Cystic Pancreatic Neoplasms

Dott. Alberto Fantin

Gastroenterologia
Azienda Ospedaliera-Università di Padova

Ferrara, 13/04/18

Cystic Pancreatic Neoplasms (CPNs)

➢ CPNs have been increasingly identified over the past two decades due to the widespread use of high-resolution non-invasive abdominal imaging

➢ CPNs are mostly detected incidentally

➢ Prevalence ranges from 2.6% to 19.6% and increases with age

➢ CPNs characterization and management is controversial because of a significant overlap in the morphology of benign and premalignant lesions

➢ Natural history is still unclear

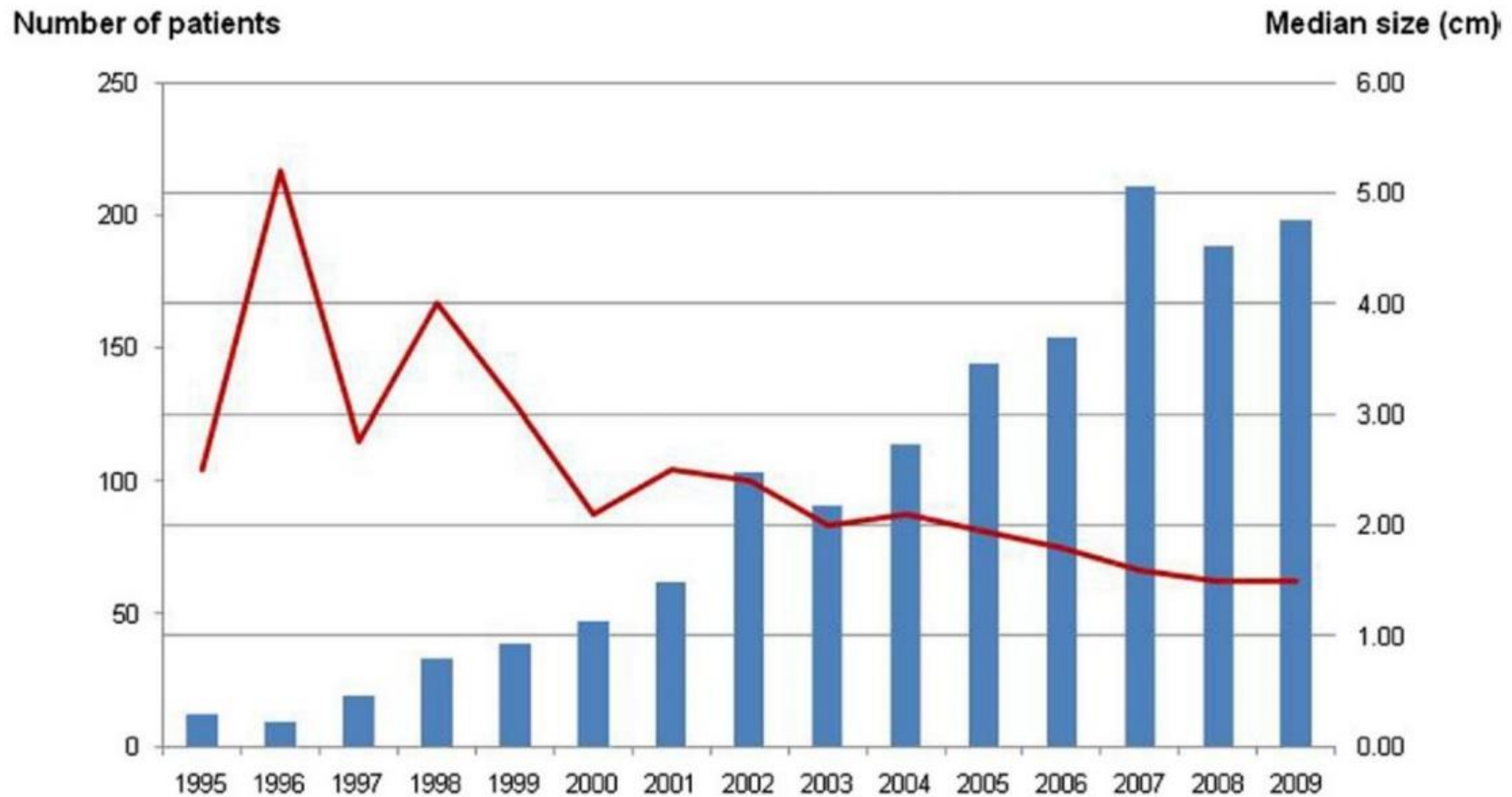Italian guidelines, DLD 2014

Background

Figure 1. The number of patients evaluated each year for a cystic lesion of the pancreas (blue bars) and the median size (red line) of the lesion at initial visit (1995 to 2010, N = 1,424).

EDITORIAL

Get Ready to Meet the Growing Demand From Patients With Pancreatic Cysts

The number of patients with a diagnosis of a pancreatic cyst is rising. Recent data suggest the prevalence of pancreatic cystic lesions in the general population is approximately 2%–3%.[1,2] Incidentally discovered cysts also are being detected at increased frequency within specific populations of patients. For example, the prevalence of pancreatic cysts in liver transplant recipients was noted at 60% in an Italian cohort of 47 patients.[3] In asymptomatic patients undergoing magnetic resonance imaging (MRI)–magnetic resonance cholangiopancreatography for various indications, the prevalence of cystic pancreatic lesions reached higher than 40%.[4] In 2016, very few clinicians

newer versions of imaging hardware and software were associated with a significant increase in cyst detection. The prevalence climbed as high as 56% in a newer version of the hardware (Skyra), compared with only 23% prevalence in an older version of the imaging hardware (Sonata). In addition, prevalence increased with older age, diabetes, and the presence of non-pancreatic malignancies. Moris et al[7] concluded that the increase in pancreatic cyst prevalence is a result of better diagnostic imaging techniques with the newer versions of MRI machines. They considered the finding of an incidental pancreatic cyst to be a "secondary effect" of newer technology, rather than a true increase in disease prevalence. The study did not stratify pancreatic cysts according to size. Therefore, it is not clear whether the increase in prevalence would hold true for cysts larger than 2 cm, because these cysts presumably would be easily detected on older versions of MRI

WHO classification of cystic pancreatic tumors, 2010

Epithelial tumours
Benign
Acinar cell cystadenoma
Serous cystadenoma

Premalignant lesions

- **IPMNs**
- **MCNs**
- **SCNs**
- **Pseudopapillary neoplasms**

90%af all pancreatic cystic tumors

Solid-pseudopapillary neoplasm

Neuroendocrine neoplasms with cystic degeneration

Mesenchymal tumours
Lymphangioma, NOS

Secondary tumours with cystic degeneration

Serous cystadenoma

Benign lesion
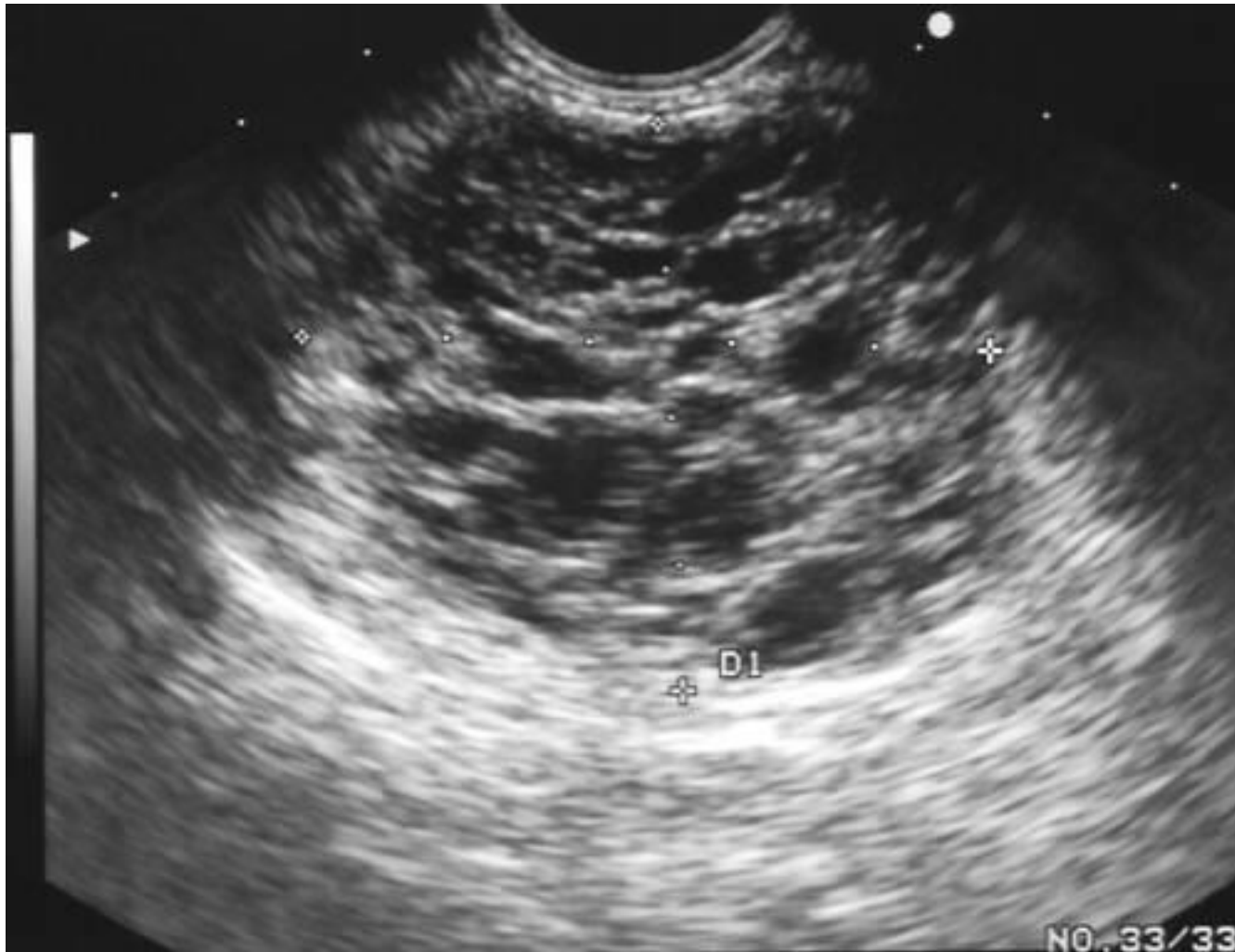
Unknown prevalence

Sex ratio M/F: 1/9

Incidentally discovery

Diagnosis "easy" by imaging procedures

No surgical resection recommended

EUS serous cystoadenoma

Serous cystic neoplasm

Serous cystic neoplasms are characterized by:

Easy radiological diagnosis (if typical features are present)
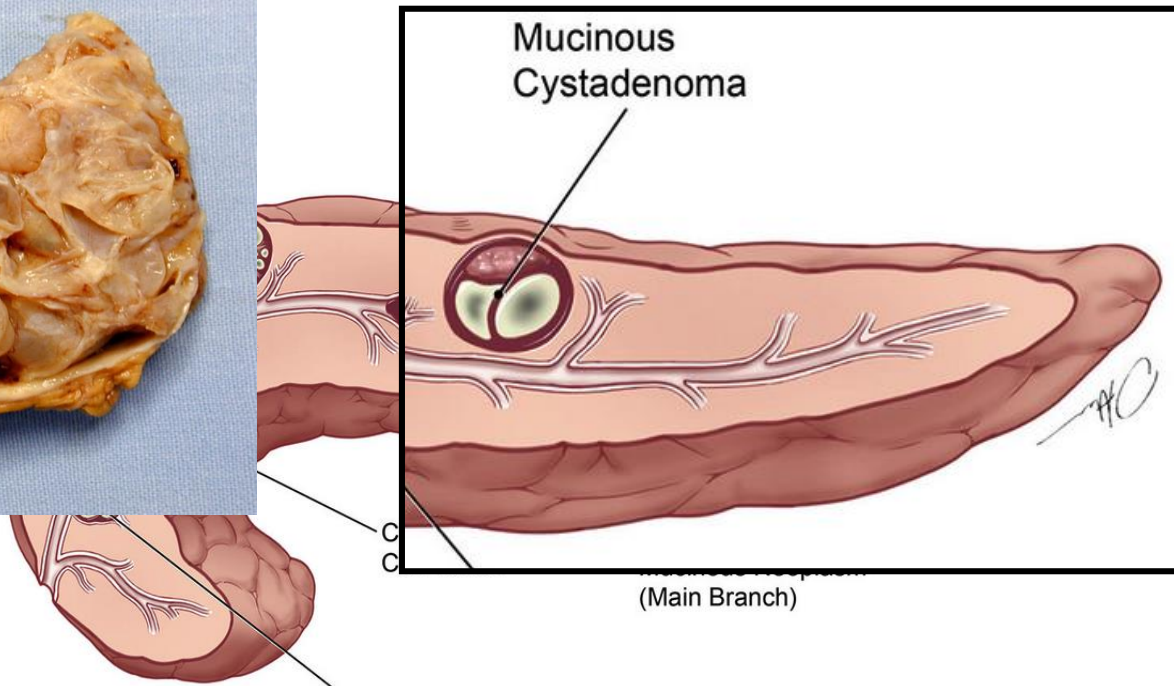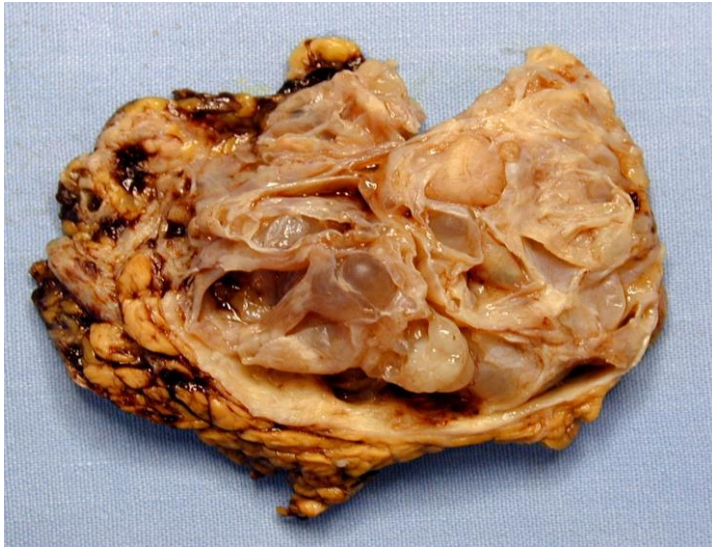
Benign biological behaviour

Extremely slow growth

OBSERVATION

REGARDLESS OF THE DIAMETER AT DIAGNOSIS

Mucinous cystic neoplasm

- Exclusively in women
- Preferentially located in the body-tail
- No communication with ductal system
- Epithelial cells producing mucin and supported by an ovarian-type stroma
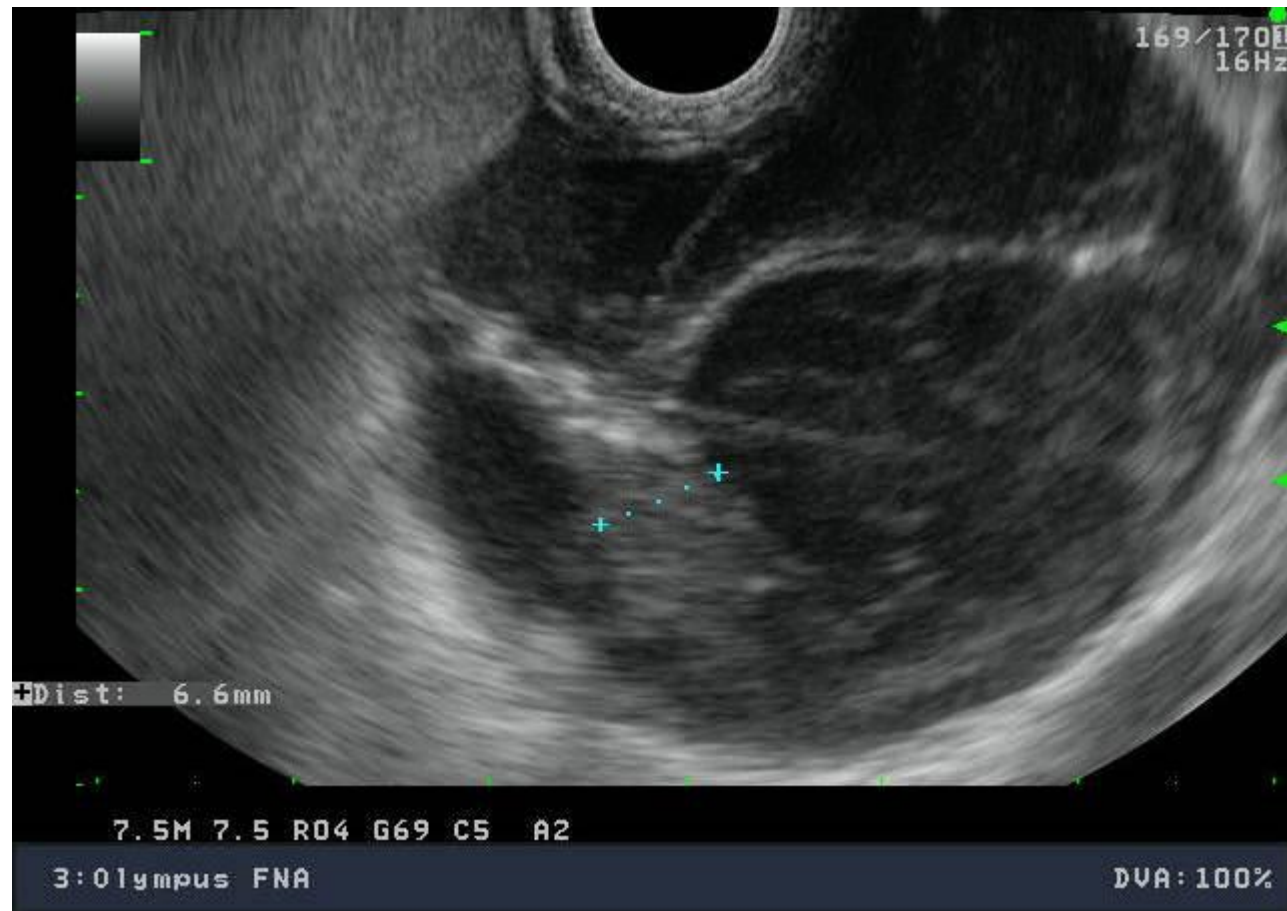
Mucinous Cystoadenoma

Precancerous lesion

No communication with MD

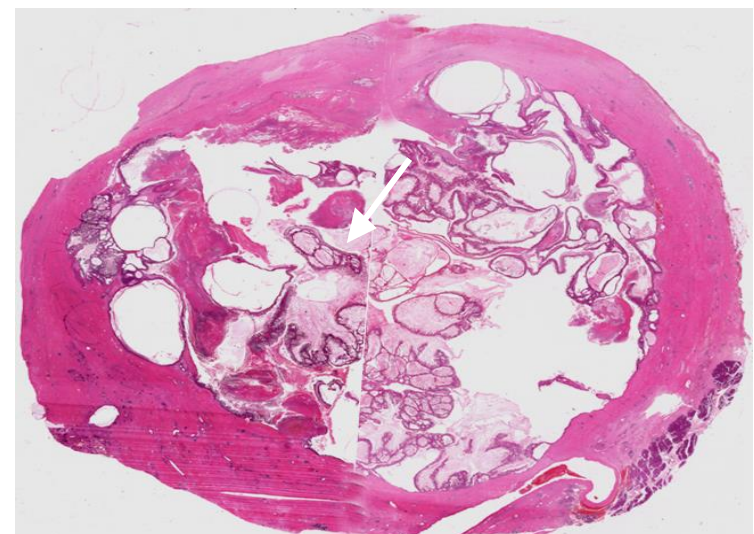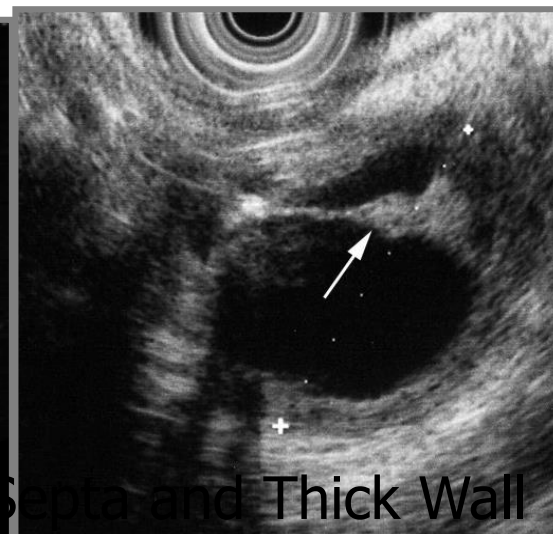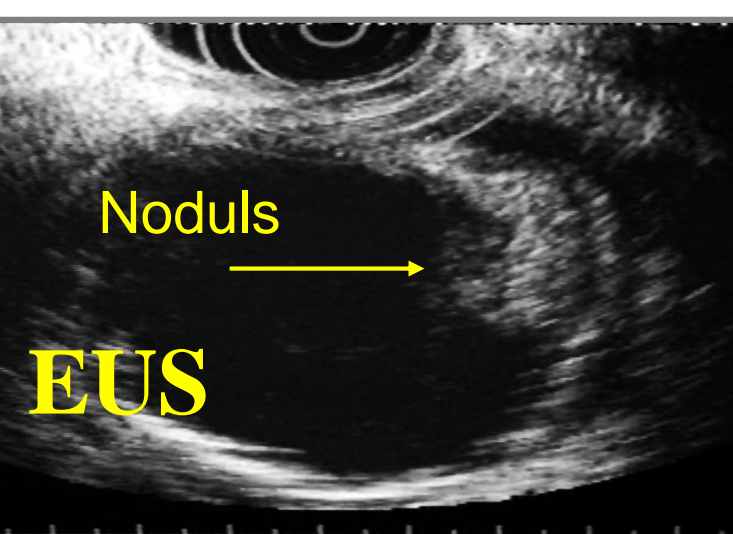Unknown prevalence
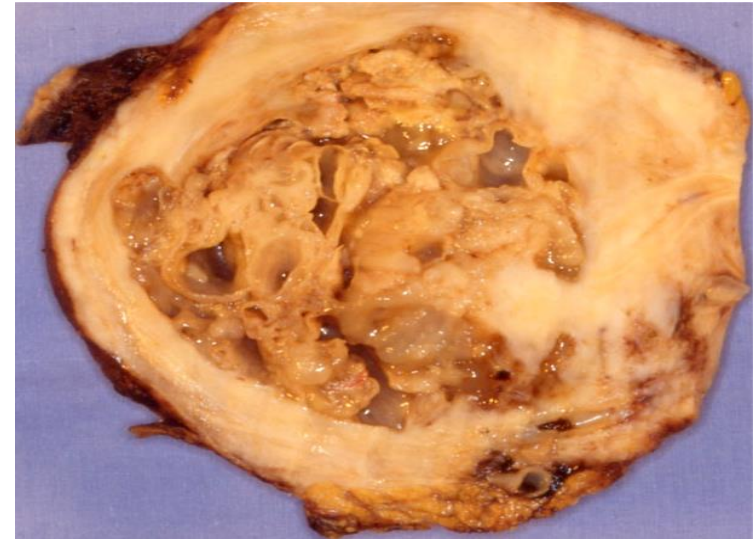
Incidentally discovery

Sex ratio M/F: 1/20

Surgical resection recommended (follow-up for lesions < 4 cm without worrisomes features ?)

EUS mucinous cystoadenoma

Signs of suspicious degeneration

TC

nodules

egg calcifications

EUS

Noduls

Septa and Thick Wall
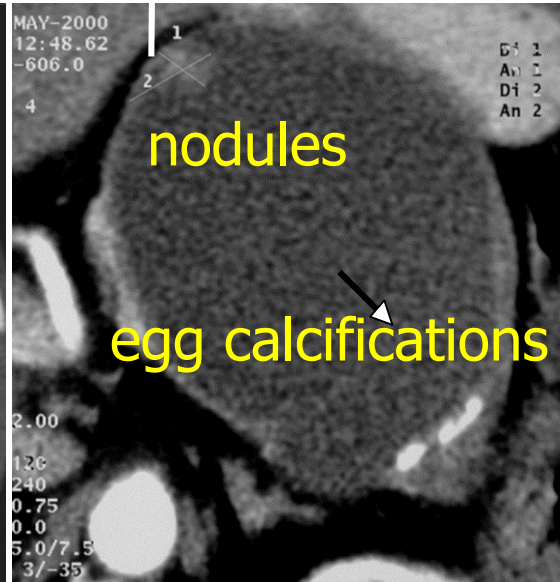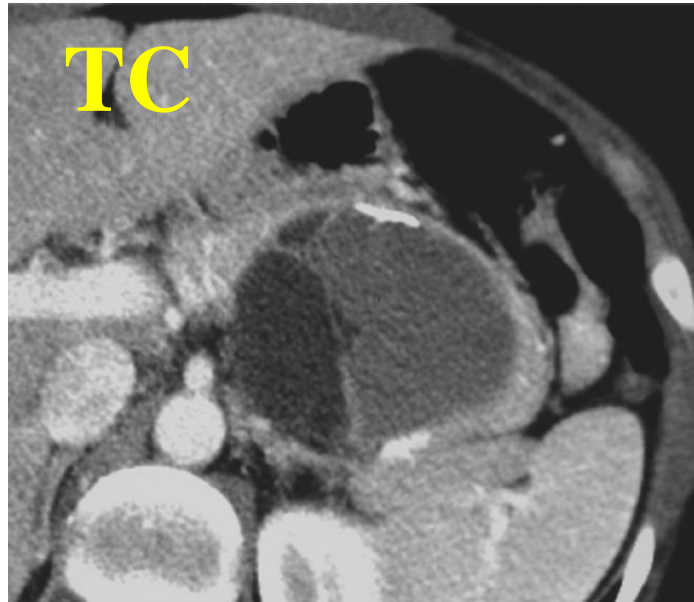
Solid pseudo-papillary tumor

Rare tumor

Young age

Malignant potential

Unknown prevalence

Sex ratio M/F: 1/10

Incidentally discovery

Surgical resection recommended

EUS solid pseudopapillary tumor
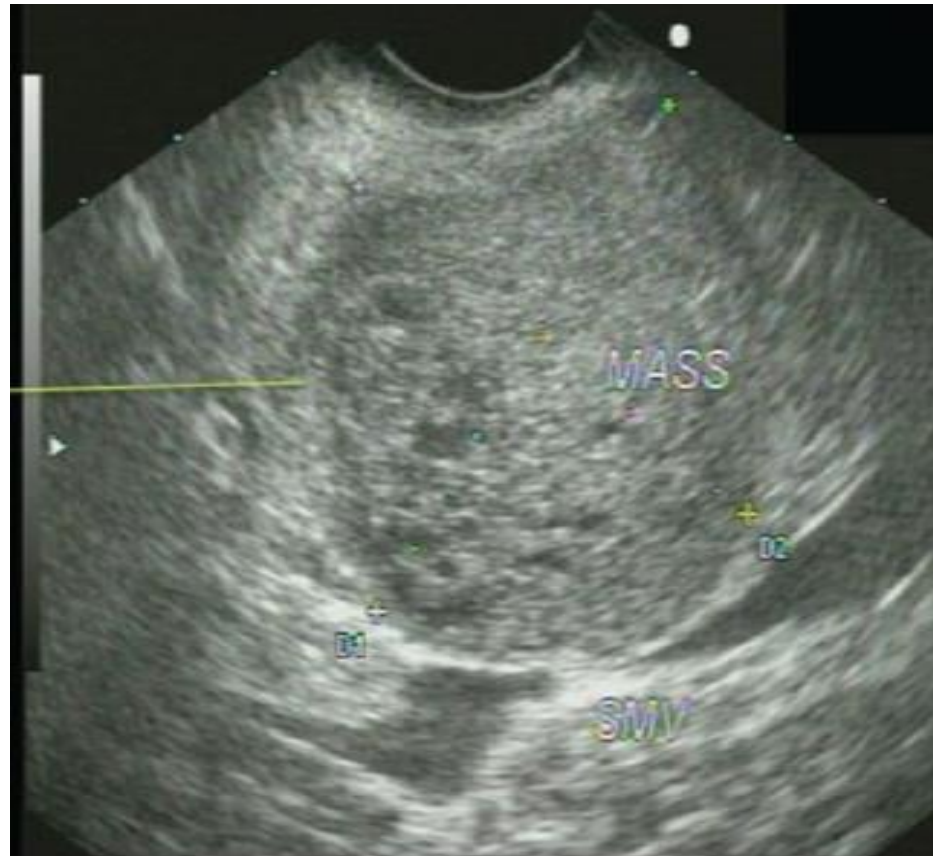
IPMN

Precancerous lesion

Involving MPD or BD

Probably the more prevalent cystic pancreatic lesion

Unknow prevalence: 10-15 %

Incidentally discovery

5 year-risk of invasive carcinoma

-    BD-IPMN 3-18 %

-    MD-IPMN: 45-62%

-    Many issues regarding the management

EUS IPMN-BD

MD-IPMN

MAIN DUCT IPMN
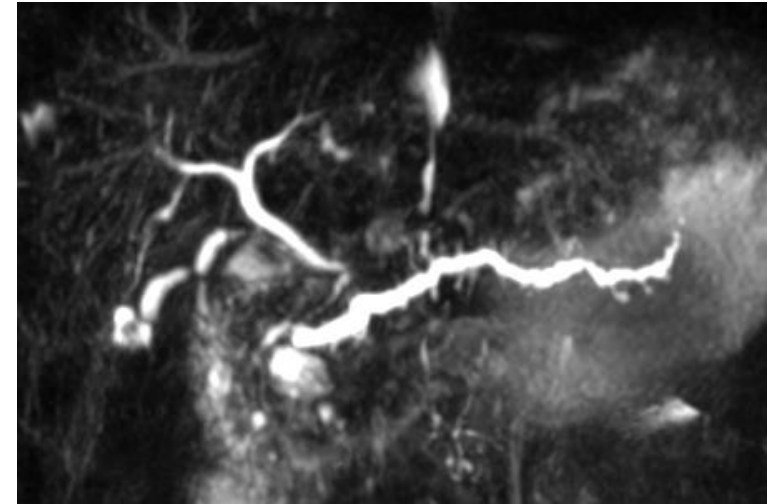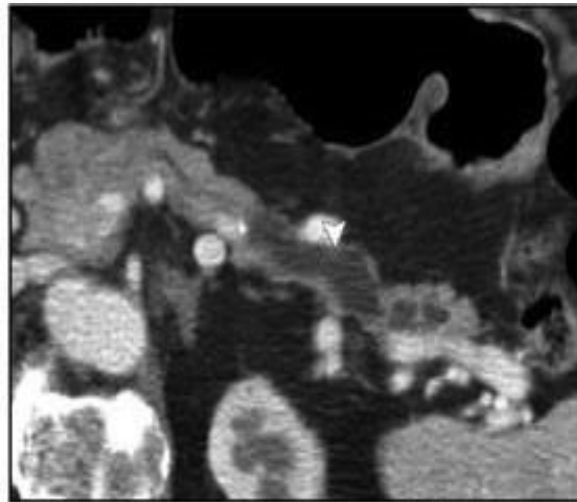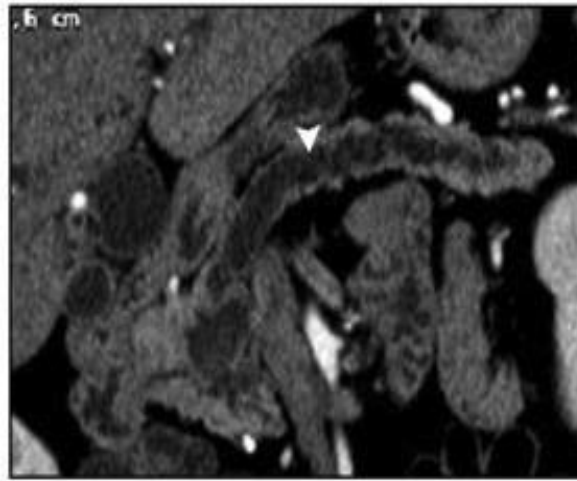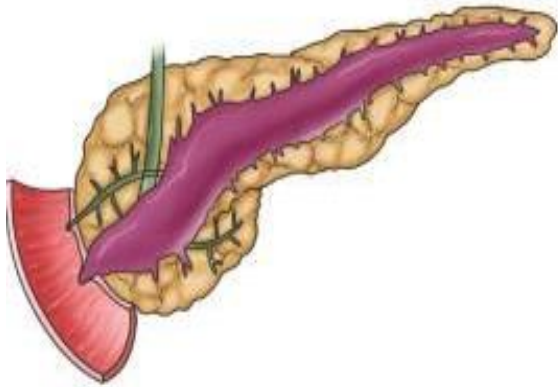
MIXED-IPMN

MIXED-TYPE IPMN
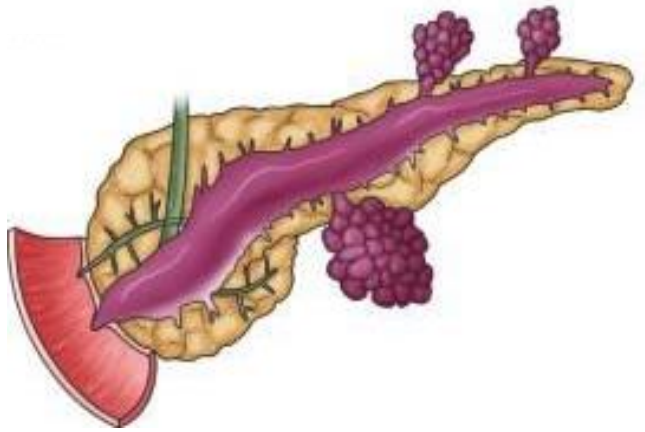
CYSTIC DILATATION OF SIDE BRANCHES OF THE DUCTAL SYSTEM >5 MM WHICH COMMUNICATE WITH A DILATED MPD
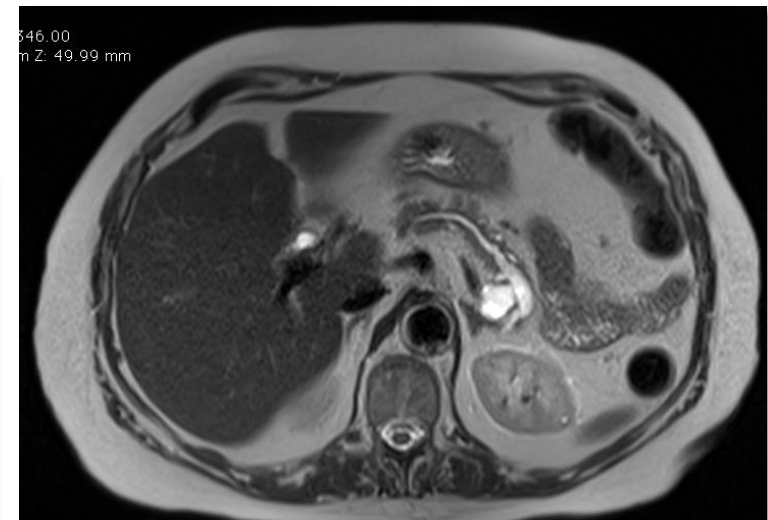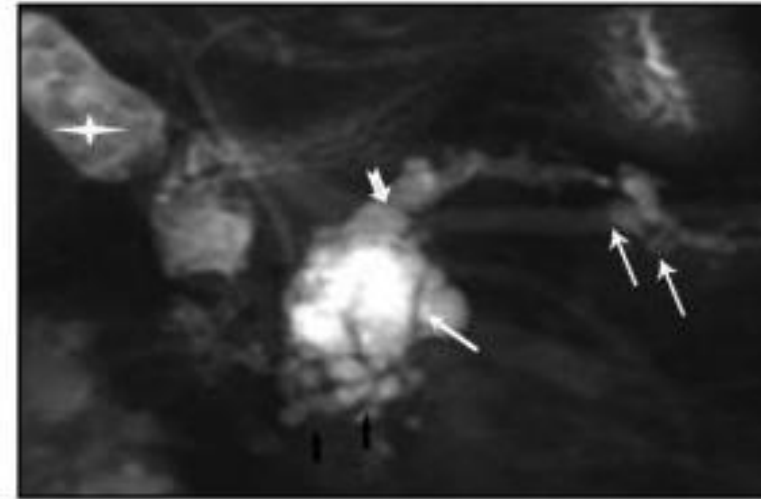
BD-IPMN

BRANCH DUCT IPMN
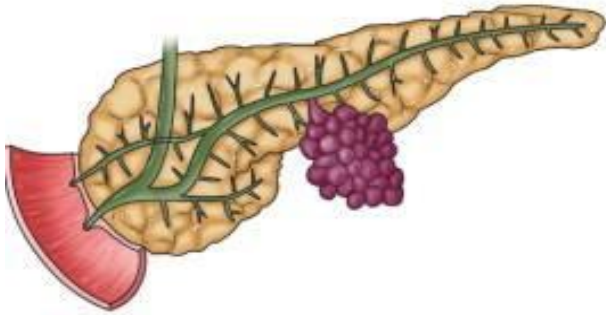
CYSTIC DILATATION OF SIDE BRANCHES OF THE DUCTAL SYSTEM >5 MM WHICH COMMUNICATE WITH A NON-DILATED MPD
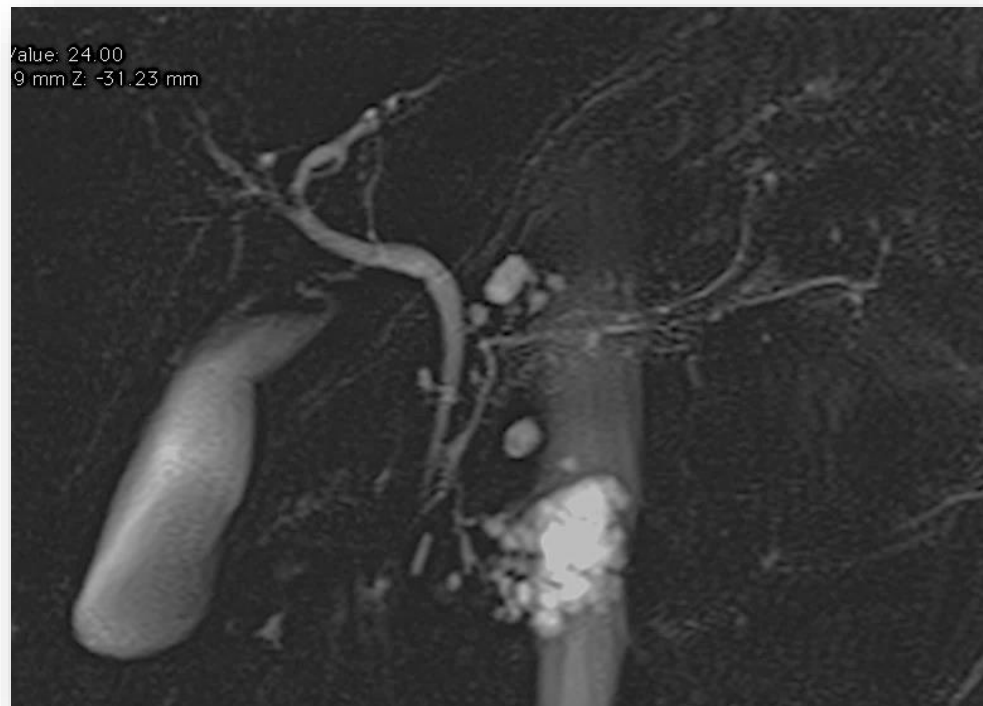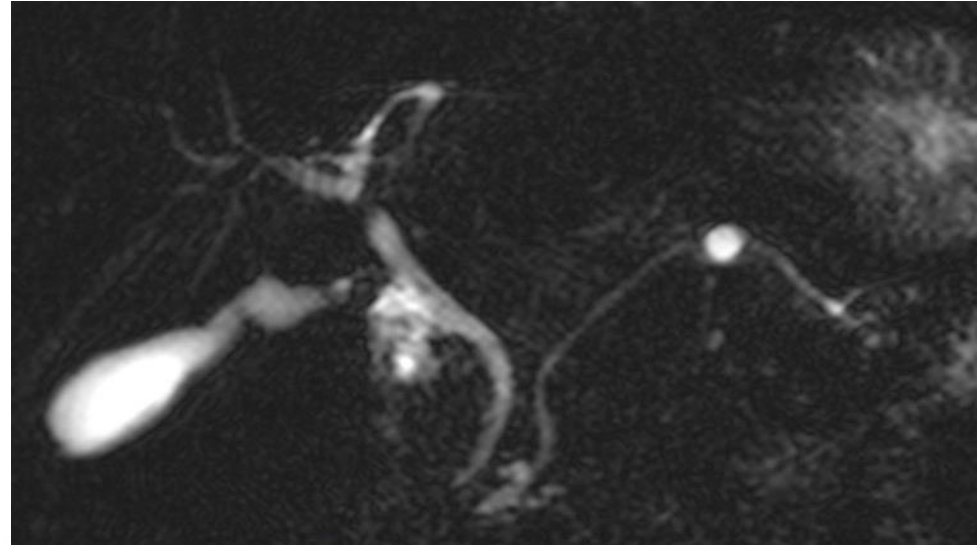
IPMN – Different Biology

DIFFERENT RISK PROFILES…

Levy et al. Clin Gastroenterol Hepatol 2006;4:460-468
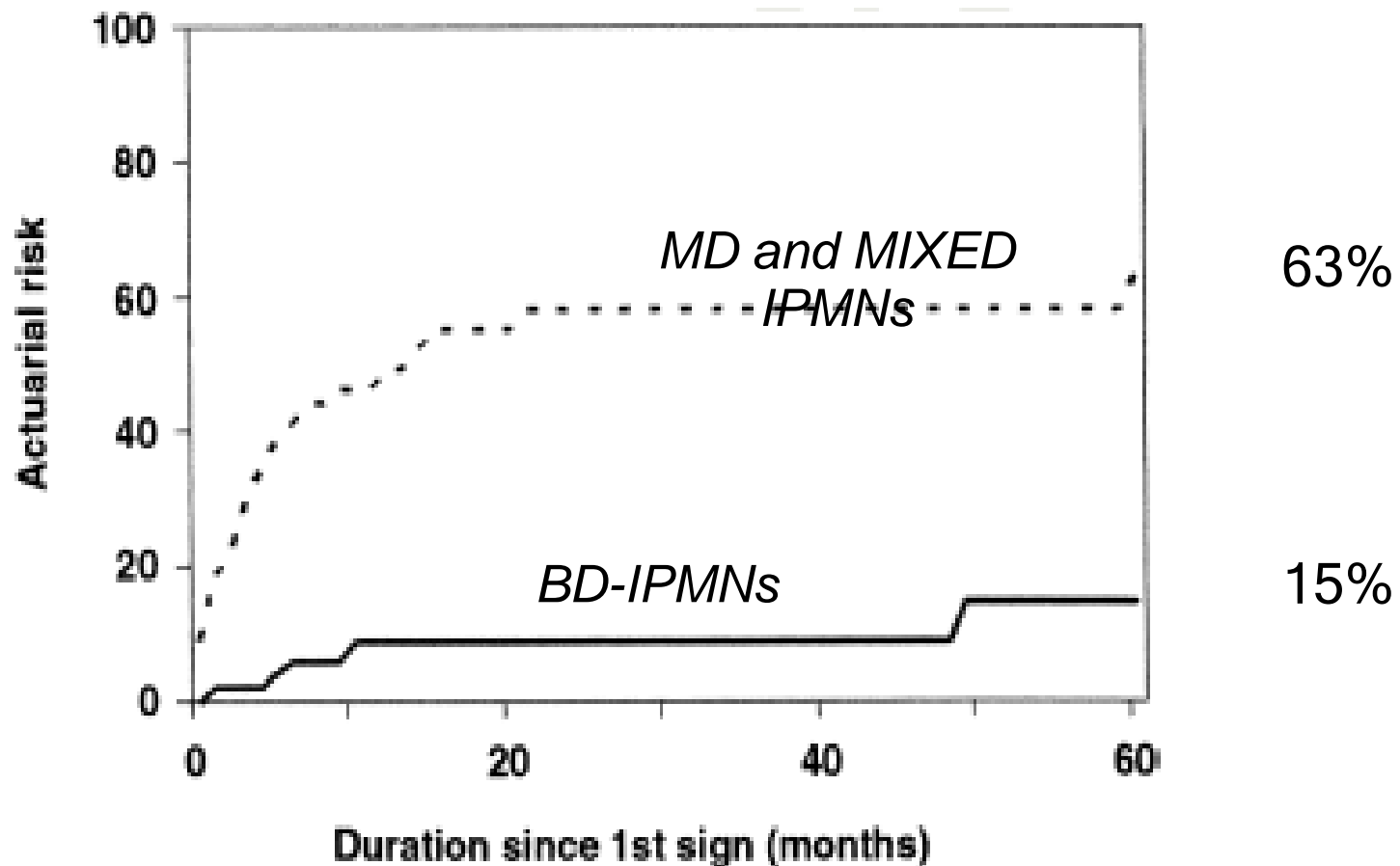
BD-IPMN – Suspect features

The elements considered to evaluate BD-IPMN today

- **Mural Nodule**

- MPD dilation

- Size (>3cm)

- Increased wall thickness

Irie H et al., AJR 2000;
Fukukura Y et al., AJR 2000
Wakabayashi T et al., Pancreas 2001

…

BD-IPMN - Role of Mural Nodules

Imaging Features to Distinguish Malignant and Benign Branch-Duct Type Intraductal Papillary Mucinous Neoplasms of the Pancreas

A Meta-analysis

Kyung Won Kim, MD, PhD,*† Seong Ho Park, MD, PhD,* Junhee Pyo, MS,‡ Soon Ho Yoon, MD,§
Jae Ho Byun, MD,* Moon-Gyu Lee, MD,* Katherine M. Krajewski, MD,† and Nikhil H. Ramaiya, MD†

TABLE 2. Summary of the Meta-analytic Pooled Diagnostic Odds Ratios for the Imaging Findings

Imaging Findings (Cut-off)	No. Studies	No. Cases	Summary Estimate			$P^{\ddagger}$ for Reporting Bias		Trim-and-Fill Estimate	
			Pooled DOR (95% CI)	P for Heterogeneity*	I^2%†			No. Missing Studies	Adjusted Pooled DOR (95% CI)
Cyst size (4 cm)	4	176	2.3 (0.7–7.9)	0.17	39.6				
(3 cm)	15	963	2.3 (1.5–3.5)	0.14	29.2	0.18	0.29	2	2.1 (1.3–3.2)
(2 cm)	4	297	1.7 (0.7–4.1)	0.23	31.1				
Mural nodule	16	1112	6.0 (4.1–8.8)	0.21	21.1	0.18	0.37	2	5.5 (3.7–8.2)
MPDD (Overall)	10	561	3.4 (2.3–5.2)	0.43	1.4	0.79	0.43	2	3.2 (2.1–4.7)
(5 mm)	4	245	4.4 (2.4–8.1)	0.74	0.0				
(6 mm)	3	153	3.2 (1.5–7.1)	0.58	0.0				
(7 mm)	3	163	3.5 (0.9–14.0)	0.07	62.8				
Thick septum/wall	6	400	3.3 (1.5–6.9)	0.28	21.1	0.04	0.01	3	2.3 (0.9–5.5)
Multilocularity	5	287	0.9 (0.5–1.7)	0.89	0.0	0.62	0.56	0	0.9 (0.5–1.7)
Multiplicity	6	566	1.2 (0.7–2.0)	0.56	0.0	0.57	0.08	0	1.2 (0.7–2.0)

*P value by Cochran-Q method to test heterogeneity of the pooled data. Values <0.10 indicate substantial heterogeneity.
†I^2 is the Higgin index for heterogeneity and values greater than 50% indicate substantial heterogeneity.
‡P values are to test publication/reporting bias using the Begg test (left column) and the Egger's test (right column). $P < 0.1$ indicate significant bias.
MPDD indicates main pancreatic duct dilatation.

IAP Guidelines

Are any of the following high-risk stigmata of malignancy present?
i) obstructive jaundice in a patient with cystic lesion of the head of the pancreas, ii) enhancing mural nodule **> 5 mm**,
iii) main pancreatic duct >10 mm

Yes → No

Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

Masao Tanaka [a], Carlos Fernández-del Castillo [b], Terumi Kamisawa [c], Jin Young Jang [d]
Philippe Levy [e], Takao Ohtsuka [f], Roberto Salvia [g], Yasuhiro Shimizu [h], Minoru Tada [i]
Christopher [j]

[a] Department of Surgery, Shimonoseki City Hospital, Shimonoseki, Japan
[b] Pancreas and Biliary Surgery Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Gastroenterology, Komagome Metropolitan Hospital, Tokyo, Japan
[d] Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea
[e] Pôle des Maladies de l'Appareil Digestif, Service de Gastroentérologie-Pancréatologie, Hopital Beaujon, Clichy Cedex, France
[f] Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[g] Department of General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust, Verona, Italy
[h] Dept. of Gastroenterological Surgery, Aichi Cancer Center, Nagoya, Japan
[i] Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[j] Cameron Division of Surgical Oncology and The Sol Goldman Pancreatic Cancer Research Center, Department of Surgery, Johns Hopkins University, Baltimore, MD, USA

Consider surgery, if clinically appropriate

Are any of the following worrisome features present?
Clinical: Pancreatitis [a]
Imaging: i) cyst >3 cm, ii) **enhancing mural nodule < 5 mm**, iii) thickened/enhancing cyst walls, iv) main duct size 5-9 mm, v) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, vi) lymphadenopathy, vii) **increased serum level of CA19-9**, **viii) cyst growth rate > 5 mm/2 years**

If yes, perform endoscopic ultrasound

No

Are any of these features present?
i) Definite mural nodule (s) **> 5 mm** [b]
ii) Main duct features suspicious for involvement [c]
iii) Cytology: suspicious or positive for malignancy

No → What is the size of largest cyst?

Yes

Inconclusive

| <1 cm	1-2 cm	2-3 cm	>3 cm
CT/MRI in 6 months, then every 2 years if no change [d]	CT/MRI 6 months x 1 year yearly x 2 years, then lengthen interval up to 2 years if no change [d]	EUS in 3-6 months, then lengthen interval up to 1 year, alternating MRI with EUS as appropriate. [d] **Consider surgery in young, fit patients with need for prolonged surveillance**	Close surveillance alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients

IPMN's history - Guidelines
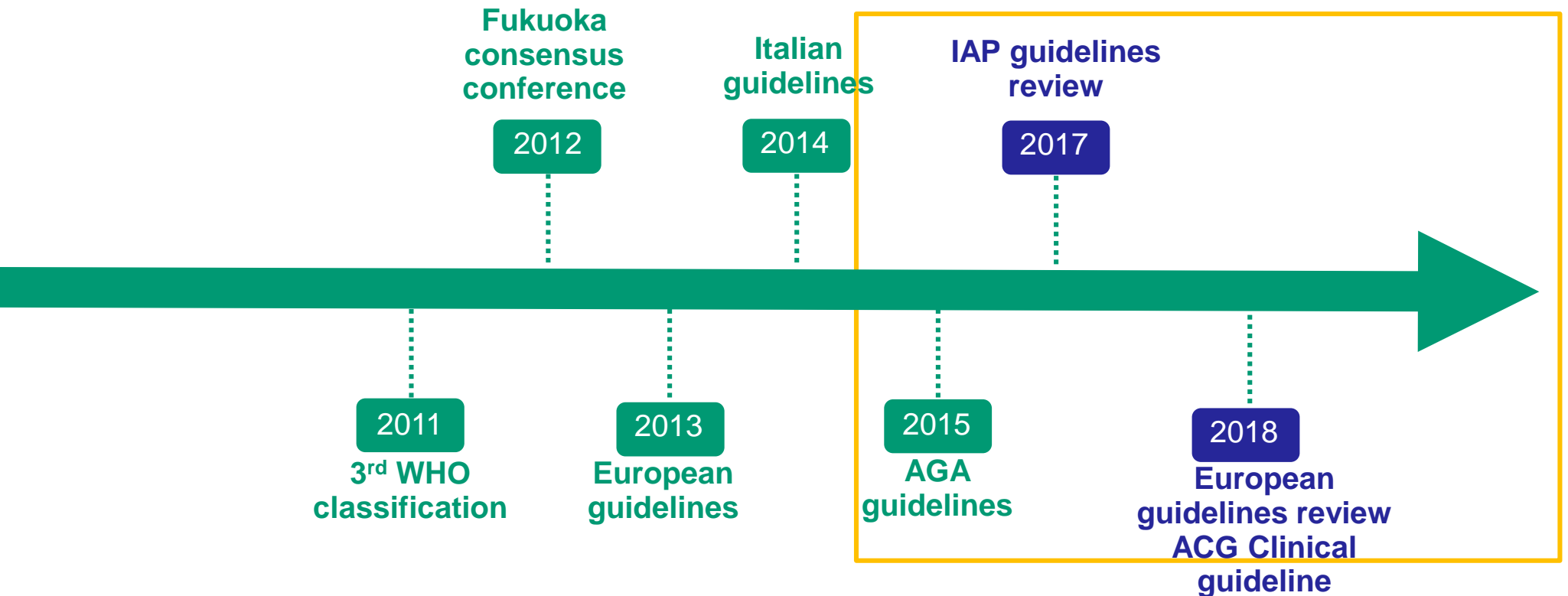
Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms

Italian Association of Hospital Gastroenterologists and Endoscopists, AIGO
Italian Association for the Study of the Pancreas, AISP

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Volkan Adsay[c], Suresh Chari[d], Massimo Falconi[e], Jin-Young Jang[f], Wataru Kimura[g], Philippe Levy[h], Martha Bishop Pitman[i], C. Max Schmidt[j], Michio Shimizu[k], Christopher L. Wolfgang[l], Koji Yamaguchi[m], Kenji Yamao[n]

European experts consensus statement on cystic tumours of the pancreas

Marco Del Chiaro[a,*], Caroline Verbeke[b], Roberto Salvia[c], Gunter Klöppel[d], Jens Werner[e], Colin McKay[f], Helmut Friess[g], Riccardo Manfredi[h], Eric Van Cutsem[i], Matthias Löhr[a], Ralf Segersvärd[a], the European Study Group on Cystic Tumours of the Pancreas

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee

Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Terumi Kamisawa[c], Jin Young Jang[d], Philippe Levy[e], Takao Ohtsuka[f], Roberto Salvia[g], Yasuhiro Shimizu[h], Minoru Tada[i], Christopher L. Wolfgang[j]

NEWS

European evidence-based guidelines on pancreatic cystic neoplasms

The European Study Group on Cystic Tumours of the Pancreas

ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts

Grace H. Elta, MD, FACG[1], Brintha K. Enestvedt, MD, MBA[2], Bryan G. Sauer, MD, MSc, FACG (GRADE Methodologist)[3] and Anne Marie Lennon, MD, PhD, FACG[4]

Evidence Based Medicine pyramid
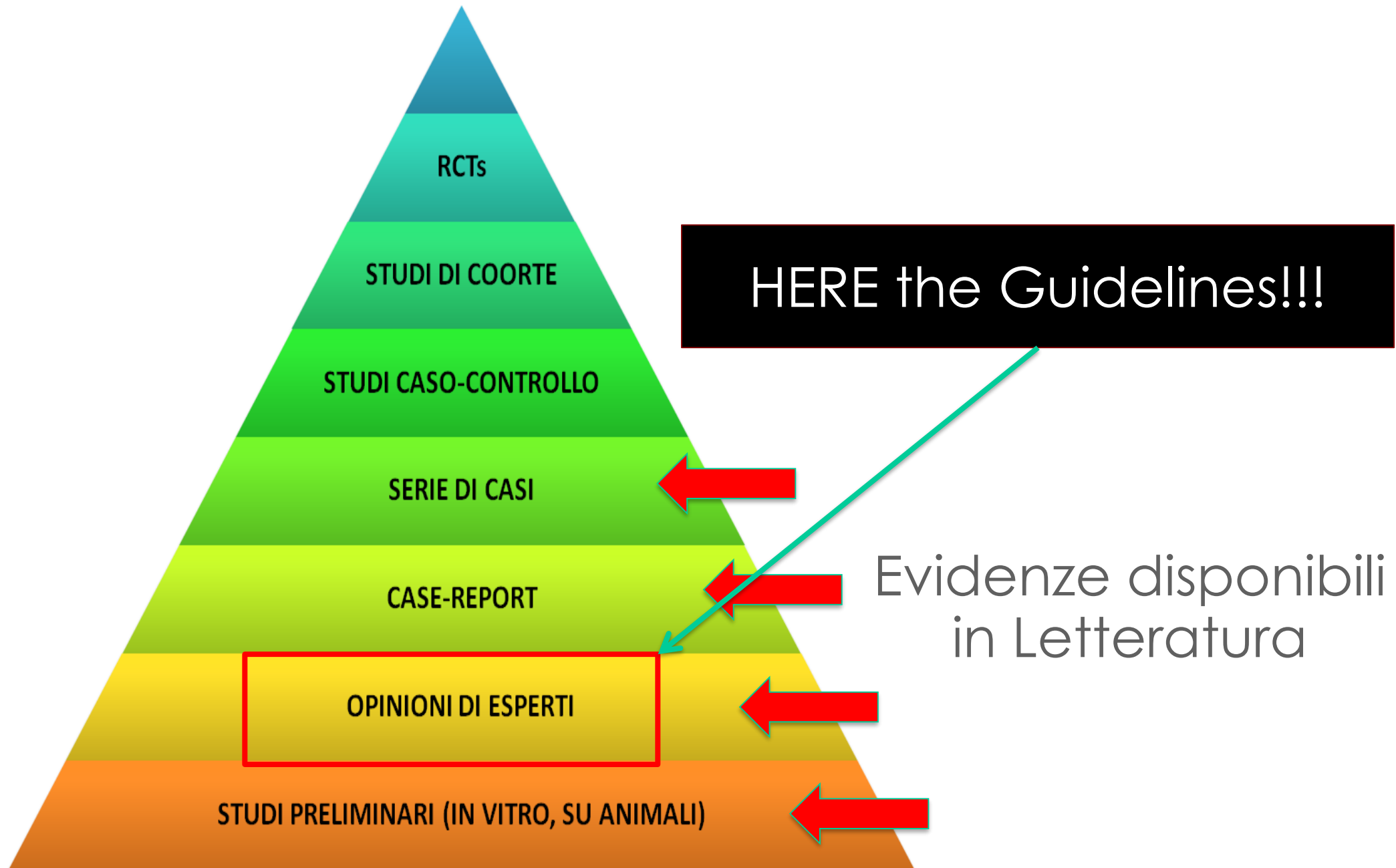
When we should do EUS

- Pancreatitis

- Cyst diameter > 3 cm

- Thickened/ehnancing cyst walls

3 Endoscopy

3.1 What are the indications for performing EUS in PCN?

EUS is recommended as an adjunct to other imaging modalities (GRADE 2C, strong agreement).

- Lymphadenopathy

- Uncertain radiological diagnosis

- Changes in the sizes of the cyst

- increased serum level of Ca 19.9

- Significant changes in the characteristics of the cyst

Pancreatic resections for cystic neoplasms: From the surgeon's presumption to the pathologist's reality

Roberto Salvia, MD, PhD, Giuseppe Malleo, MD, Giovanni Marchegiani, MD, Silvia Pennacchio, MD, Salvatore Paiella, MD, Marina Paini, MD, Antonio Pea, MD, Giovanni Butturini, PhD, Paolo Pederzoli, MD, and Claudio Bassi, MD, Verona, Italy

Preoperative radiologic workup (%)	
CEUS	428/476 (89.9)
CECT	353/476 (74.2)
MRI/MRCP	356/476 (74.8)
EUS	70/476 (14.7)

?

Table III. Accuracy of preoperative diagnosis (comparison between principal preoperative diagnosis and final pathologic report) in 476 patients resected for a pancreatic cystic neoplasm

Diagnosis	n (%)
Well-diagnosed cystic neoplasms	373 (78.4)
Misdiagnosed cystic neoplasms	103 (21.6)
Serous cystic neoplasms (n = 69)	
Well diagnosed	51 (73.9)
Misdiagnosed	18 (26.1)
Mucinous cystic neoplasms (n = 123)	
Well diagnosed	98 (79.7)
Misdiagnosed	25 (20.3)
Main duct/mixed-IPMN (n = 156)	
Well diagnosed	126 (80.7)
Misdiagnosed	30 (19.3)
Branch duct-IPMN (n = 75)	
Well diagnosed	54 (72.0)
Misdiagnosed	21 (28.0)
Cystic neuroendocrine neoplasms (n = 15)	
Well diagnosed	8 (53.3)
Misdiagnosed	7 (46.7)
Solid pseudopapillary neoplasms (n = 38)	
Well diagnosed	36 (94.7)
Misdiagnosed	2 (5.3)

IPMN, Intraductal papillary mucinous neoplasms.

Surgery 2012

Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions

Nuzhat A. Ahmad, MD, Michael L. Kochman, MD, Colleen Brensinger, MS, William R. Brugge, MD, Douglas O. Faigel, MD, Frank G. Gress, MD, Michael B. Kimmey, MD, Nicholas J. Nickl, MD, Thomas J. Savides, MD, Michael B. Wallace, MD, MPH, Maurits J. Wiersema, MD, Gregory G. Ginsberg, MD

Philadelphia, Pennsylvania, Boston, Massachusetts, Portland, Oregon, Long Island, New York, Seattle, Washington, Lexington, Kentucky, San Diego, California, Charleston, South Carolina, Rochester, Minnesota

Table 1. Kappa statistics for agreement between 8 reviewers, excluding cases rated as "indeterminate" by two or more reviewers

EUS diagnosis	Kappa
Neoplastic vs. non-neoplastic	0.243
Pseudocyst	0.384
Serous cystadenoma	0.463
Mucinous cystadenoma/adenoca	0.228
Neuroendocrine	0.399
Simple cyst	0.010
Intraductal papillary mucinous tumor	0.189
Type combined	0.317

Table 2. Accuracy of EUS for predicting neoplastic vs. non-neoplastic lesions

	All lesions		Excluding lesions as indeterminate	
	% Accurate	95% CI	% Accurate	95% CI
Overall, adjusted for clustering by reviewer	71.0	[57.3, 81.7]	77.0	[67.7, ...]
Reviewer 1	87.1	[70.2, 96.4]	87.1	[70.2, 96.4]
Reviewer 2	40.0	[22.7, 59.4]	52.2	[30.6, 73.2]
Reviewer 3	73.3	[54.1, 87.7]	73.3	[54.1, 87.7]
Reviewer 4	93.3	[77.9, 99.2]	93.3	[77.9, 99.2]
Reviewer 5	77.4	[58.9, 90.4]	82.8	[64.2, 94.2]
Reviewer 6	51.6	[33.1, 69.8]	66.7	[44.7, 84.4]
Reviewer 7	64.5	[45.4, 80.8]	71.4	[51.3, 86.8]
Reviewer 8	80.6	[62.5, 92.5]	80.6	[62.5, 92.5]

GE 2003

EUS morphology: mucinous vs non mucinous

- 341 patients

- Sens: 56 %
- Spec: 45 %

Should We Do EUS/FNA on Patients With Pancreatic Cysts? The Incremental Diagnostic Yield of EUS Over CT/MRI for Prediction of Cystic Neoplasms

Mouen A. Khashab, MD,* Katherine Kim, MHS,* Anne Marie Lennon, MD, PhD,* Eun Ji Shin, MD,*
April S. Tignor, MD, MPH,* Stuart K. Amateau, MD, PhD,* Vikesh K. Singh, MD, MSc,*
Christopher L. Wolfgang, MD, PhD,† Ralph H. Hruban, MD,‡ and Marcia Irene Canto, MD, MHS*

TABLE 1. Characteristics of 154 Study Patients and Pancreatic Cysts

Characteristic	Number (%)
Age, mean, yrs	62.31
Sex (female)	90 (58)
Patients with neoplastic cysts	133
Patients with malignant cysts	43
Nonneoplastic/low risk cysts	19
Mean size of neoplastic cysts, cm	2.42
Mean size of malignant cysts, cm	2.80
Mean size of nonneoplastic cysts, cm	3.94
Neoplastic cysts <3 cm	85 (64)
Malignant cysts <3 cm	22 (51)
Nonneoplastic cysts <3 cm	8 (38)
Surgical patients who had FNA	131
Patients with adequate FNA	106 (81)
Patients with diagnostic FNA	72 (55)
Patients who had CT	139 (90)
Patients who had MRI	53 (34)

Cystic ductal adenocarcinoma

A

Pseudocysts

B

Pancreas 2013

TABLE 2. Performance Characteristics of CT, MRI, and EUS for Neoplasia for Resected Pancreatic Cysts

	Sensitivity	Specificity	PPV	NPV
CT	48.3	78.9	93.5	19.5
MRI	34	100	100	8.33
EUS +/- FNA	75.6	73.7	95.3	29.8

Sensitivities of CT versus EUS (P < 0.0001), Sensitivity of MRI versus

(59% vs 5%; $P < 0.0001$). These results suggest that at least small pancreatic cysts without worrisome features on cross-sectional imaging should be further scrutinized by EUS.

TABLE 3. Incremental Diagnostic Yield of EUS Over CT for Detection of Neoplasia in Pancreatic Cysts

| No. Patients (n = 120)	CT Detect	EUS Detect
49	+	+
43	−	+
9	+	−
19	−	−

The incremental yield of EUS for diagnosis of neoplasia after initial CT was 43 (35.83%) of 120.

TABLE 4. Incremental Diagnostic Yield of EUS Over MRI for Detection of Neoplasia in Pancreatic Cysts

No. Patients (n = 50)	MRI Detect	EUS Detect
16	+	+
27	−	+
1	+	−
6	−	−

The incremental yield of EUS for diagnosis of neoplasia after initial MRI is 27 (54%) of 50.

Conclusions: The incremental increase in diagnostic yield of EUS and fluid analysis over CT and MRI for prediction of a neoplastic cyst is 36% and 54%, respectively. The addition of EUS-FNA to abdominal imaging significantly increases overall accuracy for diagnosis of neoplastic pancreatic cysts.
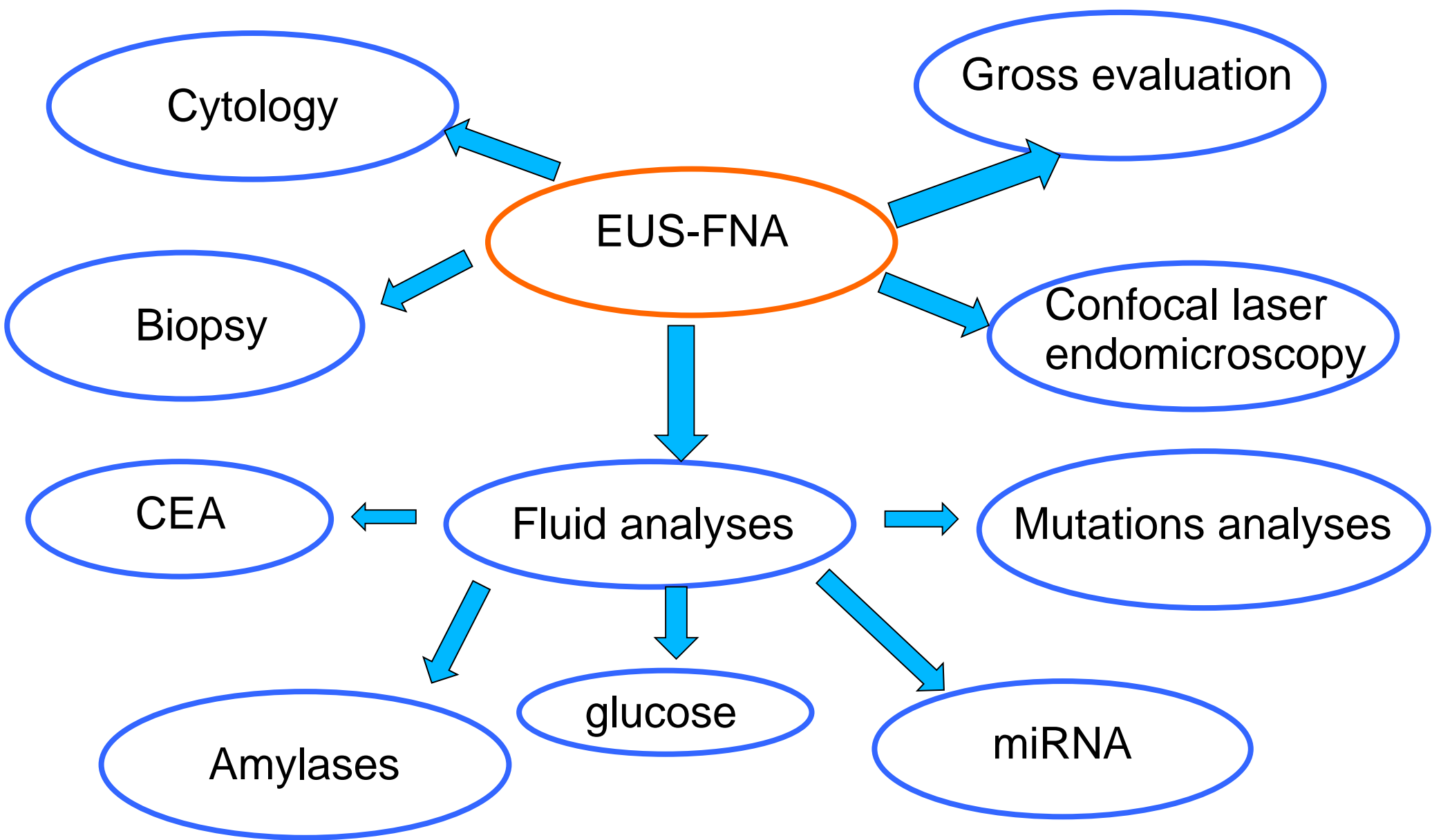
EUS-FNA TECNIQUE

- 19G, 22G, 25G standard needles

- Single pass in the cyst with aspiration of a minimum of 1 ml of liquid

- Cyst of 1-1.5 cm is the minimum to obtain fluid for at least one analysis (CEA)

- It is accepted practice to administered i.v. antibiotics (*eg.* Ciprofloxacin 400 mg) prior to cyst aspiration followed by oral antibiotics for 3 days, even if there are insufficient data to demonstrate a reduction in infectious complications

Italian guidelines, DLD 2014
ACG guidelines, Am J Gastroenterol 2007

Safety of EUS-FNA
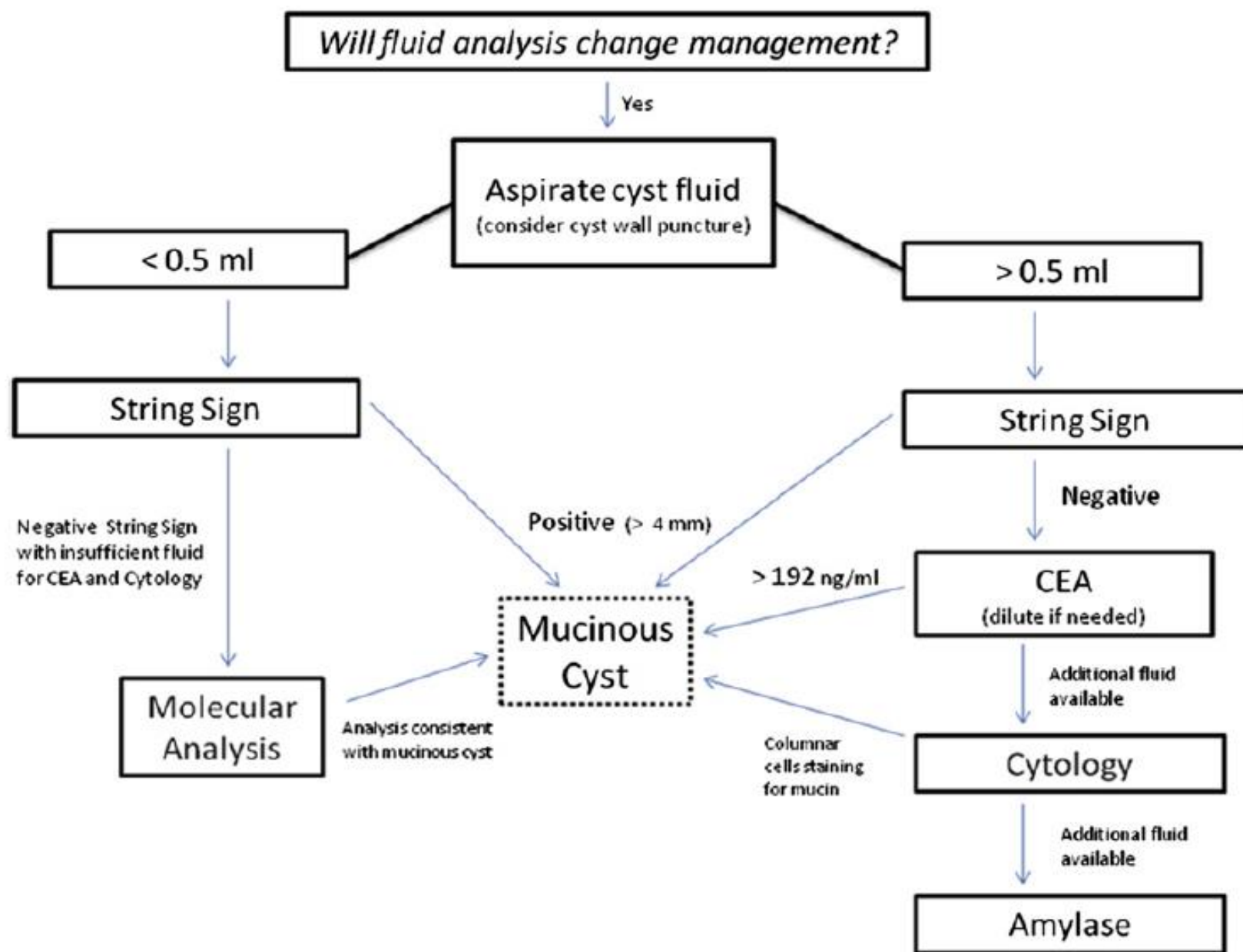
- Overall complication rate 0 %-2,5 %

- the reported complication rate of EUS-FNA in 603 patients with pancreatic cystic lesions was 2,2 % (13 of 603)

  - Pancreatitis

  - Abdominal pain

  - Retroperitoneal bleeding

  - Infection

  - bradycardia

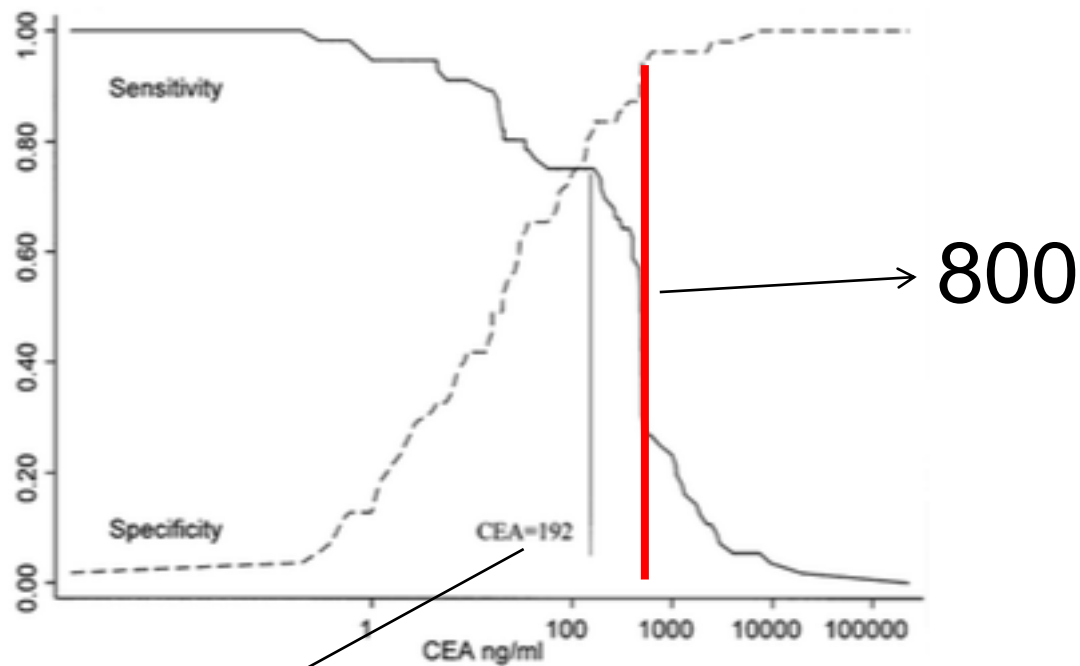*Lee Ls et al Clin Gastroenterol Hepatol* 2005

Viscosity: the "string-sign"
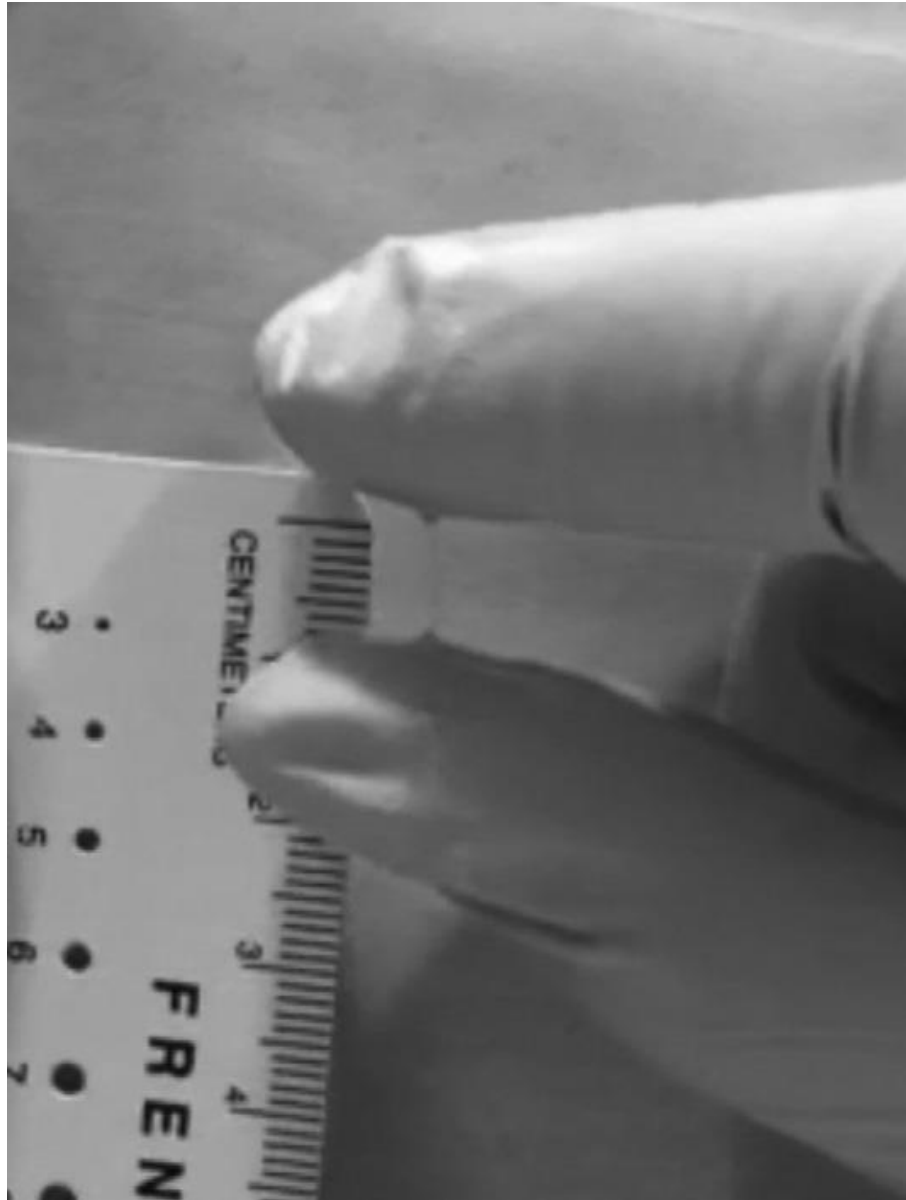
Benign lesions had a median string lenght of 0 mm compared with a significantly longer string lenght of 3.5 mm in potentially malignant/malignant cysts.

Leung KK, Ross WA, Evans D, et al. Pancreatic cystic neoplasm: the role of cyst morphology, cyst fluid analysis, and expectant management. Ann Surg Oncol 2009;16(10):2818–24.

Will fluid analysis change management?

Yes

Aspirate cyst fluid
(consider cyst wall puncture)

< 0.5 ml   > 0.5 ml

String Sign   String Sign

Negative String Sign
with insufficient fluid
for CEA and Cytology

Positive (> 4 mm)

Negative

> 192 ng/ml   CEA
(dilute if needed)

Mucinous
Cyst

Molecular
Analysis

Analysis consistent
with mucinous cyst

Columnar
cells staining
for mucin

Additional fluid
available

Cytology

Additional fluid
available

Amylase

CEA levels: mucinous vs non-mucinous

800

192

Cyst Fluid Glucose is Rapidly Feasible and Accurate in Diagnosing Mucinous Pancreatic Cysts

Thomas Zikos, MD[1], Kimberly Pham, BS[1], Raffick Bowen, PhD, MHA[2], Ann M. Chen, MD[1], Subhas Banerjee, MD[1], Shai Friedland, MD, MS[1], Monica M. Dua, MD[3], Jeffrey A. Norton, MD[3], George A. Poultsides, MD[3], Brendan C. Visser, MD[3] and Walter G. Park, MD, MS[1]

a 250   **b** 250

Table 3. Sensitivity, specificity, positive and negative likelihood ratios of glucose and CEA

Mucinous vs. non-mucinous cysts	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Lab glucose (mg/dl)	<50	95% (82–99)	57% (35–76)	2.19 (1.37–3.51)	0.08 (0.02–0.35)
Glucometer glucose (mg/dl)	<50	88% (74–95)	78% (55–91)	4.05 (1.85–8.87)	0.15 (0.07–0.35)
Reagent stick glucose	Undetectable	81% (66–91)	74% (52–90)	3.10 (1.54–6.27)	0.26 (0.13–0.50)
CEA (ng/ml)	>192	77% (58–91)	83% (52–98)	4.67 (1.30–16.80)	0.27 (0.13–0.56)
CEA or glucose[a]	CEA>192 or Glucose<50	100%	33% (11–65)	1.50 (1.00–2.23)	0.00

CEA, carcinoembryonic antigen; CI, confidence interval; LR, likelihood ratio.

[a]Glucometer glucose.

Cytology

- Low overall accuracy for detection of mucinous lesions at 58-59 %.

Pancreas 2011
Gastrointest Endoscopy 2005

FNA to establish malignancy in Mucinous cysts ?

Meta-analysis; 18 studies; 1438 patients

	Sens %	Spec %
Cytology	54	93
CEA > 192	63	88

FNA better specificity than sensitivity for malignancy

Thornton, Pancreatology 2013

EUS-FNA Cytology: case report

61 yrs-old woman submitted to
EUS after MR and PET suspicious
for mucinous cyst
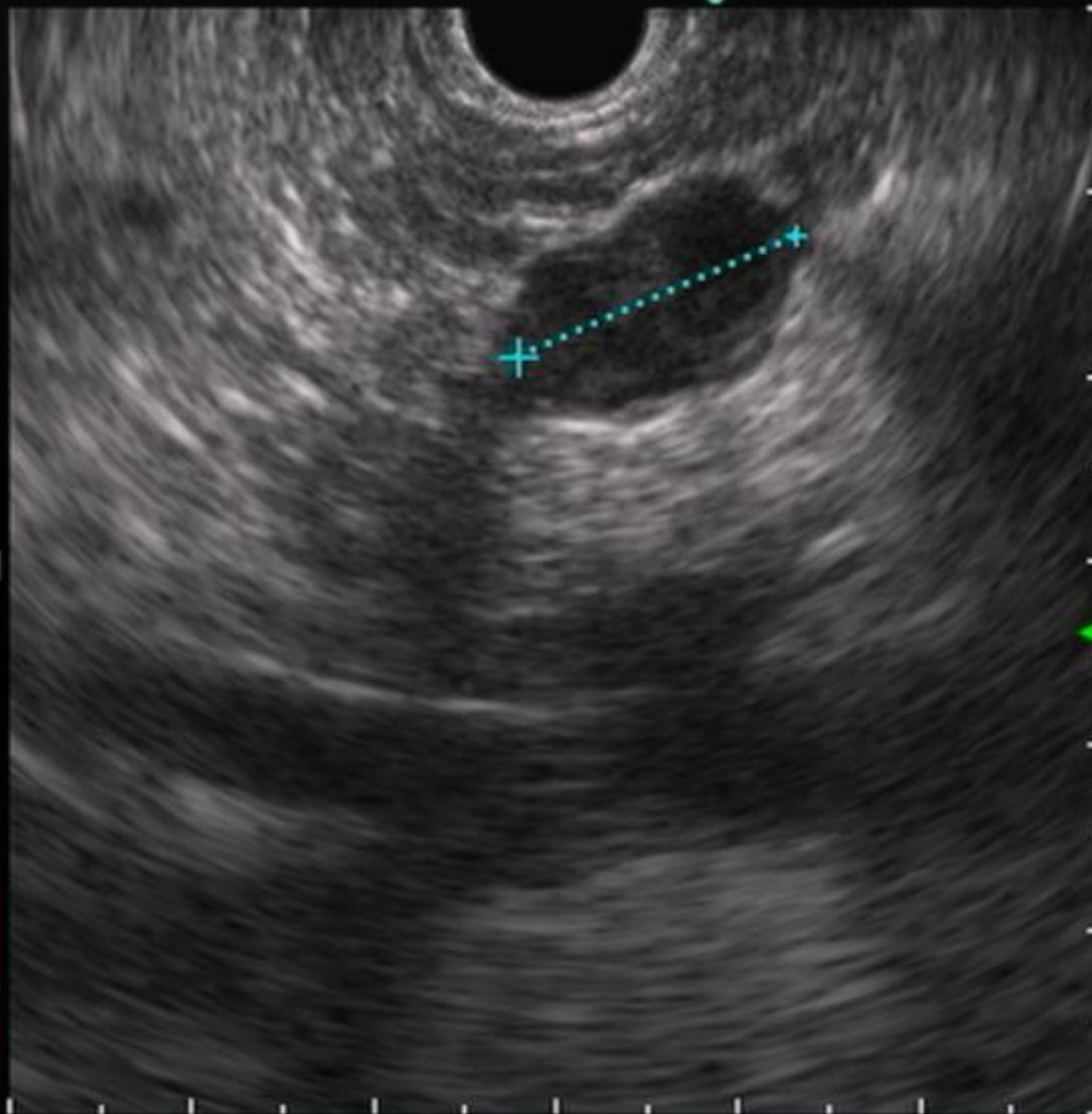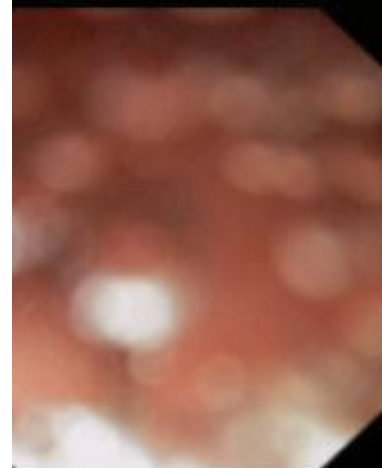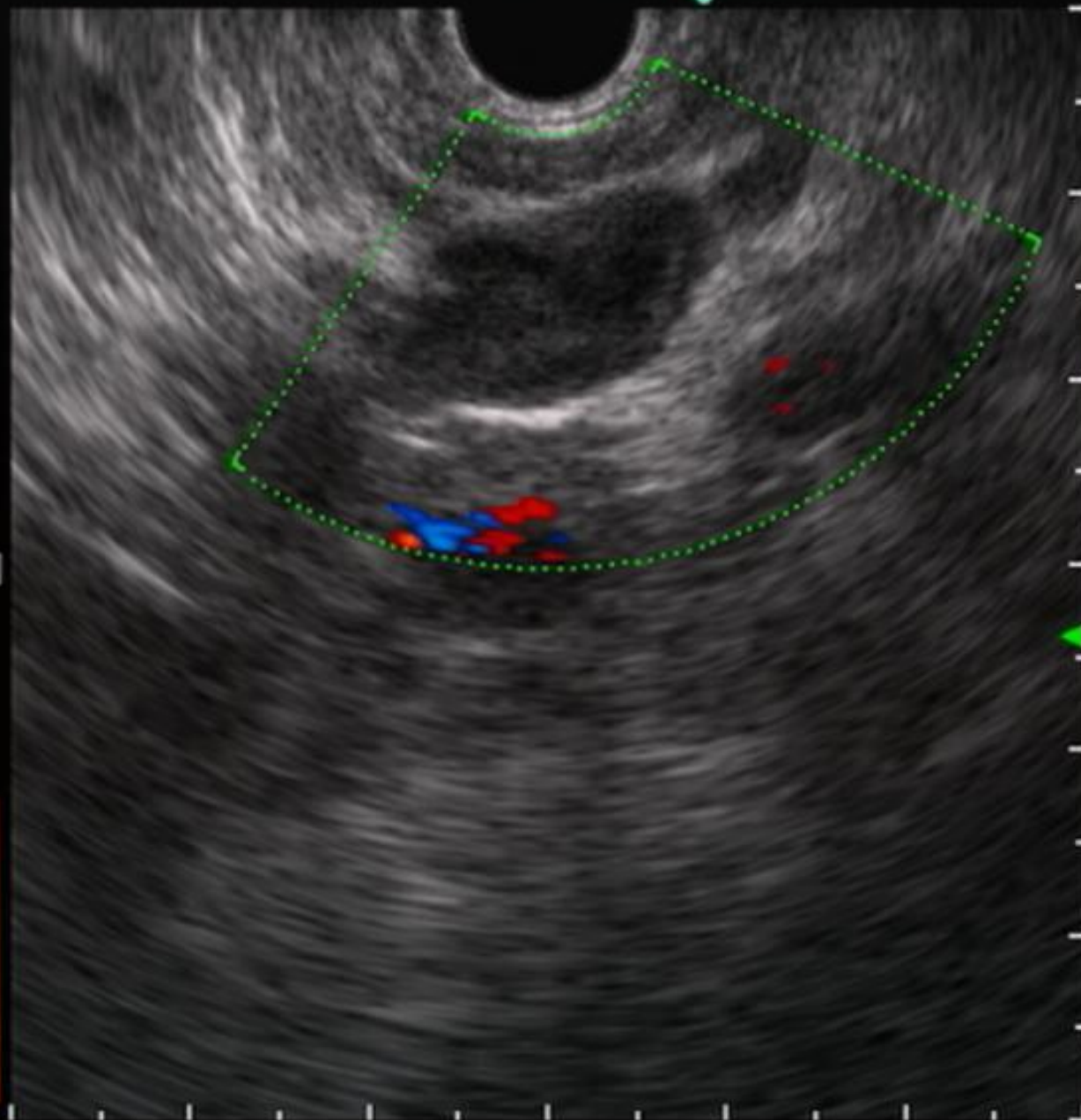
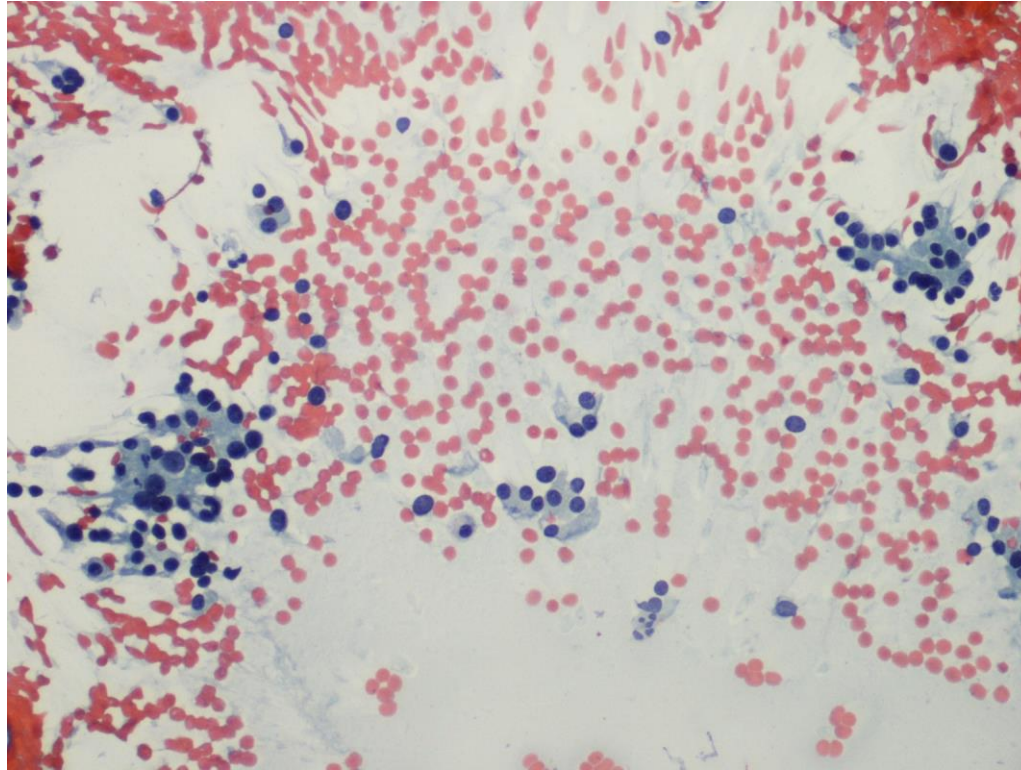# Cystic neuroendocrine tumor

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

Simeon Springer,[1,2,*] Yuxuan Wang,[1,2,*] Marco Dal Molin,[2,3,*] David L. Masica,[2,4,5,*] Yuchen Jiao,[1,2] Isaac Kinde,[1,2] Amanda Blackford,[6] Siva P. Raman,[7] Christopher L. Wolfgang,[2,8,9] Tyler Tomita,[4,5] Noushin Niknafs,[4,5] Christopher Douville,[4,5] Janine Ptak,[1,2] Lisa Dobbyn,[1,2] Peter J. Allen,[10] David S. Klimstra,[11] Mark A. Schattner,[12] C. Max Schmidt,[13] Michele Yip-Schneider,[14] Oscar W. Cummings,[14] Randall E. Brand,[15] Herbert J. Zeh,[16] Aatur D. Singhi,[17] Aldo Scarpa,[18,19] Roberto Salvia,[20] Giuseppe Malleo,[20] Giuseppe Zamboni,[19,21] Massimo Falconi,[22] Jin-Young Jang,[23] Sun-Whe Kim,[23] Wooil Kwon,[23] Seung-Mo Hong,[24] Ki-Byung Song,[25] Song Cheol Kim,[25] Niall Swan,[26] Jean Murphy,[26] Justin Geoghegan,[27] William Brugge,[28] Carlos Fernandez-Del Castillo,[29] Mari Mino-Kenudson,[30] Richard Schulick,[31] Barish H. Edil,[31] Volkan Adsay,[32] Jorge Paulino,[33] Jeanin van Hooft,[34] Shinichi Yachida,[35] Satoshi Nara,[35] Nobuyoshi Hiraoka,[35] Kenji Yamao,[36] Susuma Hijioka,[36] Schalk van der Merwe,[37] Michael Goggins,[2,9,38] Marcia Irene Canto,[38] Nita Ahuja,[8] Kenzo Hirose,[8] Martin Makary,[8] Matthew J. Weiss,[8] John Cameron,[8] Meredith Pittman,[2,3] James R. Eshleman,[1,2] Luis A. Diaz Jr.,[1,2,8] Nickolas Papadopoulos,[1,2] Kenneth W. Kinzler,[1,2] Rachel Karchin,[2,4,5,9] Ralph H. Hruban,[1,2,3,9] Bert Vogelstein,[1,2] and Anne Marie Lennon[2,8,38]

Clinical and molecular genetic features of pancreatic cyst fluid could be used to classify cysts and identify indications for surgical resection:

- IPMN: high grade of dysplasia and invasive form

- Solid pseudopapillary tumors

130 patients with resected pancreatic cysts

- 96 IPMN

- 12 serous cystoadenomas

- 12 mucinous cystic neoplasm
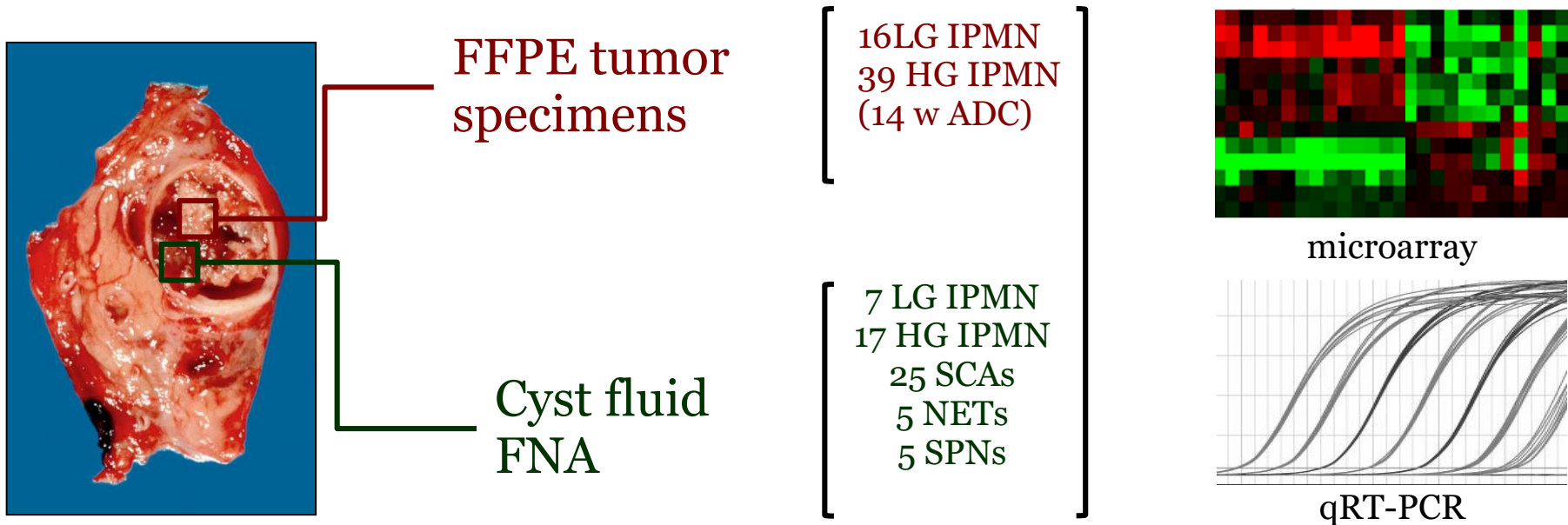
- 10 pseudopapillary neoplasm

Mutations in genes

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 and GNAS: IPMN and mucinous cysts

CTNNB1: solid pseudopapillary tumors

miRNA Biomarkers in Cyst Fluid Augment the Diagnosis and Management of Pancreatic Cysts

Clinical Cancer Research

FFPE tumor specimens

16LG IPMN
39 HG IPMN
(14 w ADC)

microarray

Cyst fluid FNA

7 LG IPMN
17 HG IPMN
25 SCAs
5 NETs
5 SPNs

qRT-PCR

9 miRNA signature (i.e., miR-24, miR-30a-3p, miR-18a, miR-92a, miR-342-3p, miR-99b, miR-106b, miR-142-3p, miR-532-3p) can accurately identify patients with high-grade IPMN and exclude nonmucinous cysts.

Matthaei H, *et al.* – *Clin Cancer Res* 2012

Microbiome

Pancreatic cyst fluid harbors a unique microbiome

Shan Li[1], Gwenny M. Fuhler[1], Nahush BN[3], Tony Jose[3], Marco J. Bruno[1], Maikel P. Peppelenbosch[1,2]
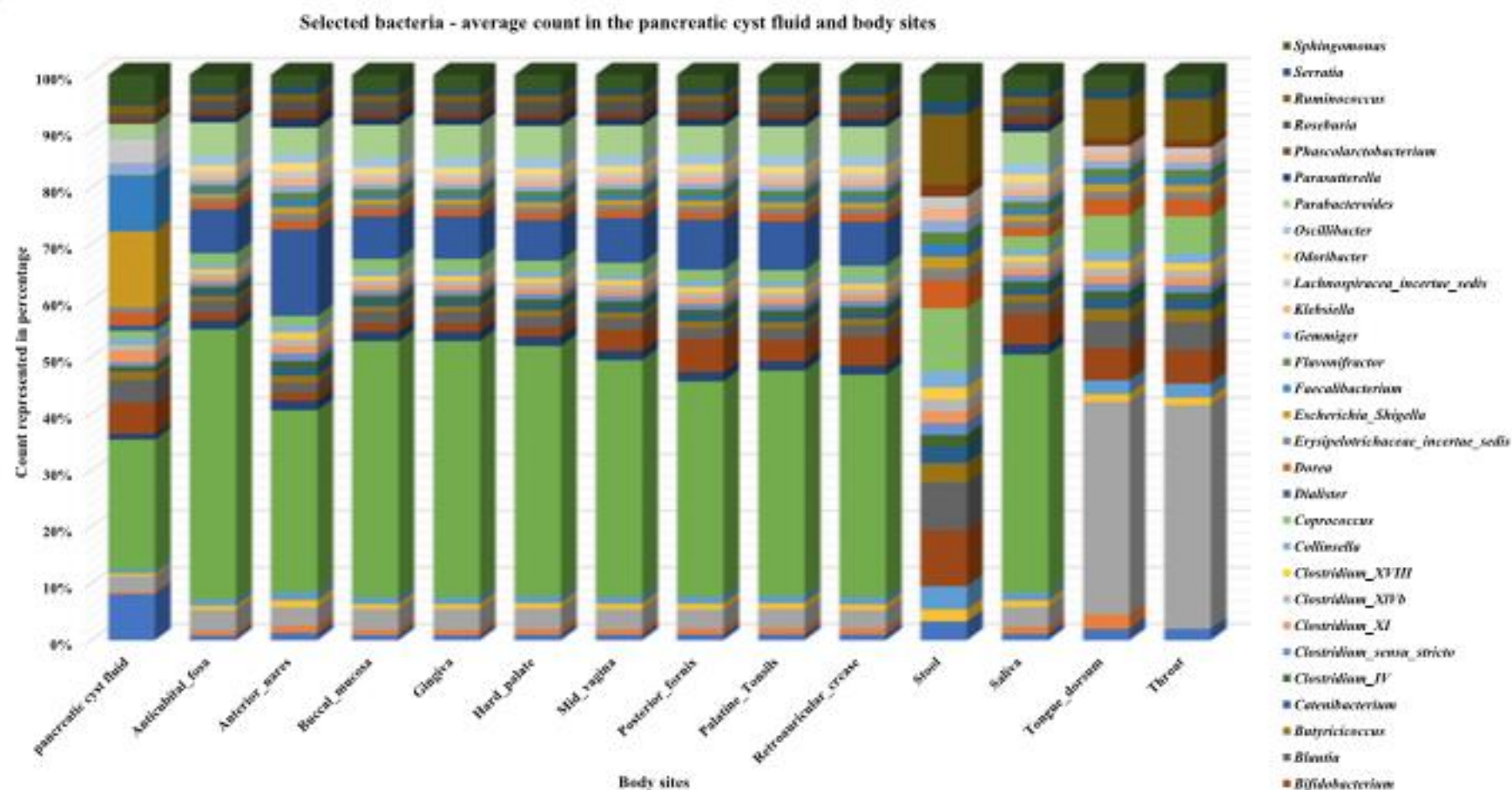and Sergey R. Konstantinov[1,4*]

Fig. 4 Pancreatic cyst microbiome is unique among other human body microbiomes. Publicly accessible databases were mined for composition of microbiomes at different human body sites and compared to those observed in PCF. It appears that there are 27 to 314 bacterial genotypes differently present in the PCF when compared to the selected body sites when analyzed via pairwise binomial test with high abundance PCF bacteria($P < 0.0001$) and ANOVA test, respectively

Table 2 Bacterial ecosystems characteristics identified from the pancreatic cyst fluids using PCR, Sanger sequencing, and next-generation sequencing (NGS)

Bacterial ecosystem characteristics

Patient characteristics		IPMN (n = 27)	MCN (n = 13)	Others (n = 11)	Pseudocysts (n = 9)	Serous cystadenoma (n = 9)
16S rRNA PCR (universal 16S rRNA gene primers)	Bacteria present	92.6%	100%	90.9%	88.9%	88.9%
	Bacteria absent	7.4%	0.0%	9.1%	11.1%	11.1%
Sanger sequencing	Bacteria detected	*Bacillus* spp. *Fusobacterium* spp., *Orpinomyces* spp. *Anaerococcus* spp., *Caldimonas* spp., *Acinetobacter* spp., *Bacillus* spp.	*Fusobacterium* spp., *Bacillus* spp., *Orpinomyces* spp., *Microcystis* spp., *Staphylococcus* spp.	*Fusobacterium* spp.	*Caldimonas* spp., *Propionibacterium* spp., *Fusobacterium* spp., *Curvibacter* spp., *Escherichia* spp., *Bacillus* spp.	*Arthrobacter* spp., *Bacillus* spp., *Bacteroides* spp., *Ruminococcus* spp.
16S rRNA (NGS) (n = 33)	Bacteria present	100% (n = 9)	100% (n = 7)	NA	100% (n = 8)	100% (n = 9)
Bacteria detected by 16S rRNA gene V3-V4 variable region NSG (n = 33)		*Bacteroides*—15.45% *Escherichia/Shigella*—9.88% *Faecalibacterium*—8.57% *Acidaminococcus*—5.75% *Sphingomonas*—4.87% *Others*—55.49%	*Bacteroides*—17.06% *Escherichia/Shigella*—10.17% *Faecalibacterium*—6.95% *Acidaminococcus*—5.22% *Sphingomonas*—6.48% *Others*—54.12%	NA	*Bacteroides*—16.59% *Escherichia/Shigella*—10.55% *Faecalibacterium*—6.81% *Acidaminococcus*—6.23% *Sphingomonas*—5.40% *Others*—54.42%	*Bacteroides*—16.73% *Escherichia/Shigella*—9.97% *Faecalibacterium*—6.64% *Acidaminococcus*—6.24% *Sphingomonas*—4.81% *Others*—55.62%

NA not applicable

Conclusions

The differential diagnosis of pancreatic cystic lesions is wide: the majority of these lesions are benign but detection of mucinous neoplasms (IPMN and MCN) is important because these cysts may be malignant or have malignant potential.

The addition of EUS/EUS-FNA to abdominal imaging significantly increases accuracy for diagnosis of neoplastic pancreatic cysts.

A combination of EUS features, fluid viscosity, fluid cytology, carcinoembryonic and amylase level, is used to differentiate pancreatic cysts. (glucose ? Molecular markers ? Microbiome ?)

Accurate diagnosis and management of pancreatic cystic lesions require careful evaluation of the clinical setting, other imaging modalities, and multidisciplinary collaboration.