Epithelial Ovarian Tumors

Relative Frequency of Major Types of “Malignant” Ovarian Tumors in Hospital Series

Proposed Pathogenesis of Ovarian Epithelial Tumors / Cancers

Epithelial Cancers (Malignant Tumors)

BENIGN
No recurrence & death

BORDERLINE (LMP)
Few recurrence or death

INVASIVE CARCINOMA
"มะเร็ง"

Differentiation (type) of Epithelial Tumors

- Serous tumors
- Mucinous tumors
- Endometrioid tumors
- Clear cell tumors
- Transitional cell tumors
- Mixed (each >= 10 %)
- Undifferentiated

Surface epithelium

Endometriosis, Benign neoplasms

Mutations / progression of genetic abnormalities

Atypical epithelial proliferation

Invasive carcinoma
Pathogenesis of epithelial ovarian cancers

- Arising from pre-existing benign lesions
  - Low-grade endometrioid CA
  - Mucinous CA, Clear cell CA
  - Low-grade serous CA (~ 10% of serous CA)

- Arising directly from surface epithelium
  - High-grade CA (serous/endometrioid)
  - Carcinosarcoma, Undifferentiated CA

- Overlapping pathways
  (Kurman & Shih, Int J Gynecol Pathol 2008; 27: 151-60)

- Arising from fallopian tube (serous CA)

Implications

- Why cancer screening in low-risk women is still not very satisfactory (CA-125, U/S, PV)?
  - Serous CA: rapid growth & commonly not associated with preceding benign/LMP tumor
- Why gross examination and adequate or extensive sampling is so important in some ovarian tumors (LMP/mucinous)?
  - More samples = More chance to detect the worst prognostic focus

Expansile (confluent) invasion

- WHO 2003: “invasion is assumed if there are complex papillae or back-to-back glands lined by malignant-appearing cells with little or no intervening stroma”
- Arbitrary ‘size threshold’: 10 mm² (3x3)
- Applied to “mucinous” and “endometrioid”
- Reflection of aggressive potential ~ Similar to Diagnostic (predictive) criteria for endometrial CA in “Curettage Specimen”

Common genetic abnormalities

- High-grade CA (most common)
  - Inactivation of BRCA1/2 tumor suppressor gene (heridity, mutation, loss of function, etc)
  - p53 mutation
- CA arising from pre-existing lesions
  - Mutations: KRAS, BRAF, PTEN, HER2, etc

Spectrum of diagnosis (WHO2003)

Benign

Borderline / LMP

- Non-invasive & Cytologically malignant
- Intraepithelial carcinoma
  - Loss of intervening stroma > 10 mm²
- Expansile (confluent) invasion
  - Loss of intervening stroma > 10 mm²

Invasive carcinoma

Relative Frequency of Subtypes of LMP Tumors in Hospital Series

- Western: Serous
- Eastern: Mucinous

Los Angeles

Serous
Mucinous
Endometrioid
Mixed & Other

Chiang Mai

Sydney

Nagoya
Differentiation of LMP Tumors

- Serous tumors
- Mucinous tumors
- Endometrioid tumors
- Clear cell tumors
- Transitional cell tumors
- Mixed (each >= 10 %)
- Undifferentiated

Borderline Ovarian Tumor Workshop 2003
(published in Human Pathol 2004;35:907-970)

- The tumors cause confusion & controversy disproportionate to their incidence
- Name: one of the most controversies
  Borderline / LMP / Atypical proliferative
- All tumors should be well sampled (1-2 sections / 1 cm maximal tumor diameter)
- Well-sampled stage I tumors had almost 100 % survival
- Disagreement & uncertainties still persist

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Serous LMP</th>
<th>Mucinous LMP</th>
<th>Mucinous LMP intestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>37-43</td>
<td>~ 37</td>
<td>40-52</td>
</tr>
<tr>
<td>Mean size (cm)</td>
<td>8-12</td>
<td>8-10</td>
<td>13-19</td>
</tr>
<tr>
<td>Bilaterality (%)</td>
<td>25-37 %</td>
<td>~ 24 %</td>
<td>0-7 %</td>
</tr>
<tr>
<td>Peritoneal/lymph node + (%)</td>
<td>20-40 %</td>
<td>~ 10 %</td>
<td>Rare</td>
</tr>
<tr>
<td>Ipsilateral endometriosis (%)</td>
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<td>~ 24 %</td>
<td>Rare</td>
</tr>
<tr>
<td>No. of locules</td>
<td>Few</td>
<td>Few</td>
<td>Numerous or few</td>
</tr>
<tr>
<td>Gross papillary structure</td>
<td>Typical</td>
<td>Typical</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Intestinal-type epithelium</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Type of associated CA</td>
<td>Serous CA</td>
<td>Endometrioid</td>
<td>Mucinous CA</td>
</tr>
<tr>
<td>(low-grade)</td>
<td></td>
<td>or mixed CA</td>
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**Characteristics**

- **Serous LMP**
  - Mean age: 37-43 years
  - Mean size: 8-12 cm
  - Bilaterality: 25-37%
  - Peritoneal/lymph node +: 20-40%
  - Ipsilateral endometriosis:
  - No. of locules: Few
  - Gross papillary structure: Typical
  - Intestinal-type epithelium: Absent
  - Type of associated CA: Serous CA (low-grade)

- **Mucinous LMP**
  - Mean age: ~37 years
  - Mean size: 8-10 cm
  - Bilaterality: ~24%
  - Peritoneal/lymph node +: ~10%
  - Ipsilateral endometriosis: Rare
  - No. of locules: Few
  - Gross papillary structure: Typical
  - Intestinal-type epithelium: Absent
  - Type of associated CA: Endometrioid or mixed CA

- **Mucinous LMP intestinal**
  - Mean age: 40-52 years
  - Mean size: 13-19 cm
  - Bilaterality: 0-7%
  - Peritoneal/lymph node +: Rare
  - Ipsilateral endometriosis: Rare
  - No. of locules: Numerous or few
  - Gross papillary structure: Infrequent
  - Intestinal-type epithelium: Present
  - Type of associated CA: Mucinous CA

**Micropapillary pattern (> 5 mm):** May be associated with other adverse histologic features

- Indicator for adequate examination

**“Intraepithelial carcinoma”:**
- Nuclear grade 3
  - Variation in size >3 times
  - Coarse chromatin
  - Prominent nucleoli

**Legend:**
- Benign 'serous' lesions
- Endosalpingiosis
- Serous 'LMP' morphology
- Invasive serous: "CA" morphology
- Ovary
- Lymph node involvement
- Non-invasive peritoneal implants
- Invasive peritoneal implants

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*Note: Images and diagrams are not transcribed.*
Mucinous tumors associated with appendiceal mucinous neoplasms/pseudomyxoma peritonei

- Typically
  - Thin-walled ovarian cyst filled with jelly-like material
  - Small appendix containing tumor
  - CK7-/CK20+/CDX2+
- Most likely secondary involvement from appendiceal neoplasms or intestinal tumors

Serous

- Serous adenocarcinoma
- Highest proportion among ovarian CA
- Prototype of epithelial cancer of the ovary
- Most are high-grade, advanced stage
- Bilateral & peritoneal carcinomatosis
- ? At least some cases = Multifocal
- Low-grade invasive CA is uncommon and may arise from LMP

“High-grade” serous CA

- Current tendency = "Wastebasket" category of ovarian high-grade CA
- With no clear cut evidence of other differentiation (endometriod-mucinous-clear cell)
- Diverse morphology but similar molecular genetics & behavior

Kurman & Shih. Int J Gynecol 2008; 27: 151-60

Mucinous

Mucinous adenocarcinoma

- Uncommon type of invasive CA
- But very common benign & LMP tumor in Thailand
- Distinction by gross appearance from benign or LMP = unreliable
- Unilateral & Most commonly stage I
- High-stage or Bilaterality = Rare in primary

Mucinous

- Gastrointestinal type mucinous tumor = Majority in LMP/CA
- Diagnosis of primary mucinous CA should be based on clinico-pathologic evaluation to rule out metastatic tumors (genital / non-genital)
- Clinical work-up required
- Stage IA = good prognosis
- Chemoresistant
Before calling “primary” mucinous CA

- Findings favor metastatic tumor
  - History or findings of other “Adeno-CA”
  - Parenchymal liver metastasis
  - Bilateral ovarian parenchymal involvement
  - Multinodular growth pattern
  - Vascular invasion in the ovary
  - CK7-negative tumor
  

CK7-negative primary ovarian mucinous tumors

- Associated with mature teratoma
  - Arising from enteric epithelium
  - May present with pseudomyxoma peritonei
- Benign mucinous : CK7- = 40%
- LMP : CK7- = 60%
- CA : CK7- = 100%
- CMU cases from 2007-2009
  ~ 16% Mucinous LMP
- Should add comments on the possibility of “more common” secondary involvement


Endometrioid

- Endometrioid adenocarcinoma
- Second most common ovarian CA
- Association with endometriosis (20-40 %)
- 15-20 % associated with synchronous endometrial CA: multifocal > metastasis
- High grade endometrioid & serous CA : morphologic overlap, ↓ reproducibility
- Sometimes “mimicked” by metastatic colorectal CA or non-epithelial ovarian neoplasms

Various features in endometrioid CA

- Cribriform glandular
- Villoglandular papillary
- Squamous differentiation
- Secretory
- Cord-like (Sertoliform)
- Microglandular
- Spindle cell

Malignant müllerian mixed tumor “Carcinosarcoma”

- Malignant epithelial & malignant mesenchymal components
- Monoclonal : molecular genetic studies
- “Metaplastic carcinoma”
- Classified as “Endometrioid tumors” category in WHO (ovarian neoplasms)
- High grade histology - Aggressive behavior

Clear cell

- Clear cell adenocarcinoma
- Association with endometriosis (40-70 %)
- Distinctive/characteristic histology
- Well-known DDx = yolk sac tumor
- Usually high-gade (grading unnecessary), more aggressive behavior in stage I than others
- Association with deep vein thrombosis (2.5x)
- Chemoresistant

Transitional cell

- Transitional cell carcinoma = Morphology similar to urothelial CA of urinary tract
- "Urothelial" or "Mullerian" differentiation by immunohistochemical studies
- "Urothelial" (CK20, uroplakin III, thrombomodulin) : "Brenner" Tumor – Benign, LMP, Malignant
- "Mullerian" : Frequently admixed with other typical types of mullerian epithelial CA
- Past history of urinary CA = R/O metastasis

Shared tendency among "mullerian" tumors

- Multifocal tumorigenesis
- Coelomic epithelium = Peritoneum & Ovarian surface epithelium
- Primary peritoneal epithelial neoplasm of the same differentiation as ovarian tumor : if synchronous, variable severity at each site : e.g. Serous LMP & Peritoneal implants
- Multifocal concept should not be applied to : "Gastrointestinal" type mucinous tumor

Immunohistochemical stains in DX

- Fact = Likelihood of Dx, Using panel recommended
- Cytokeratin (CK - broad spectrum) = epithelial differentiation found in any group of tumors
- Epithelial tumors : CK7, Epithelial membrane antigen
- Sex cord-stromal tumors : Inhibin, calretinin, CD99, CD56?
- Germ cell tumors : OCT-4, Placental-like alkaline phosphatase (PLAP), AFP (yolk sac tumor)
- Metastatic tumors : CK7/ CK20/ CDX2 (for colorectal)
- CK7 positivity does not mean ovarian origin

Undifferentiated carcinoma

- Uncommon (< 5% of epithelial CA)
- No specific criteria (no/very focal differentiating features)
- High-grade CA, frequently bilateral, aggressive behavior
- R/O metastasis (e.g. gallbladder, nasopharynx)

Grading of epithelial cancers

- Usually divided into Grade 1, 2, and 3
- .... But how to grade?
- No details in WHO Classification
- ? No uniformly accepted grading system
- Recently proposed grading system (Shimizu et al [Silverberg] 1998) provides better correlation with prognosis : Not widely used

Immunoprofiles for subtyping ?

- ? Is this necessary
- Serous : WT1, ER, p16
- Endometrioid : Vimentin, ER
- Mucinous : -
- Clear cell : Hepatocyte nuclear factor-1β
- Transitional cell
  - Brenner : Urothelial markers
  - TCC : - serous CA

The mimics ~ Ovarian metastases

- Colorectal ~ mucinous / endometrioid
- Stomach : if not typical Krukenberg (signet ring CA)
  - mucinous (± signet ring cells)
- Biliary tract/gallbladder & pancreas
  - mucinous (great mimicry), non-specific adenoCA
- Appendix
  - mucinous LMP-like (Pseudomyxoma Peritonei)
- Breast ~ variable (serous, endometrioid, mucinous)
- Gynecologic
  - Cervix ~ mucinous, Corpus ~ endometrioid
  - Lung ~ any types
  - etc.

Role of immunohistochemistry in Dx of mucinous tumors

- May help in Dx of colorectal or appendiceal primary
- BUT has limited or no value in the distinction between primary ovarian mucinous CA and metastases from non-lower intestinal tract
- Primary ovarian mucinous CA : CK7+
- Many also CK20+, CA19.9+, CEA+, CDX2+

Diagnostic approach

- Clinical data : age, serologic markers, intraoperative findings, history of any other cancer
- Gross examination & appropriate sampling
- Histologic evaluation +/- appropriate special stains

Algorithm for metastatic mucinous CA

(Seidman et al 2003)

- Bilaterality or
- Tumor size < 10 cm

Note

- Metastatic tumors are generally more frequent than primary mucinous adenoCA
- Size and bilateral rate of ovarian metastases is variable, depending on the type of primary tumors
  (Khunamornpong et al 2006, Yemelyanova et al 2008)

Metastatic “mucinous” tumors involving the ovary with CK7+ profile

- Gynecologic other than ovary
  - Cervix (HPV testing, p16)
  - Endometrium
- Non-gynecologic
  - Biliary tract/Pancreas (CK17, Dpc4)
  - Upper digestive tract
  - Lung (TTF-1)
  - Appendix
  - Large intestine

Serologic markers

- CA-125 : serous tumors, peritoneal lesions (tuberculosis, >1000 u/ml), cancers in other organs including lymphoma
- CA19-9 : non-serous mullerian or mucinous tumors, endometriosis, biliary/digestive tract cancers
- CEA : ovarian mucinous tumors, colorectal/digestive tract cancers
- Normal CA19-9 / CEA = Not R/O metastasis
- Elevated serum CA-125 is non-specific

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Pathology report

- Histologic type (grade if applicable)
- External surface status (surface growth, perforation)
- Spread of tumor outside the ovary
- Peritoneal cytology result (correlation with histologic result before reporting)
- Comments/note

“It is important that gynecologists and pathologists maintain a high index of suspicion for metastatic tumors in the diagnostic approach of ovarian tumors”
Hart WR. Pathol Int 2005; 55: 231-43

What help pathologist serve clinician?

- How to easily contact the clinician
- Correct specimen’s identification
- Intraoperative findings & clinical impression (★ in case R/O metastasis)
- Appropriate data for specimen orientation and sampling (★ staging information)
  - Which organs (& laterality) are resected?
  - What was done to specimen (surface status)?
  - Relationship between lesion & normal structures