An Approach to Pancreatic Cysts

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Introduction

• 2.4-19.6% of all scans (CTs and MRIs)
• Increasing imaging, age
• Estimated Incident risk of malignancy : 0.24%/yr
• Prevalent malignant risk of 0.25% at the time of
cyst diagnosis
• For cysts >5 mm risk of pancreatic cancer is
increased by 6.2 fold (95% CI, 1.9- to 20.9-
fold)
• Risk stratification important
• Early identification and resection reduces
pancreatic cancer-specific mortality

Stark et al. JAMA 2016; 315 (17): 1882-93
Approach to Pancreatic cysts

- Natural history data are lacking
- Evidence is limited - retrospective
- Most recommendations based on expert/consensus recommendations
- Limited data on evolving technologies – molecular markers, genetic testing & imaging
- Molecular markers + Imaging +Clinical features likely better for diagnosis


Pancreatic Cysts

- **Benign**
  - Serous cysts/serous cystadenoma (13–23%)
  - Pseudocysts
  - Lymphoepithelial cysts
  - Mucinous non neoplastic cysts

- **Malignant**
  - Mucinous cysts (11-18%)
    - MCN
    - IPMN
      - Main duct (25%)
      - Side branch (26%)
  - Pseudopapillary neoplasms (5%)
  - **Cystic NET (4-7%)**
  - **Cystic Adenocarcinoma**

Cystic Neoplasms

- Serous cystadenomas “uniformly” benign
- Mucinous neoplasms at least premalignant
  - 5 yr survival much better than ductal adenoca
    - Cystadenoma 90%
    - Cystadenocarcinoma 72%
    - Ductal adenocarcinoma w/assoc cyst 14%

Mucinous Cystic neoplasms

- Almost exclusive in women (58-55)
- Don’t communicate with the duct
- Body/tail location
- Ovarian type stroma is diagnostic
- 10-17% malignancy risk
Intraductal Papillary Mucinous Neoplasm (IPMN)

- 3 types
  - Main duct
  - Side branch
  - Mixed
- Main duct 5-10 mm diameter
- Risk of malignancy in main duct IPMN (38-68%)
- Risk of malignancy in side branch IPMN (12-47%)

Solid Pseudopapillary Neoplasm

- Mostly in younger age women (30 years)
- Mixed solid/cystic
- Local invasion, metastasis or recurrence in 8-20%
Cystic Neuroendocrine tumors

• Less likely functional/symptomatic
• Smaller than solid lesions
• Less likely to metastasize
• May be associated with MEN 1

Other benign cysts

• Simple cyst: True epithelial cyst
• Lympho epithelial cysts: Rare. Sheets of non dysplastic squamous cells and lymphocytes
• Mucinous non neoplastic cyst – rare
• No ovarian stroma and does not communicate with the panc duct
Role of EUS in evaluation of Pancreatic cysts

- Better characterization of cysts
- Morphology alone has poor sensitivity and specificity
- Fine needle aspiration
- Surveillance

Role of ERCP

- Rarely indicated
- Fish mouth papilla with mucous – IPMN
- ERCP tissue sampling has a low diagnostic yield
Cyst Fluid Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>String sign &gt; 1 cm &gt; 1 s</td>
<td>Spec. 95% PPV 94%</td>
<td>Mucinous</td>
</tr>
<tr>
<td>Cytology</td>
<td>Sens: 63%</td>
<td>Mucinous Vs malignant</td>
</tr>
<tr>
<td>Cyst wall cytology</td>
<td>Increase in diagnostic yield by 29%</td>
<td>Mucinous Vs malignant</td>
</tr>
<tr>
<td>CEA &gt;192 ng/mL</td>
<td>Sens 75%, Spec: 84%</td>
<td>Mucinous</td>
</tr>
<tr>
<td>CEA &lt;5 ng/mL</td>
<td>Sens 50%, Spec 85%</td>
<td>Serous cystadenoma, Pseudocyst, NET</td>
</tr>
<tr>
<td>Amylase &lt;250 U/L</td>
<td>Sens 44%, Spec 98%</td>
<td>Excludes pseudocyst</td>
</tr>
</tbody>
</table>

Brugge et al. Gastroenterology. 2004 May; 126(5):1330-6
Brick et al. Endoscopy. 2015;47:626–631
Hong et al. Gastrointest Endosc. 2012;75:775–782
Chiang and Lee World J Gastroenterol. 2016 Jan 21; 22(3): 1236–1245

Probe/Needle based imaging

- Confocal microscopy: Real time laser assisted imaging
- IV fluorescein used – stains vessels and delineates tissue
- Nuclei appear dark
- Direct visualization using a cholangioscope
- Accuracy for detection of neoplastic, mucinous and serous cystadenomas (pCLE) : 71,89,87.
- Limitations: 4% risk of pancreatitis, cost, expertise, manipulation of 19 g needle and sampling

Nakai et al. Gastrointest Endosc. 2015;81:1204–1214
Napoleon et al Endoscopy. 2015;47:26–32
Molecular/Biomarkers

• PCR for detection of differential gene expression to identify malignancy
• DNA, RNA and protein based markers evaluated
• GNAS – more promising
• Mutation of either KRAS or GNAS was found in 95% of IPMNs
• IPMNs: mutations in KRAS, GNAS, RNF43, TP53, p16/CDKN2A and SMAD4
• MCNs: KRAS, RNF43, TP53, p16/CDKN2A and SMAD4 gene mutation profile
• Cytokines being evaluated as well. Need more data

Kanda M. Gut. 2013 Jul; 62(7):1024-33
Amato E. J Pathol. 2014 Jul; 233(3):217-27

Low risk Pancreatic cysts

• Serous cystadenoma: Honey comb like cystic features with central calcification
• If asymptomatic – Observe - Class Ila Level C
• Macrocystic serous cystadenoma – EUS FNA
• Small asymptomatic cysts - Observe – Ila Level B
High risk Pancreatic cysts

- Enhancing solid component
- Main Panc duct >10 mm* (5-10 mm)
- Cyst diameter > 3cm - Ok to watch if no other worrisome features
- Non enhancing mural nodule
- Thickened cyst wall
- Abrupt change in MPD with distal atrophy
- Lymphadenopathy
- CT or EUS can identify accurately

Tanaka et al. Pancreatology 2012;12 (3); 183-197
Khasab et al. Pancreas 2013;42(4); 717-21

Differentiation of High risk and Low risk cysts

<table>
<thead>
<tr>
<th>Pancreatic Cysts With High Risk for Malignancy</th>
<th>Pancreatic Cysts With Low Risk for Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>Patient Characteristics</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Main pancreatic duct diameter 5-9 mm (worrisome feature) or ≥10 mm</td>
<td>Main pancreatic duct diameter &lt;5 mm</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>No lymphadenopathy</td>
</tr>
<tr>
<td>Characteristics of Cyst</td>
<td>Characteristics of Cyst</td>
</tr>
<tr>
<td>Abrupt change in the main pancreatic duct caliber</td>
<td>No change in main pancreatic duct caliber</td>
</tr>
<tr>
<td>Mural nodule</td>
<td>No mural nodule</td>
</tr>
<tr>
<td>Enhancing solid component</td>
<td>No solid component</td>
</tr>
<tr>
<td>Thickened walls</td>
<td>No thickened walls</td>
</tr>
<tr>
<td>Size ≥3 cm</td>
<td>Size &lt; 3 cm</td>
</tr>
</tbody>
</table>

Stark et al. JAMA 2016; 315 (17): 1882-93
### Indications for EUS - Intermediate risk

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical Utility</th>
<th>Positive result</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUS</td>
<td>Eval/FNA</td>
<td>Size/Mural nodule</td>
<td>75</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Mucin</td>
<td>Serous/mucinous</td>
<td>Mucin</td>
<td>78-97</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>Serous/Mucinous</td>
<td>&lt;5 ng/mL-192 ng/mL</td>
<td>100-73</td>
<td>86-84</td>
<td>NA 4.56</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td>Malignant cells Atypia</td>
<td>Poor</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Stark et al. JAMA 2016; 315 (17): 1882-93

### Symptomatic cysts

- Pain: greater likelihood for malignancy
- Main and mixed type IPMN can have symptoms
- Risk of malignancy correlates with duration and presence of symptoms
- Surgical resection in patients with pain
- *(ACCF/AHA Class I, Level B recommendation)*
Indications for surgery

- Main duct IPMN - >10 mm
- Confirmed mucinous cystic neoplasm
- Presumed side branch IPMN – cyst >3 cm (odds ratio 62.4)
- Rapid growth >1.1 mm/year
- Positive cytology
- Symptoms

(ACCF/AHA Class I, Level B recommendation)

Stark et al. JAMA 2016; 315 (17): 1882-93

Approach to Pancreatic cysts:
Problems

- No good natural history data
- Few studies with long term follow up data
- Data from specialized centers – bias
- IAP guidelines
  - Imaging, EUS-FNA, Cyst morphology, Fluid analysis, cytology
- AGA guideline
  - High or low risk based on imaging, clinical presentation
## Summary of AGA guidelines

<table>
<thead>
<tr>
<th>Initial strategy</th>
<th>Cyst characteristics</th>
<th>Surveillance strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance only</td>
<td>&lt;3 cm, no solid component, no MPD dilation</td>
<td>MRI at 1 year, repeat every 2 y and if no change at 5 y discontinue. EUS if change</td>
</tr>
<tr>
<td>EUS FNA</td>
<td>&gt;3 cm cyst, solid component, MPD dilation (2 of 3)</td>
<td>If EUS FNA negative as above</td>
</tr>
<tr>
<td>Surgery</td>
<td>Solid component and MPD dilation or suspicious EUS FNA findings</td>
<td>If HGD or Ca MRI every 2 years and if benign no follow up</td>
</tr>
</tbody>
</table>

Scheiman et al. Gastroenterology. 2015;148 (4)824-848

Stark et al. JAMA 2016; 315 (17): 1882-93
Summary

- Careful history and evaluation necessary
- At initial aspiration: CEA, amylase & Cytology
- For those with symptomatic cysts, cysts > 3cm with other alarm features – EUS+FNA and surgical evaluation
- Cysts with low risk features – continued surveillance - ? 5 years – non invasive
- Indeterminate cysts – surveillance – cyst fluid analysis
- Molecular markers when initial testing inconclusive