What To Do With Pancreatic Cysts?

Kenneth J. Chang, MD, FACG

Pancreatic Cysts

- Incidence: A growing problem
- Previous diagnostic approaches
- Emerging data: the conundrum
- New problems need new solutions
Case scenario
- 65 yo female was found to have an incidental 2.9 cm cyst in the head of the pancreas

Q 1: What would you do next?
1. Whipple resection
2. Repeat CT in 12 months
3. MRI/MRCP
4. ERCP
5. EUS/FNA
**Very common problem**

- 300 consecutive autopsy cases\(^1\)
  - 186 cysts (at least 0.4 cm) in 73 cases (24.3%)

- Review of 24,039 CTs/MRIs\(^2\)
  - 290 pts (1.2%) had pancreatic cysts
  - 168 (0.7%) w/o documentation of pancreatitis

- Review of 2,832 MDCT\(^3\)
  - 73 pts (2.6%) had pancreatic cysts
  - 8.7% among elderly (age 80-89)

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\(^3\) Laffan TA, et al. AJR 2008; 191: 802-807

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**Pathology Classification**

<table>
<thead>
<tr>
<th>Non-Mucinous</th>
<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous Neoplasms</td>
<td>Mucinous cystic neoplasms</td>
</tr>
<tr>
<td>✔️ Serous cystadenoma</td>
<td>– LGD (adenoma)</td>
</tr>
<tr>
<td>✔️ Microcystic</td>
<td>– Moderate dysplasia (borderline)</td>
</tr>
<tr>
<td>✔️ Macrocystic</td>
<td>– HGD (carcinoma in situ)</td>
</tr>
<tr>
<td>✔️ Solid</td>
<td>– Invasive carcinoma</td>
</tr>
<tr>
<td>✔️ Von-Hippel-Landau</td>
<td></td>
</tr>
<tr>
<td>✔️ Serous Cystadenocarcinoma</td>
<td><strong>IPMNs</strong></td>
</tr>
<tr>
<td>✔️</td>
<td>– LGD (adenoma)</td>
</tr>
<tr>
<td>✔️ Moderate dysplasia (borderline)</td>
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</tr>
<tr>
<td>✔️ HGD (carcinoma in situ)</td>
<td></td>
</tr>
<tr>
<td>✔️ Invasive carcinoma</td>
<td></td>
</tr>
</tbody>
</table>


### Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Pseudo</th>
<th>SCA</th>
<th>MCN</th>
<th>IPMN</th>
<th>SPPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>1:1</td>
<td>1:3-4</td>
<td>1:9</td>
<td>2:1</td>
<td>1:10</td>
</tr>
<tr>
<td>Age (y), range</td>
<td>40-70</td>
<td>60-80</td>
<td>30-50</td>
<td>60-80</td>
<td>20-40</td>
</tr>
<tr>
<td>History</td>
<td>Pancreatitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Location</td>
<td>Even</td>
<td>Body/tail &gt;Head</td>
<td>Body/tail &gt;&gt;Head</td>
<td>Head &gt;Body/tail</td>
<td>Even</td>
</tr>
</tbody>
</table>

Katz 2008 J Am Coll Surg

### Serous Cystadenoma/ Microcystic Adenoma
Intraductal Papillary Mucinous Neoplasia (IPMN)
Solid Pseudopapillary Tumors (SPPT)

- Rare neoplasms with malignant potential
- Start as solid tumors, undergo degeneration giving rise to a cystic appearance
- Growth rate can be dramatic (>10cm)
- Can arise from any part of the pancreas
- Predominantly young females

<table>
<thead>
<tr>
<th>Older Patients</th>
<th>Younger Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arise within the head and progress distally</td>
<td>Arise in the uncinate process &amp; tail</td>
</tr>
<tr>
<td>&gt;1cm Main PD strongly suggests MD-IPMN</td>
<td>Cyst communicating with PD without Main duct dilation suggests BD-IPMN</td>
</tr>
<tr>
<td>Higher risk of malignancy 57% - 92%</td>
<td>Lower risk of malignancy 6% - 42%</td>
</tr>
<tr>
<td>Resect</td>
<td>Monitor vs Resect</td>
</tr>
</tbody>
</table>

Tanaka et al. Pancreatology 2006
Solid Pseudopapillary Tumors (SPPT)

- Imaging:
  - Range from solid to cystic, typically both
  - Well marginated
  - Central calcification
  - Well vascularized with areas of hemorrhage

- EUS-FNA:
  - Branching papillae with myxoid stroma
  - The diagnostic accuracy of EUS-FNA 75%*

- Management:
  - Considered low grade malignancy
  - Surgical resection to prevent local tumor growth and distant metastases, to palliate symptoms
  - Favorable survival even in the face of advanced disease (LN mets are rare)

Pancreatic Cysts

- Incidence: A growing problem
- Previous diagnostic approaches
- Emerging data: the conundrum
- New problems need new solutions

Sendai Consensus Guidelines 2004

1. Size
2. High risk features
   - Mural nodules
   - Dilated main PD (>10mm)
   - Positive cytology

MCN mural nodules

Updated "Sendai" Guidelines 2012

Are any of the following high-risk stigmata of malignancy present?
- Obstructive jaundice in a patient with cystic lesion of the head of the pancreas
- Enhancing solid component within cyst
- Main pancreatic duct > 10 mm in size

Yes

No

Consider surgery if clinically appropriate

Are any of the following worrisome features present?

Clinical: Pancreatitis

Imaging:
- Cyst > 3 cm
- Thickened/enhancing cyst walls
- Main duct size 5-9 mm
- Non-enhancing mural nodule
- Abnormal change in caliber of pancreatic duct with distal pancreatic atrophy

Yes

No

Endoscopic ultrasound

Are any of these features present?

- Definite mural nodule
- Main duct features suspicious for involvement
- Cytology: suspicious or positive for malignancy

Yes

No

What is the size of the largest cyst?

Inconclusive

< 1 cm

1-2 cm

2-3 cm

> 3 cm

CT/MRI in 2-3 years

CT/MRI yearly x 2 years, then lengthen interval if no change

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

Close surveillance alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients

ACG Western Regional Postgraduate Course - Las Vegas, NV
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EUS-FNA and Cyst Fluid Analysis of Cystic Pancreatic Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Fluid Color</th>
<th>Viscosity</th>
<th>CEA</th>
<th>Amylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>Yellow/brown</td>
<td>Thin</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>SCN</td>
<td>Colorless</td>
<td>Thin</td>
<td>Low/Undetected</td>
<td>Variable</td>
</tr>
<tr>
<td>MCN</td>
<td>Colorless</td>
<td>Usually thick</td>
<td>++</td>
<td>Variable</td>
</tr>
<tr>
<td>MCAC</td>
<td>Colorless</td>
<td>Thick</td>
<td>+++</td>
<td>Variable</td>
</tr>
<tr>
<td>IPMN</td>
<td>Colorless</td>
<td>Usually thick</td>
<td>+ to +++</td>
<td>High</td>
</tr>
</tbody>
</table>

EUS-FNA of Pancreatic Cyst

- Cyst fluid CEA 192 ng/mL optimizes non-MCN vs. MCN
- Cyst fluid cytology is insensitive but very specific for diagnosis, malignancy and MCN vs. non-MCN
- Cyst fluid DNA may help differentiate malignant/benign and mucinous vs. non-mucinous cysts

1. Brugge WR. Gastroenterology 2004;126:1330-6
Kenneth J. Chang, MD, FACG

National Coop. Panc Cyst Study

Brugge et al, Gastroenterology, 2004

Back to Clinical Scenario

6 months later, a repeat EUS shows no change in size or morphology, but the CEA level went from 168 to 550
Q 2: Now what?

1. Whipple resection
2. Repeat CT in 12 months
3. MRI/MRCP in 3 months
4. ERCP
5. Repeat EUS/FNA in 6 months

Pancreatic Cysts

• Incidence: A growing problem
• Previous diagnostic approaches
• Emerging data: the conundrum
• New problems need new solutions
CEA

- Although may help distinguish mucinous vs non-mucinous, does not distinguish IPMN vs MCN.
- Not predictive of malignant progression\(^1\)
- Not predictive of cyst size progression\(^1\)
- Serial follow-up levels may be erratic\(^2\)

1. Othman MO. Dig Liver Dis 2012; 44:844-8
2. Nakai Y. ASGE abstract submission 2012

Serial CEA values in 87 patients

Nakai Y. Chang K. DDW 2012
Not all small side-branch IPMN are benign, despite negative cytology.

Among 20 patients with < 3cm SB-IPMN, 6 (30%) had CIS (3) or invasive cancer (3) ¹

Cyst size > 3cm (*Sendai Guideline*) NOT a predictor of malignancy among 112 surgical cases²

1. Pitman MB. Pancreatology 2008;8:277-85

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**Morphology of Pancreatic Cysts by Surgical Diagnosis**

<table>
<thead>
<tr>
<th>Unilocular</th>
<th>Microcystic</th>
<th>Macrocytic</th>
<th>Cyst w/ solid component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>SCA</td>
<td>MCN</td>
<td>MCN</td>
</tr>
<tr>
<td>Retention cyst</td>
<td>IPMN</td>
<td>IPMN</td>
<td>IPMN</td>
</tr>
<tr>
<td>IPMN</td>
<td></td>
<td>SCA</td>
<td>SCA</td>
</tr>
<tr>
<td>MCN</td>
<td></td>
<td></td>
<td>Acinar</td>
</tr>
<tr>
<td>SCA</td>
<td></td>
<td></td>
<td>Cystadenoma</td>
</tr>
</tbody>
</table>

Lymphangioma

Lymphoepithelial

Acinar cell

Adenocarcinoma

Metastasis

PET

Pittman M. Cancer Cytopathology 2010; 118:1-13
Pancreatic Cysts: Conundrum

*Imaging?*

- CEA?
- Amylase?
- Biomarkers?
- Cytology?
- Size?

The answer is on the wall...

- PAS+ cuboidal glycogen-staining cells
- SCA
- MCN
- SPPT

*Frossard AJG 2003*
The answer is on the wall…

Cytology

- Yield of cytology is low
- Usually cannot distinguish MCN vs IPMN
- May not distinguish grade of dysplasia, which also may require histology
- Cannot distinguish IPMN histologic subtype

1. Furakawa T. Gut 2011; 60:509-16
Why low yield of cytology?

- Cells don’t ready shed in cyst fluid; diluted
- Even for brush or biopsy – neoplastic epithelium can be heterogeneous (spotty); similar to Barrett’s

Back to Clinical Scenario

You are now fairly sure that the patient has IPMN
Q 3: Which is most predictive of progression to cancer?

1. Male sex
2. Size of cyst
3. Main Duct type vs Side branch type
4. IPMN histologic subtype
5. CEA level

IPMN - 4 Histologic Types

Yamaguchi, H. Modern Pathology 2007;20, 552–561
IPMN - 4 Histologic Types

- Gastric
- Oncocytic
- Intestinal
- Pancreatico-biliary

283 pts with IPMN

Furukawa Gut 2011

### Table 2: Cox proportional hazards model analysis

<table>
<thead>
<tr>
<th>All data</th>
<th>HR</th>
<th>Lower boundary</th>
<th>Upper boundary</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages*</td>
<td>$3.38 	imes 10^8$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs 0A</td>
<td>10.907</td>
<td>1.187</td>
<td>100.192</td>
<td>0.0347</td>
</tr>
<tr>
<td>IA vs 0A</td>
<td>13.132</td>
<td>1.049</td>
<td>164.320</td>
<td>0.0458</td>
</tr>
<tr>
<td>IB vs 0A</td>
<td>75.202</td>
<td>8.237</td>
<td>686.580</td>
<td>1.29 $\times 10^{-4}$</td>
</tr>
<tr>
<td>IIA vs 0A</td>
<td>44.869</td>
<td>4.610</td>
<td>436.686</td>
<td>0.0011</td>
</tr>
<tr>
<td>IIB vs 0A</td>
<td>267.942</td>
<td>28.358</td>
<td>2531.694</td>
<td>1.07 $\times 10^{-6}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphological type</th>
<th>HR</th>
<th>Lower boundary</th>
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<th>$p$ Value</th>
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<tbody>
<tr>
<td>0.435</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAS vs INT</td>
<td>1.957</td>
<td>0.705</td>
<td>5.436</td>
<td>0.1975</td>
</tr>
<tr>
<td>QNC vs INT</td>
<td>1.541</td>
<td>0.495</td>
<td>4.794</td>
<td>0.4556</td>
</tr>
</tbody>
</table>

| PB vs INT          | 4.964  | 1.642          | 15.002         | 0.0045    |

<table>
<thead>
<tr>
<th>Macroscopic type</th>
<th>HR</th>
<th>Lower boundary</th>
<th>Upper boundary</th>
<th>$p$ Value</th>
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</thead>
<tbody>
<tr>
<td>0.1702</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed vs BT</td>
<td>0.947</td>
<td>0.301</td>
<td>2.983</td>
<td>0.9261</td>
</tr>
<tr>
<td>MT vs BT</td>
<td>2.109</td>
<td>0.791</td>
<td>5.623</td>
<td>0.1360</td>
</tr>
</tbody>
</table>

Furukawa Gut 2011
Pancreatic Cysts

- Incidence: A growing problem
- Previous diagnostic approaches
- Emerging data: the conundrum
- New problems need new solutions

EUS-nCLE

(needle confocal laser endomicroscopy)

Mauna Kea Technologies AQ-Flex 19
Pancreatic Cysts: nCLE

ATRAUMATIC DIFFUSE SAMPLING
AGA #1204  An International, Multi-Center Trial on Needle-Based Confocal Laser Endomicroscopy (nCLE): Results From the In Vivo CLE Study in the Pancreas With Endosonography of Cystic Tumors (INSPECT)

ASGE #500  Diagnosis of Pancreatic Cysts: Endoscopic Ultrasound, Through-the-Needle Confocal Laser-Induced Endomicroscopy and Cystoscopy Trial (DETECT)
Yousuke Nakai, Takuji Iwashita, Do Hyun Park, Jason B. Samarasena, John G. Lee, Kenneth J. Chang

DDW 2012
nCLE

- Presence of villous structures high specificity for Mucinous Neoplasia
- But sensitivity only 59%


Can we improve nCLE with “red flag” technology?

- EUS can only detect obvious nodule
- For Barrett’s, we have endoscopy & NBI
- Why not do “cystoscopy” to guide nCLE?
EUS-guided “through the needle” Cystoscopy

<table>
<thead>
<tr>
<th></th>
<th>SCA</th>
<th>MCN</th>
<th>IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth wall</td>
<td>Clear fluid</td>
<td>Smooth wall</td>
<td>Cloudy fluid</td>
</tr>
</tbody>
</table>

Conclusions (1)

- Pancreatic cysts are increasingly recognized with routine use of cross-sectional imaging
- Wide range of diagnosis: from benign to malignant (and everything in between)
- Many have characteristic (but overlapping) imaging and demographic characteristics

Conclusions (2)

- Cyst fluid CEA does not appear to predict malignant transformation
- Clinical decision-making based on cyst size alone is inadequate
- Histologic subtyping and degree of dysplasia is important for risk-stratification and will require new techniques for tissue sampling and/or intra-cystic imaging