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Ampullary carcinoma, bile duct carcinoma and duodenal carcinoma: how to differentiate from pancreatic ductal adenocarcinoma

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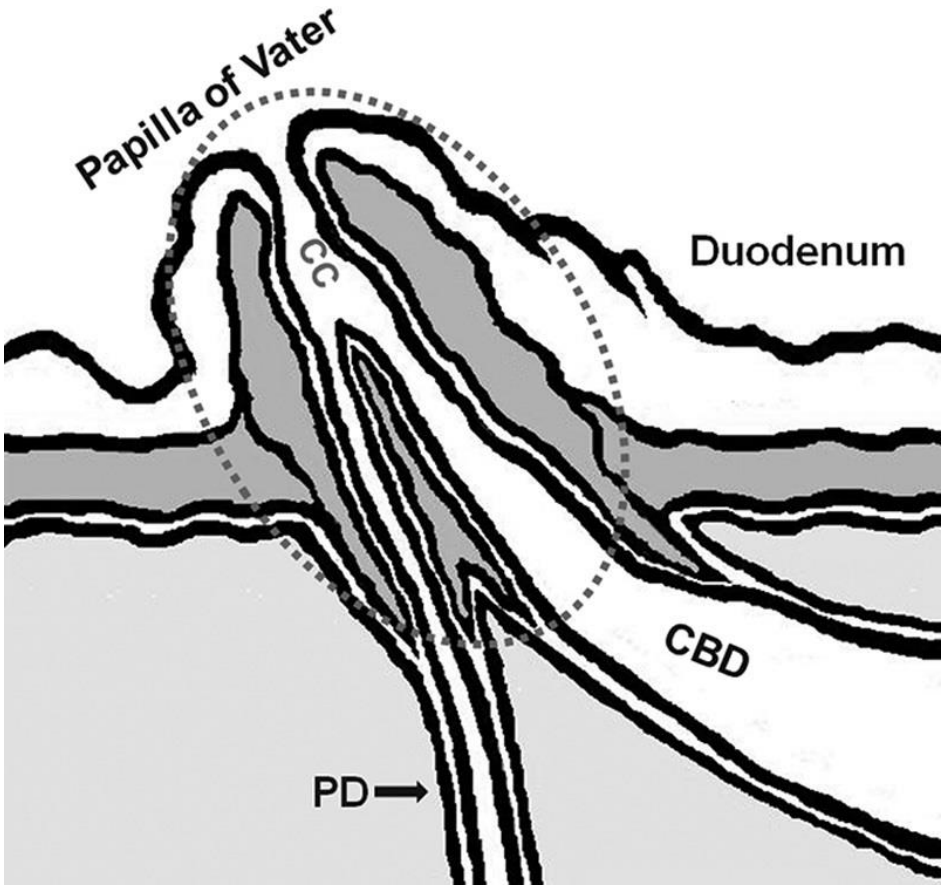
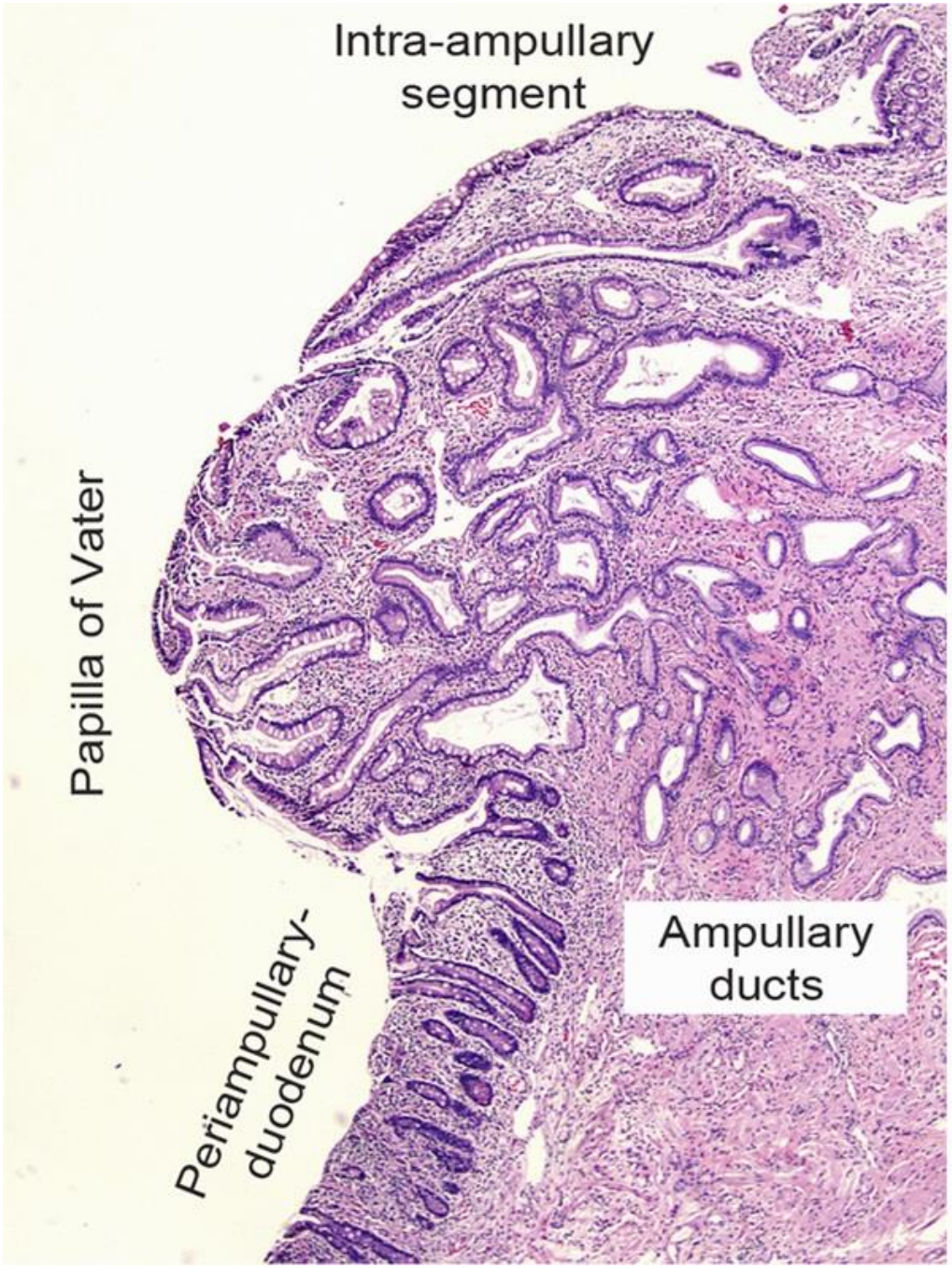
Adenocarcinomas in the periampullary region

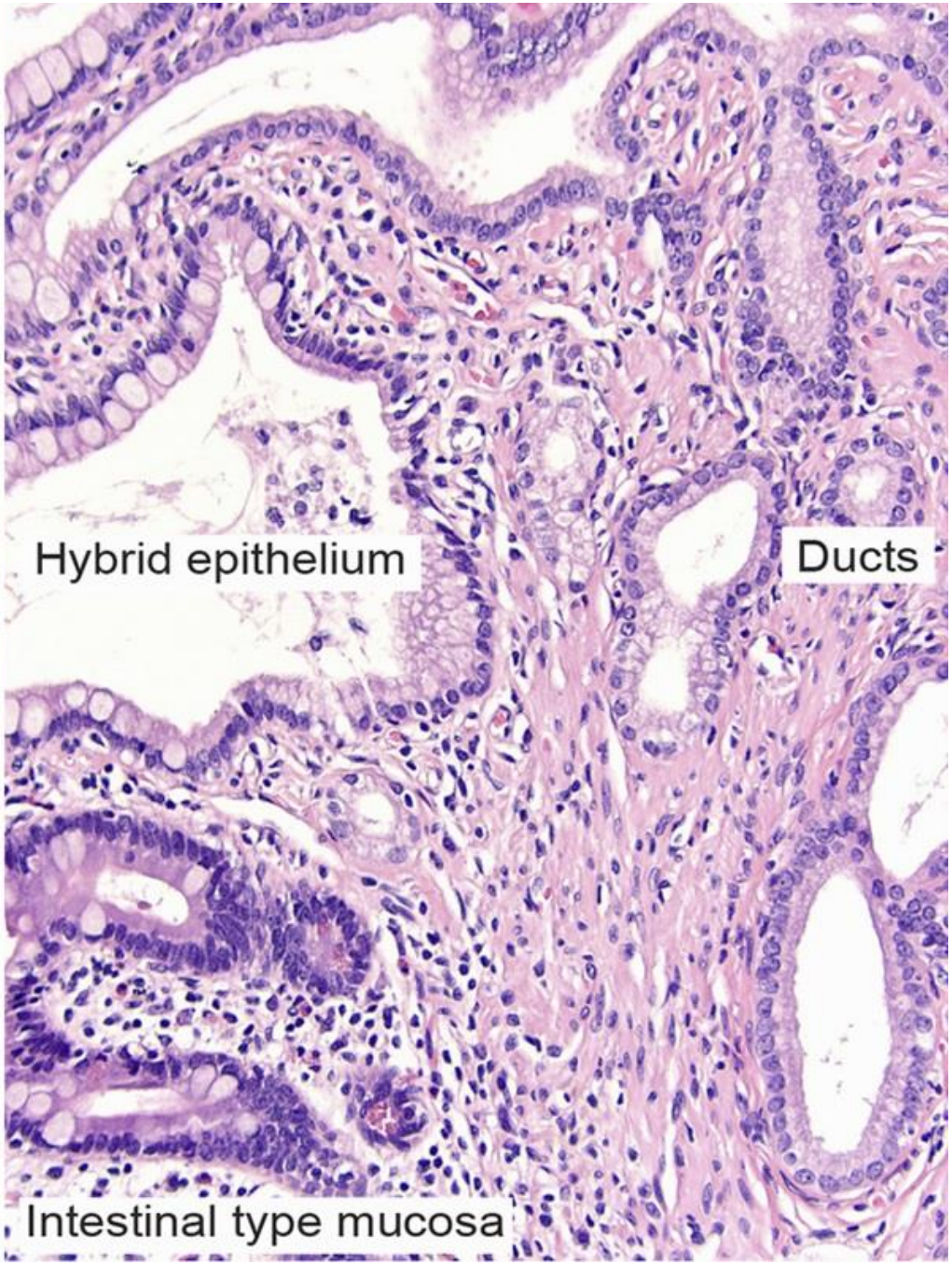
- Ampulla of Vater
- Duodenum
- Distal common bile duct
- Pancreatic duct

- Different TNM staging and adjuvant therapies
- In- or exclusion criterion for clinical trials



Adsay Y, *Am J Surg Pathol* 2012





Adsay Y, *Am J Surg Pathol* 2012

Primary site of origin of the tumour

- Mainly determined macroscopically
- Based on the location of the tumour bulk

- Patients with pancreatic cancer have a worse prognosis than patients with cholangiocarcinoma, ampullary carcinoma or duodenal carcinoma

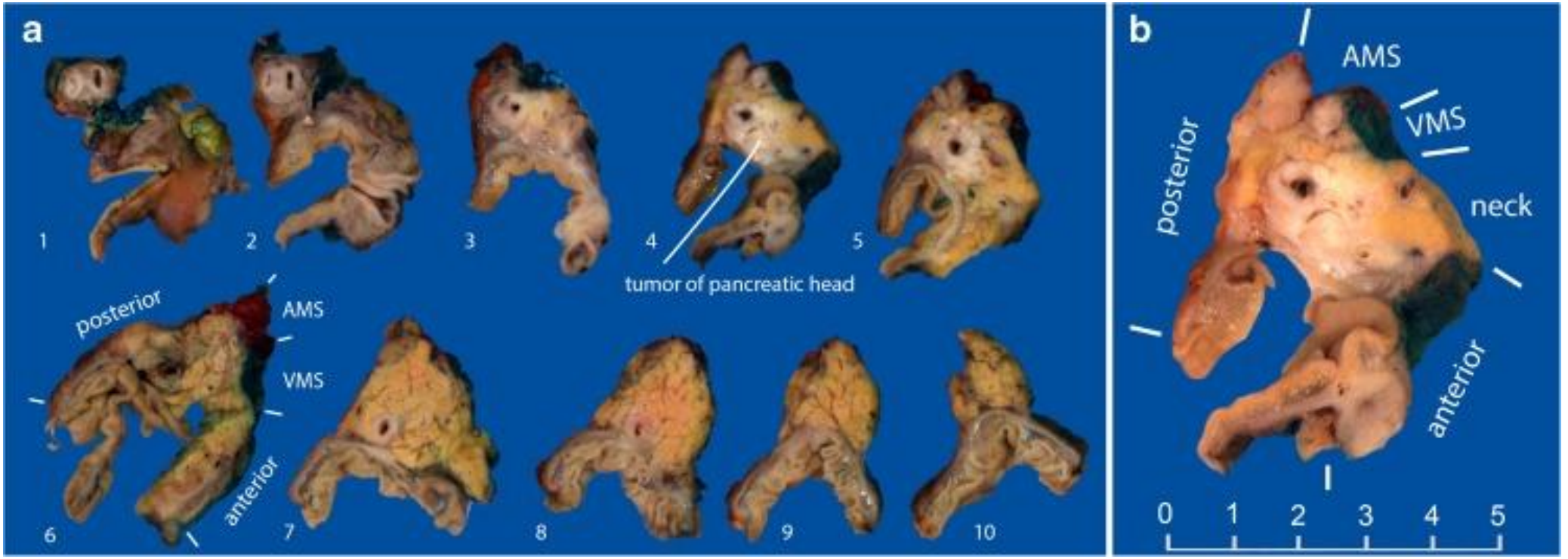
Ampullary region carcinoma vs. Pancreatic ductal adenocarcinoma

Variables	Ampullary Region Carcinomas (n = 249*)	Pancreatic Ductal Adenocarcinomas (n = 113*)	P†
Baseline demographics			
Age (y), mean (± SD)	65 (11.8)	64 (11.4)	0.576
Sex			**< 0.001**
Male	148	42	
Female	100	70	
Ratio	1.48	0.6	
Clinical characteristics			
Overall tumor size (cm), mean (± SD)	2.6 (1.5)	N/A	—
Invasive tumor size (cm), mean (± SD)	1.8 (1.0)	3.6 (1.8)	**< 0.001**
Lymph node metastasis, n (%)	89 (39%)	79 (73%)	**< 0.001**
Survival rates (%)			**< 0.001**
1 y	82	45	
3 y	58	11	
5 y	42	6	

*Subjects with missing values were excluded for each characteristic variable.
†Based on *t* test for continuous variables, χ^2 for categorical variables, and log-rank test for overall survival rates.

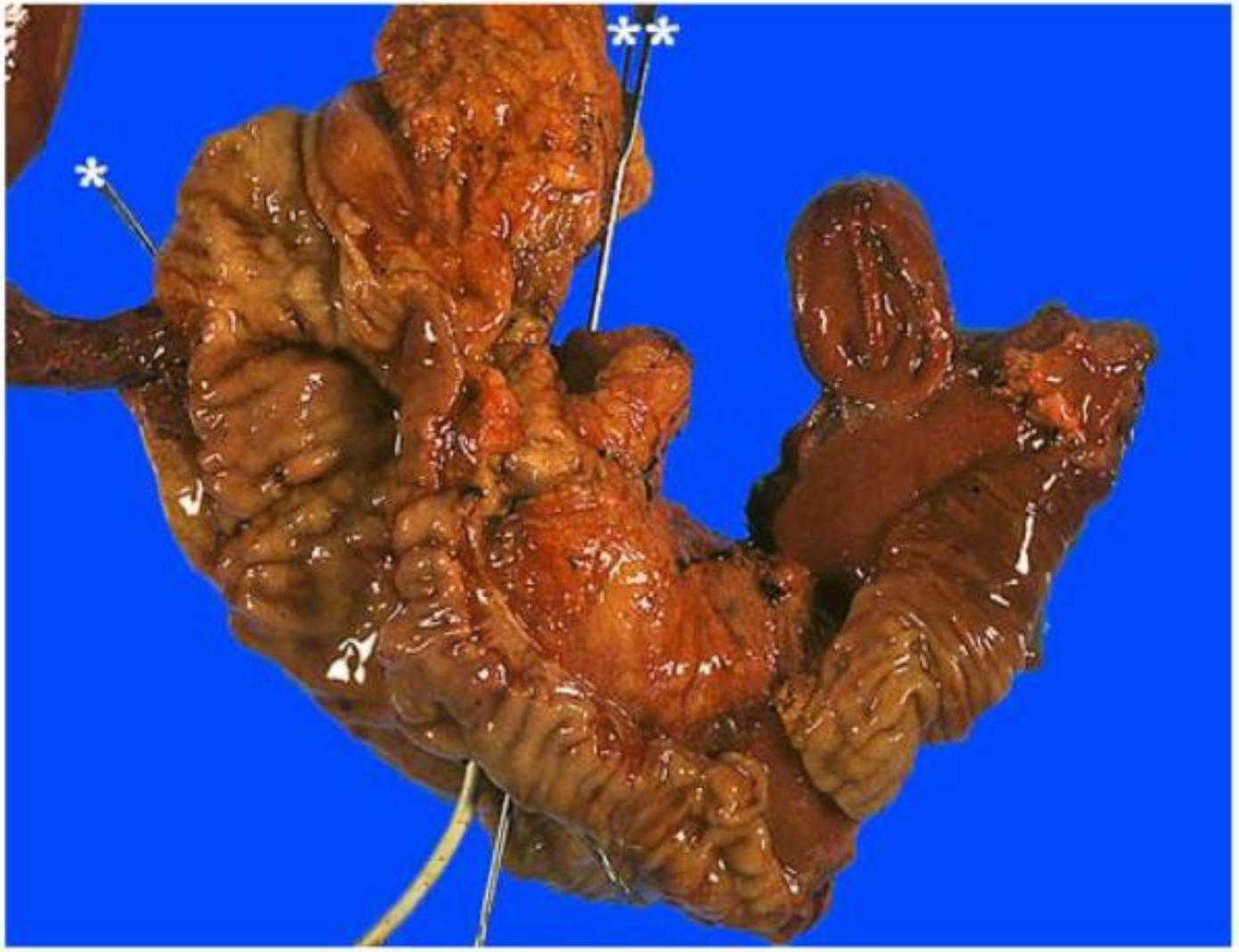
Adsay Y, *Am J Surg Pathol* 2012

Axial slicing

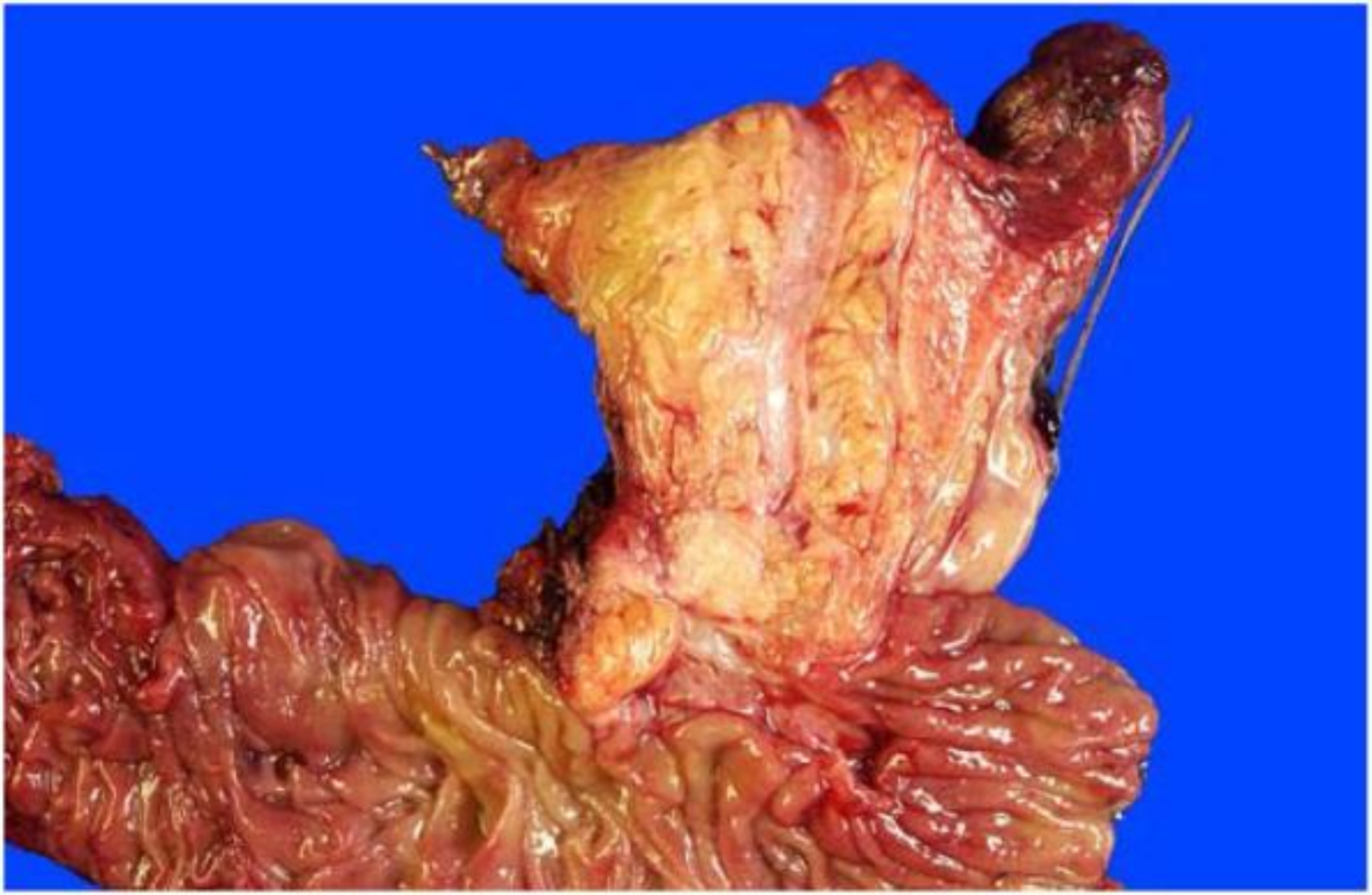


Soer E, *Virchows Arch 2018*

Bi-sectioning

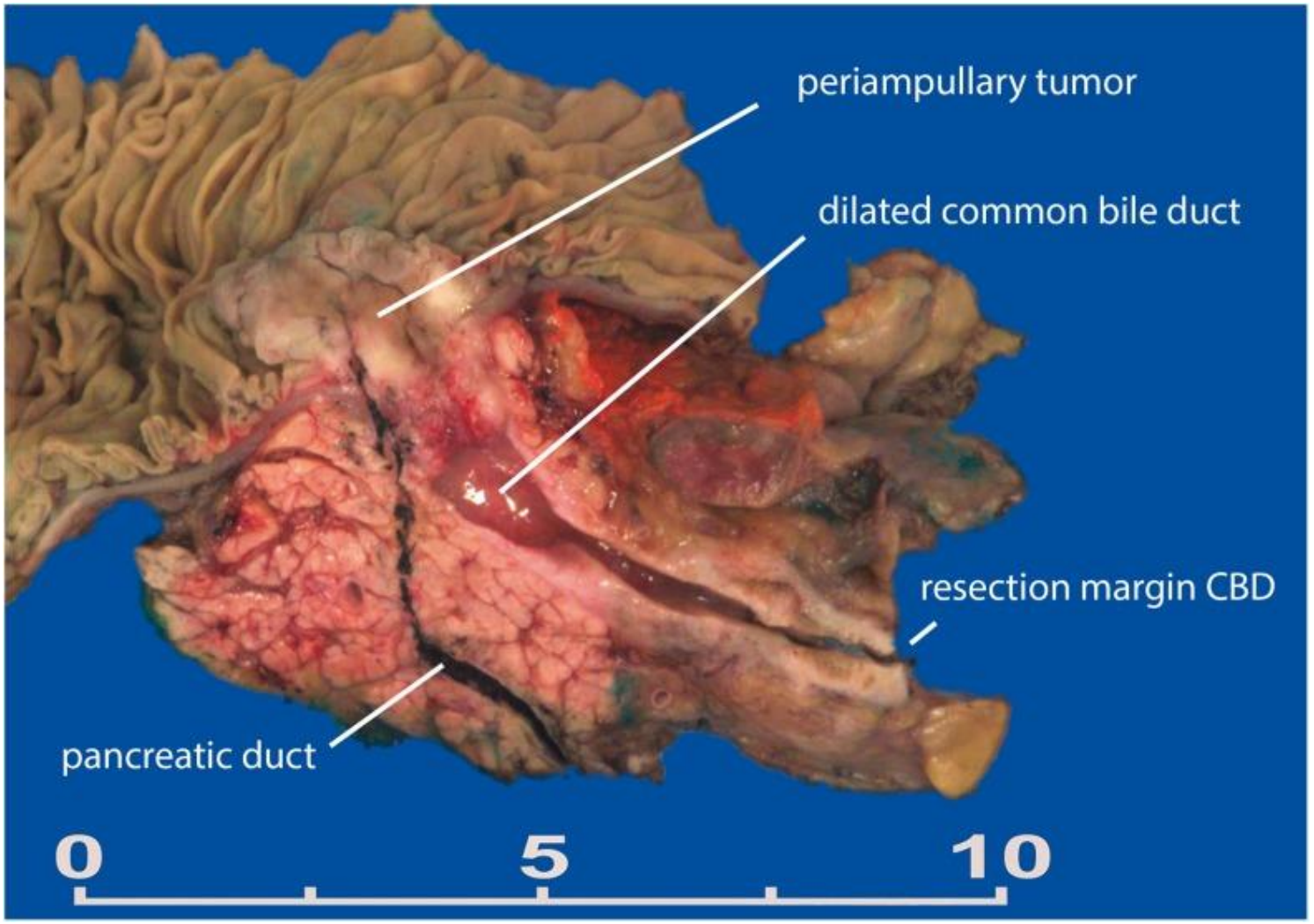


Adsay NV, *Am J Surg Pathol* 2014

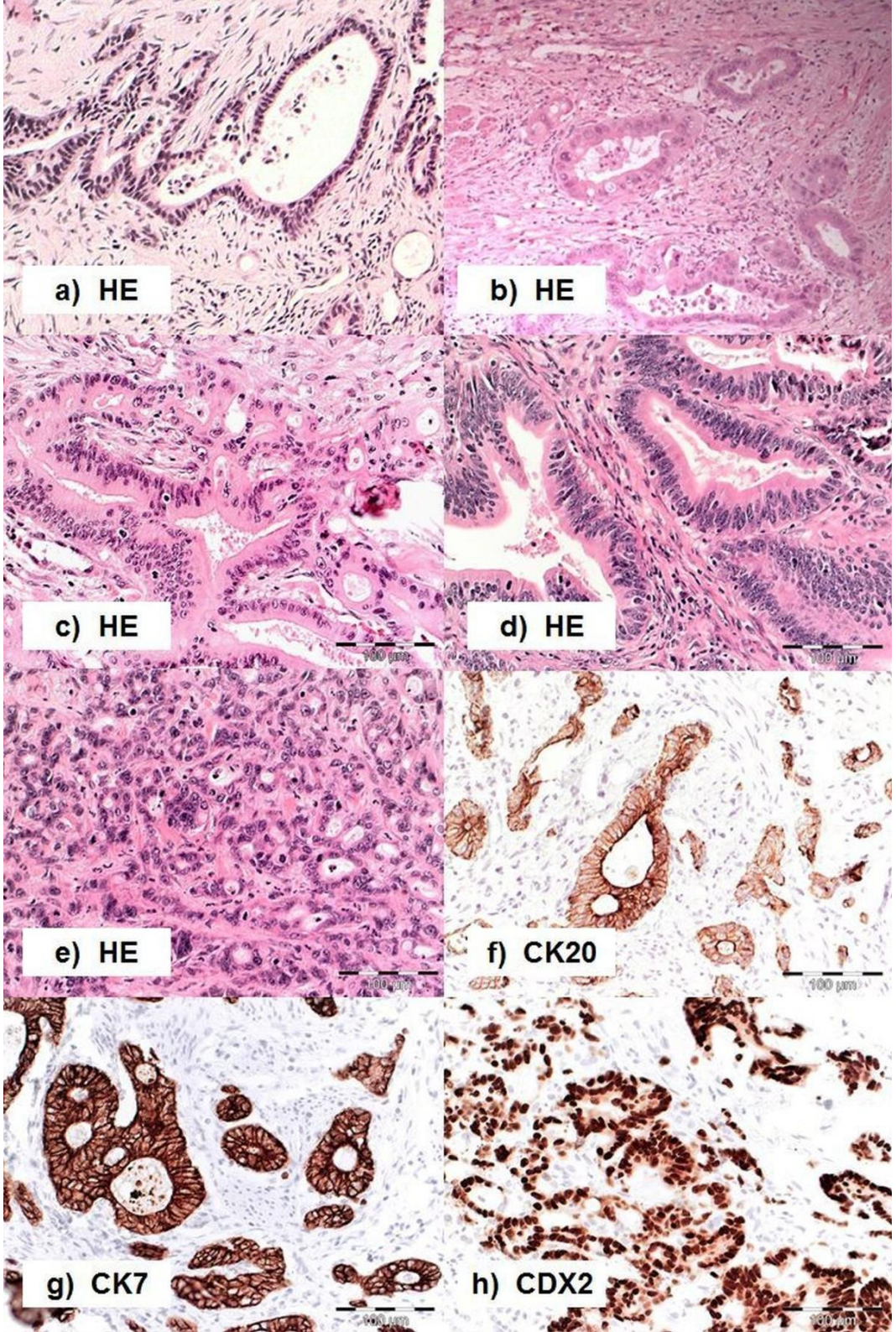


Adsay NV, *Am J Surg Pathol* 2014

Bi-sectioning



Soer E, *Virchows Arch 2018*

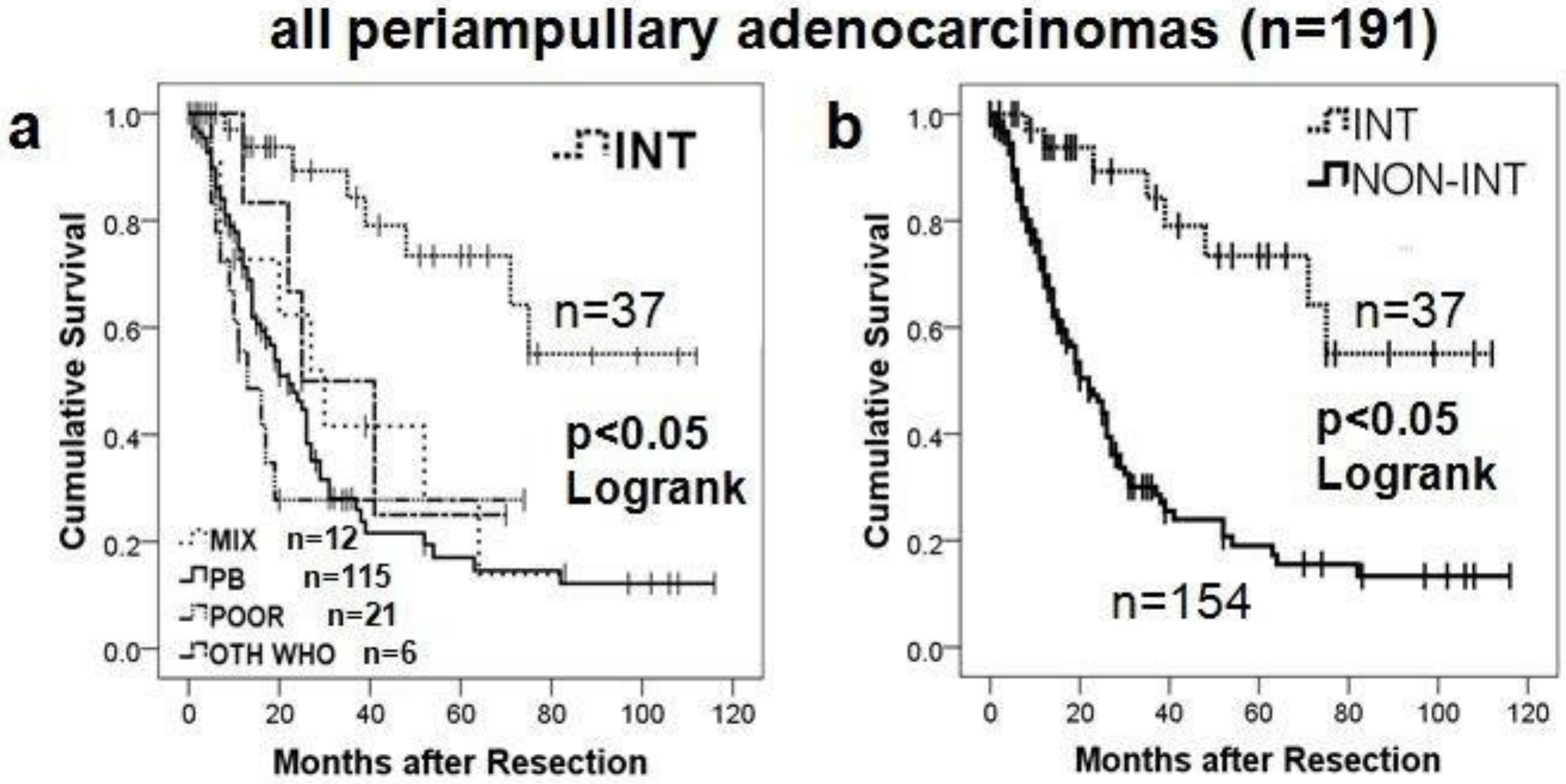


Bronsert P, *BMC Cancer* 2013

Table 1. The more frequently observed gene mutations in ampullary cancer, according to recent studies conducted by Yachida and Gingras [34,35].

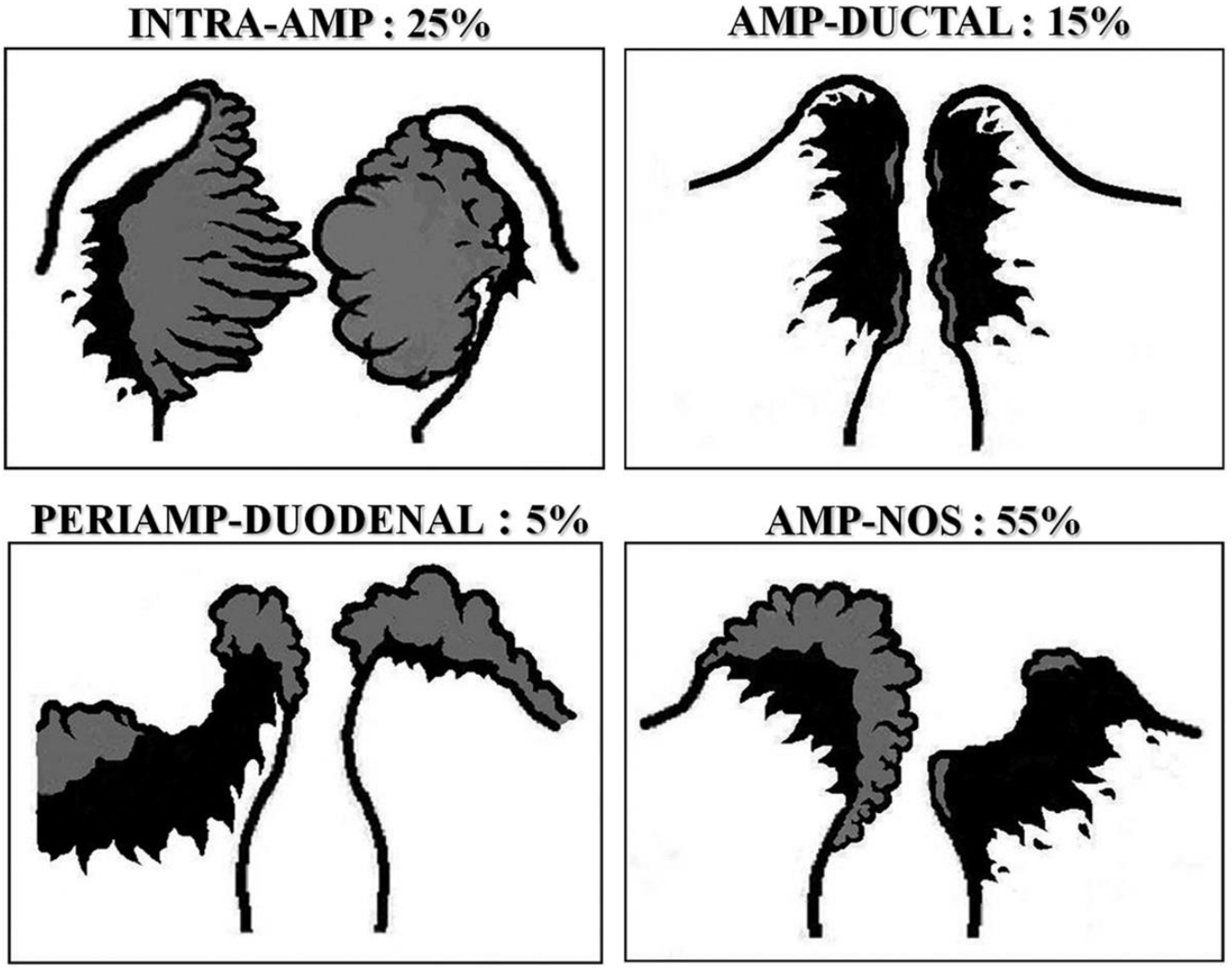
Author (Reference)	Intestinal-Type Ampullary Cancer (Percentage)	Pancreaticobiliary-Type Ampullary Cancer (Percentage)	Mixed-Type Ampullary Cancer (Percentage)
Yachida [34]	*APC* (49%) *TP53* (39%) *KRAS* (39%) *CTNNB1* (26%) *ARID2* (18%)	*KRAS* (67%) *TP53* (67%) *SMAD4* (20%) *CTNNB1* (15%) *ERBB3* (14%)	
Gingras [35]	*TP53* (64%) *KRAS* (46%) *APC* (41%) *PIK3CA* (26%) *SMAD4* (20%)	*TP53* (71%) *KRAS* (65%) *SMAD4* (18%) *CDKN2A* (16%) *PIK3CA* (13%)	*KRAS* (49%) *APC* (50%) *TP53* (41%) *SMARCA4* (27%) *PIK3CA* (23%)

Rizzo A, *Curr Oncol* 2021
Yachida S, *Cancer Cell* 2016
Gingras MC, *Cell Rep* 2016

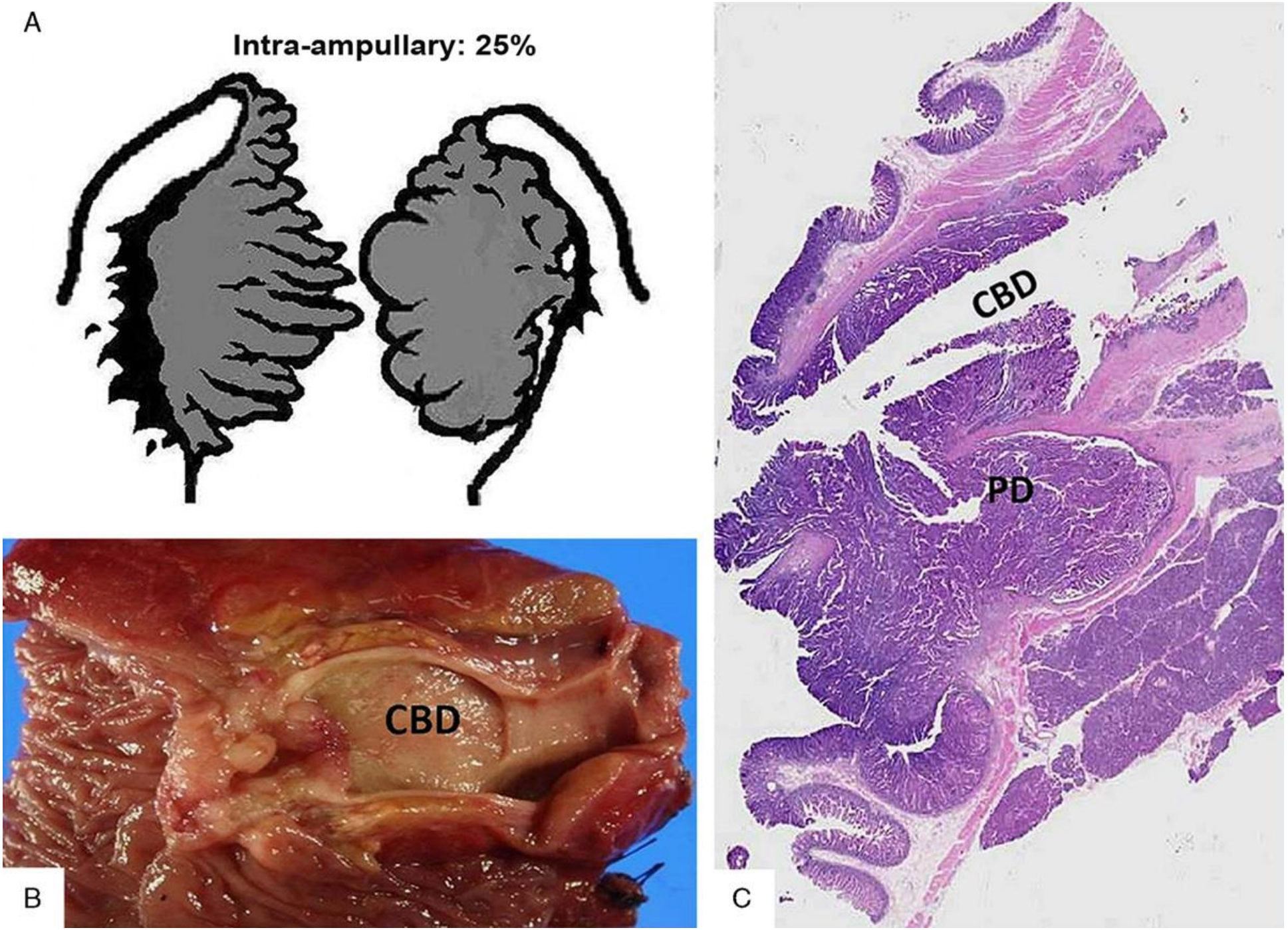


Bronsert P, *BMC Cancer* 2013

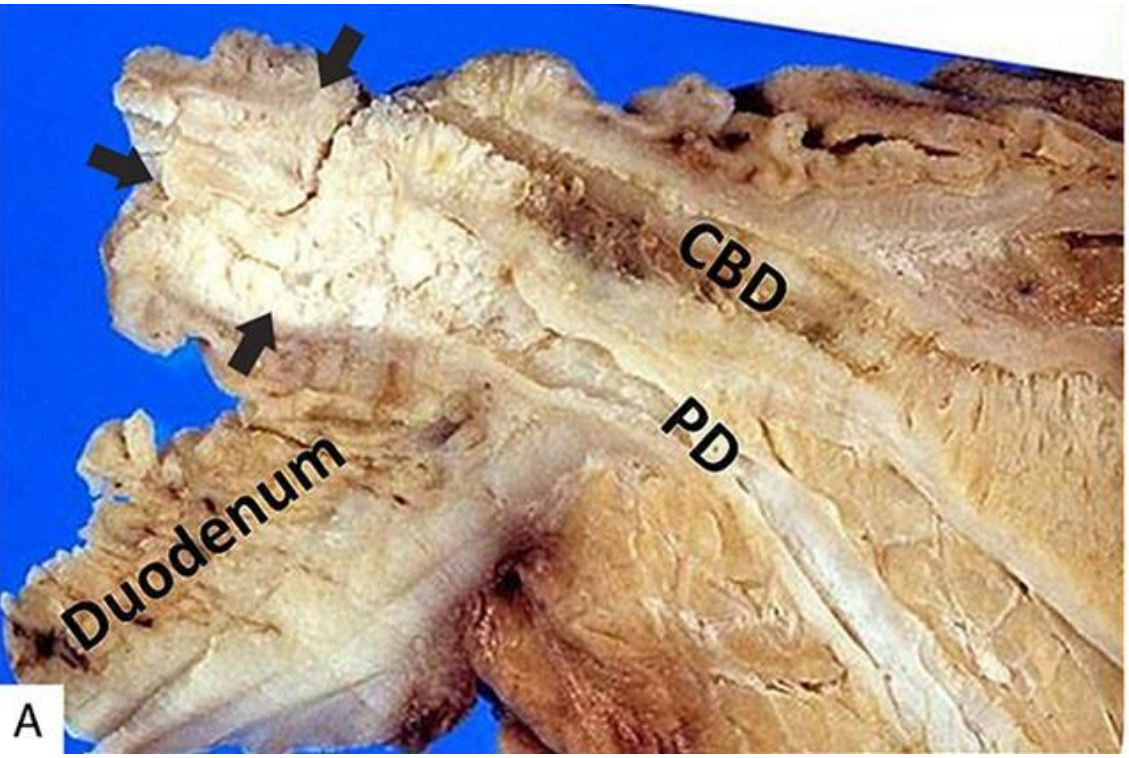
Ampullary region carcinomas: 4 distinct types

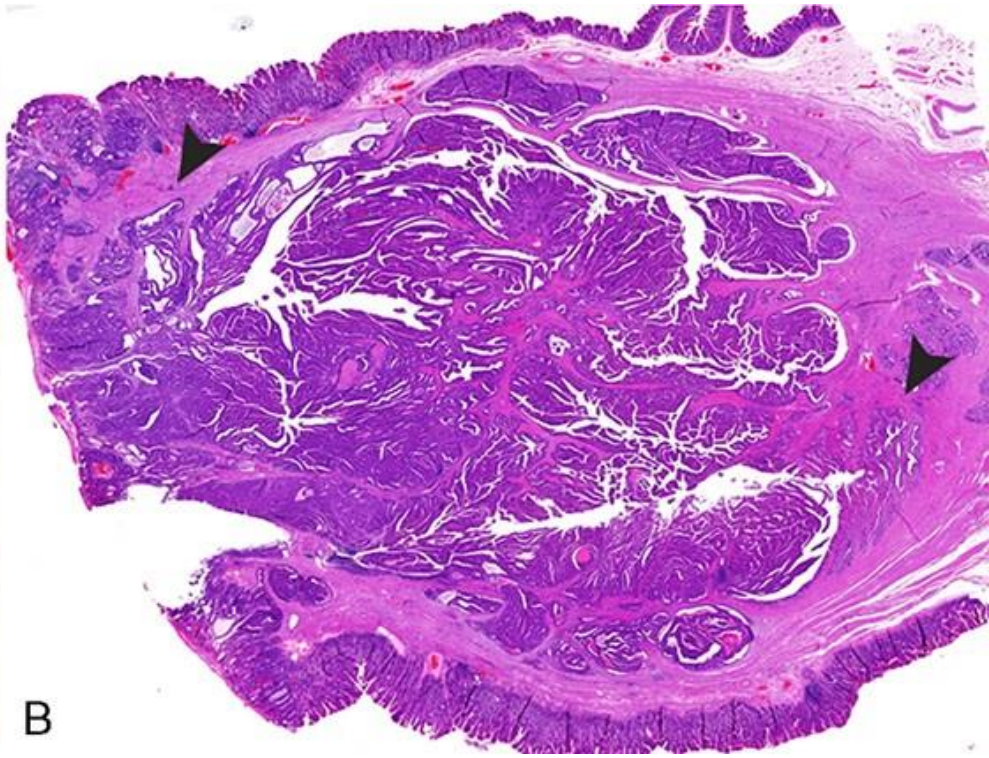


Adsay NV, *Am J Surg Pathol* 2012



Adsay NV, *Am J Surg Pathol* 2012





Adsay NV, *Am J Surg Pathol* 2012

Definition of Intra-ampullary Papillary-Tubular Neoplasm

A Neoplasm that is:

Preinvasive (dysplastic)

Mass-forming; exophytic (papillary or polypoid)

Compact

Distinct from neighboring mucosa

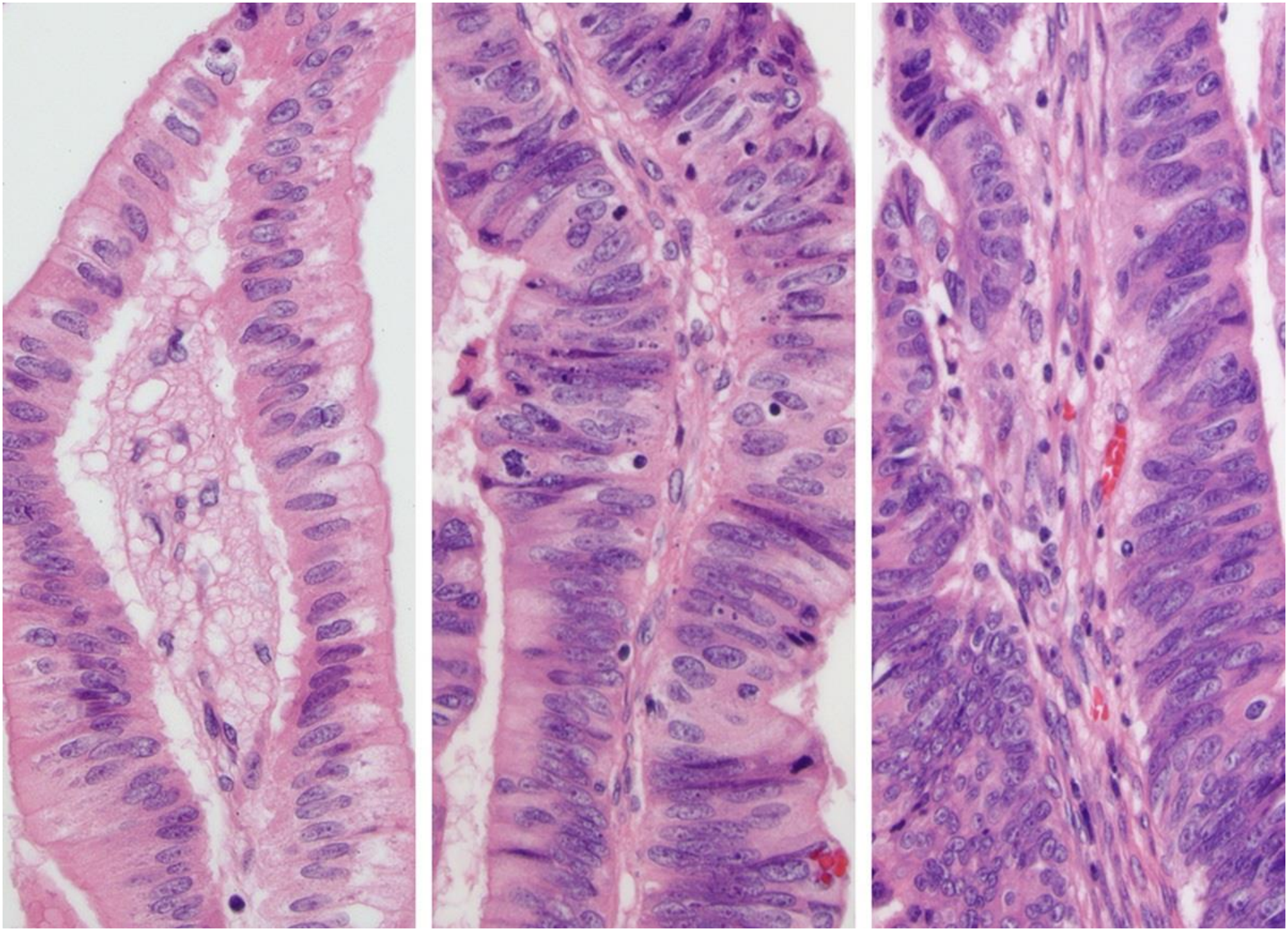
Localized almost exclusively within the ampulla

Growing predominantly (> 75%) within the channel and/or the very distal segments of the pancreatic duct or common bile duct

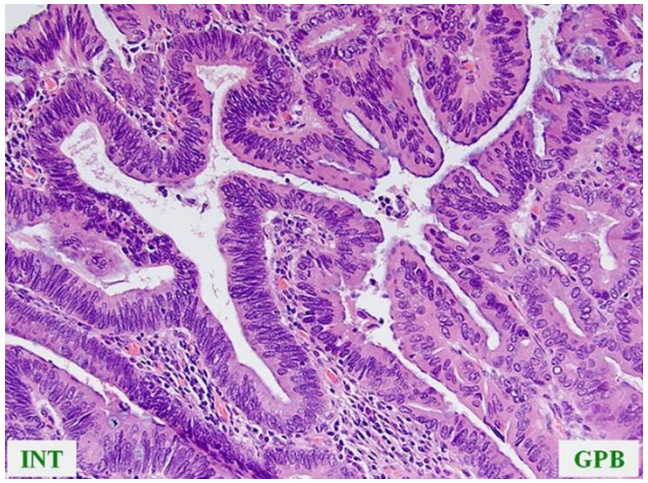
With only minimal (< 25%), if any, involvement of the duodenal aspect of the papilla

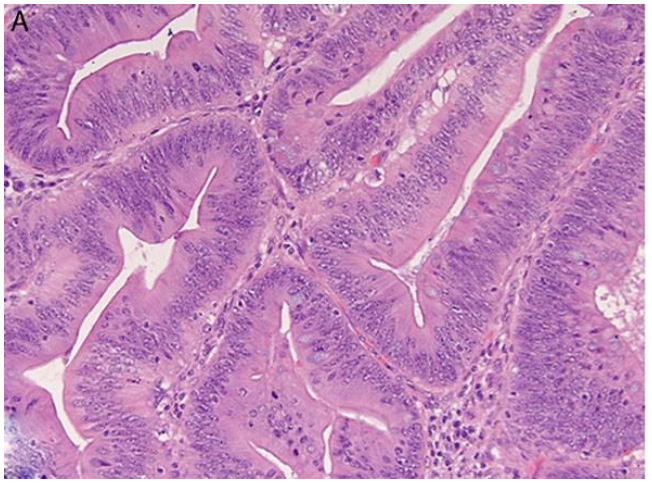
And only minimal (< 25%), if any, intramucosal extension into the proximal aspects of the common bile duct or pancreatic duct

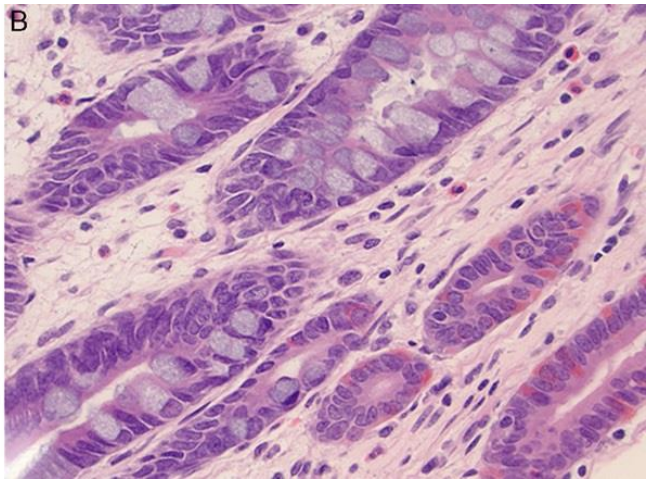
Ohike N, *Am J Surg Pathol* 2010

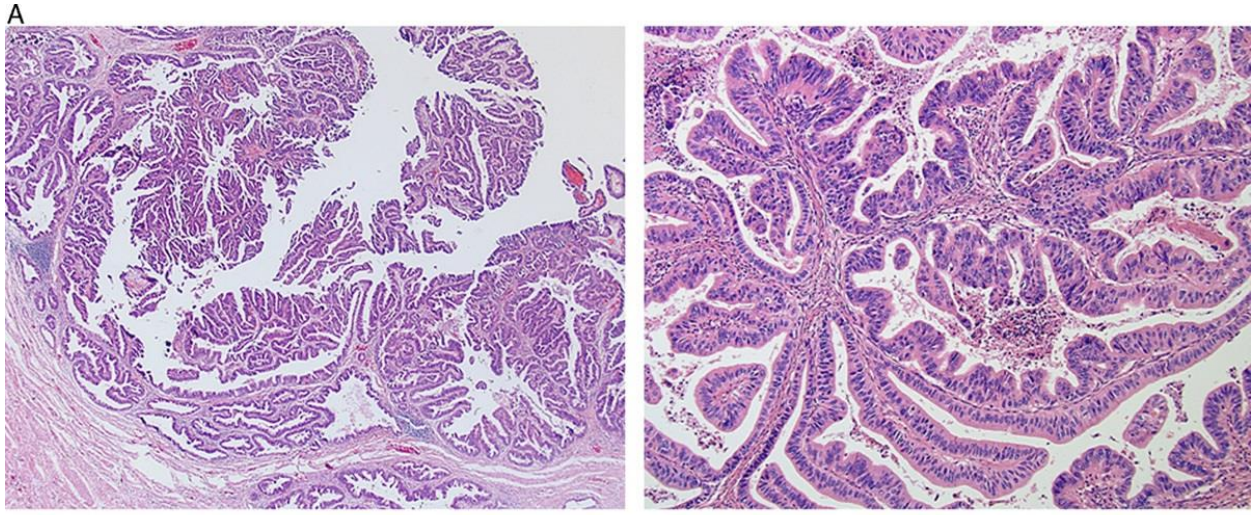


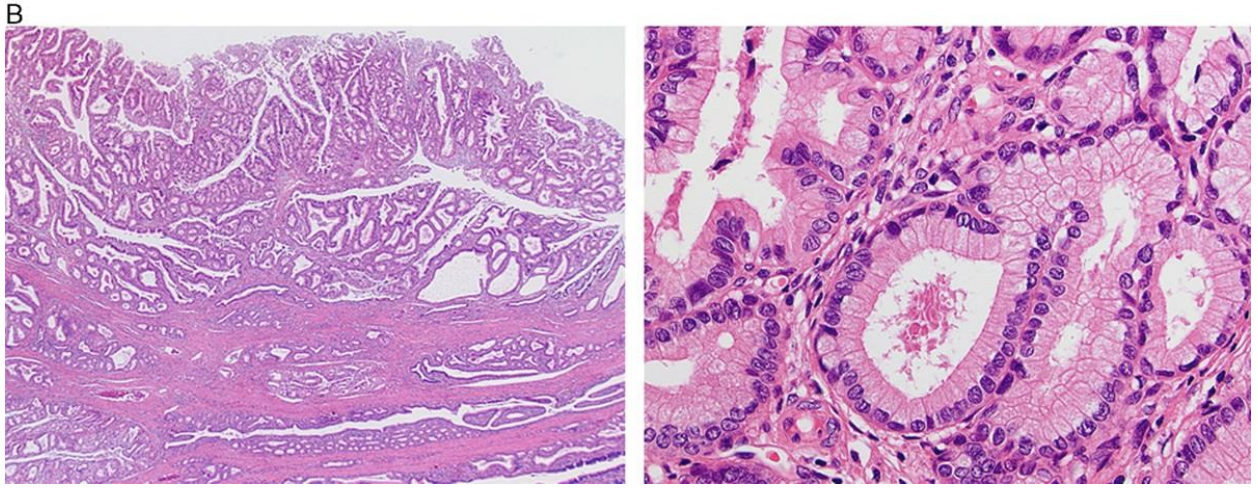
Ohike N, *Am J Surg Pathol* 2010



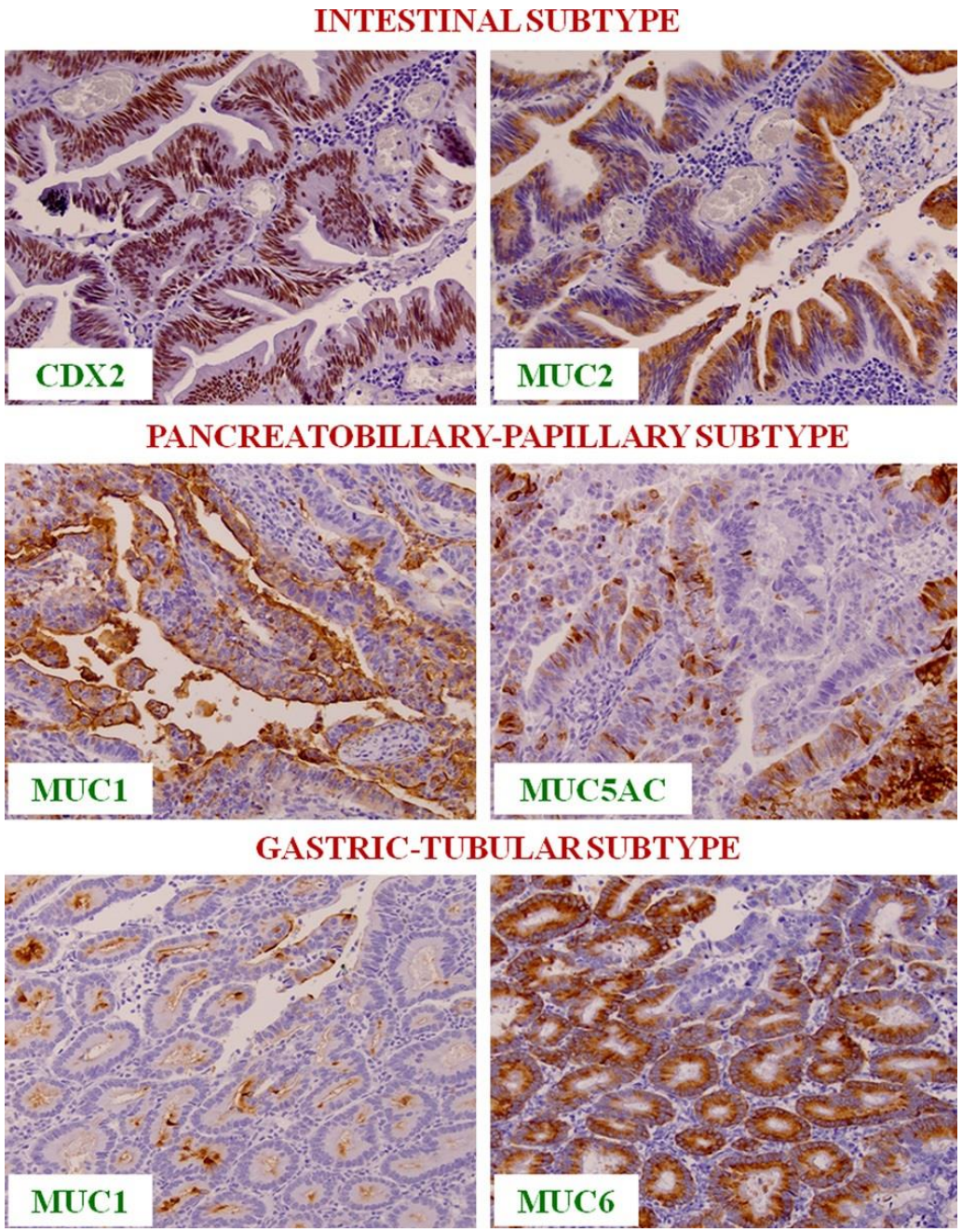


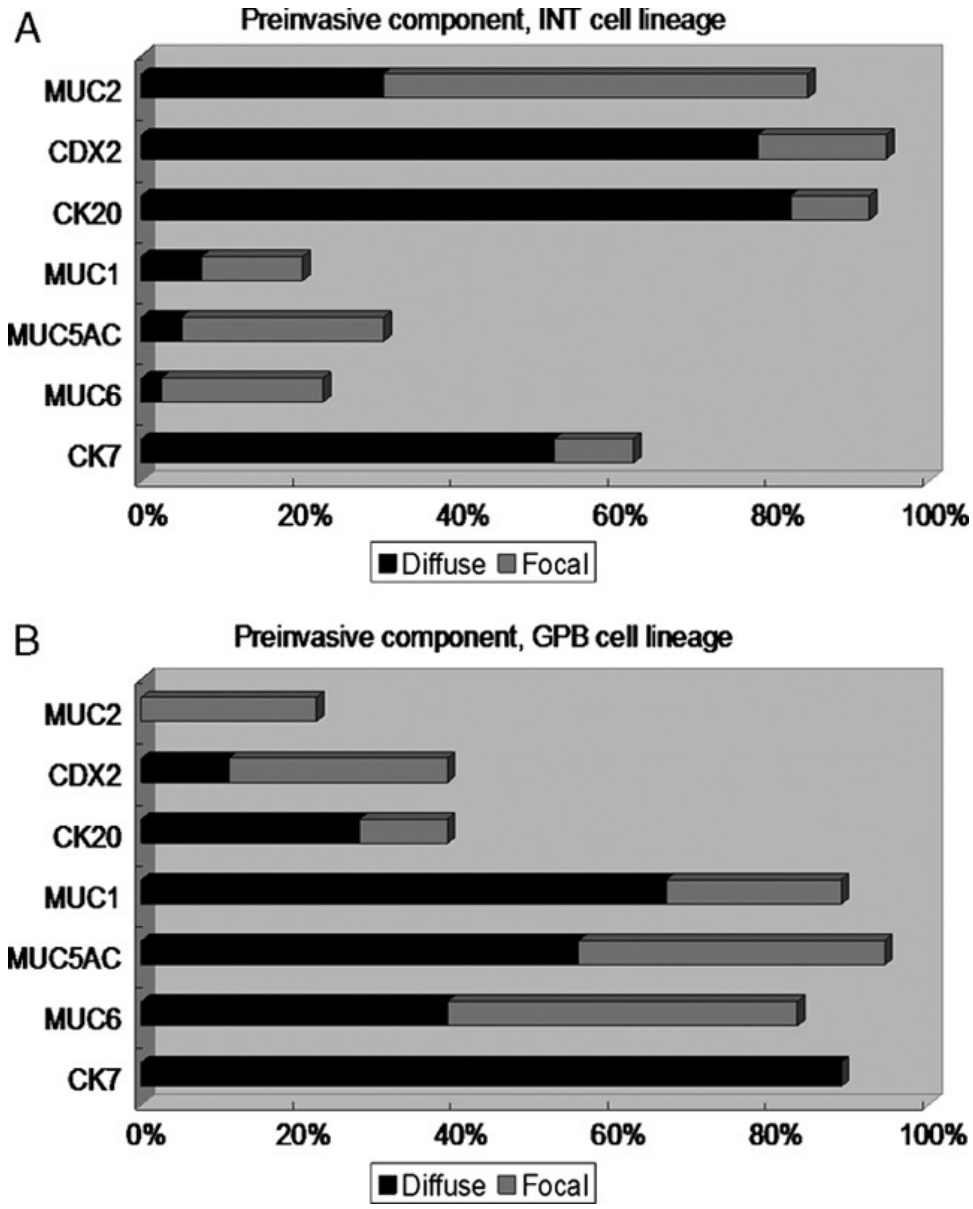




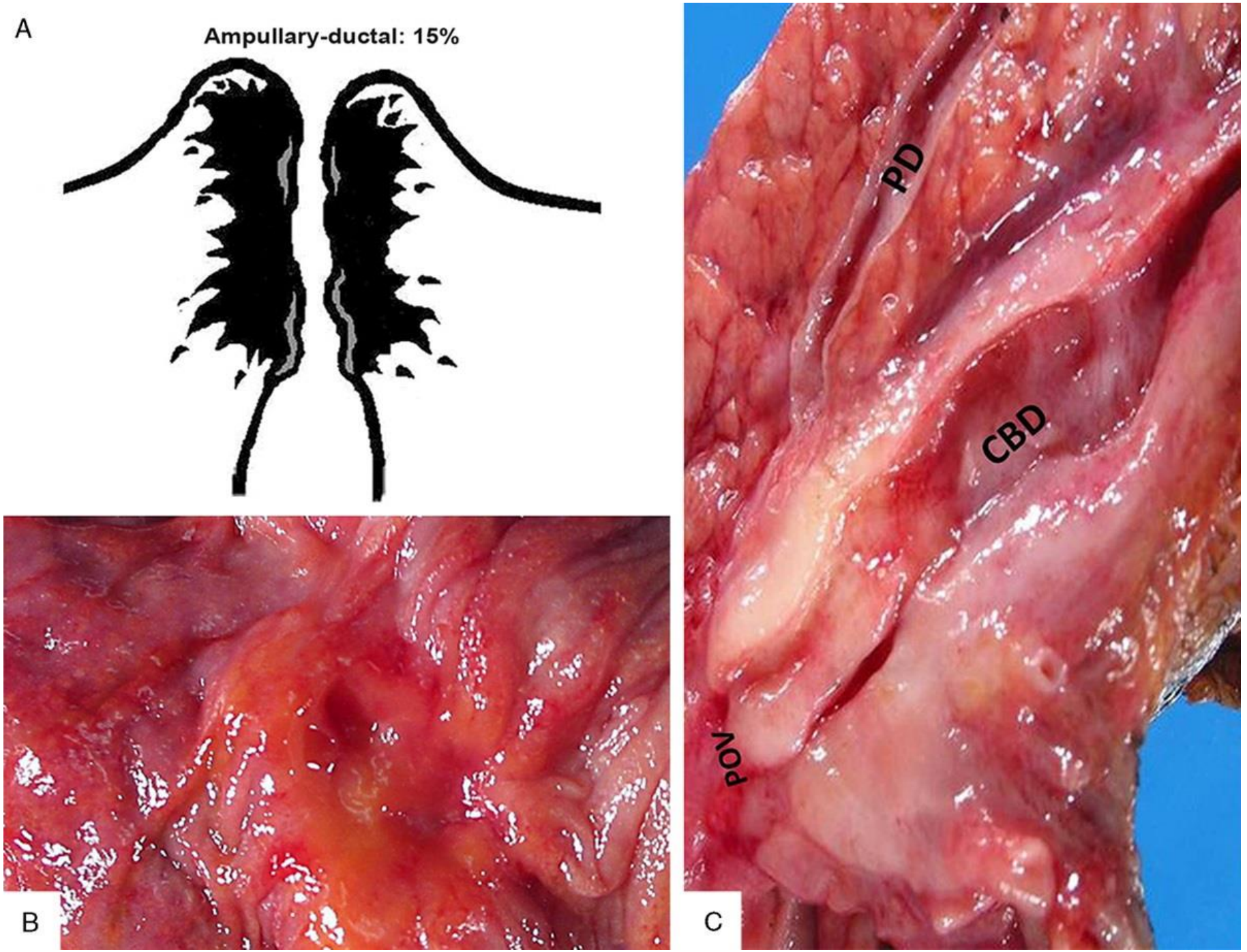


Ohike N, *Am J Surg Pathol* 2010

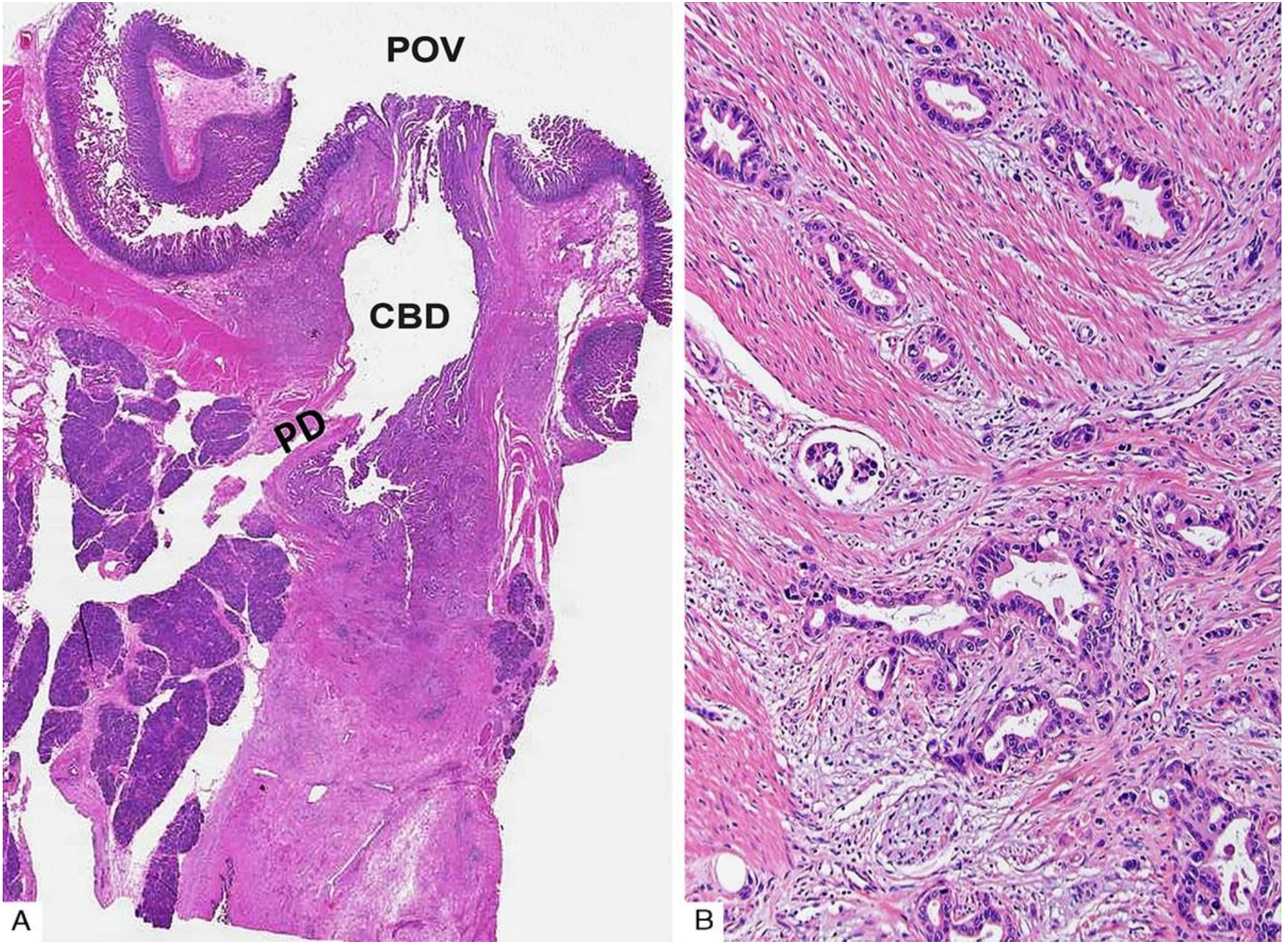




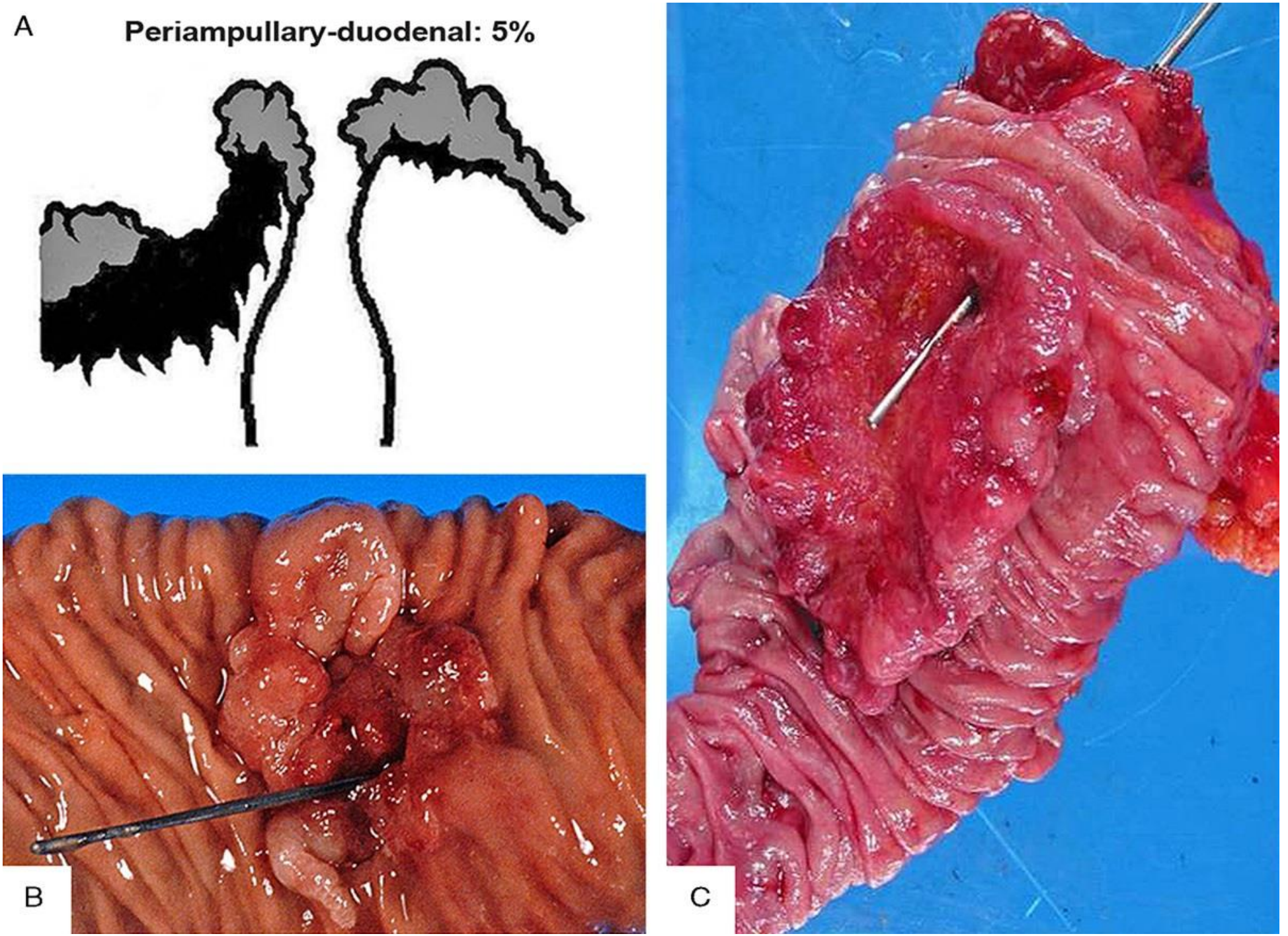
Ohike N, *Am J Surg Pathol* 2010



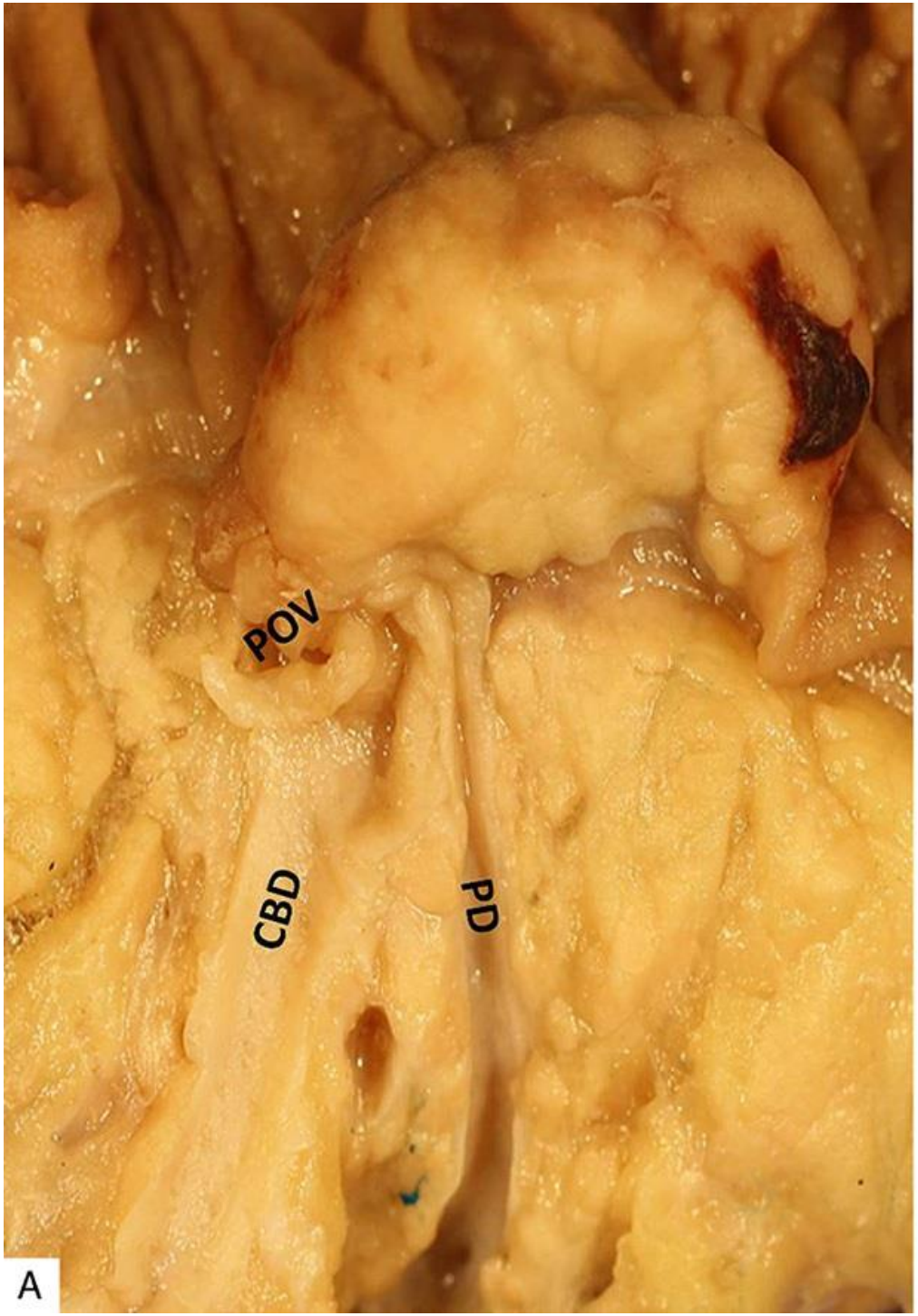
Adsay NV, *Am J Surg Pathol* 2012

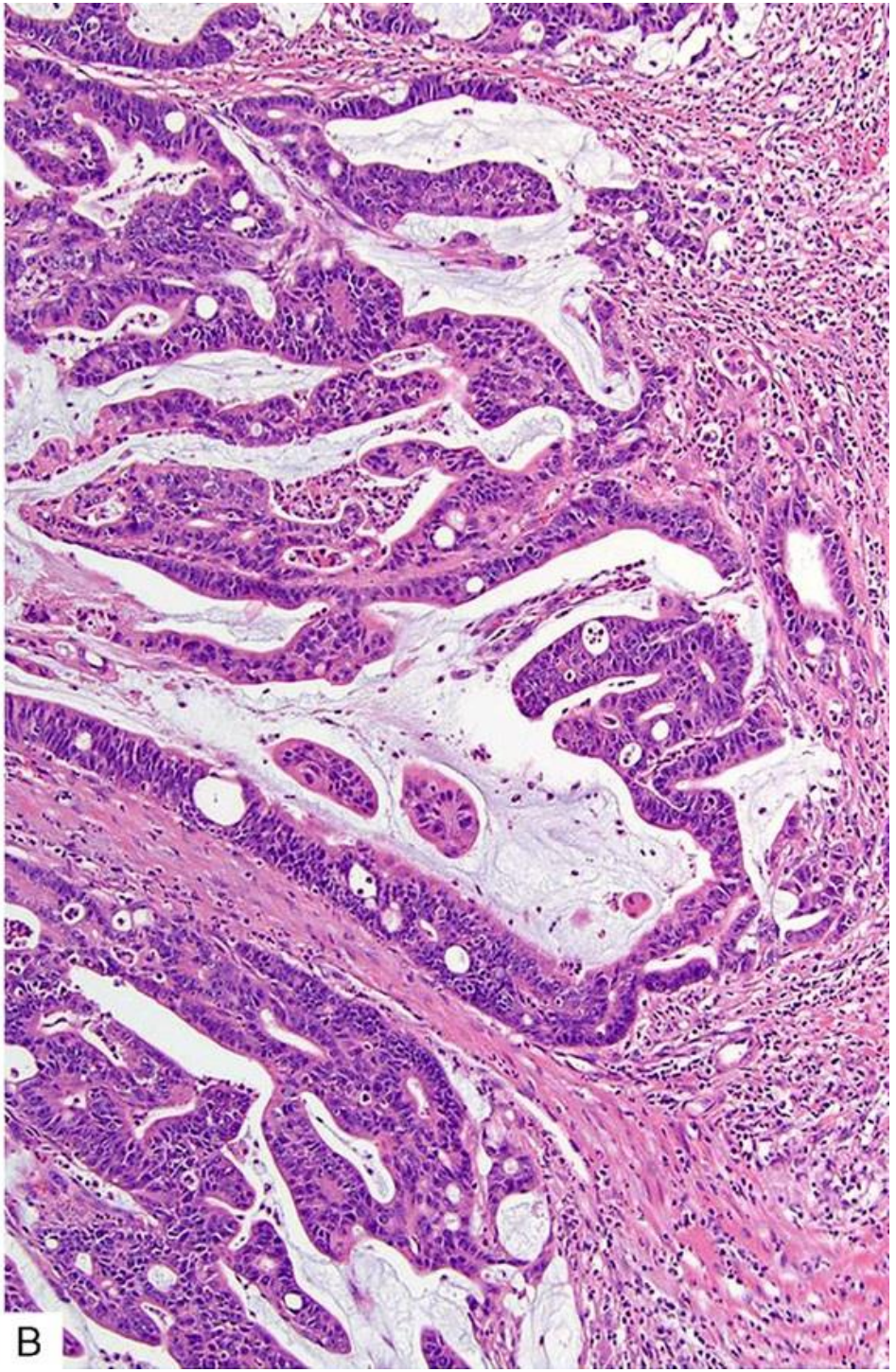


Adsay NV, *Am J Surg Pathol* 2012



Adsay NV, *Am J Surg Pathol* 2012





Adsay NV, *Am J Surg Pathol* 2012

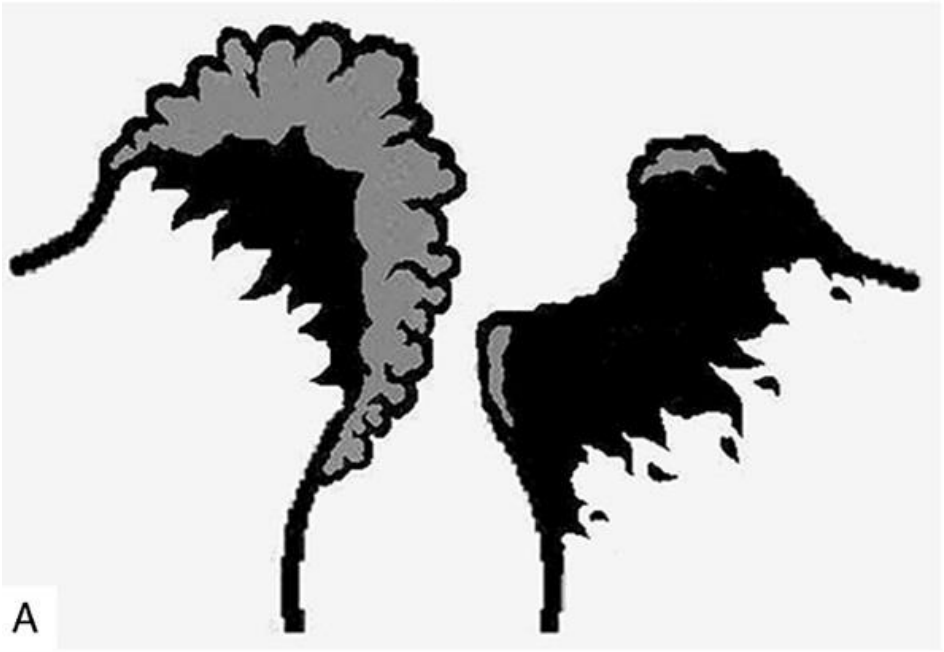
Peri-ampullary duodenal vs. duodenal adenocarcinoma

Tumor Characteristics	Periampullary-Duodenal (n = 12)	Duodenal (n = 55*)	P†
LN status			0.1823
Positive	6 (50%)	29 (71%)	
Negative	6 (50%)	12 (29%)	
Stage			0.0004
T1	0	3 (6%)	
T2	8 (67%)	7 (14%)	
T3	4 (33%)	15 (29%)	
T4	0	26 (51%)	
Size (cm), mean (SD)	4.7 (1.9)	4.0 (2.3)	< 0.0001
Survival rates (%)			0.5868
1 y	80.0	76.2	
3 y	68.6	52.5	
5 y	54.9	43.8	

*Subjects with missing values were excluded.
†Based on χ^2 for LN status and stage, t test for size, and log-rank test for overall survival rates.
LN indicates lymph node.

Adsay NV, *Am J Surg Pathol* 2012

Ampullary-NOS: 55%



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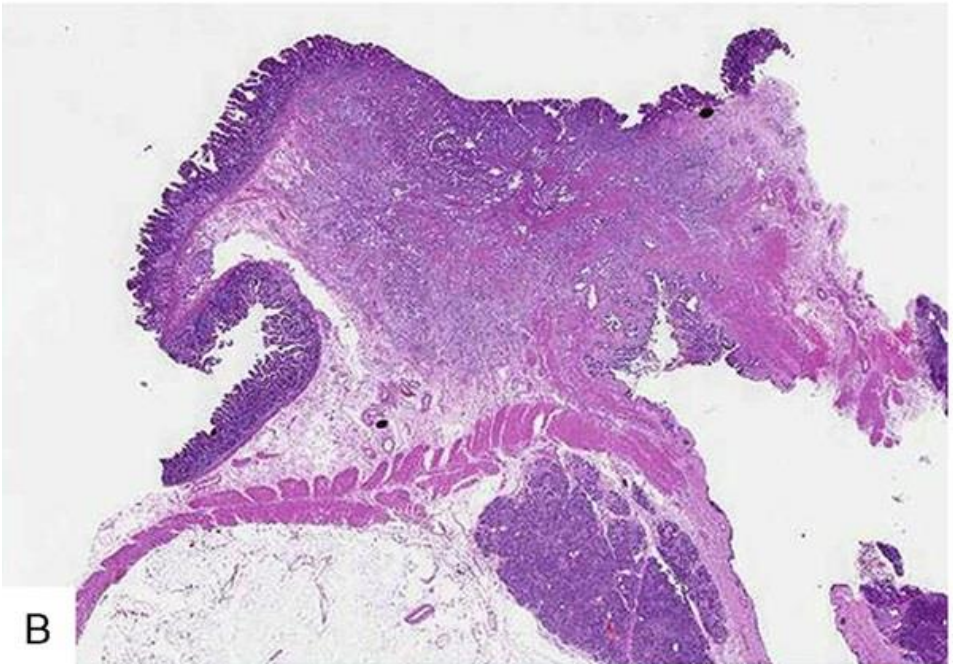

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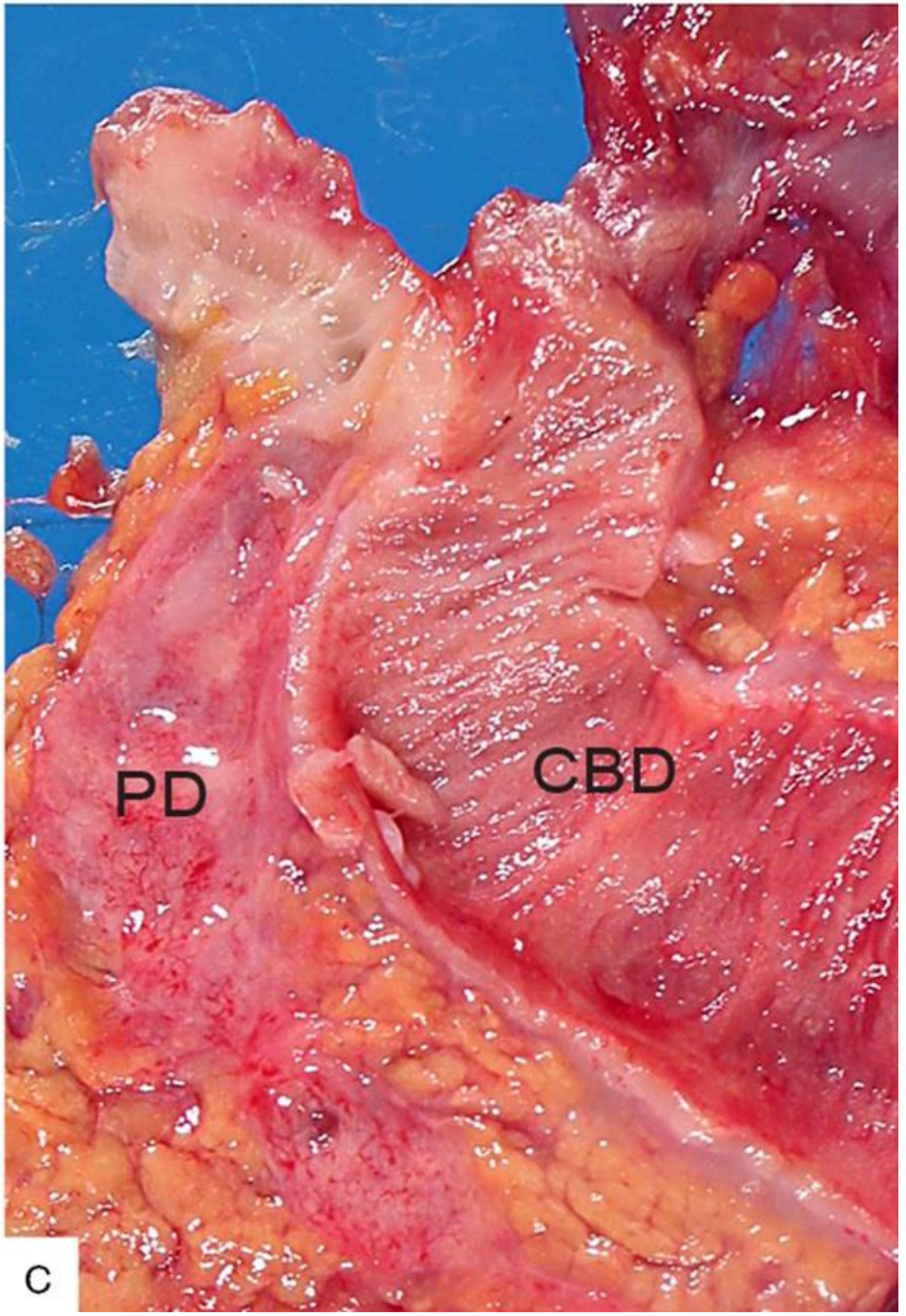

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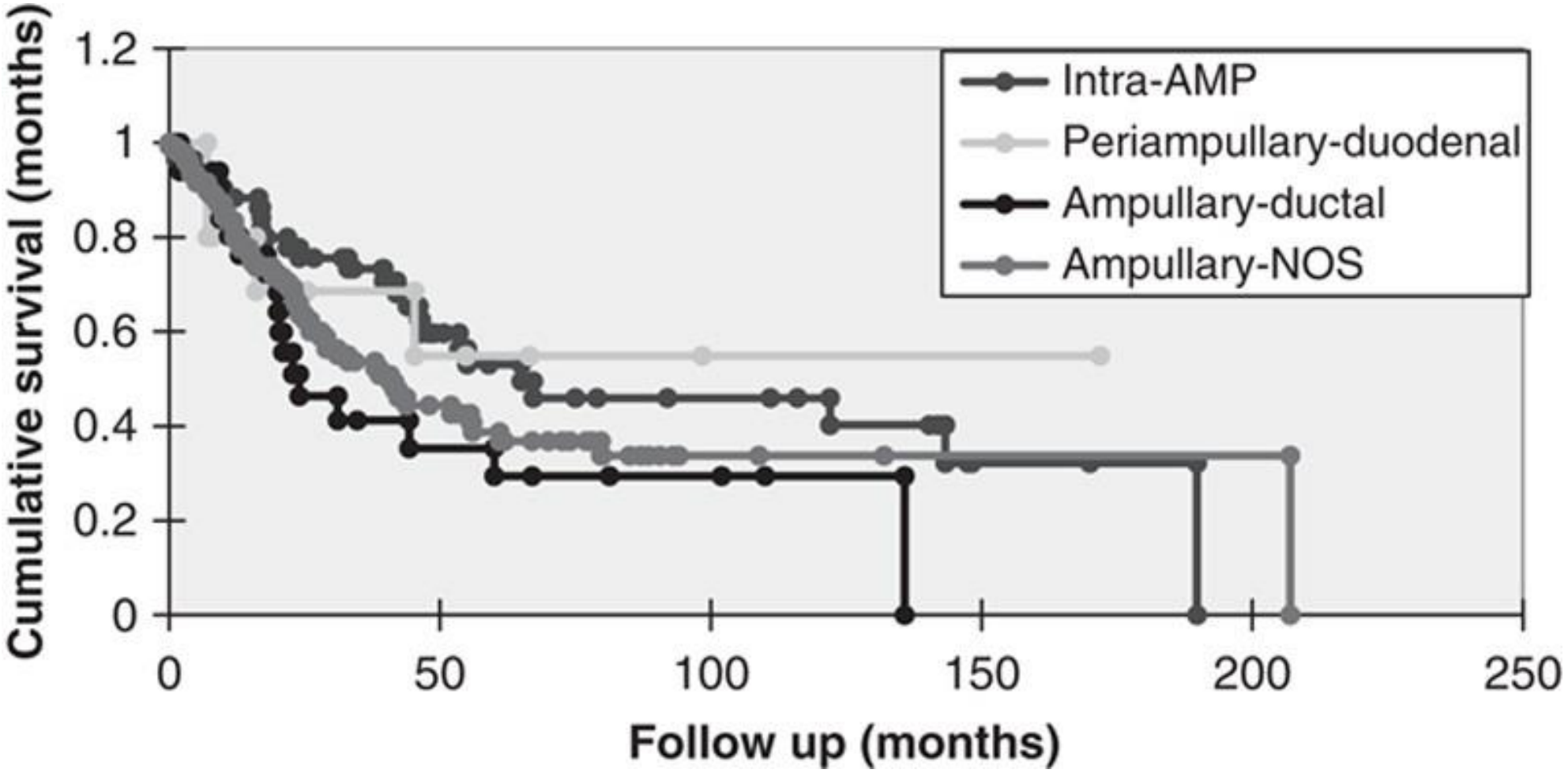
Adsay NV, *Am J Surg Pathol* 2012



Adsay NV, *Am J Surg Pathol* 2012

Comparison of clinicopathologic features

Variables	Intra-ampullary (n = 61*, 25%)	Ampullary-Ductal (n = 36*, 15%)	Periampullary-Duodenal (n = 12*, 5%)	Ampullary-NOS (n = 140*, 55%)	P†
Baseline demographics					
Age (y), mean (± SD)	64 (11.9)	69 (8.5)	59 (13.7)	65 (12.2)	**0.044**
Sex (M/F ratio)	2.2	0.9	1	1.5	0.198
Clinical characteristics					
Overall tumor size (cm), mean (± SD)	2.9 (1.3)	1.9 (0.9)	4.7 (1.9)	2.5 (1.5)	< **0.001**
Invasive tumor size (cm), mean (± SD)	1.5 (1.0)	1.7 (0.7)	3.4 (1.3)	1.8 (1.0)	< **0.001**
Invasive histology (intestinal/nonintestinal)	33/28	2/34	9/3	38/102	< **0.001**
Lymph node metastasis, n (%)	16 (28%)	13 (41%)	6 (50%)	54 (42%)	0.228
T stage (T1 + T2/T3 + T4)	52/9	14/22	8/4	86/54	< **0.001**
Survival rates (%)					
1 y	88	80	80	80	0.167
3 y	73	41	69	54	—
5 y	53	29	55	39	—

*Subjects with missing values were excluded for each characteristic variables.
†Based on ANOVA for continuous variables, χ^2 for categorical variables, and log-rank test for overall survival rates.
F indicates female; M, male; T1, stage 1; T2, stage 2; T3, stage 3; T4, stage 4.

Adsay Y, *Am J Surg Pathol* 2012

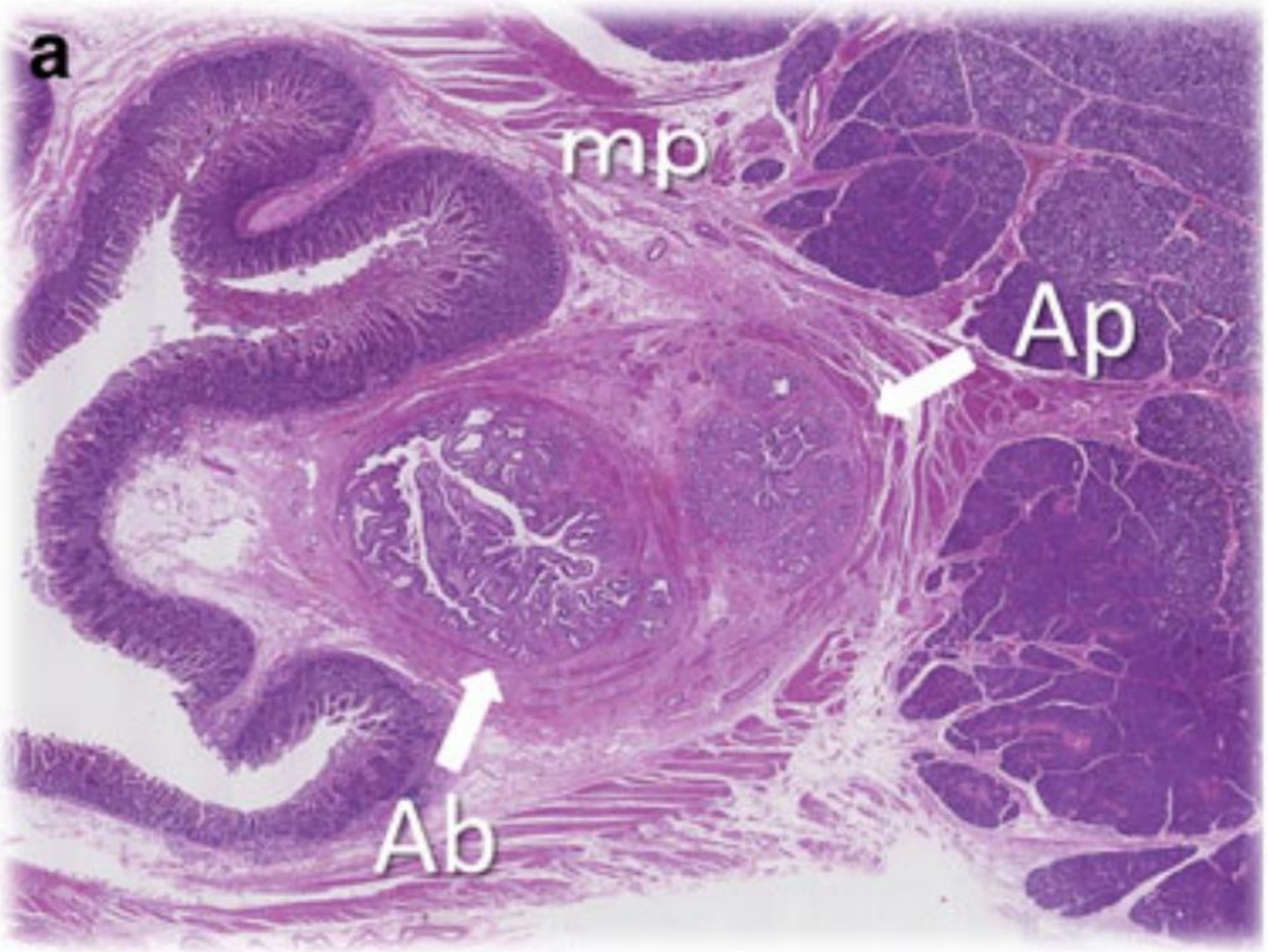
TABLE 3. Various Morphologic Patterns of Invasive Ampullary Region Adenocarcinomas in the 4 Categories

Variables	Intra-ampullary	Ampullary-Ductal	Periampullary-Duodenal	Ampullary-NOS
Signet ring-mucinous component (%)	5	0	8	11
Colloid component (%)	7	3	25	7
Micropapillary component (%)	8	14	8	7
Neuroendocrine component (%)	2	6	0	5
Squamous component (%)	2	0	0	3
Sarcomatoid component (%)	2	8	0	5

TNM staging pancreas

- T1: tumour 2 cm or less in greatest dimension
  - T1a: 0.5 cm or less
  - T1b: > 0.5 cm but < 1 cm
  - T1c: > 1 cm but no more than 2 cm
- T2: tumour > 2 cm but not > 4 cm in greatest dimension
- T3: tumour > 4 cm in greatest dimension
- T4: tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery

- N1: metastasis in 1-3 regional lymph nodes
- N2: metastasis in 4 or more regional lymph nodes



Aiura K, *J Hepatobiliary Pancreat Sci* 2011

TNM staging ampulla of Vater

- T1a: limited to ampulla of Vater or sphincter of Oddi
- T1b: tumour invades beyond the sphincter of Oddi and/or into the duodenal mucosa
- T2: tumour invades the muscularis propria of the duodenum
- T3: tumour invades the pancreas
  - T3a: tumour invades 0.5 cm or less into the pancreas
  - T3b: tumour invades > 0.5 cm into the pancreas or extends into peripancreatic duodenal tissue or duodenal serosa
- T4: involvement of superior mesenteric artery, coeliac axis or common hepatic artery

- N1: metastasis in 1-2 regional lymph nodes
- N2: metastasis in 3 or more regional lymph nodes

TNM staging duodenum (small intestine)

- T1: tumour invades lamina propria or submucosa
  - T1a: tumour invades lamina propria or muscularis mucosae
  - T2a: tumour invades submucosa
- T2: tumour invades muscularis propria
- T3: tumour invades subserosa or non-peritonealised perimuscular tissue
- T4: tumour perforates visceral peritoneum or directly invades othor organs or structures

- N1: metastasis in 1-2 regional lymph nodes
- N2: metastasis in 3 or more regional lymph nodes

TNM staging distal extrahepatic bile duct

- T1: tumour invades bile duct wall to a depth of < 5 mm
- T2: tumour invades bile duct wall to a depth of 5-12 mm
- T3: tumour invades bile duct wall to a depth of > 12 mm
- T4: tumour involves coelic axis, superior mesenteric artery or common hepatic artery

- N1: metastasis in 1-3 regional lymph nodes
- N2: metastasis in 4 or more regional lymph nodes

Key messages

- Identification of tumour origin important for prognosis, staging, adjuvant therapy, clinical trials
- Mainly based on macroscopic grounds (tumour bulk)
- Pancreatobiliary phenotype tumours have a worse prognosis compared to intestinal phenotype tumours
- 4 subtypes of ampullary region carcinomas are now distinguished