Uterine Bleeding and Uterine Cancer

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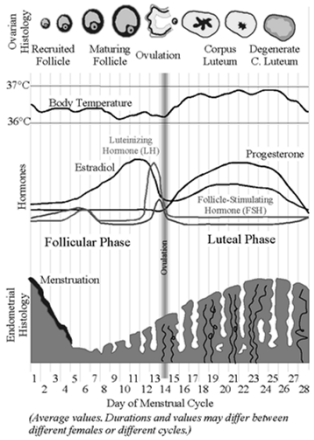
Uterine bleeding: Objectives

- **"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

- **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**

ACOG practice bulletin 136, July 2013

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**

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**

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

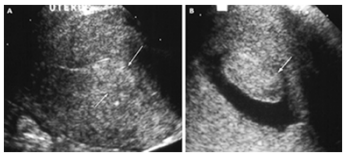
- Depends on etiology
  - Combined oral contraceptives
    - Continuous or cyclic
  - Levonorgestrel intrauterine device
  - Oral progestins (not adequate for birth control, OK for peri-menopausal women)
  - Weight loss and exercise
  - Endometrial ablation (only for premenopausal women with normal endometrial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

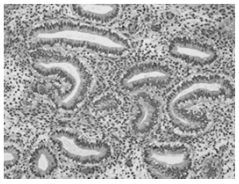
Postmenopausal bleeding

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



Endometrial hyperplasia

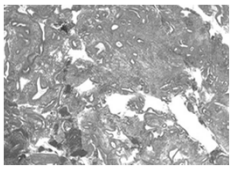
- Simple hyperplasia without atypia
  - 1% progression to cancer
  - Treat with progestins
- Complex hyperplasia without atypia
  - 3% progression to cancer
  - Treat with progestins



Normal endometrium

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

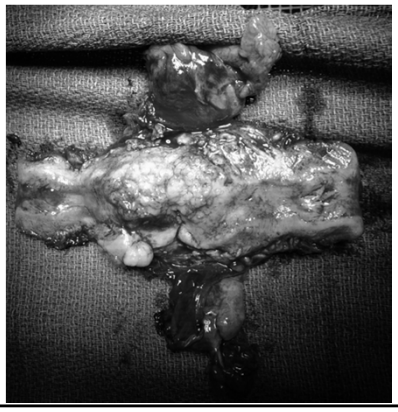


Progestin therapy options

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

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

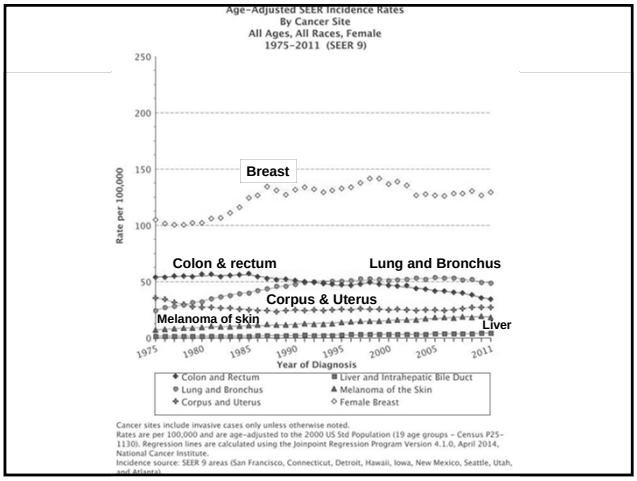
Estimated New Cancer Cases* in the U.S. in 2015

Men	Women
848,200	810,170

Men			Women
Prostate	26%	29%	Breast
Lung & bronchus	14%	13%	Lung & bronchus
Colon & rectum	8%	8%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	5%	6%	Thyroid
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Kidney & renal pelvis	5%	4%	Melanoma of skin
Oral cavity & pharynx	4%	3%	Pancreas
Leukemia	4%	3%	Leukemia
Liver & intrahepatic bile duct	3%	3%	Kidney & renal pelvis
All other sites	21%	21%	All other sites

*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

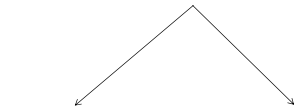
Men	Women
312,150	277,280

Men			Women
Lung & bronchus	28%	26%	Lung & bronchus
Prostate	9%	15%	Breast
Colon & rectum	8%	9%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	5%	5%	Ovary
Leukemia	5%	4%	Leukemia
Esophagus	4%	4%	Uterine corpus
Urinary bladder	4%	3%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	3%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain & other nervous system
All other sites	24%	23%	All other sites

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

Uterine Neoplasia

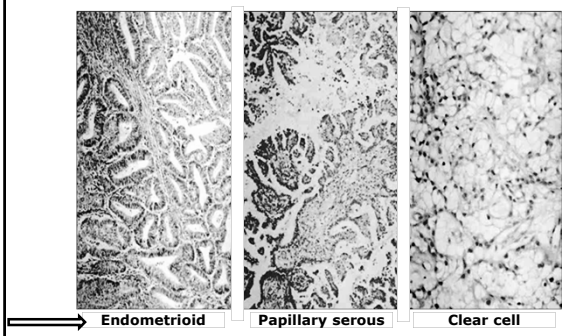
Hyperplasia **Adenocarcinoma** **Sarcoma**



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

- **Epidemiology**
  - **Age – Median 62 y**
  - **Race – Caucasian**
- **Genetics**
  - **Lynch/HNPCC (mismath repair)**
  - **Cowden's disease (PTEN)**
  - **?BRCA**
- **Unopposed estrogen**
  - **Obesity**
  - **Chronic anovulation (polycystic ovary syndrome)**
  - **Estrogen therapy, SERMs**
  - **Granulosa cell tumors**
  - **Diabetes**
  - **Nulliparity**
  - **Early menarche/Late menopause**

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

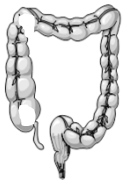
- **90% cases are sporadic**
- **Alterations**
  - **PTEN – 35% cases**
  - **TP53 – 30% cases**
  - **HER2/neu – 25% cases**
- **2-5% cases are inherited**
  - **Lynch (2-3%), Cowden's Disease**

Lynch syndrome

- Autosomal dominant inheritance
- 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

- 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

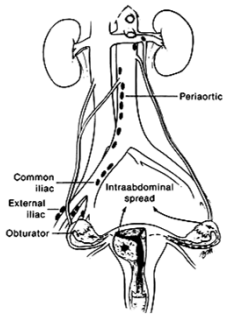
- Uterine histology
  - Endometrial biopsy (EMB – office)
  - Dilation and curettage (D&C – OR)
  - EMB has a 10% false negative rate in symptomatic women
- Vaginal ultrasonography
  - Evaluate endometrial stripe thickness
  - < 5 mm = low risk for endometrial cancer (caveat: serous adenocarcinoma)

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

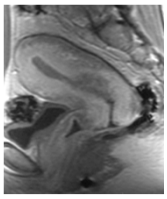
- Stage I – Confined to uterus
- Stage II – Cervical involvement
- Stage III – Regional disease
  - Vaginal, tubal or ovarian involvement
  - Pelvic or aortic lymph nodes
- Stage IV – Distant disease
  - Bowel or bladder invasion
  - Peritoneal or pulmonary disease

Surgical Staging

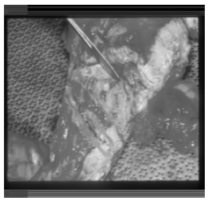
- To stage or not to stage?
  - "All" women should be staged
  - Exceptions
    - Young or perimenopausal women with
    - grade 1 endometrioid adenocarcinoma
    - Associated with atypical hyperplasia
    - Women at risk of mortality from co-morbiditie
  - Intraoperative assessment / frozen section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

ACOG Practice Bulletin Number 65, August 2005

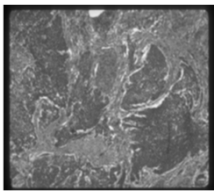
Endometrial cancer-depth of invasion



MRI



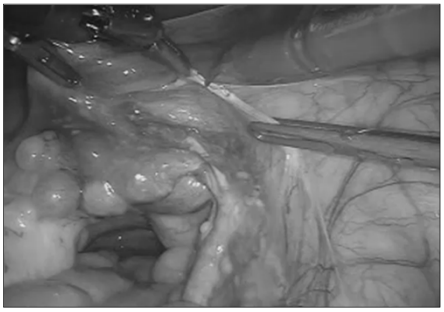
Intra-op inspection



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

TYPE I	TYPE II
Hyperestrogenism	No Estrogen Effect (?)
Peri- or post-menopausal	Post-menopausal
Hyperplastic endometrium	Atrophic endometrium
Low grade	High Grade
85% 5-year survival	50% 5-year survival
Good prognosis	Poor prognosis

Survival by Stage

Stage	Percent	5-year Survival
I	73%	86%
II	12%	66%
III	12%	44%
IV	3%	16%

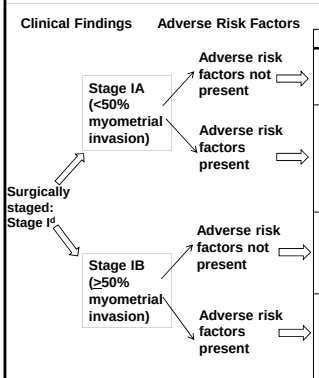
"Low" Risk Disease

- **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



Histologic Grade/Adjuvant Treatment		
G1	G2	G3
Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT (category 2B for pelvic RT)	Observe or Vaginal brachytherapy and/or Pelvic RT
Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Vaginal brachytherapy and/or Pelvic RT or Observe (Category 2B for observation)
Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy[g,n] (category 2B for chemotherapy)

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

	Premarin	Placebo
Patients	618	618
Disease Recurrence	14 (2.3%)	10 (1.6%)
Cancer-related Deaths	5 (0.8%)	4 (0.6%)
Total Deaths	23 (3.7%)	16 (2.6%)

Short course for OK in early stage if needed

Barakat RR, et al. *J Clin Oncol* 2006;24:587-92

"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
- Megestro/tamoxifen (alternating)

National Comprehensive Cancer Network Guidelines 2.2015

Recurrent Disease: Chemotherapy

Multi-agent chemotherapy

- Carboplatin/paclitaxel
- Cisplatin/doxorubicin
- Cisplatin/doxorubicin/ paclitaxel
- Carboplatin/docetaxel
- Ifosfamide/paclitaxel
  - carcinosarcoma
- Cisplatin/ifosfamide
  - carcinosarcoma

Single agent chemotherapy

- Cisplatin
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Paclitaxel
- Topotecan
- Bevacizumab
- Docetaxel
- Ifosfamide (carcinosarcoma)

National Comprehensive Cancer Network Guidelines 2.2015

Gynecologic Oncology Group trials

	Response rate (%)	Progression free survival (months)	Overall survival (months)
Adriamycin/ Cisplatin	34-40%	5.3-7.2	12.1-12.4
Adriamycin/ Paclitaxel	44%	6.0	13.6
Adriamycin/ Cisplatin/ Paclitaxel	57%	8.3	15.3
Carboplatin/ Paclitaxel	?	14	32

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**

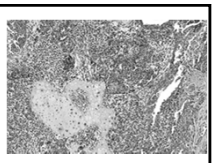
Uterine sarcoma

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

Uterine sarcoma

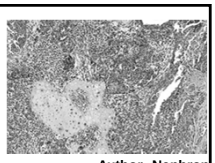
- Surgery
  - For diagnosis and prognosis
  - Only therapy with survival benefit
- Radiation therapy
  - May improve local control
- Chemotherapy
- Outcome
  - Stage I – 5-year survival 50%
  - Higher stage – 5-year survival 20%

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**