Pathology of the pancreas

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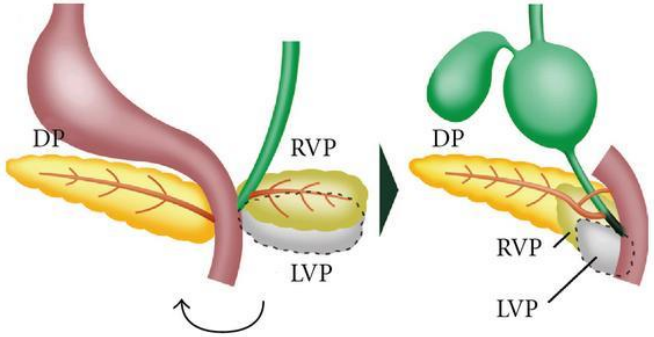
Outline of the lecture

1. Developmental/congenital anomalies
2. Pancreatitis
    1. Acute pancreatitis
    2. Chronic pancreatitis
3. Pancreatic neoplasms
    1. Cystic pancreatic neoplasias
    2. Pancreatic ductal adenocarcinoma
    3. Pancreatic neuroendocrine tumors
    4. Tumors of the periampullary region
    5. Rare pancreatic tumors
4. Biopsy methods of the pancreas and its indications

1. Developmental anomalies

- Pancreas divisum
  - Failure of fusion of the pancreatic ductal system resulting separate aperture of dorsal and ventral pancreas
  - Consequence: relative obstruction of pancreatic duct
  - Clinical complication: predisposition to chronic pancreatitis
- Pancreas annulare
  - Rare abnormality of fusion of dorsal and ventral pancreas resulting in circular pancreas tissue around the duodenum
  - Consequence: duodenal obstruction
  - Clinical complication: babies with gastric distension and vomiting

Normal development



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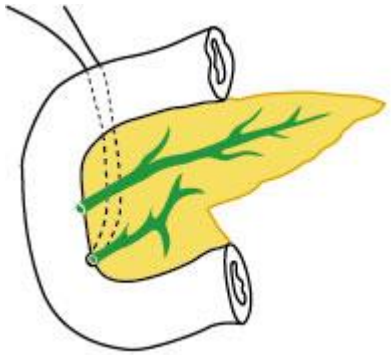

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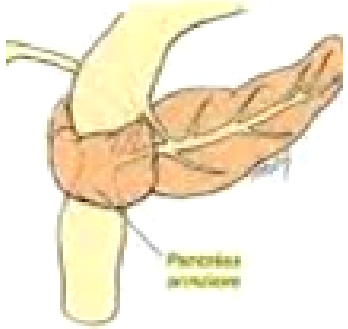
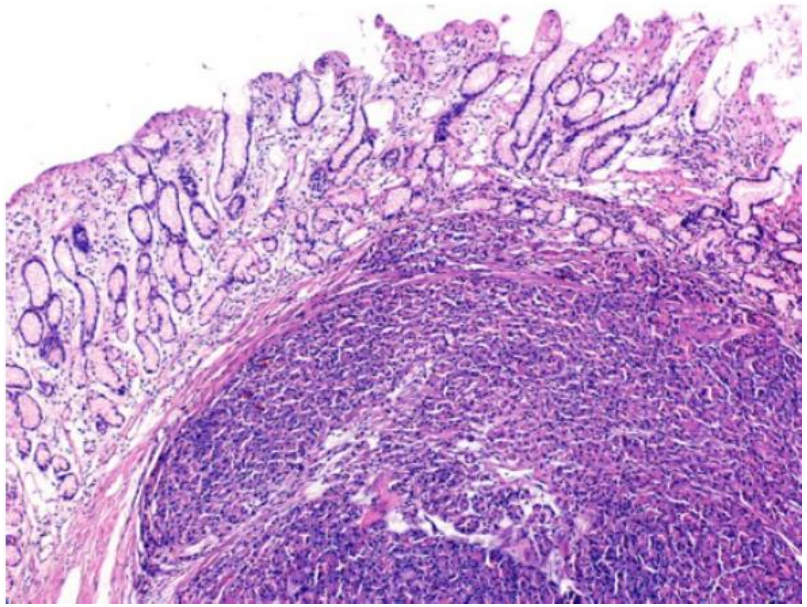


Ectopic pancreas

- Rare incidendal finding
- Stomach, duodenum, jejunum, diverticulum of Meckel, ileum
- Can be the unusual location of pancreatic tumors



Genetic diseases affecting the pancreas

- Cystic fibrosis (mucoviscidosis)
  - Mutation of the CFRT gene
  - Abnormally viscous pancreatic juice, protein plug formation
  - Chronic pancreatitis (transplant)
- Hemochromatosis
  - Mutation of the HFE gene
  - Secondary iron overload
  - Hemosiderin accumulation and fibrosis
  - Failure of exocrine and endocrine pancreas („bronze diabetes”)

Pancreatitis

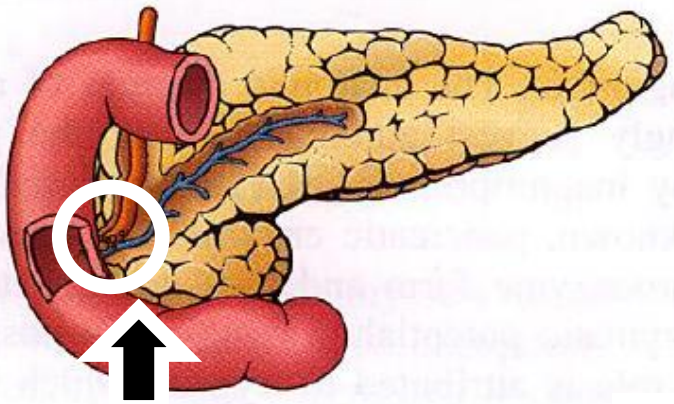
2.1. Acute pancreatitis

- Definition: Acute inflammatory reaction due to local activation of pancreatic enzymes
- Spectrum:
  - Mild: interstitial edema
  - Severe: diffuse hemorrhagic necrosis
- Acute local consequences: fat necrosis, hemorrhagic necrosis (clinically: acute abdomen syndrome)
- Acute systemic consequences: lipase level↑, Ca2+ level↓, SIRS, DIC, ARDS
- Late local consequences: pseudocyst, pseudocyst+infection=abscess, fistules

Pathogenesis & etiology

CAUSES:

DUCT OBSTRUCTION



Abrupt & complete obstruction!!

1. **Gallstones – MOST IMPORTANT**
2. Relative obstruction (high volume of pancreatic juice in lipid rich diet, spasm of the sphincter)
3. Iatrogenic (ERCP)

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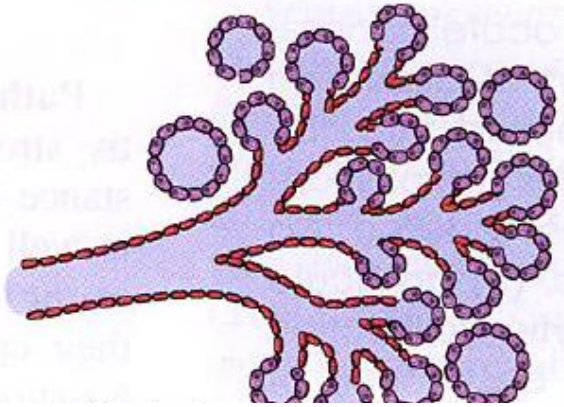
Usually diffuse and serious injury= necrotizing pancreatitis

ACINAR CELL INJURY



Damage of acinar epithelium, on-site activation of enzymes

1. Alcohol, drugs
2. Trauma, perioperative
3. Ischemia
4. Infective agents (viruses)

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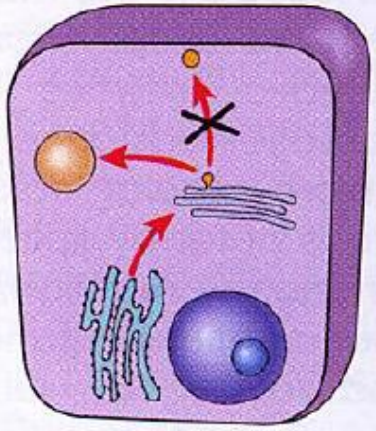
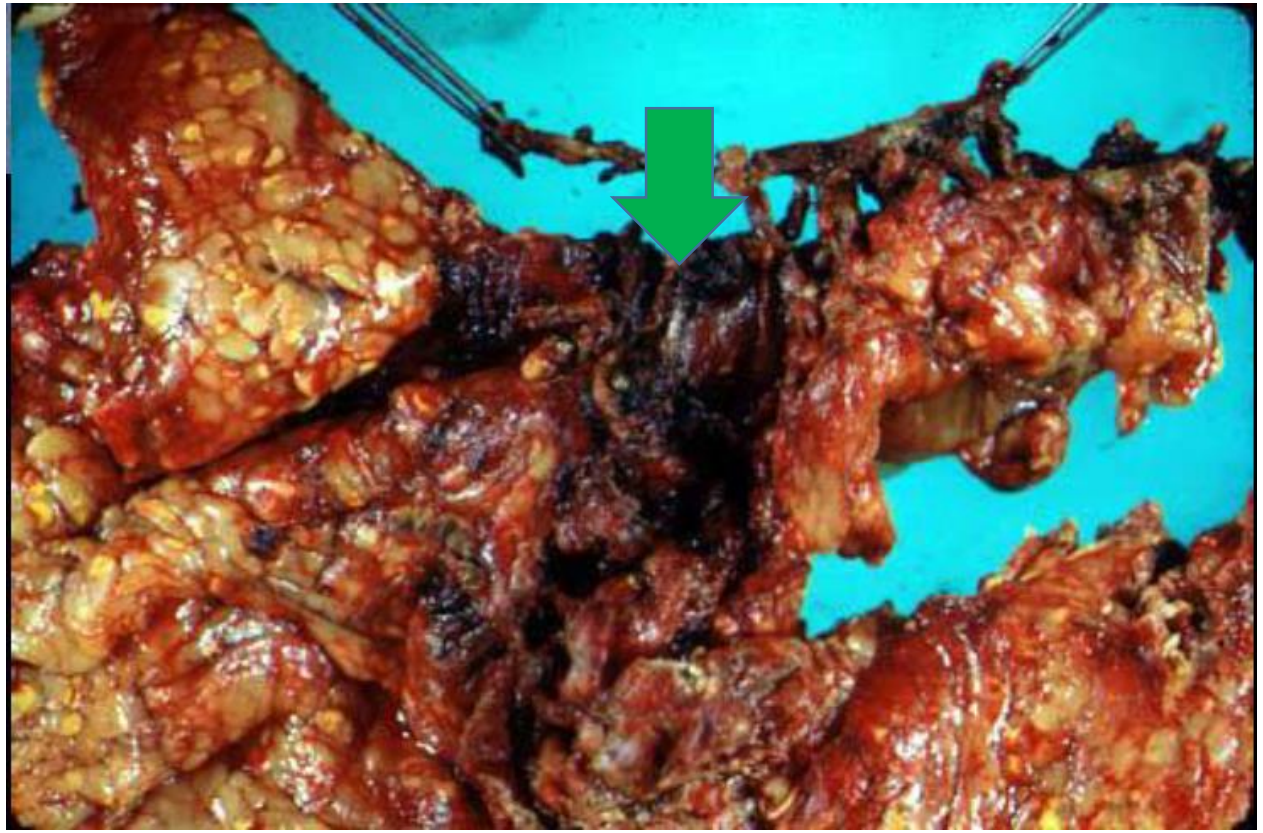
Can result mild and focal injury

DEFECTIVE INTRACELLULAR TRANSPORT

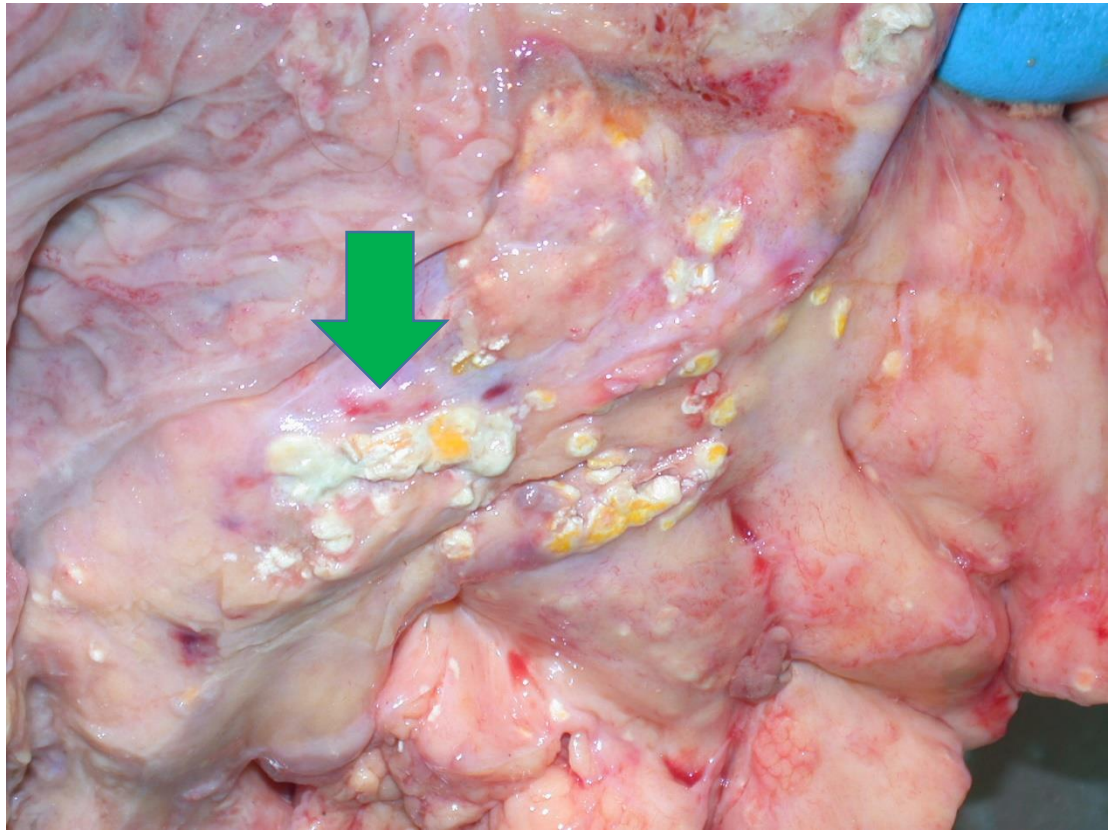


Additional mechanism in alcoholic and obstructive etiology

Morphology – macroscopy
Acute phase



Coagulative necrosis (trypsin) and hemorrhage (elastase)

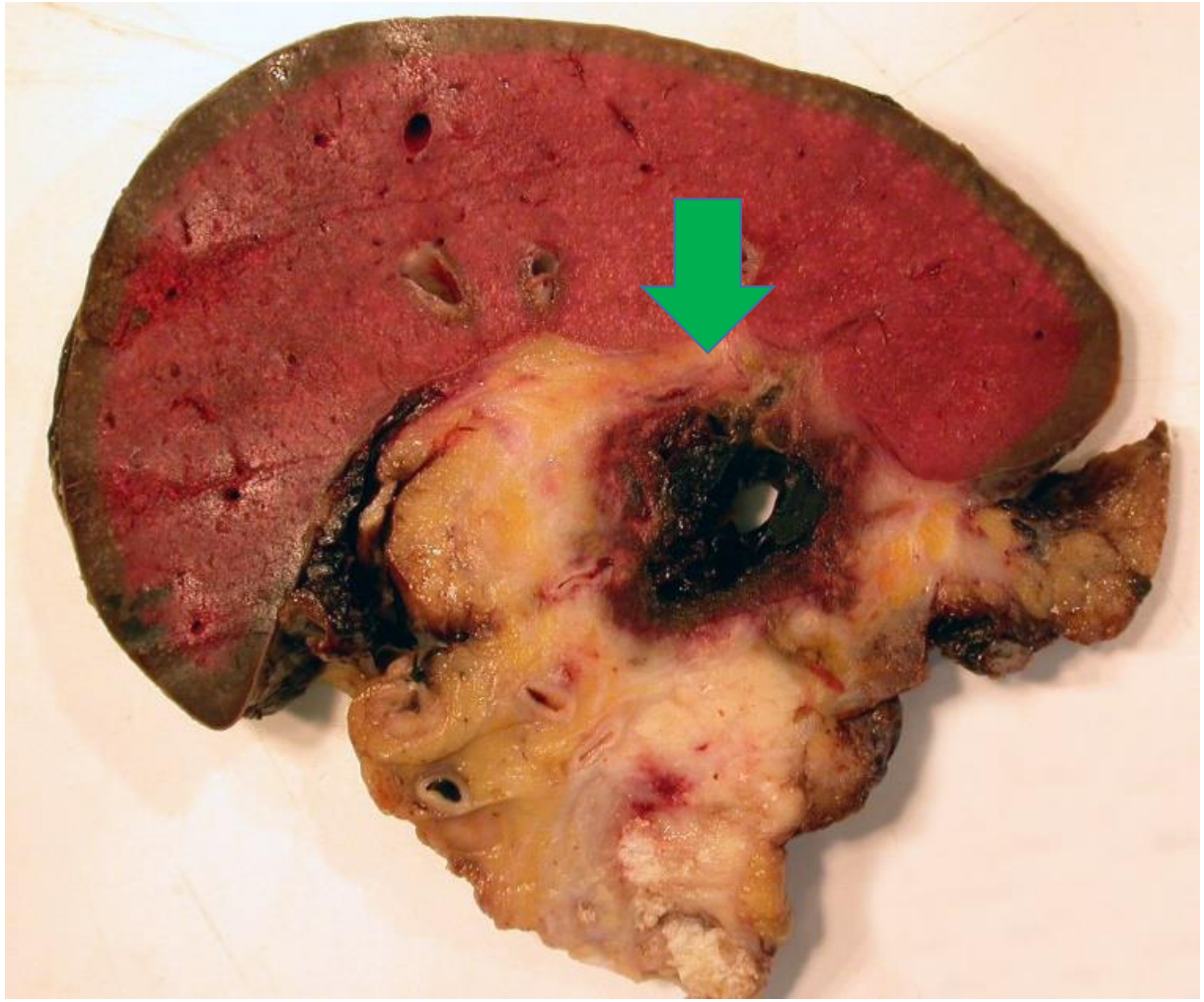


Fat necrosis (lipase)

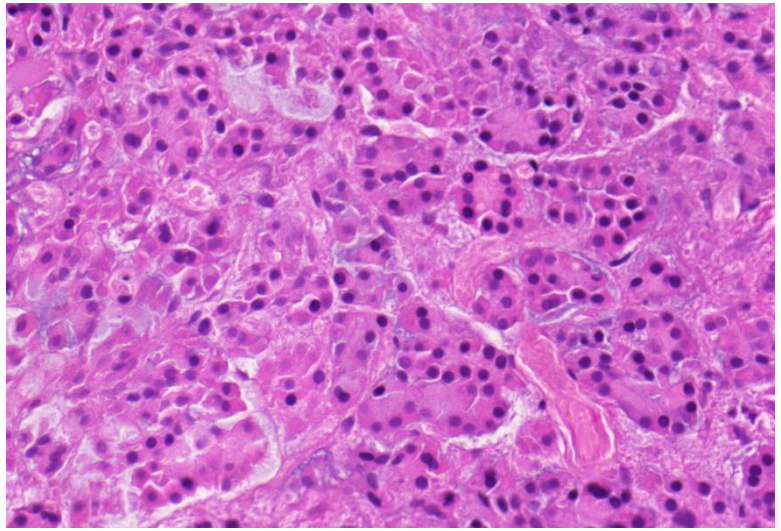
Morphology – macroscopy
Chronic phase

Pseudocyst: Cavity formation after demarcation & dissolving of necrotic tissue

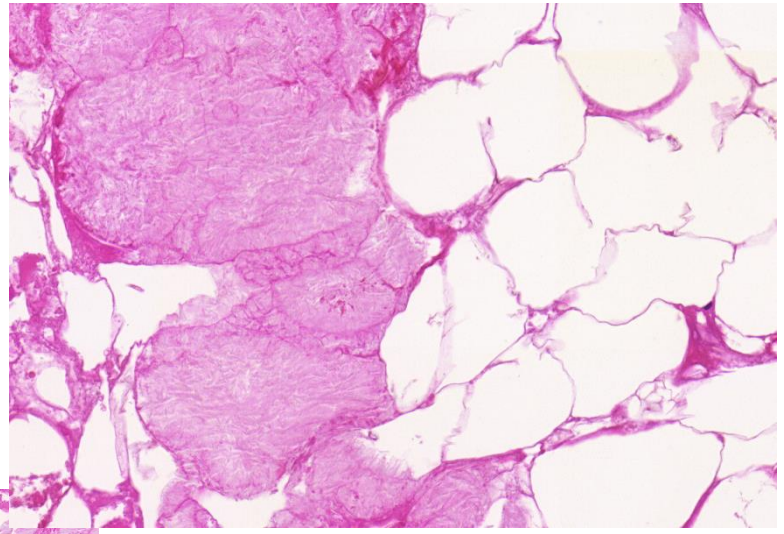
- Secondary infection results in abscess formation
- Penetration/perforation result in fistule formation



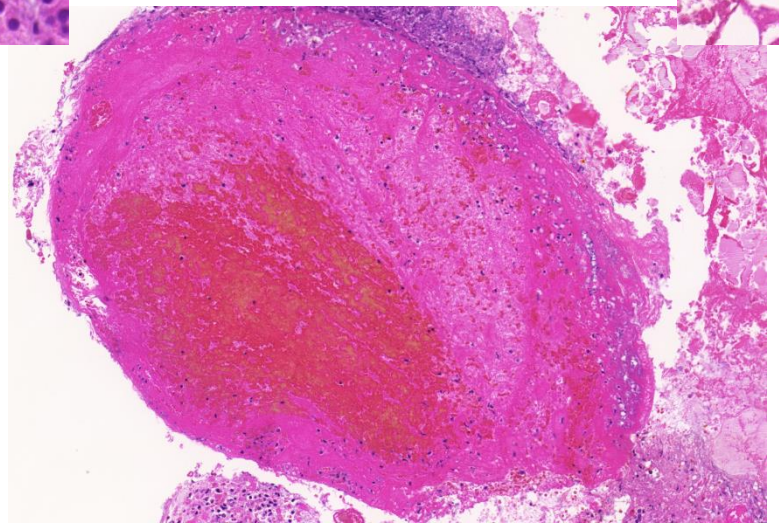
Morphology – microscopy



Coagulative necrosis



Fat necrosis



Blood vessel disruption - hemorrhage

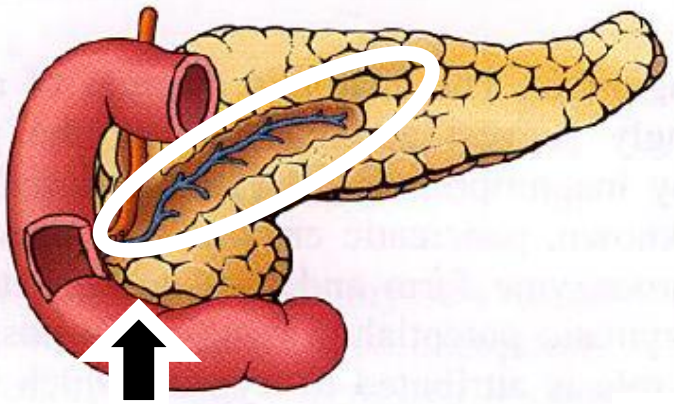
2.2. Chronic pancreatitis

- Definition: chronic injury of the exocrine glands resulting in fibrosis and acinar atrophy (loss of function)
- Mostly irreversible
- Local consequences: diffuse or „mass forming” fibrosis (affecting the head→obstruction of the bile duct=jaundice, mimics cancer!!), compression of nerves (=chronic pain), significantly increased cancer risk only in hereditary pancreatitis
- Systemic consequences: failure of exocrine function=malabsorption, cachexia, failure of endocrine function=pancreatic diabetes mellitus

Pathogenesis & etiology

CAUSES:

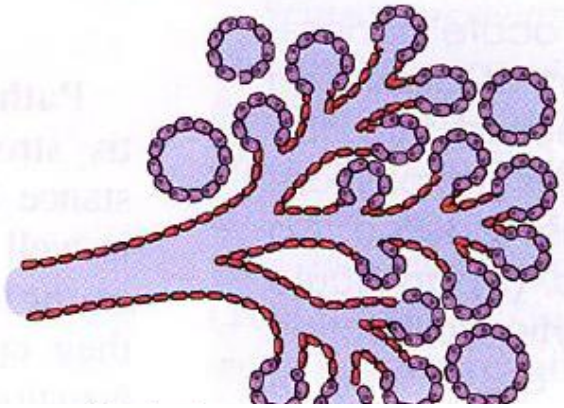
DUCT OBSTRUCTION



Slow obstruction of any segment of pancreatic duct

1. Alcohol (**T**oxic)→protein plugs+calcification=stones
2. Cystic fibrosis (**G**enetic)
3. Chronic **O**bstruktive pancreatitis→tumors

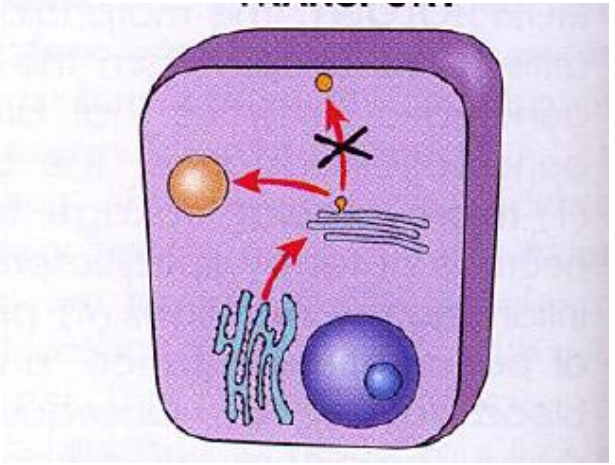
ACINI & INTERSTITIUM



Chronic acinar cell injury&interstitial processes

1. Alcohol (**T**oxic)
2. **A**utoimmune
3. **R**ecurrent acute inflammation

CELLULAR ANOMALIES



1. Failure of trypsin inhibitor (Hereditary=**G**enetic)
2. **I**diopathic

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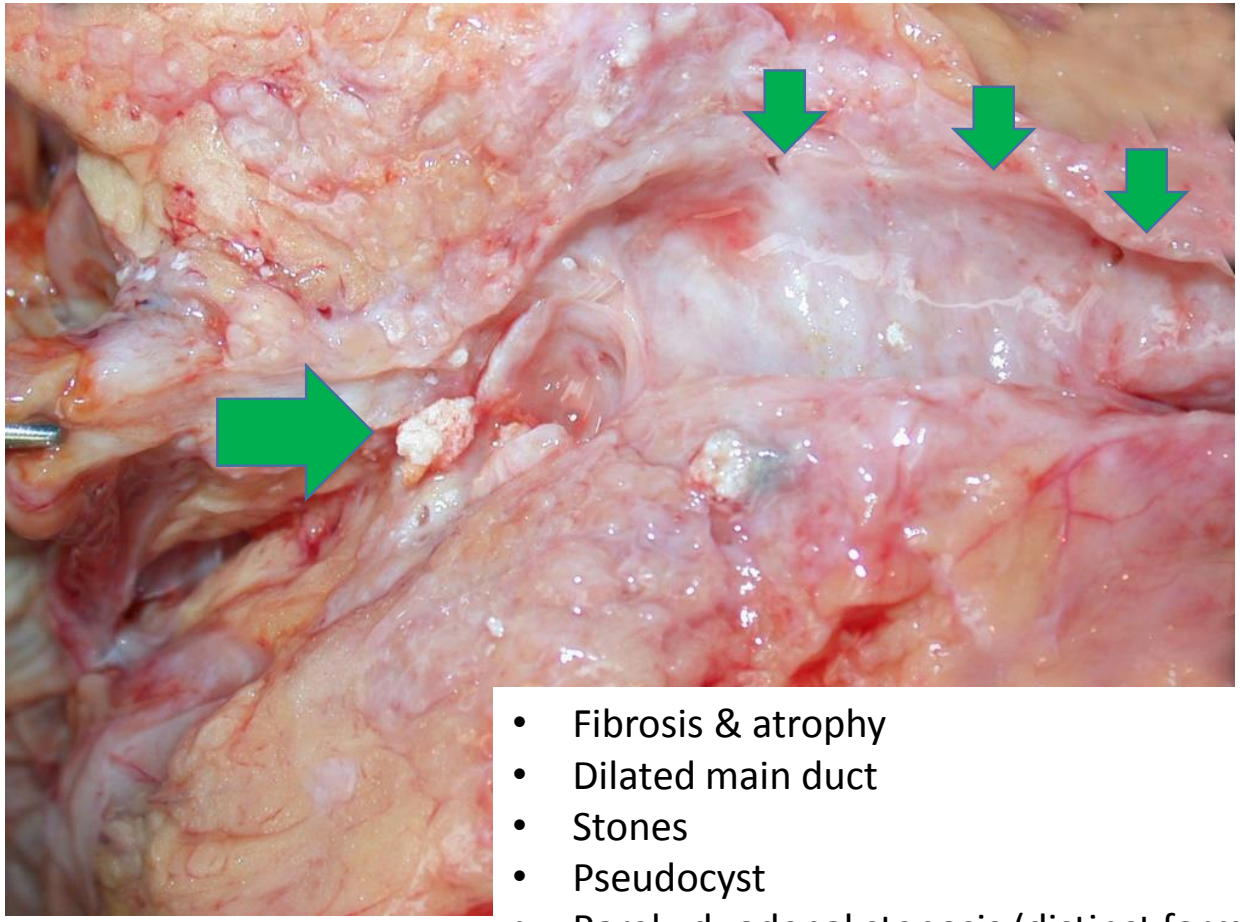
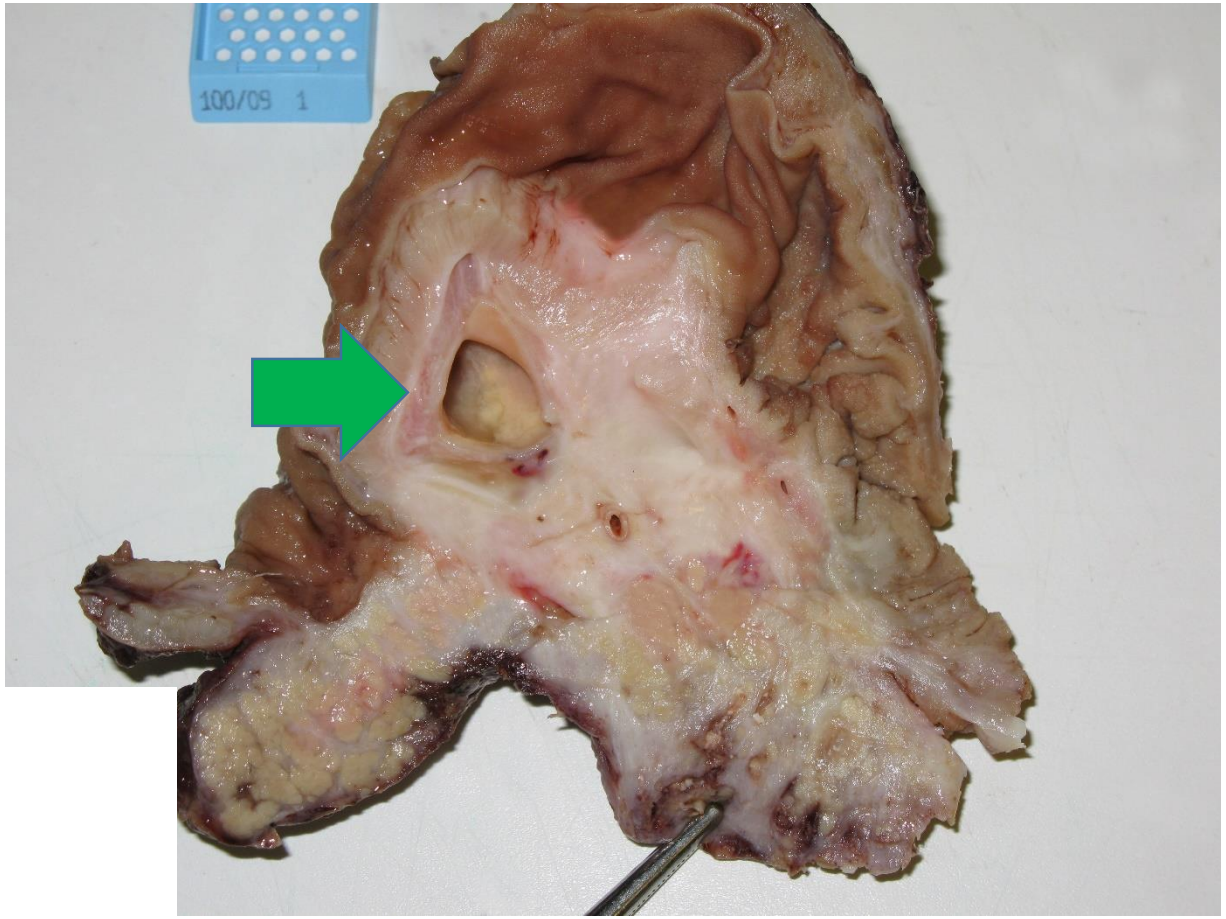
T-I-G-A-R-O

Morphology - macroscopy

- Chronic calcifying pancreatitis (alcoholic)

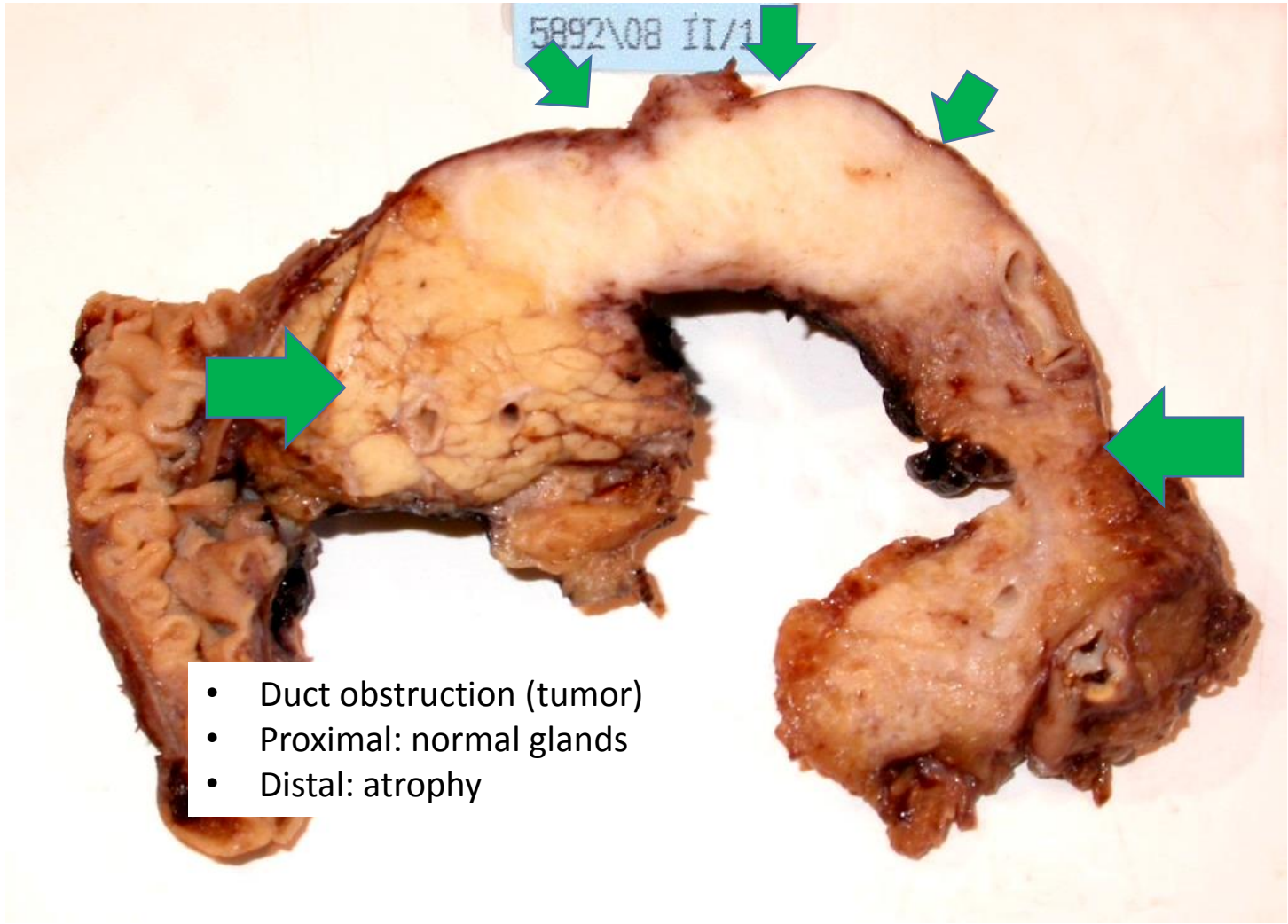




- Fibrosis & atrophy
- Dilated main duct
- Stones
- Pseudocyst
- Rarely duodenal stenosis (distinct form: paraduodenal pancreatitis)
- DDG: cancer!!

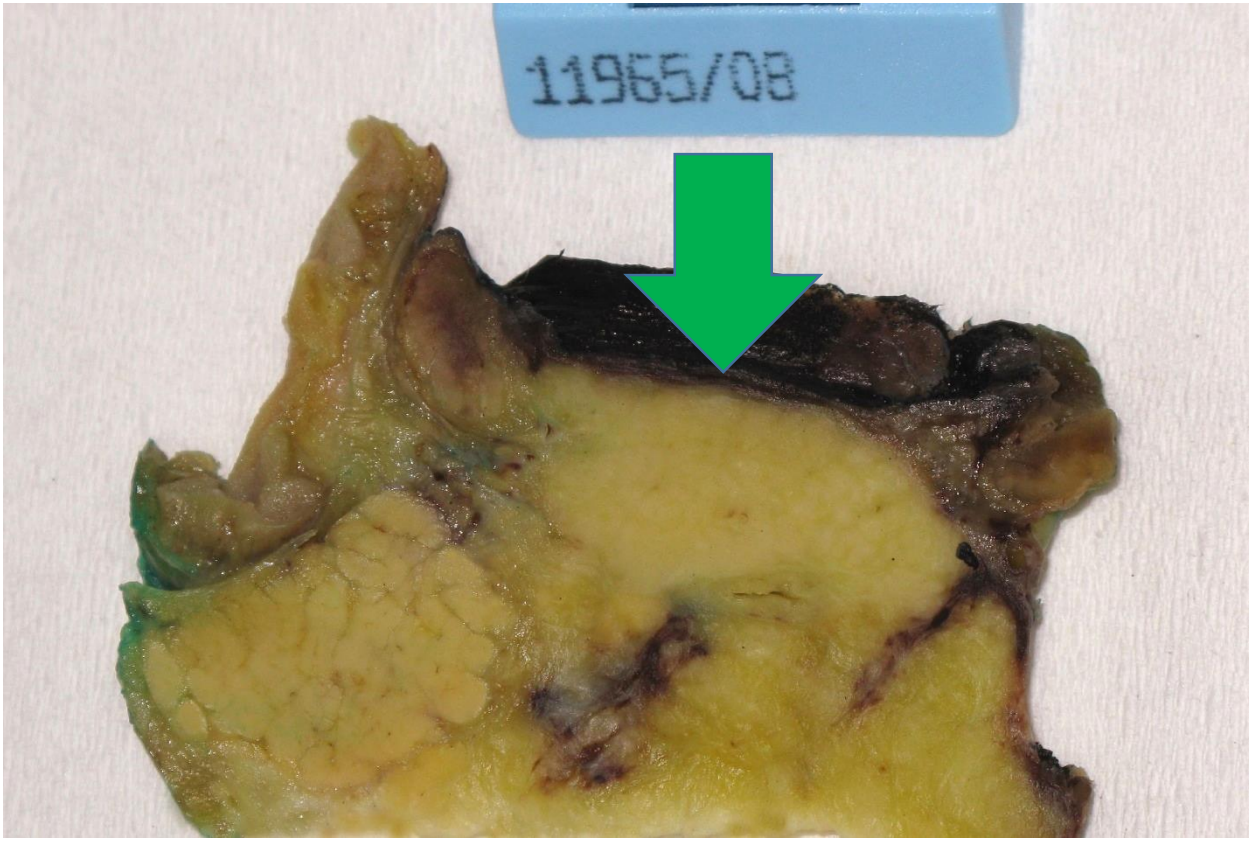
Morphology - macroscopy

- Chronic obstructive pancreatitis



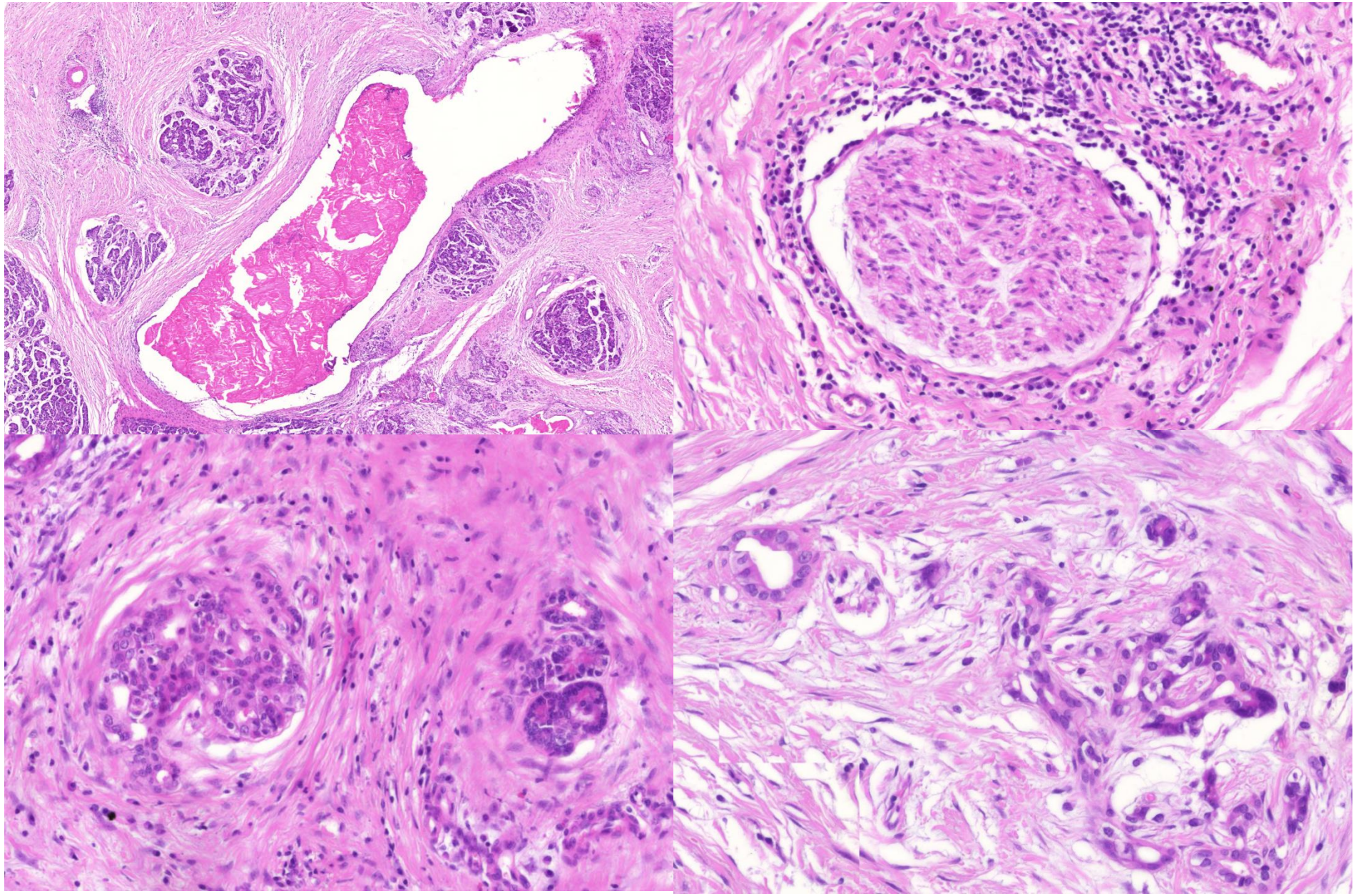
Morphology - macroscopy

- Autoimmune pancreatitis
  - Diffuse form
  - Focal „mass forming” (mimics cancer!!)



Morphology - microscopy

1. Fibrosis
2. Acinar atrophy (L-islands preserved for a long period)
3. Duct proliferation (mimics cancer!!)
4. Ductal plugs/stones
5. Nerve hypertrophy



Morphology - microscopy

- IgG4 positive plasma cells in autoimmune pancreatitis

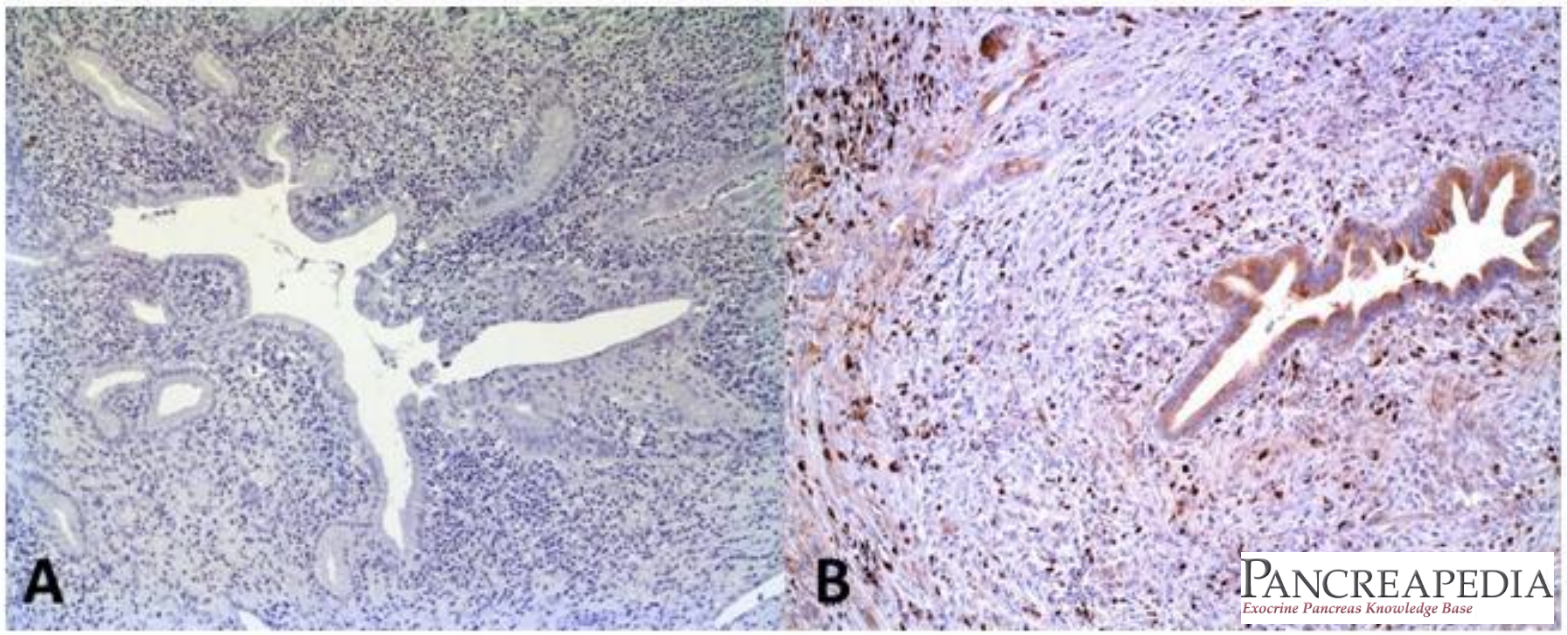
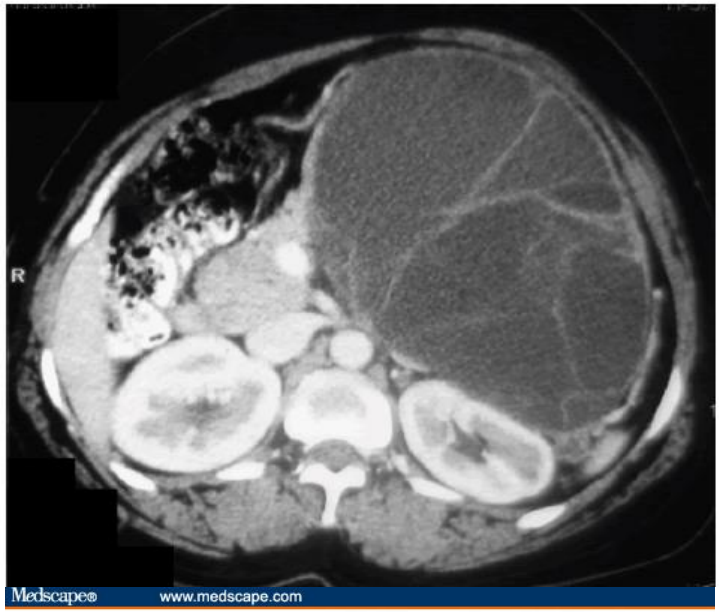


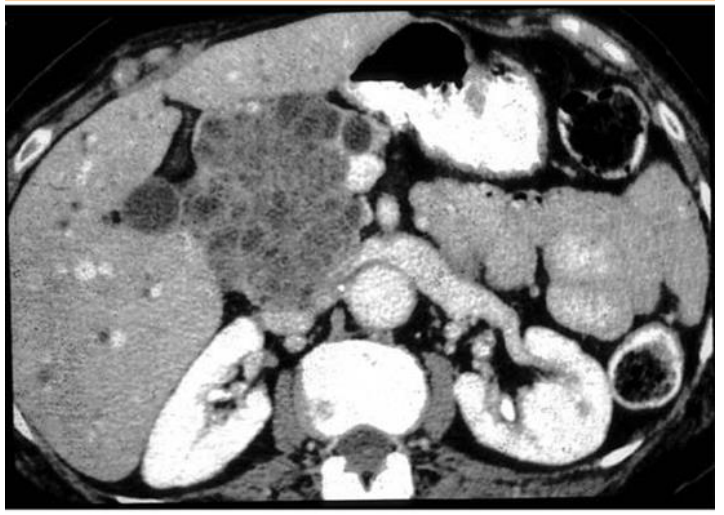
Figure 3. Immunostaining for IgG4 reveals no positive-staining plasma cells in type 2 AIP (a), but abundant IgG4-positive plasma cells in type 1 AIP (b).

Neoplasias

3.1. Cystic pancreatic neoplasias

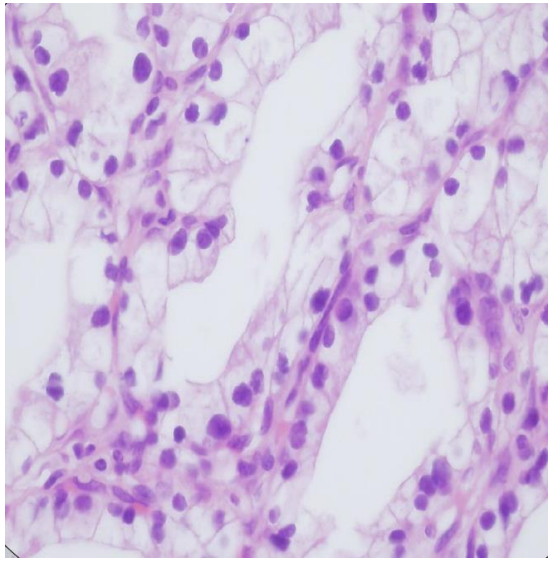
- Small cysts are common incidental findings
- Clinically significant lesions are large
- Generally not associated with jaundice
- Macro/microcystic
- Aspirate: mucinous/non-mucinous
- Surgical resection if:
  - Large size
  - Growing tendency
  - Solid component/”mural nodule”
  - Mucinous type
- Main differential diagnosis: pseudocyst!!

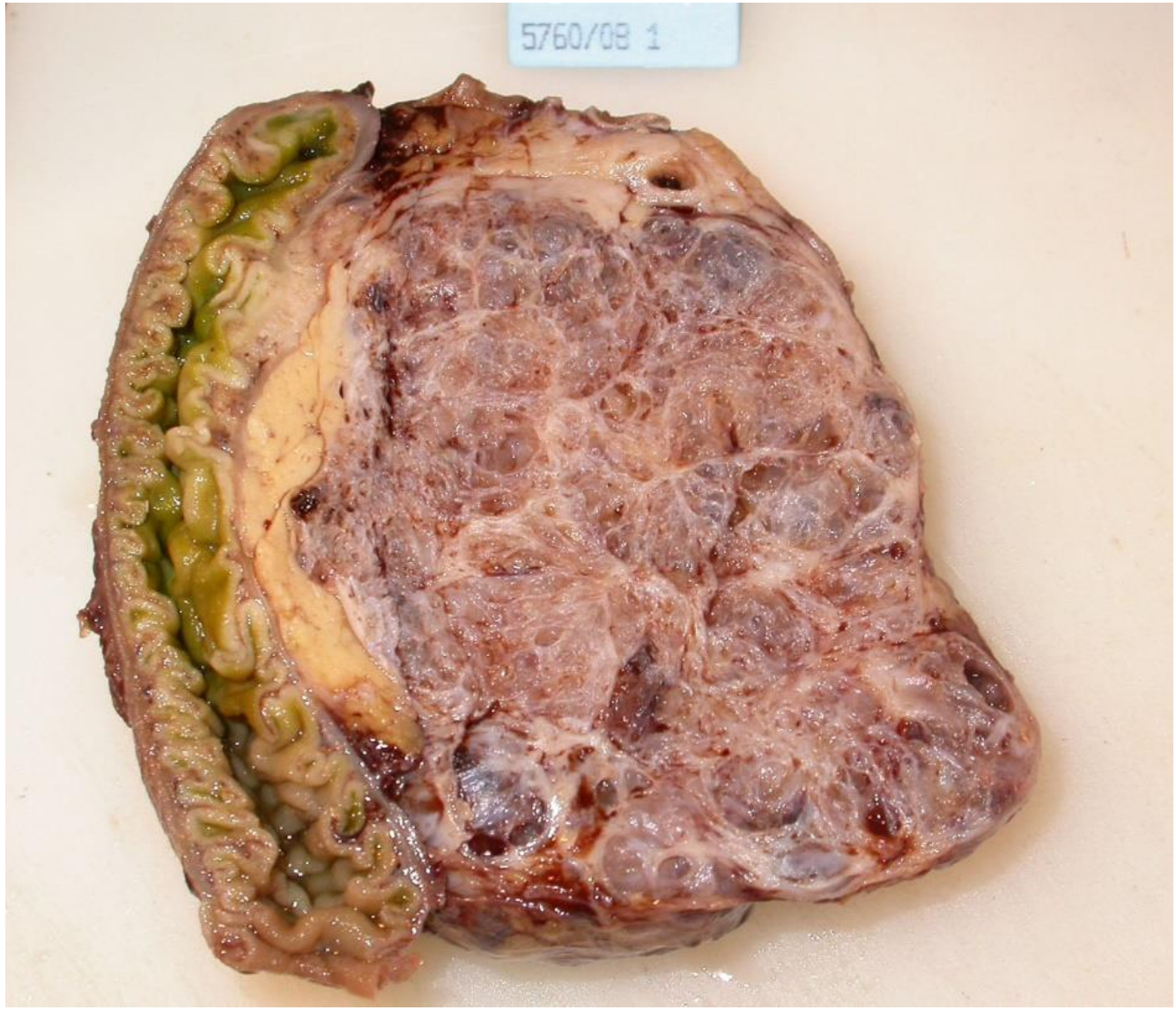




3.1.1. Serous cystadenoma

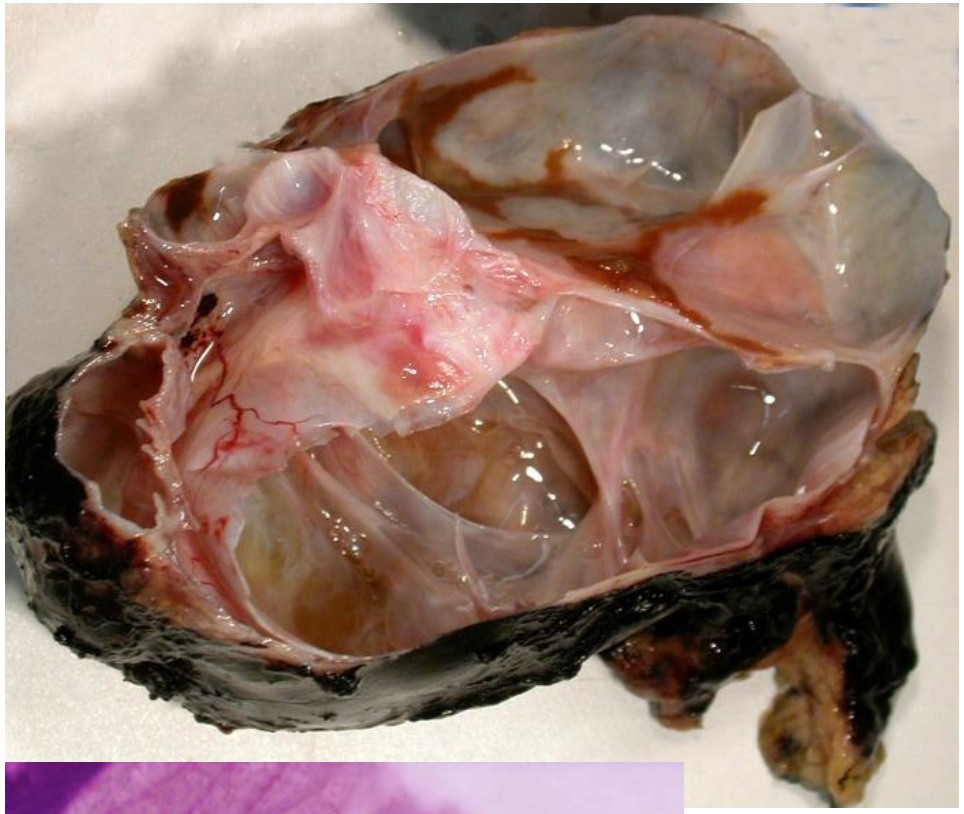
- Benign
- No malignant transformation!
- Macro: generally large size, microcystic tumor
- Aspiration: clear, usually acellular fluid
- Micro: small, uniform cuboidal clear cells

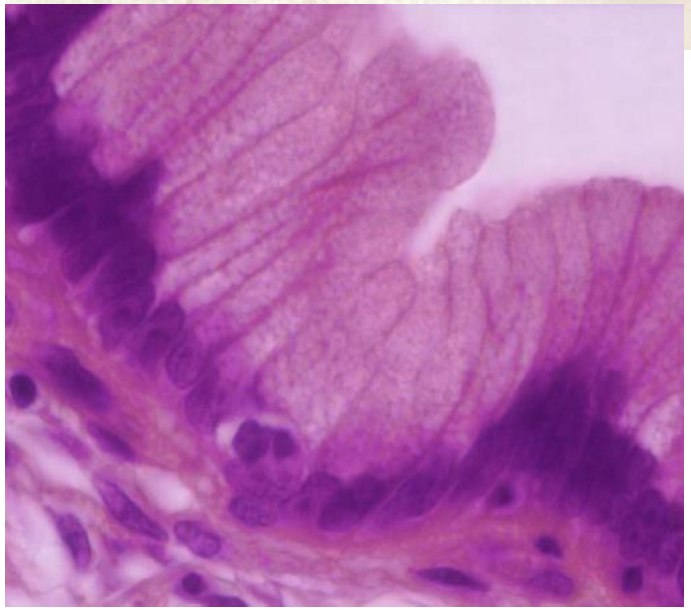




3.1.2. Mucinous cystadenoma

- Very rare
- Equivalent of mucinous cystic tumors of the ovary
- Females
- Distal pancreas
- Not communicating with pancreatic duct system
- Macro: macrocystic
- Aspiration: mucin (variable cellularity or acellular)
- Micro: mucinous columnar epithelium
- Sequence:
  - Benign
  - Borderline
  - Malignant



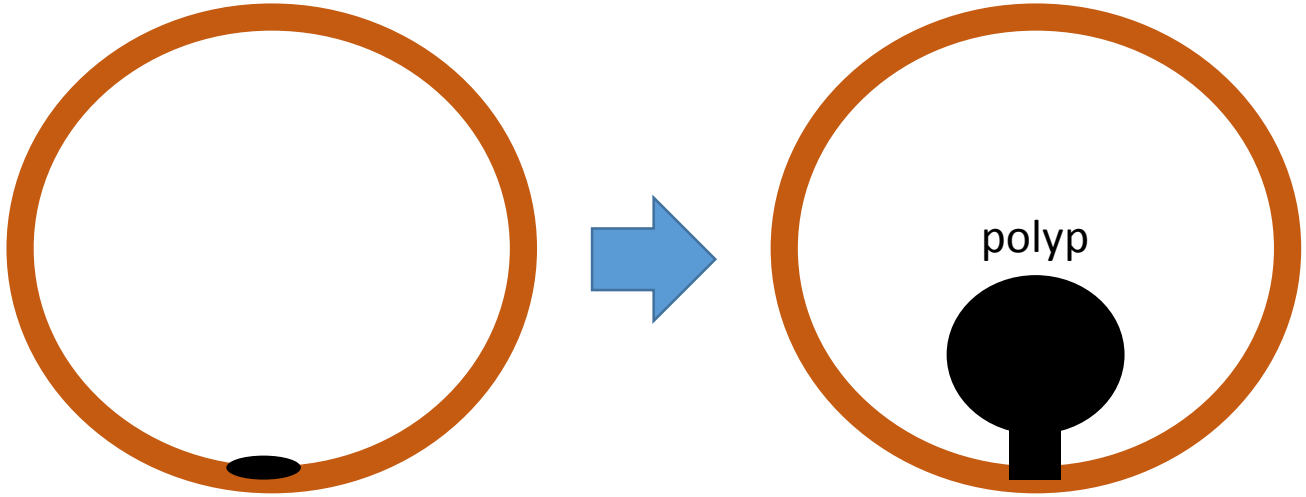


3.1.3. Intraductal Papillary Mucinous Neoplasias (IPMN)

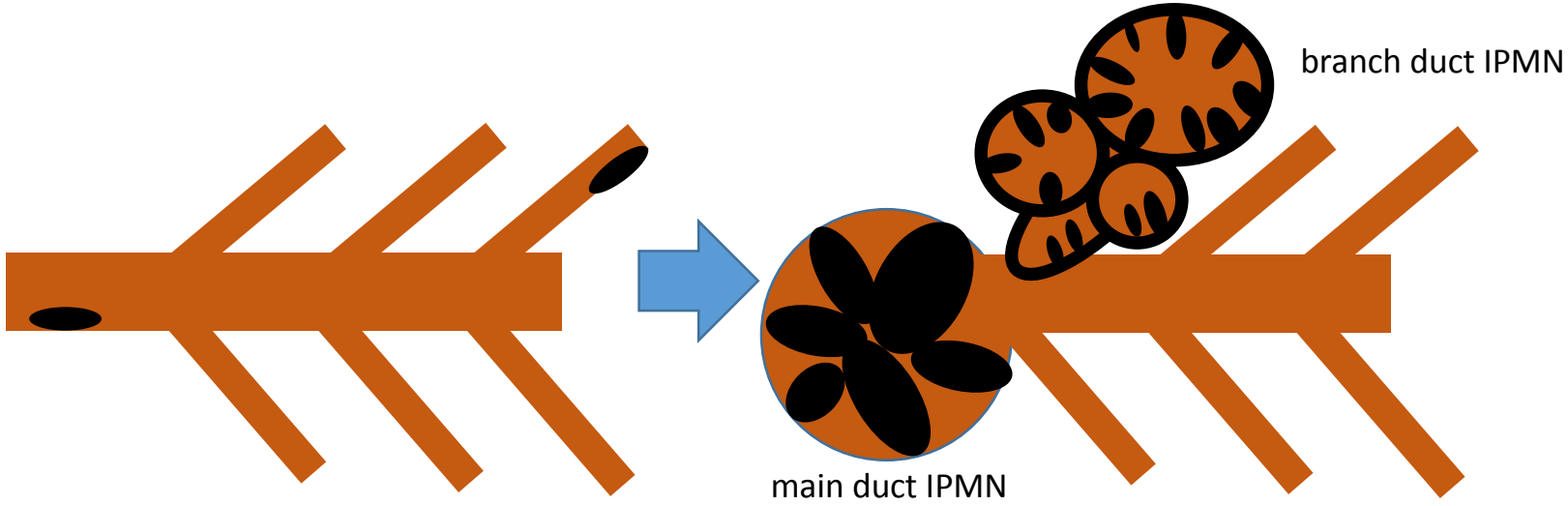
- Most common cystic tumor of the pancreas
- Both sexes
- Macro:
  - Main duct: head, branch duct: distal
  - Variable sized cysts
  - Communicating with duct system → typical endoscopic finding: mucin leakage from the papilla
- Aspiration: mucin (variable cellularity, look for atypical cells!)
- Micro: Biological similarities with GI tract adenomas (types: gastric, intestinal, biliary) with mucinous epithelium
- Sequence:
  - IPMN without dysplasia (=benign)
  - IPMN with dysplasia (=premalignant)
  - IPMN with invasive carcinoma (=malignant)

Why are IPMNs cystic and GI adenomas not?

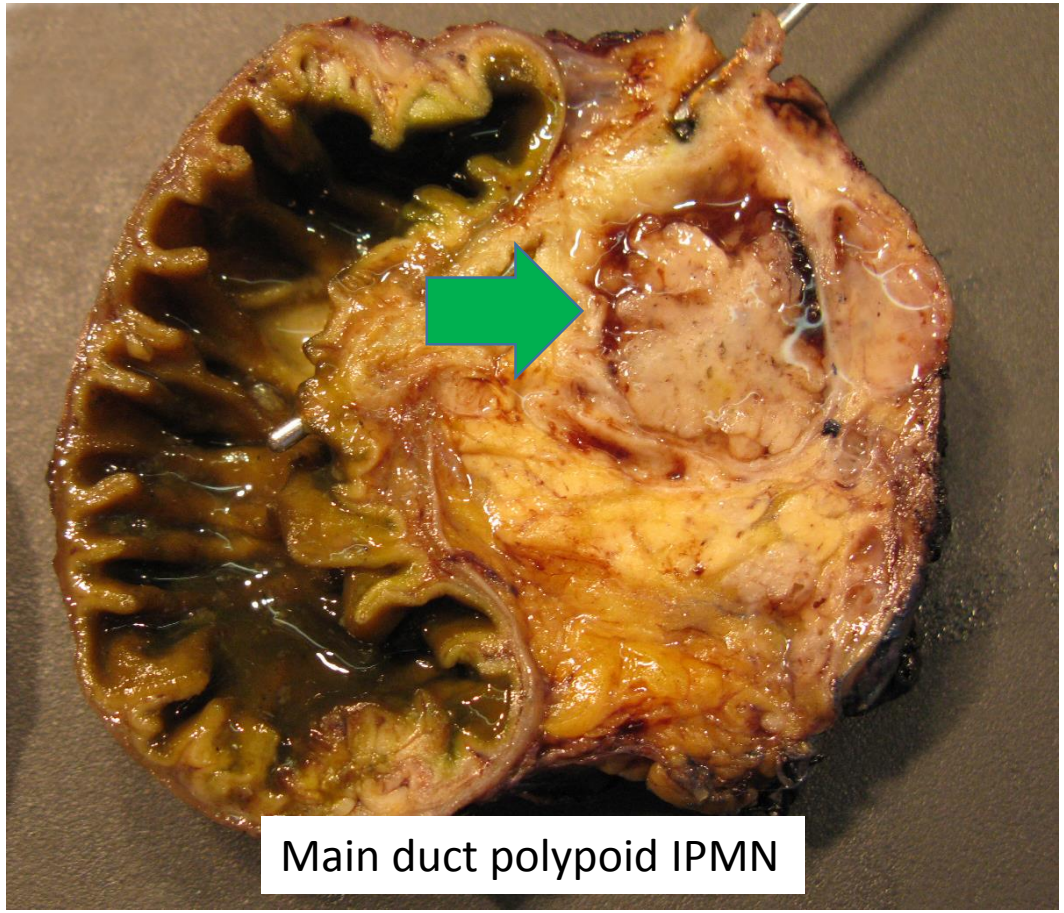
Neoplastic proliferation in GI tract mucosa
Intraluminal space is big enough for polyp formation, mucin is evacuated with faeces



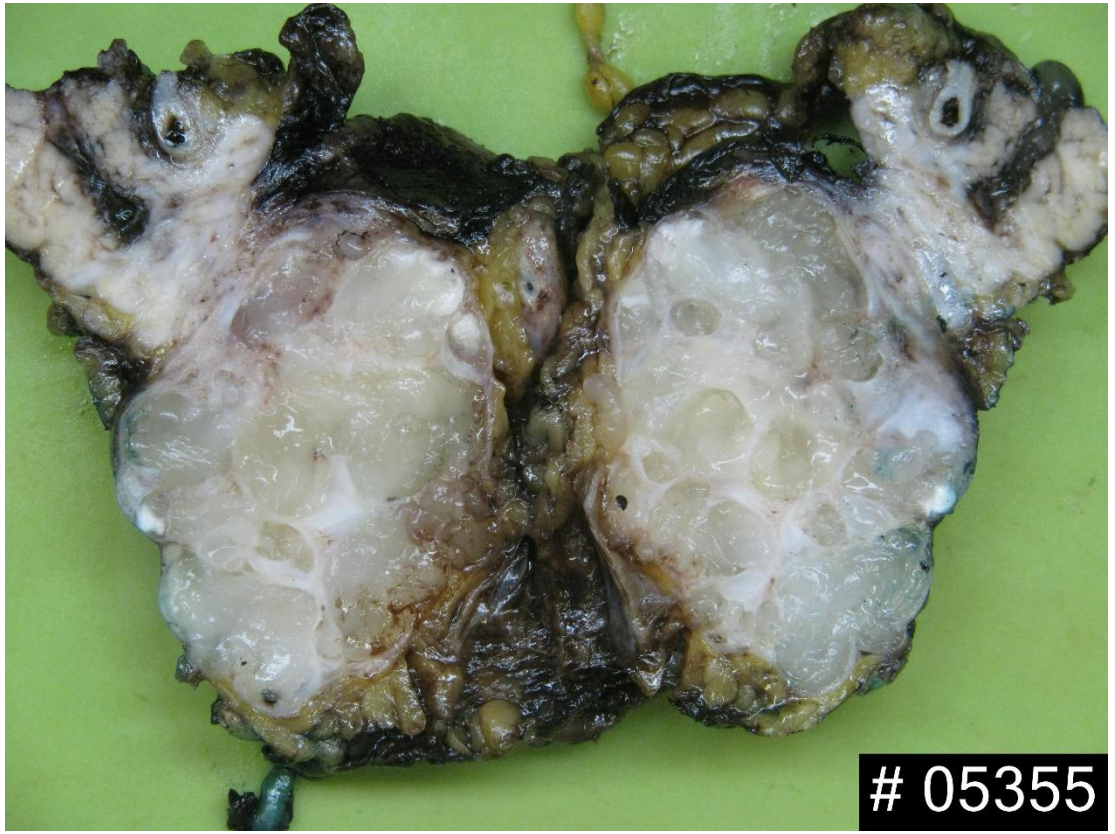
Neoplastic proliferation in pancreatic ducts
Intraluminal space is limited→ duct dilation due to excessive mucin secretion & papillary growth



Macroscopy

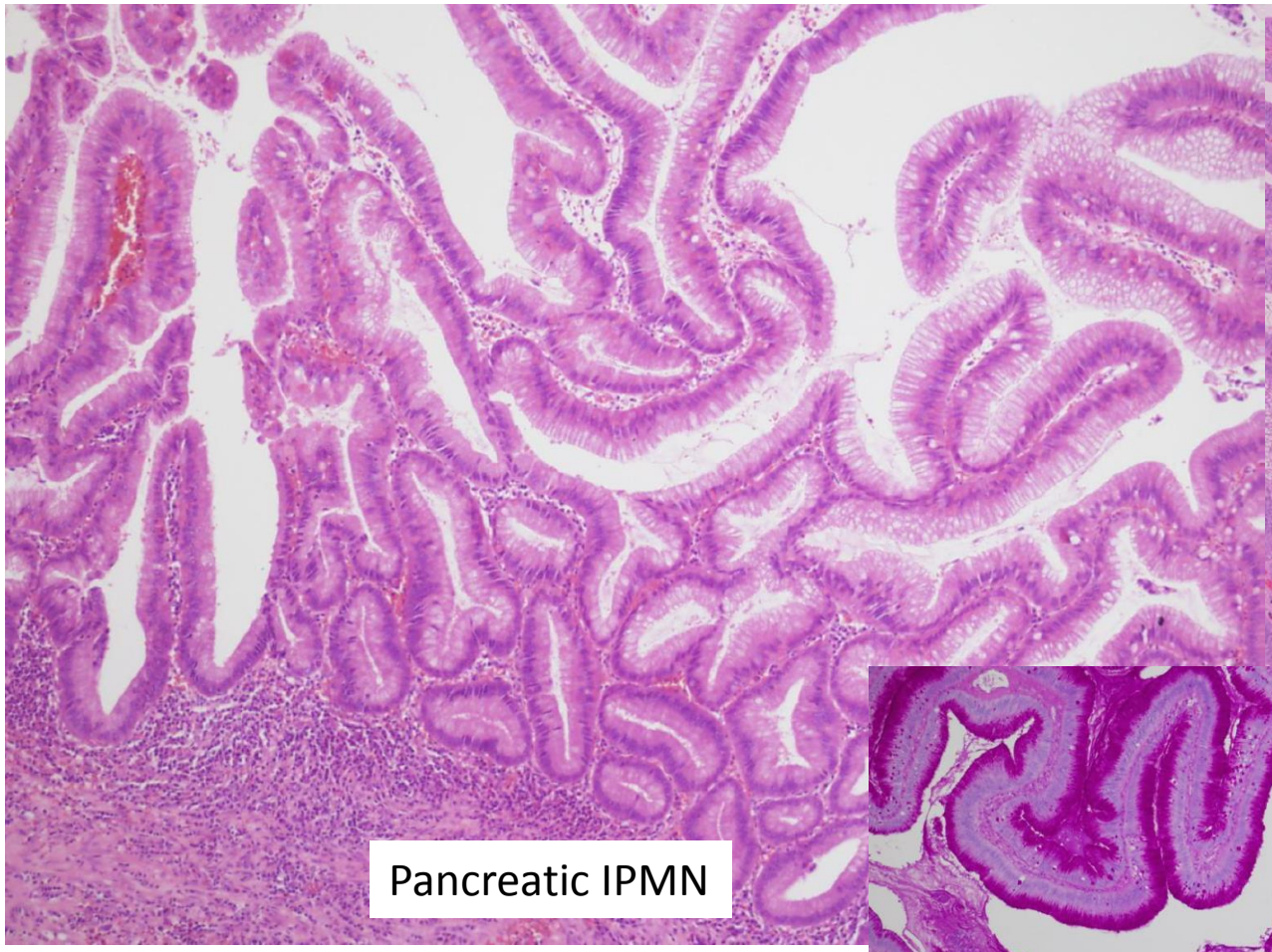


Main duct polypoid IPMN

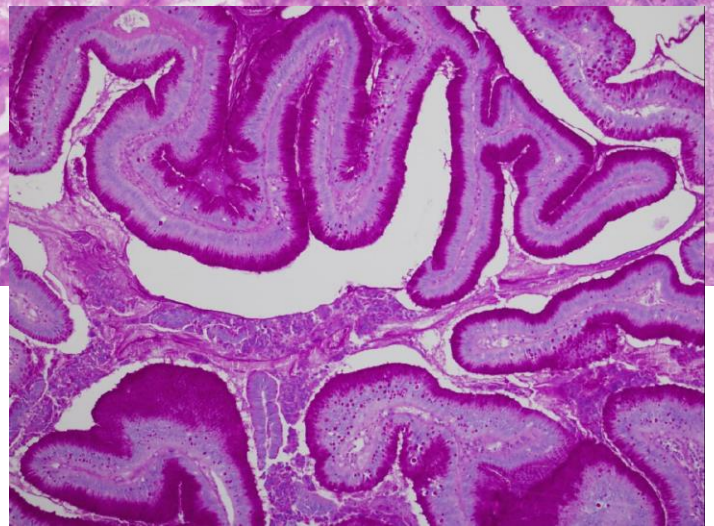


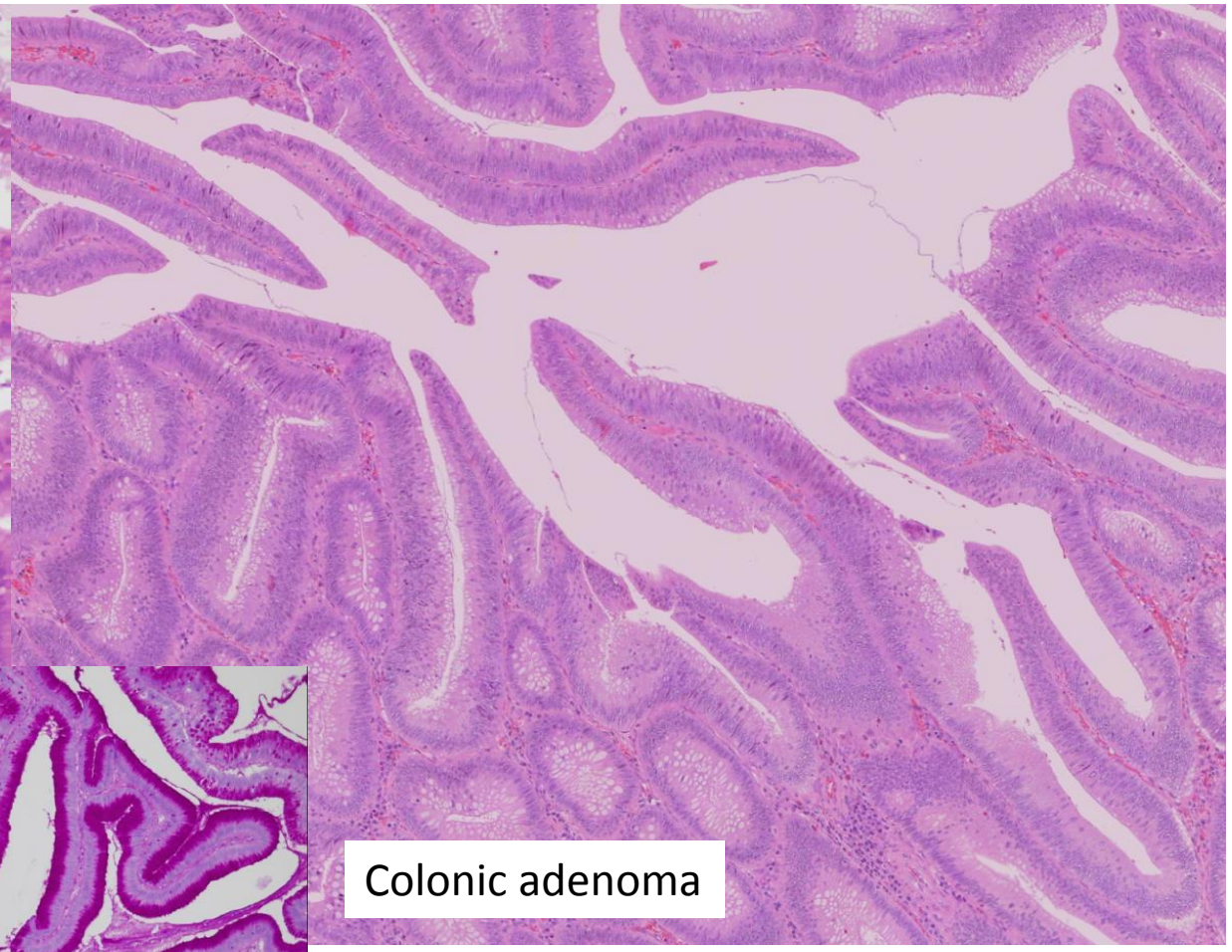
Branch duct cystic IPMN

Microscopy



Pancreatic IPMN





Colonic adenoma

3.2. Pancreatic ductal adenocarcinoma (PDAC)

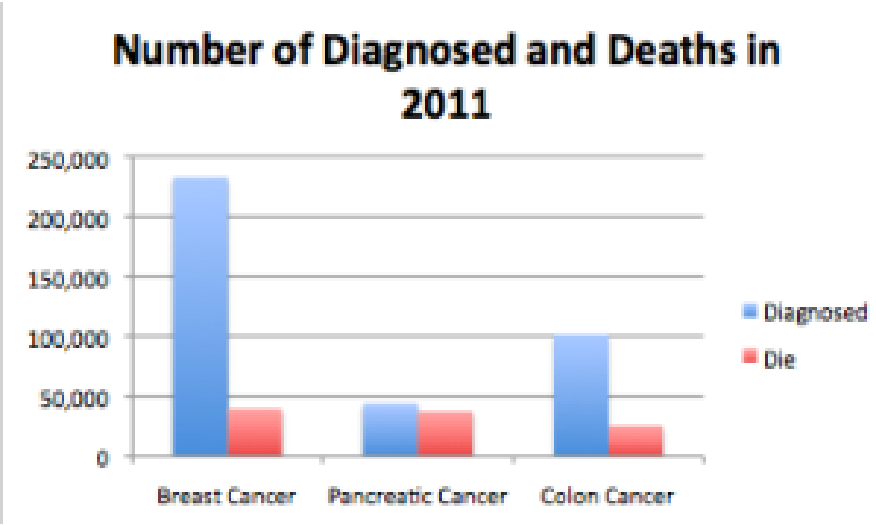
- Malignant tumor of ductal epithelium

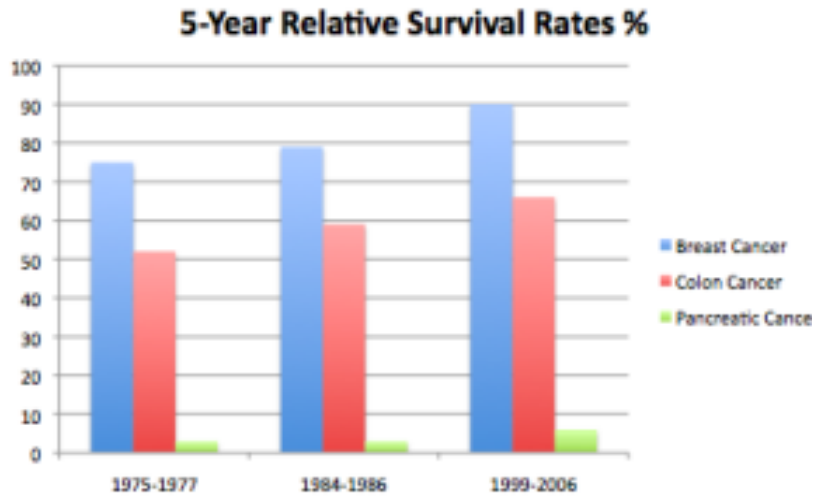
- Most common form of pancreatic cancer (>90%)

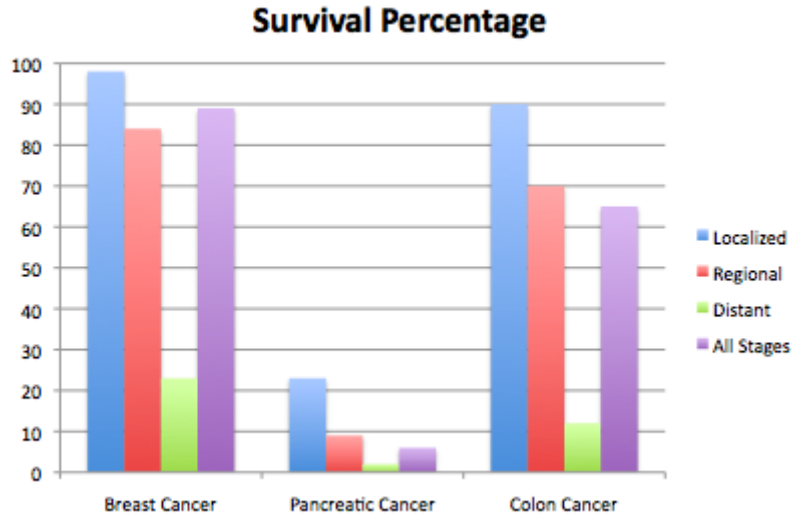
- Risk factors
  - No 1: SMOKING
  - Alcohol abuse
  - Familial accumulation occurs (associated with familial pancreatitis)

Some figures about the survival of pancreatic cancer…

Pancreatic cancer
- Incidence: No. 11.
- Mortality: No. 3.-4.







Poor survival due to:
- Bad location (not a palpable organ)
- No early symptoms
- Way of spread (lymphatic & perineural)
- No clinical tests for precancerosis=not a candidate for screening

https://policyinterns.com/2011/10/14/the-more-you-know/

Clinical signs

- Jaundice (with palpable nontender gallbladder – Courvoisier sign)
- Malabsorption
- Pain (infiltration of vertebral nerves)

Tumor markers: CEA, CA 19-9

- Not specific/sensitive enough for primary diagnosis
- Used in follow-up

Locally advanced disease at the time of dg

or

- Detection of distant metastasis of an asymptomatic primary tumor (=CUP) – especially distal forms

Metastatic disease at the time of dg

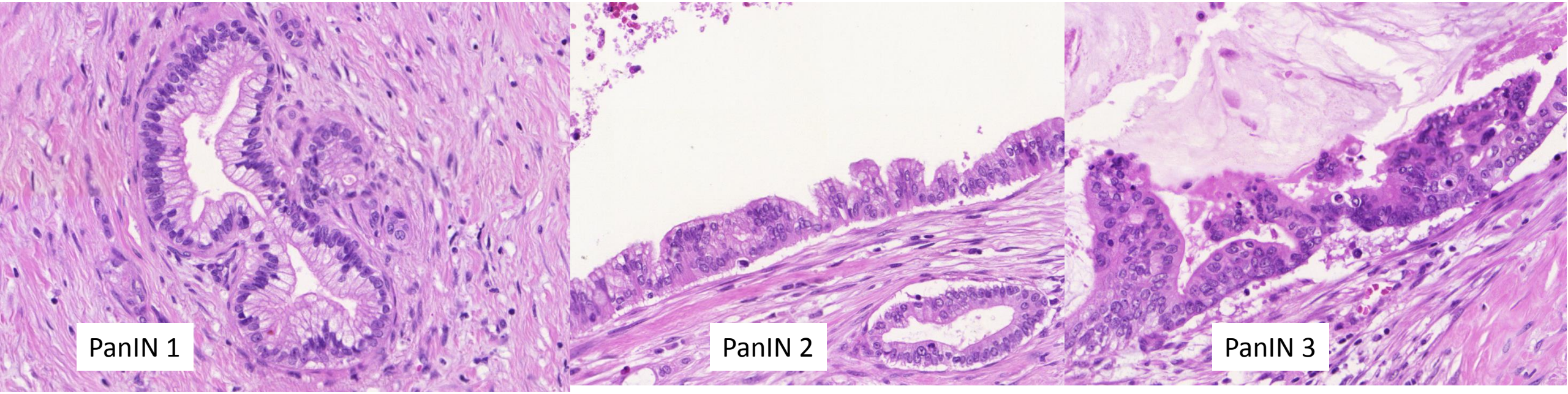
or

- Paraneoplastic syndromes
  - Migratory thrombophlebitis (Trousseau)
  - Marantic endocarditis

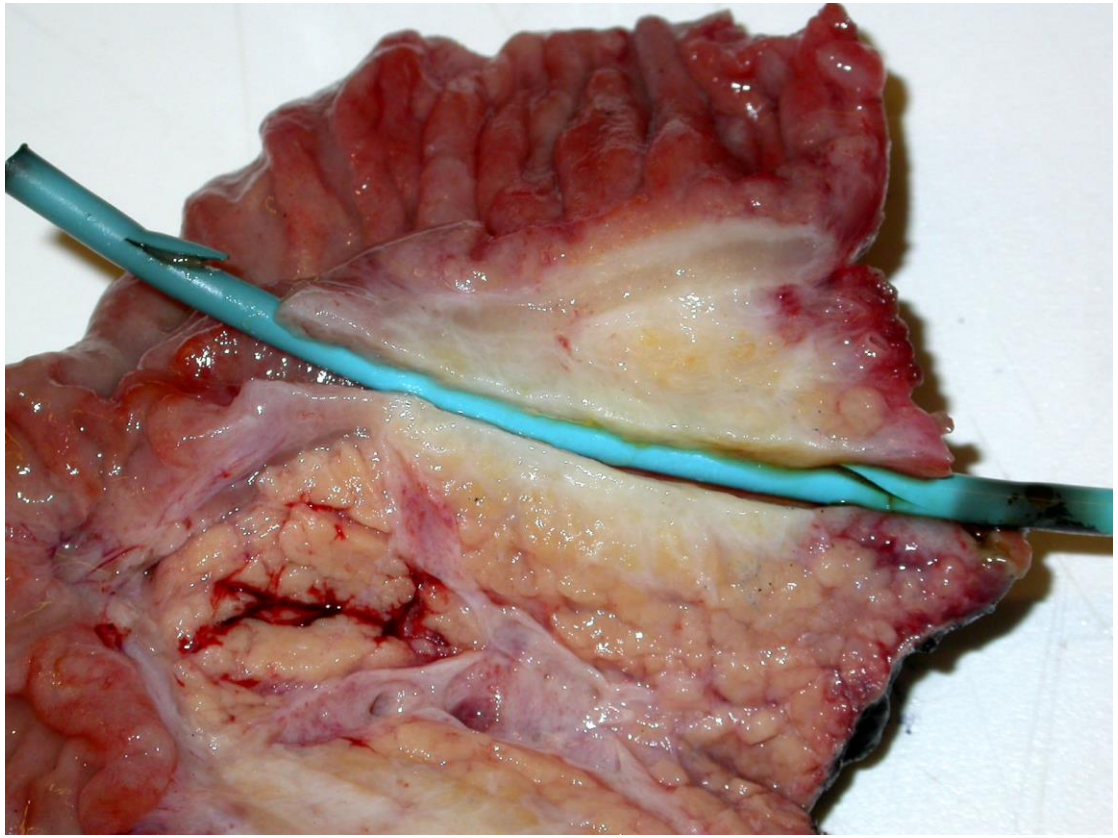
Generally high tumor volume (metastatic disease)

Carcinogenesis of PDAC

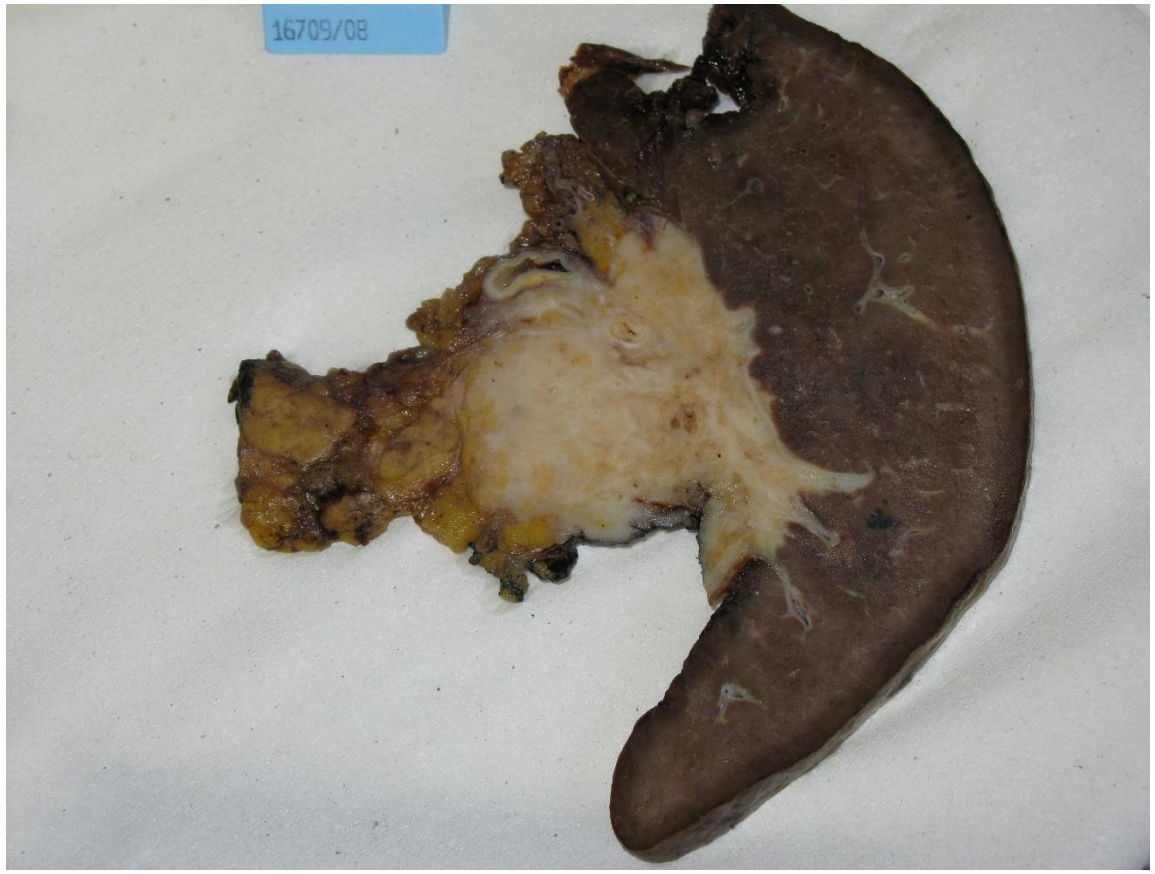
- Sequence similar to those in colonic cancer→metaplasia-dysplasia-carcinoma (step-by-step accumulation of genetic alterations eg. K-RAS, p16, SMAD4)
- Precursor lesion of ductal epithelium: PanIN= Pancreatic Intraepithelial Neoplasia (≠PIN, Prostatic Intraepithelial Neoplasia)
  - PanIN 1: mucinous metaplasia (other mucin type than in IPMNs)
  - PanIN 2: low-grade dysplasia
  - PanIN 3: high grade dysplasia
- PROBLEM: no clinical test („screening”) is availabe to detect PanIN→ diagnosis only in invasive phase


PanIN 1
PanIN 2
PanIN 3

Macroscopy of PDAC



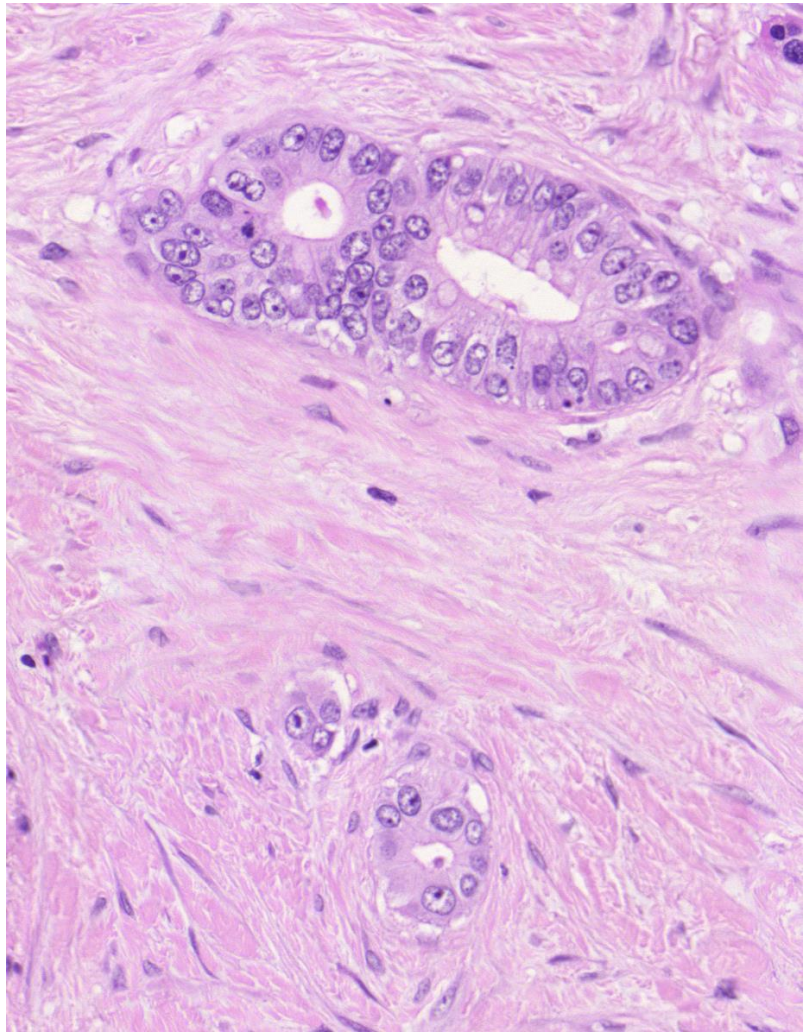
Head: 60%
Obstruction of the bile duct, rarely duodenal stenosis



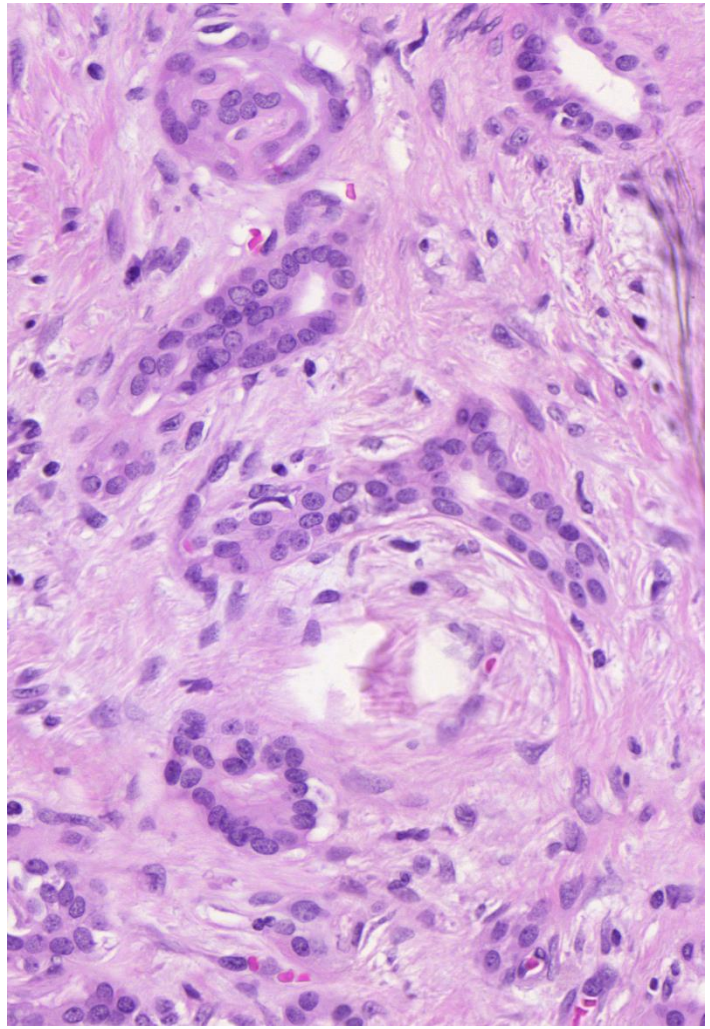
Distal: 20%
Usually asymptomatic, rarely infiltration of the splenic hilus or stomach wall

Microscopy of PDAC

- Abortive duct formation (differential diagnosis: ductal proliferation in chronic pancreatitis!!)
- Perineural invasion
- Excessive desmoplasia

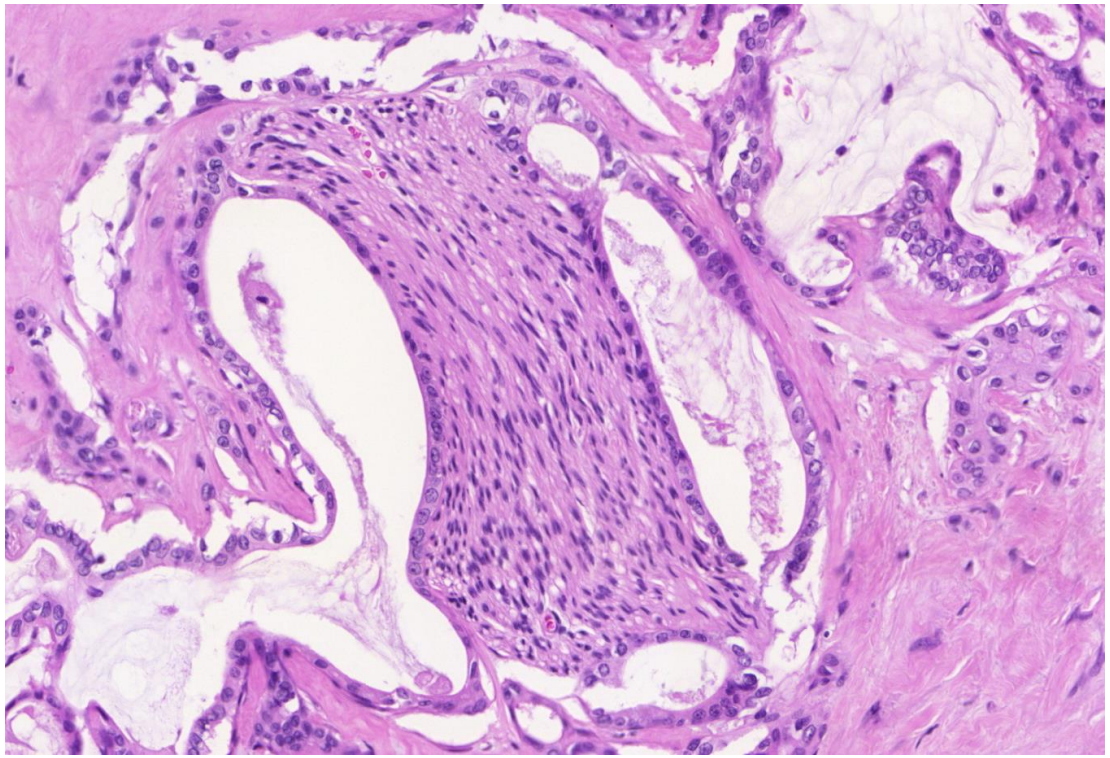


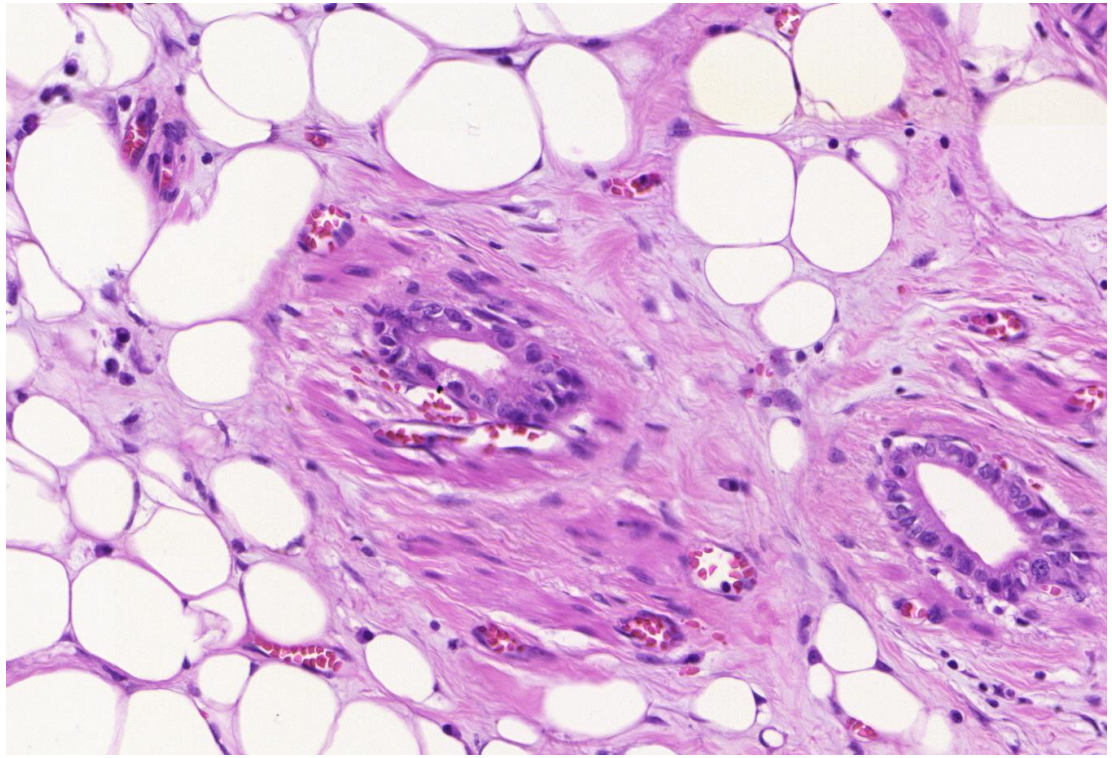
versus



Which one is the cancer?

Infiltration of nerves and retroperitoneal fat





Pathological prognostic factors

- Major importance: stage
  - Based on size T1-3: <2 cm, 2-4 cm, >4 cm, or involvement of celiac or mesenteric vessels: T4
  - Regional lymph nodes (peripancreatic, hilar, celiac trunc, mesenteric…)
  - Distant metastases: M1

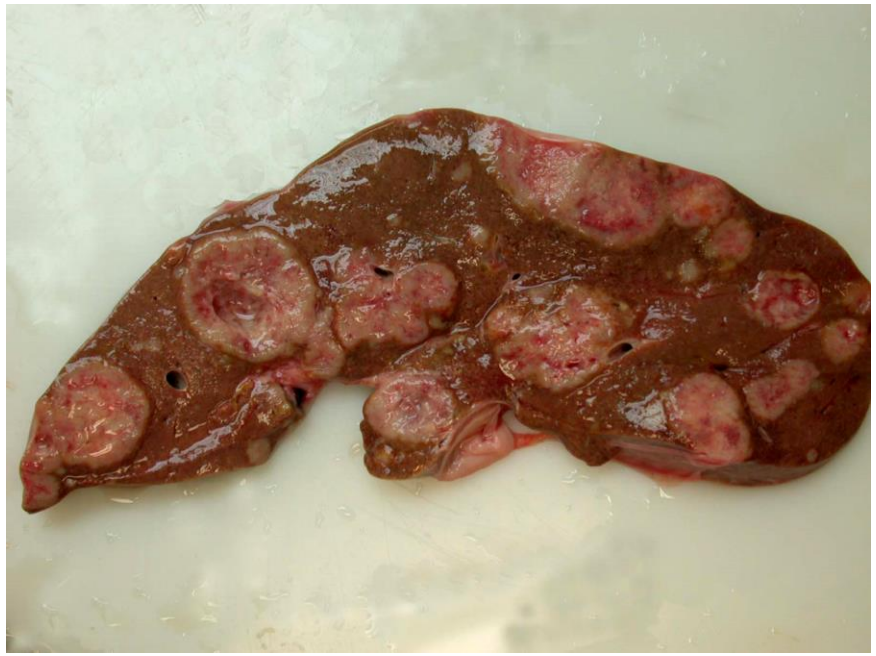
- Minor importance: grade

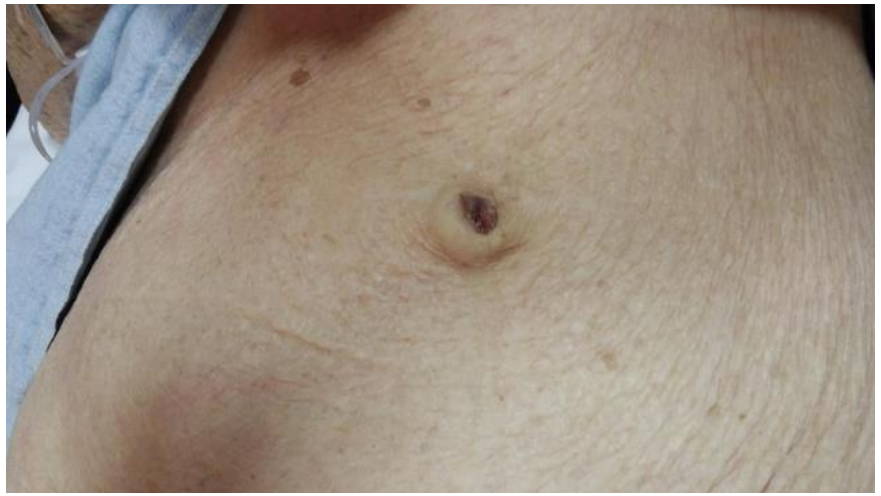
Metastases of PDAC

- Lymphatic: peripancreatic/liver hilus/mesenteric lymph nodes
- Distant lymph nodes: neck, mediastinal etc.

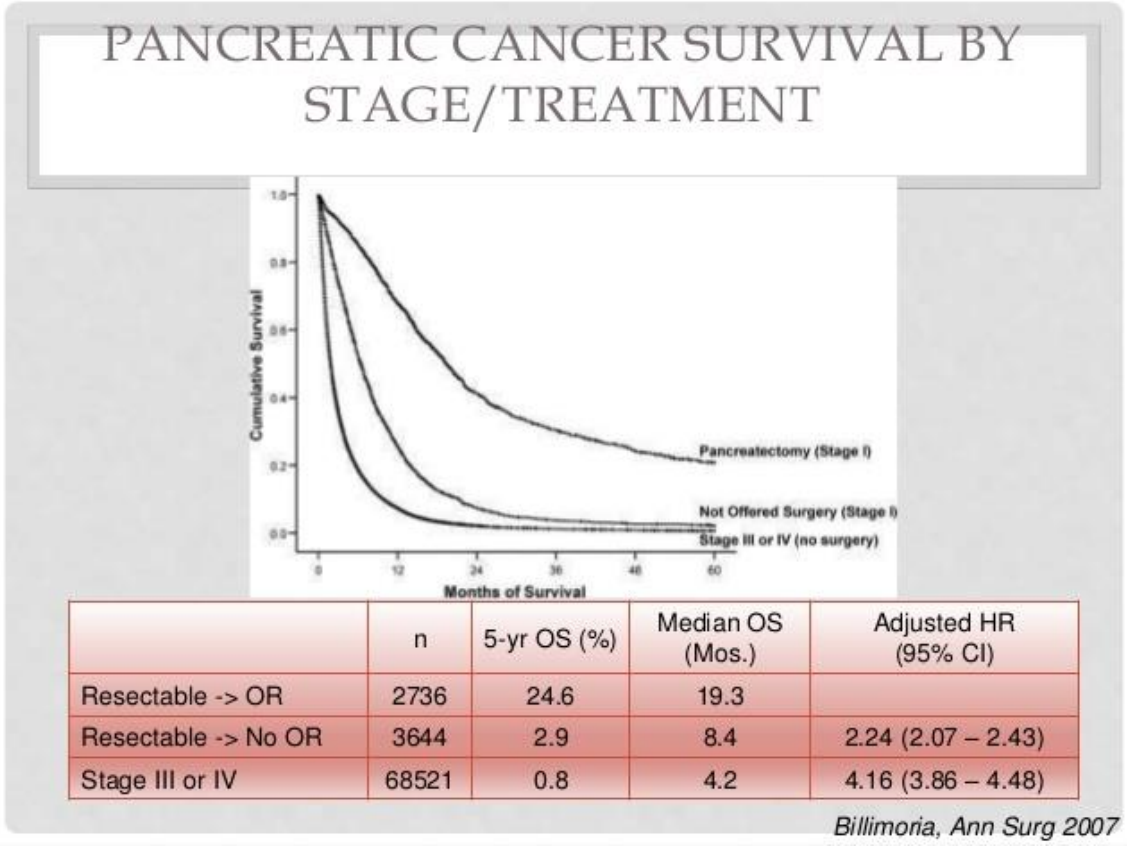
- Portal type: liver

- Cavital: peritoneal/pleural carcinosis
  - Special site: umbilical (Sister Mary Joseph nodule)



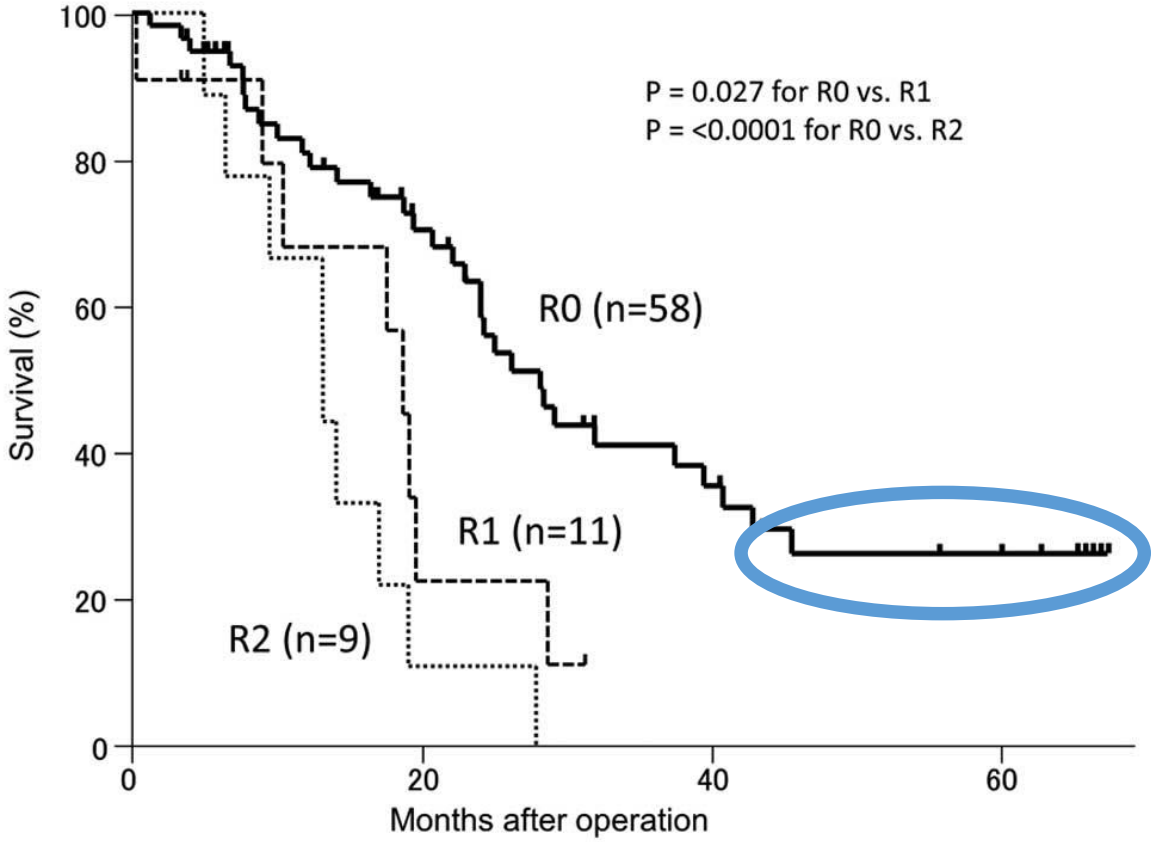


Clinicopathological prognostic factors



	n	5-yr OS (%)	Median OS (Mos.)	Adjusted HR (95% CI)
Resectable -> OR	2736	24.6	19.3	
Resectable -> No OR	3644	2.9	8.4	2.24 (2.07 – 2.43)
Stage III or IV	68521	0.8	4.2	4.16 (3.86 – 4.48)

Billimoria, Ann Surg 2007



Resectability: T1-3/M0 (PPPD-Whipple procedure)

Surgical margin

In fact, 25-30% patient with resectable tumor (cT 1-3, cM0) and R0 resection have curable disease, but the proportion of these patients is less than 10%...

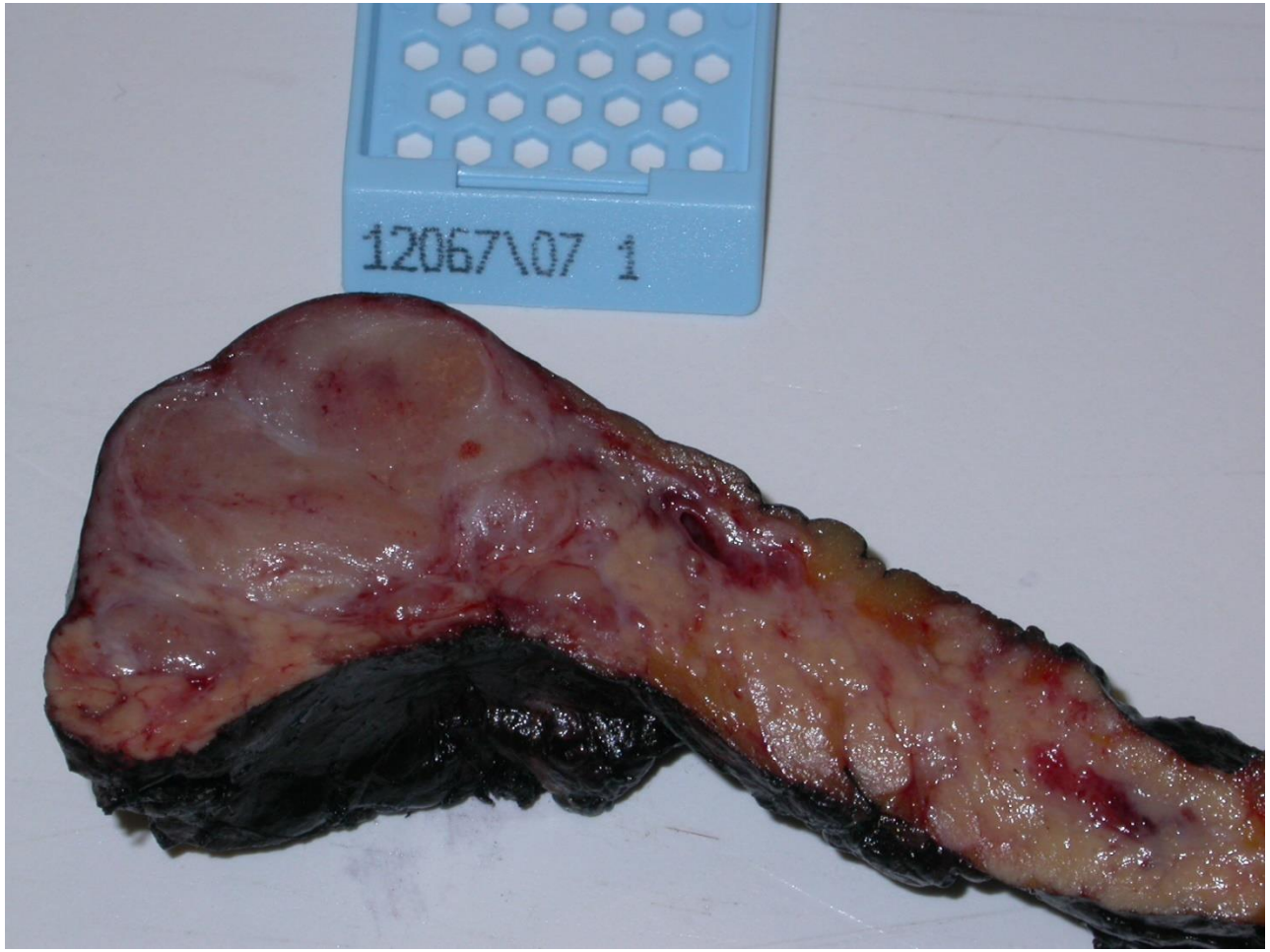
3.3. Pancreatic neuroendocrine tumors (PNET)

See also in lecture „Endocrine pathology”

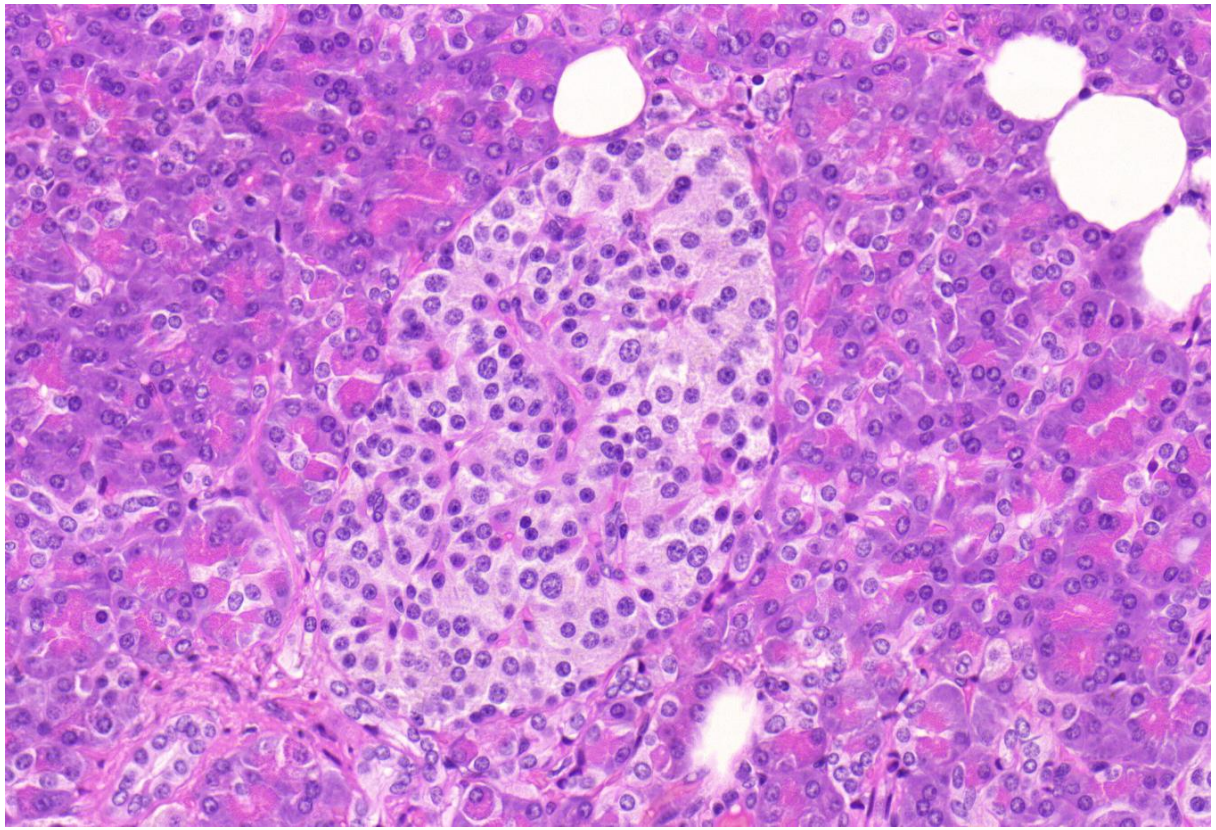
- Neoplasms of the endocrine islands
- Hereditary: MEN 1 syndrome
- Sporadic: more common
- Most common form: insulinoma (others: glucagonoma, gastrinoma, etc., and hormonally inactive)
- Malignant potential differs between grade 1-2-3 tumors
  - Except: insulinoma with size <2 cm: benign tumor

Macroscopy

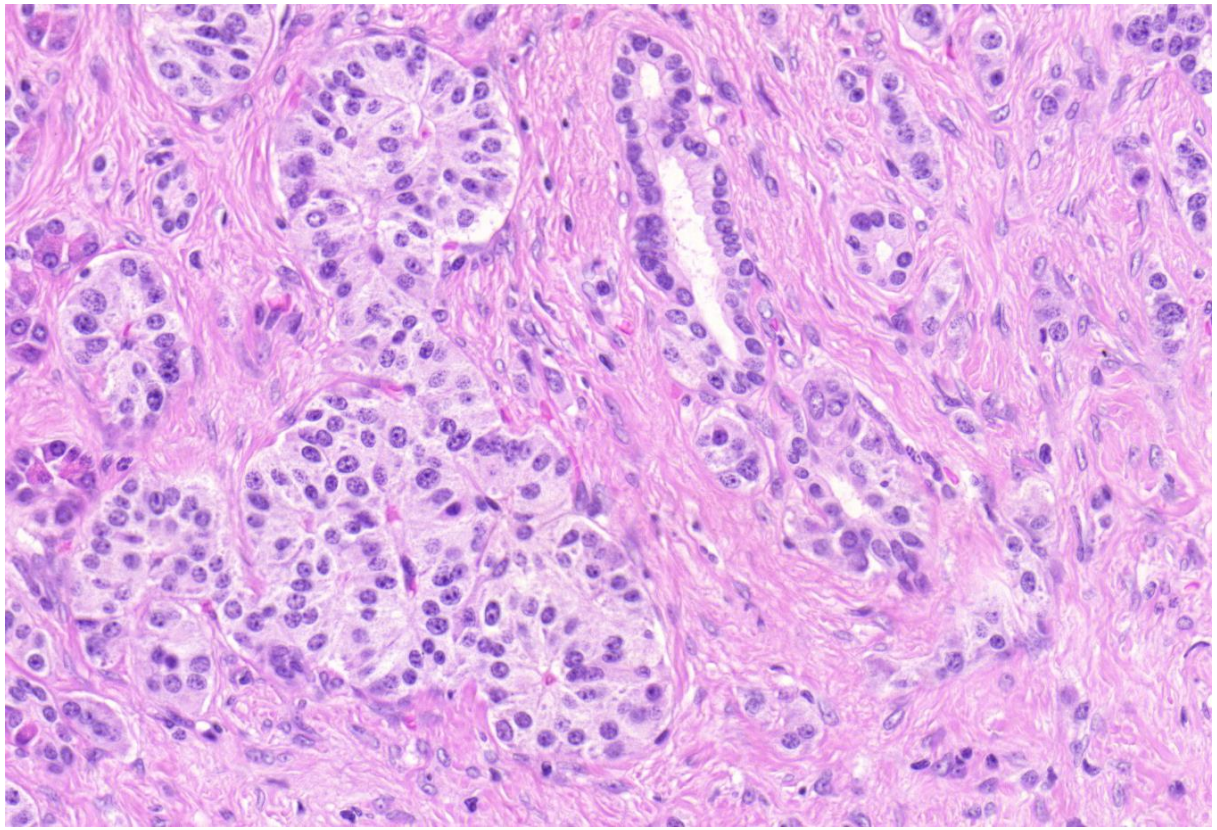
- Generally small
- Well circumscribed
- Yellowish color
- Hard consistency



Microscopy



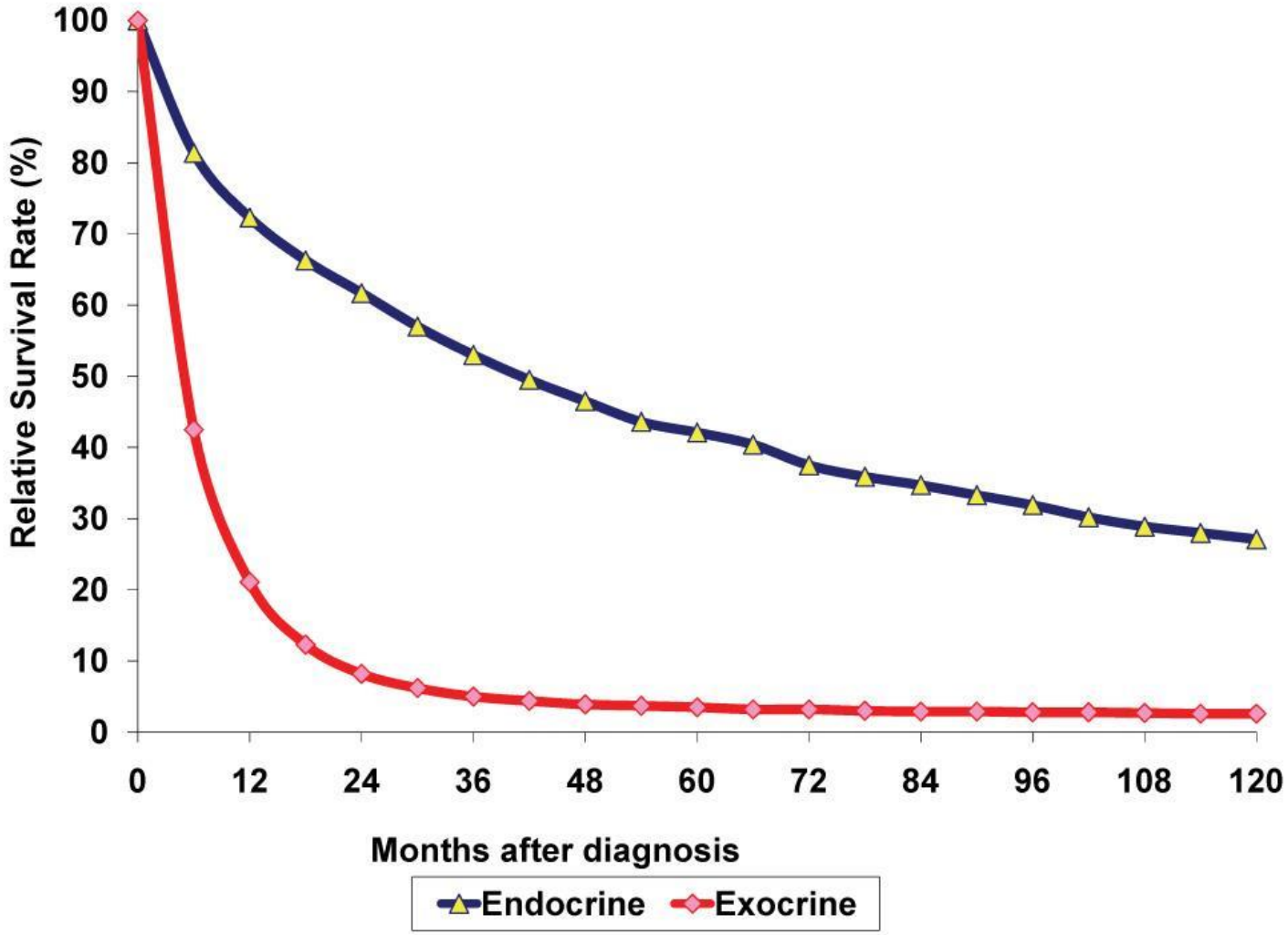
normal



tumor

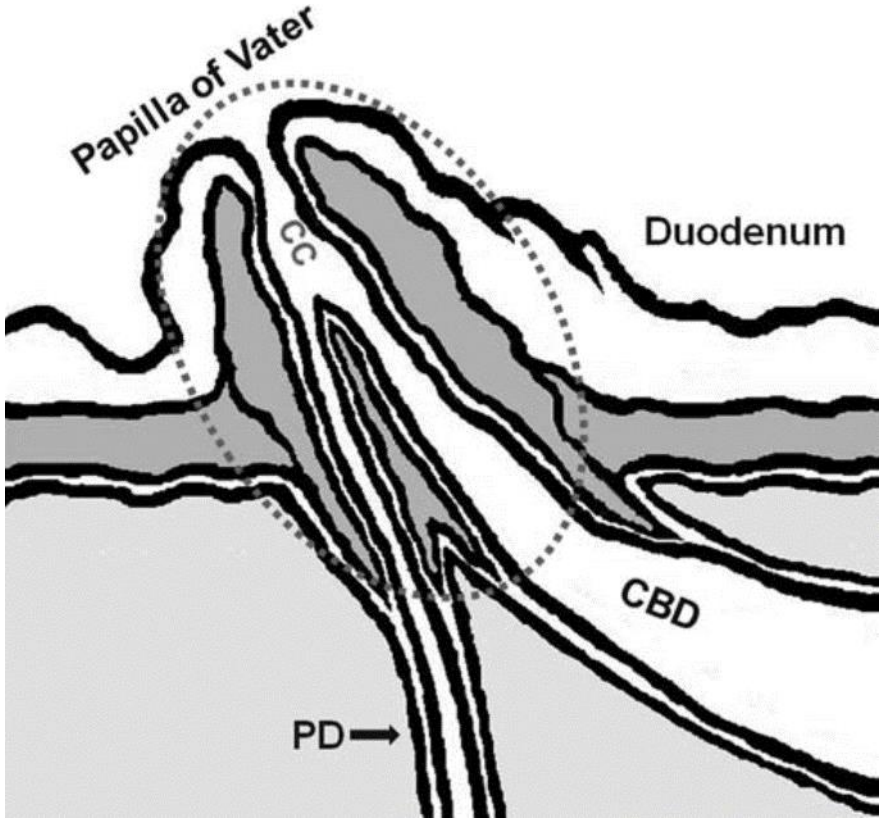
PNET have much better survival than PDAC

even in metastatic stage

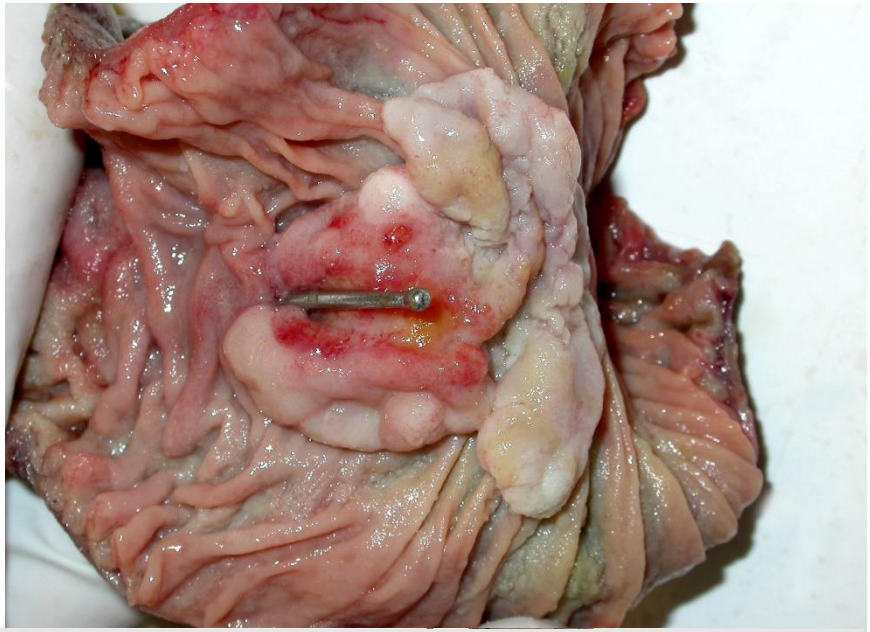


3.4. Tumors of the ampullary region

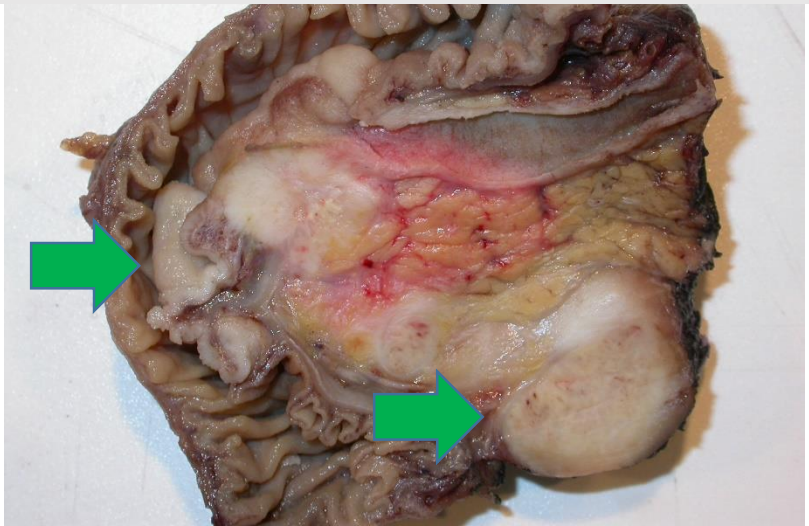
- Biological similarity with intestinal carcinoma
- Sequence: adenoma→carcinoma
- Signs: causes jaundice in by obstruction of the papilla→ earlier detectable than PDAC
- Adenoma= endoscopic resection
- Carcinoma= PPPD

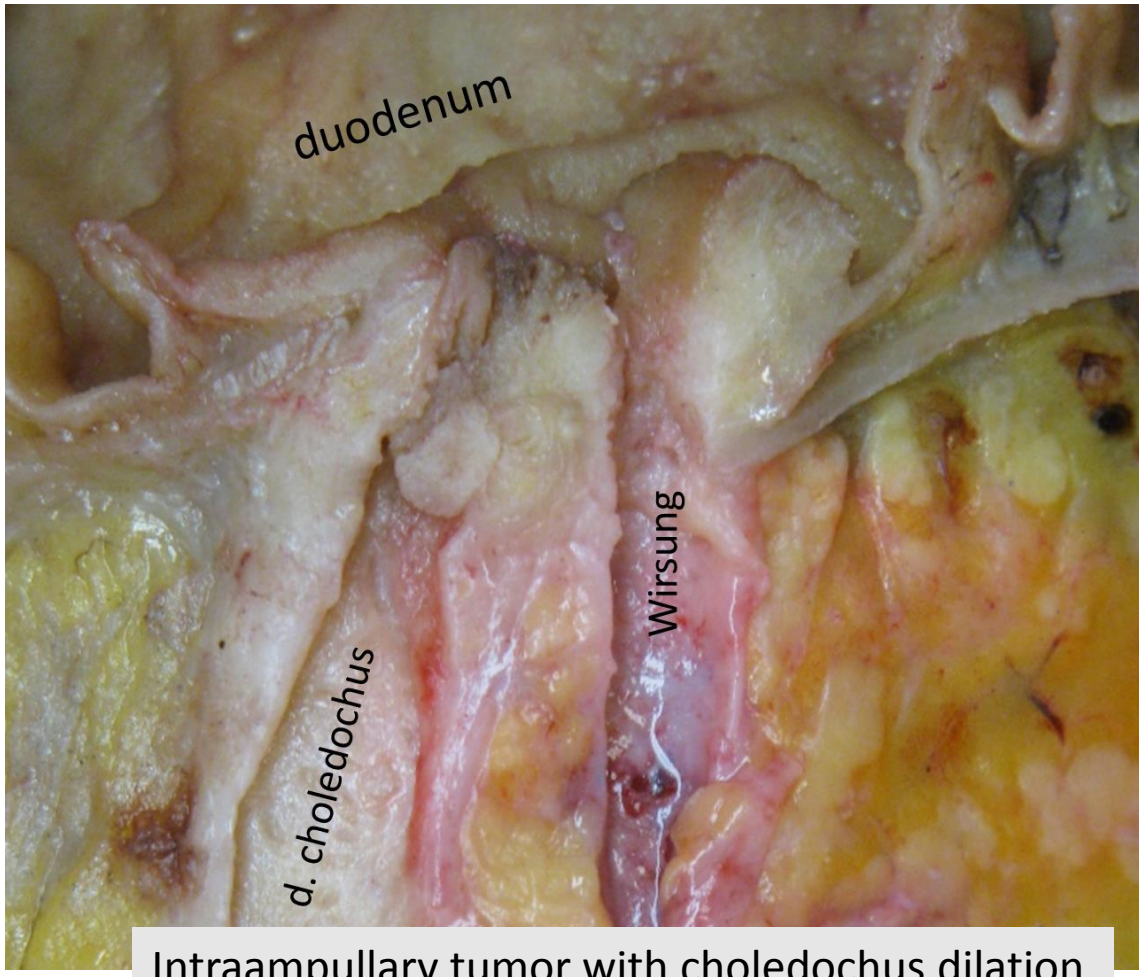


Macroscopy



Exophytic duodenal tumor with lympnode met

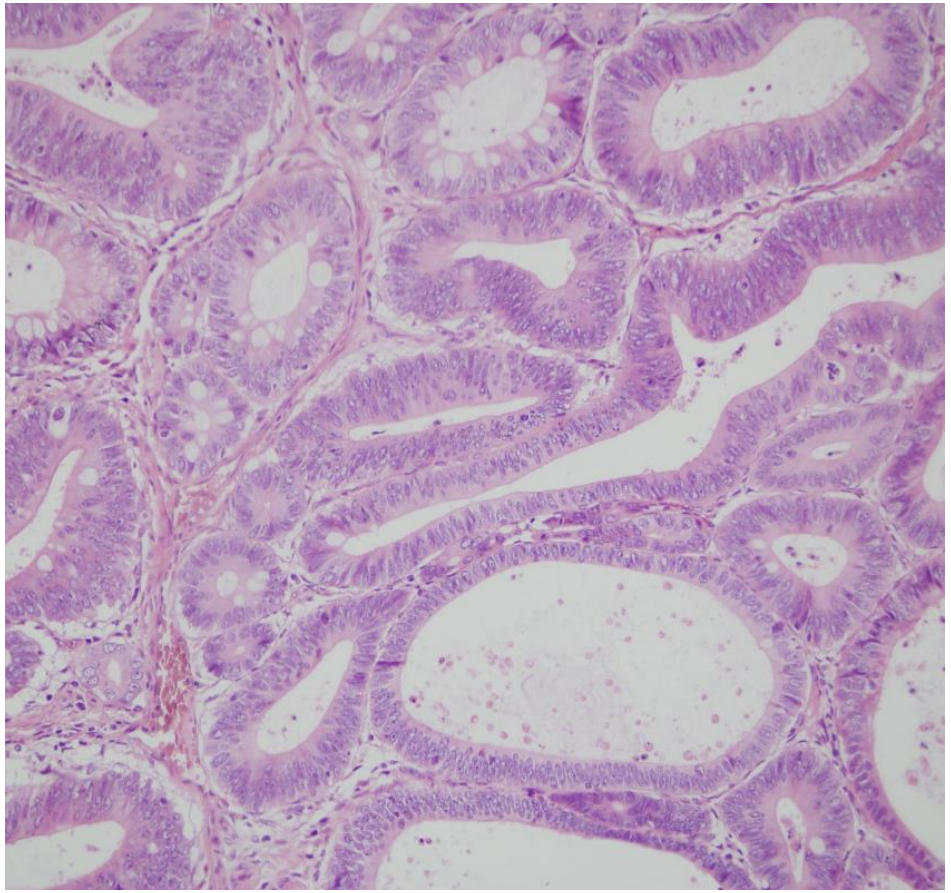




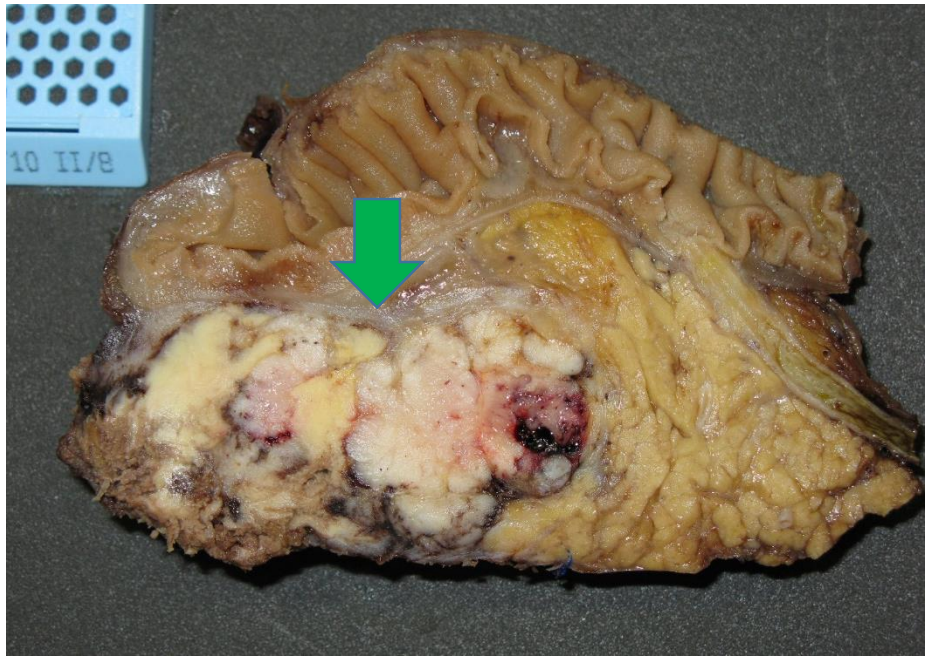
Intraampullary tumor with choledochus dilation

Microscopy

- Most common form is intestinal adenocarcinoma

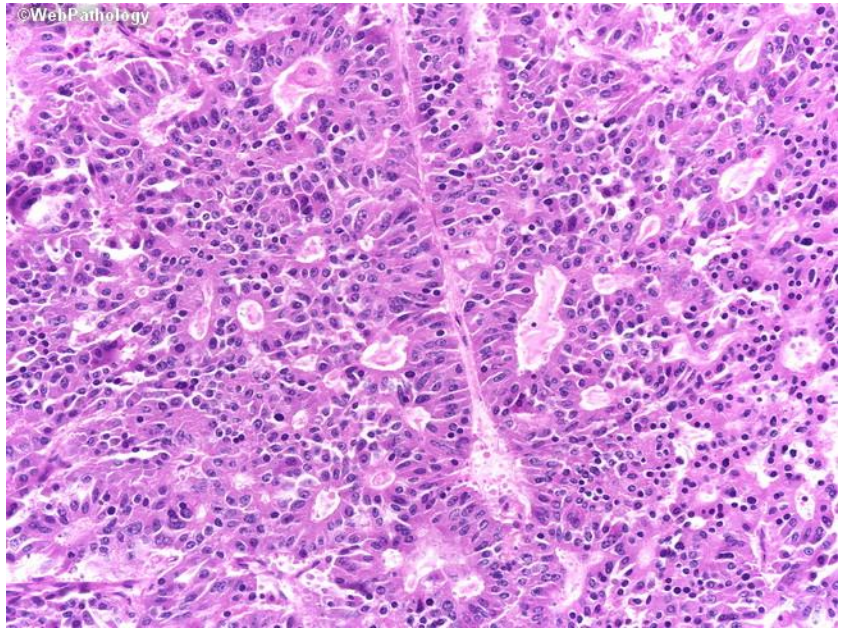


3.5. Rare pancreatic tumors



Acinar cell carcinoma

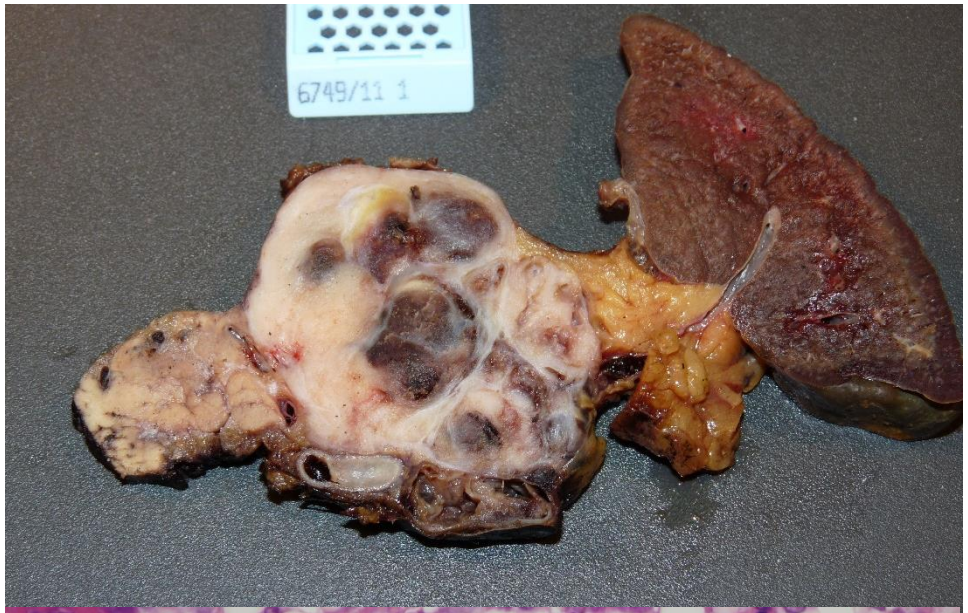
- Malignant tumor of acinar differentiation
- Better survival than PDAC (less infiltration and sensitive to chemotherapy)
- Macro: large, necrotic, bulky tumor (expansive growth)
- Micro: acinar differentiation (trypsin is detectable)

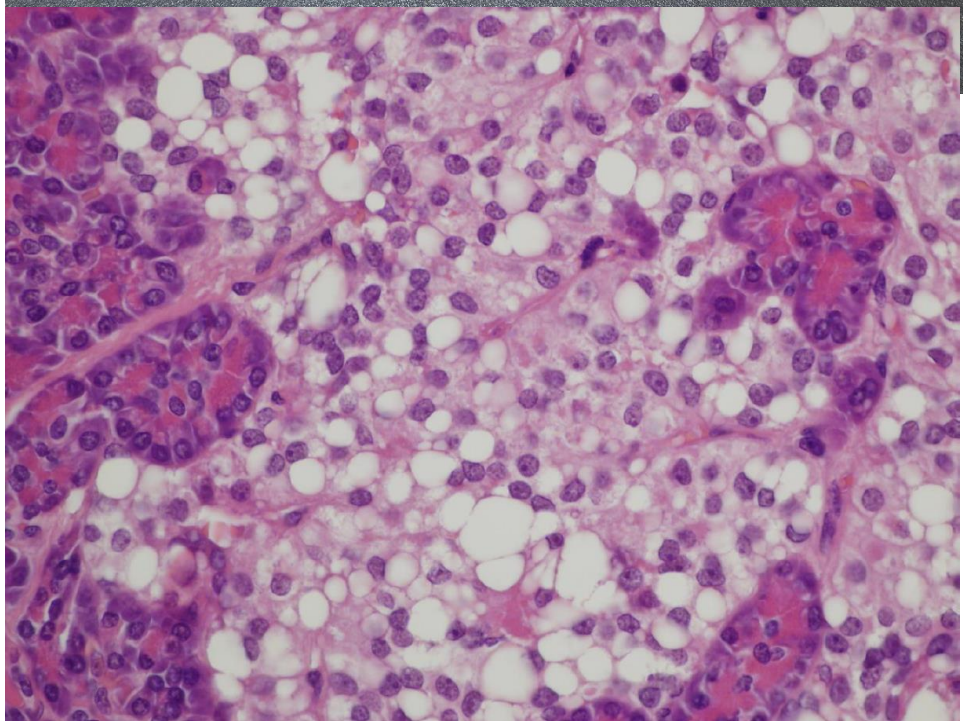


3.5. Rare pancreatic tumors

Solid pseudopapillary tumor

- Neoplasm with low malignant potential (resection is curative)
- Unknown cellular origine
- Female > male
- Young age
- Distal location
- Macro: well demarcated tumor, solid/cystic, frequently hemorrhagic
- Micro: Uniform cells

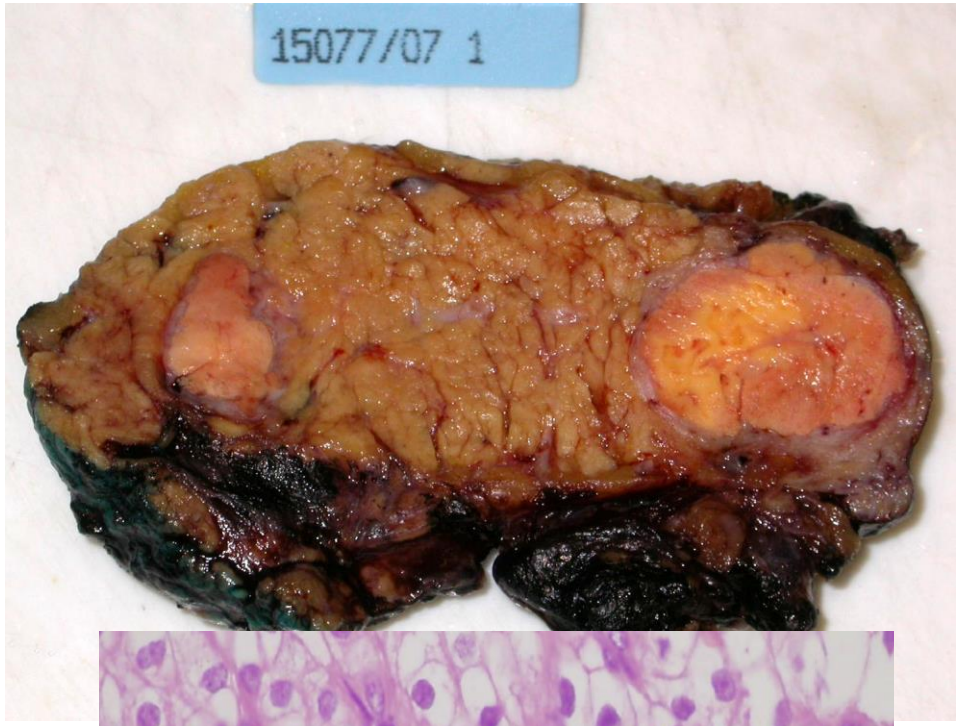


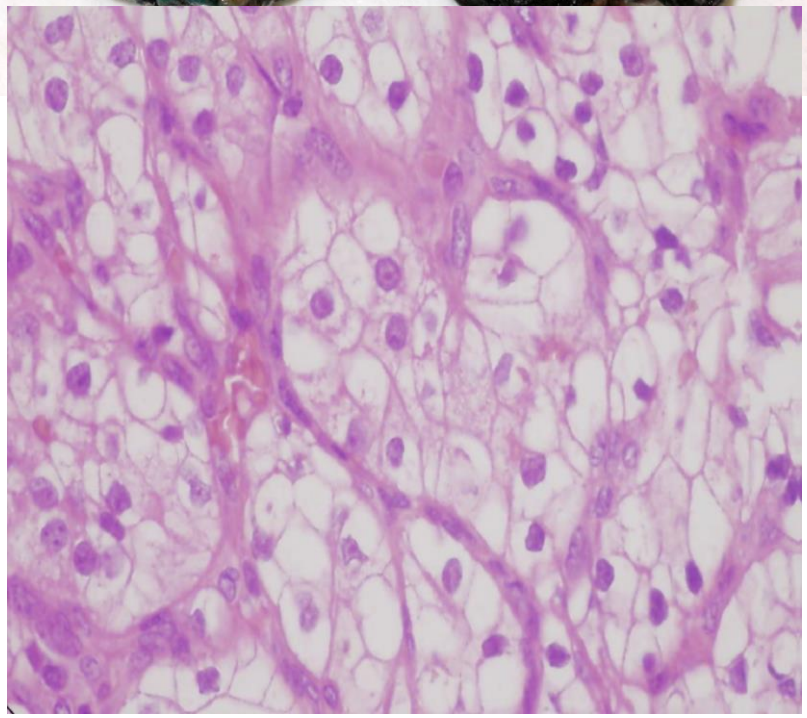


3.5. Rare pancreatic tumors

Metastases

- Most commonly from renal cell carcinoma (RCC)
- Metastasectomy can be curative in RCC





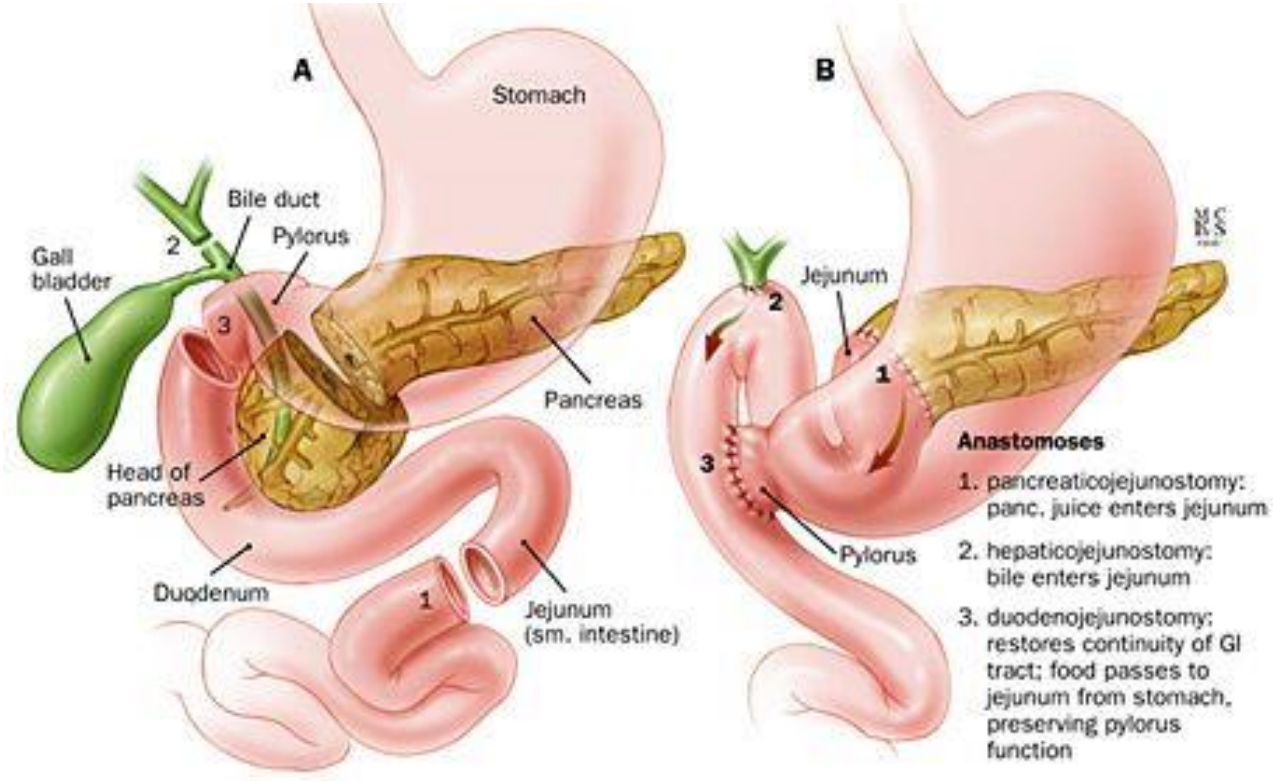
Biopsy methods of the pancreas

Major indication: focal lesion of the pancreas with or without symptoms (=incidental finding)

- Solid mass forming lesion
  - Differentiation of mass forming pancreatitis from cancer
  - Unresectable cancer: histological type
  - Methods:
    - Endoscopy ultrasound (EUS) guided FNA/CNB (resectable)
    - Transcutaneous US or CT guided FNA/CNB (non-resectable)
    - Intraoperative FNA/frozen histology (dignity, margins)
- Periampullary tumors and bile duct carcinoma
  - Differentiation of adenoma and carcinoma
  - Method: ERCP with biopsy or brush cytology
- Cystic tumors
  - Differentiation of neoplastic/non neoplastic cysts (pseudocyts)
  - Method: EUS/transcutaneous aspiration

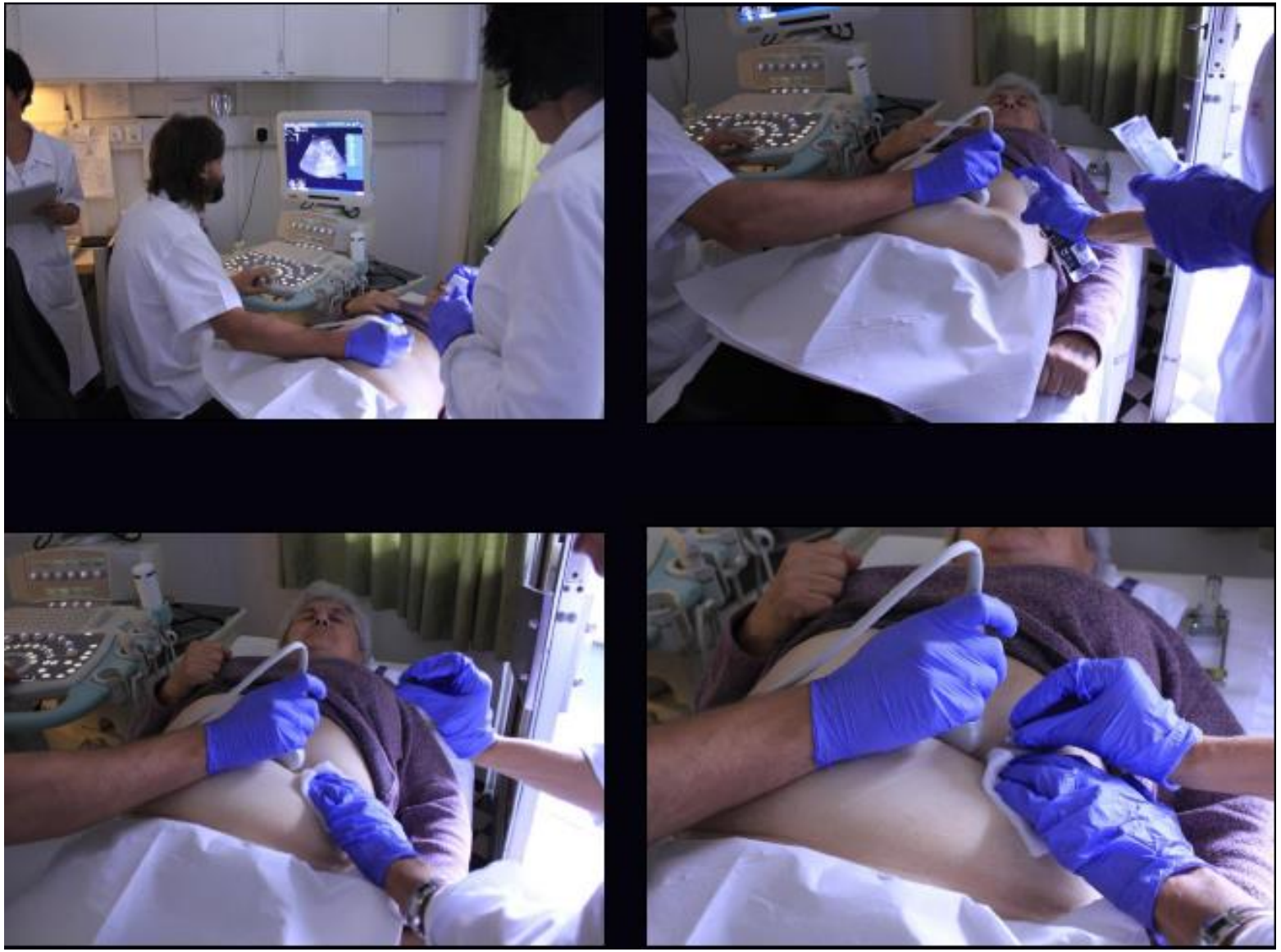
Surgical management of proximal pancreatic lesions: PPPD (pylorus preserving pancreatoduodenectomy, Whipple procedure)

- Very serious operation with high perioperative morbidity
- Decreased life quality
- Patient selection!!!



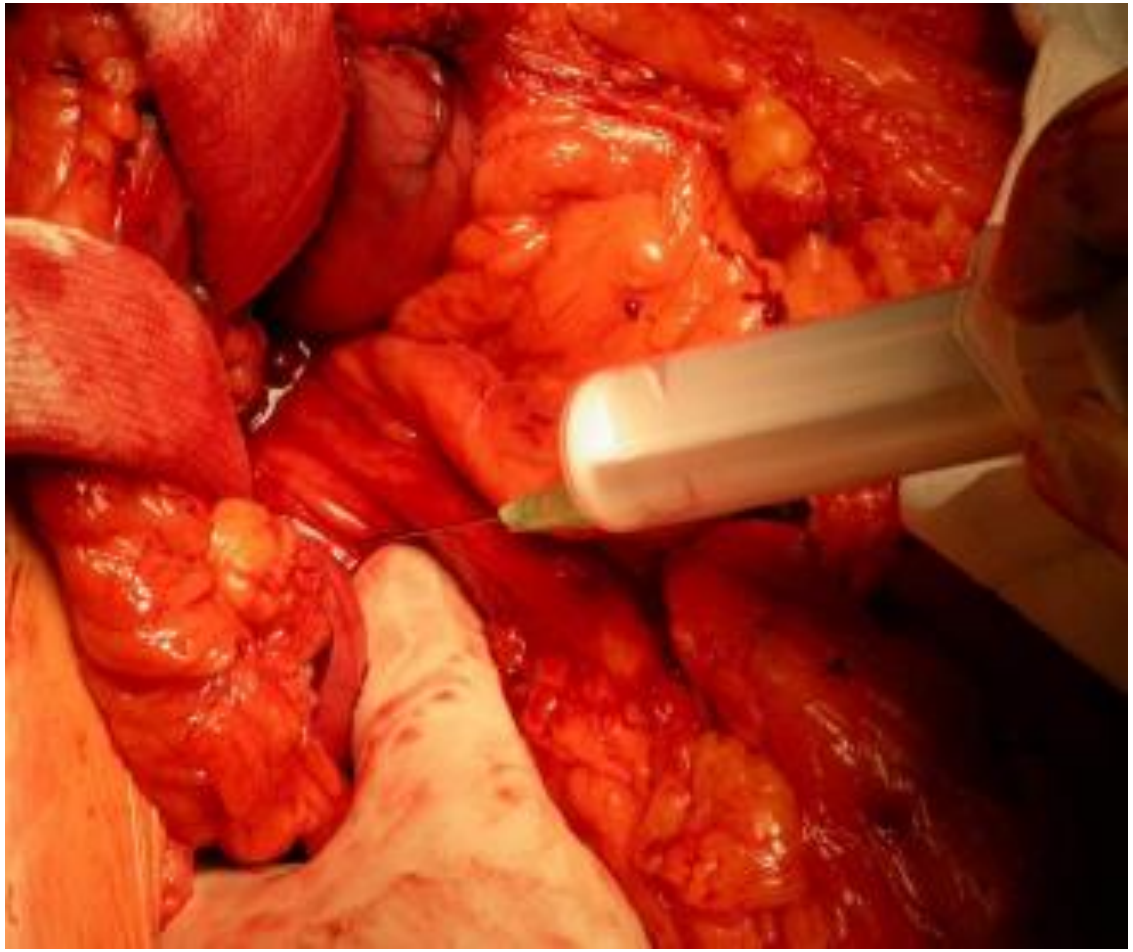
Transcutaneous biopsy

- Fast
- Cheap
- Realtime targeting with US
- Fear of tumor cell spread (needle-site metastasis: <0,1%)
- Indicated primarily in non-resectable cases/EUS guiding is not available



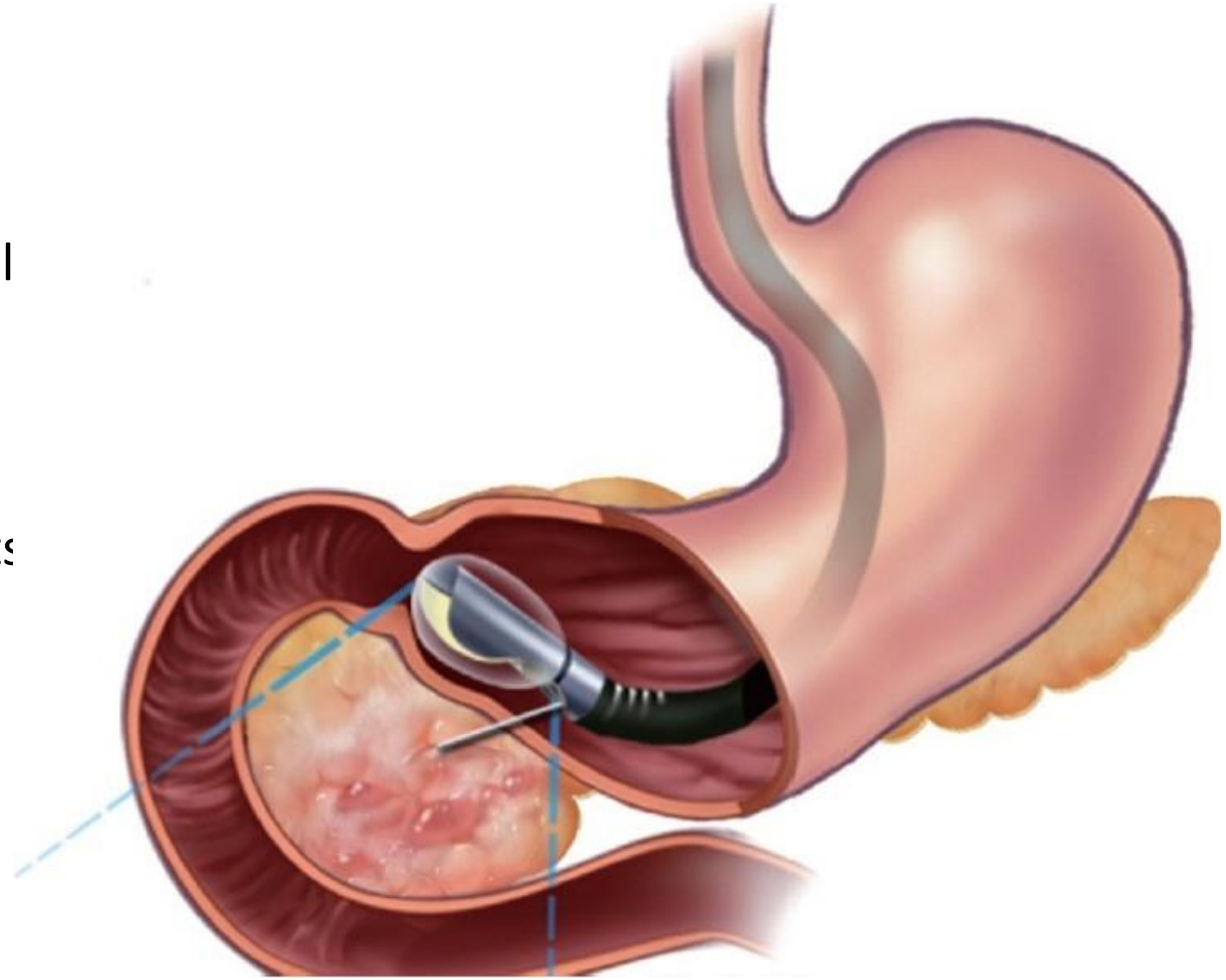
Intraoperative biopsy with palpation

- Fast
- Cheap
- Lower sensitivity
- „Old-fashioned”



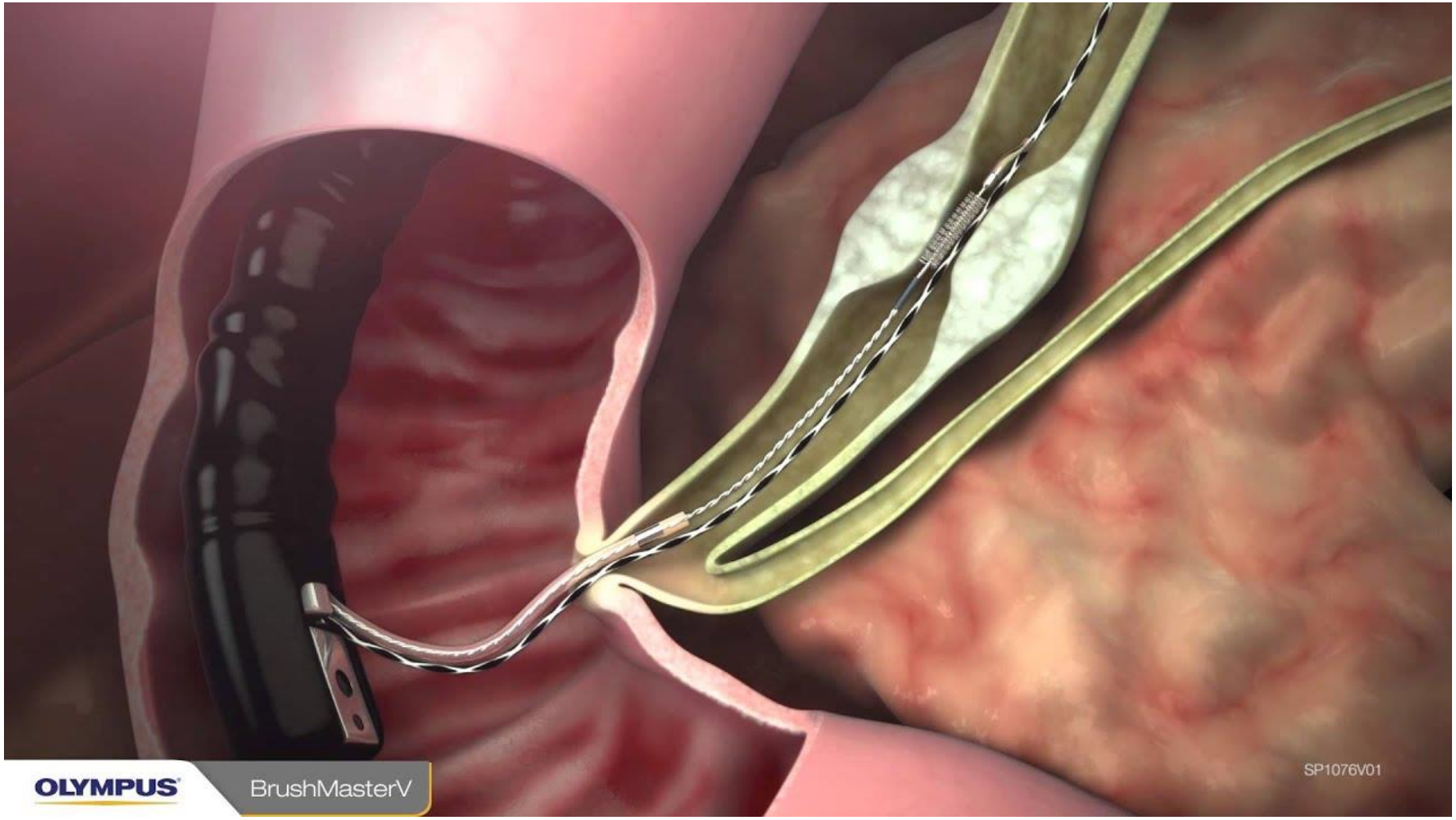
EUS guided punctation

- Expensive instruments
- High experience is needed
- No chance of tumor cell spread within the peritoneal space
- More precise targeting
- Drainage of pseudocysts



ERCP+brush cytology

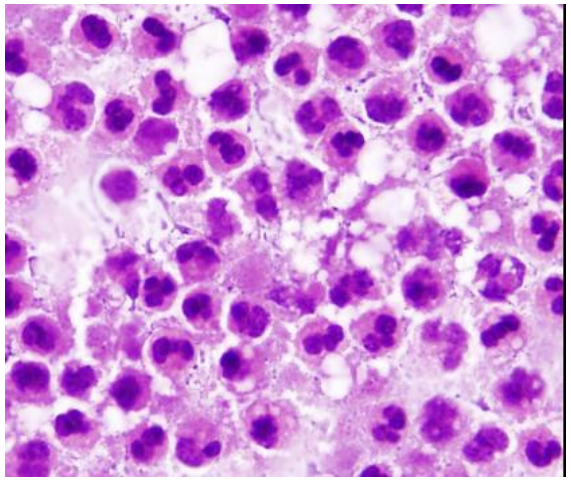
- Ampullary tumors
- Choledochus tumors
- Smears are rich in inflammatory cells & reactive epithelium→ difficult to recognise the tumor cells

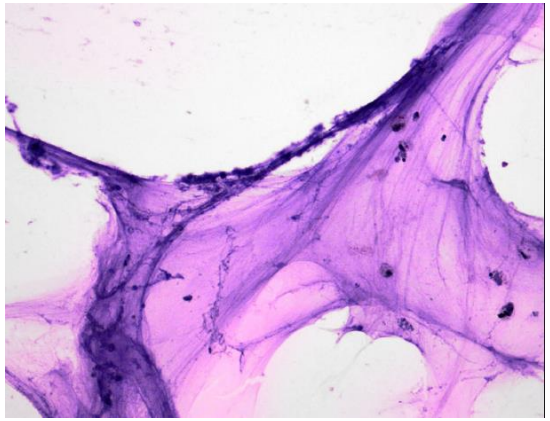


Cytological smears from cystic pancreatic lesions

- Extracellular material & cells
  - Mucin is diagnostic!
- Cellularity may be variable
  - Malignant lesions are more cellular

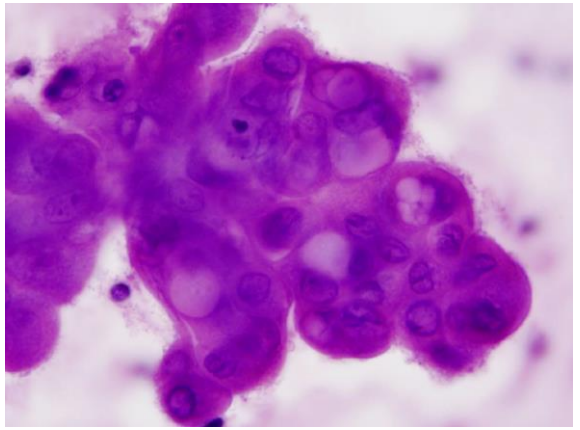
Pseudocyst: necrosis+granulocyste





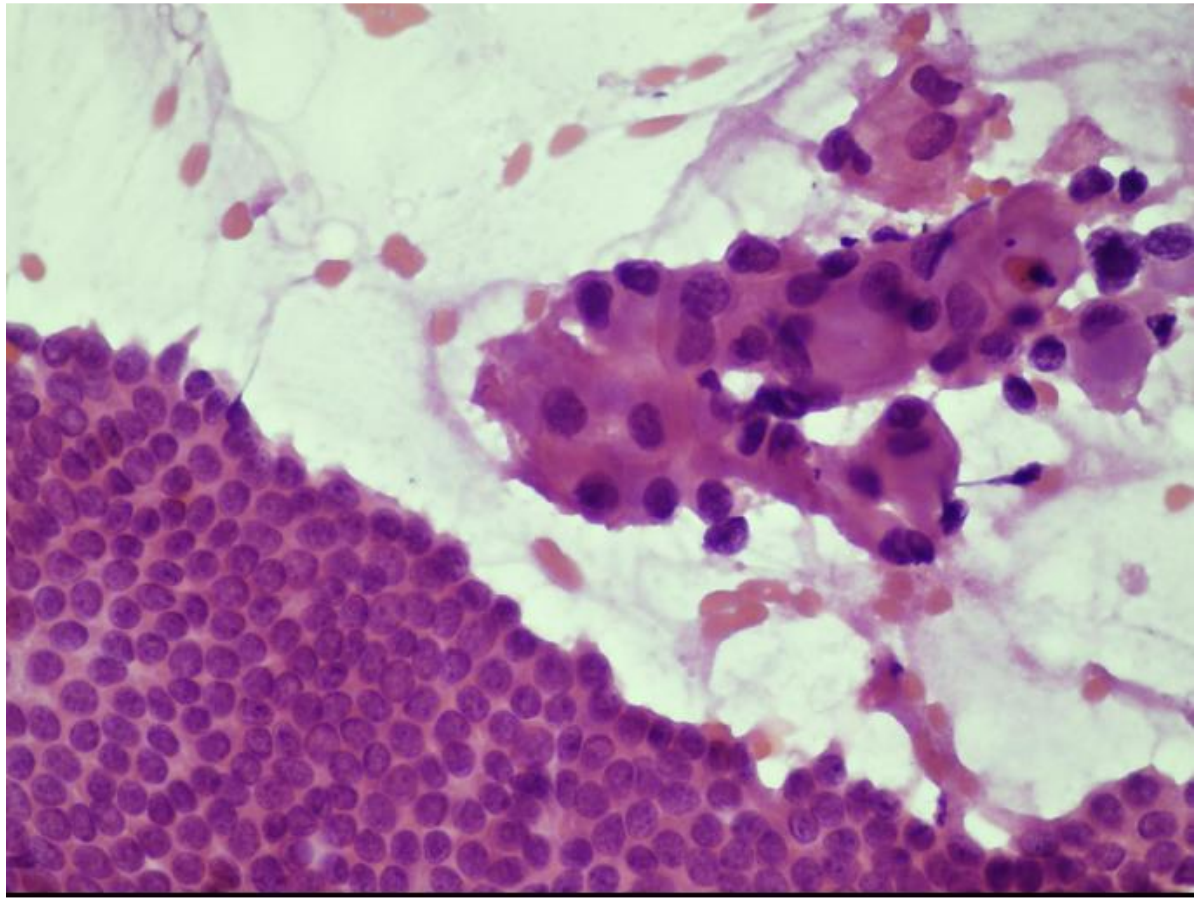
Mucinous tumor

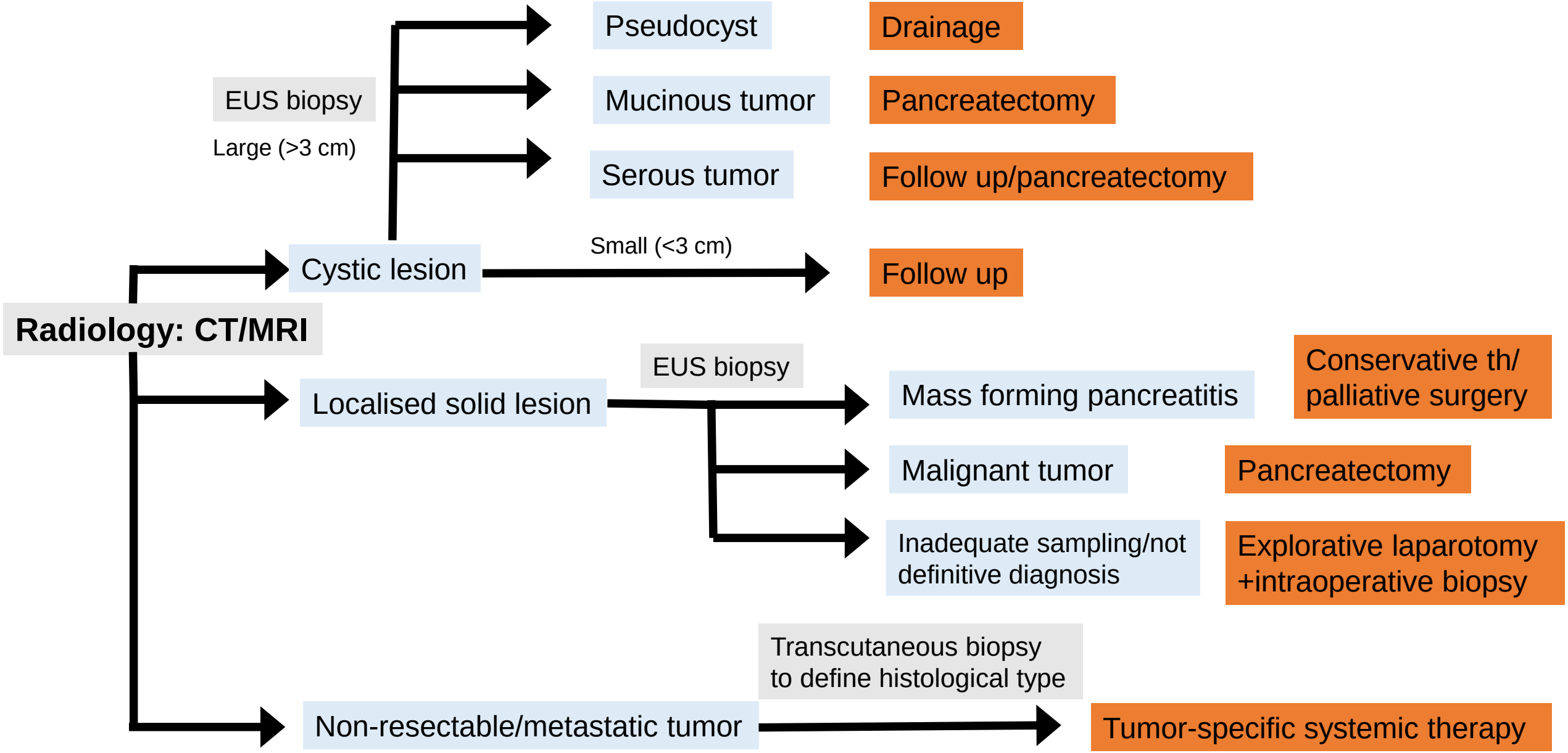
Mucinous tumor with atypical cells



Cytological smears from solid lesions

- Differentiation of reactive ducts and well differentiated adenocarcinoma is extremely difficult!
- Cellularity may be variable
  - Inadequate (non diagnostic) sampling:
    - Very desmoplastic tumor
    - Necrotic lesions
    - Needle is not hit the lesion




Radiology: CT/MRI
Cystic lesion
EUS biopsy
Large (>3 cm)
Pseudocyst
Drainage
Mucinous tumor
Pancreatectomy
Serous tumor
Follow up/pancreatectomy
Small (<3 cm)
Follow up
Localised solid lesion
EUS biopsy
Mass forming pancreatitis
Conservative th/ palliative surgery
Malignant tumor
Pancreatectomy
Inadequate sampling/not definitive diagnosis
Explorative laparotomy +intraoperative biopsy
Non-resectable/metastatic tumor
Transcutaneous biopsy to define histological type
Tumor-specific systemic therapy

Take home messages

- Acute pancreatitis is one of the most fatal inflammatory disorders – rapid diagnosis is needed!

- Chronic pancreatitis is a diverse disease with different etiologies/morphology and prognosis

- Combination of radiological and pathological methods is needed to avoid unnecessery radical surgical procedures in mass forming pancreatic lesions