

**DISTINGUISHING PANCREATIC INTRAEPITHELIAL NEOPLASIA (PANIN),
PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM
(IPMN), INTRADUCTAL ONCOCYTIC PAPILLARY NEOPLASM (IOPN),
INTRADUCTAL TUBULOPAPILLARY NEOPLASM (ITPN), MUCINOUS
CYSTIC NEOPLASM (MCN) AND SEROUS CYSTADENOMA.**

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**Pancreas Pathology Course
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PANCREATIC INTRAEPITHELIAL NEOPLASIA (PANIN)

- **Microscopic**

- Asymptomatic
- Cannot be detected on preoperative imaging studies

- Typically found **incidentally** in resected specimens.

- **Low-grade PanIN** is a common incidental finding in the general population (more than half of all individuals aged > 50 y)
- **High grade PanIN** are more frequently observed in patients with familial predisposition

Precursor lesions in the familial (n=49) and sporadic cases (n=40)

Precursor	Familial (per cm ²)	Sporadic (per cm ²)
Total PanIN	1.51	0.55*
PanIN-1	0.84	0.35
PanIN-2	0.51	0.14
PanIN-3	0.19	0.04
Total incipient IPMN	0.04	0.01*
HG Incipient IPMN	0.03	0
Total Precursor	1.55	0.56*
Total HG precursor	0.22	0.04*

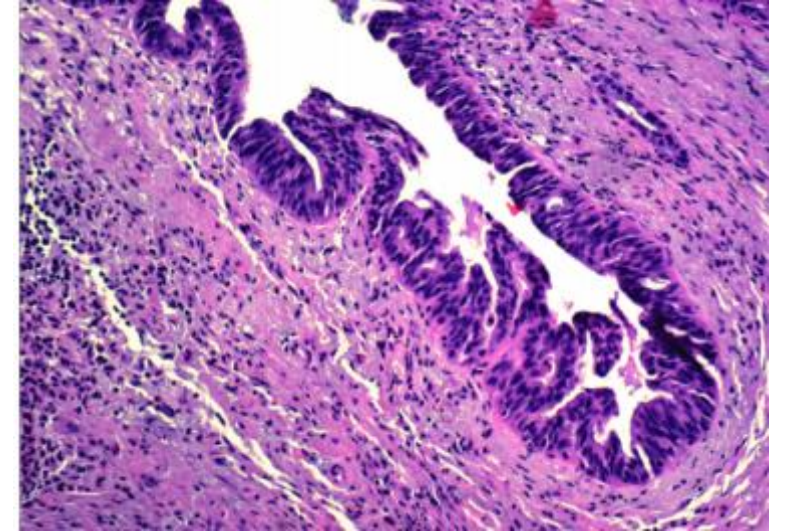
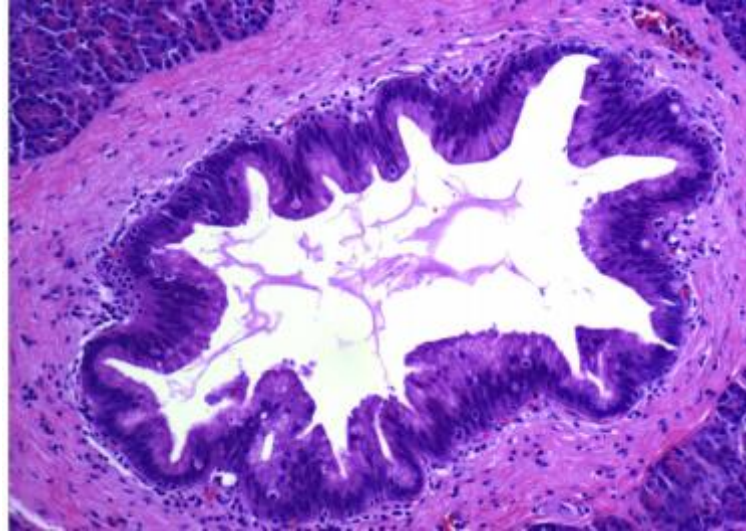
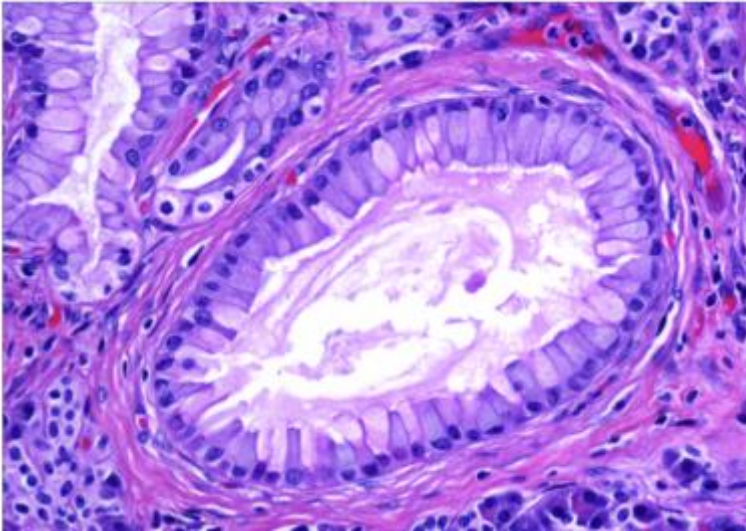
Note: HG=High grade , IPMN= intraductal papillary mucinous neoplasm, PanIN=pancreatic intraepithelial neoplasia,

Total precursor=PanIN-1 + PanIN-2 + PanIN-3 + Incipient IPMN.

Total high-grade precursor=PanIN3 + High-grade incipient IPMN.

*
=p<0.05

PANCREATIC INTRAEPITHELIAL NEOPLASIA (PanIN)



WHO 2010 PanIN-1

PanIN-2

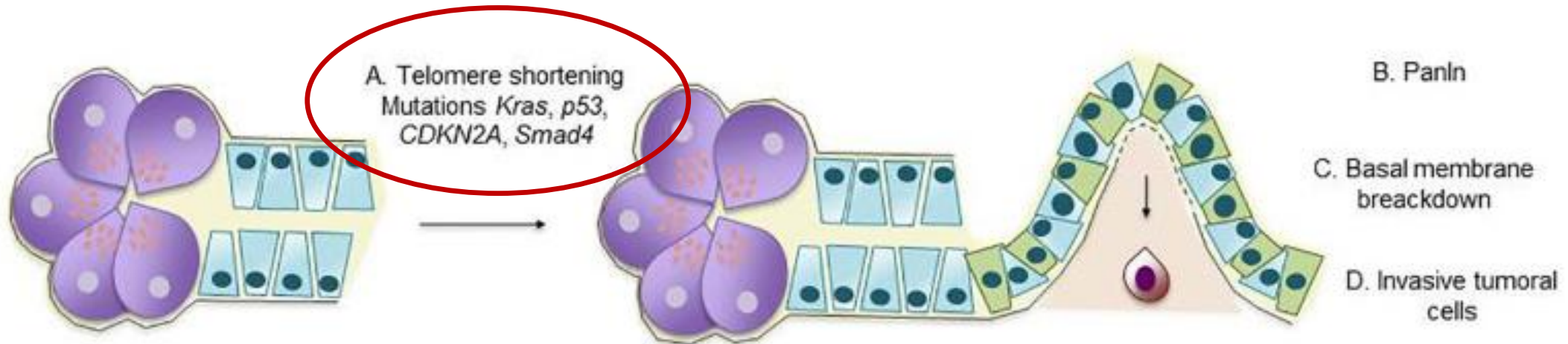
PanIN-3

WHO 2019

Low grade PanIN

**High grade PanIN
pTis**

PANCREATIC INTRAEPITHELIAL NEOPLASIA (PANIN)



- **Early molecular changes (low grade PanIN):**
 - Telomere shortening
 - Activating mutations of *KRAS* oncogene (> 90% of PanIN lesions of all grades harbour *KRAS* mutations)
- **Late molecular changes (high grade PanIN):**
 - Copy-number alterations
 - biallelic inactivation of *CDKN2A*
- **Molecular features of PanIN differ from those of IPMNs**
 - Activating mutations of *GNAS*
 - Inactivating mutations of *RNF43*

PANCREATIC INTRAEPITHELIAL NEOPLASIA (PANIN)

- **Differential diagnosis**

- **IPMNs**

- **Size** is the main feature used to distinguish these lesions:

- PanIN lesions are usually < 0,5 cm whereas IPMNs are usually > 1,0 cm in diameter.

- **Differentiation**

- Epithelial cells in almost all PanIN lesions have gastric differentiation while IPMNs can have various differentiation.

- **Intraductal spread of invasive carcinoma (ductal cancerization)**

- Seen in as many as 70% surgically resected PDACs

PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- **Macroscopic**

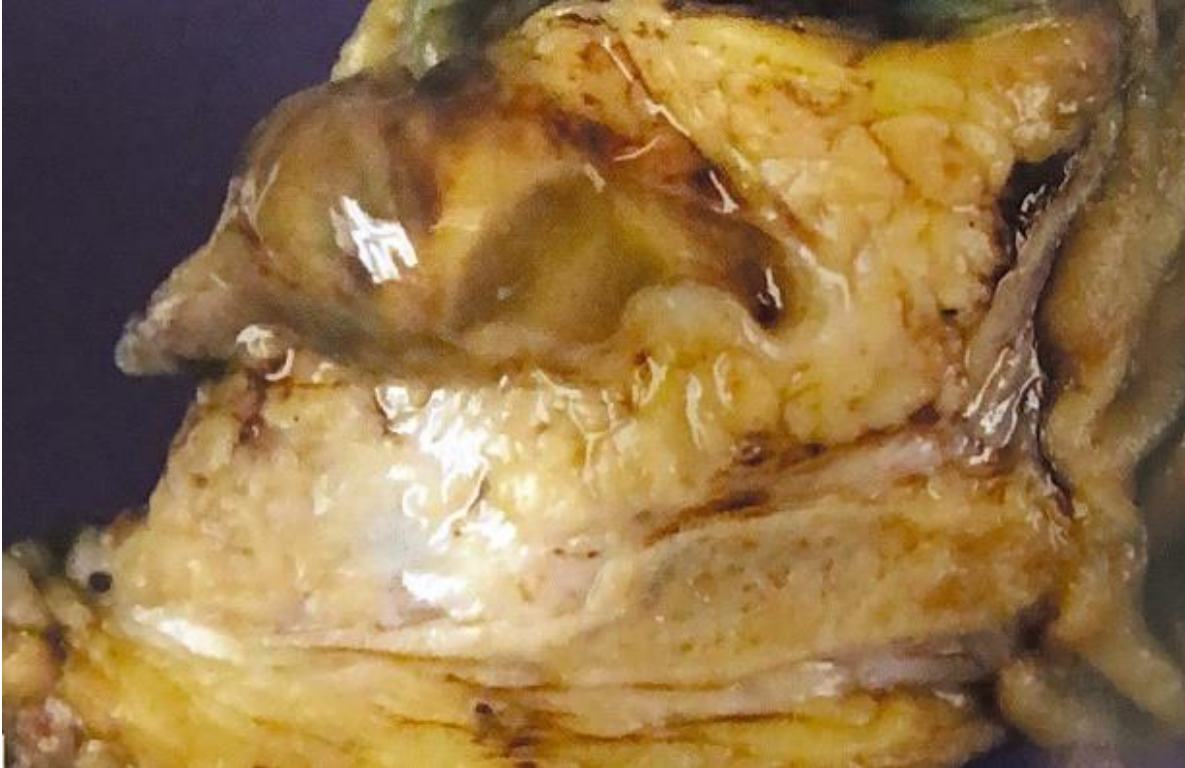
- Grossly visible (> 5 mm) intraductal epithelial neoplasm of mucin-producing cells arising in the main pancreatic duct and/or its branches

- **Imaging (clinical terminology)**

- Three subtypes:
 - **Main duct-type IPMN** (primary involvement of the main pancreatic duct with segmental or diffuse dilatation)
 - **Branch-duct type IPMN** (involve the smaller, secondary ducts without affecting MPD)
 - **Mixed duct-type IPMN** (combination of the two other types)

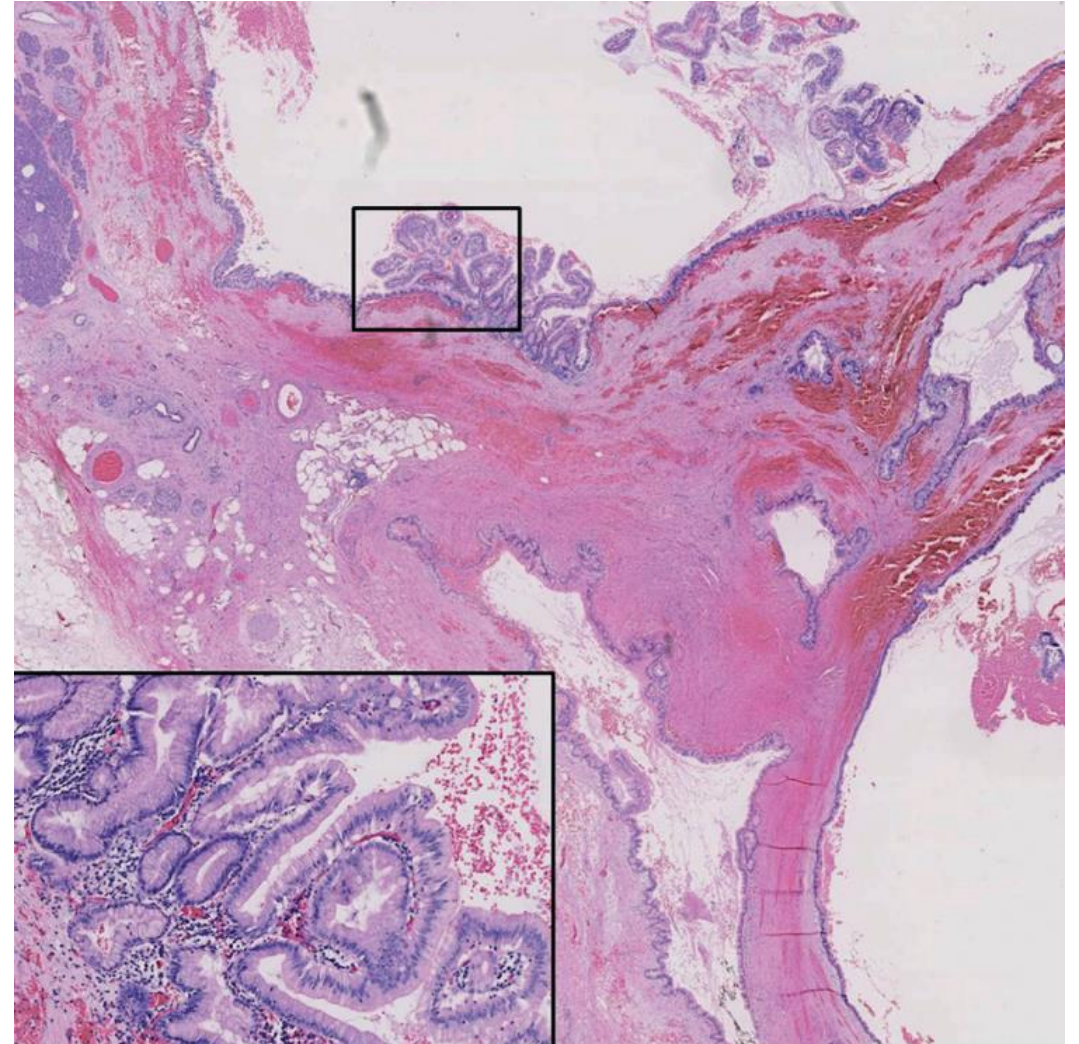
- **Localisation**

- Most are located in the pancreatic head
- Multicentric in 40% of cases



PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- Subtypes
 - **Gastric-type IPMN**
 - ✓ Most common type (70% of cases)
 - ✓ Usually occurs in branch ducts
 - ✓ Most gastric type IPMNs are low-grade lesions (some cases have focal HGD and invasive carcinoma)

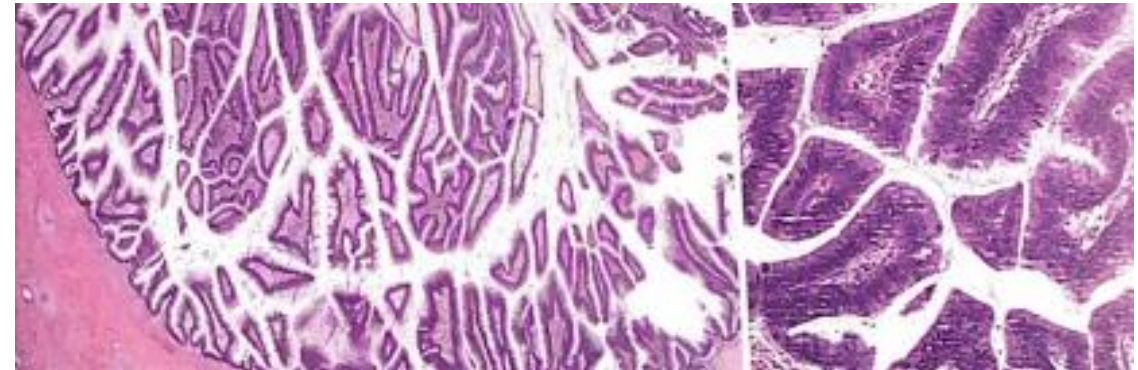


PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- Subtypes

- **Intestinal-type IPMN**

- ✓ 2nd most common type (20% of cases)
 - ✓ Usually occurs in MPD
 - ✓ Most intestinal-type IPMNs are high-grade lesions

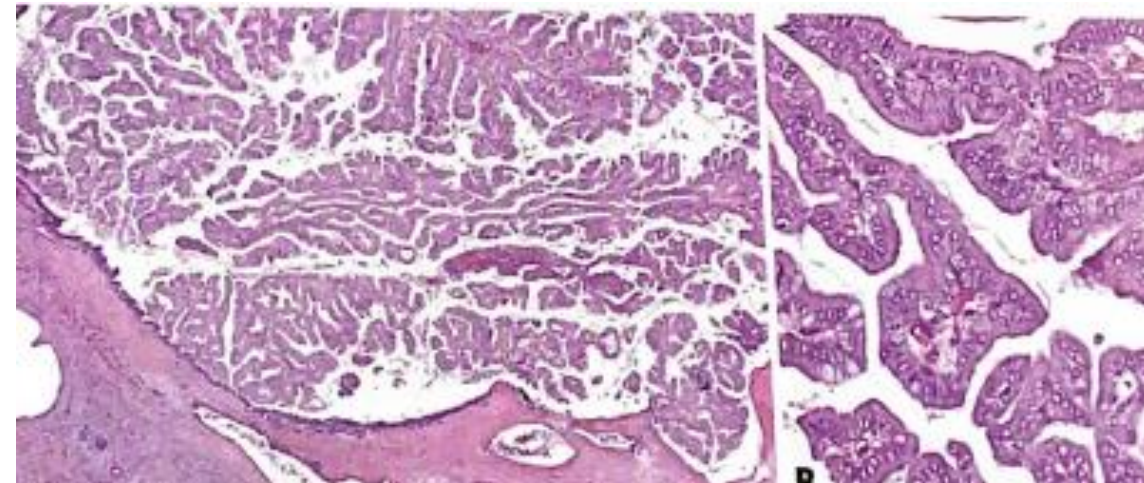


PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- **Subtypes**

- **Pancreatobiliary-type IPMN**

- ✓ The least common
 - ✓ Usually occurs in MPD
 - ✓ Most pancreatobiliary-type IPMNs are high-grade lesions



PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- Subtypes
 - Immunohistochemistry

	CK7/CK8/CK18/CK19	CK20	EMA (MUC1)	MUC2	MUC5AC	MUC6	CDX2
IPMN							
Gastric	+	-	-	-	+	-/+	-
Pancreatobiliary	+	-	+	-	+	+	-
Intestinal	+	+	-	+	+	-	+

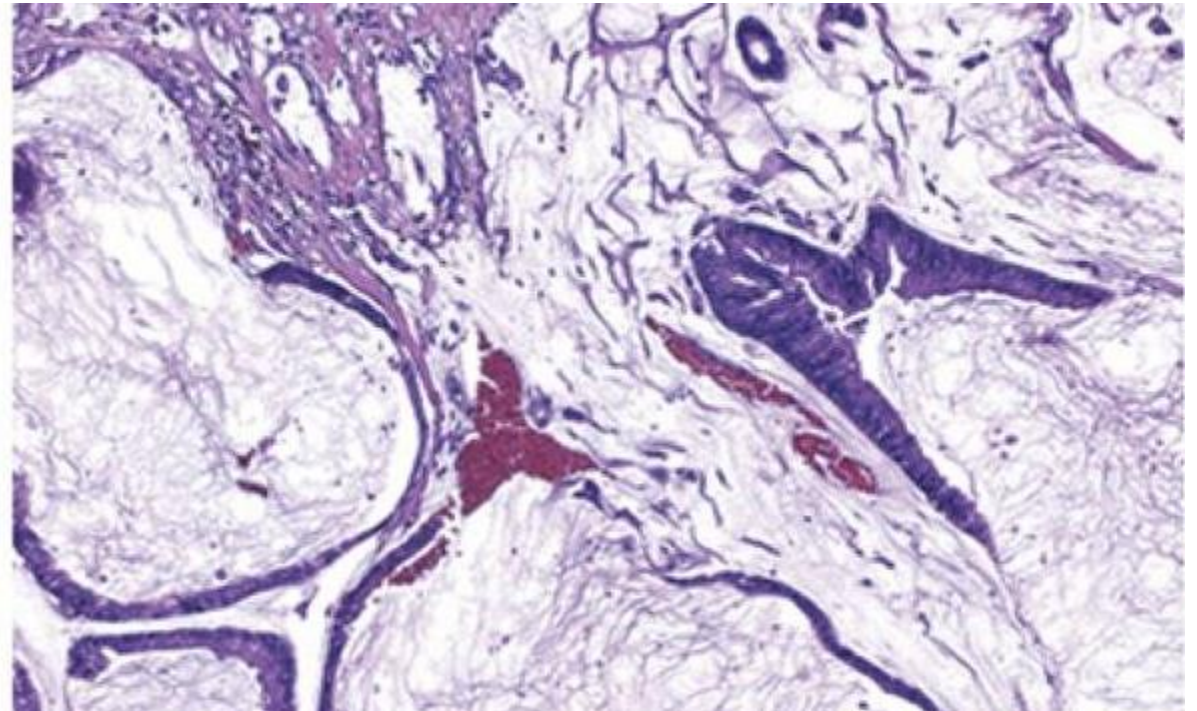
Ductal
markers

PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- **Grading**
 - Two-tiered grading system (low- and high grade dysplasia/pTis)
- **Invasive carcinoma (60% of main duct-type IPMN)**
 - **IPMN with associated invasive carcinoma** (if carcinoma arises in the area of IPMN)
 - **IPMN with a concomitant invasive carcinoma** (if carcinoma is not contiguous with IPMN)
 - ✓ almost branch-duct type
 - ✓ The invasive carcinomas are typically tubular adenocarcinomas

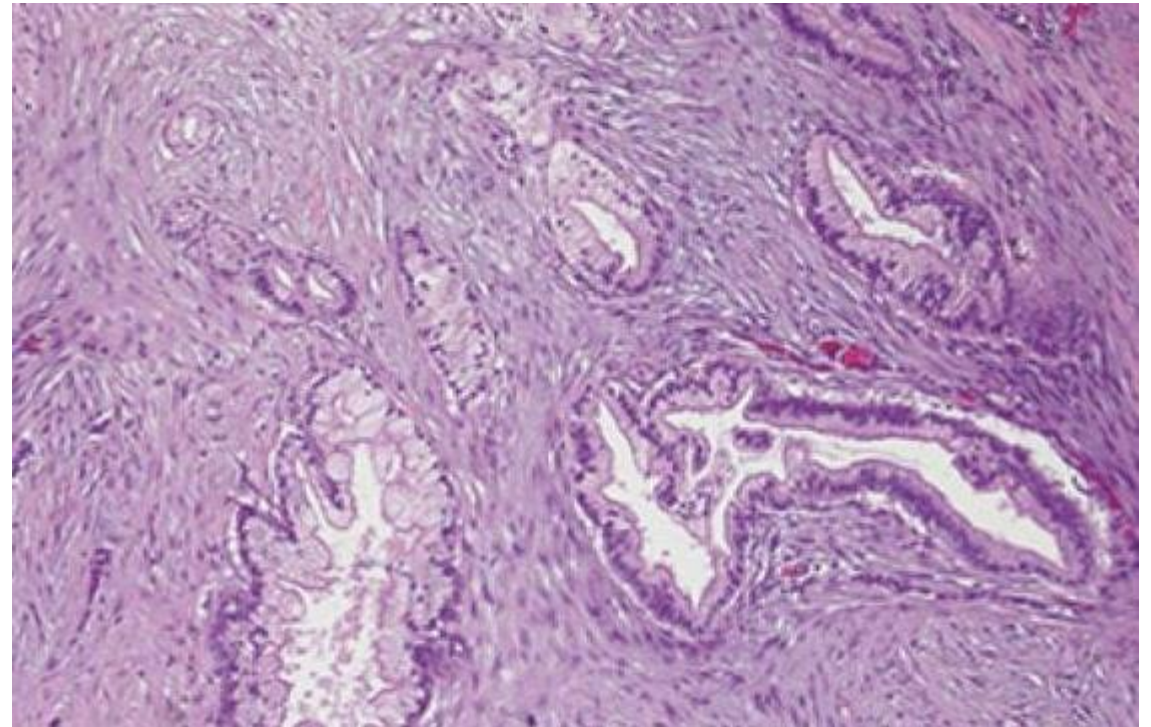
PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- Invasive carcinoma subtype
 - **Colloid carcinoma** (< Intestinal-subtype)
 - Have a better prognosis than tubular type



PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- Invasive carcinoma subtype
 - **Tubular carcinoma** (< pancreatobiliary and gastric-subtype)
 - Morphologically similar to conventional PDAC



PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- **Differential diagnosis**

- **PanIN**

- ✓ Microscopic, non invasive, < 5 mm

- **Intraductal oncocytic papillary neoplasms**

- ✓ Architecture (complex), histology

- **Intraductal tubulopapillary neoplasm**

- ✓ Tubular architecture, minimal intracellular mucin, lack of MUC5A expression

- **Mucinous cystic neoplasm**

- ✓ Women, located in the tail or body of the pancreas, no communication with the duct system, ovarian stroma

- **Retention cyst**

- Usually unilocular, lined by flat single layer of ductal epithelium without nuclear atypia
 - If involved with PanIN, could mimic IPMN

PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

- **Molecular biology**

- Not clinically relevant (WHO 2019)
- *KRAS* mutations (60-80%)
- *GNAS* mutations, codon 201 (50-70%)
 - ✓ Intestinal-subtype
 - ✓ Rare in conventional PDAC
- *RNF43* mutations (50%)
- *P53* mutations (10-40% HG-IPMN versus 40-60% of invasive carcinoma associated with IPMN)
- Loss of *SMAD4* usually occurs in the context of invasion.

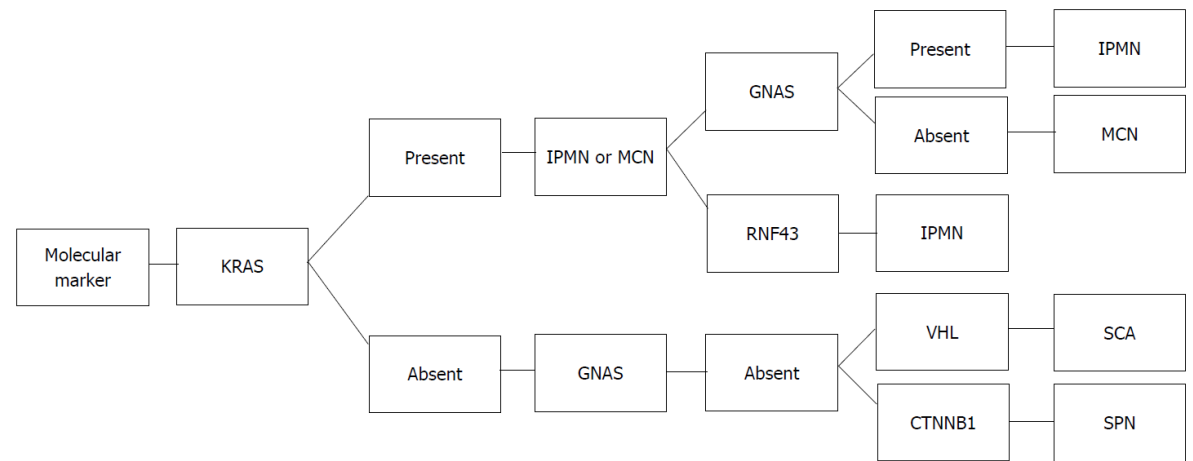
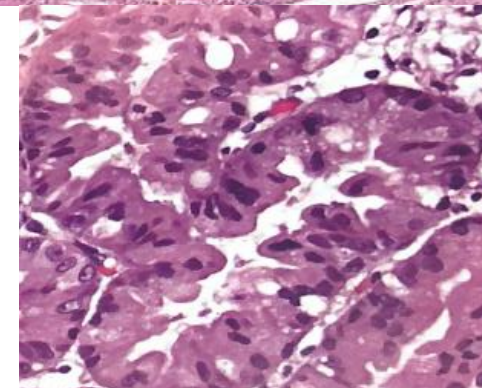
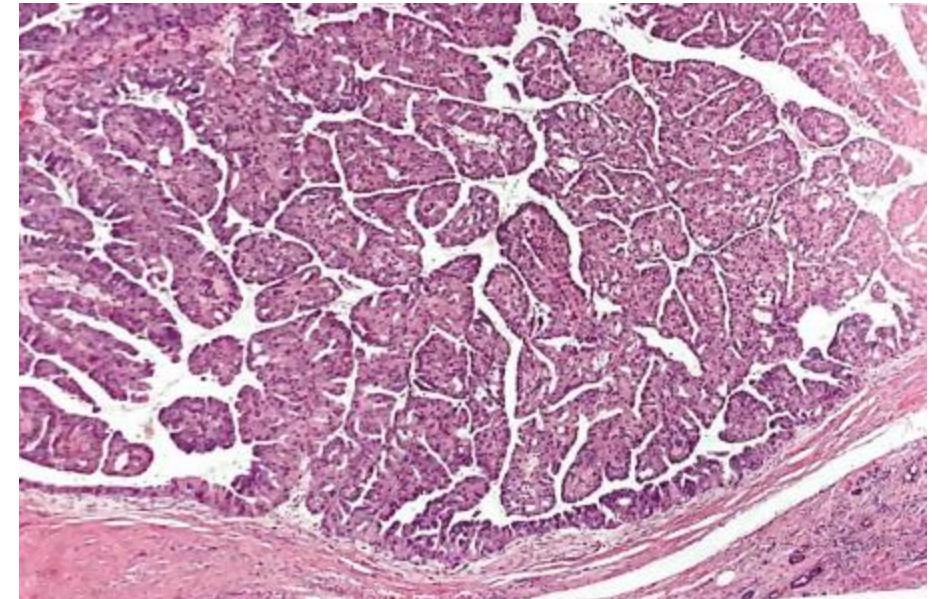


Figure 2 Proposed algorithm for cyst fluid molecular biomarker for the evaluation of pancreatic cystic lesions. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SPN: Solid pseudopapillary neoplasm; SCA: Serous cystadenoma.

PANCREATIC INTRADUCTAL ONCOCYTIC NEOPLASM (IOPN)

- 70% of IOPNs occur in the head of the pancreas and involve MPD
- 10% diffusely involve the gland
- More common in females
- HG-dysplasia
- **Molecularly distinct** from IPMNs:
 - Lack of *KRAS*, *GNAS* and *RNF43* mutations
 - Mutations in *ARHGAP26*, *ASXL1*, *EPHA8*, *ERBB4*
- Associated invasive carcinoma (30%); 5 year disease specific survival reaches nearly 100%, recurrence may occur > 10y.



PANCREATIC INTRADUCTAL ONCOCYTIC NEOPLASM (IOPN)

- **Differential diagnosis**

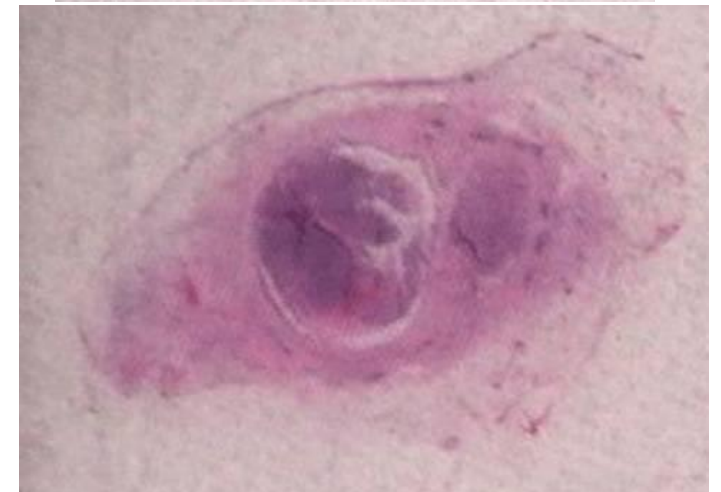
- **IPMNs**
- IOPNs with solid growth pattern should be distinguished from **acinar cell carcinoma** and **neuroendocrine neoplasms**.

- **Immunohistochemistry**

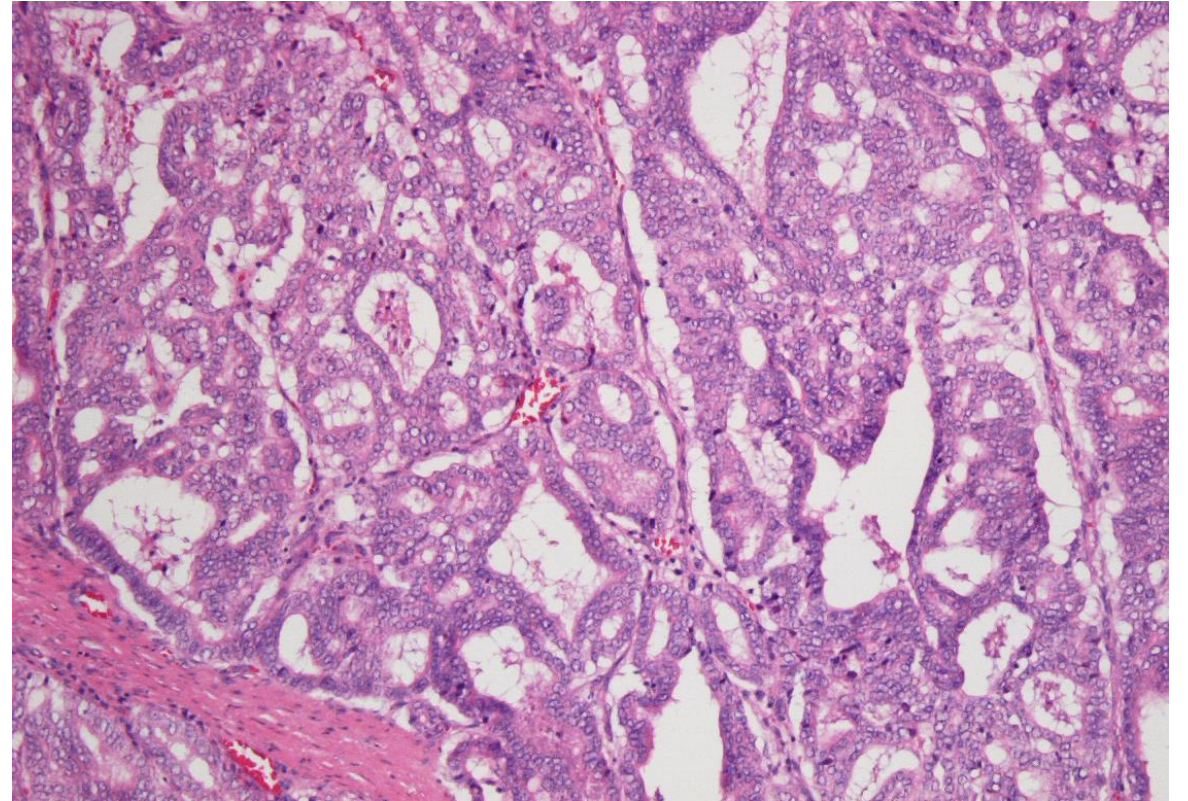
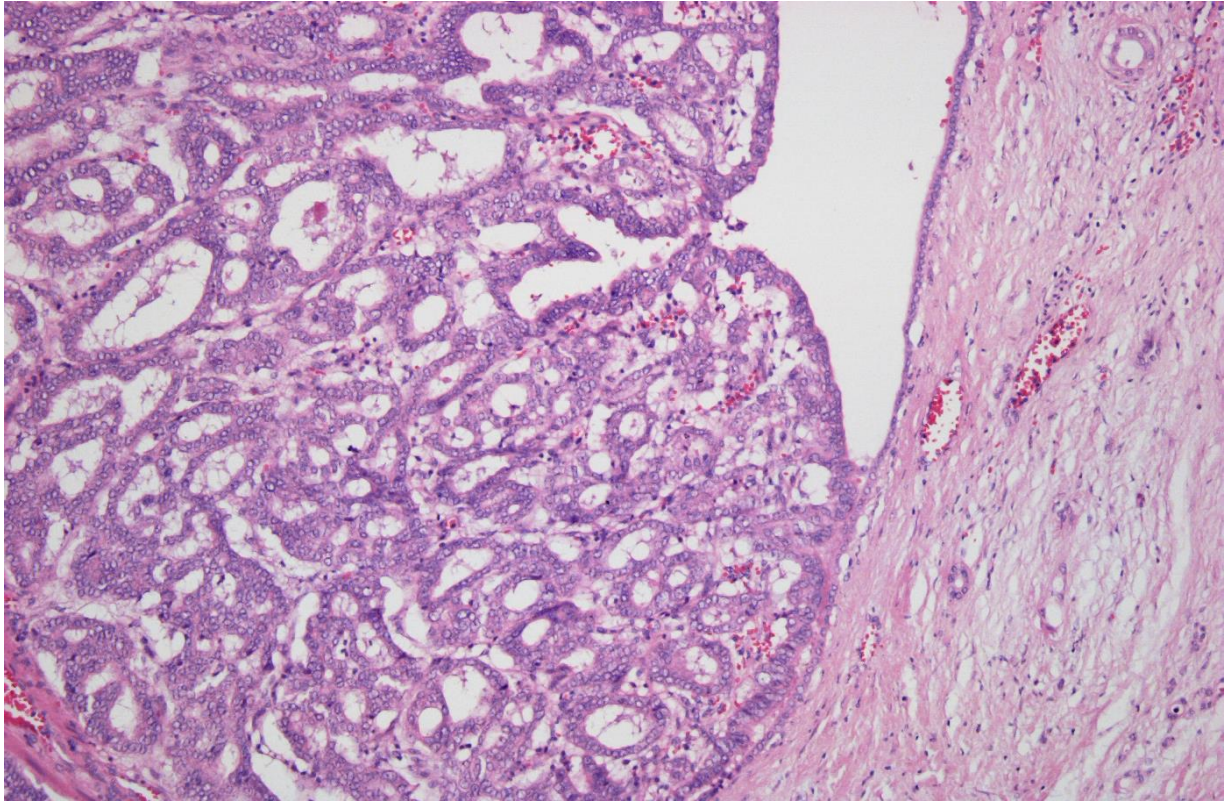
- CK7/CK8/CK18/CK19: +
- EMA and MUC6: +
- MUC2 and MUC5A: restricted to goblet cells

PANCREATIC INTRADUCTAL TUBULOPAPILLARY NEOPLASM (ITPN)

- < 1% of all pancreatic exocrine neoplasms
- 3% of intraductal neoplasms of the pancreas
- Slightly more common in females
- 70% with associated invasive carcinoma
 - Difficult to determine whether invasive carcinoma is present (sampling!)
- Five-year survival rate 71%



PANCREATIC INTRADUCTAL TUBULOPAPILLARY NEOPLASM (ITPN)



PANCREATIC INTRADUCTAL TUBULOPAPILLARY NEOPLASM (ITPN)

- Most of the reported alterations related to PDACs and IPMNs are absent in ITPNs
- Chromatin remodelling genes
- PI3K pathway
- FGFR2 fusions

TABLE 2. Comparison of Molecular Alterations Between ITPNs and IPMNs

	ITPN	IPMN	<i>P</i>	Statistics
Total no. samples	11	50		
<i>PIK3CA</i> mutation	3	0	0.005	F
<i>KRAS</i> mutation	0	26	0.001	F
<i>BRAF</i> mutation	0	1	1.000	F
TP53 overexpression	1	10	0.670	F
SMAD4 loss	1	6	1.000	F
CTNNB1 overexpression	0	9	0.191	F
PTEN expression score (median)	1	1	0.033	M-W
pAKT expression score (median)	3	1	< 0.001	M-W

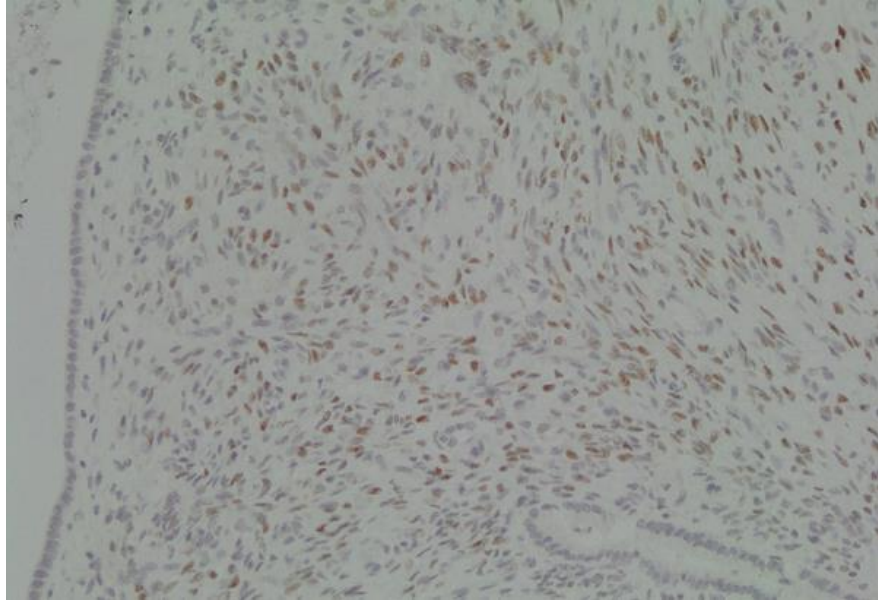
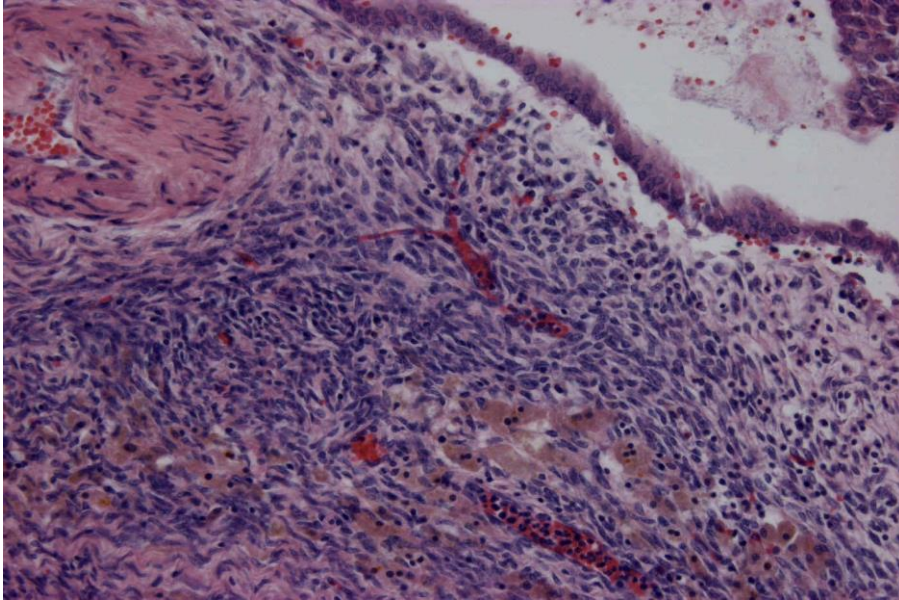
CTNNB1 indicates β -catenin; F, Fisher exact test; M-W, Mann-Whitney *U* test; pAKT, phosphorylated AKT.

PANCREATIC MUCINOUS CYSTIC NEOPLASM (MCN)

- 8% of resected cystic lesions of the pancreas
- Women (98%)
- *KRAS* mutation, codon 12 (50-66%)
- Loss of function alterations in *RNF43*
- *TP53* mutation rare (associated with aggressiveness)
- Two-tiered grading system (low and high grade/pTis)
- 15% associated with invasive carcinoma component, usually tubular-type (larger lesion, > 5 cm)
- Invasive cancer could be focal (!sampling!)
- 5 year survival
 - Without invasive component: 100%
 - With invasive component: 26%



PANCREATIC MUCINOUS CYSTIC NEOPLASM (MCN)



- **Ectopic ovarian stroma:**

- Incorporated during embryogenesis of the pancreas, may become activated in the setting of hormonal imbalance, releasing hormones and growth factors causing ductal epithelium to proliferate and form cystic neoplasm
- Ovarian-type stroma represents persistent fetal periductal mesenchyme which may respond and proliferate in response to hormonal stimulation.

PANCREATIC MUCINOUS CYSTIC NEOPLASM (MCN)

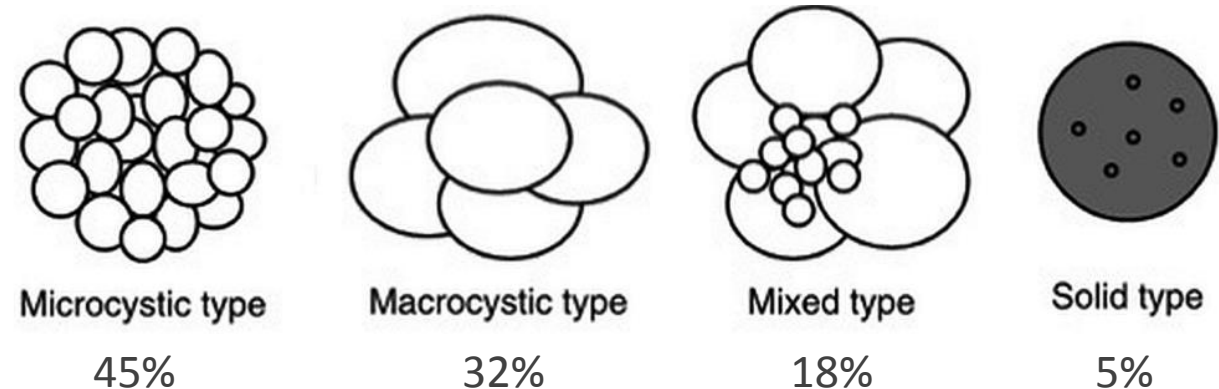
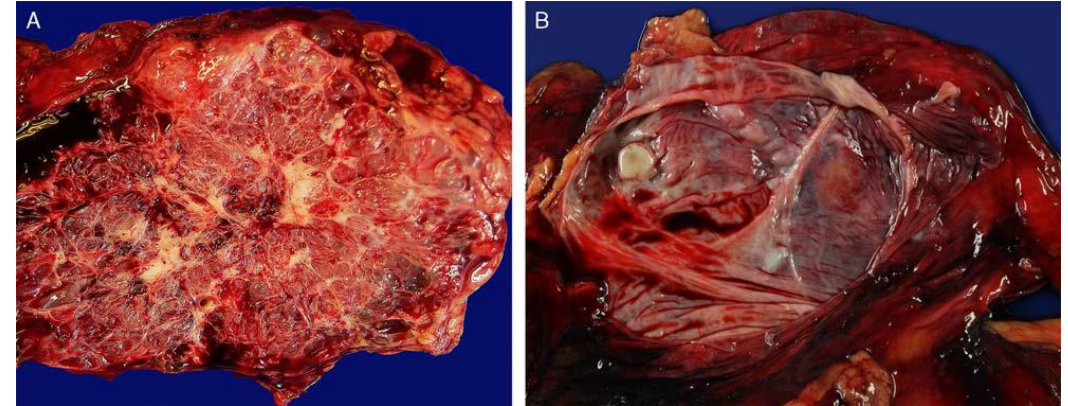
- **Differential diagnosis:**

- **Pseudocyst**

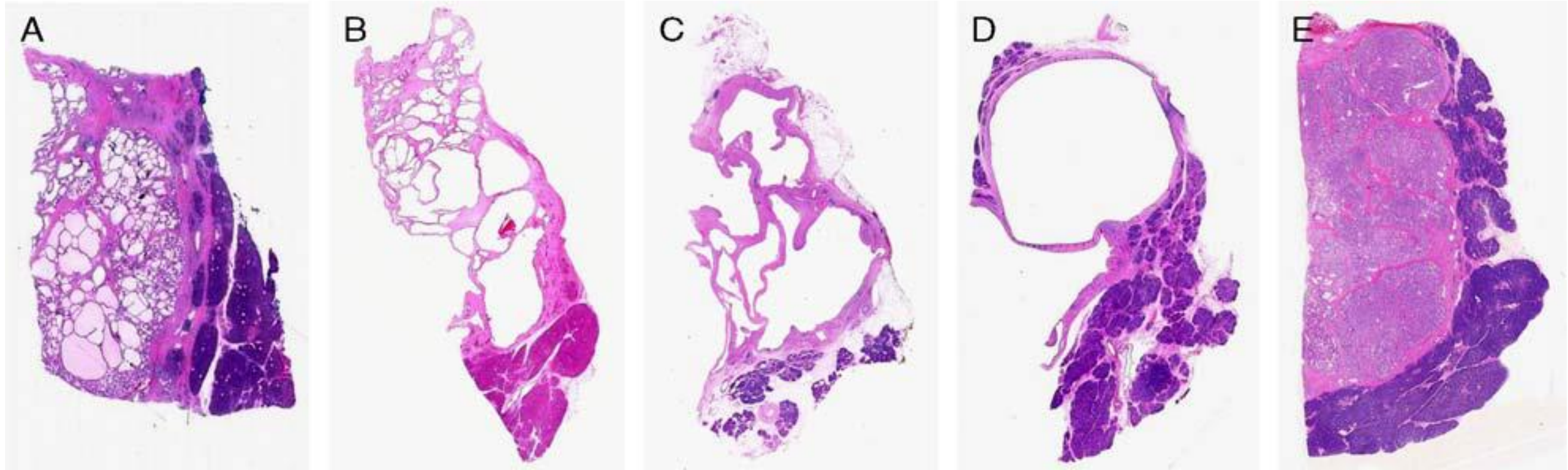
- ✓ Sometimes MCNs could present huge degenerative changes. Extensive sampling is mandatory to identify key features of diagnosis (ovarian-type stroma)

SEROUS NEOPLASMS OF THE PANCREAS

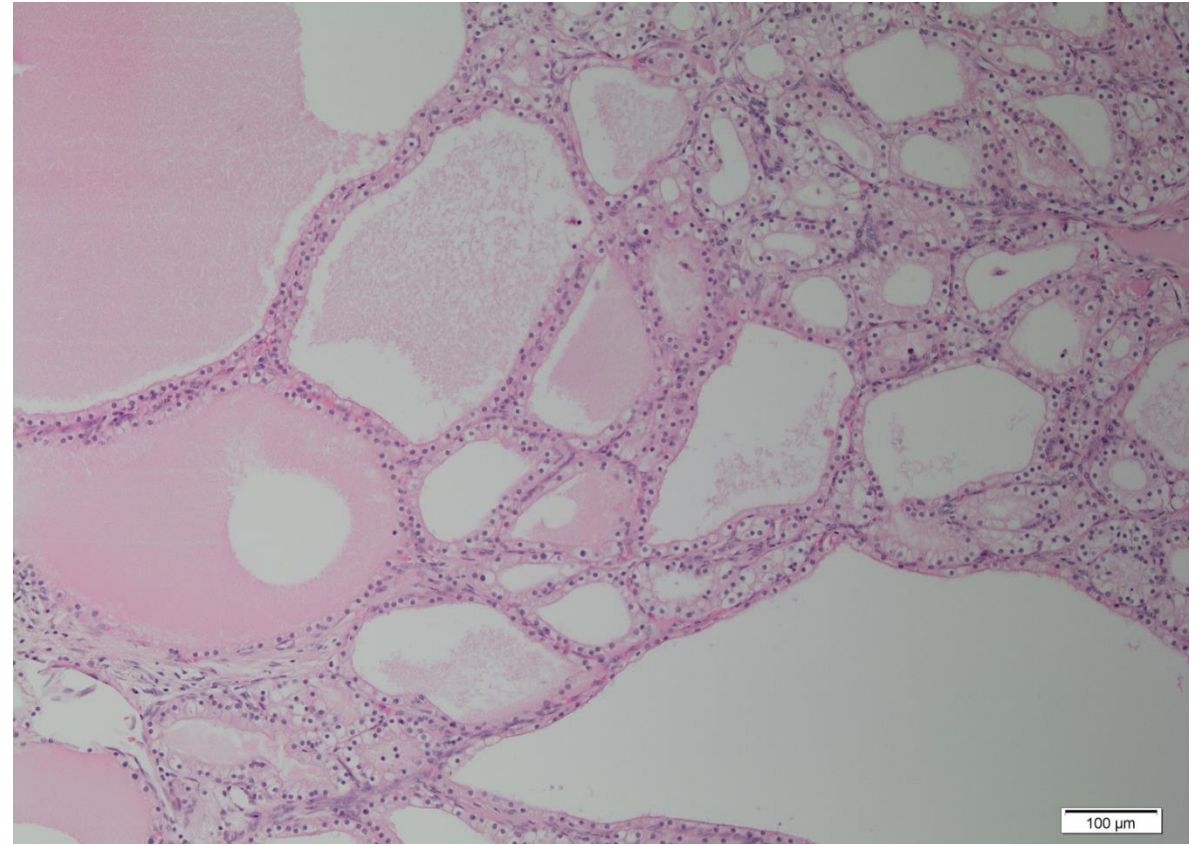
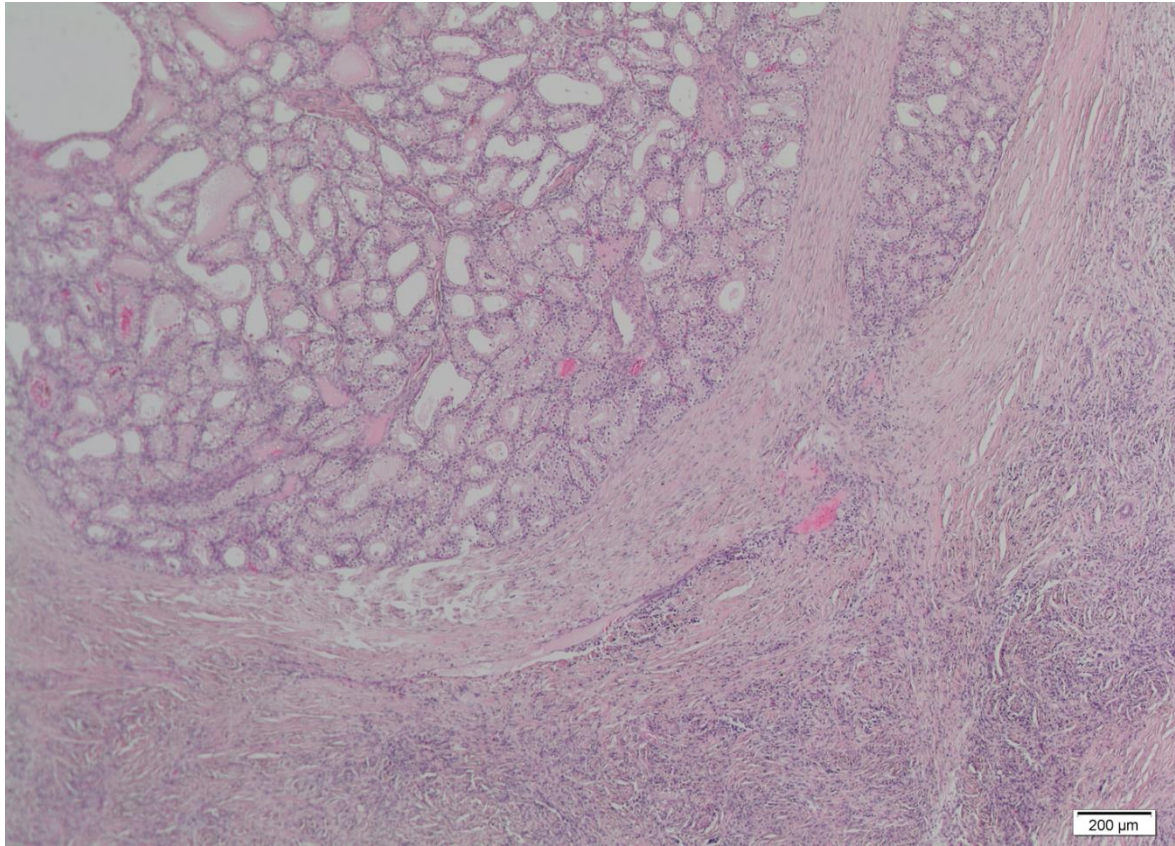
- **Microcystic and macrocystic serous cystadenoma**
- **Solid serous adenoma**
- Generally solitary
- Pancreatic body or tail
- Female predominance
- Associated with germline alteration in *VHL* (Von Hippel-Lindau syndrome)



SEROUS NEOPLASMS OF THE PANCREAS



SEROUS NEOPLASMS OF THE PANCREAS

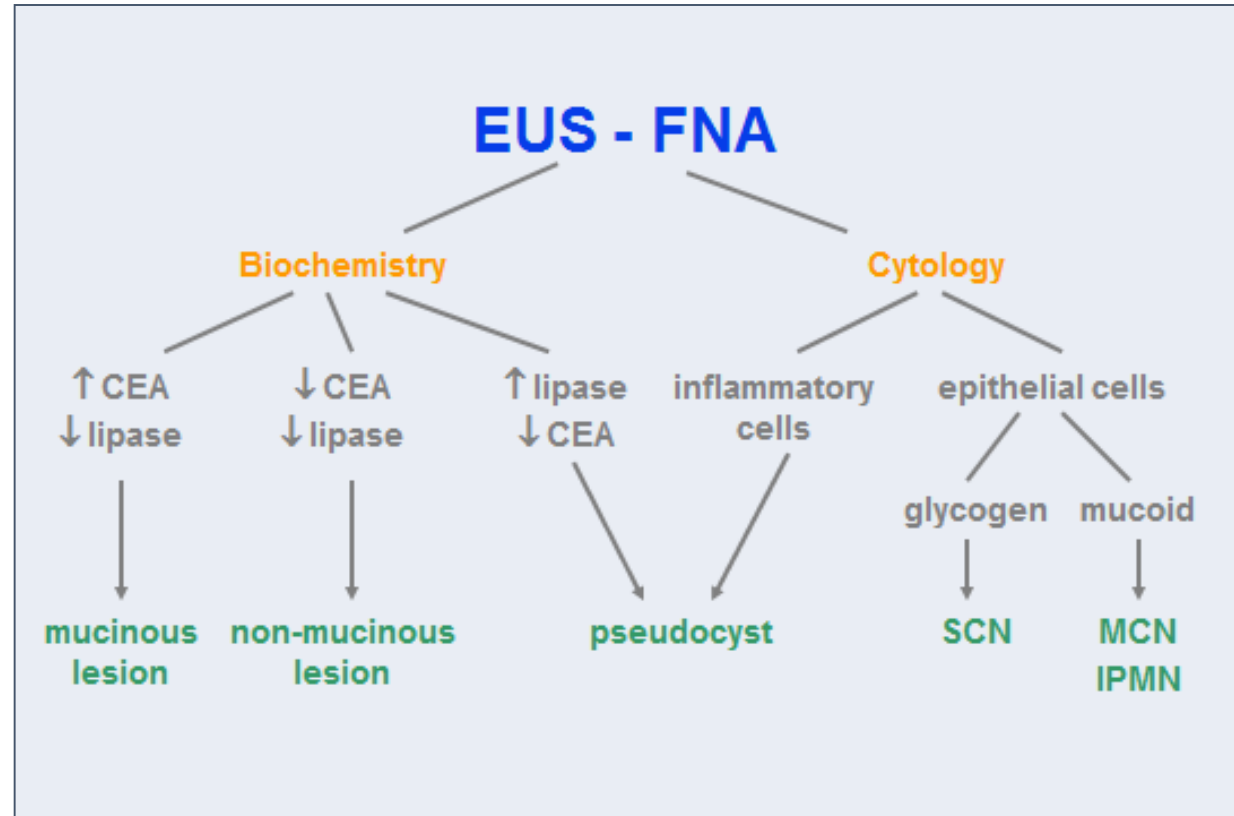


SEROUS NEOPLASMS OF THE PANCREAS

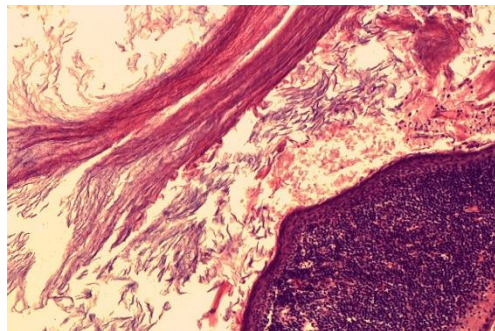
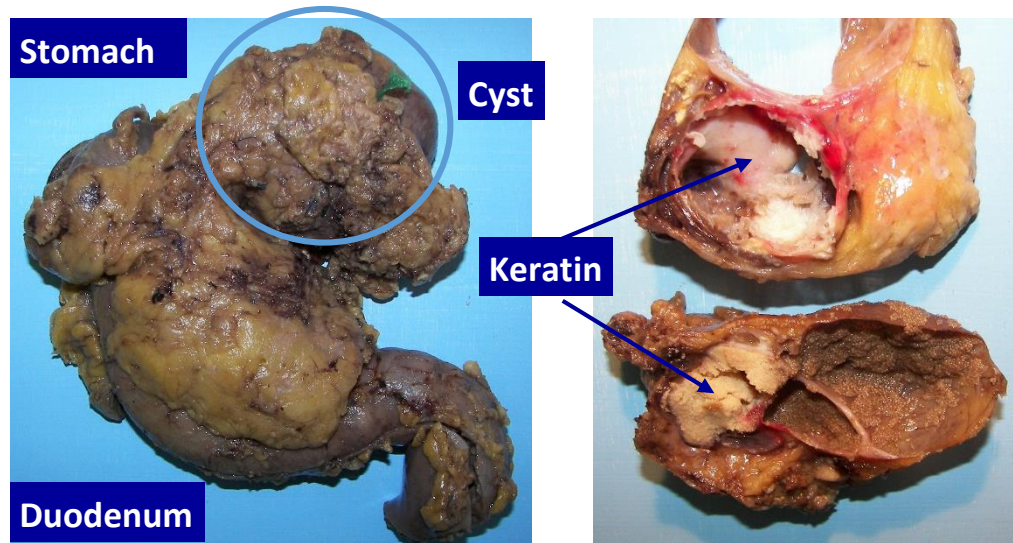
- **Invasive carcinoma (serous cystadenocarcinoma)**
 - Rare
 - Diagnosis of serous cystadenocarcinoma requires metastasis (almost always in the liver)
- **Association with pancreatic neuroendocrine neoplasm**
 - Could be associated with VHL syndrome

PANCREATIC CYSTIC LESIONS

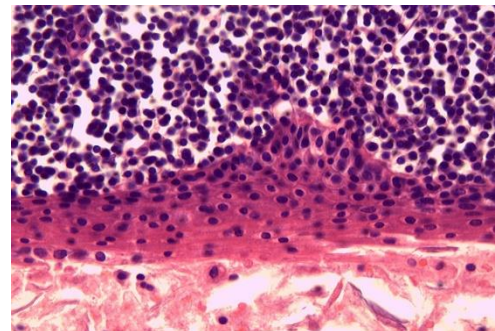
- for cyst fluid analysis
 - CEA
 - Lipase
 - Cytology
 - Molecular markers



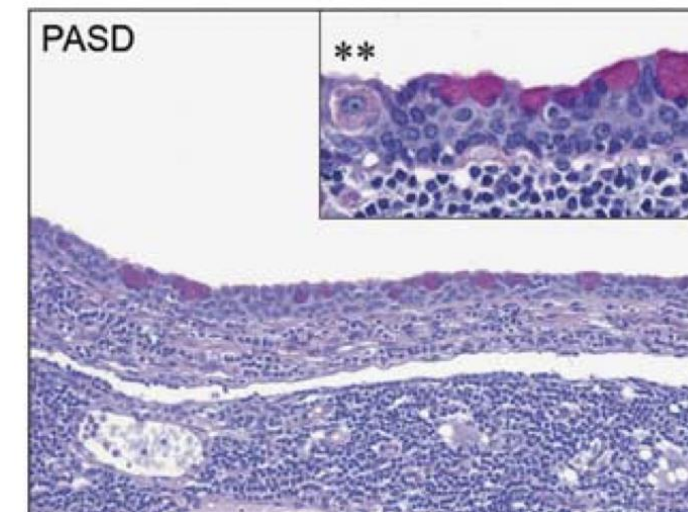
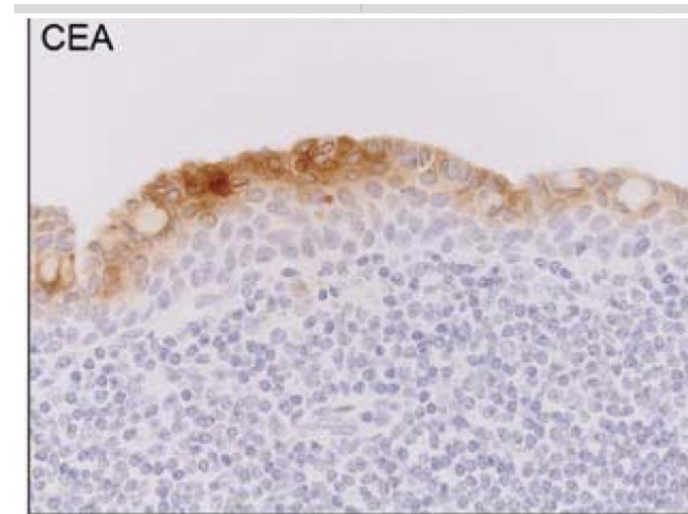
LYMPHOEPITHELIAL CYST



Cyst wall composed of lymphoid tissue covered by squamous epithelium, lumen contains keratin



Lymphoid component, squamous epithelium



CONCLUSION

- **PanIn**
 - Microscopic diagnosis
 - **Always think about association with invasive carcinoma**
 - Extensive sampling
 - Immunohistochemistry and molecular biology
-
- **Pancreatic lesions require multidisciplinary approach to make a correct diagnosis**