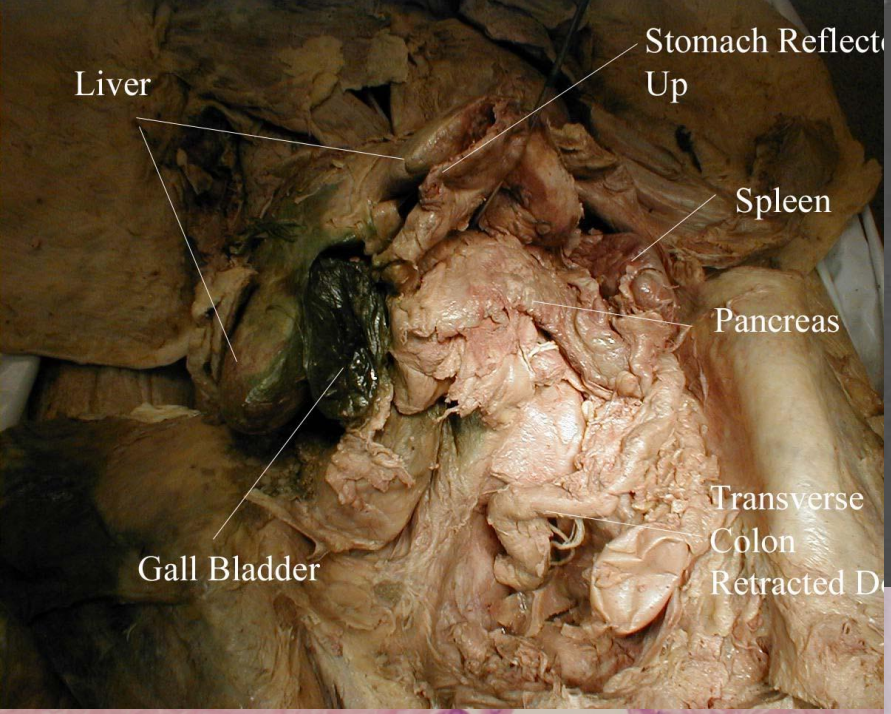
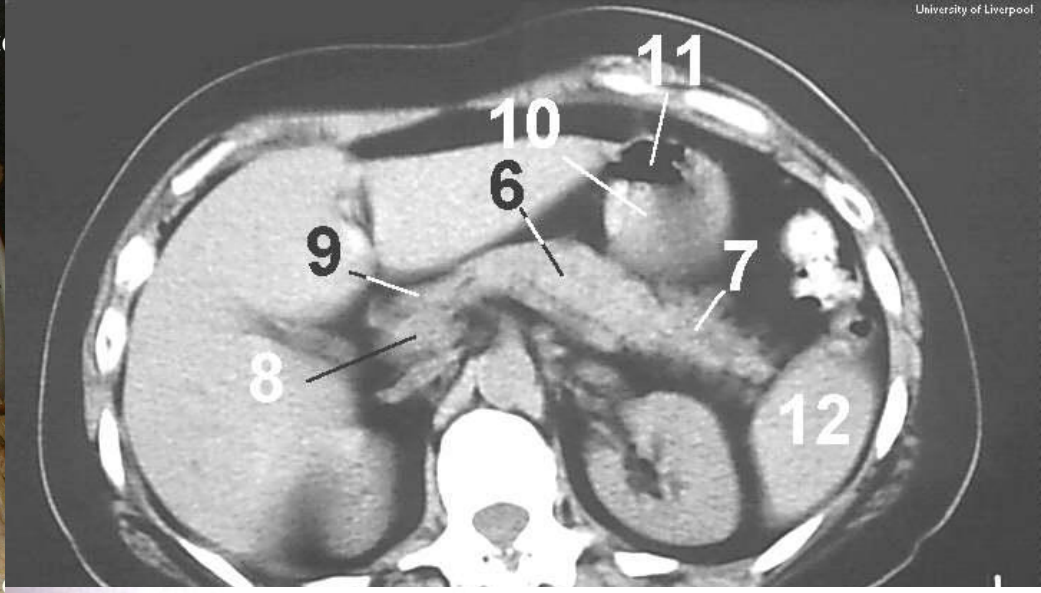
# Pathology of the exocrine pancreas


Liver
Stomach Reflecte
Up
Spleen
Pancreas
Transverse
Colon
Retracted D
Gall Bladder


University of Liverpool
11
10
6
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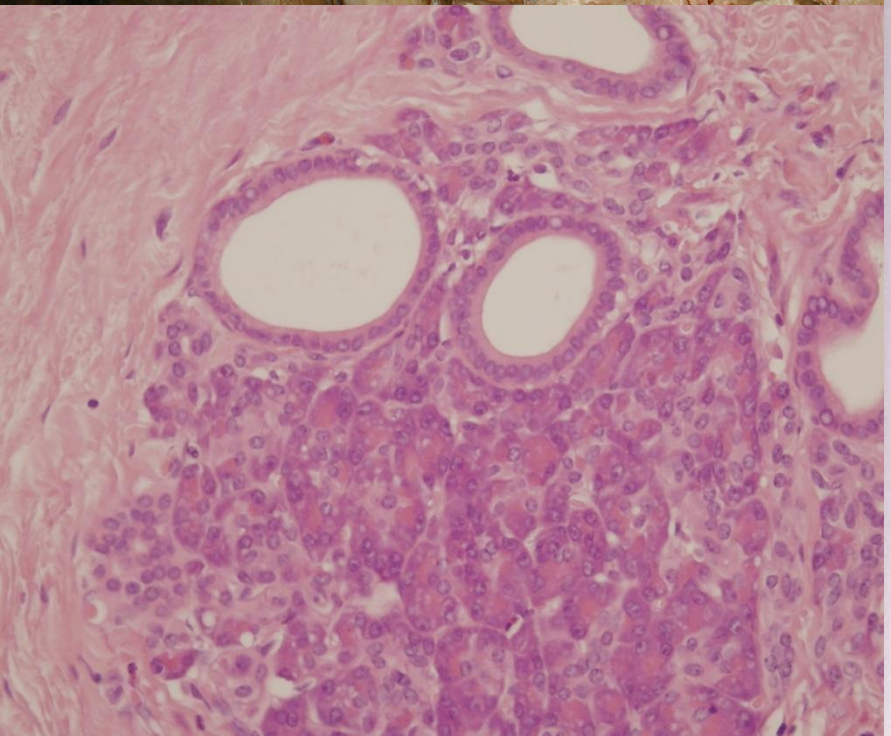
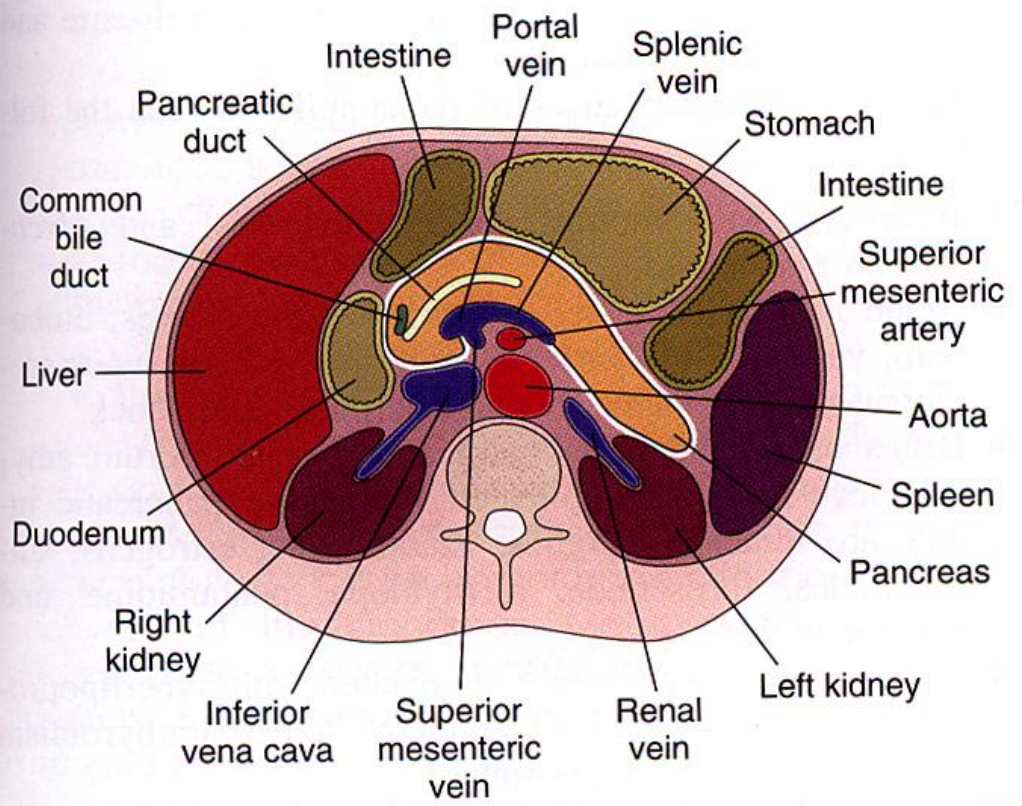
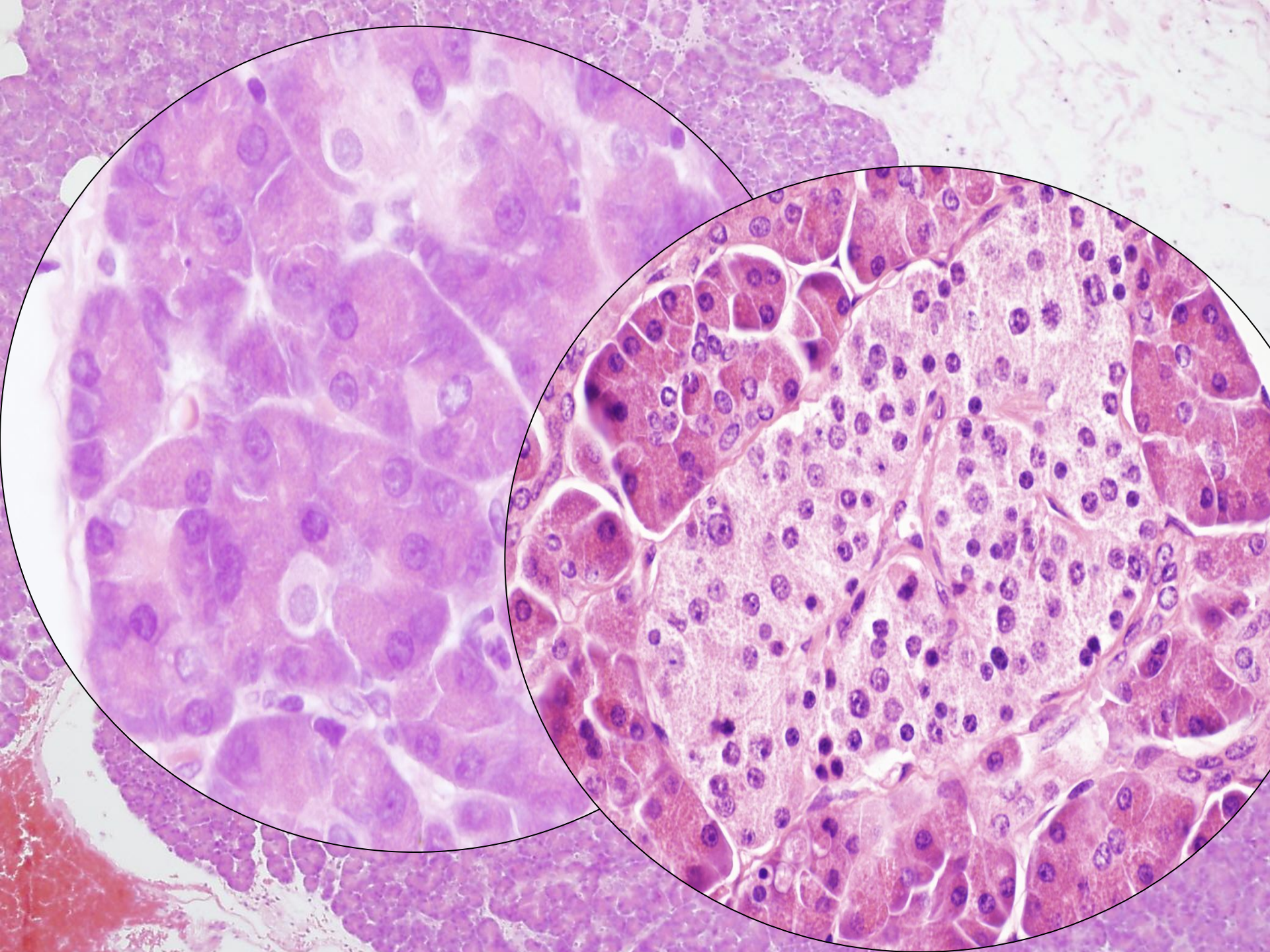
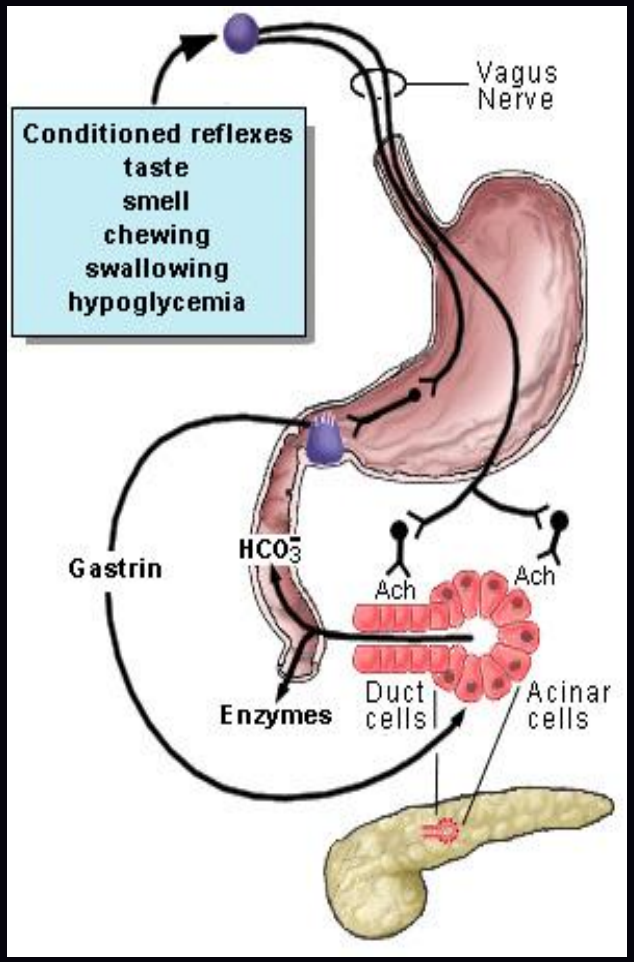
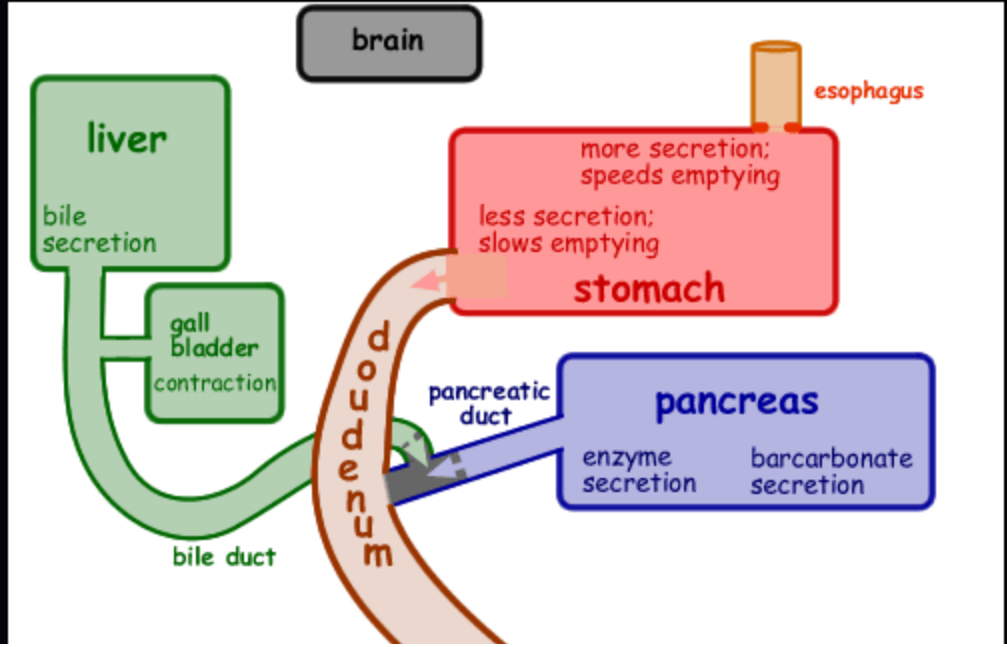



Intestine
Portal vein
Splenic vein
Pancreatic duct
Stomach
Intestine
Common bile duct
Superior mesenteric artery
Liver
Aorta
Spleen
Duodenum
Pancreas
Right kidney
Left kidney
Inferior vena cava
Superior mesenteric vein
Renal vein






*Enterokinase*,autoactivation***

*Cathepsin B****

**TRYPSINOGEN** → **TRYPSIN**

TAP (+) Amplification

| | |
|---|---|
| Trypsinogen | Trypsin |
| Chymotrypsinogen | Chymotrypsin |
| Proelastase | Elastase |
| Kallikreinogen | Kallikrein |
| Pro-carboxypeptidase | Carboxypeptidase |
| Prophospholipase | Phospholipase |
| Procolipase | Colipase |

**Normal pathway: enterokinase is located in the brush border of the small intestine*

***Normal pathway: Trypsinogen autoactivation is a unique feature of human trypsinogen*

***Abnormal pathway:cathepsin B is located within acinar cells*

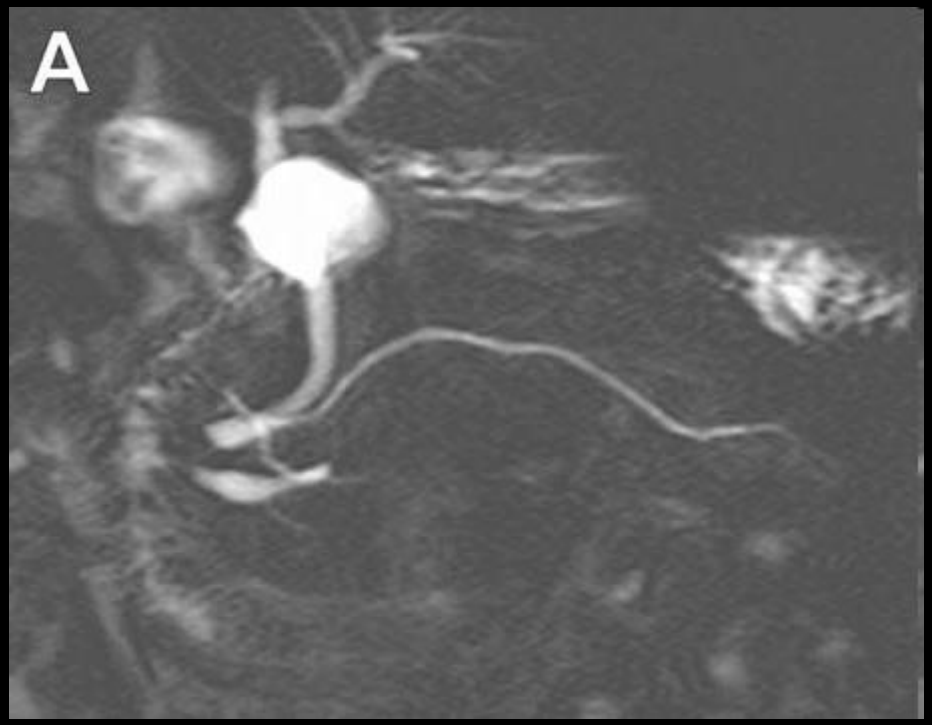
# Enzimes secreted by the pancreas

- Trypsin
- (act.: enterokinase, - secretin – cholecystokinin-
- inh.: acinic, ductal secretions )
- Chymotripsin
- Aminopeptidae
- Elastase
- Amylase
- Lipase
- Phospholipase
- Nuclease

No proenzyme

# Examination of the pancreas

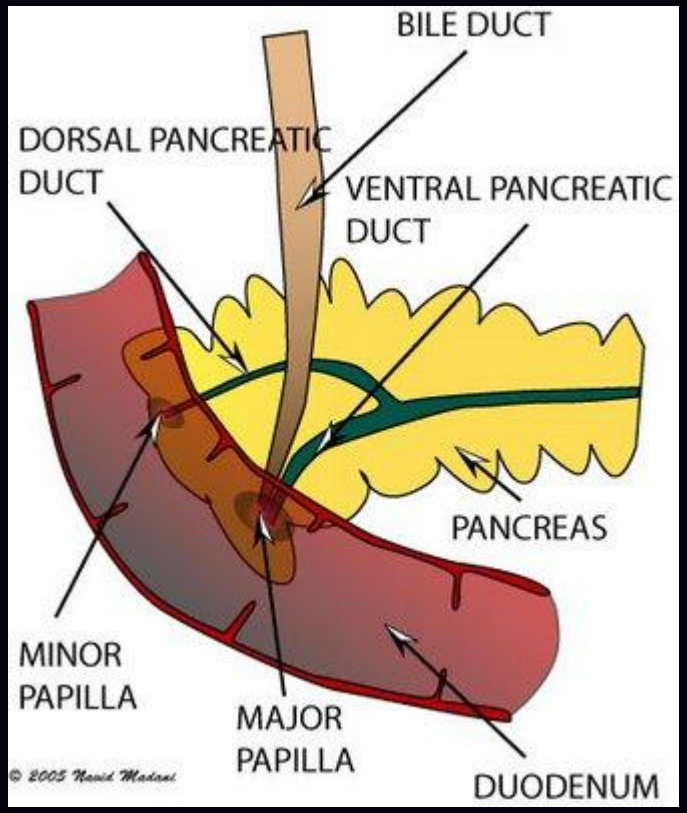
- Laboratory
- US
- CT
- MR
- Cytology - US or CT guided, percutaneous
- US endoscopy
- ERCP-pancreatic juice
- Bile duct scrape
- Intraoperative


A

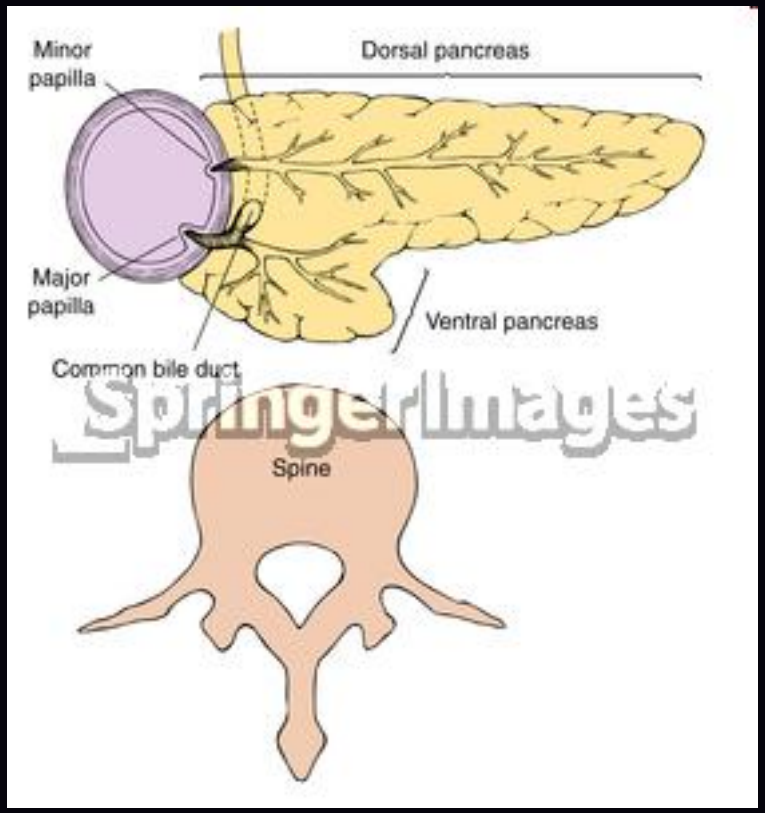
# Developmental anomalies

- Agenesis (very rare)
- Pancreas divisum 3-10 %
  - Wirsung-Santorini division (pancreatitis)
- Ectopic pancreas - 2% (microscopical size - bleeding, 2 % of the islet cell tumors arise in ~ )

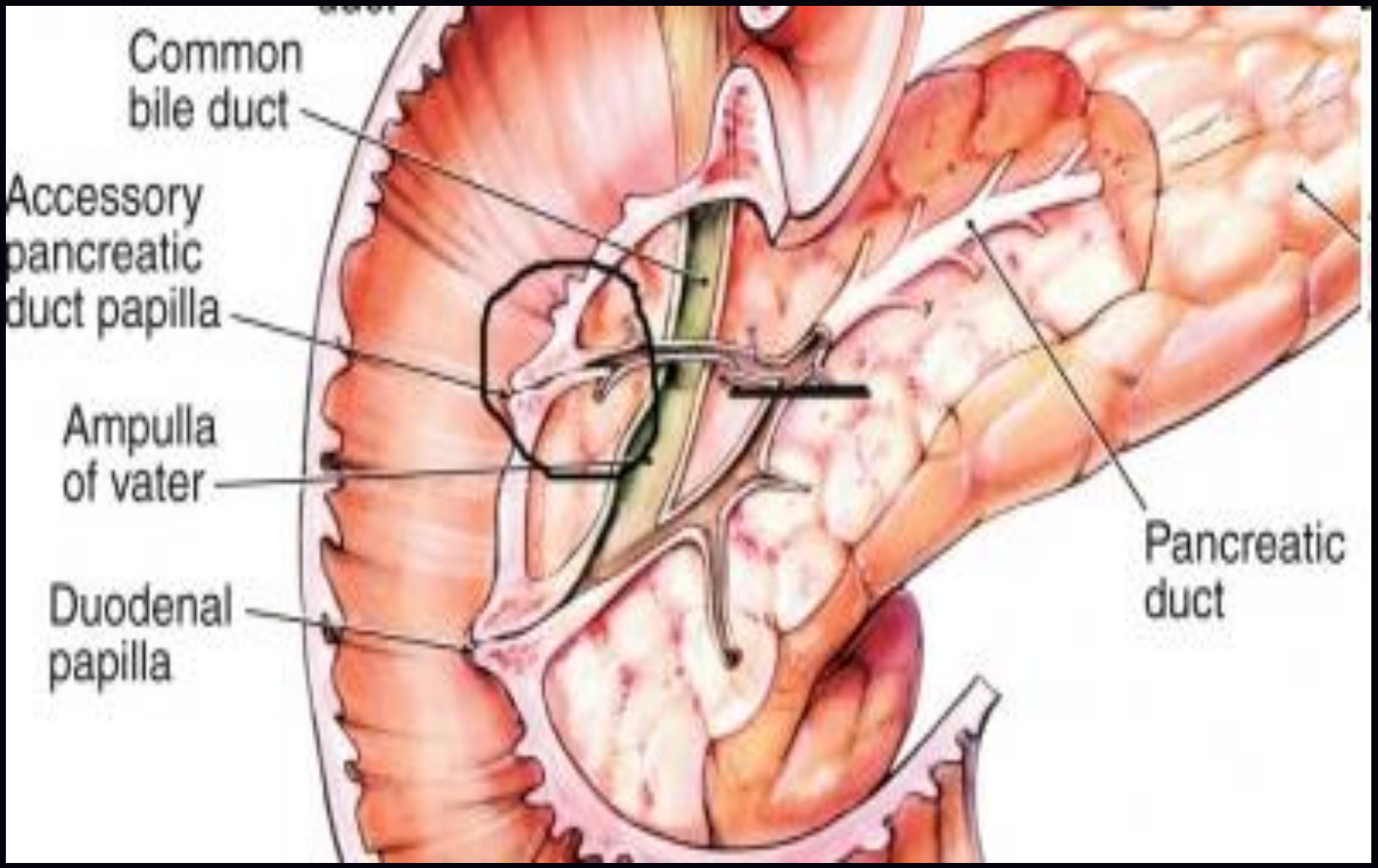
- Pancreas annulare ( mechanical obstruction - duodenum) (rare)

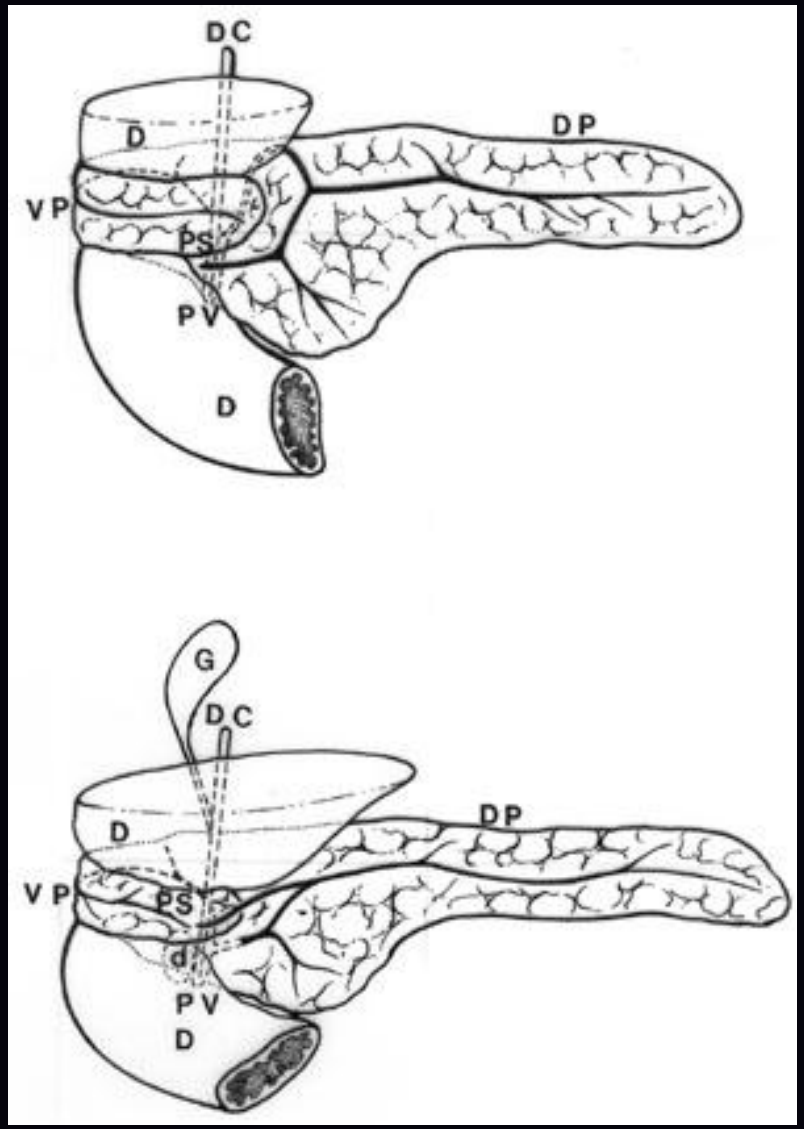



Normal

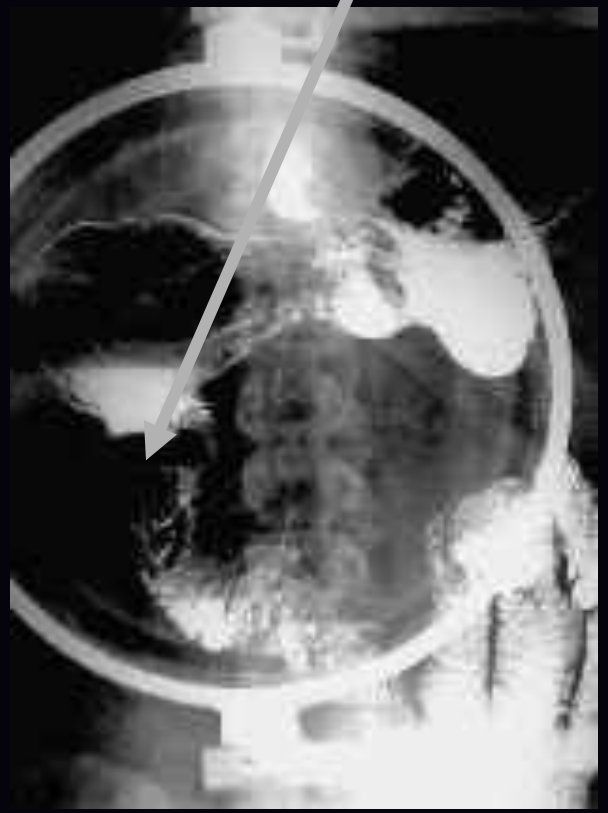


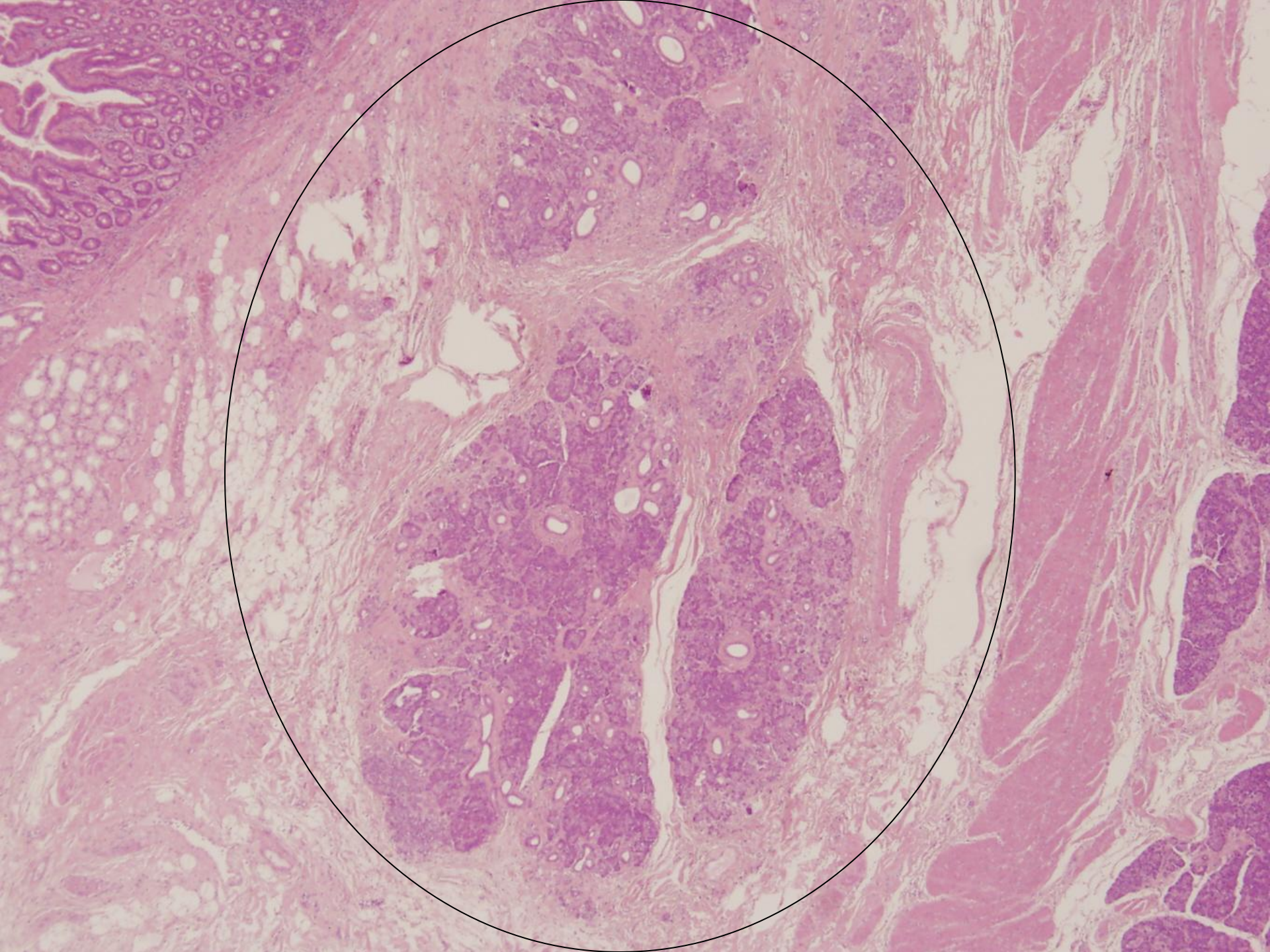

Pancreas divisum


Common bile duct
Accessory pancreatic duct papilla
Ampulla of vater
Duodenal papilla
Pancreatic duct




stenosis





# Pancreatitis

- Acute interstitial pancreatitis
- Acute necrotising haemorrhagic pancreatitis
- Chronic pancreatitis

# Acute pancreatitis

- Inc.: 10-20/100000
- Gallbladder stones in 35-65% of ~ cases
- 5 % of patients having gallbladder stones
- Alcoholism - frequency - 65%-5% (????)
- M/F 1/3 in case of gallbladder stones
- M/F 6/1 in case of alcoholism

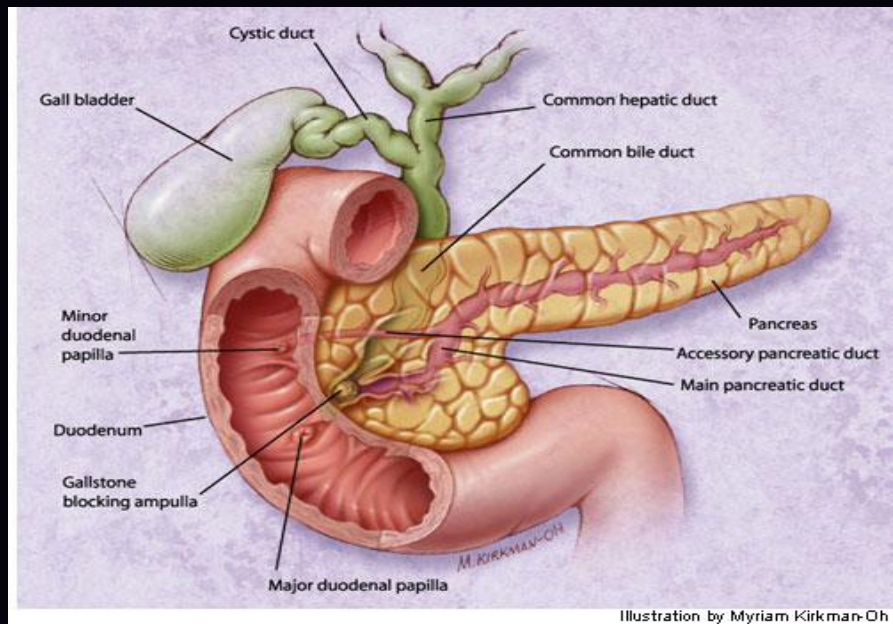


Illustration by Myriam Kirkman-Oh

# Acute pancreatitis - etiology

- Gallbladder stones
- Alcohol
- Dietary fault
- Hyperparathyreosis- hypercalcaemia
- Hyperlipoproteinaemia (I, V type)
- Iatrogenic /ERCP, postoperative/
- Infection / mumps, coxsackie virus, Mycoplasma /
- Trauma
- Vascular (PAN, SLE, Henoch-Schönlein, shock)
- Drugs ( thiazids, azathioprine, oestrogen, sulfonamide, furosemide, methyldopa, pentamidine, procainamide, etc)
- Idiopathic (10-20%)

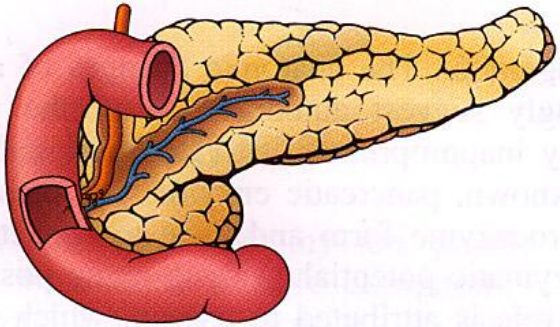
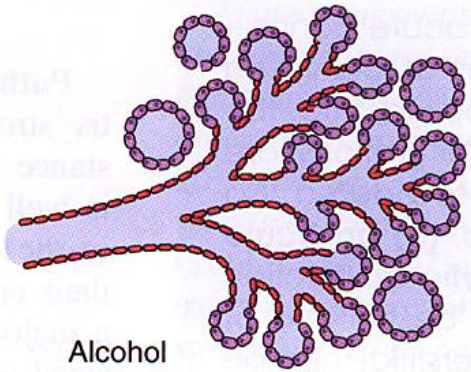
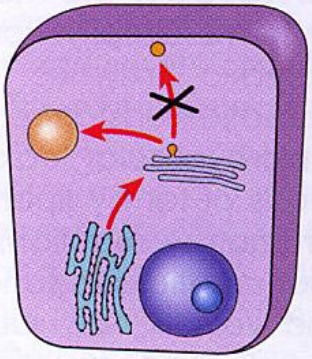
# Acute pancreatitis - etiology

„Idiopathic" (10-20%)

- *Cationic Trypsinogen (PRSS1)*
  Point mutation AD-80 % penetrance
  Trypsinogen, trypsin are resistant to inactivation ……

- Mutation of the *Serine Protease Inhibitor, Kazal Type 1 (SPINK1)* - inh: AR

**CAUSES:**

| DUCT OBSTRUCTION | ACINAR CELL INJURY | DEFECTIVE INTRACELLULAR TRANSPORT |
|---|---|---|
|  |  |  |
| Cholelithiasis<br>Ampullary obstruction<br>Chronic alcoholism<br>Ductal concretions | Alcohol<br>Drugs<br>Trauma<br>Ischemia<br>Viruses | Metabolic injury (experimental)<br>Alcohol<br>Duct obstruction |
| **MECHANISMS:** Interstitial edema → Impaired blood flow → Ischemia | Release of intracellular proenzymes and lysosomal hydrolases → Activation of enzymes (intra- or extracellular) | Delivery of proenzymes to lysosomal compartment → Intracellular activation of enzymes |

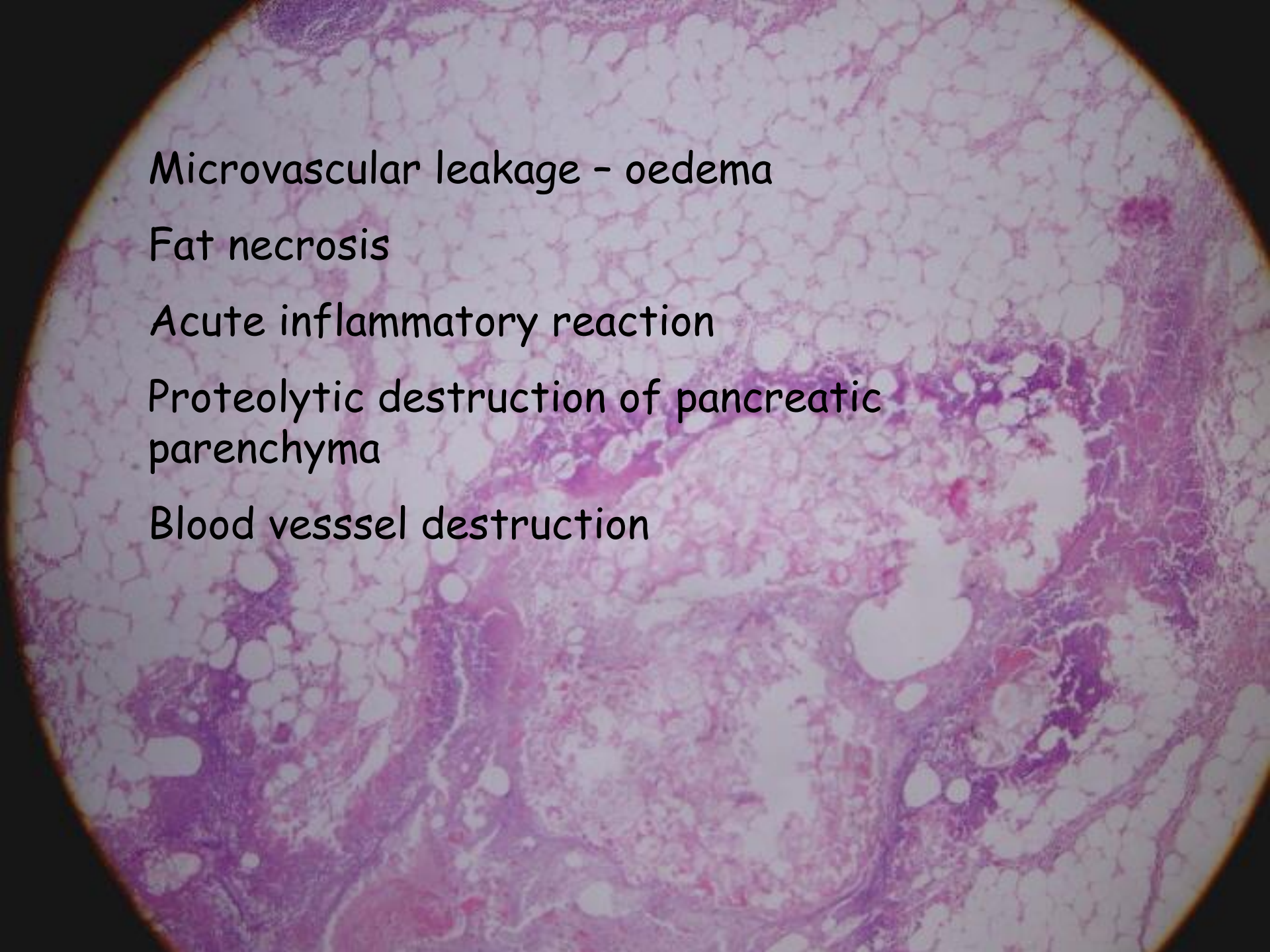
Acinar cell injury

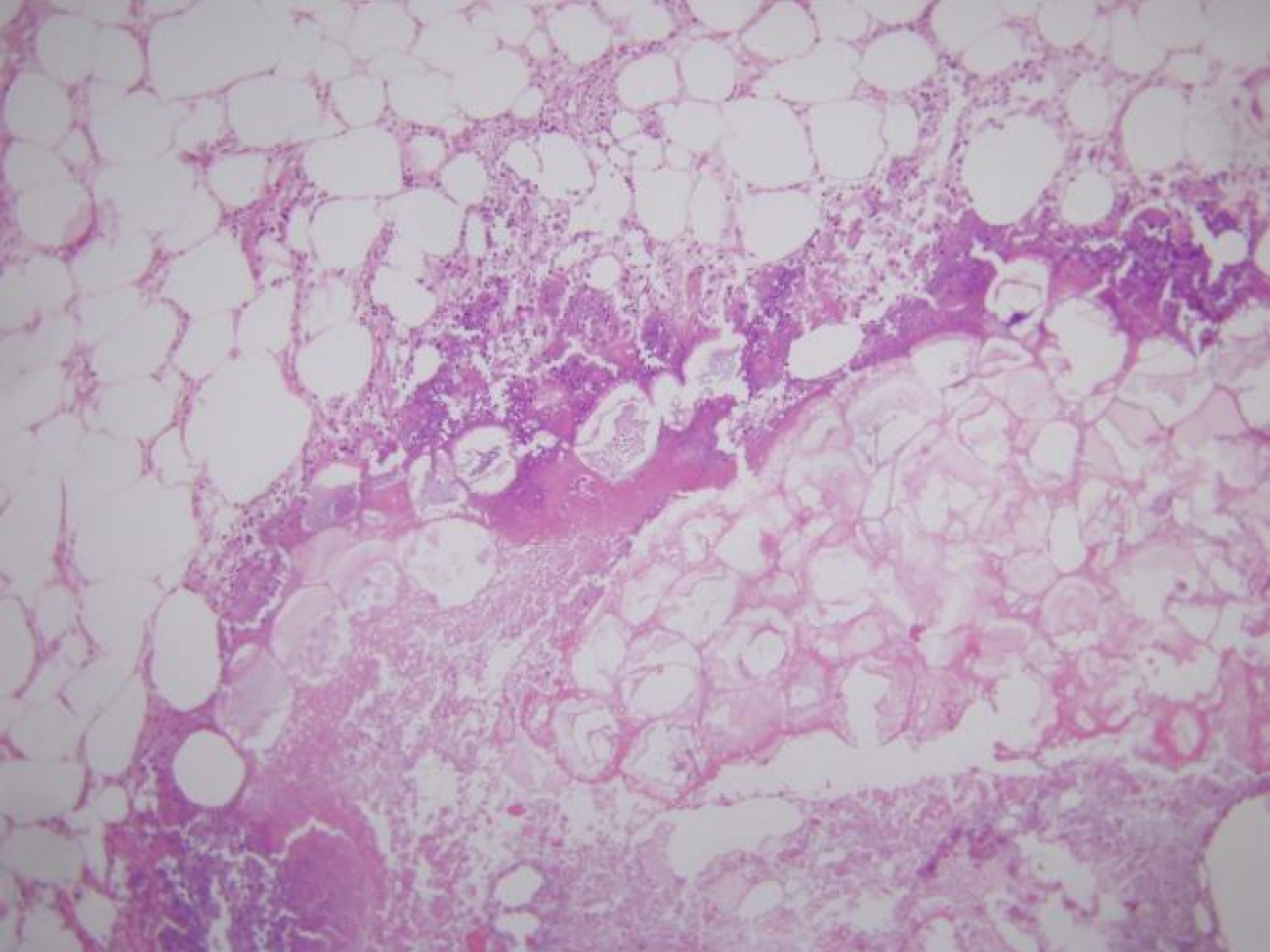
**ACTIVATED ENZYMES**

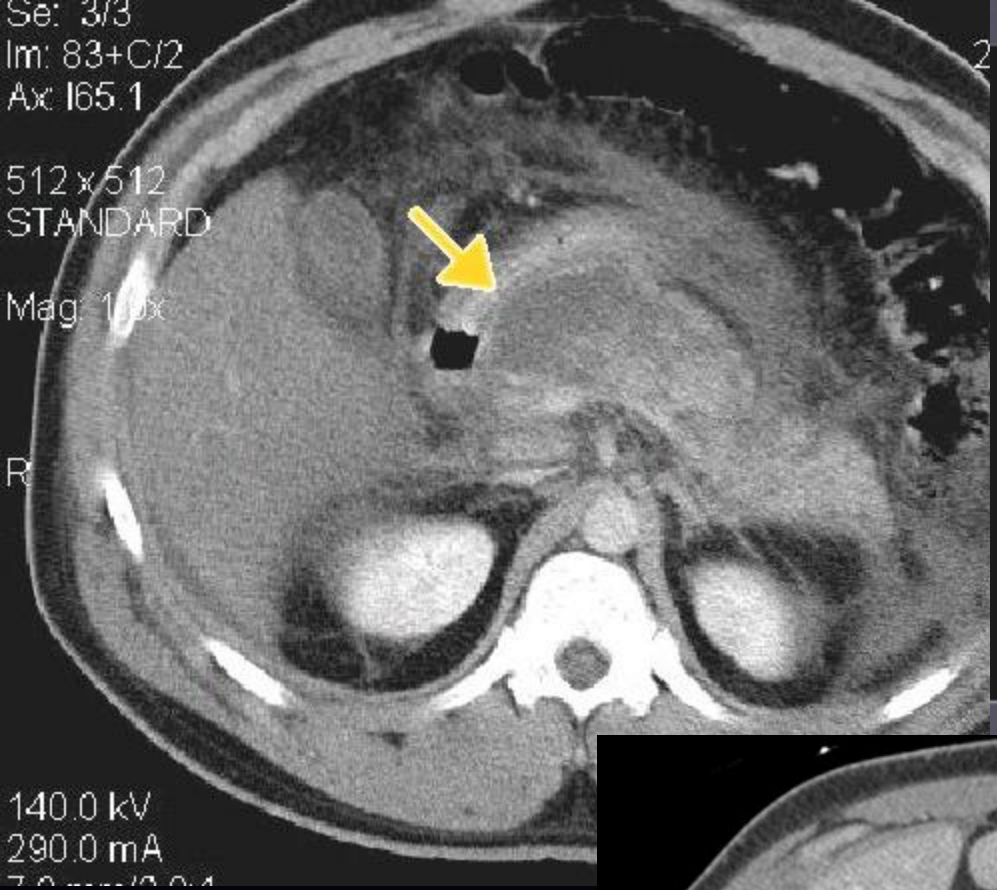
**LESIONS:**

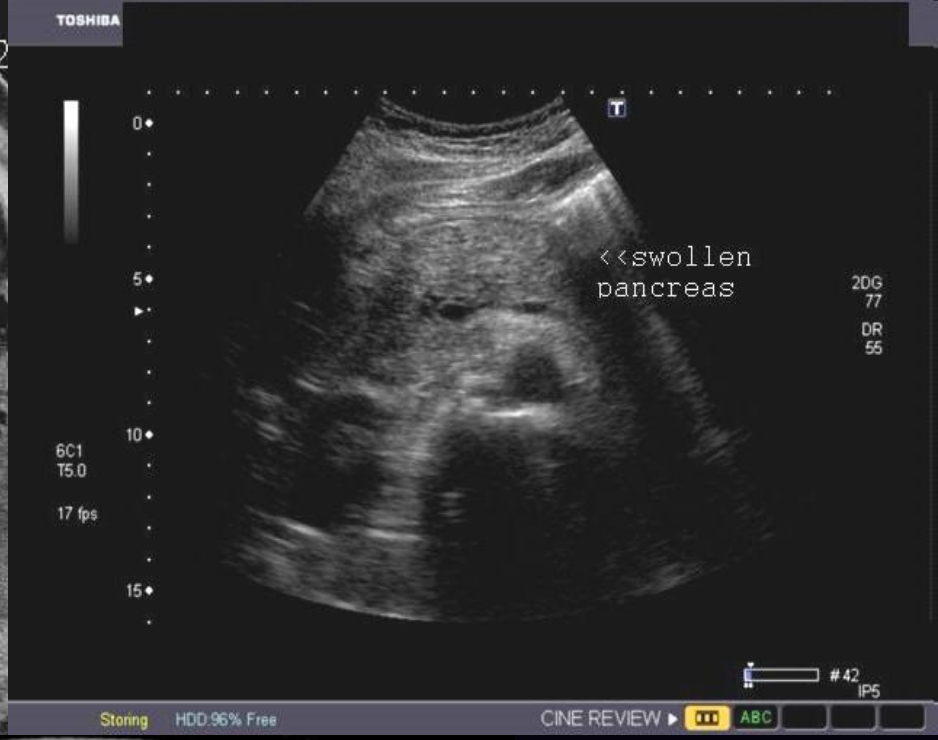
Interstitial inflammation and edema + Proteolysis (proteases) + Fat necrosis (lipase, phospholipase) + Hemorrhage (elastase)

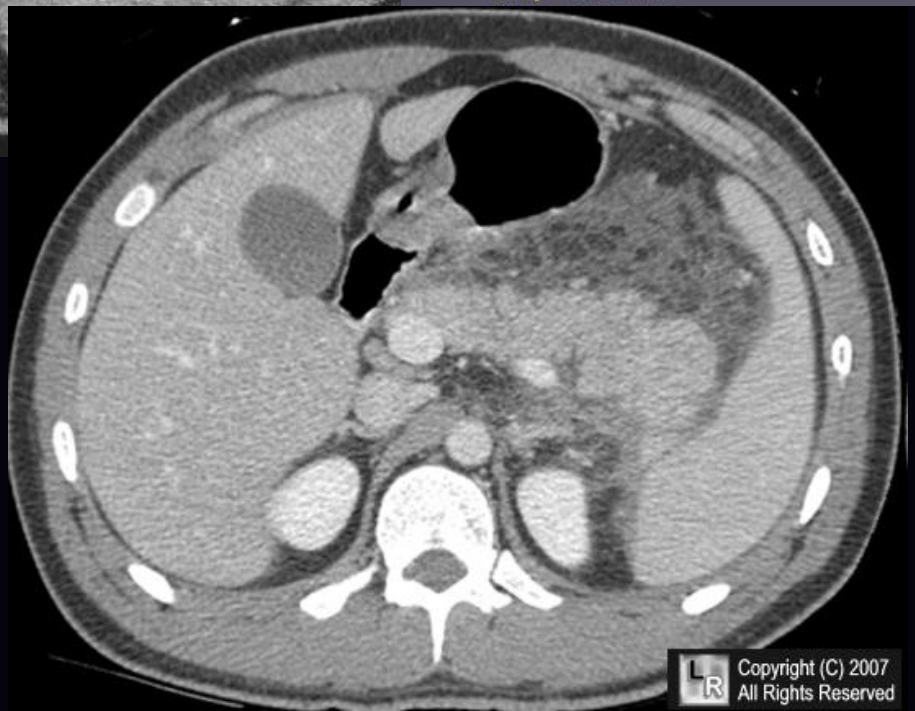
**ACUTE PANCREATITIS**


Microvascular leakage – oedema
Fat necrosis
Acute inflammatory reaction
Proteolytic destruction of pancreatic parenchyma
Blood vesssel destruction




Se: 3/3
Im: 83+C/2
Ax: I65.1
512 x 512
STANDARD
Mag: 1.0x
140.0 kV
290.0 mA


TOSHIBA
<<swollen
pancreas
6C1
T5.0
17 fps
2DG
77
DR
55
#42
IP5
Storing
HDD:96% Free
CINE REVIEW
ABC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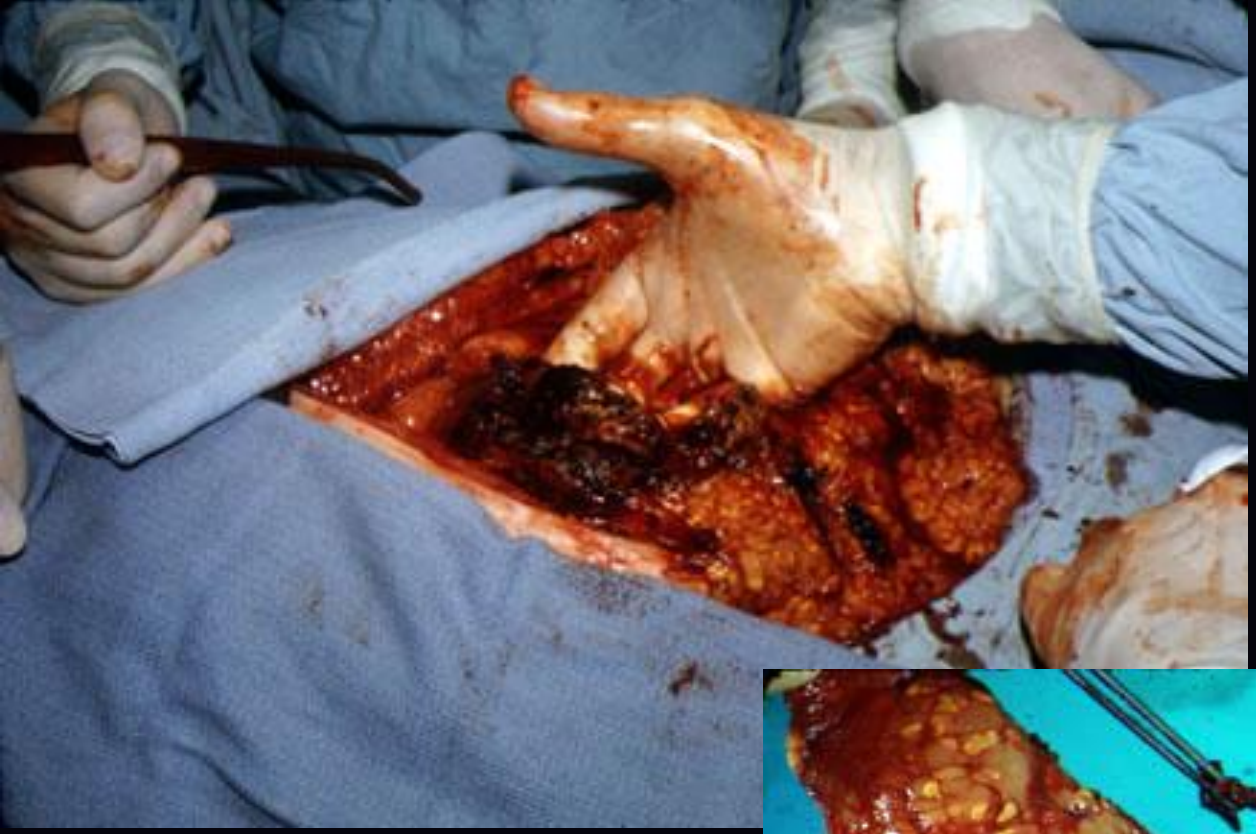
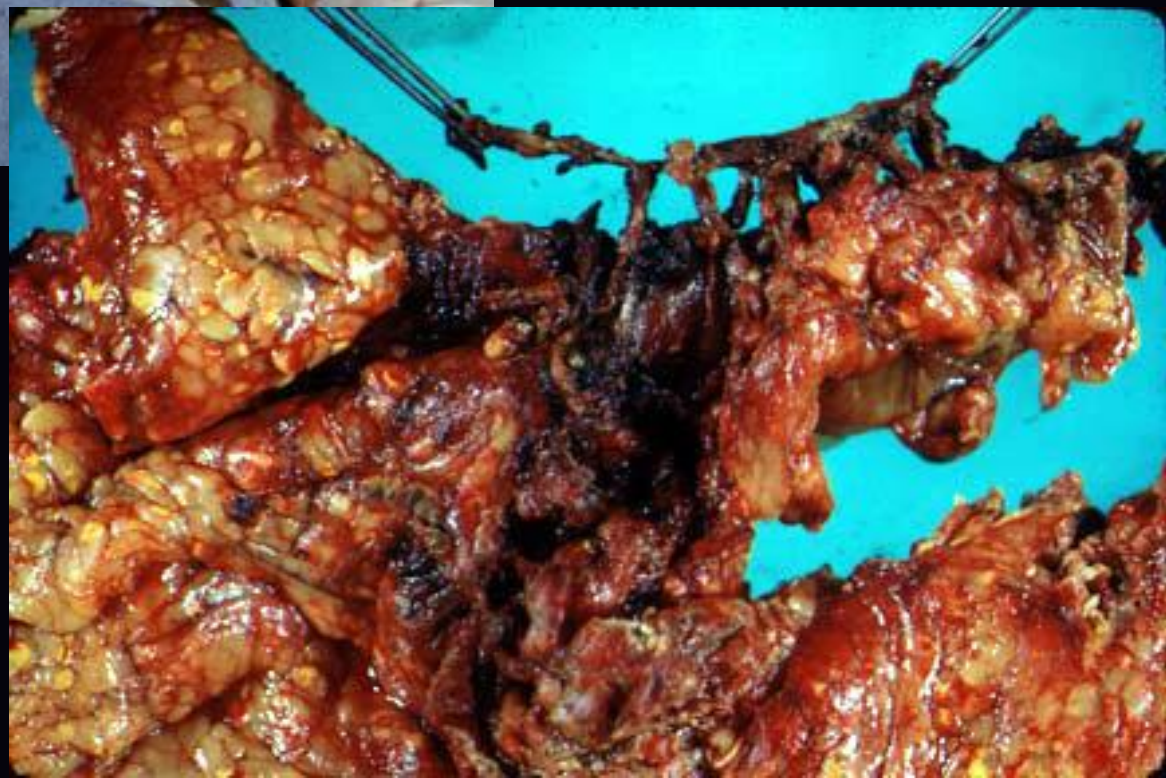
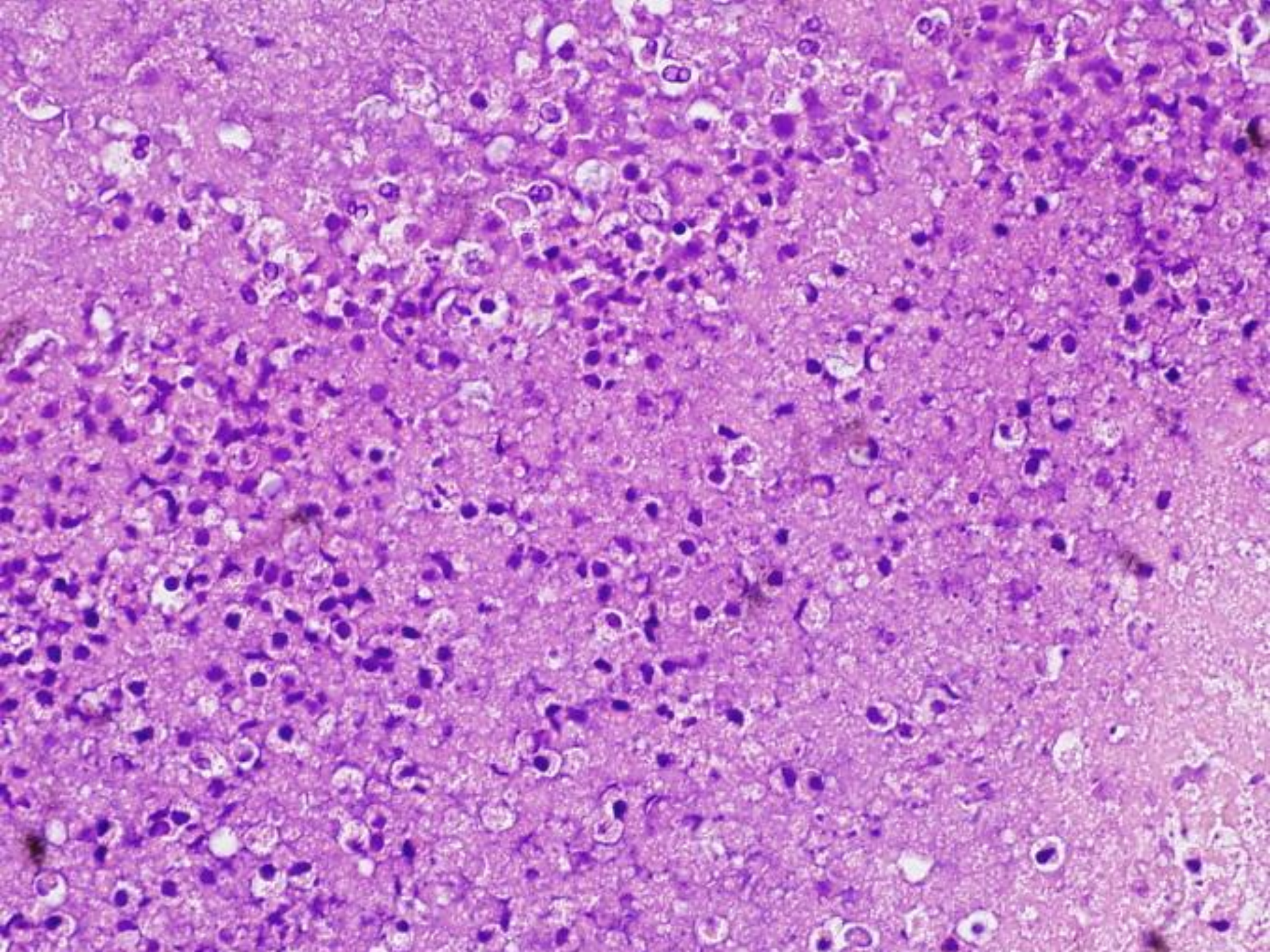
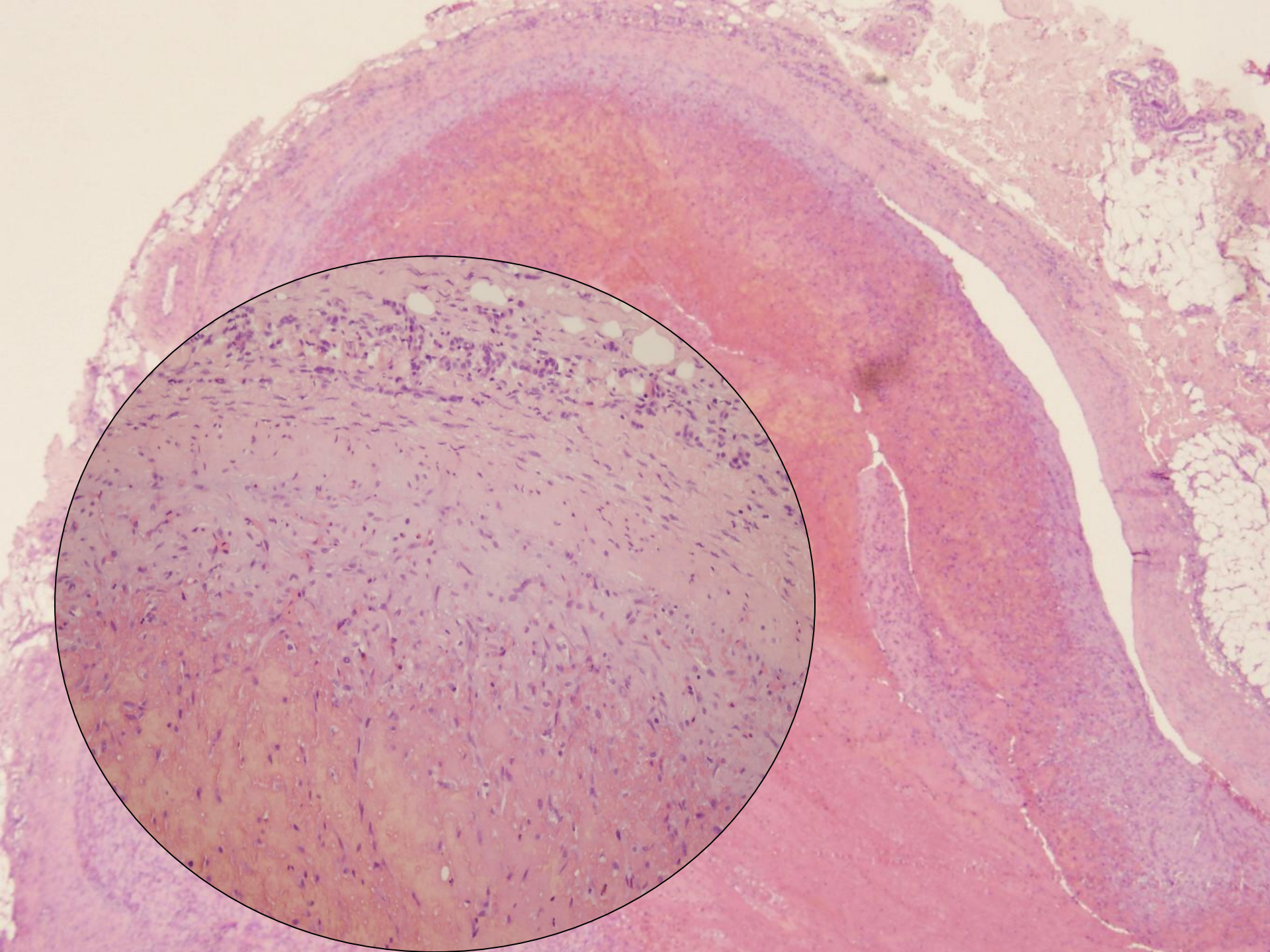
# Acut pancreatitis - morphology

- Fat necrosis
- Haemorrhage
- Necrosis
- Pseudocyst
- Abscess
- Blood vessel  erosion







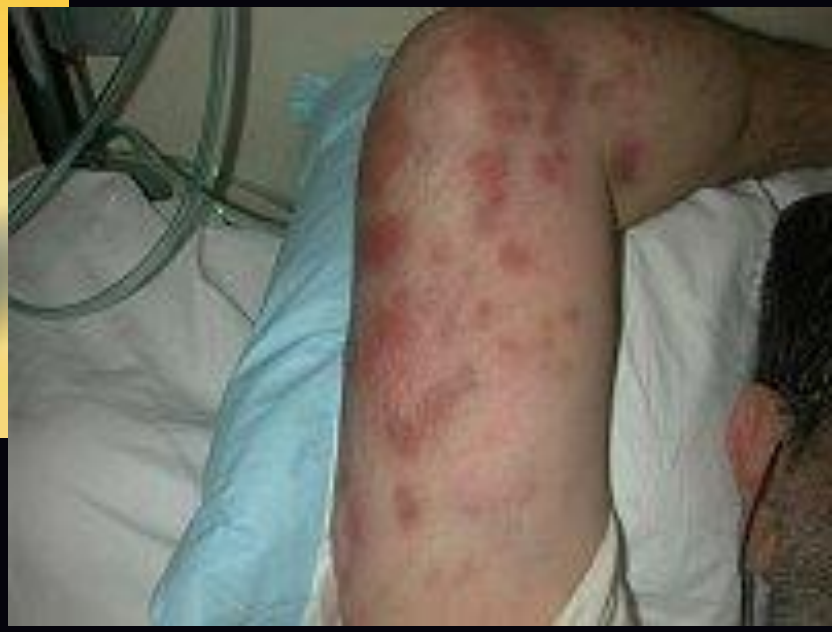


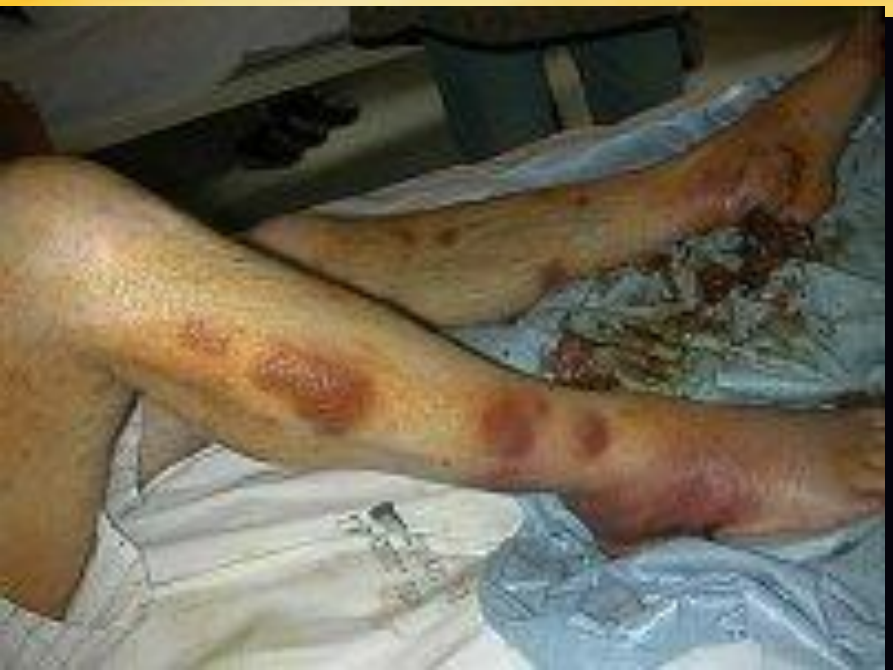
# Acute pancreatitis - symptoms

- Pain – radiating to the upper back
- Vomit
- Fever
- Passage disturbancies
- Shock
- DIC, hemolysis
- Acute renal tubular necrosis
- ARDS
- Serum amylase, lipase, elevation, hypocalcaemia

# Acute pancreatitis –shock - causes

- Blood loss
- Endotoxaemia
- Vasoactive agents in the blood (bradykinine, prostaglandine, NO, PAF)





# Acute pancreatitis - differential-diagnosis

- Cholelithiasis/cholecystitis
- Ulcer
- Mesenterial embolisation
- Appendicitis
- AMI
- Nephrolithiasis

# Chronic pancreatitis

- Chronic progressive disease
- Both functional and morphological alterations

- Low mortality

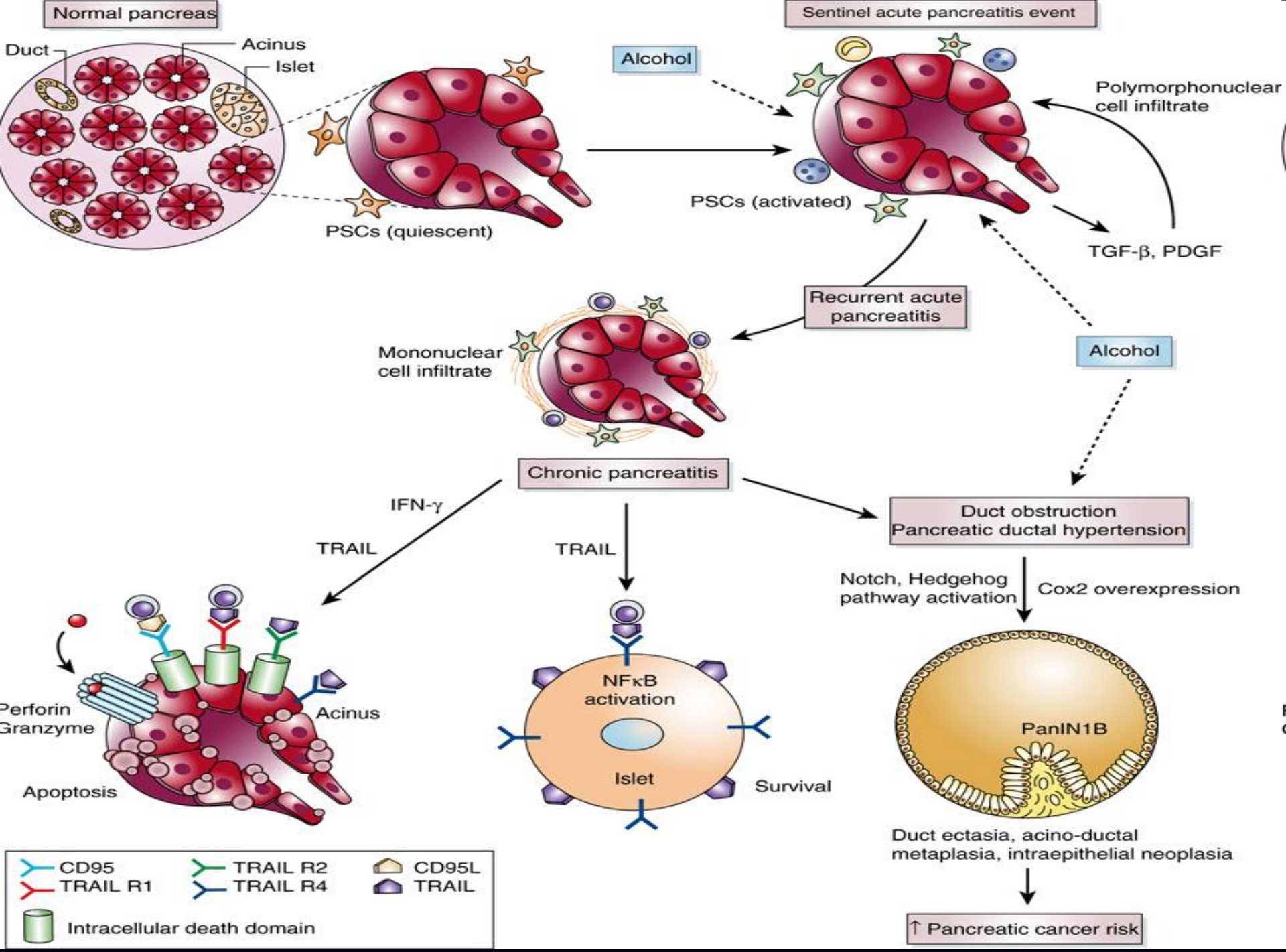
- Bad quality of life

# Chr. pancreatitis etiology

- Alcohol
- Hypercalcaemia/hyperlipoproteinaemia
- Hereditary (pancreas divisum)
- Gallstones
- Drugs
- Hereditary pancreatitis – PRSS1, SPINK1
- CFTR mutations CF transmembrane conductance regulator
- In 40 % of the cases etiology cannot be shown – (autoimmune?)

# Chr. pancreatitis pathomechanism

- Ductal obstruction – protein plugs, may be calcified
- Decrease of lithostatine secretion
- Oxidative stress – damage of the acini – abnormal protein secretion
- Progressive fibrosis- (vitious circle)-
  + intrapancreatic lipide metabolits
- Autosome hereditary pancreatitis
  (tripsin cannot be inactivated due to point mutation)


Normal pancreas
Duct
Acinus
Islet
PSCs (quiescent)
Sentinel acute pancreatitis event
Alcohol
Polymorphonuclear cell infiltrate
PSCs (activated)
TGF-β, PDGF
Recurrent acute pancreatitis
Alcohol
Mononuclear cell infiltrate
Chronic pancreatitis
IFN-γ
TRAIL
TRAIL
Duct obstruction
Pancreatic ductal hypertension
Notch, Hedgehog pathway activation
Cox2 overexpression
Perforin
Granzyme
Acinus
Apoptosis
NFκB activation
Islet
Survival
PanIN1B
Duct ectasia, acino-ductal metaplasia, intraepithelial neoplasia
↑ Pancreatic cancer risk
CD95
TRAIL R1
TRAIL R2
TRAIL R4
CD95L
TRAIL
Intracellular death domain

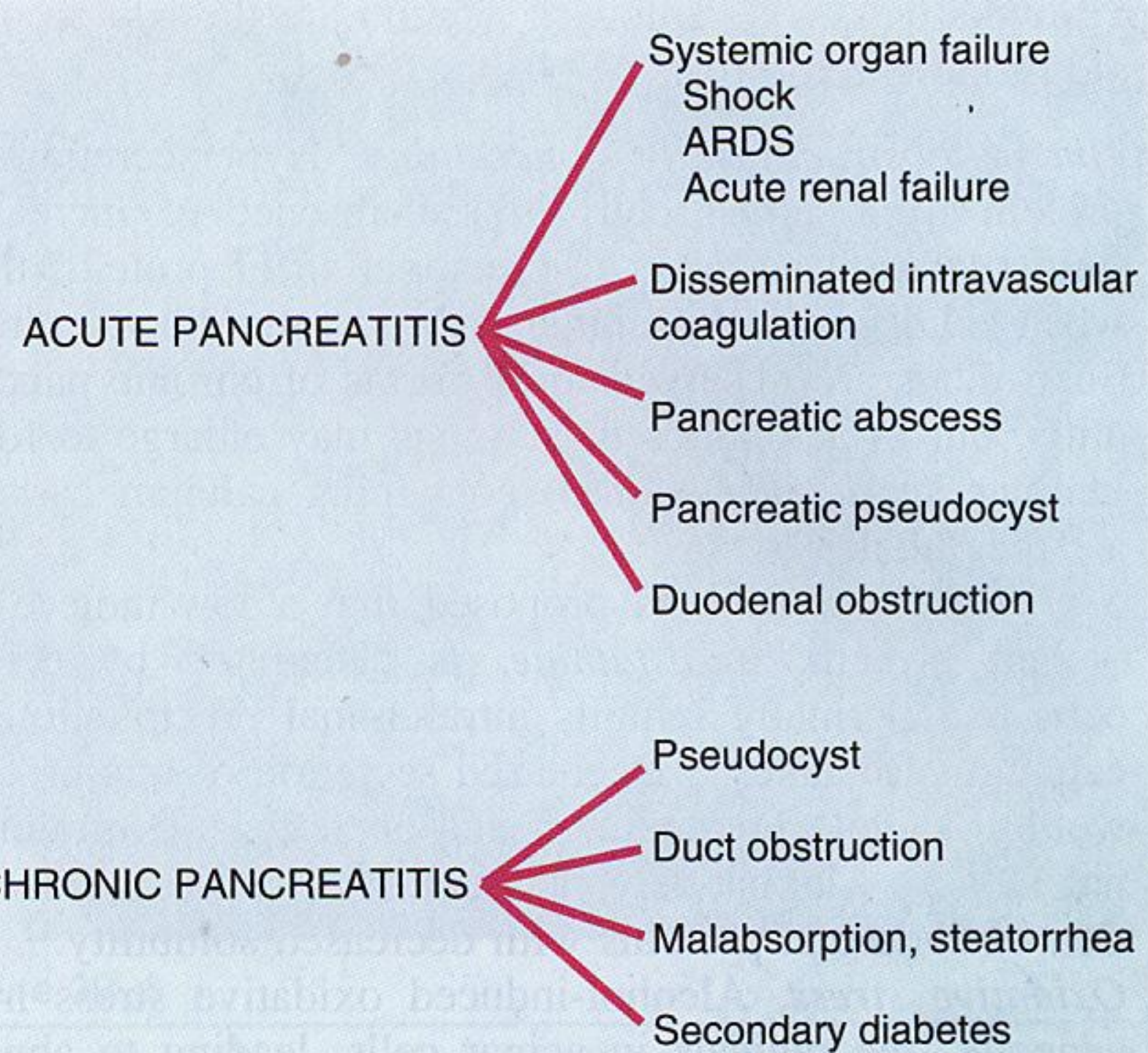
Normal pancreas consists of an exocrine component formed by acini and ducts, and an endocrine portion composed of islets. Alcohol and/or other injurious stimuli initiate the first episode of acute pancreatitis, described as the Sentinel Acute Pancreatitis Event (SAPE) by Whitcomb *et al* and characterized by an acute inflammatory infiltrate. Continued exposure to the injurious factor(s) leads to recurrent episodes of acute pancreatitis, which activate pancreatic stellate cells (PSCs) and initiating pancreatic fibrogenesis that leads to chronic pancreatitis (CP). Under the influence of IFN- released by CD4- and CD8-positive T lymphocytes, pancreatic the acini in CP neo-express CD95, TRAIL R1, and TRAIL R2 with intracellular death domains. Therefore, the acini in CP are rendered vulnerable to apoptosis by CD95L-expressing T cells and soluble TRAIL, produced locally by PSCs. A part of acinar cell death in CP is also attributed to perforin–granzyme B pathway. In contrast, the pancreatic islets retain their CD95L-positive and death-receptor-negative status and neoexpress TRAILR4, the latter lacking an intracellular death domain. NF- B is expressed in islets, which in turn activates inhibitor of apoptosis proteins (IAPs), helping to preserve islets. Finally, in CP, the pancreatic ducts are obstructed, distorted, dilated, and have elevated intraductal pressure. Long-standing ductal changes activate Notch and Hedgehog pathways, which lead to acinoductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN), thereby predisposing to the development of pancreatic cancer. (The SAPE concept is used here with the permission of Dr Whitcomb).

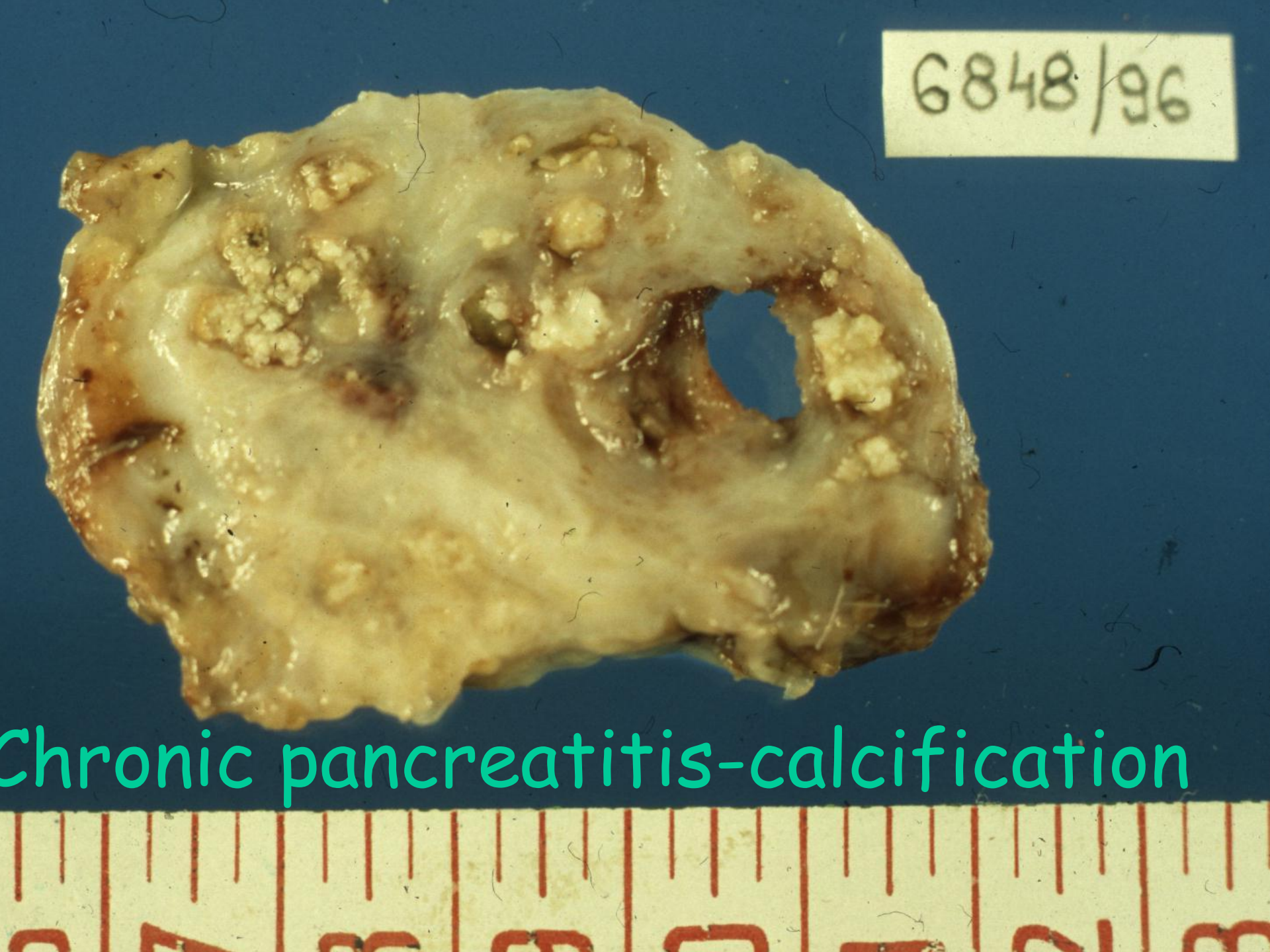
# Chronic pancreatitis - symptoms

- Pain - diverse intensity - radiating to the back
- Weight loss - malabsorbtion
- Diarrhea - steatorrhea
- Passage disturbancy
- Jaundice
- Diabetes
- Calcification
- Laboratory findings -
  alterations depend on the amount of preserved functioning exocrine tissue

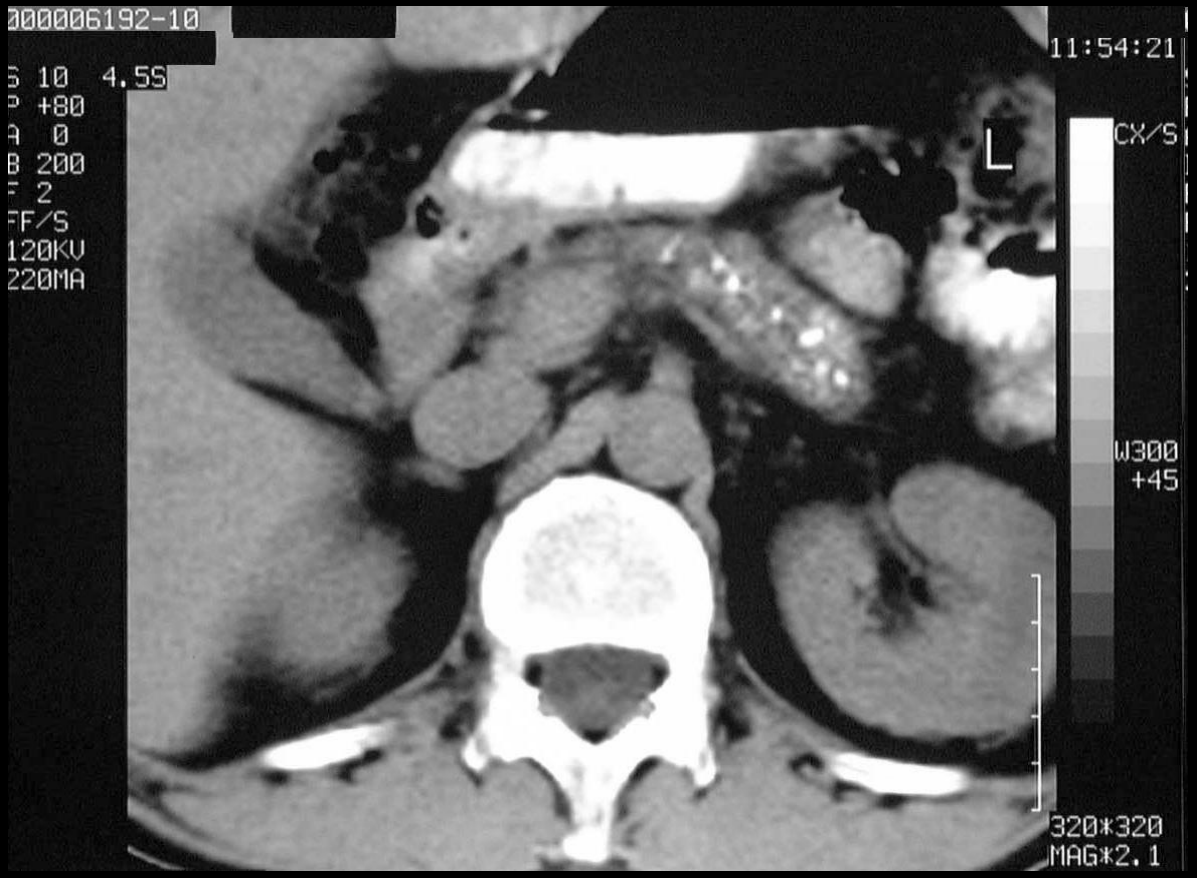
# Chronic pancreatitis morphology

- Atrophy of the acini
- Fibrosis
- Calcification
- Ductectasy
- Ductal proliferation -metaplasia, dysplasia
- Lymphocytic infiltration
- Amputation neuromas

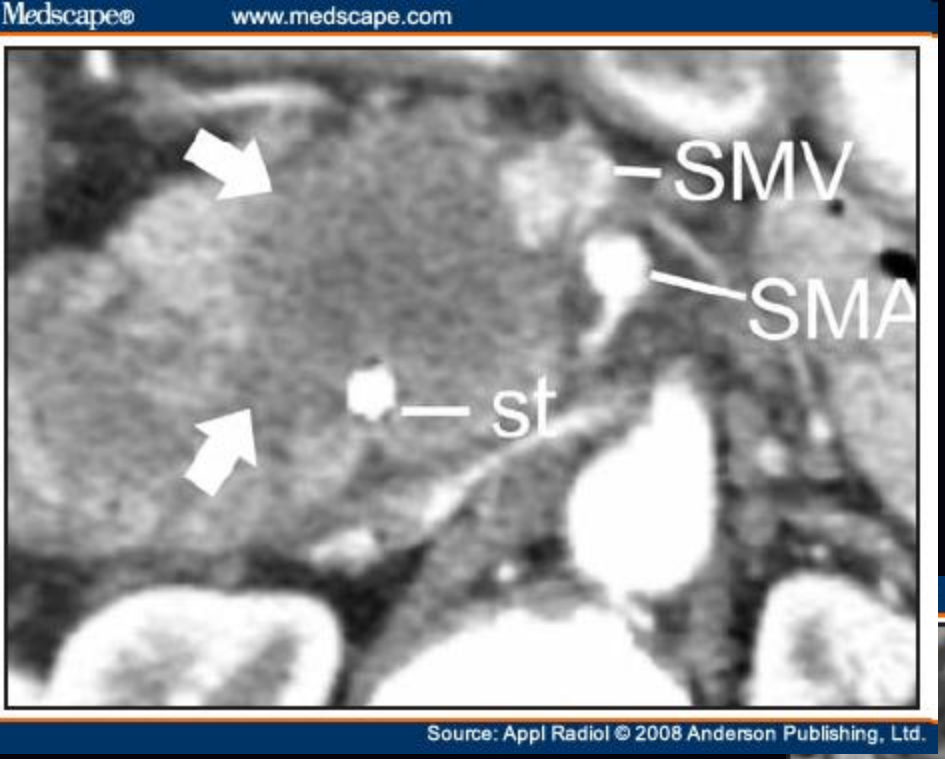

ACUTE PANCREATITIS
Systemic organ failure
Shock
ARDS
Acute renal failure
Disseminated intravascular coagulation
Pancreatic abscess
Pancreatic pseudocyst
Duodenal obstruction
CHRONIC PANCREATITIS
Pseudocyst
Duct obstruction
Malabsorption, steatorrhea
Secondary diabetes




Chronic pancreatitis-calcification

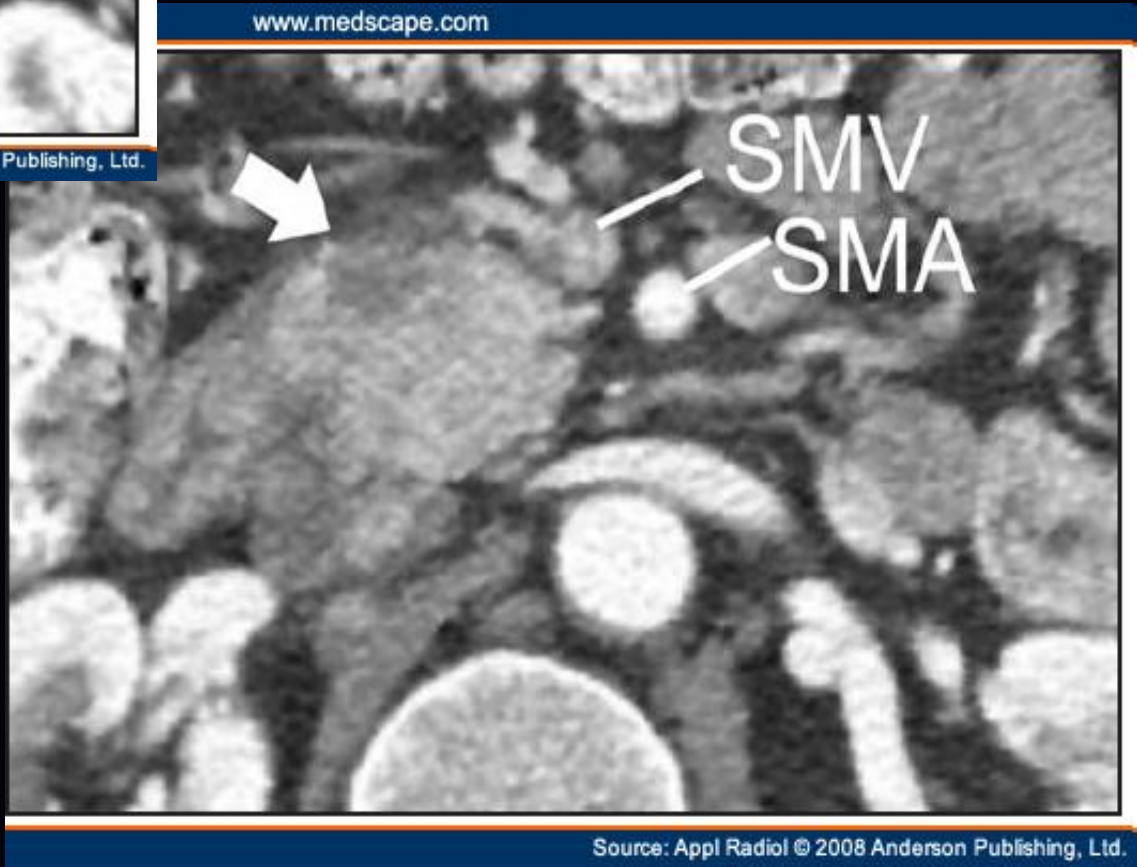



Chronic calcifying pancreatitis

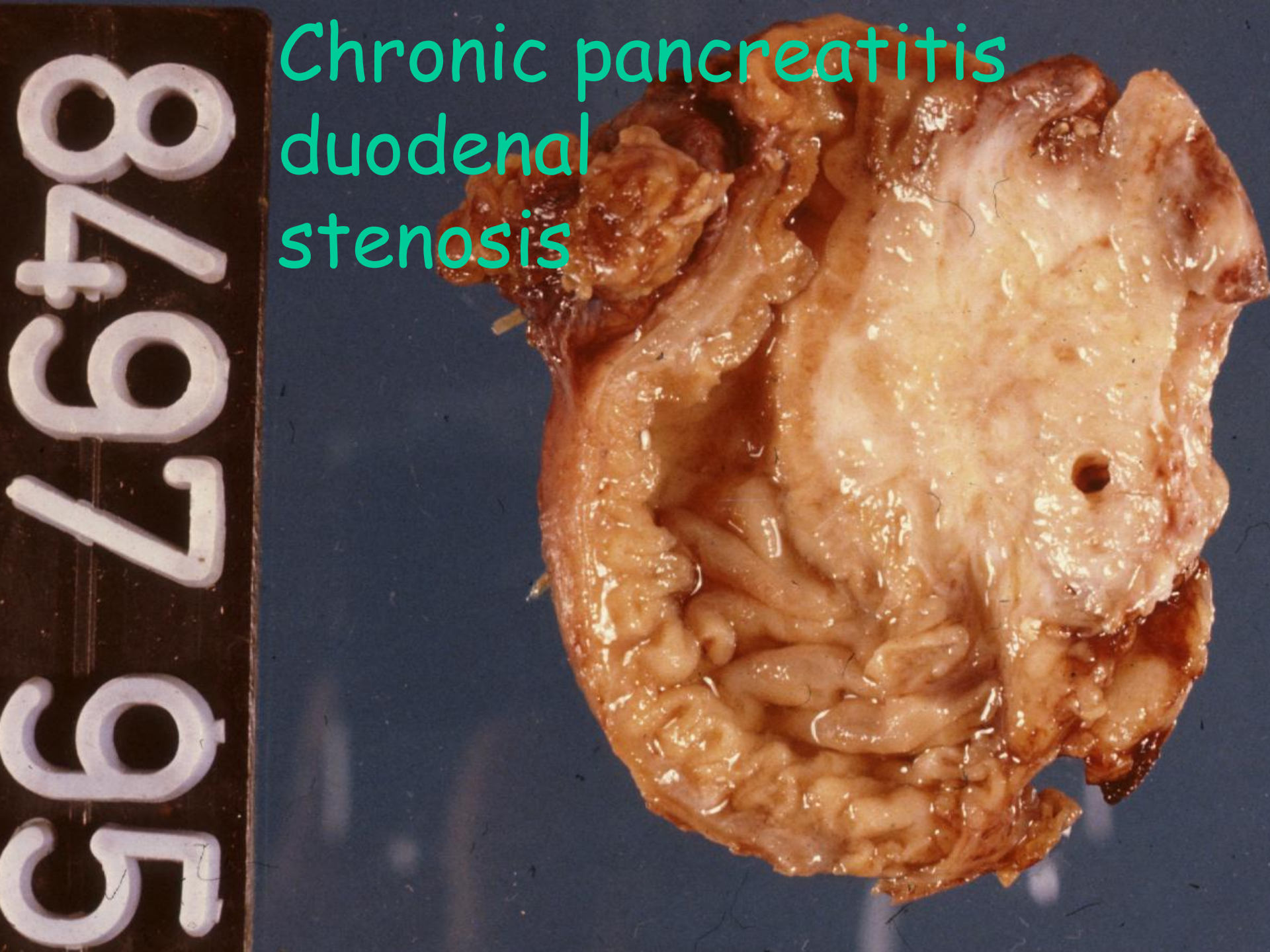


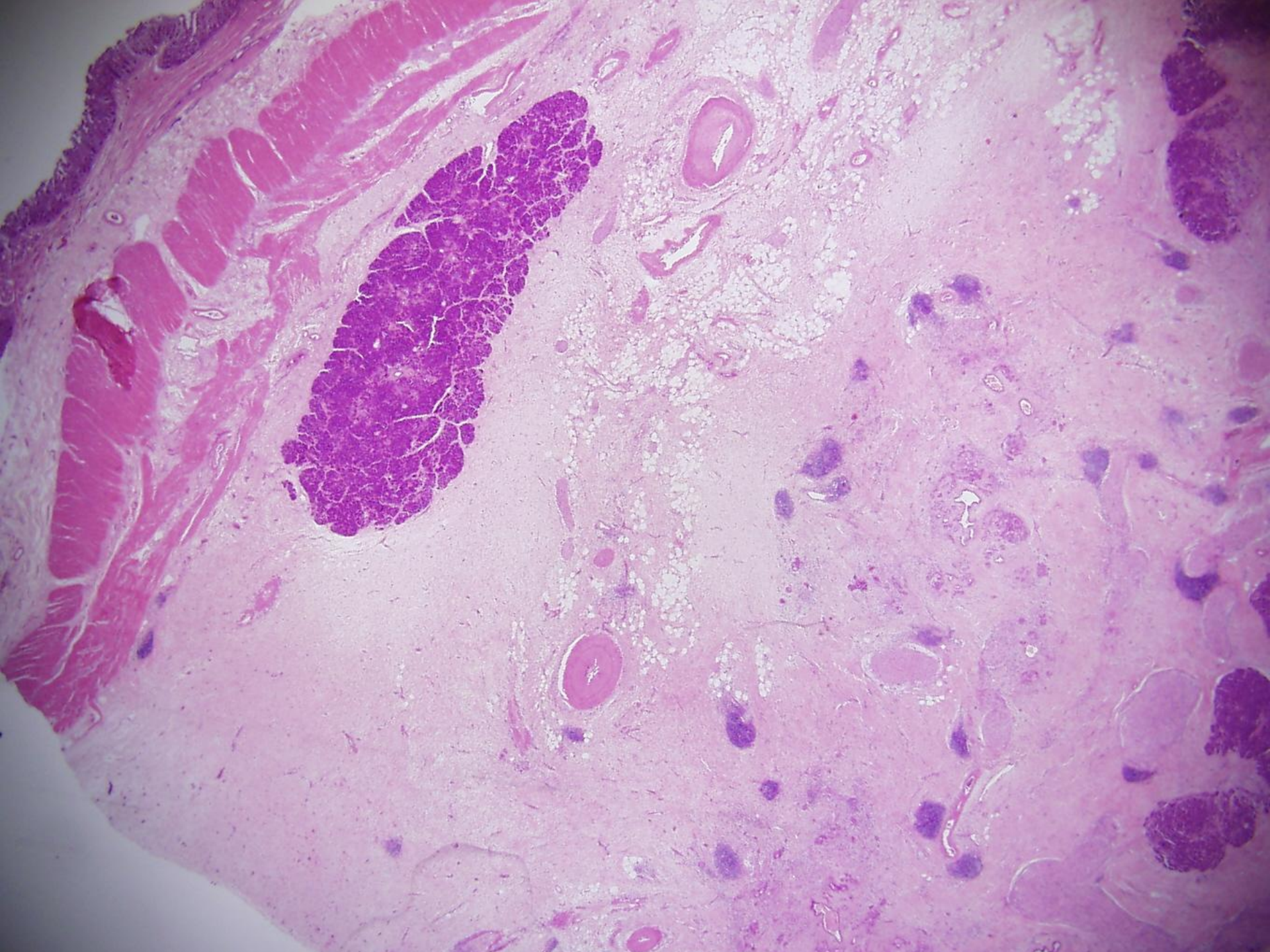

Chronic pancreatitis

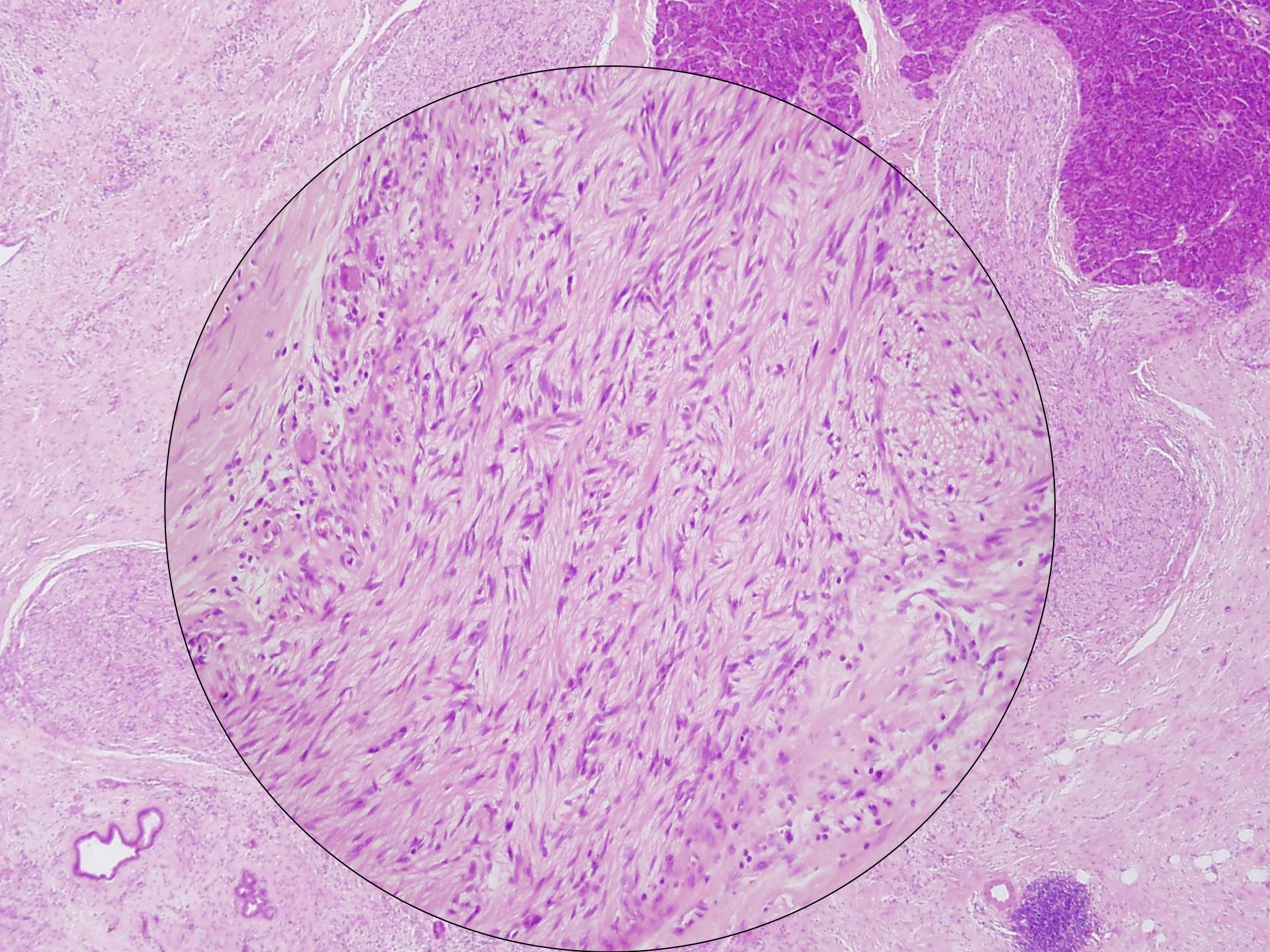
Mimicking cancer

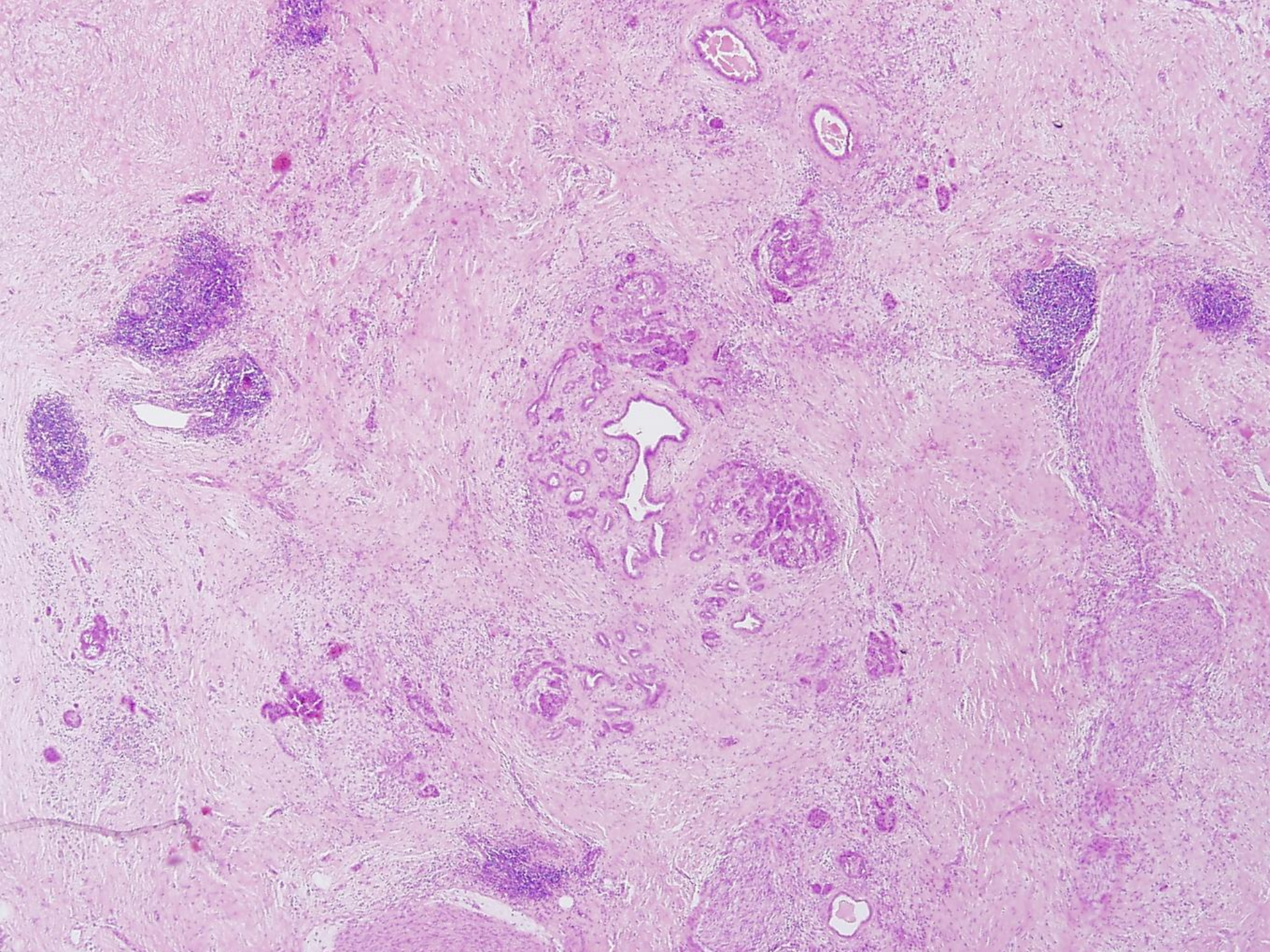


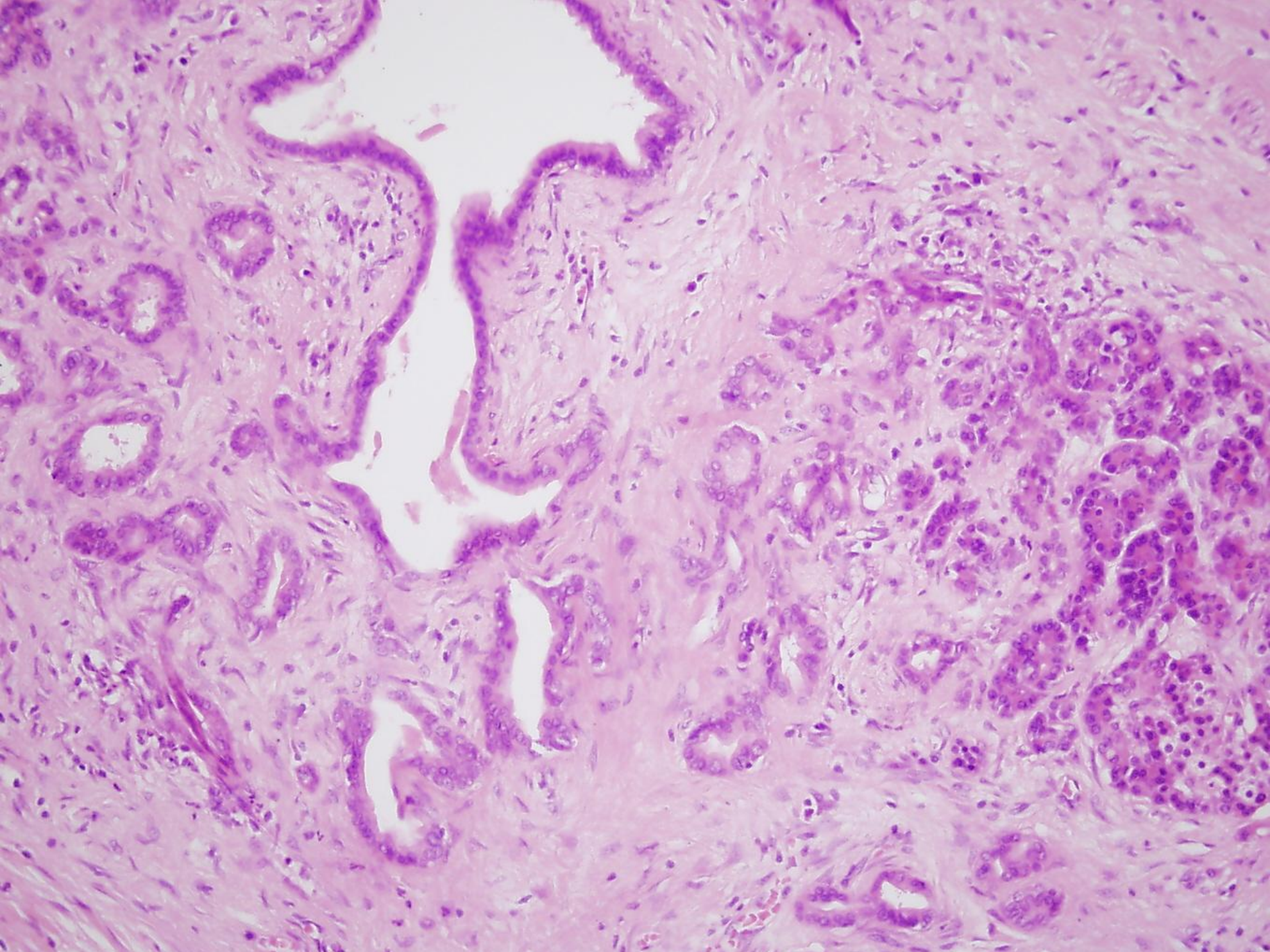
# Chronic pancreatitis duodenal stenosis

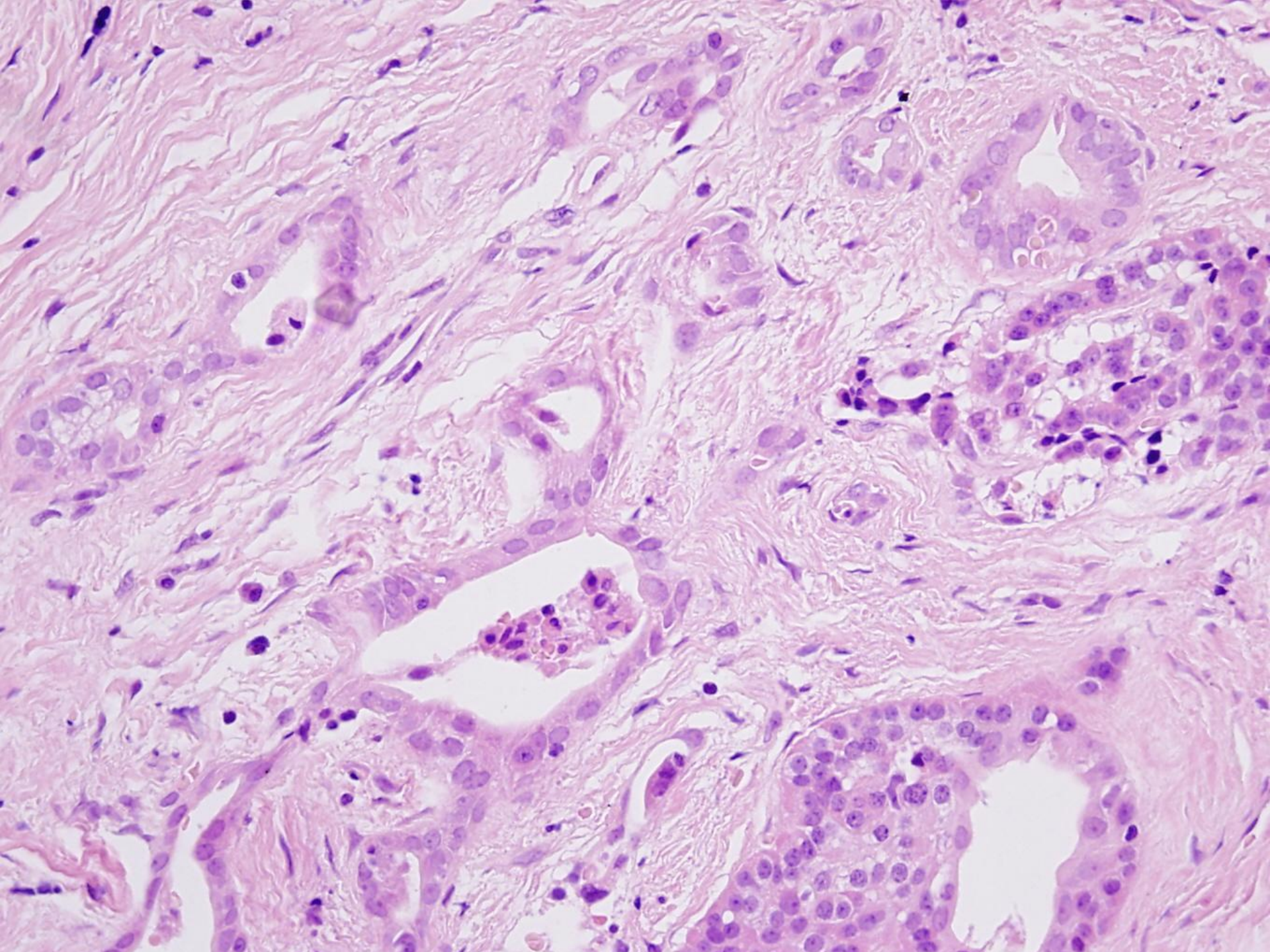


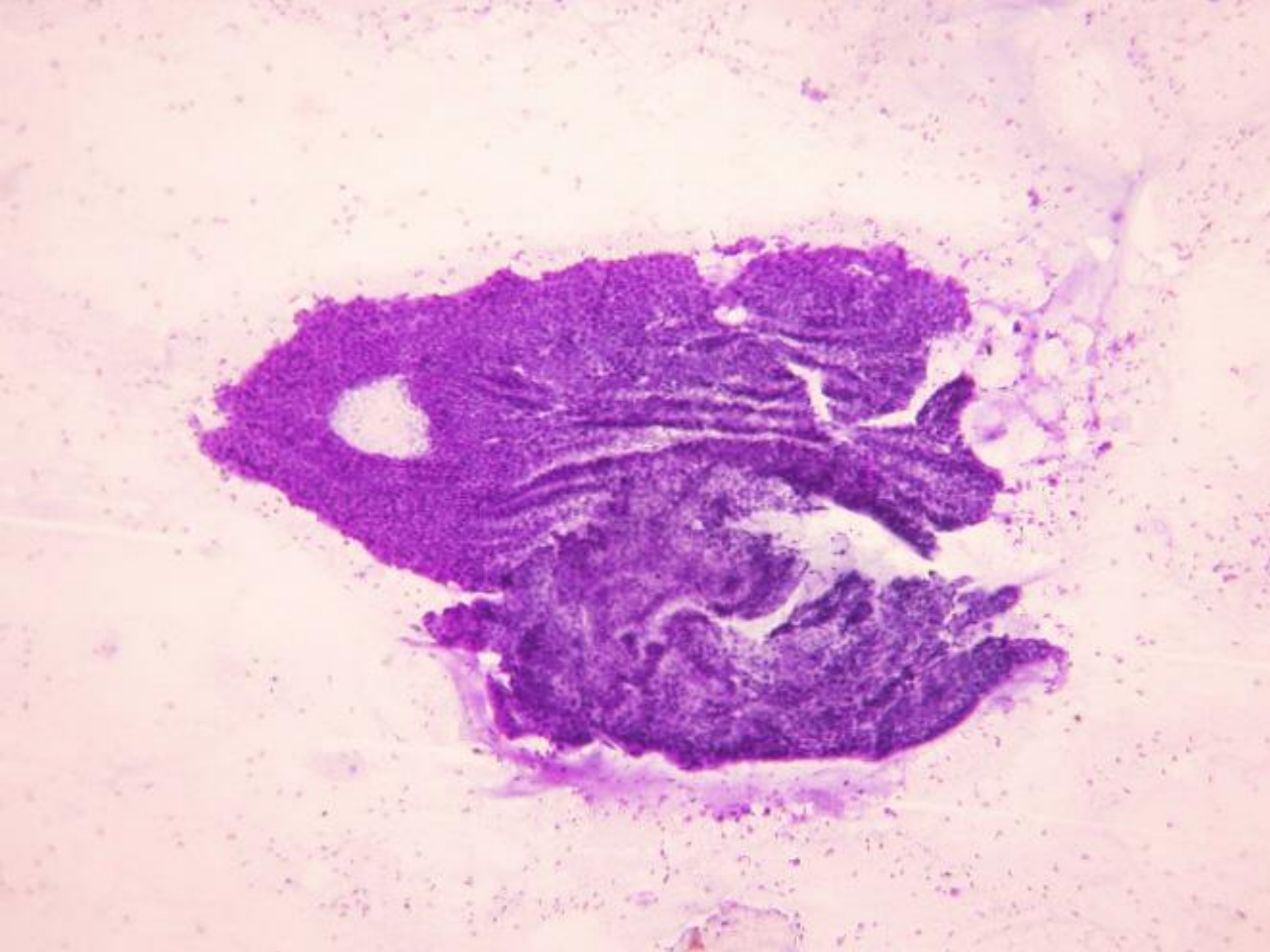


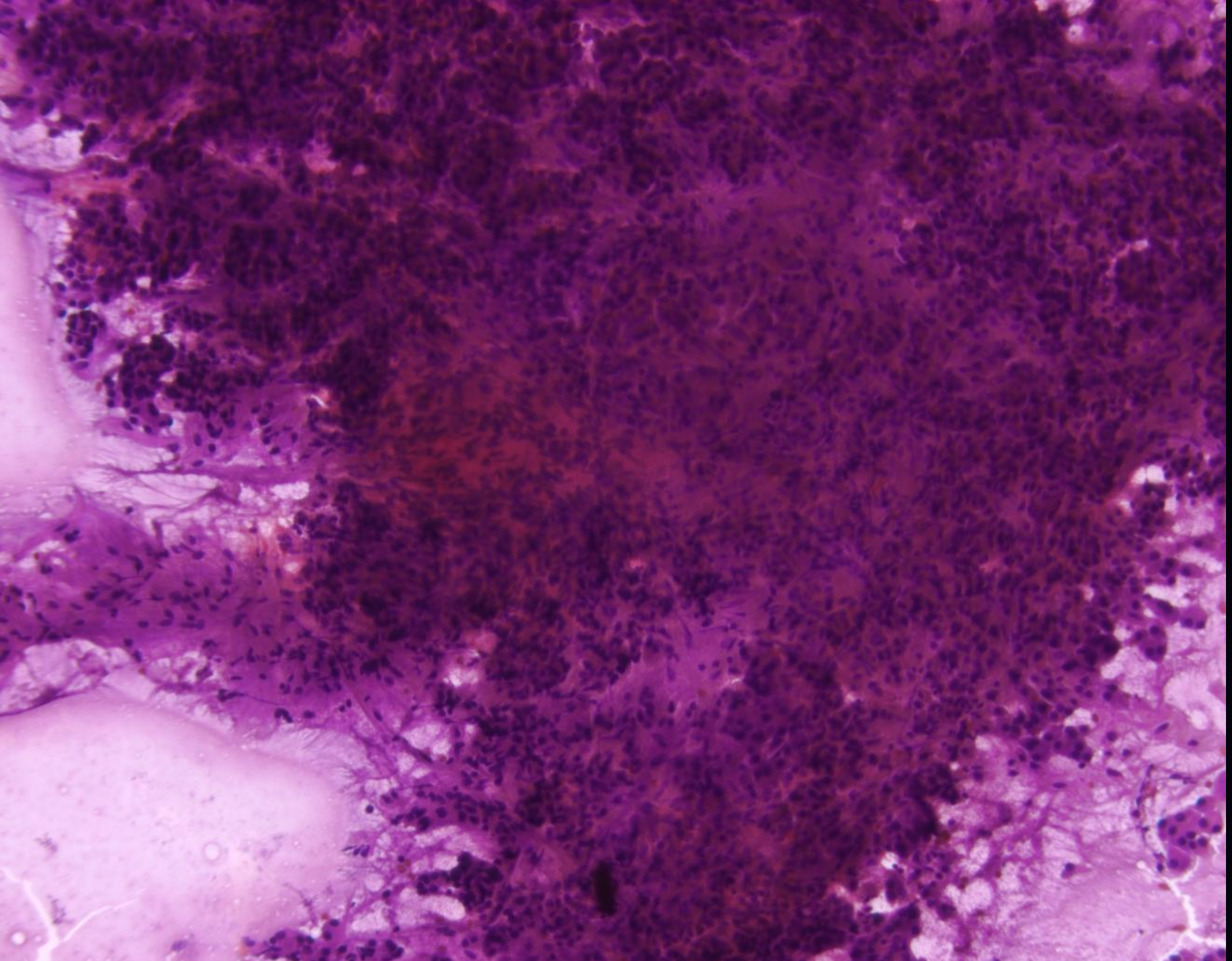


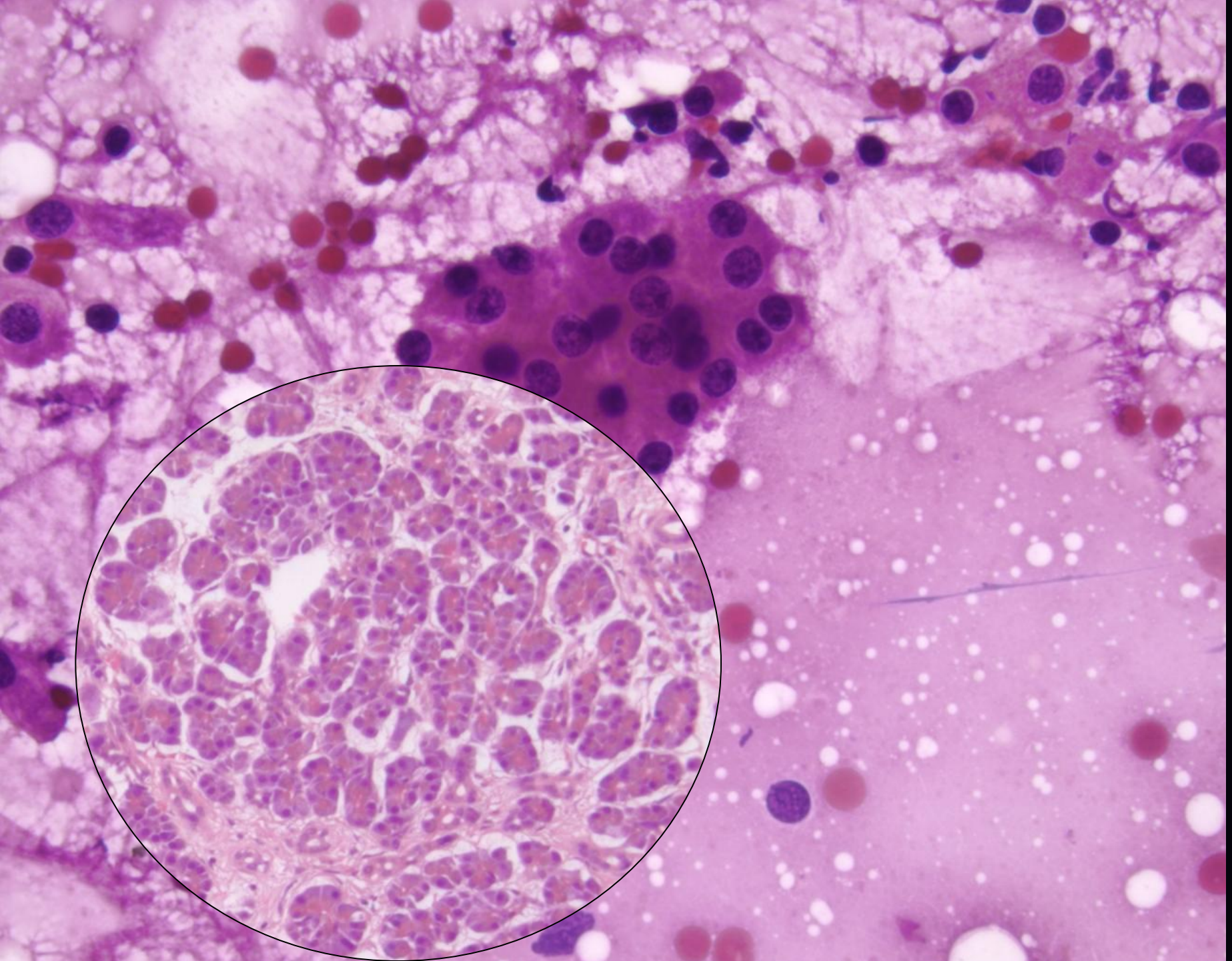


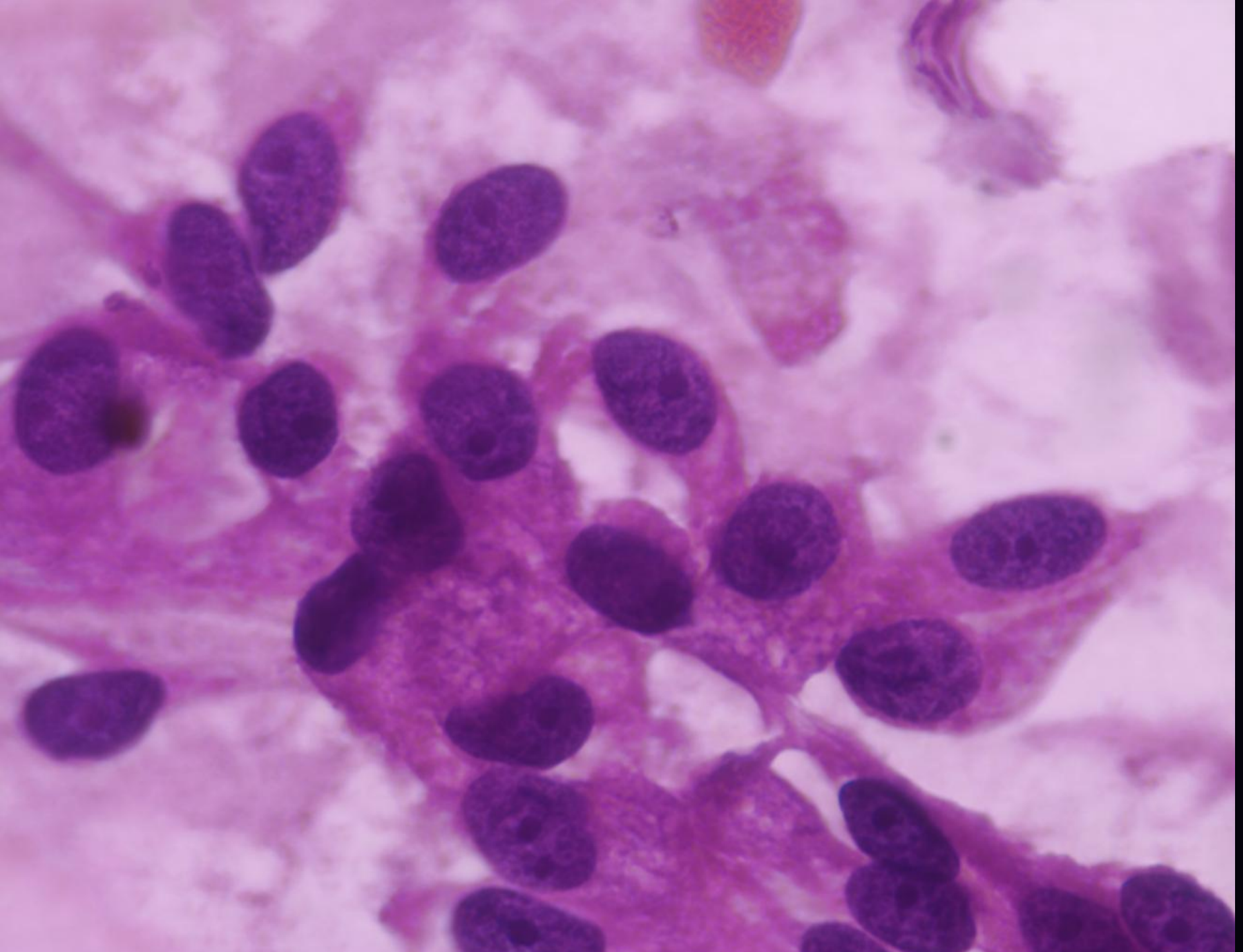


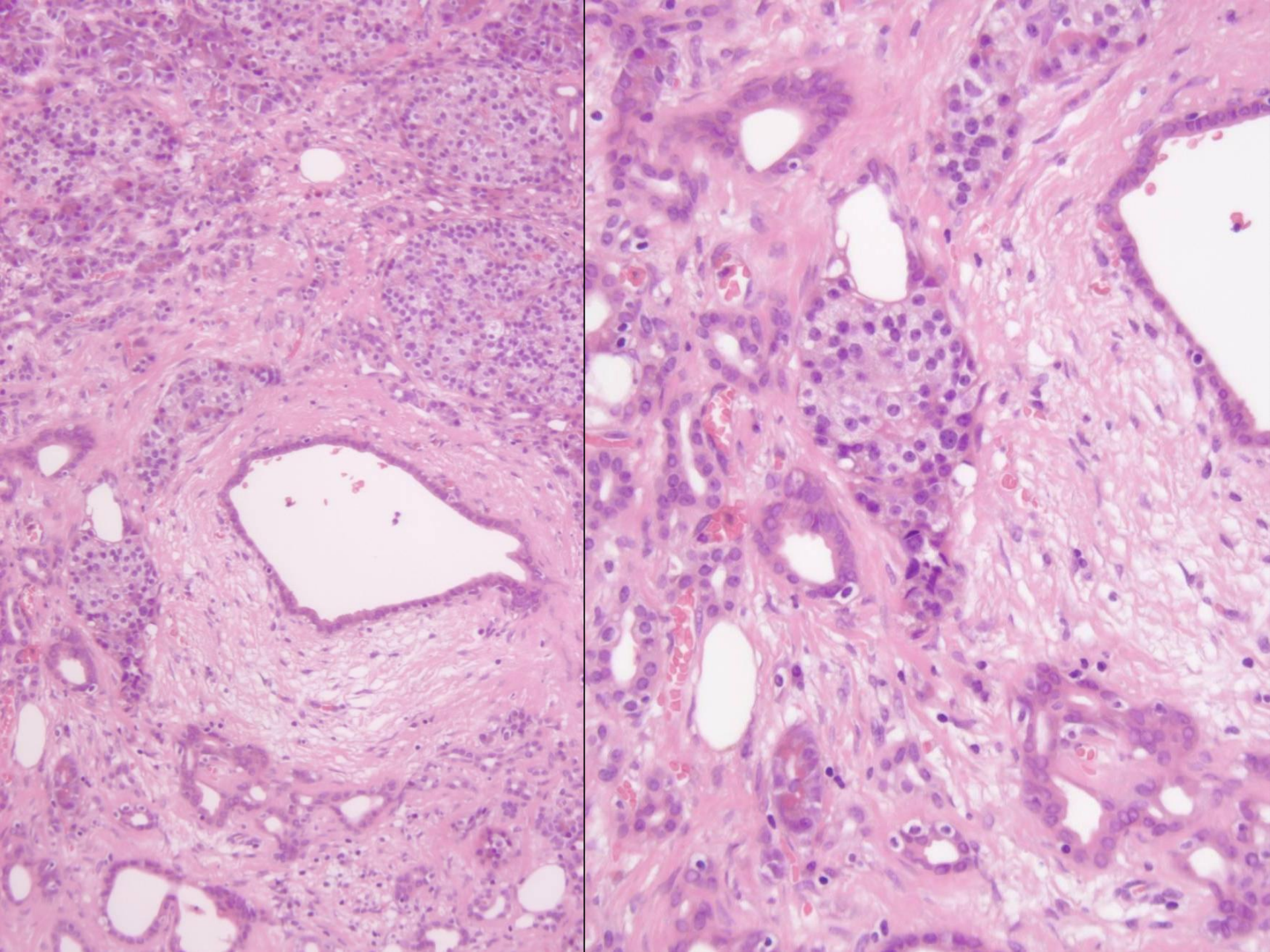


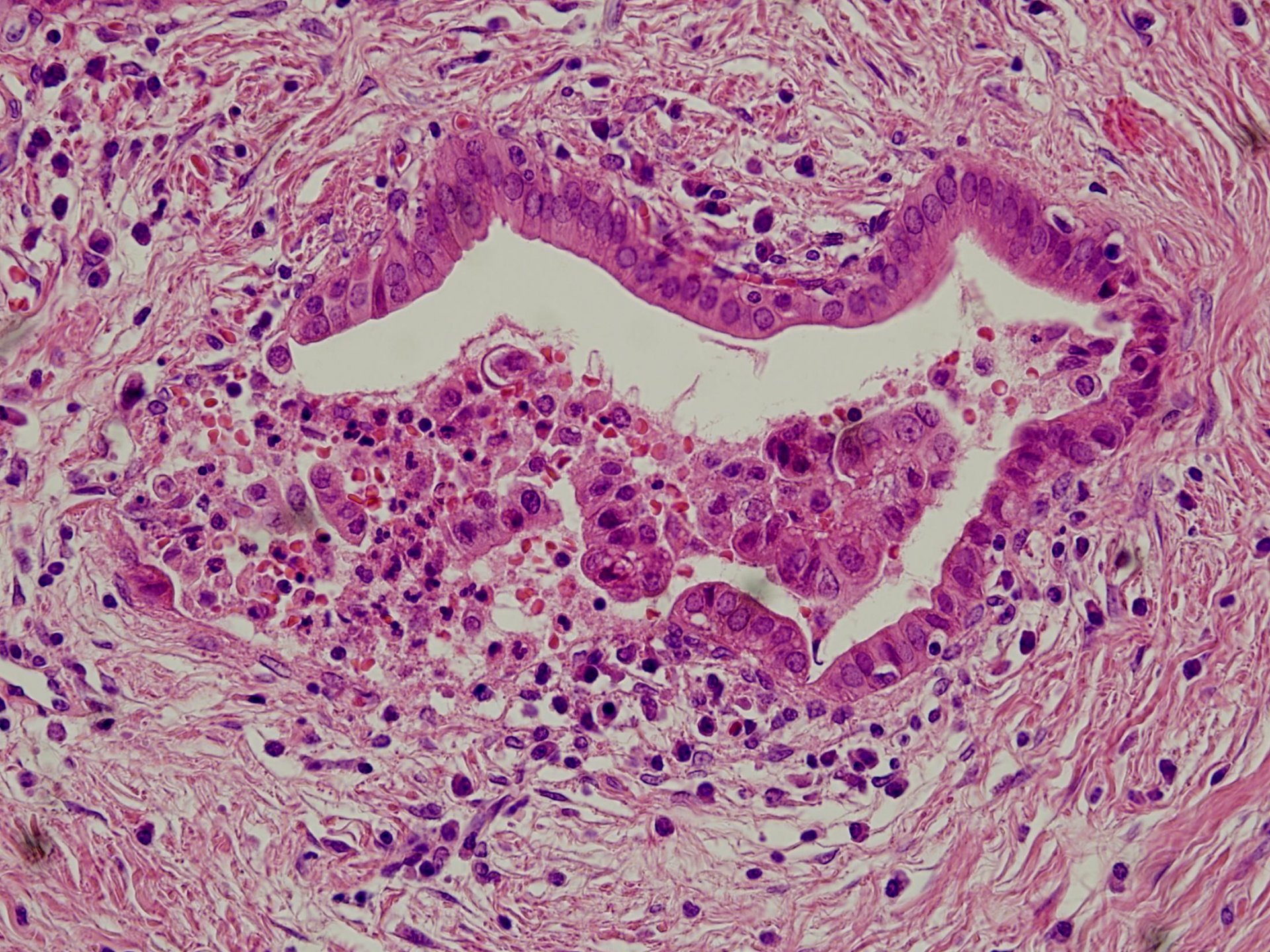


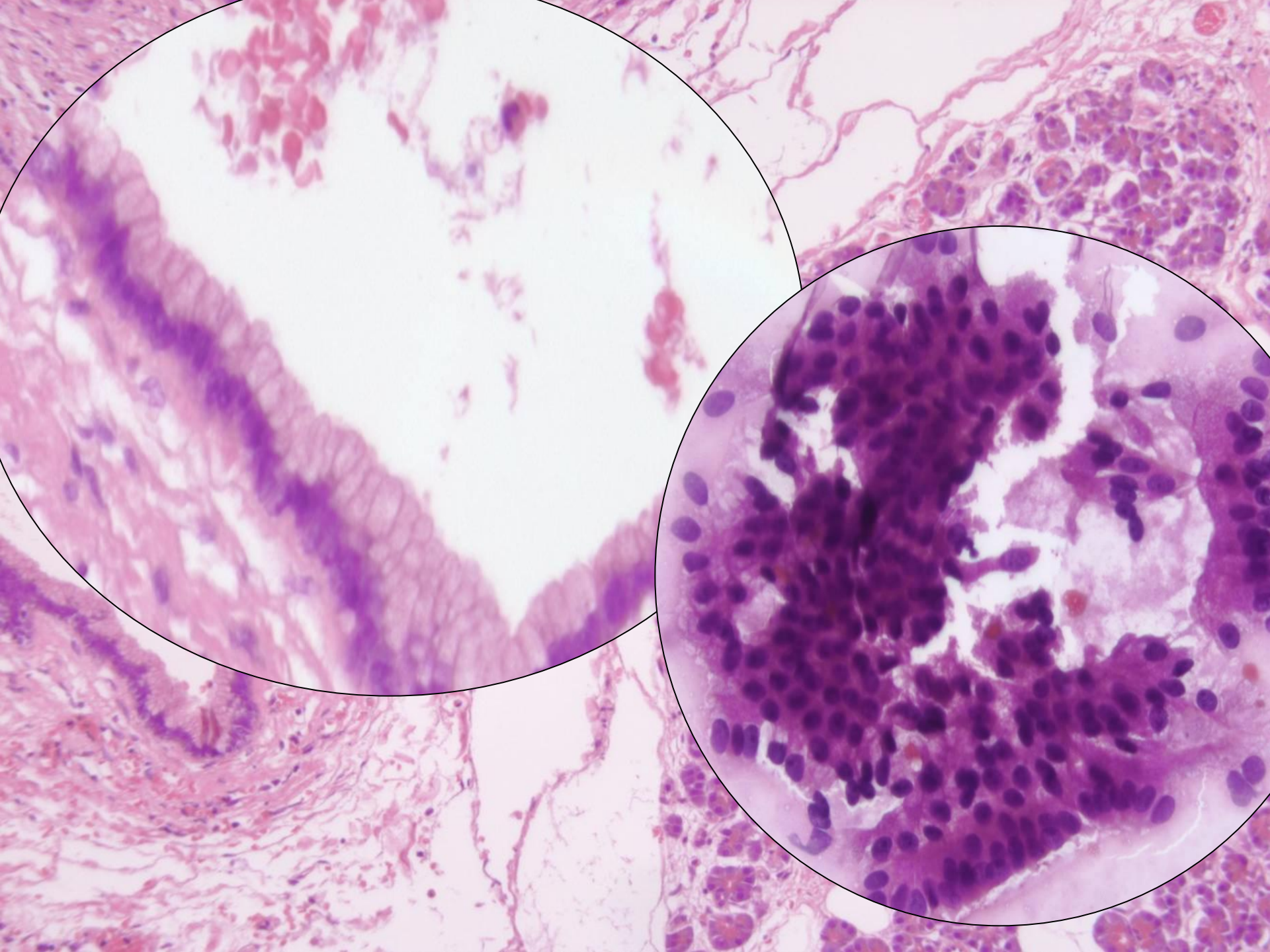


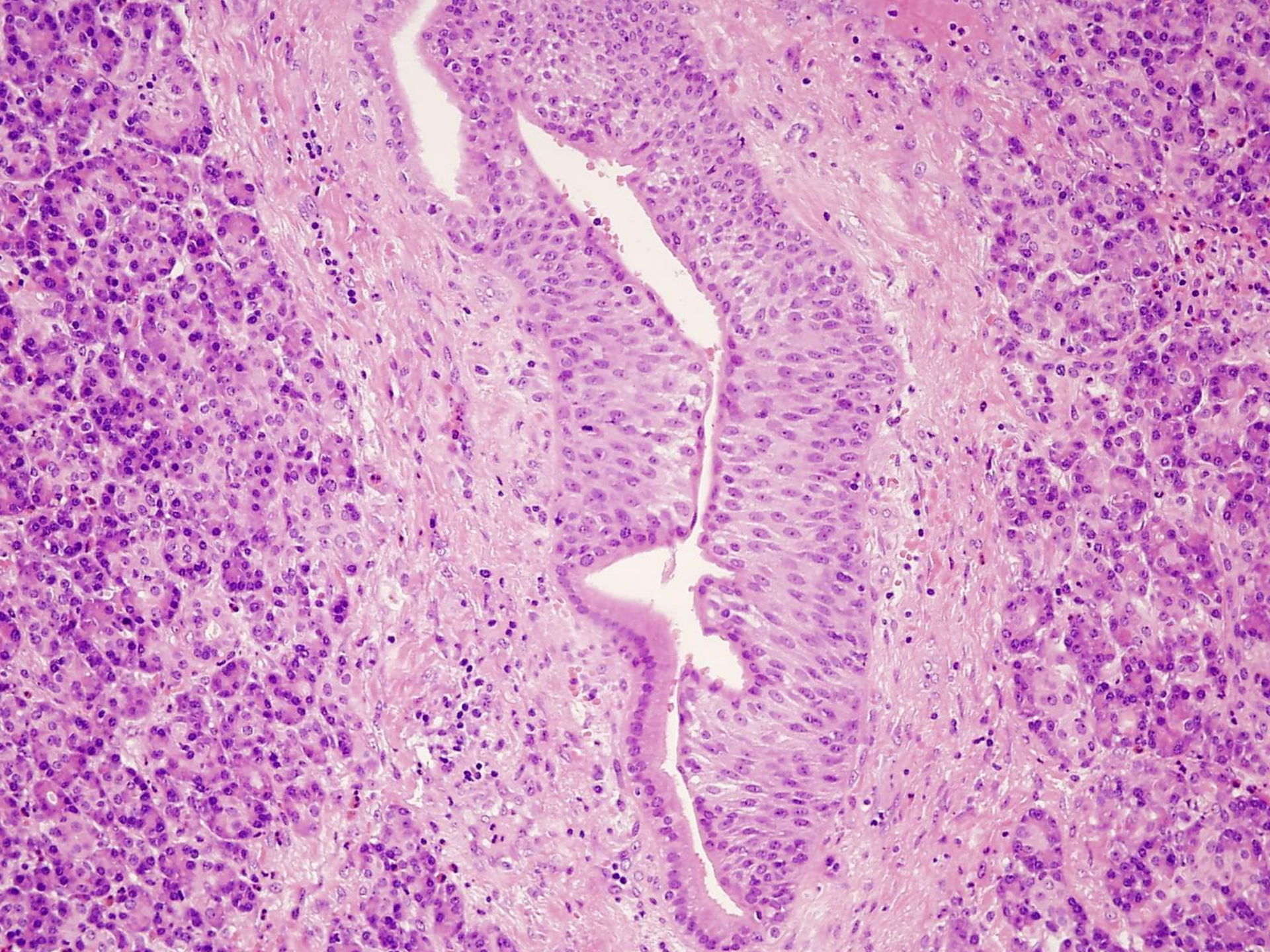












# Autoimmune pancreatitis

(Lymphoplasmocytic sclerosing pancreatitis)

IgG elevation

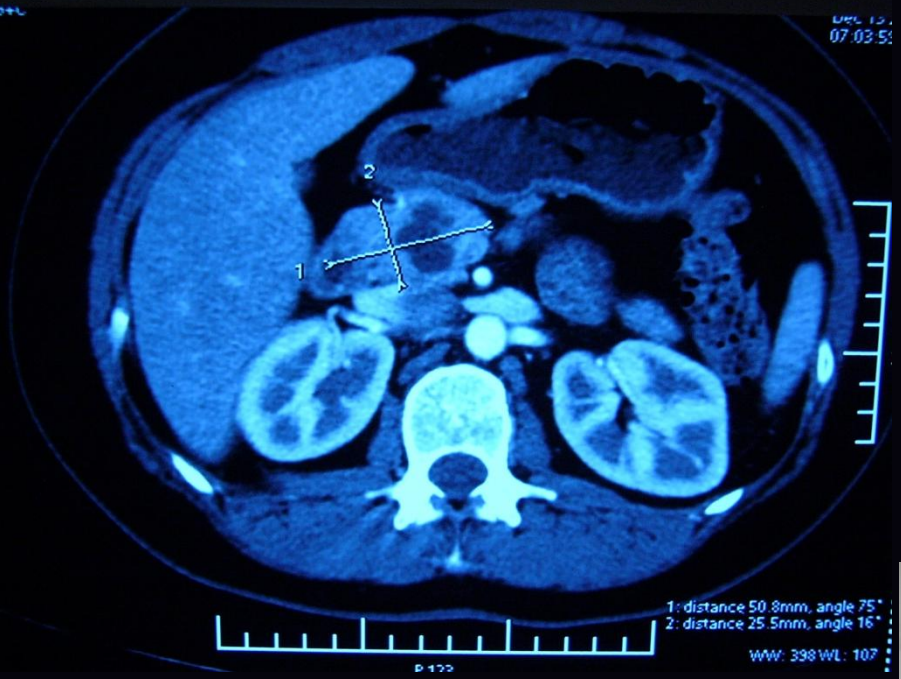
Mimicry of cancer

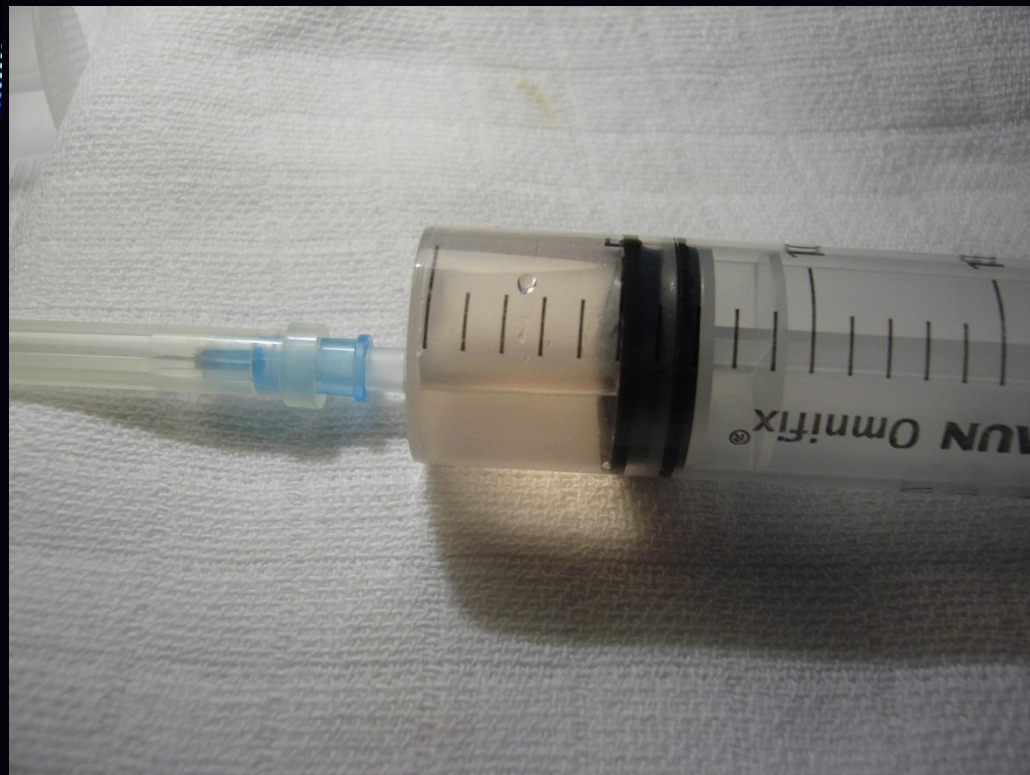
# Pancreatic pseudocyst

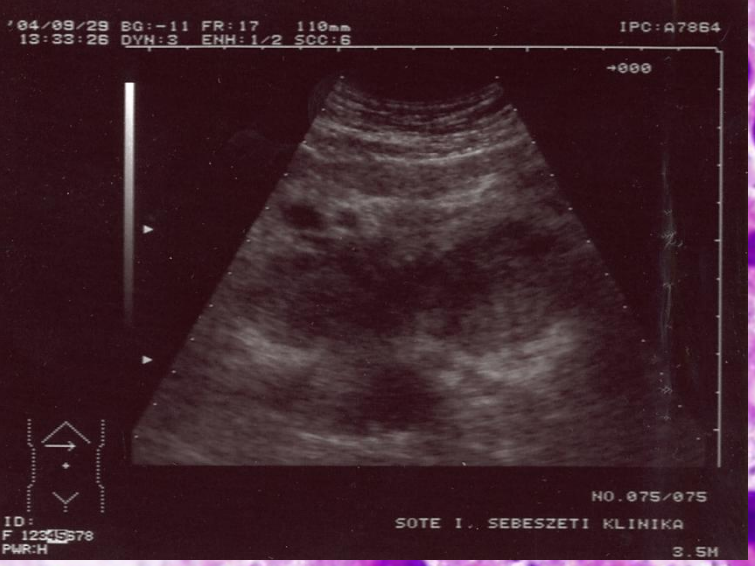
Local accumulation of pancreatic juice - occurs after pancreatitis

# Pancreatic - abscess

Occurs after pancreatitis,
Cause : colliquation necrosis
Sterile, in case, no secondary infection occurs


2
1
1: distance 50.8mm, angle 75°
2: distance 25.5mm, angle 16°
WW: 398 WL: 107


Omnifix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13:33:26 DYN:3 ENH:1/2 SCC:6
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+000
NO.075/075
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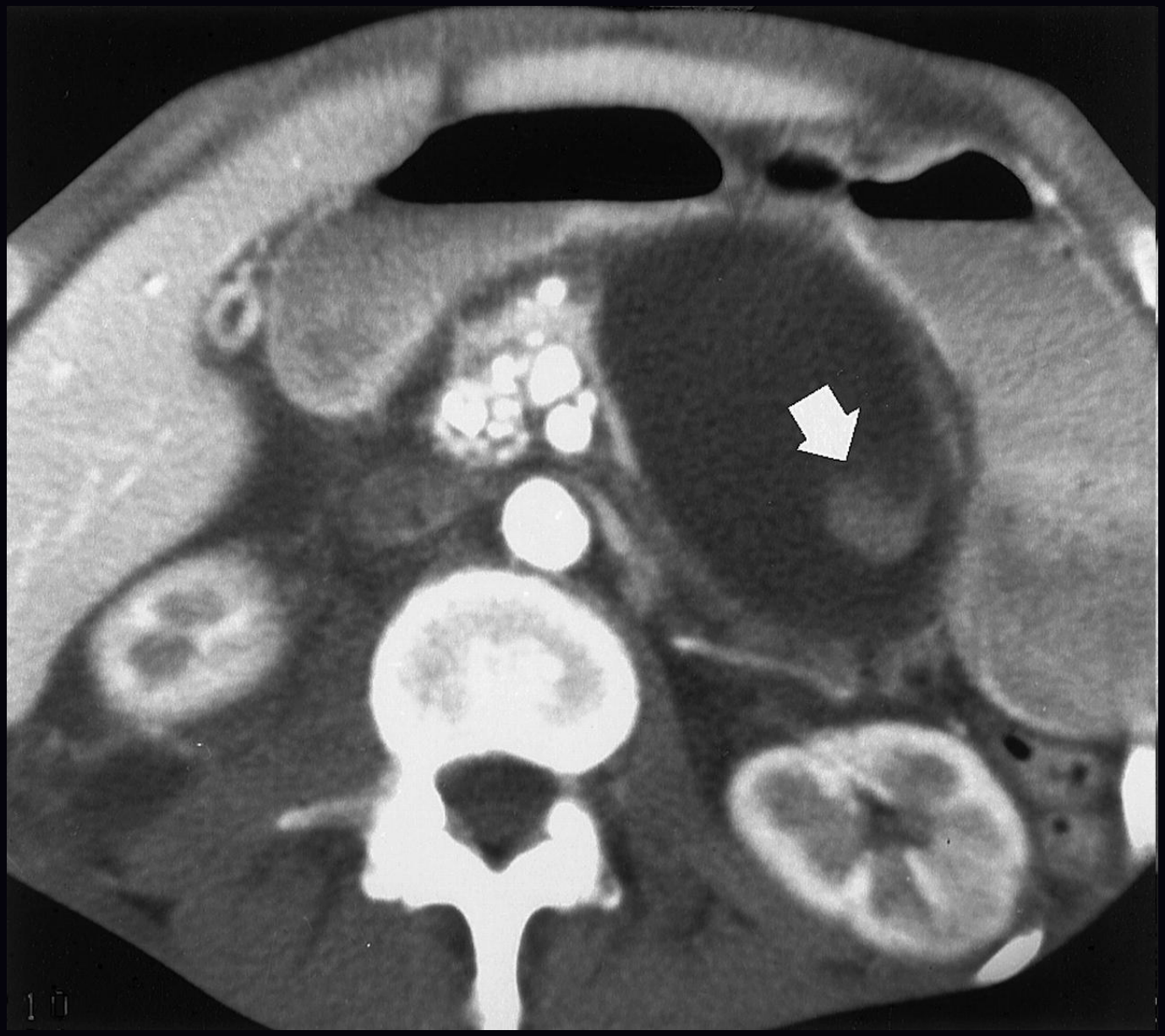
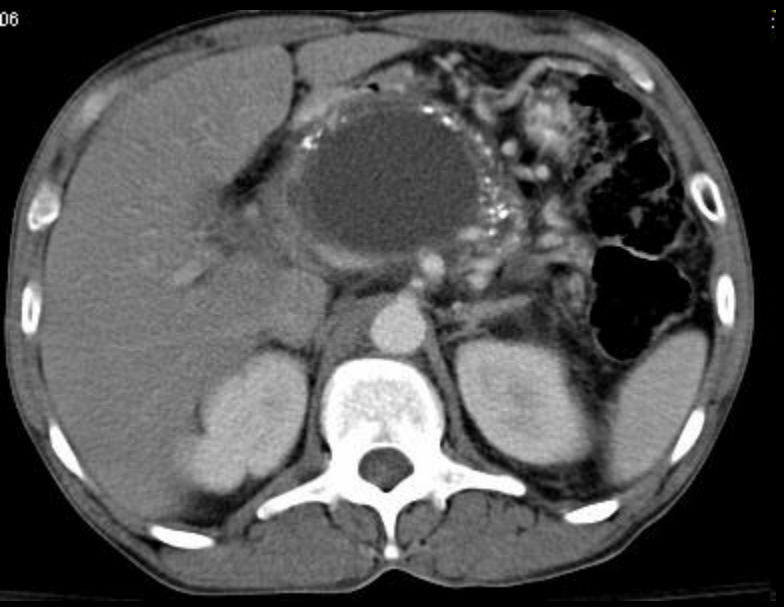
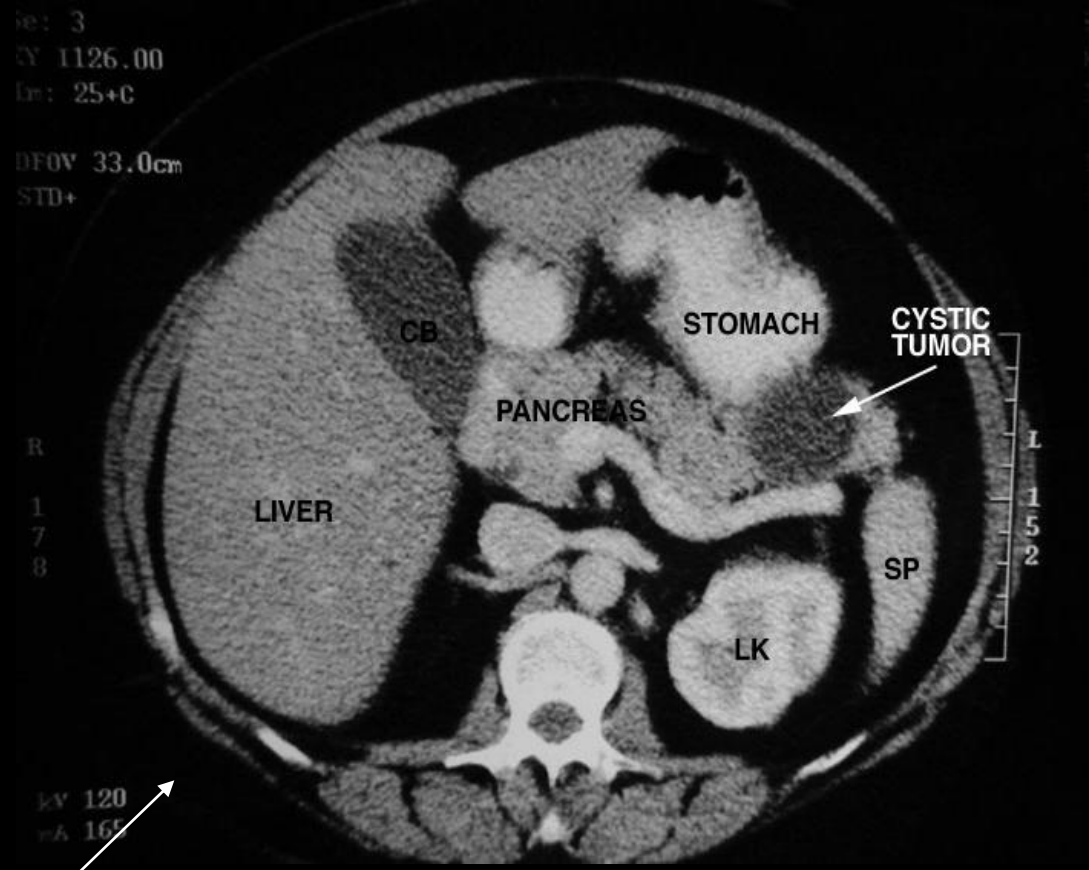
SOTE I. SEBESZETI KLINIKA
PWR:H
3.5M

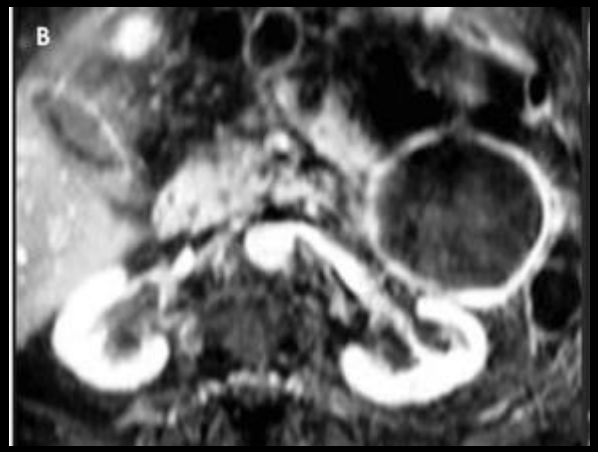


# Pseudocysts
# diff.dg.:
# cystic tumors






Pseudocysts
diff.dg.:
cystic tumors



# Tumors of the pancreas

Benign

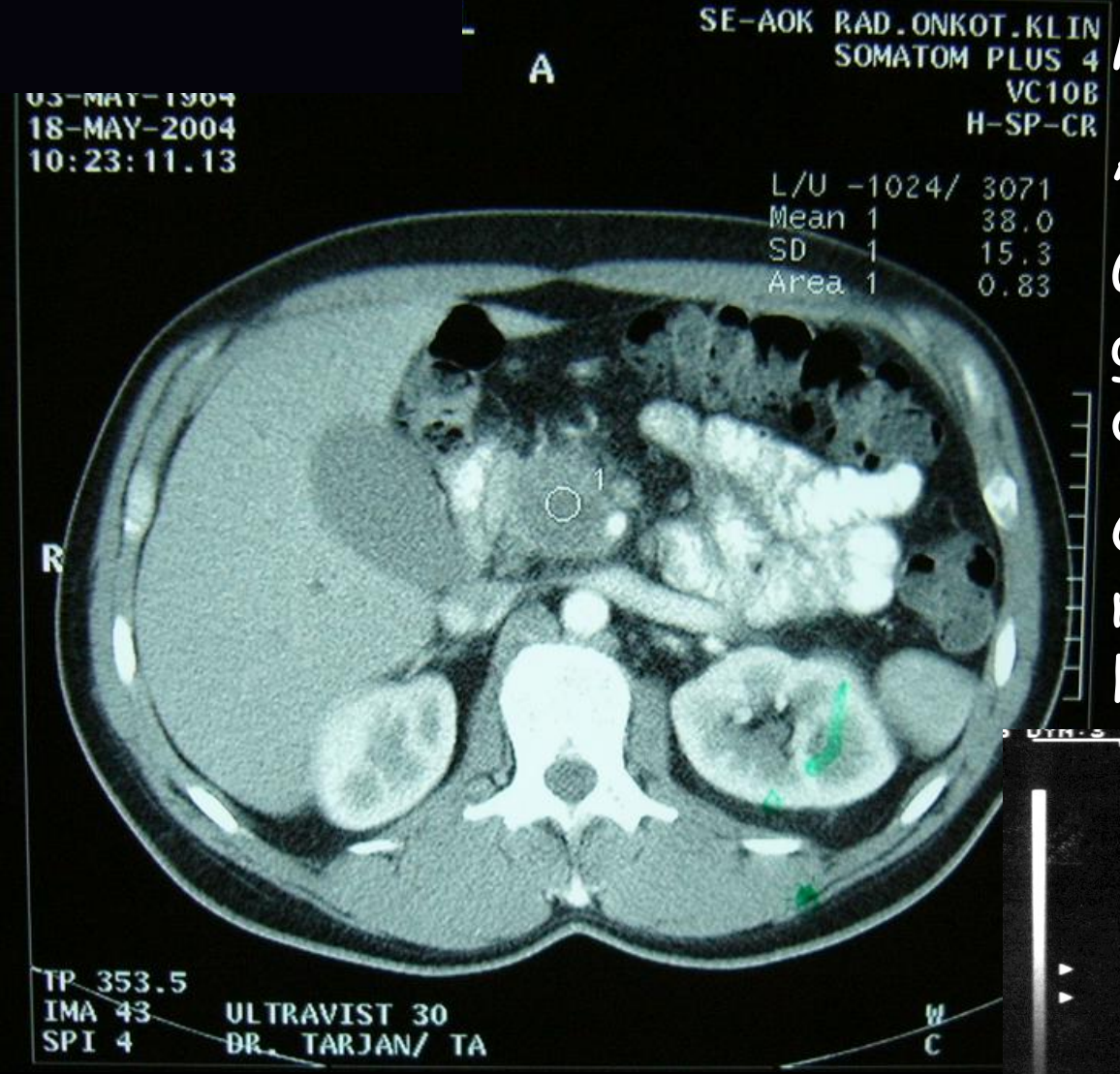
Malignant

# Malignant pancreatic tumors

- Ductal adenocarcinoma
- Anaplastic cc.
- Acinic cell cc.
- Metastatic tumors
- Lymphomas
- Sarcomas

# Pancreatic carcinoma - symptoms

- Pain
- Jaundice
- Curvoisier sign
- Weight loss
- Passage disturbances
- Migrating thrombophlebitis (Trousseau)
- Pancreatitis
- Metastasis

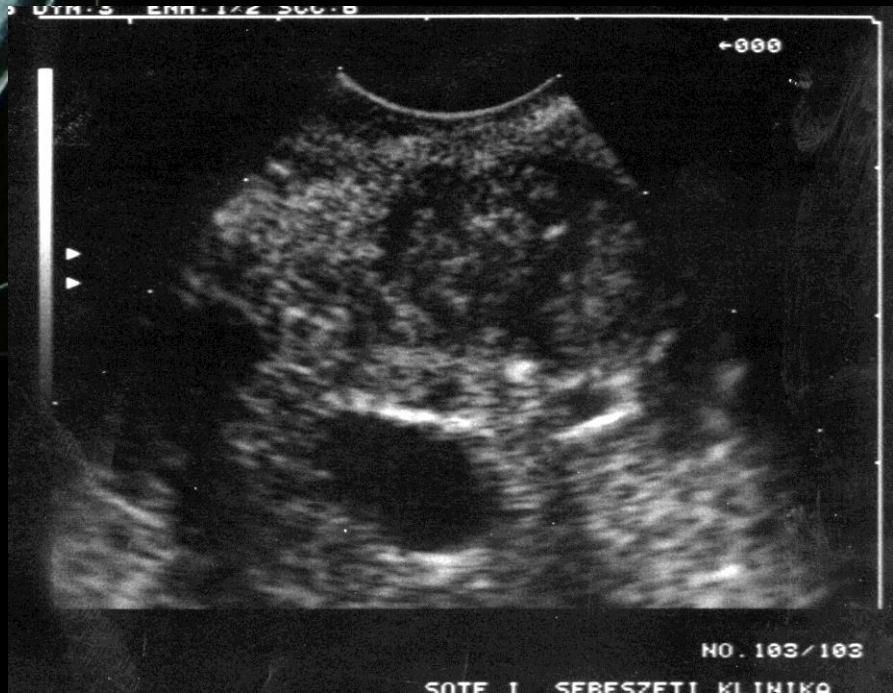


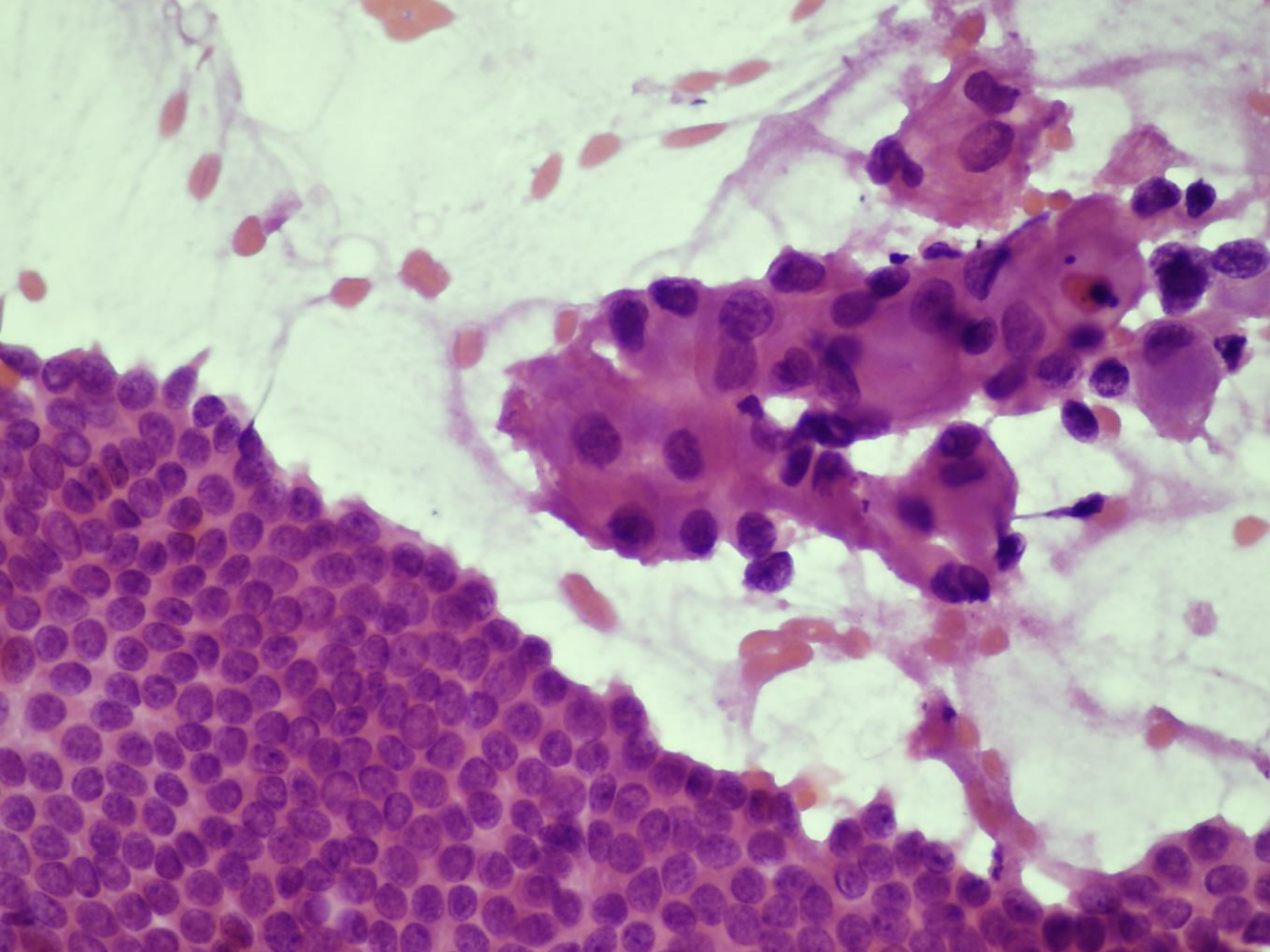

Male, 39

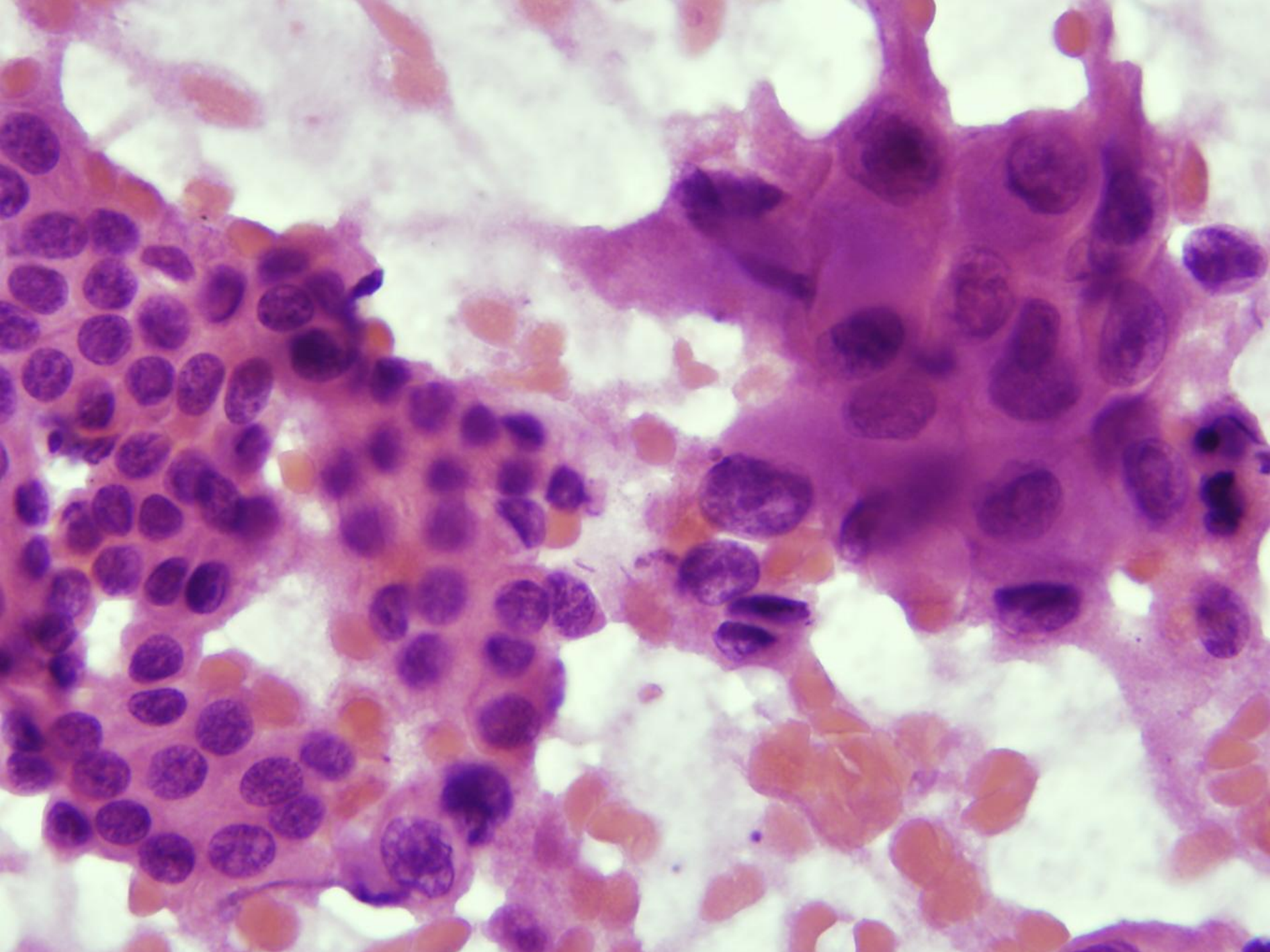
Abdominal pain

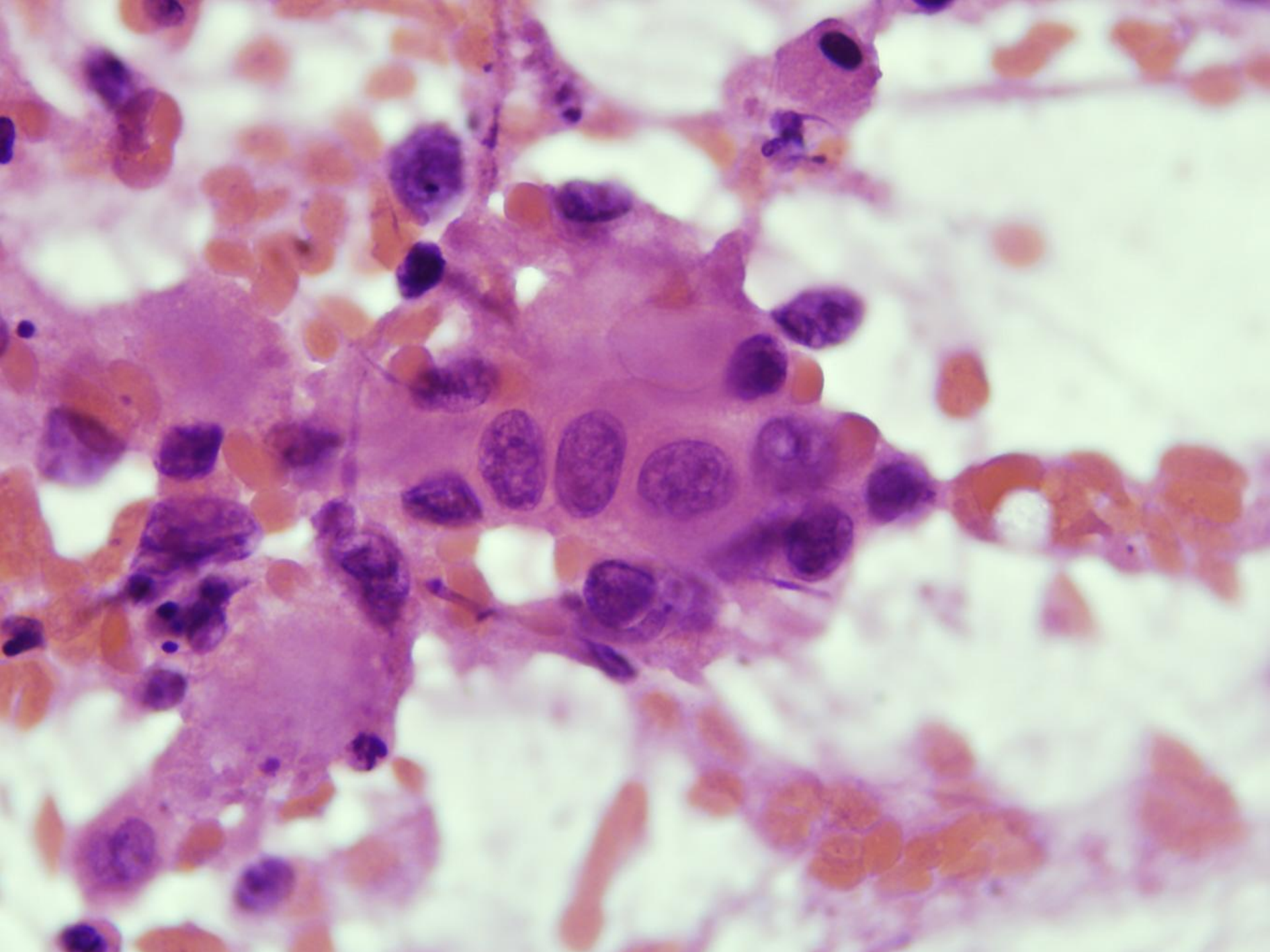
Gastroscopy: HP+ gastritis, reflux oesophagitis

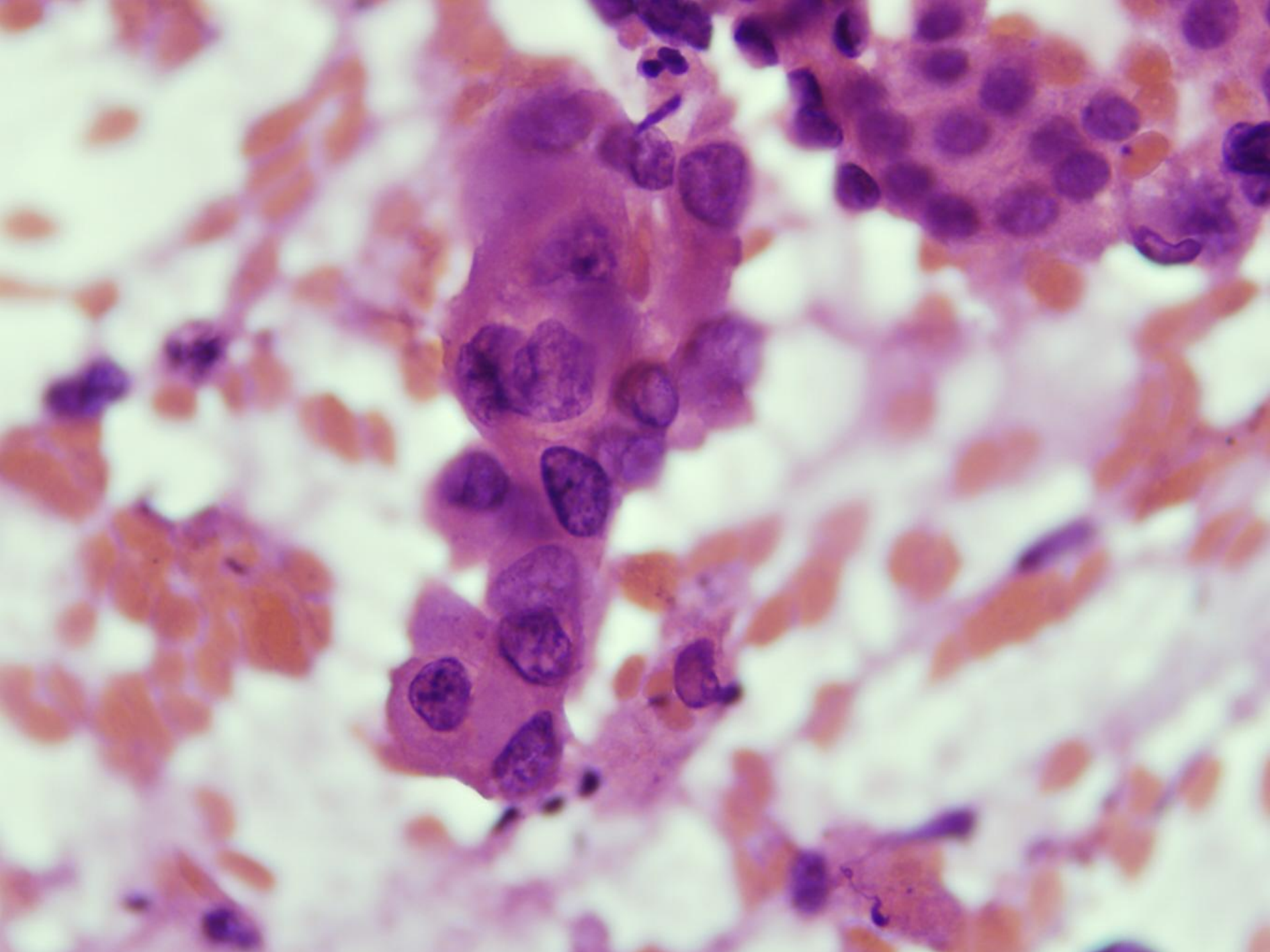
Controll examination – mild jaundice… Hepatitis?

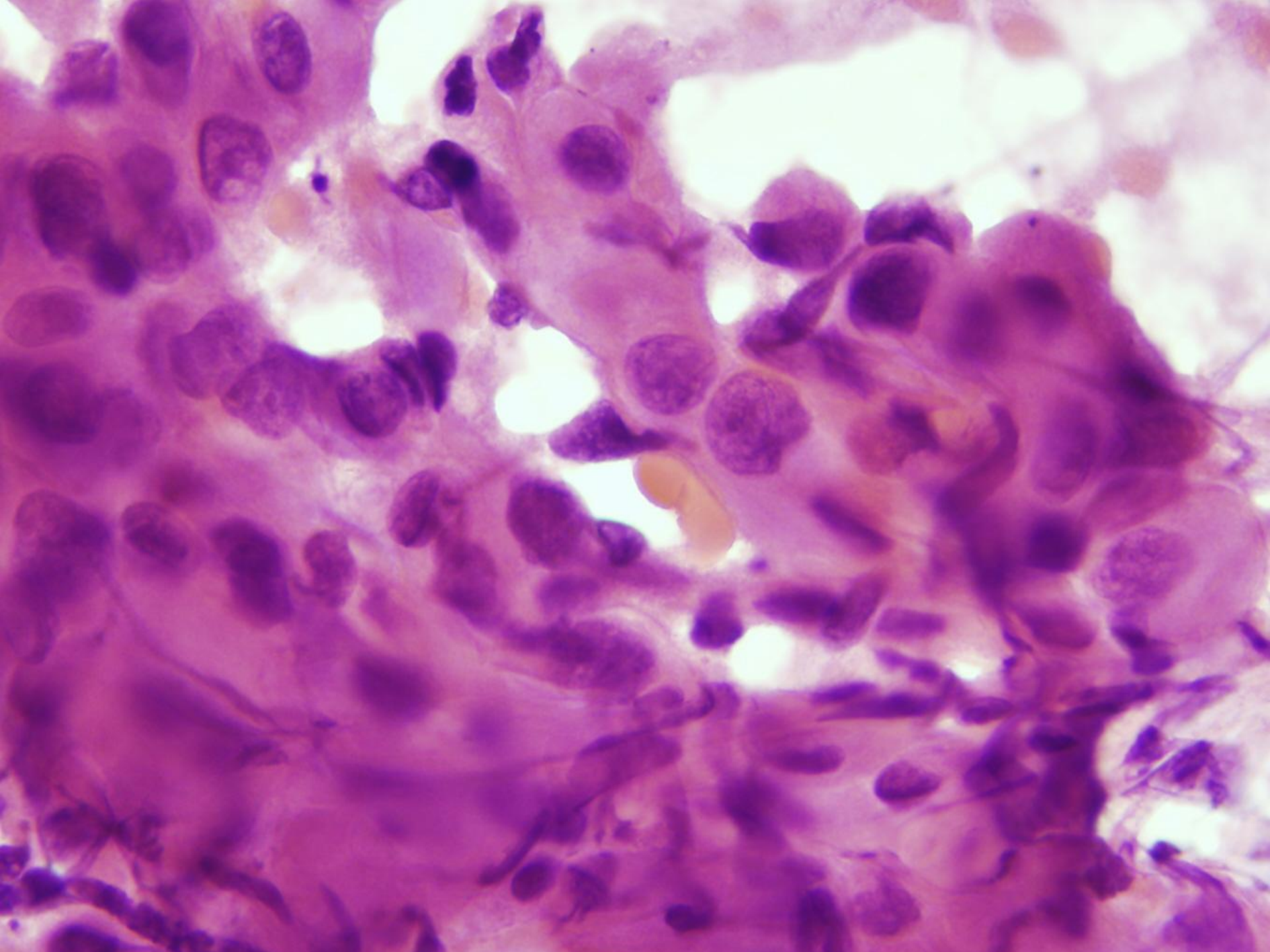


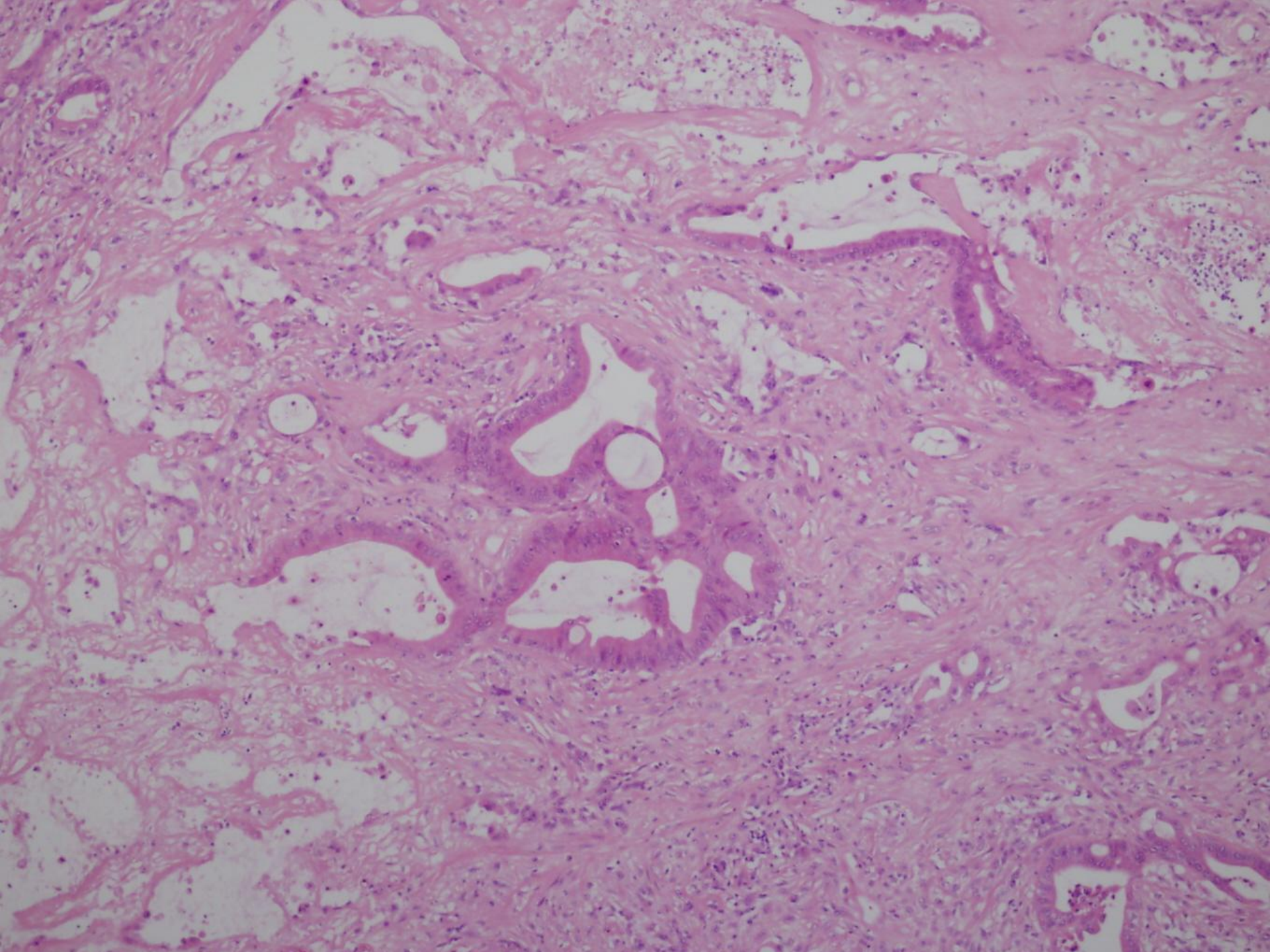


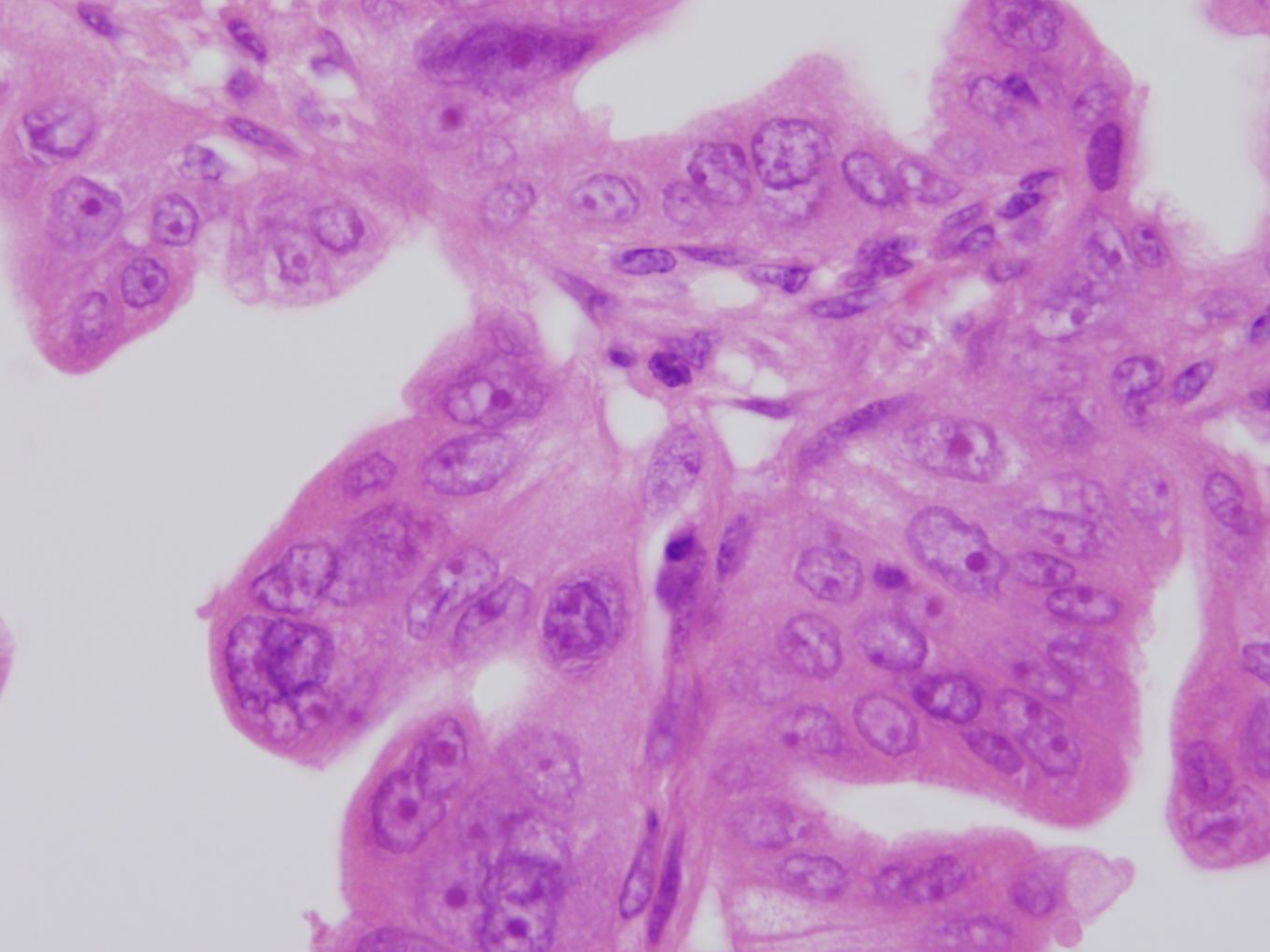


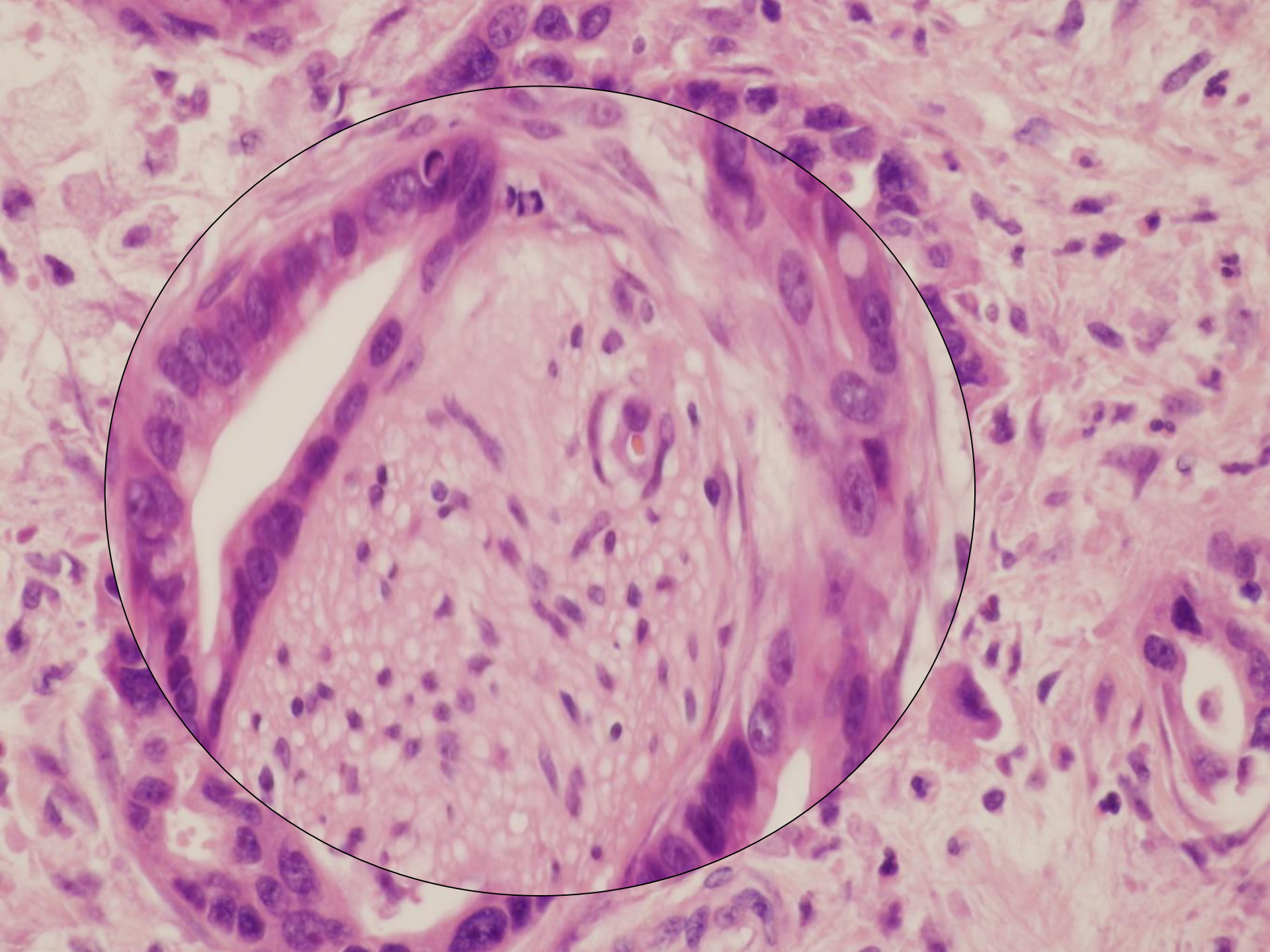


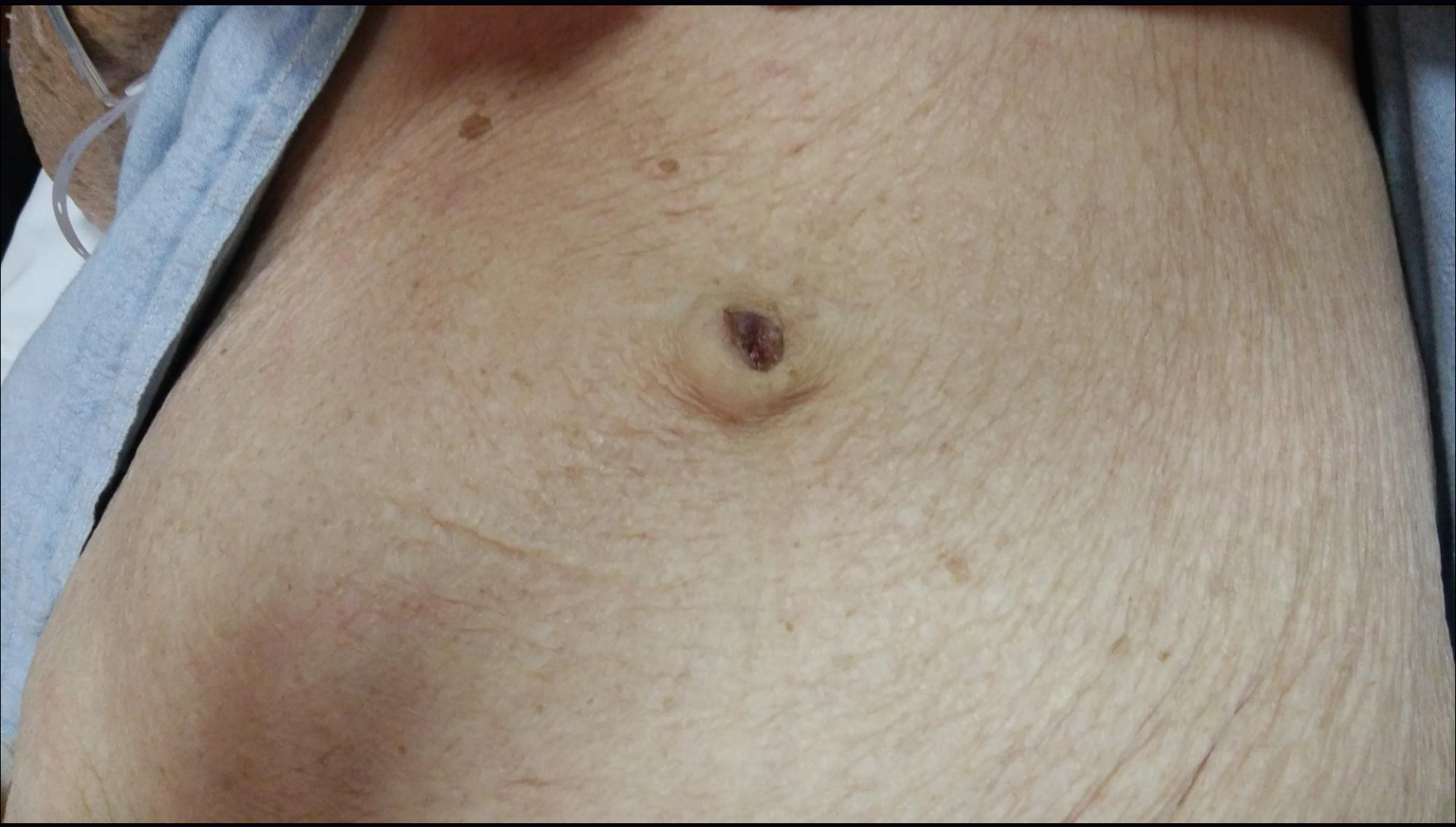


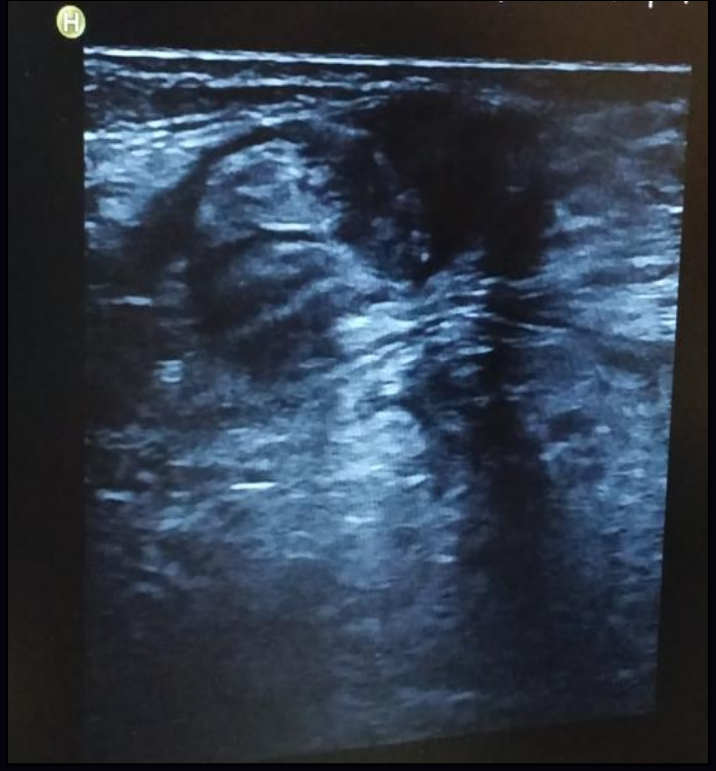


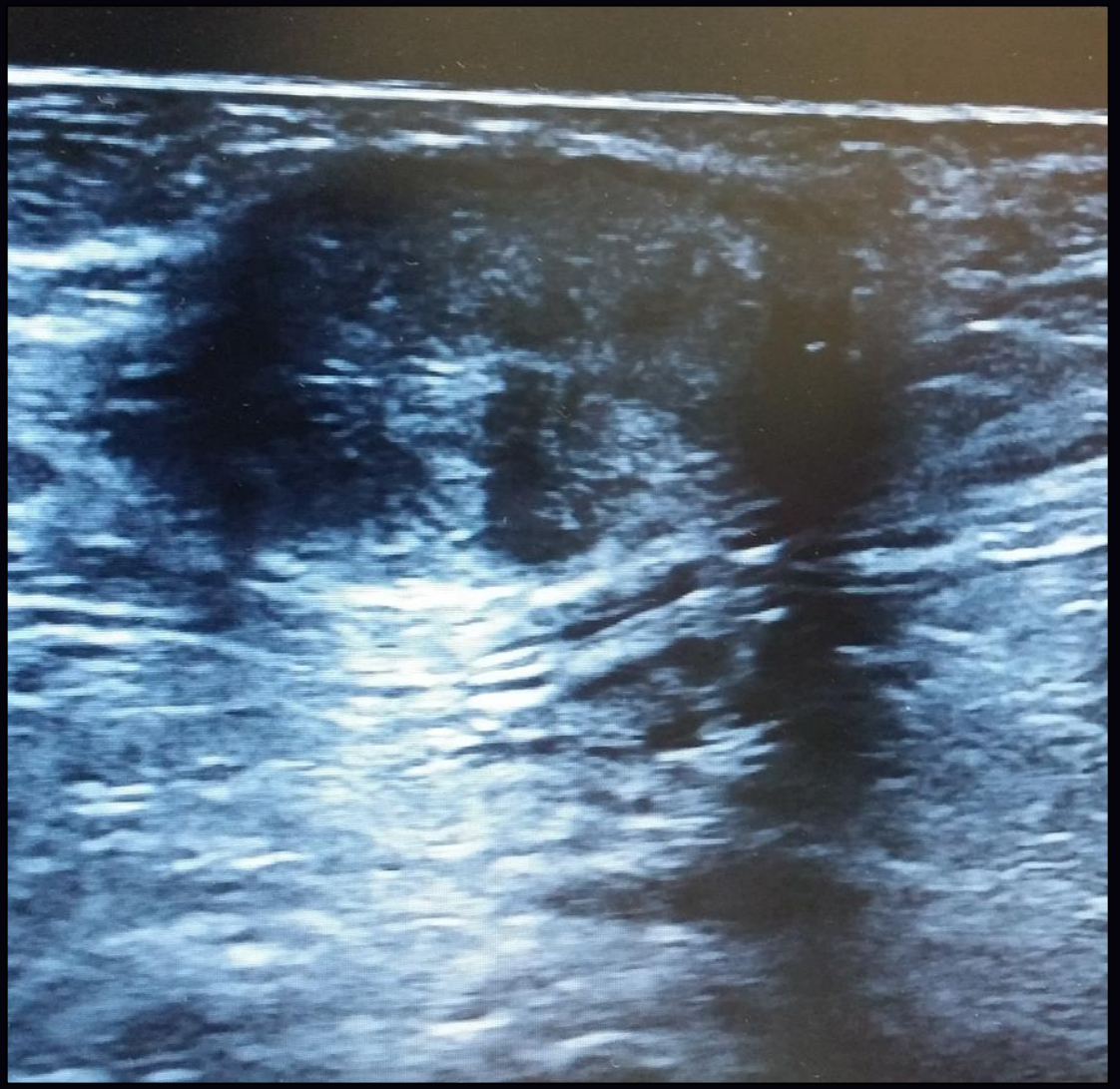


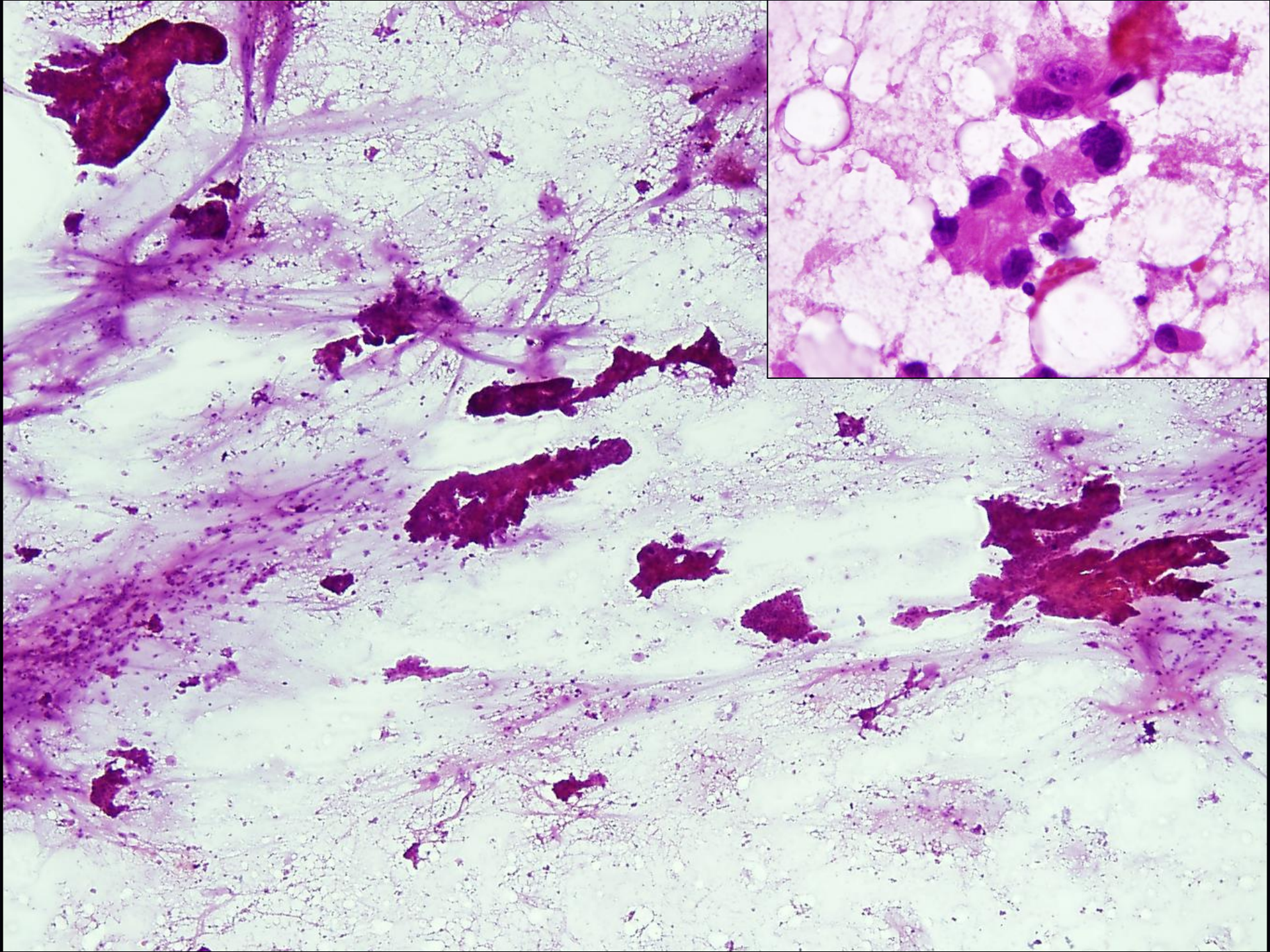


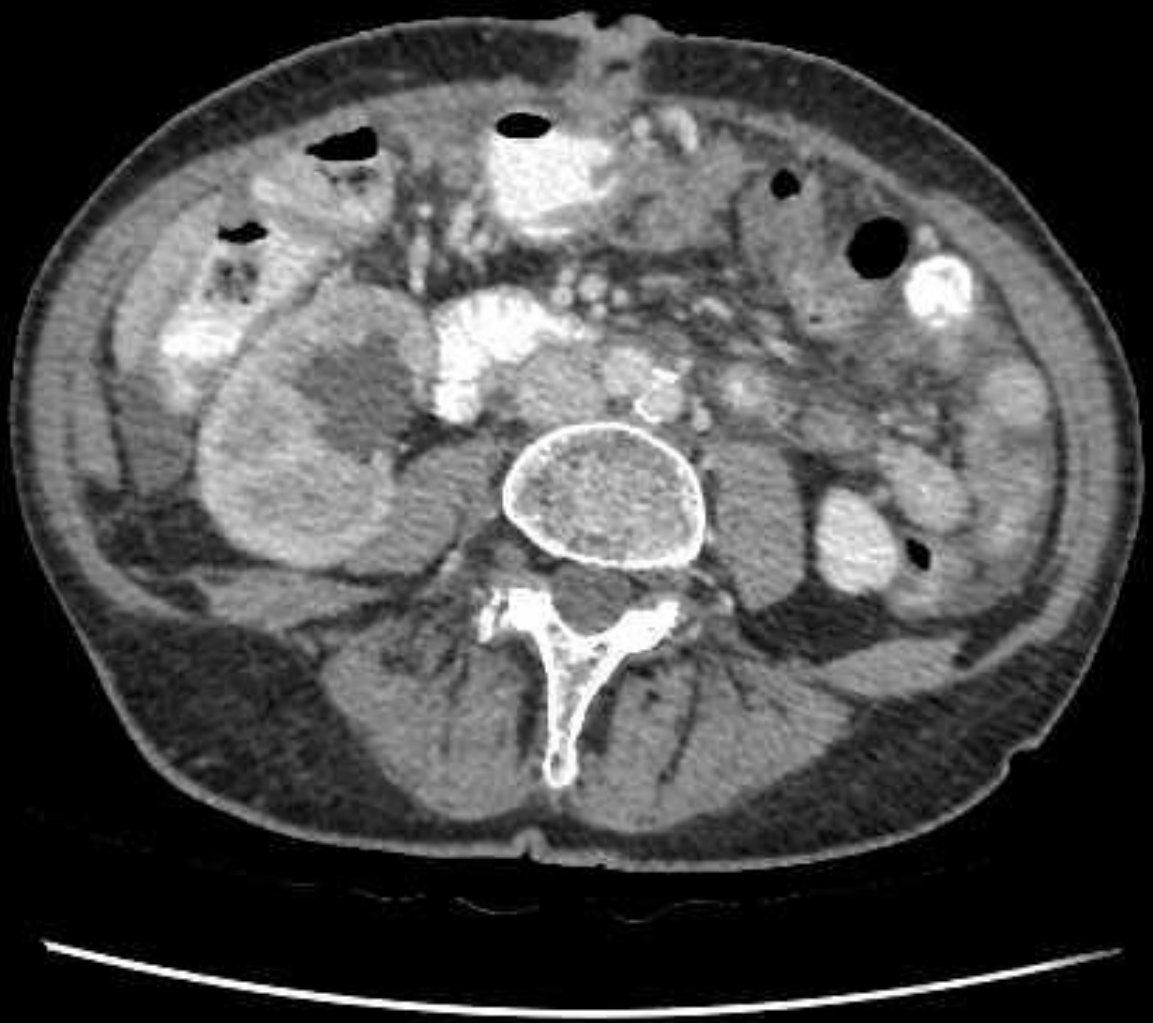








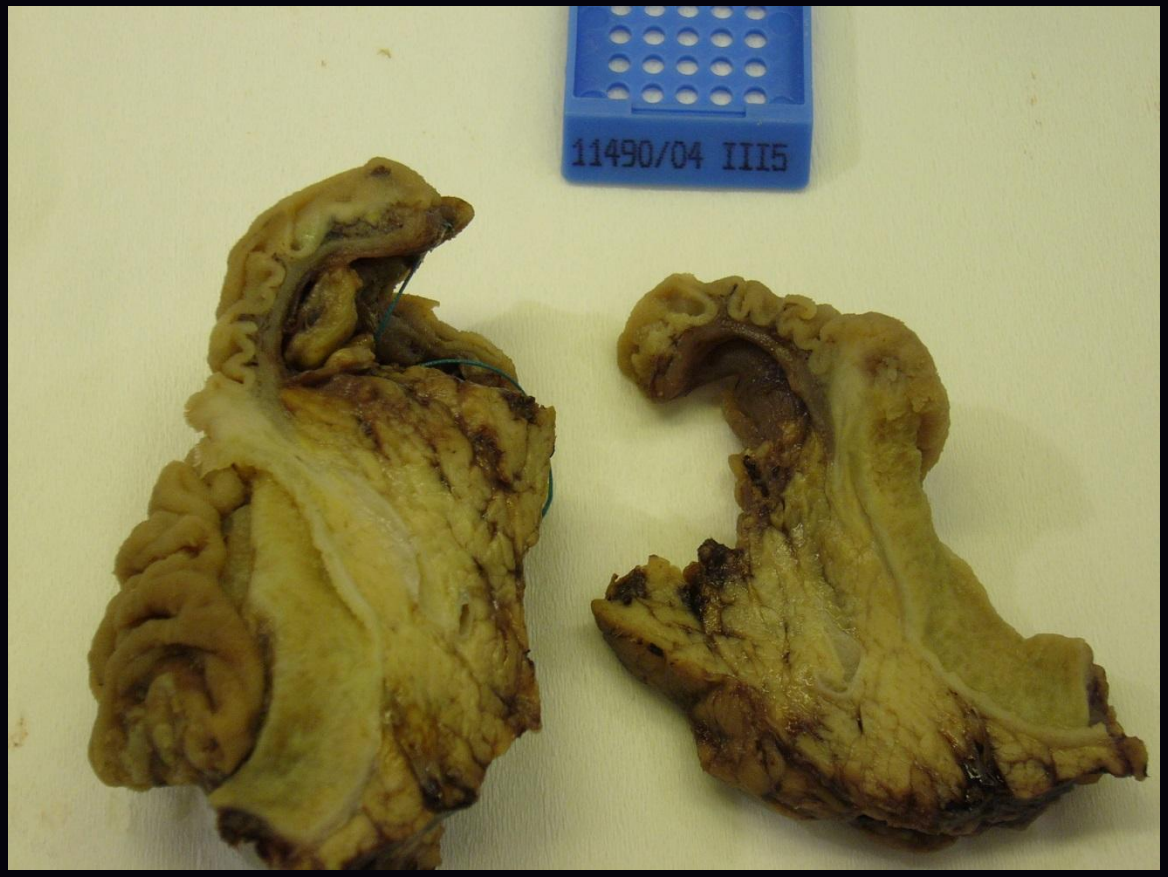


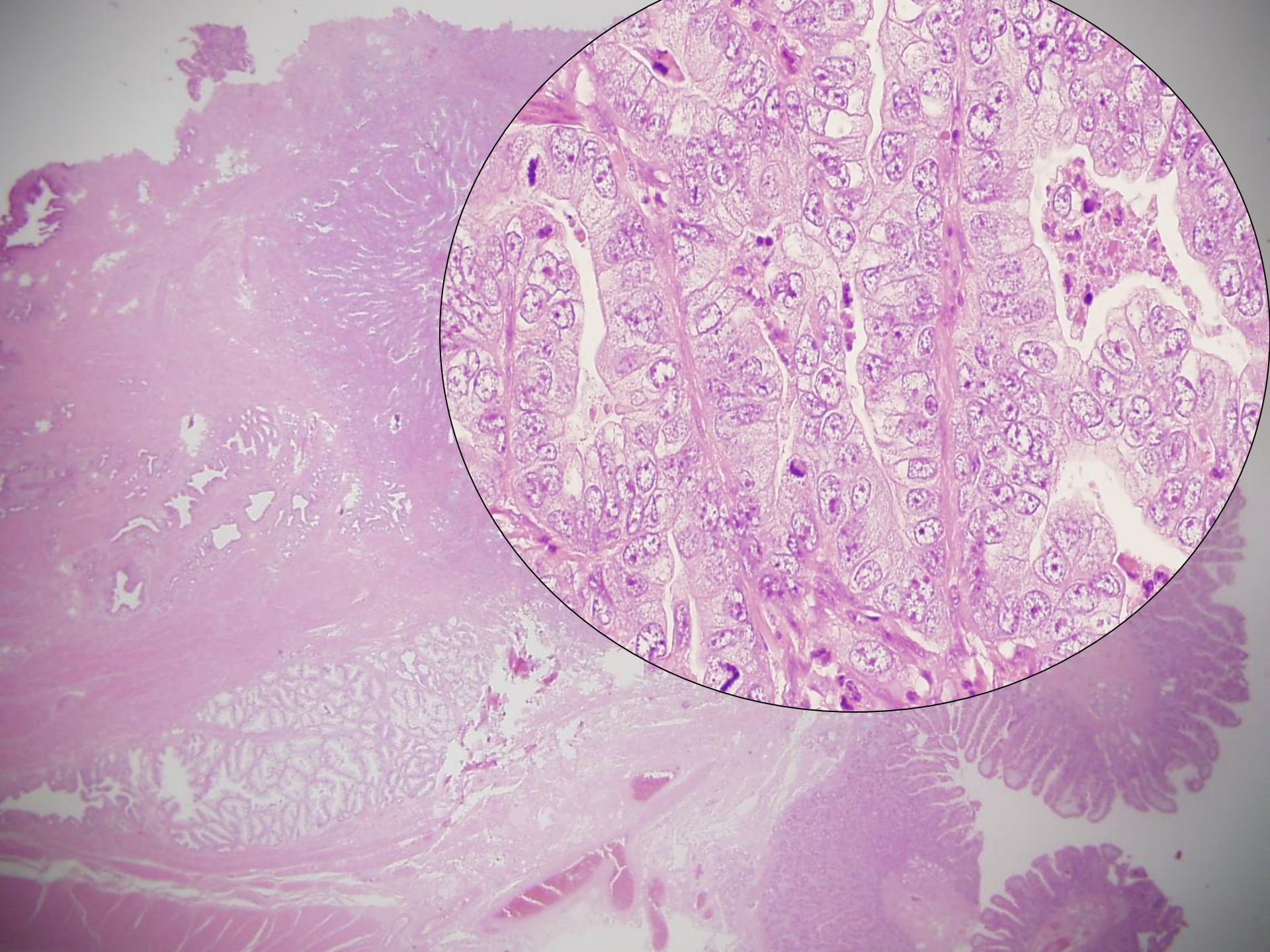


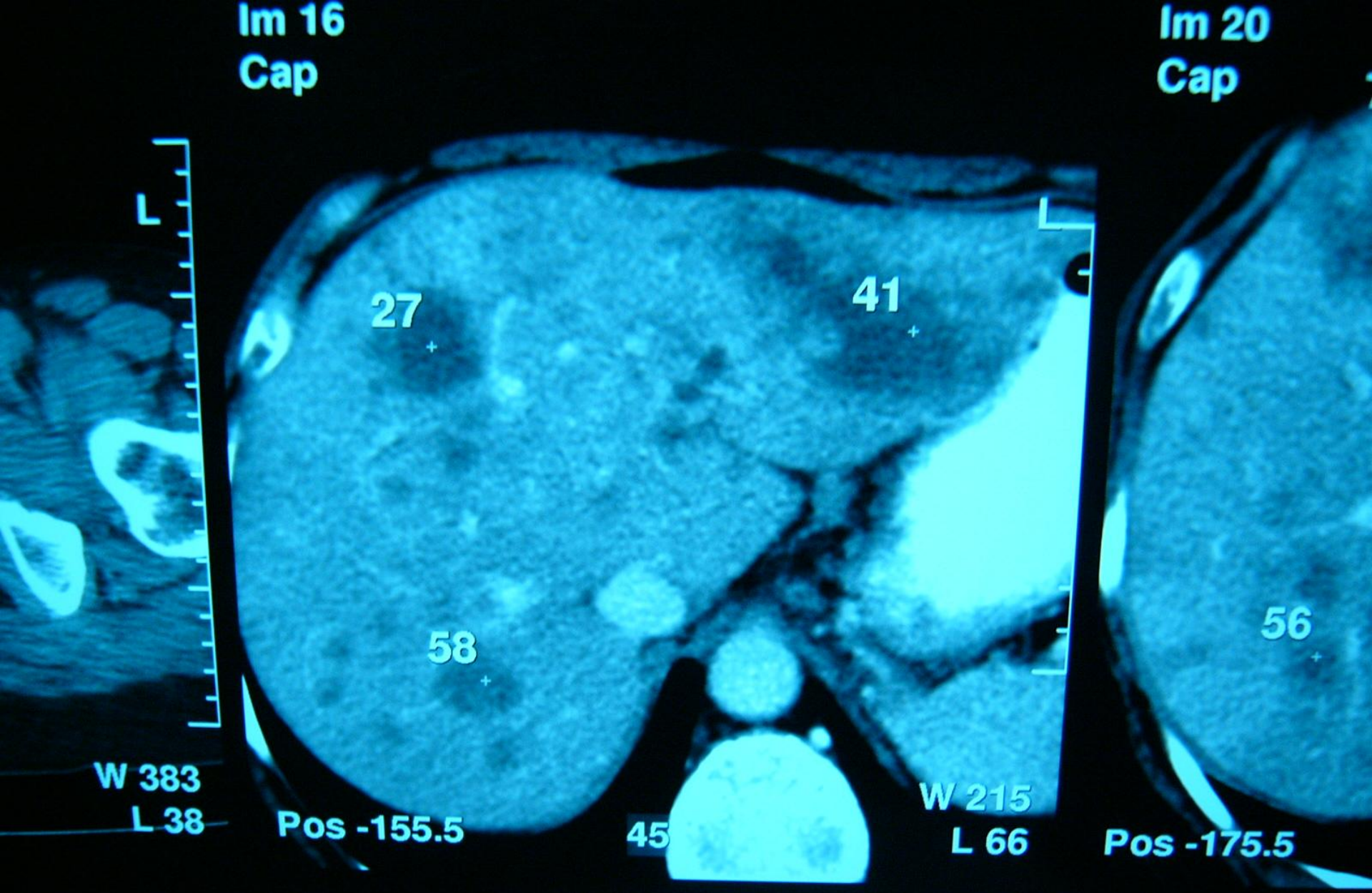
CT report:

- carcinosis peritonei
- metastasis omenti
- hydronephrosis l.d.

# Carcinoma of the Vater papilla



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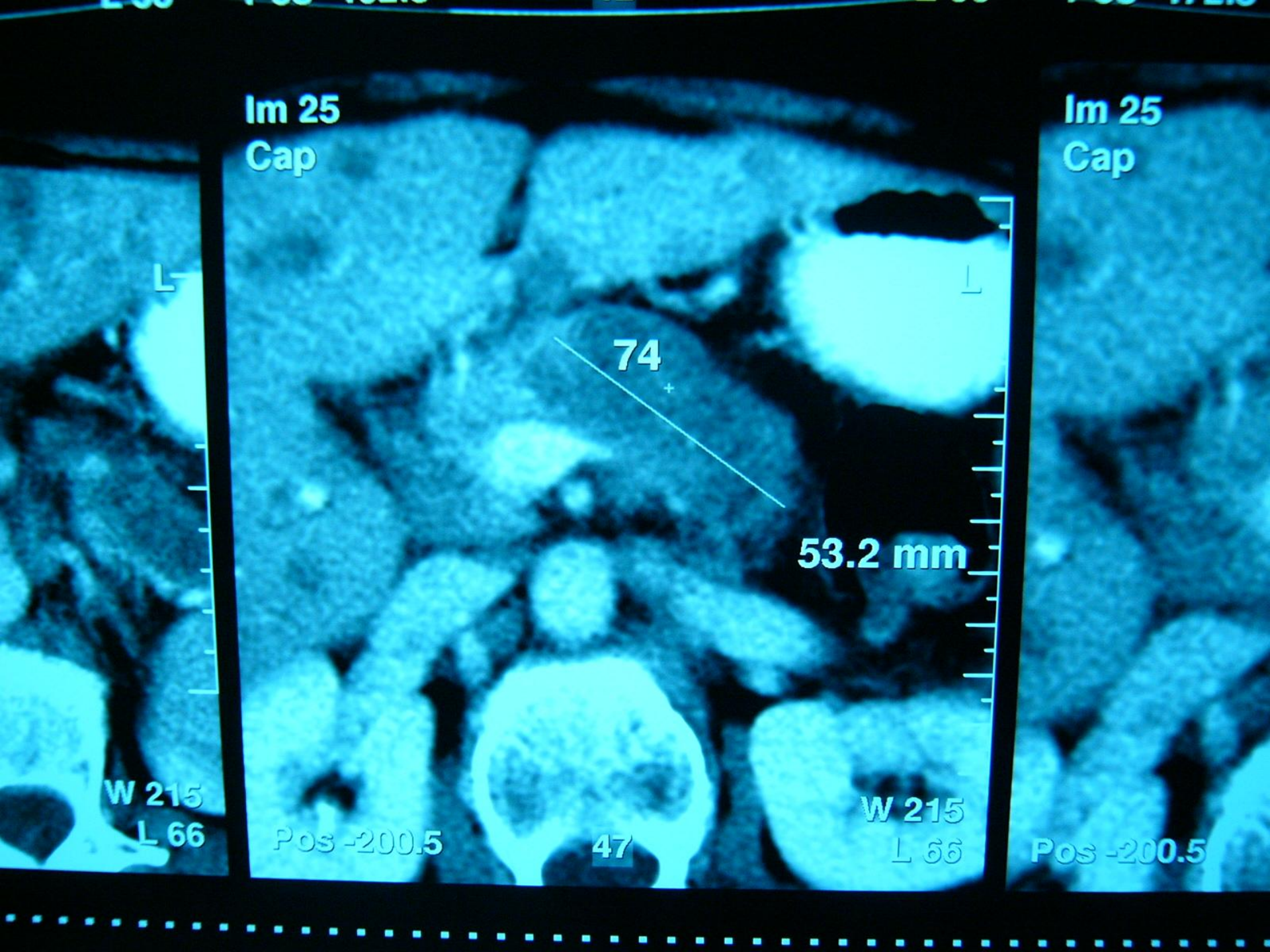
Cap
Im 20
Cap
L
27
41
58
56
W 383
L 38
Pos -155.5
45
W 215
L 66
Pos -175.5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Cap
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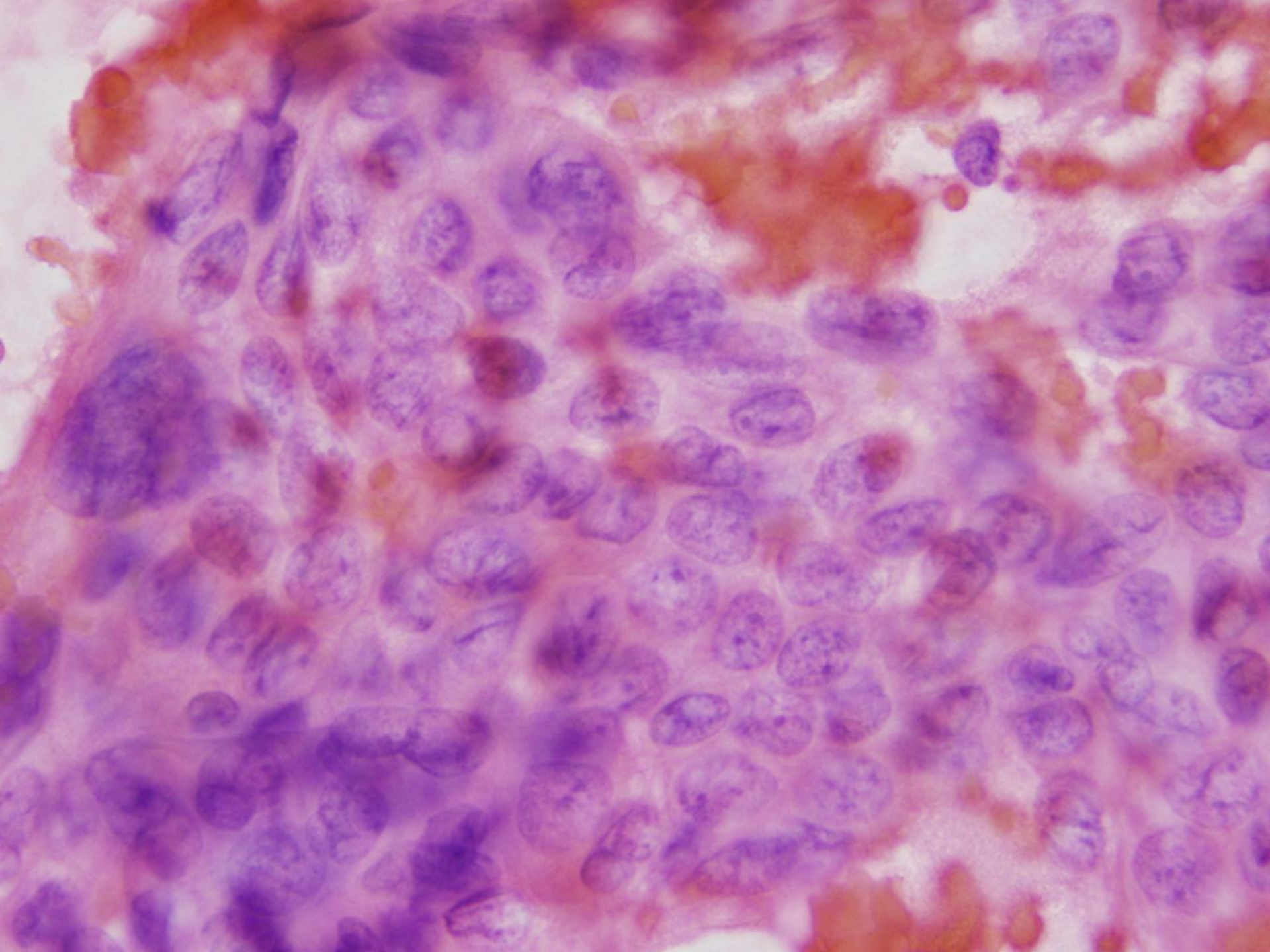
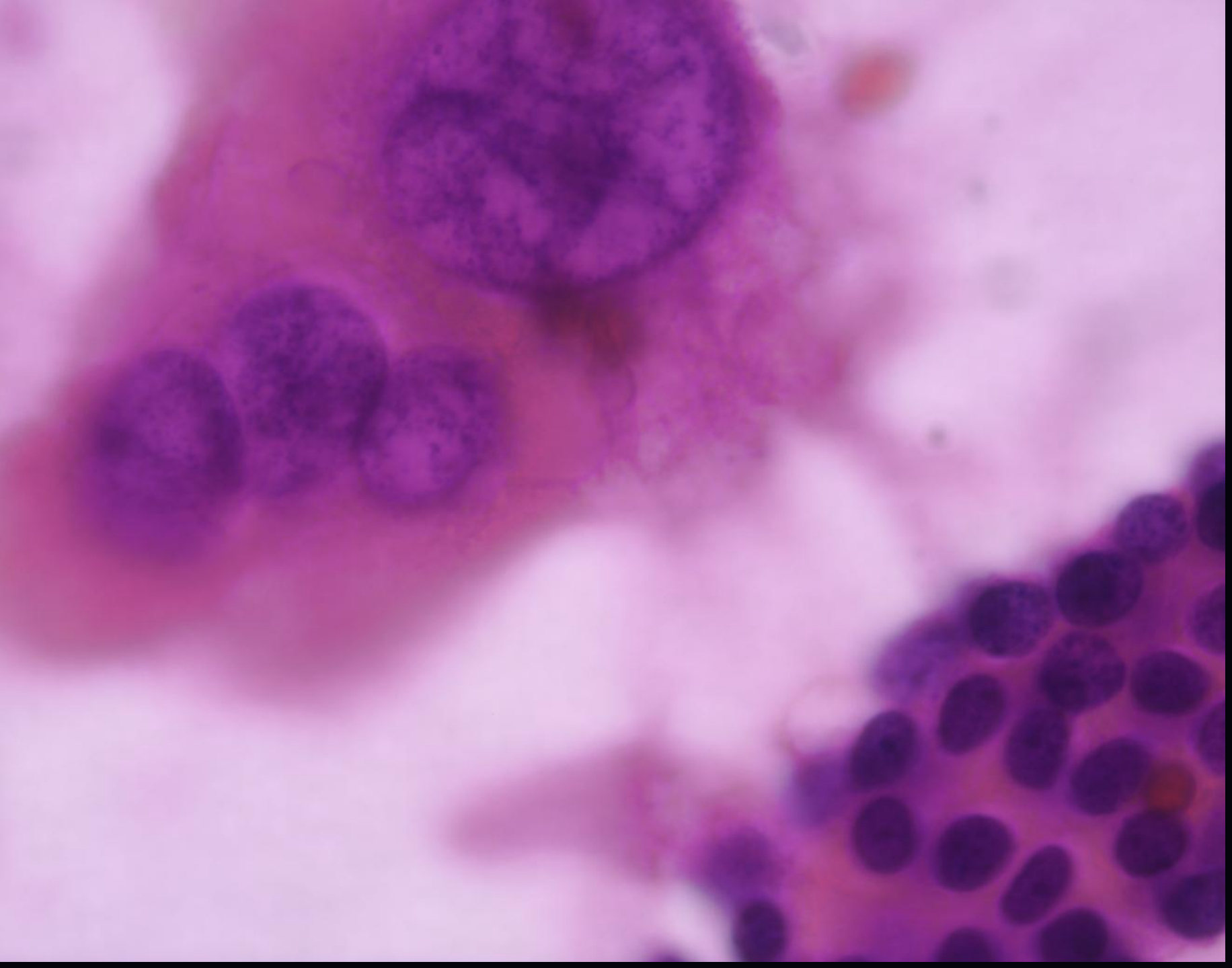
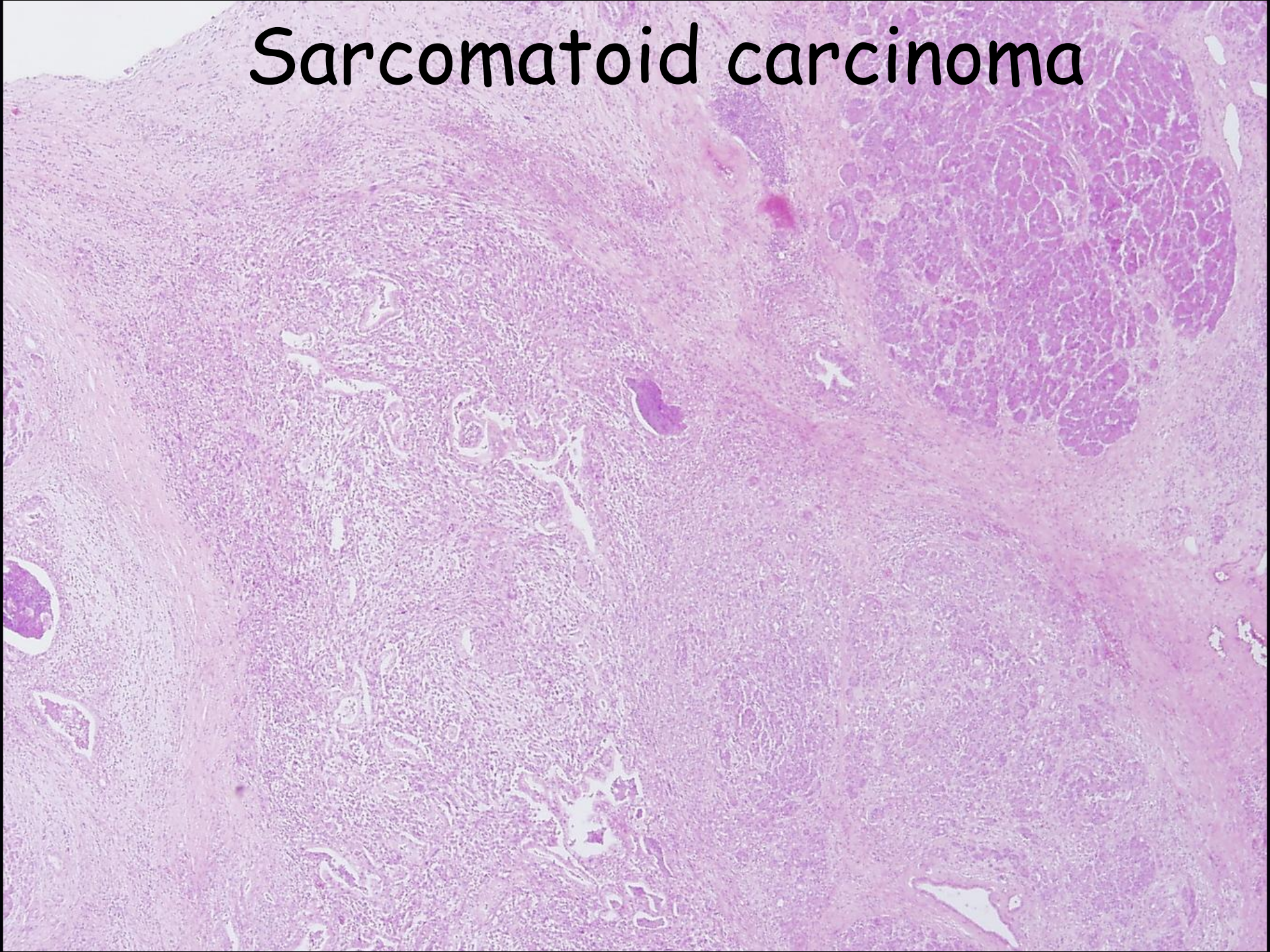
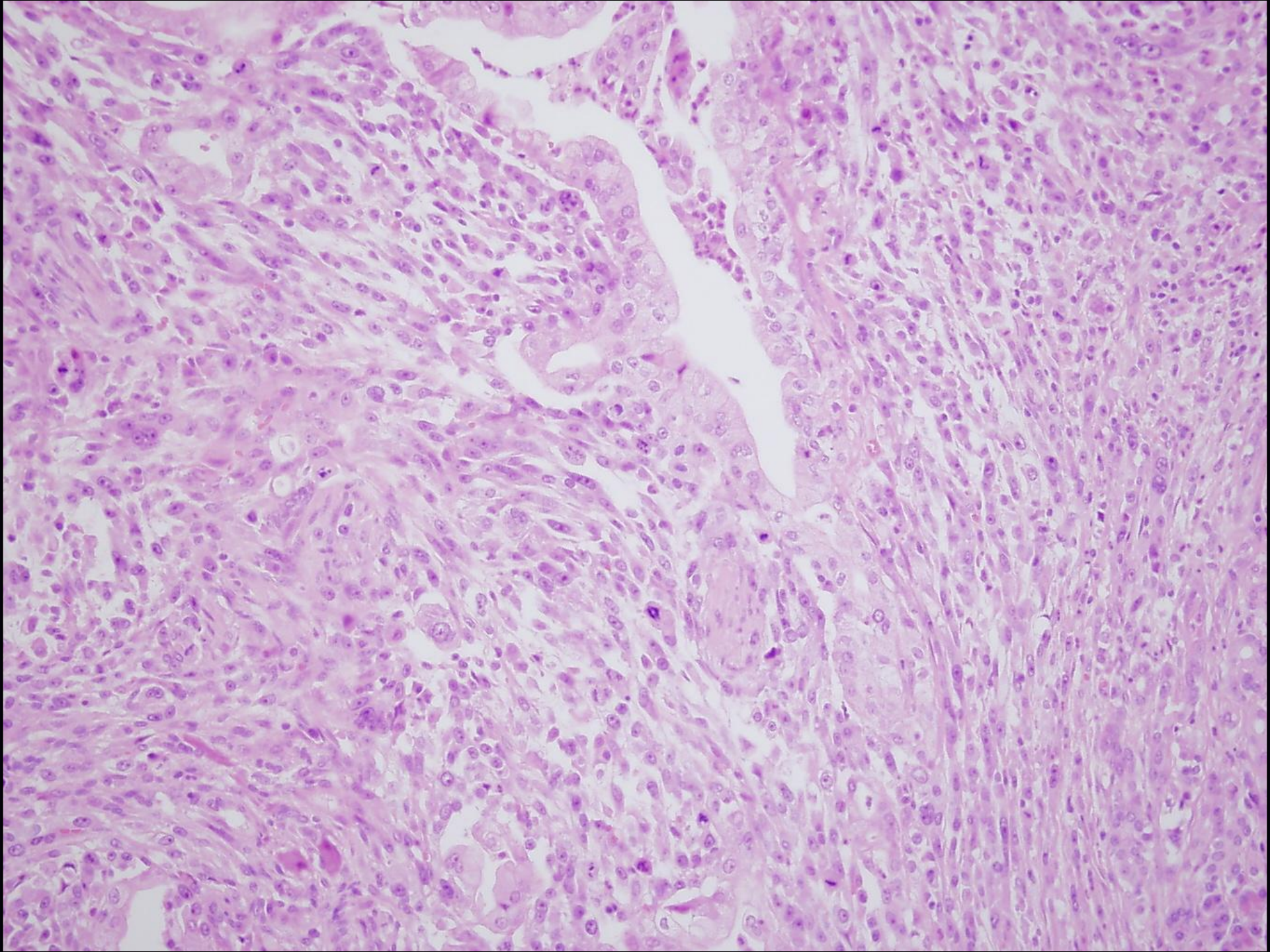
47
Im 25
Cap
W 215
L 66
Pos -200.5

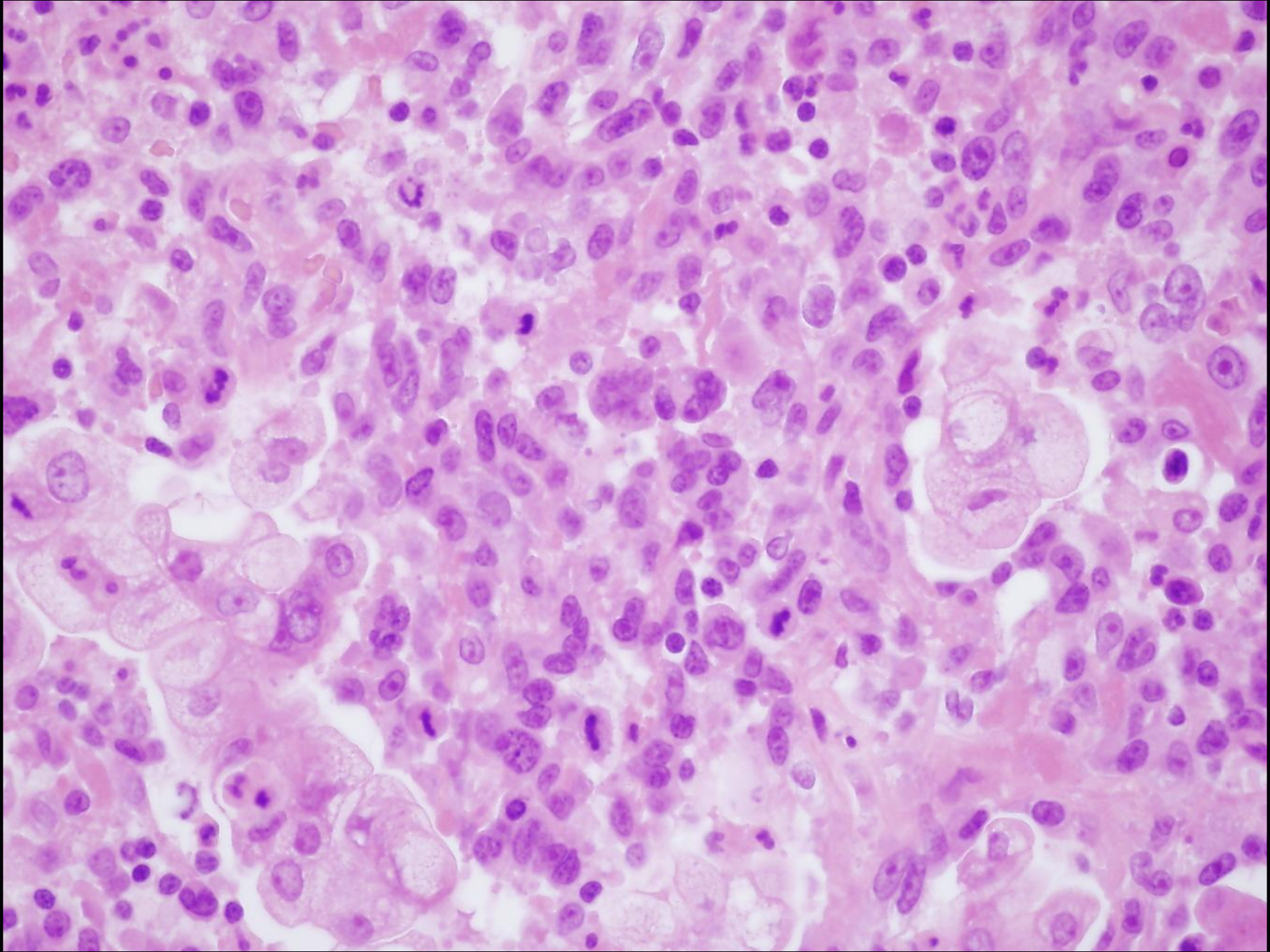


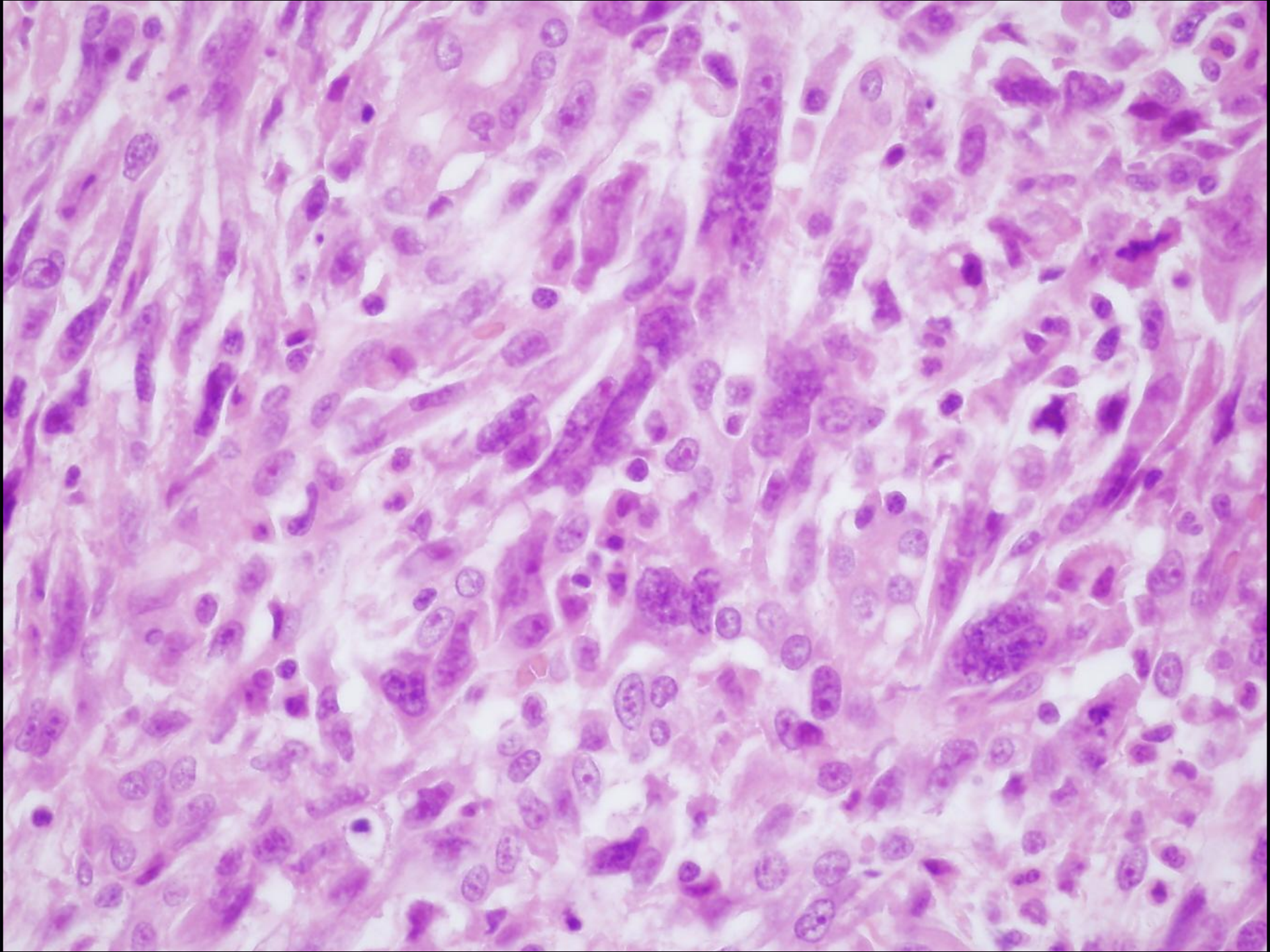


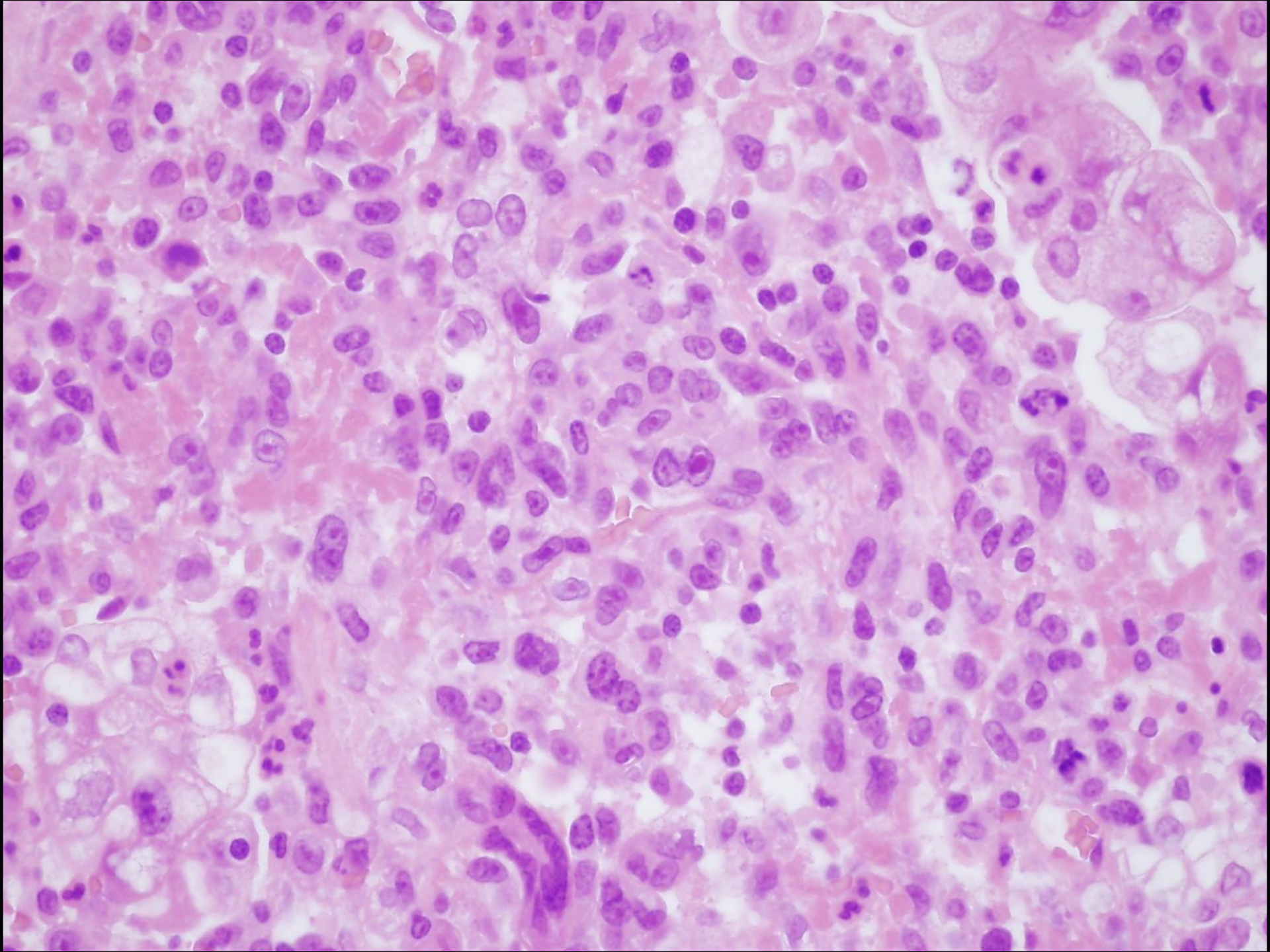
# Sarcomatoid carcinoma

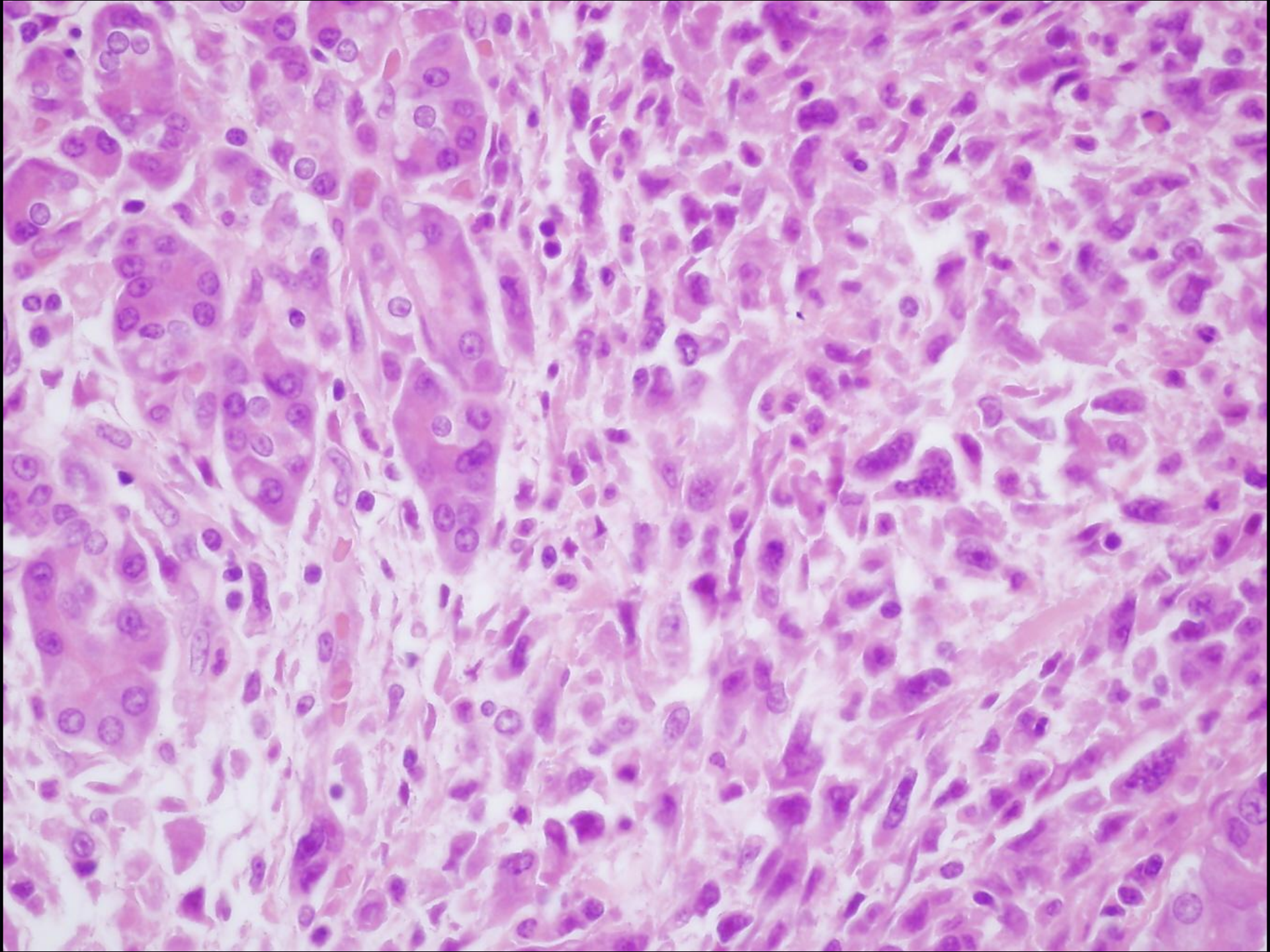












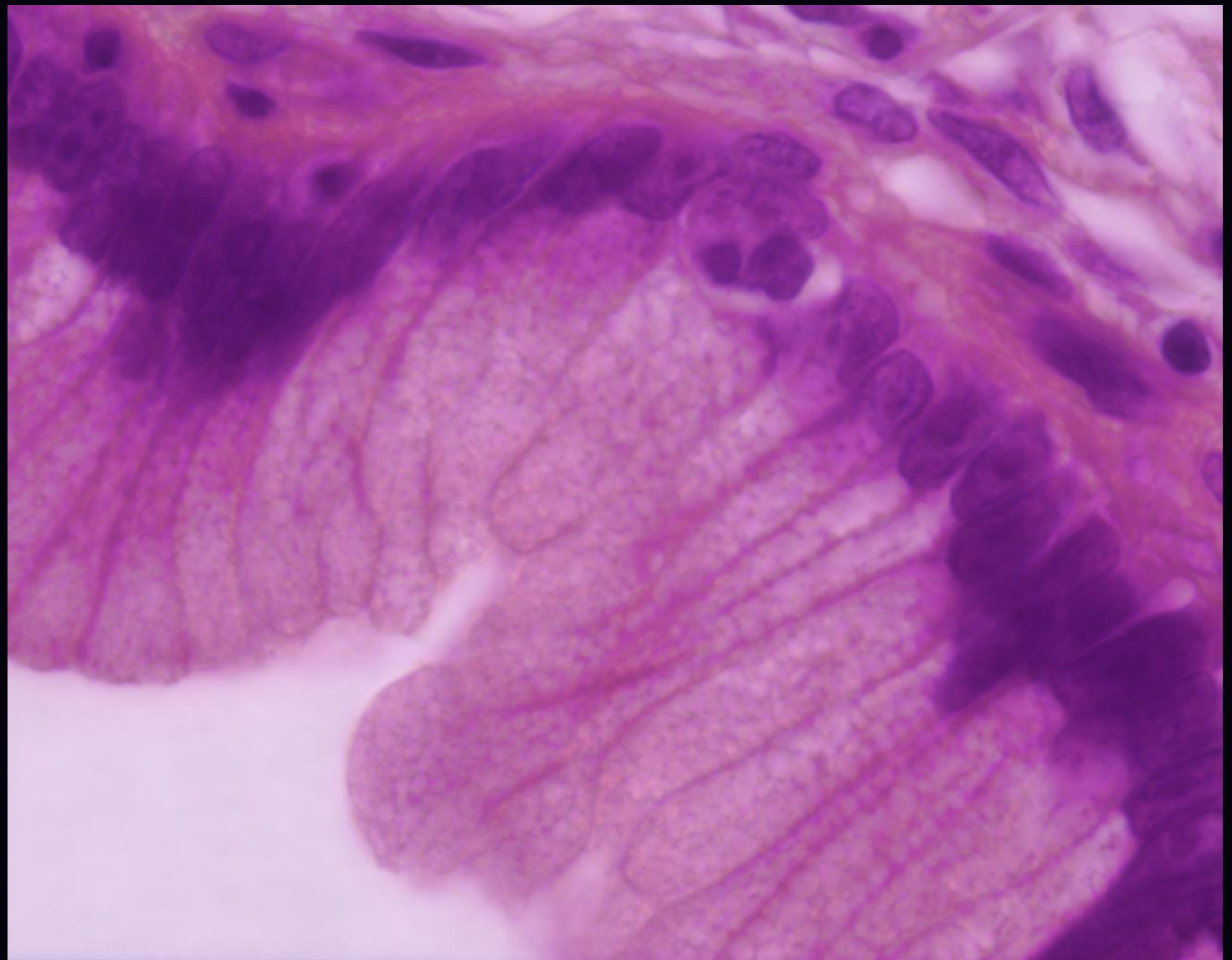
# PanIN

R.H. Hruban and colleagues
Am J Surg Pathol 25/5/:579-586,2001
http://pathology.jhu.edu/pancreas_panin

PanIN - pancreas intraepithelial neoplasia

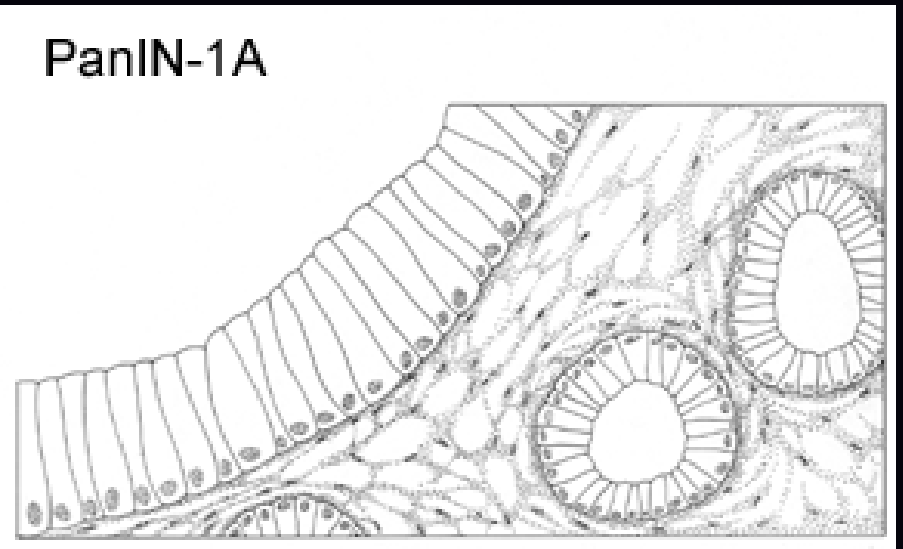
Precursor lesions of pancreas ductal adenocarcinomas

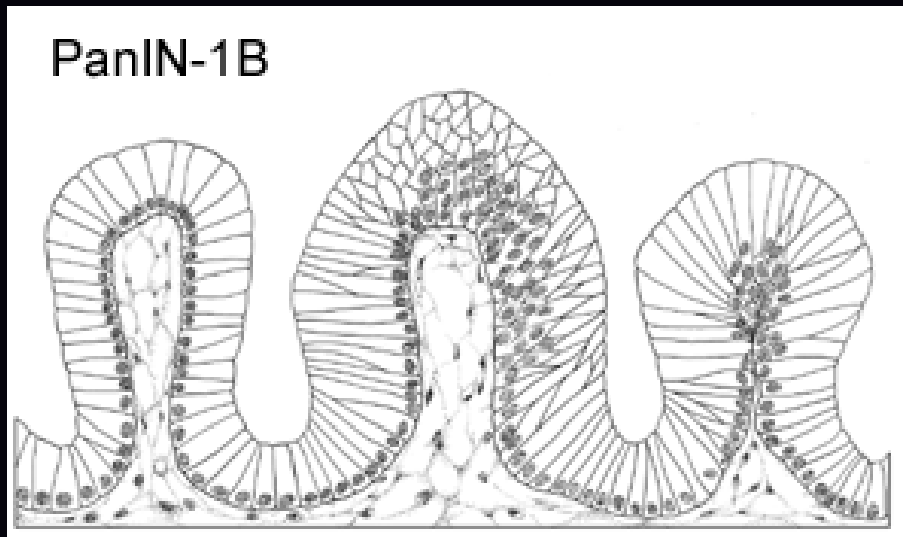
# PanIN 1

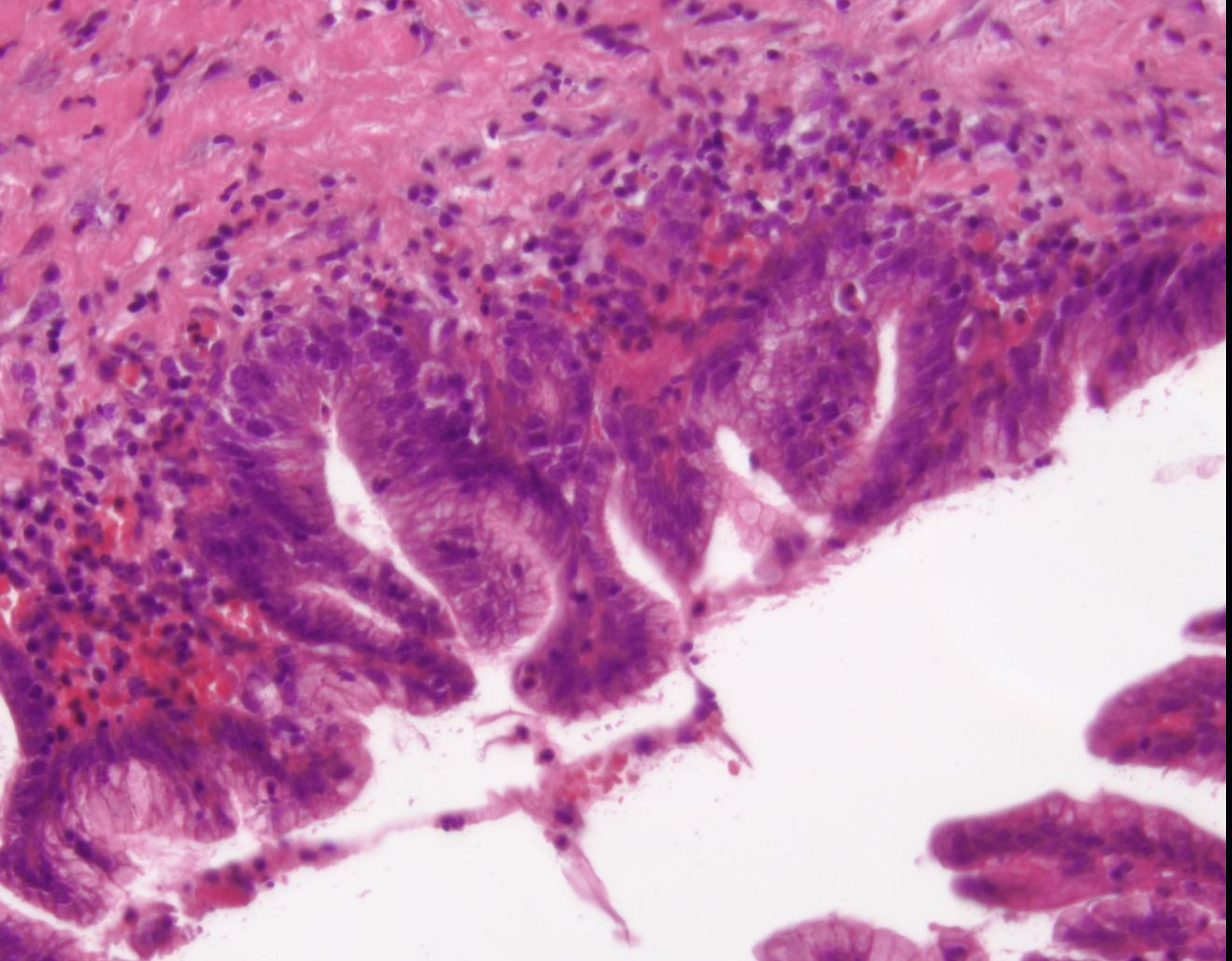


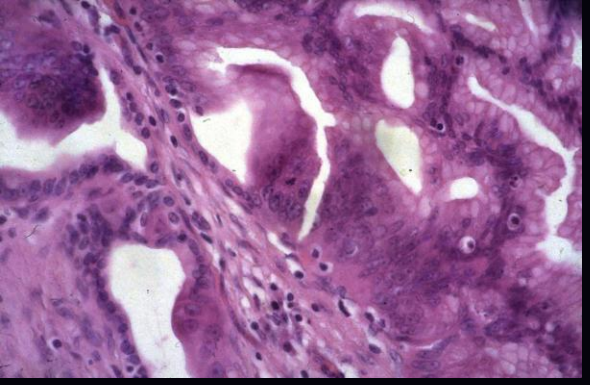
# PanIN 1

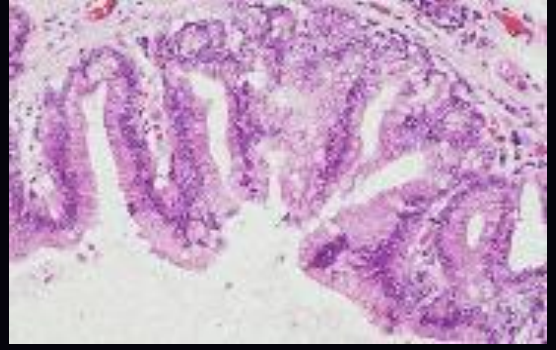
PanIN 1B: papillary, micropapillary

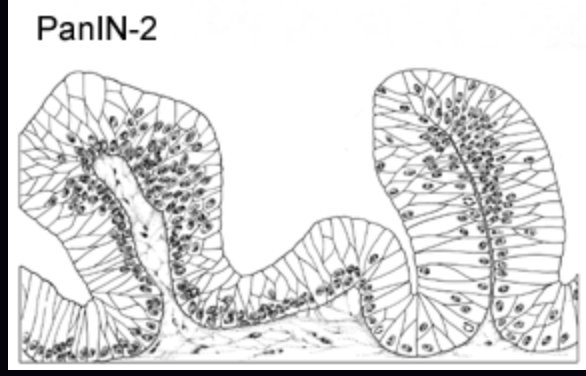


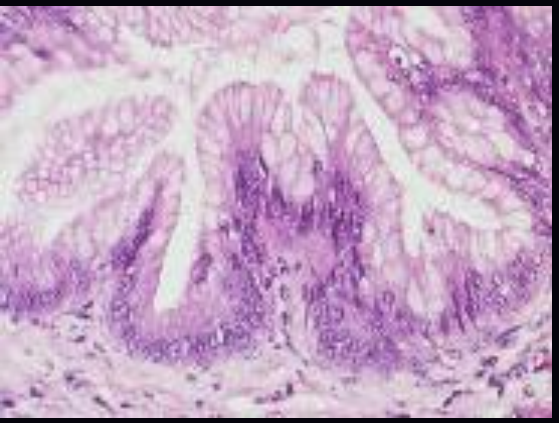



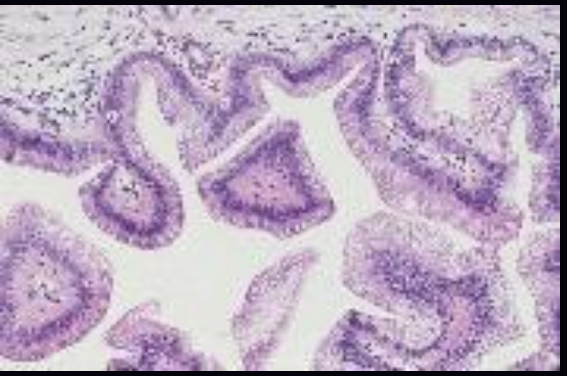


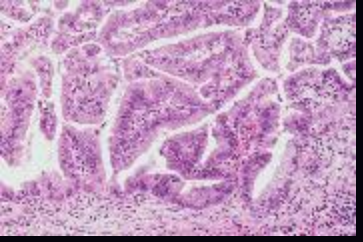


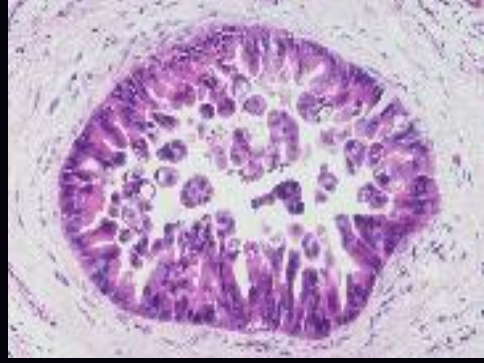



PanIN-2

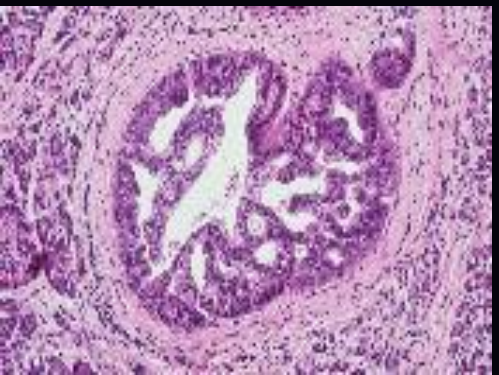


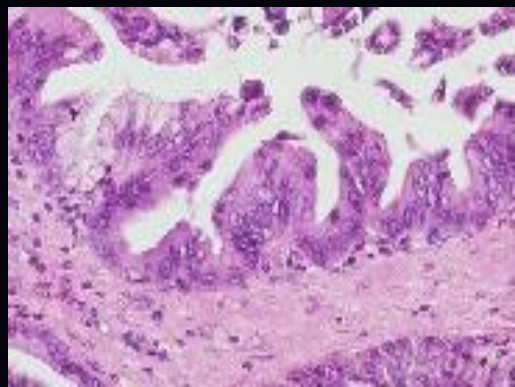


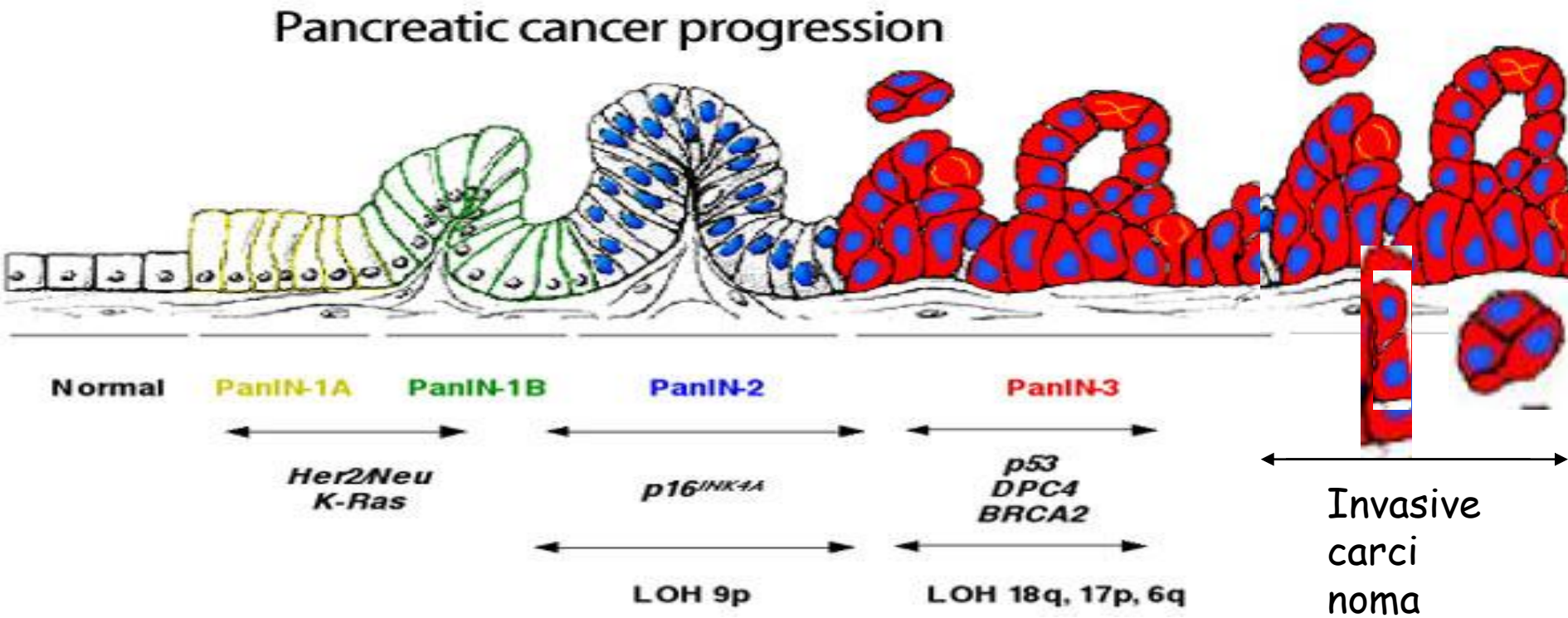


„CIS"






Pancreatic cancer progression
Normal
PanIN-1A
PanIN-1B
PanIN-2
PanIN-3
Her2Neu
K-Ras
p16INK4A
p53
DPC4
BRCA2
LOH 9p
LOH 18q, 17p, 6q
Invasive carci noma

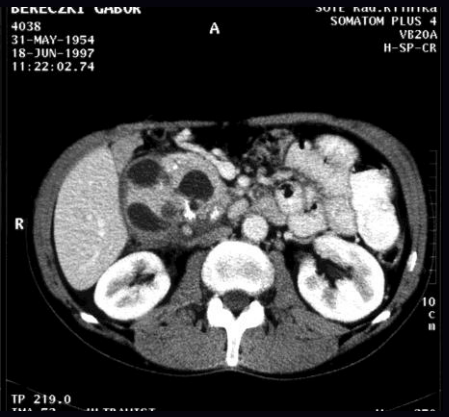
# Cystic pancreatic tumors

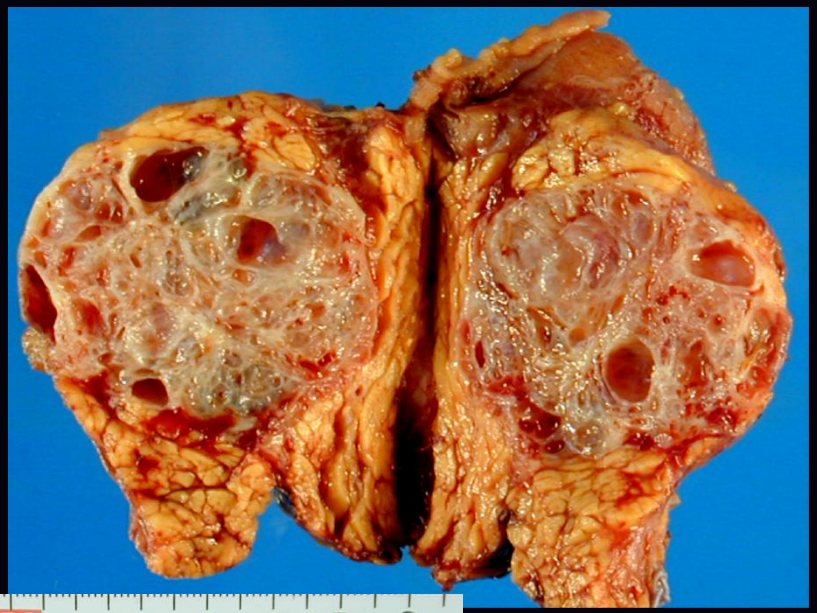
- IPMN
- Serous cystadenomas
- Mucinous tumors - !!!!
  - Mucinous cystadenomas

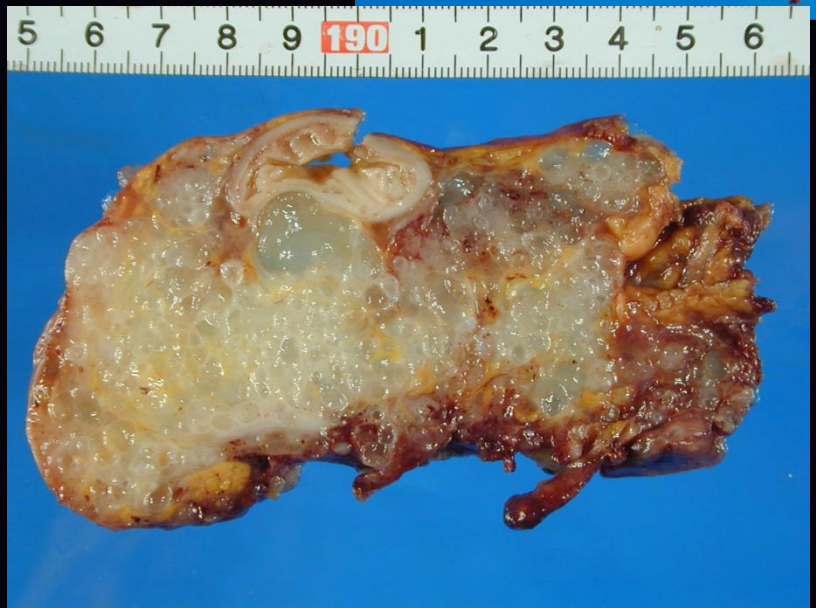
# Pancreatic tumors with low or uncertain malignant potential

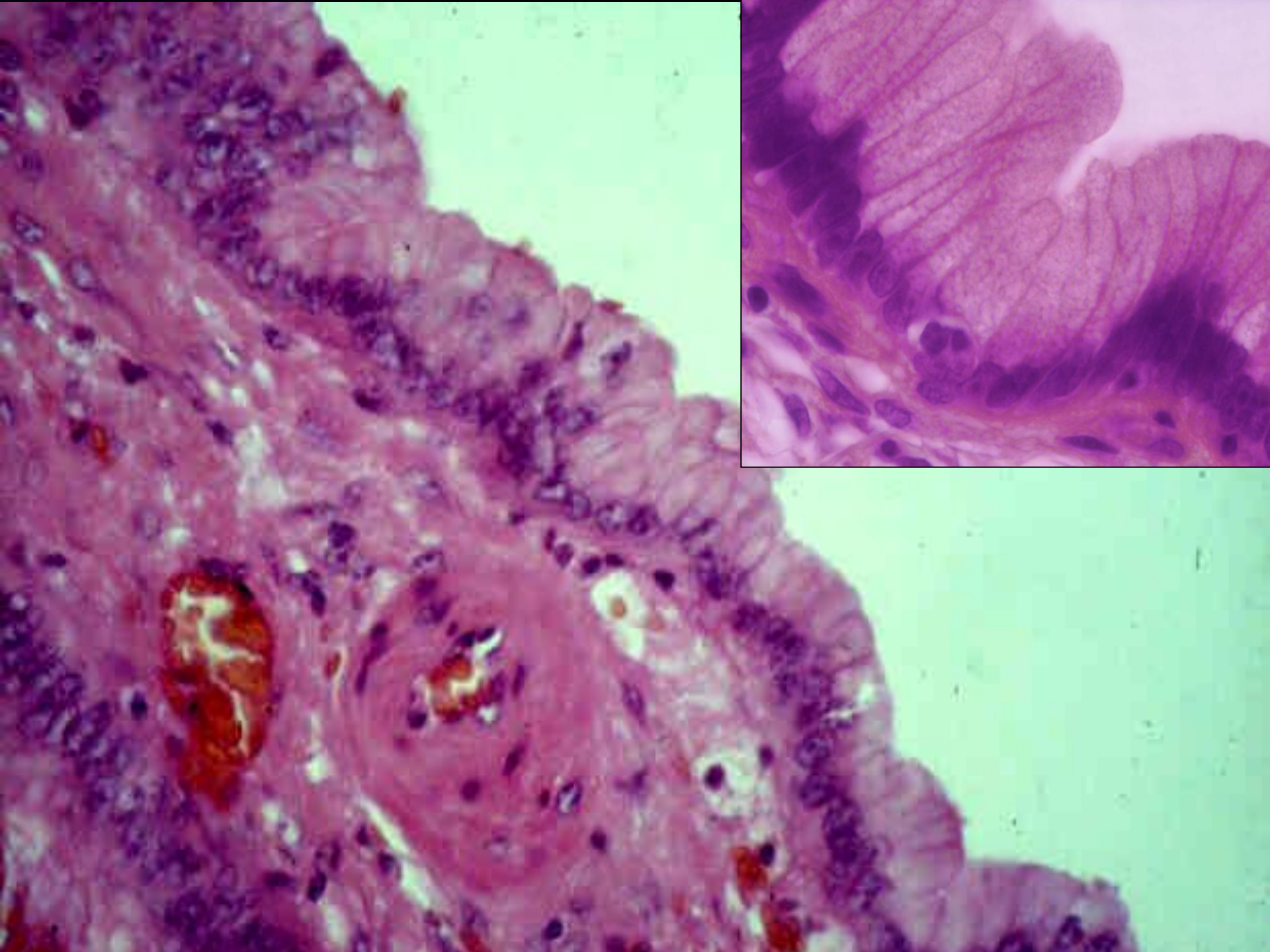
- Mucinous cystic tumors
  female, tale, - ben., bord., mal.
- Intraductal papillary mucinous neoplasia
  male, head, - ben., bord., mal.
- Solid and cystic papillary neoplasia (tumor) (SPT)
  young, female, tale

# Cystic mucinous neoplasia

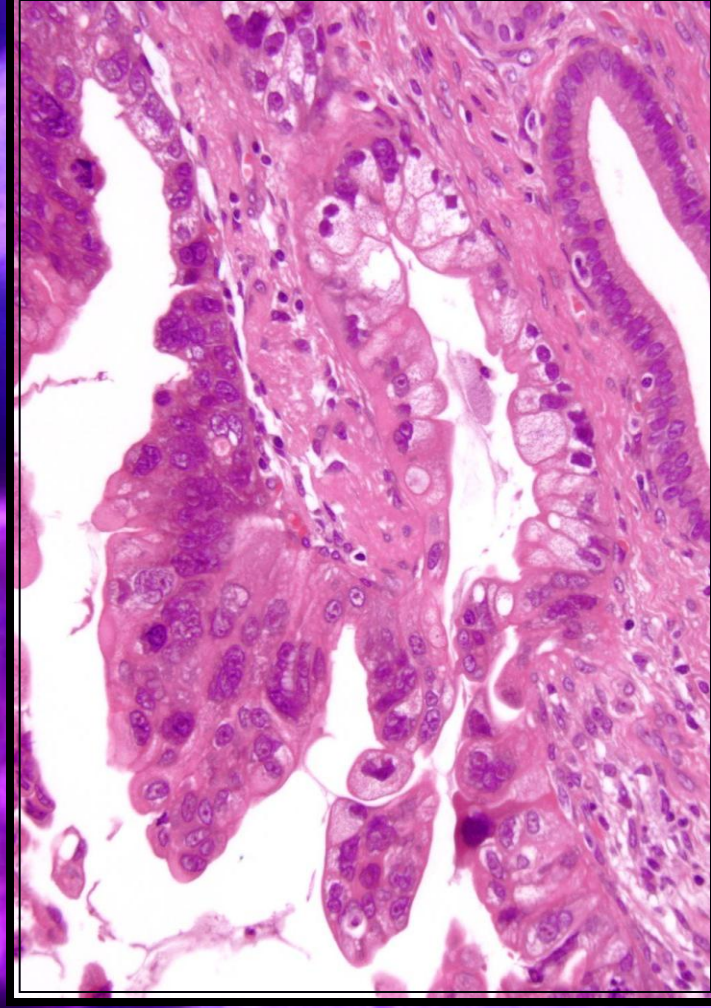




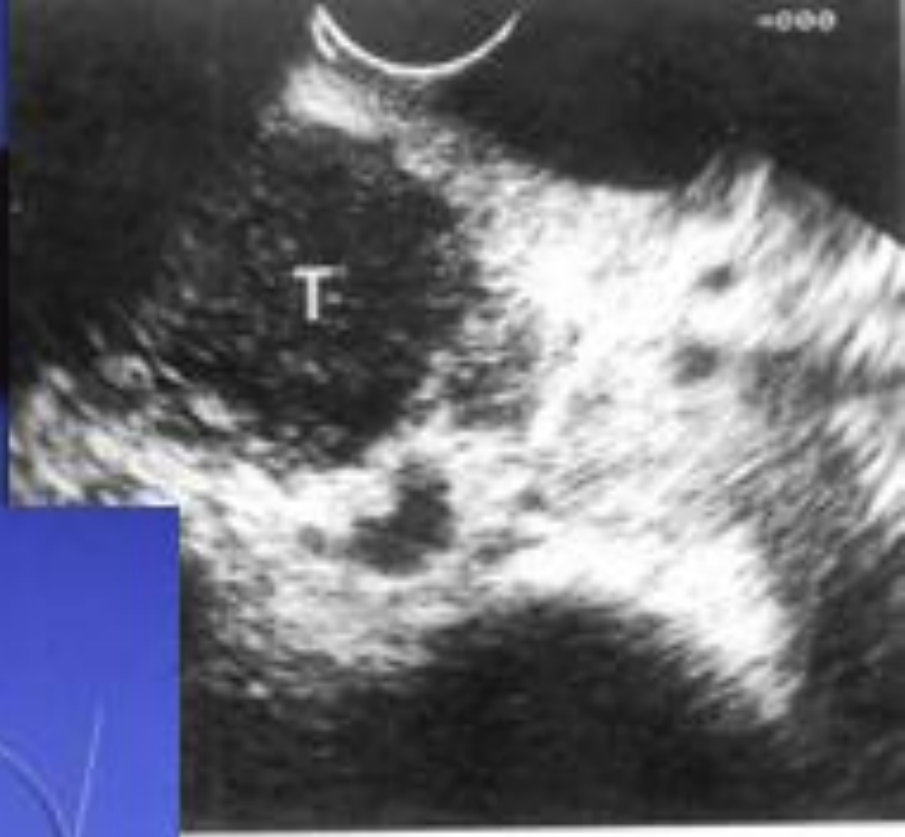


Mucinous cystadenocarcinoma

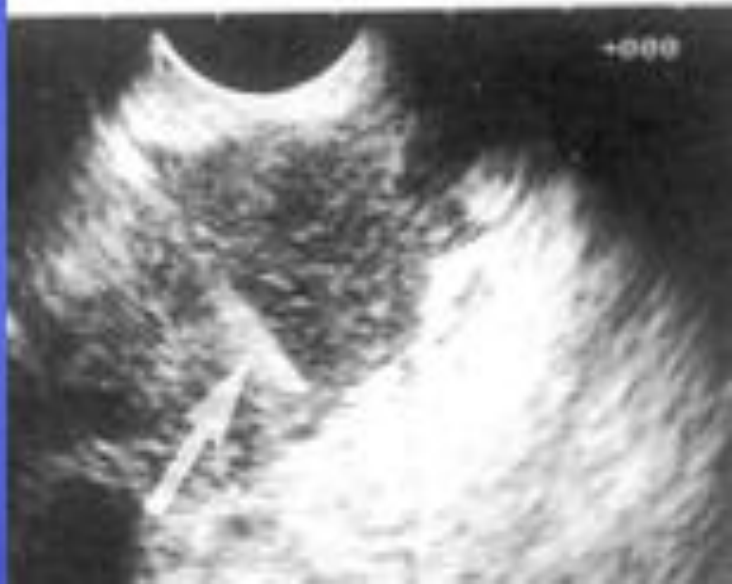


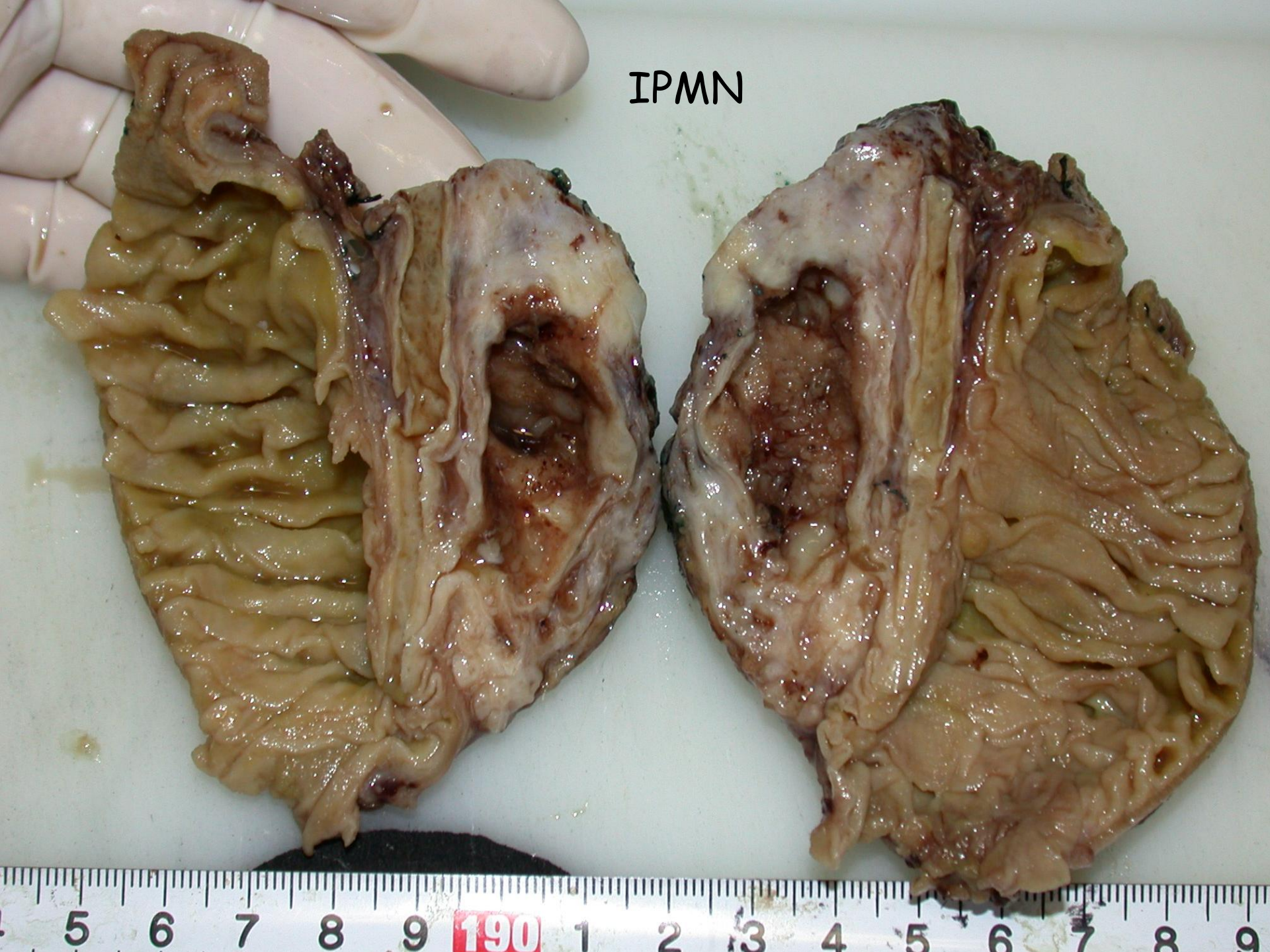
# Intraductal papillary mucinous neoplasia

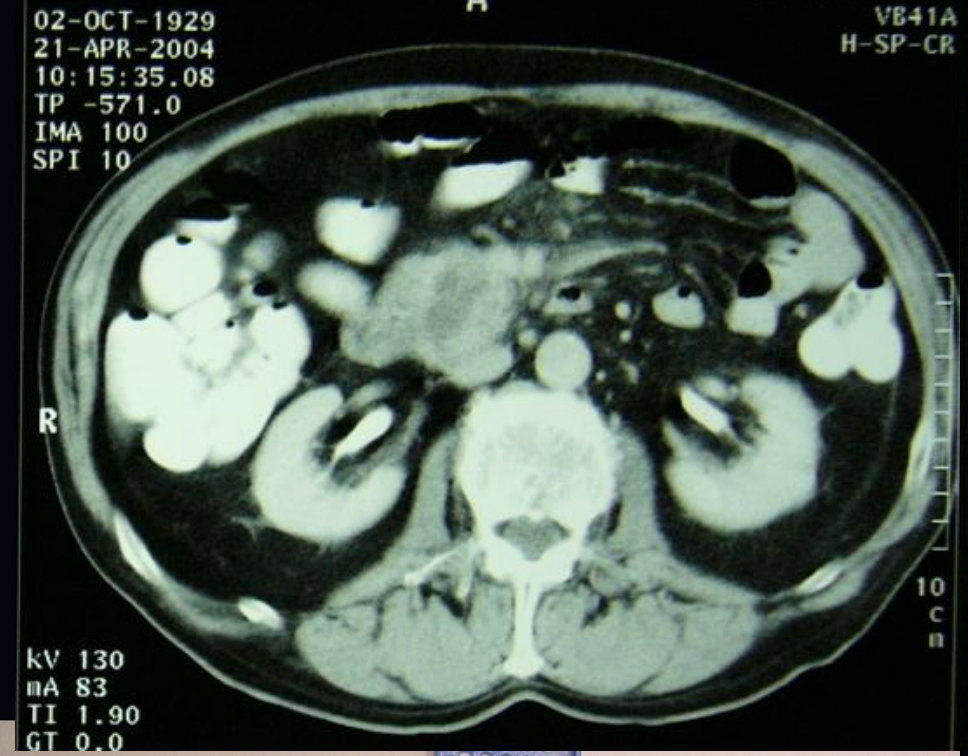
Arises in the Wirsungian duct – papillary proliferation of the columnar mucin secreting cells, that form the ducts

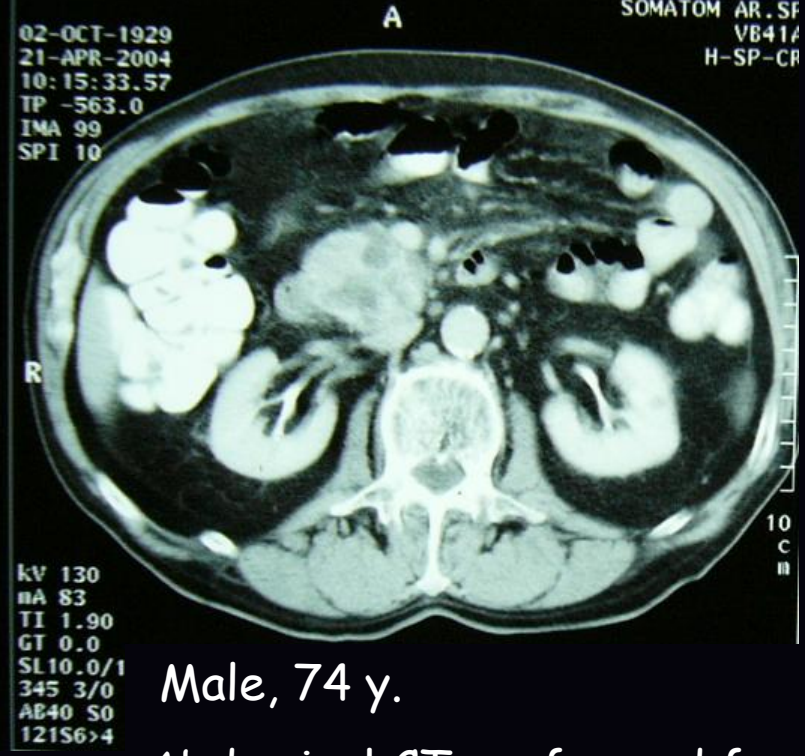



# Vilmann needle



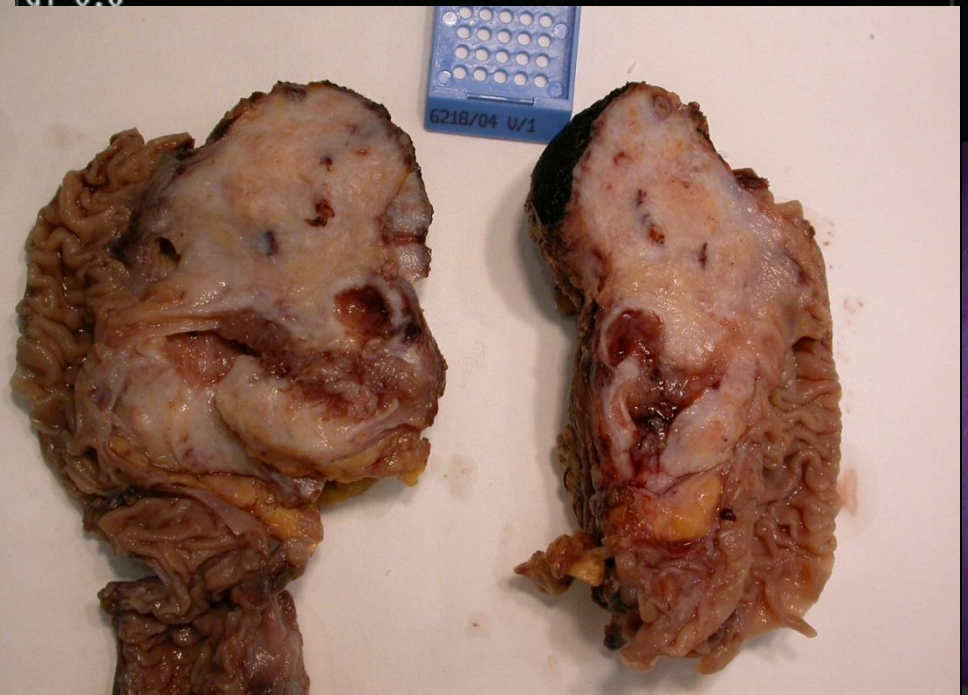

IPMN
5 6 7 8 9 190 1 2 3 4 5 6 7 8 9

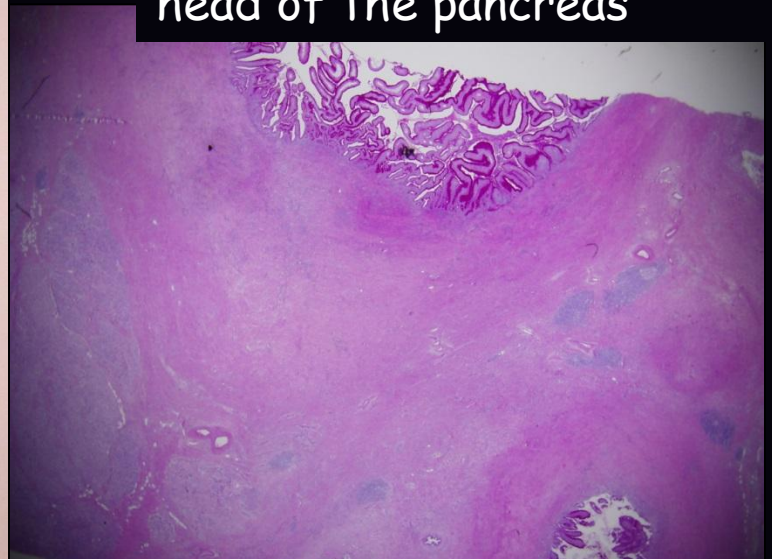


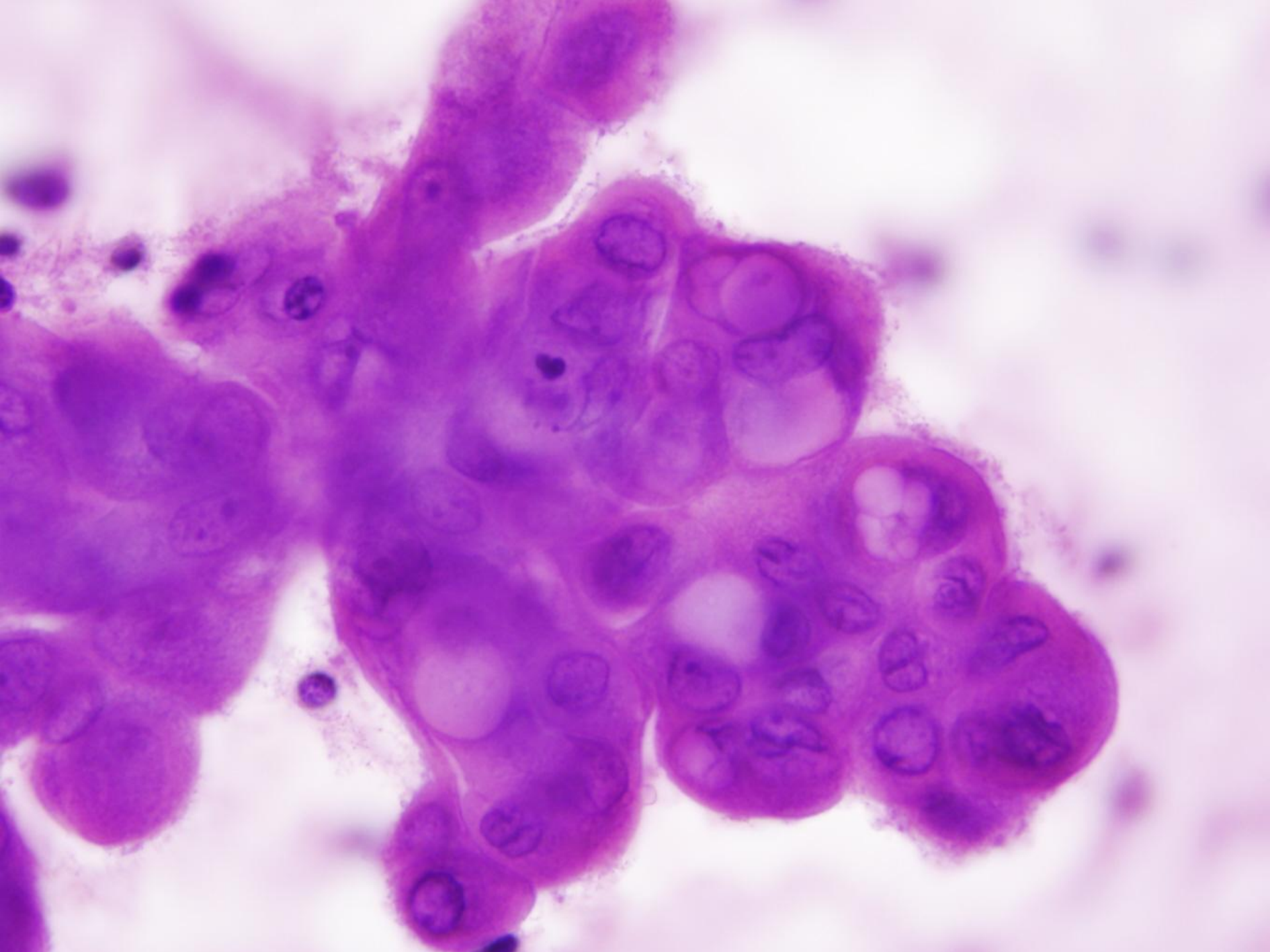



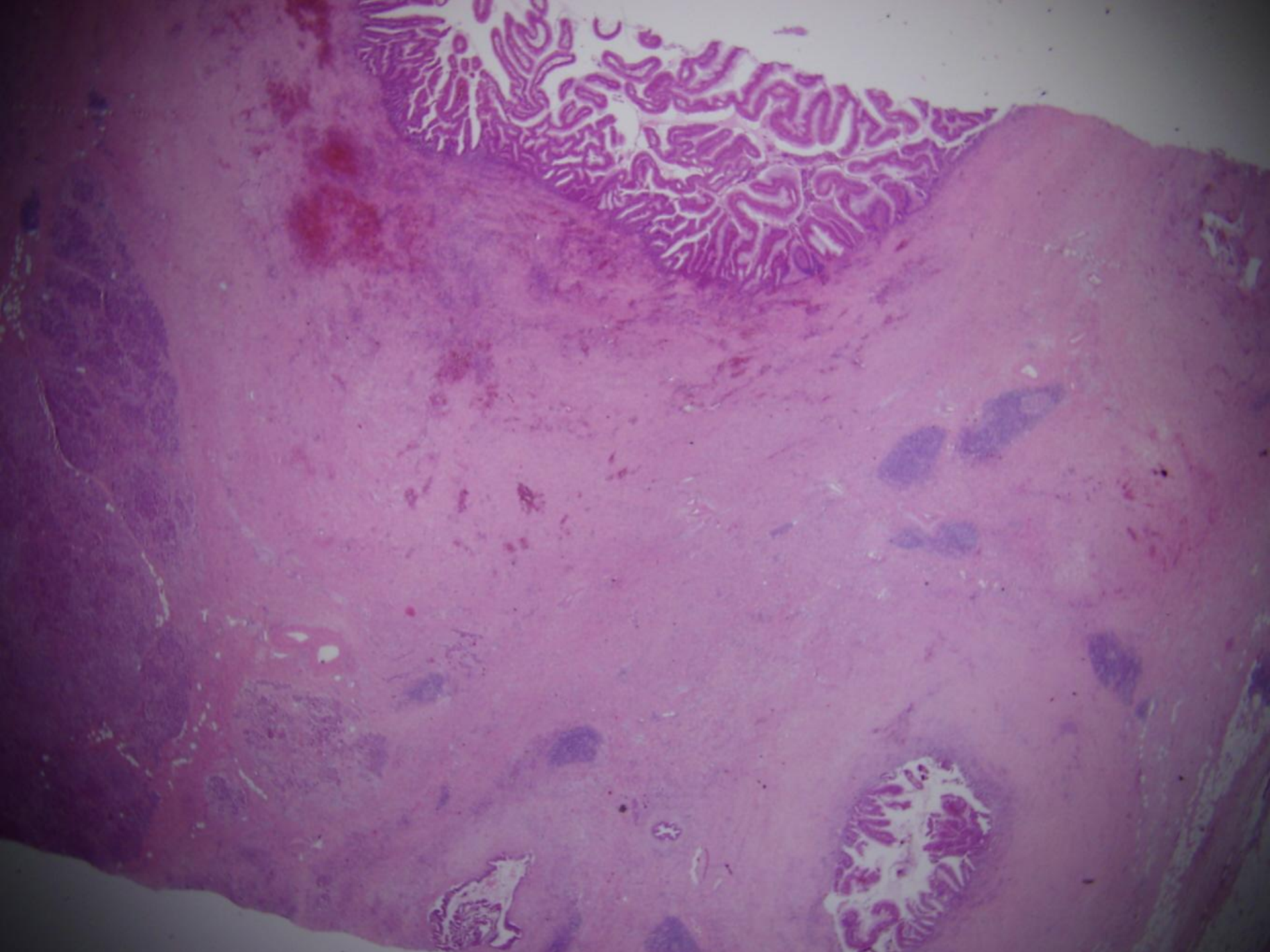

Male, 74 y.

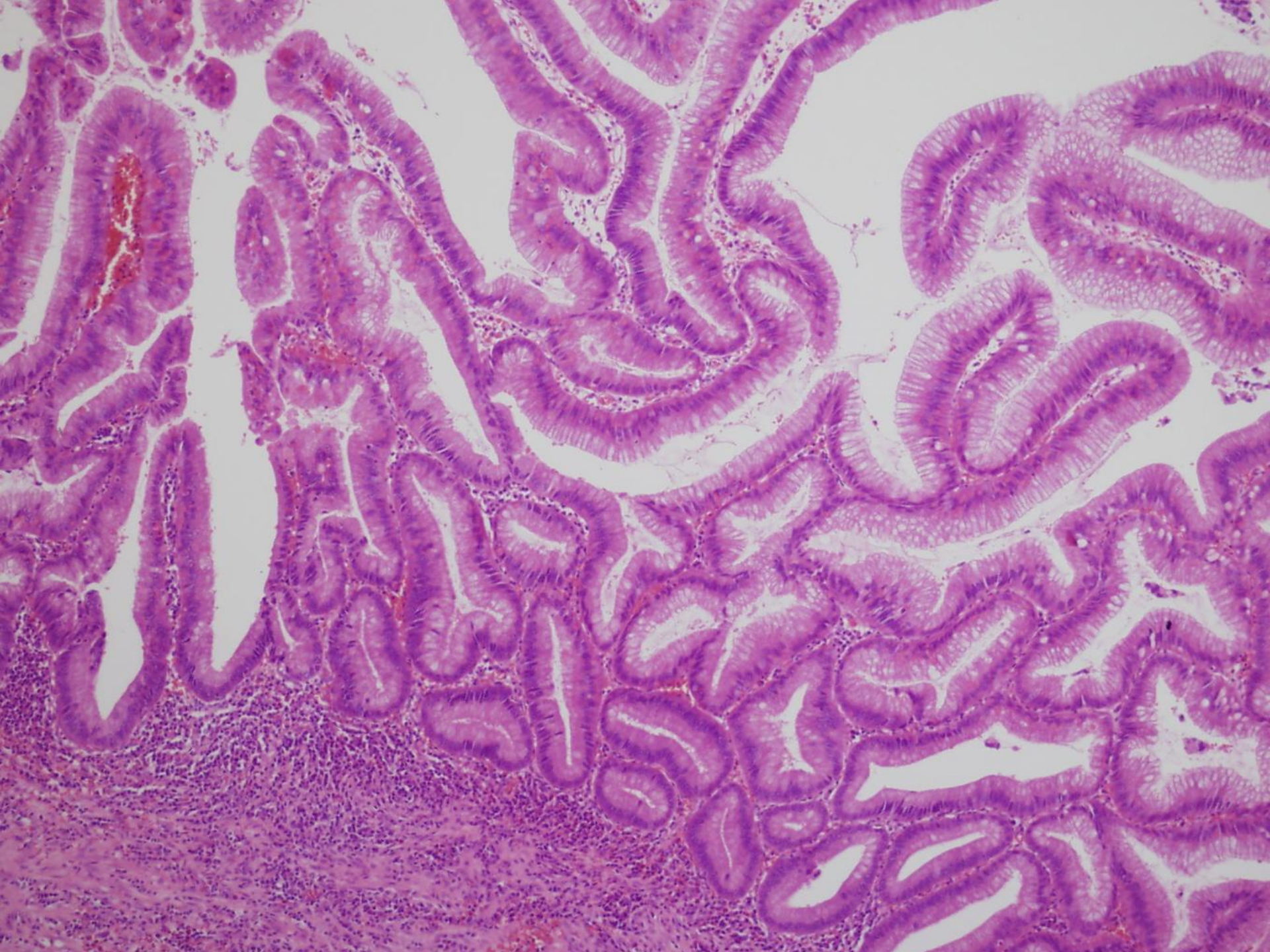
Abdominal CT performed for abdominal pain finds lesion in the head of the pancreas

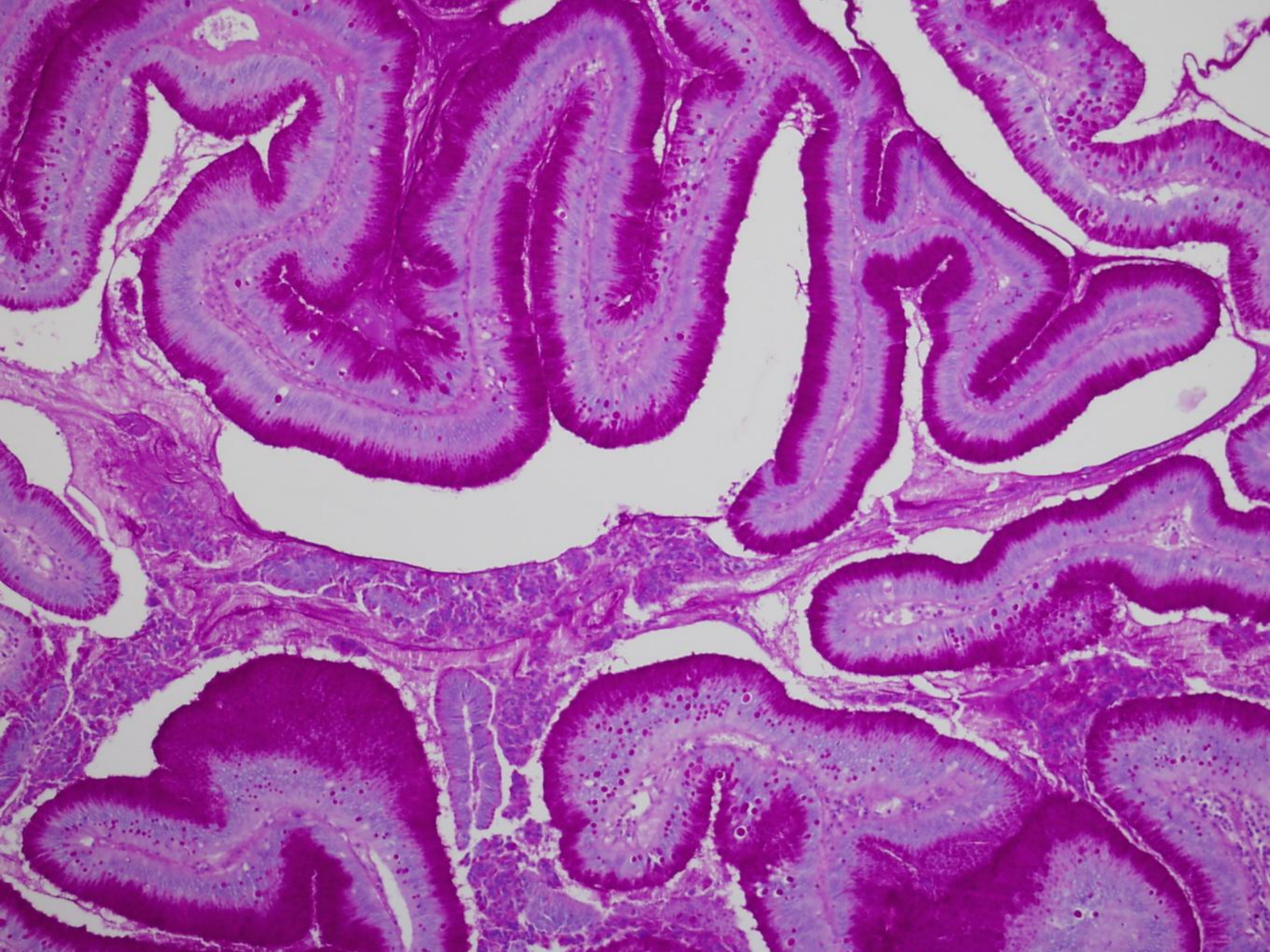


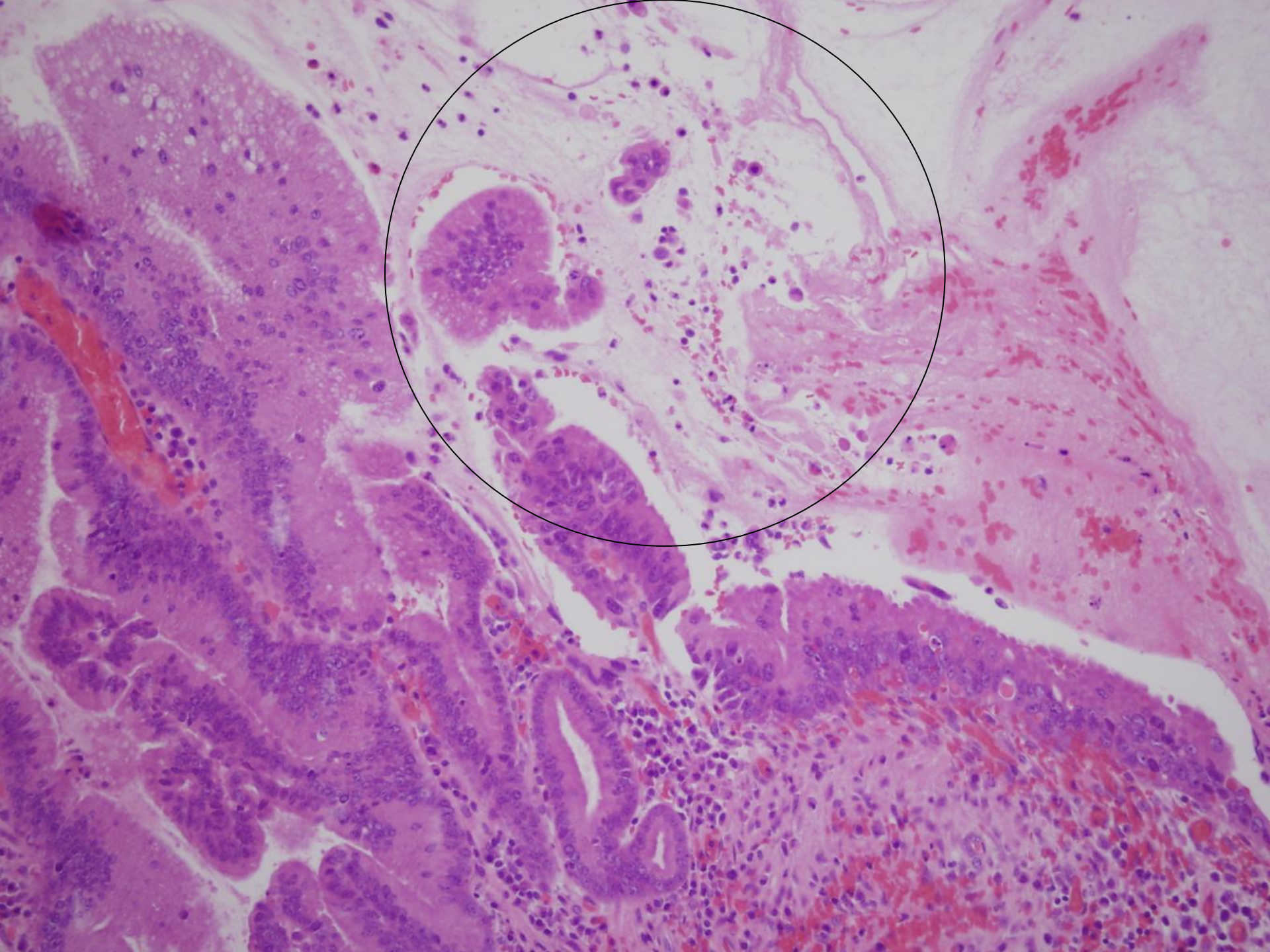



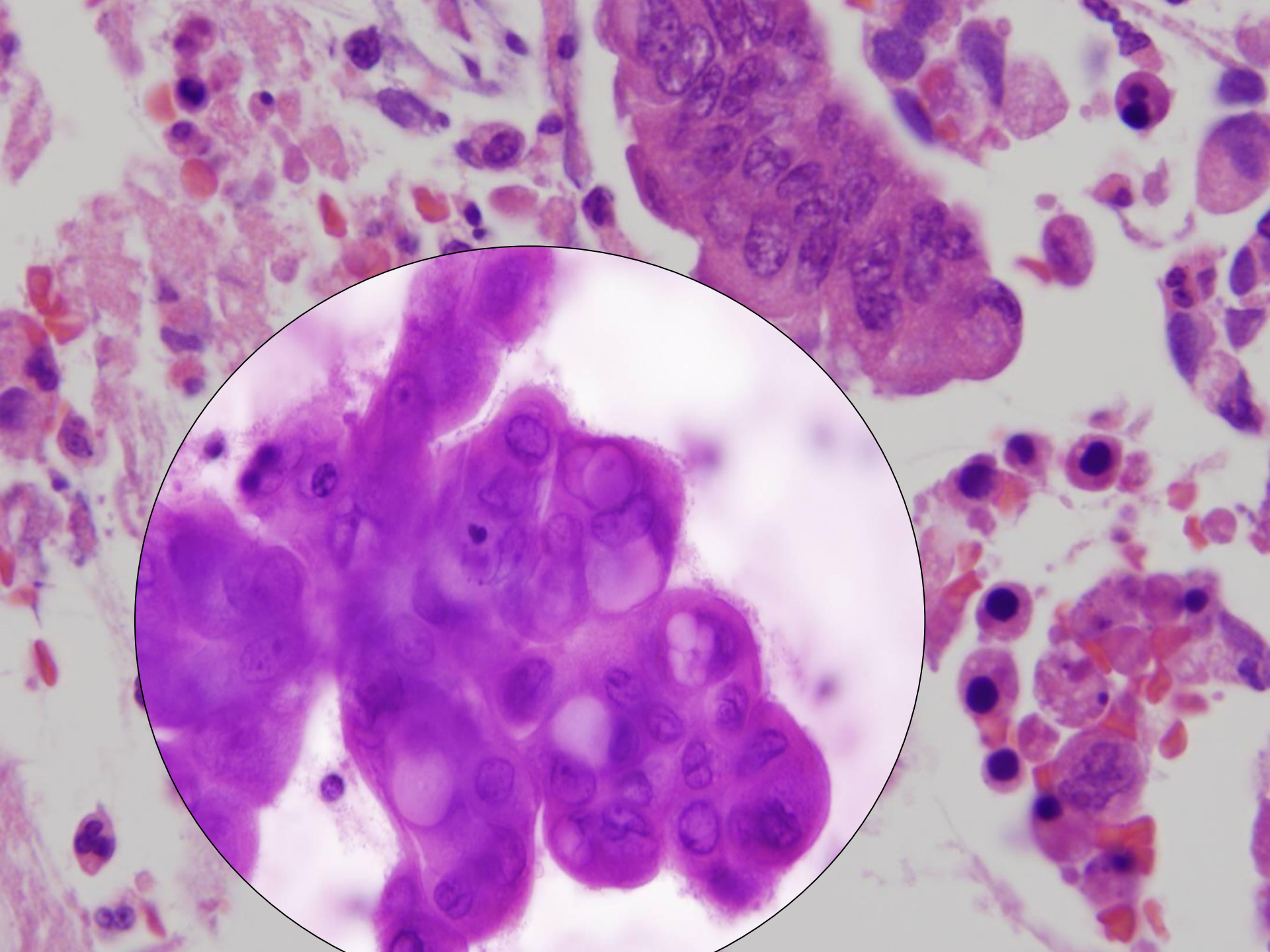




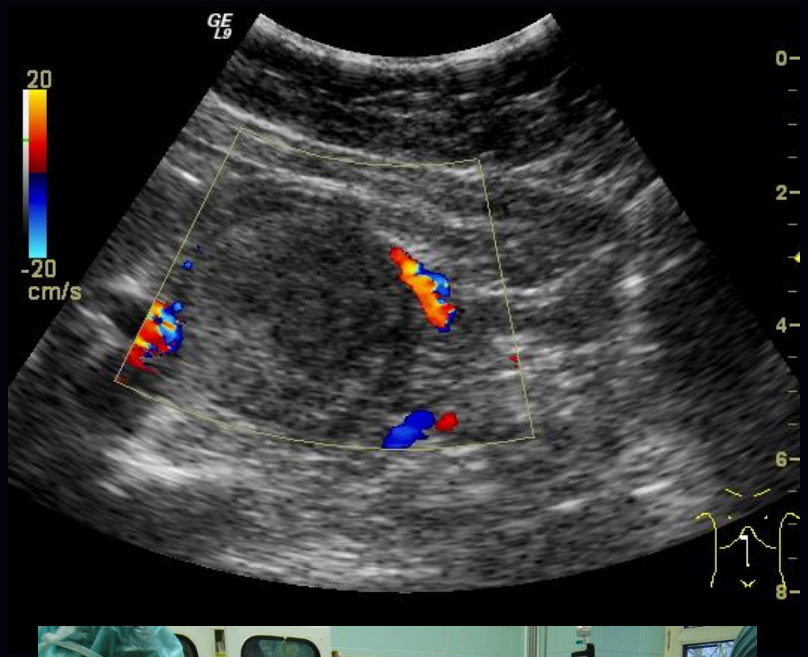


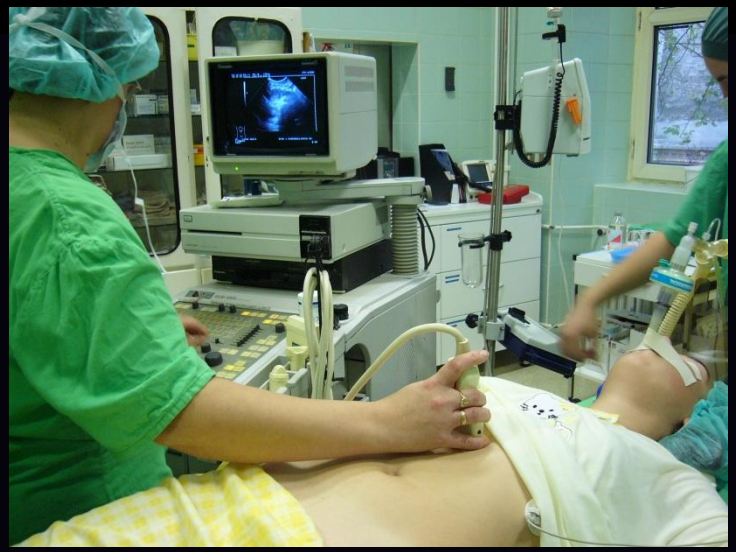


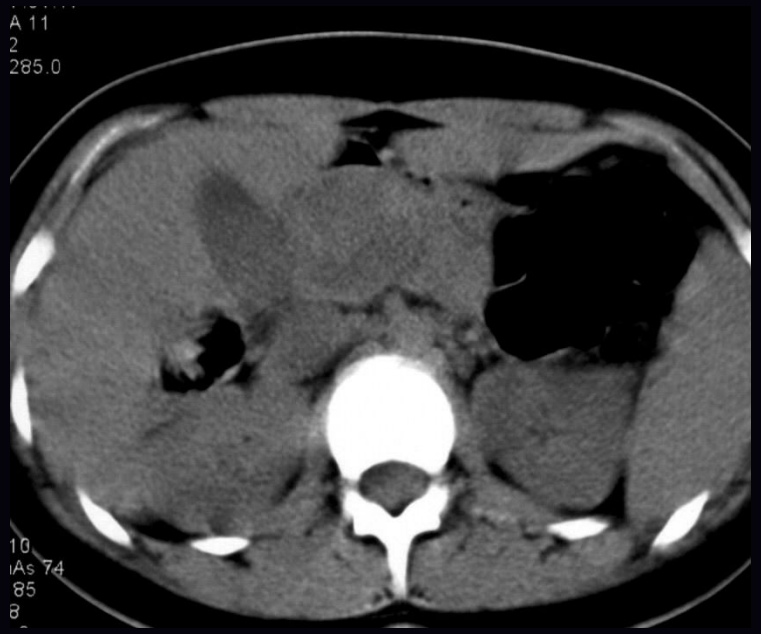


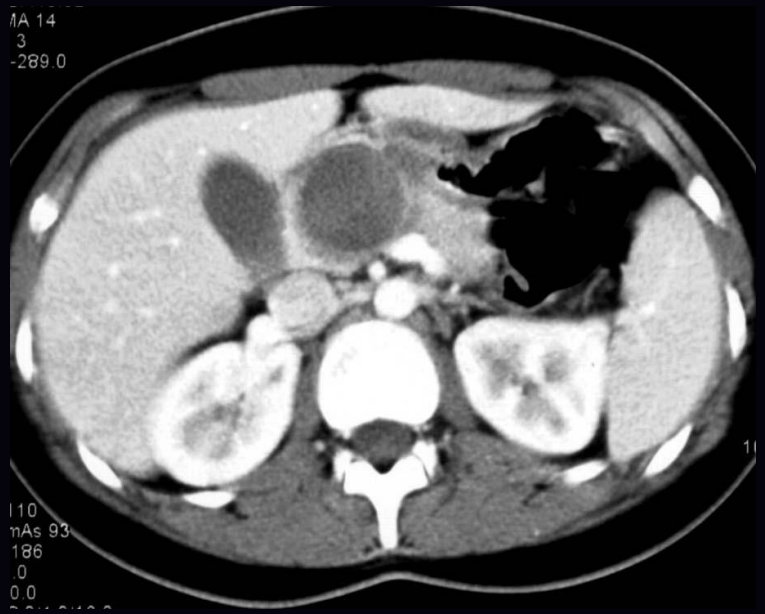


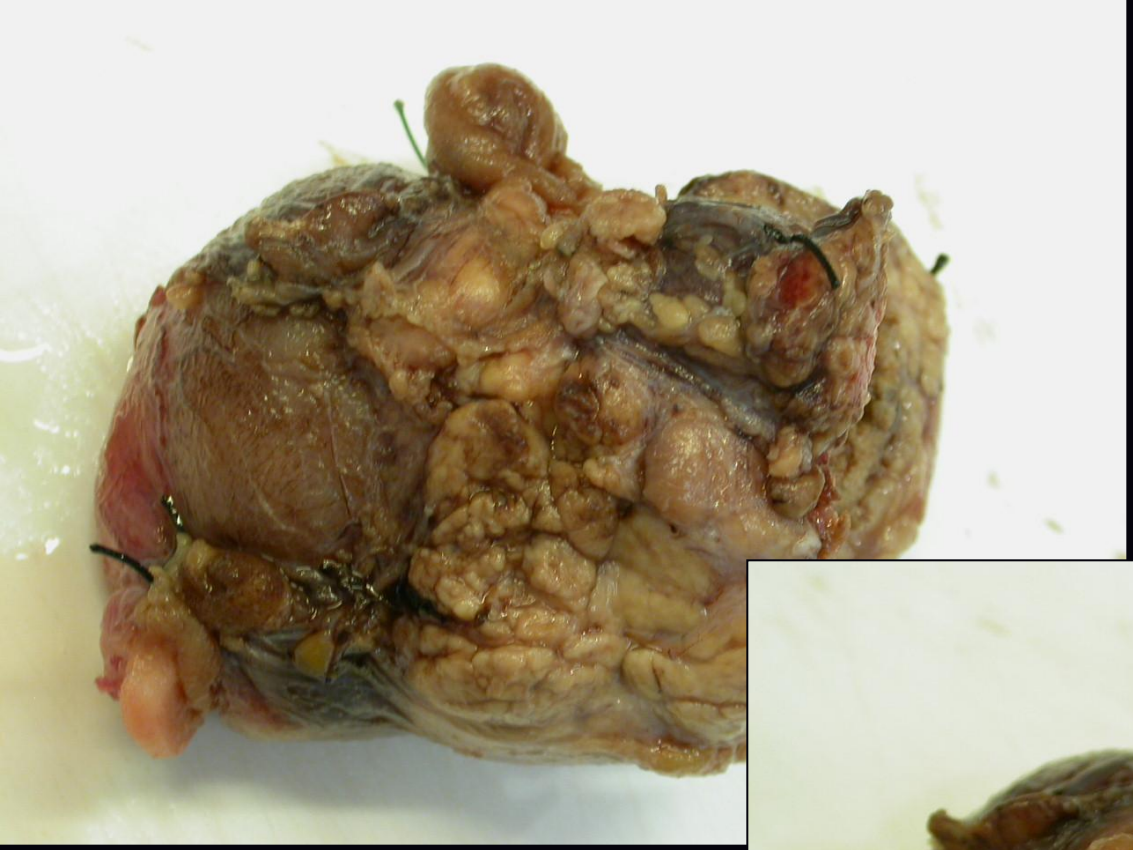
# SPT

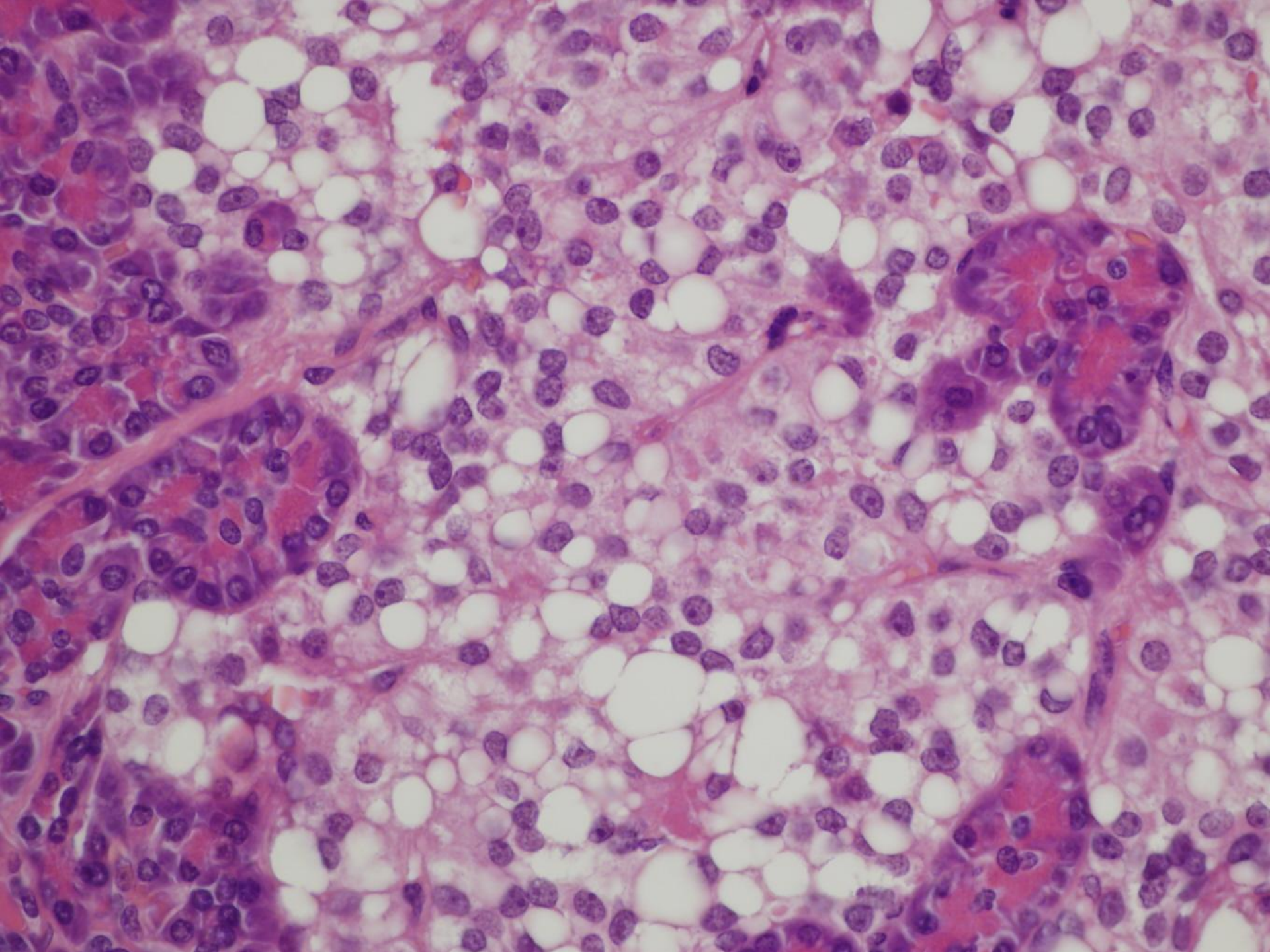

GE
L9
20
-20
cm/s
0
2
4
6
8



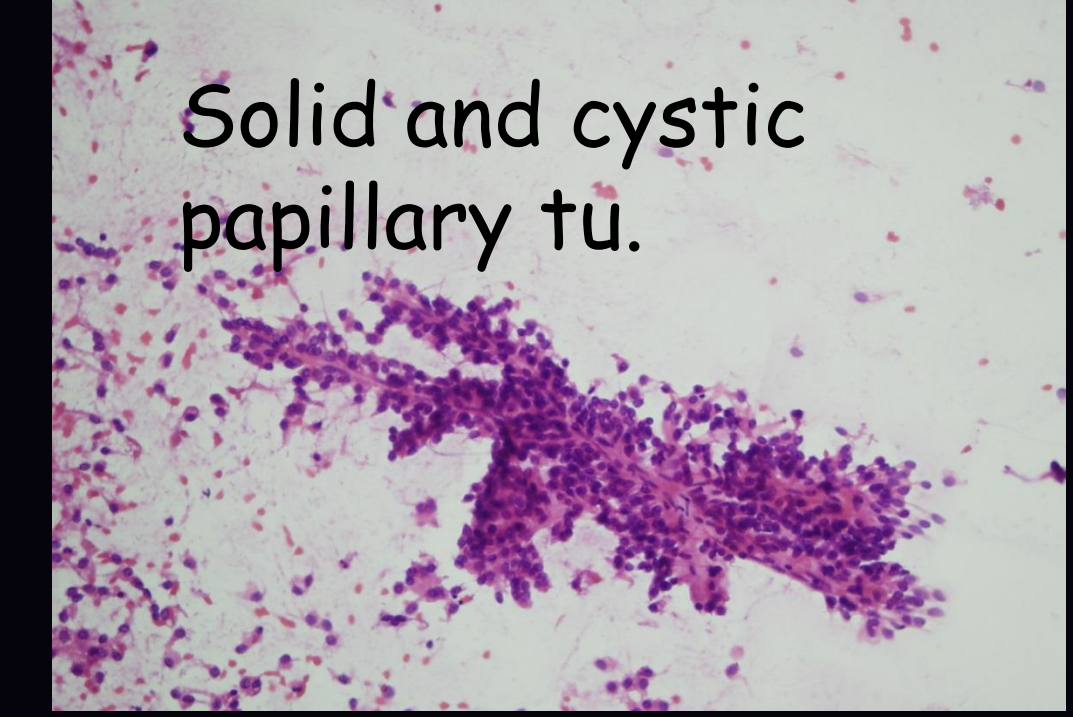

A 11
2
285.0
10
As 74
85

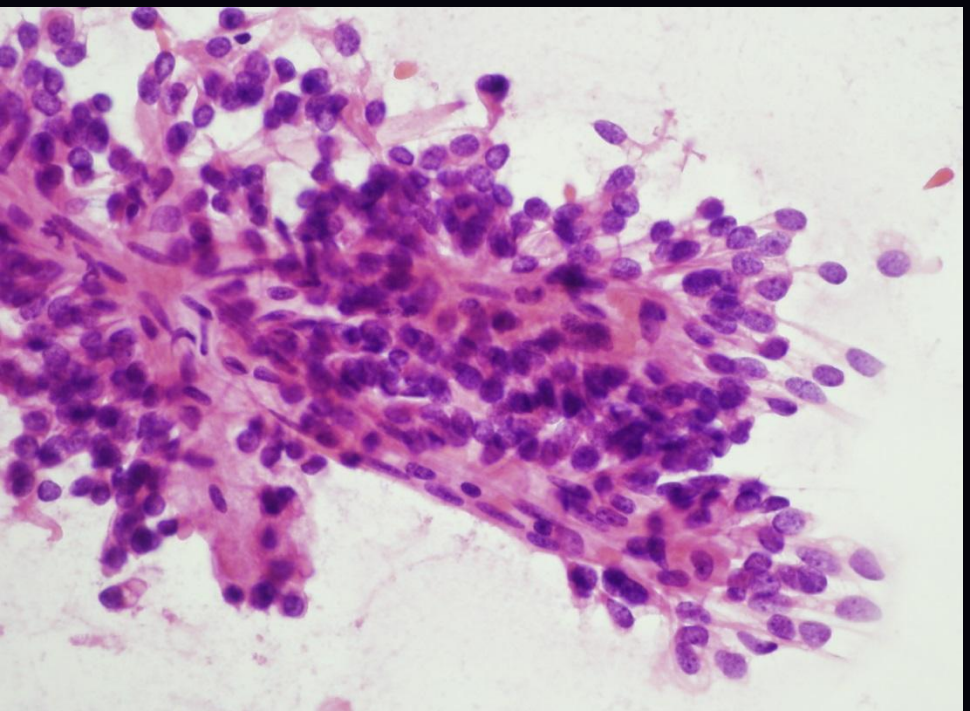

A 14
3
-289.0
10
As 93
186
.0
0.0

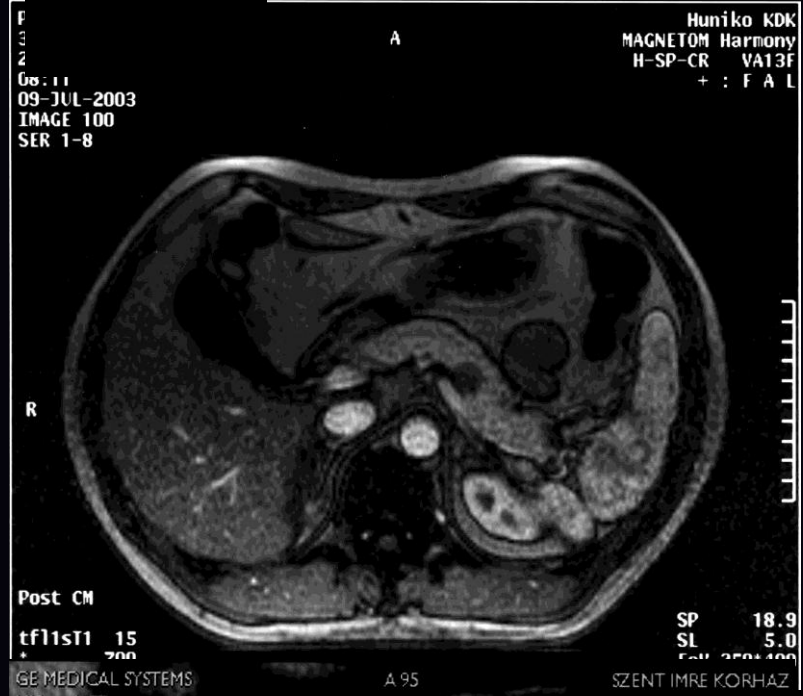


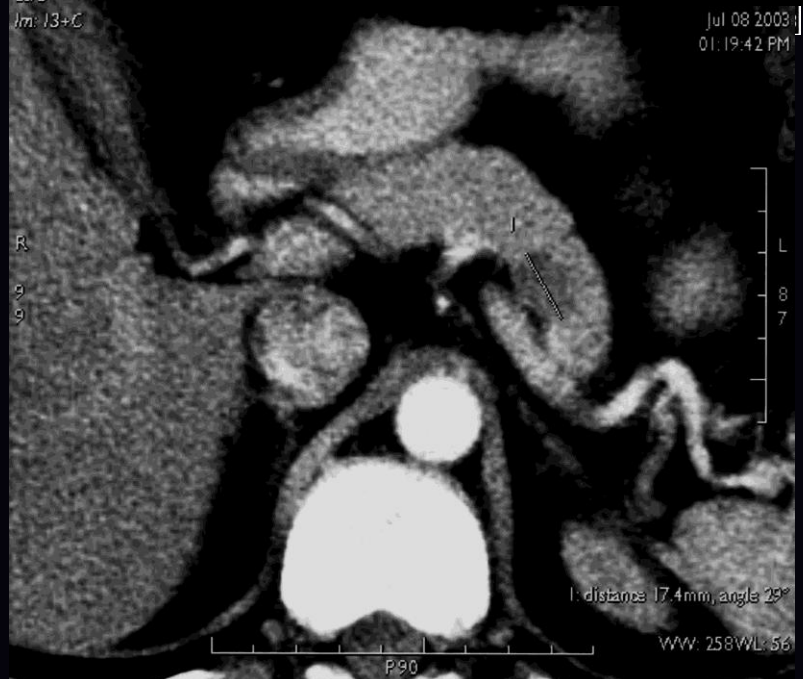


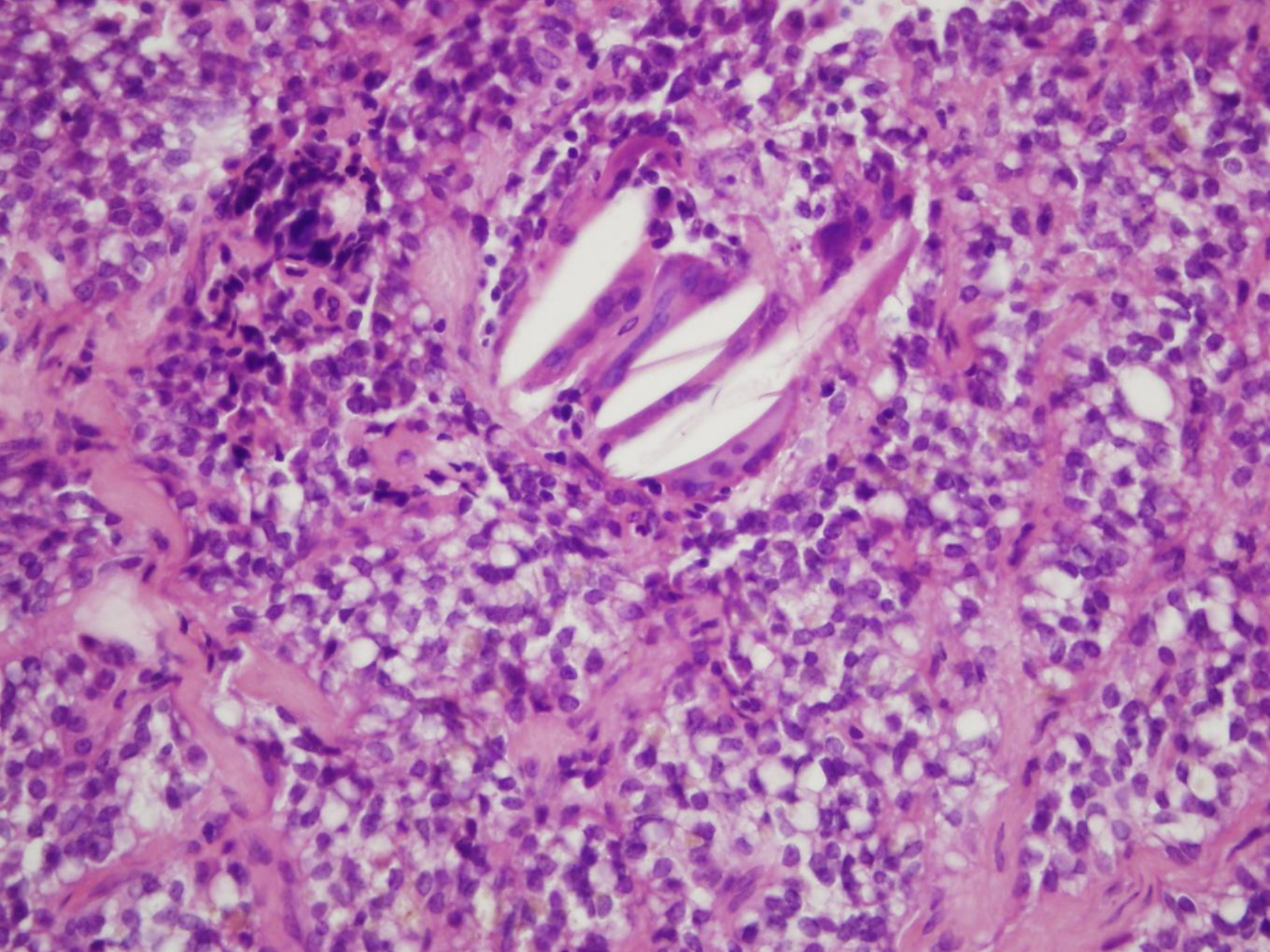
# Solid and cystic papillary tu.

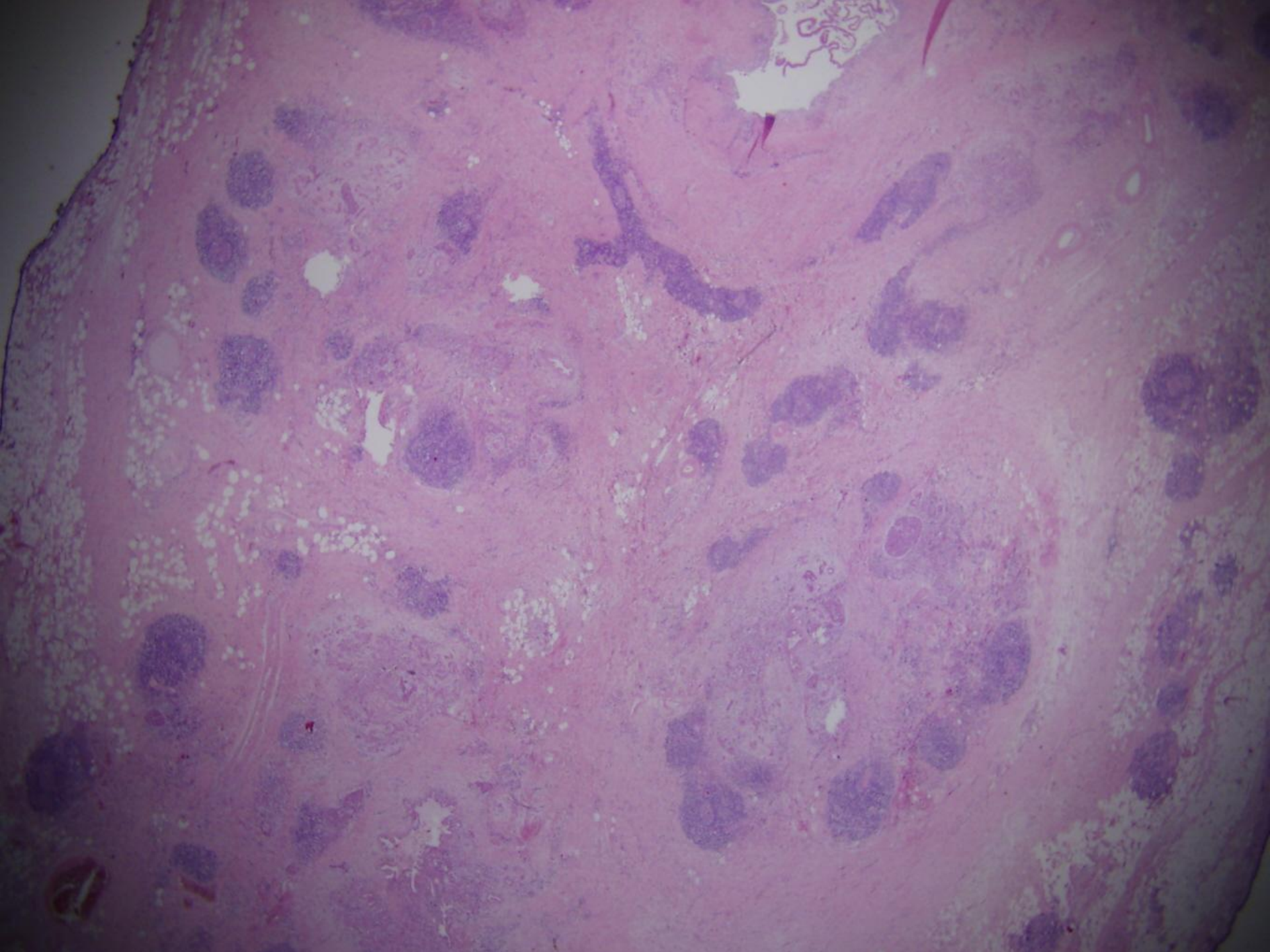










# Benign tumors of the exocrine pancreas

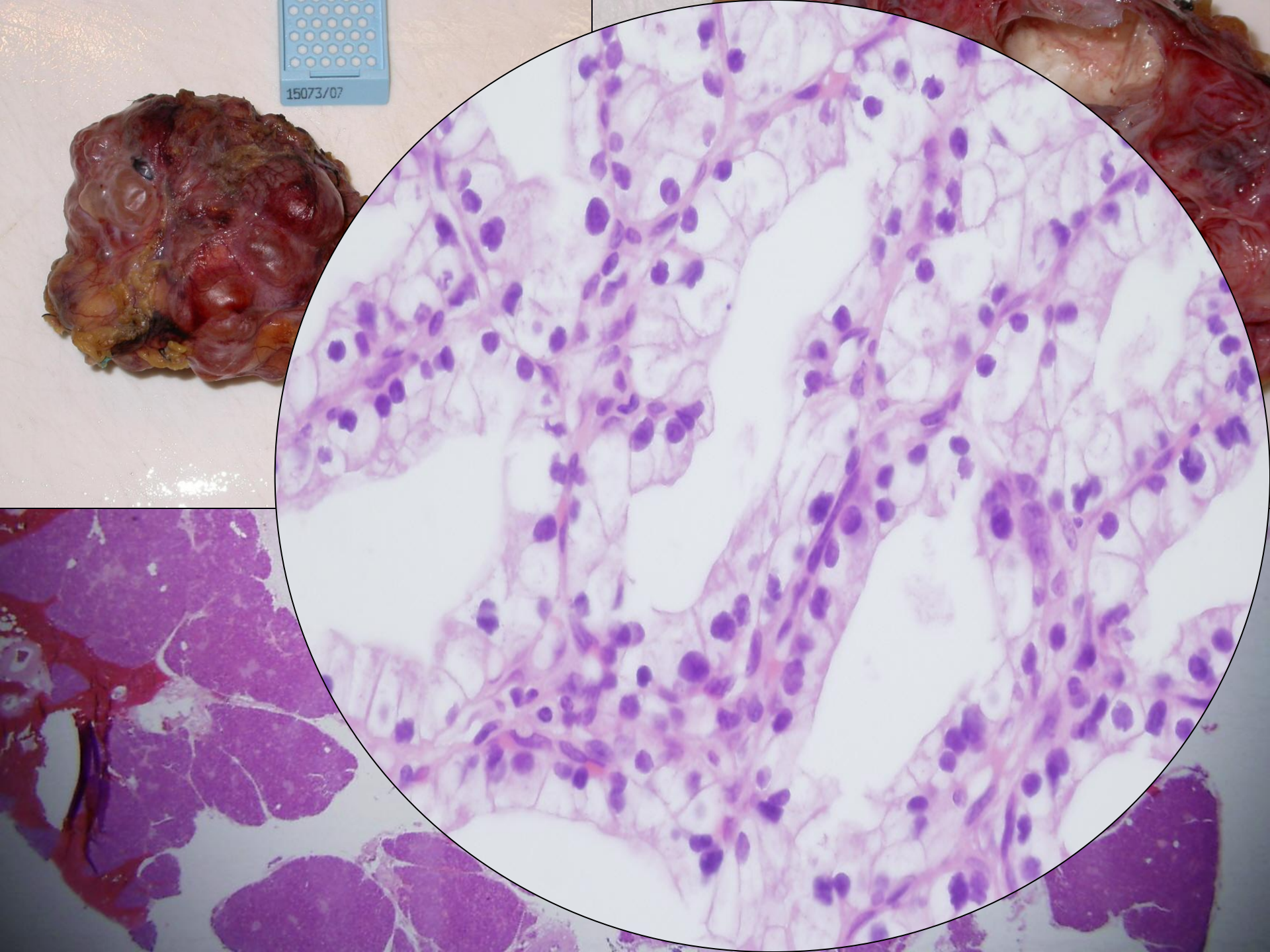
Serous cystadenoma

Cystic teratoma

Lymphangioma

Mesenchymal tumors


Microcystic adenoma


15073/07

# Metastatic tumors

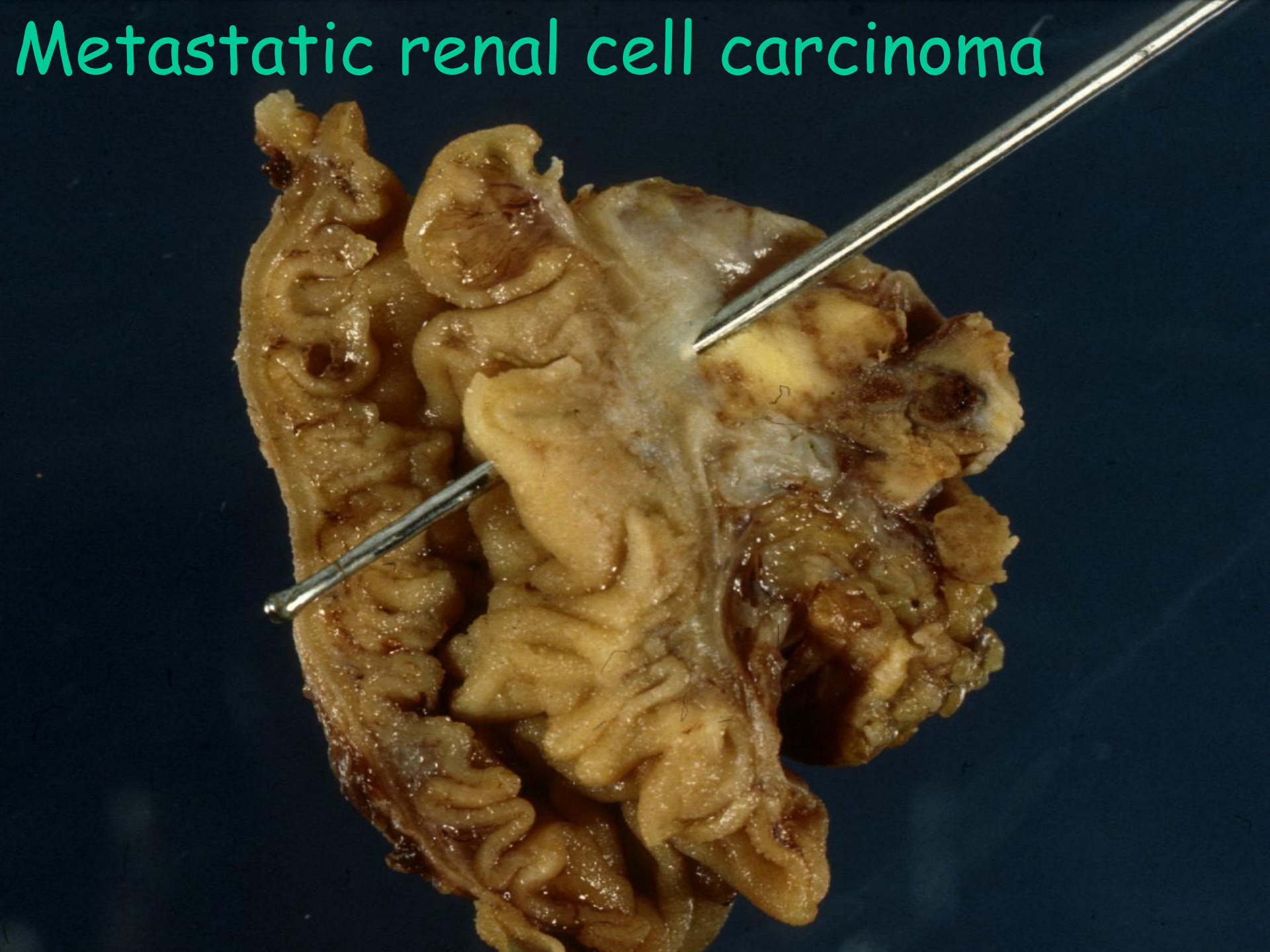
Renal cell carcinoma

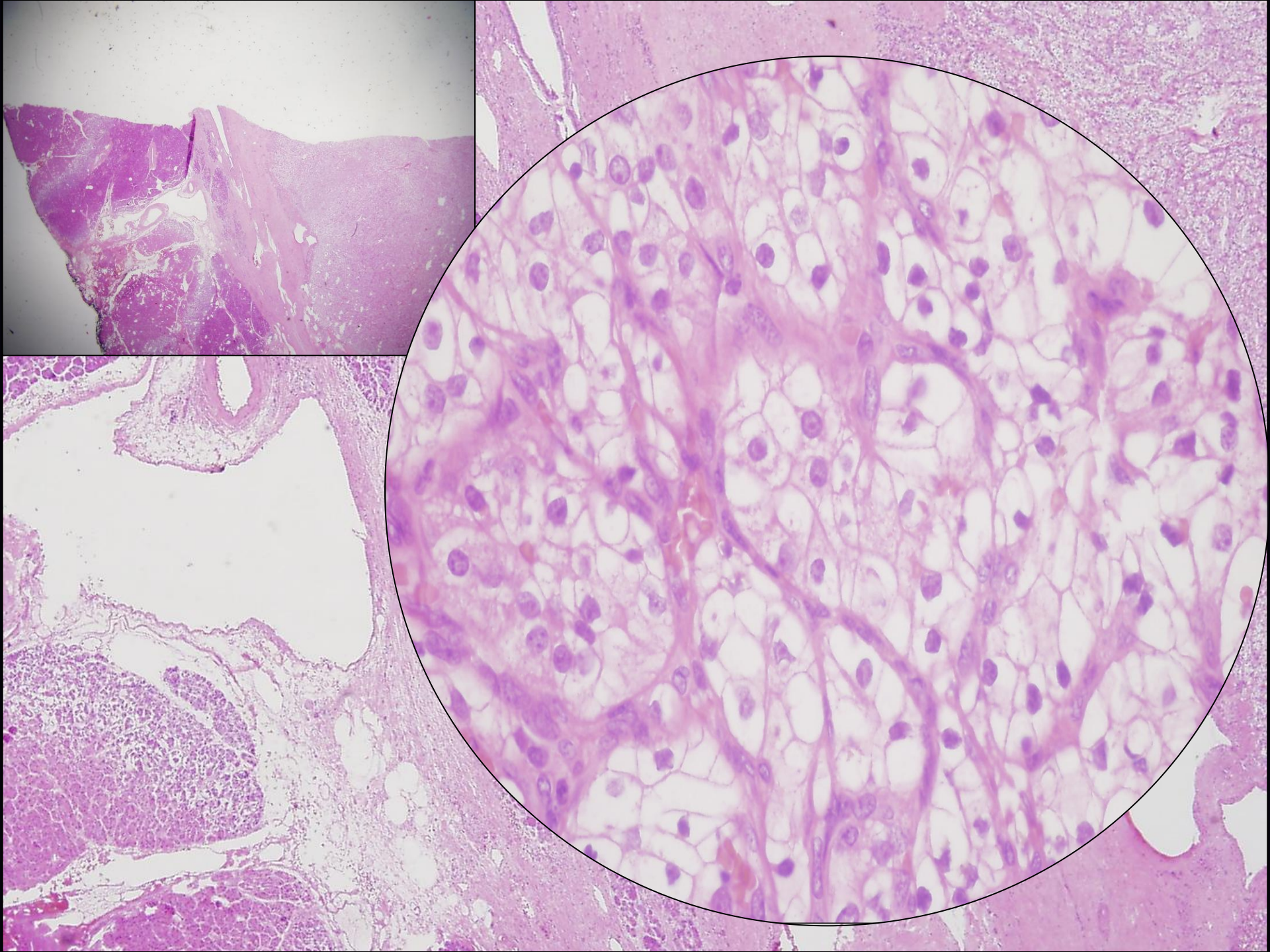
Small cell carcinoma

Germ cell tumors

Haematologic malignancies

# Metastatic renal cell carcinoma

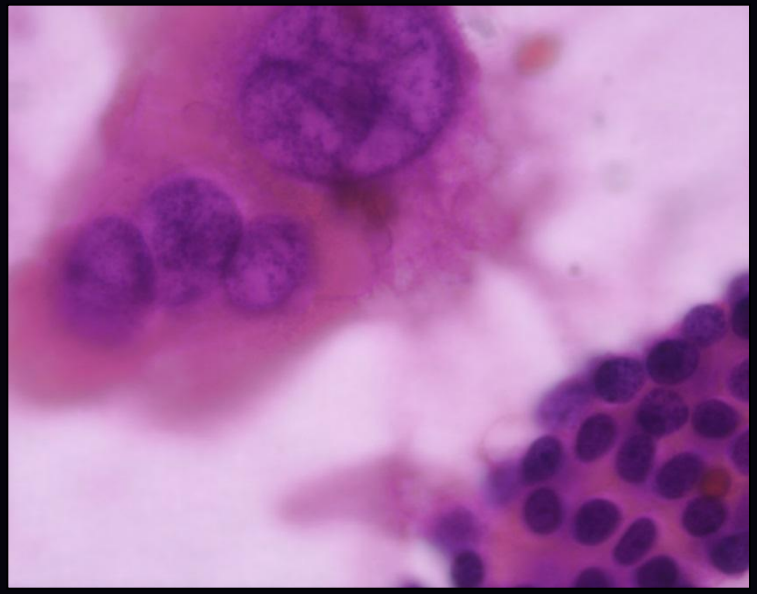


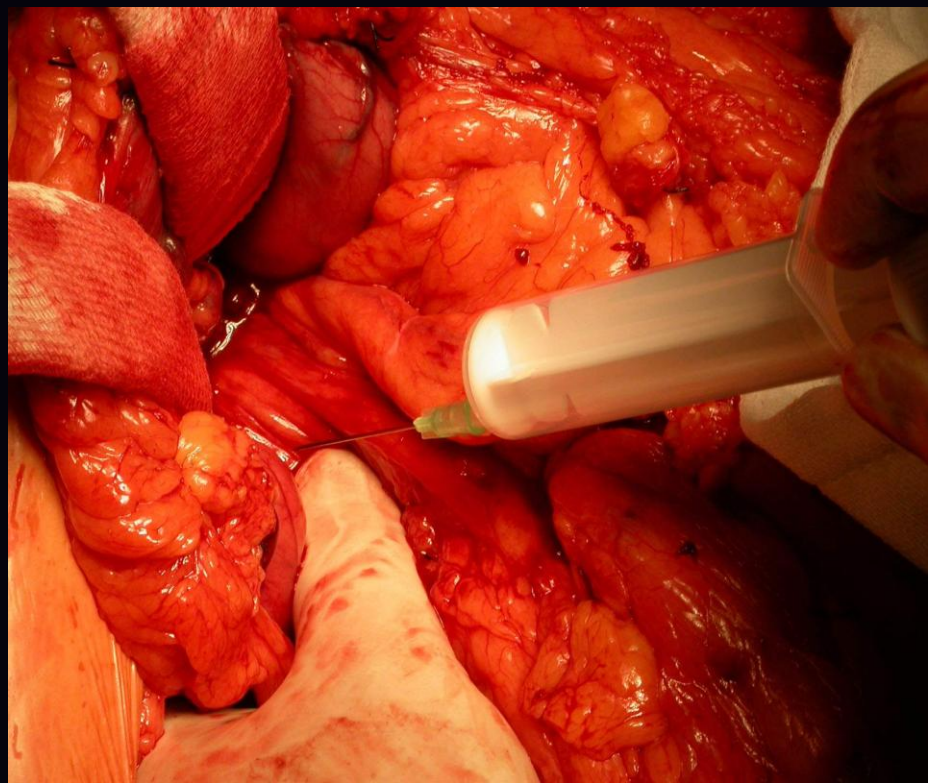


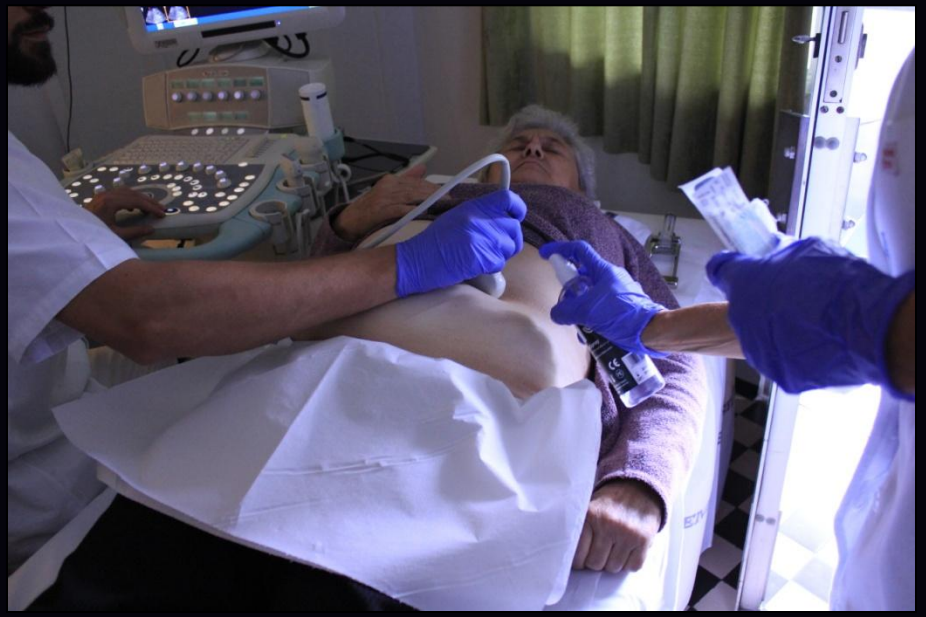
# Cytologic examination of the pancreas

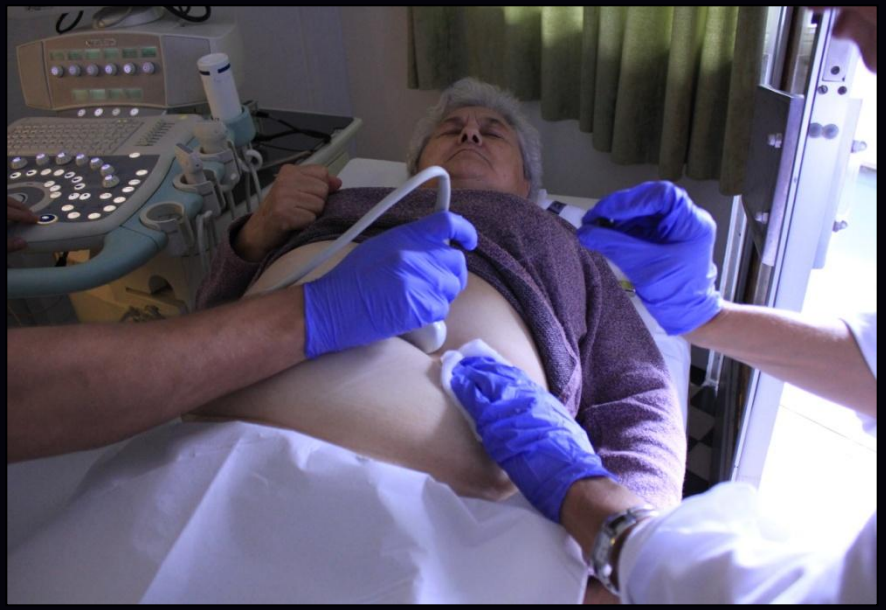
Intraoperative
US or CT guided - percutaneous
US - endoscopic
ERCP-pancreatic juice
Bile duct scrape

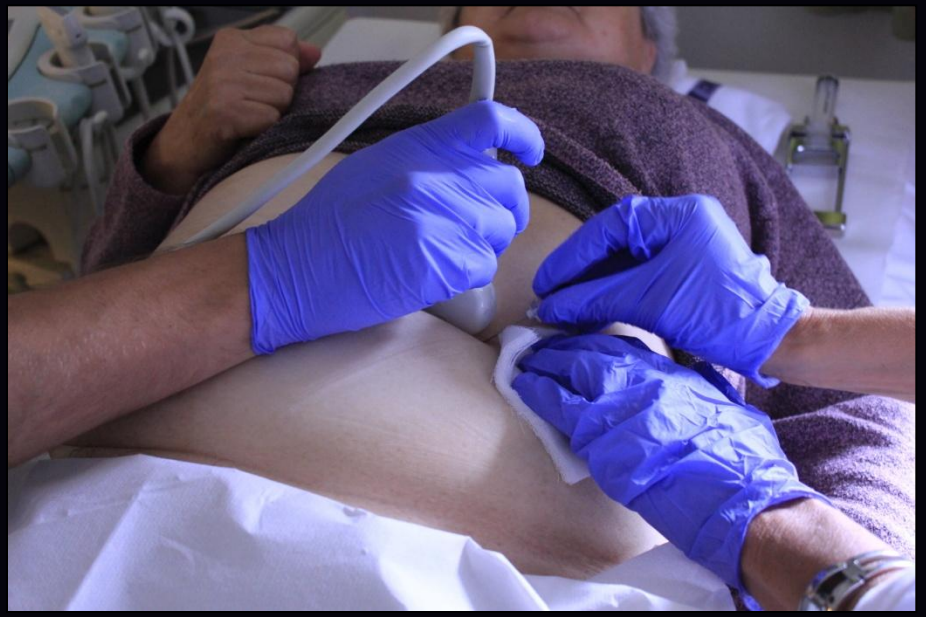
# intraoperative



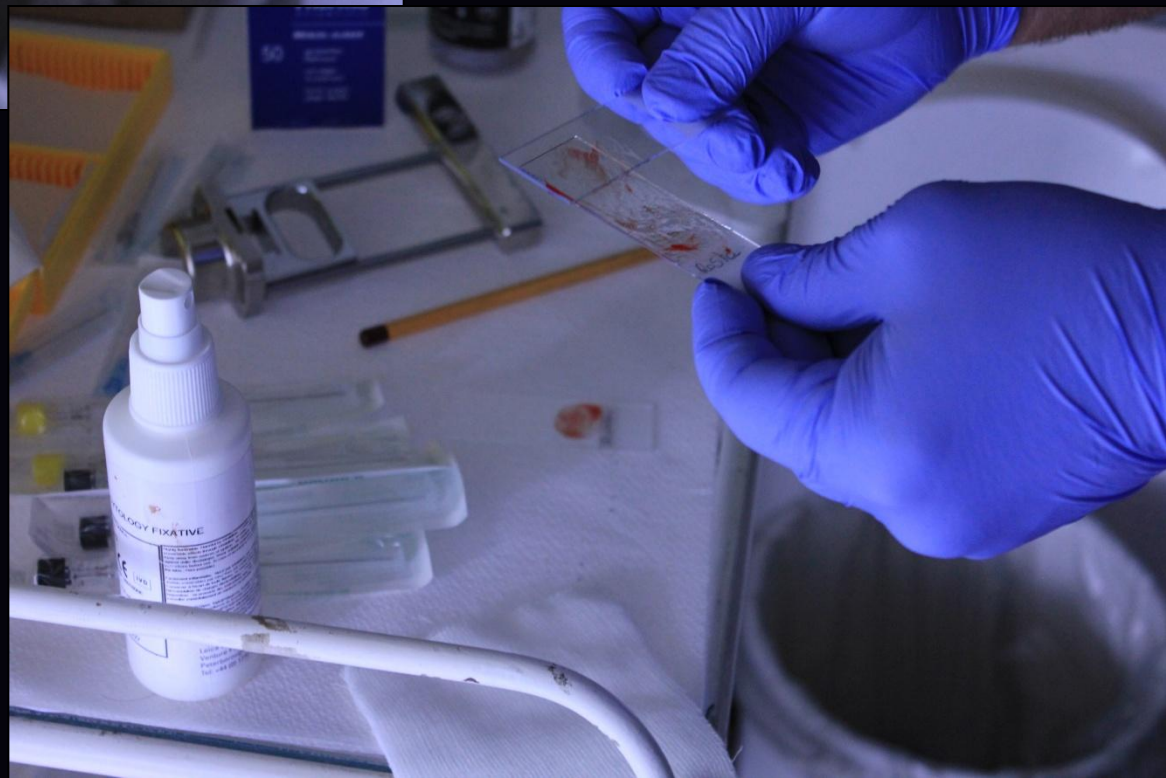


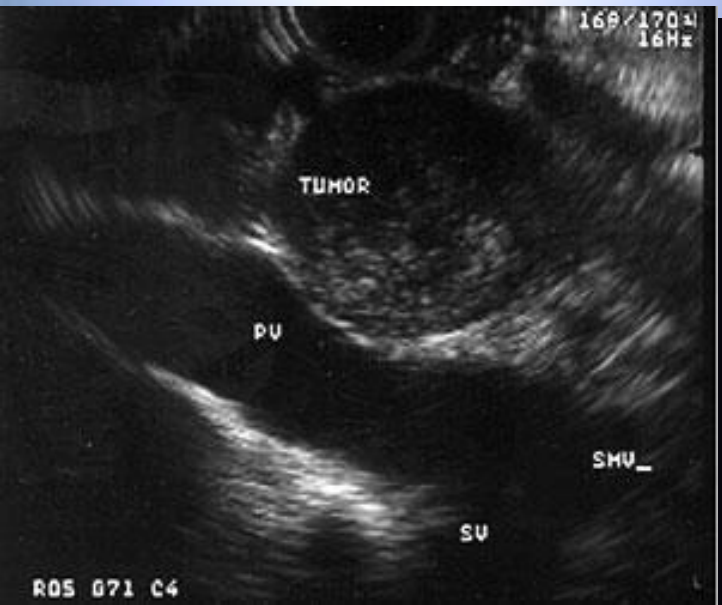


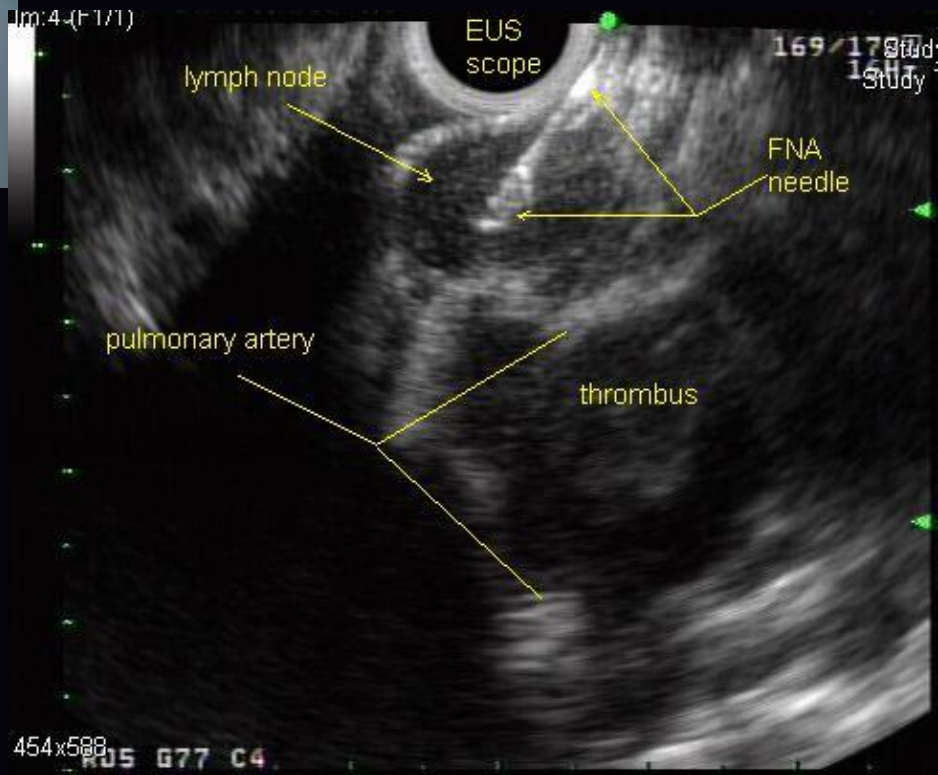


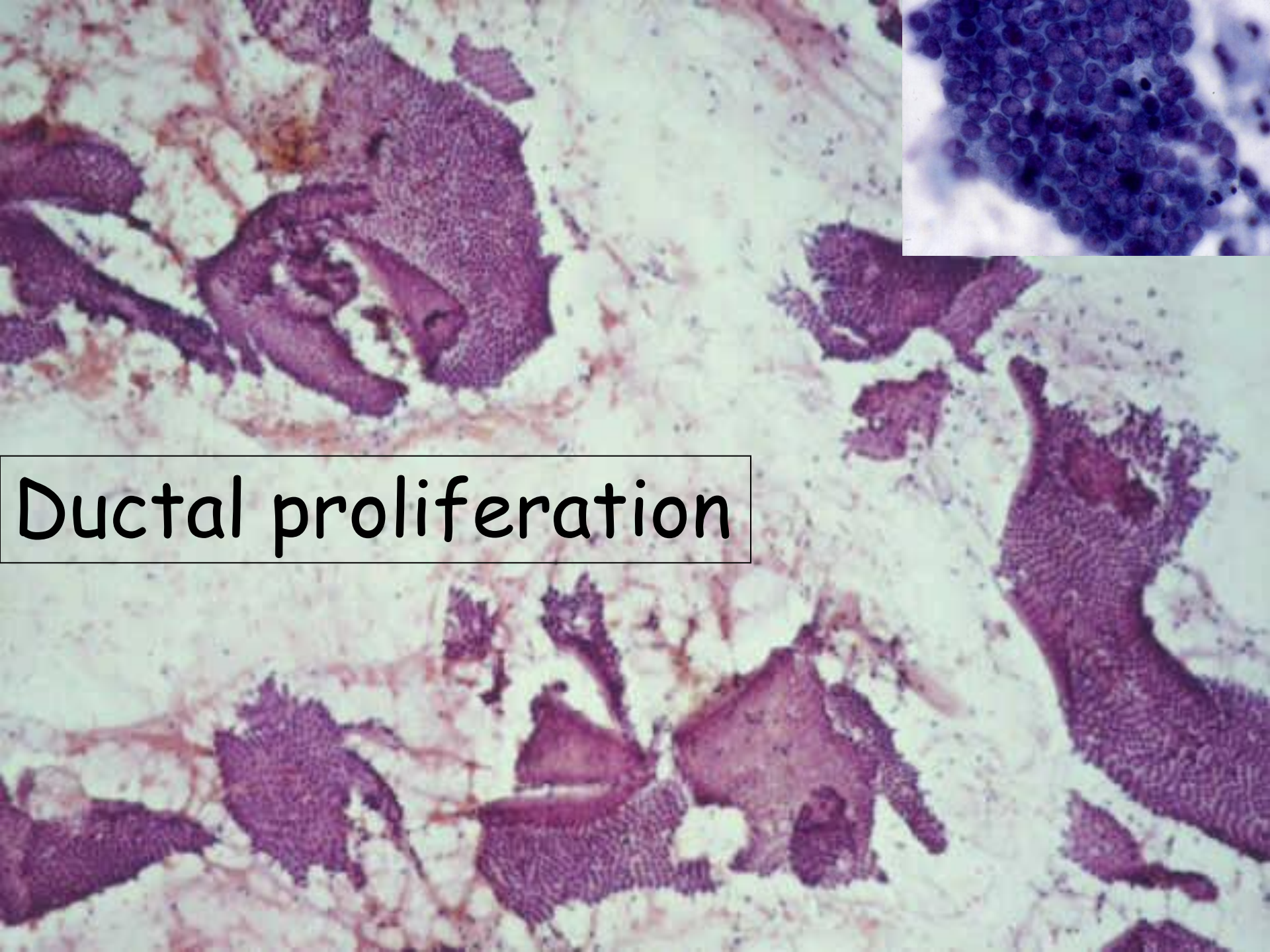


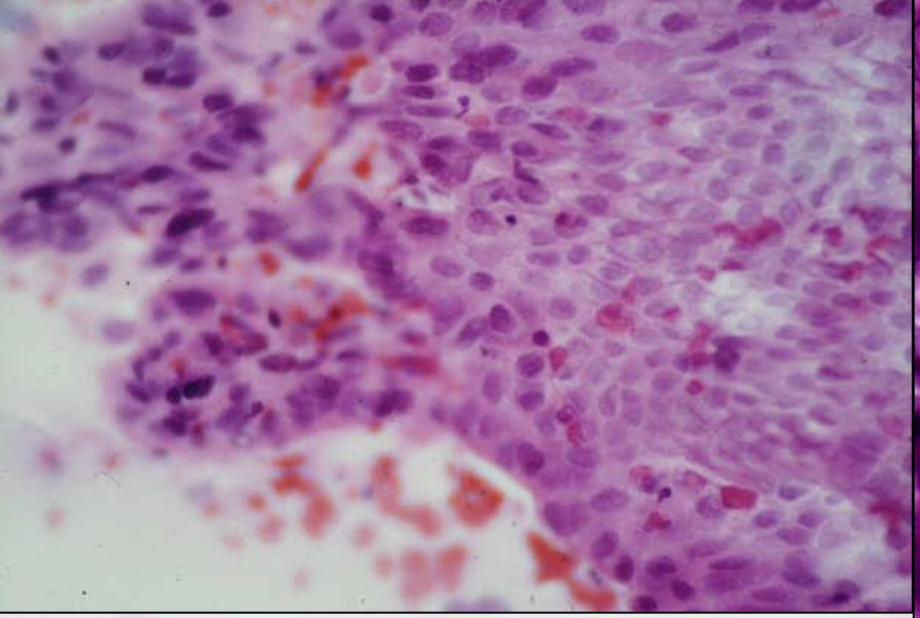
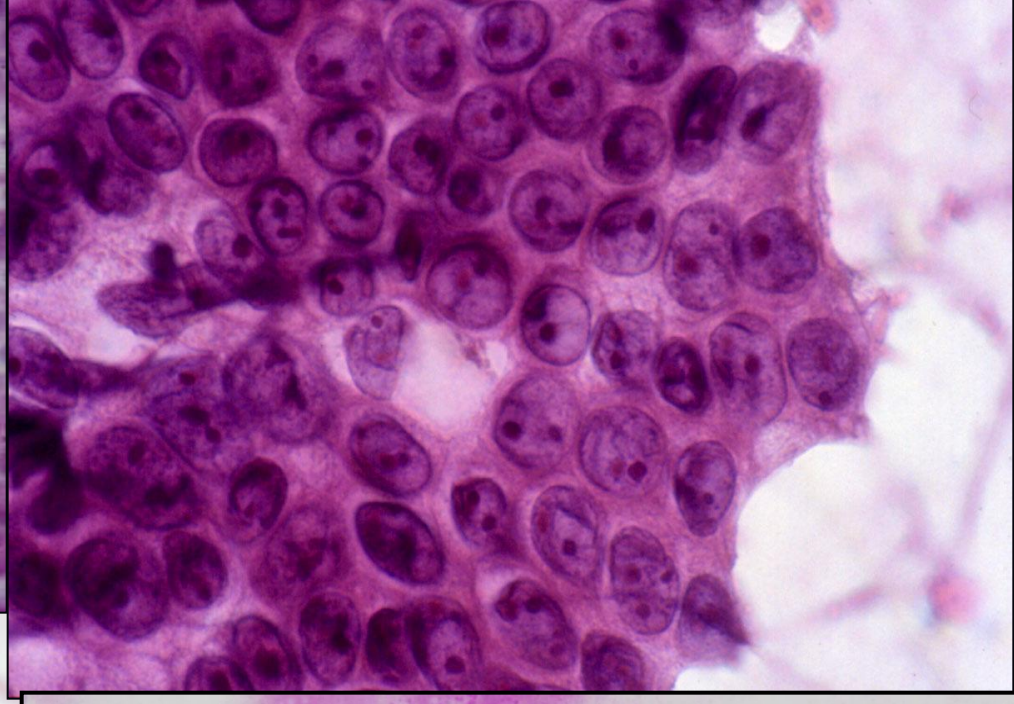
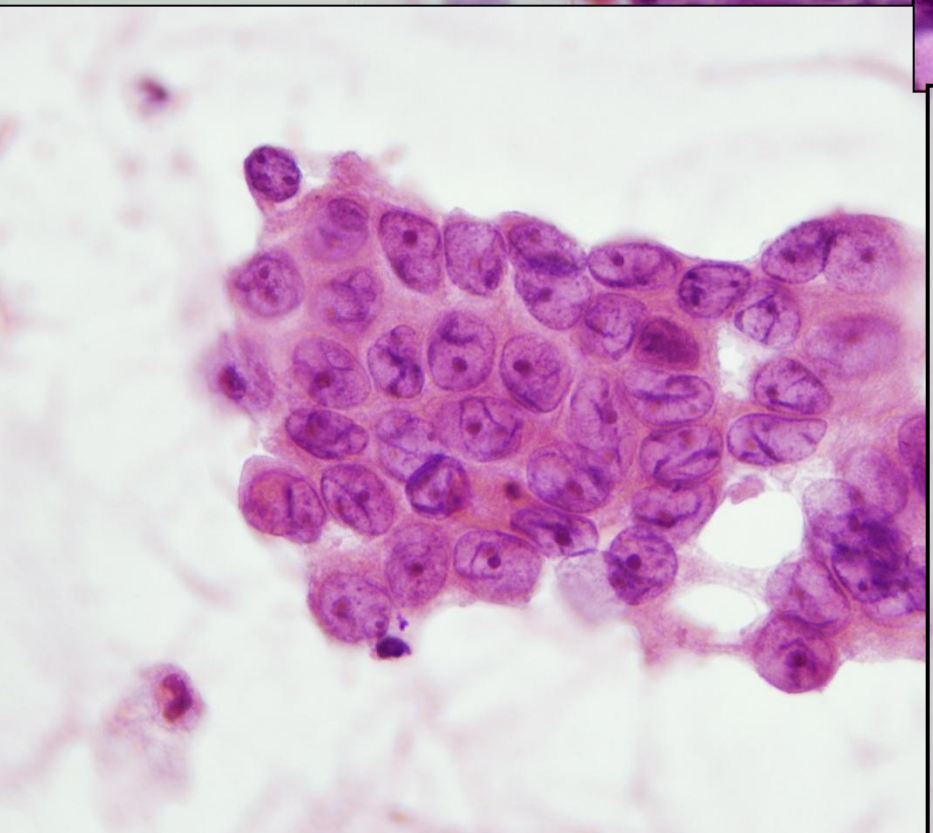
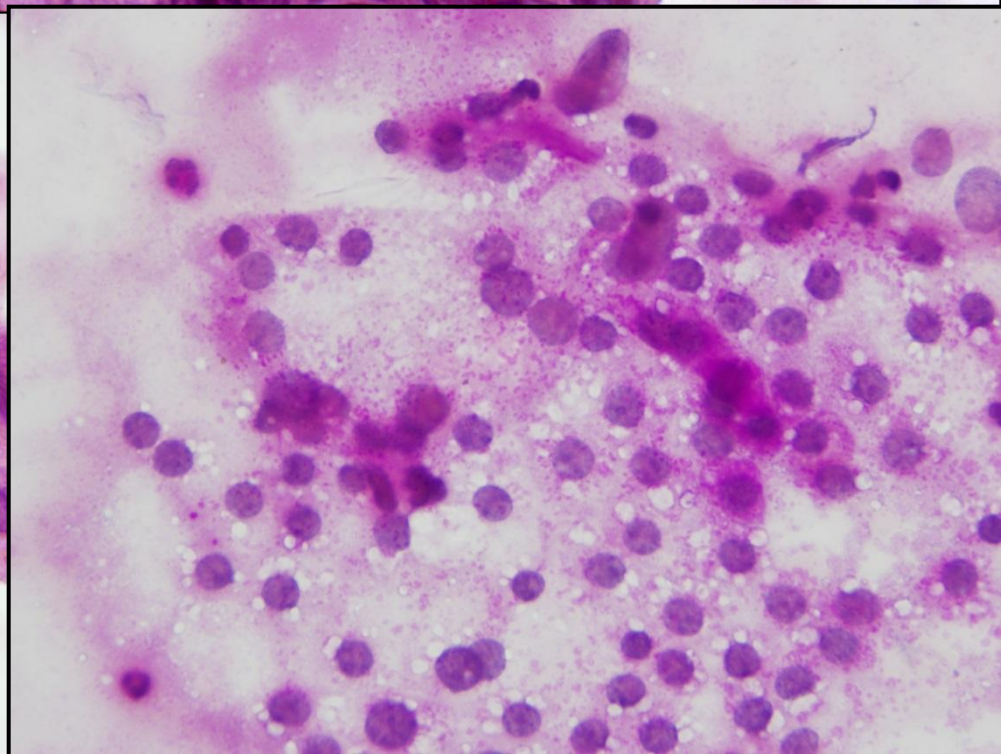

Thermo

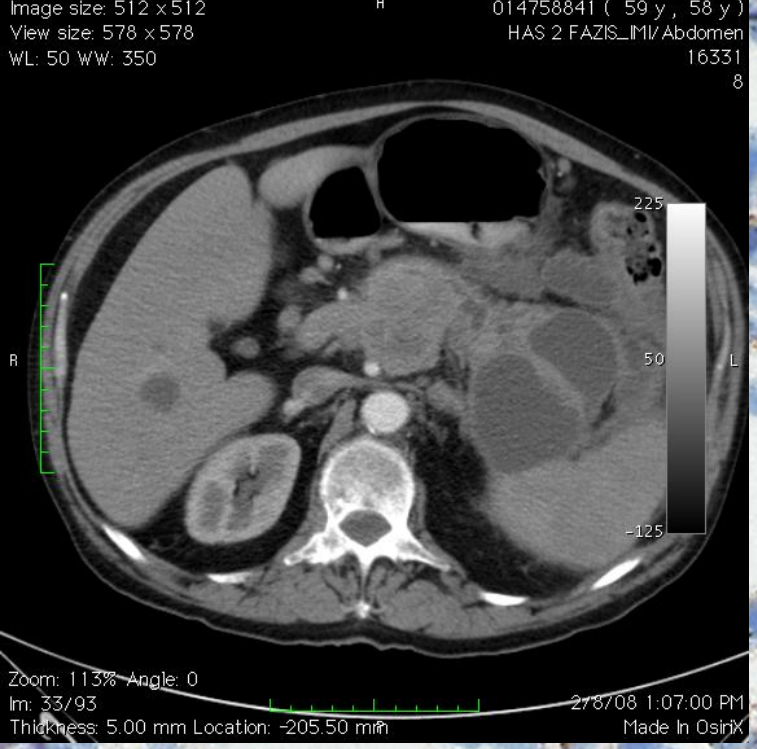



169/170
16Hz
TUMOR
PV
SMV
SV
R05 G71 C4


EUS
scope
lymph node
FNA
needle
pulmonary artery
thrombus
454x588
R05 G77 C4


Ductal proliferation




Male, 59 years old.

lesion in the pancreas, 4 cm in diameter

Cl.dg.: pancreatic carcinoma

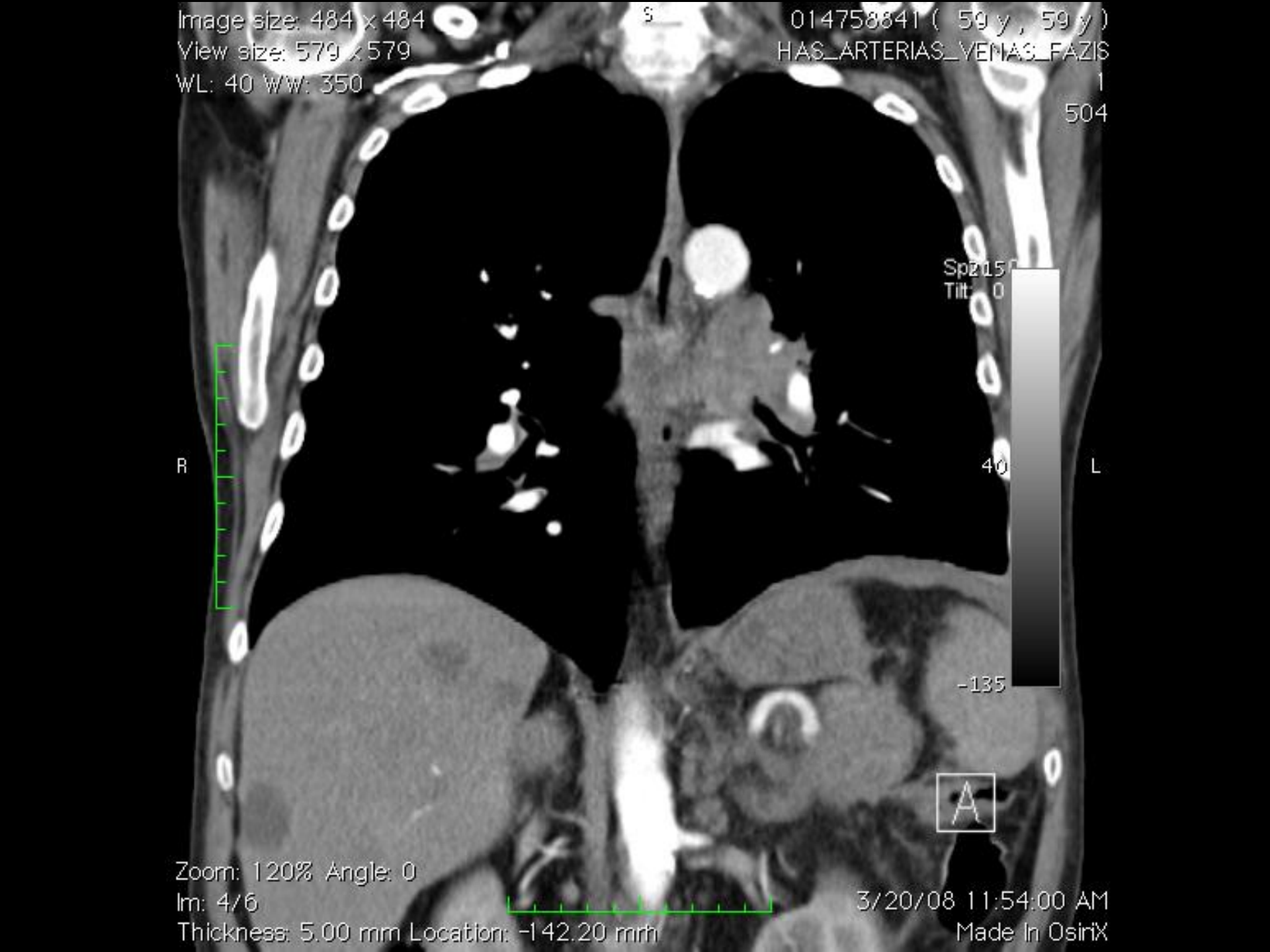


Image size: 484 x 484
View size: 579 x 579
WL: 40 WW: 350
S
0147588641 ( 59 y , 59 y )
HAS_ARTERIAS_VENAS_FAZIS
1
504
Sp 215
Tilt 0
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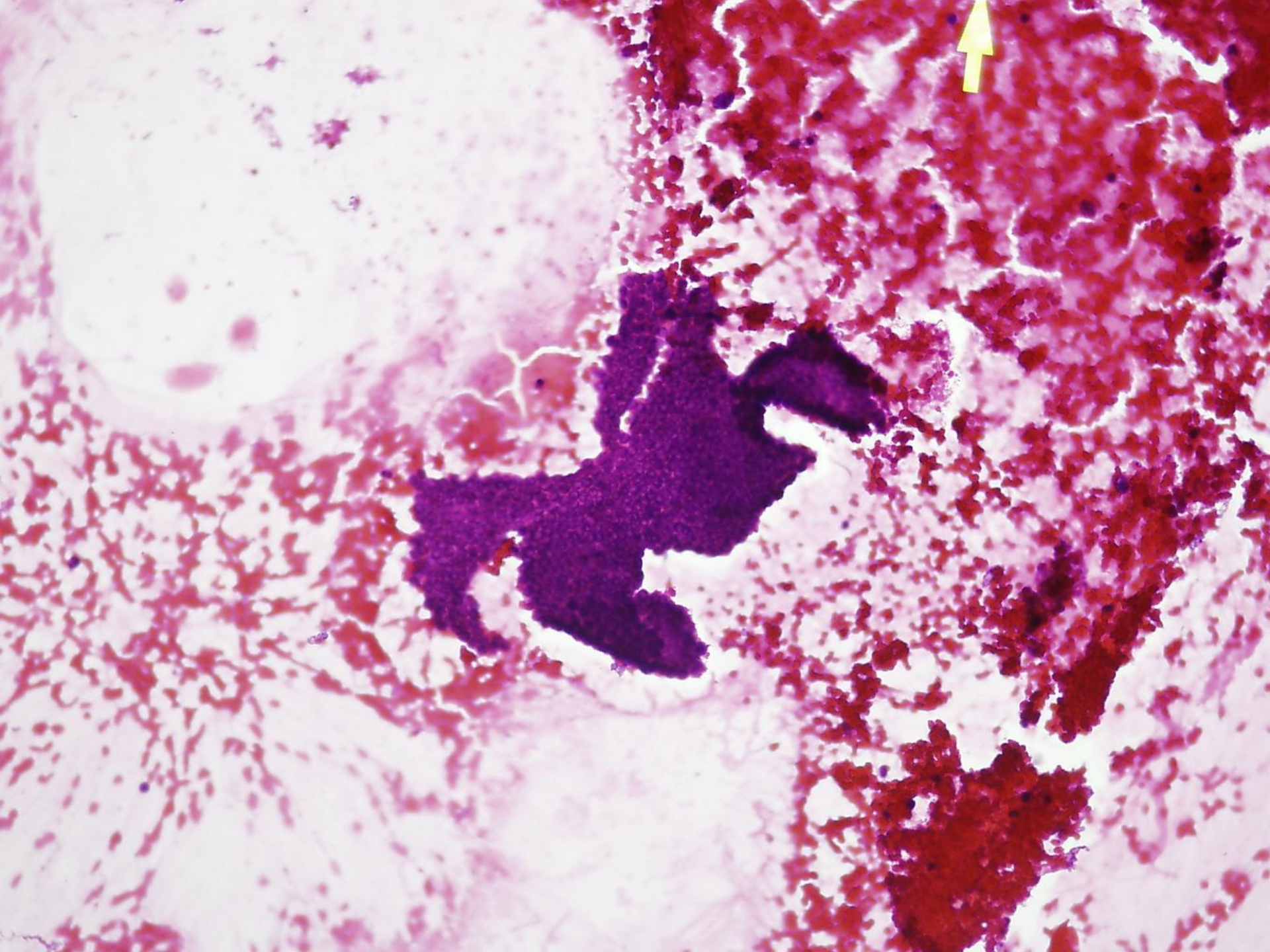
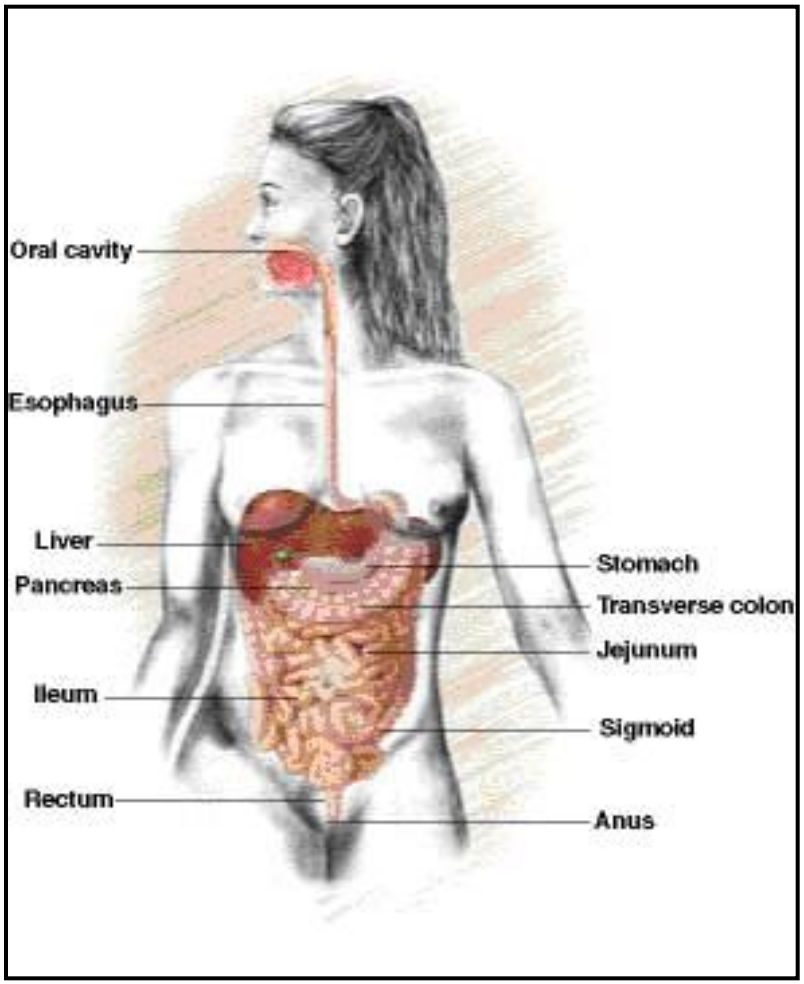
L
-135
A
Zoom: 120% Angle: 0
Im: 4/6
Thickness: 5.00 mm Location: -142.20 mm
3/20/08 11:54:00 AM
Made In OsiriX



# Diffuse neuroendocrine system (DNES) Gastro-entero-pancreatics (GEP) tumors (APUD-omas)

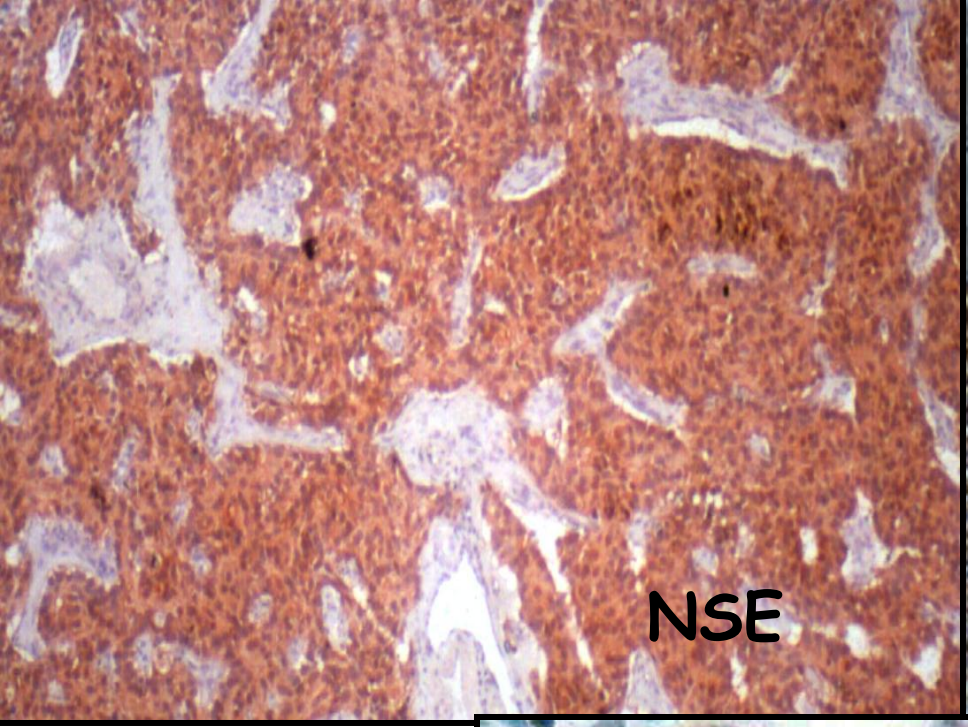


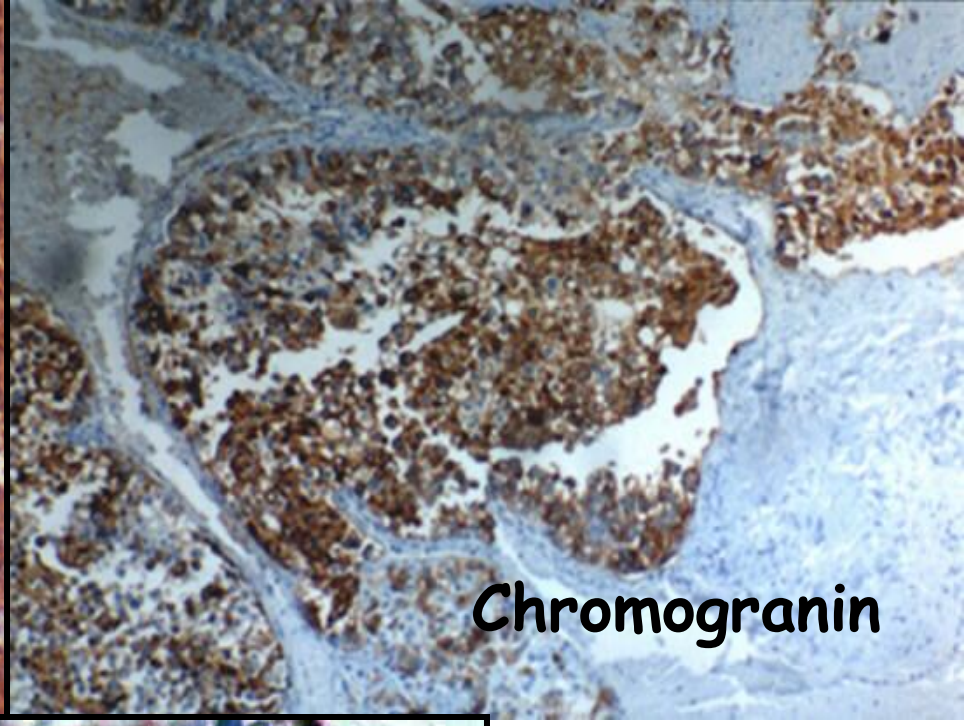
# MARKERS OF NEUROENDOCRINE DIFFERENTIATION

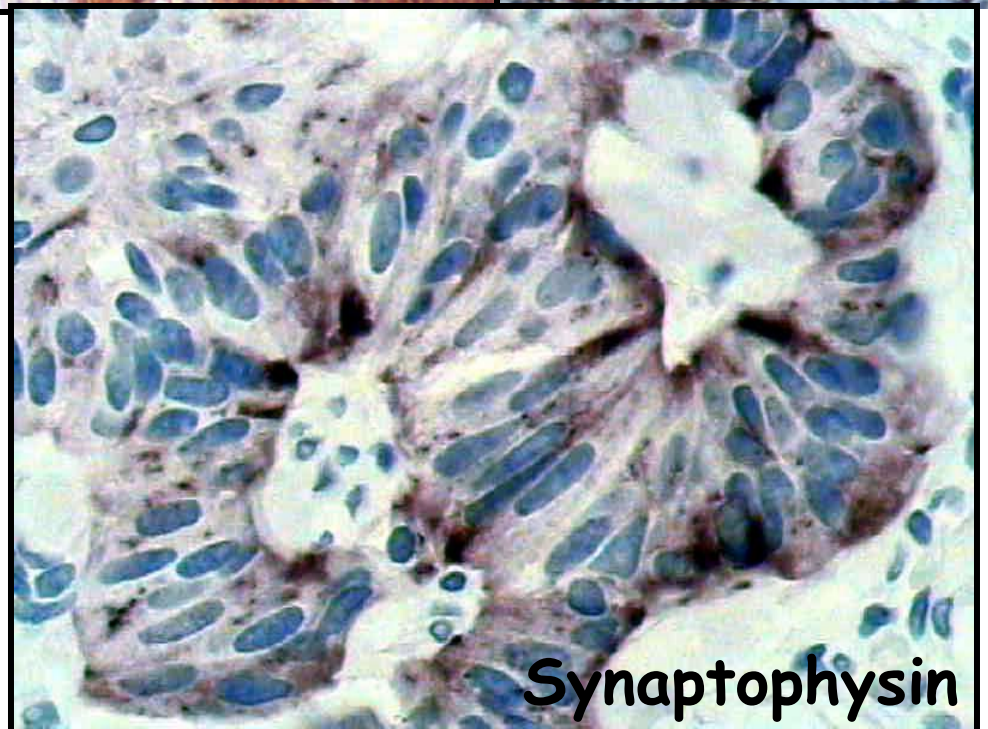
## General markers

- Vesicles
  - Chromogranin A, B
  - Synaptophysin
- Cytosole
  - NSE
  - PGP 9.5 (protein gene product)
- Membrane bound

  (receptors for adhesion molecules)
  - CD56, (N-CAM)


NSE

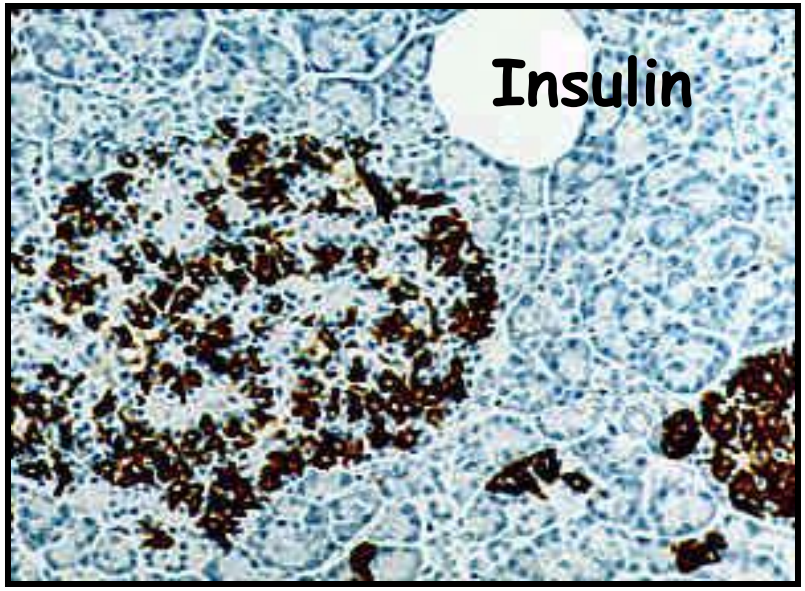

Chromogranin


Synaptophysin

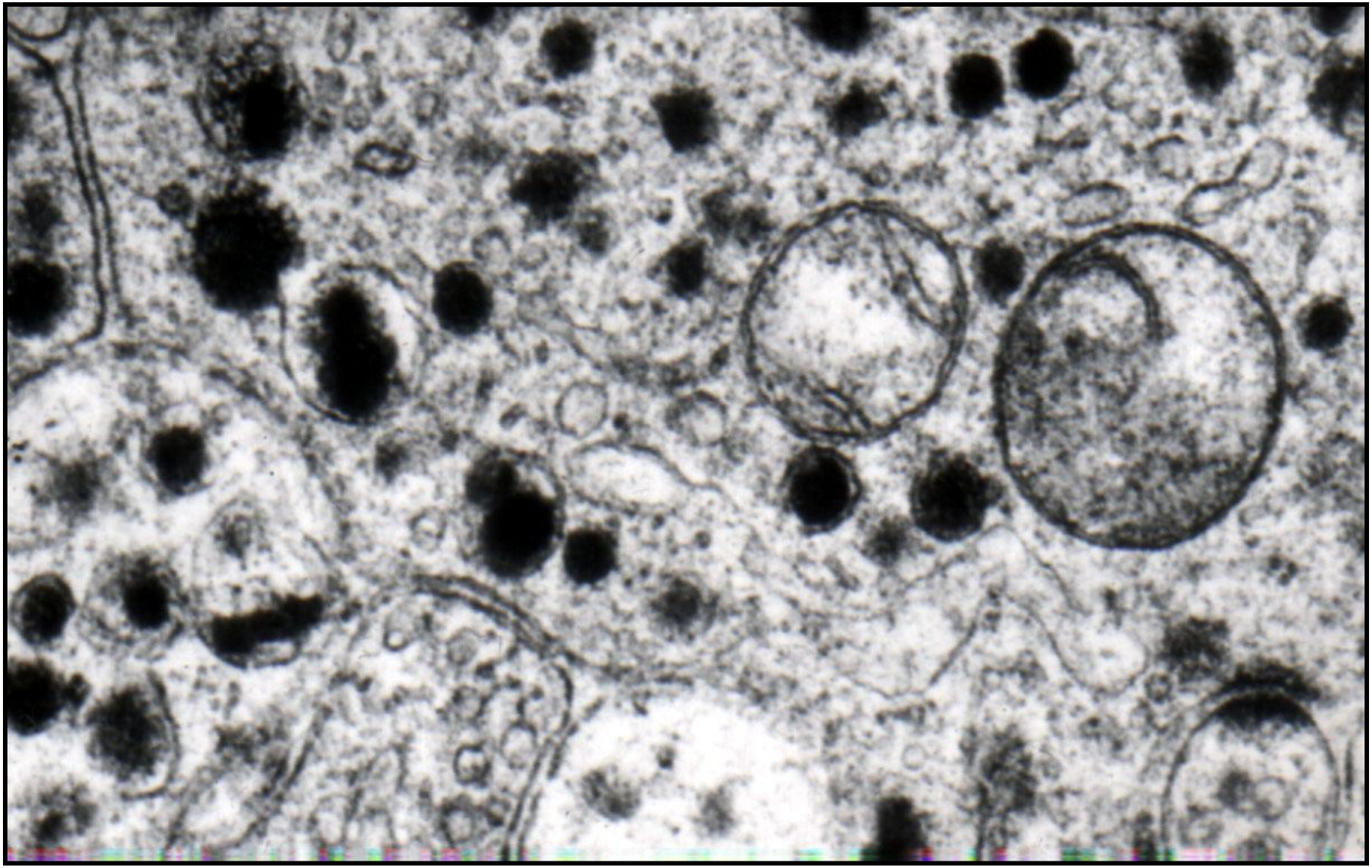
# MARKERS OF NEUROENDOCRINE DIFFERENTIATION

Specific markers

**Hormones (cell type dependent)**



# ELECTRON MICROSCOPY



# Pancreatic Islet Tumours

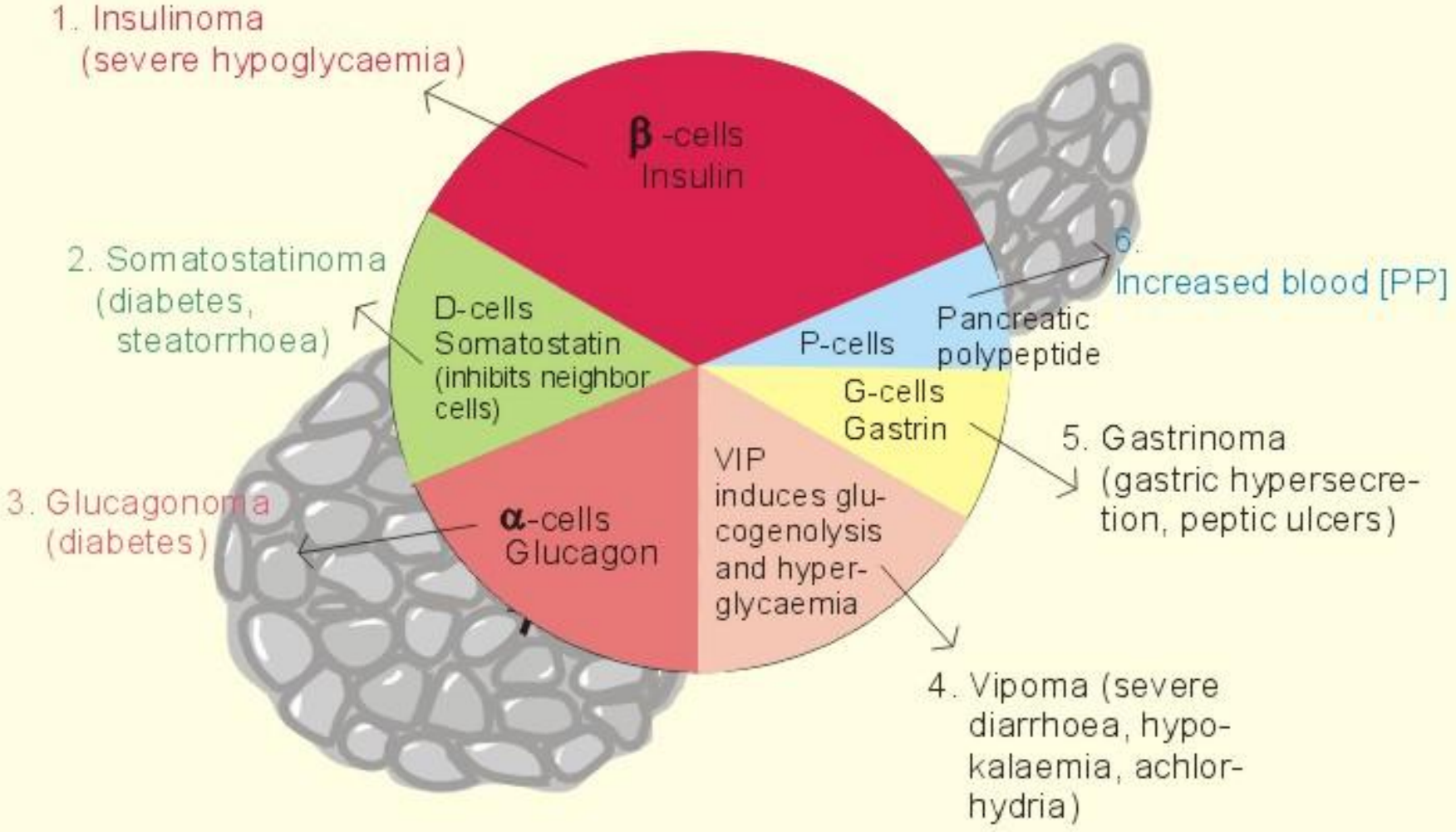



Fig.23-8

KMc

# Islet cell tumors

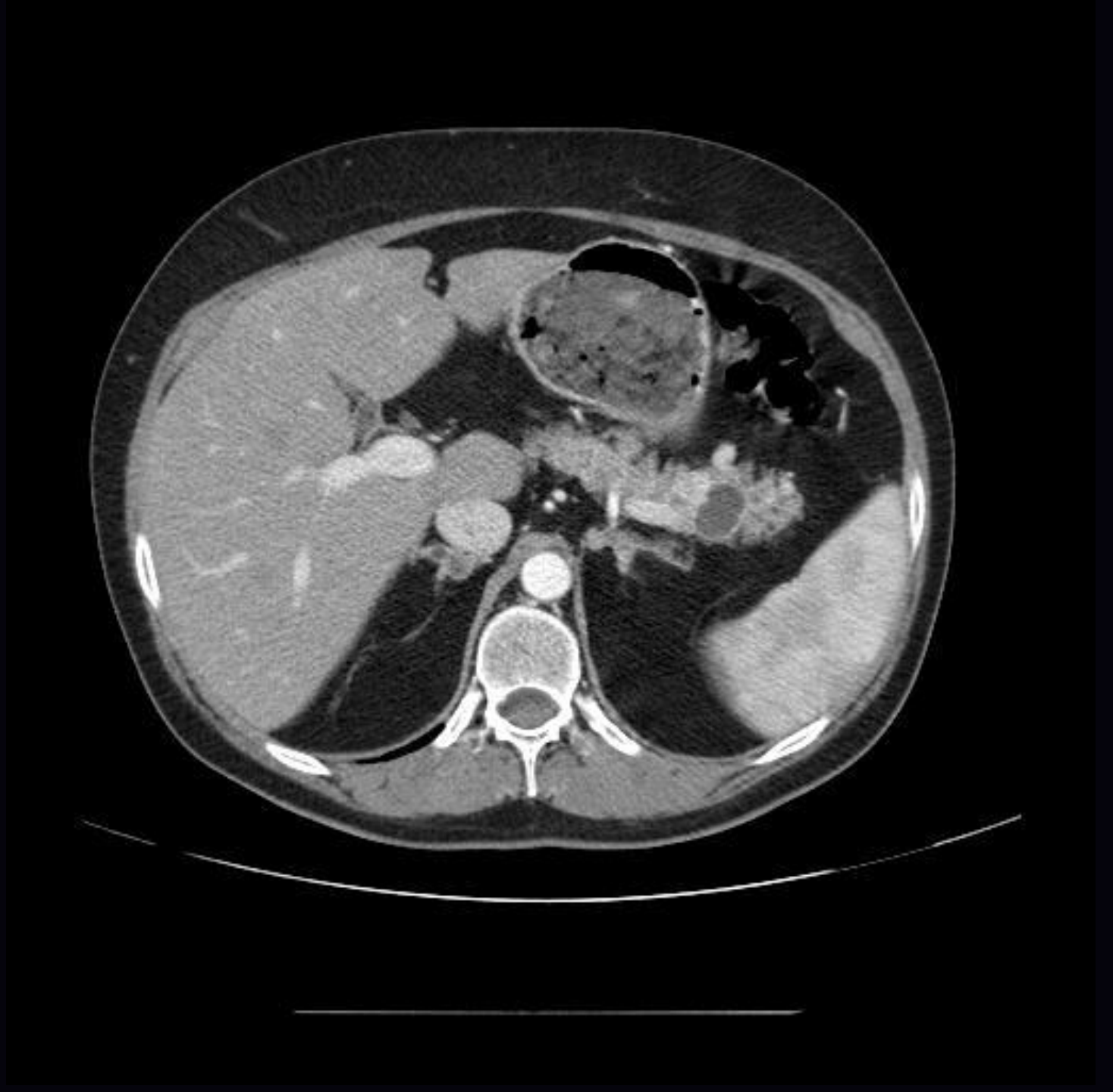
- Hormone production in 50% of the cases
- Uncertain biological behaviour
- Round, well circumscribed lesions
  - Insulinoma
  - Glukagonoma
  - VIP-oma
  - Gastrinoma
  - Somatostatinoma

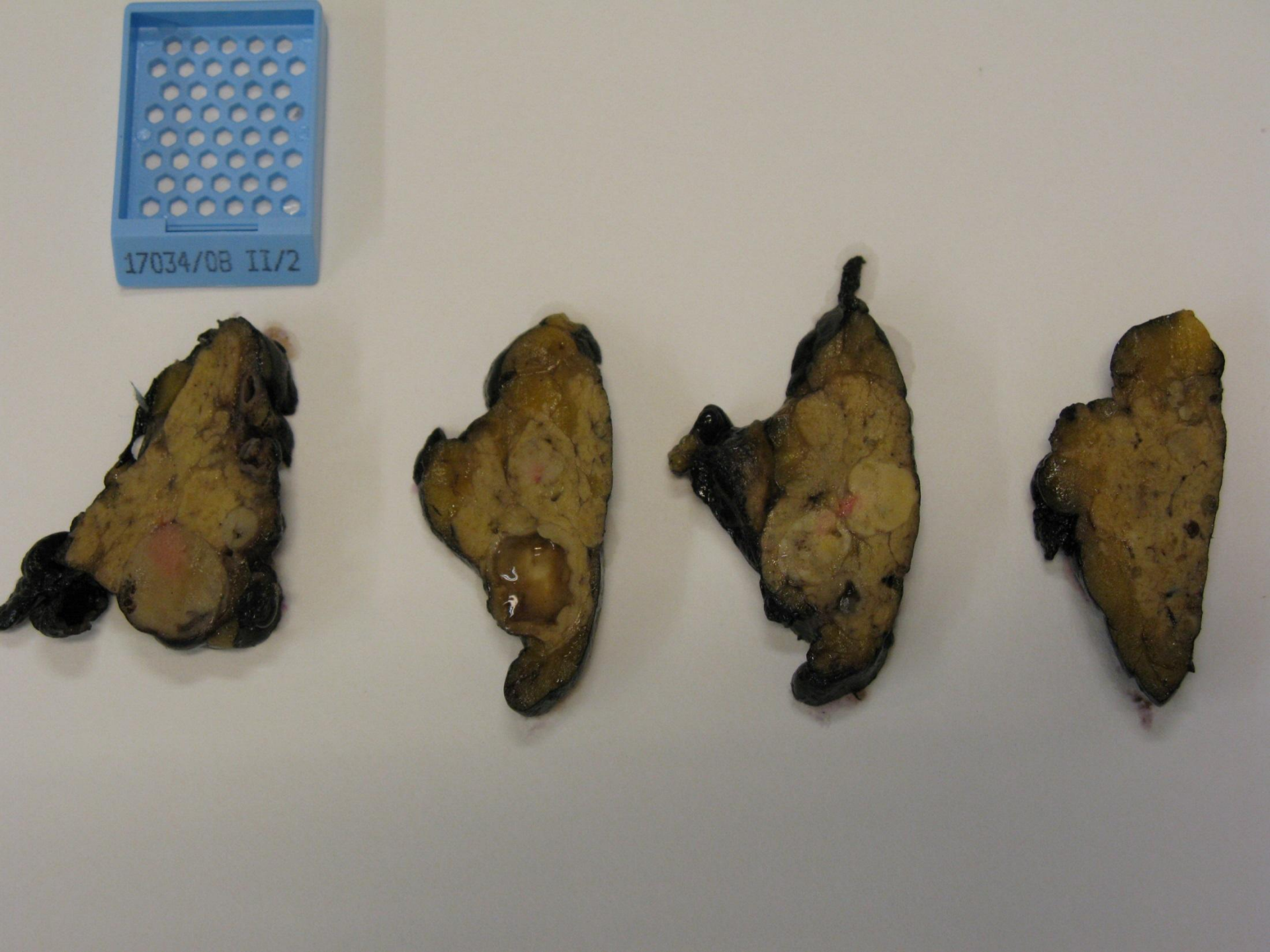
# NEUROENDOCRINE TUMORS OF THE PANCREAS

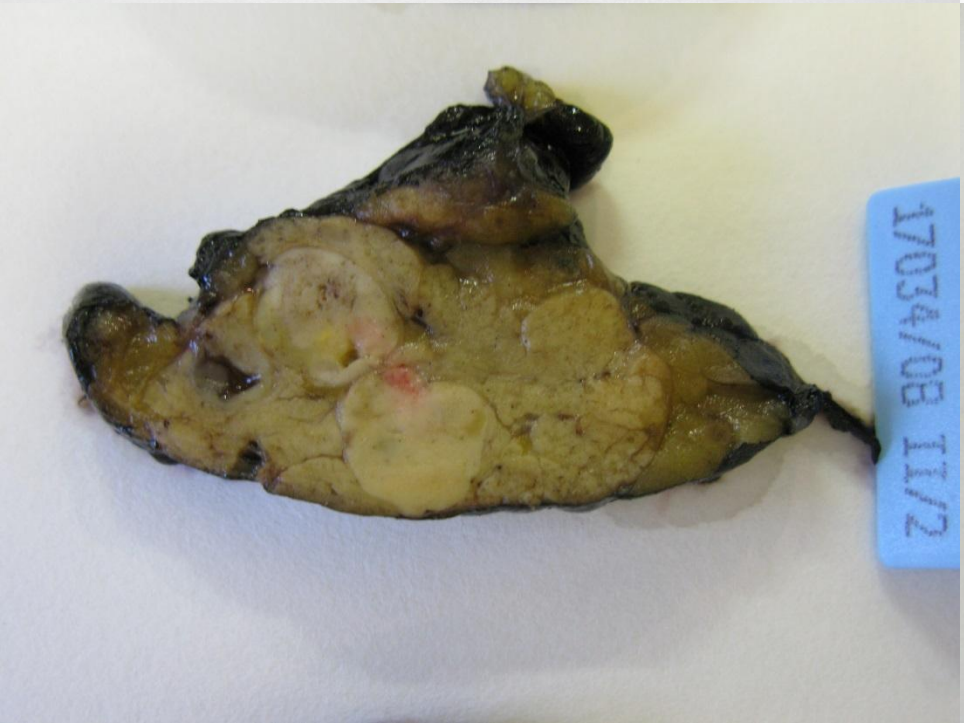
- Insulinoma – β-cells- benign
- Gastrinoma- δ-cells - carcinoma –

  Zollinger-Ellison Syndrome: parietal cell hyperplasia, multiple ulcers
- Glucagonoma – α-cells - carcinoma

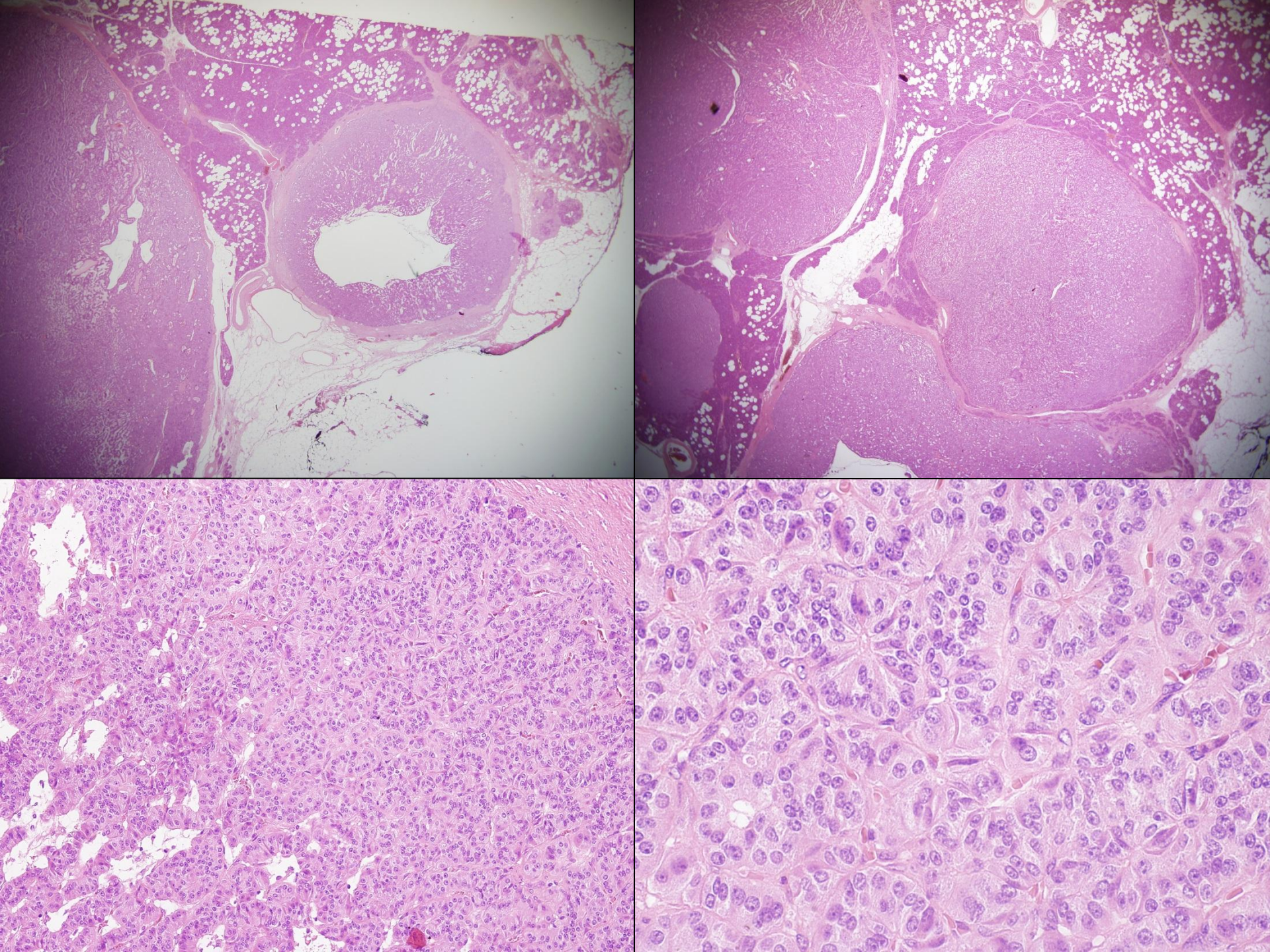
  Mild diabetes, skin rash, anaemia
- Somatostatinoma – δ-cells – carcinoma – slow bowel movements, steatorrhea
- VIPoma – PP-cells - carcinoma – Werner-Morrison Syndrome (watery diarrhea, Hypokalaemia, Achlorhydria)
- „Carcinoid" – Enterochromaffine cells – carcinoid syndrome

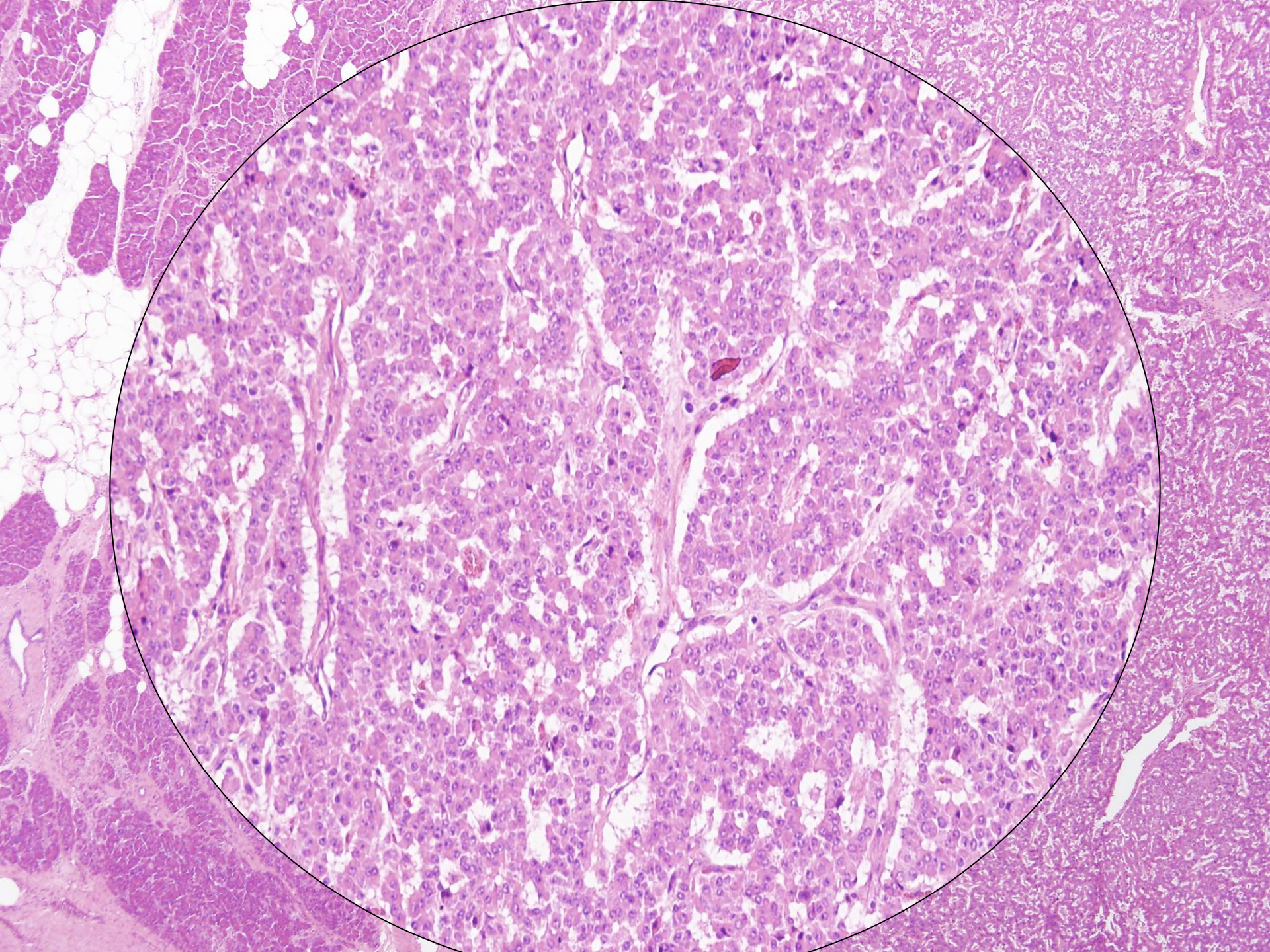



17034/08 II/2


17034/08 II/2

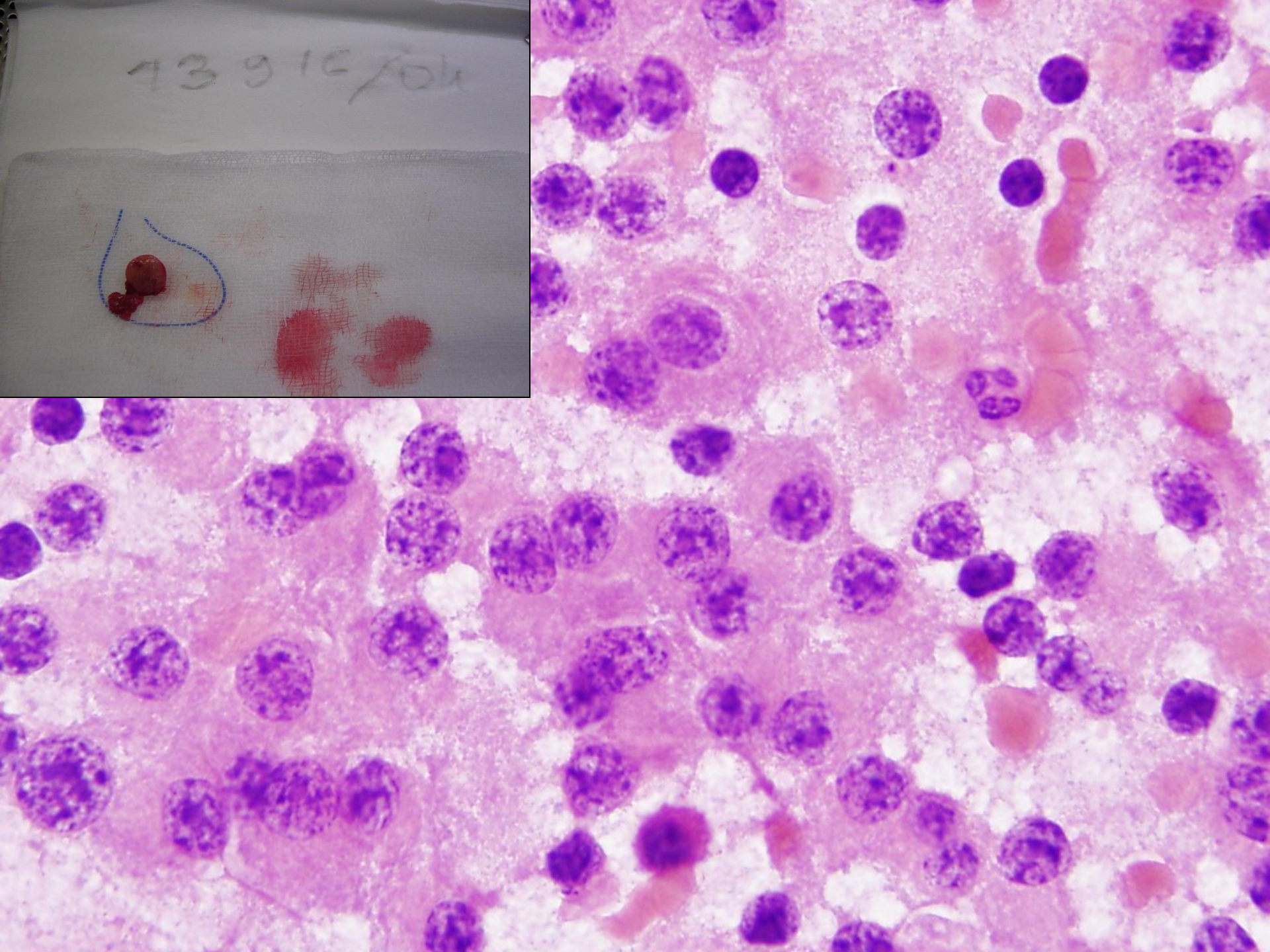

17034/08 II/2

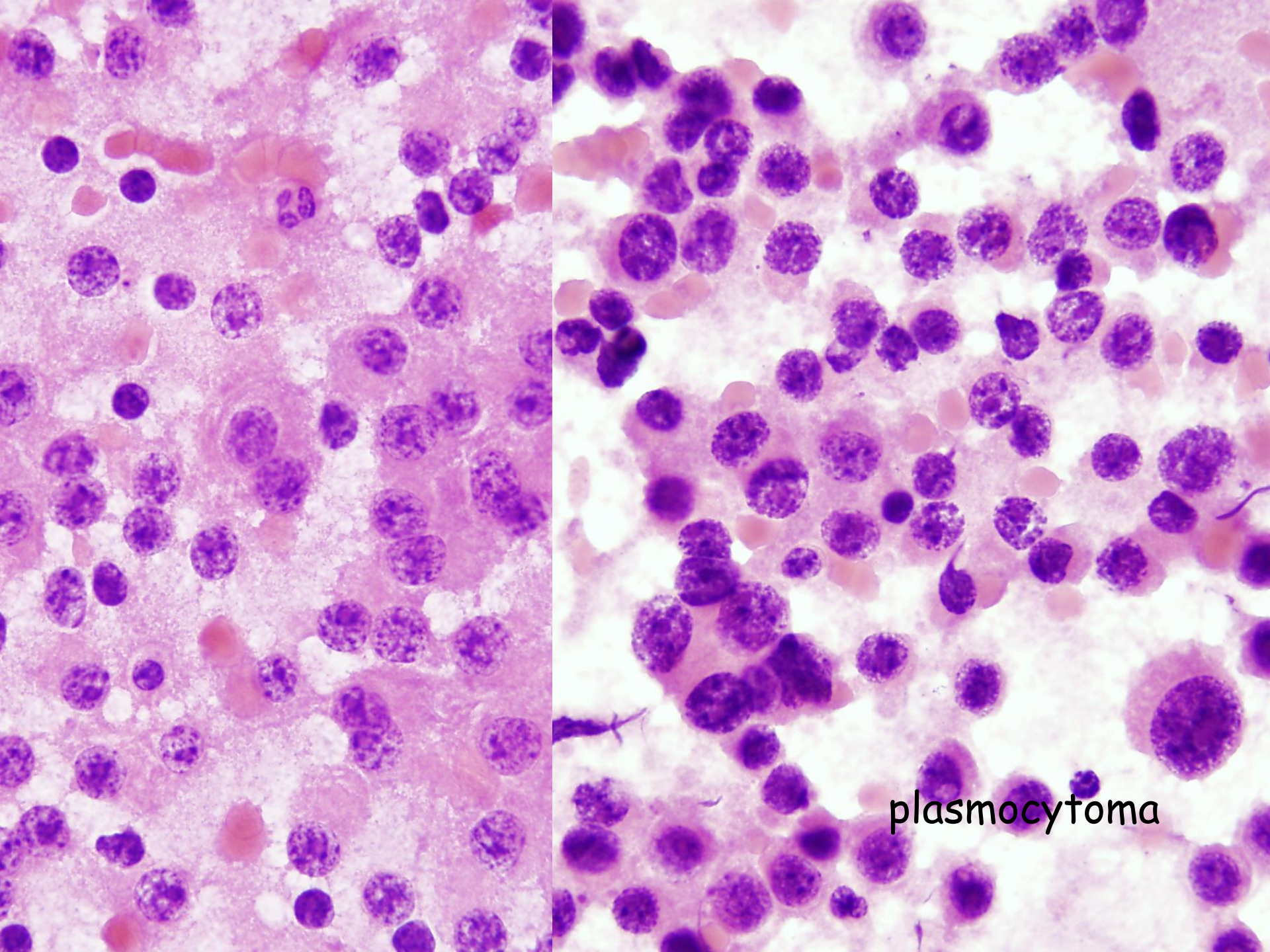




9233/96

# Islet cell tumor




plasmocytoma