
Walt Coyle, MD, FACG
Scripps Clinic

Outline

• Epidemiology
• Focus on cystic neoplasms
  – Not pseudocysts or necrosis
• International Consensus Guidelines
  – Sendai
  – Fukuoka
• AGA Guidelines
• Making sense of it all
• Conclusions
Epidemiology of Cysts

- Dramatic rise incidence
- “Tsunami”
- Great anxiety with patients
- Mixed guidelines
- Prediction imperfect

Approximately 15% Prevalence of Asymptomatic Pancreatic Cysts with Imaging

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/City</th>
<th>Method</th>
<th>Rate</th>
<th>Size</th>
<th>Multiple cyst</th>
<th>Cysts &gt; 5 cm</th>
<th>Cysts &gt; 3 cm</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang XM, Radiology 2002;223:547-53</td>
<td>Philadelphia MRI (all MRI)</td>
<td>19.5% (incl pts with panc sx)</td>
<td>10 mm</td>
<td>44%</td>
<td>5%</td>
<td>1.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laffan TA, AJR 2008;191:802-7</td>
<td>Ireland MDCT-16 during imaging for non-pancreatic disorders</td>
<td>2.6% (age&gt;80)</td>
<td>9 mm (2-38 mm)</td>
<td>15%</td>
<td></td>
<td></td>
<td>Increased with age and Asian race</td>
<td></td>
</tr>
<tr>
<td>Lee KS, AJG 2010;105:2079-2084</td>
<td>Boston MRI (incidental)</td>
<td>13.5%</td>
<td>7 mm (2-24 mm)</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td>They noted a majority of cysts not reported in routine MRI reports</td>
</tr>
<tr>
<td>De Jong K, Nio CY, Hermans JJ, Clin Gastro Hep 2010 9:806-811</td>
<td>Netherlands/Germany Screening MRI</td>
<td>2.4%</td>
<td>8 mm (2-54 mm)</td>
<td>12%</td>
<td>6%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girometti, Abdom Imaging 2011;36:196-205</td>
<td>Italy MRCP (for biliary disease)</td>
<td>45%</td>
<td>6.1 mm (3-24 mm)</td>
<td>59%</td>
<td></td>
<td></td>
<td>Mostly c/w branch type IPMN (71%)</td>
<td></td>
</tr>
</tbody>
</table>
Risk of Incidental Pancreatic Cysts Increase with Age

Lee KS, AJG 2010;105:2079-2084

Classification of Cysts
Pancreatic Cystic Lesions

Class by Mucin

- Non-mucinous
  - Pseudocyst
  - Serous cystadenoma
  - Solid pseudopapillary
  - Simple retention cyst

- Mucinous (high CEA)
  - MCN
  - SB-IPMN
  - MD-IPMN

Pancreatic Cystic Lesions

Class by risk

- Benign
  - Pseudocyst
  - Serous cystadenoma
  - Simple retention cyst

- Pre-malignant
  - MCN
  - SB-IPMN
  - MD-IPMN
  - Solid pseudopapillary

- Malignant: acinar, adenoCA, NET
Serous Cystic Neoplasm (SCN)

- 75% female
- Benign; occ sx by size
- Often central scar or calcification
- Found throughout pancreas
- Assoc with Van Hippel Landau Syn

Serous Cystic Neoplasm (SCN)

- Small cysts lined by glycogen rich cells
- Classic “honeycomb” appearance by EUS
- Occ oligocystic variant (few larger cysts: confuses dx)
- Resect only for symptoms
Mucinous Cystic Neoplasm (MCN)

- Mostly female (95%)
- Usually body/tail
- Lining is ovarian stroma
- Solitary lesions
- Mostly uni-locular
- Occ peripheral Ca++
- No communication with MPD

Mucinous Cystic Neoplasm (MCN)

- Size correlates with malignancy risk
- Solid component or nodule is worrisome feature
- Malignancy present in 11-38% of resected lesions
- Resection is curative and Rx of choice

Clin Gastro Hep 2004; 2: 1026
Solid Pseudopapillary tumor

- Female predominance
- Young patient
- Solid with cystic areas
- Heterogeneous appearance
- Slow growing
- Low risk for malignancy
- Resection recommended

Main Duct IPMN

- Male=female
- Older, 6-7th decade
- MD-IPMN carries greater risk for CA than SB IPMN
- Range from no symptoms, pancreatitis, wgt loss, EPI
- Intestinal and pance-biliary epithelium have highest risk for CA
IPMNs – Histologic classification

- Most common
- Usually BD-IPMN (70%)
- Low grade, small percentage develop carcinoma

- Intestinal = colloid carcinoma
- 20% of MD-IPMN

- 7% of MD-IPMN
- Least well characterized
- Worst prognosis
- Tubular carcinoma

- 3% of MD-IPMN
- Tubular carcinoma
MD-IPMN

- Classic feature of “fish eye” seen on endoscopy
- Seen less than 30%
- Nodules and masses very worrisome features
- Can also have mixed IPMN (SB and MD features)
- Resection is treatment of choice

Side Branch IPMN

- Male = female; usu >60 yo
- Most common form of IPMN
- Often multifocal
- Less likely to progress to malignancy
- Often incidental finding
- Subject of many expert opinions
EUS FNA and Pancreatic Cysts

- Pioneered by William Brugge and others
- Safe and often helpful for characterizing cysts
  - How safe is it?
  - How often does it change management?
  - Guidelines keep changing
- Helpful in surgical decision making

EUS FNA of cysts

<table>
<thead>
<tr>
<th>EUS/FNA of cystic pancreatic neoplasms</th>
<th>Papillary cyst</th>
<th>SCN</th>
<th>MCN</th>
<th>IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Evenly</td>
<td>Evenly</td>
<td>Tail</td>
<td>Head</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Pigmented histiocytes</td>
<td>Bland PAS +</td>
<td>Mucinous</td>
<td>Mucinous</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>Low</td>
<td>Low</td>
<td>Increased</td>
<td>High</td>
</tr>
<tr>
<td><strong>Cystic amylase</strong></td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Cystic CEA</strong></td>
<td>&lt; 200 ng/mL</td>
<td>&lt; 0.5 ng/mL</td>
<td>&gt; 200 ng/mL</td>
<td>&gt; 200 ng/mL</td>
</tr>
<tr>
<td><strong>K-RAS mutations</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>


EUS/FNA of Cysts

<table>
<thead>
<tr>
<th></th>
<th>MCN/IPMN</th>
<th>SCA</th>
<th>Pseudocyst</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUS</strong></td>
<td>Paucilocal, calcifications, mural nodules, mucin extrusion</td>
<td>Multilocular, honey-combed,</td>
<td>Unilocular, Thick-walled, debris, background CP</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>&gt;200-800 ng/ml</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Amylase</strong></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Mucin</strong></td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
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Risk of EUS FNA of Pancreatic Cysts

5% risk of complication in pancreatic cyst EUS FNA

Gastrointest Endosc 2011;73:283
Looking for the Holy Grail

- Molecular analysis of cyst fluid
  - KRAS, P53, loss of P16, SMAD4
  - ? Differentiate non-mucin, mucin, malignant
  - Needs 0.2 cc fluid
- Micro RNA of cyst fluid
  - Specialized labs
  - Promising early studies
- Circulating tumor cells (CTCs)

All high cost; prospective studies needed

Guidelines and Expert Opinion
2006 International Consensus Guidelines: aka Sendai criteria

- **Diagnosis and surveillance**
  - Cyst <1 cm – annual MRI
  - Cyst 1-3 cm: EUS and MRI.
    - If high risk stigmata -> surgery
    - If no HRS -> surveillance imaging 3-12 months

- **Indications for surgery**
  - Cyst > 3 cm
  - Or any high risk stigmata (mural nodules, dilated MPD, positive cytology)

Tanaka, Pancreatology 2006

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International Guidelines for Pancreatic Cysts

[Diagram showing diagnostic and surveillance protocols for pancreatic cysts based on size and high-risk stigmata]

Tanaka, Pancreatology 2006
2012 International Consensus Guidelines

- **“High-risk stigmata”**
  - Jaundice
  - Solid component
  - MPD size $\geq 10$ mm

- **“Worrisome features”**
  - Pancreatitis
  - Cysts $\geq 3$ cm
  - Thickened/enhancing cyst wall
  - Non-enhanced mural nodule
  - MPD size 5-9 mm
  - Abrupt change in MPD caliber with distal pancreatic atrophy

Tanaka, Pancreatology 2012;12:183-97T
Comparison of ICG for Suspected Branch IPMN

2006 Sendai
- Size < 1 cm: MR or thin slice CT in 5 years
- Size 1-2 cm: MR or CT + 4 cm every 6-12 mos
- Size > 2 cm: Symptomatic, size > 3 cm or yes positive high-risk stigmata: EUS and MRCP or ERCP

2012 Sendai
- Size < 1 cm: MR or thin slice CT in 5 years
- Size 1-2 cm: MR or CT + 4 cm every 6-12 mos
- Size > 2 cm: Symptomatic, size > 3 cm or yes positive high-risk stigmata: EUS and MRCP or ERCP

Changes in the International Consensus Criteria

- More use of EUS recommended
- Less surveillance of <1 cm cysts
- Can observe BD-IPMN >3 cm if:
  - No high risk stigmata
  - Prior: resect >3 cm
American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swarnop Veiga, Barry Ziring, Rajeev Jain, and Paul Moayyedi, and the Clinical Guidelines Committee

1Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; 2Division of Internal Medicine, Sidney Kimmel College of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania; 3Texas Digestive Disease Consultants, Dallas, Texas; 4Division of Gastroenterology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada

American Gastroenterological Association Technical Review on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

James M. Scheiman, Joo Ha Hwang, and Paul Moayyedi

1Department of Internal Medicine and Gastroenterology, University of Michigan Medical School, Ann Arbor, Michigan; 2Division of Gastroenterology, Department of Medicine, University of Washington, Seattle; Washington, and 3Division of Gastroenterology, Hamilton Health Sciences, Farncombe Family Digestive Health Research Institute, McMaster University Hamilton, Ontario, Canada

*Only applies to asymptomatic pancreatic neoplastic cysts*
- **Excludes**
  - Solid papillary lesions, Cystic adenocarcinoma, Neuroendocrine tumors
  - Main duct IPMN without BD involvement
  - High risk conditions
    - Familial pancreatic cancer and Hereditary pancreatitis
*Uses Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (Guyatt, BMJ 2008;336:924-26)*
*Meant to guide community primary care, radiologists, and gastroenterologists*
15% prevalence of asymptomatic pancreatic cysts with imaging
- 25% after age 70

Rare chance of cancer in incidentally found cyst on MRI
- 10 per 100,000 mucinous invasive

0.24%/year risk of malignant transformation

Risk factors for prevalent cancers
- Cyst size >= 3 cm (OR 2.97)
- Dilated main pancreatic duct (OR 2.4)
- Solid component (OR 7.7)

MRI preferred for surveillance
- Less radiation than CT and better definition of ductal communication with cyst
- Less invasive than EUS

15% risk of invasive malignancy in highly selected cysts undergoing resection

Surgical risks
- Mortality 2%
  - 6.6% in all hospitals (SEER)
  - 2% in centers of excellence
- Morbidity 30%

Gastro 2015;148:824-848
ISSUES RELATED TO THE CONDUCT OF SURVEILLANCE

1. The AGA recommends that before starting any pancreatic cyst surveillance program, patients should have a clear understanding of programmatic risks and benefits.

2. The AGA suggests that patients with pancreatic cysts $<3$ cm without a solid component or a dilated pancreatic duct undergo MRI for surveillance in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics.

   (Conditional recommendation, Very low quality evidence)

Gastro 2015;148:819-822
3. The AGA suggests that pancreatic cysts with at least 2 high-risk features, such as size $\geq 3$ cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with EUS-FNA.

(Conditional recommendation, Very low quality evidence)

4. The AGA suggests that patients without concerning EUS-FNA results should undergo MRI surveillance after 1 year and then every 2 years to ensure no change in risk of malignancy.

(Conditional recommendation, Very low quality evidence)

Gastro 2015;148:819-822

5. The AGA suggests that significant changes in the characteristics of the cyst, including the development of a solid component, increasing size of the pancreatic duct, and/or diameter $>3$ cm, are indications for EUS-FNA.

(Conditional recommendation, Very low quality evidence)

6. The AGA suggests against continued surveillance of pancreatic cysts if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate.

(Conditional recommendation, Very low quality evidence)

Gastro 2015;148:819-822
WHEN TO OFFER SURGERY FOR PANCREATIC CYSTS

7. The AGA suggests that patients with both a solid component and a dilated pancreatic duct and/or concerning features on EUS and FNA should undergo surgery to reduce the risk of mortality from carcinoma. (Conditional recommendation, Very low quality evidence)

8. Recommends that if surgery is considered for a pancreatic cyst, patients are referred to a center with demonstrated expertise in pancreatic surgery. (Strong recommendation, very low quality evidence)

SURVEILLANCE AFTER SURGERY

9. The AGA suggests that patients with invasive cancer or dysplasia in a cyst that has been surgically resected should undergo MRI surveillance of any remaining pancreas every 2 years. (Conditional recommendation, Very low quality evidence)

10. The AGA suggests against routine surveillance of pancreatic cysts without high-grade dysplasia or malignancy at surgical resection. (Conditional recommendation, Very low quality evidence)
Summary of Main Changes

- Selective use of EUS
- Surveillance every 2 years
- Stop surveying after 5 years
- Surgery only if ≥2 concerning features on MRI confirmed on EUS
- Surgery at expert centers only
- No surveillance after surgery if no cancer or dysplasia

Coyle Comments (expert?)

- SB-IPMNs are like Barrett’s esophagus
  - Common and results in unneeded anxiety
  - Too much surveillance; $$$
  - Risk factors for malignancy not clear
- Most patients can be surveyed q 2 yrs
- No data on stopping at 5 yrs (talk to pt)
- EUS helpful but overused and FNA is not without risk (Benefit)
- EUS for 1 or 2 high risk features
Interesting Abstracts

- Does rate of cyst growth matter
- What may be the consequences if we follow the guidelines

Most SB-IPMNs should be observed per Consensus guidelines
- Size is a worrisome feature but growth rate not defined as risk
- 284 pts without high risk or worrisome criteria: retrospective review
  - Repeated imaging (median 4)
  - Median 56 month follow up
  - Malignant development

DDW 2015
DDS 2015:60:380
### Diagnostic Performance of BD-IPMN Growth Rates and Total Growth for Predicting Invasive Carcinoma

<table>
<thead>
<tr>
<th>Growth Rate</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2mm/yr Growth</td>
<td>78</td>
<td>90</td>
<td>18</td>
<td>99</td>
<td>88</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5mm/yr Growth</td>
<td>56</td>
<td>97</td>
<td>36</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10mm Total Growth</td>
<td>100</td>
<td>95</td>
<td>40</td>
<td>100</td>
<td>95</td>
</tr>
</tbody>
</table>

### Cyst growth and Cancer

[Graph showing cyst growth and cancer progression over time]
Diagnostic Performance of BD-IPMN Growth Rates and Total Growth for Predicting Invasive Carcinoma

- Worrisome features for malignant transformation
  - > 2mm/yr cyst growth
  - >10mm total cyst growth

- Coyle Comments:
  - Retrospective and small numbers
  - Adds another feature to use during surveillance
  - NPV is very good and can reassure patients and providers

Impact of Recent Guidelines on the Role of EUS in Diagnosis of Asymptomatic Neoplastic Pancreatic Cysts

- EUS is common for evaluation of pancreatic cysts
- 2015 AGA guidelines: EUS only for cysts with at least 2 high risk features
  - Size >3cm, dilated main PD, presence of solid component
- Investigated impact of new AGA guidelines on sensitivity of EUS for pancreatic cancer and impact on EUS cases

AJG 2015,110 S; Abs 12
Methods

- Retrospective study
- EUSs performed between 2003 and 2014
- Pseudocysts were excluded
- Cysts were assessed for performance of EUS based on the presence or absence of high risk features per 2015 AGA guidelines
- Cyst aspirate and FNA results were obtained from medical records

Results

- 140 pts (68 males) underwent EUS
- Final path diagnosis: SB-IMPN in 62 (44%) and SCN in 18 (13%)
- 5 patients had cancer (3.5%)
  - All cancer pts had at least 1 high risk feature
  - Only 3 of 5 patients had at least 2 high-risk features
  - 4 of 5 patients with pancreatic cancer did NOT have a dilated main PD
  - 3 or 5 patient with cancer had cysts >3 cm
  - 4 of 5 patients had EUS and/or radiographic evidence of a solid component

AJG 2015,110 S; Abs 12
Results/Discussion

- Requirement of at least 2 high-risk features would decrease EUSs by 93%
  - Reduced sensitivity to 60%
- Using 1 high risk feature, volume of EUS would decrease by 71% and have sensitivity of 100%
- Authors conclude that limiting EUS to patients with 2 high risk features would reduce sensitivity for pancreatic malignancy
- They suggest performing EUS for patients with one or more high risk features

Where are we now?
Challenge is predicting who will develop symptomatic cancer in future

Miss cancer cure

Complications of testing
- Overtreatment
- Unnecessary costs

Approach to Pancreatic Cysts
- Use your brain and the guidelines
- Be patient specific and focused
- Reassure the patient and primary doc
- Older patient with MMP: do nothing
- If cannot have ever have surgery:
  - Why survey?
- Healthy patient with MCN, MD-IPMN, high risk features:
  - Eval for surgery vs intense surveillance

Courtesy of Tom Savides
Approach to Pancreatic Cysts

- For SB-IPMN: guidelines helpful
  - Survey less frequently
  - EUS for 1-2 high risk features
    - FNA only if will change mgt
  - Talk to patient about stopping at 5 yrs
- Refer to experienced pancreatic surgeons

The Future

- Uncover natural history
- Better imaging: more conclusive
- Biomarker to risk stratify
  - Cyst fluid
  - Blood or gene analysis would be ideal
- Role for ablation
  - Alcohol or paxlitaxol
  - Very selected patients (Barrett’s example)
Questions?

- Cyst ablation remains controversial
  - Outcomes and complications (10%)
- Ethanol believed to be main risk
- Promising data with taxol in small studies
- CHARM Study: Prosp, DB, randomized
  - Cyst aspiration followed by Ethanol (80%) or saline
  - All cysts treated with 3 mg/ml paclitaxel and 19 mg/ml gemcitabine
  - 12 month f/u: 1° endpt>> Cyst volume reduction

Is Alcohol Required for Effective Pancreatic Cyst Ablation? the Prospective Randomized CHARM Preliminary Trial Pilot Study
CHARM Study

- 22 patients; cysts 1-5 cm, SB-IPMN, mucinous by CEA and imaging
- Results: 10 in Ethanol/12 Ethanol free
- Both arms 90% reduction
- Pancreatitis: 1 case, ethanol arm
- Cyst reduction up to one year

<table>
<thead>
<tr>
<th></th>
<th>% Reduction in cyst size after 3 m</th>
<th>% Reduction in cyst size after 6 m</th>
<th>Complete Response after 6 m</th>
<th>Complete Response after 12 m</th>
<th>Major complications</th>
<th>Minor complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol arm</td>
<td>74%</td>
<td>91%</td>
<td>3/5 (60%)</td>
<td>3/4 (75%)</td>
<td>1/10 (10%)</td>
<td>3/10 (30%)</td>
</tr>
<tr>
<td>Free alcohol arm</td>
<td>81%</td>
<td>90%</td>
<td>3/5 (60%)</td>
<td>3/4 (75%)</td>
<td>0/12 (0%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Overall in both arms</td>
<td>77.5%</td>
<td>90.5%</td>
<td>6/10 (60%)</td>
<td>6/8 (75%)</td>
<td>1/22 (4.5%)</td>
<td>3/22 (14%)</td>
</tr>
</tbody>
</table>
Cyst reduction in ethanol free arm

Charm Study

- No difference in either arm
- Ethanol not required in ablation
- Adverse events related to ethanol
- Pilot study only, no long term data

Coyle Comments:
- What cysts need ablating? Long term data lacking>> reduction in malignancy
- Chemo Rx in patients with benign lesions
Case Two Presentation
2015

Walter J. Coyle, MD, FASGE, FACG

Case 2

- 73 yo male found to have abnormal CT of pancreas (CT for benign pulm lesion).
  - No abdominal pain
  - No nausea or vomiting
  - No diarrhea
  - 20lb weight loss over 6 months
  - May have had bout of pancreatitis age 52
- PMH: CAD, HTN, DM 2, CKD, COPD
- PSH: Hernia repair
Case 2

- FH: no pancreatic disease or GI cancers
- SH: Heavy tobacco use (>100 pack yr) and h/o heavy EtOH use (none for > 10 yrs)
- Meds: Invokana, losartan, Crestor, Zetia, aspirin, omeprazole, MDIs, MVIs
- ROS: non focal
- PE: VSS, non-tender, mild cachexia

Case 2

- CBC: Mild normochromic anemia
  - Ferritin: normal
- LFTs: Nl alk phos, AST: 56  ALT: 62
  - Albumin: 3.2
- Fecal elastase: <50
- Amylase/Lipase: Normal
Case 2: Diagnosis

- Mixed IPMN
  - No definite mass by EUS
  - EUS FNA of large cyst, thick septae
  - Gelatinous material
  - No abnormal cells

- Exocrine pancreatic insufficiency
  - Pancreatic enzymes begun

Case 2: Long Term Mgt

- Expectant: Close f/u

- Surgery: High risk patient
  - How much to resect
  - Leave tail vs total panc