Outline

- Epidemiology
- Staging/Evaluation
- Prognostic Factors
  - Clinicopathologic
  - Molecular
- Clinical Trials
  - PORTEC 1
  - GOG 99
  - PORTEC 2
  - GOG 249
Epidemiology

- 2018, 65,950 new cases of uterine cancer, 4th
  - 12,550 deaths
  - 1% increase/year, non-endometrioid

Pathology
- Endometrioid carcinoma: adenocarcinoma and adenocarcinoma-variants (with squamous differentiation; secretory variant; villoglandular variant; and ciliated cell variant)
  - Mucinous adenocarcinoma
  - Serous adenocarcinoma
  - Clear cell adenocarcinoma
  - Undifferentiated carcinoma
  - Neuroendocrinetumors
  - Mixed carcinoma (carcinoma composed of more than one type, with at least 10% of each component)
  - Carcinosarcoma
Racial Disparity

• Among black women, high incidence of non-endometrioid histologies
  – Poorer survival

• Compared to white patients, black patients are less likely to receive:
  – Hysterectomy
  – Chemotherapy
  – Radiotherapy
Genetics

• Germline Mutations
  – Lynch Syndrome: mutation in mismatch repair genes
    • 3% of endometrial cancers are related to Lynch Syndrome
    • Lifetime risk of endometrial cancers by age 70 years
      – 46-54% for MLH1 mutations
      – 21-51% for MSH2 mutations
      – 16-49% for MSH6 mutations
      – 13-24% for PMS2 mutations
  – Cowden Syndrome: breast, thyroid and endometrial cancer
    • PTEN mutation
    • 28% lifetime risk of endometrial cancer
# Staging

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tumor confined to the corpus uteri</td>
</tr>
<tr>
<td>IA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>II&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tumor invades cervical stroma, but does not extend beyond the uterus&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>III&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Local and/or regional spread of the tumor</td>
</tr>
<tr>
<td>IIIA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tumor invades the serosa of the corpus uteri and/or adnexae&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Vaginal involvement and/or parametrial involvement&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Metastases to pelvic and/or para-aortic lymph nodes&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>IIIC1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Positive pelvic nodes</td>
</tr>
<tr>
<td>IIIC2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Positive para-aortic nodes with or without positive pelvic lymph nodes</td>
</tr>
<tr>
<td>IV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tumor invades bladder and/or bowel mucosa, and/or distant metastases</td>
</tr>
<tr>
<td>IVA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tumor invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Distant metastasis, including intra-abdominal metastases and/or inguinal nodes</td>
</tr>
</tbody>
</table>
Traditional Classification

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Grade</td>
<td>1-2</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Atypical Hyperplasia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Early Stage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Non-endometrioid</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Prognostic Factors

### Clinical Factors
- Grade
- Pathologic subtype
- Age
- Lymphovascular space invasion
- Depth of myometrial invasion
- Stage
- Size
- Microcystic elongated and fragmented pattern (MELF)

### Molecular Factors
- TP53 mutation
- P13/AKT/mTOR pathway defects
- L1CAM Expression
- HER2 mutation
- Loss of function PTEN
- MSI
- KRAS mutation
## Risk Stratification: GOG

### Clinicopathologic Risk Factors

**GOG 99 HIR**
- > 70 years old with one factor
  - Grade 2-3
  - Outer 1/3 MI
  - LVSI
- ≥ 50 years old with two risk factors
- Any age with three risk factors

**GOG 249 HIR**
- > 70 years old with one factor
  - Grade 2-3
  - Outer ½ MI
  - LVSI
- ≥ 50 years old with two risk factors
- Any age with three risk factors
- Stage II endometrioid carcinoma
Risk Stratification: NCCN

Clinicopathologic Risk Factors

- Risk Factors
  - Age $\geq 60$
  - Depth of invasion
  - LVSI
- Consider vaginal brachytherapy if 1 factor present, strongly consider if two risk factors present

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Histologic Grade</th>
<th>Adjuvant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>G1, G2</td>
<td>Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age $\geq 60$ y</td>
</tr>
<tr>
<td>G3</td>
<td>Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age $\geq 70$ y or LVSI (category 2B)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>G1</td>
<td>Vaginal brachytherapy preferred or Consider observation if age $&lt;60$ y and no LVSI</td>
</tr>
<tr>
<td>G2</td>
<td>Vaginal brachytherapy preferred or Consider EBRT if $\geq 60$ y and/or LVSI or Consider observation if age $&lt;60$ y and no LVSI</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>RT (EBRT and/or vaginal brachytherapy) $\pm$ systemic therapy (category 2B for systemic therapy)</td>
<td></td>
</tr>
</tbody>
</table>
LVSI in PORTEC 1 and 2

- N=954, three-tiered scoring for LVSI

Risk of Distant Metastasis

A

Distant Metastasis

Time (years)

Substantial LVSI
Focal LVSI
No LVSI

p<0.001

Bosse, Eur J Ca 2015
LVSI in PORTEC 1 and 2

- N=954, three-tiered scoring for LVSI

Risk of Pelvic Recurrence

Recurrence by Treatment

Bosse, Eur J Ca 2015
Progression-free survival (%)

Log-rank $P = 0.02$

- **POLE** (ultramutated)
- **MSI** (hypermutated)
- Copy-number low (endometrioid)
- Copy-number high (serous-like)

Months
Molecular Classification

- **POLE (DNA Polymerase epsilon) ultramutated**
  - Best prognosis
  - Frequent mutations in POLE domain
  - 4% of endometrioid carcinoma
- **MSI hypermutate (MMRd)**
  - High mutation rates
  - High methylation rate, low PTEN expression
  - 39% of endometrioid carcinomas
- **Copy number low (NSMP)**
  - SOX17 and KRAS frequently mutated
  - High PR rate, RAD50 expressed
  - 49% of endometrioid carcinomas
- **Copy number high (p53mut)**
  - Worst prognosis
  - Frequent p53 mutations, unique PTEN mutation
  - 8% of endometrioid carcinoma
PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center)\(^{fg}\)

- **POLE** sequencing
  - No **POLE** hotspot mutation
    - DNA MMR protein immunohistochemistry
      - Expression lost
        - **MSI-H**
      - Expression retained
        - **p53** immunohistochemistry
          - Normal/Wild-type pattern
            - **Copy number-low**
          - Aberrant/Mutant pattern
            - **Copy number-high**
  - **POLE** hotspot mutation
Molecular Prognosis Confirmation Studies

• N=947, PORTEC-1 and 2 patients
PORTEC

- Post-operative stage I, n=715
  - Grade 1, > 0.5 MI
  - Grade 2, any MI
  - Grade 3, < 0.5 MI
- Primary endpoint: OS and LR
  - Median f/u = 52 months

**REGIMEN 1**
Pelvic RT 46 Gy
No vaginal brachytherapy

**REGIMEN 2**
No further therapy

TAH & BSO *without* LN sampling
Peritoneal cytology not required

Creutzberg al., Lancet, 2000
PORTEC- Overall Survival

- Cumulative (%)
- Time after randomisation (months)

Creutzberg al., Lancet, 2000
PORTEC- Local Recurrence

Cumulative (%) vs Time after randomisation (months)

- No radiotherapy
- Radiotherapy

13.7% vs 4.2%, <0.001

Creutzberg al., Lancet, 2000
### PORTEC- Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Pelvic RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year LR</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>5-year OS</td>
<td>85%</td>
<td>81%</td>
</tr>
<tr>
<td>Any treatment complications</td>
<td>6%</td>
<td>25%</td>
</tr>
<tr>
<td>Grade 3-4 complications</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>
GOG 99

- Post-operative stage IB-occult II, n=392
- Primary endpoint: Recurrence free survival

**REGIMEN 1**
- Pelvic RT 50.4 Gy
- No vaginal brachytherapy

**REGIMEN 2**
- No further therapy

TAH & BSO with selective pelvic/para-aortic LN sampling
Peritoneal cytology assessed

Keys et al., Gyne Oncol, 2004
GOG 99

• A non-significant improvement in survival was noted in RT group
  – 92% versus 86%, p=0.55
  – ½ of deaths not due to endometrial cancer
• RT group had superior pelvic control at 2 years
  – 12% versus 3%, p<0.01
  – Of the 3 recurrence in RT arm, 2 did not receive RT
• Recurrence rate at 5.5 years without RT was 15%
• 15% complication rate in RT arm, 6% in Obs arm

Keys et al., Gyne Oncol, 2004
GOG 99- Survival

Proportion Surviving

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>166</td>
<td>36</td>
<td>202</td>
</tr>
<tr>
<td>Surgery + XRT</td>
<td>160</td>
<td>30</td>
<td>190</td>
</tr>
</tbody>
</table>

Months on Study
GOG 99- Local Recurrence

Keys et al., Gyne Oncol, 2004
GOG 99- Subgroup Analysis

• Target population had lower risk of recurrence than expected
• HIR (high intermediate risk) patient classification developed
  – Age ≥ 70 with 1 factor: grade 2-3, +LVI, outer 1/3 MI
  – Age ≥ 50 with 2 factors: grade 2-3, +LVI, outer 1/3 MI
  – Any age with all 3 factors

<table>
<thead>
<tr>
<th></th>
<th>4-yr OS</th>
<th>4-yr LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic RT</td>
<td>88%</td>
<td>27%</td>
</tr>
<tr>
<td>No RT</td>
<td>74%, p=NS</td>
<td>13%</td>
</tr>
</tbody>
</table>

Keys et al., Gyne Oncol, 2004
# Comparison of Risk Groups: GOG & PORTEC

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>PORTEC</th>
<th>GOG 99</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60 vs. &gt;60</td>
<td>&lt;50 vs. &lt;70 vs. &gt;70</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade 1-2 vs. 3</td>
<td>Grade 1 vs. 2-3</td>
</tr>
<tr>
<td>Deep Invasion</td>
<td>&lt;50% vs. &gt;50%</td>
<td>&lt;66% vs. &gt;66%</td>
</tr>
<tr>
<td>LVI</td>
<td>---</td>
<td>Absent vs. present</td>
</tr>
<tr>
<td><strong>High-risk definition</strong></td>
<td>At least 2 of 3 factors</td>
<td>Any age and 3 factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 50 and 2 factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 70 and 1 factor</td>
</tr>
<tr>
<td><strong>Results in high risk group</strong></td>
<td>10-yr locoregional relapse</td>
<td>4-year relapse (any):</td>
</tr>
<tr>
<td></td>
<td>RT: 5%</td>
<td>RT: 14%</td>
</tr>
<tr>
<td></td>
<td>No RT: 23%</td>
<td>No RT: 27%</td>
</tr>
<tr>
<td></td>
<td>With GOG high-risk criteria</td>
<td>4-yr isolated local relapse:</td>
</tr>
<tr>
<td></td>
<td>RT: 8%</td>
<td>RT: 5%</td>
</tr>
<tr>
<td></td>
<td>No RT: 22%</td>
<td>No RT: 13%</td>
</tr>
</tbody>
</table>

Adapted from Creutzberg, 2007
PORTEC 2 Trial

• Eligibility
  – Age>60 and stage IC, grade 1 or 2
  – Age>60 and stage IB, grade 3
  – Any age, stage IIA, any grade

TAH & BSO *without* LN sampling unless suspicious
Primary endpoint: vaginal relapse

REGIMEN 1
Pelvic RT 46 Gy
No vaginal brachytherapy

REGIMEN 2
Adjuvant vaginal brachytherapy
  HDR 21 Gy/3 fxn
  LDR 30 Gy/1 fxn

Nout et al., Lancet 26: 2010
PORTEC 2 Trial

<table>
<thead>
<tr>
<th></th>
<th>EBRT (n=214)</th>
<th>VBT (n=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between surgery and radiotherapy (days)</td>
<td>43.4 (0.8)</td>
<td>42.5 (0.8)</td>
</tr>
<tr>
<td>Duration of radiotherapy (days)</td>
<td>30.9 (0.2)</td>
<td>12.9 (0.4)</td>
</tr>
<tr>
<td>Dose (Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>46.0 (0.9)</td>
<td>--</td>
</tr>
<tr>
<td>VBT: HDR*</td>
<td>--</td>
<td>21.1 (0.1)</td>
</tr>
<tr>
<td>VBT: MDR*</td>
<td>--</td>
<td>28.5 (0.5)</td>
</tr>
<tr>
<td>VBT: LDR*</td>
<td>--</td>
<td>29.0 (0.3)</td>
</tr>
<tr>
<td>Median VBT cylinder diameter (mm [range])</td>
<td>--</td>
<td>30 (20–40)</td>
</tr>
<tr>
<td>VBT length of 100% isodose (mm)</td>
<td>--</td>
<td>46.5 (0.7)</td>
</tr>
</tbody>
</table>

Data are mean (SE) unless otherwise indicated. EBRT = external beam radiotherapy. VBT = vaginal brachytherapy. HDR = high-dose rate. MDR = medium-dose rate. LDR = low-dose rate. *VBT was delivered with HDR in 182 (85.4%) patients, with LDR in 19 (8.9%) patients, and with MDR in eight (3.8%) patients.

Table 2: Treatment characteristics

Nout et al., *Lancet* 26: 2010
PORTEC 2 Trial

Nout et al., Lancet 26: 2010
## PORTEC 2 Trial

### Table 4: Recurrence and survival for patients at true high-intermediate risk after pathology review (n=366)

<table>
<thead>
<tr>
<th></th>
<th>Events/total</th>
<th>Estimated 5-year (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>Log-rank p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaginal recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>4/183</td>
<td>1.9% (0.6-5.8)</td>
<td>1.00</td>
<td>0.39</td>
</tr>
<tr>
<td>VBT</td>
<td>2/183</td>
<td>1.5% (0.4-6.5)</td>
<td>0.48 (0.09-2.64)</td>
<td></td>
</tr>
<tr>
<td><strong>Pelvic recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>1/183</td>
<td>0.6% (0.1-4.0)</td>
<td>1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>VBT</td>
<td>6/183</td>
<td>3.3% (1.5-7.3)</td>
<td>6.10 (0.73-50.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Locoregional recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>5/183</td>
<td>2.4% (0.9-6.5)</td>
<td>1.00</td>
<td>0.42</td>
</tr>
<tr>
<td>VBT</td>
<td>8/183</td>
<td>4.8% (2.4-9.7)</td>
<td>1.58 (0.52-4.86)</td>
<td></td>
</tr>
<tr>
<td><strong>Distant metastases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>10/183</td>
<td>5.0% (2.6-9.4)</td>
<td>1.00</td>
<td>0.79</td>
</tr>
<tr>
<td>VBT</td>
<td>11/183</td>
<td>6.4% (3.6-11.5)</td>
<td>1.12 (0.48-2.64)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>24/183</td>
<td>80.2% (71.4-89.0)</td>
<td>1.00</td>
<td>0.89</td>
</tr>
<tr>
<td>VBT</td>
<td>25/183</td>
<td>84.5% (78.6-90.4)</td>
<td>1.04 (0.59-1.82)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>19/183</td>
<td>82.1% (73.5-90.7)</td>
<td>1.00</td>
<td>0.66</td>
</tr>
<tr>
<td>VBT</td>
<td>22/183</td>
<td>86.2% (80.5-91.9)</td>
<td>1.15 (0.62-2.13)</td>
<td></td>
</tr>
</tbody>
</table>

EBRT = external beam radiotherapy. VBT = vaginal brachytherapy. * Both log-rank tests and Cox proportional hazards models are stratified for FIGO (International Federation of Gynecology and Obstetrics) stage.
## PORTEC 2 Results

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>5 yr Vaginal Rel.</th>
<th>5 yr Pelvic Rel.</th>
<th>5 yr DM</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Brachy</td>
<td>214</td>
<td>1.8%</td>
<td>3.8%</td>
<td>8.9%</td>
<td>84.8%</td>
</tr>
<tr>
<td>Pelvic RT</td>
<td>213</td>
<td>1.6%</td>
<td>4.6%</td>
<td>5.7%</td>
<td>79.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p=0.74)</td>
<td>(p=0.02)</td>
<td>(p=0.46)</td>
<td>(p=0.57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>10 yr Vag Rel.</th>
<th>10 yr Pelv Rel.</th>
<th>10 yr DM</th>
<th>10 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Brachy</td>
<td>214</td>
<td>3.4%</td>
<td>6.3%</td>
<td>10.4%</td>
<td>69.5%</td>
</tr>
<tr>
<td>Pelvic RT</td>
<td>213</td>
<td>2.4%</td>
<td>0.9%</td>
<td>8.9%</td>
<td>67.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p=0.55)</td>
<td>(p=0.004)</td>
<td>(p=0.49)</td>
<td>(p=0.72)</td>
</tr>
</tbody>
</table>

Conclusion: vaginal brachytherapy should be treatment of choice for high-intermediate risk endometrial cancer

Wortman et al., *BJC* 2018
Nout et al., *Lancet* 26: 2010
PORTEC 2 10-year Update

Pelvic Recurrence

Wortman et al., BJC 2018
GOG 249

- N=601
- Primary outcome was RFS

Stage I-II
- ≥70 yo with 1 Risk Factor
- ≥50 yo or older with 2 Risk Factors
- ≥18 yo with 3 Risk Factors
  - Risk Factors: grade 2-3, Outer 1/2 depth invasion, LVSI
  - Clear cell and pap serous included

Pelvic RT
- 45-50.4 Gy in 25-28 fx 3D or IMRT
- VBT boost allowed for cervix + or clear cell

VBT + 3c Carbo/Taxol
- 6-7 Gy @ 0.5 cm depth x 3 fractions
- 10-10.5 Gy @ surface x 3 6 Gy @ surface x 5
- 3-5 cm length

Randall et al., JCO 2019
GOG 249

- Median FU was 53 months
- 5-year RFS: 76% (RT) vs 76% (VBT + CT), p=NS
- 5-year OS: 87% (RT) vs 85% (VBT + CT), p=NS
- 5-year pelvic and PALN recurrence
  - 4% (RT) vs 9% (VBT + CT)
- No differences in
  - Vaginal cuff recurrence: 2.5%
  - Distant recurrence: 18%
- Increased fatigue and neurotoxicity in VBT and chemotherapy arm

Randall et al., JCO 2019
GOG 249

Relapse Free Survival

Overall Survival

Randall et al., JCO 2019
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