Select problems in cystic pancreatic lesions

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Disclosure

Five Prime Therapeutics – shareholder
Adicet Bio – shareholder
Bristol-Meyer Squibb – advisory board

Pancreatic cystic lesions

1. Injury-related and inflammation-related cysts (30%)
   Pseudocyst, paraduodenal pancreatitis, hydatid cyst
2. Miscellaneous /congenital cyst (<5%)
   Epidermoid, lymphoepithelial, or duplication cysts
3. Neoplastic cysts (60%)
   Pancreatic intraepithelial neoplasia, “retention cyst”, “simple mucinous cyst”
   Intraductal papillary mucinous neoplasm, including oncocytic variant,
   intraductal tubulopapillary neoplasm
   Mucinous cystic neoplasm
   Serous cystic neoplasm, acinar cystadenoma, lymphangioma
   Solid pseudopapillary neoplasm
   Solid neoplasms with cystic change or intraductal spread of invasive carcinoma: pancreatic ductal adenocarcinoma, neuroendocrine neoplasm, acinar cell carcinoma, pancreatoblastoma

Intraductal papillary mucinous neoplasm

Outline

- Assessing and reporting margin status
- Utility of molecular markers
- Uncommon cystic lesions

Clinical History - case 1

- 60 year old man with a mass in the pancreatic head
- Surgeon sends Whipple resection specimen
- Requests intraoperative diagnosis of pancreatic neck resection margin
Question 1.
Is the pancreatic neck margin:

a. malignant?
   - Invasive adenocarcinoma
b. preneoplastic?
   - Pancreatic intraepithelial neoplasia (PanIN)
   - Intraductal papillary mucinous neoplasm (IPMN)
c. benign?
   - Chronic pancreatitis
   - Normal

Question 2.
Surgical management impact of diagnosis?

Not infiltrative
Lobulocentric

Mucinous epithelium without cytologic atypia

Baltimore Consensus Meeting

- From three-tiered to two-tiered classification system for
  - Pancreatic intraepithelial neoplasia (PanIN)
  - Intraductal papillary mucinous neoplasm (IPMN)
  - Mucinous cystic neoplasm (MCN)
- Clinically relevant diagnostic options
  - Low-grade or high-grade PanIN
  - IPMN, low-grade or high-grade
  - MCN, low-grade or high-grade


Not all IPMN cysts have tall finger-like papillae
Grossly identifiable >1 cm cyst

Consequence of PanIN or IPMN at margin?

- If patient has invasive cancer
  - Only PanIN at margin, regardless of grade, does not affect survival
- If patient does not have invasive cancer
  - High-grade PanIN at margin may warrant additional surgery
  - IPMN less clear
    - All patients require careful clinical follow-up after resection
Pancreatic neck margin diagnosis – case 1

• Low-grade mucinous epithelium (low-grade PanIN or low-grade IPMN)

Alternatively

• No invasive carcinoma or high grade dysplasia

Pancreatic adenocarcinoma with cystic degeneration

Pancreatic duct diameter >1 cm

Dilated and partially denuded main duct with low grade mucinous epithelium

IPMN or PanIN?
Level 1

Atypical glands adjacent to muscular blood vessel

Level 3 - Large dilated glands
Invasive carcinoma in IPMN

- Attempt to document relationship
  - Distinguish “derived from” (arising in area of) IPMN versus “concomitant” (not contiguous with) IPMN
    - Sample entire lesion
    - Liberally sample uninvolved pancreas
    - Verify continuity or discontinuity
- Measure size of invasive component independent of non-invasive component

Invasive adenocarcinoma and concomitant IPMN

Adenocarcinoma arising in MCN
AJCC 8th edition cancer staging manual
Pancreas exocrine

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>High grade dysplasia</td>
</tr>
<tr>
<td>T1 ≤ 2 cm</td>
<td></td>
</tr>
<tr>
<td>T1a ≤ 0.5 cm</td>
<td></td>
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<tr>
<td>T1b &gt; 0.5 cm and &lt; 1 cm</td>
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<tr>
<td>T1c 1-2 cm</td>
<td></td>
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<tr>
<td>T2 &gt; 2 cm and ≤ 4 cm</td>
<td></td>
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<tr>
<td>T3 &gt; 4 cm</td>
<td></td>
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<tr>
<td>T4</td>
<td>Tumor involves celiac axis, superior mesenteric artery and/or common hepatic artery, irrespective of size</td>
</tr>
</tbody>
</table>

If multifocal invasive adenocarcinoma (1.5 cm, 1.1 cm, and 0.5 cm) derived from IPMN, how do you report the pT stage?

A. pT1c (m) based on largest focus of 1.5 cm
B. pT2 (m) based on sum (3.1 cm)
C. pT3 (m) based on entire span of tumor (4.3 cm)

Clinical History - case 2

- 60 year old man with pancreatic head mass
- Whipple resection specimen
- Gross examination reveals a 1.4 cm unilocular cyst

Grossing practice alteration

- To determine invasive tumor size
  - Take a full cross-section of largest dimension of the grossly identifiable tumor flanked by non-tumorous pancreatic parenchyma
  - Verify by histologic examination
Two questions:
1. Any helpful tools?
2. Clinical impact?

Molecular markers of pancreatic cysts

- **IPMN (n=96)**
  - KRAS (78%), GNAS (58%), RNF43 (38%), TP53 (9%)
  - CTNNB1 (6%)
- **MCN (n=12)**
  - KRAS (50%), RNF43 (8%)
- **SCA (n=12)**
  - VHL (42%)
- **SPN (n=10)**
  - CTNNB1 (100%), PIK3CA (20%), TP53 (10%)

* Nearly all PanIN have KRAS mutation


Cysts with mucinous lining

<table>
<thead>
<tr>
<th></th>
<th>Gross</th>
<th>Size</th>
</tr>
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<tbody>
<tr>
<td>PanIN</td>
<td>Microscopic</td>
<td>&lt; 0.5 cm</td>
</tr>
<tr>
<td>IPMN</td>
<td>Macroscopic</td>
<td>&gt; 1 cm</td>
</tr>
</tbody>
</table>

Diagnostic options:
- **Incipient IPMN**, if long finger-like papillae, villous intestinal or oncocytic differentiation, or GNAS mutation
- **Intraductal neoplasm**, 0.7 cm, lined by low-grade gastric type epithelium; see comment

Pancreas 2005;31:344-349
“Simple mucinous cyst”

- Other terms
  - “Mucinous non-neoplastic cyst”, “cystic mucinous duct lesion”
    - KRAS mutations (55%)
    - High-grade dysplasia (8%)
- Features
  - Macroscopic cyst (> 1 cm)
  - Communication to ductal system (8%)
  - No ovarian stroma
  - Non-papillary gastric-type mucinous epithelium (MUC5AC and/or MUC6 positive)
- Pathogenesis and natural course is unknown; still needs to be studied

Clinical History - case 3

- 55 year old woman with solid/cystic mass in the pancreatic head
- Whipple resection specimen
What one diagnostic stain do you perform?

A. Synaptophysin  B. Cytokeratin 7  C. Trypsin  D. Beta-catenin  E. GLUT-1

Rare cystic variant acinar cell carcinoma
“Acinar cell cystadenocarcinoma”
Intraductal tubulopapillary neoplasm

- Intraductal growth
  - Circumscribed nodules of back-to-back tubular glands
  - Cuboidal cells with minimal to moderate eosinophilic to amphophilic cytoplasm and moderate to marked nuclear atypia
- Immunoreactive for
  - CK7 (100%), MUC1 (88%), MUC6 (68%), and focal/rarely lineage markers
- Genetics
  - Absence of KRAS and BRAF mutations
Distinguishing features

<table>
<thead>
<tr>
<th></th>
<th>Architecture</th>
<th>Cytology</th>
<th>Stain</th>
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</thead>
<tbody>
<tr>
<td>IPMN</td>
<td>Papillary</td>
<td>Can have intracytoplasmic mucin</td>
<td></td>
</tr>
<tr>
<td>IPMN (oncocytic subtype)</td>
<td>Solid or tubular</td>
<td>Abundant granular eosinophilic cytoplasm</td>
<td><img src="image1" alt="Image" /></td>
</tr>
<tr>
<td>ITPN</td>
<td>Tubular or cribriform</td>
<td>Cuboidal cells; minimal to moderate eosinophilic to amphophilic cytoplasm</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>Acinar cell carcinoma</td>
<td>Solid with acinar structures</td>
<td>Trypsin and/or chymotrypsin positive</td>
<td><img src="image3" alt="Image" /></td>
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Take home points

• Knowledge of primary cystic pancreatic lesions is still evolving
  – Clinically relevant and “more splitting” to enhance further studies
    • From 3 to 2 tier classification
    • Derived vs concomitant
    • pT stage based on size
  – Less common cystic entities
    • Simple mucinous cyst
    • Acinar cell carcinoma
    • Intraductal tubulopapillary neoplasm