

Pancreatic Cystic Neoplasms: *Guidelines and beyond*

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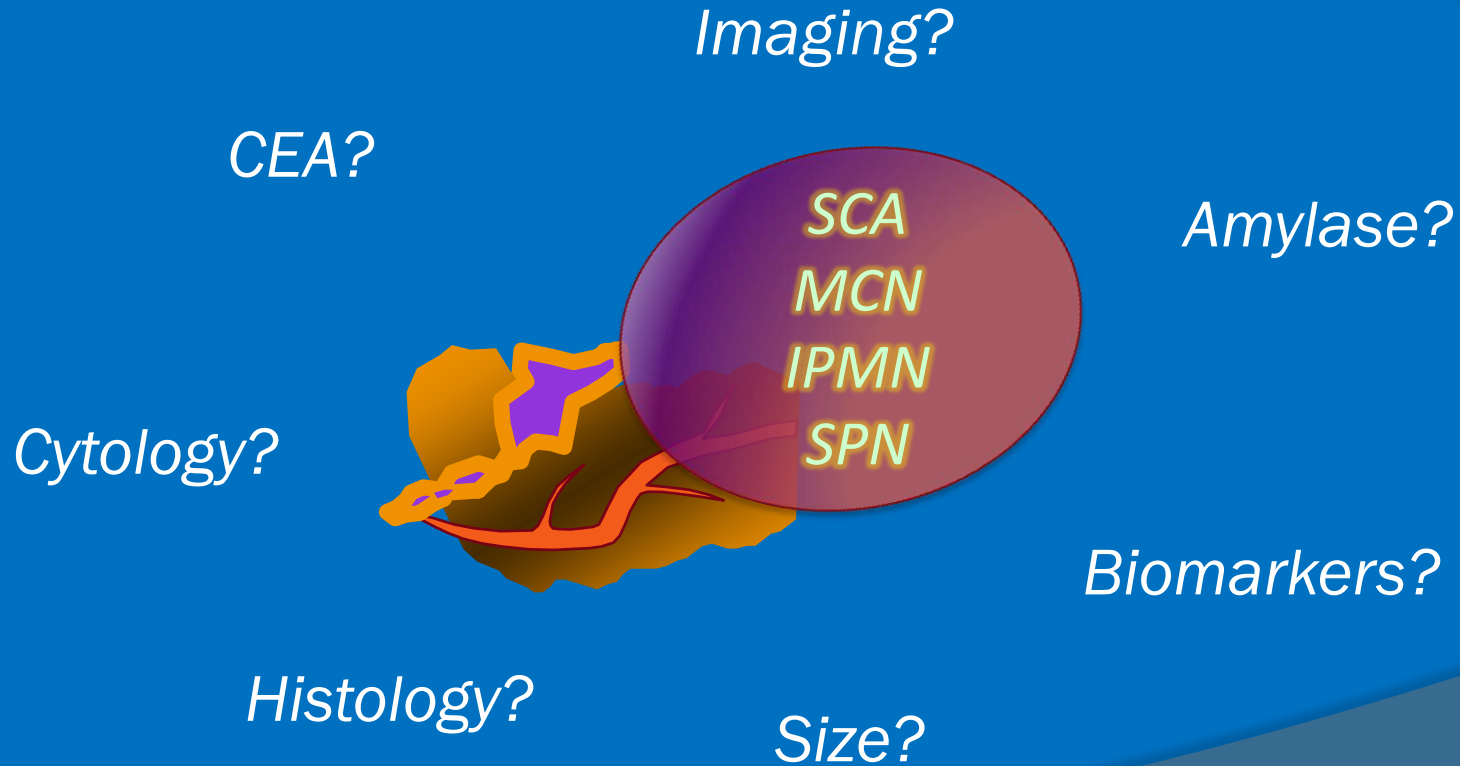
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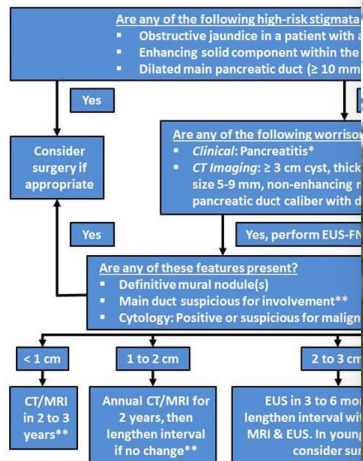


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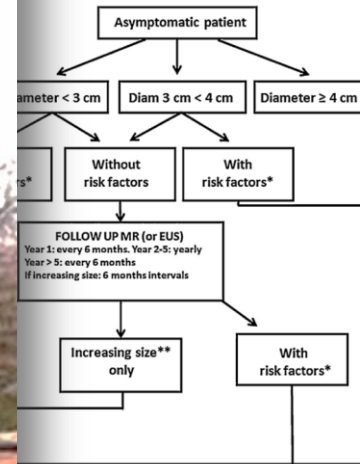
Pancreatic Cystic Neoplasms: Still a clinical challenge



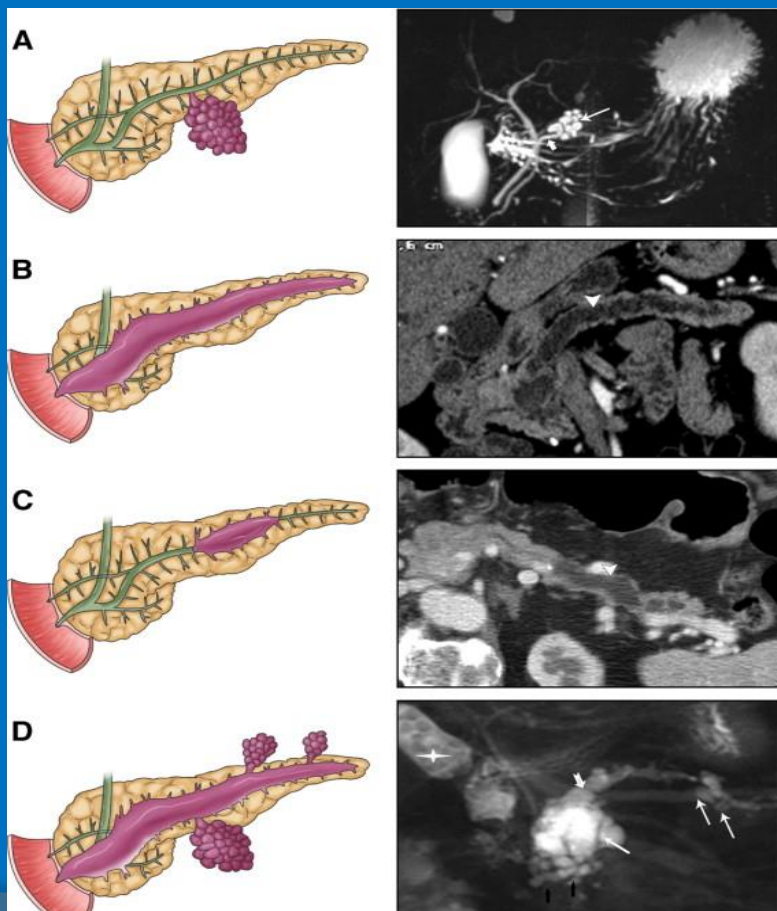
Fukuoka Guidelines for



Consensus Guidelines 2013



Pancreatic Cystic Neoplasms – Risk of Cancer



Subtype	Risk of Malignancy
Main Duct (MD-IPMN)	36-68%
Mixed (Mixed-IPMN)	38-65%
Branch (BD-IPMN)	12-47%
Mucinous Cystic Neoplasm (MCN)	10-17%
Solid Pseudopapillary Neoplasm (SPN)	8-20%
Cystic Pancreatic Neuroendocrine Tumor (cPNET)	6-31%

Sendai Consensus Guidelines 2004

Risk Factors:

1. Size > 3cm
2. High risk features
 - ✓ Mural nodules
 - ✓ Dilated main PD (> 10mm)
 - ✓ Positive Cytology

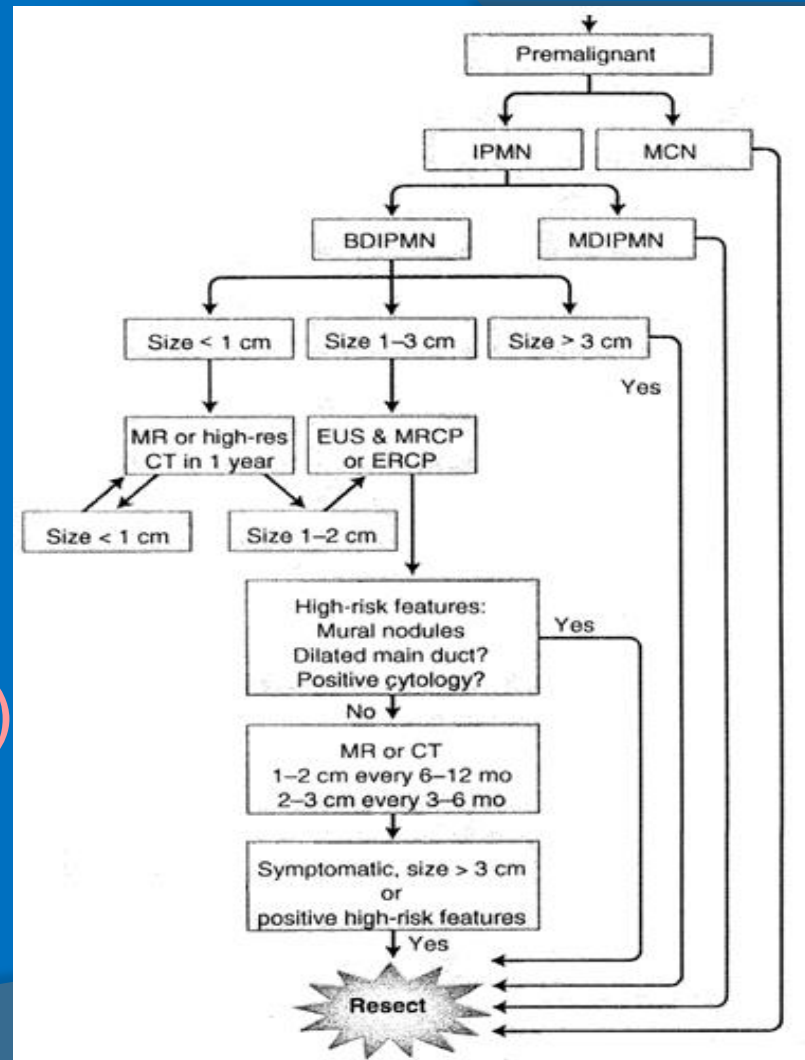


TABLE 1. Comparison of Pancreatic Cyst Guidelines

	2012 Fukuoka Guidelines	2013 European Guidelines	2015 AGA Guidelines
Process	Multidisciplinary experts	Multidisciplinary experts	AGA committee
Cyst type	Mucin-producing cysts (IPMNs, MCNs)	Neoplastic cysts (IPMNs, MCNs, SPNs, SCNs)	Asymptomatic neoplastic cysts
Target	High-grade dysplasia and PDAC	High-grade dysplasia and PDAC	PDAC
Methods	Scientific review	Scientific review, grading	Technical review, GRADE
Key decisions	Surgery EUS-FNA Surveillance schedule	Surgery No routine EUS-FNA Surveillance schedule	Surgery EUS-FNA Surveillance schedule Stopping surveillance

GRADE indicates Grading of Recommendations Assessment, Development and Evaluation.

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Lennon, AM; Canto, MI. Pancreas 2017;46: 745–750

TABLE 1. Selected features of BD-IPMNs for predicting high risk of malignancy by the guidelines

Fukuoka 2012	European 2013	AGA 2015
<p>High-risk stigmata</p> <ul style="list-style-type: none"> • Obstructive jaundice • Enhancing solid component • MPD ≥ 10 mm <p>Worrisome features</p> <ul style="list-style-type: none"> • Cyst >3 cm • Thickened/enhancing cyst wall • MPD 5-9 mm • Nonenhancing mural nodule • Abrupt change in PD caliber with distal pancreatic atrophy 	<ul style="list-style-type: none"> • Mural nodule • Dilatated MPD • Growth rate of cyst (cysts growing over 2 mm/year) • Presence of symptoms (abdominal pain, pancreatitis, new-onset diabetes, jaundice) • Increased serum levels of CA 19.9 • Cyst size >4 cm 	<p>High-risk features</p> <ul style="list-style-type: none"> • Cyst >3 cm • Associated solid component • Dilatated MPD

AGA, American Gastroenterological Association; BDIPMNs, branch-duct intraductal papillary mucinous neoplasms; MPD, main pancreatic duct; PD, pancreatic duct.

TABLE 2. Surgical resection recommendations for pancreatic cysts according to current guidelines

Diagnosis	Fukuoka 2012	European 2013	AGA 2015
MCN	Resection	Resection	Resection
SPN	Not mentioned	Resection	Resection
MD-IPMN	Resection	Resection	Yes, however*
Mixed-IPMN	Resection	Resection	Yes, however*
BD-IPMN	<ul style="list-style-type: none"> • Pancreatitis (for relief of symptoms) • Obstructive jaundice • Solid component • MPD ≥ 1 cm • +Cytologic features suggestive of adenocarcinoma • Definite mural nodule on EUS • MPD features suspicious for involvement§ • >3 cm cyst in young surgically fit patient 	<ul style="list-style-type: none"> • Acute pancreatitis jaundice, diabetes • Mural nodule • MPD >6 mm • Size ≥ 4cm • Rapidly increasing size† • Elevated serum CA19-9 level‡ 	<ul style="list-style-type: none"> • Solid component <i>and</i> MPD ≥ 5 mm (both on EUS <i>and</i> MRI) • <i>and/or</i> concerning features on EUS†

AGA, American Gastroenterological Association; BD-IPMN, branch duct-intraductal papillary mucinous neoplasm; EUS, endoscopic ultrasonography; MCN, mucinous cystic neoplasm; MD-IPMN, main duct-intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; SPN, solid-pseudopapillary neoplasm.

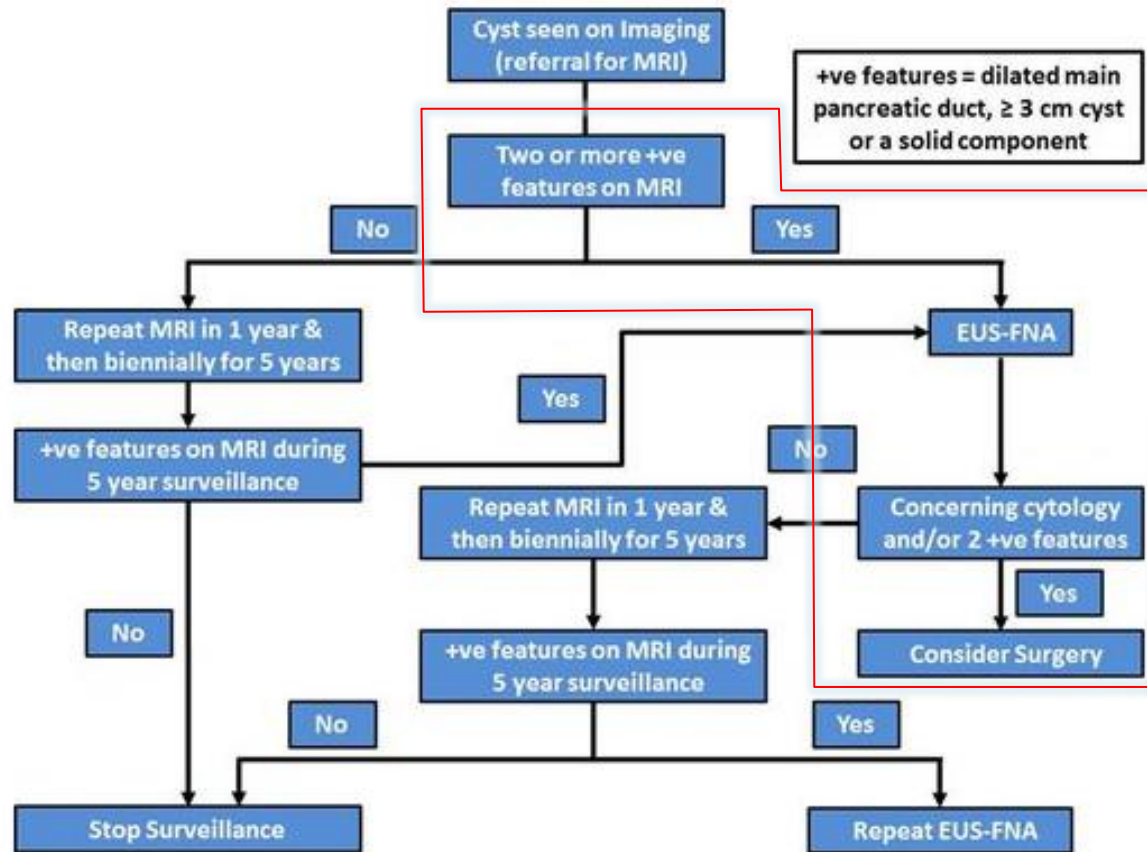
*AGA does not recommend surgery for MPD alone, but also requires presence of a nodule or malignant cytologic features.

†Definite mural nodule, cytologic features positive for malignancy.

‡Relative indication for surgery according to European Guideline.

§Presence of thickened walls, intraductal mucin, or mural nodules is suggestive of MPD involvement; in their absence, MPD involvement is inconclusive.

AGA Guidelines for Pancreatic Cysts



"Fake" Guidelines ?

- Amsterdam – 115 resected patients¹
 - AGA missed 12% of HGD/cancer
- U. Penn – 239 resected patients²
 - AGA and Fukuoka missed 13% of HGD/cancer
- Columbia, Yale, Jefferson – 269 resected patients³
 - AGA missed 93% of HGD/cancer
- Texas, Brigham – 152 resected patients⁴
 - AGA and Fukuoka missed 25% and 18% of cancer

1. Lekkerkerker et al. GIE 2017;85:1025-31

2. Ma, G. et al. J Am Coll Surg 2016;223:729-737

3. Xu et al. Medicine (2017) 96:35

4. Lee et al. Endoscopy International Open 2017; 05: EE116–EE122

TABLE 5. Comparison of the current guidelines based on pathological outcome

Final outcome based on pathology	Proposed treatment strategy according to the guideline	N = 75 patients			P value
		IAP guideline (2012), N patients (% total)	European guideline (2013), N patients (% total)	AGA guideline (2015), N patients (% total)	
Surgery not indicated (n = 39)	Surveillance	8 (10.7)	7 (9.3)	17 (22.7)	<.01
	Surgery	31 (41.3)	32 (42.7)	22 (29.3)	
Surgery indicated (n = 36)	Surveillance	0 (0)	0 (0)	4 (5.3)	.03
	Surgery	36 (48.0)	36 (48.0)	32 (43)	

Comparison of the outcome in surgically treated patients with suspicion of an intraductal papillary mucinous neoplasm (IPMN) based on the International Association of Pancreatology, European guidelines of the European Study Group on Cystic Tumours of the Pancreas and American Gastroenterological Association institute guideline.⁵⁻⁷

TABLE 4. Preoperative and postoperative diagnosis and the accuracy of the preoperative diagnosis

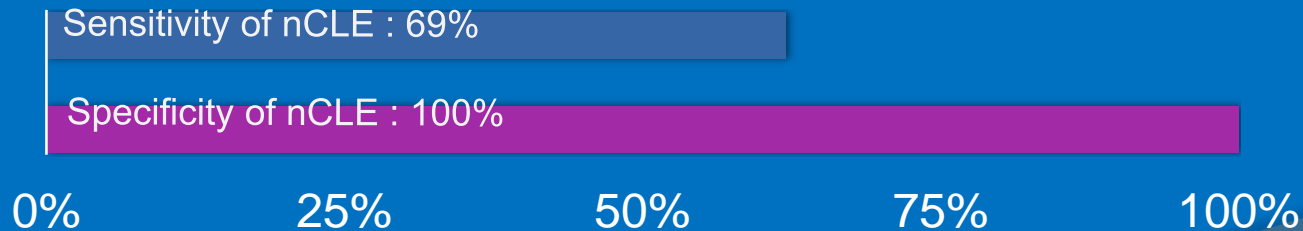
Diagnosis	Preoperative diagnosis N = 115 (%)	Definitive diagnosis N = 115 (%)	Correctly diagnosed preoperatively N/total N (%)
Overall			83/115 (72.2)
Benign or (pre)malignant			99/115 (86.1)
(Pre)malignant			
MD/MT-IPMN	51 (44.3)	55 (47.8)	49/55 (89.0)
SB-IPMN	22 (19.1)	15 (13.0)	12/1 (80.0)
MCN	29 (25.2)	14 (12.2)	13/14 (92.9)
Cystic adeno- or acinar cell carcinoma	4 (3.5)	4 (3.5)	2/4 (50.0)
SPN	3 (2.6)	4 (3.5)	2/4 (50.0)
Unknown	2 (1.7)	1 (0.9)	
NET	1 (0.9)	3 (2.6)	1/3 (33.3)
Benign			
SCN	3 (2.6)	9 (7.8)	3/9 (33.3)
Lymphoepithelial cyst	0 (0)	1 (0.9)	0/1 (0)
Lymphangioma	0 (0)	1 (0.9)	0/1 (0)
Retention cyst	0 (0)	2 (1.7)	0/2 (0)
Chronic pancreatitis/PFC	0 (0)	6 (5.2)	0/6 (0)

IPMN, Intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MD, main duct; MT, mixed type; NET, neuroendocrine tumor; SB, side branch; SPN, solid pseudopapillary neoplasm; SCN, serous cystic neoplasm; PFC, pancreatic fluid collection.

A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy

Bertrand Napoléon¹, Anne-Isabelle Lemaistre², Bertrand Pujol¹, Fabrice Caillol³, Damien Lucidarme⁴, Raphaël Bourdariat⁵, Blandine Morellon-Mialhe², Fabien Fumex¹, Christine Lefort¹, Vincent Lepilliez¹, Laurent Palazzo⁶, Geneviève Monges⁷, Bernard Filoche⁴, Marc Giovannini³

CONTACT Multi-center, 31 patients
100% specificity for serous cyst adenomas



EUS nCLE: Serous Cystadenoma

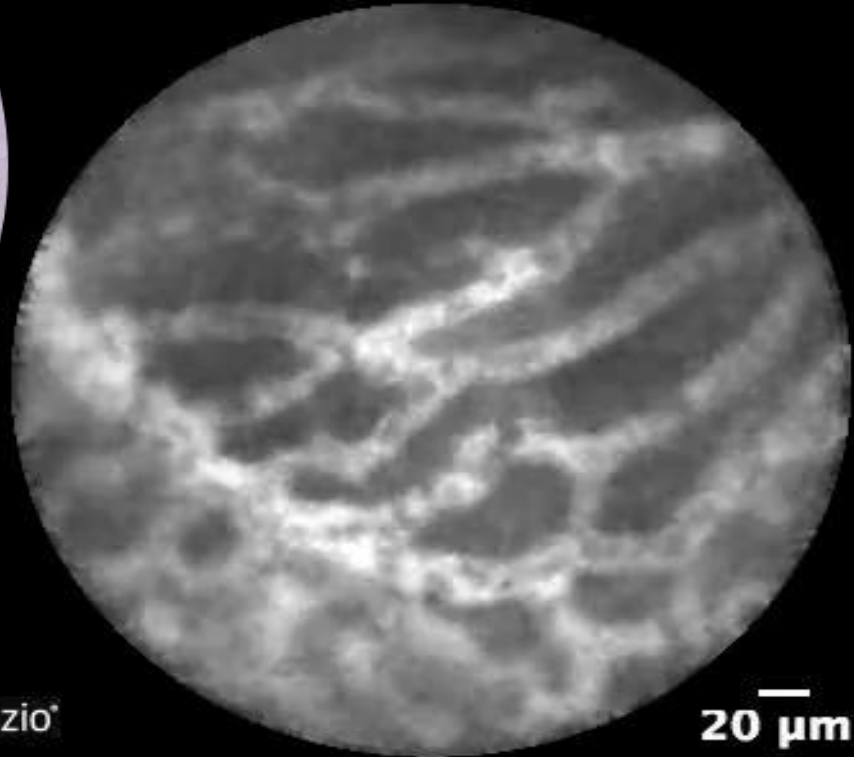
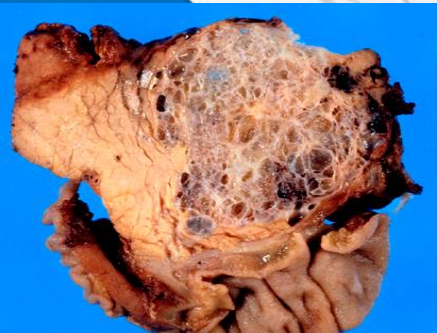
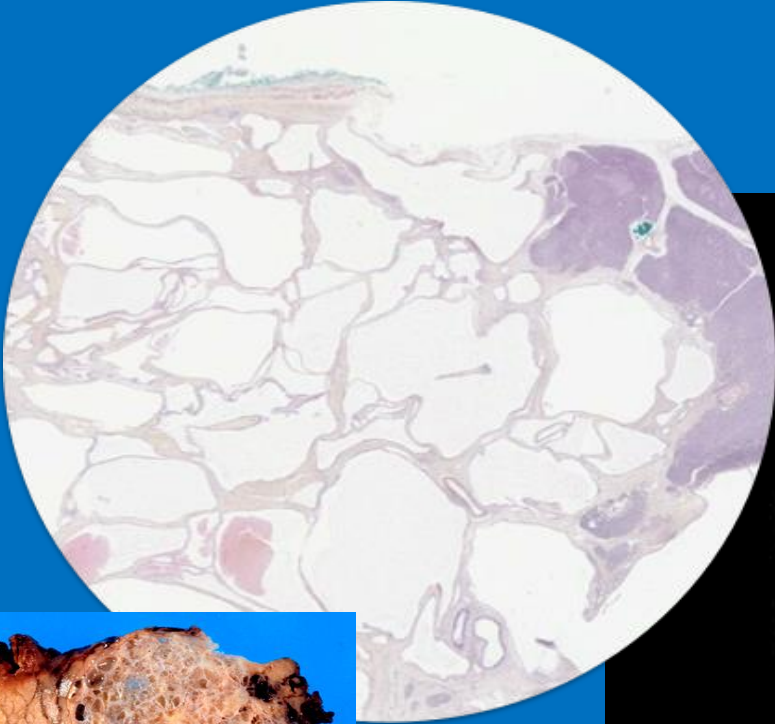


Table 2. Performance Characteristics of American Gastroenterological Association and Fukuoka High-Risk and Worrisome Criteria for Detection of Advanced Neoplasia

Criteria	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
AGA high-risk criteria				
Solid component + PDD (n = 21)	18.3 (10.1–29.3)	95.2 (90.8–97.9)	61.9 (38.4–81.9)	73.4 (67.0–79.1)
Concerning EUS/positive cytology (n = 18)	28.3 (16.8–42.3)	97.5 (92.7–99.5)	83.3 (58.6–96.4)	75.2 (67.5–81.8)
≥ 1 criteria (n = 35)	35.2 (24.2–47.5)	94.0 (89.3–97.1)	71.4 (53.7–85.4)	77.5 (71.1–83.0)
AGA worrisome criteria				
Solid component w/o PDD (n = 50)	35.2 (24.2–47.5)	85.1 (78.8–90.1)	50.0 (35.5–64.5)	75.7 (68.9–81.6)
PDD w/o solid (n = 70)	47.9 (35.9–60.1)	78.6 (71.6–84.5)	48.6 (36.4–60.8)	78.1 (71.1–84.1)
Increasing PD size (n = 16)	17.4 (7.8–31.4)	94.1 (88.7–97.4)	50.0 (24.7–75.3)	77.1 (70.0–83.3)
Cyst size ≥ 3 cm (n = 101)	42.3 (30.6–54.6)	57.7 (49.9–65.3)	29.7 (21.0–39.6)	70.3 (61.9–77.8)
≥ 1 criteria (n = 157)	83.1 (72.3–91.0)	41.7 (33.6–48.9)	37.6 (29.8–45.4)	85.4 (75.6–92.1)
≥ 2 criteria (n = 64)	45.1 (33.2–57.3)	81.0 (74.2–86.6)	50.0 (37.2–62.8)	77.7 (70.8–83.6)
Fukuoka high-risk criteria				
Jaundice (n = 12)	16.9 (9.1–27.7)	100.0 (97.8–100.0)	100.0 (73.5–100.0)	74.0 (67.8–79.6)
Enhancing solid (n = 6)	2.8 (0.3–9.8)	97.6 (94.0–99.3)	33.3 (4.3–77.7)	70.4 (64.1–76.2)
PDD ≥ 10 mm (n = 11)	11.3 (5.0–21.0)	98.2 (94.9–99.6)	72.7 (39.0–94.0)	72.4 (66.1–78.1)
≥ 1 criteria (n = 27)	28.2 (18.1–40.1)	95.8 (91.6–98.3)	74.1 (53.7–88.9)	75.9 (69.6–81.5)
Fukuoka worrisome criteria				
Cyst size ≥ 3 cm (n = 101)	42.3 (30.6–54.6)	57.7 (49.9–65.3)	29.7 (21.0–39.6)	70.3 (61.9–77.8)
Pancreatitis (n = 35)	19.7 (11.2–30.9)	87.5 (81.5–92.1)	40.0 (23.9–57.9)	72.1 (65.4–78.1)
Thickened enhancing wall (n = 9)	0 (0.0–5.1)	94.6 (90.1–97.5)	0 (0.0–33.6)	69.1 (62.7–75.0)
PDD 5–9 mm (n = 59)	36.6 (25.5–48.9)	80.4 (73.5–86.1)	44.1 (31.2–57.6)	75.0 (68.0–81.1)
Solid component (n = 50)	35.2 (24.2–47.5)	85.1 (78.8–90.1)	50.0 (35.5–64.5)	75.7 (68.9–81.6)
Change in PD caliber (n = 29)	21.1 (12.3–32.4)	91.7 (86.4–95.4)	51.7 (32.5–70.6)	73.3 (66.8–79.2)
≥ 1 criteria (n = 172)	87.3 (77.0–98.8)	34.5 (27.4–42.2)	36.0 (27.4–42.2)	86.6 (76.7–97.8)

AGA, American Gastroenterological Association; AN, advanced neoplasia; EUS, endoscopic ultrasound; NPV, negative predictive value; PDD, pancreatic duct dilation; PPV, positive predictive value.

Ma, G. et al. J Am Coll Surg 2016;223:729-737

pre-

Advanced Neoplasia (Ca, HGD) Missed by Guidelines

Characteristic	239 pts	Invasive carcinoma	HGD
AN missed by AGA high-risk features	AGA		
Cases missed, n	6	24	
Mean cyst size, mm (SD)	34.7 (27.5)	28.5 (14.4)	
Symptoms, n (%)	4 (66.7)	19 (79.2)	
Abdominal pain	2 (33.3)	9 (37.5)	
Pancreatitis	1 (16.7)	8 (33.3)	
Jaundice	1 (16.7)	2 (8.3)	
Cytology, n (%)			
Non-high-grade atypia	4 (66.7)	9 (37.5)	
Mucinous cystic neoplasm	1 (16.7)	3 (12.5)	
Acellular	0 (0)	3 (12.5)	
Normal	1 (16.7)	9 (37.5)	

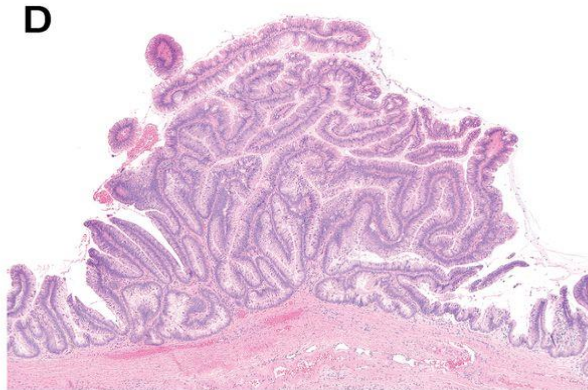
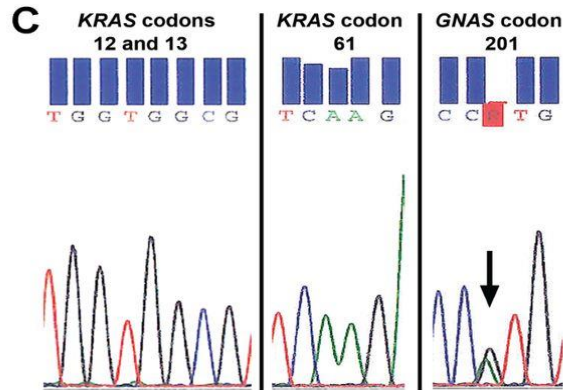
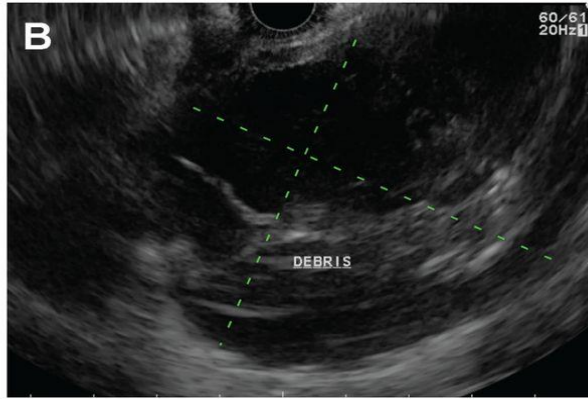
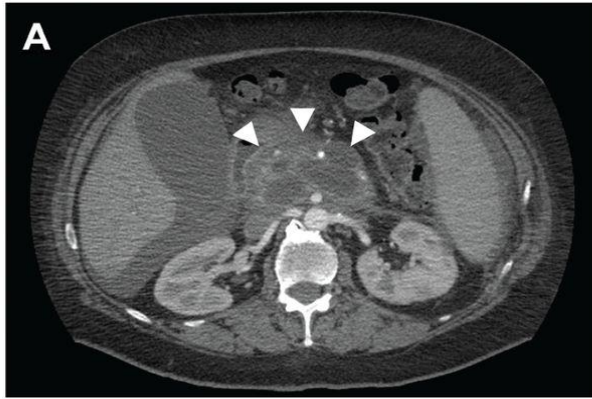
Characteristic	239 pts	Invasive carcinoma	HGD
AN missed by Fukuoka high-risk features	Fukuoka		
Cases missed, n	7	23	
Mean cyst size, mm (SD)	37.3 (24.0)	29.3 (18.5)	
Symptoms, n (%)	5 (71.4)	11 (47.8)	
Abdominal pain	4 (57.1)	6 (26.1)	
Pancreatitis	1 (14.3)	5 (21.7)	
Jaundice	0 (0)	0 (0)	
Cytology, n (%)			
Non-high-grade atypia	5 (71.4)	8 (34.8)	
Mucinous cystic neoplasm	1 (14.3)	4 (17.4)	
Acellular	0 (0)	3 (13.0)	
Normal	1 (14.3)	8 (34.8)	

Summary: Current Guidelines

- Recent AGA guidelines are not superior to the Fukuoka or European guidelines in identifying advanced neoplasia (AN) in suspected PCNs
- All guidelines have only fair PPV for detection of AN, which would lead to avoidable resections in patients without AN
- Additionally, the high-risk features of all guidelines do not accurately identify all patients with AN (↓NPV), and can miss patients with AN

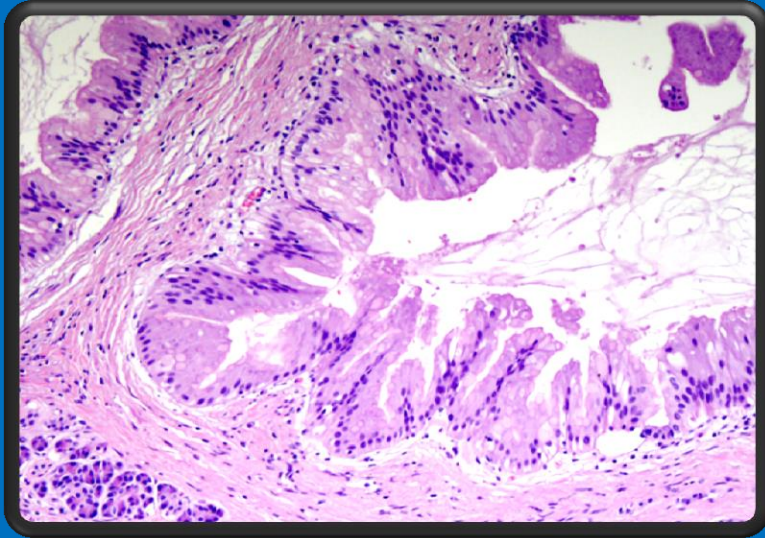
Other Diagnostic Tools

- Mucin examination - "string sign"
- Cyst fluid genetic testing
- Through the needle (TTN) endomicroscopy (nCLE)
- TTN cystoscopy
- TTN biopsy

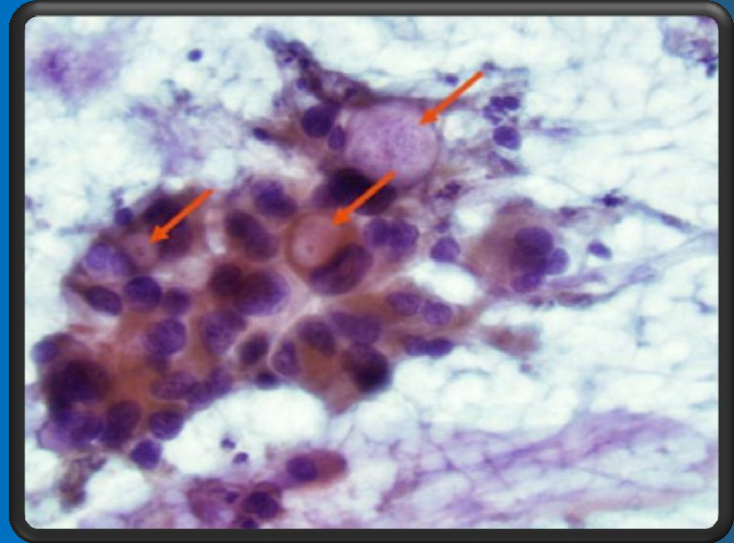


About 40%
of IPMN will
have GNAS
mutation

The answer is on the wall...



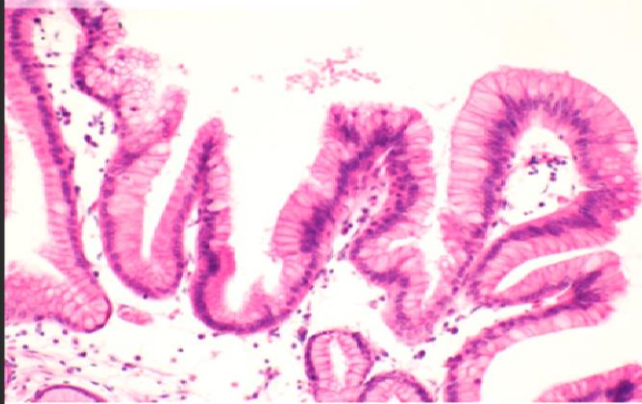
IPMN



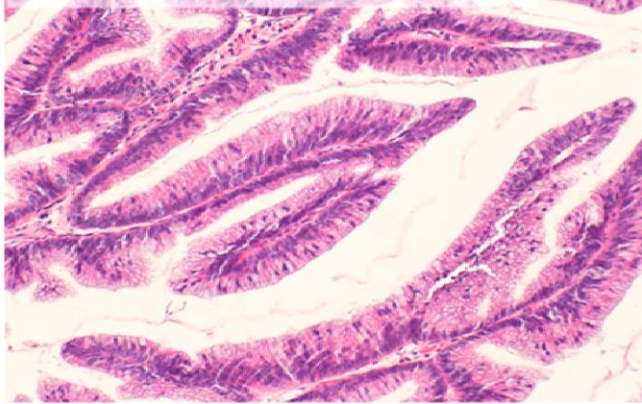
....but cytology alone is not good enough

IPMN - 4 Histologic Sub-types

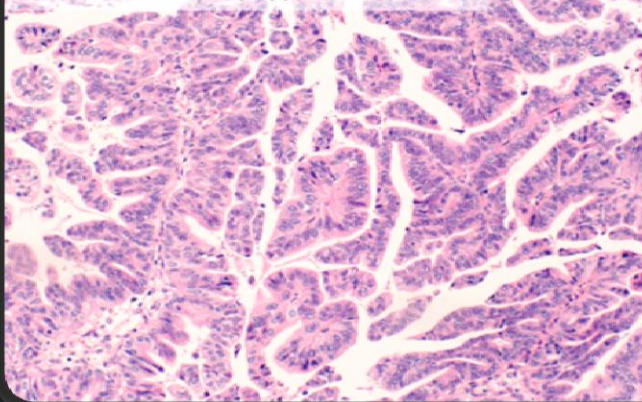
a Gastric type, adenoma



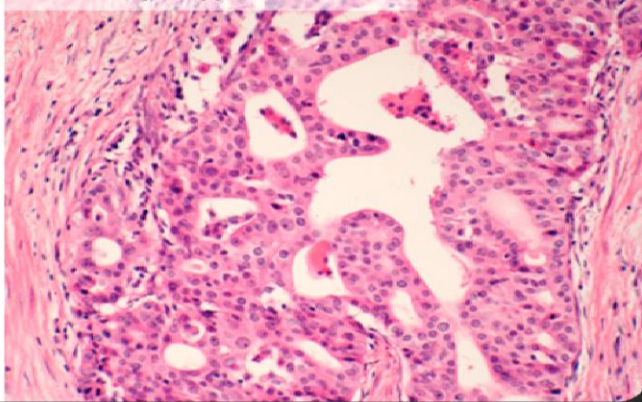
b Intestinal type, borderline neoplasm



c Pancreatobiliary type, carcinoma



d Oncocytic type, carcinoma

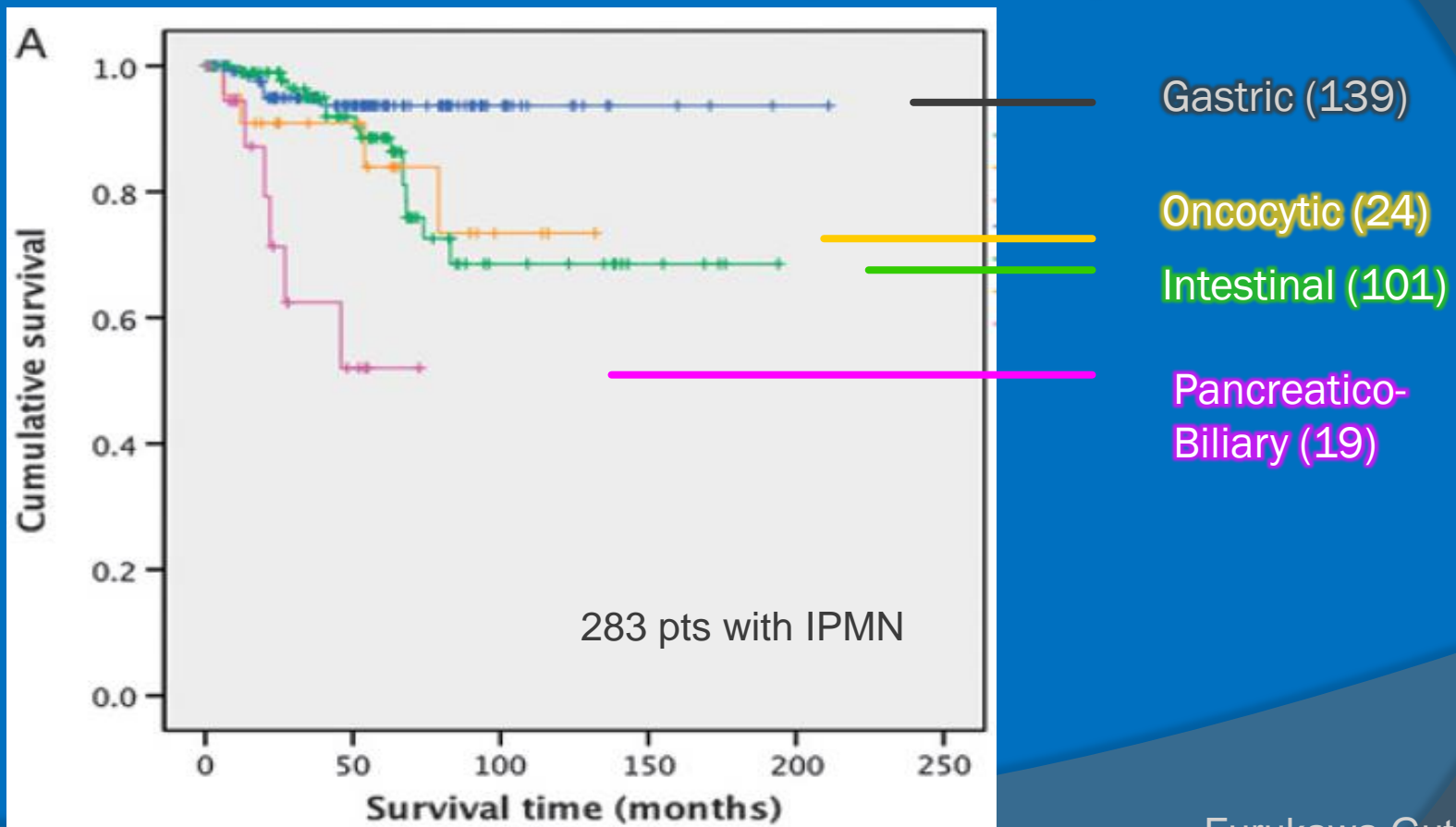


IPMN – Subtyping by Mucin Stain

TABLE 1: Subtype classification of IPMN by immunohistochemical analysis and arising invasive carcinoma [48–50].

IPMN (subtype)	Expression profile	Invasive carcinoma
Intestinal (MD-IPMN)	MUC5AC ⁺ , MUC2 ⁺ , CDX-2 ⁺ (MUC1 ⁻ , MUC6 ⁻)	Colloidal carcinoma
Pancreatobiliary (MD-IPMN)	MUC5AC ⁺ , MUC1 ⁺ (MUC2 ⁻ , MUC6 ^{+/-})	Tubular (ductal) carcinoma
Gastric (BD-IPMN)	MUC5AC ⁺ , (MUC6 ⁺) (MUC1 ⁻ , MUC2 ⁻)	Tubular (ductal) carcinoma
Oncocytic (MD-IPMN)	MUC5AC ⁺ , MUC6 ⁺ (MUC2 ^{+/-}) (MUC1 ^{+/-})	Oncocytic carcinoma

IPMN - 4 Histologic Sub-Types



Malignant transformation and overall survival of morphological subtypes of intraductal papillary mucinous neoplasms of the pancreas: A network meta-analysis

Table 1

Characteristic of the included studies.

19 Studies, 1954 pts

Study	Study year	Period of data collected	Patients, n	Age, y	Male, %	Macroscopic type	Morphological subtype
Adsay et al. [27]	2004	NR	74	NR	NR	NR	GF, IN, PB
Chadwick et al. [41]	2009	1998–2007	52	NR	NR	NR	GF, IN, PB
Distler et al. [20]	2013	1995–2010	103	65.6	53.4	All	GF, IN, PB, Onc
Furukawa et al. [21]	2011	1985–2008	283	65.0	67.8	All	GF, IN, PB, Onc
Hara et al. [42]	2013	2007–2011	36	67.1	69.4	All	GF, IN, PB, Onc
Hibi et al. [43]	2007	1989–2004	19	66.0	78.9	All	GF, IN, Onc
Hisaka et al. [37]	2013	1996–2012	57	67.0	71.7	All	GF, IN, PB, Onc
Hong et al. [44]	2009	1990–2005	37	61.0	64.9	All	GF, IN, PB, Onc
Ishida et al. [38]	2007	1988–2006	61	65.3	73.8	All	GF, IN, PB, Onc
Kang et al. [22]	2013	2000–2009	213	63.8	60.6	All	GF, IN, PB, Onc
Kim et al. [39]	2011	1996–2010	142	61.7	71.8	All	GF, IN, PB, Onc
Marchegiani et al. [45]	2014	1990–2013	171	68.0	55.0	MD, mixed	GF, IN, PB, Onc
Miyasaka et al. [46]	2010	NR	140	66.6	60.9	All	GF, IN, PB, Onc
Nakata et al. [47]	2011	1986–2008	171	68.0	61.5	All	GF, IN, PB, Onc
Okada et al. [48]	2010	1991–2008	80	67.0	70.0	All	GF, IN, PB, Onc
Takasu et al. [40]	2011	2000–2007	61	66.5	73.8	All	GF, IN, PB, Onc
Tamura et al. [49]	2014	1997–2012	55	70.0	55.0	MD	GF, IN, PB, Onc
Xiao et al. [50]	2011	1990–2009	30	64.3	53.3	All	PB, Onc
Yamada et al. [23]	2014	1993–2012	169	67.0	62.1	All	GF, IN, PB, Onc

All: main-duct, branch-duct mixed IPMNs, MD: main-duct, GF: gastric, IN: intestinal, PB: pancreatobiliary, Onc: oncocytic, NR: not reported.

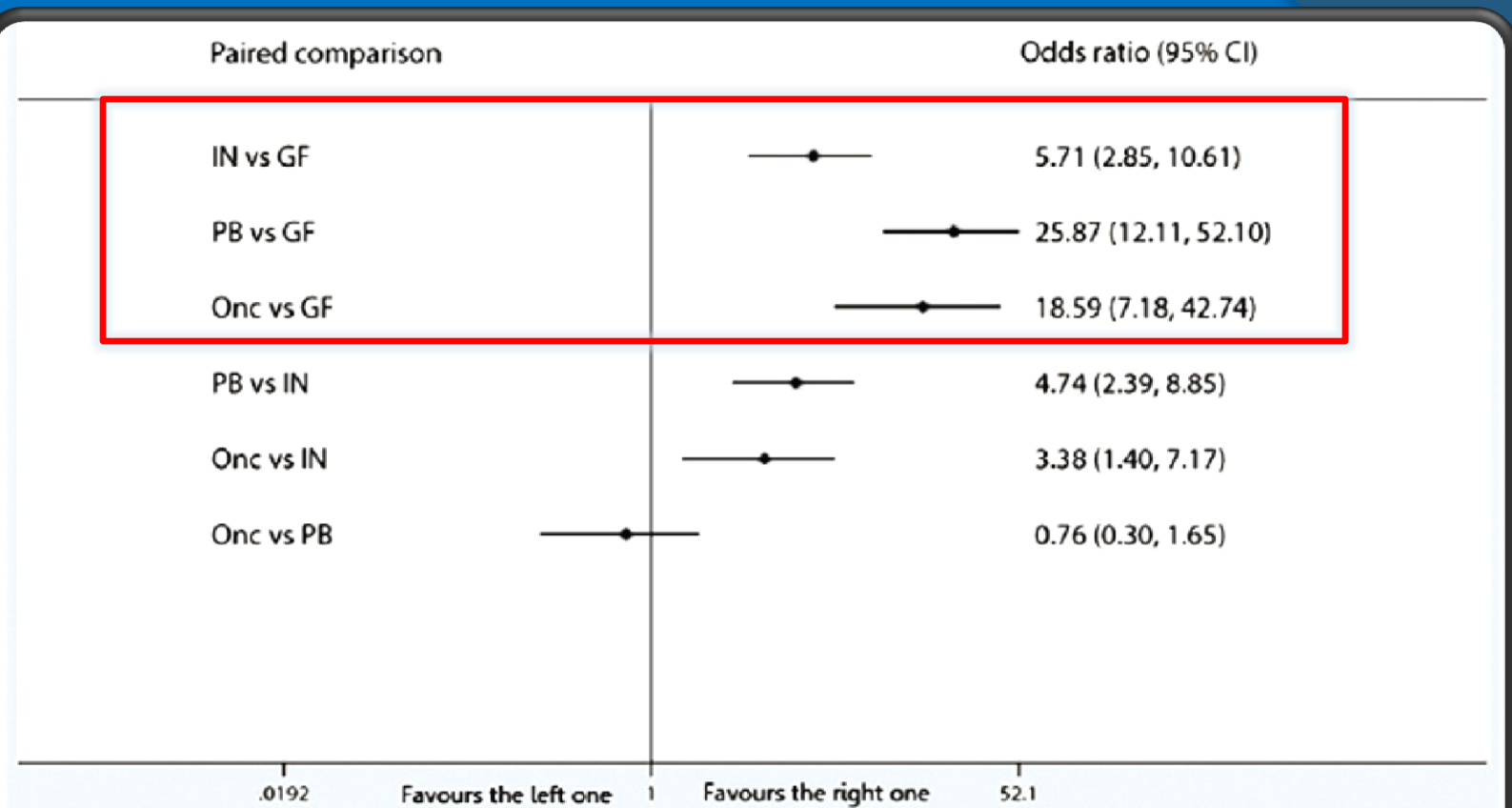


Fig. 2. Invasive intraductal papillary mucinous neoplasm for each pair-wise comparison.

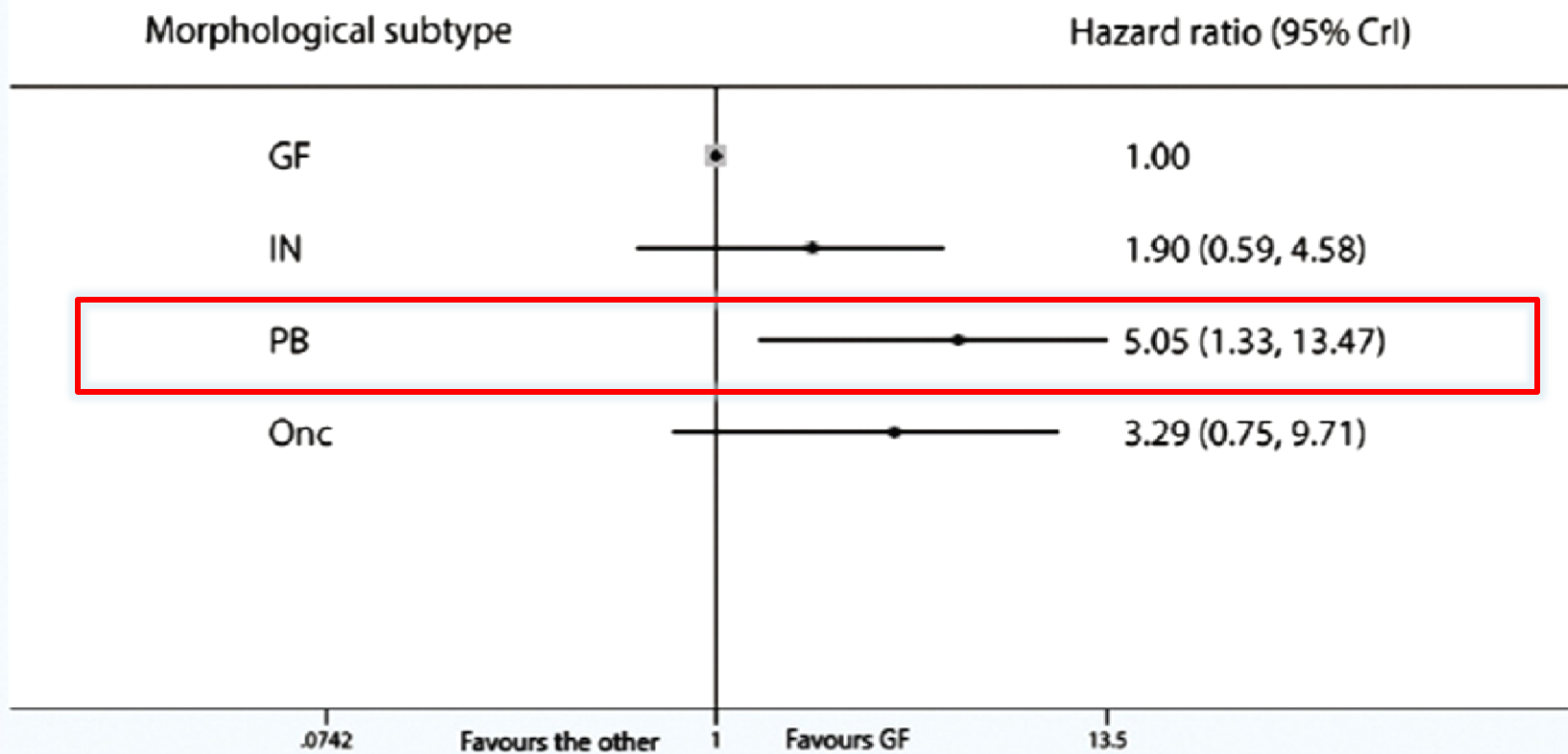
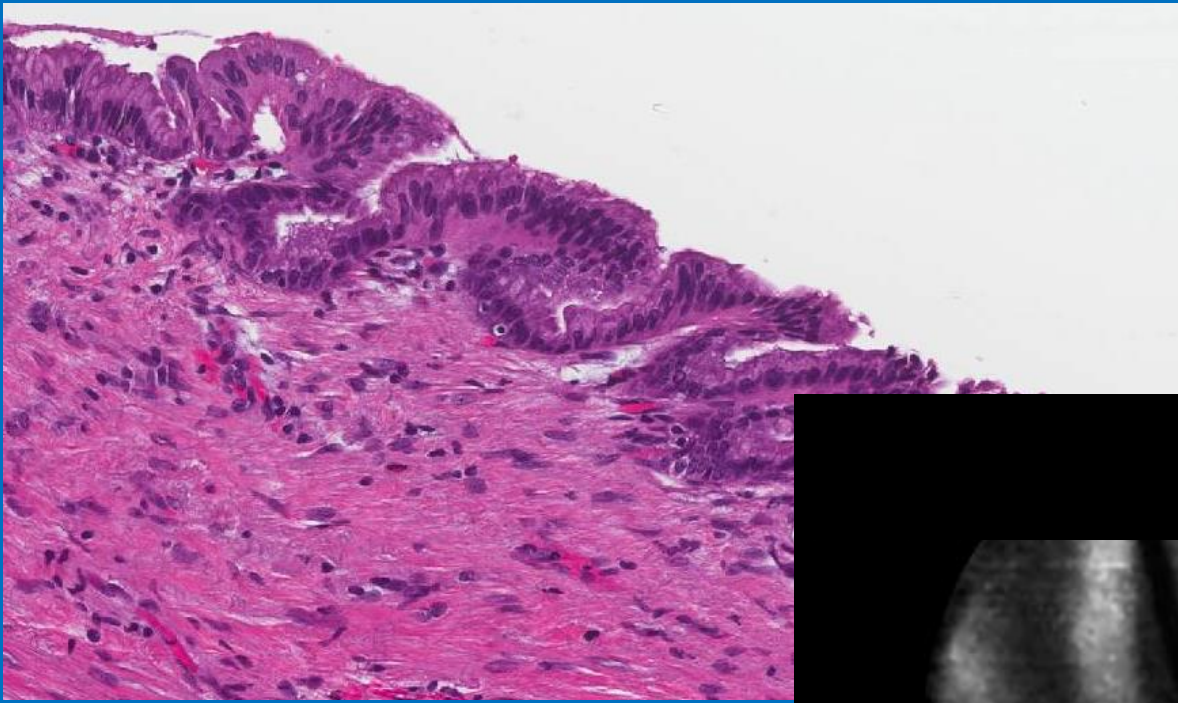
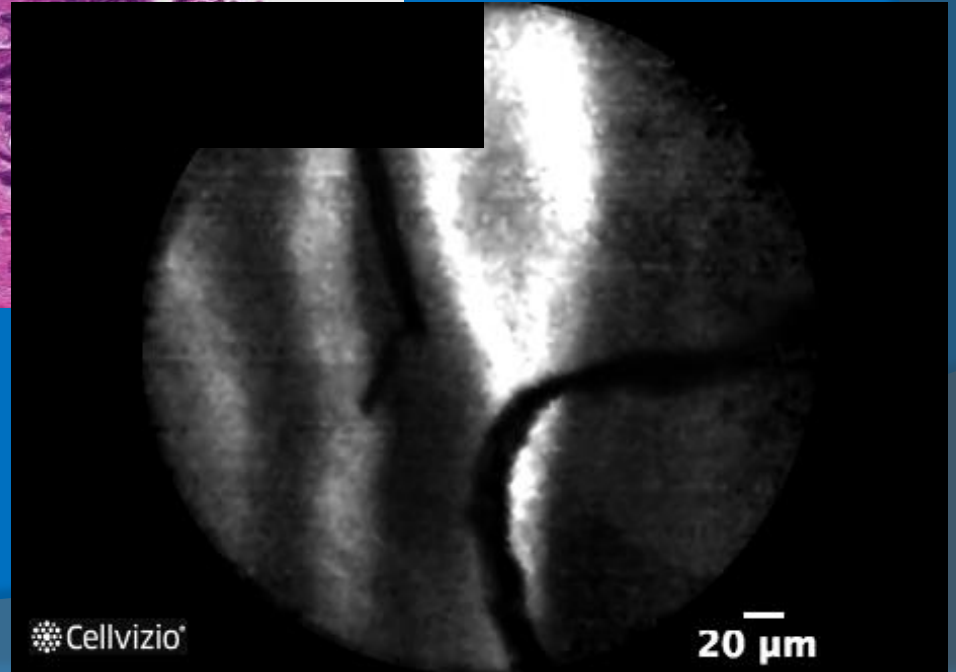


Fig. 3. Overall survival for each subtype, compared with overall survival for gastric-type intraductal papillary mucinous neoplasm.

nCLE - IPMN



Gastric Subtype



IPMN – Gastric Subtype may have ↑CEA

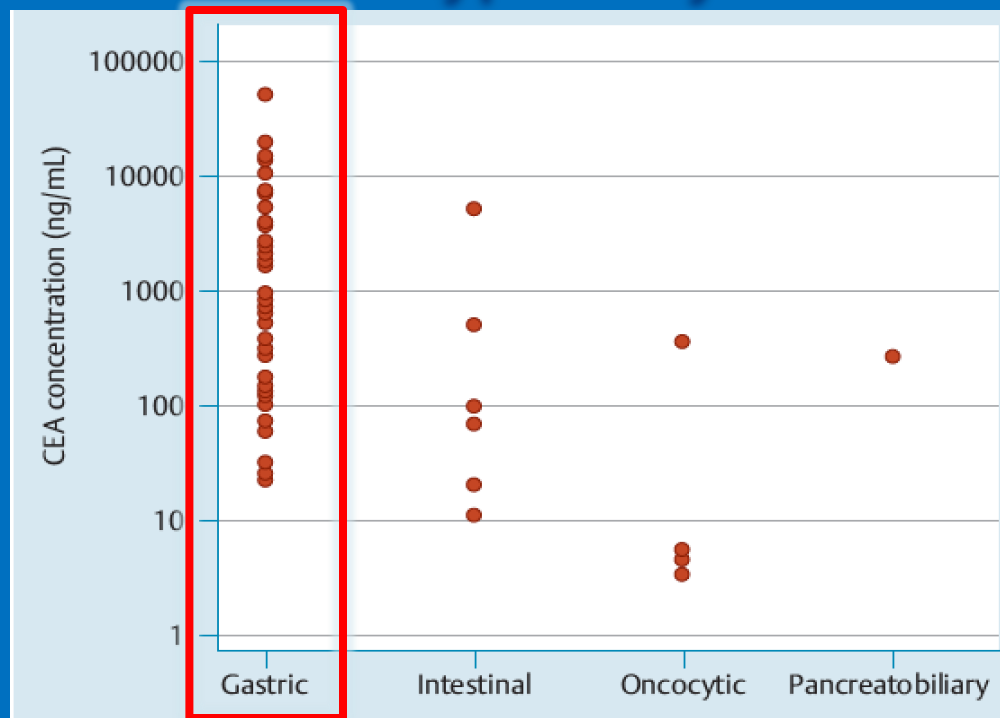
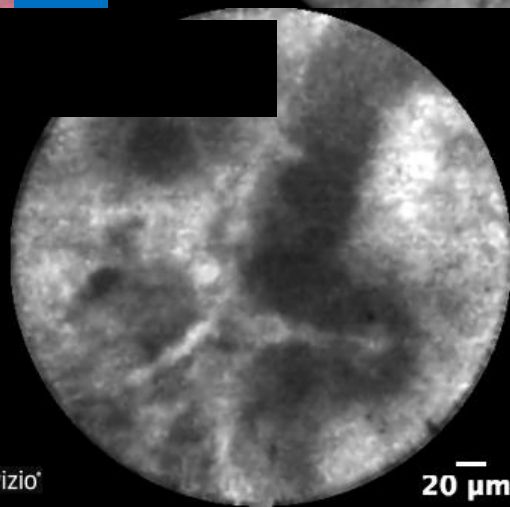
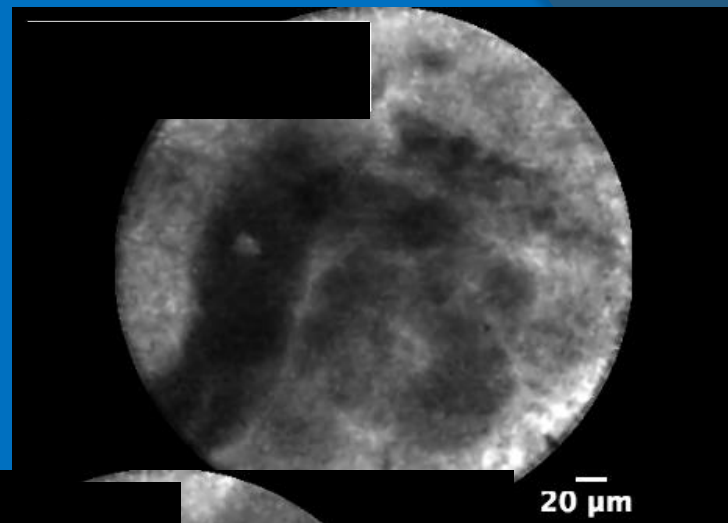
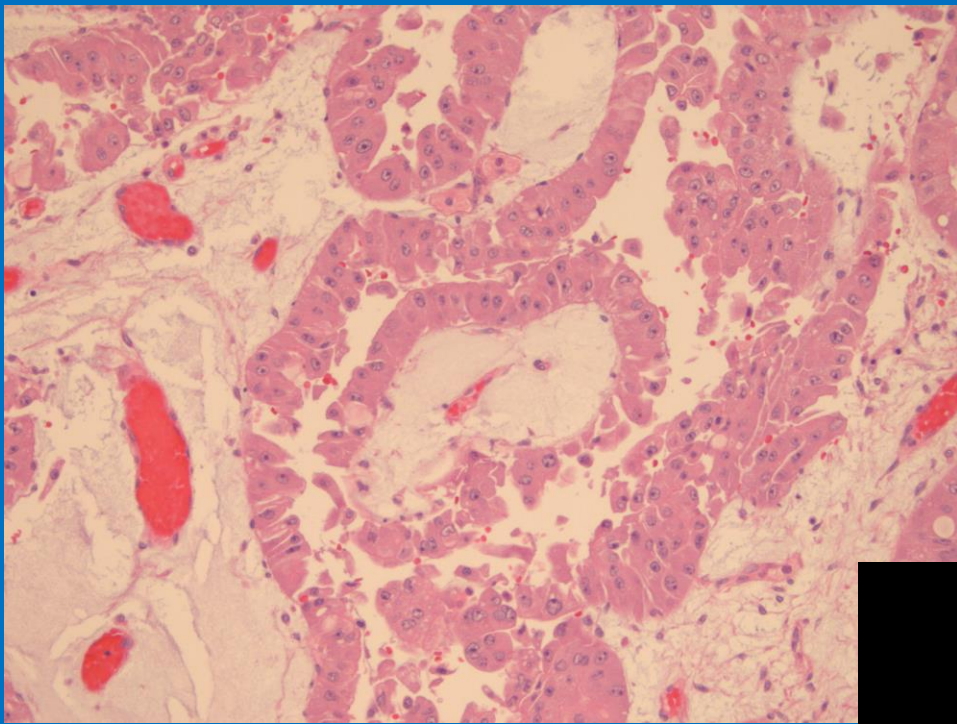


Fig.1 Cyst fluid carcinoembryonic antigen (CEA) concentrations (log scale) according to epithelial subtypes of intraductal papillary mucinous neoplasms (n=60). Epithelial subtype was significantly associated with cyst fluid CEA concentration ($P=0.012$, Kruskal–Wallis test).

nCLE - IPMN



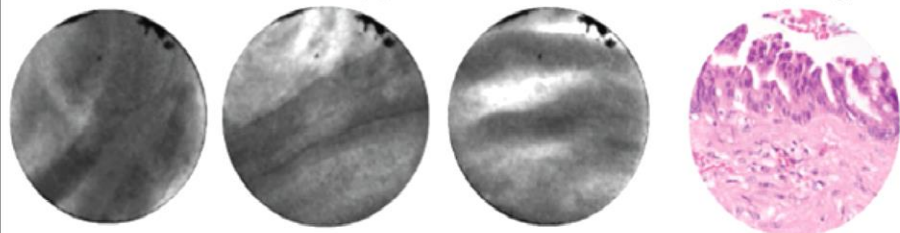
Oncocytic Subtype

Confocal Endomicroscopy Characteristics of Different Intraductal Papillary Mucinous Neoplasm Subtypes

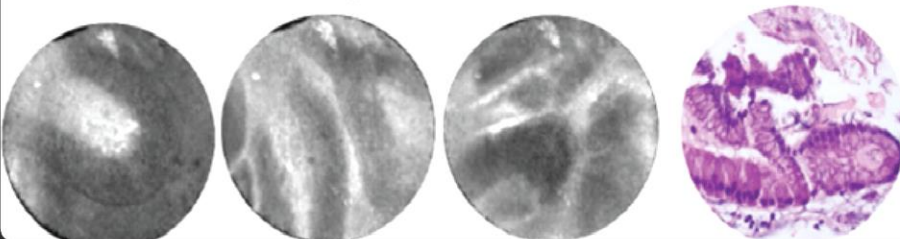
Amrit K Kamboj¹, John M Dewitt², Rohan M Modi³, Darwln L Conwell⁴, and Somashekar G Krishna⁴

Pancreatobiliary type

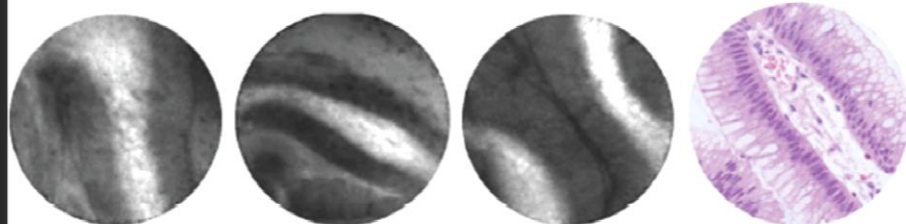
Histopathology



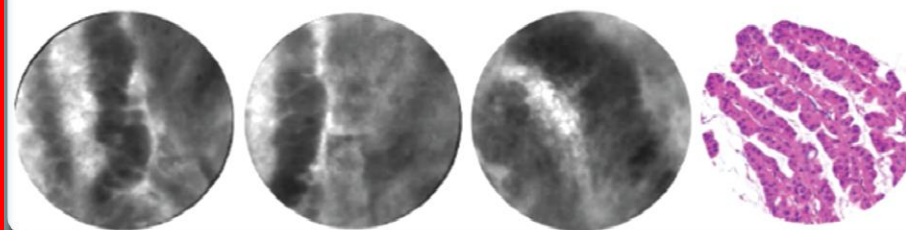
Gastric type



Intestinal type

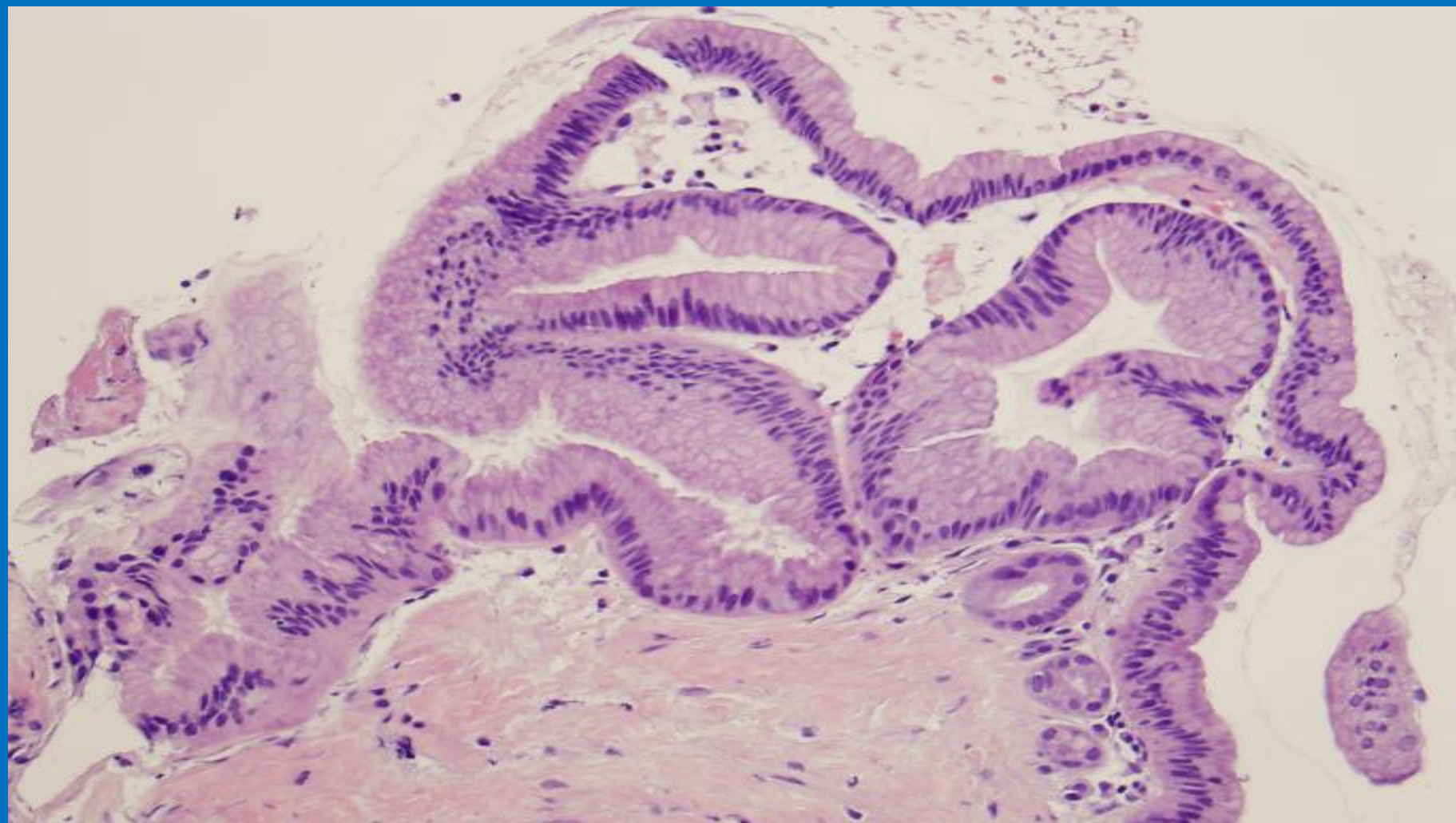


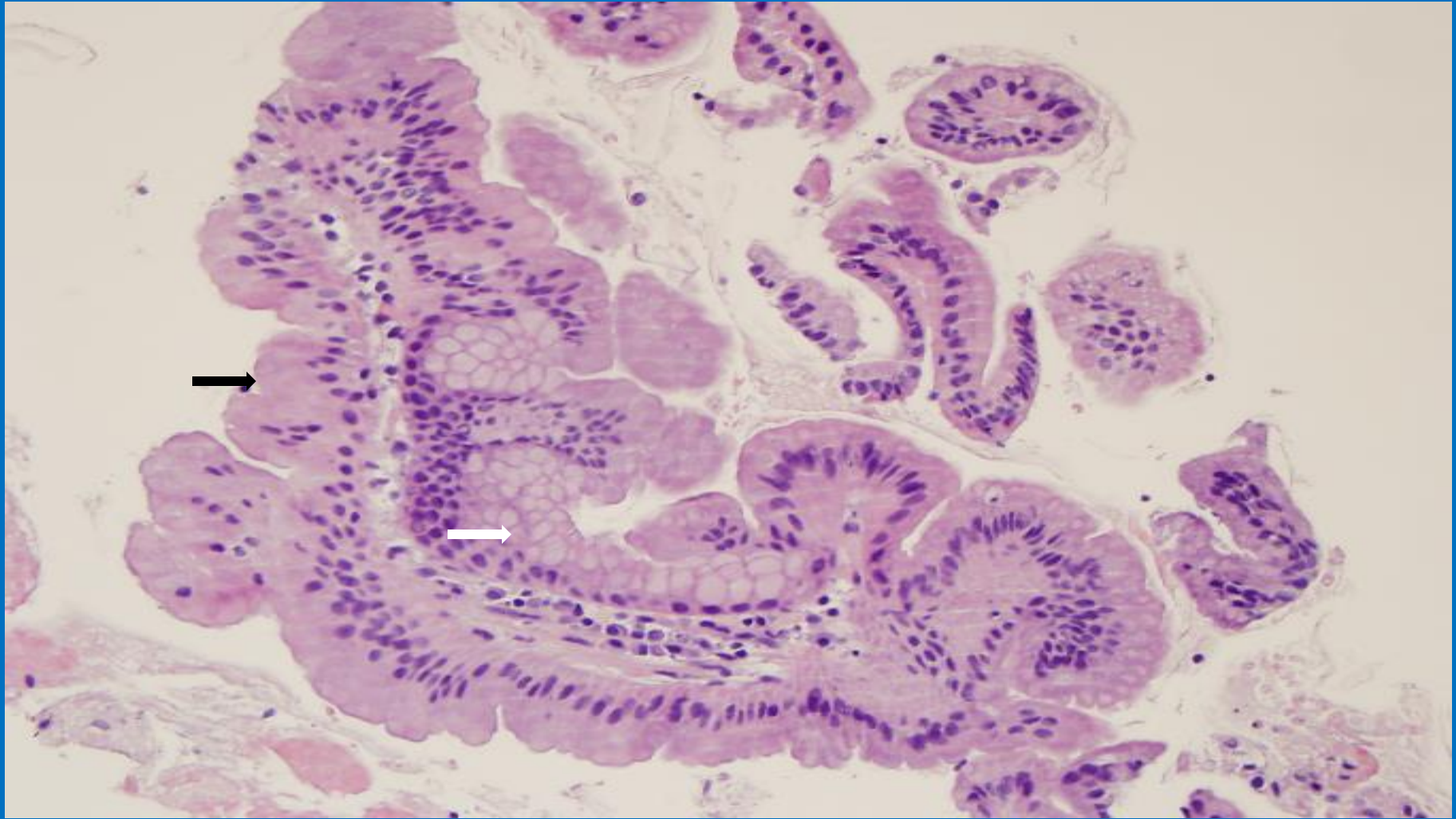
Endocystic type

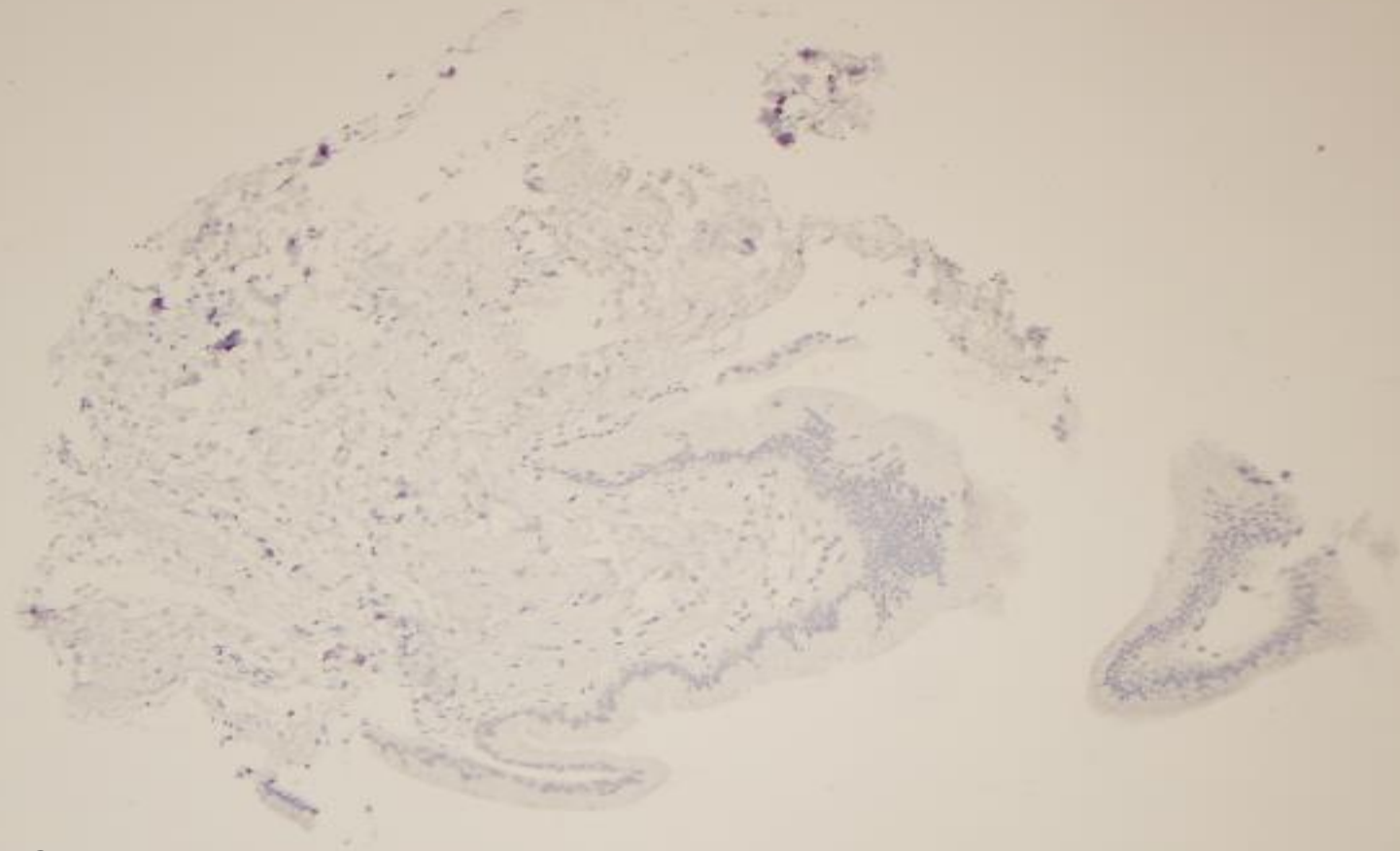


EUS Through the Needle (TTN) Biopsy



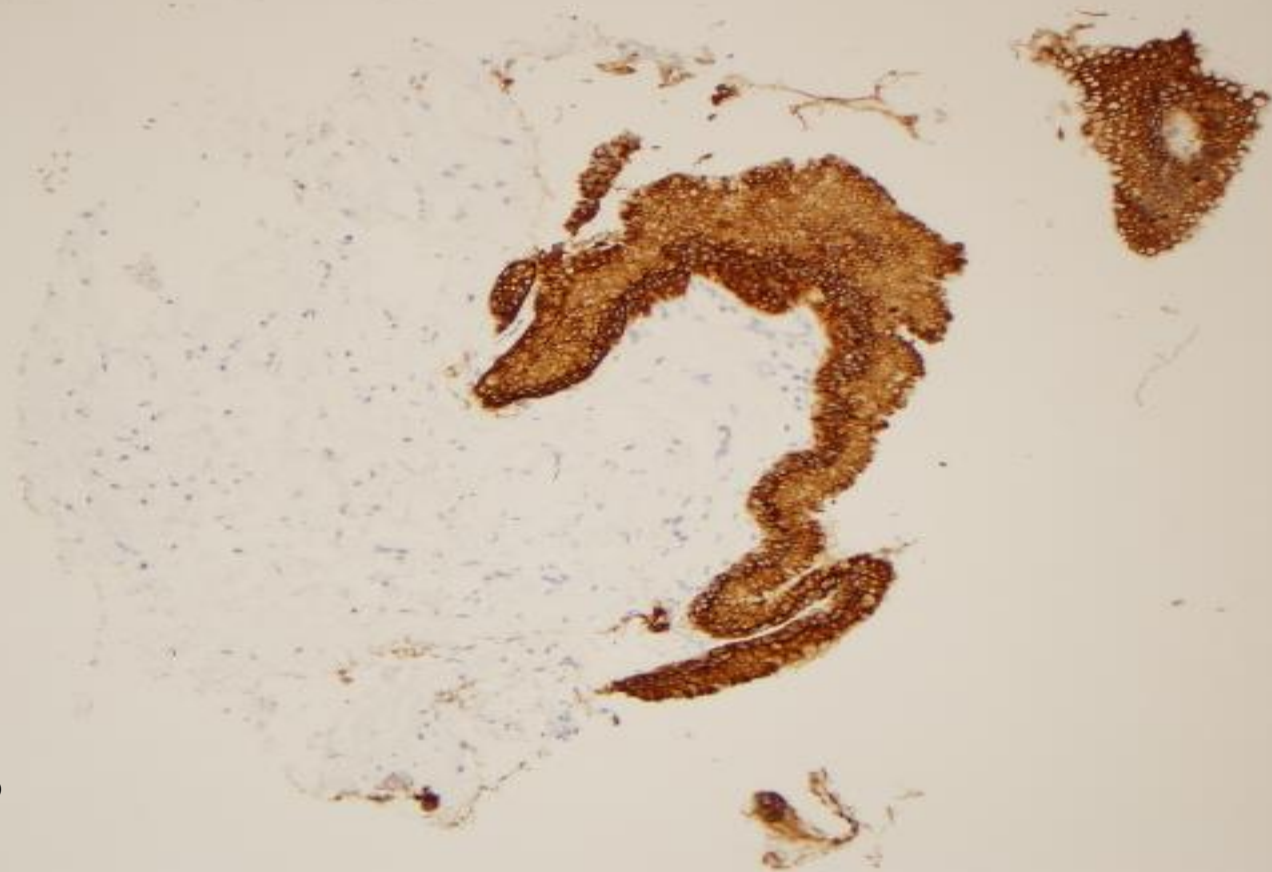


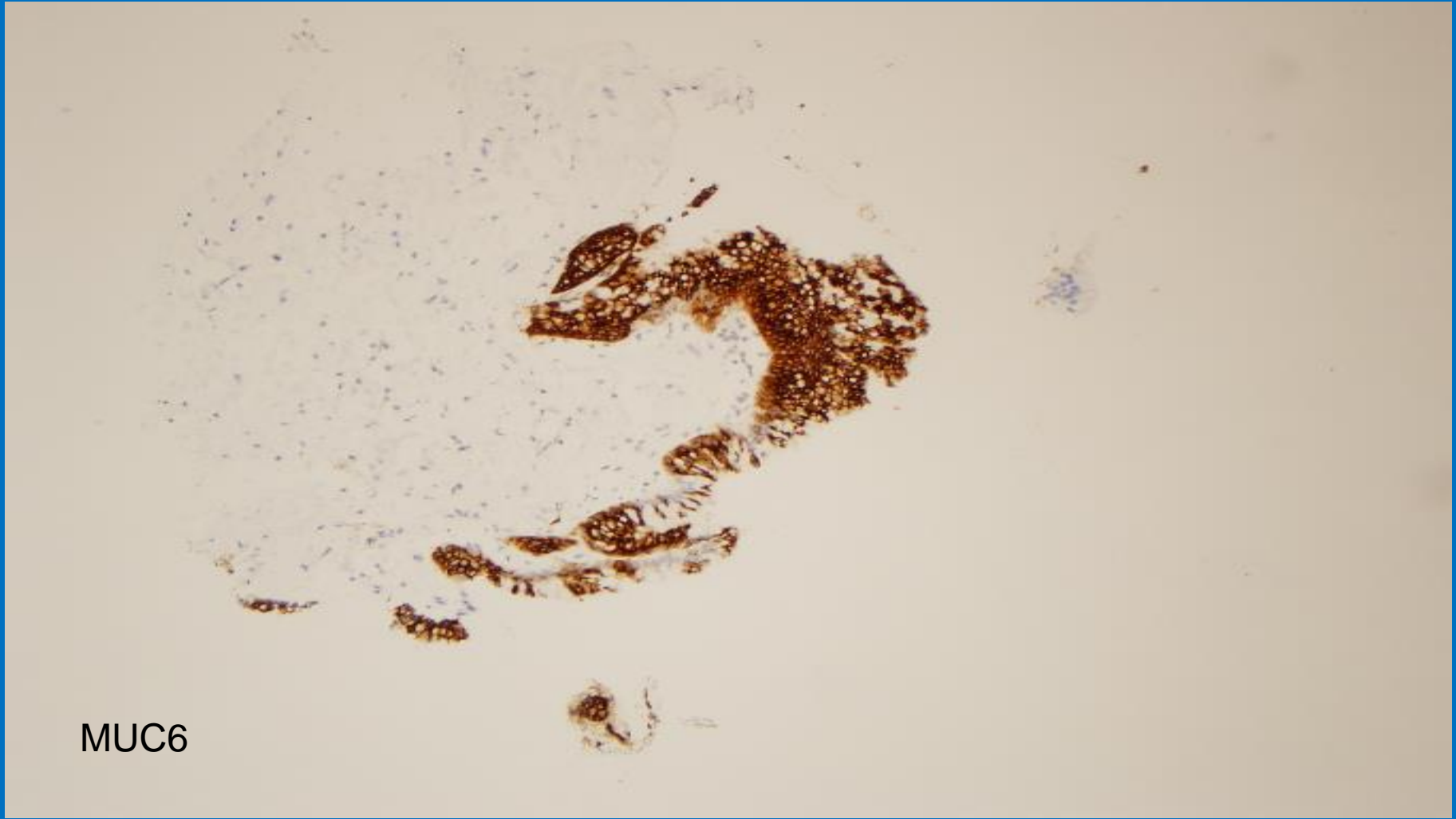




MUC2

MUC5



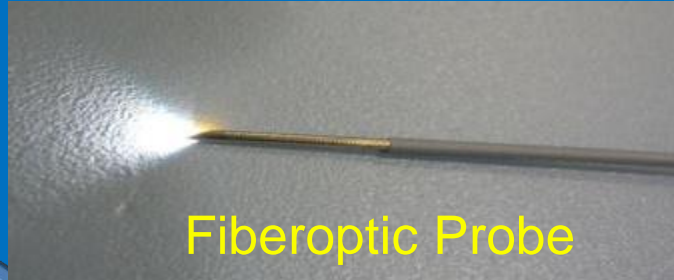


MUC6

Endoscopic Ultrasound (EUS)-Guided Through the Needle Forceps Biopsy (TTNFB) of Pancreatic Cystic Lesions Demonstrate Significantly Higher Diagnostic Yield Over Fine Needle Aspiration

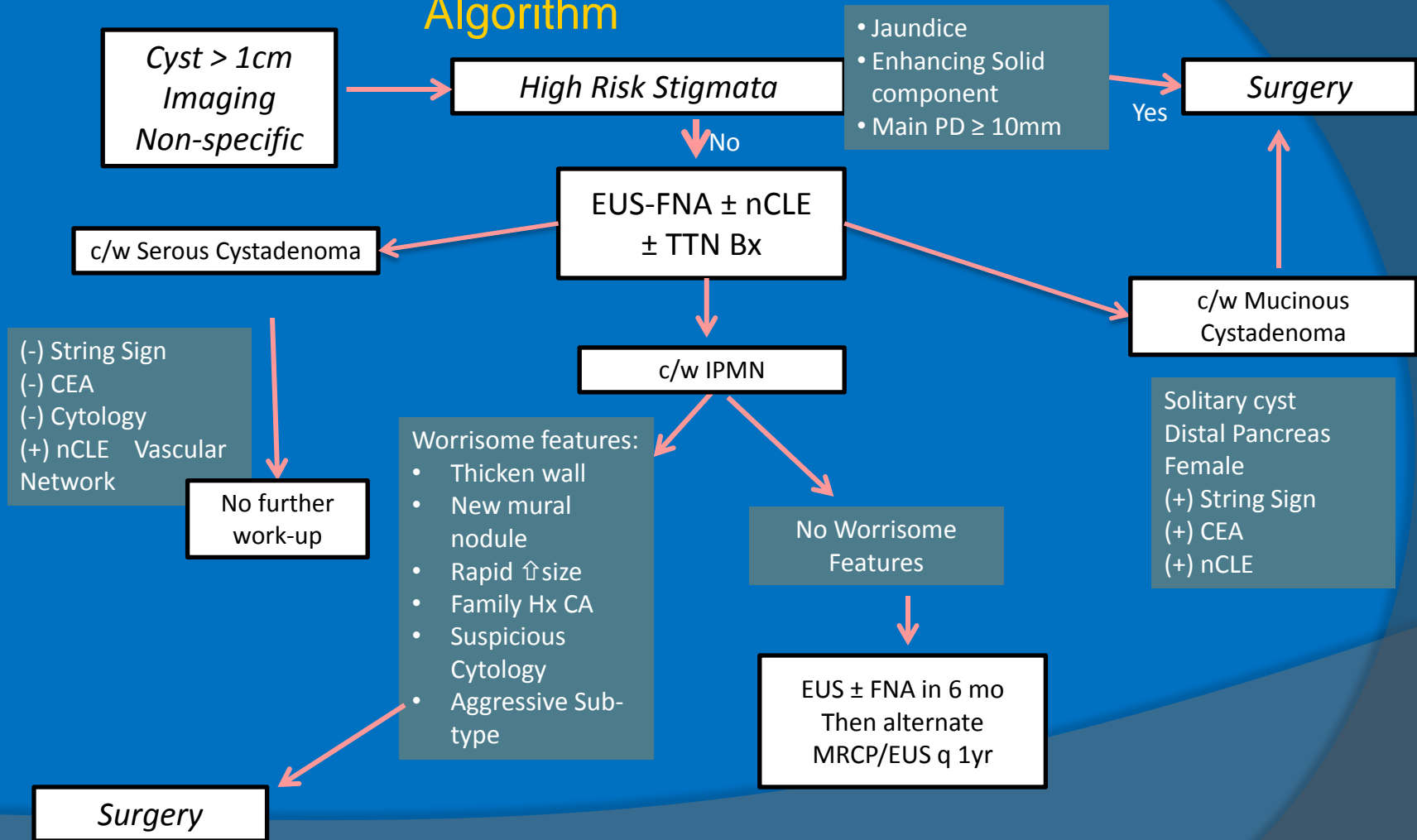
- 15 cystic lesions (mean 26.6mm)
- Technical success was 87% (13/15).
- 1 AE: intra-cystic bleeding (self-limited)
- No pancreatitis
- EUS-guided TTNFB with histologic analysis yielded a diagnosis in 11/15 patients (73%) vs 0/15 (0%) patients using EUS-FNA and cytologic analysis ($p < 0.01$)
- 7 of 8 IPMNs were able to be subtyped based on histologic analysis and MUC staining

EUS-TTN Imaging & Biopsy



TTN forceps

Algorithm



Pancreatic Cystic Neoplasms: *Guidelines and beyond*

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Professor and Chief, Gastroenterology

Vincent & Anna Kong Endowed Chair, GI Endoscopic Oncology

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UC Irvine Health