Rational Approach to Pancreatic Cystic Lesions

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Case 1

- 73-year-old woman undergoes a MRI for radicular symptoms, adrenal cyst noted – dedicated abdominal MRI recommended
- Multiple pancreatic cyst found in body, largest 2cm
- MRI cannot confirm communication with the PD, and EUS – FNA is recommended
MRI

EUS

Provided by Erik Wamsteker, MD
EUS and Mural Nodules

- Mucus accounts for 2/3
  - Change in position/fna
- EUS features more frequent with mucus
  - Echogenicity
  - Smooth Edge
  - Hyperechoic Rim
  - Improved accuracy from 57-79%

Zhong et al CGH 2012;10:192-198

EUS-FNA and Pancreatic Cysts

- EUS best for identifying small masses and associated nodules
- Cyst fluid CEA most accurate test to identify mucinous lesion
- ROC analysis: cyst fluid CEA > 192 – differentiate mucinous vs. non-mucinous (AUC .79)
  - CEA better than EUS morphology or cytology (50-60%)
  - CEA <5 suggested PC or serous lesion with a 50% sensitivity and 95% specificity while a CEA >800 suggested a mucinous lesion (sensitivity 48%, specificity 98%)
- Cytology insensitive: revealed malignancy in only 48% of mucinous cancers
- Molecular testing remains of uncertain value

Pancreatic Cystic Lesions

- Increasingly recognized
  - Widespread use and improved cross sectional imaging
- Spectrum of benign to malignant lesions
  - Pseudocysts
  - Serous cystadenomas
  - Mucinous cystadenomas
  - Intraductal papillary mucinous neoplasm (IPMN)

Pancreatic Cystic Lesions:
Key issue: Imaging alone?

- Clinician evaluation
  - Symptoms related to lesion?
    - Pain
    - Obstructive jaundice
    - Weight loss
  - Pancreatitis—past or present?
- Imaging Evaluation
  - Cross Sectional imaging vs. EUS
Pancreatic Cystic Lesions

Decision Points

- Differential diagnosis of the cyst
  - Neoplastic vs. Non-neoplastic
  - Risk of malignancy
- Likelihood of harm
  - With and without testing
  - With and without treatment
- Particularly relevant for asymptomatic patient
MCN

### Pseudocyst

**Clinical**
- Gender
- Age
- Ethanol abuse
- Pancreatitis history
- Malignant potential
- Location

**Imaging studies**
- Septae
- Locularity
- Calcifications

- Female (2-3:1)
- 60's
- No association
- Yes (uncommon)
- No (rare)
- Evenly distributed

- Yes
- Multiple small (usually)
- Yes (central sunburst or stellate)

**SEROUS CYSTADENOMA**

**Differential Diagnosis**

**Mucinous cystic neoplasm**

**Clinical**
- Gender
- Age
- Ethanol abuse
- Pancreatitis history
- Malignant potential
- Location

**Imaging studies**
- Septae
- Locularity
- Calcifications

- Female (-100%)
- Adenoma (50-60’s) Ca (60-70)
- No association
- Yes (uncommon)
- Yes
- Body/tail

- Yes
- Multilocular (usually)
- Yes (peripheral, curvilinear)

Differential Diagnosis
Intraductal Papillary Mucinous Neoplasm

Clinical
- Gender
- Age
- Ethanol abuse
- Pancreatitis history
- Malignant potential
- Location

Imaging studies
- Septae
- Locularity
- Calcifications

- Male (3-4:1)
- 60’s
- No association
- Yes (uncommon)
- Yes
- Head

- No
- Multilocular (usually)
- No


IPMN-SIDE BRANCH
**Consensus IPMN Guideline**

Size < 1 cm
- MR or thin slice CT
- In 1 year

Size 1-3 cm
- High-risk stigmata:
  - Mural nodules
  - Dilated main duct
  - Positive cytology
  - MR or CT
  - 1-2 cm every 6-12 mo* 
    - No
  - 2-3 cm every 3-6 mo
  - Yes

Size > 3 cm
- Symptomatic, size > 3cm or positive high-risk stigmata
- Resection

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

_Tanaka et al. Pancreatology 2006;6:17-32_

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**Prevalence of cysts according to age-extrapolated from overall prevalence data**

<table>
<thead>
<tr>
<th>Age band</th>
<th>Total number of subjects</th>
<th>Cyst prevalence (95% CI)</th>
<th>Cyst prevalence &gt; 2cm*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>557</td>
<td>0.5% (0.07-1.21%)</td>
<td>0.03%</td>
</tr>
<tr>
<td>40-49</td>
<td>1027</td>
<td>2.6% (0.4 to 6.7%)</td>
<td>0.17%</td>
</tr>
<tr>
<td>50-59</td>
<td>970</td>
<td>4.0% (1 to 10%)</td>
<td>0.27%</td>
</tr>
<tr>
<td>60-69</td>
<td>665</td>
<td>10% (0.3 to 32%)</td>
<td>0.67%</td>
</tr>
<tr>
<td>70-79</td>
<td>154</td>
<td>25% (3 to 60%)</td>
<td>1.67%</td>
</tr>
<tr>
<td>80+</td>
<td>46</td>
<td>37% (24 to 51%)</td>
<td>2.47%</td>
</tr>
</tbody>
</table>
Combining Systematic Review Data with SEER Database

- Risk that cyst harbors malignancy using SEER cystadenocarcinoma statistics = 0.017%
- Risk that cyst harbors malignancy using ALL SEER pancreatic carcinoma = 0.25%

With thanks to Joel Rubenstein

What are the implications?

- Imaging tests applied to conditions with low pretest likelihood for malignancy do not change post test probability unless they are highly accurate
- Marked operator dependence for imaging and cytology
- Tumor markers show overlap
### Summary of pooled data evaluating pancreatic cyst features predictive of malignancy

| Feature                     | No. studies | No. patients | Sensitivity (95% CI) | Specificity (95% CI) | LR +ve (95% CI) | LR –ve (95% CI) |
|-----------------------------|-------------|--------------|-----------------------|----------------------|----------------|----------------|----------------|
| > 3cm                       | 6           | 644          | 74% (68-80%)          | 49% (44-54%)         | 1.47 (1.24-1.75)| 0.53 (0.39-0.72)|
| Dilated pancreatic duct     | 4           | 609          | 32% (25-38%)          | 80% (75-84%)         | 1.93 (0.78-4.79)| 0.85 (0.66-1.10)|
| Solid component to cyst     | 7           | 816          | 48% (42-54%)          | 91% (88-93%)         | 4.42 (2.42-8.07)| 0.60 (0.39-0.94)|

Interval growth not significant!

Scheiman et al. Gastro, in press

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### Outcome of cysts that have surveillance

- **62 studies**
  - **10,496 patients**
  - **34,460 patient years follow up**
  - **154 invasive cancers**

<table>
<thead>
<tr>
<th>Suspected cyst type</th>
<th>Number studies</th>
<th>Number cancers</th>
<th>Patient year follow up</th>
<th>Incidence per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>22</td>
<td>42</td>
<td>6,240</td>
<td>0.24%</td>
</tr>
<tr>
<td>IPMN</td>
<td>37</td>
<td>112</td>
<td>14,830</td>
<td>0.72%</td>
</tr>
<tr>
<td>SCN</td>
<td>3</td>
<td>0</td>
<td>1,551</td>
<td>0%</td>
</tr>
</tbody>
</table>
Benefits of surgery

- Save life by resection invasive cancer early
- Prevent cancer by remove precancerous cysts
  - No data
- Improve symptoms that cyst is causing

Harms of surgery

- Operative/post operative mortality
- Short term morbidity related to surgery
  - e.g. pancreatic fistulas
- Long term morbidity related to surgery
  - e.g. malabsorption, diabetes mellitus
Mortality and Morbidity of Surgery

- 74 studies
  - 5,484 patients
  - Post-op mortality = 2.1% (95% CI = 1.5 – 2.7%)
- SEER database on 792 patients reported a post-op mortality of 6.6%
- 49 studies
- 3,392 patients
- Major morbidity = 30% (25-35%)


Pancreatic Cystic Lesions
Potential Management Strategies

- Additional Imaging Studies
  - CT
  - MRI (MRCP may show ductal communication with IPMN)
  - EUS +/- FNA
- Cyst fluid Characterization
- Risk/Benefit assessment of surgical resection
- Watchful Waiting
Pancreatic Cystic Lesions - Role of EUS

- Endosonographic architecture
  - Not sufficient for accurate classification
  - Solid mass and invasive tumor – malignant
- EUS appearance
  - Serous: numerous small cysts with thin septae
  - Mucinous: macrocystic – uni- or multilocular
  - IPMN: mural nodules may show invasive features and target for FNA
- Differentiation from adherent mucus challenging
Pancreatic Cystic Lesions

Invasive Approach?

- **EUS FNA**: safe and well tolerated <1% complication rate
  - Technique: limit passes, antibiotics
- **Fluid analysis**
  - Cytology: insensitive
  - Amylase/Lipase: confusing
  - Tumor Markers: CEA most useful
- **Cyst wall imaging?**
  - Spyglass
  - Confocal

Pancreatic Cystic Lesions

Multicenter Study

- 341 patients EUS + FNA
- 112 surgical resection (68 mucinous, 7 serous, 27 inflammatory, 5 endocrine, 5 other)
- ROC analysis: cyst fluid CEA > 192 – differentiate mucinous vs. non-mucinous (AUC .79)
- CEA better than EUS morphology or cytology (50-60%)
- Cyst fluid CEA most accurate test to identify mucinous lesion

*Brugge et al. Gastroenterology 2004;126:1330-1336*
Pancreatic Cystic Lesions

DNA analysis

- Redpath- commercially available test
- PANDA study: multicenter EUS-FNA study-interim analysis
  - Cytology, CEA
  - DNA quantity (OD) and quality (cycle threshold on qPCR)
  - Allelic loss (15 microsatellites)
  - K-ras mutation
- Conclusion from 41 patients whose lesions were removed that DNA quality and quantity were most accurate indicator of malignancy
- Criticism: Is this the clinical issue we struggle with?


IPMN vs. MCN vs. SCN

- Can we distinguish them preoperatively?
  - IPMN -Communication with duct
  - Ovarian stroma at resection- MCN
  - Molecular testing?
    - KRAS or GNAS in 96% of IPMNs
    - GNAS 100% specific to IPMNs (66% sensitive)
    - KRAS and GNAS present in 0% of serous cystadenomas

EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study

- Key Issues:
  - Patient Selection
  - Safety
  - Long term outcomes
  - Not ready for prime time!
### “Worrisome” Category and Implications

**Criteria**

<table>
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<tr>
<th>Cyst ≥3cm</th>
<th>Abrupt change in MPD caliber w/ distal atrophy</th>
</tr>
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<tbody>
<tr>
<td>Thick/enhanced cyst walls</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Non-enhanced mural nodule</td>
<td>MPD 5-9 mm</td>
</tr>
</tbody>
</table>

- All “Worrisome” on MRI should undergo EUS
- Cysts >3 cm (even without worrisome features on MRI) can undergo EUS

### Cyst Fluid Analysis - 2012

- “Still Investigational”
- “Recommended for small BD-IPMNs w/o worrisome features in centers with expertise in EUS-FNA and cytological interpretation”*
- Recommend against FNA of any cyst of any size w/ “worrisome” features due to potential leakage of contents to peritoneum → pseudomyxoma peritone
Resection - Main Duct IPMN

- Resect all MD-IPMN ≥10 mm
- MD-IPMN 5-9 mm = “Worrisome” and can be observed rather than immediately resected
- Margin to moderate dysplasia or less
- Pre-operative use of intraductal EUS and pancreatoscopy to direct margin & avoid mucin leakage

Resection – Branch Duct IPMN

2006
- Cyst >3 cm
- Mural Nodule
- Dilated main PD
- Positive cytology

2012
- Cysts >3 cm w/o high-risk stigmata → Observe
- High-Risk Stigmata
  - Rapidly increasing size
  - High-grade atypia
- Consider surgery in fit patients <65 yo with cysts >2 cm due to cumulative risk
Resection – Mucinous Cystic Neoplasms

**2006**
- Resect ALL
- Include splenectomy and lymph node dissection for all

**2012**
- Resect ALL*
- Consider parenchyma-sparing resections, spleen preservation and laparoscopic approach in MCN <4 cm w/o mural nodules

Surveillance – Unresected Cyst

- **<1 cm**
  - CT/MRI in 2-3 years

- **1-2 cm**
  - CT/MRI yearly x 2 years, then lengthen interval if no change

- **2-3 cm**
  - EUS in 3-6 months, then lengthen interval alternating MRI with EUS as appropriate

- **>3 cm**
  - Close surveillance alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients
AGA Technical Review

- Quality of data very poor
- Diagnosis will always be challenging because cystadenocarcinoma is rare
- Extreme uncertainty around benefit of removing cyst with HGD
- Unlikely to be major benefit from removing invasive malignancy
- Significant morbidity and mortality from surgery

Scheiman JM, Gastroenterology
148:4; 824–848.e22, 2015

AGA Guideline

Pancreatic Cysts
Clinical Decision Support Tool

- Image of decision tree with various scenarios and outcomes.
- Key features and diagnostic criteria.

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148:4; 824–848.e22, 2015
Pancreatic Cystic Lesions
Summary and Conclusions

- Careful history in light of diagnostic considerations
- Pseudocyst unlikely in absence of Pancreatitis
- Surgery for all symptomatic and mucinous lesions guiding principle
  - Selective use of preoperative imaging and tissue/fluid sampling
  - Individualize strategy of surveillance
  - Patient preferences key
  - Trade off of delayed surgery and risk of development of unresectable disease
  - Multidisciplinary Approach


Case Study 2

- 79-yr-old male h/o CP s/p Puestow ‘87 txf OSH w/ jaundice, nausea and non-bloody emesis
- PMHx: CP w/PEI, DM, CVA, COPD
- PSHx: Choly, Back Surg, Vascular stents
- Social: Retired Marine and HS teacher, 2 ppd x 30 yrs, no etoh
CT Scan

- Surgically absent GB
- CBD 1.2 cm
- Cystic spaces HOP
- Calcifications
- Atrophy of the body and tail
- PD 2 cm to ampulla

ERCP
Role of EUS +/- FNA

- Sample main duct for CEA
- Target nodule
- Molecular testing?
- Confocal?
- Cytology?