Acinar Cell Carcinoma
and differential diagnosis from
Pancreatic Neuroendocrine Neoplasm
&
Solid Pseudopapillary Neoplasm

Pancreatic Pathology course

Belgian Society of Pathology - Working Group of Digestive Pathology

14 May 2022

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Dept. of Pathology

Ghent University Hospital

Overview

- **Acinar cell carcinoma**
  - Macroscopy & Histopathology
  - Immunohistochemistry (& Molecular pathology)
  - Prognosis & Management
- **Variants**
  - Acinar cell cystadenocarcinoma
  - Mixed acinar carcinoma
  - Intraductal nodular and papillary variants
- **Differential diagnosis**
  - From neuroendocrine neoplasm
  - From solid pseudopapillary neoplasm
  - From hepatoid carcinoma
  - From pancreatoblastoma
  - From intraductal papillary neoplasms

PANCREATIC ACINAR CELL CARCINOMA

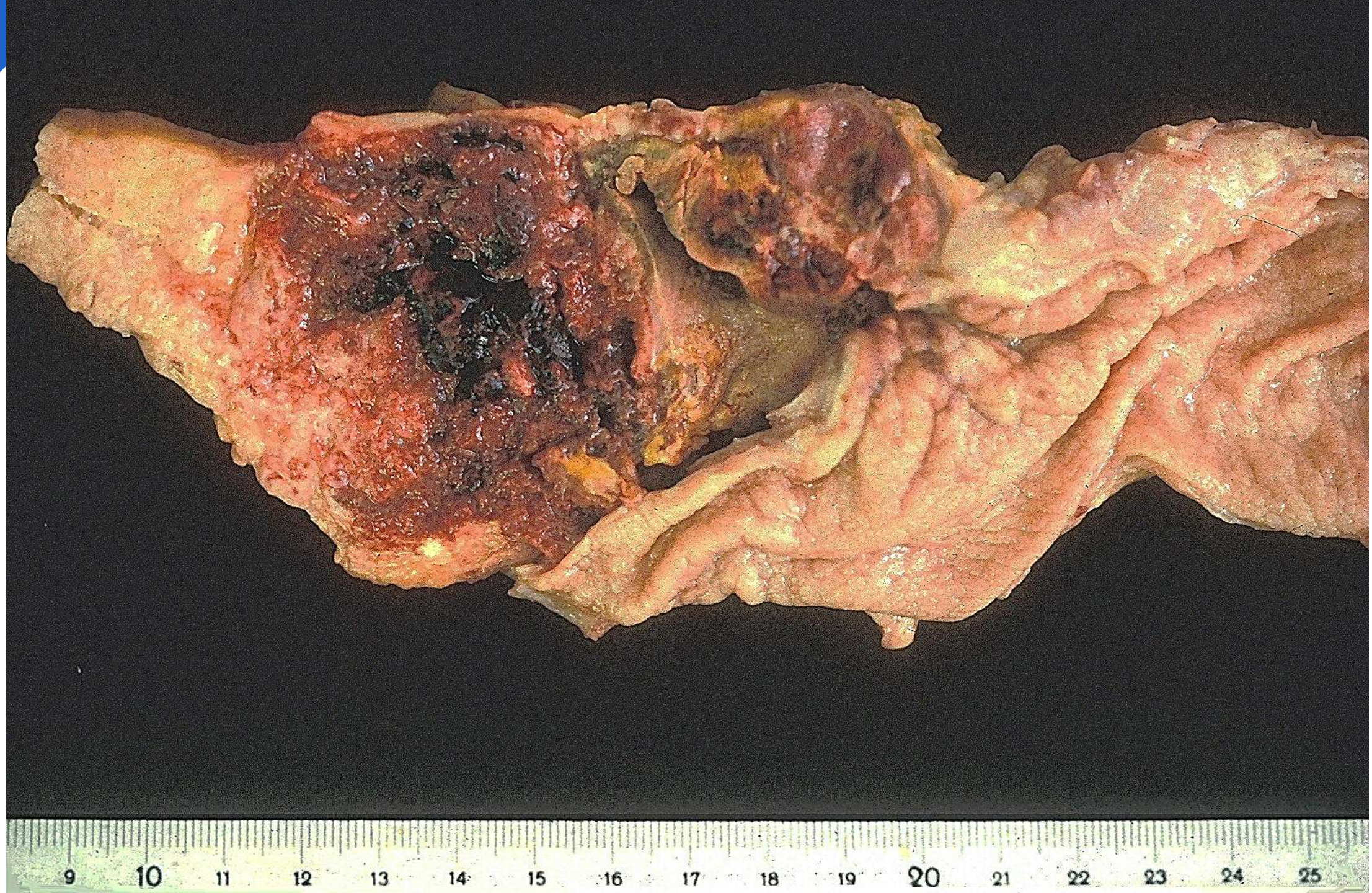
- High grade malignant neoplasm with acinar cell differentiation
- Rare (1-2% adults)
- Mean age 60 (range 3-90)
- M/F = 2:1
- Symptoms: weight loss, abdominal pain, nausea, vomiting, rarely jaundice
  - Lipase hypersecretion syndrome (10-15%)
    - Subcutaneous fat necrosis, polyarthragia, eosinophilia
- Serum AFP levels may be elevated
- Most f. head, followed by tail and body

Hoorens et al. Am J Pathol. 1993;143:685-98
Klimstra et al. Am J Sug Pathol. 1992;16:815-37
La Rosa et al. Am J Surg Pathol. 2012;36:1782-95

Prof. Dr. Günter Klöppel
Hamburg
Brussel
Kiel
München

Macroscopy

- Well-circumscribed
- Partially encapsulated
- Generally large (average 10 cm)
- Pink to red/brown
- Solid
- Soft consistency
- Often haemorrhage, necrosis, cystic degeneration
- May show intraductal growth
- May invade adjacent structures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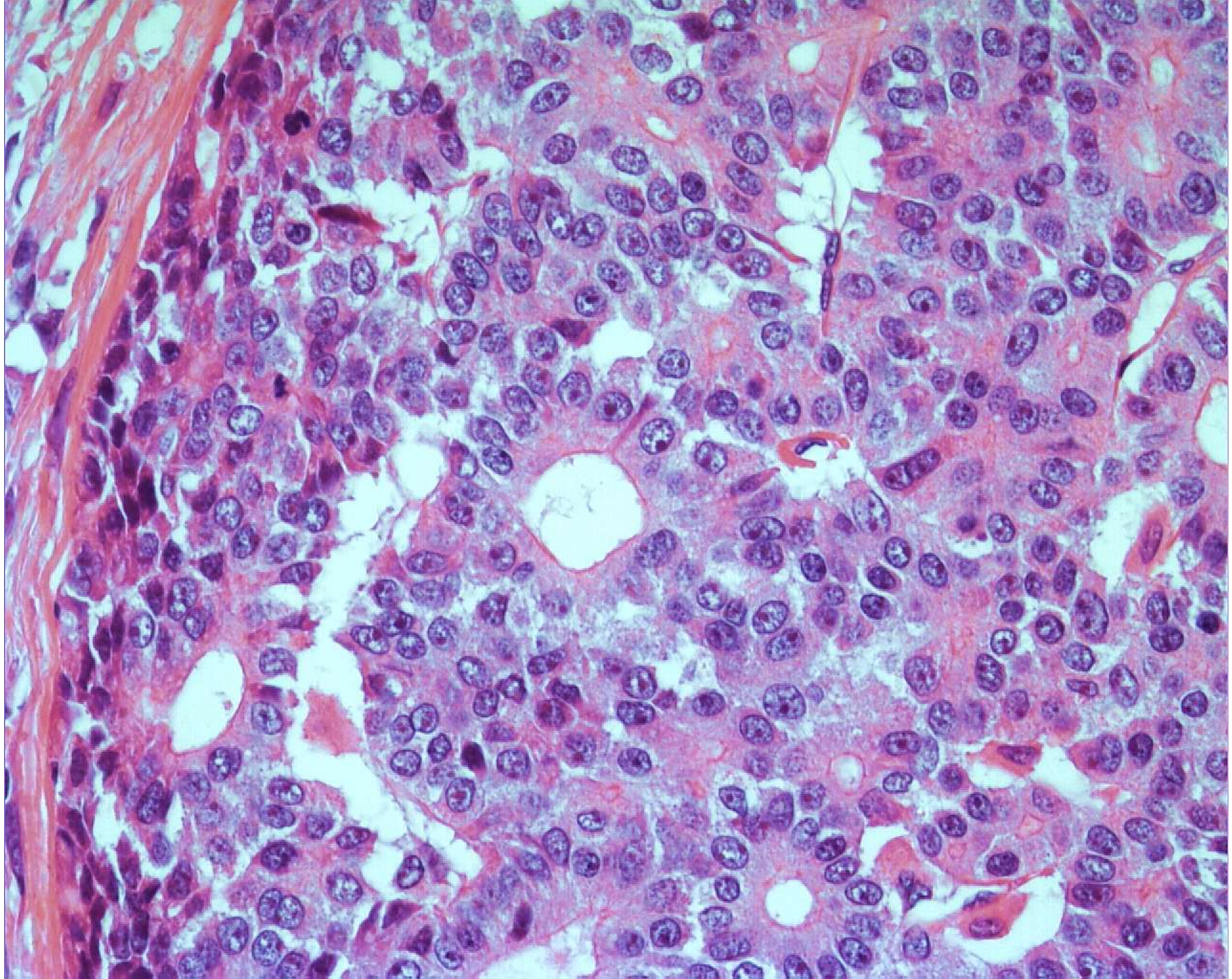
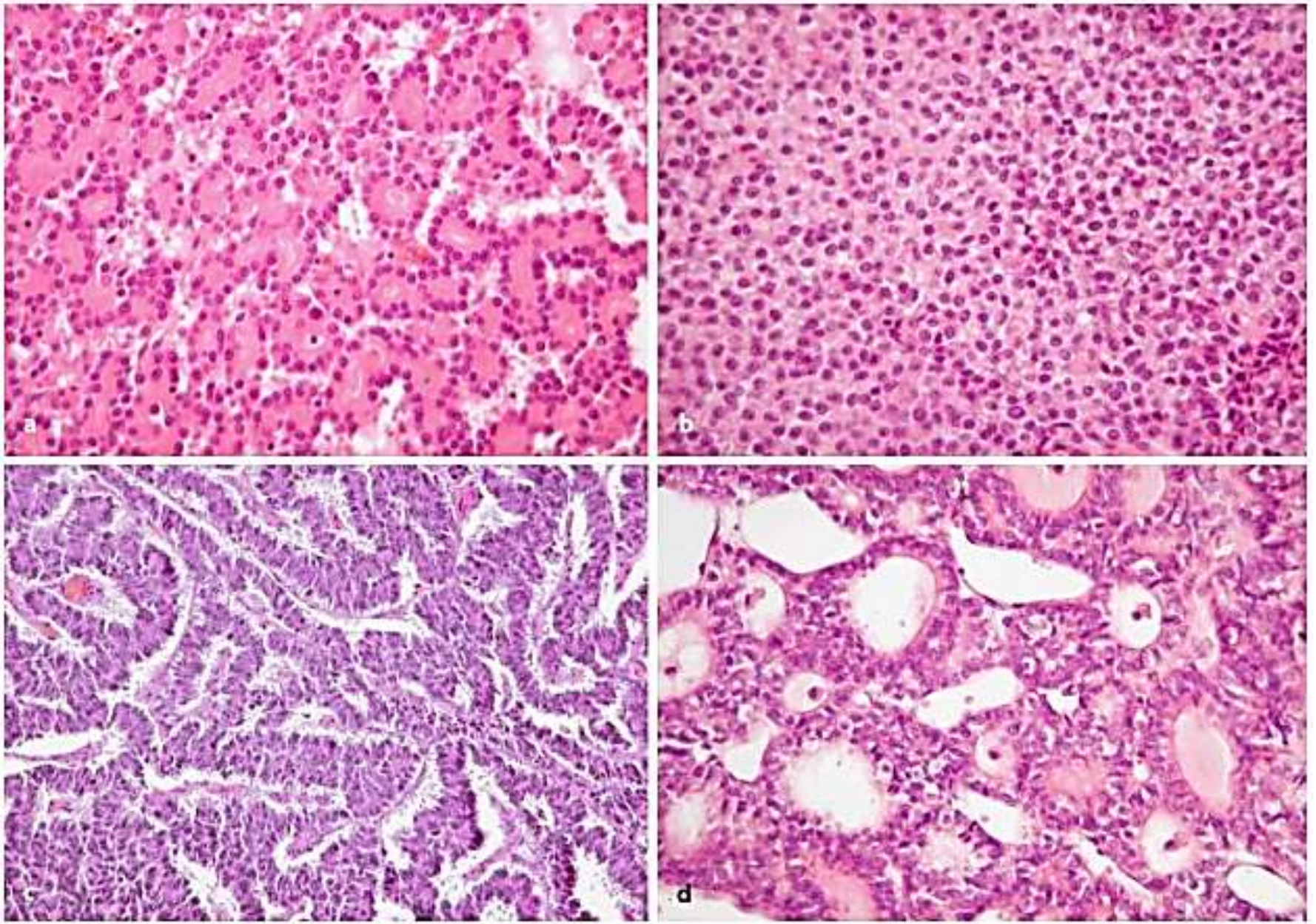
Histopathology

- Lobular, highly cellular, limited fibrovascular stroma
- Pushing rather than infiltrative border
- **Acinar, solid**, glandular, trabecular growth pattern
- Granular eosinophilic cytoplasm with zymogen granules (weakly PASD+)
- Uniform round vesicular nuclei with single prominent nucleolus
- Mitotic activity generally high
- F. vascular invasion/ less f. perineural invasion





Sipos et al. Pathologe. 2005;26:37-40

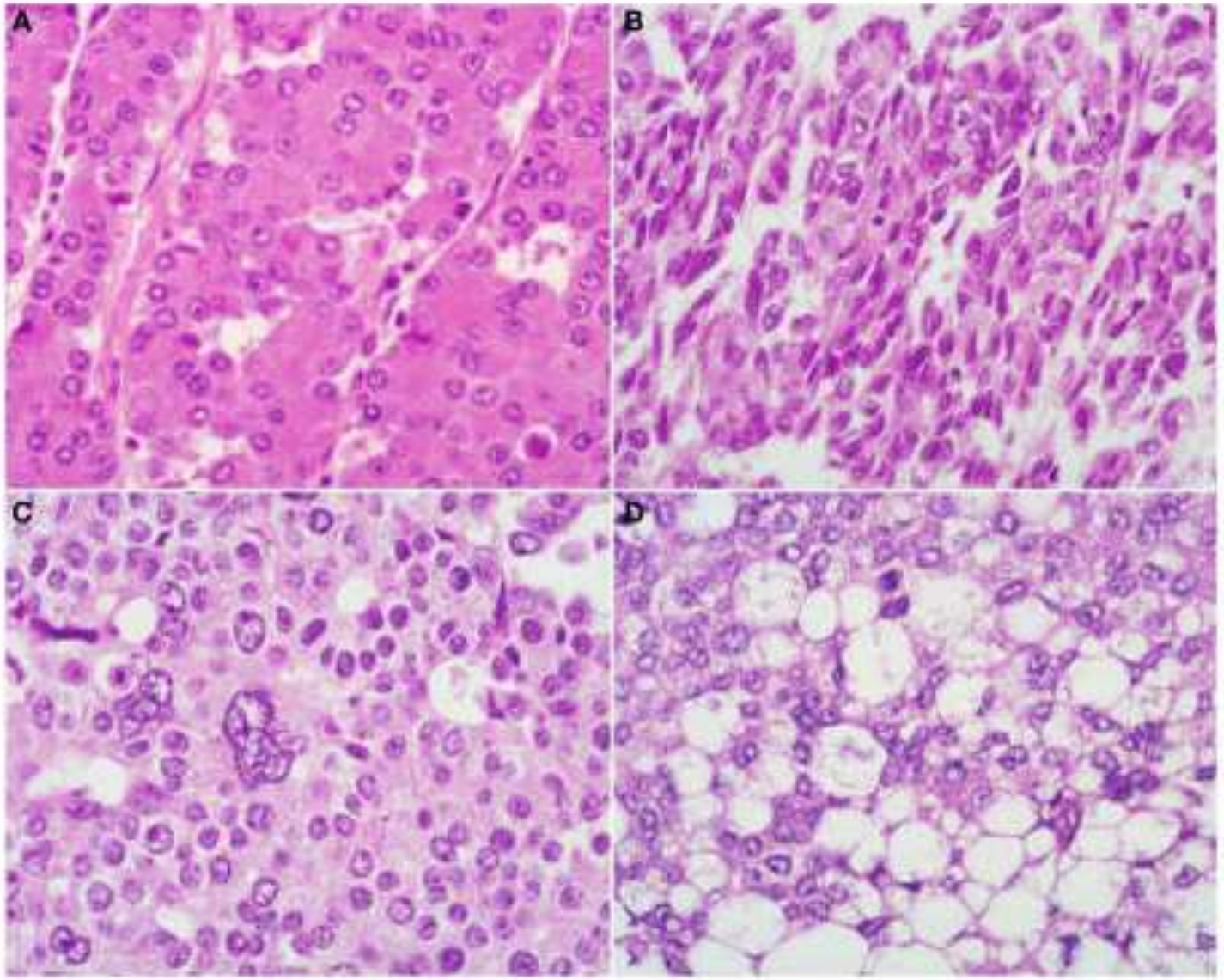


FIGURE 4 | Uncommon histological features of pancreatic acinar cell carcinomas include oncocytic cells (A), spindle cells (B), pleomorphic cells (C) and clear cells (D).

La Rosa et al. Front Med (Lausanne). 2015;15:41.

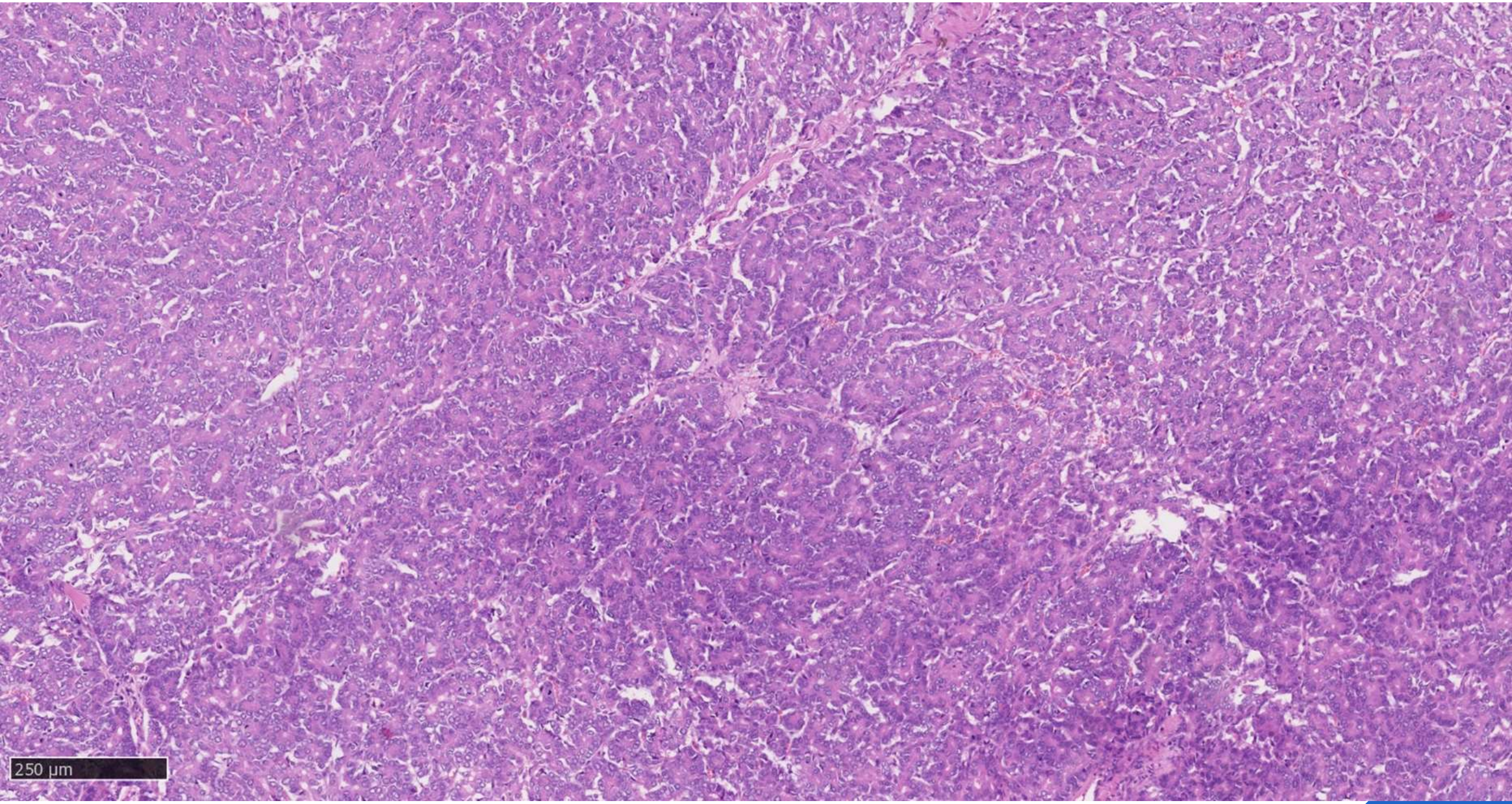
Immunohistochemistry

- Demonstration of acinar differentiation
- Useful markers include Trypsin, Chymotrypsin, Lipase and BCL10*
  - Trypsin, Chymotrypsin and BCL10 antibodies are most sensitive
  - Simultaneous use of 2 of them allows detection of nearly 100%
  - *CPA1-Carboxypeptidase A1***
- Nuclear expression of β-catenin in small number, patchy or diffuse
- NE markers (CGA/SYP) often focally positive

- AFP, HepPar-1, Glypican-3, Albumin mRNA-ISH may be positive

*Monoclonal anti-BCL10 Ab (clone 331,1)

*La Rosa et al. Virchows Arch. 2008;454:133-142
**Uhlig et al. Am J Surg Pathol. 2022;46:97-104
La Rosa et al. Am J Surg Pathol. 2012;36:1782-95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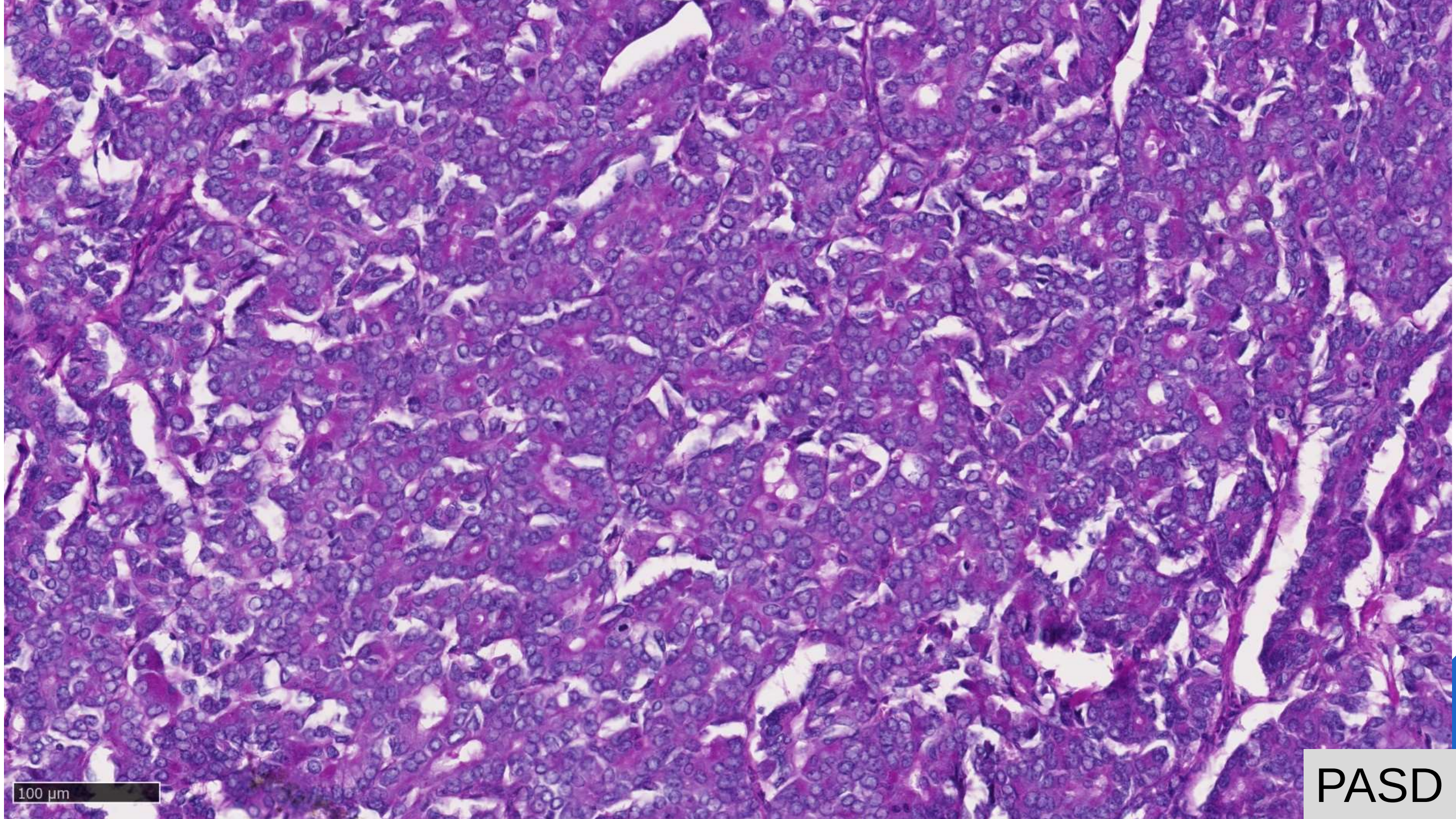
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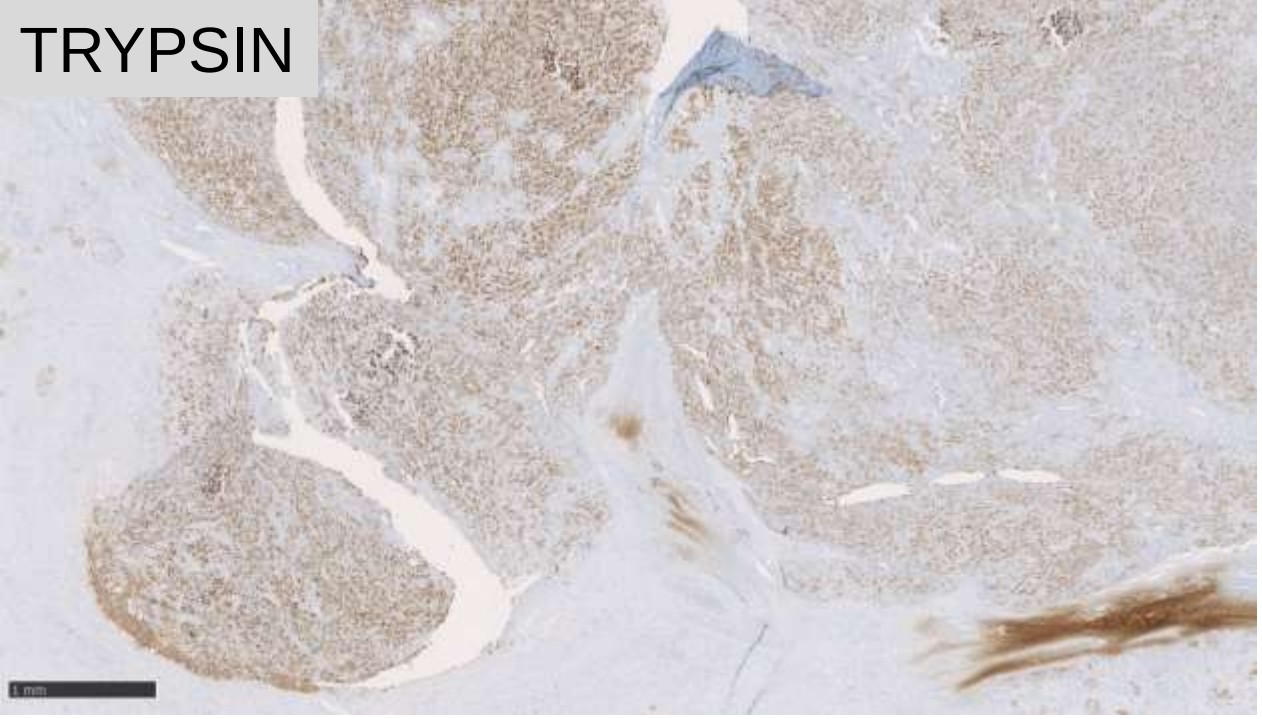
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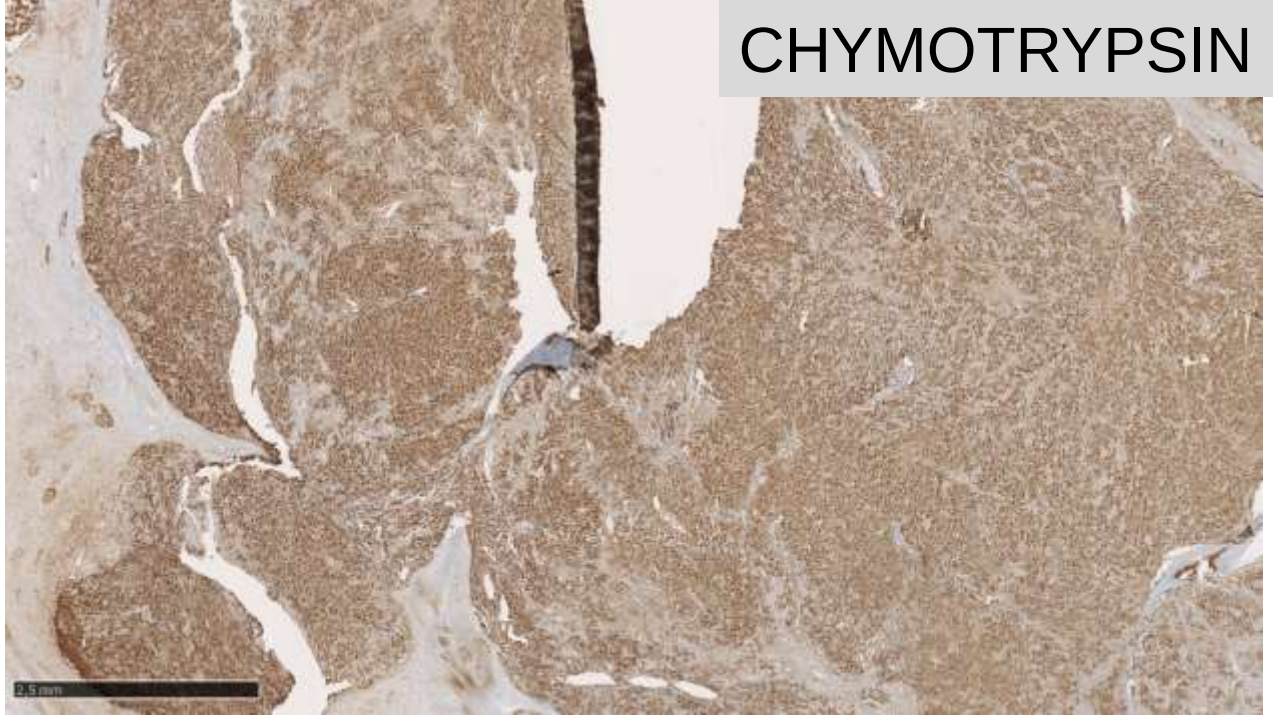
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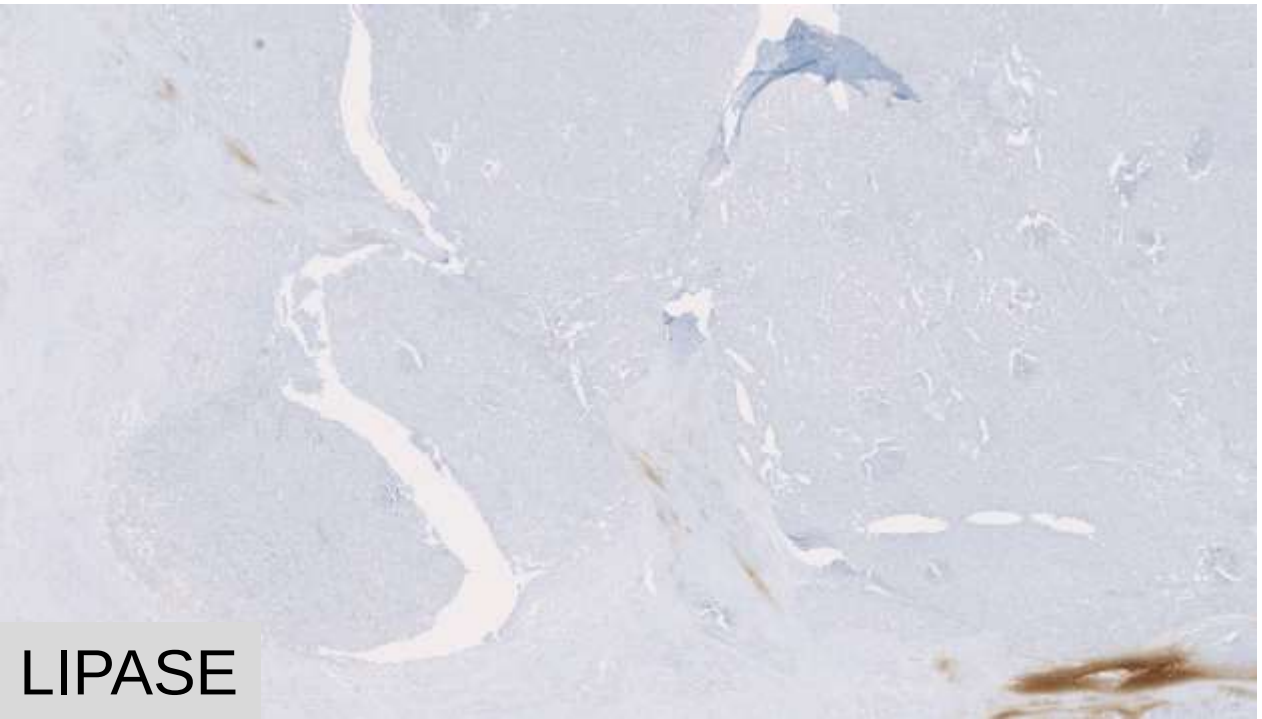
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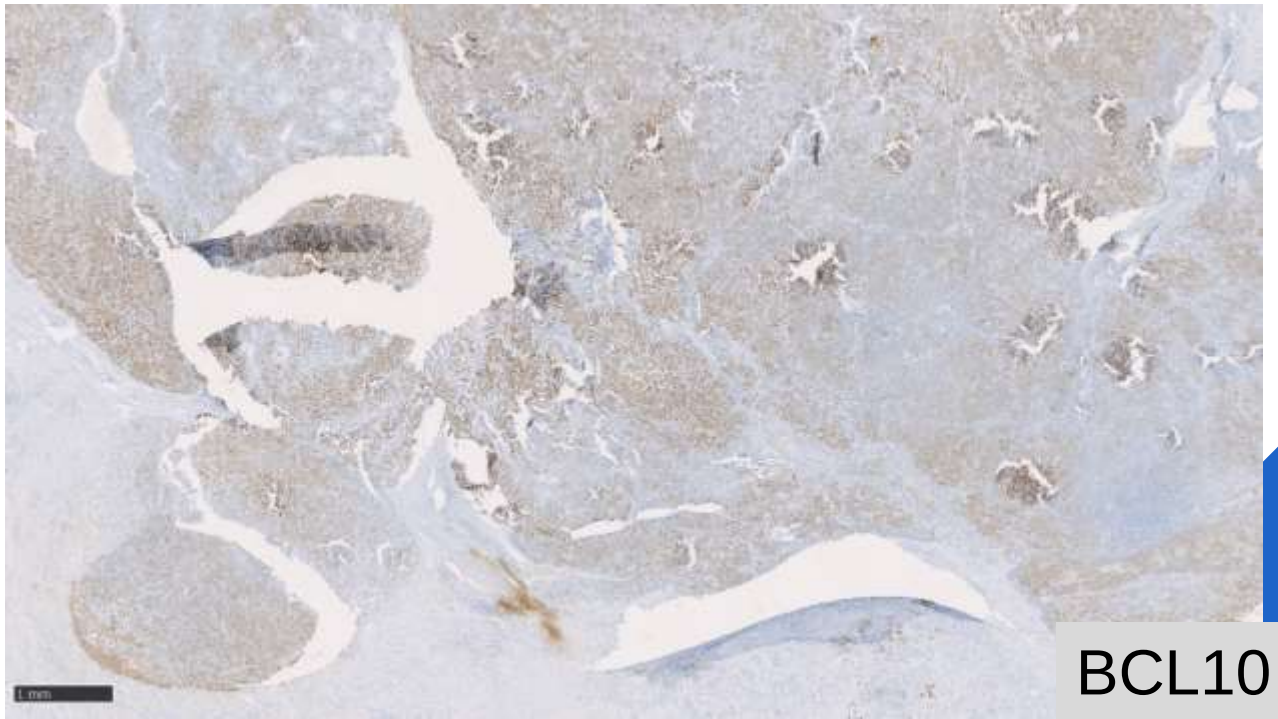
BCL10

Molecular pathology

- *KRAS* mutations extremely rare
- *TP53*, *SMAD4*, *CDKN2A* in <25%

Prognosis & Management

- Aggressive
- Prognosis slightly better than PDAC
- 5-yr survival rate resectable vs. unresectable tumors: 36-72% vs. 9-22%
- 50% present with metastatic disease (ln, liver, peritoneum)

- Acinar cell carcinoma with intraductal growth has a better prognosis

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Acinar cell cystadenocarcinoma

- Acinar cell carcinoma exclusively characterized by variable-sized cysts
- Non-degenerative cyst formation
- Extremely rare
- Behaviour similar to conventional acinar cell carcinoma

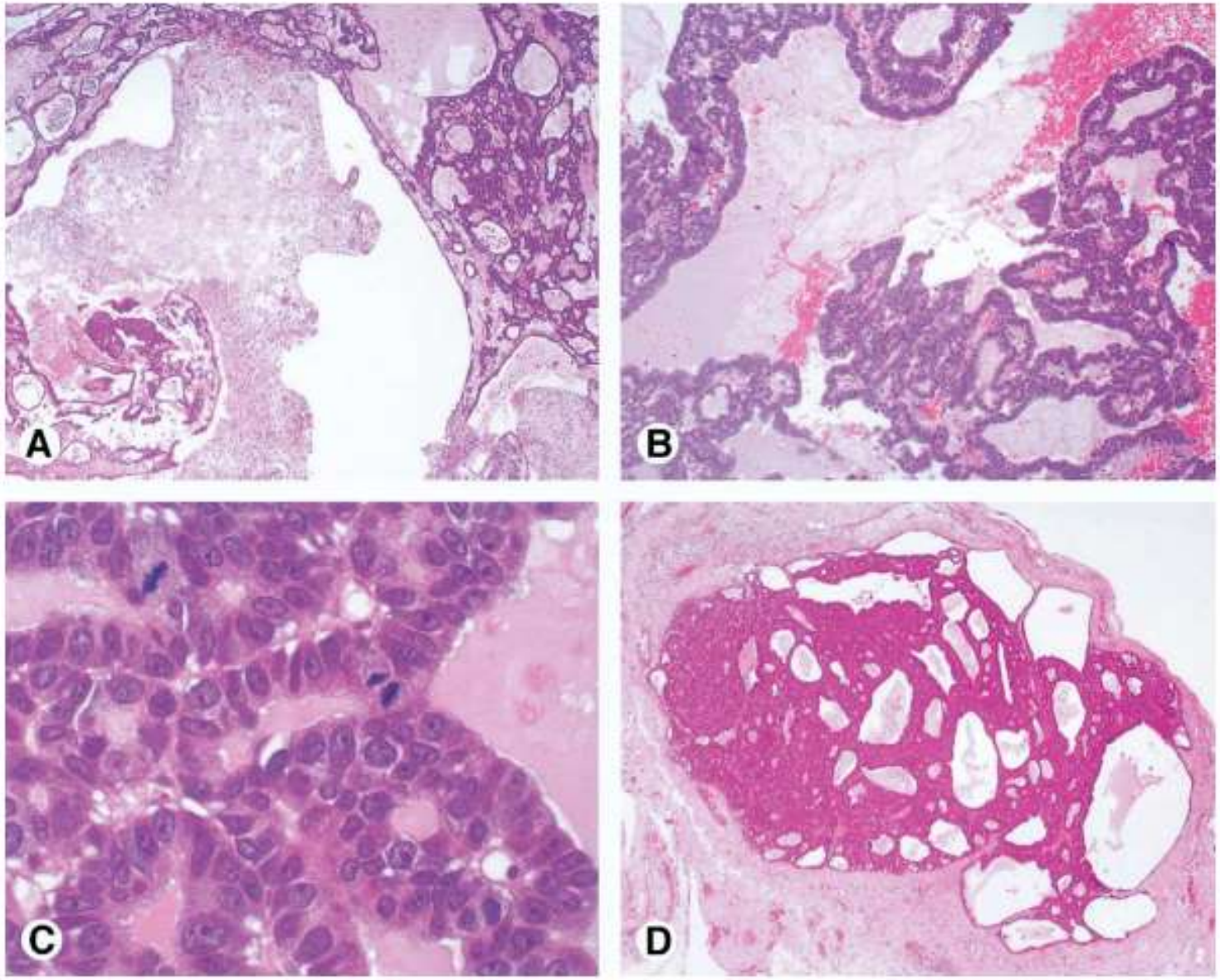


FIGURE 2. (A and B) Tumor consisting of cysts and tubular structures lined by a single layer of low cuboid or columnar epithelium and containing eosinophilic material. (Hematoxylin and eosin; original magnification A, × 40; B, × 100.) (C) At higher magnification, the tumor cells show the typical features of acinar cells. Note the high mitotic rate. (Hematoxylin and eosin; original magnification × 400.) (D) Metastatic implant in the peritoneum overlapping the primary tumor. (Hematoxylin and eosin; original magnification × 40.)

Colombo et al. Hum Path. 2004;35:1568-71

Mixed acinar carcinomas

- Pancreatic carcinomas with mixed differentiation are rare
- Often primary component demonstrates acinar differentiation
- Mixed carcinomas are defined as having ≥30% of each line of differentiation
  - Mixed acinar-neuroendocrine carcinoma: most common
  - Mixed acinar-ductal carcinoma
  - Mixed acinar-ductal-neuroendocrine carcinoma

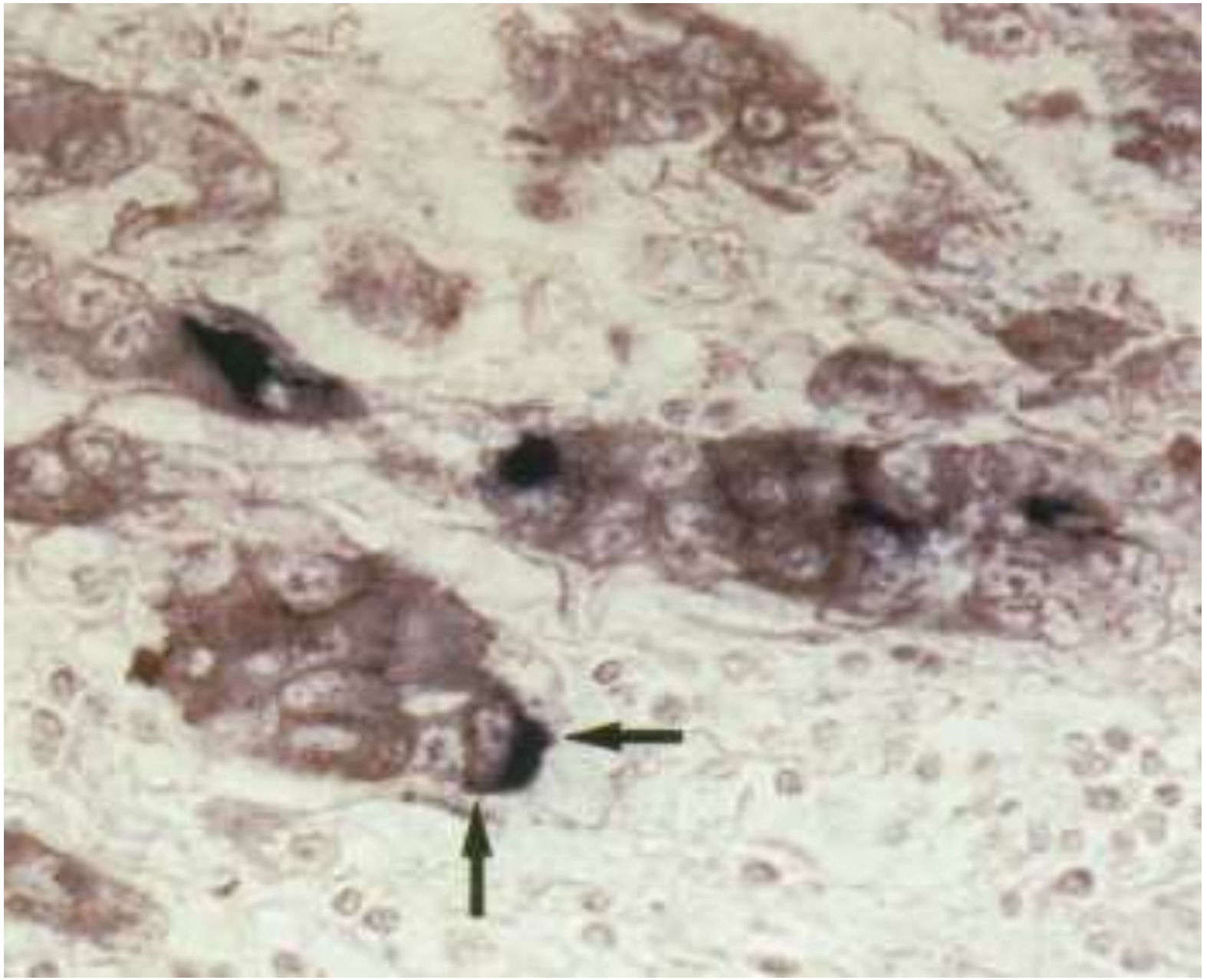
Mixed acinar-neuroendocrine carcinoma

- IHC co-expression of acinar and NE markers
- Most f. intimate mixture of the two cell types
- Most amphicrine differentiation

  Individual tumour cells express both acinar and NE markers

  Do not meet definition for MiNEN: requires morphological recognizable different components
- Best regarded as **subtype of acinar cell carcinoma**

  Same clinical behaviour and genomic features



Hoorens et al. Am J Pathol. 1993;143:685-98

Intraductal variants

- Nodular growth pattern with extension into ducts as macroscopically visible polypoid projections

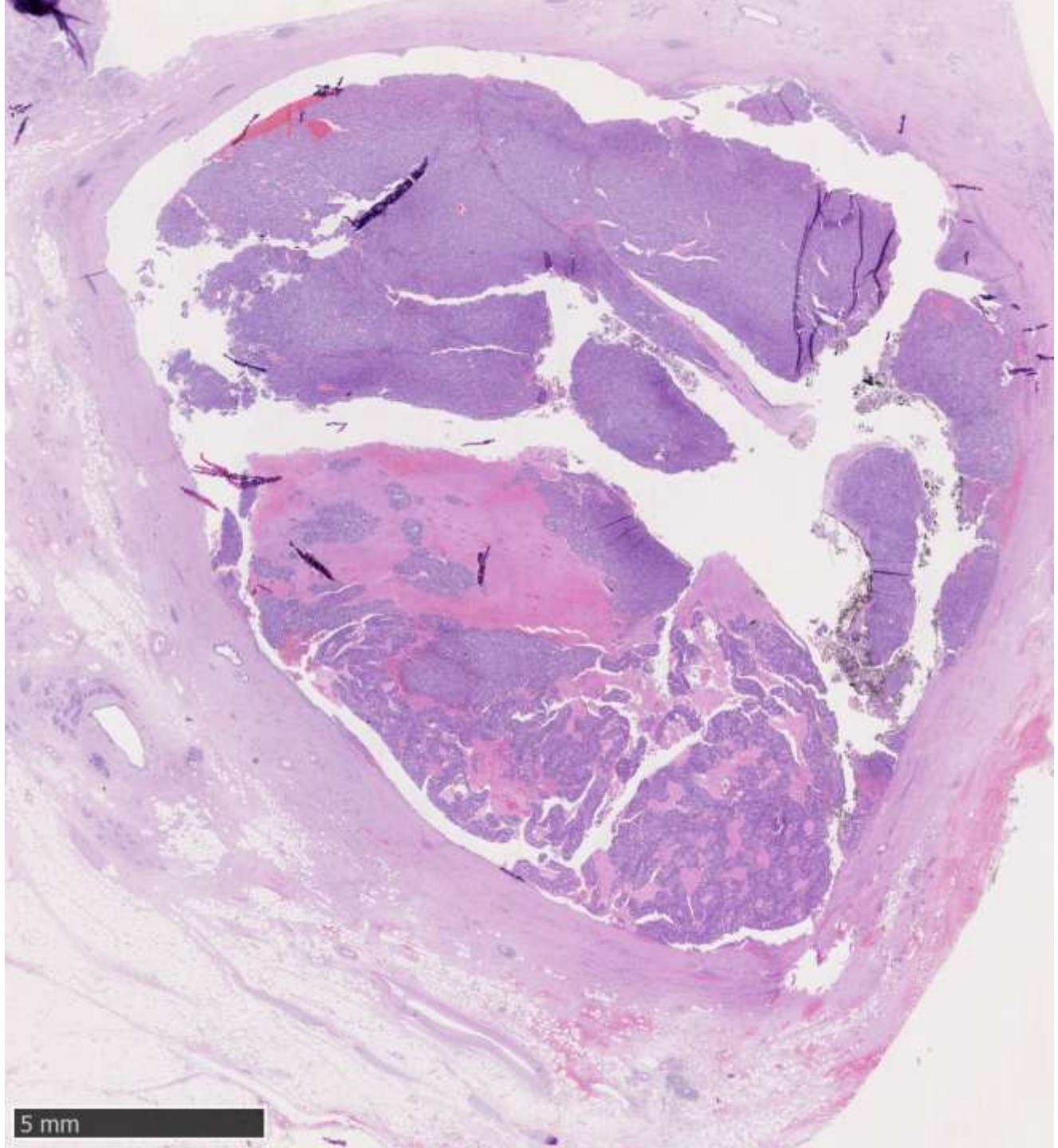
Or

- Papillary or papillocystic growth pattern with papillae with fibrovascular cores with intraductal growth

Or

- Diffuse involvement of the pancreatic duct without distict tumoral mass outside ducts

Mimicking IPMN: IHC to show acinar differentiation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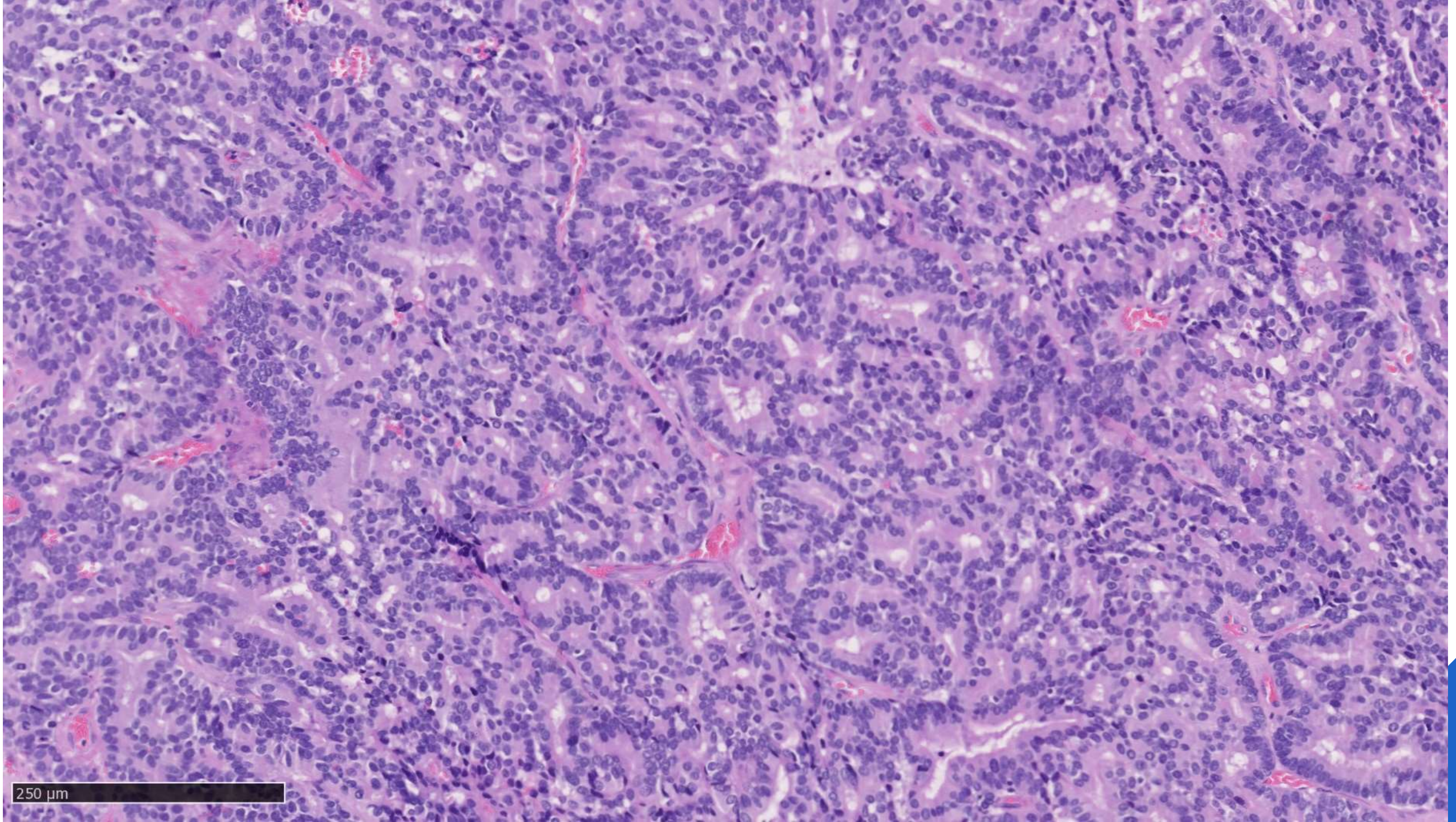
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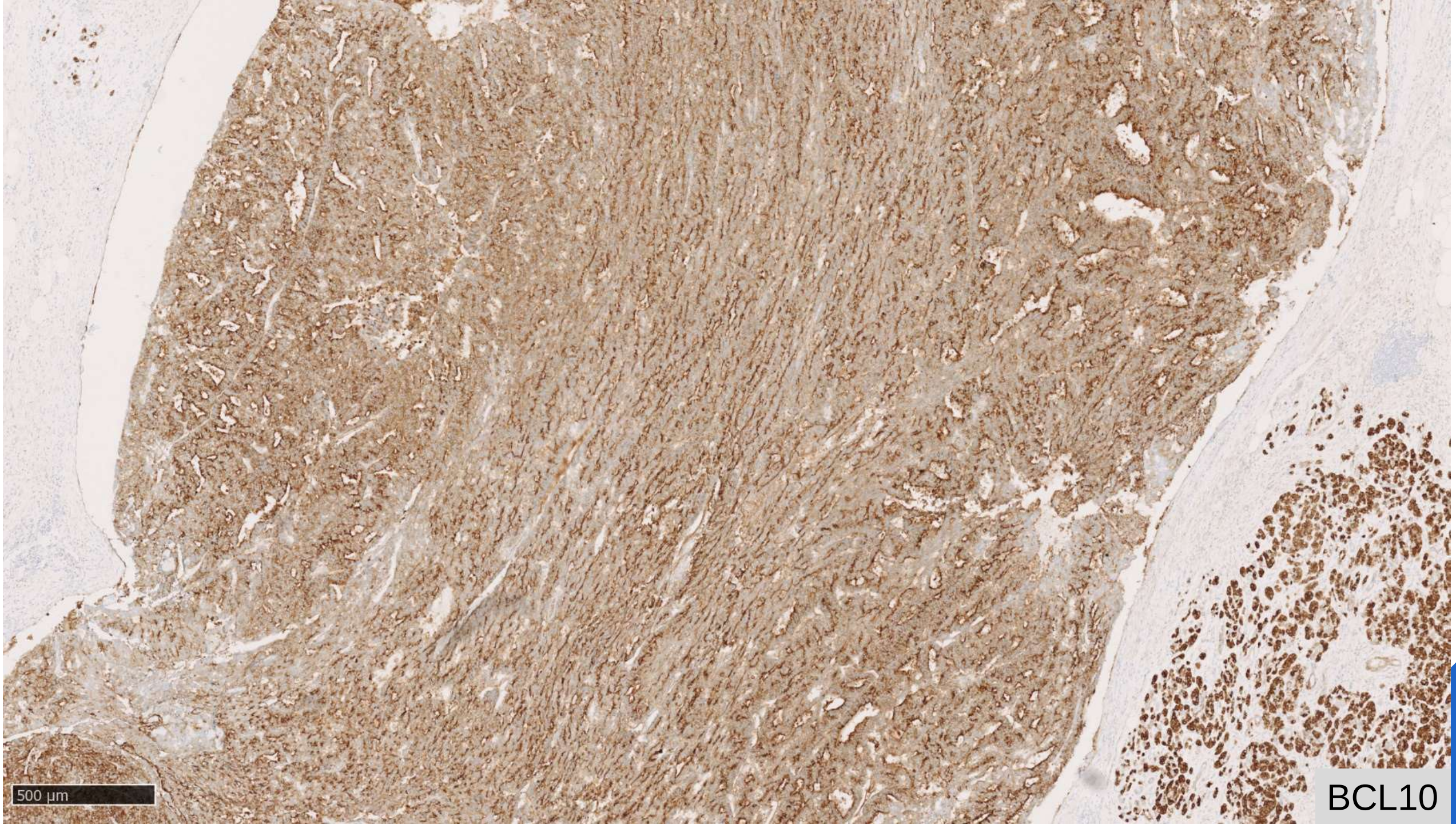
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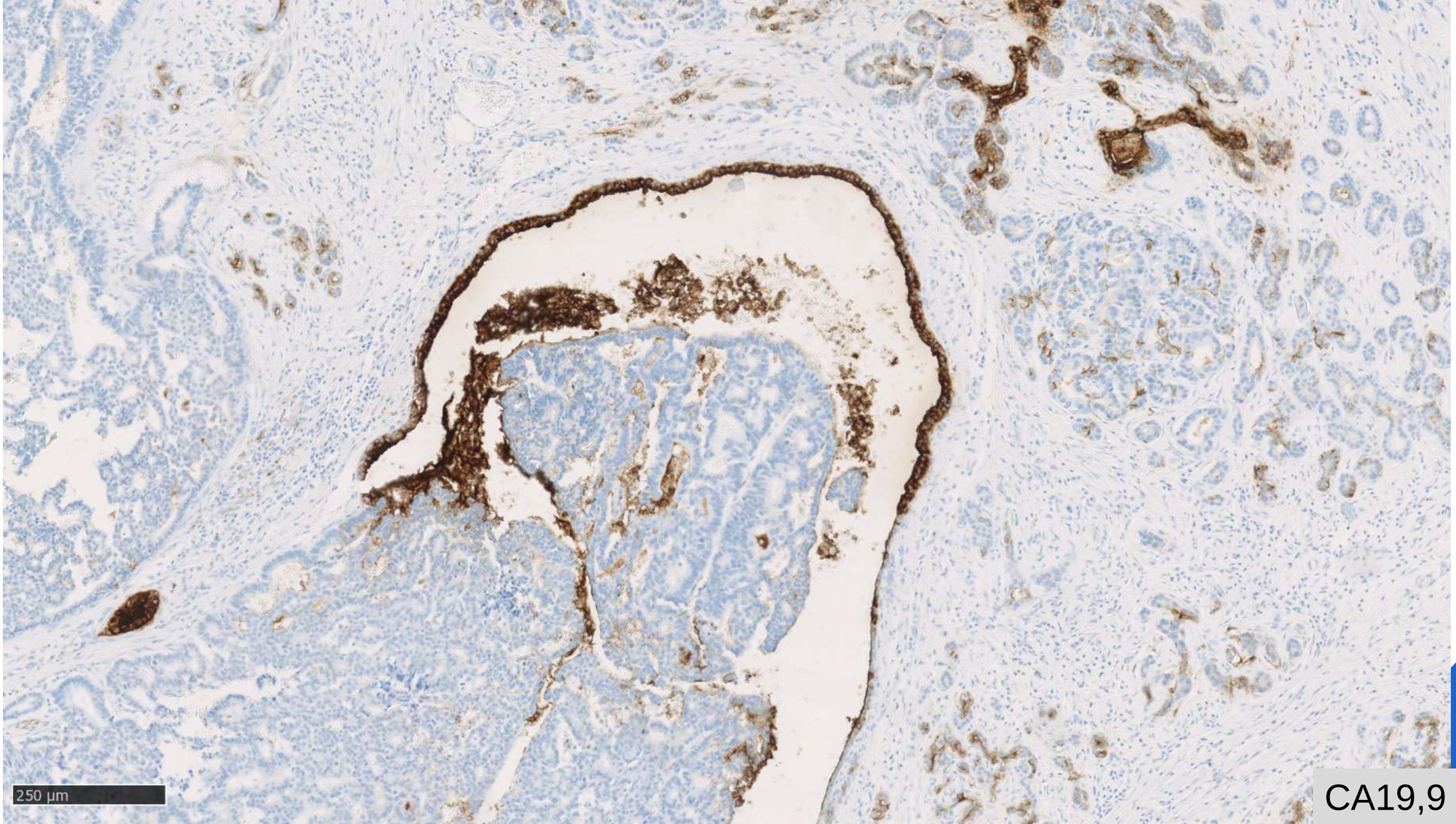
BCL10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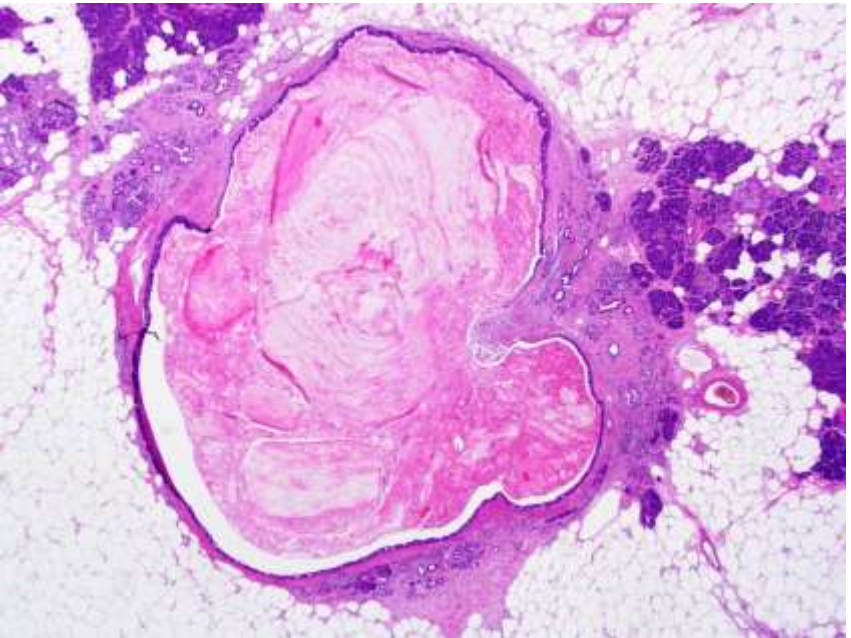
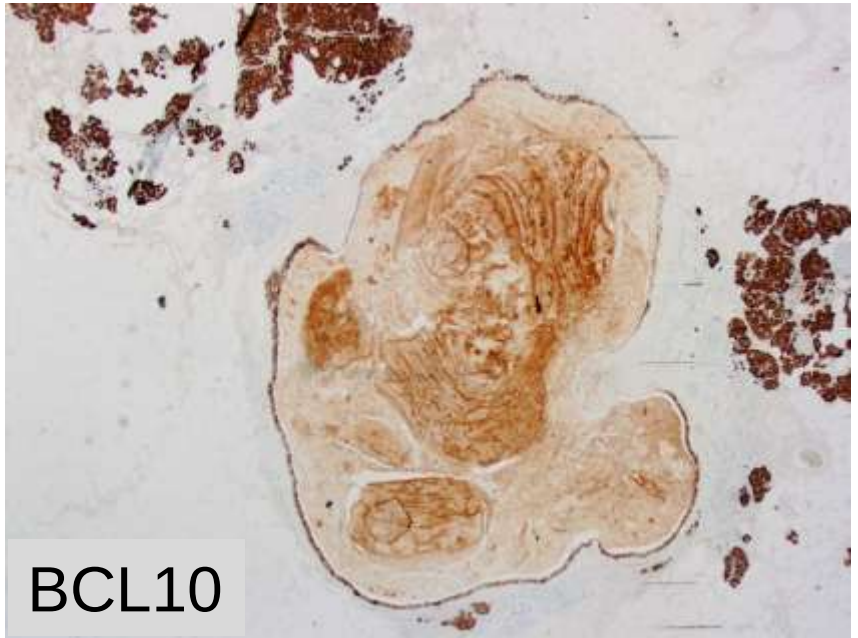
CA19,9

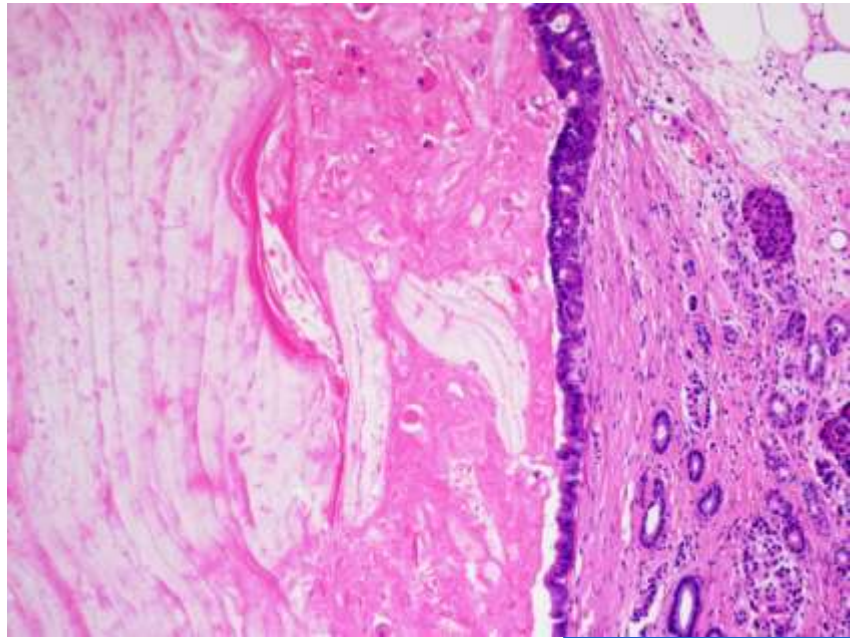
Acinar cell carcinoma totally unrelated to

- Acinar cystic transformation of the pancreas

  Older term: Acinar cell cystadenoma







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PANCREATIC NEUROENDOCRINE NEOPLASMS

New features of the WHO 2019 classification of GI NENs

Well differentiated NENs	Ki67 index		Mitotic index	
Neuroendocrine tumour (NET) G1	<3	%	<2	/10 HPF
Neuroendocrine tumour (NET) G2	3-20	%	2-20	/10 HPF
Neuroendocrine tumour (NET) G3	>20	%	>20	/10 HPF
Poorly differentiated NENs				
Neuroendocrine carcinoma (NEC) G3	>20	%	>20	/10 HPF
Small cell type				
Large cell type				
Mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN)				

Rindi et al. Mod Pathol. 2018;31:1770-1786

Neuroendocrine Neoplasms

NET and NEC

Classification Guide

Advanced Accelerator Applications

A Novartis Company

In collaboration with

Prof. Dr. Anne Hoorens
Ghent University, Belgium

Prof. Dr. Günter Klöppel
Technical University of Munich, Germany

Acinar cell CA with nested/trabecular growth pattern, small uniform nuclei

Mimic WD NET

- Mitosis readily visible
- Lacks salt and pepper chromatin

Acinar cell CA with solid growth, more irregular nuclei

Mimic large cell NEC

- Necrosis
- Prominent nucleoli
- High mitotic count

IHC to show acinar differentiation

Possibility of mixed acinar-neuroendocrine carcinoma should be considered for a pancreatic neoplasm expressing neuroendocrine markers when the morphological features are not perfectly typical of a well-differentiated neuroendocrine tumour (NET)

ONCOLOGY LETTERS 14: 547-552, 2017

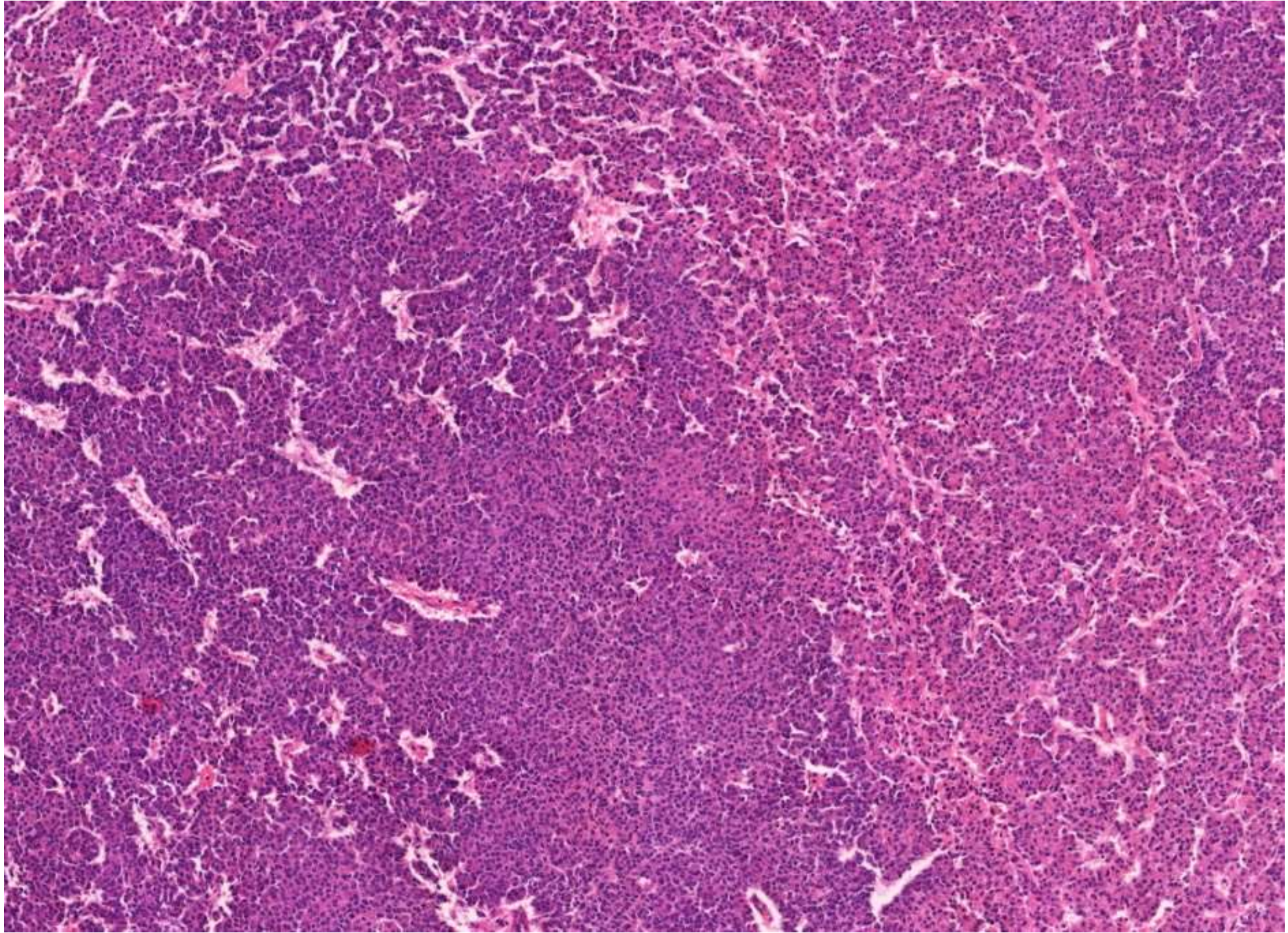
Treatment of a mixed acinar-endocrine carcinoma with uptake on ^{68}Gallium-DOTATOC positron emission tomography-computed tomography: A case report

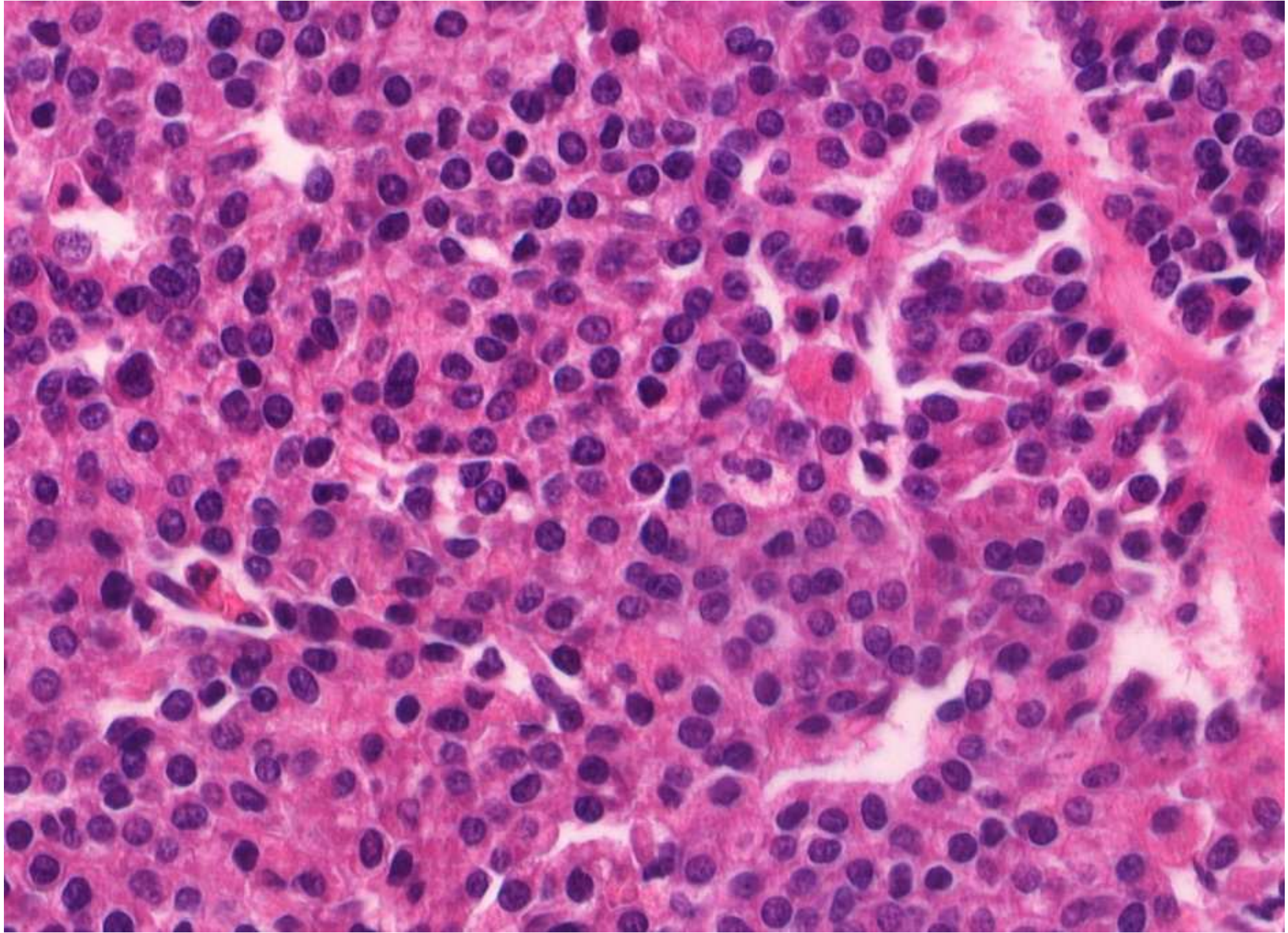
ANNELEEN DE BOTH[1], MARC DE MAN[1], ROBERTO TROISI[2], HANS VAN VLIERBERGHE[3], ANNE HOORENS[4] and KAREN GEBOES[1]

Departments of [1]Gastroenterology and Digestive Oncology, [2]General, Hepato-Biliary and Liver Transplantation Surgery, [3]Gastroenterology and Hepatology, and [4]Anatomopathology, Ghent University Hospital, 9000 Ghent, Belgium

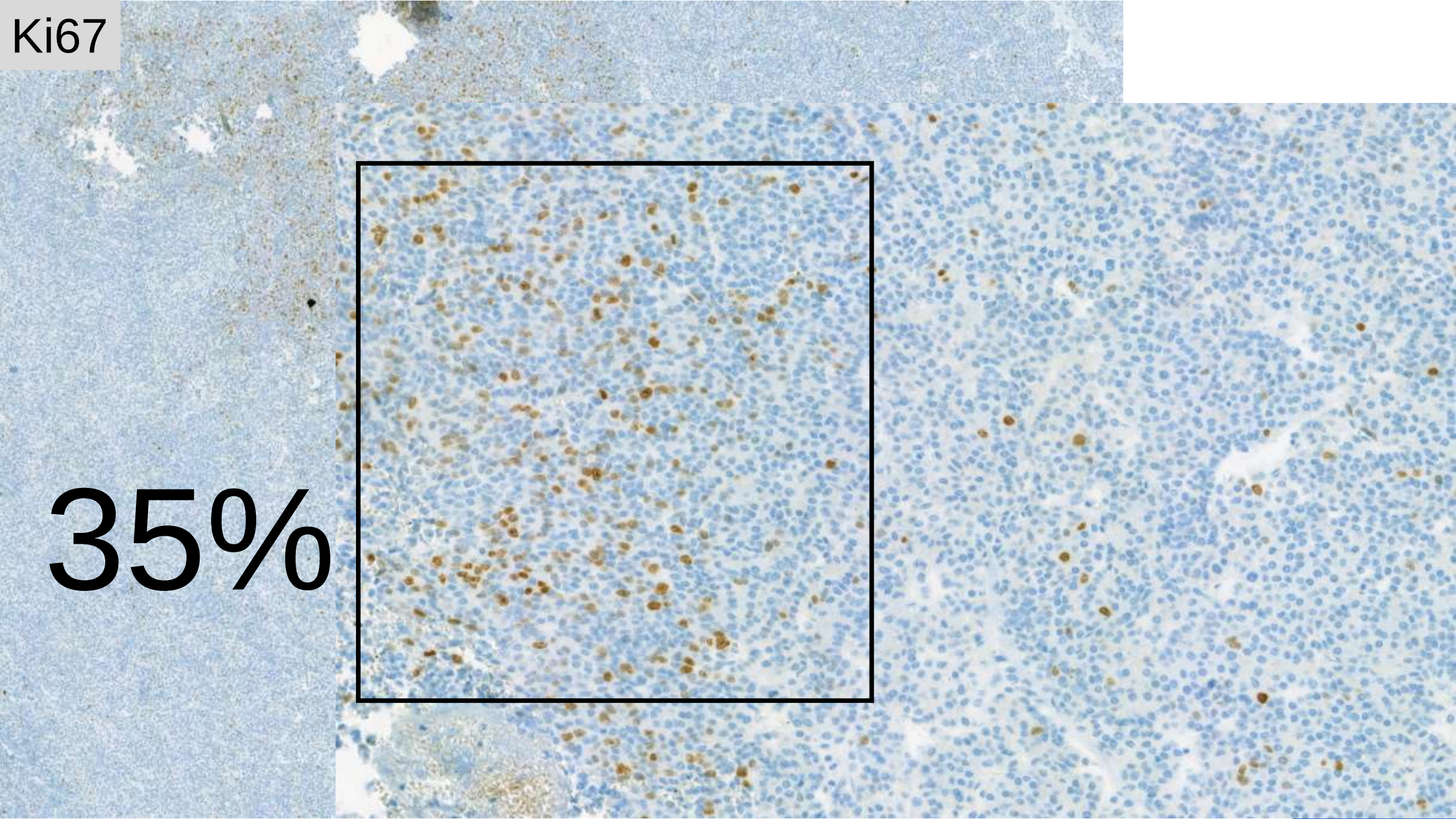
Received October 9, 2016; Accepted January 26, 2017

DOI: 10.3892/ol.2017.6242

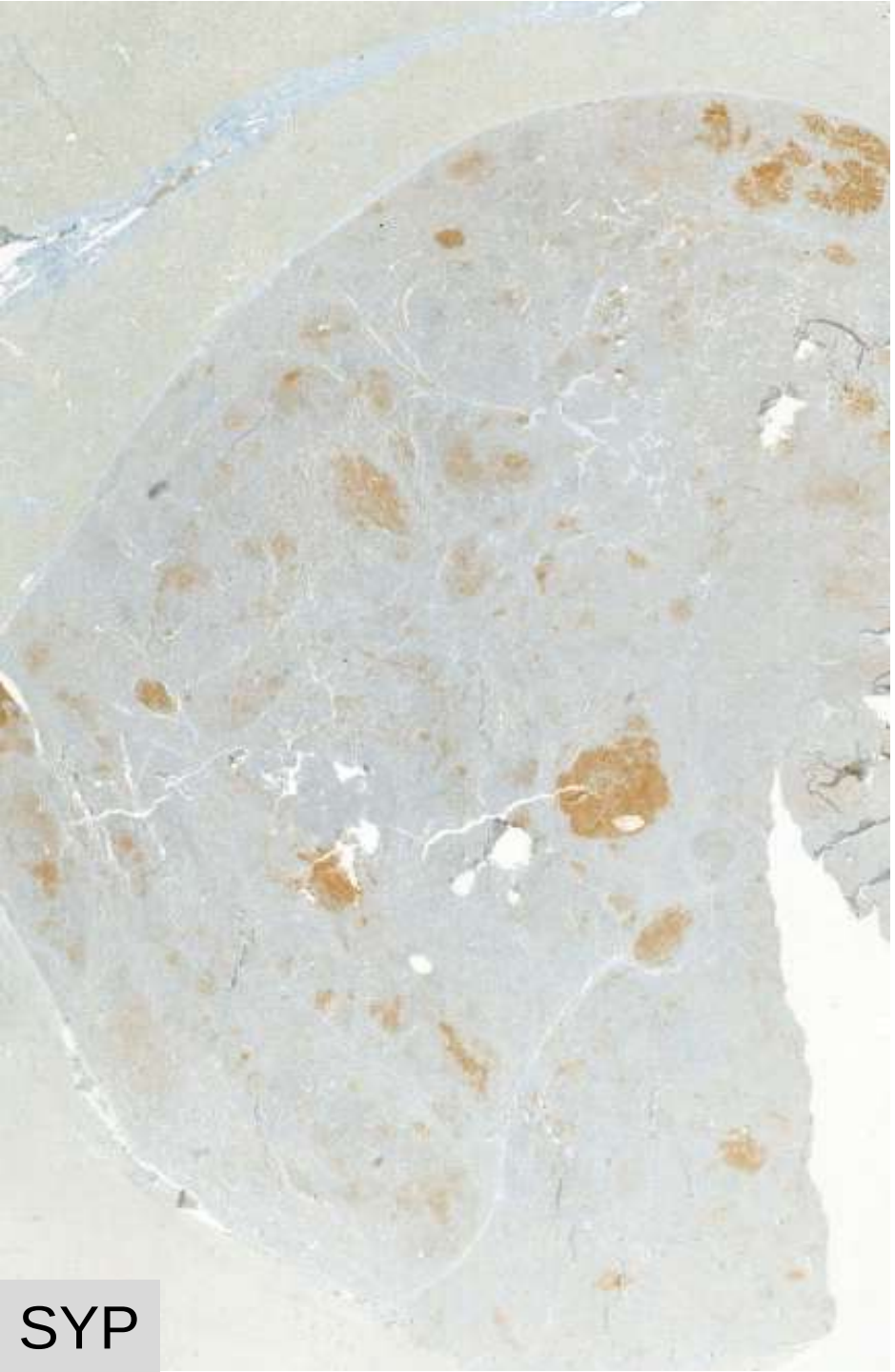




Ki67



35%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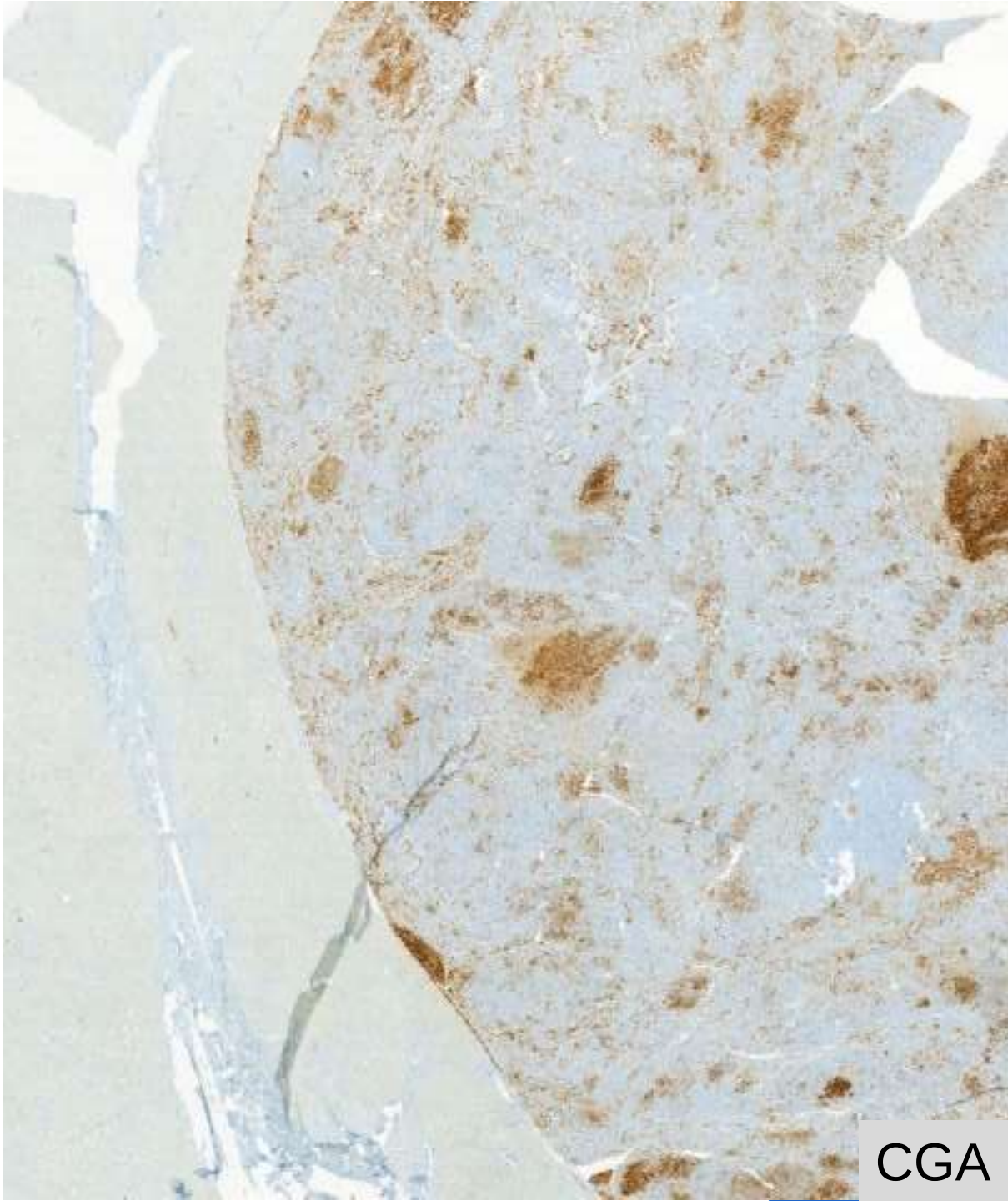
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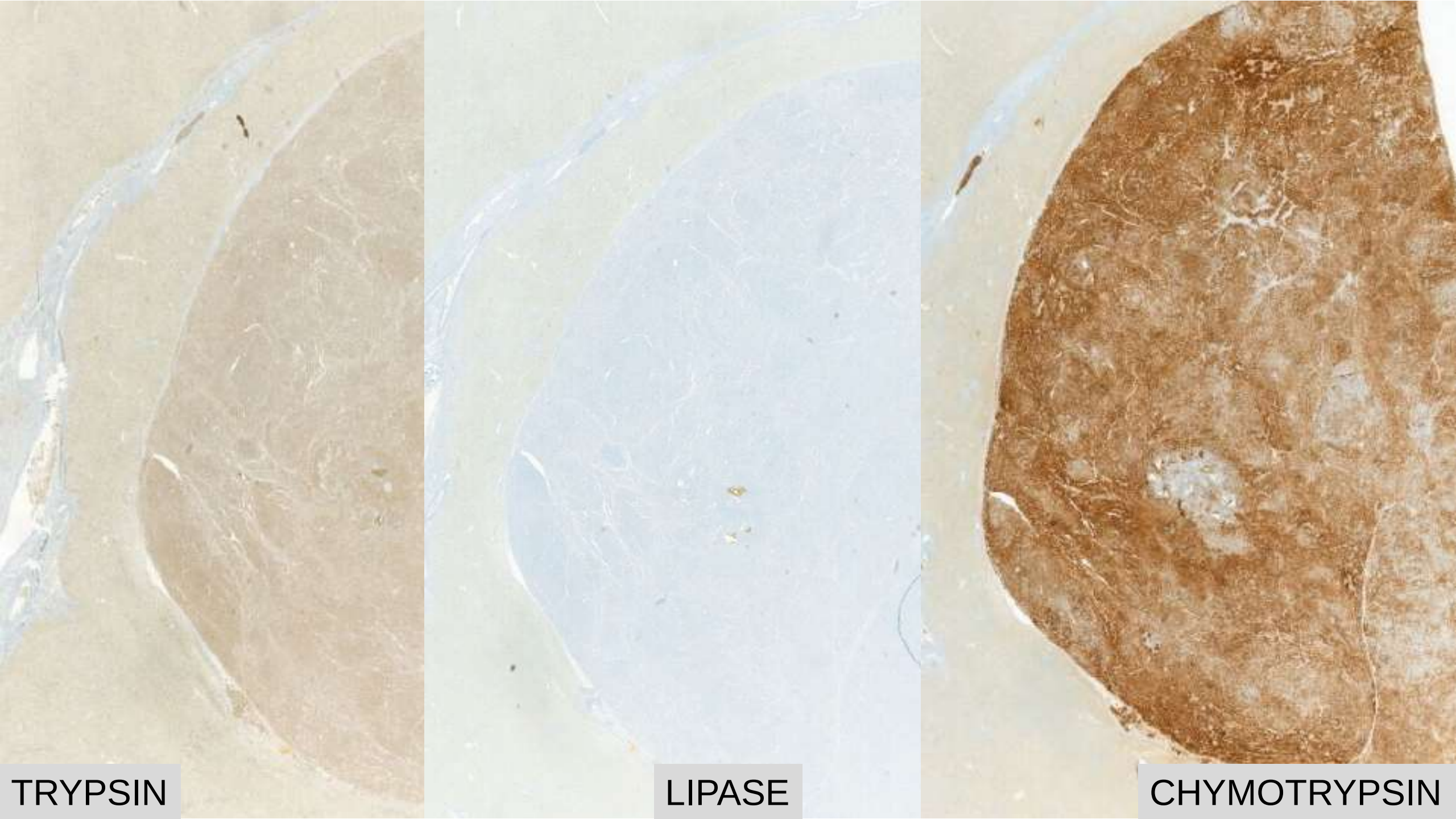
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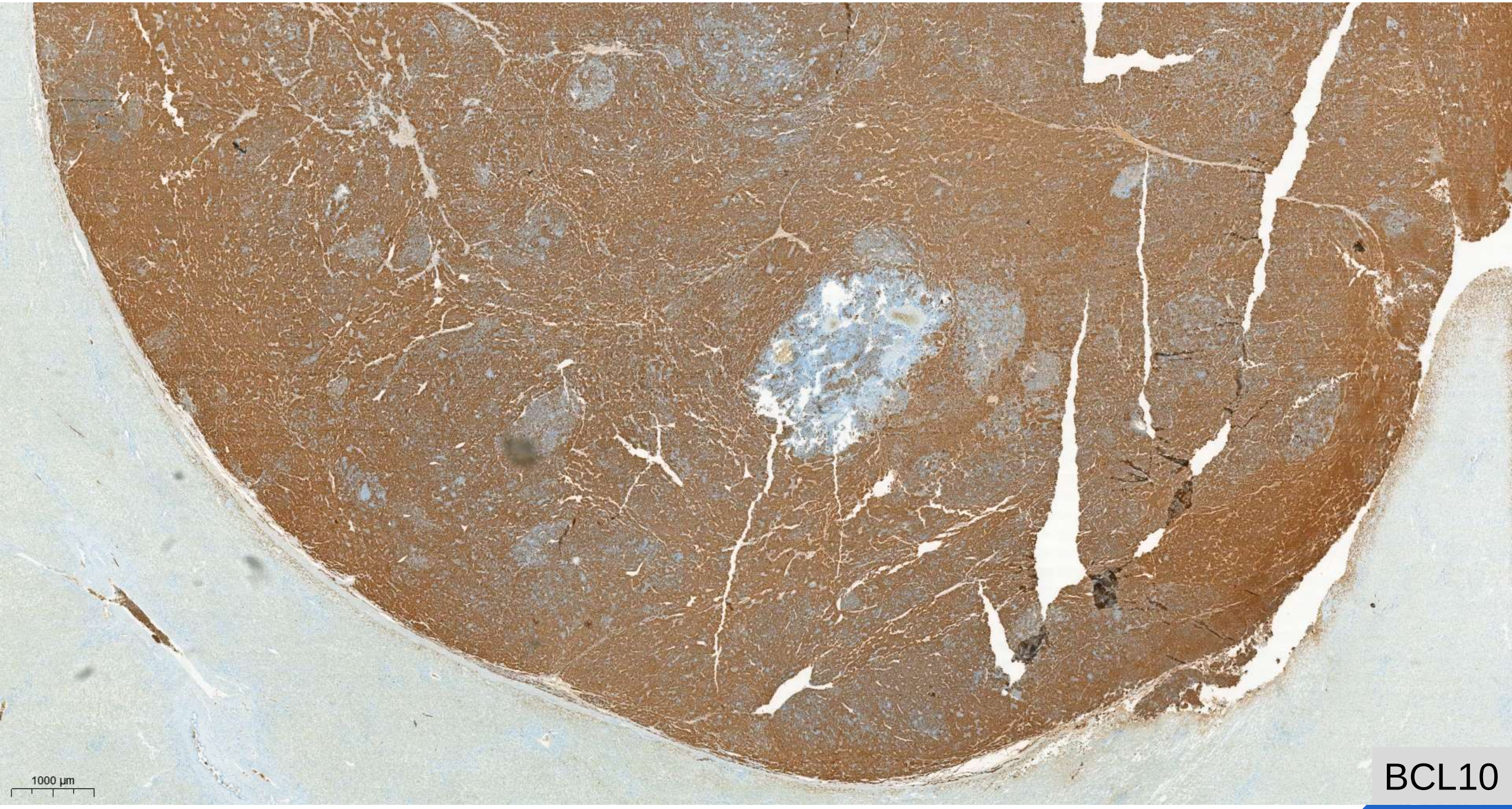
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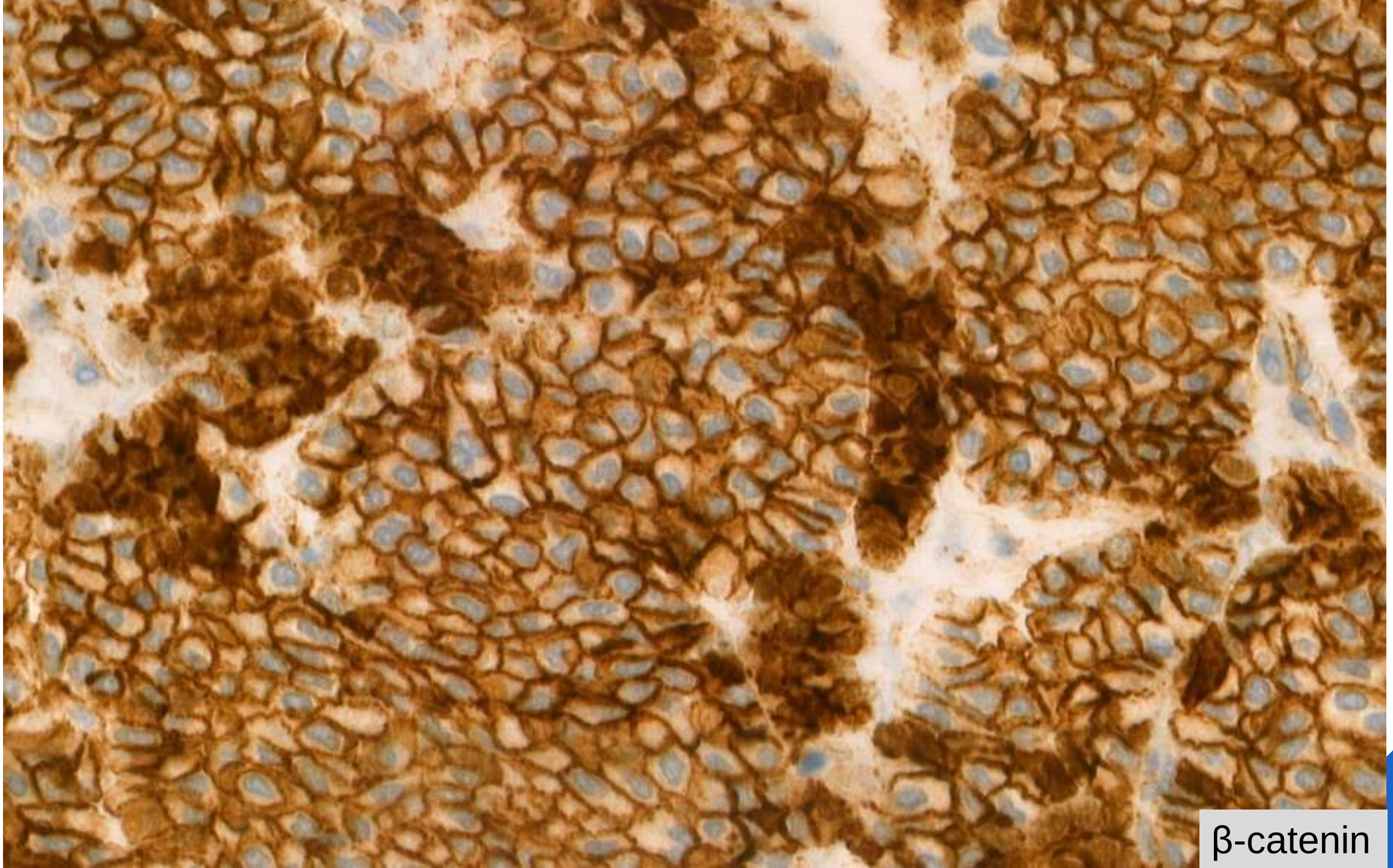
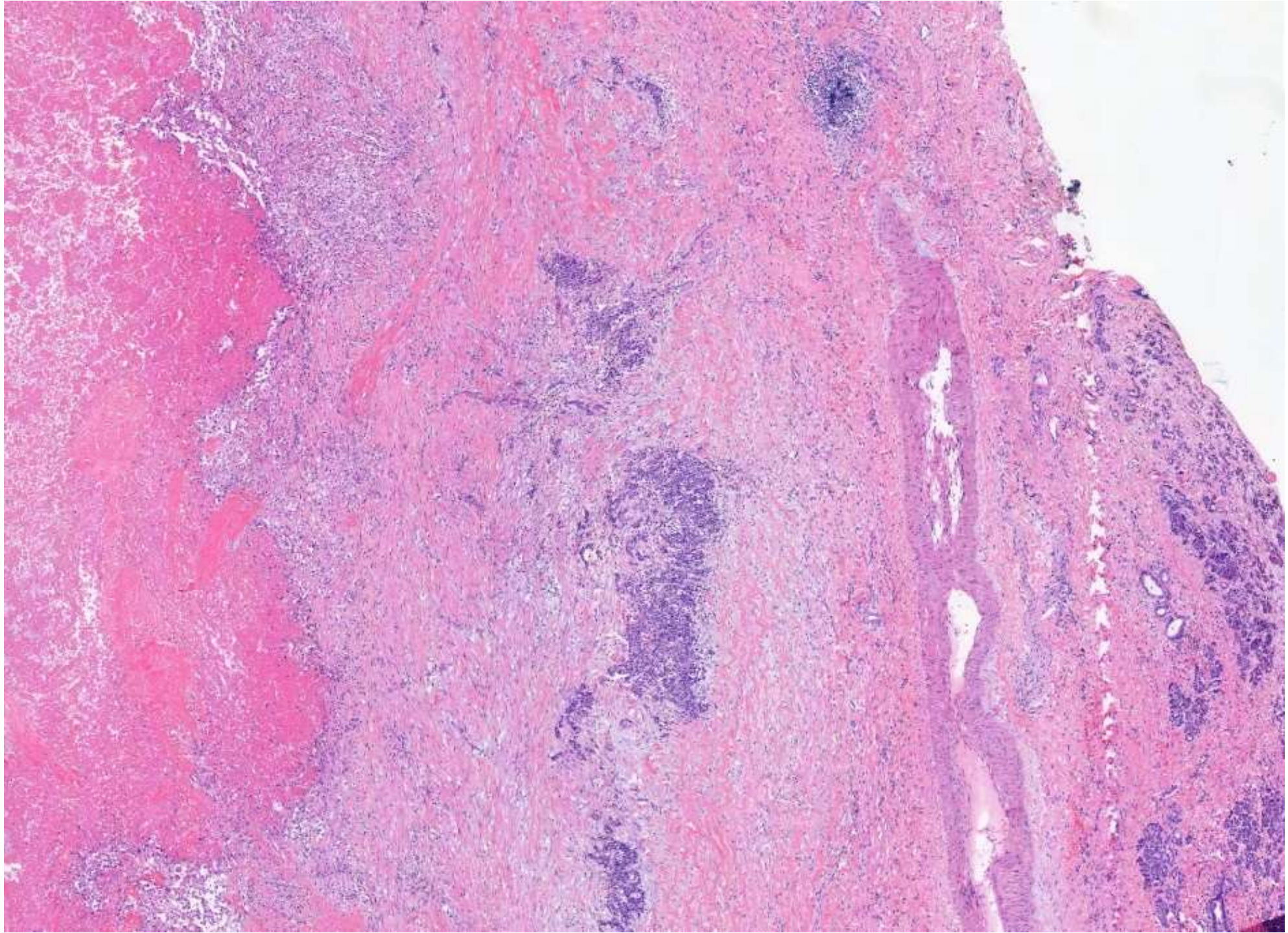
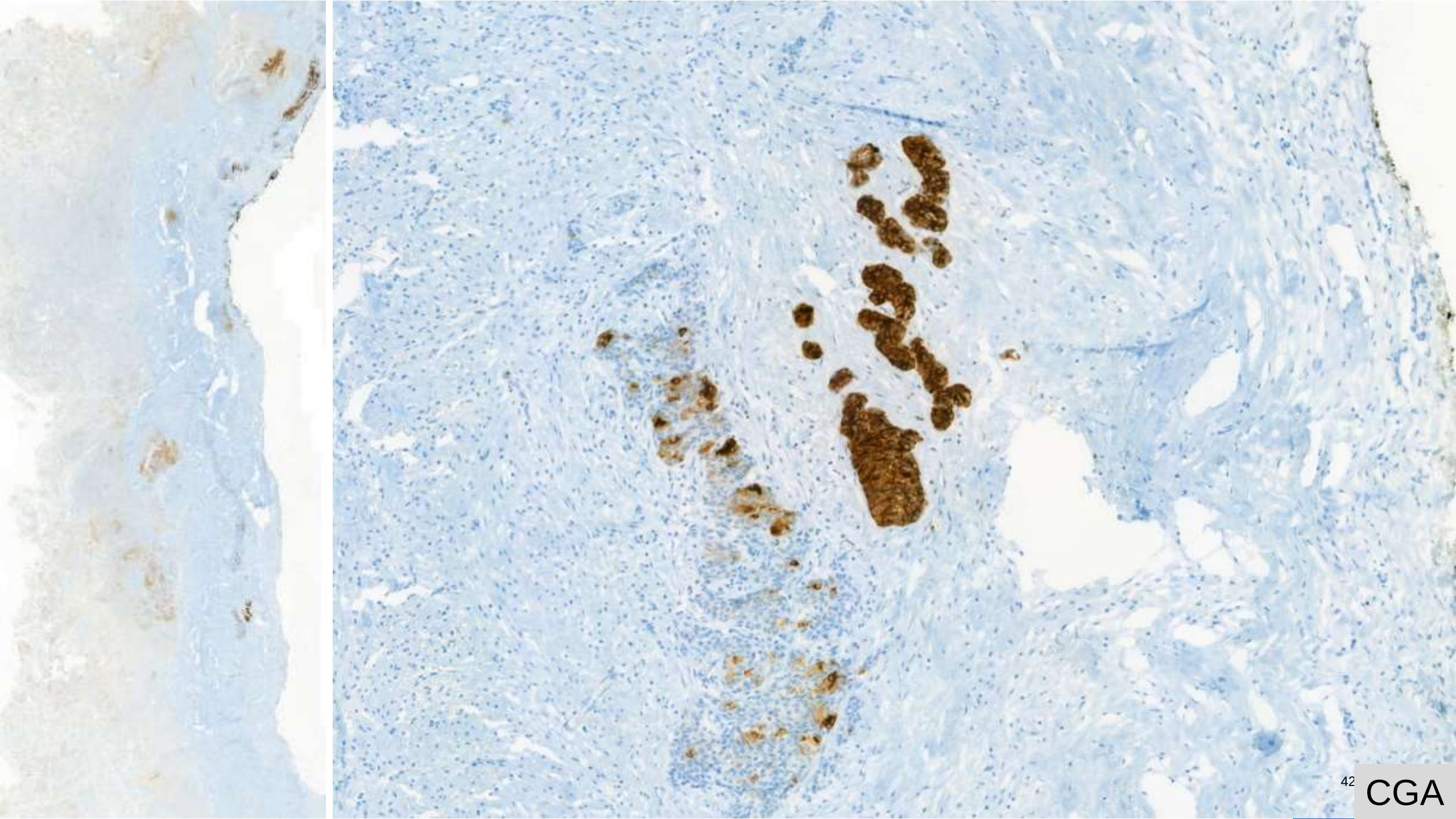
BCL10


β-catenin





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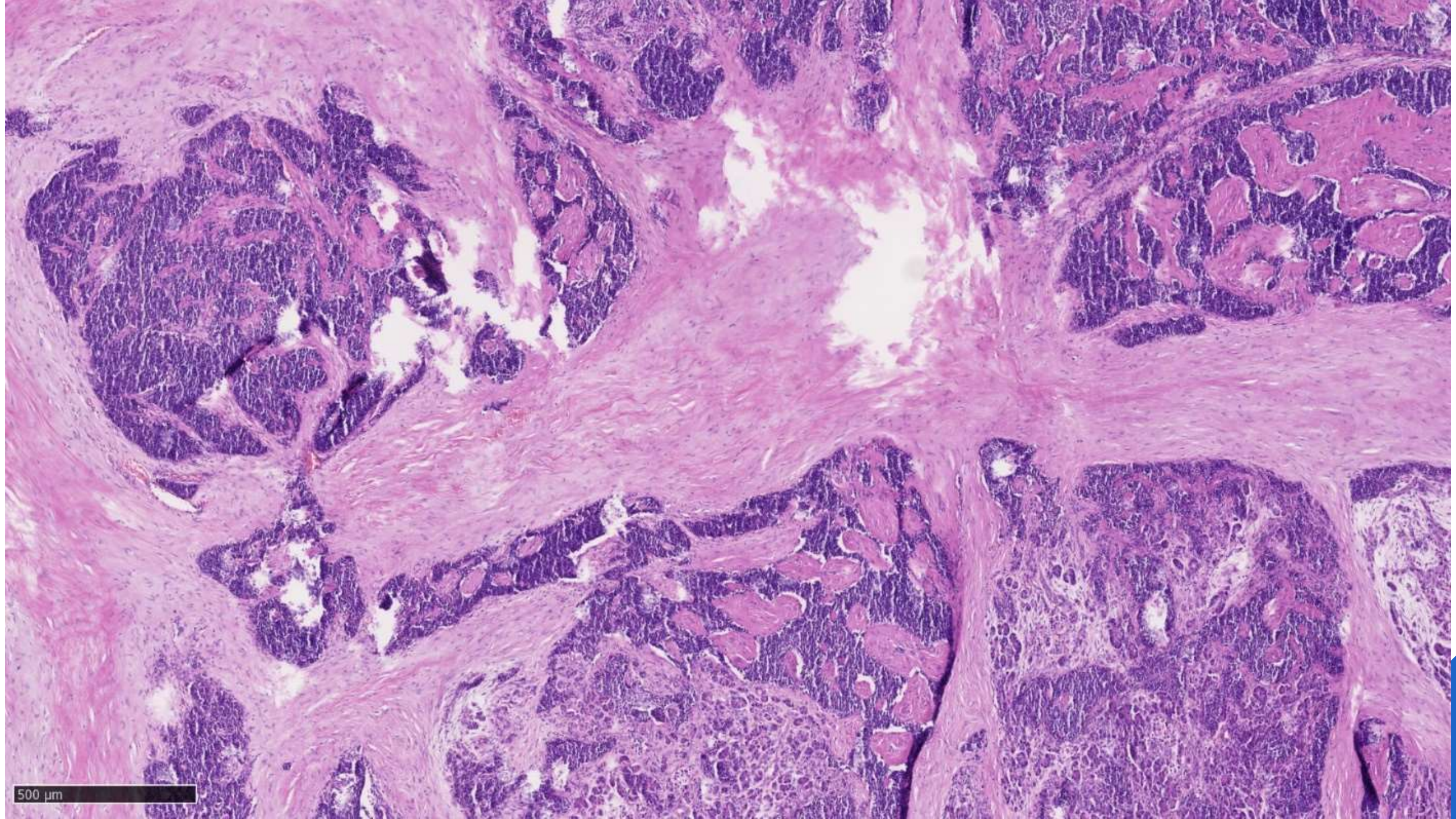
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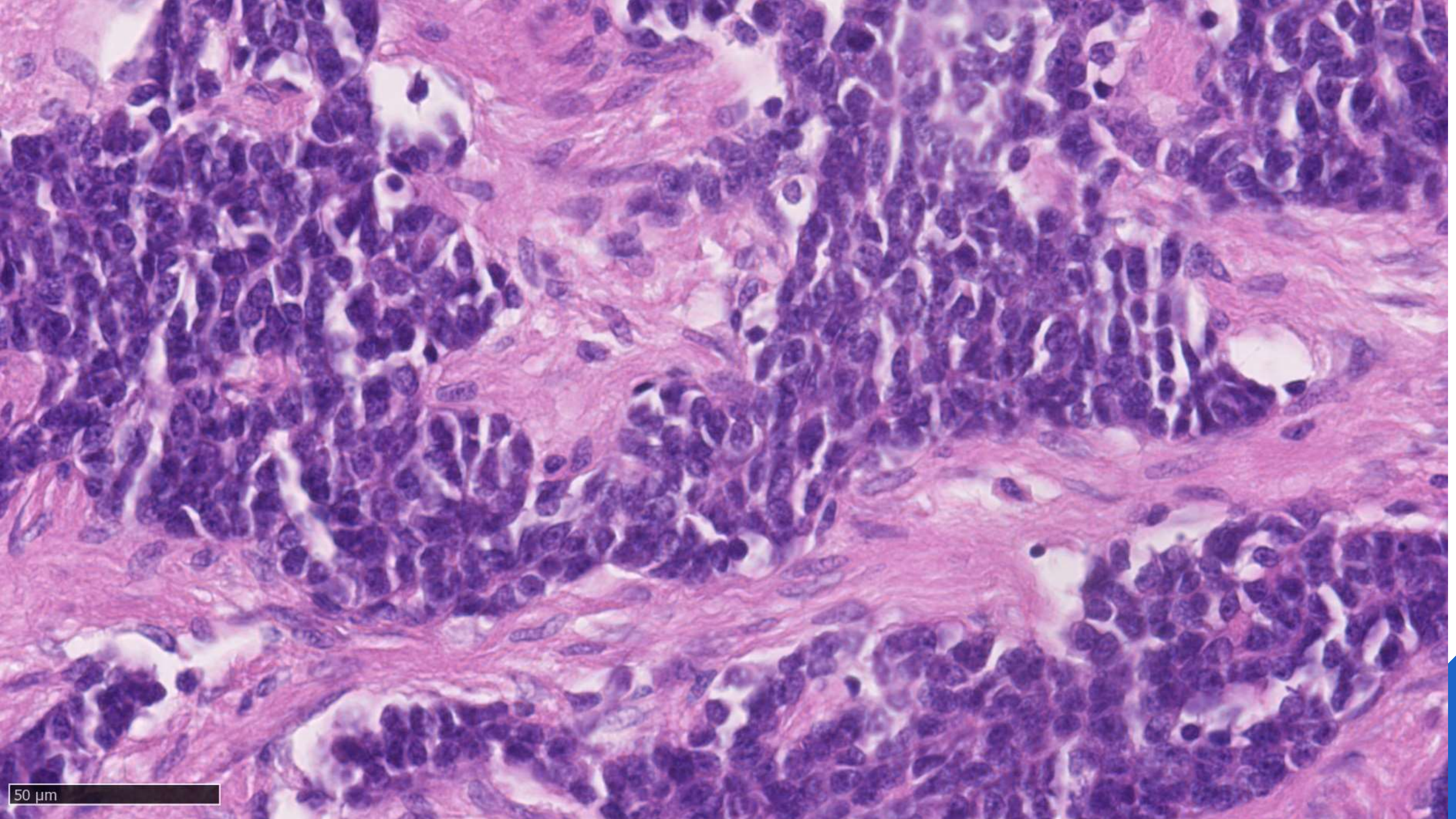
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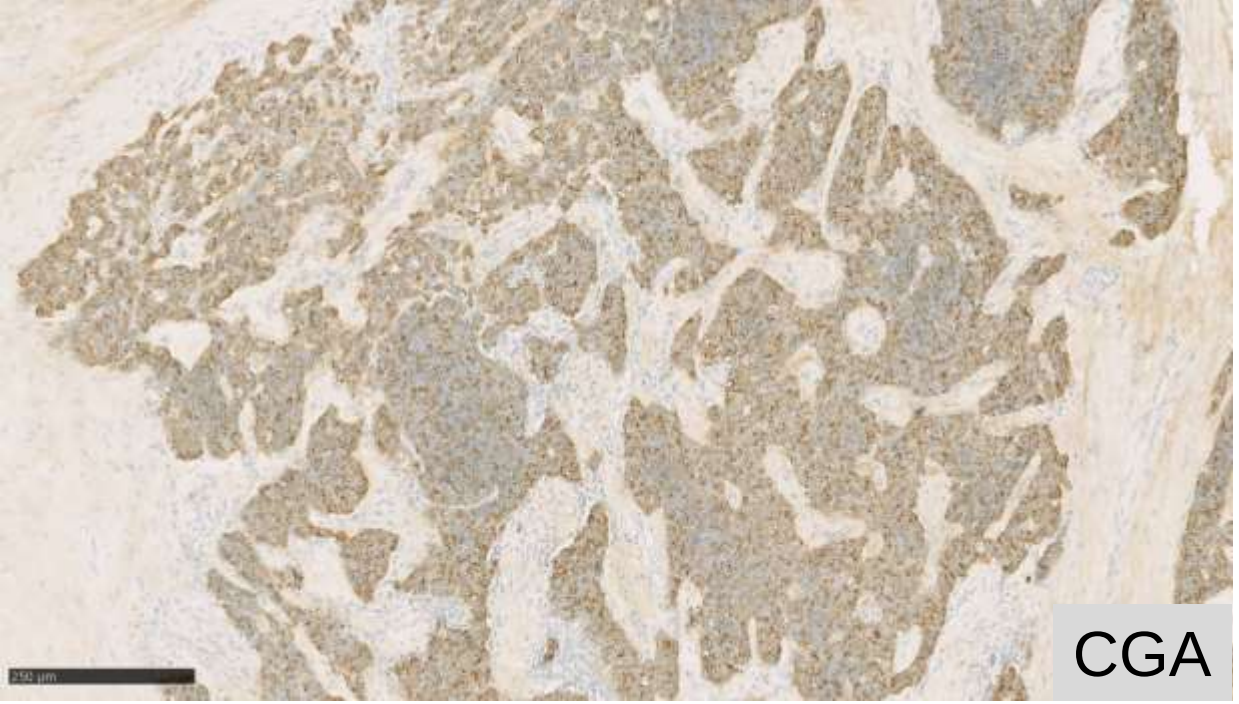
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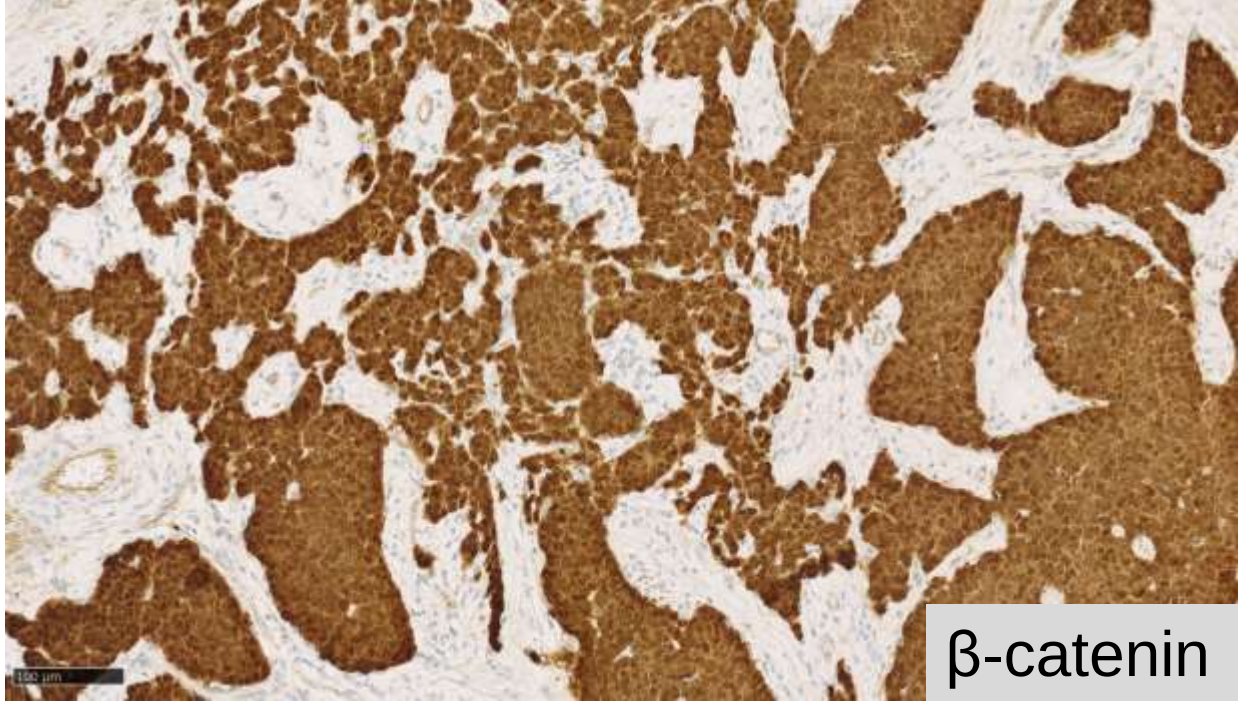
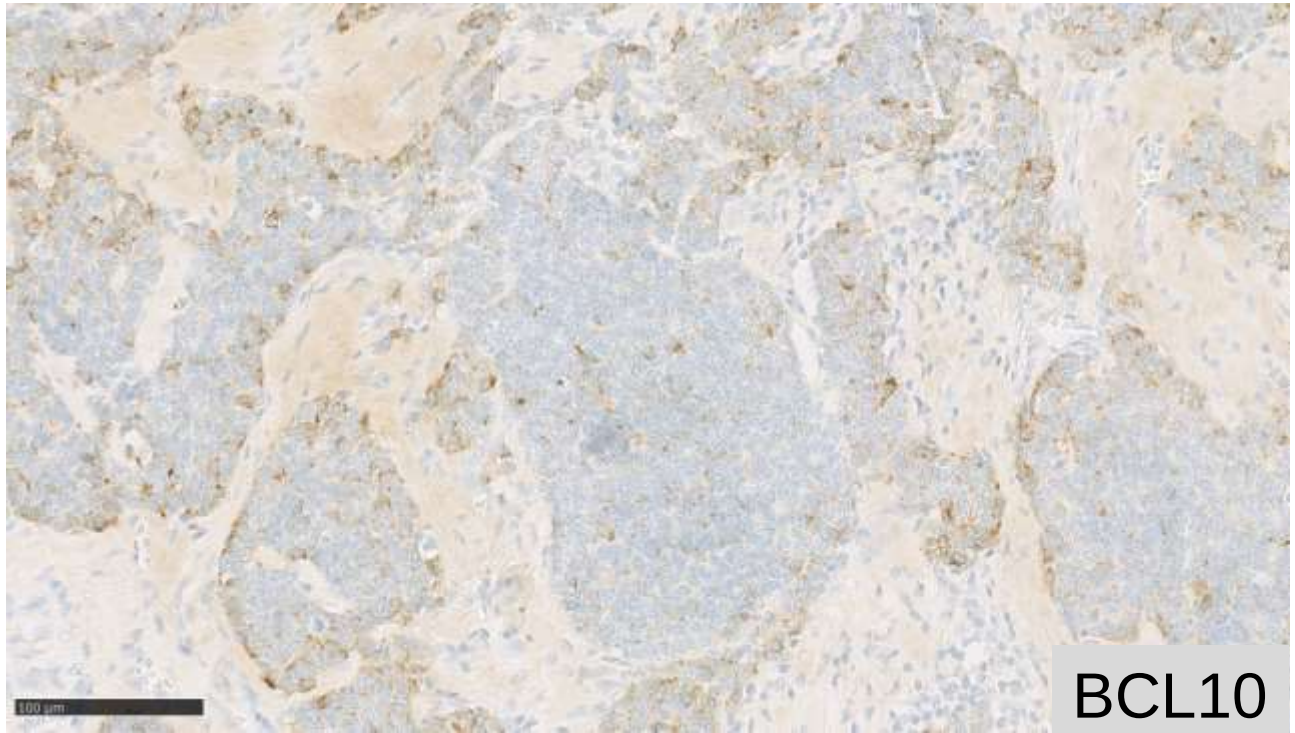

β-catenin


BCL10

SOLID PSEUDOPAPILLARY NEOPLASM (SPN)

- Low-grade malignant epithelial neoplasm
- Lacks specific line of pancreatic epithelial differentiation
- Rare (1-3% of exocrine pancreatic neoplasms)
- Adolescent girls/young women (90%) - Mean age 30
- 30% of all pancreatic neoplasms in patients aged <40
- Often found incidentally

  Intratumoral haemorrhage after abdominal trauma can produce acute abdomen
- Slight preference for tail

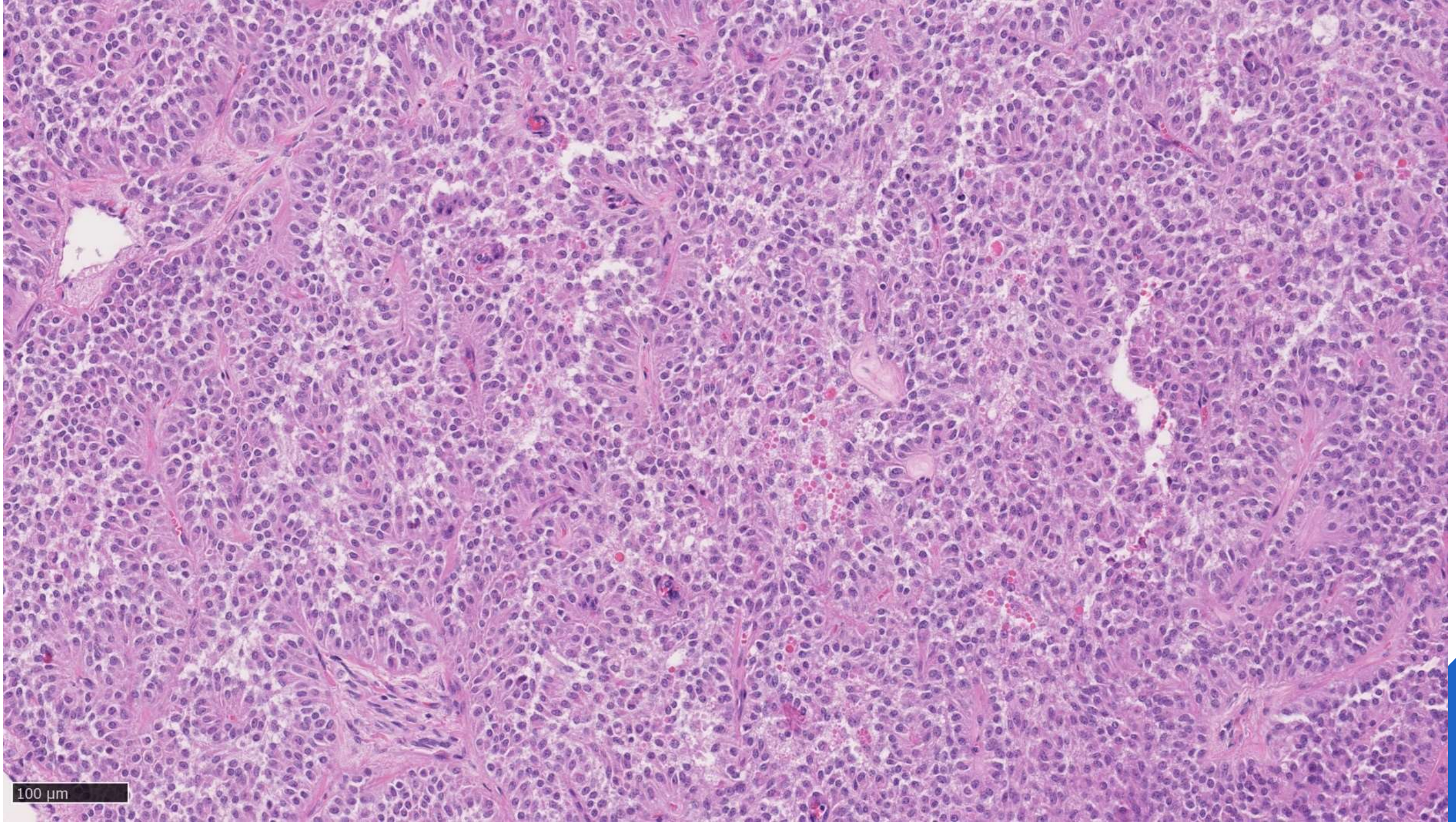
Klöppel et al, Virchows Arch., 1981;392:171-83
Terris B. et al., 2014;31:484-90
McCluney et al, ANZ J Surg. 2018;88:891-5

Macroscopy

- Solitary, round, well-demarcated
- Large (8–10 cm)
- Small solid areas, large areas of haemorrhagic necrosis, large cystic spaces
- Small tumours more solid
- Rarely extends into duodenal wall or other adjacent structures

Histopathology

- Poorly cohesive monomorphic cells clinging to hyalinized/myxoid fibrovascular cords
- Pseudopapillae formed when neoplastic cells detach from fibrovascular stalks
- Haemorrhage and pseudocystic changes
- Cholesterol crystals, foreign body giant cells, foamy histiocytes, calcifications may occur
- May focally infiltrate surrounding pancreatic tissue
- Vascular and perineural invasion rare
- Neoplastic cells are eosinophilic or vacuolated, often containing PASD-positive hyaline globules (zymogen-like α1-antitrypsin granules)
- Round/oval nuclei, may be grooved or indented, finely dispersed chromatin without prominent nucleolus
- Bizarre nuclei may occasionally occur
- Mitoses uncommon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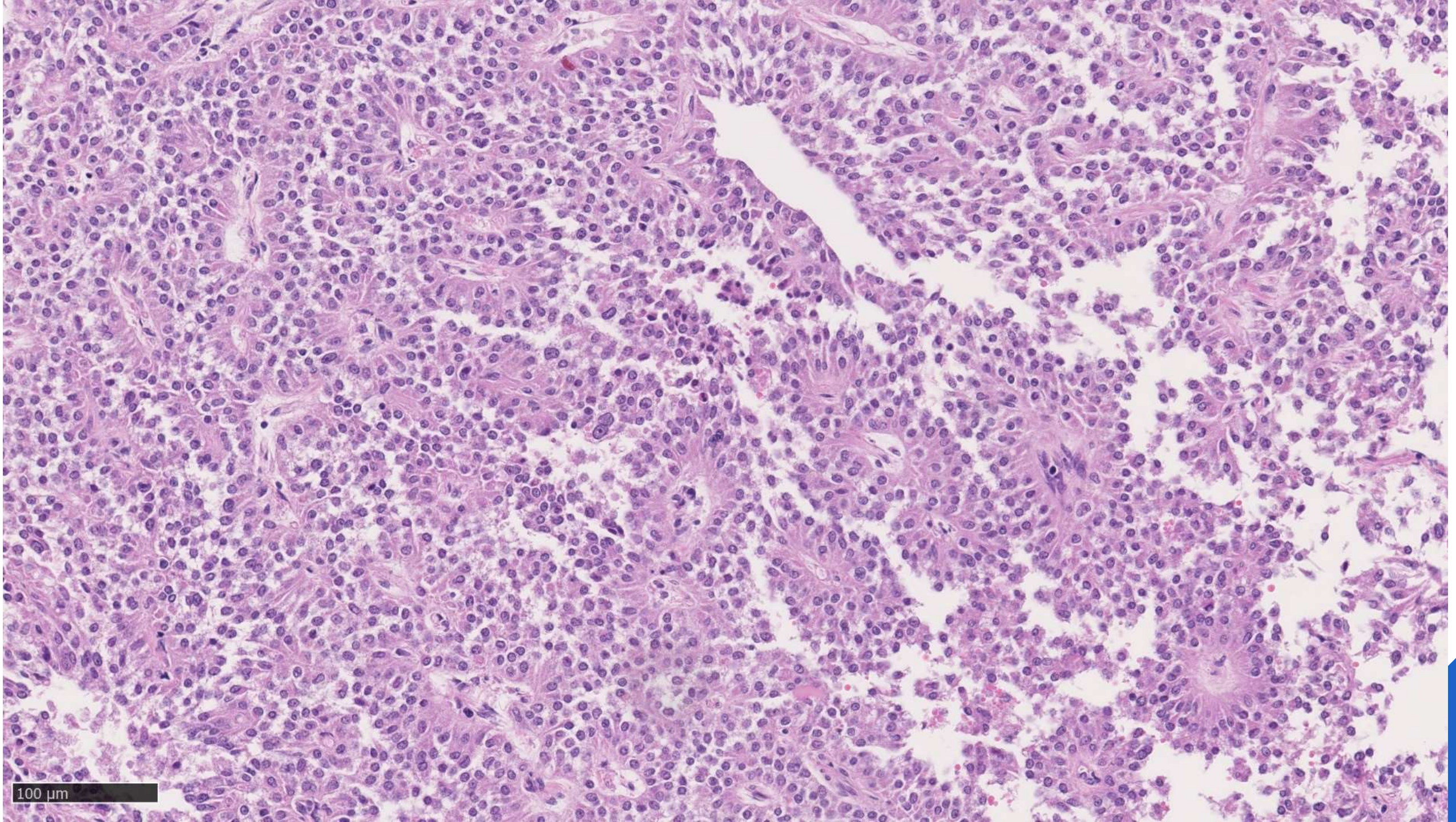
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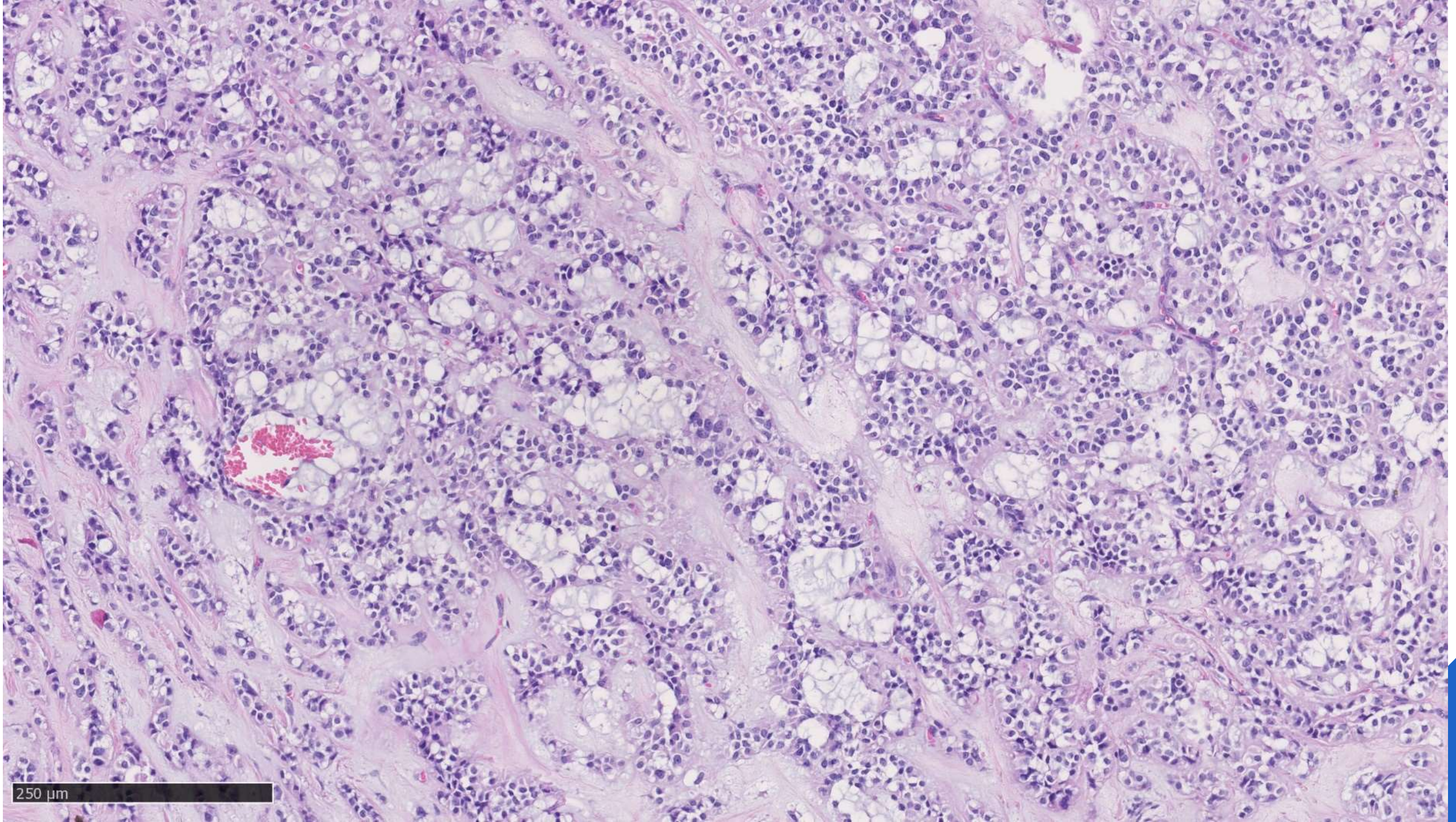
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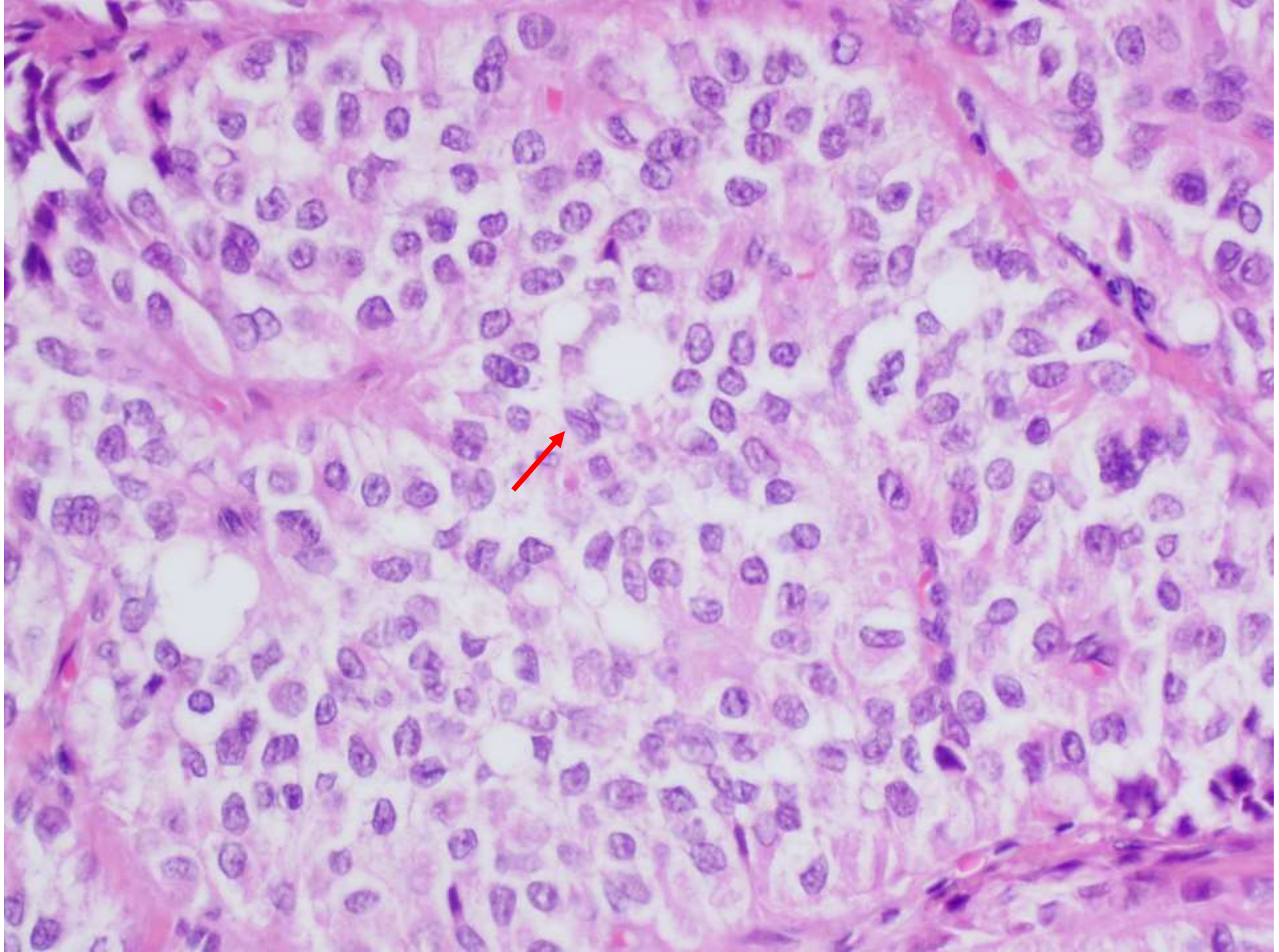
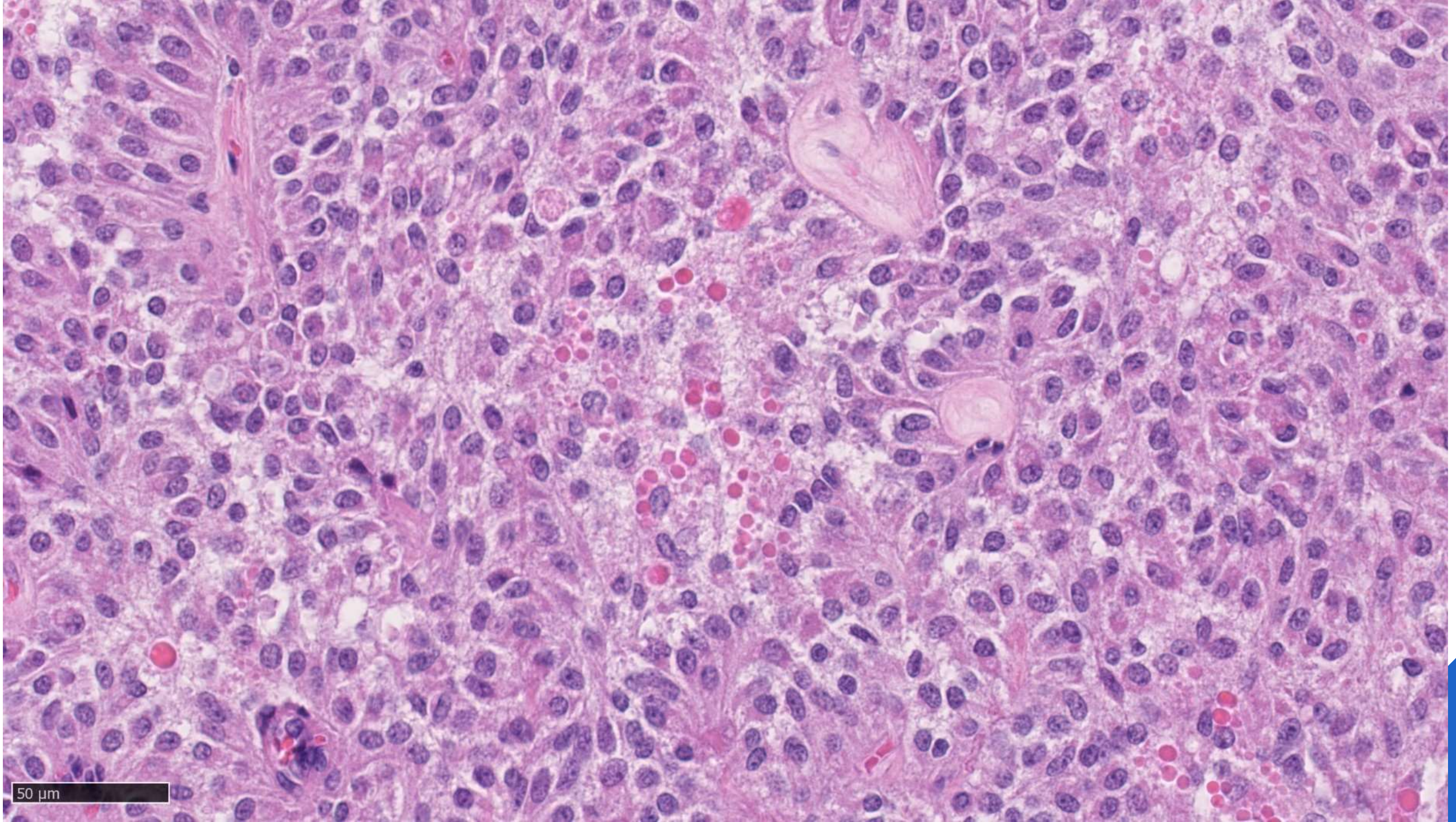
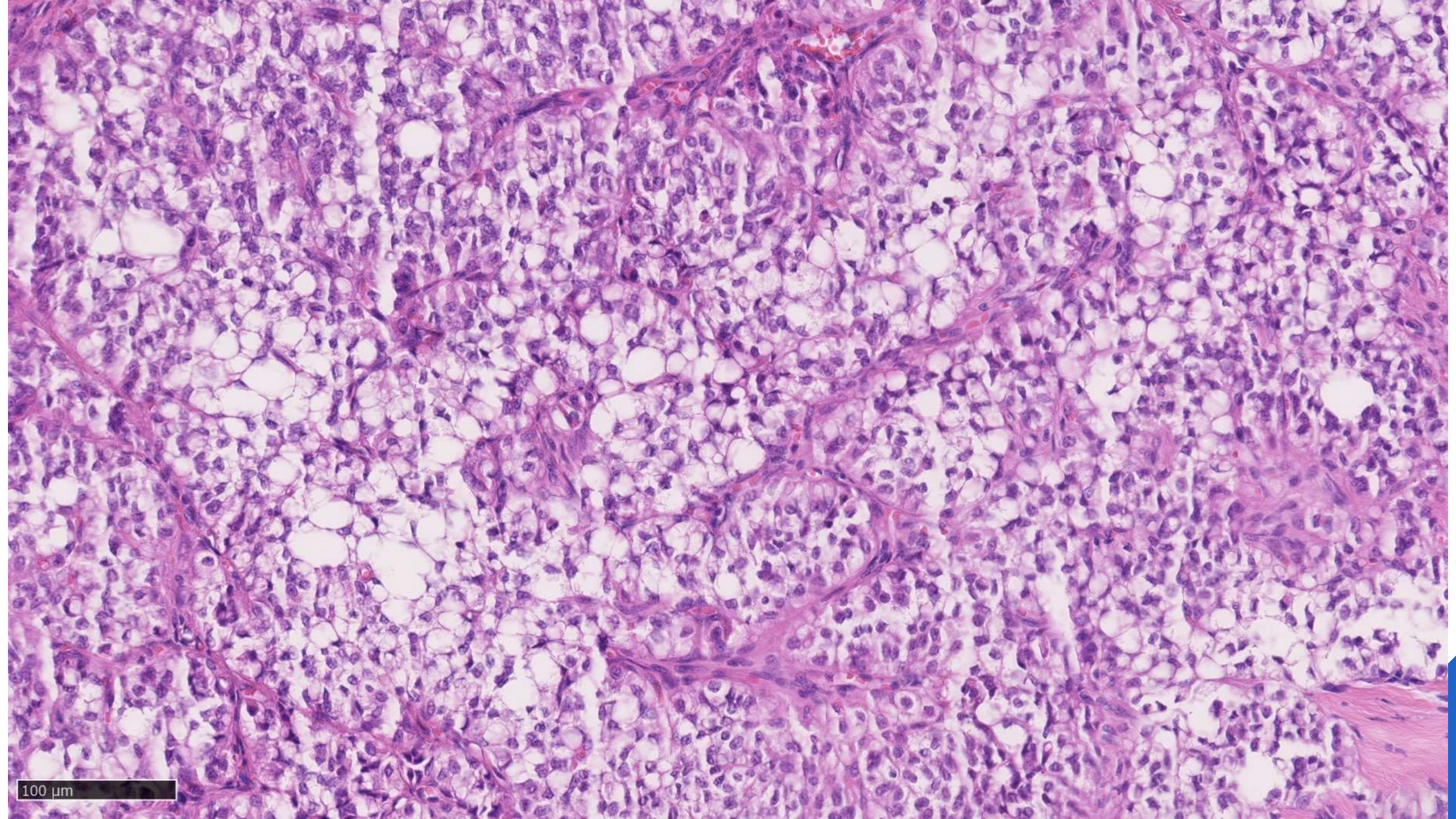



50 µm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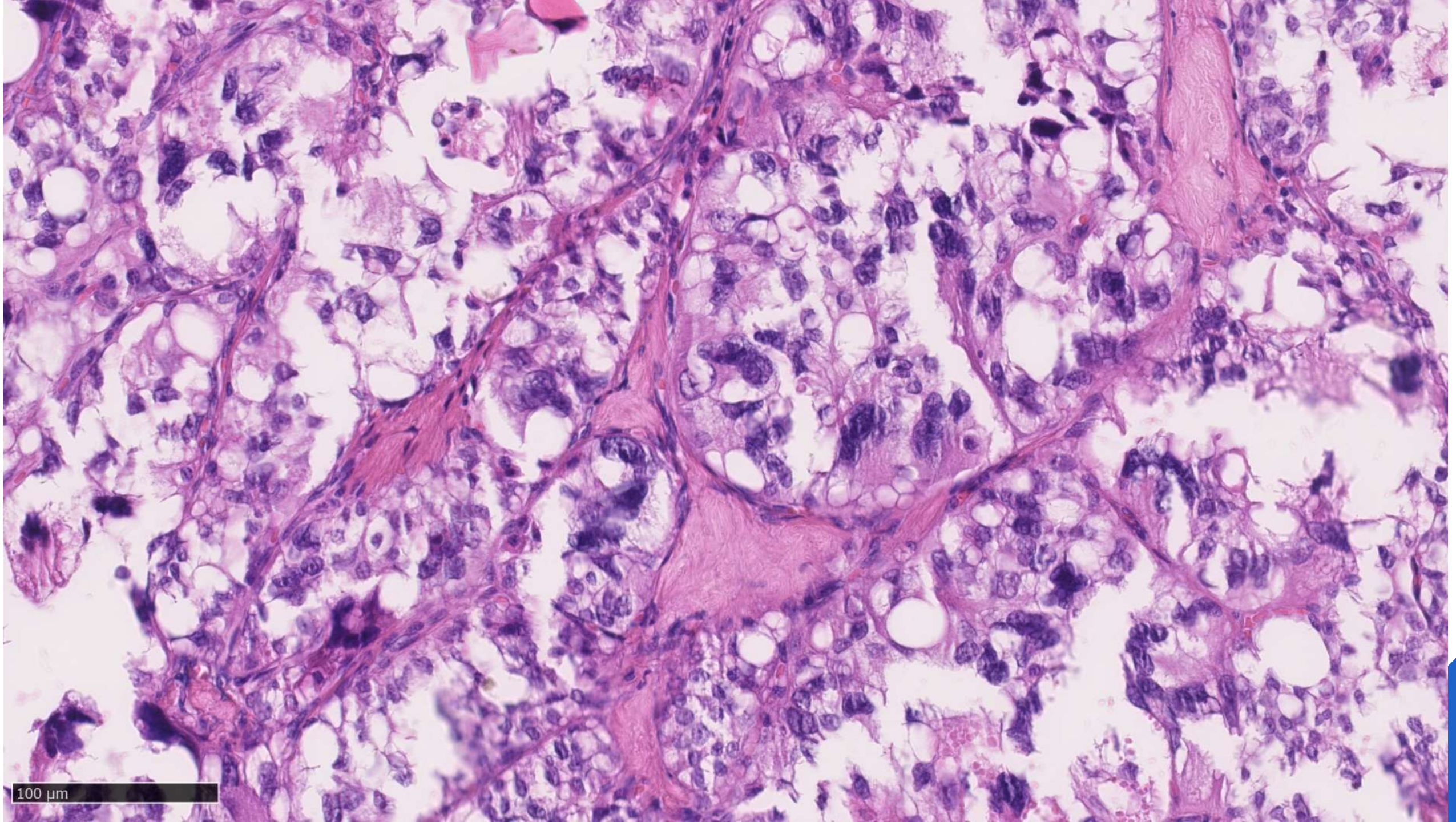

100 µm

Immunohistochemistry

- Nuclear/cytoplasmic expression of β-catenin
- Also express, VIM, PR, CD10, CD99 (dot-like), CD56
- CKs detected in 30-70%, depending on method of antigen retrieval
- 50% express KIT (CD117) - no *KIT* mutation
- SYP may be focally positive, CGA negative
- Consistently negative for trypsin, chymotrypsin, lipase, BCL10

Solid component of SPNs may mimic WD-NEN(NET) or ACC

- Nuclear expression of β-catenin
- Absent labelling for CGA, trypsin and BCL10

Molecular pathology

- Somatic activating mutation in exon 3 of *CTNNB1*

Prognosis

- Metastases 5-15% (even years after resection primary) peritoneum/liver
- Long-term prognosis generally excellent for localized, metastatic, and recurrent disease, with long disease-free periods after complete surgical resection
- Few patients died of metastasizing SPN, mostly tumours with undifferentiated component

  Subtype*: SPNs with foci of high-grade malignant transformation
  - Extremely aggressive
  - Diffuse sheets of cells with increased nuclear atypia and abundant mitoses

Metastatic behaviour not predicted by perineural invasion, angioinvasion and/or deep infiltration of surrounding structures

All SPNs currently classified as low-grade malignant neoplasms

*Tang et al. Am J Sug Pathol. 2005;29:512-9

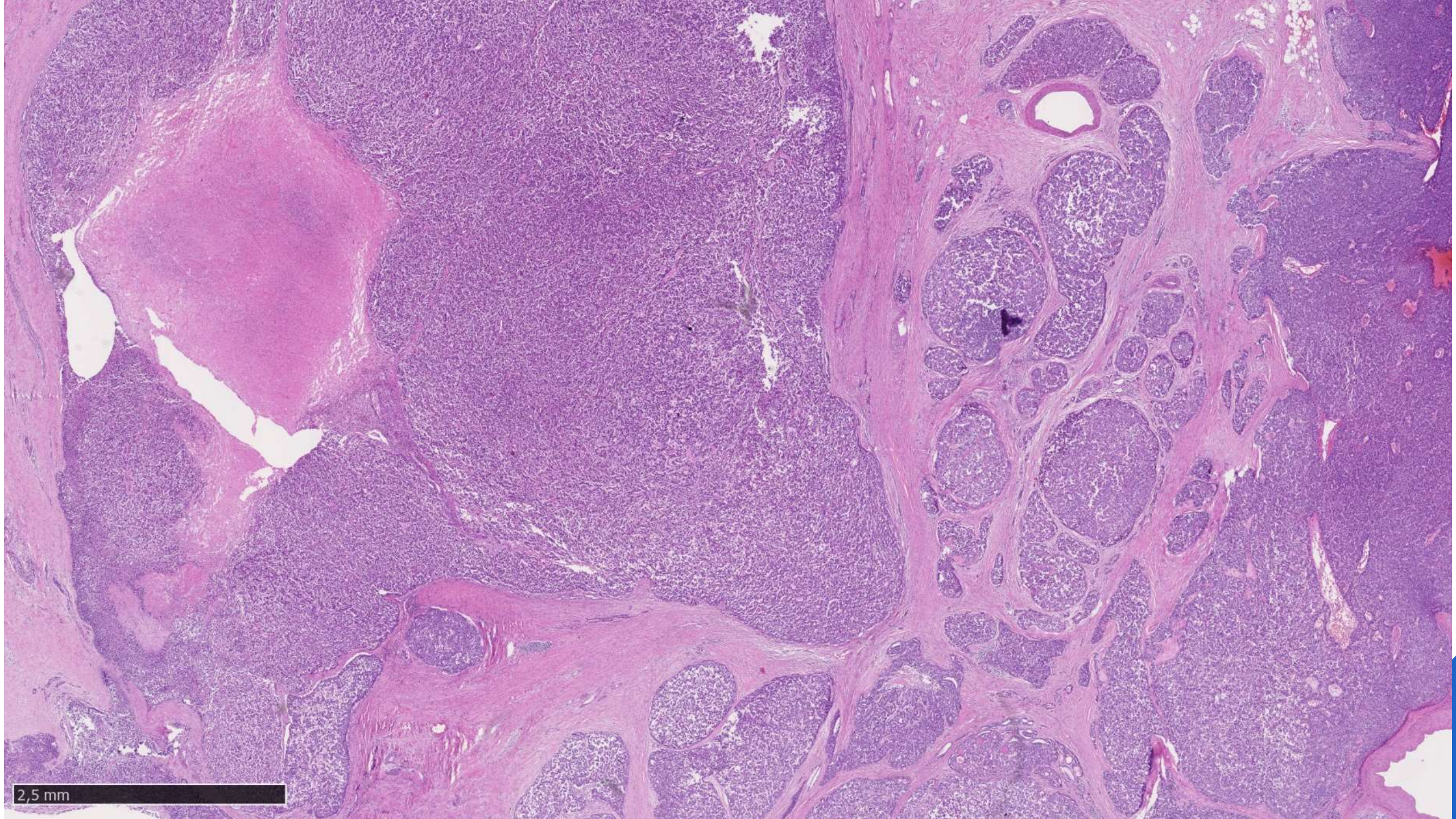
Hepatoid carcinoma

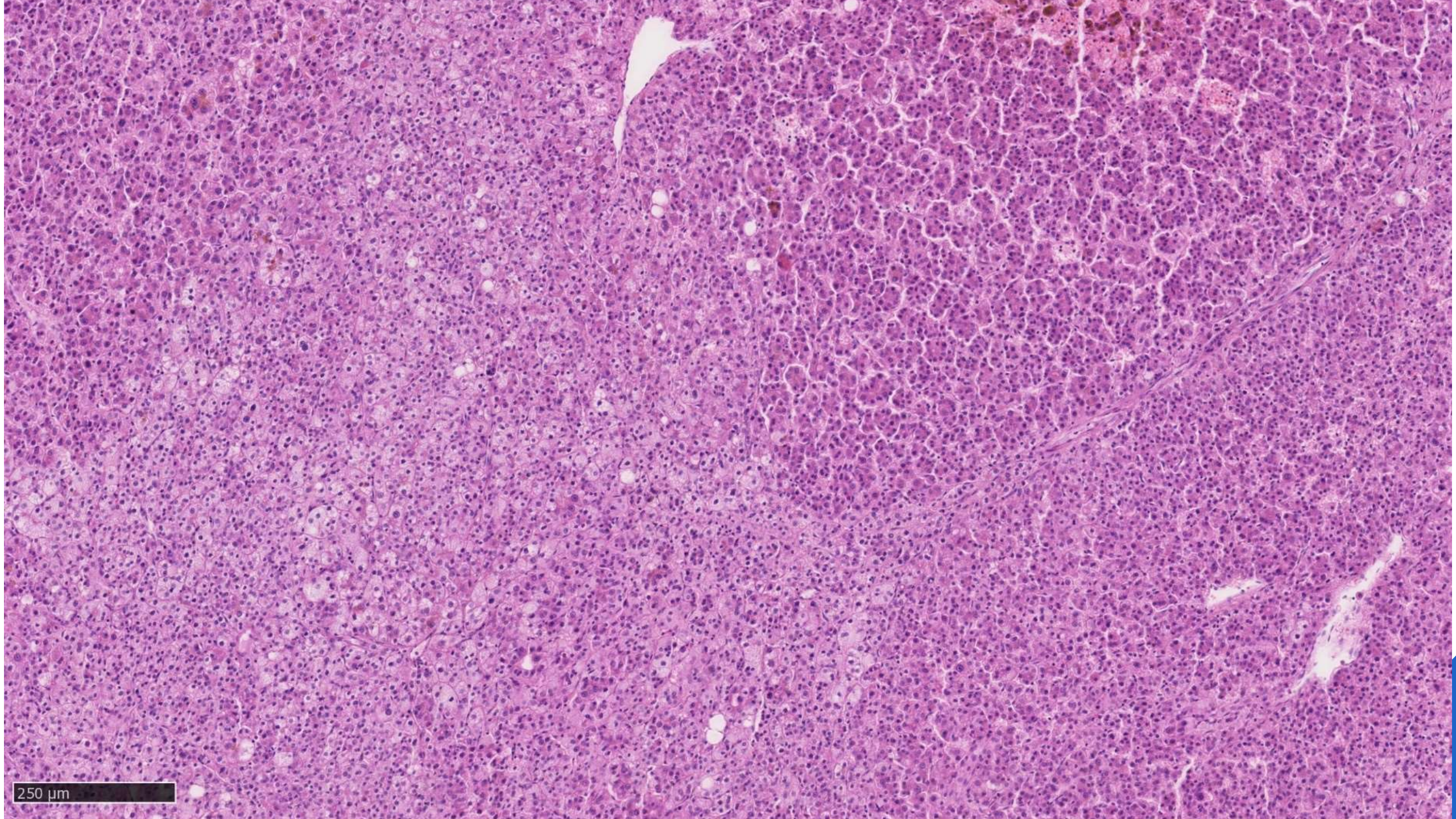
- Extremely rare
- Subtype PDAC, some probably related to acinar cell carcinoma
  - ACC: AFP, HepPar-1, Glypican-3 and Albumin-ISH may be positive
- Carcinoma with ≥50% cells displaying histological and IHC evidence of hepatocellular differentiation
- Large polygonal cells with abundant eosinophilic cytoplasm

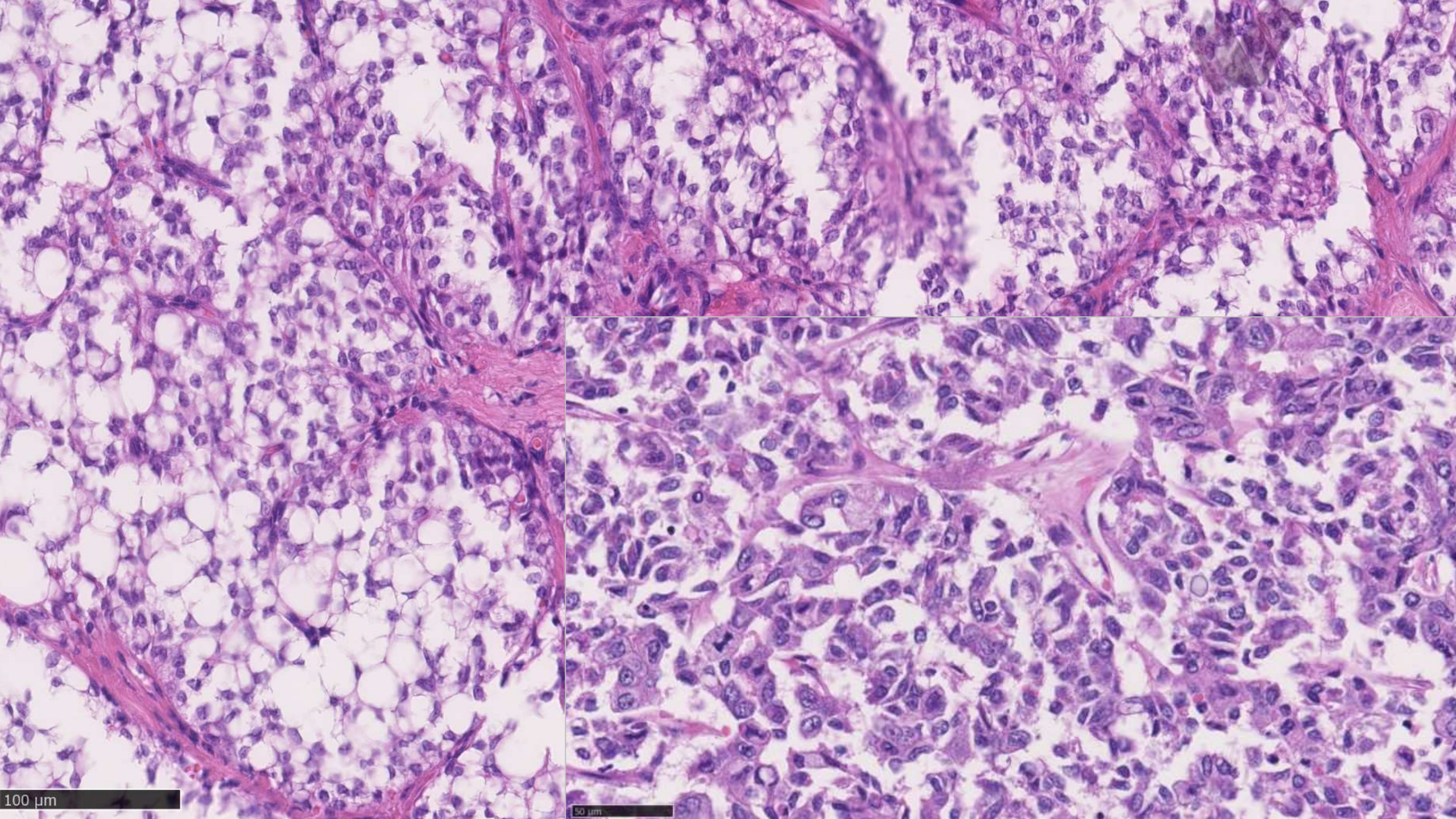
Albumin mRNA-FISH and arginase IHC

More reliable markers of hepatocellular differentiation

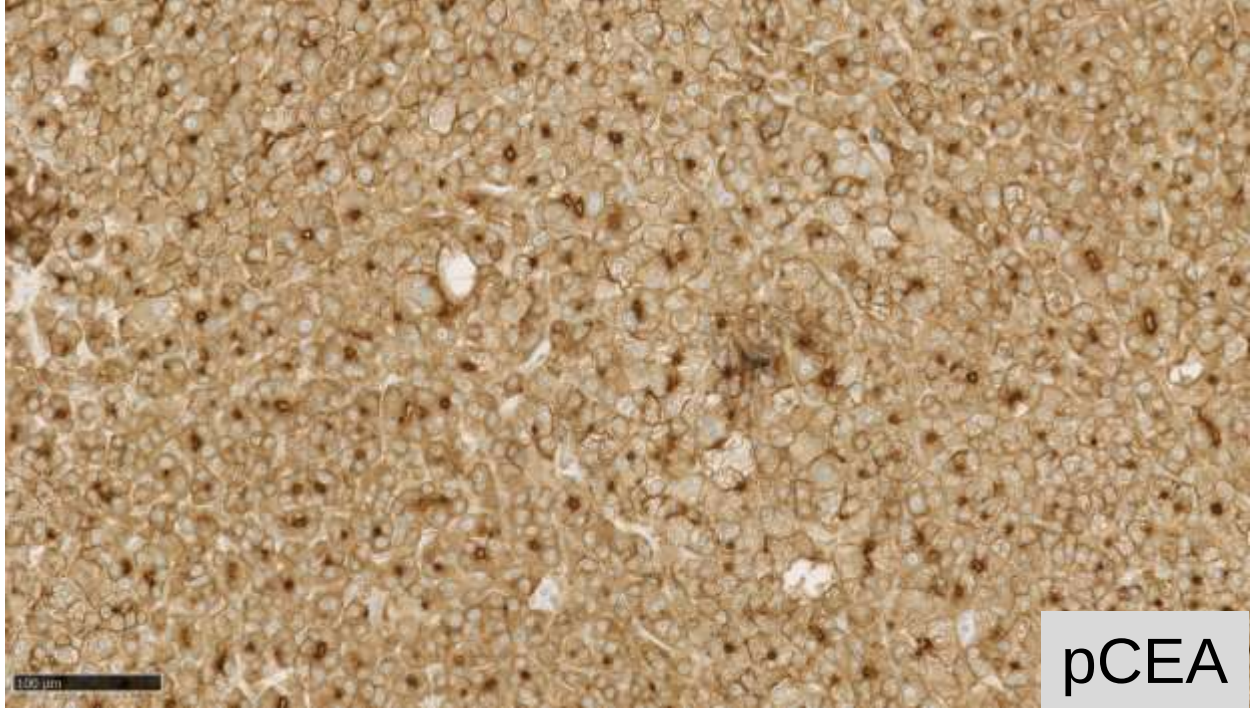
Paner et al. Cancer. 2000;88:1582-9
Hughes et al. Am Surg. 2004;70:1030-3
Vanoli et al. Virchows Arch. 2015; 467;237-45
Cingolani et al, Hum. Pathol. 2000;31:938-44
Askan et al. Am J Clin Pathol. 2016;146:163-9

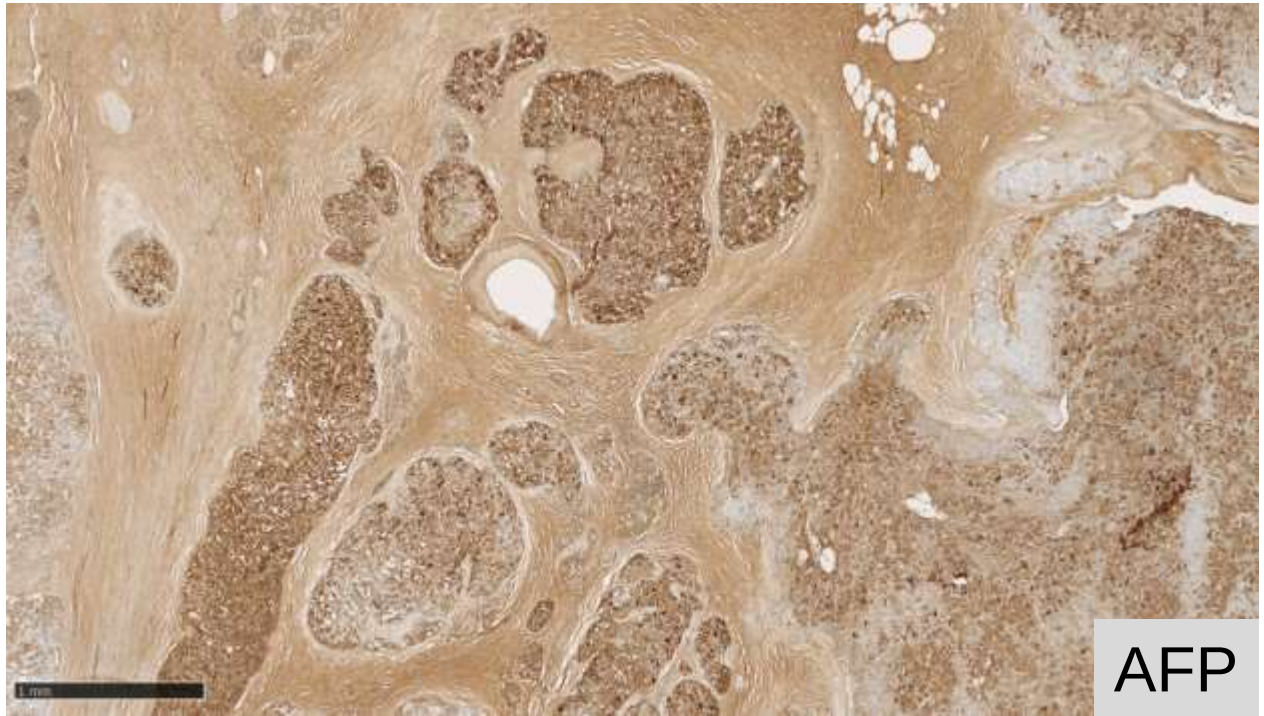

2,5 mm

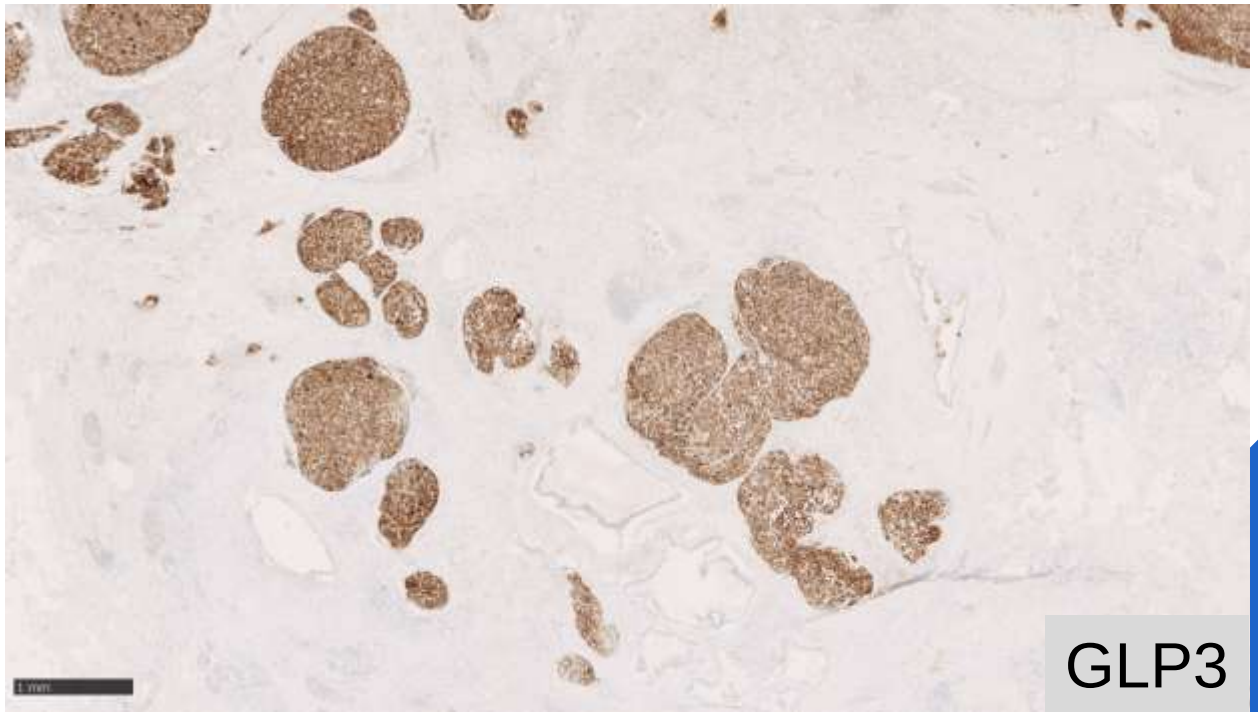

250 µm

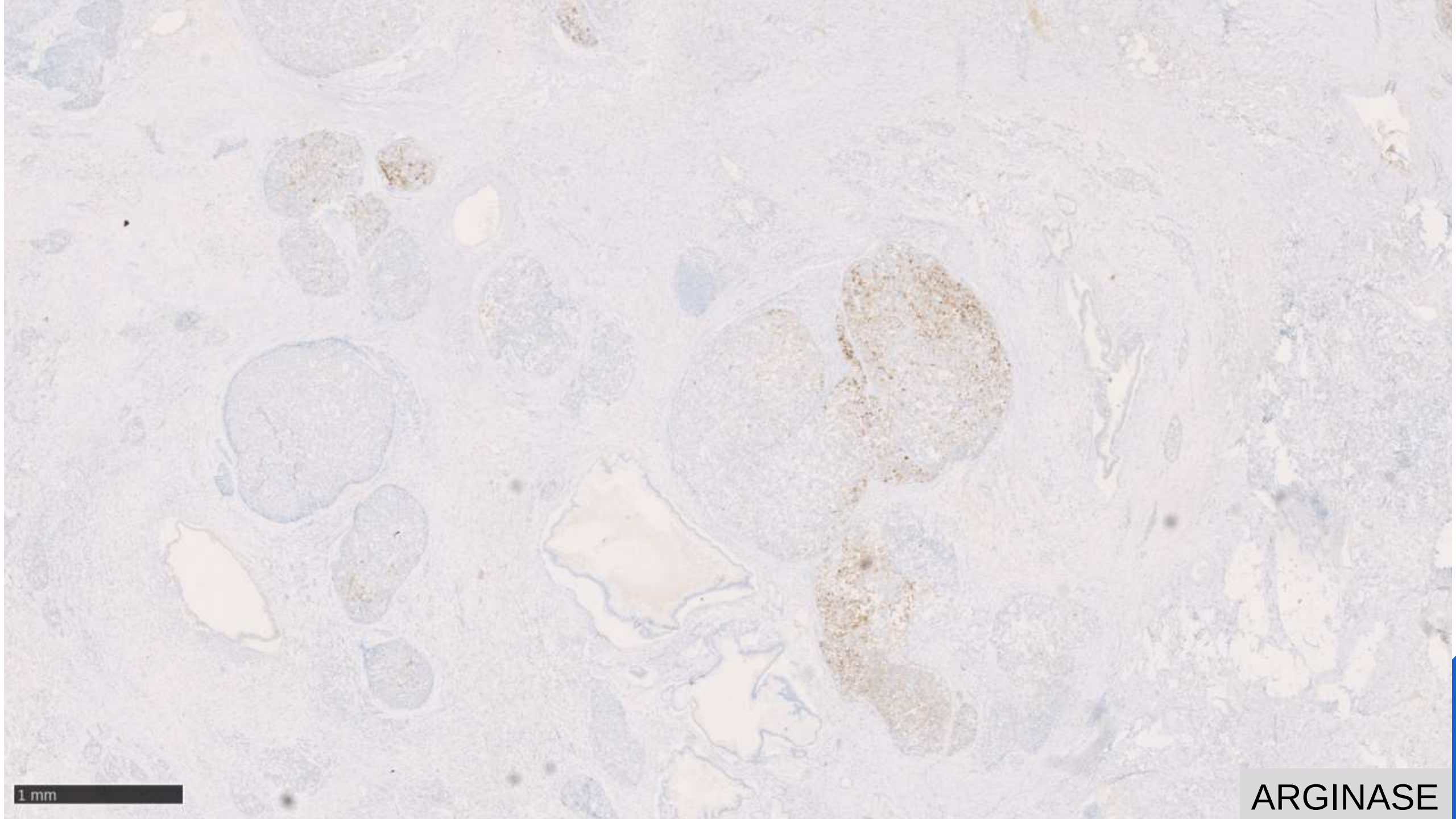

100 µm
50 µm


HepPar1


pCEA


AFP


GLP3

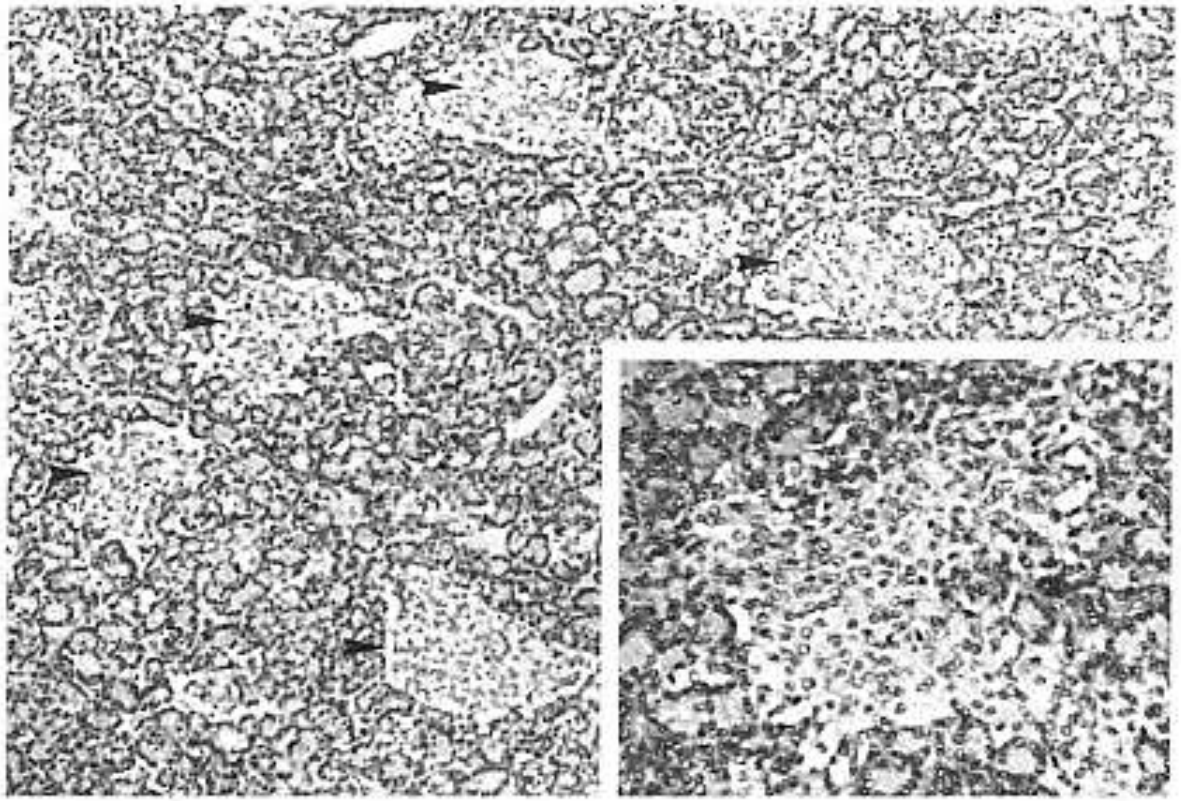

1 mm
ARGINASE

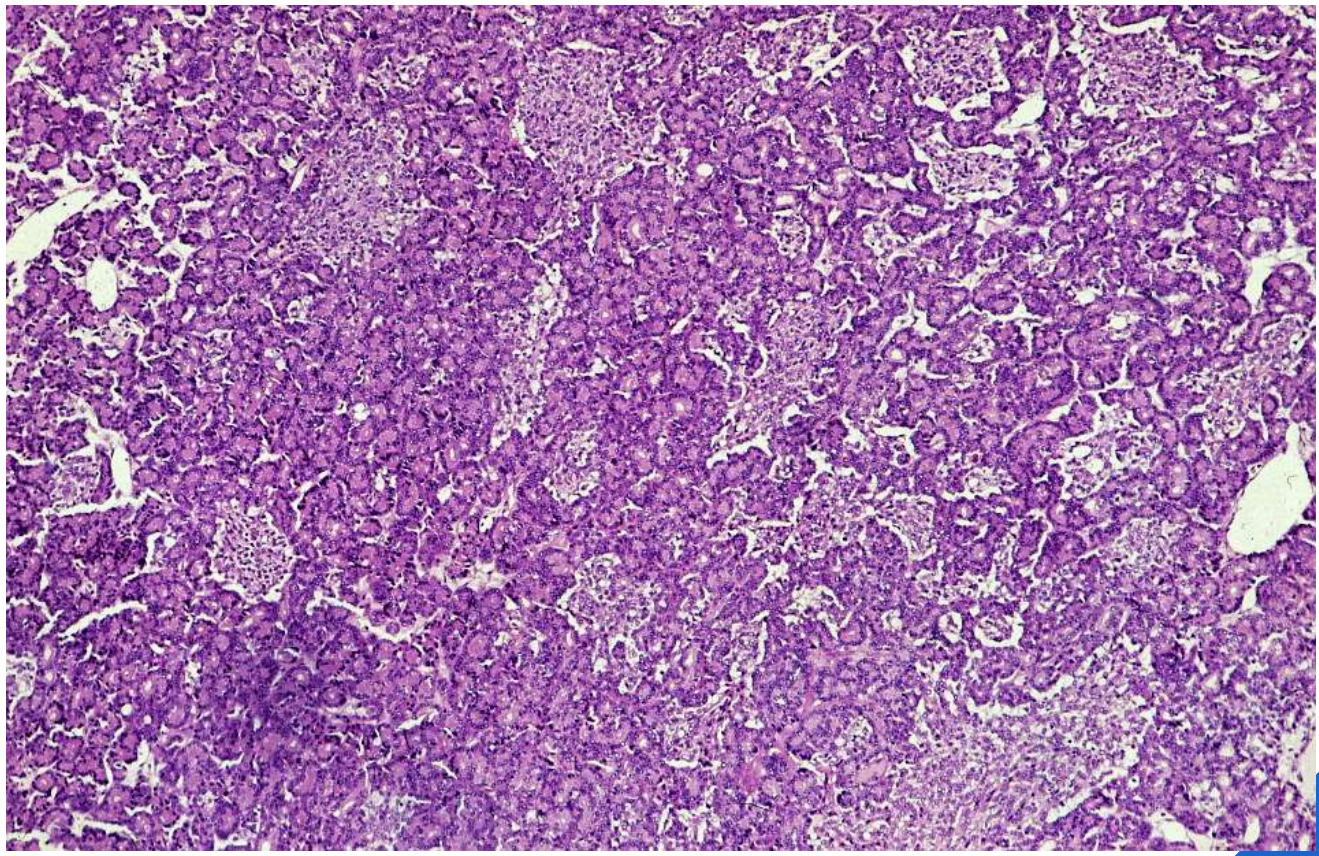
Pancreatoblastoma

- Extremely uncommon malignant epithelial neoplasm
- Almost exclusively in children, mean age 5
- M = F
- Characterized by cells showing multiple lines of differentiation
  - Prominent acinar differentiation and squamoid nests (morules)
  - Ductal and endocrine differentiation generally focal
  - Hypercellular stroma

- Labelling for pancreatic enzymes (trypsin, chymotrypsin, lipase) and BCL10
- Squamoid nests: nuclear and cytoplasmic positivity for β-catenin

Hoorens et al. Vitchows Arch. 1994;424:485-490
Bien et al. Eur J Cancer. 2011;47:2347-52
Cavalinni et al. Pancreatology. 2009;9:73-80





Hoorens et al. Virchows Arch. 1994;424:485-90

Intraductal papillary neoplasms

- Acinar cell carcinoma may grow into ducts
  - May mimic intraductal papillary mucinous neoplasm (IPMN)

- Intraductal oncocytic papillary neoplasm (IOPN)
  - Can have solid growth
  - Composed of eosinophilic cells
  - Distinction may be difficult

IHC to show acinar differentiation, no mucins in ACC

CONCLUSION

Acinar cell carcinomas

- Lobular growth, high cellul, scant/absent fibrous stroma
- Granular eosinophilic cytoplasm
- Uniform nuclei with single prominent nucleolus
- Moderate/abundant necrosis
- Immunohistochemical evidence of acinar cell differentiation

Main differential diagnosis NEN & SPN

	ACC	SPN	NEN	PB
Macroscopy	Circumscribed Soft	Circumscribed Soft	Circumscribed Soft	Circumscribed Soft
Age	Over 50	3rd decade	Any	1st decade
M:F	2:1	1:9	1:1	2:1
Architecture	Solid, Acinar	Pseudopapillae	Nested, trabecular, gyriform	Lobular
Nuclear	Nucleoli	Longitudinal nuclear grooves	Salt/pepper chromatin	Round to oval
Cytoplasm	Eosinophilic apical granularity	Cytoplasmic hyaline globules	Plasmacytoid	Granular
Other	Increased mitoses	Foamy histiocytes		Squamoid nests

	ACC	SPN	NEN	PB
Pankeratin	+	+/-	+/(-)	+
Vimentin	-	+	-/(+)	-
BCL10 and/or Trypsin	+	-	-	+
SYP with/without CGA	Focal (can diffuse)	SYP+ CGA-	+	Focal
Beta-catenin	-/+	+	-	- (squamoid nests +)
CD10	-	+	-	-

Thanks for your attention!

Questions?