Ovarian Carcinoma

Objectives

Intermediate Level - Recent advances in our understanding of ovarian cancer have shown that many ovarian cancers do not arise in the ovary or from ovarian tissue. This lecture will present our current understanding of the most common types of “ovarian cancer.”

Goals - The learner will understand:
The current understanding of the origins of ovarian cancer
The likely sources of many serous carcinomas involving the ovary
The origin of endometrioid ovarian cancer

Objectives - The learner will be able to
Gross ovarian tumors in the appropriate manner
Assess the likely origin of ovarian cancer
Inspect and gross ovaries and fallopian tubes removed prophylactically to prevent ovarian cancer

Basics of Ovarian Epithelial Tumors

Overview of histologic subtypes

Dualistic categorization
Diagnostic issues of serous LMP tumors

Current theories of pathogenesis
DIFFERENTIAL DIAGNOSIS OF OVARIAN MASS

Physiologic -
follicle development: follicular and corpus luteum cysts
cystic follicle < 3 cm diam
follicular cyst > 3 cm diam
epithelial inclusion cysts
inclusion cyst < 1 cm diameter
cystadenoma > 1 cm diam

Neoplastic - epithelial, sex cord/stromal, germ cell, metastatic
Unknown - endometriosis
Infectious - tubo-ovarian abscess (PID)

OVARIAN NEOPLASMS:
CLASSIFICATION

OVARIAN NEOPLASMS - CELLS OF ORIGIN

Surface epithelium and inclusion cysts = epithelial tumors
Metastatic (5%)
Oocytes = germ cell tumors (15-20%)
Stroma + theca + granulosa = sex cord-stromal tumors

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The Origin and Pathogenesis of Epithelial Ovarian Cancer: A Proposed Unifying Theory.

Kurman, Robert; Shih, Ie-Ming; MD, PhD

**FIGURE 2.** Transfer of normal tubal epithelium to the ovary. A, Anatomical relationship of fallopian tube with the ovary at the time of ovulation. The fimbria envelops the ovary. B, Ovulation. The ovarian surface ruptures with expulsion and transfer of the oocyte to the fimbria. The fimbria is in intimate contact with the ovary at the site of rupture. C, Tubal epithelial cells from the fimbria are dislodged and implant on the denuded surface of the ovary resulting in the formation of an inclusion cyst.

**FIGURE 3.** Proposed development of low-grade (LG) and high-grade (HG) serous carcinoma. A, One mechanism involves normal tubal epithelium that is shed from the fimbria, which implants on the ovary to form an inclusion cyst. Depending on whether there is a mutation of KRAS/BRAF/ERRB2 or TP53, a LG or HG serous carcinoma develops from a serous borderline tumor, which, in turn, arises from a serous cystadenoma. Another mechanism involves exfoliation of malignant cells from a serous tubal intraepithelial carcinoma (STIC) that implants on the ovarian surface resulting in the development of a HG serous carcinoma. B, A schematic representation of direct dissemination or shedding of STIC cells onto the ovarian surface on which the carcinoma cells ultimately establish a tumor mass that is presumably arising from the ovary. Of note, there may be stages of tumor progression that precede the formation of a STIC.
SEROUS TUMORS

Epithelial Ovarian Tumors: Patterns of growth

• Benign - Cystadenoma
  – cysts with a single layer of the epithelium, >1 cm in diameter
  – 80% of all ovarian tumors
  – any age

• Borderline - Tumor of low malignant potential aka. Atypical proliferative epithelial tumors
  – papillary structures with stratified (tufted) epithelium, >10%
  – 30-45 y/o
  – 95% benign, in 5% malignant transformation to carcinoma

• Malignant - Carcinoma
  – invasive malignant epithelium >5mm, or
  – marked cytologic atypia + confluent epithelial growth >5mm
  – 45-70 y/o

Cystadenoma
Thin walled, but may be multiloculated
Lack soft papillary excrescences
80% of all ovarian tumors
Occur at any age
Borderline serous tumor
(Atypical proliferative epithelial tumors)
Papillary structures with stratified (tufted) epithelium, >10%
Age range usually between 30-45 y/o
95% benign, in 5% malignant transformation to carcinoma
2 Pathway Model

Low-grade pathway

- Oxyphilic adenoma
- AFI
- High-grade adenoma
- Low-grade carcinoma
- High-grade carcinoma

High-grade pathway

Well Cornell Medical College

Singer, Stohr et al., Am J Surg Pathol 2005

Transmembrane G protein-coupled receptors

<table>
<thead>
<tr>
<th>tubal epithelial and Müllerian carcinoma</th>
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<tbody>
<tr>
<td>- Escape from cell cycle arrest</td>
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<td>- BRCA mutation/LOH</td>
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<td>- mu-Her</td>
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<td>- yu3 signature</td>
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<td>- DNA damage</td>
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<td>- TP53 mutations</td>
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Ruptured follicle

- Inflammatory mediators
- Hemorrhage-rich milieu

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Development of Serous Carcinoma

2 Pathway Model

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<th>Pathway 1</th>
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<tr>
<td><strong>Source</strong></td>
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<td><strong>Molecular genetic changes</strong></td>
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<td>Low-grade serous CA (grade 1)</td>
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MUCINOUS TUMORS
Mucinous tumors of the ovary
- Mucinous ovarian tumors: cystadenomas (common), LMPs (somewhat common), carcinomas (rare)
- Mucinous carcinomas metastatic to the ovary (common)
- MAY LOOK LIKE cystadenoma or LMP!
- Mucinous proliferations associated with teratoma, mucinous carcinoid, Brenner tumor, Sertoli-Leydig tumor (rare)
MUCINOUS LMP on FROZEN
REMIND THE SURGEON TO REMOVE THE APPENDIX AND INSPECT COLON FOR LESIONS

MUCINOUS LMP EVALUATION
if any of the below are found, extensive sampling necessary to r/o carcinoma  TAKE 2 SECTIONS PER CM

• invasion with single foci of less than 5mm (or total less than 10mm²) dx: Microinvasion, no change in (good) prognosis
• marked cytologic atypia – dx: Intraepithelial carcinoma, no change in (good) prognosis
• marked cytologic atypia and confluent epithelial growth of more than 5mm - dx: Invasive mucinous carcinoma

MUCINOUS LMP
Definition- Epithelial stratification and tufting in >10% of lining

• Intestinal type - (mucinous with goblet cells) may be primary, or may represent a metastasis from a mucinous GI tumor
• Mullerian type - (endocervical type) almost always primary, may be associated with endometriosis, rarely may represent a met from the cervix
• Sero-mucinous type - (endocervical + tubal type) always primary, 30% - 50% associated with endometriosis
### PRIMARY OVARIAN MUCINOUS TUMOR METASTATIC CARCINOMA

**GROSS:**
- > 10 CM
- < 10 CM

**UNILATERAL LT=RT BILATERAL or RT pseudomyxoma peritonei**

**IMMUNOS:**
- CK 7: STRONG POS NEG
- CK20: WEAK OR NEG POS
- CDX-2: NEG OR WEAK POS

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### MUCINOUS TUMORS

**PATIENTS’ PROGNOSIS**

**5 YR SURVIVAL**

- OVARIAN MUCINOUS LMP 100%
- APPENDICEAL LMP + DPAM 85-75%
- OVARIAN MUCINOUS CA,stage I 95-85%
- OVARIAN MUCINOUS CA,stage II< 10%
- metastatic GI mucinous ca +PMCA10%

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### ENDOMETRIOID & CLEAR CELL TUMORS
The Origin and Pathogenesis of Epithelial Ovarian Cancer: A Proposed Unifying Theory.

Kurman, Robert; Shih, Ie-Ming; MD, PhD


FIGURE 3. Proposed development of low-grade (LG) and high-grade (HG) serous carcinoma. A, One mechanism involves normal tubal epithelium that is shed from the fimbria, which implants on the ovary to form an inclusion cyst. Depending on whether there is a mutation of KRAS/BRAF/ERRB2 or TP53, a LG or HG serous carcinoma develops, respectively. LG serous carcinoma often develops from a serous borderline tumor, which, in turn, arises from a serous cystadenoma. Another mechanism involves exfoliation of malignant cells from a serous tubal intraepithelial carcinoma (STIC) that implants on the ovarian surface resulting in the development of a HG serous carcinoma. Of note, there may be stages of tumor progression that precede the formation of an SC.

ENDOMETRIOID LMP

-arise in endometriosis
-patterns of growth: adenofibroma with crowded glands resembling complex hyperplasia of the endometrium, or villoglandular architecture

ENDOMETRIOID LMP EVALUATION

if any of the below is found, extensive sampling necessary to rule out carcinoma

-invasion with single foci of less than 5mm (or total less than 10mm²) dx: microinvasion, no change in (good) prognosis

-marked cytologic atypia - dx: intraepithelial carcinoma, no change in (good) prognosis

-marked cytologic atypia + confluent epithelial growth of more than 5mm - dx: invasive endometrioid carcinoma
ENDOMETRIOID CARCINOMA

- Arise from endometriosis - LMP - carcinoma
- Patterns of growth: tubular glands or villoglandular structures with straight lumenal profile, cribriform glands (cookie-cutter pattern), or solid; squamous metaplasia may be present

ENDOMETRIOID ADENOCARCINOMA squamous differentiation vs. metastatic colon carcinoma

- CK7+
- CK20-

CLEAR CELL CARCINOMA

- Arise from endometriosis - marked cytologic atypia - coca
- Patterns of growth:
  - Tubulo-cystic
  - Papillary (thick hyalinized papillae)
  - Solid

May be mixed with serous and endometrioid differentiation

PROGNOSIS for all stages - 30% 5yr survival

ENDOMETRIOID TUMORS

PATIENTS’ PROGNOSIS

- Endometrioid LMPs 100%
- Endometrioid ca stage I 100%
- Endometrioid ca all stages 40%-70%
STAGING OF OVARIAN TUMORS

I - limited to the ovaries
   Ia - one ovary
   Ib - both ovaries
   Ic - ascites or ovarian surface involvement or ruptured capsule

II - extension to pelvis (eg. Fallopian tubes)

III - extension beyond pelvis (eg. omentum, lymph nodes)

IV - distant mets (eg. pleural effusion)

Epidemiology

- Approximately 23,000 cases/yr in the US and 15,000 deaths
- Incidence >13/100k in the US, <5/100k in developing countries
- Peak age 60
- Epidemiologic studies usually not stratified by histologic types

EPIDEMIOLOGIC RISK FACTORS

- Genetic: BRCA1 & BRCA2 mutations, Lynch syndrome II (colon, endometrium, ovary, bladder ca) - 10% of cancer cases
- Environmental?
  - Significant regional variations (US, UK - high incidence, Japan - low incidence),
  - In immigrants the rate is similar to the rate of the place of immigration rather than original country

- Dietary factors? Environmental carcinogens?
  - Eg. Drinking of full milk every day increase ovarian cancer risk 3x

- Protective reproductive factors:
  - Less frequent ovulation (high parity, OCP use),
  - Hysterectomy and tubal ligation (protective against endometriosis, trans-tubal environmental carcinogens)
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