ENDOMETRIAL CANCER

FLAME LECTURE: 228

LO / CHERUKURI 12.26.19

LEARNING OBJECTIVES

- To identify risk factors for endometrial hyperplasia/cancer
- To describe symptoms and physical findings
- To understand outpatient and inpatient gynecologic procedures and their indications and possible complications
- Prerequisites:
  - NONE
- See also – for closely related topics
  - FLAME LECTURE 214: Evaluation of Abnormal Uterine Bleeding
  - FLAME LECRUE 215: Medical & Surgical Treatment of Abnormal Uterine Bleeding
  - FLAME LECTURE 229: Postmenopausal Bleeding

EPIDEMIOLOGY

- Most common gynecologic malignancy in developed countries and 2nd most common in developing countries (behind cervical cancer)
- In the United States
  - Over 54,000 new cases/year
  - Mortality rate is 1.7-2.4 per 100,000 women
  - Caucasian women have a 2.81% lifetime risk
  - Average age of diagnosis is 63 years old
  - 70% of women are diagnosed at Stage I, with reported 90% 5-year survival rate

Incidence
1. Endometrial
2. Ovarian
3. Cervical

Mortality
1. Ovarian
2. Cervical
3. Endometrial

HISTOPATHOLOGY

- **Type 1 Tumors:** 80% of endometrial carcinomas
  - Endometrioid histology
  - Grade 1 or 2
  - Favorable prognosis, estrogen-responsive, may be preceded by endometrial hyperplasia
- **Type 2 Tumors:** 10-20% of endometrial carcinomas
  - Grade 3
  - Endometrioid or non-endometrioid histology (serous, clear cell, mucinous, squamous, transitional cell, mesonephric and undifferentiated)

RISK FACTORS FOR TYPE 1

Factors Influencing Risk	Estimated Relative Risk
Menstrual Irregularities	1.5
Early age at menarche	1.5-2
Diabetes Mellitus	2
Older Age	2-3
History of Infertility	2-3
Tamoxifen use	2-3
Late age at natural menopause	2-3
Nulliparity	3
Polycystic Ovary Syndrome	3
Obesity	2-5
Estrogen-producing tumor	>5
Lynch Syndrome	6-20
Unopposed Estrogen therapy	10-20

The main risk factor is **prolonged exposure to unopposed estrogen**! Any condition that increases the amount of estrogen can increase the risk of developing type 1 endometrial cancer!

Adipose tissue converts androgens to estrone

PROTECTIVE FACTORS

- Decreased lifetime estrogen exposure / Decreased menstrual cycles with turnover of endometrium
  - **Combination oral contraceptives (OCPs)**
  - Progestin-containing contraceptives
  - Combination estrogen and progesterone hormone replacement (HRT)
  - High parity
  - Pregnancy
  - Smoking (only in postmenopausal women) through increased hepatic metabolism of estrogens
  - Healthy diet & exercise

CLINICAL PRESENTATION

Abnormal Uterine Bleeding is present in 75% to 90% of cases

POSTMENOPAUSAL

- **ANY bleeding** (including spotting)
- 3% to 20% of women with postmenopausal bleeding have endometrial carcinoma
- 5 % to 15% of women with postmenopausal bleeding have endometrial hyperplasia

AGE 45 TO MENOPAUSE

- Intermenstrual bleeding
- Heavy bleeding: total volume >80 mL
- Prolonged bleeding: >7 days
- Frequent bleeding: <21 days between episodes

<45 YEARS OLD

- Persistent bleeding that occurs in the setting of a history of unopposed estrogen exposure (obesity, chronic anovulation)
- Failed medical management of persistent bleeding
- Persistent bleeding in women with high risk (Lynch Syndrome, Cowden Syndrome)

DIFFERENTIATION

- Differential Diagnosis:
  - Uterine Fibroids
  - Endometrial Polyps
  - Adenomyosis
  - Endometrial Hyperplasia
  - Ovarian Cysts
  - Thyroid Dysfunction
- Initial Evaluation:
  - Pelvic Exam
  - Transvaginal Ultrasound
  - Endometrial Biopsy
- Differential Studies to Consider:
  - CA-125 level (Ovarian CA)
  - Pap Smear (Cervical CA)
  - Pregnancy test
  - Serum Studies (Endocrine/Heme Issue)
    - TSH, LH, FSH, Prolactin, CBC, clotting studies

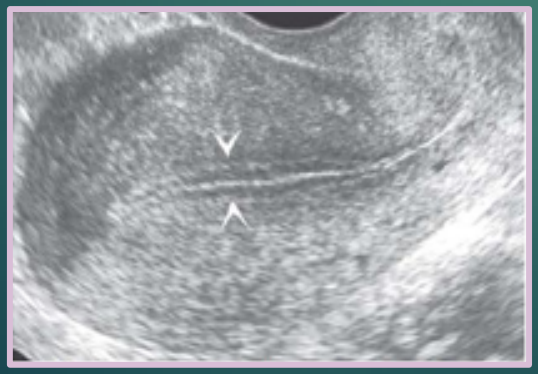
INITIAL EVALUATION

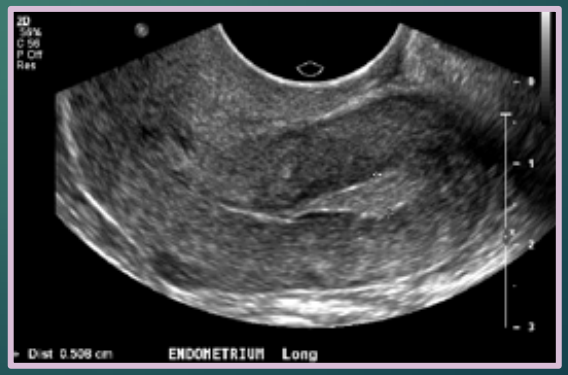
- Pelvic exam: evaluate size, mobility and axis of the uterus
  - An enlarged, fixed uterus may be consistent with uterine leiomyomas or pelvic malignancy and warrant further evaluation
  - Uterine leiomyomas can cause abnormal uterine bleeding and can change surgical planning
  - Ensure the bleeding is uterine and not due to a cervical or vaginal laceration
- Laboratory:
  - Women of reproductive age: urine or serum hCG to exclude pregnancy
  - CBC and Clotting Studies if bleeding is heavy and anemia or coagulopathy is suspected

TRANSVAGINAL ULTRASOUND

- Endometrial thickness is the initial study to evaluate for endometrial carcinoma in postmenopausal women
- Endometrial thickness of **<4 mm** is considered "normal" but if the woman continues to have abnormal bleeding, an endometrial biopsy should be performed
- Premenopausal women **REQUIRE** an endometrial biopsy

Normal Endometrial Stripe between arrows (<4 mm)





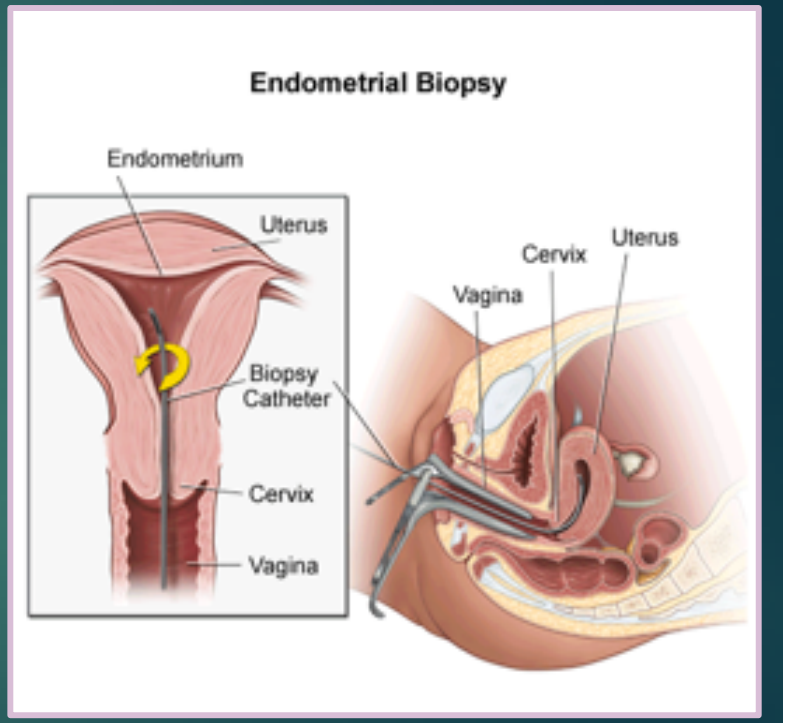
Thickened Endometrial Stripe (5 mm)

OTHER IMAGING

- Pelvic or abdominal imaging to assess myometrial invasion or cervical involvement is **unnecessary** if surgical staging is planned
- MRI with contrast is the best radiographic modality for detecting lymph node metastasis, cervical involvement, or myometrial invasion
- Chest radiograph should be performed as part of initial search for metastasis following diagnosis

ENDOMETRIAL BIOPSY

- Most commonly performed in the outpatient setting
- May be performed without anesthesia or with only local anesthesia
- Minimal or no cervical dilation is required
- Risk of uterine perforation is 0.1 to 0.2%
- Sampling time is approximately 5 to 15 seconds
- Only absolute contraindication is the presence of a viable and desired pregnancy

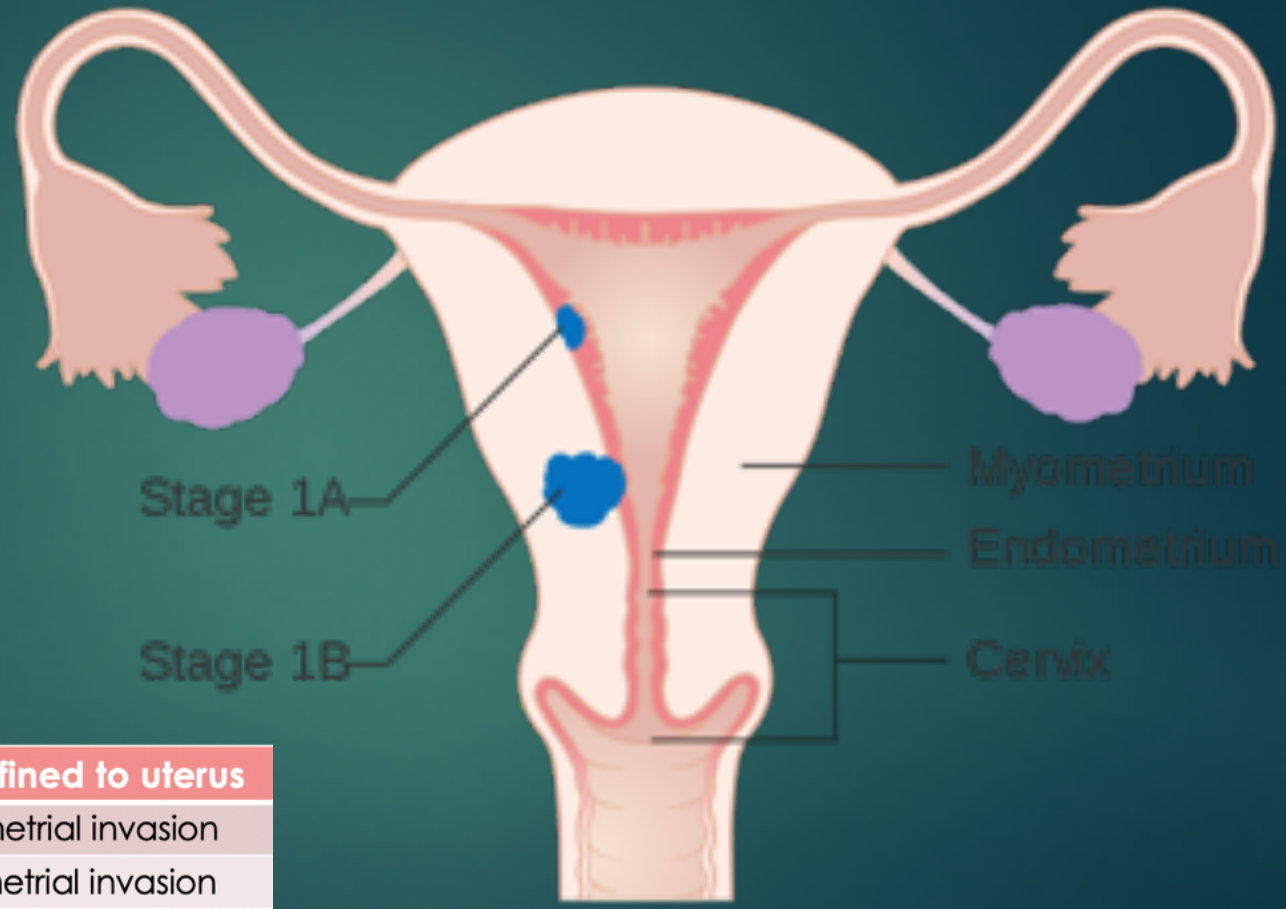


STAGING

Endometrial carcinoma is surgically staged using the International Federation of Gynecology and Obstetrics' Surgical Staging System for Endometrial Cancer

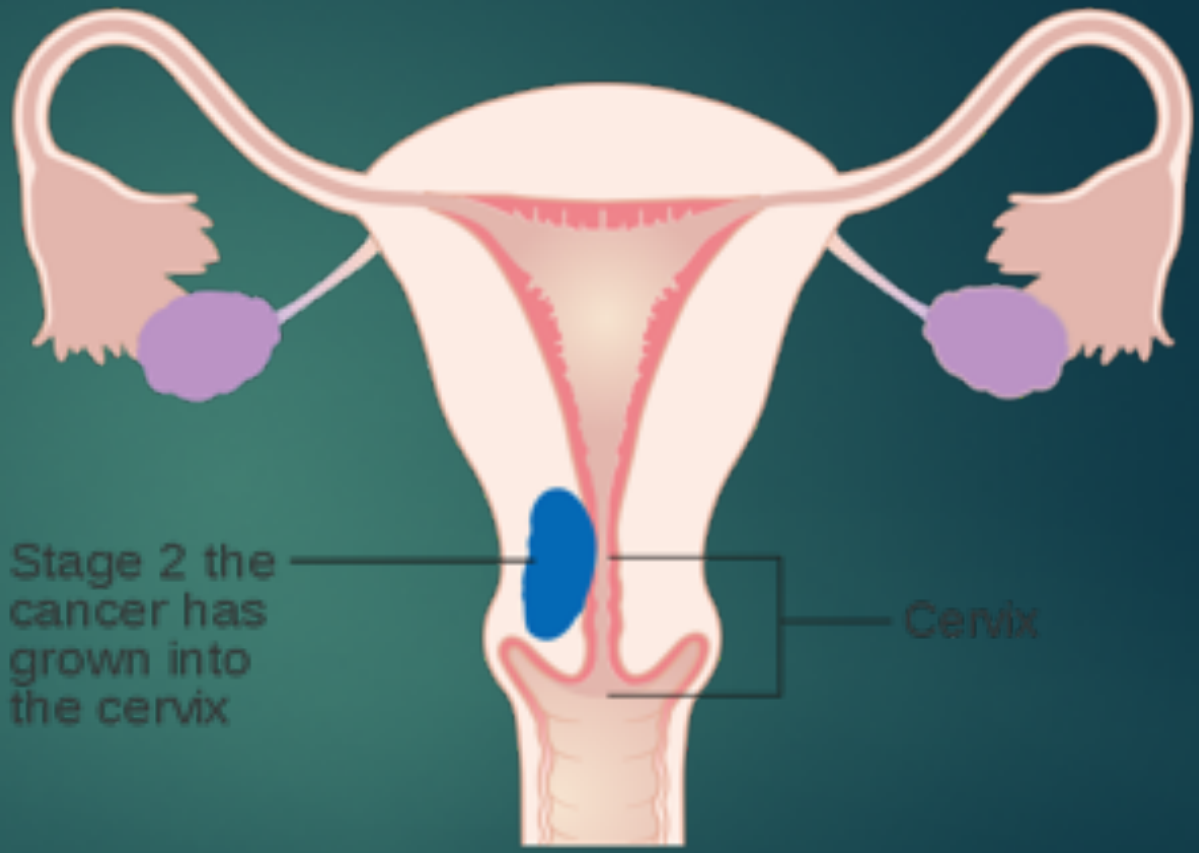
Stage I	**Tumor confined to uterus**
IA	<50% myometrial invasion
IB	≥50% myometrial invasion
Stage II	**Tumor invades cervical stroma, not beyond uterus**
Stage III	**Local and/or regional spread of tumor**
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa
IIIB	Vaginal or parametrial involvement
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic lymph nodes
IIIC2	Positive para-aortic lymph nodes +/- pelvic lymph nodes
Stage IV	**Invasion of bladder/bowel mucosa, and/or metastasis**
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastasis and/or inguinal lymph nodes

STAGE 1



Stage I	Tumor confined to uterus
IA	<50% myometrial invasion
IB	≥50% myometrial invasion

STAGE 2



Stage II	**Tumor invades cervical stroma, not beyond uterus**

STAGE 3

Stage III	Local and/or regional spread of tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa
IIIB	Vaginal or parametrial involvement
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
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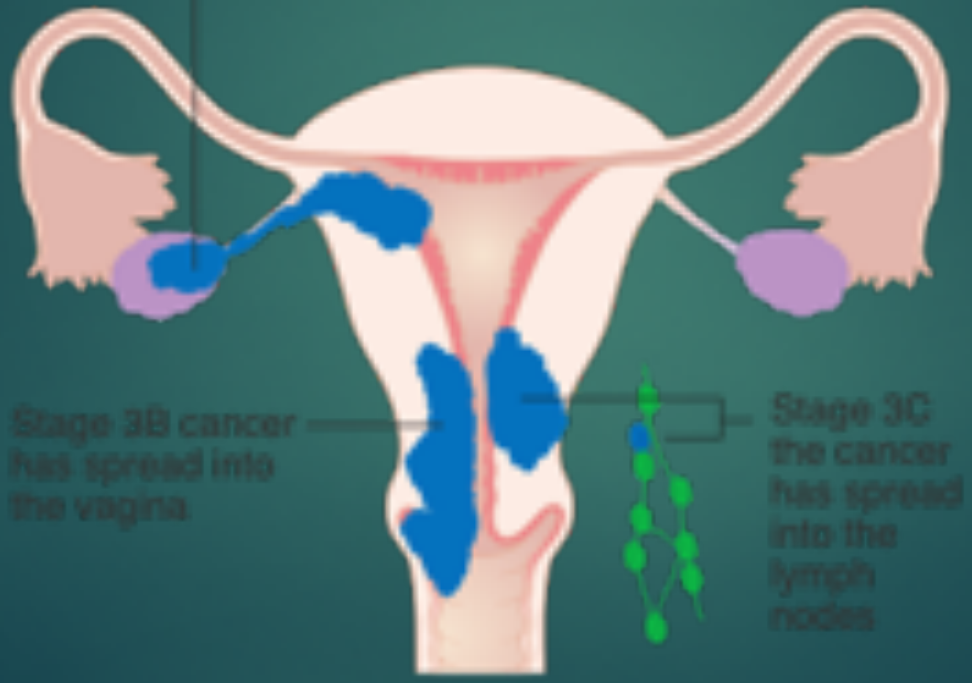
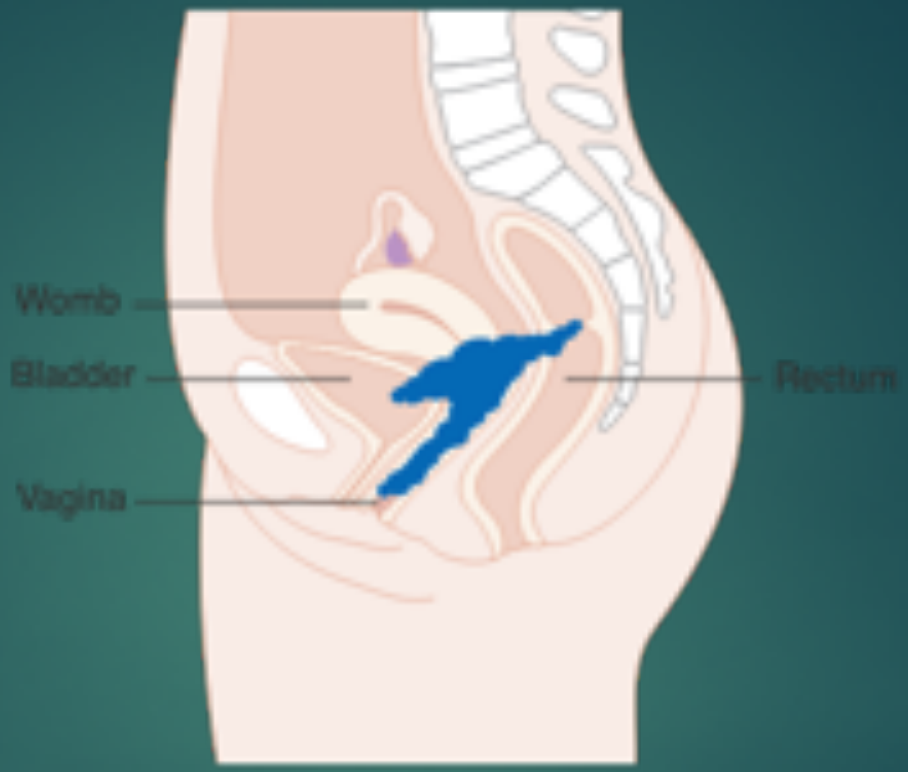


STAGE 4



Stage IV	Invasion of bladder/bowel mucosa, and/or metastasis
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastasis and/or inguinal lymph nodes

SURGICAL TREATMENT

- Gold standard for staging: total abdominal hysterectomy with bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection (TAH-BSO PPALND)
- Usually curative for patients with low risk disease
- Laparoscopic or Robot-Assisted approaches are also possible
  - Vaginal hysterectomies are not recommended and are reserved for patients who are poor candidates for abdominal surgery
- Experts debate whether full surgical staging is needed
  - In patients with grade 1 or 2 disease with presumed stage IA or IB disease, studies have shown that if they receive TAH-BSO with sampling of enlarged nodes on palpation only, have a greater than 90% 5-year survival rate

SURGICAL COMPLICATIONS

- **Blood Loss**
- **Infection:** empiric therapy with Metronidazole + Gentamicin
- **Thromboembolic Disease:** 2% to 5% of patients after PPALND
  - Septic Thrombophlebitis: febrile with no signs of localizing infection after 48 hours of empiric antibiotic therapy. Treat with Heparin.
- **Lymphedema:** 1.5% to 28% after PPALND
- **Bladder Dysfunction:** 70% to 85% of women up to 12 months
  - Stress urinary incontinence in 30%
- **Lymphocele:** 6% of patients
  - Often asymptomatic but can present with pelvic pressure or pain and can cause hydronephrosis secondary to external compression of the ureter

ADJUVANT TREATMENT

LOW RISK

- Grade 1 of endometrioid histology confined to endometrium
- Patient may wish to preserve fertility and can be treated with progestin therapy (megestrol acetate)
- <5% risk of recurrence after surgery

INTERMEDIATE RISK

- Stage II or lower, or grade 2-3
- Postoperative vaginal brachytherapy (recommended over whole pelvic irradiation)

HIGH RISK

- Stage 3 or higher or serous or clear cell histology
- Chemotherapy: Carboplatin + Paclitaxel

FOLLOW-UP

- Physical exam every 3 months for 3 years
  - Sterile speculum exam & pelvic exam
  - Then every 6 months for subsequent 2 years, after which the patient can be followed annually
  - Radiologic evaluation **not indicated** for surveillance, only indicated to investigate possible recurrence of disease
- Management of menopausal symptoms
  - 25% of women who undergo TAH-BSO for endometrial carcinoma are **premenopausal,** many develop menopausal symptoms after surgery
  - Discussion on quality of life is very important
  - Estrogen therapy can be considered ONLY in those with early-stage endometrial cancer

IMPORTANT LINKS / REFERENCES

- ACOG PRACTICE BULLETIN 149: ENDOMETRIAL CANCER
- UpToDate: Overview of Endometrial Carcinoma
- UpToDate: Endometrial Carcinoma: Clinical Features & Diagnosis
- UpToDate: Endometrial Sampling Procedures
- UpToDate: Endometrial Carcinoma: Staging and Surgical Treatment