An Update on the Diagnosis, Grading, and Staging of Appendiceal Mucinous Neoplasms
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Session Outline
Topic 1: Classification and Staging of Low-Grade Appendiceal Mucinous Neoplasm (LAMN)
- Peritoneal Surface Oncology Group International (PSOGI) Classification Proposal
- AJCC 8th Edition Staging Update

Topic 2: Classification and Grading of Mucinous Adenocarcinoma
- PSOGI and AJCC 8th Edition Terminology and Grading Schemes
- Challenges in Classifying Peritoneal Disease

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Dr. Pai declares he has no conflict of interest to disclose.

The Problem of Terminology
- Peritoneal Surface Oncology Group International (PSOGI; “peritoneal group”) recognized a persistent lack of uniform diagnostic terminology in appendiceal mucinous neoplasia.
- An international working group of 71 participants (surgical pathology, surgical oncology, medical oncology) on appendiceal mucinous neoplasia led by Dr. Norman Carr of North Hampshire Hospital and University Hospital Southampton in the UK.

Classification used by participants prior to PSOGI consensus proposal:

<table>
<thead>
<tr>
<th>No. of Responses</th>
<th>Confined to Muscosa</th>
<th>Dissecting Muscosa</th>
<th>Pushing Invasion</th>
<th>Infiltrative Invasion</th>
<th>Signet Ring Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>?</td>
<td>Low-grade mucinous neoplasm (LAMN)</td>
<td>Mucinous adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Adenoma</td>
<td>Low-grade mucinous neoplasm (LAMN)</td>
<td>Mucinous adenocarcinoma</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>?</td>
<td>Low-grade mucinous adenocarcinoma</td>
<td>High-grade mucinous adenocarcinoma</td>
<td>High-grade mucinous adenocarcinoma with signet ring cells</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>?</td>
<td>Low-grade mucinous adenocarcinoma</td>
<td>High-grade mucinous adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**PSOGI Diagnostic Terminology for Primary Appendiceal Neoplasms**

**Neoplasms without infiltrative invasion**
- Low-grade appendiceal mucinous neoplasm (LAMN)
- High-grade appendiceal mucinous neoplasm (HAMN) (new diagnostic category; rare)
- Serrated polyp with or without dysplasia
- Conventional adenoma, resembling colorectal type (rare)

**Neoplasms with infiltrative invasion**
- Mucinous adenocarcinoma
- Mucinous adenocarcinoma with signet ring cells (≤50% signet ring cells)
- Mucinous signet ring cell carcinoma (>50% signet ring cells)
- Non-mucinous adenocarcinoma

Definition of LAMN (PSOGI)
- Mucinous neoplasm with low-grade cytology and any of the following:
  - Loss of lamina propria and muscularis mucosae
  - Fibrosis of submucosa
  - Undulating, flattened, or villous epithelial growth
  - "Pushing invasion" (expansile or diverticulum like growth)
  - Dissection of acellular mucin in the wall
  - Mucin and/or neoplastic cells outside of the appendix

- Use of the term "mucinous adenoma" was not supported by the majority of the group.
High-Grade Appendiceal Mucinous Neoplasm (HAMN, New diagnostic category)

- Mucinous neoplasm with high-grade cytologic features but without infiltrative invasion.
- This includes cases where the high-grade cytology is focal.
- Very rare neoplasm – must entirely submit the appendix to evaluate for invasion and for cellular deposits on the appendiceal serosa.
- Two-thirds of patients with high-grade cytology without invasion in the primary appendix developed recurrent adenocarcinoma in the peritoneum (including all of the cases reported in the literature, none of the cases had the entire appendix submitted).


Mimics of Appendiceal Mucinous Neoplasms

- Appendiceal serrated polyps
- Ruptured Appendiceal Diverticula
- Endometriosis with intestinal metaplasia
- Acute appendicitis with mucosal hyperplasia
Serrated Polyp without Dysplasia

Serrated Polyp w/ Low-Grade Dysplasia
(Resembling a Traditional Serrated Adenoma)

LAMN: Should it be staged?

- PSOGI Participants:
  39 of 60 (65%) respondents within the group responded “Yes”.

- When staging LAMN, do you stage neoplastic epithelium, mucin, or both?

- The AJCC 8th edition provides some clarification.

LAMN: AJCC 8th Edition

- Tis (LAMN): LAMN confined to the muscularis propria. Mucin or mucinous epithelium may extend into the muscularis propria.

- T1 and T2 categories are not applicable to LAMN.

pTis (LAMN): Pushing into muscularis propria
AJCC 8th Edition: pTis (LAMN)

- Requires that the entire appendix be submitted for histologic examination.
- Literature evidence indicates that patients with pTis (LAMN) do not develop tumor recurrence and are essentially cured by appendectomy.
- However, this requires correlation with intraoperative findings.

LAMN: AJCC 8th Edition

<table>
<thead>
<tr>
<th>T Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>Tumor* extends through the muscularis propria into the subserosa or mesoappendix.</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor penetrates the visceral peritoneum, including acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix.</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor directly involves adjacent organs or structures, including acellular mucin or mucinous epithelium (does not include luminal or mural spread into adjacent cecum).</td>
</tr>
</tbody>
</table>

Acellular mucin in subserosa (pT3)

pT4a LAMN Due to Acellular Mucin

pT4a LAMN Due to Acellular Mucin

- Low risk of peritoneal recurrence:
  Of the cases reported in the literature, ~3% (2 of 58 patients) have developed peritoneal recurrence.
- Potential for over-staging: acellular mucin may be seen on the serosal surface due to “carry-over” related to specimen handling.


Mucin on visceral peritoneal surface due to “carry-over” from sectioning

Potential for over-staging LAMN, as sectioning can “carry-over” mucin onto the serosa.
Mucin on visceral peritoneal surface with inflammatory reaction and neovascularization

pT4a LAMN Due to Cellular Mucin

- High risk for peritoneal recurrence:
  Of the cases reported in the literature, ~36% (5 of 14 patients) have developed peritoneal recurrence.

LAMN: AJCC 8th Edition

<table>
<thead>
<tr>
<th>M Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Intraperitoneal acellular mucin without identifiable tumor cells.</td>
</tr>
<tr>
<td>M1b</td>
<td>Intraperitoneal metastasis only, including peritoneal cellular mucinous deposits.</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to sites other than the peritoneum.</td>
</tr>
</tbody>
</table>

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- PSOGI and AJCC 8th Edition Terminology and Grading Schemes
- Challenges in Classifying Peritoneal Disease
**Mucinous Adenocarcinoma**

- Defined by infiltrative destructive invasion
- High-grade cytologic features typically present and may show a mix of both low and high cytologic grade.
- PSOGI and the AJCC 8th edition advocate a three-tier grading of mucinous neoplasia based mostly on literature evaluating outcome in patients with stage IV peritoneal disease.

**Three-Tiered Grading in Appendiceal Mucinous Neoplasia (Stage IV)**

<table>
<thead>
<tr>
<th>AJCC Grade for Primary and Intraperitoneal Disease</th>
<th>PSOGI Grade for Intraperitoneal Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1, well differentiated</td>
<td>Low-grade</td>
<td>Low cytologic grade &amp; no infiltrative invasion</td>
</tr>
<tr>
<td>G2, moderately differentiated</td>
<td>High-grade</td>
<td>High cytologic grade without signet ring cells</td>
</tr>
<tr>
<td>G3, poorly differentiated</td>
<td>High-grade with signet ring cells</td>
<td>High cytologic grade with signet ring cells</td>
</tr>
</tbody>
</table>

AJCC grades G2 and G3 are considered high-grade.

**Two-Tier versus Three-Tier Grading Schemes: Which is Better?**

**Two-Tiers: Therapeutic Decision Making**

- Patients with low-grade (G1) peritoneal disease benefit from cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) with no benefit from systemic chemotherapy.
- Patients with high-grade (G2 and G3) peritoneal disease are often treated with systemic chemotherapy with the option of CRS-HIPEC at some institutions. The role of CRS-HIPEC is not entirely well-delineated although is used aggressively at many institutions with evidence of survival benefit.

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**Prognostic Groups** (10-yr overall survival, Stage IV)

<table>
<thead>
<tr>
<th>Prognostic Groups</th>
<th>AJCC Grade</th>
<th>PSOGI Grade</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 / PMP1 / Well-differentiated</td>
<td>~50%</td>
<td>Low-grade</td>
<td>~50%</td>
</tr>
<tr>
<td>G2 / PMP2 / Mod-differentiated</td>
<td>~30%</td>
<td>High-grade</td>
<td>~30%</td>
</tr>
<tr>
<td>G3 / PMP3 / Poorly-differentiated</td>
<td>~10-20%</td>
<td>High-grade</td>
<td>~10-20%</td>
</tr>
</tbody>
</table>

**Molecular Differences between Groups**

<table>
<thead>
<tr>
<th>Molecular Features</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS mutation</td>
<td>61%</td>
<td>72%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>GNA13 mutation</td>
<td>35%</td>
<td>37%</td>
<td>13%</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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Moderately Differentiated (G2) Mucinous Adenocarcinoma

Poorly Differentiated (G3) Mucinous Signet Ring Cell Carcinoma
Poorly Differentiated (G3) Mucinous Signet Ring Cell Carcinoma

AJCC: The Problem of Terminology

- Throughout the AJCC 8th edition chapter the terms "well-differentiated mucinous adenocarcinoma" and "low-grade appendiceal mucinous neoplasm" are used interchangeably.
- In the section on histologic grading, the AJCC states “G1 mucinous tumors with peritoneal involvement may be categorized as LAMN with peritoneal involvement”.

PSOGI: The Problem of Terminology

- A principle endorsed by PSOGI is that the classification of the primary appendiceal tumor is different than the peritoneal disease.
- This approach necessitates using different names for the appendiceal primary and the peritoneal disease, which can result in some confusion.

AJCC vs. PSOGI: Terminology for Low-Grade Primary & Peritoneal Disease

- My approach: I use the term "low-grade appendiceal mucinous neoplasm" for both the primary and peritoneal neoplasm.
- Exception: Discordant grades between the primary and peritoneal disease do exist and complicate classification.

Discordant Grades between Primary & Peritoneal Disease

- Discordant grading between primary and peritoneal disease does occur.
  - AJCC 8th edition not clear what overall grade to assign, but most PSOGI participants agreed that the grade of the peritoneal disease more likely influences prognosis and should be used for staging purposes.
- Scenario #1:
  - Primary: Low-grade appendiceal mucinous neoplasm (G1)
  - Peritoneum: Mucinous adenocarcinoma, moderately differentiated (G2)
  - Overall grade should be assigned as G2.
- Scenario #2:
  - Primary: Focal high-grade cytology in o/w low-grade neoplasm
  - Peritoneum: Low-grade (G1)
  - Overall grade should be assigned as G1.

Distinguishing Low- and High-Grade Cytology within Peritoneal Disease

- PSOGI did not provide specific histologic criteria for distinguishing low-grade from high-grade cytology.
- "Grey zone" cases that straddle between grades.

Low (G1) | High (G2) | High (G3)
---|---|---
Grey Zone | Cytoarchitectural atypia | Grey Zone
**Distinguishing Low- and High-Grade Cytology within Peritoneal Disease**

- Criteria for high-grade cytology that I use are the same as for the rest of the luminal GI tract:
  - Nuclear enlargement and rounding of the nuclei
  - Nuclear hyperchromasia
  - Irregular chromatin
  - Macronucleoli
  - Increased mitotic activity
  - Loss of nuclear polarity

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**Moderately Differentiated (G2) Mucinous Adenocarcinoma: Additional Features**

- High cellularity at low-power (2x objective) magnification (seen in most of cases).

- Destructive, infiltrative stromal and/or organ invasion.
  - “Small cellular mucin pool” pattern of invasion is common.

- Lymph node metastases in ~20% of cases.
Moderately Differentiated (G2) Mucinous Adenocarcinoma
“Small Cellular Mucin Pool” Pattern of Invasion

Isolated Glands in Stroma (Not infiltrative invasion)
Best classified as Low-Grade (G1, well-differentiated)

Pushing, Not Infiltrative Invasion, Best Classified as Low-Grade (G1, well-differentiated)
Challenges in Peritoneal Disease

- Predominantly low-grade (G1) disease but with a:
  - Focal area of increased cytologic atypia.
  - Focal area of questionable infiltrative invasion.
- Signet ring cells versus cellular degeneration imparting a signet ring-like morphology.

Distinguishing Between Grade G2 and Grade G3 in Mucinous Neoplasia

- In general, G3 tumors are defined by the presence of signet ring cells.
- How many signet ring cells are required to classify a lesion as G3?
- Is there a difference between signet ring cells floating within mucin and infiltrating signet ring cells?

**Signet ring cells**
- “Signet ring cells” with degenerative changes floating in mucin pools (in most cases these cells comprised less than 5% of the tumor burden).
- Patients with degenerative cells with signet ring-like morphology had significantly better overall survival compared to those with infiltrating signet ring cells.
- Degenerative changes imparting signet ring-like morphology ≠ G3 grade.
Conclusions

• PSOGI provided diagnostic criteria for LAMN and the AJCC 8th edition clarified staging of LAMN.

• Both the AJCC and PSOGI emphasize the importance of distinguishing between low-grade and high-grade disease and advocate for a three-tier grading scheme.

• Distinguishing between grades in peritoneal disease can be challenging. Discordant grading between primary and peritoneal disease exists. “Grey zone” cases likely affect reproducibility of grading peritoneal disease.

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