



# Ovarian & Endometrial Cancer

**Kristin Bixel, MD**

*Assistant Professor*

*Division of Gynecologic Oncology*

*Department of Obstetrics and Gynecology*

*The Ohio State University Wexner Medical Center*

**MedNet21**  
Center for Continuing Medical Education

 **THE OHIO STATE UNIVERSITY**  
WEXNER MEDICAL CENTER

## Disclosures

- Advisory Board (Merck)
- Unrestricted research grant from Intuitive to GOG to fund randomized controlled trial (GOG3043/ROCC)

## Objectives

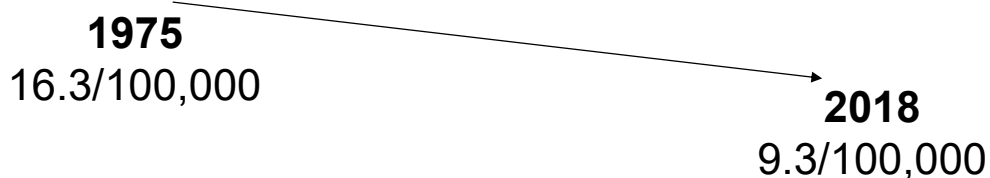
- Understand the incidence/risk factors for ovarian cancer and endometrial cancer
- Review presenting symptoms and initial evaluation for patients with these malignancies
- Provide an overview of the approach to management (surgical and medical)
- Discuss the genetic landscape of ovarian and endometrial cancer and how this can be leveraged to improve outcomes for our patients

## Ovarian cancer



## Incidence

- 1.1% of all new malignancies
  - 21,410 new cases/year
  - 13,770 deaths/year



- Knowledge of preventative measures
- Risk reducing surgery

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<https://seer.cancer.gov/statfacts/html/ovary.html#content>

## Survival

Relative  
survival  
38.3%

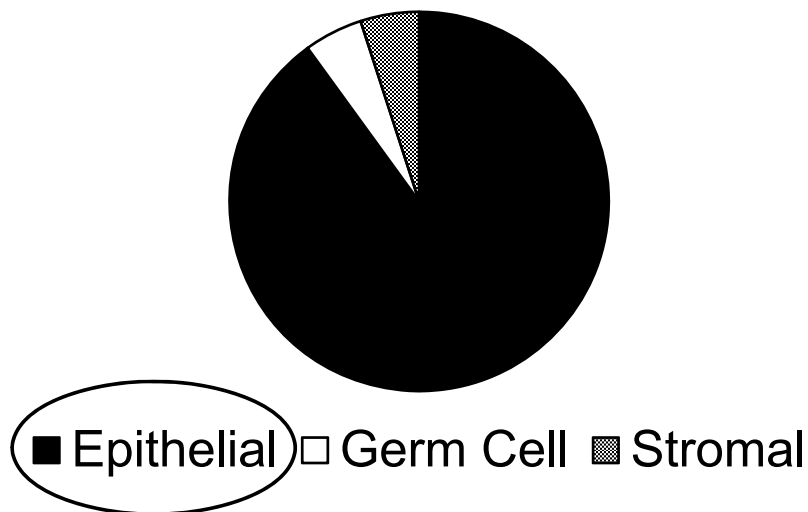
Relative  
survival  
49.1%

- Advancements in technology (surgery/postop care)
- Advancements in therapy (frontline/maintenance/recurrence)

<https://seer.cancer.gov/statfacts/html/ovary.html>

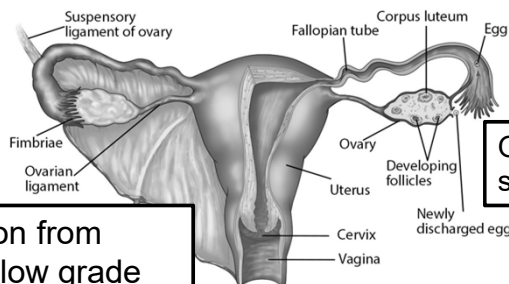
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## Origins of ovarian cancer



## Pathogenesis

Malignant transformation in the fallopian tube → shedding to ovary/peritoneum



Ovulation → damage to surface epithelium

Progression from borderline → low grade serous carcinoma

Soong et al. Gynecol oncol. 2019  
 Maccio. Cytokine. 2012  
 Image: Author: Zoneling (CC BY-SA 4.0)

## Risk factors

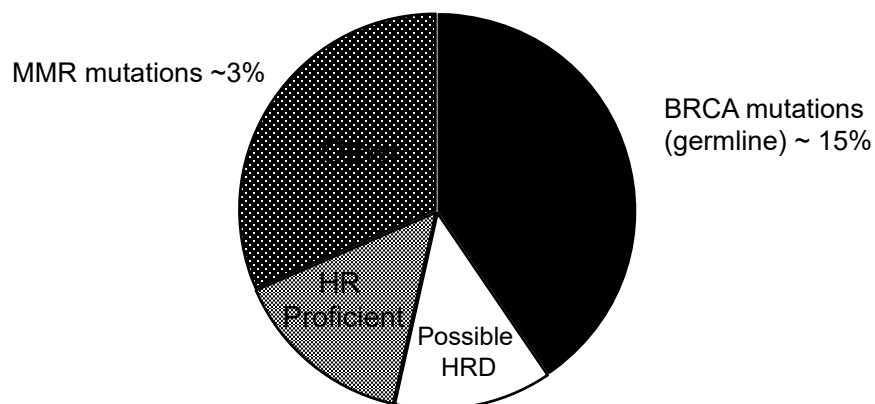
- Age
- Nulliparity/infertility
- Early menarche
- Late menopause
- Genetics
  - HBOC
  - Lynch syndrome
  - + family history (breast, ovarian)
- Endometriosis

### Protective factors:

- BSO
- Hysterectomy
- IUD
- Oral contraceptives
- Tubal ligation
- Breastfeeding
- Parity

Lheureux et al. Lancet. 2019  
 Wheeler L.J. Obstet Gynecol. 2019  
 Cibula et al. Hum Reprod Update. 2011  
 Collaborative Group on Epidemiological Studies of Ovarian cancer. Lancet. 2008

## Genetic landscape of EOC



15-25% genetic predisposition  
 Recommend testing **ALL** women with EOC

Konstantinopoulos et al. Cancer Discovery. 2015

## Why is this disease so deadly?

- No detectable pre-invasive lesion

- No screening test

- CA 125
- Ultrasound
- Multimodal

- Symptoms vague

UKCTOCS trial  
ROCA vs US vs none  
No benefit

PLCO cancer screening RCT  
CA 125/US  
No benefit  
\*False positive → 15% serious complication\*

## Presentation

### Acute

- Ascites
- Pleural effusions
- Bowel obstruction
- VTE

### Subacute

- Bloating/distention
- Early satiety, nausea, anorexia
- Urinary urgency/frequency
- Pelvic or abdominal pain
- Watery discharge or PMB

Goff et al. JAMA. 2004  
Goff et al. Cancer. 2007  
Olson et al. Obstet Gynecol. 2001

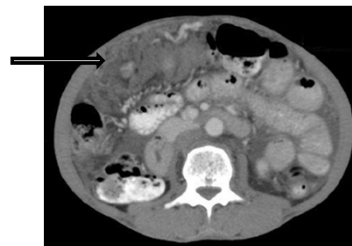
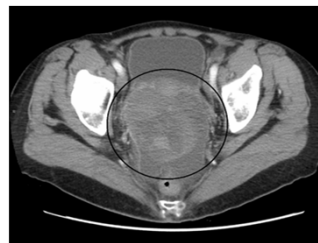
# Ovarian cancer symptom index

- Any symptom >12 times/month for <1 year
  - Pelvic/abdominal pain
  - Urinary urgency/frequency
  - Increased abdominal size/bloating
  - Difficulty eating/feeling full
- Sensitivity: 56.7% (early stage); 79.5% (advanced)
- Specificity: 86-90% (age dependent)

Goff et al. JAMA. 2004  
Goff et al. Cancer. 2007

## Evaluation: Imaging

- Pelvic ultrasound
  - Complex (solid/cystic)
  - Internal vascularity
  - Irregular borders
  - Ascites
- CT scan
  - Ascites
  - Lymphadenopathy
  - Carcinomatosis



Images: commons.wikimedia.org

## Evaluation: Labs

- Tumor markers
    - CA125
    - CEA
    - (+/- CA 19-9)
    - (LDH, hCG, AFP)
    - (inhibins)
  - CBC, chemistry, LFT's (+/- coags)
- } CA 125/CEA ratio >25 favors GYN origin

## Tissue diagnosis

- Surgical resection\*
- Biopsy
- Cytology
  - Acceptable if CA 125/CEA ratio >25



## Surgical staging

- Washings
- TAH, BSO\*
- Omentectomy
- Pelvic and para-aortic lymphadenectomy (bilateral)
- Peritoneal biopsies

\*fertility sparing surgery may be appropriate in select cases

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## Staging (FIGO/AJCC)

Stage	Description
I	Limited to ovaries/tubes
II	Extension beyond ovaries (confined to pelvis)
III	Nodes, peritoneal spread (abdomen)
IV	Distant

>2/3 diagnosed with advanced stage at presentation

# Management

- Surgery
  - Establish diagnosis
  - Determine extent of disease/staging
  - Cytoreduction
  - Restore/preserve anatomy
- Chemotherapy
- Maintenance therapy
- Surveillance

## Timing of surgery for advanced ovarian cancer

Primary  
debulking  
surgery

vs

NACT → interval  
tumor reductive  
surgery

Factors to consider:  
Extent of disease/resectability  
Performance status/frailty  
Age/nutritional status  
Medical co-morbidities

Wright et al. Gynecol Oncol. 2016  
Vergote et al. NEJM. 2010  
Kehoe et al. Lancet. 2015  
Fagotti et al. Int J Gynecol Cancer. 2020

## So why not NACT for all?

Several trials demonstrate non-inferiority to PDS

BUT...

Median OS low in these trials (~30 months)

Vergote. NEJM. 2010  
Kehoe et al. Lancet. 2015  
Fagotti. Int J Gynecol Cancer. 2020

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## Residual disease matters

Median OS by residual disease at completion of surgery

NGR: 106 months  
<0.5cm: 66 months  
0.5-1cm: 48 months  
1-2 cm: 33 months

Chi et al. Gynecol Oncol. 2006

## Location, location, location...

- Compared adherence to NCCN guidelines and survival by location of treatment (Utilizing California Cancer Registry)
  - NCI-CCC (n=5)
  - Non NCI high-volume hospital ( $\geq 10$  cases/year, n=29)
  - Low-volume hospital (<10 cases/year, n=158)
- Treatment at an NCI-CCC was an independent predictor of adherence to treatment guidelines
- Location of treatment was associated with survival
  - Median OS 77.9 mo (NCI) vs 51.9 mo (HVH) vs 43.4 months (LVH), p <0.0001

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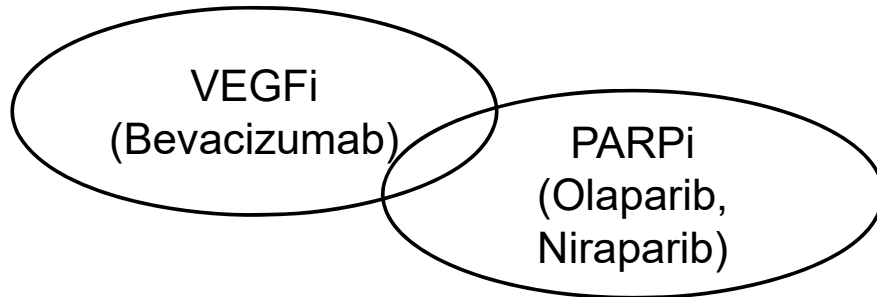
Bristow et al. J Am Coll Surg. 2015

## Adjuvant chemotherapy

- Cisplatin vs carboplatin
    - GOG 158
  - IV vs IP/IV
    - GOG 172
    - GOG 252
  - Standard vs weekly paclitaxel
    - JGOG 3016
    - GOG 262
  - +/- bevacizumab
    - GOG 218
    - ICON 8
- Take home:  
Platinum + taxane  
chemotherapy

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# Maintenance therapy



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# HR deficiency (HRD) and cancer

Alterations in HR genes  
(**BRCA 1/2**, ATM, BARD1, BRIP1, RAD51, etc etc)



Inability to repair DNA



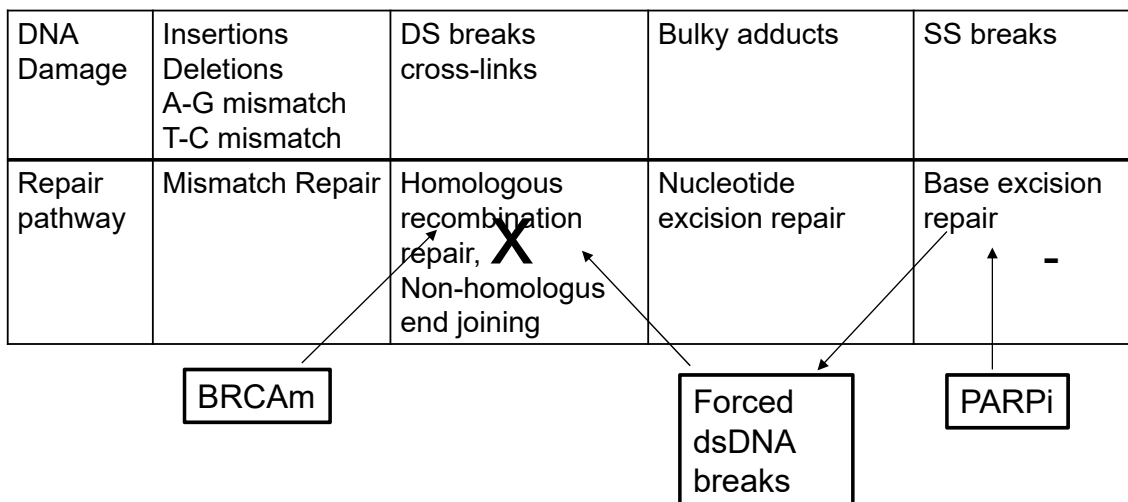
Genomic instability (loss of normal checks/balances)



Tumorigenesis

But....this same process confers sensitivity to PARPi

# Synthetic lethality



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## Three RCT's demonstrating benefit of PARPi in frontline maintenance therapy

- SOLO1
  - Olaparib
  - BRCAm
- PRIMA
  - Niraparib
  - All comers
- PAOLA
  - Olaparib + bevacizumab
  - BRCAm/HRD

~ 40-70% reduction in risk of recurrence or death from disease

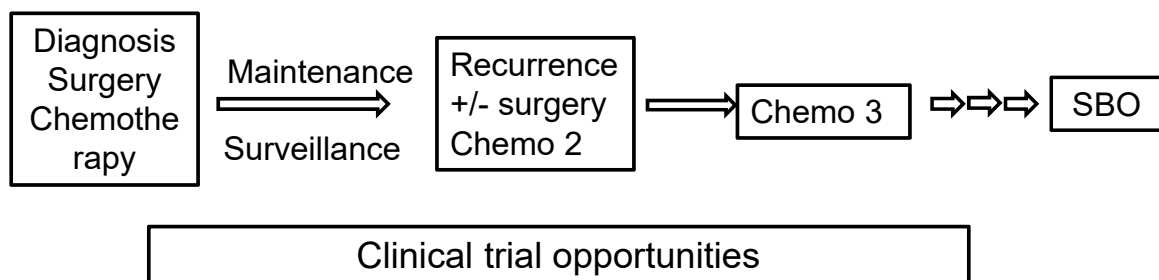
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# Surveillance

- Every 3 months x 2 years → every 6 months x 3 years
  - History
  - Exam
  - Imaging as clinically indicated
  - Tumor markers (we do...but should we???)

nccn.org  
Rustin et al. Lancet. 2010

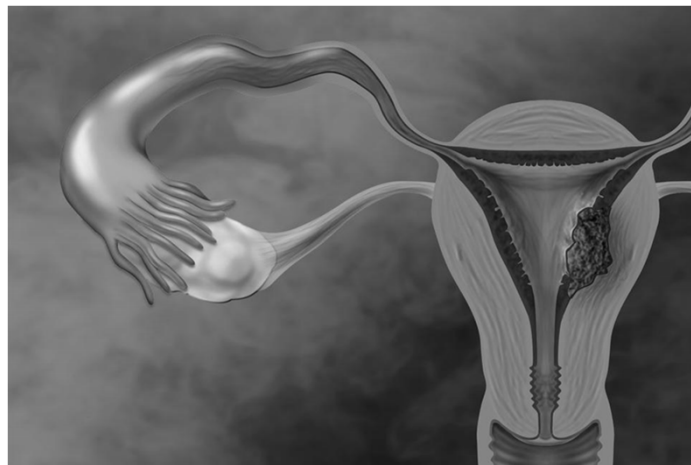
# Disease trajectory/recurrence



## Pearls...

- We have come a long way but have a long way to go.
- Surgery and chemotherapy critical
- Genetic counseling/testing for all with EOC
- Strong consideration for PARPi maintenance therapy
- Most women with advanced disease will recur
- Establishing clear communication regarding expectations/goals critical

## Endometrial cancer





# Incidence

- Most common gynecologic malignancy in US
- 3.5% of all new cancer diagnosis (rising)
  - 66,570 new cases
  - 12,940 deaths
- 5-year relative survival 81% (unchanged)

<https://seer.cancer.gov/statfacts/html/corp.html>  
Image: Commons.Wikimedia.org

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# Histology

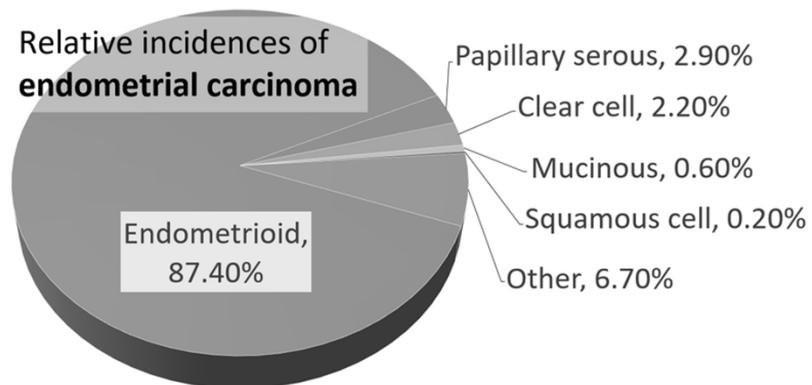
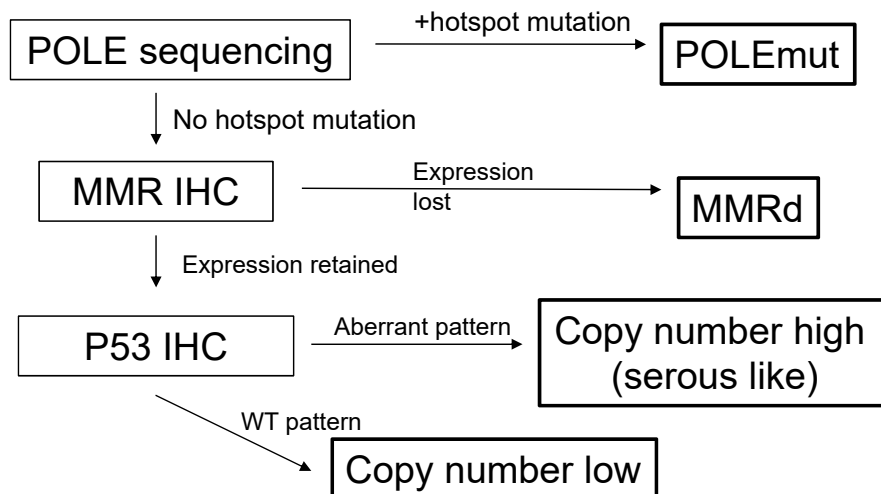


Image: Author: Mikael Häggström, M.D. (CC0 1.0)

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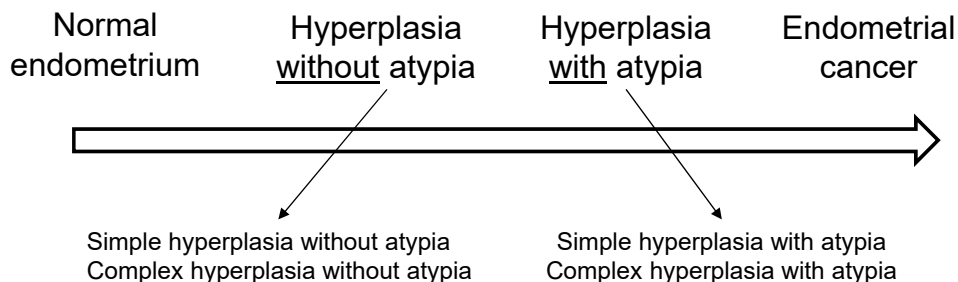
# Molecular subtypes



Concin et al. Int J Gynecol Cancer. 2021  
 Murali et al. J Nat Compr Canc Netw. 2018  
 Leon-Castillo et al. J Clin Oncol. 2020  
 NCCN Guidelines Version 1.2022 Endometrial Carcinoma

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# Pathophysiology (Endometrioid/copy number low)



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## Risk factors

- Excess estrogen exposure
  - Endogenous (Obesity, PCOS, estrogen secreting tumor)
  - Exogenous (Unopposed estrogen therapy, tamoxifen)
- Age
- Diabetes/HTN
- Family history
  - Lynch syndrome
  - Cowden syndrome
  - BRCA?

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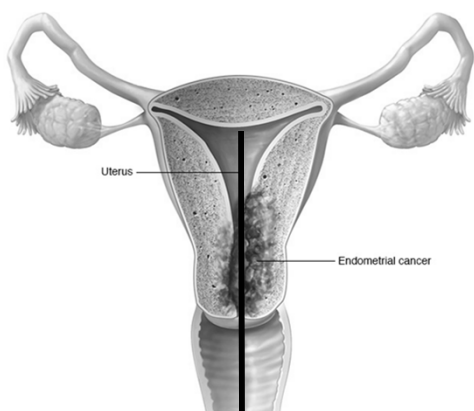
## Presentation

- Abnormal uterine bleeding
  - Intermenstrual bleeding
  - Heavy/prolonged menses
  - Irregular menses
  - **Postmenopausal bleeding**
- Cramping/pelvic pain
  
- Rarely present with symptoms of metastatic disease

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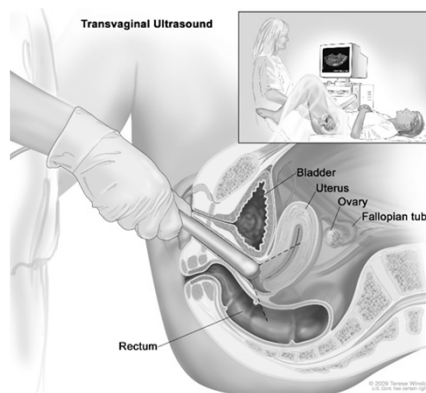
# Evaluation

## Endometrial biopsy



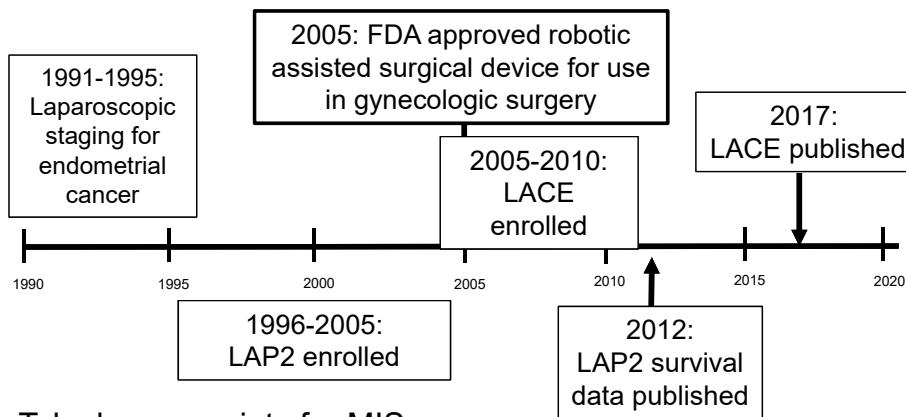
Author: Lolaia (CC BY-SA 4.0)

## Transvaginal ultrasound



Source: Cancer.gov

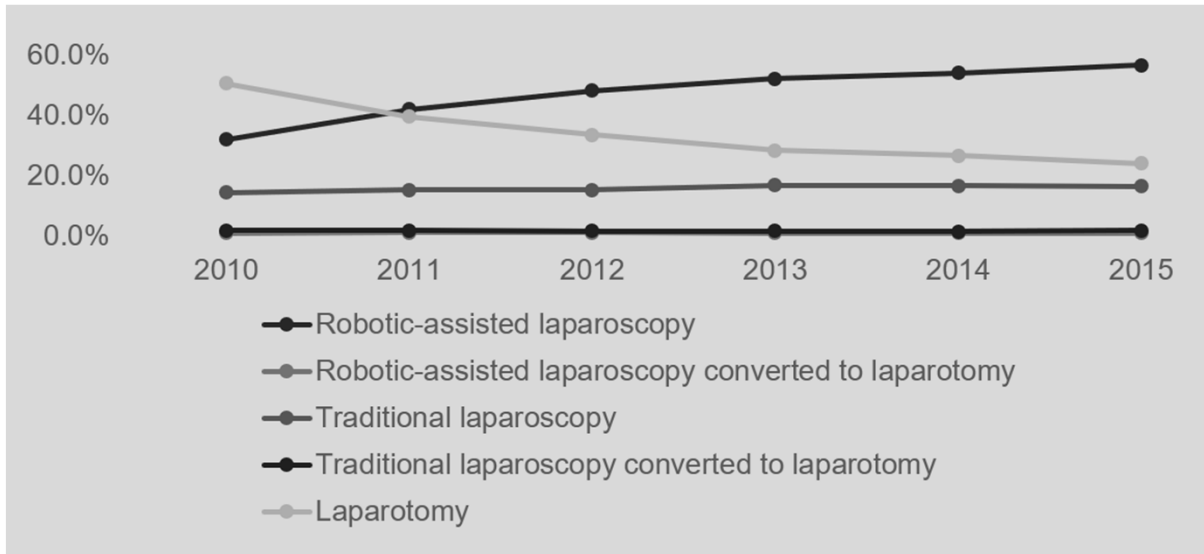
# Surgery for endometrial cancer



Take homes points for MIS:

- Feasible
- Decreases postop complications/shortens LOS
- Results in similar oncologic outcomes

## Surgical approach over time



Bixel et al. J Minim Invasive Gynecol. 2021

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## Surgical staging

- Hysterectomy
- BSO
- Lymph node evaluation
  - Sentinel mapping algorithm
  - Selective lymphadenectomy
  - Complete lymphadenectomy

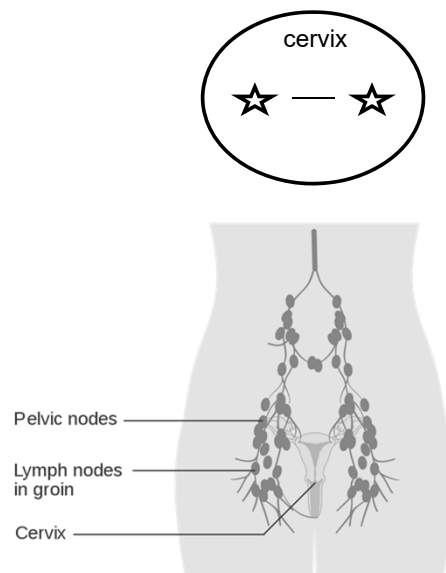
# Sentinel mapping algorithm

## 1. Injection of cervix for SLN mapping

- Indocyanine green (fluorescent dye)
- Isoflufan blue (blue dye)
- Technetium-99 (radionucleotide)

## 2. Evaluate retroperitoneum

- Excise mapped SLN
- Remove ANY suspicious nodes
- If no mapping on a hemipelvis → side specific LND is performed



NCCN Guidelines Version 1.2022 Endometrial Carcinoma  
Image: Author: Cancer Research UK (CC BY-SA 4.0)

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# FIGO staging

Stage		Description
I	A	Confined to uterus, < 50% myoinvasion
	B	Confined to uterus, > 50% myoinvasion
II		Cervical stromal invasion
III	A	Serosa/ adnexa
	B	Vagina/ parametria
	C1	Pelvic nodes
	C2	PA nodes
IV	A	Bladder/ bowel mucosa
	B	Distant mets (includes upper abd, inguinal nodes)

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# Adjuvant therapy

- The great (forever) debate!

<b>Low risk</b>	<b>Low-intermittent risk</b>	<b>High-intermittent risk</b>	<b>High risk</b>
No invasion, low risk histology	Superficial invasion, low risk histology	Age, grade 2-3, deep invasion, LVSI)	High risk histology, advanced stage
Surveillance	Surveillance	RT vs Observation	Chemo Chemo +RT RT

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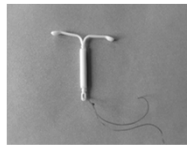
## What is next?

Adjuvant therapy based on molecular classification rather than traditional histology/stage

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## Special circumstances: Desires fertility

- Who?
  - Endometrioid, grade 1
  - Limited to endometrium
  - No contraindications to treatment OR pregnancy
- Options?
  - Progestin therapy
  - (STRONGLY advise addressing comorbidities)



NCCN Guidelines Version 1.2022 Endometrial Carcinoma  
Image: commons.Wikimedia.org

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## Special circumstances: Non-surgical candidates

- Who?
  - Poor performance status
  - Complex co-morbidities
  - Inability to tolerate surgery
  - Early stage disease
- Options?
  - Primary radiation
  - Progestin therapy



## Genetics

- **Lynch syndrome**
  - Mutation MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
  - Risk of endometrial cancer 15-60%
- **Cowden syndrome**
  - *PTEN* mutation
  - Risk of endometrial cancer 13-28%
- ?BRCA

5-10% of patients with endometrial cancer have cancer predisposition syndrome

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## The argument for universal screening for Lynch

- Cascade testing → prevention of disease
- Provides prognostic information
- May guide subsequent therapy
  - Pembrolizumab (FDA approved 2017)
  - Dostarlimab (FDA approved 2021)
  - Pembrolizumab/lenvatinib (FDA approved 2021)

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## Pearls

- Minimally invasive surgery is preferred
  - Laparoscopic/robotic surgery
  - Sentinel lymph node mapping algorithm
- Prognosis excellent for most
- Adjuvant therapy based on risk of recurrence
  - Currently based on traditional histology/staging information
  - Optimal adjuvant approach continues to be debated
  - Molecular classification likely the future