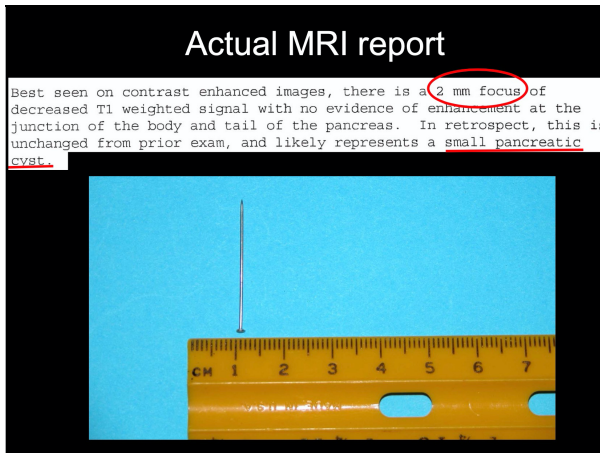




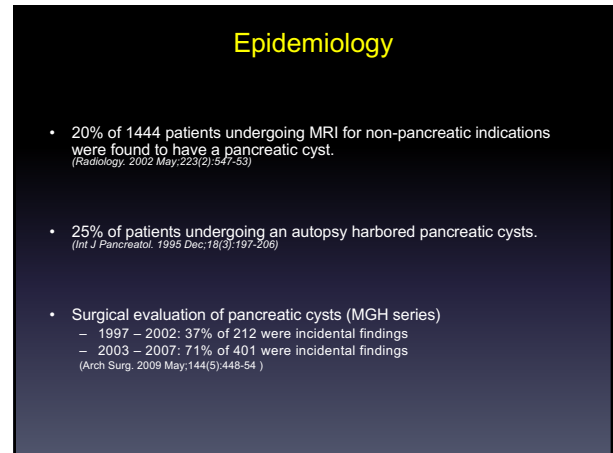
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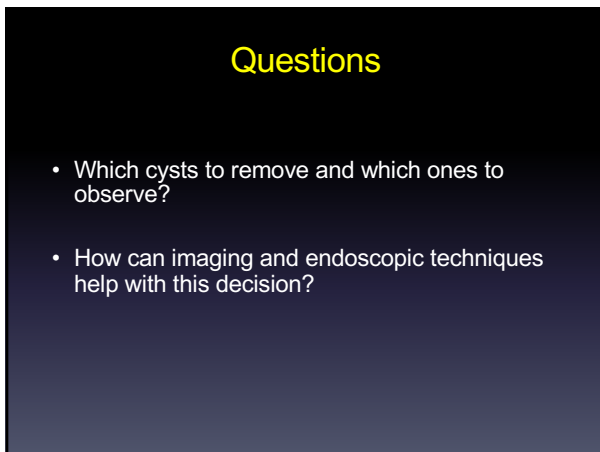
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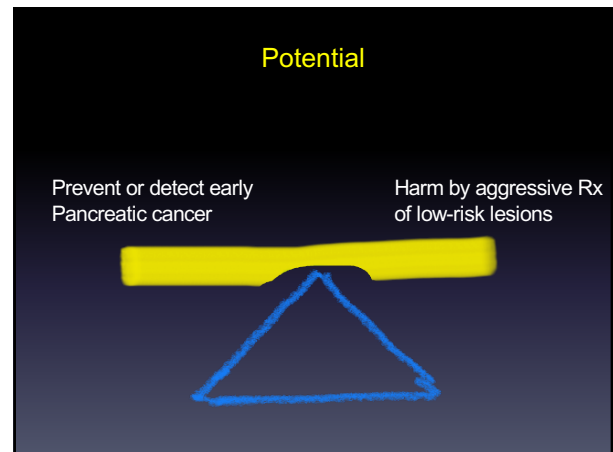
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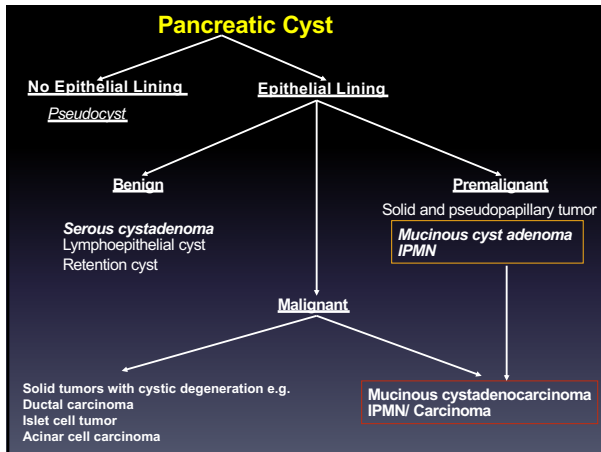
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Incidence

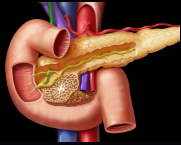
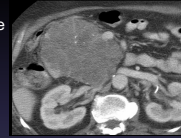

717 Cystic neoplasms of the pancreas
(589 resected + 128 under observation)
MGH 1990 - 2007

- Branch – Duct IPMN – 31%
- Main-Duct IPMN – 21%
- Serous Cystadenoma – 20%
- MCN – 12%
- Indeterminate mucinous lesions – 5%
- Cystic Islet cell tumors – 4%
- Solid pseudopapillary tumor – 3%
- Other – 4%

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Serous cystic tumors (SCT)

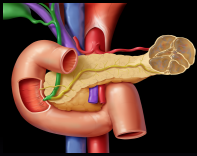
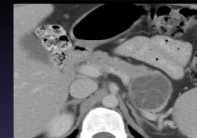

Occur in both sexes
Benign (essentially)
Microcystic and oligocystic variety
Microcystic variant common, honeycomb appearance
May have central scar
Usually asymptomatic
FNA- thin and usually bloody
Cytology- Glycogen rich cuboidal cells
Low CEA (<5 ng/mL)
Mutation in VHL gene
Resect if symptomatic

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Mucinous cystic neoplasms (MCN)

Occur in women
Pre-malignant lesion
Septated or unilocular; body, tail location
Egg shell calcification ~20%
Cytology- sensitivity 35%, specificity 80%
CEA elevated (>200 ng/mL ~80% accurate)
KRAS mutation specific, not sensitive
Ovarian stroma requisite for diagnosis
Resection recommended

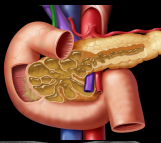
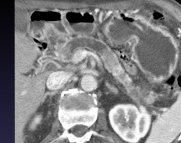
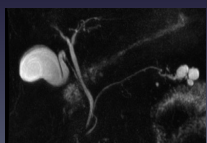
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Intraductal papillary mucinous neoplasm (IPMN)

Occur in both sexes, Premalignant lesion

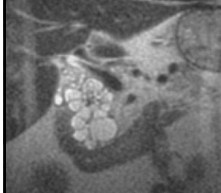
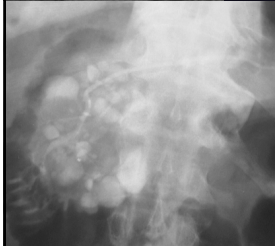
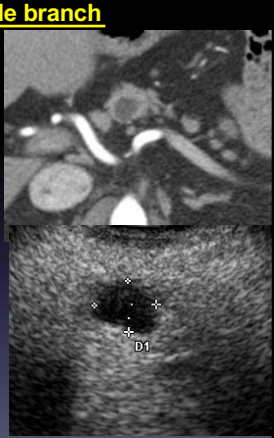
Main duct IPMN: High risk, Resection recommended
Symptoms, duct >10mm, mural nodule associated with malignancy

Branch duct IPMN: Low risk, can monitor
Size >3.5 cm, solid component, symptoms associated with malignancy
Cytology- sensitivity 35%, specificity 80%
CEA elevated (>200 ng/mL ~80% accurate)
KRAS/GNAS mutation specific, not sensitive

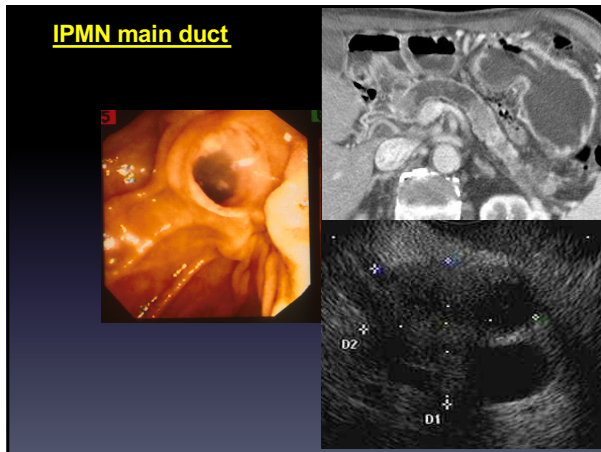




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IPMN side branch

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Risk of Invasive Malignancy in Mucinous Cystic Tumors

- Main Duct IPMNs: 38-68%
- Mucinous Cystic Neoplasms: 10-20%
- BD-IPMNs: 12-47%

(Referral bias in surgical series overstates true malignancy risk)

Le Borgne J. Ann Surg 1999
Kiely JM. J Gastrointest Surg 2003
Sohn TA. Ann Surg 2004
Stark A. JAMA 2016

Spinelli KS. Ann Surg 2004
Rodriguez JR. Gastroenterology 2007
Schmidt CM. Ann Surg 2007
Allen PJ. Ann Surg 2006

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DIAGNOSIS

- Cyst Fluid Analysis (EUS-guided)
 - CEA, amylase, cytology
- Molecular Pathology Techniques
 - DNA analysis
 - Micro RNA analysis
- Enhanced endoscopic techniques
 - EUS-guided direct micro-cystic biopsy
 - EUS guided cyst-pancreatography
 - Direct invivo cyst endomicroscopy

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How Pancreatic Cancer Develops

- Neoplastic transformation in cell morphology is paralleled/preceded by genetic alterations

- The detection of established DNA mutations may serve to improve the diagnostic yield of cytology in pancreatic cancer.

Hruban et. al. Am J Surg Pathol 2003

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EUS-FNA + cyst fluid analysis is helpful...

	Viscosity	CEA	Cytology	Amylase	DNA mutation analysis
MCN	High	High	Mucinous epithelium	Low	KRAS (specific, not sensitive)
IPMN	High	High	Mucinous epithelium	High	KRAS/IGNAS (specific, not sensitive)
SCA	Low	Low	PAS+ cuboidal	Low	VHL (specific)
PC	Low	Low	Inflammatory cells	High	

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ORIGINAL RESEARCH FULL REPORT: CLINICAL—PANCREAS | VOLUME 149, ISSUE 6, P1501-1510, NOVEMBER 01, 2015

A Combination of Molecular Markers and Clinical Features Improve the Classification of Pancreatic Cysts

Simeon Springer · Yuxuan Wang · Marco Dal Molin · ... Ralph H. Hruban · Bert Vogelstein · Anne Marie Lennon · Show all authors · Show footnotes

Type of Cyst	Composite Molecular Markers				Composite Molecular AND Clinical ¹ Markers			
	Any of these Present	Any of these Absent	Sensitivity (95% CI)	Specificity (95% CI)	Any of these Present	Any of these Absent	Sensitivity (95% CI)	Specificity (95% CI)
SCA	<i>TP53</i> chr3 LOH ^{2,3}	<i>KRAS</i> <i>GNAS</i> <i>RNF43</i> chr12 loss chr1p loss	100% (74-100%)	91% (84-95%)	Age ≥25 years	Abdominal pain Communication with MPD MPD dilation	100% (74-100%)	98% (94-99.8%)
SFN	<i>CTNNB1</i>	<i>KRAS</i> <i>GNAS</i> <i>RNF43</i> chr11 LOH	100% (69-100%)	100% (97-100%)	Age <55 years	Jaundice Multiple cysts Weight loss	89% (52-99.7%)	92% (85-96%)
MCN	None	<i>CTNNB1</i> <i>GNAS</i> chr3 LOH chr1q loss chr22 loss	100% (74-100%)	73% (66-82%)	Age <75 years	Sex (male) Communication with MPD Multiple cysts	90% (56-99.8%)	97% (91-99%)
IPMN	<i>GNAS</i> <i>RNF43</i> ² chr9 LOH chr1q loss chr1p loss	None	76% (66-84%)	97% (85-99.9%)	Age ≥85 years Communication with MPD MPD dilation Abdominal pain	None	94% (86-98%)	84% (64-95%)

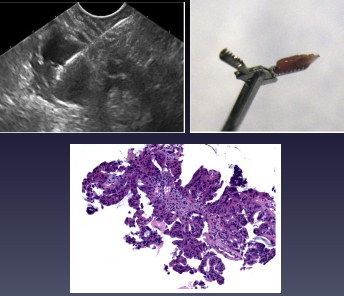
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Feasibility and safety of microforceps biopsy in the diagnosis of pancreatic cysts ^(CME)

Omer Basar, MD,¹ Osman Yucel, MD,² Dennis J. Yang, MD,³ Jason Samarasena, MD,⁴ David Forcione, MD,⁵ Christopher J. DiMaio, MD,⁶ Mihir S. Wagh, MD,⁷ Kenneth Chang, MD,⁸ Brenna Casey, MD,⁹ Carlos Fernandez-del Castillo, MD,¹⁰ Martha B. Pitman, MD,¹¹ William R. Brugge, MD¹²

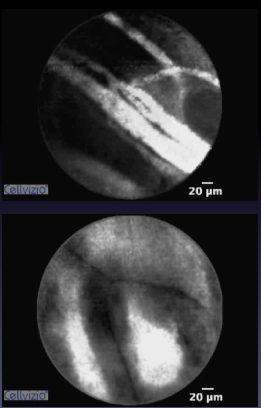
Boston, Massachusetts, USA; Ankara, Turkey; Gainesville, Florida; Aurora, California; New York, New York; Denver, Colorado, USA

- Micro-biopsy catheter
- Advanced through a 19G FNA needle
- Sample wall for histology
- Improved diagnostic yield from 47 to 62%
- 1 intra-cystic bleeding



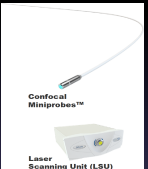
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Direct Cyst Endomicroscopy "Optical Biopsy"




Serous cystadenoma
- Increased vascularity
- ? Acinar cells

IPMN
- papillary projections
- dysplasia



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EUS-Guided Cyst-Pancreatography



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Guidelines

1. AGA - 2015
2. IAP (Fukuoka) – 2017
3. ACG - 2018
4. European Study Group – 2018
5. Amer Coll Radiology - 2017

EDITORIAL

Pancreatic cyst guidelines: Which one to live by?

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Table 3. High-risk characteristics for mucinous pancreatic cysts

Symptoms
Jaundice secondary to the cyst
Acute pancreatitis secondary to the cyst
Elevated serum CA 19-9 when no benign cause for elevation is present
Imaging findings
Mural nodule or solid component within the cyst or pancreatic parenchyma
Main pancreatic duct diameter of >5 mm
Change in main duct caliber with upstream atrophy
Size ≥3 cm
Increase in cyst size ≥3 mm/year
Cytology
High-grade dysplasia or pancreatic cancer

ACG Guidelines 2018

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Box 1 | Indications for evaluation of PCN with EUS

2015 AGA¹⁸ guideline

- At least two of the following concerning features:
 - Cyst diameter >30 mm
 - Nodule
 - PD dilatation

2017 IAP¹⁹ guideline

- Growth rate ≥5 mm over 2 years
- Increased levels of serum CA19-9
- PD dilatation between 5 and 9 mm
- Cyst diameter ≥30 mm
- Acute pancreatitis (caused by IPMN)
- Enhancing mural nodule (<5 mm)
- Abrupt change in calibre of PD with distal pancreatic atrophy
- Lymphadenopathy
- Thickened/enhancing cyst walls

2018 European²⁰ guideline

- EUS-(FNA) should only be performed when the results are expected to change clinical management.
- EUS-(FNA) is recommended if the PCN has either clinical or radiological features of concern identified during the initial investigation or surveillance

AGA, American Gastroenterological Association; CA19-9, cancer antigen 19-9; European, European Study Group on Cystic Tumours of the Pancreas; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IAP, International Association of Pancreatology; IPMN, intraductal papillary mucinous neoplasm; PCN, pancreatic cystic neoplasm; PD, pancreatic duct.

Huijgevoort et al. Nature Reviews 2019

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Table 3 | Indications for surgical resection of pancreatic cysts by different guidelines

Guideline	Cyst type	Absolute indications for surgery ^a	Relative indications for surgery ^b
2015 AGA ¹	MCN	+ MCN	—
	IPMN	+ PD ≥ 5 mm (on MRI and EUS) and solid component or cytology positive for malignancy	—
2017 IAP ²	MCN	+ MCN	—
	IPMN	+ Cytology suspicious or positive for malignancy + Jaundice (tumour-related) + Enhancing mural nodule (≥ 5 mm) + PD dilatation ≥ 10 mm	+ Growth rate ≥ 5 mm over 2 years + Increased levels of serum CA19-9 + PD dilatation between 5 and 9 mm + Cyst diameter ≥ 30 mm + Acute pancreatitis (caused by IPMN) + Enhancing mural nodule (< 5 mm) + Abrupt change in diameter of PD with distal pancreatic atrophy + Lymphadenopathy + Thickened or enhancing cyst walls
2018 European ³	MCN	+ Cyst diameter ≥ 40 mm + Enhancing mural nodule + Symptoms (that is jaundice (tumour-related), acute pancreatitis (caused by MCN), new-onset diabetes mellitus)	—
	IPMN	+ Positive cytology for malignancy or high-grade dysplasia + Solid mass + Jaundice (tumour-related) + Enhancing mural nodule (≥ 5 mm) + PD dilatation ≥ 10 mm	+ Growth rate ≥ 5 mm per year + Increased levels of serum CA19-9 (> 37 U/mL) ⁴ + PD dilatation between 5 and 9.9 mm + Cyst diameter ≥ 40 mm + New-onset diabetes mellitus + Acute pancreatitis (caused by IPMN) + Enhancing mural nodule (< 5 mm)

AGA, American Gastroenterological Association; CA19-9, cancer-associated antigen 19-9; EUS, Endoscopic ultrasonography; IAP, International Association of Pancreatic Cyst Guidelines; IPMN, Intraductal Papillary Mucinous Neoplasm; MCN, Mucinous Cystic Neoplasm; PD, Pancreatic Duct; MRI, Magnetic Resonance Imaging.

Huijgevoort et al. Nature Reviews 2019

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Table 2 Approach to surveillance of pancreatic cysts without high risk or worrisome features at diagnosis

Size	IAP (Fukuoka) 2012	IAP (Fukuoka) 2017	ACG 2018	ACR 2018	European 2018	AGA 2015
< 1 cm	CT/MRI in 2-3 yr	CT/MRI in 6 mo then every 2 yr	MRI q 2 yr (lengthen after 4)	MRI/CT q 1 year for cysts < 1.5 cm and q 6 mo for cysts 1.5-2.5 cm × 4 and then lengthen interval; stop after stability over 10 yr	Surveillance q 6 mo	MRI in 1 yr, then every 2 for 5 yr Stop if stable
1-2 cm	CT/MRI annually × 2 yr, then lengthen interval if stable	CT/MRI in 6 mo × 1 yr A Annually × 2 yr, then lengthen interval if stable	MRI q 1 yrs FCR 3 yr Then q 2 yr FCR 4 yr	for cysts > 2.5 cm q 6 mo MRI/CT and then stop if stable or over 10 yr; for cysts > 80 yr of age, q 2 year imaging	Surveillance q 6 mo	Surveillance q 6 mo with MRI and/or EUS, CA19-9 if stable
2-3 cm	EUS in 3-6 mo, then lengthen interval, alternate MRI with EUS as appropriate	EUS in 3-6 mo, then lengthen interval, alternate MRI with EUS as appropriate	EUS/MRI q 6mo for 3 yr then yearly for 4 yr			
> 3 cm	Alternate MRI/EUS every 3-6 mo	Alternate MRI/EUS every 3-6 mo	EUS/MRI q 6mo for 3 yr then yearly for 4 yr			

¹These guidelines use < 1.5 cm, 1.5-2.5 and > 2.5 as cut off values. CT, Computed tomography; MRI, magnetic resonance imaging; EUS, Endoscopic ultrasonography; ACG, American College of Gastroenterology; AGA, American Gastroenterological Association.

Hasan et al. WJG 2019

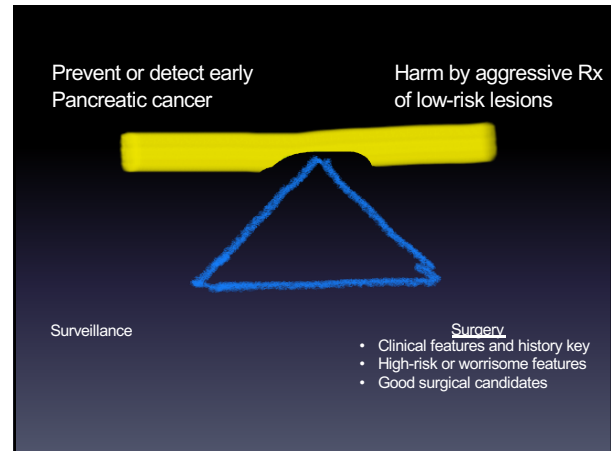
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Table 3 Comparison of performance between pancreatic cyst guidelines

Studies	Comparisons	Outcome	Result	Performance
Righinolli et al ^[1] , 2017	Fukuoka, AGA, and Sendai Criteria ¹	Pancreatic Cyst with invasive cancer	AGA ROC 0.76, Fukuoka ROC 0.78, Sendai ROC 0.65 (P < 0.001)	AGA and Fukuoka guidelines with higher diagnostic accuracy for neoplastic cysts compared to Sendai
Xu et al ^[2] , 2017	AGA, Fukuoka, and American College of Radiology ²	Advanced neoplasia (HGD or cancer) in resected pancreatic cysts	(Sen, Spec, PPV, NPV) AGA: 73%, 88.2%, 10%, and 84.1% Fukuoka: 73.2%, 45.6%, 19.5%, 96.4% ACR: 53.7%, 61%, 19.8%, and 98%	AGA with higher specificity, but lower sensitivity than Fukuoka and ACR
Ma et al ^[3] , 2016	AGA and Fukuoka ³	Advanced neoplasia (HGD or cancer) in resected pancreatic	Fukuoka: 28.2%, 95.8%, 74.1%, 75.9% AGA: 35.2%, 66%, 29.6%, 25.4%	No significant difference between the two guidelines
Singhi et al, 2016	AGA	Advanced neoplasia (HGD or cancer)	AGA: 62%, 79%, 57%, 82%	Low accuracy of AGA guidelines and continued surveillance of benign lesions (i.e., SCAs)
Lekkerkerker et al ^[4] , 2017	Fukuoka, AGA, European Guidelines	Advanced neoplasia (in patients with suspected IPMN)	Accuracy Fukuoka: 54% AGA: 59% European: 53%	AGA guidelines would have rec'd against surgery in most patients with benign lesions and would have missed significantly more HGD/CA

¹These studies have considered high risk or worrisome features as sufficient for indication for resection (for example a cyst size > 3 cm would have qualified for an indication for surgery).
²In these studies the presence of high risk stigmata or worrisome features with positive EUS/FNA were required. EUS, Endoscopic ultrasonography; ACR, American College of Gastroenterology; AGA, American Gastroenterological Association.

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Thank You

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