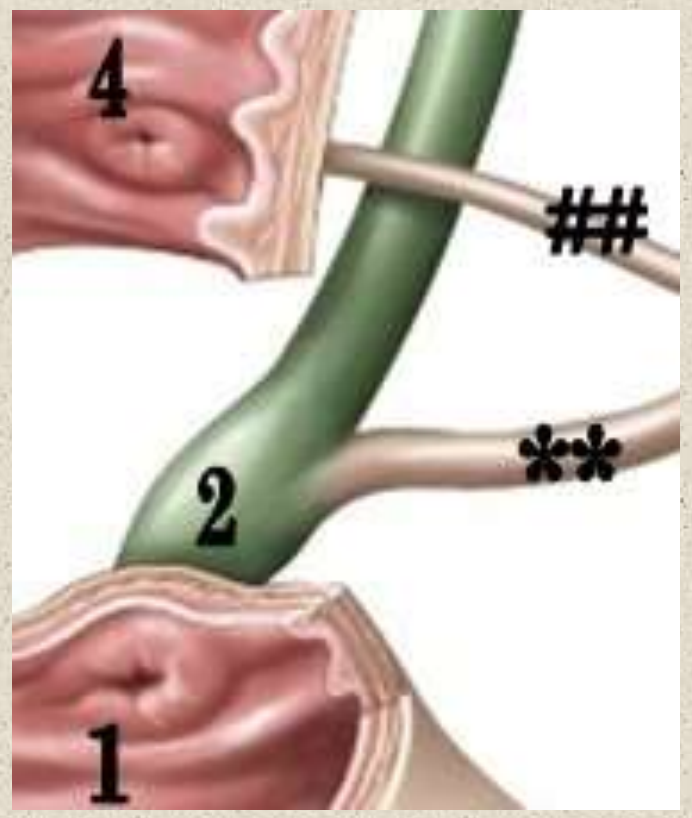
Pancreatic tumour slide seminar – Jan 2018

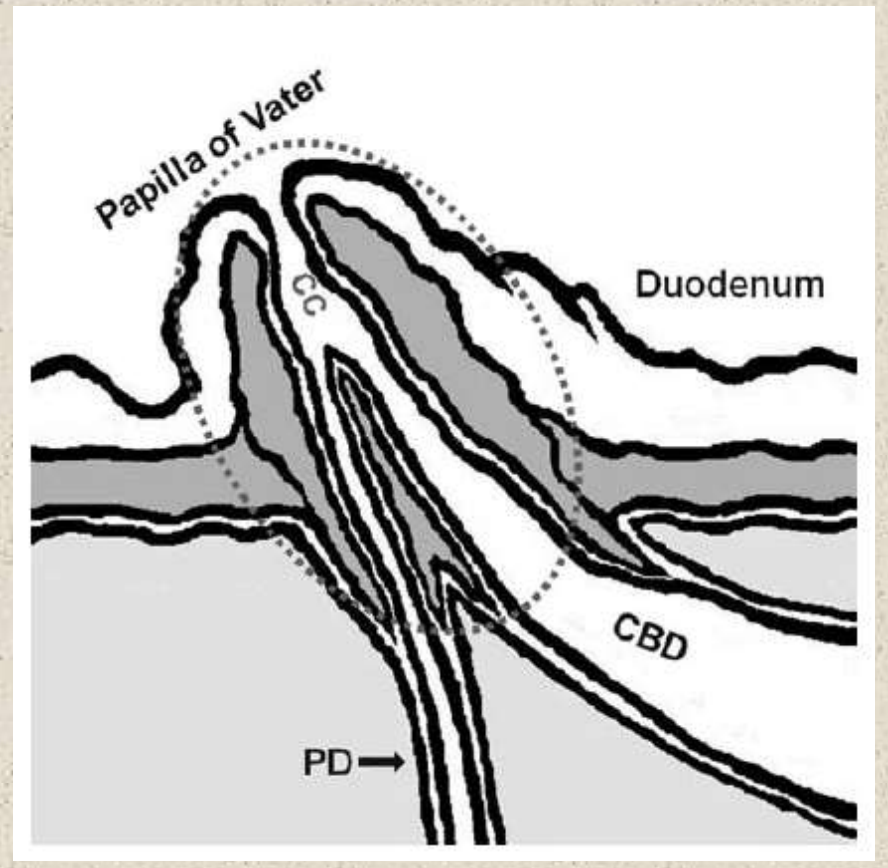
Newton ACS Wong

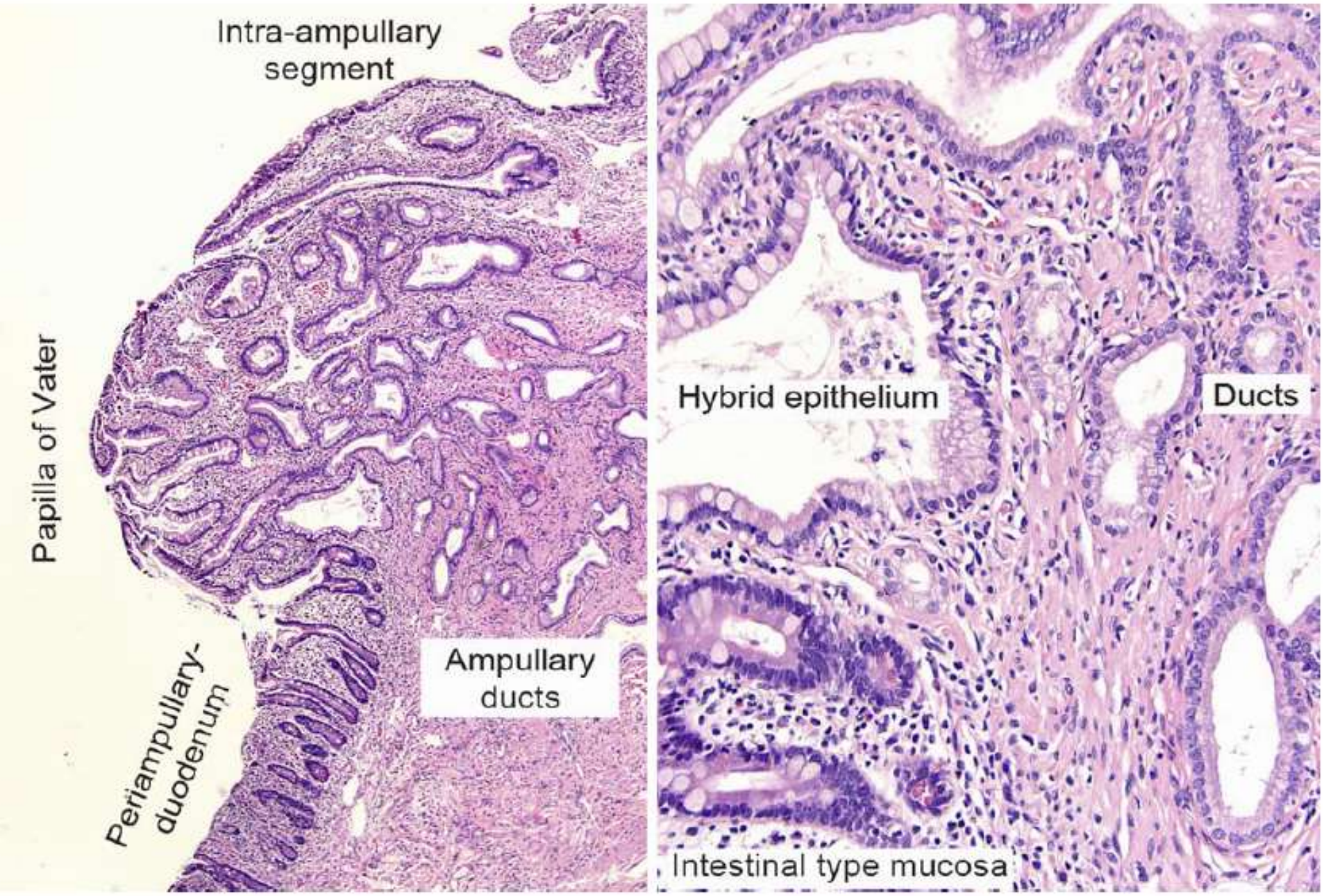
Department of Cellular Pathology

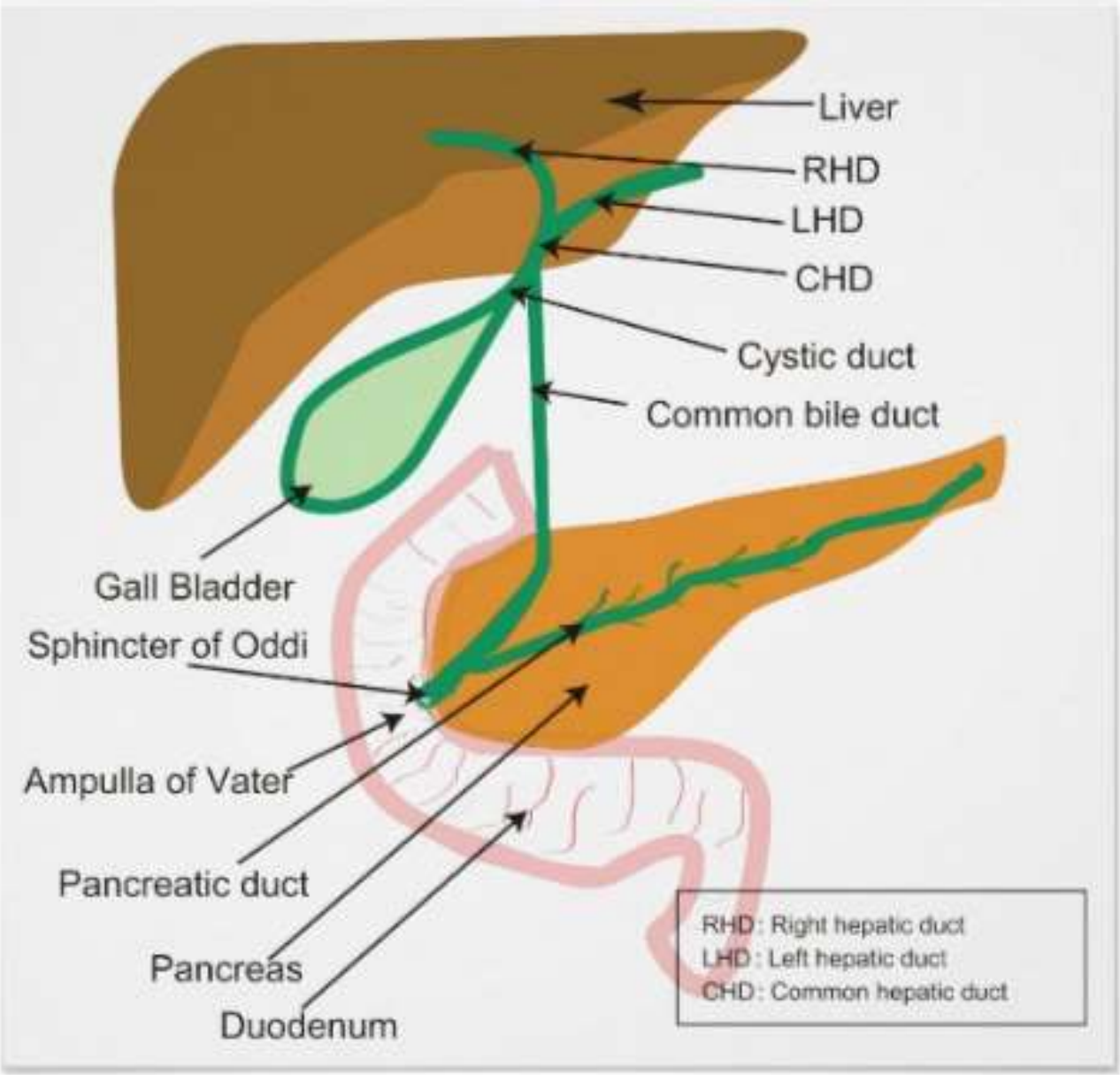
Southmead Hospital

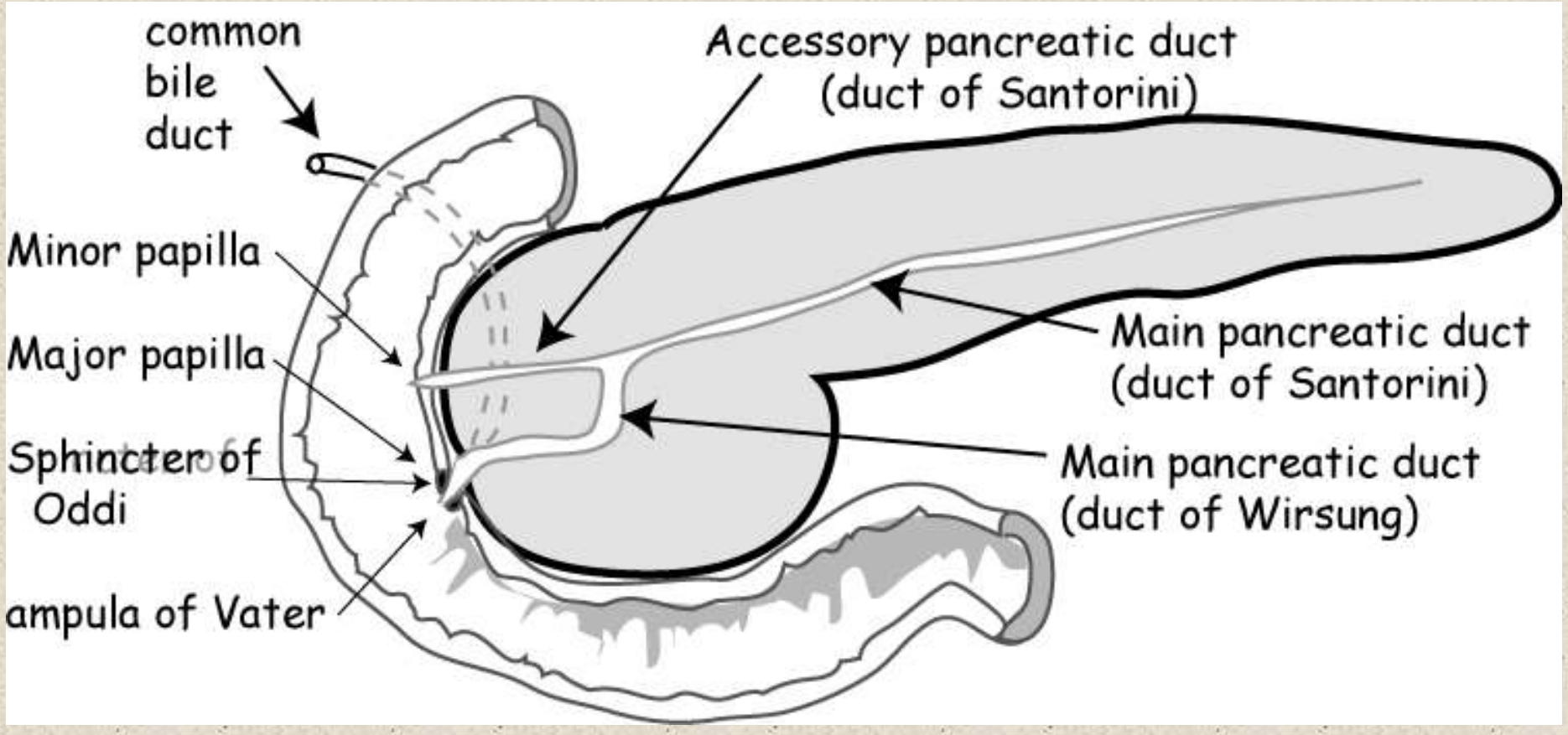
Report what is clinically relevant

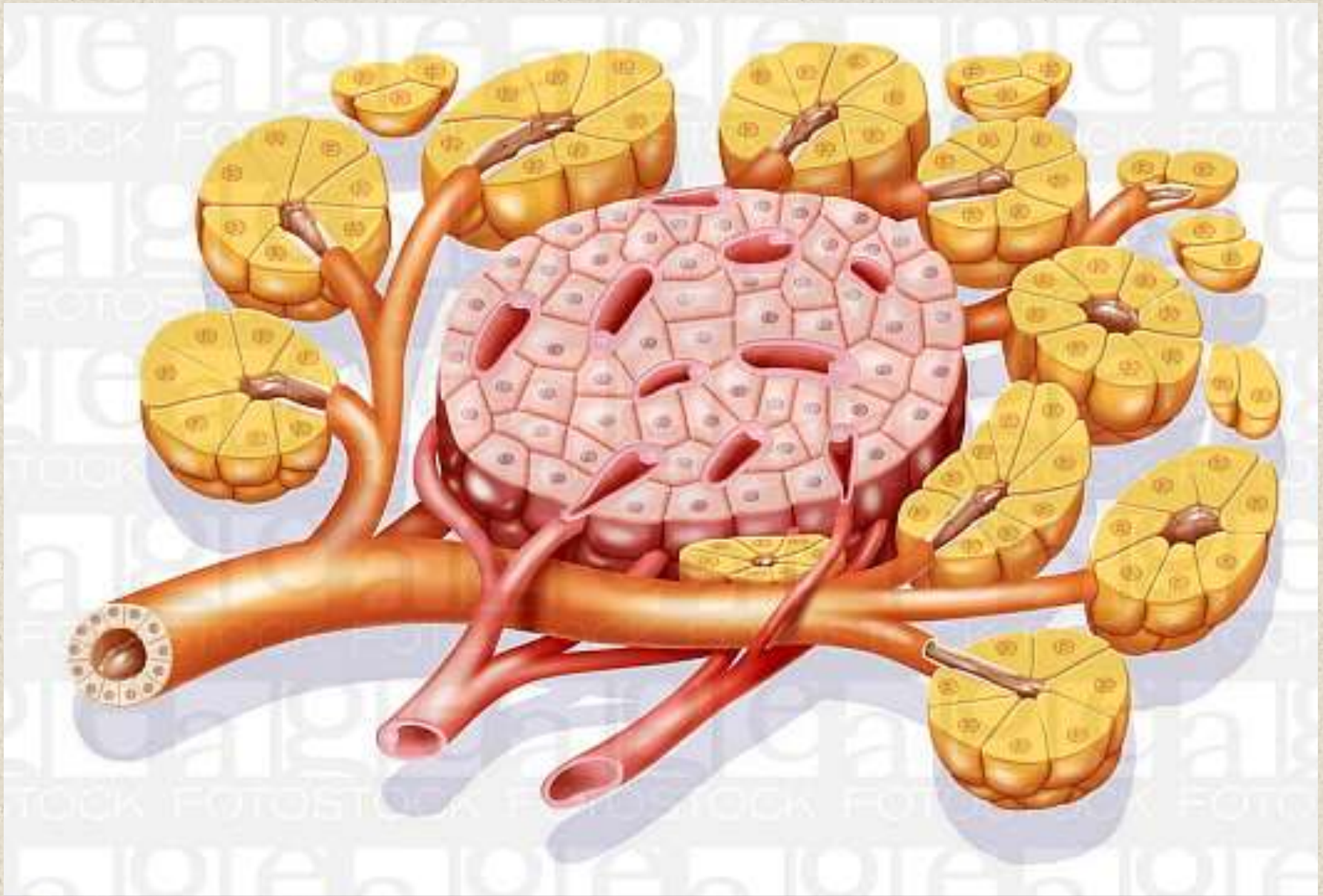

4
##
**
2
1

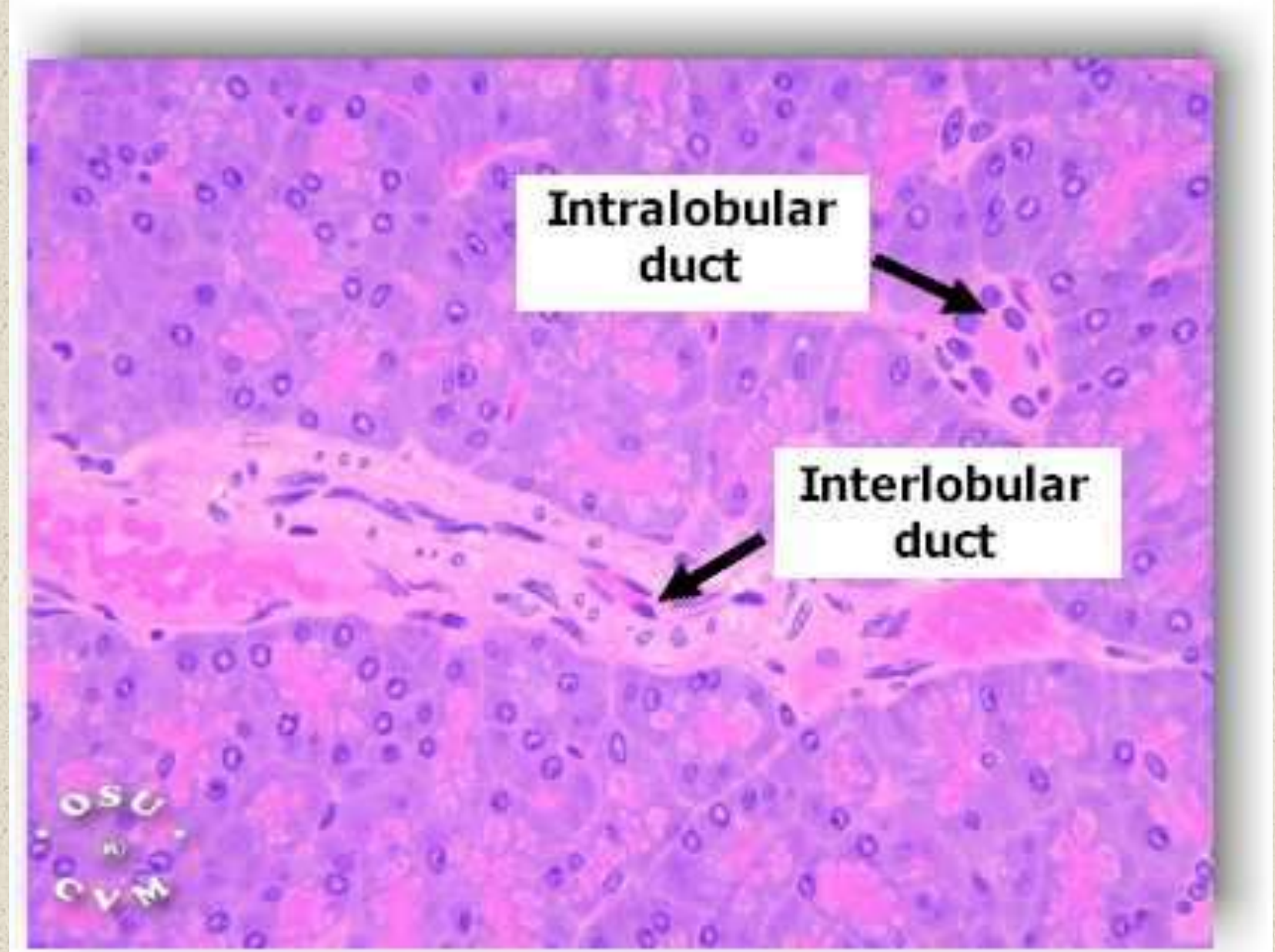

Papilla of Vater
CC
Duodenum
CBD
PD


Intra-ampullary segment
Papilla of Vater
Periampullary-duodenum
Ampullary ducts
Hybrid epithelium
Ducts
Intestinal type mucosa


Liver
RHD
LHD
CHD
Cystic duct
Common bile duct
Gall Bladder
Sphincter of Oddi
Ampulla of Vater
Pancreatic duct
Pancreas
Duodenum
RHD : Right hepatic duct
LHD : Left hepatic duct
CHD : Common hepatic duct

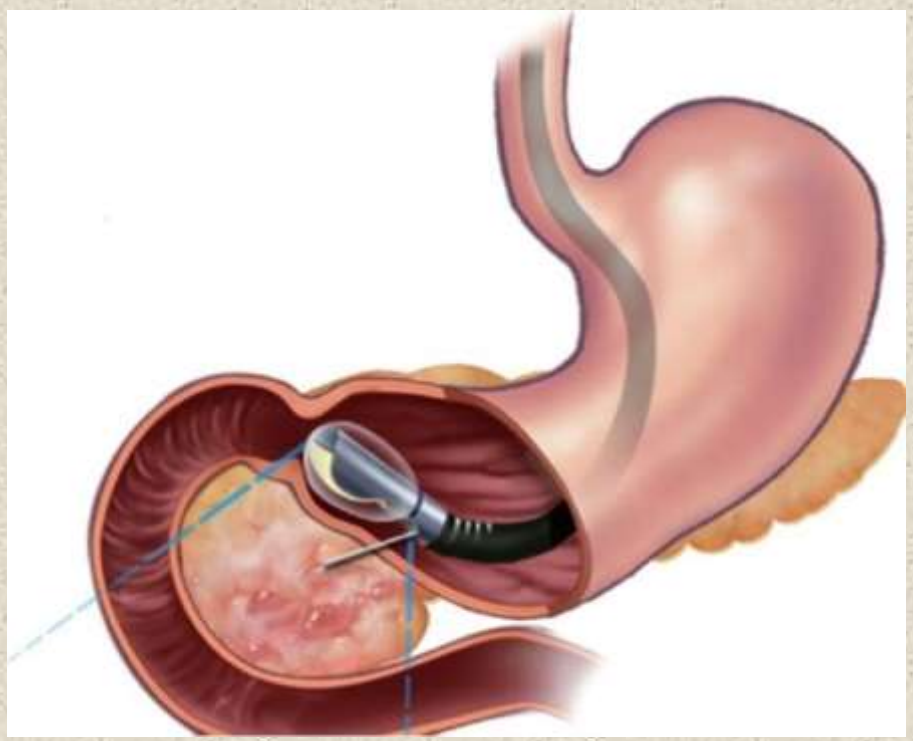

common
bile
duct
Accessory pancreatic duct
(duct of Santorini)
Minor papilla
Major papilla
Main pancreatic duct
(duct of Santorini)
Sphincter of
Oddi
Main pancreatic duct
(duct of Wirsung)
ampula of Vater

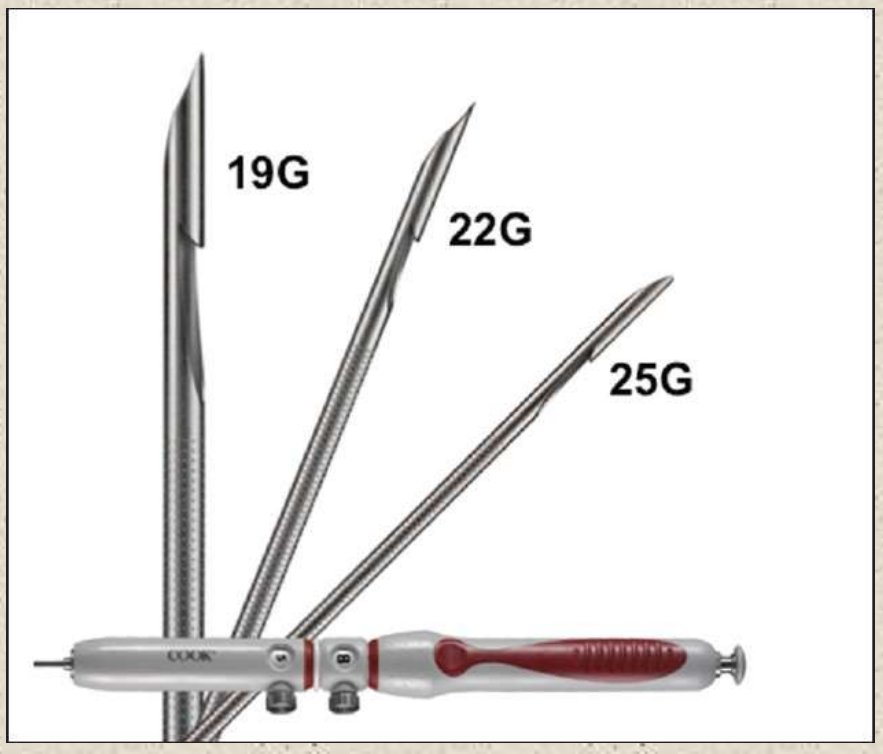



Intralobular duct
Interlobular duct

EUS-FNA/B

- Solid or cystic lesions
- Cell block it all!





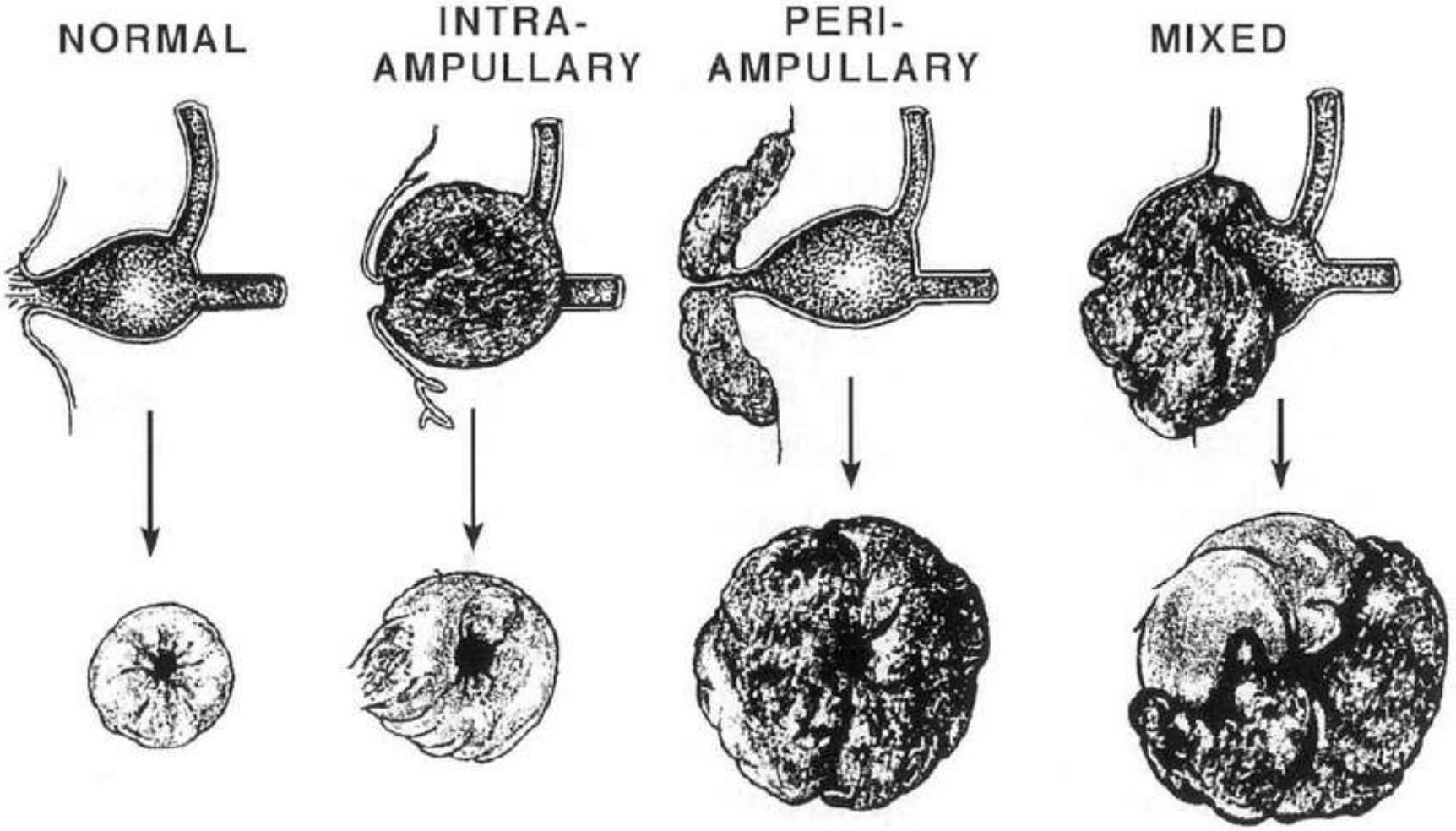
Case P3

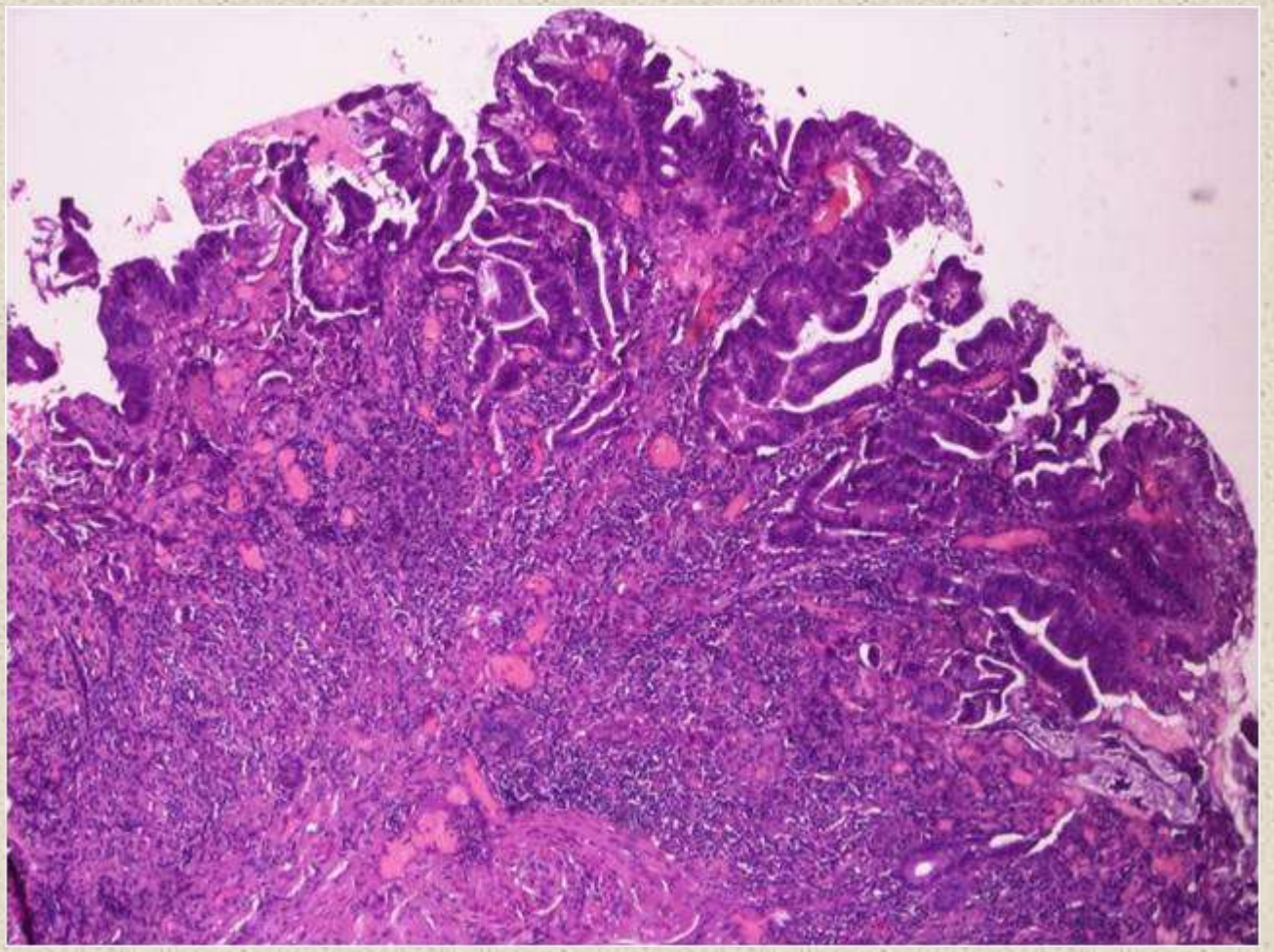
- 49 Female
- Classic Whipple's for cancer (stented). Tumour measuring 20 x 20 x 10 mm, which distorts the ampulla and abuts the adjacent duodenal wall.

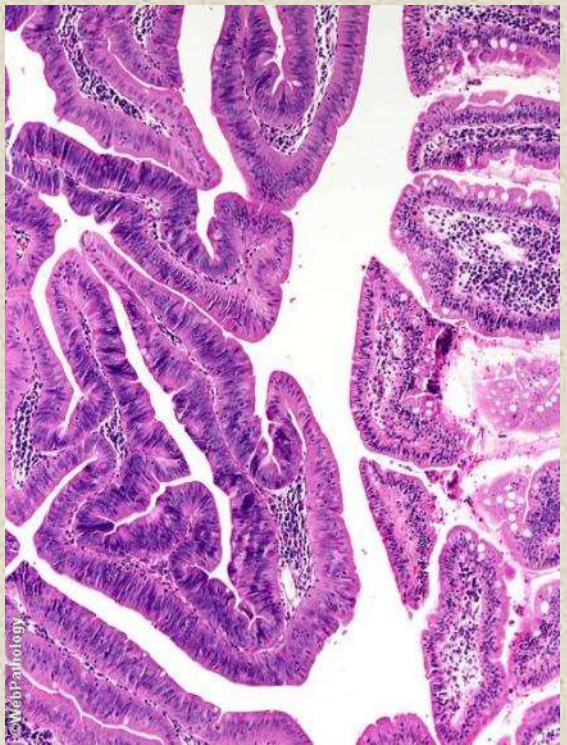
Case P3

- Diagnosis:

(Peri-)Ampullary adenocarcinoma


NORMAL
INTRA-
AMPULLARY
PERI-
AMPULLARY
MIXED




WebPathology

The Royal College of Pathologists

Pathology: the science behind the cure

Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct

March 2017

Authors: Professor Fiona Campbell, Royal Liverpool University Hospital
Dr Alison Cairns, St James' University Hospital, Leeds
Dr Fraser Duthie, Queen Elizabeth University Hospital, Glasgow
Professor Roger Feakins, Barts Health NHS Trust, London

Adenocarcinomas originating in the ampulla of Vater have intestinal-type and/or pancreatobiliary-type differentiation, and this should be stated in the report. Immunohistochemistry may be helpful in making the distinction since intestinal-type carcinoma is CK20+, CDX2+ and MUC2+ while pancreatobiliary-type carcinoma is CDX2-, MUC1+ and MUC2-.[42] Pancreatobiliary-type adenocarcinoma of the ampulla has a poorer prognosis.[11]

TNM7

Maximum depth of invasion (pT) †:

pT0: No residual tumour

pTis: Carcinoma *in situ*

pT1: Tumour limited to ampulla of Vater or sphincter of Oddi

pT2: Tumour invades duodenal wall

pT3: Tumour invades pancreas

pT4: Tumour invades peripancreatic soft tissues / adjacent organs or structures

TNM8

pT1a: Tumour limited to ampulla of Vater or sphincter of Oddi

pT1b: Tumour invades beyond the sphincter of Oddi and/or into the duodenal submucosa

pT2: Tumour invades the muscularis propria of the duodenum

pT3a: Tumour invades 5 mm or less into the pancreas

pT3b: Tumour invades more than 5 mm into the pancreas or extends into peripancreatic tissue or duodenal serosa but without involvement of the coeliac axis or the superior mesenteric artery

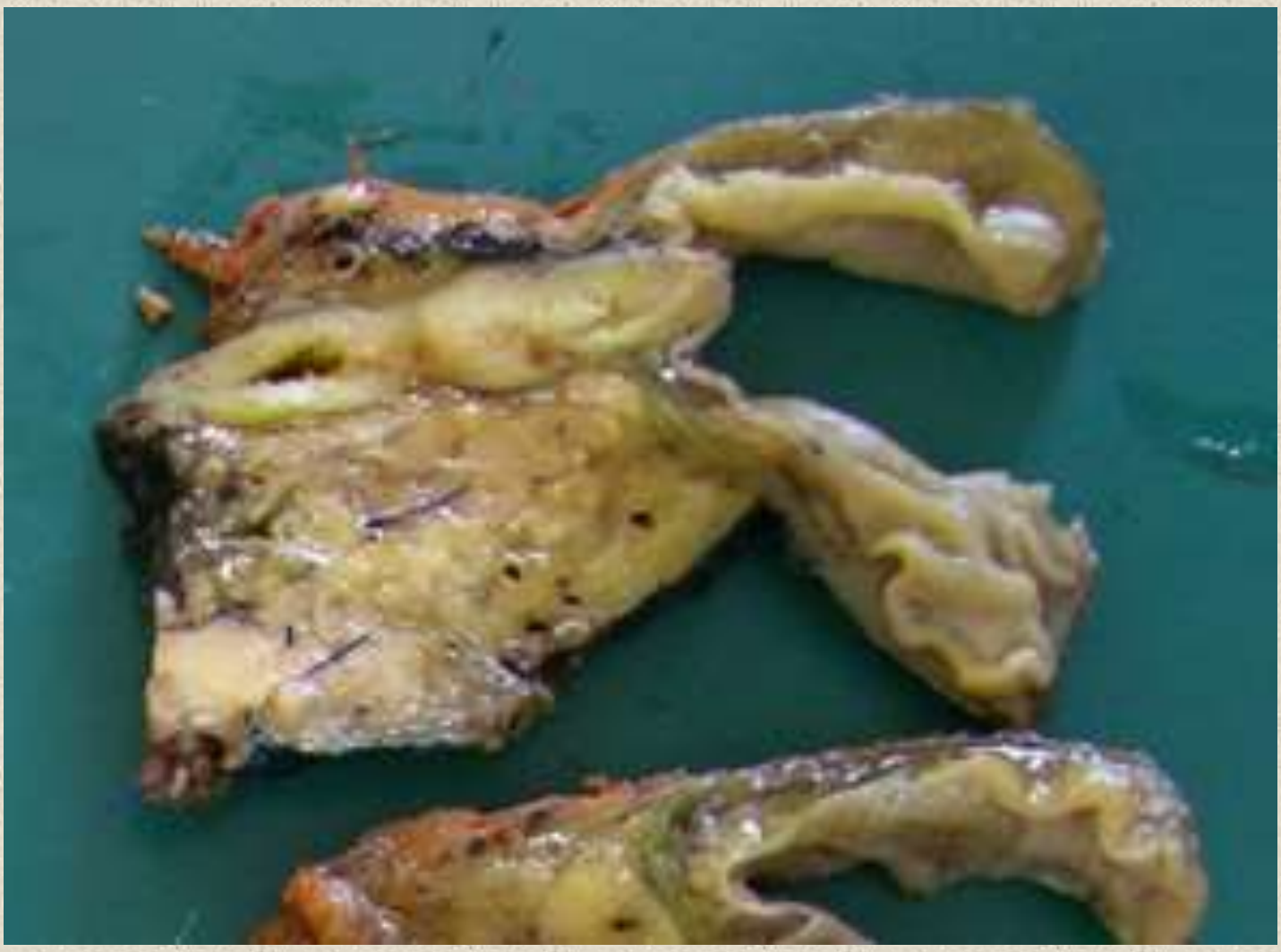
pT4: Tumour with vascular involvement of the superior mesenteric artery, coeliac axis, or common hepatic artery

N stage †: pN0 (Regional lymph nodes not involved)

pN1 (Metastases in 1 or 2 regional lymph nodes)

pN2 (Metastases in 3 or more regional lymph nodes)

Case 12664/12



Case 12664/12

- Diagnosis:

Distal cholangiocarcinoma

TNM7

T0: No residual tumour

Tis: Carcinoma *in situ*

T1: Tumour confined to the bile duct

T2: Tumour invades beyond the wall of the bile duct

T3: Tumour invades gall bladder/liver/pancreas/duodenum/other adjacent organs

T4: Tumour involves the coeliac axis or the superior mesenteric artery

TNM8

T1: Tumour invades bile duct wall to a depth less than 5 mm

T2: Tumour invades bile duct wall to a depth of 5 mm up to 12 mm

T3: Tumour invades bile duct wall to a depth of more than 12 mm

T4: Tumour involves the coeliac axis, the superior mesenteric artery and/or the common hepatic artery

N stage †: pN0 (Regional lymph nodes not involved)

pN1 (Metastases in 1 to 3 regional lymph nodes)

pN2 (Metastases in 4 or more regional lymph nodes)

Case P5

- 67 Male
- Likely pancreatic adeno-carcinoma. Not stented before surgery. There is a tumour within the head of pancreas measuring 28 x 26 x 22 mm. Tumour does not appear to extend to the adjacent duodenum.

Case P5

- Diagnosis:

Pancreatic ductal adenocarcinoma (PDAC)

PanIN

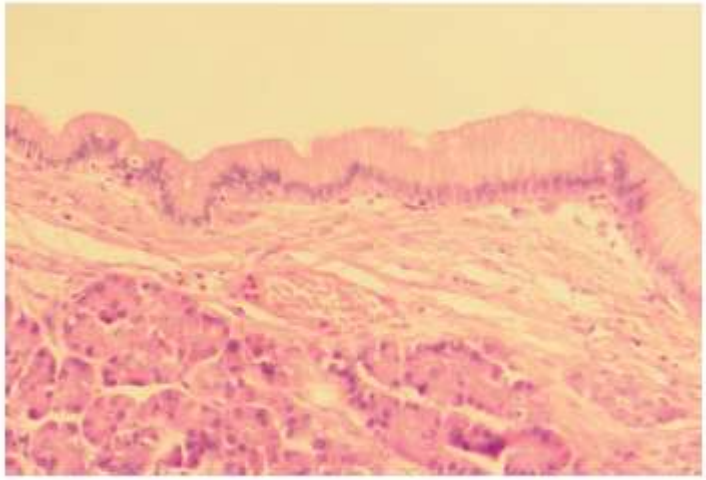


Figure 3. Pancreatic intraepithelial neoplasia (PanIN)-1A: flat lesion with tall columnar, mucinous epithelium.

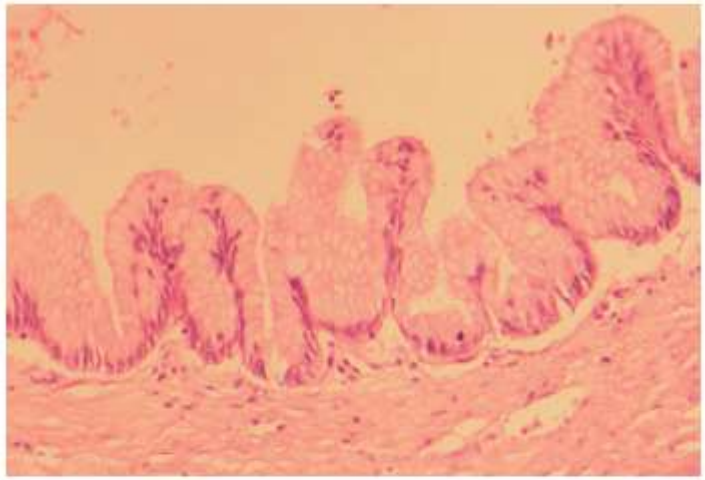


Figure 4. Pancreatic intraepithelial neoplasia (PanIN)-1B: papillary architecture with tall columnar, mucinous epithelium.

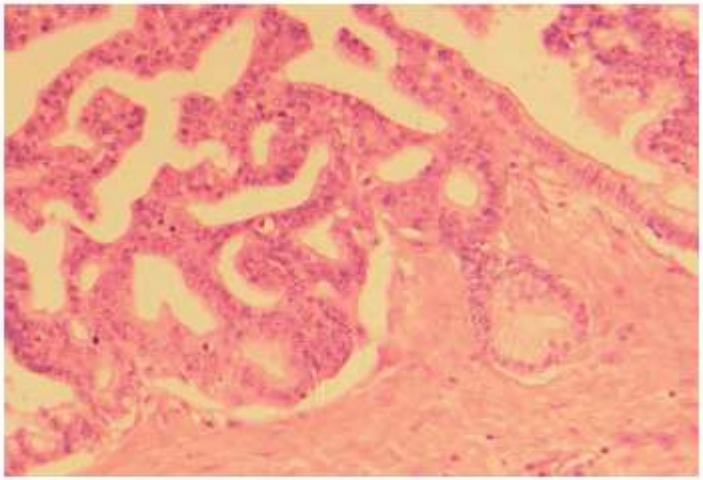


Figure 6. Pancreatic intraepithelial neoplasia (PanIN)-3: papillary architecture with cribriform areas and 'budding off' of a small cluster of epithelial cells. Cells with marked loss of polarity, mitoses and prominent nucleoli.

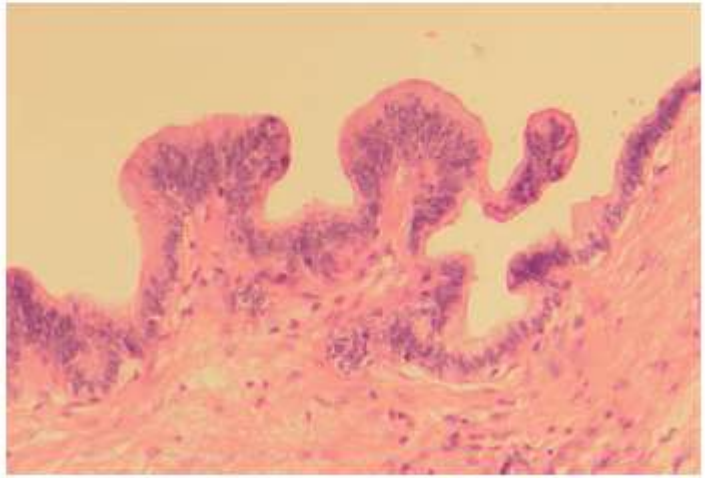


Figure 5. Pancreatic intraepithelial neoplasia (PanIN)-2: papillary architecture with pseudostratified tall columnar epithelium.

A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas

Olca Basturk, MD, Seung-Mo Hong, MD, PhD,† Laura D. Wood, MD, PhD,‡ N. Volkan Adsay, MD,§ Jorge Albores-Saavedra, MD,‖ Andrew V. Biankin, MD,¶ Lodewijk A.A. Brosens, MD, PhD,# Noriyoshi Fukushima, MD,** Michael Goggins, MD,‡ Ralph H. Hruban, MD,‡ Yo Kato, MD,†† David S. Klimstra, MD,* Günter Klöppel, MD,‡‡ Alyssa Krasinskas, MD,§ Daniel S. Longnecker, MD,§§ Hanno Matthaei, MD,‖‖ G. Johan A. Offerhaus, MD, PhD,# Michio Shimizu, MD,¶¶ Kyoichi Takaori, MD, PhD,## Benoit Terris, MD,*** Shinichi Yachida, MD, PhD,††† Irene Esposito, MD,‡‡‡ and Toru Furukawa, MD, PhD§§§*

Abstract: International experts met to discuss recent advances and to revise the 2004 recommendations for assessing and reporting precursor lesions to invasive carcinomas of the pancreas, including pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm, and other lesions. Consensus recommendations include the following: (1) To improve concordance and to align with practical consequences, a 2-tiered system (low vs. high grade) is proposed for all precursor lesions, with the provision that the current PanIN-2 and neoplasms with intermediate-grade dysplasia now be categorized as low grade. Thus, "high-grade dysplasia" is to be reserved for only the uppermost end of the spectrum ("carcinoma in situ"–type lesions). (2) Current data indicate that PanIN of any grade at a margin of a resected pancreas with invasive carcinoma does not have prognostic implications; the clinical significance of dysplasia at a margin in a resected pancreas with IPMN lacking invasive carcinoma remains to be determined. (3) Intraductal lesions 0.5 to 1 cm can be either large PanINs or small IPMNs. The term "incipient IPMN" should be reserved for lesions in this size with intestinal or oncocytic papillae or *GNAS* mutations. (4) Measurement of the distance between an IPMN and invasive carcinoma and sampling of intervening tissue are recommended to assess concomitant versus associated status. Conceptually, concomitant invasive carcinoma (in contrast with the "associated" group) ought to be genetically distinct from an IPMN elsewhere in the gland. (5) "*Intraductal spread of invasive carcinoma*" (aka, "colonization") is recommended to describe lesions of invasive carcinoma invading back into and extending along the ductal system, which may morphologically mimic high-grade PanIN or even IPMN. (6) "*Simple mucinous cyst*" is recommended to describe cysts >1 cm having gastric-type flat mucinous lining at most minimal atypia without ovarian-type stroma to distinguish them from IPMN. (7) Human lesions resembling the acinar to ductal metaplasia and atypical flat lesions of genetically engineered mouse models exist and may reflect an alternate pathway of carcinogenesis; however, their biological significance requires further study. These revised recom-

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TABLE 1. Proposed Revised Terminology of PanIN, IPMN, and MCN

Former Terminology (Based on 2004 Classification[2] and 2010 WHO)	Revised Terminology (2015)
PanIN-1a	Low-grade PanIN
PanIN-1b	Low-grade PanIN
PanIN-2	Low-grade PanIN
PanIN-3 (*carcinoma in situ*)	High-grade PanIN

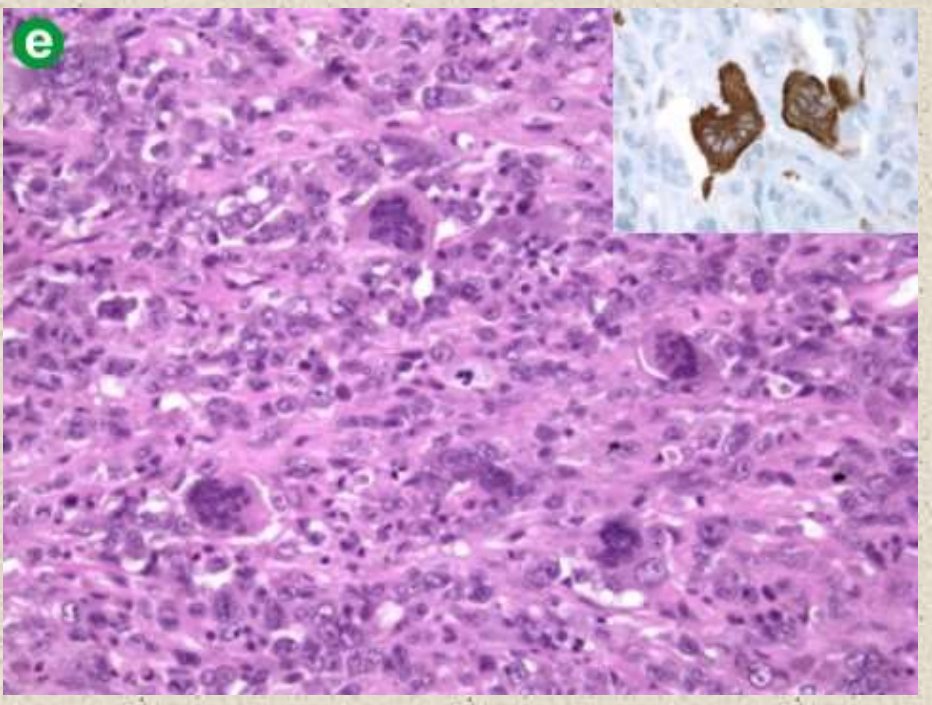
Pancreas

T1	**Tumour 2 cm or less**
	T1a Tumour 0.5 cm or less
	T1b Tumour greater than 0.5 cm and less than 1 cm
	T1c Tumor greater than 1 cm but no more than 2 cm
T2	**Tumour more than 2 cm but no more than 4 cm**
T3	**Tumour more than 4 cm in greatest dimension**
T4	**Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery**
N1	**Metastases in 1 to 3 nodes**
N2	**Metastases in 4 or more nodes**

M category unchanged

Stage			
Stage IA	**T1**	**N0**	**M0**
Stage IB	**T2**	**N0**	**M0**
Stage IIA	**T3**	**N0**	**M0**
Stage IIB	**T1, T2, T3**	**N1**	**M0**
Stage III	**T1, T2, T3**	**N2**	**M0**
	T4	**Any N**	**M0**
Stage IV	**Any T**	**Any N**	**M1**

T2	Tumour limited to the pancreas, more than 20 mm in greatest dimension
T3	Tumour extends beyond pancreas, but without involvement of coeliac axis or superior mesenteric artery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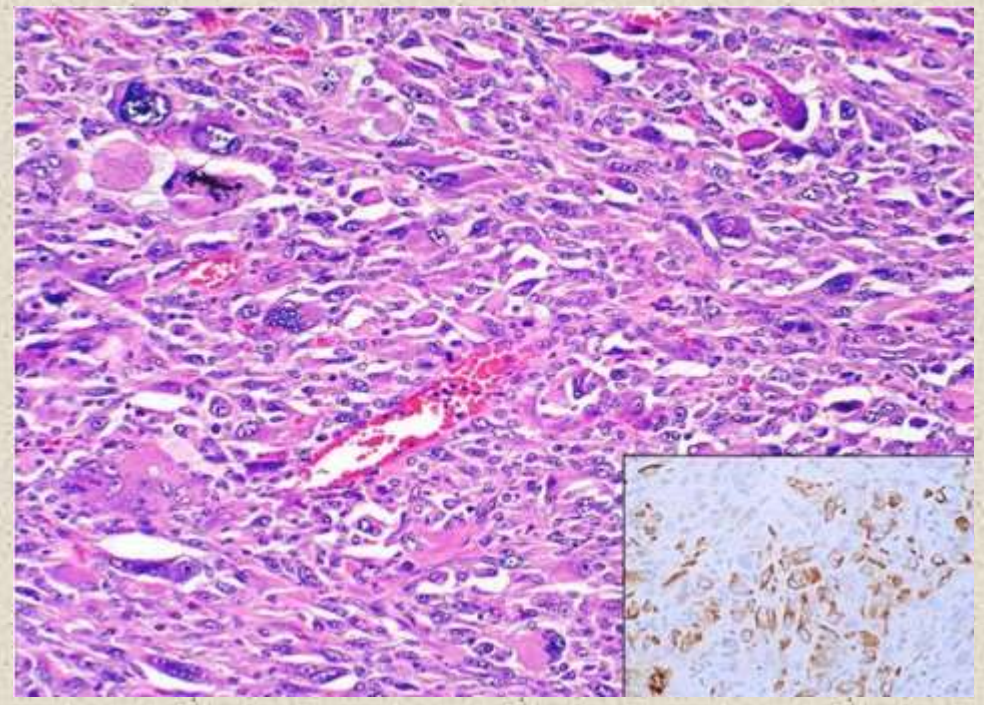
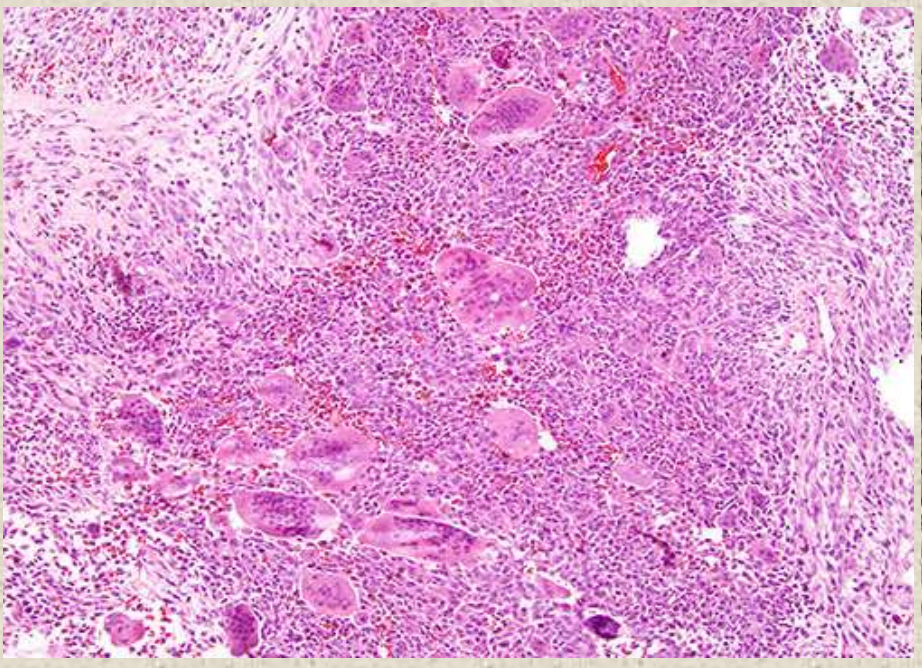
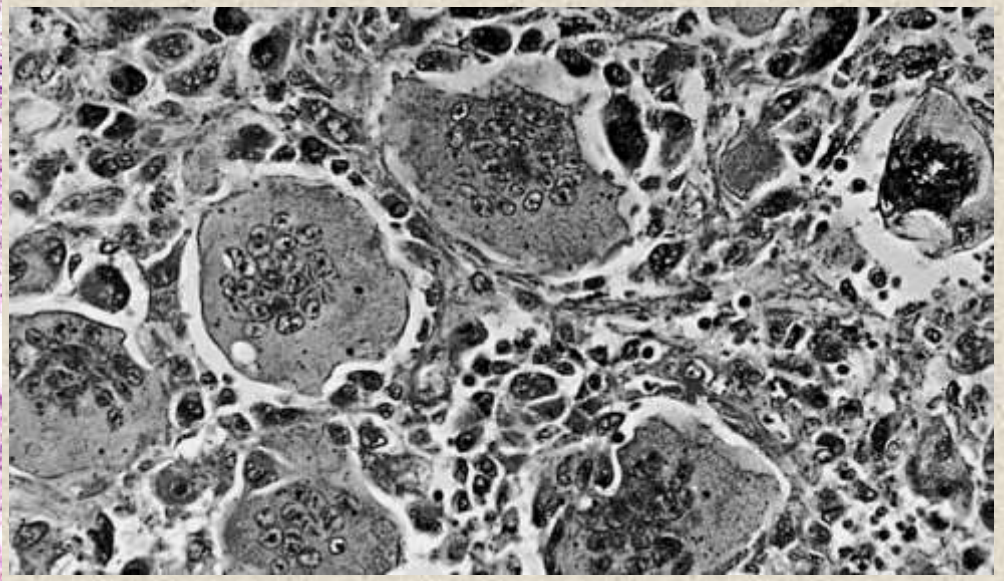






Case 16377/11

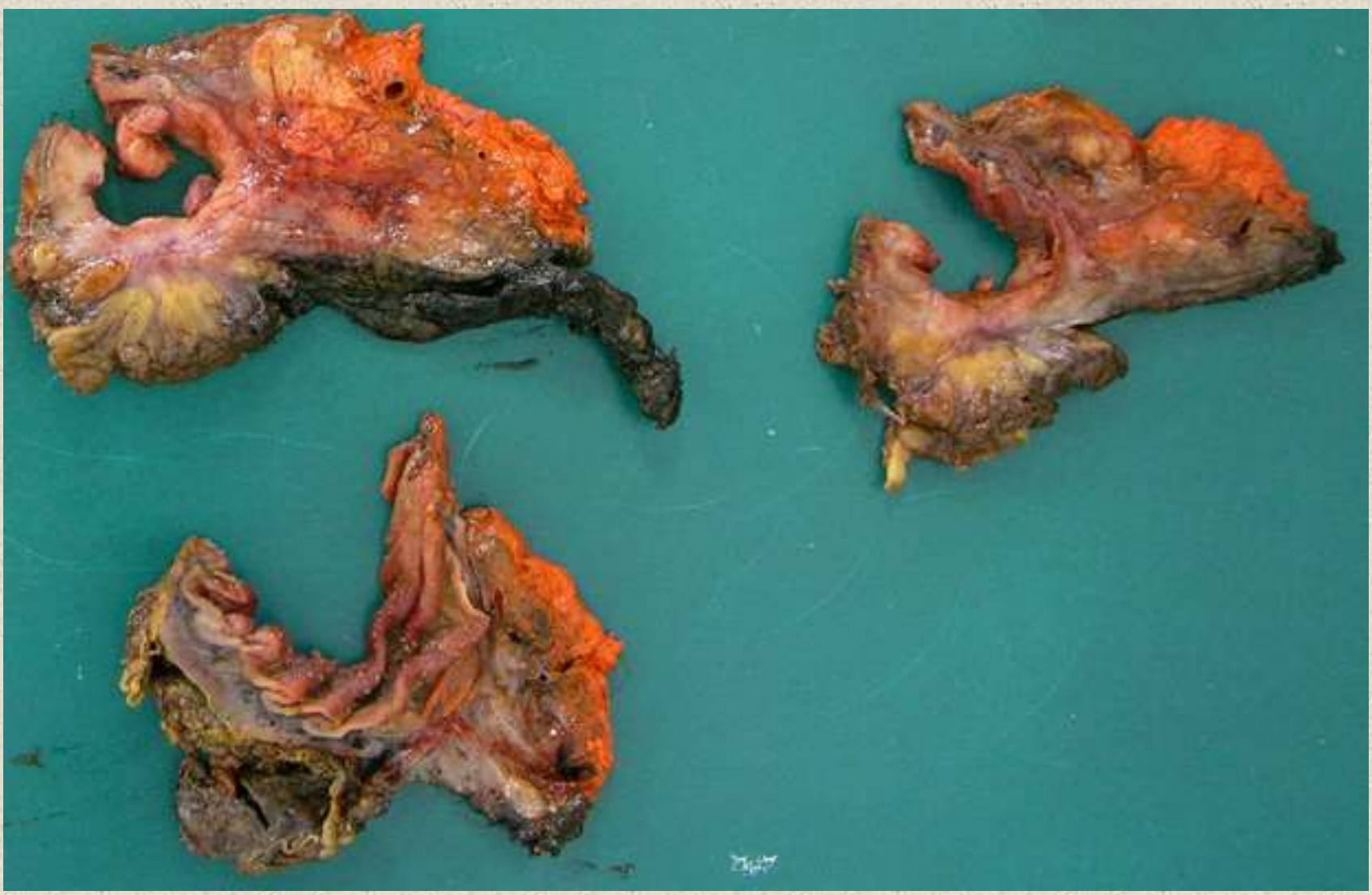
- Diagnosis:

Anaplastic (undifferentiated) carcinoma with osteoclast like giant cells

Case 16377/11

- Cytology
- May only show focal CK positivity
- Don't mistake for sarcoma or melanoma
- Poor prognosis

Case 13534/12



Case 13534/12

- Diagnosis:

Primary duodenal adenocarcinoma

Case 13534/12

- Primary duodenal adenocarcinoma, exclude:

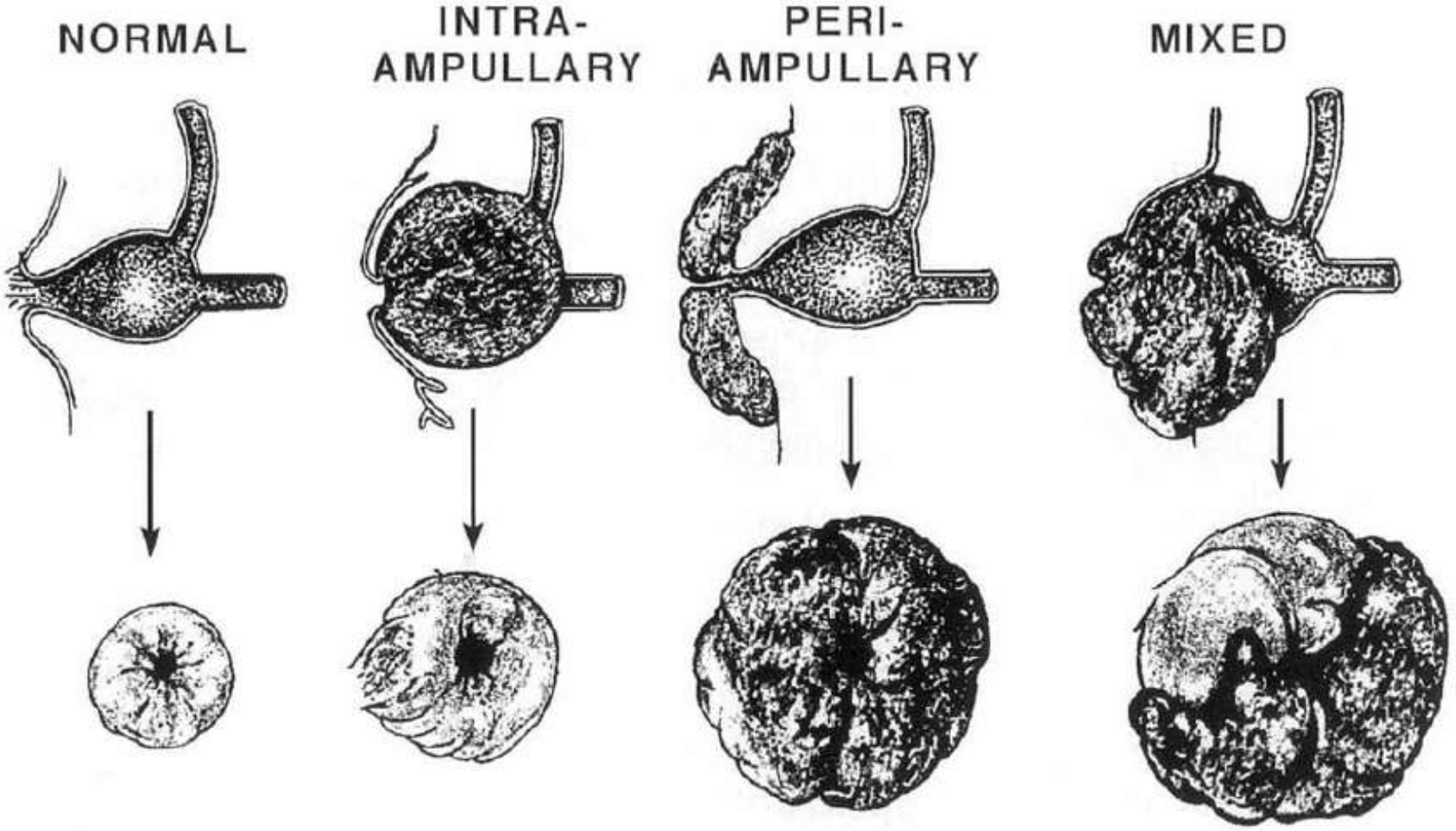
Case 13534/12

- Primary duodenal adenocarcinoma, exclude:
  - FAP
  - Coeliac disease
  - Crohn's disease

TNM8 Small intestinal

- pT
  - 1a: lamina propria / M mucosae
  - 1b: submucosa
  - 2: M propria
  - 3: subserosa / extramural
  - 4: peritoneum
- pN
  - 1: 1-2 nodes involed
  - 2: 3+ nodes involved

Cholangio vs. ampullary vs. PDAC vs. duodenal


NORMAL
INTRA-
AMPULLARY
PERI-
AMPULLARY
MIXED

Cholangio vs. ampullary vs. PDAC vs. duodenal

- Macro
- Micro – background dysplasia (e.g. adenoma, PanIN, IPMN)
- IHC not helpful (CK7, CK20, CDX2, CA125, MUCs)

- Ductal AdCa:
  - Adjuvant chemo (ESPAC4)
- Ampullary AdCa:
  - Adjuvant chemo (ESPAC4)
- Cholangioca:
  - Adjuvant chemo (BILCAP)
- Duodenal AdCa:
  - Don't know!

Case P7

- 64 **Female**
- Pancreatic cyst with cyst fluid showing CEA 5500, no prior history of acute pancreatitis. Mainly unilocular cyst measuring 110 mm in maximum diameter. This cyst is filled with tan coloured mucoid fluid and has a rough inner lining. At its distal (splenic) and posterior aspects, the cyst wall is particularly thickened and contains numerous small daughter cysts (measuring up to 5 mm in diameter).

Case P7

- Diagnosis:

Mucinous cystic neoplasm of pancreas

Mucinous cystic neoplasm of pancreas

- AKA:
  - Mucinous cystadenoma
  - Hepatobiliary or biliary cystadenoma [with mesenchymal stroma]

Mucinous cystic neoplasm of pancreas

- Young females
- Tail >>> Head
- Stroma less prominent in males (liver)
- Luteal-like cells (inhibin IHC)
- Malignant potential so complete excision

Case P2 (macro)

- 76 Female
- Cystic lesion in pancreatic body. ?Mucinous at EUS. A unilocular cyst which measures 34 x 30 x 25 mm. The cyst contains mucoid material. This cyst is surrounded by numerous cystically dilated ducts.

Case P2

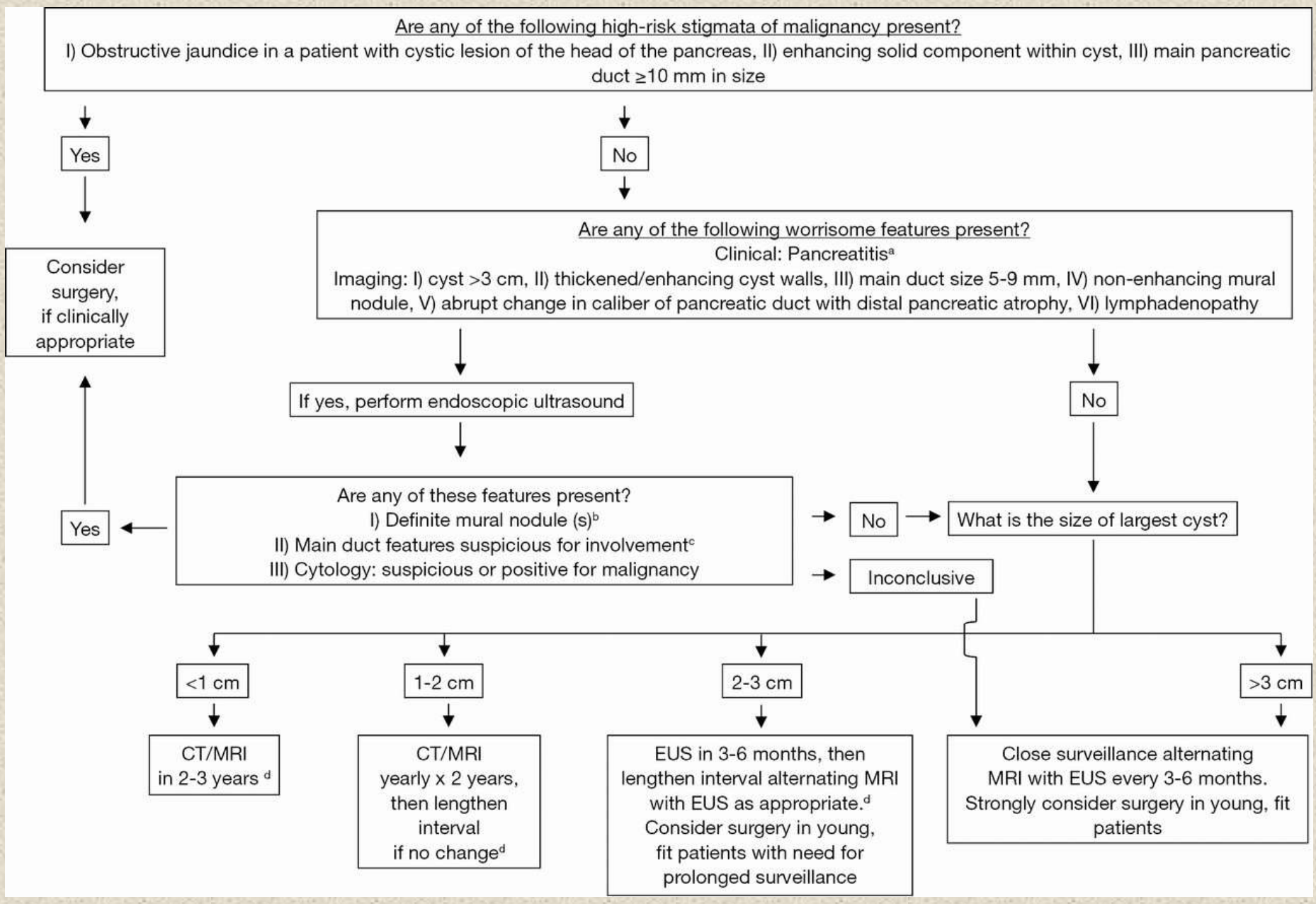
Case P2

- Diagnosis:

Intraductal papillary mucinous neoplasm (IPMN)

IPMN

- Main duct (higher malignant risk), side branch/duct or mixed duct
- Head > Tail
- Epithelial type (pancreaticobiliary, foveolar, intestinal)
- Grade (2 or 3 point scale)
- Premalignant


Are any of the following high-risk stigmata of malignancy present?
I) Obstructive jaundice in a patient with cystic lesion of the head of the pancreas, II) enhancing solid component within cyst, III) main pancreatic duct ≥10 mm in size
Yes
No
Consider surgery, if clinically appropriate
Are any of the following worrisome features present?
Clinical: Pancreatitis[a]
Imaging: I) cyst >3 cm, II) thickened/enhancing cyst walls, III) main duct size 5-9 mm, IV) non-enhancing mural nodule, V) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, VI) lymphadenopathy
If yes, perform endoscopic ultrasound
No
Yes
Are any of these features present?
I) Definite mural nodule (s)[b]
II) Main duct features suspicious for involvement[c]
III) Cytology: suspicious or positive for malignancy
No
What is the size of largest cyst?
Inconclusive
<1 cm
1-2 cm
2-3 cm
>3 cm
CT/MRI in 2-3 years [d]
CT/MRI yearly x 2 years, then lengthen interval if no change[d]
EUS in 3-6 months, then lengthen interval alternating MRI with EUS as appropriate.[d] Consider surgery in young, fit patients with need for prolonged surveillance
Close surveillance alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients

IPMN vs. PanIN

Histopathology 2010, **57**, 503–514. DOI: 10.1111/j.1365-2559.2010.03610.x

REVIEW

Pancreatic intraepithelial neoplasia – can we detect early pancreatic cancer?

Beate Haugk
Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Haugk B
(2010) *Histopathology* **57**, 503–514

Pancreatic intraepithelial neoplasia – can we detect early pancreatic cancer?

Pancreatic cancer is one of the most lethal cancers, with an incidence equalling mortality. Pancreatic cancer is a heterogeneous group in which pancreatic ductal adenocarcinoma (PDAC) is the most common. It is now established that PDAC develops through stepwise progression from precursor lesions. Detection and treatment of these precursor lesions would allow curative treatment. Three precursor lesions for PDAC have been identified. Two of these – mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) – are rare, radiologically detectable, cystic precursor lesions which can be cured if treated at the preinvasive stage. The third and most common precursor lesion has recently been defined as pancreatic intraepithelial neoplasia (PanIN). PanINs are microscopic lesions with no clinical correlate. They display a spectrum of cyto-architectural changes (PanIN-1, PanIN-2 and PanIN-3) mirrored in an increasing accumulation of molecular genetic changes, with PanIN-3 sharing many of the alterations with PDAC. Great advances in the understanding of pancreatic carcinogenesis have opened avenues for diagnosis and chemoprevention. However, access to the pancreas is limited, molecular tests are at the early stages and too little is known about the natural history of early PanINs to justify resection. Currently, screening focuses upon high-risk individuals only.

Table 1. Precursor lesions of pancreatic ductal adenocarcinoma

	Mucinous cystic neoplasms MCNs	Intraductal papillary mucinous neoplasms IPMNs	Pancreatic intraepithelial neoplasia PanINs
Average age (years)	40–50	60–70	Increasing with age
Gender	Almost exclusively female	Male > female	Male = female
Location in pancreas	Tail and body	Head >> body/tail	Head > body/tail
Macroscopic features	Grossly cystic	Grossly cystic with papillae Usually >10 mm	Usually not grossly visible Usually <5 mm
	Mucoid contents	Mucoid contents	
	No connection to duct	Connected to main and/or branch duct	
Microscopic features	Mucinous epithelium	Mucinous epithelium (gastric, intestinal, pancreatico-biliary, oncocytic type)	Mucinous epithelium (gastric foveolar type)
	Ovarian type stroma	Collagenous stroma	Periductal collagenous stroma
WHO-classification	MCN: adenoma (mild dysplasia) MCN: borderline (moderate dysplasia)	IPMN: adenoma (mild dysplasia) IPMN: borderline (moderate dysplasia)	PanIN-1A and PanIN-1B PanIN-2
	MCN: carcinoma *in-situ* (severe dysplasia)	IPMN: carcinoma *in-situ* (severe dysplasia)	PanIN-3
	MCN: invasive carcinoma	IPMN: invasive carcinoma	PDAC

IPMN, Intraductal mucinous neoplasm; MCN, mucinous cystic neoplasm; PanIN, pancreatic intraepithelial neoplasia.

A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas

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Abstract: International experts met to discuss recent advances and to revise the 2004 recommendations for assessing and reporting precursor lesions to invasive carcinomas of the pancreas, including pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm, and other lesions. Consensus recommendations include the following: (1) To improve concordance and to align with practical consequences, a 2-tiered system (low vs. high grade) is proposed for all precursor lesions, with the provision that the current PanIN-2 and neoplasms with intermediate-grade dysplasia now be categorized as low grade. Thus, "high-grade dysplasia" is to be reserved for only the uppermost end of the spectrum ("carcinoma in situ"–type lesions). (2) Current data indicate that PanIN of any grade at a margin of a resected pancreas with invasive carcinoma does not have prognostic implications; the clinical significance of dysplasia at a margin in a resected pancreas with IPMN lacking invasive carcinoma remains to be determined. (3) Intraductal lesions 0.5 to 1 cm can be either large PanINs or small IPMNs. The term "incipient IPMN" should be reserved for lesions in this size with intestinal or oncocytic papillae or *GNAS* mutations. (4) Measurement of the distance between an IPMN and invasive carcinoma and sampling of intervening tissue are recommended to assess concomitant versus associated status. Conceptually, concomitant invasive carcinoma (in contrast with the "associated" group) ought to be genetically distinct from an IPMN elsewhere in the gland. (5) "*Intraductal spread of invasive carcinoma*" (aka, "colonization") is recommended to describe lesions of invasive carcinoma invading back into and extending along the ductal system, which may morphologically mimic high-grade PanIN or even IPMN. (6) "*Simple mucinous cyst*" is recommended to describe cysts >1 cm having gastric-type flat mucinous lining at most minimal atypia without ovarian-type stroma to distinguish them from IPMN. (7) Human lesions resembling the acinar to ductal metaplasia and atypical flat lesions of genetically engineered mouse models exist and may reflect an alternate pathway of carcinogenesis; however, their biological significance requires further study. These revised recom-

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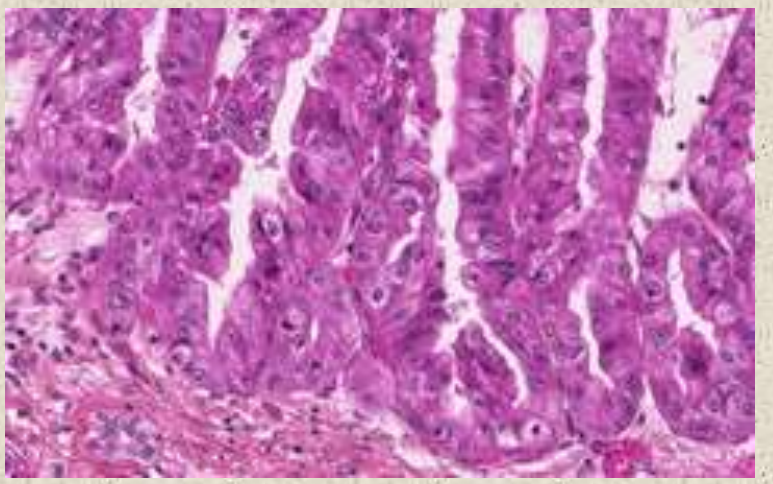
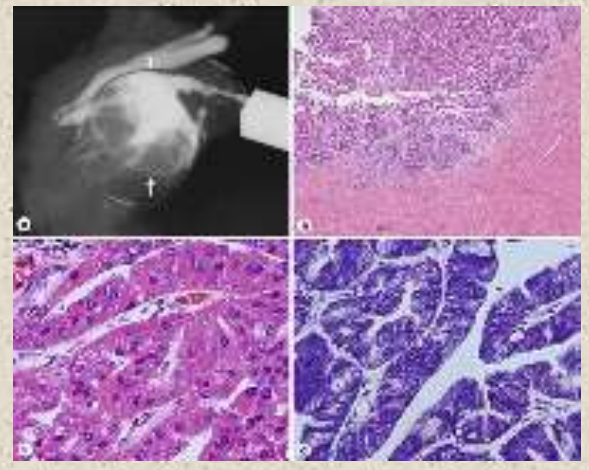
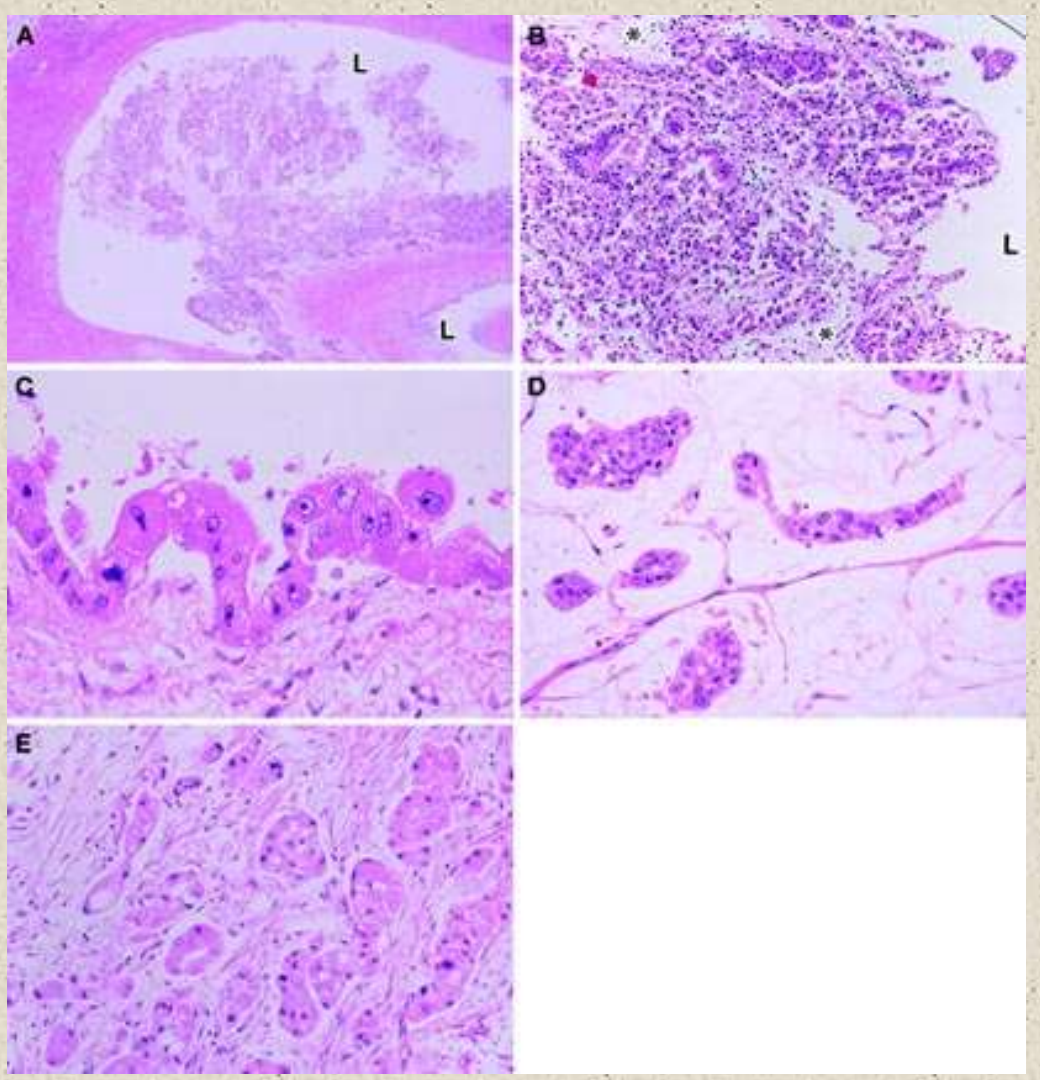
Intraductal oncocytic papillary neoplasm (IOPN)

- Variant of IPMN
- Cytology (mistaken for acinar cell carcinoma)
- Gives rise to …

Intraductal oncocytic papillary neoplasm (IOPN)







Case 16104/12

- Diagnosis:

Colloid/oncocytic carcinoma of pancreas

Colloid / oncocytic carcinoma

- Various combinations of colloid (mucinous) and oncocytic features
- Colloid arise from IPMN or MCN?
- Oncocytic arise from IOPN?
- Colloid ca – better prognosis?

Case P8

- 69 Male
- Main body of pancreas tumour - ?neuroendocrine. A lobulated tumour measuring 45 x 25 x 25 mm. This tumour has a central scar but shows otherwise a uniform spongy cut surface with neither haemorrhage nor necrosis.

Case P8

- Diagnosis:

Microcystic serous cystadenoma of pancreas

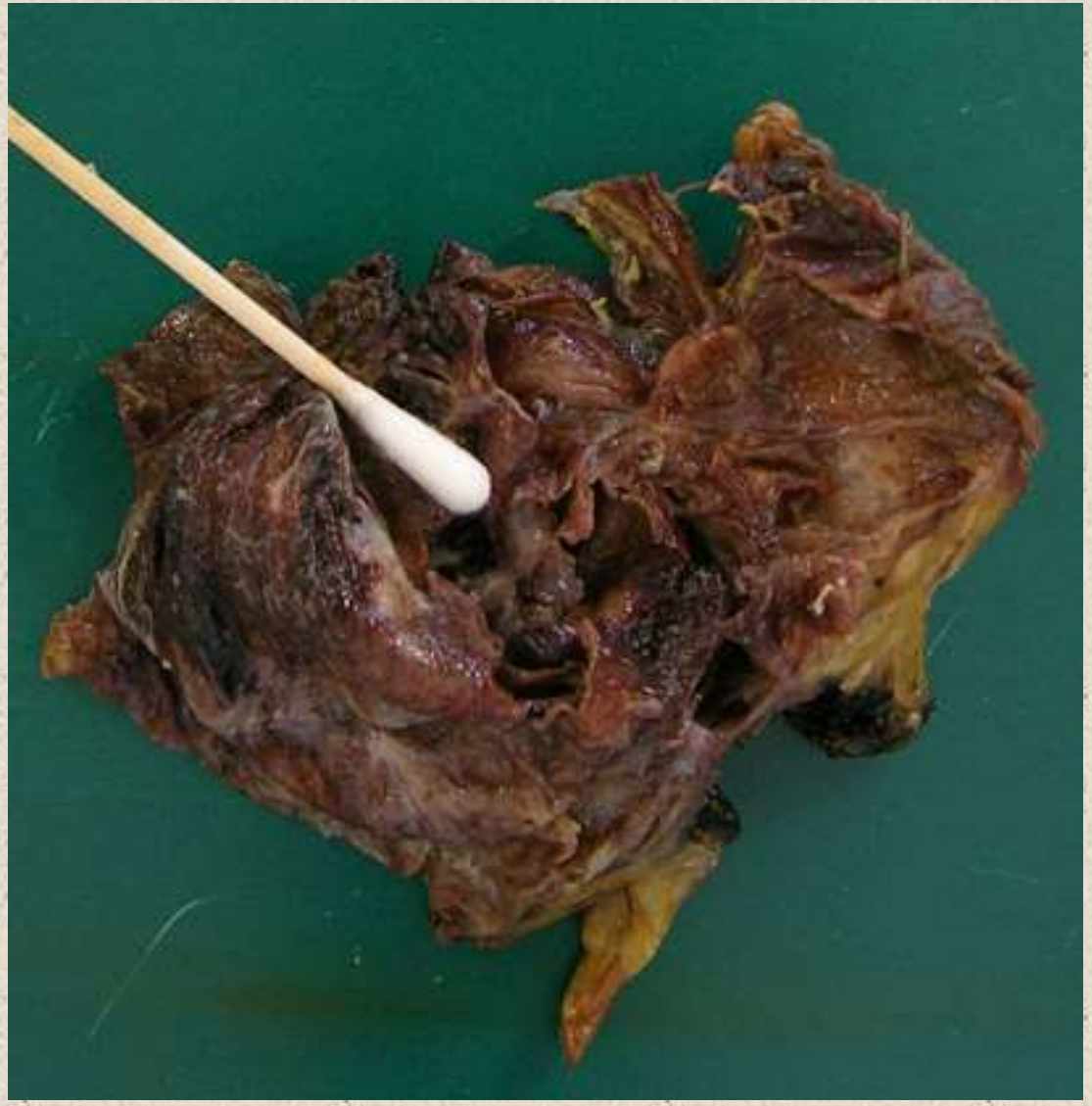
Serous cystadenoma of pancreas

- Microcystic (1 cm) / Macro or Oligocystic / Unicystic / Solid
- Central scar
- Clear glycogen rich cyto, cuboidal
- Inhibin +ve
- Monomorphic dark nuclei
- ‘Benign’ but malignant and locally aggressive variants

Case P6

- 45 Male
- Distal pancreatectomy (spleen preserving) for pancreatic cystic tumour. Cyst fluid showed raised CEA so ?mucinous cystadenoma. The distal two thirds of the tail is replaced by a complex (due to infolding of the wall) but apparently unilocular cyst which contains white material.

Case P6



Case P6

- Diagnosis:

Lymphoepithelial cyst of pancreas

Lymphoepithelial cyst of pancreas

- Extra-pancreatic
- Male 50+
- Why? (Not HIV related)
- Elevated cyst fluid CEA level (mesenteric/mesothelial cyst)
- DD: Dermoid cyst, splenic epidermoid cyst

Case P9

- 74 Male
- Further piece of wall of cystic lesion next to pancreas. Fibrous tissue fragment measuring 10 x 9 x 3 mm.

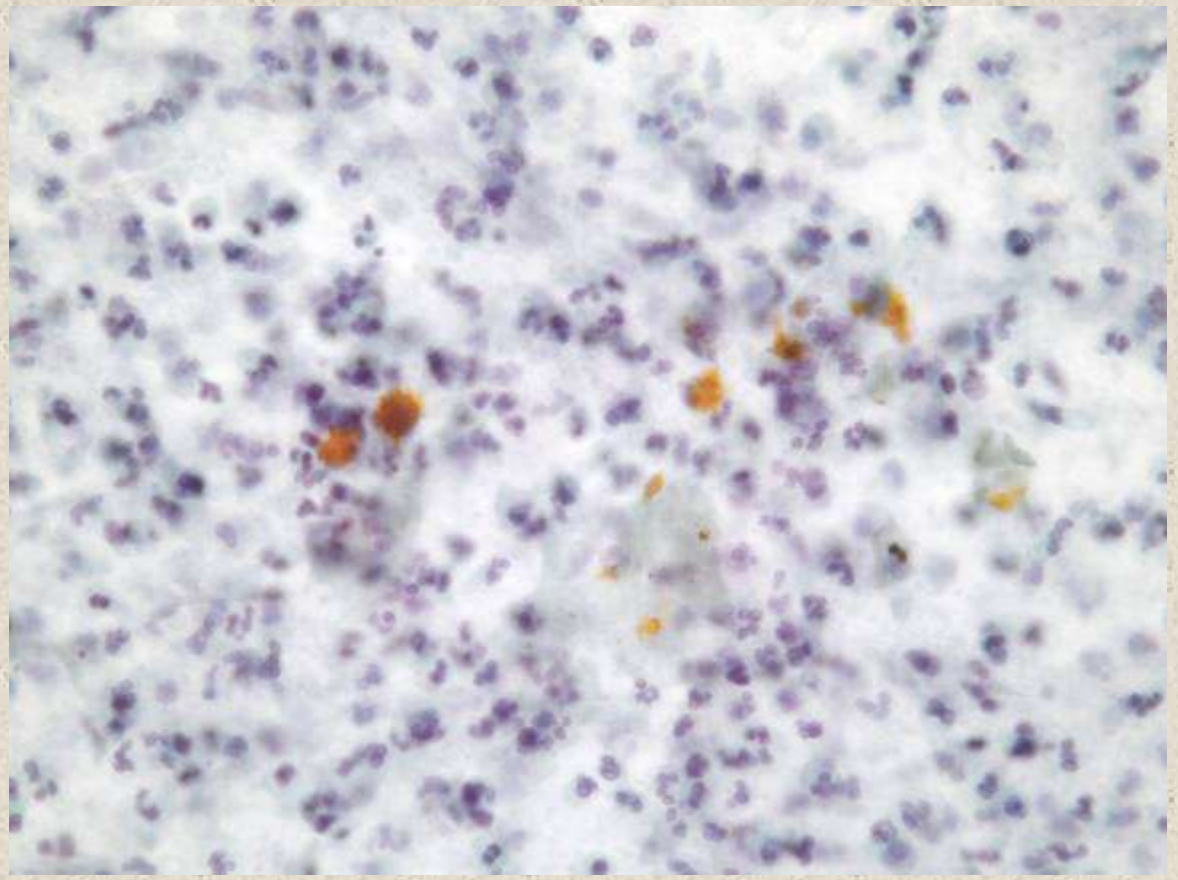
Case P9

- Diagnosis:

Pancreatic pseudocyst

Pseudocyst

- Chronic pancreatitis
- Cytology



Characteristic	Pseudocyst	Serous Cyst	Mucinous Cyst	IPMN
Epidemiology				
Gender	F=M	F>>M (4/1)	F>>>M(10/1)	F=M
Age	40-60	60-70	50-60	60-70
Image Findings				
Location	Anywhere	Anywhere	Body and Tail>>> Head	Head> diffuse > body tail
Appearance	Rounded, thick walled, atrophy, calcification pancreatitis	Beehive shaped multicystic, central calcification	Septated macrocysts, mural nodules	Lobulated, contact with duct. Polycystic.
Connects to ducts	Yes	No	Very rare	Yes
Fluid Analysis				
Cytology	Inflammatory	Glycogen rich, cuboidal cells	Mucin rich, columnar cells	Mucin rich, columnar cells
Mucin	Negative	Negative	Positive	Positive
Amylase	Very high	Low	Low	High
CEA	Low	Low	High	High
Glucose	**Not reduced**	**Not reduced**	**Reduced**	**Reduced**

Case P4

- 57 Female
- Lesion on CT suggested being in distal pancreas. At surgery palpable lesion. A well circumscribed nodule within the pancreatic tail which measures 9 x 8 x 8 mm.

Case P4

- Diagnosis:

Neuroendocrine tumour of pancreas

Pancreatic NET

- Hormone IHC (insulin, glucagon, somatostatin, VIP)
- Grading and staging:
  - BSG guidelines 2012
  - RCPath dataset 2012

The Royal College of Pathologists

Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for neuroendocrine tumours of the gastrointestinal tract including pancreas (3rd edition)

Authors: Professor Timothy J Stephenson, Sheffield Teaching Hospitals
Dr Simon S Cross, The University of Sheffield,
Professor Runjan Chetty, Oxford University

Unique document number	G081
Document name	Dataset for neuroendocrine tumours of the gastrointestinal tract including pancreas
Version number	3
Produced by	Professor Timothy J Stephenson, Sheffield Teaching Hospitals; Dr Simon S Cross, Sheffield University and Professor Runjan Chetty, Oxford University, on behalf of the College's Cancer Services Working Group. The authors are consultant or honorary consultant histopathologists, actively engaged in the diagnosis and multidisciplinary care of patients with neuroendocrine tumours, and in the professional associations that promote research and guideline development on their diagnosis and treatment.
Date active	September 2012

Appendix I WHO 2000/2004 classification of gastrointestinal[6] and pancreatic neuroendocrine tumours[14]

Site	Well-differentiated neuroendocrine tumour (Benign behaviour)*	Well-differentiated neuroendocrine tumour (Uncertain behaviour)	Well-differentiated neuroendocrine carcinoma (Low-grade malignant)	Poorly differentiated neuroendocrine carcinoma (High-grade malignant)
Pancreas	Confined to pancreas Functioning insulinoma <20 mm Non-functioning tumours <20 mm No vascular invasion No perineural invasion <2 mitoses/10 HPF/Ki-67 index ≤2%	Confined to pancreas and one or more of the following: ≥20 mm Perinneural invasion Vascular invasion 2–10 mitoses/10 HPF/Ki-67 index >2%	Invasion of adjacent organs presence of metastases	High grade, poorly differentiated large cell, intermediate cell or small cell carcinoma. Ki-67 index >30%

Table 2 Grading system for gastrointestinal neuroendocrine tumours[20-24]

Grade	Mitotic count (10 HPF)*	Ki-67 index (%)**
G1	<2	≤2 (5)***
G2	2–20	>2 (5)***–20
G3	>20	>20

* 10 HPF = 2 mm^2 based on each hpf being 0.2 mm^2 with at least 40 fields evaluated in areas at highest mitotic density.

** Ki-67 index: % of tumour cells in a 2000 cell sample from the areas of highest nuclear labelling.

*** Note that the exception to the 2% MIB1 threshold is the pancreas. A large study[24] showed that when a 5% rather than 2% Ki-67 labelling index cut-off was applied, Ki-67 was an independent predictor of prognosis.

24. Scarpa A, Mantovani W, Capelli P, Beghelli S, Boninsegna L, Bettini R *et al*. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol* 2010;23:824–833.

Gut 2012;**61**:6–32. doi:10.1136/gutjnl-2011-300831

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)

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ABSTRACT

These guidelines update previous guidance published in 2005. They have been revised by a group who are members of the UK and Ireland Neuroendocrine Tumour Society with endorsement from the clinical committees of the British Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland (and its Surgical Specialty Associations), the British Society of Gastrointestinal and Abdominal Radiology and others. The authorship represents leaders of the various groups in the UK and Ireland Neuroendocrine Tumour Society, but a large amount of work has been carried out by other specialists, many of whom attended a guidelines conference in May 2009. We have attempted to represent this work in the acknowledgements section. Over the past few years, there have been advances in the management of neuroendocrine tumours, which have included clearer characterisation, more specific and therapeutically relevant diagnosis, and improved treatments. However, there remain few randomised trials in the field and the disease is uncommon, hence all evidence must be considered weak in comparison with other more common cancers.

syndrome should be suspected. Level of evidence 4, Grade of recommendation C.

- In all patients, secondary tumours and other gut cancers should be considered. Level of evidence 4, Grade of recommendation C.

Diagnosis (biochemical measurements)

If a patient presents with symptoms suspicious of a gastroenteropancreatic NET:

- Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoleacetic acid. Level of evidence 3, Grade of recommendation C.
- Specific biochemical tests should be requested depending on which syndrome is suspected. Level of evidence 3, Grade of recommendation C.

Imaging

- For detecting the primary tumour a multimodality approach is best. CT, MRI and somatostatin receptor scintigraphy (SSRS) are recommended. Gallium-68 (^{68}Ga) positron emission tomography (PET)/CT is recommended for the detection of an unknown primary. Level of evidence 3, Grade of recommendation A/B.
- Additional imaging modalities may include

APPENDIX 5

PATHOLOGY

The cut-off values for mitotic count and Ki-67 index of the WHO 2010 grading scheme[6] are identical to those of the ENETS grading system[8, 9] and defined as follows (Table 4) :

- G1: mitotic count <2 mitoses/10 HPF and/or Ki-67 index ≤ 2%
- G2: mitotic count 2-20 mitoses/10 HPF and/or Ki-67 index 3-20%
- G3: mitotic count >20 mitoses/10 HPF and/or Ki-67 index >20%.

Table 1. WHO 2010 classification of gastroenteropancreatic NETs.[6]

1. Neuroendocrine tumour (NET) G1
2. Neuroendocrine tumour (NET) G2
3. Neuroendocrine carcinoma (NEC; G3; large cell or small cell type)
4. Mixed adenoneuroendocrine carcinoma (MANEC)

Table 2. TNM staging criteria for NETs of the digestive tract and pancreas according to UICC TNM 7th edition.[10]

	pT1	T2	T3	T4
				organs
Pancreas	Limited to pancreas and size <2 cm	Limited to pancreas And size >2 cm	Outside pancreas but no invasion of coeliac axis/SMA any size	Invasion of coeliac axis / SMA

Table 3. TNM staging criteria for NETs of the stomach, appendix and pancreas according to the ENETS system.[8, 9]

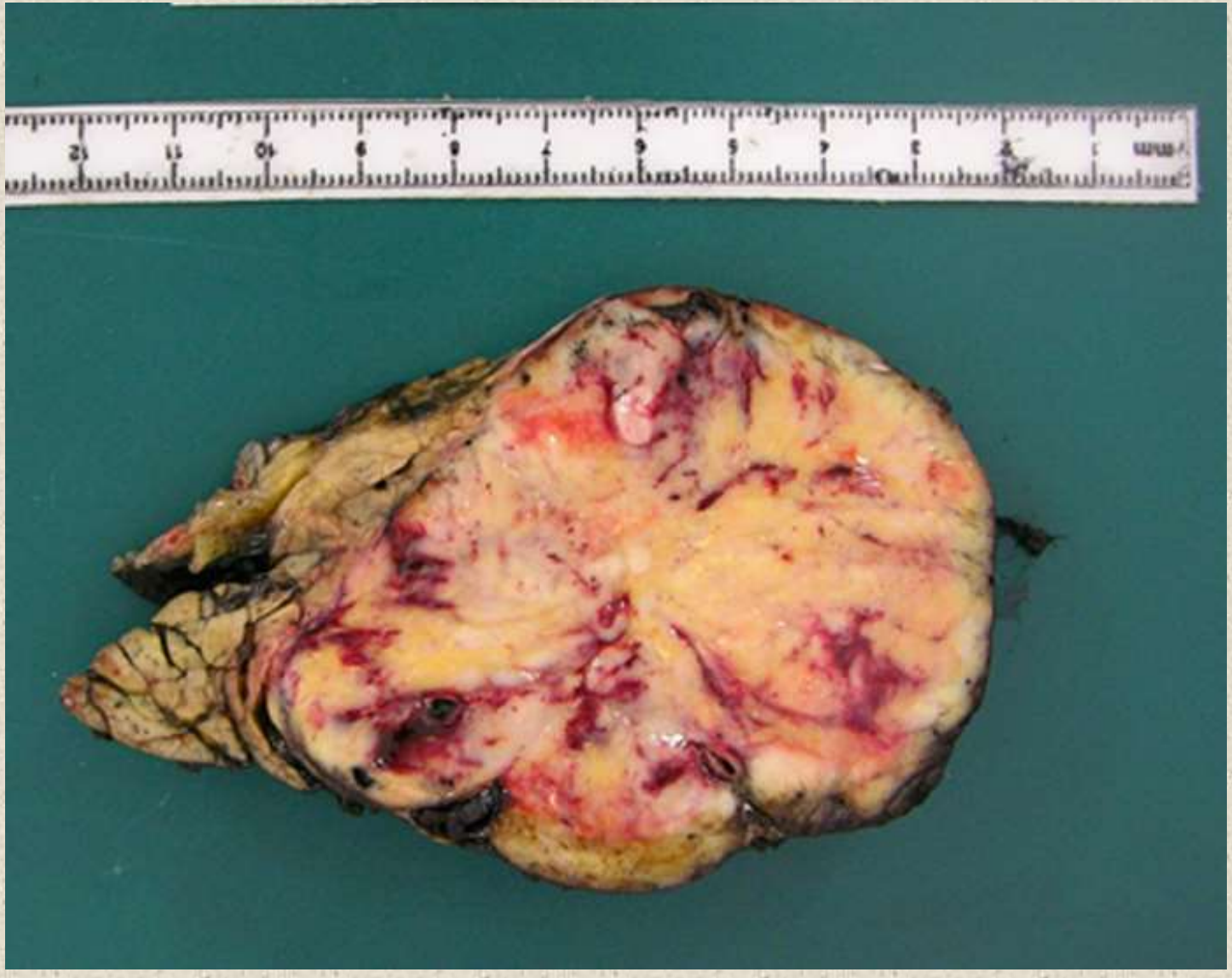
	pT1	T2	T3	T4
Pancreas	Limited to pancreas and size <2 cm	Limited to pancreas and size 2–4 cm	Limited to pancreas and size >4 cm or invasion of duodenum or bile duct	Invasion of coeliac axis / SMA, stomach, spleen, colon, or adrenal gland

TNM8: same same same same + serosal breach

Case P1 (macro)

- 47 Male
- Known FAP patient. ?desmoid tumour in tail of pancreas. A well circumscribed tumour measuring 9 x 8 x 6 cm. The tumour shows a white/yellow cut surface with widespread haemorrhage.

Case P1



Case P1

- Diagnosis:

Solid pseudopapillary neoplasm of pancreas

	Acinar Cell Ca	Pancreatic NET	Solid Pseudopapillary Neoplasm
Keratin	++	+ +	−/+
Vimentin	−	−	+ +
Trypsin	++	−	−
Chromogranin	−	+ +	−
Synaptophysin	−	+ +	+
CD56	−	+ +	+ +
a_1-Antitrypsin	+	−/+	+ +
CEA	−	+	−
Nuclear Beta catenin	−	−	+ +

(also dot like CD10 +ve and PR +ve)

−, usually negative; −/+, usually negative, may be positive; +, often positive; + +, consistently positive.

Solid Pseudopapillary Neoplasm

- Younger females
- 10-15% metastasis
- Link with FAP? (germline *APC* mutation vs. *CTNNB1* mutation in SPPN)

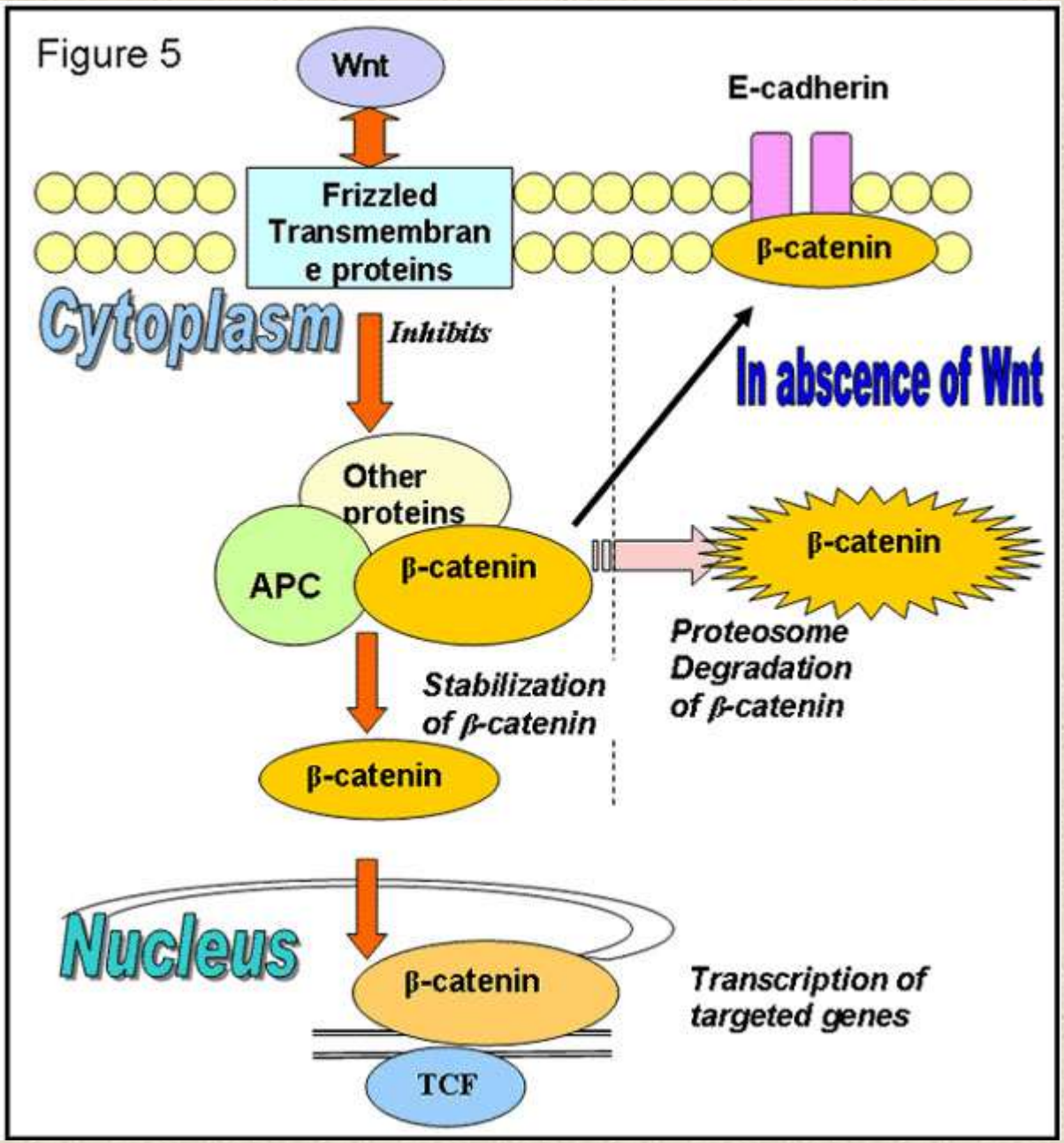


Figure 5
Wnt
E-cadherin
Frizzled Transmembrane proteins
β-catenin
Cytoplasm
Inhibits
In abscence of Wnt
Other proteins
APC
β-catenin
β-catenin
Proteosome Degradation of β-catenin
Stabilization of β-catenin
β-catenin
Nucleus
β-catenin
Transcription of targeted genes
TCF

Case P11

- 70 Female
- Mass in pancreatic body. Vascular on EUS. ?Neuroendocrine tumour. EUS-FNA performed.

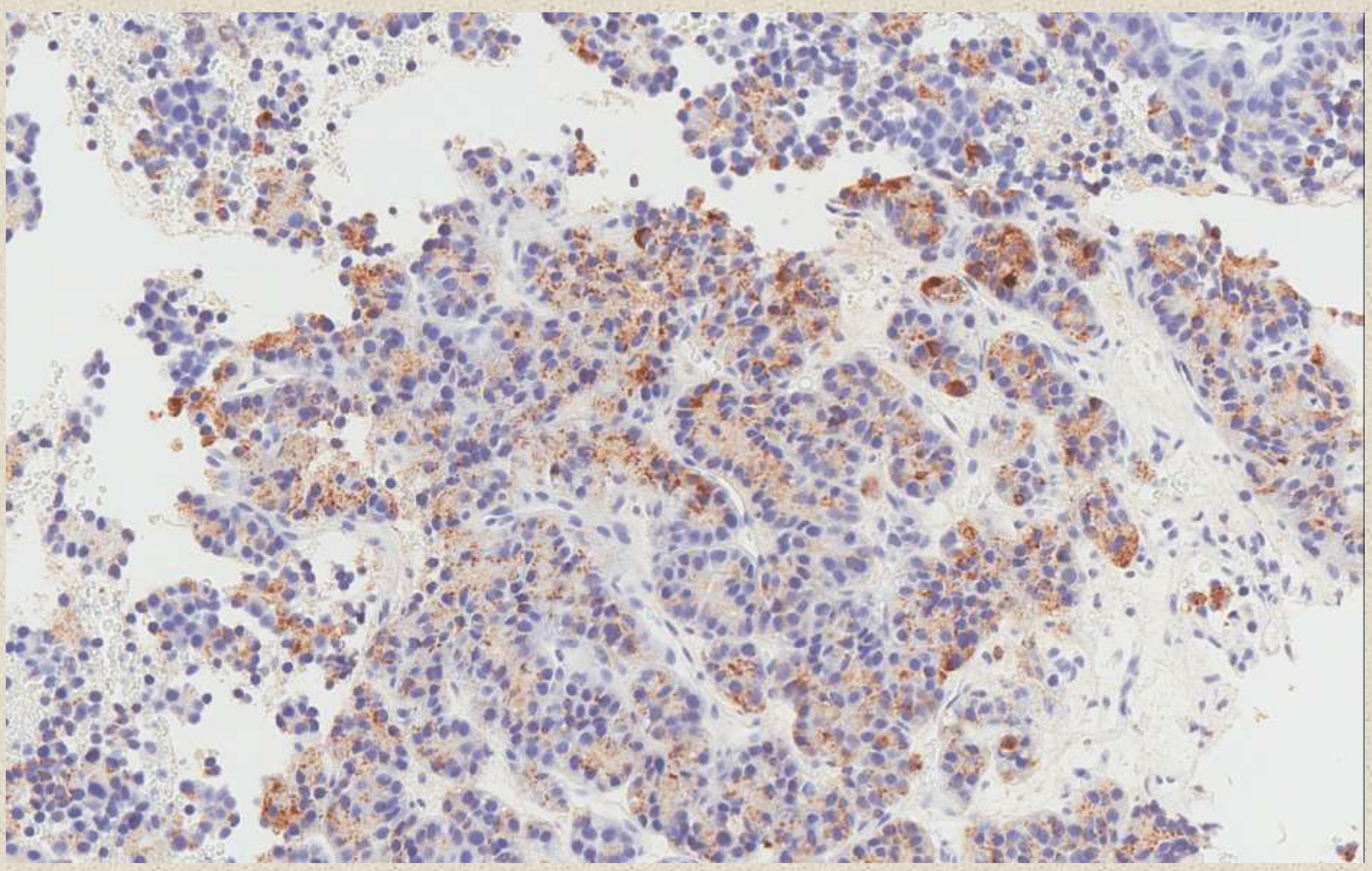
Case P11

- Diagnosis:

Acinar cell carcinoma of pancreas

	Acinar Cell Ca	Pancreatic NET	Solid Pseudopapillary Neoplasm
Keratin	++	+ +	−/+
Vimentin	−	−	+ +
Trypsin	++	−	−
Chromogranin	−	+ +	−
Synaptophysin	−	+ +	+
CD56	−	+ +	+ +
a_1-Antitrypsin	+	−/+	+ +
CEA	−	+	−
Nuclear Beta catenin	−	−	+ +
DPAS+ cyto	++	−	−

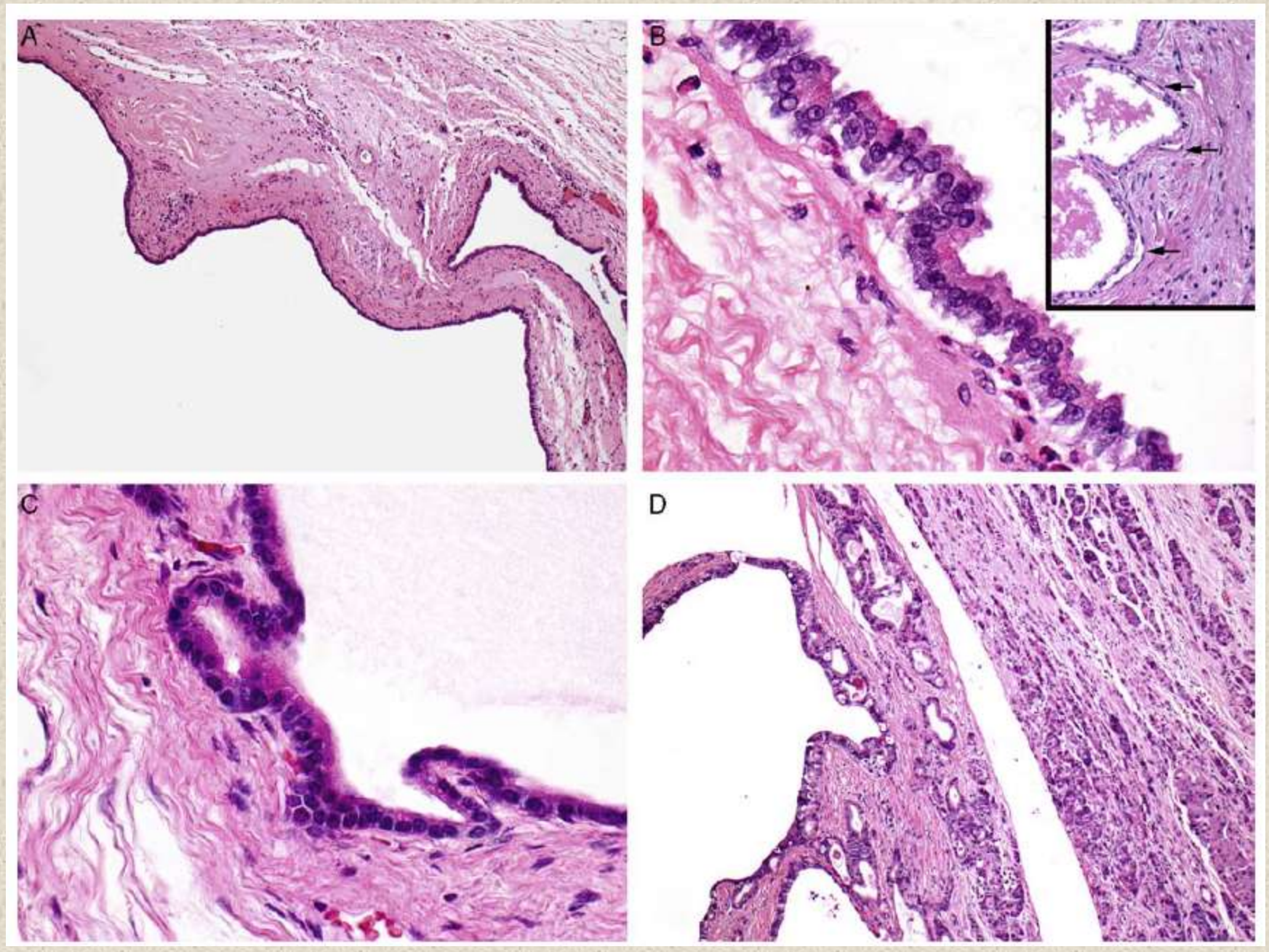
−, usually negative; −/+, usually negative, may be positive; +, often positive; + +, consistently positive.

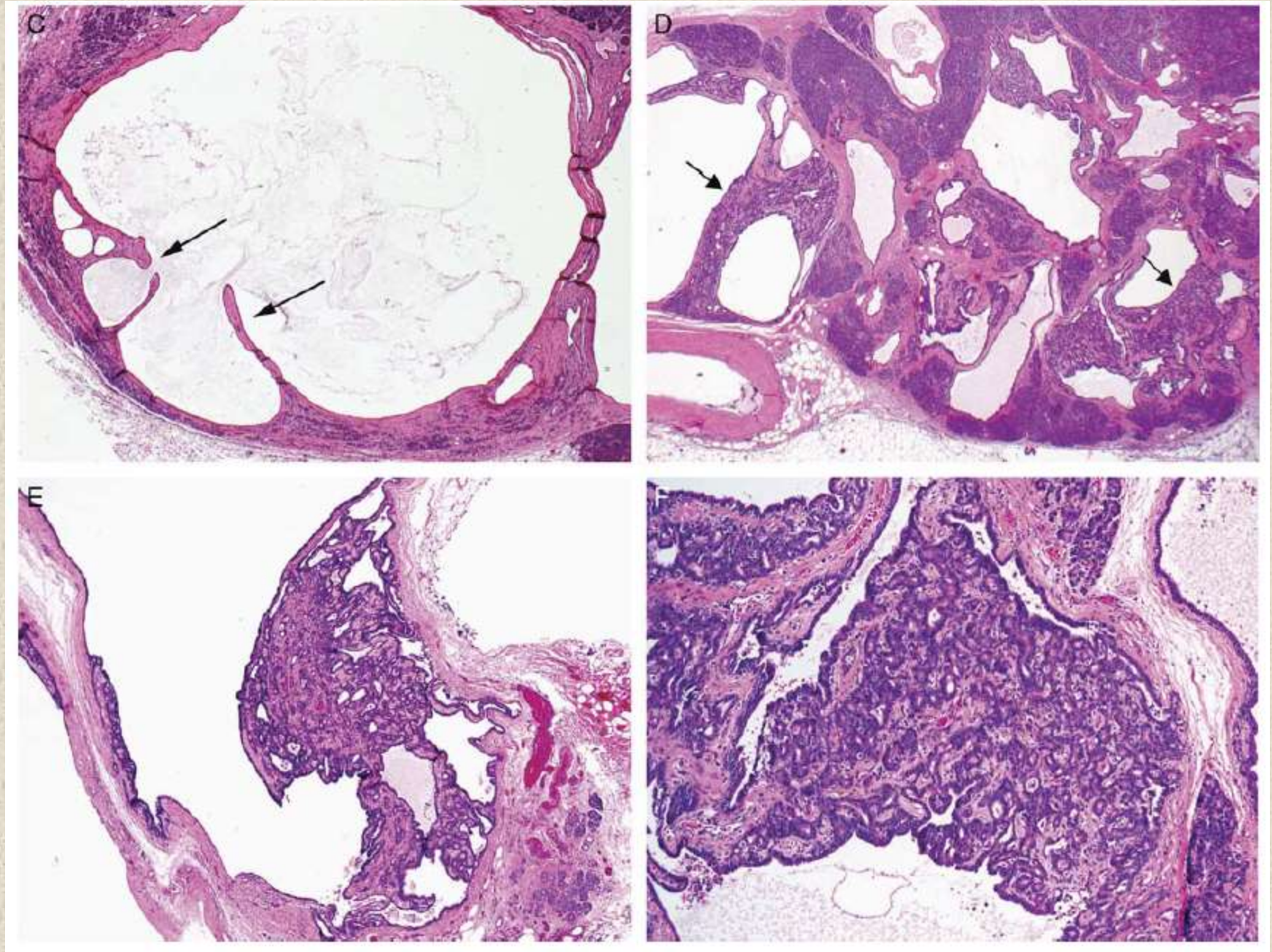


Acinar cell carcinoma

- Older males
- Poor prognosis
- Cystic variant:

  Acinar cell cystadenoma or cystadenocarcinoma


A
B
C
D


C
D
E
F

Case P10

- 64 Male
- Larger lesion in neck of pancreas, enucleated. Smaller lesion in tail of pancreas. A 6 mm diameter nodule is present close to the proximal end of the specimen.

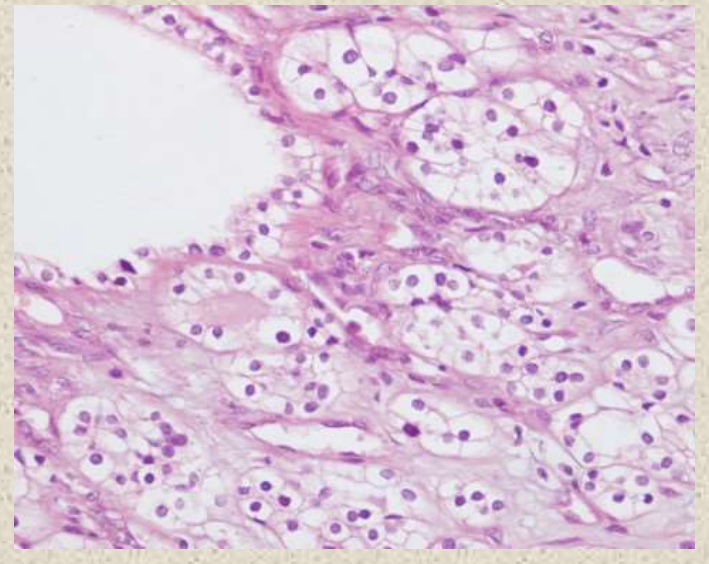
Case P10

- Diagnosis:

Metastatic renal cell carcinoma

Secondary neoplasms

- RCC (cw. Solid serous cystadenoma)



- Melanoma
- Colorectal carcinoma