
<td>354</td>
<td>360</td>
<td>31.9%</td>
<td>0.33 [0.17, 0.64]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>544</td>
<td>562</td>
<td>41.2%</td>
<td></td>
<td></td>
<td>0.28 [0.16, 0.51]</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tau² = 0.00;</td>
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</tr>
<tr>
<td>Chi² = 0.82,</td>
<td></td>
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</tr>
<tr>
<td>df = 1 (P = .36);</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>I² = 0%</td>
<td></td>
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</tr>
</tbody>
</table>

Test for overall effect: Z = 4.23 (P < .0001)

### Kong et al. JNCI 2012

Favors EBRT | Favors No EBRT
---|---
0.1|0.2|0.5|1|2|3|4|5|10

Favors EBRT | Favors No EBRT
---|---
0.1|0.2|0.5|1|2|3|4|5|10

### mansoor@rh.regionh.dk
Long Term Outcomes after External Beam Radiation (EBRT) for Early Stage Endometrial Cancer: Oslo Trial – revisited!

Overall survival in patients <60 years - ITT

Overall survival <60 years of age at treatment

logrank p=0.013

Number at risk
Control 140
EBRT 155

Lindemann et al. JCO 2013

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Cochrane Meta-analysis
Toxicity & QoL

- **Acute grade 3-4 (5) toxicity**
  - 2 trials; n=1328; HR=4.68; CI=1.35-16.16
  - Fatal complications: 4

- **Late grade 3-4 toxicity**
  - 6 trials; n=3501; HR=2.58; CI=1.61-4.11

- **Deteriorated Quality of Life**
  - Urinary incontinence, diarrhea, fecal leakage limited daily activities
  - Worsen physical functioning
  - Bodily pain

Kong et al. JNCI 2012
26-30 September 2014, Madrid, Spain

Risk of Secondary Cancer

Univariate Cox regres HR: 1.99 (95% CI: 1.27-3.10)

Lindemann et al. JCO 2013
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Adjuvant EBRT / Brachytherapy

Adjuvant EBRT + Chemotherapy

Adjuvant Chemotherapy

Conclusions
## Phase III Trials of Adjuvant Radiotherapy with Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>GOG 34 Morrow et al.</th>
<th>Finnish Study Kuoppala et al.</th>
<th>GOG184 Homeslay et al.</th>
<th>NSGO9501/ILAIDE Hogberg et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population (Stage)</strong></td>
<td>1-3</td>
<td>1A-B, G3 1C-3A</td>
<td>3-4</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>181</td>
<td>157</td>
<td>586</td>
<td>534</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>RT</td>
<td>RT (split) CEP/RT/CEP/RT/CEP</td>
<td>RTAP6 RTTAP6</td>
<td>RT RT+CT</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.63*</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>HR 0.69 NS</td>
</tr>
<tr>
<td><strong>Cancer Specific Survival</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HR 0.55*</td>
</tr>
</tbody>
</table>

**Notes:**
- RT: Radiotherapy
- Doxo8: Doxorubicin 8 cycles
- CEP: Cyclophosphamide + Epirubicin + 5-Fluorouracil
- AP6: Adriamycin + Cisplatin + 5-Fluorouracil
- TAP6: Adriamycin + Cisplatin + 5-Fluorouracil
- RT+CT: Radiotherapy + Chemotherapy

**Statistical Significance:**
- *: p < 0.05

26-30 September 2014, Madrid, Spain

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NSGO EC-9501/EORTC-55991/ILIAD

RT → CT

Stage Ic-G3
II, IIIa, IIIc

RT

PFS: HR 0.63 (CI 0.44-0.89); OS: HR 0.69 (CI 0.46-1.03); CSS: HR 0.55 (CI 0.35-0.88)

Högberg et al., EJC 2010

26-30 September 2014, Madrid, Spain

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### Pelvic lymph node metastases (%)

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No invasion</td>
<td>0</td>
<td>3-4</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>0-3</td>
<td>5-10</td>
<td>7-9</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>0-11</td>
<td>17-19</td>
<td>28-34</td>
</tr>
</tbody>
</table>

*Chi et al., IJGC, 2008*  
*Creasman et al., Cancer, 1987*

LNE not performed in NSGO-EC-9501

Is the difference in survival due to effect on node-positive patients only (stage IIIc)?
Adjuvant EBRT / Brachytherapy

Adjuvant EBRT + Chemotherapy

Adjuvant Chemotherapy

Conclusions
### Phase III Trials of Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>GOG Randall et al. JCO ’06</th>
<th>Italian Study Maggi et al. BJC ’06</th>
<th>JGOG 2033 Susumtu et al. Gyn Oncol ’08</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population (Stage)</strong></td>
<td>III-IV</td>
<td>IC (26%)</td>
<td>!C (61%; 55% grade 1)</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>396</td>
<td>345</td>
<td>385</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>WART A⁶⁰ P⁵⁰ x 8</td>
<td>RT C⁶⁰⁰ A⁴⁵ P⁵⁰ x 5</td>
<td>RT C³³³ A⁴⁰ P⁵⁰ x 3</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>Significant</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>Significant</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

PFS: Progression-Free Survival  
OS: Overall Survival  
RT: Radiation Therapy  
WART: Whole Adjuvant Radiation Therapy  

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Serous and clear-cell carcinomas

GOG 122 - OS

Serous n=43 (21 %)  Clear cell n=7 (3.5 %)

Serous n=43 (21 %)

NSGO-EC9501/EORTC-55991

HR 0.94 (95 % CI 0.42-2.08) p=0.9

Serous n=74 (20 %)  Clear cell n=66 (18 %)
GOG 249: Randomized Phase III Trial of Pelvic Radiation Therapy vs. Brachytherapy followed by TC Chemotherapy in Patients with High-Intermediate Risk Stage I & II Endometrial Cancer

**Eligible:**
- Stage I* endometrioid-type endometrial carcinoma, with high-intermediate risk factors with (+) or without (-) cytology
- Stage II* endometrial carcinoma (any histology), with or without risk factors
- Stage I-II* serous or clear cell endometrial carcinoma with negative cytology, with or without other risk features

**Regimen I:**
- Pelvic Radiation Therapy (4500/25 fractions-5040 cGy/28 fractions) over 5-6 weeks
- Optional Vaginal Cuff Boost ONLY for Stage II patients and Stage I patients with papillary serous and clear cell carcinomas

**Regimen II:**
- Vaginal Cuff Brachytherapy + 3 cycles of chemotherapy* consisting of:
  - Paclitaxel 175 mg/m2 (3hr) + Carboplatin AUC 6 q 21 days

* FIGO 2009 Staging Criteria

N = 601
## GOG 249

### 5-year survival - FIGO

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ia</th>
<th>Ib</th>
<th>Ic</th>
<th>IIa</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>93</td>
<td>92</td>
<td>91</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td>G2</td>
<td>91</td>
<td>93</td>
<td>86</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>G3</td>
<td>80</td>
<td>82</td>
<td>75</td>
<td>68</td>
<td>65</td>
</tr>
</tbody>
</table>

Creasman et al., IJGO, 2007
Interpretation of a Radiotherapist

• “If a man is offered a fact which goes against his instincts, he will scrutinize it closely, and unless the evidence is overwhelming, he will refuse to believe it.

• If, on the other hand, he is offered something which affords a reason for acting in accordance to his instincts, he will accept it even on the slightest evidence. The origin of myths is explained in this way.”

Bertrand Russell
author, mathematician, & philosopher (1872 – 1970), Nobel Prize Laureate
## GOG 249

### 5-year survival - FIGO

<table>
<thead>
<tr>
<th>Stage</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>93</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Ib</td>
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<td>93</td>
<td>82</td>
</tr>
<tr>
<td>Ic</td>
<td>91</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>IIa</td>
<td>90</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>IIb</td>
<td>81</td>
<td>77</td>
<td>65</td>
</tr>
</tbody>
</table>

Creasman et al., IJGO, 2007
A phase III Trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high risk endometrial cancer.

ENGOT-EN2-DGCG / EORTC-55102

Chief Investigators: Mirza (DGCG); Amant (EORTC)

**Endometrioid:**
- Stage I - G3; II

**Non-endometrioid:**
- Stage I-II

**Chemotherapy**
Carboplatin-Paclitaxel x 6
+ Brachytherapy

**Observation**
+ Brachytherapy

n=678

Supported by

Danish Cancer Society

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Conclusions

"primum non nocere"

• No direct survival benefit of LNE

• No improvement in survival by adjuvant radiotherapy

• Improvement in survival from adjuvant concomitant chemo-radiation may come from chemo alone

• Trials are needed to establish role of adjuvant chemotherapy