

Mustafa A. Arain, MD

ASSOCIATE PROFESSOR OF MEDICINE
DIVISION OF GASTROENTEROLOGY
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Disclosures

- Consultant for Boston Scientific, Cook, Medtronic and Olympus
- Acknowledge Dr. Dai for slide content

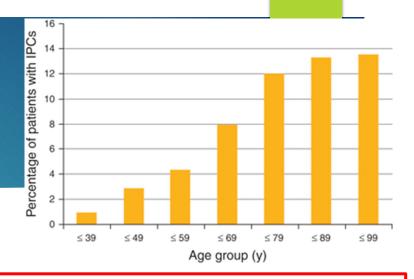
Overview

- Background and Epidemiology
- Categories of cysts
- Management and Diagnostic studies
- Guidelines and Challenges

Pancreatic cysts

- Frequently incidentally found
 - 70 % asymptomatic
- Otherwise non-specific symptoms
 - abdominal/back pain
 - weight loss
 - jaundice
 - steatorrhea
 - palpable mass

Increased incidence with age



				and the second second second		
Table 1. Prevalence of	pancreatic cysts.	. mean and median c	ist diameter.	and mean cvst	t number accord	ing to patient age

Patient age (years)	No. of patients per age group (n=616)	No. of patients with cysts a (n=83)	Mean diameter of largest cyst±s.d. (mm)	Median diameter of largest cyst (mm)	Mean number of cysts per patient ± s.d. ^b
≤39	114	1 (<1%)	3	3	1
40-49	134	6 (4.4%)	5.2±2.5	4	1.5 ± 1.2
50-59	147	10 (6.8%)	4.3±1.8	4	1.8±1.3
60-69	114	23 (20.2%)	7.4 ± 5.2	6	2.3 ± 1.9
70-79	69	29 (42.0%)	8.5±5.7	7	2.3±1.8
80-89	33	12 (36.6%)	8.0 ± 6.9	5	2.2±1.8
90-99	5	2 (40.0%)	14.0±11.3	14	1
70-79 80-89	69 33	29 (42.0%) 12 (36.6%)	8.5±5.7 8.0±6.9	7 5	2.3±1.8

^aThe percentage of patients with pancreatic cysts per age group is noted in parentheses.

^bThe median number of cysts per patient for each age group was identical and equal to 1.

What is the overall risk of malignancy?

- Annual prevalence of 1,137 mucin producing pancreatic adenocarcinomas
- Concurrent prevalence of nearly 3.5 million cysts in the same population (2.5%)

Annual crude and age-specific prevalence rates of mucin-producing adenocarcinoma in 40- to 84-year old US patients with pancreatic cysts.

	Estimated Cases of Mucin-Producing Adenocarcinoma*	Estimated Patients with Pancreatic Cysts [†]	Prevalence Rate per 100,000	95% Confidence Interval
Crude Population	1137	3,428,874	33.2	(21.9, 44.5)
40-49 year olds	111	588,594	18.9	(10.4, 27.4)
50-59 year olds	225	860,240	26.2	(21.1, 31.3)
60-69 year olds	278	950,729	29.2	(18.6, 39.8)
70-79 year olds	351	1,211,505	29.0	(18.4, 39.6)
80-84 year olds	172	499,669	34.4	(23.1, 45.7)

What is the overall risk of malignancy?

- Incidental cyst
 - 10 in 100,000 mucinous invasive cancer
 - 17 in 100,000 ductal cancer
- Annual malignant transformation rate: 0.24% (AGA Guidelines, Pancreatic Cysts, 2015)

Classification by Cyst Lining

No lining

Pseudocyst

Mucinous

• MCN, IPMN

Serous

• SCN, VHL

Squamous

Lymphoepithelial cyst

Acinar

Acinar cell carcinoma

Solid tumor degeneration

 Ductal Adenocarcinoma, Lymphangioma, Neuroendocrine, Sarcoma, Pancreatoblastoma, SPEN

Differential Diagnosis

Asymptomatic pancreatic cyst

Non-neoplastic

Cystic neoplasm

Cystic degeneration of solid neoplasms

Pseudocyst

Retention cyst

Lymphoepithelial cyst

Serous cystadenoma (SCA) Mucinous Cystic Neoplasm (MCN)

Intraductal
Papillary Mucinous
Neoplasm (IPMN)

Solid Pseudopapillary Neoplasm Ductal Adenocarcinoma

> Acinar Cell Carcinoma

Neuroendocrine

Pancreatic pseudocyst

- Transition from acute peripancreatic fluid collection
- 4 weeks
- Well-defined wall
- Amylase/lipase
- Communication or sealed off
- Rare infection
- Dark, turbid fluid on FNA



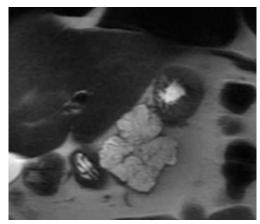
Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus

Interstitial edematous **Necrotizing** pancreatitis pancreatitis Acute (peri)panreatic Acute necrotic fluid collection collection < 4 Homogenous fluid Intra and/or extra weeks adjacent to pancreatic necrotic pancreas without a collection without recognizable wall a well-defined wall Walled off necrosis Pancreatic pseudocyst An encapsulated. ≥ 4 Intra and/or extra well-defined, usually weeks pancreatic necrotic extrapancreatic fluid collection with a collection with well-defined wall minimal solids

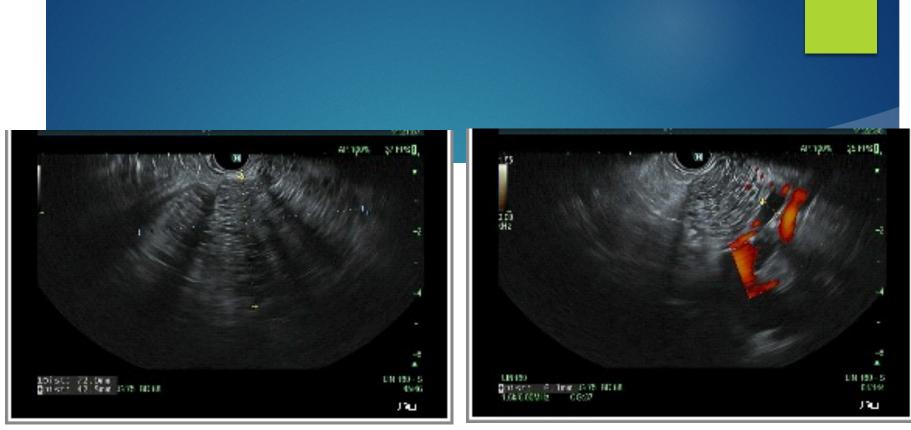
Serous cystadenoma

- Females, 60-70 yo
- Body/tail > head
- Microcystic > macrocystic
- Honeycomb appearance
- Stellate scar with calcification
 - pathognomonic on CT
 - sunburst
- Case reports of cystadenocarcinoma

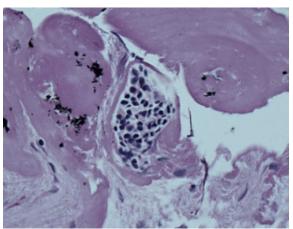






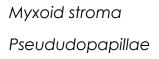


Glycogen-staining cuboidal cells on PAS stain

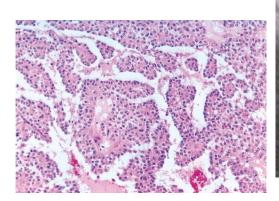


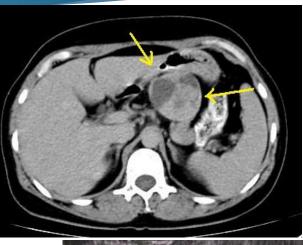
Solid Pseudopapillary Neoplasm

- Rare
- Typical CT appearance
 - Solid and fluid within capsule
 - hemorrhagic
- Low grade malignancy
- Liver mets 15%
- Young women <35</p>
- Surgical resection







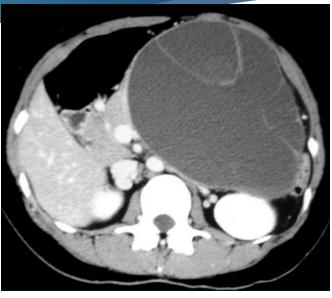




Mucinous cystic neoplasm

- Unilocular or oligocystic
- Women, 50-60s yo
 - 95 % female
- Body/tail
- Ovarian like stroma
- Malignant potential over time
- ▶ 15 30% prevalence of malignancy
- Surgery
 - 5 yr survival 75-96%

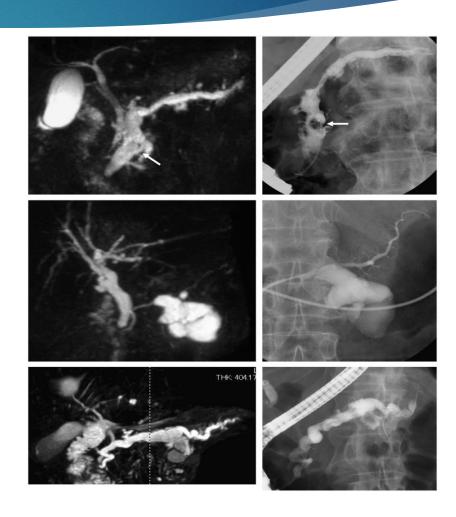






Intraductal papillary mucinous neoplasm (IPMN)

- Grape like clusters, cystic dilation of pancreatic ducts
- Not heavily favored towards females
- Duct involvement
 - Main duct IPMN > 5 mm
- Malignant risk
 - multifocal field



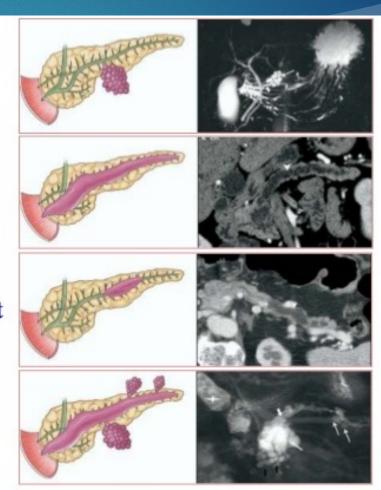
Morphologic Classification of IPMN

Branch pancreatic duct

Diffuse main pancreatic duct

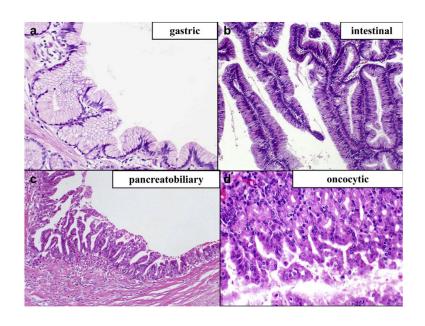
Segmental main pancreatic duct

Mixed (main & branch ducts)



Intraductal Papillary Mucinous Neoplasm

- Cell lineage of the "papillary component" of IPMNs critical
- Majority of BD-IPMNs are of the <u>gastric</u> type
 - typically low grade, only a small percentage developing into carcinoma
- Intestinal type large and complex IPMNs can have invasive carcinoma (colloid type)



Intraductal Papillary Mucinous Neoplasm

Main Duct: prevalence of malignancy as high as 40% at time of resection

- <u>Branch Duct</u>: prevalence of malignancy at time of resection 25%
 - Rate of pdac 3.3% at 5 years, 15% at 15 years

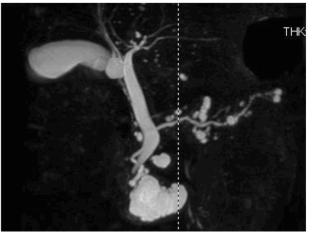
Evaluation

- Labs
 - consider CA 19-9
- Cross sectional imaging
 - MR study
- Endoscopic ultrasound
 - fine needle aspiration
 - cyst wall biopsy
 - confocal endoscopy

MRI/MRCP

- Characteristics
 - number
 - size
 - main pancreatic duct communication
 - solid components
- Limited in terms of type of cyst





Endoscopic ultrasound

- Size
- Mural nodules
- Communication with the main duct
- Ampulla
- Sample
 - > 1 cm for measurable fluid
 - Cytology (sensitivity 40-60%)
 - CEA, amylase
 - Selected situations: Molecular testing, MSI testing
- Reaccumulation not therapeutic











Diagnosis of Pancreatic Cystic Neoplasms: A Report of the Cooperative Pancreatic Cyst Study

WILLIAM R. BRUGGE,* KENT LEWANDROWSKI,* ELIZABETH LEE-LEWANDROWSKI,* BARBARA A. CENTENO,\$ TARA SZYDLO,* SUSAN REGAN, CARLOS FERNANDEZ DEL CASTILLO, ANDREW L. WARSHAW, and THE INVESTIGATORS OF THE CPC STUDY

- Prospective study
- 341 patients, 112 with histology

DIAGNOSIS OF PANCREATIC CYSTIC NEOPLASMS 1333

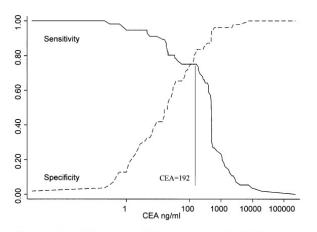


Figure 3. Sensitivity and specificity curves of cyst fluid CEA concentrations (ng/mL; log scale) for differentiating between mucinous and nonmucinous cystic lesions. An optimal cutoff value of 192 ng/mL correlated with the crossover of the sensitivity and specificity curves.

Table 3. Accuracy of the Tested Tumor Markers in Differentiating Between Mucinous and Nonmucinous Lesions

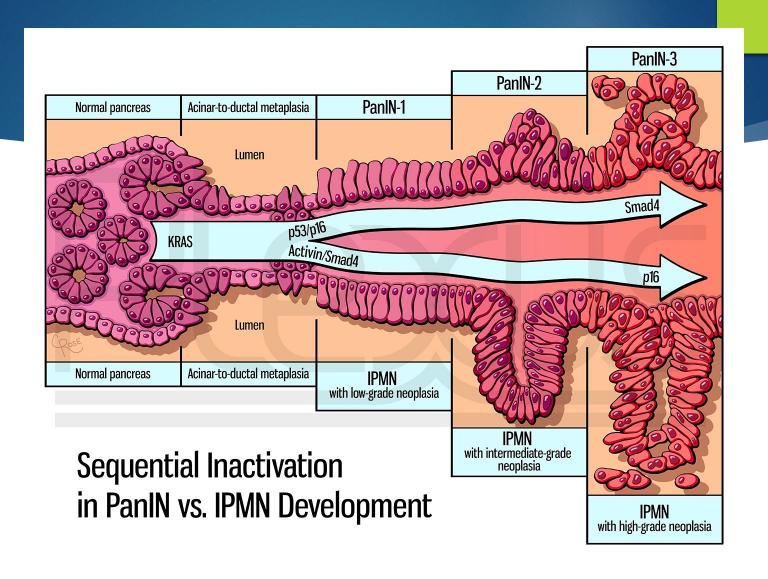
Tumor marker	Sensitivity	Specificity	Accuracy	ROC	P value ^a	Cut off
CEA	.73	.84	.79	.7930	<.001	192
CA125	.83	.37	.60	.5910	.183	9
CA15-3	.19	.94	.57	.5011	.816	121
CA19-9	.68	.62	.66	.6654	.004	2900
CA72-4	.80	.61	.72	.7423	.001	7

ROC, receiver operator characteristics curve (area); Cut off: calculated optimal cutoff values for each marker (ng/mL).

^aP value: significance vs. chance in predicting a mucinous lesion.

Cyst Fluid - CEA and Amylase

	Amylase	CEA
Pseudocyst	+	-
SCA	-	-
MCN	-	+
IPMN	+	+
SPN	-	-



Cyst Fluid – Molecular Testing

Table 2. Frequency of Molecular Features in Different Cyst Types

	IPMN ^a (n = 96)	MCN (n = 12)	SCA (n = 12)	SPN (n = 10)
KRAS	75 (78)	6 (50)	0 (0)	0 (0)
GNAS	56 (58)	0 (0)	0 (0)	0 (0)
RNF43	36 (38)	1 (8)	0 (0)	0 (0)
CDKN2A	3 (3)	0 (0)	0 (0)	0 (0)
CTNNB1	6 (6)	0 (0)	0 (0)	10 (100)
SMAD4	5 (5)	0 (0)	0 (0)	0 (0)
TP53	9 (9)	0 (0)	0 (0)	1 (10)
VHL	0 (0)	0 (0)	5 (42)	0 (0)
BRAF	1 (1)	0 (0)	0 (0)	0 (0)
NRAS	0 (0)	0 (0)	0 (0)	0 (0)
PIK3CA	0 (0)	0 (0)	0 (0)	2 (20)
LOH chr3 (VHL)	4 (4)	0 (0)	7 (64)	0 (0)
LOH chr9 (CDKN2A)	8 (8)	0 (0)	0 (0)	0 (0)
LOH chr17 (RNF43)	11 (11)	0 (0)	1 (9)	0 (0)
LOH chr17 (TP53)	5 (5)	0 (0)	0 (0)	0 (0)
LOH chr18 (SMAD4)	10 (10)	1 (8)	0 (0)	0 (0)
Aneuploidy ^b	48 (50)	2 (17)	6 (50)	6 (60)

	KRAS	GNAS	VHL	CTNNB1
IPMN	+	+	-	-
MCN	+	-	-	-
SCA	-	-	+	-
SPN	-	-	-	+

NOTE. Values are n (%).

Chr, chromosome.

^aIncludes 1 intraductal tubulopapillary neoplasm.

^bAneuploidy of at least 1 chromosome observed. Details are provided in Supplementary Table 3.

Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia

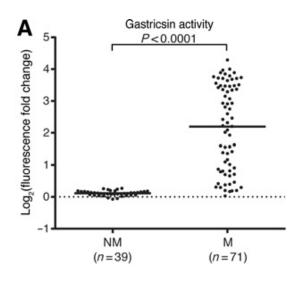
Singhi AD, et al. Gut 2018;67:2131-2141.

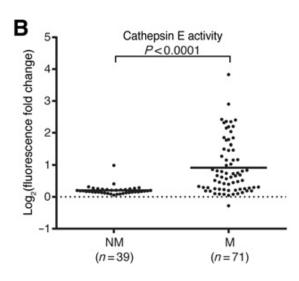
Parameter	Sensitivity (95% CI)	Specificity (95% CI)
IPMNs		
KRAS and/or GNAS mutations	100% (0.92 to 1.00)	96% (0.84 to 0.99)
Presence of multiple cysts	54% (0.40 to 0.67)	72% (0.56 to 0.84)
Increased fluid viscosity	82% (0.69 to 0.91)	80% (0.66 to 0.90)
Elevated CEA*	57% (0.40 to 0.73)	70% (0.53 to 0.83)
IPMNs with advanced neoplasia		
TP53, PIK3CA and/or PTEN alterations	88% (0.62 to 0.98)	95% (0.88 to 0.98)
KRAS and/or GNAS mutations with TP53, PIK3CA and/or PTEN alterations	88% (0.62 to 0.98)	97% (0.89 to 0.99)
GNAS MAF >55% or TP53/PIK3CA/PTEN MAFs at least equal to KRAS/GNAS MAFs	100% (0.77 to 1.00)	100% (0.95 to 1.00)
Main pancreatic duct dilatation	47% (0.24 to 0.71)	74% (0.63 to 0.83)
Presence of a mural nodule	35% (0.15 to 0.61)	94% (0.86 to 0.98)
Malignant cytopathology†	35% (0.15 to 0.61)	97% (0.91 to 1.00)
IPMNs and MCNs		
KRAS and/or GNAS mutations	89% (0.79 to 0.95)	100% (0.88 to 1.00)
Increased fluid viscosity	77% (0.65 to 0.86)	89% (0.73 to 0.96)
Elevated CEA*	57% (0.42 to 0.71)	80% (0.61 to 0.92)
IPMNs and MCNs with advanced neoplasia		
TP53, PIK3CA and/or PTEN alterations	79% (0.54 to 0.93)	95% (0.88 to 0.98)
KRAS and/or GNAS mutations with TP53, PIK3CA and/or PTEN alterations	79% (0.54 to 0.93)	96% (0.89 to 0.99)
GNAS MAF >55% or TP53/PIK3CA/PTEN MAFs at least equal to KRAS/GNAS MAFs	89% (0.66 to 0.98)	100% (0.95 to 1.00)
Main pancreatic duct dilatation	42% (0.21 to 0.66)	74% (0.63 to 0.82)
Presence of a mural nodule	32% (0.14 to 0.57)	94% (0.86 to 0.98)
Malignant cytopathology†	32% (0.13 to 0.57)	98% (0.91 to 1.00)

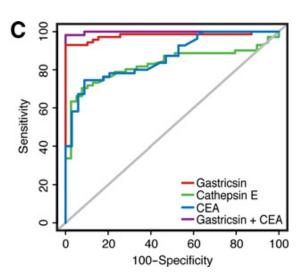
Global Protease Activity Profiling Provides Differential Diagnosis of Pancreatic Cysts

Sam L. Ivry^{1,2}, Jeremy M. Sharib³, Dana A. Dominguez³, Nilotpal Roy⁴, Stacy E. Hatcher³, Michele T. Yip-Schneider⁵, C. Max Schmidt⁵, Randall E. Brand⁶, Walter G. Park⁷, Matthias Hebrok⁴, Grace E. Kim⁸, Anthony J. O'Donoghue⁹, Kimberly S. Kirkwood³, and Charles S. Craik¹

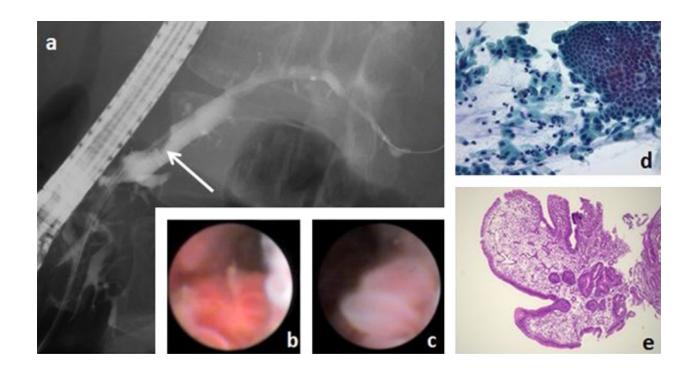
Clin Cancer Res; 23(16) August 15, 2017







ERCP - Pancreatoscopy



Journal of Hepato-Biliary-Pancreatic Sciences

<u>Volume 21, Issue 6, pages 410-417, 14 OCT 2013 DOI: 10.1002/jhbp.44 http://onlinelibrary.wiley.com/doi/10.1002/jhbp.44/full#jhbp44-fig-0002</u>



Table 5. Further Workup Beyond Computed Tomography for Incidental Cystic Lesions of the Pancreas of Indeterminate Risk

			Diagnostic Per	formance ^a	
	Clinical Utility	Positive Result	Sensitivity, %	Specificity, %	Positive LR
Endoscopic ultrasound	Accurate cyst size determination	Size	NA	NA	NA
	May be most sensitive method to detect mural nodules	Presence of a mural nodule	75	83	4.4170
Cyst fluid analysis			111111		
Mucin	Determine mucinous vs serous lesion	Presence of extracellular mucin indicates mucinous lesion	78-97	100	NA ^{40,71}
Carcinoembryonic antigen	Determine mucinous vs serous lesion	Fluid level <5 ng/mL indicates serous lesion	100	86	NA ^{72,73}
	Cannot reliably identify malignancy	Fluid level >192 ng/mL indicates mucinous lesion	73	84	4.56 ⁷⁴
Cytology	Identification of lesions at high risk	Malignant cells present	Роог	96	NA ⁷⁵⁻⁷⁷
	for malignancy	High-grade atypia (includes both atypical epithelial cells and positive cells)	72-83	85-88	4.80-6.92 ⁷⁷⁻⁷⁹

Abbreviations: LR, likelihood ratio; NA, not applicable.

^a Reported sensitivity, specificity, and LR indicate the diagnostic performance of a positive result for the corresponding test listed in the first column.

Clinical challenges

- IPMNs associated with pancreatic malignancy
- Source of anxiety for patients as IPMNs are common
- Most can be monitored...alternative is surgery with high morbidity (20-40%) and definite mortality (1-2%)
- Keeping up with the guidelines!

Goals

- Identification of high risk lesions
- Optimal (evidence based) surveillance strategy
- Reassurance for most!

Pancreatic Cyst Guidelines

- Tanaka M, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, Salvia R, Shimizu Y, Tada M, Wolfgang CL. **Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas.** <u>Pancreatology 2017</u>; 17: 738-753 [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007
- Vege SS, Ziring B, Jain R, Moayyedi P; Clinical Guidelines Committee; American Gastroenterology Association. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. <u>Gastroenterology 2015</u>; 148: 819-822; quize12- 13 [PMID: 25805375 DOI: 10.1053/j.gastro.2015.01.015]
- Megibow AJ, Baker ME, Morgan DE, Kamel IR, Sahani DV, Newman E, Brugge WR, Berland LL, Pandharipande PV. Management of Incidental Pancreatic Cysts: A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol 2017; 14: 911-923 [PMID: 28533111 DOI: 10.1016/j.jacr.2017.03.010]
- European Study Group on Cystic Tumours of the Pancreas. **European evidence-based guidelines on pancreatic cystic neoplasms**. <u>Gut 2018</u>; 67: 789-804 [PMID: 29574408 DOI: 10.1136/gutjnl-2018-316027]
- Elta GH, Enestvedt BK, Sauer BG, Lennon AM. **ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts.** Am J Gastroenterol 2018; **113**: 464-479 [PMID: 29485131 DOI: 10.1038/ajg.2018.14]

Risk Stratification

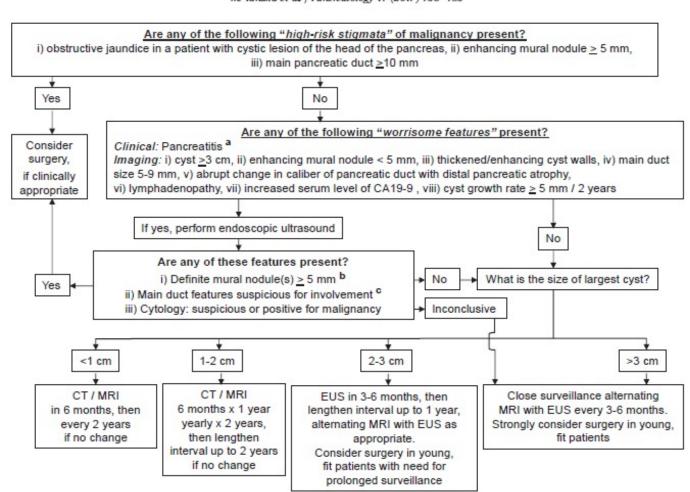
Table 4. Features of Pancreatic C	ysts With High and Low Risk for Malignan	cy at Time of Initial Presentation and Imaging

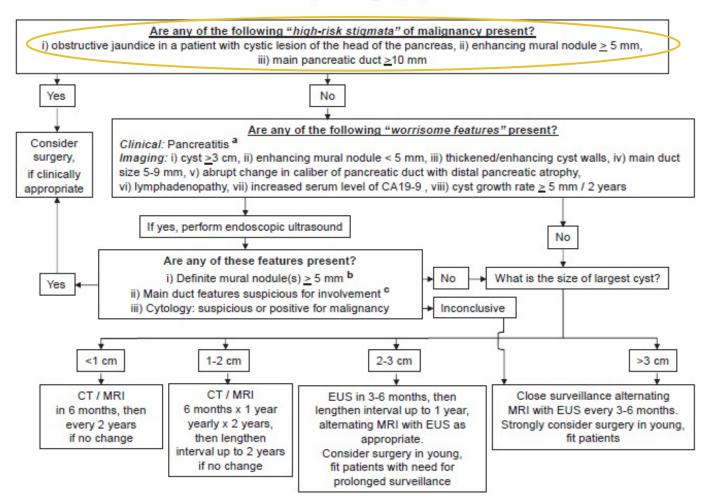
Pancreatic Cysts With High Risk for Malignancy	Pancreatic Cysts With Low Risk for Malignancy
Patient Characteristics	
Symptomatic	Asymptomatic
Main pancreatic duct diameter 5-9 mm (worrisome feature) or ≥10 mm	Main pancreatic duct diameter < 5 mm
Lymphadenopathy	No lymphadenopathy
Characteristics of Cyst	
Abrupt change in the main pancreatic duct caliber	No change in main pancreatic duct caliber
Mural nodule	No mural nodule
Enhancing solid component	No solid component
Thickened walls	No thickened walls
Size ≥3 cm	Size <3 cm

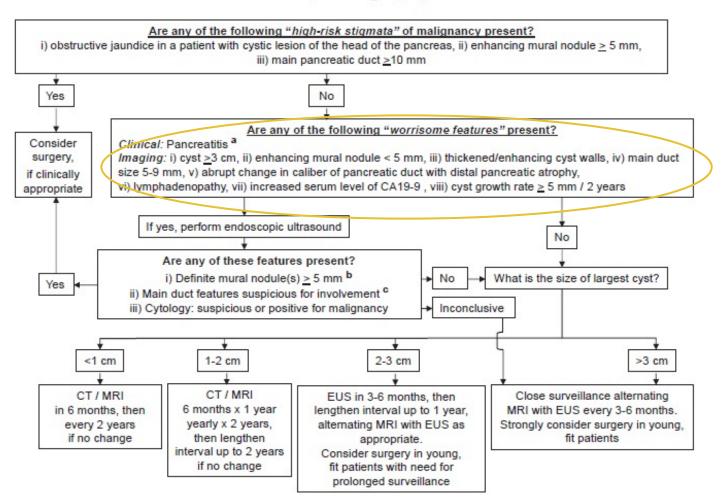
Stark A, Donahue RD et al. *Ponc*reptic Gyst Disease 2016; JAMA (17): 1882 — 93.

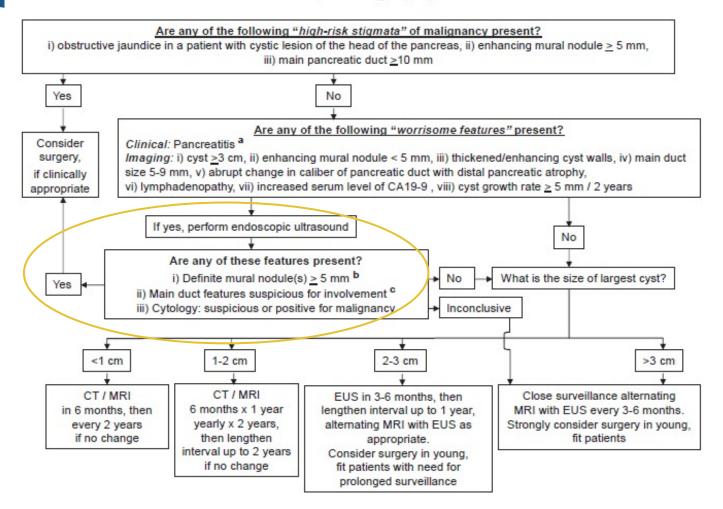
Fukuoka/Sendai Guidelines ('12, revised in '17) AGA Guidelines (2015) ACG Guidelines (2018)

Step-wise Approach... Revised Fukuoka/Sendai 2017









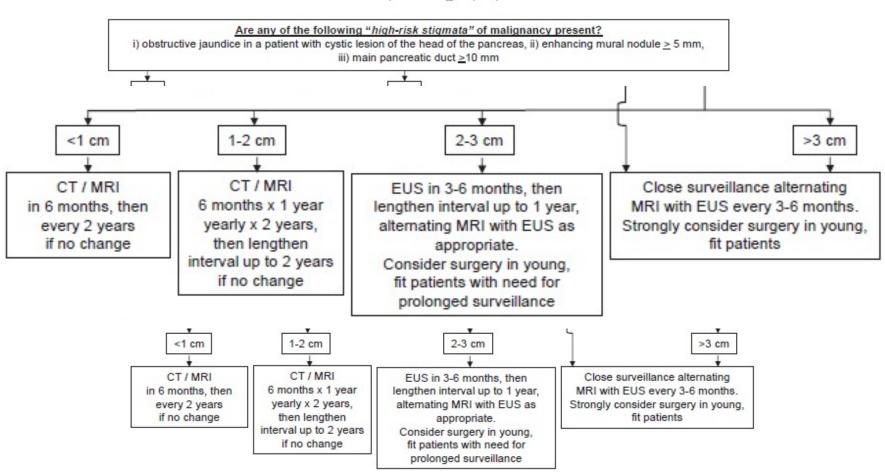
Comparison of Guidelines

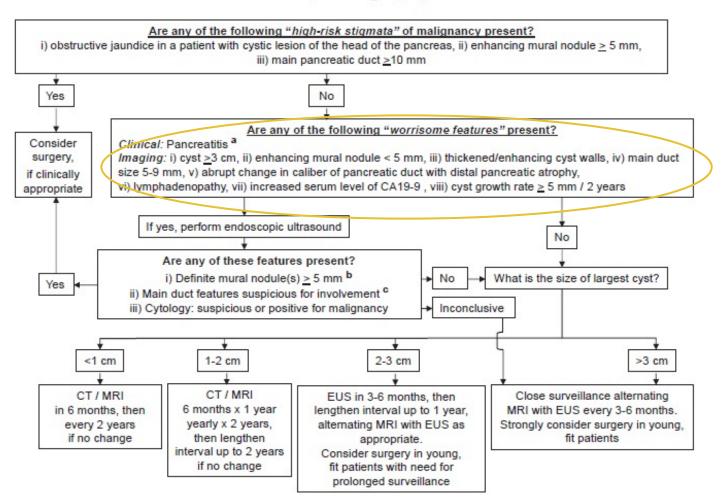
Table 1 Variables considered in the initial evaluation of pancreatic cystic neoplasms

		European	ACG	AGA	IAP	ACR
Symptoms	Jaundice	AI	HR	HR	HR	HR
	Pancreatitis	RI	HR		WF	
Imaging based cyst characteristics	Main pancreatic duct dilation	> 10 mm AI 5-10 mm RI	> 5 mm HR	HR	> 10 mm HR 5-10 mm WF	> 10 mm HR 7-10 mm WF
	Associated mass		HR	HR	HR	HR
	Mural nodule	> 5 mm AI < 5 mm RI	HR	HR	> 5 mm HR < 5 mm WF	WF
	Cyst size	≥4 cm RI	≥3 cm HR		> 3 cm WF	> 3 cm WF
	Parenchymal atrophy				WF	
	Lymphadenopathy				WF	
Serum based	CA19-9	RI	HR		WF	
	New onset diabetes	RI				

AI: Absolute indication; RI: Relative indication; HR: High risk; WF: Worrisome features.

Surveillance





Surveillance

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 after4)	cysts < 1.5 cm and	× 2 with MRI and/or	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 m × 1 yr A Annually × 2 yr, then lengthen interval if stable	MRI q 1 yrs FOR 3 yr Then q 2 yr FOR 4 yr	q6 mo for cysts 1.5- 2.5 cm × 4 and then lengthen interval; stop after stability over 10 yr ¹		
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	For cysts > 2.5 cm q6 mo MRI/CT and then stop if stable for over 10 yr; for patients > 80 yr of age, q2 year imaging ¹		
> 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			

Summary

- Pancreatic cystic lesions are common and
- Malignant potential varies but overall low
- EUS with cyst fluid analysis may be used to determine etiology,
 CEA, cytology...molecular testing
- Multiple guidelines: reassurance, multidisciplinary approach, evaluate for high-risk features, surveillance