Ovarian & Endometrial Cancer

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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

1975
16.3/100,000

2018
9.3/100,000

- Knowledge of preventative measures
- Risk reducing surgery

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

Survival

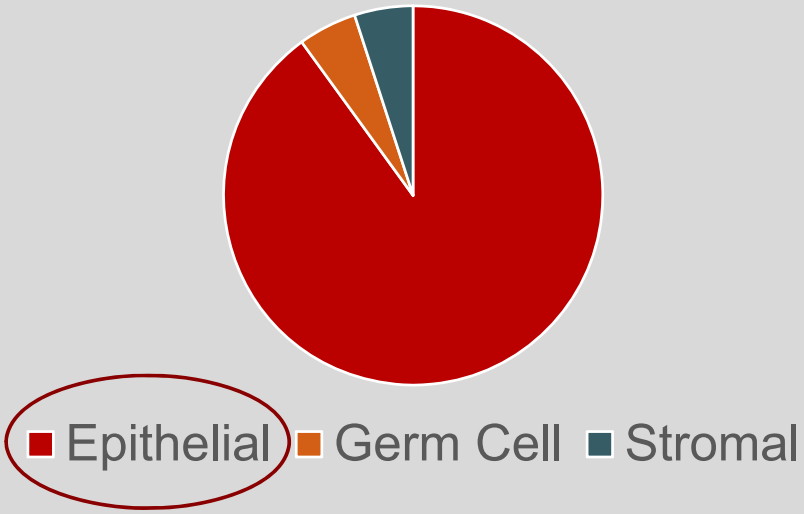
Relative survival 38.3%

Relative survival 49.1%

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

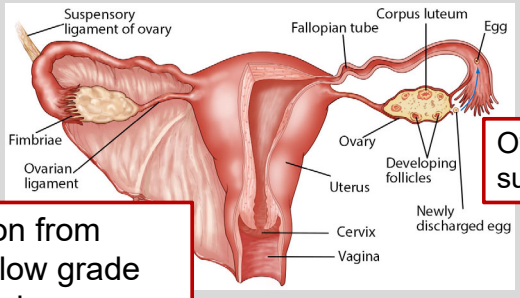
https://seer.cancer.gov/statfacts/html/ovary.html

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)

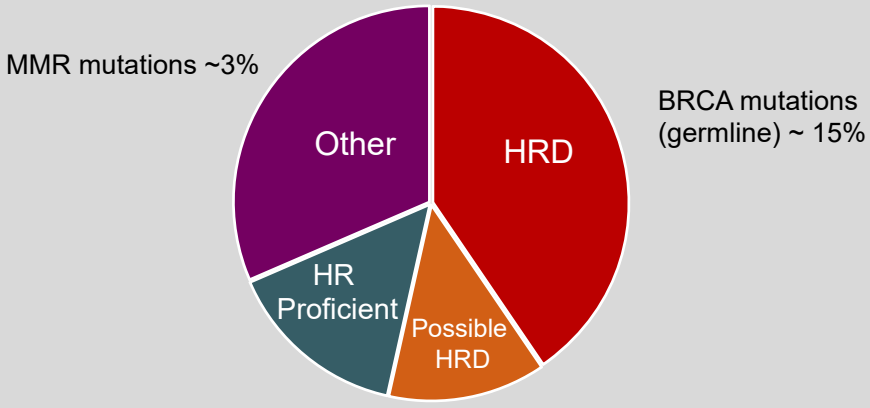
Risk factors

- 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

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

Genetic landscape of EOC

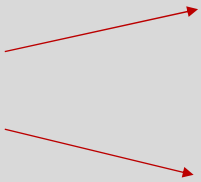


15-25% genetic predisposition
Recommend testing **ALL** women with EOC

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

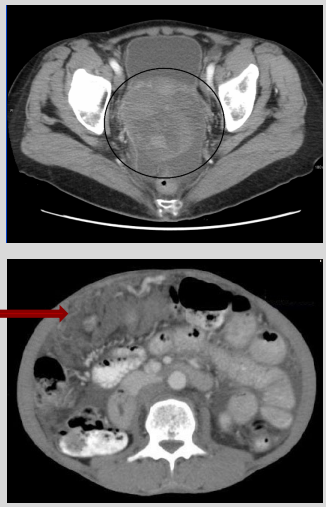
Ovarian cancer symptom index

- 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

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

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 (≥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

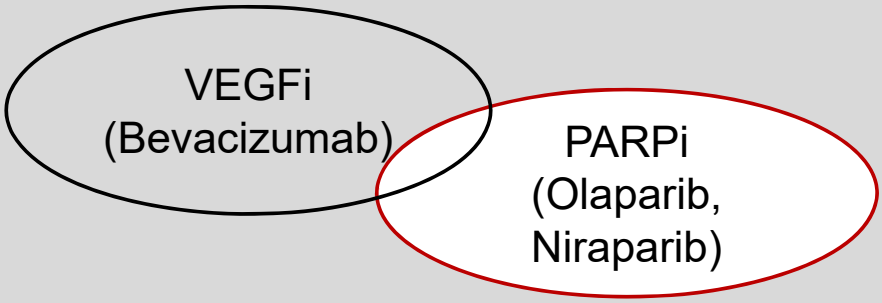
Bristow et al. J Am Coll Surg. 2015

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

Maintenance therapy



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

DNA Damage	Insertions Deletions A-G mismatch T-C mismatch	DS breaks cross-links	Bulky adducts	SS breaks
Repair pathway	Mismatch Repair	Homologous recombination repair, X Non-homologus end joining	Nucleotide excision repair	Base excision repair -

BRCAm

Forced dsDNA breaks

PARPi

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

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

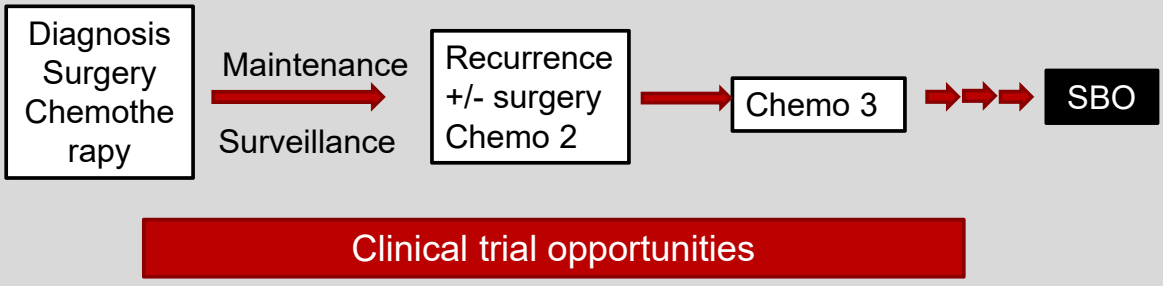
~ 40-70% reduction in risk of recurrence or death from disease

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

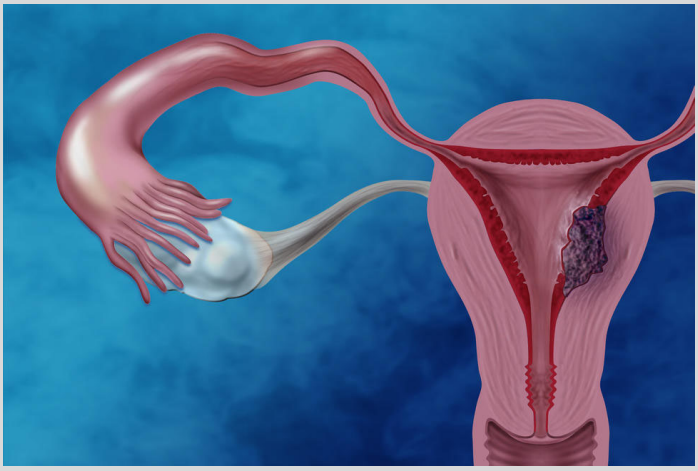


Image: cancer.gov

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

Histology

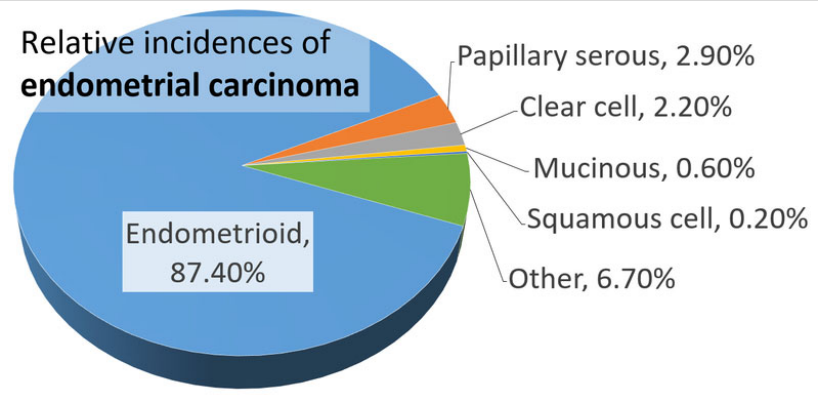
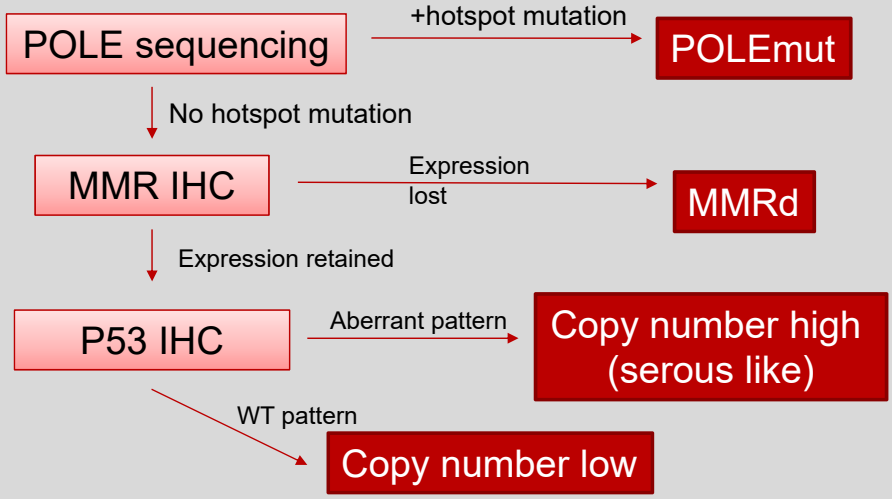


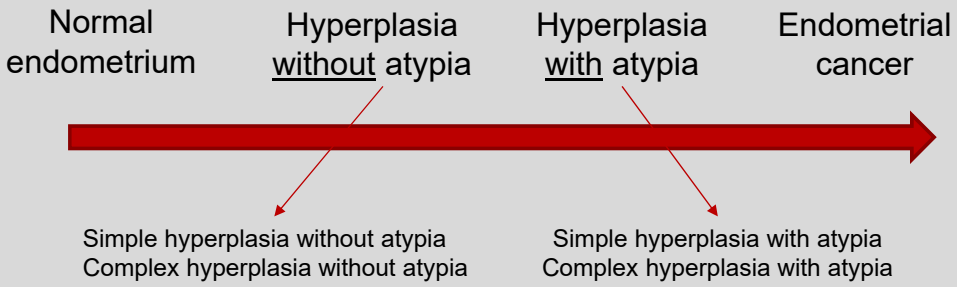
Image: Author: Mikael Häggström, M.D. (CC0 1.0)

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

Pathophysiology (Endometrioid/copy number low)



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?

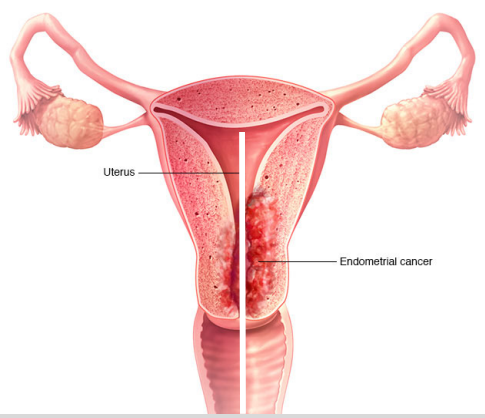
Presentation

- Abnormal uterine bleeding
  - Intermenstrual bleeding
  - Heavy/prolonged menses
  - Irregular menses
  - **Postmenopausal bleeding**
- Cramping/pelvic pain

- Rarely present with symptoms of metastatic disease

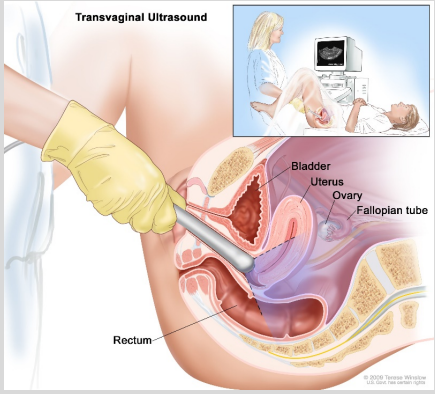
Evaluation

Endometrial biopsy



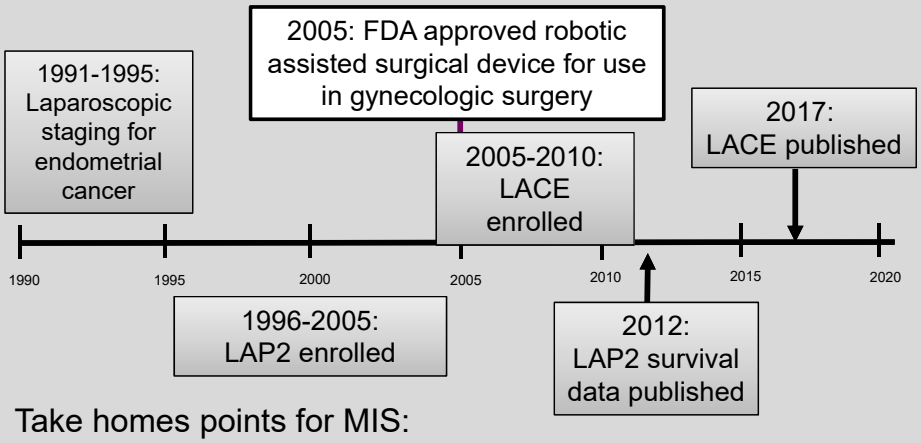
Author: Lolaia (CC BY-SA 4.0)

Transvaginal ultrasound



Source: Cancer.gov

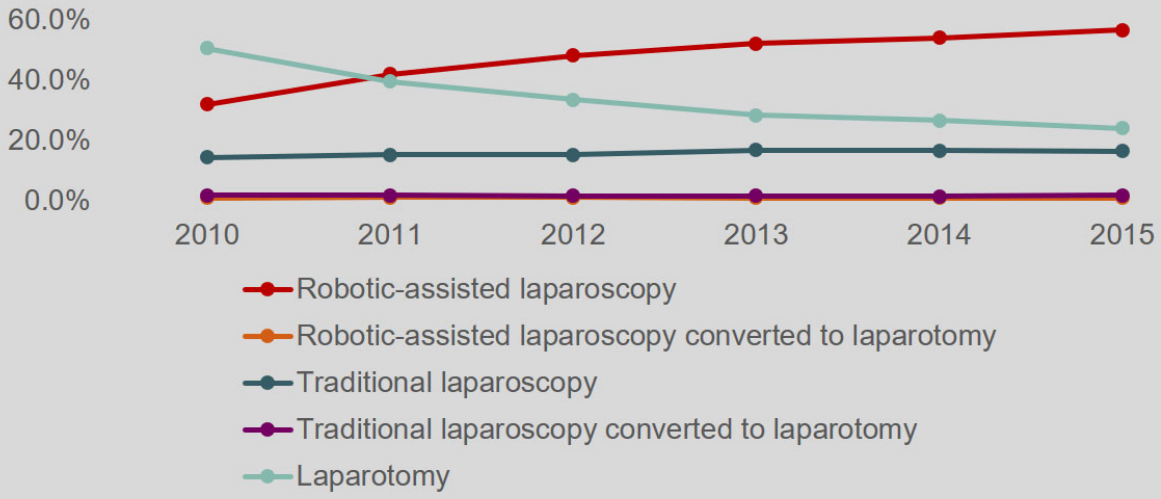
Surgery for endometrial cancer



Take homes points for MIS:

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

Surgical approach over time



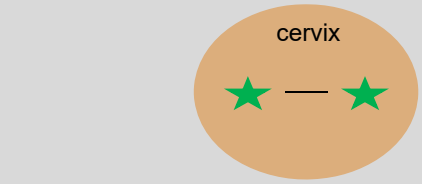
Bixel et al. J Minim Invasive Gynecol. 2021

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)
   - Isofulfan 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



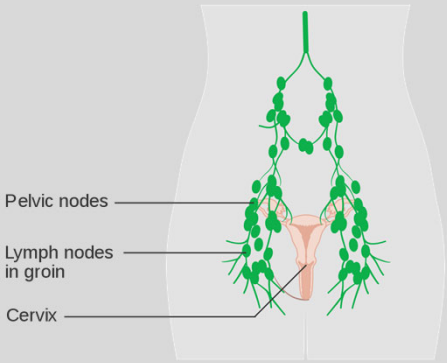


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Image: Author: Cancer Research UK (CC BY-SA 4.0)

FIGO staging

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

85%

Adjuvant therapy

- The great (forever) debate!

Low risk	Low-intermittent risk	High-intermittent risk	High risk
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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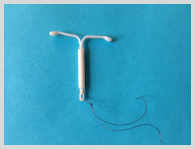
Special circumstances: Desires fertility

- 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

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

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)

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