Appendiceal GCC and LAMN
Navigating the Alphabet Soup in the Appendix

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Syllabus
• Summary provided
• Complete presentation
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Ludwig Wittgenstein
• Austrian born philosopher
• Famous treatise *Tractatus*
• Logical structure and limitations of language
• Meaning of words as used in a language

Appendiceal tumors
Low grade appendiceal mucinous neoplasm
• Peritoneal spread, chemotherapy
• 5-year survival 50-60%
• 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 muscularis mucosa

LAMN vs. adenoma

- Intactness of muscularis mucosa
- No mucin (cellular or acellular) in the appendiceal wall
- In borderline cases, go with LAMN

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>Pushing invasion</td>
<td>Destructive invasion</td>
</tr>
<tr>
<td>- No desmoplasia or destructive invasion</td>
<td>- Complex growth pattern</td>
</tr>
<tr>
<td></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
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></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 (2017 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

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
  - Correlation of depth with outcome

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>0/7</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>Pal 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>T4a</td>
<td>Involvedent 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
- Entire appendix was not submitted
- Risk of overtreatment
- Pathology report:
  “Acellular mucin on serosal surface has a low risk of recurrence, and categorization of this finding as T4a is based on limited data. Treatment options should be evaluated in light of this information.”

**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
Misraji, 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**

**Pseudomyxoma peritonei**

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

**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

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

**Primary sites**
- Appendix
- Colorectum
- Ovary
- Pancreas

Grading of peritoneal disease

**WHO 2010**
- 2-tier scheme
  - Low grade
  - High grade
- Criteria
  - Cytologic atypia
  - Architecture

**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>
<tr>
<td>- Low grade</td>
<td></td>
</tr>
<tr>
<td>- High grade</td>
<td></td>
</tr>
<tr>
<td>3-tier scheme</td>
<td></td>
</tr>
<tr>
<td>- Well-differentiated (G1)</td>
<td></td>
</tr>
<tr>
<td>- Moderately differentiated (G2)</td>
<td></td>
</tr>
<tr>
<td>- Poorly differentiated (G3)</td>
<td></td>
</tr>
<tr>
<td>Criteria</td>
<td></td>
</tr>
<tr>
<td>- Cytologic atypia</td>
<td></td>
</tr>
<tr>
<td>- Architecture</td>
<td></td>
</tr>
<tr>
<td>No defined criteria</td>
<td></td>
</tr>
<tr>
<td>Extent of gland formation not applicable to mucinous tumors</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 (2012)</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

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

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

**Challenges in grading**

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

Davison, Mod Pathol 2014
Challenges in grading

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

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

LAMN, T4a

Peritoneum: signet ring cell carcinoma

Pseudo-signet ring cells
Challenges in grading
Signet ring cell component
• >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

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>
</tbody>
</table>

Combined peritoneal surgery (tumor debulking) with HIPEC (hyperthermic intraperitoneal chemotherapy) | Role of surgery and HIPEC controversial |
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’

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>

<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>
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

Diagnosis of GCC

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

Ki67, typically <20%, not necessary for diagnosis
GCC: single filing in muscularis propria

GCC: perineural and vascular invasion

GCC: extracellular mucin pools

GCC: small tubules with minimal atypia
GCC with adenocarcinoma

Adenocarcinoma component
• GCC-like but with higher cytologic and architectural atypia
• Adenocarcinoma
  Well-differentiated
  Moderately-differentiated
  Poorly differentiated

GCC with adenocarcinoma

• Cytologically atypical cells
• Loss of cohesive clusters
  -Large irregular clusters
  -Single cell infiltration
  -Frank SRC: sheets of signet ring cells

GCC with AC: irregular clusters

GCC with AC: irregular clusters
Terminology

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

Taggart, Arch Path Lab Med 2013
Wen/Kakar, Hum Pathol (in press)
### Other terminology

**Tang, AJSP 2008**

<table>
<thead>
<tr>
<th>Adenocarcinoma ex GCC, signet ring cell type (Type B)</th>
<th>Adenocarcinoma ex GCC, poorly differentiated (Type C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Irregular large clusters, but lack of confluent sheets of cells</td>
<td>-Confluent sheets of signet ring cells</td>
</tr>
<tr>
<td>-Discohesive single file or single cell infiltrating pattern</td>
<td>-Poorly differentiated adenocarcinoma</td>
</tr>
<tr>
<td>-Significant cytologic atypia</td>
<td>-Undifferentiated carcinoma</td>
</tr>
<tr>
<td>-Desmoplasia</td>
<td>-Stage IV: 5-yr survival 0%</td>
</tr>
<tr>
<td>-Stage IV: 5-yr survival 38%</td>
<td></td>
</tr>
</tbody>
</table>

- Irregular clusters vs sheets is difficult
- No provision for well/mod diff adenocarcinoma
- Few single cells: not clear

---

### GCC with adenocarcinoma

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

### My approach

**Mixed GCC-adenocarcinoma**
- Approximate proportion of each
- Equivalent term from Tang scheme in the comment if possible
- Ki-67 not necessary, may provide prognostic information
- Clarify that this is not a neuroendocrine tumor; treat like adenocarcinoma
**Clinical impact**

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

**Challenges in GCC**

- Goblet cell ‘carcinoid’
- GCC or GCC-AC is not a neuroendocrine carcinoma

**Goblet cell ‘carcinoid’**

- Can be misinterpreted as neuroendocrine tumor
- GCC is not grade like NET: Ki-67 index is not required
- GCC is staged and treated like adenocarcinoma, not like NET

**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
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

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)

GCC: summary

- Use appropriate terminology
- Comment
  - State that this is not a neuroendocrine tumor or neuroendocrine carcinoma
  - Include commonly used synonyms
- Do not grade based on Ki-67 index
- Avoid using the term adeno-neuroendocrine carcinoma
- Use staging scheme for adenocarcinoma, not NET
### Tumor Board list

<table>
<thead>
<tr>
<th>Date</th>
<th>Sex</th>
<th>Last Name</th>
<th>First Name</th>
<th>DX</th>
<th>AM</th>
<th>PK</th>
<th>KI-67</th>
<th>Probable</th>
<th>Probable</th>
<th>Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/3/2018</td>
<td>M</td>
<td>Ludwig</td>
<td>Wittgenstein</td>
<td>GCC: summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5/10/2018</td>
<td>M</td>
<td>Ludwig</td>
<td>Wittgenstein</td>
<td>GCC: summary</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/17/2018</td>
<td>M</td>
<td>Ludwig</td>
<td>Wittgenstein</td>
<td>GCC: summary</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/24/2018</td>
<td>M</td>
<td>Ludwig</td>
<td>Wittgenstein</td>
<td>GCC: summary</td>
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<td></td>
</tr>
<tr>
<td>5/31/2018</td>
<td>M</td>
<td>Ludwig</td>
<td>Wittgenstein</td>
<td>GCC: summary</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Ludwig Wittgenstein

- PhD oral exam
- His book *Tractatus* used as dissertation
- Told the examiners: You’ll never understand it

### GCC: summary

- Use appropriate terminology
- Comment
  - State that this is not a neuroendocrine tumor or neuroendocrine carcinoma
  - Include commonly used synonyms
- Do not grade based on Ki-67 index
- Avoid using the term adeno-neuroendocrine carcinoma
- Use staging scheme for adenocarcinoma, not NET
**GCC: summary**

- Use appropriate terminology
- Comment
  - State that this is not a neuroendocrine tumor or neuroendocrine carcinoma
  - Include commonly used synonyms
- Do not grade based on Ki-67 index
- Avoid using the term adeno-neuroendocrine carcinoma
- Use staging scheme for adenocarcinoma, not NET
The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: An analysis of the National Cancer Data Base.
WHO 2010
Appendiceal adenoma: intact muscularis mucosa
LAMN: Low grade carcinoma, rests on fibrous stroma, obliteration of MM

Prophylactic HIPEC in CRC?
Concept:
Some CRC have a high risk of developing peritoneal carcinomatosis,
or e.g. T4 tumors, pre-or intraop. tumor rupture, minimal local PC
→ "prophylactic" HIPEC during primary surgery helpful?
• One-armed study (n=22) with matched-pair analysis:
  - 5-year incidence of developing PC: 9% vs. 43% (p=0.004)
  - 5-year overall survival: 81% vs. 70% (p=0.04)

Better outcome with neoadjuvant chemotherapy
Inclusion of only a subgroup of 3 studies with appropriate data

• **Ludwig Wittgenstein**

  - An aim of the *Tractatus* is to reveal the relationship between language and the world: what can be said about it, and what can only be shown. Wittgenstein argues that language has an underlying logical structure, a structure that provides the limits of what can be said meaningfully.

  - Wittgenstein