Adjuvant Therapies in Endometrial Cancer

Emma Hudson
Endometrial Cancer

- Most common gynaecological cancer
- Incidence increasing in Western world
- 1-2% cancer deaths
- 75% patients postmenopausal
- 97% epithelial tumours
- 3% sarcomas
Treatment

- Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy
  - pelvic and para-aortic Lymphadenectomy
- Adjuvant Treatment
  - Radiotherapy+/- Brachytherapy
  - Chemotherapy
  - Hormonal therapy
Prognostic Factors

- **Stage**
  - IA : tumor limited to endometrium
  - IB : invasion to less than one half the myometrium
  - IC : invasion to more than one half the myometrium
  - IIA : endocervical glandular involvement only
  - IIB : cervical stromal invasion
  - IIIA: tumor invades serosa and/or adnexa, and/or positive peritoneal cytology/ascites
  - IIIB : vaginal metastases
  - IIIC : metastases of pelvic and/or para-aortic lymph nodes
  - IVA : tumor invasion of bladder and/or bowel mucosa
  - IVB : distant metastases
Prognostic Factors

- Stage
- Depth of myometrial involvement
- Grade
- Lymphovascular space invasion
- Histological subtype
  - Serous papillary
  - Clear cell
- Age
Radiotherapy - the Evidence

- Adjuvant Radiotherapy for Stage 1 Endometrial Cancer: Systematic Review and Meta-analysis
  - PORTEC 1
  - GOG
  - Aalders (1968-1974)
  - Soderini (abstract only)
  - 1770 patients

Systematic Review and Meta-analysis

- PORTEC, GOG and Soderini – surgery +/- EBRT
- Aalders – surgery + brachytherapy +/- EBRT
- All reduced locoregional recurrence rate
- No difference in distant recurrence or survival

Meta-analysis on all stage I endometrial cancer patients who had adjuvant radiotherapy versus no radiotherapy

### A

**Comparison:** Adjuvant radiotherapy for stage I endometrial cancer

**Outcome:** 01 Figure 1: All Stage I patients; External beam radiotherapy vs. No external beam radiotherapy

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>38/599</td>
<td>36/202</td>
<td>10.19 (4.02, 27.14)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>29/266</td>
<td>26/277</td>
<td>0.84 (0.57, 1.23)</td>
<td>0.09</td>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>PORTEC</td>
<td>67/374</td>
<td>54/361</td>
<td>36.20 (1.27, 1.71)</td>
<td>0.00</td>
<td>0.03</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Total (95% CI): 170, 900

Test for overall effect: Z = 0.04 (P = 0.97)

### B

**Comparison:** Adjuvant radiotherapy for stage I endometrial cancer

**Outcome:** 02 Figure 1b: Loco-regional recurrence

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>38/599</td>
<td>36/202</td>
<td>15.42 (0.95, 0.59)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>29/266</td>
<td>26/277</td>
<td>32.28 (0.28, 0.54)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>PorTEC</td>
<td>67/374</td>
<td>54/361</td>
<td>2.70 (0.18, 2.50)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Total (95% CI): 170, 900

Test for heterogeneity: CH² = 3.34, df = 3 (P = 0.12), P = 0.49%

Test for overall effect: Z = 0.34 (P = 0.001)

### C

**Comparison:** Adjuvant radiotherapy for stage I endometrial cancer

**Outcome:** 03 Figure 1c: Distant recurrence

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>40/350</td>
<td>19/208</td>
<td>20.34 (0.02, 1.93)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>29/266</td>
<td>26/277</td>
<td>3.36 (0.06, 0.54)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>PorTEC</td>
<td>67/374</td>
<td>54/361</td>
<td>34.78 (0.39, 3.91)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Total (95% CI): 170, 900

Test for heterogeneity: CH² = 3.34, df = 3 (P = 0.45), P = 0%

Test for overall effect: Z = 1.33 (P = 0.18)

### D

**Comparison:** Adjuvant radiotherapy for stage I endometrial cancer

**Outcome:** 04 Figure 1d: Endometrial carcinoma-related death

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>15/150</td>
<td>17/202</td>
<td>23.21 (0.04, 1.86)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>26/263</td>
<td>25/277</td>
<td>35.18 (0.37, 1.97)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>PORTEC</td>
<td>32/354</td>
<td>22/360</td>
<td>37.63 (0.86, 2.49)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Total (95% CI): 170, 900

Test for heterogeneity: CH² = 0.14, df = 2 (P = 0.57), P = 0%

Test for overall effect: Z = 1.21 (P = 0.23)

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Subgroup Analysis

- **Patients with 1 Risk Factor**
  - No statistically significant difference in deaths from all causes or death from endometrial cancer

- **Patients with 2 Risk Factors**
  - Trend towards reduction in both deaths from all causes and endometrial cancer-related deaths but not statistically significant
  - Small number of patients

- **Patients with No Risk Factors**
  - Statistically significant increased risk of endometrial related death (including treatment related deaths)

Subgroup analysis of patients with at least 2 high risk factors, Stage Ic and grade 3

A

Review: Adjuvant radiotherapy for stage I endometrial cancer
Comparison: 03 Figure 3: Subgroup analysis of patients with at least 2 high risk factors, Ic and grade 3
Outcome: 01 Figure 3a: Death from all causes

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalders 1980</td>
<td>8/64</td>
<td>14/51</td>
<td>33.48 [0.31, 1.43]</td>
<td>0.66</td>
<td>0.66 [0.48, 1.42]</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>GOG</td>
<td>16/62</td>
<td>22/70</td>
<td>66.52 [0.49, 1.19]</td>
<td>0.82</td>
<td>0.82 [0.48, 1.42]</td>
<td>0.00</td>
<td>0.08</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>106</td>
<td>121</td>
<td>100.00</td>
<td>0.76</td>
<td>0.76 [0.49, 1.19]</td>
<td>0.00</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Total events: 24 (Treatment), 36 (Control)
Test for heterogeneity: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)

B

Review: Adjuvant radiotherapy for stage I endometrial cancer
Comparison: 03 Figure 3: Subgroup analysis of patients with at least 2 high risk factors, Ic and grade 3
Outcome: 02 Figure 3b: Endometrial carcinoma-related deaths

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>8/62</td>
<td>14/70</td>
<td>48.14 [0.29, 1.43]</td>
<td>0.65</td>
<td>0.65 [0.29, 1.43]</td>
<td>0.00</td>
<td>0.17</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>8/44</td>
<td>14/51</td>
<td>51.86 [0.31, 1.43]</td>
<td>0.66</td>
<td>0.66 [0.31, 1.43]</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>106</td>
<td>121</td>
<td>100.00</td>
<td>0.65</td>
<td>0.65 [0.38, 1.14]</td>
<td>0.00</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Total events: 16 (Treatment), 28 (Control)
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Subgroup analysis of patients without high-risk features, i.e. patients with either stage Ia/b or grade 1/2

A
Review: Adjuvant radiotherapy for stage I endometrial cancer
Comparison: 04 Figure 4: Subgroup analysis of patients without high risk features 1a/b or grade 1/2
Outcome: 01 Figure 4a: Death from all causes

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>14/128</td>
<td>14/132</td>
<td>64.07</td>
<td>1.03</td>
<td>[0.51, 2.08]</td>
<td>0.00</td>
<td>0.15</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>9/131</td>
<td>3/126</td>
<td>35.93</td>
<td>2.89</td>
<td>[0.80, 10.42]</td>
<td>0.00</td>
<td>0.42</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>259</td>
<td>258</td>
<td>100.00</td>
<td>1.49</td>
<td>[0.56, 3.95]</td>
<td>0.00</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Total events: 23 (Treatment), 17 (Control)
Test for heterogeneity: $\chi^2 = 1.93$, df = 1 (P = 0.17), I² = 48.1%
Test for overall effect: Z = 0.81 (P = 0.42)

B
Review: Adjuvant radiotherapy for stage I endometrial cancer
Comparison: 04 Figure 4: Subgroup analysis of patients without high risk features 1a/b or grade 1/2
Outcome: 02 Figure 4b: Endometrial carcinoma-related deaths

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>O - E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG</td>
<td>7/128</td>
<td>3/132</td>
<td>48.21</td>
<td>2.41</td>
<td>[0.64, 9.10]</td>
<td>0.00</td>
<td>0.46</td>
</tr>
<tr>
<td>Aalders 1980</td>
<td>9/131</td>
<td>3/126</td>
<td>51.79</td>
<td>2.89</td>
<td>[0.80, 10.42]</td>
<td>0.00</td>
<td>0.45</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>259</td>
<td>258</td>
<td>100.00</td>
<td>2.64</td>
<td>[1.05, 6.66]</td>
<td>0.00</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Total events: 16 (Treatment), 6 (Control)
Test for heterogeneity: $\chi^2 = 0.04$, df = 1 (P = 0.85), I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)
Toxicity

- PORTEC
  - Late complications 26% vs 4%

- GOG
  - 6 cases intestinal obstruction vs 1
  - 2 radiation related deaths

Summary

- Adjuvant Pelvic External Beam Radiotherapy
  - Reduces locoregional recurrence (RR 0.28)
  - No difference in distant recurrence
  - No difference in overall survival
  - No difference in disease-specific survival

Summary

- Low Risk Early Endometrial Cancer
  - Increased risk of endometrial cancer/treatment related deaths

- High Risk Early Endometrial Cancer
  - Trend towards reduction in risk of death

External Beam Pelvic Radiotherapy should be considered in Patients with Multiple High-Risk Features but it carries an inherent risk of damage and toxicity and should be avoided in Patients with no Risk Factors.
MRC ASTEC and NCIC CTG EN.5

- 112 centres, 7 countries, 905 women
- Intermediate risk early stage disease - FIGO stage 1A -1B grade 3, 1C-2A grade 1-2
- High risk early stage disease-serous papillary and clear cell, 1C-2A grade 3, 2B
- Randomised to observation vs EBRT
- Primary outcome - overall survival

The Lancet:373;9658;137-146, 2009
MRC ASTEC and NCIC CTG EN.5

- Radiotherapy 40-46Gy in 20-25 daily fractions
- Brachytherapy- clinicians preference similar in both arms
- Patient and tumour details well matched
- Slightly more high risk women in observation group 25% vs 20%

The Lancet:373;9658;137-146, 2009
Results

- No difference in OS HR 1.05
- 5yr OS 84%
- No difference in disease specific survival 90% (observation) vs 89% (EBRT)
- No difference in disease specific recurrence-free survival 84.7% (observation) vs 85.3% (EBRT)
- Reduction in isolated pelvic/vaginal recurrence HR 0.46
- 5 year cumulative reduction 6.1% vs 2.9%

The Lancet:373;9658;137-146, 2009
Isolated Vaginal or Pelvic Initial Recurrence

HR=0.46; 95%CI=0.24-0.89; p=0.02

Lancet:373;9658;137-146
# Subgroup Analysis

## A Overall survival

<table>
<thead>
<tr>
<th>Risk group</th>
<th>EBRT</th>
<th>Observation</th>
<th>(O–E)</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk</td>
<td>44/358</td>
<td>40/335</td>
<td>3.01</td>
<td>20.25</td>
</tr>
<tr>
<td>High risk</td>
<td>22/89</td>
<td>27/113</td>
<td>0.86</td>
<td>11.99</td>
</tr>
</tbody>
</table>

**Lymphadenectomy vs no lymphadenectomy**

<table>
<thead>
<tr>
<th></th>
<th>EBRT</th>
<th>Observation</th>
<th>(O–E)</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymphadenectomy</td>
<td>48/313</td>
<td>51/326</td>
<td>1.88</td>
<td>24.08</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>19/139</td>
<td>17/127</td>
<td>-0.23</td>
<td>8.95</td>
</tr>
</tbody>
</table>

Risk group: interaction test, p=0.83

Lymphadenectomy vs no lymphadenectomy p=0.79

## B Disease specific survival

<table>
<thead>
<tr>
<th>Risk group</th>
<th>EBRT</th>
<th>Observation</th>
<th>(O–E)</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk</td>
<td>27/358</td>
<td>20/335</td>
<td>3.89</td>
<td>11.40</td>
</tr>
<tr>
<td>High risk</td>
<td>17/89</td>
<td>22/113</td>
<td>0.12</td>
<td>9.55</td>
</tr>
</tbody>
</table>

**Lymphadenectomy vs no lymphadenectomy**

<table>
<thead>
<tr>
<th></th>
<th>EBRT</th>
<th>Observation</th>
<th>(O–E)</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymphadenectomy</td>
<td>33/313</td>
<td>28/326</td>
<td>4.25</td>
<td>14.96</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>12/139</td>
<td>14/127</td>
<td>-1.89</td>
<td>6.46</td>
</tr>
</tbody>
</table>

Risk group: interaction test, p=0.45

Lymphadenectomy vs no lymphadenectomy p=0.22

Lancet:373;9658;137-146
MRC ASTEC and NCIC CTG EN.5: Toxicity

- Increased acute toxicity 27% vs 57%
- Increased severe acute toxicity <1% vs 3%
- Increased late toxicity 45% vs 61%
- Increased severe late toxicity 3% vs 7%

- No treatment related deaths
MRC ASTEC and NCIC CTG EN.5: Updated Metaanalysis

- GOG and PORTEC included
- No effect on OS HR 1.04
- Absolute benefit of >3% excluded

The Lancet:373;9658;137-146, 2009
### A Overall survival

<table>
<thead>
<tr>
<th></th>
<th>EBRT Events</th>
<th>EBRT Total</th>
<th>Observation Events</th>
<th>Observation Total</th>
<th>HR (95% CI)</th>
<th>N</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermediate risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PORTEC</td>
<td>57</td>
<td>354</td>
<td>48</td>
<td>360</td>
<td>714</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>GOG</td>
<td>14</td>
<td>128</td>
<td>14</td>
<td>132</td>
<td>260</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>ASTEC+EN.5</td>
<td>44</td>
<td>368</td>
<td>40</td>
<td>335</td>
<td>693</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>135</td>
<td>840</td>
<td>102</td>
<td>827</td>
<td>1657</td>
<td>0.58 to 1.16 (0.90 to 1.53)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: p=0.51; test for overall effect: p=0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-year rate of (EBRT-observation) = -2%, 95% CI = -6% to 1%

<table>
<thead>
<tr>
<th></th>
<th>EBRT Events</th>
<th>EBRT Total</th>
<th>Observation Events</th>
<th>Observation Total</th>
<th>HR (95% CI)</th>
<th>N</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOG</td>
<td>16</td>
<td>62</td>
<td>22</td>
<td>70</td>
<td>132</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>ASTEC+EN.5</td>
<td>22</td>
<td>89</td>
<td>27</td>
<td>113</td>
<td>202</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>38</td>
<td>151</td>
<td>49</td>
<td>183</td>
<td>334</td>
<td>0.88 (0.59 to 1.29)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: p=0.33; test for overall effect: p=0.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-year rate of (EBRT-observation) = 3%, 95% CI = -6% to 10%

<table>
<thead>
<tr>
<th></th>
<th>EBRT Events</th>
<th>EBRT Total</th>
<th>Observation Events</th>
<th>Observation Total</th>
<th>HR (95% CI)</th>
<th>N</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PORTEC</td>
<td>57</td>
<td>354</td>
<td>48</td>
<td>360</td>
<td>714</td>
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<td>190</td>
<td>36</td>
<td>202</td>
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<tr>
<td>ASTEC+EN.5</td>
<td>67</td>
<td>452</td>
<td>68</td>
<td>453</td>
<td>905</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>154</td>
<td>996</td>
<td>152</td>
<td>1015</td>
<td>2011</td>
<td>1.04 (0.84 to 1.29)</td>
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<tr>
<td>Heterogeneity: p=0.47; test for overall effect: p=0.70</td>
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5-year rate of (EBRT-observation) = -1%, 95% CI = -4% to 2.4%

### B Disease-specific survival

<table>
<thead>
<tr>
<th></th>
<th>EBRT Events</th>
<th>EBRT Total</th>
<th>Observation Events</th>
<th>Observation Total</th>
<th>HR (95% CI)</th>
<th>N</th>
<th>HR</th>
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<tbody>
<tr>
<td><strong>Intermediate risk</strong></td>
<td></td>
<td></td>
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<tr>
<td>PORTEC</td>
<td>23</td>
<td>354</td>
<td>18</td>
<td>360</td>
<td>714</td>
<td>1.22</td>
<td></td>
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<tr>
<td>GOG</td>
<td>7</td>
<td>128</td>
<td>3</td>
<td>132</td>
<td>260</td>
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<tr>
<td>ASTEC+EN.5</td>
<td>27</td>
<td>358</td>
<td>20</td>
<td>335</td>
<td>693</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>840</td>
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<td>827</td>
<td>1667</td>
<td>1.46 (0.99 to 2.17)</td>
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<td>Heterogeneity: p=0.66; test for overall effect: p=0.06</td>
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5-year rate of (EBRT-observation) = -2%, 95% CI = -6% to <1%

<table>
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<th>EBRT Events</th>
<th>EBRT Total</th>
<th>Observation Events</th>
<th>Observation Total</th>
<th>HR (95% CI)</th>
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<td><strong>High risk</strong></td>
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<td>GOG</td>
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<td><strong>Subtotal (95% CI)</strong></td>
<td>25</td>
<td>151</td>
<td>36</td>
<td>183</td>
<td>334</td>
<td>0.81 (0.50 to 1.30)</td>
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<td>Heterogeneity: p=0.29; test for overall effect: p=0.38</td>
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5-year rate of (EBRT-observation) = 3%, 95% CI = -5% to 9%

<table>
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<th>EBRT Events</th>
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<th>Observation Events</th>
<th>Observation Total</th>
<th>HR (95% CI)</th>
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<th>HR</th>
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<tbody>
<tr>
<td><strong>Overall</strong></td>
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<td>PORTEC</td>
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<td>GOG</td>
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<td>202</td>
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<td>0.93</td>
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<tr>
<td>ASTEC+EN.5</td>
<td>45</td>
<td>452</td>
<td>42</td>
<td>453</td>
<td>595</td>
<td>1.13</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>83</td>
<td>996</td>
<td>77</td>
<td>1015</td>
<td>2011</td>
<td>1.11 (0.83 to 1.50)</td>
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</table>

5-year rate of (EBRT-observation) = -1%, 95% CI = -4% to 1%
MRC ASTEC and NCIC CTG EN.5: Summary

The ASTEC/EN.5 trial has shown no evidence of a benefit for external beam radiotherapy for early endometrial cancer at intermediate or high risk of recurrence, in terms of overall, disease-specific, and disease-specific recurrence-free survival. Combining these findings with data from other trials, we can exclude even a very small benefit of radiotherapy on overall survival.

With clear evidence from ASTEC/EN.5 that adjuvant external beam radiotherapy is associated with more acute and long-term toxicity than observation with or without brachytherapy, adjuvant radiotherapy after surgery to achieve isolated local control is not justified as the treatment of choice.

The Lancet:373;9658;137-146, 2009
The high risk PORTEC group

- High risk patients excluded from randomisation
- 104 patients with stage IC, grade 3 endometrial cancer registered, received adjuvant EBRT
- Patients with Grade 3, 1C disease
  - Increased rate locoregional relapse
  - Increased rate distant metastases
  - Decreased overall survival
  - Grade 3 was the most important adverse prognostic factor for relapse and death

Creutzberg et al; J Clin Onc 2004; 22: 1234-1241
The High Risk PORTEC Group

<table>
<thead>
<tr>
<th></th>
<th>Locoregional Recurrence Rate</th>
<th>Five-year distant metastases rates</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2</td>
<td>1-3%</td>
<td>3-8%</td>
<td>83-85%</td>
</tr>
<tr>
<td>Grade 3, 1B</td>
<td>1-3%</td>
<td>20%</td>
<td>74%</td>
</tr>
<tr>
<td>Grade 3, 1C</td>
<td>14%</td>
<td>31%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Creutzberg et al; J Clin Onc 2004; 22:1234-1241
The high risk PORTEC group

CONCLUSION: Patients with stage IC, grade 3 endometrial carcinoma are at high risk of early distant spread and endometrial carcinoma-related death. Novel strategies for adjuvant therapy should be explored to improve survival for this patient group.

Creutzberg et al; J Clin Onc 2004; 22: 1234-1241
Brachytherapy

- Prospective study Piver et al.
- 3 arm: post-op EBRT, pre and post op brachytherapy
- No difference in OS
- 5 year DFS 99%- recurrences salvageable
Brachytherapy

- Portec 1 – 75% pelvic recurrence treated radically
- ASTEC
  - Higher risk group
  - Lower incidence loco-regional recurrence 6.1%
  - ? Because of brachytherapy
- Portec 2 awaited
Chemotherapy

- **GOG 34**
  - Stage 1 and 2 disease, 224 patients
  - Adjuvant RT +/- doxorubicin
  - Slow to recruit, No difference in OS or PFS

- **Italian Study**
  - Stage 1 and 2 disease, 345 patients
  - Adjuvant chemotherapy (cyclophosphamide, cisplatin and doxorubicin) vs pelvic EBRT
  - No difference in OS or PFS
Chemotherapy

- EORTC-55991
  - High risk patients, 382 patients
  - Adjuvant EBRT +/- chemotherapy (variety of regimens)
  - 27% didn’t complete chemotherapy
  - Increase 5 yr PFS 7% (72%-79%)
  - Increase in 5 yr OS of 8% (74%-82%)

Hogberg T et al; J Clin Onc 2007 25(18S)
Chemotherapy-High Risk

- Retrospective study of stage 2 papillary serous carcinoma
- 55 surgically staged patients, 10-observation, 26 EBRT alone, 19 platinum/taxane chemotherapy + EBRT
- Reduction in risk of recurrence 11% (CT+/-RT) VS 50% (RT alone) vs 50% (observation)*
- Increase PFS 86% (CT+/-RT) vs 41% (no chemo)*
- Increase OS 88% (CT+/-RT) vs 64% (no chemo)
- 70% recurrences extra pelvic and not salvageable

* Statistically significant
PFS by chemotherapy versus no chemotherapy (RT alone+OBS group), p=0.028

PFS by OBS, RT alone and CT+/−RT group, p=.081

Chemotherapy

PORTEC 3
Chemoradiotherapy with concurrent cisplatin and adjuvant carboplatin AUC 5 and paclitaxel
Hormonal Therapy

- Limited data
- Multicentre trial
- Stage 1B grade 1-2: observation vs medroxyprogesterone acetate (MPA) 100mg bd 12/12
- Stage 1C/ grade 3: EBRT +/- MPA
- Node positive pelvic/paraaortic RT +/- MPA
- No difference in DFS
What Adjuvant Therapy Should we use?

- **Low risk disease**
  - >95% survival
  - Adjuvant therapy maybe detrimental

- **Intermediate risk, 1 risk factor**
  - Decrease in local recurrence by EBRT
  - No difference on OS

- **High risk, 2 or more risk factors**
  - Decrease in local recurrence with EBRT
  - Kong et al – trend to increasing OS
  - ASTEC no benefit
  - Increase PFS and OS with combination chemotherapy
## Treatment Options

<table>
<thead>
<tr>
<th>Endometrial Carcinoma</th>
<th>Risk factors</th>
<th>Proposed Treatment</th>
</tr>
</thead>
</table>
| **Low risk**
  Stage 1-2A                                 | 1A/B grade 1-2                                    | No further treatment                                                               |
| **Intermediate risk**
  Stage 1-2A                                   | 1A/B grade 3
  1C-2A grade 1-2                               | Vaginal Vault Brachytherapy                     |
| **High risk, stage 1-2A**
  Advanced disease stage 2B-3                    | 1C grade 3
  1C LVSI
  Grade 3 LVSI
  2A grade 3
  2B-3 any grade
  1B-3 with clear cell/serous papillary         | EBRT + Vaginal Vault Brachytherapy
  Consider concurrent chemoradiation and adjuvant chemotherapy in context of PORTEC 3 |

Thank you

Questions?