TuftsMedicine
Integrated Network

Pancreatic Cysts in 2023

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Disclosures

- None

Outline

- Approach to diagnosis
- Prevalence and malignancy risk of PCLs
- Types of PCLs
- Cross-sectional imaging and EUS
- EUS cyst fluid analysis
- Management of PCLs
- Guidelines
- Post-operative surveillance and future directions

Approach to diagnosis

- History and physical exam
- Demographics
- Location
- Imaging characteristics
- Cytology and pathology
- Fluid analysis
- Adjunctive techniques

Questions to ask

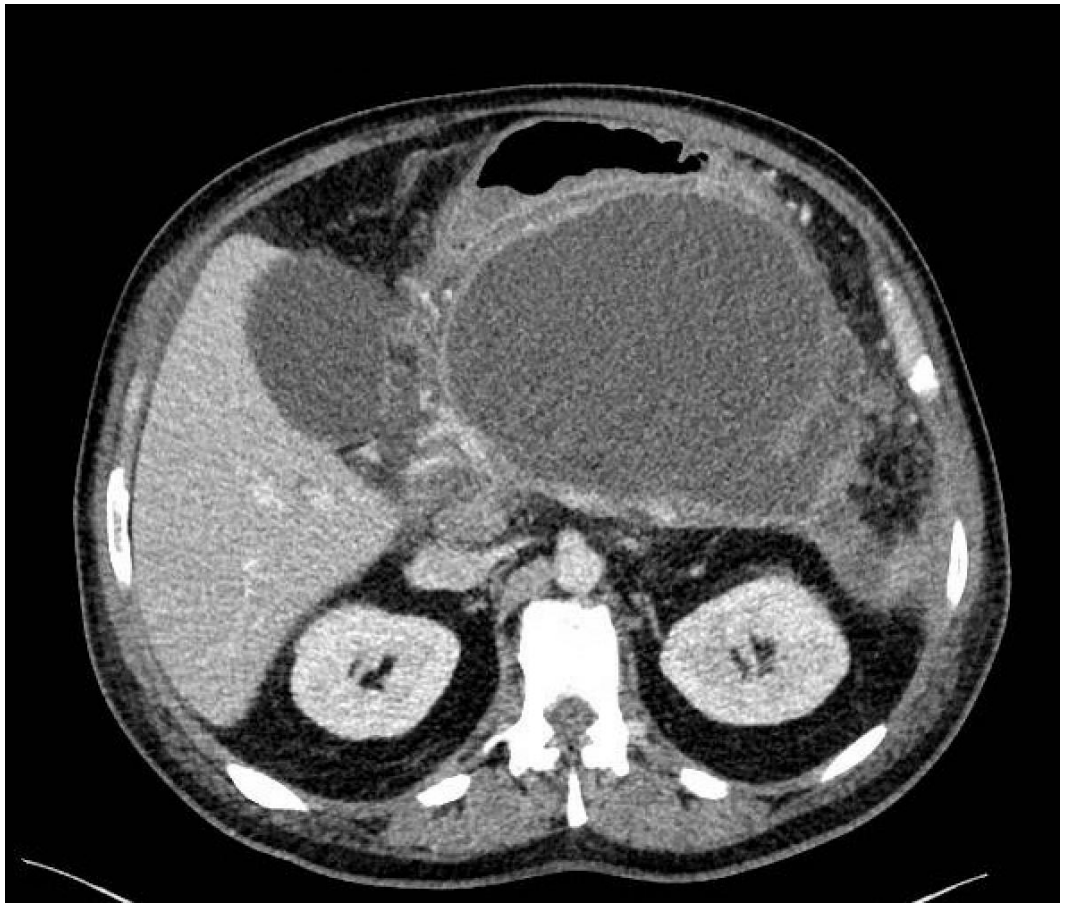
- Is the cyst symptomatic?
  - Abdominal pain
  - Nausea and vomiting
  - Jaundice
  - Weight loss
- History of acute and/or chronic pancreatitis
- New-onset diabetes mellitus
- Family history of pancreatic cancer
- Dedicated pancreas imaging

Is the lesion even a true cyst?

- Rule out a pseudocyst or walled-off necrosis
  - Preceding history of pancreatitis or trauma
  - Collection of pancreatic secretions that have extravasated from a duct disrupted by inflammation or obstruction
  - No epithelial lining

Pseudocysts and walled-off necrosis - imaging

- Classic findings
  - Septae, loculations, debris, and wall calcifications
- Ductal communication on EUS and/or MRI/MRCP
- High amylase and no epithelial cells



Caveats

- Neoplasms can cause acute pancreatitis in up to 20% of individuals over 40
- Incidental cyst may be a cystic neoplasm that caused the episode of pancreatitis

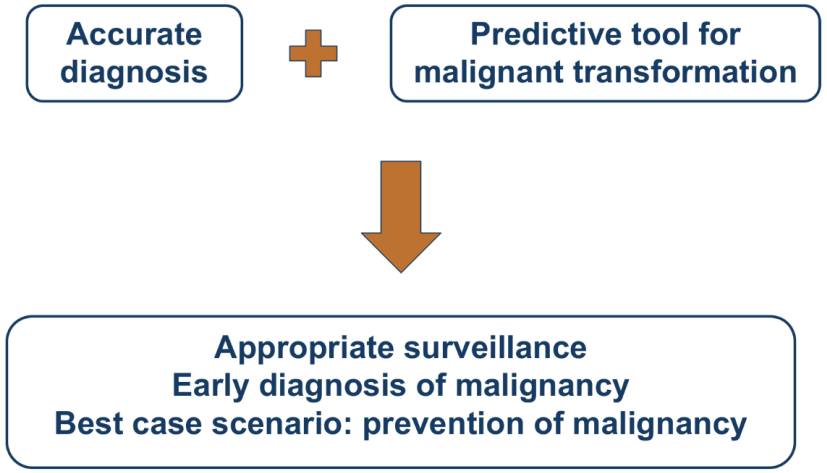
Farrell JJ, Gut Liver 2015

Importance of true PCLs

- PCLs are common
- Some PCLs can progress to cancer
- Patient anxiety
- Getting rid of PCLs is not easy
- Cost of cyst analysis and surveillance is high

Goals of managing PCLs

- Desirable outcomes
  - Benign PCL - observation
  - Premalignant PCL - resection before malignant transformation
  - Malignant PCL - resection
- Undesirable outcomes
  - Benign PCL - resection
  - Premalignant PCL - resection after malignant transformation occurs
  - Malignant PCL being observed



Prevalence

- Prevalence of 2.4-24.3% in asymptomatic adult population
- Detection varies between imaging modalities
  - 0.2% on ultrasound to > 20% on MRI
- Age-based prevalence
  - 0.5% < 40 years
  - 25% 70-79 years
  - 37% > 80 years

“This man-made epidemic in pancreatic cysts can be attributed to the tens of millions of abdominal scans that are conducted each year in the United States for unrelated causes”

Lee KS, et al. Am J Gastro 2010; Scheiman JM, et al. Gastro 2015; Pergolini I, et al. Gastroenterology 2017; Zerboni G, et al. Pancreatology 2019; Grossberg AJ, et al. CA Cancer J Clin 2020

True prevalence?

- Unclear but incidence is increasing
  - Awareness
  - Better imaging
  - Aging population

Estimating malignancy risk of PCLs

- Short answer: we do not know (math problem: denominator issue)
- Assuming all pancreatic cancer arises from cysts
  - SEER database studies
    - 0.25% probability cysts harbors malignancy at time of diagnosis
    - 0.24% per year conversion rate to invasive cancer
- Retrospective series of surgically resected cysts
  - 15% incidence of cancer in 27 studies of 2796 patients

Elta GH, et al. Am J Gastroenterol 2018

Few PCLs progress to pancreatic cancer

- 90% of pancreatic ductal adenocarcinoma arises from pancreatic intraepithelial neoplasia (PanIN)
- 5-10% arise in backdrop of cystic lesion
- Pancreatic cancer-related mortality is stable

Grossberg AJ, et al. CA Cancer J Clin 2020

Types of PCLs

- Non-mucinous lesions (no malignant potential)
  - Serous cystic neoplasms (SCN)
  - Simple cyst
  - Lymphoepithelial cyst
- Mucin-producing cysts (malignant potential)
  - Mucinous cystic neoplasms (MCN)
  - Intraductal papillary mucinous neoplasms (IPMN)
- Non-mucinous lesions but with malignant potential
  - Solid pseudopapillary neoplasms (SPN)
- Malignant
  - Cystic pancreatic adenocarcinoma
  - Cystic pancreatic neuroendocrine tumor

Clinical and demographic features

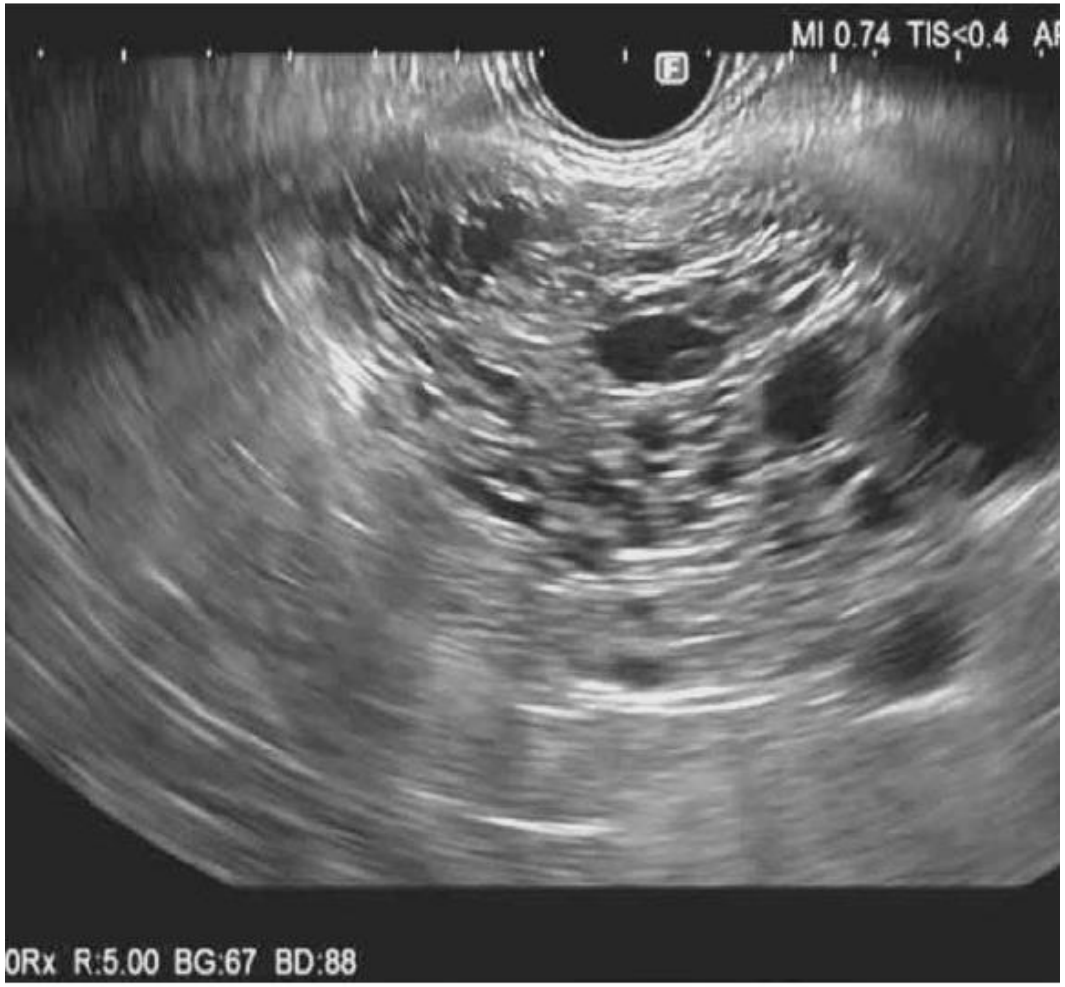
Cyst Type	Age of Presentation	Gender Predisposition	Clinical Presentation	Distribution	Morphologic Features	Malignant Potential
IPMN	>65–70 years [9,10]	M > F	1/3 of patients symptomatic (epigastric pain, back pain, weight loss), acute pancreatitis, new-onset diabetes, obstructive jaundice	Head and neck > body/tail	PD dilatation, BD- and mixed IPMN multiloculated	Depends on main PD involvement. MD-IPMN and mixed-IPMN malignant in 45–60%. High-risk: main PD > 1 cm, solid component or enhancing nodule, jaundice, HGD
Mucinous cyst	<70 years	F > M	Abdominal pain, weight loss, acute pancreatitis	Body or tail	Solitary, unilocular with ovarian-like stroma, peripheral calcification, no PD dilation	Malignant 4–12%; HGD 6–13%. High-risk: >6 cm, irregular thick wall, peripheral calcification
Serous cystadenoma	55 years	F >> M	Rarely jaundice and weight loss	3/4 in body or tail	Solitary, "Central scar", no PD dilation	Low malignant risk, ~5% aggressive
Solid pseu-dopapillary neoplasm	<30 years	F > M	Jaundice and weight loss uncommon	Any location, more commonly tail	Solitary, solid component, mural nodule, peripheral calcification	Low-grade malignant neoplasms, infrequently metastatic

IPMN Intraductal papillary mucinous neoplasms, M—male, F—female, PD—pancreatic duct, BD—branch duct, MD—main duct, HGD—high-grade dysplasia.

Singh RR, et al. Diagnostics (Basel) 2023

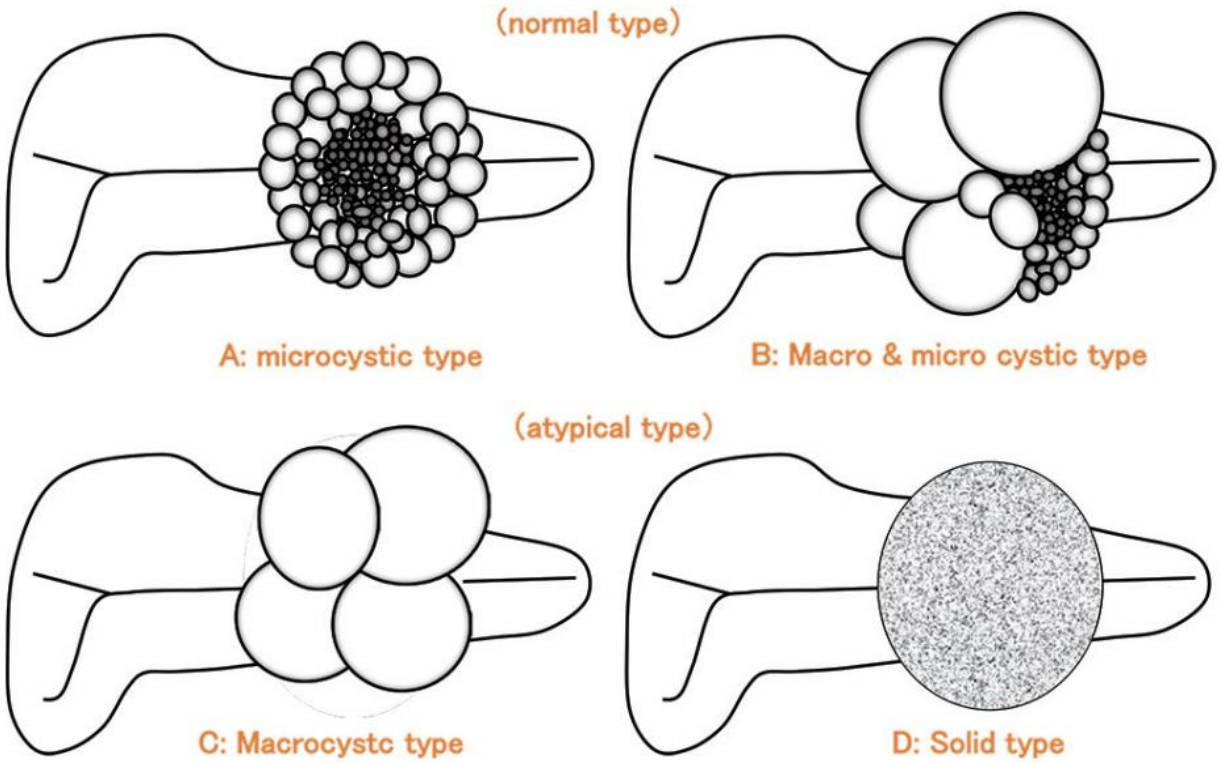
Serous cystic neoplasm

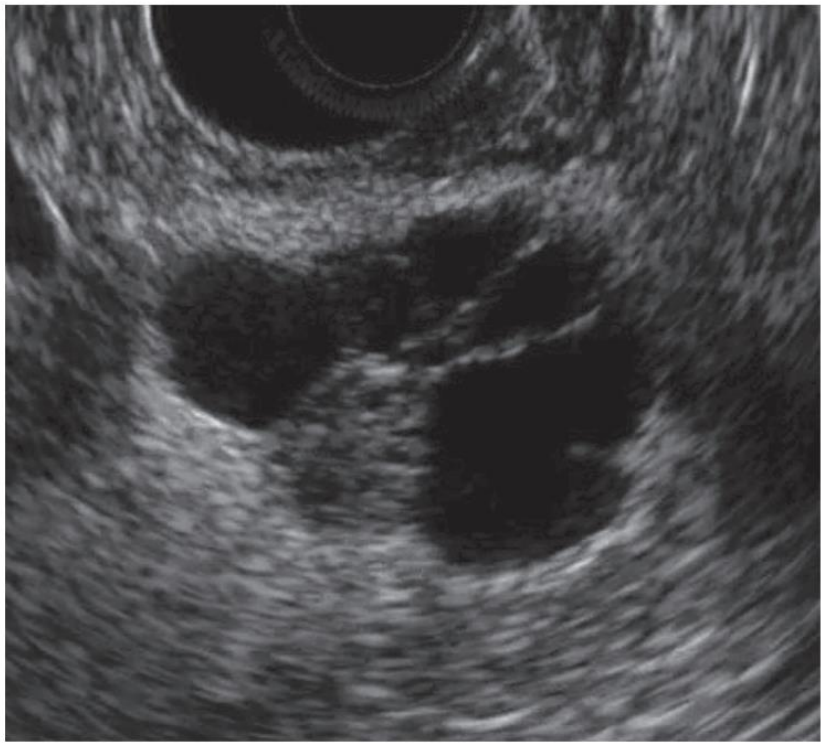
- Benign and most common in women
- Body-tail region of the pancreas
- Classic microcystic and honeycomb appearance with a central scar
- Pathology
  - Well-circumscribed masses enclosed in a fibrous capsule containing numerous small fluid-filled cysts
- Conservative management
  - Surgery for symptomatic or very large lesions
  - 0.1% risk of cancer
- Lack of consensus on surveillance imaging



Jais B, et al. Gut 2016

SCN – atypical appearances

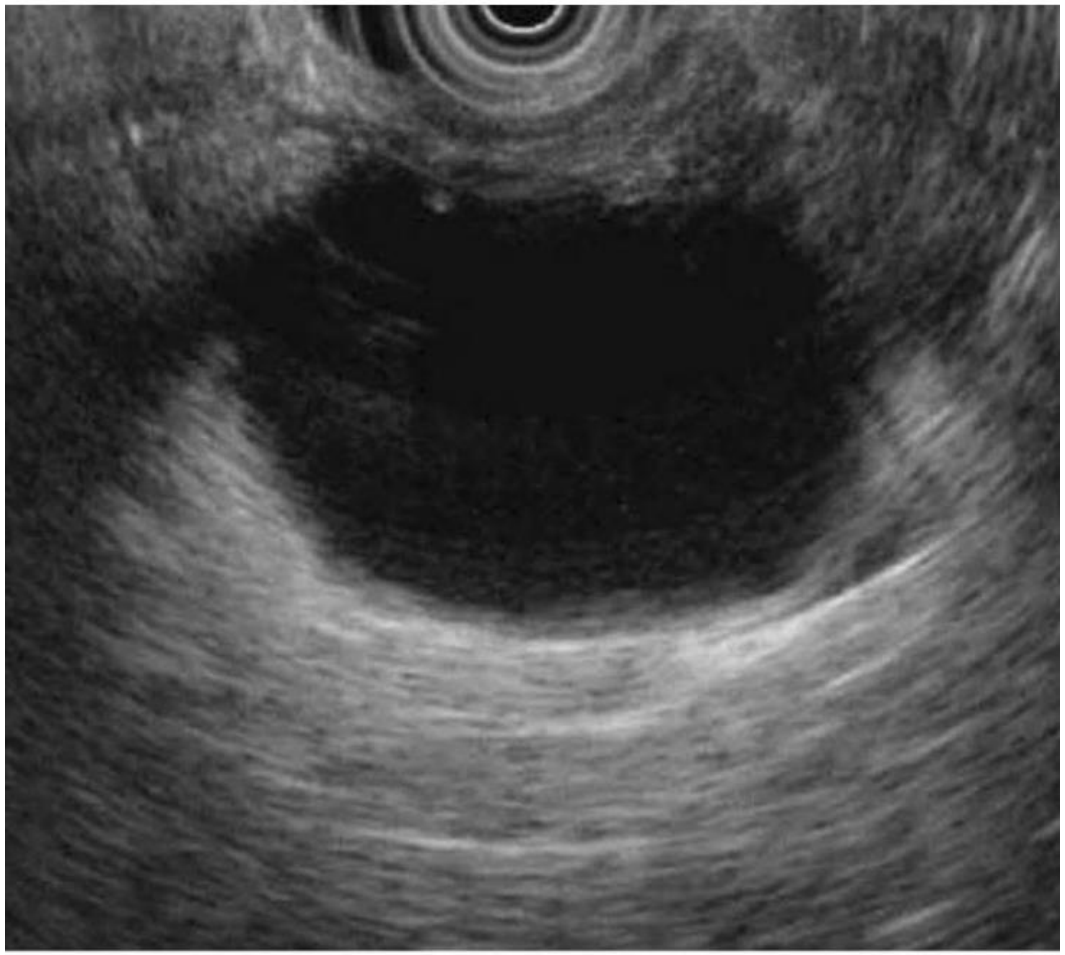




Hijioka, et al. Endosc Ultrasound 2015

Mucinous cystic neoplasm

- Women (>98%) of middle age
- Tail of the pancreas without communication with main pancreatic duct
- Unilocular or septated solitary macrocystic lesions
- Pathology
  - Spindle cell stroma containing epithelioid cells similar to ovarian stroma
- Surgery recommended
  - 3 cm or 4 cm
  - Nodule



Canakis A, et al. Dig Dis Sci 2022

Malignant potential of MCNs

- True lifetime risk of malignant transformation unknown
- Study of 90 resected MCNs
  - 5.5% with high-grade dysplasia (HGD)
  - 4.4% with cancer
- Cysts < 3 cm
  - 0.4% HGD or invasive cancer
- European Study Group surgical resection criteria
  - Symptoms, > 4 cm, and/or nodule
- Surveillance imaging not required unless pathology shows malignancy

van Huijgevoort NCM, et al. Nat Rev Gastroenterol Hepatol 2019; European Study Group, Gut 2018

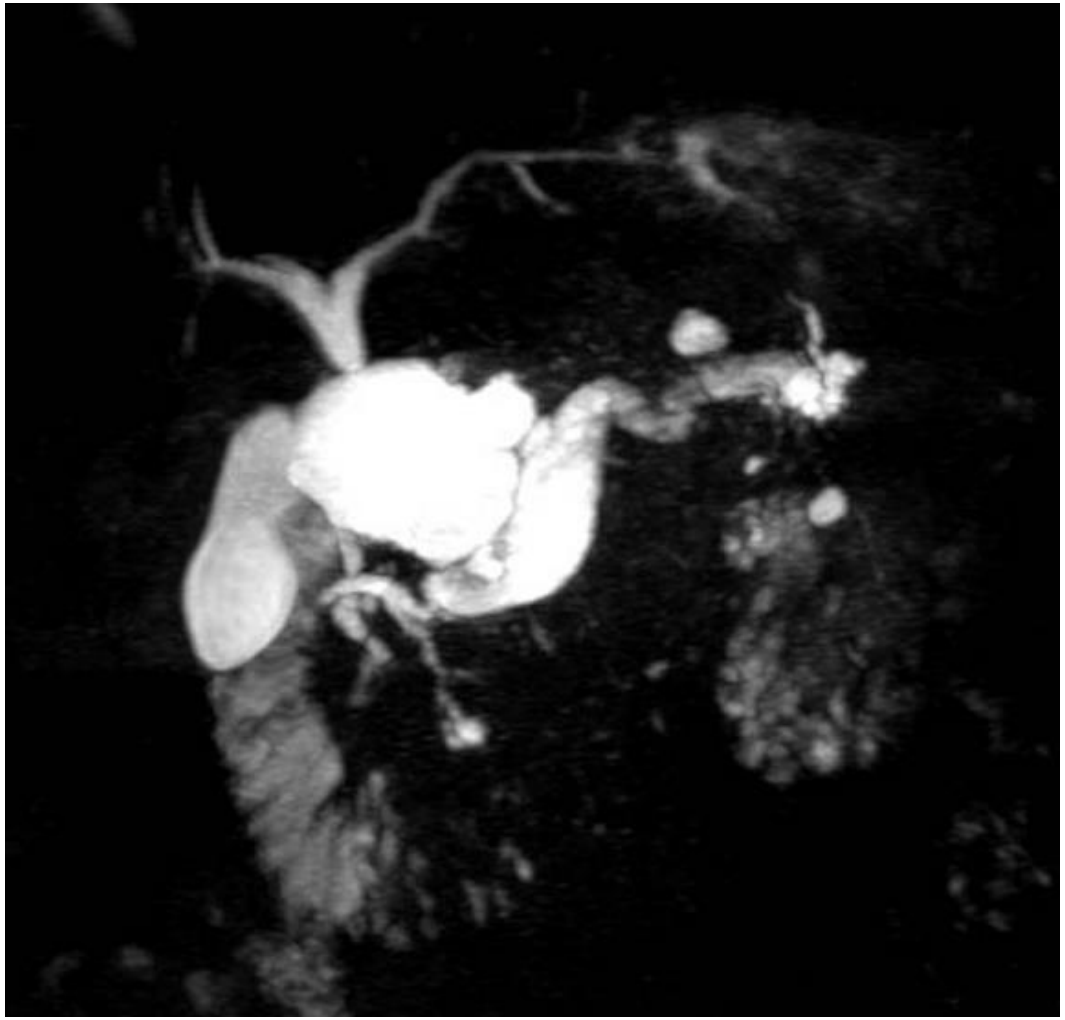
Intraductal papillary mucinous neoplasm

- Older patients with equal gender distribution
- Often in the head of the pancreas
  - Solitary or multifocal
- Categorized based on site of involvement of pancreatic duct
  - Main-duct (MD) IPMN
  - Mixed-type (MT) IPMN
  - Side-branch (SB) IPMN
- Pathology
  - Gastric, intestinal, pancreatobiliary, and oncocytic subtypes
  - Dysplastic epithelium resembling colorectal villous adenomas with papillae covered by columnar epithelium

Elta GH, et al. Am J Gastroenterol 2018; Kang MJ, et al. Pancreas 2013

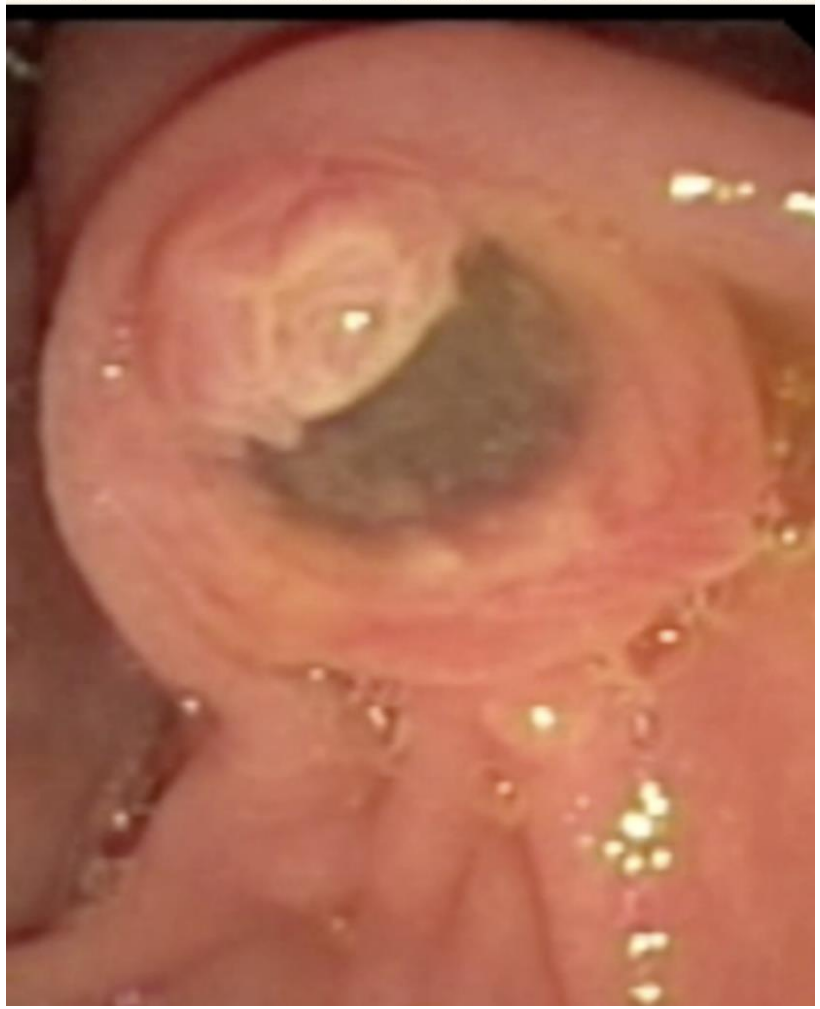
MD-IPMN and MT-IPMN

- MD-IPMN
  - 61.6% (mean) harbor HGD or cancer at time of resection
- Mixed-type IPMN
  - 41% (mean) harbor HGD or cancer at time of resection
- Resection is recommended



Sahora K, et al. Surgery 2014

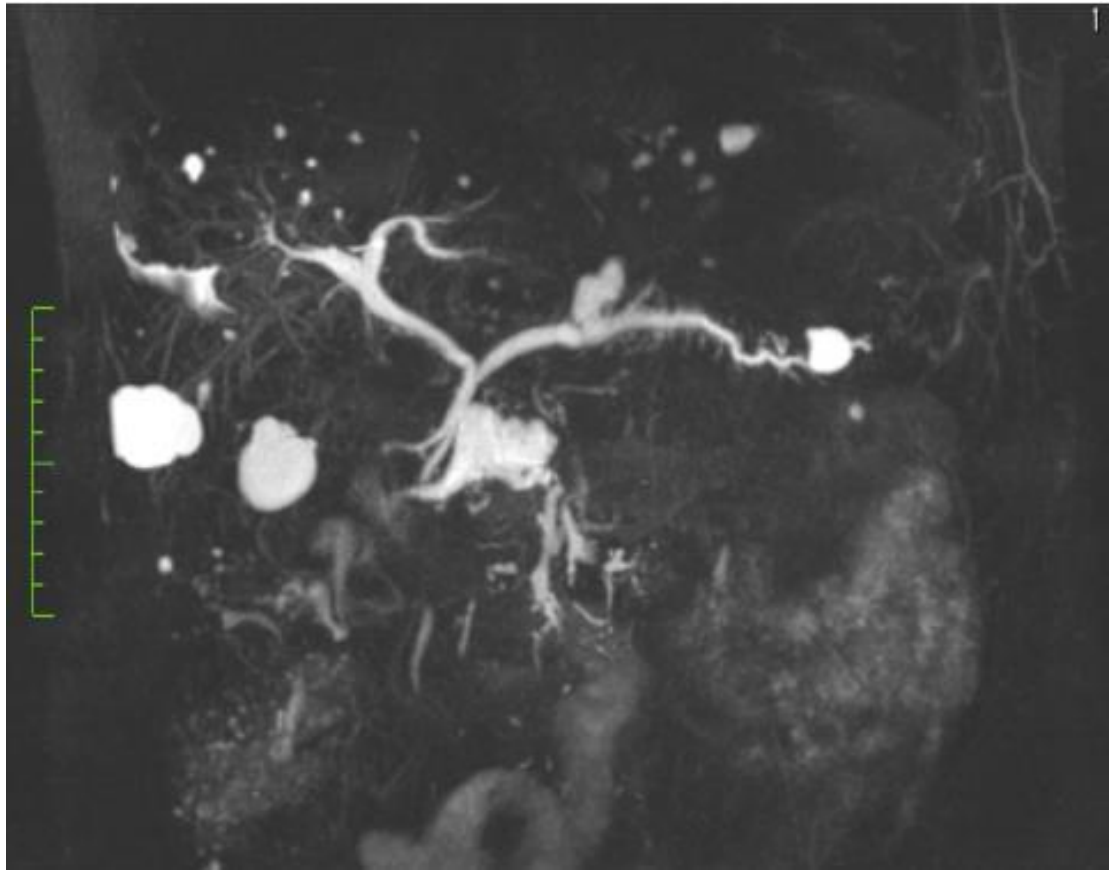
“Fish-mouth” ampulla



Zhang TT, et al. Br J Radiol 2019

BD-IPMN

- Most common type of PCL
- “Grape-like” cluster
- Multifocal in 40%
- 25.5% (mean) harbor HGD or cancer at time of resection
- Resection recommended in patients with at least 1 worrisome or high-risk feature



Elta GH, et al. Am J Gastroenterol 2018

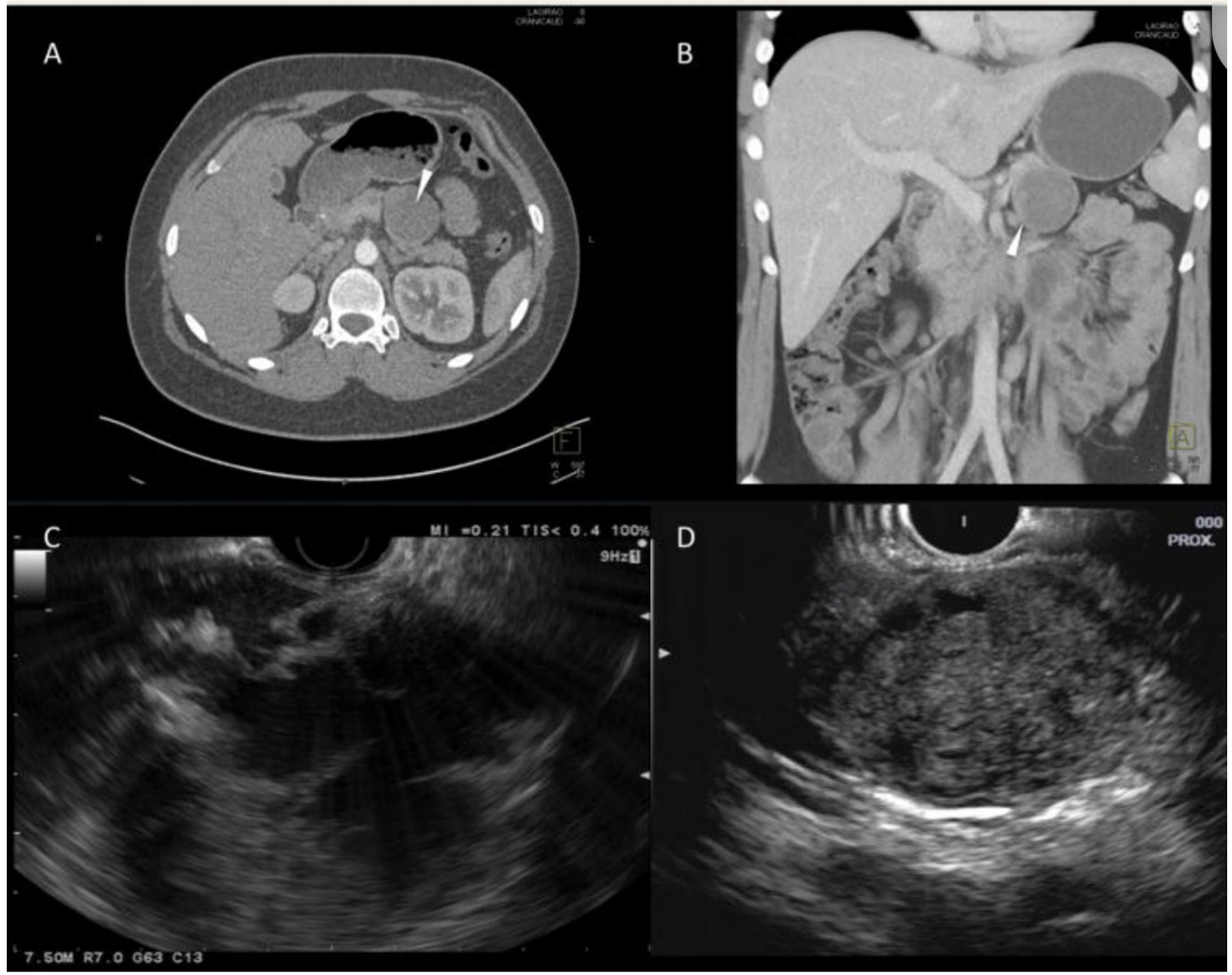
Long-term risk of IPMNs

- Systematic review and meta-analysis of 3236 patients with low- and high-risk IPMN
- Low-risk
  - Pooled cumulative incidence of high-grade dysplasia or pancreatic cancer of 0.02% (95% CI, 0.0–0.23%) at 1 year, 3.12% (95% CI, 1.12–5.90%) at 5 years, and **7.77% (95% CI, 4.09–12.39%) at 10 years** for low-risk IPMNs
- High-risk
  - Pooled cumulative incidence was 1.95% (95% CI, 0.0–5.99%) at 1 year, 9.77% (95% CI, 3.04–19.29%) at 5 years, and **24.68 (95% CI, 14.87–35.90%) at 10 years** for high-risk IPMNs

Choi SH, et al. Clin Gastroenterol Hepatol 2017

Solid pseudopapillary neoplasms

- Younger women
- Tail of the pancreas
- Low-grade malignant neoplasms
- Metastatic disease in 5-15% of cases
- Well-encapsulated and potentially cured with resection
- 5-year disease-specific survival > 98%



Law JK, et al. Pancreas 2014

Diagnosis of PCLs - imaging

- Two goals of imaging
  - Cyst type
  - Malignancy
- MRI is preferred over CT scan
- MRI is superior for detecting IPMN
  - Sensitivity 97% vs. 81% for CT
- CT vs. MRI – similar in differentiating benign vs. malignant cysts
  - Review of 19 studies (N=1060)
  - CT sensitivity 58-69% and specificity 65-83%
  - MRI sensitivity 65-77% and specificity 58-89%

Jones MJ, et al. Pancreatology 2013; Expert Panel on Gastrointestinal Imaging; Fábrega-Foster K et al. J AM Coll Radiol 2020

PET/CT scan

- Helps differentiate benign vs. malignant IPMN
  - Sensitivity of 80%, specificity of 95%, and accuracy of 87%
- Prospective study of 31 cysts (25 benign and 6 malignant)
  - 94% accuracy → higher than CT (77%) and MRI (87%)

Serafini S, et al. Cancers (Basel) 2020; Kauhanen S, et al. J Nucl Med 2015

When is EUS needed?

- AGA (2015) – 2 high-risk features
- Fukuoka (2017) – 1 worrisome feature
- ACG (2018) – 1 worrisome feature
- European Study Group (2018) – 1 clinical or radiologic concerning feature

High-risk, worrisome, and concerning features

Guideline	Indications
American Gastroenterological Association (AGA) (2015)	>2 high risk features: • PCL Size > 3 cm • Dilated main pancreatic duct • Presence of a solid component
International Consensus Guidelines (2017)	With any of the below features: • PCL size > 3 cm • Thickened/enhanced PCL wall • MPD 5–9 mm • Abrupt change in MPD with distal pancreatic atrophy • Lymphadenopathy • Elevated CA 19-9 • Rapid growth (>5 mm/2 years)
American College of Gastroenterology (2018)	With any of the below features: • MPD > 5 mm • IPMN or MCN > 3 cm • Change in MPD caliber with upstream atrophy • Size increase > 3 mm/year • Jaundice secondary to PCL • Pancreatitis secondary to PCL • Presence of mural nodule or solid component
European (2018)	Radiologic or clinical features of concern for malignancy: Radiologic: • MPD ≥ 5mm • Size increase ≥ 5 mm/year • Presence of mural nodule or solid component Clinical: • Jaundice secondary to PCL • New onset diabetes • Increased CA 19-9

PCL: pancreatic cystic lesion; MPD: main pancreatic duct; CA 19-9: carbohydrate antigen 19-9; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm.

Rangwani S, et al. Diagnostics (Basel) 2023

Not all features are equal

- Jaundice, contrast-enhancing nodule or solid component, or MPD ≥ 10 mm
  - Positive predictive value for malignancy of 56–89%
- Cyst size ≥ 30 mm without radiological or clinical risk factors
  - Positive predictive value for malignancy of 27-33%

Sahora K, et al. Ann Surg 2013; Fritz S, et al. Ann Surg 2014

EUS in real-world clinical practice

- Unclear diagnosis
- Intermediate to high probability of malignancy
- Change management

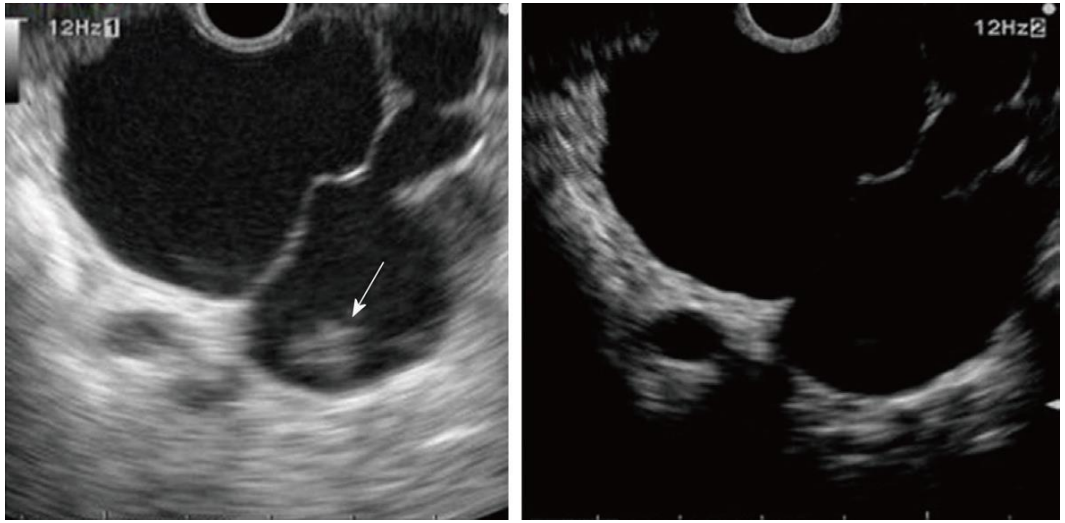
Diagnosis of PCLs – EUS imaging alone

- Advantages
  - Wall thickness, borders, septations, masses, mural nodules, and PD communication
- Disadvantages
  - Invasive
  - Operator dependent and poor interobserver agreement
- Mucinous vs. non-mucinous
  - Low diagnostic accuracy at 51% of EUS imaging alone
- Nodules vs. mucin globules
  - Mucin globules appear hypoechoic with a hyperechoic rim

Scheiman JM, et al. Gastro 2015

Contrast-enhanced EUS (CE-EUS)

- Real-time imaging after administration of intravenous contrast agent
  - Assesses vascularity
- Best modality for mural nodules
  - Hyperenhancement predicts malignancy
- Meta-analysis of over 500 patients
  - Sensitivity of 88% and specificity of 77% in detecting mural nodules
- Should be followed with FNA (B)



Kamata K, et al. Endoscopy 2016; Harima H, et al. World J Gastroenterol 2015

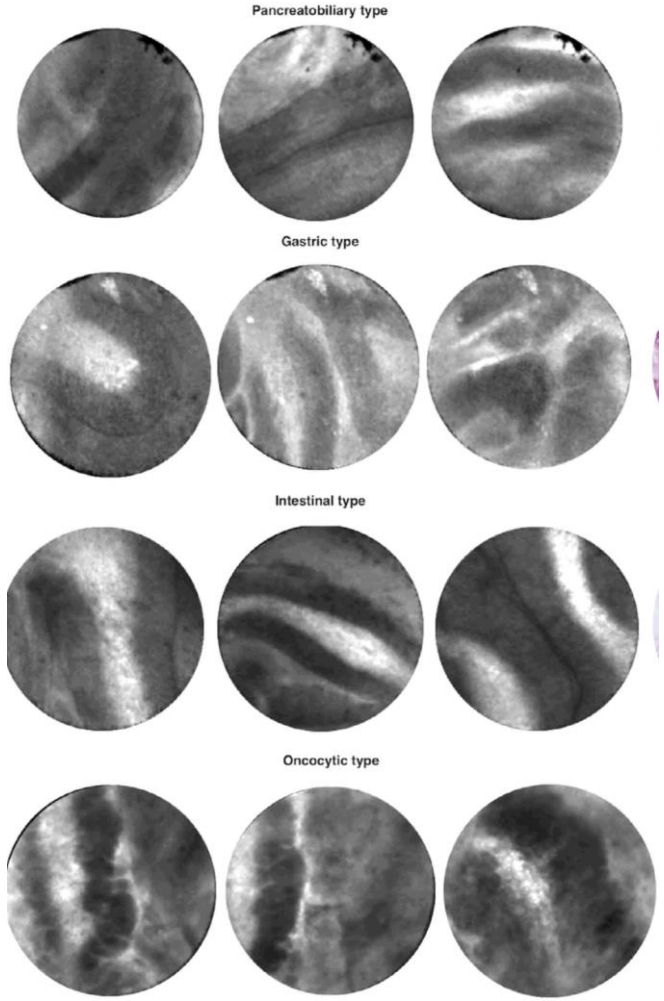
Confocal laser endomicroscopy (CLE)

- Needle-probe through a 19-gauge needle
- Real-time images of inner cyst wall after IV injection of fluorescein
- SCN
  - Superficial vascular networks
- MCN
  - Horizontal-type epithelial bands of variable thickness without papillary conformation
- IPMN
  - Finger-line papillary projections with an inner vascular core

Napoleon B, et al. Endosc Int Open 2020; Konda VJ, et al. Endoscopy 2013

CLE

- Multicenter, prospective validation study
  - Sensitivity of 95%, specificity of 100%, and accuracy of 97% for diagnosis of mucinous lesions
- > accuracy over cytology and CEA
  - 97% vs. 71%
- Limitations
  - Expensive and not widely available
  - Learning curve
  - 3-9% risk of adverse events



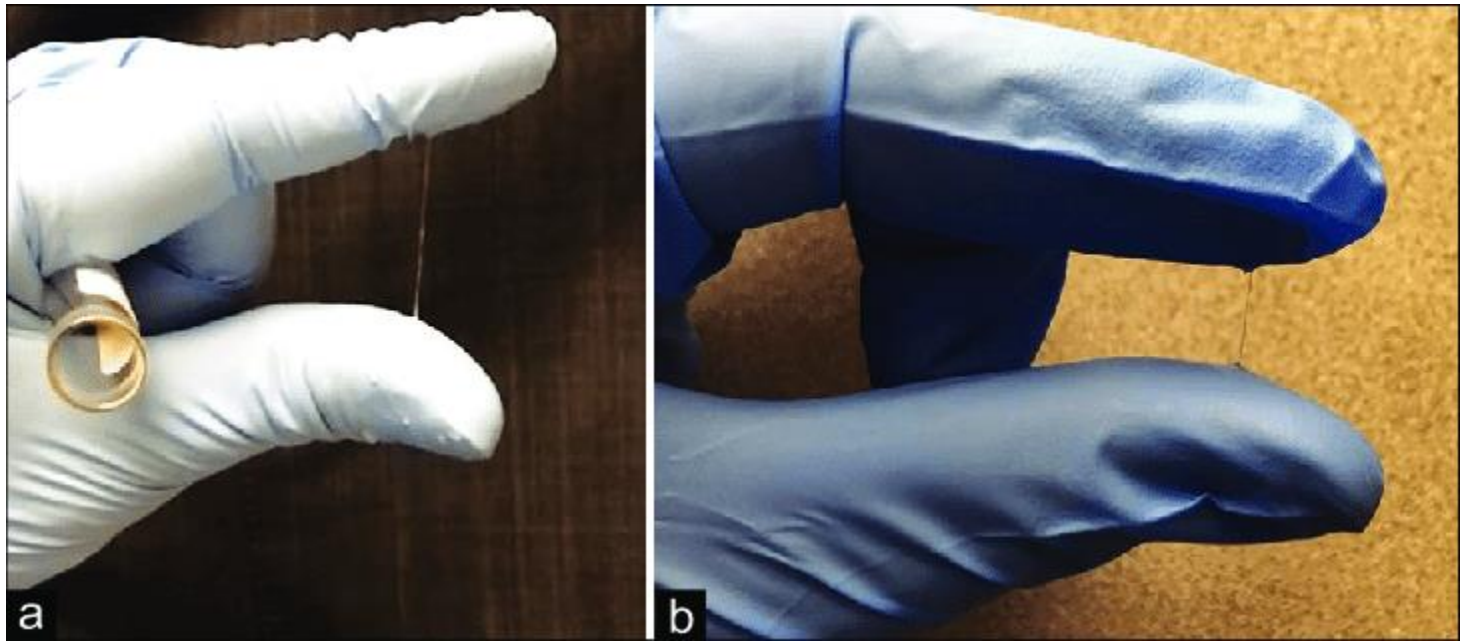
Napoleon B, et al. Endoscopy 2019; Krishna SG, et al. Clin Gastroenterol Hepatol 2020

EUS-FNA(B) cyst fluid analysis

- String sign
- Cytology
- Carcinoembryonic antigen (CEA)
- Amylase
- Glucose
- DNA-based testing
  - *KRAS, GNAS, BRAF,* and others

String sign

- Highly specific for mucinous lesions
- Defined as fluid extending for at least 1 cm and 1 second



Bick BL, et al. Endoscopy 2015

EUS-FNA(B) - cytology

- Mucinous vs. non-mucinous
  - Sensitivity of 54-63% and specificity 88-93% based on two meta-analysis
- Malignant vs. benign
  - Sensitivity of 65% but high specificity of 91%
- Main limitation is insufficient material (2/3)
- Increase diagnostic yield
  - FNA of cyst wall once collapsed
  - Use of FNB

Elta GH, et al. Am J Gastroenterol 2018; Thornton GD, et al. Pancreatology 2013, Thosani N, et al. Dig Dis Sci 2010

EUS-FNA(B) - CEA

- Original cyst fluid marker to differentiate mucinous vs. non-mucinous
- Cutoff of 192 ng/ml
  - Sensitivity of 75% and specificity of 84%
- Extremely low CEA levels (less than 5 ng/ml)
  - SCN or pseudocyst
- Does not predict malignancy

Scheiman JM, et al. Gastro 2015; Cizginer S, et al. Pancreas 2013; Brugge WR, et al. Gastroenterology 2004

EUS-FNA(B) - amylase

- Excludes pseudocysts in 98% cases when < 250 IU/l

van der Waaij LA, et al. Gastrointest Endosc 2005

EUS-FNA(B) - glucose

- Superior diagnostic accuracy compared to CEA
- Cutoff of less than 50 mg/dl for mucinous cysts
  - Sensitivity of 89-92% and specificity 75-86%
- Pseudocysts may also have low glucose

Simons-Linares CR, et al. Pancreatology 2020; Faias S, et al. Gastrointest Endosc 2021

EUS-FNA(B) – DNA-based testing

- Mucinous vs. non-mucinous
- Characterize mucinous subtypes (MCN vs. IPMN)
- Detect grades of neoplasia

KRAS and *GNAS* mutations

- Excellent for identifying mucinous PCLs
  - 89% sensitive and 100% specific for mucinous cysts
- *KRAS* and/or *GNAS* mutations
  - 100% sensitive for IPMN
- *GNAS* mutations
  - 100% specific for IPMN
  - Not present in MCN

Singhi AD, et al. Gut 2018; McCarty TR, et al. Gastrointest Endosc 2021; Shibata H, et al. Anticancer Res 2017

TP53, *PIK3CA*, and *PTEN*

- Detection of advanced neoplasia
  - HGD or invasive adenocarcinoma
  - Sensitivity of 46% and specificity of 100%
- Combination with cytology
  - Sensitivity of 76% and specificity of 100%
- Combination with *KRAS/GNAS* genes
  - Sensitivity of 79% and specificity of 96%

Table 1
Key genetic mutations and/or deletions in pancreatic cysts

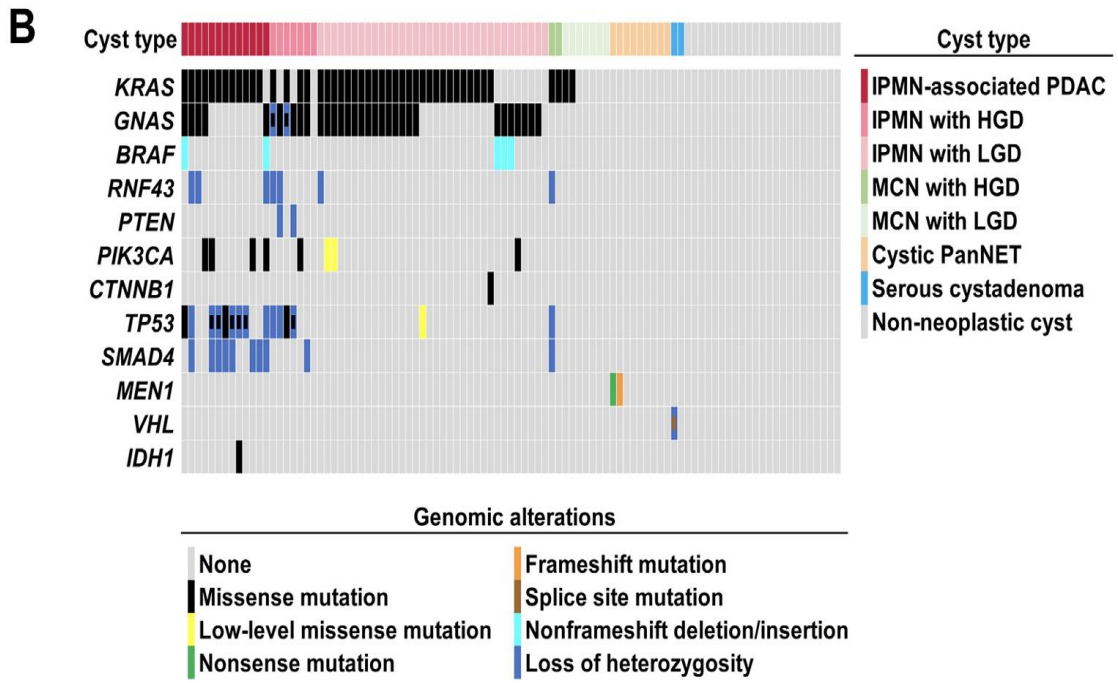
Pancreatic Cyst Type	*KRAS*	*GNAS*	*RNF43*	*VHL*	*CTNNB1*	*TP53*	*PIK3CA*	*PTEN*	*CDKN2A*	*SMAD4*
Intraductal papillary mucinous neoplasm	+	+	+	–	–	+[a]	+[a]	+[a]	+[a]	+[a]
Mucinous cystic neoplasm	+	–	–	–	–	+[a]	+[a]	+[a]	+[a]	+[a]
Serous cystadenoma	–	–	–	+	–	–	–	–	–	–
Solid-pseudopapillary neoplasm	–	–	–	–	+	+[b]	+[b]	–	–	–
Non-neoplastic cysts	–	–	–	–	–	–	–	–	–	–

[a] Alterations in these genes are associated with advanced neoplasia.
[b] Although mutations in these genes have been described, they are rare findings.
+, presence; –, absence.

Rosenbaum, et al. Cancer Cytopathol 2017; Singhi AD, et al. Gastrointest Endosc 2016

PancreaSeq® testing

- 22-gene next-generation sequencing DNA panel
- *GNAS* mutations
  - Sensitivity of 90% and specificity of 100% for mucinous cyst
- Combination of *GNAS* and *TP53/SMAD4/CTNNB1/mTOR*
  - Sensitivity of 88% and specificity of 98% for advanced neoplasia



Paniccia A, et al. Gastroenterology 2023

VHL mutations and/or deletions

- Occur in 89-100% of SCNs

Springer S, et al. Gastroenterology 2015

Practical approach to DNA testing

- Uncertainty of diagnosis and/or when it alters clinical decision making
- Predicts which cysts are high risk rather than which ones will progress

Risks of EUS-FNA(B)

- EUS-FNA of PCLs
  - 603 patients, complications in 13 (2.2%), 12 required hospitalization
  - 6 with pancreatitis (1%) – one had undergone ERCP same-day
  - 4 with abdominal pain
  - Other: retroperitoneal bleed, infection, bradycardia

Lee LS, et al. Clin Gastroenterol Hepatol 2005

Putting it all together

Cyst fluid markers	Sensitivity	Specificity	Comments
Cyst fluid cytology	65%	91%	For malignancy
Cyst fluid cytology	54–63%	88–93%	For mucinous cysts
CEA > 192 ng/mL	75%	84%	For mucinous cysts
CEA < 5 ng/mL	50%	95%	For serous cystadenoma, cystic neuroendocrine tumor, pseudocyst
Glucose < 50 mg/dL	89% to 92%	75% to 86%	For mucinous cysts, pseudocysts
Amylase < 250 U/L	44%	98%	Excludes pseudocysts
KRAS/GNAS mutations	89%	100%	For mucinous cysts

Canakis A, et al. Dig Dis Sci 2022

EUS-guided-through-the-needle-biopsy (TTNB)

- Micro forceps advanced through a 19-gauge needle to biopsy cyst wall
- Superior to FNA cytology
  - Meta-analysis of 8 studies (N=426)
  - Specific type of cyst (72.5% vs 38.1%)
  - Mucinous cysts (56.2% vs. 29.5%)
  - SCN (12.4% vs. 1.2%)
- TTNB compared to standard of care (CEA, cytology, and DNA testing)
  - Comparable for identifying mucinous vs. non-mucinous
  - TTNB superior in diagnosing specific type of cyst

Westerveld DR, et al. Endosc Int Open 2020; Zhang ML, et al. Cancer Cytopathol 2018

TTNB limitations

- No standardized technique
- Samples may not accurately reflect pathology of entire cyst
- Complication rate of 7-10%
  - Pancreatitis
  - Bleeding

Kovacevic B, et al. Endoscopy 2021

Approach to management of mucinous PCLs

- Clinical presentation and imaging
  - Identify symptoms and high-risk features
    - If present, refer to pancreas center and consider resection
    - If absent, enroll in surveillance protocol based on cyst size
- Surveillance intervals are aggressive
- Limited mention of when to stop

Issues to address

- Is the patient a surgical candidate?
- What is the likelihood of causing harm with testing and/or treatment?
- Is upfront risk of surgery justified by the long-term risk of malignancy?
- If so, does it provide a survival benefit to the patient?

Medical comorbidities

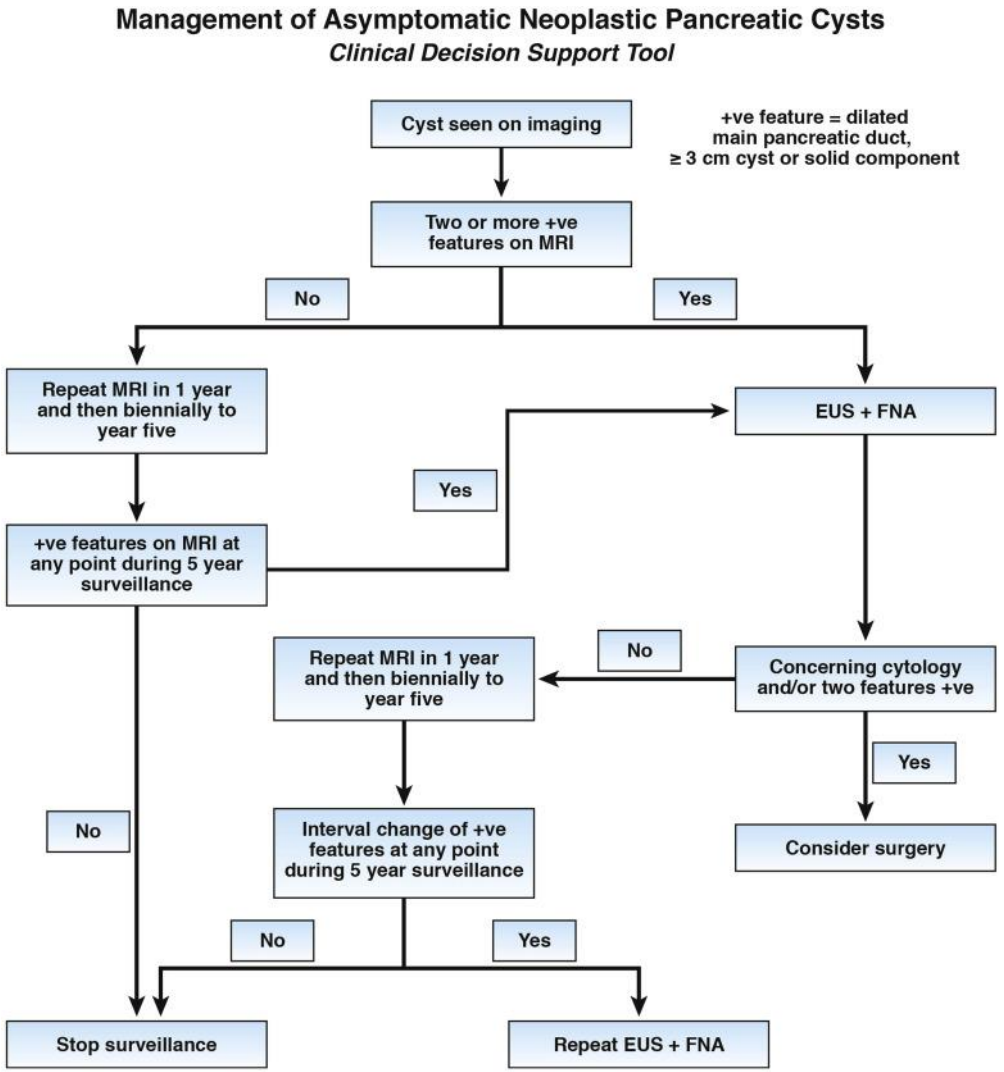
- Patients with IPMNs and high Charlson Comorbidity Index (≥ 7)
  - Survival time of 43 months compared to 180 months for patients with lower scores
  - 11-fold higher risk of dying from non-IPMN-related causes within 3 years
- Adult Comorbidity Evaluation-27
  - Study of 793 patients with IPMNs
  - More likely to die from non-IPMN related causes

Sahora K, et al. Clin Gastroenterol Hepatol 2015; Kawakubo K, et al. Pancreas 2013

Risks of pancreatic surgery

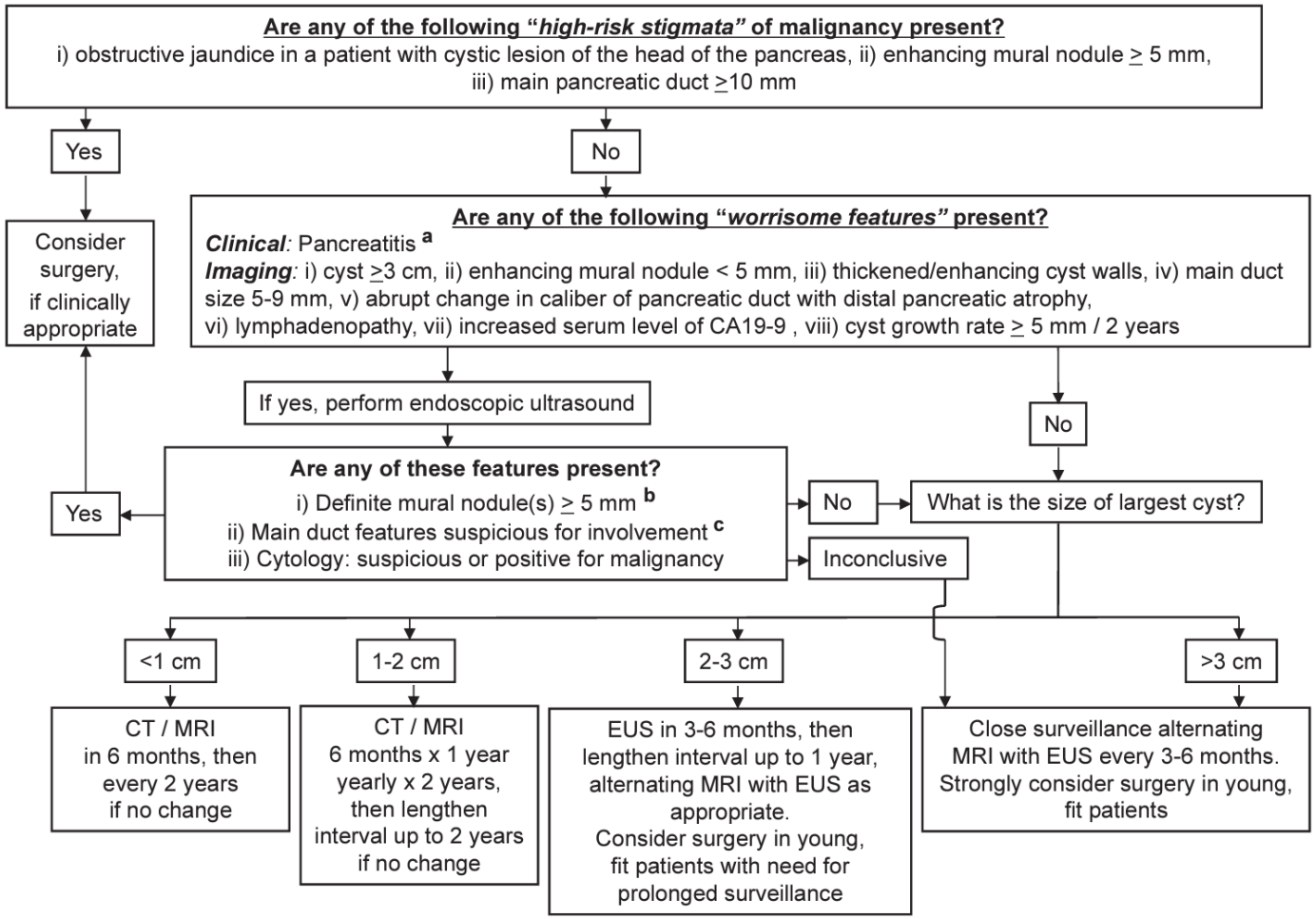
- Pancreatic surgery is complex
  - Morbidity of approximately 20–40% and mortality 1-2% in high-volume centers

Guidelines – AGA (2015)



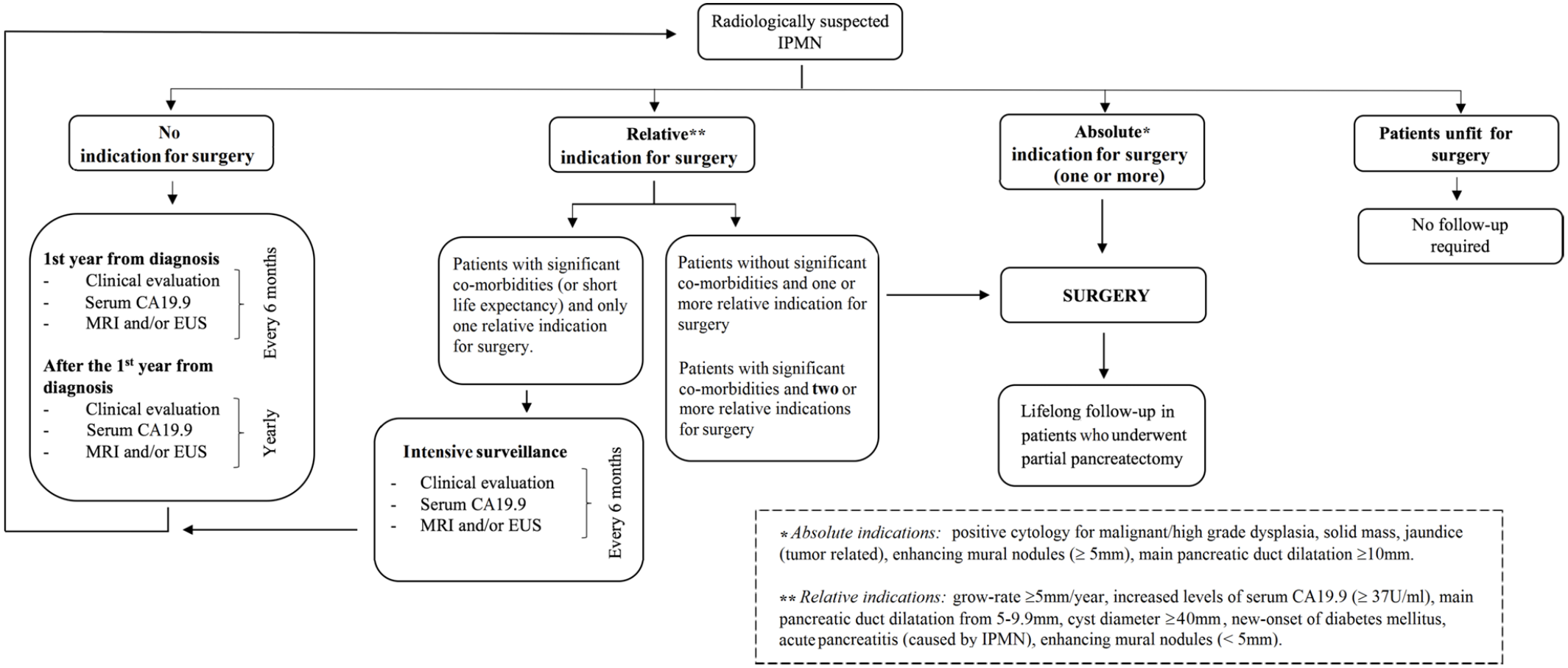
Vege SS, et al. Gastroenterology 2015

Guidelines - Revised International Consensus Guidelines (2017)



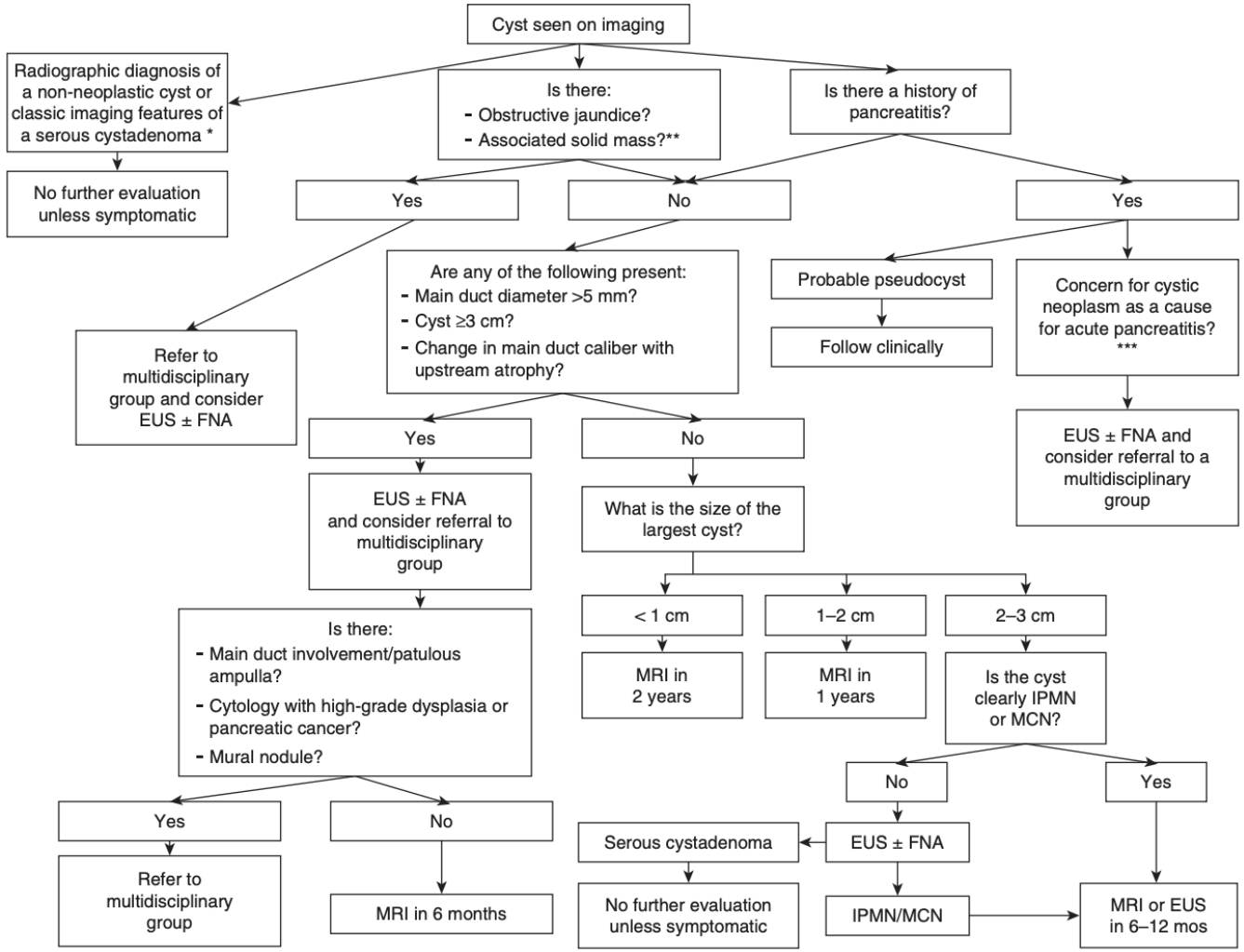
Tanaka M, et al. Pancreatology 2017

Guidelines – European Study Group (2018)



European Study Group, Gut 2018

Guidelines – ACG (2018)



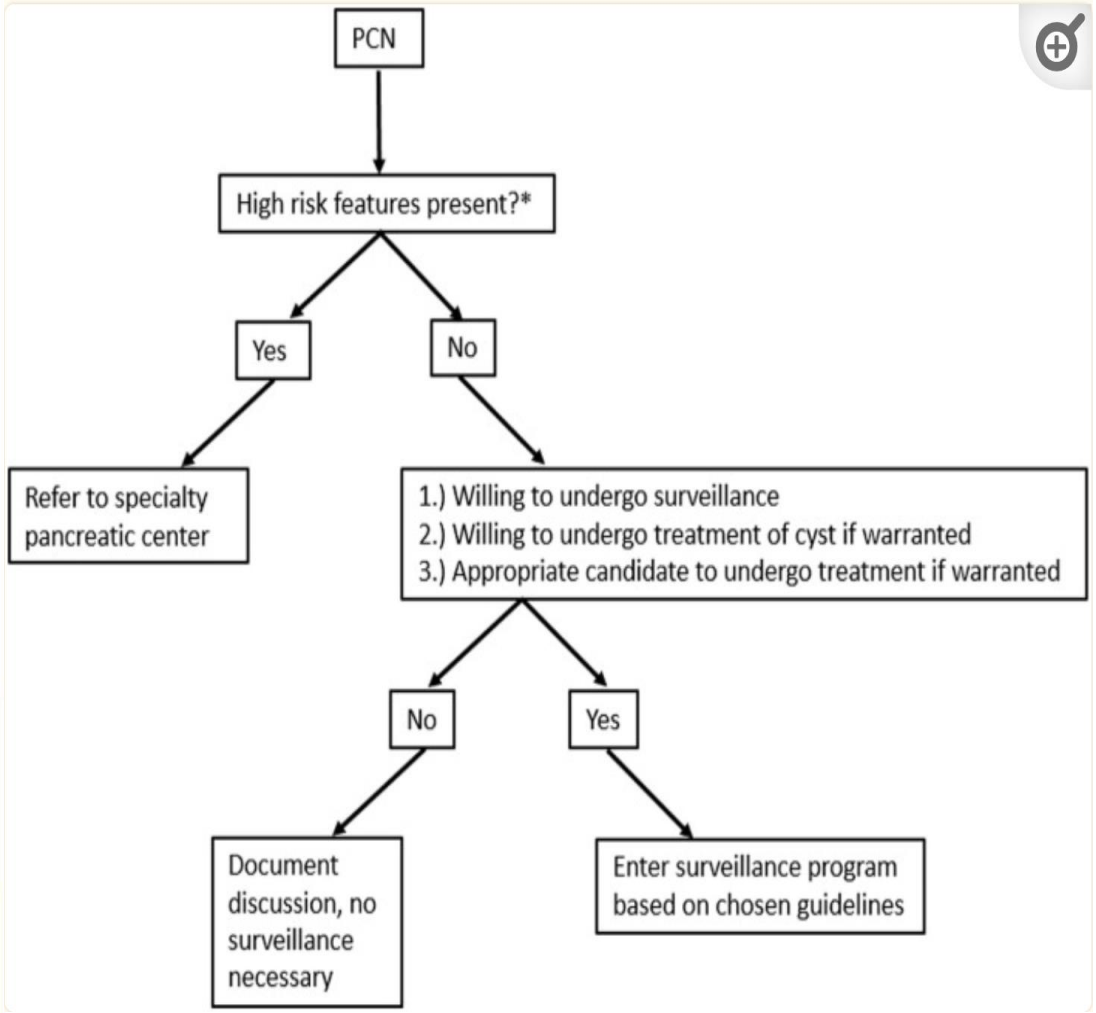
Elta GH, et al. Am J Gastroenterol 2018

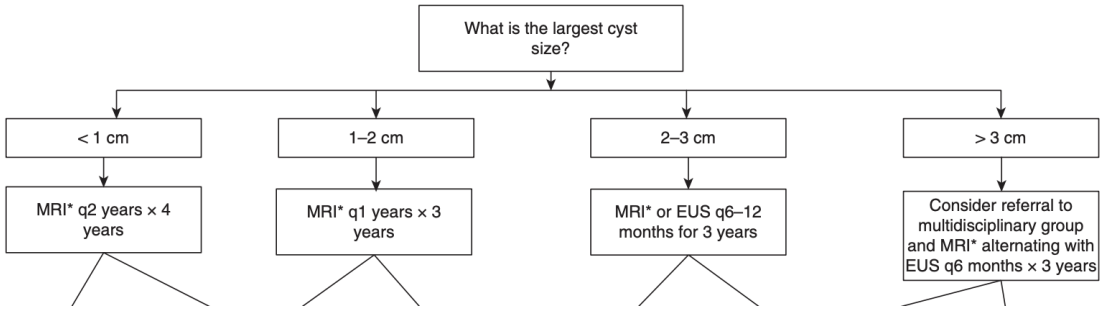
Criticism of AGA guidelines

- Controversial to stop surveillance after 5 years
- Study of 144 patients with low-risk BD-IPMNs
  - Worrisome or high-risk features developed in 18% of BD-IPMNs well beyond 5 years of observation
- Cohort study of 1,036 BD-IPMNs without worrisome features
  - 4% and 1% of cysts developed worrisome features and pancreatic cancer after a median 62 months

Crippa S, et al. Am J Gastroenterol 2017; Marchegiani et al. Am J Gastroenterol 2019

Simplified algorithm





Buerlein RCD, et al. Ther Adv Gastrointest Endosc 2021

Important considerations

- No proven survival benefit to surveillance
- Psychological distress with annual surveillance
- Cost
- Loss to follow-up
- Patient education

Post-operative surveillance

- No surveillance required
  - SCN
  - MCN without cancer
- Surveillance required
  - IPMNs: all require postoperative surveillance
  - Remnant pancreas often has IPMNs
- Solid pseudopapillary neoplasm
  - yearly basis x 5 years

Elta GH, et al. Am J Gastroenterol 2018

Future directions

- EUS ablation techniques
  - Ethanol and/or chemotherapeutic agents
  - Radiofrequency ablation

Conclusions

- Pancreatic cysts are common, particularly as one ages
- The risk of progression to cancer is small (but not zero!)
- Few data exist on the natural history and management of PCLs
- Diagnosis is best made with MRI and EUS/FNA (B)
- Guidelines differ on their recommendations
- Individualized approach with guideline-based structure
- Multi-disciplinary teams (gastroenterology, surgery, radiology, and pathology) are important

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