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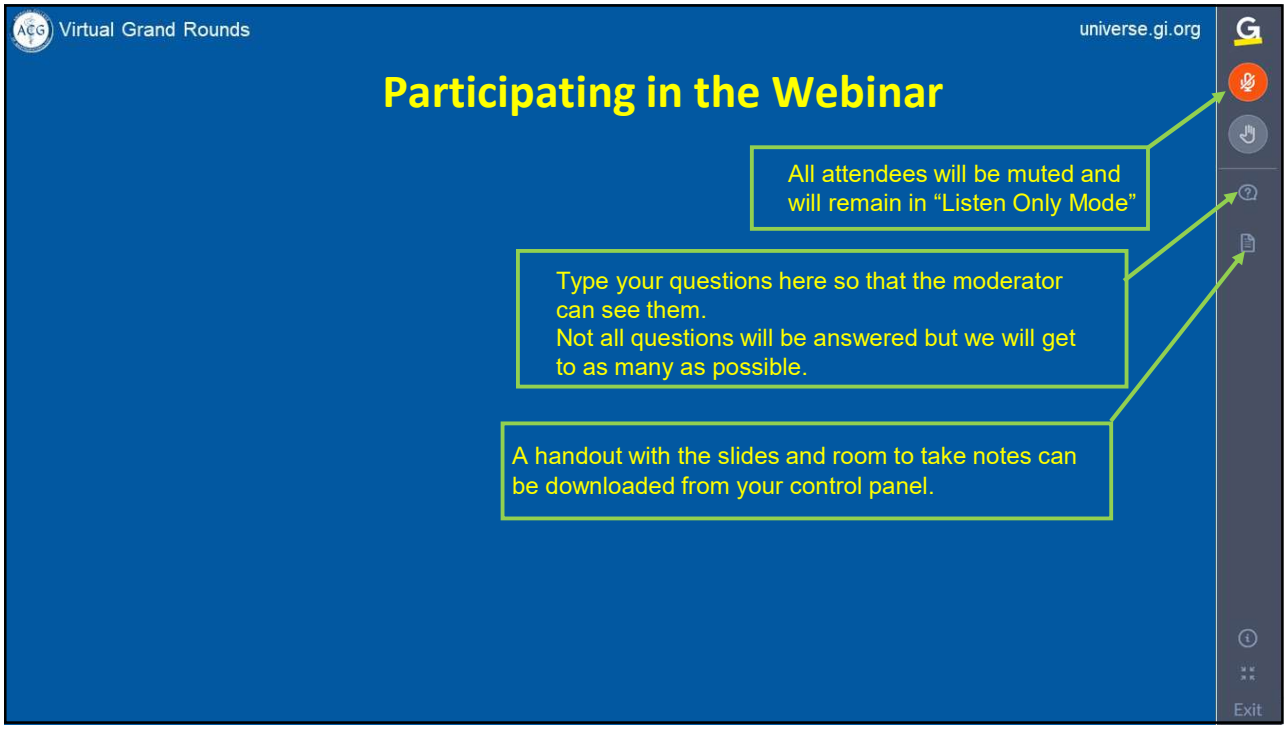
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Faculty: S. Priya Narayanan, MD, Michel Fishman, and Juan Murua
At Noon and 8pm Eastern

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
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Disclosures

V. Raman Muthusamy, MD, MAS, FACG

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, FACG

CancerSEEK: Patent Holder

John M. DeWitt, MD, FACG

Ariel Precision Medicine: Consultant
Boston Scientific Corporation: Consultant

**All of the relevant financial relationships listed for these individuals have been mitigated*

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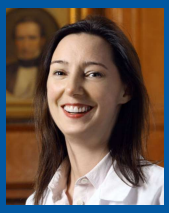

Anne Marie Lennon, MD, PhD, MBBCh, FACG

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Diagnostic Evaluation of Pancreatic Cystic Lesions

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

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Prevalence

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

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

Scheiman et al. Gastroenterology 2015;824-48

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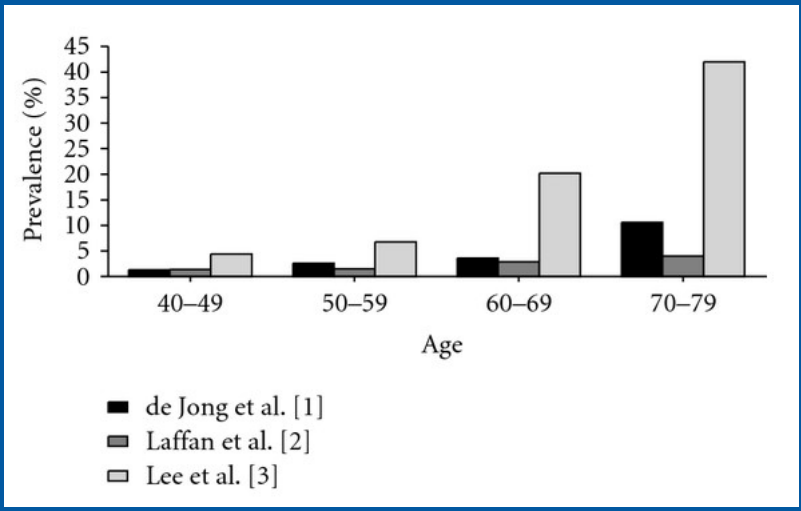
Prevalence Increases With Age



de Jong K, et al. Gastro Res Pract. 2012

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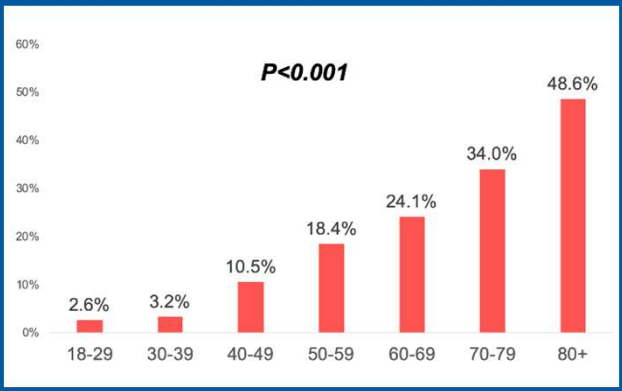
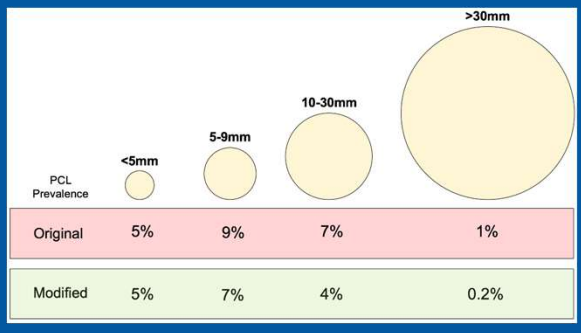
Modern Estimate of Cyst Prevalence



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



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

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What's the Risk? Data From Surgical Series

Cyst Type	Outcome	Number of Studies	Number of Patients	Estimate (95% CI)	I^2
All	Cancer	27	2796	**15%** (12-18)	76.5%
IPMN	Cancer	111	10,812	**25%** (23-27)	82%
IPMN	**HGD**/Cancer	99	9,249	**42%** (39-45)	88%
MCN	Cancer	12	603	**15%** (9-22)	81%
SCN	Cancer	5	295	**2.2%** (0.3-5.7)	52%

Surgical data – The risk is real
Bias?

Scheiman et. al. Gastroenterology 2015;824-48

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Longitudinal Risk of Cancer

Cyst Type	Number of Studies	N	Follow Up in Pt-Yrs	Cancers	Incident cases/yr	I^2
All	22	6240	18,079	**42**	**0.24% (0.12-0.36)**	29.5%
IPMN	37	3980	14,830	**112**	**0.72% (0.48-1.08)**	74%

Per-year risk is low!

Scheiman et al. Gastroenterology 2015;824-48

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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%)

Scheiman et al. Gastroenterology 2015;824-48

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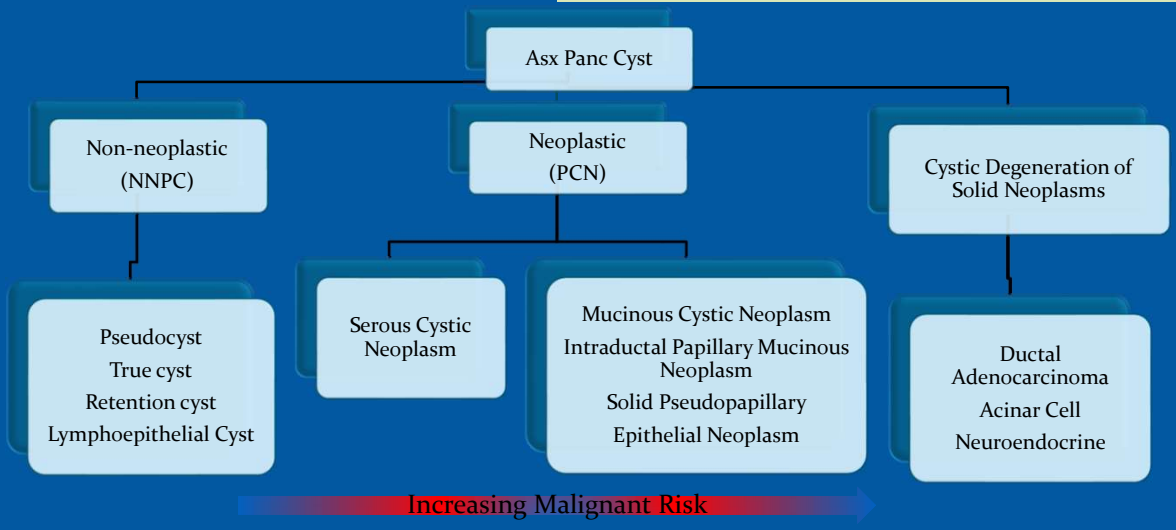
Differential Diagnosis

Goal: Differentiate Mucinous from Non-mucinous cysts



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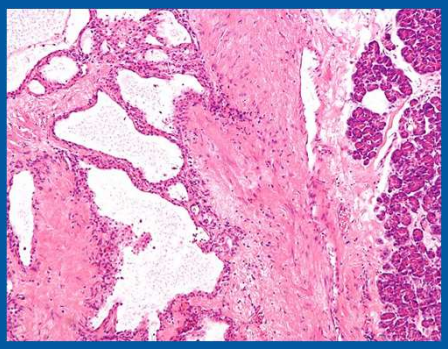
Pancreatic Cystic Neoplasms

- 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

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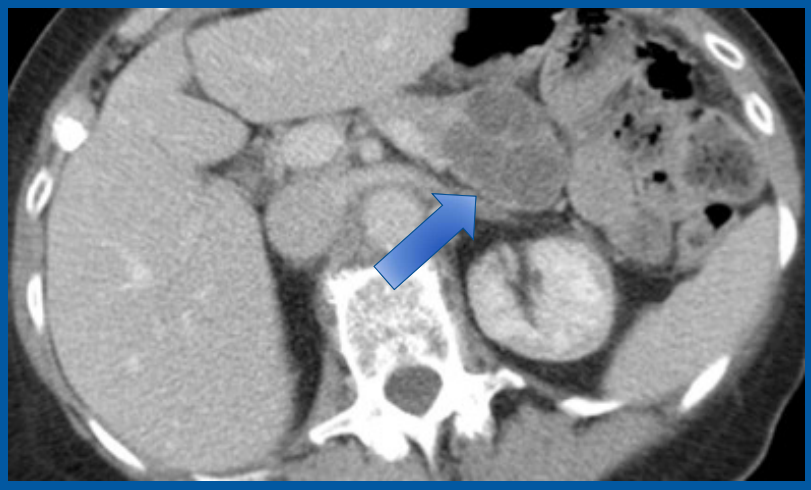
Cross-sectional Imaging: SCN



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Pancreatic Cystic Neoplasms: MCN

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

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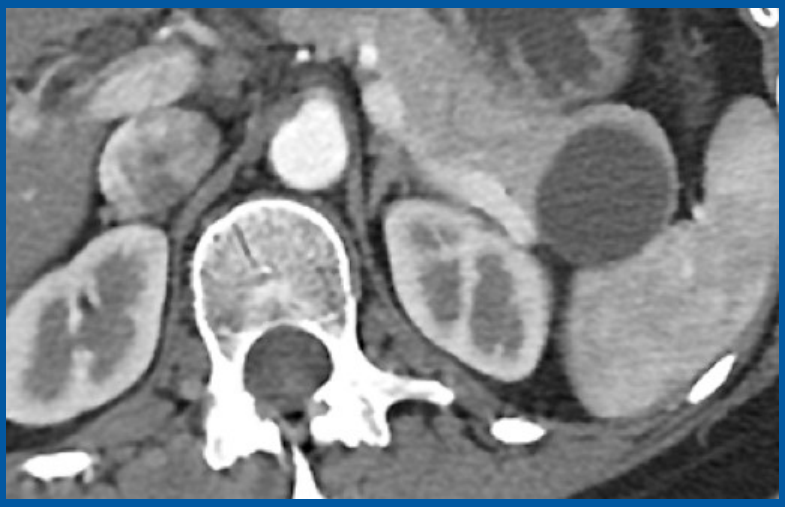
Cross-sectional Imaging: MCN



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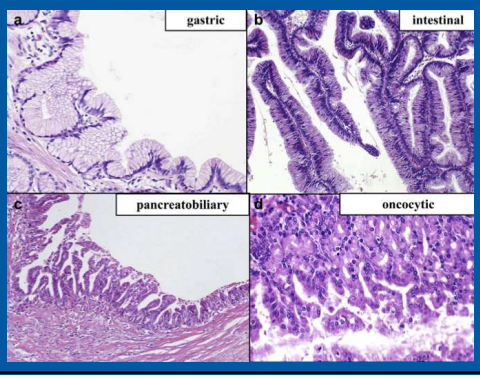
Pancreatic Cystic Neoplasms

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



Tanaka M, et al. Pancreatology; 12:183-97

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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

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Cross-sectional Imaging: Main Duct IPMN

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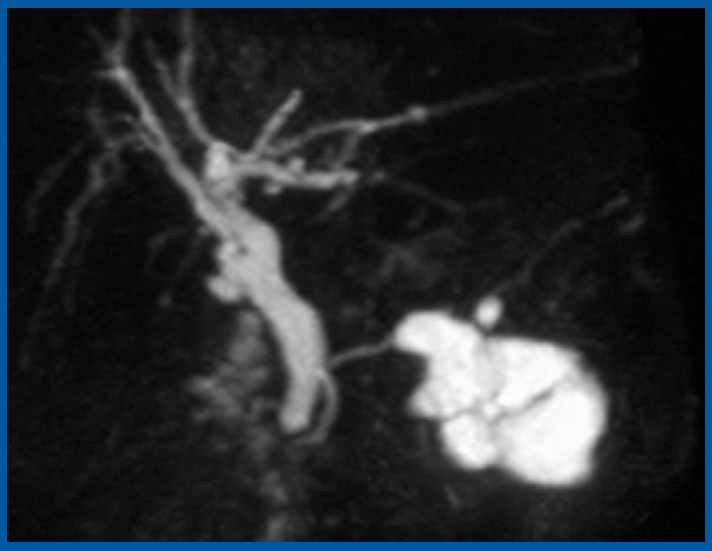
Cross-sectional Imaging: Branch Duct IPMN



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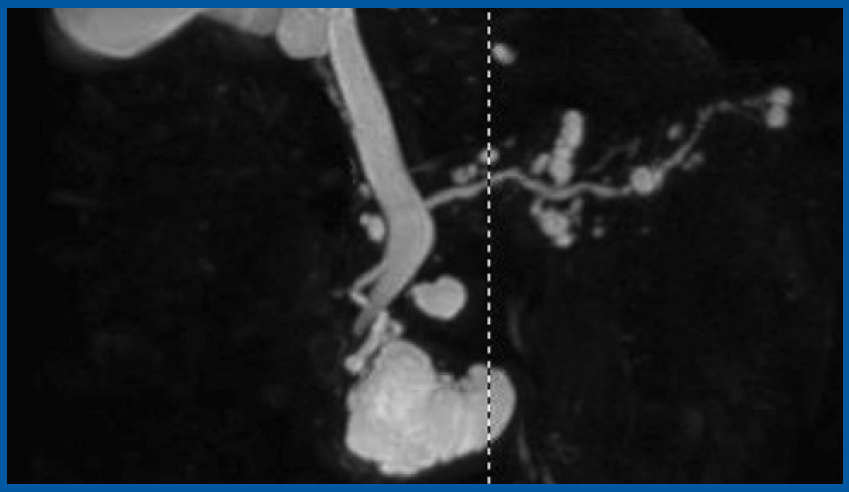
Cross-sectional Imaging: Multifocal Branch Duct IPMN



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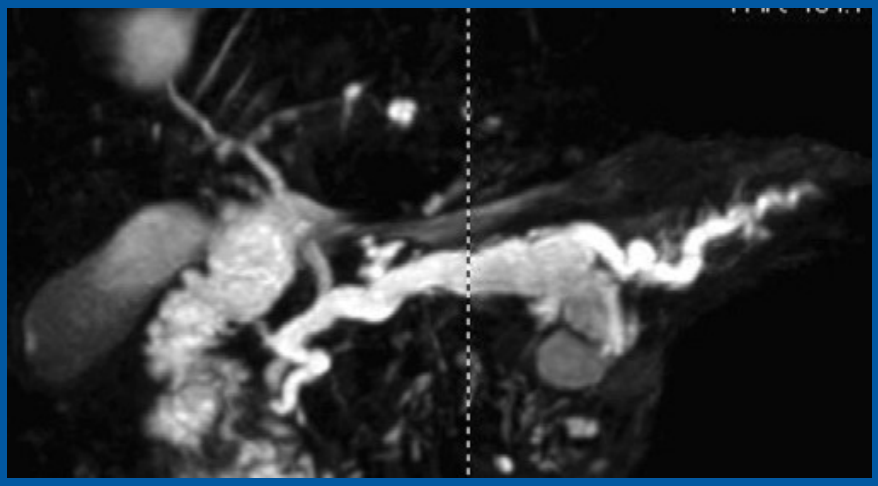
Cross-sectional Imaging: Mixed Type IPMN



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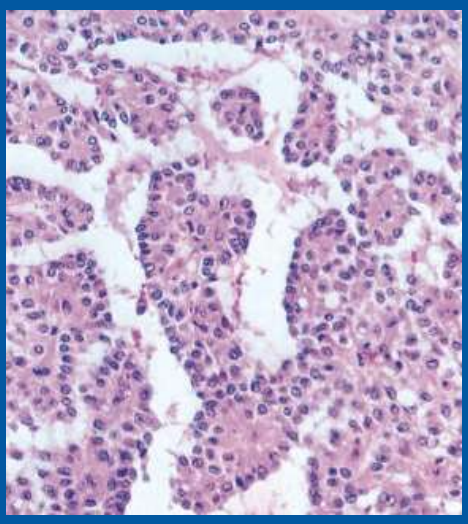
Pancreatic Cystic Neoplasms

- Solid Pseudopapillary Neoplasm (SPN)
  - Low grade malignant neoplasm
  - Young women (<35 years)
  - monomorphic cells (often difficult to distinguish from neuroendocrine), pseudopapillae
  - hemorrhagic
  - Surgical resection



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Cross-sectional Imaging: SPN

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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

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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

Elta G et al. ACG Guideline, AJG 2018, Vol 113, pp. 464-479.
Udare A et al. JMRI, 54:4, October 2021, pp 1126-1137.

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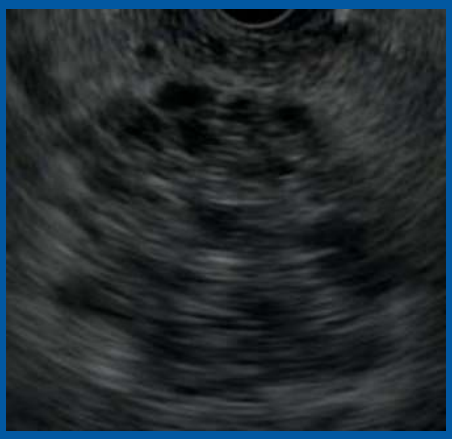
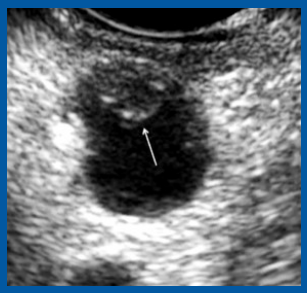
What is the Role of EUS?





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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

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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

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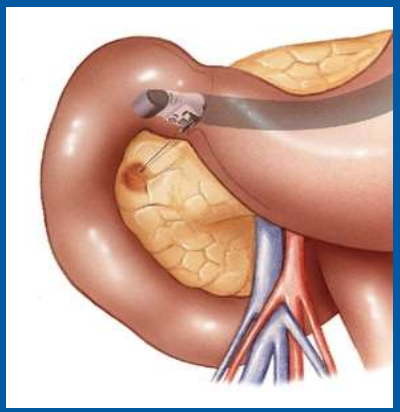
EUS-FNA

- 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)



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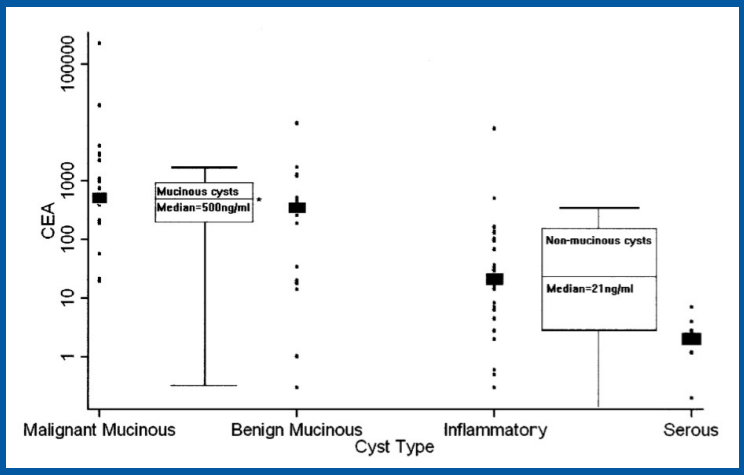
EUS-FNA: Cyst Fluid Analysis: Cooperative Pancreatic Cyst Study



Brugge W et al. Gastroenterology, 2004 May;126(5):1330-6.

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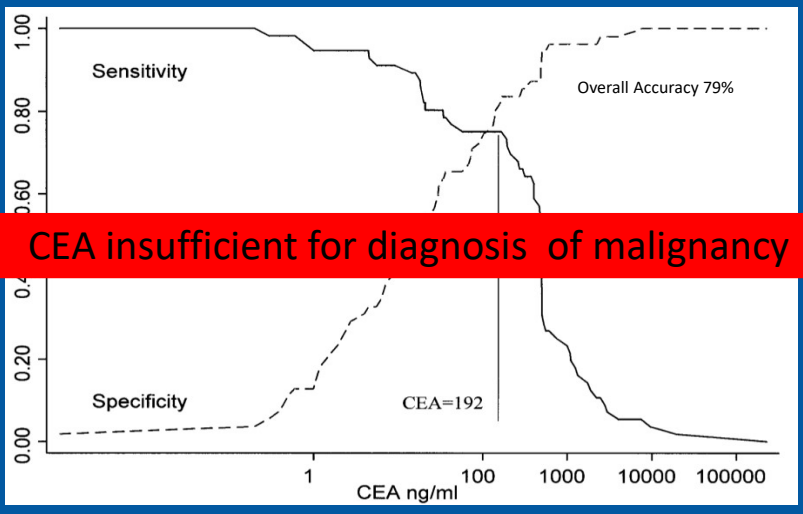
EUS-FNA: Cyst Fluid Analysis



CEA insufficient for diagnosis of malignancy

Brugge W et al. Gastroenterology, 2004 May;126(5):1330-6.

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EUS-FNA: Cyst Fluid Analysis

	Fluid Color	Viscosity	CEA (>192)	Amylase
Pseudocyst	Dark, Yellow/Brown	Thin	Low	High
SCN	Clear/Bloody	Thin	Low	Variable
MCN	Clear	Thick	High	Variable
IPMN	Clear	Thick	High	High

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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

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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.

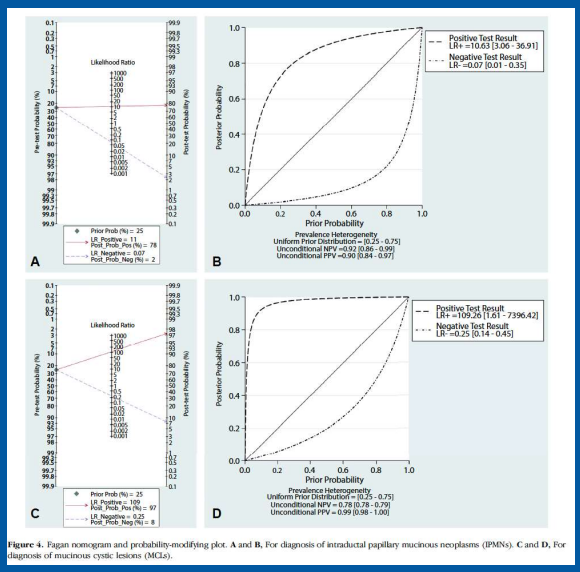

Figure 4. Fagan nomogram and probability-modifying plot. A and B, For diagnosis of intraductal papillary mucinous neoplasms (IPMNs). C and D, For diagnosis of mucinous cystic lesions (MCLs).

McCarthy, TR et al. Gastrointest Endosc. 2021 May;93(5):1019-1033.e5.

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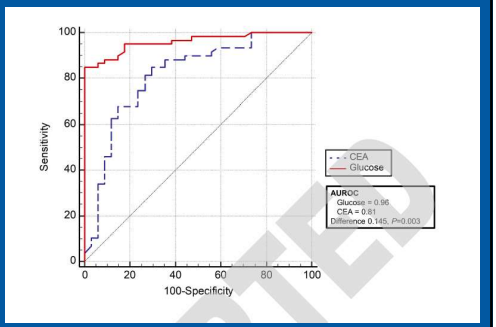
Cyst Fluid Glucose Levels

- 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%.**



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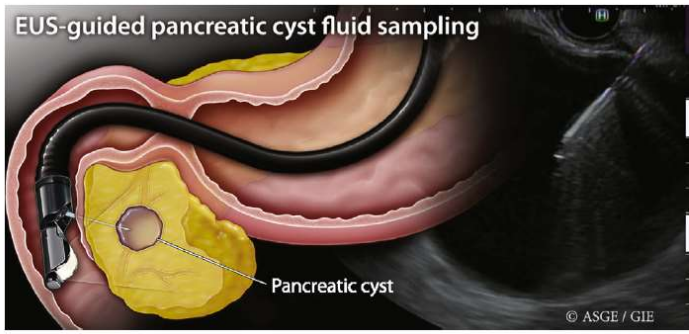
Meta-Analysis of Cyst Fluid Glucose Levels



Diagnostic Yield of Pancreatic Fluid Cyst Glucose or CEA (Alone or in Combination) to Differentiate Mucinous Versus Non-Mucinous Cystic Neoplasms

Mucinous vs Non-Mucinous Cystic Neoplasms	Estimate	95% Confidence Interval	Heterogeneity (I^2)
Intracystic Glucose Alone (8 studies, n=609)			
Sensitivity	0.91	0.88 to 0.94	0.00
Specificity	0.86	0.81 to 0.90	24.16
Diagnostic Accuracy	0.94	0.91 to 0.96	
CEA Alone (7 studies, n=534)			
Sensitivity	0.56	0.46 to 0.66	57.14
Specificity	0.96	0.90 to 0.99	38.06
Diagnostic Accuracy	0.85	0.82 to 0.88	

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

McCarty TR, et al. Gastrointest Endosc. 2021 Oct;94(4):698-712.e6.

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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

Thosani et al. Dig Dis Sci. 2010 Oct;55(10):2756-66.
Thornton G, et al. Pancreatology. 2013 Jan-Feb;13(1):48-57.

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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).

Al-Haddad M et al. Gastrointest Endosc. 2007 May;65(6):894-8.
Lariño-Noia J et al. Rev Esp Enferm Dig. 2018 Aug;110(8):478-484.

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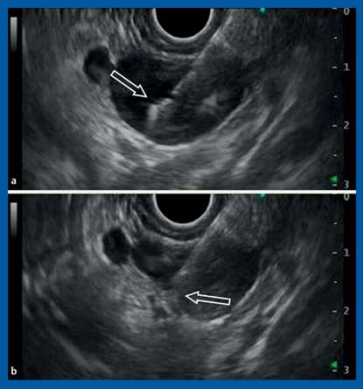
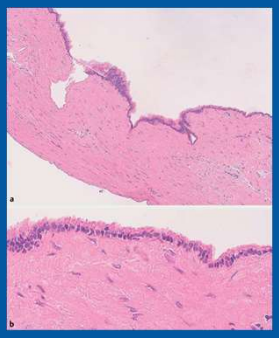
Specialized Biopsy Forceps

Endoscopic ultrasound-guided histological diagnosis of a mucinous non-neoplastic pancreatic cyst using a specially designed through-the-needle microforceps





- Works thru 19G EUS-FNA needle

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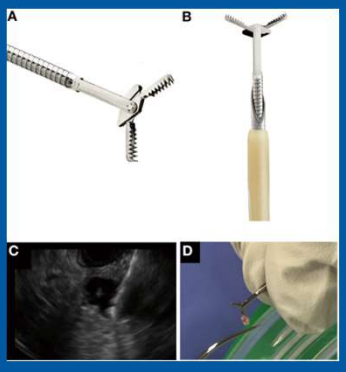
TTN Forceps Biopsy

- 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

Yang D et al. Clin Gastroenterol Hepatol. 2019 Jul;17(8):1587-1596

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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%

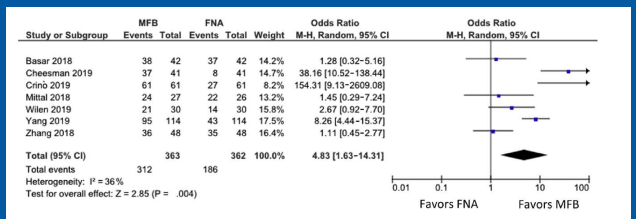

Figure 3. Meta-analysis comparing rates of sample adequacy between microforceps biopsy and standard fine-needle aspiration (cytology/cyst fluid analysis). Microforceps biopsy (MFB) was significantly superior to FNA in targeting pancreatic cysts (odds ratio, 4.83; 95% confidence interval, 1.63-14.31; $P = .004$; $I^2 = 36\%$). *CI*, Confidence interval; *M-H*, Mantel-Haenszel test; *MFB*, microforceps biopsy.

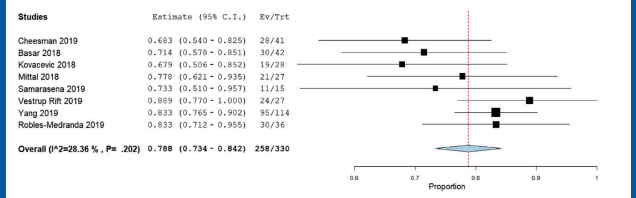

Figure 4. Pooled analysis assessing rates of diagnostic accuracy of microforceps biopsy in targeting pancreatic cyst lesions. Diagnostic accuracy in targeting pancreatic cysts was 78.8% (73.4%-84.2%; $I^2 = 28.36\%$). *CI*, Confidence interval; *Ev/Trt*, events/treated.

Facciorusso A, Gastrointest Endosc. 2020 Jul;92(1):1-8.e3.

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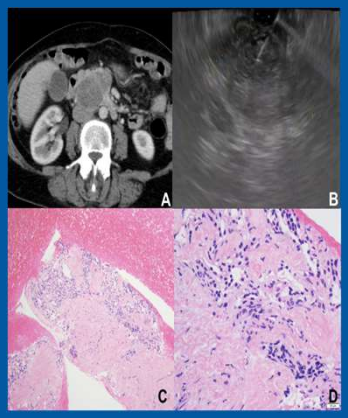
EUS-FNB for Pancreatic Cysts

Table 2: Fine Needle Biopsy and Core Histologic Diagnosis

	Total Patients (n = 44) N, (%)
Tissue Adequacy	38 (86.4)
Mean Number of Needle Passes ± SD	3.2 ± 1.2
Mean Specimen Length (mm ± SD)	13.1 ± 10.3
Diagnosis based on Core Biopsy	
SCN	22 (50.0)
IPMN	7 (15.9)
Adenocarcinoma	5 (11.4)
Neuroendocrine tumor	2 (4.5)
Diffuse Large B-cell Lymphoma	1 (2.3)
MCN	1 (2.3)
Non-diagnostic	6 (13.6)
Adequate FNA Specimen based on Touch Prep of FNB Specimen	30 (68.2)
Discordant FNA and core biopsy findings	8 (26.7)
Upstaging pathology based on core biopsy	8
Adverse Events	4 (9.1)



Overall FNB Diagnostic Rate= 86.4%

Phan J et al, Gastroenterology. 2020 Feb;158(3):475-477.

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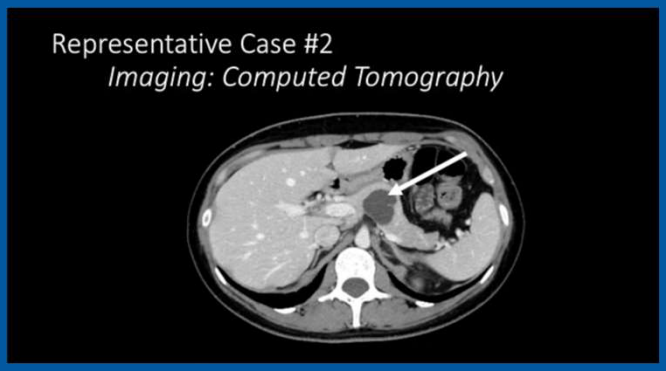
Case History: Pancreas Cyst

- 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



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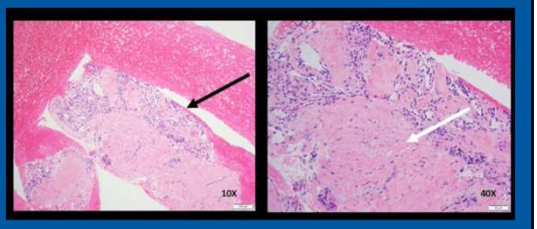
Case History: EUS-FNB



- **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)

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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

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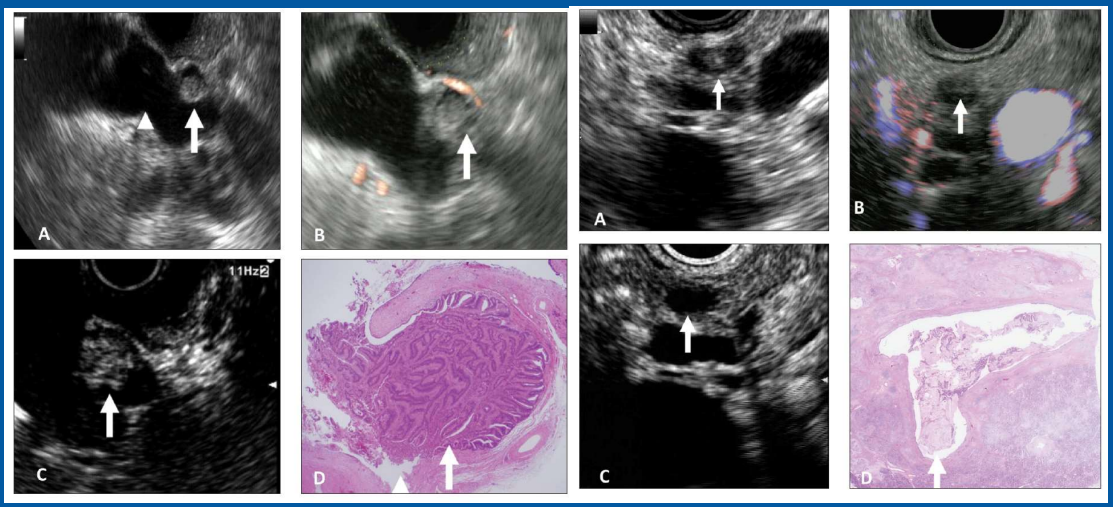
What's Next? Contrast Enhanced EUS



12 mural nodules, 5 without
CEUS with sensitivity of 100%, specificity of 80%, accuracy 92%

Yamashita et al. Journal of Ultrasound Med, 2013

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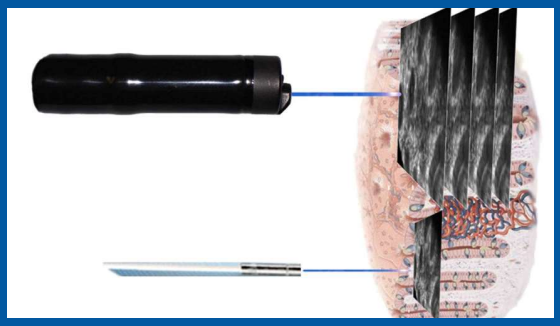
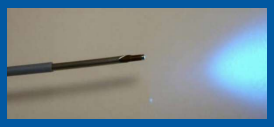
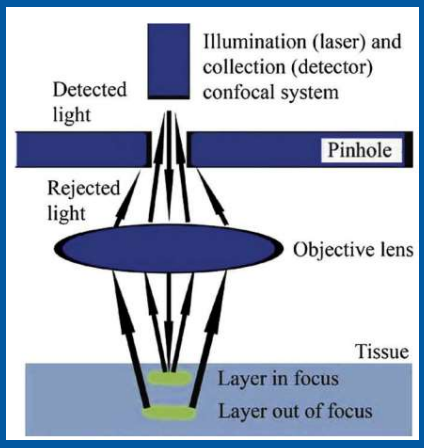
What's Next: Extending Our Reach

- Needle-based confocal laser endomicroscopy (nCLE)







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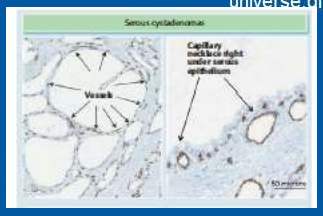
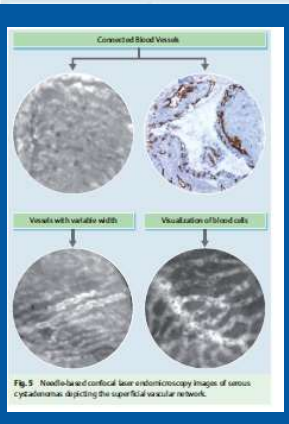
nCLE for Serous Cystic Neoplasms: Superficial Vascular Network

- 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)





Endoscopy. 2015 Jan;47(1):26-32.

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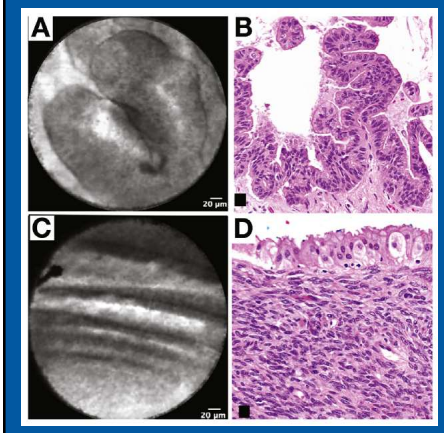
nCLE for Cystic Neoplasms:



PANCREAS, BILIARY TRACT, AND LIVER

Endoscopic Ultrasound-Guided Confocal Laser Endomicroscopy Increases Accuracy of Differentiation of Pancreatic Cystic Lesions

Somashekar G. Krishna,* Phil A. Hart,* Ahmad Malli,* Andrew J. Kruger,‡ Sean T. McCarthy,* Samer El-Dika,* Jon P. Walker,* Mary E. Dillhoff,§ Andrei Manilchuk,‖ Carl R. Schmidt,§ Timothy M. Pawlik,§ Kyle Porter,¶ Christina A. Arnold,# Zobeida Cruz-Monserrate,* and Darwin L. Conwell*

Table 2. Diagnostic Parameters for the Diagnosis of Mucinous PCLs Using Standard of Care (Cyst Fluid CEA and/or Cytology) and EUS-nCLE in Subjects With Surgical Histopathology

Diagnostic criteria[a]	Sensitivity	Specificity	Accuracy	NPV	PPV
Pathologic diagnosis (n = 65)					
Either CEA ≥192 or cytology (mucin)	74% (60%–86%)	61% (36%–83%)	71% (58%–81%)	48% (27%–69%)	83% (69%–93%)
EUS-nCLE	98% (89%–100%)	94% (73%–100%)	97% (89%–100%)	94% (73%–100%)	98% (89%–100%)

CEA, carcinoembryonic antigen; EUS, endoscopic ultrasound; nCLE, needle-based confocal laser endomicroscopy; NPV, negative predictive value; PCL, pancreatic cystic lesion; PPV, positive predictive value.
[a]All diagnostic parameters with 95% CI.

- 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)

Krishna S et al. Clinical Gastroenterology & Hepatology 2020;18:432-440.

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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

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Take-Home Points

- 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

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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

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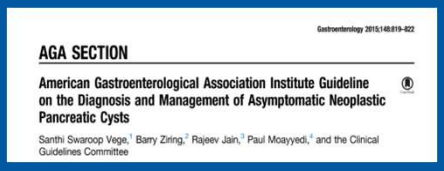
Guidelines


Gastroenterology 2015;148:819–822

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee


Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

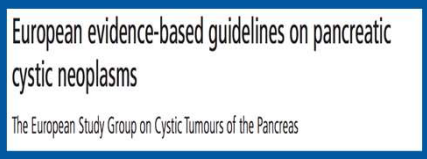
Masao Tanaka [a,*], Carlos Fernández-del Castillo [b], Terumi Kamisawa [c], Jin Young Jang [d], Philippe Levy [e], Takao Ohtsuka [f], Roberto Salvia [g], Yasuhiro Shimizu [h], Minoru Tada [i], Christopher L. Wolfgang [j]


ORIGINAL ARTICLE CLINICAL PRACTICE MANAGEMENT

Management of Incidental Pancreatic Cysts: A White Paper of the ACR Incidental Findings Committee

EC Editor's Choice SA-CME

Alec J. Megibow, MD, MPH[1], Mark E. Baker, MD[2], Desiree E. Morgan, MD[3], Ihab R. Kamel, MD, PhD[4], Dushyant V. Sahani, MD[5], Elliot Newman, MD[1], William R. Brugge, MD[6], Lincoln L. Berland, MD[7], Pari V. Pandharipande, MD, MPH[8,9]


European evidence-based guidelines on pancreatic cystic neoplasms

The European Study Group on Cystic Tumours of the Pancreas


ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts

Grace H. Elta, MD, FACG[1], Brintha K. Enestvedt, MD, MBA[2], Bryan G. Sauer, MD, MSc, FACG (GRADE Methodologist)[3] and Anne Marie Lennon, MD, PhD, FACG[4]

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Cyst 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

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All pancreatic cyst guidelines are 'expert opinion'

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Clinical Case

- 70-year-old female
- Asymptomatic
- Imaging:
  - 2.7 cm cyst
  - Main pancreatic duct 3mm
  - No 'high risk' features

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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

Elta G et al. American Journal of Gastro 2018;113:464

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Should you do an EUS?

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What do the guidelines say?

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	2015 AGA guidelines	2017 IAP	2018 European guidelines	2018 ACG guidelines	2017 ACR guidelines
Indications for EUS	At least 2 high-risk features	Worrisome features	Clinical or radiologic features of concern AND results are expected to change clinical management	When the diagnosis is unclear, and results are likely to alter management	Worrisome or high-risk features

Lennon AM, Vege S. CGH 2022

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WHEN DO I DO AN EUS?

When the diagnosis is unclear

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WHEN DO I DO AN EUS?

When it alters the patient's management

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SHOULD WE FNA?

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Guidelines

Considered if:

a) diagnosis is unclear

b) the results are likely to alter management

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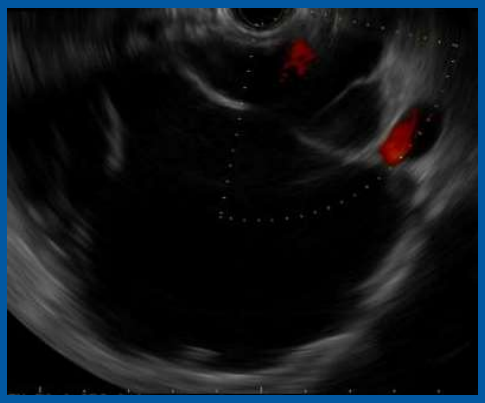
When do I FNA?

When it will change management



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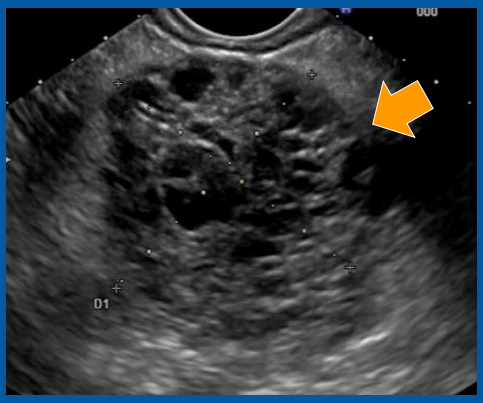
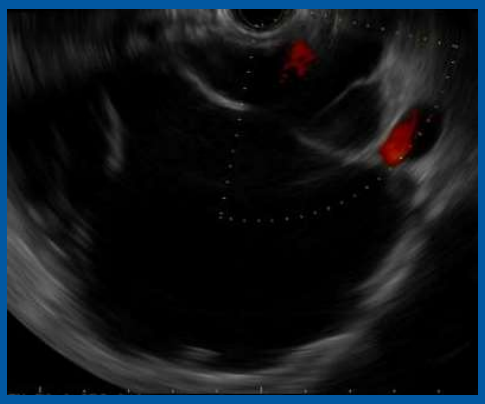
When do I FNA?

When it will change management





Microcystic SCA

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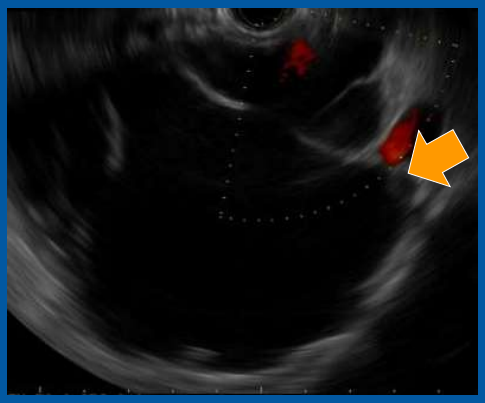
When do I FNA?

When it will change management



Unclear diagnosis

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EUS-FNA – what are the risks?

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

Wan K-X et al. Gastrointest Endoscopy 2011;73:283-290
Yoon WJ et al. Endoscopy 2014;46:382-387

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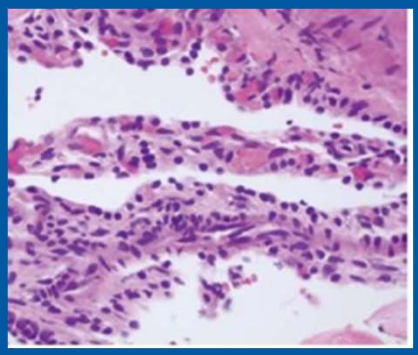
Cytology



Type of Cyst
Sensitivity 54%
Specificity 93%

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

Thornton GD et al. Pancreatology 2013; Thosani N et al. Dig Dis Sci 2010;55:2756-66

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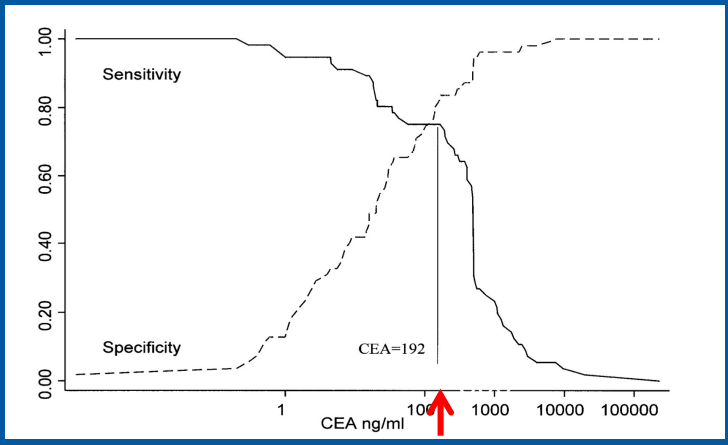
Cyst Fluid CEA



Sensitivity 63%
Specificity 93%

Thornton GD et al. Pancreatology 2013

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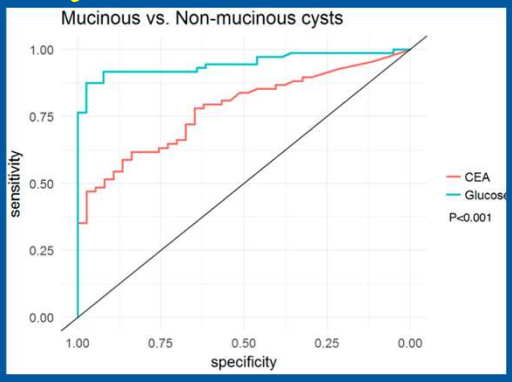
Cyst Fluid Glucose



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

Simons-Linares CR et al. Pancreatology 2020;20:1386-92; McCarty TR. GIE 2021.

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Molecular Markers

Cyst Type	Serous Cysts	MCN	IPMN
KRAS		+	+
GNAS			+
VHL	+		

Consider – not yet standard

Springer S et al. Science Translational Medicine 2019. Singhi A et al. *GIE* 2016;83:1107

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Molecular Markers

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

88% sensitivity
98% specificity

high-grade dysplasia

Paniccia A et al. Gastro 2022

Consider – not yet standard

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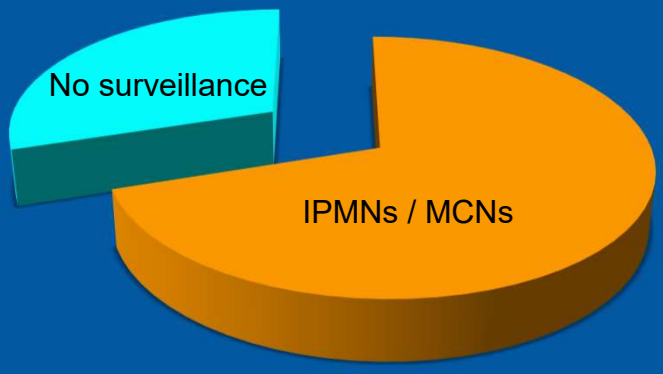
Is EUS-FNA helpful?



Identified 30% cysts did not require surveillance

Singhi A et al. *GIE* 2016;83:1107

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How do you follow IPMNs/MCNs?

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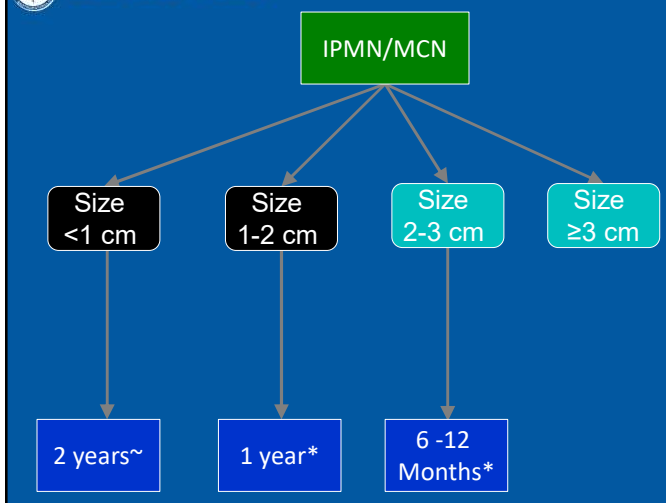

ACG

MRI

MRI or EUS

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

Elta G, et al. ACG Clinical Guidelines Pancreatic Cysts. Am J Gastro 2018;113:464-479

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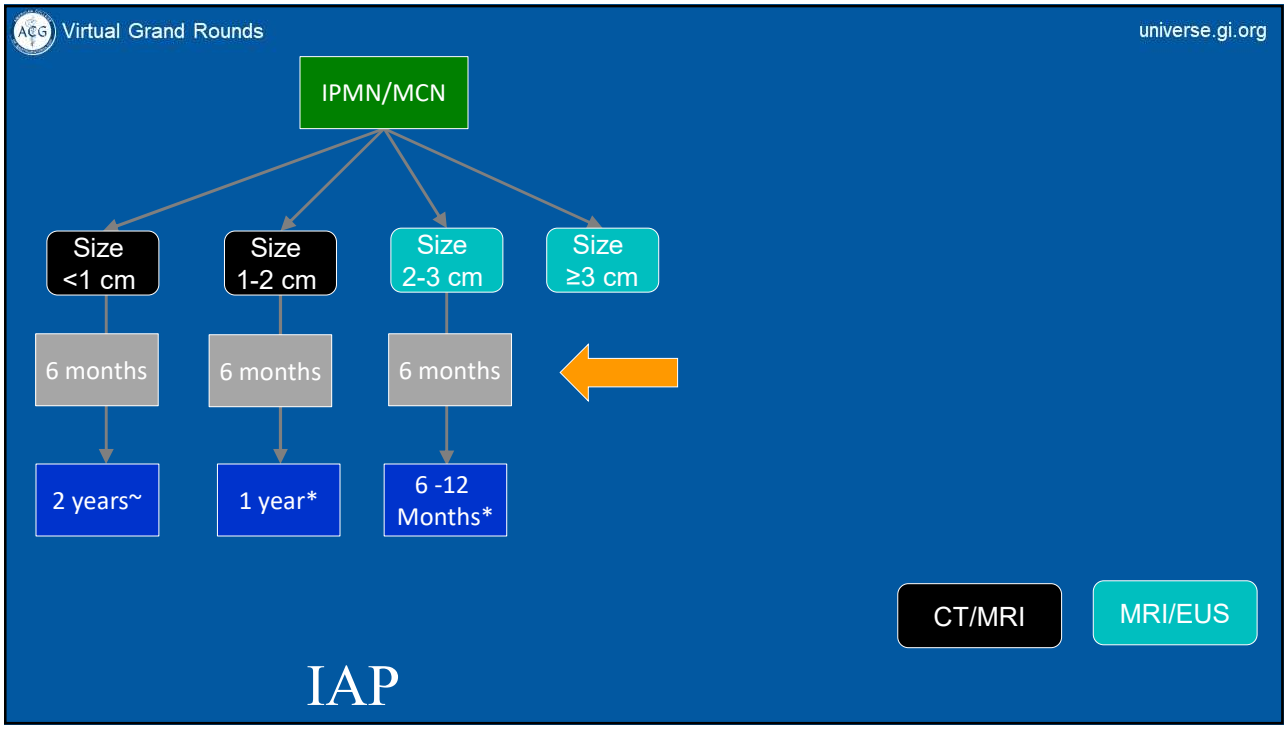
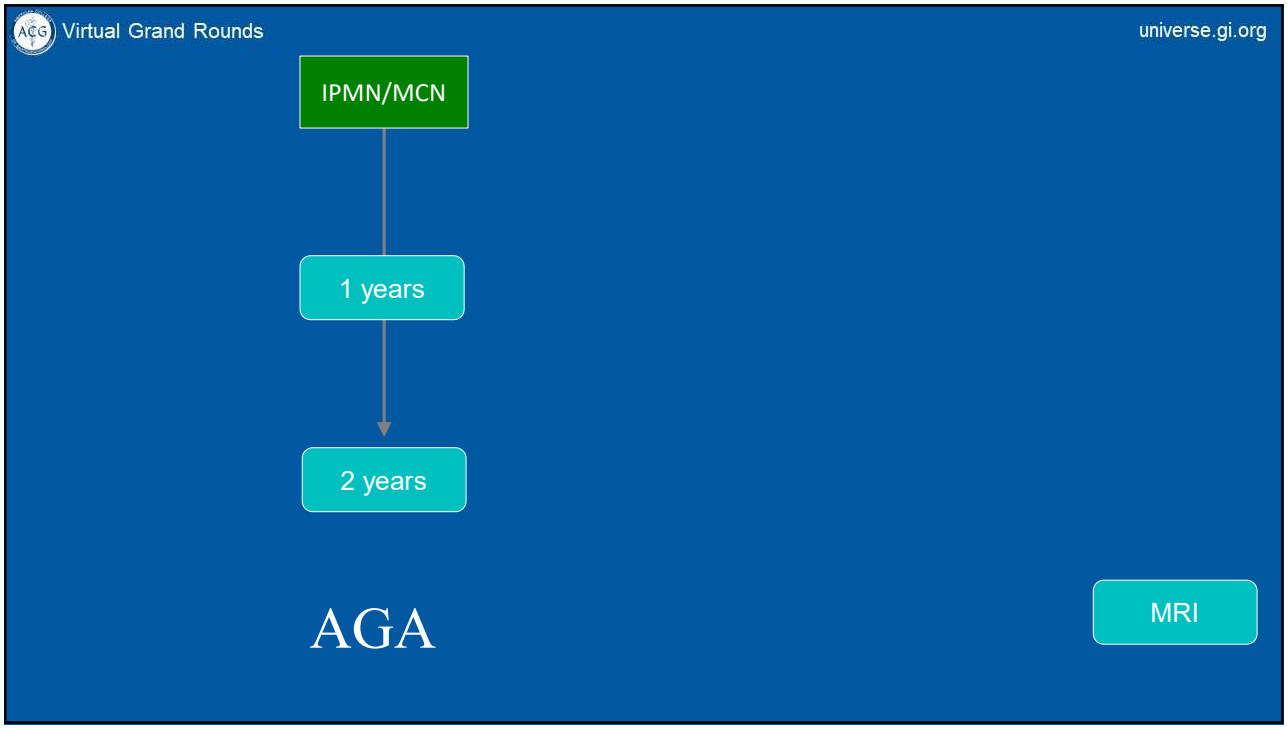

Virtual Grand Rounds
universe.gi.org
IPMN/MCN
Size <1 cm
Size 1-2 cm
Size 2-3 cm
Size ≥3 cm
6 months
6 months
6 months
2 years~
1 year*
6 -12 Months*
CT/MRI
MRI/EUS
IAP

89


Virtual Grand Rounds
universe.gi.org
IPMN/MCN
1 years
2 years
MRI
AGA

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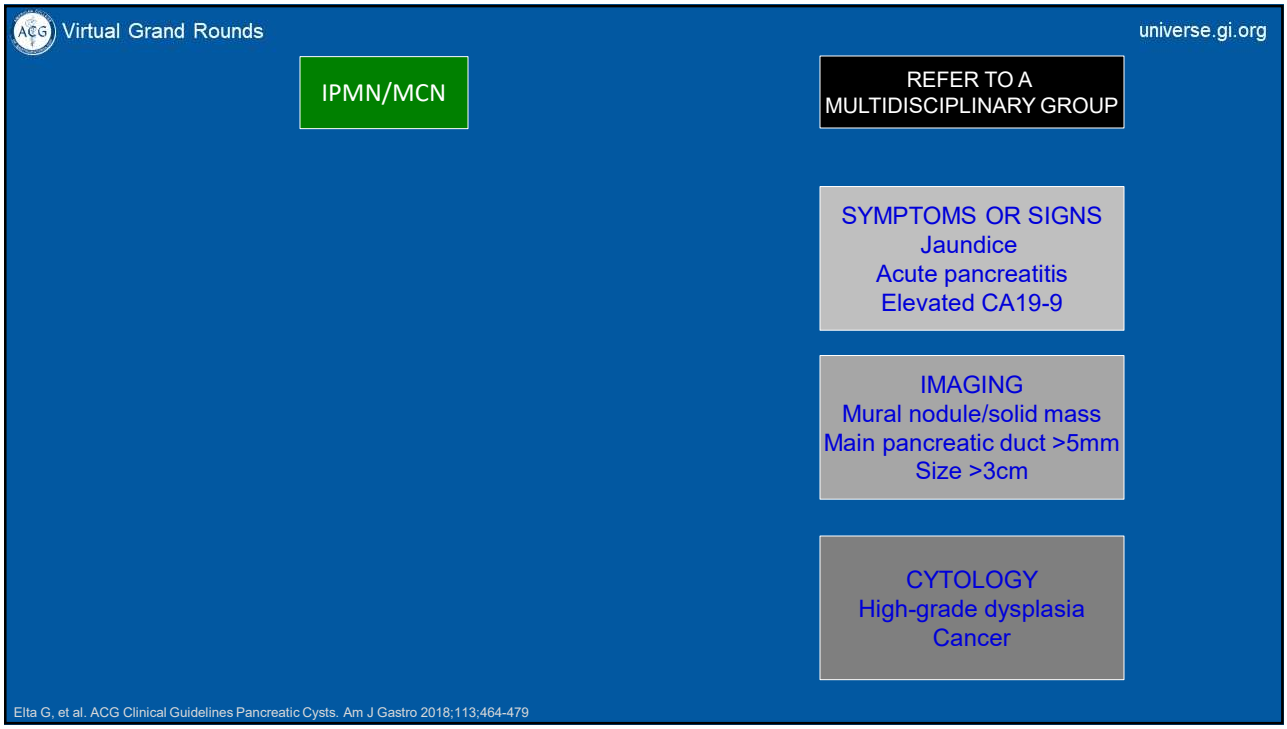
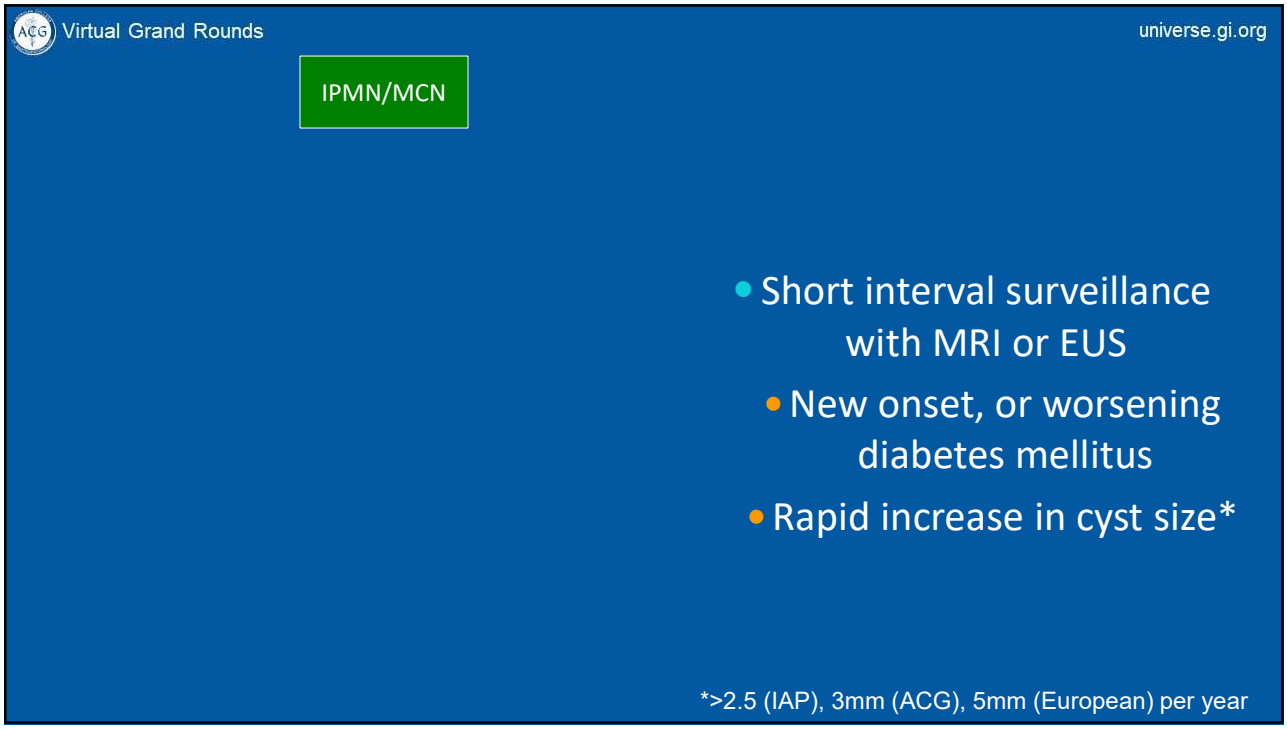

Virtual Grand Rounds
universe.gi.org
IPMN/MCN
REFER TO A MULTIDISCIPLINARY GROUP
SYMPTOMS OR SIGNS
Jaundice
Acute pancreatitis
Elevated CA19-9
IMAGING
Mural nodule/solid mass
Main pancreatic duct >5mm
Size >3cm
CYTOLOGY
High-grade dysplasia
Cancer
Elta G, et al. ACG Clinical Guidelines Pancreatic Cysts. Am J Gastro 2018;113:464-479

91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IPMN/MCN
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

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5 years later

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

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When do you stop surveillance?

Surveillance should be discontinued if a patient is no longer a surgical candidate

Elta G, et al. ACG Clinical Guidelines Pancreatic Cysts. Am J Gastro 2018;113;464-479

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When do you stop surveillance?

Radiology: Stop at age 80

ACG: Assess utility >75 years

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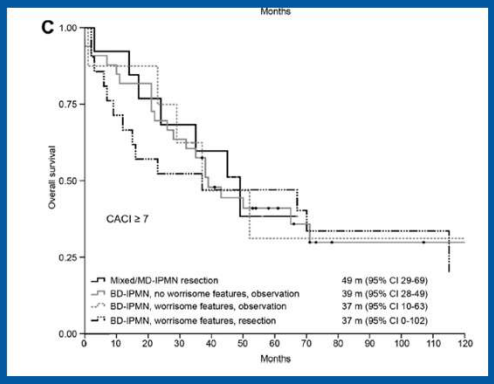
Charlson comorbidity index ≧7



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

Sahora K et al. Clin Gastro Hep 2015

96

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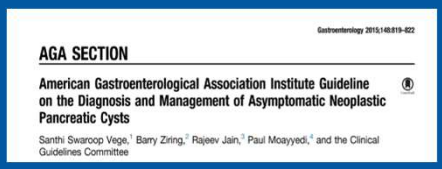
Stopping Surveillance



Gastroenterology 2015;149:819–822

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee

ORIGINAL ARTICLE CLINICAL PRACTICE MANAGEMENT

Management of Incidental Pancreatic Cysts: A White Paper of the ACR Incidental Findings Committee

EC Editor's Choice SA-CME

Alec J. Megibow, MD, MPH[a], Mark E. Baker, MD[b], Desiree E. Morgan, MD[c], Ihab R. Kamel, MD, PhD[d], Dushyant V. Sahani, MD[e], Elliot Newman, MD[f], William R. Brugge, MD[g], Lincoln L. Berland, MD[h], Pari V. Pandharipande, MD, MPH[i,j]

AGA – 5 years

Radiology – 10 years

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Continue Surveillance

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

ELSEVIER

Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Terumi Kamisawa[c], Jin Young Jang[d], Philippe Levy[e], Takao Ohtsuka[f], Roberto Salvia[g], Yasuhiro Shimizu[h], Minoru Tada[i], Christopher L. Wolfgang[j]

European evidence-based guidelines on pancreatic cystic neoplasms

The European Study Group on Cystic Tumours of the Pancreas

ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts

Grace H. Elta, MD, FACG[1], Brintha K. Enestvedt, MD, MBA[2], Bryan G. Sauer, MD, MSc, FACG (GRADE Methodologist)[3] and Anne Marie Lennon, MD, PhD, FACG[4]

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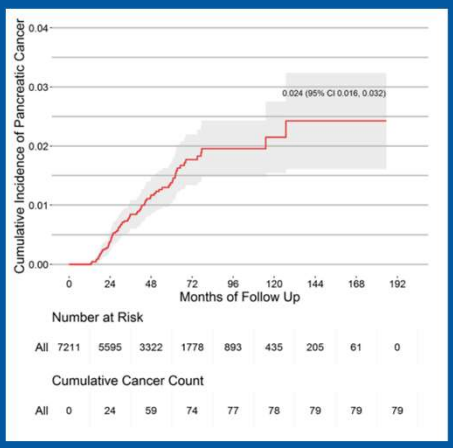
Stop Surveillance



1.1% pancreatic cancer

Gobind, AS et al. Dig Dis and Sciences 2020

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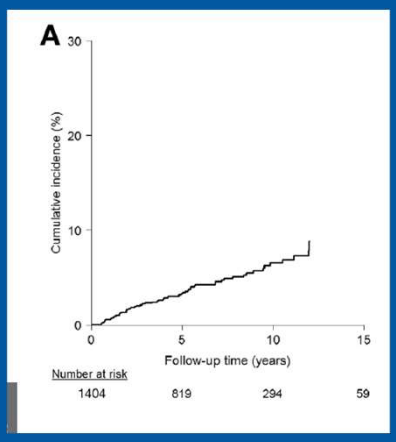
Continue Surveillance



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

Oyama et al. Gastro 2020

100

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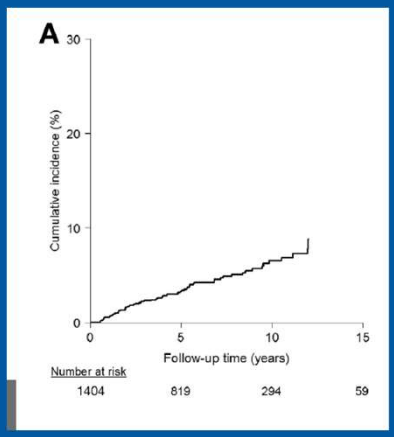
Continue Surveillance



10-fold higher risk PDAC vs age matched controls

Oyama et al. Gastro 2020

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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

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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

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Thank You

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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

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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

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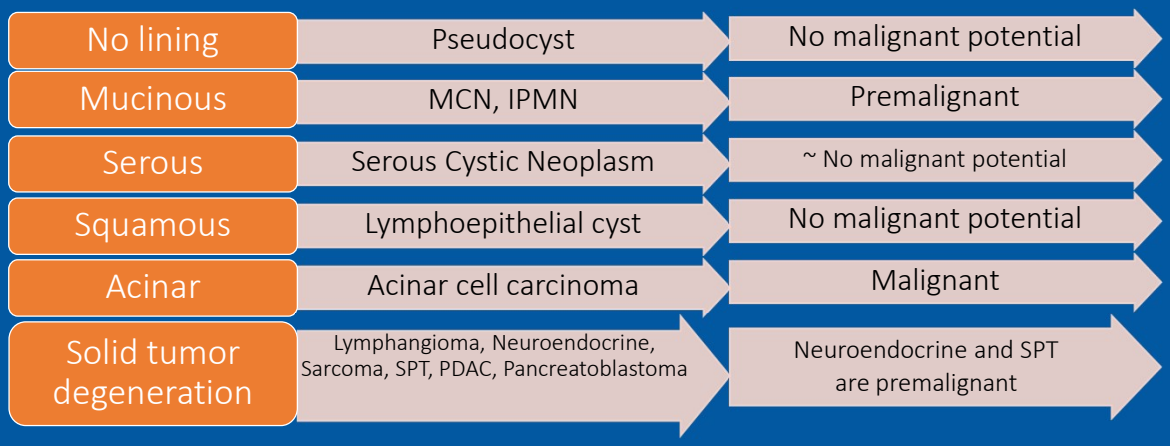
Classification of Pancreatic Cysts by Cyst Lining and Malignant Potential



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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

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EUS-RA Device
Tae Woong Medical

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EUS RFA Pancreatic Cystic Endocrine Tumor

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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.

	Neuroendocrine tumor	Pancreatic cystic neoplasm
Number of lesions	14	16 IPMN 1 MCA
Location		
- Head	3	10
- Body	6	4
- Tail	5	3
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

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EUS RFA of PETs and PCNs: A prospective multicenter study

Table 2
Results of endoscopic ultrasound-guided radiofrequency ablation in the 31 pancreatic lesions.

	6 months follow-up	12 months follow-up
Neuroendocrine tumors (n = 14), n (%)		
Significant response	10 (71.4)	12 (85.7)
- Disappearance or necrosis	9 (64.3)	12 (85.7)
- Decrease in diameter >50%	1 (7.1)	0 (0)
Failure[*]	4 (28.6)	2 (14.3)
Pancreatic cystic neoplasms (n = 17), n (%)		
Significant response	11 (64.7)	12 (70.6)
- Disappearance or necrosis	8 (47.1)	11 (64.7)
- Decrease in diameter >50%	3 (17.6)	1 (5.9)
Failure[*]	6 (35.3)	5 (29.4)

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

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

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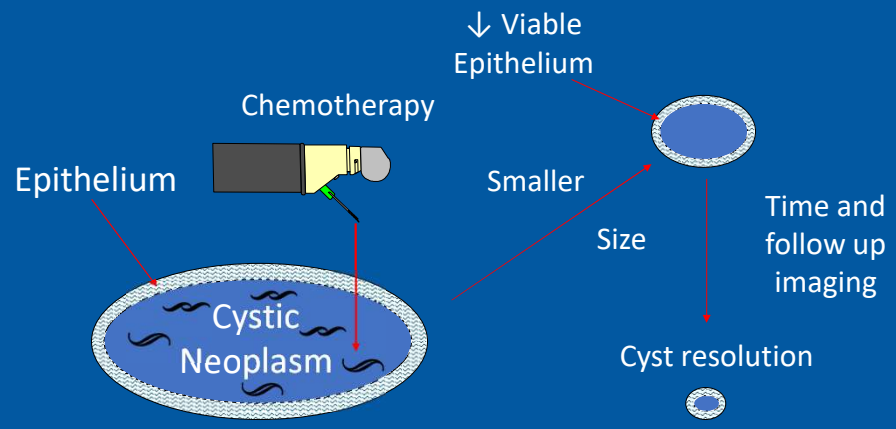
EUS Guided Cyst Ablation with Chemotherapy Injection



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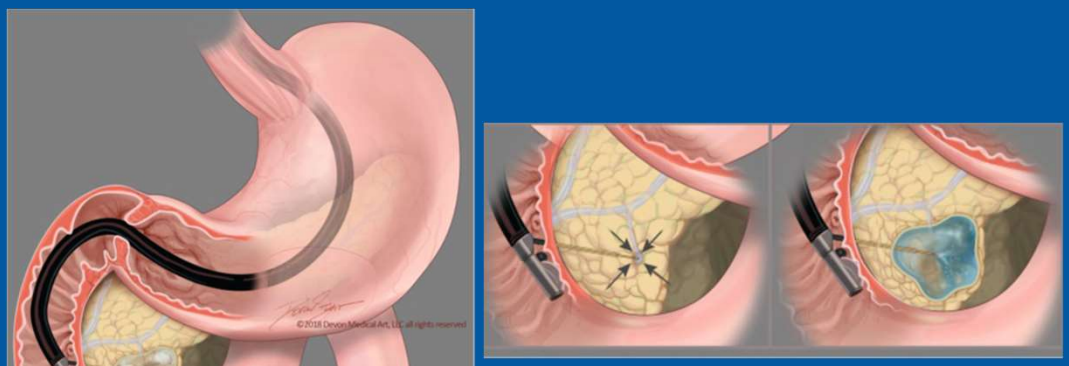
Pancreatic Cyst Ablation with EUS FNI



Moyer MT, Maranki JL, DeWitt JM.
Curr Gastroenterol Rep 2019;21(5):19.

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Pancreatic Cyst Ablation

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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

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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

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Studies of Pancreatic Cyst Ablation Published 2005-2017

Author (year)	Enrolled	Ablative Agent	Size (cm)	MCN (n, %)	IPMN (n, %)	SCN (n, %)	PC (n, %)	Indeterminate (n, %)
Gan (2005)	25	↑ETOH	1.9	14 (56)	3 (12)	3 (12)	1 (4)	2 (8)
DeWitt (2009)	42	ETOH vs saline → ETOH	2.0	17 (41)	17 (41)	5 (12)	3 (6)	0 (0)
Oh (2011)	52	ETOH + PTX	3.1	9 (17)	0 (0)	15 (29)	2 (4)	26 (50)
DeWitt (2014)	22	ETOH + PTX	2.5	12 (55)	6 (27)	4 (18)	0 (0)	0
Gomez (2016)	23	ETOH	2.8	4 (17)	15 (65)	NR	NR	NR
Moyer (2016)	10	ETOH vs. saline → GEM + PTX	2.9	7 (70)	2 (20)	0 (0)	0 (0)	1 (10)
Park (2016)	91	ETOH	3.0	12 (13)	9 (10)	33 (36)	9 (10)	28 (31)
Choi (2017)	164	ETOH + PTX	3.2	71 (43)	11 (7)	16 (10)	0 (0)	63 (40)

Gan SI GIE 2005, DeWitt J GIE 2009, Oh HC Gastro 2011, DeWitt JM Endoscopy 2014, Gomez V GIE 2016, Moyer MT EIO 2016, Park JK Pancreas 2016, Choi JH Endoscopy 2017

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Studies of Pancreatic Cyst Ablation Published 2005-2017

Author (year)	Enrolled	Ablative Agent	Complete Resolution (%)	Partial Resolution (%)	No response (%)
Gan (2005)	25	↑ETOH	35	13	65
DeWitt (2009)	42	ETOH vs. saline → ETOH	33	NR	NR
Oh (2011)	52	ETOH + PTX	56	12	32
DeWitt (2014)	22	ETOH + PTX	50	25	25
Gomez (2016)	23	ETOH	9	43	48
Moyer (2016)	10	ETOH vs. saline → GEM + PTX	EtOH (75%) Saline (67%)	NR	NR
Park (2016)	91	ETOH	45	41	14
Choi (2017)	164	ETOH + PTX	72	20	8

Gan SI GIE 2005, DeWitt J GIE 2009, Oh HC Gastro 2011, DeWitt JM Endoscopy 2014, Gomez V GIE 2016, Moyer MT EIO 2016, Park JK Pancreas 2016, Choi JH Endoscopy 2017

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Studies of Pancreatic Cyst Ablation

Author (year)	Enrolled	Ablative Agent	Total (%)	Pancreatitis (%)	Abd pain (%)	Other AEs (n)
Gan (2005)	25	↑ETOH	0	0	0	0
DeWitt (2009)	42	ETOH vs. saline → ETOH	31	2.4	24	Intracystic bleeding (1)
Oh (2011)	52	ETOH + PTX		2	2	Fever (1), pericystic spillage (1), SVT (1)
DeWitt (2014)	22	ETOH + PTX	29	10	13	Peritonitis and ileus (1), perigastric cyst (1)
Gomez (2016)	23	ETOH	8	4	4	0
Moyer (2016)	10	ETOH vs. saline → GEM + PTX	10	10	0	0
Park (2016)	91	ETOH	29 (29)	3 (3)	18 (17)	fever (8)
Choi (2017)	164	ETOH + PTX	9.8	3.2	0	Fever (1), pericystic spillage (1), intracystic bleeding (1), pseudocyst (2), abscess (2), PVT (1), SVT (1), MPD stricture (1)

Gan SI GIE 2005, DeWitt J GIE 2009, Oh HC Gastro 2011, DeWitt JM Endoscopy 2014, Gomez V GIE 2016, Moyer MT EIO 2016, Park JK Pancreas 2016, Choi JH Endoscopy 2017

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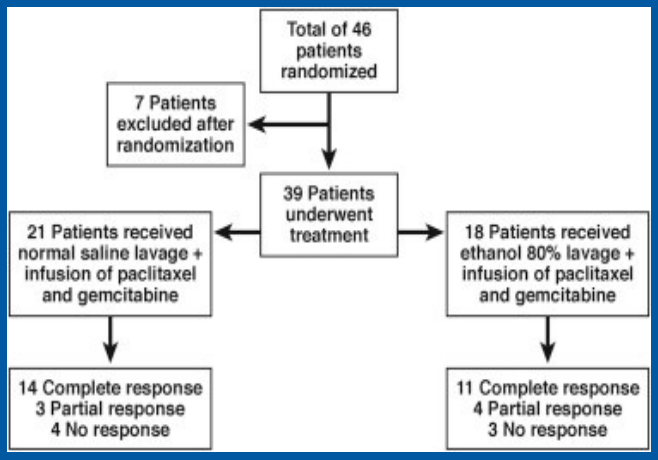
The Safety and Efficacy of an Alcohol-Free Pancreatic Cyst Ablation Protocol



- 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

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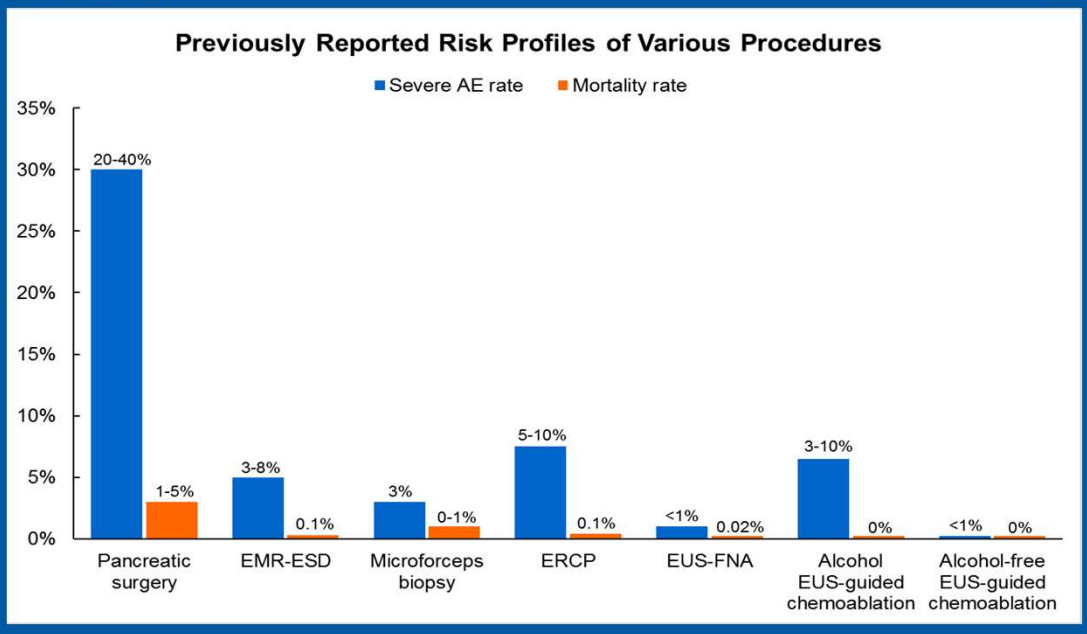

Slide courtesy of Matt Moyer MD

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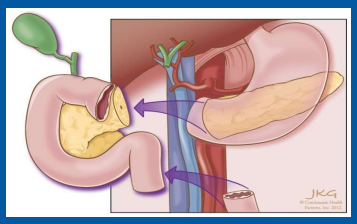
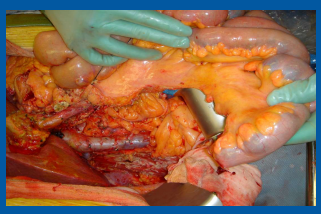
Complications and Costs for Surgery vs. EUS FNI for pancreatic cysts

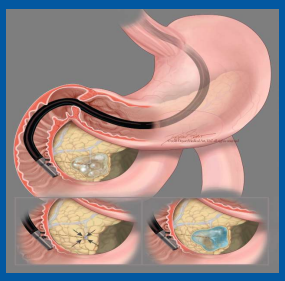


Whipple surgery

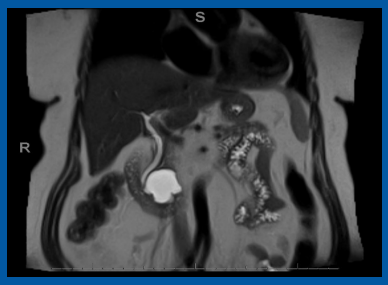


Mortality 1-5%, SAE 20-40%

$153,215 USD*



EUS guided ablation



Mort 0%, SAE 3-10%

$5,146 USD*

National Summary of Inpt Charges by Medicare Severity Diagnosis Related Group, FY 2016

Slide courtesy of Matt Moyer MD

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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

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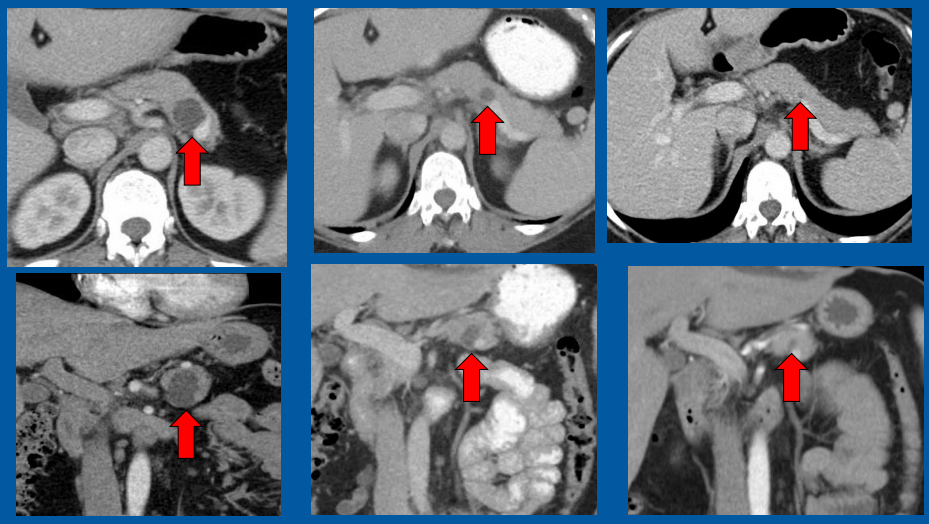
Follow up CT scans



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

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Study Timeline

PRE-Ablation

BEFORE 1st EUS Cyst Exam and Ablation:

STEP 1: Screening/eligibility (e.g., review CT, labs)

STEP 2: Obtain informed consent

↓

1st EUS Cyst Exam and Ablation:

STEP 3: Assess cyst eligibility

STEP 4: Decide whether to ablate

STEP 5: Randomization

↙ ↘

Ethanol lavage: EtOH + Paclitaxel-Gemcitabine

Ethanol-Free: Saline + Paclitaxel-Gemcitabine

Ablation

STEP 6: EUS with fine needle aspiration (including cytological, chemical and molecular analysis, followed by treatment)

POST-Ablation

0-2 hours

STEP 7: Post-procedure monitoring for AEs

72 Hours

STEP 8: Phone interview for AEs, patient reported outcomes

30 Days

STEP 9: Phone interview for AEs, patient reported outcomes

3 months

STEP 10: EUS evaluation and ablation as needed (e.g., size > 15mm)

12 months

STEP 11: In-person visit for MRI-MRCP, patient reported outcomes, plan long term follow-up

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

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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

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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

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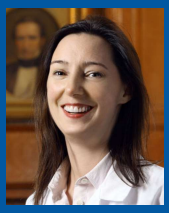
Questions

universe.gi.org

V. Raman Muthusamy, MD, MAS, FACG



Anne Marie Lennon, MD, PhD, MBBCh, FACG

John M. DeWitt, MD, FACG

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