An Algorithmic approach to solid neoplasms of the pancreas

JOHNS HOPKINS
MEDICAL INSTITUTIONS

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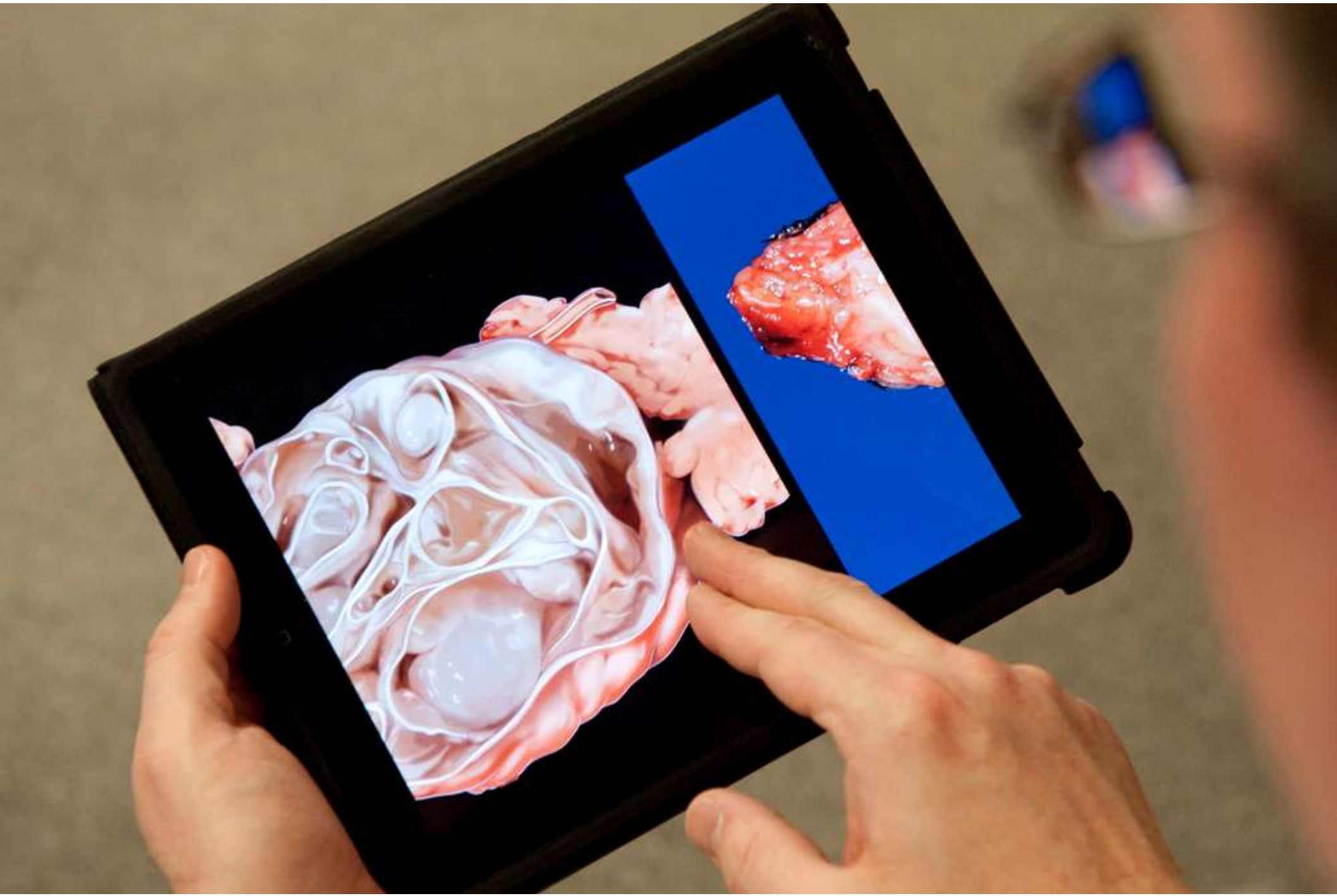
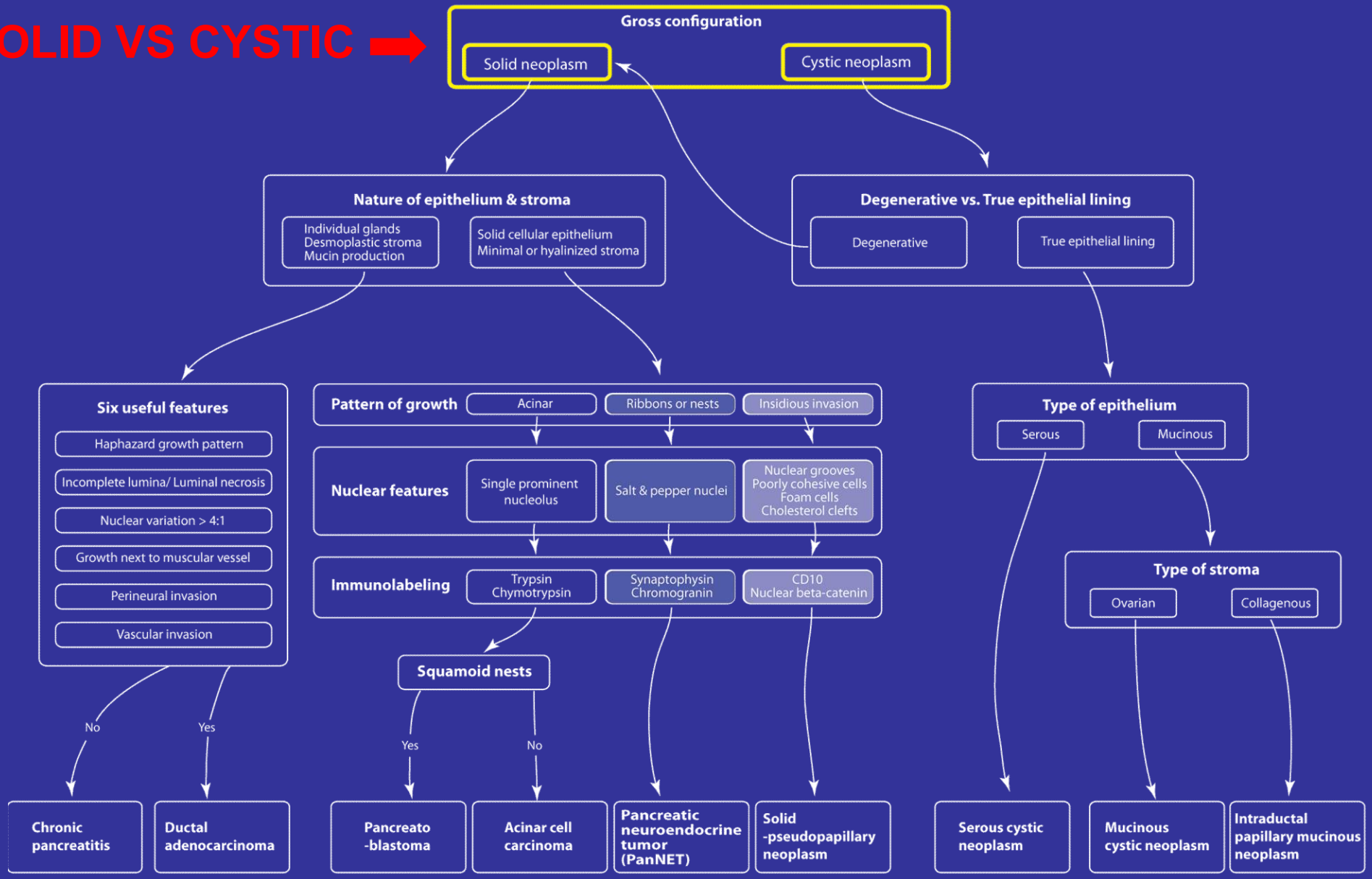
Disclosure

- I receive royalty payments from Myriad Genetics for the PALB2 invention.
- Selected images from the AFIP Fascicle with permission
- The pancreas pathology iPAD APPs are free through the iTunes Store

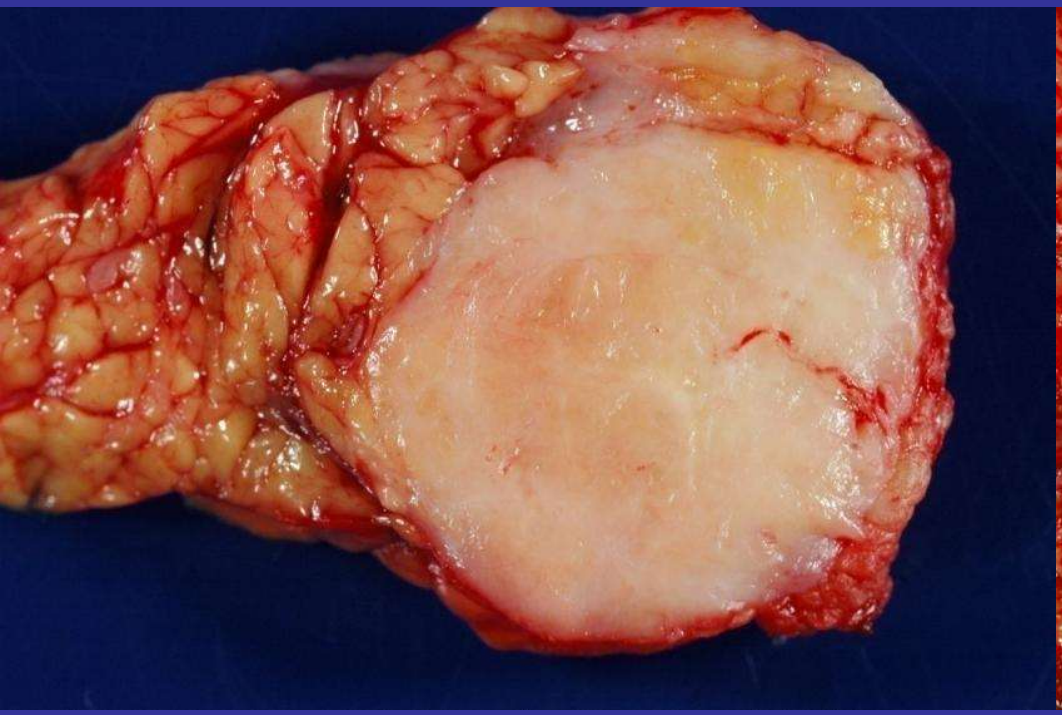


SOLID VS CYSTIC

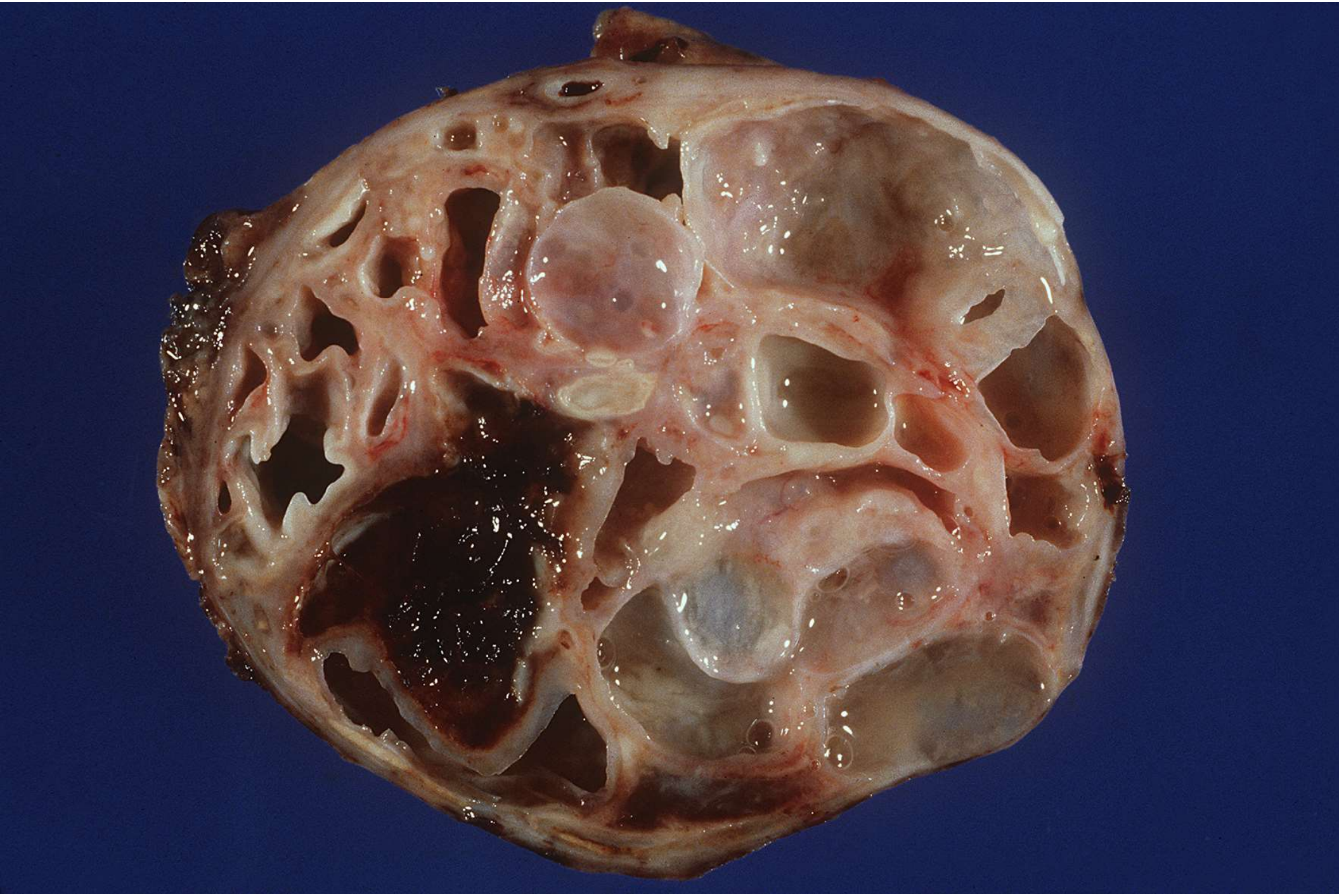


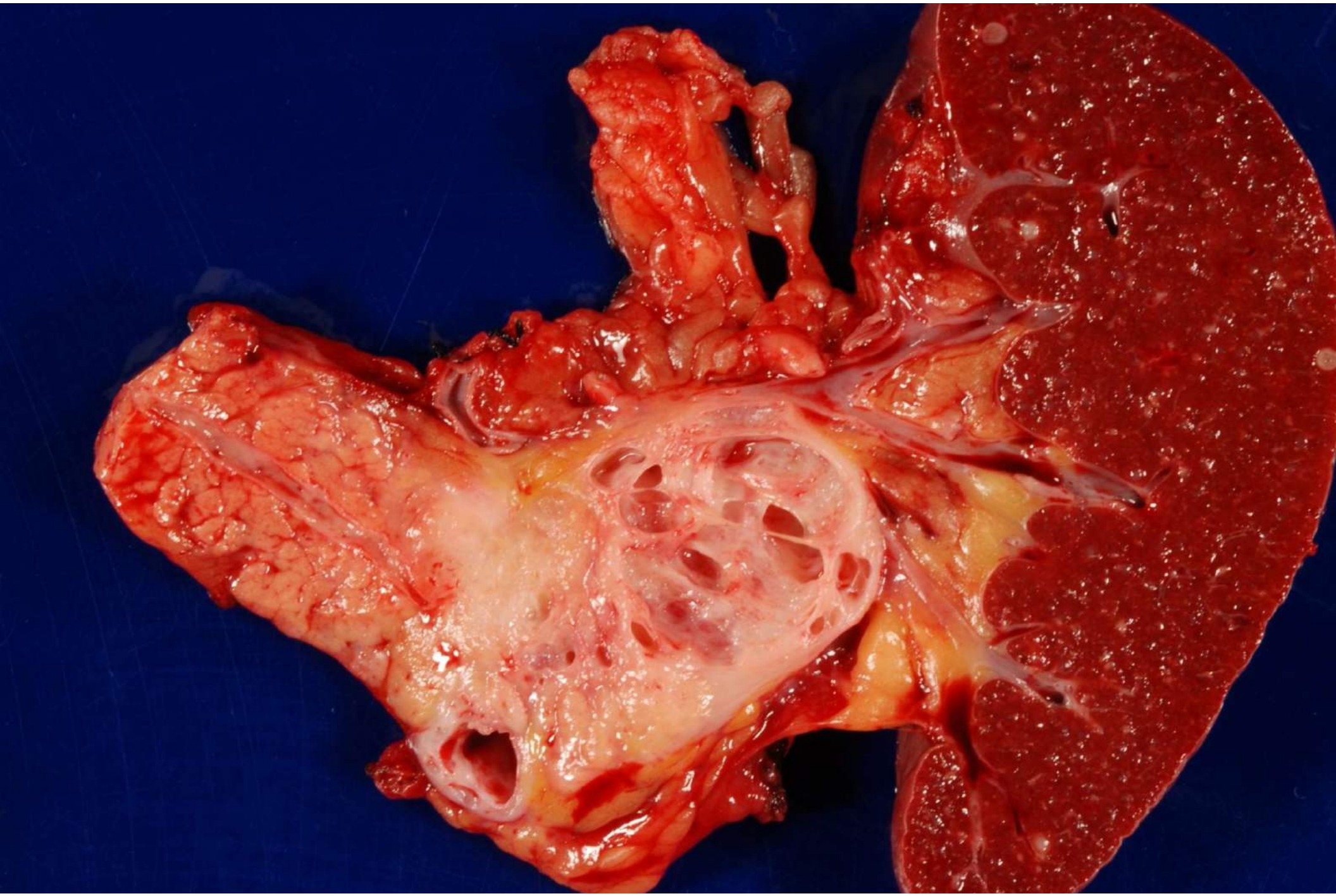
Based on AFIP Fascicle, 4th Edition

1. Is it Solid or Cystic?

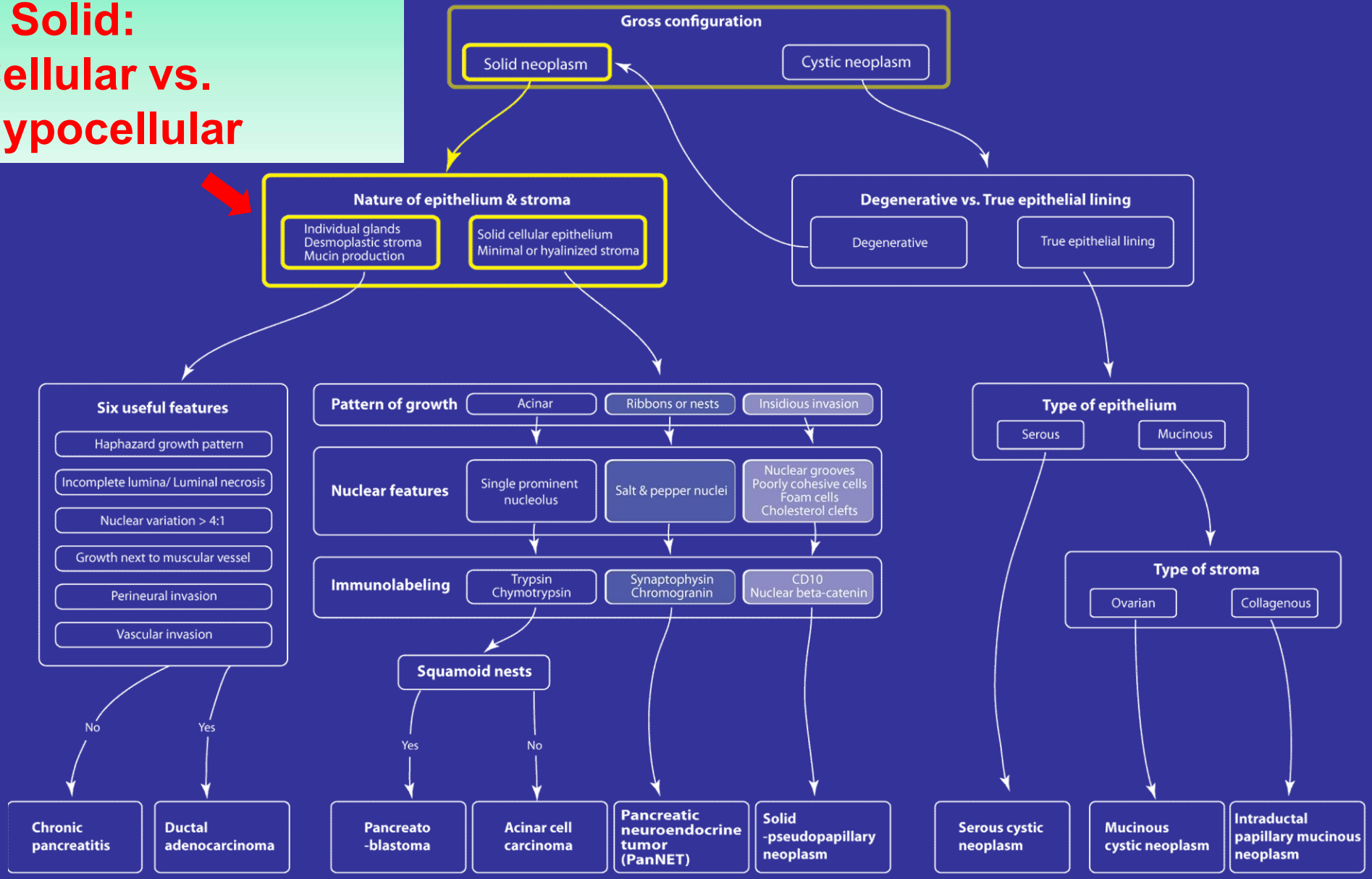



1cm





If Solid: Cellular vs. Hypocellular



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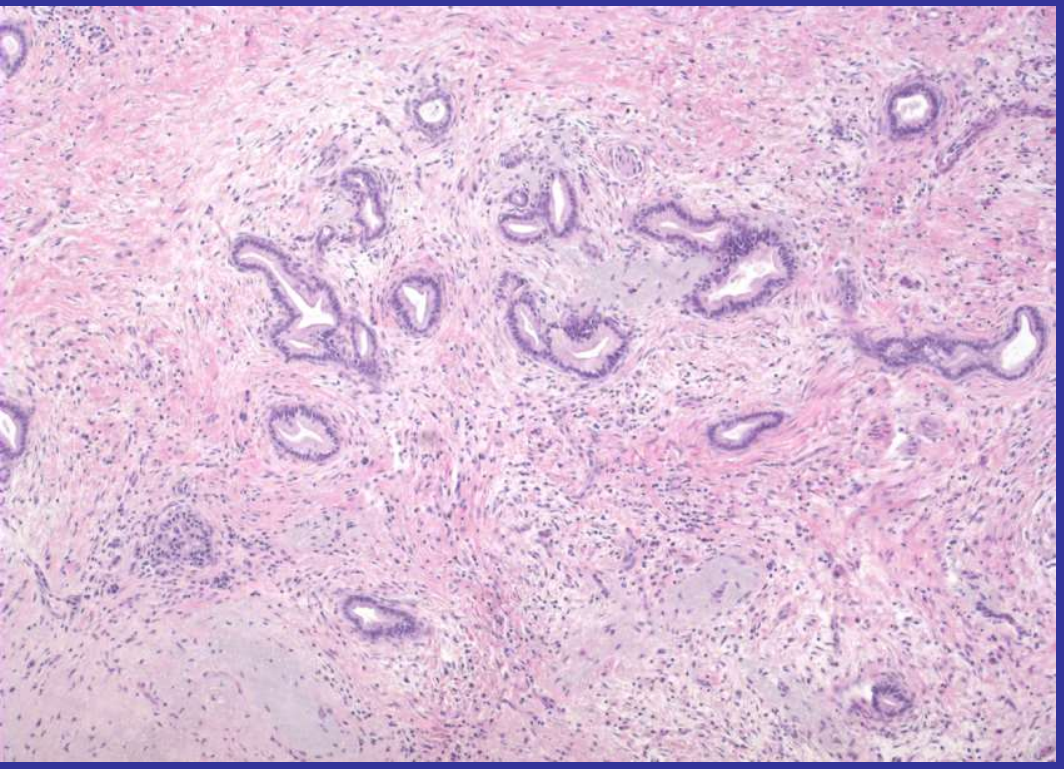
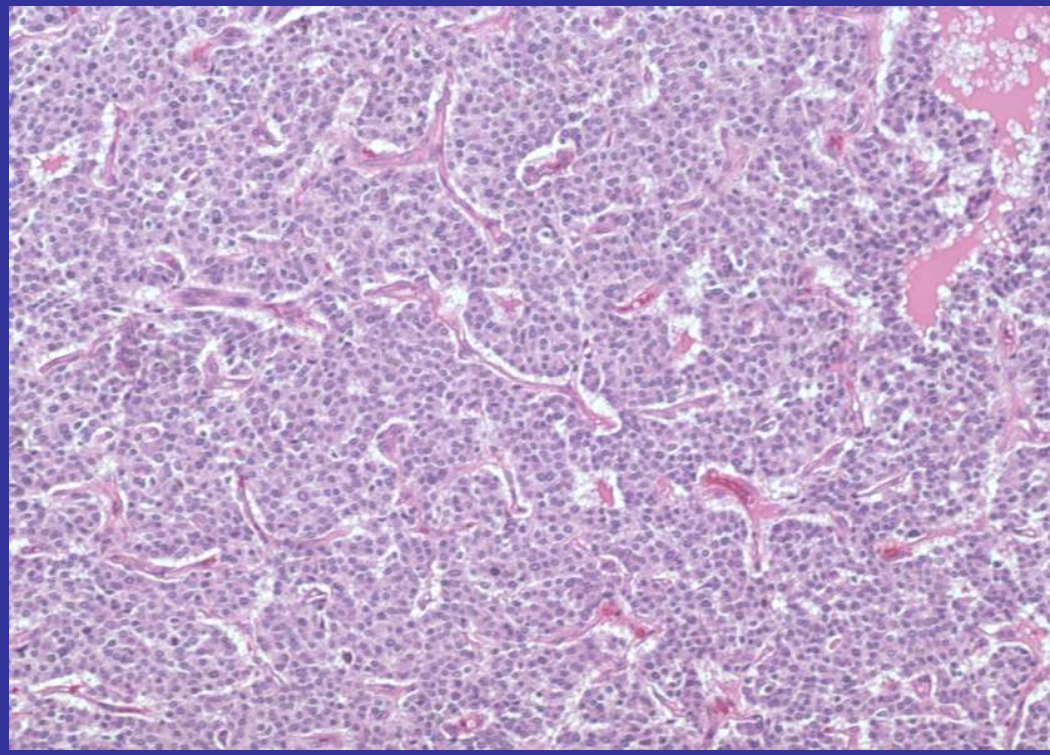
Nature of Epithelium and Stroma

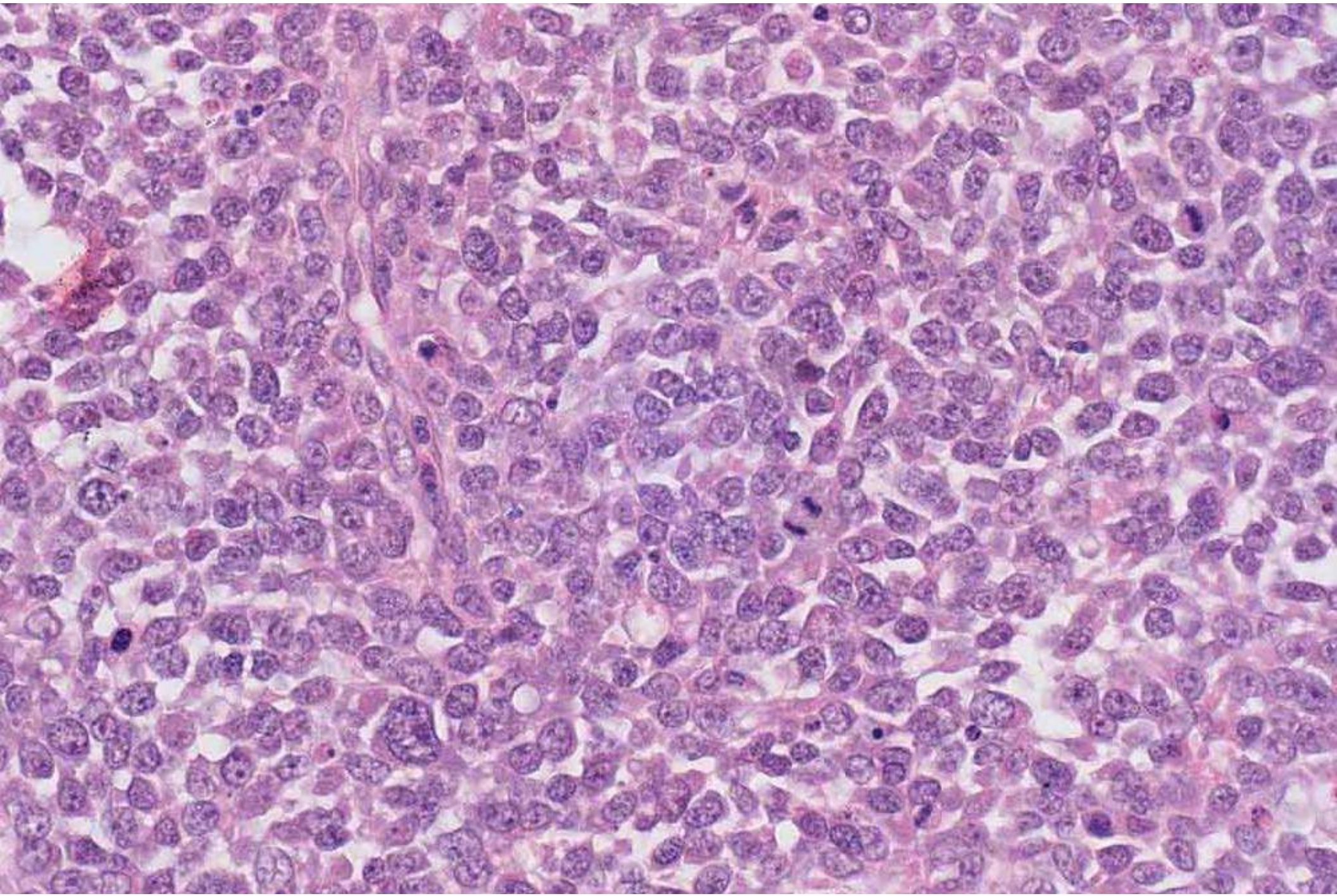
Individual glands; desmoplastic stroma; mucin production

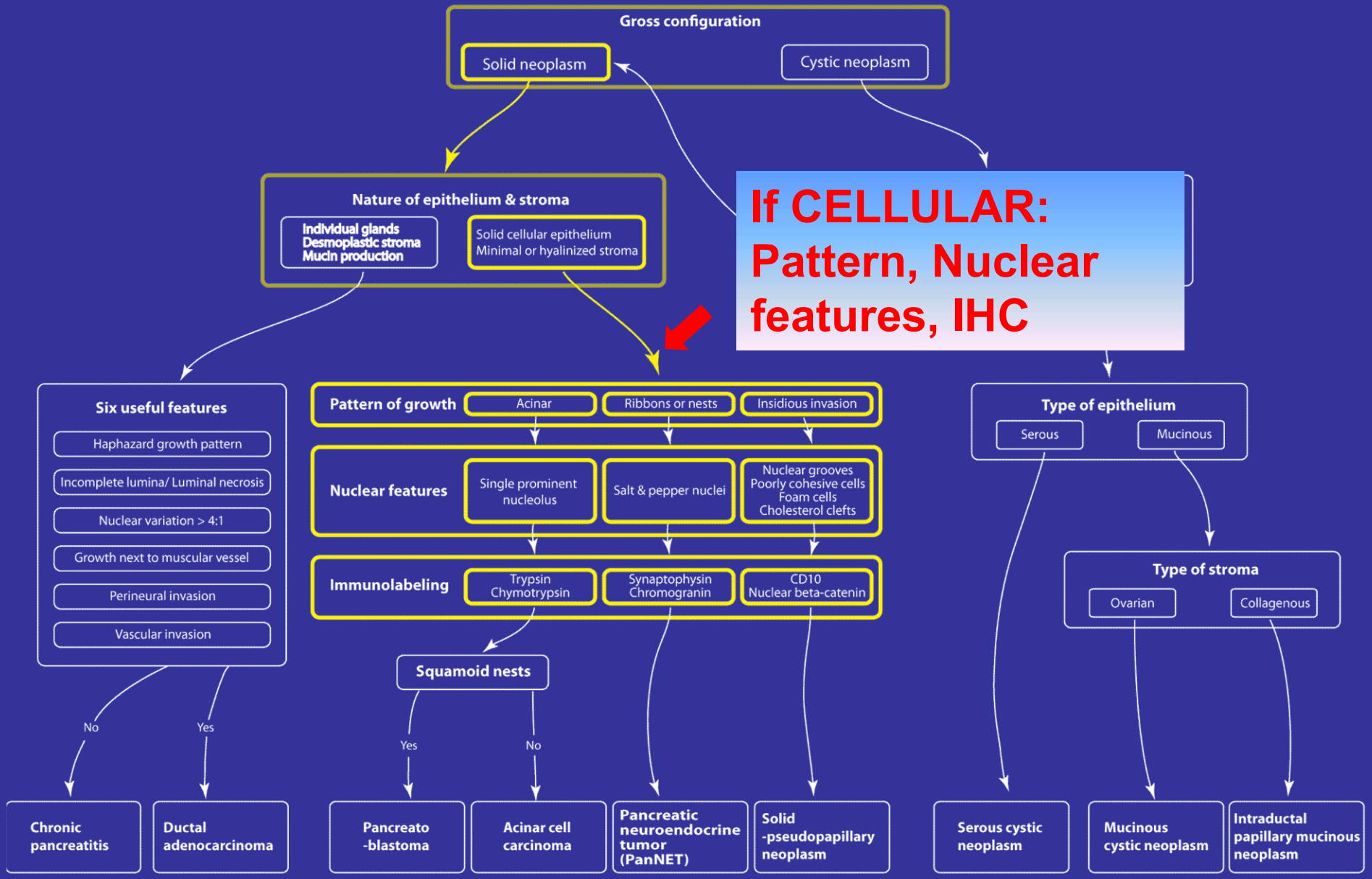


Solid, cellular epithelium; minimal or hyalinized stroma



Solid Cellular Neoplasms with Minimal Stroma

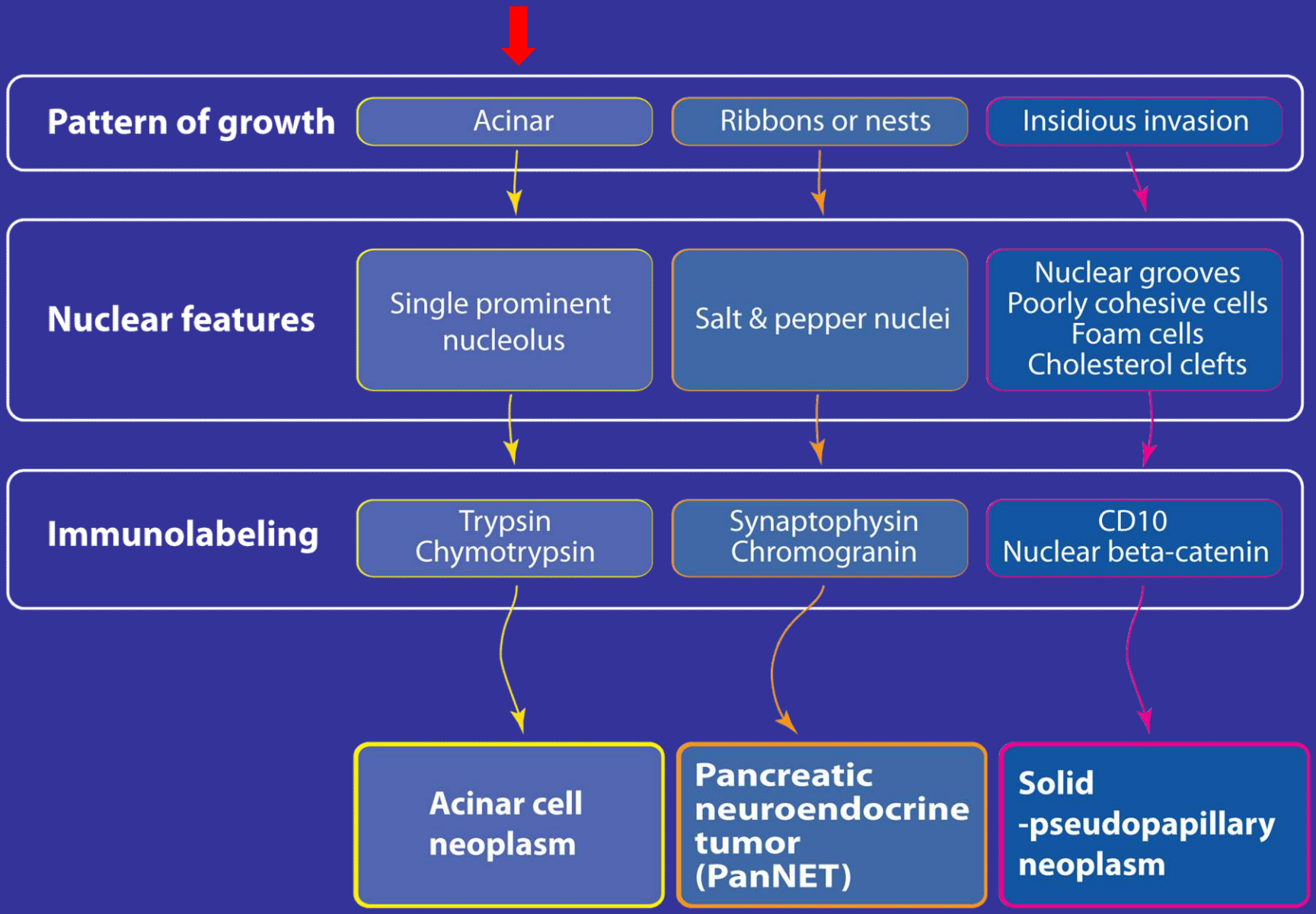




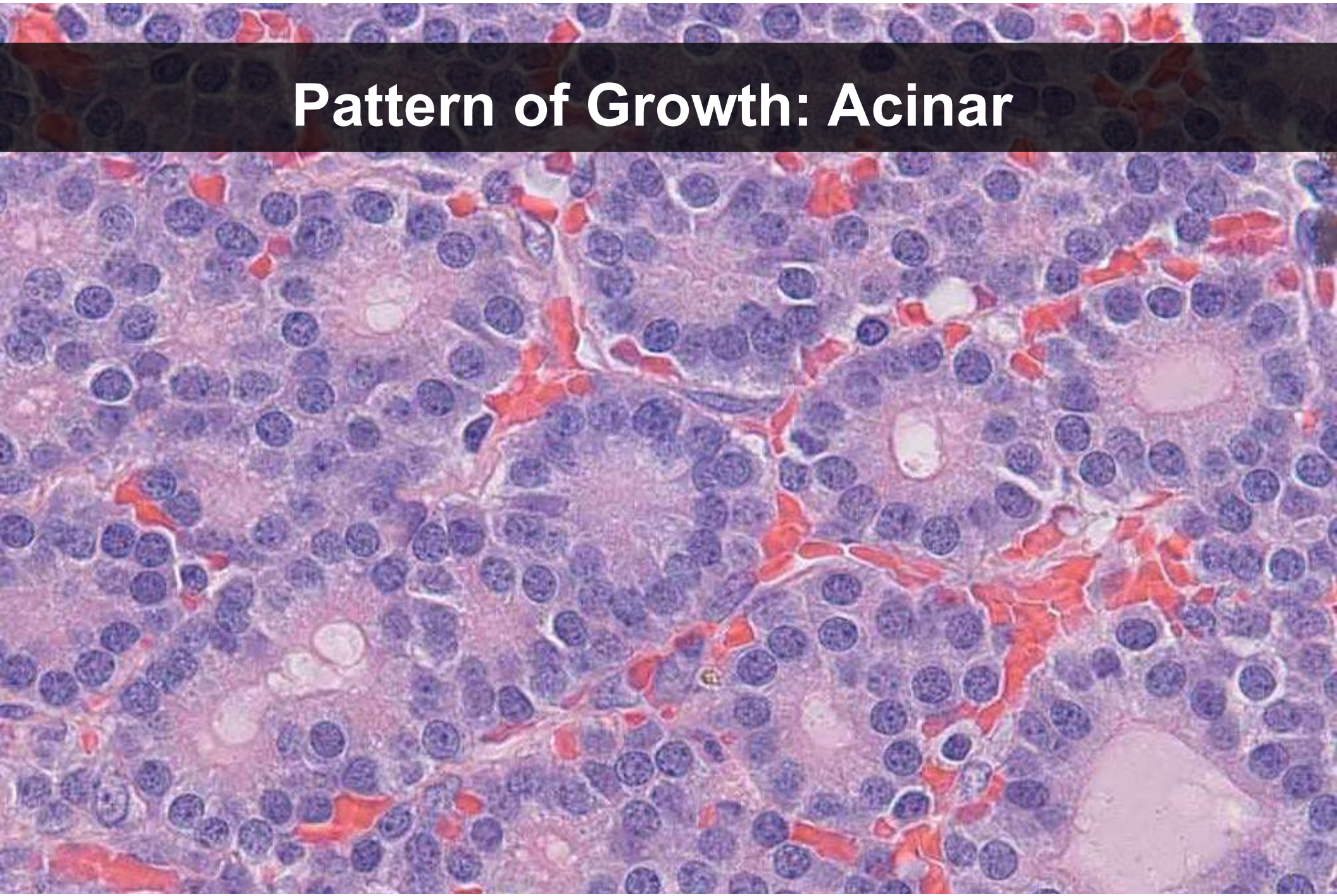
Based on AFIP Fascicle, 4th Edition

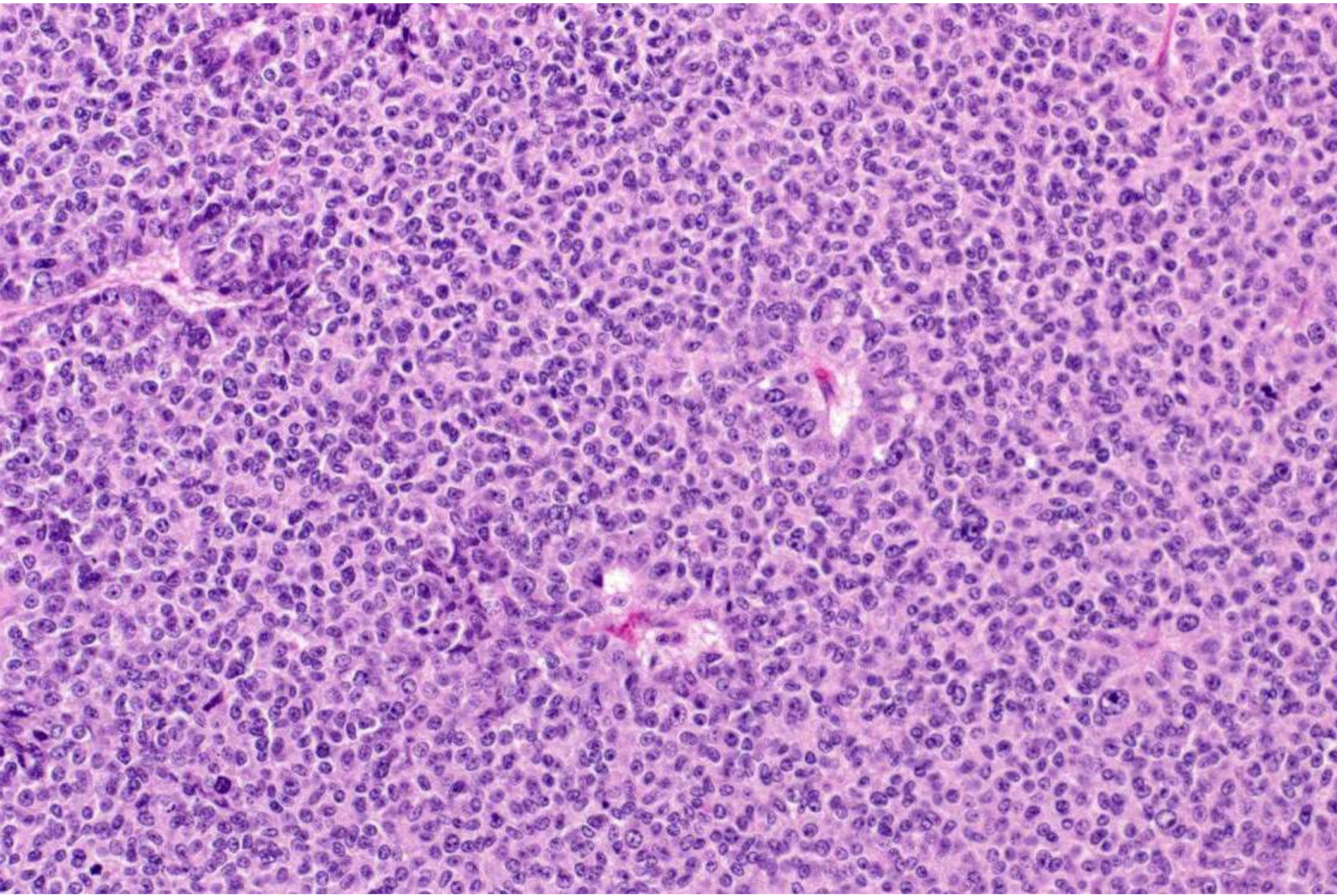
Solid, cellular epithelium; minimal or hyalinized stroma

1. Pattern of Growth
2. Nuclear Features
3. Immunolabeling


Pattern of growth
Acinar
Ribbons or nests
Insidious invasion
Nuclear features
Single prominent nucleolus
Salt & pepper nuclei
Nuclear grooves
Poorly cohesive cells
Foam cells
Cholesterol clefts
Immunolabeling
Trypsin
Chymotrypsin
Synaptophysin
Chromogranin
CD10
Nuclear beta-catenin
Acinar cell neoplasm
Pancreatic neuroendocrine tumor (PanNET)
Solid -pseudopapillary neoplasm

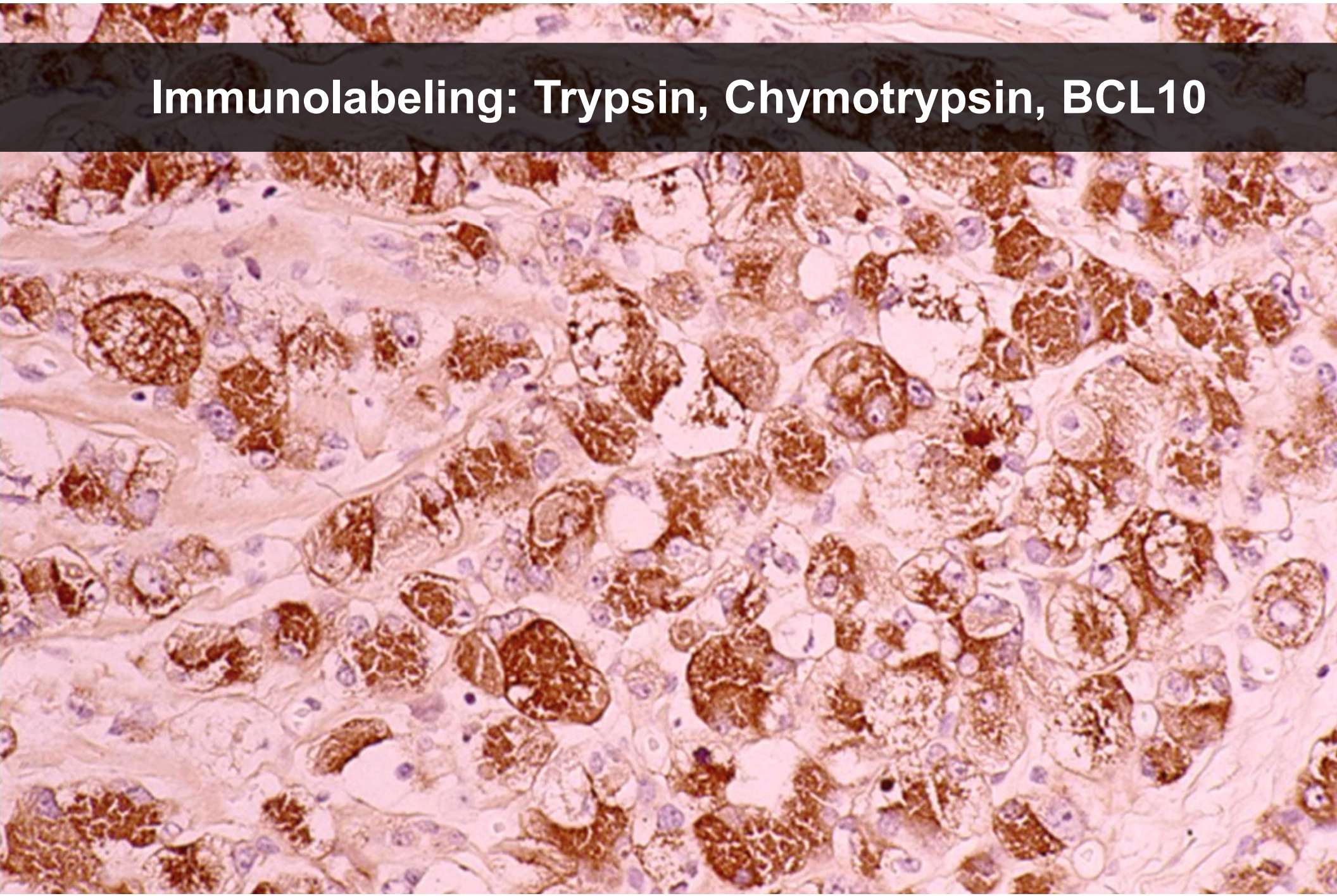
Pattern of Growth: Acinar

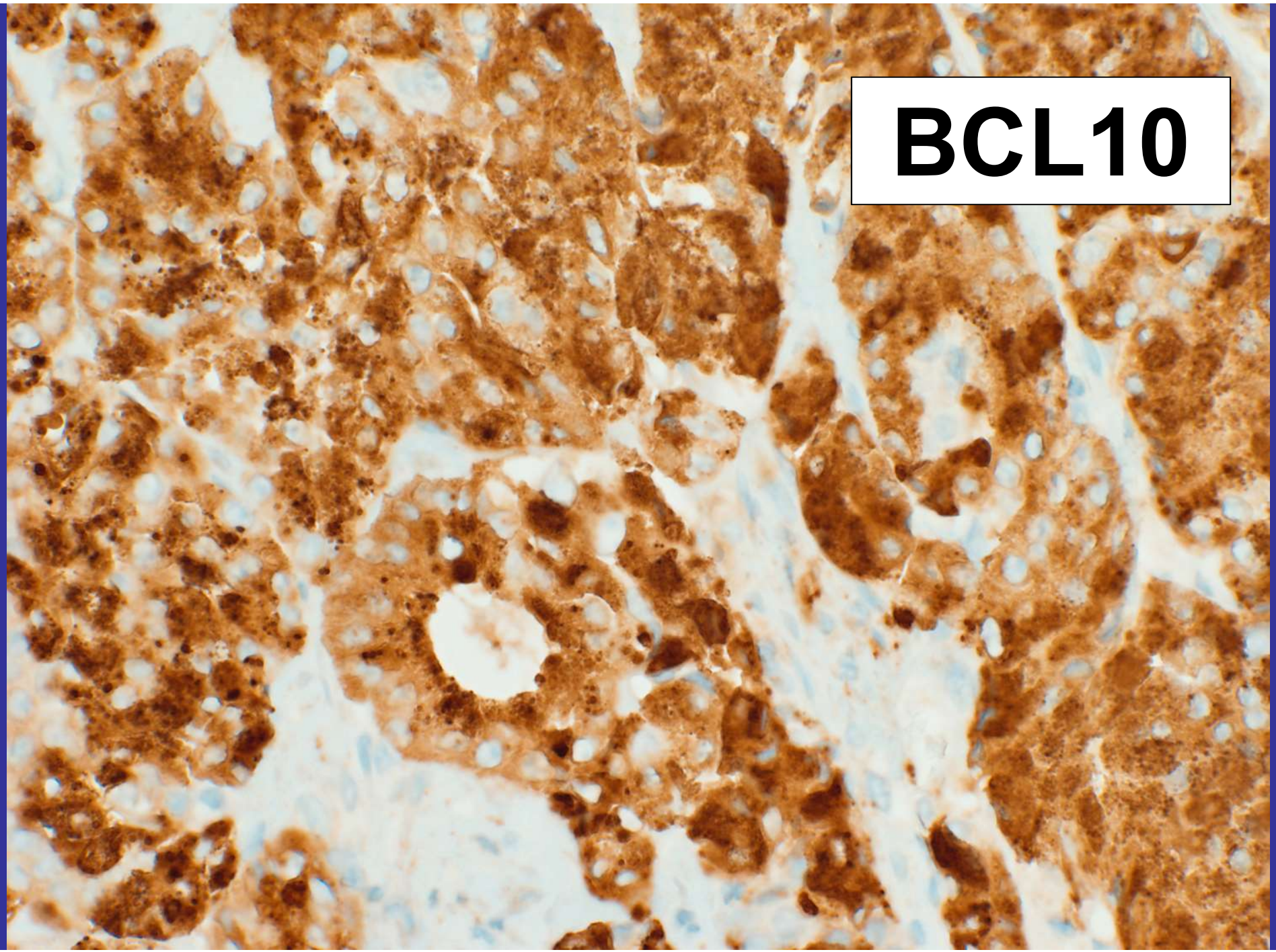


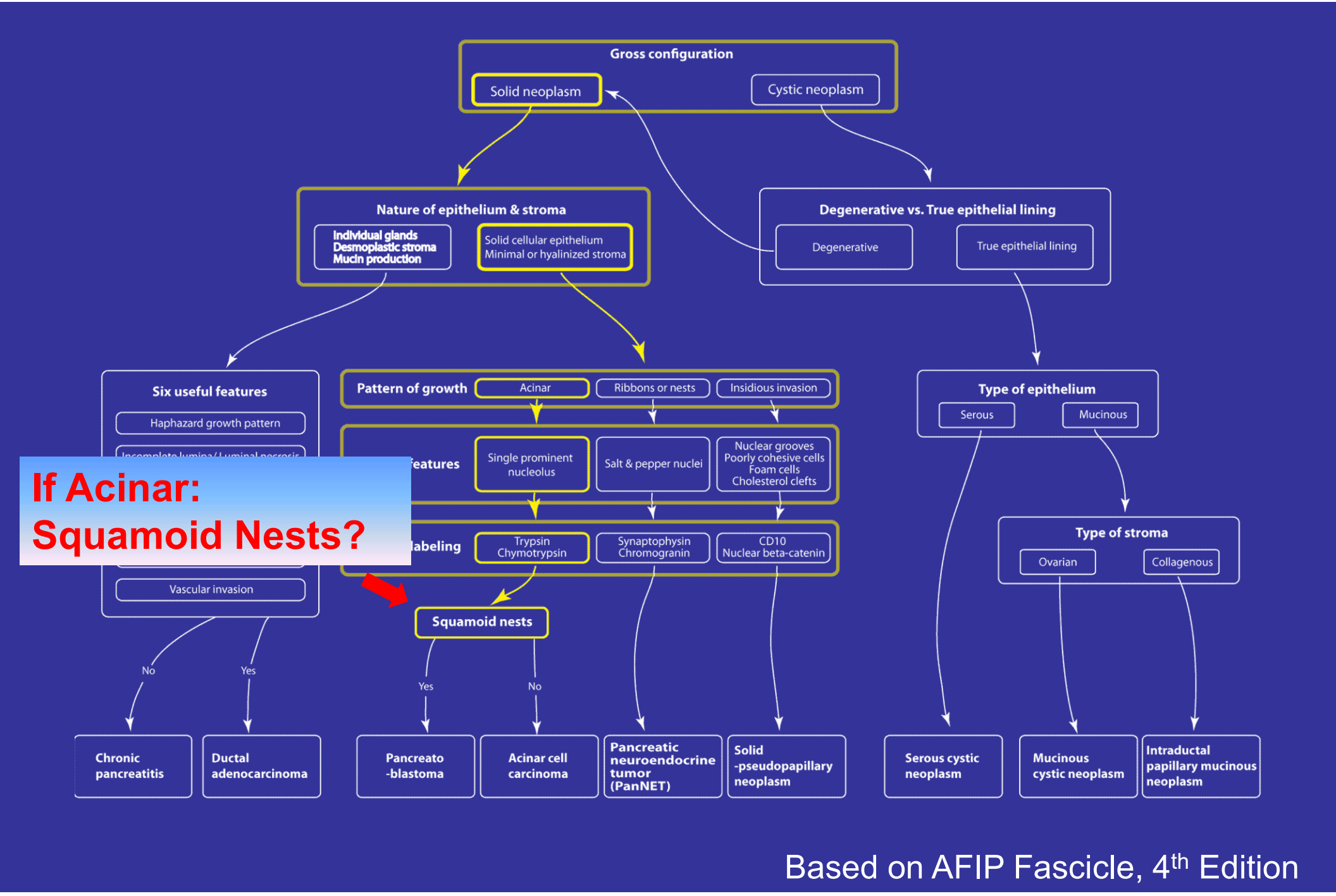


Nuclear Feature: Single Prominent Nucleoli

Immunolabeling: Trypsin, Chymotrypsin, BCL10




BCL10



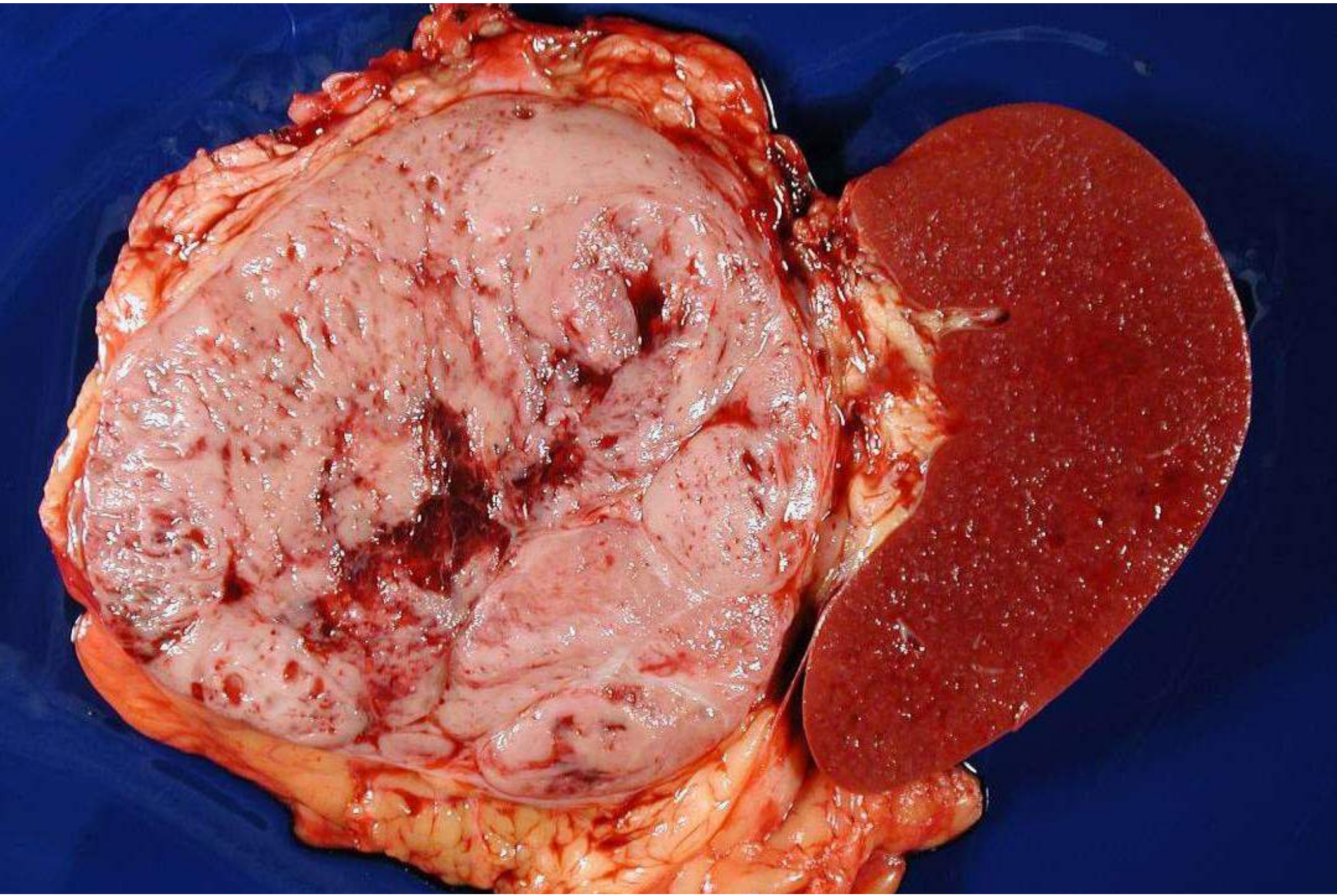
Based on AFIP Fascicle, 4th Edition

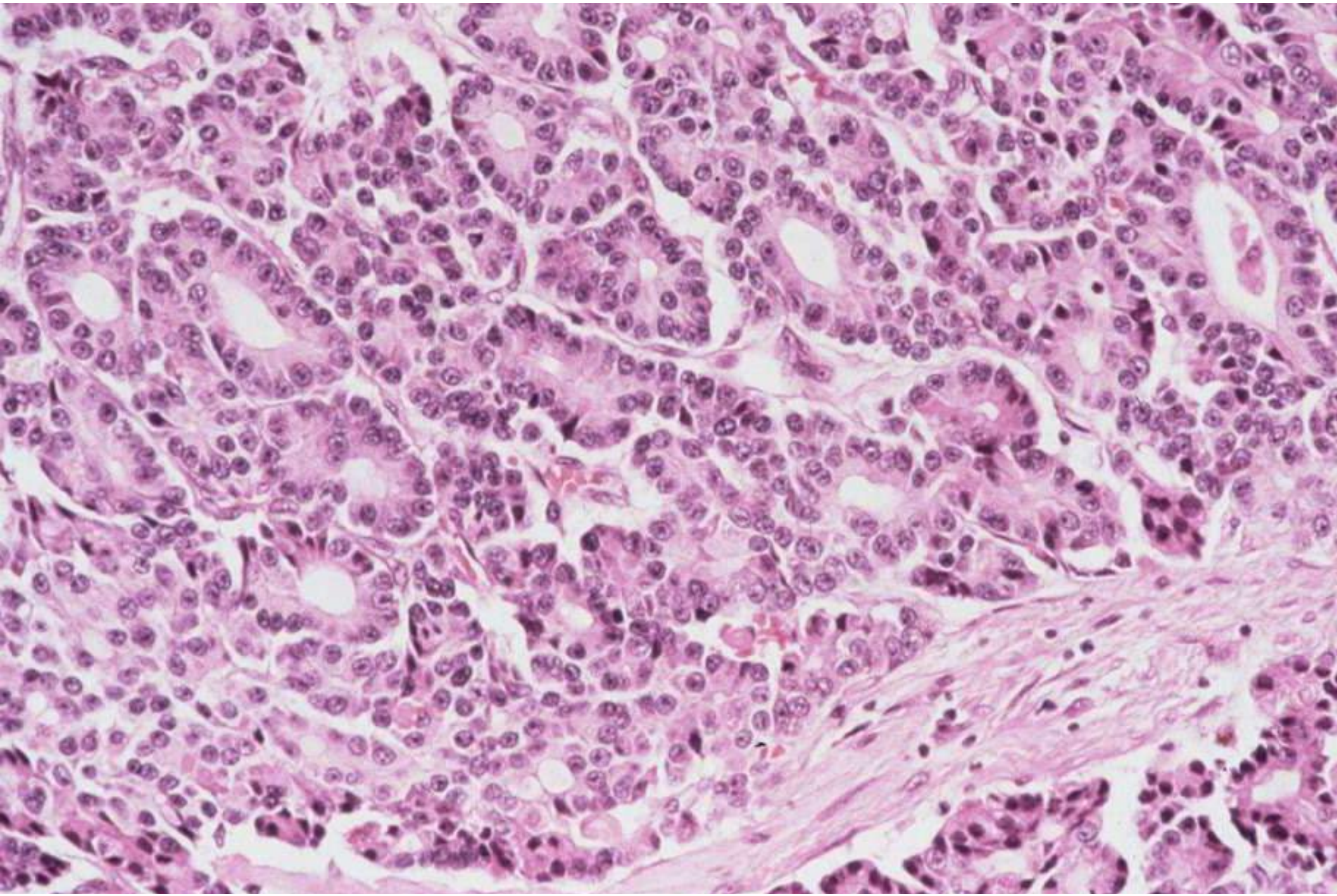
Acinar Cell Carcinoma

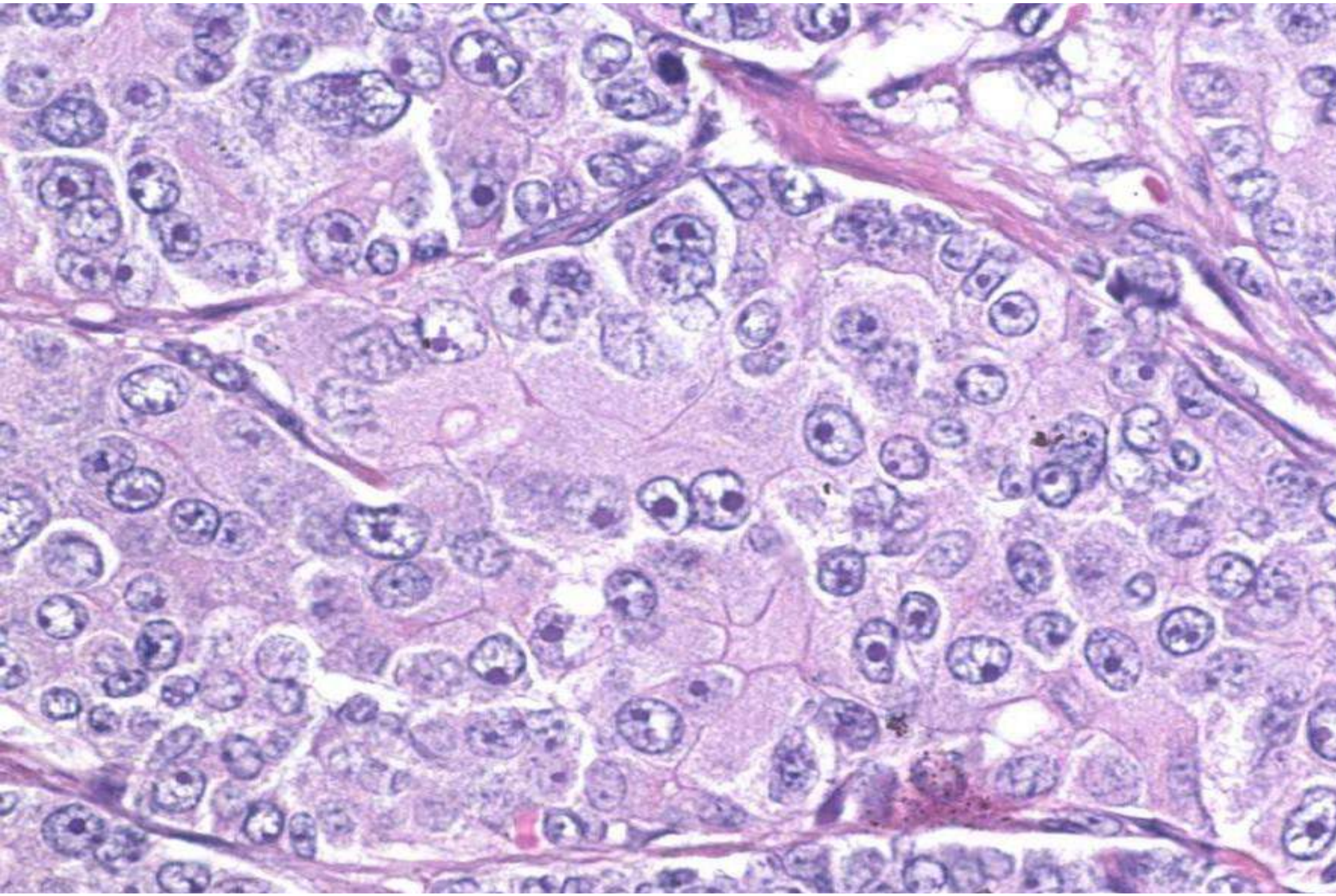
Squamoid Nests Absent

Acinar Cell Carcinomas Clinical

- Age – mostly adults (mean 62 years)
- Gender – male > female
- Symptoms – usually non-specific with weight-loss, abdominal pain, and nausea and vomiting
- Lipase – about 15% develop the syndrome of arthralgias, eosinophilia and subcutaneous fat necrosis





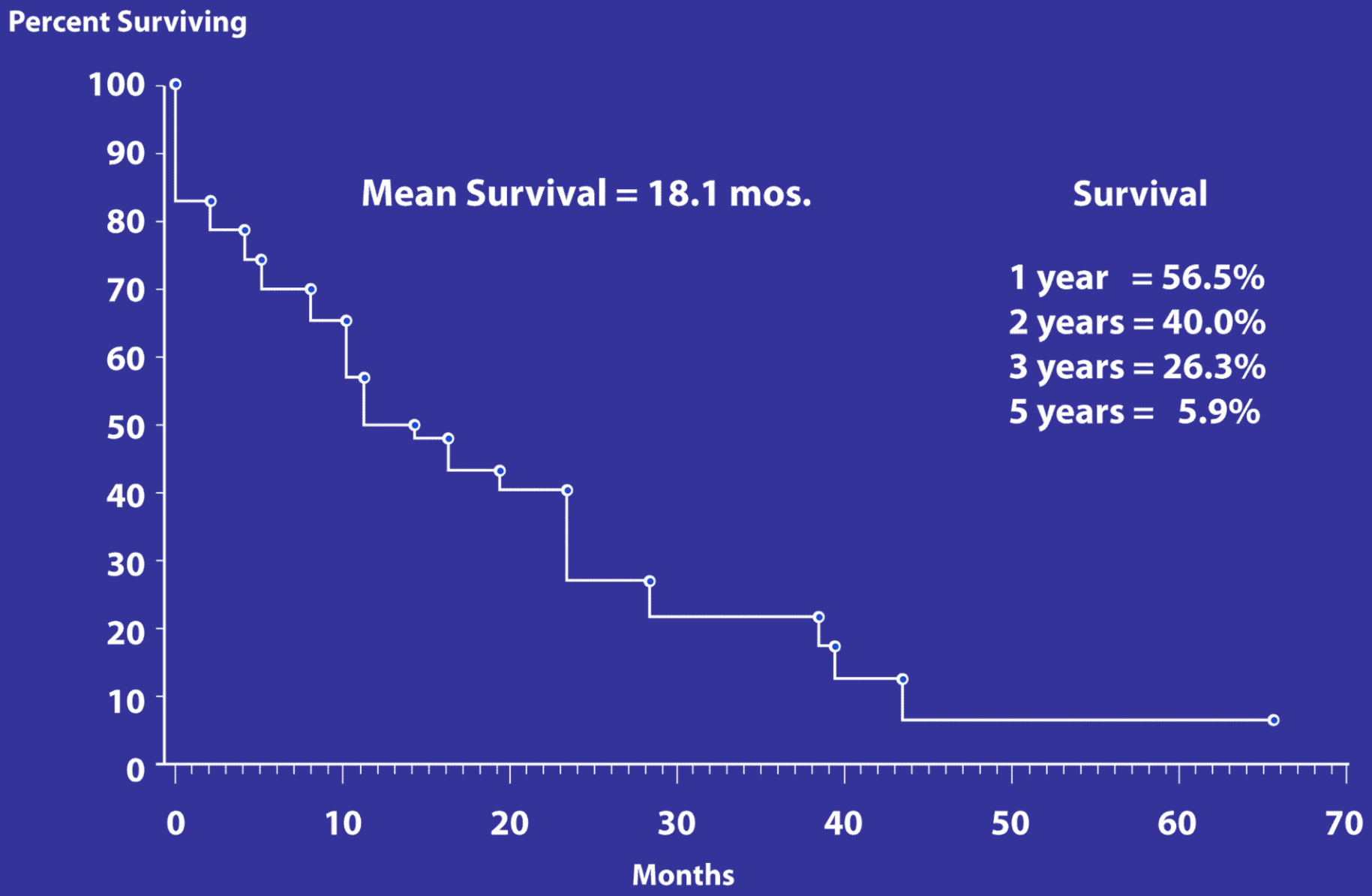


Acinar Cell Carcinoma Staining

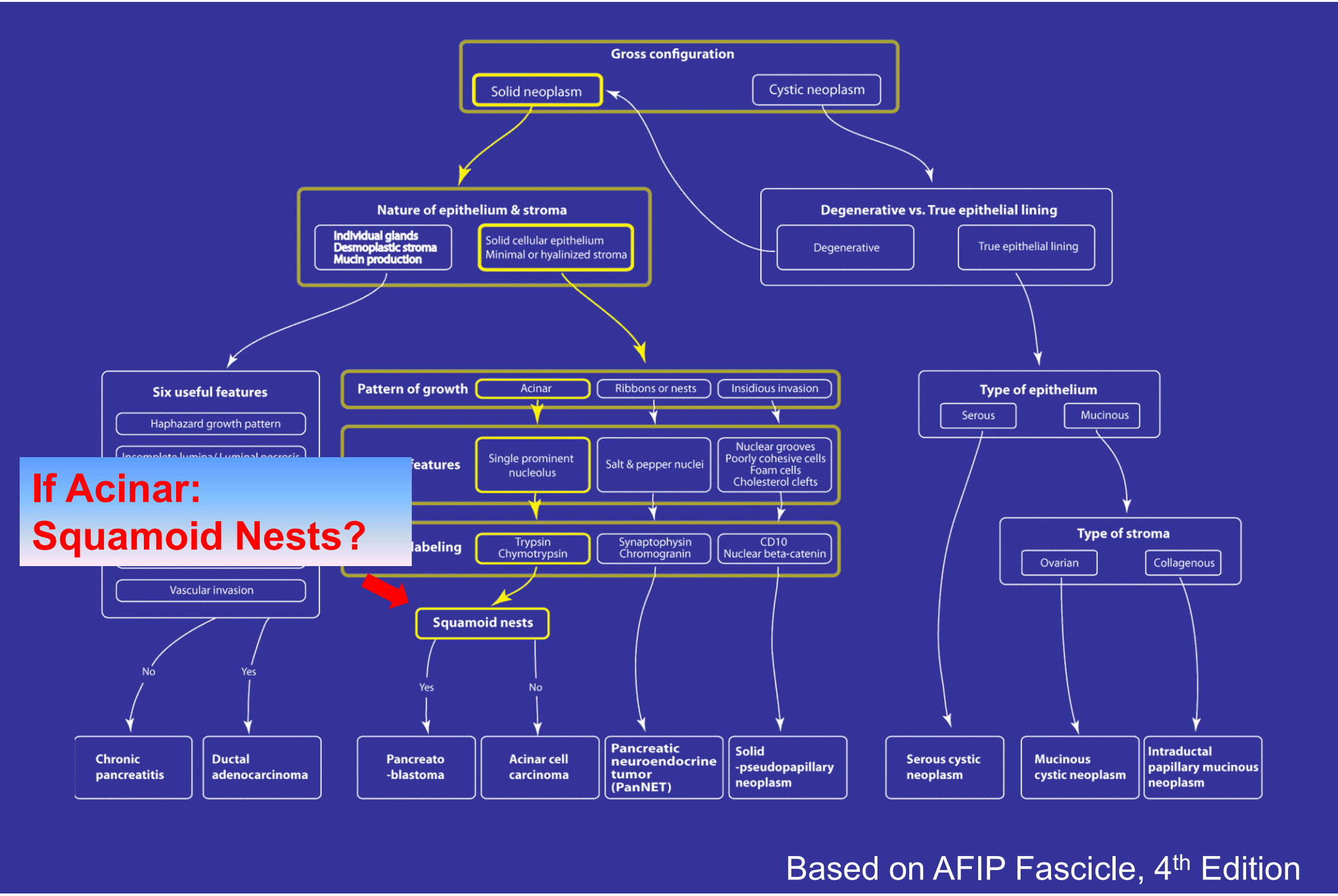
- PASD – highlights apical granules
- Mucicarmine – negative
- Immunohistochemistry –

90-100%	Bcl10
90-100%	trypsin
75%	lipase
40%	chymotrypsin
30%	amylase
42%	minor neuroendocrine

Klimstra, Am J Surg Pathol, 1992

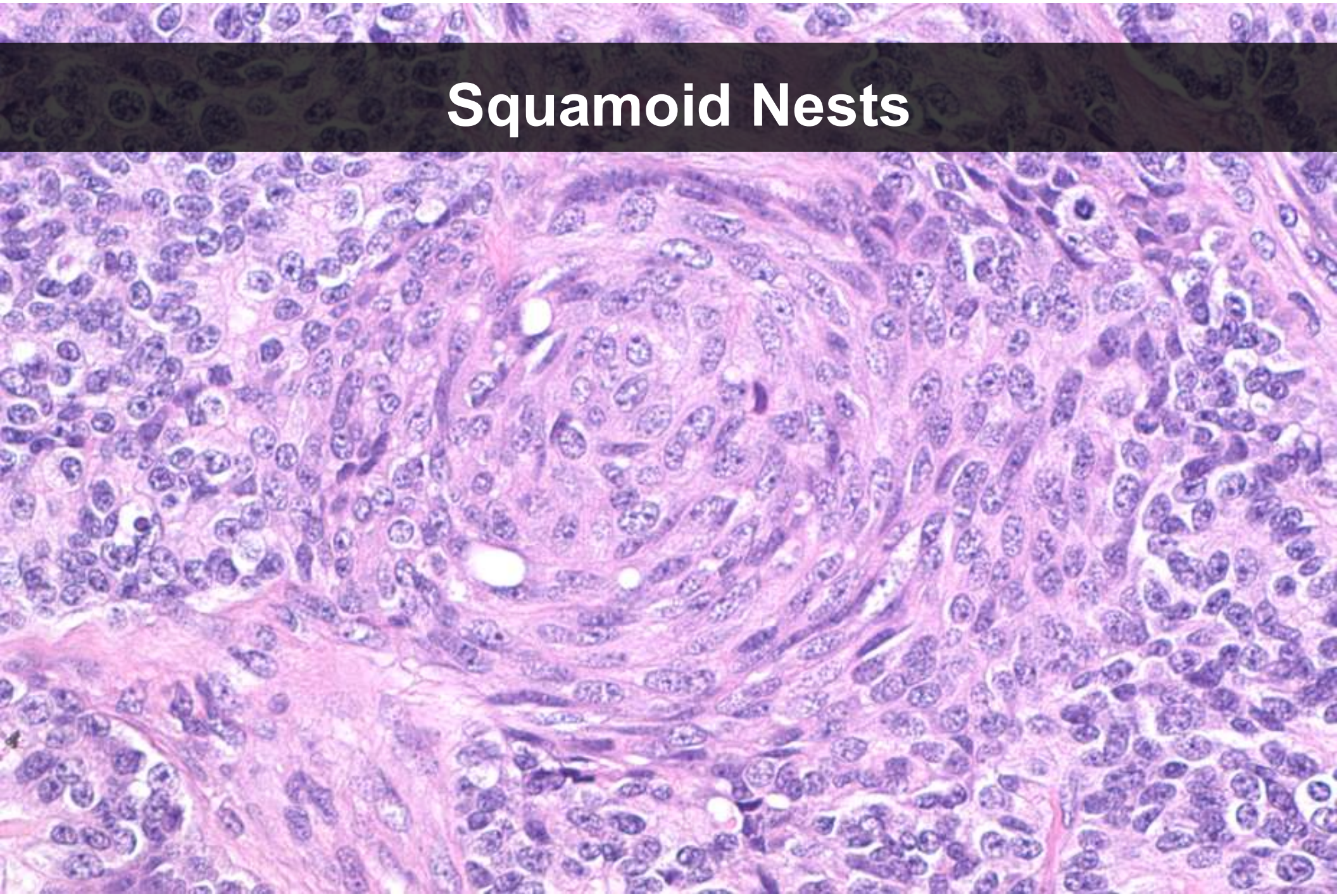


Klimstra et al, Am J Surg Pathol



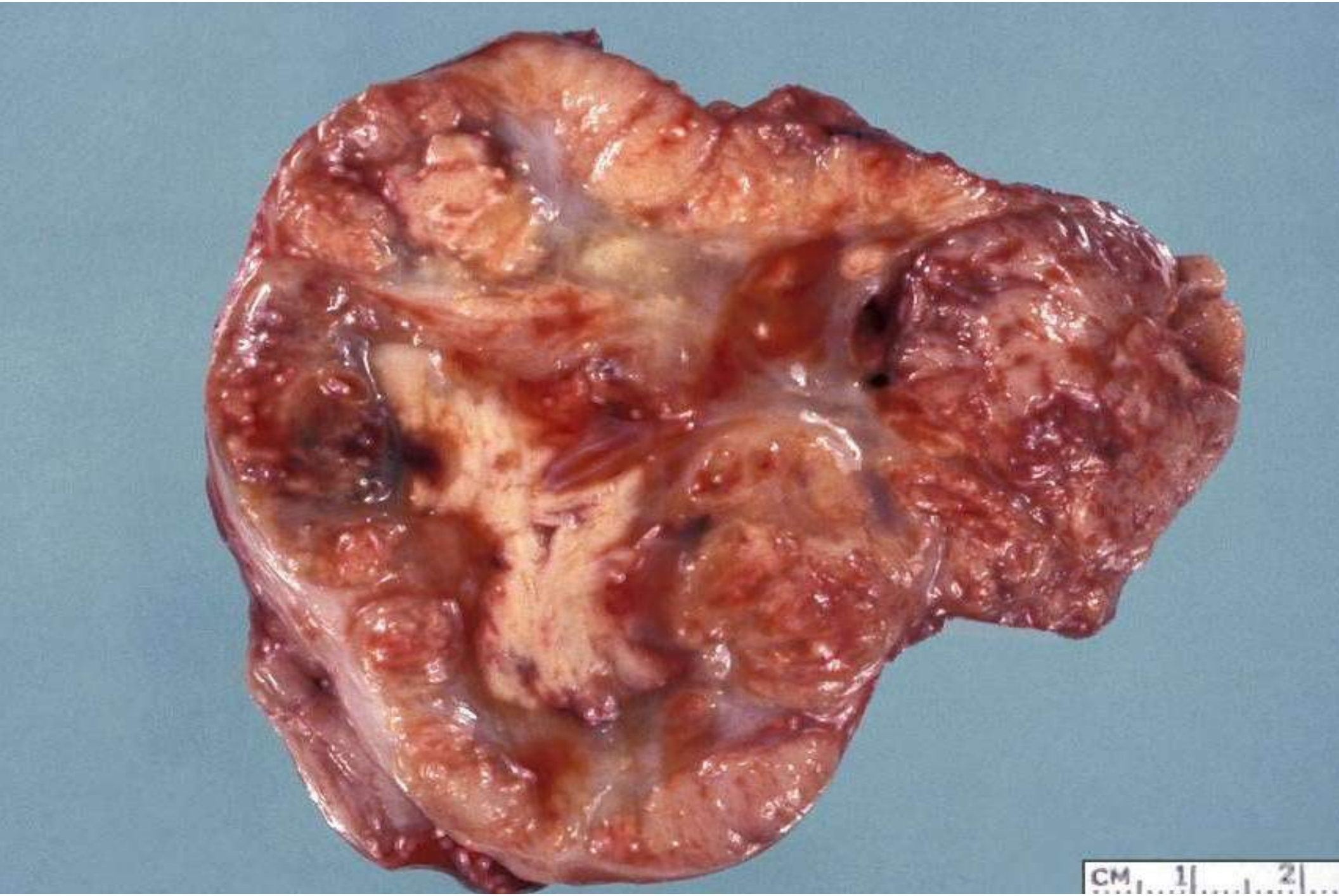
Based on AFIP Fascicle, 4th Edition

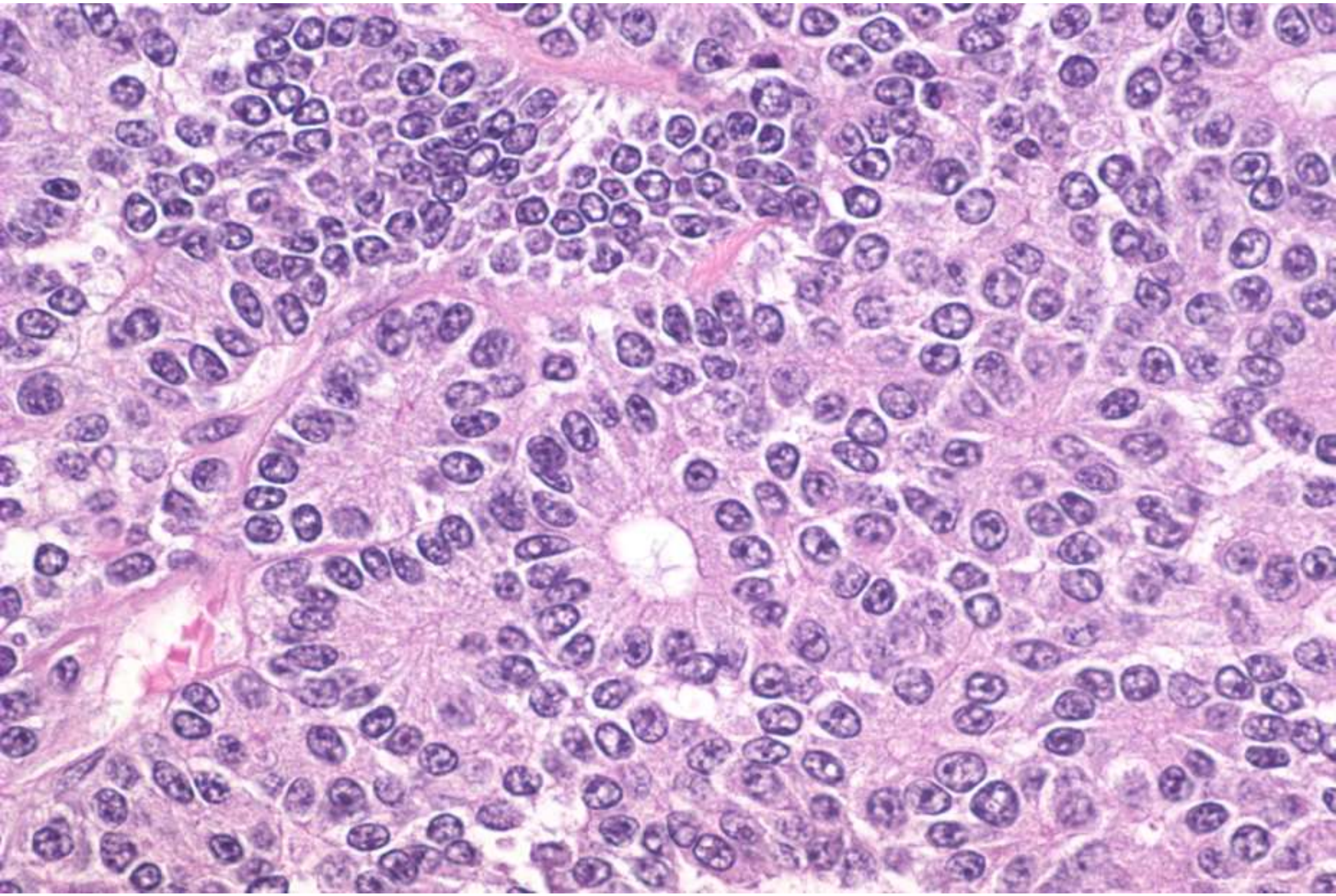
Squamoid Nests

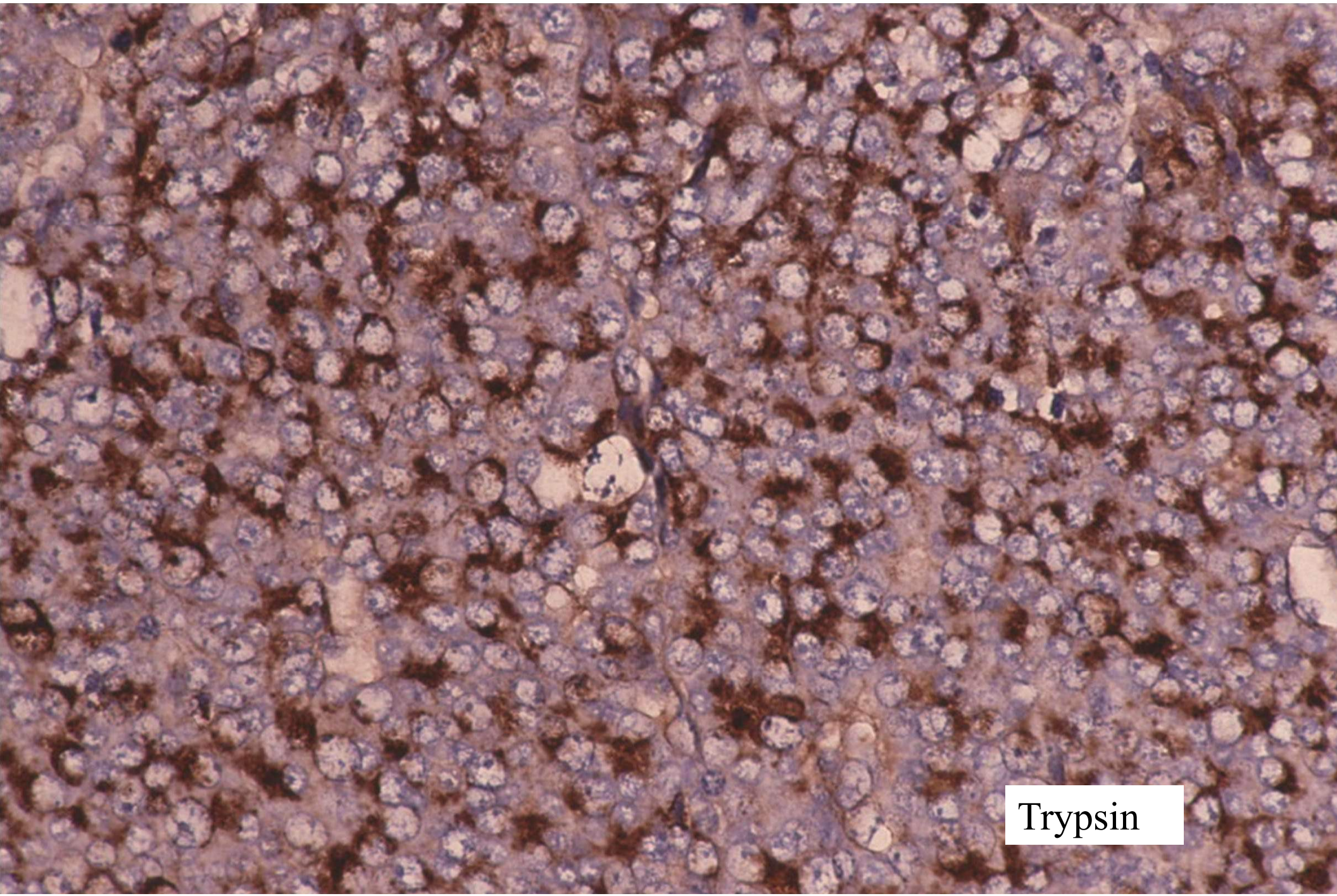


Pancreatoblastoma

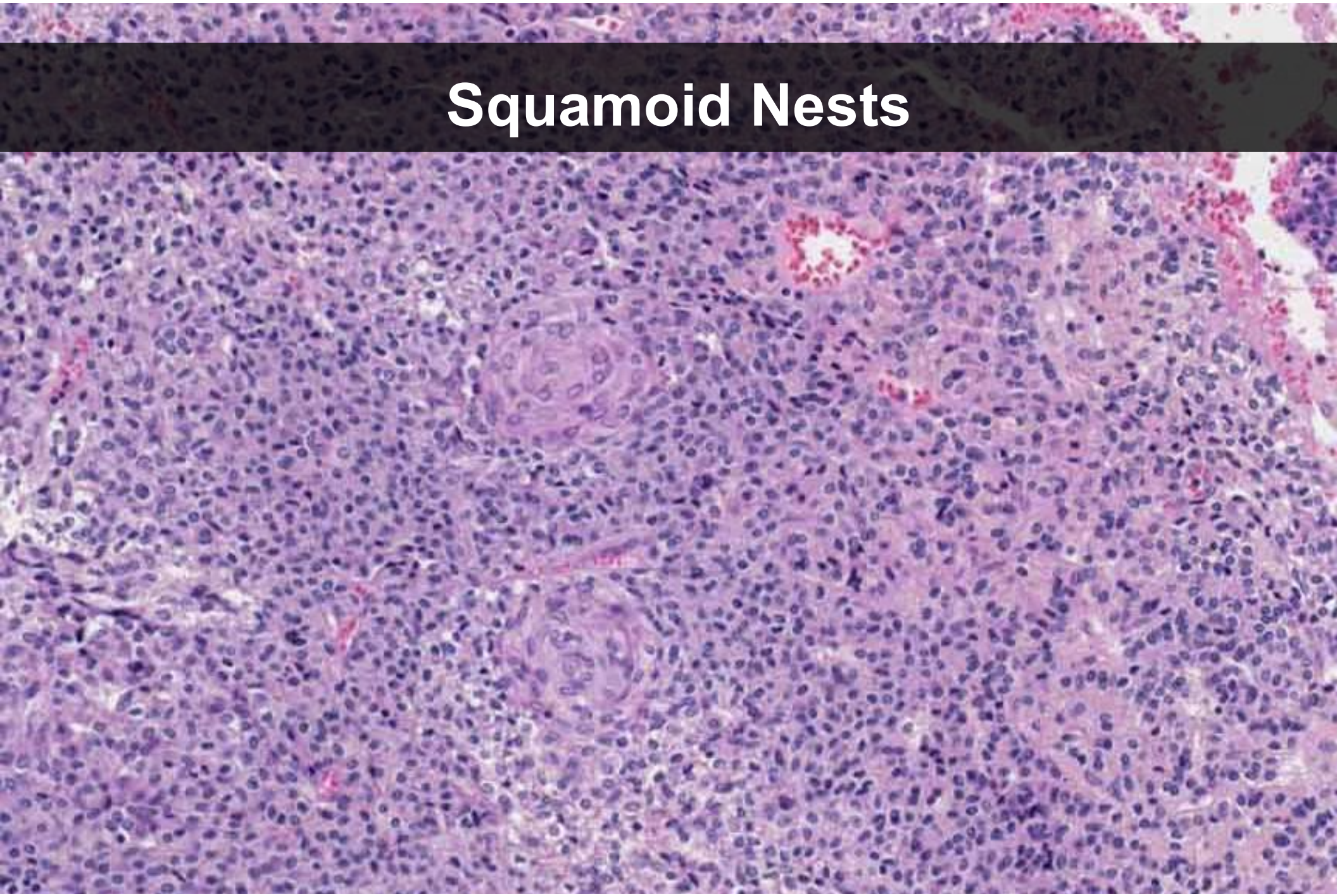
- Occurs primarily in children (1-15 years)
- Undifferentiated component – back to back small cells with a syncytial pattern
- Differentiated component – squamous, acinar, neuroendocrine
- Survival better than for ductal adenocarcinoma


CM
1
2




Trypsin

Squamoid Nests



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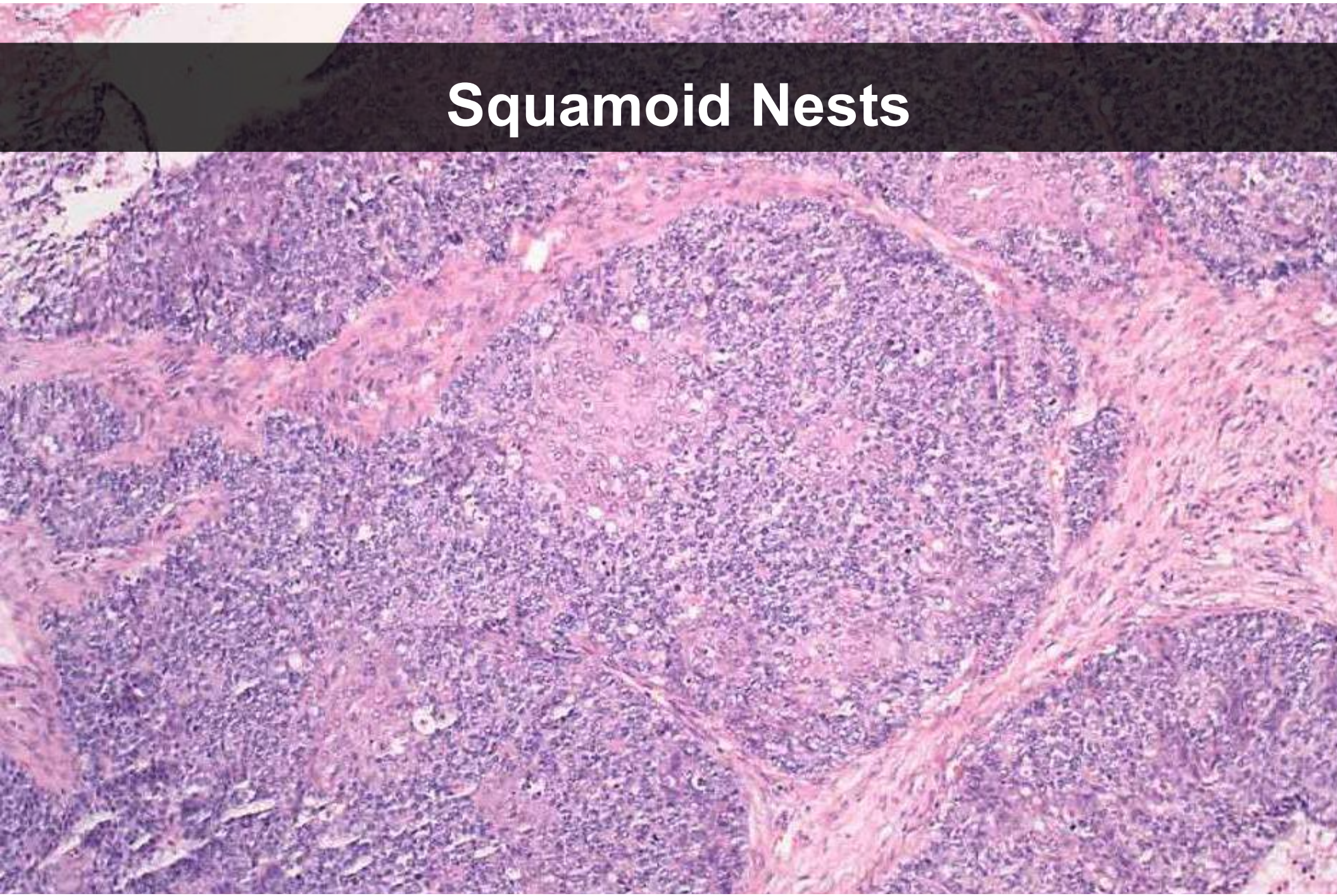

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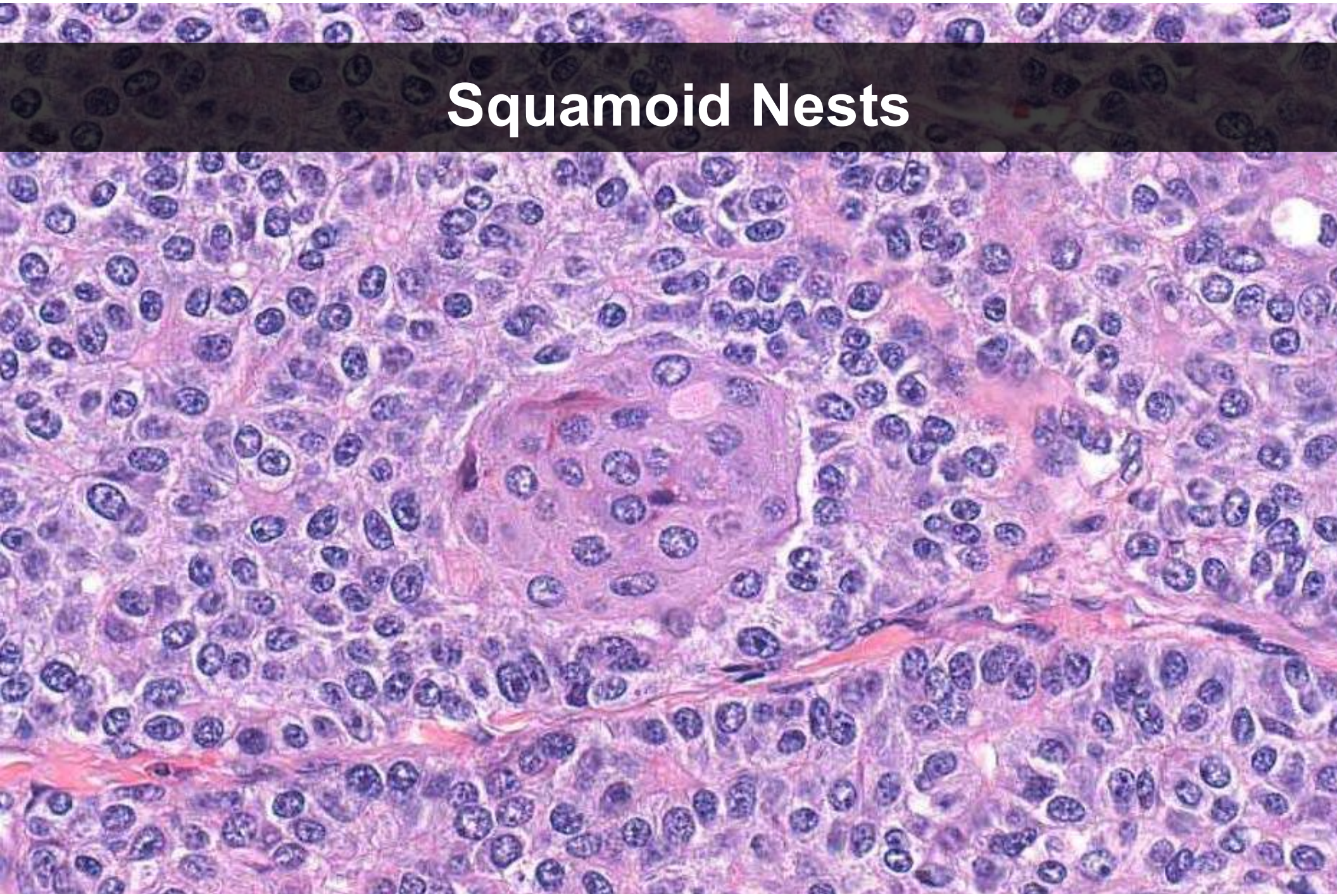
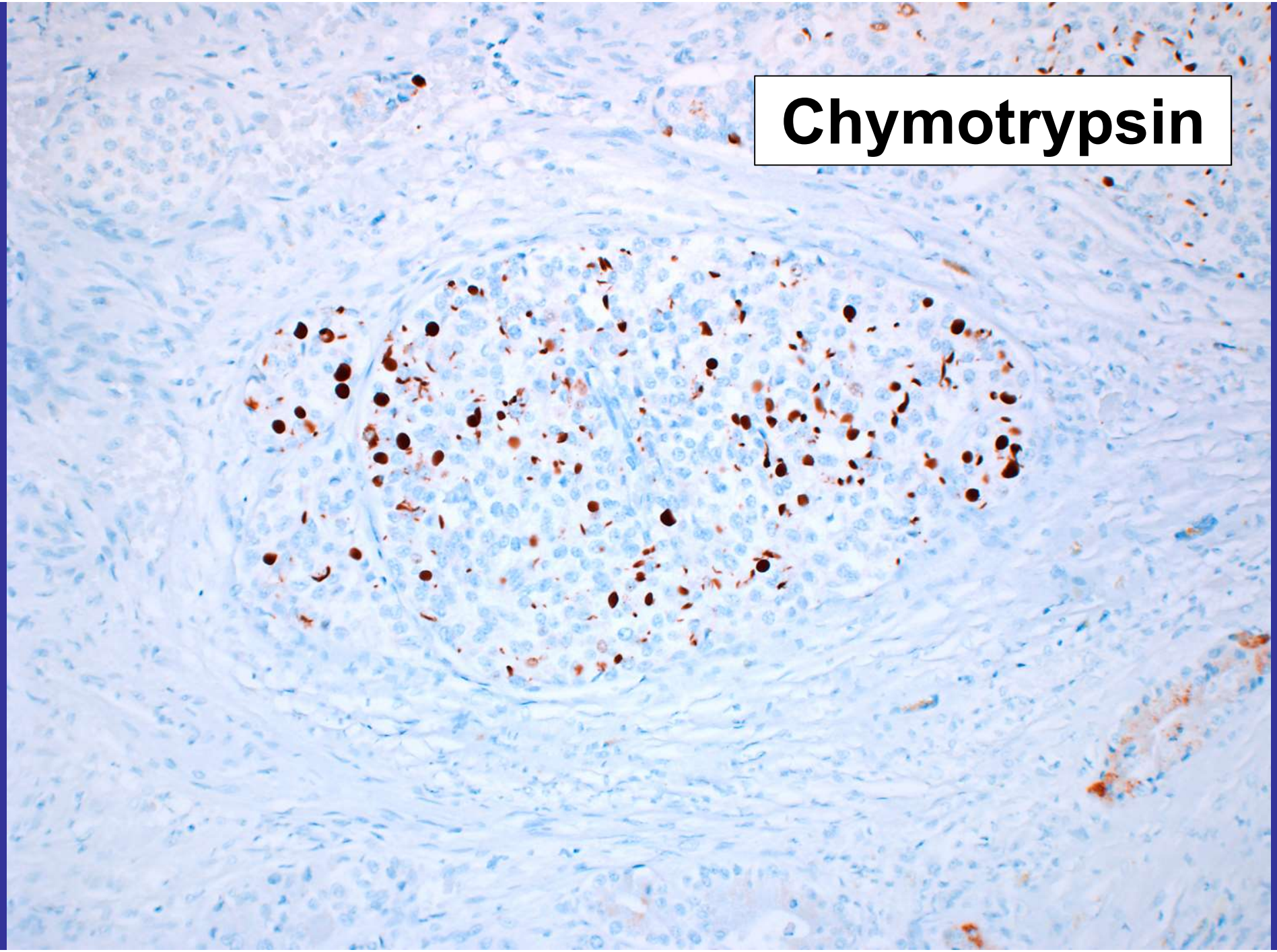
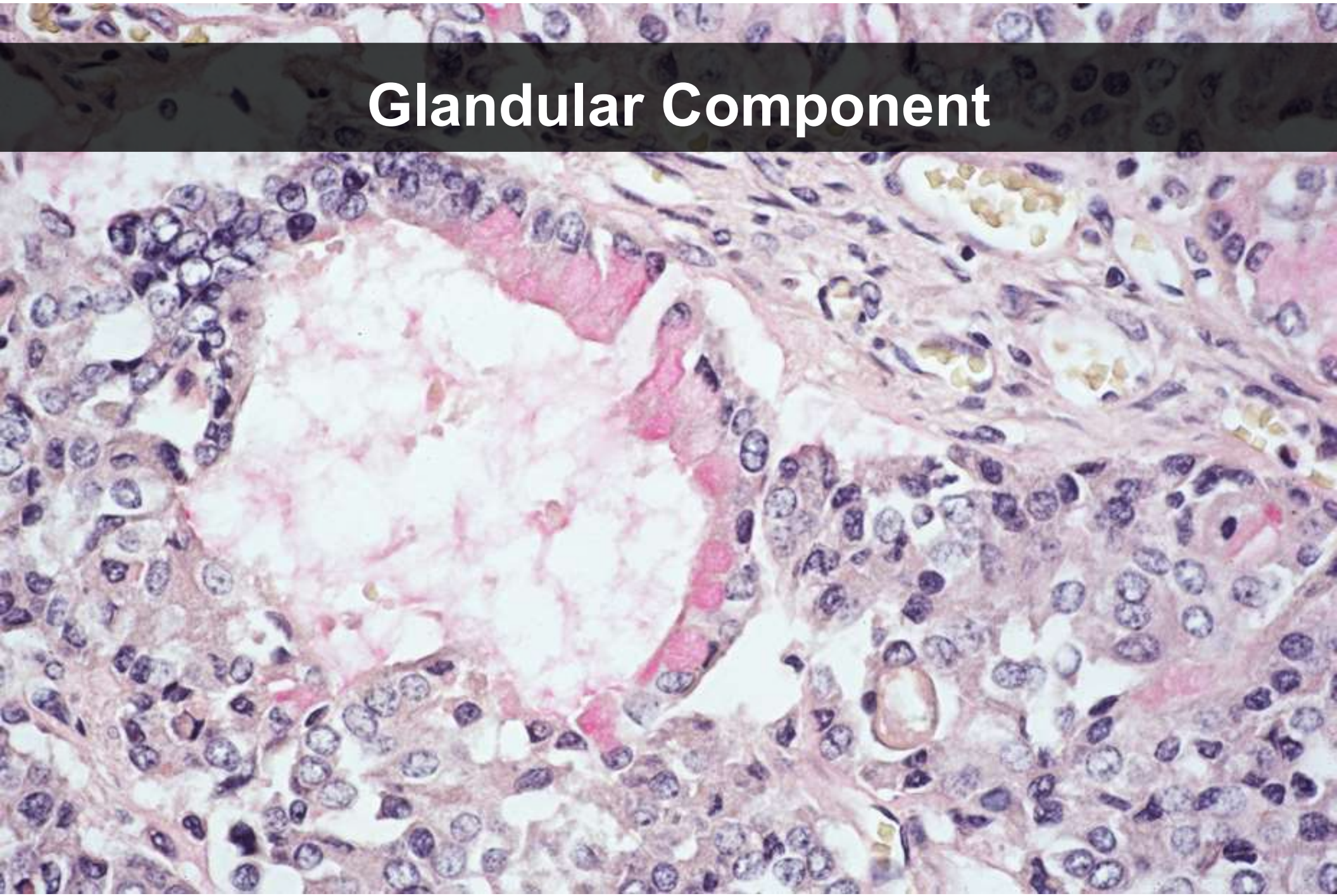
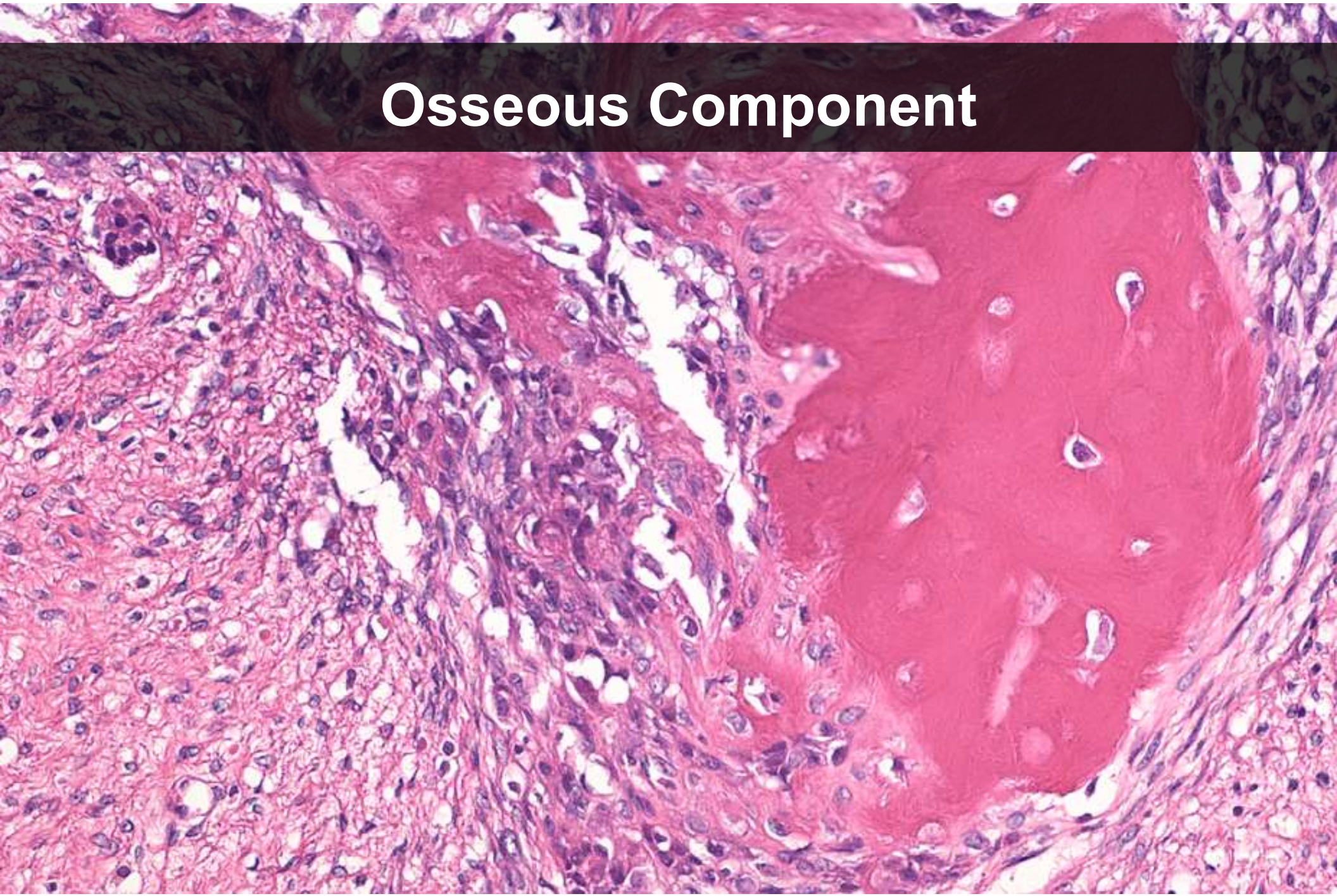



Chymotrypsin

Glandular Component



Osseous Component



Genetic Alteration in Pancreatoblastomas

- Associated with Beckwith-Wiedemann Syndrome
- 86% LOH on 11p*
- 56% β-catenin mutations
- 22% loss of *DPC4*
- 11% *APC* (Germline)
- 0% K-*ras*, *p53*

* Similar to other infantile embryonal tumors such as hepatoblastomas

Am J Pathol 159:1619

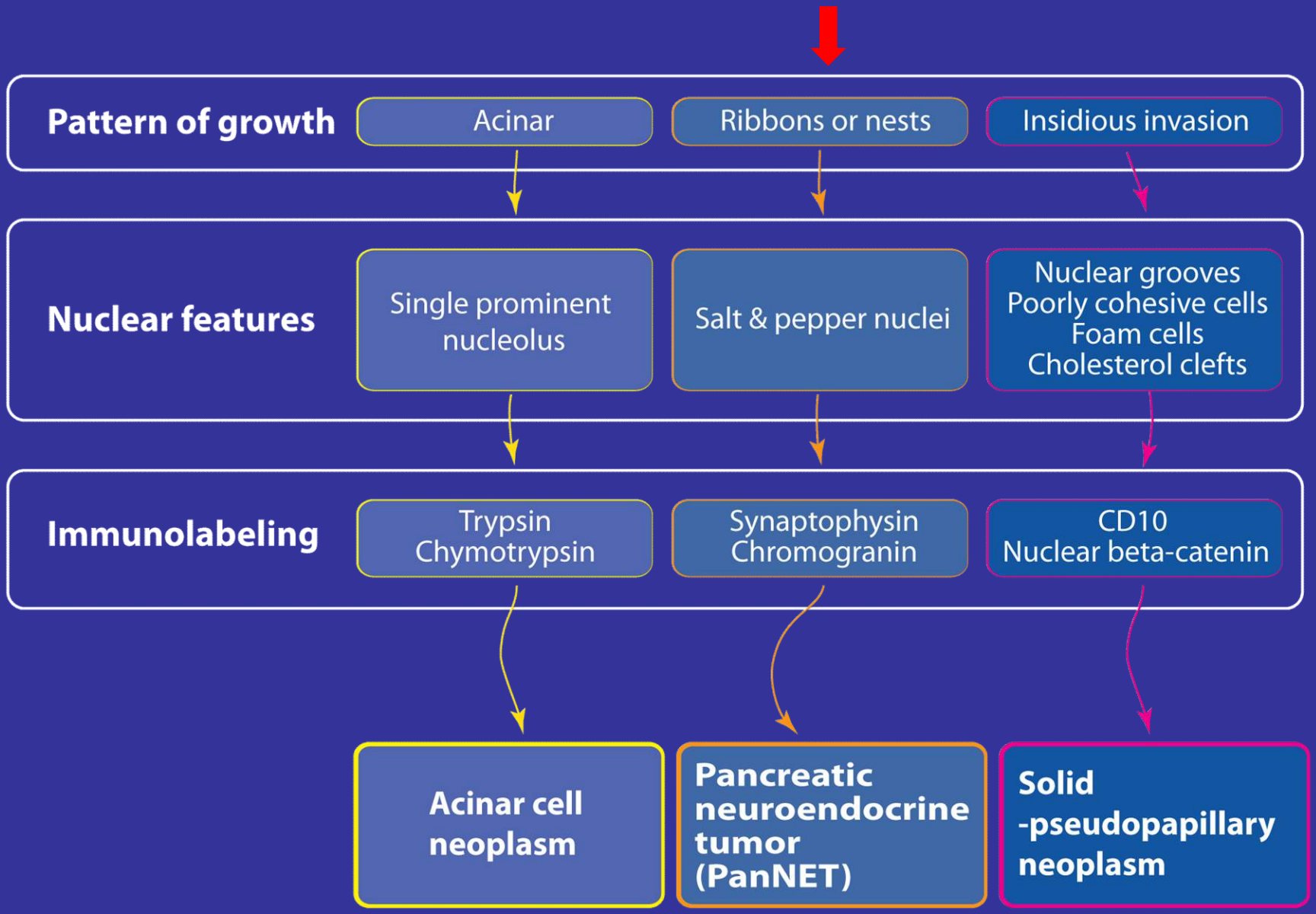
Pancreatoblastoma

- Fully malignant neoplasms
- 40% present with metastases
- Mean survival of 17 months
- Poorer survival in adults

Am J Surg Pathol 19:1371

Pancreatoblastoma vs. Acinar Cell Carcinoma

Squamoid Nests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Ribbons or nests
Insidious invasion
Nuclear features
Single prominent nucleolus
Salt & pepper nuclei
Nuclear grooves
Poorly cohesive cells
Foam cells
Cholesterol clefts
Immunolabeling
Trypsin
Chymotrypsin
Synaptophysin
Chromogranin
CD10
Nuclear beta-catenin
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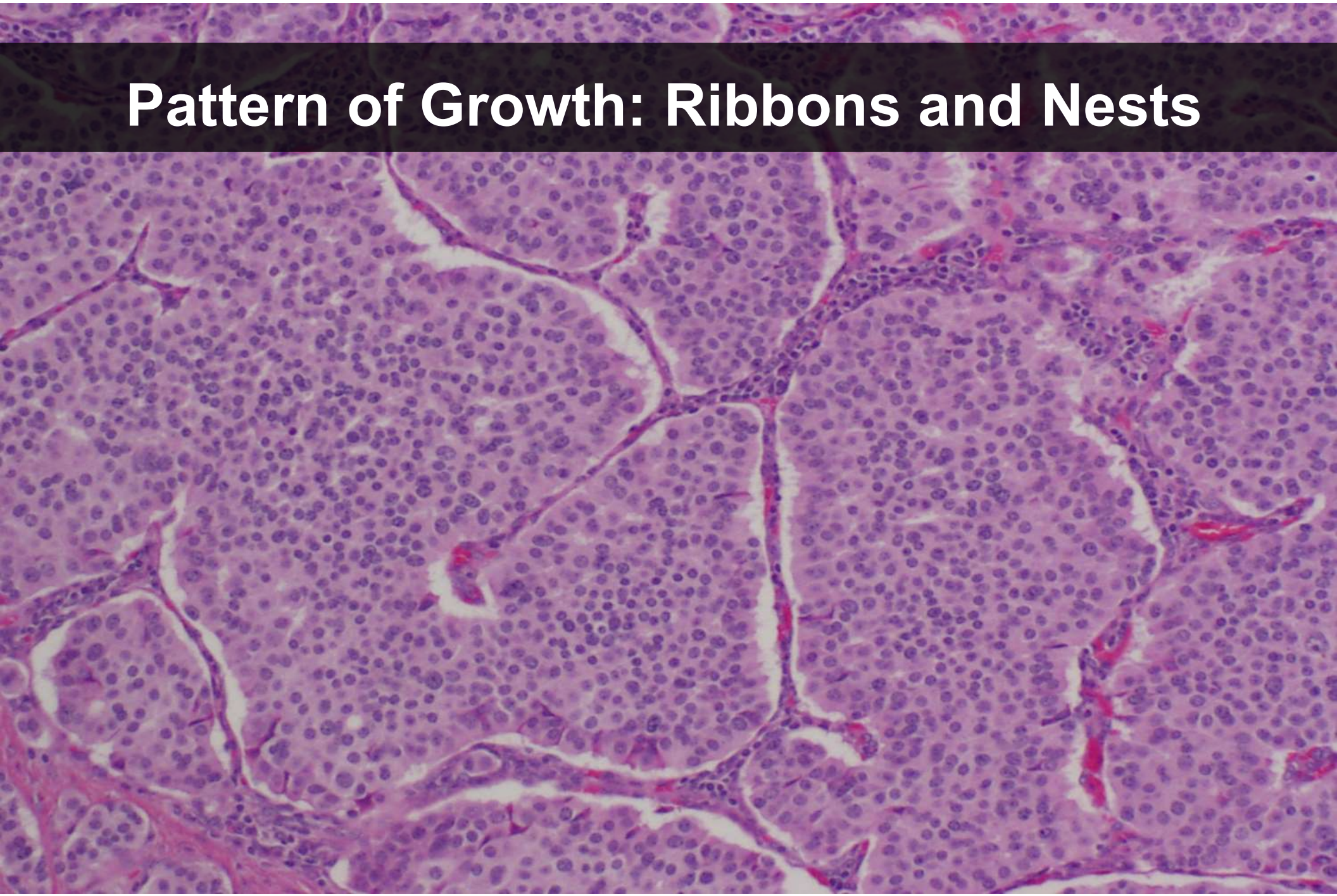
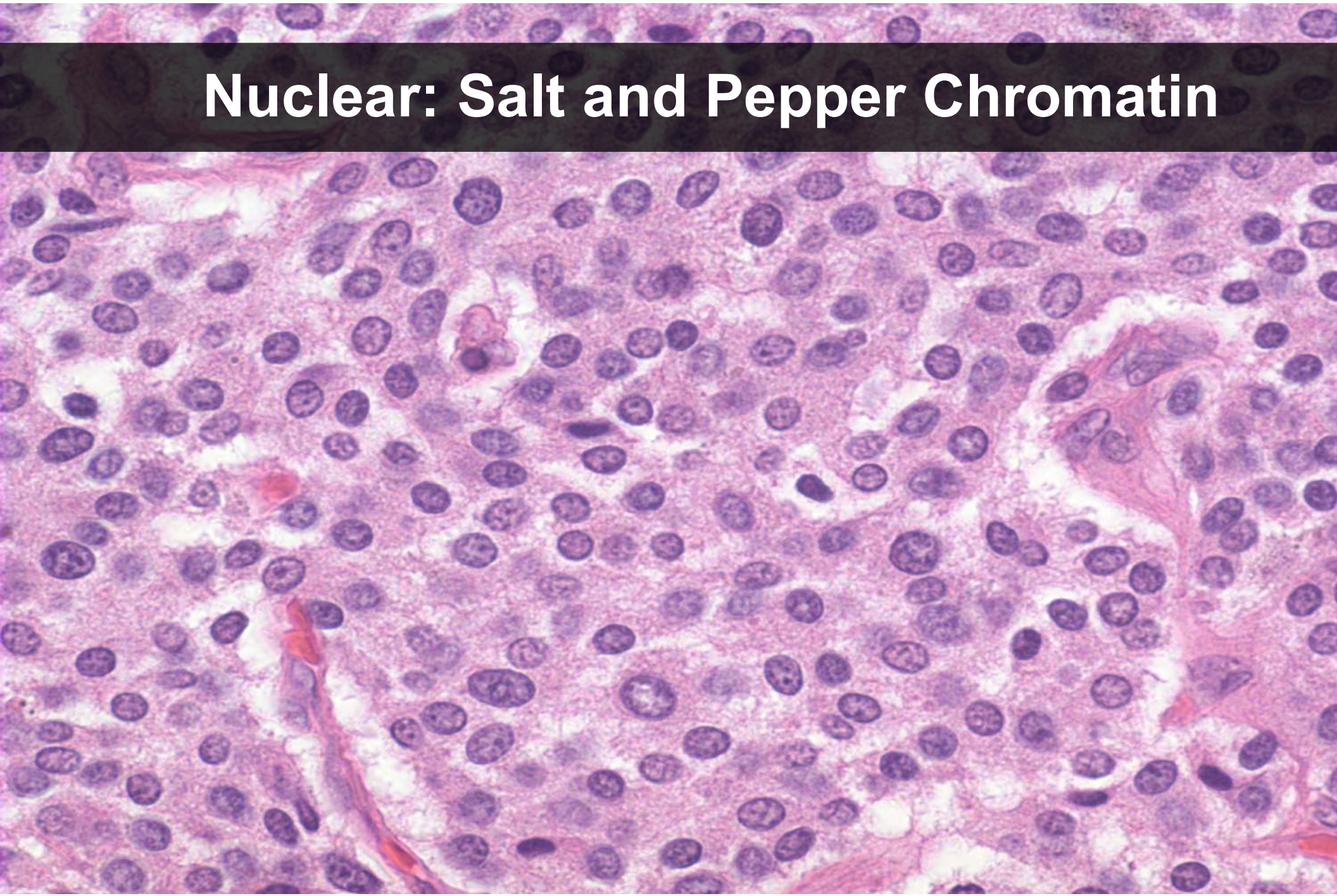
Pancreatic neuroendocrine tumor (PanNET)
Solid -pseudopapillary neoplasm

Pattern of Growth: Ribbons and Nests

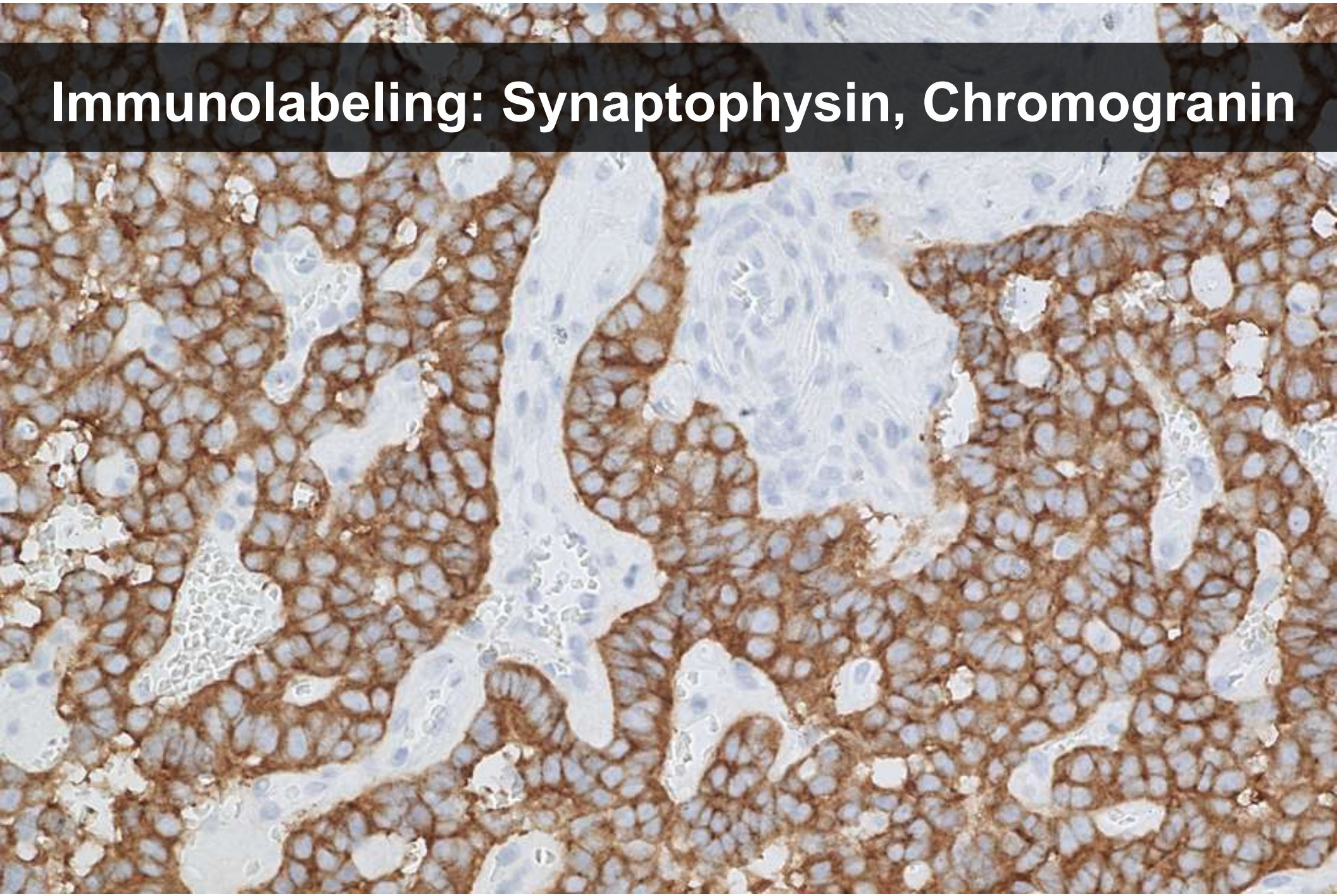
Pattern of Growth: Ribbons and Nests



Nuclear: Salt and Pepper Chromatin



Immunolabeling: Synaptophysin, Chromogranin



Pancreatic Neuroendocrine Tumor

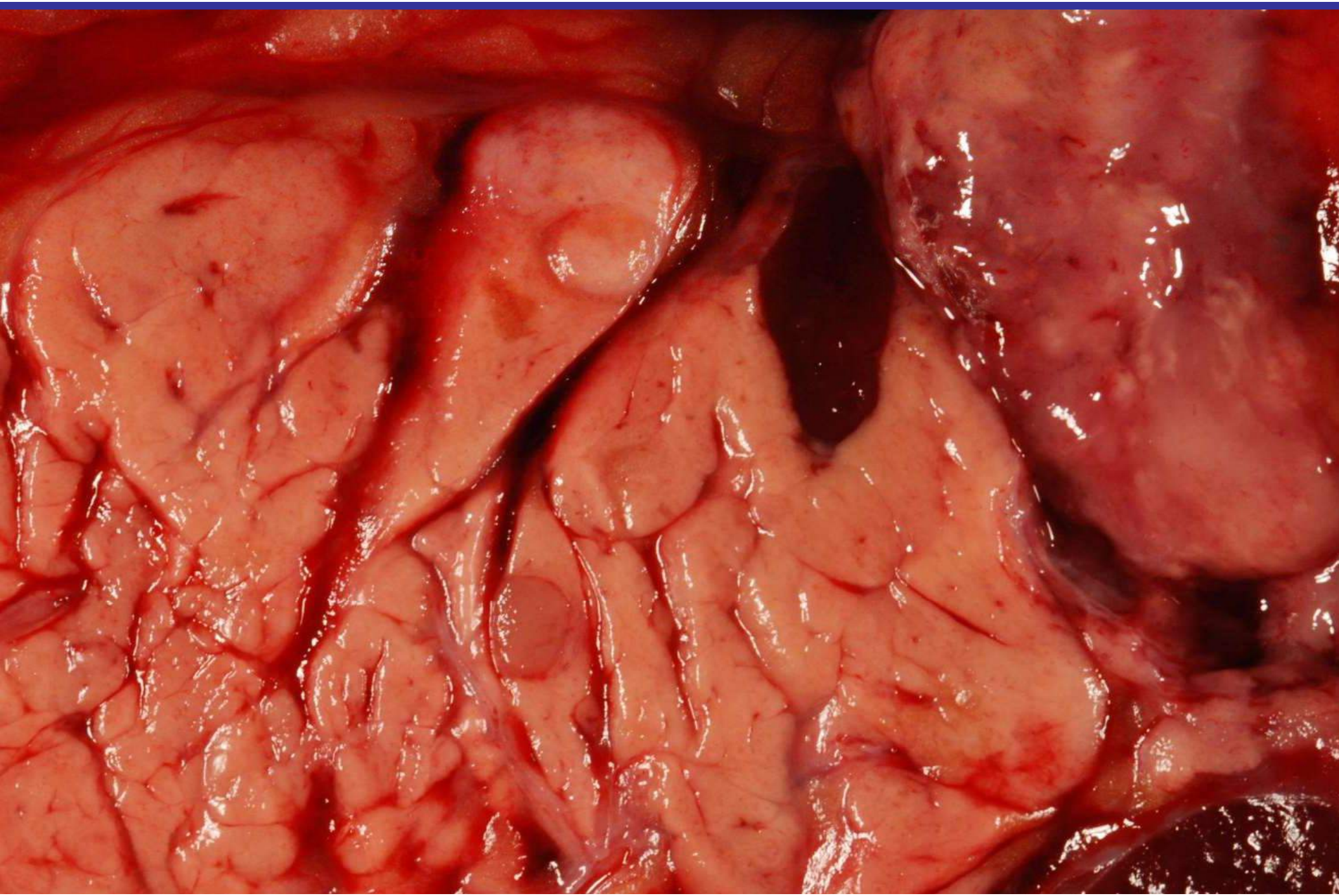
Genetic Syndromes

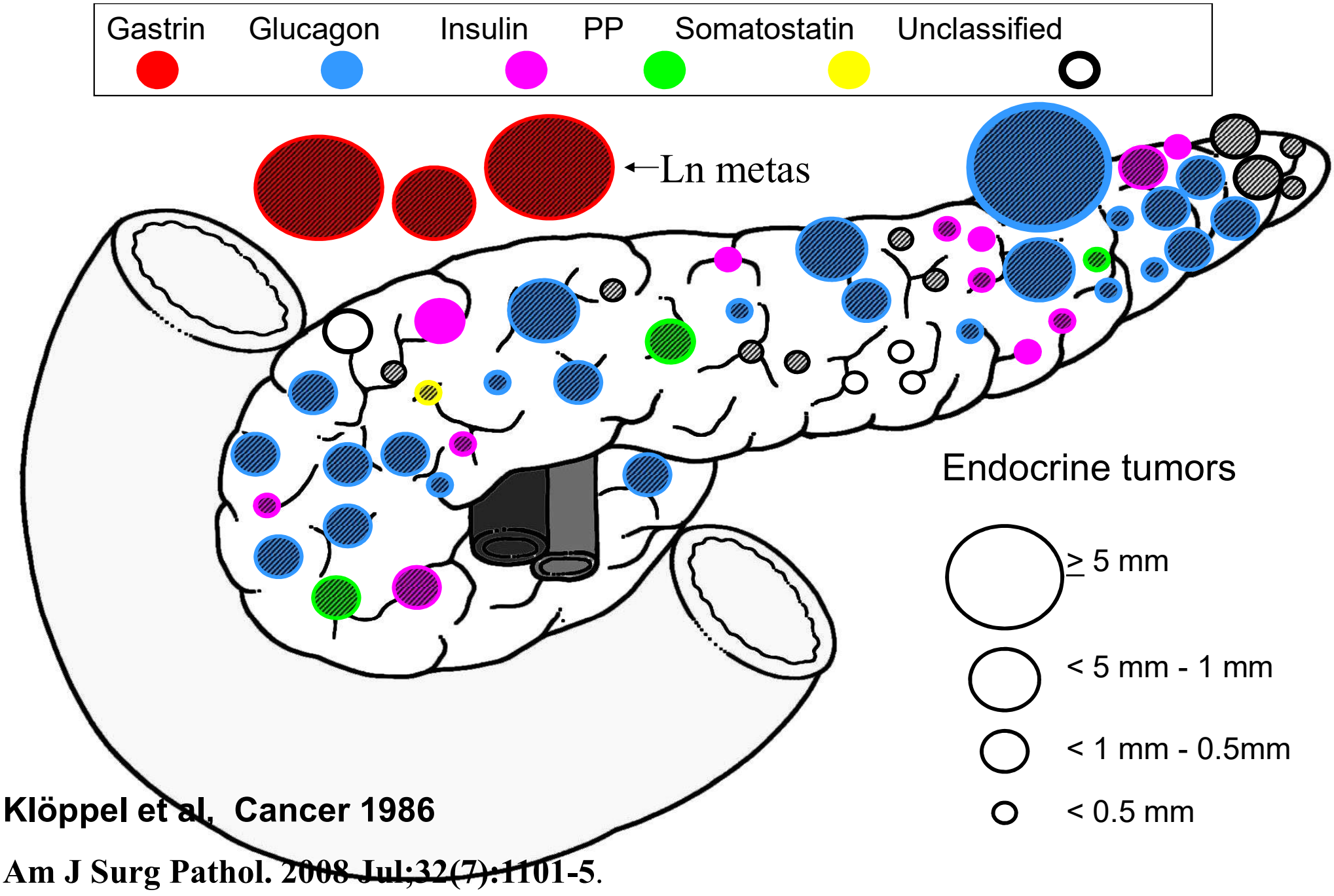
Genetic Syndromes

- Multiple Endocrine Neoplasia 1
- von Hippel-Lindau
- Tuberous Sclerosis
- Pheochromocytoma
- Cushing's Syndrome

MEN-1

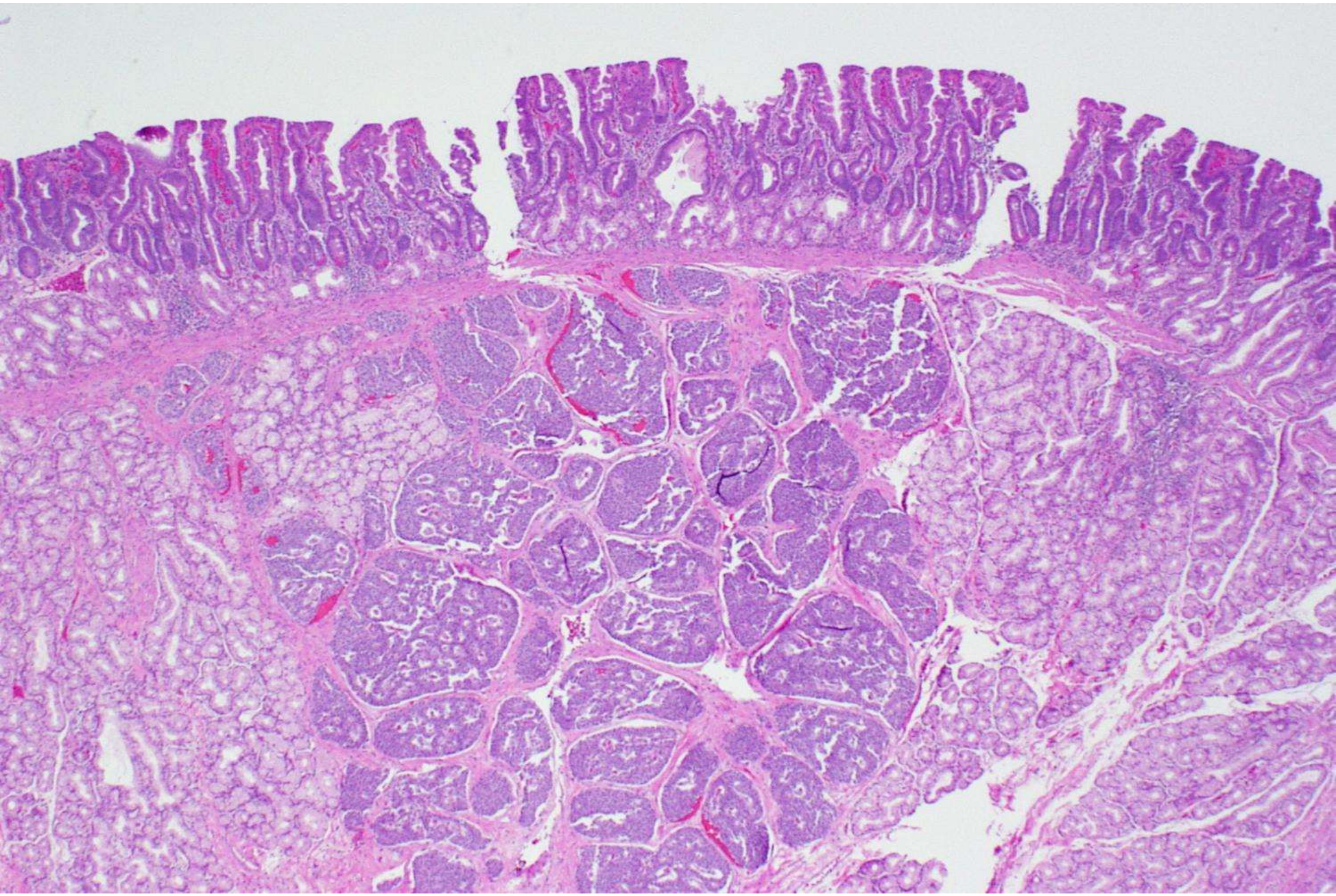
- Gene: Tumor suppressor gene on chromosome 11 (11q13)
- Pituitary: Prolactinomas, mass effect
- Parathyroid: Hyperparathyroidism, nephrolithiasis
- Pancreas-duodenum: Multicentric, Gastrinomas, ulcers



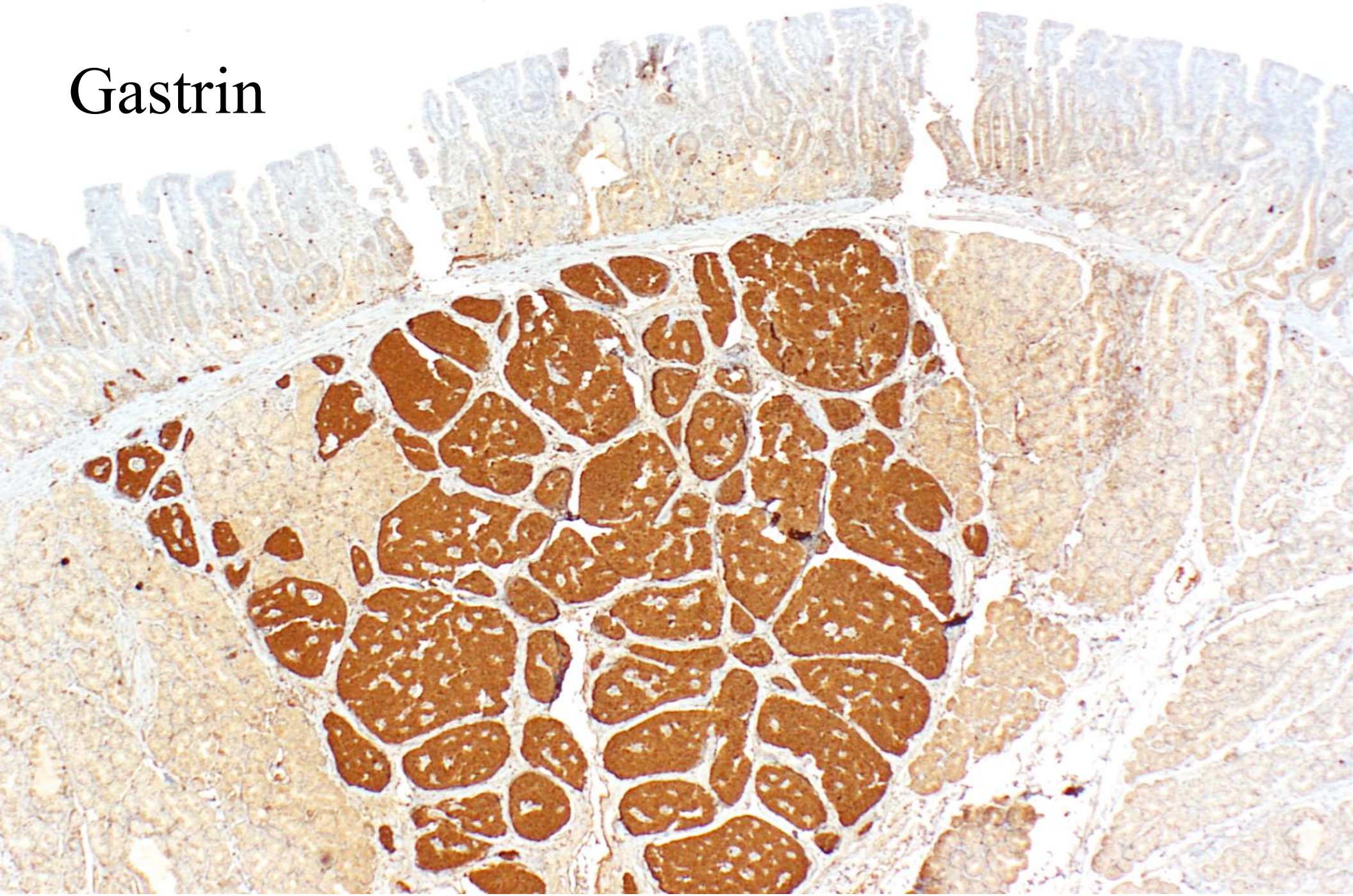


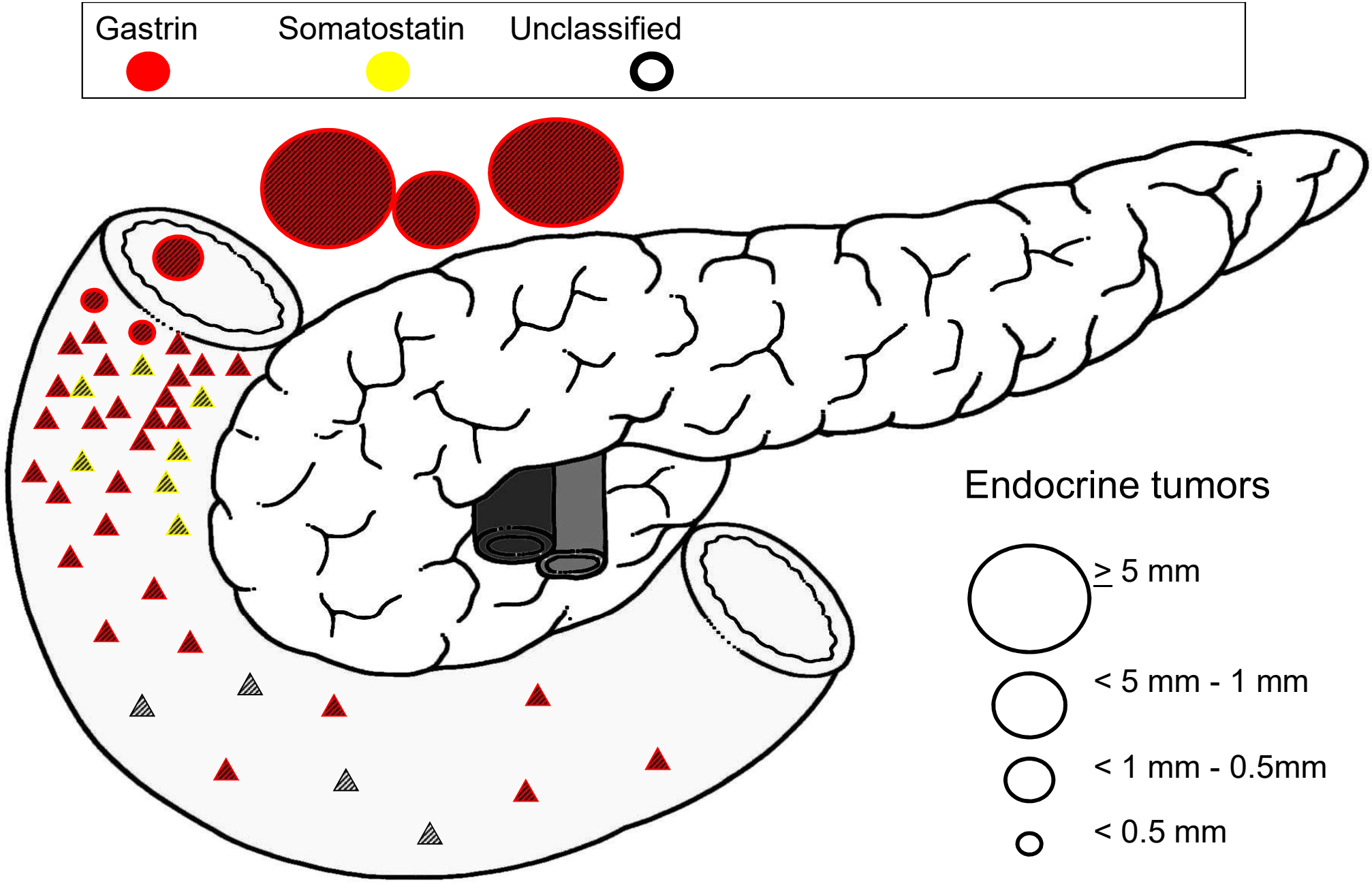
Klöppel et al, Cancer 1986

Am J Surg Pathol. 2008 Jul;32(7):1101-5.



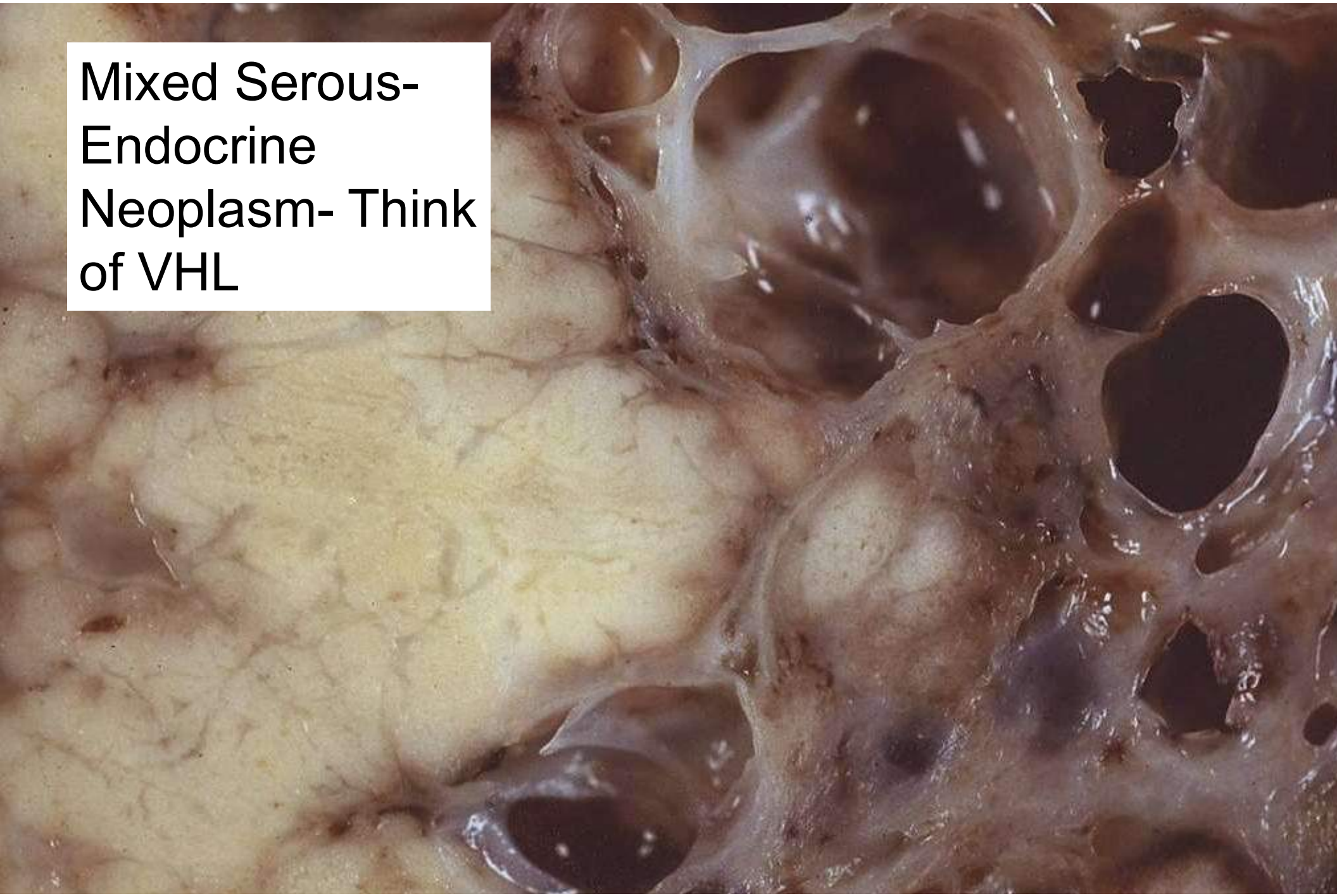
Gastrin





▲ Endocrine cell hyperplasia in the duodenum

Anlauf et al Gastroenterology 2005, AND Am J Surg Pathol. 2008 Jul;32(7):1101-5.

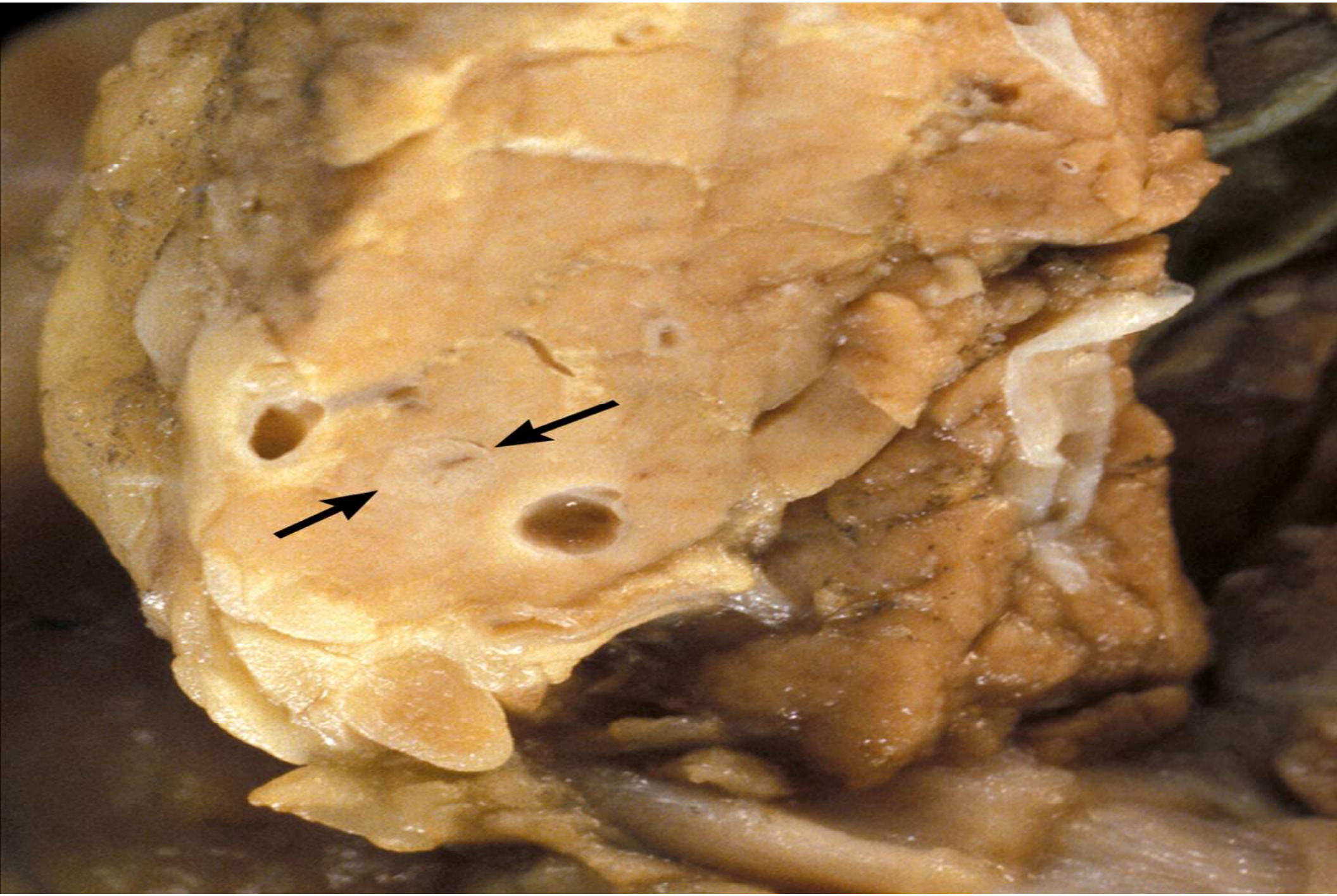

Mixed Serous-
Endocrine
Neoplasm- Think
of VHL

Classification

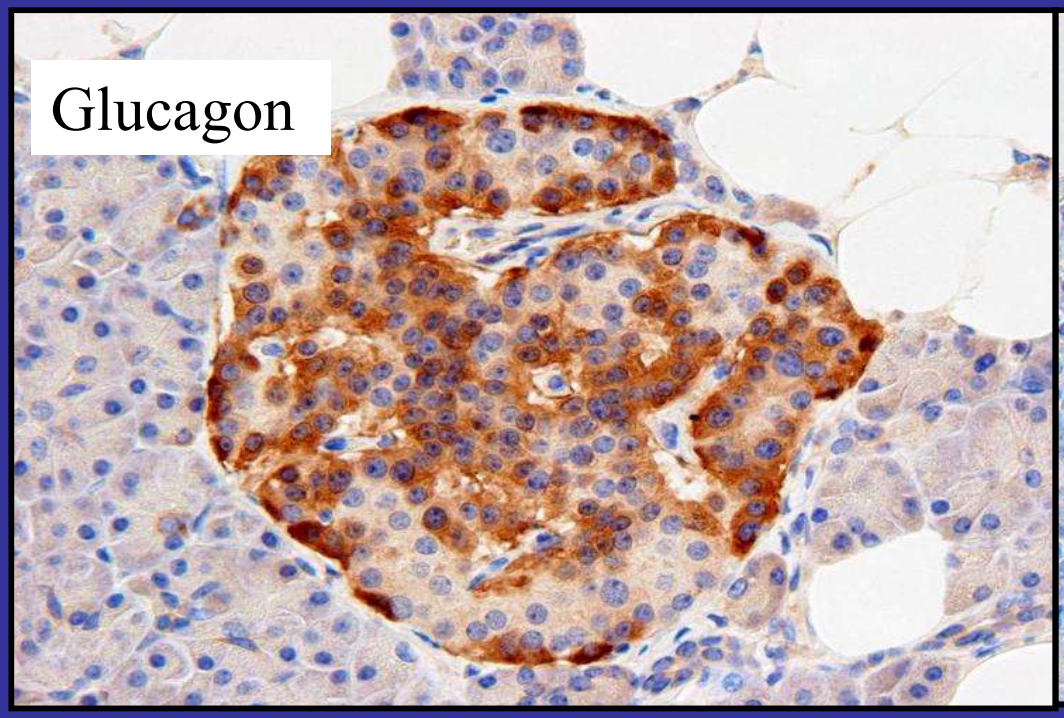
- Neurondocrine microadenoma (<0.5 cm)
- Well-differentiated pancreatic neuroendocrine tumor
  - **Nonfunctional** (≥0.5 cm)
  - **Functional**
    - Insulinoma
    - Glucagonoma
    - Somatostatinoma
    - Gastrinoma
    - VIPoma
- Poorly-differentiated neuroendocrine carcinoma (classification is changing in the new WHO)
  - Small cell carcinoma
  - Large cell endocrine carcinoma

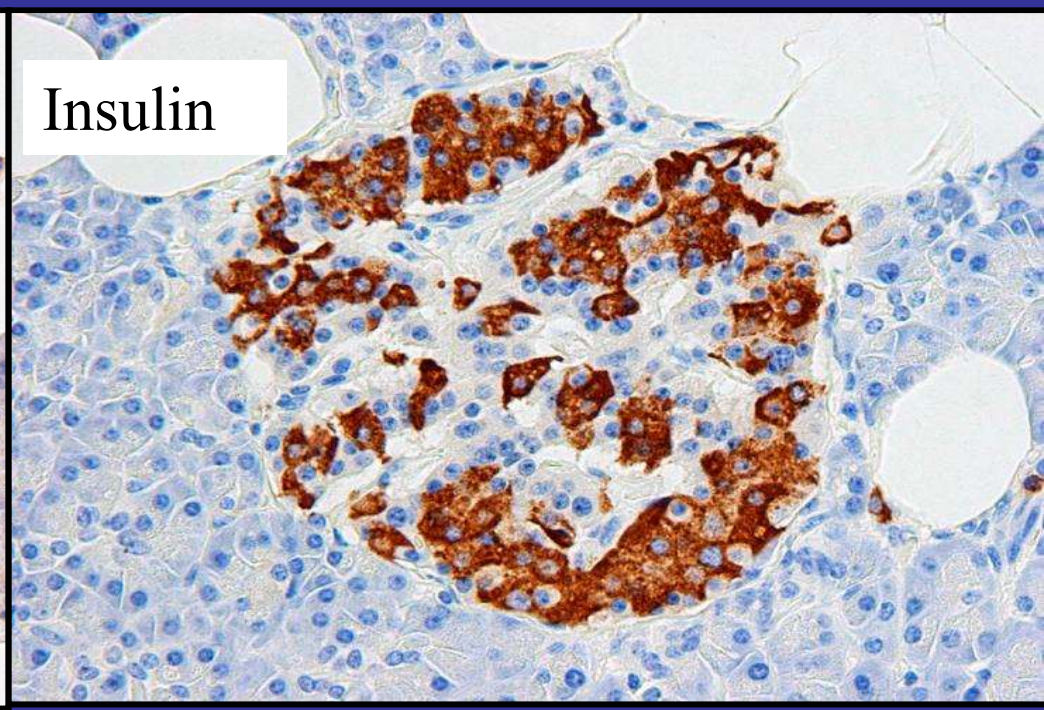
Microadenoma

- Well differentiated, <5 mm
- Usually incidental
- Prevalent in MEN1 syndrome
- Sporadic in 1-10% of population
- Nonfunctional
- Benign

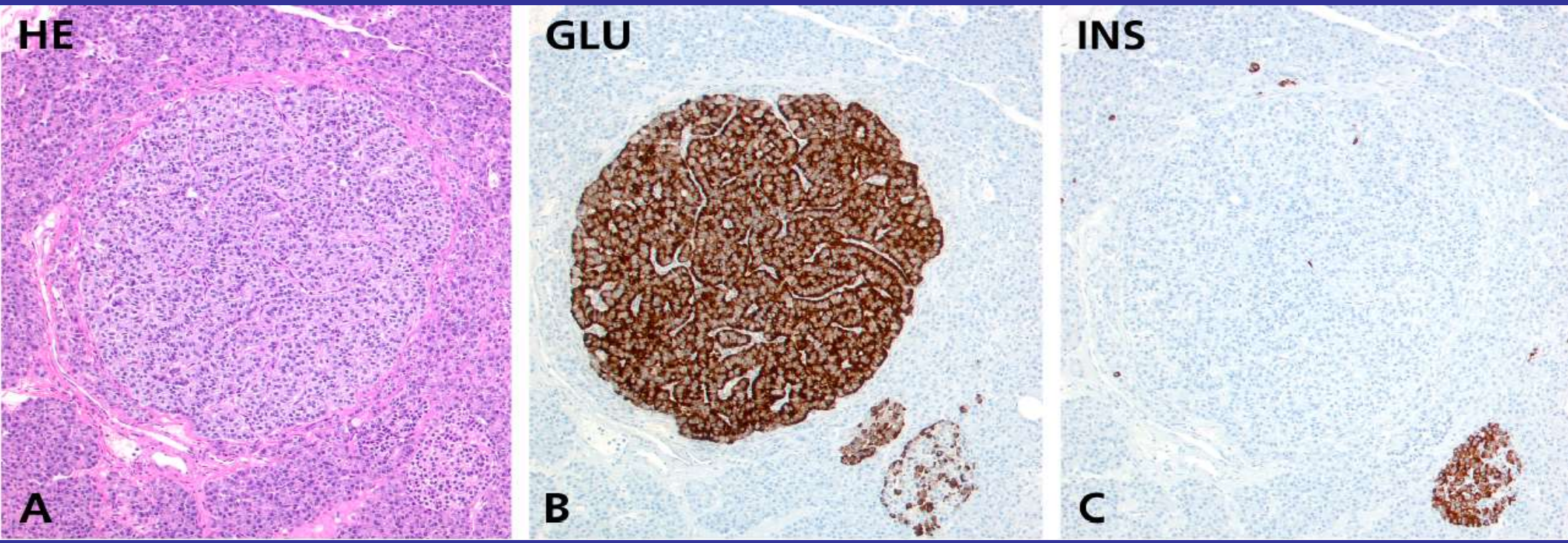


Normal peptide cell pattern

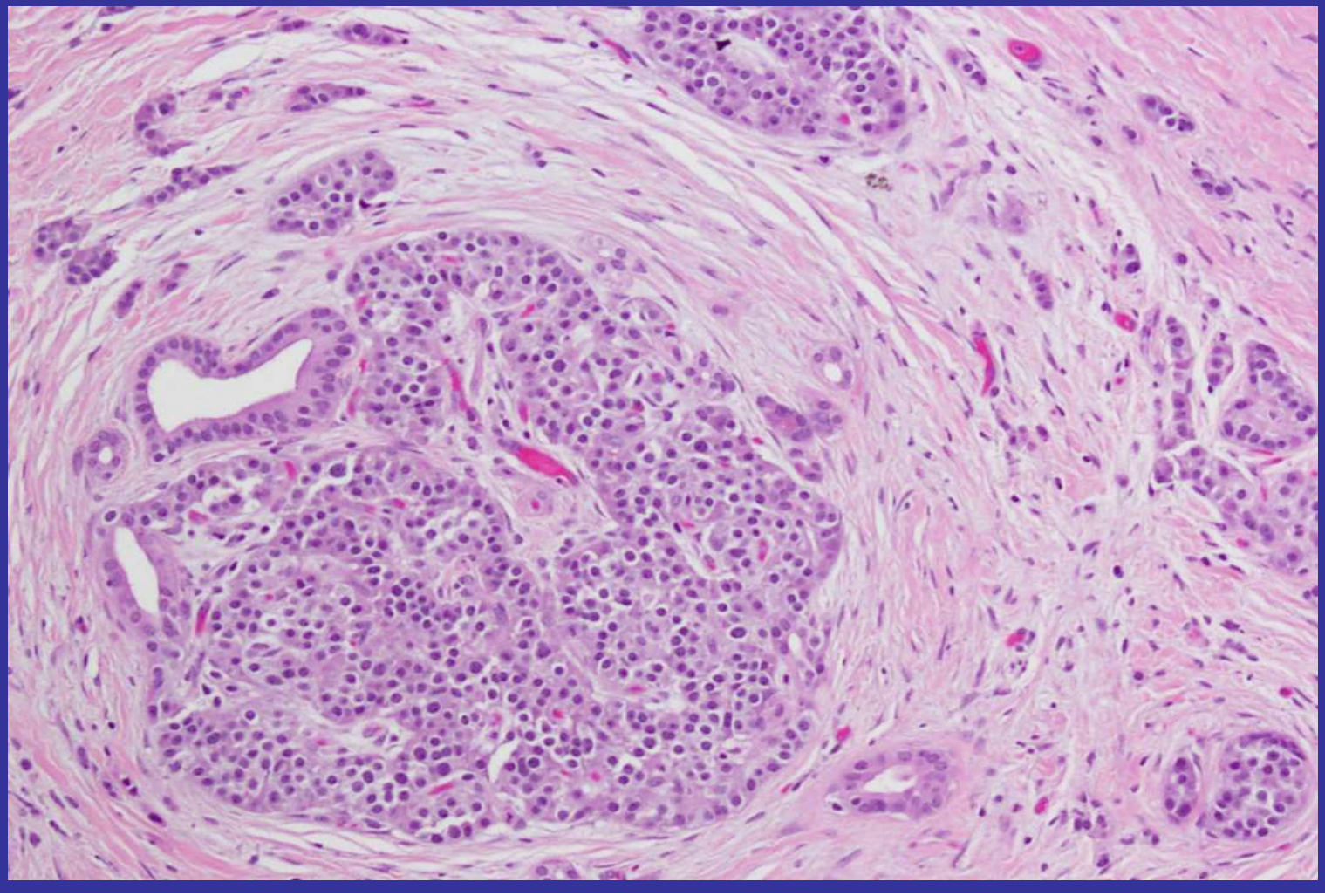




Peptide Expression in Microadenomas



Islet Cell Aggregation in Chronic Pancreatitis



Well-differentiated Pancreatic Neuroendocrine Tumors

(≥0.5cm, and Ki67<20%)

Well-differentiated Pancreatic Neuroendocrine Tumors

- Nonfunctional (≥0.5 cm, 50-60%)
- Functional (40-50%)
  - Insulinoma (40%), gastrinoma (25%), glucagonoma (15%), VIPoma (10%), somatostatinoma (5%), others (5%)
- 1-4% of pancreatic neoplasms
- Prevalence has been estimated to be 0.2–2 per million persons per year
- Wide age range, most 30-60 yrs (mean = 50 yrs)
- Male = female

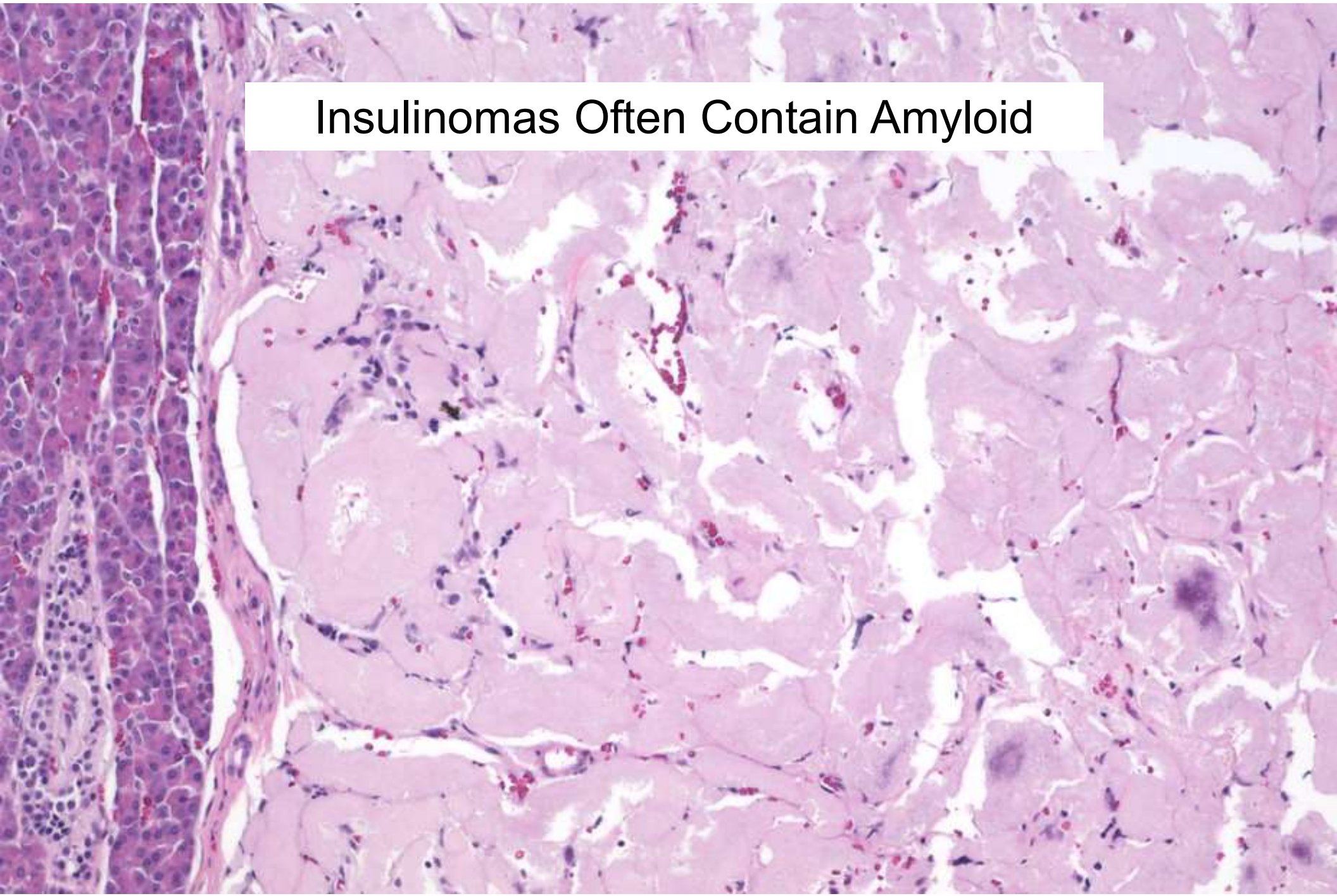
Insulinoma

- Whipple's triad:

1. Symptoms and signs of hypoglycemia,
2. Concomitant plasma glucose level of 45 mg/dL (2.5 mmol/L) or less, and
3. Reversibility of symptoms with the administration of glucose

- ~ 9% behave in a malignant manner

Insulinomas Often Contain Amyloid



Glucagonoma

- Hyperglycemia
- Anemia, diarrhea and weight loss
- Hypoaminoacidemia
- Necrolytic migratory erythema

http://www.mdconsult.com

VIPoma

- **Verner Morrison syndrome**
- Chronic watery diarrhea with resultant dehydration, hypokalemia, achlorhydria (WDHA-syndrome, or pancreatic cholera syndrome)

Syndromic PanNETs

- Pancreatic neuroendocrine tumors should only be designated “syndromic” or “functional” when they are associated with a clinical syndrome
- The expression of a hormone does NOT make a pancreatic neuroendocrine tumor “syndromic” or “functional”

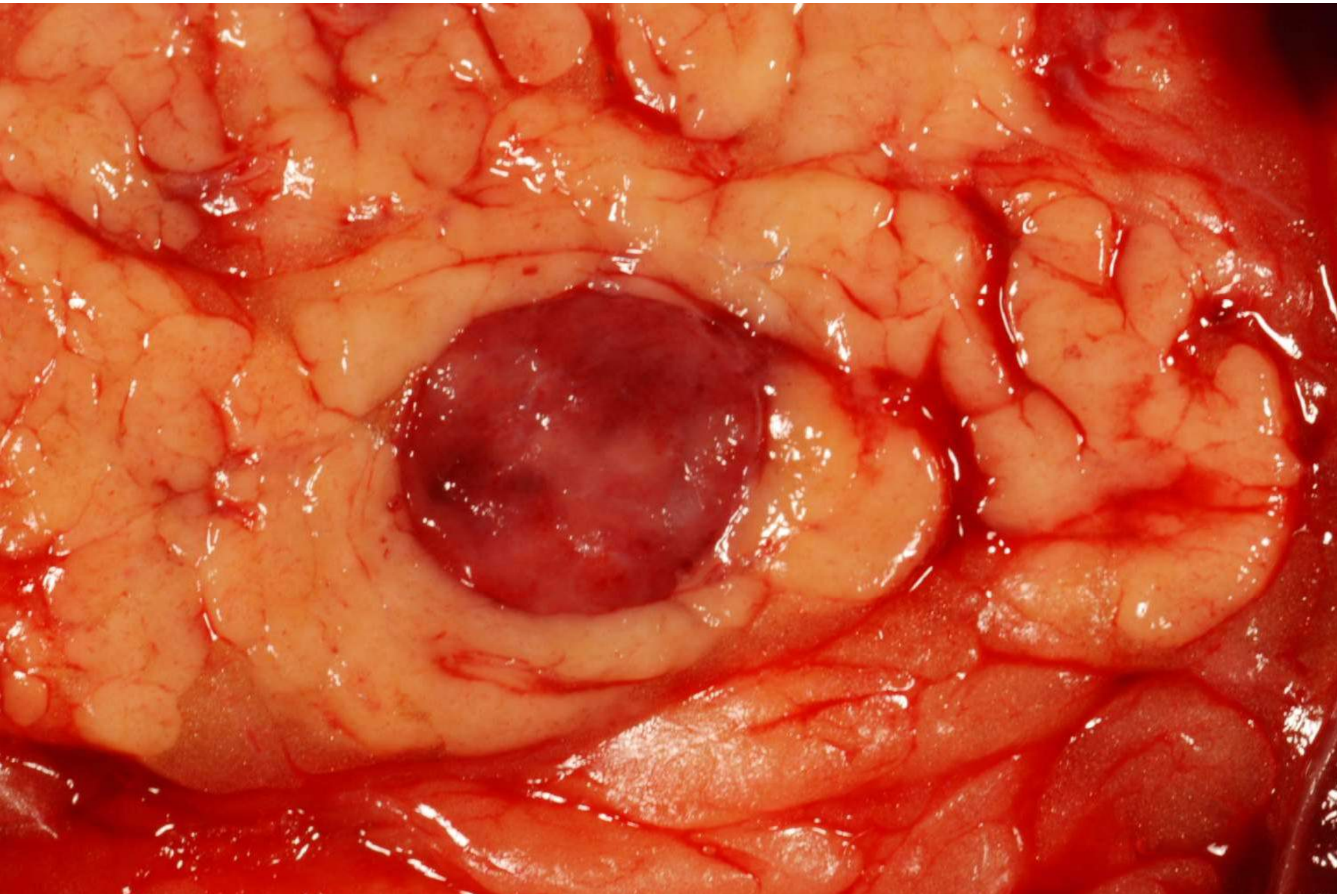
Gross

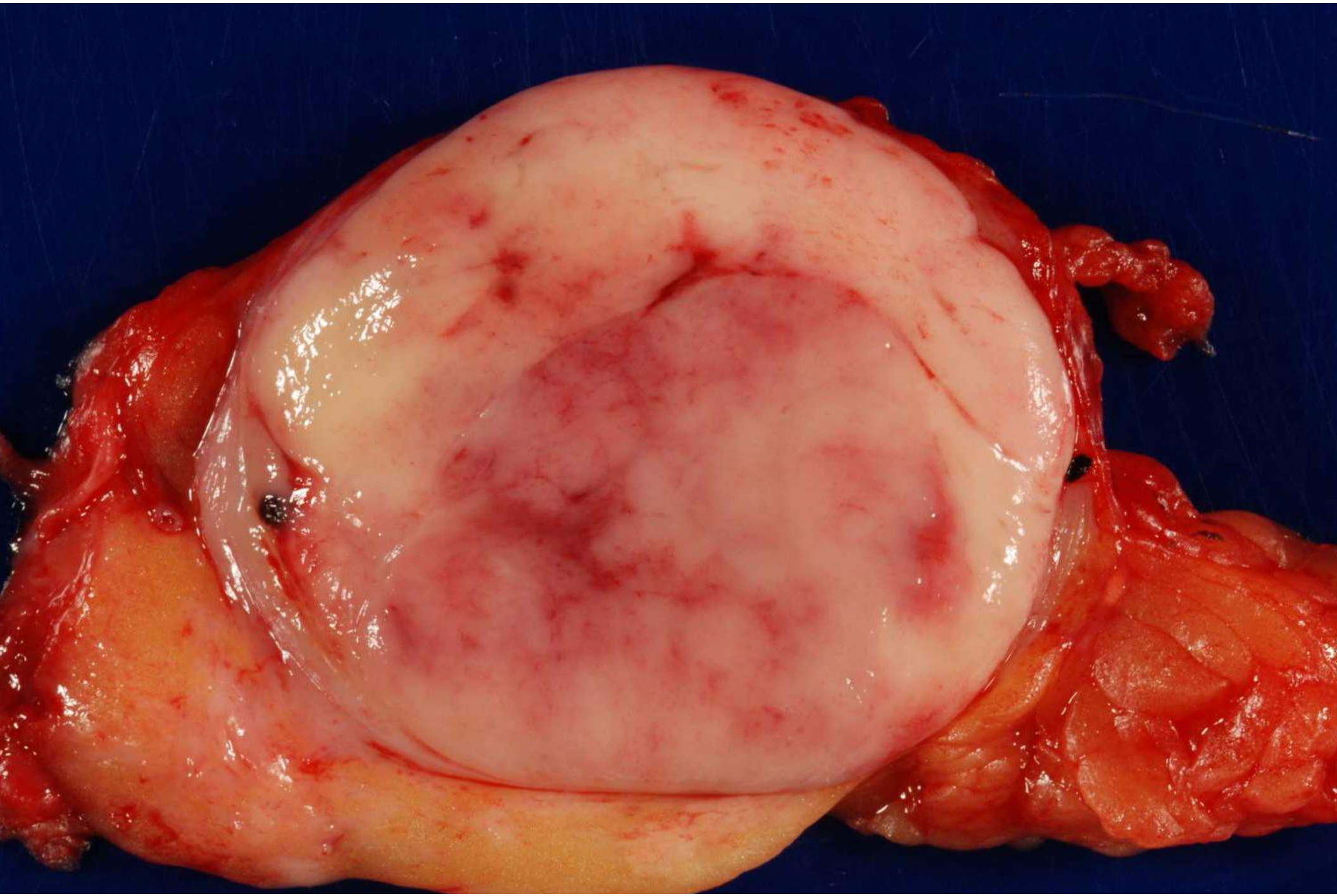
Most well-differentiated pancreatic neuroendocrine tumors are well-demarcated, solitary, and white-yellow or pink-brown

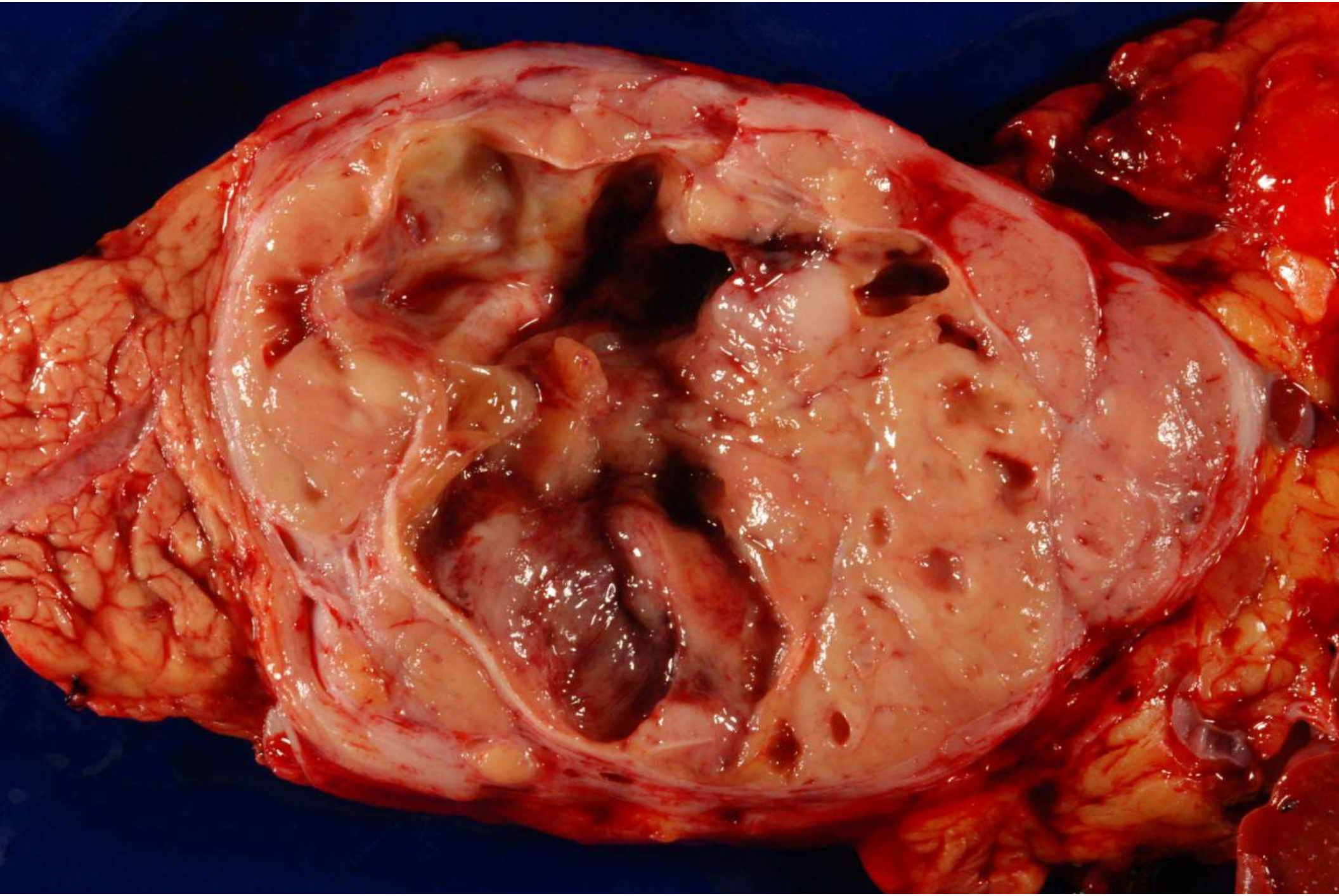
They can be soft and fleshy or densely fibrotic

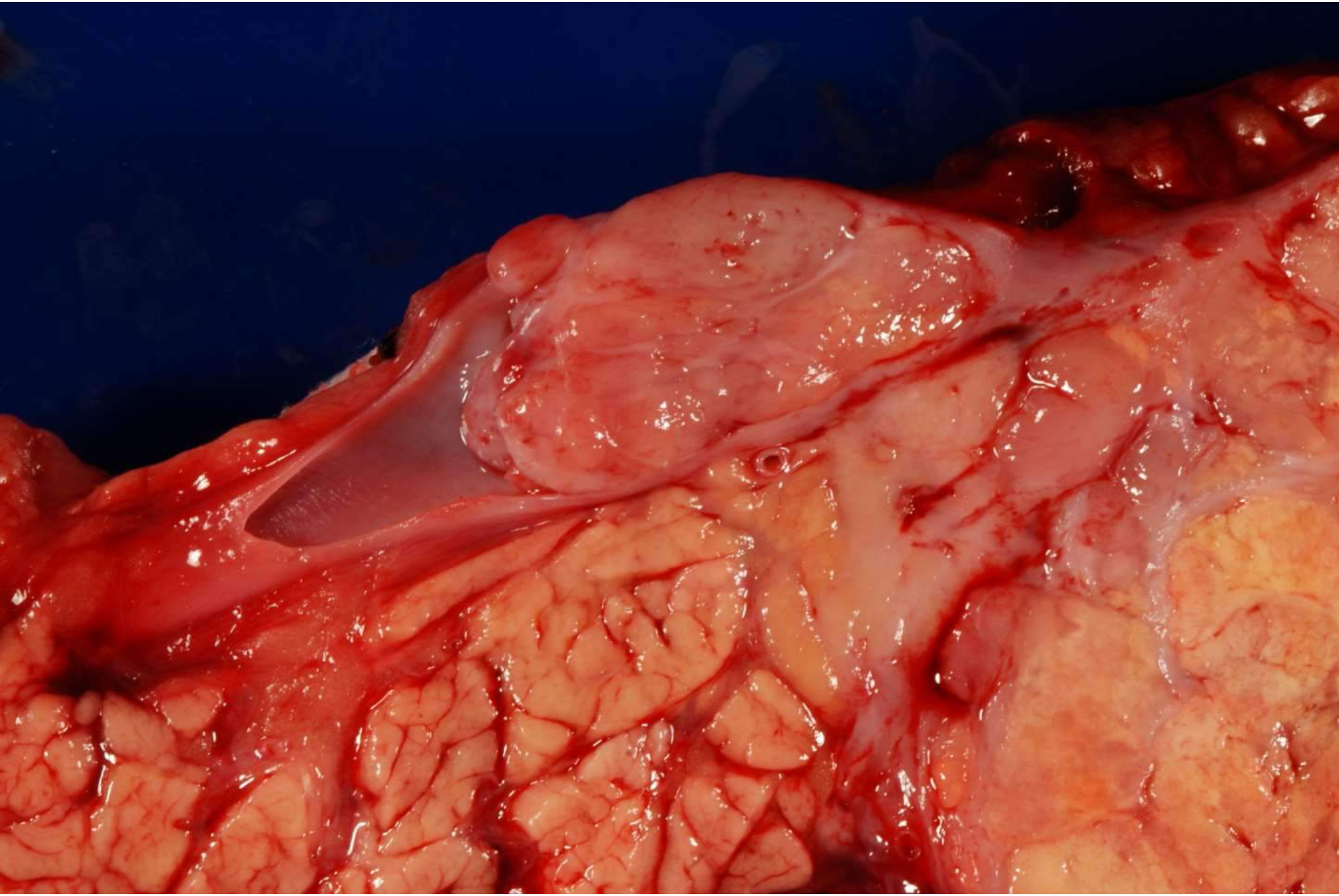
Areas of hemorrhage or necrosis can occur, usually in larger neoplasms

Rarely, pancreatic NETs are cystic



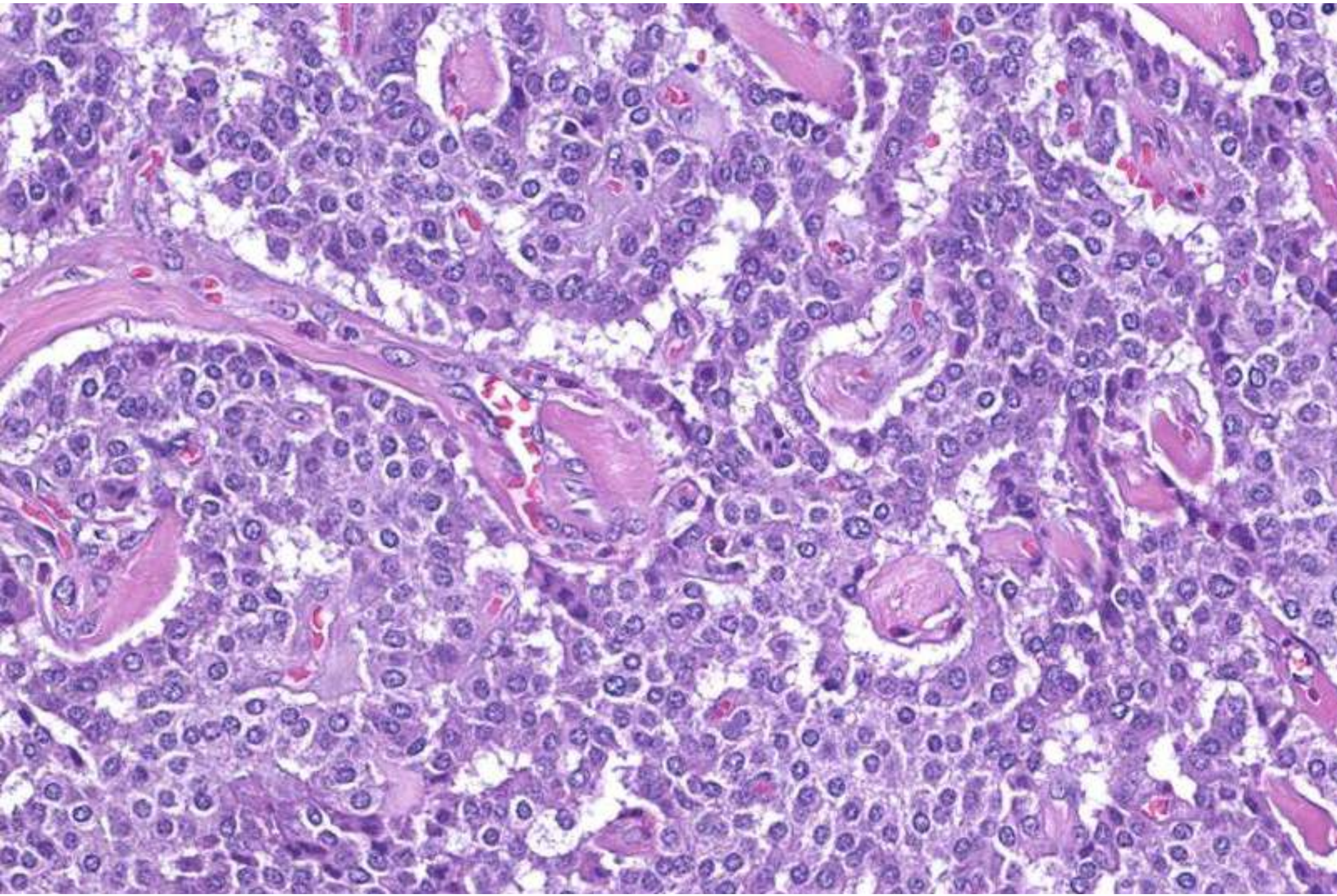






Microscopy

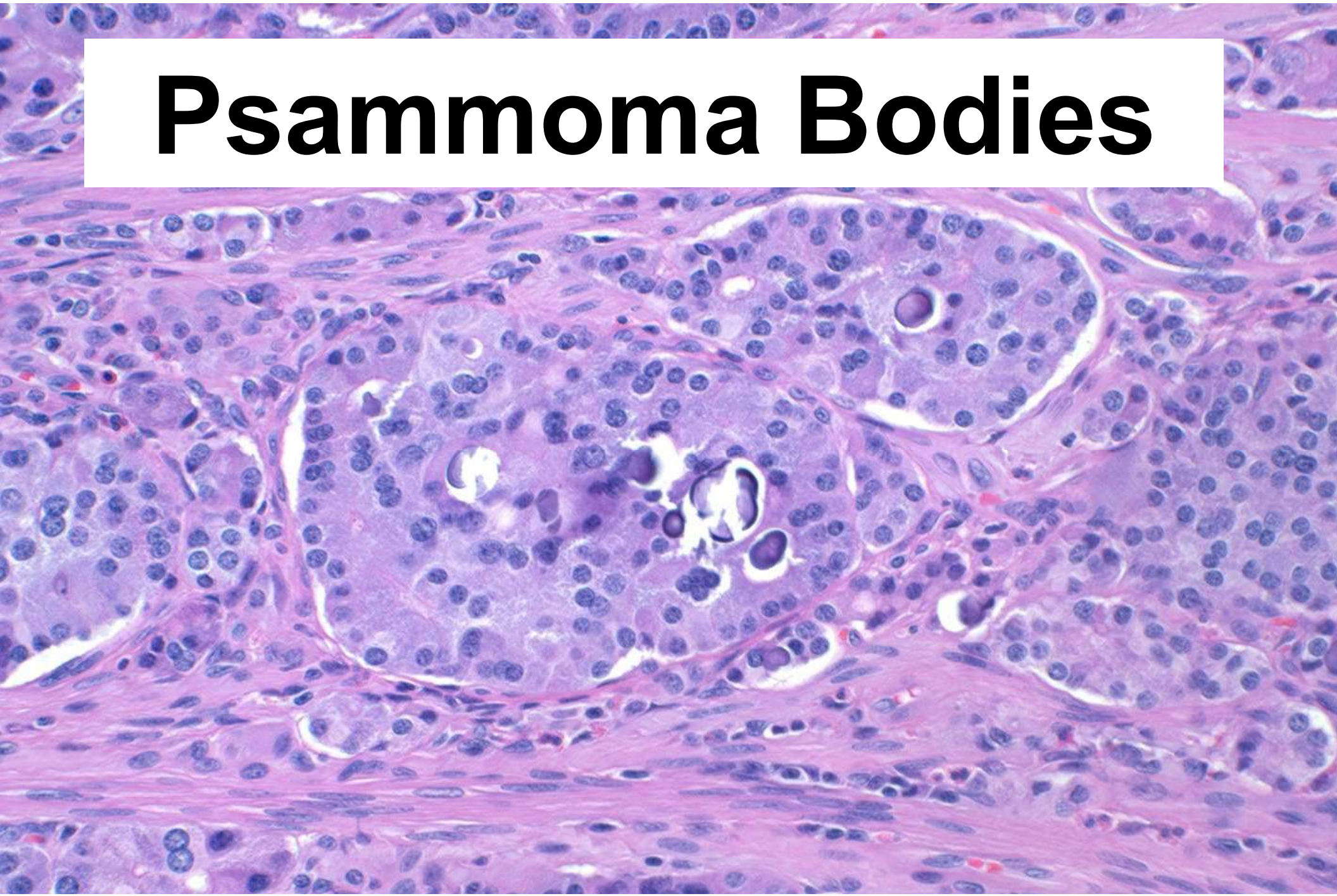
- Various “organoid” histological patterns, characterized by a nesting, trabecular, glandular, gyriform, tubuloacinar or pseudorosette arrangements
- Uniform, finely granular amphophilic to eosinophilic cytoplasm and a centrally located round to oval nucleus that may display a distinct nucleolus
- Characteristically coarsely clumped chromatin pattern (“salt and pepper”)
- By definition, they have <20 mitoses per 10hpf



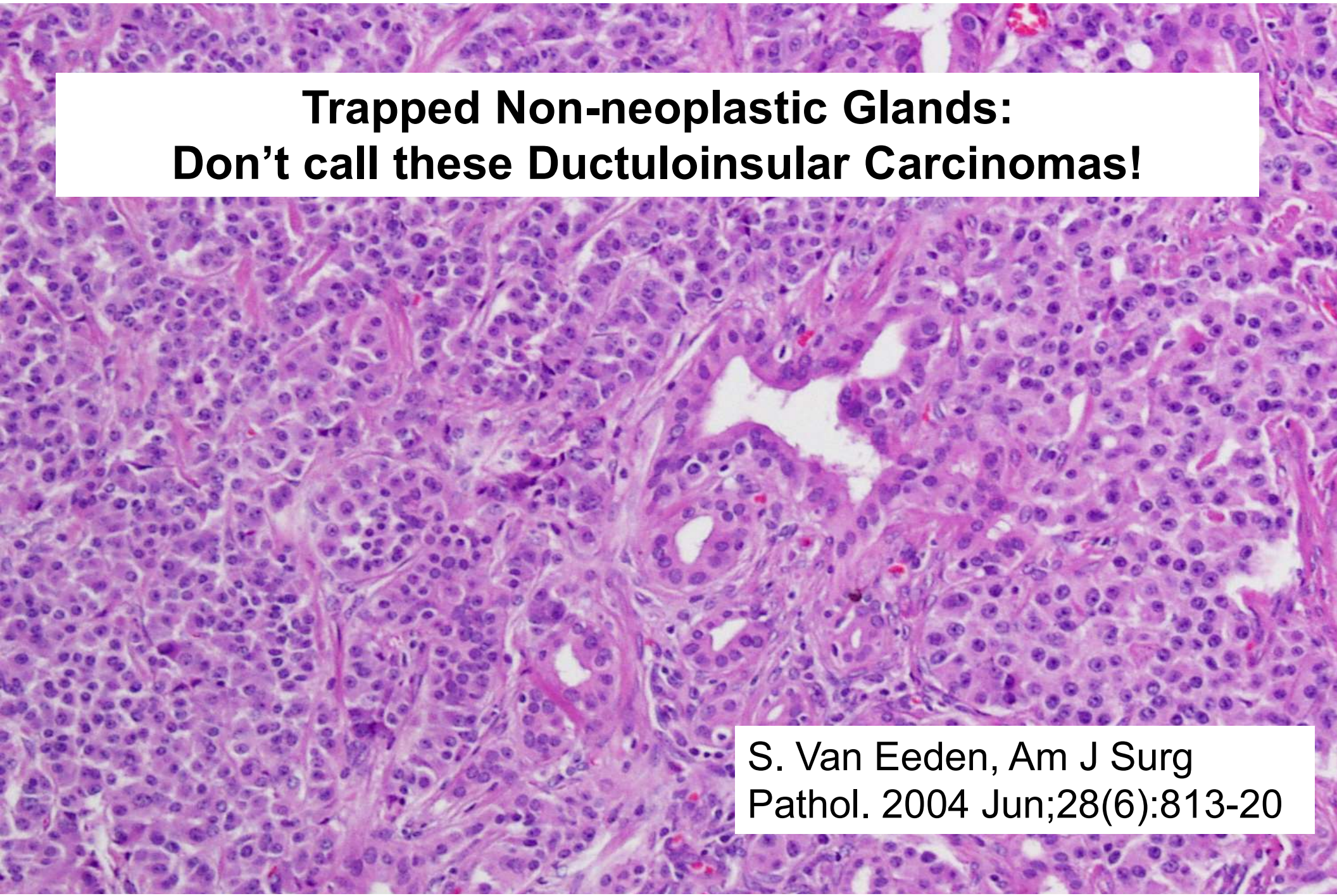
Microscopy

- Amyloid more common in insulinomas
- Psammoma bodies are more common in somatostatinomas
- Trapped non-neoplastic glands

Psammoma Bodies



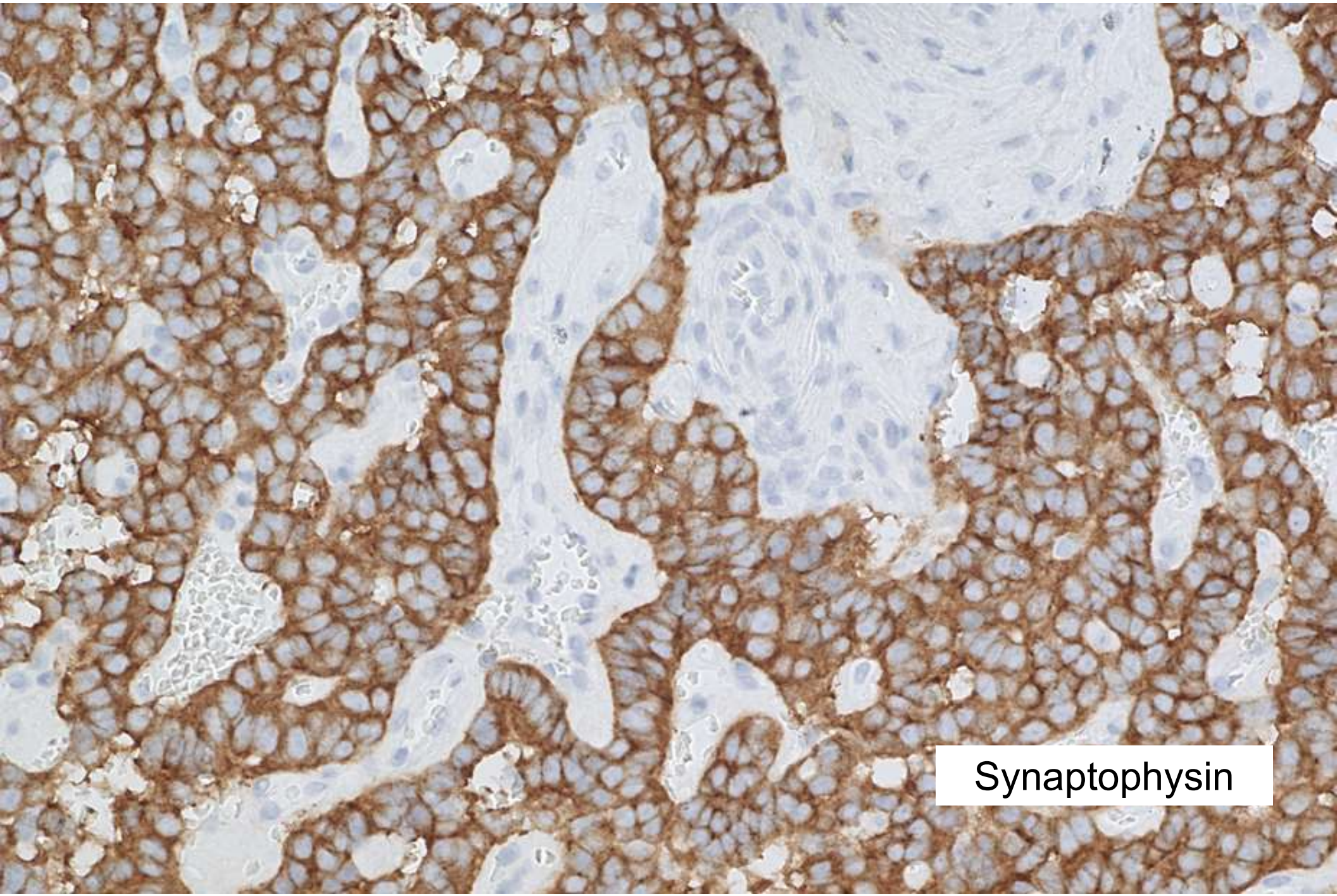
Trapped Non-neoplastic Glands: Don’t call these Ductuloinsular Carcinomas!



S. Van Eeden, Am J Surg Pathol. 2004 Jun;28(6):813-20

Immunohistochemitry

- Synaptophysin and chromogranin expressed strongly and diffusely
- Keratins 8 and 18, and keratin 19 (keratin 19 is a prognostic marker)
- Lineage markers including PDX1 and Isl1 and Pax8 suggest pancreatic origin for endocrine neoplasms of unknown primary

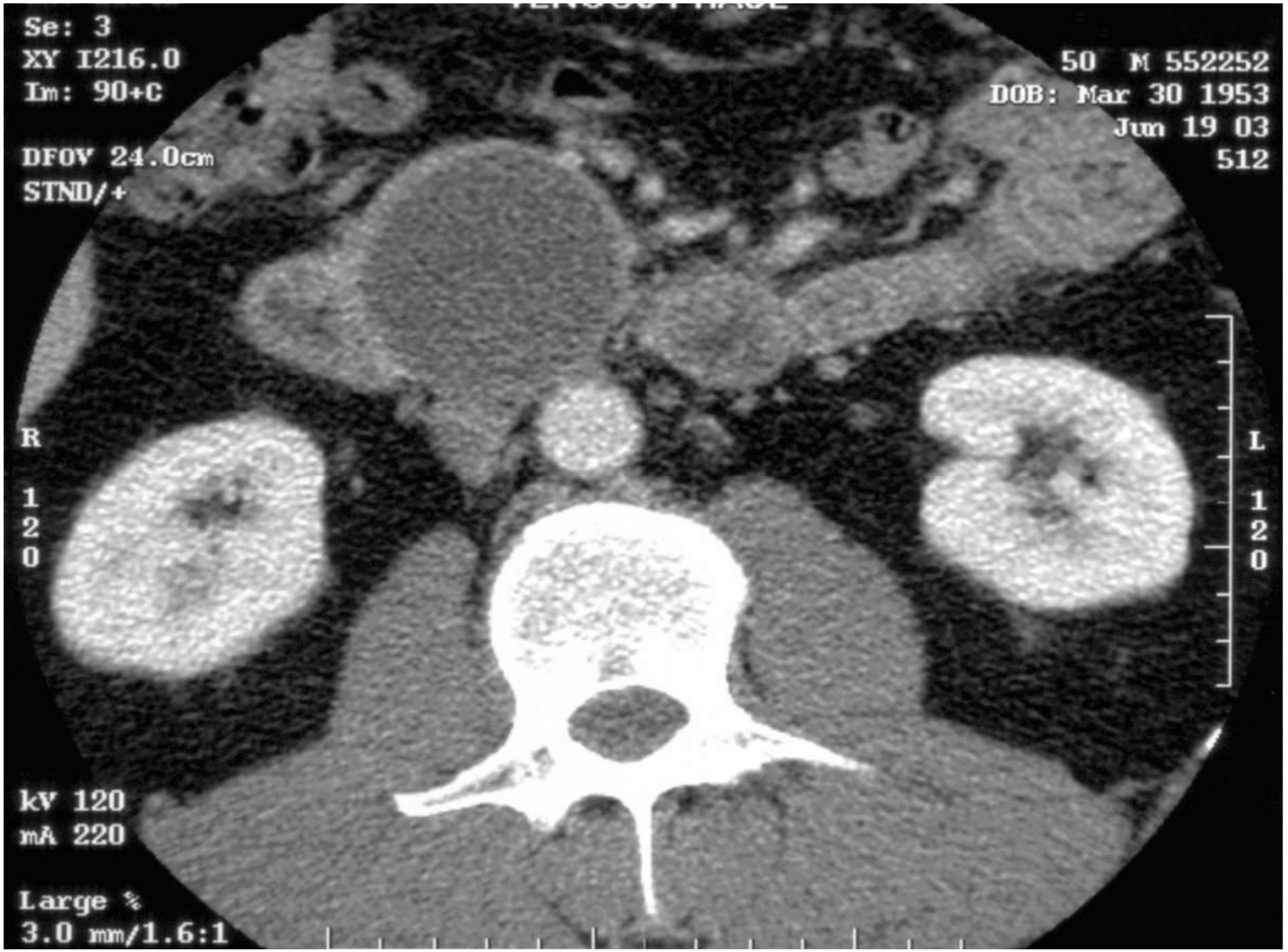

Synaptophysin

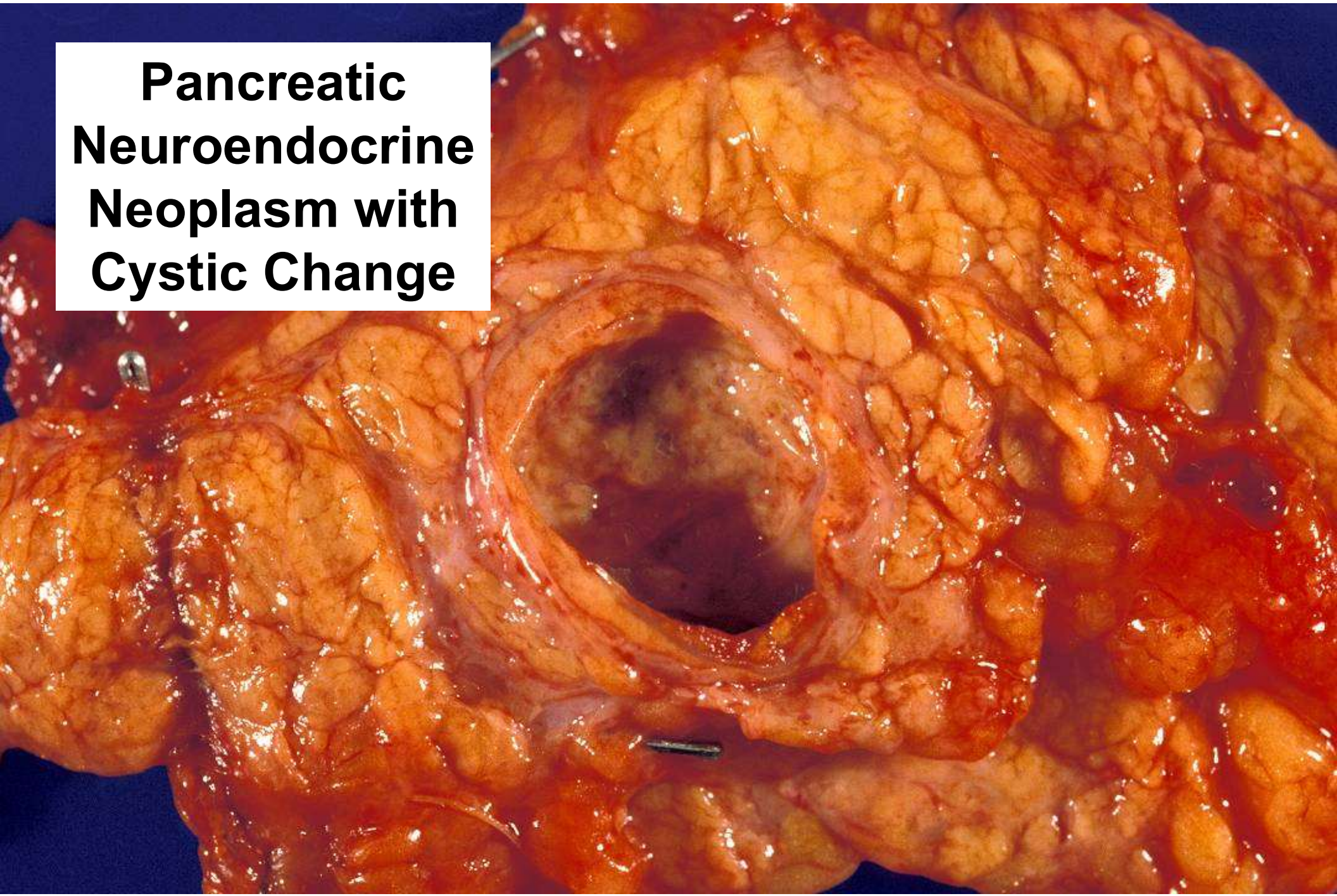
Immunohistochemitry

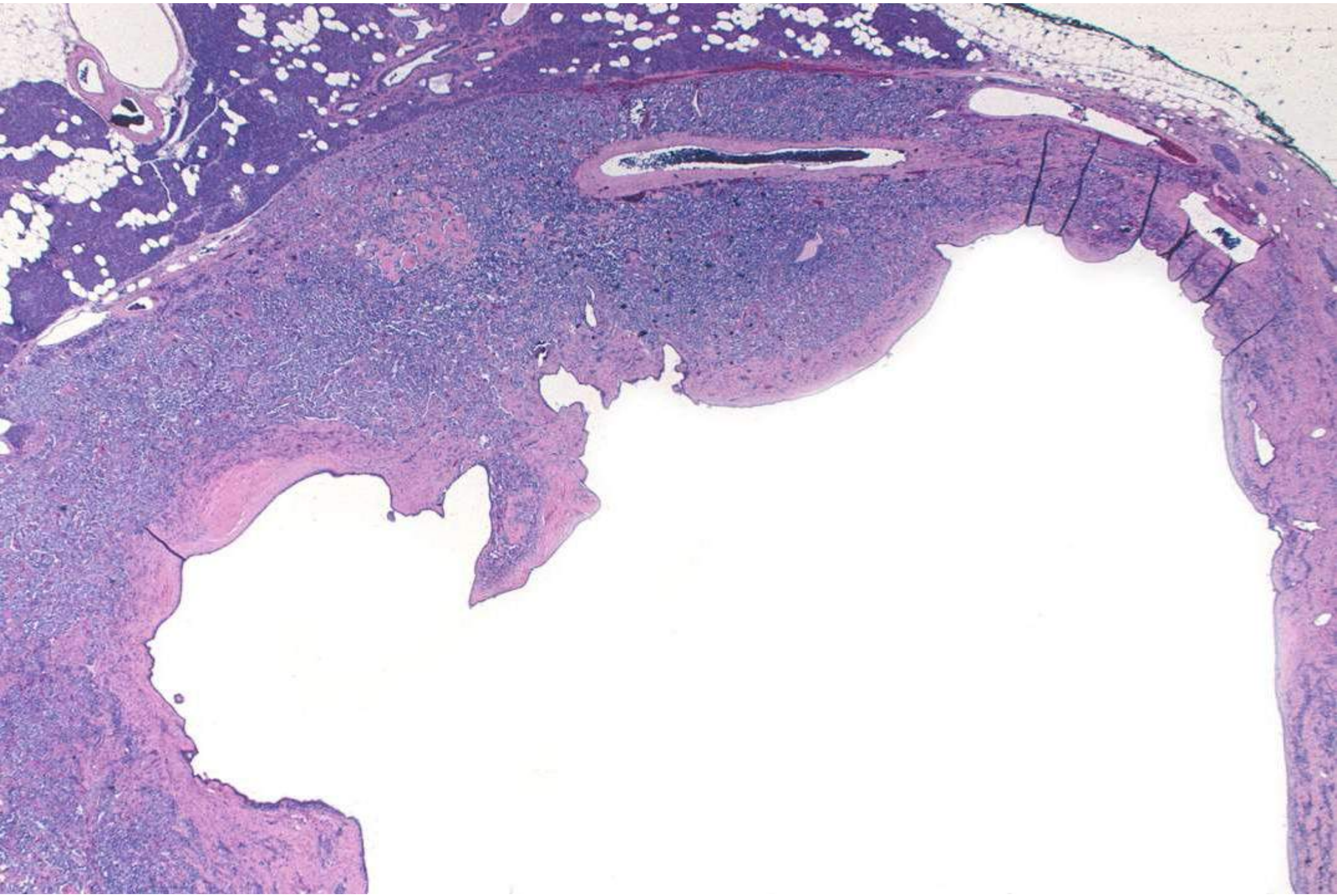
- Expression of a peptide does not equal “functioning” or “syndromic”

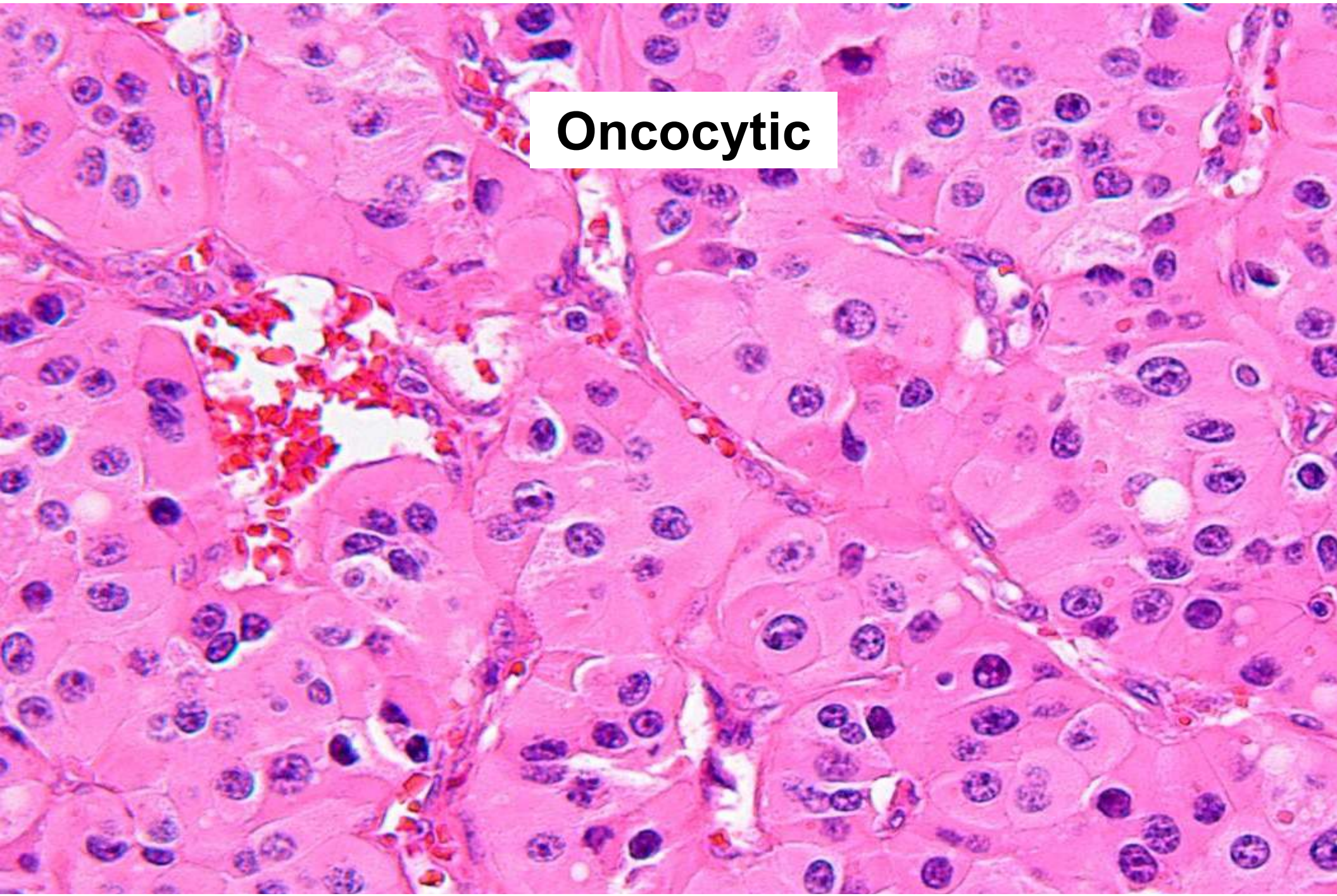
Morphologic Variants

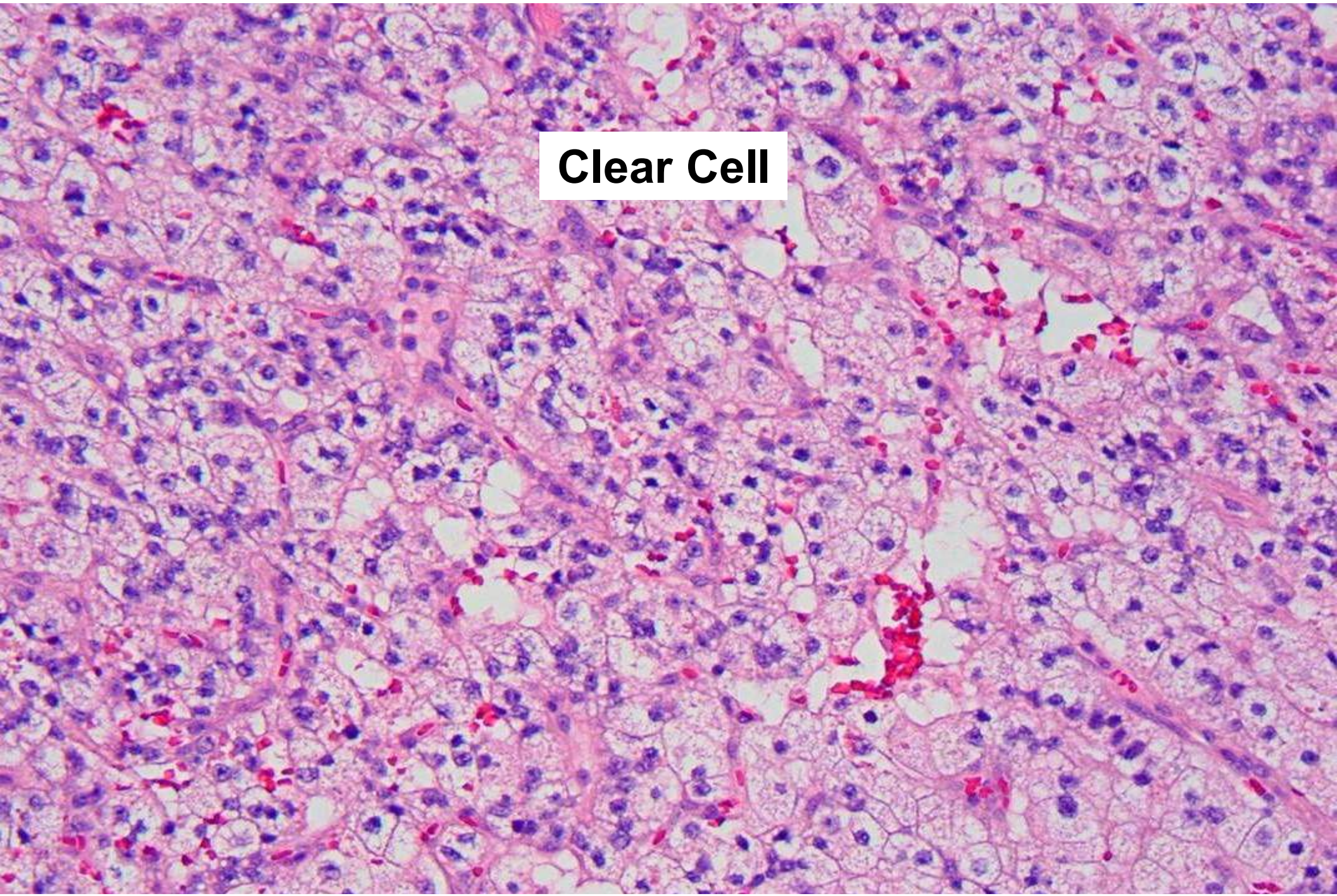
- Cystic
- Oncocytic
- Clear cell
- Pleomorphic
- Serotonin expressing fibrotic

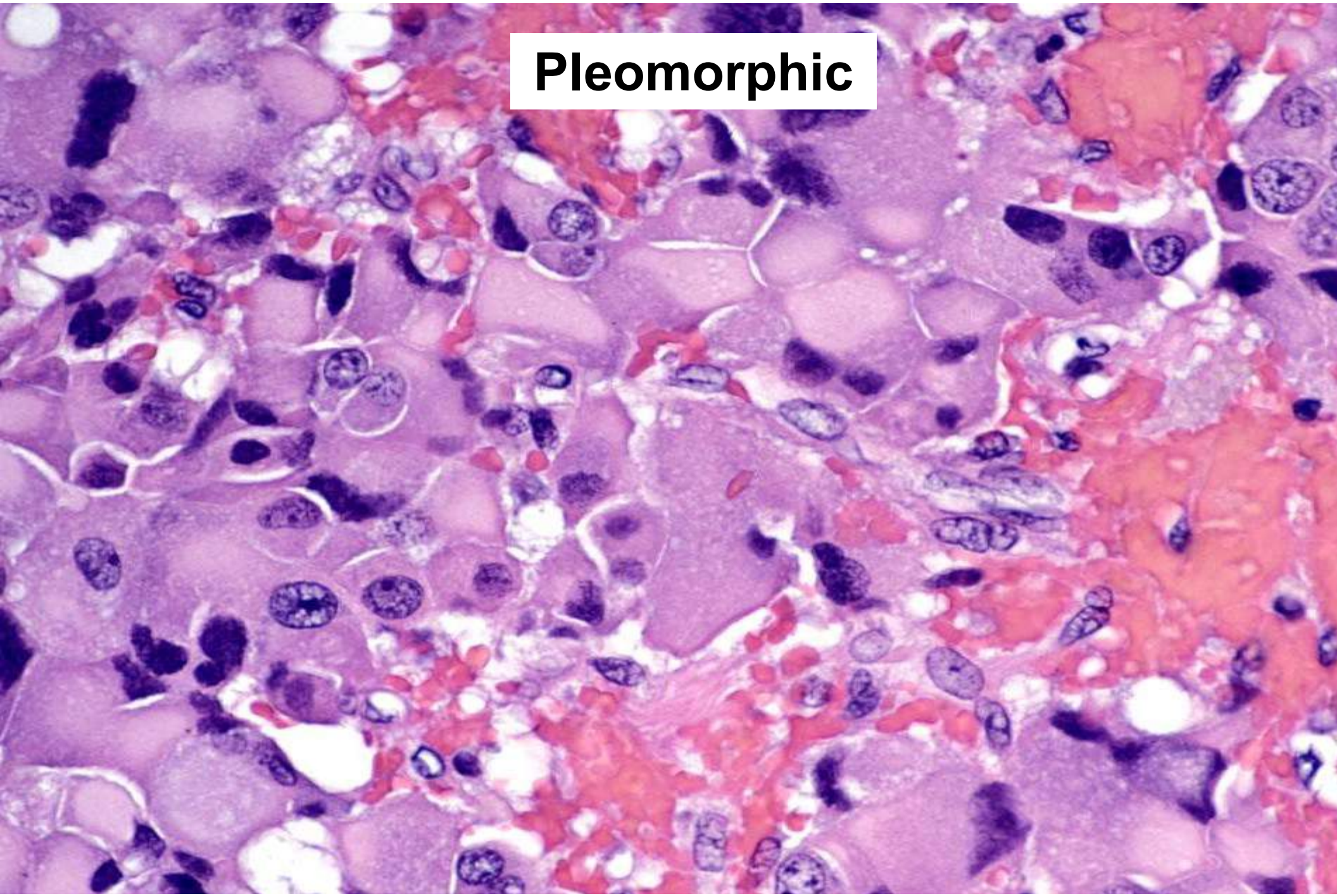

Se: 3
XY I216.0
Im: 90+C
DFOV 24.0cm
STND/+
50 M 552252
DOB: Mar 30 1953
Jun 19 03
512
R
L
120
120
kV 120
mA 220
Large %
3.0 mm/1.6:1


Pancreatic
Neuroendocrine
Neoplasm with
Cystic Change

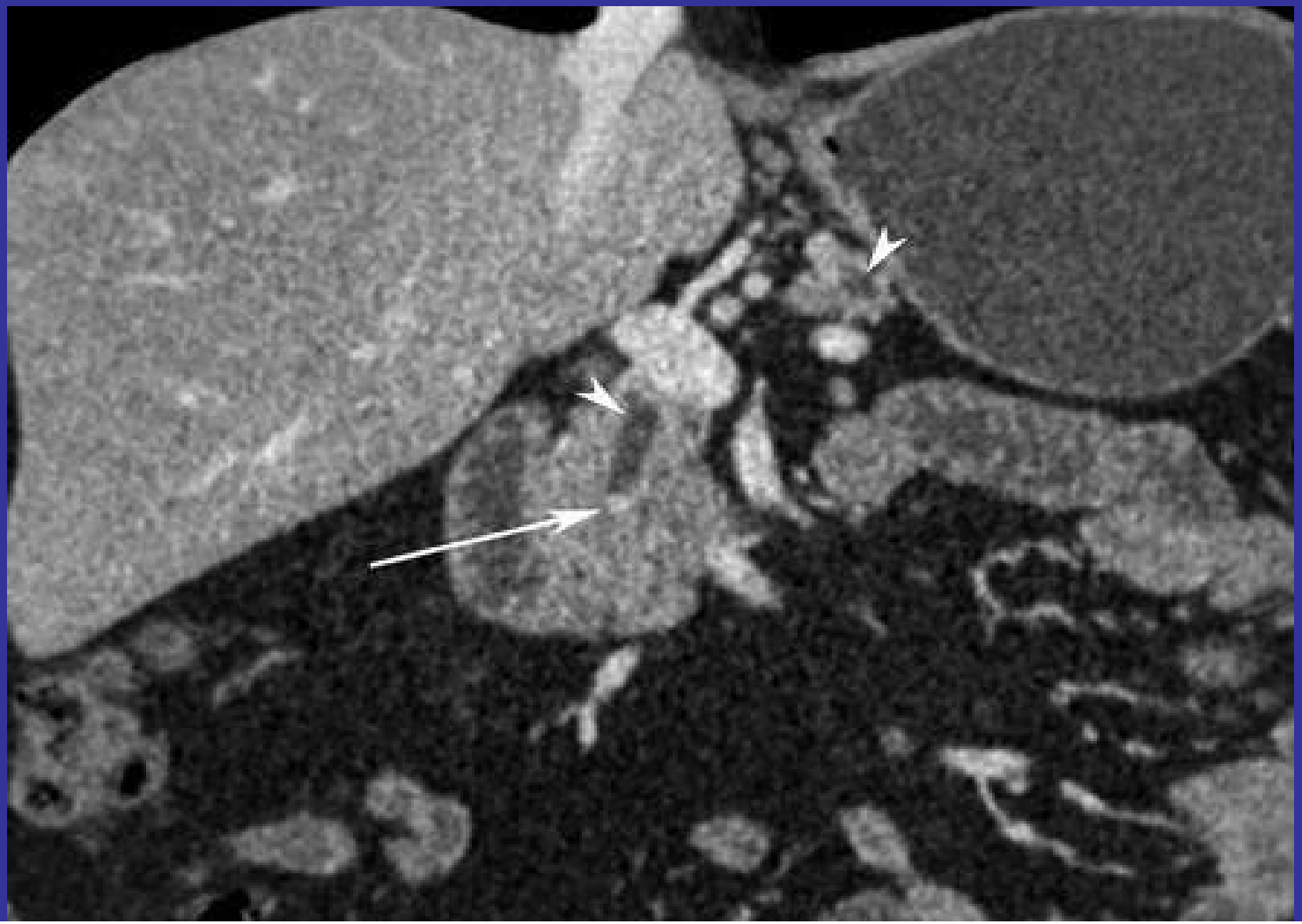


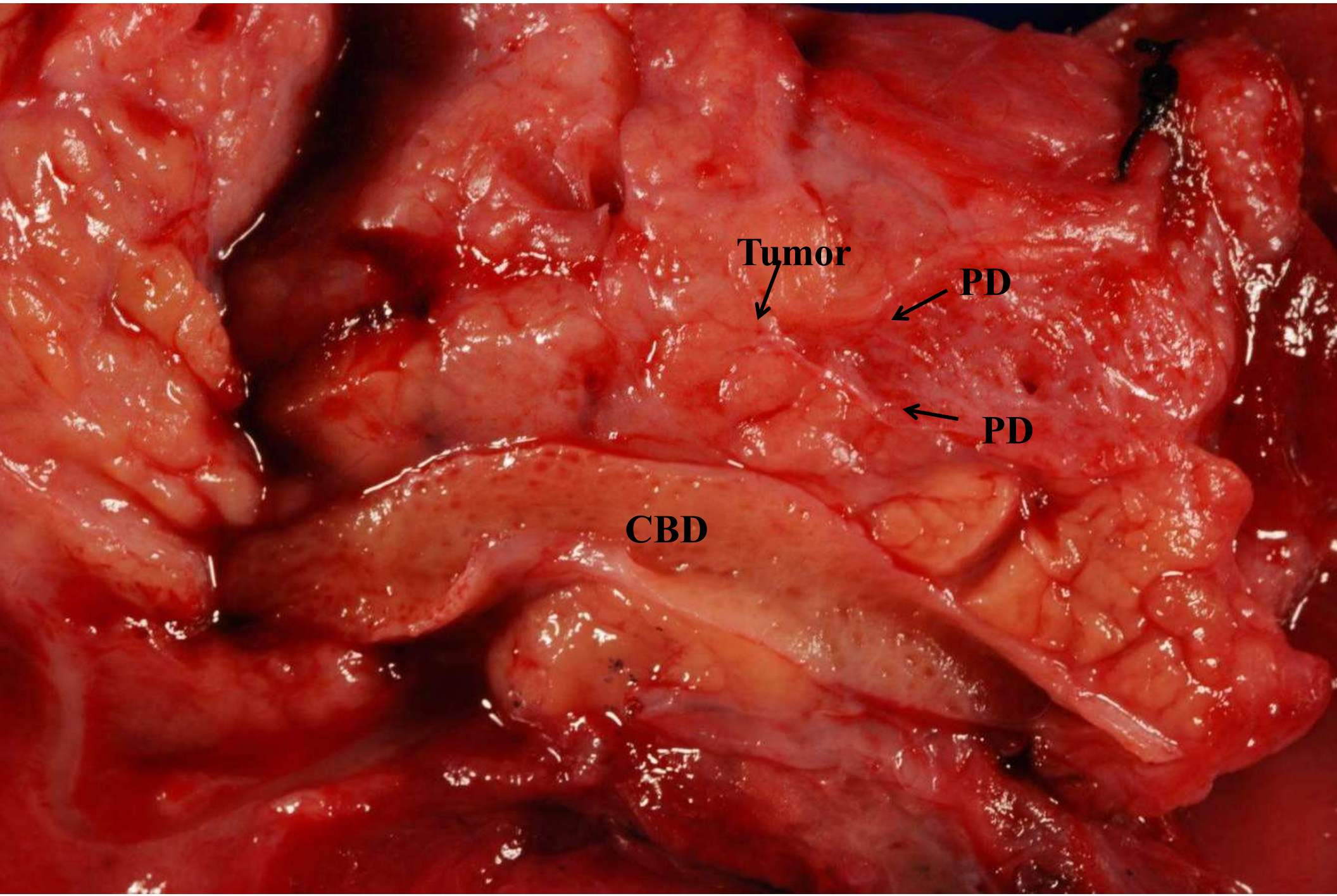

Oncocytic

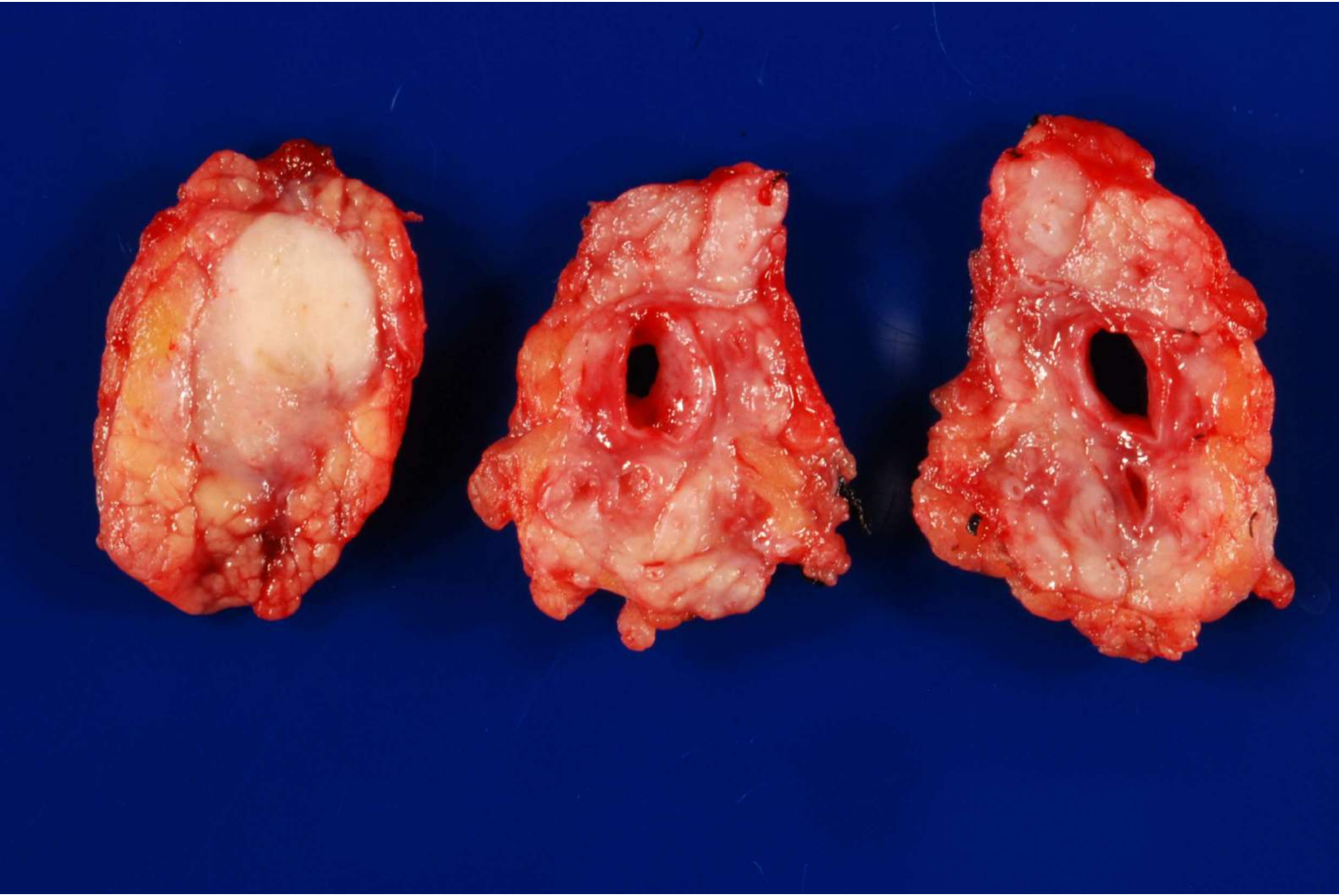

Clear Cell

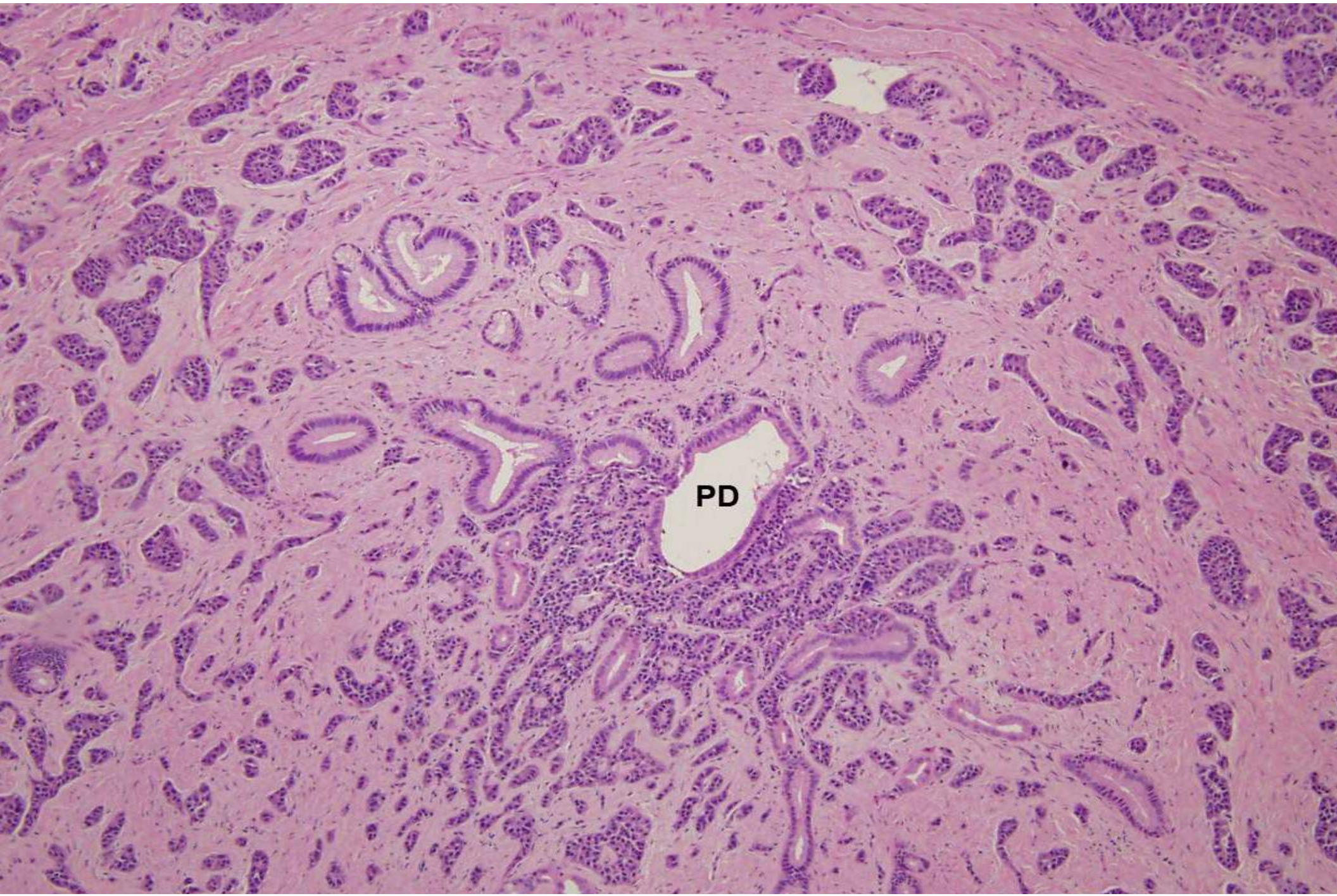

Pleomorphic

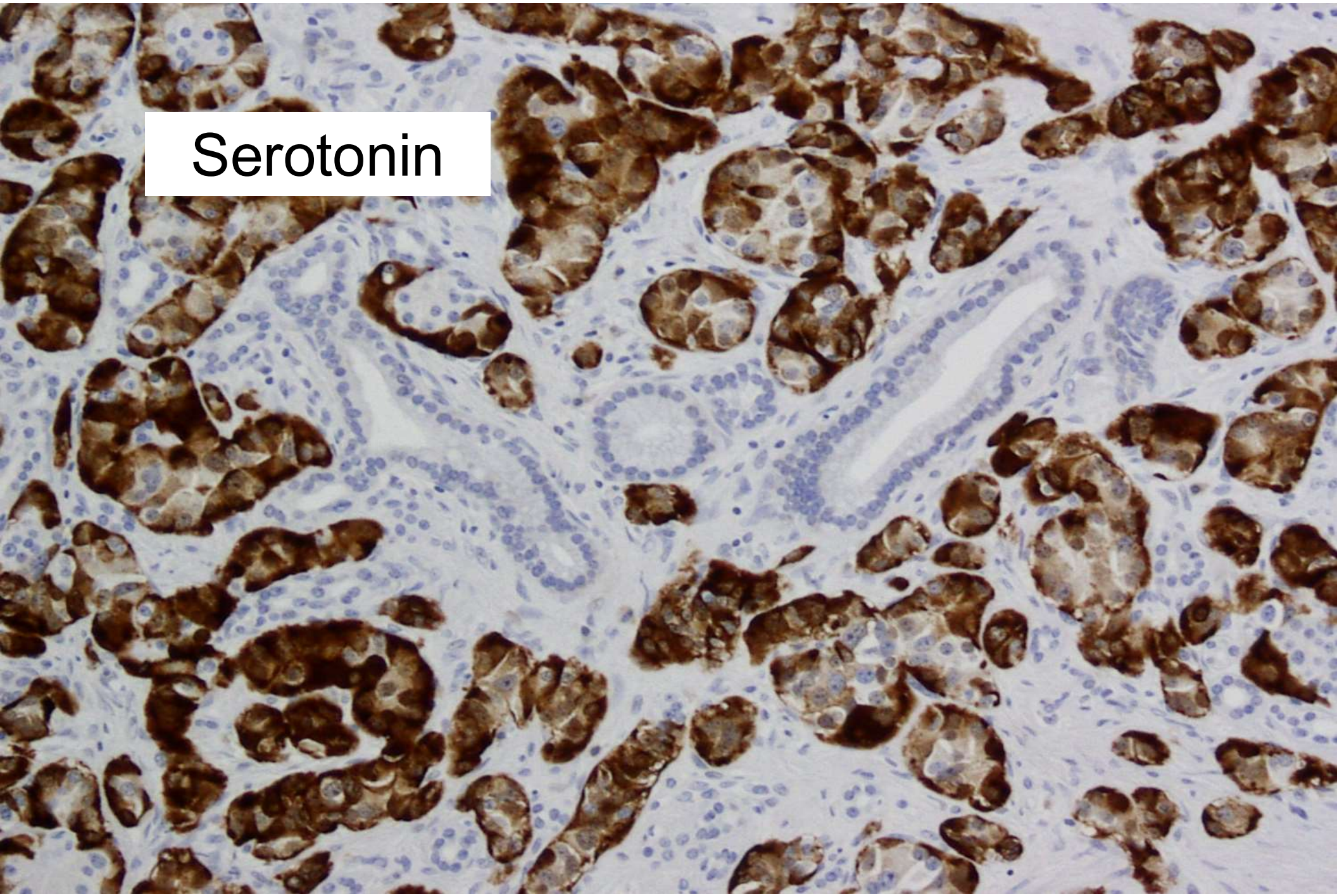
Small Serotonin-producing Duct-obstructing PanNET




Tumor
PD
PD
CBD




PD

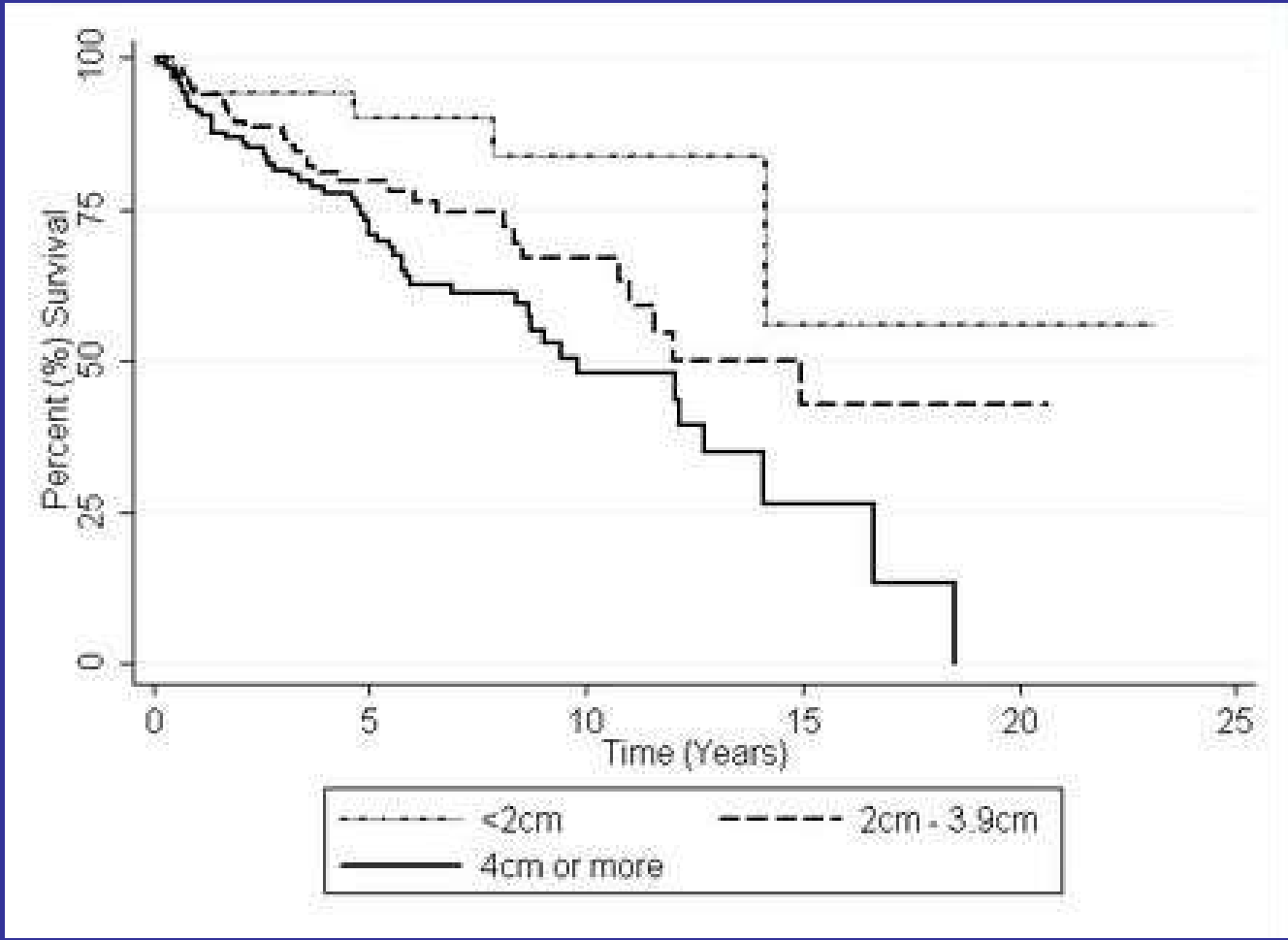

Serotonin

Prognostic Factors

- Natural history unpredictable
- Functional *vs*. nonfunctional
  - Insulinomas usually cured by excision (90% cured)
  - ALL others: 40-70% recur or metastasize
- Survival of PanNETs other than insulinomas after resection
  - 5 yr = 65%; 10 yr = 45%
- Adverse prognostic factors
  - Metastases
  - Size of primary
  - Mitotic rate

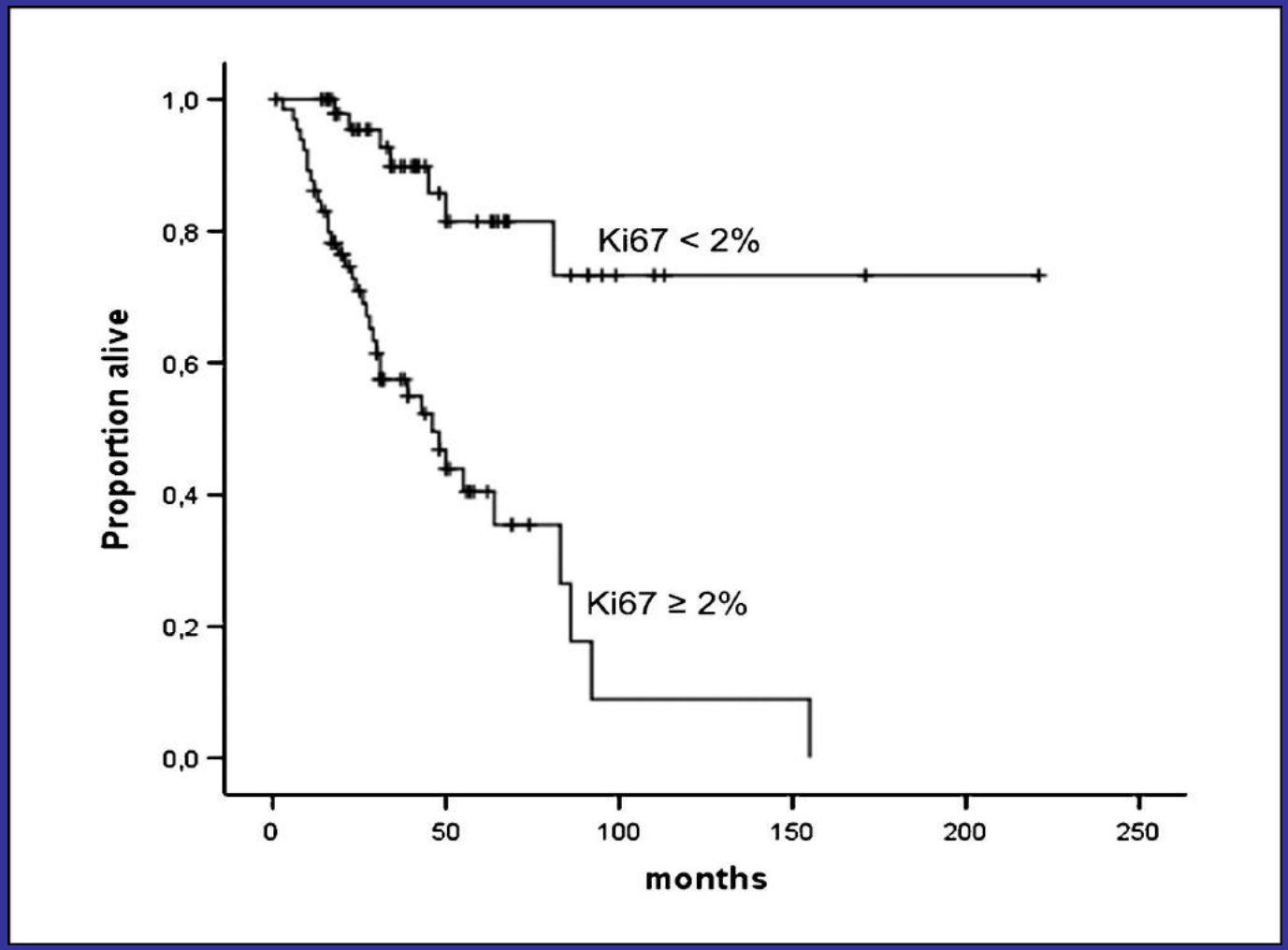
Survival with Size

Data From the Johns Hopkins Database: Size of the tumor(p=0.0018)

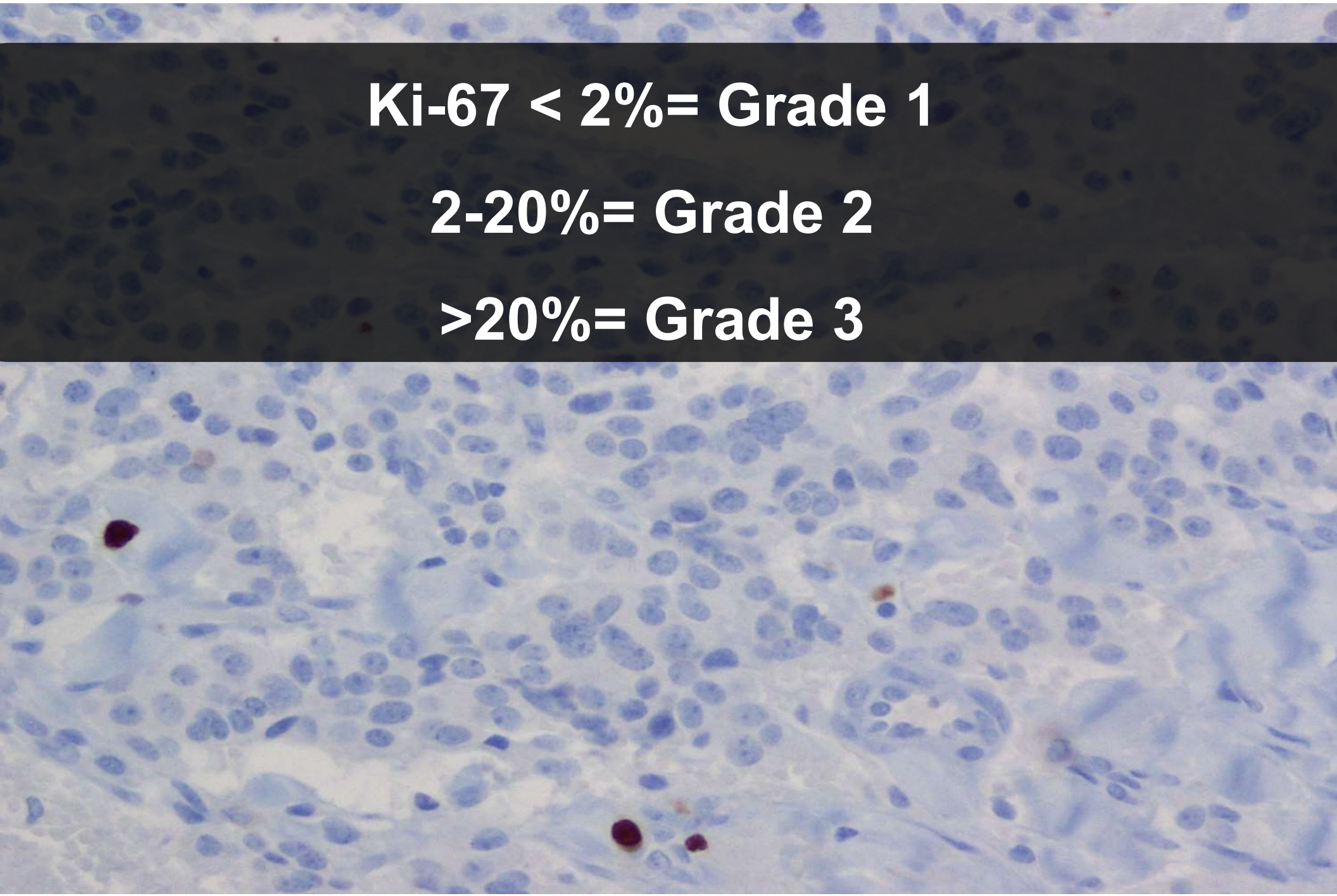


Barish Edil

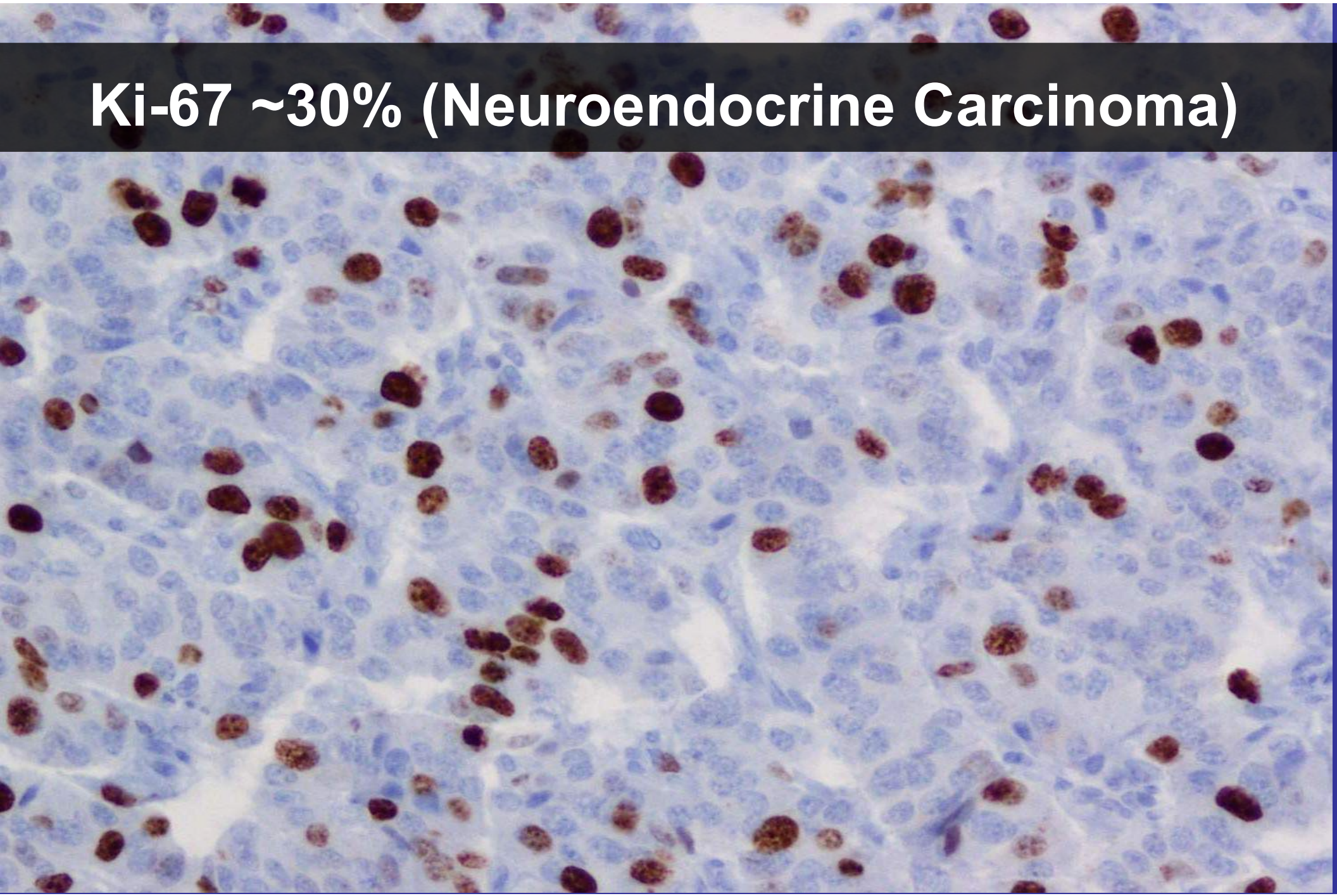
Ki-67 and Overall Survival



Ekeblad S et al. Clin Cancer Res 2008;14:7798-7803


Ki-67 < 2%= Grade 1
2-20%= Grade 2
>20%= Grade 3

Ki-67 ~30% (Neuroendocrine Carcinoma)

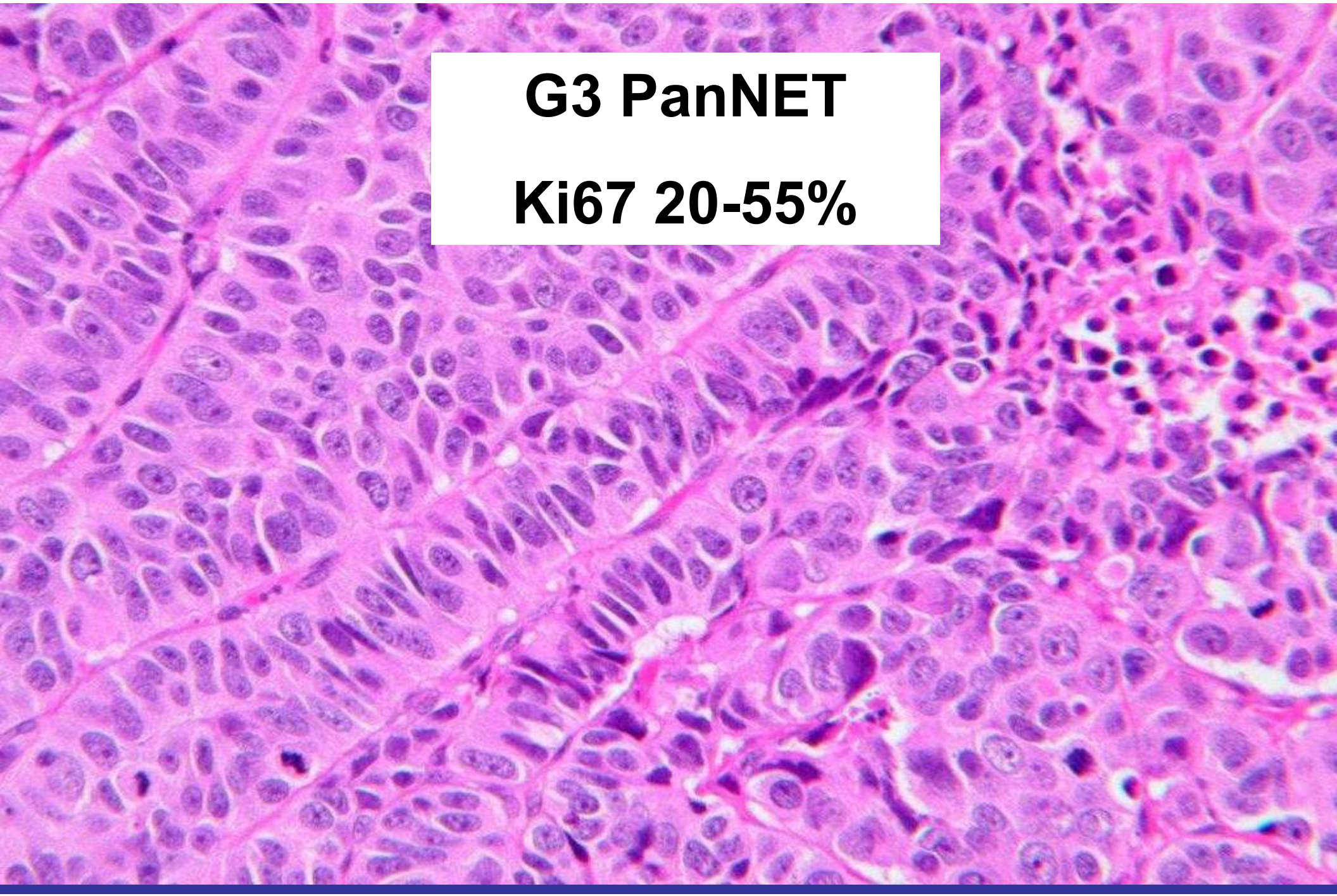


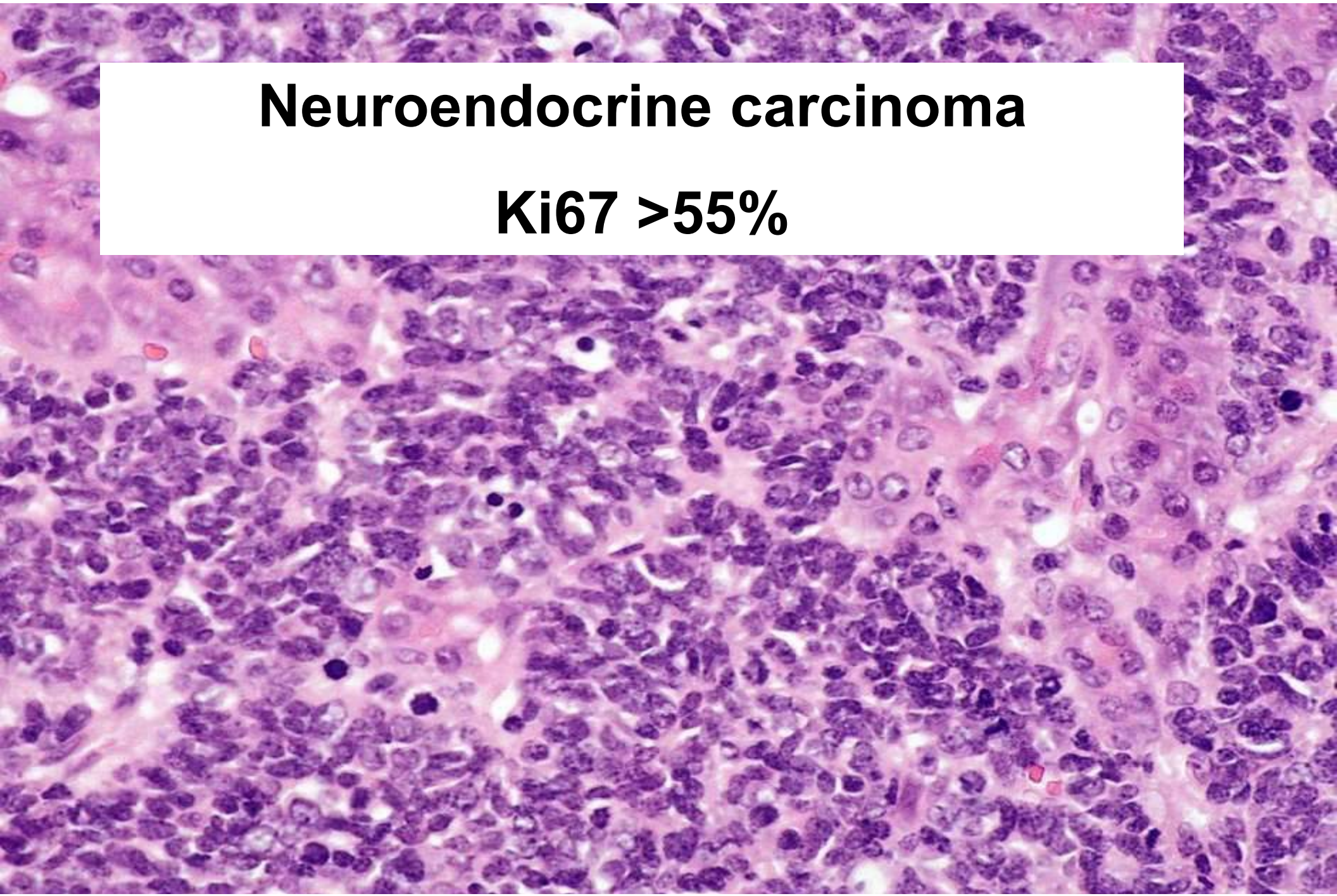
Neuroendocrine Carcinomas

- Defined by the presence of > 20 mitoses per 10 high power fields or Ki67>20%
- New WHO will separate out those that look like well-differentiated PanNETs but have a high mitotic rate (G3 PanNETs), from those with a high-grade morphology (NECs)

Neuroendocrine Carcinomas

- Rare; 2-3% of endocrine neoplasms
- Adults; male predominance
- Highly aggressive
- Small cell and large cell types
- By definition, >20 mitoses per 10 hpf
- Must exclude a metastasis / direct invasion

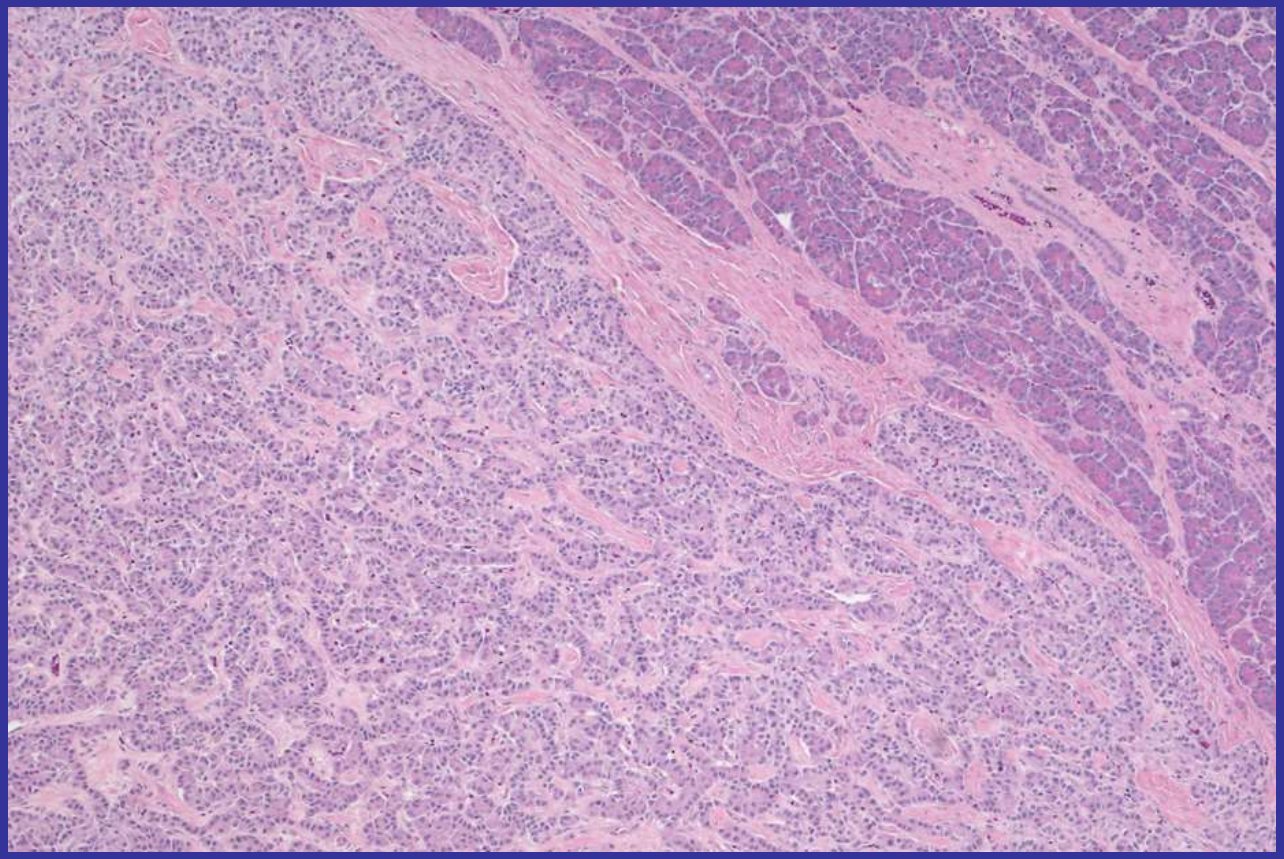

G3 PanNET
Ki67 20-55%


Neuroendocrine carcinoma
Ki67 >55%


Mitoses

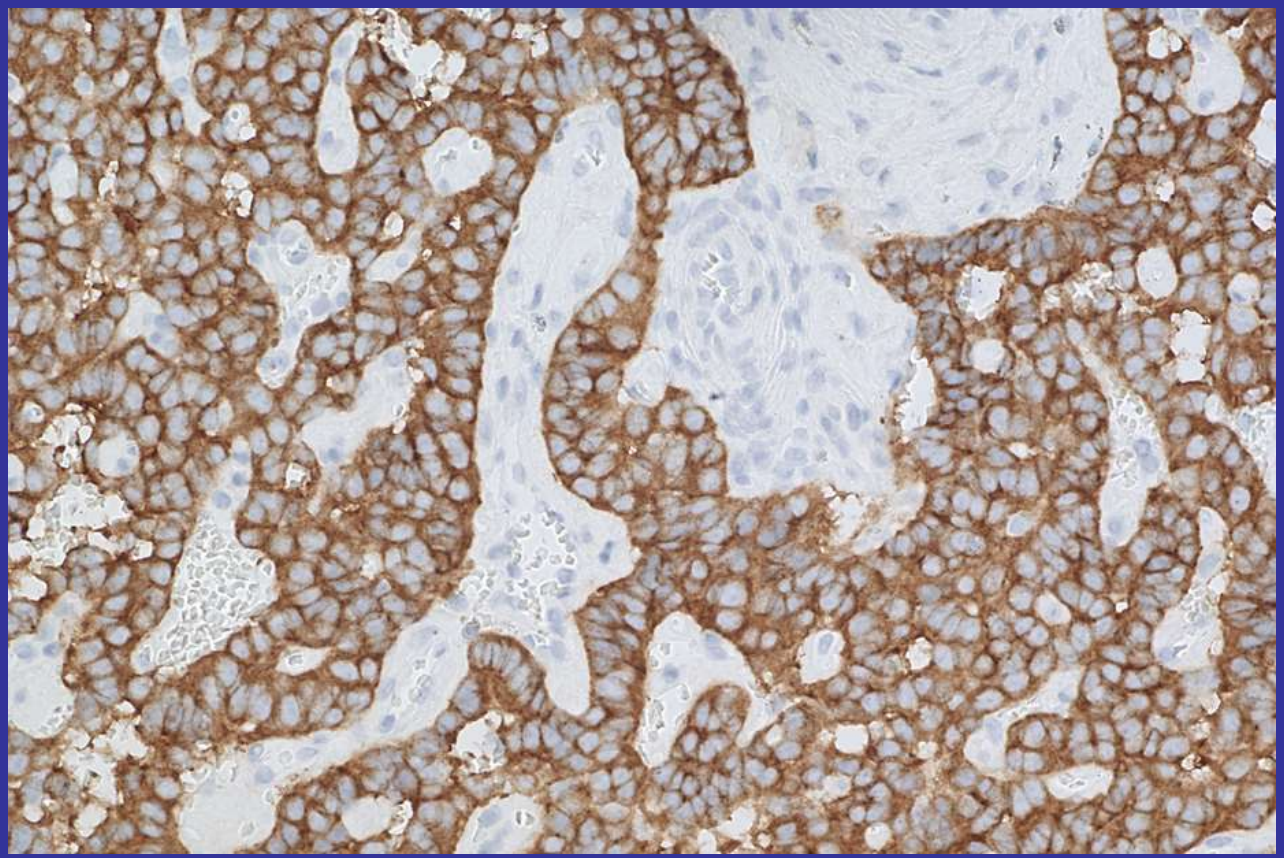
Take Home Message #1

Solid Cellular Neoplasm=Think of PanNET



Take Home Message #2

Hormone expression does NOT make a neoplasm syndromic

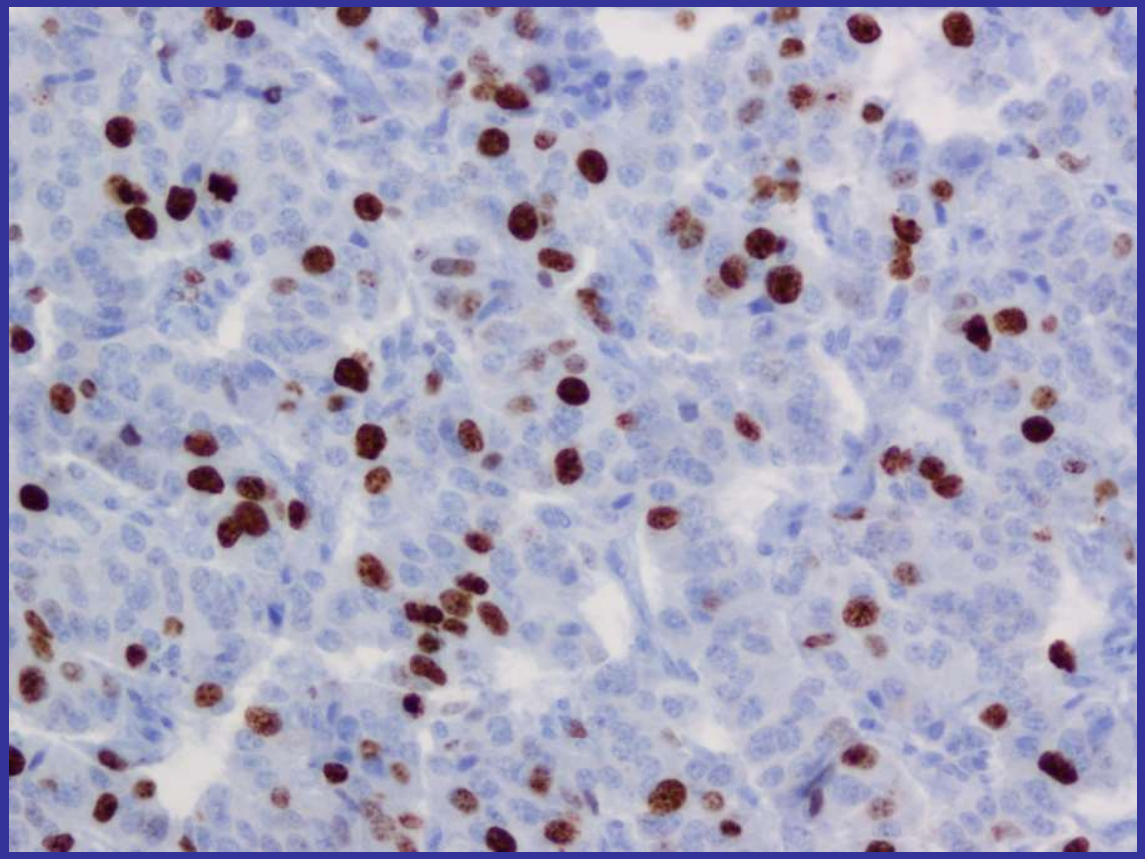


Take Home Message #3

Look at the duodenum in MEN-1

Take Home Message #4

Report the mitotic rate (count or Ki-67)



Thank You!

@Hopkins_GI_Path