

What is New in Gynecologic Cancer?

Professor, Division of Gynecologic Oncology

Neag Cancer Center

University of Connecticut

Research Professor Electrical and Computer Engineering

Molly A. Brewer, DVM, MD, MS



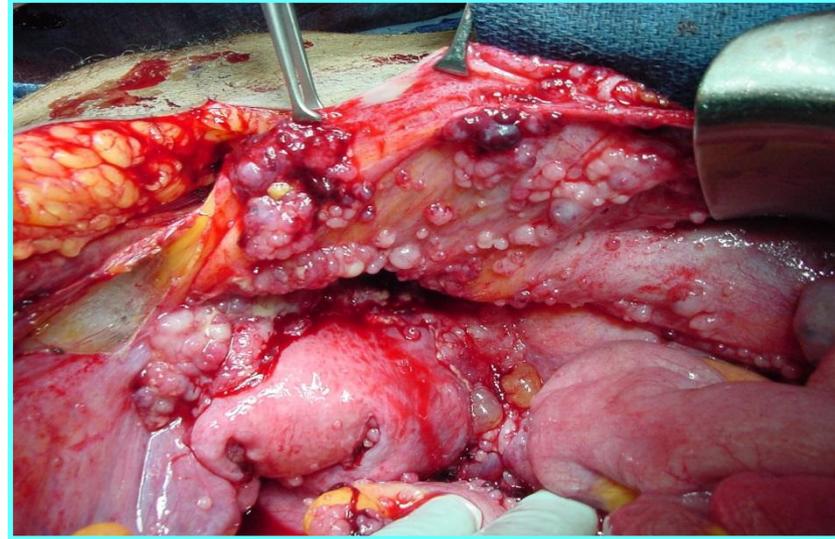
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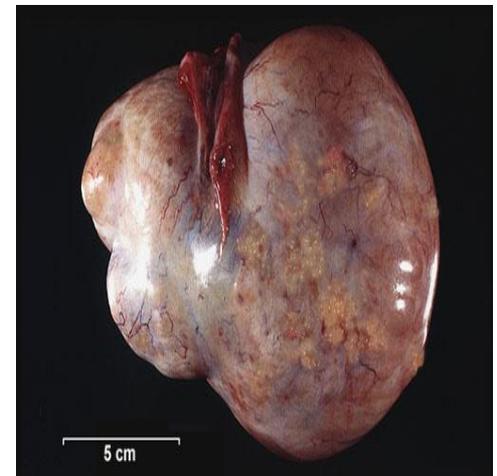
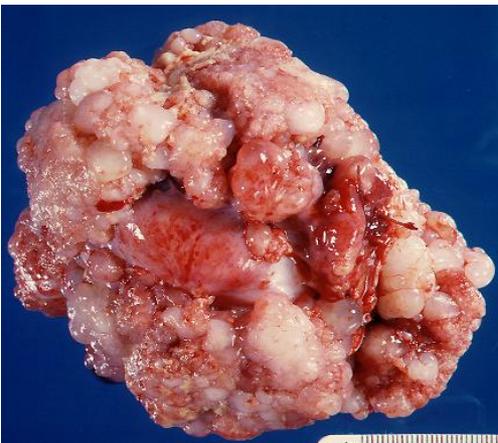
Objectives:

- New screening and diagnostic approaches for ovarian cancer
- How to best triage patients with a pelvic mass
- Updates for cervical cancer screening
- Updates on endometrial cancer

I have no conflicts



Ovarian Cancer



Challenges: Ovarian Cancer

Relatively rare cancer: 1.5-1.7% lifetime risk

Major obstacles:

- Undefined premalignant lesions
- Poor access to evaluate the ovary
- Poor screening technology
- Little known about prevention
- Early metastasis
- Symptoms usually occur after metastasis
- Ovarian cancer is diagnosed 70% of the time in Stage III or IV where the survival is 30% or less

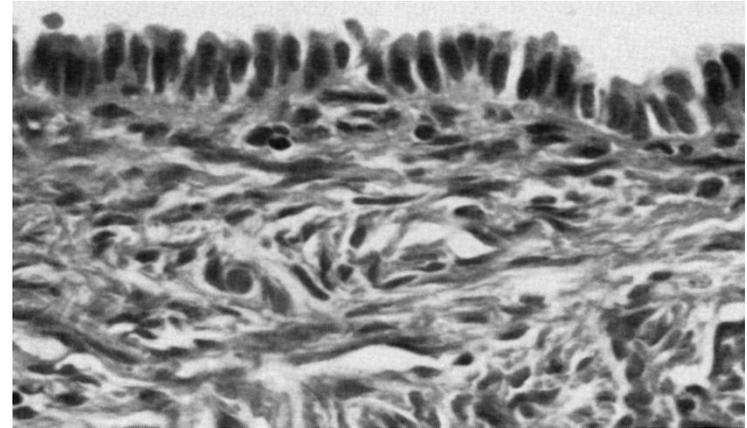
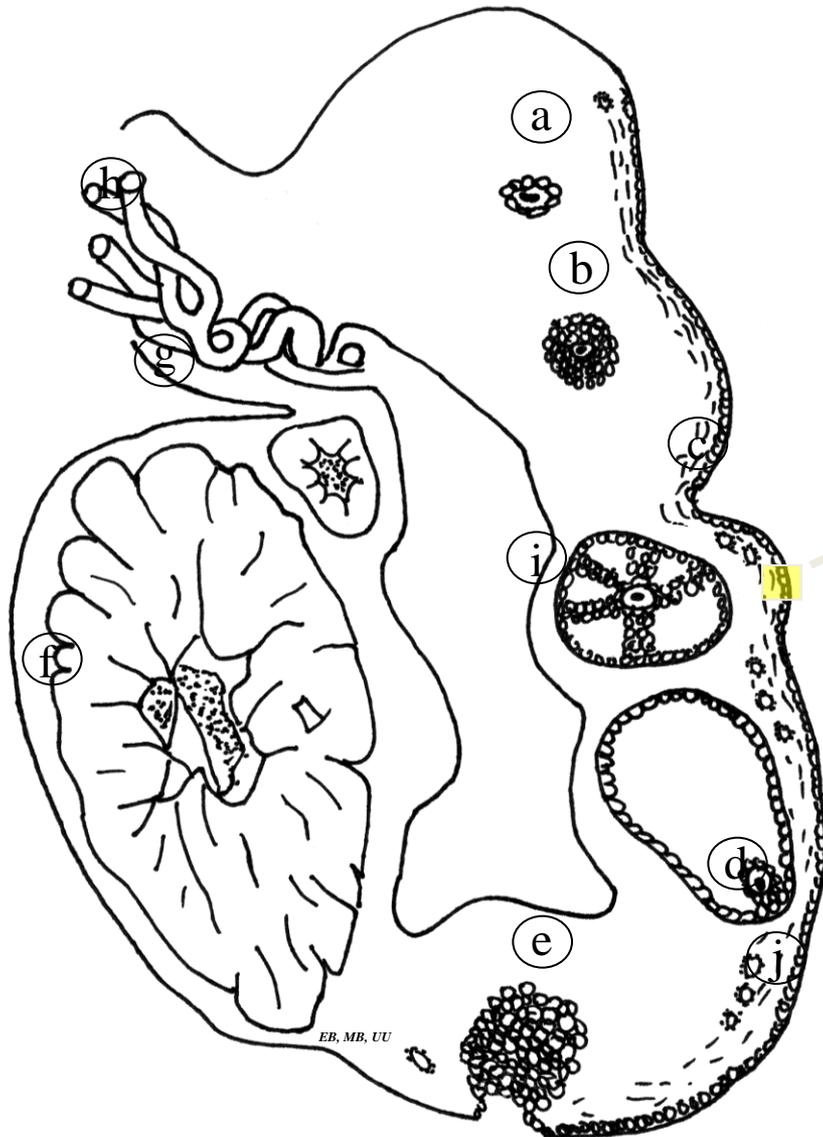
Ovarian Cancer: Epidemiology

- Increased risk/ increased ovulation:
 - early menarche/late menopause
 - fertility drugs (?)
 - nulliparity
 - breast cancer
 - family history (breast/ovarian cancer)
 - genetic mutations (BRCA1/2)
 - Endometriosis (clear cell)
- Decreased risk/ decreased ovulation:
 - oral contraceptive use
 - breastfeeding
 - multiparity
 - late menarche/ early menopause
 - retinoids
- Natural History: unknown

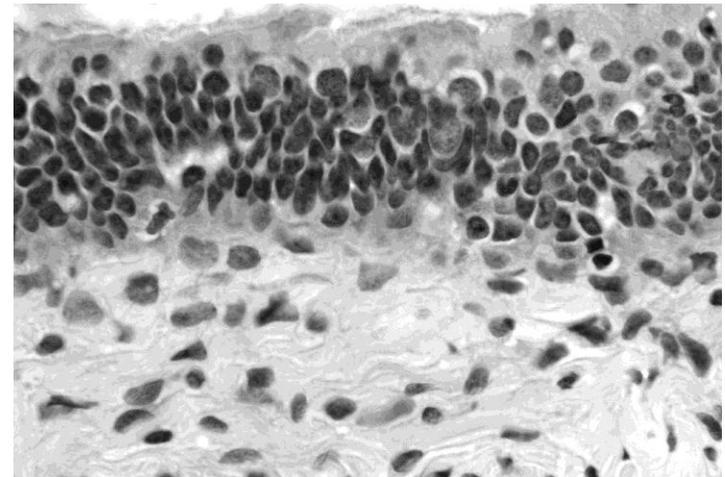
Do serous ovarian cancers originate from the ovary or the tube?

- 2-12% of BRCA 1/2+ women have cancer at the time of BSO
- 75% originate in the tubal epithelium
- By the time most ovarian cancers are diagnosed, there is involvement of both ovaries and tubes
- How to best identify these patients?

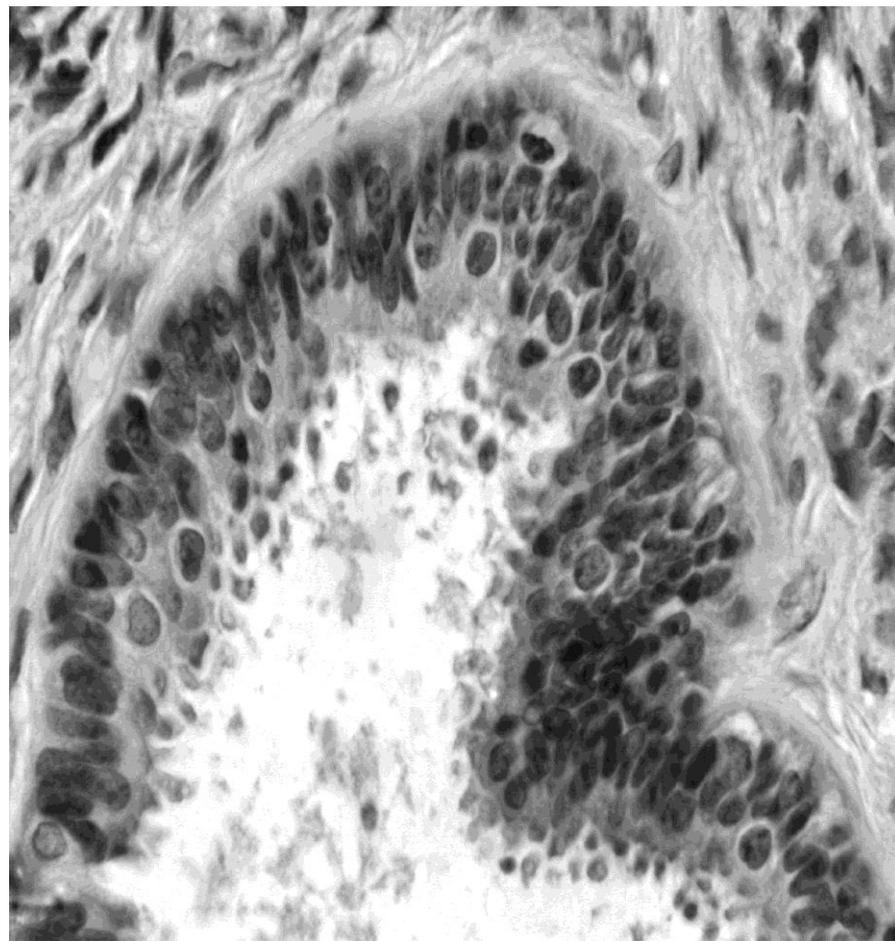
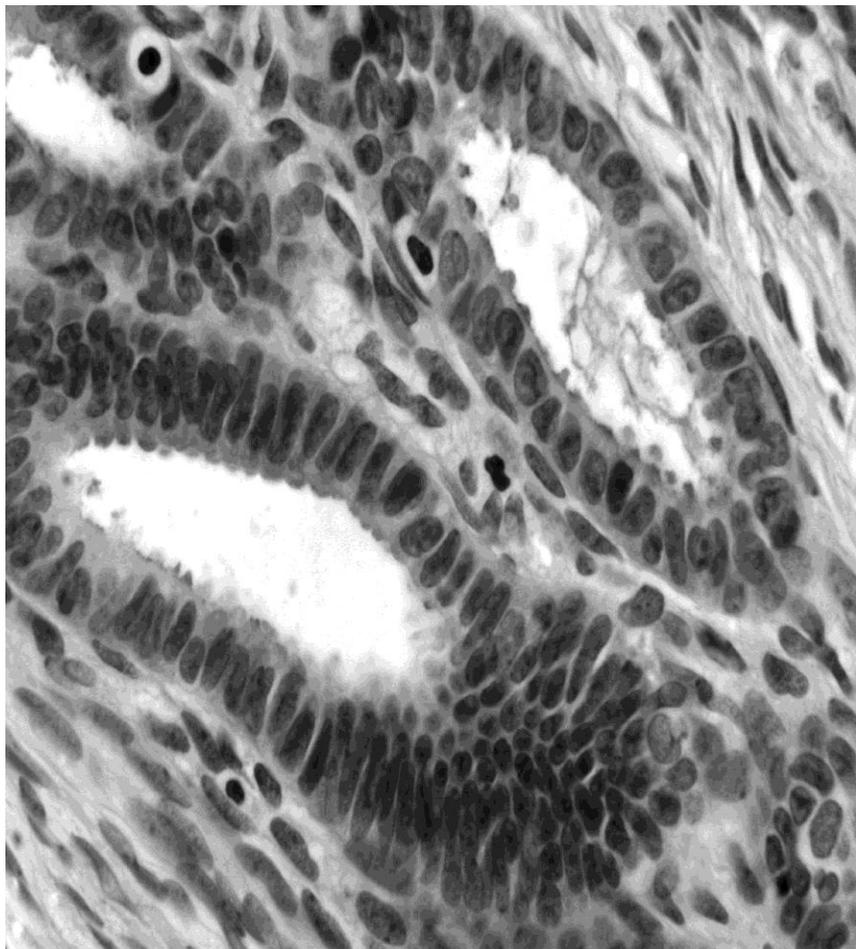
Structure of the Ovary



and stroma



Ovarian Inclusion Cysts

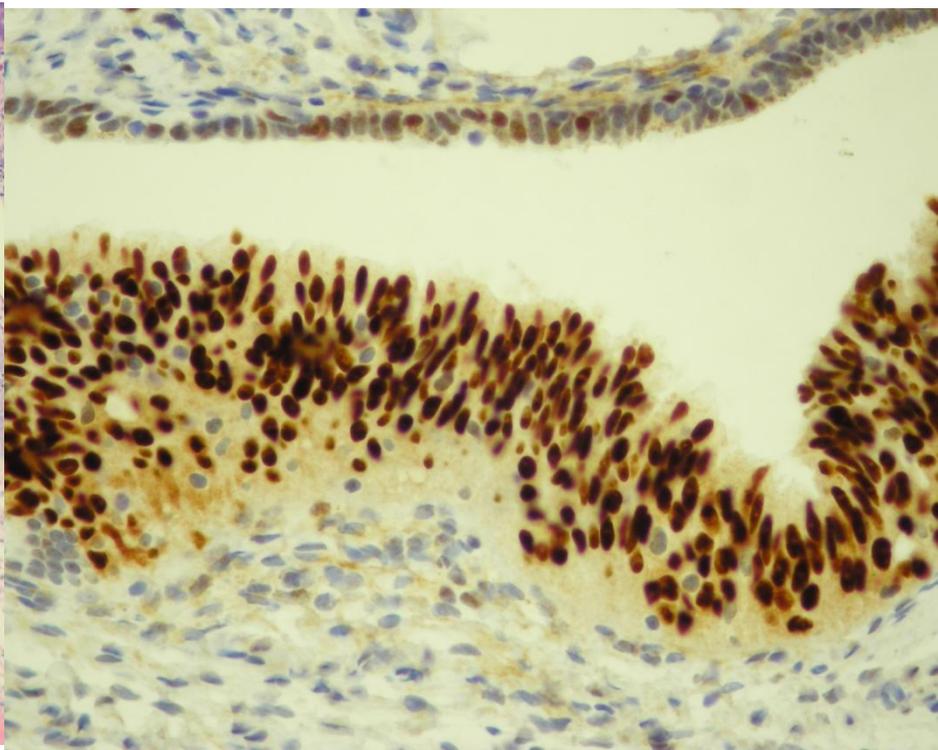
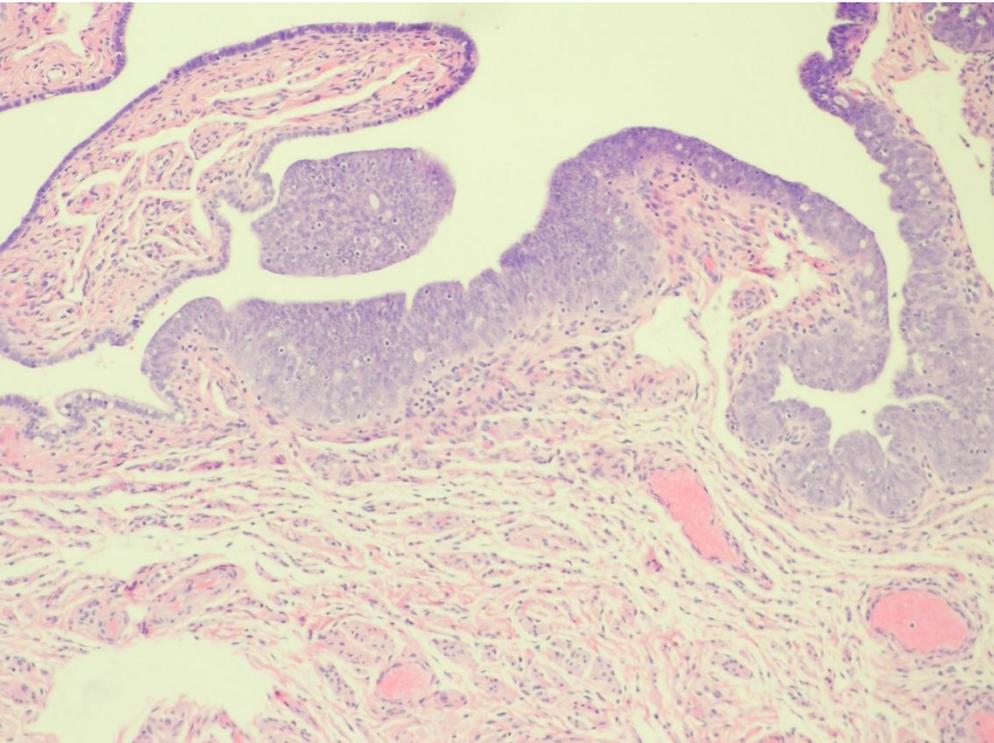


Fallopian Tube

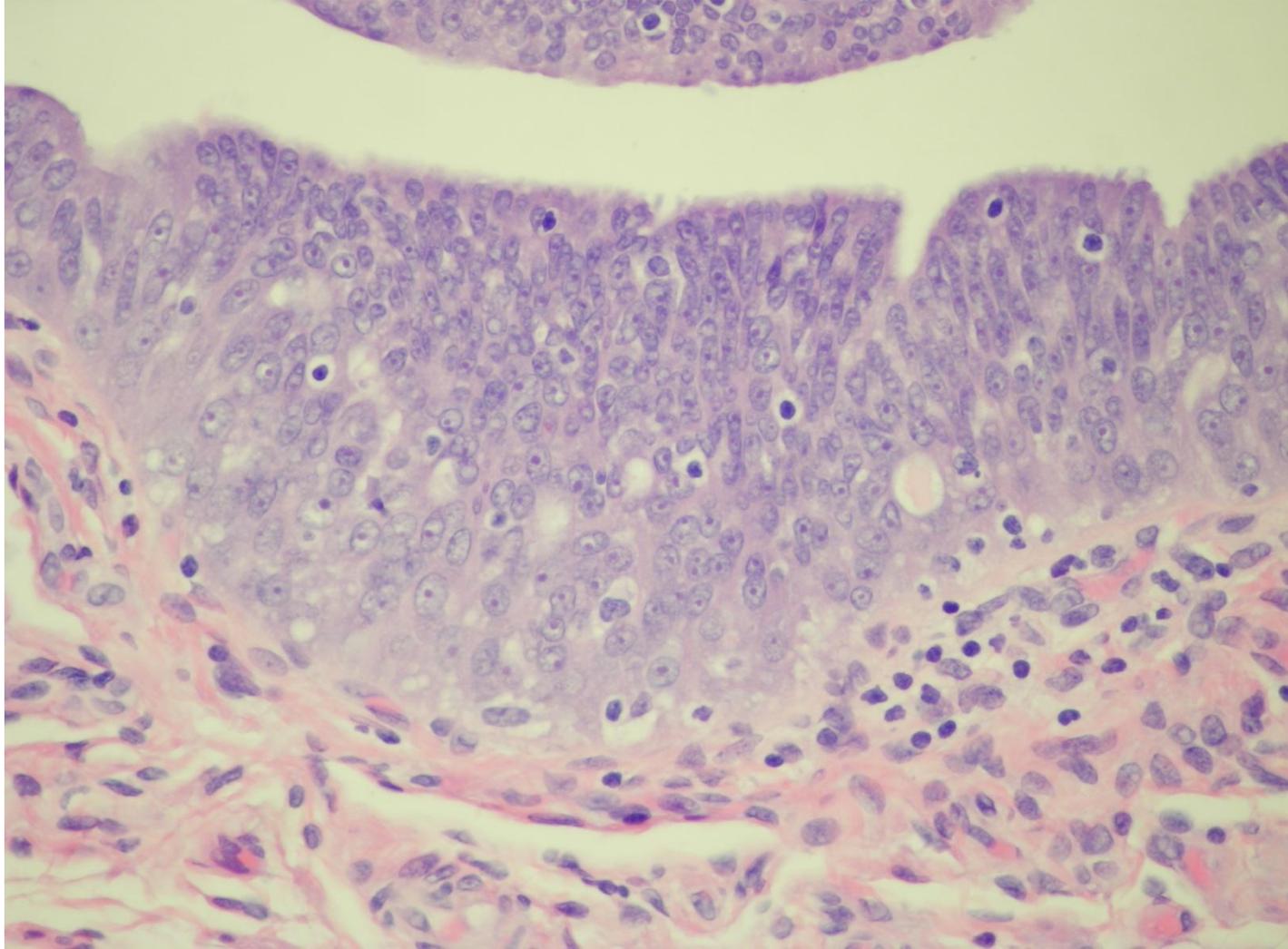
- Identification of "dysplastic" epithelial changes in the fallopian tubes of women with BRCA1 or BRCA2 mutations (Piek et al, 2003)
- SEE-FIM protocol with routine examination of the fimbria assumed to be the site of origin for many HGSCs with identification of serous tubal intraepithelial carcinomas (STICs) in risk-reducing salpingo-oophorectomies (Medeiros et al 2006)
- STICs seen in 20-60% of HGSCs in sporadic cancers established STIC and the distal tube as an important source of these tumors (Kindelberger et al, 2007)
- p53 signatures - bland-appearing cell outgrowths with p53 mutations - in the tube and their genetic similarity to STICs, a morphologically, genetically and histochemically defined serous carcinogenic sequence (Xian et al, 2010)

Serous Tubal Intraepithelial Neoplasia

P53 IHC



Serous Tubal Intraepithelial Neoplasia



Current state of the art

- Precursors in the tube, which likely remain localized for months to a few years, cannot be detected by current technology.
- Based on frequency of a co-existing STIC, the tube is implicated in HGSC –including ovarian and peritoneal – in from 19 to 59 per cent of cases (Carlson et al, Roh et al, Pryzbycin et al, Tang et al)
- Should we be removing all tubes even though there is no data?
- Does the STIC resemble DCIS of breast where there is limited probability of progression to invasive cancer and has been overtreated?
- If a subset of tumors emerge *de novo* from the ovarian or peritoneal surfaces, they may never be preventable by screening.

Taking A Family History: The Basics

- When do you take a family history?
 - Always!
- Why?
 - 1) to identify patients with an increased risk for cancer
 - 2) to develop specific screening and management guidelines based on their cancer risk
- Who do you include?
 - First, second and third degree relatives,
 - Both maternal and paternal sides of the family
- What do you ask?
 - Type of cancer (primary site) AND age of onset
- Where can patients get additional information about relatives?
 - Death certificates, tumor registry

How to Take a Family History

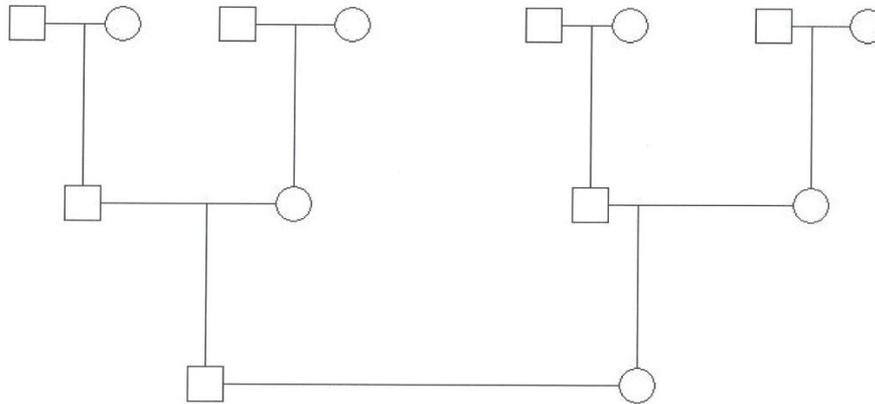


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Family History / Pedigree

(Patient Identification)

ancestry: _____ ancestry: _____



Legend:

Signature:

Date:

Factors that can limit risk assessment in a pedigree

- Limited family structure
 - Small family
 - No or few female relatives
 - Relatives died at a young age of non-cancer related causes (before cancer would be diagnosed)
- Family structure can affect the accuracy of mutation probability models. Risk assessments are quoted within the context of a limited family history
- All patients with ovarian cancer now referred for genetic testing: 11.7-16.6 % of women with ovarian cancer are BRCA carriers and 2 % are HNPCC carriers

Risk Assessment Criteria

- Any individual ≤ 40 yo with breast cancer, first or second degree relative
- One case of ovarian cancer
- One case of male breast cancer
- ≥ 2 cases of breast cancer in first or second degree relatives if one is diagnosed at ≤ 50 or is bilateral
- Ashkenazi Jewish families
- Patient with both breast and ovarian cancers

Ovary/Fallopian tube removal in the BRCA population

- 792 women: 509 underwent RRSO
- 85% reduction in BRCA1-associated gynecologic cancer risk (hazard ratio [HR] = 0.15; 95% CI, 0.04 to 0.56)
- 72% reduction in BRCA2-associated breast cancer risk (HR = 0.28; 95% CI, 0.08 to 0.92).

Bilateral Oophorectomy

Women not receiving estrogen who underwent PO <45 years of age were 2X more likely to die:

	OR
• Estrogen related cancer	5.71
• Non-cancer	1.71
• Vascular	1.41
• Neurological/mental	2.34

Metastasis

- Recent evidence suggests that metastasis is an earlier event than previously thought
- Only very small numbers of shed malignant cells are capable of metastasizing (0.01%)
- The persistence of cancer cells in the vasculature does not necessarily result in seeding to distant sites
- Emerging evidence in breast cancer suggests that early tumors may already hold the genetic profile needed for metastasis

Screening for Ovarian Cancer

Low risk women

Do not screen

High Risk Women

Screen with multiple caveats

Sporadic	Familial	Hereditary
Single occurrence in family	Two or more first-degree or second-degree affected relatives	Multiple affected individuals in multiple generations
Late age of onset (after 60 y)	Onset typically after 50 y	Early age of onset (often less than 50 y)
Unilateral	Primarily unilateral or late-onset bilateral	Bilateral/multifocal disease
Lack of other cancers in the family, or only common cancers of late onset	Evidence of skipped generations, no clear inheritance pattern	Presence of ovarian cancer, male breast cancer, Jewish ancestry, multiple other unusual and/or early onset malignancies
Primarily caused by age an other nongenetic factors	Multiple minor/moderate inherited genetic factors interacting with environment	Single major cancer susceptibility gene mutation, autosomal dominant inheritance

Ultrasound

- 1,072 premenopausal ovarian masses
- 570 were functional cysts and corpus lutea (53%)
- 264 were endometriotic cysts (25%)
- 192 were benign neoplasms (18%)
- 46 malignancies (4%)

Ultrasound

- 5/236 (2.1%) complex adnexal masses were cystic ovarian tumors with thick septa but no solid areas.
- 14% had ascites present
- 67% had benign tumors, 30% had ovarian cancer, 3% had LMP tumors
- High risk of cancer=complex/solid morphology, CA 125 value > 35 units/mL
- PPV of 84.7% and NPV of 92.4% and correctly identified 77.3% of patients with stage I and stage II ovarian cancer and 98.6% of patients with stage III and stage IV ovarian cancer.

Ovarian Masses

- Age 20–29, cystic teratomas, serous cystadenomas, and mucinous cystadenomas are responsible for 72, 15, and 11% of benign ovarian neoplasms, respectively
- At age 40–49, the same 3 tumor types make up 43, 46, and 8%, of benign neoplasms
- The risk of a neoplasm being borderline is 2.4% at 20–29 and 6.3% at 40–49
- The risk for malignancy is 4% at 20–29 and 35% at 40–49

Diagnostic ability of CT

- Low-dose unenhanced computed tomography (CT) in asymptomatic women
- 118 (4.1%), mean age 56.2 had an adnexal mass (108 unilateral, 10 bilateral; mean size, 4.1 cm) all benign
- 4 cancers developed in 15-44-month interval among the remaining 2751
- CT is a poor screening technology for ovarian cancer

Diagnostic ability of MRI

- Combination of US and MR findings was false positive for malignancy in only 7 of the 72
- No false negative cases of invasive ovarian malignancy
- 19 had 'malignant' findings at US downgraded correctly by MR imaging to surgically correlated complex benign diagnoses.
- MR imaging was most valuable for women who had normal or only slightly elevated levels of CA-125

CA-125 testing

- Premenopausal women with a known adnexal mass
- Elevations can be seen with
 - Endometriosis
 - Pelvic inflammatory disease
 - Leiomyomas
 - Cystic teratomas
 - Pleural infections
 - Menstrual cycle

HE4 (human epididymis secretory protein 4) and Risk for Malignancy (ROMA)

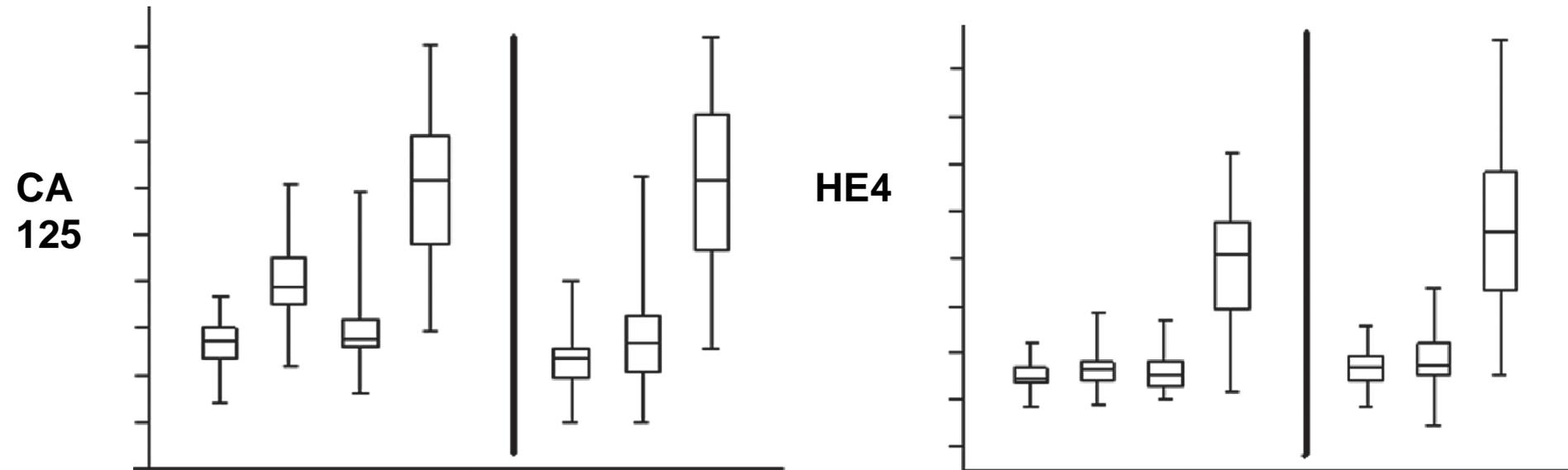
- Premenopausal women: sensitivity and specificity were
 - 92.3% and 59.4% for CA125,
 - 84.6% and 94.2% for HE4
 - 84.6% and 81.2% for ROMA,
- Postmenopausal women: sensitivity and specificity :
 - 94.3% and 82.3% for CA125,
 - 78.2% and 99.0% for HE4
 - 93.1% and 84.4% for ROMA.

CA125 and HE4

Premenopausal
HC En Cy OC

Postmenopausal
HC En OC

Premenopausal Postmenopausal
HC En Cy OC HC En OC



HC= healthy controls
En= endometriosis
Cy= cyst
OC= ovarian cancer

- HE4, CA 125 and ROMA results were abnormal
 - in 1.5%, 13.6% and 25.8% of healthy women
 - in 1.1%, 30.2% and 12.3% of patients with benign diseases
- HE4 had significantly higher concentrations in ovarian cancer than in other malignancies ($p < 0.001$).
- Tumor marker sensitivity in ovarian cancer was 79.3% for HE4, 82.9% for CA 125 and 90.1% for ROMA

OVA1

- CA 125-II, transthyretin [prealbumin], apolipoprotein A1, beta 2 microglobulin, and Transferrin
- Results are interpreted by proprietary software, and an OVA1 score is given, which differs based on menopausal status.
- A high probability of malignancy is defined as at least 5.0 in premenopausal women and at least 4.4 in postmenopausal women.

OVA1

- 516 eligible women who were recommended surgery based on the practitioner's assessment.
- At surgery, 151 cancers were identified.
- OVA1 had a sensitivity of 92.5%, specificity 42.8%, positive predictive value 42.3%, and negative predictive value 92.7%
- Does not take the place of clinical decision making for women found to have an adnexal mass
- Adjunct to clinical decision making. Providers should still use the best risk of malignancy scoring system that performs optimally in their practice

ROCA (Risk of Ovarian Cancer Algorithm)

- Postmenopausal women with annual CA125
- If low risk based on algorithm → CA125 1 yr
- If moderate risk based on algorithm → repeat CA125 3 months
- If high risk based on algorithm → TVS
- Positive predictive value of 40%
- Specificity was 99.9%

Management Guidelines for Adnexal Masses

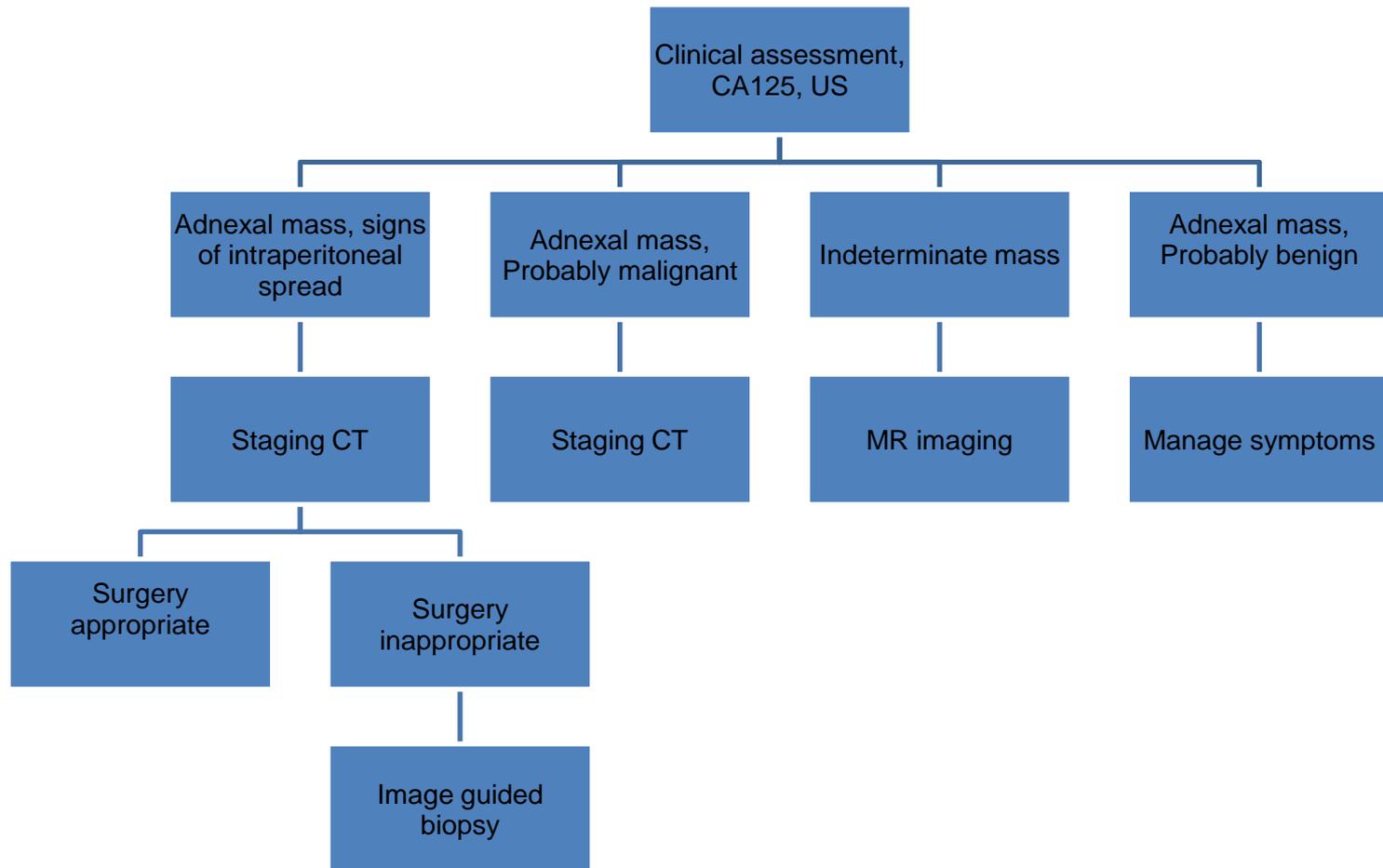
- In asymptomatic women with pelvic masses TVUS is the imaging modality of choice
- No alternative imaging modality has demonstrated sufficient superiority to TVUS to justify its routine use
- Any CA 125 elevation in a postmenopausal woman with a pelvic mass is highly suspicious for malignancy

Management Guidelines for Adnexal Masses

- Women with ovarian cancer whose care is managed by physicians who have advanced training and expertise in the treatment of women with ovarian cancer, such as gynecologic oncologists, have improved overall survival rates compared with those treated without such collaboration

Management Guidelines for Adnexal Masses

- Simple cysts up to 10 cm in diameter on ultrasound findings are almost universally benign and may safely be followed without intervention, even in postmenopausal patients
- Unilateral salpingo-oophorectomy or ovarian cystectomy in patients with germ cell tumors, stage I stromal tumors, tumors of low malignant potential, and stage IA, grade 1–2 invasive cancer who undergo complete surgical staging and who wish to preserve fertility does not appear to be associated with compromised prognosis



Case 1

- 42 yo presents for gynecologic care
- FH mother with ovarian cancer at 30, maternal aunt with pancreatic cancer at 49, maternal cousin with colon cancer at 55
- RLQ pain
- TVS with enlarged right ovary
- CA125 58
- Would you refer her? Genetic counseling?

Case 2

- 65 yo with cystic complex ovarian mass found on exam, asymptomatic
- No family h/o cancer
- CA125 85
- Would you refer her?



Cervical cancer



The paradigm for screening has
changed dramatically

- Screening by Papanicolau (Pap) test should not be used for women aged <21 years, regardless of initiation of sexual activity,
- Screening interval of 3 years should be maintained for women aged 21-30 years.
- ACS and ACOG explicitly recommend against yearly screening.

- Among those aged 22-30 years, the proportion reporting having had a Pap test within the preceding 12 months decreased from 78.1% to 67.0%.
- Among women aged 22-30 years, who should be screened every 3 years, the proportion who reported never having had a Pap test increased from 6.6% to 9.0%

- The current model of cervical carcinogenesis suggests that HPV infection results is either transient or persistent.
- Most HPV infection is transient and poses little risk of progression.
- Persistent infection at 1 year and 2 years strongly predicts subsequent risk of CIN 3 or cancer regardless of age

- In a cohort of untreated patients with CIN 3, the cumulative incidence of invasive cancer was reported to be 30.1% at 30 years.
- Most HPV-related types of cervical neoplasia are very slow to progress. On average, a severe dysplasia may take 3–7 years to progress to invasive cervical cancer.

Screening Methods for Cervical Cancer: Joint Recommendations of the American Cancer Society, the American Society for Society Colposcopy and Cervical Pathology, and the American for Clinical Pathology

Population	Recommended Screening	Comment
Women younger than 21 years	No screening	
Women aged 21–29 years	Cytology alone every 3 years	
Women aged 30–65 years	Human papillomavirus and cytology co-testing (preferred) every 5 years Cytology alone (acceptable) every 3 years	Screening by HPV testing alone is not recommended
Women older than 65 years	No screening is necessary after adequate negative prior screening results	Women with a history of CIN 2, CIN 3 or adenocarcinoma in situ should continue routine age-based screening for at least 20 years
Women who underwent total hysterectomy	No screening is necessary	Applies to women without a cervix and without a history of CIN 2, CIN 3, adenocarcinoma in situ, or cancer in the past 20 years
Women vaccinated against HPV	Follow age-specific recommendations (same as unvaccinated women)	

Women with negative cytology and positive HPV
co-testing results who are aged 30 years and older
Level A Evidence

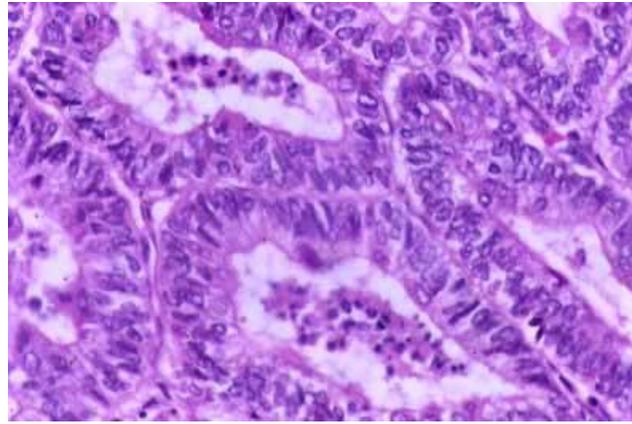
- Repeat co-testing in 12 months. If the repeat cervical cytology test result is LSIL or higher or the HPV test result is still positive, the patient should be referred for colposcopy. Otherwise, the patient should return to routine screening
 - OR
- Immediate HPV genotype-specific testing for HPV-16 alone or HPV-16/18 should be performed. If positive should be referred directly for colposcopy. Women with negative results from tests for HPV-16 or HPV-16/18 should be retested in 12 months

Case 1

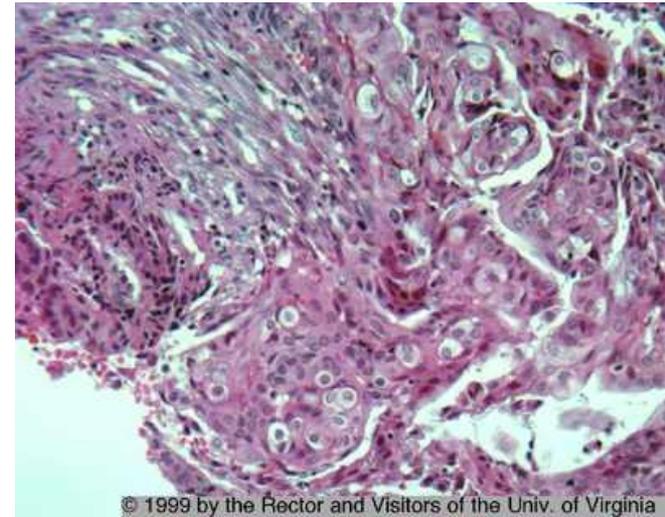
- 42 yo, no h/o abnormal Pap smears, last Pap 1.5 years ago
- ASCUS Pap, HPV +
- Colposcopy negative, 6 cervical biopsies -,
- ECC SCC
- Exam erythematous area anterior cervix
- Bx adeno-squamous carcinoma

Case 2

- 45 yo with ASCUS HPV+, last Pap 3 years ago negative
- Biopsies CIN3, ACIS
- Cone adenocarcinoma 5X9 mm invasion
- Radical hysterectomy 3 mm residual disease



Endometrial Cancer



- Who should be considered for genetic testing?
- To stage or not to stage?
- Can these patients with grade 1 be treated by a generalist?
- Do patients with grade 3 histology need to be staged?

HNPCC: Endometrial Cancer

- 1.8% of all endometrial cancer have HNPCC
- 7/10 did not meet standard criteria for HNPCC
- Mean age 54 years
- 8.6% diagnosed with endometrial cancer < 50 years old had HNPCC

HNPPC: Lifetime cancer risk

- Colorectal cancer (men) 28 – 75%
- Colorectal cancer (women) 24 – 52%
- Endometrial cancer 27 – 71%
- Ovarian cancer 3 – 13%
- Gastric cancer 2 – 13%
- Urinary tract cancer 1 – 12%
- Brain tumor 1 - 4%
- Bile duct/gallbladder cancer 2%
- Small bowel cancer 4 - 7%

Mutation Carriers

	MLH1	MSH2	MSH6	Total
Mutation carriers	70	67	109	246
Subjects with colorectal cancer (%)	51	31	24	34
Subjects with endometrial carcinoma	10	13	19	15
Subjects with other Lynch associated cancer (%)*				
Ovarian carcinoma	1	4	6	4
Small bowel cancer	1	3	0	1
Transitional cell carcinoma	0	4	3	2

Median Age/Range of Diagnosis of HNPCC Cancer

	<i>MLH1</i>	<i>MSH2</i>	<i>MSH6</i>
Colorectal cancer	47 (25-79)	44 (20-82)	53 (32-84)
Endometrial cancer	51 (46-54)	46 (36-55)	56 (47-67)
Ovarian cancer	52 (52-52)	47 (45-48)	49 (35-51)

Diagnosis of HNPCC

- Family h/o colon/endometrial cancer at young age
- IHC on tumor tissue with absence of expression of MLH1, MSH2, MSH6 or PMS2
- PCR for definitive diagnosis
- Sporadic endometrial cancers may be associated with epigenetic silencing of MLH1
- Gene sequencing based on IHC

Clinical Staging, FIGO 1971

Stage I	Confined to corpus
Ia	Cavity less than 8cm
Ib	Cavity greater than 8 cm
Stage II	Corpus & Cervix
Stage III	Outside the corpus but not outside pelvis
Stage IV	Outside the true pelvis, or obvious involvement of bladder or rectal mucosa.

Surgical Staging, FIGO 1988

Stage	Description
Ia	Tumor limited to endometrium
Ib	Invasion to less than 50% myometrium
Ic	Invasion to more than 50% myometrium
IIa	Endocervical gland involvement only
IIb	Cervical stromal invasion
IIIa	Uterine serosa, adnexa, <u>positive cytology</u>
IIIb	Vaginal Metastases
IIIc	Metastases to pelvic or periaortic nodes
IVa	Invasion of bladder and/or bowel mucosa
IVb	Distant metastases, intraperitoneal, inguinal

Surgical Staging, FIGO 2010

Stage	Description
Ia	Invasion < 50% myometrium + cytology
Ib	Invasion > 50% myometrium + cytology
IIa	Endocervical gland involvement only
IIb	Cervical stromal invasion
IIIa	Uterine serosa, adnexa
IIIb	Vaginal Metastases
IIIc	Metastases to pelvic or periaortic nodes
IVa	Invasion of bladder and/or bowel mucosa
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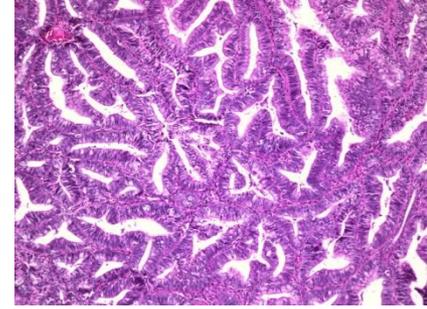
Staging vs No Staging

	Frozen Section	Permanent Section
• Low risk	109 (62.6)	90 (51.7)
• Intermediate risk	17 (9.8)	34 (19.5)
• High risk	48 (27.6)	50 (28.7)
• Total	174	174

Authors' conclusions: If staging was based on frozen section, 12.8% of patients would be undertreated

My conclusion: rely on the permanent section for treatment decisions, management should be with gynecologic oncology

Atypical Endometrial Hyperplasia



Stage	IA	IB	IC	IIB	IIIC	Total
Grade 1	4	14	2	2	1	23
Grade 2	0	1	1	0	0	2
Total	4	15	3	2	1	

Authors' Conclusion: 25/88 (28.4%) of AEH had carcinoma on final pathology: All patients with AEH should be staged

My conclusion: low incidence of high grade cancer in AEH but they should be managed by gynecologic oncology

Role of Lymphadenectomy

- 191 women (88 standard surgery group, 103 lymphadenectomy group) had died, with a hazard ratio (HR) of 1.16 (95% CI 0.87–1.54; $p=0.31$) in favor of standard surgery
- Conclusion: lymphadenectomy does not alter survival
- My conclusion: UK radiates many more patients than us

	Standard surgery (N=704)	Lymphadenectomy (N=704)
Radiotherapy	227 (33%)	228 (33%)
External beam +/-brachytherapy	173 (25%)	165 (23%)
Brachytherapy only	54 (8%)	63 (9%)
No Radiotherapy	471 (67%)	469 (67%)
Unknown	6	7

Authors' conclusion: lymphadenectomy does not reduce rate of XRT

My conclusion: UK radiates patients that we would either not treat or who would receive chemotherapy

Treatment 2004

- Surgery: TAH/BSO
 - Staging: Grade 1 deep invasion, grade 2 superficial invasion, all grade 3
- Radiation
 - Positive lymph nodes
 - High risk: deep invasion, LVSI
- Chemotherapy
 - Papillary serous: Taxol/Platinum +/- WART

Treatment 2013

- Surgery: TLH/BSO
 - Staging: Grade 1 deep invasion, grade 2 superficial invasion, all grade 3????
 - Staging for Grade 3 or deep Grade 2 w/wo LVSI may determine XRT fields
- Chemotherapy
 - All moderate or high risk
 - All positive nodes
- Radiation vaginal brachytherapy vs whole pelvic
 - Positive lymph nodes?? Better than chemotherapy?
 - High risk: deep invasion, LVSI vaginal brachytherapy +/- whole pelvic radiation
 - Lymphadectomy + pelvic XRT highest complication rate~30%

Treatment in 2015

- Less invasive surgery: role of sentinel nodes?
- Chemotherapy for intermediate/high risk disease
- ? Role of XRT
- Targeted therapy: avastin, EGFR inhibitors, other target blockers

Can Generalists Safely Treat Endometrial Cancer?

- Too many patients are upstaged at the time of surgery
- Cytoreductive surgery improves prognosis
- Grade I cancers are Grade 3 on final pathology 30% of the time
- General surgeons do not do adequate lymph node sampling
- Recurrent disease is rarely cured unless it is a vaginal recurrence.

