Endometrial Cancer: Common but Predominantly Curable.

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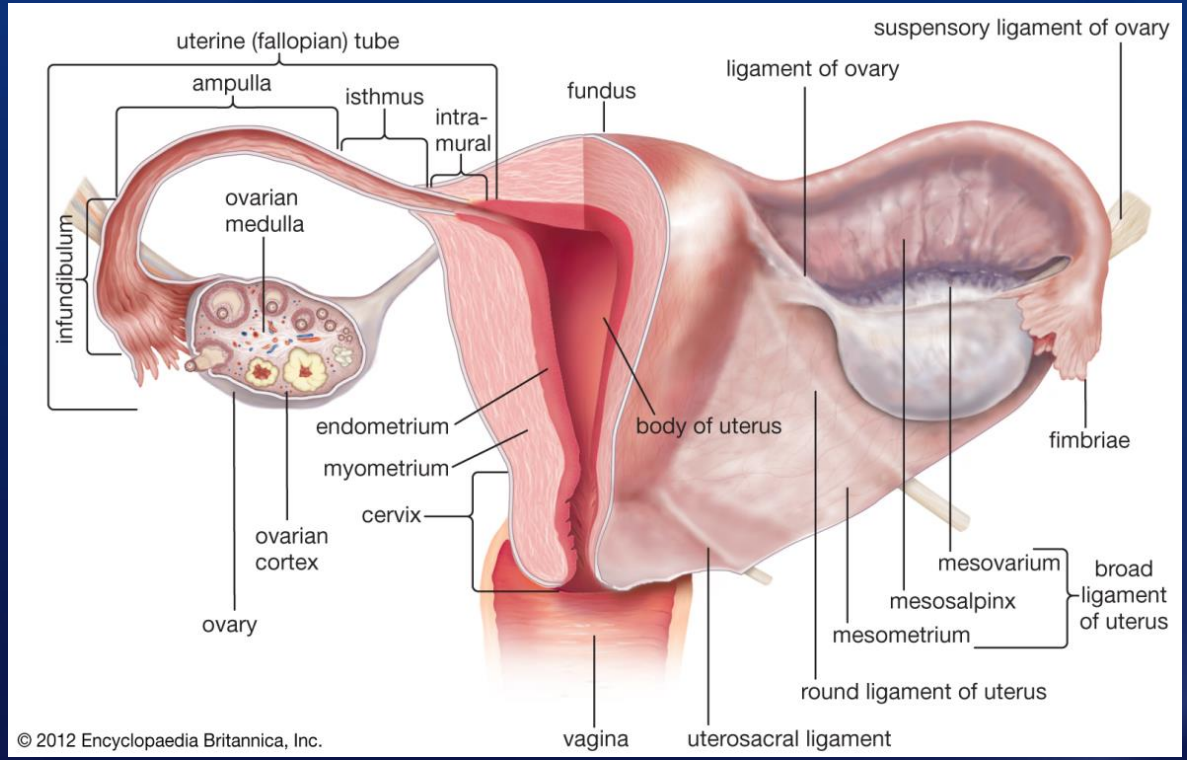
Off-label/Investigational Use

None

Objectives

- Review the anatomy and physiology of the uterus/endometrium.
- Present risks factors for the development of endometrial cancer
- Review the patient presentation, history, signs and symptoms suggestive of endometrial cancer.
- Review the treatment options for endometrial cancer including: surgery, radiation, and immunotherapy.

Anatomy


uterine (fallopian) tube
ampulla
isthmus
intra-
mural
fundus
suspensory ligament of ovary
ligament of ovary
ovarian
medulla
infundibulum
endometrium
myometrium
cervix
body of uterus
fimbriae
ovarian
cortex
ovary
mesovarium
broad
ligament
of uterus
mesosalpinx
mesometrium
round ligament of uterus
vagina
uterosacral ligament
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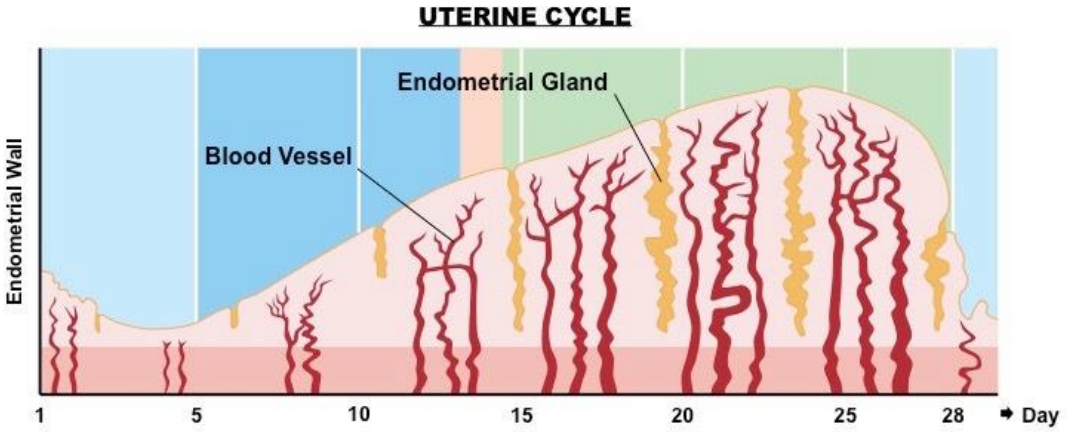
Normal Endometrial Physiology



Follicular phase
- Follicles release estrogen which causes the uterine wall (endometrium) to thicken

Ovulation
- When the follicle ruptures and develops into a corpus luteum, progesterone is produced

Luteal phase
- Progesterone and estrogen are released from the corpus luteum and thicken the endometrium

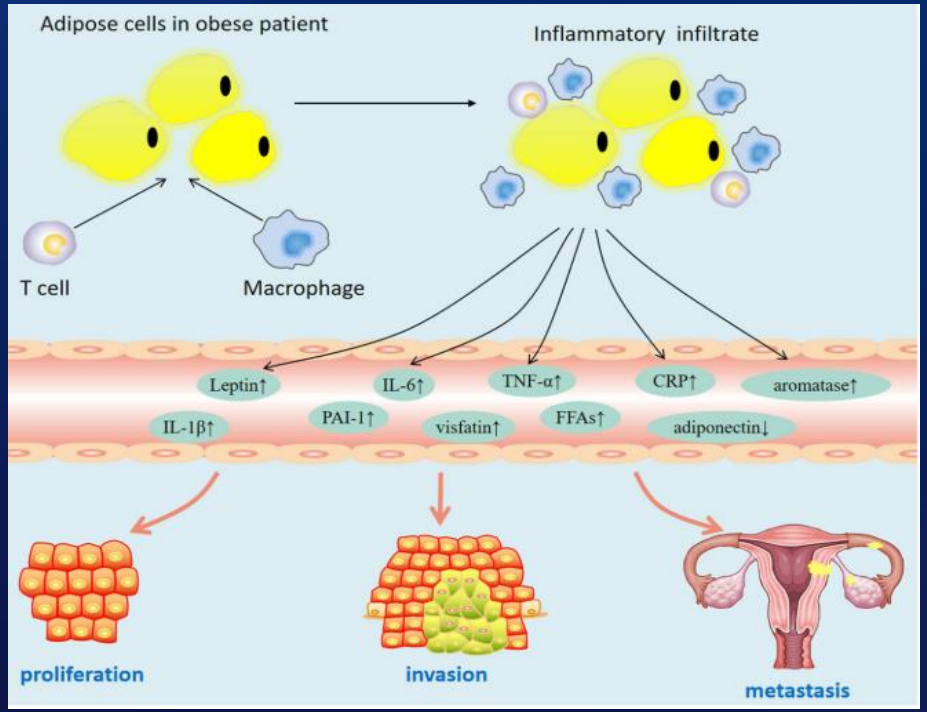
Menstruation
- The endometrium is sloughed away when the corpus luteum degenerates – a new cycle begins

Endometrial Cancer Statistics

- Most common cancer of the female reproductive organs
- American Cancer Society estimates:
  - 65,620 new cases diagnosed in 2020
  - increase 61,800 cases in 2019
  - ~12,590 women will die from cancers of the uterine body.
- Post-menopausal women: average age of diagnosis 60 years, uncommon <45 years
- More common in white women (30% higher incidence), black women have higher mortality rate (x2.5).

Endometrial Cancer Physiology

- Dysfunctional adipose tissue in obesity



Yang, X. and J. Wang (2019). "The Role of Metabolic Syndrome in Endometrial Cancer: A Review." Frontiers in Oncology 9.

Risk Factors

OVERWEIGHT WOMEN AND OBESE WOMEN HAD ESTIMATED ODDS RATIOS OF DEVELOPING ENDOMETRIAL CANCER OF 1.43 AND 3.33 RESPECTIVELY, COMPARED TO NORMAL-WEIGHT WOMEN.

Risk Factor	Relative risk (RR)/Overall Risk (OR) (other statistics are noted when used)
Increasing age	1.4% endometrial cancer prevalence in women 50 to 70 years old
Unopposed estrogen therapy	2 to 10
Tamoxifen therapy	2
Early menarche	NA
Late menopause (after age 55)	2
Nulliparity	2
Polycystic ovary syndrome (chronic anovulation)	3
Obesity	For type I endometrial cancer: OR 1.5 for overweight (BMI 25.0 to <30 kg/m^2), 2.5 for class 1 obesity (30.0 to <35 kg/m^2), 4.5 for class 2 obesity (35.0 to 39.9 kg/m^2), and 7.1 for class 3 obesity (≥40.0 kg/m^2). For type II: OR 1.2 for overweight (BMI 25.0 to <30 kg/m^2), 1.7 for class 1 obesity (30.0 to <35 kg/m^2), 2.2 for class 2 obesity (35.0 to 39.9 kg/m^2), and 3.1 for class 3 obesity (≥40.0 kg/m^2).
Diabetes mellitus	2
Estrogen-secreting tumor	NA

Jenabi E , Poorolajal J. The effect of body mass index on endometrial cancer: a meta-analysis. Public Health. 2015; doi:10.1016
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Obesity

- Trust for America's Health
  - Increase in obesity rates (BMI >30) in the US.
  - National average of 30.9%.
- Florida adult obesity
  - Increased from 28.4% in 2018 to 30.7% in 2019.
- First time in US history, 9 states above 35%; Alabama, Arkansas, Iowa, Kentucky, Louisiana, Mississippi, Missouri, North Dakota, and West Virginia.
- When compared to women with a body mass index (BMI) less than 25, overweight women (BMI 25 to 29.9) are twice as likely and obese women (BMI>30) are three times as likely to develop endometrial cancer.

Genetic Component

- Lynch syndrome (hereditary nonpolyposis colorectal cancer)
  - 80% increased risk for colorectal cancer and a
  - 60% increased risk for endometrial cancer (22-50% lifetime risk)
  - NCCN guideline: genetic testing for all women diagnosed with endometrial cancer before age 50 & family history of Lynch syndrome.
- Cowden syndrome
  - Autosomal dominant, PTEN mutations
  - 13-19% lifetime risk

Signs and Symptoms

- Abnormal uterine bleeding
  - Irregular menses
  - Anovulation
  - Intermenstrual spotting
  - Postmenopausal bleeding

- Advanced disease: abdominal/pelvic pain, abdominal distension, bloating, early satiety, change in bowel or bladder function.

Evaluation

- NCCN guidelines:
  - History and physical examination
  - Endometrial biopsy
  - Expert pathology review to determine histopathologic subtype
  - Because of a high false-negative rate (10%), a negative biopsy in symptomatic patients requires follow-up with a fractional dilation and curettage (D&C) under anesthesia.
  - Imaging studies (eg, CT, MRI, PET) and optional CA-125 testing for evaluation of extrauterine disease

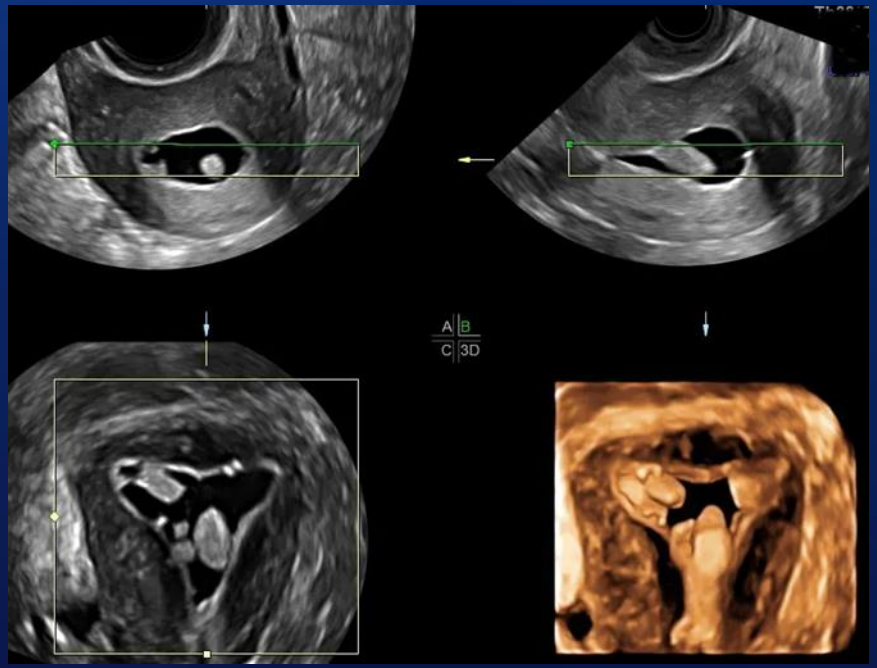
Evaluation

- ACOG
  - Pelvic ultrasound
  - Biopsy

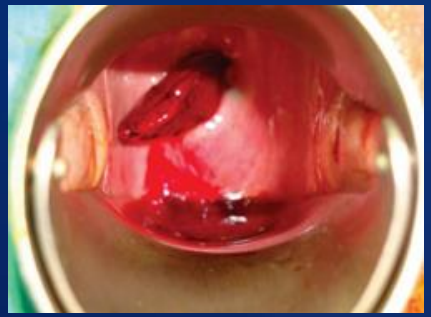
Differential Diagnosis

- The main presenting symptom of endometrial cancer is **post-menopausal bleeding**. Its differential diagnoses include:
  - **Vulvar causes** – vulvar atrophy, vulvar pre-malignant or malignant conditions.
  - **Cervical causes** – cervical polyps, cervical cancer
  - **Endometrial causes** – hyperplasia without malignancy, benign endometrial polyps, endometrial atrophy.

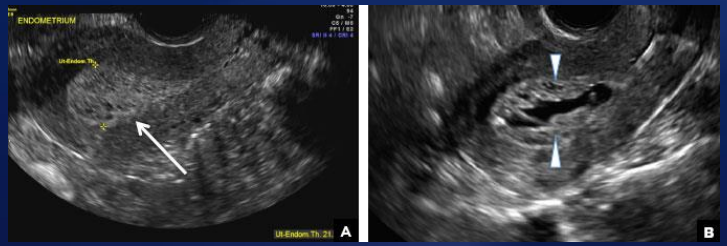
Differential Diagnosis



Intrauterine polyps



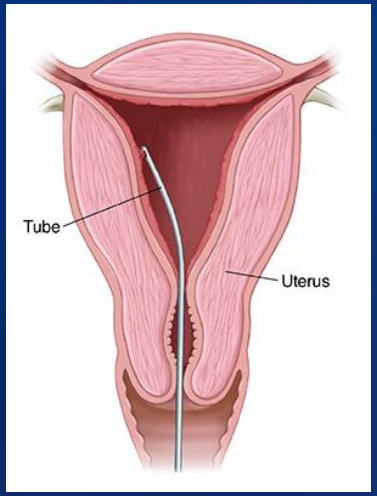
Endocervical polyp



Endometrial hyperplasia

Endometrial Biopsy

- In-office procedure
- Minimally invasive
- Suction pipelle to obtain endometrium
- Adequate endometrial sample for histology, with a high sensitivity and specificity for detection of hyperplasia and malignancy.



Endometrial Hyperplasia

- Chronic estrogen stimulation unopposed by the counterbalancing effects of progesterone
- Non-neoplastic entities: proliferation of endometrial glands of irregular size and shape
  - disordered proliferative endometrium
  - benign hyperplasia
  - Simple and complex hyperplasias without atypia
- Precancerous neoplasms: neoplastic features but without invasion
  - Endometrial intraepithelial neoplasms (EIN)
  - All atypical complex hyperplasia

Progestin Therapy

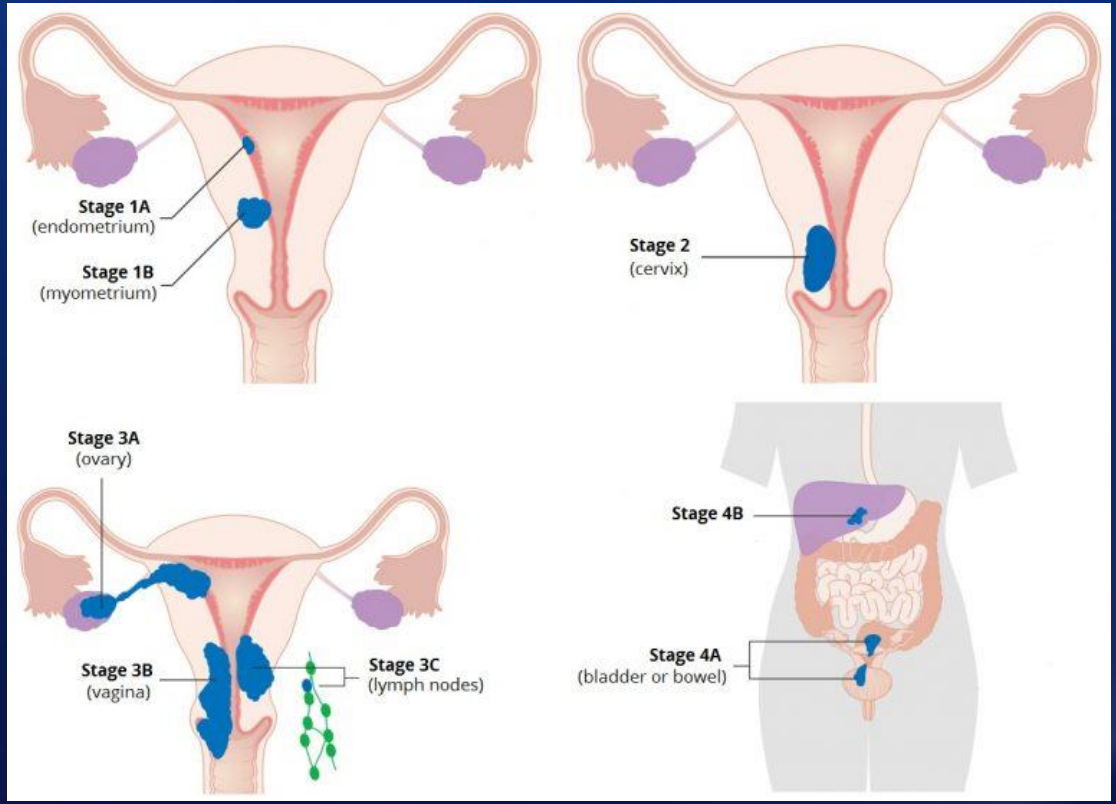
- Megace
- Provera
- Vaginal progesterone
- Depo Provera
- Levonogestrel IUD
- Medroxyl

- Repeat EMB in 3 to 6 months.

Endometrial Cancer

- Type 1: low-grade endometrioid (FIGO 1&2), estrogen sensitive, favorable prognosis
- Type 2: high grade endometrioid (FIGO 3), nonendometrioid: serous, clear cell, mixed cell, undifferentiated, carcinosarcoma. Not estrogen sensitive, atrophic endometrium. Poor prognosis.
  - 30% will have extrauterine disease without myometrial invasion

FIGO Staging



Surgical treatment

- 2009: surgical staging system adopted

TABLE 1	Summary of 2009 endometrial cancer staging
■ Stage I simplified to describe invasion of less than (IA) or more than half the myometrium (IB)	
■ Stage II disease now limited to cervical stromal invasion by classifying endocervical involvement of the cervix as part of stage I disease	
■ Eliminated the separate classification of positive peritoneal cytology as Stage IIIA, which is now limited to disease involving the serosa of the uterus or adnexa	
■ Separated Stage IIIC into metastases involving the pelvic lymph nodes (IIIC1) versus para-aortic lymph nodes (IIIC2)	

- MIGS – preferred staging approach
  - Improved recovery, decreased LOS, decreased post-operative complications

Surgical Treatment

- Minimally invasive
- Laparoscopic
- Robotic-assisted

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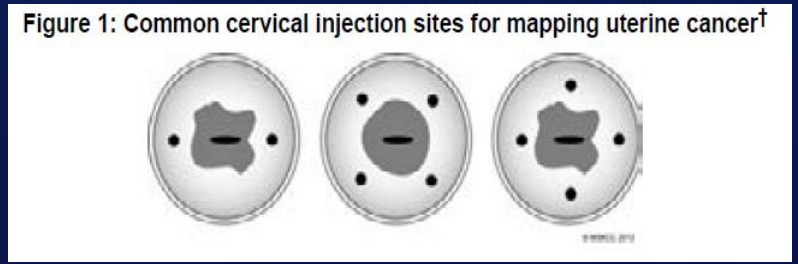
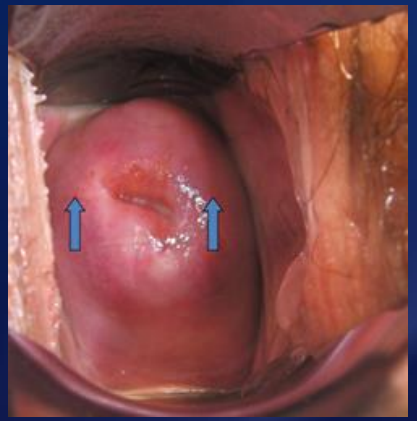
Sentinel Lymph Nodes

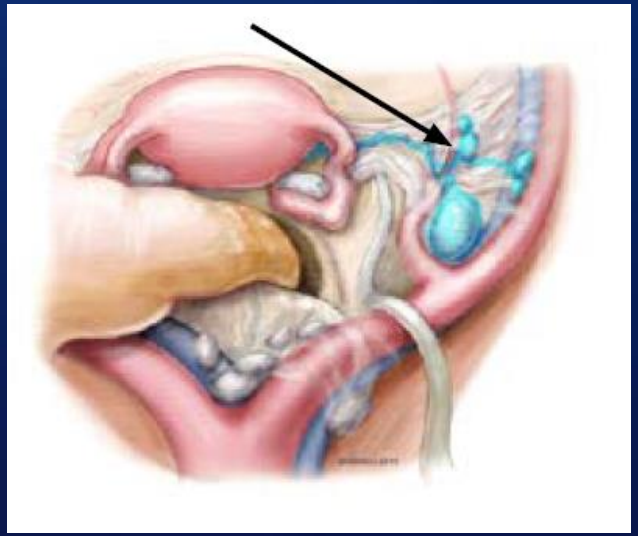
- William Halsted 1882: Metastatic disease to regional lymph nodes is one of the most important prognostic factors in solid malignancy
- Cancer spreads from lesions to lymph nodes via tumor emboli, not by direct extension along lymphatics
- Indocyanine green – injected into paracervical space (3 & 9 o'clock).





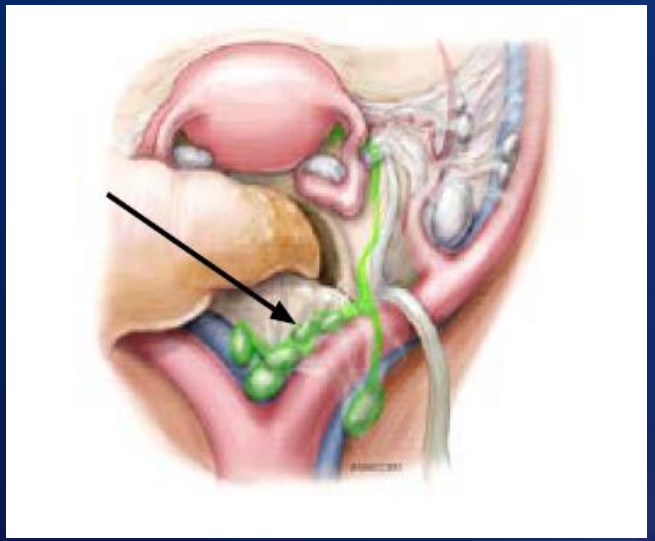
Sentinel Lymph Node Mapping

Most common location



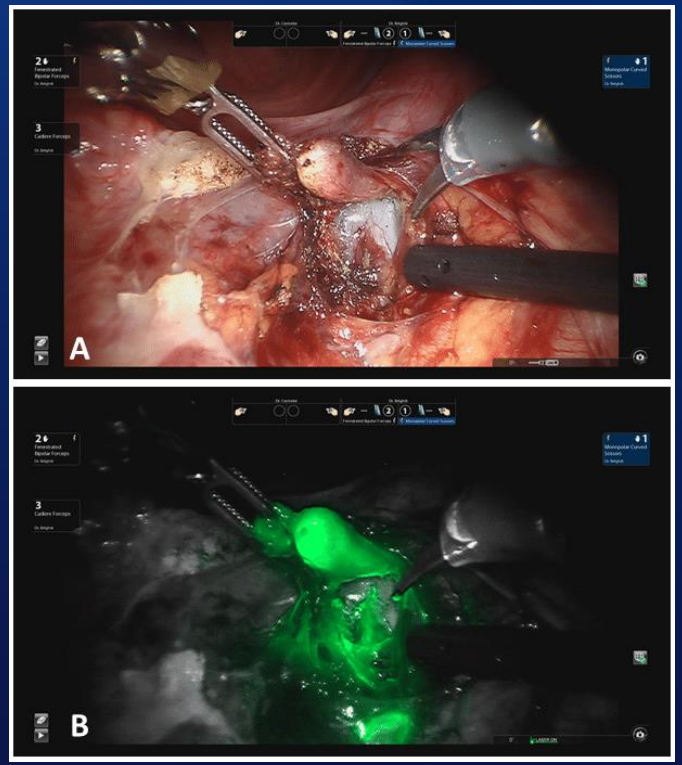
Retroperitoneal

Less common location

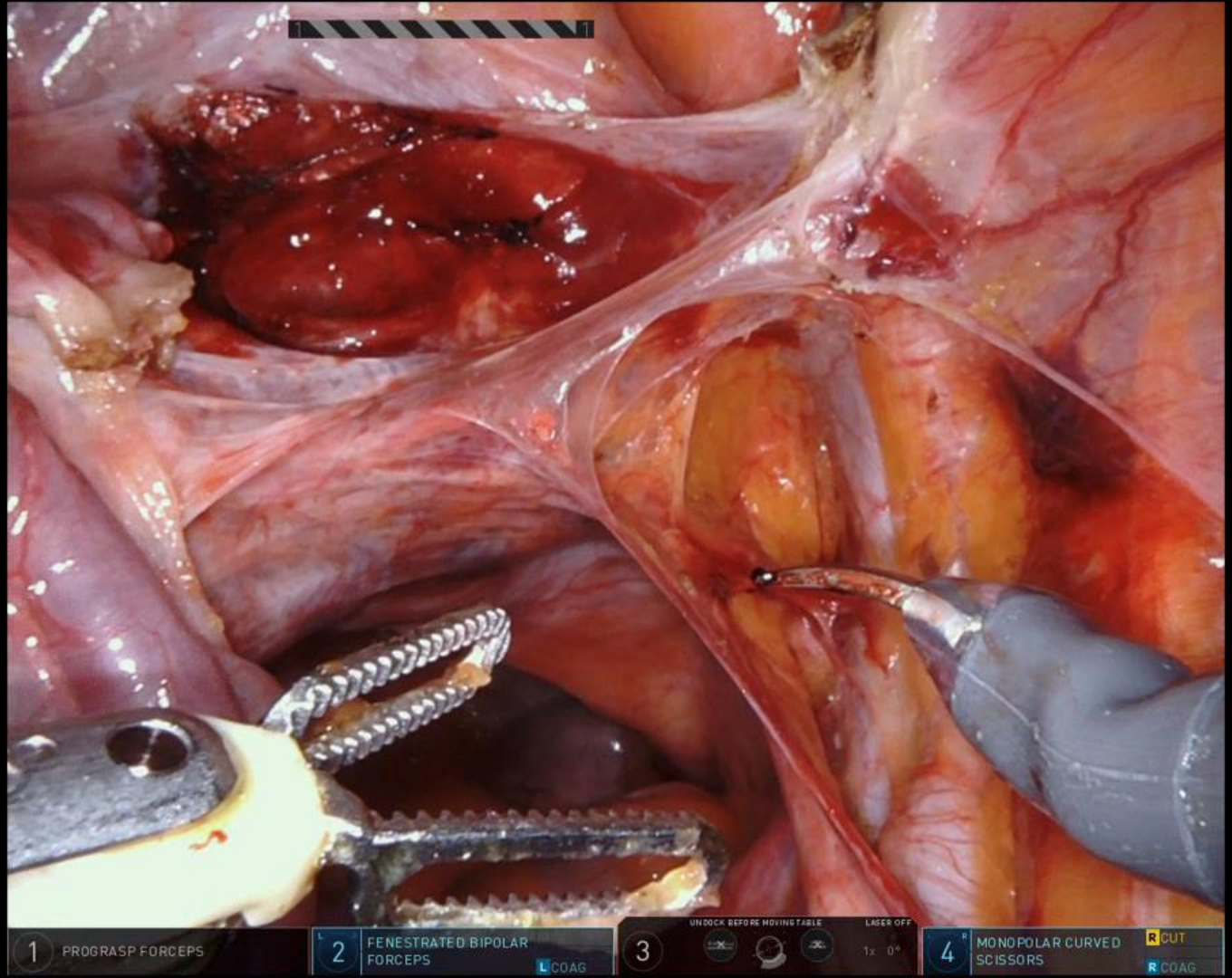


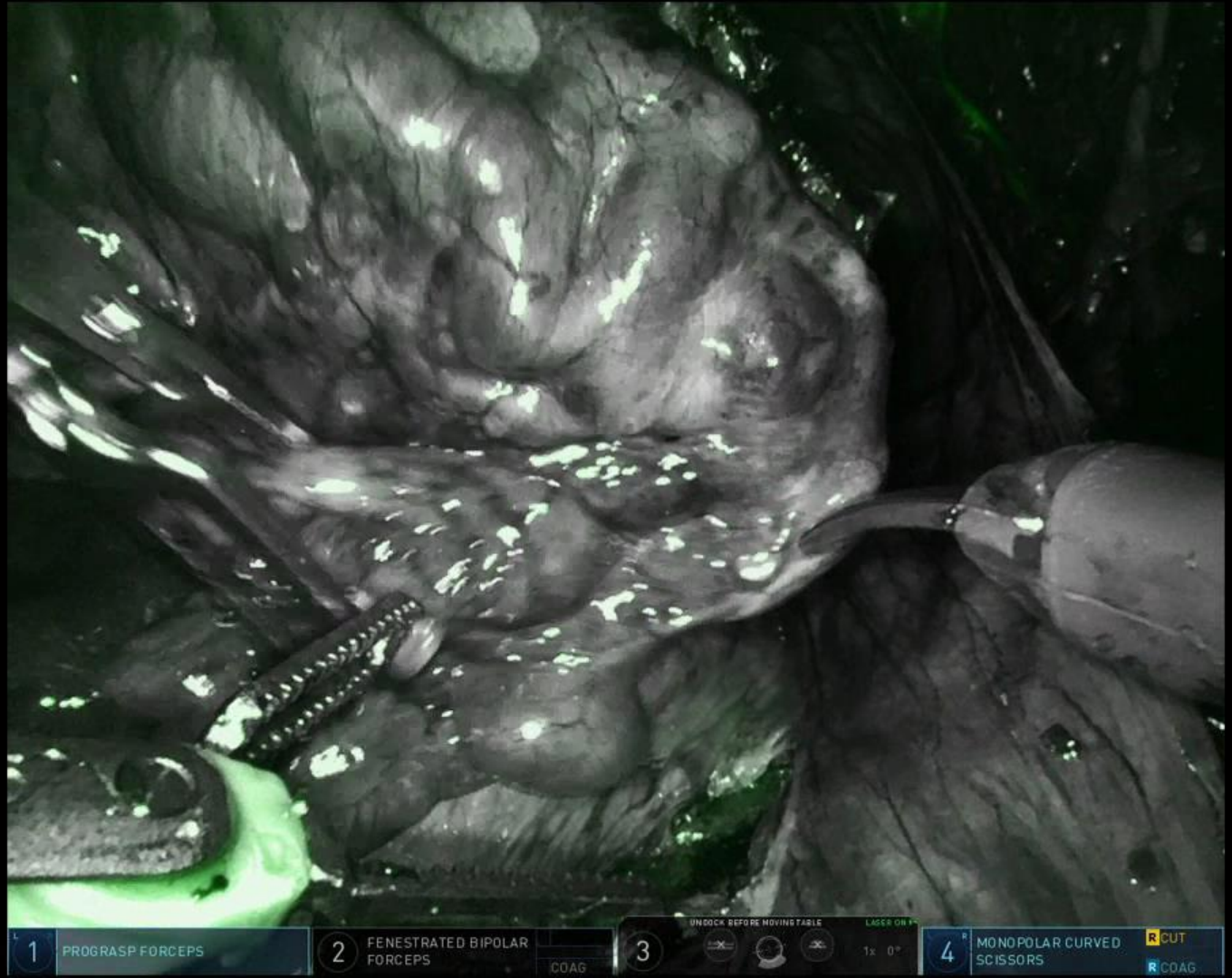
Presacral

Sentinel Lymph Node Mapping



- Indocyanine green tracks to nearby lymph nodes.
- Robotic feature: firefly


1
PROGRASP FORCEPS
2
FENESTRATED BIPOLAR FORCEPS
L COAG
3
UNDOCK BEFORE MOVING TABLE
LASER OFF
1x 0°
4
MONOPOLAR CURVED SCISSORS
R CUT
R COAG


1
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COAG
3
UNDOCK BEFORE MOVING TABLE
LASER ON
1x 0°
4
MONOPOLAR CURVED SCISSORS
R CUT
R COAG

Adjuvant Treatments

- 2014, the American Society of Radiation Oncology (ASTRO)
  - Grade 1 or 2 tumors with < 50% myometrial invasion – None
  - Vaginal brachytherapy:
    - Grade 3 tumors without myometrial invasion
    - Grade 1 or 2 tumors with high risk factors
  - Pelvic radiation:
    - Grade 3 tumors with ≥50% myometrial invasion or cervical stroma invasion
    - Grade 1 or 2 tumors with ≥50% myometrial invasion with high risk factors
  - External beam radiation therapy as well as adjuvant chemotherapy:
    - positive nodes, or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum

Adjuvant Treatments

- Use of vaginal brachytherapy in patients also undergoing pelvic external beam radiation is not generally warranted
- For patients with metastatic disease, concurrent chemoradiation followed by adjuvant chemotherapy is indicated; alternative sequencing strategies with external beam radiation and chemotherapy are also acceptable

Adjuvant Treatments

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

CLINICAL FINDINGS | **HISTOLOGIC GRADE/ADJUVANT TREATMENT[f,g,m,n]**

Surgically staged: Stage I[d] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Vaginal brachytherapy if any risk factors[o,p]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion and no lymphovascular space invasion[o]
IB[l]	G1, G2	Vaginal brachytherapy preferred or Consider observation if no risk factors[o]
	G3	RT (vaginal brachytherapy and/or EBRT) ± systemic therapy[q]

Surgically staged:[d] Stage II[l,r] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
II	G1, G2	Vaginal brachytherapy and/or EBRT[s]
	G3	EBRT ± vaginal brachytherapy ± systemic therapy (category 2B for systemic therapy)

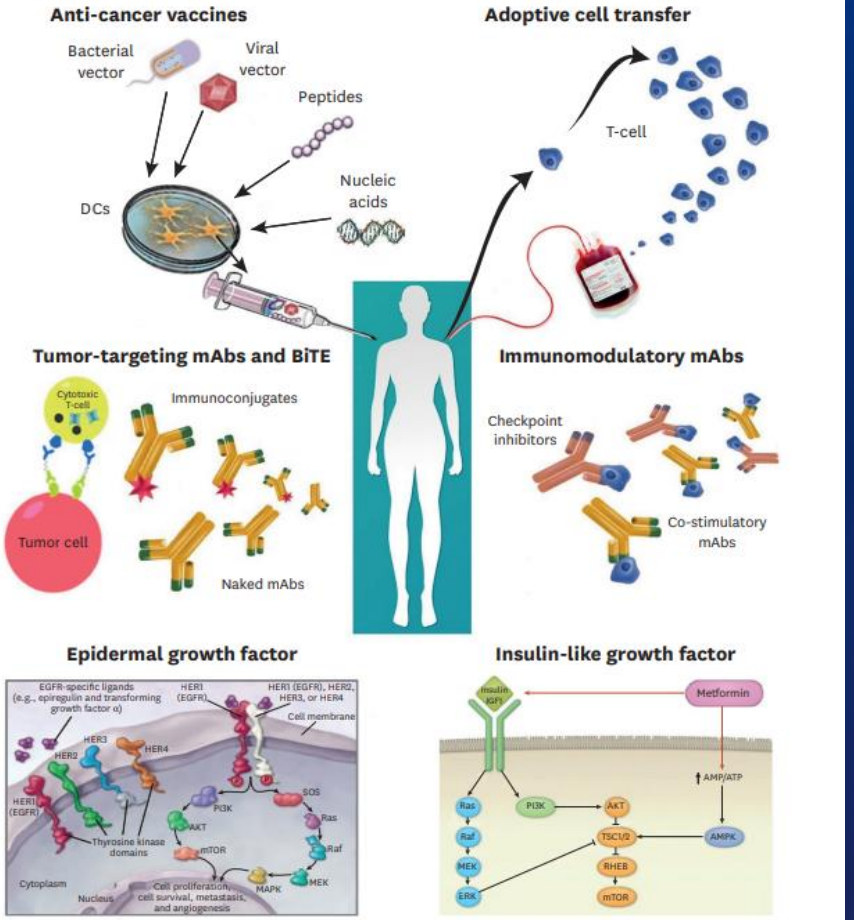
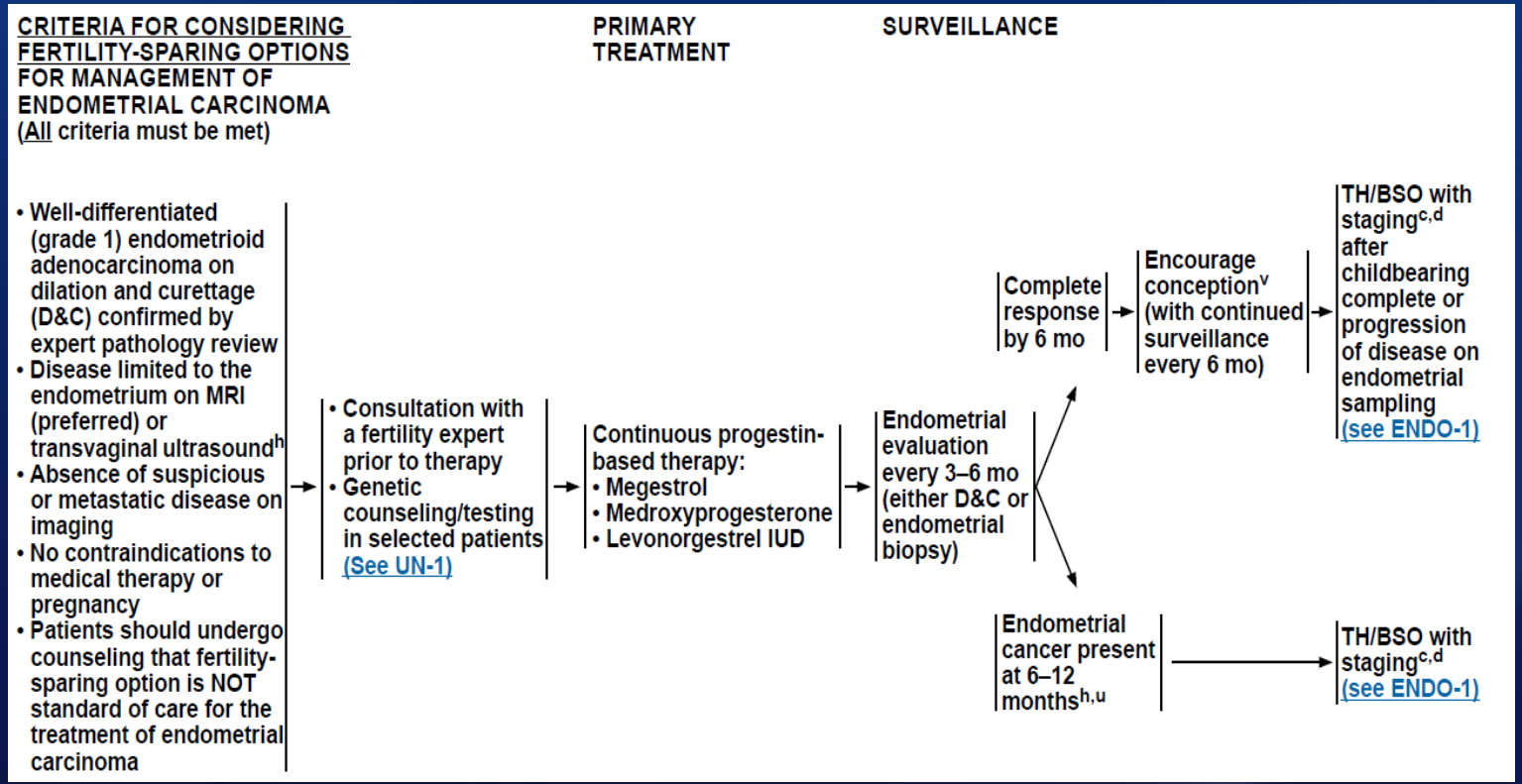


Fig. 1. Immunotherapeutic options available for treatment of EC.
BiTE, Bispecific T cell engager; DC, dendritic cell; EC, endometrial cancer; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; IGF, insulin-like growth factor; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase.

Fertility Sparing



Fertility Sparing

- In younger women with noninvasive, grade 1 cancers who wish to preserve fertility, NCCN, SGO, and ACOG all recommend progestin therapy.
- Total hysterectomy and bilateral salpingo-oophorectomy is indicated when childbearing is complete, or sooner if cancer is still present after 6-9 months of therapy or disease progression occurs.
- Women receiving fertility-sparing treatment should be monitored closely with endometrial biopsy every 3 months

Estimated Risk of Disease Recurrence

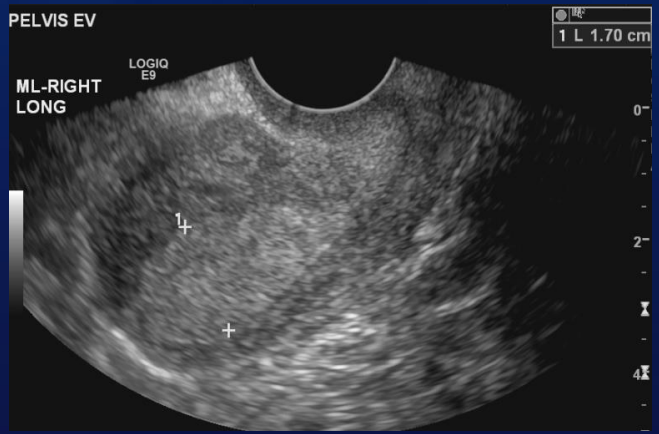
- Low risk: Endometrioid cancers that are confined to the endometrium
- Intermediate risk: Disease that is confined to the uterus but invades the myometrium, or demonstrates occult cervical stromal invasion; includes some patients with stage IA disease, stage IB disease, and a subset of patients with stage II disease
- High risk: Includes gross involvement of the cervix (a subset of stage II disease; stage III or IV disease, regardless of grade; papillary serous or clear cell uterine tumors)

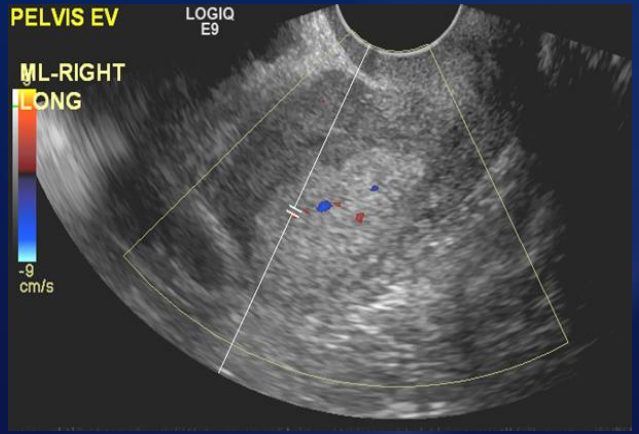
Case Review

- ML – 70 yr old G2P1 with PMB June 2013
  - Blood in urine December, vaginal bleeding in March passing blood clots
  - LMP age 45
  - No HRT

Case Review – ML

- Workup
  - Uterus, endometrium, biopsy: Endometrioid carcinoma, FIGO grade 1, with focal areas of squamous differentiation.
  - Pelvic US – 1.7cm endometrial thickness with abnormal vascular pattern



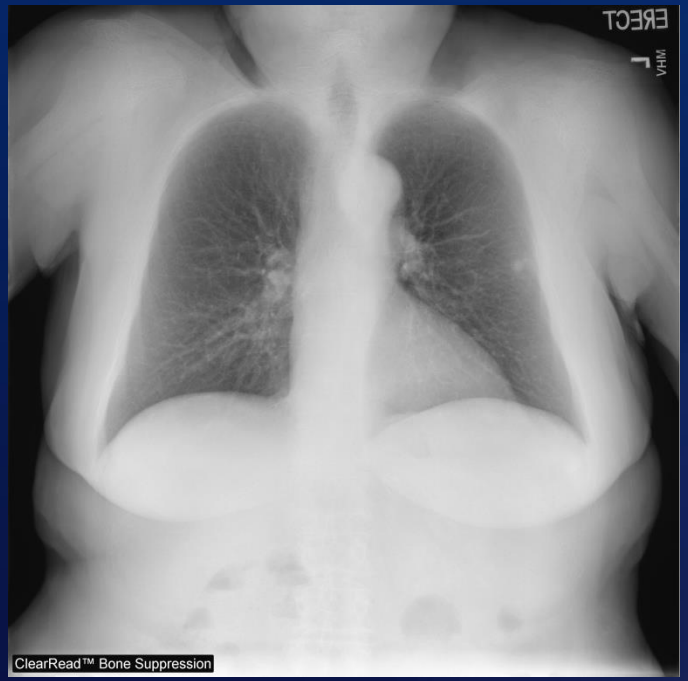


Case Review - ML

- June 2013 - Da Vinci robotically assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy.
  - Frozen section, no residual carcinoma.
  - Pelvic lymph node dissection was not performed
- Grade 1 endometrioid carcinoma of the uterus with focal squamous differentiation invading 1/6 mm of the myometrium. Final staging T1aN0M0. No LVS invasion reported. No nodes sampled. No adjuvant treatment given. Tumor cells were strongly ER positive and PR negative.

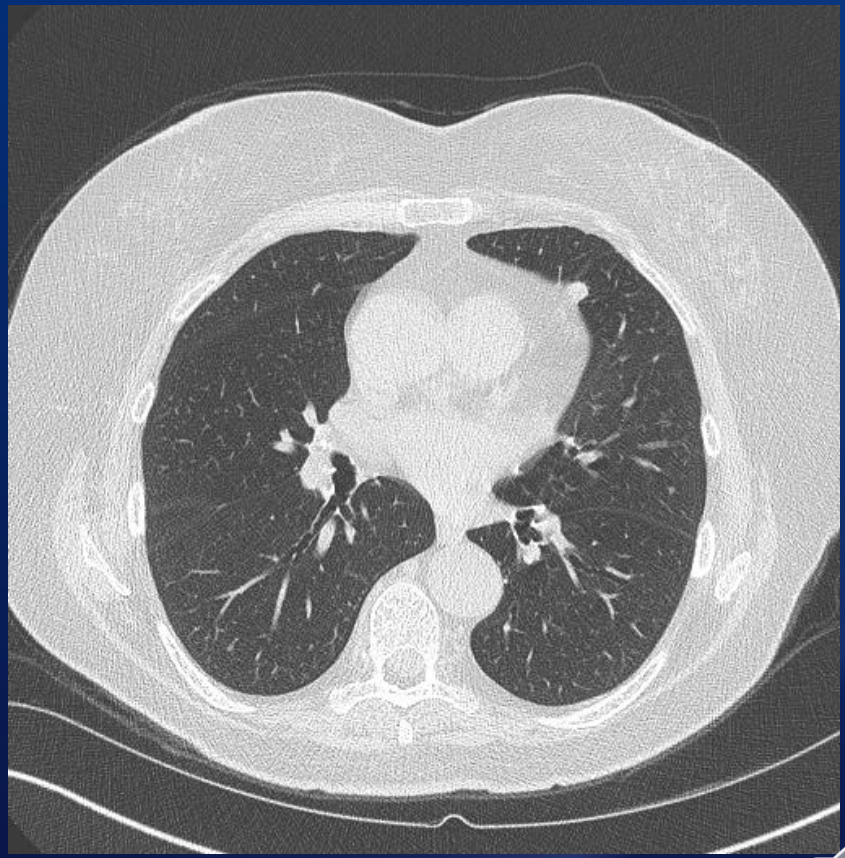
Case Review - ML

- Surveillance – q6 months x 3 years, annually. Chest x-ray annually
- June 2019



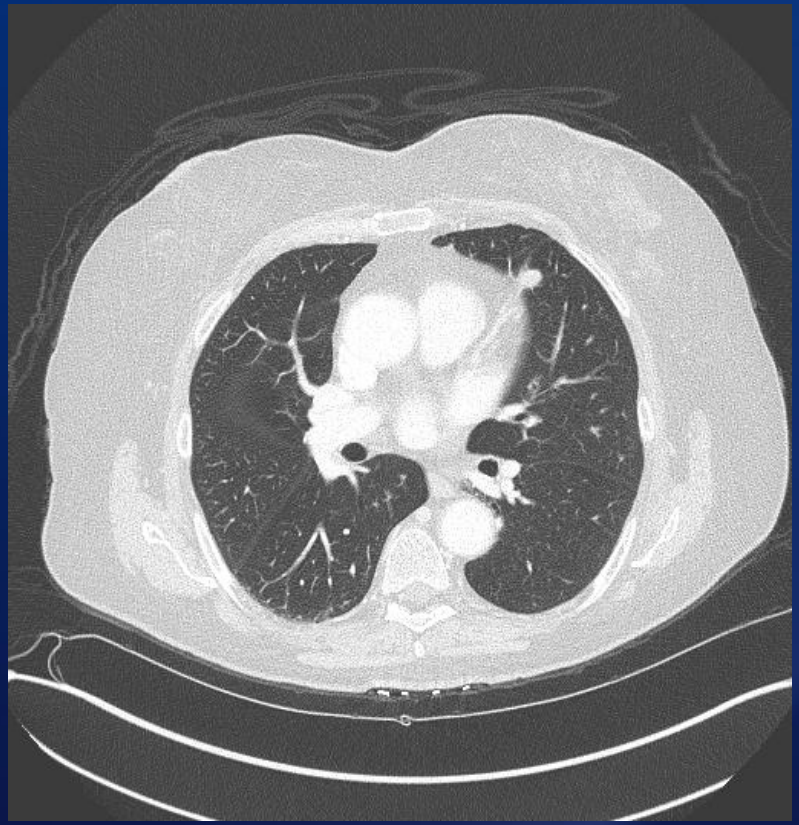
Case Review - ML

- June 2019 – 7mm nodule along accessory left minor fissure



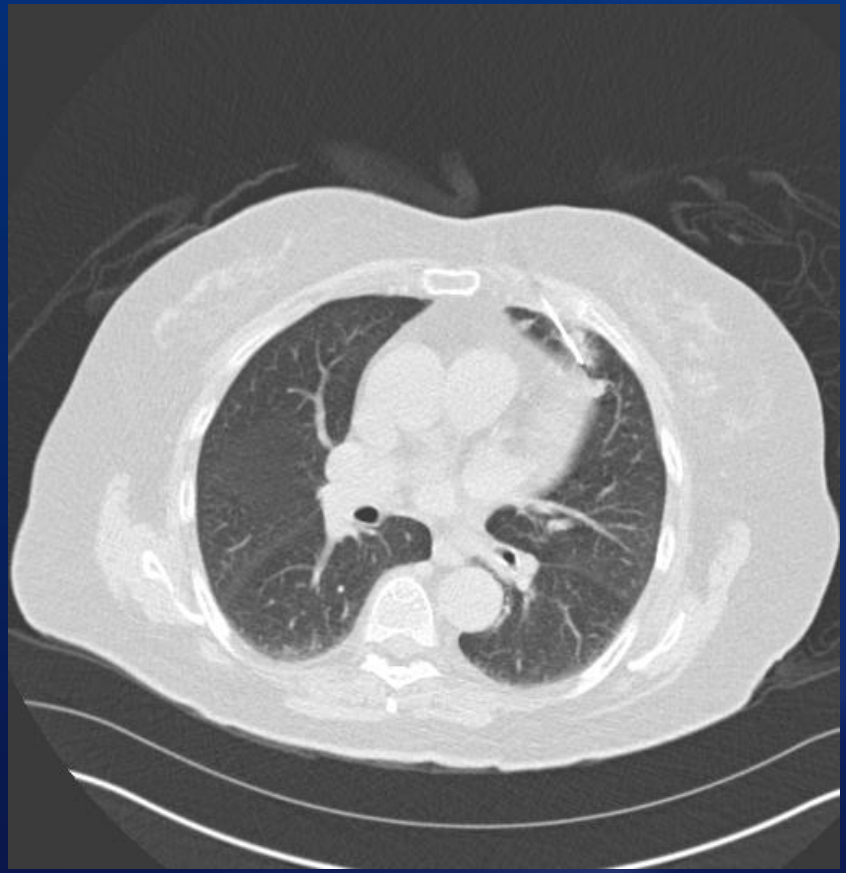
Case Review - ML

- Sept 2019 - Left upper lobe nodule along a left minor fissure, previously 9mm, increased to 12 mm



Case Review - ML

- Oct 2019 – CT guided lung biopsy revealing adenocarcinoma (unable to do additional stains)



Case Review - ML

- Dec 2019 - left upper lobe lung wedge resection and mediastinal node dissection.
  - Negative margins of resection.
  - Pathology showed an adenocarcinoma consistent with endometrial origin.
  - Tumor cells were positive for PAX8, focal positive for ER and negative for TTF1 and negative for Napsin A.
  - All nodes were negative.
- Currently starting letrozole therapy.

Take Home

- Most common cancer of the female reproductive organs
- Post-menopausal women: average age of diagnosis 60 years, uncommon <45 years (genetic, anovulatory)
- More common in white women, black women have higher mortality rate.
- Signs: Post-menopausal bleeding
- Work-up: EMB, pelvic US
- Minimally-invasive surgery, sentinel lymph node biopsy for staging

Take Home

- Adjuvant therapies dependent upon staging
  - Chemotherapy
  - Vaginal brachytherapy
  - Hormonal therapies
  - Immunotherapies
- Surveillance key to finding recurrence.

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Thank you!

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