Pelvic Serous Carcinoma: 2014 W.H.O. Update

Practical Implications for Pathologists

Joseph Rabban MD MPH
Pathology Department
University of California, San Francisco

Outline of Talk

- Changes to 2014 WHO system for pelvic serous tumors
- High grade serous carcinoma versus low grade serous carcinoma
- New recommendations for assigning primary tumor origin
- Special issues with serous borderline tumors

What happened between 2003 WHO and 2014 WHO?

20th Century Model of Ovarian Cancer
- Single disease
- Multiple morphologies
- Origin from surface lining cells
- Unclear pathogenesis
- Unclear risk reduction
- Unclear early detection

21st Century Model of Ovarian Cancer
- Multiple unique diseases
  - Each with unique:
    - Pathogenesis, origin
    - Responses to treatment
    - Risk reduction options
    - Early detection options

Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—Shifting the paradigm
Robert J. Kuman MD*, In-Ning Shih H.D. PhD
Human Pathology (2011) 42, 918-931

Current Opinion in Obstetrics and Gynecology 2007, 193-9
Ovarian Carcinomas in 2014 WHO

- High grade serous carcinoma (HGSC)
- Low grade serous carcinoma (LGSC)
- Clear cell carcinoma
- Endometrioid adenocarcinoma
- Mucinous carcinoma

3 Major Changes to Pelvic Serous Tumors in 2014 WHO

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Tumor Class</td>
<td>Surface epithelial – stromal tumors</td>
<td>Epithelial tumors</td>
</tr>
</tbody>
</table>

Rationale:

<table>
<thead>
<tr>
<th></th>
<th>New Evidence</th>
<th>Implications</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Tumor origin is fallopian tube mucosa (either in tube as STIC or in ovary as epithelial inclusion cyst)</td>
<td>Fallopian tube is target for risk reduction, early detection</td>
</tr>
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</table>

Proposed Tubal Origins of Ovarian HGSC versus LGSC

- Tubal HGSC (STIC)  
  
- Ovarian HGSC

- PS3

- Spread

- Inclusion gland  
  
- Benign tubal mucosa  
  
- Ovarian HGSC

- PS3
Proposed Tubal Origins of Ovarian HGSC versus LGSC

Benign tubal mucosa

Inclusion gland

BRAF KRAS MAPK pathway

Ovarian Serous Borderline Tumor

Ovarian LGSC

Ovarian Serous Borderline Tumor

p53

Tubal HGSC (STIC)

benign

spread

Ovarian HGSC

BRAF KRAS MAPK pathway

Ovarian Serous Borderline Tumor

Ovarian LGSC

3 Major Changes to Pelvic Serous Tumors in 2014 WHO

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<td>Serous Carcinoma</td>
<td>Two tumors: HGSC, LGSC</td>
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<td>One tumor, grade 1,2,3</td>
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Rationale:

New Evidence: Distinct behavior, response to therapy, genetics, pathogenesis, origin
Implications: Distinct surgical planning, adjuvant therapy, genetic counseling, risk reduction

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<td>3</td>
<td>Transitional cell carcinoma</td>
<td>Unique tumor</td>
</tr>
<tr>
<td></td>
<td>Eliminated. Viewed as variant of HGSC</td>
<td></td>
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Rationale:

New Evidence: "TCC" has same properties as HGSC
Implications: Diagnosis of HGSC includes many different patterns beyond papillary (TCC, endometrioid, solid)
### Outline of Talk

- Changes to 2014 WHO system for pelvic serous tumors
- High grade serous carcinoma versus low grade serous carcinoma
- New recommendations for assigning primary tumor origin
- Special issues with serous borderline tumors

### LGSC: Clinico-pathologic Features

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<tr>
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<th>HGSC</th>
<th>LGSC</th>
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<tr>
<td>Incidence</td>
<td>~5 % of all ovarian cancers</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Average 4th to 5th decade</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td>No traditional HGSC risk factors</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>&gt;75% are advanced stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Median survival</td>
<td>~80-96 months</td>
<td></td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>~33 months if optimal cytoreduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>~14 months if suboptimal cytoreduction</td>
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- No major syndrome known

- 20% risk if prior history of advanced stage serous borderline tumor

- ~ risk if prior ovulation induction for fertility

- BRCA hereditary syndrome: ~25 %

- No P53 mutation

- BRAF KRAS MAPK pathway defects: No

- Common

- Precursor lesion: STIC

- Borderline tumor

- Platinum chemotherapy sensitive: Yes

- Uncommon

- PARP inhibitor sensitive: Yes

- Unlikely

- Neoadjuvant chemotherapy candidate: Yes

- No

- MAPK pathway inhibitor candidate: No

- Yes

---

Romero 2013 Gyn Oncol
Fader 2013 Ob Gynecol
HGSC

- **Architecture**
  - Papillary
  - Micro-papillary
  - Solid
  - Pseudo-endometrioid (cribriform)
  - Transitional cell carcinoma-like

- **Cytology**
  - High nucleus-cytoplasm ratio
  - Pleomorphism
  - Nuclear hyperchromasia
  - Brisk / atypical mitoses
  - Macro-nucleoli

HGSC: Papillary pattern

HGSC: Transitional cell cancer-like pattern

Pleomorphism, high N/C ratio, brisk mitoses
HGSC: Transitional cell cancer-like pattern

HGSC: Pseudo-endometrioid pattern

HGSC: Pseudo-endometrioid pattern

HGSC

- Immunophenotype

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<th>Mullerian origin</th>
<th>+ PAX8, CK7</th>
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<td>Extra-uterine serous differentiation</td>
<td>+ WT1</td>
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<td>High grade serous carcinoma</td>
<td>Aberrant p53, p16</td>
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**p53 and Pelvic HGSC**

**Normal p53 gene**

- **p53 IHC stain result**: Weak patchy staining ("Normal" / Wild type)

**p53 gene mutation**

- **p53 IHC stain result**:
  - ~80%: Diffuse, strong staining
  - ~20%: Completely negative

**p53 Stain Interpretation in Pelvic Serous Carcinoma**

- **Pattern of p53 IHC staining**:
  - Strong/diffuse: Aberrant p53
  - Completely negative: HGSC
  - Weak/patchy: Wild type p53 (normal)

**Stain Interpretation**:

- Aberrant p53: HGSC
- HGSC: Check for internal control

**Diagnosis**:

- Aberrant p53
- HGSC
- Wild type p53

* HGSC
**p16 Stain Interpretation in Pelvic Serous Carcinoma**

- Diffuse / strong = Aberrant p16
- Patchy or negative = Wild-type p16

**Use both p53 and p16 stains for HGSC**

- Cannot use p53 alone if result is wild type
- 4% of HGSC are wild type p53 / aberrant p16

**Always do both stains together**

**LGSC**

- Architecture
  - Papillary branching
  - Micro-papillary
  - Bud-like
  - Macro-papillary
  - Cribriform

- Cytology
  - Uniform, monotonous
  - Focal moderate atypia (<3:1 variable size)
  - Mitoses < 12 / 10 hpf
  - Atypical mitoses uncommon

**MD Anderson Criteria for LGSC**

**Grading System**

<table>
<thead>
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<th>Grading System</th>
<th># of Grading Tiers</th>
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<tbody>
<tr>
<td>FIGO</td>
<td>3</td>
</tr>
<tr>
<td>Shimizu-Silverberg</td>
<td>3</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>2</td>
</tr>
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*The diagnostic utility of TP53 and CDKN2A to distinguish ovarian high-grade serous carcinoma from low-grade serous ovarian tumors*
### FIGO Universal Grading of Pelvic Cancer (any type)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Solid Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;6 %</td>
</tr>
<tr>
<td>2</td>
<td>6 % – 50%</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 50%</td>
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### Shimizu-Silverberg Universal Grading of Ovarian Cancer (any type)

<table>
<thead>
<tr>
<th>Points</th>
<th>Architecture</th>
<th>Atypia</th>
<th>Mitoses /10 hpf</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glandular</td>
<td>Mild</td>
<td>0-9</td>
</tr>
<tr>
<td>2</td>
<td>Papillary</td>
<td>Moderate</td>
<td>10-24</td>
</tr>
<tr>
<td>3</td>
<td>Solid</td>
<td>Severe</td>
<td>&gt;24</td>
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<table>
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<tr>
<th>Total Points</th>
<th>Overall Grade</th>
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<td>3 – 5</td>
<td>1</td>
</tr>
<tr>
<td>6, 7</td>
<td>2</td>
</tr>
<tr>
<td>8, 9</td>
<td>3</td>
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### MD Anderson Classification of Ovarian Serous Carcinoma

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<th>Nuclei</th>
<th>Mild-Moderate Atypia</th>
<th>Marked Atypia</th>
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<tr>
<td>Nuclear appearance</td>
<td>Uniform</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td>Nuclear size/shape</td>
<td>&lt; 3 : 1 variability</td>
<td>&gt;3 : 1 variability</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>None to small</td>
<td>Macro</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Evenly dispersed</td>
<td>Coarse</td>
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### MD Anderson Classification of Ovarian Serous Carcinoma

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<th>Classification</th>
<th>Associated Borderline Tumor</th>
<th>Progression Free Survival</th>
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<tr>
<td>LGSC</td>
<td>60 % of cases longer</td>
<td></td>
</tr>
<tr>
<td>HGSC</td>
<td>2 % of cases shorter</td>
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Additional Advantages of 2-tier grading:

- More predictive than other grading systems
- Reproducible (Malpica 2007 AJSP)
- Eventually was validated by:
  - p53/p16 immunophenotype
  - Molecular pathogenesis
  - Response to therapy
  - Association with inherited mutations
- Used by 2014 W.H.O.
LGSC: Micropapillary Buds (avascular)

<3:1 varying size/shape
No mitoses
No macronucleoli

LGSC: Papillary Branching (vascularized)

LGSC: Papillary Branching (vascularized)

<3:1 varying size/shape
No mitoses
No macronucleoli

LGSC: Papillary Branching + Buds
LGSC: Papillary Branching + Buds

LGSC: Papillary Branching + Buds

- <3:1 varying size/shape
- No mitoses
- No macronucleoli

LGSC: Branching + Cribriform Pattern

LGSC: Branching + Cribriform Pattern
LGSC: Cribriform Pattern

LGSC: Columnar cells

Positive WT1 Excludes Endometrioid Tumor

LGSC with Necrosis
Most LGSC Present at Advanced Stage

Pelvic Lymph Node Metastasis

Omental Involvement

Lung Metastasis

LGSC

- Immunophenotype

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Wild type p53 in LGSC

Wild Type p53 and p16 staining

Wild Type p53 and p16 staining

LGSC

Wild type p53

Wild type p16

Diagnostic Challenges Distinguishing LGSC versus HGSC

LGSC with:
- Focal mitotic activity
- Notable moderate atypia
- Rare severe atypia

HGSC with:
- Only moderate nuclear atypia
- Abundant cytoplasm
- Architecture of borderline tumor or cystadenofibroma
- Micropapillary architecture
Diagnostic Challenges Distinguishing LGSC versus HGSC

LGSC with:
- Focal mitotic activity
- Notable moderate atypia
- Rare severe atypia

HGSC with:
- Only moderate nuclear atypia
- Abundant cytoplasm
- Architecture of borderline tumor or cystadenofibroma
- Micropapillary architecture

Resolve by:
- p53, p16 Immunostaining

HGSC with only moderate atypia + rare mitoses

HGSC with only moderate atypia + abundant cytoplasm

HGSC with only moderate atypia + abundant cytoplasm
HGSC with only moderate atypia + abundant cytoplasm
Aberrant p53
Aberrant p16

HGSC with uniform micropapillary architecture

HGSC with uniform micropapillary architecture

HGSC with uniform micropapillary architecture

HGSC with uniform micropapillary architecture

P53
HGSC mimicking Serous Borderline Tumor (conventional type)

HGSC mimicking Serous Borderline Tumor (micropapillary type)

HGSC mimicking Serous Borderline Tumor (micropapillary type)

HGSC mimicking Serous Borderline Tumor (micropapillary type)

- Severe Atypia
- High Mitotic rate
HGSC mimicking Serous Cystadenofibroma

Severe Atypia
High Mitotic rate

LGSC has same survival as HGSC

Ali et al. 2013 Int J Gyn Path
Why should pathologists distinguish HGSC vs LGSC?

Management Reasons to Distinguish HGSC vs LGSC

<table>
<thead>
<tr>
<th>Consider Neoadjuvant chemotherapy?</th>
<th>HGSC</th>
<th>LGSC</th>
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<tbody>
<tr>
<td>Consider PARP inhibitor drug trials?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
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<td>No</td>
<td>Yes</td>
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<td>Consider hormonal therapy?</td>
<td>No</td>
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<td>Yes</td>
<td>Low priority</td>
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Neoadjuvant Chemotherapy for Advanced Stage Ovarian Cancer

- Same survival as primary surgery
- But:
  - Decreased Morbidity
  - Decreased Mortality
  - Decreased Cost
  - Informs About Response of Selected Chemotherapy Agents

NCCN Guidelines Version 1.2015 Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

- CLINICAL PRESENTATION
  - WORKUP
    - Obtain family history
    - Refer for genetic risk evaluation
    - Abdominal/pelvic exam
    - Chest imaging
    - Complete blood count
    - Chemistry profile with liver function test
- PRIMARY TREATMENTS
  - Laparotomy and/or abdominal/pelvic CT/MRI as clinically indicated
  - CA-125 or other tumor markers as clinically indicated
LGSC is Often Resistant to Platinum Chemotherapy

~ 50% have residual disease after first round

Clinical Behavior of Stage II-IV Low-Grade Serous Carcinoma of the Ovary

David M. Gershenson, MD, Charlotte C. Sun, MD, Karen H. Lu, MD, Robert L. Coleman, MD, Anil K. Sood, MD, Anna M. Malpica, MD, Michael T. Deavers, MD, Elise G. Silva, MD, and Diane E. Bodurka, MD
Gershenson 2006 Obstet Gynecol

Similar Findings:
Schmeler 2008 Gynecol Oncol
Gershenson 2009 Gynecol Oncol
Schmeler 2011 Gynecol Oncol
Ali 2013 Int J Gynecol Pathol

LGSC is Often Resistant to Neoadjuvant Chemotherapy

Only ~ 5% have any response

Clinically Advanced Stage Pelvic Cancer

Biopsy of Omental Tumor or Paracentesis of Malignant Ascites

Mullerian Adenocarcinoma (positive PAX8, WT1)

-Serous carcinoma, gynecologic origin
-Ovarian serous carcinoma

LGSC is Second Most Common Tumor Type in Advanced Stage Ovarian Cancer

<table>
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<th>Sub-Type</th>
<th>% of All Advanced Stage Cases</th>
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<tbody>
<tr>
<td>HGSC</td>
<td>87.7%</td>
</tr>
<tr>
<td>LGSC</td>
<td>5.3%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>4.5%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2.5%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.2%</td>
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Kobel et al. 2010 LGP
Clinically Advanced Stage Pelvic Cancer

- Biopsy of Omental Tumor or Paracentesis of Malignant Ascites

HGSC

- Neoadjuvant Chemo Tx or Primary Surgery Then Adjuvant Chemo Tx

LGSC

- Primary Surgery Then Adjuvant Chemo Tx

Diagnostic Challenges Distinguishing LGSC versus HGSC

- Morphology and immunostaining criteria not studied in:
  - Core biopsy / FNA of peritoneal disease
  - Cytology of malignant ascites

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Targeted Drugs in Clinical Trials for Pelvic Serous Carcinoma

For HGSC (BRCA mutation):

- Targeted inhibitors of PARP1 protein
  - Olaparib
  - Veliparib
  - Rucaparib

For LGSC:

- Targeted inhibitor of MEK protein
  - Selumetinib
Normal DNA Repair Mechanisms

Double Strand Breaks: Repair by BRCA1 / 2 proteins

Single Strand Breaks: Repair by PARP1 protein

If BRCA mutation, PARP1 “permits” Cells to Still Proliferate

Double Strand Breaks: Repair by BRCA1 / 2 proteins

Single Strand Breaks: Repair by PARP1 protein

Alteration #1: Germline mutation BRCA1 or 2

Targeted Cell Death Occurs if PARP1 Inhibitor plus BRCA1 or 2

Double Strand Breaks: Repair by BRCA1 / 2 proteins

Single Strand Breaks: Repair by PARP1 protein

Alteration #1: Germline mutation BRCA1 or 2

Alteration #2: PARP1 Inhibitor Targeted Drug

Targeted Drugs in Clinical Trials for Pelvic Serous Carcinoma

For HGSC (BRCA mutation):

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**Normal MAPK Cell Signaling Cascade Drives Proliferation**

**Mutations in MAPK Cell Signaling Cascade Promote Tumor Growth**

**MEK Inhibitor Drugs Shut Down Tumor Cell Proliferation**
### Targeted Drugs in Clinical Trials for Pelvic Serous Carcinoma

**For LGSC:**

- Targeted inhibitors of MEK protein in trials
  - Selumetinib
  - Trametinib

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### Rationale for Hormonal Therapy in LGSC

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<tr>
<th>Receptor</th>
<th>LGSC</th>
<th>HGSC</th>
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<tbody>
<tr>
<td>Estrogen Receptors</td>
<td>58 %</td>
<td>27 %</td>
</tr>
<tr>
<td>Progesterone Receptors</td>
<td>43 %</td>
<td>17 %</td>
</tr>
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Wong 2007 Int J Gynecol Pathol

Some survival benefit for LGSC with hormonal + chemo therapy

Gershenson 2012 Gym Oncol
Schlumbrecht 2011 Cancer
Genetic mutations can be found in up to 1/4 of all pelvic cancers

Unselected Pelvic Cancers

Fanconi Anemia – BRCA Pathway Genes

- **BRCA1, BRCA2** ~80%
- RAD51C, RAD51D
- BRF1
- BARD1
- CHEK2
- MRE11A
- NBN
- PALB2
- RAD50

Mismatch Repair Genes

- MLH1, MSH2, PMS2, MSH6

TP53

Walsh et al, 2011 PNAS

Most LGSC is not due to inherited gene mutation

- No significant rate of germline mutations
  - Walsh 2011 PNAS
  - Fujinara 2012 AJSP
  - Lakhani 2004 Clin Can Res
  - Mavaddat 2011 Canc Epid Biom Prev
  - Norquist 2013 Gyn Oncol

- No significant rate of “cancer pedigree” by personal/family history
  - Vineyard 2011 Gyn Onc

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<td>Consider hormonal therapy?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Consider genetic counseling referral for risk of hereditary syndrome?</td>
<td>Yes</td>
<td>Low priority</td>
</tr>
</tbody>
</table>

Outline of Talk

- Changes to 2014 WHO system for pelvic serous tumors
- High grade serous carcinoma versus low grade serous carcinoma
- New recommendations for assigning primary tumor origin
- Special issues with serous borderline tumors
How do we assign origin of advanced stage HGSC

- Traditional approaches:
  - Any ovarian involvement = ovarian origin
  - Dominant-mass = primary origin

- Problems
  - No consensus or standardization
  - Observer variation
  - Problematic in neoadjuvant treated cases
  - Biologic validity is untested
  - Does not address the new paradigm of fallopian tube findings

New proposal from international consensus group:

Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR)

How do we assign origin of advanced stage HGSC

- New paradigm:
  - Fallopian tube STIC is the earliest stage of HGSC

<table>
<thead>
<tr>
<th>Setting</th>
<th>% with STIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental salpingectomy in general population</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Prophylactic salpingectomy in BRCA mutation carrier</td>
<td>&lt; 8%</td>
</tr>
<tr>
<td>Salpingectomy in stage I ovarian HGSC</td>
<td>~ 100%</td>
</tr>
<tr>
<td>Salpingectomy in advanced stage HGSC</td>
<td>~ 60%</td>
</tr>
</tbody>
</table>

New proposal from international consensus group:

Use the presence of STIC to define the tube as primary origin
How do we assign origin of advanced stage HGSC

- New proposal from international consensus group:
  
  Use the presence of STIC to define the tube as primary origin

<table>
<thead>
<tr>
<th>Pelvic HGSC</th>
<th>% of all cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary fallopian tube cancer</td>
<td>83 %</td>
</tr>
<tr>
<td>Primary ovarian cancer</td>
<td>17 %</td>
</tr>
<tr>
<td>Primary peritoneal cancer</td>
<td>0 %</td>
</tr>
</tbody>
</table>

Singh 2015 Histopath

Advantages

- Simple rules
- Reproducible
- Applicable in neoadjuvant treated cases
- In sync with new paradigm of pathogenesis

How do we assign origin of advanced stage HGSC

- New proposal from international consensus group:
  
  Use the presence of STIC to define the tube as primary origin

- Unresolved issue: Uterine HGSC

<table>
<thead>
<tr>
<th>Primary uterine HGSC</th>
<th>WT1 negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary extra-uterine HGSC</td>
<td>WT1 positive</td>
</tr>
</tbody>
</table>

Diagnostic Criteria for STIC

- Gross specimen management
- Morphologic criteria
- Immunohistochemical criteria
- Diagnostic pitfalls
STIC in Microscopic

Process Tubes via SEE-FIM Protocol

Fix in Formalin Several Hours
Slice Fimbriae Parallel to Plicae
Embed Entire Fimbriae

2-3 mm Intervals
Entire tube if RRSO or if Cancer Case

Entire Fimbriae: 1-2 cassettes usually
Ampullary Portion of Tube 1 cassette

Automatic deeper levels not necessary if slices are 2-3 mm

Diagnosis of STIC

Morphology
Architecture
Cytology
Immunophenotype
Aberrant p53
Increased Ki-67 (MIB-1)
### Diagnosis of STIC

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Architecture</th>
<th>Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crowding, tufting, piling up, stratification</td>
<td>High N/C ratio</td>
</tr>
<tr>
<td></td>
<td>Loss of polarity</td>
<td>Moderate / severe nuclear atypia</td>
</tr>
<tr>
<td></td>
<td>Loss of cilia</td>
<td>Mitoses</td>
</tr>
<tr>
<td></td>
<td>Loss of peg cells</td>
<td>+/- Macronucleoli</td>
</tr>
</tbody>
</table>

**Notes:**
- Normal Fallopian Tube Mucosa
- STIC

*Serous Carcinogenesis in the Fallopian Tube: A Descriptive Classification*

Eline Joffre, nct., Ann Bolhuis, nct., Marina W. Stree, nct., Doreen Koedijk, nct.,
Euny Shigaki, nct., Alexia M. Arora, nct., William H. Bower, nct.,
Yongchun Liu, nct., and Christopher J. Geis, nct.

IJGP, 2008; 27: 1
STIC

STIC Diagnostic Criteria Do Not Depend on BRCA mutation status

Morphology Suspicious But Not Diagnostic of STIC

Morphology Suspicious But Not Diagnostic of STIC
Diagnosis of STIC

**Morphology**
- Architecture
- Cytology

**Immunophenotype**
- Aberrant p53
- Increased Ki-67 (MIB-1)

Other markers, not as well studied: p16, HMGA2, Stathmin

### p53 Stain Pattern Interpretation

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong + diffuse</td>
<td>Aberrant</td>
</tr>
<tr>
<td>Completely absent</td>
<td>Aberrant</td>
</tr>
<tr>
<td>Variable strength</td>
<td>Normal (wild type)</td>
</tr>
</tbody>
</table>

### Ki-67 Stain Pattern Interpretation

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as adjacent normal mucosa</td>
<td>Normal</td>
</tr>
<tr>
<td>Higher than adjacent normal mucosa (&gt;10%)</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Aberrant p53 in STIC

STIC

Aberrant P53

Aberrant Ki 67
Aberrant P53
Aberrant Ki 67

Both Morphology and Immunostains Should Be Concordant for STIC

Abnormal proliferations that fall short of criteria for STIC
### Abnormal proliferations that fall short of criteria for STIC

- Outcome based evidence of clinical significance is lacking
- Prone to observer variation
- No consensus on nomenclature

<table>
<thead>
<tr>
<th>Serous tubal intraepithelial lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal intraepithelial lesion in transition</td>
</tr>
<tr>
<td>Atypical mucosal proliferation</td>
</tr>
</tbody>
</table>

- No guidelines for management

  *Current UCSF approach is observation only*

### Alterations that are not clinically significant to report

- Secretory cell outgrowth (SCOUT)
- p53 signature (normal morphology but p53 aberrant)

### Alterations that are likely within normal spectrum of benign tubes

- “hyperplasia” without atypia (no formal terminology)
### Alterations that are likely within normal spectrum of benign tubes

- “hobnail” growth without atypia (no formal terminology)

### Differential Diagnosis of STIC

- Tangential Sectioning Artifact
- Metaplasias (transitional cell, mucinous)
- Inflammatory Reactions
- Mucosal Endometriosis
- Mucosal Adenofibroma
- Submucosal Adenomatoid Tumor
- Metastatic Cancer

### Outline of Talk

- Changes to 2014 WHO system for pelvic serous tumors
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- New recommendations for assigning primary tumor origin

### Special Issues with Serous Borderline Tumors (SBT)

- Chemotherapy indications
  - LGSC in ovarian SBT
  - LGSC in extra-ovarian sites
Special Issues with Serous Borderline Tumors (SBT)

- Chemotherapy indications

  - LGSC in ovarian SBT
  - LGSC in extra-ovarian sites

- LGSC in ovarian SBT

  Stromal invasive criteria (> 5 mm)
  Expansile invasion criteria

LGSC in Ovarian Serous Borderline Tumor

> 5 mm span of stromal invasion

Special Issues with Serous Borderline Tumors (SBT)

- Chemotherapy indications

  - LGSC in ovarian SBT
  - LGSC in extra-ovarian sites

- LGSC in extra-ovarian sites (so-called “invasive” implants)

  Destructive infiltrative growth into underlying tissue
  Solid nests / micropapillae within clefts in stroma

LGSC versus Micropapillary Type SBT
Special Issues with Serous Borderline Tumors (SBT)

- Most SBT exhibit hierarchical branching growth

Special Issues with Serous Borderline Tumors (SBT)

- Micropapillary variant associated with extra-ovarian LGSC
Micropapillary variant associated with extra-ovarian LGSC

- Non-hierarchical branching
- Broad papillae with finger-like projections
- Broad papillae lined by cribriform proliferation
- > 5 mm span in conventional type SBT

Valuable to report at Frozen Section diagnosis in order to assist surgeon in considering staging procedure

Outline of Talk

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