Management of Cystic Lesions of the Pancreas

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Objectives

• Know the differential diagnosis of pancreatic cysts
• Be familiar with the role for imaging (CT and MRI)
• Understand when to obtain an EUS +/- FNA
• Apply the most recent guidelines to optimally manage pancreatic cysts
  – International consensus (Sendai 2006 and Fukuoka 2012)
  – National clinical (AGA 2015)
**Pancreatic cancer**

- Pancreatic cancer is the 4th leading cause of cancer death in United States
- 45,000 Americans diagnosed yearly
- The average life expectancy with metastatic disease is 3-6 months
- Pancreatic cancer has the highest mortality rate of all major cancers
- 1.2% individual risk

Siegel R. *CA Cancer J Clin* 2013 Jan;63(1):11-30

**Pancreatic cancer development**

**Colon**
- Adenoma-Carcinoma Sequence:
- Intervention by polypectomy

**Pancreatic**
- PanIN-Carcinoma Sequence:
- Potential for intervention
Pancreatic tumors

<table>
<thead>
<tr>
<th>Solid</th>
<th>Cystic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Serous Cystadenoma</td>
</tr>
</tbody>
</table>

Prevalence of pancreatic cysts

- 2,832 CT scans
- Incidental cysts 2 – 38 mm
- Prevalence of cysts: 2.6%
- Age risk factor
- Prevalence >70 years:
  - 10% (mostly side-branch IPMN)
- Only 2-5% will turn into cancer

Laffan TA. *Am J Roentgenol* 2008;191(3):802-7;
De Jong K. *Pancreas* 2012;41:278-282
Differential diagnosis of pancreatic cysts

Benign (or low risk)
- Pseudocysts
- Serous cystadenoma
- Intraductal papillary mucinous neoplasms (IPMN) (side branch type)—no high-risk features

Malignant potential
- Mucinous cystadenoma/cystic neoplasm
- IPMN (main duct)
- IPMN (branch duct)—high-risk features
- Solid pseudopapillary neoplasm (SPN)

Cancer
- Adenocarcinoma
- Neuroendocrine tumor

Common cystic lesions

- Pseudocyst
  ~ 80%, even
- Intraductal papillary mucinous neoplasm (IPMN)
  ~10%, head
- Serous Cystadenoma (SCA)
  ~5%, even
- Mucinous cystic neoplasm (MCN)
  ~5%, body/tail
Uncommon cystic lesions

- Solid pseudopapillary neoplasm (SPN)
- Lymphoepithelial cyst
- Mucinous nonneoplastic cyst
- Congenital “simple cyst”
- von Hippel-Lindau syndrome
- Cystic fibrosis
- Polycystic kidney disease

Goal is to differentiate benign from malignant cysts

<table>
<thead>
<tr>
<th>Malignant Potential</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
<td></td>
</tr>
</tbody>
</table>
- Main duct
- Side branch duct |
| Mucinous cystic neoplasm (MCN) |
| Serous cystadenoma (SCA) |
| Pseudocysts |

Mucinous
Monitoring or Resection

Non-Mucinous
No monitoring
Benign cysts

Pseudocyst/walled-off pancreatic necrosis

- H/O pancreatitis
- No epithelial lining
- Contains pancreatic secretions, necrotic debris or blood
- Thin or thick wall
- Solitary, unilocular or septated
Pseudocyst cytology and fluid

- Inflammatory cells in wall
- Pigment-laden macrophages
- Cyst fluid
  - High amylase
  - No mucin
  - Low CEA

Serous cystadenoma

- Female > males (3:1)
- 5th to 7th decade
- Anywhere in pancreas
- Central stellate “sunburst” scar 30%
- 70-90% microcystic or honeycomb appearance (>6 cysts <3 mm)
- Macrocystic/oligocystic variant
- >50% incidental finding
- Benign, slow growing
Serous cystadenoma cytology and fluid

- Fluid thin, often bloody
- Fluid analysis: CEA <5, low amylase
- Cuboidal epithelial cells with glycogen
- Small cysts grow 1 mm per year

Cysts with malignant potential
Mucinous cystic neoplasm

- >95% female
- Age 40-60 years
- >95% body/tail
- Peripheral calcium
- Single cyst, incidental
- Mucin-secreting epithelial cells
- Ovarian-like stroma
- Malignant potential (6-27% incidence)

Mucinous cystic neoplasm cytology and fluid

- Viscous mucoid fluid
- CEA >200, low amylase
- Malignant >4 cm usually

CEA staining
Solid pseudopapillary neoplasm (SPN)

- Least common of pancreatic cystic neoplasms (<4% resected)
- Also called papillary cystic tumor of the pancreas and papillary cystic neoplasm
- Young (30’s) women (>90%)
- Commonly in body and tail
- Malignant potential (15%)
- Surgical removal is curative

Cystic neuroendocrine tumors

- 8% resected pancreatic cystic neoplasms
- Most asymptomatic found incidentally
- Occurs in men and women
- Typical age 60-70 years
- Low CEA, high yield of EUS cytology
- Cystic lesion with hypervascular rim or solid component
- Malignant potential
- Surgical removal is curative
Intraductal papillary mucinous neoplasms (IPMN)

- Proliferation of mucinous cells of pancreatic duct
- Cystic dilations of ductal system with overproduction of mucus
- Can affect main duct, side (branch) ducts or both
- Symptoms: None or abdominal pain, pancreatitis, jaundice or diabetes

Types of IPMN

- Main duct
- Branch duct
IPMN characteristics

- **Branched duct**
  - 90% of IPMN's
  - Mostly incidental
  - 30-40% multifocal
  - Slow growth
  - 5-15% cancer

- **Main duct**
  - 10% of IPMN's
  - Symptoms in up to 2/3
  - Most dysplastic (>80%)
  - 63% cancer in 5 years
  - Surgery for all

Predictors of malignancy in branch-duct IPMN

- Increasing cyst size
- Presence of a mural nodule
- Cyst growth rate (4.1 mm vs 1.0 mm/year; \( P = 0.001 \))

Risk of malignancy in bd-IPMN

Slow-growing cysts have a lower rate of malignancy

Kang MJ. Clin Gastroenterol Hepatol 2011;9(1):87-93

The role of imaging studies and EUS +/- FNA
Imaging studies

- CT and MRI/MRCP scans
  - 40-60% accurate for predicting the correct histological diagnosis
  - 70-90% accurate in differentiating aggressive vs. non-aggressive features
- Repeating x-ray imaging problematic
  - 1.5-2% of cancers in the USA are estimated to be related to radiation from CT scans

MRI/MRCP preferred

- Identify connection with pancreatic duct
- No ionizing radiation
EUS in pancreatic cysts

- Characterize the number and locations of cysts
- Evaluate pancreatic parenchyma in detail
- Determine presence and number of septations
- Detect worrisome features for malignancy
  - Mural nodules
  - Associated mass
- Obtain fine needle aspiration
  - Cyst fluid for analysis
  - Mass, nodule or cyst wall thickening

EUS morphology is inaccurate

- EUS morphological criteria for mucinous vs. non-mucinous cysts not useful
- US multicenter study with 12 centers and 341 patients

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous vs. non-mucinous</td>
<td>51%</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>75%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-neoplastic</td>
<td>50%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Brugge WR. Gastroenterology 2004;126:1330-1336
EUS cytology is not sensitive

- Sensitivity of cytology is 54%
- Specificity of cytology is 93%

Thornton GD. *Pancreatology* 2013;13:48-57

Sensitivity and specificity curves for cyst fluid CEA for diagnosing mucinous cystic lesions

Brugge WR. *Gastroenterology* 2004;126:1330-1336
Differentiating between mucinous and non-mucinous lesions

<table>
<thead>
<tr>
<th></th>
<th>EUS</th>
<th>Cytology</th>
<th>CEA (Cut-off 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>32/57 (56.1%)</td>
<td>19/55 (34.5%)</td>
<td>42/56 (75%)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>25/55 (45.4%)</td>
<td>45/54 (83.3%)</td>
<td>46/55 (83.6%)</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>57/112 (50.9%)</td>
<td>64/109 (58.7%)</td>
<td>88/111 (79.2%)*</td>
</tr>
</tbody>
</table>

*p < 0.001

CEA sensitivity and specificity

- Sensitivity of cytology is 63%
- Specificity of cytology is 88%
- Positive likelihood ratio is 4.37
- The higher the CEA level, the higher the specificity and the lower the sensitivity

Thornton GD. Pancreatology 2013;13:48-57
Advanced techniques

- DNA/Molecular analysis
- Needle based confocal microscopy

Tumor suppressor gene mutations

*STR: Short Tandem Repeat sequences (microsatellites)

STEP 1

Point Mutation

STEP 2

Loss of Heterozygosity (Allelic Imbalance)
Pancreatic cyst DNA analysis study

- 113 patients with pancreatic cysts who underwent surgery
  - 40 malignant
  - 48 premalignant
  - 25 benign cysts
- Cyst fluid k-ras mutation in the diagnosis of mucinous cysts
  - Odds ratio 20.9
  - Sensitivity 45% and specificity 96%
- Components of DNA analysis detecting malignant cysts
  - Allelic loss amplitude over 82% (AUC 0.9)
  - High DNA amount (optical density ratio >10, AUC 0.79)

All malignant cysts with negative cytologic evaluation (10/40) diagnosed as malignant by using DNA analysis

Khalid A. Gastrointest Endosc 2009;69(6):1095-102

KRAS testing

- 618 cysts and 142 with surgical pathology
- KRAS mutations had a specificity of 100% for mucinous cysts
- Sensitivity of 54%
- Combination of KRAS point mutations and elevated CEA improved the sensitivity of both tests to 83% and maintained a high specificity of 85% for mucinous differentiation

Nikiforova MN. Mol Pathol 2013;26(11):1478-87
Confocal for pancreatic cysts

- Mucinous cysts have villous structures
- Serous cysts have superficial vascular networks (87% confocal accuracy)
- Overall pooled sensitivity for nCLE is 68%
- Accuracy for classifying PCLs based on their malignant potential is 46%

Konda VJ. *Endoscopy* 2013;45(12):1006-13; Karia K. *Clin Endosc* 2016;49:462-466
Factors to consider

Patient
- Age
- Symptoms
- Comorbidities
- Patient preference

Cyst
- Size
- Characteristics
- Morphology
- FNA results
- Natural history

Surgery
- Morbidity
- Mortality
- Long-term affects
  - Diabetes
  - Exocrine insufficiency

Cysts to send to surgery

- Main duct IPMN
- Mucinous cystic neoplasm
- Cystic malignancies
  - Adenocarcinoma
  - Neuroendocrine tumors
- Solid pseudopapillary neoplasms
Pancreatic cancer in patients followed for bd IPMN

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of PDACs</th>
<th>Follow-up period</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamaguchi et al. (2002)^60</td>
<td>76</td>
<td>7</td>
<td>NA*</td>
<td>9.2</td>
</tr>
<tr>
<td>Uehara et al. (2008)^41</td>
<td>60</td>
<td>5</td>
<td>Median 87 months</td>
<td>8.0</td>
</tr>
<tr>
<td>Inagakul et al. (2010)^42</td>
<td>236</td>
<td>22</td>
<td>NA</td>
<td>9.3</td>
</tr>
<tr>
<td>Kanno et al. (2010)^43</td>
<td>159</td>
<td>7</td>
<td>NA</td>
<td>4.4</td>
</tr>
<tr>
<td>Tanno et al. (2010)^44</td>
<td>168</td>
<td>9</td>
<td>NA</td>
<td>5.4</td>
</tr>
<tr>
<td>Ikeuchi et al. (2010)^45</td>
<td>145</td>
<td>5</td>
<td>Mean 55.9 months</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Not applicable as study is a retrospective analysis. Abbreviations: IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma.

Sendai/IAP 2006 consensus IPMN guidelines

Recommend surgical resection ≥1 feature:
- Symptoms i.e. obstructive jaundice
- Main pancreatic duct ≥1 cm
- Intramural nodule/ solid component
- Cyst cytology suspicious or positive for cancer
- Cyst ≥3 cm (worrisome, but not by itself)

Tanaka M. Nat Rev Gastro Hepatol 2011;8:56-60

Tanaka M. Pancreatology 2006;6(1-2):17-32
Sendai/IAP 2006 algorithm

*The length of follow-up can be lengthened after 2 years of no change.

Small Sendai-negative bd-IPMNs are not harmless

- 287 resected pancreatic cysts
- 123 side branch IPMNs
- 69 “Sendai negative” (asymptomatic, <3 cm, no mural nodules, no wall thickening or PD dilation)
- Malignancy in 17/69 (25%) on surgery

Fukuoka/IAP 2012 IPMN guidelines

Recommend for surgical resection:

- Symptoms i.e. obstructive jaundice
- Main pancreatic duct >5 mm
- Abrupt caliber transition of pancreatic duct with distal pancreatic atrophy
- Presence of a solid mural nodule
- Thickened wall
- Cyst cytology suspicious or positive for cancer
- Cyst ≥3 cm in young patient

Tanaka M. Panreatology 2012;6(1-2):17-32
AGA 2015 clinical guidelines

- **MRI surveillance**
  - Pancreatic cyst <3 cm without a solid component or a dilated PB
  - MRI in 1 year then every 2 years for a total of 5 years, then stop if no change

- **EUS-FNA**
  - Pancreatic cyst >3 cm with higher risk features such as a dilated PD or associated solid component
  - If no concerning UES features, MRI as above

- **Surgery**
  - Solid nodules and a dilated PD or concerning features

Vege SS. *Gastroenterology* 2015;148:819–822
Fukuoka 2012 vs. AGA 2015 guideline comparison

- Retrospective study of 239 patients undergoing surgical resection for suspected mucinous pancreatic cysts
- Applied both criteria and analyzed performance in predicting advanced neoplasia (HGD or cancer)
- Found advanced neoplasia in 30% patients
  - No significant differences between guidelines in ability to predict advanced neoplasia
  - High risk features in both guidelines did not accurately identify all patients with advanced neoplasia

ASGE 2016 guidelines

- EUS-FNA in any of the following:
  - Size >3 cm
  - Presence of an epithelial nodule
  - Association with a dilated main duct
  - Suspicion for a mass lesion
  - Option for cysts <3 cm without other high-risk indications

Methusamy VR. Gastrointest Endosc 2016;84:1–9

Additional guidelines:
JAMA

Stark A. JAMA 2016;315:1882-1893
Additional guidelines: UpToDate

Khalid A. UpToDate 2016

Endoscopic therapy
**EUS-guided cyst ablation**

- EUS-FNI ethanol +/- PTX
- ↓ Viable epithelium
- ↓ CEA
- Smaller size
- Cyst resolution
- Time and follow up imaging

Gan SI. *Gastrointest Endosc* 2005;61(6):746-52

**EUS-guided ablation technique**

1. Cyst fluid aspiration
2. Ethanol lavage (injection & aspiration)
3. Paclitaxel injection

Oh HC, Brugge WR. *Gastrointest Endosc* 2013;377(4):526-33
### EUS-guided cyst ablation studies

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Patient N</th>
<th>Symptoms</th>
<th>Cyst size mm</th>
<th>Agent used</th>
<th>Flup (mo)</th>
<th>Resolution %</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen 2005</td>
<td>25</td>
<td>no</td>
<td>19 (6-37)</td>
<td>Eloh</td>
<td>6-12</td>
<td>35</td>
<td>-</td>
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<tr>
<td>Oh 2008</td>
<td>14</td>
<td>no</td>
<td>25.5 (17-52)</td>
<td>Eloh + placlitaxel</td>
<td>31</td>
<td>79</td>
<td>Pain = 1 AP = 1</td>
</tr>
<tr>
<td>Oh 2009</td>
<td>10</td>
<td>no</td>
<td>29.5 (20-68)</td>
<td>Eloh + placlitaxel</td>
<td>8.5</td>
<td>60</td>
<td>AP = 1</td>
</tr>
<tr>
<td>DeWitt 2009</td>
<td>42</td>
<td>no</td>
<td>10-50</td>
<td>Eloh vs saline</td>
<td>3-4</td>
<td>33</td>
<td>Pain = 10 AP = 2</td>
</tr>
<tr>
<td>Oh 2011</td>
<td>47</td>
<td>no</td>
<td>31.8 (17-68)</td>
<td>Eloh + placlitaxel</td>
<td>21.7</td>
<td>62</td>
<td>AP = 1 SV occl. = 1</td>
</tr>
<tr>
<td>DiMaio 2011</td>
<td>13</td>
<td>no</td>
<td>20</td>
<td>Eloh</td>
<td>13</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>DeWitt 2014</td>
<td>22</td>
<td>pain 55% none 45%</td>
<td>25 (15-43)</td>
<td>Eloh + placlitaxel</td>
<td>27</td>
<td>50</td>
<td>AP = 3 Peritonitis =</td>
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<tr>
<td>Gomez In press 2016</td>
<td>23</td>
<td>Not stated</td>
<td>&gt;10</td>
<td>Eloh</td>
<td>40</td>
<td>52</td>
<td>AP = 1 PC = 1</td>
</tr>
</tbody>
</table>

### Making sense of the guidelines and algorithms
Dilemma of pancreatic cysts

- Common – 3-10% of abdominal CT have incidental pancreatic cysts
- Most small (<3 cm) pancreatic cysts are benign branch-duct IPMN
- Cyst sampling for mucinous lesions; however
  - Neither cytology nor fluid CEA is perfect in deciding mucinous versus non-mucinous
  - Natural history of mucinous cystadenomas is unknown
  - Branch-duct IPMN are mucinous, but have low malignant potential
- Only treatment is surgical resection
  - Significant morbidity with surgery
  - Who benefits from surgery?

Management approach

- Analysis of multiple factors
  - Patients age, comorbidities, symptoms and wishes
  - Cyst characteristics including location and size of cyst, fluid analysis and cytology results
  - Surgical risks and benefits
- Multi-disciplinary team approach
  - GI, radiology and surgery
Take home points

- Pancreatic cysts are commonly found
- Use imaging (MRI/MRCP) and EUS to classify type of cyst
- Cyst fluid analysis (CEA) and cytology in high risk lesions
- Apply current guideline-based surveillance strategies, although all are flawed
- Surgical resection for mucinous cystic neoplasms, SPN, main duct IPMN and high-risk branch duct IPMN
- EUS-guided cyst ablation should be considered experimental