Pancreatic Cysts: Making Sense of Differing Guidelines

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OUTLINE

• Background on Pancreatic Cysts
• Diagnosis and Differentiation
• Guidelines
  – National Clinical: AGA 2015
CASE

60 yo female with vague abdominal pain

Clinical Dilemma of Pancreatic Cysts
Facing the Epidemic of Pancreatic Cysts

Pancreatic cysts are increasingly found.

Only 2-5% of pancreatic cysts will degenerate into cancer.

2. ACS Cancer Facts and Figures 2014

How Do We Identify Cysts with Malignant Potential?
Most Common Cystic Lesions

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

GOAL: Differentiate Types of Cysts

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

Mucinous: Monitoring or Resection
Non-Mucinous: No monitoring
Main duct IPMN (Md-IPMN)

- M=F, >60yo
- Minority of all IPMNs (25%)
- Symptoms- Up to 2/3
- Location- Head
- Imaging
  - PD dilation >10mm
  - “Fish mouth” ampulla
- Cytology- Mucin producing columnar epithelium
- Malignant potential
  - Most dysplastic (>80%)
  - Cancer 57-92%
  - High rate of progression

Tanaka et al., Pancreatology 2006  Belyaev et al., J Clin Gastroenterol 2008

Surgery for All

EUS-FNA of Md-IPMN with Malignancy

Courtesy of Dr. Harry Aslanian
Side Branch Duct IPMN (Sb-IPMN)

- M=F, >60yo
- Majority of IPMNs (75%)
- Most asymptomatic
- Location - Head, but can be anywhere
- Imaging:
  - Normal caliber PD
  - Can be multi-focal
- Malignant potential:
  - Slow growth
  - Annual incidence of cancer 2%

Surgery for some

EUS Predictors of Malignancy in Sb-IPMN

Size and mural nodule predictors of malignancy

138 resected IPMN


Tanaka et al., Pancreatology 2006  Jang et al., Korean J Gastro 2008
Mucinous cystic neoplasm (MCN)

- Female (95%), >40yo
- Most asymptomatic
- Location- Body/tail
- Imaging
  - Multilocular, macrocystic
  - Solitary
  - No PD communication
- Cytology- Ovarian-type stroma
- Malignant Potential
  - 6-36% incidence of cancer

Surgey

Oh et al, AJG 2008
Tanaka et al., Pancreatology 2006

Serous Cystadenoma (SCA)

- Female >50%, >60yo
- Symptoms if >4cm
- Location- Any
- Imaging
  - "Honey Comb" appearance
  - Central scar
  - Macrocystic/oligocystic
- Cytology- Glycogen+ cuboidal cells
- Malignant potential
  - Low/none

Observation

OBSERVATION

SURGERY IF

- Symptomatic
- Dx in question

Tanaka et al., Pancreatology 2006
EUS of Serous Cystadenoma

Making the Diagnosis
Tools

• Patient demographics and history
• Cyst characteristics
  – CT
  – MRI
  – Endoscopic Ultrasound (EUS)
    • Fine Needle Aspiration (FNA)

Diagnosis: CT and MRI

• CT and MRI
  – 40-60% accurate for predicting correct histologic diagnosis
• MRI preferred
  – Identify connection w/ pancreatic duct (PD)
  – No ionizing radiation
Diagnosis: EUS

- EUS advantages
  - Number and location of cysts
  - Presence and type of septations
  - Background pancreas parenchyma detail
  - Worrisome features of malignancy
    - Mural nodules
    - Associated mass
  - Fine needle aspiration (FNA)

EUS morphology alone → Unreliable!

- Morphologic criteria for mucinous cysts vs non-mucinous cysts NOT that useful
  - Accuracy 51%, Sensitivity 56%, Specificity 45%
  - US multicenter study, 12 centers, 341 patients

Brugge et al., Gastroenterology 2004
Beyond Just Looking.....

CYST FLUID ANALYSIS:
Differentiating Mucinous from Non-Mucinous Lesions

- CEA is far from perfect

CEA >800: 98% spec, 48% sens

- Cytology results are variable

Cytology: 93% spec, 54% sens

1. Van der Waaij, GIE 2005  
2. Thornton et al., Pancreatology 2013
“Positive String Sign”

- 71 cysts
  - High measured viscosity
    - 80% sens, 100% spec for mucinous lesions
- 79 cysts
  - Median “string sign” = surrogate for measured viscosity
    - 0mm in benign cysts
    - 3.5mm in mucinous cysts


Advanced Techniques

Khalid et al, GIE 2009

DNA/Molecular Analysys

- DNA quantity
- DNA quality
- KRAS point mutation (oncogene)
- GNAS mutation (oncogene)
- Loss of heterozgyosity (LOH) mutation (tumor suppressor gene)

Konda et al, GIE 2011 and Endoscopy 2013

Needle Based Confocal Endomicroscopy (nCLE)
### Cyst characteristics: Summary

<table>
<thead>
<tr>
<th></th>
<th>IPMN</th>
<th>MCN</th>
<th>SCA</th>
<th>Pseudocyst</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M = F</td>
<td>Female</td>
<td>F &gt;50%</td>
<td>M &gt; F</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&gt;60s</td>
<td>40s-60s</td>
<td>&gt;60s</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Head</td>
<td>Body/Tail</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>Dilated main PD or side branches +/- multifocal “grapelike” if branch-duct</td>
<td>Unilocular; +/- septations and wall calcifications No PD connection</td>
<td>Microcytic / honeycomb Central scar on CT scan (20%) (BEWARE: macro/oligocystic variant)</td>
<td>Thick wall, associated inflammatory changes (BEWARE: need Hx of pancreatitis)</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Mucinous columnar epithelium</td>
<td>Ovarian stroma</td>
<td>Glycogen+ cuboidal cells</td>
<td>No epithelium; fibrosis, granulation tissue</td>
</tr>
<tr>
<td><strong>Malignant potential</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
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</table>
**SENDAI 2006: International IPMN Consensus Guidelines**

- Any worrisome findings?
  - Dilated main PD or abrupt caliber transition
  - Solid component or mural nodule
  - Thickened wall
  - Obstructive jaundice
  - Cytology suspicious or positive for malignancy
  - Size >3cm WITH high risk features

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

**FUKUOKA (Updated SENDAI) 2012: International IPMN Consensus Guidelines**

- Any worrisome findings?
  - **YES→CONSIDER SURGERY**
  - **NO→SURVEILLANCE**
Surveillance of Sb-IPMN

- <1 cm
  - CT or MRI in 2-3 years
  - If stable, increase interval

- 1-2 cm
  - Annual CT or MRI X 2 years
  - Lengthen interval, alternating EUS + MRI as “appropriate”

- 2-3 cm
  - EUS in 3-6mths

- >3 cm
  - Close surveillance
  - Alternate EUS with MRI Q3-6mths

Small, Sendai Negative Sb-IPMNS: Not Harmless

- 287 resected cysts → 123 side branch IPMNs
- 69 Sendai “negative” (ie <3cm/no mural nodules or PD dilation)
  - 17/69 (25%) = malignancy on histology

Fritz et al, Ann Surg 2012
AGA 2015: Clinical Guidelines

• MRI SURVEILLANCE
  – Pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct
  – MRI surveillance in one year and then every two years for a total of five years → stop if no change or patient no longer a surgical candidate

• EUS-FNA
  – Pancreatic cysts ≥ 3 cm and/or cysts with higher risk features such as a dilated main pancreatic duct or
  – Patients with two year history of cyst growth
  – Patients without concerning EUS/FNA results should be offered MRI surveillance after one year and then every two years to ensure no change

• SURGERY
  – Significant change in cyst characteristics including the development of a solid component and/or increasing pancreatic duct size are indications for EUS/FNA
  – Both solid nodule and a dilated pancreatic duct and/or concerning features on EUS and FNA

Every recommendation made was cited as having “WEAK EVIDENCE”
## Agreement Level Among Guidelines

<table>
<thead>
<tr>
<th>HIGH RISK FEATURES:</th>
<th>Sendai 2006</th>
<th>Fukuoka 2012</th>
<th>AGA 2015</th>
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<tbody>
<tr>
<td>PD dilation &gt;10mm</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Solid component/nodule/mass</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>+Cytology</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Size &gt;3cm alone</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Size &gt;3cm + other high risk feature</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<table>
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<tr>
<th>PREFERRED SURVEILLANCE TOOL:</th>
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<tbody>
<tr>
<td>&lt;1cm</td>
<td>CT/MRI</td>
<td>CT/MRI</td>
<td>MRI</td>
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<tr>
<td>1-2cm</td>
<td>CT/MRI</td>
<td>CT/MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>2-3cm</td>
<td>CT/MRI</td>
<td>EUS</td>
<td>MRI</td>
</tr>
<tr>
<td>&gt;3cm and/or any HIGH RISK features</td>
<td>EUS</td>
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<table>
<thead>
<tr>
<th>SURVEILLANCE CESSATION</th>
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* if stable for 5 years

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### Comparing Fukuoka Consensus 2012 to AGA Clinical 2015 Guidelines

- Retrospective study of 239 pts undergoing surgical resection for suspected mucinous pancreatic cysts over 4 yr period
- Applied both criteria and analyzed their performance in predicting advanced neoplasia (AN = invasive cancer or HGD)
- AN 30%
  - No significant difference between the guidelines in predicting AN
  - High risk features in both guidelines do not accurately identify all patients with AN

Approach to Pancreatic Cysts

- Multidisciplinary (radiology, surgery, GI)
- Patient factors → Surgical candidate
  - Age
  - Comorbidities
  - Symptoms
- Cyst factors
  - Location → Determines type of surgery
  - Size
  - Differentiate cyst (sampling, advanced imaging)

Approach to Pancreatic Cysts

- Talk to your patient
  - Not surgical candidate → Why survey at all?
  - Small cysts <1cm do not need EUS
- Interpret guidelines in context of each patient
- Sb-IPMNs most common incidental finding
  - Over-surveillance → $$$, anxiety
- Cysts with any worrisome features or rapidly enlarging
  - ALWAYS discuss with a pancreatic surgeon
Clinical Relevance of the Increasing Incidence of IPMN

- Pancreatic cysts are increasingly being found
- Attempt to classify type of cyst with imaging (CT, MRI, EUS) in order to determine malignant potential
- Surveillance guidelines (both consensus and clinical) available but have flaws
- Approach to pancreatic cysts should be multidisciplinary and tailored to each patient