The pathology landscape: benign, premalignant & malignant pancreatic cystic lesions

Pieter Demetter

Department of Pathology

Erasme University Hospital

Université libre de Bruxelles (ULB)

PREVALENCE OF UNSUSPECTED PANCREATIC CYSTS ON MDCT

Hôpital Erasme ULB

Prevalence of Cysts

Parameter	Patients Screened (% of total)	Patients with Cyst	Cyst Prevalence per 100 (95% CI)	Odds Ratio[a] (95% CI)
Total	2,832 (100)	73	2.6 (2.0–3.2)	—
Age (y)				
20–39	332 (11.7)	0	0	—
40–49	439 (15.5)	6	1.4 (0.2–2)	1.00 (ref)
50–59	711 (25.1)	11	1.5 (0.6–2)	1.13 (0.416–3.09)
60–69	626 (22.1)	18	2.9 (1.5–4.1)	2.13 (0.84–5.43)
70–79	528 (18.6)	22	4.0 (2.4–5.9)	3.14 (1.26–7.80)
80–89	183 (6.5)	16	8.7 (4.6–12.9)	6.91 (2.66–17.96)
≥90[b]	13 (0.5)	0	0	—

Laffan TA, *AJR Am J Roentgenol* 2008

Box 1 Classification of pancreatic cystic lesions (PCLs)
Non-neoplastic cysts
Pseudocyst
Simple or congenital cyst
Retention cyst
Neoplastic cysts [pancreatic cystic neoplasms (PCNs)]
Mucinous cystic lesions
Intraductal papillary mucinous neoplasm (IPMN)
Mucinous cystic neoplasm (MCN)
Non-Mucinous cystic neoplastic lesions
Serous cystic neoplasm (SCN)
Solid-pseudopapillary neoplasm (SPN)
Cystic neuroendocrine neoplasm
Acinar-cell cystic neoplasm
Other neoplastic lesions
Ductal adenocarcinoma with cystic degeneration

Brugge WR, *J Gastrointest Oncol* 2015

PANCREATIC CYSTS

- Pseudocysts
  - Surrounded by fibrous and granulation tissue
  - Associated with acute or chronic pancreatitis
- True cysts
  - Lined by epithelium

PRIMARY CYSTIC LESIONS OF THE PANCREAS (522 CASES)

Hôpital Erasme ULB

Type of Tumor	No. of Patients	%
Epithelial Tumors		
Serous cystadenoma	170	32.6
Mucinous cystadenoma	149	28.5
Cystadenocarcinoma	79	15.1
Intraductal papillary mucinous tumor	55	10.6
Pseudopapillary and solid tumor	22	4.2
Teratoma	2	0.4
Acinous cystadenocarcinoma	1	0.2
Adenosquamous carcinoma	1	0.2
Mucinous cystic adenocarcinoma	7	1.3
Nonepithelial Tumors		
Cystic islet cell tumor	13	2.5
Vascular tumor		
Lymphangioma	4	0.8
Hemangiopericytoma	1	0.2
Leiomyosarcoma	1	0.2
Lymphoma	1	0.2
Pseudotumors		
Single cyst	8	1.5
Polycystic disease		
Exclusively pancreatic	2	0.4
With hepatorenal disease	2	0.4
von Hippel-Lindau disease	4	0.8

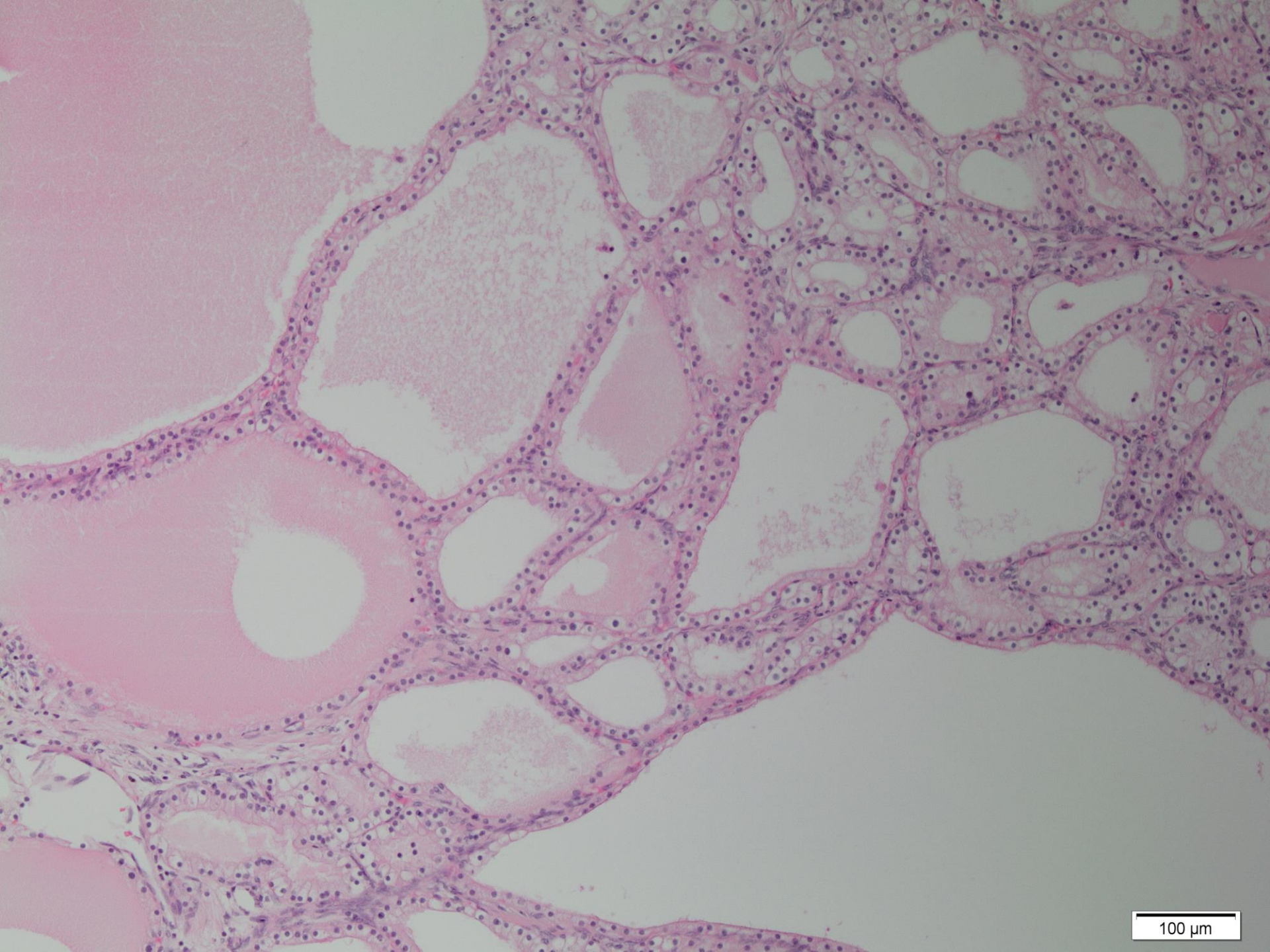
Data from French Surgical Association survey, 1984–1996.

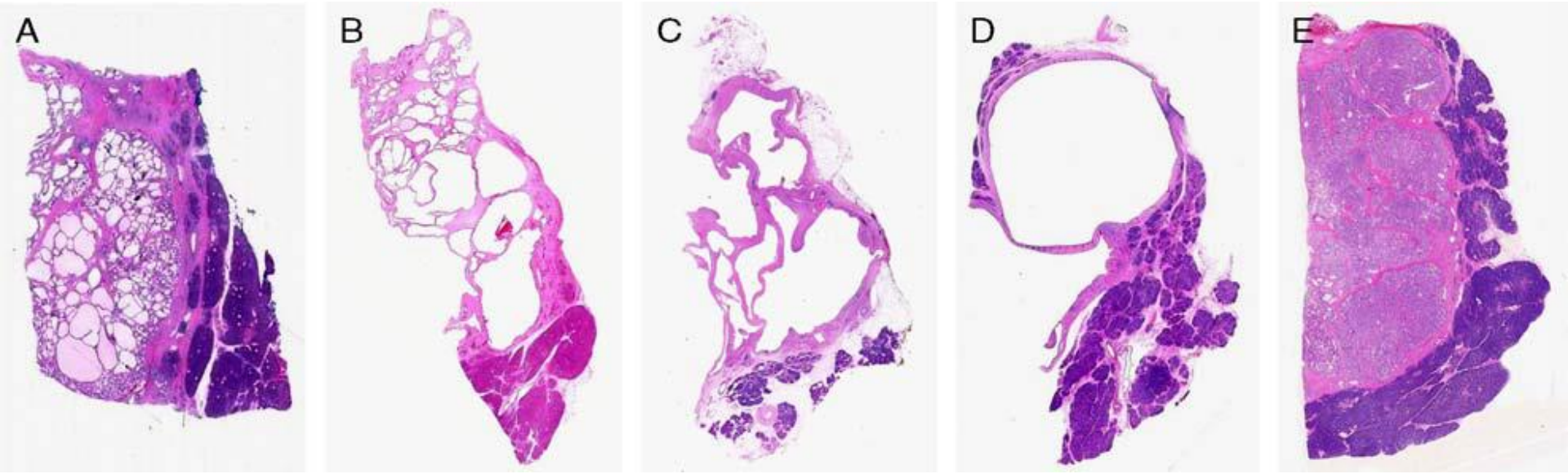
Le Borgne J, *Ann Surg* 1999

SEROUS CYSTADENOMA

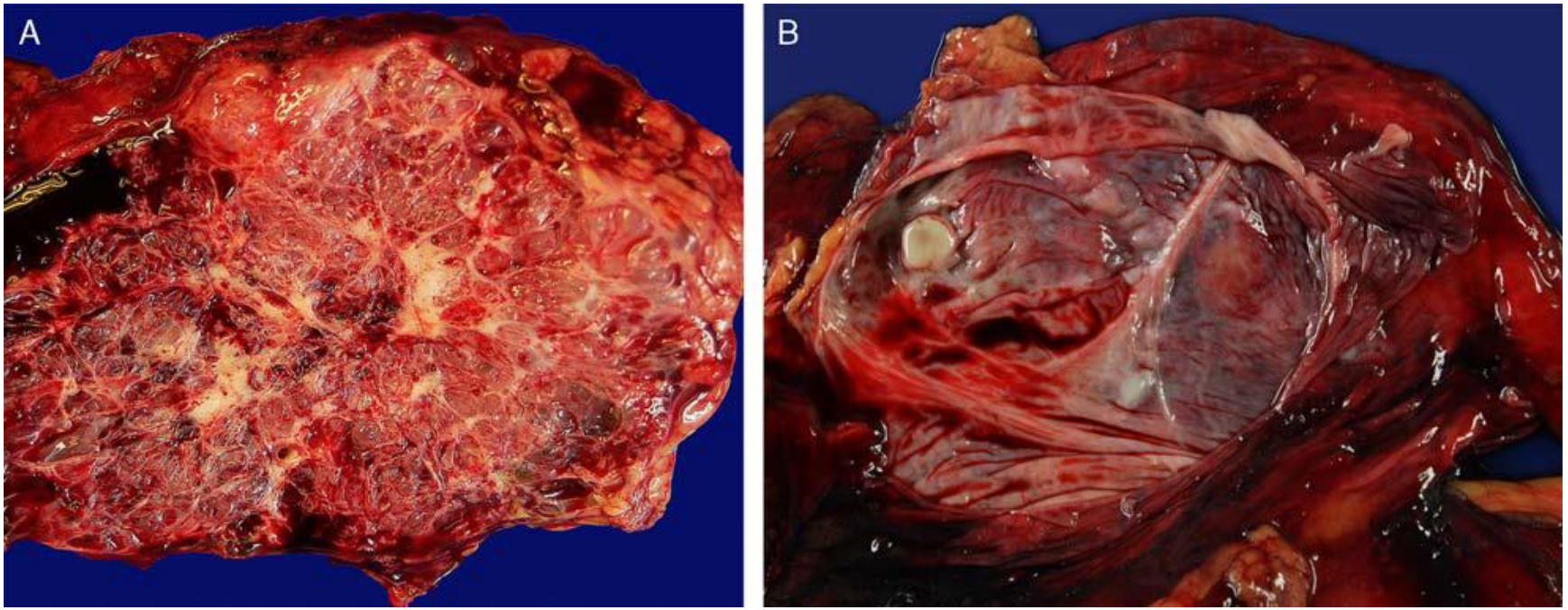
- Accounts for about one third of pancreatic cysts
- Mean age at presentation around 60 years
- 75% of the affected individuals are females
- > 50% in the body or tail
- 70% of serous cystadenomas has a *VHL* mutation

Sakorafas GH, *Surg Oncol* 2011
Tseng JF, *Ann Surg* 2005
Moore PS, *Am J Pathol* 2001

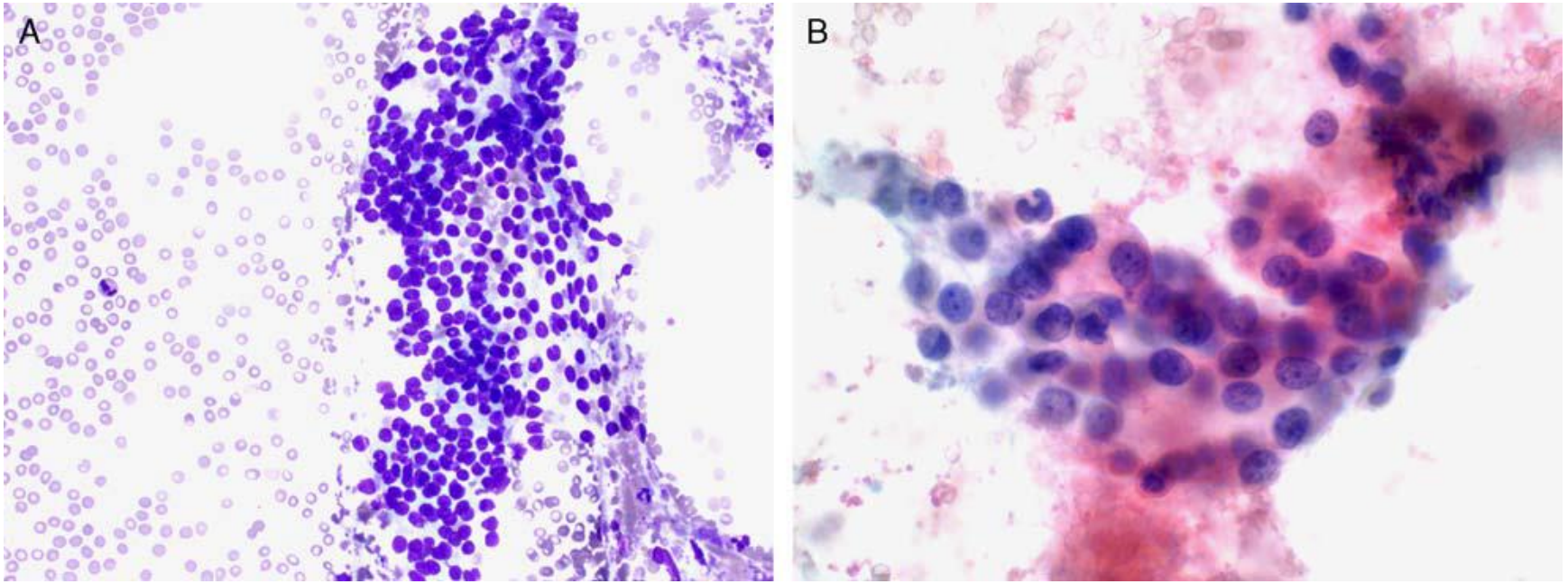

100 µm



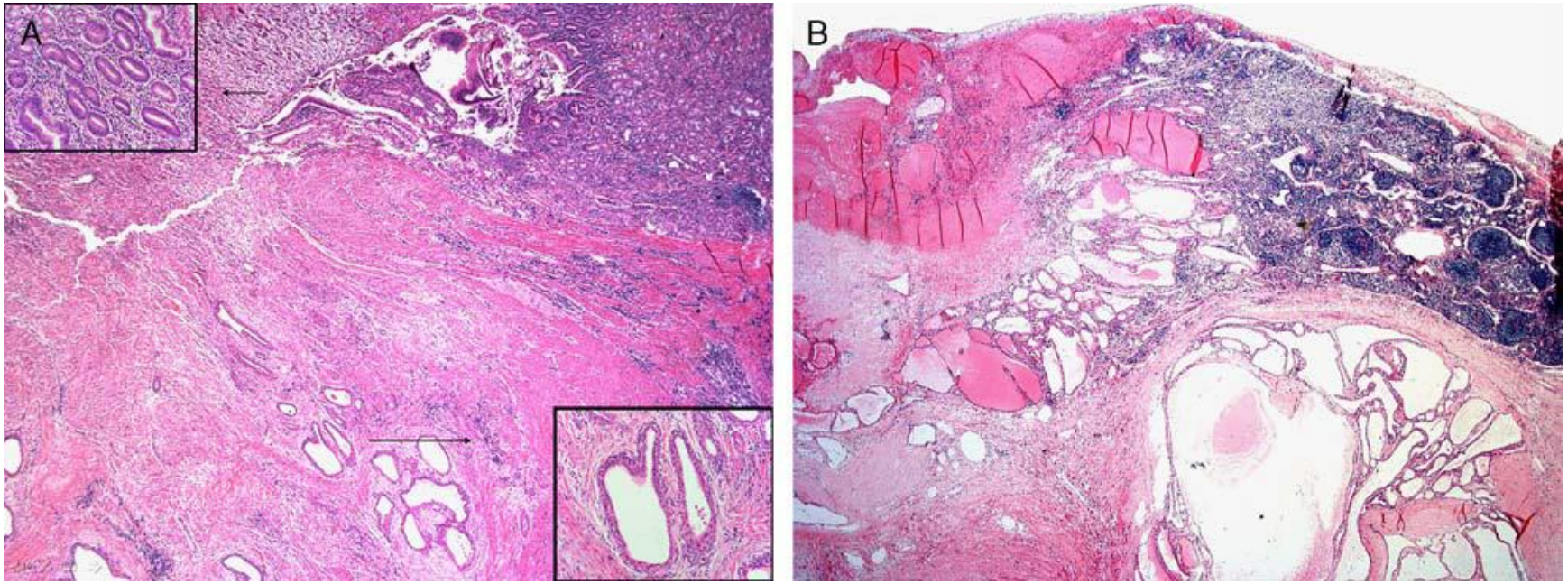
Reid MD, *Am J Surg Pathol* 2015



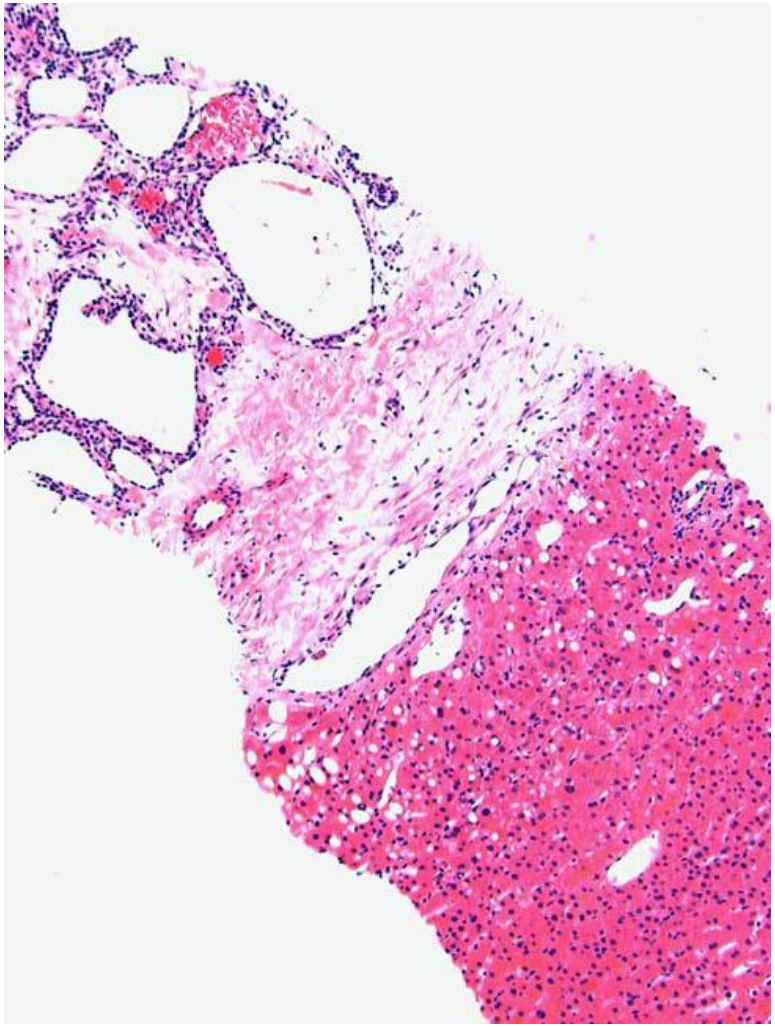
Reid MD, *Am J Surg Pathol* 2015



Reid MD, *Am J Surg Pathol* 2015



Reid MD, *Am J Surg Pathol* 2015



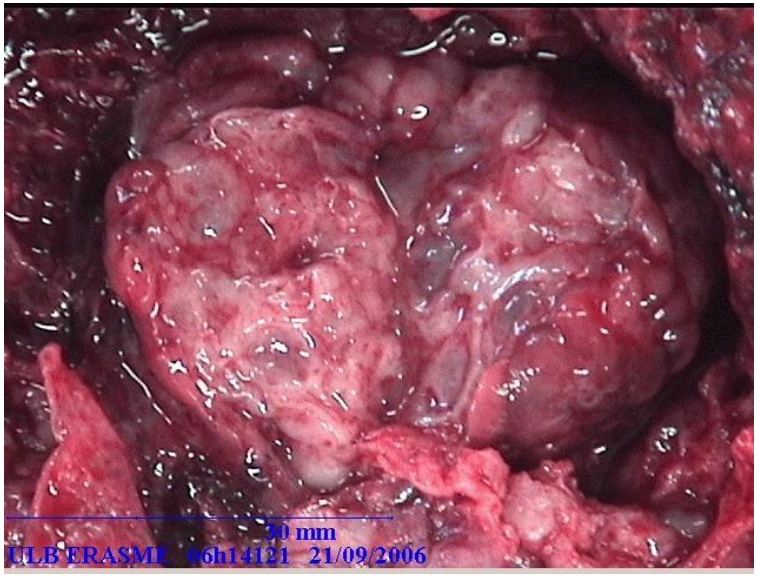
Reid MD, *Am J Surg Pathol* 2015

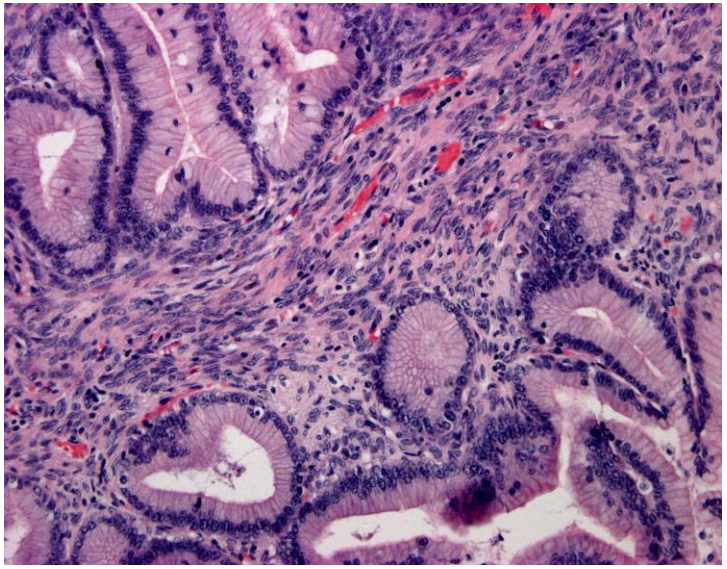
MUCINOUS CYSTADENOMA

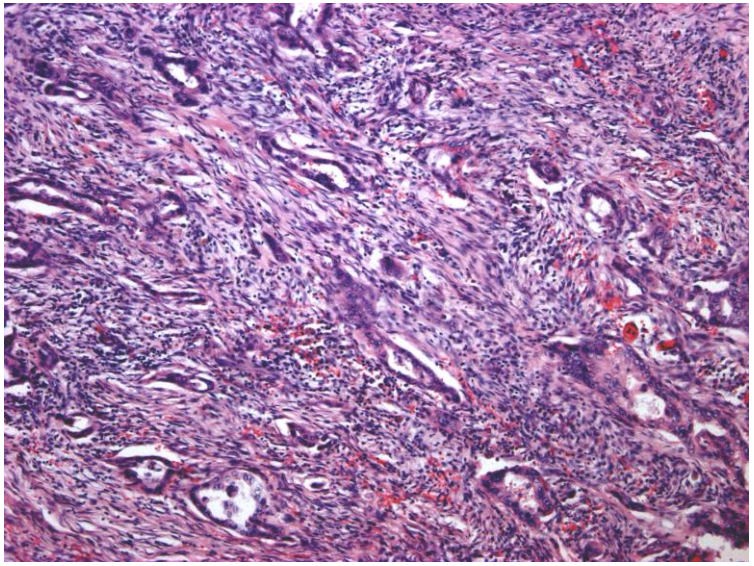
- In surgical series up to 23% of resected cysts
- Age at presentation 40-50 years
- Almost exclusively in females
- > 90% in the body or tail

Valsangkar NP, *Surgery* 2012
Reddy RP, *Clin Gastroenterol Hepatol* 2004
Yamao K, *Pancreas* 2011

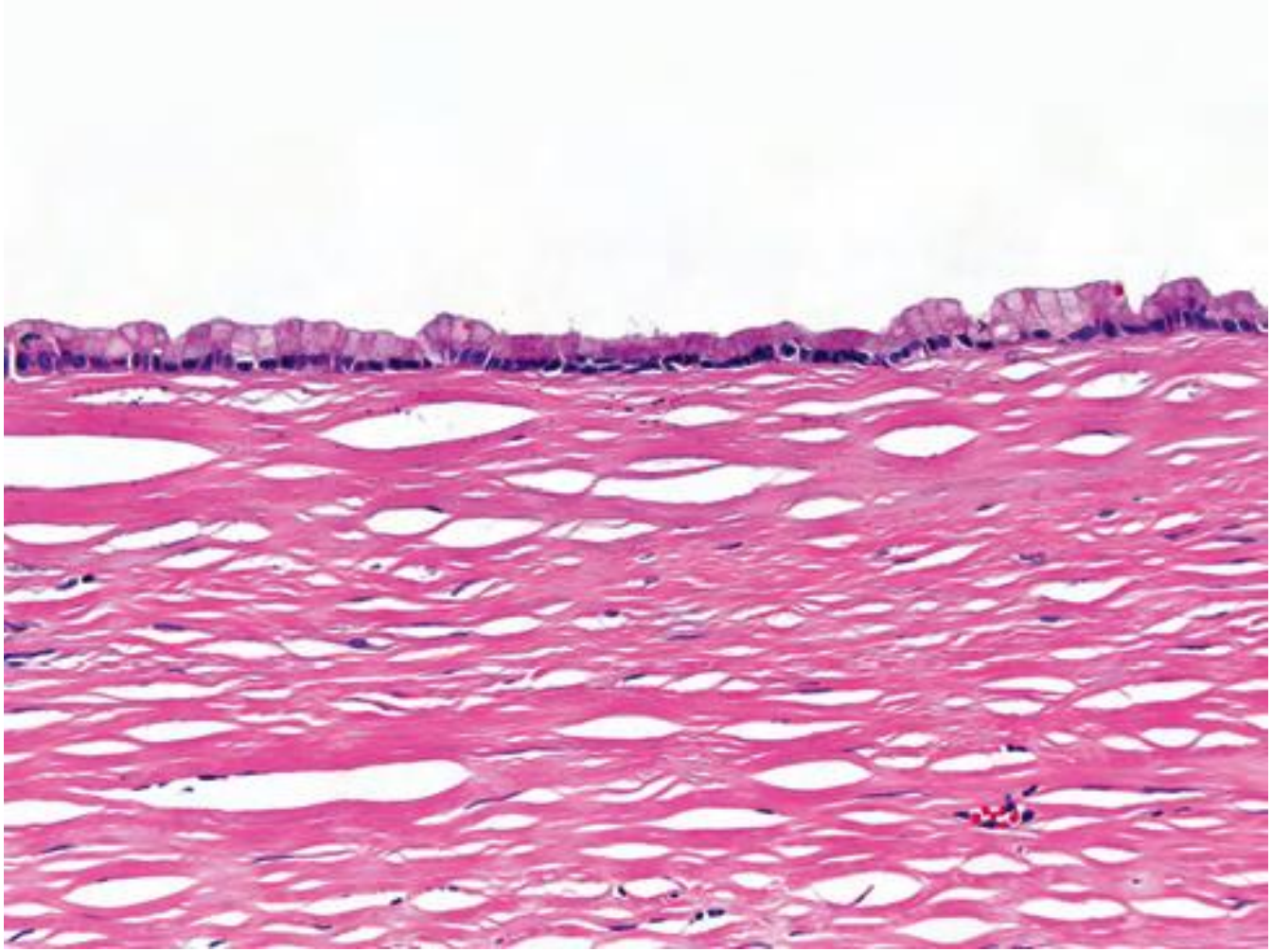
MUCINOUS CYSTADENOMA (WITH ASSOCIATED INVASIVE CANCER)







SIMPLE MUCINOUS CYST



Basturk O, *Am J Surg Pathol* 2015

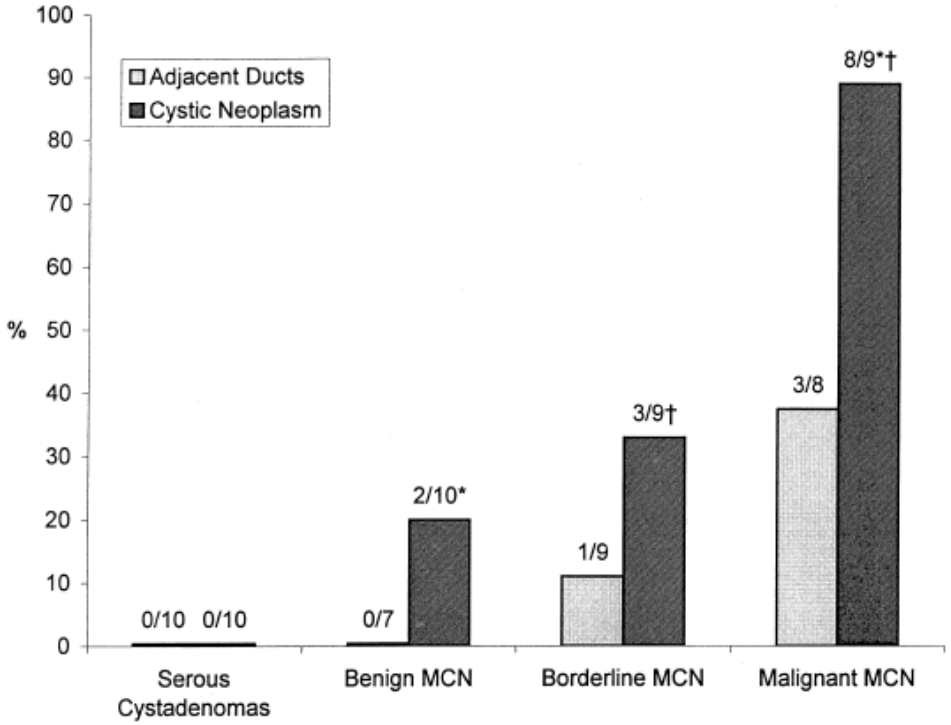


Figure 3. Frequency of K-ras mutations within mucinous cystic neoplasm (MCN) epithelia and in adjacent pancreatic ducts. *, $p < 0.006$; †, $p < 0.05$.

Jimenez RE, *Ann Surg* 1999

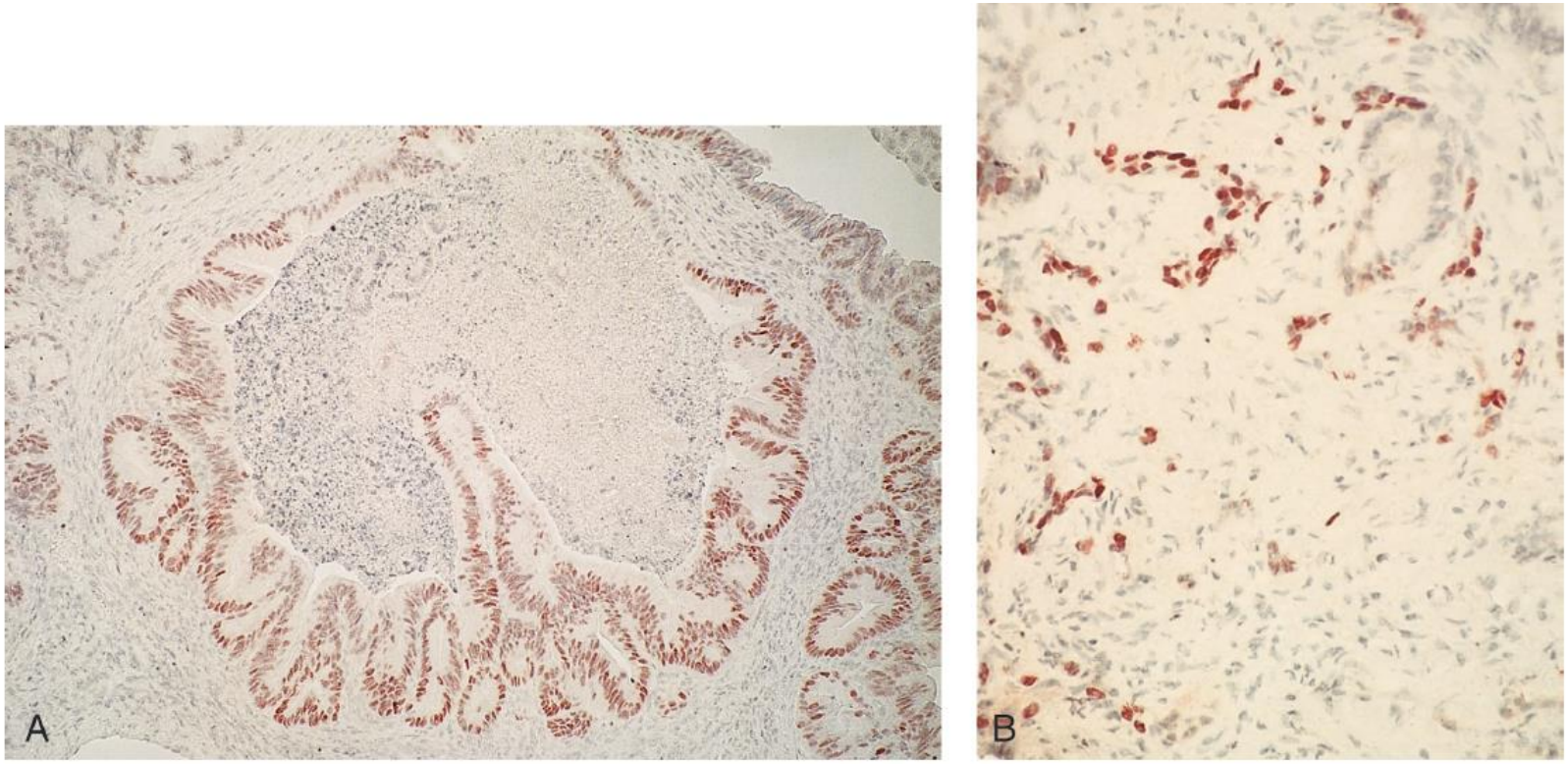


Figure 4. p53 immunohistochemistry in MCN. (A) p53 overexpression in cystic lesion with severe dysplasia (paraffin section, ABC reaction, 100×). (B) Positive staining within invasive cells (paraffin section, ABC reaction, 150×).

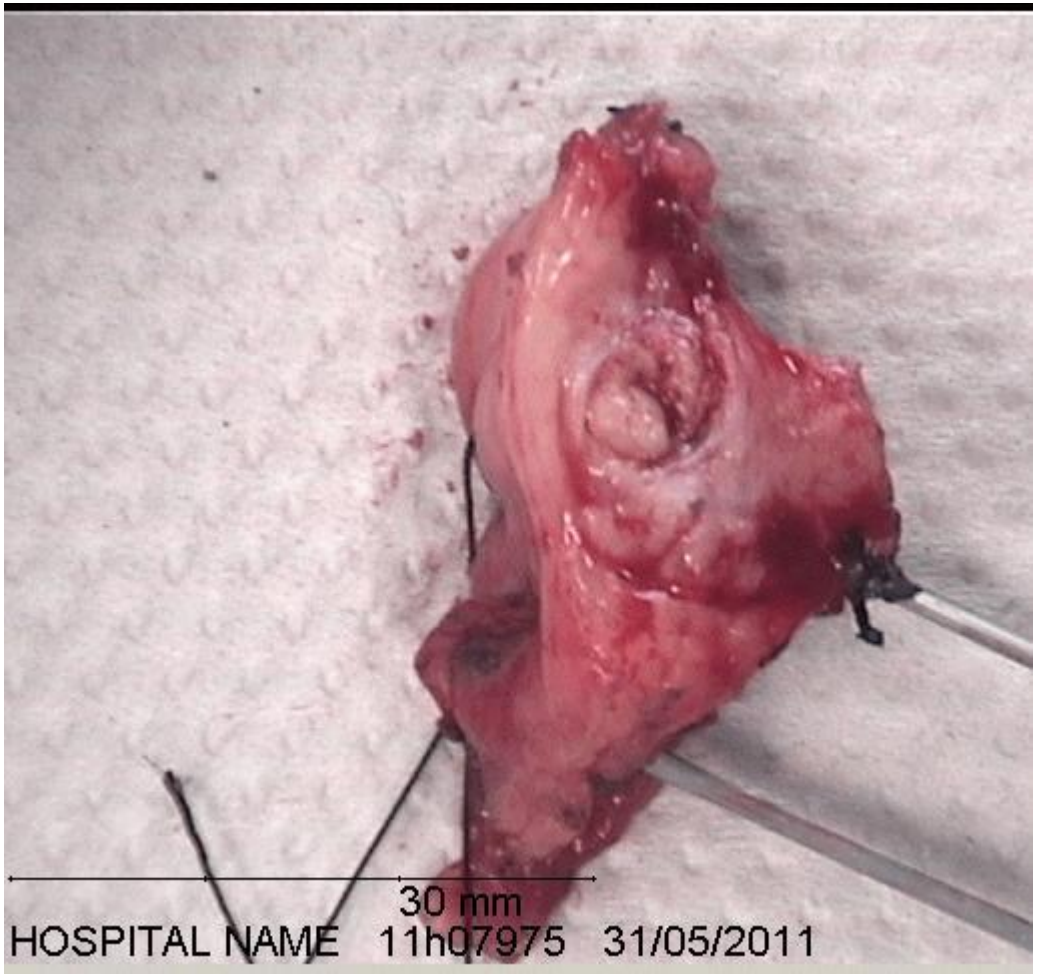
Jimenez RE, *Ann Surg* 1999

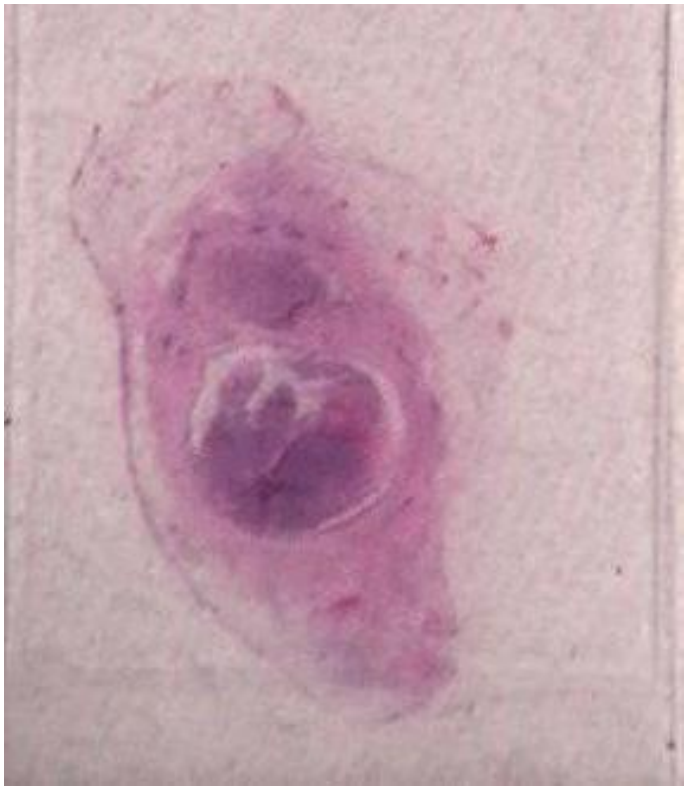
INTRADUCTAL PAPILLARY MUCINOUS TUMOUR (IPMT)

- In surgical series up to 36% of resected cystic lesions
- Often identified in the elderly
- May present in males
- Often multifocal, often identified in the pancreatic head
- Main duct type, branch duct type or mixed type

Gaujoux S, *J Am Coll Surg* 2011
Dudeja V, *Semin Oncol* 2015

INTRADUCTAL PAPILLARY MUCINOUS TUMOUR (IPMT)

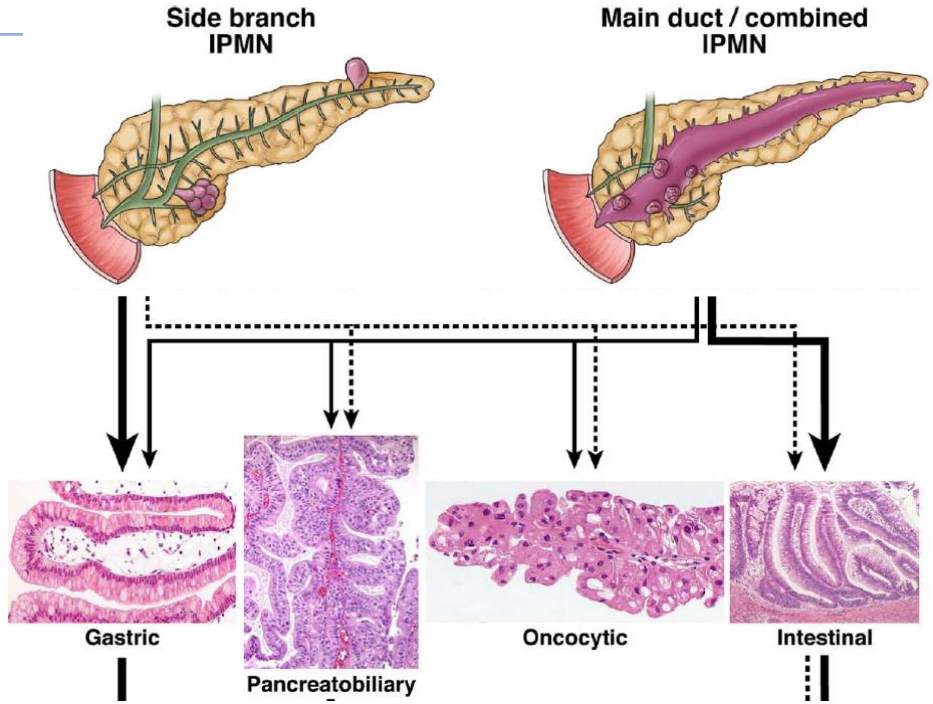




Histological subtypes of IPMT

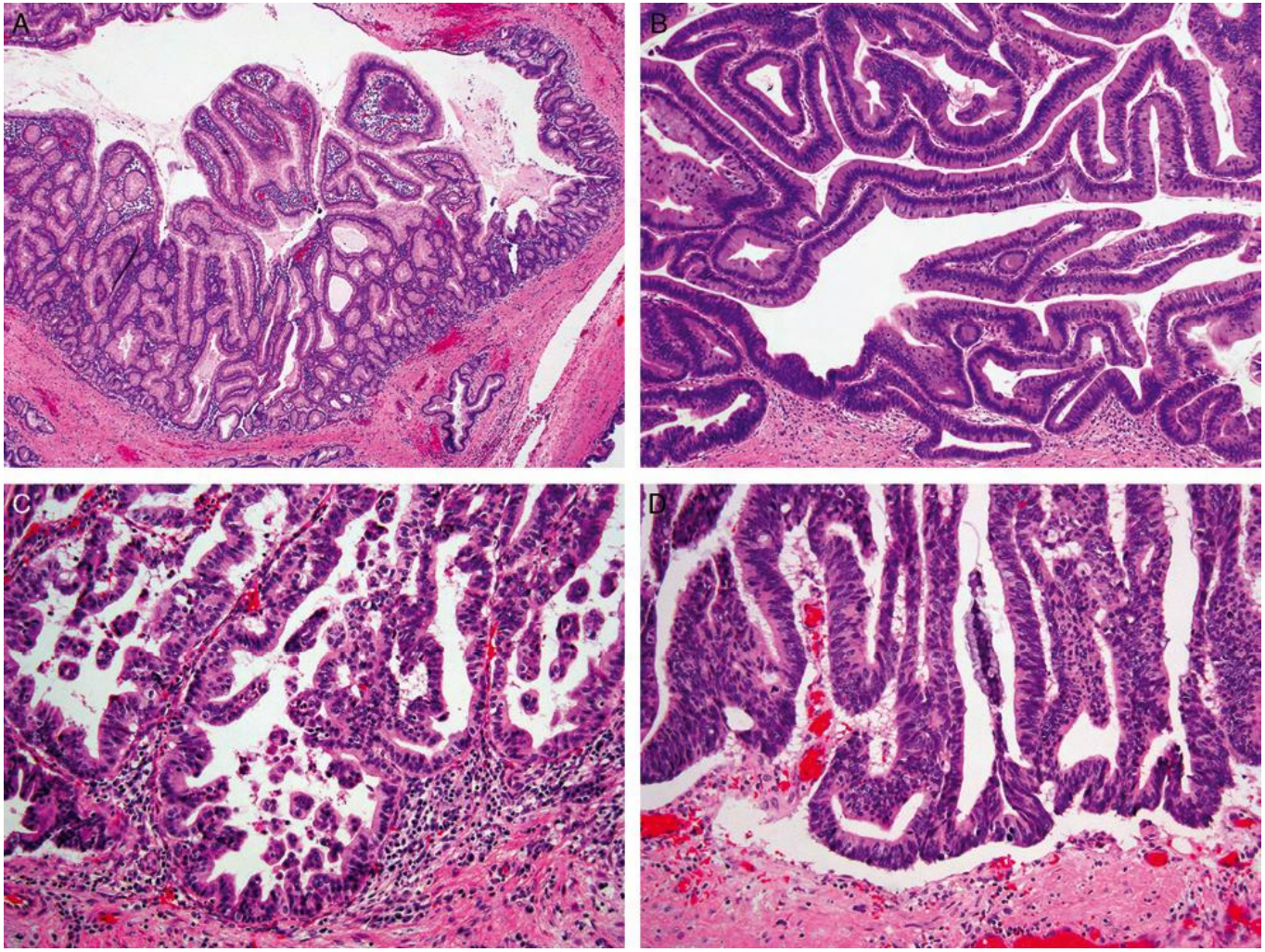
Morphologic classification

Histologic subtypes



	Gastric	Intestinal	Pancreatobiliary	Oncocytic
Immuno-histochemistry				
MUC 1	–	–	+	+
MUC 2	–	+	–	–
MUC 5AC	+	+	+	+

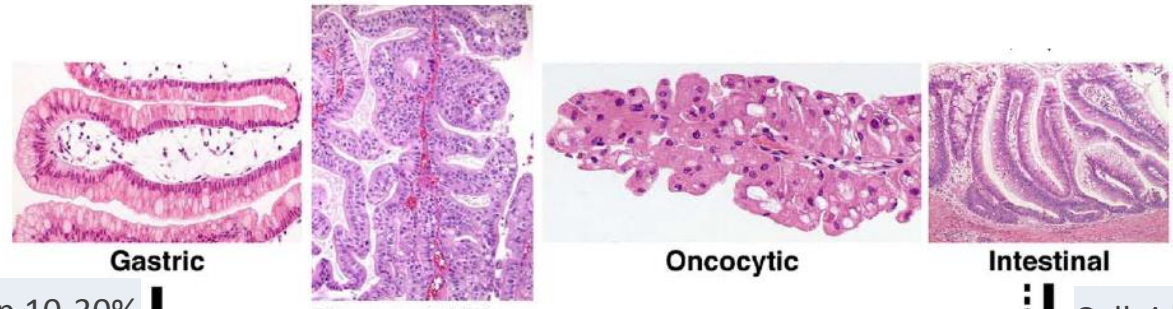
Fernandez-Del Castillo, *Gastroenterology* 2010; Sadakari, *Surgery* 2010



Basturk O, *Am J Surg Pathol* 2015

Histological subtypes of IPMT

Histologic subtypes

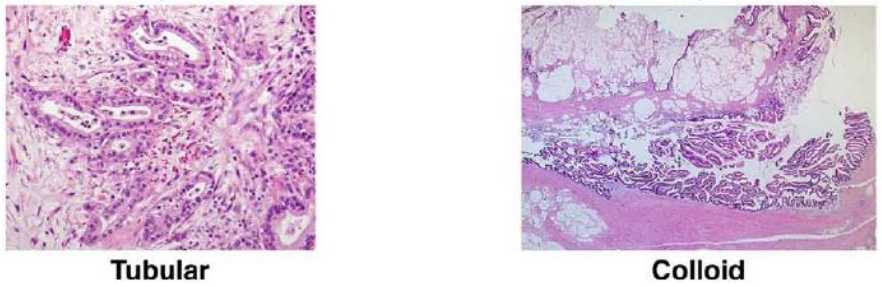


Tubular C in 10-30%

Tubular C in > 50%

Colloid C in 30-50%

Invasive carcinoma type

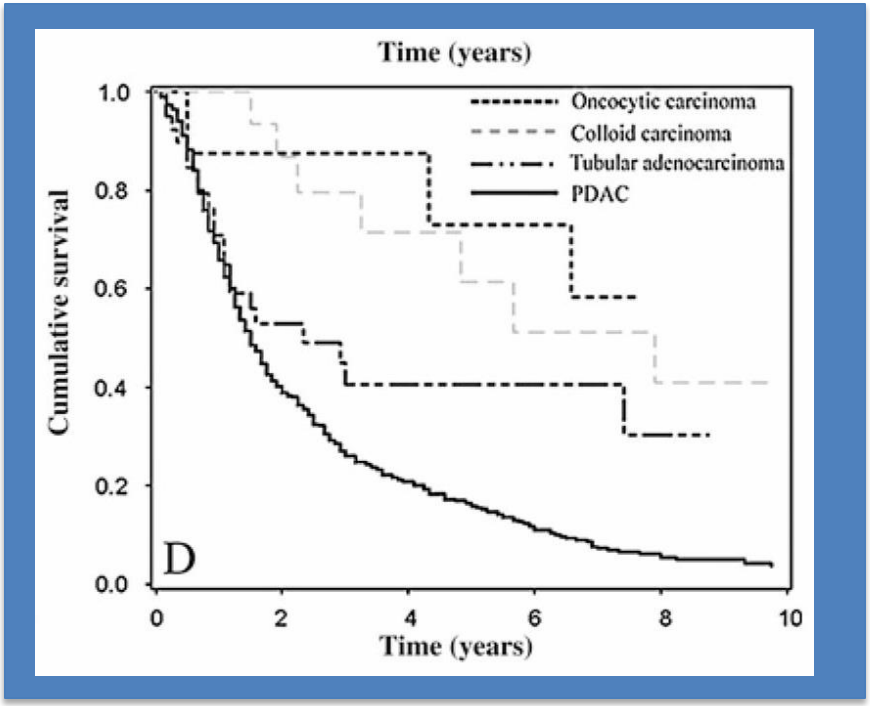


- gastric-type 66%
- intestinal-type 16%
- pancreatobiliary-type 13%
- oncocytic-type 5%

- intestinal-type 100%

Mino-Kenudson M, *Gut* 2011

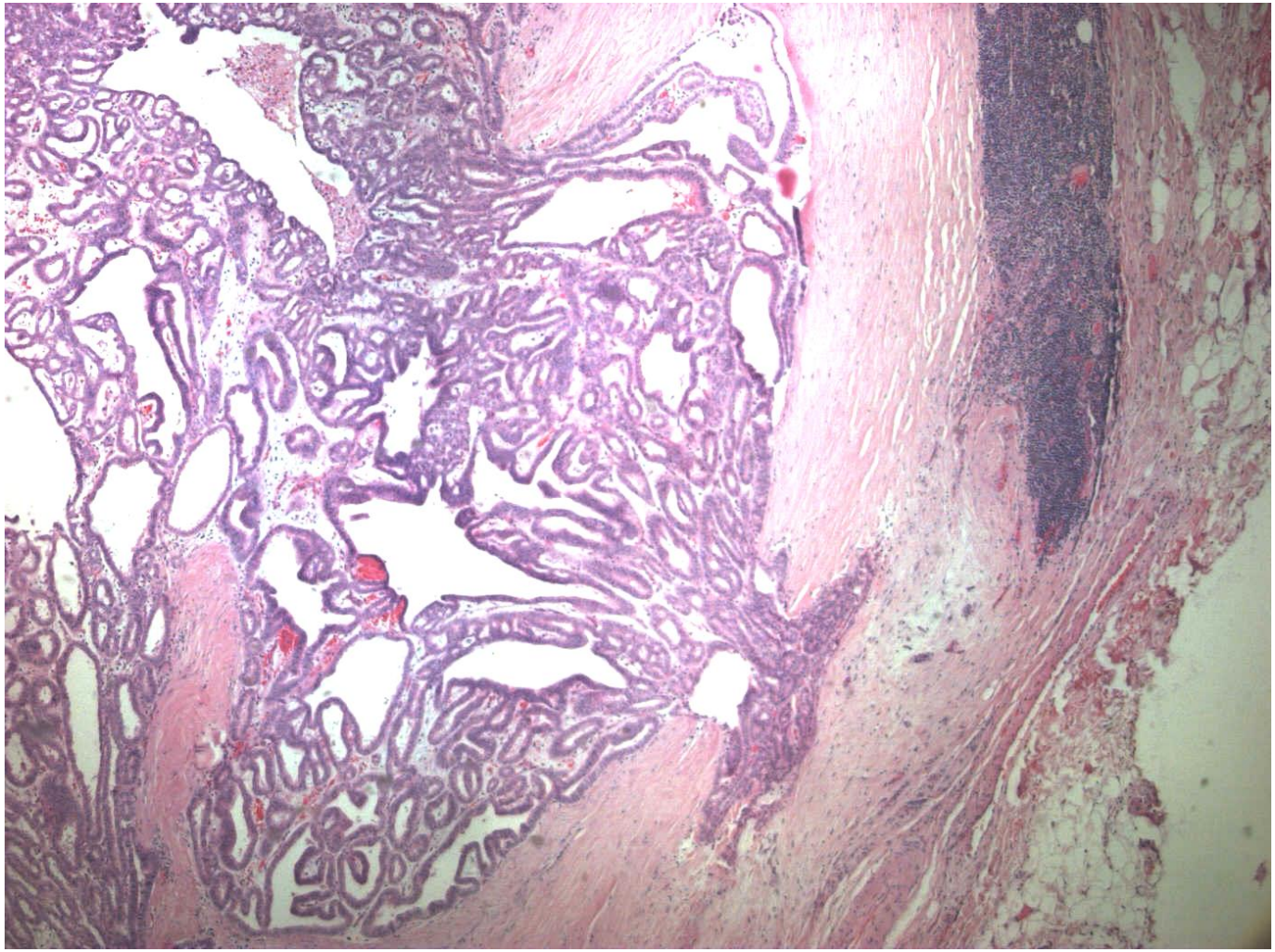
Prognosis according to histological subtypes of IPMT



	Median survival (m)	5 y surv (%)	10 y surv (%)
Oncocytic	132	69	51
Colloid carcinoma	95	61	41
Tubular adenocarcinoma	35	37	29
PDAC	18	16	4

Mino-Kenudson M, *Gut* 2011

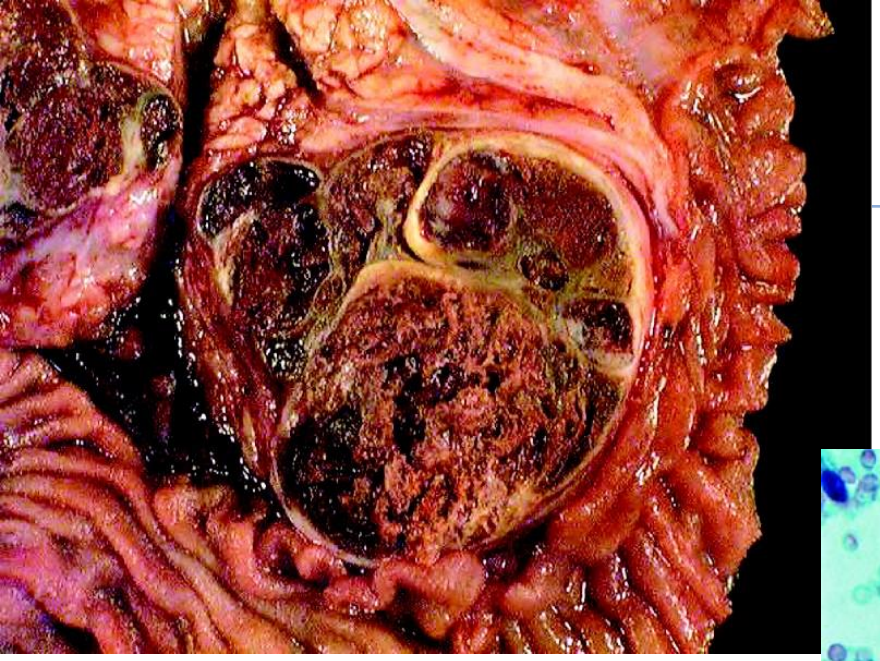
Intraductal tubulopapillary neoplasm (ITPN)

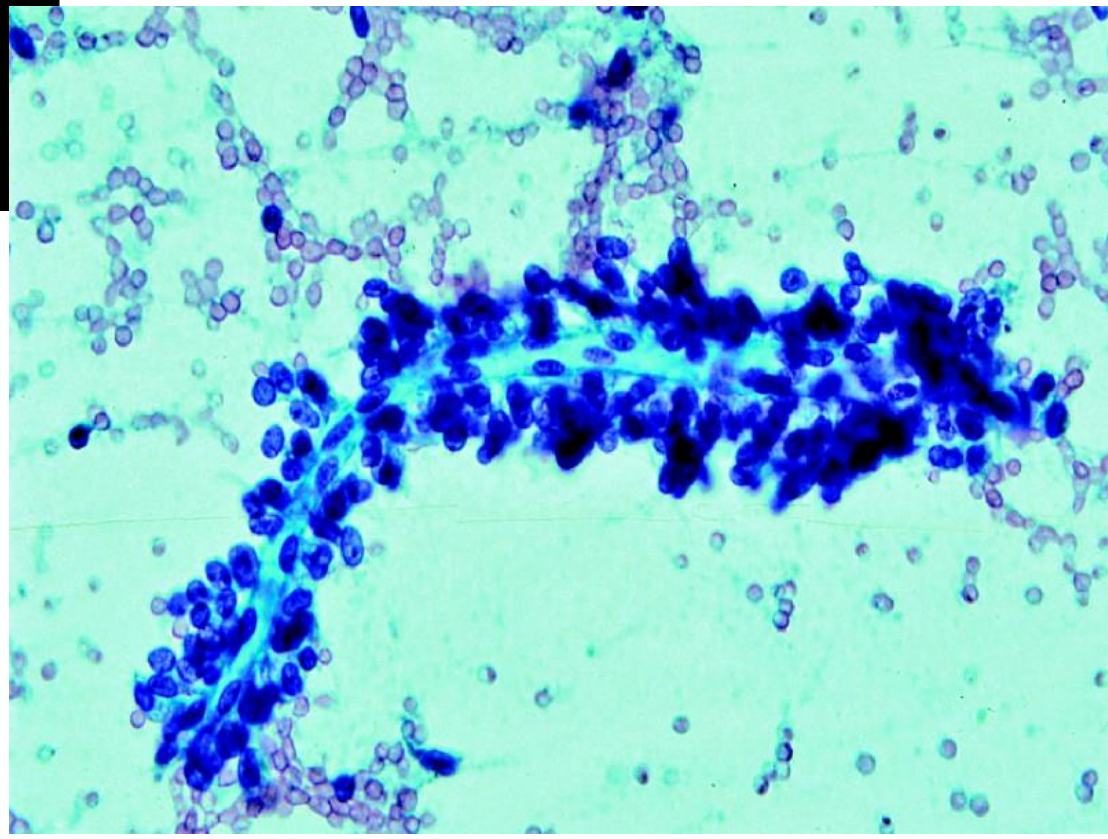


SOLID PSEUDOPAPILLARY NEOPLASM

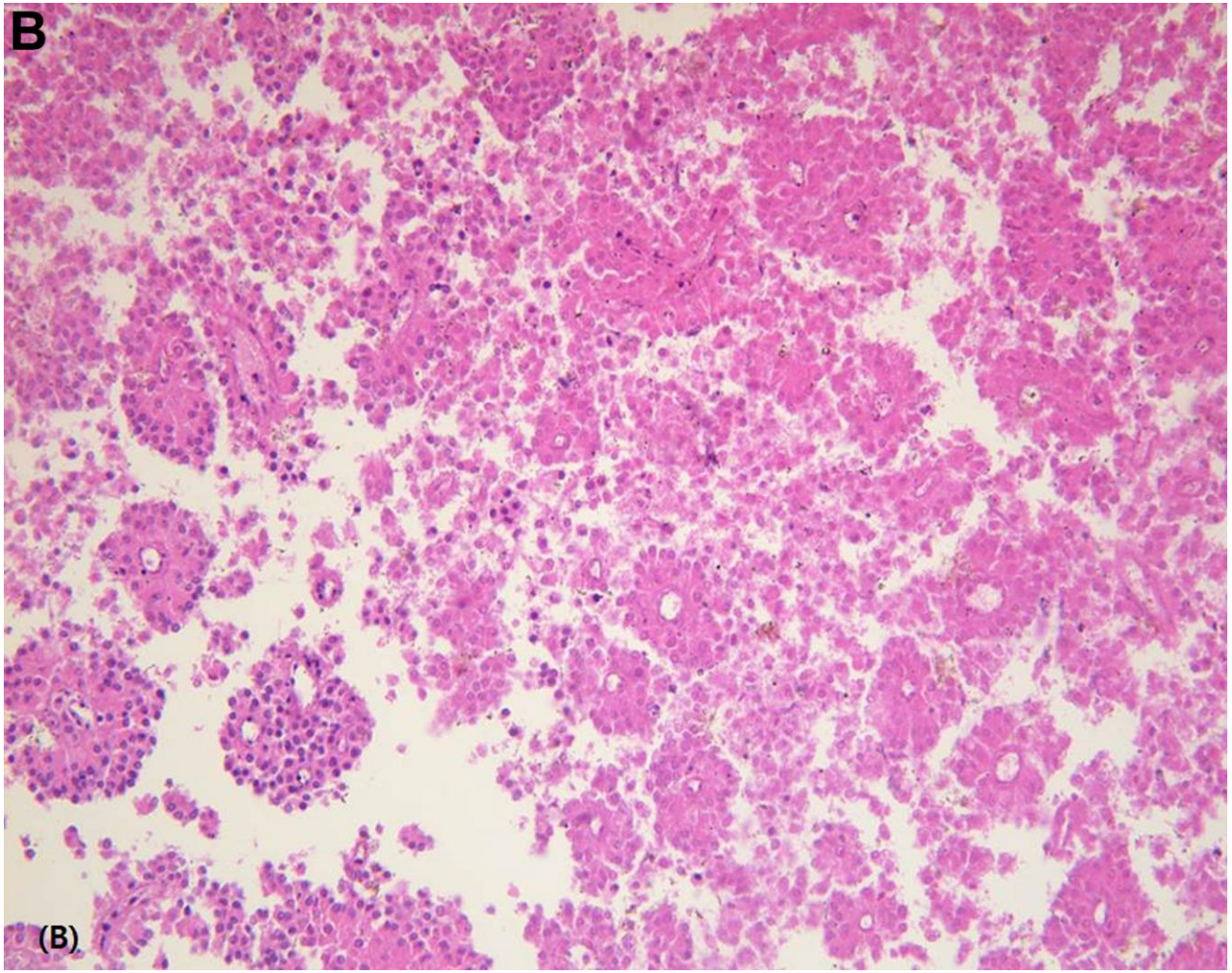
- Generally occurs in young women
- Only 5% of cystic neoplasms
- 30% of all pancreatic neoplasms < 40 years of age
- About 70% in the body or tail
- Frequently diagnosed incidentally
- Low-grade malignant
- (Partially) cystic in 50% of cases

Valsangkar NP, *Surgery* 2012
Santini D, *JOP* 2006
Jani N, *Endoscopy* 2008





Jani N, *Endoscopy* 2008



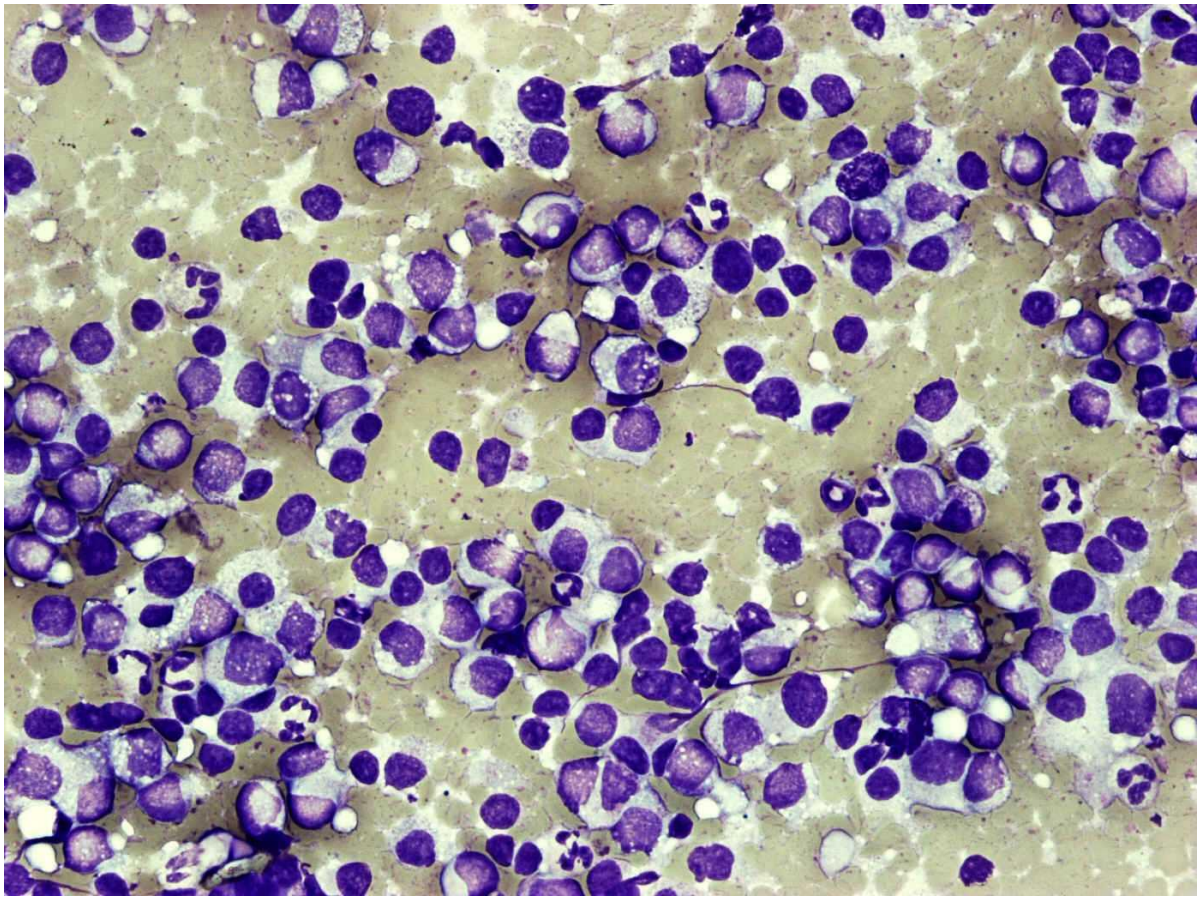
Kim Y, *Int Med Case Rep J* 2015

SOLID PSEUDOPAPILLARY NEOPLASM: CORE PANEL OF MARKERS

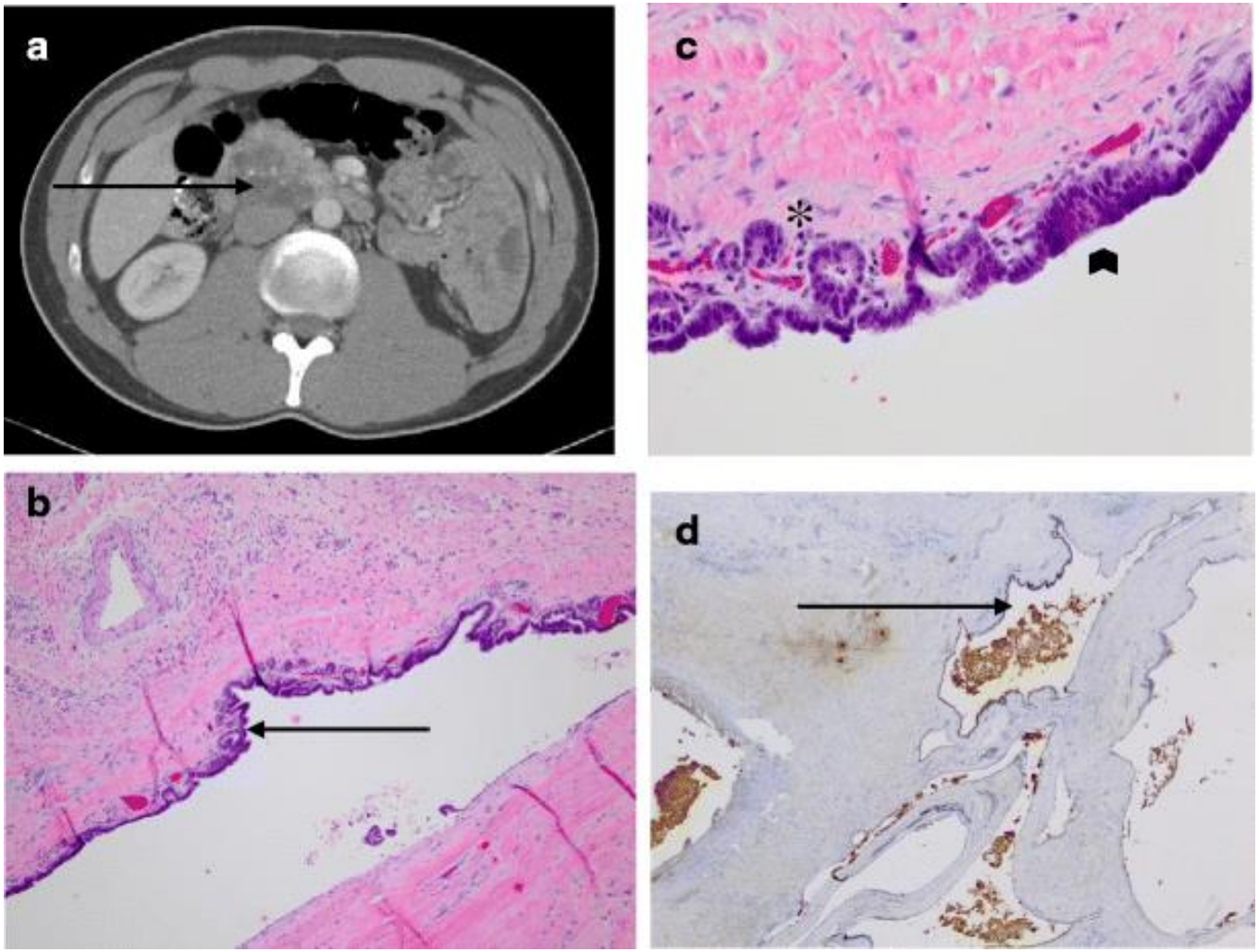
- β-catenin
- CD10
- Chromogranin
- Vimentin

CYSTIC NEUROENDOCRINE TUMOURS

- 10% of neuroendocrine tumours are cystic



ACINAR CELL CYSTADENOMA



Wolf AM, *J Gastrointest Surg* 2013

Table 1. EUS features and cyst fluid characteristics of common pancreatic cysts.

		Pseudocyst	MCN	IPMN	SCN	SPN	NET¶
Gender difference		M = F	F > M	F = M	F > M	F > M	M > F¶
Location		Anywhere	Body & tail>head	Head>body & tail	Body & tail>head	Body & tail>head	Body & tail>head¶
EUS features		Mostly unilocular; Anechoic, or contains debris	Unilocular or oligolocular; May have mural nodule	Multiple cysts communicated to PD; Dilated PD on MD-IPMN	Honeycombing appearance; central calcification in one third	Mixed solid-cystic; well defined margin	Mixed solid-cystic, or cystic
Cyst fluid analysis	CEA	Low	High	High	Low	NA	Low*
	Amylase	High	Usually low, but can be high*	High	Low	NA	Low*
	Cytology	Inflammatory cells	Extracellular mucin or mucinous epithelial cells may be seen; Atypical cells may be seen	Extracellular mucin or mucinous epithelial cells may be seen; Atypical cells may be seen	Acellular or hypocellular sample; Cuboidal cells with cytoplasmic glycogen†	Branching papilla with fibrovascular core; IHC: positive for vimentin &CD10‡	Plasmacytoid cells with roundto oval nuclei; IHC: positive for synaptophysin, chromogranin£

MCN = mucinous cystic neoplasm; IPMN = intraductal papillary mucinous neoplasm; SCN = serous cystadenoma; SPN = solid pseudopapillary neoplasm; NET = neuroendocrine tumor; PD = pancreatic duct; MD-IPMN = main duct IPMN; NA = not available; lNET is usually solid with a well defined margin, however, it can be cystic in 10% of the cases (Reference 35); *Reference 36; ¶Reference 37; £Reference 38; †Reference 39; ‡Reference 40.

Mohamadnejad M, *Arch Iran Med* 2013

Table 3. Mutational profiling of the 52 intraductal pancreatic neoplasms according to pathological data

Genes	Total ($n = 52$)	Gastric ($n = 6$)	Intestinal ($n = 36$)	Pancreaticobiliary ($n = 3$)	Oncocytic ($n = 3$)	ITPN ($n = 4$)	LG ($n = 3$)	IG ($n = 17$)	HG ($n = 28$)	Carcinoma ($n = 4$)	LG + IG ($n = 20$)	HG + carcinoma ($n = 32$)
GNAS	38 (73%)	6 (100%)	30 (83%)	1 (33%)	1 (33%)	1 (25%)	3 (100%)	15 (88%)	17 (61%)	4 (100%)	18 (90%)	21 (66%)
KRAS	24 (46%)	5 (83%)	14 (39%)	2 (67%)	2 (67%)	0	2 (67%)	11 (65%)	9 (32%)	2 (50%)	13 (65%)	11 (34%)
TP53	5 (10%)	0	3 (8%)	2 (67%)	0	0	0	0	5 (18%)	0	0	5 (15%)
BRAF	3 (6%)	0	3 (8%)	0	0	0	0	0	2 (7%)	1 (25%)	0	3 (9%)
CTNNB1	2 (4%)	0	2 (6%)	0	0	0	0	1 (6%)	1 (4%)	0	1 (5%)	1 (3%)
IDH1	2 (4%)	0	2 (6%)	0	0	0	0	1 (6%)	1 (4%)	0	1 (5%)	1 (3%)
STK11	2 (4%)	0	2 (6%)	0	0	0	0	1 (6%)	1 (4%)		1 (5%)	1 (3%)
PTEN	2 (4%)	1 (17%)	0	1 (25%)	0	0	0	1 (6%)	1 (4%)	0	1 (5%)	1 (3%)
ATM	1 (2%)	0	1 (3%)	0	0	0	0	0	1 (4%)	0	0	1 (3%)
CDH1	1 (2%)	0	1 (3%)	0	0	0	0	0	0	1 (25%)	0	1 (3%)
CDKN2A	1 (2%)	0	1 (3%)	0	0	0	0	1 (6%)	0	0	1 (5%)	0
FGFR3	1 (2%)	0	1 (3%)	0	0	0	0	0	1 (4%)	0	0	1 (3%)
NRAS	1 (2%)	0	0	0	0	1 (25%)	0	0	1 (4%)	0	0	1 (3%)
SMAD4	1 (2%)	1 (17%)	0	0	0	0	0	1 (6%)	0	0	1 (5%)	0
SRC	1 (2%)	0	1 (3%)	0	0	0	0	0	0	1 (25%)	0	1 (3%)

LG, low-grade dysplasia; IG, intermediate-grade dysplasia; HG, high-grade dysplasia. ITPN, intraductal tubulopapillary neoplasm.

Amato E, *J Pathol* 2014

RARE PANCREATIC CYSTS

- Lymphoepithelial cyst
  - Men > women
  - Head = body = tail
  - > incidental finding

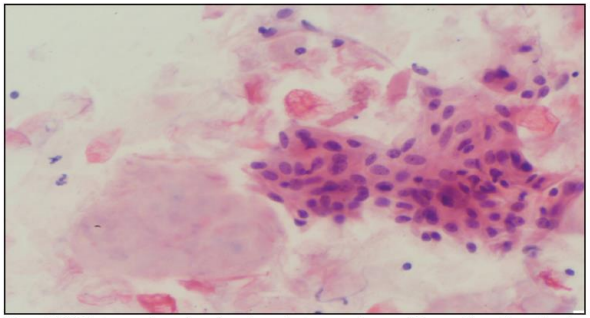
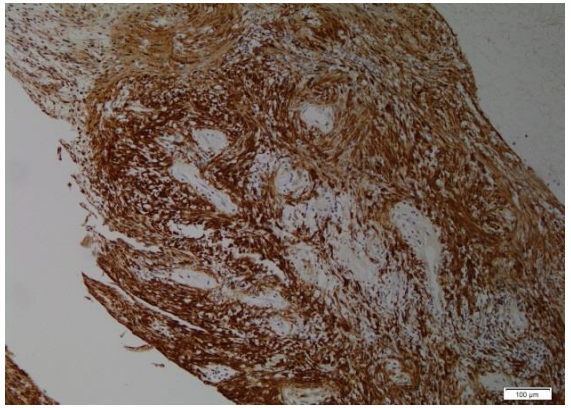


Figure 2) *High-power view of cytology from the pancreatic cyst. Fine-needle aspirate showing well-differentiated squamous epithelium, keratinaceous and amorphous debris, and some lymphoid cells*

Karim Z, *Can J Gastroenterol* 2010

- Cystic schwannoma
  - Women > men
  - S-100 and vimentin positive



- Hydatid cyst
  - > endemic areas
  - Positive serologic test for Echinococcus granulosus