The World Health Organization

Reporting System for Pancreaticobiliary Cytopathology

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Content material for this talk

The World Health Organization Reporting System for Pancreaticobiliary Cytopathology

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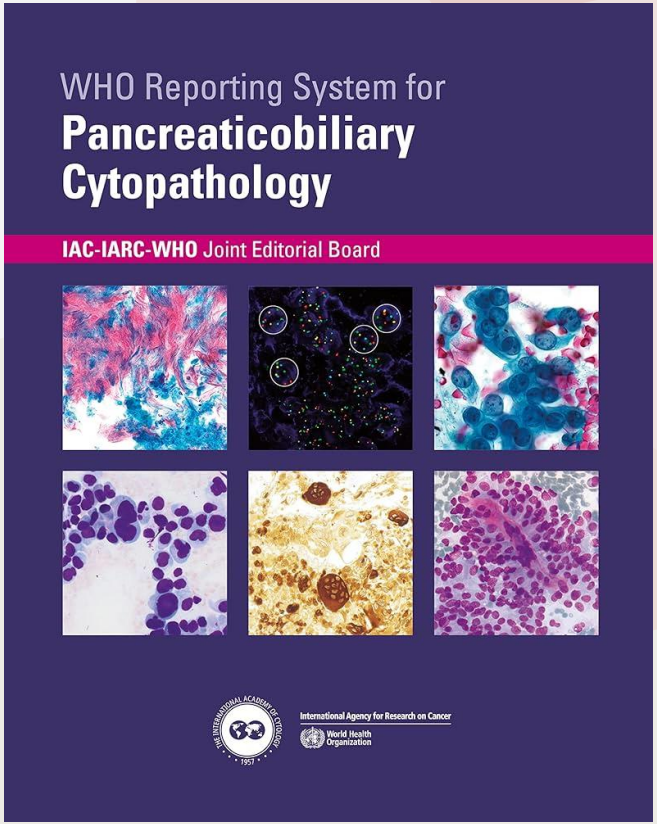
The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology



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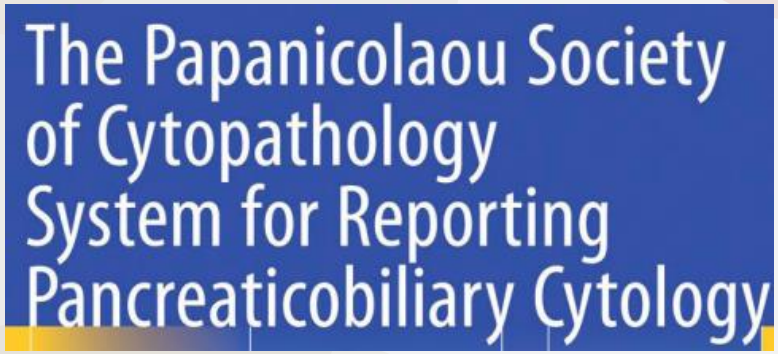
01 Introduction to the WHO Reporting System

- Developed jointly by World Health Organisation, the international Academy of Cytology and International Agency for Research on Cancer in 2022
- Revises the Papanicolaou Society of Cytopathology (PSC) system for Reporting Pancreaticobiliary Cytology
- Features 7 diagnostic categories that aligns with the WHO classification of Digestive System Tumours (5th ed, 2019)
- Aims to provide an evidence-based terminology system with associated risk of malignancy and diagnostic management recommendations

Diagnostic categories WHO Reporting System (2022)
1. Non diagnostic
2. Benign
3. Atypical
4. PaN-Low
5. PaN-High
6. Suspicious for malignancy
7. Malignant

01 Recap on the PSC Reporting system (2015)



Papanicolaou Society of Cytopathology System for Reporting Pancreatico-biliary Cytology

I. Nondiagnostic
II. Negative (for malignancy)

- Benign pancreatic tissue (in appropriate clinical setting)
- Acute pancreatitis
- Chronic pancreatitis
- Autoimmune pancreatitis
- Pseudocyst
- Lymphoepithelial cyst
- Splenule/accessory spleen

III. Atypical
IV. Neoplastic

Benign

- Serous cystadenoma
- Neuroendocrine microadenoma
- Lymphangioma

Other

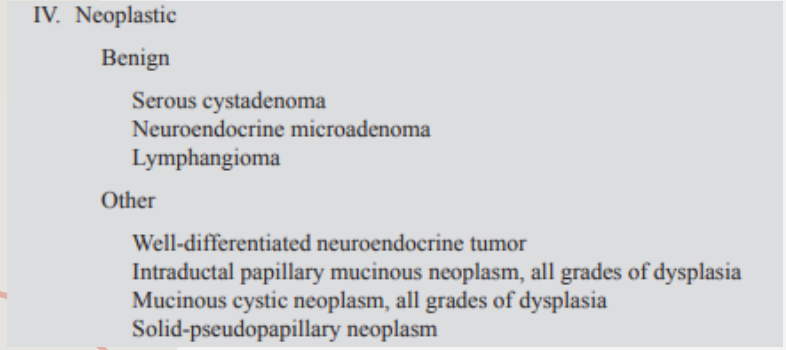
- Well-differentiated neuroendocrine tumor
- Intraductal papillary mucinous neoplasm, all grades of dysplasia
- Mucinous cystic neoplasm, all grades of dysplasia
- Solid-pseudopapillary neoplasm

V. Suspicious (for malignancy)
VI. Positive or Malignant

- Ductal adenocarcinoma of the pancreas and its variants
- Cholangiocarcinoma
- Acinar cell carcinoma
- Poorly differentiated (small and large cell) neuroendocrine carcinoma
- Pancreatoblastoma
- Lymphoma
- Metastatic malignancy

01

Controversial issues related to the PSC Reporting system (2015)



IV. Neoplastic

Benign

Serous cystadenoma
Neuroendocrine microadenoma
Lymphangioma

Other

Well-differentiated neuroendocrine tumor
Intraductal papillary mucinous neoplasm, all grades of dysplasia
Mucinous cystic neoplasm, all grades of dysplasia
Solid-pseudopapillary neoplasm

- Inclusion of both benign, premalignant and low-grade malignant neoplasms in the "neoplastic category"
- Difficult to determine a meaningful ROM for the neoplastic category as a whole and even for the "Other" group, because the "Other" category includes a range of low-grade dysplastic lesions with a low ROM and high-grade dysplastic intraductal lesions with a much higher ROM.
- Does not align with categorization as per the WHO Classification of Digestive System Tumours (5th ed, 2019).

01 Principal differences between WHO and PSC

PSC Reporting System (2015)	WHO Reporting System (2022)
	Benign • Serous cystadenoma • Lymphangioma
Neoplastic: Benign • Serous cystadenoma • Lymphangioma	**PaN-low** • IPMN with low grade atypia • MCN with low grade atypia
Neoplastic: Other • Intraductal papillary mucinous neoplasm (IPMN) • Mucinous neoplasm (MCN) • Well differentiated neuroendocrine tumour • Solid-pseudopapillary neoplasm	**PaN-high** • IPMN with high grade atypia • MCN with high grade atypia
	Malignant • Well differentiated neuroendocrine tumour • Solid-pseudopapillary neoplasm

02 Diagnostic categories

pancreatic cytology

Definitions, ROM, discussion of a few specific entities, and recommendations

02 Insufficient/Inadequate/Nondiagnostic

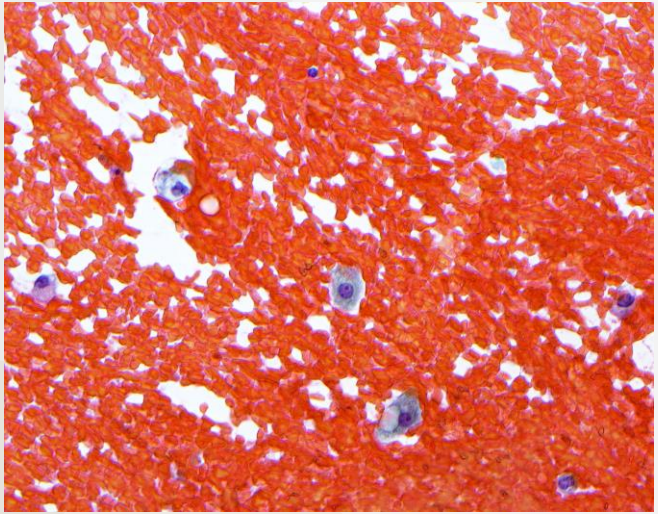
A specimen categorized as “inadequate/insufficient/ nondiagnostic” is one that for qualitative and/or quantitative reasons does not permit a diagnosis of the targeted lesion.

No established number of cells or epithelial tissue fragments defining minimum cellularity.

Must take into consideration imaging findings and chemical analysis of cyst fluids.

Risk of Malignancy: 5 - 25 %

02 Insufficient/Inadequate/Nondiagnostic



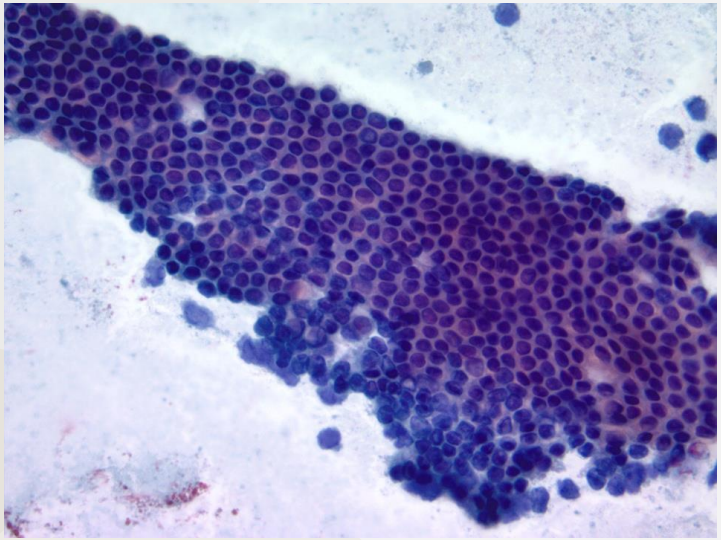
Bloody FNAB with histiocytes, inadequate for diagnosis

Reasons for this category

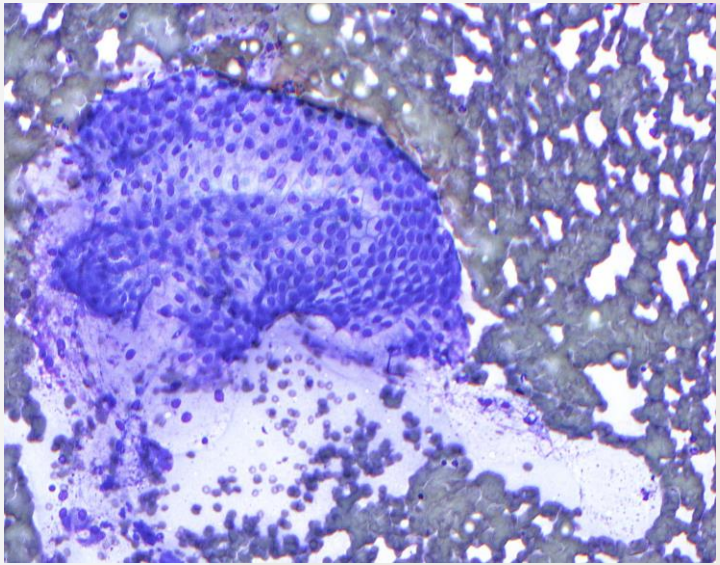
- Obscuring blood, contaminant gastrointestinal epithelium* or other material
- Normal pancreatic tissue in the context of a targeted solid or cystic mass*
- Acellular FNAB of a solid mass or duct brushing
- Acellular FNAB of a cyst without evidence of a mucinous etiology such as thick, colloid-like extracellular mucin or elevated CEA (> 192 ng/mL)

Risk of Malignancy: 5 - 25 %

02 Contaminant gastrointestinal epithelium only



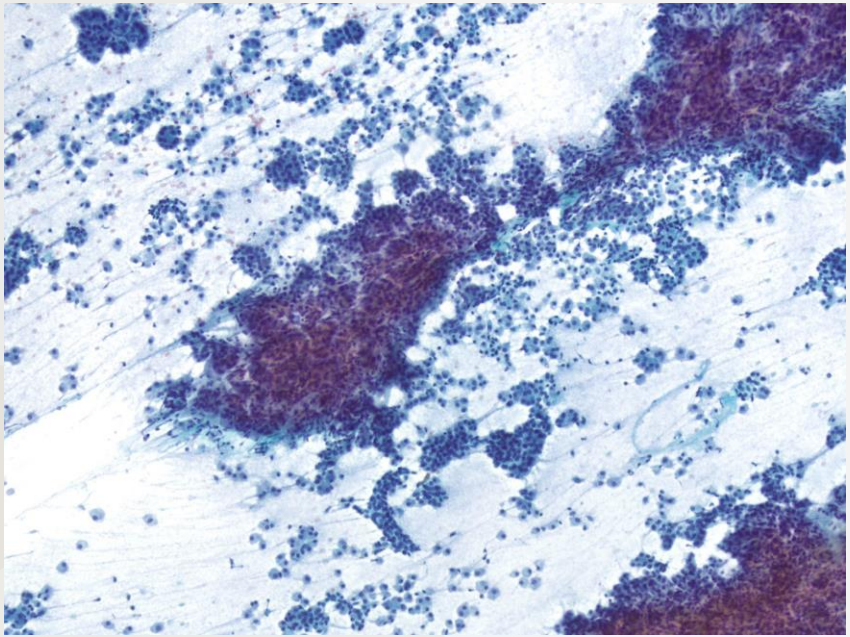
Benign duodenal epithelium
Non diagnostic



Benign gastric epithelium
Diagnostic pitfall when mucinous cyst is the clinical consideration!

02

Nondiagnostic ?

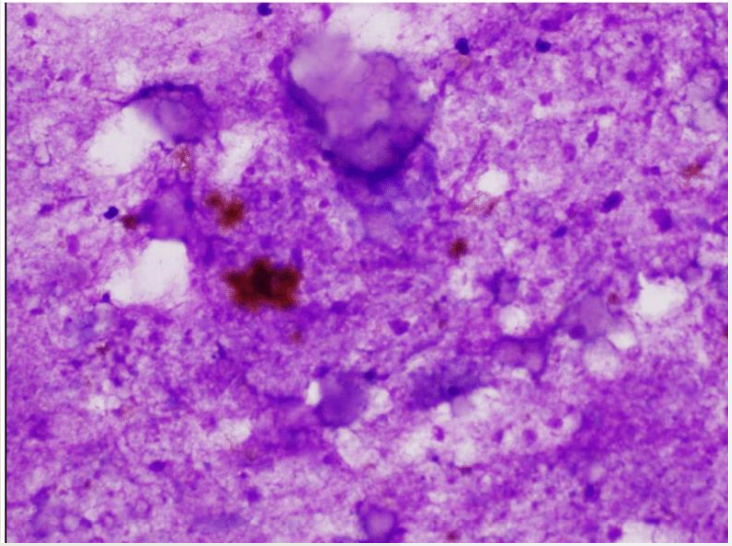


Benign pancreatic tissue only

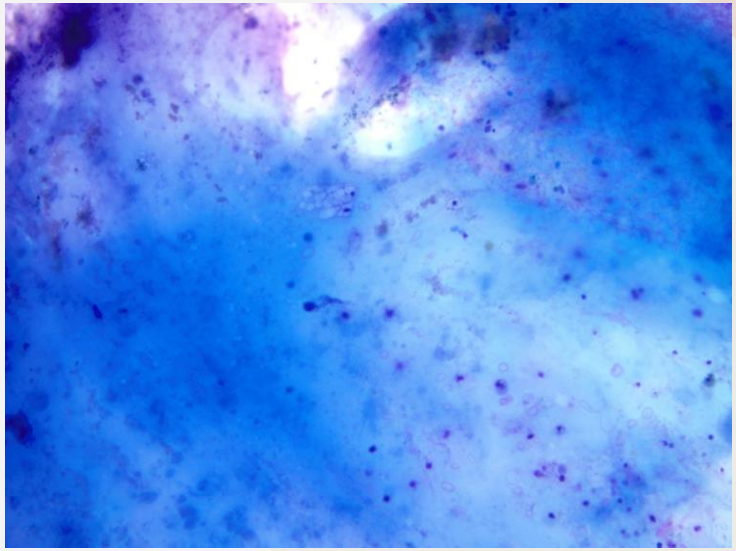
- In the setting of a distinct solid or cystic lesion of imaging, benign pancreatic acinar/ductal epithelial cells in are classified as “non-diagnostic”
- Some labs may classify such cases as “benign”, with a caveat in the report to indicate that the biopsy is not likely representative.
- Most of our NUH cytopathologists prefer to classify as “non-diagnostic”

02

Acellular cyst contents?



Degenerate cyst contents
May be compatible with pseudocyst in the right clinical context



Thick, colloid like mucin
PaN-low: Mucinous neoplasm

02 Benign/Negative for malignancy

Demonstrates unequivocal benign cytopathological features, which may or may not be diagnostic of a specific process or benign neoplasm.

5. Chapter 4: Diagnostic category: Benign / Negative for malignancy

- Introduction
- Definition
- Discussion and background
- Risk of malignancy and management recommendations

Benign non-neoplastic processes

- Normal pancreatic and biliary parenchyma and contaminants
- Acute pancreatitis
- Cholangitis
- Chronic pancreatitis
- Groove/paraduodenal pancreatitis
- Autoimmune and IgG4-related pancreatitis
- Lymphoepithelial cyst
- Pseudocysts
- Splenule (accessory spleen)

Benign neoplastic processes

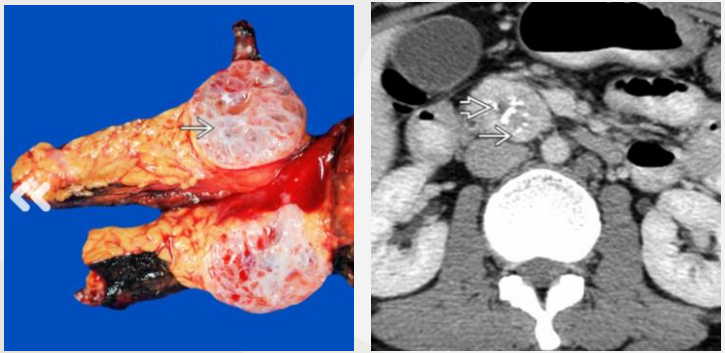
- Serous cystadenoma
- Schwannoma
- Lymphangioma
- Other rare benign neoplasms

Sample reports: Benign / Negative for malignancy

Risk of Malignancy: 0 - 15 %

02

Serous cystadenoma

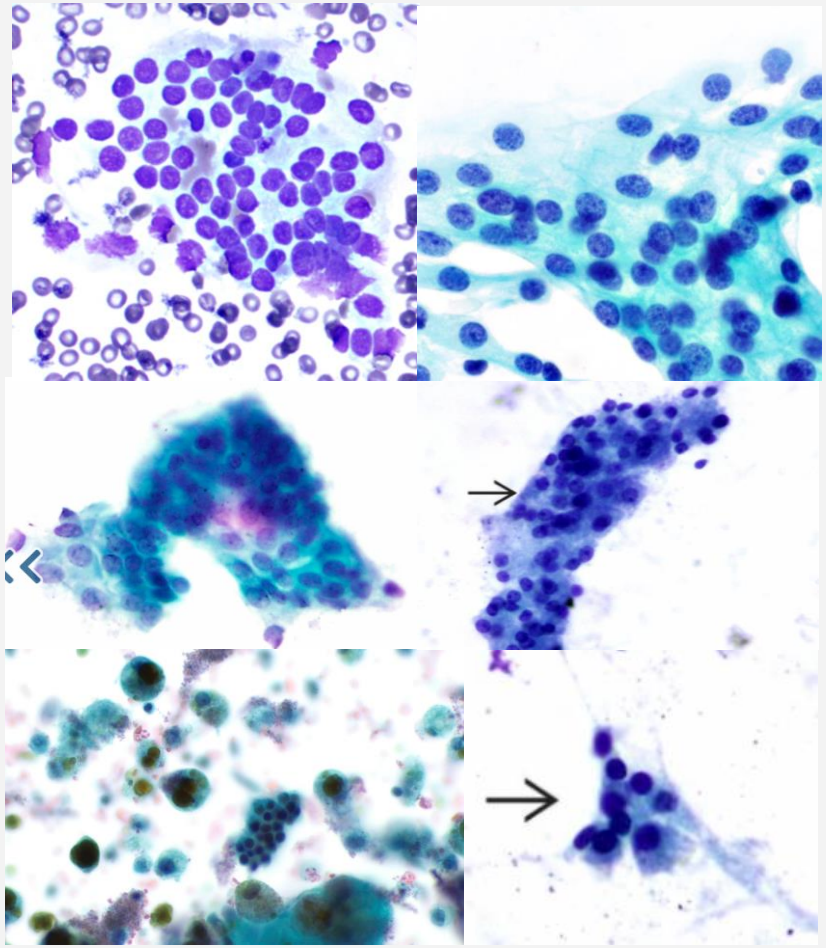


Serous cystadenoma
Gross: well-circumscribed multiloculated mass
CT: characteristic central stellate scar

Most common benign pancreatic cystic neoplasm. 2/3 female; strong association with VHL

Imaging:

- MRI: T2 hyperintense, T1 hypointense
- EUS: Well circumscribed, multiloculated mass with central stellate scar and calcifications.
- Does not communicate with pancreatic duct system



Key cytopathological features

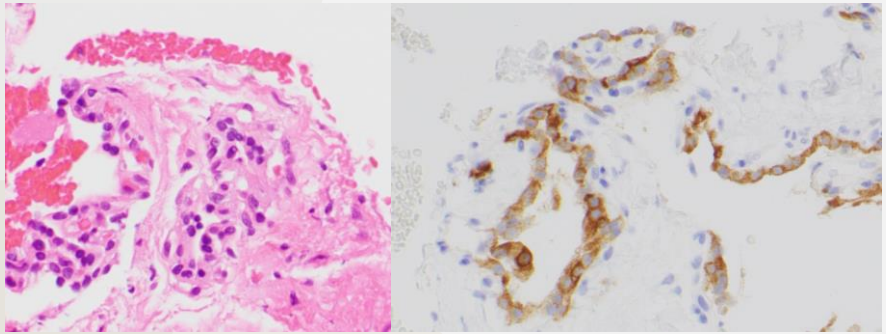
- Sparsely cellular, bland tumour cells in loose fragments or sheets
- Cuboidal cells with granular/clear cytoplasm
- Small round nuclei with indistinct nucleoli

Often “Non-diagnostic”:

- Microcysts may not produce cyst fluids
- Oligocystic SCA may only yield histiocytes and haemosiderin laden macrophages.

02

Serous cystadenoma



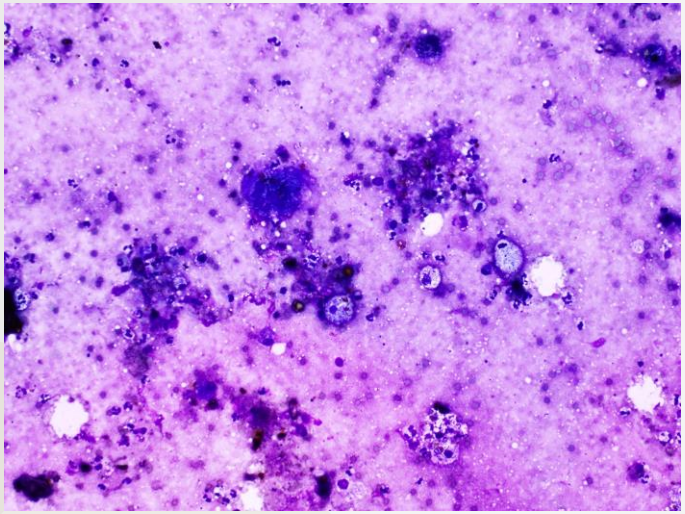
Serous cystadenoma
cyst lining cells show cytoplasmic staining for a-inhibin

IHC: A-inhibin is a sensitive marker – shows cytoplasmic staining in 88% of cases

Cyst fluid analysis:

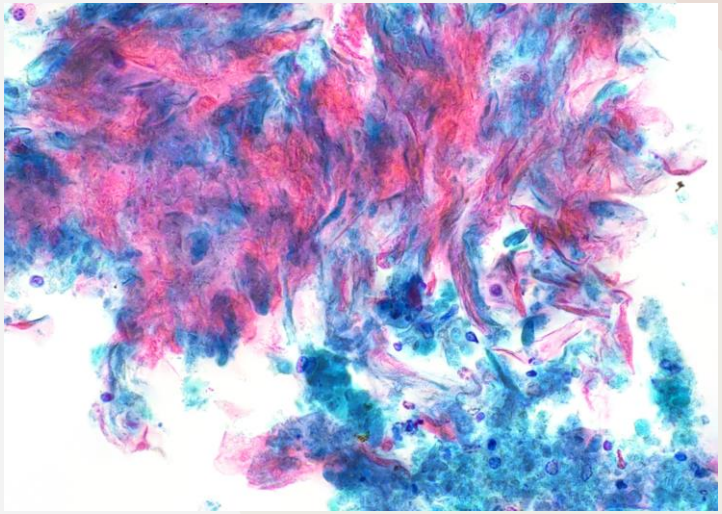
- Low/undetectable CEA/CA19-9
- Low amylase

02 Pseudocysts and lymphoepithelial cysts



Pseudocyst
Dirty, necrotic background with foamy histiocytes

Biochemical tests helpful: Always elevated amylase (thousands ng/mL), low CEA



Lymphoepithelial cyst
Keratinaceous and granular debris, polymorphous lymphocytes, cholesterol crystals and histiocytes.

Diagnostic pitfall: CEA CA19-9 and amylase may be elevated!

02

Atypical

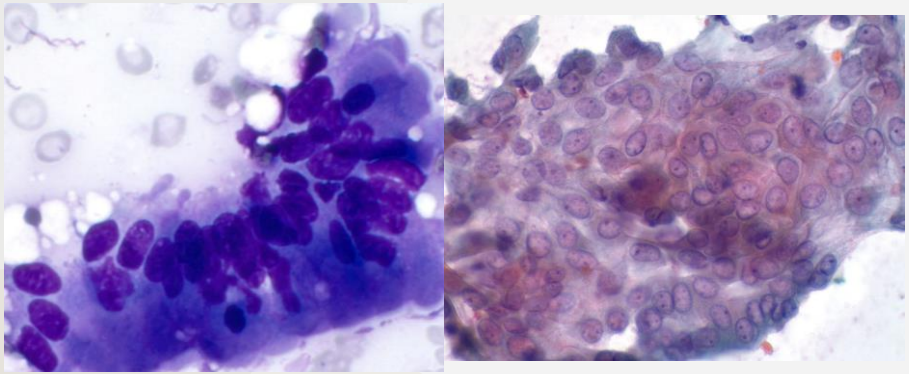
A specimen categorized as “atypical” demonstrates features **predominantly seen in benign lesions and minimal features that may raise the possibility of a malignant lesion**, but with insufficient features either in number or quality to diagnose a benign, PaN-low, PaN-high, or malignant process or lesion.

Examples include:
1. Scant or poorly prepared but atypical material
2. Mainly benign cytopathological features present, but some features that may raise the possibility of malignancy.
3. Any atypical feature in a case showing otherwise insufficient material.

Risk of Malignancy: 0 - 14 %

02

Atypical



Atypical

Left: Pseudostratified nuclei but maintained low N:C ratio
Right:Mild anisonucleosis and nuclear pallor with focal nuclear membrane irregularities. Honeycomb architecture is maintained

Some common causes for 'atypical' interpretation:

- Loss of architectural polarity
- Minor degree of nuclear crowding
- Mild alteration of the honeycomb pattern
- Slight nuclear membrane irregularity without marked clefting
- Parachromatin clearing without other cytopathological features of adenocarcinoma
- Small nucleoli without true macronucleoli
- Minor anisonucleosis, 2:1

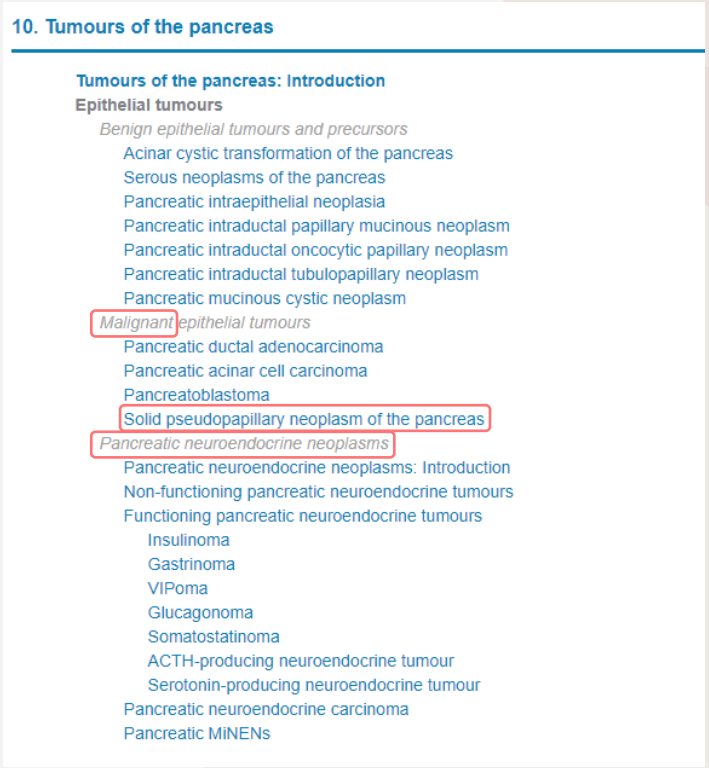
02 Changes from the PSC system

For lesions indeterminate for PanNET and solid pseudopapillary neoplasm:

- PSC system: Atypical

- WHO system: Suspicious for malignancy

Reason: PanNET and solid pseudopapillary neoplasm are categorized as malignant neoplasms per the fifth-edition WHO classification of digestive system tumours.



WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1). https://publications.iarc.fr/579.

02 Pancreatobiliary neoplasm, low risk/grade (PaN-low)

A specimen categorized as “PaN-low” has features of an intraductal and/or cystic neoplasm with low-grade epithelial atypia.

7. Chapter 6: Diagnostic category: Pancreaticobiliary neoplasm, low-risk/grade

- Introduction
- Definition
- Discussion and background
- Risk of malignancy and management recommendations

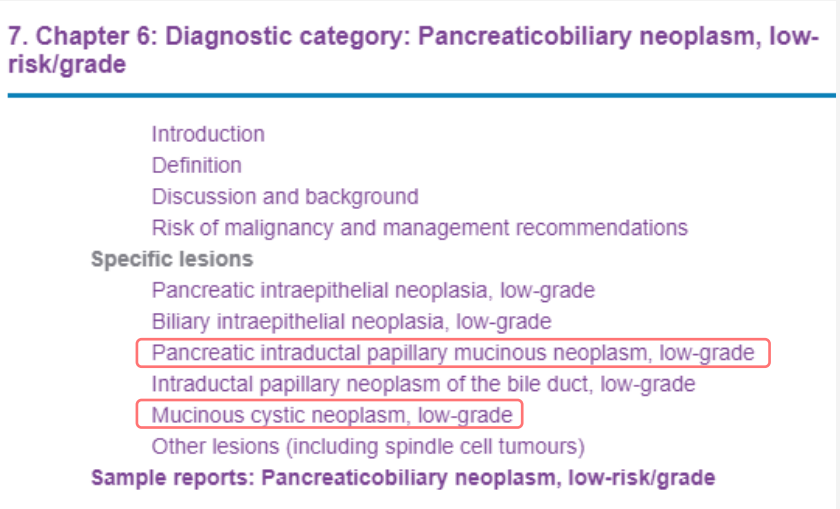
Specific lesions

- Pancreatic intraepithelial neoplasia, low-grade
- Biliary intraepithelial neoplasia, low-grade
- Pancreatic intraductal papillary mucinous neoplasm, low-grade
- Intraductal papillary neoplasm of the bile duct, low-grade
- Mucinous cystic neoplasm, low-grade
- Other lesions (including spindle cell tumours)

Sample reports: Pancreaticobiliary neoplasm, low-risk/grade

Risk of Malignancy: 5 - 20 %

02 Pancreatobiliary neoplasm, low risk/grade (PaN-low)



7. Chapter 6: Diagnostic category: Pancreaticobiliary neoplasm, low-risk/grade

- Introduction
- Definition
- Discussion and background
- Risk of malignancy and management recommendations

Specific lesions

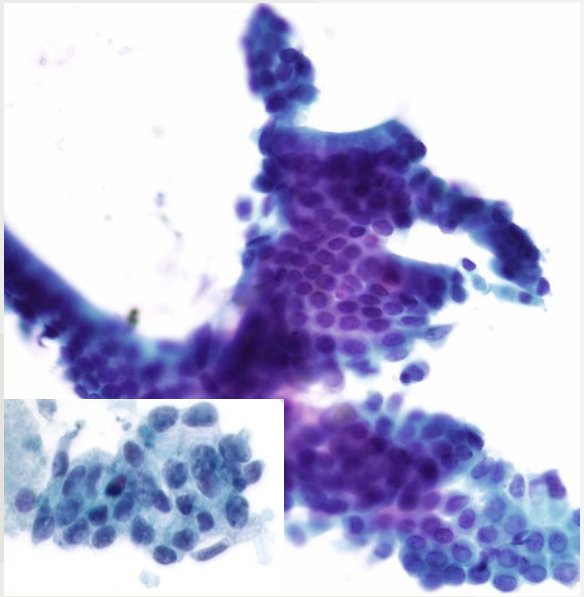
- Pancreatic intraepithelial neoplasia, low-grade
- Biliary intraepithelial neoplasia, low-grade
- Pancreatic intraductal papillary mucinous neoplasm, low-grade
- Intraductal papillary neoplasm of the bile duct, low-grade
- Mucinous cystic neoplasm, low-grade
- Other lesions (including spindle cell tumours)

Sample reports: Pancreaticobiliary neoplasm, low-risk/grade

- With the removal of PanNET and SPN from the PSC “neoplastic” category and the inclusion of SCA in the WHO system “benign” category, the “pancreatic neoplasm” category is left almost exclusively containing cystic mucinous and intraductal neoplasms
- Other specific lesions not relevant since they are not readily diagnosed on cytology alone.
- Spindle cell tumours – used when further ancillary testing is not possible, but for which a benign diagnosis is expected.

02

Low-grade IPMN



Low grade IPMN
Papillary fronds of mucinous epithelium with minimal atypia.

20-50% of resected pancreatic tumours. Usually asymptomatic. Mucin extravasation from patulous ampulla of Vater essentially diagnostic of intestinal-type IPMN

CT and endoscopic findings of multiloculated cysts connected to the main/branch pancreatic duct.

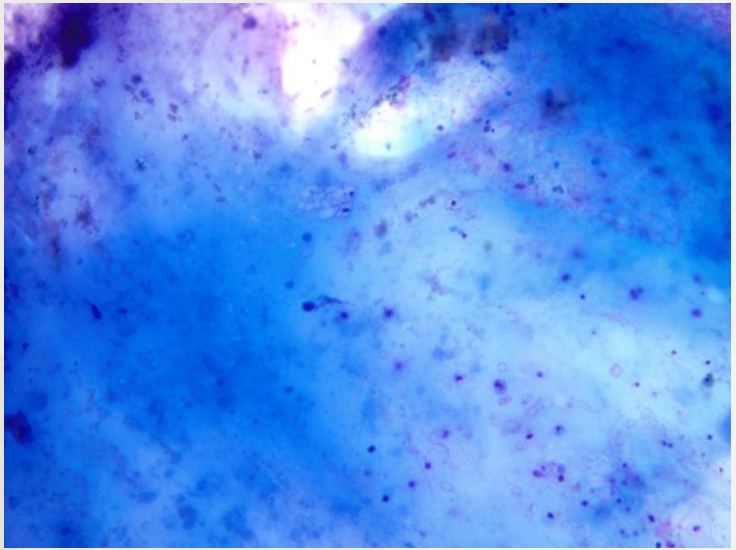
Key cytopathological features:

- Columnar mucinous epithelium with mild to moderate cytoarchitectural atypia (typically gastric and/or intestinal type)
- Papillary or single cells
- Epithelial cells about the size of a duodenal enterocyte
- intranuclear inclusions reported to be specific when distinguishing between gastric contaminant epithelium
- Mucin, thick or thin

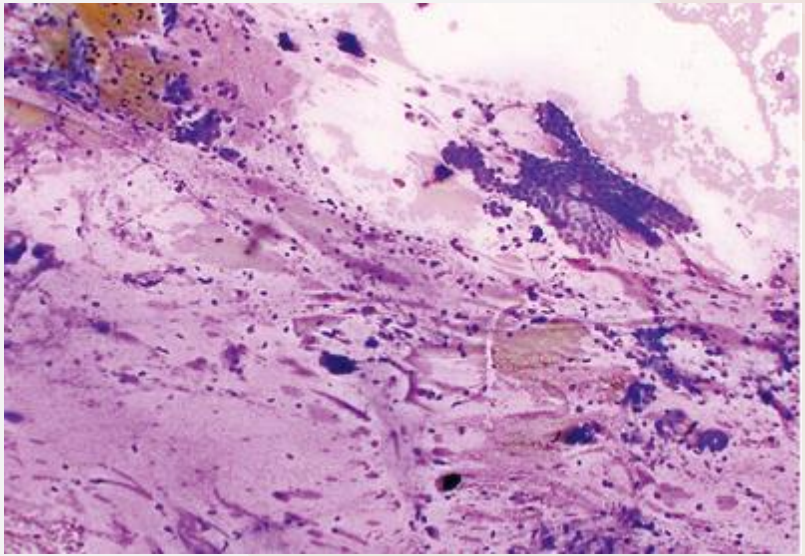
Ancillary testing often helpful:
- Cyst fluid CEA >192 ng/ml best test to classify cyst as mucinous
- Presence of GNAS and KRAS mutations support IPMN.

02

Diagnostic mucin?



Thick colloid like mucin
Diagnostic of neoplastic mucin even without mucinous epithelium



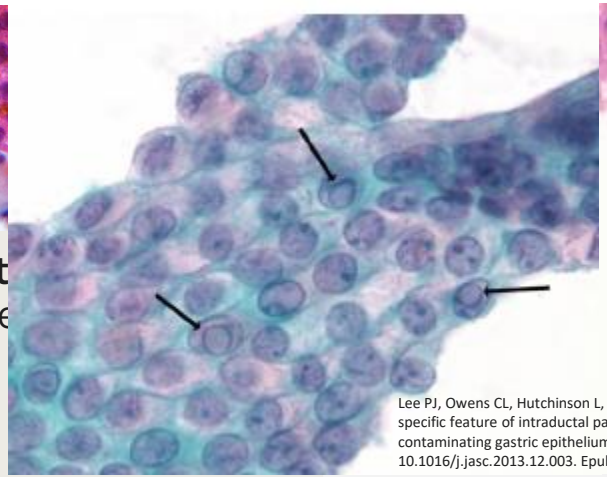
Thin, wispy mucin
Indeterminate for origin – gastrointestinal contaminant vs thin mucin of IPMN

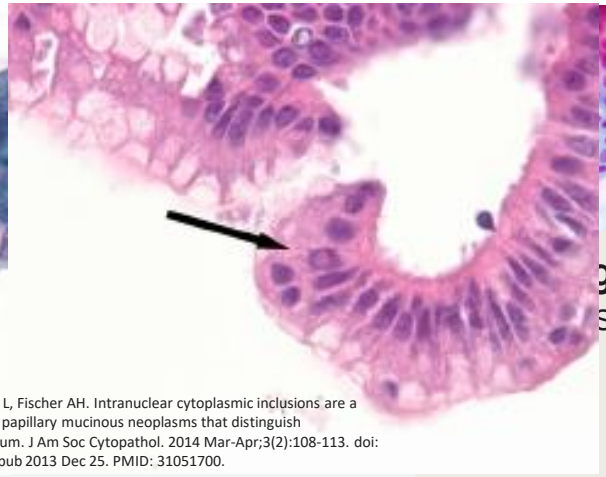
02 Lesional or contaminant epithelium?

Gastric cont
Evenly space

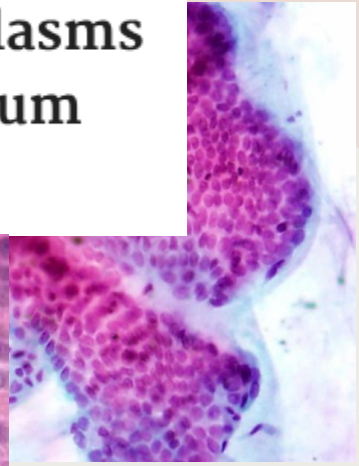
Intranuclear cytoplasmic inclusions are a specific feature of intraductal papillary mucinous neoplasms that distinguish contaminating gastric epithelium

Paul J Lee [1], Christopher L Owens [2], Lloyd Hutchinson [2], Andrew H Fischer [2]



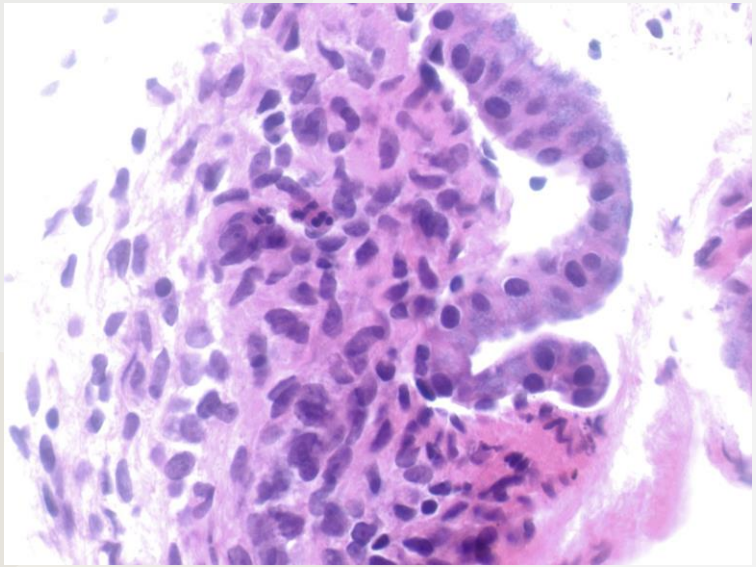


Lee PJ, Owens CL, Hutchinson L, Fischer AH. Intranuclear cytoplasmic inclusions are a specific feature of intraductal papillary mucinous neoplasms that distinguish contaminating gastric epithelium. J Am Soc Cytopathol. 2014 Mar-Apr;3(2):108-113. doi: 10.1016/j.jasc.2013.12.003. Epub 2013 Dec 25. PMID: 31051700.



grade IPMN
s with minimal atypia

02 Low-grade mucinous cystic neoplasm



MCN (microforceps biopsy):
Subepithelial ovarian type stroma allows for specific diagnosis

Predominantly female, 90% in body or tail of pancreas.

Majority do not communicate with main pancreatic duct.

Not readily distinguished from low grade IPMN as subepithelial ovarian stroma is not usually sampled on aspiration – but may be seen in microforceps biopsies. (CD10, ER PR IHC positive)

Ancillary testing often helpful:

- Cyst fluid CEA >192 ng/ml best test to classify cyst as mucinous
- Small subset harbours KRAS mutations.

02

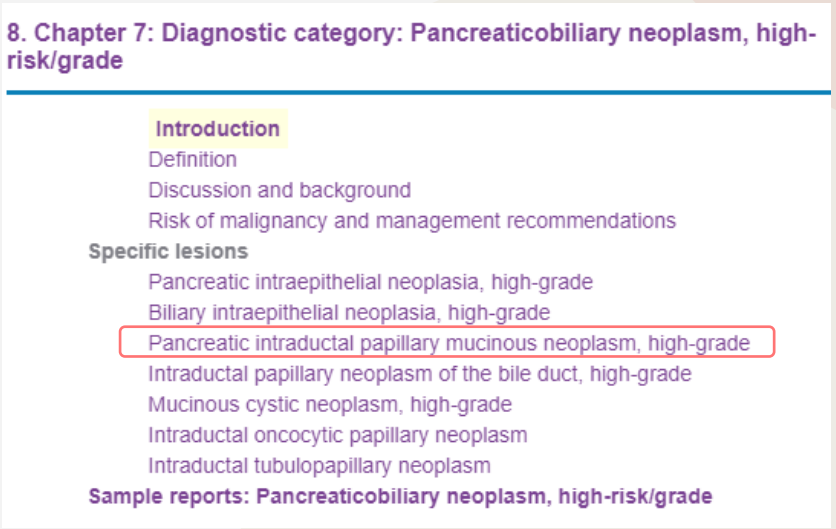
Practical points

Mucinous cystic neoplasms (MCNs) share similar cytopathological features with intraductal papillary mucinous neoplasms (IPMNs), especially side-branch IPMN, and distinction between the two is difficult if not impossible in the absence of ovarian-like stroma; thus, **it is acceptable to render a cytopathological diagnosis of "neoplastic mucinous cyst", to include MCN and IPMN in the differential diagnosis.**

02 Pancreatobiliary neoplasm, high risk/grade (PaN-High)

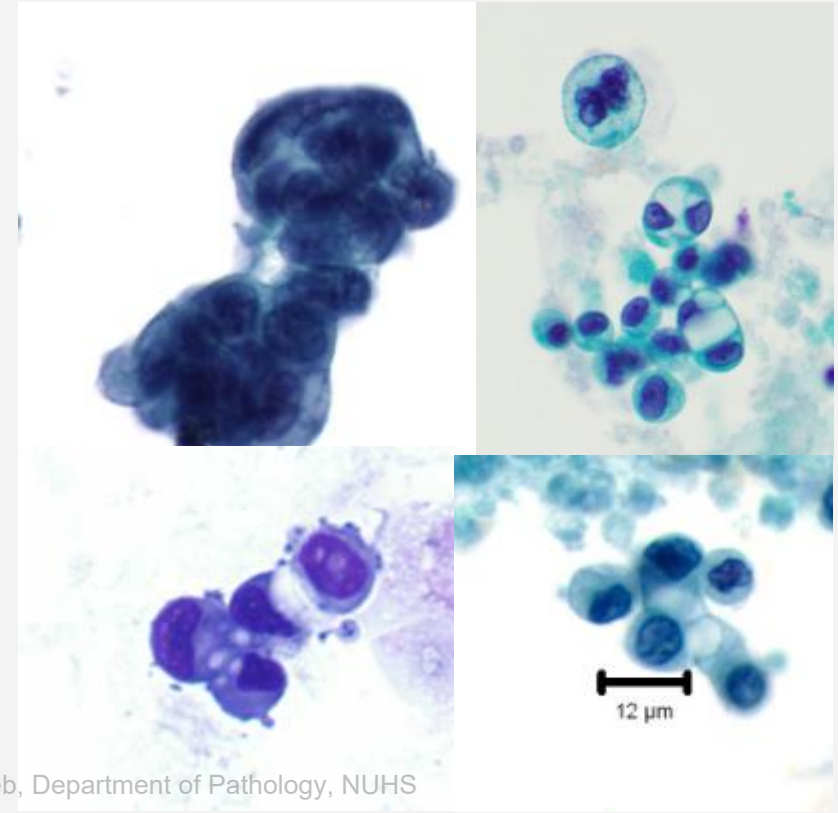
A specimen categorized as “PaN-High” has features of an intraductal and/or cystic neoplasm with high-grade epithelial atypia.

The PaN-high category is dominated by IPMN-high-grade, which is a grossly visible cystic lesion involving the main and/or branch pancreatic ducts.



Risk of Malignancy: 60 – 95 %

02 High-grade mucinous cysts



Pathweb, Department of Pathology, NUHS

Definition of high-grade epithelial atypia:

- Cells smaller than a 12 µm duodenal enterocyte
- High N:C ratio
- Abnormal chromatin, which can be hypochromatic or hyperchromatic
- with or without a background of cellular necrosis.

- In the presence of thick, colloid like extracellular mucin and/or elevated CEA, the primary differential diagnosis is high grade IPMN vs MCN.

- Ovarian stroma is not likely to be seen on FNAB

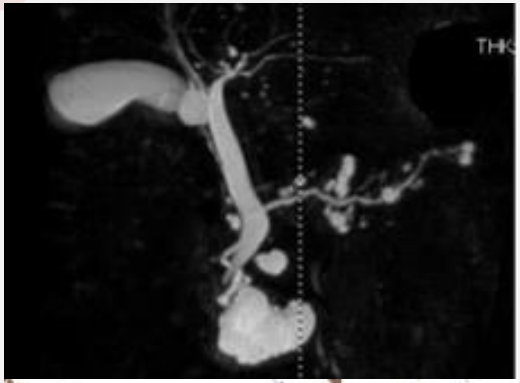
02

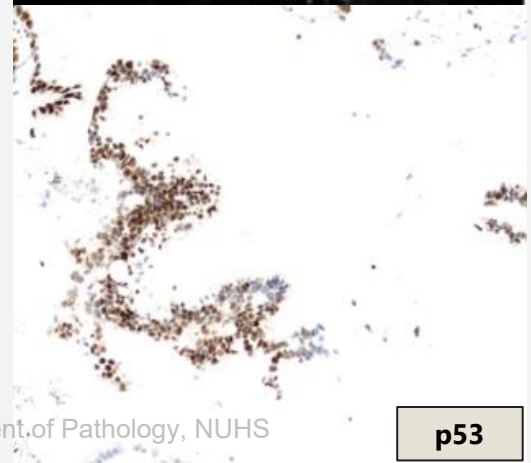
Practical points

If only small tissue fragments of high-grade atypia or a solitary cystic mass without connection to the duct are present, **a generic diagnosis of a "mucinous cyst with HGA" is sufficient,** because resection is warranted regardless of the specific cyst type.

02

Helpful adjuncts





p53

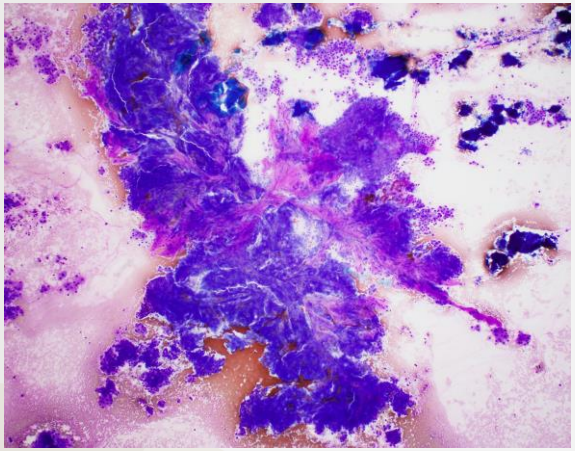
Imaging features that may correspond to high-grade dysplasia or invasive carcinoma:

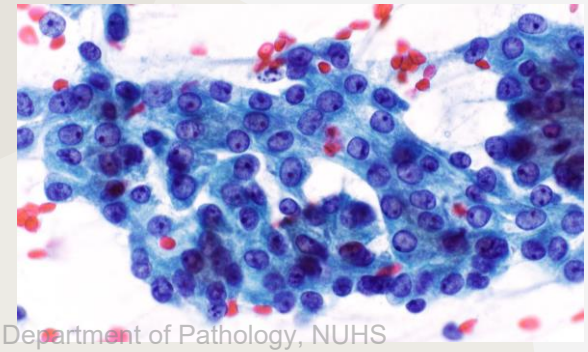
- Main duct diameter > 10mm or enhancing mural nodule > 5mm
- A main duct diameter between 5 and 9.9 mm or a cyst diameter > 40 mm are worrisome features warranting FNAB to evaluate for high-grade cytopathology

Molecular testing of cyst fluid or IHC:

- Late mutations in the adenoma-carcinoma progression e.g. TP53, CDKN2A, SMAD4, PIK3CA, aneuploidy/loss of heterozygosity.
- p53 mutant expression, loss of nuclear staining for SMAD4 or p16 on IHC.

02 Intraductal oncocytic papillary neoplasm





Pathweb, Department of Pathology, NUHS

Formally classified as a subtype of IPMN but is now a specific entity.
Forms large cystic tan brown masses within dilated ducts.

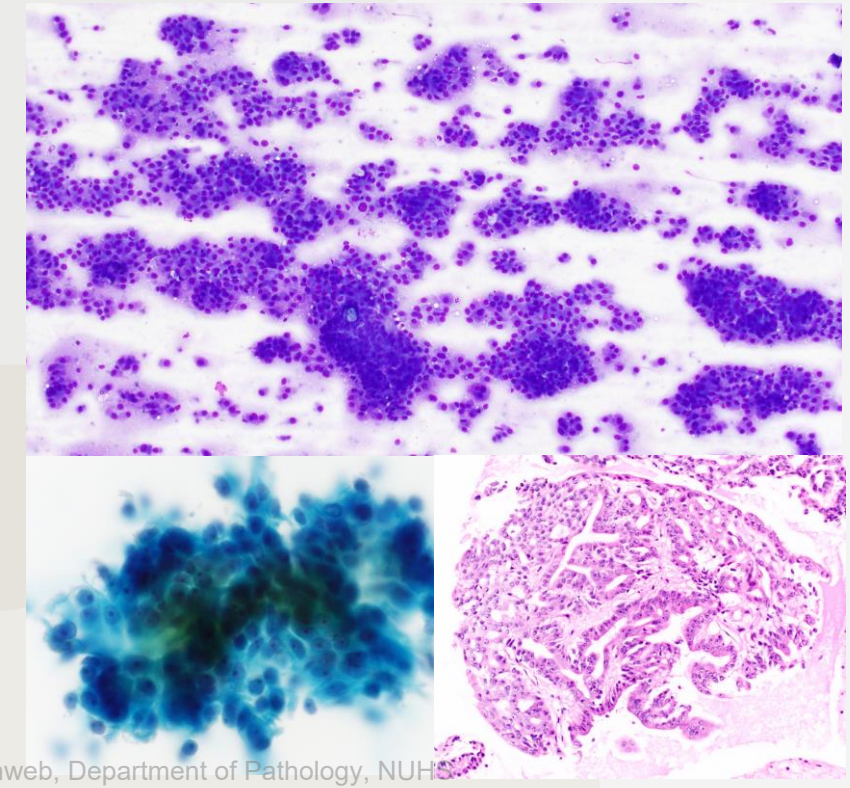
Distinctive cytopathological features:

- Complex branching sheets with papiillae
- Oncocytic cells with magenta(Giemsa/HC)/ green (Pap) cytoplasm
- Oval to irregular nuclei with eccentric nucleoli
- Mitosis, apoptotic debris and necrosis may be present.

IHC: MUC6, EMA, mesothelin positive.

Genetics: recurrent rearrangements in PRKACA PRKACB (distinct from IPMN)

02 Intraductal tubulopapillary neoplasm (ITPN)



Pathweb, Department of Pathology, NUH

Distinct entity among intraductal neoplasms.
70% invasive.

Key Cytopathological features:

- Hypercellular smears
- Overlapping, branching sheets
- Enlarged cuboidal tumour cells with high N:C ratio and prominent nucleoli
- Cell block shows cribriform units
- No mucin
- Indistinguishable with invasive ca on cytopathology material alone.

- **IHC:** CK19, CK7 positive

- **Genetics:** Do not share genetic alterations associated with ductal adenocarcinoma or IPMN

02

Suspicious for Malignancy

A specimen characterized as “suspicious for malignancy” demonstrates some cytopathologic features suggestive of malignancy but with insufficient features in either number or quality to make an unequivocal diagnosis of malignancy.

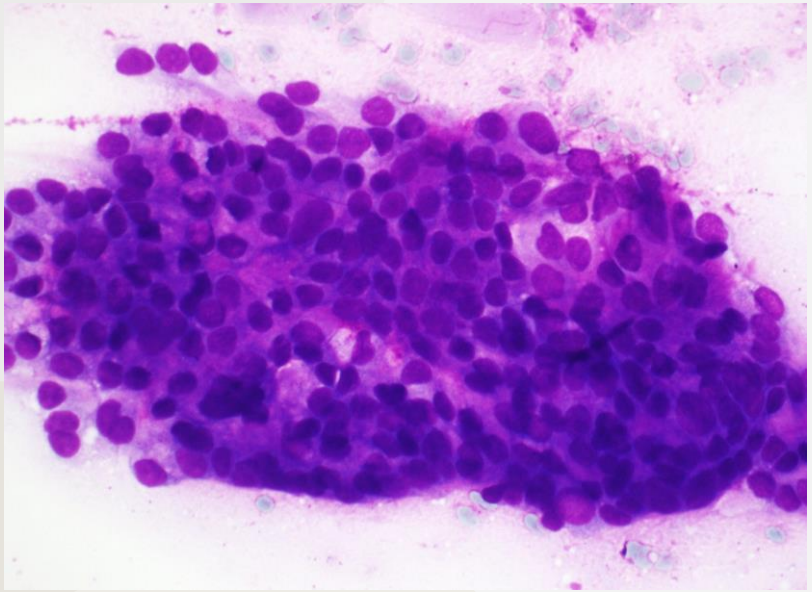
The cytopathologist should include details of the features that are suspicious and that have led to the categorization of a specimen as “suspicious for malignancy,” to minimize the tendency to use this category as a waste basket.

A discussion of any features limiting or compromising the evaluation should be noted, and the need for correlation with clinical and imaging findings should be emphasized

Risk of Malignancy: 80 - 100 %

02

Suspicious for malignancy



Suspicious for pancreatic ductal adenocarcinoma
Architectural disorganization (drunken-honeycomb pattern) but lacks significant anisonucleosis and visible cytoplasmic mucin for a definitive diagnosis as malignant

Common reasons for this interpretation:

- Scant specimen of a well-differentiated adenocarcinoma or rare ductal cells with marked cytopathological atypia, especially when the mass is not distinct on imaging.
- Neoplastic mucinous cysts with high grade, atypia, necrosis and high-risk imaging findings, concerning for invasion.
- Lack of adequate material for characterisation of neuroendocrine tumours, acinar cell ca, and other malignancies

02

Malignant

A specimen categorized as “malignant” demonstrates unequivocal cytopathological features of malignancy.

Interpretation of the findings should take into consideration relevant clinical and imaging features. (ie. Hypoglycaemia in functioning NET, lipase hypersecretion in acinar cell ca, double duct sign in PDAC..)

10. Chapter 9: Diagnostic category: Malignant

- Introduction
- Definition
- Discussion and background
- Risk of malignancy and management recommendations

Specific lesions

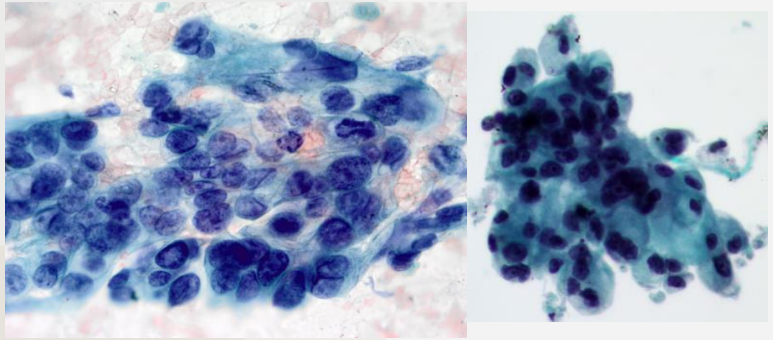
- Cholangiocarcinoma
- Pancreatic ductal adenocarcinoma
- Pancreatic acinar cell carcinoma
- Neuroendocrine tumour
- Neuroendocrine carcinoma
- Pancreatoblastoma
- Solid pseudopapillary neoplasm
- Pancreatic lymphomas
- Metastases to the pancreas
- Other lesions (including spindle cell tumours)

Sample reports: Malignant

Risk of Malignancy: 97 - 100 %

02

Pancreatic ductal adenocarcinoma



Pancreatic ductal adenocarcinoma

Usually at least locally advanced at diagnosis, majority at head of pancreas. High serum CA19-9 characteristic.

Key diagnostic cytopathological features:

- Highly cellular with drunken honeycomb architecture.
- Anisonucleosis (extent of 1:4 or greater), irregular nuclei with prominent nucleoli and atypical mitotic figures
- Background may be clean or necrotic

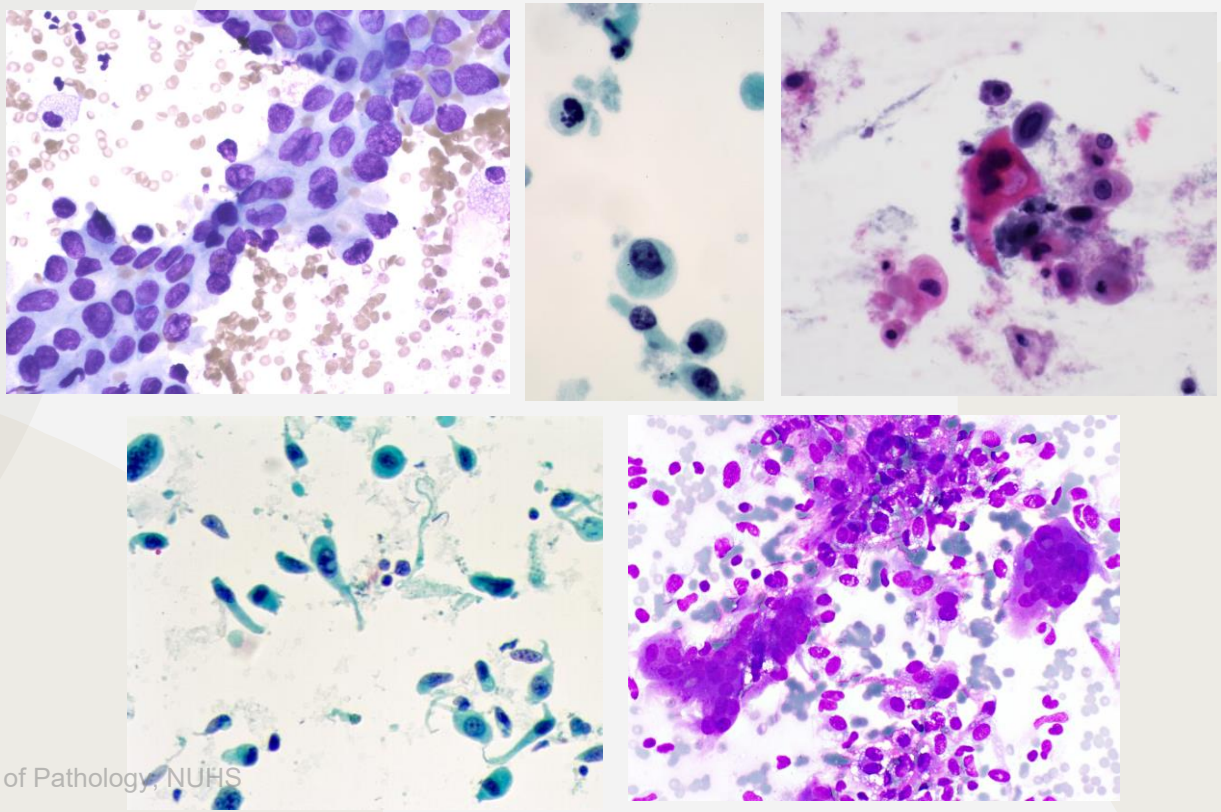
Varying subtypes – adenosquamous, colloid, undifferentiated etc

IHC: aberrant p53 expression, loss of nuclear staining for SMAD4.

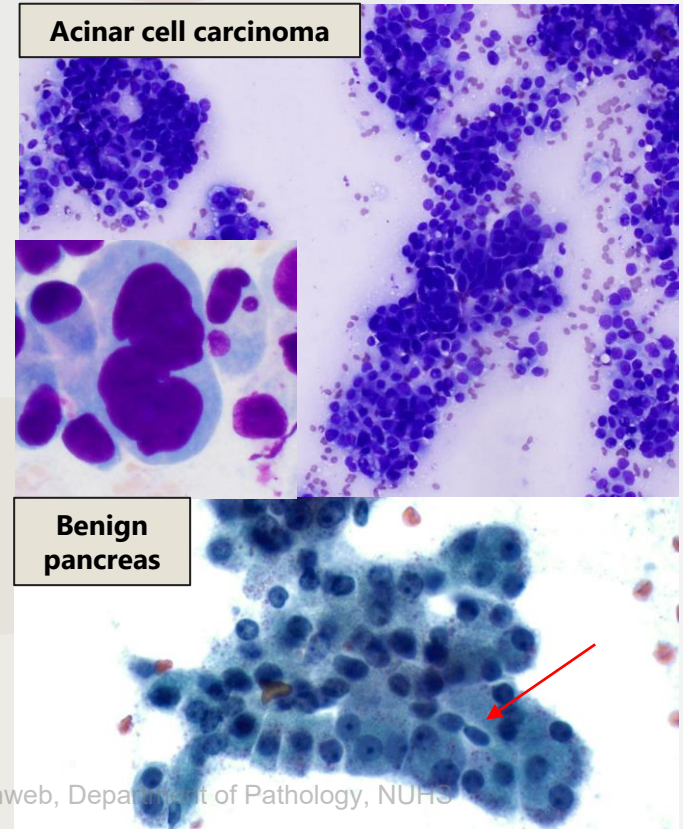
Next-gen sequencing for driver mutations (KRAS,TP53, SMAD4 etc) can help in diagnosis and treatment.

02

Pancreatic ductal adenocarcinoma



02 Pancreatic acinar cell carcinoma



Not associated with raised serum CEA and Ca19-9.
Clinical clue – lipase hypersecretion syndrome (rare)

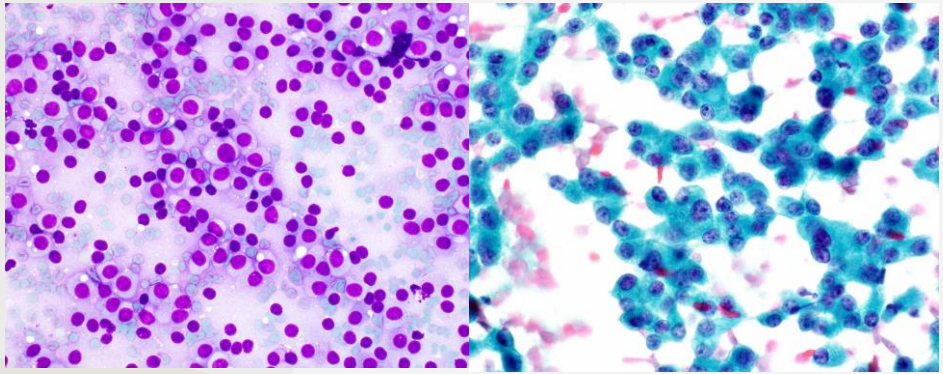
Key diagnostic cytopathological features:

- Dense 3D fragments with lobulated, trabecular and small acinar architecture.
- Naked nuclei
- Large irregular nuclei, eosinophilic granular cytoplasm, single prominent nucleolus (not always)
- Granular background due to spilled zymogen granules

IHC:

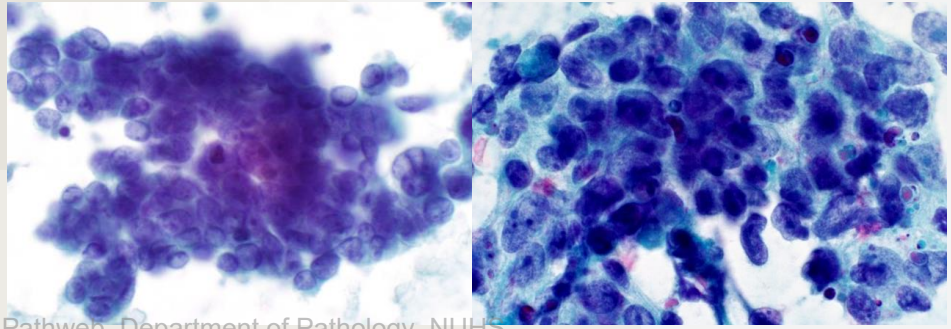
- Trypsin, chymotrypsin, BCL10, Ki-67: 10-50%.
- Scattered synaptophysin/chromogranin (diffuse expression indicates NET/NEC/mixed acinar-NE ca)
- B-catenin at most patchy (diffuse supports SPN)

02 Pancreatic neuroendocrine tumours and carcinoma



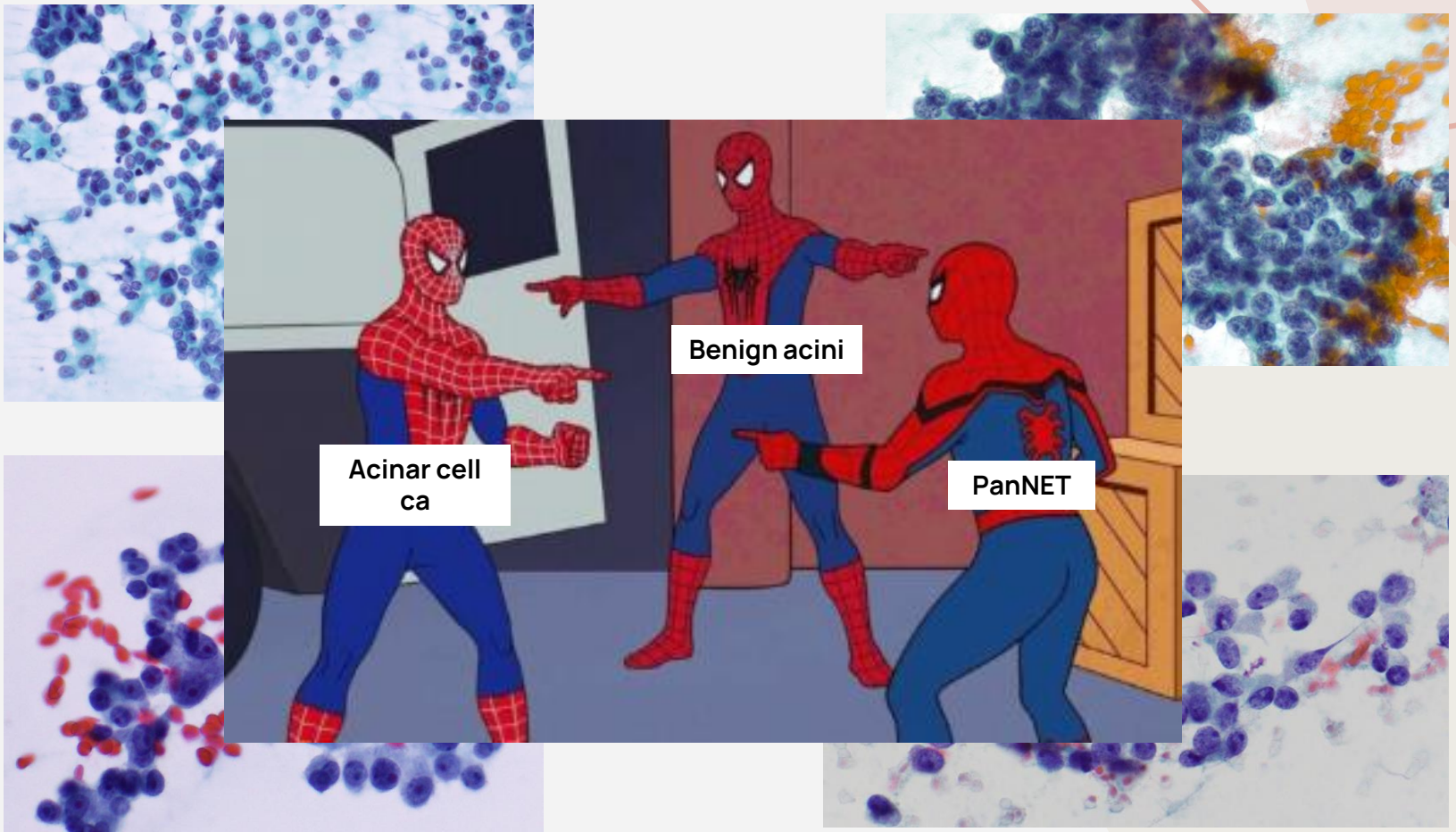
PanNETs (>5mm):
Cellular smears with epitheloid to plasmacytoid cells, stippled chromatin, fine granular cytoplasm.

Subdivided into 3 grades depending on Ki-67 and mitotic index.



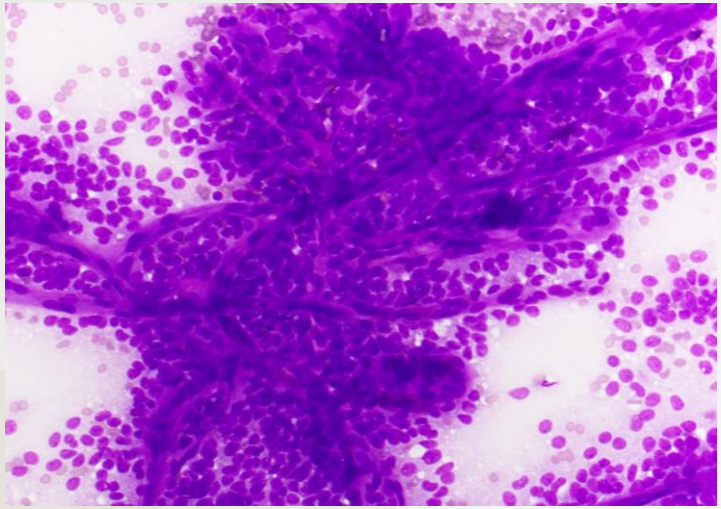
PanNECS:
Small cell morphology analogous to pulmonary small cell carcinoma or large cell morphology; Highly cellular, high N:C ratios with necrosis.

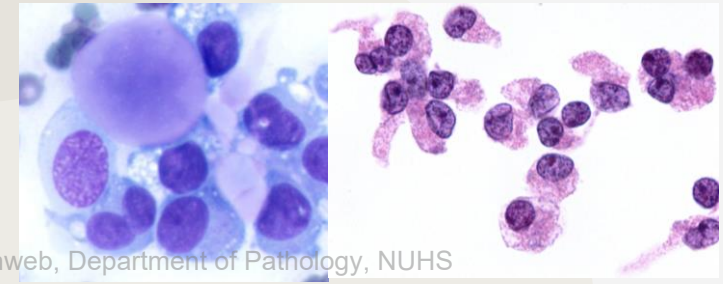
Ki-67 > 20 % by definition but usually exceeds 50%. Usually retains synaptophysin staining.


Benign acini
Acinar cell ca
PanNET

02

Solid pseudopapillary neoplasm





Occur predominantly in young females.

Imaging findings: well-defined solid-cystic mass with peripheral calcifications

Key diagnostic cytopathological features:

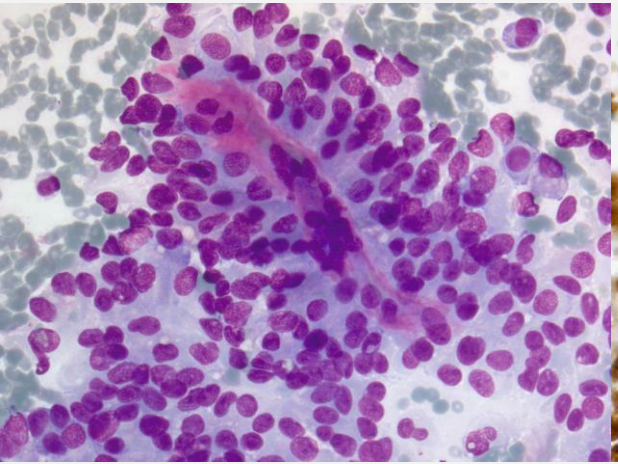
- Branching papillary fronds – three layers (central vascular core, myxoid stroma, neoplastic cells)
- Cercariform cells, round/coffee bean nuclei
- Finely granular chromatin
- Metachromatic cytoplasmic hyaline granules
- Background cyst debris

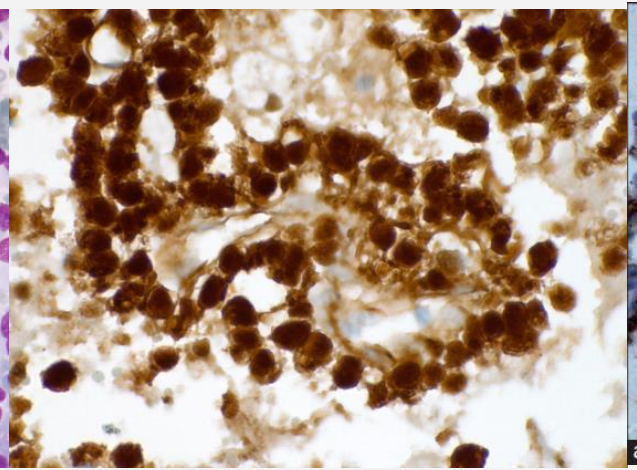
IHC:

- Nuclear expression of B-catenin.
- Unique CD99 dot like paranuclear staining pattern.

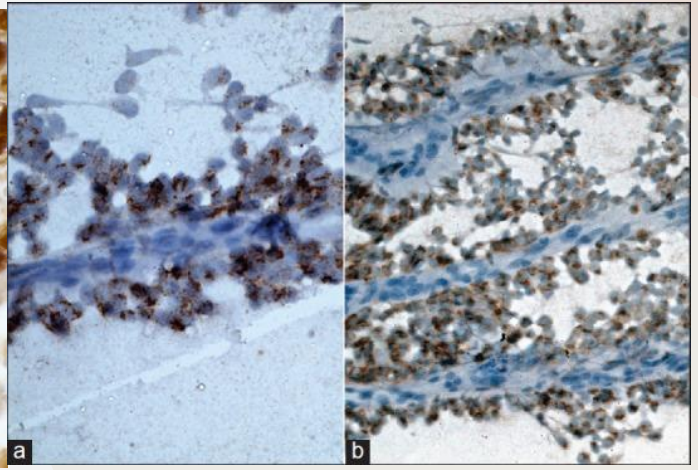
02

Solid pseudopapillary neoplasm





B catenin: nuclear + cytoplasmic staining



CD99: dot like paranuclear staining

Ghosh R, Mallik SR, Mathur SR, Iyer VK. CD 99 immunocytochemistry in solid pseudopapillary tumor of pancreas: A study on fine-needle aspiration cytology smears. J Cytol. 2013 Jul;30(3):151-5. doi: 10.4103/0970-9371.117645. PMID: 24130404; PMCID: PMC3793349.

03 Brief review on biliary cytopathology

03

Biliary cytopathology

The relevant categories for biliary lesions include: non-diagnostic, benign, atypical, suspicious for malignancy, and malignant.

Although specific biliary lesions are listed in Pan-low and Pan-high, the categorisation used is usually “atypical” and “suspicious for malignancy” as distinction between BilIN-low vs reactive atypia and BilIN-high vs cholangiocarcinoma is not possible on cytology. The cytomorphological criteria for IPN are not well established due to its rarity.

Diagnostic categories for biliary lesions WHO Reporting System (2022)
1. Non diagnostic ✓
2. Benign ✓
3. Atypical ✓
4. PaN-Low • BilIN-low • IPN-B (low-grade)
5. PaN-High • BilIN-high • IPN-B(high grade)
6. Suspicious for malignancy ✓
7. Positive for malignancy ✓ • Cholangiocarcinoma

03

Biliary lesions: Atypical

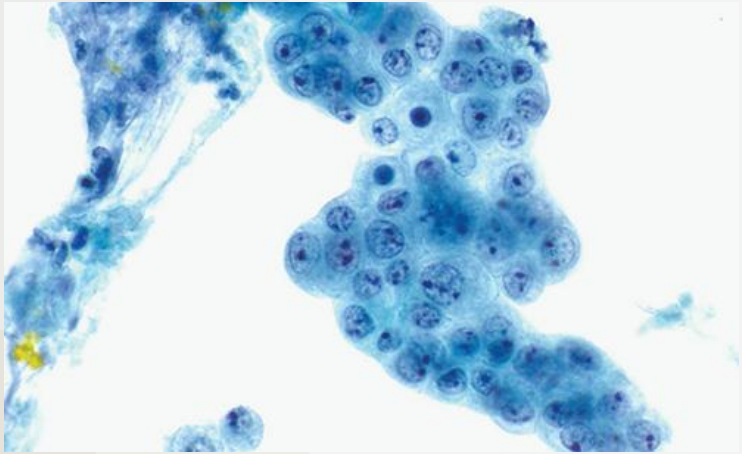
In bile duct brushings, the “atypical” category is applied for which the atypia observed is beyond that seen in reactive/inflammatory changes while being quantitatively and qualitatively insufficient for categorization as “Suspicious for malignancy”.

The use of “Atypical” in bile duct brushing (BDB) cytopathology is very high, owing to the high threshold required for the diagnosis of malignancy with this specimen type.

Risk of Malignancy: 25 - 77 %

03

Atypical

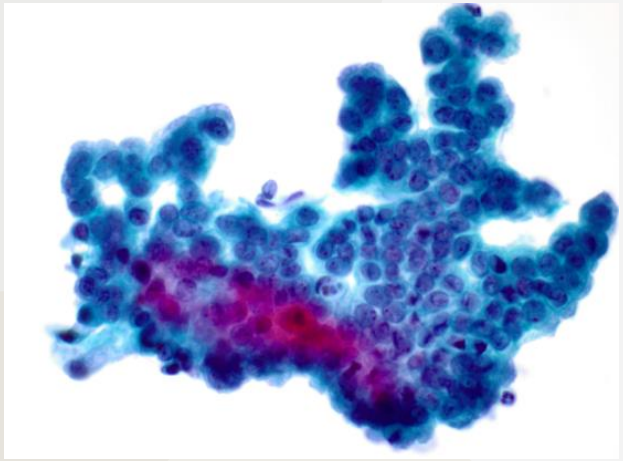


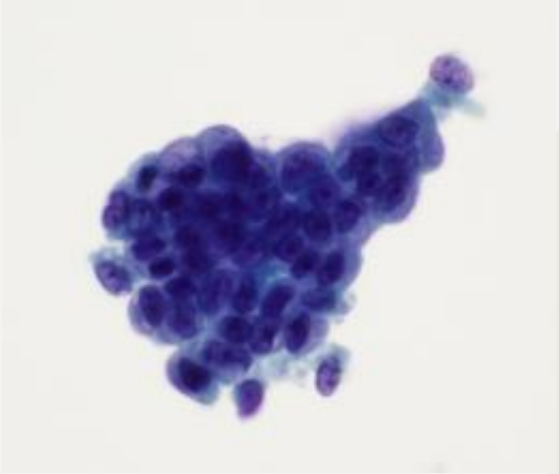
Atypical bile duct epithelium from brushings of a strictured and stented duct: Mildly atypical cells in relatively uniform sheet with enlarged nuclei and prominent nucleoli, but with smooth nuclear membranes and open vesicular chromatin.

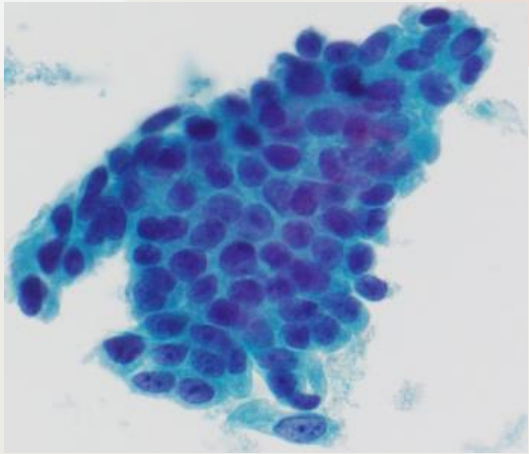
Some common causes for 'atypical' interpretation (applicable in both pancreaticobiliary mass lesions and bile duct brushings specimens):

- Loss of architectural polarity
- Minor degree of nuclear crowding
- Mild alteration of the honeycomb pattern
- Slight nuclear membrane irregularity without marked clefting
- Parachromatin clearing without other cytopathological features of adenocarcinoma
- Small nucleoli without true macronucleoli
- Minor anisonucleosis, 2:1

03 Atypical – bile duct brushings







03 Biliary lesions: Suspicious for malignancy

A specimen categorized as “Suspicious for malignancy” demonstrates some cytopathological features suggestive of malignancy, but with features insufficient in either number or quality to make an unequivocal diagnosis of malignancy.

Most commonly used – scant specimen of a well diff adenoca or rare ductal cells with marked cytologic atypia especially when there is no distinct mass on imaging.

A “Suspicious for malignancy” categorization is common for bile duct brushings where the architectural and cytological atypia is difficult to distinguish from reactive and reparative atypia due to indwelling stents, stones, or underlying inflammatory conditions including primary sclerosing cholangitis.

Risk of Malignancy: 74 - 100 %

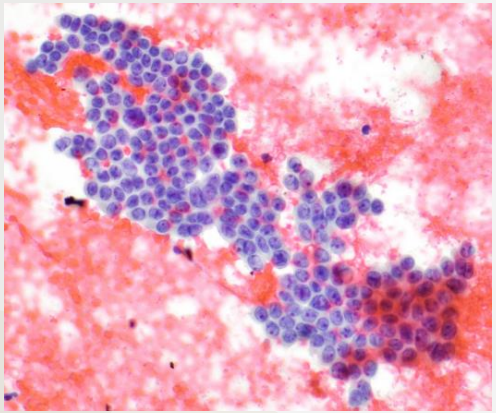
03 Suspicious for malignancy vs Malignant

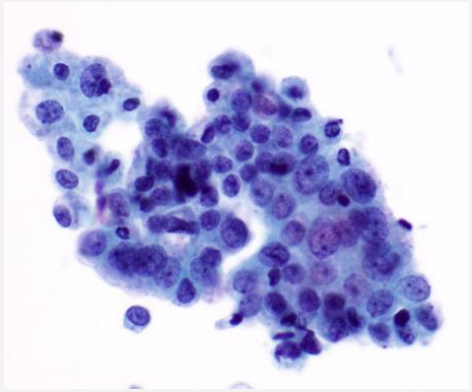
In the presence of a stone, an indwelling stent, or a history of primary sclerosing cholangitis, caution should be exercised because of the presence of coexisting reactive changes. A definitive diagnosis of malignancy should only be rendered when the cytopathological features are very pronounced.

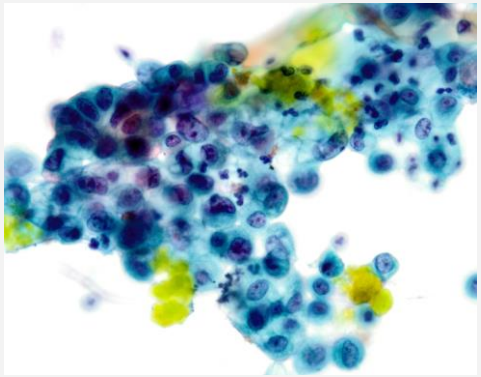
If atypical cells of interest are present in a cell block, p53 and/or SMAD4 IHC may be of value (abnormal in roughly half of large duct cholangiocarcinoma).

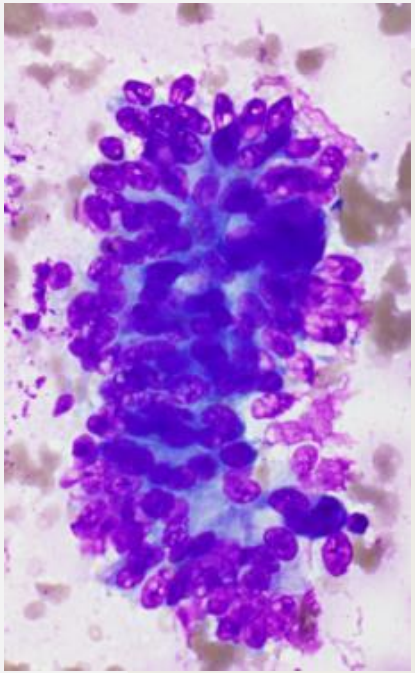
FISH and next generation sequencing can also increase the sensitivity of detecting cholangiocarcinoma

03 Suspicious for malignancy vs Malignant









04 Clinical recommendations and sample reports

04 Clinical management options by category Pancreatic lesions

Diagnostic category	Estimated ROM (%)[a]	Clinical management options[b]
1. Insufficient/inadequate/nondiagnostic	5–25	Repeat FNAB
2. Benign/negative for malignancy	0–15	Correlate clinically
3. Atypical	30–40	Repeat FNAB
4. PaN-low	5–20	Correlate clinically
5. PaN-high	60–95	Surgical resection in surgically fit patients Conservative management optional
6. Suspicious (for malignancy)	80–100	If patient to be surgically managed, treat as positive If patient requires pre-operative therapy, repeat FNAB
7. Positive (for malignancy)	99–100	Per clinical stage

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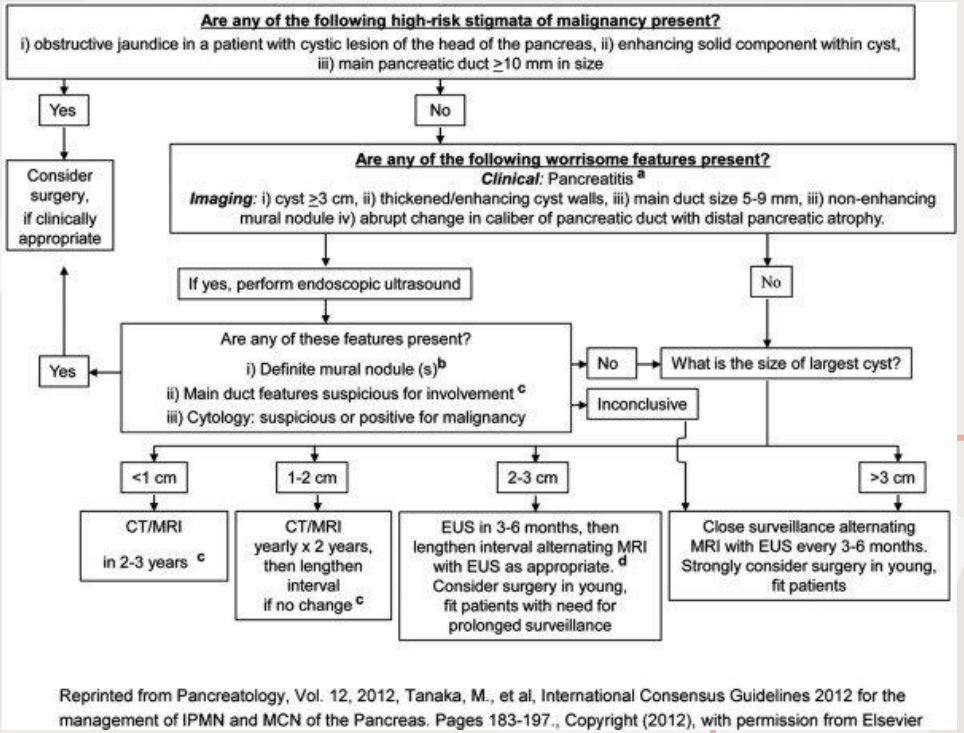
04 Clinical management options by category PaN-low



Reprinted from Pancreatology, Vol. 12, 2012, Tanaka, M., et al, International Consensus Guidelines 2012 for the management of IPMN and MCN of the Pancreas. Pages 183-197., Copyright (2012), with permission from Elsevier

The Fukuoka revised guidelines for management of mucinous cystic... | Download Scientific Diagram (researchgate.net)

04 Clinical management options by category Biliary lesions

Diagnostic category	Estimated ROM (%)[a]	Clinical management options[b]
Insufficient/inadequate/nondiagnostic	28–69	Repeat ERCP with cholangioscopy, brushing, and biopsies
Benign/negative for malignancy	26–55	Correlate clinically
Atypical	25–77	Repeat ERCP with cholangioscopy, brushings, and biopsies; consider ancillary testing with FISH and/or NGS
PaN-low	NA[c]	
PaN-high	NA[c]	
Suspicious (for malignancy)	74–10	
Malignant	96–10	

Reproduced with permission from Internatic
Organization Joint Editorial Board. WHO Report
Research on Cancer; forthcoming (IAC-IARC-W
ERCP, endoscopic retrograde cholangiopancrea
generation sequencing. [a] Estimated ROMs are b
strictures may depend on a variety of factors, in
Some clinical management suggestions are outl
and thus, there are no data on bile duct categor

Integrating next-generation sequencing to endoscopic retrograde cholangiopancreatography (ERCP)-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures

Aatur D Singhi [1], Marina N Nikiforova [1], Jennifer Chennat [2], Georgios I Papachristou [2], Asif Khalid [2], Mordechai Rabinovitz [2], Rohit Das [3], Savreet Sarkaria [3], M Samir Ayasso [3], Abigail I Wald [1], Sara E Monaco [1], Michael Nalesnik [4], N Paul Ohori [1], David Geller [5], Allan Tsung [5], Amer H Zureikat [5], Herbert Zeh [6], J Wallis Marsh [7], Melissa Hogg [8], Kenneth Lee [9], David L Bartlett [5], James F Pingpank [5], Abhinav Humar [10], Nathan Bahary [11], Anil K Dasyam [12], Randall Brand [2], Kenneth E Fasanella [2], Kevin McGrath [2], Adam Slivka [2]

Affiliations + expand

PMID: 30971436 PMCID: PMC6943248 DOI: 10.1136/gutjnl-2018-317817

04 Summary table

Diagnostic category	Specific diagnoses
Non diagnostic	-
Benign	**Normal pancreatic and biliary parenchyma and contaminants** Acute pancreatitis Cholangitis Chronic pancreatitis Groove/paraduodenal pancreatitis Autoimmune and IgG4-related pancreatitis **Lymphoepithelial cyst** **Pseudocysts** Splenule (accessory spleen) **Serous cystadenoma** Schwannoma Lymphangioma Other rare benign neoplasms
Atypical	-
PaN-Low	Pancreatic intraepithelial neoplasia, low-grade Biliary intraepithelial neoplasia, low-grade **Pancreatic intraductal papillary mucinous neoplasm, low-grade** Intraductal papillary neoplasm of the bile duct, low-grade **Mucinous cystic neoplasm, low-grade** Other lesions (including spindle cell tumours)

Diagnostic category	Specific diagnoses
PaN-High	Pancreatic intraepithelial neoplasia, high-grade Biliary intraepithelial neoplasia, high-grade **Pancreatic intraductal papillary mucinous neoplasm, high-grade** Intraductal papillary neoplasm of the bile duct, high-grade **Mucinous cystic neoplasm, high-grade** Intraductal oncocytic papillary neoplasm Intraductal tubulopapillary neoplasm
Suspicious for malignancy	-
Malignant	**Cholangiocarcinoma** **Pancreatic ductal adenocarcinoma** **Pancreatic acinar cell carcinoma** **Neuroendocrine tumour** **Neuroendocrine carcinoma** Pancreatoblastoma **Solid pseudopapillary neoplasm** Pancreatic lymphomas Metastases to the pancreas Other lesions (including spindle cell tumours)

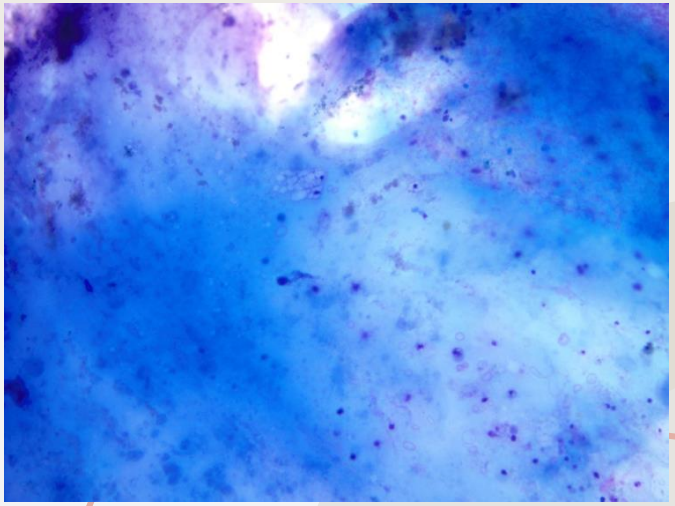
04 Sample reports (Pan-low)

Nature of specimen:
FNAB of a unilocular cyst in the head of pancreas.

Category: PaN-low

Diagnosis:
Thick, colloid-like extracellular mucin consistent with a neoplastic mucinous cyst. See comment.

Comment: A mucinous etiology is based on the quality and quantity of extracellular mucin, which is inconsistent with gastrointestinal contamination. Grade is indeterminate because of the absence of neoplastic epithelium, but high-grade epithelial atypia is absent, as is background necrosis. Correlation with imaging features required.



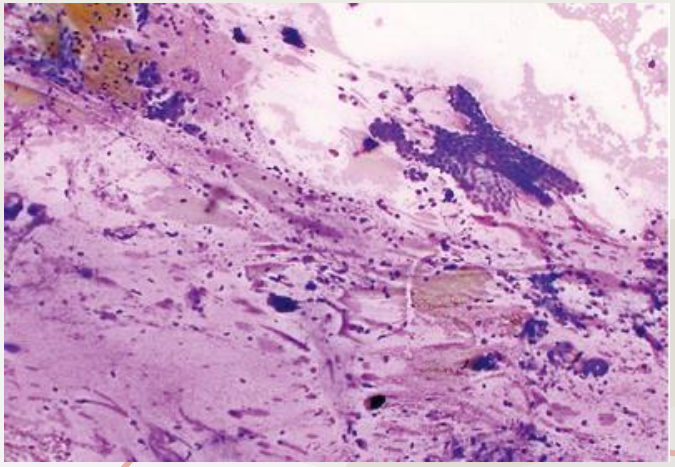
04 Sample reports (Pan-low)

Nature of specimen:
FNAB of a cyst in the body of the pancreas.

Category: PaN-low

Diagnosis:
Neoplastic mucinous cyst, based on elevated cyst fluid CEA (568 ng/mL). See comment.

Comment: The specimen is acellular, showing thin extracellular mucin and elevated cyst fluid CEA (568 ng/mL), findings consistent with a neoplastic mucinous cyst. Amylase is 1034 U/L. Grade is indeterminate because of the absence of neoplastic epithelium, but high-grade epithelial atypia is absent, as is background necrosis. Correlation with imaging features required. Molecular analysis is pending and may be informative.



+ High CEA

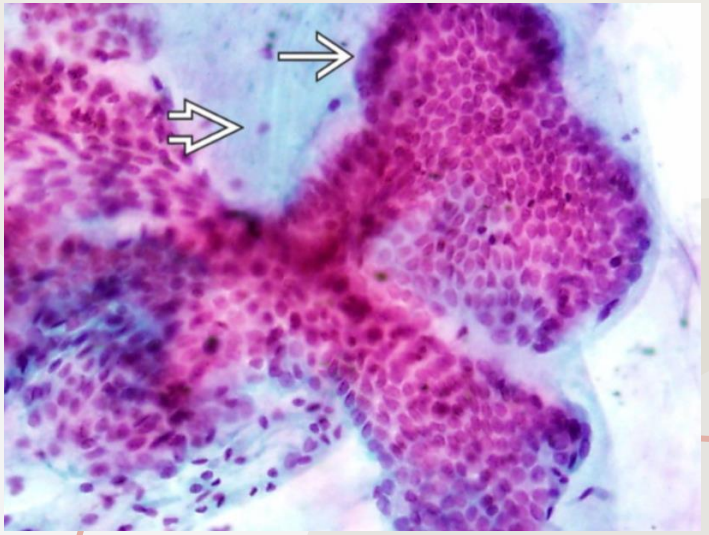
04 Sample reports (Pan-low)

Nature of specimen:
FNAB of multicystic mass in head of pancreas with connection to the main pancreatic duct on imaging.

Category: PaN-low

Diagnosis:
Low-grade neoplastic mucinous cyst. See microscopic description.

Microscopic description: The specimen is highly cellular, showing papillary tissue fragments of mild to moderately atypical mucinous epithelial cells and background extracellular mucin. Features of high-grade atypia are not identified, and background necrosis is absent. The findings support a low-grade (low- to intermediate-grade) intraductal papillary mucinous neoplasm.



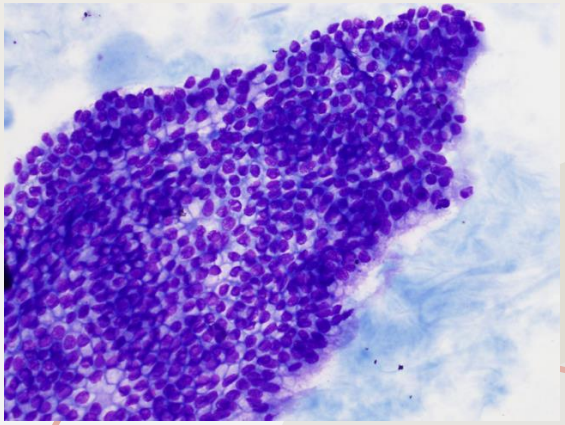
04 Sample reports (Pan-low)

Nature of specimen: FNAB of multilocular cyst in the tail of pancreas.

Category: PaN-low

Diagnosis: Low-grade neoplastic mucinous cyst. See comment.

Comment: The specimen is mildly cellular, showing mildly atypical mucinous epithelium, extracellular mucin, and histiocytes. The differential diagnosis includes low-grade intraductal papillary mucinous neoplasm and low-grade mucinous cystic neoplasm. Correlation with imaging is required.



Conclusion

The new WHO Reporting System for Pancreaticobiliary Cytopathology is designed to improve communication between clinicians and cytopathologists, with improved accuracy in ROM.

The WHO system provides the current best practice application of ancillary testing, including IHC and molecular testing.

The WHO system provides a direct and dynamic link to the WHO classification for Digestive System Tumours, 5th edition.

References

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Thank you!