Uterine Neoplasms
Pathology and Management Review

Dr. Mark Laudenschlager & Dr. Jed Delmore
Objectives

- Case based presentation to cover
  - Common uterine neoplasm diagnosis
  - Common uterine neoplasm pathophysiology
  - Management of common uterine neoplasms
Conflict of Interest
# American Cancer Society Statistics 2018

## New Cases by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Breast</td>
<td>266,120</td>
</tr>
<tr>
<td>Lung</td>
<td>112,350</td>
</tr>
<tr>
<td>Colo-Rectal</td>
<td>64,640</td>
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<tr>
<td>Uterus</td>
<td>64,230</td>
</tr>
<tr>
<td>Thyroid</td>
<td>40,900</td>
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<tr>
<td>N-H Lymphoma</td>
<td>32,950</td>
</tr>
<tr>
<td>Pancreas</td>
<td>26,240</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,270</td>
</tr>
<tr>
<td>Kidney</td>
<td>22,660</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,290</td>
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## Deaths by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Deaths</th>
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</thead>
<tbody>
<tr>
<td>Lung</td>
<td>70,500</td>
</tr>
<tr>
<td>Breast</td>
<td>40,920</td>
</tr>
<tr>
<td>Colo-Rectal</td>
<td>23,240</td>
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<tr>
<td>Pancreas</td>
<td>23,310</td>
</tr>
<tr>
<td>Ovary</td>
<td>14,070</td>
</tr>
<tr>
<td>Uterus</td>
<td>11,350</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10,100</td>
</tr>
<tr>
<td>Liver &amp; Bile duct</td>
<td>9,660</td>
</tr>
<tr>
<td>N-H Lymphoma</td>
<td>8,400</td>
</tr>
<tr>
<td>Brain/Nervous Syst.</td>
<td>7,340</td>
</tr>
</tbody>
</table>
Gynecologic Malignancies
2018

ACS, 2018
Case #1

34 year old G0P0 with a long history of abnormal uterine bleeding. No contraception for 10 years. Current weight is 340#, History and exam are notable for hirsutism and hypertension.

TV sonogram shows a 42 mm endometrial stripe.

Hysteroscopy/D&C: Atypical endometrial hyperplasia/EIN
Histology Review
Endometrial Cancer Precursors

- Atypical endometrial hyperplasia
- EIN (Endometrial Intraepithelial Neoplasia)
Endometrial Cancer Precursors
WHO Criteria

Proliferative Endometrium

↓

Endometrial Hyperplasia

↓

Atypical Endometrial Hyperplasia

↓

Endometrial Carcinoma

Kurman et al. Cancer 1985;56:403-12
Endometrial Intraepithelial Neoplasia (EIN)

- **Clonal** proliferation of architecturally and cytologically altered premalignant endometrial glands, prone to malignant transformation to endometrioid (Type I) endometrial adenocarcinoma.

- Non-invasive, genetically altered neoplasms that arise **focally** and may convert to malignant phenotype upon acquisition of additional genetic damage.
AEH or EIN

- **GOG 167**
  - Post-hysterectomy findings in women with atypical endometrial hyperplasia.
  - 123/289 (42.6%) women found to have endometrial carcinoma on final pathology.
  - 43/123 (34%) demonstrated myometrial invasion or Grade 2 or Grade 3 carcinomas.

Cancer 2006;106:812-819.
EIN/ Atypical Endometrial Hyperplasia
Surgical Therapy

- Total Hysterectomy (By the least morbid route)
- BSO in menopausal women
- ?? Preserving ovaries in pre-menopausal women. (I wouldn’t)
- Supracervical hysterectomy and morcellation are inappropriate.
- Staging lymphadenectomy is not needed
Case #2

64 year old G2P2 with a four month history of menopausal bleeding.
TV sonogram shows a 12 mm endometrial stripe.
Endometrial Biopsy: Grade 2 endometrial cancer
Histology Review
Uterine Malignancy

Diagnosis

- Endometrial biopsy
- Dilation and curettage
- Hysteroscopy
- Histologic type and grade
- Presence or absence of vaginal metastases
- Rule out primary endocervical carcinoma
## Endometrial Cancer

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Type I</th>
<th>Type II</th>
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</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>Unopposed estrogen</td>
<td>Age</td>
</tr>
<tr>
<td>Race</td>
<td>White &gt; Black</td>
<td>White = Black</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Well differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Histology</td>
<td>Endometrioid</td>
<td>Non-endometrioid</td>
</tr>
<tr>
<td>Stage</td>
<td>I/II</td>
<td>III/IV</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favorable</td>
<td>Not favorable</td>
</tr>
<tr>
<td>Ploidy</td>
<td>Diploid</td>
<td>Aneuploid</td>
</tr>
</tbody>
</table>
F.I.G.O.
International Federation of Gynecology & Obstetrics

- Universally available
- Clinical vs. Surgical
- Once established, the stage is not changed
- Should have prognostic significance
- Aids in worldwide outcome reporting
- May assist in treatment decisions
Staging

Gynecologic Malignancies

Clinical
  - Cervix
  - GTN
  - Vagina

Surgical
  - Ovary
  - Uterine
  - Vulva
Endometrial Cancer Staging
FIGO 2009

Stage I  The carcinoma is confined to the corpus uteri
IA  No or < ½ myometrial invasion
IB  Invasion ≥ ½ of the myometrium

Stage II  Tumor involves the cervical stroma, but does not extend beyond the uterus

Stage III  Local and/or regional spread of the tumor
IIIA  Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB  Vaginal and/or parametrial involvement
IIC  Metastases to the pelvic and/or para-aortic lymph nodes
     IIC1  Positive pelvic lymph nodes
     IIC2  Positive para-aortic lymph nodes with or without positive pelvic lymph nodes

Stage IV  Tumor invades the bladder and/or bowel mucosa
IVA  Tumor invades bladder and/or bowel mucosa
IVB  Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Note:  All tumors are Graded 1,2 or 3.
Endocervical gland involvement is to be considered Stage I.
Positive cytology has to be reported separately without changing stage.
Sentinel Node Testing
Endometrial Cancer Therapy

- **Hysterectomy, BSO and Lymphadenectomy**
- The lymphadenectomy helps establish prognosis and guide postoperative therapy decisions. The lymphadenectomy may not alter survival.

- **Prognostic factors guiding post-operative therapy**
  - Grade
  - Histology
  - Myometrial invasion
  - Vascular space invasion
  - Node status
Postoperative Treatment

- Observation
- Pelvic radiation
- Combination chemotherapy & radiation
- Systemic chemotherapy
- Hormone therapy
Stage I Endometrial Cancer Postoperative Management

NCCN Guidelines Version 1.2018
Endometrial Carcinoma
NCCN Evidence Blocks™

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Adverse Risk Factors</th>
<th>Histologic Grade/Adjuvant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA (&lt;50% myometrial invasion)</td>
<td>Adverse risk factors not present</td>
<td>G1 Observe</td>
</tr>
<tr>
<td>Stage IB (≥50% myometrial invasion)</td>
<td>Adverse risk factors present</td>
<td>G1 Observe or Vaginal brachytherapy</td>
</tr>
<tr>
<td>Surgical staging: Stage I</td>
<td>Adverse risk factors not present</td>
<td>G1 Observe or Vaginal brachytherapy and/or EBRT</td>
</tr>
<tr>
<td></td>
<td>Adverse risk factors present</td>
<td>m</td>
</tr>
</tbody>
</table>

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page ENDO-9. All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. 

1The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.
2See Principles of Evaluation and Surgical Staging (ENDO-C).
3See Principles of Radiation Therapy for Uterine Neoplasms (ENDO-A).
4See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).
5Potential adverse risk factors include the following: age, positive lymphovascular invasion, tumor size, and lower uterine segment or surface cervical glandular involvement. See Discussion for additional information on adverse risk factors.
6Consider additional imaging if not previously done. See Principles of Imaging for Endometrial Carcinoma (ENDO-A).
7Adjuvant therapy determinations are made on the basis of pathologic findings.
8Initiate EBRT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.
9The role of adjuvant chemotherapy in invasive, high-grade, uterine-confined disease is the subject of current studies. Hormonal therapy is not used for high-grade disease.

See Surveillance (ENDO-9)
Stage II-IV  Endometrial Cancer Postoperative Management

NCCN Guidelines Version 1.2018
Endometrial Carcinoma
NCCN Evidence Blocks™

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

**CLINICAL FINDINGS**

- Surgically staged: d
  - Stage IIIA
  - Stage IIIB
  - Stage IIIC1
  - Stage IIIC2
  - Stage IVA, IVB

**ADJUVANT TREATMENT** f,g,n

- Systemic therapy and/or EBRT ± vaginal brachytherapy
- Systemic therapy and/or EBRT + vaginal brachytherapy
- Systemic therapy and/or EBRT ± vaginal brachytherapy
- Systemic therapy ± EBRT ± vaginal brachytherapy

---

`d` The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).

`f` See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

`g` See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).

`n` Adjuvant therapy determinations are made on the basis of pathologic findings.

`Additional imaging if not previously done. (See Principles of Imaging ENDO-A)`

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**Surveillance** (ENDO-9)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page ENO-1.

All recommendations are category 2A unless otherwise indicated.

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Case #3

81 year old G3P3 with recent onset of menopausal bleeding.
Weight is 102#
TV sonogram shows a 6 mm endometrial stripe.
Hysteroscopy/D&C: Papillary Serous Carcinoma
Histology Review
Natural History of Type II Endometrial Cancer
NCCN Guidelines Version 1.2018
Endometrial Carcinoma
NCCN Evidence Blocks™

HIGH-RISK CARCINOMA HISTOLOGIES

ADDITIONAL WORKUP

- Biopsy findings:
  - Serous carcinoma
  - Clear cell carcinoma
  - Undifferentiated/dedifferentiated carcinoma
  - Carcinosarcoma

  • CA-125 (optional)
  • Imaging

ADJUVANT TREATMENT

Stage IA

- Observe
- Chemotherapy
  ± vaginal brachytherapy (preferred)
  or
  EBRT
  ± vaginal brachytherapy

Stage IB, II, III, IV

- Chemotherapy
  ± EBRT
  ± vaginal brachytherapy

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

- Minimally invasive surgery (MIS) is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
- The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
- See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
- See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).
- See Principles of Imaging for Endometrial Carcinoma (ENDO-A).
- Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor.
- Observation only for select patients with no residual serous or clear cell carcinoma in the hysterectomy specimen.

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See Surveillance (ENDO-8)
Case #4

76 year old G4P4 with menopausal bleeding. History of sigmoid colon cancer with previous therapy for sigmoid colon cancer with chemotherapy, radiation therapy and sigmoid colectomy with primary anastomosis.

Endometrial biopsy: Carcinosarcoma
Histology Review
Uterine Sarcomas
Uterine Sarcoma Staging

**Table 2**
AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Uterine Sarcomas (includes Leiomyosarcoma and Endometrial Stromal Sarcoma)

<table>
<thead>
<tr>
<th>Definition of Primary Tumor (T)</th>
<th>Definition of Regional Lymph Node (N)</th>
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<tbody>
<tr>
<td><strong>Leiomyosarcoma and Endometrial Stromal Sarcoma</strong></td>
<td><strong>All Uterine Sarcomas</strong></td>
</tr>
<tr>
<td>T Category</td>
<td>FIGO Stage</td>
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<tr>
<td>TX</td>
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<tr>
<td>T0</td>
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<tr>
<td>T1</td>
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<tr>
<td>T1a</td>
<td>IA</td>
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<tr>
<td>T1b</td>
<td>IB</td>
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<td>T2</td>
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<td>T2a</td>
<td>IIA</td>
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<td>T3b</td>
<td>IIIB</td>
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<td>T4</td>
<td>IVA</td>
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<table>
<thead>
<tr>
<th>Definition of Distant Metastasis (M)</th>
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<td><strong>All Uterine Sarcomas</strong></td>
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<td>M Category</td>
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<tr>
<td>M1</td>
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<table>
<thead>
<tr>
<th>Histologic Grade (G)</th>
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<tbody>
<tr>
<td>G</td>
</tr>
<tr>
<td>GX</td>
</tr>
<tr>
<td>G1</td>
</tr>
<tr>
<td>G2</td>
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<td>G3</td>
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Low-Grade Endometrial Stromal Sarcoma Management

NCCN Guidelines Version 1.2018
Uterine Sarcoma

PATHOLOGIC FINDINGS/HISTOLOGIC GRADE

Low-grade ESS

Stage I
- Observe, especially if menopausal or prior BSO or Estrogen blockade (category 2B)

Stage II, III, IVA
- Estrogen blockade\(^5\) ± EBRT\(^6\)
  (category 2B for EBRT)

Stage IVB
- Estrogen blockade\(^6\) ± palliative EBRT

ADDITIONAL THERAPY

See Surveillance (UTSARC-4)

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\(^5\)See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

\(^6\)See Systemic Therapy for Uterine Sarcoma (UTSARC-B).

\(^6\)See Uterine Sarcoma Classification (UTSARC-C).

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Uterine Sarcoma Management

NCCN Guidelines Version 1.2018
Uterine Sarcoma

PATHOLOGIC FINDINGS/
HISTOLOGIC GRADE\(b\)

- High-grade ESS
- UUS
- uLMS

Stage I
- Observe or Consider systemic therapy (category 2B)\(^g\)

Stage II, III
- Consider systemic therapy\(^g\) and/or Consider EBRT\(^f\)

Stage IVA
- Systemic therapy\(^g\) and/or EBRT\(^f\)

Stage IVB
- Systemic therapy\(^g\) ± palliative EBRT\(^f\)

See Surveillance (UTSARC-4)

\(^a\)See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
\(^g\)See Systemic Therapy for Uterine Sarcoma (UTSARC-B).
\(^b\)See Uterine Sarcoma Classification (UTSARC-C).

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Natural History of Uterine Sarcomas
The End