New Insights into Ovarian Cancer Pathology

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Ovarian Epithelial Tumors

WHO 1999 and 2003

- Serous
- Mucinous
- Endometrioid
- Clear cell
- Transitional
- Squamous
- Mixed
- Undifferentiated

Benign 60%

BL 10%

Ca 30%
EPITHELIAL OVARIAN TUMORS
A heterogeneous group

Histologic type, Precursor lesions, Genetic alterations …
Histologic Subtypes of Ovarian Carcinomas

- Serous – high grade
- Serous – low grade
- Clear cell
- Endometrioid
- Mucinous
New classification: Frequency

- HG serous
- LG serous
- Clear cell
- Endometrioid
- Mucinous
- Unclassifiable
These subtypes differ from each other with respect to:

1. Risk factors and precursor lesions
2. Patterns of spread
3. Molecular genetic alterations
4. Response to chemotherapy
5. Outcome
High-grade Serous Cancers

Köbel M et al.
Biomarker profiles across subtypes

Köbel M et al.
Serous Carcinoma
HEREDITARY SUSCEPTIBILITY TO OVARIAN CANCER

BRCA2 (30%)
   Lifetime risk 15-30%

BRCA1 (65%)
   Lifetime risk 30-60%

HNPCC (7%)

Hereditary (10%)

Sporadic (90%)

Serous “Intraepithelial” Carcinoma
STIC

P53
R248W
(Exon 7)

p53

WT1

Ki67
How about less than STIC?
P53 Signature
BRCA Promotes P53 Signature to TIC

Normal $\xrightarrow{\text{P53}}$ P53 signature $\xrightarrow{\text{BRCA1}}$ TIC

**Hereditary** : BRCA1 mutation constitutive

Normal $\xrightarrow{\text{P53}}$ P53 signature $\xrightarrow{\text{BRCA1}}$ TIC

**Sporadic** : BRCA1 methylation/mutation new event
Classification of Gyn Cancers based on Origin and Mutations

- Endosalpingiosis
- Fallopian Tube
- STIC
- TP53
- BRCA1
- Chromosomal instability
- Genetic chaos
- High-grade Serous Ca
- Endosalpingiosis
High Grade Serous Carcinoma
HGSC – Pathogenetic Model

P53 loss

↓

BRCA1 inactivation

↓

Chromosomal instability (Genetic chaos)

↓

Widespread copy number change

↓

Secondary events (diversification)

↓

Tertiary events (evolution)

Individual tumors

DDL Bowtell Nature Rev Cancer 2010
Chromosomes from six ovarian cancers showing: chromosomal instability
Serous carcinoma, G3
Low grade  High grade
Serous Borderline Tumor
Peritoneal Implants (SBT)

- Non-invasive
  - Epithelial
  - Desmoplastic
- Invasive

Bell DA, et al
Cancer 1988; 62:2212
Serous Tumors
(Pathogenesis - Dualistic model)

Bg → SBT → SBT-MP → MP Ca (Inv) → Low Gr Serous Ca

*KRAS* and *BRAF* mutations (70%)

High Grade Serous Ca

*p53* mutations, LOH 17q (80%)
*BRCA* inactivation (80%)
*HER-2/neu* amplification/overexpression

Singer et al
Am J Pathol 2002
Mucinous Tumors of the Ovary
(From benign to malignant)

- **1960s**: Adenoma
  - 1960s: Carcinoma

- **1970s**: Borderline
  - 1970s: Carcinoma

- **1980s**: Metastatic Ca
  - 1980s: Carcinoma

- **1990s**: Appendiceal t + PP
  - 1990s: Carcinoma
Mucinous Tumors (Ovary)

- Benign: 75% 80%
- Borderline: 10% 17%
- Carcinomas: 15% 3%

Koonings, 1998
Mucinous glands

Carcinoma

Cystadenoma

Borderline
Epithelial Ovarian Tumors

K-ras Mutations (12, 13)

Benign

Borderline

Malignant

These subtypes differ from each other with respect to:

1. Risk factors and precursor lesions
2. Patterns of spread
3. Molecular genetic alterations
4. Response to chemotherapy
5. Outcome
## Ovarian Carcinomas:
Stage at presentation (early vs advanced) according to Histologic Subtype

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clear Cell</th>
<th>Endometrioid</th>
<th>Mucinous</th>
<th>Low-Grade Serous</th>
<th>High-Grade Serous</th>
<th>Carcinoma NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>26.2%</td>
<td>29.4%</td>
<td>8.5%</td>
<td>1.9%</td>
<td>30%</td>
<td>4.0%</td>
</tr>
<tr>
<td>III-IV</td>
<td>4.9%</td>
<td>3.5%</td>
<td>1.1%</td>
<td>4.9%</td>
<td>84.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>All</td>
<td>10.4%</td>
<td>10.3%</td>
<td>3.6%</td>
<td>3.5%</td>
<td>70%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Gilks CB et al.
Mod Pathol 2009; 22:215A
Endometrioid and Clear Cell Tumors develop from Ovarian Endometriosis

- Retrograde menstruation
- Endometriosis
- Borderline tumor
- Carcinoma
Ovarian Atypical Endometriosis → Endometrioid or Clear Cell Carcinomas

15-32% of cases
Genetic Alterations of Endometrioid Carcinomas of the Ovary

- Beta-Catenin: 20-40%
- **ARID1A**: 30%
- **PTEN**: 15-20%
- **PIK3CA**: 20%
- MSI: 15%
- **K-RAS**: 4-35%
- **TP53**: 10%
Classification of Gyn Cancers based on Origin and Mutations

- Endometriosis
- Clear Cell Ca
- ARID 1A
- PIK3CA
- PTEN
- KRAS
Clear Cell Carcinoma

Endometriotic Chocolate Cyst

Adenofibroma
**Target Genes**

- **Detoxification**
  - UGT1A1
  - ANXA4
  - CPT-11 resistance
  - Paclitaxel resistance

- **Chemoresistance**

- **Antiapoptosis**
  - ACE2
  - Ferritin

- **Glycogen Storage**
  - DPPIV
  - G6Pase
  - G6P
  - Glucokinase
  - HNF-1beta
  - GLUT2
  - Insulin
  - Glucagon

- **Free iron in the contents of endometrioma**

- **Chronic oxidative stress**

- **Glucose**
  - GLUT2
  - HNF-1
  - HNF-3

**Previously Extracted Text**


- Free iron in the contents of endometrioma

- Chronic oxidative stress

- UGT1A1 → CPT-11 resistance

- ANXA4 → Paclitaxel resistance

- DPPIV

- Osteopontin

- ACE2

- Ferritin

- G6Pase

- G6P

- Glucokinase

- HNF-1beta

- GLUT2

- Insulin → Glucagon

- hCG

- Osteopontin

- Rufix
# Molecular Genetic Alterations in Clear Cell Carcinomas of Ovary

<table>
<thead>
<tr>
<th>Gene</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARID1A</td>
<td>46%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>33%</td>
</tr>
<tr>
<td>K-RAS</td>
<td>15-30%</td>
</tr>
<tr>
<td>C-Met</td>
<td>22%</td>
</tr>
<tr>
<td>Her-2</td>
<td>10%</td>
</tr>
<tr>
<td>PPMD1D</td>
<td>10%</td>
</tr>
<tr>
<td>PTEN</td>
<td>5%</td>
</tr>
<tr>
<td>b-Catenin</td>
<td>5%</td>
</tr>
<tr>
<td>TP53</td>
<td>5%</td>
</tr>
</tbody>
</table>
Classification of Gyn Cancers based on Origin and Mutations

- Endosalpingiosis
- Fallopian Tube
- STIC

- High-grade Serous Ca:
  - TP53
  - BRCA1
  - Chromosomal instability
  - Genetic chaos

- Endometriosis
- Endometrioid Ca

- Clear Cell Ca:
  - ARID 1A
  - PIK3CA
  - PTEN
  - KRAS

- CTNNB1
- MSI
- PTEN
- ARID 1A
## The five most common types of ovarian carcinoma

<table>
<thead>
<tr>
<th></th>
<th>High-grade serous</th>
<th>Clear cell</th>
<th>Endometrioid</th>
<th>Mucinous</th>
<th>Low-grade serous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual stage at diagnosis</strong></td>
<td>Advanced</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Early or advanced</td>
</tr>
<tr>
<td><strong>Presumed tissue of origin / precursor lesion</strong></td>
<td>Fallopian tube or tubal metaplasia in inclusions of OSE</td>
<td>Endometriosis, adenofibroma</td>
<td>Endometriosis, adenofibroma</td>
<td>Adenoma–borderline – carcinoma sequence; teratoma</td>
<td>Serous borderline tumor</td>
</tr>
<tr>
<td><strong>Genetic risk</strong></td>
<td>BRCA1/2</td>
<td>?</td>
<td>HNPCC</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Significant molecular abnormalities</strong></td>
<td>p53 and pRb pathway</td>
<td>HNF-1β ARID1A</td>
<td>PTEN, β-Catenin, K-ras MI, ARID1A</td>
<td>K-ras</td>
<td>BRAF or K-ras</td>
</tr>
<tr>
<td><strong>Proliferation</strong></td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Response to primary chemotherapy</strong></td>
<td>80%</td>
<td>15%</td>
<td>?</td>
<td>15%</td>
<td>26-28%</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Poor</td>
<td>Intermediate</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Favorable</td>
</tr>
</tbody>
</table>

### Notes
- High-grade serous
- Clear cell
- Endometrioid
- Mucinous
- Low-grade serous
Hig-grade Serous

PTEN
b-catenin

PIK3CA
20q amp

KRAS

TP53/Rb pathway
Chromosomal instability

Mucinous

Endometrioid

Clear Cell

Low-grade

Hig-grade Serous

KRAS
BRAF
ERB2
Thank you for your attention