Update on Pancreatic Cystic Lesions

Tamas A Gonda, MD
Division of Digestive and Liver Diseases
Columbia University Medical Center

Pancreatic Cystic Lesions

1) Pseudocyst
   no lining, thus no malignant potential

2) Cystic neoplasm:
   • Non-mucinous
     – Serous cystadenoma
   • Mucinous
     – Mucinous cystic neoplasm (MCN)
     – IPMN

3) Solid tumors with cystic degeneration
   – Cystic pancreatic endocrine tumor

MGH 1978-2000
**Pancreatic Pseudocysts**

- Fluid collection > 4 weeks old surrounded by a defined wall
- Occur after acute pancreatitis in 10% of cases
- Can resolve without intervention in up to 40% of cases
- Old surgical teaching of “6 week and 6 cm” rule no longer applies
- Depending on size and location can cause complications:
  - Pain, obstruction, fistula
  - Spontaneous infection
  - Digestion of adjacent vessel → pseudoaneurym → hemosuccus pancreaticus

Bradley EL, Arch Surg 1993
Cameron JL, Acute pancreatitis 1983
O'Malley VP, Am J Surg 1985

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**Pancreatic Pseudocysts**

- Things to consider in a symptomatic, febrile or enlarging pseudocyst before deciding on method of drainage:
  - Location
  - Loculation
  - Mature wall
  - Debris and necrosis
  - Presence of a pseudo-aneurysm (considered an absolute contraindication unless embolization performed first)

- Multi-disciplinary approach at Columbia
Pancreatic Pseudocysts

- Endoscopic drainage first performed in 1989
- Studies have reported technical success rates for EUS guided pseudocyst drainage of 84-94%
- Recurrence rates of 3-18%
- Complication includes immediate and delayed bleeding, perforation, secondary infection and stent migration
- Higher complication rates in those with necrosis
- Important to discuss risks/benefits with patients

Cremer M et al Gastrointest Endosc 1989
Baron TH et al Gastrointest Endosc 2002
Varadarajulu S et al Gastrointest Endosc 2008
Pancreatic Pseudocysts

- Previously called serous adenomas, microcystic adenomas
- Women, 7th decade
- Most often found incidentally; more common in body and tail
- Rarely: abdominal pain, jaundice, pancreatitis
- Are benign lesions / malignant transformation exceedingly rare

Fuji H et al Int J Pancreatol 1998

Serous Cystadenomas

- Previously called serous adenomas, microcystic adenomas
- Women, 7th decade
- Most often found incidentally; more common in body and tail
- Rarely: abdominal pain, jaundice, pancreatitis
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Fuji H et al Int J Pancreatol 1998
Serous Cystadenomas

- Multiple small (<1-2 cm) fluid filled micro-cysts
- Dense fibrous septations produce “honeycomb appearance”
- Pathognomonic central “sunburst calcification” seen in only 10%

CT scan

- Swiss cheese-like appearance with external lobulation
- Central calcification
Serous Cystadenomas

EUS

- Pathognomonic honeycomb appearance
- Cytology positive in only 50% (cuboidal glycogen-staining cells without cytologic atypia)

Serous Cystadenocarcinoma

- Very rare
- Six reported cases
- Usually reported as direct invasion into adjacent LNs, structures

Abe et al Am J of Gastro 1998
Matsumoto et al J Clin Gastroenterol 2005
Mucinous Cystic Neoplasms (MCNs)

- Previously called macrocystic adenomas
- Almost exclusively (> 90%) in women (mean age 50 yrs)
- Incidental finding in body and tail of pancreas
- Abdominal pain, DM, pancreatitis, mass, weight loss, jaundice much less common
- Multiple large fluid-filled cavities (each > 1-2 cm) with septations
- Peripheral egg-shell calcification (seen in only 15 %) is specific to MCNs

Mucinous Cystic Neoplasms

- Some have defined MCN only if ovarian-like stroma is present (estrogen and progesterone +)
- Other features:
  - Female gender
  - Body and tail of pancreas
  - Multilocular cyst without communication with ductal system
**Mucinous Cystic Neoplasms**

**CT scan**
- Well-defined cyst in the body of the pancreas with internal septations and few compartments
- Peripheral calcification

**EUS**
- FNA shows viscous fluid
- Elevated tumor markers
  - Accuracy of cyst fluid CEA (79%) significantly greater than that of EUS morphology or cytology
  - Cut-off of 192 ng/ml for differentiating mucinous vs non-mucinous cysts
- Mucinous cuboidal or columnar epithelial cells in 50% (can be confused by contaminant gastric or duodenal epithelial cells)

Sperli C et al Cancer 1996
Brugge WR Gastro 2004
International Consensus Guidelines for Management of MCN of the Pancreas 2006

“Unless there are contraindications for operation, all MCNs should be resected”

Tanaka, M et al, Pancreatology 2006

International Consensus Guidelines for Management of MCN of the Pancreas 2012

Recognize the low prevalence of cancer
Almost no risk of malignancy in <4 cm lesions with no mural nodules

Young patients -> long term surveillance
Location -> easier resection

Overall recommendation: resect all in fit patients
Mucinous Cystadenocarcinoma

- Thick-walled
- Associated mass
- >5 cm
- Malignant cytology
- Older
  - Survival rates for resected mucinous cystadenocarcinomas: variable (50% at 10 yrs to 17% at 5 yrs)

Intraductal Papillary Mucinous Neoplasm (IPMN)

- First described as “mucinous ductal ectasia”
- Villous adenoma of the pancreatic duct
- Initially described in Japan
- Frequency seems to be increasing
- Since the 1990s increasingly reported in the Western world
  - Previously misclassified
  - Widespread use of imaging studies leading to incidental findings
  - Aging population
- Appears to be a true increase in the relative frequency

Ohhashi K Prog Dig Endosc 1982
IPMN

- Characterized by proliferation of neoplastic mucinous cells in pancreatic ducts that often form prominent papillary structures
- Leads to cystic dilatation of the ducts
- Mucin secreting columnar papillary epithelium and distended main pancreatic duct displaying profuse papillary fronds

Kloppel G Hepatogastro 1998
Brugge WR NEJM 2004

IPMN subtypes

Better prognosis;
More common
Unlikely to be associated with invasive carcinoma

Oncocytic – least common but mostly adenoacrcinoma at presentation
IPMN

- Subdivided into three main types:
  - Main duct type (IPMN-MD)
  - Side branch duct type (IPMN-Br)
  - Mixed variant (ie main duct and side branch type)

- Spreads along duct before spreading radially into parenchyma

- Long indolent phase (for decades): subset may have progression to invasive carcinoma

- Better overall outcome than ductal adenocarcinoma

IPMN MD versus IPMN Br

IPMN MD
Prevalence of carcinoma
(57-92%, mean 70%)

IPMN-Br
Prevalence of carcinoma
(6-46%, mean 25%)
IPMN: Risk of malignancy

- Older age at presentation
- Symptomatic pt
- Main duct involvement
- Dilation of PD>10mm
- Presence of mural nodules
- > 3cm size (side branch IPMN)
- Thickened septae in cyst

- Risk of recurrence
  - High if invasive cancer present (60-70%)  
  - Low if adenoma/borderline tumor (<10%)


Multifocal SB IPMN

Cyst size progression

Management based on largest cyst
Overall similar risk of progression to unifocal disease
IPMN

**ERCP**
- Widely patent (gaping or fish-mouth) papilla extruding mucus
- Pancreatogram showing a dilated main duct with a pancreatoscope inserted
- Papillary projections seen during pancreatoscopy

**IPMN: Treatment**
- Surgical resection
  - Only involved part of pancreas is removed
  - Margins examined intra-op with frozen section
  - 5 yr survival 94-100% for benign and non-invasive carcinoma and 31-60% for invasive
- Continued surveillance to assess neoplasm in remnant

Schnelldorger et al Arch Surg 2008
Sugiyama et al J Gastroenterol 2008
Approach to newly discovered Pancreatic Cysts

- Symptoms
- Imaging review – especially helpful for SCA, MD IPMN
- Consider EUS FNA if it will change management or surveillance plan
- Consider ERCP if MD IPMN is a concern; extent of disease is unknown
- Consider mutational analysis is select cases

- Needle based endomicroscopy

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<table>
<thead>
<tr>
<th>Type</th>
<th>Sex Predilection</th>
<th>Peak Decade of Life</th>
<th>% of Cystic Neoplasms</th>
<th>Malignant Potential and Natural History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma</td>
<td>Female</td>
<td>7th</td>
<td>32–39</td>
<td>Resection curative; serious cystadenocarcinoma extremely rare</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>Female</td>
<td>5th</td>
<td>10–45</td>
<td>Resection curative, regardless of degree of epithelial dysplasia; poor prognosis when invasive adenocarcinoma present</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>Equal distribution</td>
<td>6th–7th</td>
<td>21–33</td>
<td>Excellent prognosis for lesions showing only adenomatous and borderline cytologic atypia; poor prognosis when invasive carcinoma present</td>
</tr>
<tr>
<td>Solid pseudopapillary neoplasm</td>
<td>Female</td>
<td>4th</td>
<td>&lt;10</td>
<td>Indolent neoplasm with rare nodal and extranodal metastases; excellent prognosis when completely resected</td>
</tr>
<tr>
<td>Cystic endocrine neoplasm</td>
<td>Equal distribution</td>
<td>5th–6th</td>
<td>&lt;10</td>
<td>Similar to solid neuroendocrine neoplasm</td>
</tr>
<tr>
<td>Ductal adenocarcinoma with cystic degeneration</td>
<td>Slight male predominance</td>
<td>6th–7th</td>
<td>&lt;1</td>
<td>Dismal prognosis, similar to solid adenocarcinoma</td>
</tr>
<tr>
<td>Acinar-cell cystadenocarcinoma</td>
<td>Male</td>
<td>6th–7th</td>
<td>&lt;1</td>
<td>Similar to solid type; aggressive neoplasm with slightly better prognosis than ductal adenocarcinoma</td>
</tr>
</tbody>
</table>

EUS FNA based differential diagnosis

• CEA
  – Mucinous (IPMN, MCN) vs non mucinous (PC, SCA)
  – NO correlation between level and CA risk
• Amylase
  – Communication with PD (PC, IPMN) vs no communication (SCA, MCN)
• Mutational analysis – Kras
  – Marker of mucinous cysts
  – NO clear correlation between malignancy risk
• GNAS mutation
  – Highly specific for IPMN
• VHL mutation
  – Highly specific for SCA

Interpretation of Cyst Fluid Analysis

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<th>Amylase</th>
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<tr>
<td>Serous Cystadenoma (SCA)</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
<td>&gt;192</td>
<td>High</td>
</tr>
<tr>
<td>Mucinous Cystic Neoplasm (MCN)</td>
<td>&gt;182</td>
<td>Low</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Other</td>
<td>Low</td>
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# Molecular Markers in Cyst Diagnosis – predictors of malignancy

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<tr>
<th>SENS</th>
<th>SPEC</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukouka 2012 (2)</td>
<td>90%</td>
<td>46%</td>
<td>97%</td>
</tr>
<tr>
<td>AGA 2015</td>
<td>0%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Elev DNA (1)</td>
<td>77%</td>
<td>66%</td>
<td>87%</td>
</tr>
<tr>
<td>Kras (1)</td>
<td>44%</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>&gt;2 LOH + Kras (1)</td>
<td>50%</td>
<td>96%</td>
<td>86%</td>
</tr>
<tr>
<td>Composite Composite (2)</td>
<td>66% 90%</td>
<td>81% 83%</td>
<td>88% 97%</td>
</tr>
<tr>
<td>GNAS/RNF43/LOH/anne</td>
<td>75%</td>
<td>92%</td>
<td>83%</td>
</tr>
<tr>
<td>Clinical + Molecular (3)</td>
<td>89%</td>
<td>69%</td>
<td>88%</td>
</tr>
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## Expanded Interpretation of Cyst Fluid Analysis

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<td>High</td>
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<td>Other</td>
<td>Low</td>
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<td>No</td>
<td></td>
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</table>
Optical biopsy of cysts

19G FNA needle
Fluoroscein

Confocal Endomicropscoopy - IPMN

Gastric type IPMN with no dysplasia

High grade dysplasia
International Consensus Guidelines for Management of IPMN and MCN of the Pancreas: Algorithm for IPMN-Br

- **Size < 1cm**
  - MRI or thin slice CT
  - In 1 year
  - Size < 1cm
  - Size 1-2 cm

- **Size 1-3cm**
  - EUS and MRCP or ERCP
  - High Risk Stigmata:
    - Mural nodules
    - Dilated Main Duct
    - Positive cytology
  - No
  - MRI or CT
    - 1-2 cm every 6-12 mo
    - 2-3 cm every 3-6 mo

- **Size > 3cm**
  - Resection

Tanaka, M et al, Pancreatology 2006
Updated Recommendation - 2012

Management of pancreatic cysts: AGA vs. Fukuoka

### 2012 International Guideline

- **When to offer surgery in asymptomatic patients**
  - ANY of these features:
    - Positive cytology
    - High risk stigmata
      - 1. Solid component
      - 2. Dilated PD
      - 3. Thickened cyst wall
      - 4. Main duct 5-9 mm
      - 5. Distal PD dilation with atrophy
  - Cyst > 3cm in surgically fit

### 2015 AGA Guideline

- **When to offer surgery in asymptomatic patients**
  - Positive cytology
  - EUS confirmation of TWO or more high risk features

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**Image Description**

- Diagram illustrating decision-making process for surgery based on cyst features.
### Management of pancreatic cysts: AGA vs. Fukuoka

<table>
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<tr>
<th>When to offer EUS</th>
<th>2012 International Guideline</th>
<th>2015 AGA Guideline</th>
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<tr>
<td></td>
<td>ANY worrisome feature present:</td>
<td>TWO or more high risk features:</td>
</tr>
<tr>
<td></td>
<td>- pancreatitis</td>
<td>- dilated main PD</td>
</tr>
<tr>
<td></td>
<td>- cyst &gt;3cm</td>
<td>- mural nodule/solid component</td>
</tr>
<tr>
<td></td>
<td>- Thick, enhancing wall</td>
<td>- cyst &gt;3 cm</td>
</tr>
<tr>
<td></td>
<td>- Main PD &gt;5mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Mural nodule</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Change in caliber of PD with atrophy</td>
<td></td>
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### Surveillance in patients NOT undergoing surgery

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<tr>
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<th>2012 International Guideline</th>
<th>2015 AGA Guideline</th>
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<tr>
<td>Surveillance in patients NOT undergoing surgery</td>
<td>&lt;1 cm Every two years with CT/MRI</td>
<td>&lt;3 cm without one WF Every 2 years and stop after 5 if no change</td>
</tr>
<tr>
<td></td>
<td>1-2 cm Yearly for two years and then lengthen interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3 cm (&gt;3 cm) Every 3-6 months and perhaps lengthen if no change</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• Approach to cystic lesions in the pancreas
  – 1. Cystic degeneration of a mass?
  – 2. Mucinous lesion?
  – 3. Worrisome features?

• Added value of EUS
  – Confirm diagnosis
  – Slightly higher sensitivity in identifying worrisome features

• Surveillance –
  – “balanced vigilance”
  – in low risk lesions worry less??