Ovarian Cancer

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Outline

- Incidence and Risk Factors
- Histology
- Staging
- Diagnosis, Clinical Manifestations
- Management of Early Stage Disease
- Management of Advanced Disease
- Management of Recurrent Disease
- Risk Reduction
- Questions

Incidence

Site of Cancer	Estimated New Cases	Estimated Deaths	Case to Death Rate
1. Breast	268,600	41,760	15.5%
2. Lung	228,150	142,670	62.5%
3. Prostate	174,650	31,620	18.1%
4. Colorectal	145,600	51,020	35.0%
5. Melanoma	96,480	7,230	7.5%
6. Bladder	80,470	17,670	22.0%
7. Lymphoma	74,200	19,970	26.9%
8. Kidney/GU	73,820	14,770	20.0%
9. Uterine	61,880	12,160	19.7%
10. Leukemia	61,780	22,840	37.0%
17. Ovarian Cancer	22,530	13,980	62.1%

- Leading cause of GYN cancer death in US
- Second most common GYN cancer in US
- 1 in 75 American Women will be diagnosed
- 1 in 100 American women will die from OVCA

SEER 2020

Risk Factors

- Increasing age
- Family history
- Hereditary breast and ovarian cancer syndromes
  - BRCA1/2, RAD51C/D, BRIP1, Lynch
  - Account for ~1/4 of ovarian cancer cases
  - Younger age at diagnosis compared to sporadic cases
- Endometriosis
  - Clear cell, endometrioid histologies
- Nulliparity, early menarche, late menopause

Protective Factors

- Removal of ovaries and fallopian tubes (BSO)
- Oral contraceptive use
  - >50% reduction with over 10 years of use
- Tubal ligation/removal (salpingectomy)
- Hysterectomy
- Breastfeeding
- Pregnancy/childbirth

Histology

- **Epithelial ovarian cancer – account for 90% of cases**
  - High grade serous: 70-80%
  - Low grade serous: <5%
  - Clear cell: 10%
  - Endometrioid: 10%
  - Mucinous: 3%
  - Carcinosarcoma (MMMT): <5%
- **Borderline Tumors** – not benign, not malignant
  - Atypia without invasion
  - No adjuvant treatment

Histology

- **Sex Cord Stromal Tumors: >10%**
- **Stromal Tumors**
  - Fibromas
  - Thecomas
  - Leydig cell tumors
  - Steroid cell tumors
- **Sex Cord Tumors**
  - Granulosa cell tumors (Adult/Juvenile)
  - Sertoli cell tumors
  - Sertoli Leydig cell tumors
  - Sex cord tumor with annular tubules
- **Germ cell tumors**
  - Dysgerminomas
  - Yolk sac
  - Immature teratomas

FIGO/TNM Staging

- **Stage I** – Ovary
- **Stage II** – Pelvis
- **Stage III** – Abdominal metastasis outside of the pelvis
- **Stage IV** – Extra-abdominal disease

Staging

- **Stage 1 - confined to ovary**
- IA: Limited to one ovary or fallopian tube, capsule intact, no tumor on surface, negative washings/ascites
- IB: Limited to both ovaries (capsule intact), no tumor on surface, negative washings/ascites
- IC1: Surgical spill
- IC2: Capsule ruptured before surgery or tumor on the surface
- IC3: Malignant cells in ascites or peritoneal washings

Staging

- **Stage II – confined to pelvis**
- IIA: extension/implants on the uterus/fallopian tubes
- IIB: extension/implants on other pelvic tissues (bladder peritoneum, pelvic side wall)
- **Stage III – metastasis outside of pelvis**
- IIIA1i: Positive retroperitoneal lymph nodes (<10mm)
- IIIAii: Positive retroperitoneal lymph nodes (>11mm)
- IIIA2: Microscopic peritoneal metastasis
- IIIB: Macroscopic peritoneal metastasis (<2cm)
- IIIC: Macroscopic peritoneal metastasis (>2cm)

Staging

- **Stage IV – distant metastasis**
- IVA: pleural effusion with positive cytology
- IVB: hepatic or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes), transmural intestinal involvement

Prognosis by Stage

- Stage I: 90%
- Stage II: 70%
- Stage III: 40%
- Stage IV: 17%

Symptoms

- Pelvic pain
- Bloating, distention
- Urinary urgency, frequency
- GI complaints – anorexia, constipation, early satiety
- Suspicious/palpable pelvic mass on abdominal exam
- Acute symptoms – VTE, pleural effusion, abdominal ascites, bowel obstruction

Diagnosis

- Physical exam
- CT chest, abdomen pelvis with PO/IV contrast
- Tumor markers – CA125, CEA, CA 19-9
- GI evaluation, as indicated

Ovarian Cancer Treatment

- Requires multi-modality approach
- Staging or Debulking Surgery
  - Residual disease matters
- Chemotherapy
  - Platinum-based doublet regimen is first-line
- Radiation
  - Palliation/consolidation
- Despite this, ~80% of women with advanced stage disease will recur

Management of Early Stage Ovarian Cancer

Staging Surgery

- Hysterectomy, BSO, pelvic and para-aortic lymph node dissection, biopsies, omentectomy
- Surgery can be performed open (laparotomy) or minimally invasive (MIS)
- Fertility preserving surgeries can be considered in select patients

Adjuvant Therapy: Chemo vs. Observation

	% Alive	Hazard Ratio (HR)	*P* Value
5-year RFS			
Adjuvant Chemo vs Observation	76 vs 65	0.64 (0.50-0.82)	0.001
5-year OS			
Adjuvant Chemo vs Observation	82 vs 74	0.67 (0.50-0.90)	0.008

Adjuvant Therapy

Benefit for chemo in HR early stage

- ICON-1: n=477 heterogeneous staging
  - CT: better RFS (HR 0.65) OS (HR 0.66)
- ACTION: n=448 heterogeneous staging
  - CT: better RFS (HR 0.64) trend CSS (HR 0.73)

In the case of incomplete staging

- CT: better RFS (HR 0.73) CSS (HR 0.58)

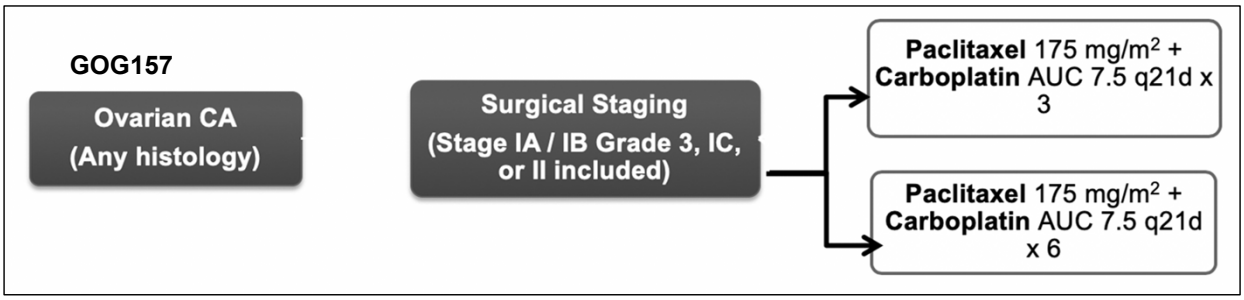
ICON collaboration JNCI 2003, Bell Gyn Onc 2006, Chan Gyn Onc 2010

Adjuvant Therapy

Patient Selection

- High Risk – 5 year DFS: 40-80%
- Stage IC, II
- Clear cell
- Grade 3 tumors
- Low Risk – 5 year DFS: 90%
- Stage IA, IB
- Grade 1

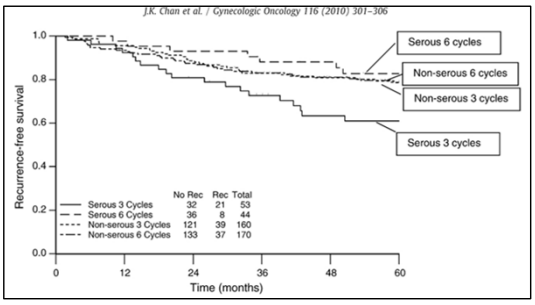
Adjuvant Therapy: 3 vs 6 cycles

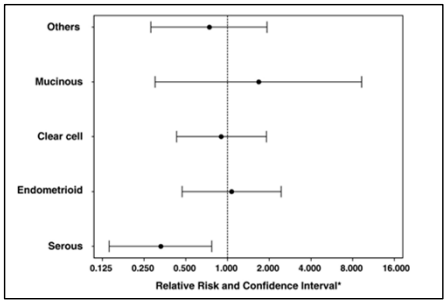


N = 427	3 Cycles	6 Cycles	HR	P Value
5-Year RFS	75%	80%	0.76* (0.51-1.13)	0.18*
5-Year OS	81%	83%	1.02 (0.66-1.57)	0.94

Adjuvant Therapy: 3 vs 6 cycles

Exploratory Sub-analysis of GOG157





6 cycles may be of benefit in patients with serous histology only

Management of Advanced Ovarian Cancer

Management of Advanced Stage Disease

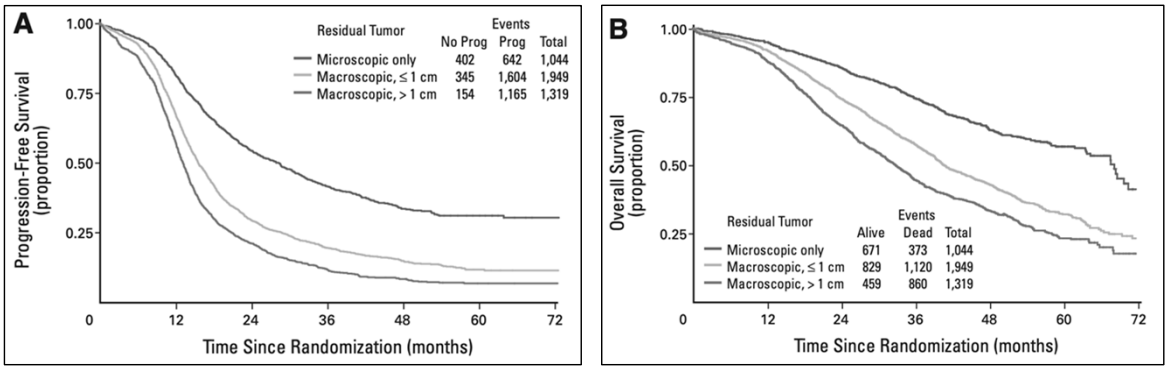
Upfront treatment approach depends on disease burden, medical co-morbidities and performance status

Primary cytoreductive surgery, followed by 6 cycles of carboplatin/paclitaxel

OR

3-4 cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel, interval cytoreductive surgery, 3 additional chemotherapy cycles

Residual Disease after Surgery Matters….



Microscopic residual disease (R0 resection) is associated with significantly improved PFS and OS benefit compared to macroscopic disease <1cm or >1cm.

Bookman, JCO

Primary Surgery vs. NACT – EORTC 55971 Trial

Phase 3 RCT

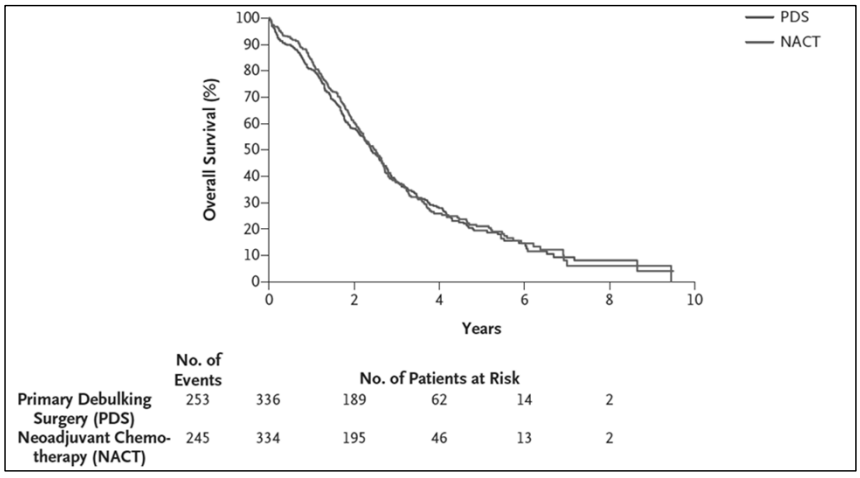
NACT = 334

PCS = 336

HR death: 0.98

HR progression: 1.01

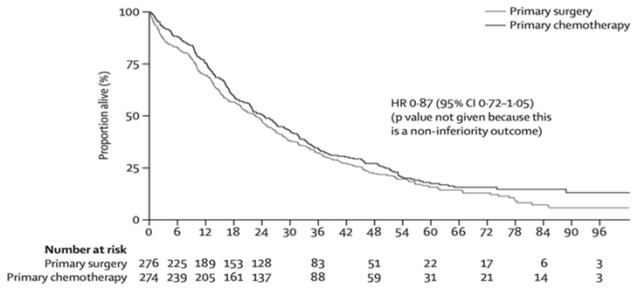
Complete resection of all macroscopic disease was strongest predictor of OS



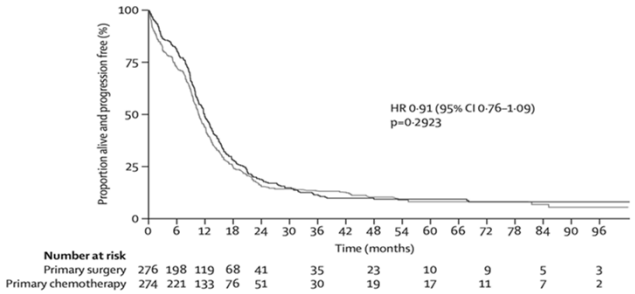
Vergote, NEJM, 2010

Primary Surgery vs. NACT – CHORUS Trial

PFS



OS



Phase 3, non-inferiority, RCT

Primary surgery was non-inferior for OS versus primary chemotherapy (HR 0.98)

Higher incidence of G3/4 AE (24% vs. 14%)

Carboplatin in Primary Ovarian CA

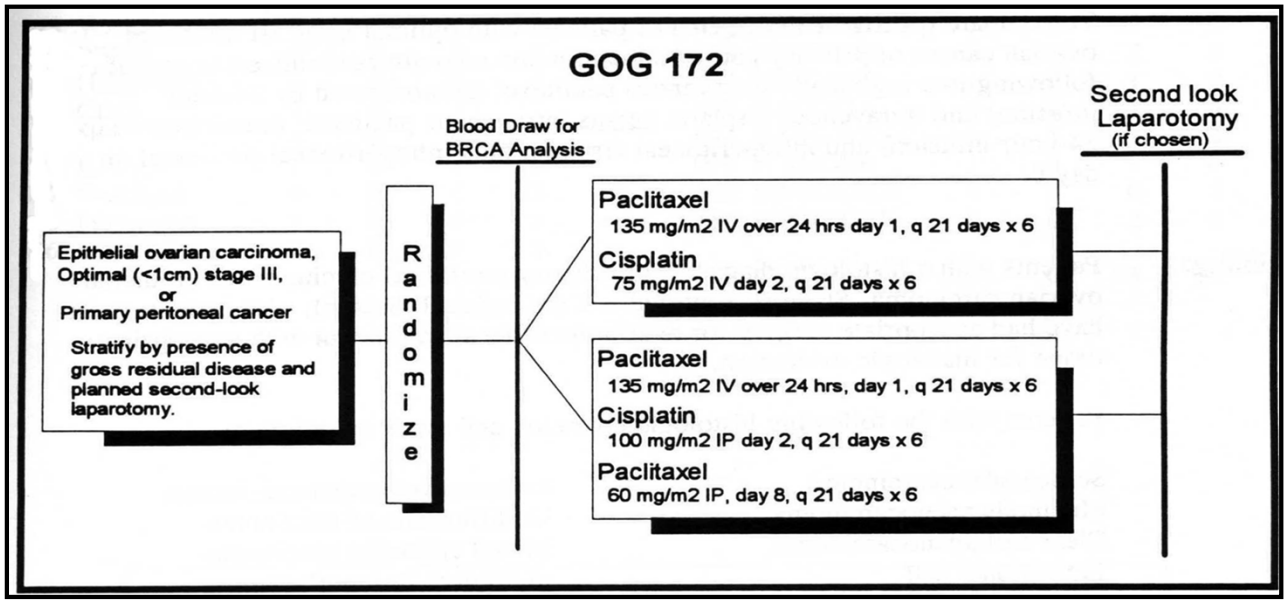
GOG 158 (Ozols, JCO 2003) – a non-inferiority trial

- 792 women with optimally resected Stage III ovarian cancer
  Cisplatin 75mg/m2 plus **paclitaxel** 135 mg/m2 (400 patients)
  Carboplatin AUC 7.5 plus **paclitaxel** 175 mg/m2 (392 patients)
- **Results**:
  Median PFS: 20.7 vs 19.4 months (T-Carbo vs T-Cis) p>0.05
  Median OS: 57.4 vs 48.7 months (T-Carbo vs T-Cis) p>0.05
- **Tolerability**:
  No difference in median # of cycles completed
  Cis caused more nephrotoxicity, nausea/vomiting, and leukopenia
  Carbo caused more thrombocytopenia (significantly)

Other Considerations

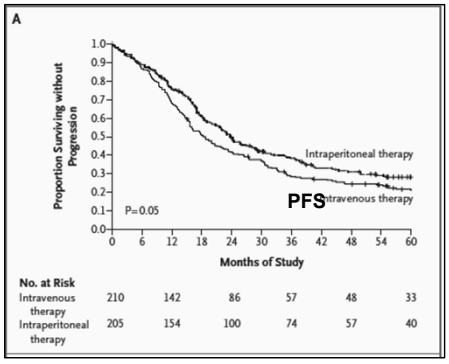
- Intraperitoneal (IP/IV) chemotherapy
- Bevacizumab
- PARP inhibitors
- Hyperthermic intraperitoneal chemotherapy (HIPEC)

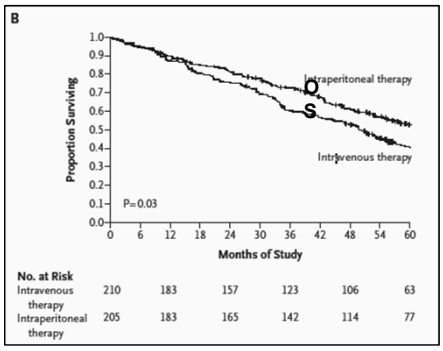
IV/IP Chemotherapy



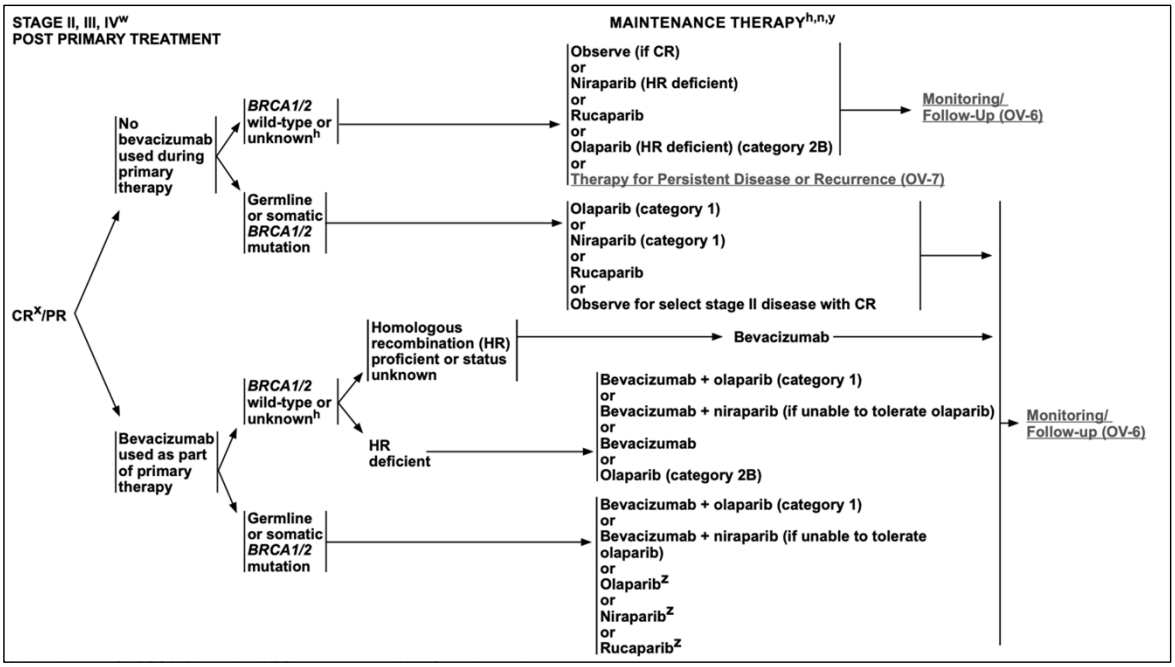
GOG172

- **PFS**: 23.8 vs. 18.3m
- **OS**: 65.6 vs. 49.7m
- Only 42% of IP/IV patients completed therapy
- Reduced QOL for IP/IV therapy
- Higher G3 heme (76 vs. 64%), GI (46 vs. 24%) and neurologic toxicity (19 vs. 9%)





Front-Line Maintenance



Bevacizumab

- **Recombinant monoclonal antibody targeting VEGF**
- **Two P3 trials in frontline setting**
- **ICON7**
- **GOG218**

GOG 218

- Evaluated bevacizumab as combination and maintenance for 1st line
- N=1873
- Mean follow-up 17 mos
- **PFS**: No difference for Groups I v II, 11 v. 10 months
- PFS improved for concurrent + maintenance group: 14 months
- **No diff in OS**: 39 months

Burger et al 2011

ICON7

- Evaluated Bevacizumab as combo + maintenance (12 cycles), N=1528
- PFS: 24 vs 22 mos (P=0.04)
- OS: 45.5 vs 44.6 mos(P=0.85)
- QOL: No difference
- **Conclusion:** PFS benefit without OS with addition of bevacizumab and increased toxicity
- **Subset Analysis:** For women with: suboptimal surgery, or inoperable surgery (stage III/IV), bevacizumab had improved outcomes
  - N=502 women (33% of initial study)
  - PFS improved 18.1 vs 14.5 mos (P=0.002)
  - OS improved 39.3 vs 34.5 mos (P=0.03)

PARP inhibitors

- PARP proteins repair single-strand DNA breaks via homologous recombination, thereby avoiding double stranded breaks that are more difficult to repair
- Synthetic lethality for susceptible cells leads to cell death
- PARPi in Ovarian Cancer
  - Olaparib
  - Niraparib
  - Rucaparib

Uterine Cancer

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Objectives

- Be able to identify patients who need to undergo evaluation for endometrial cancer.
- Initial workup
- Treatment of endometrial cancer.
- Fertility sparing options
- Surveillance after treatment
- New molecular staging for endometrial cancer

Case

33yo G0 presents for annual exam/WWE

PMH: HTN, Obesity (325lbs)

PSH: l/s Chole

FHX: Father died from colon cancer 50

OB/GYN: Periods “always irregular, every 2-12 weeks

Pap smears have been completed and normal

G0 despite no birth control.

Case

- **Exam:**
  - Mostly unremarkable
  - Obese female
  - Cervix appears normal
  - Pelvic limited by pt’s body habitus
  - No bleeding on exam
- What would you recommend for additional workup?

Endometrial "Uterine" Cancer

- Most Common GYN Cancer (4th most common cancer in women)
- 1/40 women in the US will develop in Lifetime
- Almost always presents with DUB/PMB
- Risk related to estrogen exposure (and this is INCREASING)
  - **OBESITY**
  - Anovulation (no progesterone), Infertility
  - Exogenous exposure (ERT, Tamoxifen)
  - Age
- Type 1 "Garden Variety endometrioid" vs. Type 2

Genetic Mutations

- Lynch Syndrome: HNPCC
  - Autosomal dominant disorder
  - DNA mismatch repair genes
    - *MLH1*, *MSH2*, *MSH6*, *PMS2, EP CAM*
  - 27 – 71% lifetime risk
- Cowden Syndrome
  - Autosomal dominant disorder
  - Mutation in the PTEN tumor suppressor gene
  - 13 – 19% lifetime risk

Endometrial Cancer Screening

- Not routinely recommended
  - +/- for pts with confirmed LYNCH syndrome
- No data to justify screening ultrasounds or biopsies with or after Tamoxifen use
- Thankfully, endometrial cancer reliably causes bleeding early in the disease course.

Endometrial Cancer Workup

- AUB with risk factors or PMB = Endometrial Biopsy
  - Risk Factors for estrogen exposure (obesity, anovulatory, PCOS, tamoxifen, taking estrogen) and irregular menstrual bleeding = Endometrial Biopsy at any age
- *READ THE BIOPSY report carefully. Make sure really negative (vs inadequate sample)*
- Pelvic US- look at EMS (want to be <5mm for PMB)
  - Consider other sources of bleeding, uterine size, ovarian masses
- Don't forget the pap
- CT: only needed if high grade or non-endometrioid pathology (serous, etc.)

Endometrial Cancer

	Type I	Type II
Histology	Endometrioid	UPSC, Clear Cell
Grade	Low grade (Grade 1-2)	High Grade (Grade 2-3)
Pt Characteristics	Obese, G0, Anovulation	Older, Black
Unopposed Estrogen	Yes	No
Growth	Slow	Fast
Precursor Lesion	EIN/CAH	EIC
Prognosis	Good	Worse
Molecular Features	PTEN, MSI	P53, HER2

Treatment

- Surgery
  - Surgically staged
  - Hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node dissection
  - Preferrable done minimally invasive (Robotic versus Laparoscopic)
    - Robotic offers the ability to perform this on morbidly obese patients
    - Very few patients are not a candidate for surgery

Treatment - Alternatives to surgery

- **Very few patients are not a candidate for surgery**
- Radiation
  - Definitive radiation is an option for patients who are not surgical candidates with pelvic confined disease
  - Palliative radiation can help with bleeding in certain situations
- Hormonal therapy
  - Used for Grade 1 and 2 endometrioid cancers
  - More to come on this…..

Fertility Sparing Options

- FSS is defined as the preservation of ovarian tissue in one or both adnexa and the uterus.
- Preservation of fertility is regarded as one of the most important issues related to quality of life in younger patients with cancer.
- Infertility resulting from cancer treatment may be associated with psychosocial distress.

Fertility Sparing Options

- Selection criteria for conservative management
  - Well differentiated carcinoma
  - Absence of deep myometrial invasion on MRI
  - Absence of suspicious pelvic or para-aortic LNs
  - Absence of synchronous ovarian tumor
  - No contraindications to medical treatment
  - Patient's desire to complete the follow up protocol
  - **PATIENT ACCEPTS THAT THIS IS NOT STANDARD OF CARE**

Fertility Sparing Workup

- Consultation with a fertility expert (REI)
- Molecular evaluation for inherited cancer syndrome (MMR)
- Pelvic MRI to evaluate for myometrial invasion and locally metastatic disease
- **Weight management referral**

Treatment Options to Preserve Fertility

- Continuous progestin therapy
  - Megestrol
  - Medroxyprogesterone
  - Levonorgestrel IUD
- Consider dual therapy (systemic and local)
- Weight Management
  - Surgery
  - GLP-1

Fertility Sparing Follow Up

- Endometrial sampling every 3 months
  - EMB versus D&C
- Should have a response by 6 months
- If endometrial cancer persists at 9-12 months → repeat pelvic MRI
  - Reconsider surgical management
  - Can consider ovarian preservation

Fertility Sparing Follow Up

- Need to counsel on treatment between pregnancies if the patient desires more than one child.
- Can consider definitive surgery after completion of childbearing
- Pregnancy rates depend on modification of the patient's risk factors for developing endometrial cancer
  - Many risk factors are those for infertility

Staging FIGO 2018

- Stage I - Tumor confined to the corpus uteri, including endocervical glandular involvement
  - IA – Tumor limited to the endometrium or invading less than half the myometrium
  - IB - Tumor invading one half or more of the myometrium
- Stage II – Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus.
- Stage III – Tumor involving the serosa, adnexa, vaginal, or parametrium
  - IIIA – Tumor involving the serosa and/or adnexa
  - IIIB – Vaginal or parametrial involvement
  - IIIC – Mets to pelvic and para aortic lymph nodes
- Stage IV – Tumor invading the bladder mucosa and/or bowel mucosa

2023 FIGO Staging

- Basis of FIGO 2023 staging system
- Molecular analysis:
  - 4 clinically significant molecular subgroups
    - POLE mutation
    - Microsatellite instability-high (MSI-H)
    - Mismatch repair deficient (dMMR)
    - No specific molecular profile (NSMP)
    - P53 absent
  - Still undergoing prospective trials to escalate or de-escalate care

Adjuvant Therapy

- The new molecular staging system has complicated this algorithm.
- For early-stage low grade disease usually surveillance or vaginal brachytherapy.
- For advanced disease or high-grade cancer can be a combination of chemotherapy, radiation, and immunotherapy depending on uterine and molecular features.

"The one thing we know about endometrial cancer is that we cure some people with a hysterectomy"

Surveillance

- Once treatment is complete (surgery +/- adjuvant therapy)
  - Symptom analysis and physical exam every 3 months for the first 2 years.
  - After the first 2 years, this is spread out to every 6 months for the next 3 years.
- Considered cured 5 years after completion of treatment

Society of Gynecologic Oncology

1. Don't screen low risk patient with Ca-125 or US for ovarian cancer
2. Don't perform pap tests for surveillance of patients with h/o endometrial cancer
3. Don't perform colposcopy in patients treated for cervical cancer with Pap test of LGSIL or less
4. Avoid routine imaging for cancer surveillance in patients with gynecologic cancer, specifically ovarian, endometrial, cervical, vulvar, and vaginal cancer
5. Don't delay basic level palliative care for patients with advanced or relapsed gynecologic cancer, and when appropriate, refer to specialty level palliative medicine

Conclusions

- Endometrial cancer is the most common of the gyn cancers
- TVUS and endometrial sampling is the cornerstone of diagnosis of endometrial cancers.
- Type 1 cancers are related to an excess of estrogen, most commonly secondary to obesity
- Type 2 cancers cancers are not associated with excess estrogen and are more aggressive
- Surgery including hyst/BSO/SLND is the mainstay of staging

Conclusions

- FIGO 2023 staging system takes into account molecular analysis of the cancer.
- Adjuvant therapy is dependent on both stage and molecular analysis of the tumor.
- Surveillance is every 3 months for the first 2 years, followed by every 6 months for the next 3 years.
- Routine paps and imaging are NOT recommended for routine surveillance in endometrial cancer.