The new classifications of ovarian, fallopian tube, and primary peritoneal cancer and their clinical implications

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I have no disclosures.
“If you want to make enemies, try to change something”

President Woodrow Wilson
• 28th president, 1913 – 1921
• Marshalled the US through WWI to the Treaty of Versailles
• Initiated the draft, income tax, others
• Oversaw US involvement in the Mexican Revolution
• Won the 1919 Nobel Peace Prize
What is the role of grading and staging cancer?
What is the role of grading and staging cancer?

• To describe the characteristics of the cancer architecture and cells
• To provide reproducible metrics to be used within a tumor and across tumors
• To describe and organize reproducible tumor characteristics that correlate with prognosis
• To inform and organize treatment recommendations
• To provide a platform from which to understand and dissect historical information, and
• To provide a platform from which to build, direct, and analyze prospective clinical advances.

With thanks and apologies to Dave Mutch and Jaime Prat, Gyn Oncol, 2014
Endometriosis: precursor of CCC and low grade endometrioid EOC

Tubes: STICs, HGSOC

Ovary: SBOT, LGSOC
Example histology

HGSOC

Mucinous

Clear cell

LG SOC

Endometrioid

Prat WHO/FIGO lecture
WHO 2014 Histopathologic Criteria for Ovarian Cancers

Major changes

• Formal adoption of the 2 step grading system
• Papillary cystic BOT → SBOT/atypical proliferating tumor
• Papillary surface BOT → SBOT, micropapillary type, noninvasive LGSOC
• “Grade 2” tumors are candidates for p53 immunostaining
• Endocervical MBOT → seromucinous

Supporting reasons

• Supported by science
• Cystic serous tumor with >10% BOT is now SBOT
• ↑risk of peritoneal implants, (27 v 13%) for micropapillary; 50% probability LGSOC in peritoneal SBOT base
• Likely HGSOC, support by p53 staining
• Resembles SBOTs with 1/3 associated with endometriosis and ARID1a\text{mut}

Prat (lecture); Meinhold-Heerlein, et al, Arch Gynecol Obstet, 2016
## WHO 2014 Diagnostic Criteria per Cancer Type

<table>
<thead>
<tr>
<th>TYPE</th>
<th>% of total</th>
<th>Molecular Characteristics</th>
<th>Other Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGSOC</td>
<td>70%</td>
<td>TP53&lt;sup&gt;mut&lt;/sup&gt;, genomic instability</td>
<td>STIC precursor, no BOT</td>
</tr>
<tr>
<td>LGSOC</td>
<td>3.5%</td>
<td>KRAS&lt;sup&gt;mut&lt;/sup&gt;, BRAF&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>Mutations more common in SBOT</td>
</tr>
<tr>
<td>CCC</td>
<td>10%</td>
<td>ARID1a&lt;sup&gt;mut&lt;/sup&gt;, PIK3CA&lt;sup&gt;mut&lt;/sup&gt;, PIK3CA&lt;sup&gt;amp&lt;/sup&gt;</td>
<td>15-30% with endometriosis</td>
</tr>
<tr>
<td>ENDO ↓gr</td>
<td>10%</td>
<td>ARID1a&lt;sup&gt;mut&lt;/sup&gt;, PIK3CA&lt;sup&gt;mut&lt;/sup&gt;, PTEN LOH, β catenin&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>EBOT frequency of mutations similar to invasive, 15-30% associated with endometriosis</td>
</tr>
<tr>
<td>ENDO ↑gr</td>
<td>10%</td>
<td>TP53&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>EBOT frequency of mutations similar to invasive, 15-30% associated with endometriosis Recategorized as HGSOC</td>
</tr>
<tr>
<td>Mucinous</td>
<td>3.6%</td>
<td>80%&lt;sup&gt;+&lt;/sup&gt; KRAS&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>Intestinal type only</td>
</tr>
</tbody>
</table>
Discriminating diagnostic criteria ovarian cancer types

HGS: high grade, any serous component and a solid or undifferentiated component, includes high grade endometrioid

LGS: ≤3X variation in nuclear size and ≤13 mitoses/HPF

<table>
<thead>
<tr>
<th>OCCC</th>
<th>HNF1β</th>
<th>HGSOC</th>
<th>LGE/SOCHGSOC</th>
<th>MUC5</th>
<th>p16/p53</th>
<th>vimentin</th>
<th>WT1</th>
<th>Ki-67 (Median, 95% CI) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade serous</td>
<td>80</td>
<td>0</td>
<td>10</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>64</td>
</tr>
<tr>
<td>High-grade serous</td>
<td>76</td>
<td>5</td>
<td>15</td>
<td>80</td>
<td>4</td>
<td>56</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Clear cell</td>
<td>11</td>
<td>82</td>
<td>17</td>
<td>33</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>77</td>
<td>8</td>
<td>58</td>
<td>26</td>
<td>18</td>
<td>6</td>
<td>10</td>
<td>61</td>
</tr>
<tr>
<td>Mucinous</td>
<td>76</td>
<td>7</td>
<td>15</td>
<td>0</td>
<td>73</td>
<td>0</td>
<td>10</td>
<td>7</td>
</tr>
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</table>

This data is derived from staining of a 500 case population-based case series, and has been published earlier. It is important to note that in some cases of a given cell type, other cells are indicated by shading.

CI indicates confidence interval; ER, estrogen receptor; HNF, hepatocyte nuclear factor.

WHO 2014 Diagnostic Criteria per Cancer Type

Hierarchical diagnosis for the nonpathologist

Looking ugly, sheets of cells with large nuclei cells

Y, or sort of

Wanna be sure?

Y

P53 immunostaining: abundant expression (GoF) or complete absence (LoF)

Y

HGSOC
WHO 2014 Diagnostic Criteria per Cancer Type

**Hierarchical diagnosis for the nonpathologist**

*Looks ugly, sheets of cells with large nuclei cells*

N?

Y, or sort of

Wanna be sure?

Y

P53 immunostaining: abundant expression (GoF) or complete absence (LoF)

Y

↓

HGSOC
WHO 2014 Diagnostic Criteria per Cancer Type

Hierarchical diagnosis for the nonpathologist

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P53 immunostaining: abundant expression (GoF) or complete absence (LoF)

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HGSOC

N?

Funny cells with white cytoplasm

Y \rightarrow OCCC
WHO 2014 Diagnostic Criteria per Cancer Type

Hierarchical diagnosis for the non-pathologist

- **Looks ugly, sheets of cells with large nuclei cells**
  - **Y, or sort of**
    - **Wanna be sure?**
      - **Y**

- **P53 immunostaining:**
  - **abundant expression (GoF)**
  - **or complete absence (LoF**
    - **Y**

  - **HGSOC**

- **Funny cells with white cytoplasm**
  - **N?**
  - **Y ➔ OCCC**
  - **Funny cells with red cytoplasm**
    - **Y ➔ mucinous**
WHO 2014 Diagnostic Criteria per Cancer Type

Hierarchical diagnosis for the nonpathologist

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Papillary structures, purple blobs

Y ➔ LGSOC
WHO 2014 Diagnostic Criteria per Cancer Type

Hierarchical diagnosis for the nonpathologist

- **Looks ugly, sheets of cells with large nuclei cells**
  - Y, or sort of
  - **Wanna be sure?**
    - Y

**P53 immunostaining:**
- abundant expression (GoF)
  - Y
- complete absence (LoF)
  - Y

- **Funny cells with white cytoplasm**
  - Y ➔ **OCCC**
  - Y ➔ **mucinous**

- **Papillary structures, purple blobs**
  - Y ➔ **LGSOC**

- **Glandular structures, no blobs**
  - Y ➔ **endometrioid**
Prognostic impact of separating HGSOC and LGSOC

Prognostic differences in other ovarian cancer types
Stage III cases, H/LGSO/EC lumped (GOG111, 114, 132, 152, 158, 172)

Progression-free survival

Prognostic differences in other ovarian cancer types

Stage III cases, H/LGSO/EC lumped (GOG111, 114, 132, 152, 158, 172)

Progression-free survival

Overall survival

## Treatment guidance by histologic type

<table>
<thead>
<tr>
<th>TYPE</th>
<th>% Early stage presentation</th>
<th>Histology-specific treatment guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGSOC</td>
<td>20%</td>
<td>Chemotherapy, anti-angiogenic therapy, DNA repair inhibition therapy, radiation</td>
</tr>
<tr>
<td>LGSOC</td>
<td>30+%</td>
<td>*Consensus conference: chemotx or clinical trial</td>
</tr>
<tr>
<td>CCC</td>
<td>25%</td>
<td>*</td>
</tr>
<tr>
<td>ENDO</td>
<td>30%</td>
<td>*, **</td>
</tr>
<tr>
<td>Mucinous</td>
<td>? all</td>
<td>*Is advanced stage/metastatic ovarian? r/o GI source</td>
</tr>
</tbody>
</table>

* No validated type-specific treatment
**High grade reclassified and treated as HGSOC
### WHO 2014 Classification Value and Pitfalls

<table>
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<tr>
<th>Value</th>
<th>Pitfalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarifies relationship of SBOT to LGSOC</td>
<td>Only 5% progression to LGSOC?</td>
</tr>
<tr>
<td>Guidance re gr 2 serous cancers</td>
<td>Careful review of p53 staining not to miss LoF mutations</td>
</tr>
<tr>
<td>Reclassifies endocervical mucinous</td>
<td>We still don’t understand mucinous cancers</td>
</tr>
<tr>
<td>Uses genomics as back up</td>
<td>Does not incorporate molecular characteristics in classification</td>
</tr>
</tbody>
</table>
What is the role of grading and staging cancer?
FIGO 2014 Classification Changes and Justifications

**Major changes**

- Designate histologic site
- Stage III now
  - any LN + any spread beyond pelvis
  - IIIA1 is LN+ only
  - IIIA2 micro disease + LN+
- Stage IV + effusion v parenchyma/inguinal/other non abdominal nodal sites

**Supporting reasons**

- Scientifically supported, no longer lumps FT with ovary
- Retrospectively ~10% IIIA are LN+ behave like I/II; LGSOC can arise in nodal endosalpingiosis
- Retrospective data → differential outcome for effusion-only stage IV

*From Prat and FIGO Committee on Gynecologic Oncology, I J Gyn Oncology, 2014*
New FIGO Classification: questions & controversies?

Is subgroup breakdown of stage IV valuable?

- IVA v B: may be artificial and dependent upon tools used in evaluation
- Increasing VATS in some centers/countries \(\rightarrow\) what stage is pleural + bx?

AGO evaluation 240 consecutive IV pts:
- 88% HGSOC, 90% LN\(^+\), 72% ECOG 0
- median OS 25 (A) v 28mo for (B)
- excluded cases with abdominal wall mets only (\(?\)did better)
- VATS was performed in undefined # and pleural cavity opened in suspicious cases

Why would + effusion end up worse?

New FIGO Classification: *questions & controversies?*

Do data justify making any LN\(^+\) any stage III?

Retrospective: 417 R0 GOG-182 IIIC cases (all histology)
- Any intraperitoneal disease >2cm, HR ≥ 1.38 v LN+ only
- LN\(^+\) & >2 cm, HR 1.8 v LN+ only (>2cm/LN- HR 1.21)
(Rungruang et al, Gyn Oncol 2012)
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Case series: 36 pts upstaged to IIIC by +LN
- outcome = stage I/II  (Cliby et al, Gyn Oncol, 2006)
New FIGO Classification: questions & controversies?

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Case series: 36 pts upstaged to IIIC by +LN
  • outcome = stage I/II  (Cliby et al, Gyn Oncol, 2006)

Case series: 118 pt, pelvic only disease, TTP
  • I/II LN- v I/II LN+ v IIIA/B (LNV) v IIIA/B (no LNV)
  • I/II +/- LN did relatively same
  • “…simply reflect the prognostic impact of small versus large tumor size…”
    (Ferrandina et al, Gyn Oncol, 2007)
New FIGO Classification: questions & controversies?

Does the new classification add overall prognostic value?

• If so, are we willing to lose all prior historical control data?
• Does it change therapeutic recommendations?

Comparison using cases classified by FIGO 1999 v 2014

• 878 patients reclassified to FIGO 2014 and analyzed
• Multivariate analyses adjusted for age, cell type (serous/not), grade, surgical outcomes, chemosensitivity

New FIGO Classification: *questions & controversies?*

### Table 2. Progression free survival in multivariate analysis

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<tr>
<td>IC</td>
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<td>IC2</td>
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<td>Stage II</td>
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<tr>
<td>IIA</td>
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<td>IIB</td>
<td>0.551 (0.148–2.053)</td>
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<td>IIIA1(i)</td>
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<td>Stage IV</td>
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Multivariate analysis was performed in stage I by adjusting age, cell type (serous vs. non-serous), grade, and surgical staging methods (complete staging vs. comprehensive staging). Multivariate analysis was performed in stage II, III, and IV, respectively, by adjusting age, cell type (serous vs. non-serous), grade, and surgical outcomes (no gross residual, residual <1 cm, and residual ≥1 cm).
New FIGO Classification: *questions & controversies?*

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New FIGO Classification: questions & controversies?

Table 3. Overall survival in multivariate analysis

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<tr>
<td>IIB</td>
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<td>IIIA2</td>
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<td>IIIA2</td>
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<td>IIIA1(ii)</td>
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<td>IIIA1(ii)</td>
<td>2.162 (0.357–13.10)</td>
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<td>IIIB</td>
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<td>0.212</td>
<td>IIIIB</td>
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<td>IIIC</td>
<td>3.390 (0.830–13.85)</td>
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<td>IVA</td>
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<td>IVB</td>
<td>1.139 (0.826–1.569)</td>
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</table>

Bottom line: no clear prognostic benefit across system

## No EOC treatment changes from FIGO 2014

<table>
<thead>
<tr>
<th>Stage</th>
<th>Current worldwide recommendations</th>
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<td>1A, B</td>
<td>Comprehensive staging and debulking surgery, LN sampling</td>
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<tr>
<td>1C any HGSOC</td>
<td>Comprehensive staging and debulking surgery, LN sampling</td>
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<td>Adjuvant chemotherapy 3-6 cycles platinum/taxane</td>
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<tr>
<td>Any II - IV</td>
<td>Comprehensive staging, LND, and debulking surgery</td>
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<td>Adjuvant chemotherapy 6 cycles platinum/taxane</td>
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<td>Country-specific maintenance treatment options</td>
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<tr>
<td>III/IV</td>
<td>Consider NACT chemotherapy, 3-4 cycles platinum/taxane</td>
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<td>Interval debulking to R0, additional 3-4 cycles platinum/taxane</td>
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<td>Country-specific maintenance treatment options</td>
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</tbody>
</table>
Changing staging: *Food for thought*

- **Concerns**
  - Most changes were based on retrospective studies
  - Stage is determined by surgical findings
  - Data harmonization
  - Added staging complexity for unclear benefit
  - Presumes all ovarian/FT tumors are the same

- **Thoughts**
  - Limited level of evidence, unclear value benefit
  - Quality/aggressiveness of staging biases data, can invalidate prognostication
  - Stage shift occurred due to changes in medical management and surgical technique. FIGO 2014 magnifies the shift. What is the prognostic reliability?
  - Clinical applicability of subsetting IC, IIIA, IV are unclear.
  - Unclear that this staging is optimal for germ cell, stromal cell, etc
That was excellently observ'd, say I, when I read a Passage in an Author, where his Opinion agrees with mine. When we differ, there I pronounce him to be mistaken.

— Jonathan Swift

“I want you to find a bold and innovative way to do everything exactly the same way it’s been done for 25 years.”

“What if we don’t change at all ... and something magical just happens?”