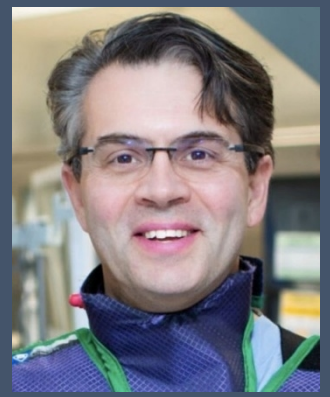
NYU Langone Health

CYSTS WITH A TWIST: UNRAVELING THE MYSTERIES OF PANCREATIC LESIONS



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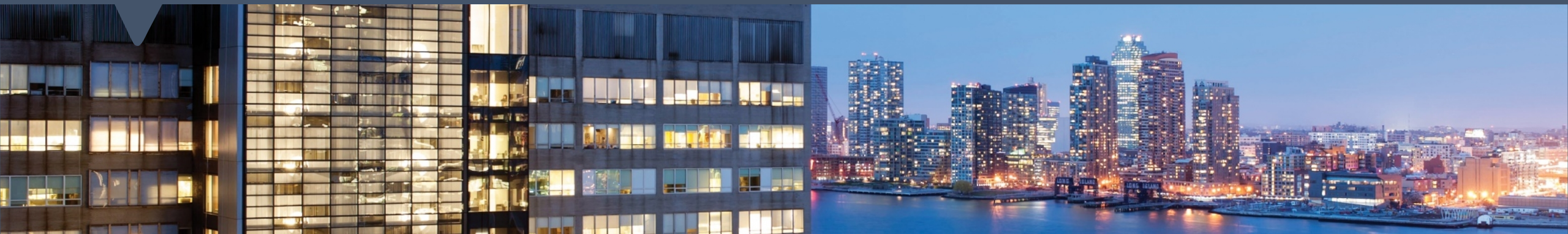
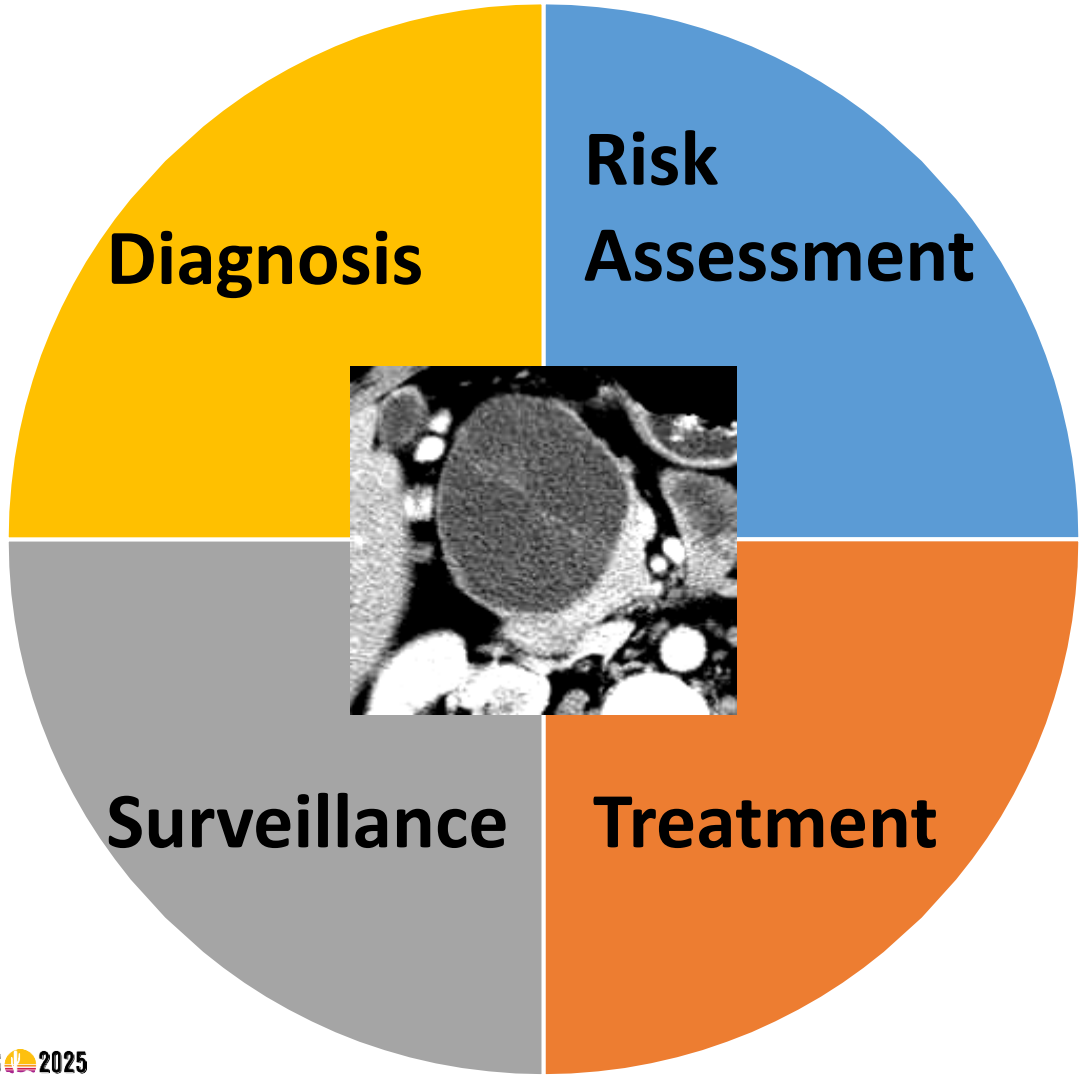
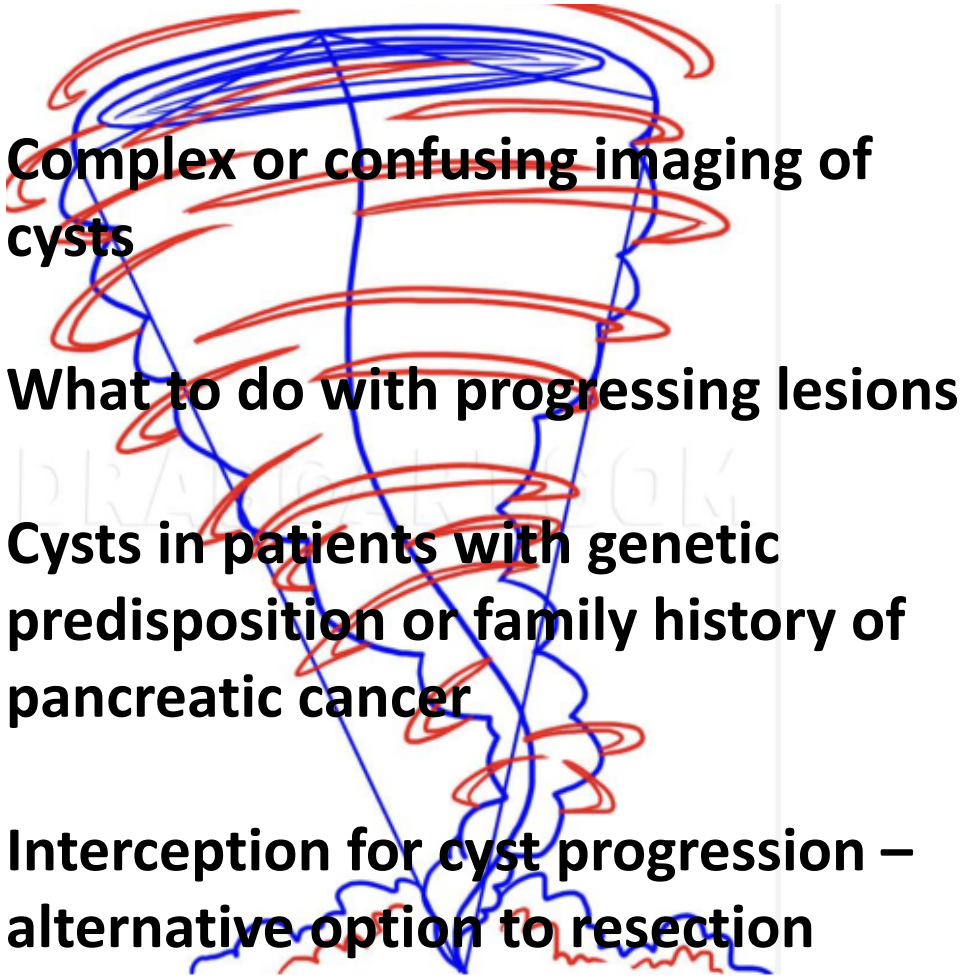


Outline

NO TWIST



TWIST

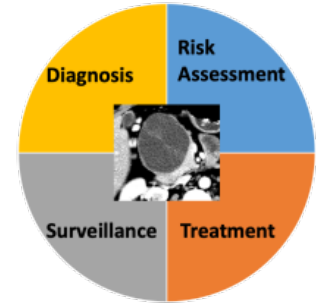


Complex or confusing imaging of cysts

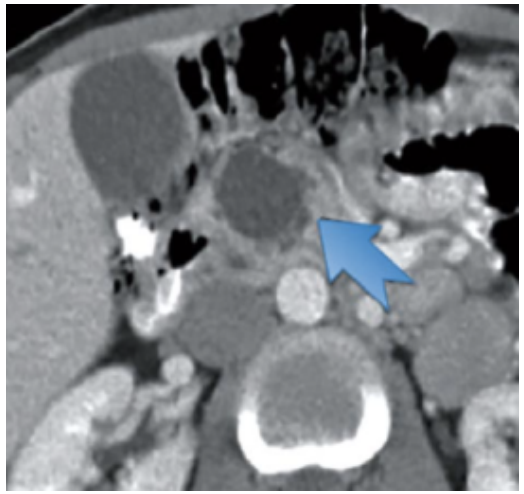
What to do with progressing lesions

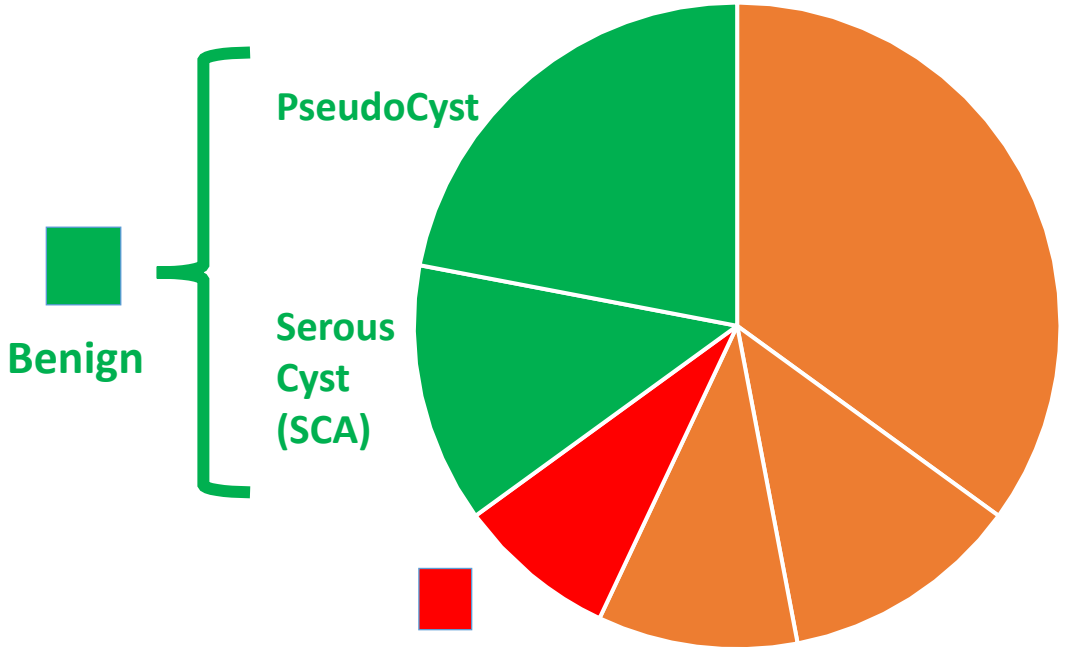
Cysts in patients with genetic predisposition or family history of pancreatic cancer

Interception for cyst progression – alternative option to resection

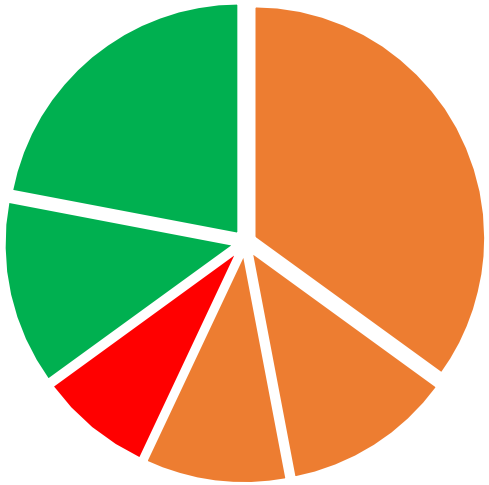


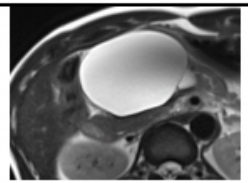
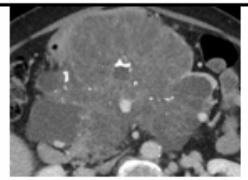
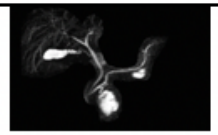
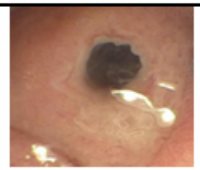
Risk stratification Step 1: Cyst type identification

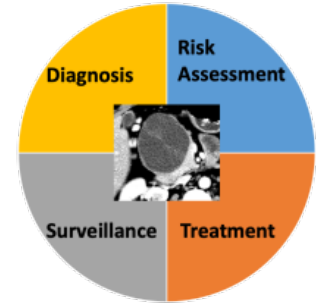




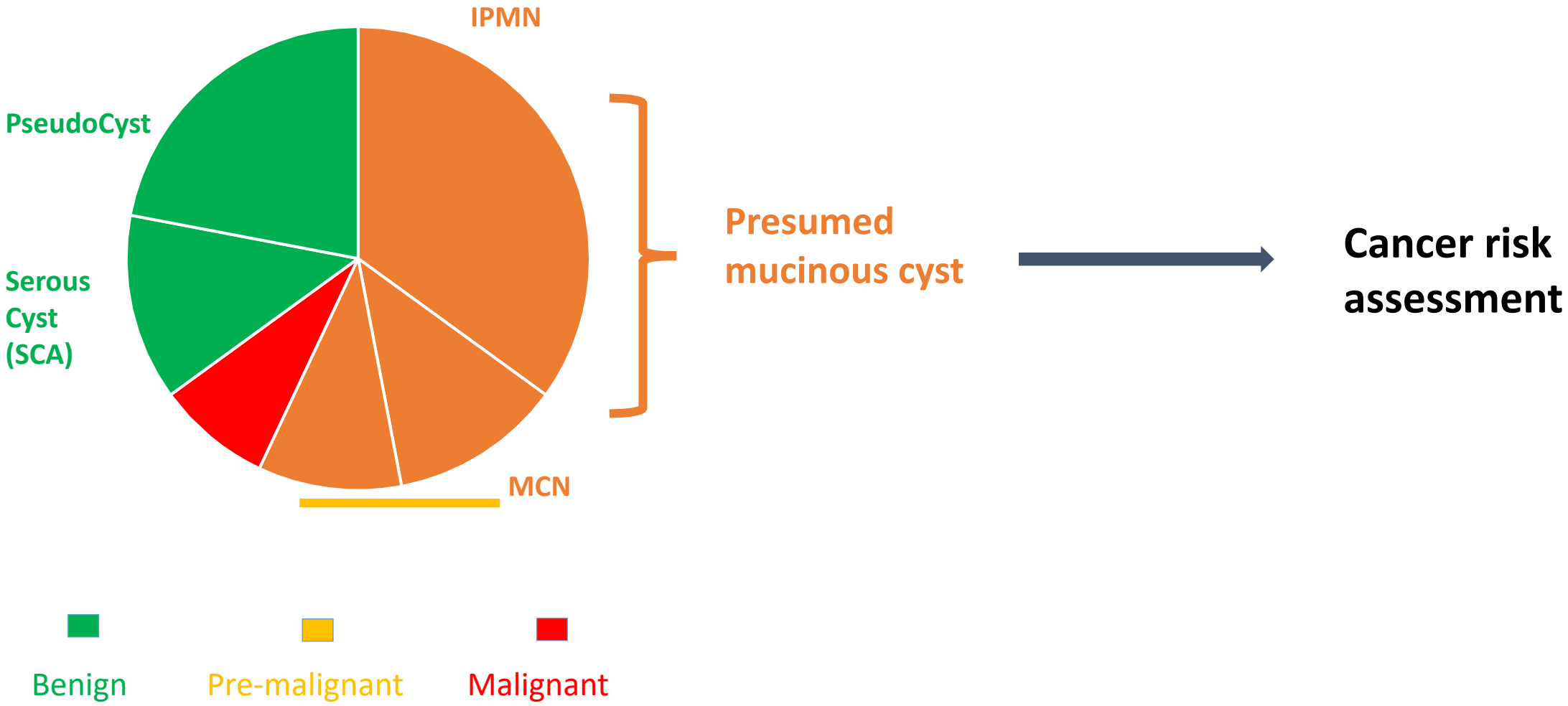
Most common pancreatic cysts

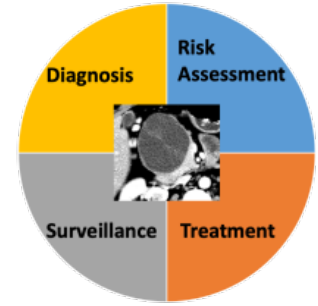


Cyst type	Patient characteristics & clinical presentation	Imaging findings		Malignant potential
Pseudo-cyst	Associated with antecedent Acute or chronic pancreatitis	Uni/multilocular May be connected to MPD		0%
SCA	60% female 5th-7th decade of life Mostly asymptomatic	Micro/oligocystic Central scar No PD communication		0%
IPMN	Variable age & gender Mostly asymptomatic Rarely presents with pancreatitis	Communication with PD Multiplicity		Advanced neoplasia 1-46%
		MPD dilation Fish mouth papilla		Advanced neoplasia 30-90%
MCN	90% women 5th-7th decade of life Mostly asymptomatic or mass effect	Mostly pancreatic tail Uni/oligolocular Thick wall Eggshell calcifications 25%		Advanced neoplasia 5-15%
SPT	90% women 2nd-3rd decade of life Mostly asymptomatic or mass effect	Heterogenous Eggshell calcifications		Carcinoma 10-15%
CNET	Variable age & gender Mostly asymptomatic or mass effect 10% maybe functional	Enhancing, thickened cyst wall		Carcinoma 10%

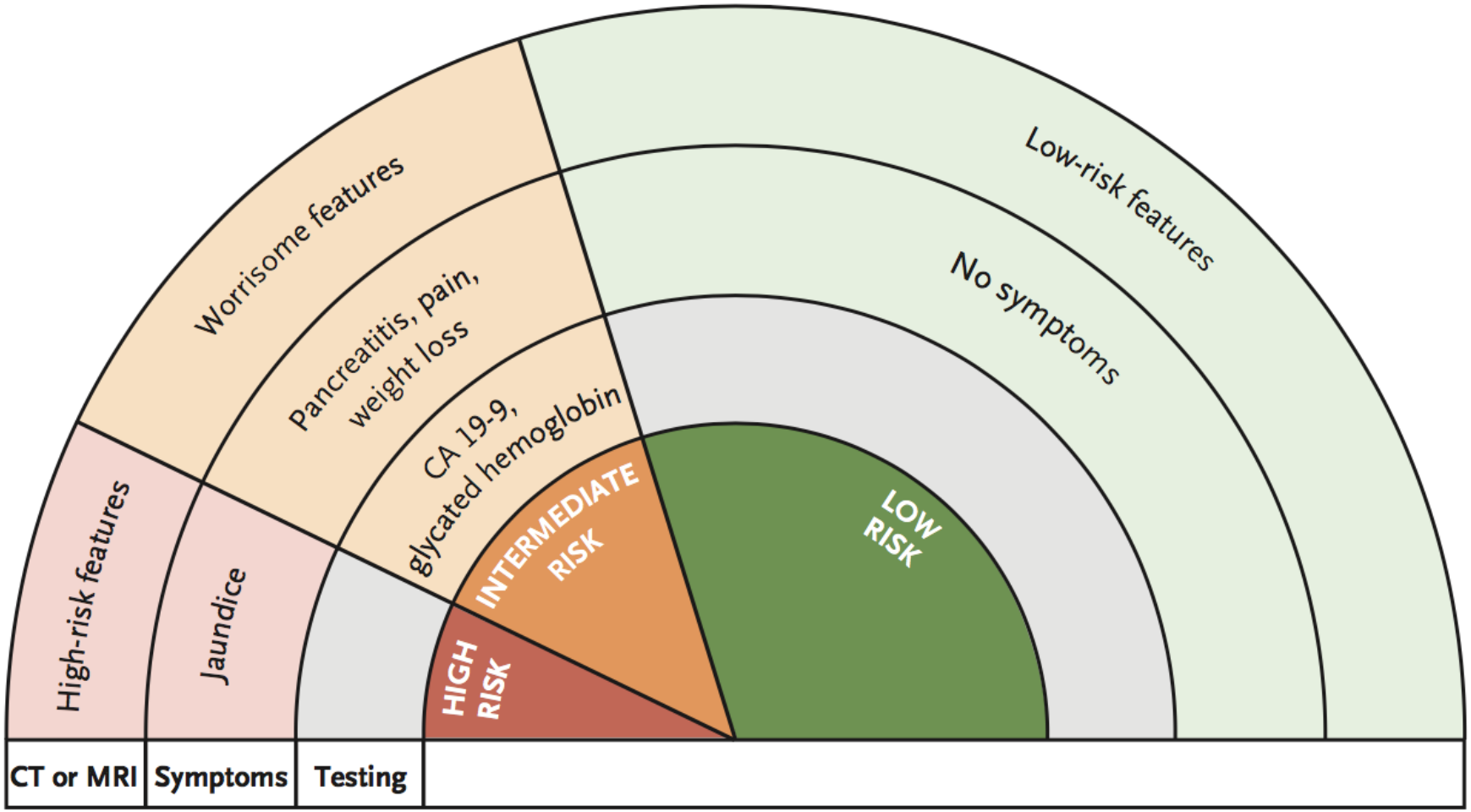


Step 2
Risk assessment in mucinous cysts or presumed mucinous cysts





Risk assessment of presumed mucinous cyst



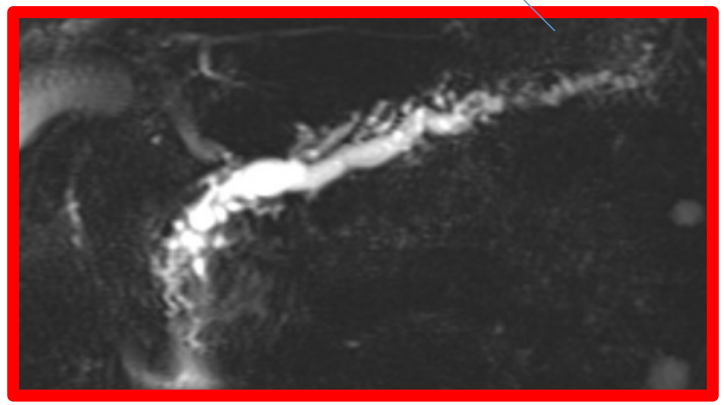
Gonda T, Cahen D, Farrell J
NEJM 2024

Risk stratification of cystic precursors

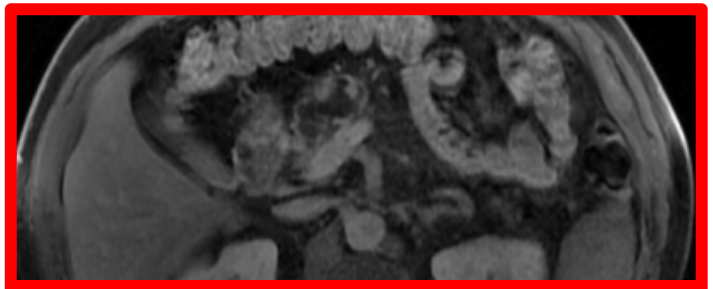
Biliary obstruction

Jaundice

High Risk Stigmata



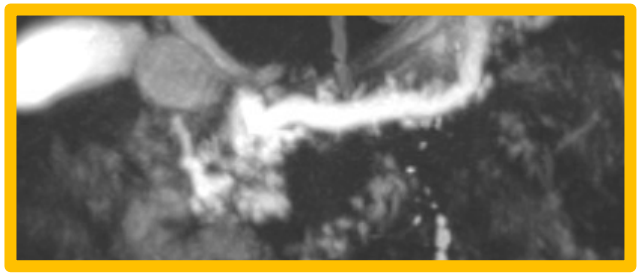
Main duct dilation >10 mm



Solid mass or >10 mm enhancing mural nodule

Risk stratification of cystic precursors

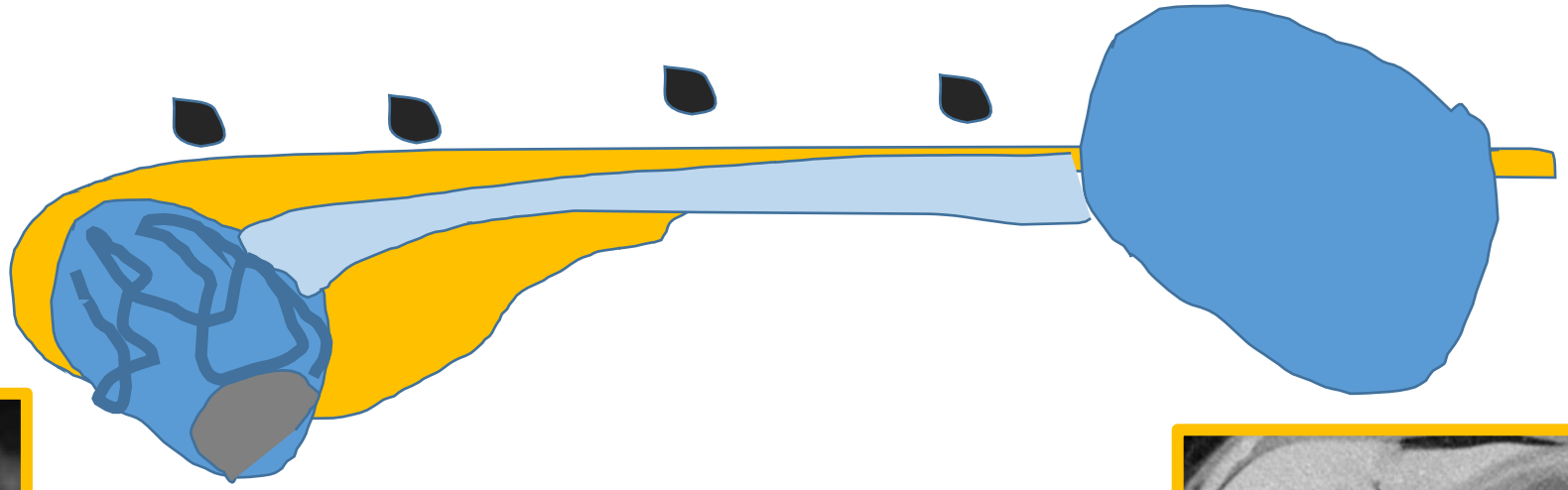
Worrisome Features

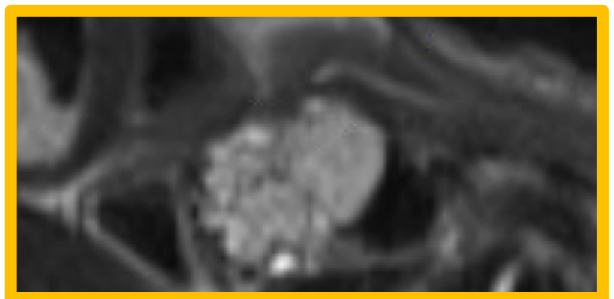


MPD stricture and 5-10 mm dilation and atrophy

Pancreatitis

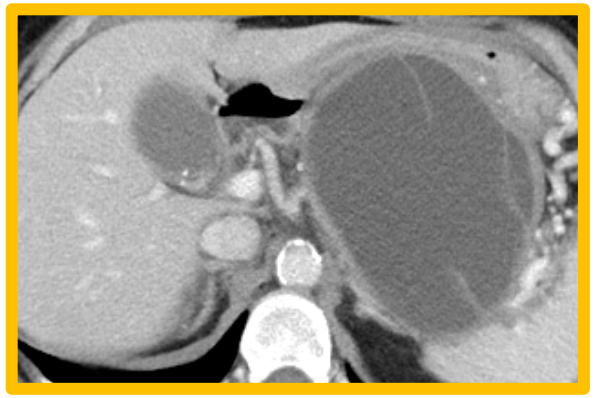
Lymphadenopathy





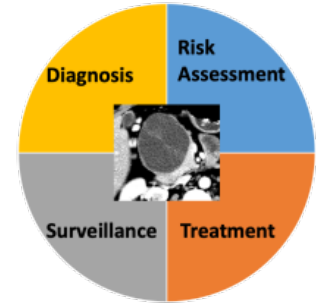
Enhancing septations

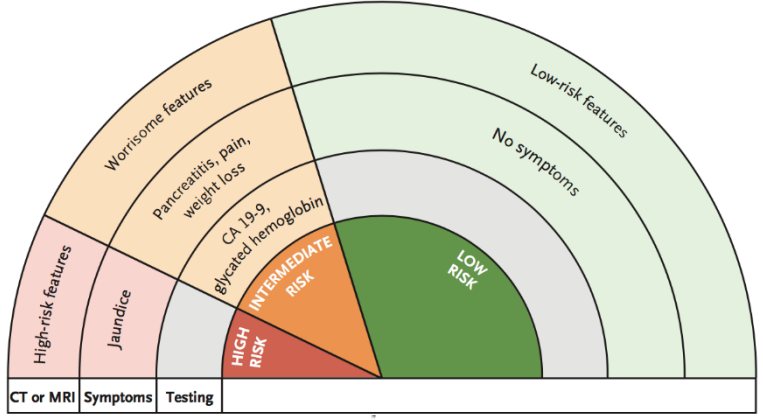
<5 mm Enhancing mural nodule

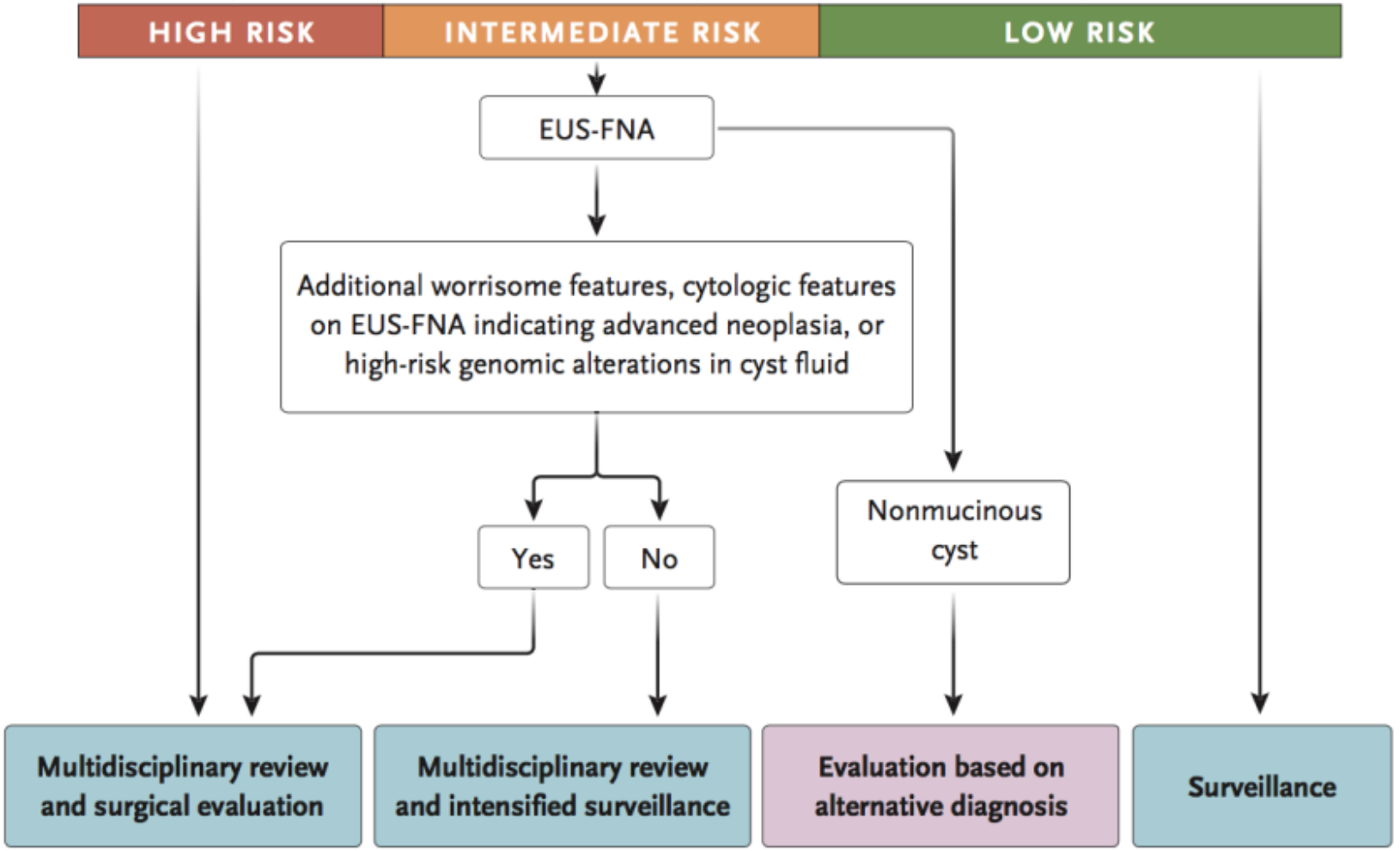


Cyst Size >3 cm

Risk assessment of pancreatic cysts

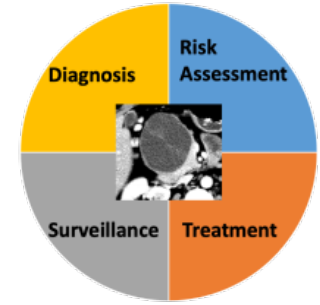


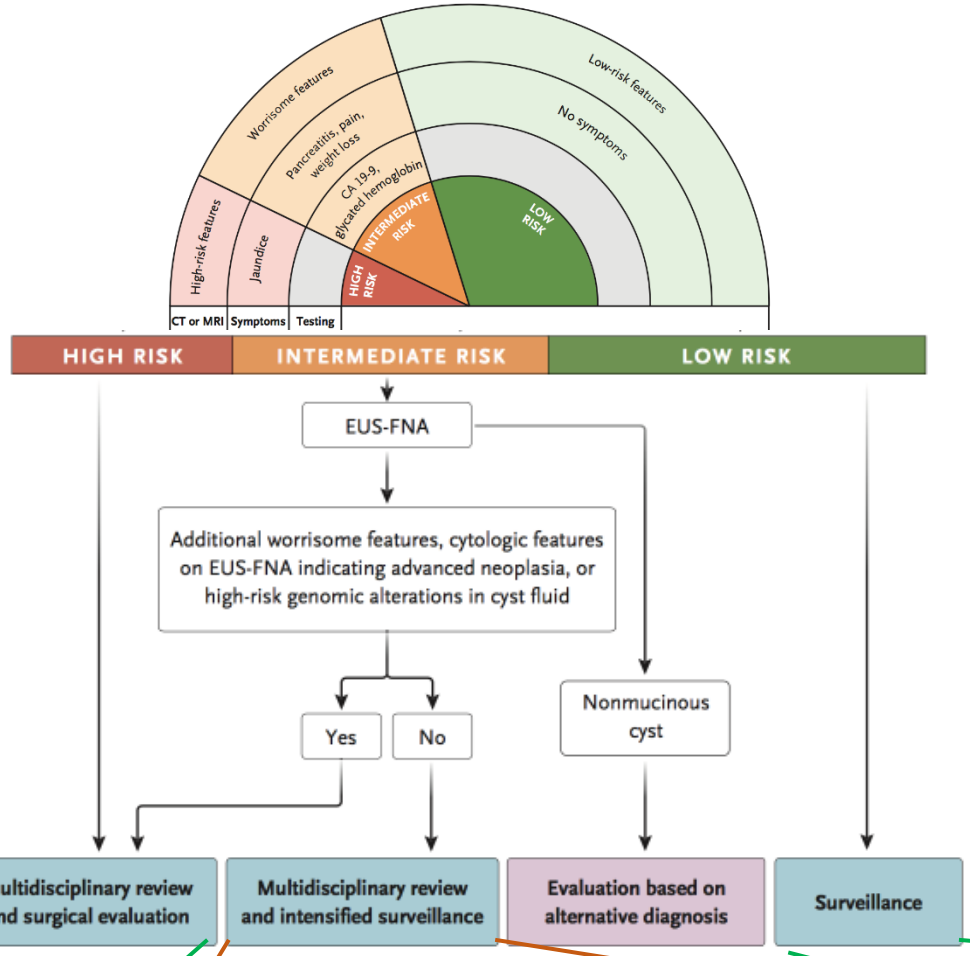




Gonda T et al NEJM 2024

Surveillance Decisions





High risk surveillance

After shared decision making in select patients with high risks cysts and high comorbidity indeces

Consideration of non-surgical interception / ablation

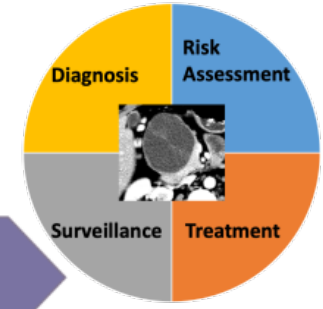
Intensified surveillance

Presence of worrisome features without diagnosis of malignancy

Low risk surveillance

Per protocol or guidelines surveillance

Surveillance of (?mucinous) pancreatic cysts



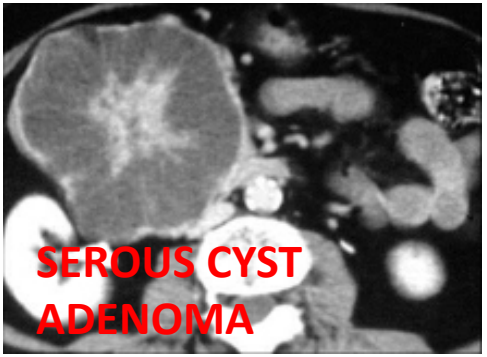
Low risk surveillance
Per protocol or guidelines surveillance

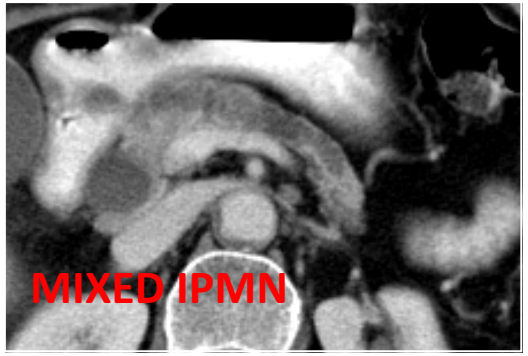
Intensified surveillance

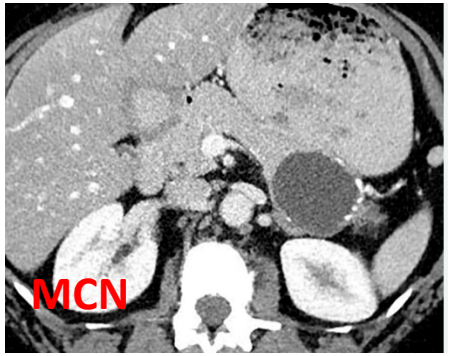
Cyst Size and Features	Year 1	Years 2–5	After >5 Years of Stability
<1 cm without worrisome features or high-risk stigmata	**12 Months** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels **Or consider** • Ceasing surveillance
1–2 cm without worrisome features or high-risk stigmata	**6–12 Months** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 1–2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 2 years** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels **Or consider** • Ceasing surveillance
2–3 cm without worrisome features or high-risk stigmata	**Alternating every 6 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Either in 6–12 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Every year** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels • Continue surveillance
>3 cm or worrisome features (when surgical resection is not pursued)	**Alternating every 3 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Alternating every 3–6 months** • MRI or endoscopic ultrasonography • Measurement of CA 19-9 and glycated hemoglobin levels	**Every 6–12 months** • MRI • Measurement of CA 19-9 and glycated hemoglobin levels • Continue surveillance

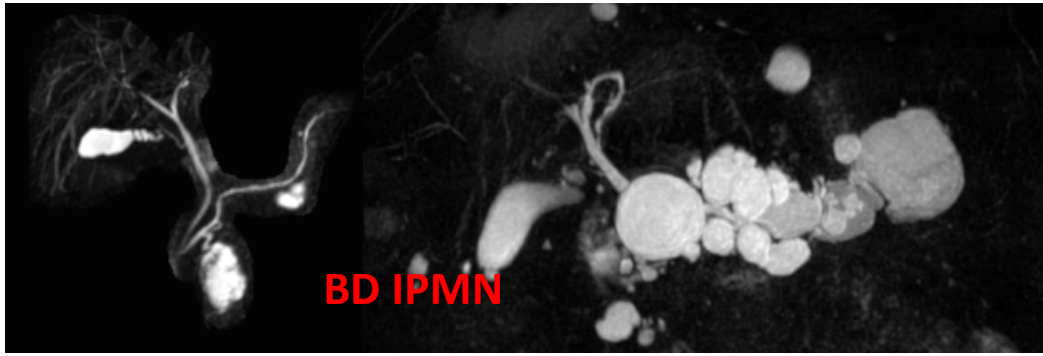
Adequacy of imaging based diagnosis and risk stratification

- Imaging and demographics may accurately diagnose cysts in >80% of cases



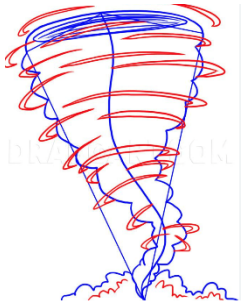






- EUS is generally indicated when the cysts meet at least an intermediate risk threshold and/or the cyst type is unknown

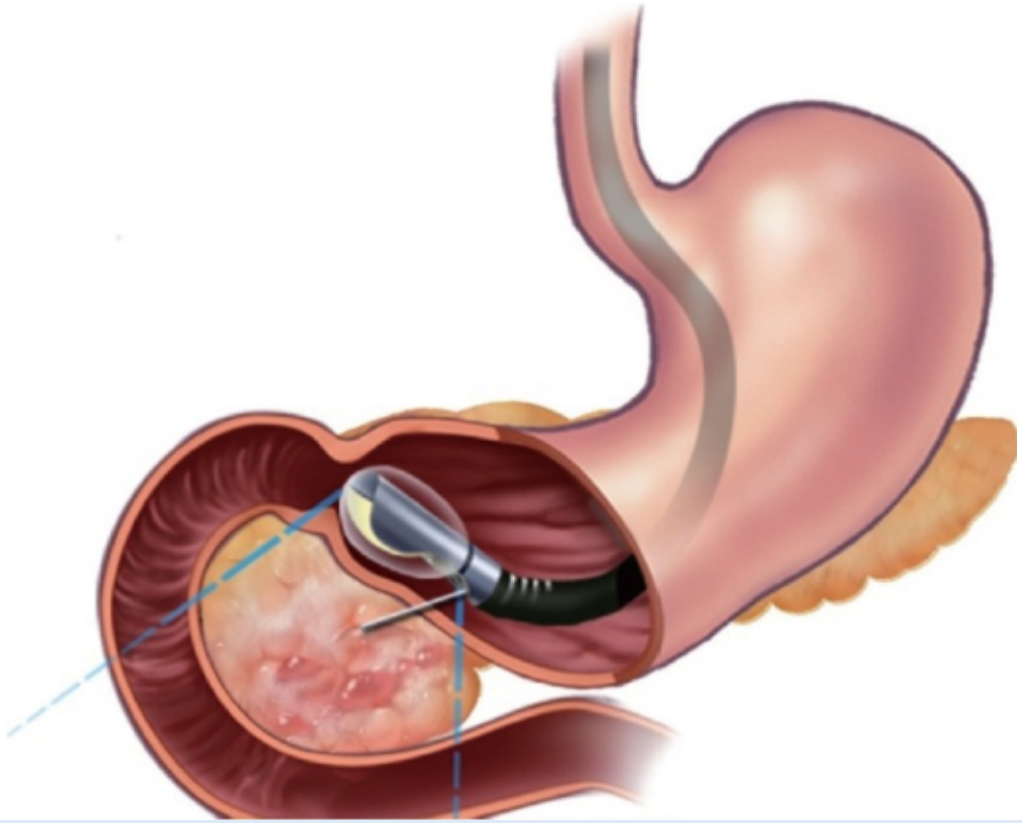
Complex cyst in a 47 yo F with transient flank pain



Impact question

Is this a SCA or an IPMN/mucinous neoplasm?

EUS Cyst Fluid Analysis in Cyst Type Diagnosis



CEA ≥ 192

SN = 56%
SP = 96%
ACCURACY 85%

Glucose <50

SN = 86%
SP = 91%
ACCURACY 94%

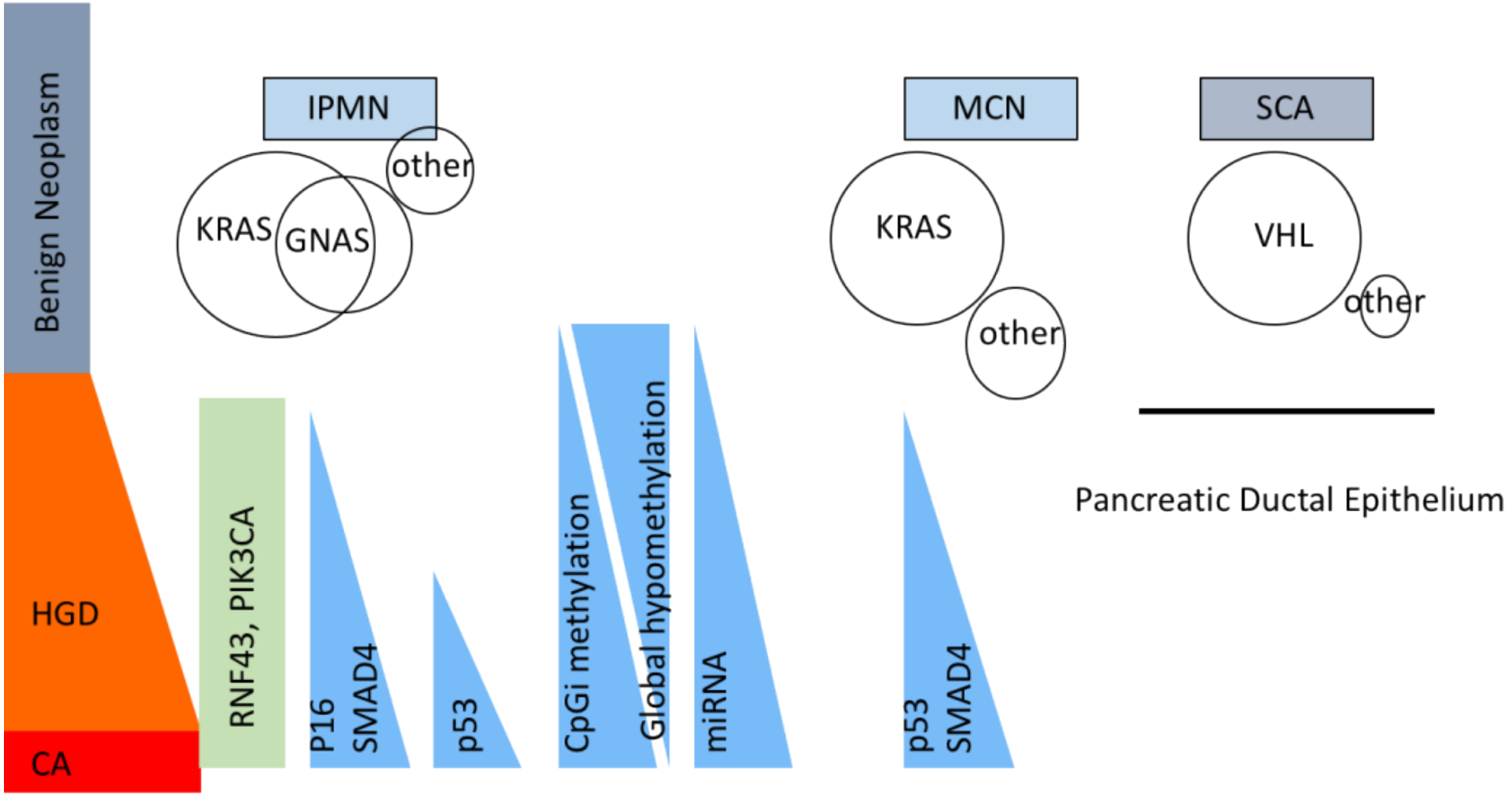
CEA > 192 OR Glucose < 50

SN = 72%
SP = 97%
ACCURACY 97%

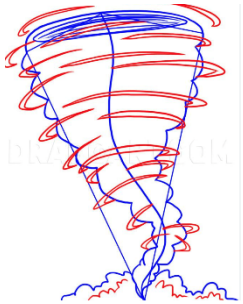
10-20% of cystic lesions are uncertain type after combined B-mode EUS imaging and cyst fluid evaluation

McCArthy TR et al. *GIE*. 2021; Gonda et al. *Clin N Am.* 2023.

EUS Cyst Fluid Molecular Analysis in Cyst Type Diagnosis

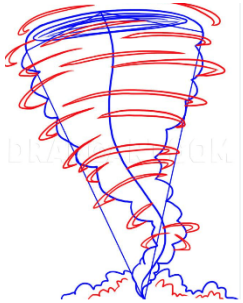


EUS in Cyst Type Diagnosis



Tool	Mucinous vs. Non-Mucinous
Imaging	CT, MRI: Accuracy 40%-60% EUS: Accuracy 50-70%
Biomarkers (FNA)	CEA +glucose Sensitivity 72%, Specificity 97%
Cytology (FNA)	Sensitivity 80%, Specificity 40%
Molecular Analysis (FNA)	Sensitivity 54%-84%, Specificity 98%
Combination biomarker, cytology, molecular	Sensitivity >92%; Specificity 98%

Serous cystadenoma versus IPMN



Radiology report:

CEA 121
Amylase 4000
Glucose < 5
KRAS G12D mutation present
GNAS present

Surgical Pathology:
IPMN with HGD

Cyst progression

MRI without change in 2018, 2019
MRI 2020: minimal change in size
MRI 2022: 25% increase

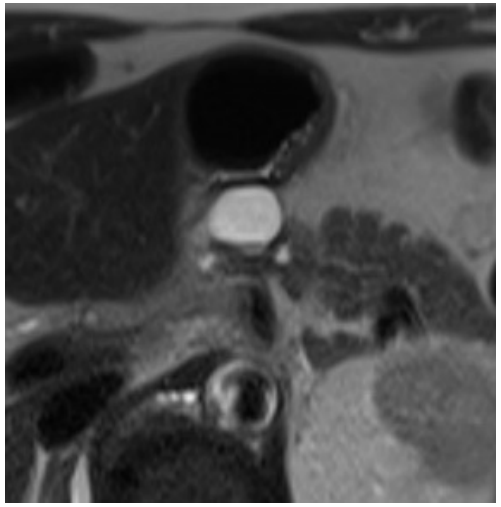
3.4 cm cyst on MRI → EUS evaluation

Impact question

Is this a transformed IPMN?

Evaluation of a mural nodule

B mode EUS

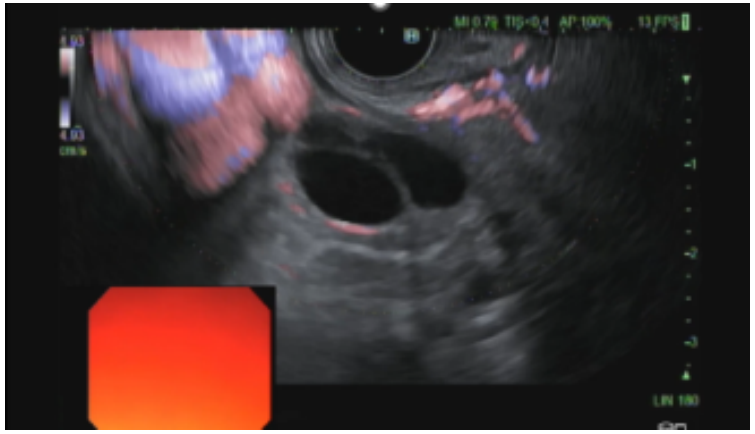


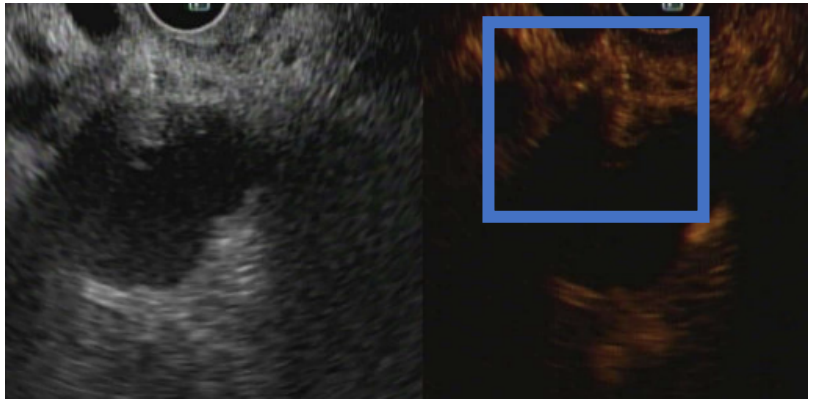
B mode EUS vs MRI

	EUS +	EUS –
MRI +	31%	2%
MRI -	55%	12%

Kamata K et al. *Endoscopy*. 2016; Khashab M et al. *Pancreas*. 2013.

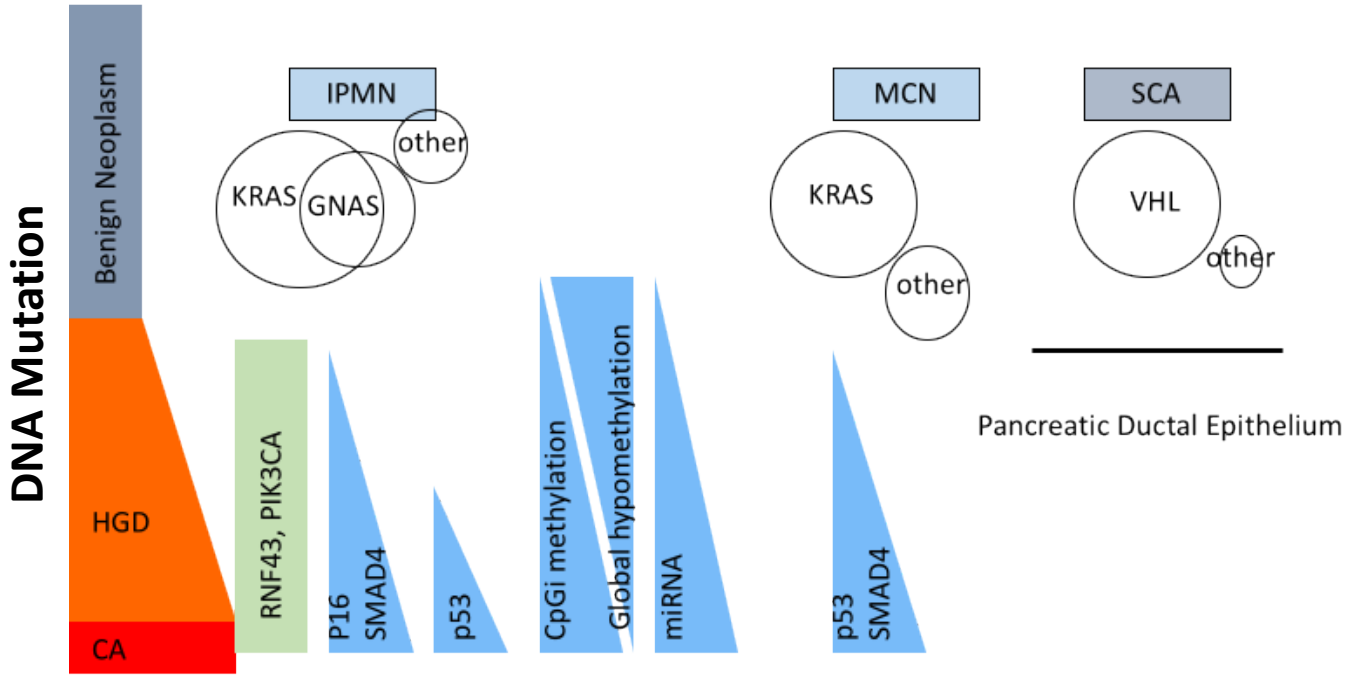
Contrast Enhanced EUS (CE-EUS)

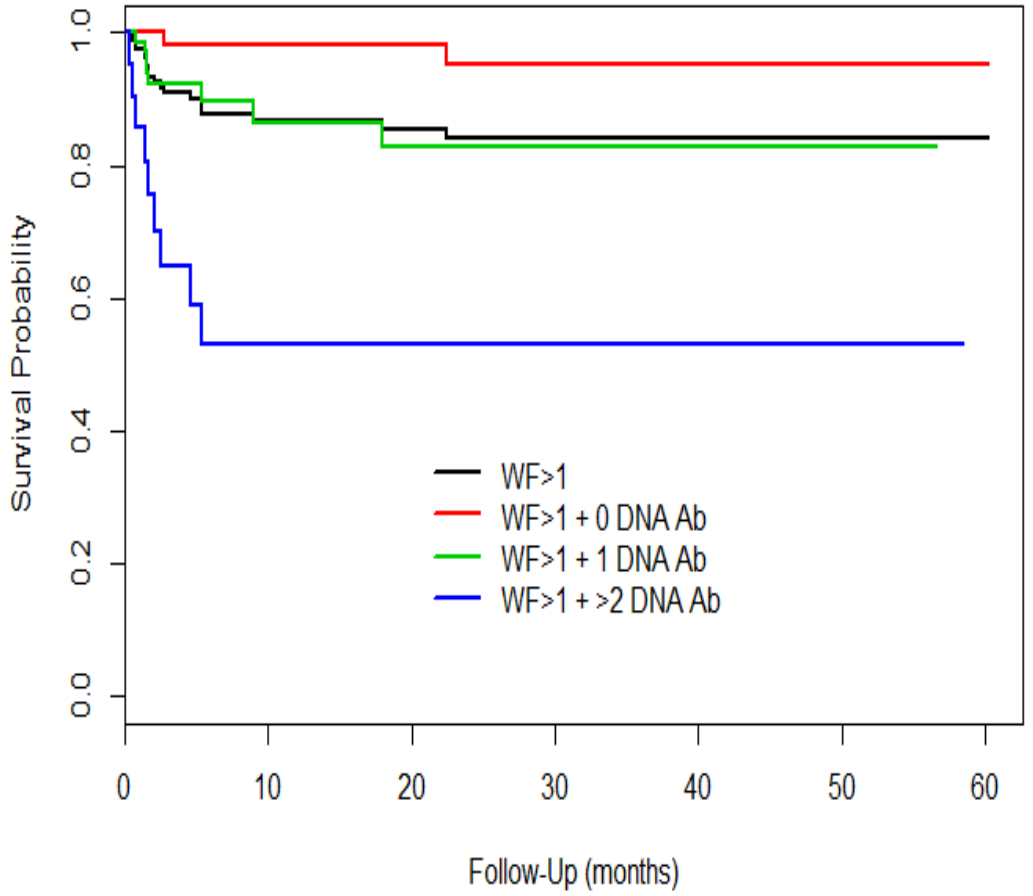




EUS FNA Cytology: non diagnostic
Biopsy: Mucinous epithelium with low grade dysplasia
CEA 500; Amylase 7890
Kras: pos, high clonality; LOH: neg; GNAS: mutation present
RNF43 and CDKN2A mutation detected

When to rely or use molecular markers in risk stratification?





Farrell JJ et al GIE 2019

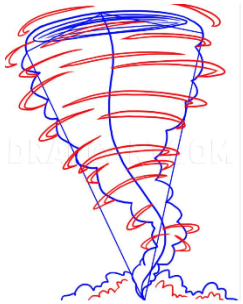
Table 1. Cyst-Fluid Characteristics and Genes Altered in Common Types of Pancreatic Cysts.*

Cyst Type	Macroscopic and Cytologic Features	CEA Level	Glucose Level	Amylase Level	Altered Genes	
					Associated with Cyst Type	Associated with Advanced Neoplasia
Pseudocyst	Macrophages and lymphocytes, debris	Variable	High	High	None	None
SCA	Proteinaceous debris and blood, glycogen-rich cuboidal epithelial cells	Very low	High	Low	*VHL*	None
IPMN	Thick mucinous fluid, mucinous epithelial cells, papillary structures†	High	Low	High	*KRAS*, *GNAS*	*TP53*, *CTNNB1*, *CDKN2A*, *SMAD4*, genes involved in mTOR pathway‡
MCN	Thick mucinous fluid, mucinous epithelial cells, ovarian-type stroma†	High	Low	Low	*KRAS*	*TP53*, *CDKN2A*, *CTNNB1*, *SMAD4*, genes involved in mTOR pathway‡
SPT	Hemorrhagic debris; monomorphic, discohesive small cells; hyaline globules and grooved nuclei	Variable	Normal	Low	*CTNNB1*	None
CNET	Uniform cells in loosely cohesive clusters; coarse, granular, chromatin-containing nuclei	Variable	Normal	Low	*MEN1*	None

Molecular markers in risk stratification of mucinous cysts

Study	Molecular Biomarker(s) of Interest	Detection Method	Outcome Evaluated	Sensitivity	Specificity
Guo (2016) [37]	LOH	Mix of sequencing techniques	Presence of PCL Harboring Malignancy	89%	69%
Singhi (2018) [43]	*KRAS* and/or *GNAS* Mutation & *TP53/PIK3CA*, and/or *PTEN* Mutation	NGS	Presence of IPMN with High-Grade dysplasia or IPMN Harboring Malignancy	88%	97%
Khalid (2009) [52]	LOH	Sanger Sequencing	Presence of PCL Harboring Malignancy	90%	67%
	DNA Quantity	Spectrophotometry	Presence of PCL Harboring Malignancy	75%	79%
Winner (2015) [53]	*KRAS* Mutation & ≥2 LOH Mutations	Sanger Sequencing	Presence of PCL Harboring Malignancy	50%	96%
Paniccia (2023) [58]	*KRAS/BRAF/NRAS/GNAS* Mutation	NGS	Presence of High-Grade Dysplasia or PCL Harboring Malignancy	90%	100%
	KRAS/BRAF/NRAS/GNAS LOH OR *KRAS/BRAF/NRAS/GNAS and TP53/SMAD4/CTNNB1/MTOR* Mutation	NGS	Presence of High-Grade Dysplasia or PCL Harboring Malignancy	89%	98%
Faias (2018) [59]	*KRAS and/or GNAS Mutation*	Sanger Sequencing	High-Risk Mucinous/Malignant Cyst	63%	82%
Hata (2017) [64]	Hypermethylation: *SOX17, BNIP3, FOXE1, PTCHD2,SLIT2, EYA4 and SFRP1* loci	Methylation-Specific Droplet-Digital PCR	Presence of High-Grade Dysplasia or PCL Harboring Malignancy	78.4% *(SOX17 locus)*	85.6% *(SOX17 locus)*
Das (2014) [67]	mAb Das-1	Immunohistochemistry	Presence of High-Risk IPMN or IPMN Harboring Malignancy	85%	95%
		ELISA	Presence of High-Risk IPMN or IPMN Harboring Malignancy	89%	100%

High risk individuals and cysts



58 yo F with BRCA 2 mutation is found to have a 1.8 cm cyst

Impact question

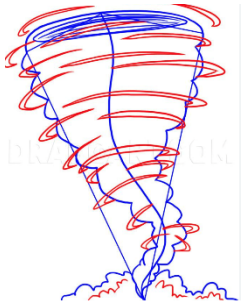
Does the combination of cyst + BRCA2 increase her PDAC risk?

65 yo M with an incidental 1.9 cm cyst asks about genetic testing

Impact question

Should patients with cysts undergoing genetic testing?

When is germline genetic testing for PDAC recommended?

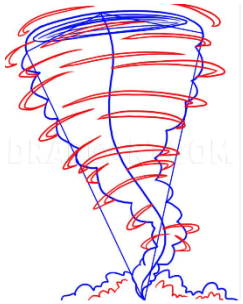


National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES[a]

DIAGNOSIS	TESTING CRITERIA
Exocrine pancreatic cancers →	Recommend genetic counseling and germline testing[m] for • All individuals diagnosed with exocrine pancreatic cancer[n] • First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[o]



Current screening recommendation based on germline mutation status or family history

- UTPSTF recommends against screening in the general population

- Generally, 4 main categories of people eligible for screening across all familial/genetic guidelines:

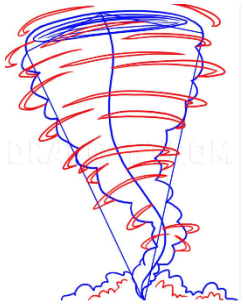
1. **PGV alone:** *ATM*, BRCA2*, PALB2*, CDKN2A* or *STK11* PGV carriers, regardless of family history
2. **PGV + family history:** *BRCA1,* Lynch syndrome (*MLH1, MSH2, MSH6, PMS2,** EPCAM**) PGV carriers, and ≥1 first- or second-degree relative**
3. ***PRSS1* PGV + personal history of pancreatitis**
4. **Family history meets Familial Pancreatic Cancer (FPC) criteria**

High Risk Individuals

EUS and MRI findings in patients screened for PDAC

Gene Category	Imaging modality	N (%)	Normal Index EUS N, (%) P-value	Pancreatic Cyst N, (%) P-value	Pancreatic Mass N, (%) P-value	MPD Changes N, (%) P-value	Parenchymal Changes N, (%) P-value
FHPC (Control)	EUS	90	31 (34%)	36 (40%)	7 (7%)	20 (22%)	25 (27%)
	MRI	52	10 (19%)	37 (71%)	3 (6%)	9 (17%)	4 (8%)
PGV (Includes all below)	EUS	81	42 (52%) p = 0.03	15 (19%) p < 0.01	7 (9%) p = 1	11 (14%) p = 0.17	25 (30%) p = 0.74
	MRI	48	26 (54%) p < 0.01	16 (33%) p < 0.01	5 (10%) p = 0.48	2 (4%) p = 0.053	6 (13%) p = 0.51
BRCA BRCA1, BRCA2	EUS	49	28 (57%) p = 0.01	8 (16%) p < 0.01	5 (10%)	4 (8%) p = 0.04	14 (29%)
	MRI	29	15 (52%) p < 0.01	10 (34%) p < 0.01	4 (14%)	1 (3%)	3 (10%)
Other HR deficient (ATM, CHEK2, PALB2)	EUS	16	8 (50%)	4 (25%)	1 (6%)	3 (19%)	4 (25%)
	MRI	10	6 (60%) p < 0.01	3 (30%) p = 0.03	0 (0%)	0 (0%)	1 (10%)
DNA Mismatch Repair (MLH1, MSH2, MSH6)	EUS	13	4 (31%)	3 (23%)	1 (8%)	3 (23%)	5 (39%)
	MRI	7	3 (43%)	3 (43%)	1 (14%)	1 (14%)	2 (29%)
CKDN2A	EUS	3	2 (67%)	0 (0%)	0 (0%)	1 (33%)	1 (25%)
	MRI	2	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

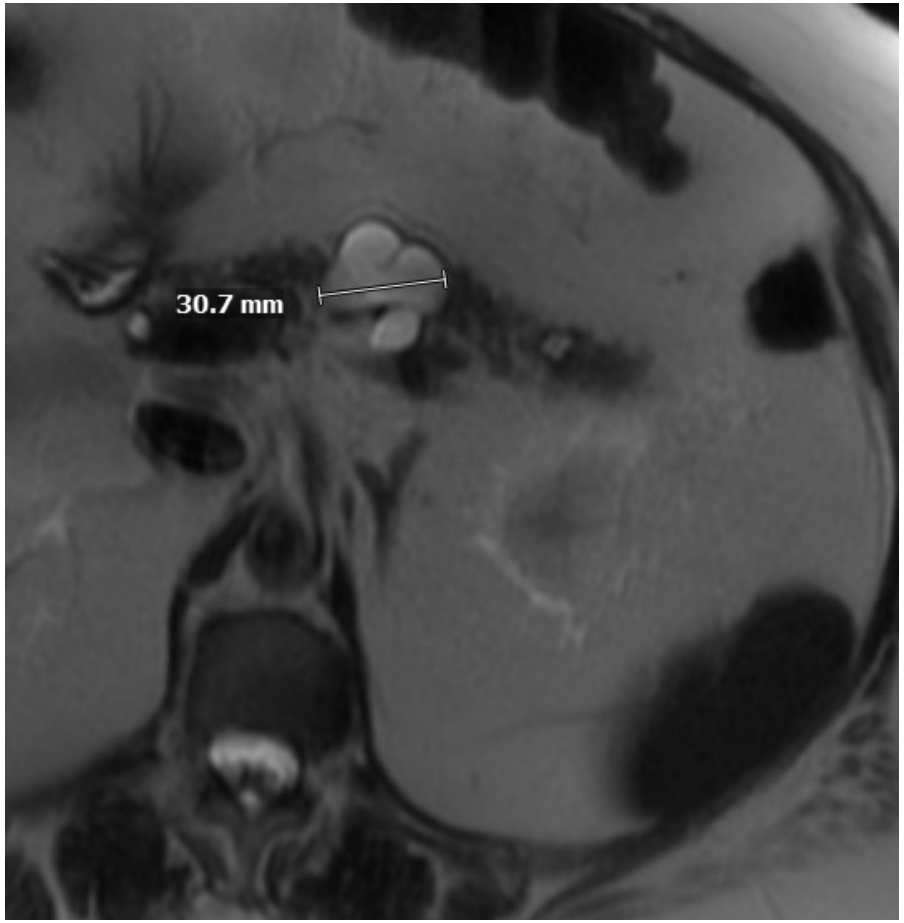
Cystic lesions in high risk individuals



- Higher Prevalence of cysts (35-50%) in HRI then average risk individuals
- Risk of cyst progression in HRI
  - IPMN + HRI vs IPMN
    - → somewhat greater progression rate; no increased CA risk
  - HRI + IPMN vs HRI
    - → much stronger correlation with PGV status then cyst status
    - → in studies that show slightly increased cancer risk nearly as many cancers are IPMN concomitant as IPMN derived

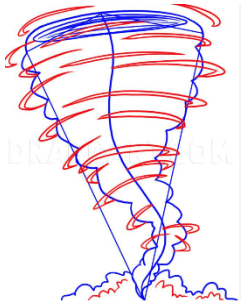
Haimi I et al Clin North Am 2024; Dbouk M et al Pancreatology 2021

High risk cysts in high risk patients



76 yo M with multiple comorbidities
Cysts have enlarged > 40% in one year
EUS FNA showed 2-3 mm possible mural nodule, cytology with indeterminate dysplasia and KRAS, GNAS, SMAD4 and CDKN2A mutation

Non surgical treatment of cysts – why and when to think of ablation?



Alternative to surgical resection with lower morbidity

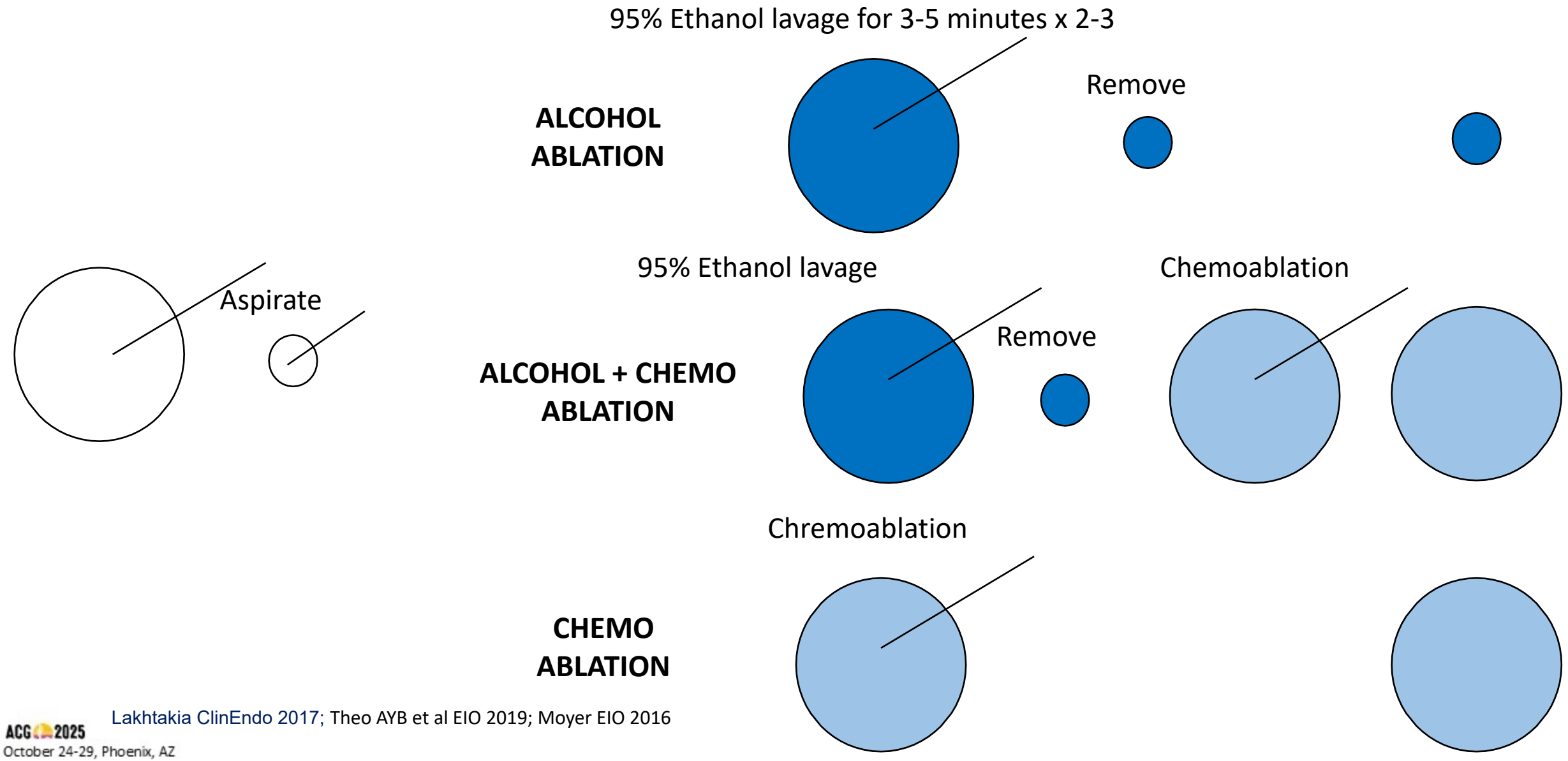
Requires long term efficacy for high risk pre-malignant lesions

- IPMNs or MCNs with worrisome features or high risk stigmata in borderline surgical candidates
- Goal is durable response

Prophylactic intervention for intermediate risk patients to reduce burden of surveillance and risk of progression

- IPMNs or MCNs (and maybe large and symptomatic Serous lesions)
- Partial response - ? Long term benefit

Chemical and chemoablation



Lakhtakia ClinEndo 2017; Theo AYB et al EIO 2019; Moyer EIO 2016

EUS-guided thermal / non-chemical ablation approaches

	EUS RFA	EUS RFA	EUS MWA	EUS IRE
Set-up	19G RFA needle Own generator	1Fr catheter Uses ERBE	19 MWA needle Own generator	19G needle
Clinical use status	In clinical use	Withdrawn	FDA submission	Pre-clinical

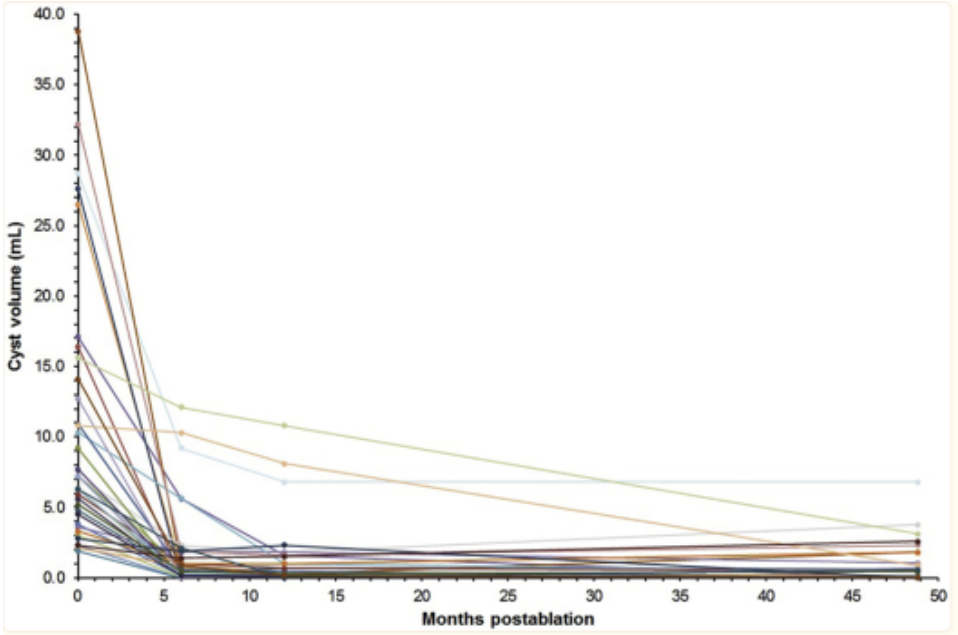
EUS Ablation of Cystic Lesions

95% EtOH

Conditions (no. patients)	Complete (CR) or partial resolution (PR)
5 – 80 % ETOH (25)	35 % CR 7 % PR
80 % ETOH (25) SALINE (17)	33 % CR[2] 0 % CR
80 % ETOH (13)	38 % CR
80 % ETOH (23)	9 % CR 44 % PR

Alcohol free

	Complete response after 6 months	Complete response after 12 months
Alcohol arm	2/4 (50 %)	3/4 (75 %)
Alcohol-free arm	4/6 (67 %)	4/6 (67 %)
Overall in both arms	6/10 (60 %)	7/10 (70 %)



EUS RFA

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)

DDW 2025 : Krishna et al	N=25
Complete response	37%
Partial response	53%
AE rate	10.9%

EUS-guided Cyst Ablation – Adverse events

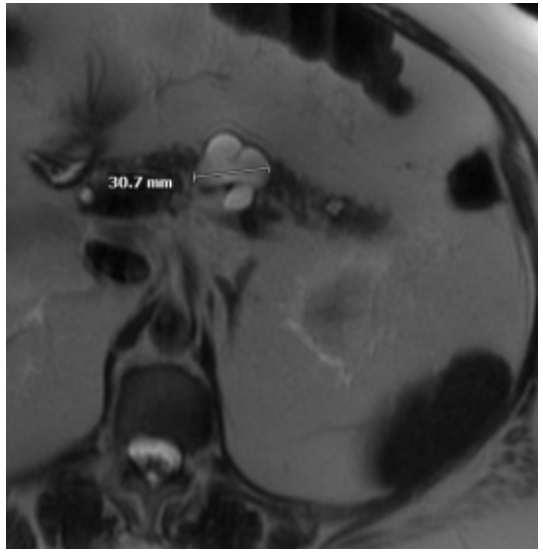
Chemical or Chemoablation

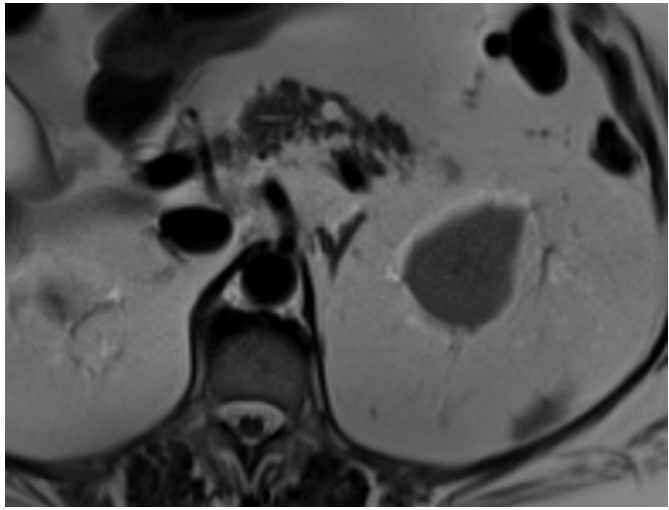
Author	Study Year	Ablative Strategy	Number of Treated Patients	Adverse Events, (n)
Oh *et al.* [7]	2008	Ethanol (88-99%) + Paclitaxel	14	**18%** Mild abdominal pain (1); Acute pancreatitis (1)
Oh *et al.* [56]	2009	Ethanol (99%) + Paclitaxel	10	**10%** Acute pancreatitis (1)
Oh *et al.* [6]	2011	Ethanol (99%) + Paclitaxel	52	**10%** ever without infection (1); Mild abdominal pain (1); Mild pancreatitis (1); Splenic vein obliteration (1); Peri-cystic spillage (1)
Choi *et al.*	2017	Ethanol (99%) + Paclitaxel	164	**18%** Fever without infection (1); Peri-cystic spillage (1); Intra-cystic bleeding (1); Acute pancreatitis (6); Pseudocyst formation (2); Abscess formation (2); Portal vein thrombosis (1); Splenic vein obliteration (1); MPD stricture (1)
Kim *et al.* [57]	2017	Ethanol (100%) or Ethanol (100%) + Paclitaxel	8 (Ethanol) 28 (Ethanol + Paclitaxel)	**16%** Mild abdominal pain (4); Acute pancreatitis (4); Intra-cystic bleeding (1)
Moyer *et al.* [58]	2017	Ethanol (80%) + Paclitaxel + Gemcitabine	18	**20%** Mild abdominal pain (4); Acute pancreatitis (1)
		Saline + Paclitaxel + Gemcitabine	21	None

Radiofrequency ablation

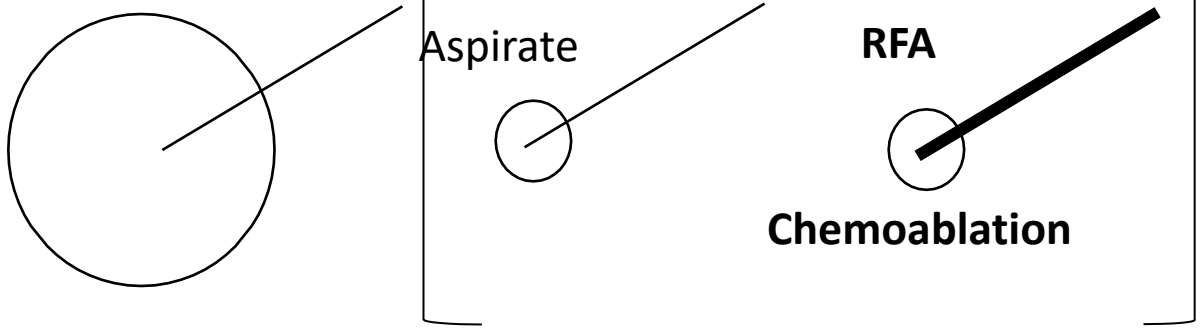
	PNETs		Cysts		PDAC	
	N	AEs	N	AEs	N	AEs
Barthet Endo 2019	14	2 (infected necrosis*; PD stricture)	16	1 (infected necrosis)*		
Song Endo18	8	2(mild pain)	2	0		
Crino SF JGLD 2016					8	3 (mild abdo pain)
Scopellti Surg Endo 2018					10	(4 - asymptomatic peripancreatic fluid
Oleinikov JCEM 2019	18	2 (mild pancreatitis)				
De Nucci EIO	10	2 (mild pain)				
Oh D Endos Ultras 2022					22 (107)	3 mild pain 1 peritonitis
Oh D Endoscopy21			13	1 mild pain		
TOTAL	**50**	**5%grade III/IV 12% mild**	**31**	**3%gradeIII/IV 3% mild**	**40**	**3% gradeIII/IV 20% mild**

EUS RFA procedure





EUS Guided Cysts Ablation



Favor RFA
Complex
Septated
Mural nodules

1-2 X

CT/MRI in 6 months

Greater then ? 50% reduction and no WFs

↓

SOC surveillance

Less then ? 50% reduction and no WFs

↓

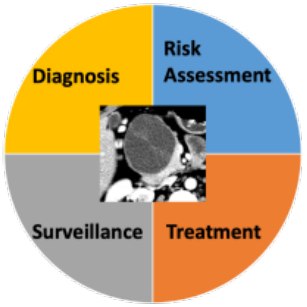
Repeat EUS RFA

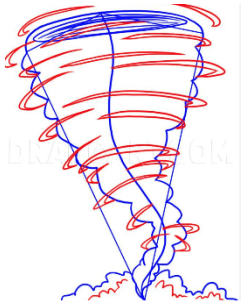
High to intermediate risk patients

Comorbidities that may preclude surgery

Favor Chemo
Large
Unilocular
MCN>IPMN

Conclusion





- Diagnostic uncertainty about cyst type
  - EUS FNA based cyst fluid analysis has very high accuracy for identification of cyst type
- Cyst progression on cross sectional imaging
  - EUS based imaging and FNA with molecular diagnostic can help with decision making
  - Mural nodules →use contrast enhanced EUS
  - Enlarging cysts → use molecular diagnostics
- Ask about family history and do germline testing in all with first degree relative
- No definitive impact of high risk status on current cyst surveillance
- Consider cyst ablation in select patients with higher risk cysts