An Update on the Diagnosis, Grading, and Staging of Appendiceal Mucinous Neoplasms
Reet Pai, MD

University of Pittsburgh Medical Center
Pittsburgh, PA
Session Outline

**Topic 1: Classification and Staging of Low-Grade Appendiceal Mucinous Neoplasm**
- 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
- “Grey zone areas” in classifying peritoneal disease
The Problem of Terminology

• Peritoneal Surface Oncology Group International (PSOGI) recognized persistent lack of uniform diagnostic terminology in appendiceal mucinous neoplasia

• A working group of 71 participants (surgical pathology, surgical oncology, medical oncology) from 13 countries on appendiceal mucinous neoplasia led by Dr. Norman Carr of Basingstoke Hospital in the United Kingdom

• Adopted a consensus on diagnostic terminology published in the *American Journal of Surgical Pathology* in 2016
## The Problem of Terminology

Classification schemes used by participants prior to PSOGI consensus proposal.

<table>
<thead>
<tr>
<th>No. of Responses</th>
<th>Confined to mucosa</th>
<th>Dissecting Mucin</th>
<th>Pushing invasion</th>
<th>Infiltrative Invasive</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>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>?</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>
</tr>
<tr>
<td>6</td>
<td>?</td>
<td>?</td>
<td>Low-grade mucinous adenocarcinoma</td>
<td>High-grade mucinous adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Adenoma</td>
<td></td>
<td></td>
<td></td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>
WHO (2010) Diagnostic Terminology for Primary Appendiceal Neoplasms (excluding neuroendocrine tumors)

- Low-grade appendiceal mucinous neoplasm (LAMN)
- Mucinous adenocarcinoma
  - >50% mucin, <50% signet ring cells
- Signet ring cell carcinoma
  - >50% signet ring cells
- Non-mucinous adenocarcinoma – similar to conventional colorectal carcinoma
- Precursor lesions (conventional adenoma, SSA/P, TSA, HP)
PSOGI (2016) Diagnostic Terminology for Primary Appendiceal Neoplasms

Non-Invasive Neoplasms

— 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)*

PSOGI (2016) Diagnostic Terminology for Primary Appendiceal Neoplasms

Invasive Neoplasms

- Mucinous adenocarcinoma
  - Mucinous adenocarcinoma with signet ring cells (≤50% signet ring cells)
- Signet ring cell carcinoma (>50% signet ring cells)
- Non-mucinous adenocarcinoma

Definition of LAMN (PSOGI 2016)

• Mucinous neoplasm with low-grade cytology and any of the following:
  • Loss of muscularis mucosae
  • Fibrosis of submucosa
  • Undulating or flattened 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

• Typically see circumferential involvement of the mucosa by a mucin-rich epithelium involving at least 1 segment of the appendix

• Use of the term “mucinous adenoma” was not supported by the majority of the panel.
LAMN: Loss of lamina propria and muscularis mucosae with submucosal fibrosis
Flattened Epithelium

Undulating growth
LAMN: Diverticulum-like growth
LAMN: Acellular Mucin on Visceral Peritoneal Surface
High-Grade Appendiceal Mucinous Neoplasm (HAMN, New diagnostic category)

- Mucinous neoplasms with high-grade cytology but with the neoplasm confined to the appendix without invasion.
- Very rare neoplasm – must entirely submit the appendix to evaluate for invasion.
- 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\(^1,2\), none of the cases had the entire appendix submitted).

---

High-Grade Appendiceal Mucinous Neoplasm (HAMN)
Low-power features of LAMN
HAMN: High-Grade Cytologic Features
HAMN: High-Grade Cytologic Features
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 without Dysplasia
Serrated Polyp with Low-Grade Dysplasia
(resembling a Traditional Serrated Adenoma)
LAMN: Should it be staged?

- PSOGI Participants:
  39 of 60 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)
pTis (LAMN): Pushing into muscularis propria
AJCC 8th Edition: pTis (LAMN)

• Most are incidental lesions; patients present with acute appendicitis (~60%)

• 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.
<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, <em>including acellular mucin</em> or mucinous epithelium involving the serosa of the appendix.</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor directly involves adjacent organs or structures, <em>including acellular mucin</em> or mucinous epithelium (does not include luminal or mural spread into adjacent cecum).</td>
</tr>
</tbody>
</table>

*For T3 category, “tumor” is not defined. Does acellular mucin count?
Acellular mucin in mesoappendix
(likely not pT3 - will have to wait for clarification by authors)
pT4a LAMN Due to Acellular Mucin

- Acellular mucin is present on the visceral peritoneal surface.
- Potential for over-staging: acellular mucin may be seen on the serosal surface due to “carry-over” related to specimen handling.
- Of the cases reported in the literature\(^1,2\), \(\sim 5\%\) patients with acellular disease localized to the right lower quadrant have developed recurrence.

Mucin on visceral peritoneal surface with inflammatory reaction and neovascularization
Mucin on visceral peritoneal surface due to “carry-over” from sectioning

Potential for over-staging LAMN, as knife artifact can “carry-over” mucin onto the surface of the serosa.
pT4a LAMN Due to Cellular Mucin

- Extra-appendiceal neoplastic epithelium is present within mucin on the visceral peritoneal surface of the appendix.
- For tumors localized to the right lower quadrant at initial presentation, 42% of patients with cellular disease on the visceral peritoneal surface of the appendix have developed recurrence\(^1,2\).

---

<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 mucinous deposits containing tumor cells. Includes involvement of abdominopelvic organs (serosa of bowel, surface of ovary, liver, spleen) regardless of whether implants infiltrate underlying tissue.</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to sites other than the peritoneum.</td>
</tr>
</tbody>
</table>
Acellular Intraperitoneal Mucinous Disease (M1a)

Young 1991
• 5 patients with acellular peritoneal mucin and clinical follow-up with 1 patient developing recurrence 18 years after presentation

Davison 2014
• 5 patients with acellular peritoneal mucin and clinical follow-up with no patients developing recurrent disease (median follow-up 32 months).

• Suggests that patients with acellular mucinous peritoneal disease have a decreased risk of recurrence compared with patients with easily identifiable cellular mucin.

PSOGI (2016) Diagnostic Terminology for Primary Appendiceal Neoplasms

Invasive Neoplasms

- Mucinous adenocarcinoma
  - Mucinous adenocarcinoma with signet ring cells (≤50% signet ring cells)
- Signet ring cell carcinoma (>50% signet ring cells)
- Non-mucinous adenocarcinoma

Mucinous Adenocarcinoma

- Defined by infiltrative destructive invasion

- High-grade cytologic features present, at least focally, and may have areas of both low and high cytologic grades.

- May have a signet ring cell component

- PSOGI and AJCC 8th edition advocate a three-tier grading of mucinous neoplasia.
Three-Tiered Grading in Appendiceal Mucinous Neoplasia

National Cancer Database (NCDB): 5971 patients classified as having primary appendiceal neoplasms with mucinous histology. No pathology re-review performed and criteria for grading not explicitly discussed.

Three-Tiered Grading in Appendiceal Mucinous Neoplasia

G1 / PMP1 = Low-grade peritoneal disease
G2 / PMP2 = High-grade peritoneal disease
G3 / PMP3 = High-grade peritoneal disease with signet ring cells

**AJCC 8th Edition - Mucinous Neoplasia**

<table>
<thead>
<tr>
<th>AJCC (8th Edition) Grade</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1, well differentiated</td>
<td>Low cytologic grade (corresponds to LAMN)</td>
</tr>
<tr>
<td>G2, moderately differentiated</td>
<td>High cytologic grade without signet ring cells</td>
</tr>
<tr>
<td>G3, poorly differentiated</td>
<td>High cytologic grade, usually with signet ring cells</td>
</tr>
</tbody>
</table>

- Modification of the scheme proposed by Davison et al.
- G2 and G3 mucinous adenocarcinomas are considered high-grade.

Two-Tiers: Therapeutic Decision Making

- Patients with disseminated low-grade (G1) disease benefit from cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) with no role for systemic chemotherapy.

- Patients with disseminated high-grade (G2 and G3) 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.
Two-Tier versus Three-Tier Grading Schemes: Which is Better?

**Prognostic Groups**  
(10-year overall survival)

<table>
<thead>
<tr>
<th>Prognostic Group</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 / PMP1 / Well-differentiated:</td>
<td>~50%</td>
</tr>
<tr>
<td>G2 / PMP2 / Mod-differentiated:</td>
<td>~30%</td>
</tr>
<tr>
<td>G3 / PMP3 / Poorly-differentiated:</td>
<td>~10 to 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>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>GNAS mutation</td>
<td>35</td>
<td>37</td>
<td>13</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Mucinous Adenocarcinoma, Moderately Differentiated (G2)
Mucinous Adenocarcinoma, Moderately Differentiated (G2)
Mucinous Adenocarcinoma, Moderately Differentiated (G2)
Signet Ring Cell Carcinoma (>50% signet ring cells), Poorly Differentiated (G3)
Signet Ring Cell Carcinoma (>50% signet ring cells), Poorly Differentiated (G3)
Signet Ring Cell Carcinoma (>50% signet ring cells),
Poorly Differentiated (G3)
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 tumors with peritoneal involvement may be categorized as LAMN with peritoneal involvement”.

• The proposed CAP protocol also states that “in cancer protocols the histologic type of G1 tumors with peritoneal involvement is best recorded as LAMN”.

PSOGI: The Problem of Terminology

• A controversial principle endorsed by PSOGI is that the classification of the primary appendiceal tumor is different than the metastatic peritoneal disease.

• This approach necessitates using different names for the appendiceal primary and the metastatic peritoneal disease, which can result in considerable confusion (in my opinion).

• As far as I know, this approach to nomenclature is currently not been adopted for any other tumor type in the luminal GI tract and was not adopted by the AJCC 8th edition.
## AJCC vs. PSOGI: Terminology

<table>
<thead>
<tr>
<th>Primary Neoplasm</th>
<th>PSOGI Terminology for Peritoneal Disease</th>
<th>AJCC Terminology for Primary and Peritoneal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>Low-grade mucinous carcinoma peritonei</td>
<td>Low-grade appendiceal mucinous neoplasm (G1)</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma without signet ring cells</td>
<td>High-grade mucinous carcinoma peritonei</td>
<td>Mucinous adenocarcinoma, moderately differentiated (G2)</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma with signet ring cells</td>
<td>High-grade mucinous carcinoma peritonei with signet ring cells</td>
<td>Mucinous and/or signet ring cell adenocarcinoma, poorly differentiated (G3)</td>
</tr>
</tbody>
</table>

My opinion: once you decide what to call the primary appendiceal neoplasms, their metastases should align with that name (some exceptions).
Exceptions: Discordant Grades between Primary & Peritoneal Disease

• Discordant grading between primary and disseminated disease does occur
  • AJCC 8\textsuperscript{th} 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 appendix: LAMN (G1)
  • Peritoneal disease: Mucinous adenocarcinoma (G2)
  • Overall grade should be assigned as G2.

• Scenario #2:
  • Primary appendix: HAMN
  • Peritoneal disease: LAMN (G1)
  • Overall grade should be assigned as G1.
## My Approach To Peritoneal Disease

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>AJCC Grade</th>
<th>AJCC Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade appendiceal mucinous neoplasm</td>
<td>G1, well-differentiated</td>
<td>IVA</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma (without signet ring cells)</td>
<td>G2, moderately differentiated</td>
<td>IVB – peritoneal metastasis</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma with signet ring cells (≤50%)</td>
<td>G3, poorly differentiated</td>
<td>IVC – non-peritoneal metastasis</td>
</tr>
<tr>
<td>Signet ring cell carcinoma (&gt;50%)</td>
<td>G3, poorly differentiated</td>
<td></td>
</tr>
</tbody>
</table>
Cytoarchitectural atypia occurs on a continuum. How we divide cytoarchitectural atypia into two grades is really not well defined.
Histologic Features of Low-Grade (G1) Peritoneal Disease

- Low cytologic grade
- Low cellularity at low-power (2x objective) magnification
- Lacks the following features:
  - Any high-grade cytology
  - Destructive stromal and/or organ invasion
  - Desmoplasia
  - Lymph node metastases (rare cases reported)
  - Signet ring cells
Low-grade Appendiceal Mucinous Neoplasm (M1b, stage IVA)
Low-grade Appendiceal Mucinous Neoplasm (M1b, stage IVA)
Mucinous Adenocarcinoma, Moderately Differentiated (G2)

- High-grade cytology
  - Mix of low-grade and high-grade areas (common)
  - Diffuse high-grade cytology

- Destructive stromal and/or organ invasion

- High cellularity at low-power (2x objective) magnification (~75% of cases)

- Lymph node metastases in ~20% of cases
Criteria for High-Grade Cytology in Peritoneal Disease

• Use criteria similar to that employed for the rest of the luminal GI tract:
  – Marked nuclear enlargement and rounding of the nuclei
  – Nuclear hyperchromasia
  – Irregular chromatin
  – Macronucleoli
  – Increased mitotic activity
  – Loss of nuclear polarity
Mucinous adenocarcinoma, moderately differentiated (G2)
Patterns of Stromal/Organ Invasion

• Numerous small epithelial clusters floating in small pools of mucin (*common pattern of invasion*)

• Tubule formation within desmoplastic stroma

• Predominance of complex architectural growth (cribriform)
Small Mucin Pool Pattern of Invasion
Small Mucin Pool Pattern of Invasion with Diffuse High-Grade Cytology
Infiltrating Glands
Cribriform Growth
Isolated Glands in Stroma (Not invasion)
Best classified as Low-Grade (G1, well-differentiated)
Patterns of Organ Involvement: Invasion
Patterns of Organ Involvement: Not Invasion
Grey Zone Areas in Peritoneal Disease

- Questionable areas of increased cytologic atypia in otherwise low-grade disease

- Focal areas of possible destructive invasion in otherwise predominantly low-grade disease

- Questionable signet ring cells versus signet-ring cell like morphology due to cellular degeneration
Predominantly Low-grade with areas of increased proliferation
Microscopic area (single field & <10% of tumor) with increased cytologic atypia
Low-grade with area of increased proliferation
Microscopic area (single low-power 40x field) with possible invasion; often found in tumors involving other bowel sites
Predominantly Low-Grade Disease with Areas of Increased Proliferation

- Eight patients: none progressed to high-grade disease on follow-up and none died of disease at last clinical follow-up (median follow-up 94 months)

- Trend to accelerated time to progression compared to other patients with low-grade neoplasms (HR 2.4, 0.82-7.2 but not statistically significant)
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?
Degenerative changes imparting signet ring cell like morphology (we did not classify these as signet ring cells)
Significance of signet ring cells in high-grade mucinous adenocarcinoma of the peritoneum from appendiceal origin

S. Joseph Sirintrapun MD\textsuperscript{a,*}, Aaron U. Blackham MD\textsuperscript{b}, Greg Russell MS\textsuperscript{c}, Konstantinos Votanopoulos MD\textsuperscript{b}, John H. Stewart MD\textsuperscript{b}, Perry Shen MD\textsuperscript{b}, Edward A. Levine MD\textsuperscript{b}, Kim R. Geisinger MD\textsuperscript{d}, Simon Bergman MD\textsuperscript{a}

• “Signet ring cells” floating in mucin pools; in most (80%) cases, these cells comprised less than 5% of the tumor burden (We classified these case as degenerative changes, not SRCs).

• Patients with focal signet ring cells within mucin pools did significantly better than patients with signet ring cells invading tissue (median overall survival of 0.5 years versus 2.4 years, \(p=0.004\))

Additional Issues with Grading

- Assessing grade on small biopsy samples
  - G2 tumors can show a mix of low and high cytologic grades.
  - A small biopsy may only sample low-grade areas.

- Grade progression can occur
  - Patients with low-grade disease can recur with high-grade (G2) disease
Conclusions

• PSOGI provided diagnostic criteria for low-grade appendiceal mucinous neoplasms and the AJCC 8th edition clarified staging of LAMN.

• AJCC and PSOGI diagnostic terminology for appendiceal mucinous neoplasms.
  – Importance of distinguishing between low-grade mucinous neoplasm and high-grade mucinous adenocarcinoma with or without signet ring cells.

• “Grey zone” cases and discordant grading exist resulting in issues with reproducibility in grade assessment