Adjuvant Treatment in Endometrial Cancer: Addressing Dilemmas

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Definition

- Adjuvant treatment is defined as the treatment imparted after the main treatment

- Adjuvant Treatment: A compulsion

- Avoid if possible

- But do not hesitate, if there is a need
Why Adjuvant Treatment?

- Despite curative resection, some pts actually have remaining viable tumor cells.
- These cells, if not treated, will grow & lead to clinical recurrence later.
- Rx of clinical recurrence is mostly difficult.
- Effectiveness of adjuvant Rx like RT is inversely related to tumor burden (more effective when tumor is microscopic).
Aim of adjuvant treatment

• Reduction in the recurrence rate
• Improvement in survival
• Improved quality of life
General principles of Adjuvant Rx

- Significant risk of recurrence (>10-15%)
- Salvage probability
- Rx should be effective
- Toxicity should be within acceptable limits
- Team approach
Adjuvant RT in Endometrial cancer

• Stage I: Role of adjuvant RT is debatable
• Stage II onwards: Not controversial
• Why debatable in Stage I?
• Overtreatment (toxicity) vs under-treatment (Rec)
• Therefore adjuvant therapy should have balance between local control and associated toxicity
Adjuvant RT in Stage I: Surgeon’s Perspective

- Additional treatment will lead to higher toxicity
- Literature does not show survival gain
- Local recurrences are salvageable
- Confidence
Adjuvant RT in Stage I: Radiation Oncologist’s Perspective

- Consistent reduction in local recurrence: robust literature
- Toxicity within acceptable limits
- Local recurrences are hardly salvageable
- Comfort
Adjuvant RT Endometrial Carcinoma: other Issues

- Nature & extent of surgery
- Lymph node Sampling/dissection
- Adequacy of lymph node removal
- Appropriate no. of L nodes
- Emerging role of chemotherapy
# Current Protocol

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*Adverse risk Factors [Myoinvasion, Age >60 years, LVSI]  
** Stage IV: Palliative RT/ Chemotherapy
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CLINICAL INVESTIGATION

FIFTEEN-YEAR RADIOTHERAPY OUTCOMES OF THE RANDOMIZED PORTEC-1 TRIAL FOR ENDOMETRIAL CARCINOMA

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Carla C. Wárlám-Rodenhuis, M.D.,‡ Jan J. Jobsen, M.D., Ph.D.,§ Jan-Willem M. Mens, M.D.,¶
Ludy C. H. W. Lutgens, M.D., Ph.D.,** Elisabeth Pras, M.D., Ph.D.,††
Lonneke V. van de Poll-Franse, Ph.D.,‡‡ and Wim L. J. van Putten, M.Sc.‖

For the PORTEC Study Group
STUDY DESIGN

• Multicenter RCT involving 19 institutions of Netherlands
• 715 patients of FIGO stage I EC recruited from 1990 to 1997
• 354 patients were randomly assigned to EBRT & 361 to NAT
• 5 yr and 10 yr results published in 2000 (Lancet) and 2005 (IJROBP)
• Median FU = 13.3 years
• EBRT-46Gy/23#/4.5 weeks delivered by AP-PA parallel opposed fields (30%), 3-field (18%) or 4-field techniques (52%)
Fig. 1. Probability of locoregional (vaginal and/or pelvic) relapse for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).
FAILURE FREE SURVIVAL

Fig. 2. Probability of failure-free survival for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).
STUDY FINDINGS

• No difference in overall survival with EBRT

• Reduction in locoregional recurrence in HIR group receiving EBRT

• No significant difference in LRR in LIR group receiving adjuvant radiation
GOG 99 TRIAL

• 392 patients with stage IB, IC, or IIA, all grades (surgical LN-ve)
• TAH+BSO and selective lymph node dissection
• Adjuvant EBRT vs observation
• 2yr recurrence → 3% vs 12% in favour of EBRT (p< 0.01)

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<tr>
<th>Outcome</th>
<th>EBRT (%)</th>
<th>Observation (%)</th>
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<tr>
<td>Vag recurrence</td>
<td>1</td>
<td>6.4</td>
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<tr>
<td>Distant failure</td>
<td>5.3</td>
<td>6.4</td>
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<tr>
<td>4yr OS</td>
<td>92</td>
<td>86</td>
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<tr>
<td>2yr recurrence (HIR)</td>
<td>6</td>
<td>26</td>
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PORTEC-II TRIAL

- 427 patients of EC (age>60yrs, IBG3/ IC G1-2)
- After TAH+BSO pts randomized to VBT vs. pelvic EBRT
- Median FU ➔ 3.75 years

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<th>Outcome</th>
<th>VBT</th>
<th>EBRT</th>
<th>P value</th>
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<tbody>
<tr>
<td>5yr vaginal recurrence</td>
<td>1.8%</td>
<td>1.6%</td>
<td>0.74</td>
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<tr>
<td>5yr LRR</td>
<td>5.1%</td>
<td>2.1%</td>
<td>0.17</td>
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<tr>
<td>Isolated pelvic recurrence</td>
<td>1.5%</td>
<td>0.5%</td>
<td>0.3</td>
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<tr>
<td>Distant metastasis</td>
<td>8.3%</td>
<td>5.7%</td>
<td>0.46</td>
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<tr>
<td>5yr overall survival</td>
<td>85%</td>
<td>80%</td>
<td>0.57</td>
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<tr>
<th>Trial</th>
<th>Histology</th>
<th>Risk groups</th>
<th>Lymph node dissection</th>
<th>Study arms</th>
<th>Locoregional recurrence</th>
<th>Survival</th>
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<td>PORTEC1</td>
<td>Endometrioid</td>
<td>Intermediate risk:&lt;br&gt;Grade 1, &gt;50% myometrial invasion&lt;br&gt;Grade 2, any myometrial invasion&lt;br&gt;Grade 3, &lt;50% myometrial invasion&lt;br&gt;High-intermediate risk:&lt;br&gt;Age &lt;60 years, grade 1 or 2, &gt;50% myometrial invasion&lt;br&gt;Age &gt;60 years, grade 3, &lt;50% myometrial invasion</td>
<td>Not required</td>
<td>EBRT vs. observation</td>
<td>EBRT improved over observation at 5 years (intermediate risk: 4 vs. 14%, ( P&lt;0.001 )) [HIR = 5 vs. 18%, ( P&lt;0.001 )]</td>
<td>EBRT equivalent to observation at 5 years for overall survival (81 vs. 85%, ( P=0.31 ))</td>
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<tr>
<td>GOG-99</td>
<td>Endometrioid</td>
<td>Intermediate risk:&lt;br&gt;any grade, stage IB, IC, or occult IIA or IIB&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;High-intermediate risk:&lt;br&gt;Age &lt;60 years with three risk factors&lt;br&gt;Age 60-69 years with two risk factors&lt;br&gt;Age ≥70 with one risk factor&lt;br&gt;Risk factors: grade 2 or 3, +LVSi, outer 1/3 myometrial invasion (stage IC&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Comprehensive</td>
<td>EBRT vs. observation</td>
<td>EBRT improved over observation at 2 years (all = 3 vs. 12%, ( P&lt;0.007 )) [HIR = 6 vs. 26%, ( P&lt;0.001 )]</td>
<td>EBRT equivalent to observation at 4 years for overall survival (92 vs. 86%, ( P=0.55 ))</td>
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<td>ASTEC/EN.5</td>
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<td>EBRT vs. observation VBT allowed for both arms</td>
<td>EBRT improved over observation at 5 years for isolated vaginal recurrence (3.2 vs. 6.1%, ( P=0.02 ))</td>
<td>EBRT equivalent to observation at 5 years for overall survival (84 vs. 84%, ( P=NS ))</td>
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<td>PORTEC2</td>
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<td>Intermediate risk:&lt;br&gt;Endometrioid, stage IA or IIB&lt;sup&gt;a&lt;/sup&gt;, grade 3&lt;br&gt;Endometrioid, stage IC or IIA&lt;sup&gt;a&lt;/sup&gt;, grade 1 or 2</td>
<td>Not required</td>
<td>EBRT vs. VBT</td>
<td>EBRT equivalent to VBT at 5 years for isolated vaginal recurrence (1.6 vs. 1.8%, ( P=0.74 )) and all locoregional recurrences (2.1 vs. 5.1%, ( P=0.17 ))</td>
<td>EBRT equivalent to VBT at 5 years for overall survival (79.6 vs. 84.8%, ( P=0.57 ))</td>
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Radiotherapy options

- Intra-vaginal Brachytherapy: IVBT alone
- Pelvic EBRT +/- IVBT
- Extended field RT: Pelvis + PA nodes
- Whole abdominal RT: WART
- Interstitial Brachytherapy
- IMRT, IGRT
Dose Practices

**Brachytherapy alone**
- **HDR**
  - 7 Gy (at 0.5 cm from surface of applicator) × 3 sessions, each 1 week apart.

**Brachytherapy in Combination with EBRT**
- **HDR**
  - 6 Gy (at 0.5 cm from surface of applicator) × 2 sessions 1 week apart

**EBRT doses**
- 45 Gray in 25# over 5 weeks (stage I)
- 50.4 Gray in 28# over 5.5 weeks (stage II-III)

**Chemotherapy (Stage III)**
- Sandwich/Sequential 6 cycles of chemotherapy (Paclitaxel/Carboplatin)
IVBT alone

- Vagina is a potential site of recurrence
- Pelvic node rec. is negligible
- About 10-15% risk (Intermediate risk group)
- Common site of recurrence in both trials
- Pelvic RT may be effective but sign. toxicity
- Vaginal RT alone may be of same efficacy, more convenient, less toxic
- Various trials have shown the risk reduction from 12-15% to <5%
Four Field
Dose Practices

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