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)

![Ovulatory cycle diagram](Author: Lyrl | CC BY-SA 3.0)
Anovulation

- Physiologic
  - Adolescence
  - Peri-menopause
  - Lactation
  - Pregnancy

- Pathologic
  - Hyperandrogenic (PCOS, congenital adrenal hyperplasia, androgen producing tumors)
  - Hypothalamic dysfunction
  - Hyperprolactinemia
  - Thyroid disease
  - Pituitary disease
  - Premature ovarian failure
  - Iatrogenic (radiation/chemo)
  - Medications

Abnormal uterine bleeding causes

- Structural (PALM)
  - Polyp
  - Adenomyosis
  - Leiomyoma
  - Malignancy or hyperplasia

- Non-structural (COEIN)
  - Coagulopathy
  - Ovulatory dysfunction
  - Endometrial
  - Iatrogenic (ASA, warfarin)
  - Not yet classified

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
### Age 19-39

- 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)

### 40-menopause

- 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 curettage)
- 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</td>
<td>10-20 mg daily or cyclic 12-14 d/month</td>
</tr>
<tr>
<td>(Provera)</td>
<td></td>
</tr>
<tr>
<td>Depot medroxyprogesterone</td>
<td>150 mg IM every 3 months</td>
</tr>
<tr>
<td>(DepoProvera)</td>
<td></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

<table>
<thead>
<tr>
<th></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.

American Cancer Society, Inc.
http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/index
Estimated Cancer Deaths in the U.S. in 2015

Men         Women
312,150     277,280

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men (%)</th>
<th>Women (%)</th>
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<tbody>
<tr>
<td>Lung &amp; bronchus</td>
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<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>

Uterine Neoplasia

Hyperplasia  Adenocarcinoma  Sarcoma

Type I
- Endometrioid
- Mucinous
- PTEN
- MMR/MSI
- KRAS
- β-catenin
- microRNA

Type II
- Serous
- Clear cell
- Carcinosarcoma
- TP53
- HER-2/neu
- p16

Pathology

- Endometrioid
- Papillary serous
- Clear cell

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>Genetics</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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Oral contraception</td>
<td><strong>Women at risk should be counseled on healthy lifestyle and awareness of symptoms</strong></td>
</tr>
<tr>
<td>Progesterone therapy/contraception</td>
<td></td>
</tr>
<tr>
<td>Progesterone intra-uterine device</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
</tbody>
</table>

## SERMs and Cancer

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-estrogenic effect on uterus</td>
<td><strong>90% cases are sporadic</strong></td>
</tr>
<tr>
<td>NSABP data (Tamoxifen)</td>
<td><strong>Alterations</strong></td>
</tr>
<tr>
<td>2-3x risk adenocarcinoma</td>
<td>PTEN – 35% cases</td>
</tr>
<tr>
<td>Higher risk sarcoma (17/100,000 vs. 0)</td>
<td>TP53 – 30% cases</td>
</tr>
<tr>
<td>STAR trial showed raloxifene with lower risk</td>
<td>HER2/neu – 25% cases</td>
</tr>
<tr>
<td><strong>Recommendations</strong></td>
<td>2-5% cases are inherited</td>
</tr>
<tr>
<td>Alert patients regarding risk</td>
<td>Lynch (2-3%), Cowden’s Disease</td>
</tr>
<tr>
<td>Any bleeding should be evaluated with biopsy</td>
<td></td>
</tr>
</tbody>
</table>
### Lynch syndrome

- Autosomal dominant inheritance
- Penetrance 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

<table>
<thead>
<tr>
<th>Colon cancer</th>
<th>Extracolonic tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early age of diagnosis</td>
<td>Endometrial cancer</td>
</tr>
<tr>
<td>Proximal colon lesions</td>
<td>60% lifetime risk</td>
</tr>
</tbody>
</table>

- 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

### 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)

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Lu, K. Obstet Gynecol 2005; NCCN
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

Surgical Staging

- 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

ACOG Practice Bulletin Number 65, August 2005
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></th>
<th>TYPE I</th>
<th>TYPE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperestrogenism</td>
<td>No Estrogen Effect (?)</td>
<td></td>
</tr>
<tr>
<td>Peri- or post-menopausal</td>
<td>Post-menopausal</td>
<td></td>
</tr>
<tr>
<td>Hyperplastic endometrium</td>
<td>Atrophic endometrium</td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>High Grade</td>
<td></td>
</tr>
<tr>
<td>85% 5-year survival</td>
<td>50% 5-year survival</td>
<td></td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Poor prognosis</td>
<td></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, LVSIV, 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</td>
</tr>
<tr>
<td>Stage IB (≥50% myometrial invasion)</td>
<td>Adverse risk factors present</td>
<td>Observe or Vaginal Brachytherapy and/or Pelvic RT (Category 2B for observation)</td>
</tr>
</tbody>
</table>

*National Comprehensive Cancer Network Guidelines 2.2015*
**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*

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**“High” Risk Disease**

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

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**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: Hormonal Therapy

- Progestational agents
- Aromatase inhibitors
- Megestro/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</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>− carcinosarcoma</td>
<td>Topotecan</td>
</tr>
<tr>
<td>Cisplatin/ifosfamide</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>− carcinosarcoma</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Ifosfamide (carcinosarcoma)</td>
<td>Bevacizumab (carcinosarcoma)</td>
</tr>
</tbody>
</table>
Gynecologic Oncology Group trials

<table>
<thead>
<tr>
<th>Treatment</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

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

**Salani, Backes. Am J Obstet Gynecol 2011**
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