Appendiceal GCC and LAMN
Navigating the Alphabet Soup in the Appendix

Sanjay Kakar, MD
University of California, San Francisco

Appendiceal tumors
Low grade appendiceal mucinous neoplasm
- Peritoneal spread, chemotherapy
- But not called ‘adenocarcinoma’
Goblet cell carcinoid
- Not a neuroendocrine tumor
- Staged and treated like adenocarcinoma
- But called ‘carcinoid’

Outline
- Appendiceal LAMN
- Peritoneal involvement by mucinous neoplasms
- Goblet cell carcinoid
  - Terminology
  - Grading and staging
  - Important elements for reporting
LAMN

WHO 2010: Low grade carcinoma
• Low grade
• ‘Pushing invasion’

LAMN vs. adenoma

<table>
<thead>
<tr>
<th>LAMN</th>
<th>Appendiceal adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade cytologic atypia</td>
<td>Low grade cytologic atypia</td>
</tr>
<tr>
<td>At minimum, muscularis mucosa is obliterated</td>
<td>Muscularis mucosa is intact</td>
</tr>
<tr>
<td>Can extend through the wall</td>
<td>Confined to lumen</td>
</tr>
</tbody>
</table>

Appendiceal adenoma: intact muscularis mucosa
## LAMN: Pushing invasion, obliteration of m mucosa

![Image of tissue section](image)

## LAMN vs adenocarcinoma

<table>
<thead>
<tr>
<th>LAMN</th>
<th>Mucinous adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>High grade</td>
</tr>
<tr>
<td><strong>Pushing invasion</strong></td>
<td><strong>Destructive invasion</strong></td>
</tr>
<tr>
<td>- No desmoplasia or</td>
<td>- Complex growth pattern</td>
</tr>
<tr>
<td>destructive invasion</td>
<td>- Angulated infiltrative</td>
</tr>
<tr>
<td></td>
<td>glands or single cells</td>
</tr>
<tr>
<td></td>
<td>- Desmoplasia</td>
</tr>
<tr>
<td></td>
<td>- Tumor cells floating</td>
</tr>
<tr>
<td></td>
<td>in mucin</td>
</tr>
</tbody>
</table>

WHO 2010
Davison, Mod Pathol 2014
Carr, AJSP 2016

## Complex growth pattern

![Image of tissue section](image)
Few floating cells common in LAMN

Implications of diagnosis

<table>
<thead>
<tr>
<th></th>
<th>LAMN</th>
<th>Mucinous adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN metastasis</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Hematogenous spread</td>
<td>Rare</td>
<td>Can occur</td>
</tr>
<tr>
<td>Peritoneal metastasis</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Treatment</td>
<td>Follow-up imaging</td>
<td>Rt hemicolecotomy - Systemic chemo if needed</td>
</tr>
</tbody>
</table>
Grade

- By definition, LAMN is low grade
- Focal or diffuse high grade changes in tumors which architecturally resemble LAMN
  - No destructive invasion or desmoplasia

High grade appendiceal mucinous neoplasm (HAMN)

- HAMN is not part of WHO 2010 classification
- Included: AJCC 8th edition
  - CAP protocol (2018 version)

HAMN: rare tumor

- Architecture like LAMN, no destructive invasion or desmoplasia
- Focal or diffuse high grade cytologic atypia
High grade features: cribriform growth pattern

HAMN: high grade features, no destructive invasion

LAMN: staging

- WHO 2010: Low grade carcinoma
- AJCC and CAP: LAMN should be staged
**LAMN: staging challenges**

- Erroneous interpretation as mucinous adenocarcinoma
- T category is difficult to apply
  - Depth of cellular or acellular mucin

**LAMN: depth of invasion and recurrence**

<table>
<thead>
<tr>
<th>Study</th>
<th>Confined to MP</th>
<th>Acellular mucin beyond MP</th>
<th>Cellular LAMN beyond MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umetsu/Kakar 2016</td>
<td>0/21</td>
<td>0/5</td>
<td>4/7</td>
</tr>
<tr>
<td>Higa 1973</td>
<td></td>
<td>0/7</td>
<td>4/7</td>
</tr>
<tr>
<td>Misraji 2003</td>
<td>0/27</td>
<td>*</td>
<td>20/31</td>
</tr>
<tr>
<td>Pai 2009</td>
<td>0/16</td>
<td>1/14</td>
<td>21/27</td>
</tr>
<tr>
<td>Yantiss 2009</td>
<td>-</td>
<td>1/44**</td>
<td>2/10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0/64</td>
<td>2/70 (3%)</td>
<td>51/82 (62%)</td>
</tr>
</tbody>
</table>

**LAMN staging: AJCC 8th edition**

<table>
<thead>
<tr>
<th>Category</th>
<th>Change/update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis (LAMN)</td>
<td>LAMN extending into muscularis propria, but not beyond it</td>
</tr>
<tr>
<td>T1, T2</td>
<td>Not applicable to LAMN</td>
</tr>
</tbody>
</table>
| T3        | Cellular LAMN into subserosa?
|           | Acellular mucin into subserosa |
| T4a       | Involvement of serosal surface
|           | Cellular LAMN or acellular mucin |
LAMN: Acellular mucin on serosal surface

Based on limited data
Risk of overtreatment
Pathology report:
"Acellular mucin on serosal surface has a very low risk of recurrence, and categorization of this finding as T4a is based on limited data."

LAMN: Acellular mucin as T4a

LAMN

Elements in pathology reporting
- Submit the entire appendix
- Extent of disease: both cellular and acellular mucin (T category)
- Margin assessment
- Absence of high risk features:
  No high grade cytology or complex growth
  No destructive invasion or desmoplasia
**LAMN**

Do not use obsolete terms
- Mucocele
- Mucinous cystadenoma

**HAMN**

Elements in pathology reporting
- Extent of high grade changes
- Use mucinous adenocarcinoma staging scheme
  - Outcome may be similar to mucinous AC?

AJCC, 8th Edition
Misdraji, AJSP 2003

**Peritoneal involvement**

- Terminology
- Grading
- Treatment
**Pseudomyxoma peritonei**

- Mucinous ascites
- Omental cake
- Mucin accumulation in peritoneum due to involvement by mucinous neoplasm

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**Peritoneal involvement**

<table>
<thead>
<tr>
<th>Low grade</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMN with peritoneal involvement, or Mucinous adenocarcinoma, low grade with peritoneal involvement</td>
<td>Mucinous adenocarcinoma, high grade with peritoneal involvement</td>
</tr>
<tr>
<td>Mucinous carcinoma peritonei, low grade</td>
<td>Mucinous carcinoma peritonei, high grade</td>
</tr>
<tr>
<td>Disseminated peritoneal adenomucinosis (DPAM)</td>
<td>Peritoneal mucinous adenocarcinoma (PMAC)</td>
</tr>
</tbody>
</table>

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**Appendix shows LAMN**

- LAMN with peritoneal involvement
- Include synonyms in a comment

**Appendix: no LAMN or not known**

- Mucinous carcinoma peritonei, low grade
- Mucinous adenocarcinoma, low grade
**Peritoneal involvement**

<table>
<thead>
<tr>
<th>Primary sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Appendix</td>
</tr>
<tr>
<td>• Colorectum</td>
</tr>
<tr>
<td>• Ovary</td>
</tr>
<tr>
<td>• Pancreas</td>
</tr>
</tbody>
</table>

**High grade**

- Mucinous adenocarcinoma, high grade with peritoneal involvement
- Mucinous carcinoma peritonei, high grade
- Peritoneal mucinous adenocarcinoma (PMAC)

**Grading of peritoneal disease**

**WHO 2010**

- 2-tier scheme
  - Low grade
  - High grade

**Criteria**

- Cytologic atypia
- Architecture

**High grade**

- Complex growth
- Stratification
- Loss of polarity
- Prominent nucleoli
- Frequent mitoses
- Signet ring cells
Grading of peritoneal disease

<table>
<thead>
<tr>
<th>WHO 2010</th>
<th>AJCC 7th edition/CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-tier scheme</td>
<td></td>
</tr>
</tbody>
</table>
- Low grade |
- High grade |
| 3-tier scheme |
- Well-differentiated (G1) |
- Moderately differentiated (G2) |
- Poorly differentiated (G3) |

Criteria
- Cytologic atypia
- Architecture

No defined criteria
- Extent of gland formation not applicable to mucinous tumors

<table>
<thead>
<tr>
<th>Study</th>
<th># of cases</th>
<th>Grading scheme</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronnett (2001)</td>
<td>109</td>
<td>DPAM PMCA-I/D PMCA</td>
<td>75% 50% 14%</td>
</tr>
<tr>
<td>Smeenk (2007)</td>
<td>103</td>
<td>DPAM PMCA-I PMCA</td>
<td>75% 42% 0%</td>
</tr>
<tr>
<td>Guo (2012)</td>
<td>92</td>
<td>DPAM PMCA-I/D PMCA</td>
<td>80% 67% 50%</td>
</tr>
<tr>
<td>Shetty (2012)</td>
<td>211</td>
<td>PMP1 PMP2 PMP3</td>
<td>86% 63% 32%</td>
</tr>
<tr>
<td>Davison (2014)</td>
<td>151</td>
<td>G1 G2 G3</td>
<td>91% 61% 23%</td>
</tr>
<tr>
<td>NCDB database</td>
<td>3105</td>
<td>Well differentiated Moderately differentated Poorly differentiated</td>
<td>57% 32% 11%</td>
</tr>
</tbody>
</table>

Gestalt grading scheme

- Looks good: G1
- Looks bad: G3
- All others: G2
**AJCC 8th edition/CAP**
*(modified Davison scheme)*

**G1**
- Low grade cytologic atypia (similar to LAMN)
- Includes acellular mucin
- Cellularity <20%
- No destructive invasion of implants

**G2**
- Mix of low and high grade cytologic atypia, or diffuse high grade cytologic atypia
- Architectural complexity
- Destructive invasion of implants
- Cellularity >20%

**G3**
- Signet ring cells infiltrating the stroma
- Poorly differentiated adenocarcinoma component

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**Invasive implants**
- Mucinous tumors on visceral organs like liver, colon etc. not sufficient
- Destructive invasion and desmoplasia

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**Grading parameters**
- Cytoarchitectural atypia
- Cellularity
- Invasive implants
- Signet ring cells
Peritoneum: signet ring cell carcinoma

Pseudo-signet ring cells

Signet ring cells in grading

- >10% cutoff has been suggested for G3 designation (not specified in AJCC)
- Disregard cells in mucin resembling signet ring cells
- Consider only if infiltrating signet ring cells in stroma

Sirintrapun, Hum Pathol 2014
Davison, Mod Pathol 2014
Challenges in grading

• Invasive implants
• Signet ring cells
• Small or borderline G2 component
• Discrepant grading in appendix and peritoneum

Challenges in grading

Small or borderline G2 component
• Significance unclear
• Descriptive report stating that there is a minor G2 component

Challenges in grading

Discrepant grade in appendix and peritoneum
• Uncommon
• Higher grade peritoneal disease generally drives prognosis
### AJCC 8th: M categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Acellular mucin with disseminated peritoneal involvement</td>
</tr>
<tr>
<td>M1b</td>
<td>Peritoneal mucinous deposits containing tumor cells</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to sites other than peritoneum</td>
</tr>
</tbody>
</table>

### Stage: Definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>Any T or N, M1a (acellular mucin) Any T or N, M1b (G1)</td>
</tr>
<tr>
<td>IVb</td>
<td>Any T or N, M1b (G2, G3)</td>
</tr>
<tr>
<td>IVc</td>
<td>Any T or N, M1c (Any G)</td>
</tr>
</tbody>
</table>

### Grade: impact on treatment

<table>
<thead>
<tr>
<th>Stage IVa M1a: acellular mucin M1b: G1 tumors</th>
<th>Stage IVb M1b: G2, G3 tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined peritoneal surgery (tumor debulking) with HIPEC (hyperthermic intraperitoneal chemotherapy)</td>
<td>Role of surgery and HIPEC controversial</td>
</tr>
<tr>
<td>Systemic chemotherapy not useful</td>
<td>Systemic chemotherapy</td>
</tr>
</tbody>
</table>

### HIPEC: Hot chemotherapy leads to hot debate

Debate at ASCO meeting
- ‘Heating drugs makes them more effective’
- ‘Precious little data that heated chemotherapy does anything’
LAMN Tis with peritoneal disease

- LAMN confined to muscularis propria (Tis) but with peritoneal disease
- TisN0M1: does not make sense
- Explanations:
  - Not entirely submitted
  - Defect has 'sealed'
- Suggestion: pTxN0M1

Peritoneal involvement: summary

- Use appropriate terminology
- Include synonymous terms in report
- Use 3-tier grading scheme (AJCC 8th edition)
- Uncommon situations
  - Grade discrepancy: appendix and peritoneum
  - Minor component of higher grade

Goblet cell carcinoid

- Terminology
- Grading and staging
- Important elements for reporting
## Terminology

- Pure GCC
- GCC with adenocarcinoma
- GCC with well-differentiated neuroendocrine tumor

## Goblet cell carcinoid

- Primarily in appendix
- Rare reports: colon, ampulla

**Unique features**

- Recapitulates the crypts (crypt cell adenocarcinoma)
- Dual features
  - Exocrine: goblet cells, mucin
  - Endocrine: NET-like areas, IHC, EM

## Pure goblet cell carcinoid
Pure goblet cell carcinoid

- Crypt-like clusters of ‘goblet cells’
- No large irregular clusters or sheets
- Cytologic atypia mild
- Mitoses rare
- No desmoplasia or destructive invasion

GCC: single filing in muscularis propria

GCC: small tubules with minimal atypia
GCC: perineural and vascular invasion

GCC: extracellular mucin pools

GCC with adenocarcinoma

Variety of terms
- Adenocarcinoma ex GCC (Tang scheme)
- Mixed GCC-adenocarcinoma
- Crypt cell adenocarcinoma
GCC with adenocarcinoma

- Type A: Pure GCC
- Adenocarcinoma ex GCC, type B
  - Loss of cohesive groups
  - Large irregular clusters
  - More cytologic atypia
- Adenocarcinoma ex GCC, type C
  - Poorly differentiated
  - Diffuse single cells or sheets of signet ring cells

Tang, AJSP 2008

GCC with AC: irregular clusters (type B)

GCC with well-diff AC (type B)
Terminology

• Goblet cell carcinoid
• Mixed GCC-adenocarcinoma
  - Proportion of adenocarcinoma
    <25%, 25-50%, >50%
  - Subtype and differentiation

Clinical impact

Pure GCC vs. mixed GCC-AC
• GCC-adenocarcinoma have worse outcome, treatment largely similar
• Rt. hemicolecotomy
  ?GCC limited to submucosa
• Adjuvant chemotherapy especially if LN+ or peritoneal spread
• Possible prophylactic oophorectomy

Taggart, Arch Path Lab Med 2013
Wen/Kakar, Hum Pathol 2017
**Mixed GCC-adenocarcinoma**

- WHO 2010 recommended term ‘mixed adenoneuroendocrine carcinoma’ should not be used
- Can be misinterpreted as neuroendocrine carcinoma (NEC)
- Platinum-based chemotherapy used in NEC, but not in GCC

**Common errors**

<table>
<thead>
<tr>
<th>Incorrect interpretation</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET staging scheme should be used for GCC</td>
<td>41%</td>
</tr>
<tr>
<td>Ki-67 necessary for grading</td>
<td>43%</td>
</tr>
<tr>
<td>Oncologists interpreted mixed GCC-AC as poorly differentiated NEC</td>
<td>2 cases</td>
</tr>
</tbody>
</table>

Wen/Kakar, Hum Pathol (in press)

**Goblet cell carcinoid**

- GCC: pattern of spread like an adenocarcinoma
- Genetic changes
  - No KRAS mutation
  - p53, APC mutation rare
  - Mutations in chromatin remodeling genes

Wen/Kakar, USCAP 2017
Terminology

Next WHO (if I were to write it)

• Goblet cell carcinoma (GCC)
• Grading scheme
  - Grade 1: Pure GCC
  - Grade 2: GCC with atypia or areas with well to moderately differentiated adenocarcinoma
  - Grade 3: GCC with signet ring cell carcinoma or poorly differentiated adenocarcinoma

48/F with history of colon adenocarcinoma in polyp
Oophrectomy for tumor
• Use appropriate terminology
• Comment
  - State that this is not a NET or NEC
  - Include commonly used synonyms
• Do not grade based on mitoses/Ki-67 index
• Staging scheme for adenocarcinoma, not NET
• Do not use the adenoneuroendocrine carcinoma