University of Kentucky
Annual New Cancers
University of Kentucky
Annual Recurrent Cancers
Overview

- 3-5% of all uterine malignancies
- 2 per 100,000 women in USA
- Arise from endometrial stroma, glands or uterine muscle. Other mesenchymal tumors are rare
- 20 years after pelvic radiotherapy
- Black women more common
Classification
Ober, 1959

- Homologous
  - Pure
    - Stromal sarcoma (endolymphatic stromal myosis)
    - Leiomyosarcoma
    - Angiosarcoma
    - Fibrosarcoma
  - Mixed
    - Carcinosarcoma
Heterologous

- Pure
  - Rhabdomyosarcom
  - Chondrosarcoma
  - Osteosarcoma
  - Liposarcoma

- Mixed
  - Mixed mullerian tumor (MMT)
Classification
SGO Endorsed

- Leiomyosarcoma
- Endometrial Stromal Sarcoma
- Mixed homologous Mullerian Sarcomas (carcinosarcoma)
- Mixed heterologous Mullerian Sarcomas (mixed mesodermal sarcoma)
- Other uterine sarcomas
<table>
<thead>
<tr>
<th>Mitoses</th>
<th>Atypia</th>
<th>Diagnosis</th>
<th>Metastatic Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Any</td>
<td>Myoma</td>
<td>Very low</td>
</tr>
<tr>
<td>5-9</td>
<td>None</td>
<td>Myoma with high mitotic activity</td>
<td>Very low</td>
</tr>
<tr>
<td>5-9</td>
<td>Gr 1</td>
<td>Smooth muscle tumor of uncertain malignant potential</td>
<td>Low</td>
</tr>
<tr>
<td>5-9</td>
<td>Gr 2,3</td>
<td>LMS</td>
<td>Moderate</td>
</tr>
<tr>
<td>≥10</td>
<td>Gr 1</td>
<td>LMS</td>
<td>High</td>
</tr>
<tr>
<td>≥ 10</td>
<td>Gr 2,3</td>
<td>LMS</td>
<td>Very high</td>
</tr>
</tbody>
</table>
Uterine Sarcoma

- **Endometrial stromal sarcoma**
  - Age 45
  - Ifosfamide

- **Leiomyosarcoma**
  - Age 55
  - Adriamycin/Ifosfamide
  - Gemcitabine/Taxotere (GOG #131-G)

- **Mixed mullerian tumor**
  - Age 65
  - Ifosfamide v. Ifos/Taxol (GOG #161)
  - Carbo/Taxol (GOG #232-B)
Uterine Sarcoma
Endometrial Cancer
Risk Factors

- Anovulation-PCO
- Exogenous estrogen
- Endogenous estrogen
- Family history
- Nulliparity
- Age
- Infertility
- Tamoxifen
- Early menarche
- Late menopause
- Diabetes
- Hypertension
- Granulosa cell tumors
- History of breast or colon cancer
- Menstrual irregularities
### Endometrial Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (20-50 lb)</td>
<td>3</td>
</tr>
<tr>
<td>Obesity (&gt;50 lb)</td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2-3</td>
</tr>
<tr>
<td>Late menopause</td>
<td>2.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.8</td>
</tr>
<tr>
<td>Tamoxififen</td>
<td>7.5</td>
</tr>
<tr>
<td>Unopposed ERT</td>
<td></td>
</tr>
</tbody>
</table>
Presentation
## Postmenopausal Bleeding

<table>
<thead>
<tr>
<th>Etiologic Factor</th>
<th>Lahey Clinic (%)</th>
<th>Mayo Clinic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERT</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Atrophy</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Cancer</td>
<td>19.5</td>
<td>18</td>
</tr>
<tr>
<td>EAC</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Cervix</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Atrophic vaginitis</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Endometrial polyps</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>Cervical polyps</td>
<td>6.5</td>
<td>14</td>
</tr>
</tbody>
</table>
# Endometrial Cancer with PMB

<table>
<thead>
<tr>
<th>Age</th>
<th>Total cases</th>
<th>Total # EAC</th>
<th>% Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>161</td>
<td>15</td>
<td>9.3</td>
</tr>
<tr>
<td>60-69</td>
<td>92</td>
<td>15</td>
<td>16.3</td>
</tr>
<tr>
<td>70-79</td>
<td>43</td>
<td>12</td>
<td>27.9</td>
</tr>
<tr>
<td>&gt;80</td>
<td>5</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>
Atypical Endometrial Cells
## Endometrial Cells on Pap

*Postmenopausal*

<table>
<thead>
<tr>
<th>Cells</th>
<th>Total</th>
<th>Hyperplasia</th>
<th>Polyps</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>74</td>
<td>9</td>
<td>1</td>
<td>1 (1%) +</td>
</tr>
<tr>
<td>Atypical</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>31</td>
<td>1</td>
<td>0</td>
<td>23 (74%) *</td>
</tr>
</tbody>
</table>

+ Ovarian cancer

*2 cervical, 1 breast, 1 ovary, 19 endometrial cancers*
Hormones and Endometrial Cancer
Histopathology
Leiomyosarcoma
Leiomyosarcoma

Bizarre nuclei
Leiomyosarcoma
Uterine Sarcoma
Uterine Sarcoma
Uterine Sarcoma
Leiomyosarcoma
# Endometrial Cancer Histology

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>Frequency</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>66%</td>
<td>88%</td>
</tr>
<tr>
<td>Adenoacanthoma</td>
<td>16%</td>
<td>91%</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>5%</td>
<td>62%</td>
</tr>
<tr>
<td>Papillary serous</td>
<td>8%</td>
<td>63%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>3%</td>
<td>43%</td>
</tr>
<tr>
<td>Secretary</td>
<td>2%</td>
<td>89%</td>
</tr>
</tbody>
</table>
Survival

UPSC – Uterine papillary serous carcinoma
CC – Clear cell carcinoma
G3EC – Grade 3 endometrioid carcinoma
Uterine Cancer
Staging and Prognosis
# Uterine Sarcoma

## Five Year Survival (%)

<table>
<thead>
<tr>
<th></th>
<th>Stage I</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>98</td>
<td>38</td>
</tr>
<tr>
<td>LMS</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>MMT</td>
<td>50</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
# Uterine Sarcoma

## % Five Year Survival

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
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<td>8</td>
</tr>
<tr>
<td>MMT</td>
<td>50</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
# Endometrial Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>Stage II</td>
<td>12</td>
<td>66</td>
</tr>
<tr>
<td>Stage III</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>Stage IV</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>

Petterson F, ed: Annual report on treatment Gyn Ca, vol 22; Stockholm, 1994, FIGO
Endometrial Cancer

Five year survival, %
Endometrial Cancer
Prognosis

- Stage (I-IV)
- Depth of invasion (A,B,C)
- Histologic differentiation (grade 1,2,3)
- Histologic cell type
- Lymphvascular space invasion
- Pelvic cytology
## Endometrial Cancer

**Clinical Staging, FIGO 1971**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Confined to corpus</td>
</tr>
<tr>
<td>IA</td>
<td>Sounds to $\leq 8cm$</td>
</tr>
<tr>
<td>IB</td>
<td>Sounds to $&gt; 8cm$</td>
</tr>
<tr>
<td>Stage II</td>
<td>Cervical involvement</td>
</tr>
<tr>
<td></td>
<td>ECC, cervical biopsy, gross involvement</td>
</tr>
<tr>
<td>Stage III</td>
<td>Beyond uterus, confined to pelvis</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Bladder or rectal mucosa</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Extrapelvic metastasis</td>
</tr>
</tbody>
</table>
Endometrial Cancer
Surgical Staging, 1988

- Total hysterectomy, bilateral salpingo-oophorectomy
- Pelvic washing
- Pelvic and para-aortic lymph node sampling
- Omentectomy, upper abdominal biopsies and washings for serous histology
Surgical Recommendations
GOG Manual, 1997

- Prognostic not therapeutic
- Removal of all suspicious nodes
- Removal of one-half of pelvic nodes
- PA nodes from inferior mesenteric artery to common iliac, when indicated
- Recommended for > 50% invasion or grade 3 lesions
So, When Do I Do the Nodes?

- Balance between morbidity and utility
  - Lymphadenectomy is *not* risk free
- Preoperative grade
  - Accurate in 85% of cases
- Intraoperative evaluation
  - Frozen section 90% accurate for MM invasion
- Ueland’s “counsel”
  - IA gr 1,2 and IB gr 1 insufficient nodal risk to justify additional expense and morbidity
Endometrial Cancer
Stage I

Stage I  Confined to uterus

IA  Limited to endometrium

IB  Inner ½ myometrium

IC  Outer ½ myometrium
Five year survival (%)  
Stage I
## Differentiation and Depth

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>IB</td>
<td>11 88%</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>20</td>
<td></td>
<td>88%</td>
</tr>
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</table>

*88%*
## Uterine Sarcoma Survival

### 5-year survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cell Type</th>
<th>S</th>
<th>S+R</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>MMS</td>
<td>52 %</td>
<td>48 %</td>
<td>29 %</td>
</tr>
<tr>
<td></td>
<td>LMS</td>
<td>58 %</td>
<td>75 %</td>
<td>33 %</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
<td>47 %</td>
<td>88 %</td>
<td>50 %</td>
</tr>
<tr>
<td>II-IV</td>
<td>MMS</td>
<td>5 %</td>
<td>16 %</td>
<td>0 %</td>
</tr>
<tr>
<td></td>
<td>LMS</td>
<td>0 %</td>
<td>13 %</td>
<td>0 %</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
<td>0 %</td>
<td>33 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>
# Uterine Sarcoma

## % Site of Recurrence

<table>
<thead>
<tr>
<th></th>
<th>MMT-Ho (N=165)</th>
<th>MMT-He (N=134)</th>
<th>LMS (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>9</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Distant</td>
<td>33</td>
<td>46</td>
<td>56</td>
</tr>
<tr>
<td>None</td>
<td>58</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Type</td>
<td>MMT Homo</td>
<td>MMT Hetero</td>
<td>LMS</td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
<td>------------</td>
<td>-----</td>
</tr>
<tr>
<td>Lymph Node Metastases (%)</td>
<td>10</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>
Pelvic Node Metastases (%)
Stage I
Five year survival (%)  
Stage I
Endometrial Cancer

Stage II

Stage II  Cervical involvement

IIA  Endocervical glands

IIB  Cervical stroma
Endometrial Cancer
Stage III

Stage III Extra-uterine disease

IIIA Serosa, adnexa, (+) cytology
IIIB Vaginal metastases
IIIC Lymph node metastases
Endometrial Cancer

Stage IV

Stage IV Regional, distant metastases

IV A Bowel or bladder mucosa

IV B Distant metastases
Treatment
Primary Treatment

- Surgery
- Radiotherapy
  - Medically inoperable
  - 15% survival decrement each stage
- Hormone therapy
  - Only for grade 1 tumors in young women
  - Dilatation and curettage
Confined to Uterus

Surgical staging
(Omit LN if extrauterine ds)

Stage I,II ESS
No further therapy

Stage I,II other
Stage III ESS
Whole pelvic XRT
(+ Hormone Tx for ESS)

Extra-uterine disease

Resection if possible

Stage IIIC, IV
Stage IIIA,B other
XRT
+/- Chemotherapy
+/- Hormone therapy

Stage I,II ESS
No further therapy

Stage I,II other
Stage III ESS
Whole pelvic XRT
(+ Hormone Tx for ESS)

Stage IIIC, IV
Stage IIIA,B other
XRT
+/- Chemotherapy
+/- Hormone therapy
Recurrence

- No prior XRT
  - Vaginal
    - Surgery
  - Pelvic
    - Whole pelvic XRT
  - Extra-pelvic

- Prior XRT
  - Surgery
    - +/- Chemotherapy
    - +/- Hormone therapy
  - WAR XRT
    - +/- Chemotherapy
    - +/- Hormone therapy
Chemotherapy
NCCN Guidelines, 2004

- Ifosfamide for carcinosarcoma
- Doxorubicin for LMS
- Single agent cisplatin, Taxol, Taxotere, Gemzar
- Hormone therapy
  - Megace
  - Provera
  - Tamoxifen
  - GnRH analogs
Adjuvant Treatment

- Radiation therapy
  - High risk (IIB, III)
- Chemotherapy
  - UPSC, III and IV
- Chemoradiation
  - Residual pelvic disease
- Sequential
  - Advanced, persistent
- Hormonal therapy
Endometrial Cancer
Recent GOG Studies

- **GOG #209**  Stage III, IV, Recurrent
  - Cisplat/Adria/Taxol vs. Carbo/Taxol
- **GOG # 232-B** Uterine MMT
  - Carbo/Taxol
- **GOG #131-G** Uterine LMS
  - Gemcitabine/Taxotere
Pelvic Radiation Fields

- L₅/S₁ to inferior border of obturator foramen
- 2 cm lateral to obturator fossa
  - 15 cm wide
- Para-aortic window
  - T₁₂ to L₅/S₁
  - 10 cm wide
  - Salvage 37% with PA window (Morrow ’91)
Adjuvant Radiotherapy

- Decreased vaginal and pelvic recurrence
- No change in overall survival
  - Morrow, Gyn Onc 1991
- **PORTEC European RCT** (Creutzberg, Lancet 2000)
  - 715 patients, intermediate risk cancers
  - Decreased pelvic recurrence (4% v. 14%)
  - Overall survival same (81% vs 85%)
  - 80% salvage with XRT in observation arm
  - ↑ Complication rate for XRT (25% vs 6%)
Adjuvant Radiotherapy
Straughn et al. Gyn Onc, 2002

- Retrospective, single center
- Stage I endometrial cancer (N= 613)
- 53% low risk (IA, IB g1)
  - No radiation
  - 2% recurrence, 6/7 pelvic
- 47% intermediate risk (IB g2,3, IC)
  - 70% no radiation
  - 8% recurrence (no XRT), 4% recurrence (XRT)
  - 56% pelvic recurrence
  - 8/9 recurred in pelvis, 7 salvaged
Radiation Morbidity
Whole Pelvic

- 5% enteric morbidity
- 15-25% enteric following lymphadenectomy
- 10 fold ↑ complication rate for whole pelvis vs. cuff
Hormone Therapy

- 70% gr 1 ER/PR (+)
- 55% gr 2 ER/PR (+)
- 41% gr 3 ER/PR (+)
- Response to progesterone
  - PR (+) = 80%
  - PR (-) = 5%
Adjuvant Hormone Therapy

RCT data

- No survival advantage to adjuvant hormone therapy following surgery
  - Vergote ‘89
  - Britain ‘88
  - Lewis ‘74
Endometrial Cancer
Chemotherapy

- Stage III, IV, recurrent
- No RCT data saying combo > single agent
- Cisplatin/Adriamycin  RR= 50-75%
- Adriamycin/Taxol
  - GOG # 163  No survival difference
- Cisplatin/Adriamycin/Taxol
  - GOG # 177  Survival advantage, but toxic
  - GOG # 184  Closed ‘04, unpublished
  - GOG # 209  Active
Surveillance

- Low risk (IA, IB g1-2)
  - Annual evaluation
- Intermediate risk (IB g3, IC, IIA)
  - 4 to 6 months
- High risk (IIB, C, III, IV)
  - 3 months
  - CXR
  - CT scan as indicated
Conclusions

1. Most endometrial cancers present with bleeding, at early stage, and with favorable outcome
2. Surgical staging is important
3. Trend toward less adjuvant radiotherapy for stage I cancers
4. Advanced stage, clear cell and UPSC poorly responsive to therapy