



[@Vik_Deshpande](https://www.youtube.com/c/vikramdeshpandePathology)



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

Neoplasms of the Liver

Top challenges

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Pathologist

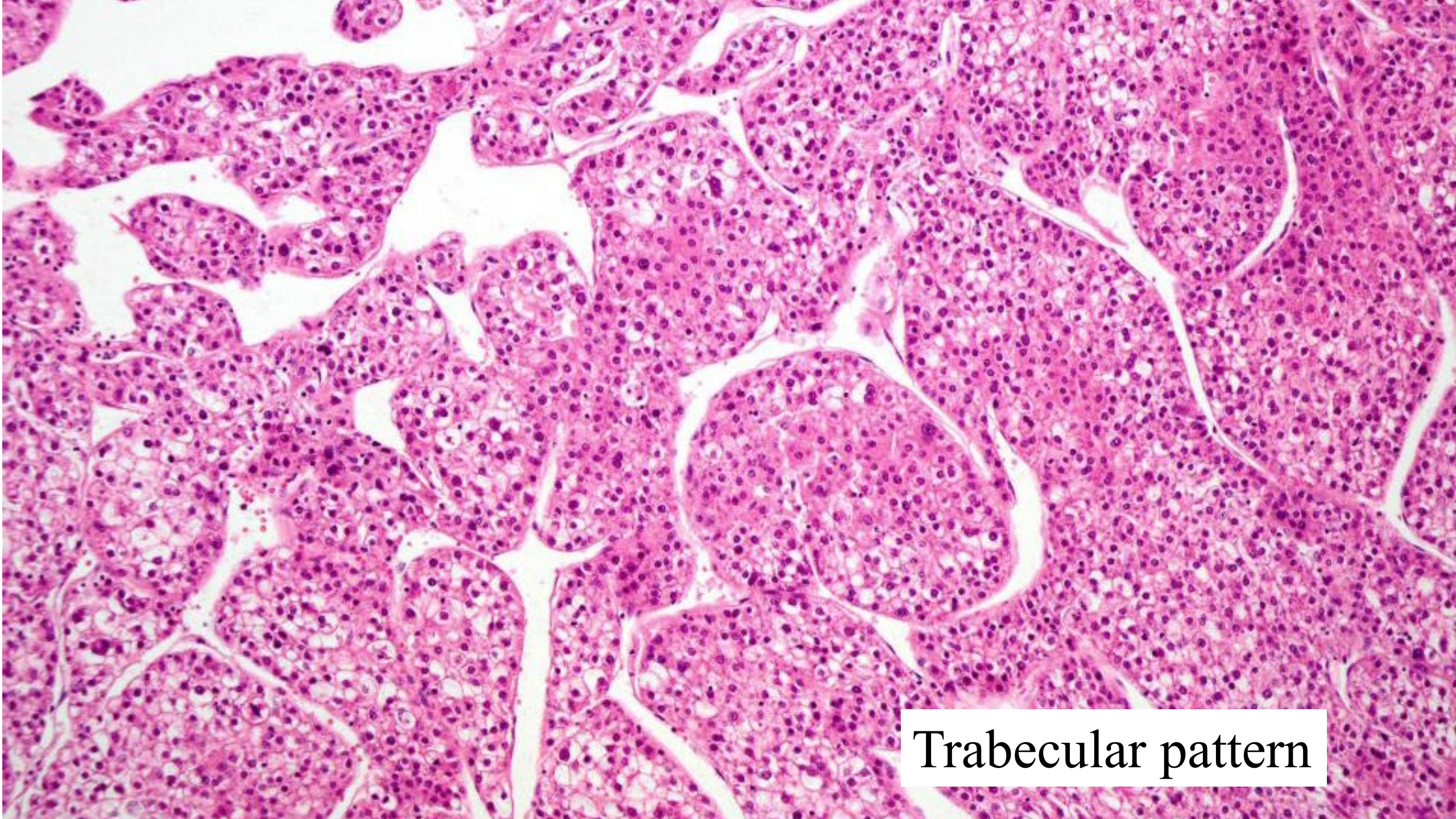
Director of GI pathology

Beth Israel Deaconess Medical Center

Editor-in-Chief

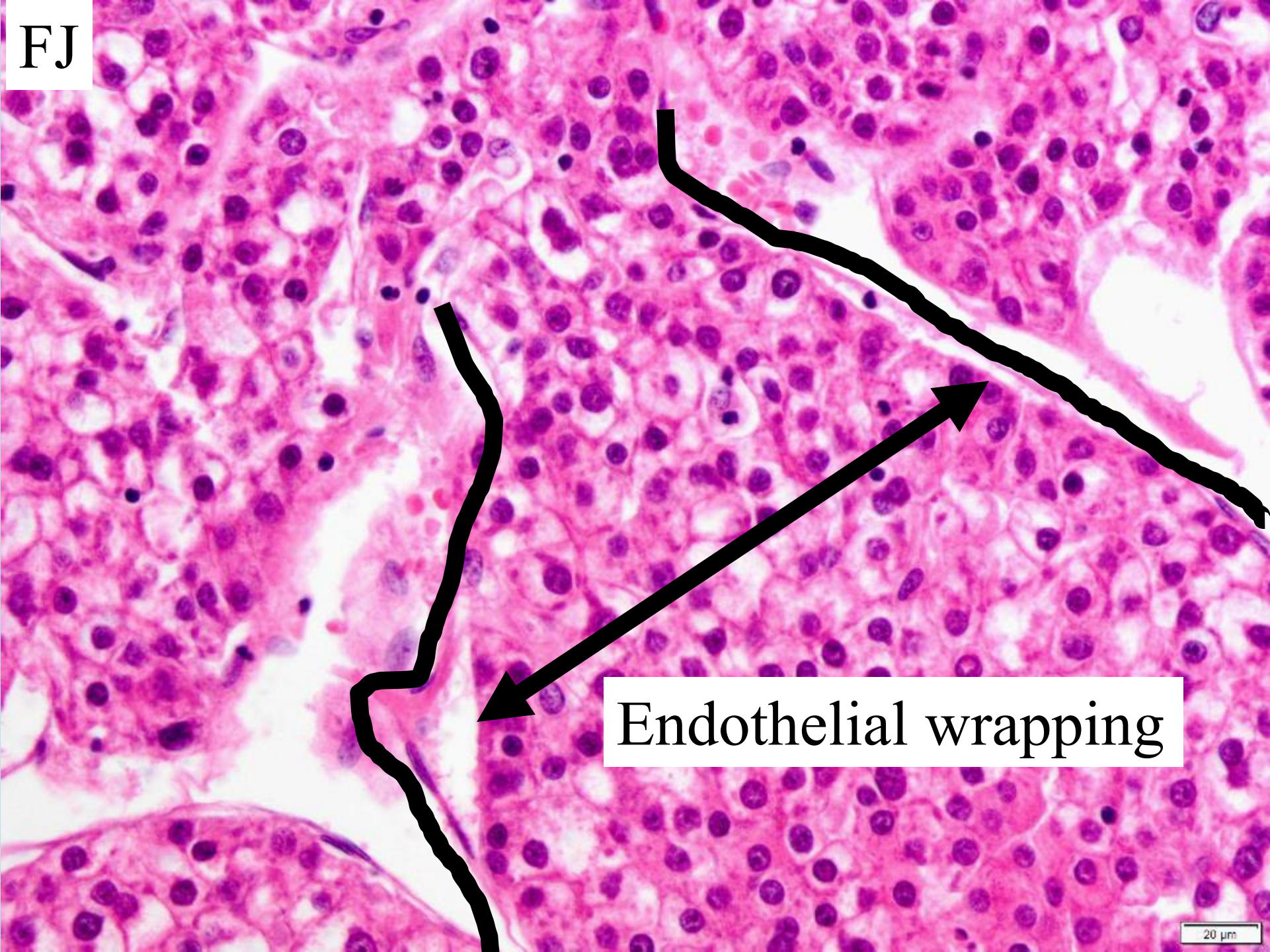
Journal of Clinical Pathology

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Trabecular pattern

FJ



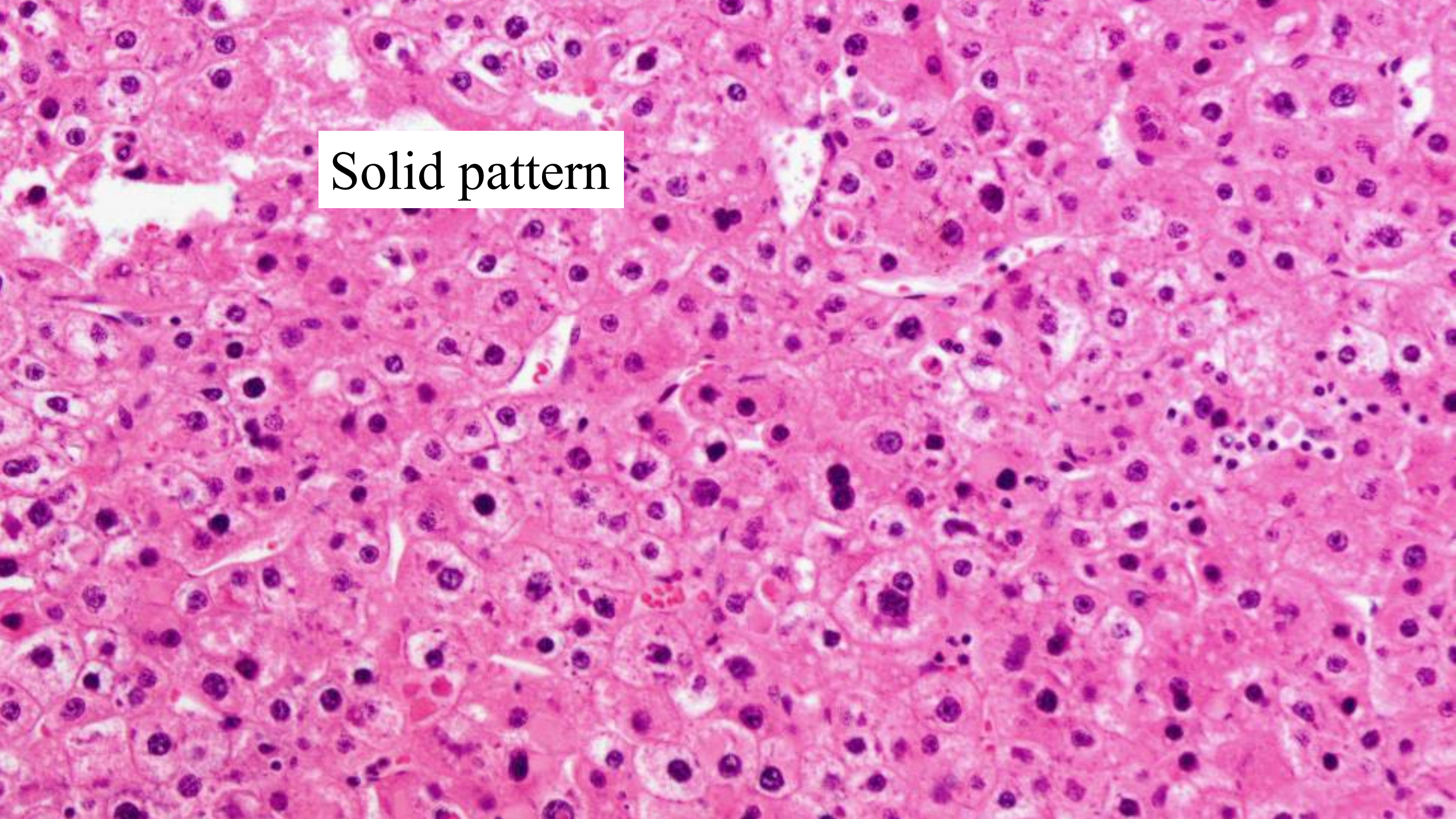
Endothelial wrapping

20 µm

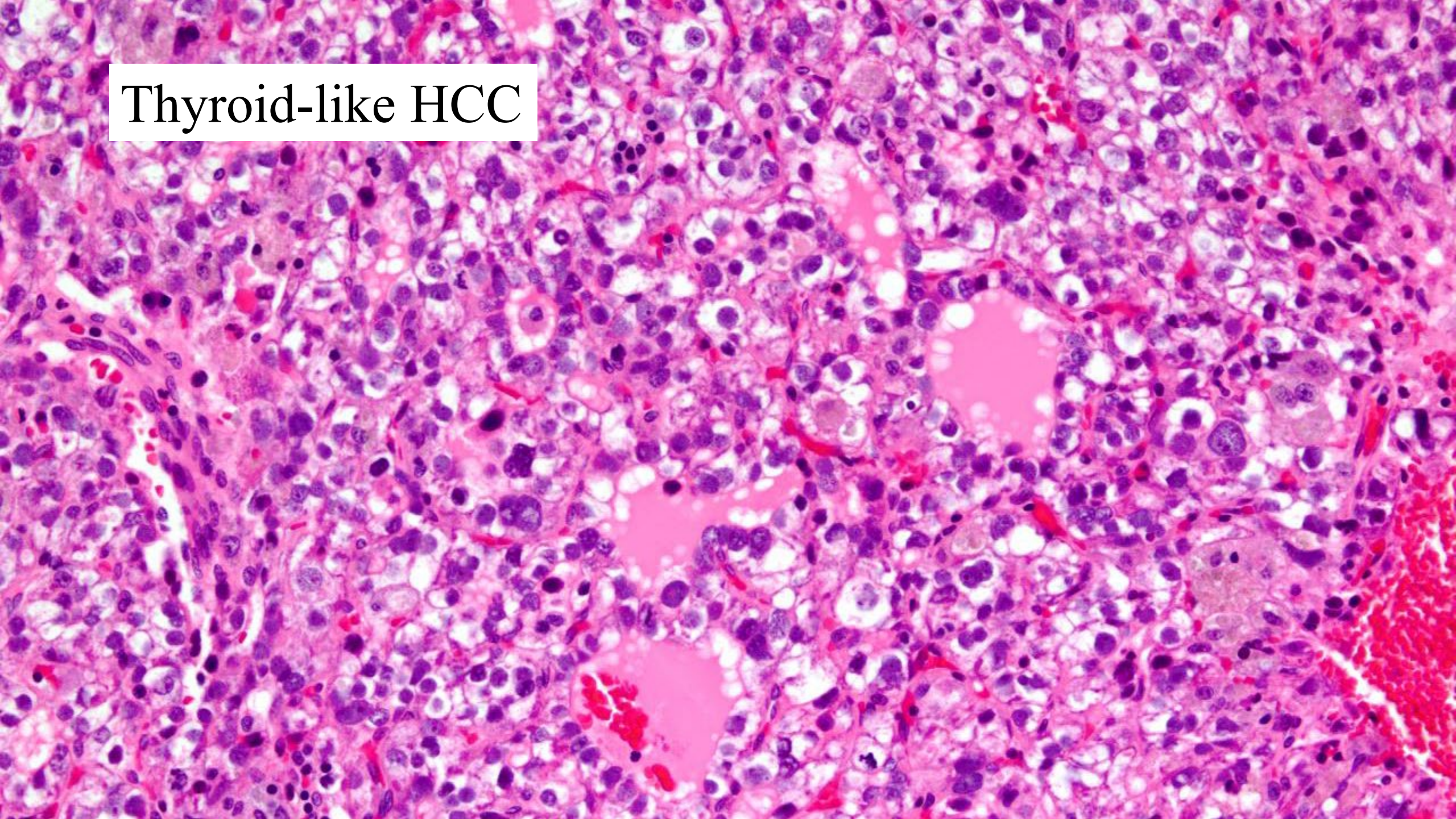
Glandular' pattern



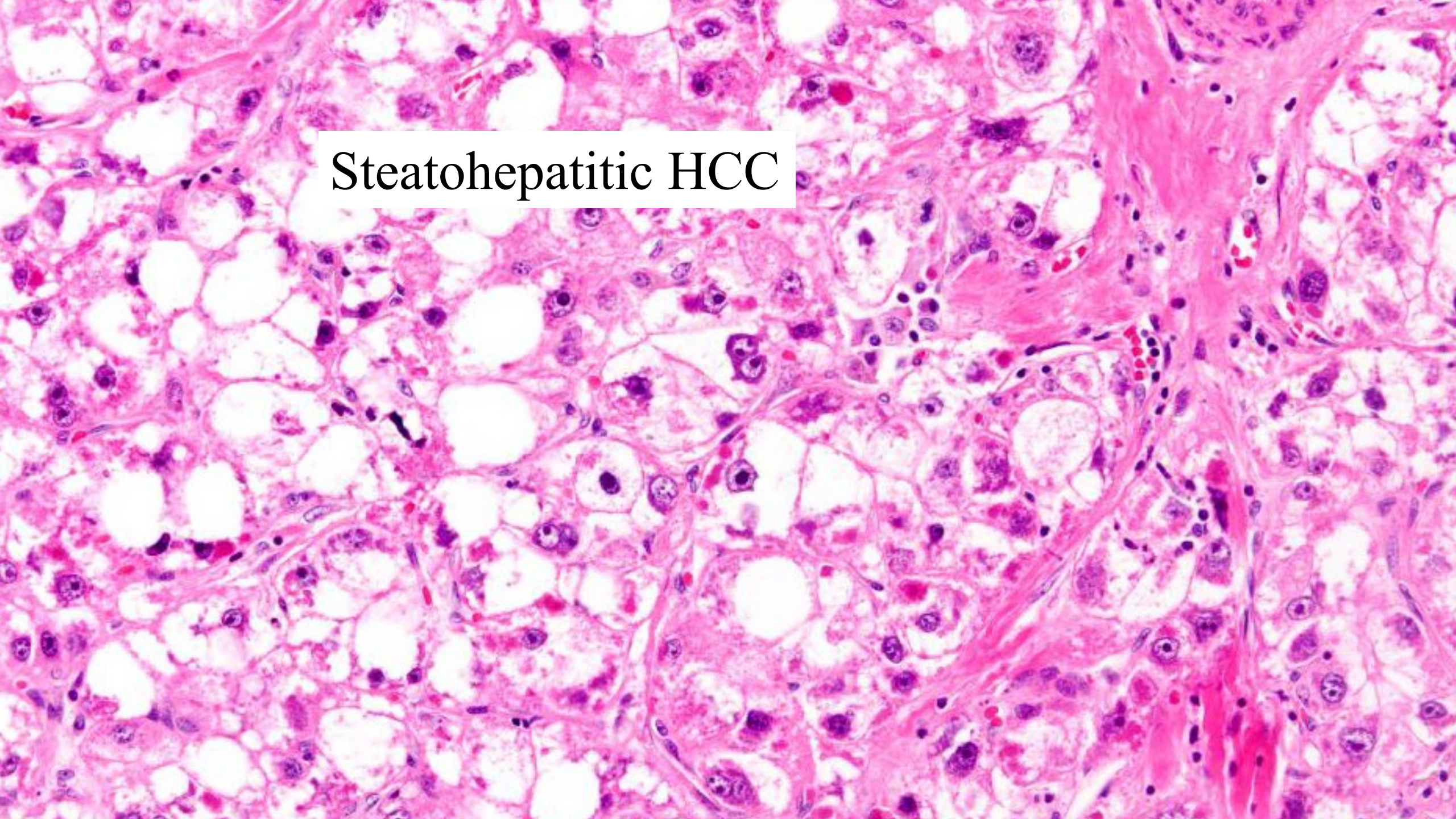
Solid pattern



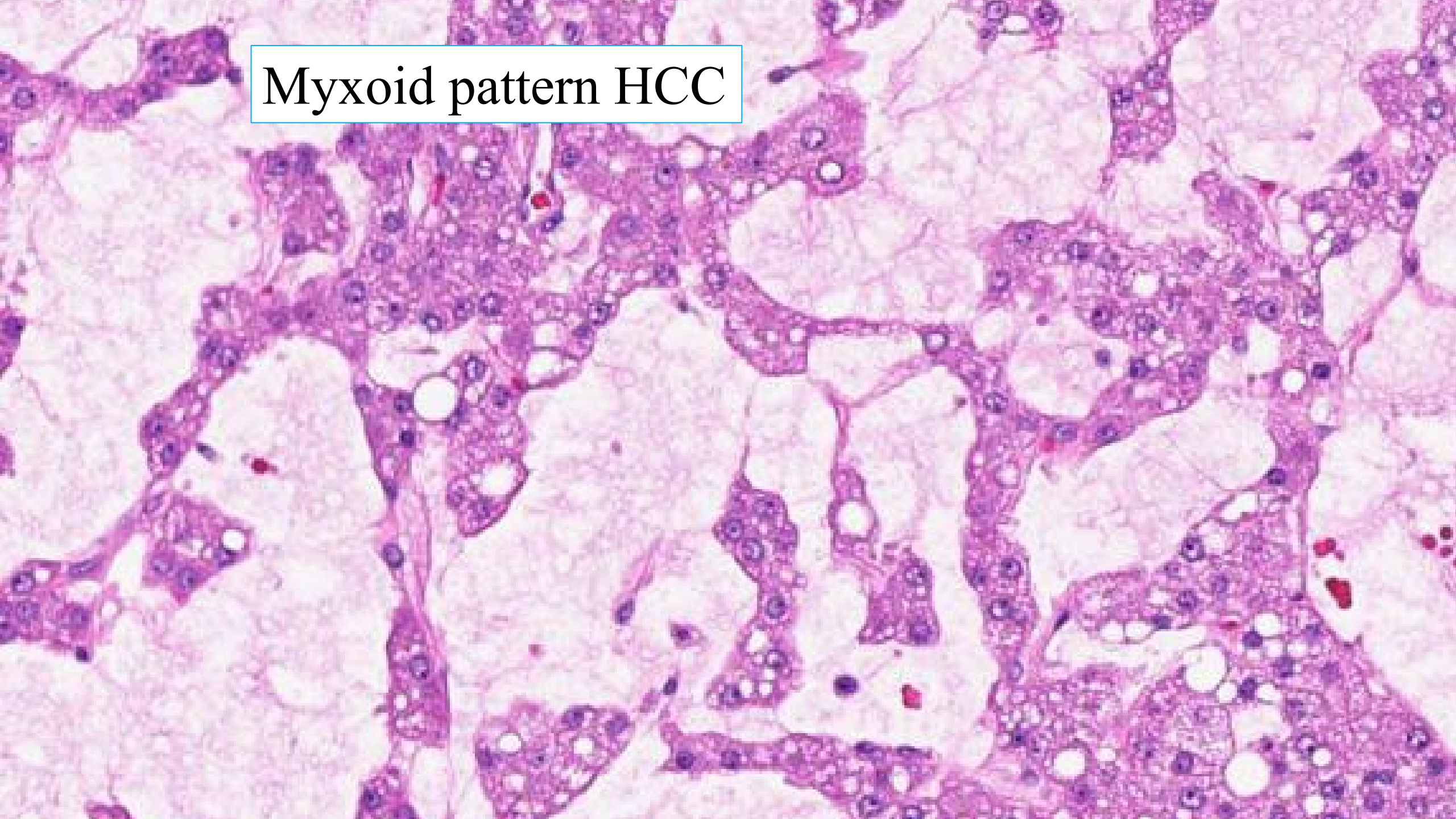
Thyroid-like HCC



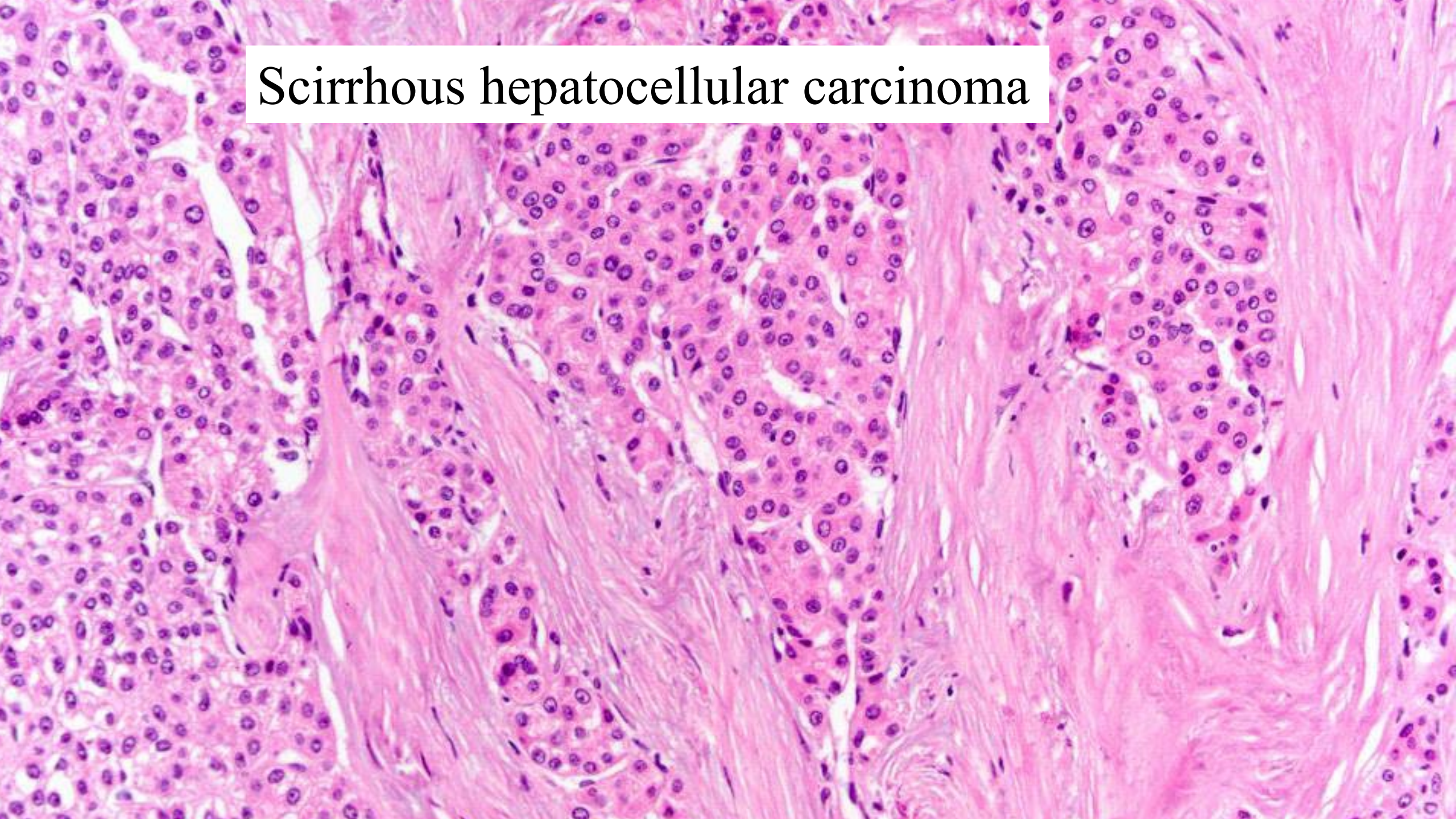
Steatohepatitic HCC



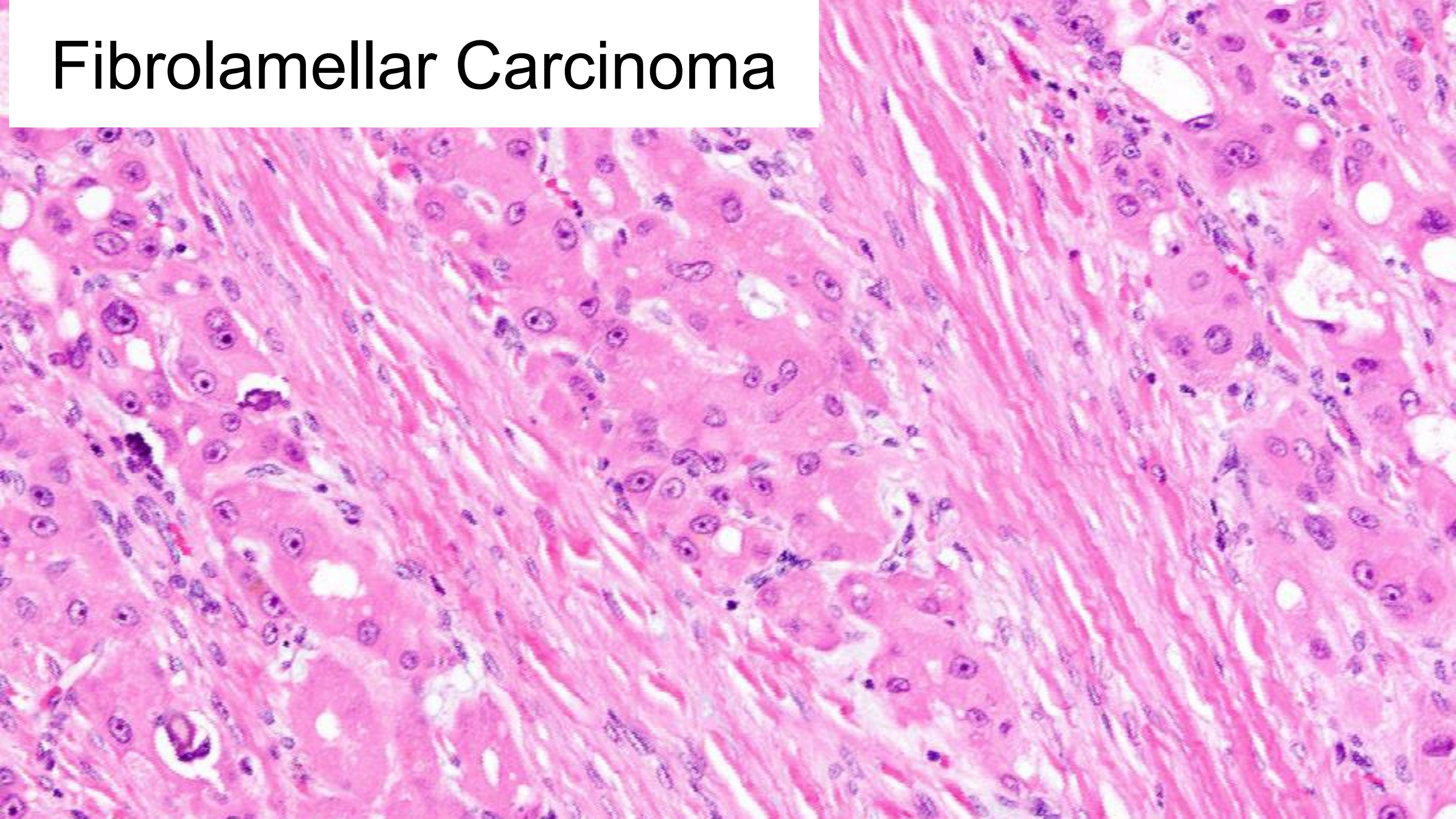
Myxoid pattern HCC



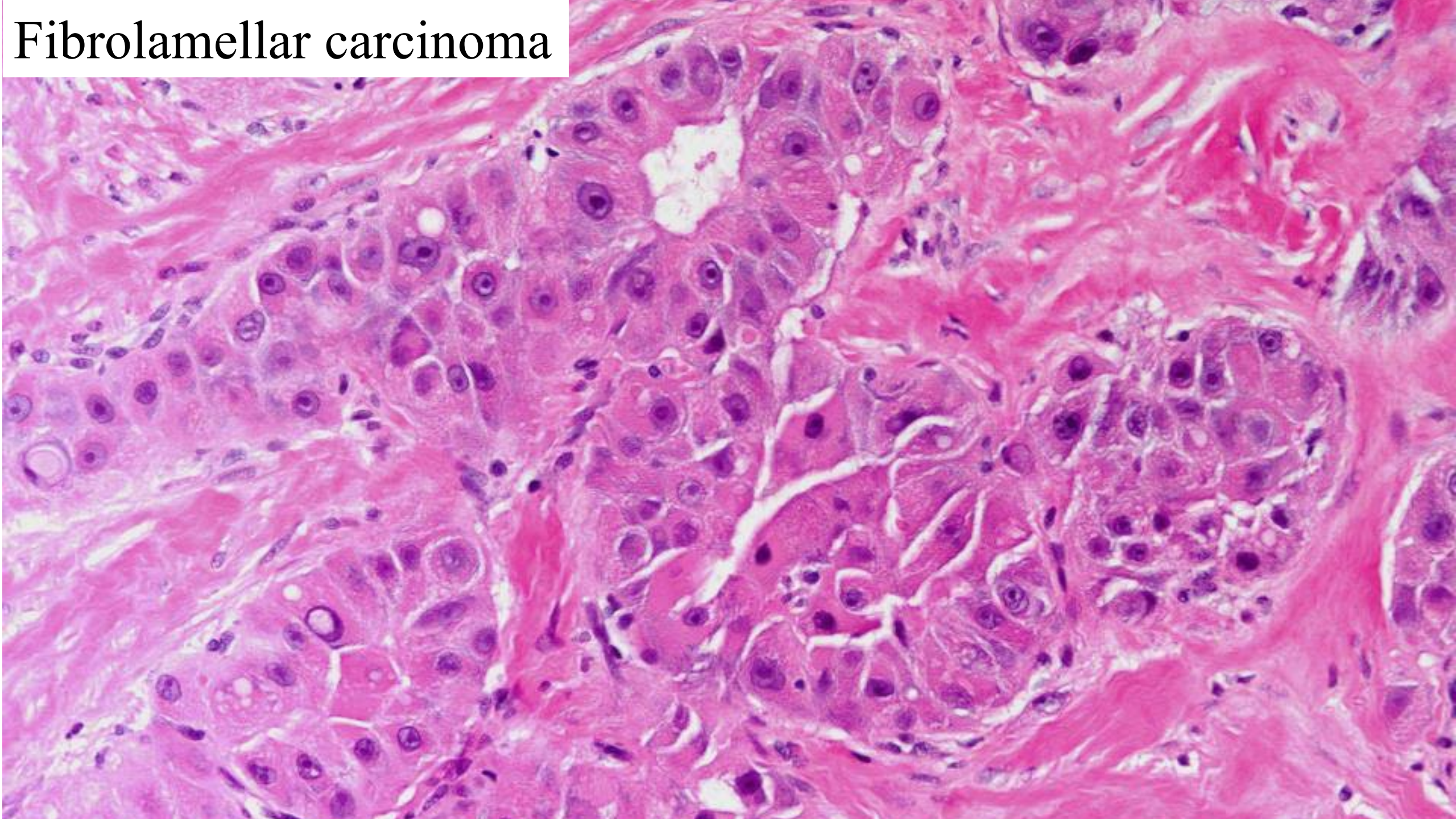
Scirrhous hepatocellular carcinoma



Fibrolamellar Carcinoma



Fibrolamellar carcinoma



Diagnostic Assays for Fibrolamellar Carcinoma

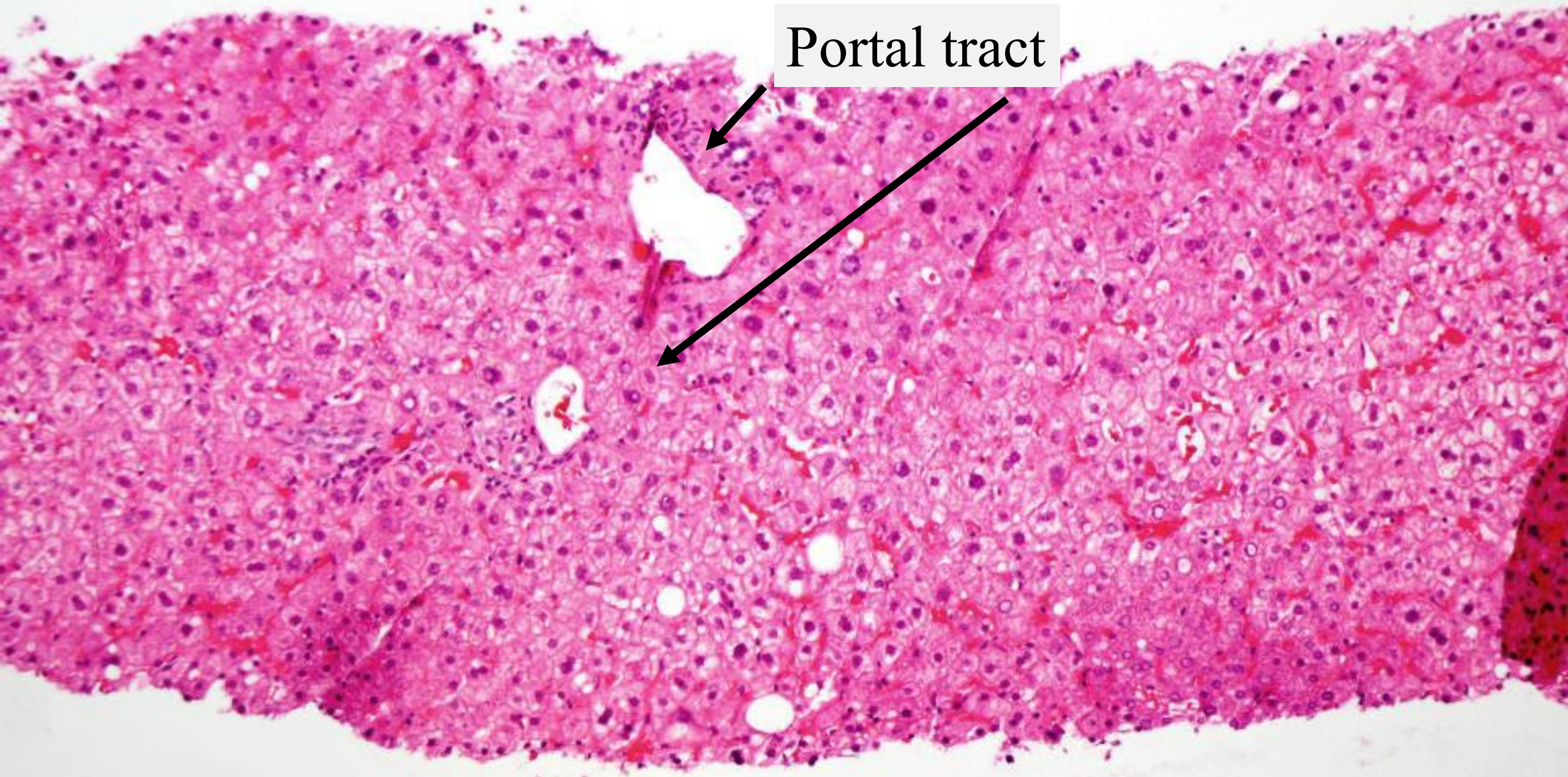
- Combined presence of CD68 and keratin 7
 - Unusual in conventional hepatocellular carcinoma
- KP1
clone
- FISH/fusion assay for DNAJB1-PRKACA fusion



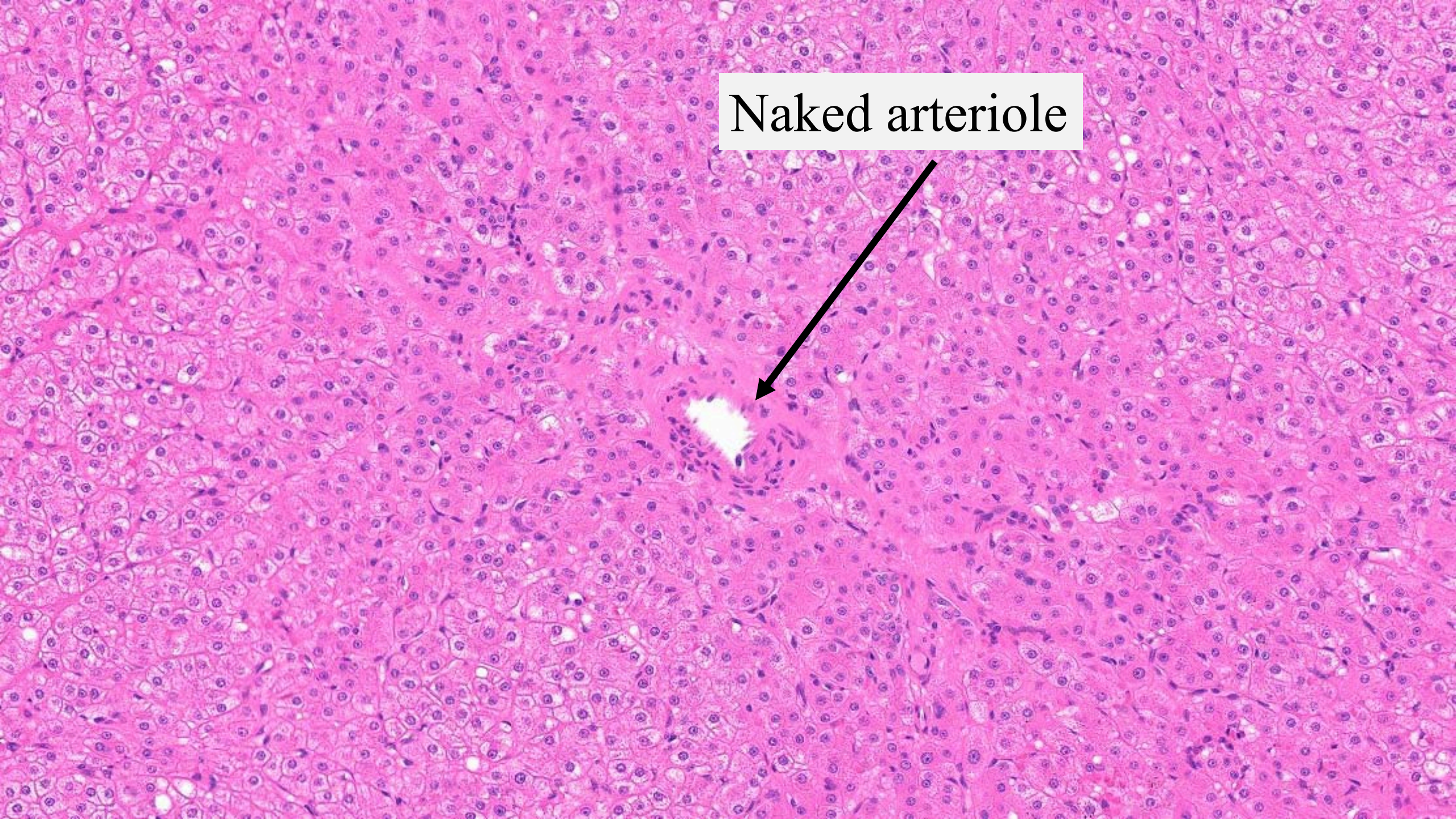
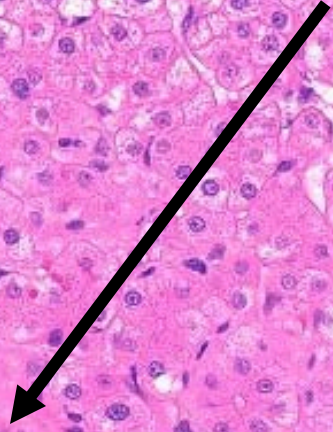
Problem 1

Did the radiologist miss the lesion?

Portal tract



Naked arteriole

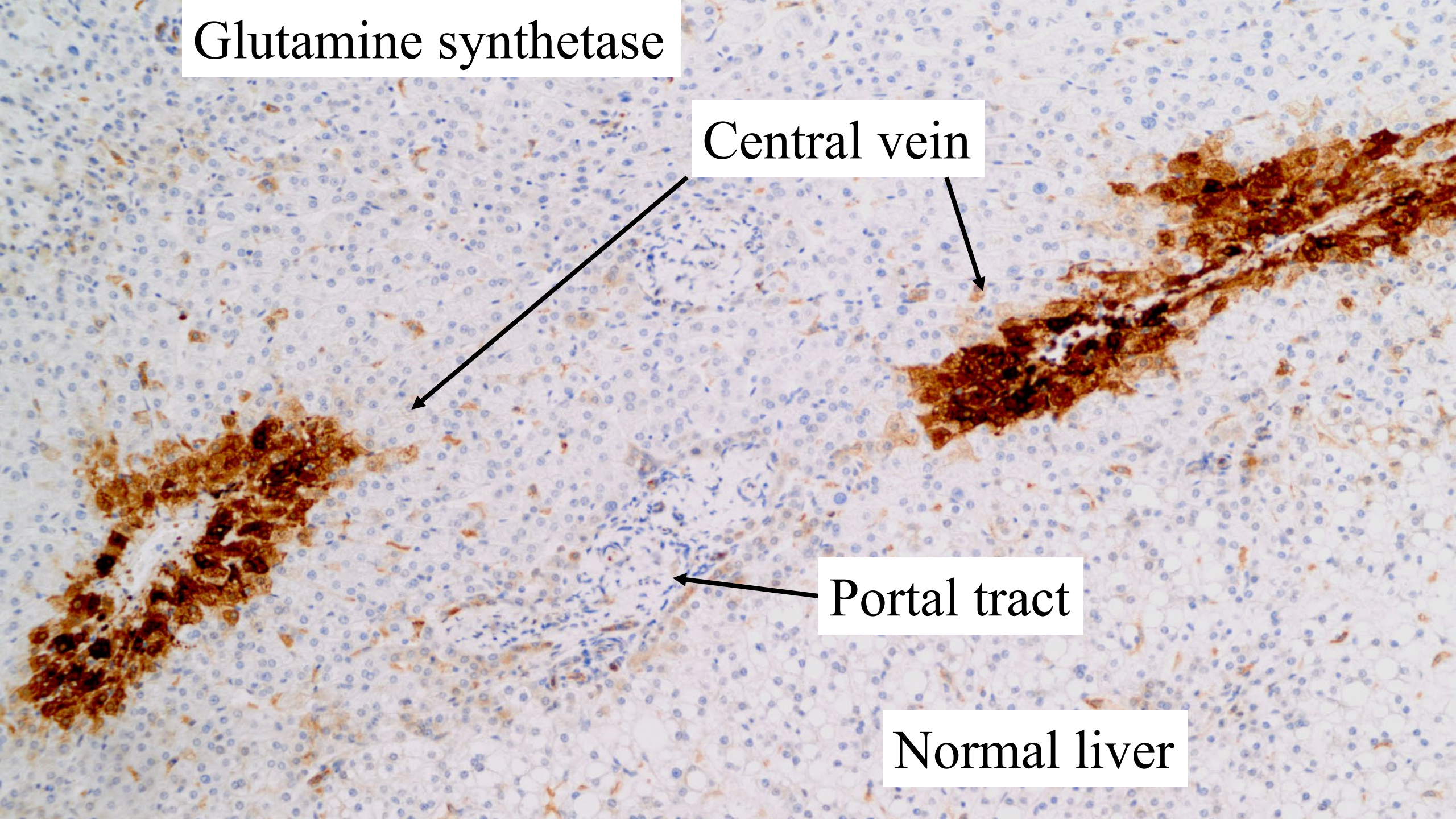


Glutamine synthetase

Central vein

Portal tract

Normal liver



Problem 2

Looks like liver, looks lesional– but is it malignant?

hepatocellular carcinoma?

Pseudotumors

- FNH
- Regenerative hepatocellular pseudotumor
- Macroregenerative nodule

Well differentiated hepatic neoplasm

Dysplastic nodule

HCC

Benign

Malignant

Neoplasms

- Hepatic adenoma



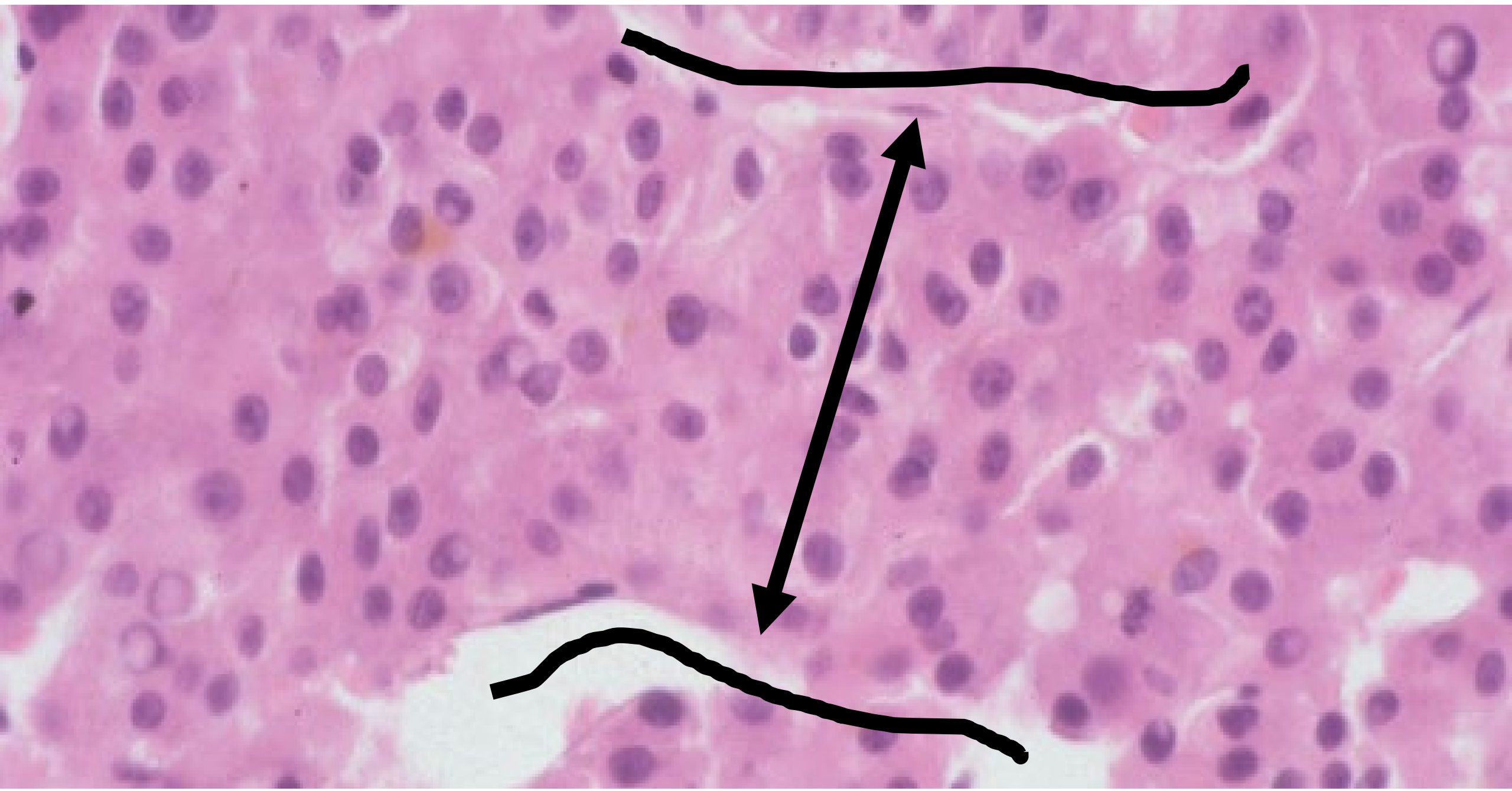
HCC vs Benign Hepatic Proliferation

	Benign hepatocellular proliferation	Malignant hepatocellular proliferation
Plates => 4 cell thick	No	Yes
N/C ratio Nuclear density	Absent	Present nuclear density > 2x normal
Mitosis	Rare	Common
Reticulin	Intact	Present/absent
Iron free foci	Absent	Present
Glypican 3	Typically negative	Positive 69%

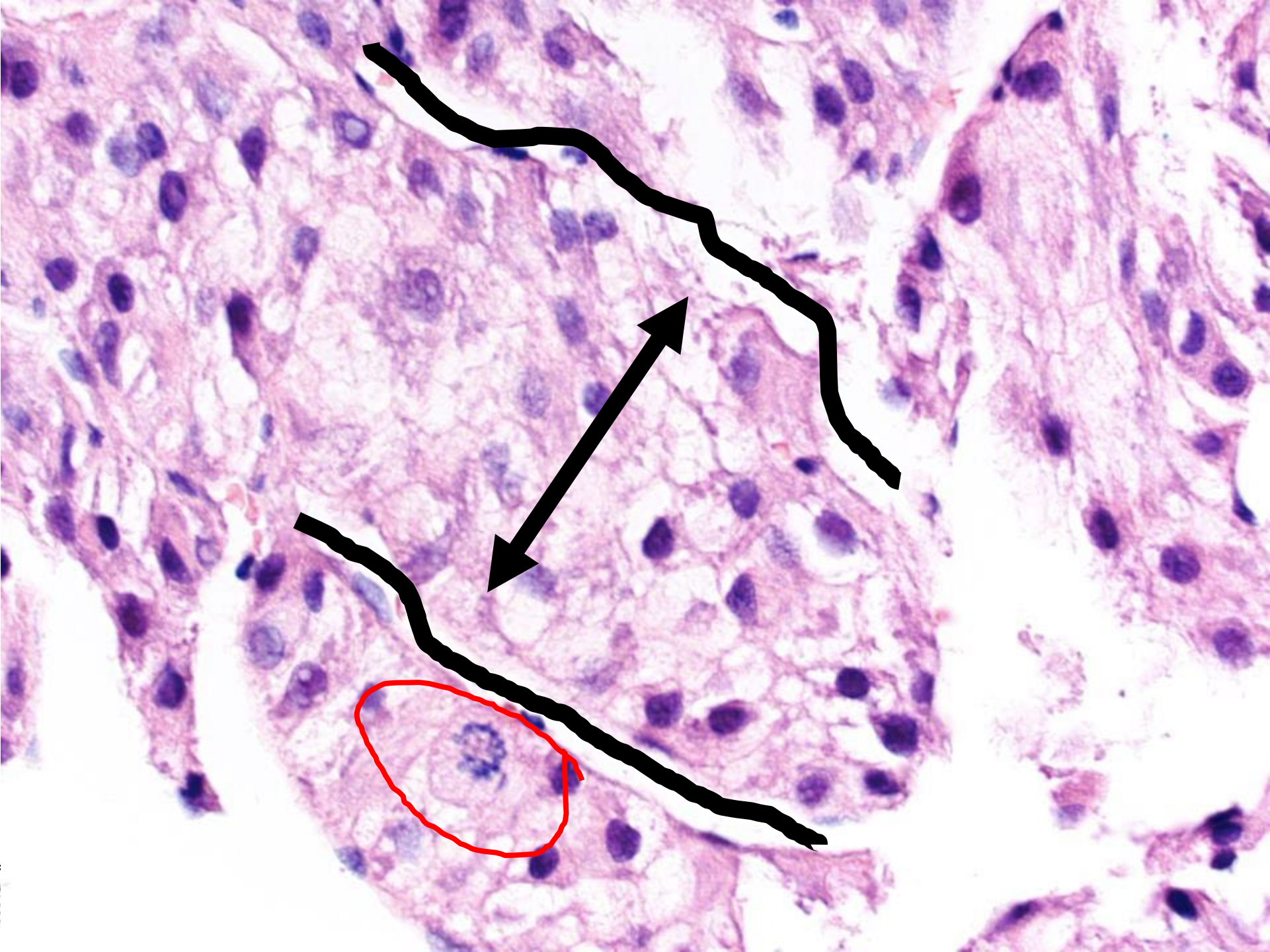
Ki67, CD34

EZH2, AFP, Hsp 70

Hepatic plates > 4 cell thick hepatic plates = HCC



Cellblock

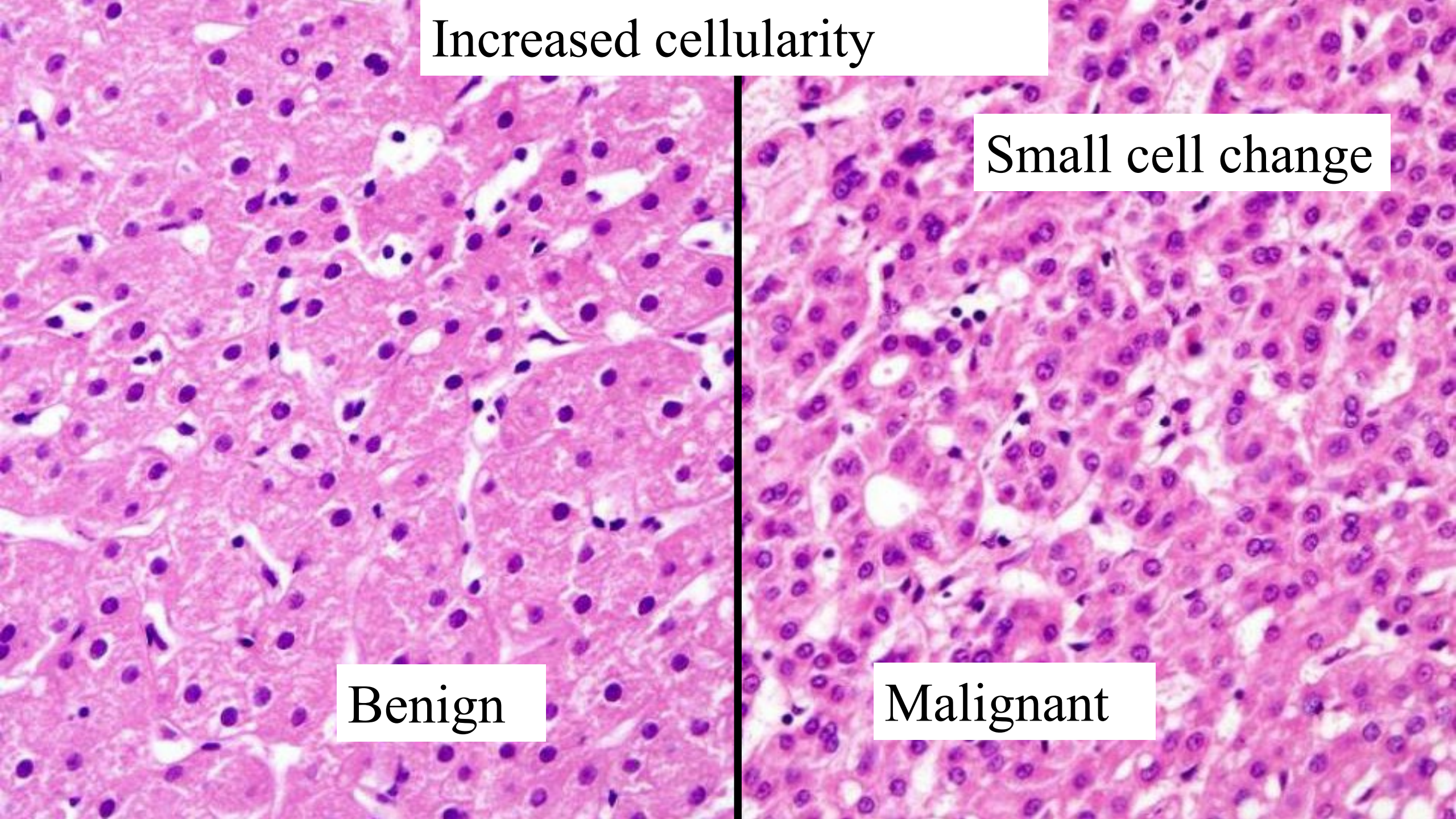


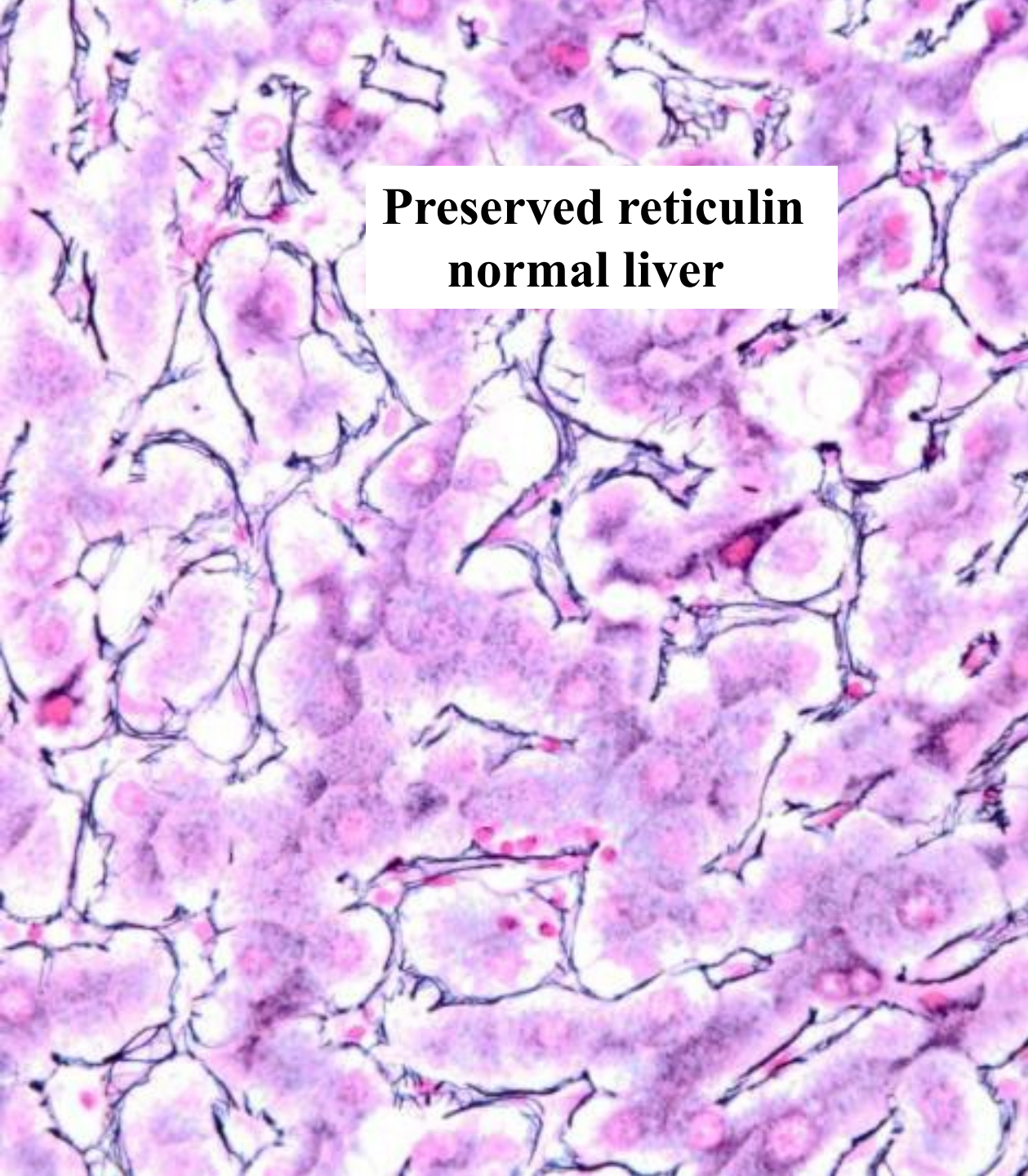
Increased cellularity

Small cell change

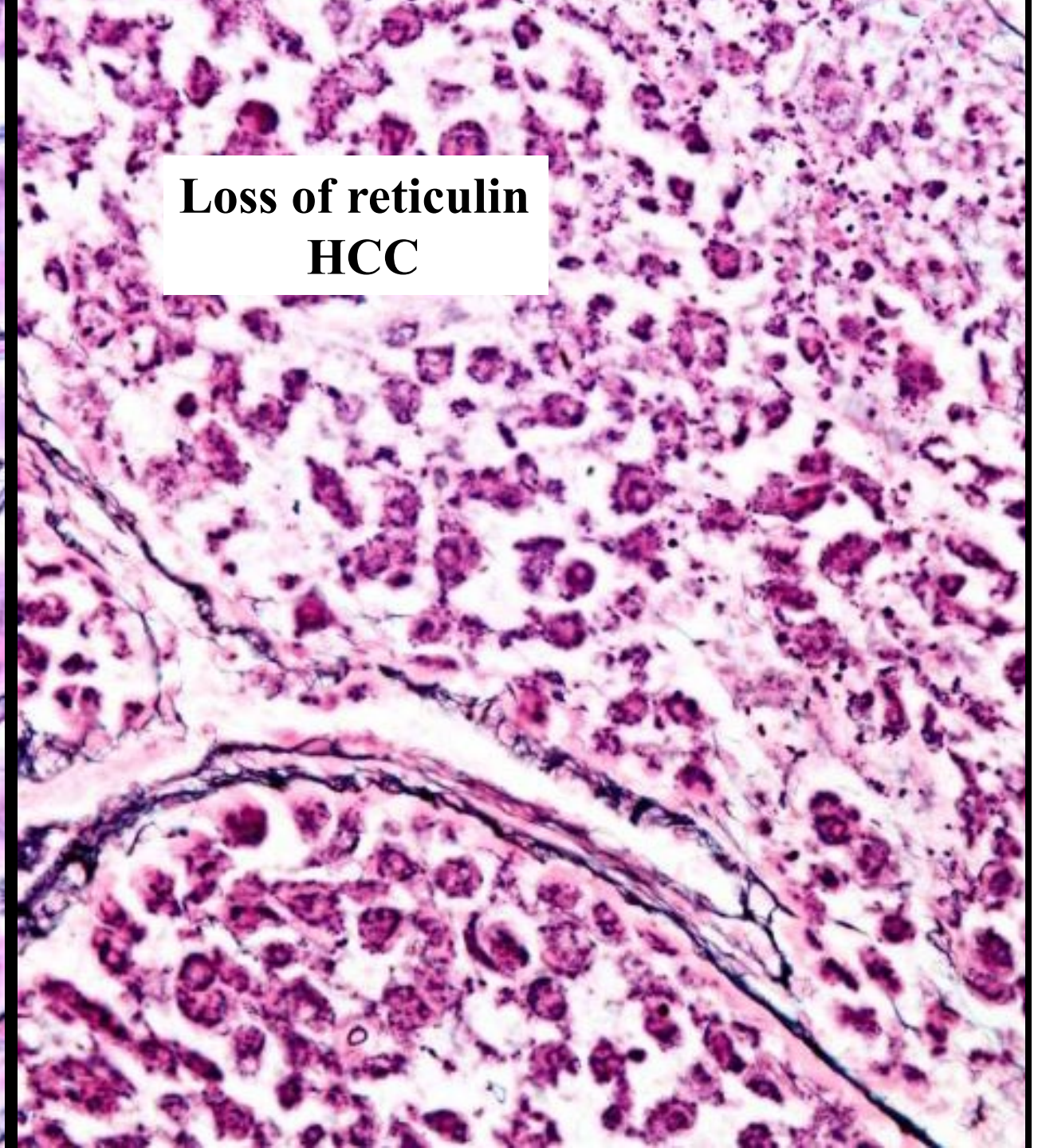
Benign

Malignant



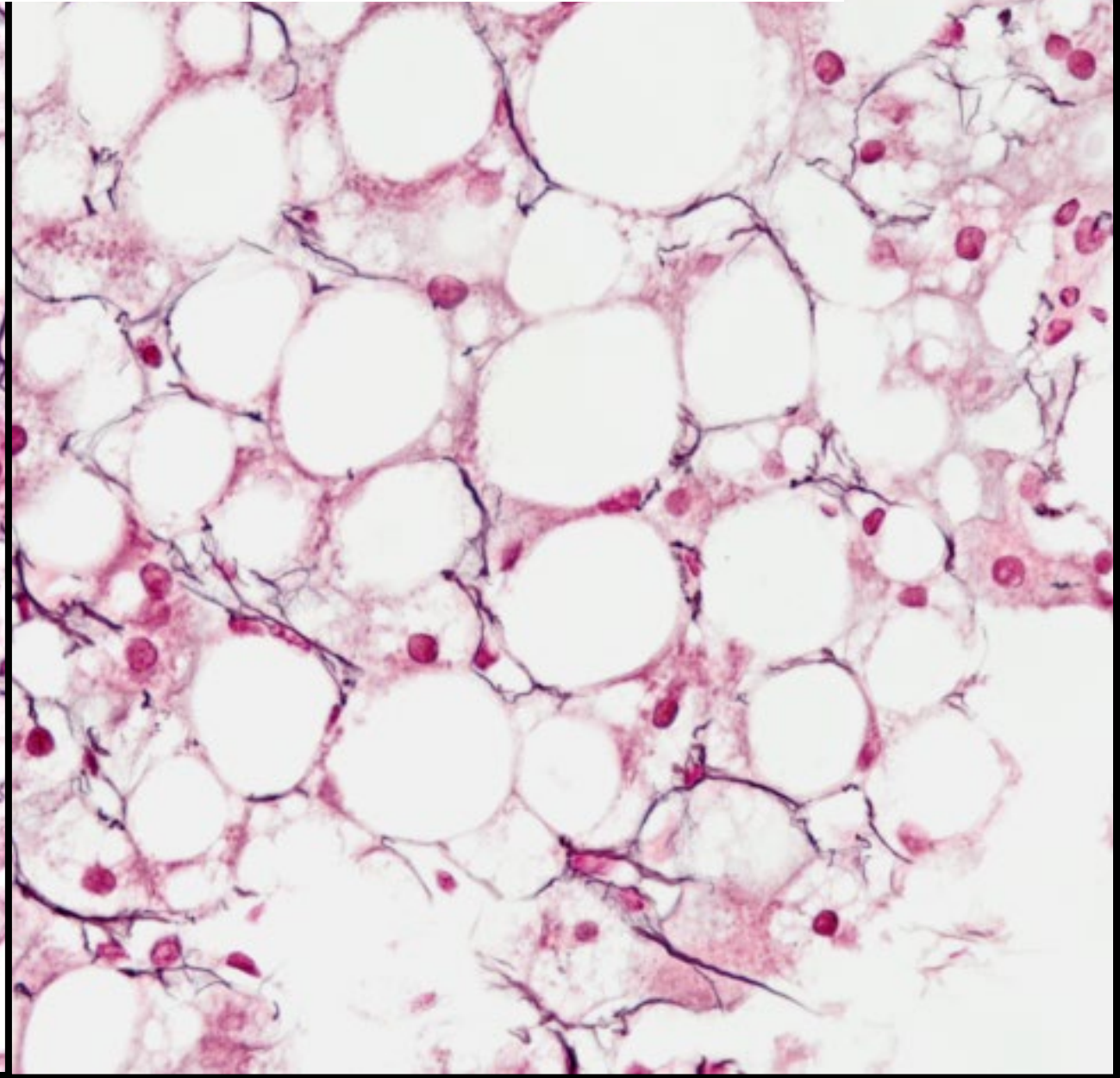
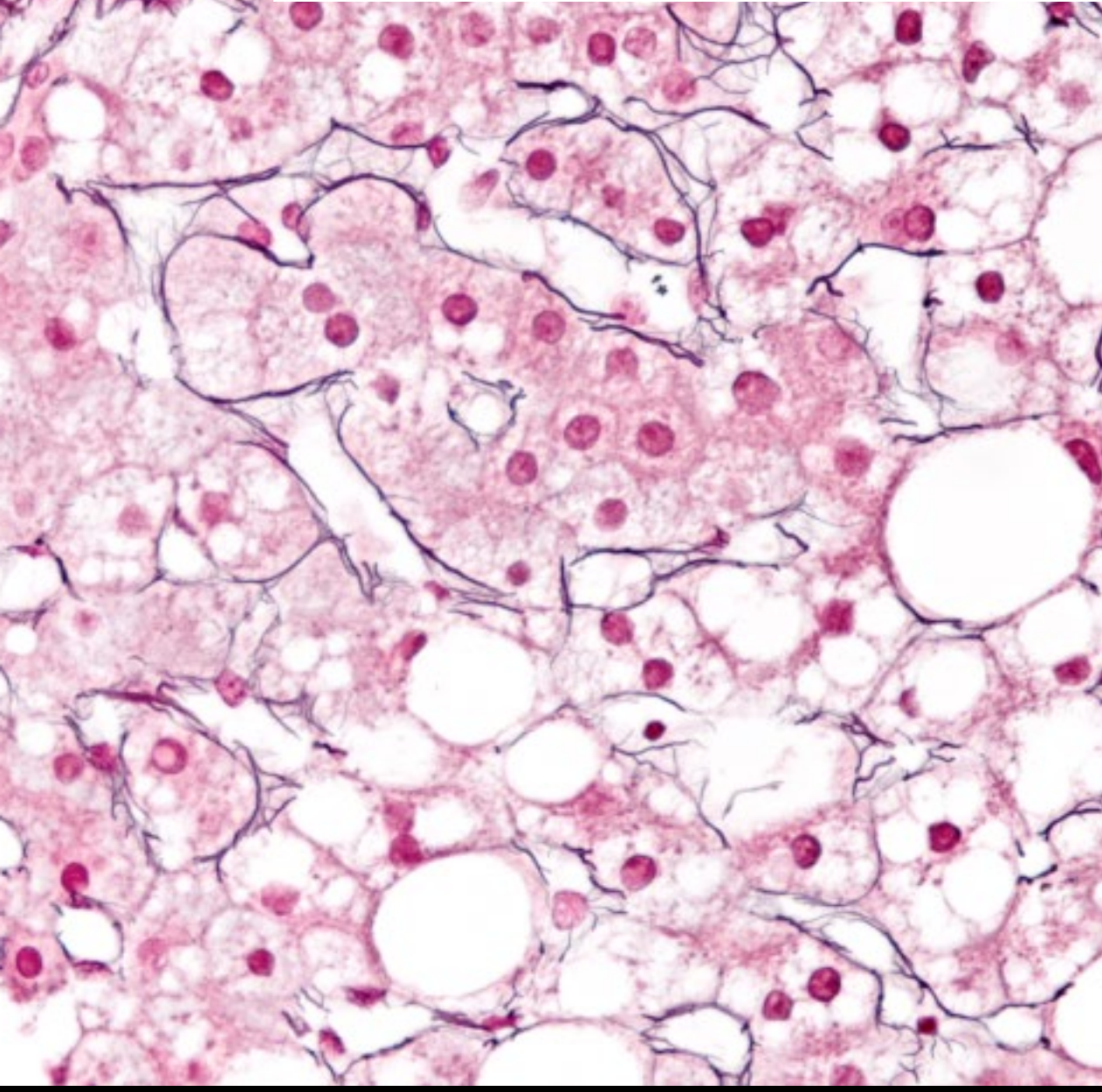


**Preserved reticulin
normal liver**



**Loss of reticulin
HCC**

Reticulin loss in Benign Fatty Liver





Some high grade dysplastic positive

A significant proportion of well differentiated HCCs
are negative

Lipofuscin may stain positive

Glypican 3

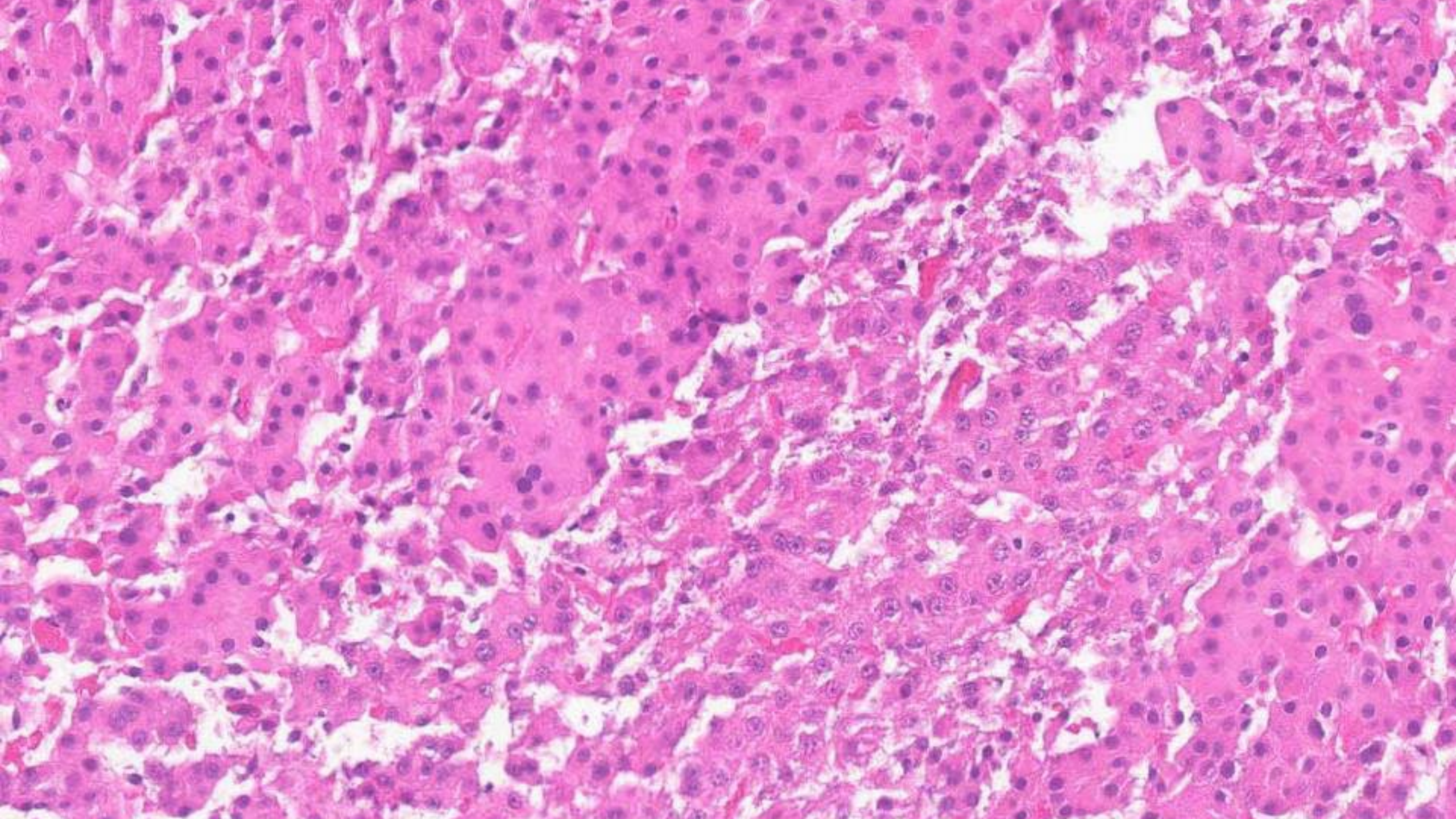
Hepatocellular carcinoma

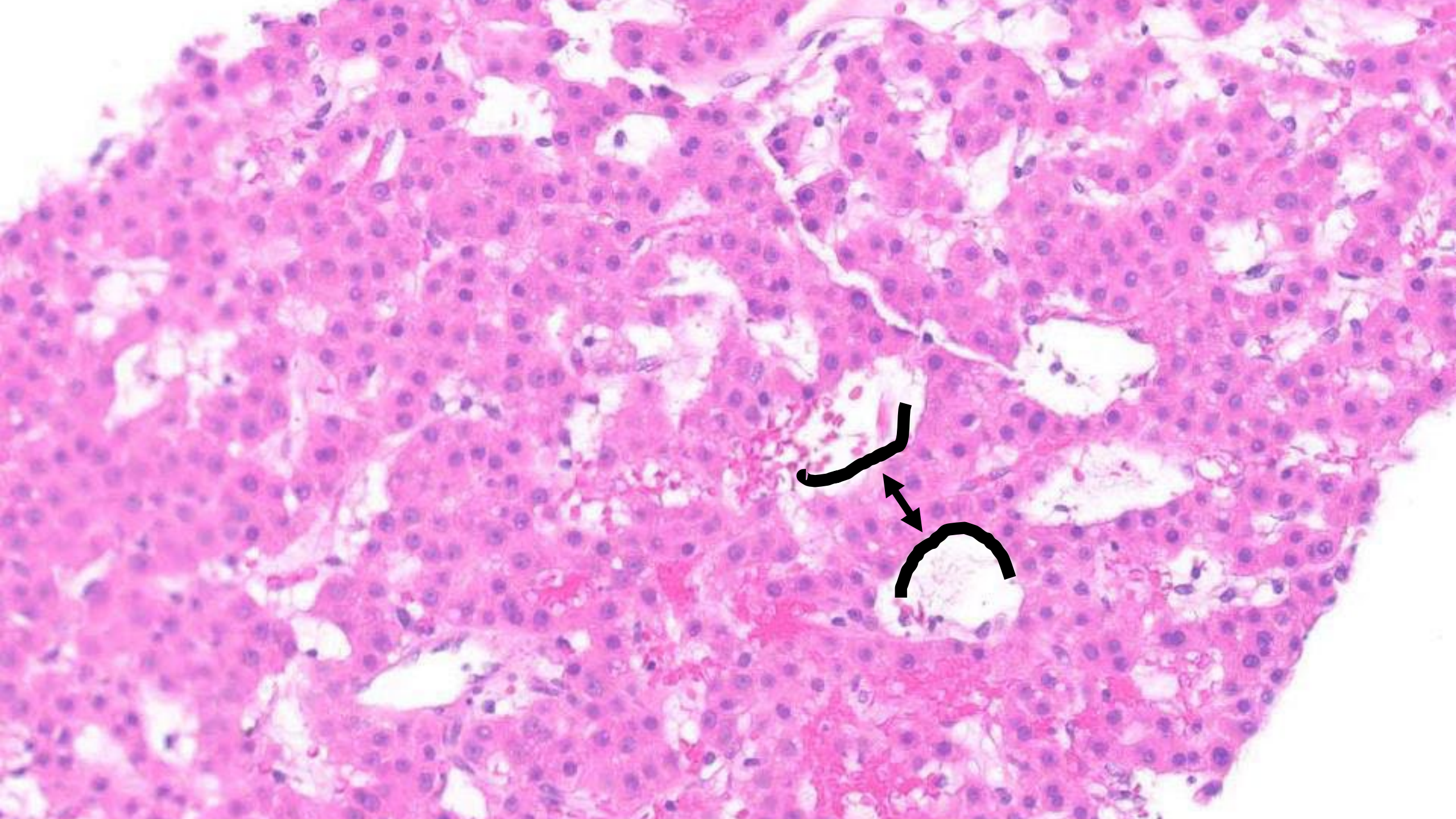
84/M

14 cm liver mass



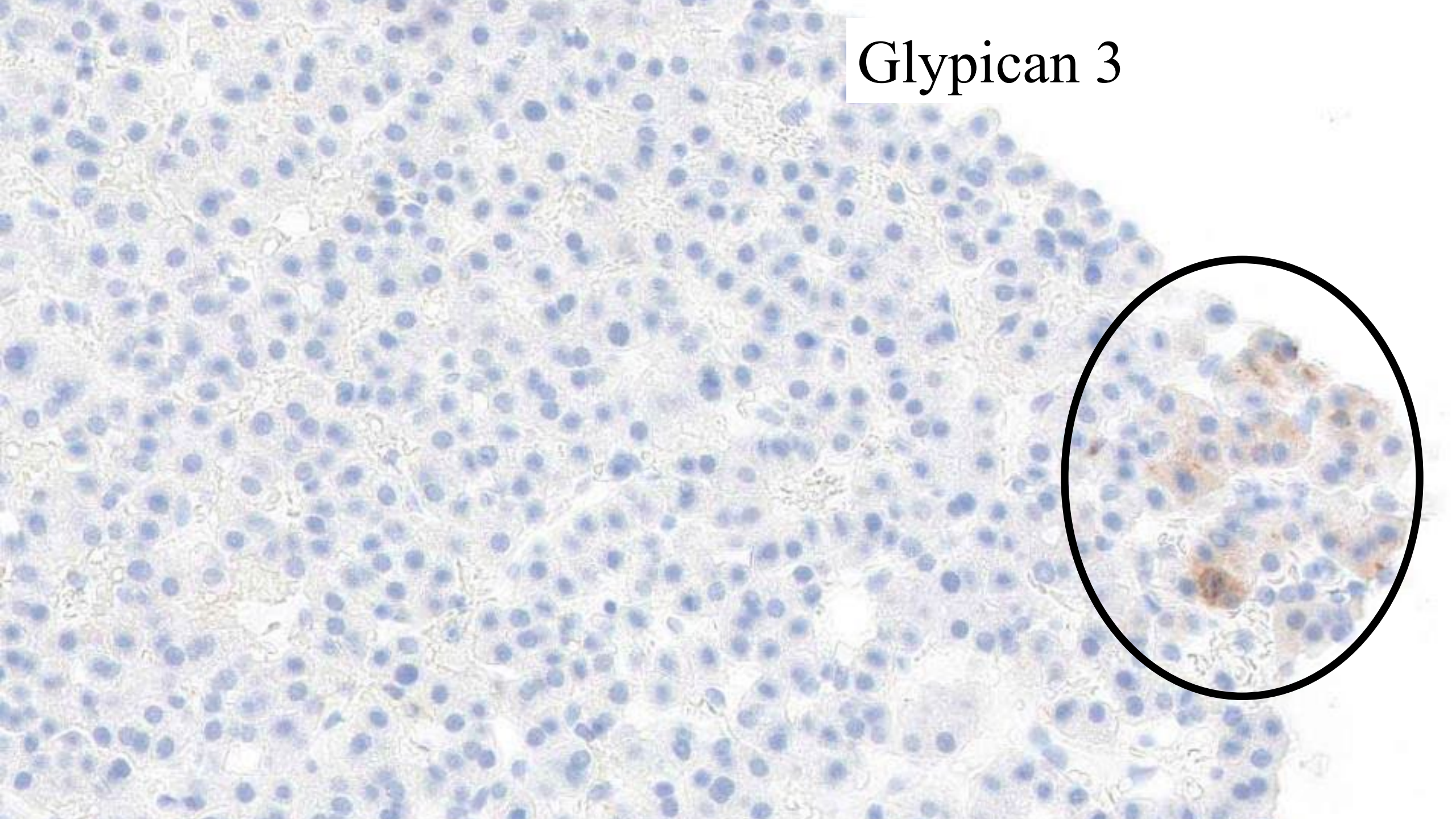






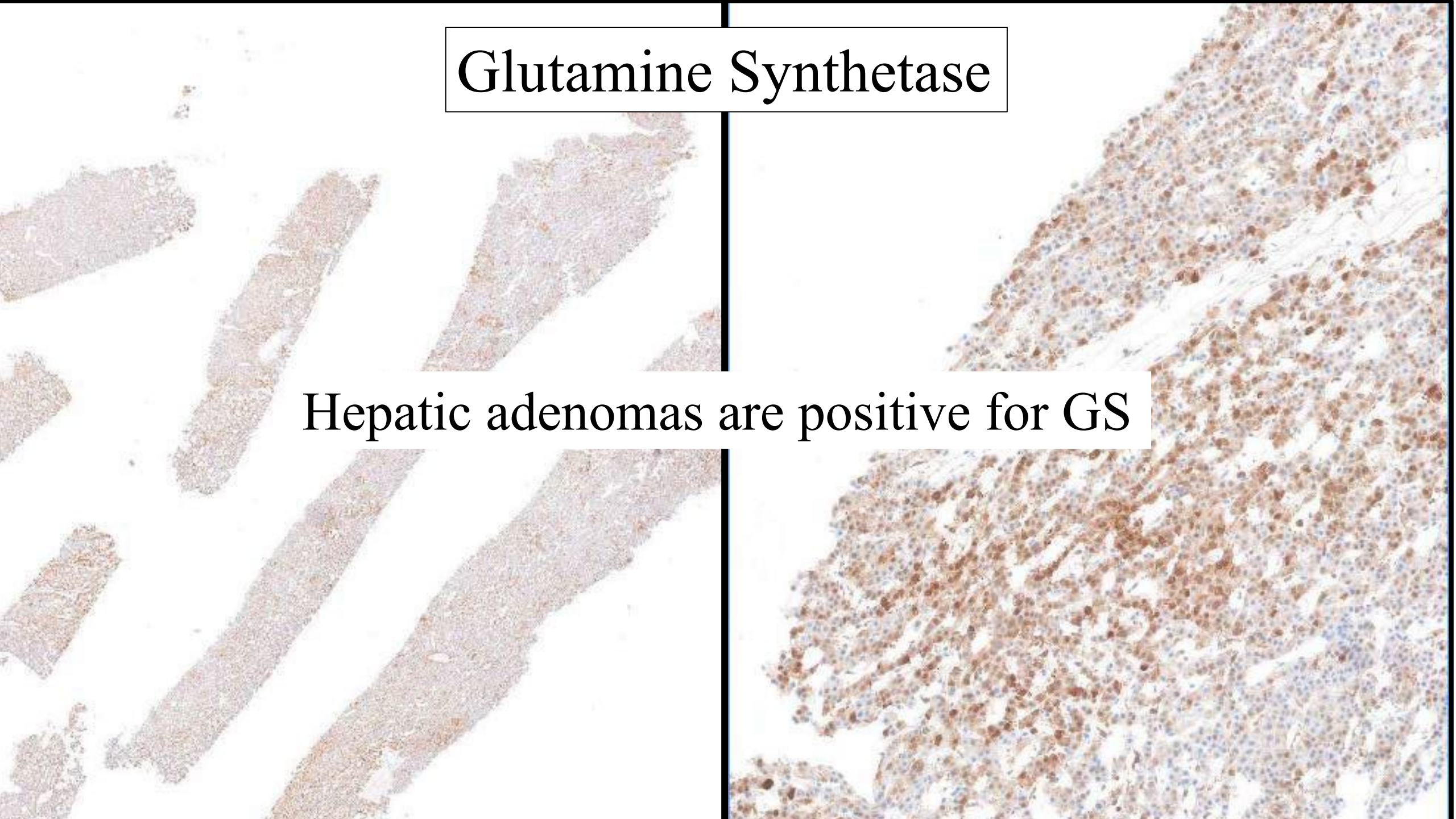


Glypican 3

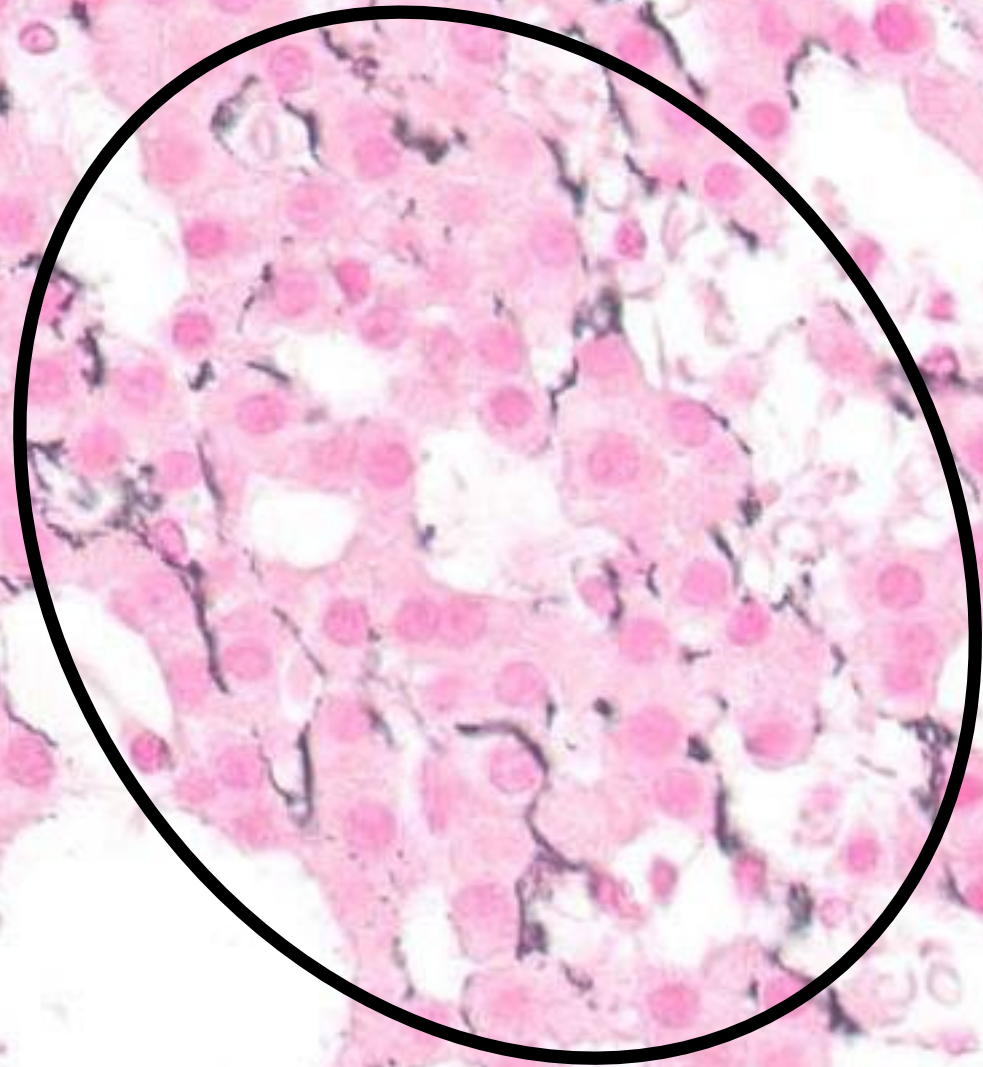


Glutamine Synthetase

Hepatic adenomas are positive for GS



Reticulin



Hepatocellular Carcinoma

- Thick hepatic plates (subtle)
- Loss of reticulin (helpful)
- Glutamine synthetase + (helpful – somewhat)

Age



Uncomfortable calling HCC?

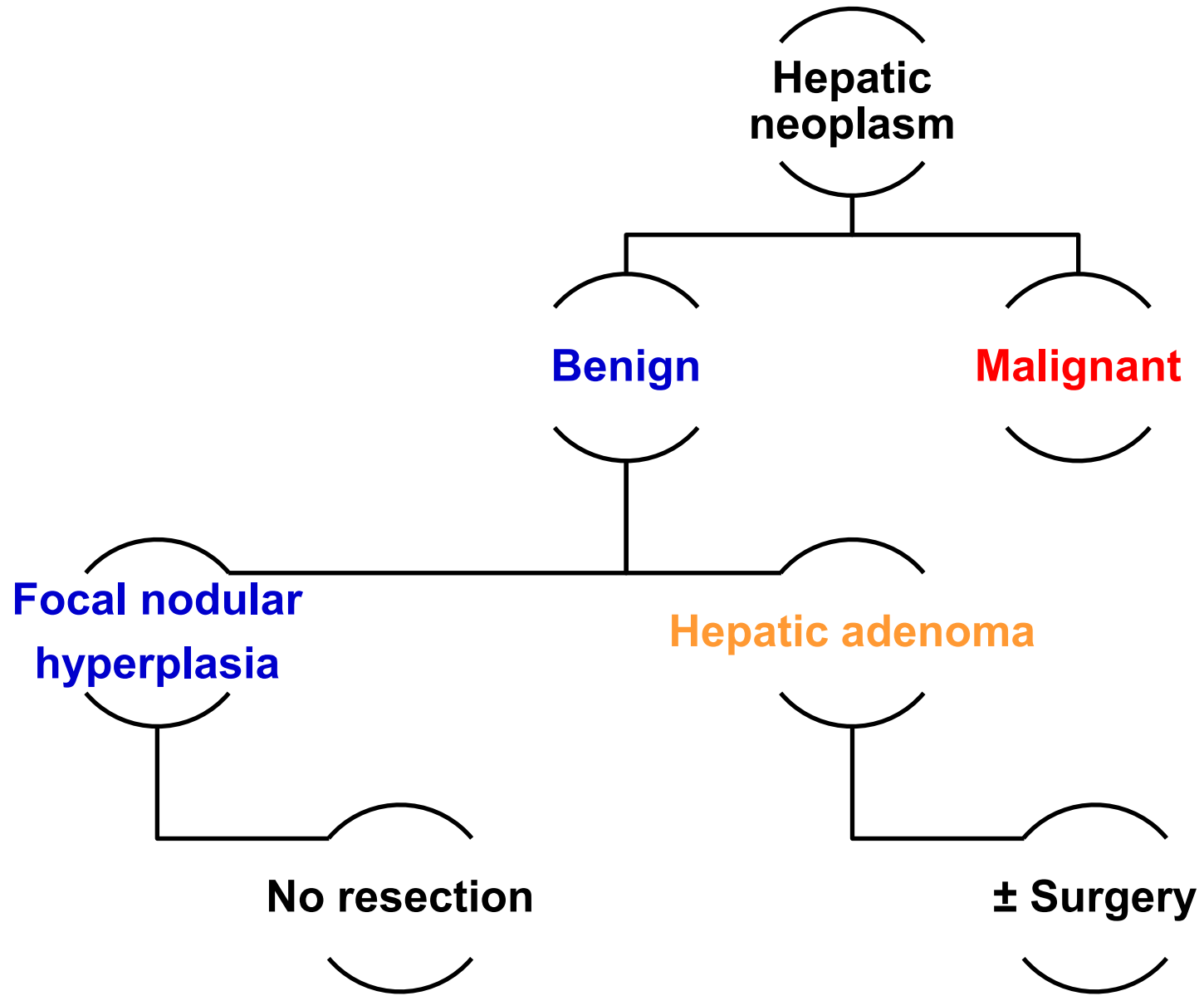
Well differentiated hepatocellular neoplasm.
See note.



Problem 3

- Cells look like hepatocytes
- Lesional tissue and not normal liver
- Does not look malignant

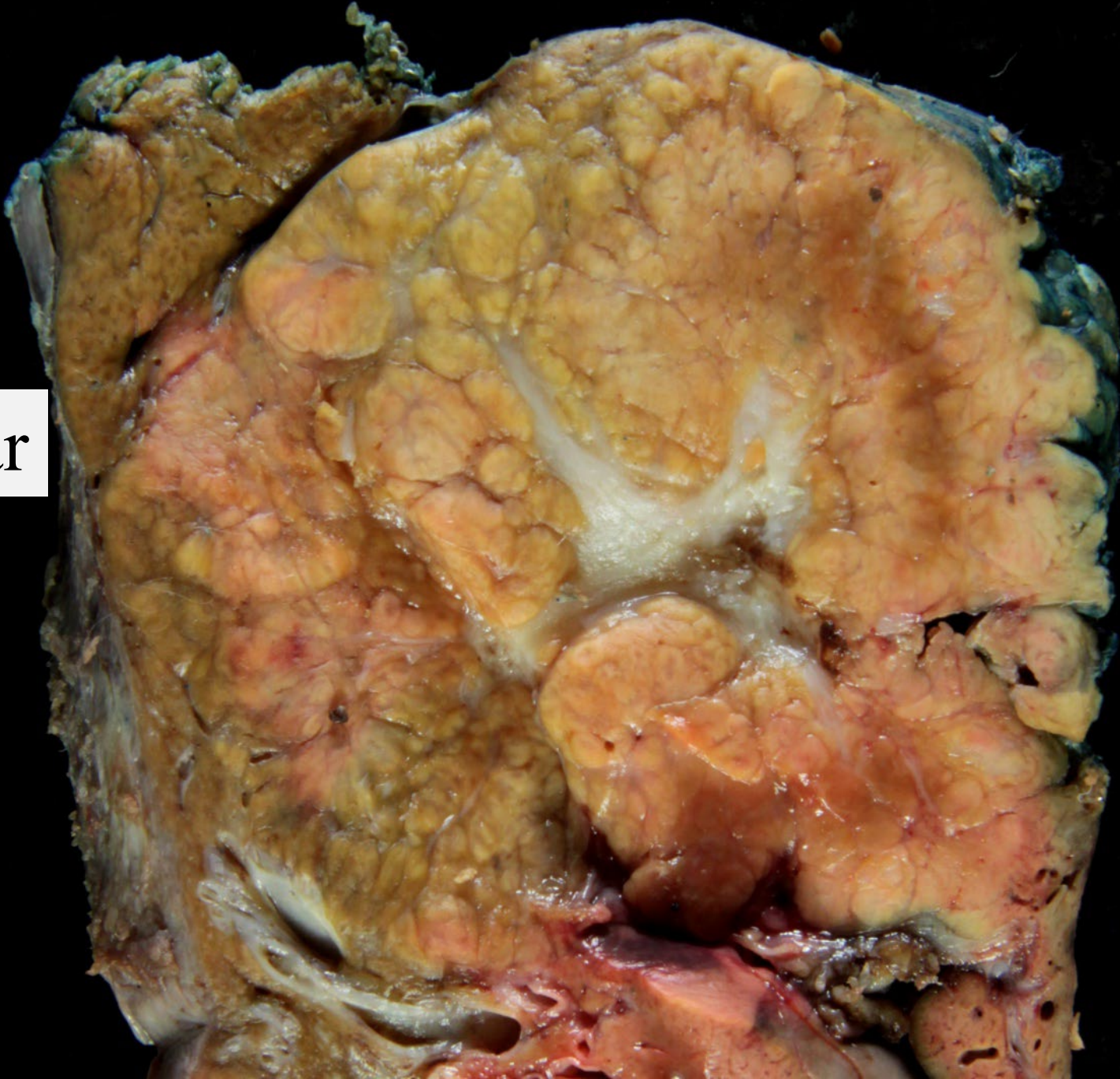




Focal Nodular Hyperplasia

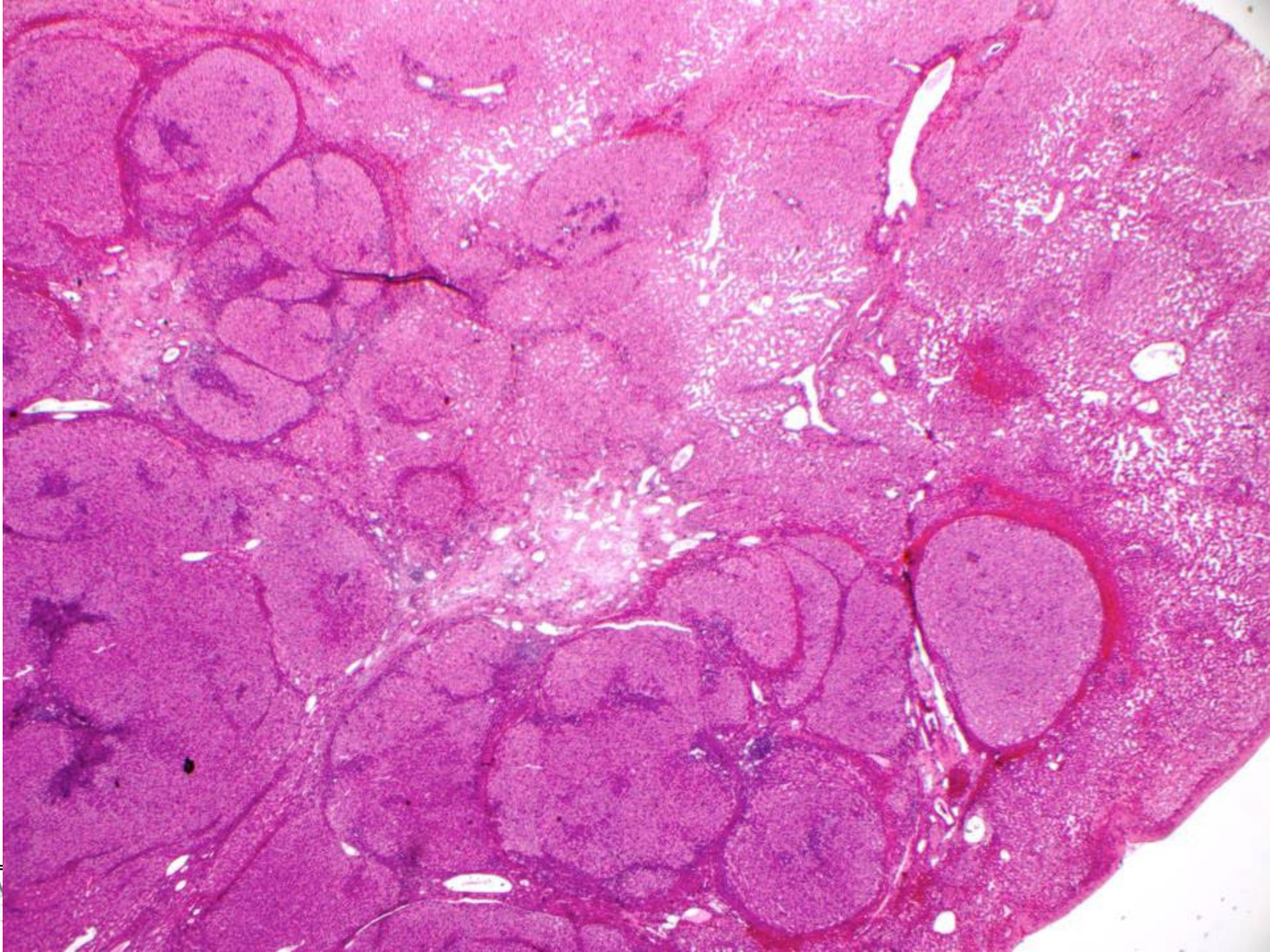


Focal Nodular Hyperplasia



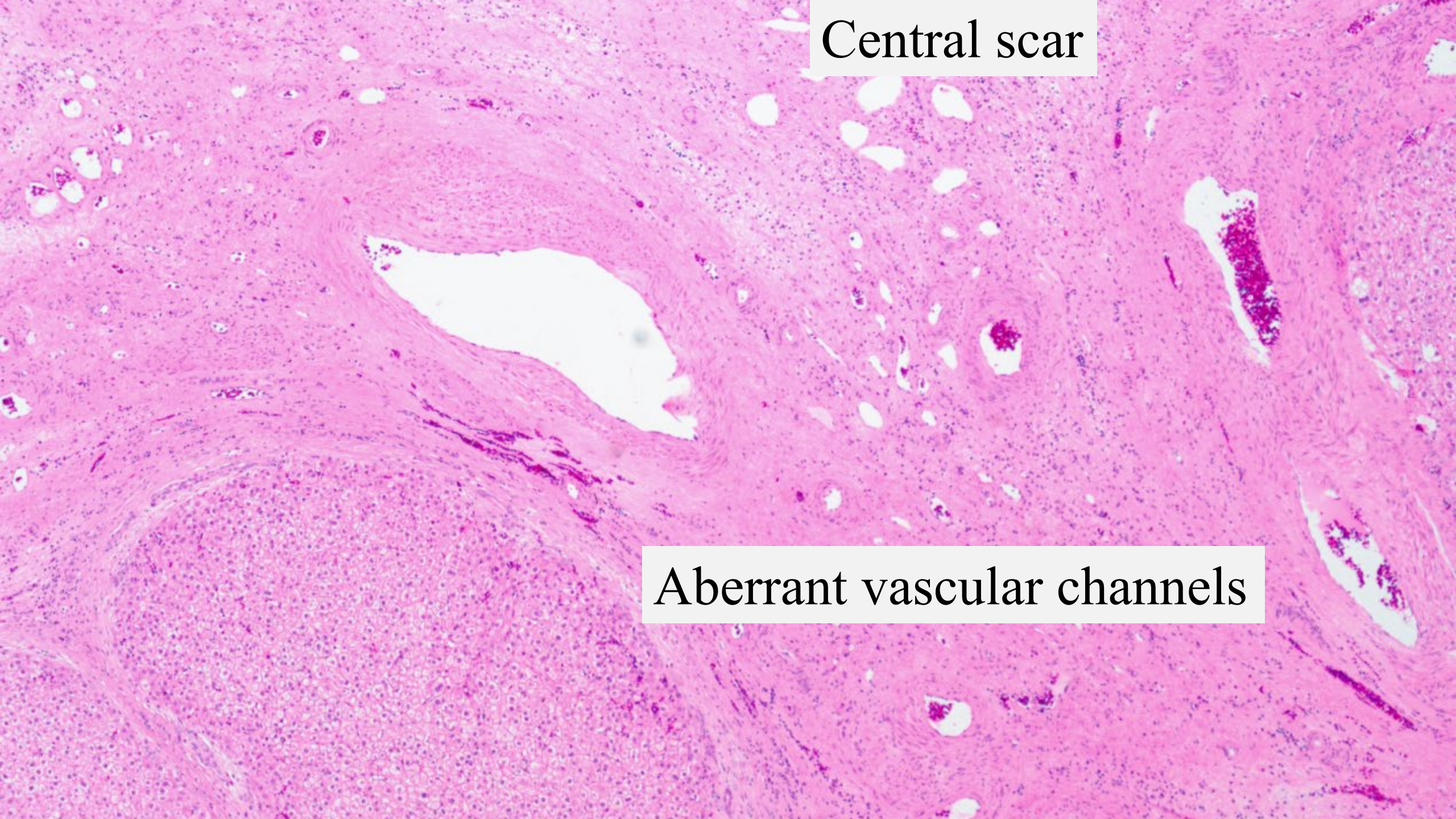
Central scar

Central scar



Central scar

Aberrant vascular channels



Bile ductular proliferation

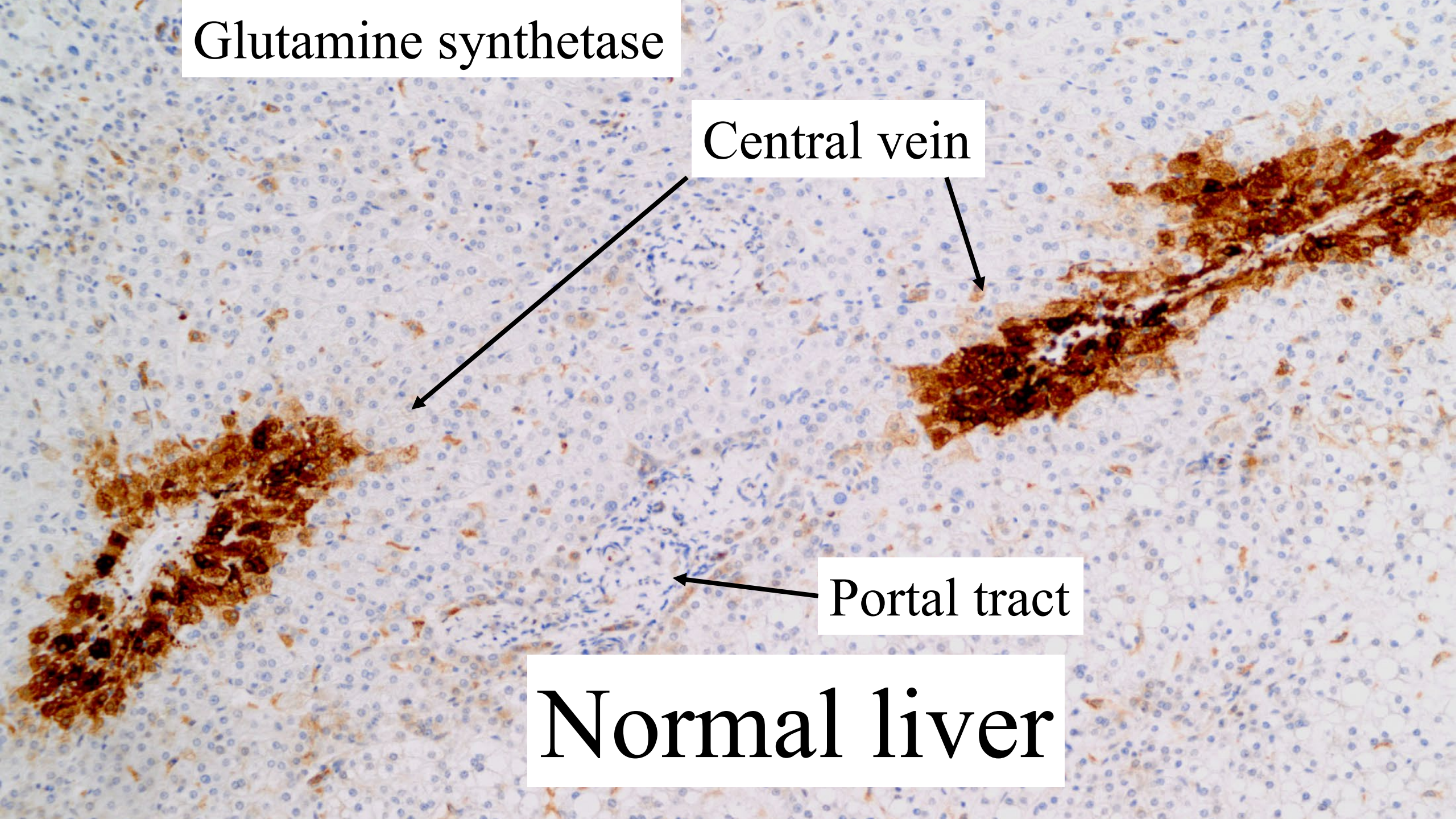


Glutamine synthetase

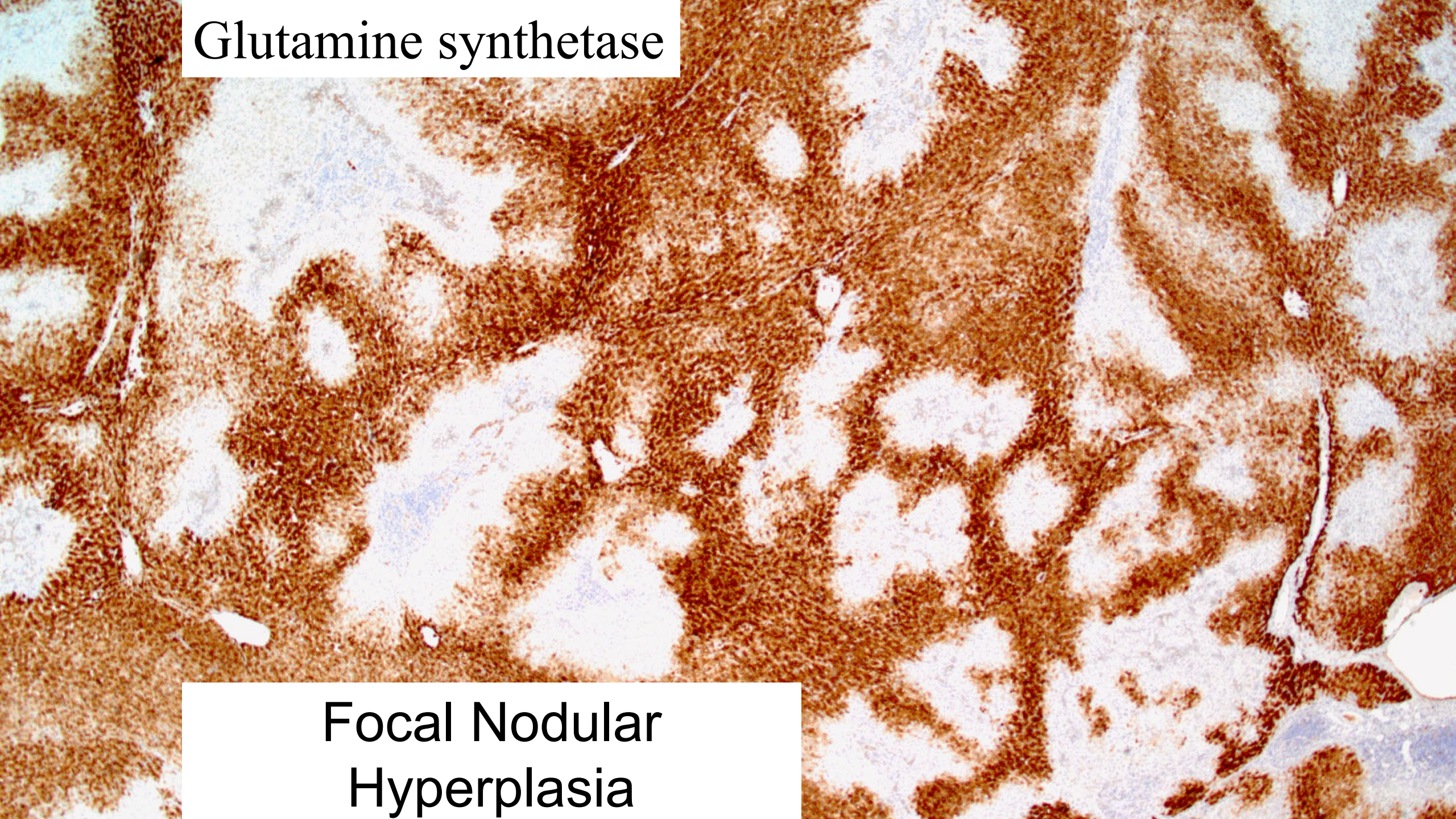
Central vein

Portal tract

Normal liver



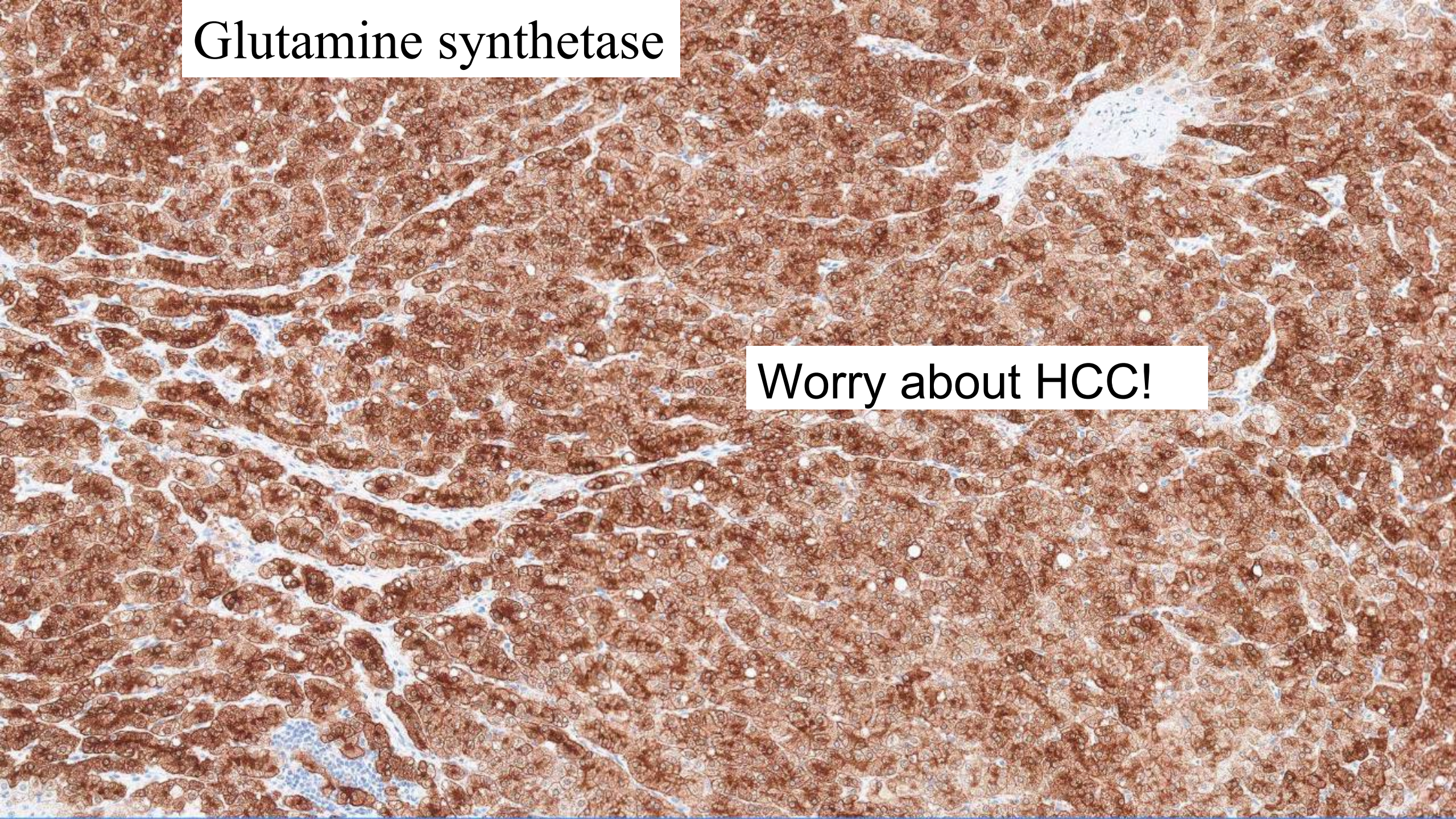
Glutamine synthetase

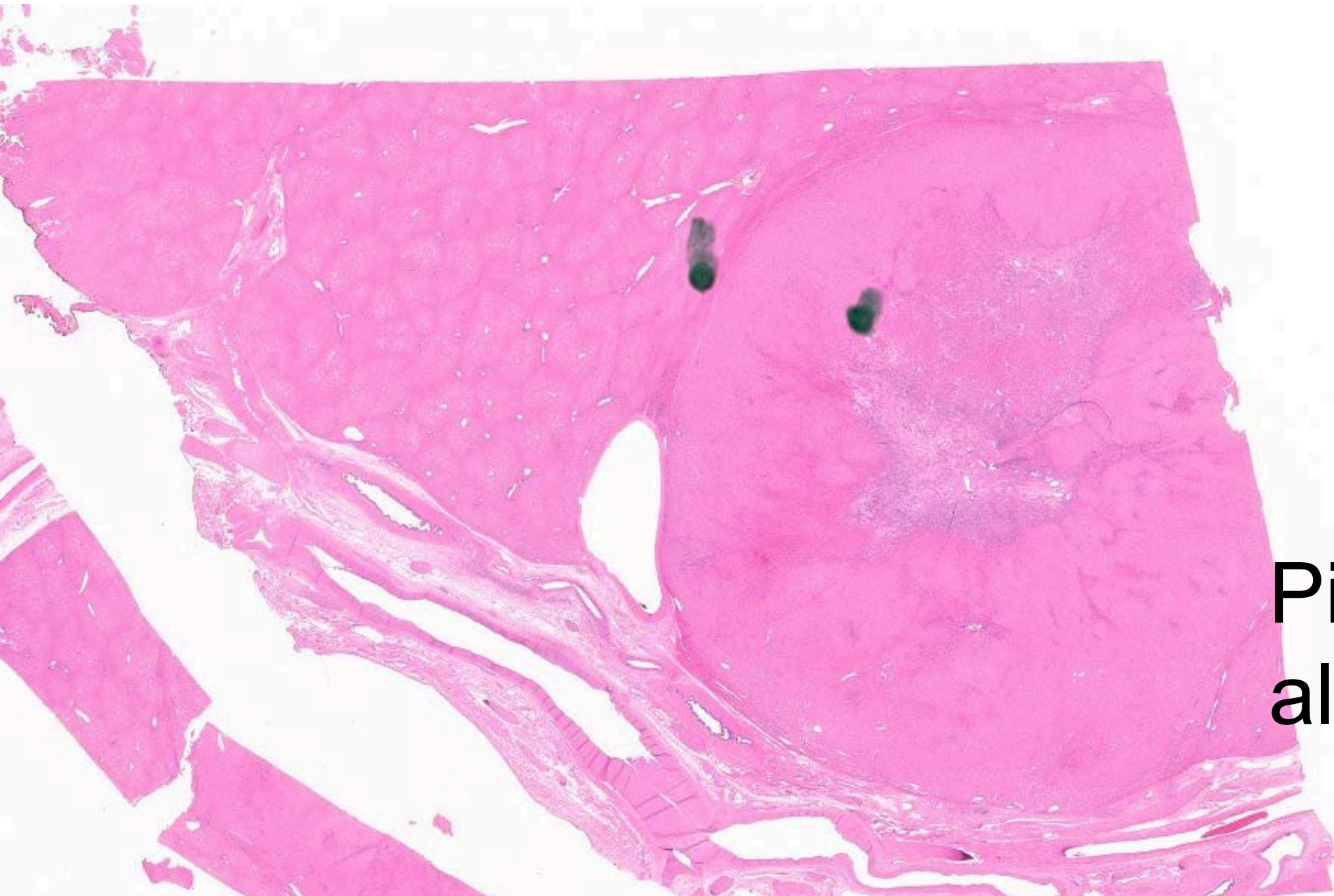


Focal Nodular
Hyperplasia

Glutamine synthetase

Worry about HCC!

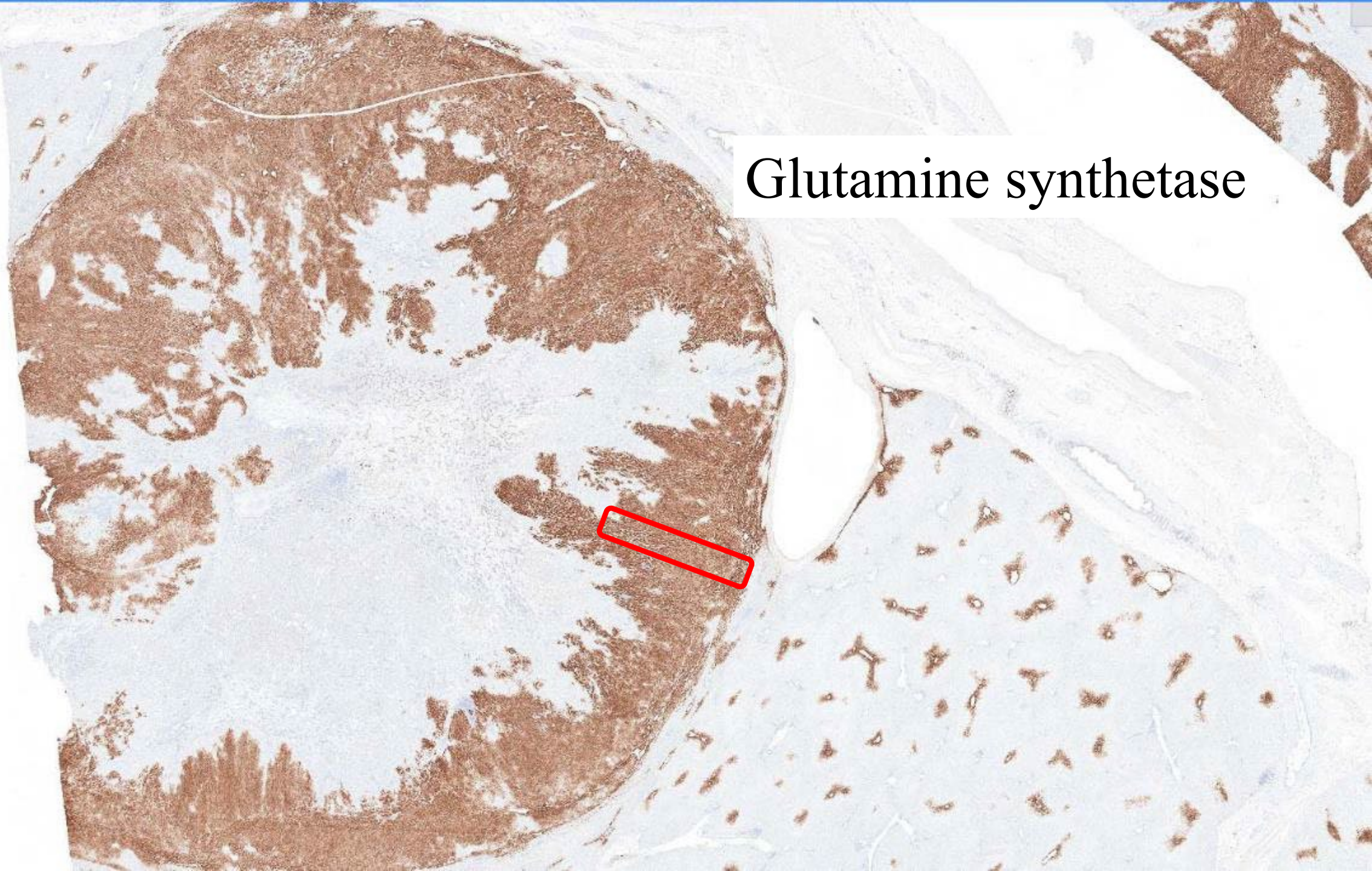




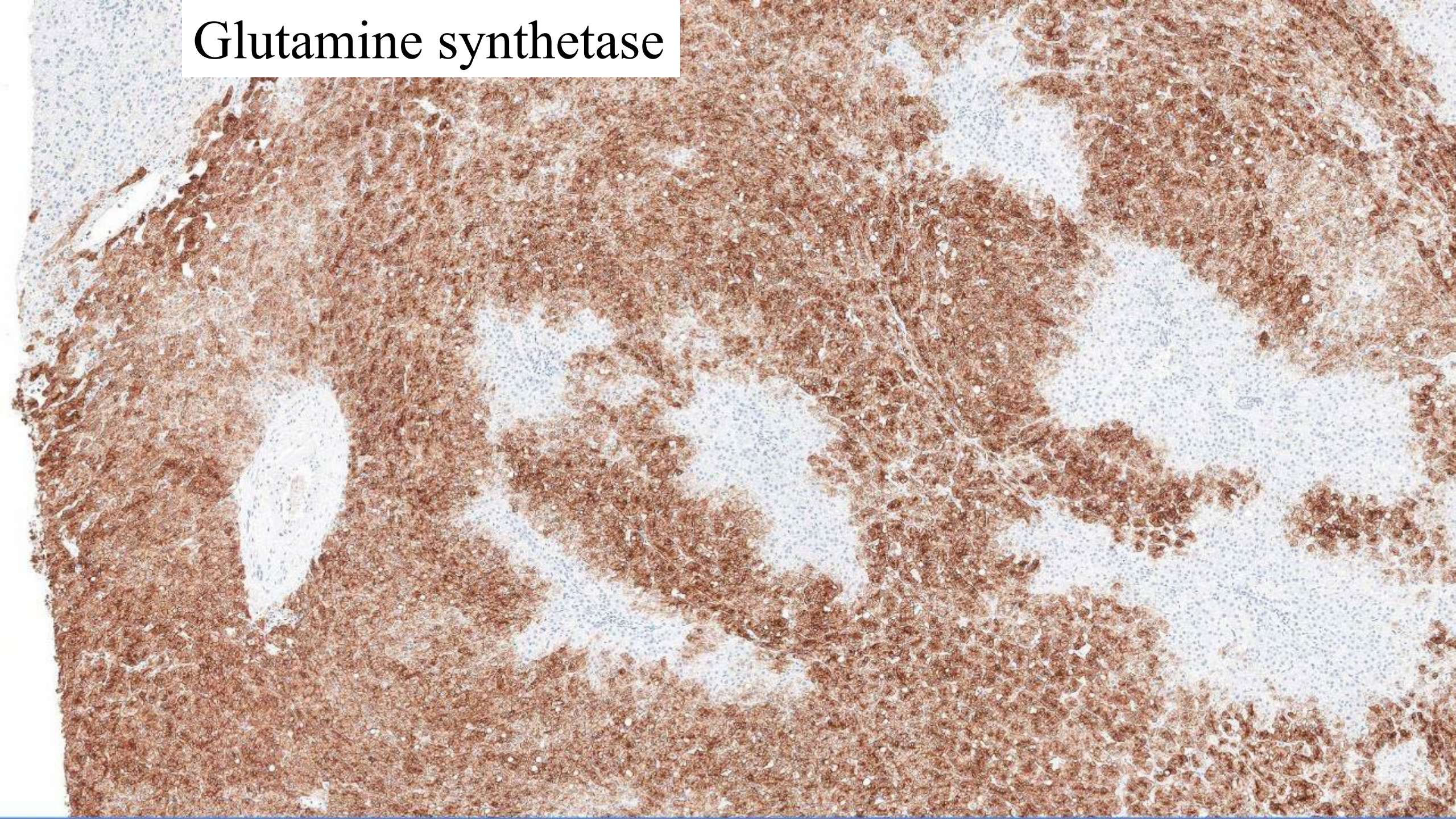
Central scar

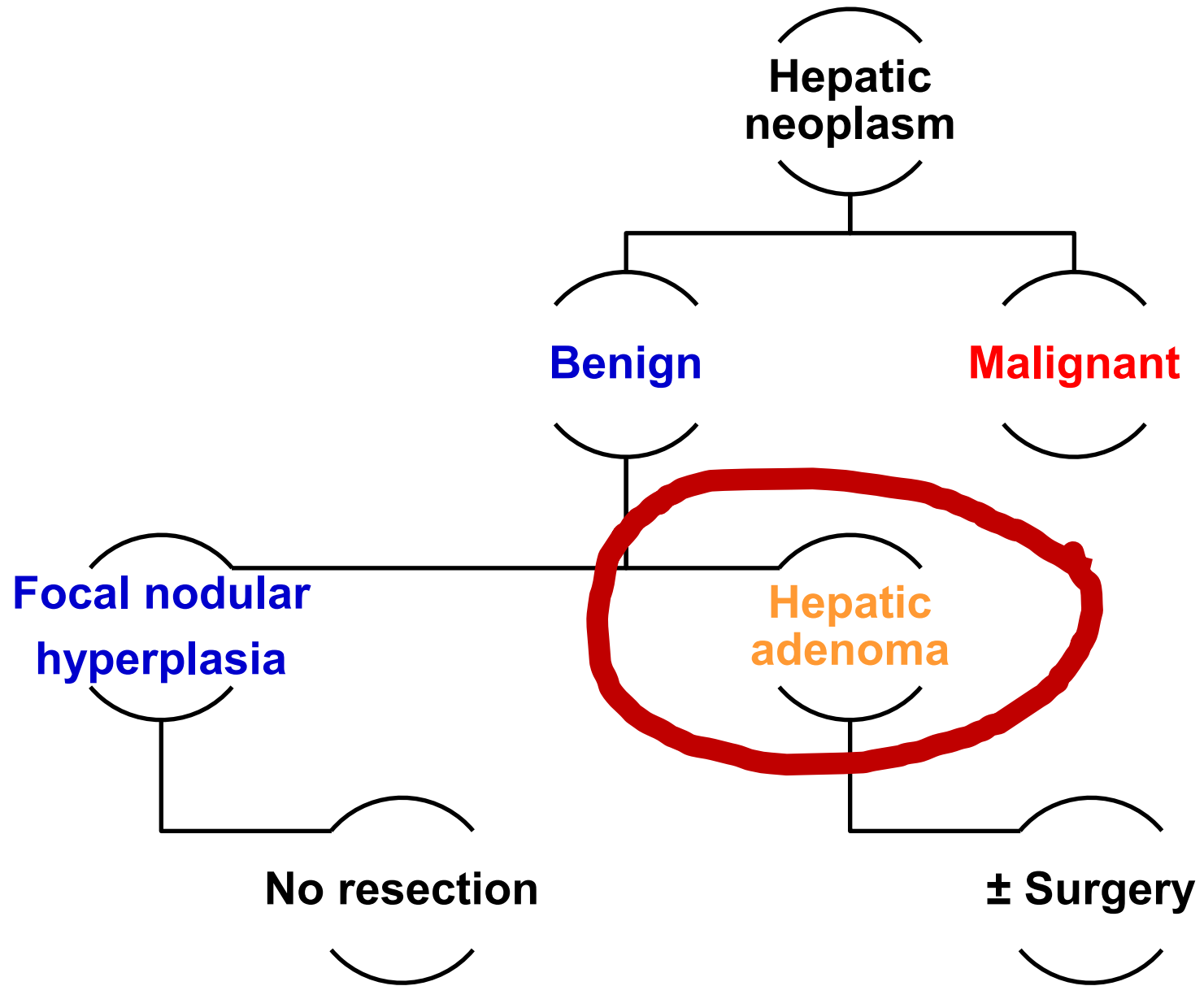
**Pitfall
alert !**

Glutamine synthetase



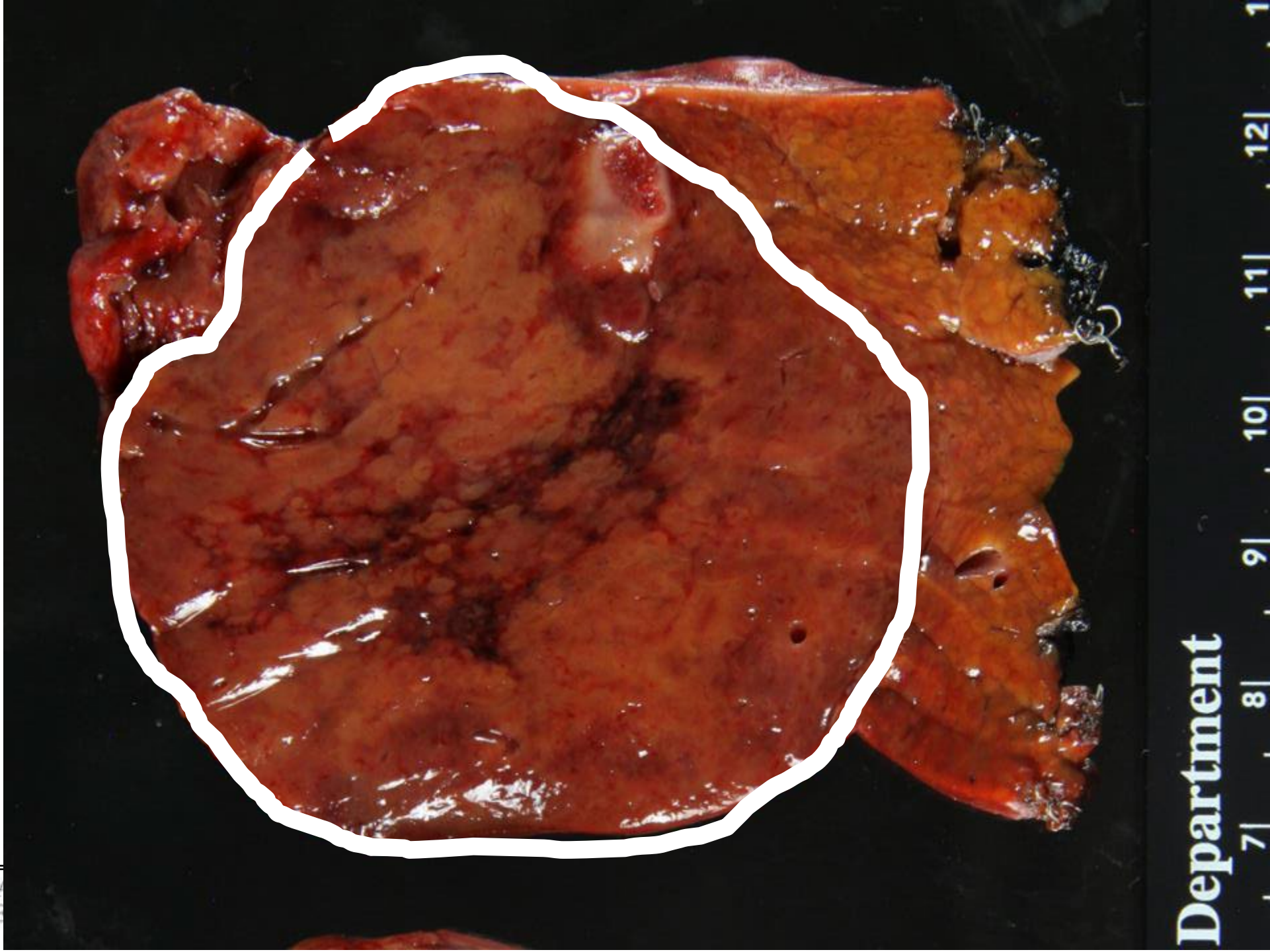
Glutamine synthetase







MA
GE



Department

7|

8|

9|

10|

11|

12|

1

SCHOOL

Hepatic adenoma



Definition:

Mass-forming liver lesion composed of a “pure” population of hepatocytes

Question 4: Subclassifying hepatic adenoma

Does it matter? And how does one do it?

Management of Hepatic Adenoma

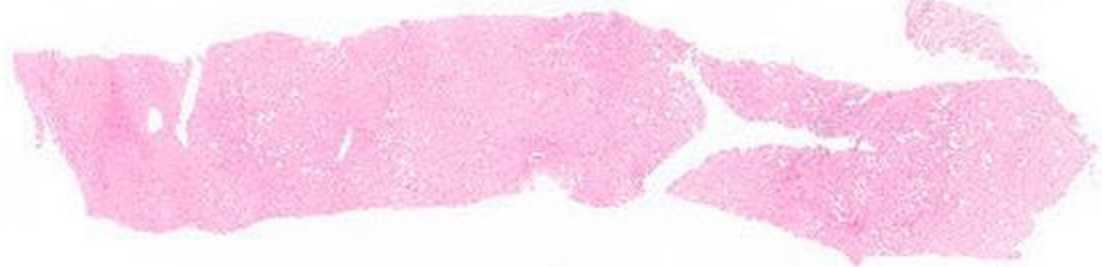
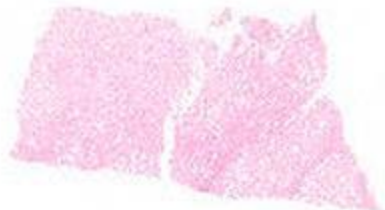
➤ Beta catenin
+ adenoma

More likely
transform
to HCC

Less likely
to
transform
to HCC

HNF1a
inactivated
adenoma
aka “fatty adenoma”

Inflammatory adenoma

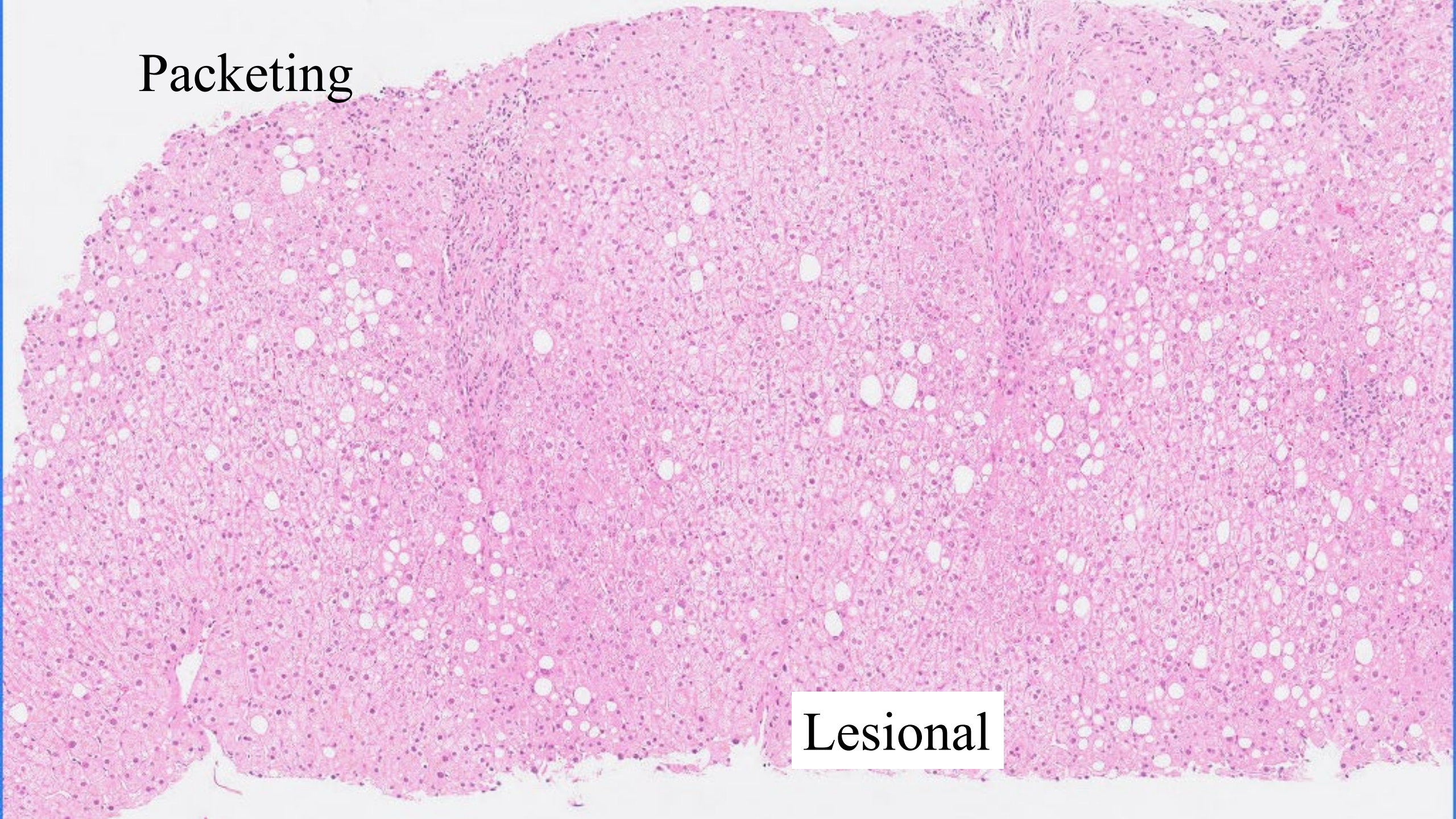


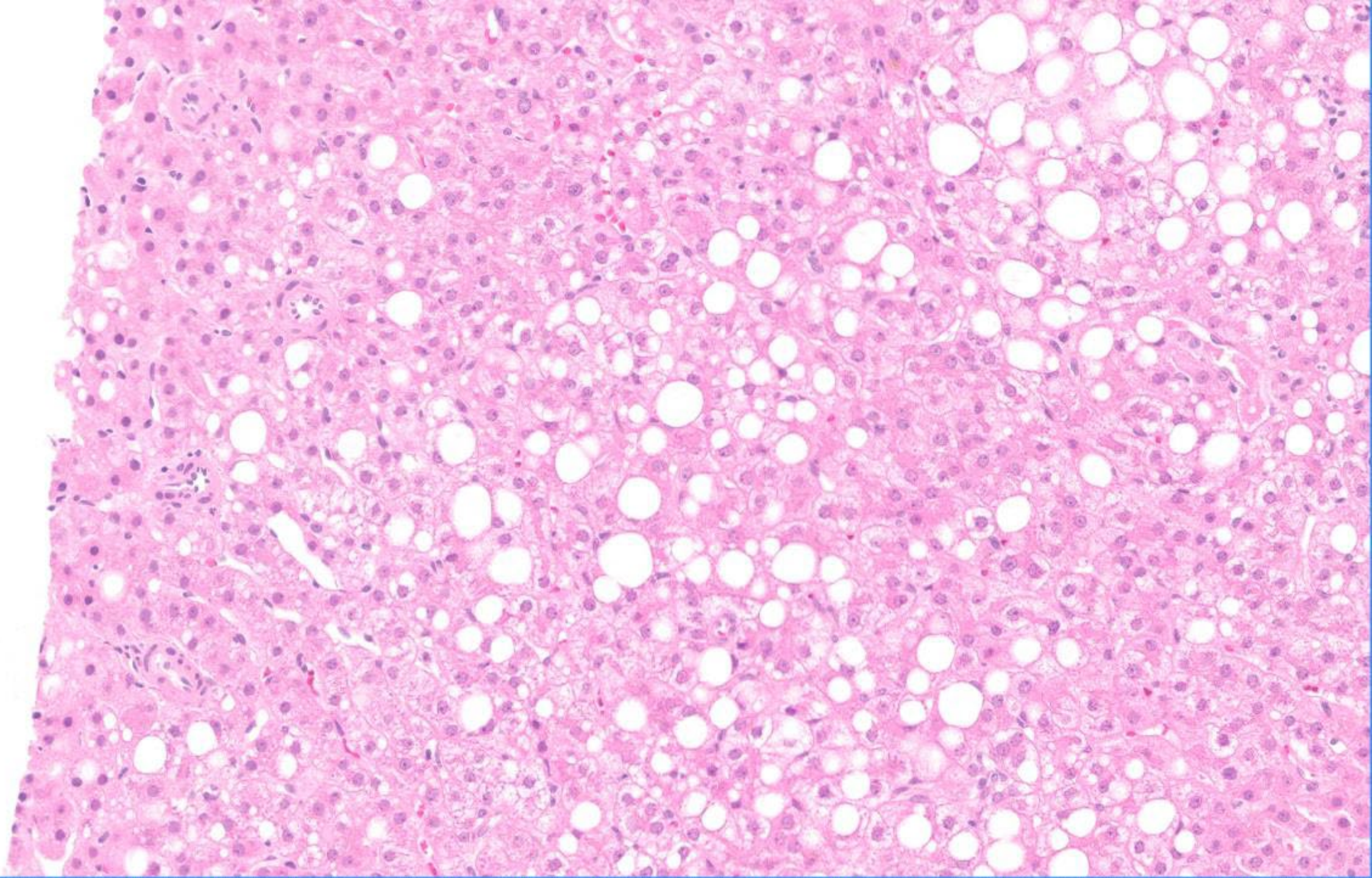
Glutamine synthetase



Packeting

Lesional



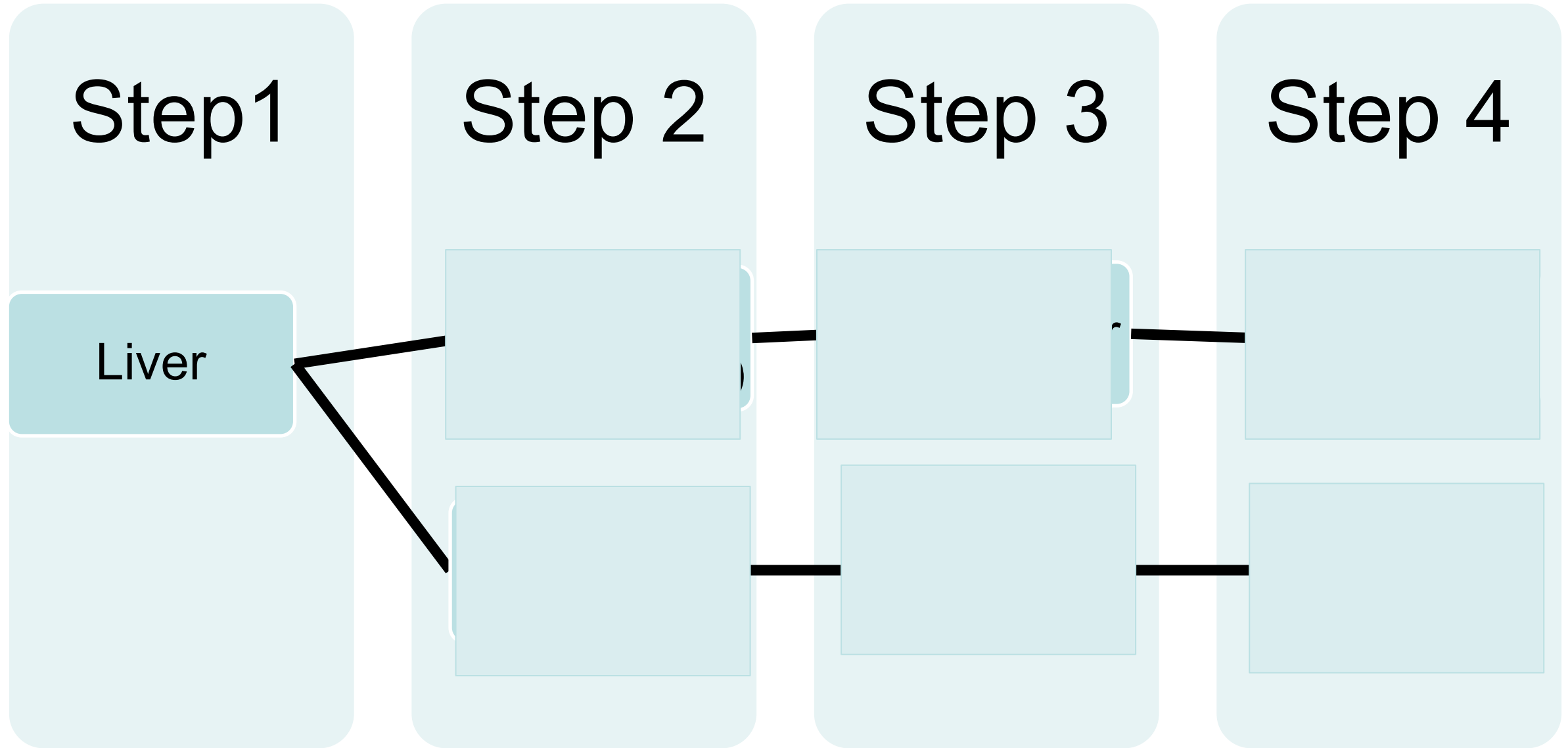


L-FABP1

HNF1a inactivated adenoma
aka “fatty adenoma”



HNF1a inactivated adenoma aka “fatty adenoma”



Management of Hepatic Adenoma

➤ Beta catenin
+ adenoma

More likely
transform
to HCC

Less likely
to
transform
to HCC

HNF1a
inactivated
adenoma
aka “fatty adenoma”

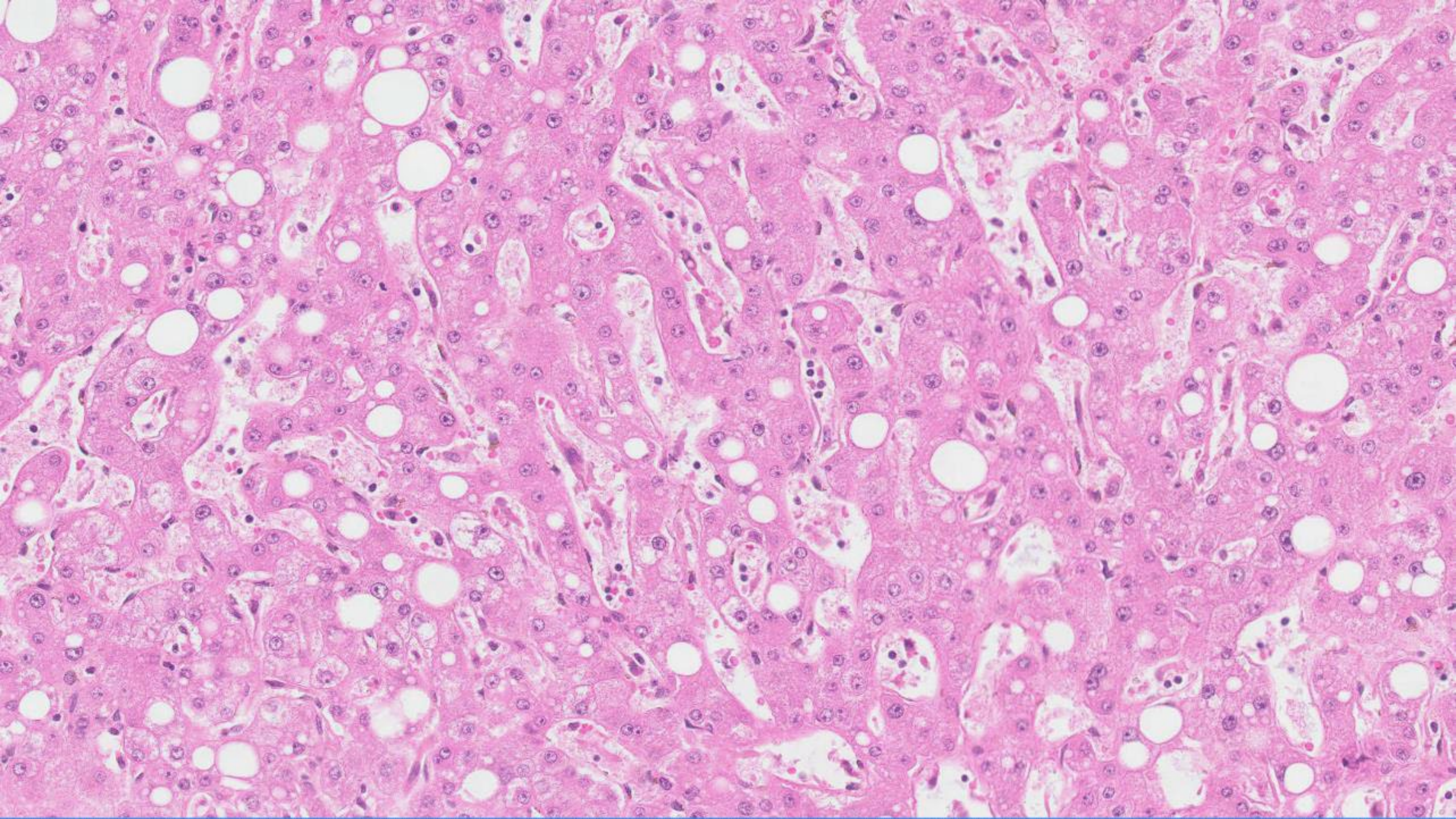
Inflammatory adenoma

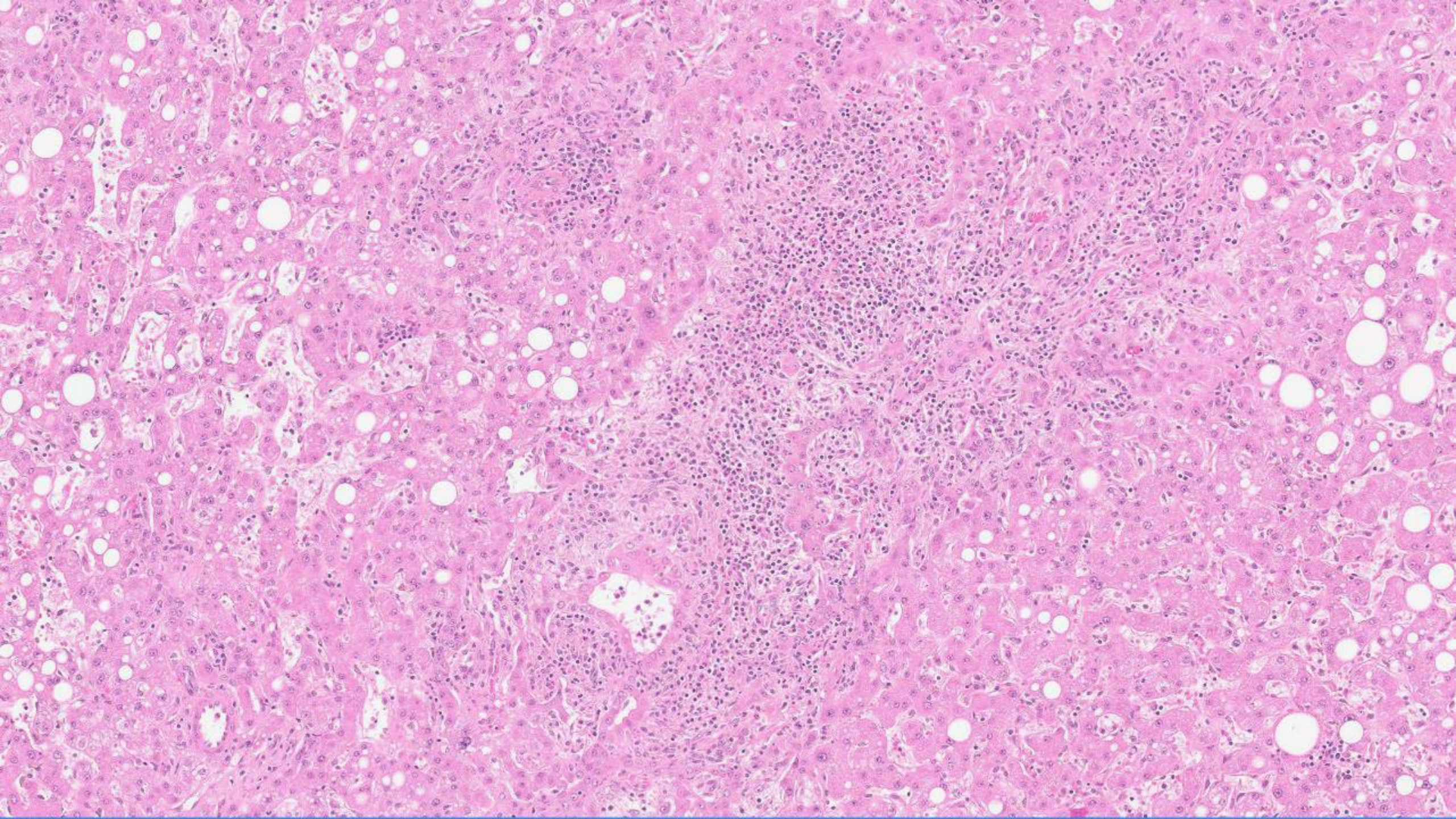




L

N





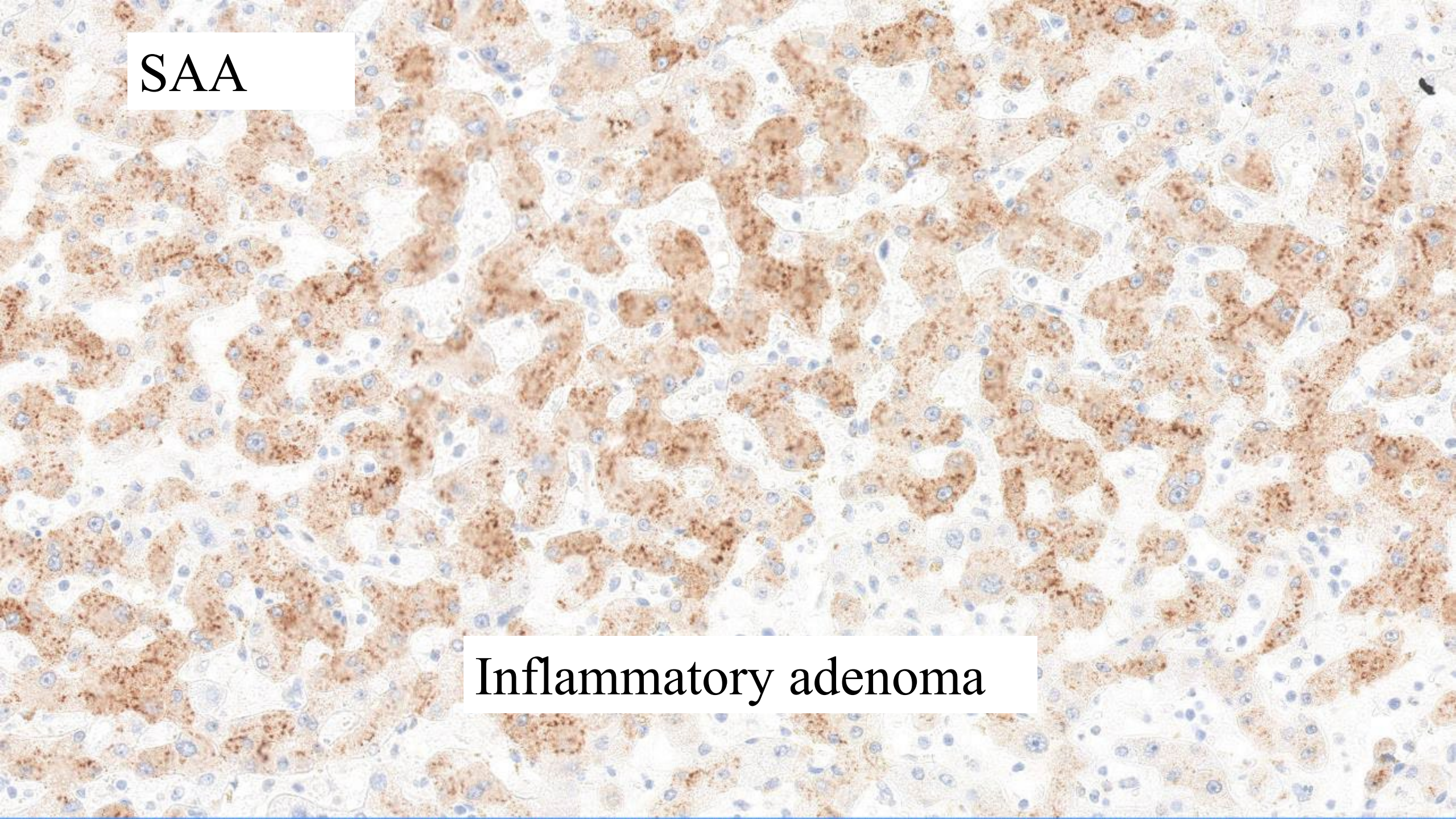
A histological slide of liver tissue stained with hematoxylin and eosin (H&E). The image shows a dense population of hepatocytes with prominent nuclei and some cytoplasmic vacuolization. There is a significant inflammatory infiltrate, particularly in the central areas, consisting of numerous small, dark-staining cells. The overall architecture is somewhat disorganized, with loss of normal portal tracts. Two white text boxes are overlaid on the image: one in the upper left and one in the lower right.

Portal tract?

Inflammatory hepatic adenoma

SAA

Inflammatory adenoma



Management of Hepatic Adenoma

➤ Beta catenin
+ adenoma

More likely
transform
to HCC

Less likely
to
transform
to HCC

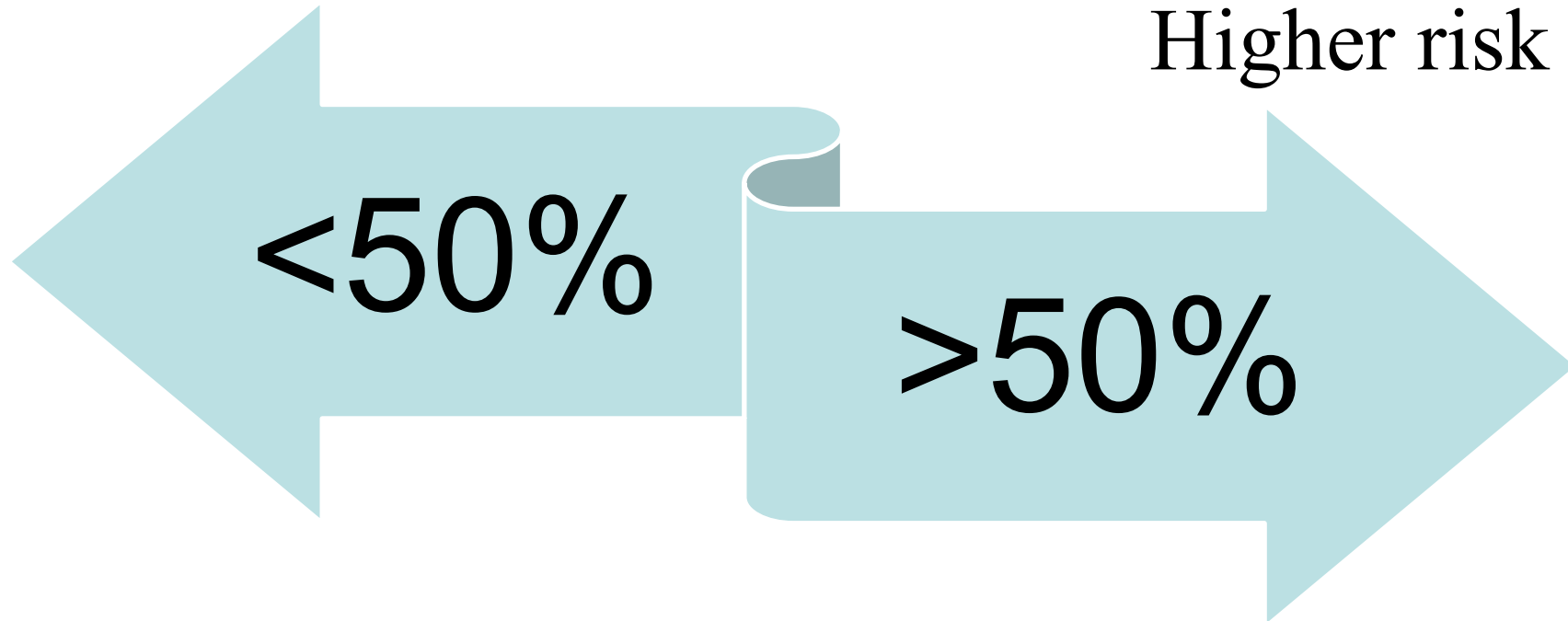
HNF1a
inactivated
adenoma
aka “fatty adenoma”

Inflammatory adenoma



Glutamine synthetase

Higher risk for HCC



Low risk for HCC

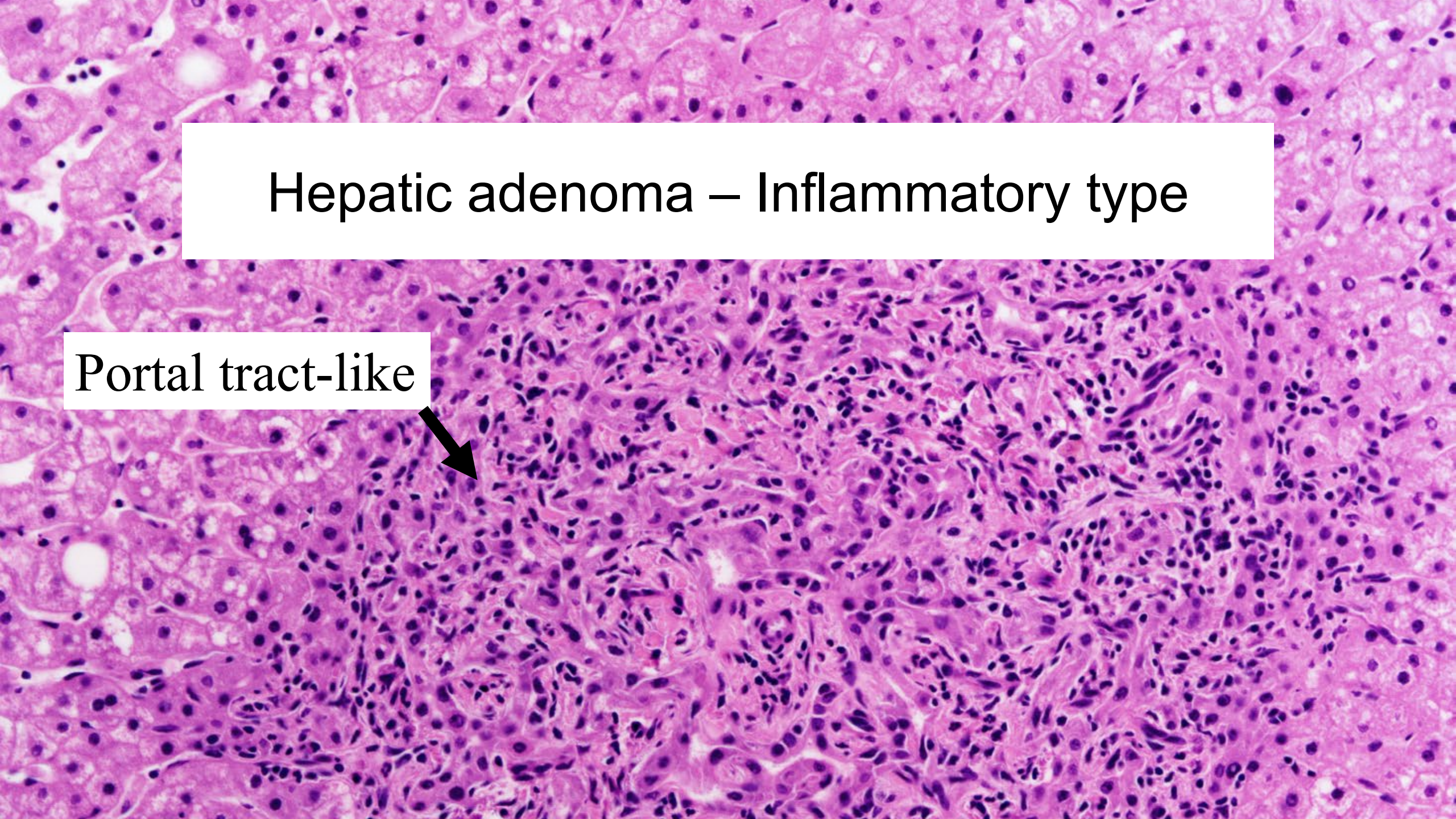


Hepatic adenoma – Inflammatory type

telangiectasia

A histological micrograph of hepatic adenoma, inflammatory type, stained with hematoxylin and eosin (H&E). The image shows a dense population of hepatocytes with a disorganized architecture. Two specific features are highlighted with white text boxes and black arrows: 'telangiectasia' points to a dilated, thin-walled blood vessel, and 'Portal tract-like' points to a structure resembling a portal tract, which is a cluster of bile ducts, blood vessels, and lymphatics. The overall appearance is that of a highly cellular, vascularized lesion.

Portal tract-like



Hepatic adenoma – Inflammatory type

This histological image shows a section of liver tissue stained with hematoxylin and eosin (H&E). The overall appearance is that of a hepatic adenoma of the inflammatory type. The tissue is characterized by a dense population of hepatocytes with a disorganized arrangement. A prominent feature is the presence of portal tract-like structures, which are indicated by a black arrow pointing from the text 'Portal tract-like' on the left. These structures contain a mixture of inflammatory cells, including lymphocytes and plasma cells, interspersed among the hepatocytes. The hepatocytes themselves show some degree of cellular atypia, with enlarged nuclei and prominent nucleoli. The background stroma is fibrous and contains scattered inflammatory cells.

Portal tract-like



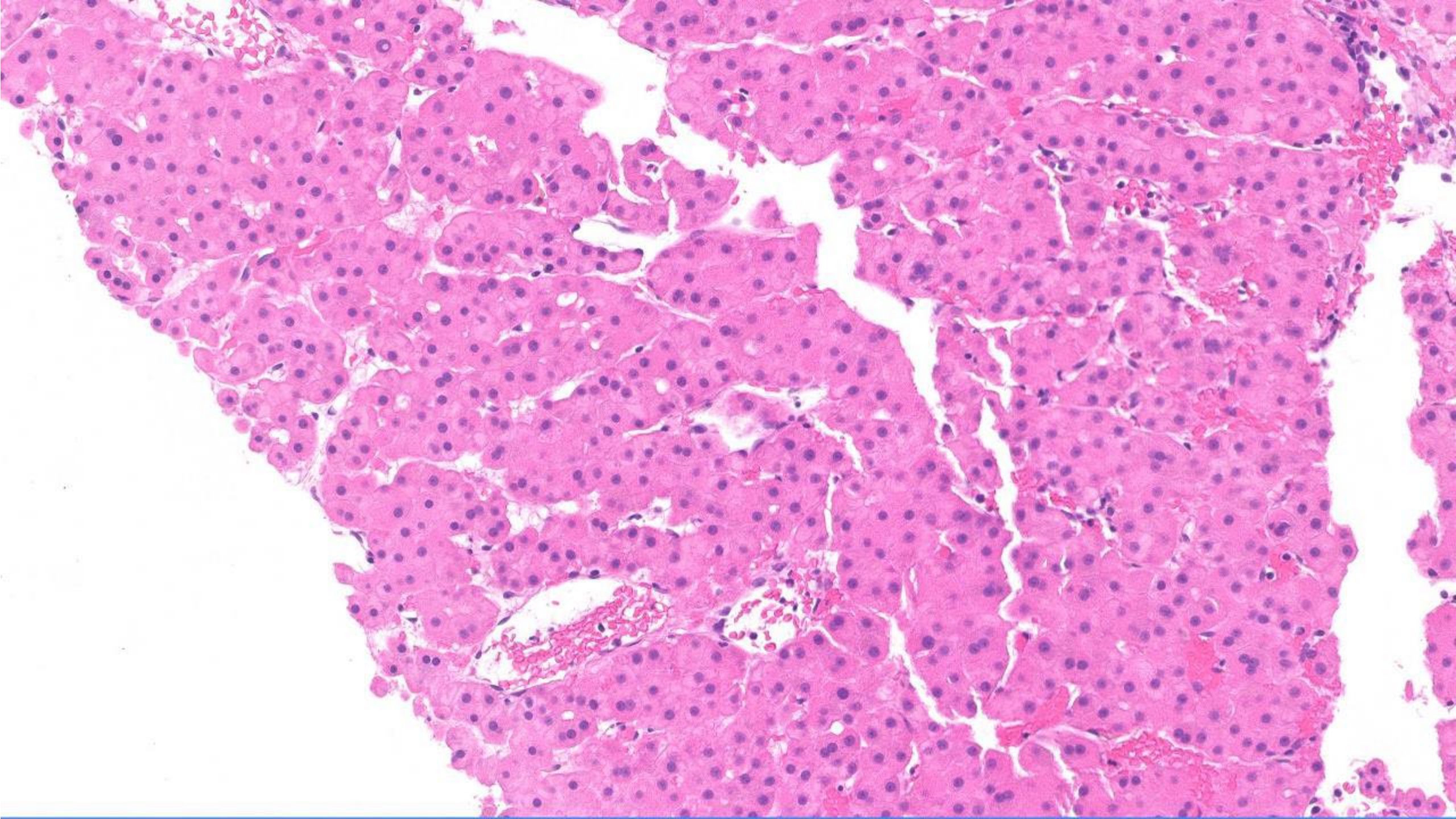
FNH vs. Inflammatory HCA

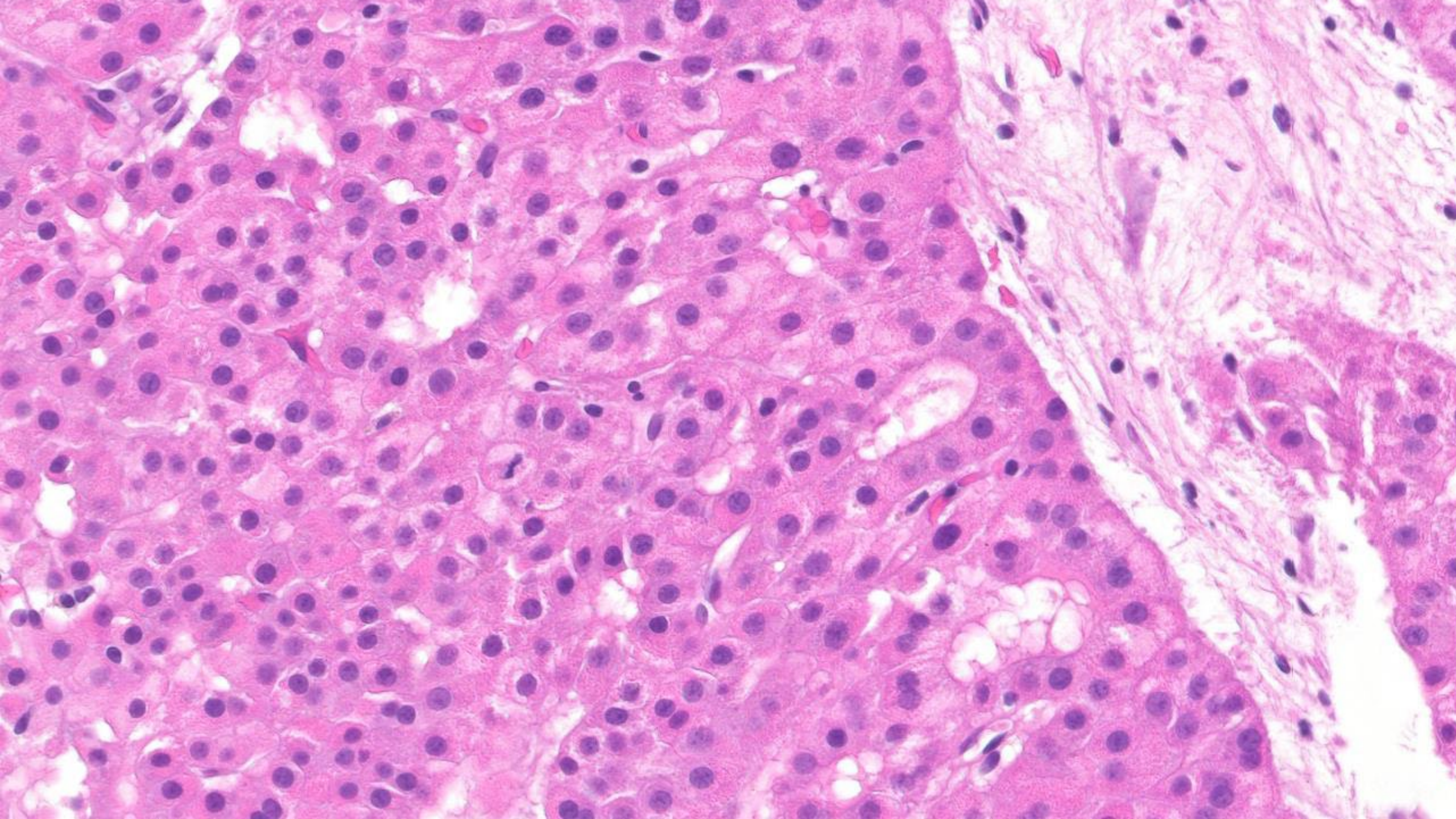
	HA inflammatory	FNH
Central scar	-	+++/-
Large irregular vascular channels	-	+++/+
Glutamine synthetase	Largely negative or diffusely positive	Map like



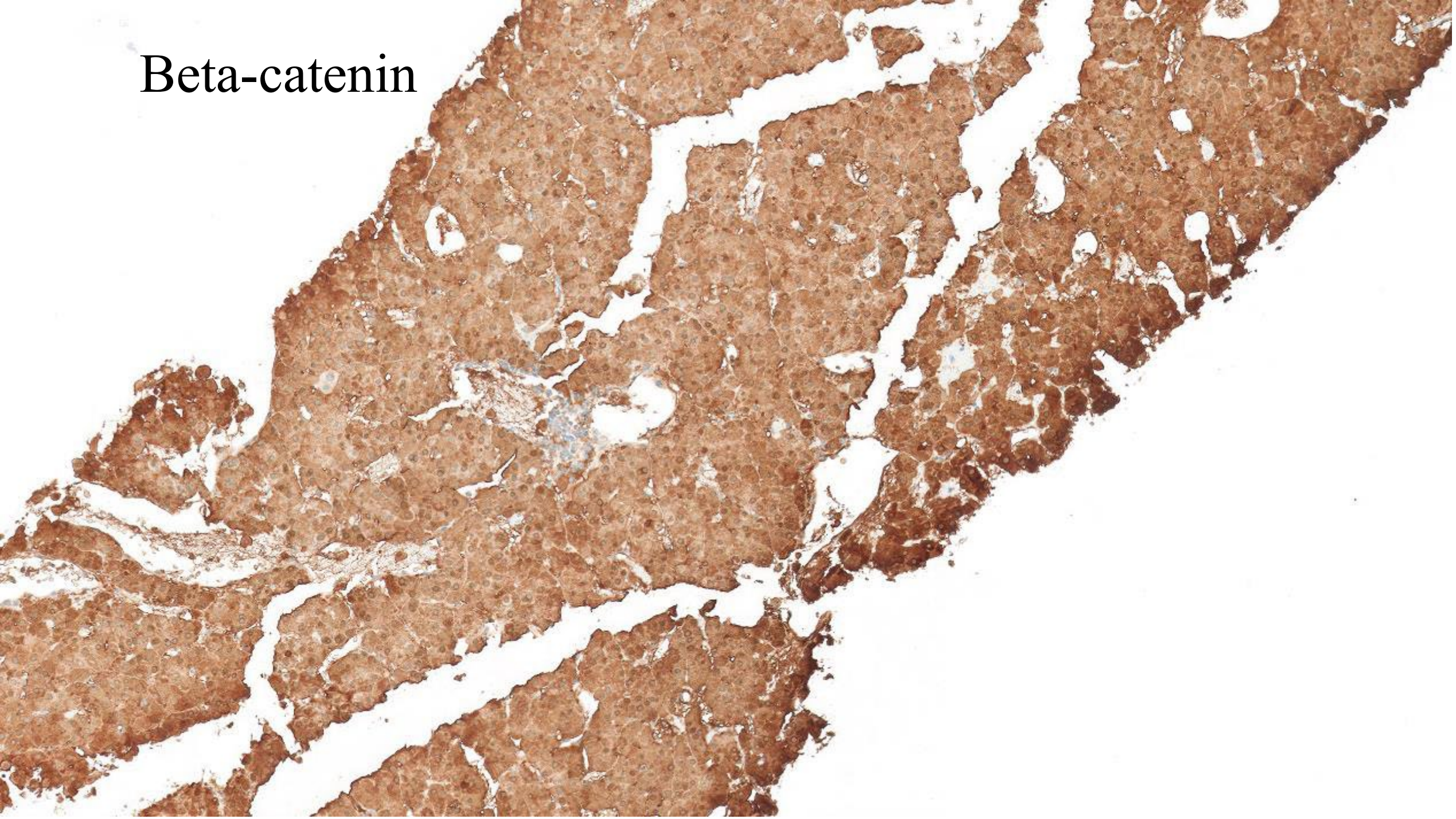
47/F



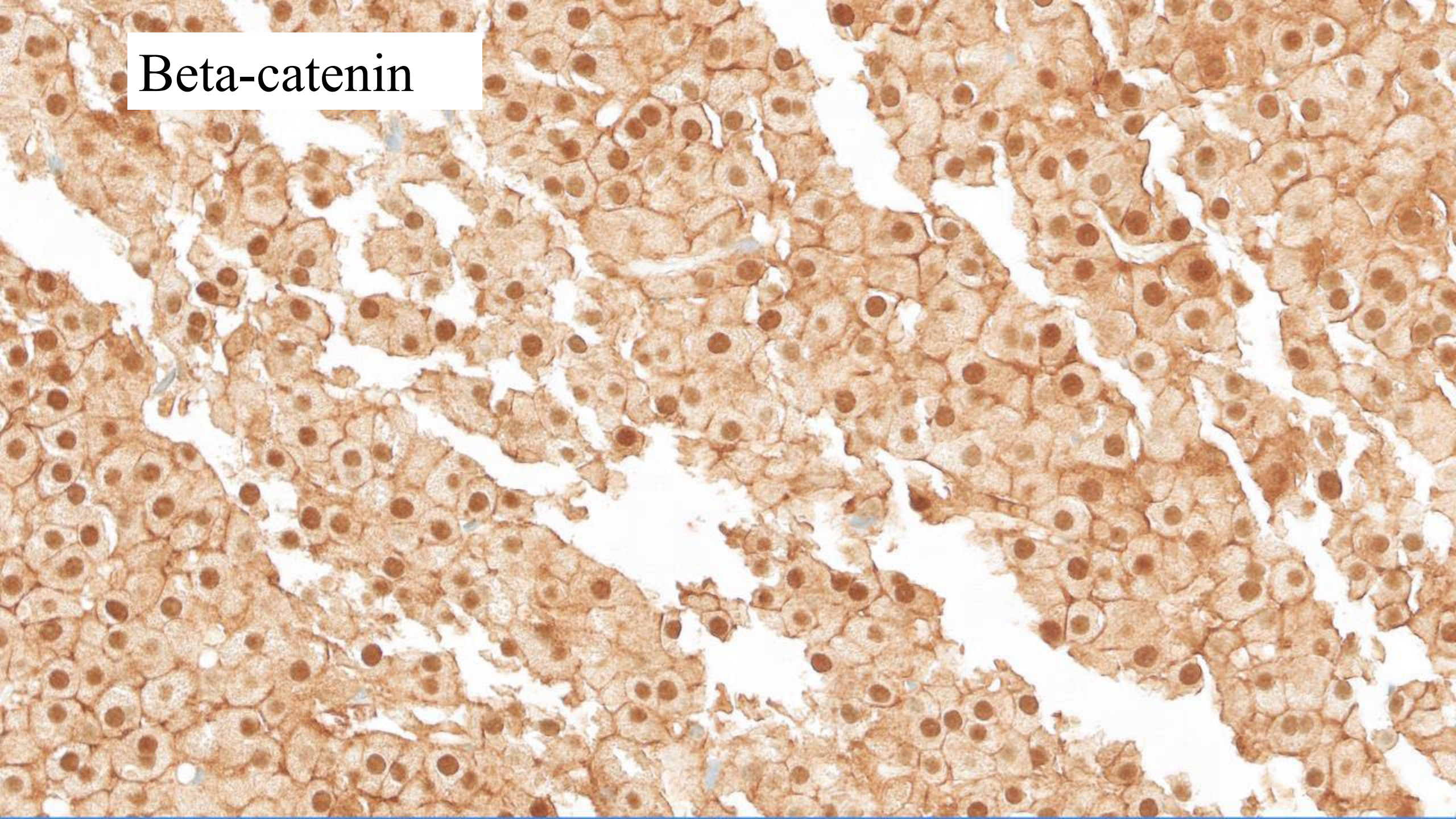




Beta-catenin



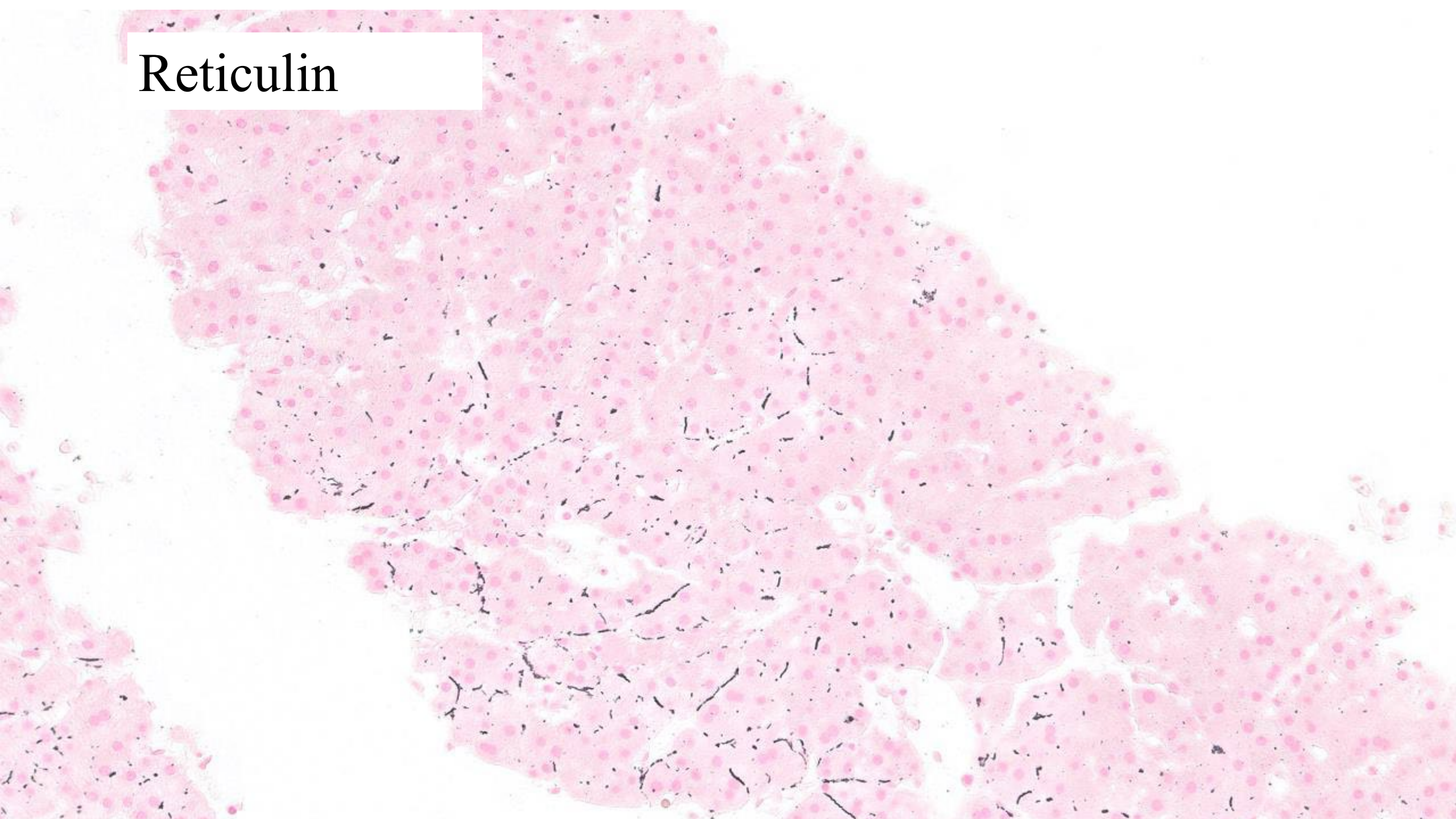
Beta-catenin



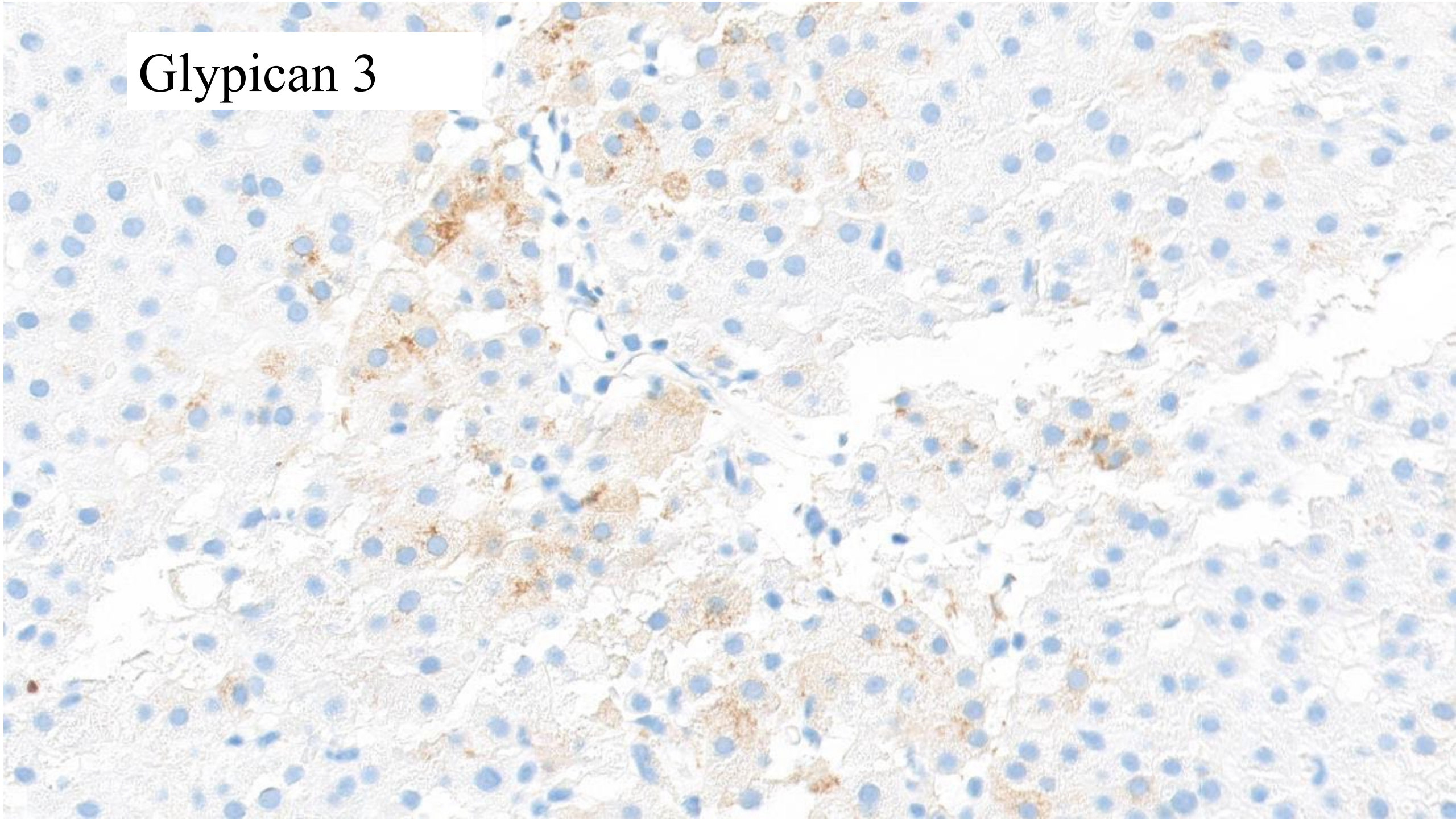


Beta-catenin mutated hepatic adenoma?

Reticulin



Glypican 3



Atypical hepatocellular neoplasm



HCC

Beta-catenin
hepatic
adenoma

Borderline lesion



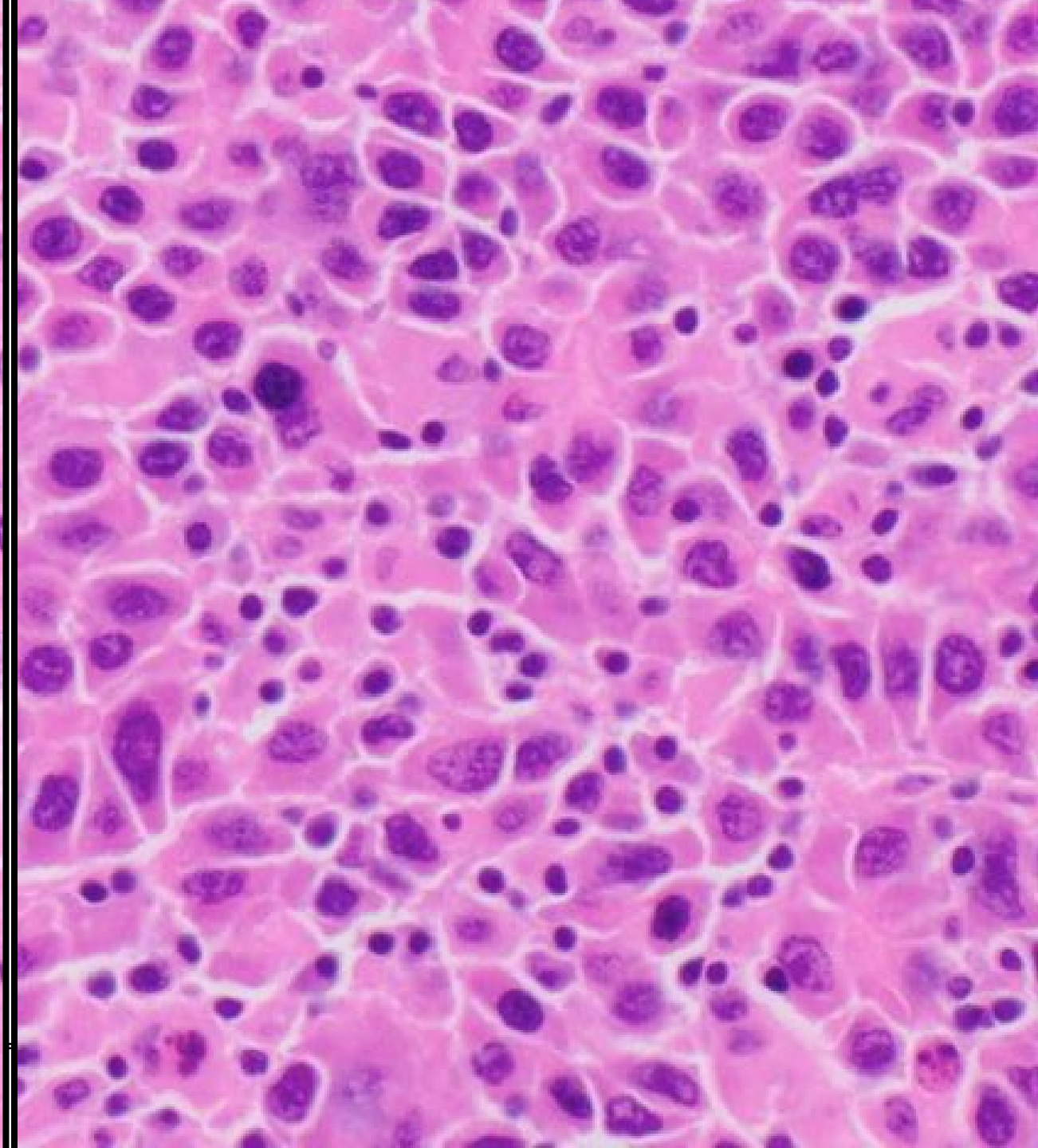
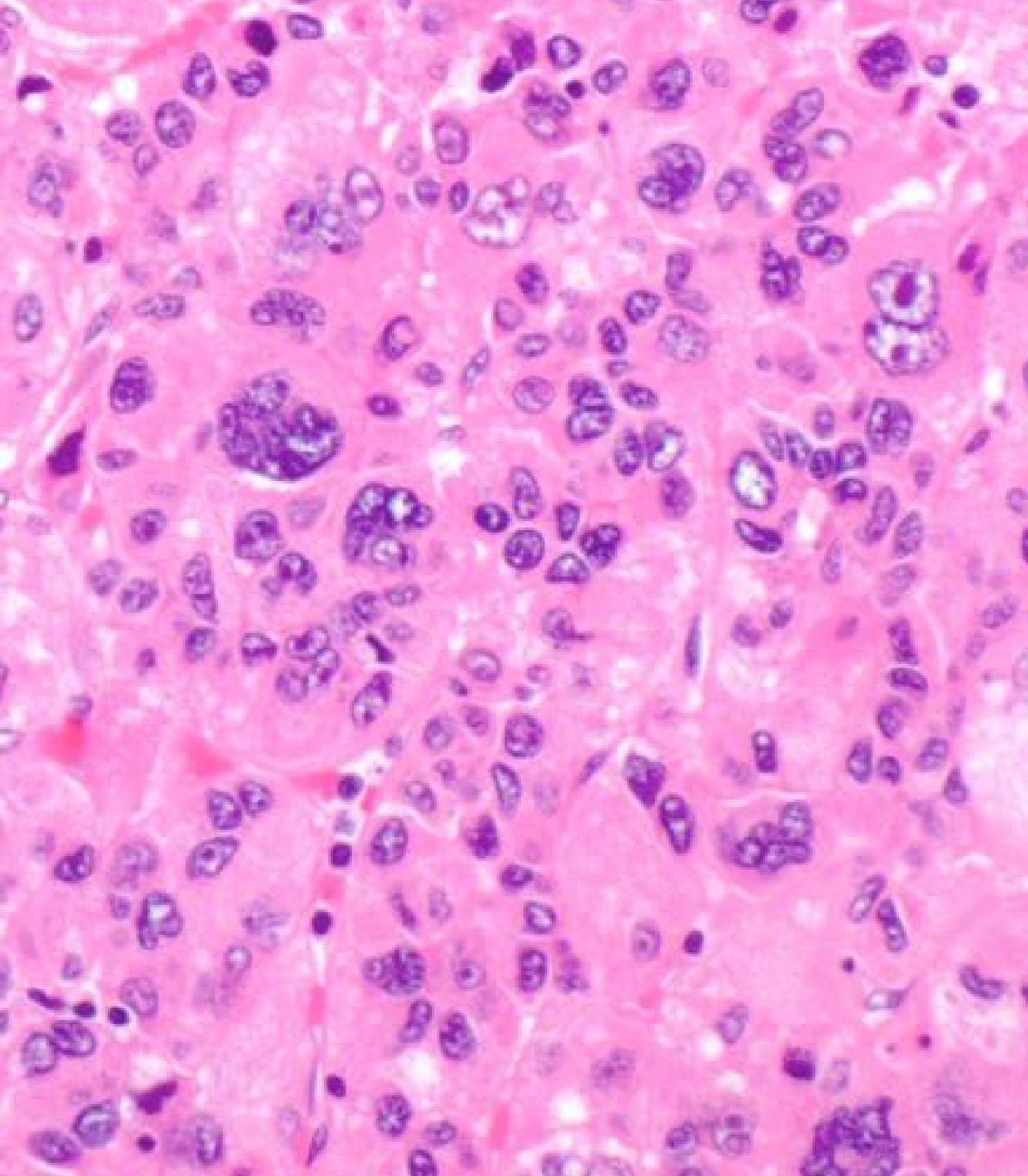
Stain	Utility	Limitations
Liver fatty-acid binding protein (LFABP)	<ul style="list-style-type: none"> Loss of cytoplasmic expression in HNF1A-inactivated HCA 	<ul style="list-style-type: none"> Loss does not distinguish H-HCA from HCC Interpretation may be difficult due to faint staining of background non-neoplastic liver Not clear if LFABP loss in moderately/poorly differentiated HCC is related to HNF1A mutations
Serum amyloid associated (SAA)	<ul style="list-style-type: none"> Diffuse strong staining in inflammatory HCA (IHCA) 	<ul style="list-style-type: none"> Focal staining can be seen in FNH Positive in H-HCA in association with tumor necrosis or hemorrhage Positive in non-neoplastic liver adjacent to any mass lesion, cirrhotic nodules and HCC
C-reactive protein (CRP)	<ul style="list-style-type: none"> Diffuse strong staining in inflammatory HCA (IHCA) 	<ul style="list-style-type: none"> Periseptal or diffuse staining in FNH Positive in non-neoplastic liver adjacent to any mass lesion, cirrhotic nodules and HCC Less specific than SAA
Glutamine Synthetase (GS)	<ul style="list-style-type: none"> Map-like or geographic staining in focal nodular hyperplasia (FNH) Diffuse expression correlates with β-catenin activation Peripheral rim staining in HCA with CTTNB1 exons 3 (S45) and 7/8 mutations 	<ul style="list-style-type: none"> Patchy staining in most HCAs without β-catenin activation Diffuse heterogeneous vs. patchy staining can be difficult in biopsies ('indeterminate' for β-catenin activation) Peripheral rim accentuation pattern can mimic map-like pattern of FNH
β -catenin	<ul style="list-style-type: none"> Nuclear staining in tumors with CTNNB1/other Wnt signaling pathway mutations 	<ul style="list-style-type: none"> Low sensitivity, particularly on needle-core biopsy
CD34	<ul style="list-style-type: none"> Increase in sinusoidal staining in FNH, HCA and HCC 	<ul style="list-style-type: none"> Diffuse sinusoidal staining not specific for HCC and may be seen in FNH and HCA
Glypican-3	<ul style="list-style-type: none"> Positive staining in HCC 	<ul style="list-style-type: none"> Low sensitivity for well differentiated HCC Can rarely be positive in cirrhotic nodules or areas of active inflammation in non-neoplastic liver Positive in yolk sac tumor Rare positivity in other malignant tumors including cholangiocarcinoma and non-liver tumors

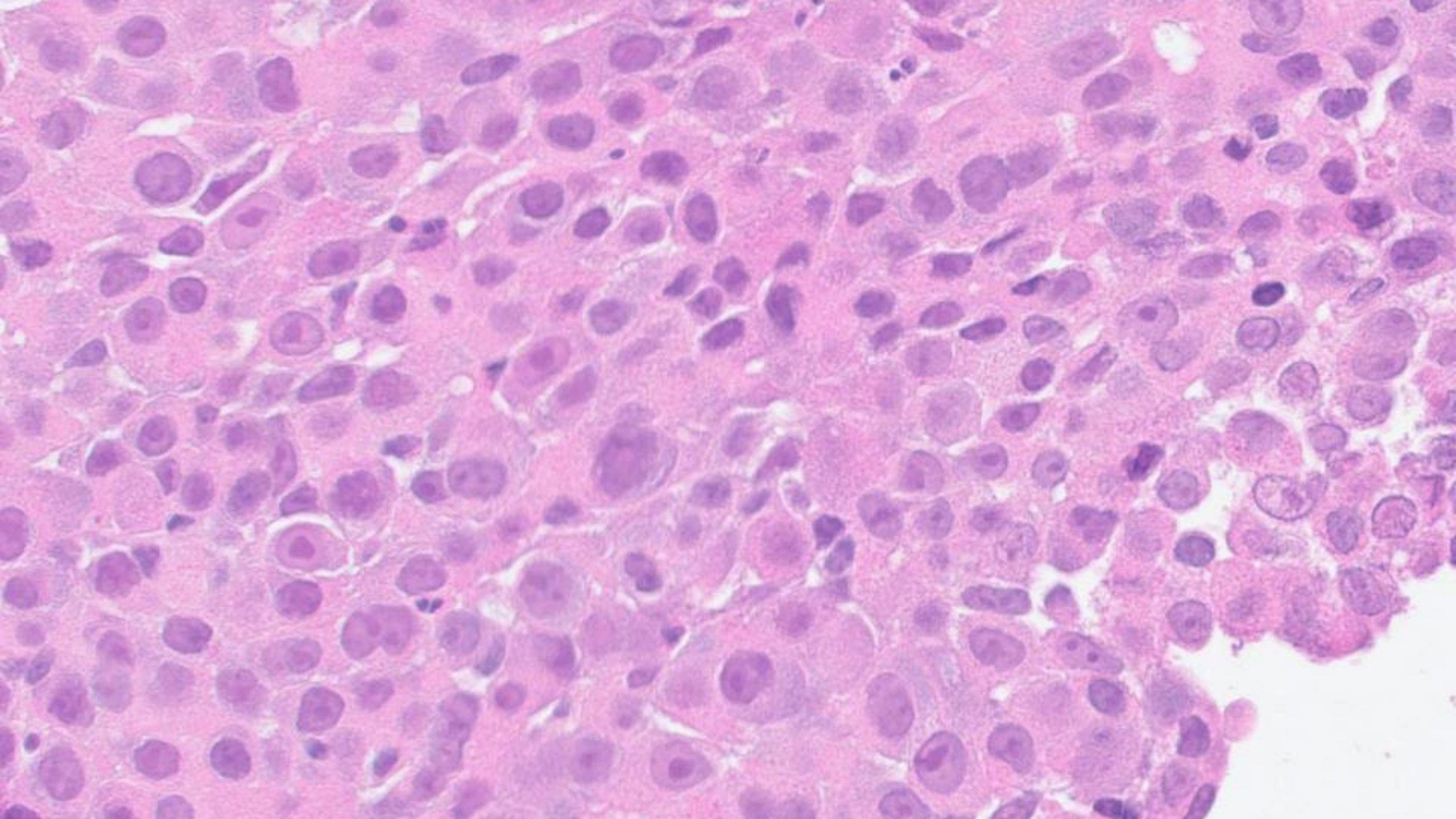
Do not use these stains for a diagnosis
of HCC

SAA, CRP, FABP

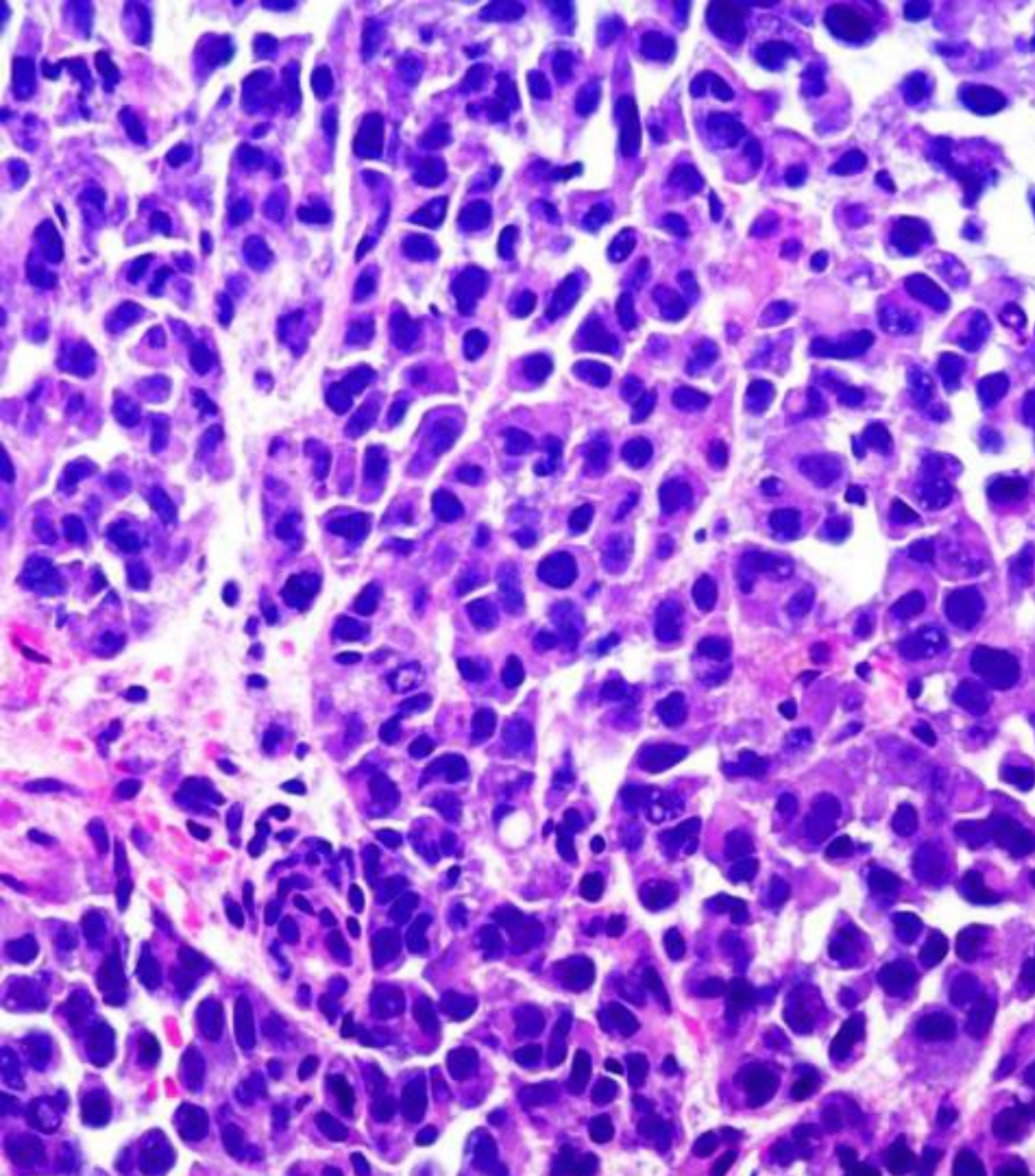


Question 5: I have a poorly differentiated carcinoma on liver biopsy.
Is this an HCC or metastatic carcinoma?



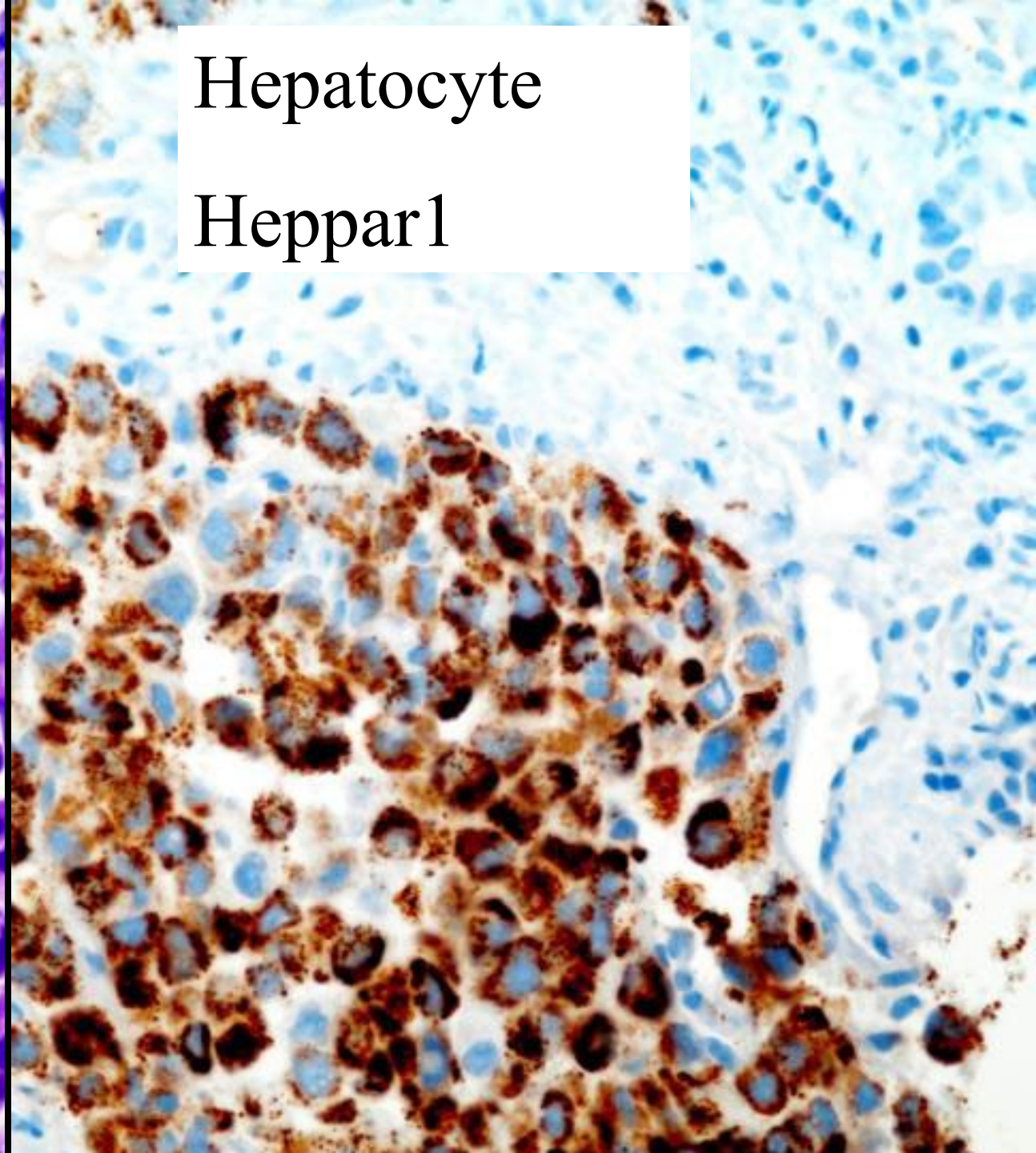


	Target	Sensitivity	Other tumors commonly positive	Poorly differentiated HCCs
AFP	Oncofetal protein	30-50%	Germ cell tumors	Typically negative
Hep Par 1	Carbamoyl phosphatase synthetase (urea cycle)	>90%, staining may be patchy	Lung, colon, esophageal, and gastric carcinoma	<50%
CD10 and polyclonal CEA	Canalicular staining – cross reactivity to biliary glycoprotein	60-90%	Diffuse cytoplasmic staining often seen in adenocarcinomas	25%
Glypican 3	Oncofetal antigen	63-80%	Non seminomatous germ cells tumors, squamous cell carcinoma lung, liposarcoma, Melanoma	57-83%
Arginase-1	Enzyme involved in the hydrolysis of arginine to ornithine and urea	96%	Rare	86%



Hepatocyte

Heppar1



Hep Par 1 is positive in 25% of esophagus/gastric tumors

**Poorly differentiated Hepatocellular carcinoma
< 50% positive**



A microscopic image of tissue stained with hematoxylin and eosin (H&E). The tissue exhibits a prominent canalicular pattern, characterized by numerous small, irregular glandular spaces lined by a single layer of cuboidal to columnar epithelial cells. The nuclei of these cells are stained blue, while the cytoplasm and surrounding stroma are stained pink. The overall architecture is consistent with a neoplastic process, such as a carcinoma. Two text boxes are overlaid on the image: one in the lower-left quadrant and another in the lower-center. The first box contains the text 'Canalicular pattern' and the second box contains the text 'Polyclonal CEA'.

Canalicular pattern

Polyclonal CEA

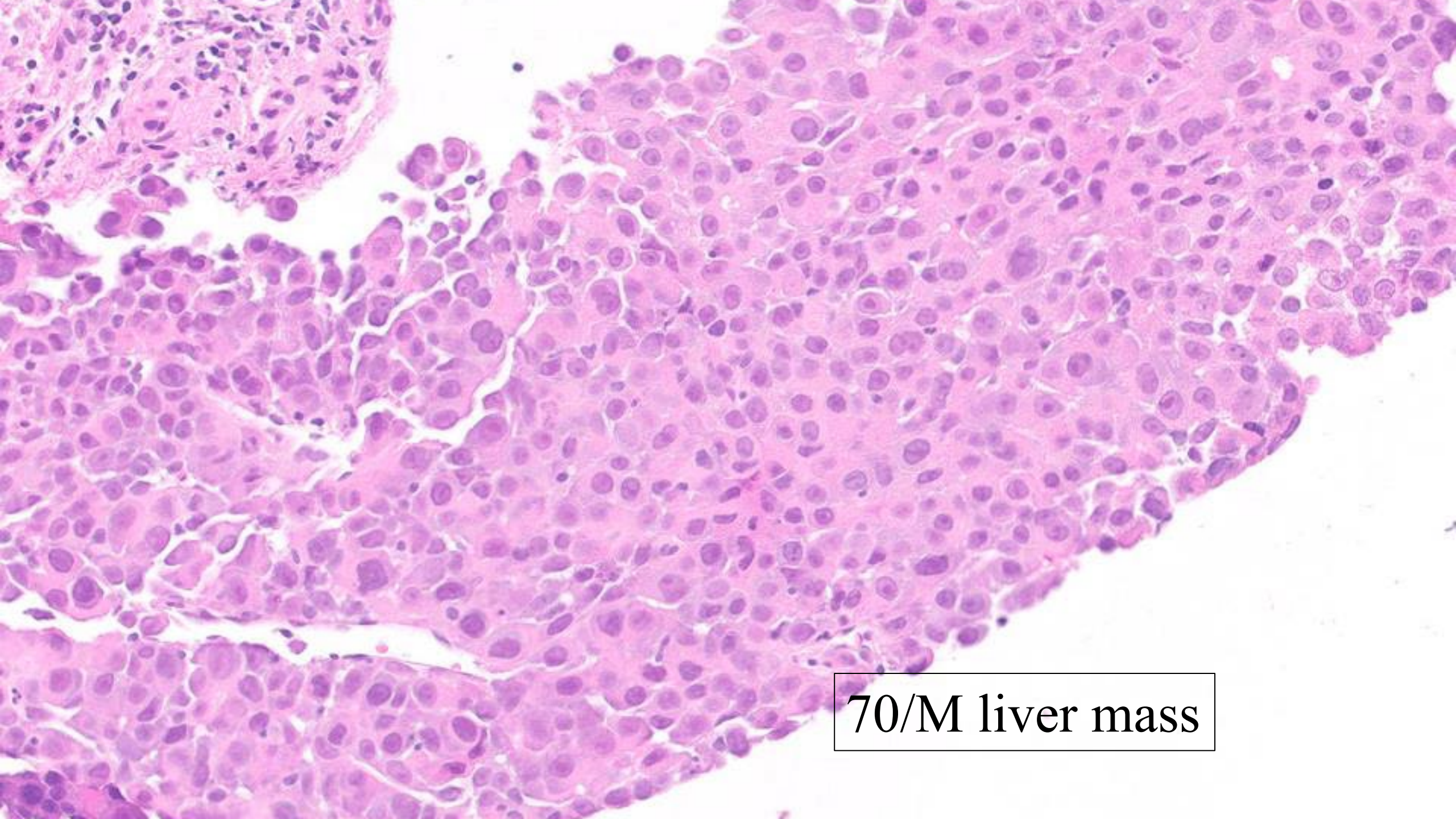
Arginase-1



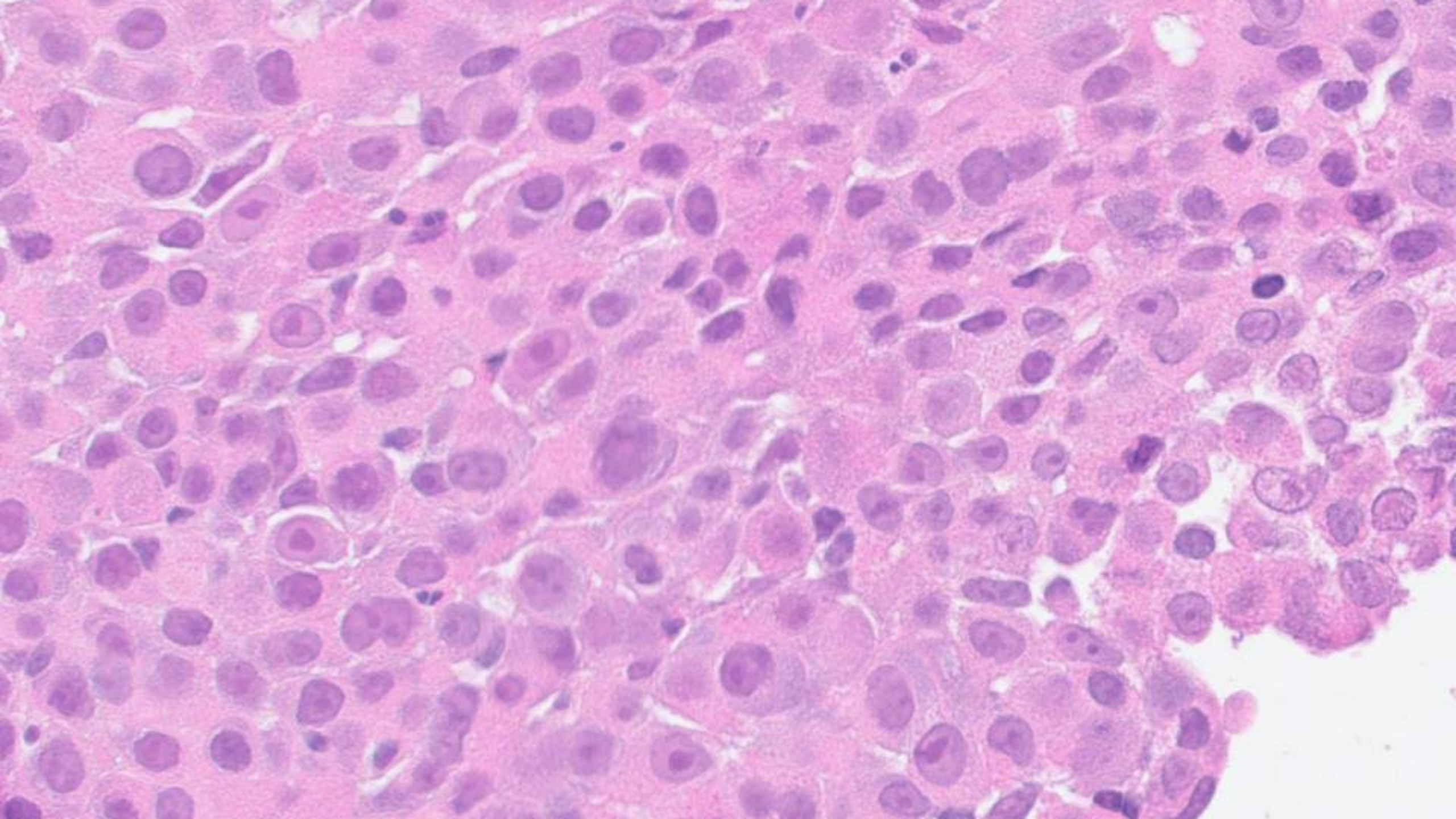
>95% specific
>95% sensitive

Arginase-1 is currently your best marker
for HCC

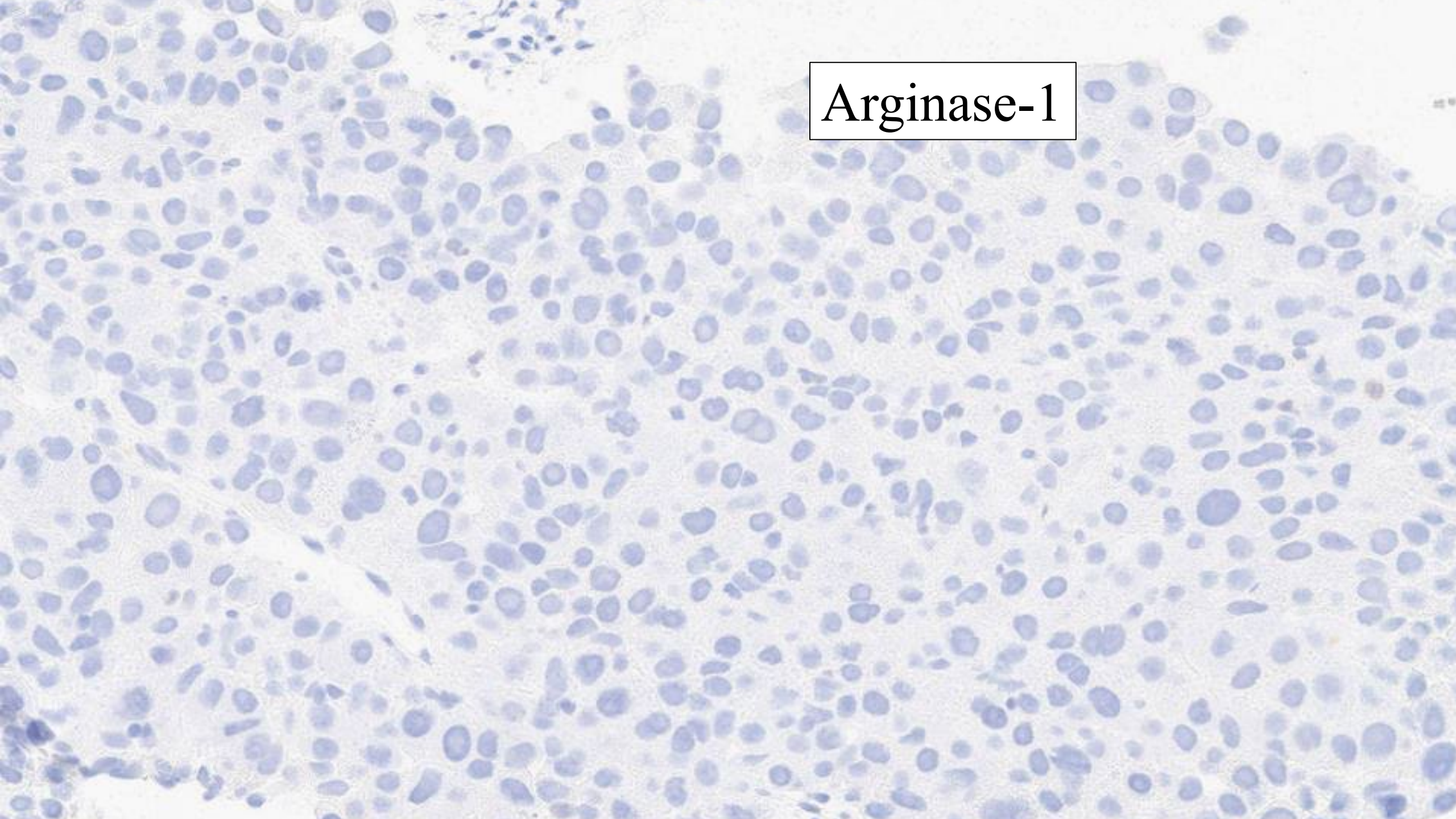




70/M liver mass



Arginase-1



Albumin CISH

The image displays a histological section of tissue, likely liver, stained for albumin using Chromogenic In Situ Hybridization (CISH). The brown staining is localized to the cytoplasm of the cells, indicating the presence of albumin mRNA. The cells are arranged in a somewhat organized pattern, with some showing more intense staining than others. The overall appearance is that of a well-differentiated hepatocellular carcinoma.

**Albumin CISH is the most sensitive marker
of hepatocellular differentiation**

Question 6: How do I classify
cholangiocarcinoma using
WHO 2019 criteria?



Classification of cholangiocarcinoma

- Intrahepatic
 - Peripheral
 - Perihilar
- Extrahepatic
 - Klatskin
 - Bile duct
 - Intrapancreatic

Anatomic classification



WHO 2019 Classification

- Small duct cholangiocarcinoma

Histologic classification

Genetic classification

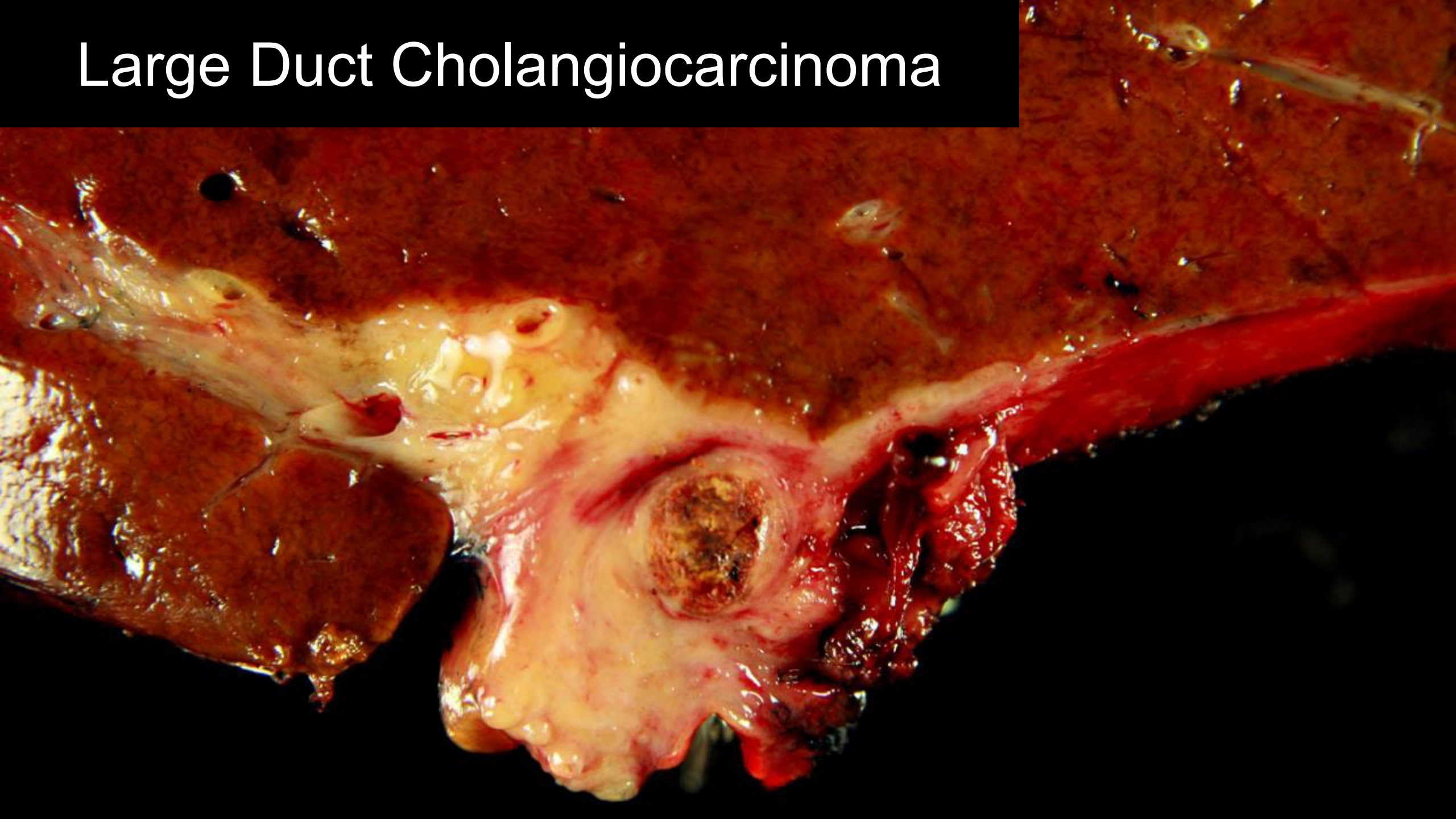
- Large duct cholangiocarcinoma



Small Duct Cholangiocarcinoma



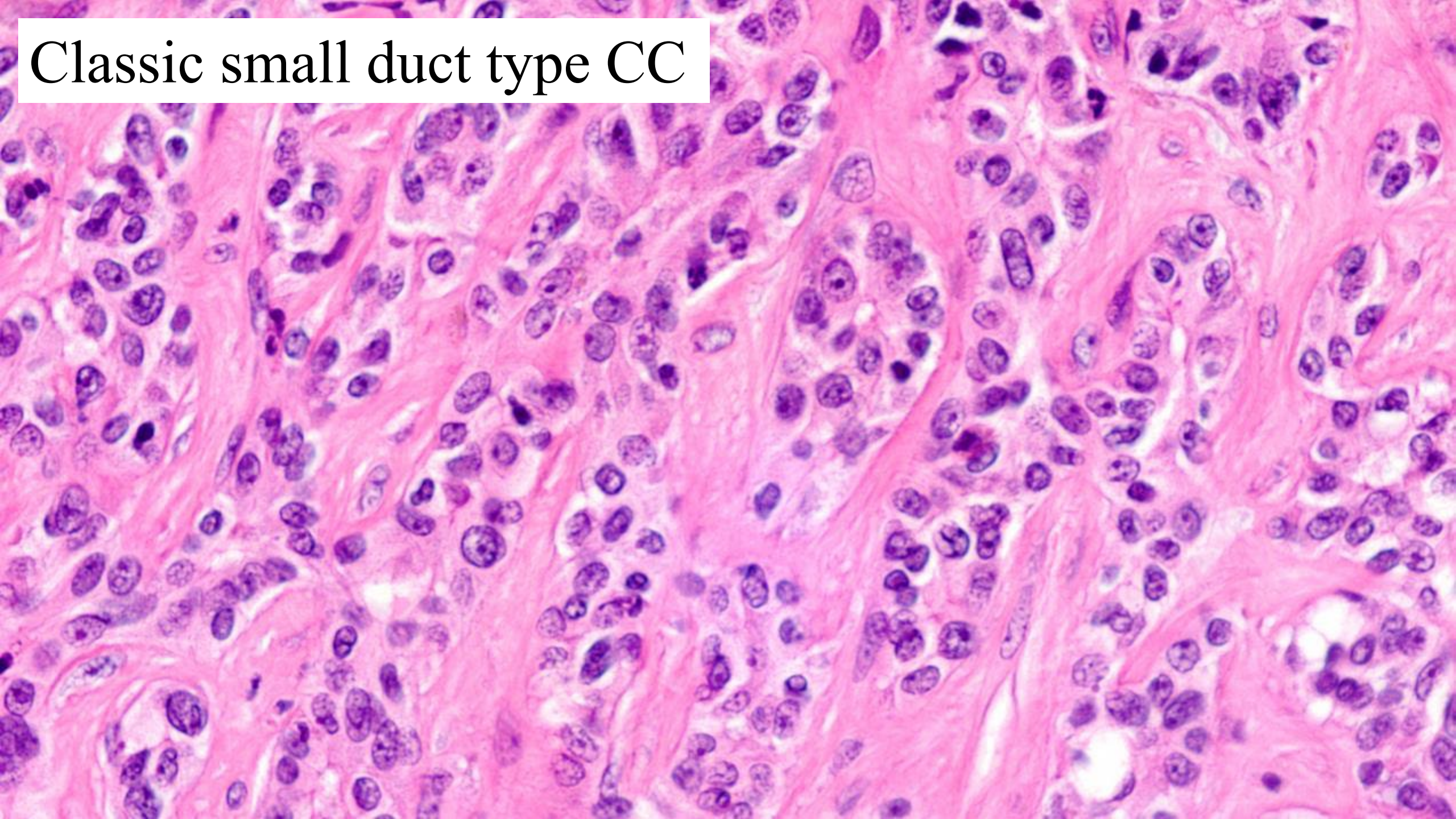
Large Duct Cholangiocarcinoma



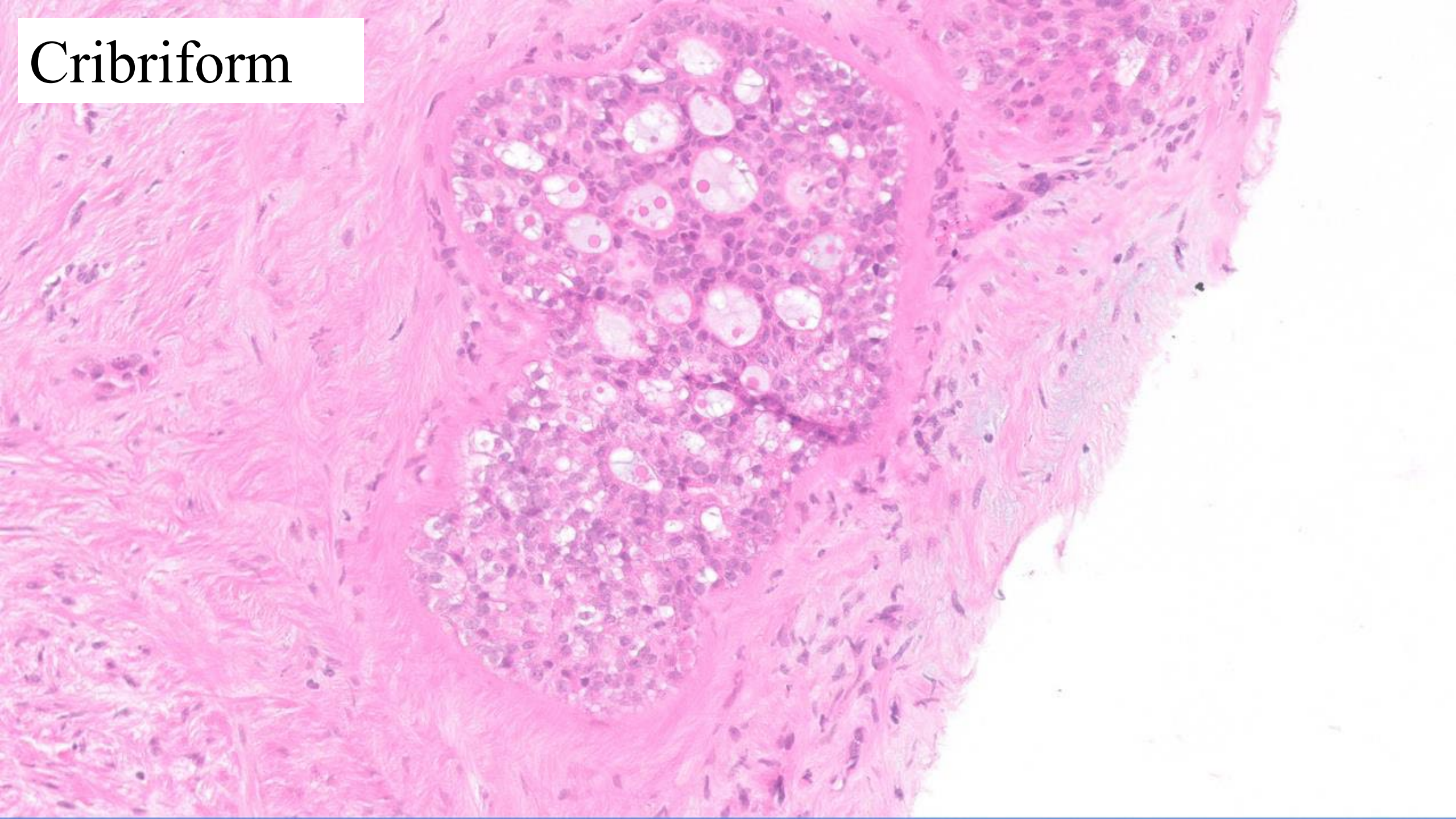
Small duct cholangiocarcinoma



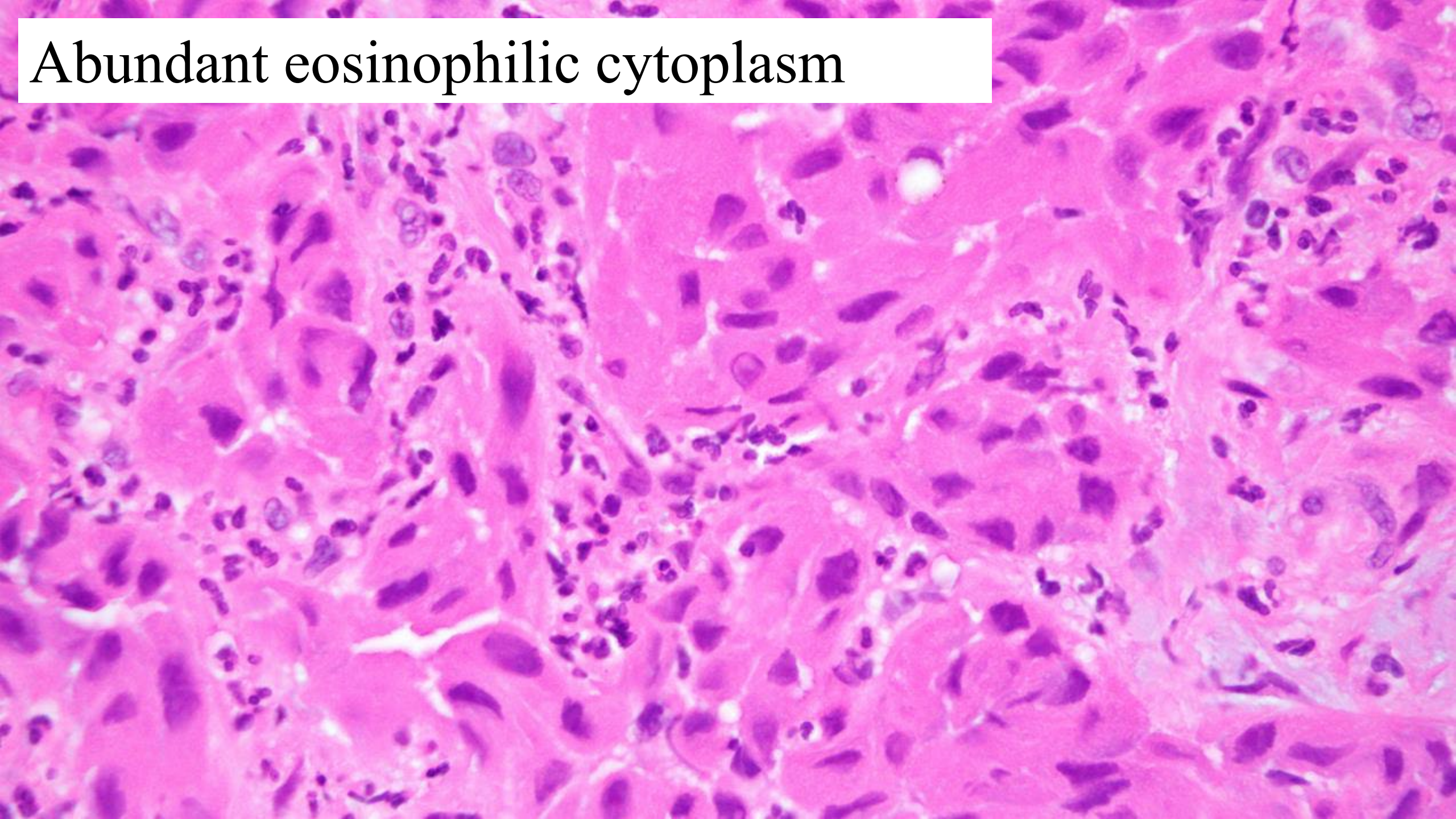
Classic small duct type CC



Cribriform

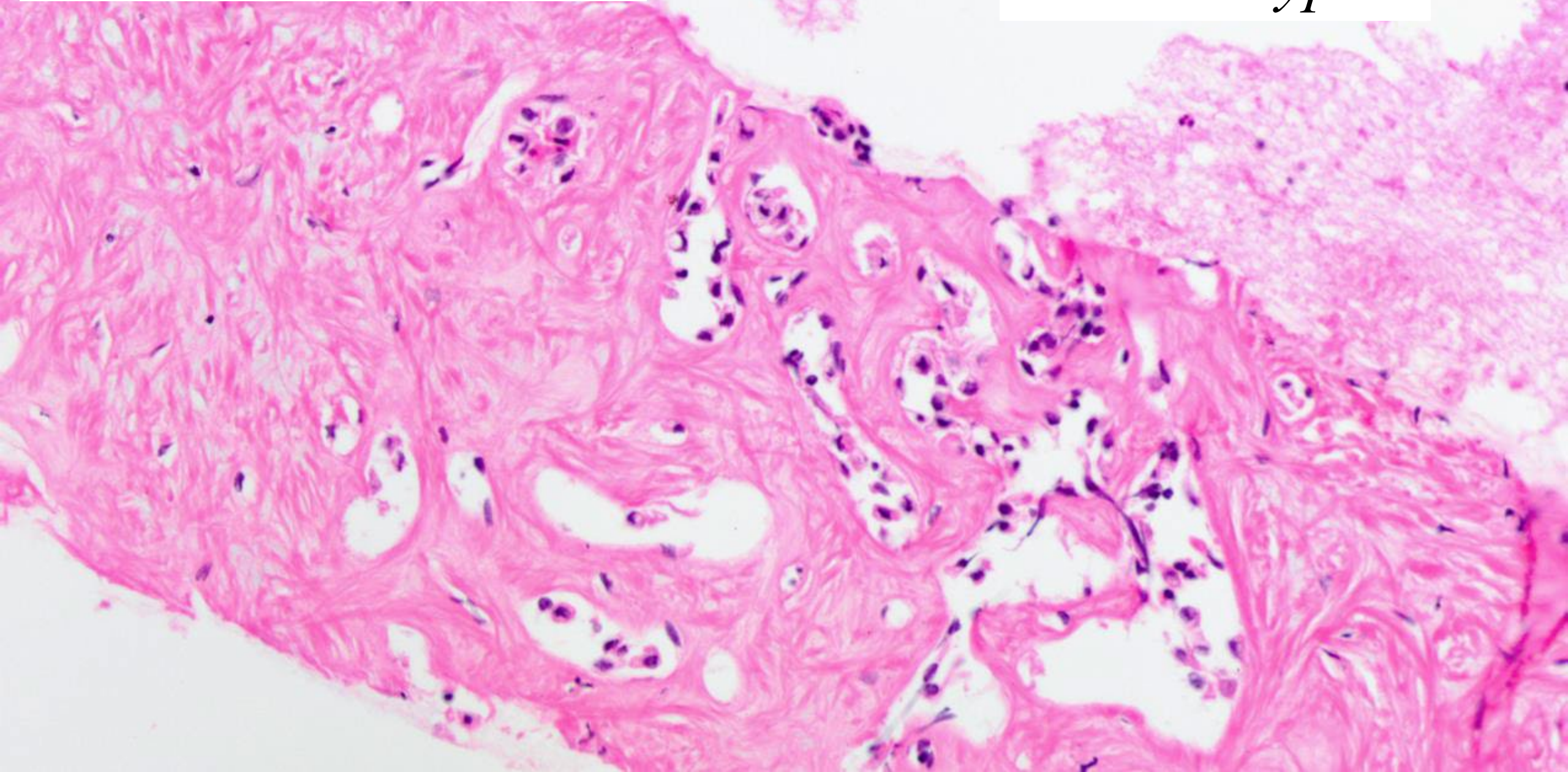


Abundant eosinophilic cytoplasm



Small duct type CC

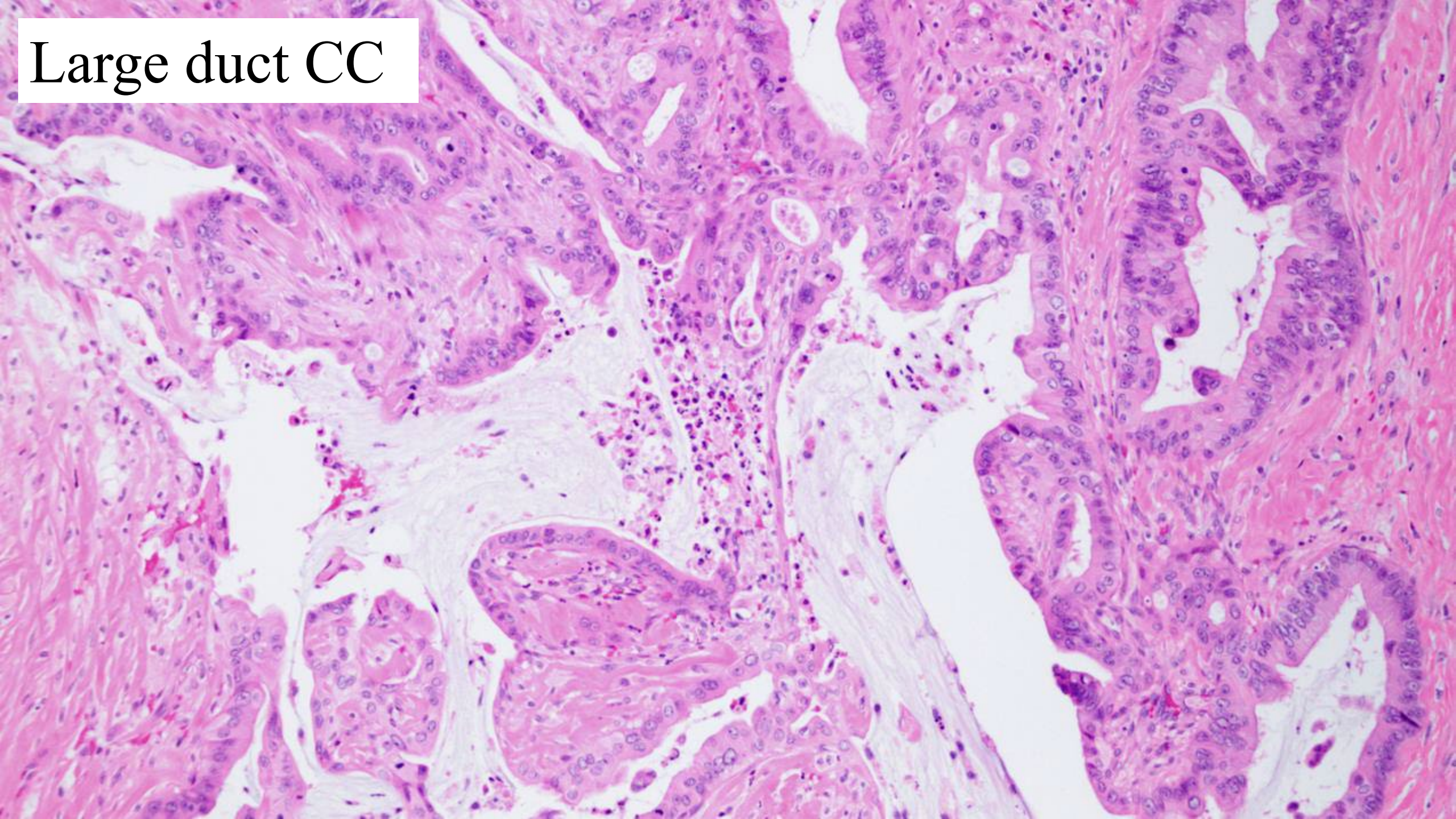
Ischemic type



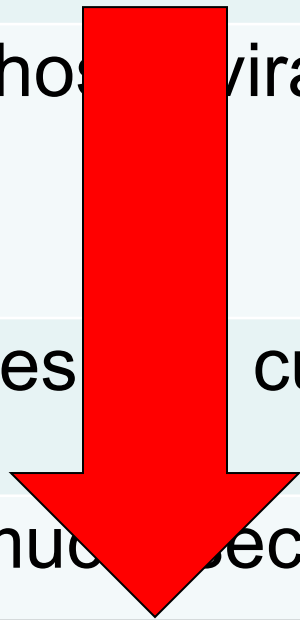
Large duct cholangiocarcinoma



Large duct CC



	Small duct type	Large duct type
Gross features	Peripheral Mass forming	Hilar Infiltrating
Targetable with FDA approved drugs		
Risks	Cirrhosis, viral hepatitis	PSC, hepatolithiasis, liver fluke
Histology	Tubules with cuboidal cells	Duct with columnar cells
Mucin	Non-mucin-secreting glands	Mucin-secreting glands



WHO 2019 Classification

Imperfect



Question 7: I have an
adenocarcinoma on a liver
biopsy – is this
cholangiocarcinoma or
metastatic adenocarcinoma?

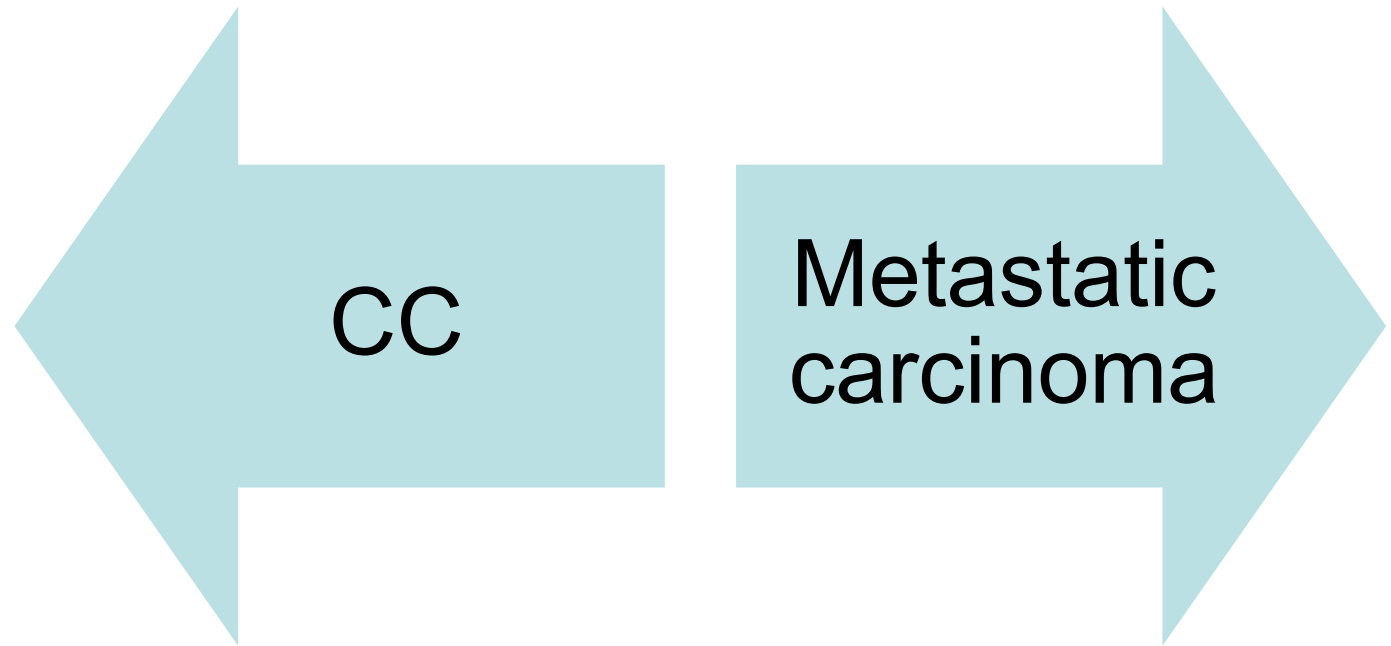
Management of liver 'adenocarcinoma'

Hepatic resection

Gemcitabine/cisplatin

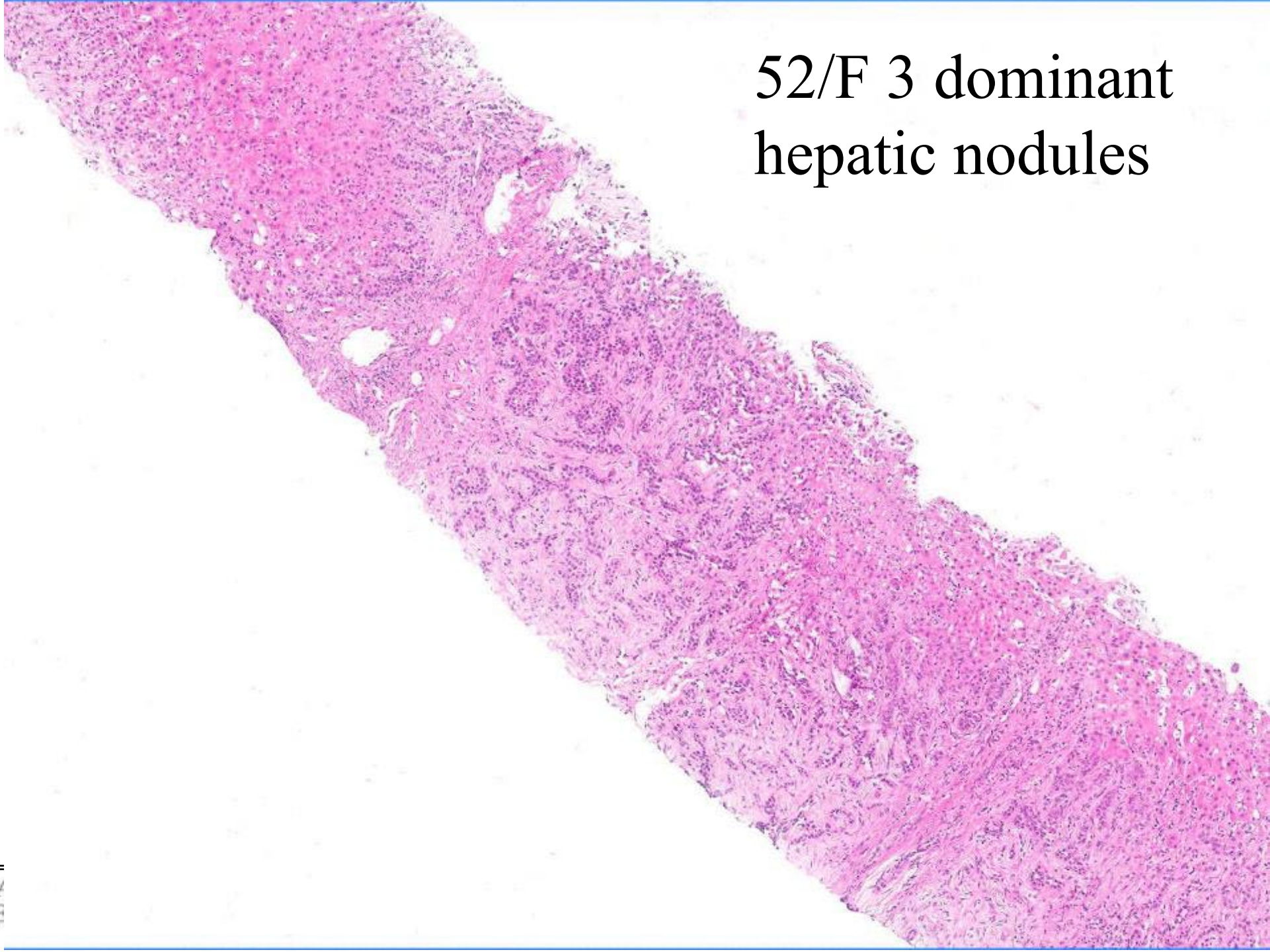
IDH inhibitor

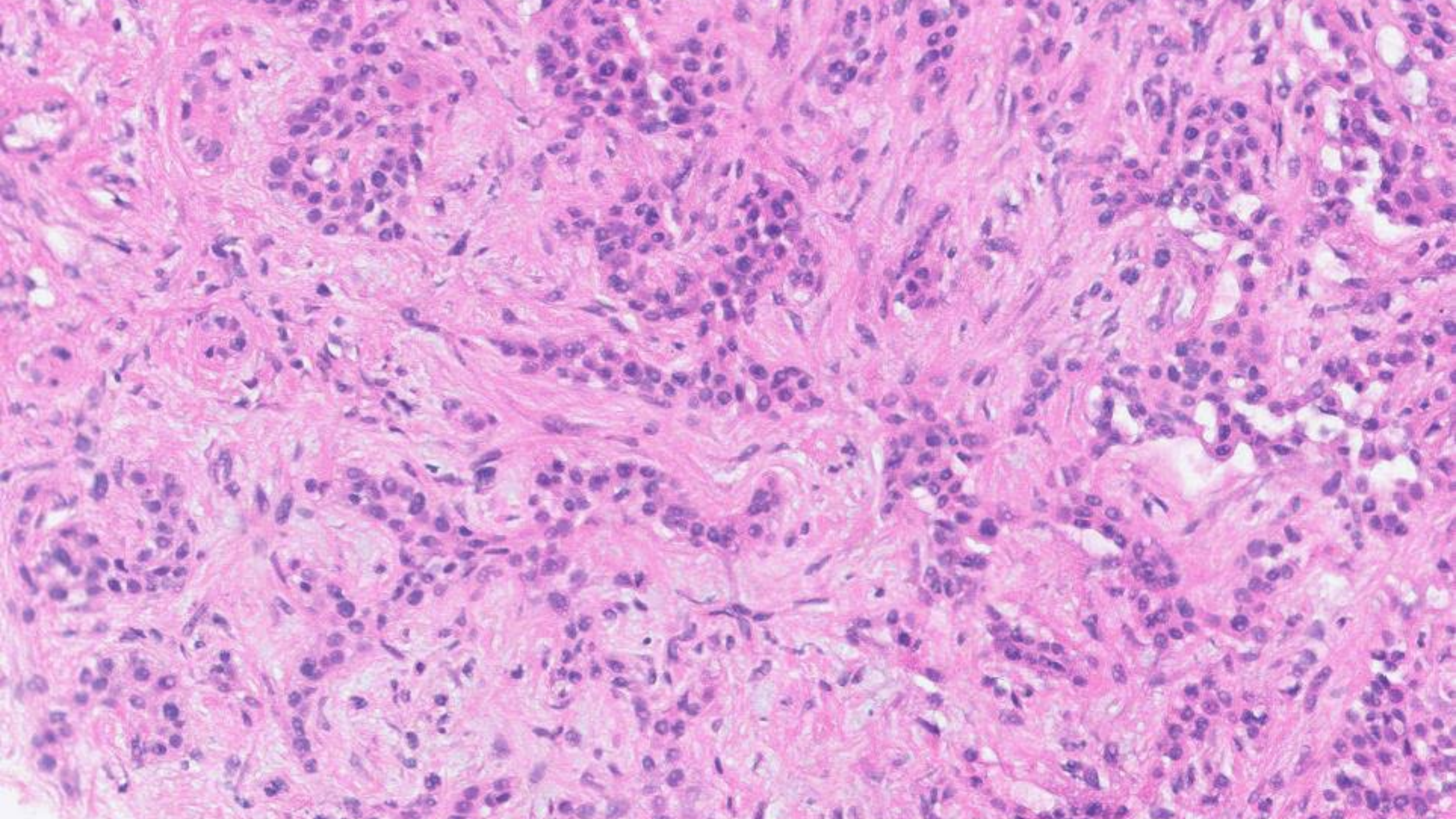
FGFR2 inhibitor



Chemotherapy

52/F 3 dominant
hepatic nodules







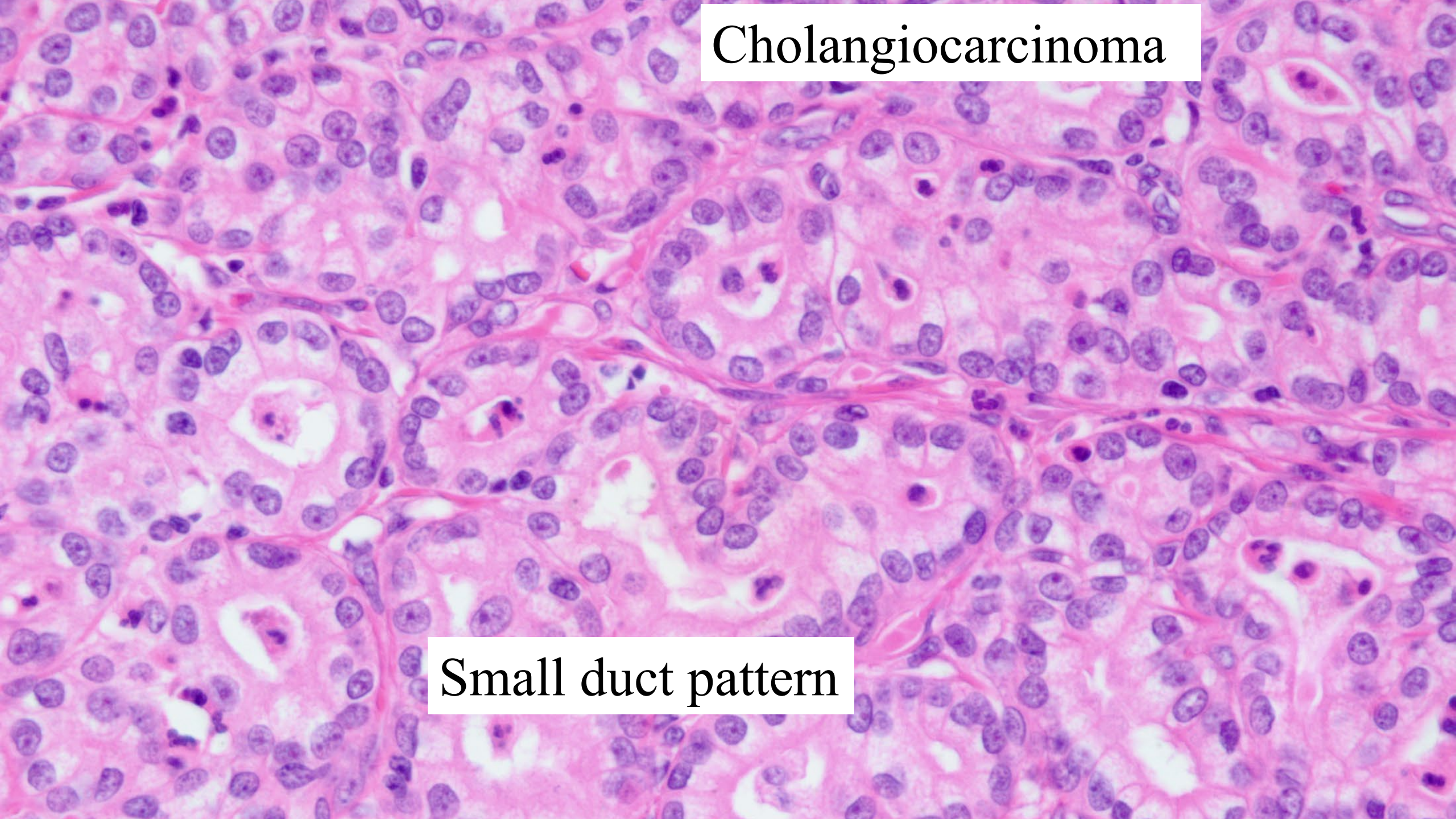
Diagnosis?

What do cholangiocarcinoma look like?



Cholangiocarcinoma

Small duct pattern



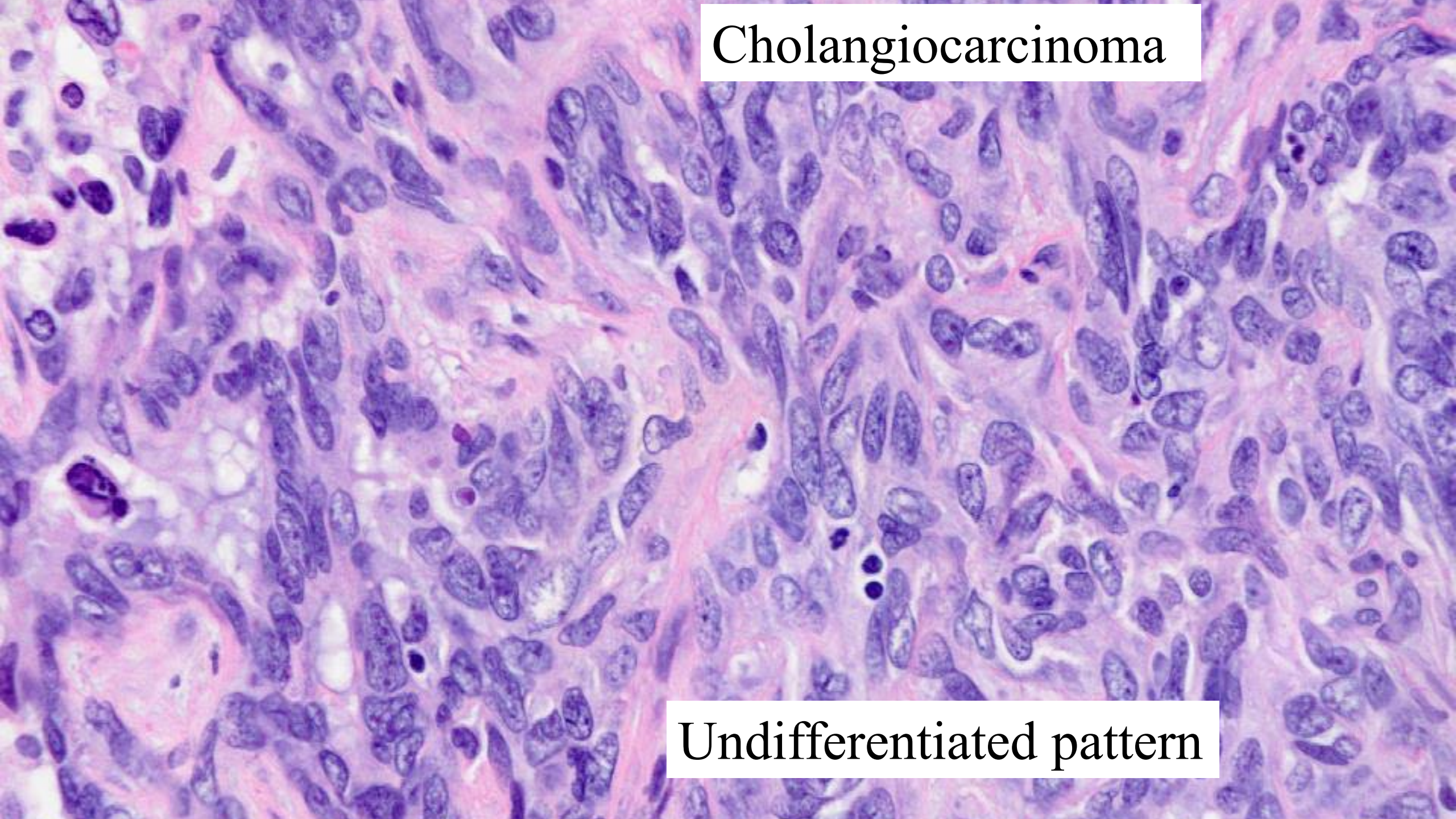
Cholangiocarcinoma

A high-magnification photomicrograph of a tissue section stained with hematoxylin and eosin (H&E). The image displays a characteristic nested pattern of malignant cells, which is typical of cholangiocarcinoma. The cells are arranged in irregular, glandular-like clusters or nests, separated by thick, fibrous bands of connective tissue. The nuclei of the malignant cells are hyperchromatic (dark purple) and show significant pleomorphism (variation in size and shape). The overall architecture is disorganized, with loss of normal glandular structure.

Nested pattern

Cholangiocarcinoma

Undifferentiated pattern



Cholangiocarcinoma



Cholangiolar pattern

Histologic Patterns of CC

- Cholangiolar

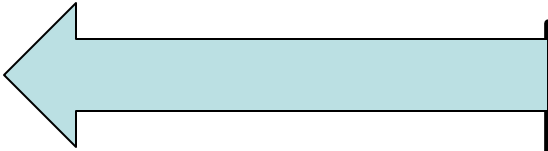
- Tubular

- Nested- neuroendocrine-like

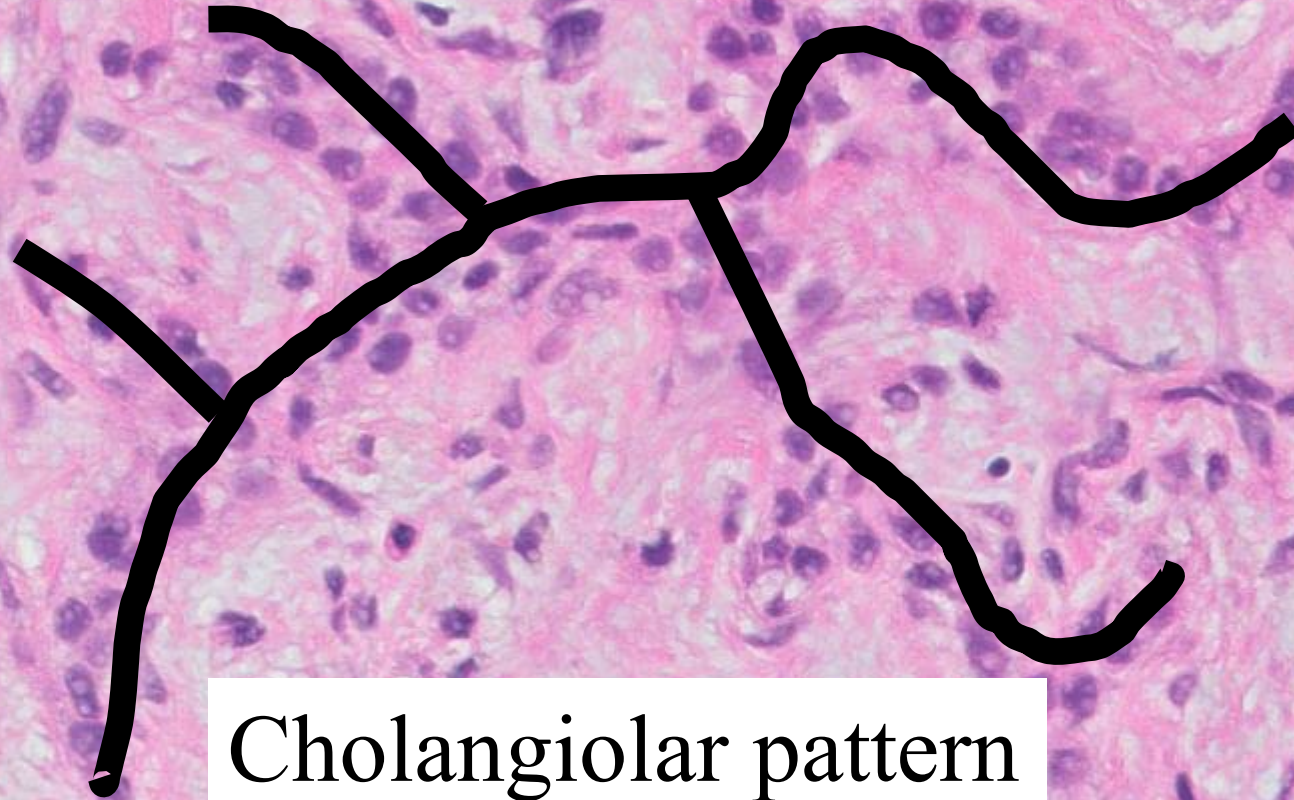
- Large duct

- Undifferentiated

Highly suggestive of
cholangiocarcinoma

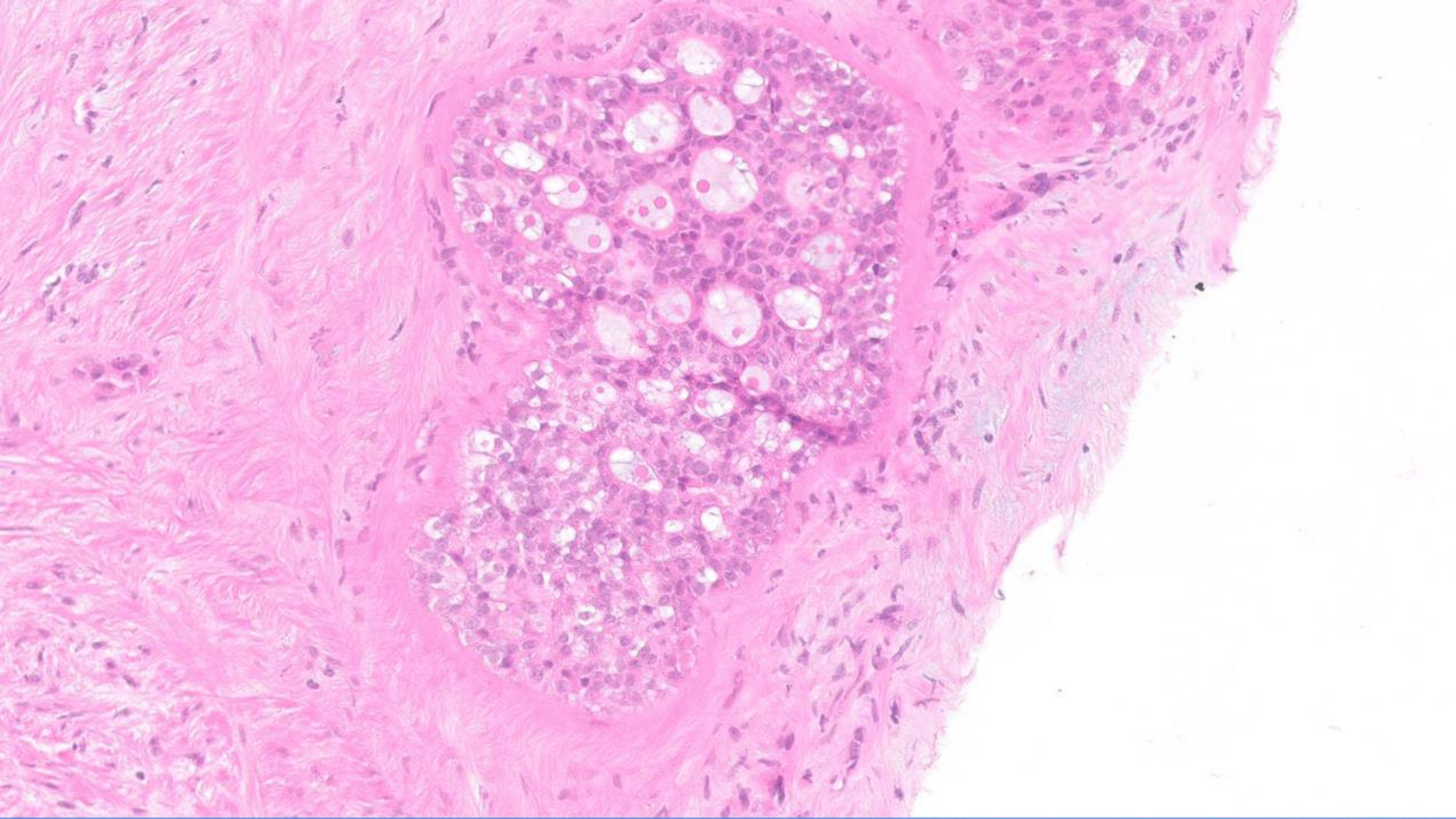


What about this tumor?



Cholangiolar pattern

Suggestive of intrahepatic cholangiocarcinoma



What about this tumor?

Cholangiocarcinoma?
Metastatic adenocarcinoma?



	Cholangiocarcinoma	Metastatic carcinoma
Keratin 7	++	++/-
Keratin 20	-/+	-/+
TTF-1/Napsin	-/+	+ (lung)
CDX2	-/+	+ (GI)
Keratin 19	++	+/-
Ca19.9	++	+/-

CC

% positive

Pax8

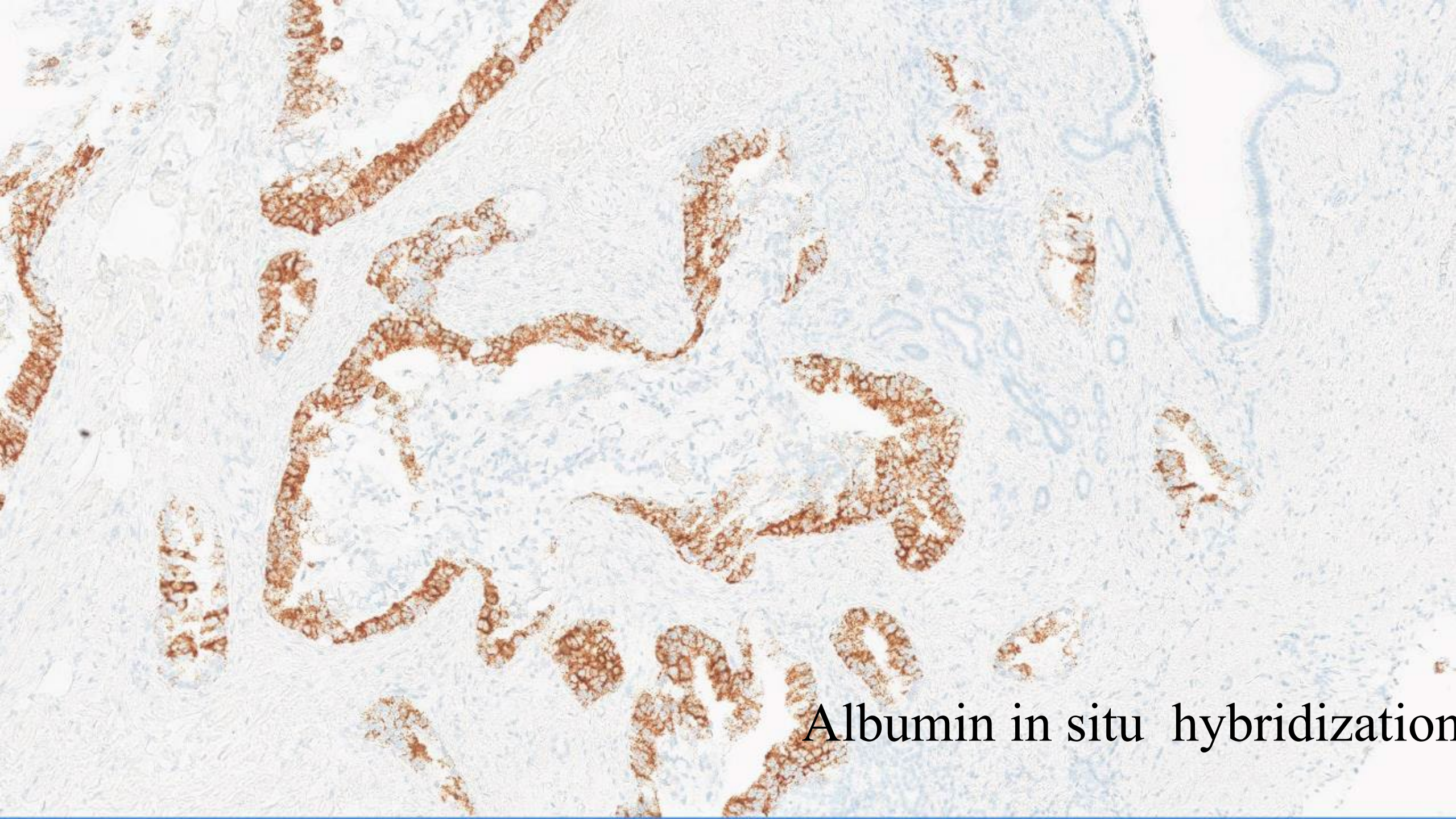
38%

Keratin 5/6

73%

Calretinin

52%



Albumin in situ hybridization

PMID	CC Positive for albumin	Non-HCC non-CC Positive for albumin	Tissue microarray vs. whole section
29746696	14/22 (64%)	1/445 (<1%)	Tissue microarrays and whole sections
31107526	22/27 (82%)	10/139*(7%)	Whole sections
31422372**	46/52 (89%)	0/37 (0%)	Whole sections
33208670	38/47 (81%)	0/28 (0%)	Whole sections
25519926	82/83 (99%)	0/332 (0%)	Tissue microarrays and whole sections

Diagnostic Histopathology 2022

Monika Vyas, MD

How do I make a diagnosis of
cholangiocarcinoma

Vyas, M. and Deshpande, V., 2022. How do I distinguish cholangiocarcinoma from metastatic carcinoma and why does it matter?. *Diagnostic Histopathology*, 28(2), pp.79-88.



Tumor type

Albumin

Small duct CC

Positive

Hepatocellular carcinoma

Positive

Other tumors of intrahepatic origin e.g.
hepatoblastoma

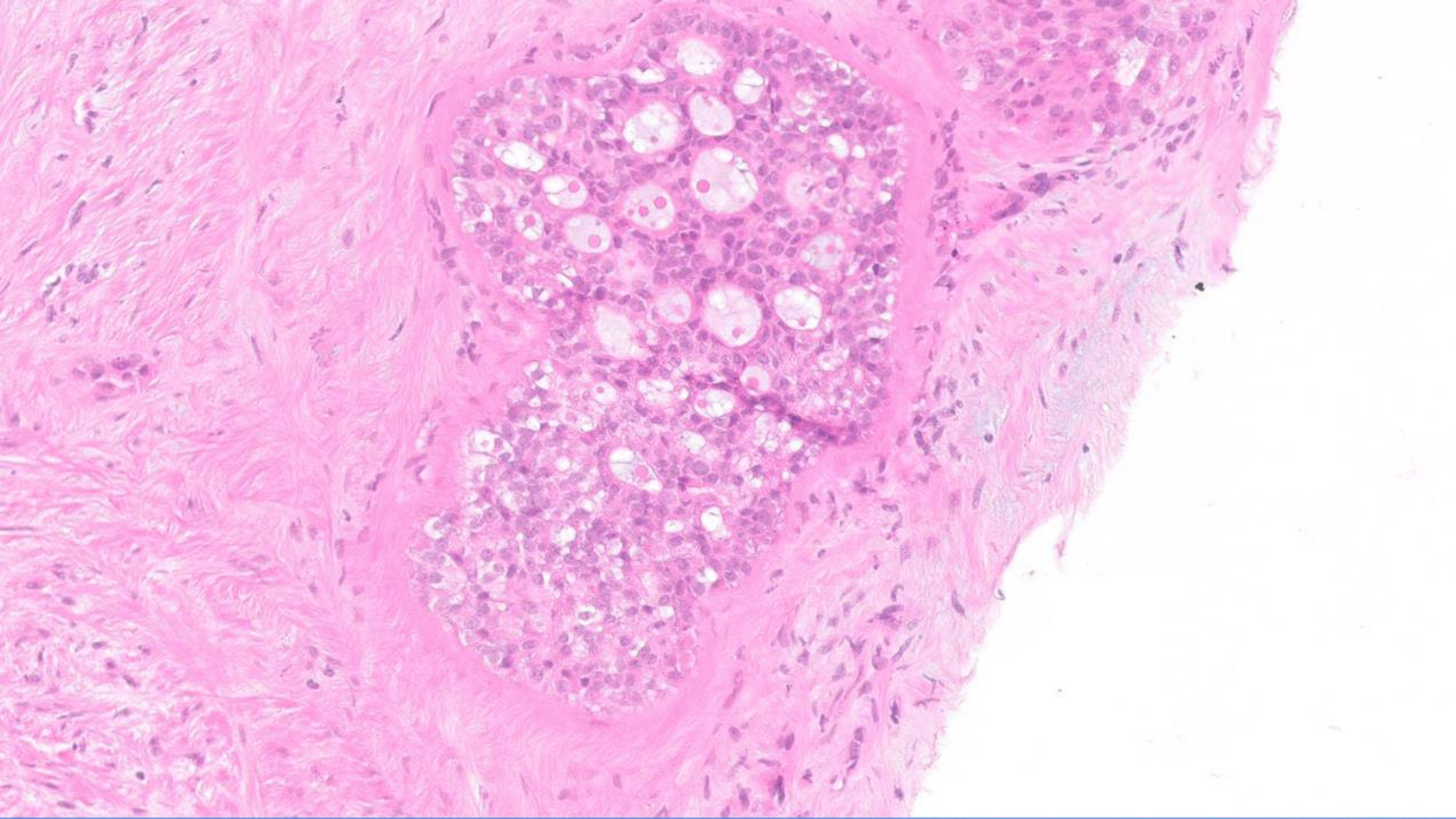
Positive

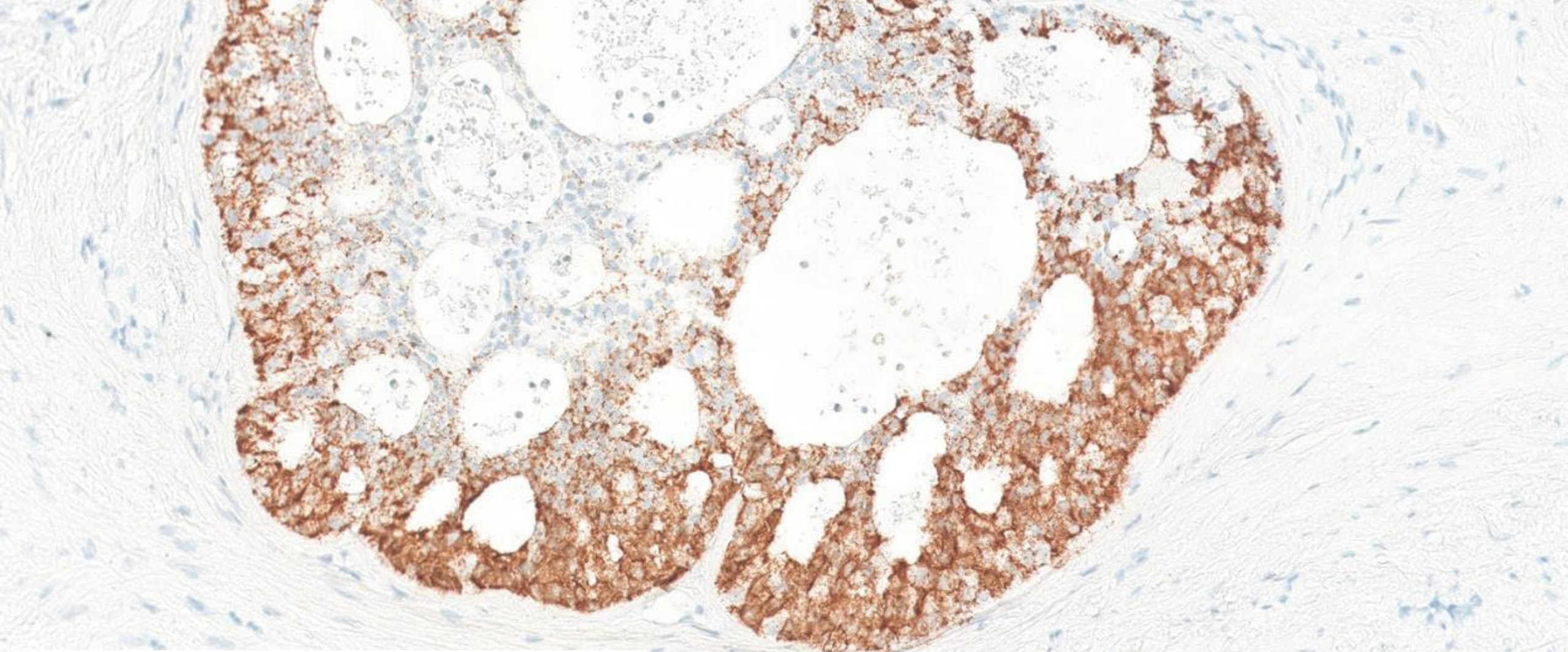
Large duct CC

Typically Negative

Other metastatic carcinomas

Negative*





Albumin CISH

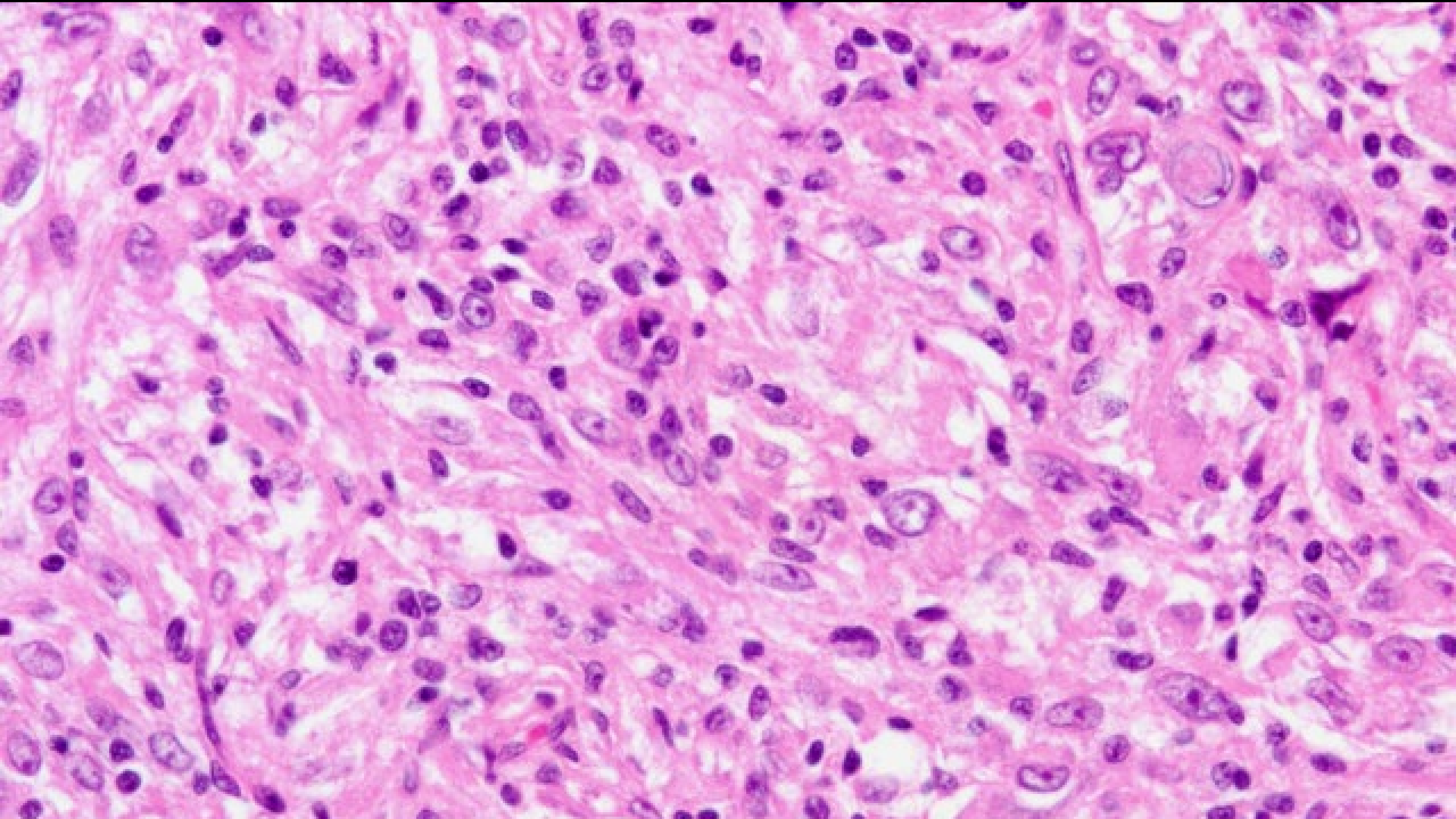
Cholangiocarcinoma

Conclusions – Cholangiocarcinoma Diagnosis

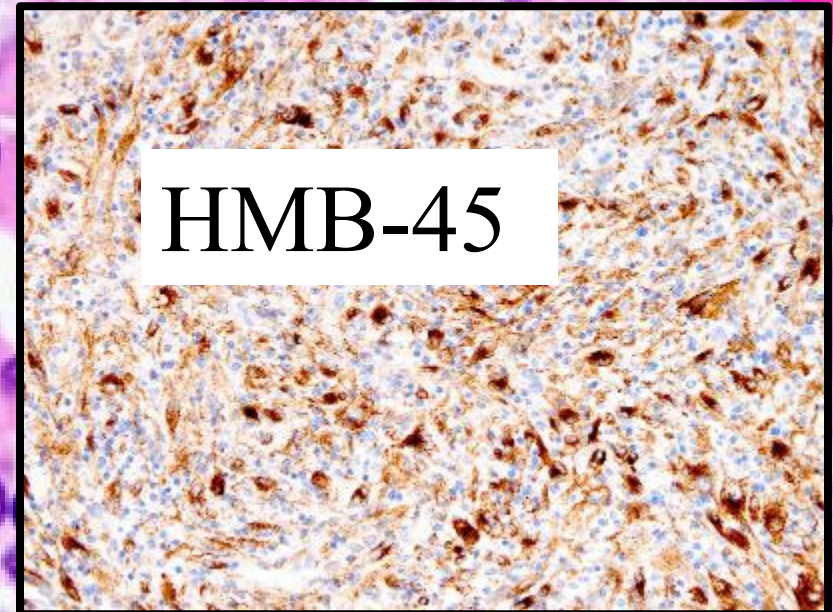
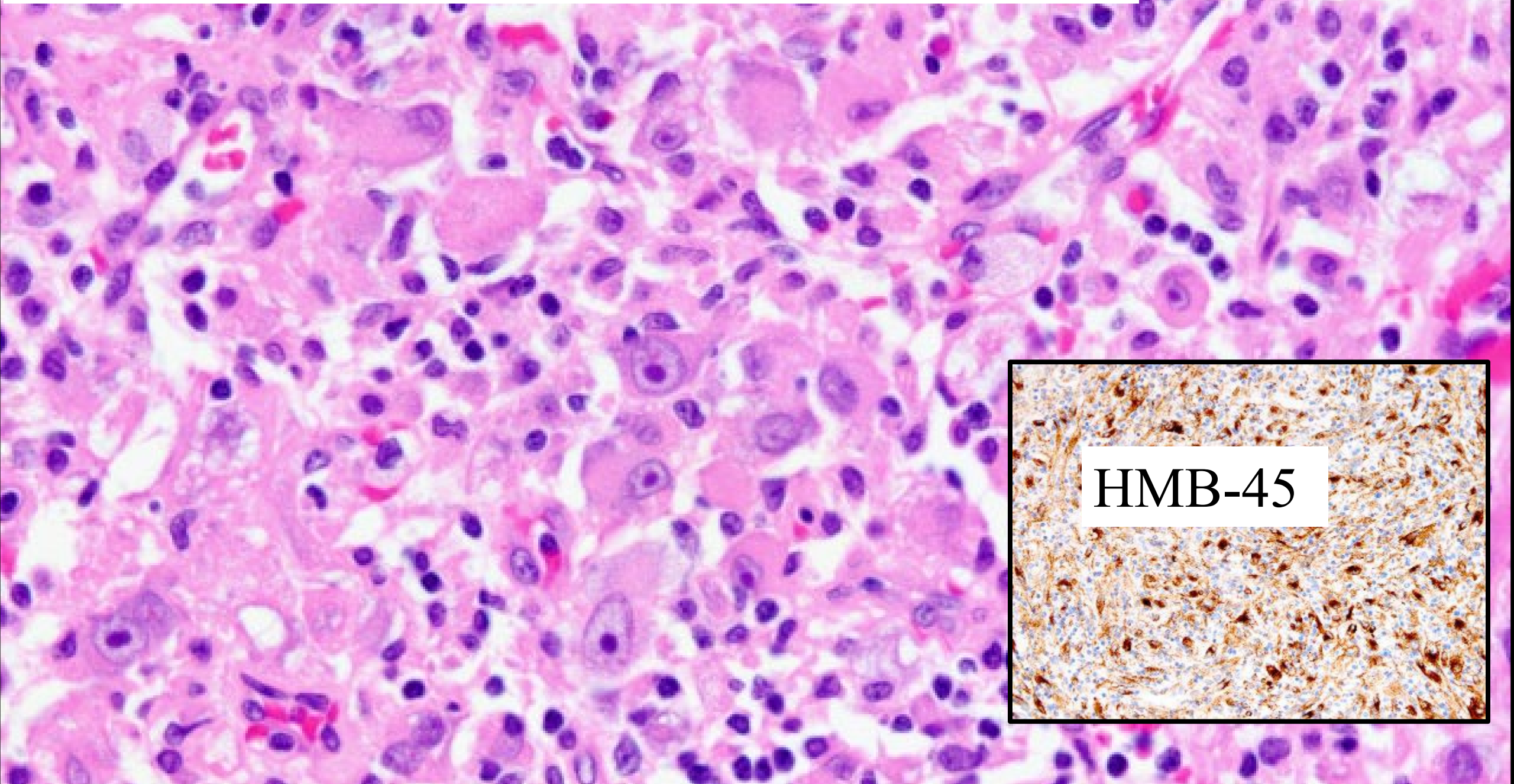
- Use limited immunohistochemical panel
- Keratin 7/19, TTF-1, CDX2
- Cholangiolar histology
- Save tissue for molecular studies



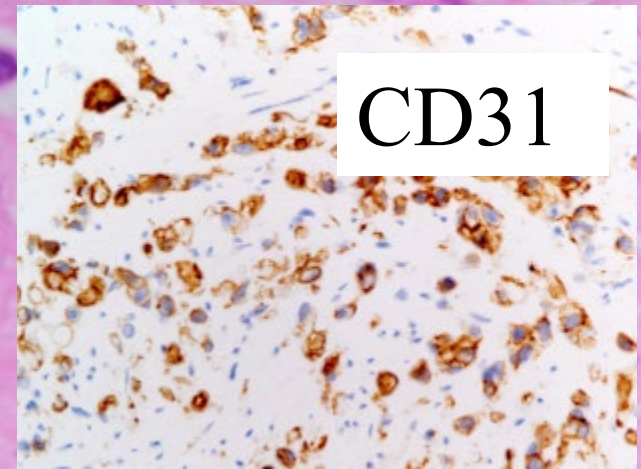
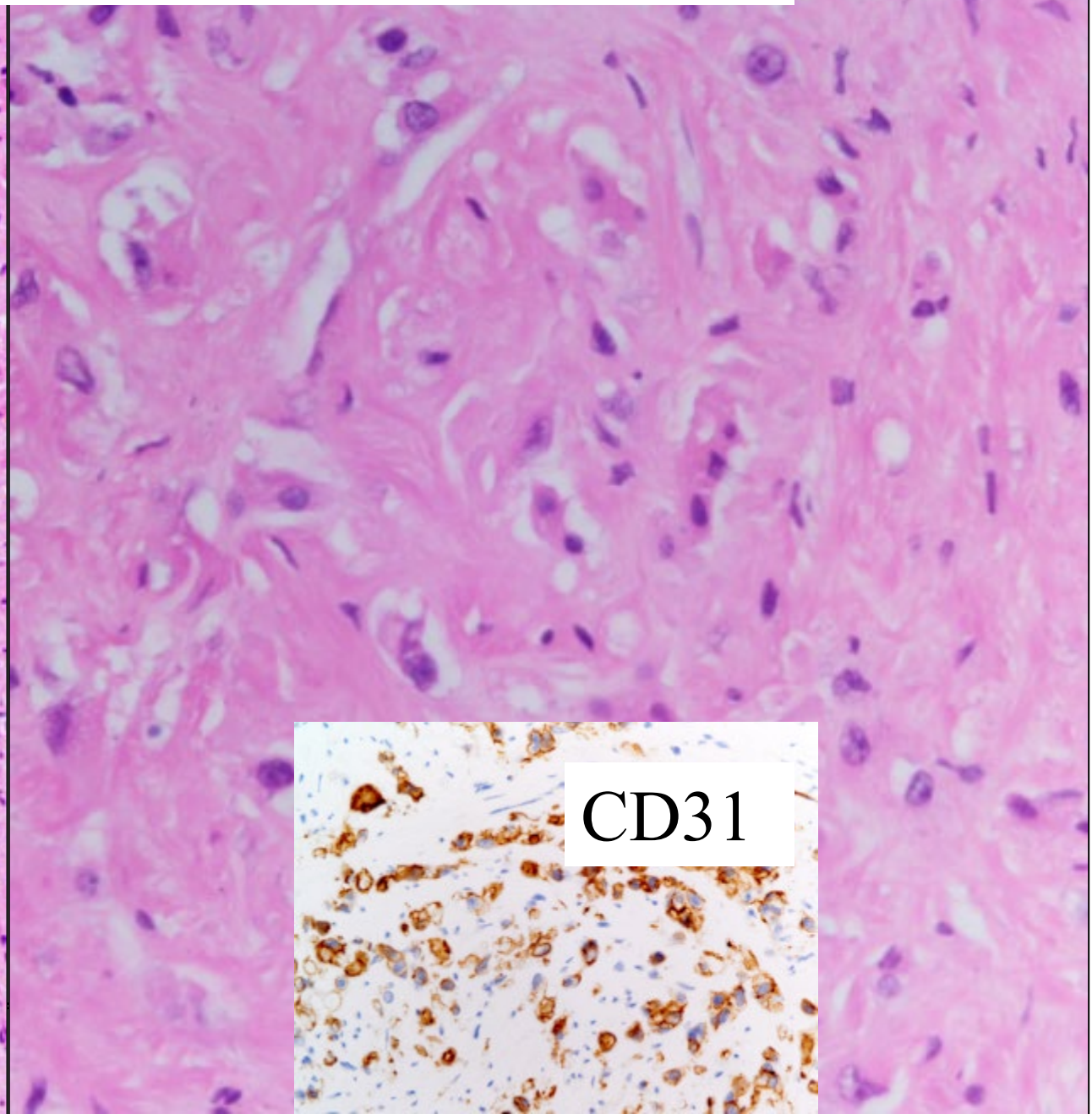
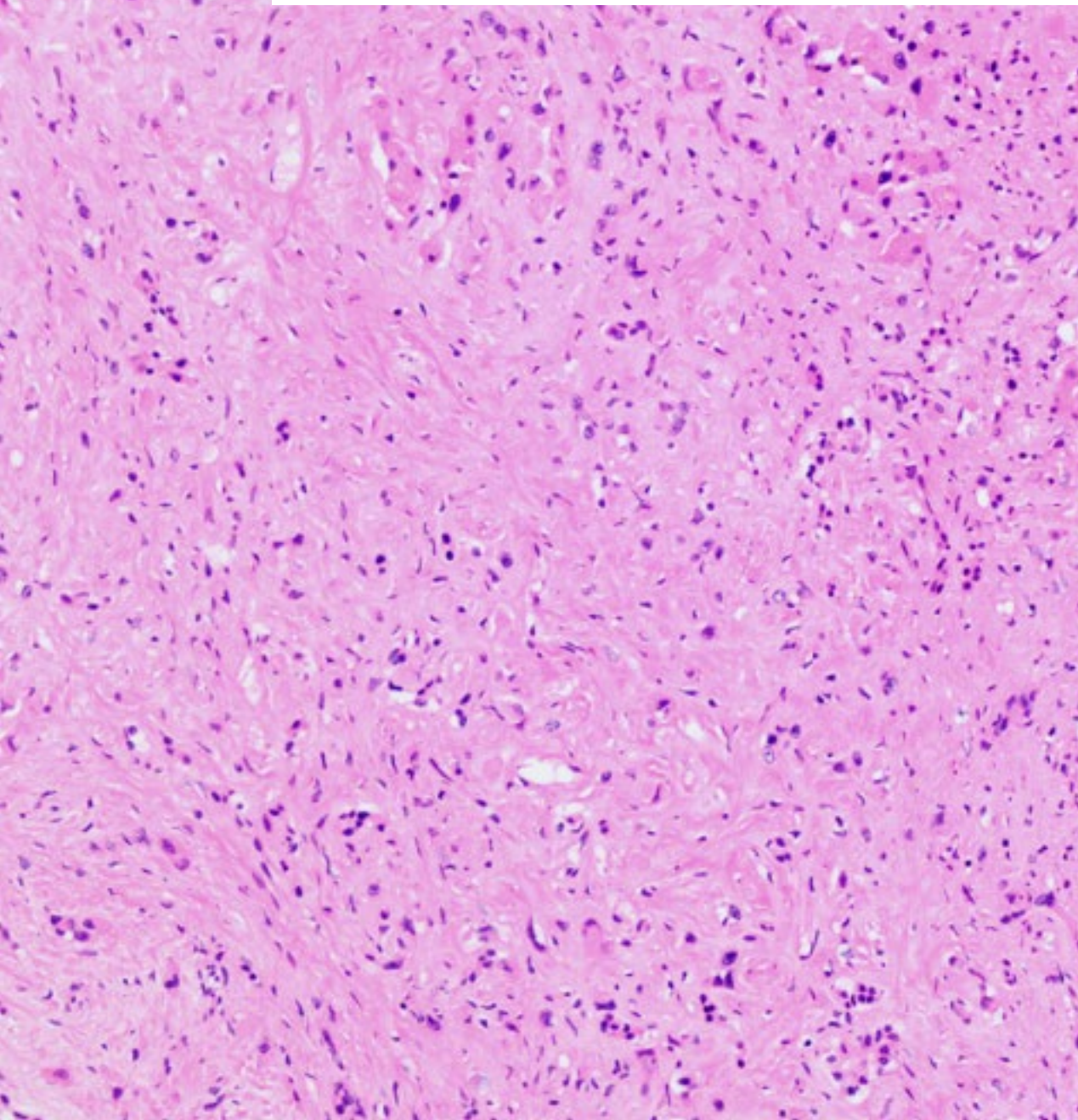
Question 6: Sure, looks hepatocellular carcinoma, but could I be missing something?



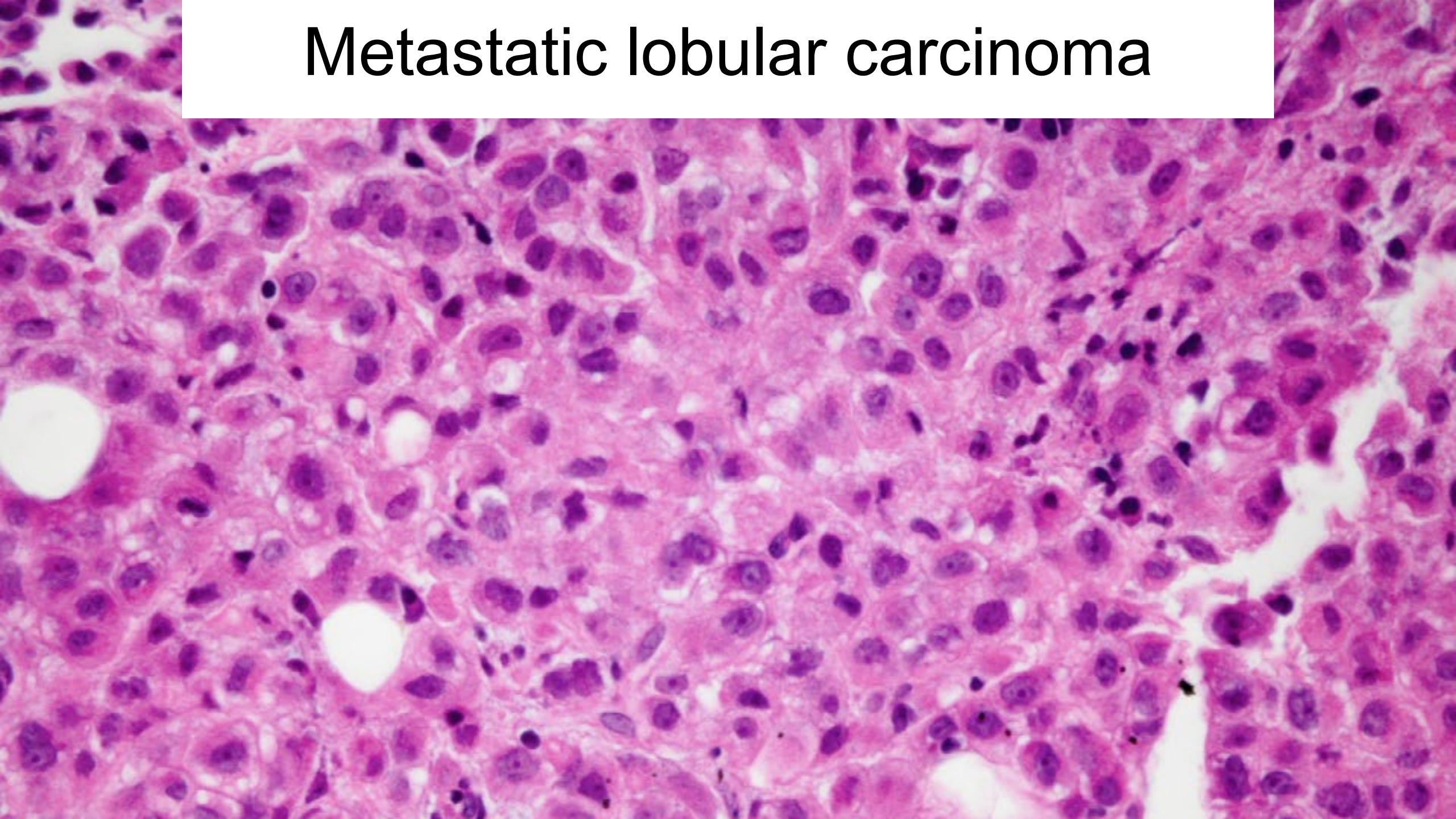
PEComa (Epithelioid angiomylipoma)



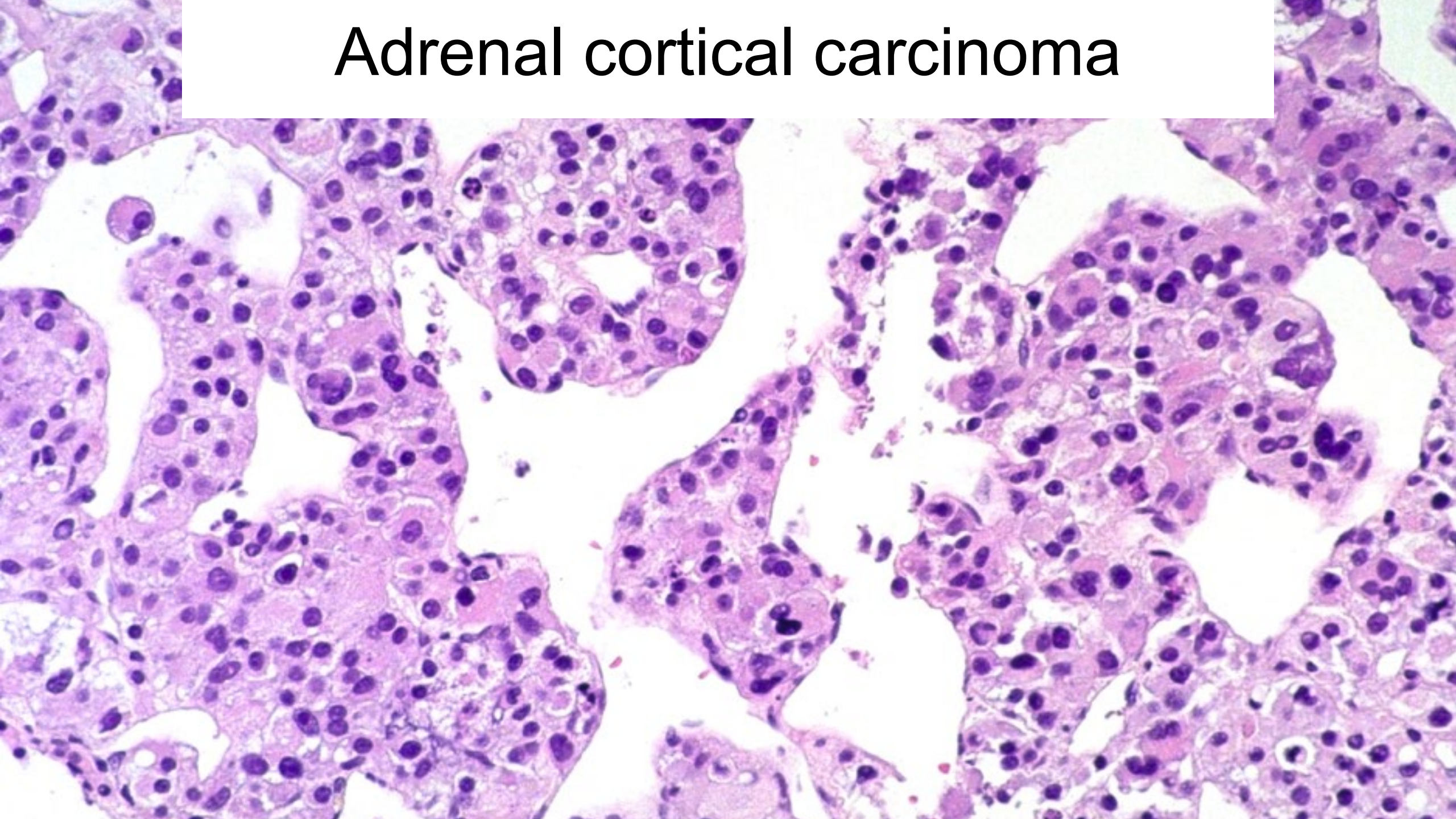
Epithelioid hemangioendothelioma



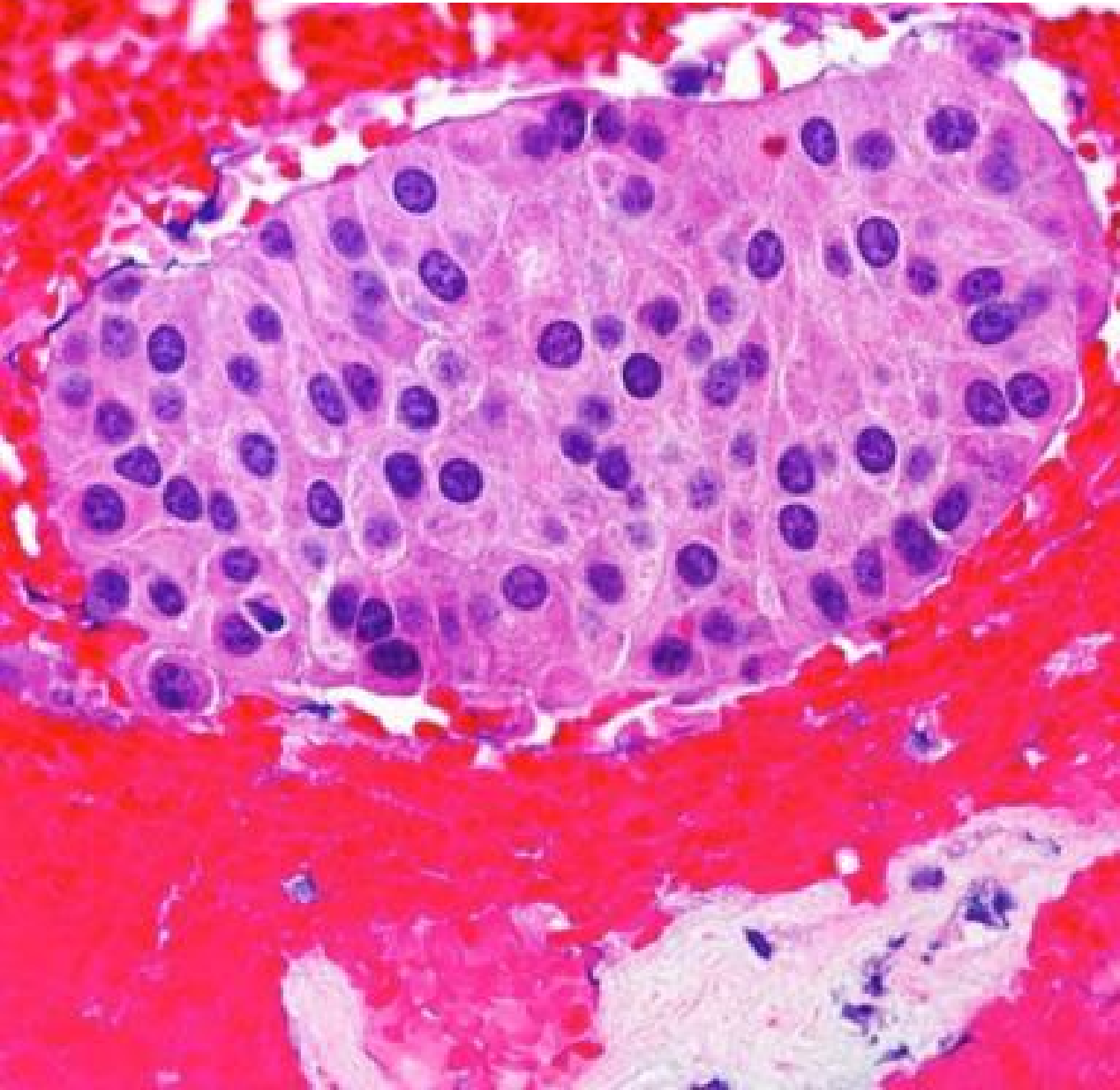
Metastatic lobular carcinoma



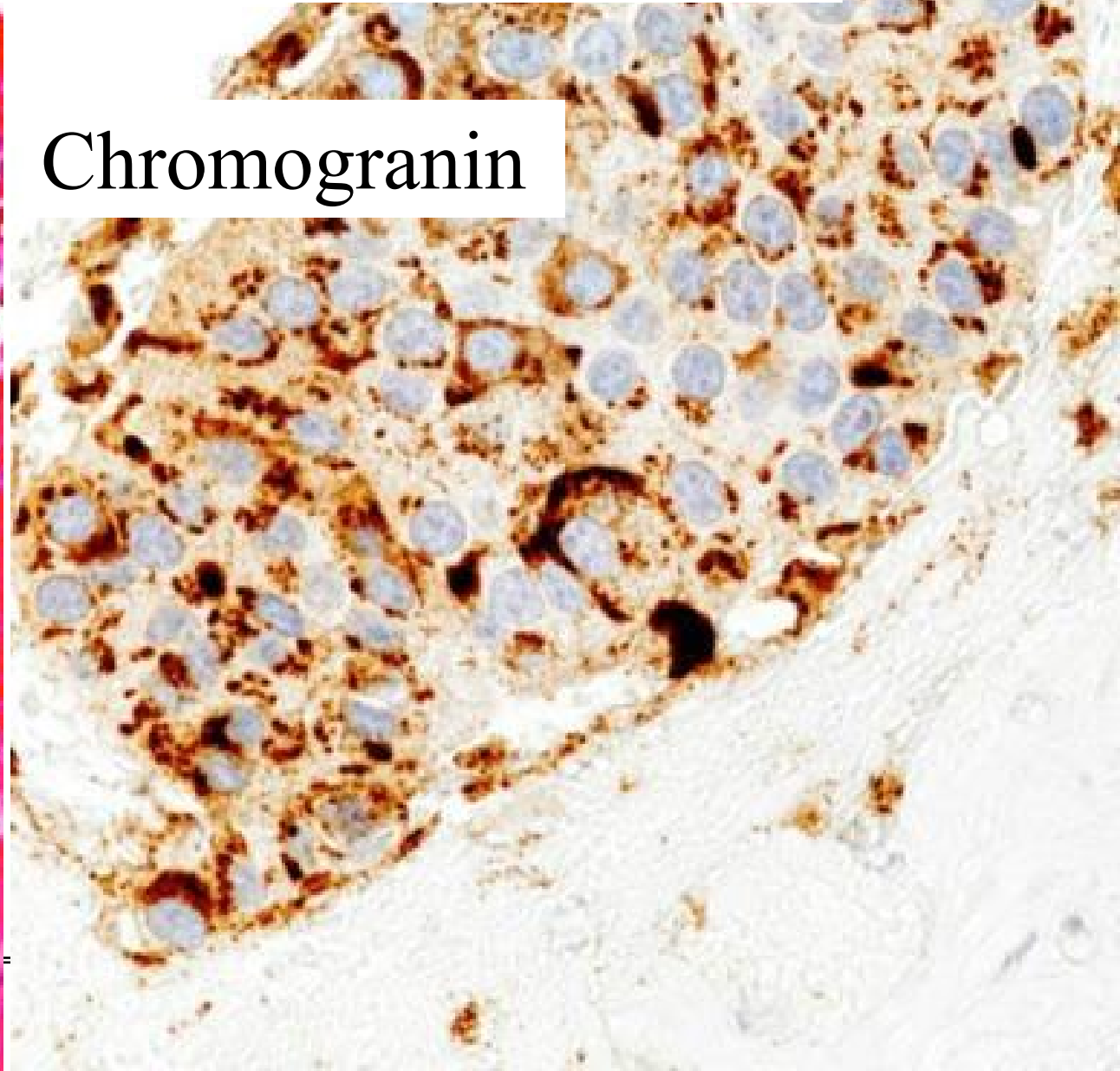
Adrenal cortical carcinoma

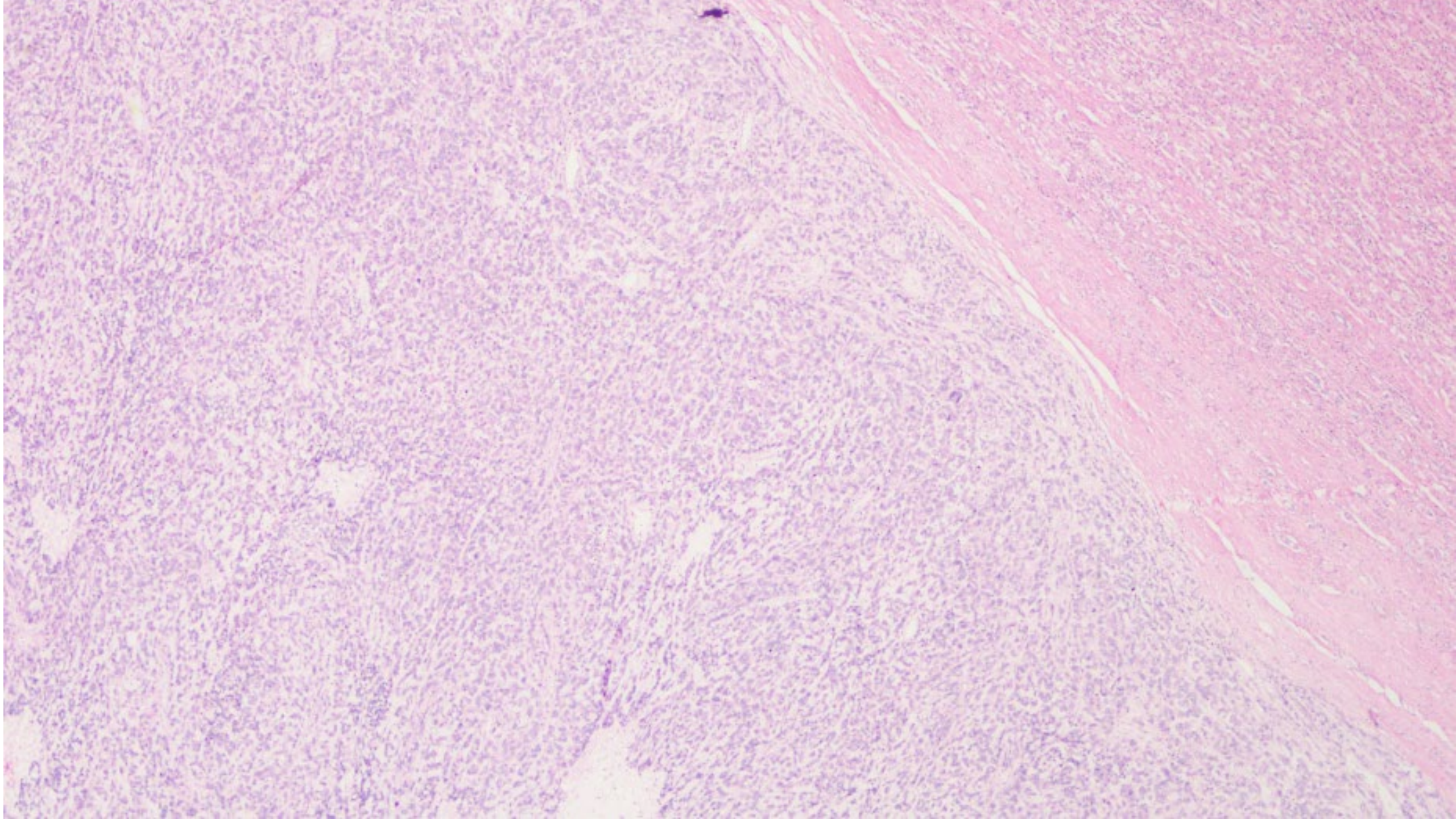


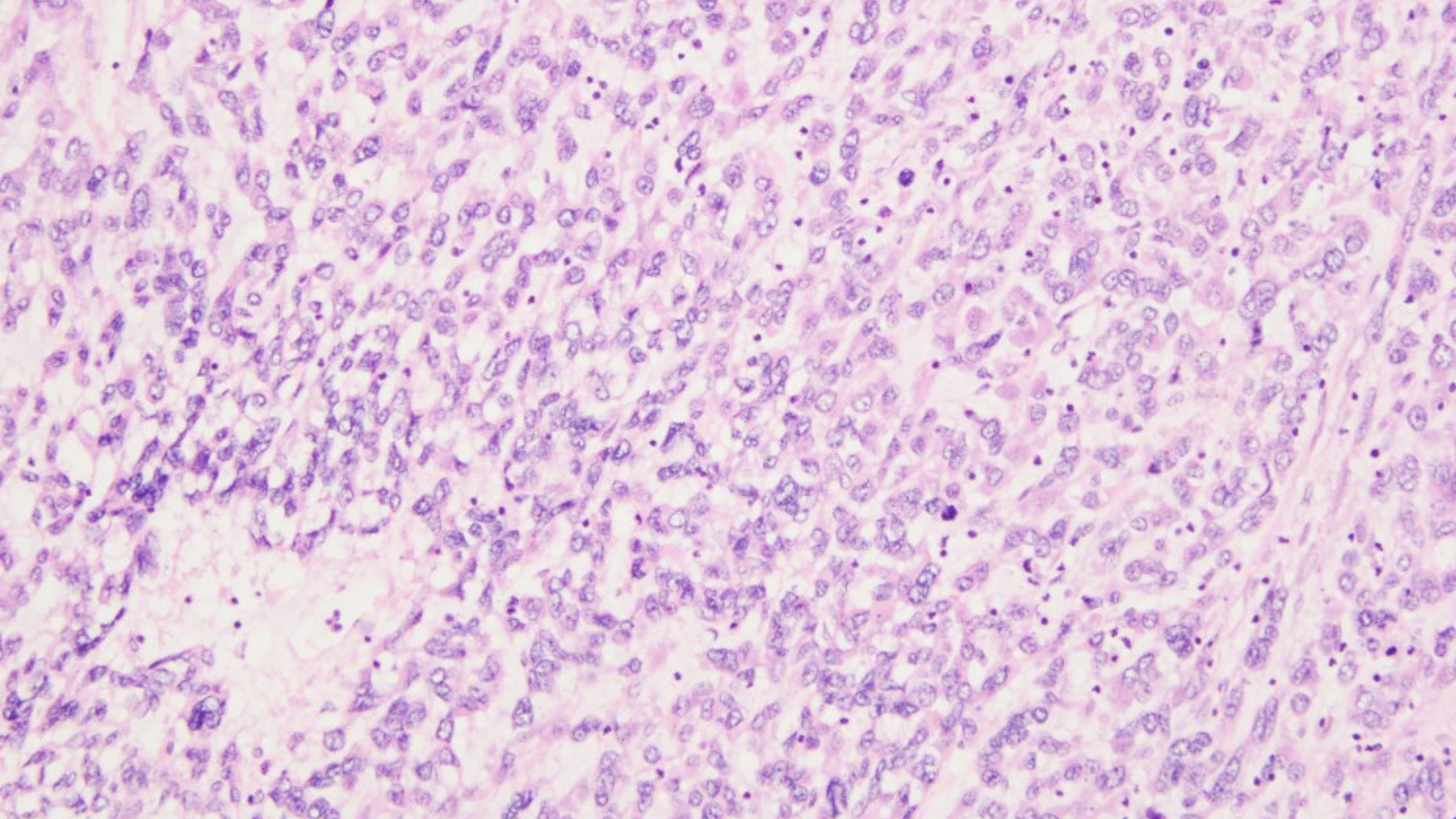
Pancreatic Endocrine Neoplasm

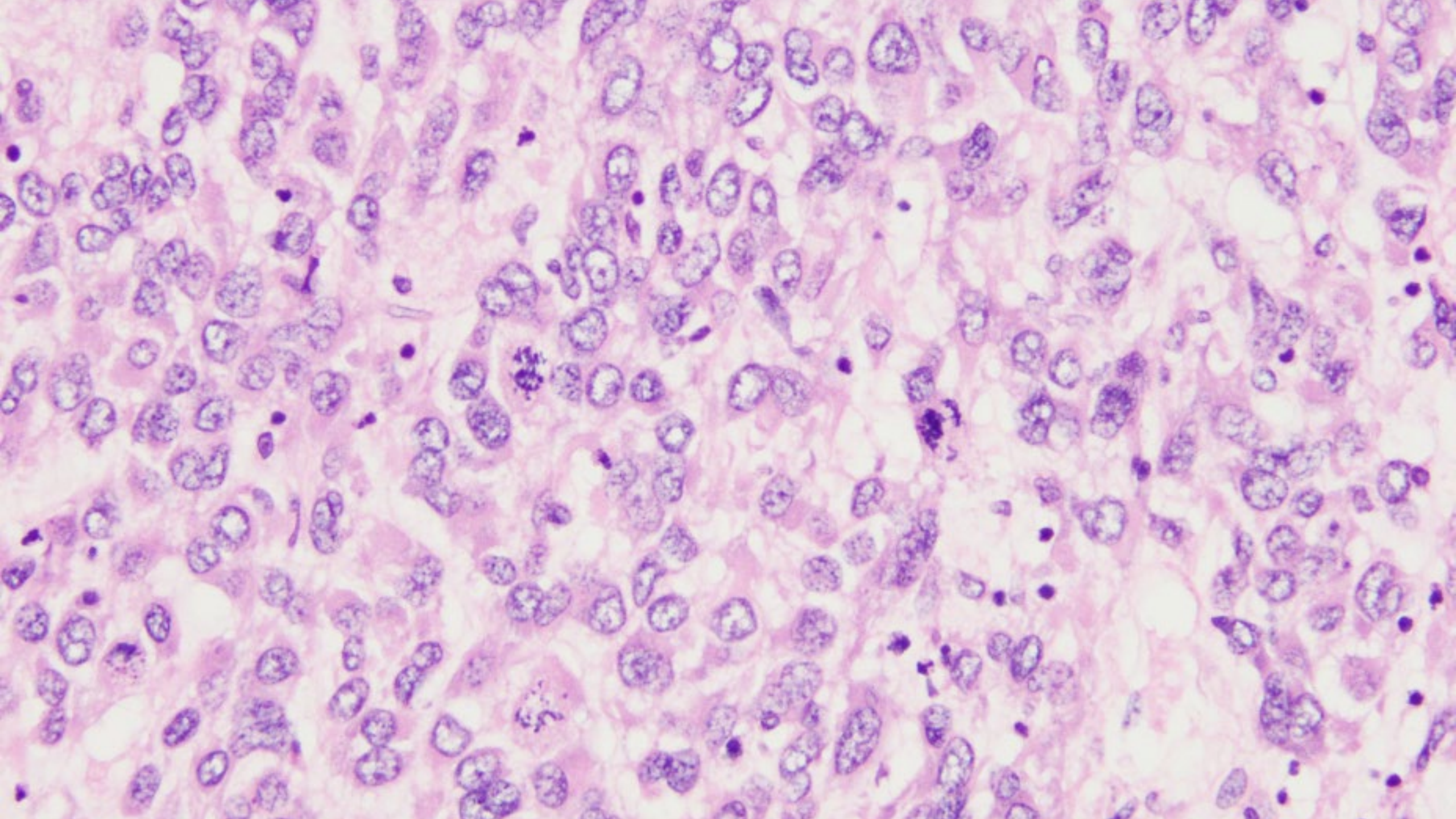


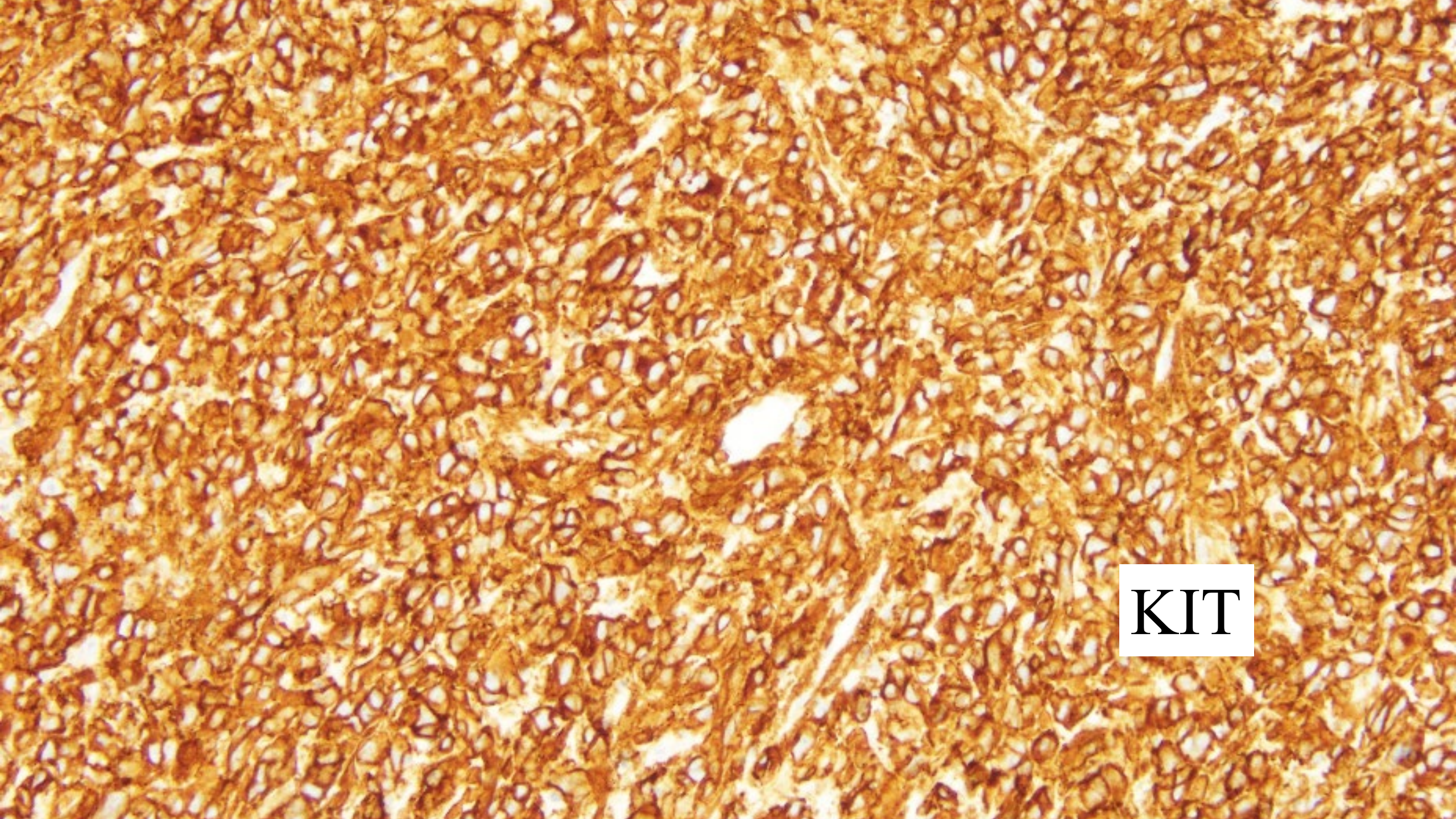
Chromogranin











KIT



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MASSACHUSETTS
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