Cystic pancreatic lesions

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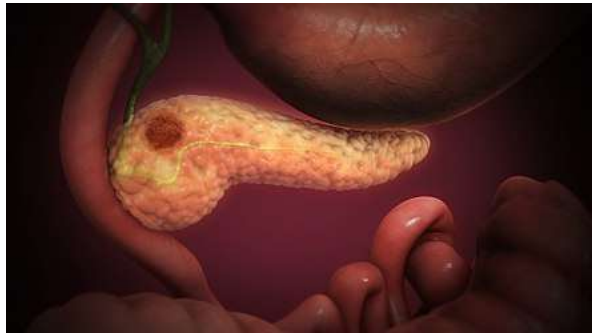
Agenda

- What are pancreatic cysts
- How we work-up pancreatic cysts
- How to identify those who need surgery?
  - European Consensus Guidelines
- EUS in Pancreatic cysts
- EUS guided biopsy in pancreatic cyst
  - Cyst biopsy study, HUS

Pancreatic cysts

Pseudocyst



Intrapancreatic Mucinous Neoplasm

Mucinous cystic Neoplasm

Serous cystic lesion (SCN)

Other cysts

Size
Growth rate
Intramural nodule
Symptoms
PD diameter

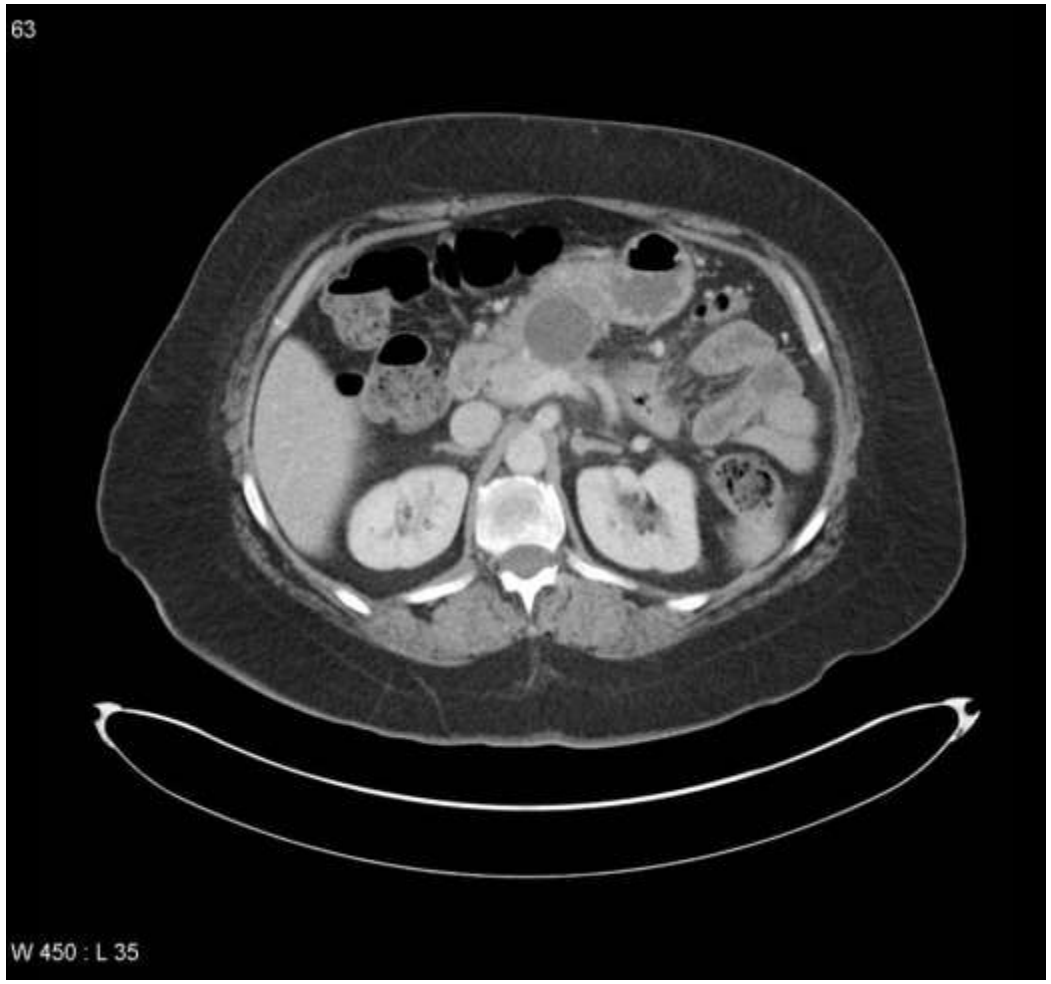
What is the prevalence of pancreatic cysts?

- AIM: Determine the prevalence of findings of unsuspected pancreatic cysts on MDCT in a population of adult imaged for disease unrelated to the pancreas.
- MATERIALS AND METHODS: Contrast-enhanced MDCT scans of the abdomen were reviewed from 2,832 consecutive examinations to identify pancreatic cysts.
- RESULTS: A total of 73 patients had pancreatic cysts, representing a prevalence of 2.6 per 100 patients (95% CI, 2.0-3.2).
- Strong correlation between pancreatic cysts and age, with no cysts identified among patients under 40 years and a prevalence of 8.7 per 100 (95% CI, 4.6-12.9) in individuals from 80 to 89 years.

Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al.
Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol. 2008;191(3):802-7.

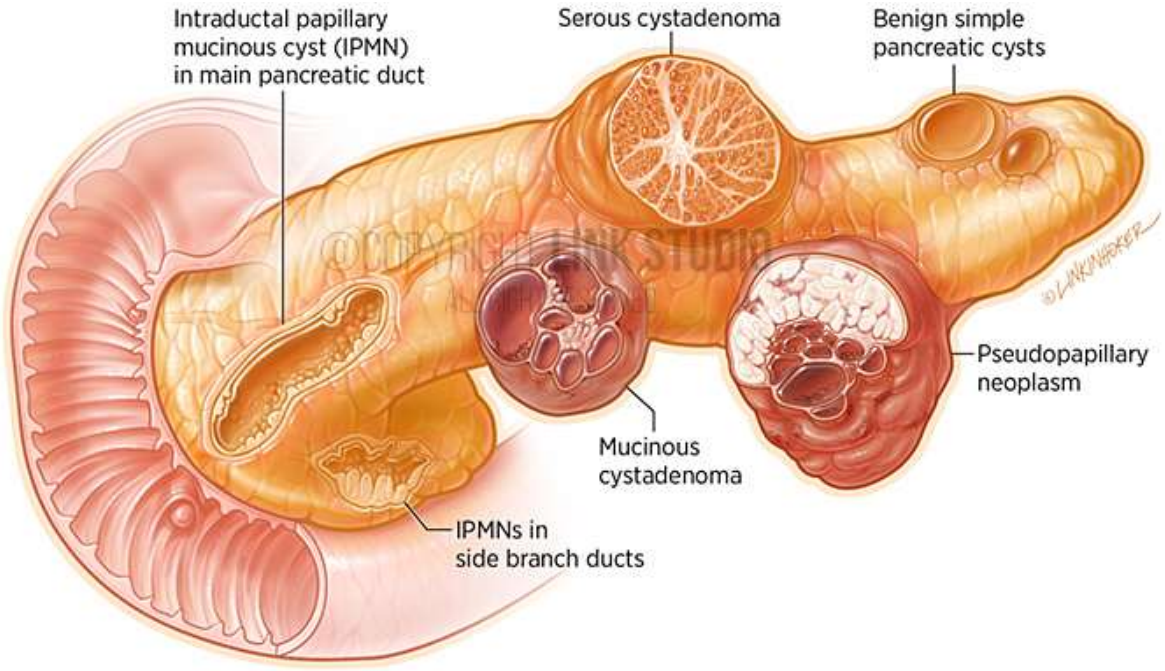
Some math

- Appoximately 5 mill. Abdominal scannings annually (USA)
- 2.6% = 130 000 Incidentally discovered pancreatic cysts annually



Pancreatic pseudocyst
Case courtesy of Dr Natalie Yang, Radiopaedia.org, rID: 6746

Types of pancreatic cysts



Pancreatic cystic neoplasm	Malignant potential
Mucinous	
Intraductal papillary mucinous neoplasms (IPMN)	Low to high
Mucinous cystic neoplasms (MCN)	Moderate to high
Nonmucinous	
Serous cystic neoplasms (SCN)	None
Solid pseudopapillary neoplasms (SPN)	Moderate
Cystic pancreatic endocrine neoplasms (CPEN)	Moderate

Table 1 | Types of pancreatic cystic neoplasm and their malignant potential.

JAMA

Emerging methods for pancreatic cyst characterisation

- Recent methods:
  - Cyst fluid genetic markers (*KRAS, GNAS*, *VHL*, *TP53, PIK3CA,* and *PTEN*.)
    - CEA + KRAS/GNAS indicate mucinous cyst
    - VHL indicate: Serous cystic adenoma
    - TP53, PIK3CA and PTEN more advanced neoplastic cyst (1)
  - Endoscopic needle based confocal laser microscopy (nCLE)
    - INSPECT study: Low sensistivity 59%, low NPV: 50% (2)
  - Contrast enhanced EUS (CE-EUS)
    - With contrast enhancing effect in the cystic wall, septae or nodule indicating cystic neoplasias. Identified 56 of 125 neoplastic cysts. 4 of 69 non-neoplastic cysts (3)
    - Differentiate depris from vascularized tissue in the cyst wall

1. Singhi AD, Zeh HJ, Brand RE, et al. American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinicopathologic study of 225 patients with supporting molecular data. Gastrointest Endosc. 2016;83(6):1107-17 e2
2.Konda VJ, Meining A, Jamil LH et al. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. Endoscopy. 2013;45(12):1006-13
3. Hocke M, Cui XW, Domagk D, Ignee A, Dietrich CF. Pancreatic cystic lesions: The value of contrast-enhanced endoscopic ultrasound to influence the clinical pathway. Endosc Ultrasound. 2014;3(2):123-30.

The challenge

”Differentiating benign from premalignant or premalignant from malignant cysts is complicated by the large overlap in morphologic, chemical, and clinical characteristics.

Imaging alone is insufficient to accurately characterize these lesions.

Cyst aspiration and fluid analysis has therefore become a major research focus through which our ability to characterize pancreatic cystic lesions has improved, although accuracy is often still lacking….”

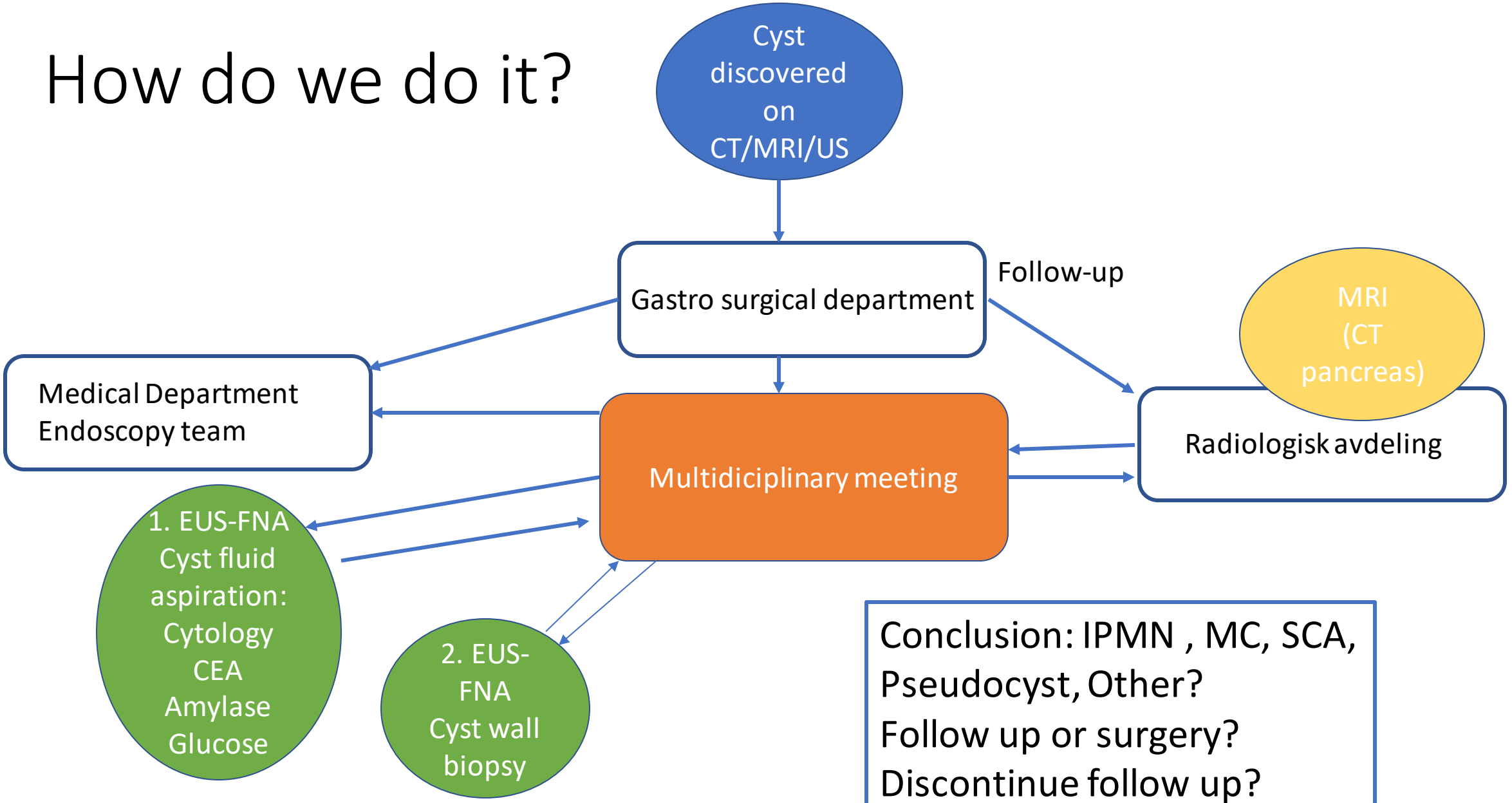
Samarasena J. B. Nakai Y., Chang, K. J.Gastrointestinal endoscopy clinics of North America. Gastrointest Endosc Clin N Am. 2012 Apr;22(2):169-85

2004: EUS morphology, cytology and tumor markers

- Aim: to determine the most accurate test for differentiating mucinous from non-mucinous cystic lesions.
- Methods: EUS FNA cyst fluid aspiration. The results of EUS imaging, cyst fluid cytology, and cyst fluid tumor markers (CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3)
- n=341, 112 undervent surgery, 29 of 52 mucinous cysts were malignant (56%) but only 8.5% of all cysts included
- Accuracy of:
  - CEA, cut-off: 192ng/l (88 of 111, 79%)
  - EUS morphology (57 of 112, 51%)
  - cytology (64 of 109, 59%) ($P < 0.05$)
- *There was no combination of tests that provided greater accuracy than CEA alone*

Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al.
Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126(5):1330-6.

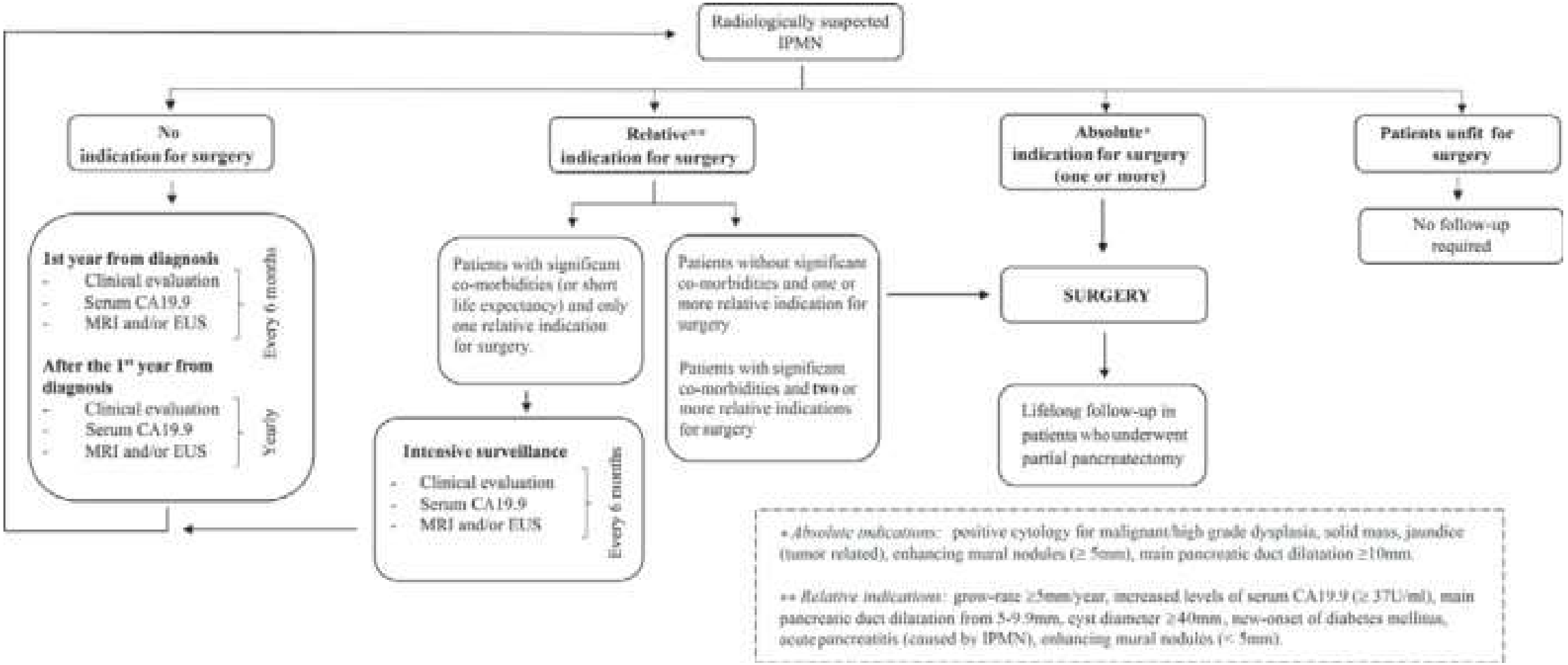
How do we do it?



Pancreatic cystic neoplasms and risk of malignancy

Subtype	Risk of malignancy, %
Non-mucinous	
Serous cystic neoplasm	–
Solid pseudopapillary neoplasm	10–16% [8, 9]
Mucinous	
Mucinous cystic neoplasm	10–15 [2]
Intraductal papillary mucinous neoplasm	33–60 [2]
Side-branch	25.5 [2]
Main-duct	33–60 [2]
Mixed-type	33–60 [2]

Scholten L, van Huijgevoort NCM, van Hooft JE, Besselink MG, Del Chiaro M. Pancreatic Cystic Neoplasms: Different Types, Different Management, New Guidelines. *Visc Med*. 2018;34(3):173-177. doi:10.1159/000489641



European Study., Group on Cystic Tumours of the Pancreas European evidence-based guidelines on pancreatic cystic neoplasms. *Gut.* 2018;67:789–804.

European evidence-based guidelines on pancreatic cystic neoplasms

Year	Evidence-based	Type of PCN	Absolute indications for surgery	Relative indication for surgery	Total pancreatectomy
2018	yes	IPMN MCN SCN PNEN SPN rare cysts	• jaundice • positive cytology (malignancy/HGD) • solid mass • pancreatic duct≥ 10 mm • enhancing mural nodules≥ 5 mm	• Growth rate≥ 5 mm/year • increased serum CA 19-9 (>37 U/ml) • pancreatic duct dilatation 5–9.9 mm • IPMN and MCN≥ 40 mm • new-onset diabetes mellitus • acute pancreatitis (caused by IPMN) • enhancing mural nodule < 5 mm	• pancreatic duct dilation + mural nodule • to consider in patients with an increased risk for malignancy

European Study., Group on Cystic Tumours of the Pancreas European evidence-based guidelines on pancreatic cystic neoplasms. *Gut.* 2018;67:789–804.

European conseus guidelines 2018: Indications for surgery in IPMN

- Relative indications for surgery in IPMN include a main pancreatic duct (MPD) diameter between 5 and 9.9 mm or a cyst diameter ≥40 mm.
- Absolute indications for surgery in IPMN, due to the high-risk of malignant transformation, include jaundice, an enhancing mural nodule >5 mm, and MPD diameter >10 mm.
- Lifelong follow-up of IPMN is recommended in patients who are fit for surgery.

European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018 May;67(5):789-804

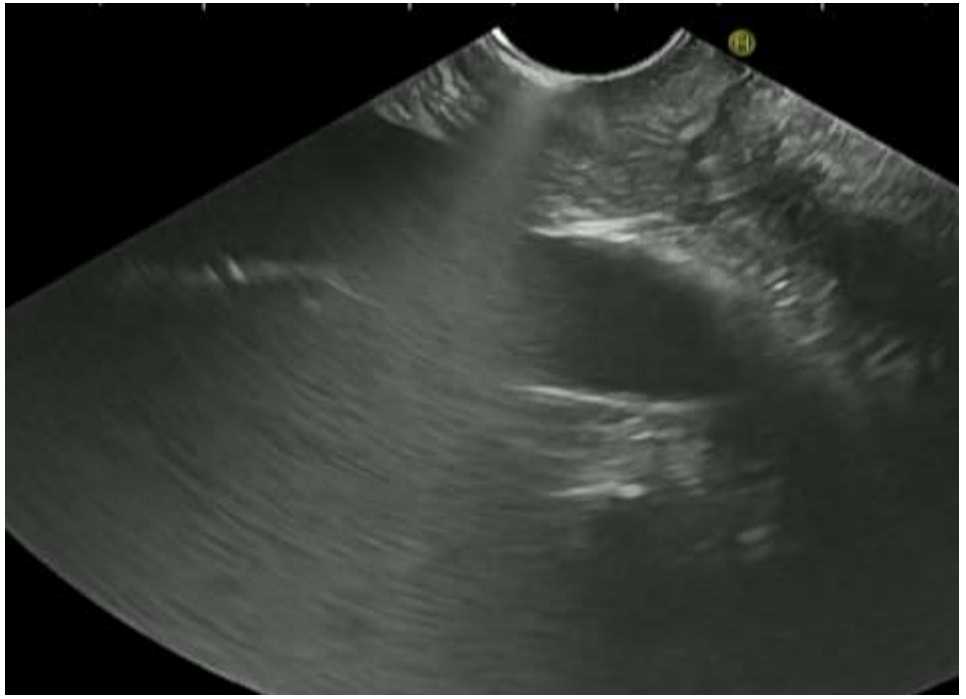
Why EUS?

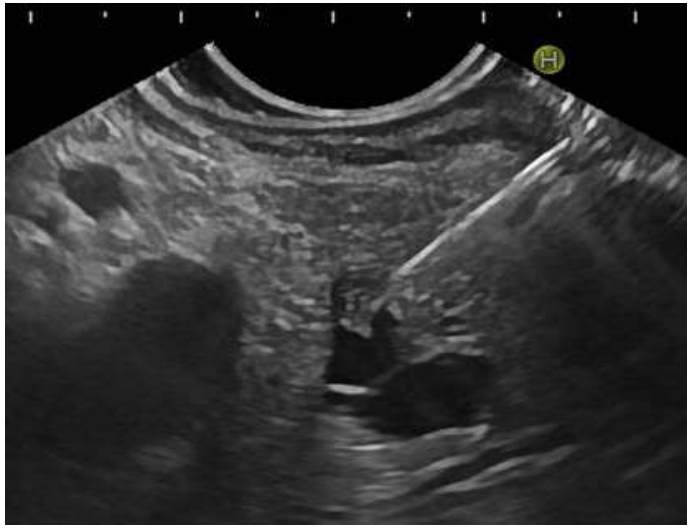
- Close to the pancreas
- Cover the whole pancreas
- Real-time resolution

- Evaluate the parenchyma and ducts; pancreatitis
- Cyst morphology
- Anatomical relations to vessels & ducts

- FNA/FNB
- Cytology, tumor markers, molecular markers, KRAS-mutation

- Intervention & therapy





When to do EUS?

- Unclear CT and MRI findings
- Growth in cyst size
- EUS results (cyst fluid analysis or biopsy) are needed to choose clinical management
- Before surgery – resectability?
- Not if diagnosis is already firm

- EUS features may give more clues –”Worrysome features”
- EUS-FNA: Amylase or lipase, CEA, glucose and cytology
- Fluid cytology increases the accuracy for differentiating
  - mucinous from nonmucinous
  - benign from malignant PCN
- Cytology is highly specific but insensitive

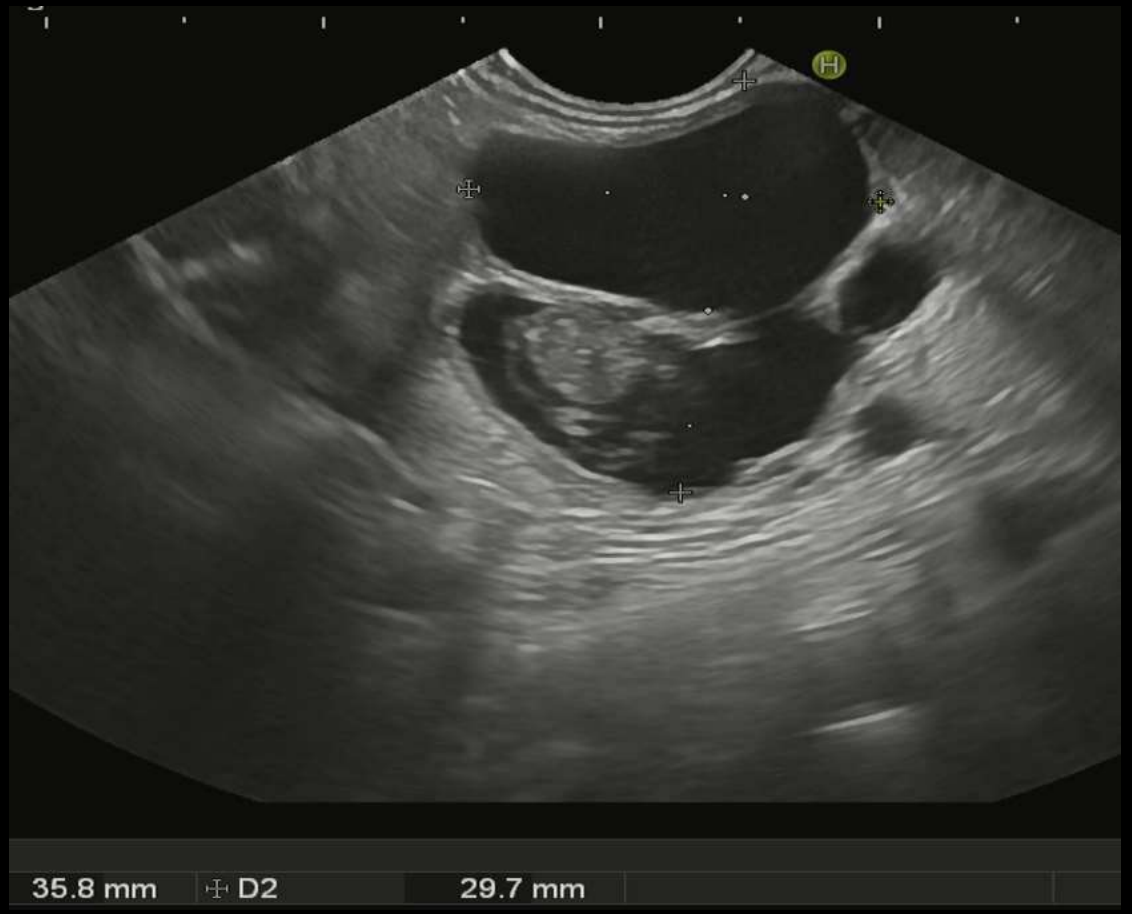
Biochemistry: CEA and glucose

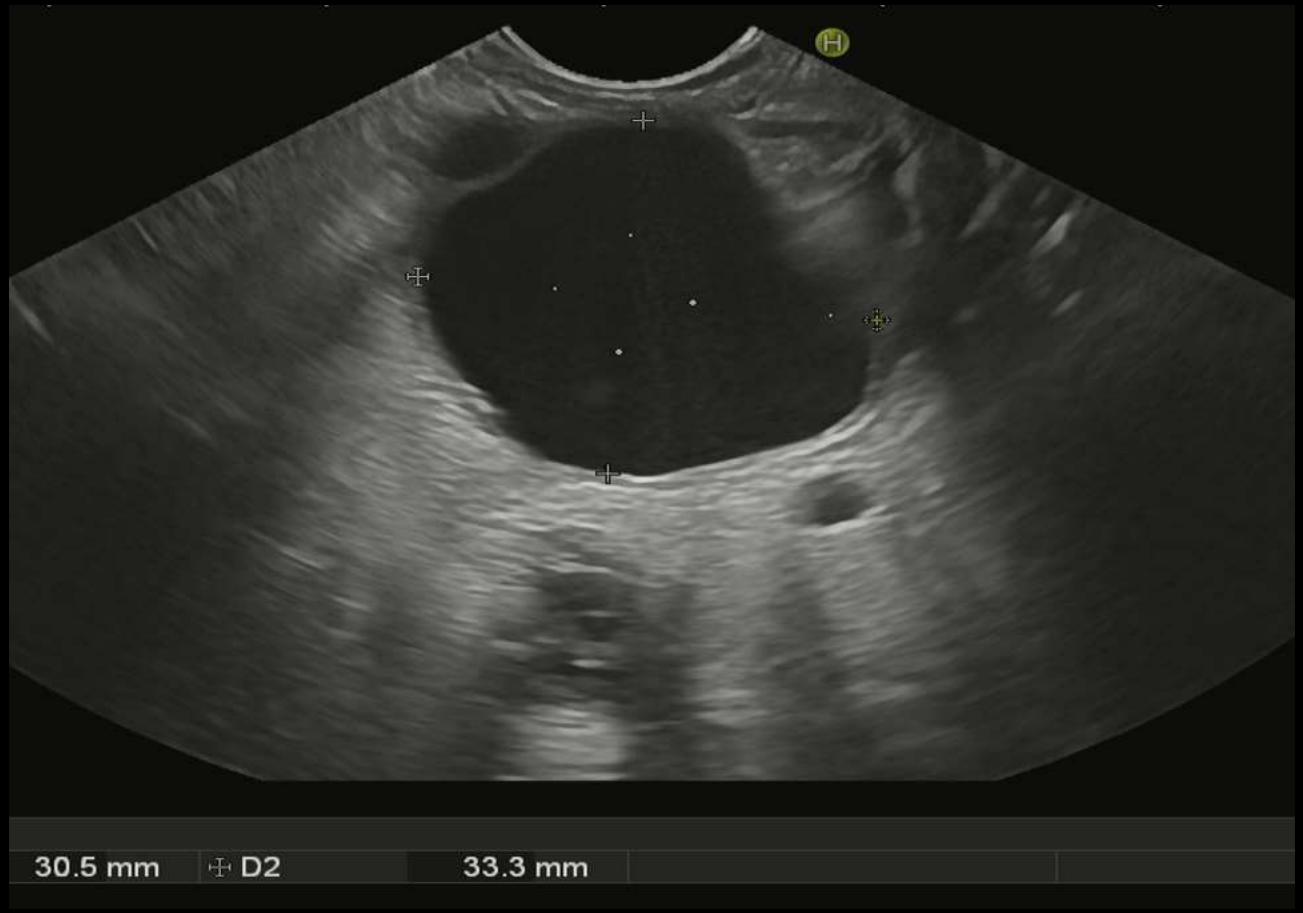
- CEA and amylase/lipase helps to differentiate mucinous from non-mucinous PCN (CEA>250)
- Accuracy is too low to establish the specific PCN type (79%)
- CEA
  - Cannot differentiate MCN from IPMN
  - nor benign mucinous cysts from those with high-grade dysplasia or cancer
- Co-analysis of CEA and glucose to distinguish mucinous from non-mucinous neoplastic PCLs had sensitivity = 87.8%, specificity = 93.3%, and diagnostic accuracy = 89.3%.

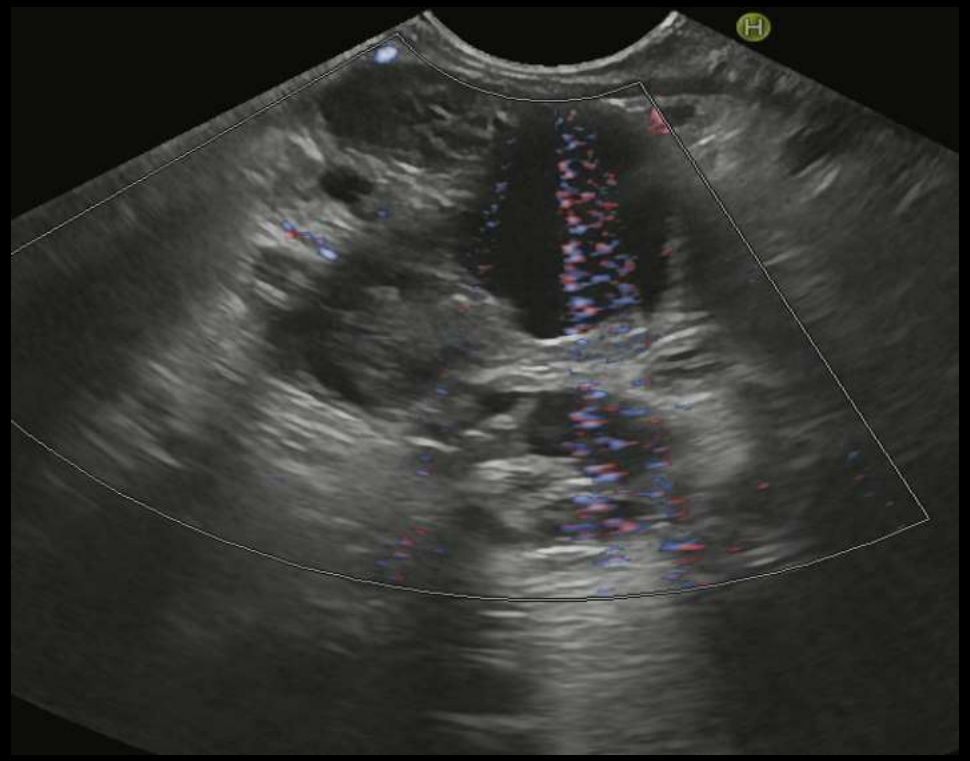
Barutcuoglu B et al.Co-analysis of pancreatic cyst fluid carcinoembryonic antigen and glucose with novel cut-off levels better distinguishes between mucinous and non-mucinous neoplastic pancreatic cystic lesions.
Ann Clin Biochem. 2022 Mar;59(2):125-133.

IMPN

- Connected with the PD
- High Amylase (>250U/L) & CEA (>192ng/ml)
- Low cyst fluid glucose < 2 mmol/L
- Classification:
  - Main Duct
  - Side branch
  - Mixed type
- Histology: Gastric-, intestinal-, biliarypancreatic type + dysplasia
- Adenoma-Carcinoma sequence
- Mutation in K-Ras 90%


35.8 mm
D2
29.7 mm

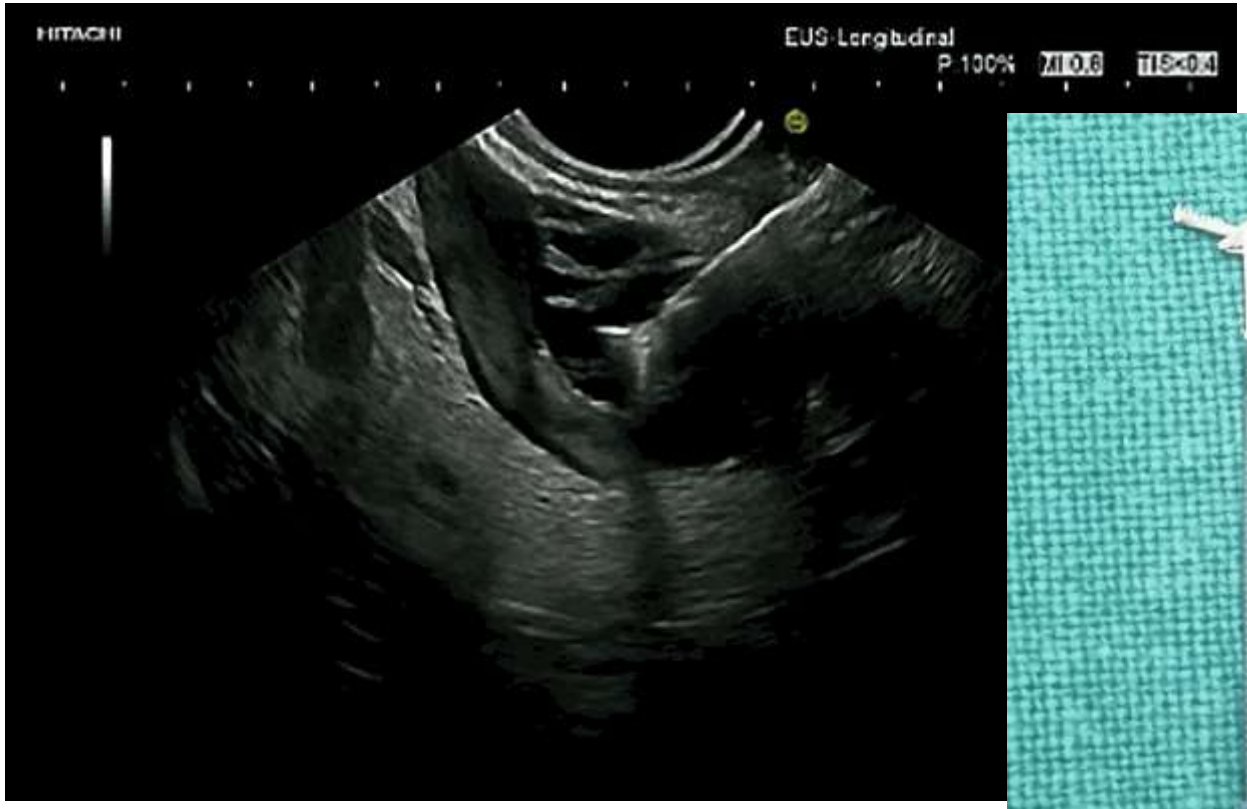

30.5 mm
D2
33.3 mm



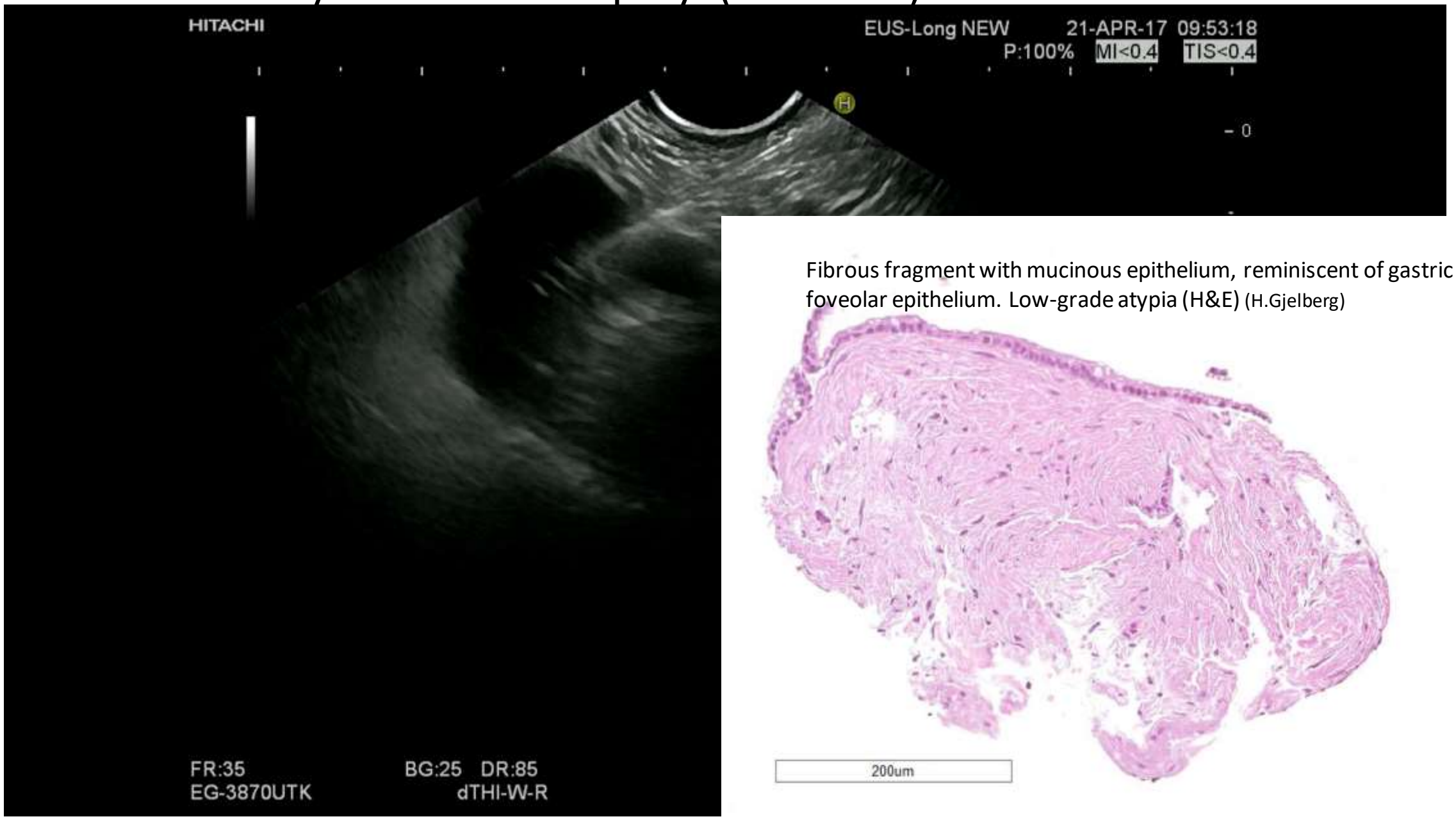
EUS guided endocystic biopsy

Watch the video
of the tissue sampling
By scanning the QR
code

- The microforceps is imaged in open position inside a septated cyst close to the portal vein.
- A micro biopsy was taken and provided enough tissue to establish the diagnosis: *Mucinous epithelium, IPMN, No cytogenic stroma observed*

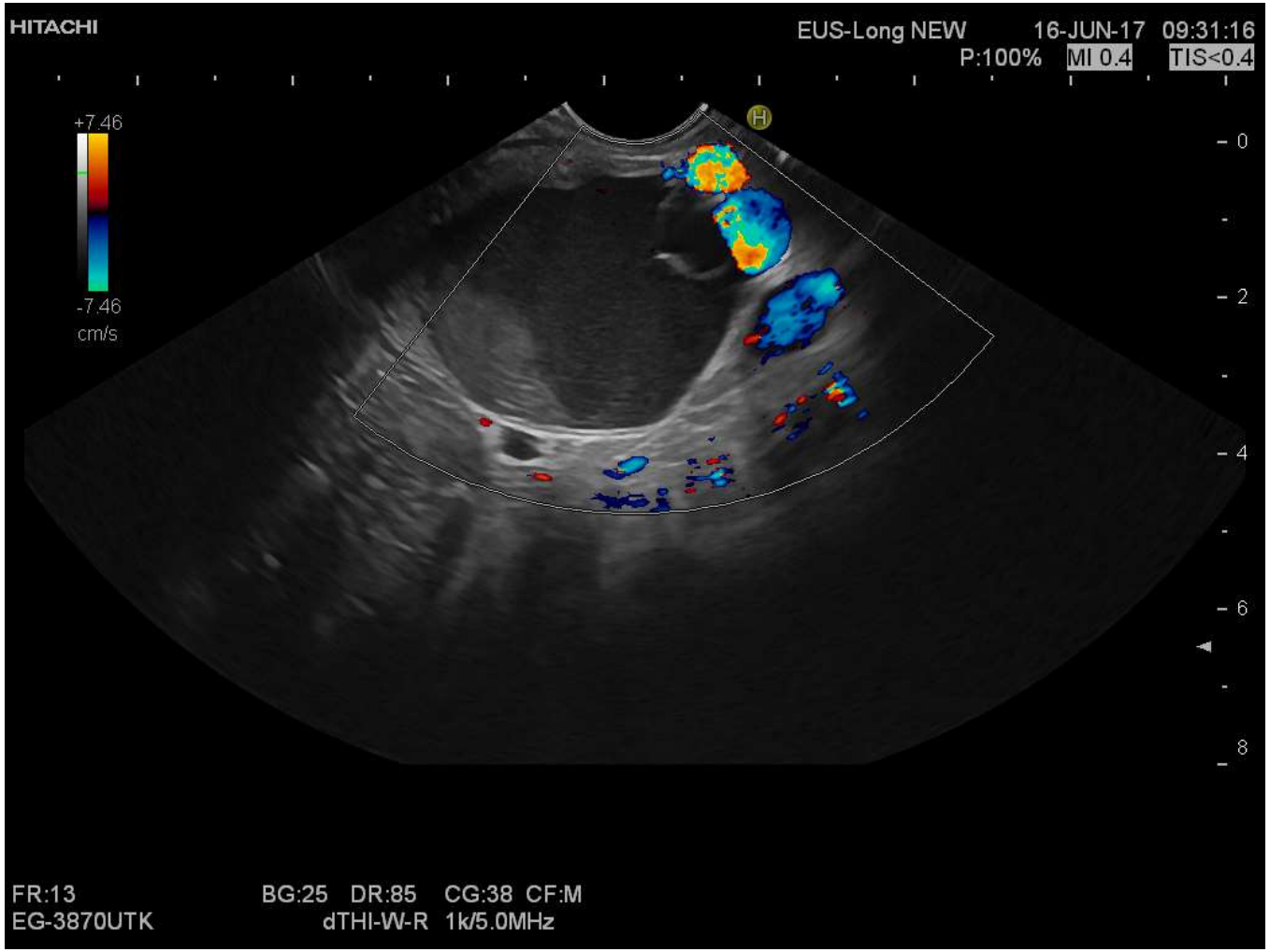


Video of cyst wall biopsy (case 6)



Fibrous fragment with mucinous epithelium, reminiscent of gastric foveolar epithelium. Low-grade atypia (H&E) (H.Gjelberg)

Case 12: 31.5x 43.5 mm cyst in the Pancreatic tail. A cyst-in-cyst configuration on the right and hyperechoic cyst fluid on the left. Colour Doppler confirmed large vessel close to the cyst wall



Small fragment of cellular stroma and mucinous epithelium with low-grade dysplasia (H&E) (H.Gjelberg)

Immunolabeling for estrogen receptor (brown color = positive cells). Concluding with Mucinous cystic neoplasia (confirmed after surgery) (H. Gjelberg)

EUS guided microbiopsies of pancreatic cysts(n=29)

Summarized results		Comment
Age (median)	68 years (33-77)	Study protocol: 18-80 years
Sex	F: 12 M: 17	N=29
Cyst size (mean)	32 x 24	33 x 25 mm
Symptomatic	7	Cyst related: 4/29, non.cyst related: 3/29
Procedure planned	34	Based on CT or MRI imaging
Not included/biopsy not performed	5	1: Ongoing double anti-platelet therapy, 1: Solid lesions on EUS, 1: unable to visualize needle tip in cyst, age >80, cyst size < 1.6 cm
Included patients	29	
Repeat procedure	1	Non-diagnostic sample in first biopsy
Procedures performed	30	
Histological representative biopsy	23/29	Diagnoses: IPMN: 14, IPMN with carcinoma: 1, pseudocyst: 5, SCA: 4, MCN: 1, cystic NET: 1, Benign non-mucinous cyst: 3
Histological non- representative biopsy	6/29	Cytology diagnostic sample: 5/29
Adverse event	5/29	Post procedure pancreatitis

Results commented

- Diagnostic biopsy results were obtained in 23/29 (79.3%) of the cases, whereas cytology was diagnostic in only 6/29 (20.7%).
- In three of the cases (5/27) post-procedure pancreatitis occurred and had to be treated over 4-11 days of hospitalisation. All of them were treated conservatively with fluids, analgesics and antibiotics.
- 2/29 patients underwent surgery and postoperative histology confirmed the histology obtained by EUS microbiopsy MCN, low grade dysplasia and cystic NET.
- One patient had inoperable cystadenocarcinoma. The other patients are currently under follow-up.

Conclusion:

- EUS guided micro-biopsies of cystic pancreatic lesions is feasible and increases diagnostic performance significantly
- In micro-biopsies, epithelium subtype and stroma was obtained and allowed grading of dysplasia and immunohistochemistry
- Cyst aetiology was established in 24 of 27 patients by Histology (23) or cytology (1) 82.8%.
- The method is efficient, but in a multi modal EUS setting, including contrast and multiple sampling, there is a risk for post procedure pancreatitis that must be considered (18.5%).

Summary pancreatic cysts

- Pancreatic cysts are common, prevalence 2.6% increasing with age
- The large majority will not develop malignancy
- Mucinous cysts (IPMN and MCA) have malignancy potential (10-60%)
- Worrisome features:
  - Size >40mm
  - PD diameter >9.9 mm
  - Intracystic nodules >4.9mm
  - Growth rate >5 mm/year
- EUS cyst fluid analysis: CEA, glu, amylase + cyt
  - EUS guided biopsy increases cyst etiology significantly and adds to confidence and risk stratification.