Uterine Bleeding and Uterine Cancer

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Uterine bleeding: Objectives

- “Dysfunctional uterine bleeding” replaced by “abnormal uterine bleeding” (AUB)
- Refresher ovulatory cycle
- Anovulation
- Differential diagnosis of AUB
  - Premenopausal
  - Postmenopausal
- Work-up
- Treatment options
Ovulatory cycle

- 21-35 days
- Duration 5 days
- Predictable by a few days (>10 day: anovulation)
### Anovulation

<table>
<thead>
<tr>
<th>Physiologic</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescence</td>
<td>Hyperandrogenic (PCOS, congenital adrenal hyperplasia, androgen producing tumors)</td>
</tr>
<tr>
<td>Peri-menopause</td>
<td>Hypothalamic dysfunction</td>
</tr>
<tr>
<td>Lactation</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td></td>
<td>Pituitary disease</td>
</tr>
<tr>
<td></td>
<td>Premature ovarian failure</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (radiation/chemo)</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
</tr>
</tbody>
</table>

ACOG practice bulletin 136, July 2013

### Abnormal uterine bleeding causes

<table>
<thead>
<tr>
<th>Structural (PALM)</th>
<th>Non-structural (COEIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyp</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>Ovulatory dysfunction</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Endometrial</td>
</tr>
<tr>
<td>Malignancy or hyperplasia</td>
<td>Iatrogenic (ASA, warfarin)</td>
</tr>
<tr>
<td></td>
<td>Not yet classified</td>
</tr>
</tbody>
</table>

ACOG practice bulletin 136, July 2013
Work-up

• Pregnancy testing
• CBC, plat, (coagulation and iron studies)
• TSH, Prolactin (repeat fasting if elevated)
• Androgens if hirsutism or adnexal mass (testosterone, DHEA, 17-OH progesterone)
• Evaluate for structural/anatomic causes with ultrasound (+/- saline infusion) (including ovaries)
• Endometrial biopsy (if risk for hyperplasia)
  • Samples ~4% of endometrium
• Hysteroscopy, D&C

Age 13-18

• Anovulation
  • 3 years after menses 60-80% have regular menses
  • Obesity
• Von Willebrands disease

• Rule out pregnancy, trauma, STI’s
• PCOS
• Endometrial evaluation (biopsy) if no other cause and/or failure of medical management
<table>
<thead>
<tr>
<th>Age 19-39</th>
</tr>
</thead>
</table>
| • PCOS (polycystic ovarian syndrome)  
  • Obesity  
  • Diabetes  
• Endometrial cancer risk age 35-44: 6.2%  
  (1.6% for 20-34 yo)  
• If prolonged unopposed estrogen or failure of medical therapy → EMB  
  (D&C/hysteroscopy if EMB non-diagnostic) |

<table>
<thead>
<tr>
<th>40-menopause</th>
</tr>
</thead>
</table>
| • Menopausal transition (mean age 51)  
• Pregnancy still possible  
• Endometrial cancer risk 13-24/100,000 women years  
• All patients will need endometrial sampling |
Treatment

- Depends on etiology
  - Combined oral contraceptives
    - Continuous or cyclic
  - Levonorgestrel intrauterine device
  - Oral progestins (not adequate for birth control, OK for peri-menopausal women)
  - Weight loss and exercise
  - Endometrial ablation (only for premenopausal women with normal endometrial biopsy and after completion of child-bearing)
  - Hysterectomy

Postmenopausal bleeding

- Atrophy
- Polyp
- Infection
- Endometrial hyperplasia
- Endometrial cancer
- Cervical abnormalities (cancer, infection)
- Vulva lesions
- Bladder/colorectal abnormalities (cancer, infection)
Postmenopausal bleeding

- Endometrial sampling (EMB, D&C)
- Cervical assessment (endocervical curretage)
- Transvaginal ultrasound (+/- saline infusion):
  - Endometrial stripe < 4 mm: 1% cancer
  - Serous carcinoma can be present with thin lining

Endometrial hyperplasia

- Simple hyperplasia without atypia
  - 1% progression to cancer
  - Treat with progestins
- Complex hyperplasia without atypia
  - 3% progression to cancer
  - Treat with progestins
Endometrial hyperplasia

- Simple hyperplasia with atypia
  - 9% progression to cancer
  - Consider hysterectomy
- Complex hyperplasia with atypia
  - 27% progression to cancer
  - 42% concomitant cancer at time of hysterectomy
  - Treat with hysterectomy (including cervix)
  - Fertility preserving treatment may be considered
- Ovaries can be preserved if no cancer or young patient with very early (stage 1, grade 1) cancer

Progestin therapy options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose and length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate (Provera)</td>
<td>10-20 mg daily or cyclic 12-14 d/month</td>
</tr>
<tr>
<td>Depot medroxyprogesterone (DepoProvera)</td>
<td>150 mg IM every 3 months</td>
</tr>
<tr>
<td>Micronized vaginal progesterone</td>
<td>100-200 mg daily or cyclic 12-14 d/month</td>
</tr>
<tr>
<td>Megestrol acetate (Megace)</td>
<td>40-200 mg/day (80 BID for atypical hyperplasia)</td>
</tr>
<tr>
<td>Levonorgestrel IUD (Mirena)</td>
<td>1-5 years</td>
</tr>
</tbody>
</table>

Trimble, Obstet Gynecol 2012
Endometrial Cancer

Learning Objectives

1. Recognize the epidemiology, genetics, and biology
2. Review treatment options for endometrial cancer
3. Discuss management of uterine sarcomas
### Estimated New Cancer Cases* in the U.S. in 2015

#### Men
- **Total**: 848,200

#### Women
- **Total**: 810,170

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>26%</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>21%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

---

**Breast**

- **Total**
- **Proportion**

**Colon & rectum**

- **Total**
- **Proportion**

**Lung and Bronchus**

- **Total**
- **Proportion**

**Corpus & Uterus**

- **Total**
- **Proportion**

**Melanoma of skin**

- **Total**
- **Proportion**

**Liver**

- **Total**
- **Proportion**

Cancer sites include invasive cases only unless otherwise noted.

Rates are per 100,000 and are age-adjusted to the 2000 U.S. Std Population (19 age groups – Census P2S-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.1.3, April 2014, National Cancer Institute.

Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Zurich)
Estimated Cancer Deaths in the U.S. in 2015

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>312,150</td>
<td>277,280</td>
</tr>
</tbody>
</table>

Men

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Uterine corpus</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

American Cancer Society, Inc.
http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/index

Uterine Neoplasia

- Hyperplasia
  - Type I
    - Endometrioid
    - Mucinous
    - PTEN
    - MMR/MSI
    - KRAS
    - β-catenin
    - microRNA
  - Type II
    - Serous
    - Clear cell
    - Carcinosarcoma
    - TP53
    - HER-2/neu
    - p16
- Adenocarcinoma
- Sarcoma
Pathology

**Clinical Features**

- Abnormal bleeding
  - Postmenopausal bleeding
  - Inter-menstrual bleeding
  - Menorrhagia (heavy bleeding)
- Abnormal discharge
- Pyometrium
- Abdominal and pelvic pain
- Papanicolaou smear abnormality (atypical glandular cells)
### Associated factors

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Unopposed estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age – Median 62 y</td>
<td>• Obesity</td>
</tr>
<tr>
<td>• Race – Caucasian</td>
<td>• Chronic anovulation (polycystic ovary syndrome)</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>• Estrogen therapy, SERMs</td>
</tr>
<tr>
<td>• Lynch/HNPCC (mismatch repair)</td>
<td>• Granulosa cell tumors</td>
</tr>
<tr>
<td>• Cowden’s disease (PTEN)</td>
<td>• Diabetes</td>
</tr>
<tr>
<td>• ?BRCA</td>
<td>• Nulliparity</td>
</tr>
<tr>
<td></td>
<td>• Early menarche/Late menopause</td>
</tr>
</tbody>
</table>

### Protective factors

- Oral contraception
- Progesterone therapy/contraception
- Progesterone intra-uterine device
- Smoking

- Women at risk should be counseled on healthy lifestyle and awareness of symptoms
SERMs and Cancer

- Pro-estrogenic effect on uterus
- **NSABP data (Tamoxifen)**
  - 2-3x risk adenocarcinoma
  - Higher risk sarcoma (17/100,000 vs. 0)
  - STAR trial showed raloxifene with lower risk
- **Recommendations**
  - Alert patients regarding risk
  - Any bleeding should be evaluated with biopsy

Genetics of Endometrial Cancer

- **90% cases are sporadic**
- **Alterations**
  - PTEN – 35% cases
  - TP53 – 30% cases
  - HER2/neu – 25% cases
- **2-5% cases are inherited**
  - Lynch (2-3%), Cowden’s Disease
## Lynch syndrome

- Autosomal dominant inheritance
- Penetration 40-60% (~60-80% for CRC)
- Genes encode proteins that function in DNA mismatch repair
- Genetic heterogeneity
  - MLH1, MSH2, MSH6, PMS2
- Phenotype is microsatellite instability (MSI)

## Clinical Features of Lynch syndrome

- Colon cancer
  - Early age of diagnosis
  - Proximal colon lesions
- Extracolonic tumors
  - Endometrial cancer
    - 60% lifetime risk
  - Lower uterine segment
  - Ovarian cancer (12%)
  - Stomach/SB cancer
  - Urinary tract cancer
  - Bile duct cancer
  - Sebaceous skin tumors
Lynch syndrome

- Women age < 50: 9% has Lynch
- ~50% present with endometrial cancer first
- ~50% present with colorectal cancer first
- Diagnosis of Lynch and subsequent screening may prevent second cancer (median interval 5.5 years)
- Annual screening with ultrasound and biopsy?
- Prevention with risk reducing hysterectomy and salpingo-oophorectomy at age 35

Lu, K. Obstet Gynecol 2005; NCCN

Diagnosis

- Uterine histology
  - Endometrial biopsy (EMB – office)
  - Dilation and curettage (D&C – OR)
  - EMB has a 10% false negative rate in symptomatic women
- Vaginal ultrasonography
  - Evaluate endometrial stripe thickness
  - < 5 mm = low risk for endometrial cancer (caveat: serous adenocarcinoma)
Clinical Features - Overview

- Establish diagnosis
- Staging (clinical versus surgical)
- Therapy
  - Surgery
  - Rarely primary radiation
  - Adjuvant therapy based on surgical-pathologic findings

Patterns of Spread

1. Direct extension
2. Trans-tubal passage
3. Lymphatic
4. Hematogenous
Surgical Staging

- Stage I – Confined to uterus
- Stage II – Cervical involvement
- Stage III – Regional disease
  - Vaginal, tubal or ovarian involvement
  - Pelvic or aortic lymph nodes
- Stage IV – Distant disease
  - Bowel or bladder invasion
  - Peritoneal or pulmonary disease

To stage or not to stage?
- “All” women should be staged
- Exceptions
  - Young or perimenopausal women with
    - grade 1 endometrioid adenocarcinoma
    - Associated with atypical hyperplasia
    - Women at risk of mortality from co-morbidities
- Intraoperative assessment / frozen section
- Sentinel lymph node assessment
Endometrial cancer-depth of invasion

- MRI
- Intra-op inspection
- Frozen Section

~70% accurate for grade and depth of invasion

Sentinel lymph node assessment
Prognostic Factors

- Tumor size >2 cm
- Histology
- Depth of myometrial invasion
- Tumor grade
- Lymph-vascular space involvement
- Lymph node involvement
- Extra-uterine spread

Summary

<table>
<thead>
<tr>
<th>TYPE I</th>
<th>TYPE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperestrogenism</td>
<td>No Estrogen Effect (?)</td>
</tr>
<tr>
<td>Peri- or post-menopausal</td>
<td>Post-menopausal</td>
</tr>
<tr>
<td>Hyperplastic endometrium</td>
<td>Atrophic endometrium</td>
</tr>
<tr>
<td>Low grade</td>
<td>High Grade</td>
</tr>
<tr>
<td>85% 5-year survival</td>
<td>50% 5-year survival</td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Poor prognosis</td>
</tr>
</tbody>
</table>
**Survival by Stage**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percent</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>73%</td>
<td>86%</td>
</tr>
<tr>
<td>II</td>
<td>12%</td>
<td>66%</td>
</tr>
<tr>
<td>III</td>
<td>12%</td>
<td>44%</td>
</tr>
<tr>
<td>IV</td>
<td>3%</td>
<td>16%</td>
</tr>
</tbody>
</table>

**“Low” Risk Disease**

- Definition – Low grade, minimal invasion, uterine-confined disease
- Overall survival (5-year) 95%
- Recurrence risk ~5%
- Recurrences almost exclusively local (vaginal)
- Radiation reserved for recurrences
  - Survival equal to those without recurrence
"Intermediate" Risk Disease

- **Definition** – endometrioid histology with based on Age, LVSI, depth of invasion, grade
- **5-year survival 75%**
- **Recurrence risk 15%**
- **Recurrences are local and distant**
- **Management controversial (observation and/or radiation and/or chemotherapy)**

### National Comprehensive Cancer Network Guidelines 2.2015
**Endometrial Carcinoma**

<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 or Vaginal brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Adverse risk factors present</td>
<td>G2 Observe or Vaginal brachytherapy and/or Pelvic RT (category 2B for pelvic RT)</td>
</tr>
<tr>
<td>Stage IB (&gt;50% myometrial invasion)</td>
<td>Adverse risk factors not present</td>
<td>G1 Observe or Vaginal brachytherapy</td>
</tr>
<tr>
<td></td>
<td>Adverse risk factors present</td>
<td>G2 Observe or Vaginal brachytherapy and/or Pelvic RT or Observe (Category 2B for observation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G3 Vaginal brachytherapy and/or Pelvic RT and/or Vaginal brachytherapy + chemotherapy (category 2B for chemotherapy)</td>
</tr>
</tbody>
</table>

Surgically staged: Stage II
Intermediate risk

- Radiation decreases recurrence but no survival benefit
- Vaginal brachytherapy as effective as pelvic radiation but with less toxicity
- Pelvic radiation versus vaginal cuff brachytherapy depends on surgical staging and uterine factors, physician and patient preference

GOG 99, PORTEC 1+2, GOG 249

Hormone Replacement after diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Premarin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>618</td>
<td>618</td>
</tr>
<tr>
<td>Disease Recurrence</td>
<td>14 (2.3%)</td>
<td>10 (1.6%)</td>
</tr>
<tr>
<td>Cancer-related Deaths</td>
<td>5 (0.8%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>23 (3.7%)</td>
<td>16 (2.6%)</td>
</tr>
</tbody>
</table>

*Short course for OK in early stage if needed*

### “High” Risk Disease

- **Definition**
  - Extrauterine disease
  - Non-endometrioid histology
- **Overall survival (5-year) 50%**
- **Recurrences are often distant**
- **Management with adjuvant chemotherapy +/- radiation**

### Type II endometrial cancers

- **Patterns of spread different from endometrioid cancers**
  - LVSI and nodal metastases up to 40%
  - Often metastasizes similarly to ovarian /fallopian tube cancers (consider omentectomy)
- **Recurrence rate >30% for stage I without adjuvant therapy**
- **Chemotherapy +/- radiation recommended for all stages (including stage I)**
# Recurrent Disease

- 85% of recurrences by 2 years, 95% by 5 years
- Diagnosed by presence of symptoms or on examination (speculum and rectovaginal exam)
  - Local recurrence
    - Vaginal bleeding
    - Pelvic pain
  - Distant metastases
    - Abdominal pain/bloating/bowel/bladder changes
    - Shortness of breath

## Recurrent Disease

- **Radiation**
  - For local recurrence – External beam and brachytherapy
  - 5-year survival 66-85%
- **Surgery**
  - Isolated central pelvic or vaginal recurrences
  - Pelvic exenteration for bulky central recurrence
- **Chemotherapy**
  - Cytotoxics
  - Biologics
  - Hormones and SERMs
Recurrent Disease: Hormonal Therapy

- Progestational agents
- Aromatase inhibitors
- Megestrol/tamoxifen (alternating)

Recurrent Disease: Chemotherapy

<table>
<thead>
<tr>
<th>Multi-agent chemotherapy</th>
<th>Single agent chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin/paclitaxel</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Cisplatin/doxorubicin</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Cisplatin/doxorubicin/paclitaxel</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Carboplatin/docetaxel</td>
<td>Liposomal doxorubicin</td>
</tr>
<tr>
<td>Ifosfamide/paclitaxel – carcinosarcoma</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Cisplatin/ifosfamide – carcinosarcoma</td>
<td>Topotecan</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide (carcinosarcoma)</td>
</tr>
</tbody>
</table>

National Comprehensive Cancer Network Guidelines 2.2015
Gynecologic Oncology Group trials

<table>
<thead>
<tr>
<th></th>
<th>Response rate (%)</th>
<th>Progression free survival (months)</th>
<th>Overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin/ Cisplatin</td>
<td>34-40%</td>
<td>5.3-7.2</td>
<td>12.1-12.4</td>
</tr>
<tr>
<td>Adriamycin/ Paclitaxel</td>
<td>44%</td>
<td>6.0</td>
<td>13.6</td>
</tr>
<tr>
<td>Adriamycin/ Cisplatin/ Paclitaxel</td>
<td>57%</td>
<td>8.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Carboplatin/ Paclitaxel</td>
<td>?</td>
<td>14</td>
<td>32</td>
</tr>
</tbody>
</table>

Targeted therapy

- **mTOR inhibitors**
  - temsirolimus, everolimus, deforolimus
  - metformin
- **EGFR family**
  - Anti-HER-2 MAb - trastuzumab
  - EGFR inhibitors – little activity
- **Antiangiogenics**
  - Anti-VEGF MAb – bevacizumab
  - VEGF-Trap
  - TK inhibit
# Recurrent disease

- **Hormonal therapy:**
  - Predictors for Response
    - Grade 1 (well differentiated)
    - Long disease-free interval
    - Positive receptors
  - Overall response rate ~ 25%
  - Overall response duration <4 months but some long term responders

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# Uterine sarcoma

- 5% of all uterine cancers
- Increased in African Americans
- **Classification**
  - Carcinosarcoma
  - Leiomyosarcoma
  - Endometrial stromal sarcoma (low grade)
  - High grade endometrial stromal sarcoma (undifferentiated sarcoma)
- Staging depends on type of sarcoma
Uterine sarcoma

- Metastatic disease and high mortality rates
- Stage I disease has recurrence rates over 50%

Uterine sarcoma

- Surgery
  - For diagnosis and prognosis
  - Only therapy with survival benefit
- Radiation therapy
  - May improve local control
- Chemotherapy
- Outcome
  - Stage I – 5-year survival 50%
  - Higher stage – 5-year survival 20%
Carcinosarcoma

- Epithelial (carcinoma) and mesenchymal (sarcoma) = Malignant Mixed Mullerian Tumor
  - Homologous (native tissues)
  - Heterologous (non-native tissues)
    - Striated muscle, cartilage, bone

Carcinosarcoma

- Epithelial component metastasizes
- High local and systemic failure rate
- Adjuvant chemotherapy for all stages +/- radiation (ifosfamide, taxane, platinum)
Leiomyosarcoma

- Almost 50% with stage I disease
- Majority recur
- 3-yr progression free survival after chemotherapy for stage I is 57%
- More likely to metastasize to lungs/liver
- Treatment with surgery, gemcitabine/docetaxel and/or doxorubicin combination

Hensley Cancer 2013, Int J Gynecol Cancer 2014

Endometrial stromal sarcoma

- Low grade tumor
- Hormone sensitive
  - Stage I: observation or hormonal therapy
    - Progestins
    - Aromatase inhibitors
- Advanced and recurrent disease
  - Hormones
  - Radiation
  - Chemotherapy (adriamycin, ifosfamide)
- May transition to poorly differentiated sarcoma
**High grade endometrial stromal sarcoma**

- Undifferentiated sarcoma
- Very poor prognosis
- Not hormone sensitive
- Clinical trials recommended
- Adjuvant chemotherapy +/- radiation

**Endometrial cancer surveillance**

- Routine imaging not recommended
- Pap tests not recommended
- Careful history for symptoms
- Detailed physical exam including speculum and rectovaginal exam
- Surveillance every 3-6 months for 2 years and every 6-12 months for year 3-5 (depending on stage and risk of recurrence)
- Weight loss and exercise, healthy lifestyle

# Conclusion

- Early presenting symptoms (bleeding)
- Majority are early stage and highly curable
- Recurrence most often locoregional
- Majority of patients will die of comorbidities rather than cancer → lifestyle modification!

- Type 2 and sarcoma have high recurrence rates and often distant component
- Chemotherapy +/- radiation is recommended