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All attendees will be muted and will remain in “Listen Only Mode”.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

**Week 26 – Thursday, June 29, 2023**
Breathing Past Burnout
Faculty: S. Priya Narayanan, MD, Michel Fishman, and Juan Murua
At Noon and 8pm Eastern

**There will be no VGR on Thursday July 6th**

**Week 28 – Thursday, July 13, 2023**
Going Green: Improving Your Endoscopy Unit’s Carbon Footprint
Faculty: Rabia A. de Latour, MD
Moderator: Swapna Gayam, MD, FACG
At Noon and 8pm Eastern

Visit [gi.org/ACGVGR](http://gi.org/ACGVGR) to Register

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ACG 2023
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VANCOUVER, CANADA

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Disclosures

V. Raman Muthusamy, MD, MAS, FACP
- Boston Scientific Corporation: Consultant, Grant/Research Support
- CapsoVision Inc: Stock Options
- Endogastric Solutions: Advisory Committee/Board Member
- Medtronic: Consultant
- Motus GI: Advisory Committee/Board Member

Anne Marie Lennon, MD, PhD, MBBCh, FACP
- CancerSEEK: Patent Holder

John M. DeWitt, MD, FACP
- Ariel Precision Medicine: Consultant
- Boston Scientific Corporation: Consultant

*All of the relevant financial relationships listed for these individuals have been mitigated
Diagnostic Evaluation of Pancreatic Cystic Lesions

V. Raman Muthusamy, MD, MAS, FACP
Medical Director of Endoscopy, UCLA Health System
Professor of Clinical Medicine
David Geffen School of Medicine at UCLA
Outline

- Epidemiology and risk of pancreatic cysts
- What are the types of pancreatic cysts and their imaging characteristics?
- Tests Performed on Cyst Fluid
- Role of Cytology/Tissue Acquisition
- Novel diagnostic methods
- Summary/Conclusions

Prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>N</th>
<th>Mean Age</th>
<th>Male (%)</th>
<th>Cyst (%)</th>
<th>Median Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laffan</td>
<td>CT</td>
<td>2832</td>
<td>58</td>
<td>51%</td>
<td>2.6%</td>
<td>8.9 mm</td>
</tr>
<tr>
<td>De Jong</td>
<td>MRI</td>
<td>2803</td>
<td>51</td>
<td>65%</td>
<td>2.4%</td>
<td>8.0 mm</td>
</tr>
<tr>
<td>Girometti</td>
<td>MRI</td>
<td>101</td>
<td>NR</td>
<td>NR</td>
<td>37.6%</td>
<td>6.0 mm</td>
</tr>
<tr>
<td>Ip</td>
<td>CT/MRI</td>
<td>2561</td>
<td>66</td>
<td>38%</td>
<td>4.2%</td>
<td>10 – 20 mm</td>
</tr>
<tr>
<td>Lee</td>
<td>MRI</td>
<td>616</td>
<td>54</td>
<td>42%</td>
<td>13.5%</td>
<td>6.0 mm</td>
</tr>
<tr>
<td>Matsubara</td>
<td>MRI</td>
<td>1226</td>
<td>69</td>
<td>54%</td>
<td>10%</td>
<td>8.0 mm</td>
</tr>
<tr>
<td>Zhang</td>
<td>MRI</td>
<td>1444</td>
<td>55</td>
<td>48%</td>
<td>19.6</td>
<td>&lt; 10.0 mm</td>
</tr>
</tbody>
</table>

Scheiman et al. Gastroenterology 2015;824-48

Prevalence 15% (range: 2 – 38%)
Risk of cancer at the time of imaging: 0.25%
Prevalence Increases With Age

![Graph showing prevalence increases with age]


Modern Estimate of Cyst Prevalence

- Thiruvengadam S, et al, DDW 2021, manuscript in review

3279 patients undergoing MRI in 2018
2962 w/o pancreatic indication

<table>
<thead>
<tr>
<th>Cyst Size</th>
<th>Original</th>
<th>Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5mm</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>5-9mm</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>10-30mm</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>&gt;30mm</td>
<td>1%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Thiruvengadam S, et al, DDW 2021, manuscript in review
### What’s the Risk? Data From Surgical Series

<table>
<thead>
<tr>
<th>Cyst Type</th>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Estimate (95% CI)</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Cancer</td>
<td>27</td>
<td>2796</td>
<td>15% (12-18)</td>
<td>76.5%</td>
</tr>
<tr>
<td>IPMN</td>
<td>Cancer</td>
<td>111</td>
<td>10,812</td>
<td>25% (23-27)</td>
<td>82%</td>
</tr>
<tr>
<td>IPMN</td>
<td>HGD/Cancer</td>
<td>99</td>
<td>9,249</td>
<td>42% (39-45)</td>
<td>88%</td>
</tr>
<tr>
<td>MCN</td>
<td>Cancer</td>
<td>12</td>
<td>603</td>
<td>15% (9-22)</td>
<td>81%</td>
</tr>
<tr>
<td>SCN</td>
<td>Cancer</td>
<td>5</td>
<td>295</td>
<td>2.2% (0.3-5.7)</td>
<td>92%</td>
</tr>
</tbody>
</table>

Surgical data – The risk is real
Bias?

---

### Longitudinal Risk of Cancer

<table>
<thead>
<tr>
<th>Cyst Type</th>
<th>Number of Studies</th>
<th>N</th>
<th>Follow Up in Pt-Yrs</th>
<th>Cancers</th>
<th>Incident cases/yr</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>22</td>
<td>6240</td>
<td>18,079</td>
<td>42</td>
<td>0.24% (0.12-0.36)</td>
<td>29.5%</td>
</tr>
<tr>
<td>IPMN</td>
<td>37</td>
<td>3980</td>
<td>14,830</td>
<td>112</td>
<td>0.72% (0.48-1.08)</td>
<td>74%</td>
</tr>
</tbody>
</table>

Per-year risk is low!
But surgery is also not without risk!

- 74 studies, 5484 pts
  - Mortality 2.1%
  - SEER database (729 pts) 6.6%

- 49 studies, 3992 pts
  - Morbidity 30%
  - Major events e.g. fistula

Surgical Caveats

- 5-year survival post-cyst resection in patients with cancer approximately 35%
- Most surgical series still have many patients without HGD/CA (typically 40%)

Outline

- Epidemiology and risk of pancreatic cysts
- What are the types of pancreatic cysts and their imaging characteristics?
- Tests Performed on Cyst Fluid
- Role of Cytology/Tissue Acquisition
- Novel diagnostic methods
- Summary/Conclusions
Differential Diagnosis

Goal: Differentiate Mucinous from Non-mucinous cysts

- **Asx Panc Cyst**
  - Non-neoplastic (NNPC)
    - Pseudocyst
      - True cyst
      - Retention cyst
      - Lymphoepithelial Cyst
  - Neoplastic (PCN)
    - Serous Cystic Neoplasm
    - Mucinous Cystic Neoplasm
    - Intraductal Papillary Mucinous Neoplasm
    - Solid Pseudopapillary Epithelial Neoplasm
  - Cystic Degeneration of Solid Neoplasms
    - Ductal Adenocarcinoma
    - Acinar Cell Neuroendocrine

Increasing Malignant Risk

Pancreatic Cystic Neoplasms

- **Serous cystic neoplasm (SCN)**
  - microcystic, macrocystic, oligocystic
  - “honeycomb” appearance
  - female predominance (75%), 60-70 years
  - body/tail > head
  - Essentially no malignant potential (25 reported cases)
  - Resect for symptoms

- cuboidal epithelium

American College of Gastroenterology
Cross-sectional Imaging: SCN

- Mucinous cystic neoplasm (MCN)
  - unilocular, oligocystic
  - Ovarian stoma
  - female predominance, 40-60 years
  - body/tail > head
  - Prevalence of malignancy ~ 15%
  - Malignant potential over time

Pancreatic Cystic Neoplasms: MCN
Cross-sectional Imaging: MCN

Pancreatic Cystic Neoplasms

- IPMN
  - Dilation of main duct, branch duct or both
  - M/F ratio roughly equal, 60-70 years
  - head > body/tail

Pancreatic Cystic Neoplasms

- IPMN
  - Main Duct – prevalence of malignancy as high as 40%
  - Always consider surgical referral
  - Branch Duct – lower prevalence of malignancy ~10-25%
  - May be multifocal
  - Variable treatment strategy
  - Mixed Type – main duct + branch duct
  - Treat as Main Duct Type

Cross-sectional Imaging: Main Duct IPMN

[Image of MRI scan showing a main duct with an arrow pointing to a lesion]
Cross-sectional Imaging: Branch Duct IPMN

Cross-sectional Imaging: Multifocal Branch Duct IPMN
Cross-sectional Imaging: Mixed Type IPMN

Pancreatic Cystic Neoplasms

- Solid Pseudopapillary Neoplasm (SPN)
  - Low grade malignant neoplasm
  - Young women (<35 years)
  - Monomorphic cells (often difficult to distinguish from neuroendocrine), pseudopapillae
  - Hemorrhagic
  - Surgical resection
What are we looking for?

- **High risk stigmata:**
  - Obstructive jaundice due to cyst
  - Enhanced solid component
  - MPD size of ≥10 mm

- **Worrisome features:**
  - Size ≥3 cm
  - Thick or enhancing wall
  - Mural Nodule (non-enhancing)
  - MPD size of 5-9 mm,
  - Abrupt change in the MPD caliber with distal pancreatic atrophy

Tanaka et al, Sendai Guidelines 2012
What are we looking for? (#2)

- Symptoms/Labs
  - Jaundice secondary to the cyst
  - Acute pancreatitis due to the cyst
  - Elevated Ca 19-9 when no benign explanation is present

- Imaging Findings
  - Mural nodule/solid component
  - Main PD diameter > 5 mm
  - Change in main PD caliber with upstream atrophy
  - Size > 3 cm
  - Increase in cyst size ≥ 3 mm/yr

- Cytology
  - High Grade Dysplasia/Cancer

For Identifying Benign vs. Malignant:
- MRI sensitivity 76% [67-84]
- MRI specificity 80% [74-85]
- MRI similar to CT
- Contrast enhanced MRI improves sensitivity

Outline

- Epidemiology and risk of pancreatic cysts
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What is the Role of EUS?

EUS Capabilities:

- EUS Imaging can:
  - Identify intracystic mucin, nodules
  - Determine relationships to vasculature, main duct, resectability
  - Provide high resolution imaging of the parenchyma

- EUS imaging alone is often inadequate to distinguish cyst types and malignant risk
When is EUS Referral Not Necessary?

- Cyst size < 1 cm
- Cyst arising in setting of acute pancreatitis (*cystgastrostomy)
- Elderly, poor surgical candidate
- Classic CT/MRI findings
  - Large hemorrhagic cyst in young woman
  - Microcystic lesion in tail with central scar

EUS-FNA

- Cyst Fluid Analysis (CFA):
  - Cytology – low yield, sensitivity 40-60%
  - Chemical Analysis
    - CEA
    - Amylase
    - kras mutation, DNA analysis – promising but still investigational
- Safe:
  - Pancreatitis 1-3.5%
  - Bleeding 1.5-6%
  - Fever 0.6% (? Need for prophylactic antibiotics)
EUS-FNA: Cyst Fluid Analysis: Cooperative Pancreatic Cyst Study

Overall Accuracy 79%

CEA insufficient for diagnosis of malignancy

EUS-FNA: Cyst Fluid Analysis

<table>
<thead>
<tr>
<th>Fluid Color</th>
<th>Viscosity</th>
<th>CEA (&gt;192)</th>
<th>Amylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>Dark, Yellow/Brown</td>
<td>Thin</td>
<td>Low</td>
</tr>
<tr>
<td>SCN</td>
<td>Clear/Bloody</td>
<td>Thin</td>
<td>Low</td>
</tr>
<tr>
<td>MCN</td>
<td>Clear</td>
<td>Thick</td>
<td>High</td>
</tr>
<tr>
<td>IPMN</td>
<td>Clear</td>
<td>Thick</td>
<td>High</td>
</tr>
</tbody>
</table>

Molecular Analysis of Cyst Fluid

- Khalid, GIE 2009 (N=113; 40 CA; 48 pre-CA; 25 benign)
  - K-ras 96% specific (OR-20.9)
  - Allelic loss amplitude (>82%), elevated DNA count (ODR>10) associated with malignancy
  - 10 cysts with negative cytology were malignant by DNA tests
- Lee, JOP 2014 (N=257, 8 cancers; only 33 w/ surgery)
  - K-ras specific (98%), but not sensitive (12%); not better than CEA/amylase
- Al Haddad, GIE 2014 (N=48; mucinous cyst in 38)
  - Sensitivity of 50%; specificity of 80%; accuracy of 56.3%
  - No significant difference in accuracy between DNA and CEA/cytology
- Al Haddad, Endoscopy 2015 (N=492; 10 centers)
  - Integrated Molecular pathology equal to Sendai 2012 for low risk lesions
  - Increased accuracy for predicting risk of CA c/t Sendai 2012
Molecular Analysis of Cyst Fluid

- Systematic Review/Meta-analysis
- EUS cyst fluid analysis for KRAS & GNAS mutations to diagnose IPMN & MCN
- 6 studies, 185 lesions
- Combination better than either alone

- For IPMN, KRAS & GNAS combination
  - Sensitivity 94% [72-99]
  - Specificity 91% [72-98]
  - Diagnostic accuracy 97 [95-98]
  - All were better than CEA

- For MCN, KRAS & GNAS combination
  - Sensitivity & Specificity similar to CEA
  - Diagnostic accuracy better than CEA 97%
  - c/t 89%, p < 0.001.


Cyst Fluid Glucose Levels

- Zikos et al, Am J Gastro 2015
  - Glucose < 50 mg/dl is associated with mucinous cysts
  - Laboratory glucose<50 mg/dl had a sensitivity of 95% and a specificity of 57% (LR+ 2.19, LR- 0.08)
  - Glucometer glucose<50 mg/dl had a sensitivity of 88% and a specificity of 78% (LR+ 4.05, LR- 0.15)
  - Reagent strip glucose had a sensitivity of 81% and a specificity of 74% (LR+ 3.10, LR- 0.26).
  - CEA had a sensitivity of 77% and a specificity of 83% (LR+ 4.67, LR- 0.27).
  - The combination of having either a glucometer glucose<50 mg/dl or a CEA level>192 had a sensitivity of 100% but a low specificity of 33% (LR+ 1.50, LR- 0.00).

- Smith et al, AJG Dec 2021 (online)
  - CEA of ≥192 ng/ml had a sensitivity of 62.7% and specificity of 88.2% in differentiating MNPCs, while glucose ≤25 mg/dl had a sensitivity and specificity of 88.1% and 91.2%.
Meta-Analysis of Cyst Fluid Glucose Levels


Cyst fluid glucose level < 50 compared to CEA > 192
No benefit to CEA + glucose to glucose alone

Outline

- Epidemiology and risk of pancreatic cysts
- What are the types of pancreatic cysts and their imaging characteristics?
- Tests Performed on Cyst Fluid
- Role of Cytology/Tissue Acquisition
- Novel diagnostic methods
- Summary/Conclusions
Summary Data on Cytology

- Usually done by spinning down and assessing cyst fluid
- Variability in what constitutes a positive cytology
- Meta-analyses
  - 2008 – Thosani et al.
    - 11 studies, 376 patients; all had histopathologic diagnosis and EUS-FNA
    - Sensitivity was 63% [56-70]; specificity was 88% [83-93]; AUC 0.89
  - 2014 – Thornton et al.
    - 18 studies, 1438 patients
    - Sensitivity was 54% [49-59] and specificity 93% [90-95]

EUS-FNA with moderate sensitivity but good specificity


EUS-guided Cytologic Brushings

- 2007 : Al-Haddad et al
  - Pilot study of 10 pts with cysts ≥20 mm; EUS-FNA followed by brush cytology
  - Brushings superior in 7/10 cases
  - 2 adverse events (1 major and 1 minor intracystic bleed)

- 2018 : Larino-Nola et al
  - RCT of EUS cytologic brushing (N=31) vs. EUS-FNA (N=34)
  - Unable to perform brushings in 3 pts; mean cyst size was 28.2 mm (16-60 mm)
  - No difference in diagnostic accuracy of EUS-EB c/t EUS-FNA by either ITT or PP analysis (44.8% vs 41.1%, p = 0.77 and 38.4% vs 45.9%, p = 0.55).

Specialized Biopsy Forceps

- Works thru 19G EUS-FNA needle

TTN Forceps Biopsy

- Yang et al, CGH, July 2019
  - 114 cysts, 7 centers, prospective open-label study, 2016-2018
  - Mean cyst size = 35 mm
  - 19 with failed TTN biopsy
  - 75/95 with successful biopsy achieved a histologic diagnosis
  - 14/14 with available surgical pathology had concordance
  - Adverse events:
    - Acute pancreatitis in 5.3%
    - Self limited bleeding in 6.1%

65.7% Diagnostic Yield with TTN Biopsy

SR & Meta-Analysis: TTN Forceps Biopsy

- 11 studies, 490 patients
- 8 compared TTNB w/ cytology/CFA
- Sample adequacy was 85.3% [78.2-92.5]
- TTNB w/ better adequacy and diagnostic accuracy
  - Diagnostic accuracy 78.8%
  - Sensitivity = 82.2%
  - Specificity = 96.8%
  - Mean 3.121 [2.98-3.25] passes
  - Bleeding 4%, pancreatitis 2%

EUS-FNB for Pancreatic Cysts

Table 2: Fine Needle Biopsy and Core Histologic Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total Patients (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients (n = 44)</td>
<td>N (N, %)</td>
</tr>
<tr>
<td>Tissue Adequacy</td>
<td>38 (86.4)</td>
</tr>
<tr>
<td>Mean Number of Needle Passes ± SD</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td>Mean Specimen Length (mm ± SD)</td>
<td>13.3 ± 10.3</td>
</tr>
<tr>
<td>Diagnosis based on Core Biopsy</td>
<td></td>
</tr>
<tr>
<td>SCN</td>
<td>22 (50.0)</td>
</tr>
<tr>
<td>IPMN</td>
<td>7 (15.9)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5 (11.4)</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Diffuse Large B-cell Lymphoma</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>MCN</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Non-diagnostic</td>
<td>6 (13.6)</td>
</tr>
<tr>
<td>Adequate FNA Specimen based on Touch</td>
<td>30 (68.2)</td>
</tr>
<tr>
<td>Prep of FNB Specimen</td>
<td></td>
</tr>
<tr>
<td>Discordant FNA and core biopsy findings</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Upstaging pathology based on core biopsy</td>
<td>8</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>4 (9.1)</td>
</tr>
</tbody>
</table>

Overall FNB Diagnostic Rate = 86.4%
Case History: Pancreas Cyst

- 28 yo female with no personal or FH of pancreas disease
- Prior EUS showed 2.7 x 2.5 cm mid body cyst; cyst fluid amylase was 291 and CEA is 0.2.
- Not enough fluid for DNA analysis; cytology negative

Representative Case #2
Imaging: Computed Tomography

NECK OF PANCREAS, CYST (ENDOSCOPIC ULTRASOUND-GUIDED CORE BIOPSY):
- Predominantly blood and benign pancreatic parenchyma with focal benign cuboidal epithelial cyst lining, consistent with serous cystadenoma
- IHC stains and PAS with and without diastase stains are confirmatory (see microscopic description and IHC report for additional details)

Case History: EUS-FNB
Outline

- Epidemiology and risk of pancreatic cysts
- What are the types of pancreatic cysts and their imaging characteristics?
- Tests Performed on Cyst Fluid
- Role of Cytology/Tissue Acquisition
- Novel diagnostic methods
- Summary/Conclusions

What’s Next? Contrast Enhanced EUS


12 mural nodules, 5 without
CEUS with sensitivity of 100%, specificity of 80%, accuracy 92%
What’s Next: Extending Our Reach

- Needle-based confocal laser endomicroscopy (nCLE)

nCLE for Serous Cystic Neoplasms: Superficial Vascular Network

- Napoleon, Endoscopy, 2015
  - 3 centers, 31 patients
  - Unknown type of panc cyst
  - EUS-FNA + nCLE
  - Final Dx:Surgery/+ cytopath or committee consensus
  - Superficial vascular network only seen in serous cystic neoplasms
    - Accuracy 87%
    - Sensitivity: 69%
    - Specificity & PPV – 100%
    - NPV – 82%
    - IOA – kappa of 0.77 (substantial)

nCLE for Cystic Neoplasms:

• Compared n-CLE w/ cytology and CEA
• 144 pts; 65 w/ surgical pathology correlation
• Mean cyst size 3.6 cm
• 3.5% pancreatitis rate (all mild)


**Outline**

• How common and risky are pancreatic cysts?
• What are the types of pancreatic cysts?
• How should we evaluate and follow them?
• Novel diagnostic methods
• Summary/Conclusions
Cysts are common, increasingly diagnosed on cross-sectional imaging tests.

They exhibit variable behavior:
- Key is to distinguish mucinous versus non-mucinous
- Clinical and imaging characteristics often unreliable
- EUS-FNA with cyst fluid analysis can assist in cyst characterization, but is still quite imprecise
- Diagnostic and treatment algorithms are evolving as new technology and increasing data become available
- Novel EUS-guided imaging and tissue sampling modalities may allow for more definitive diagnoses of cystic neoplasms, avoiding further surveillance for benign cysts.

Take-Home Points

Surveillance of Pancreatic Cystic Neoplasms: Making Sense of the Guidelines

Anne Marie Lennon MD PhD FACG
Professor of Medicine, Surgery, Radiology and Oncology
Director, Division of Gastroenterology and Hepatology
The Johns Hopkins Hospital
Guidelines

• Majority of guideline recommendations conditional
  – Significant no. patients could have a different approach

• Almost all recommendations have a low or very low quality evidence
All pancreatic cyst guidelines are ‘expert opinion’

Clinical Case

• 70-year-old female
• Asymptomatic
• Imaging:
  – 2.7 cm cyst
  – Main pancreatic duct 3mm
  – No ‘high risk’ features
Should you start surveillance?

Patients who are not medically fit for surgery should not undergo further evaluation of incidentally found pancreatic cysts, irrespective of cyst size


Should you do an EUS?
What do the guidelines say?

<table>
<thead>
<tr>
<th>Indications for EUS</th>
<th>Worrisome features</th>
<th>Clinical or radiologic features of concern AND results are expected to change clinical management</th>
<th>When the diagnosis is unclear, and results are likely to alter management</th>
<th>Worrisome or high-risk features</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 high-risk features</td>
<td>Worrisome features</td>
<td>Clinical or radiologic features of concern AND results are expected to change clinical management</td>
<td>When the diagnosis is unclear, and results are likely to alter management</td>
<td>Worrisome or high-risk features</td>
</tr>
</tbody>
</table>

Lennon AM, Vege S. CGH 2022
WHEN DO I DO AN EUS?

When the diagnosis is unclear

WHEN DO I DO AN EUS?

When it alters the patient's management
SHOULD WE FNA?

Guidelines

Considered if:

a) diagnosis is unclear

b) the results are likely to alter management
When do I FNA?
When it will change management

Microcystic SCA
When do I FNA?

When it will change management

EUS-FNA – what are the risks?

- Pancreatitis 1.1%
- Fever 0.3%
- Bleeding 0.3%
- Infection 0.2%

Wan K-K et al. Gastrointest Endoscopy 2011;73:283-290
Cytology

Type of Cyst
Sensitivity 54%
Specificity 93%

High-grade dysplasia & cancer
Sensitivity 65%
Specificity 91%


Cyst Fluid CEA

Sensitivity 63%
Specificity 93%

Thornton GD et al. Pancreatology 2013
Cyst Fluid Glucose

Glucose <50 mg/dL
Sensitivity 91% & Specificity 86% IPMN/MCN

Molecular Markers

<table>
<thead>
<tr>
<th>Cyst Type</th>
<th>Serous Cysts</th>
<th>MCN</th>
<th>IPMN</th>
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<tbody>
<tr>
<td>KRAS</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>GNAS</td>
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<td></td>
<td>+</td>
</tr>
<tr>
<td>VHL</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consider – not yet standard
Molecular Markers

- **TP53**
- **SMAD4**
- **CTNNB1**
- **mTOR**

88% sensitivity for high-grade dysplasia
98% specificity

Consider – not yet standard

Is EUS-FNA helpful?

Identified 30% cysts did not require surveillance
How do you follow IPMNs/MCNs?

Size <1 cm
Size 1-2 cm
Size 2-3 cm
Size ≥3 cm

2 years~
1 year*
6-12 Months*

ACG

*Surveillance can be lengthened after 3 years
~Surveillance can be lengthened after 4 years

IPMN/MCN

- Size <1 cm: 6 months
- Size 1-2 cm: 6 months
- Size 2-3 cm: 6 months
- Size ≥3 cm: 6 months

IAP

AGA

- 1 year
- 2 years

AGA

- MRI

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- **IPMN/MCN**
- **SYMPTOMS OR SIGNS**
  - Jaundice
  - Acute pancreatitis
  - Elevated CA19-9
- **IMAGING**
  - Mural nodule/solid mass
  - Main pancreatic duct >5mm
  - Size >3cm
- **CYTOLOGY**
  - High-grade dysplasia
  - Cancer

- Short interval surveillance with MRI or EUS
- New onset, or worsening diabetes mellitus
- Rapid increase in cyst size*

* >2.5 (IAP), 3mm (ACG), 5mm (European) per year
5 years later

- 75-year-old
- Hypertension
- Asymptomatic
- Imaging:
  - 2.9 cm cyst
  - Main pancreatic duct 3mm
  - No high risk features

When do you stop surveillance?

Surveillance should be discontinued if a patient is no longer a surgical candidate
When do you stop surveillance?

Radiology: Stop at age 80

ACG: Assess utility >75 years

Charlson comorbidity index ≥7

11-fold higher risk of non-IPMN related death within 3 years

Sahora K et al. Clin Gastro Hep 2015
Stopping Surveillance

AGA – 5 years
Radiology – 10 years

Continue Surveillance

ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts
Grace H. Blu, MD, FACG; Satish K. Rana, MD, MSH; Byung-S. Kim, MD; Jason A. Ren, MD, MSH; FACG; Gastroenterology; and Anne Allum, Schevitz, MD, FACP, FASGE
Stop Surveillance

Gobind, AS et al. Dig Dis and Sciences 2020

1.1% pancreatic cancer

Continue Surveillance

Cumulative incidence: 3.3% @ 5 yrs, 6.6% 10 yrs, 15% at 15 yrs

Oyama et al. Gastro 2020
Continue Surveillance

10-fold higher risk PDAC vs age matched controls

Oyama et al. Gastro 2020

Take Home Points

- Pancreatic Cyst Guidelines - Expert Opinions
- Perform surveillance only in patients fit surgery
- Consider EUS +/- FNA
  - Diagnosis unclear
  - Alter patient management
- Consider stopping surveillance in patients multi-comorbidities, or limited life expectancy
Future

- We need to move beyond imaging and cyst morphology

- Diagnostic and predictive markers
  - Prevalent neoplasia in high-risk cysts
  - Classify low versus high-risk
    - Safe minimize / stop surveillance
    - Intensive surveillance / surgery

Thank You
Update on Endoscopic Ultrasound-Guided Pancreatic Cyst Ablation

John M. DeWitt, MD, FACG
Professor of Medicine
Director of EUS
Indiana University Health
Indianapolis, IN
Email: jodewitt@iu.edu

Objectives

1. List types of pancreatic cystic tumors considered for ablation
2. Identify methods used for ablation by EUS
3. Understand results of some of the studies evaluating these technologies
4. Describe potential limitations and pitfalls to treatment of these diseases
Classification of Pancreatic Cysts by Cyst Lining and Malignant Potential

- **No lining**: Pseudocyst
  - No malignant potential
- **Mucinous**: MCN, IPMN
  - Premalignant
- **Serous**: Serous Cystic Neoplasm
  - ~ No malignant potential
- **Squamous**: Lymphoepithelial cyst
  - No malignant potential
- **Acinar**: Acinar cell carcinoma
  - Malignant
- **Solid tumor degeneration**: Lymphangioma, Neuroendocrine, Sarcoma, SPT, PDAC, Pancreatoblastoma
  - Neuroendocrine and SPT are premalignant

Why offer EUS pancreatic cyst ablation?

**Patient reasons**
1. May lower cancer risk
2. May lower costs over time
3. Psychological benefit
4. Avoid more invasive procedures
5. May improve outcomes and survival

**Potential problems**
1. Complications
2. Incomplete ablation or buried cancer
3. Costs high at time of procedure
4. No change in life expectancy or outcomes
EUS-RA Device
Tae Woong Medical

EUS RFA Pancreatic Cystic Endocrine Tumor
EUS RFA of PETs and PCNs: A prospective multicenter study

Table 1

| Description of the 31 pancreatic lesions in 29 patients that were included in the study. |
|--------------------------------------------|----------|-------------------------------|
| Metric                                  | Neuroendocrine tumor | Pancreatic cystic neoplasm |
| Number of lesions                        | 14       | 16 IPMN                      |
|                                          |          | 1 MCA                        |
| Location                                | - Head   | 3                             |
|                                          | - Body   | 6                             |
|                                          | - Tail   | 5                             |
| Mean size (range), mm                    | 13.1 (10–20) | 28 (9–60)                  |
| CgA level (range), U/mL                  | 344 (84–1230) | NA                          |
| Mural nodes, n (%)                       | NA       | 12 (70.6%)                   |
| Thick cystic wall, n (%)                 | NA       | 4 (23.5%)                    |

Barthet M et al. Endoscopy 2019;51:836-42

Table 2

<table>
<thead>
<tr>
<th>Results of endoscopic ultrasound-guided radiofrequency ablation in the 31 pancreatic lesions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metric</td>
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<tr>
<td>Neuroendocrine tumors (n=14), n (%)</td>
</tr>
<tr>
<td>Significant response</td>
</tr>
<tr>
<td>- Disappearance or necrosis</td>
</tr>
<tr>
<td>- Decrease in diameter &gt;50%</td>
</tr>
<tr>
<td>Failure[†]</td>
</tr>
<tr>
<td>Pancreatic cystic neoplasms (n=17), n (%)</td>
</tr>
<tr>
<td>Significant response</td>
</tr>
<tr>
<td>- Disappearance or necrosis</td>
</tr>
<tr>
<td>- Decrease in diameter &gt;50%</td>
</tr>
<tr>
<td>Failure[‡]</td>
</tr>
</tbody>
</table>

* No change in size or decrease in diameter<50%.

Barthet M et al. Endoscopy 2019;51:836-42
EUS Guided Cyst Ablation with Chemotherapy Injection

- ↓ Viable Epithelium
- Smaller Size
- Cyst resolution
- Time and follow up imaging

Pancreatic Cyst Ablation with EUS FNI

Which Pancreatic Cysts Are Eligible for EUS FNI?

• Indications
  • Benign mucinous or indeterminate pancreatic cysts
  • 2-5 cm in size with 0-5 septations

• Absolute Contraindications
  • Pregnancy
  • Inability to tolerate sedation
  • Malignant cytology
  • Benign cyst (SCN, PC, LEC)
  • Limited life expectancy
Which pancreatic cysts should be considered for EUS FNI?

• Relative Contraindications
  • Dilated main pancreatic duct
  • Epithelial nodules, thick walls/septations, solid component
  • PD or CBD duct stricture
  • >6 septations
  • Uncorrectable coagulopathy
  • Dilated main pancreatic duct ≥5 mm
  • High grade dysplasia

Studies of Pancreatic Cyst Ablation Published 2005-2017

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Enrolled</th>
<th>Ablative Agent</th>
<th>Size (cm)</th>
<th>MCN (n, %)</th>
<th>IPMN (n, %)</th>
<th>SCN (n, %)</th>
<th>PC (n, %)</th>
<th>Indeterminate (n, %)</th>
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<tr>
<td>Gan (2005)</td>
<td>25</td>
<td>↑ETOH</td>
<td>1.9</td>
<td>14 (56)</td>
<td>3 (12)</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>DeWitt (2009)</td>
<td>42</td>
<td>ETOH vs saline</td>
<td>2.0</td>
<td>17 (41)</td>
<td>17 (41)</td>
<td>5 (12)</td>
<td>3 (6)</td>
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<td>Oh (2011)</td>
<td>52</td>
<td>ETOH + PTX</td>
<td>3.1</td>
<td>9 (17)</td>
<td>0 (0)</td>
<td>15 (29)</td>
<td>2 (4)</td>
<td>26 (50)</td>
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<tr>
<td>DeWitt (2014)</td>
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<td>ETOH + PTX</td>
<td>2.5</td>
<td>12 (55)</td>
<td>6 (27)</td>
<td>4 (18)</td>
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<td>Gomez (2016)</td>
<td>23</td>
<td>ETOH</td>
<td>2.8</td>
<td>4 (17)</td>
<td>15 (65)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Moyer (2016)</td>
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<td>ETOH vs. saline</td>
<td>2.9</td>
<td>7 (70)</td>
<td>2 (20)</td>
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<td>0 (0)</td>
<td>1 (10)</td>
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<td>Park (2016)</td>
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<td>3.0</td>
<td>12 (13)</td>
<td>9 (10)</td>
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<td>28 (31)</td>
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<tr>
<td>Choi (2017)</td>
<td>164</td>
<td>ETOH + PTX</td>
<td>3.2</td>
<td>71 (43)</td>
<td>11 (7)</td>
<td>16 (10)</td>
<td>0 (0)</td>
<td>63 (40)</td>
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### Studies of Pancreatic Cyst Ablation

#### Published 2005-2017

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Enrolled</th>
<th>Ablative Agent</th>
<th>Complete Resolution (%)</th>
<th>Partial Resolution (%)</th>
<th>No response (%)</th>
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<td>Gan (2005)</td>
<td>25</td>
<td>↑ETOH</td>
<td>35</td>
<td>13</td>
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<tr>
<td>DeWitt (2009)</td>
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<td>ETOH vs. saline → ETOH</td>
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<td>NR</td>
<td>NR</td>
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<tr>
<td>Oh (2011)</td>
<td>52</td>
<td>ETOH + PTX</td>
<td>56</td>
<td>12</td>
<td>32</td>
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<tr>
<td>DeWitt (2014)</td>
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<td>ETOH + PTX</td>
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<td>ETOH (75%) Saline (67%)</td>
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<td>41</td>
<td>14</td>
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<td>72</td>
<td>20</td>
<td>8</td>
</tr>
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### Studies of Pancreatic Cyst Ablation

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Enrolled</th>
<th>Ablative Agent</th>
<th>Total (%)</th>
<th>Pancreatitis (%)</th>
<th>Abd pain (%)</th>
<th>Other AEs (n)</th>
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<tbody>
<tr>
<td>Gan (2005)</td>
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<td>↑ETOH</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>ETOH vs. saline → ETOH</td>
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<td>2.4</td>
<td>24</td>
<td>Intracystic bleeding (1)</td>
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<td>Fever (1), pericystic spillage (1), SVT (1)</td>
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<td>4</td>
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<td>fever (8)</td>
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<tr>
<td>Choi (2017)</td>
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<td>ETOH + PTX</td>
<td>9.8</td>
<td>3.2</td>
<td>0</td>
<td>Fever (1), pericystic spillage (1), intracystic bleeding (1), pseudocyst (2), abscess (2), PVT (1), SVT (1), MPD stricture (1)</td>
</tr>
</tbody>
</table>
The Safety and Efficacy of an Alcohol-Free Pancreatic Cyst Ablation Protocol

- Alcohol free
  - Resolution: 67%
  - SAEs: none
  - Minor AE: none
- Alcohol (control)
  - Resolution: 61%
  - SAEs 6%
  - Minor: 22%

Moyer MT et al. Gastroenterology 2017;153:1295-1303

Previously Reported Risk Profiles of Various Procedures

- Severe AE rate
- Mortality rate

Slide courtesy of Matt Moyer MD
Complications and Costs for Surgery vs. EUS FNI for pancreatic cysts

Whipple surgery
Mortality 1-5%, SAE 20-40%
$153,215 USD*

EUS guided ablation
Mort 0%, SAE 3-10%
$5,146 USD*

Cyst ablation in October 2014 of 3 cm mucinous cyst
4 mL of ethanol (4 lavages) followed by
4 mL of paclitaxel (2 mg/mL) and left in place
Follow up CT scans

Baseline 2/2014
30 x 20 mm

12/2014; T+2 mos.
7 x 10 mm

5/2015; T+7 mos.
2 x 2 mm

CHARM 2 PROTOCOL

- Chemotherapy for ablation and resolution of mucinous pancreatic cysts: a prospective, randomized, double-blind, multi-center clinical trial
- R01 CA222648-01A1:
- PI: Matt Moyer, MD
- Sub I: John DeWitt, MD
  - Email: jodewitt@iu.edu

American College of Gastroenterology
Pancreatic Cyst Ablation: Knowledge Gaps

- Which cysts to ablate?
- Are BD IPMNs safe to treat?
- Which agents to use?
- Alcohol free cocktail?
- Are complications worth the benefit?
- Long term resolution durable?
- RCT vs. surgery needed

Conclusions

- Opportunity for treatable lesions instead of surgery or surveillance
- Ablation of pancreatic cystic tumors are feasible
  - RFA
  - Injection
- RFA best reserved for solid /mixed lesions not amenable to injection
- EUS FNI ablation rates with of 60-70% with chemotherapy
- Ethanol
  - Does not appear to be required to achieve ablation
  - Minimizes adverse events
Questions

V. Raman Muthusamy, MD, MAS, FACG

Anne Marie Lennon, MD, PhD, MBCh, FACG

John M. DeWitt, MD, FACG