Appendiceal GCC and LAMN
Navigating the Alphabet Soup in the Appendix

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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
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>Destructive invasion</td>
</tr>
<tr>
<td>-No desmoplasia or</td>
<td>-Complex growth pattern</td>
</tr>
<tr>
<td>destructive invasion</td>
<td>-Angulated infiltrative glands or single cells</td>
</tr>
<tr>
<td></td>
<td>-Desmoplasia</td>
</tr>
<tr>
<td></td>
<td>-Tumor cells floating in mucin</td>
</tr>
</tbody>
</table>

WHO 2010
Davison, Mod Pathol 2014
Carr, AJSP 2016
Complex growth pattern
Angulated infiltrative glands, desmoplasia
Tumor cells in extracellular mucin
Few floating cells common in LAMN
Few floating cells common in LAMN
## Implications of diagnosis

<table>
<thead>
<tr>
<th>LAMN</th>
<th>Mucinous adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN metastasis</td>
<td>Rare</td>
</tr>
<tr>
<td>Hematogenous spread</td>
<td>Rare</td>
</tr>
<tr>
<td>Peritoneal metastasis</td>
<td>Common</td>
</tr>
<tr>
<td>Treatment</td>
<td>Follow-up imaging</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)

Carr, AJSP 2016: Peritoneal Surface Oncology Group International (PSOGI)
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>Misdraji 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>
<tr>
<td>T3</td>
<td>Cellular LAMN into subserosa</td>
</tr>
<tr>
<td></td>
<td>?Acellular mucin into subserosa</td>
</tr>
<tr>
<td>T4a</td>
<td>Involvement of serosal surface</td>
</tr>
<tr>
<td></td>
<td>Cellular LAMN or acellular mucin</td>
</tr>
</tbody>
</table>
LAMN: Acellular mucin on serosal surface
LAMN: Acellular mucin as T4a

• 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

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
Elements in pathology reporting

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

HAMN

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
<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>
## Peritoneal involvement

### Low grade

<table>
<thead>
<tr>
<th>Condition</th>
<th>Appendix shows LAMN</th>
<th>Appendix: no LAMN or not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMN with peritoneal involvement</td>
<td>• LAMN with peritoneal involvement</td>
<td>• Mucinous carcinoma peritonei, low grade</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma, low grade with peritoneal involvement</td>
<td>• Include synonyms in a comment</td>
<td>• Mucinous adenocarcinoma, low grade</td>
</tr>
<tr>
<td>Mucinous carcinoma peritonei, low grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated peritoneal adenomucinosis (DPAM)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Peritoneal involvement

**High grade**

<table>
<thead>
<tr>
<th>Mucinous adenocarcinoma, high grade with peritoneal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous carcinoma peritonei, high grade</td>
</tr>
<tr>
<td>Peritoneal mucinous adenocarcinoma (PMAC)</td>
</tr>
</tbody>
</table>

**Primary sites**

- Appendix
- Colorectum
- Ovary
- Pancreas
## Grading of peritoneal disease

### WHO 2010

<table>
<thead>
<tr>
<th>2-tier scheme</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>- Cytologic atypia</td>
</tr>
<tr>
<td>High grade</td>
<td>- Architecture</td>
</tr>
</tbody>
</table>

- 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>3-tier scheme</td>
</tr>
<tr>
<td>- Low grade</td>
<td>- Well-differentiated (G1)</td>
</tr>
<tr>
<td>- High grade</td>
<td>- Moderately differentiated (G2)</td>
</tr>
<tr>
<td></td>
<td>- Poorly differentiated (G3)</td>
</tr>
<tr>
<td>Criteria</td>
<td>No defined criteria</td>
</tr>
<tr>
<td>- Cytologic atypia</td>
<td>- Extent of gland formation not applicable to mucinous tumors</td>
</tr>
<tr>
<td>- Architecture</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td># of cases</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Ronnett (2001)</td>
<td>109</td>
</tr>
<tr>
<td>Smeenk (2007)</td>
<td>103</td>
</tr>
<tr>
<td>Guo (2012)</td>
<td>92</td>
</tr>
<tr>
<td>Shetty (2013)</td>
<td>211</td>
</tr>
<tr>
<td>Davison (2014)</td>
<td>151</td>
</tr>
<tr>
<td>NCDB database</td>
<td>3105</td>
</tr>
</tbody>
</table>
Gestalt grading scheme

- Looks good: G1
- Looks bad: G3
- All others: G2
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Low grade cytologic atypia (similar to LAMN)&lt;br&gt;- Includes acellular mucin&lt;br&gt;- Cellularity &lt; 20%&lt;br&gt;- No destructive invasion of implants</td>
</tr>
<tr>
<td>G2</td>
<td>Mix of low and high grade cytologic atypia, or diffuse high grade cytologic atypia&lt;br&gt;- Architectural complexity&lt;br&gt;- Destructive invasion of implants&lt;br&gt;- Cellularity &gt; 20%</td>
</tr>
<tr>
<td>G3</td>
<td>Signet ring cells infiltrating the stroma&lt;br&gt;- Poorly differentiated adenocarcinoma component</td>
</tr>
</tbody>
</table>

**AJCC 8th edition/CAP (modified Davison scheme)**

Davison, Mod Pathol 2014
Grading parameters

• Cytoarchitectural atypia
• Cellularity
• Invasive implants
• Signet ring cells
Invasive implants

- Mucinous tumors on visceral organs like liver, colon etc. are not sufficient
- Destructive invasion and desmoplasia
LAMN: Noninvasive ovarian implant
LAMN: Noninvasive ovarian implant
LAMN: Invasive implant

Davison, Mod Pathol 2014
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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>Any T or N, M1a (acellular mucin)</td>
</tr>
<tr>
<td></td>
<td>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</th>
<th>Stage IVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a: acellular mucin</td>
<td>M1b: G2, G3 tumors</td>
</tr>
<tr>
<td>M1b : G1 tumors</td>
<td>Role of surgery and HIPEC controversial</td>
</tr>
</tbody>
</table>

- Combined peritoneal surgery (tumor debulking) with HIPEC (hyperthermic intraperitoneal chemotherapy)
- Systemic chemotherapy not useful
- Systemic chemotherapy
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: pTxE0M1
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 dingle cells or sheets of signet ring cells

Tang, AJSP 2008
GCC with AC: irregular clusters (type B)
GCC with well-diff AC (type B)
GCC with poorly-diff adenocarcinoma (type C)
Terminology

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

Taggart, Arch Path Lab Med 2013
Wen/Kakar, Hum Pathol 2017
Clinical impact

Pure GCC vs. mixed GCC-AC

- GCC-adenocarcinoma have worse outcome, treatment largely similar
- Rt. hemicolecetomy
  - GCC limited to submucosa
- Adjuvant chemotherapy especially if LN+ or peritoneal spread
- Possible prophylactic oophorectomy
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
<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
Ki67, typically <20%, not necessary for diagnosis
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
GCC: summary

- 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