Pancreatic Cysts and Approach to Pancreatic Lesions

Linda S. Lee, MD
Associate Director of Endoscopy; Director, Women’s Health in GI
Co-Director, Pancreas Center
Brigham and Women’s Hospital
Associate Professor of Medicine
Harvard Medical School
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Agenda

- Background
- Cyst characteristics and diagnosis
- Management: Surgery, surveillance, EUS
We’re Seeing Pancreatic Cysts Often!

- Up to 20% MRI
- 3% CT
- Over 20% autopsies

Pancreatic Cysts and Cancer

- At most 0.25% cysts with invasive cancer at diagnosis
- 0.24% invasive cancer per year in pancreatic cysts during follow-up

Types of Pancreatic Cysts

- Benign
  - Serous cystadenoma
  - Pseudocyst
  - Lymphoepithelial cyst
  - Lymphangioma
  - Cavernous hemangioma
  - Retention cyst
  - Mucinous nonneoplastic cyst

- Premalignant/malignant
  - Mucinous cystic neoplasm
  - Intraductal papillary mucinous neoplasm (IPMN)
  - Solid pseudopapillary tumor (SPEN)
  - Neuroendocrine tumor
  - Acinar cell carcinoma
  - Metastases to pancreas (ovarian cystadenocarcinoma)
Key Questions

1. Is the cyst malignant?

2. What type of cyst is it? Mucinous or nonmucinous?

3. What is the likelihood the cyst will progress to malignancy?

Cyst Characteristics and Diagnosis
Serous Cystadenoma

- Very rarely malignant
- 20% Growth

References:
Serous Cystadenoma

Very rarely malignant
Growth

Serous Cystadenoma

Very rarely malignant
Growth

Issues: Improving preop diagnosis (63-92%);
Cyst fluid loss of heterozygosity at VHL, VEGF?
Needle confocal endomicroscopy?
When to resect

Mucinous Cystic Neoplasm

Issues: Differentiating from BD-IPMN

Resect all?

Invasive cancer 15% resected MCN

Risk factors for malignancy:
- Nodule
- Size >6cm

AND <0.4% MCN <3cm without nodule had HGD or cancer

Intraductal Papillary Mucinous Neoplasm (IPMN)

- **Branch duct**: 3%
- **Main duct**: 50-70%
- **Mixed type**: 35%

**Risk factors for malignancy:**
- Solid component: OR 7.7
- Solid component > 3 cm: OR 3.0
- Main PD ≥ 3 mm: OR 2.4
- Mural nodule: OR 2.4

IPMN: Not All Risk Factors are the Same

“Hi-risk features for malignancy”
(enhancing nodule, MPD ≥ 1cm, cytology HGD or cancer, jaundice)

“Worrisome features for malignancy”
(size > 3cm, MPD 5-9mm, minor symptoms, pancreatitis, non-enhancing nodules, cytology atypical cells)

<table>
<thead>
<tr>
<th></th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi-risk</td>
<td>60%</td>
</tr>
<tr>
<td>Worrisome</td>
<td>96%</td>
</tr>
</tbody>
</table>

52% had progression
20% invasive cancer
9% HGD
Postop mortality 8%

IPMN: Sicker Patients Die From Other Reasons

Charlson comorbidity index ≥7 BAD

Non-IPMN related death within 3 years of diagnosis 11x higher

Median survival 43 months vs. 180 months (p=0.001)

- In 725 presumed/ path proven IPMN, 24% patients died
  55% within 5 years of IPMN diagnosis
  78% from non-IPMN related causes

Sahora K et al. CGH 2015.
Solid Pseudopapillary Neoplasm

Young women
Encapsulated, heterogeneous
EUS-FNA helpful >80% diagnostic
Low grade malignant potential
Surgical resection

Gil et al. ANZ J Surg 2013; Hart PA and Chari ST. Pancreatology 2015;
Diagnosis

- **MRI** of the pancreas with MRCP
  - Malignant? 76-91% accurate
  - Mucinous? 71-91% accurate
  - Specific cyst? 55-76% accurate

- **EUS-FNA**
  - Malignant? 60% sensitivity, 90% specificity
  - Mucinous? ~51-75% accurate

Chiang AL and Lee LS. World J GI 2015.
Diagnosis: Radiology with MRI

1. Is it a cyst?
   - No
     - Tumor
     - Fat
     - Diverticula
     - Aneurysm
   - Yes

2. Is there a duct communication?
   - Yes
     - IPMN
     - Pseudocyst
   - No

3. Is it microcystic?
   - Yes
     - Serous cystadenoma
     - Mucinous cystadenoma
     - Cystic neuroendocrine tumor
     - Lympho-epithelial cyst
   - No

4. Is it macrocystic?

5. Is there any mural nodules?
   - MCN-IPMN-NET-SPEN-Adenocarcinoma

6. Is there a main duct dilatation?

7. How is the Liver?
   - Cirrhosis/HCC
   - Cystic metastasis
   - FNH-Adenoma

Diagnosis with EUS: Mucinous vs. Nonmucinous

<table>
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<tr>
<th>EUS findings</th>
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<td>Morphology</td>
<td>51% accuracy</td>
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Low interobserver agreement for diagnosis of a cyst based on morphology

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<td><strong>String sign ≥1 cm, ≥1 sec</strong></td>
<td><strong>95% specificity, 94% PPV</strong></td>
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String Sign

- Place drop of fluid between fingers and measure maximum length before breaking

String Sign

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<td>Cyst fluid cytology</td>
<td>63% sensitivity</td>
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<tr>
<td>Cyst wall cytology</td>
<td>29% increased diagnostic yield</td>
</tr>
<tr>
<td>CEA &gt;192 ng/mL</td>
<td>75% sensitivity, 84% specificity</td>
</tr>
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CEA not validated
Does not distinguish malignant/ benign

Cyst Fluid CEA

- Higher CEA cutoff, increased specificity, decreased sensitivity

Van der Waaj GIE 2005.
## Diagnosis with EUS: Mucinous vs. Nonmucinous

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<td>CEA $&gt;192$ ng/mL</td>
<td>75% sensitivity, 84% specificity</td>
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<tr>
<td>KRAS mutation</td>
<td>45% sensitivity, 96% specificity</td>
</tr>
<tr>
<td>CEA + KRAS</td>
<td>76-100% sensitivity, 93% specificity</td>
</tr>
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### Diagnosis with EUS: Other Cyst Fluid Markers

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<th>Cyst Fluid Markers</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>CEA&lt;5 ng/mL</td>
<td>50%</td>
<td>95%</td>
</tr>
<tr>
<td>Amylase &lt;250 U/L</td>
<td>44%</td>
<td>98%</td>
</tr>
<tr>
<td>KRAS + allelic loss</td>
<td>25-37%</td>
<td>94-6%</td>
</tr>
<tr>
<td>GNAS</td>
<td>-</td>
<td>Highly specific for IPMN</td>
</tr>
<tr>
<td>KRAS/GNAS</td>
<td>89%</td>
<td>100%</td>
</tr>
</tbody>
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- Cyst Fluid Markers:
  - CEA<5 ng/mL: Serous, pseudocyst, cystic neuroendocrine
  - Amylase <250 U/L: Excludes pseudocyst
  - KRAS + allelic loss: Malignancy
  - GNAS: IPMN
  - KRAS/GNAS: Mucinous

- Sensitivity and Specificity:
  - CEA<5 ng/mL: 50% / 95%
  - Amylase <250 U/L: 44% / 98%
  - KRAS + allelic loss: 25-37% / 94-6%
  - GNAS: Not applicable
  - KRAS/GNAS: 89% / 100%

- References:
  - Brugge et al. Gastro 2004
  - Hong et al. GIE 2012
  - Khalid et al. GIE 2009
  - Singhi et al. Gut 2017
Diagnosis Malignant vs. Non-malignant Cysts

Nodule
Solid component
Dilated main PD
Size >3cm
Cytology

TP53/PIK3CA/ PTEN
89% sensitivity, 100% specificity HGD or cancer

Mural Nodules

• How good are we at detecting mural nodules?

- Not good: detect 40-60%
- EUS sensitivity 75%, specificity 83%
- CT sensitivity 47%, specificity 89%
Mural Nodules

- Mucus
  - Hypoechoic compared to adjacent soft tissue
  - Smooth edged
  - Hyperechoic rim

- Nodule
  - Iso/ hyperechoic
  - Not smooth edged
  - No hyperechoic rim

- Diagnostic accuracy 57% to 79% after education

Zhong et al. CGH 2011.
Mural Nodules: Can We Do Better?

- Contrast enhanced harmonic EUS
  - Injected contrast agent visualizes vascularity of nodules, cyst wall, septa
  - Differentiates mural nodule from mucus

Technique of EUS-FNA

- Cyst ≥1 cm
- 22 gauge needle
- 1 pass, drain entire cyst, then FNA collapsed cyst wall for cytology
- Target nodule/ solid component with needle
- Assess for string sign, cyst fluid CEA, amylase; potentially KRAS, GNAS
- Prophylactic antibiotics
- Safe: ~2.2% complication of 603 pts, no surgery

Diagnosis: EUS vs. MRI?

- Comparable for size, detecting septa, communication with main PD, main PD dilation
- EUS superior for classifying pancreatic cysts
- EUS may be superior for detecting mural nodules

Diagnosis: Limitations of EUS

- Poor diagnostic accuracy of cytology
- Limited sensitivity of cyst fluid markers
- Interobserver agreement moderately good only for solid component
- Role: Inconclusive imaging or worrisome or high risk features

Management: Surgery, Surveillance, EUS?
Management Guidelines

Identify patients at higher risk of cancer for surgery and EUS

2006 Sendai (IAP) 2012 IAP 2015 AGA

- Suspected MCN, IPMN
- Pancreatic protocol CT or MRI
- 1 risk factor → EUS or surgery*
- Frequent surveillance by cyst size*
- No recommendation to stop surveillance

- All incidental cysts*
- MRI pancreas with MRCP*
- Increased threshold to ≥2 risk factor*
- In 1 year and then every 2 years*
- Stop after 5 years of stability, surgically unfit*, and select resected cysts

* Freqeunt surveillance by cyst size*
Surgery

Who?

- Symptoms
- Malignant cyst
- High risk for malignancy

### Surgery: Who? IAP versus AGA

<table>
<thead>
<tr>
<th>2012 IAP</th>
<th>2015 AGA: 2 risk factors AND/OR EUS-FNA</th>
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<tbody>
<tr>
<td>All MCN, MD-IPMN and mixed IPMN</td>
<td>Solid component + dilated main PD</td>
</tr>
<tr>
<td>BD-IPMN with <strong>ANY ONE</strong> risk factor:</td>
<td>Concerning EUS-FNA</td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td></td>
</tr>
<tr>
<td>Solid component</td>
<td></td>
</tr>
<tr>
<td>Main PD ≥1 cm</td>
<td></td>
</tr>
<tr>
<td>Mural nodule on EUS</td>
<td></td>
</tr>
<tr>
<td>Cytology suspicious or positive for adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>&gt;3 cm in young, surgically fit patients</td>
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# Surgery: Who? Refined IAP?

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<td>Concerning EUS-FNA</td>
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<tr>
<td>Enhancing nodule</td>
<td></td>
</tr>
<tr>
<td>Main PD ≥1 cm</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
</tr>
<tr>
<td>Cytology HGD or cancer</td>
<td></td>
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Surveillance

Who?

• No symptoms
  +
• Following resection of certain cysts OR
  Low risk of malignancy

MRI

## Surveillance of Resected Cysts

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<th>Pathology</th>
<th>2012 IAP</th>
<th>2015 AGA</th>
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<tr>
<td>Serous cystadenoma</td>
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<td>Mucinous cystic neoplasm</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>IPMN with normal margin and no residual</td>
<td>Consider 2 and 5 years</td>
<td>None</td>
</tr>
<tr>
<td>IPMN with normal margin and residual cysts</td>
<td>As per nonresected cysts</td>
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<td>None</td>
</tr>
<tr>
<td>IPMN with normal margin and residual cysts</td>
<td>As per nonresected cysts</td>
<td></td>
</tr>
<tr>
<td>IPMN with any dysplasia at margin</td>
<td>Every 6 months</td>
<td>None (except HGD like cancer)</td>
</tr>
<tr>
<td>IPMN with cancer</td>
<td>Every 3 months</td>
<td>2 and 4 years</td>
</tr>
</tbody>
</table>

Surveillance of Nonresected Cysts

- Low risk of malignancy (<3cm, no solid component, nodule, dilated PD, EUS-FNA not concerning):

<table>
<thead>
<tr>
<th>2012 IAP</th>
<th>2015 AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/ MRI interval based on cyst size</td>
<td>Repeat MRI in 1 year and then q2 years</td>
</tr>
<tr>
<td>&lt;1cm: every 2-3 yrs</td>
<td></td>
</tr>
<tr>
<td>1-2cm: qyr x2 yrs then lengthen</td>
<td></td>
</tr>
<tr>
<td>2-3cm: EUS in 3-6 m then ↑ &amp; alternate MRI</td>
<td></td>
</tr>
<tr>
<td>&gt;3cm: alternate MRI and EUS q3-6 m</td>
<td></td>
</tr>
<tr>
<td>No explicit recommendations to stop</td>
<td>Stop after 5 years of stable cyst or nonsurgical patients</td>
</tr>
</tbody>
</table>

EUS

Who?

- High risk cysts
- Indeterminate cyst after MRI

<table>
<thead>
<tr>
<th>2012 IAP: Any ONE</th>
<th>2015 AGA</th>
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<tbody>
<tr>
<td>Pancreatitis</td>
<td>≥2 high risk features</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>Solid component</td>
</tr>
<tr>
<td>Nodule</td>
<td>Dilated PD</td>
</tr>
<tr>
<td>Dilated main PD</td>
<td>&gt;3 cm</td>
</tr>
<tr>
<td>Thick cyst wall</td>
<td>Changes in cyst</td>
</tr>
<tr>
<td>Δ PD caliber + atrophy</td>
<td>Solid component</td>
</tr>
<tr>
<td></td>
<td>Increasing PD</td>
</tr>
<tr>
<td></td>
<td>≥3 cm</td>
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Incidental pancreatic cyst on imaging

Patient evaluation:
Symptoms (pancreatitis, weight loss, jaundice) and exam
MRI pancreas/ MRCP

≥2 high risk features*

Yes
EUS-FNA

≥2 high risk features* and/or concerning EUS-FNA

Yes
Consider surgery

No
MRI in 1 year, then q2yrs until 5 years*

Yes
Stop surveillance*

No
Change with high risk feature(s) during 5 years of surveillance

*High risk features: solid component, >3cm, dilated PD

AGA Guideline Not That Accurate

- 41 pts with surgically resected pancreatic cysts: 62% sensitivity, 79% specificity
- Missed 45% IPMN with cancer or HGD
- BWH data:
  - Missed malignant cysts: 19% by Fukuoka and 25% by AGA
  - Surgeries prevented: 69% by Fukuoka and 74% by AGA

<table>
<thead>
<tr>
<th></th>
<th>AGA</th>
<th>Fukuoka</th>
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<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>154 pts MRI + EUS</td>
<td>18%</td>
<td>95%*</td>
</tr>
<tr>
<td>152 resected cysts</td>
<td>75%</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>81%</td>
<td>69%</td>
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</table>

Singhi et al. GIE 2015; Lee et al. EIO 2016.
But Maybe 5 Year Follow-up Isn’t That Crazy…

• 310 pts with asymptomatic pancreatic cysts on EUS, median f/u 87 months, all > 5 yrs

• 1% (3 pts) developed invasive pancreatic adenocarcinoma
  ➢ 1 high risk feature in 1 pt
  ➢ 2 high risk features in 2 pts

Kwong et al. CGH 2016.
New Cyst Fluid Biomarkers?

IPMN
GNAS

DNA
transcription
RNA
transcription
Protein

BRAF, CDKN2A, CTNNB1, GNAS,
KRAS, NRAS, PIK3CA, RNF43,
SMAD4, VHL; loss of
heterozygosity at CDKN2A, RNF43,
SMAD4, TP53, and VHL; PTEN

Mucinous v. nonmucinous cyst
?microRNA
Proteomics: mucin
Metabolomics: glucose, kynurenine

Serous cystadenoma
VEGF, VHL

Cytokine G-CSF?

Needle-based Confocal Endomicroscopy

Serous cystadenoma
Superficial vascular network

IPMN
Papillary projections

69% sensitivity, 100% specificity
3-6.6% pancreatitis

89% sensitivity, 100% specificity

Napoleon B et al. Endoscopy 2015; Krishna S et al. GIE 2015: AB.
Micro-biopsy Forceps

Storm AC and Lee LS. World J Gastro 2016.
Cyst Ablation

- Etoh may not be necessary
- Maybe safer without Etoh

Long-term results:
- 72% initial complete resolution
- 98% remained resolved at 6y f/u
- Unilocular and cyst <35mm predict complete resolution

Case

- 36yo female with abnormally heavy periods
- MRI pelvis: fibroids in uterus and 3.4 cm pancreatic cystic mass
Case

- 2008 MRI pancreas
- 2008 EUS: 4cm consistent with serous cystadenoma
Case

- 2009 MRI stable
- 2011 MRI: 6.8 cm, main PD 5 mm, atrophy in tail
Case

2011 EUS
- Cytology nondiagnostic
- CEA <0.2 ng/mL
- Amylase 46.4 U/L
- No k-ras or LOH mutations

What type of cyst is this?
- Patient underwent distal pancreatectomy
- Pathology: serous cystadenoma
Case

- 73yo female with history of thyroid cancer, hepatitis B, schizophrenia with incidental pancreatic cysts known since 2011, new compared with 2006. Multiple cysts in pancreas with largest 2cm in tail with nondilated main PD.

- 2012 MRI stable
- 2013 mild progression cyst in tail with mild PD dilation
Case

- MRI pancreas 7/2013
Case

- CEA 54,104 ng/mL
- Amylase 1182 U/L

What type of cyst is this?

- Cytology: suspicious for malignancy
- Pathology: mixed type IPMN with HGD and adenocarcinoma
Case

- 80yo female with hyperparathyroidism, anemia, asthma, bullous pemphigoid, goiter, dizziness and weight loss with CT showing pancreatic cysts. “Wants to live another 20 years.”
Case

- MRI: numerous cysts in pancreas, largest in head 2.8 cm, no nodules or mass

What else do you want to know?
Case

EUS:

- CEA >8000
- Amylase 49
- Cytology atypical cells

What type of cyst? What would you recommend?

Surgical pathology: IPMN LGD
Conclusions

• Important to differentiate mucinous from nonmucinous pancreatic cysts
• Evaluate pancreatic cysts with MRI pancreas/ MRCP
• Compare to baseline imaging
• EUS select patients based on imaging findings: high risk or inconclusive MRI
• EUS comparable to MRI although may be superior for detecting nodules and small masses
• EUS imaging alone inadequate for cyst diagnosis
• Cyst fluid analysis flawed: string sign, cyst wall cytology, CEA, KRAS and GNAS most useful currently
• Symptomatic, malignant, or high risk cyst → surgery
• Surveillance for low risk unresected and select resected cysts
• No further evaluation in surgically unfit patients
• Newer techniques and tools including molecular cyst fluid markers, contrast-enhanced harmonic EUS, needle-based confocal endomicroscopy and micro-biopsy forceps may help
• EUS ablation techniques may offer less invasive treatment
Limitations of EUS-FNA

- Poor diagnostic accuracy of cytology
- Limited sensitivity of cyst fluid markers
- Cannot differentiate between MCN and BD-IPMN
- Cannot differentiate between mixed/ MD-IPMN and BD-IPMN