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@Vik_Deshpande

Neoplasms of the Liver
Top challenges

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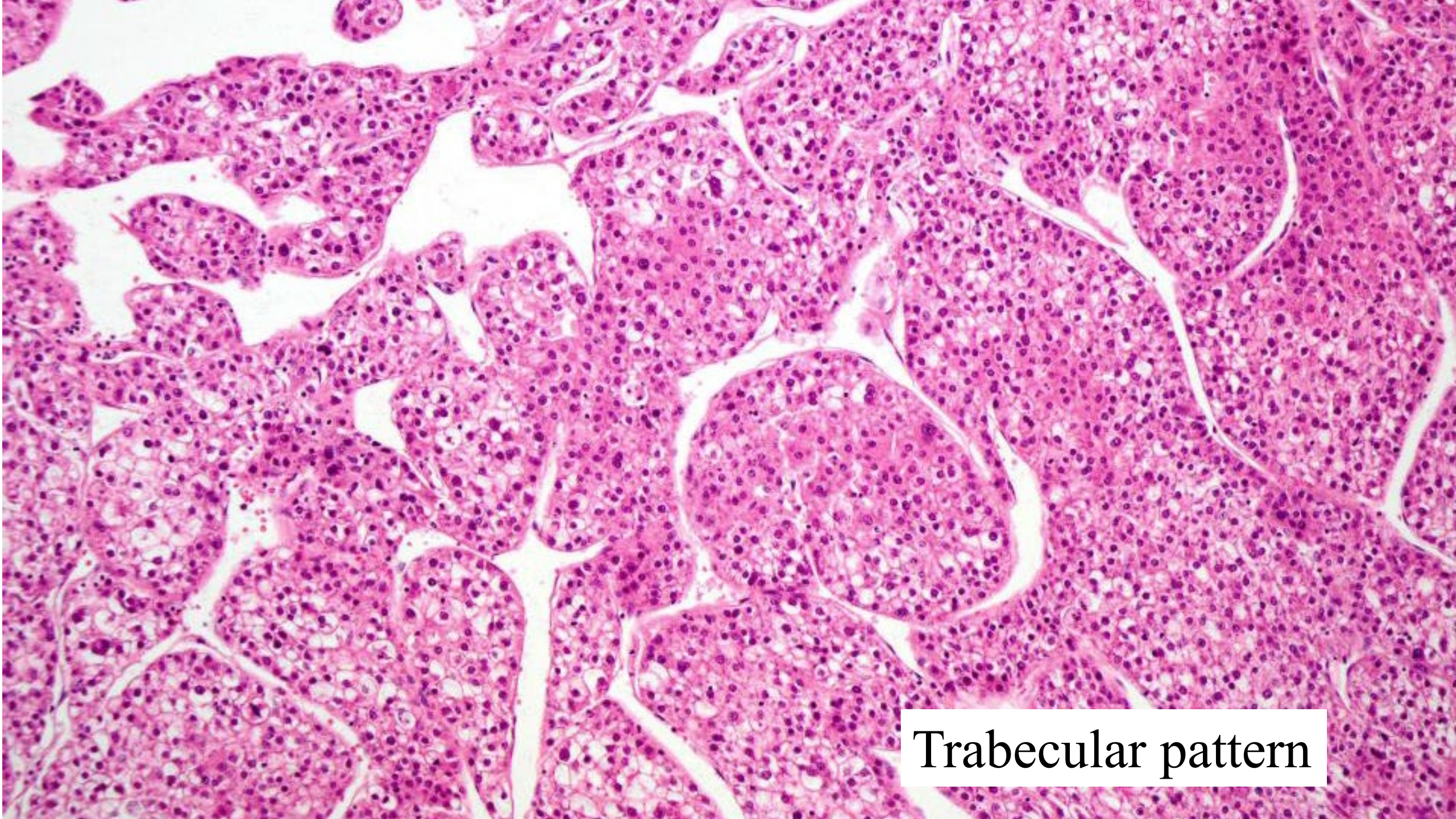
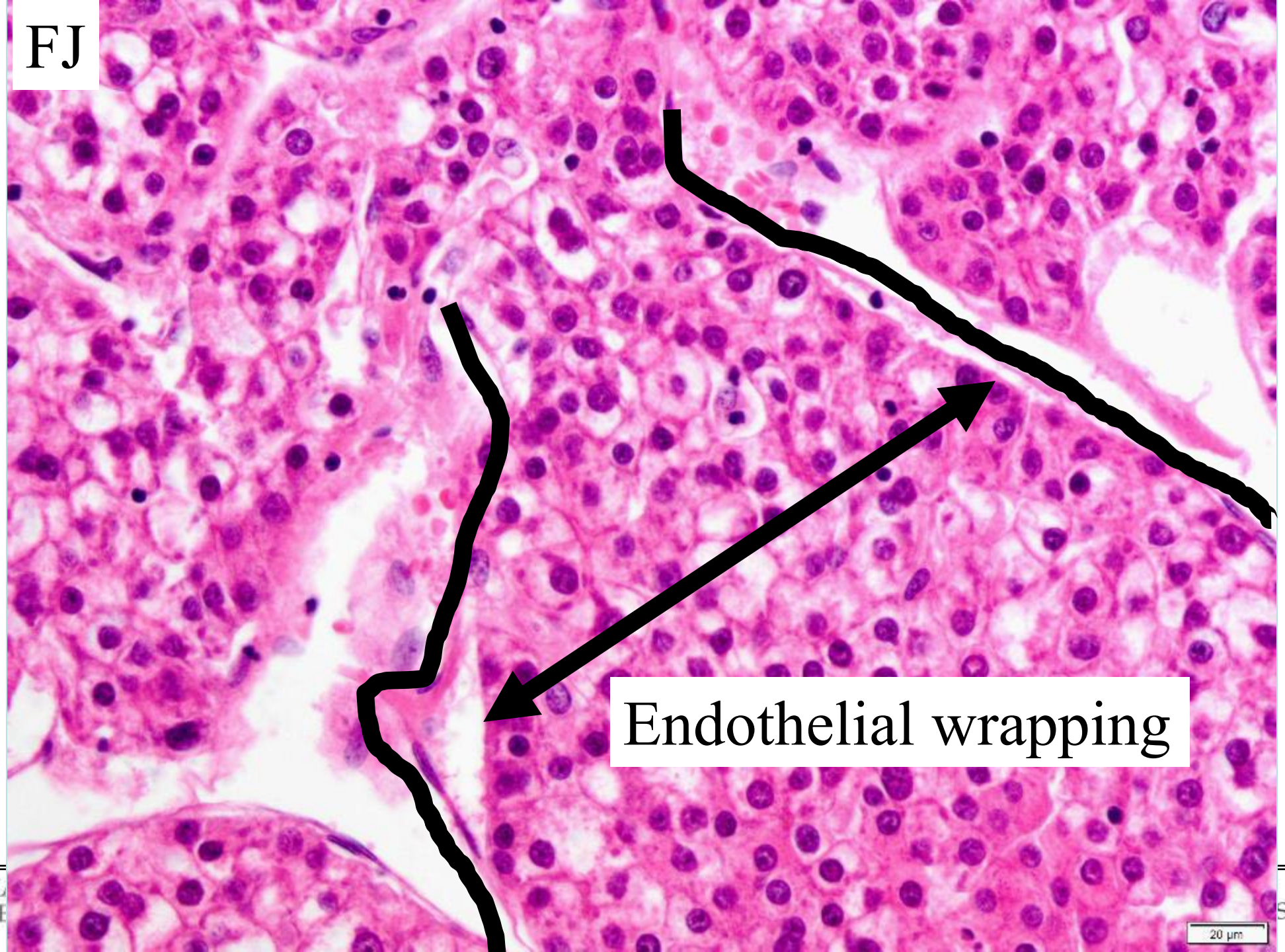
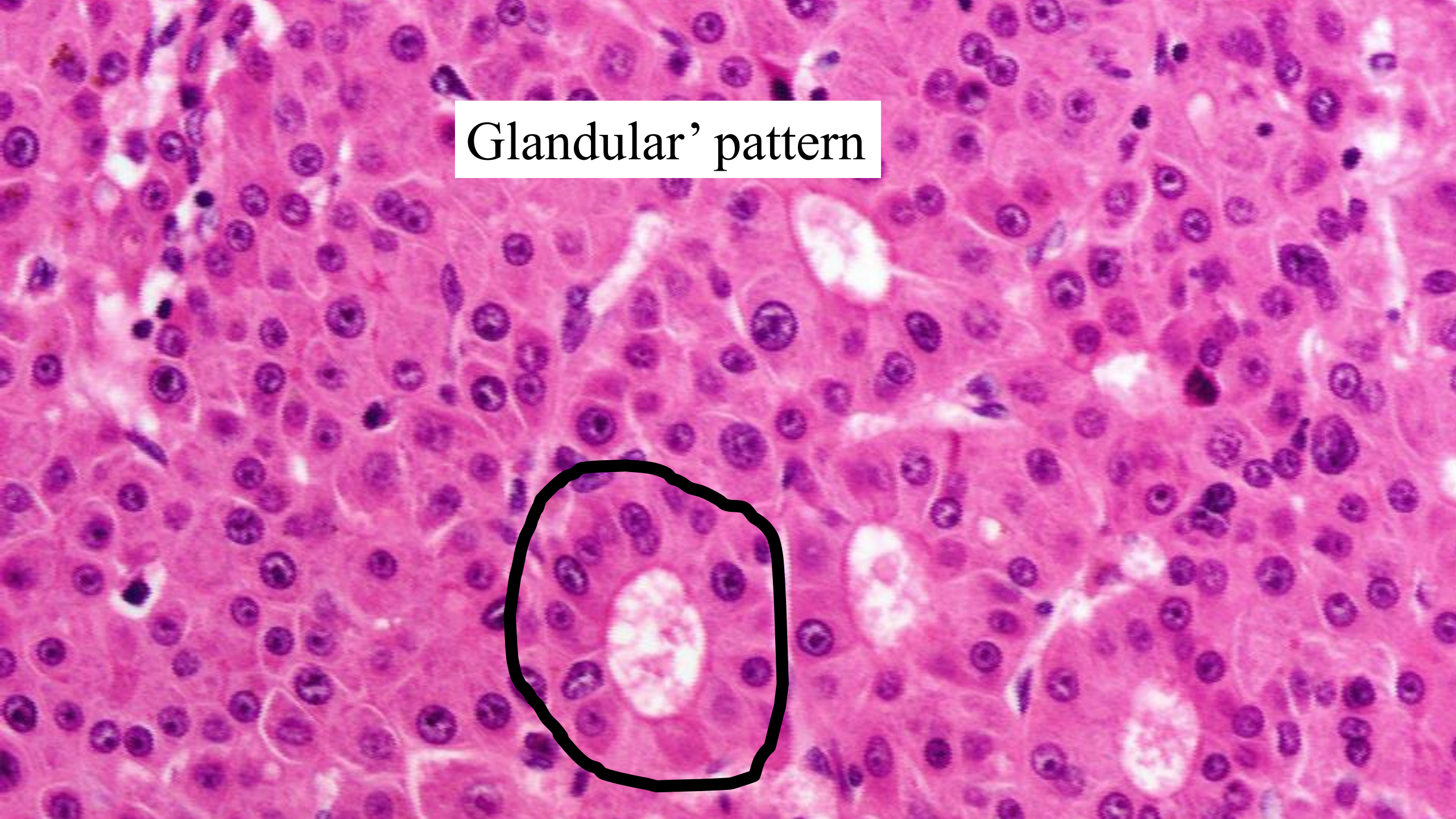
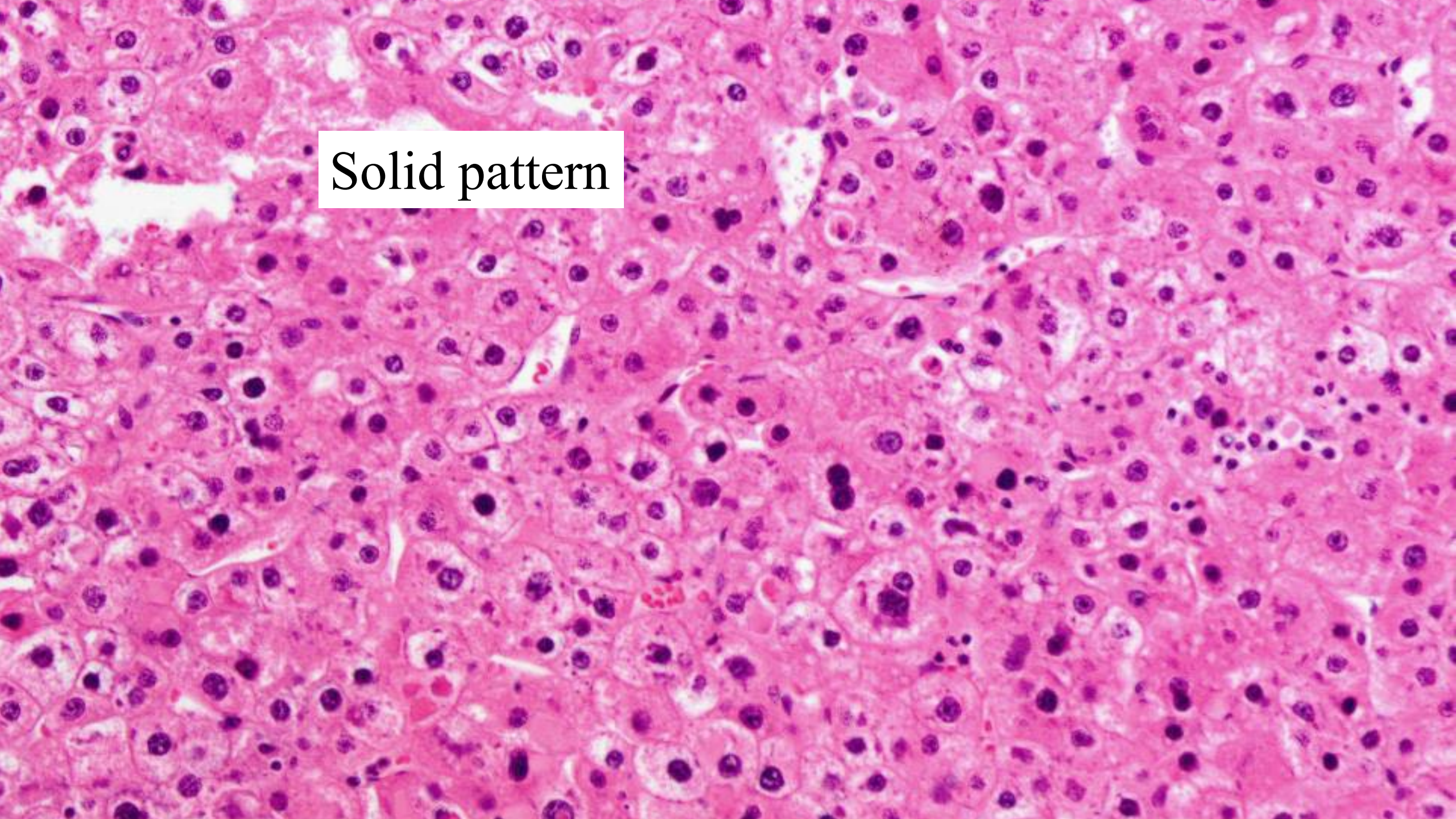
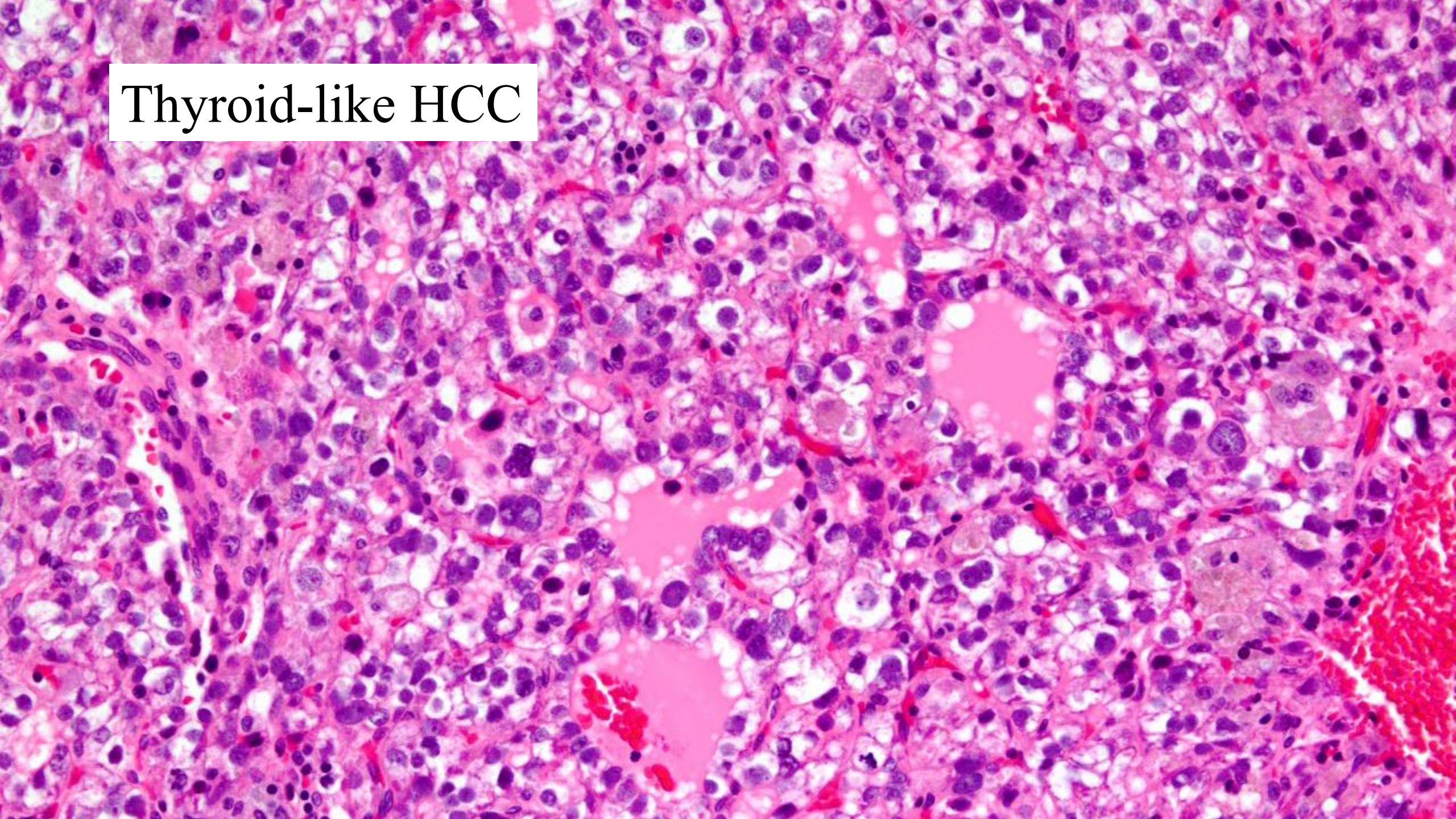
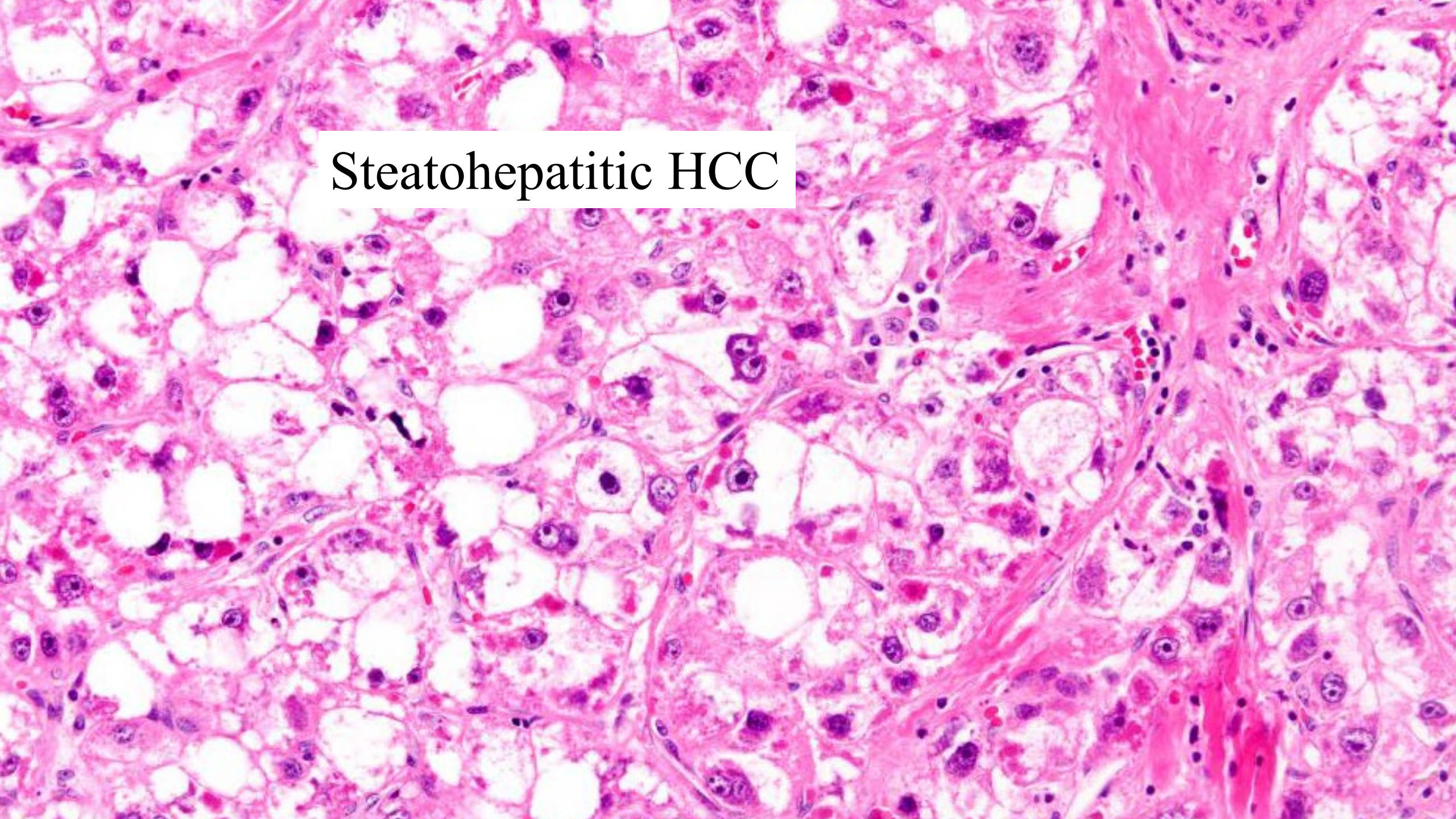

Trabecular pattern

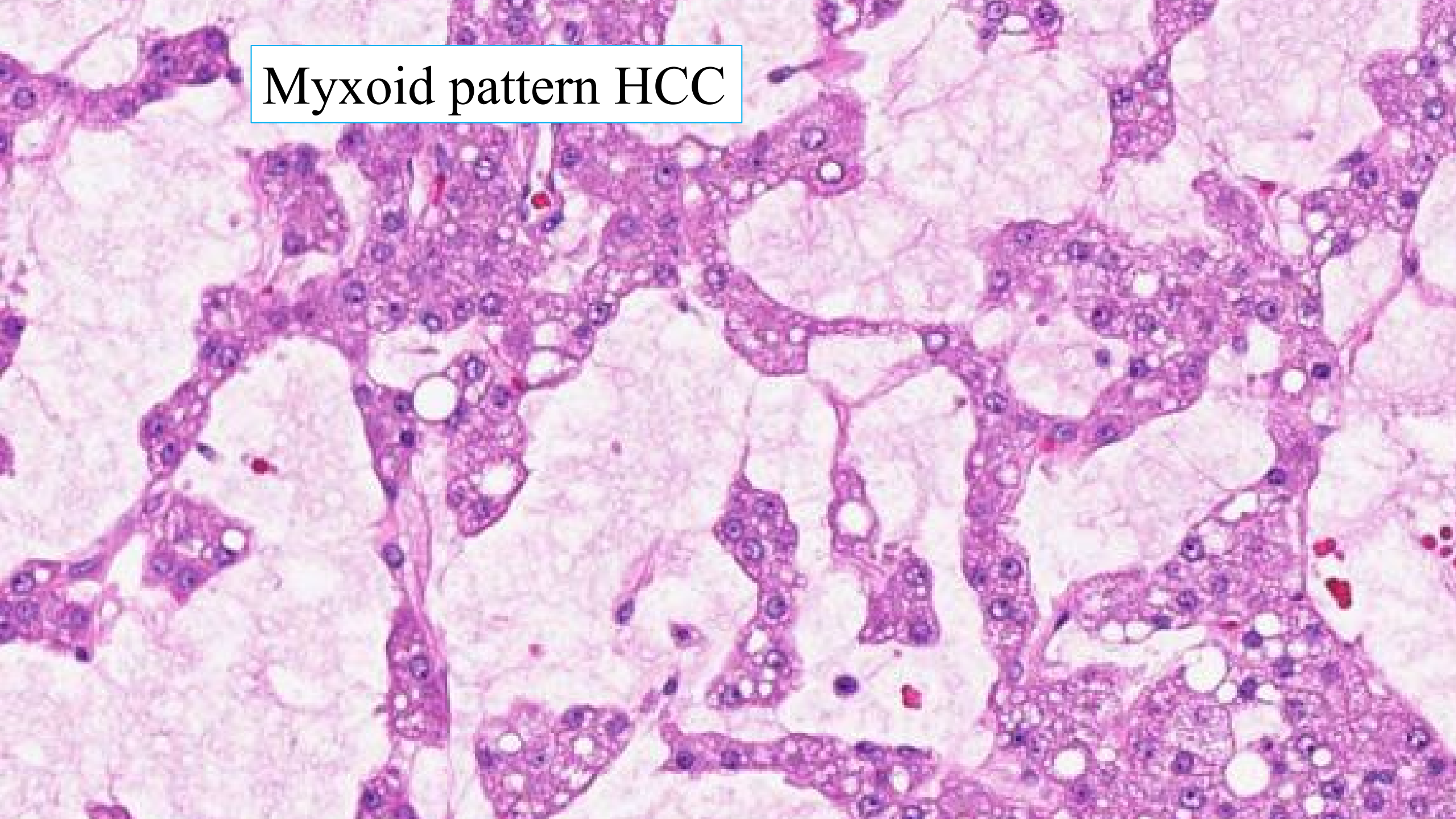

FJ
Endothelial wrapping
20 µm

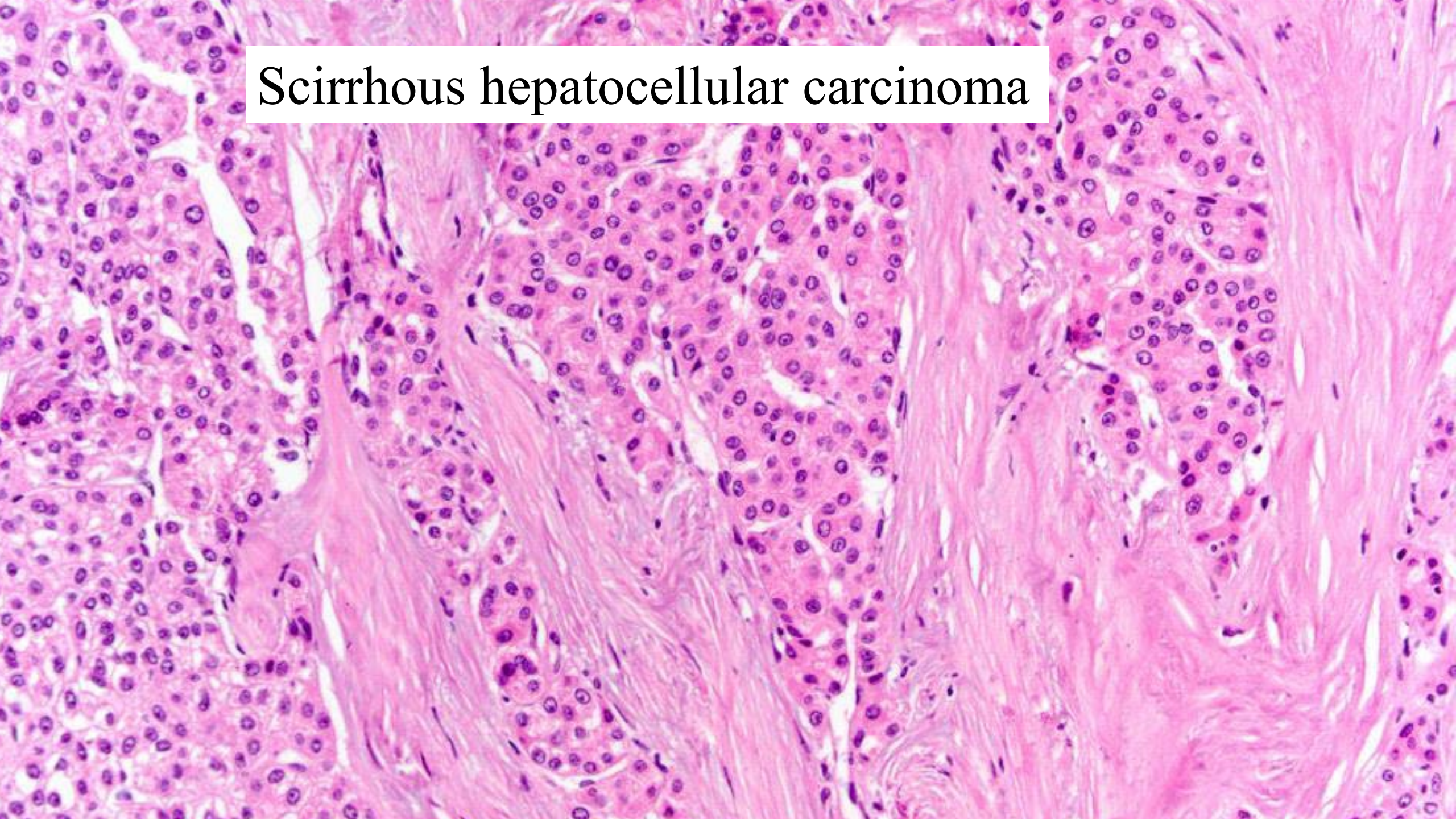

Glandular’ pattern


Solid pattern

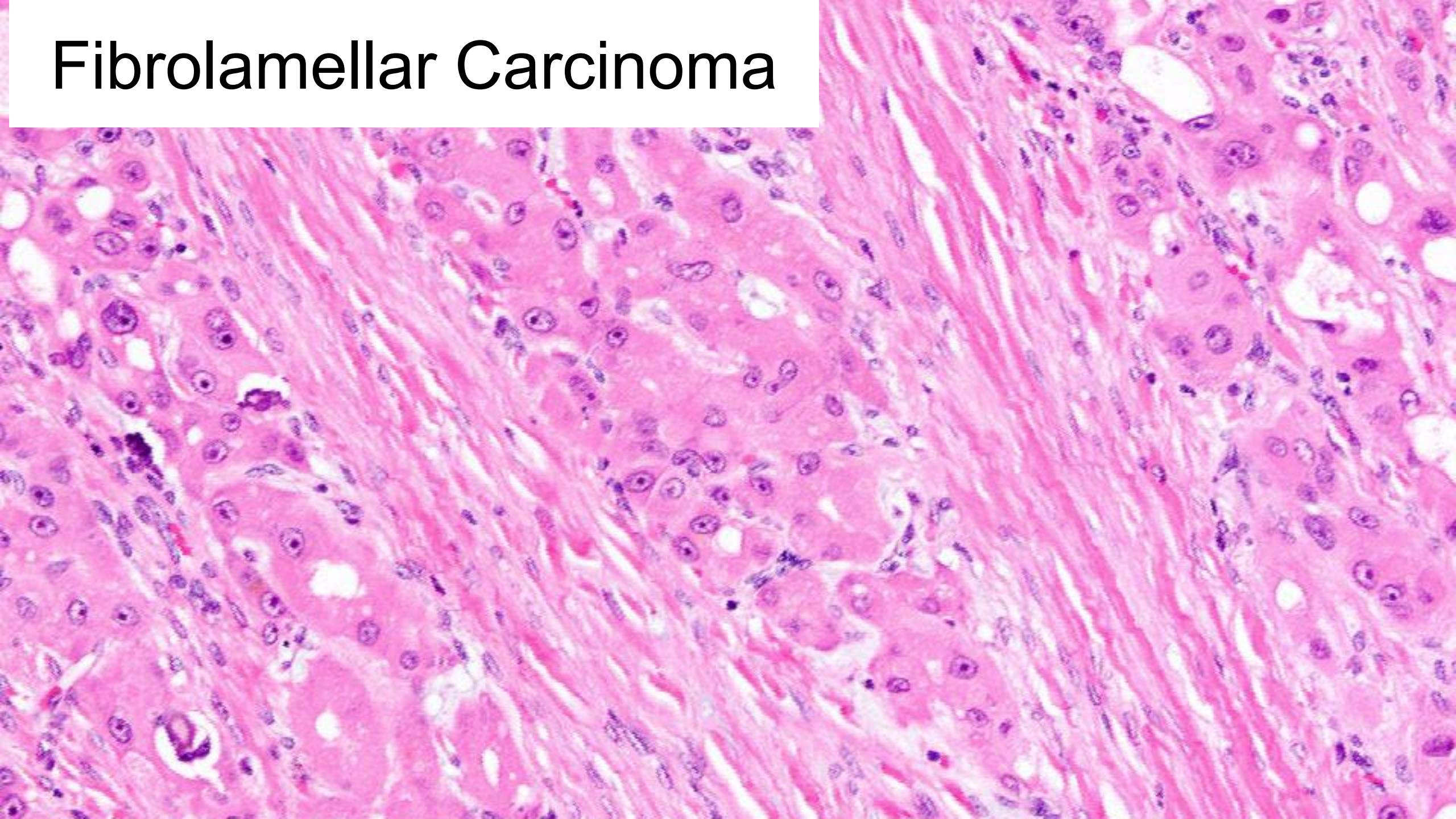

Thyroid-like HCC


Steatohepatitic HCC

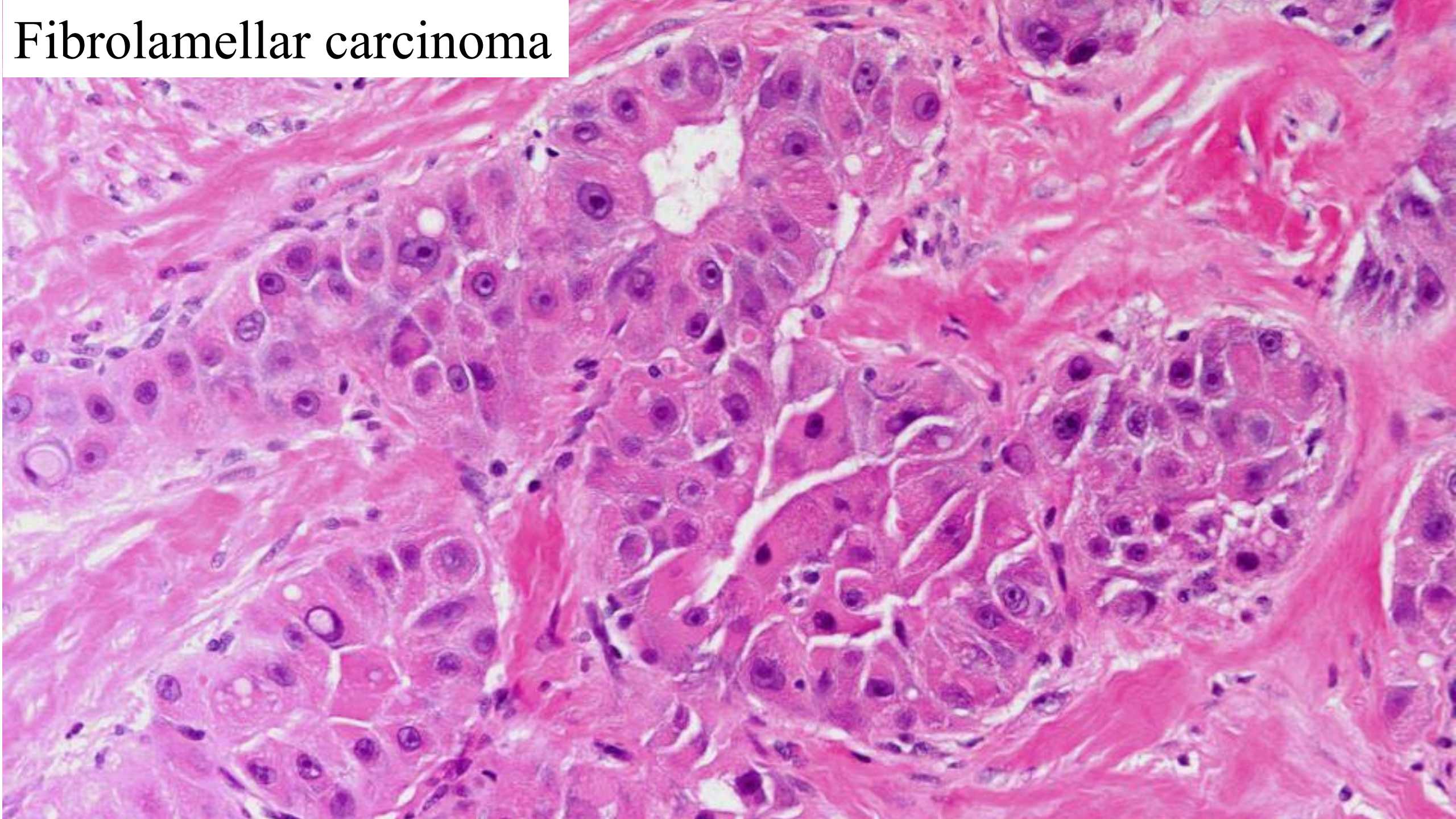

Myxoid pattern HCC


Scirrhous hepatocellular carcinoma

Fibrolamellar Carcinoma



Fibrolamellar carcinoma



Diagnostic Assays for Fibrolamellar Carcinoma

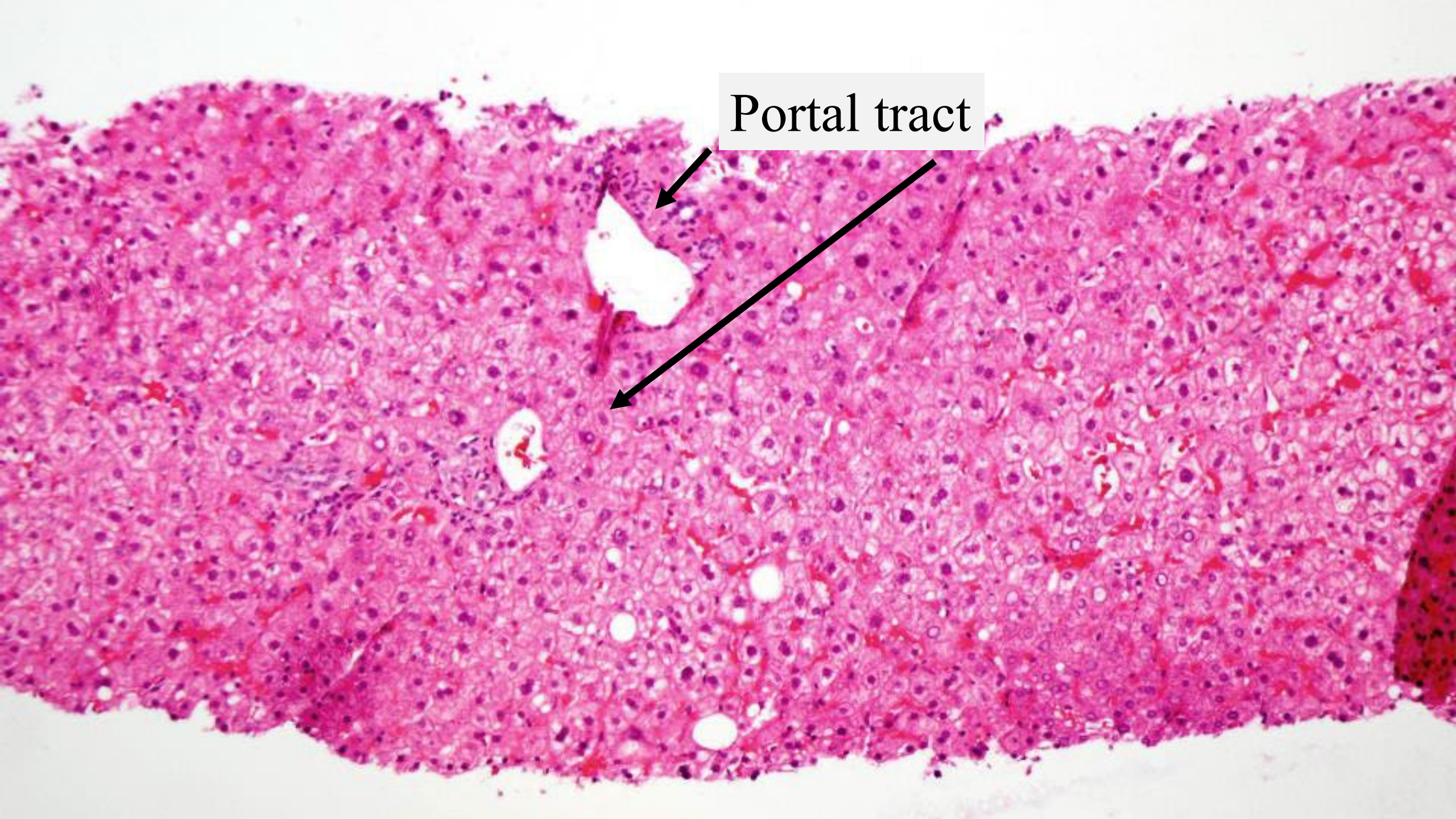
- Combined presence of CD68 and keratin 7
  - Unusual in conventional hepatocellular carcinoma

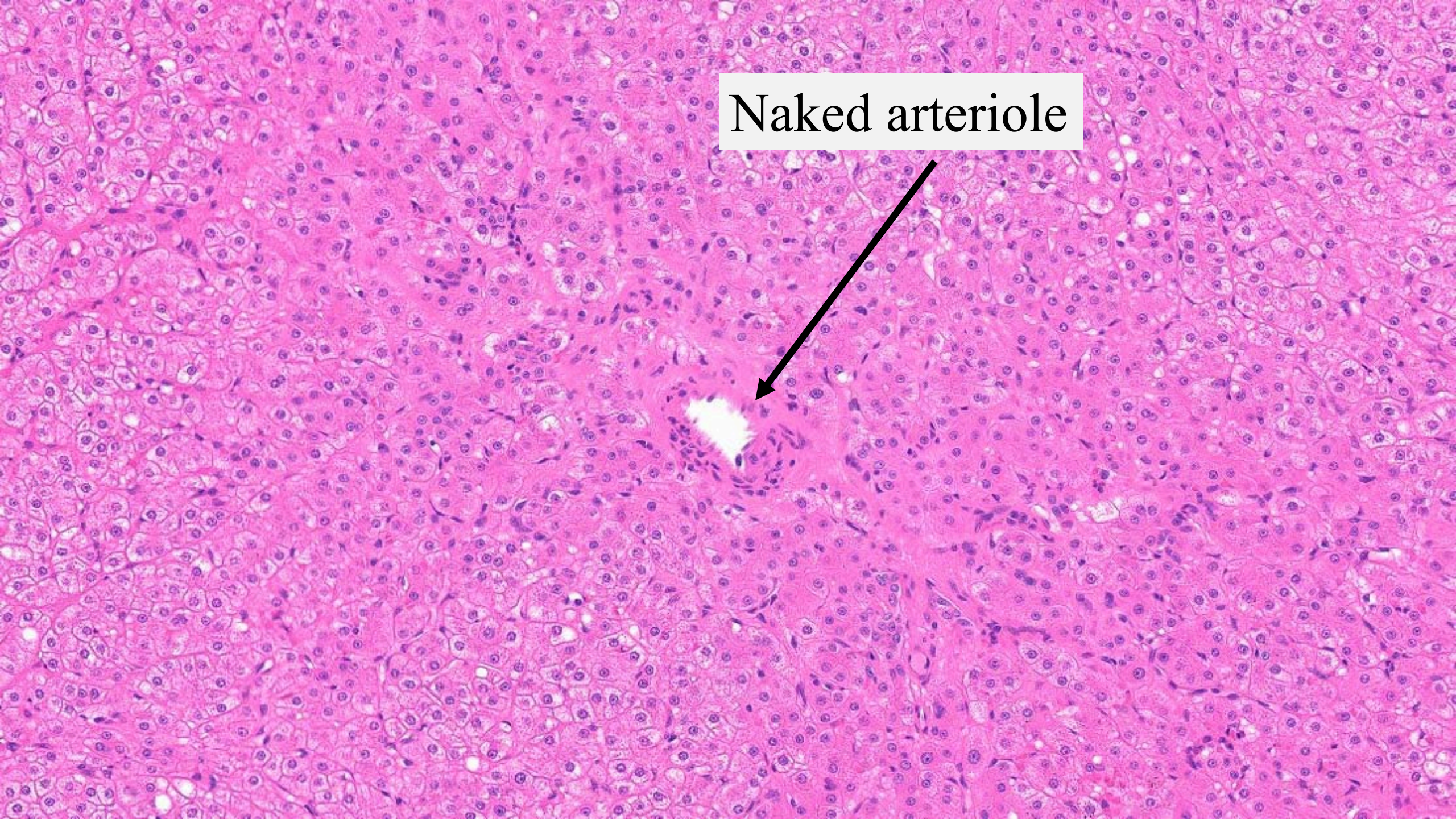
KP1 clone

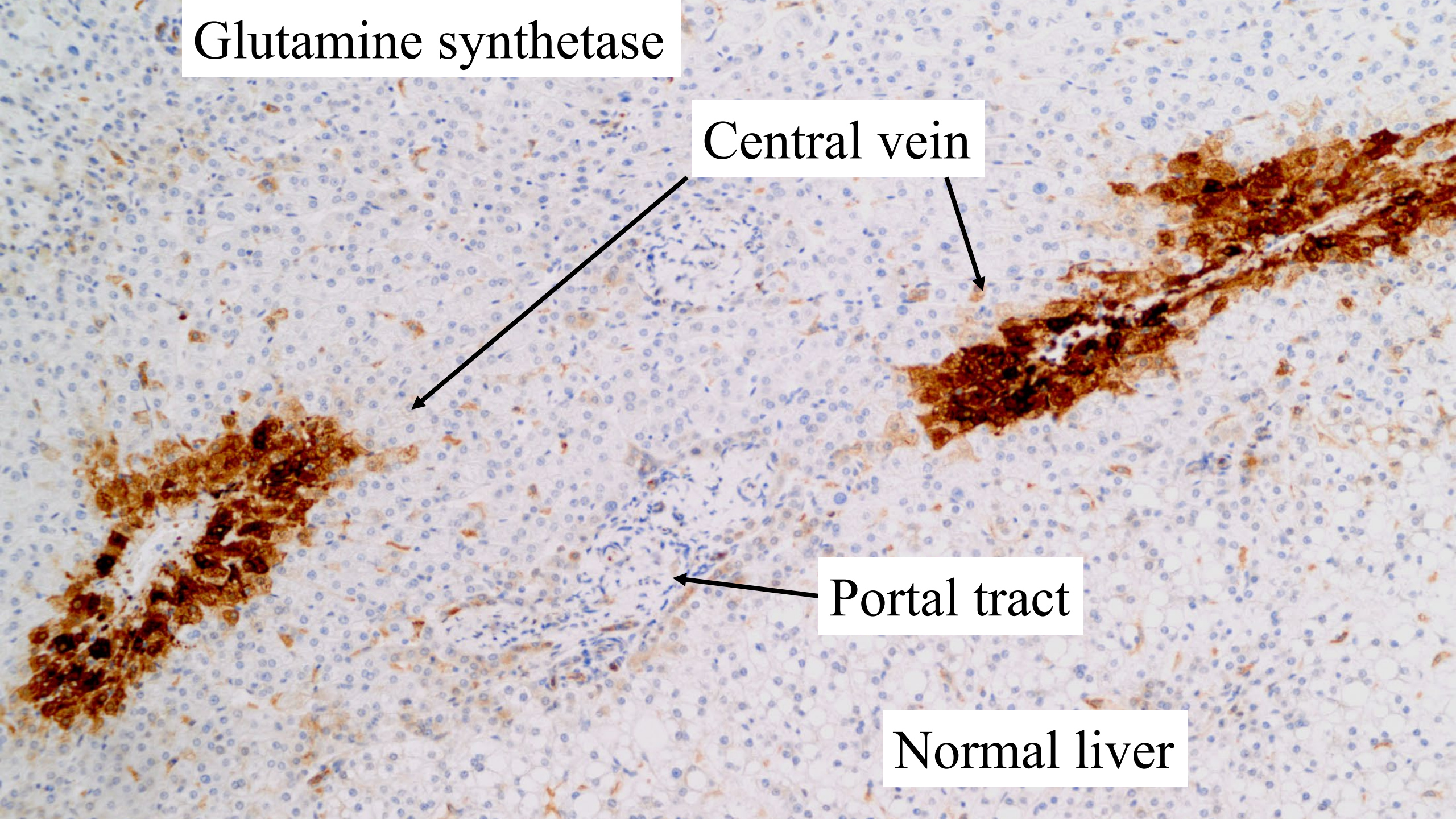
- FISH/fusion assay for DNAJB1-PRKACA fusion

Problem 1

Did the radiologist miss the lesion?


Portal tract

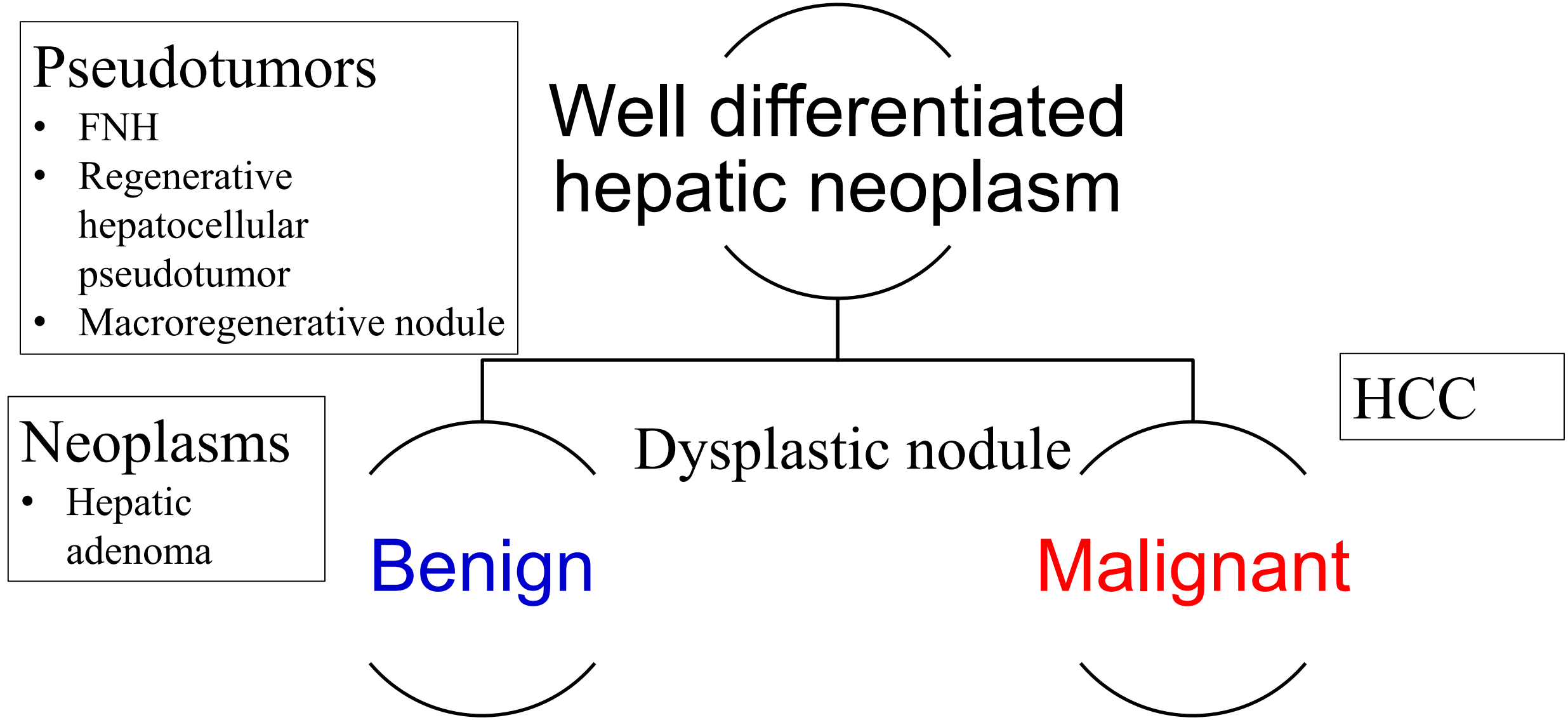

Naked arteriole


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
Neoplasms
• Hepatic adenoma
Dysplastic nodule
HCC
Benign
Malignant

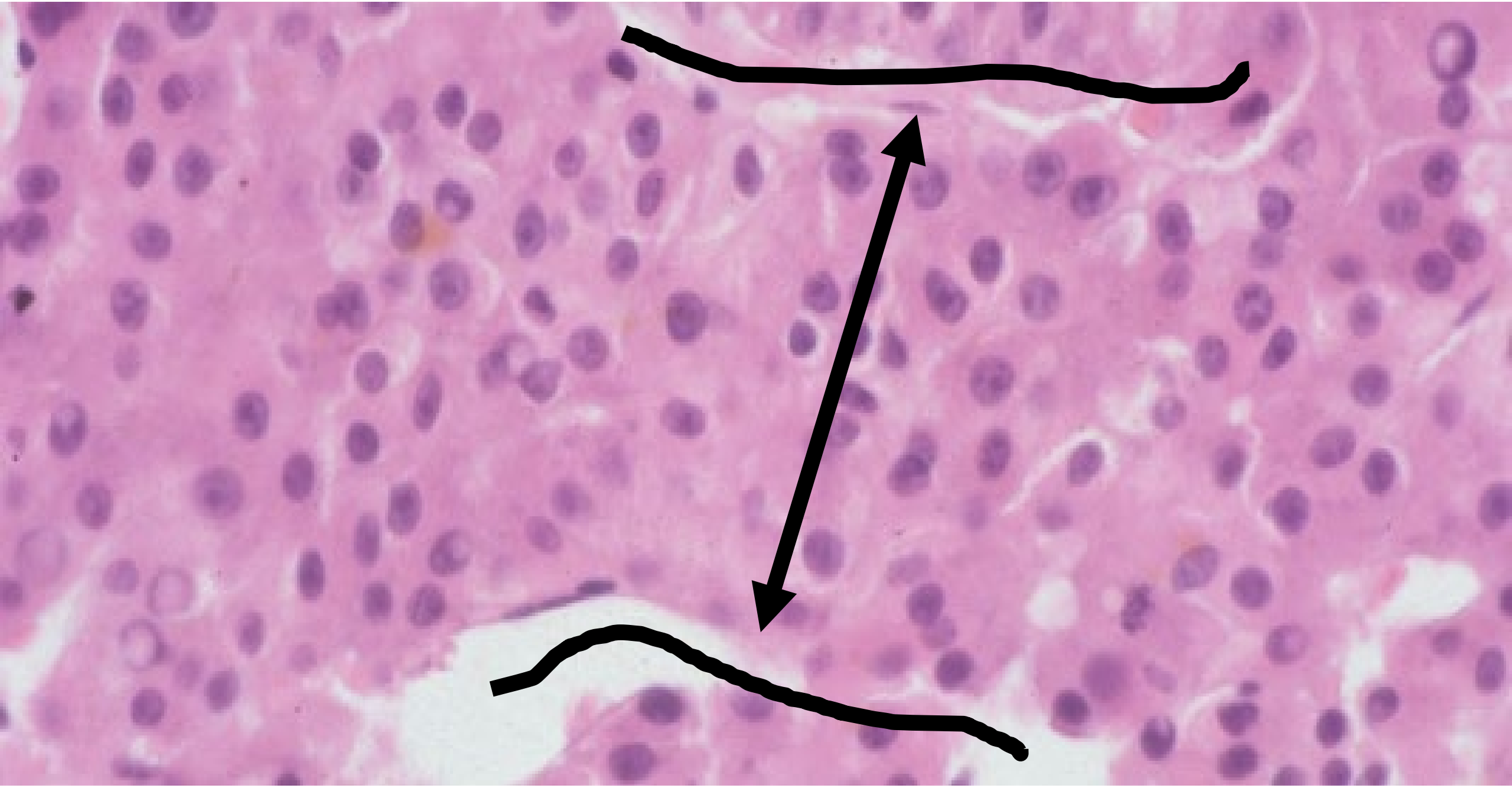
HCC vs Benign Hepatic Proliferation

	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%

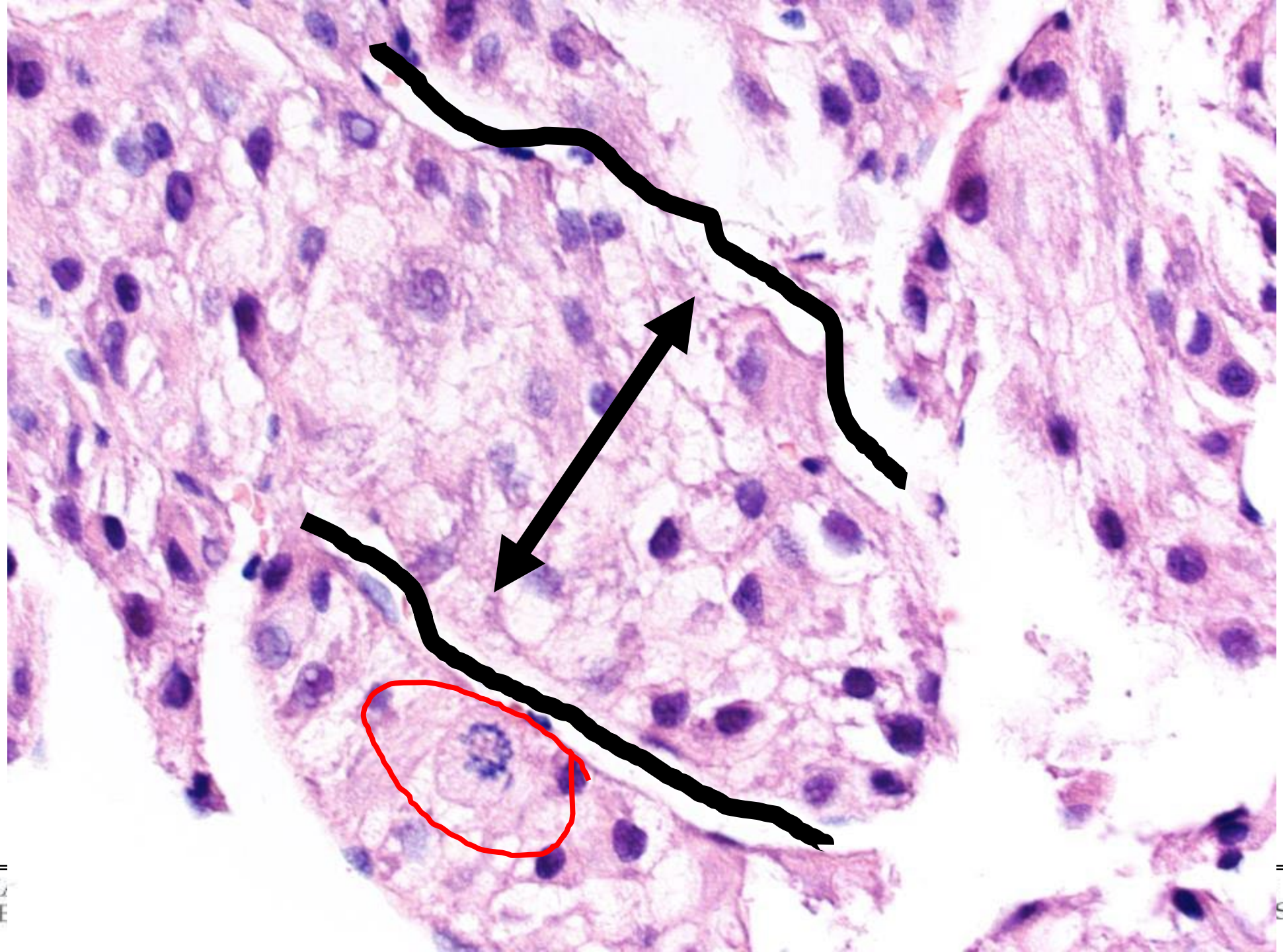
Ki67, CD34

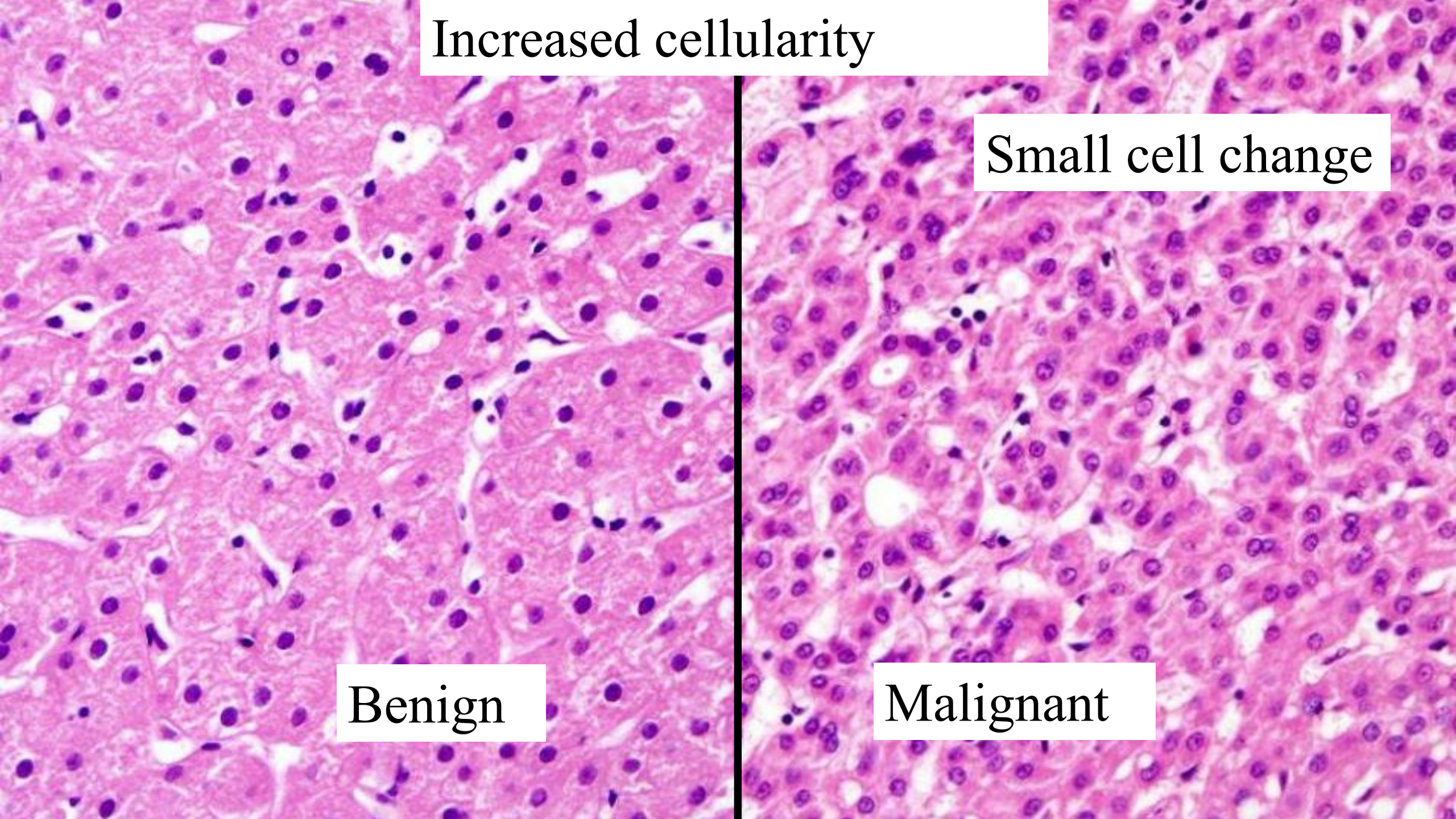
EZH2, AFP, Hsp 70

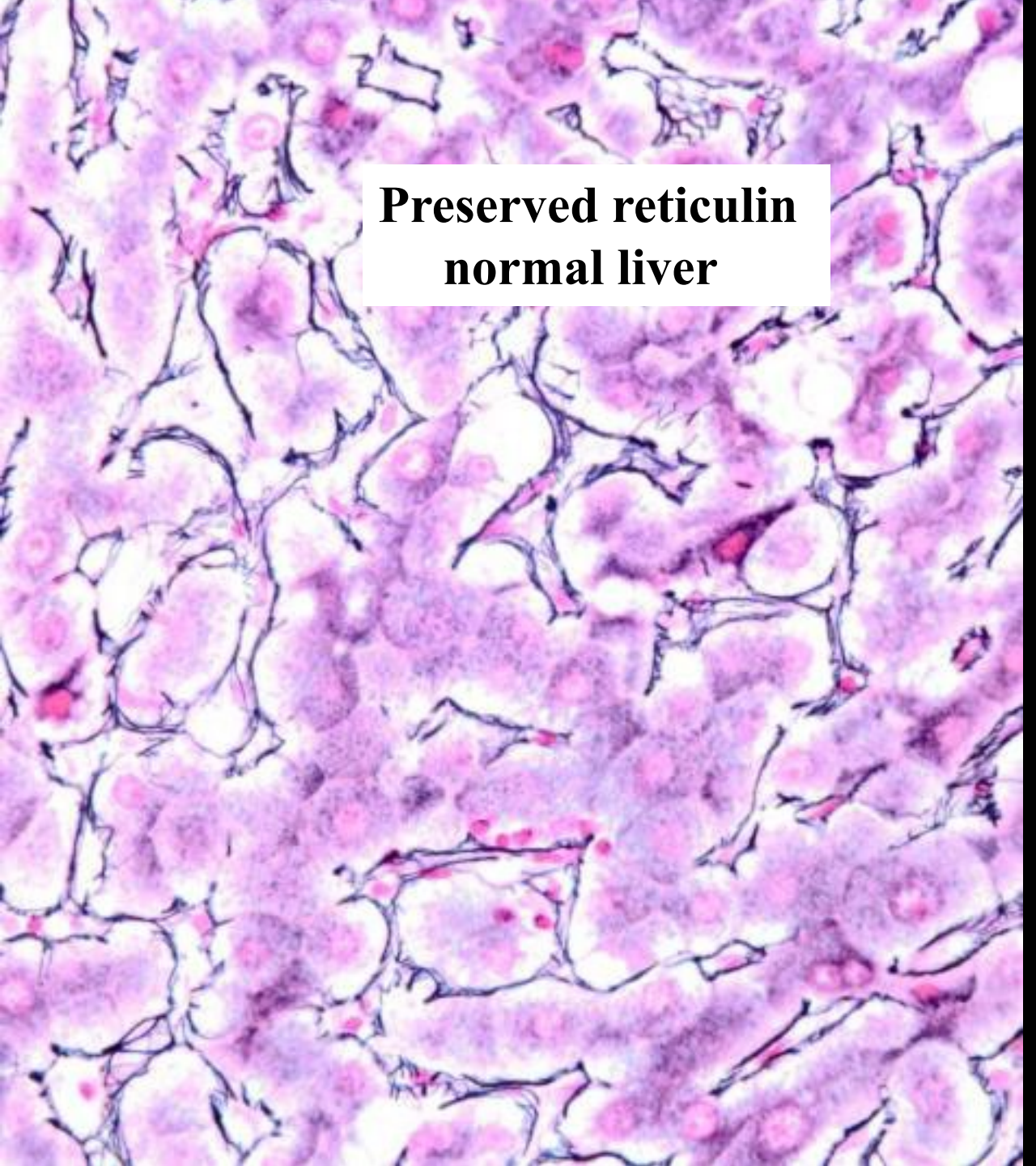
Hepatic plates > 4 cell thick hepatic plates = HCC

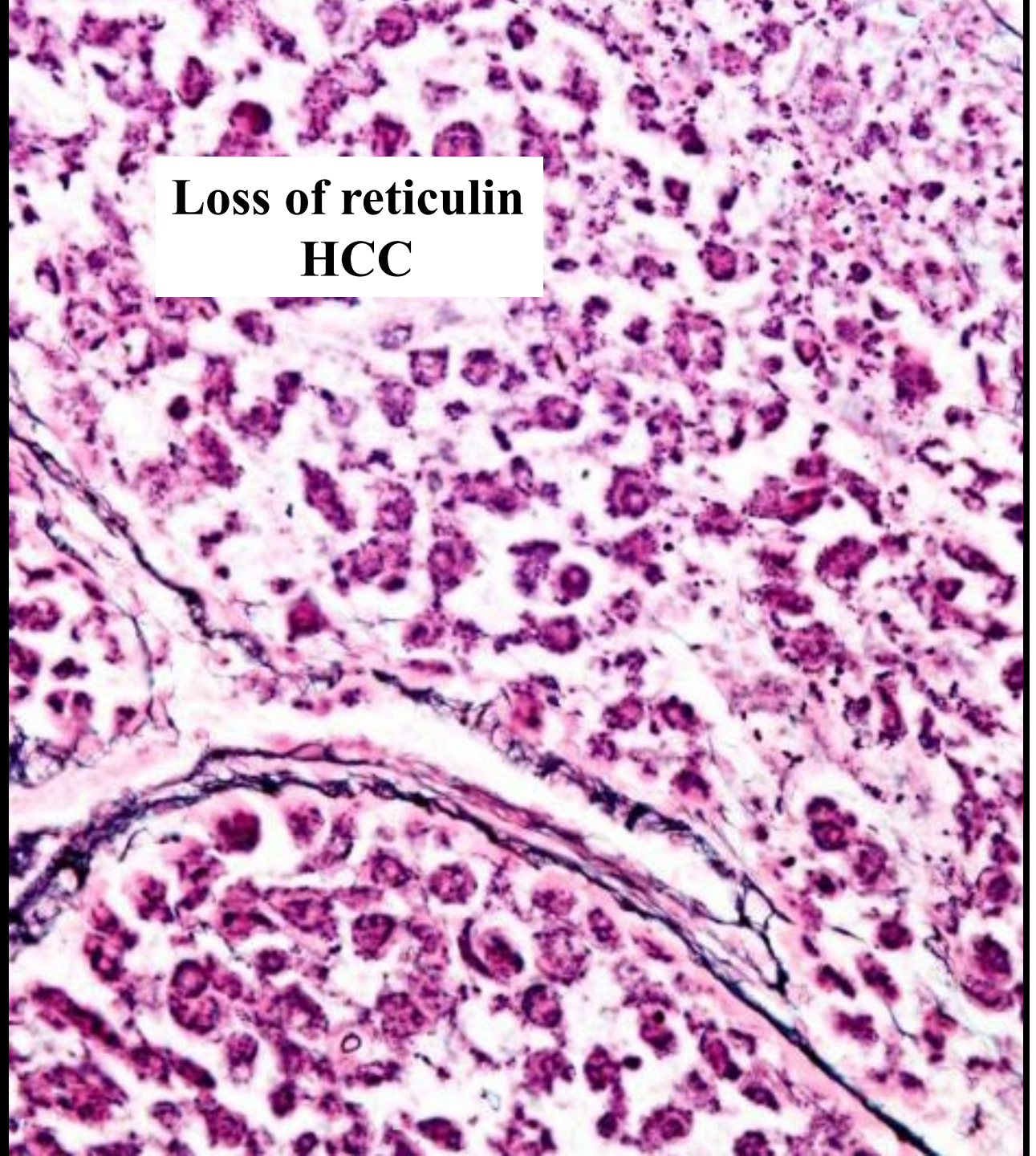


Cellblock

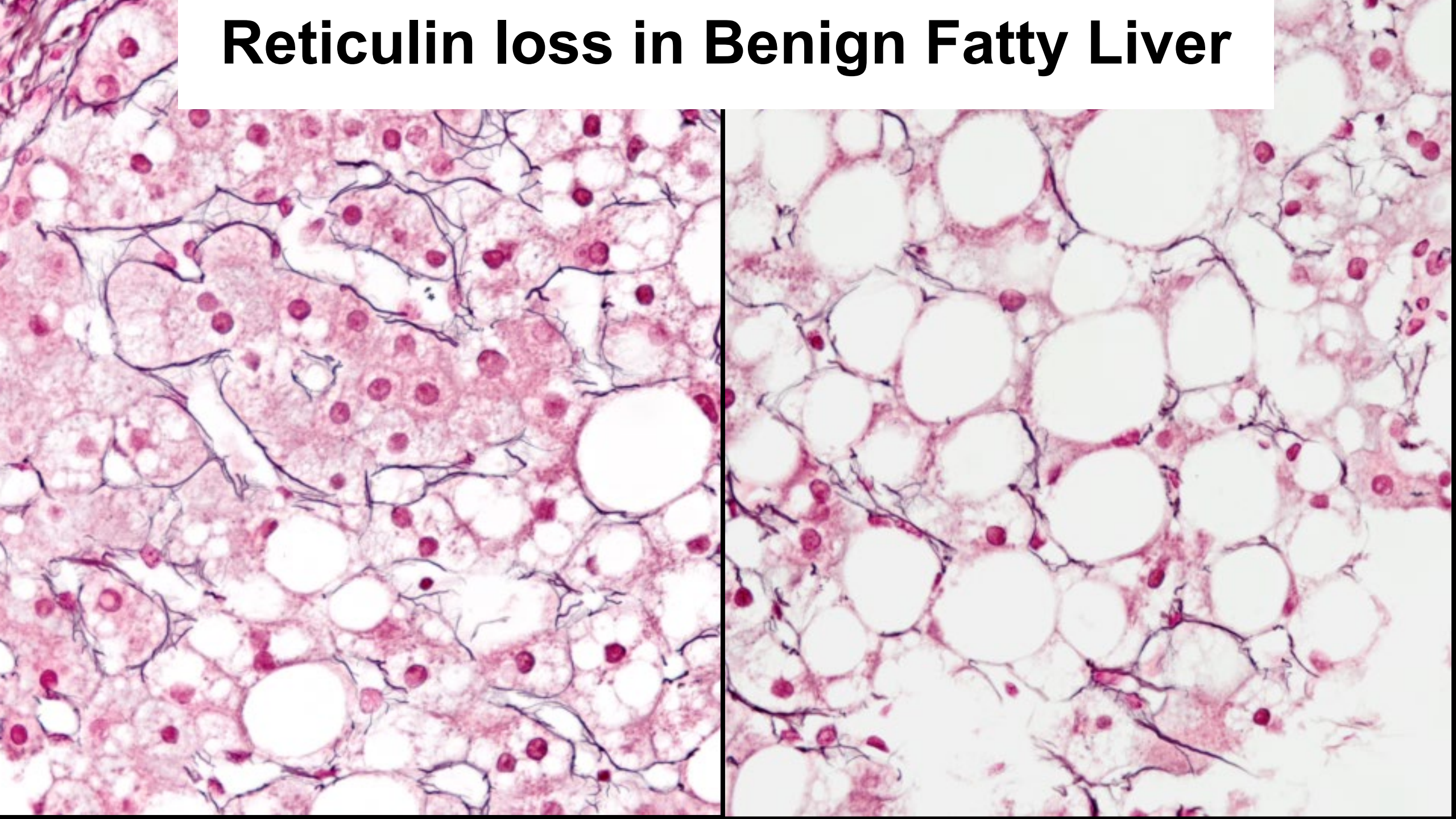


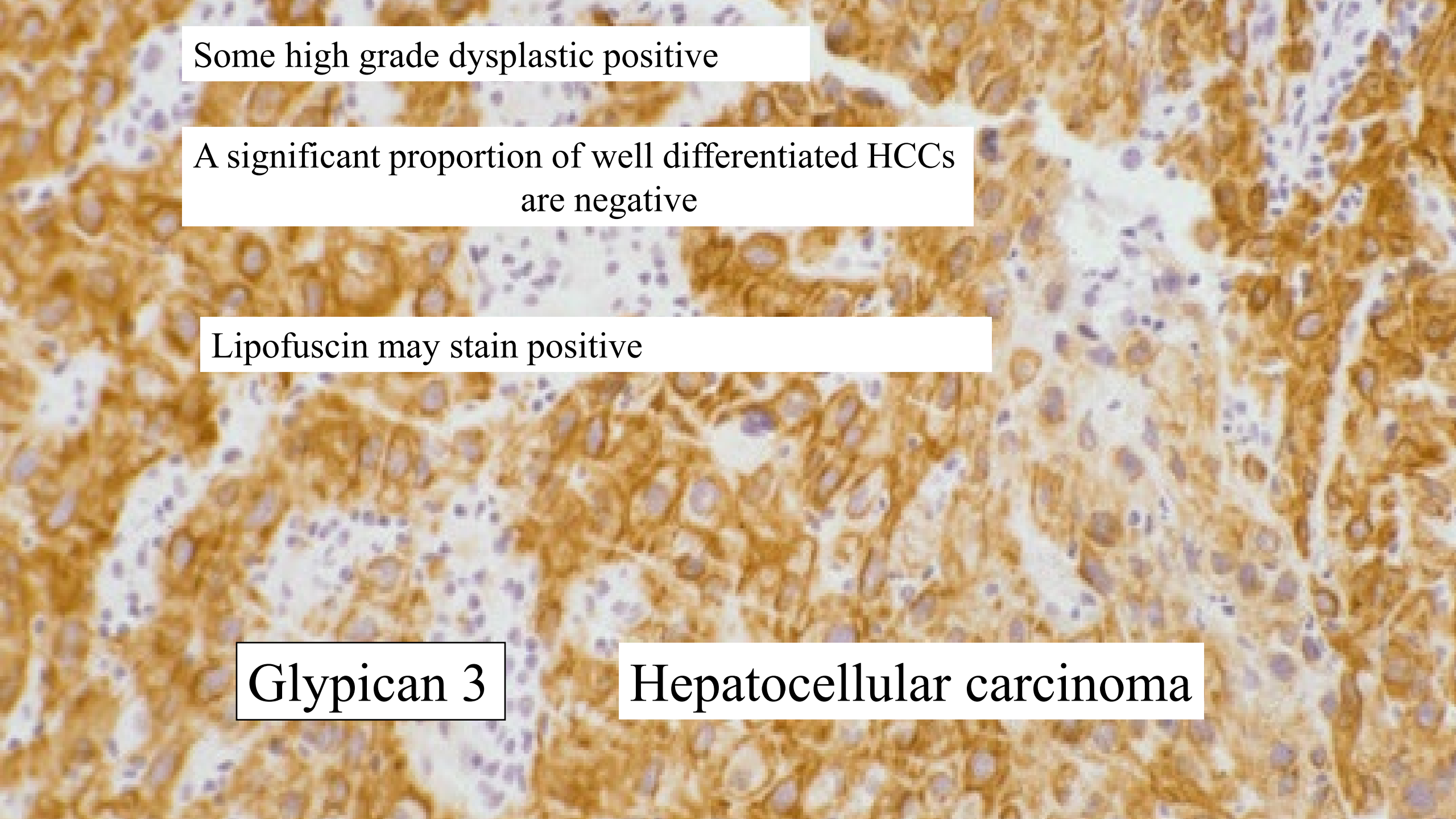

Increased cellularity
Small cell change
Benign
Malignant


Preserved reticulin
normal liver


Loss of reticulin
HCC

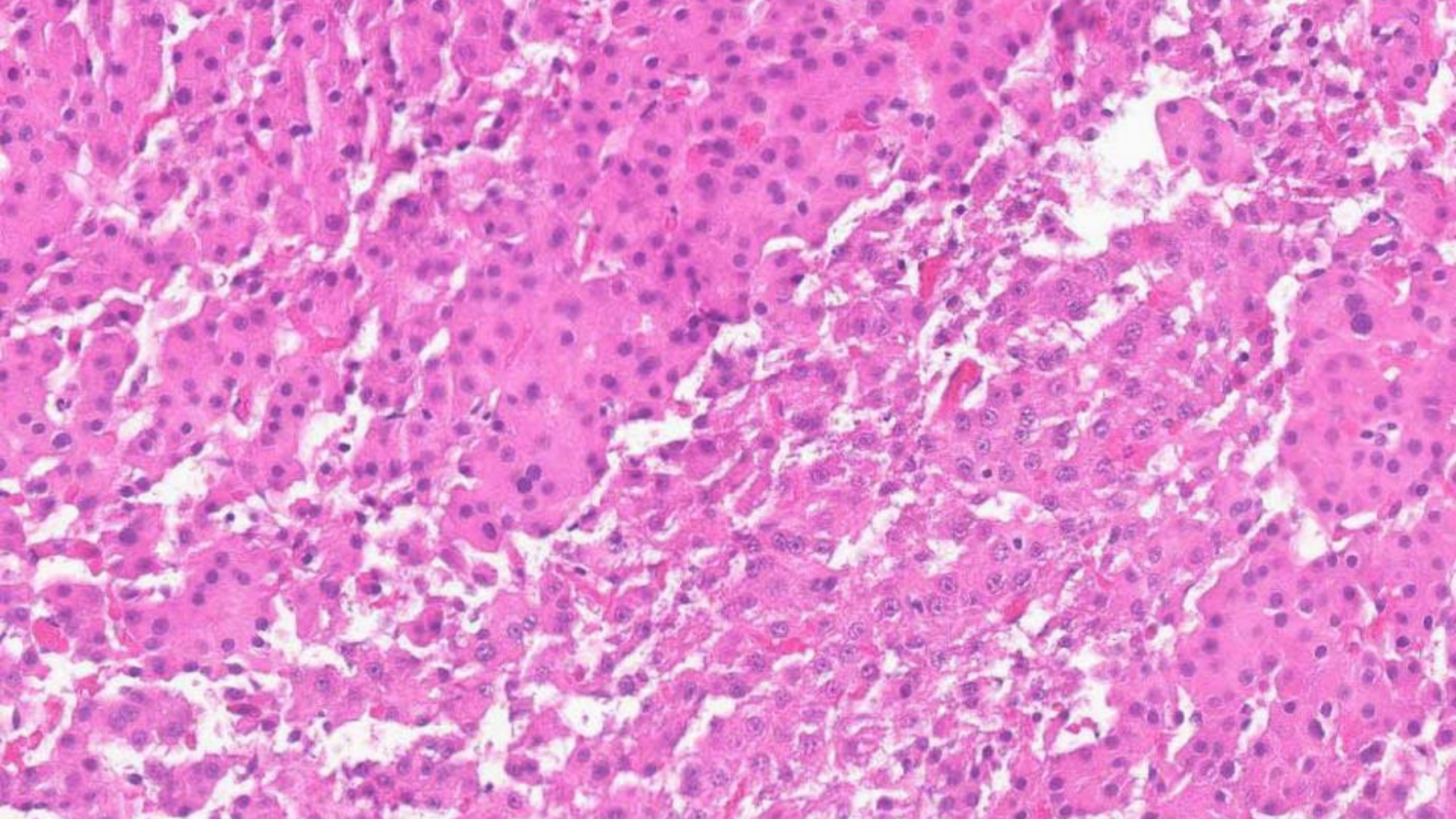
Reticulin loss in Benign Fatty Liver

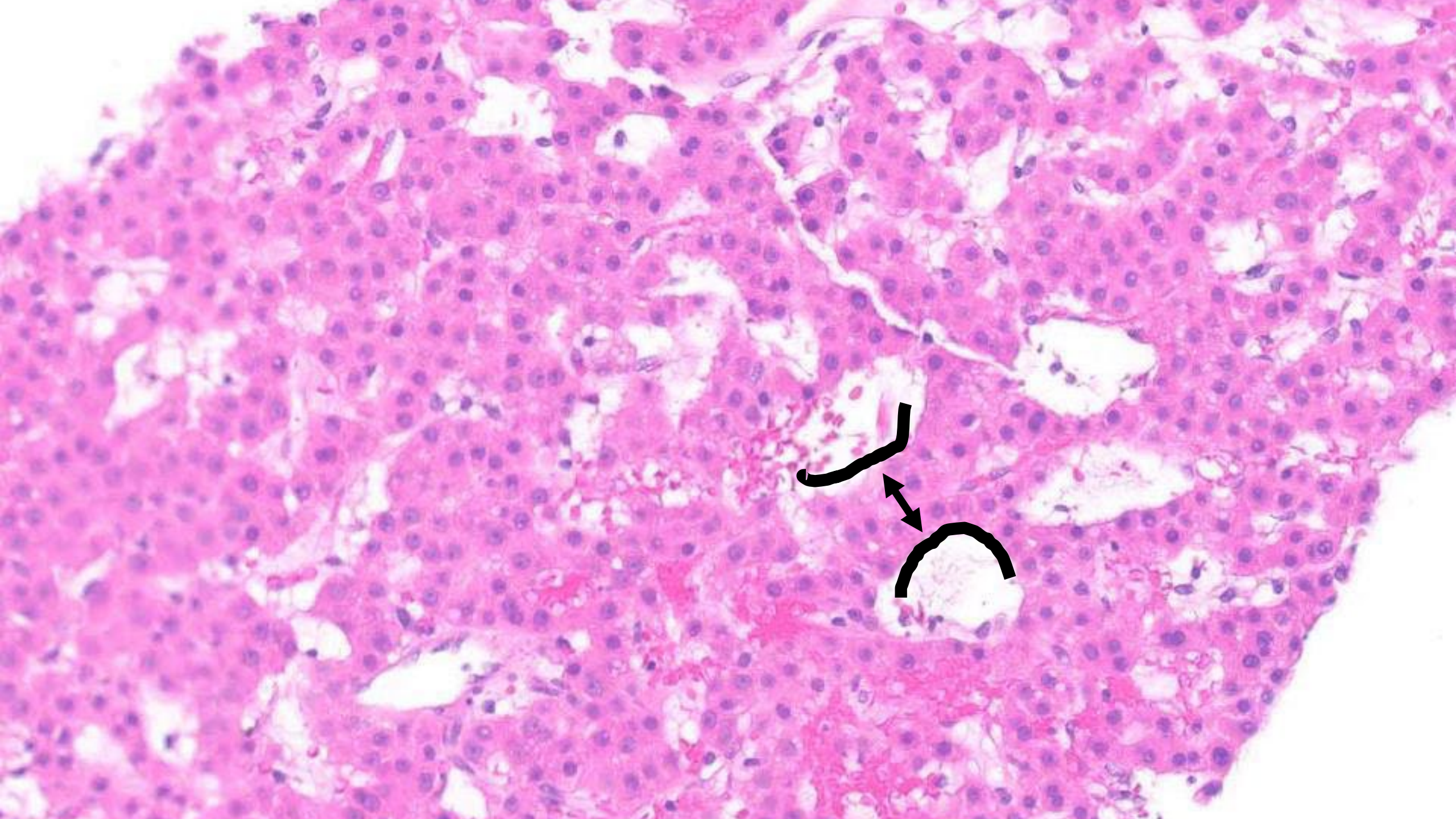



Some high grade dysplastic positive
A significant proportion of well differentiated HCCs are negative
Lipofuscin may stain positive
Glypican 3
Hepatocellular carcinoma

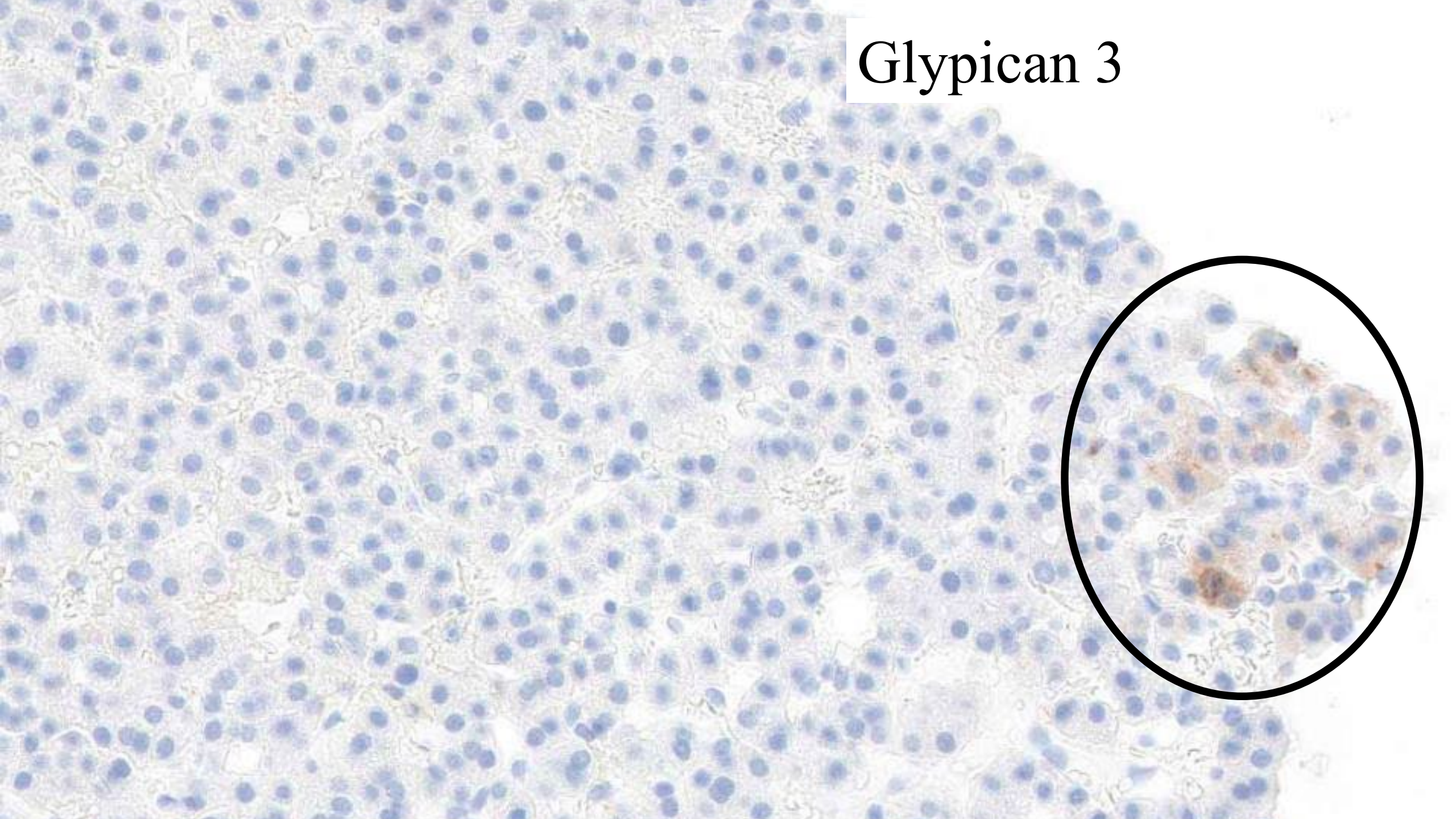
84/M

14 cm liver mass

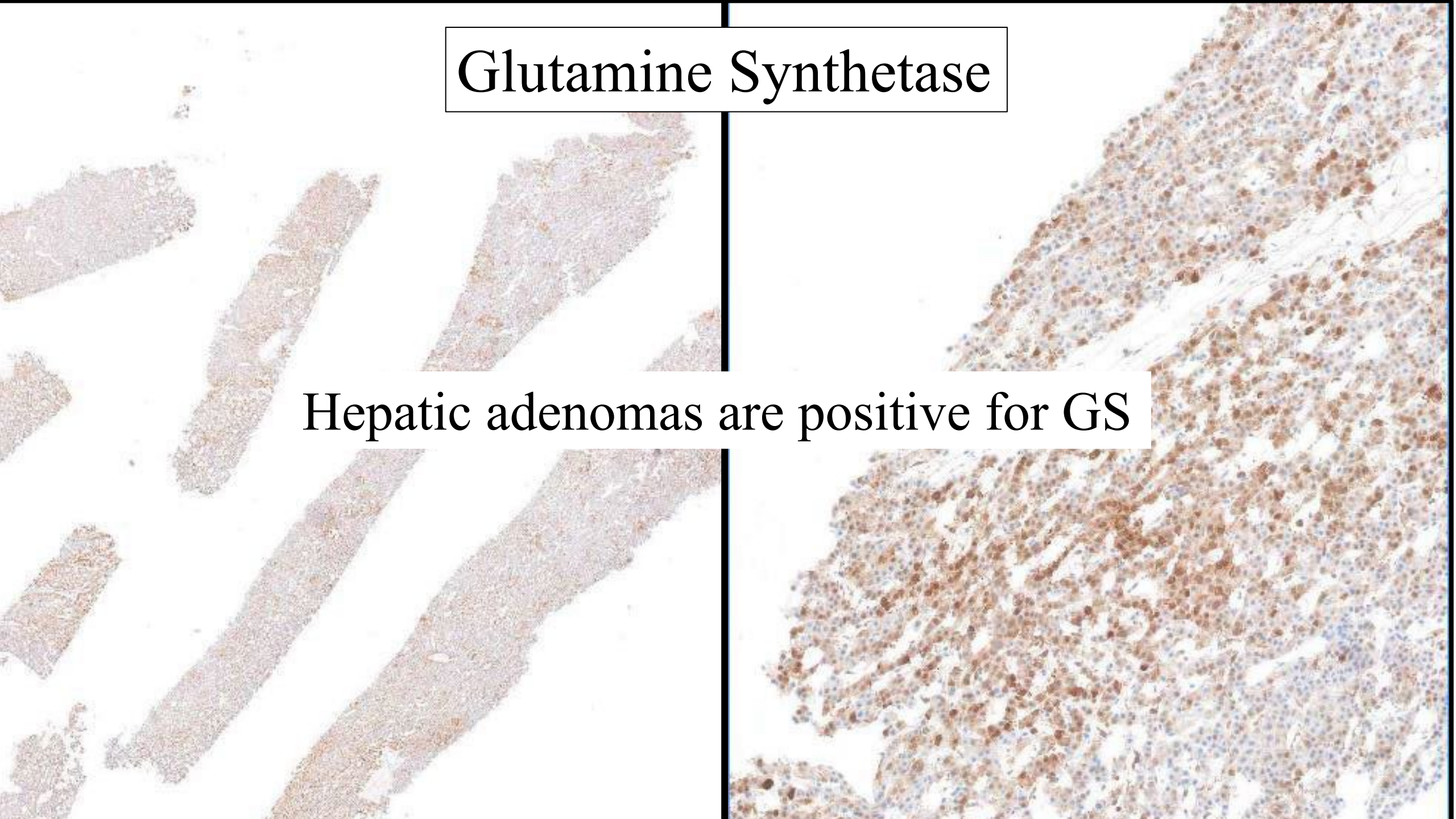




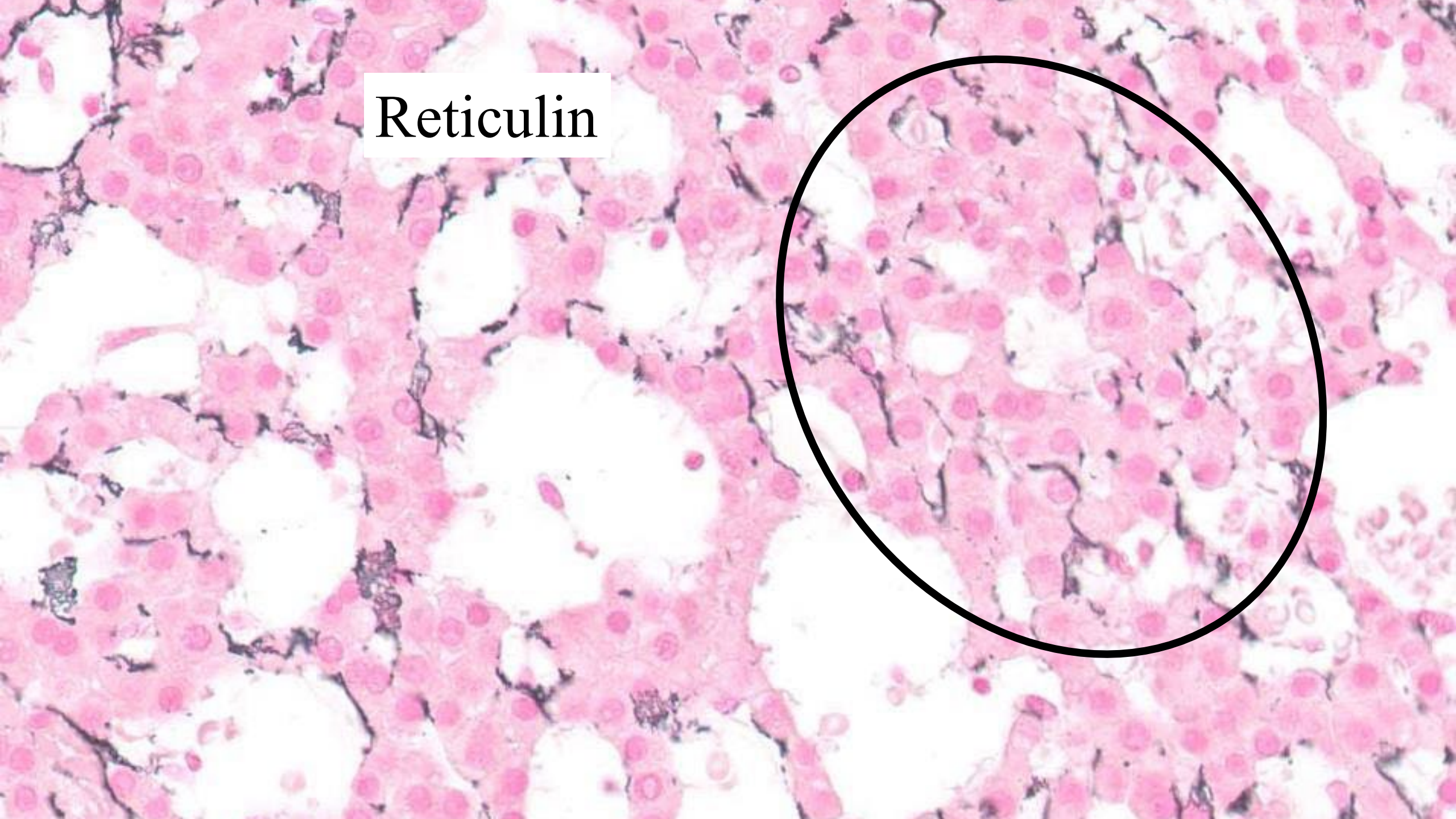
Glypican 3



Glutamine Synthetase



Hepatic adenomas are positive for GS


Reticulin

Hepatocellular Carcinoma

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

Age

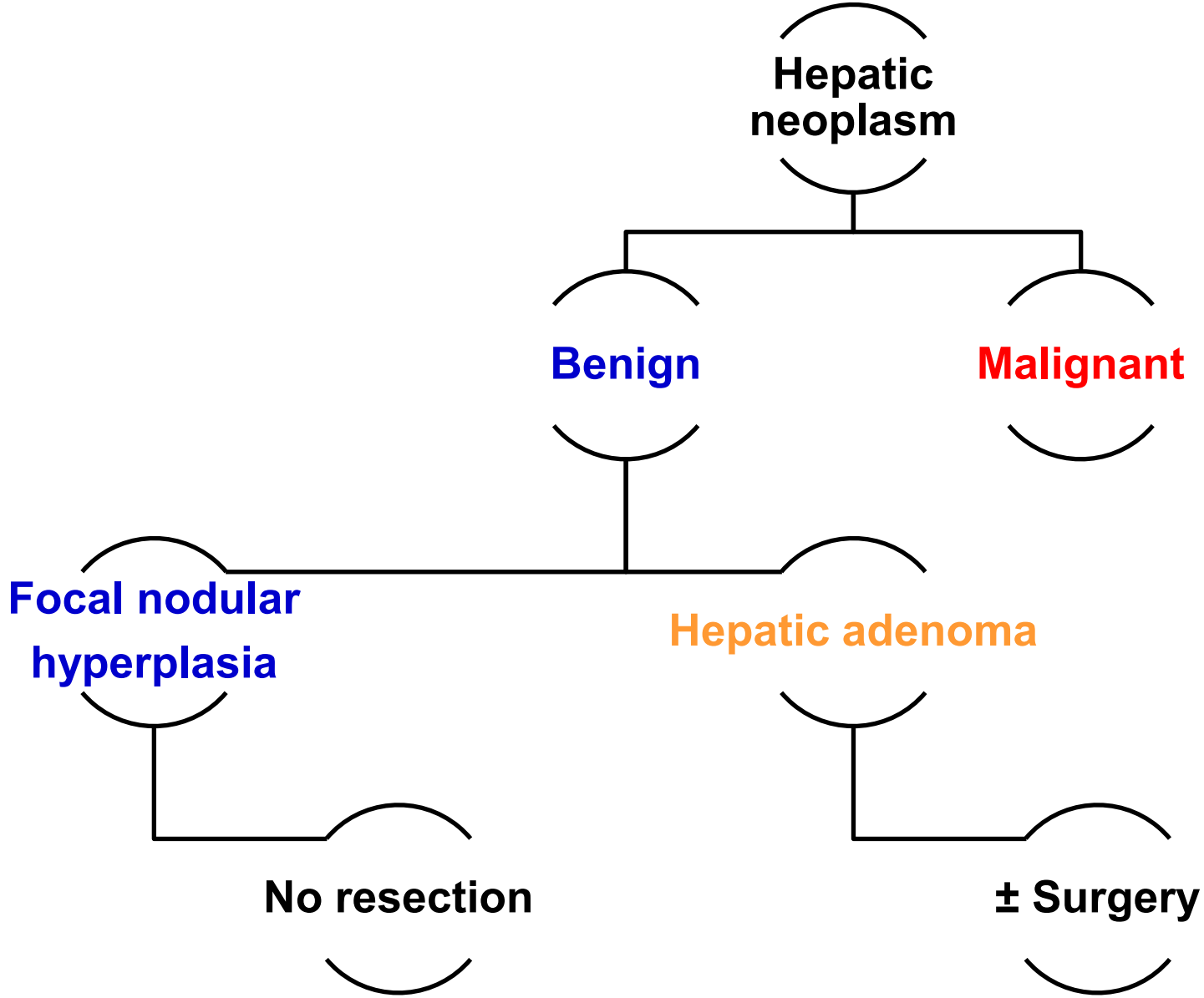
Uncomfortable calling HCC?

Well differentiated hepatocellular neoplasm.
See note.

Problem 3

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

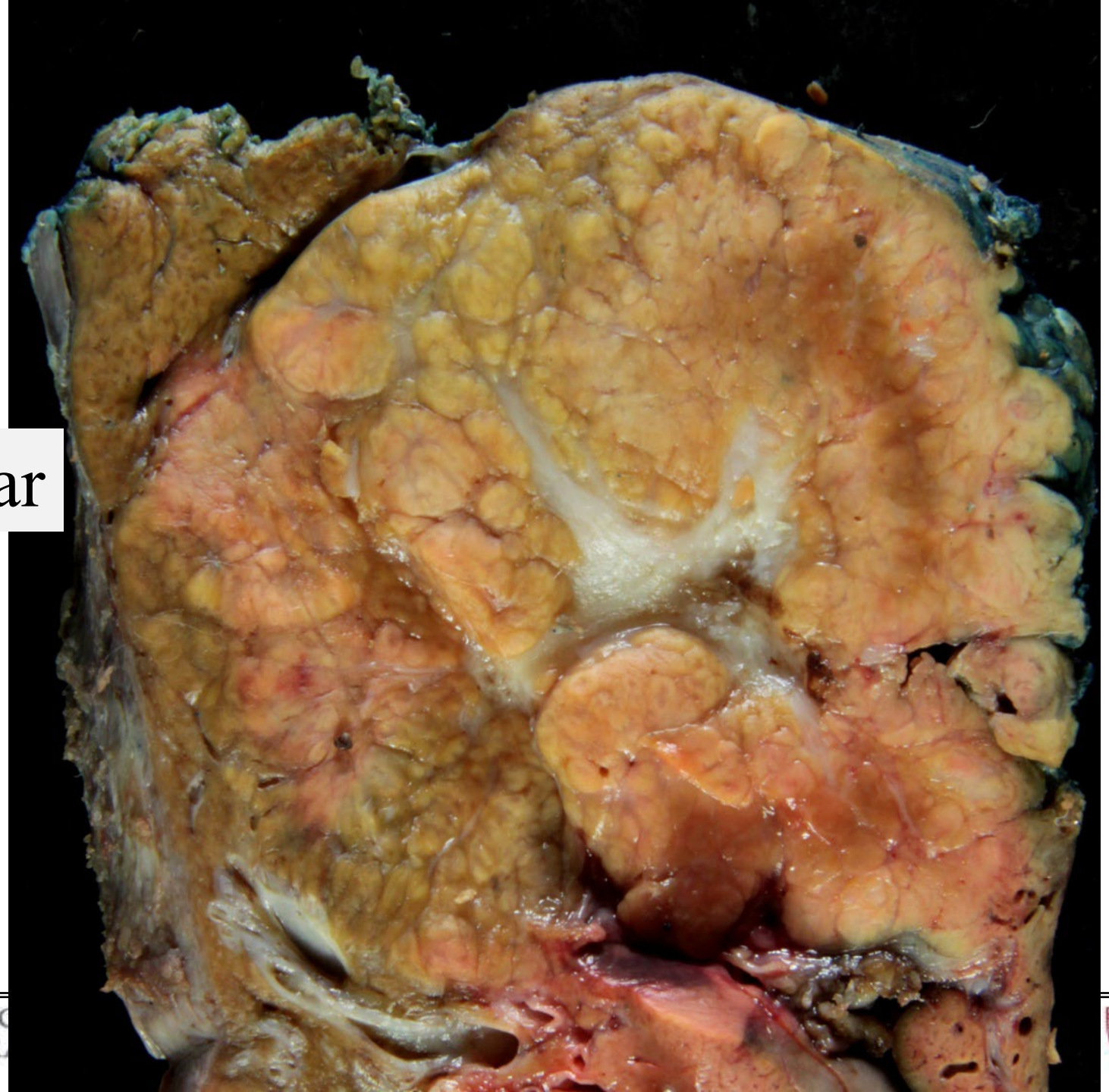



Hepatic neoplasm
Benign
Malignant
Focal nodular hyperplasia
Hepatic adenoma
No resection
± Surgery

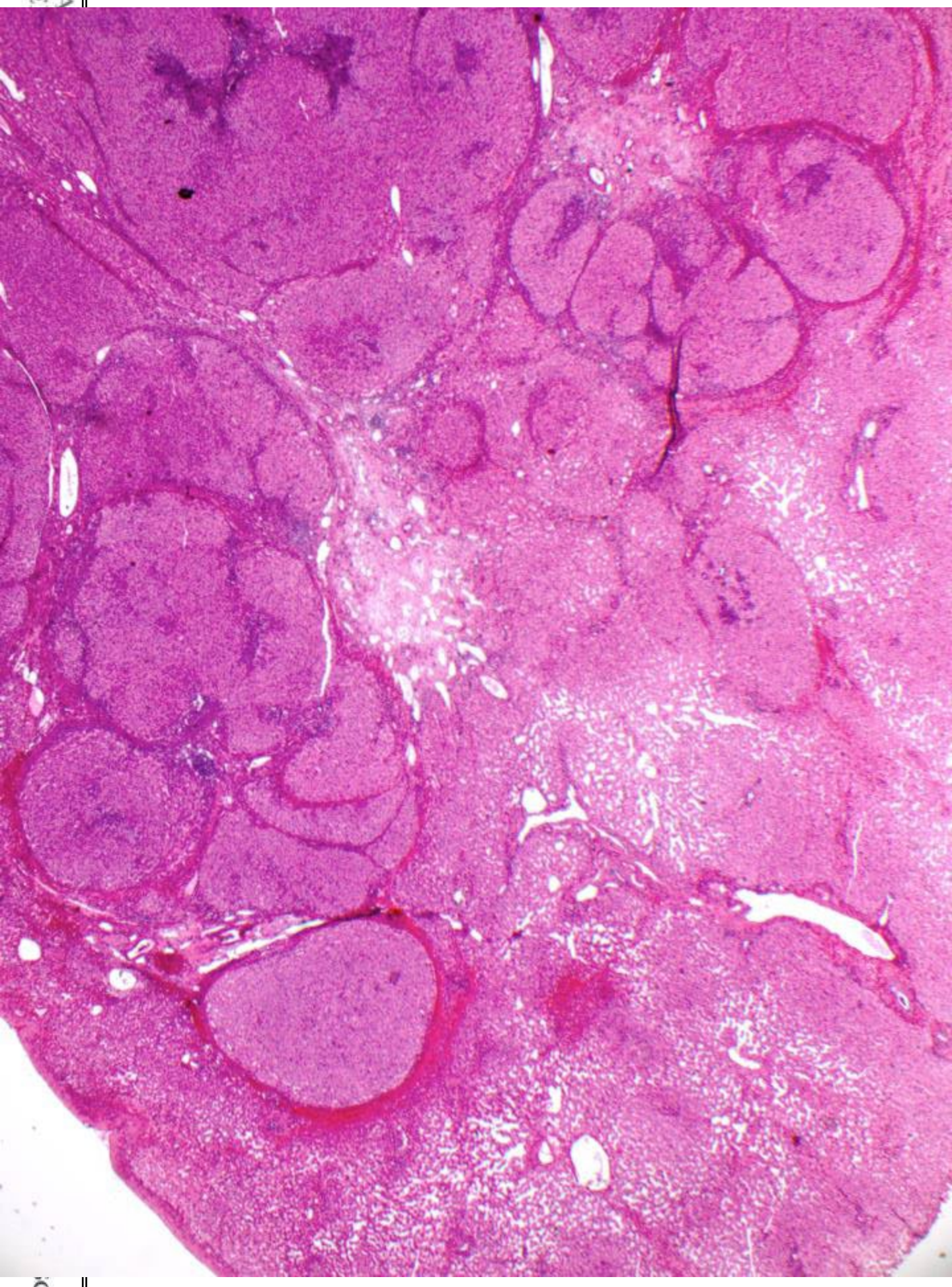
Focal Nodular Hyperplasia

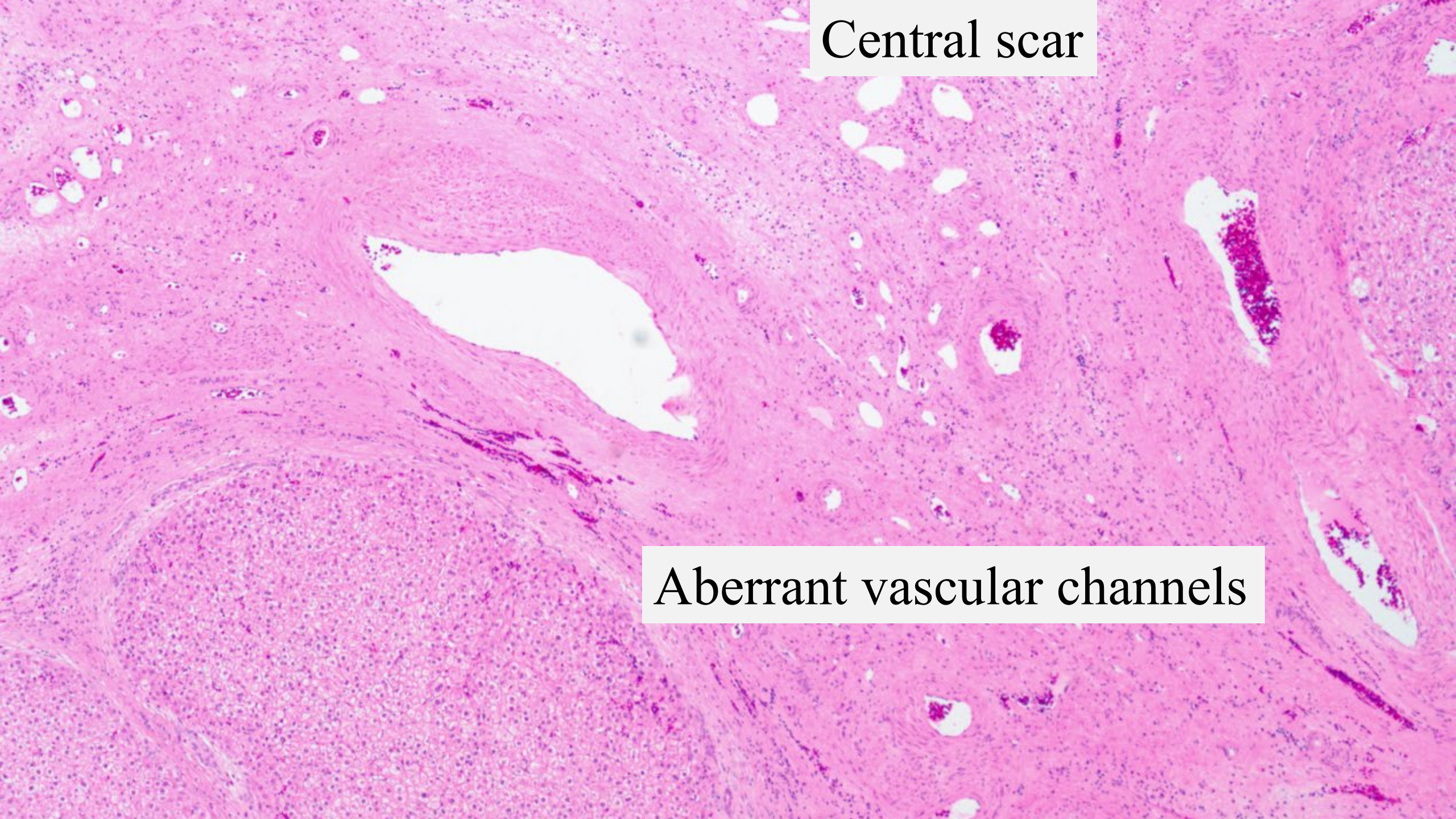
Focal Nodular Hyperplasia

Central scar

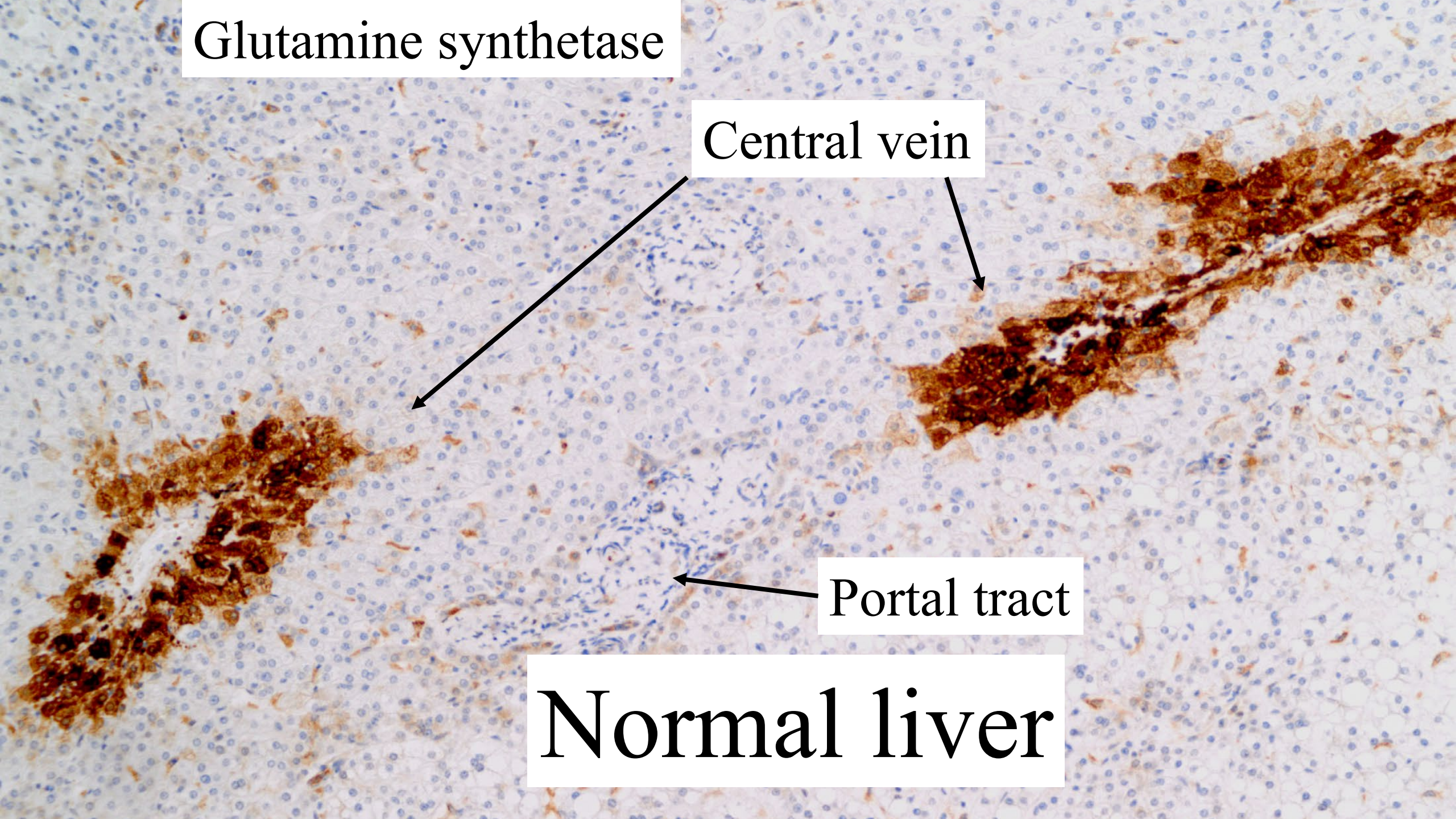


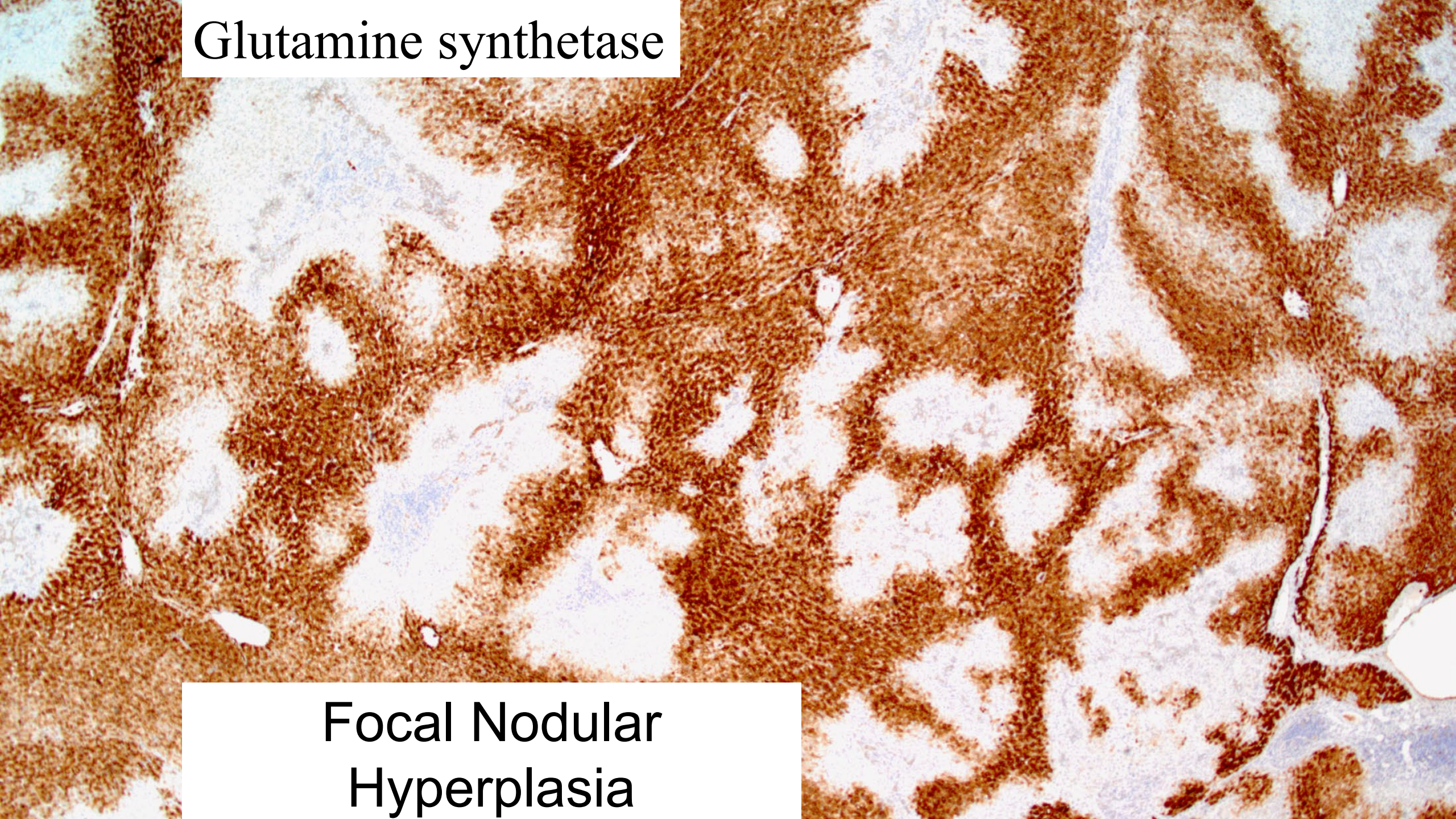
Central scar

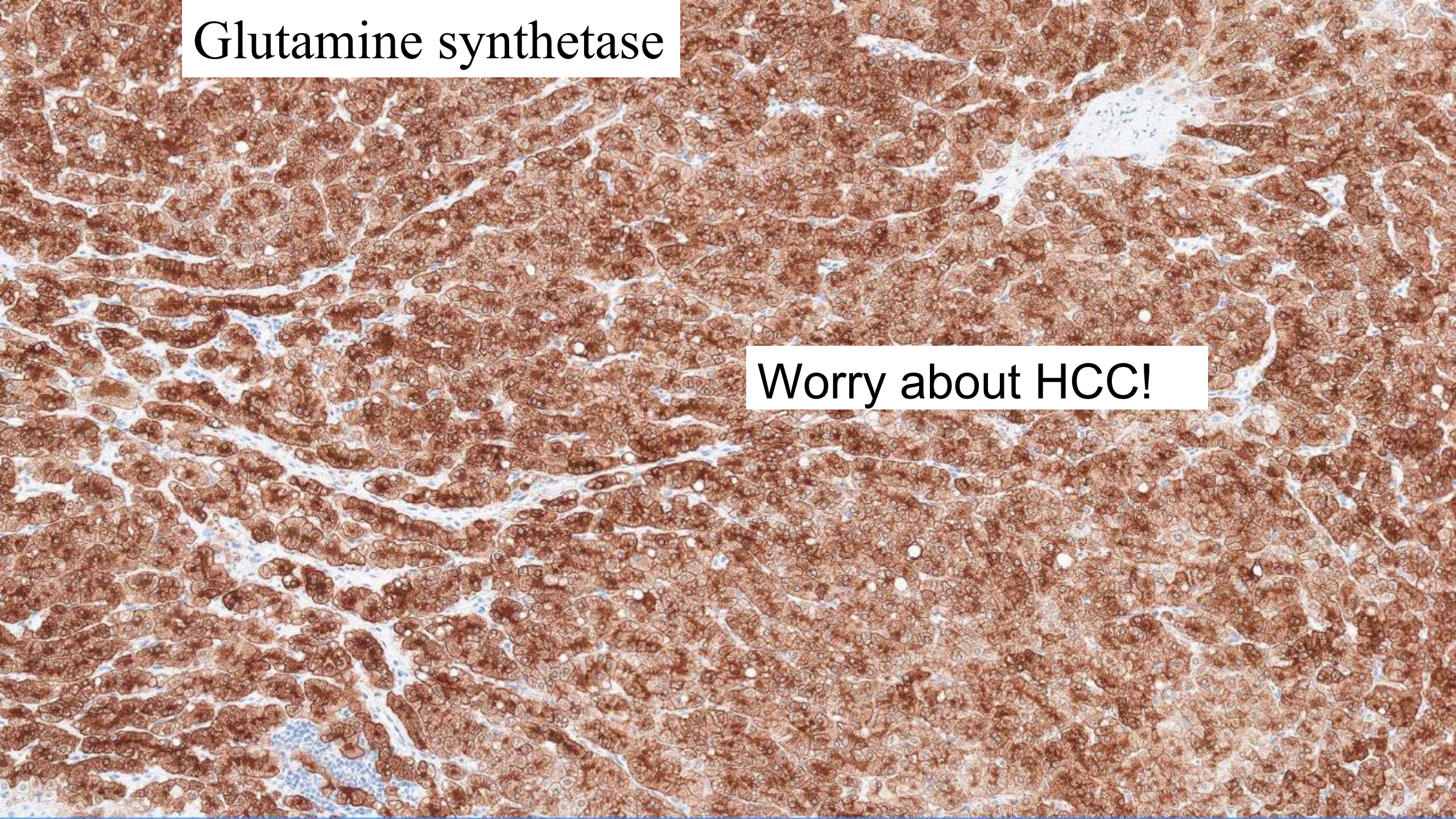


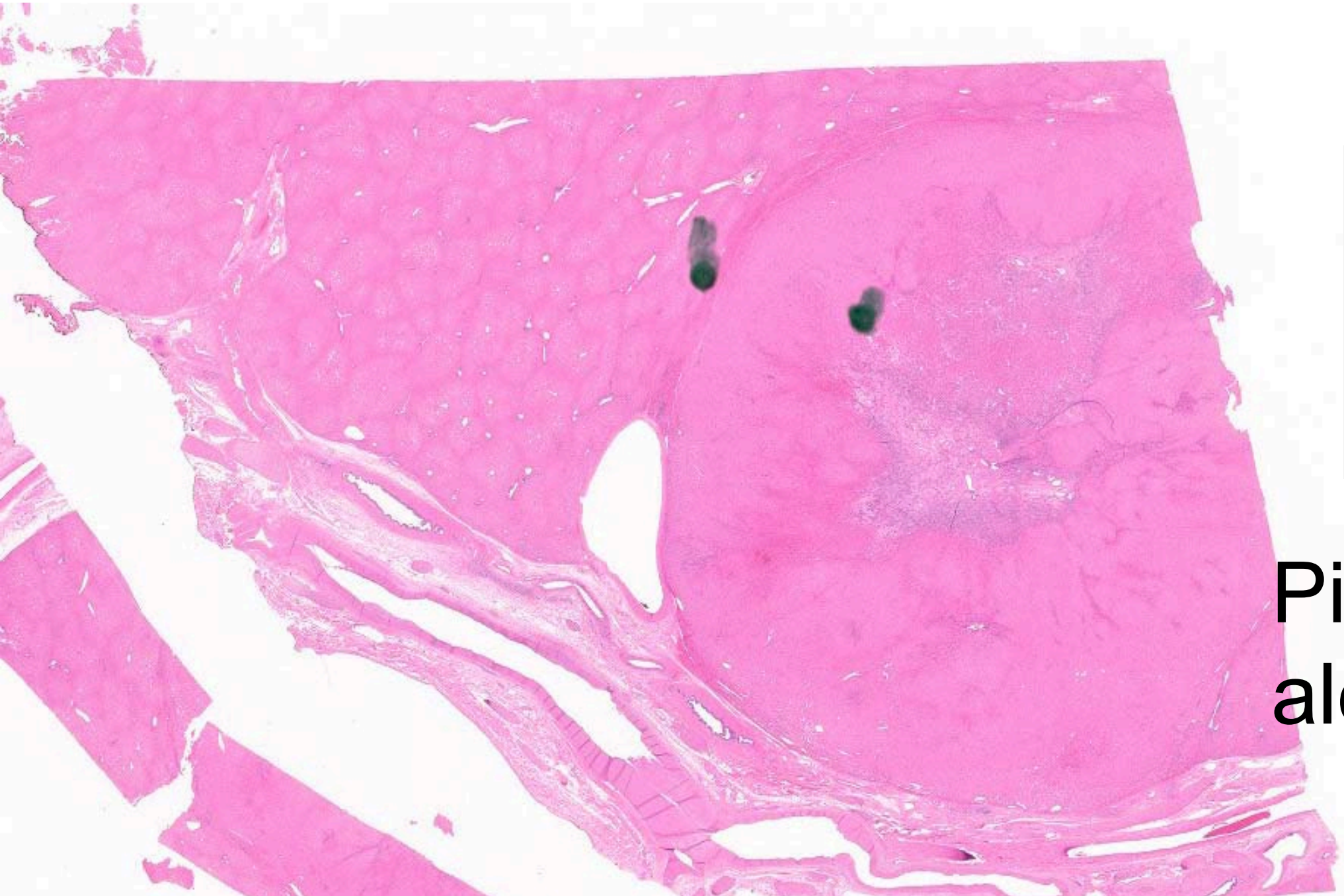

Central scar
Aberrant vascular channels


Bile ductular proliferation


Glutamine synthetase
Central vein
Portal tract
Normal liver

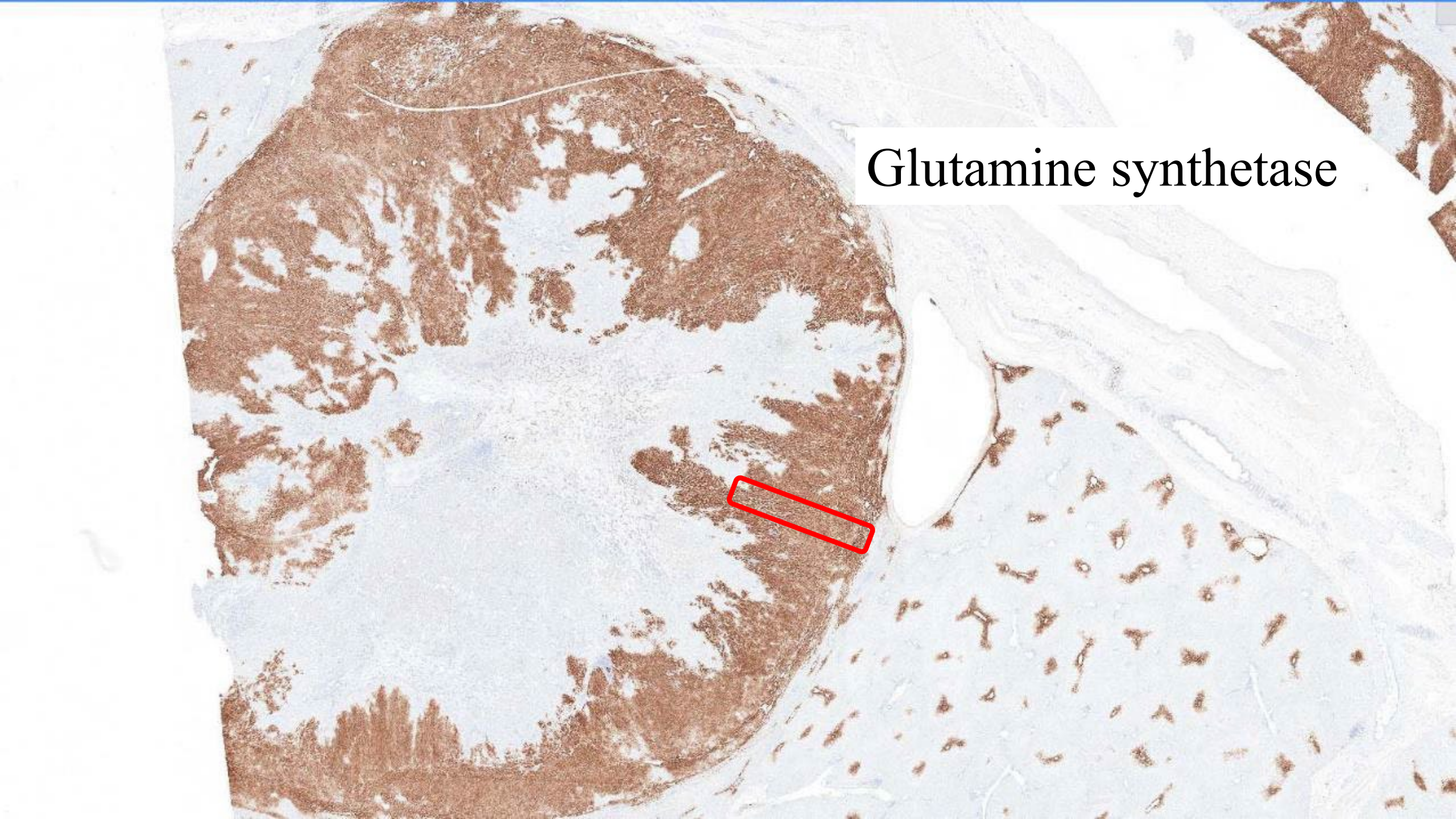

Glutamine synthetase
Focal Nodular Hyperplasia

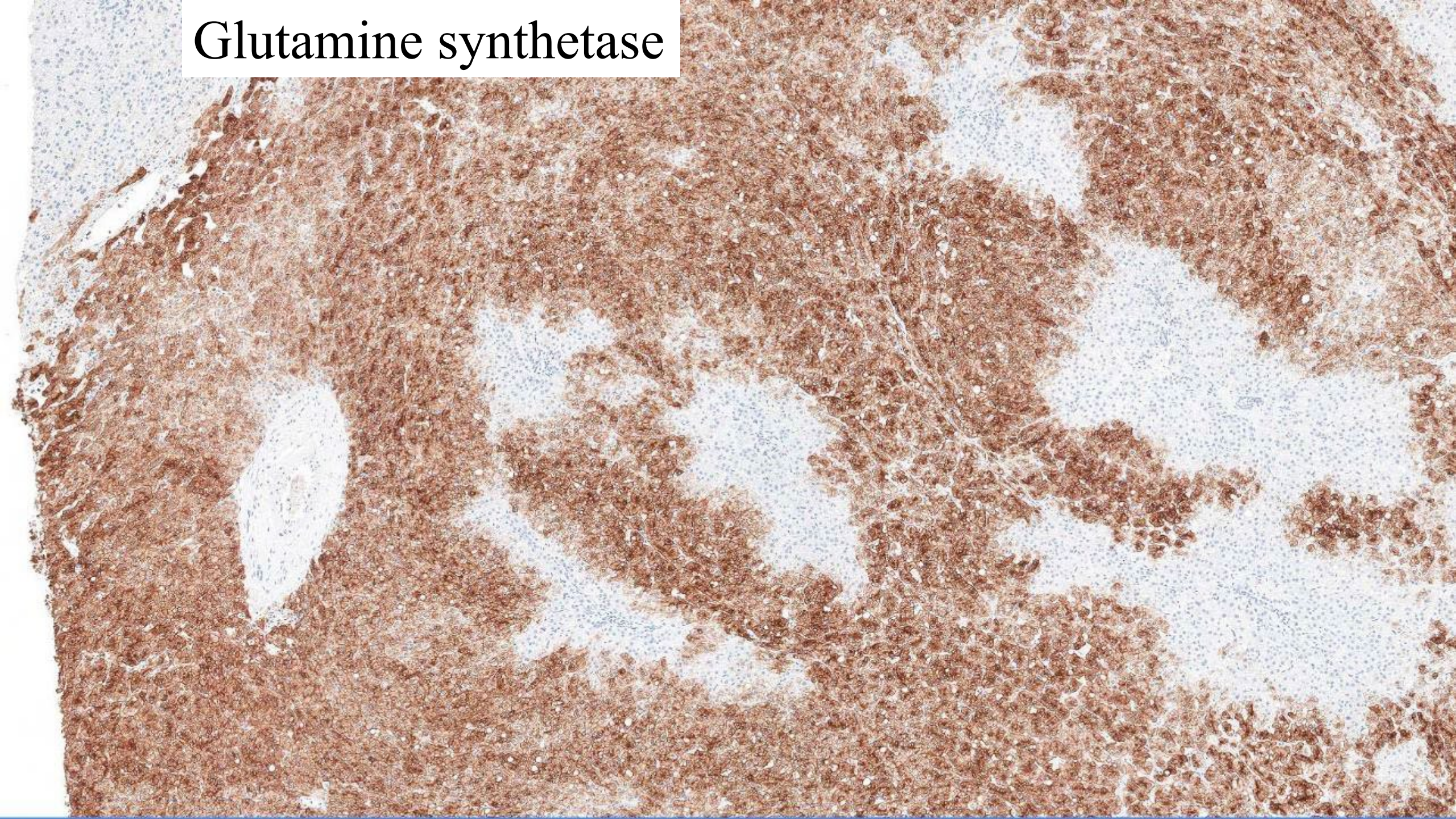

Glutamine synthetase
Worry about HCC!

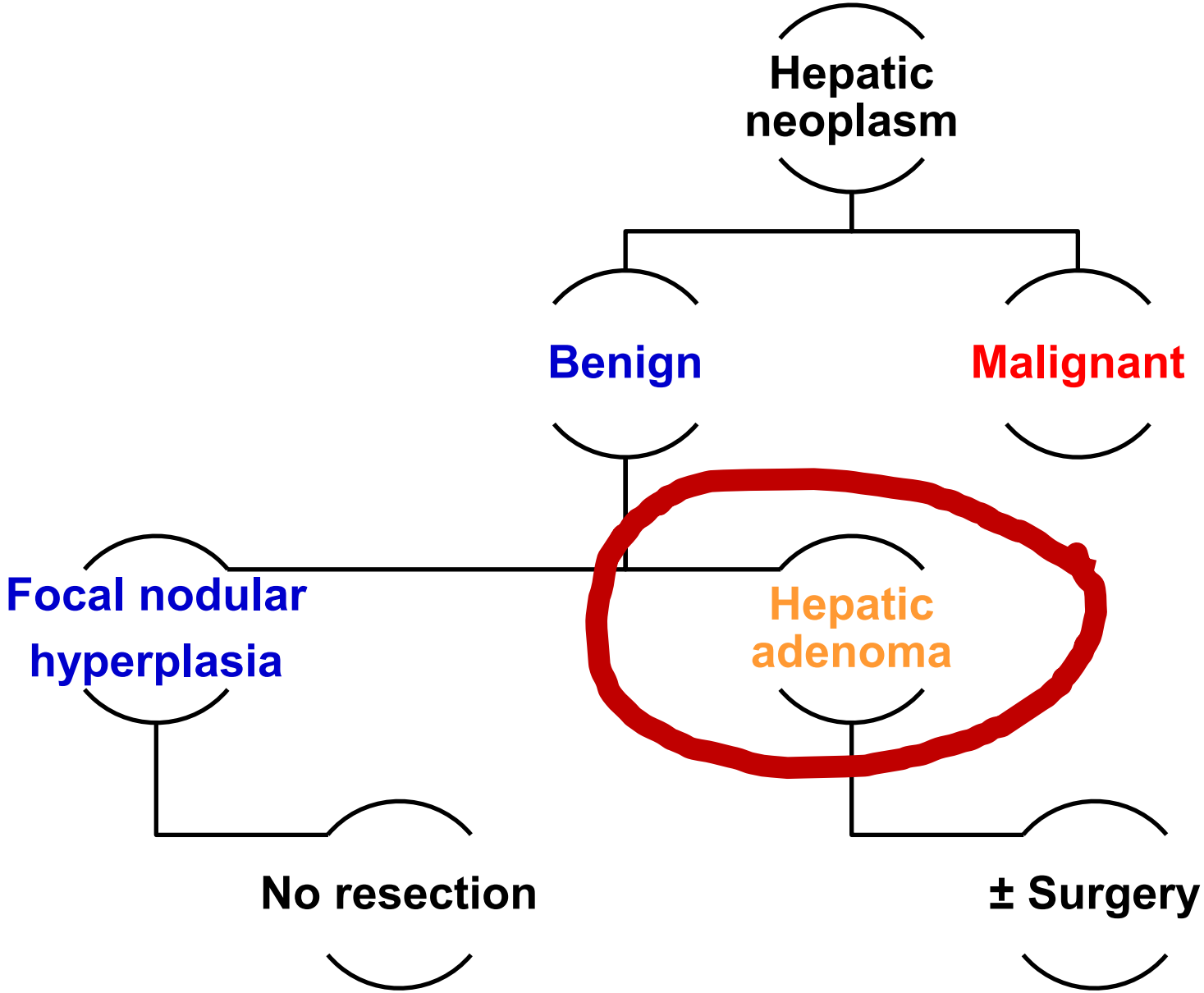


Central scar

Pitfall alert !


Glutamine synthetase


Glutamine synthetase


Hepatic neoplasm
Benign
Malignant
Focal nodular hyperplasia
Hepatic adenoma
No resection
± Surgery

Department
7
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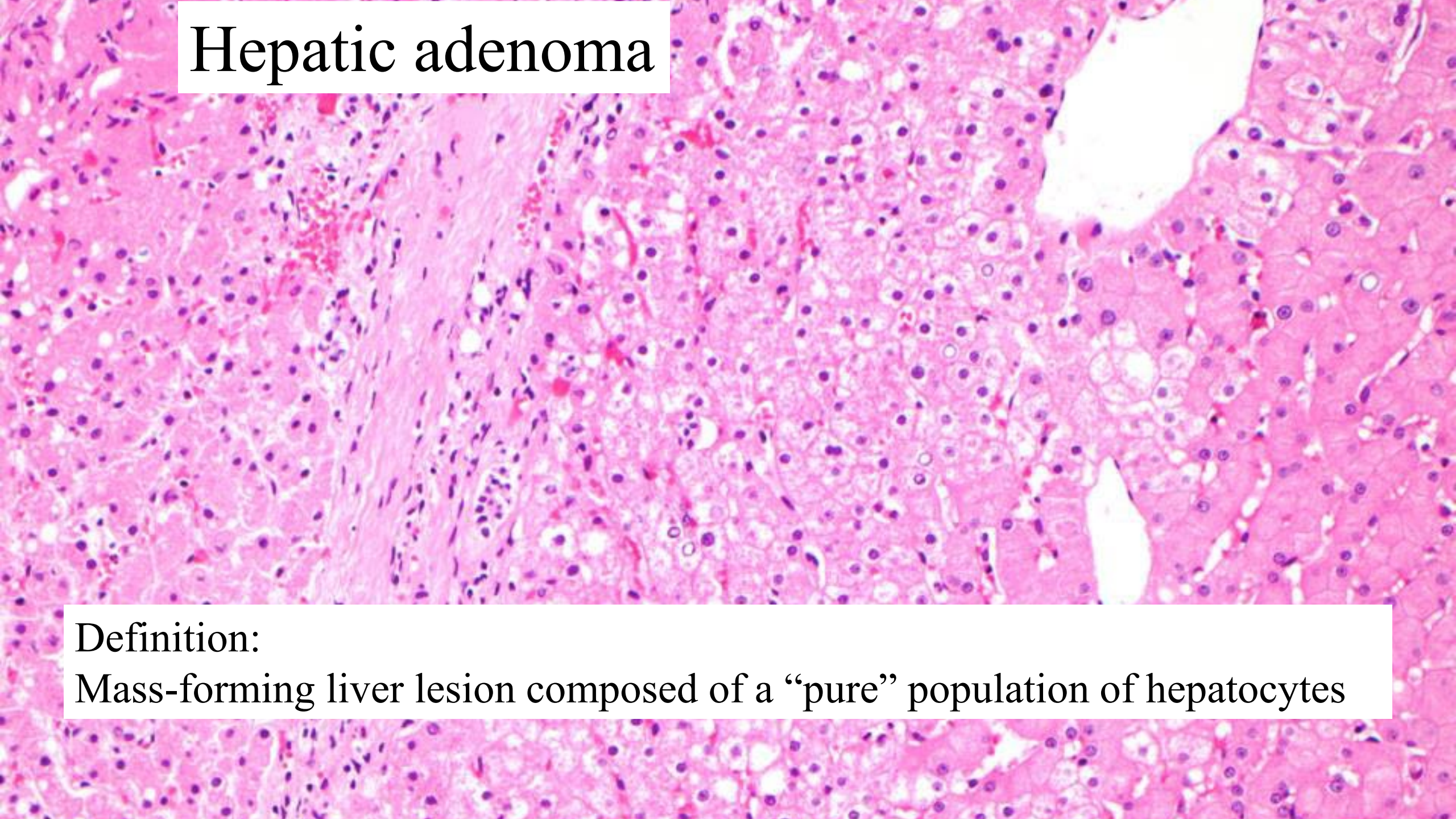
10
11
12

Hepatic adenoma

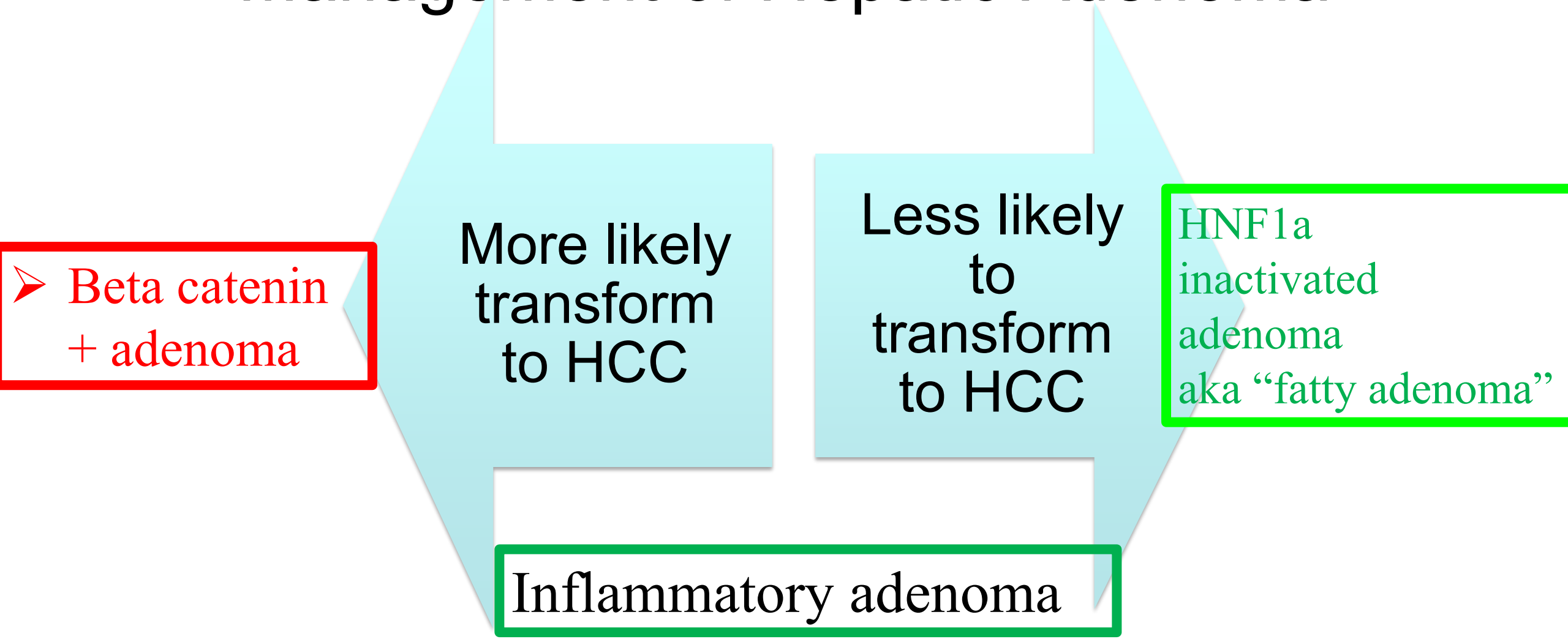


Definition:
Mass-forming liver lesion composed of a “pure” population of hepatocytes

Question 4:
Subclassifying hepatic adenoma

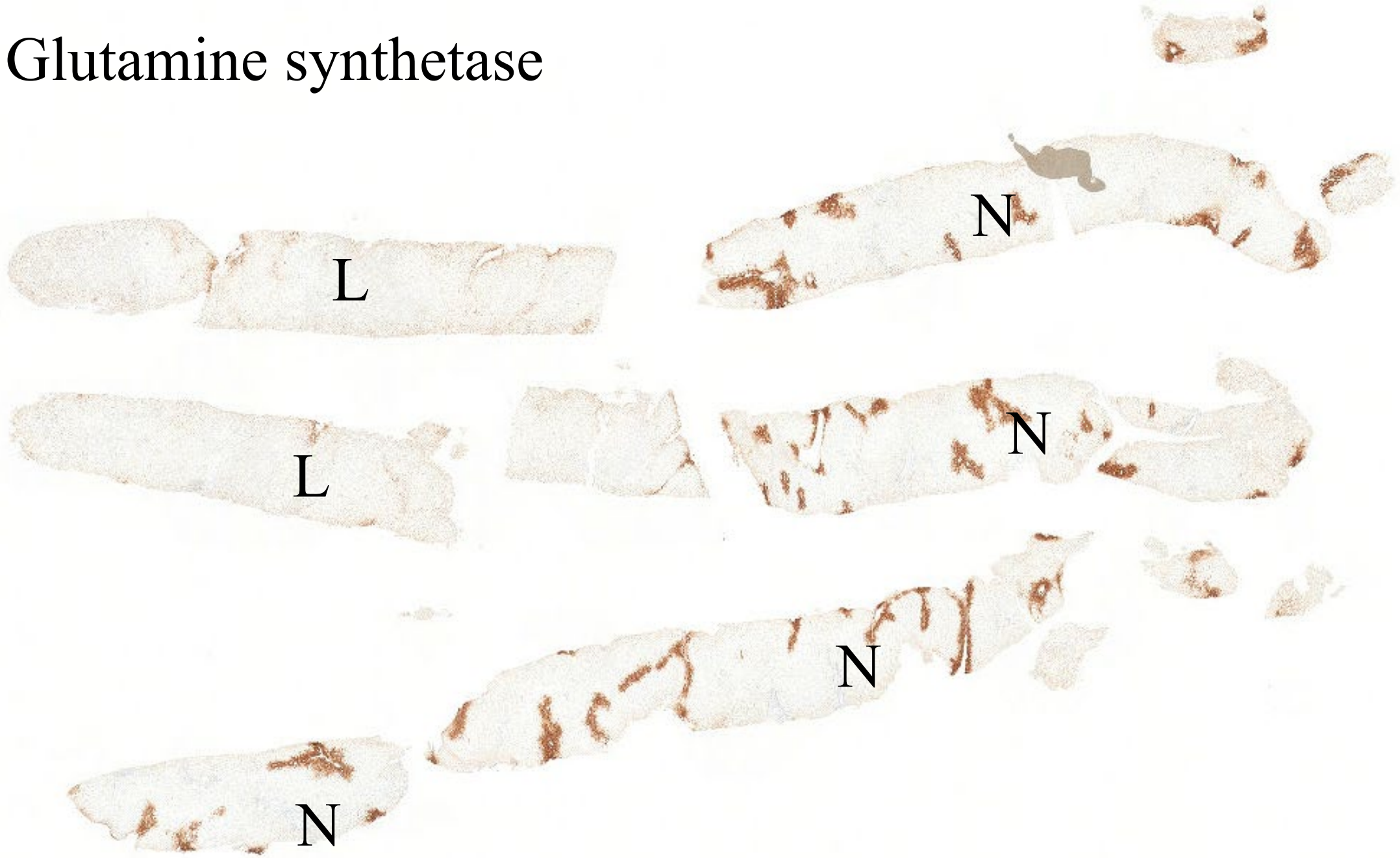
Does it matter? And how does one do it?

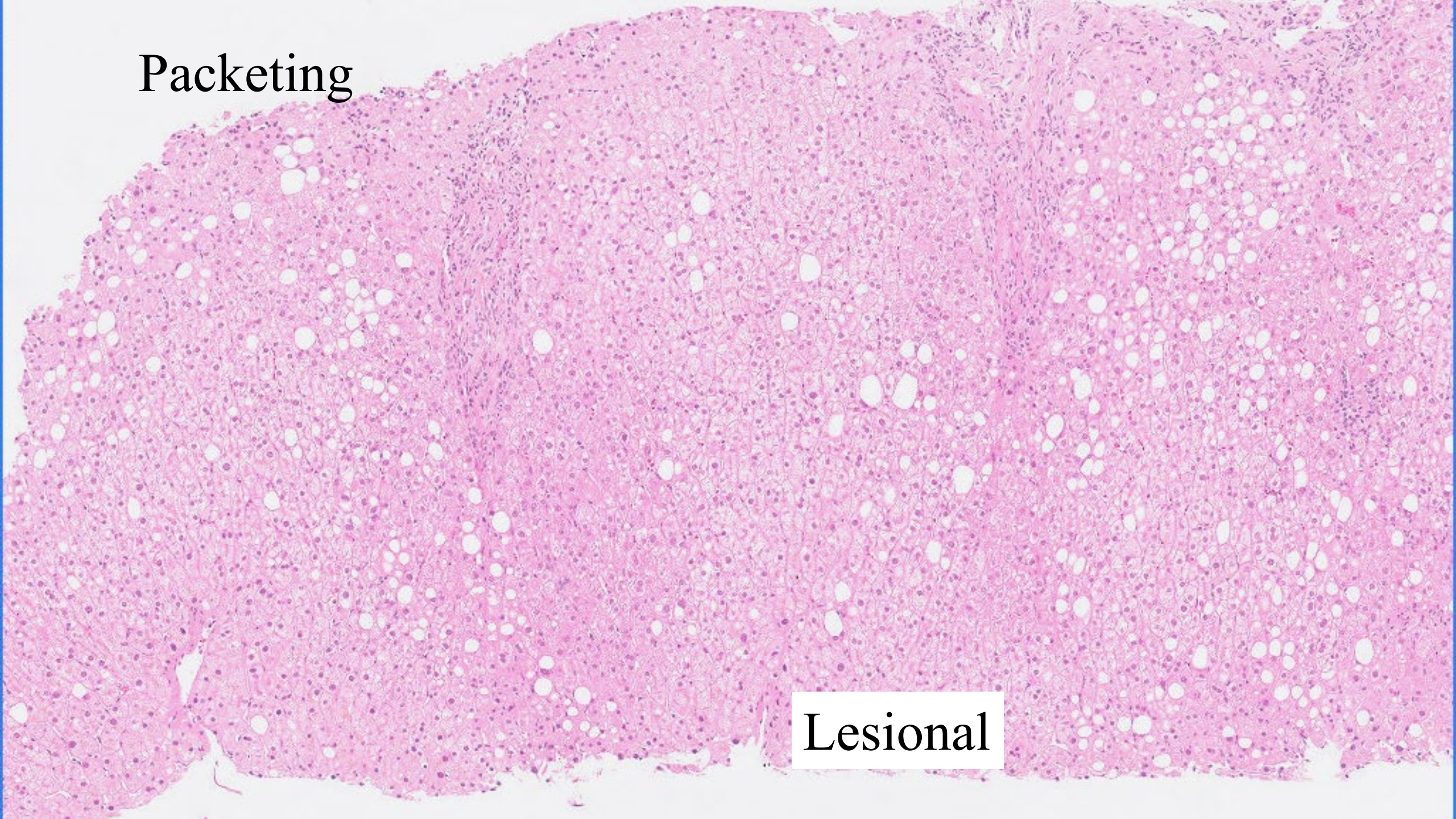
Management of Hepatic Adenoma

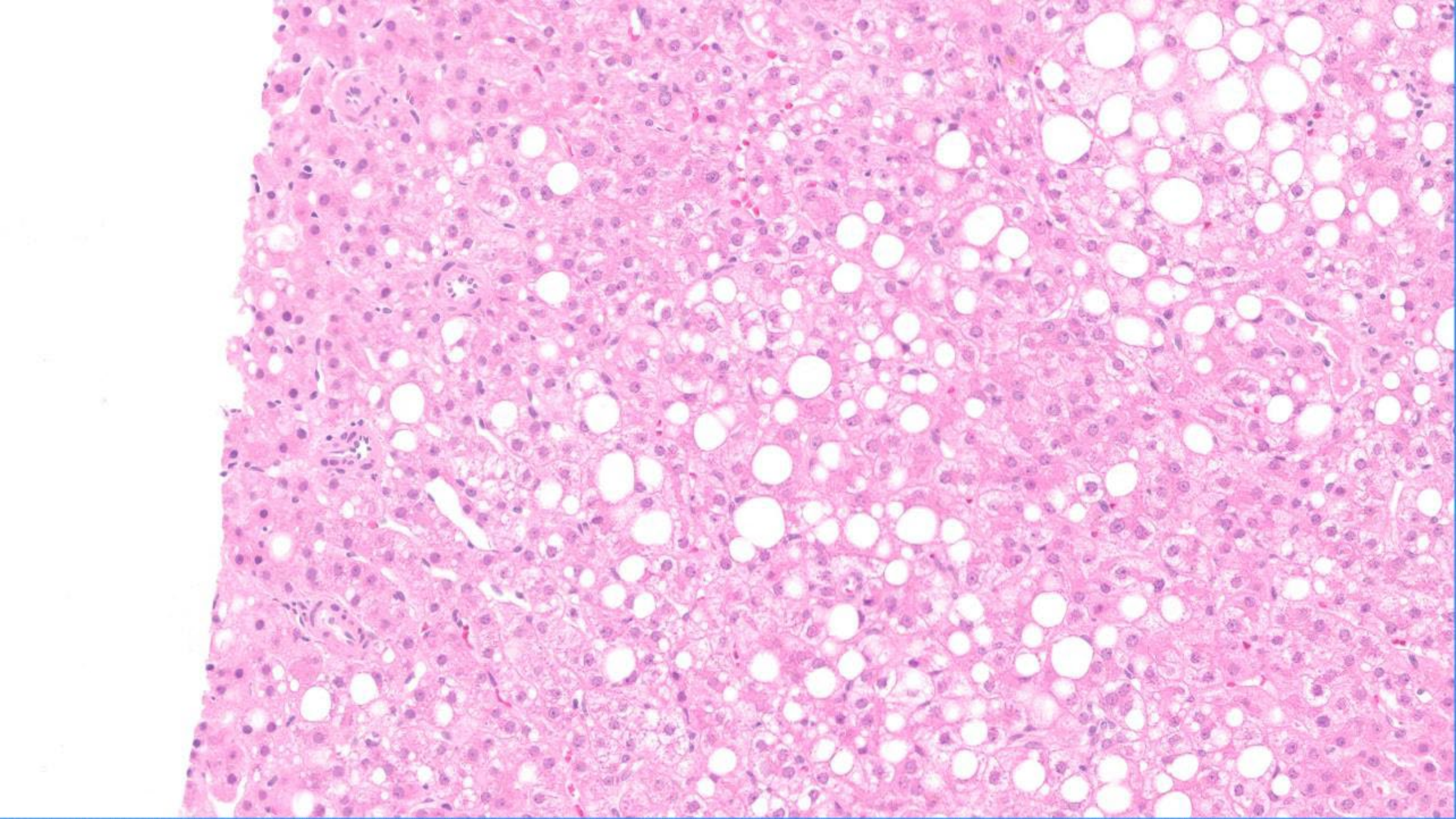


Risk stratification based on a combination of clinical, radiologic, histologic, and molecular features is necessary for appropriate management.

Glutamine synthetase



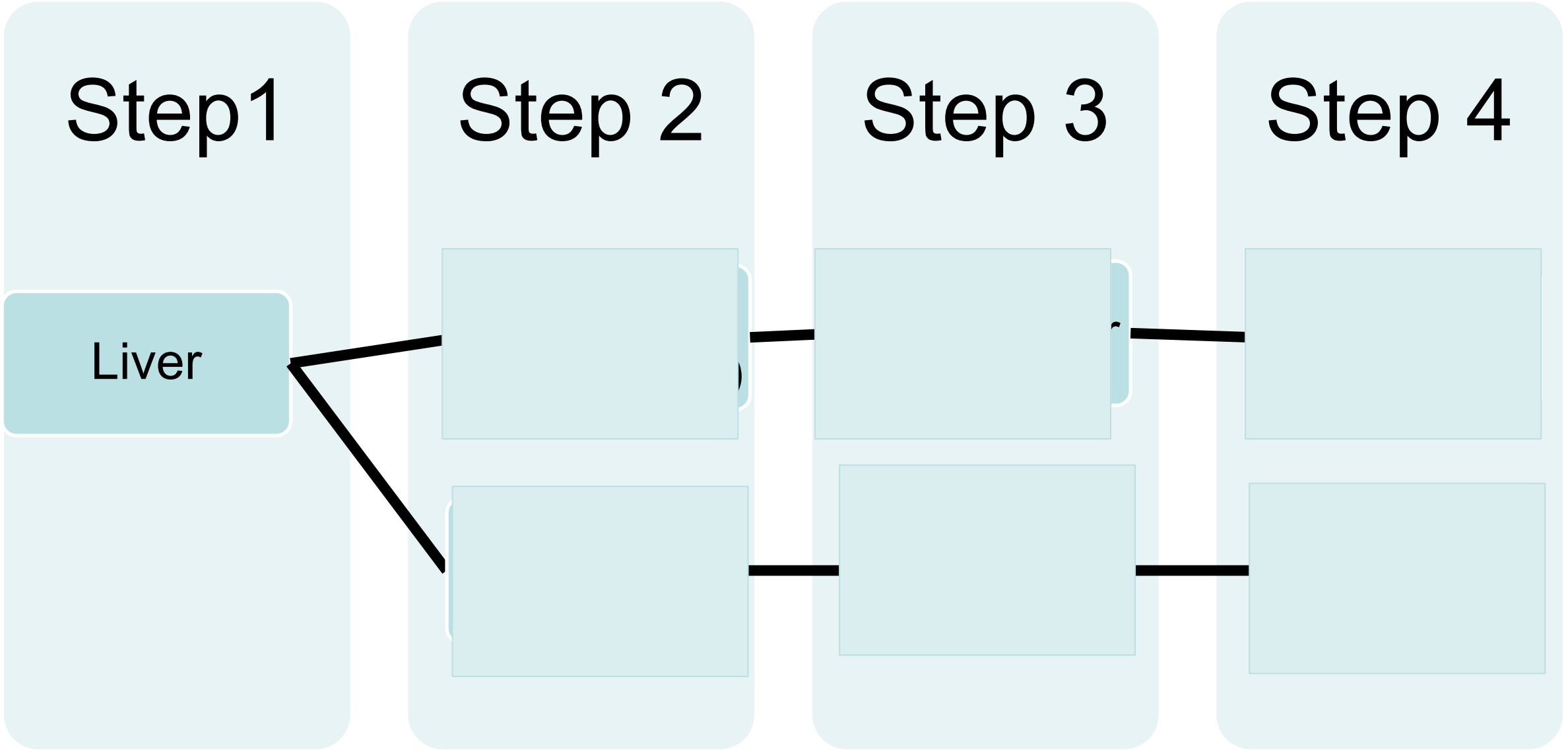

Packeting
Lesional



L-FABP1

HNF1a inactivated adenoma
aka “fatty adenoma”

HNF1a inactivated adenoma aka “fatty adenoma”



Management of Hepatic Adenoma

- Beta catenin + adenoma

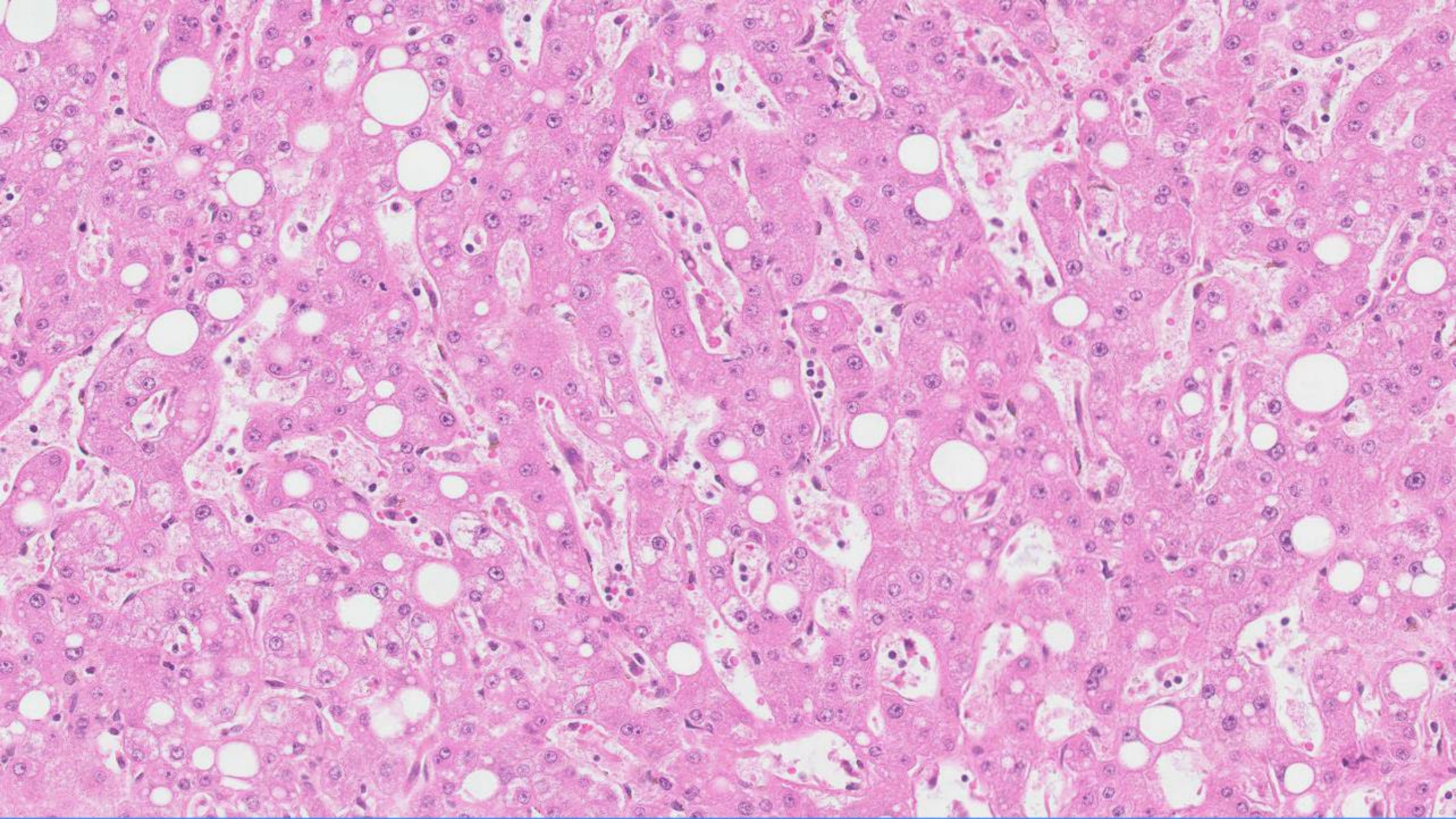
More likely transform to HCC

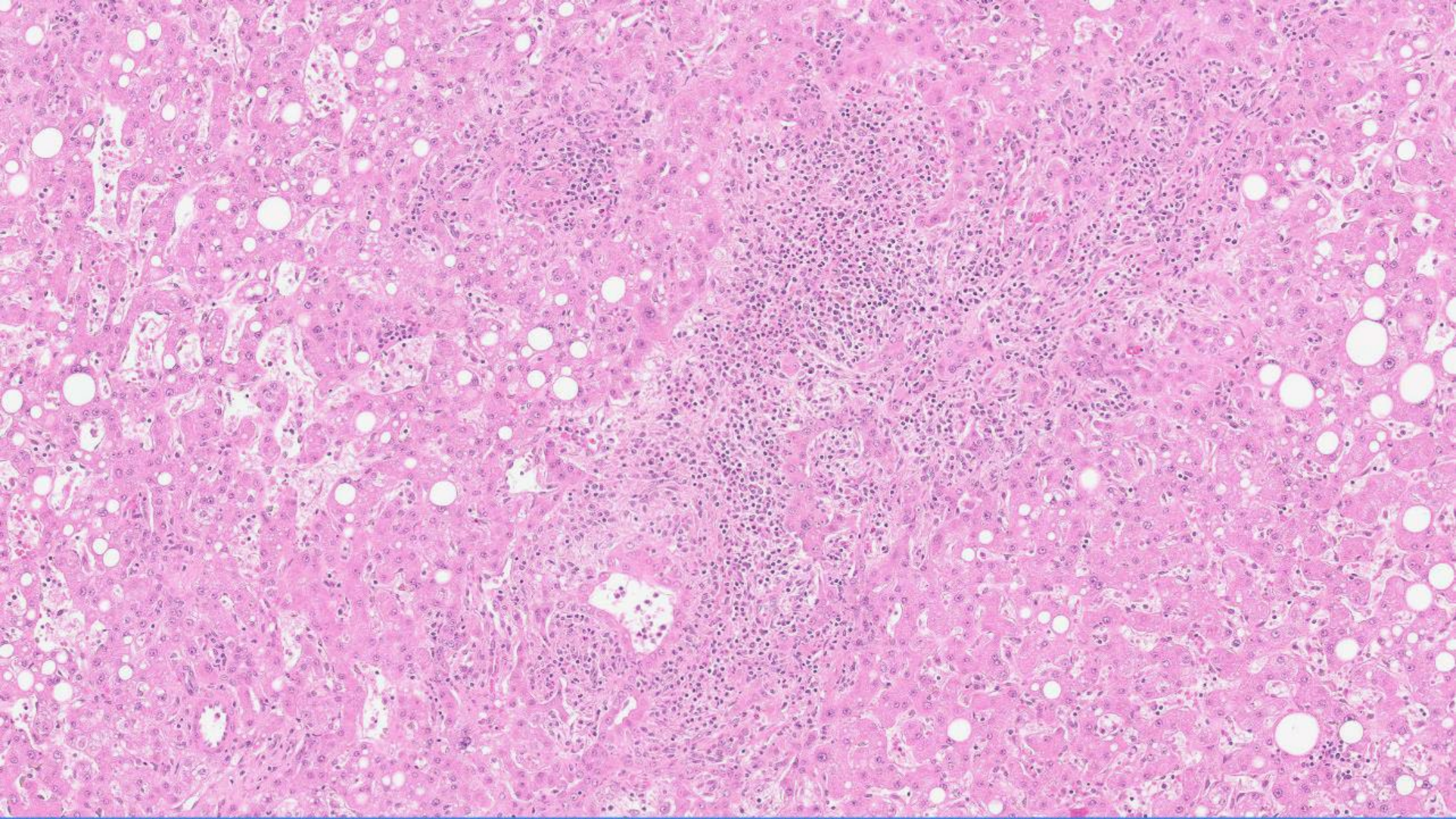
Inflammatory adenoma

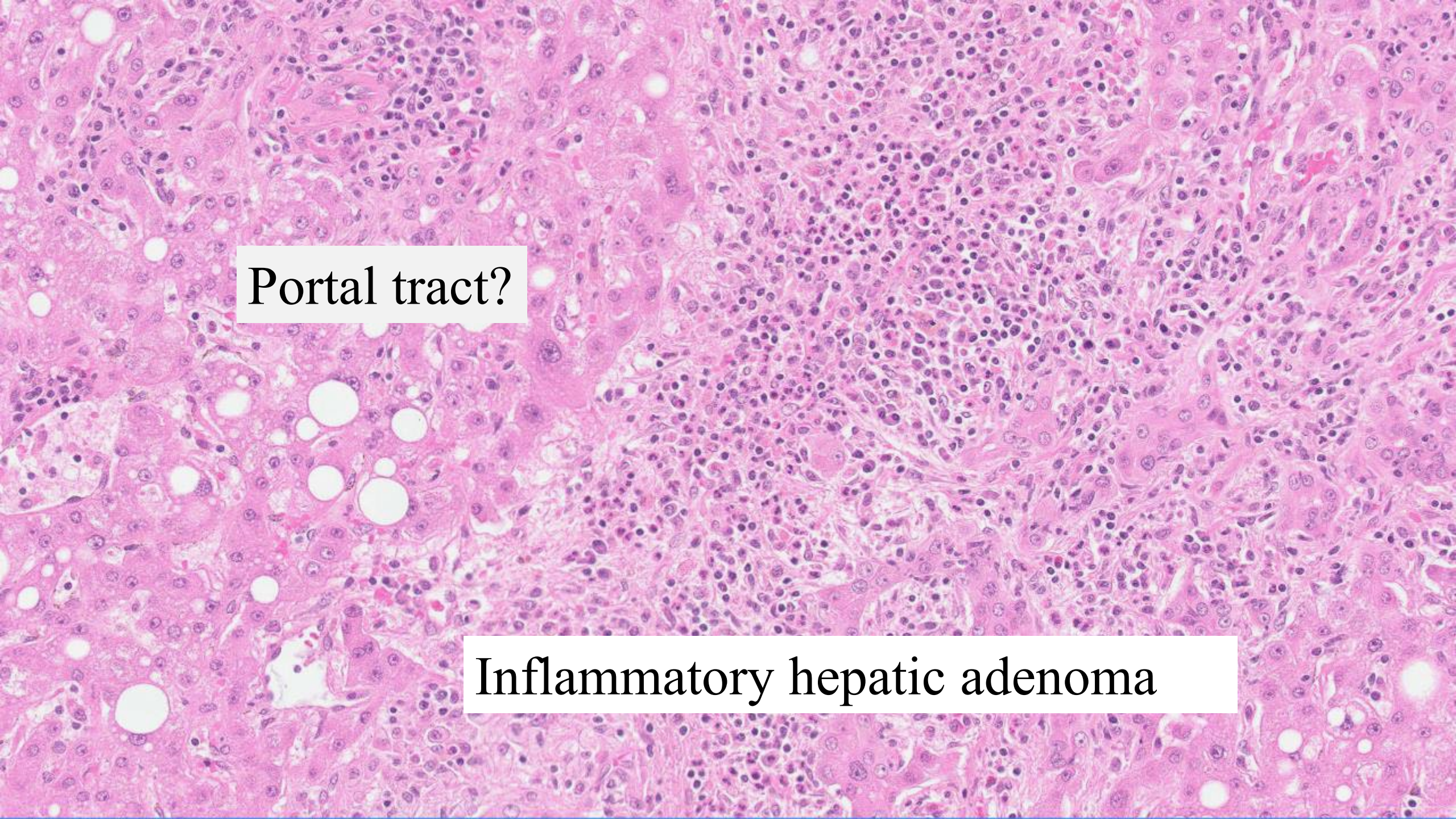
Less likely to transform to HCC

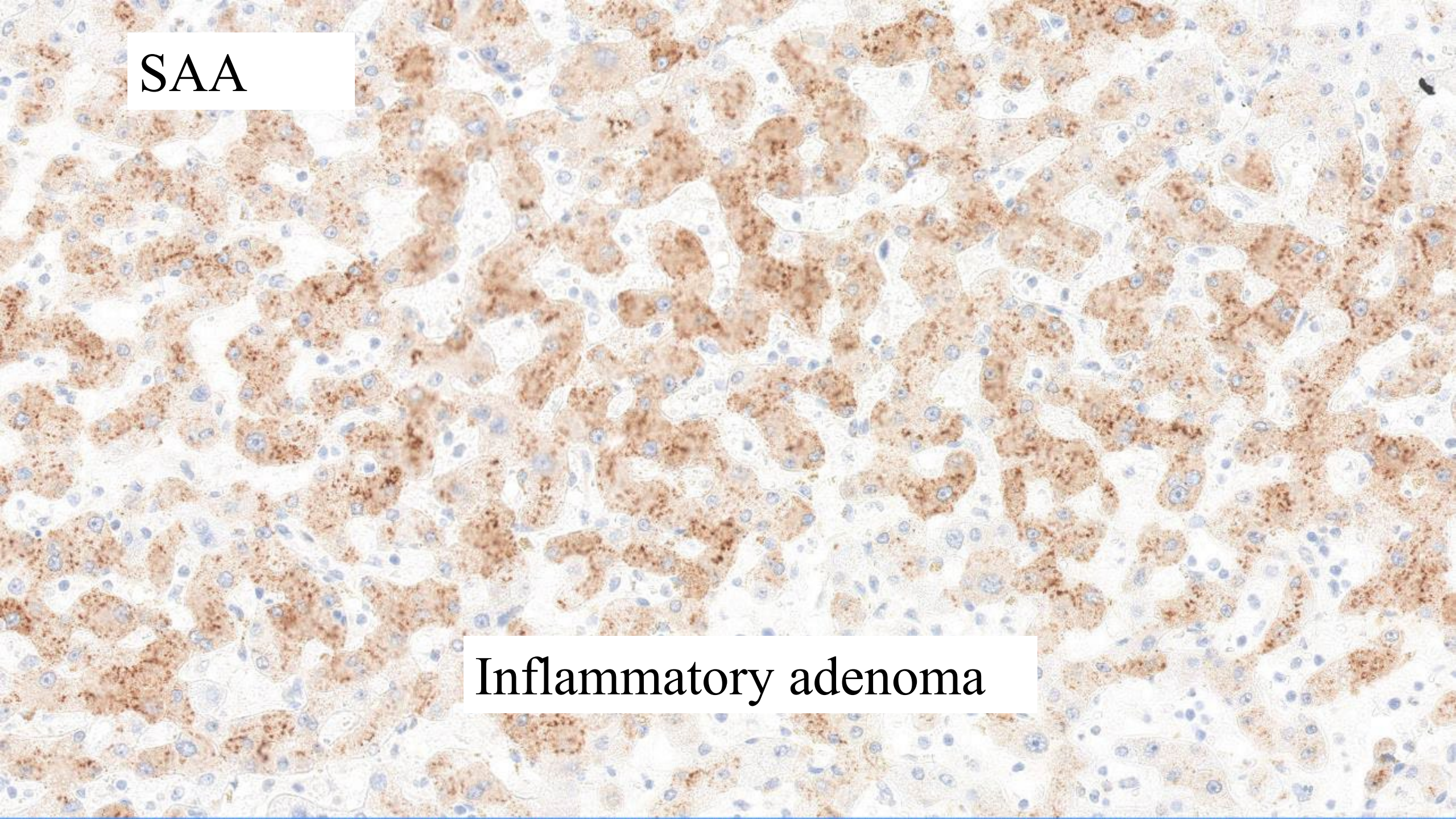
HNF1a inactivated adenoma aka "fatty adenoma"


L
N






Portal tract?
Inflammatory hepatic adenoma


SAA
Inflammatory adenoma

Management of Hepatic Adenoma

- Beta catenin + adenoma

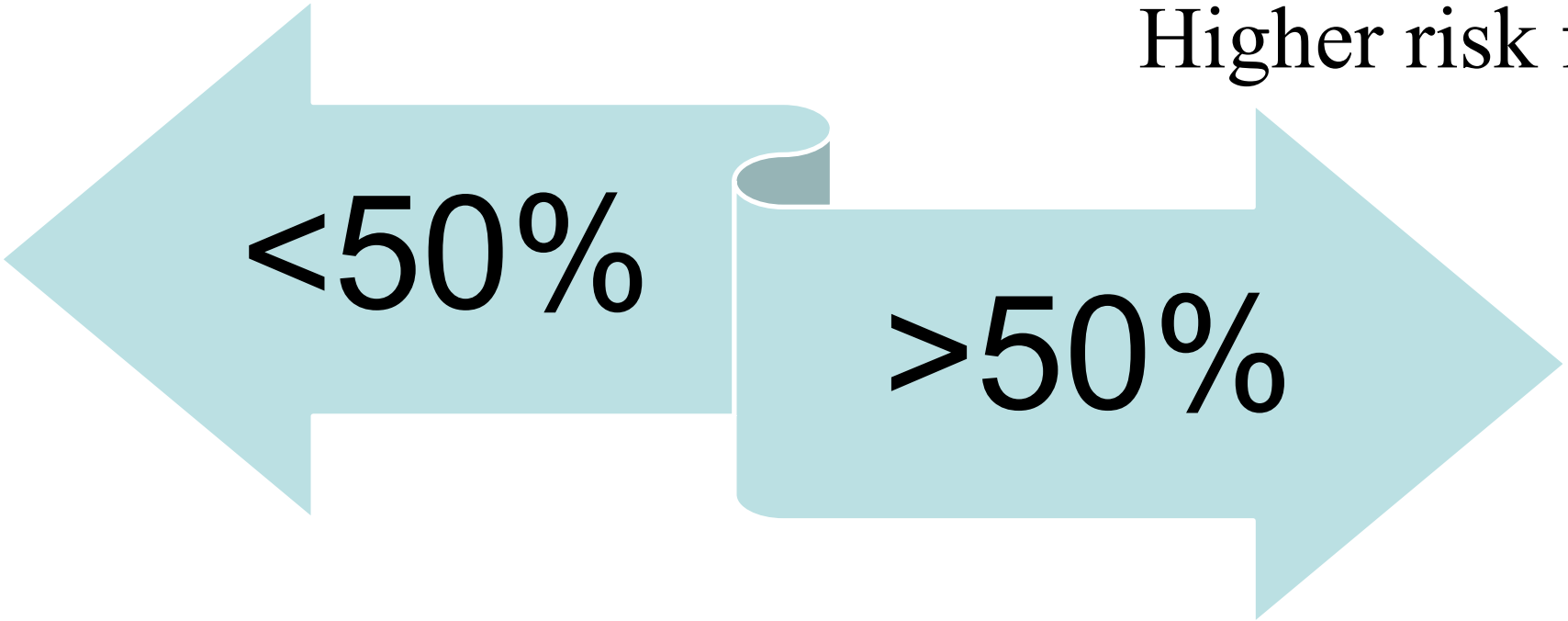
More likely transform to HCC

Less likely to transform to HCC

HNF1a inactivated adenoma aka "fatty adenoma"

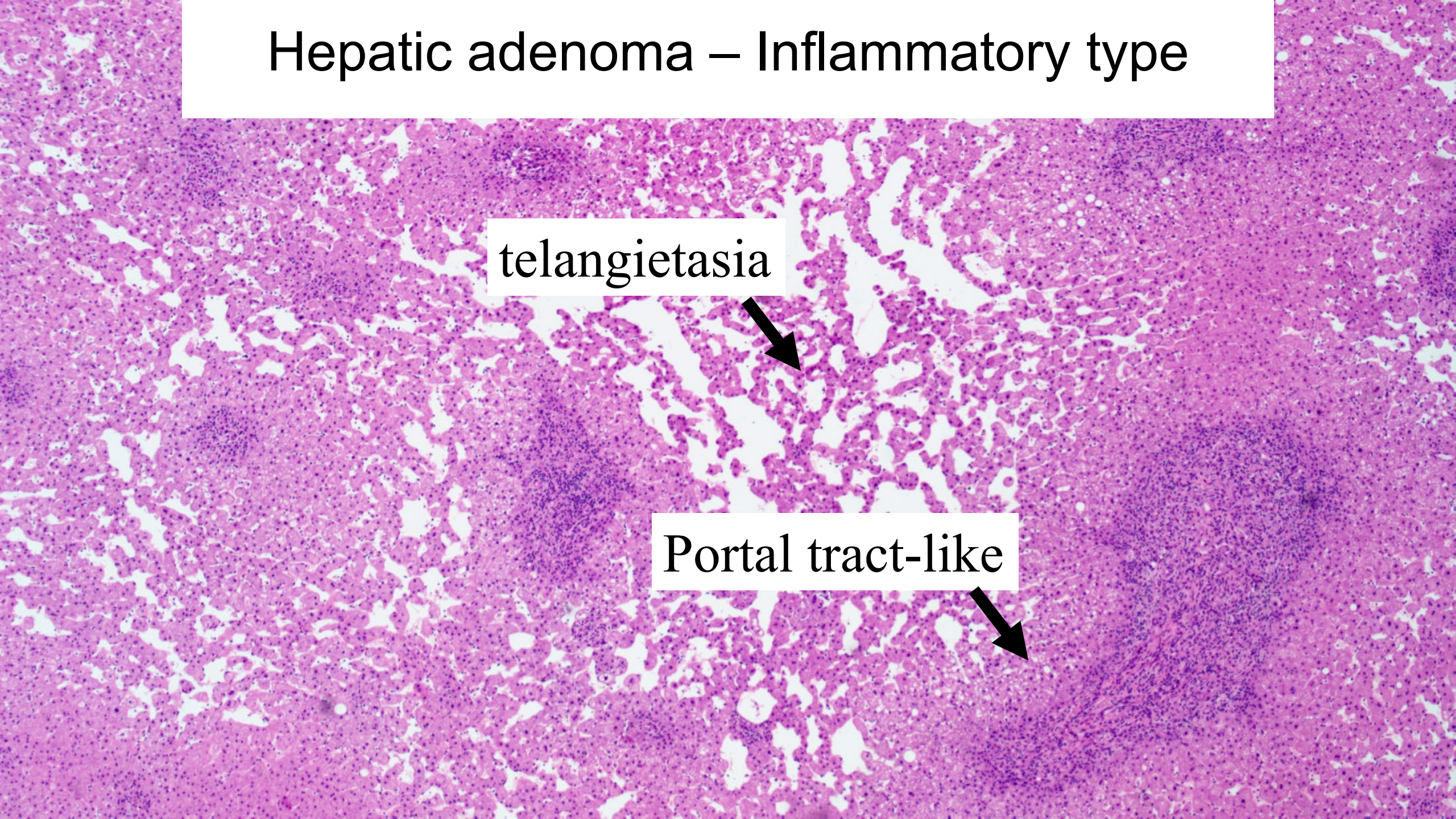
Inflammatory adenoma

Glutamine synthetase

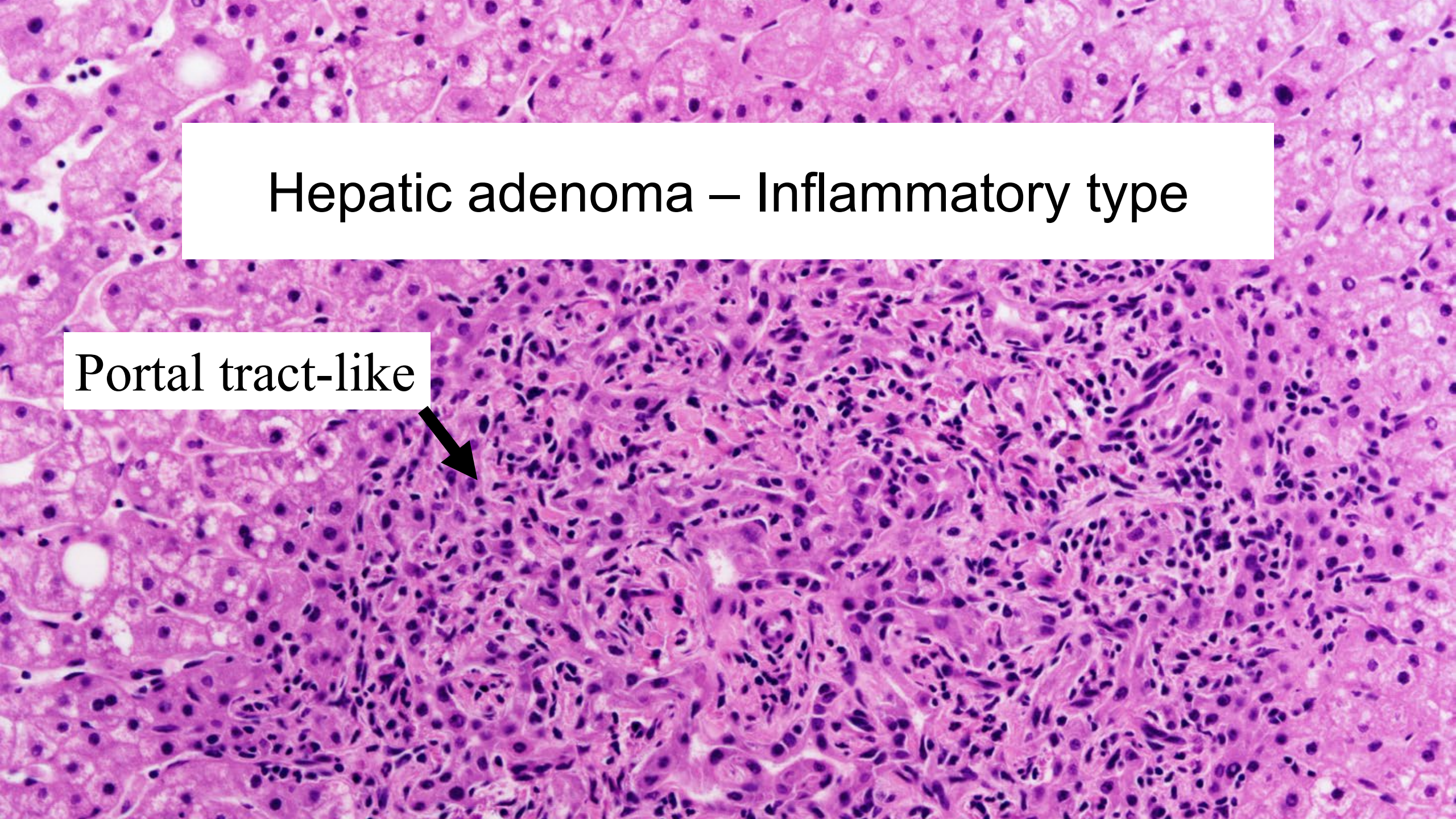


Low risk for HCC

Hepatic adenoma – Inflammatory type



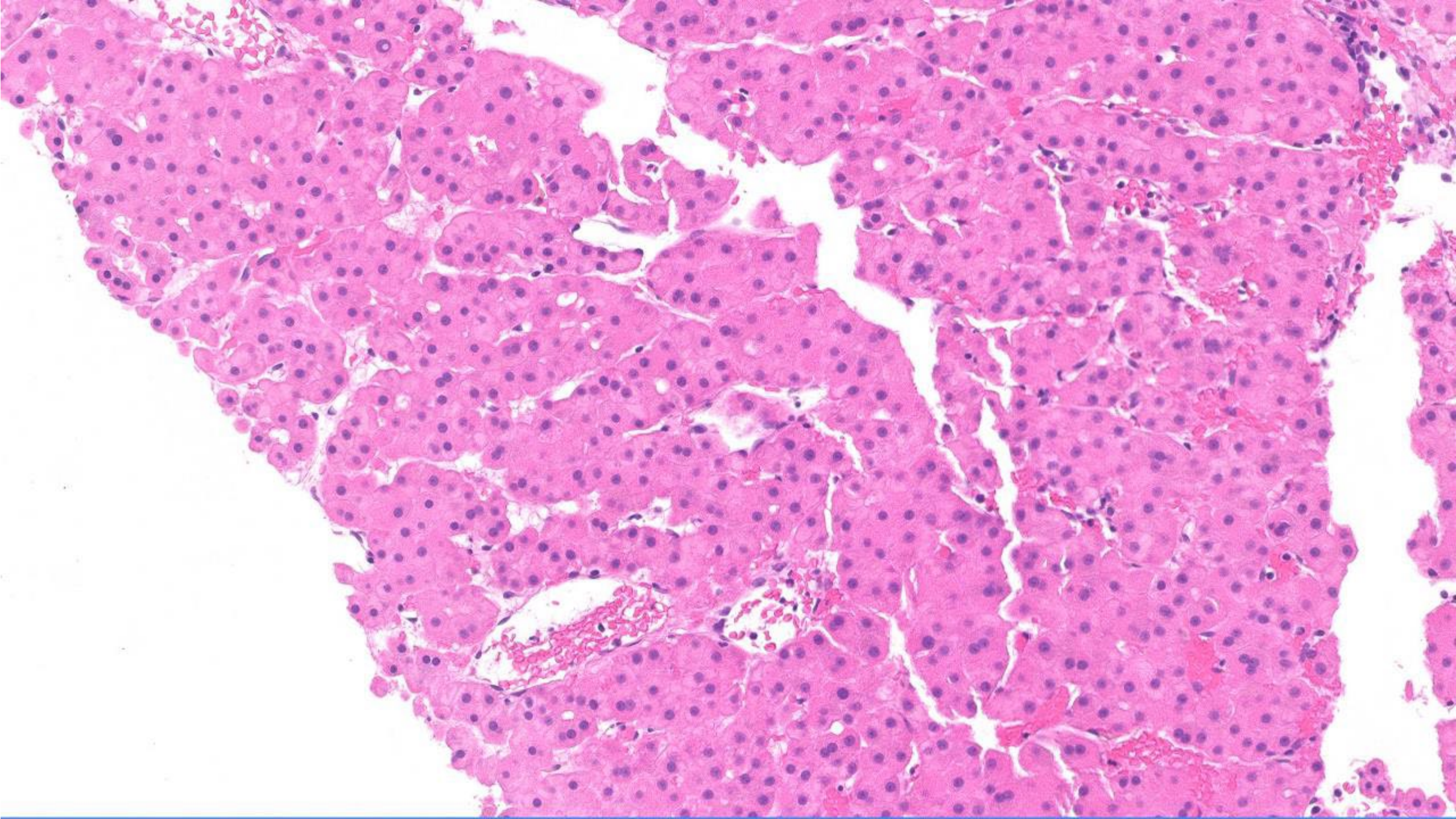
Hepatic adenoma – Inflammatory type

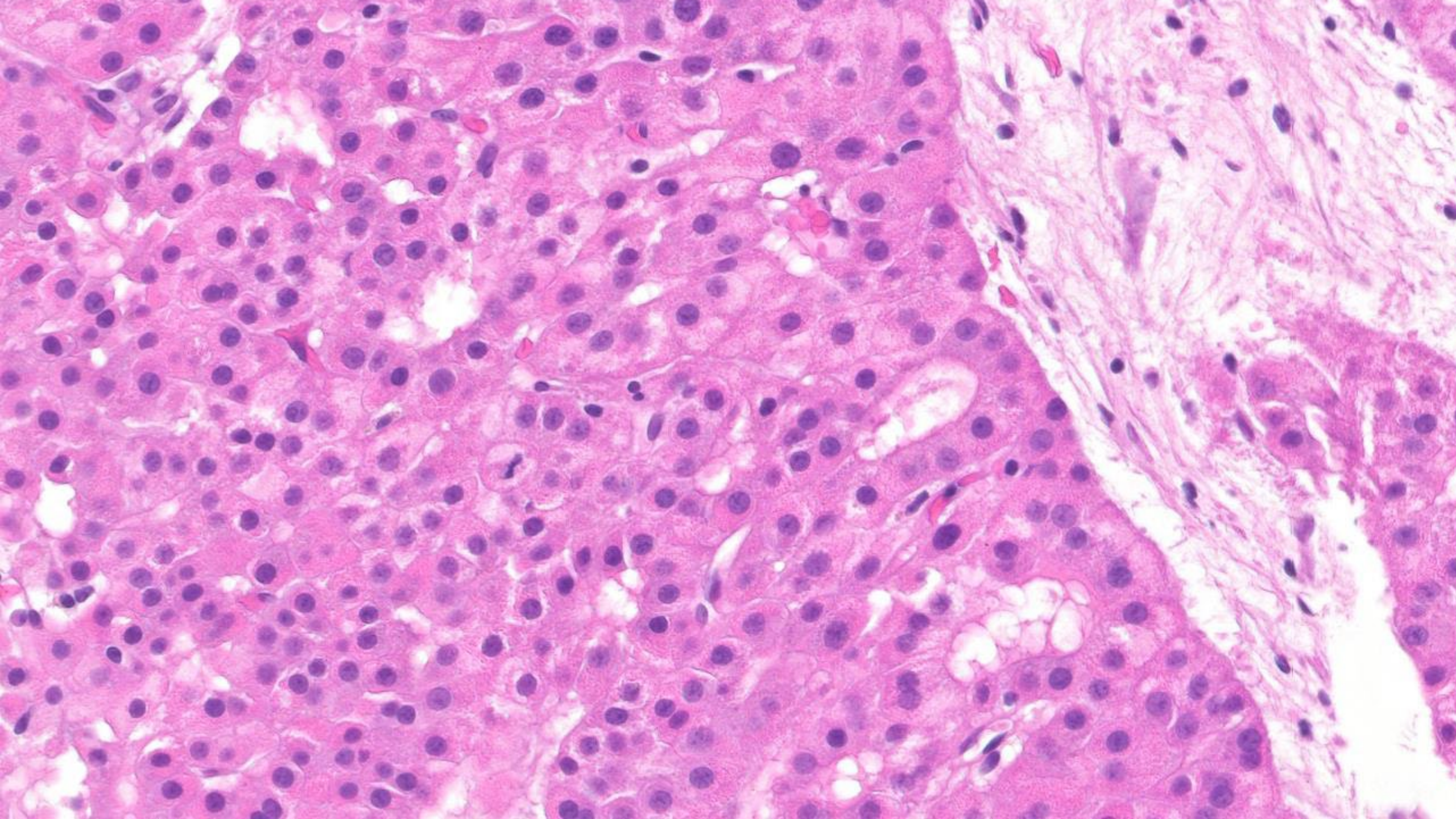


FNH vs. Inflammatory HCA

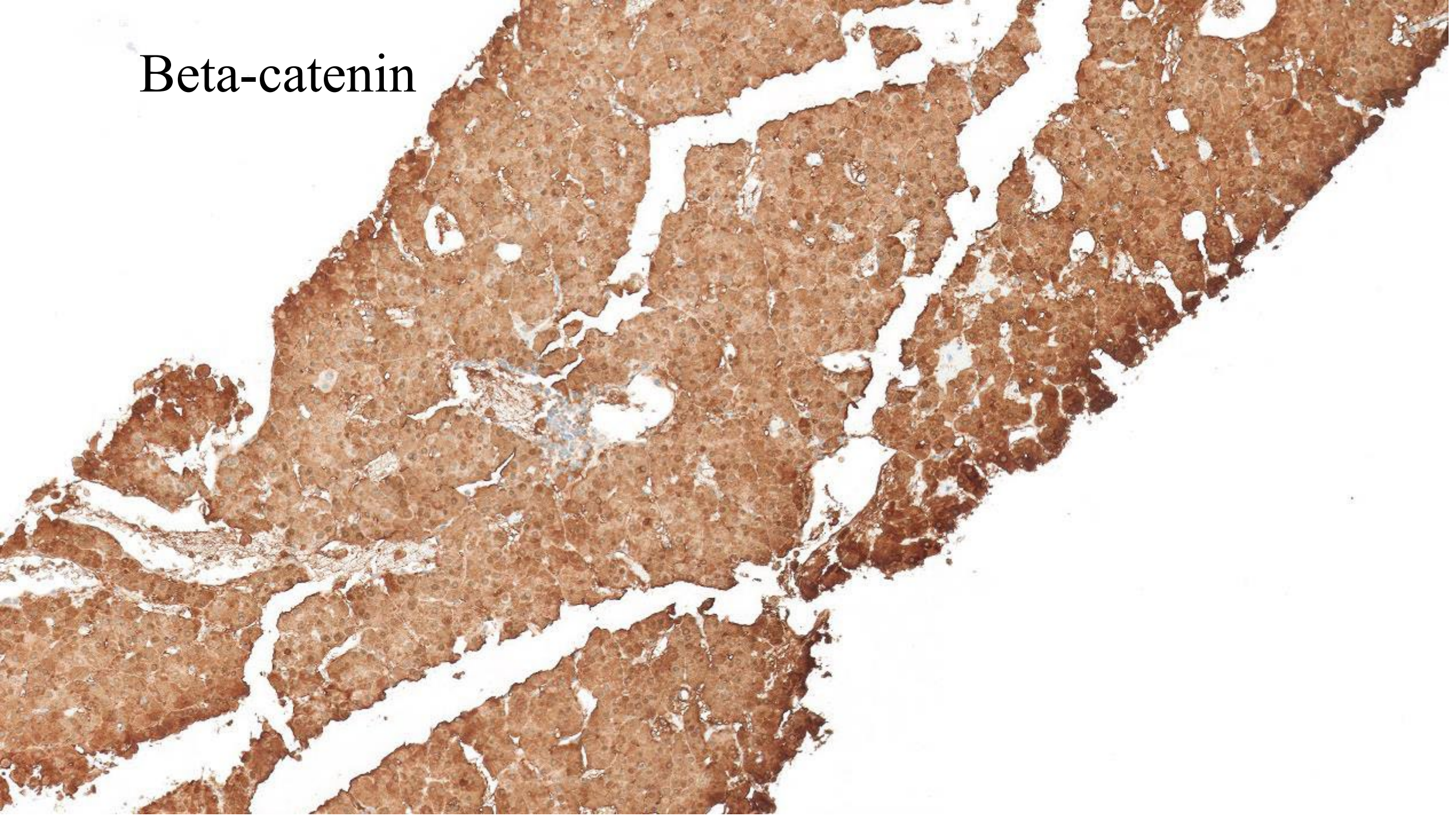
	HA inflammatory	FNH
Central scar	-	+++/-
Large irregular vascular channels	-	+++/+
Glutamine synthetase	Largely negative or diffusely positive	Map like

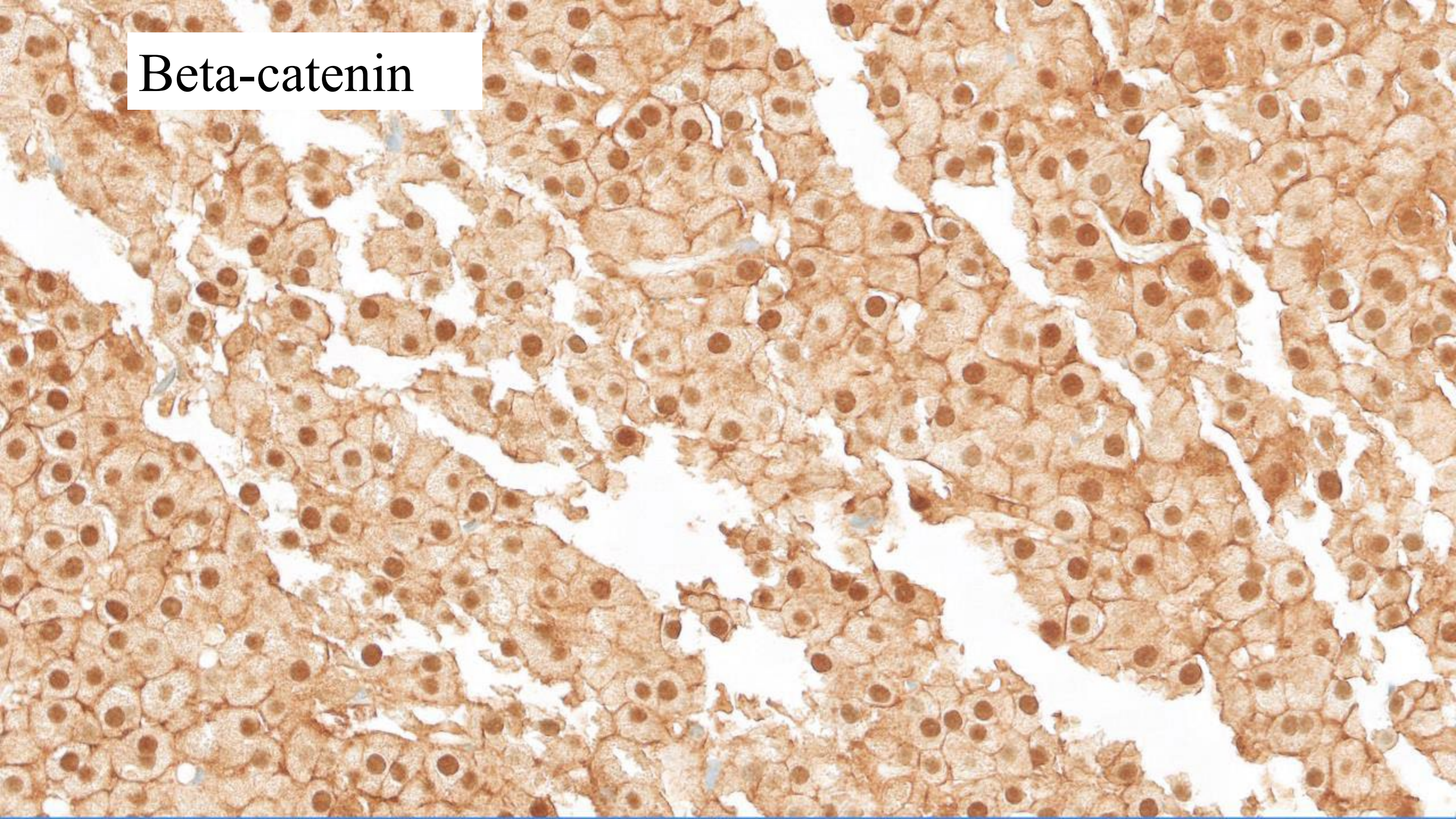
47/F

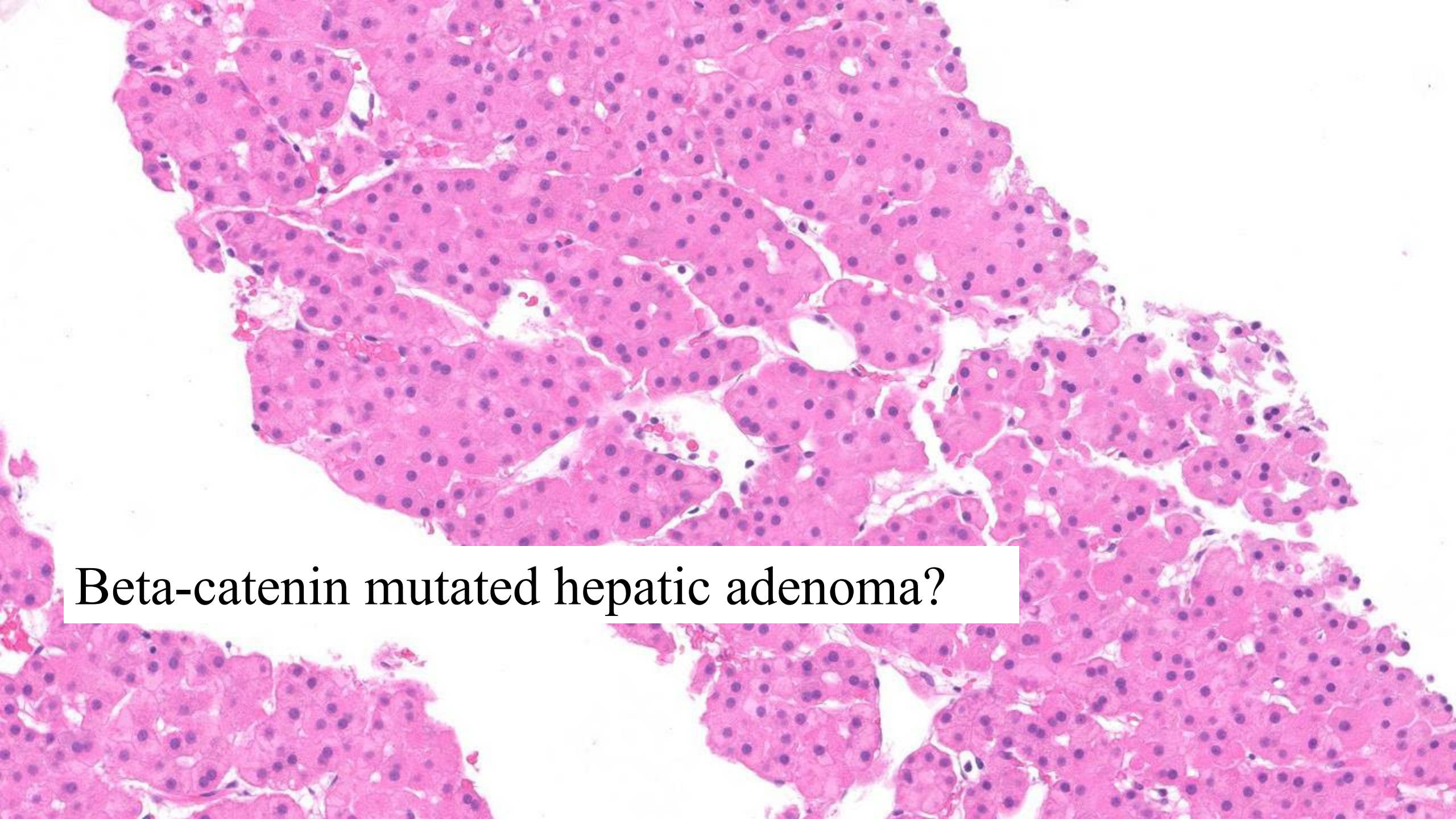




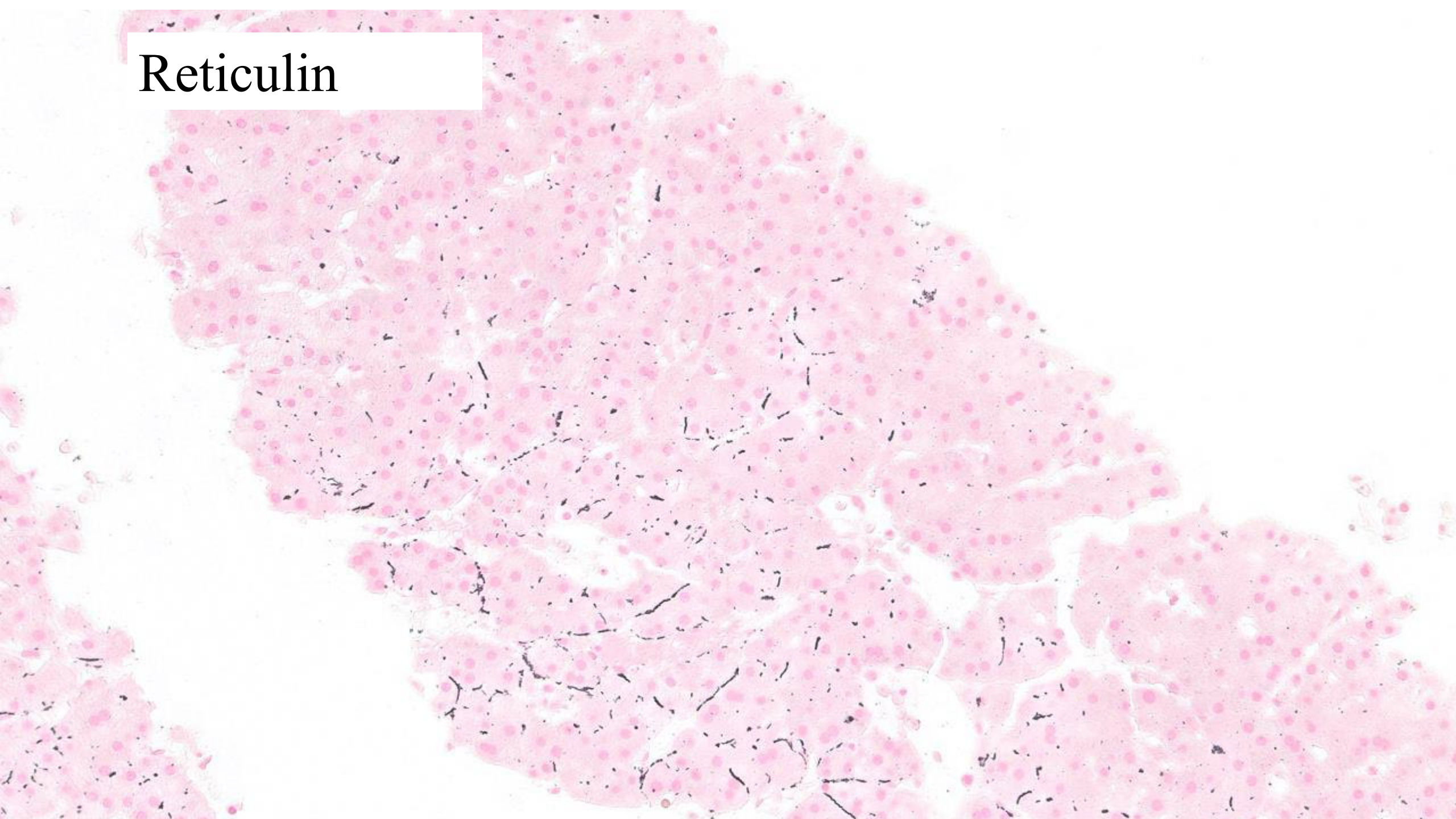
Beta-catenin

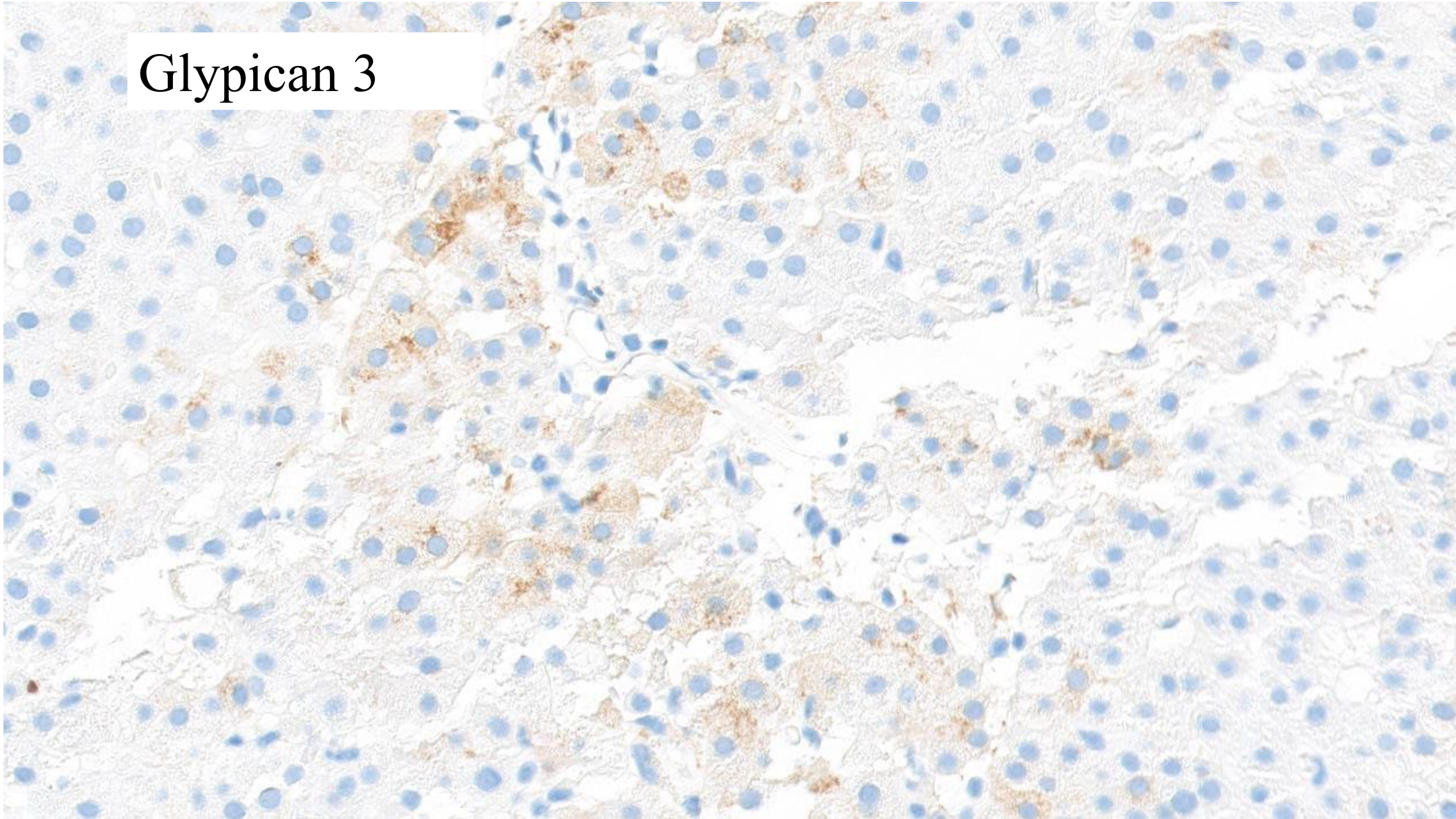



Beta-catenin

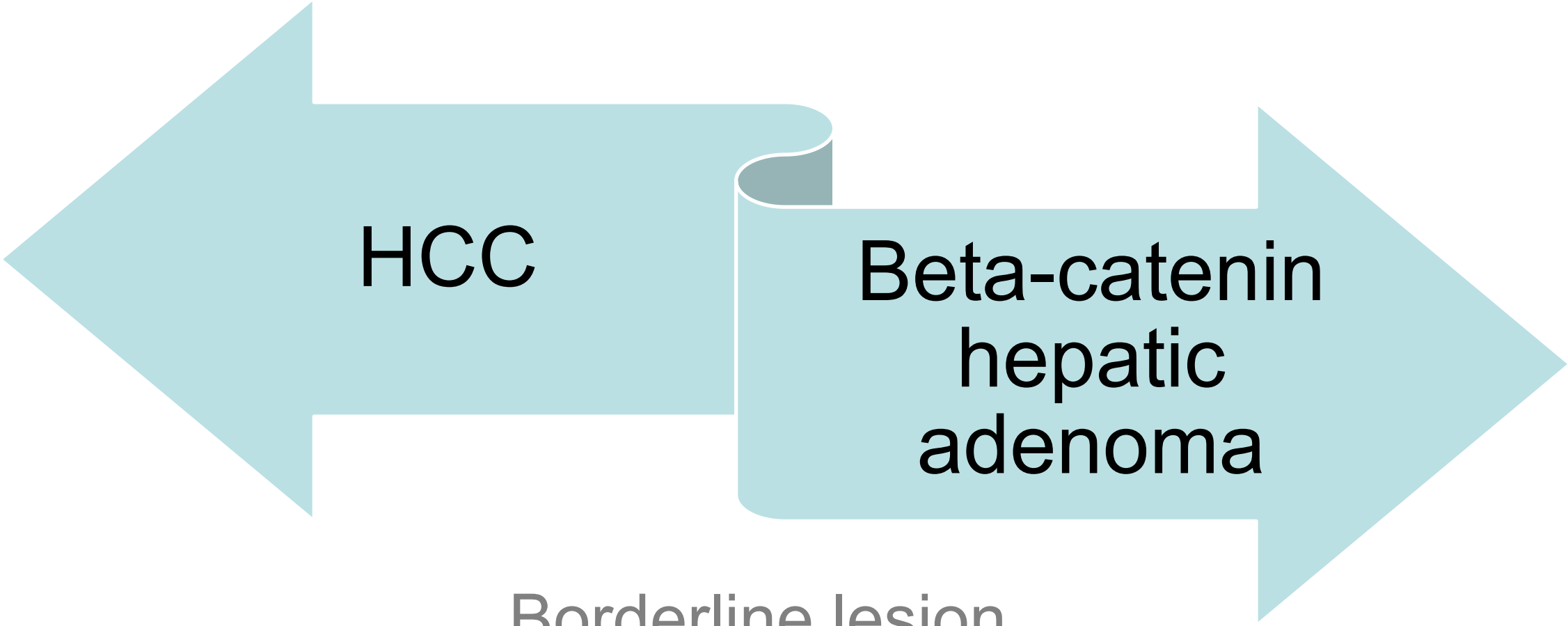

Beta-catenin mutated hepatic adenoma?

Reticulin




Glypican 3

Atypical hepatocellular neoplasm



Borderline lesion

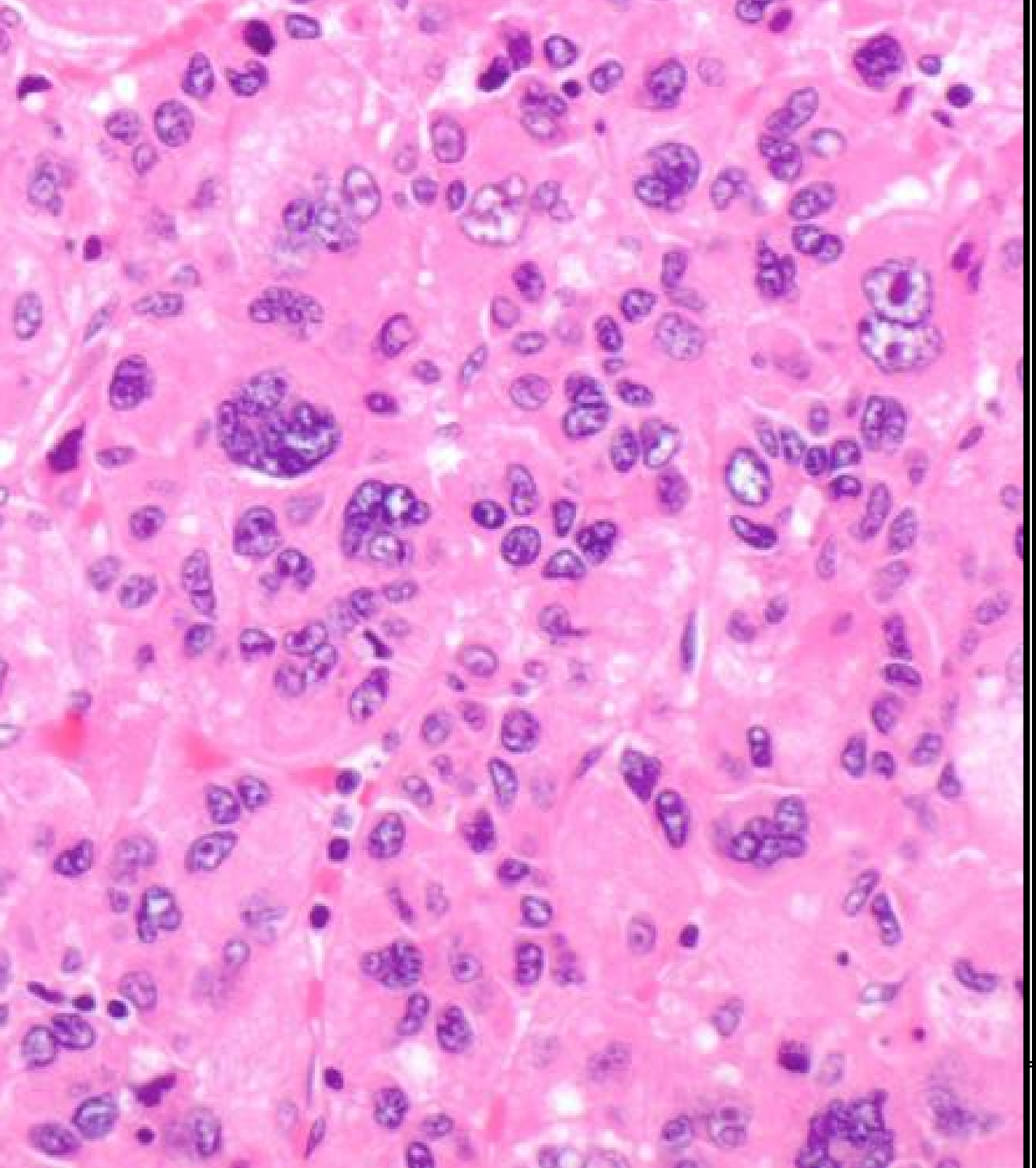
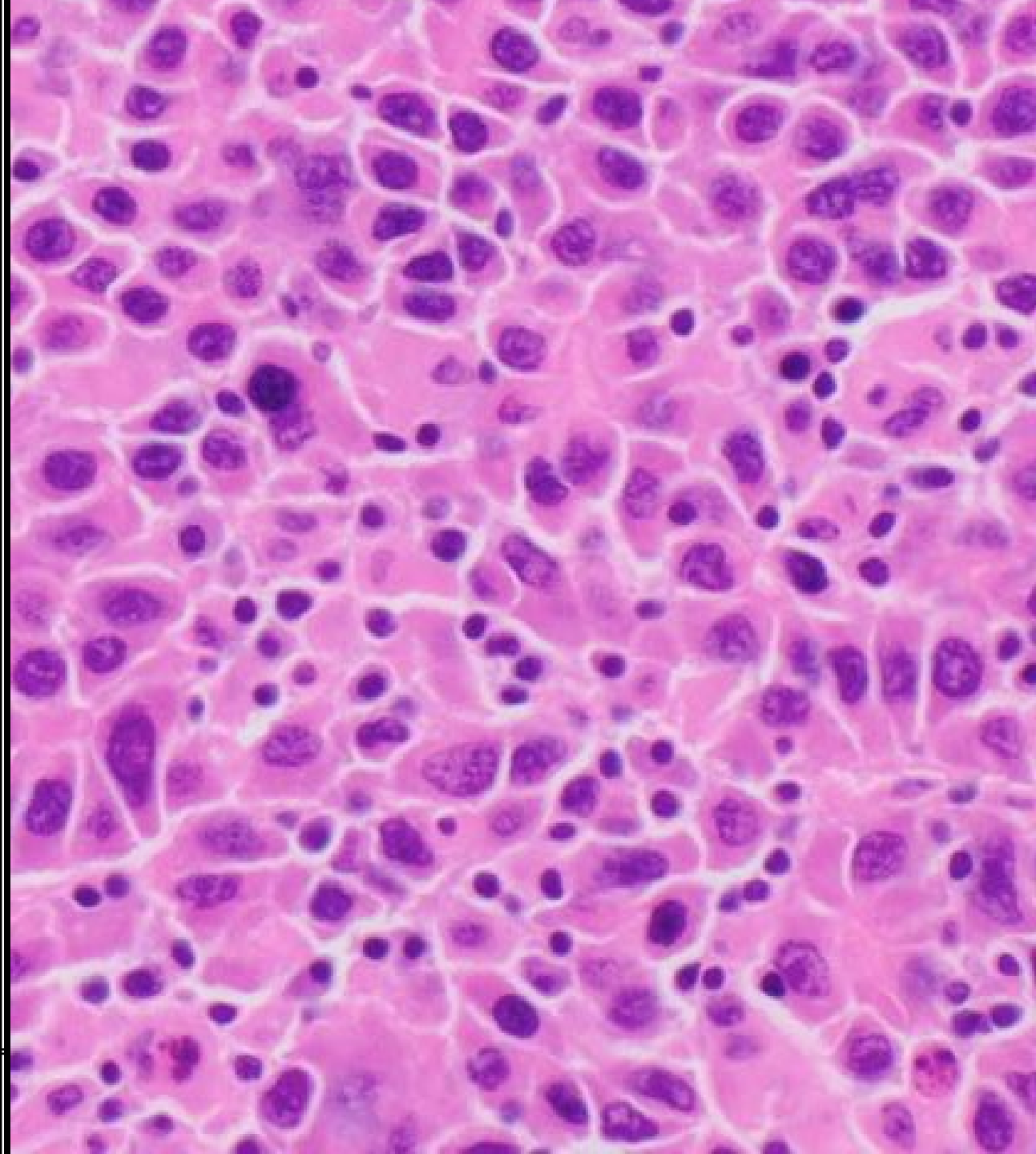
Stain	Utility	Limitations
Liver fatty-acid binding protein (LFABP)	• Loss of cytoplasmic expression in HNF1A-inactivated HCA	• Loss does not distinguish H-HCA from HCC • Interpretation may be difficult due to faint staining of background non-neoplastic liver • Not clear if LFABP loss in moderately/poorly differentiated HCC is related to HNF1A mutations
Serum amyloid associated (SAA)	• Diffuse strong staining in inflammatory HCA (IHCA)	• 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)	• Diffuse strong staining in inflammatory HCA (IHCA)	• 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)	• 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	• 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	• Nuclear staining in tumors with CTNNB1/other Wnt signaling pathway mutations	• Low sensitivity, particularly on needle-core biopsy
CD34	• Increase in sinusoidal staining in FNH, HCA and HCC	• Diffuse sinusoidal staining not specific for HCC and may be seen in FNH and HCA
Glypican-3	• Positive staining in HCC	• 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

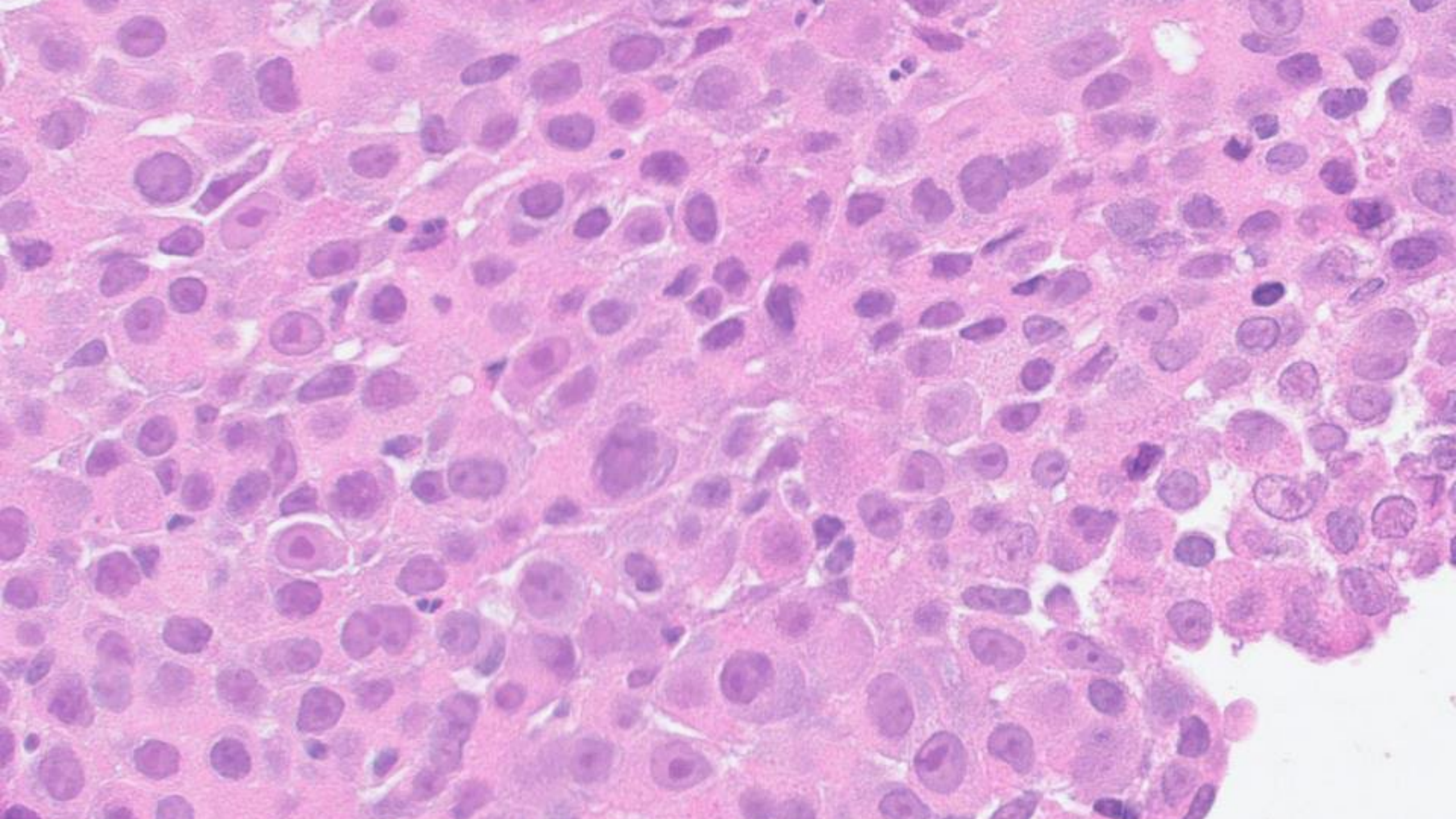
Balitzer, Dana, Kakar, Sanjay My approach to hepatic adenoma. Diagnostic Histopathology 2022

Do not use these stains for a diagnosis of HCC

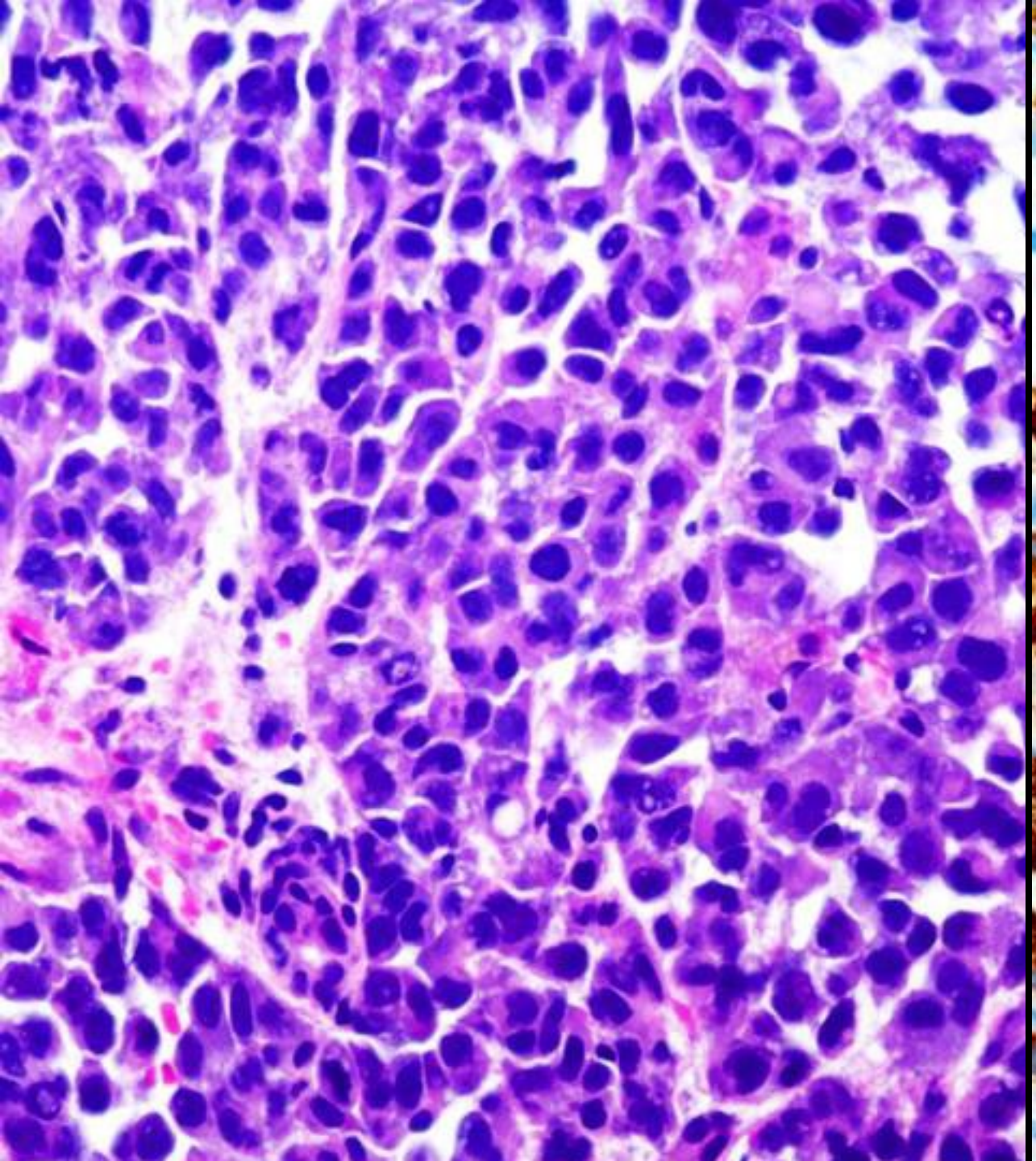
SAA, CRP, FABP

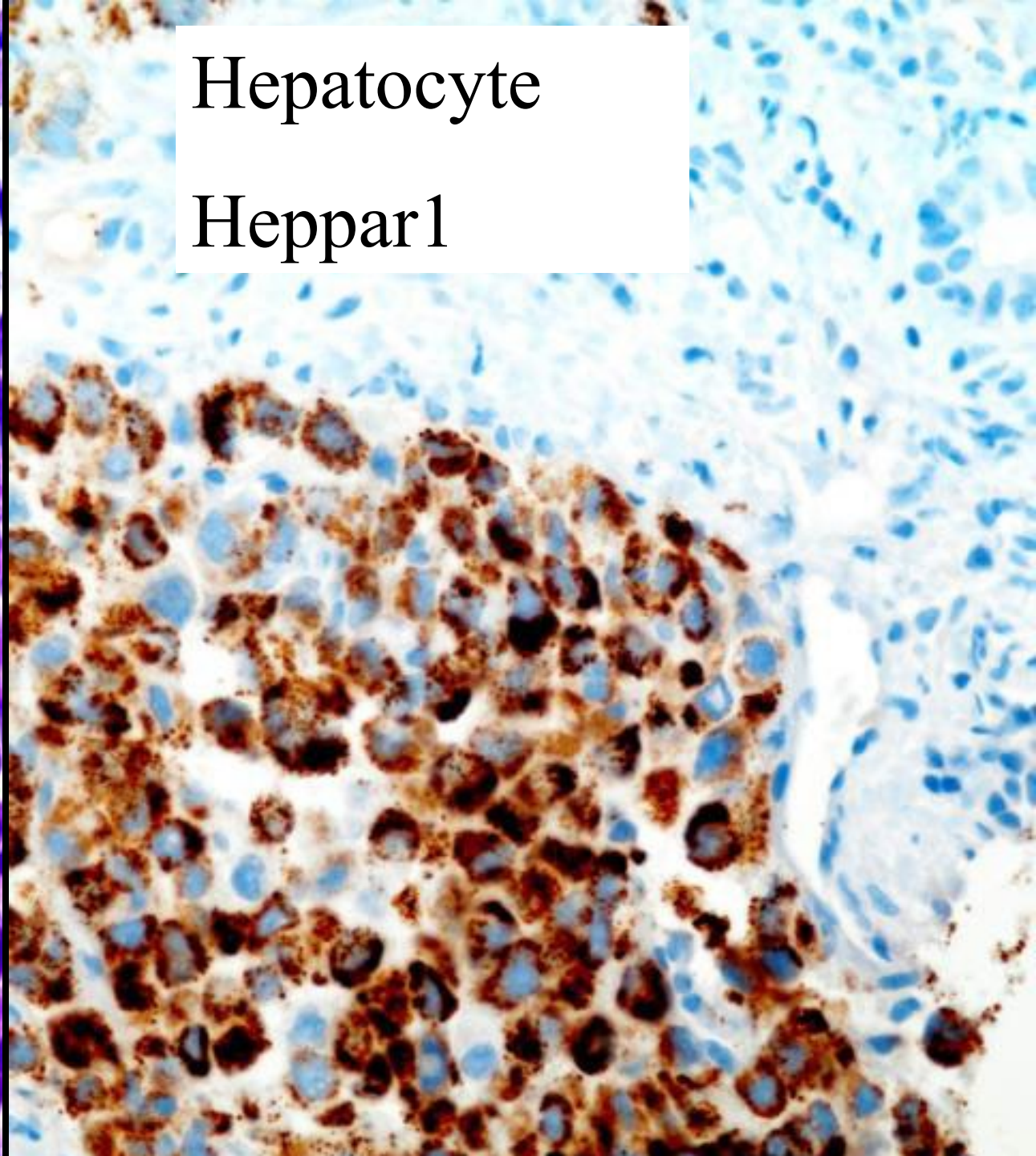
Question 5: I have a poorly differentiated carcinoma on liver biopsy.
Is this an HCC or metastatic carcinoma?



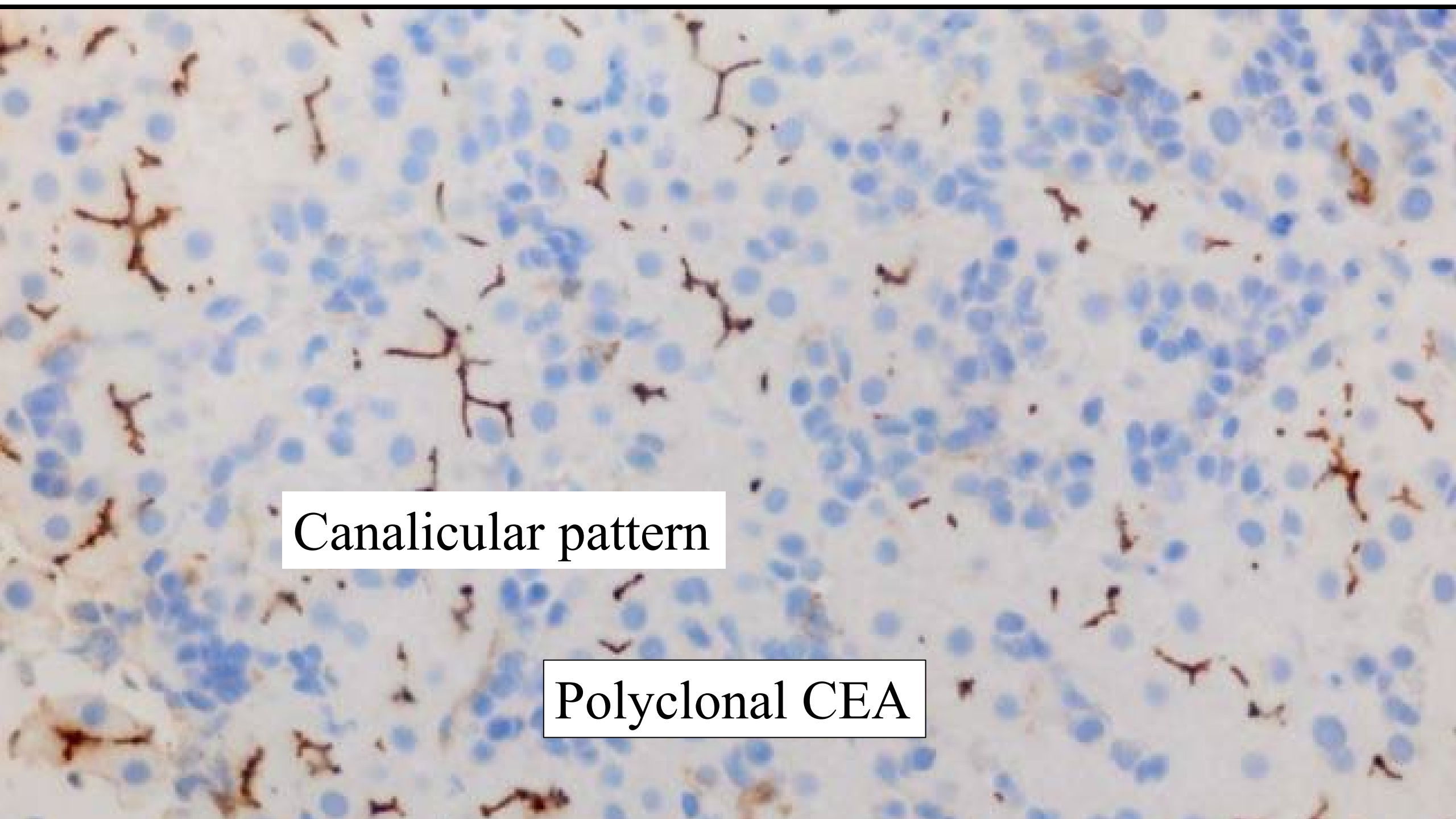
	Target	Sensitivity	Other tumors commonly positive	Poorly differentiated HCCs
AFP	Oncofetal protein	30-50%	Germ cell tumors	Typically negative
Hep Par 1	Carbamoyl phosphatase synthetase (urea cycle)	>90%, staining may be patchy	Lung, colon, esophageal, and gastric carcinoma	<50%
CD10 and polyclonal CEA	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%

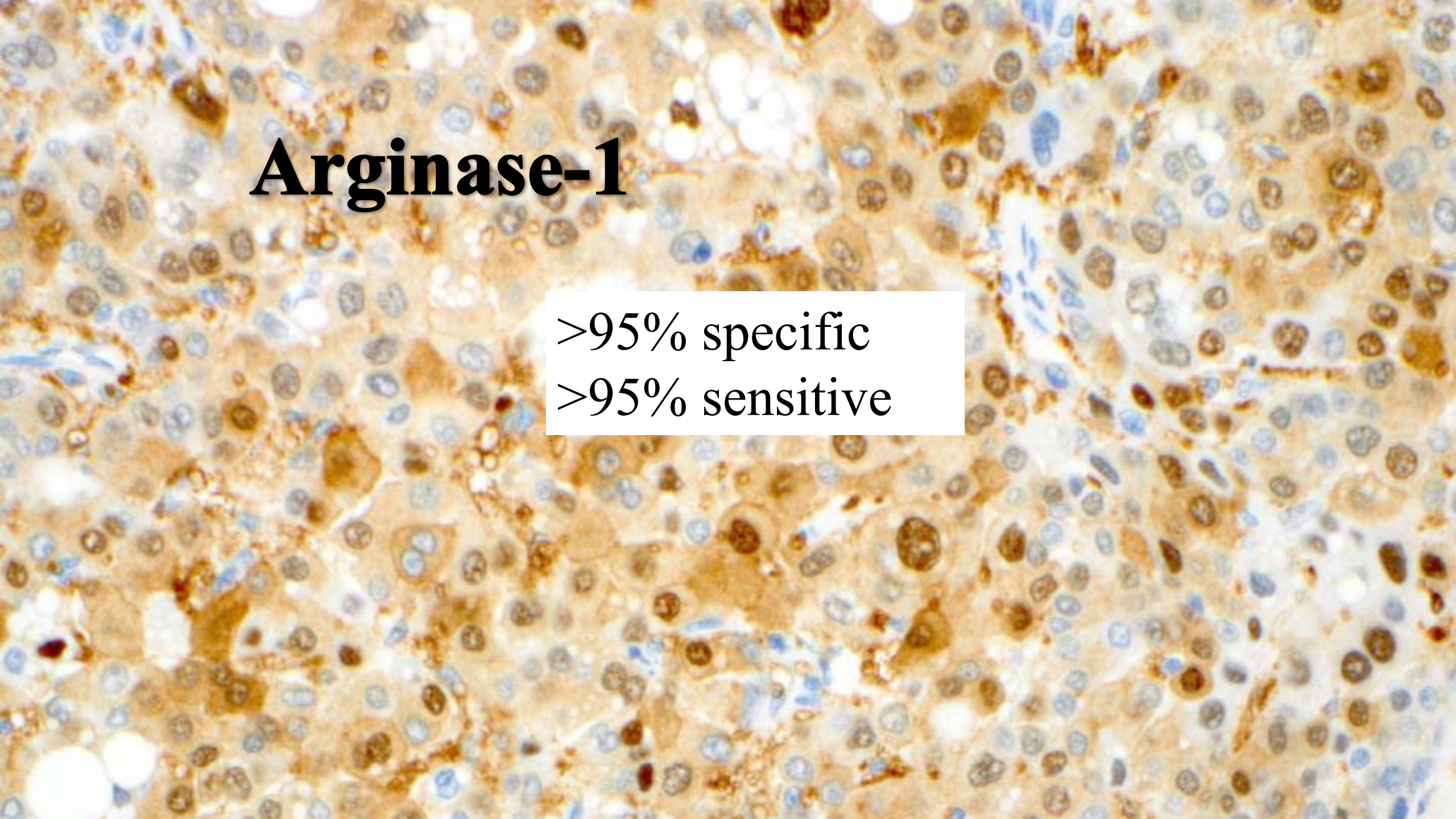



Hepatocyte
Heppar1

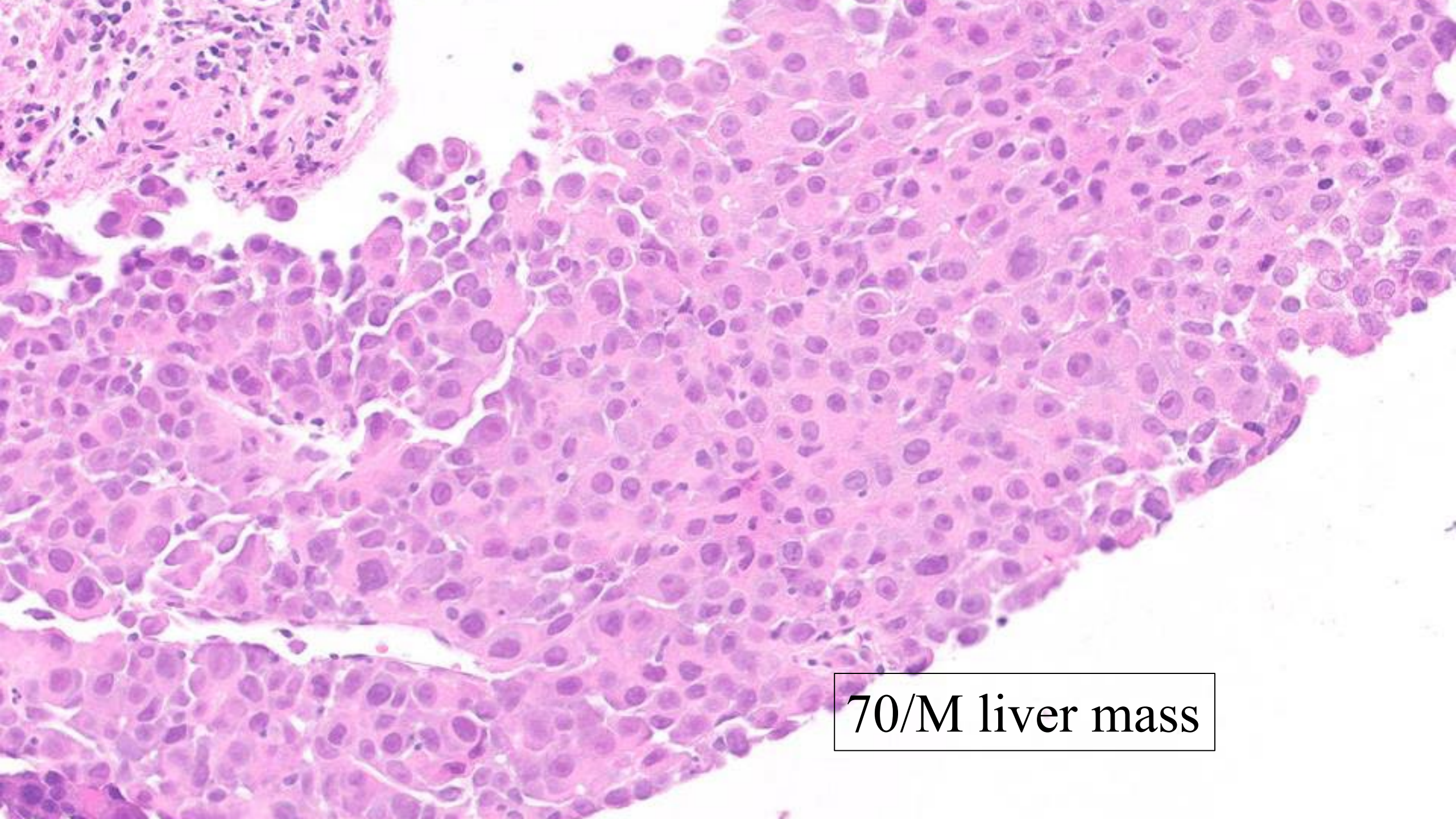
Hep Par 1 is positive in 25% of esophagus/gastric tumors

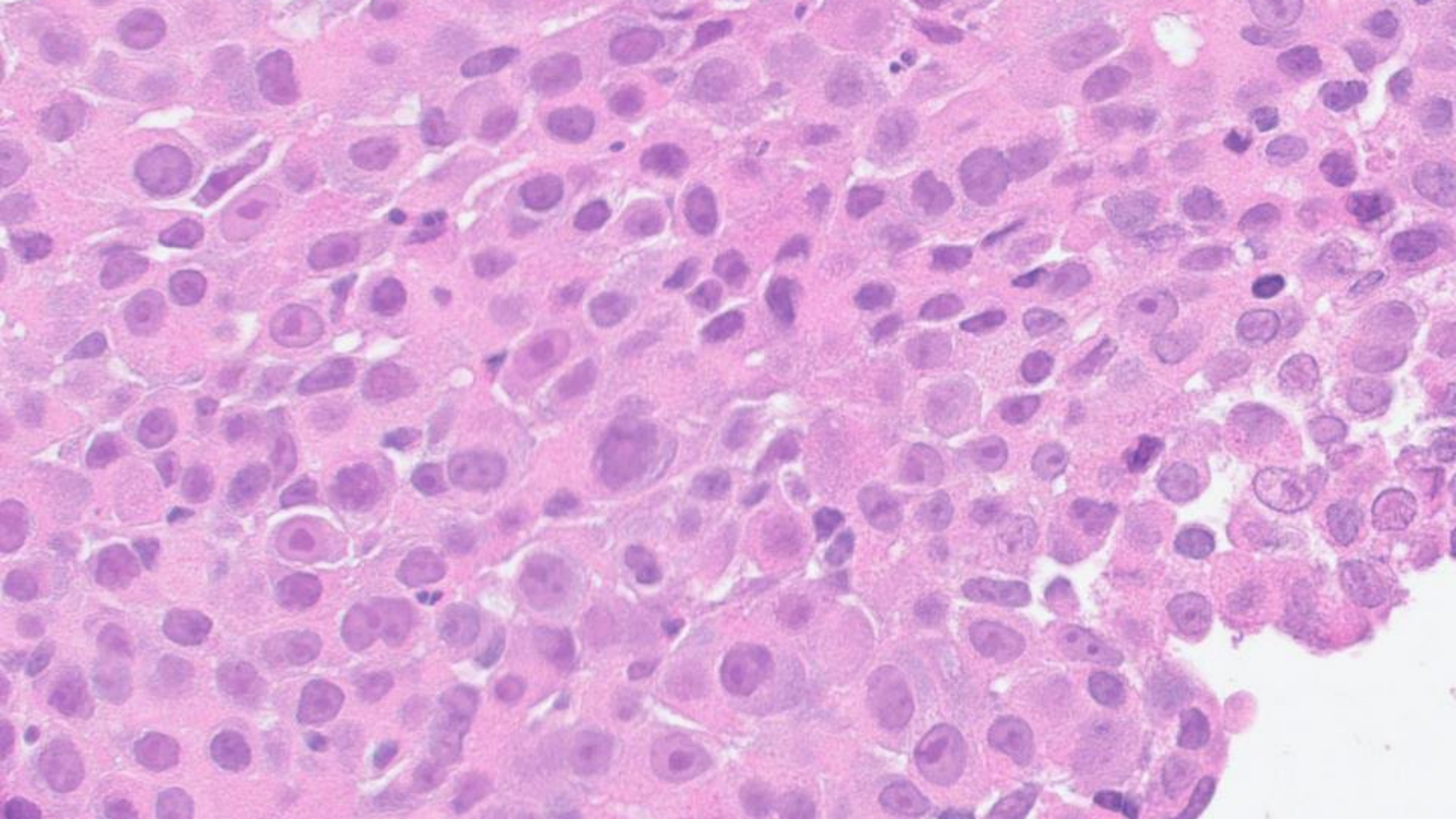
Poorly differentiated Hepatocellular carcinoma
< 50% positive

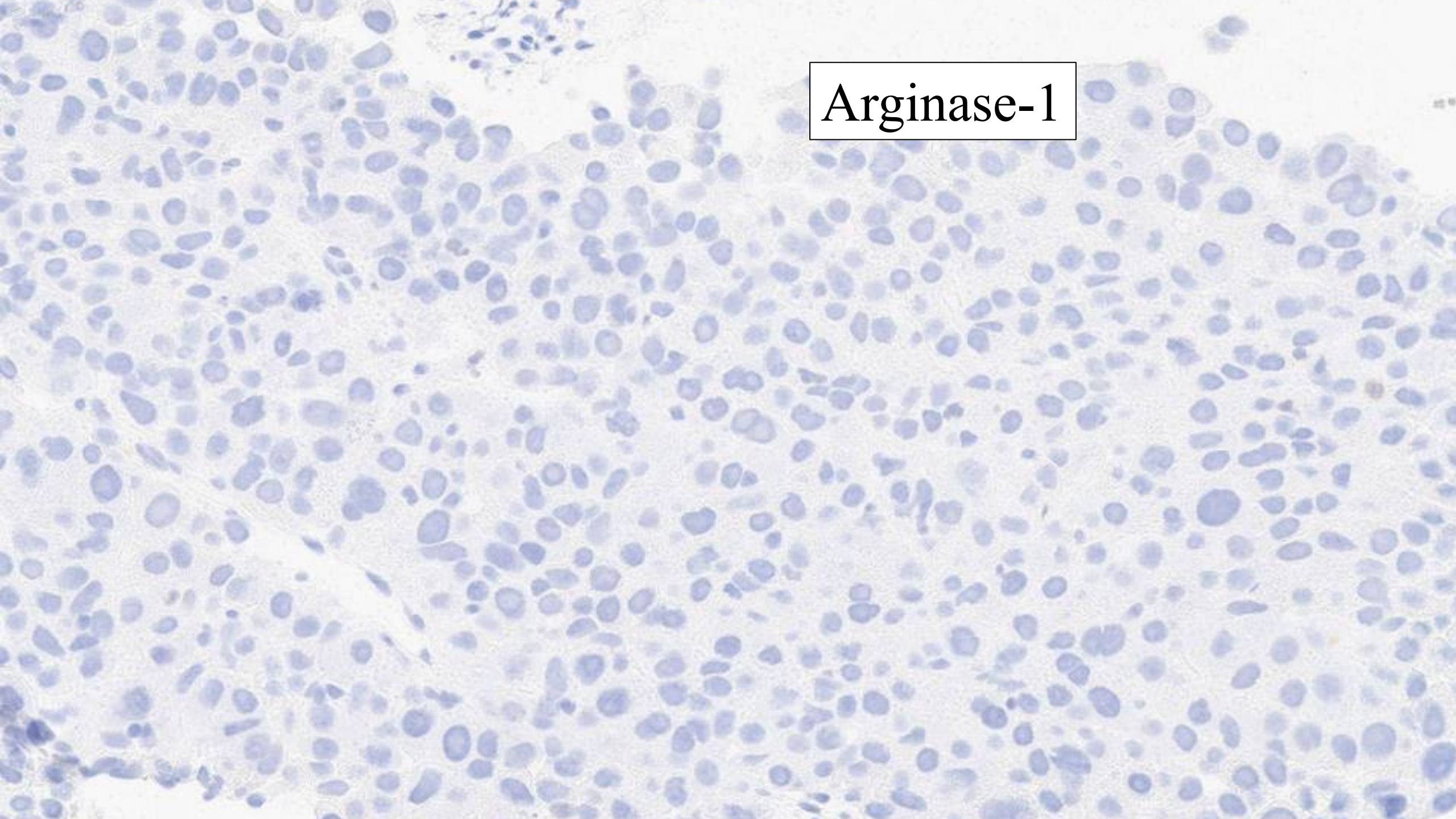

Canalicular pattern
Polyclonal CEA


Arginase-1
>95% specific
>95% sensitive

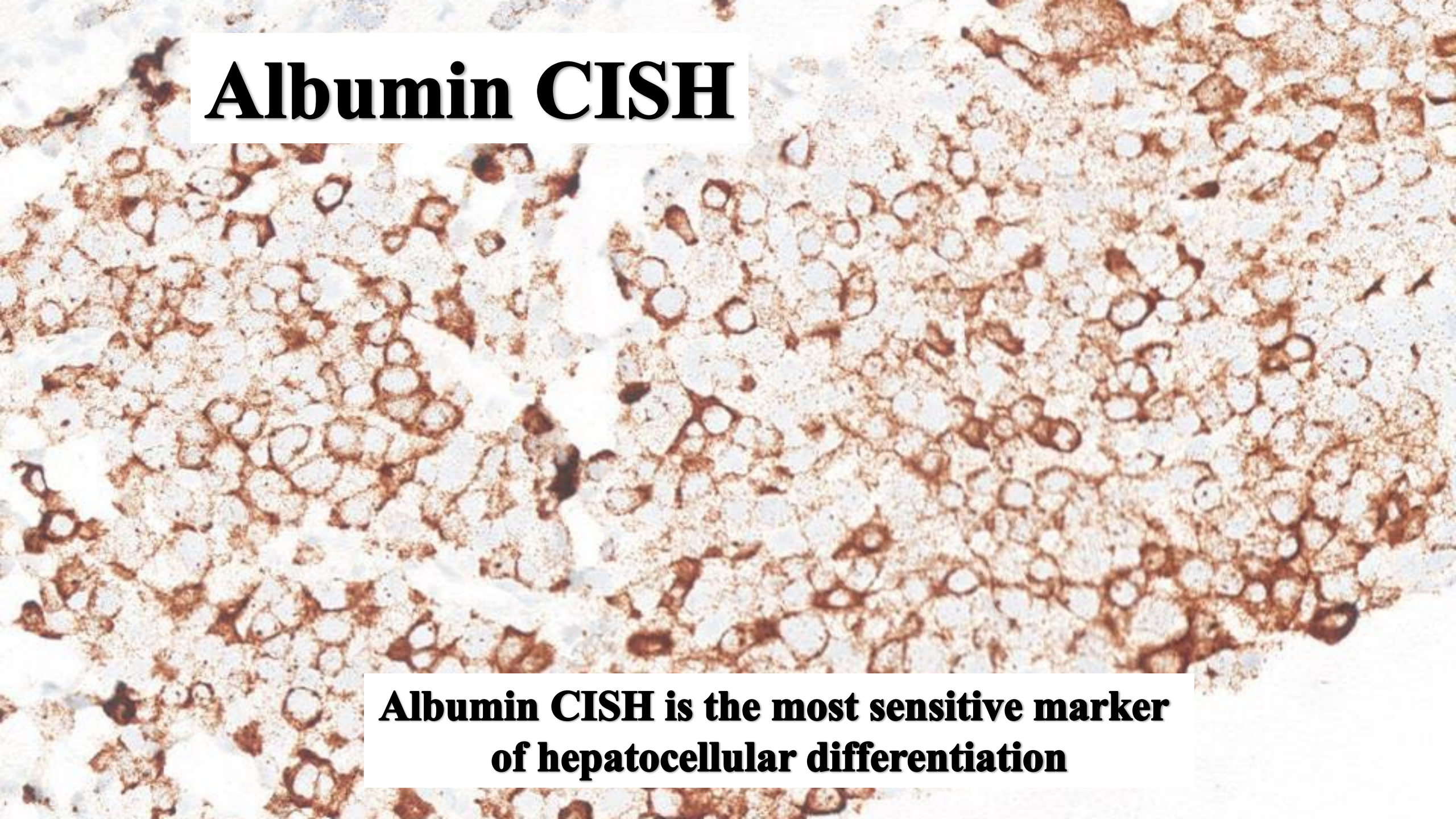
Arginase-1 is currently your best marker for HCC


70/M liver mass




Arginase-1

Albumin CISH



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

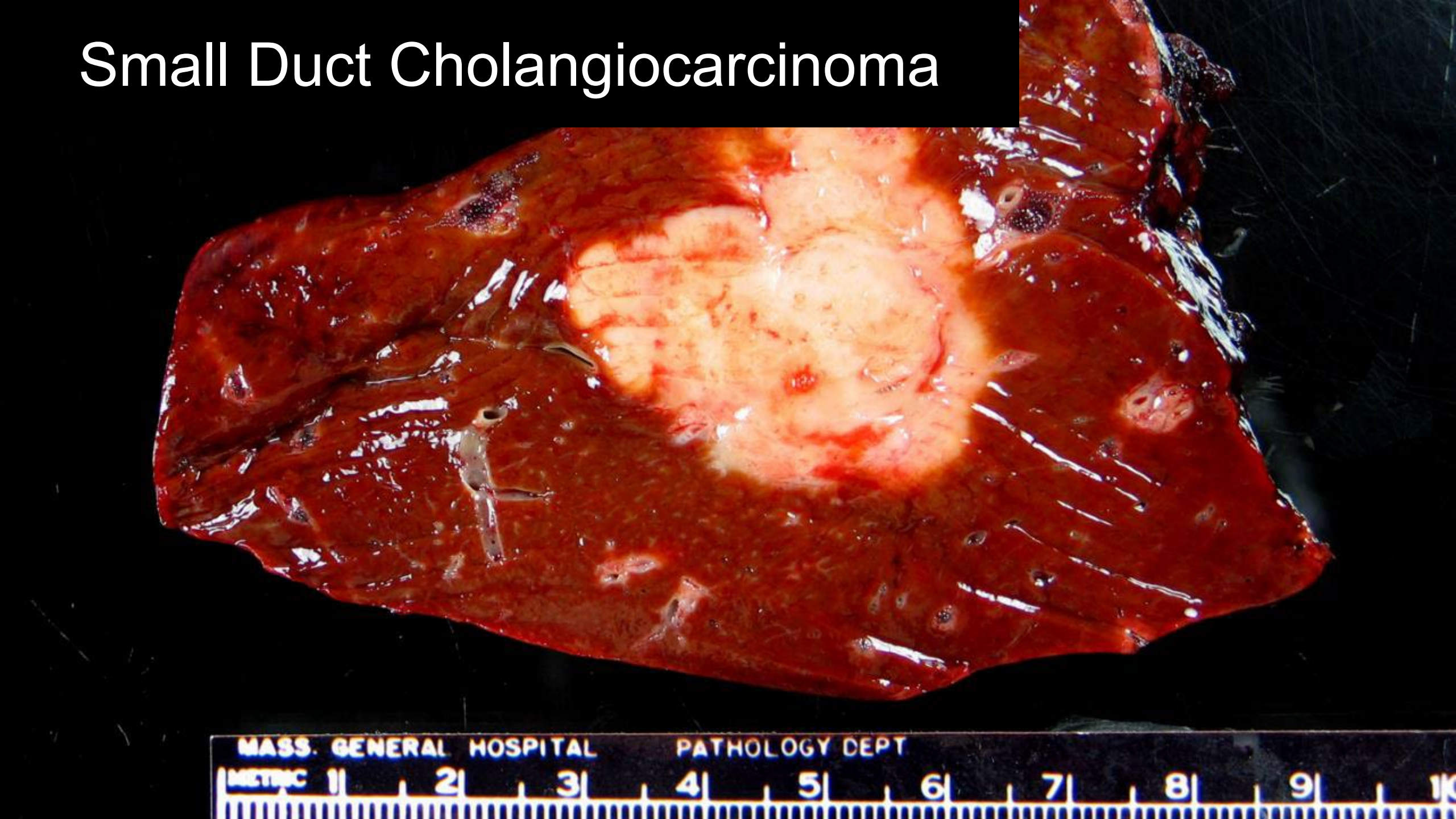
WHO 2019 Classification

- Small duct cholangiocarcinoma

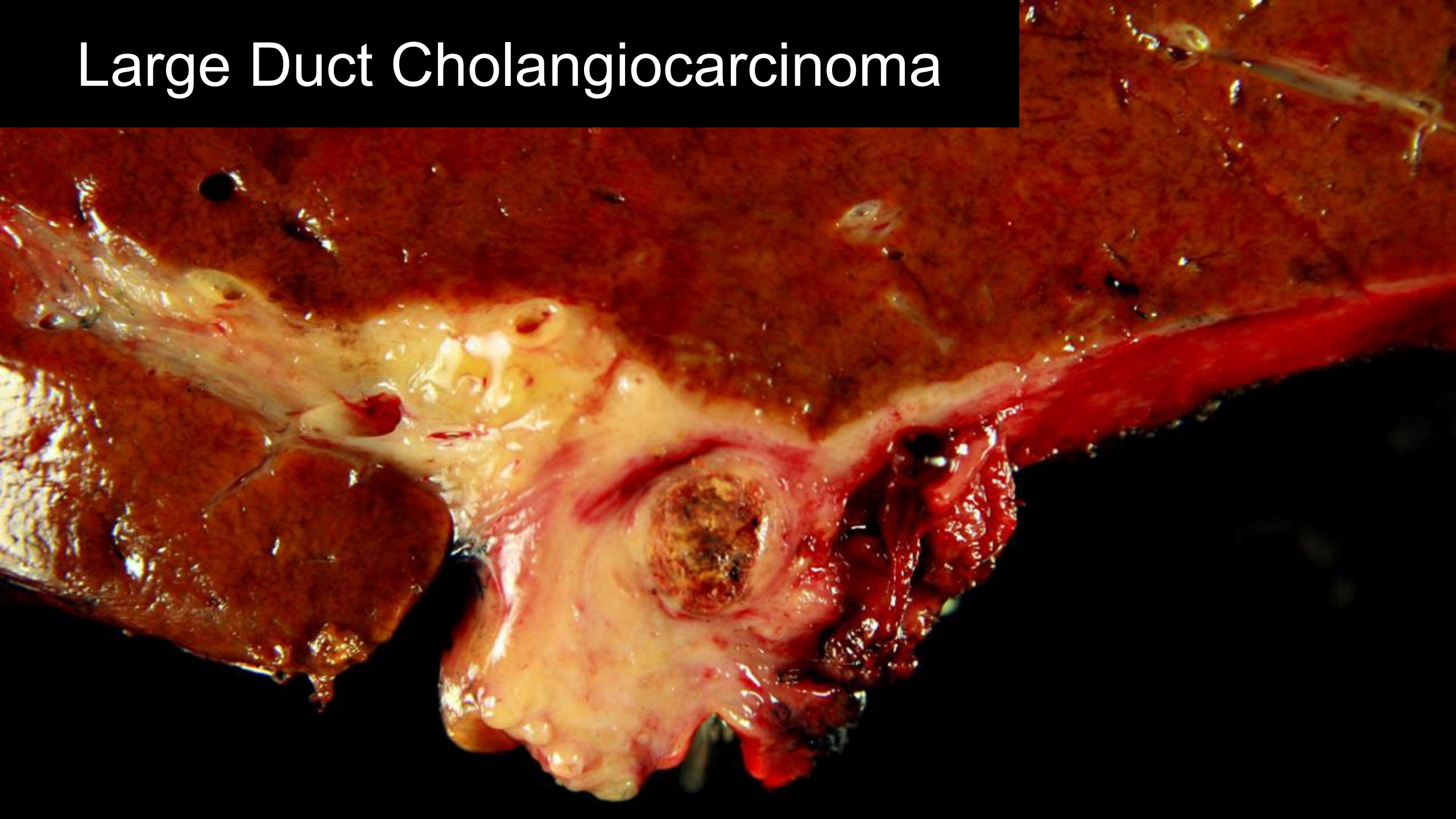
Histologic classification	Genetic classification

- Large duct cholangiocarcinoma

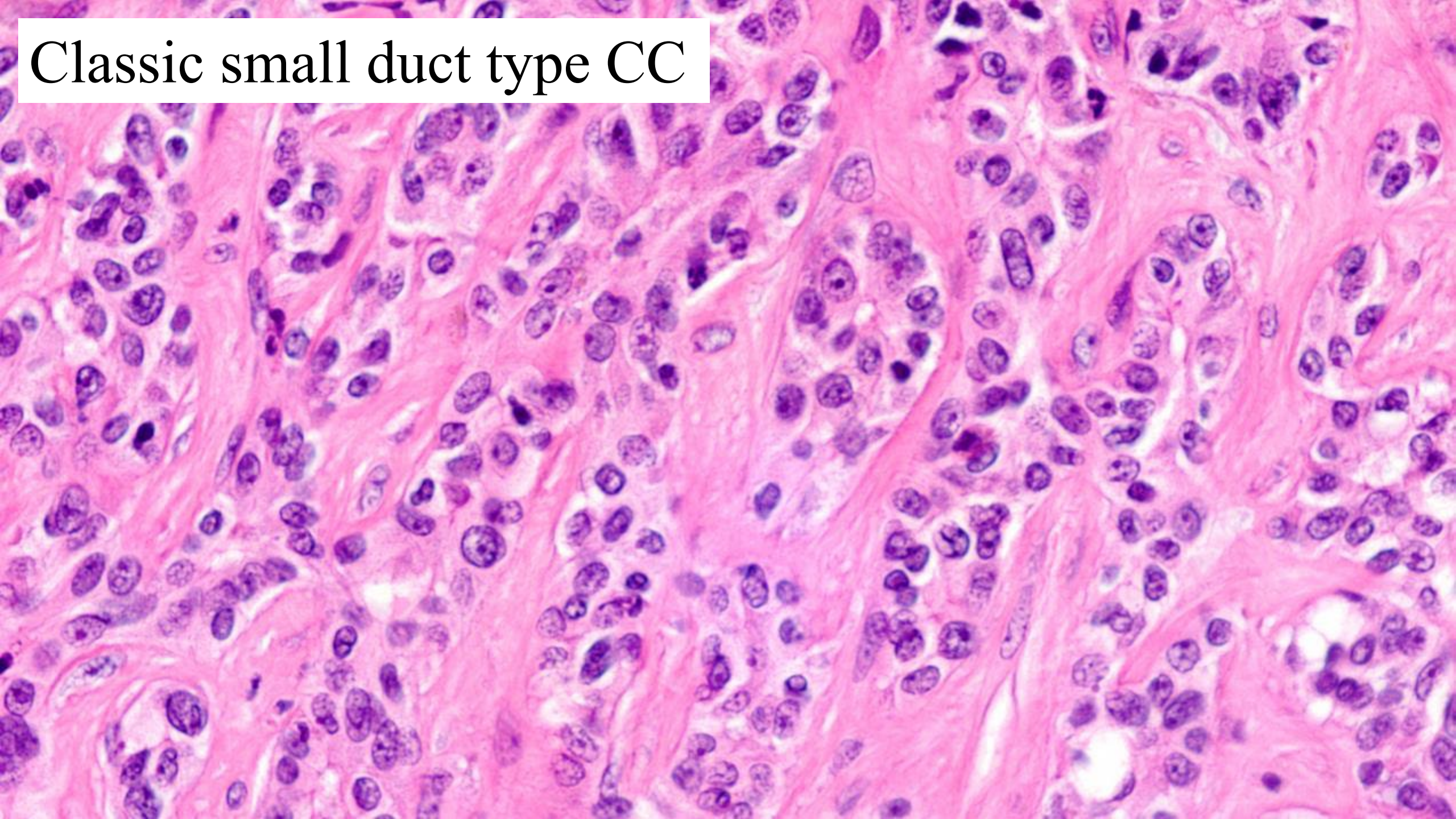
Small Duct Cholangiocarcinoma



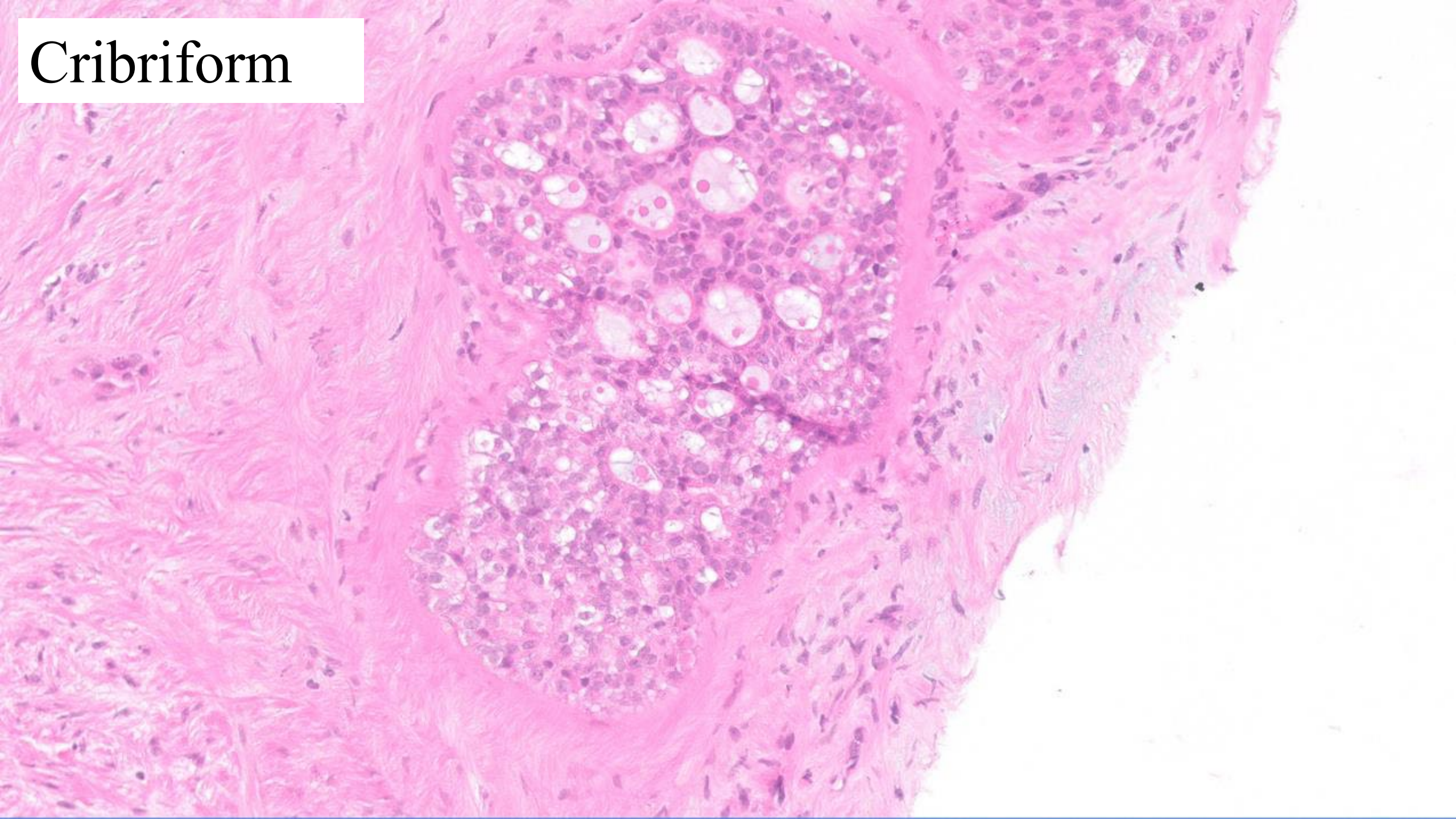
Large Duct Cholangiocarcinoma

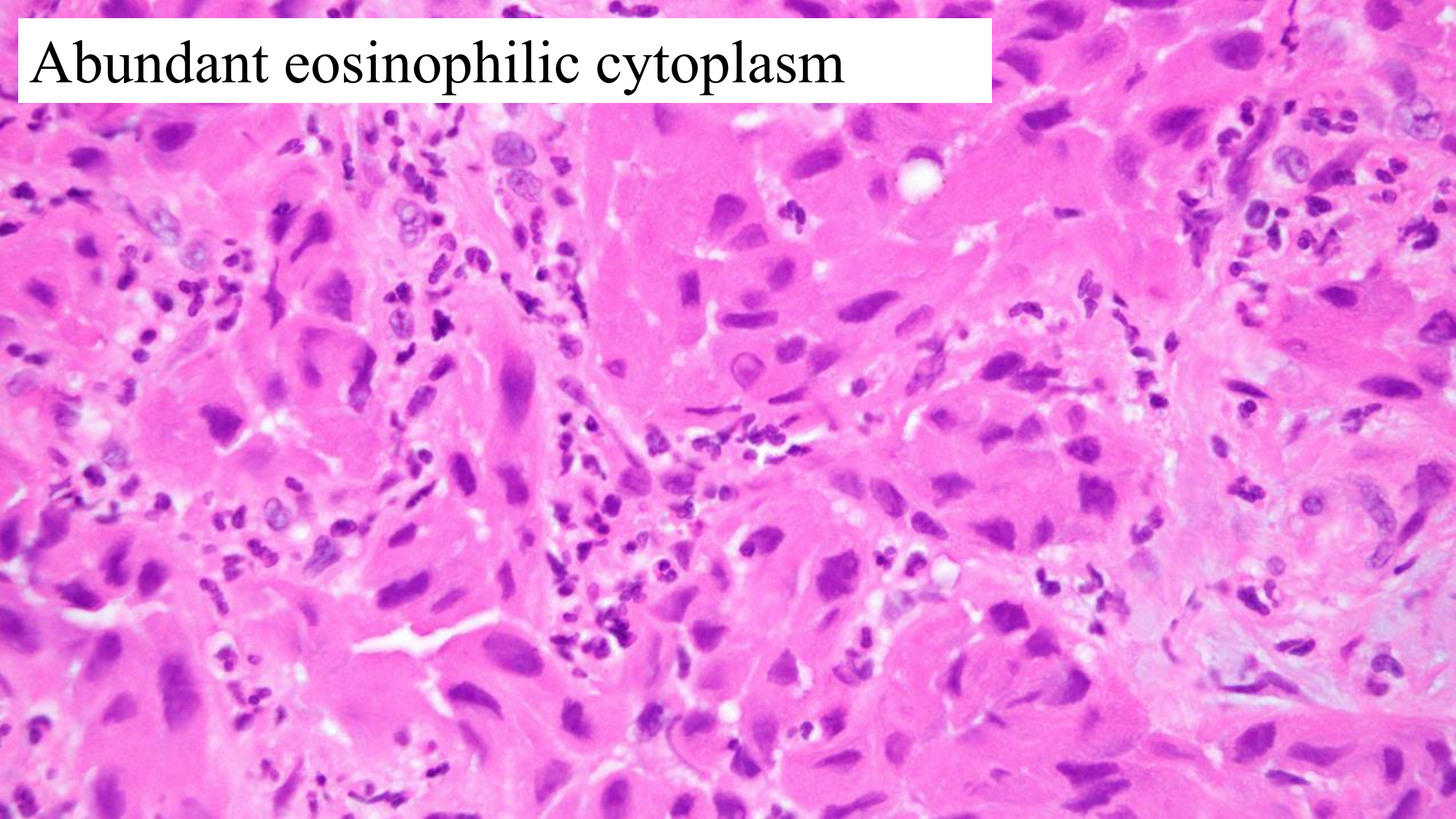


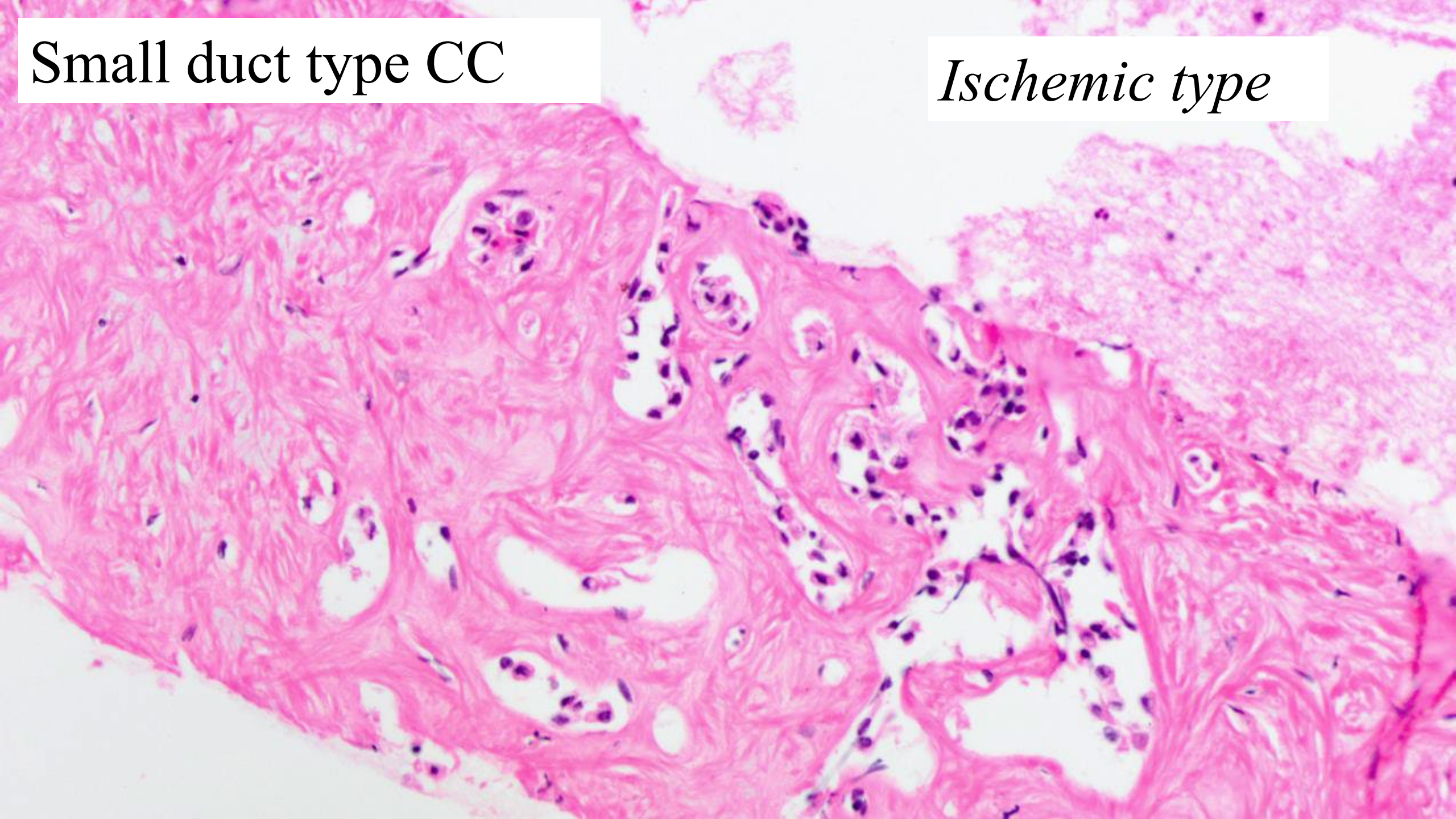
Small duct cholangiocarcinoma


Classic small duct type CC

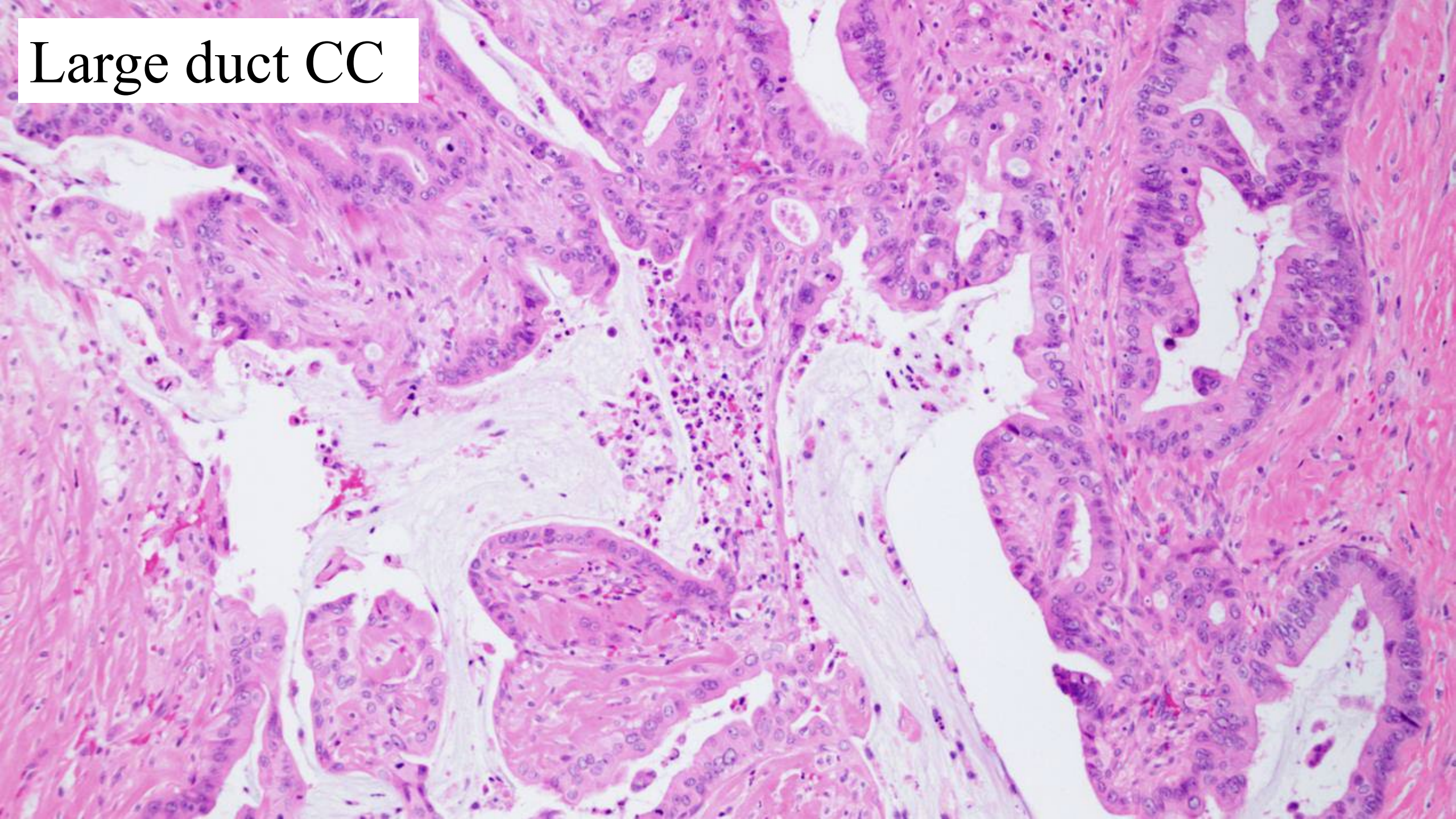
Cribriform




Abundant eosinophilic cytoplasm

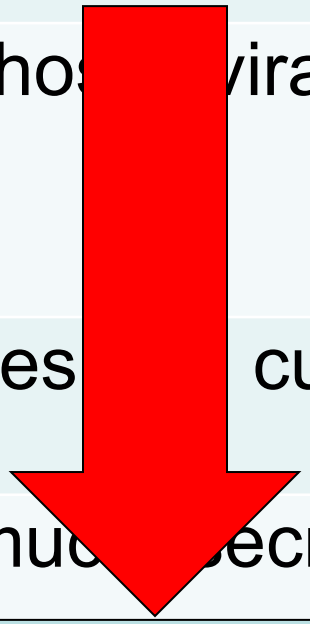

Small duct type CC
Ischemic type

Large duct cholangiocarcinoma


Large duct CC

	Small duct type	Large duct type
Gross features	Peripheral Mass forming	Hilar Infiltrating
Risks	Cirrho viral hepatitis	PSC, hepatolithiasis, liver fluke
Histology	Tubules cuboidal cells	Duct with columnar cells
Mucin	Non–muc ecreting glands	Mucin-secreting glands

Targetable with FDA approved drugs



WHO 2019 Classification

Imperfect

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

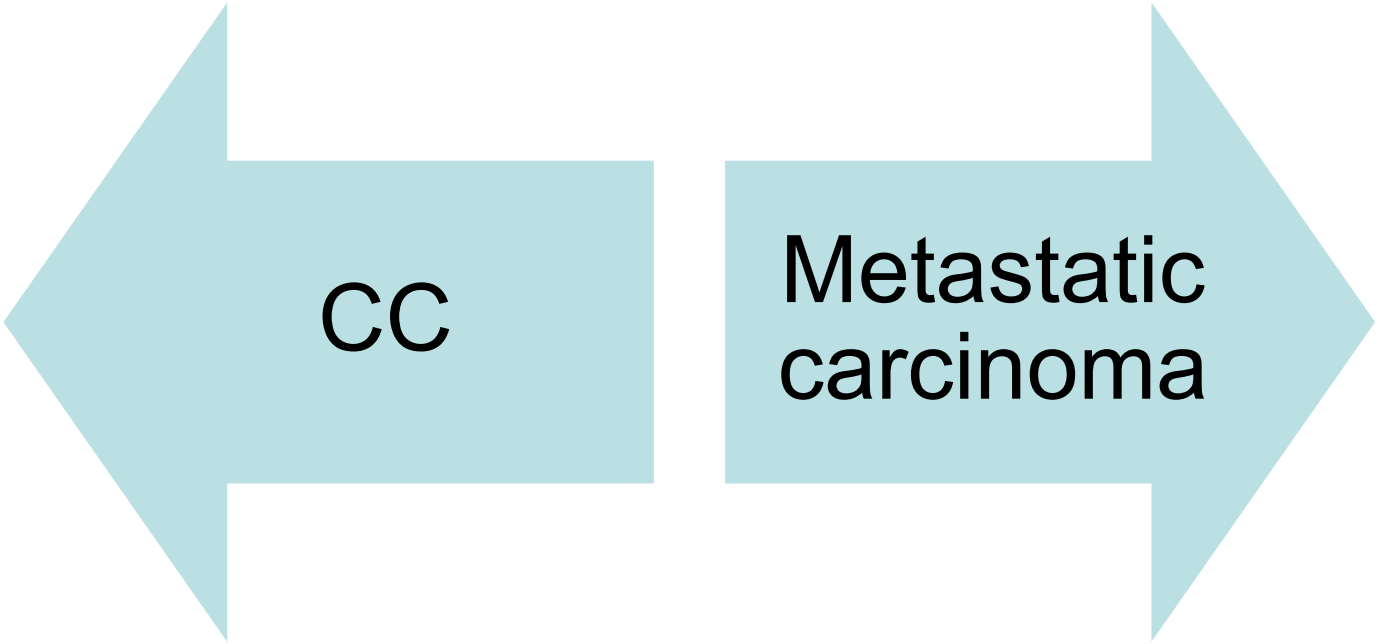
Management of liver ‘adenocarcinoma’

Hepatic resection

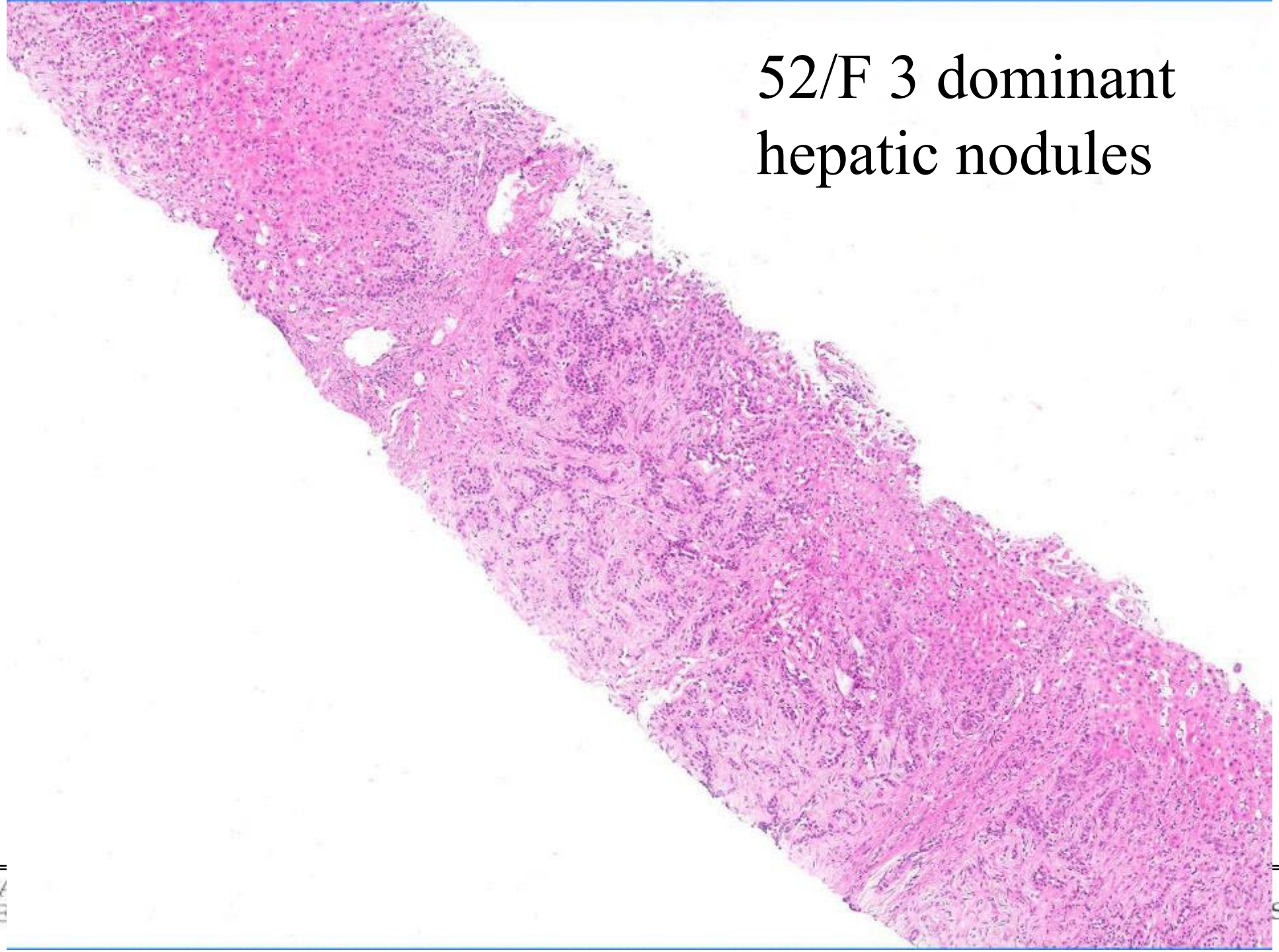
Gemcitabine/cisplatin

IDH inhibitor

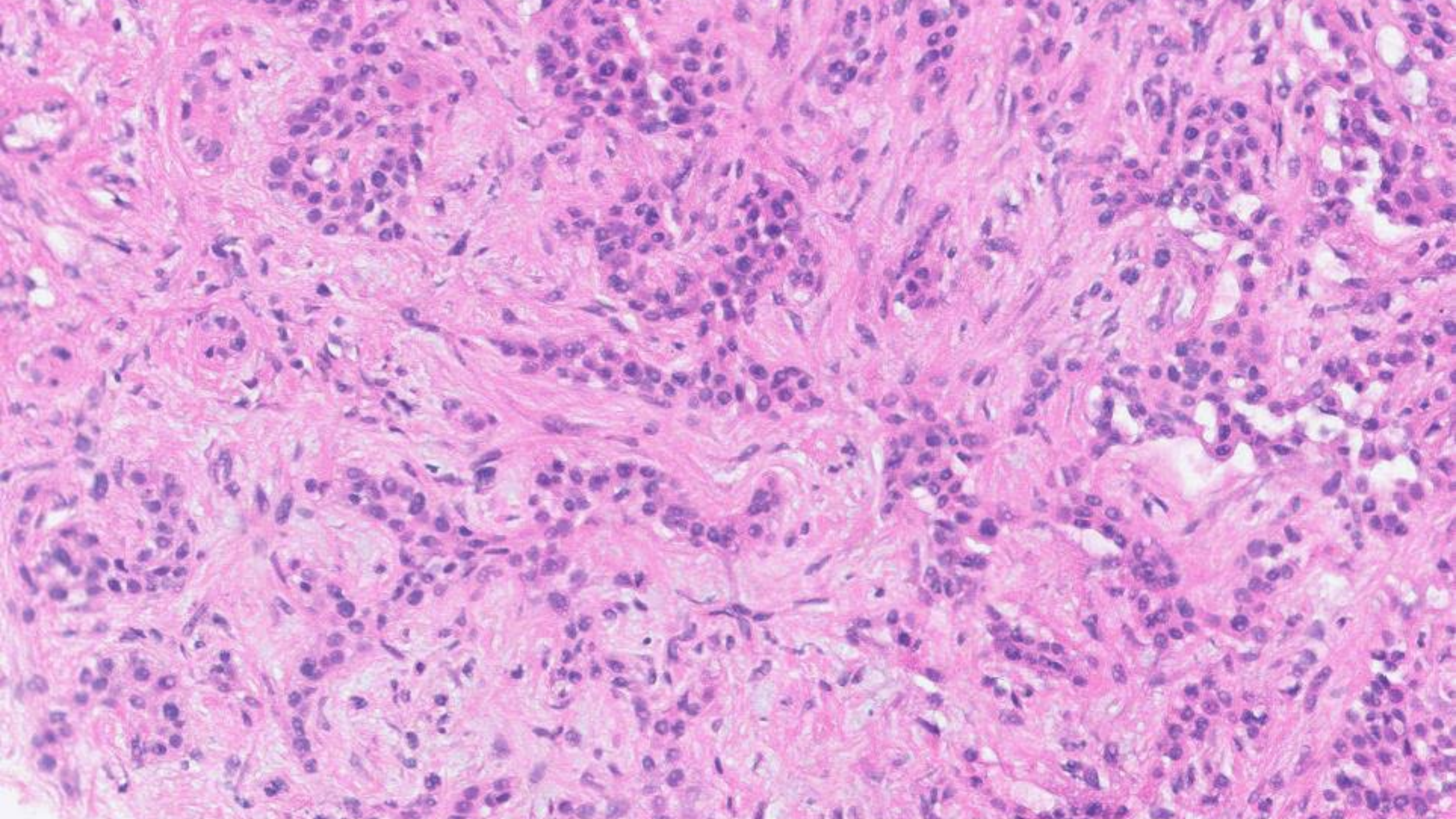
FGFR2 inhibitor

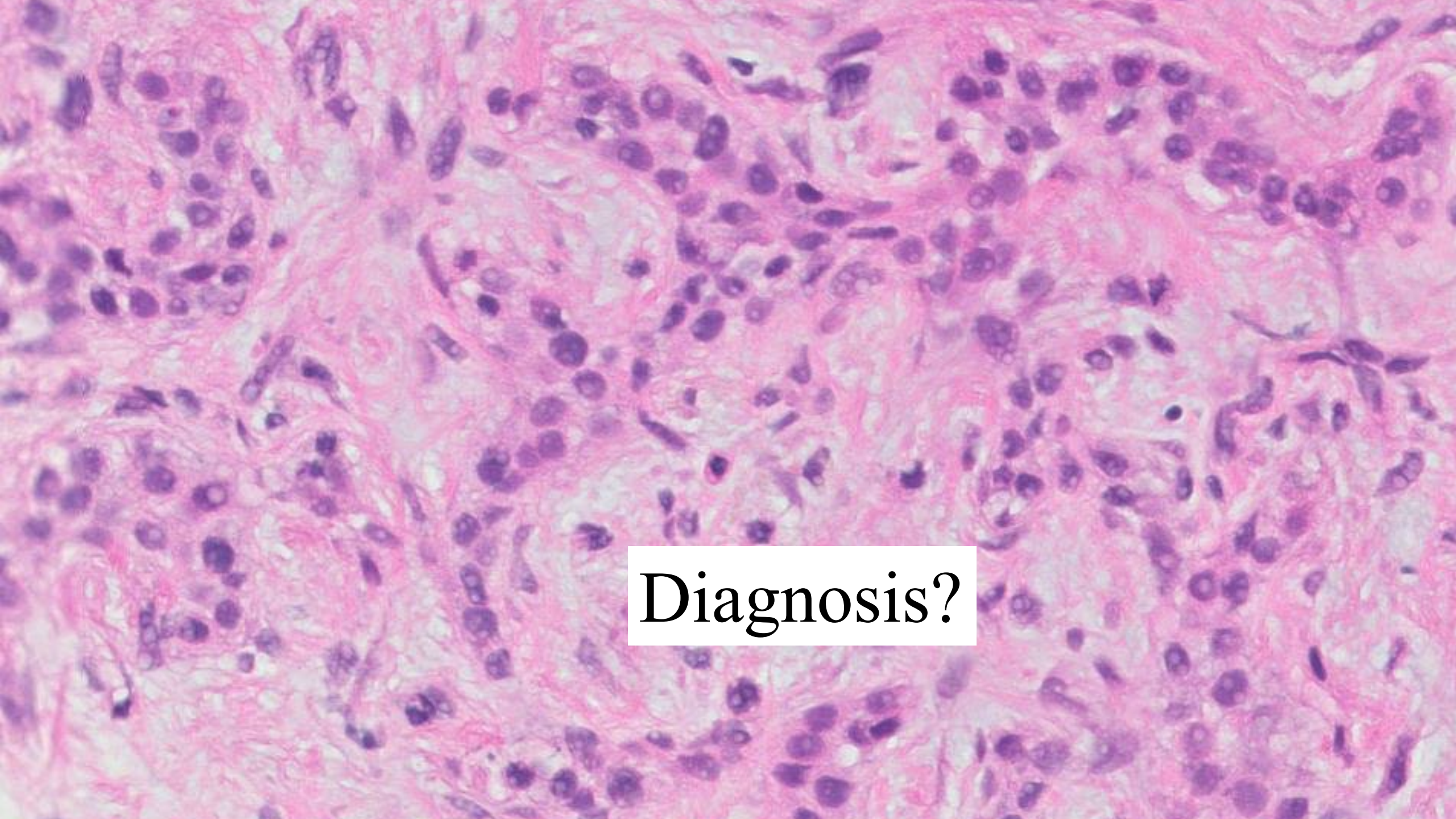


Chemotherapy

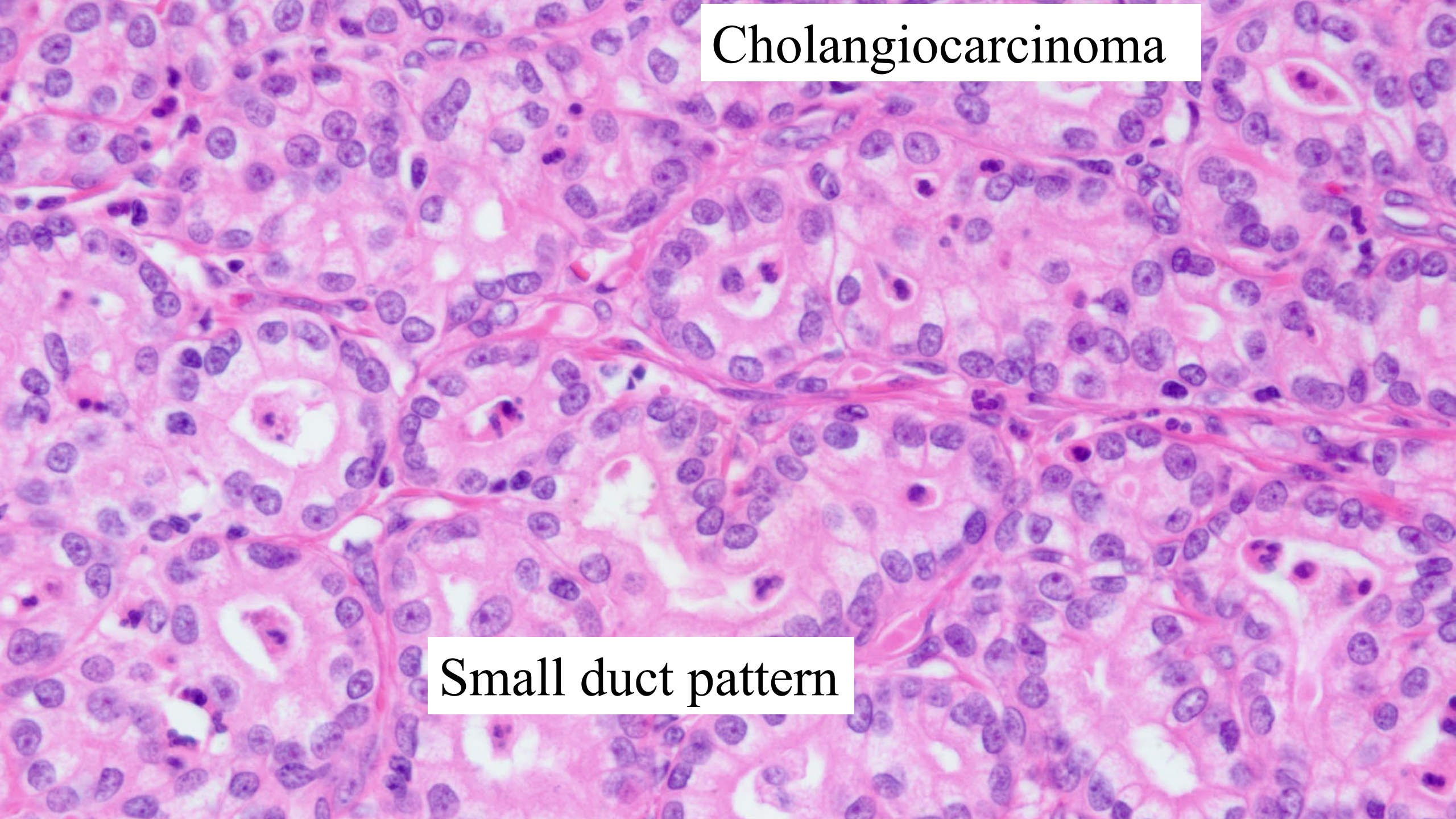


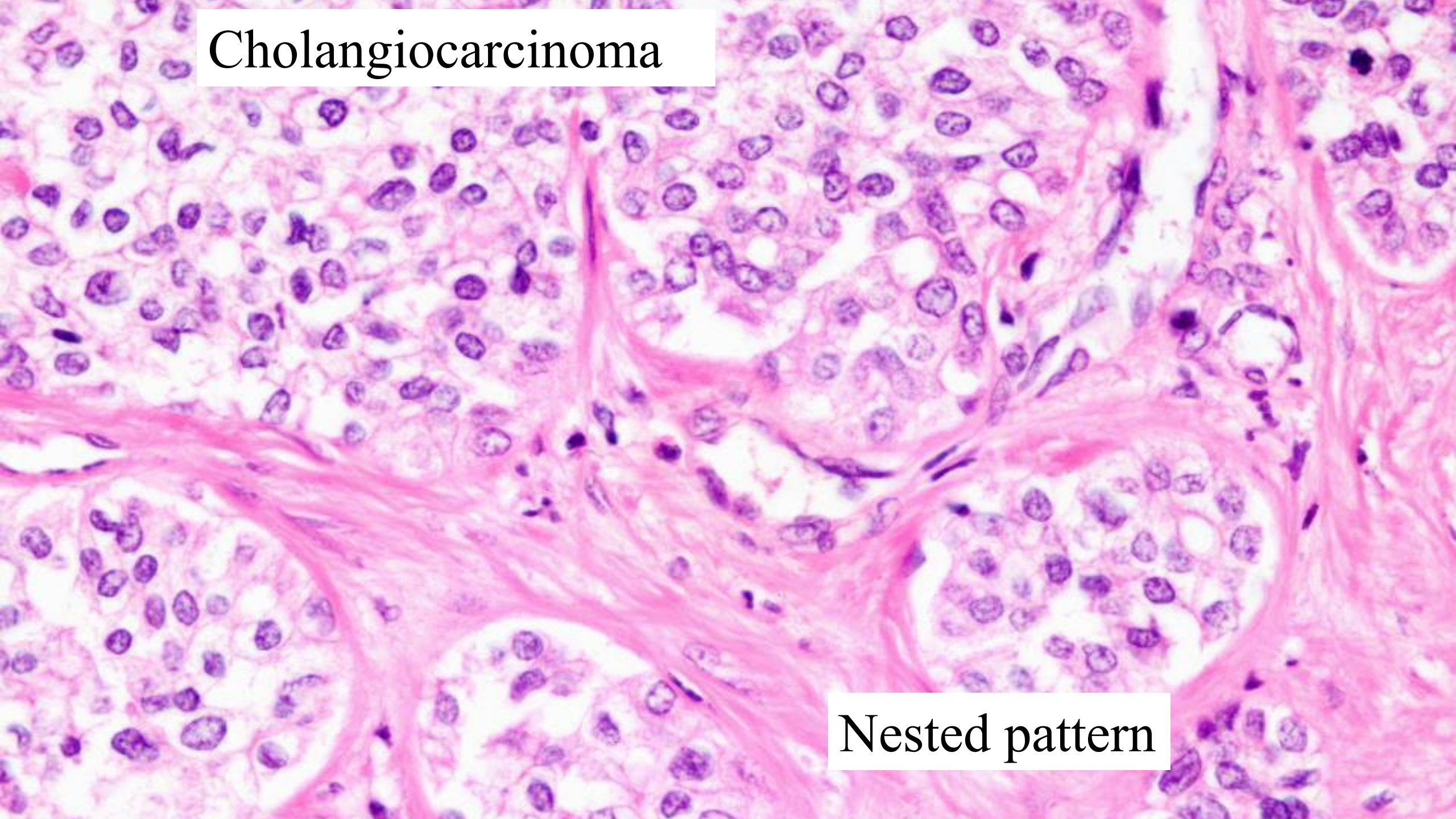
52/F 3 dominant hepatic nodules

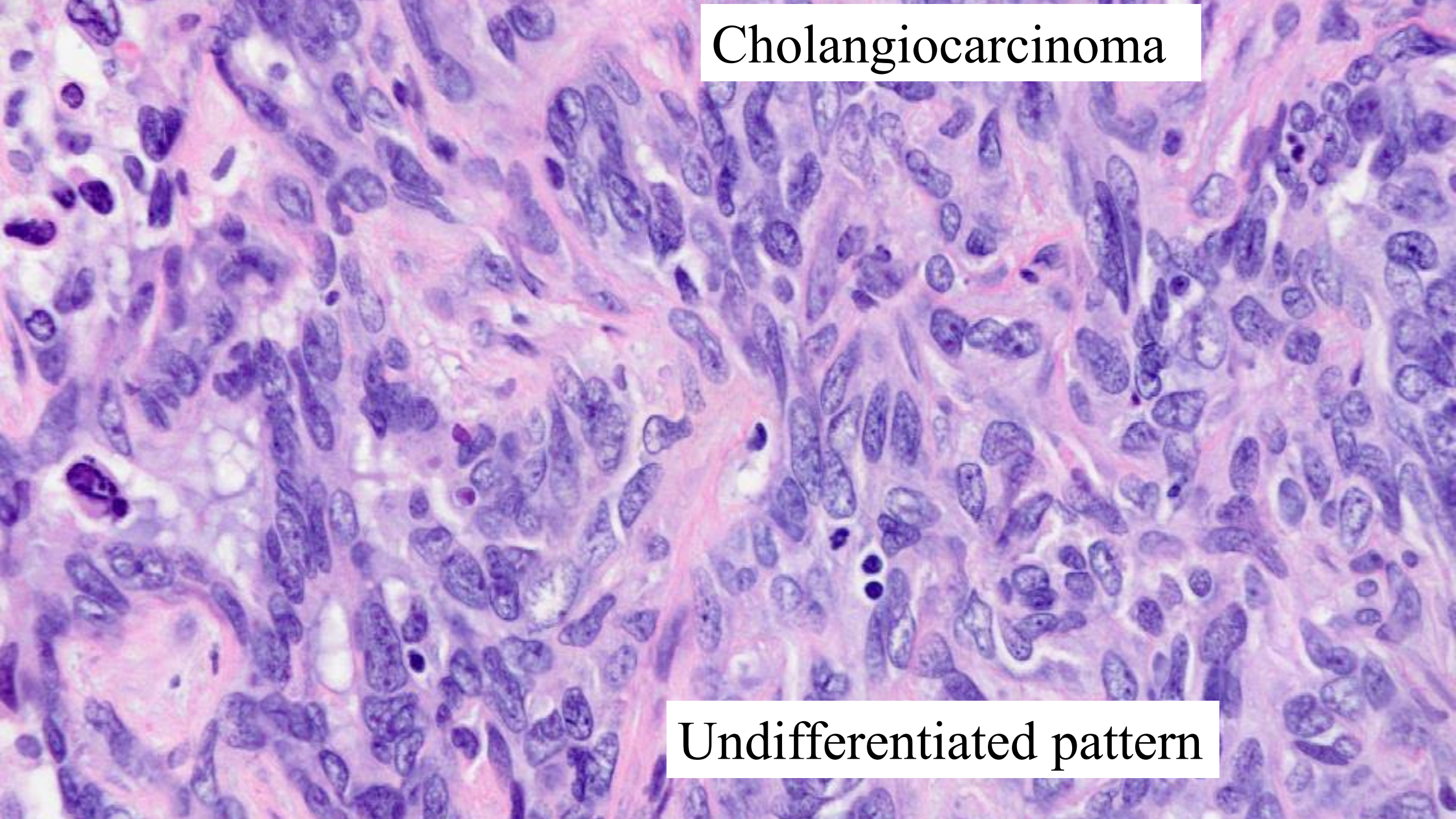



Diagnosis?

What do cholangiocarcinoma look like?


Cholangiocarcinoma
Small duct pattern


Cholangiocarcinoma
Nested pattern


Cholangiocarcinoma
Undifferentiated pattern

Cholangiocarcinoma

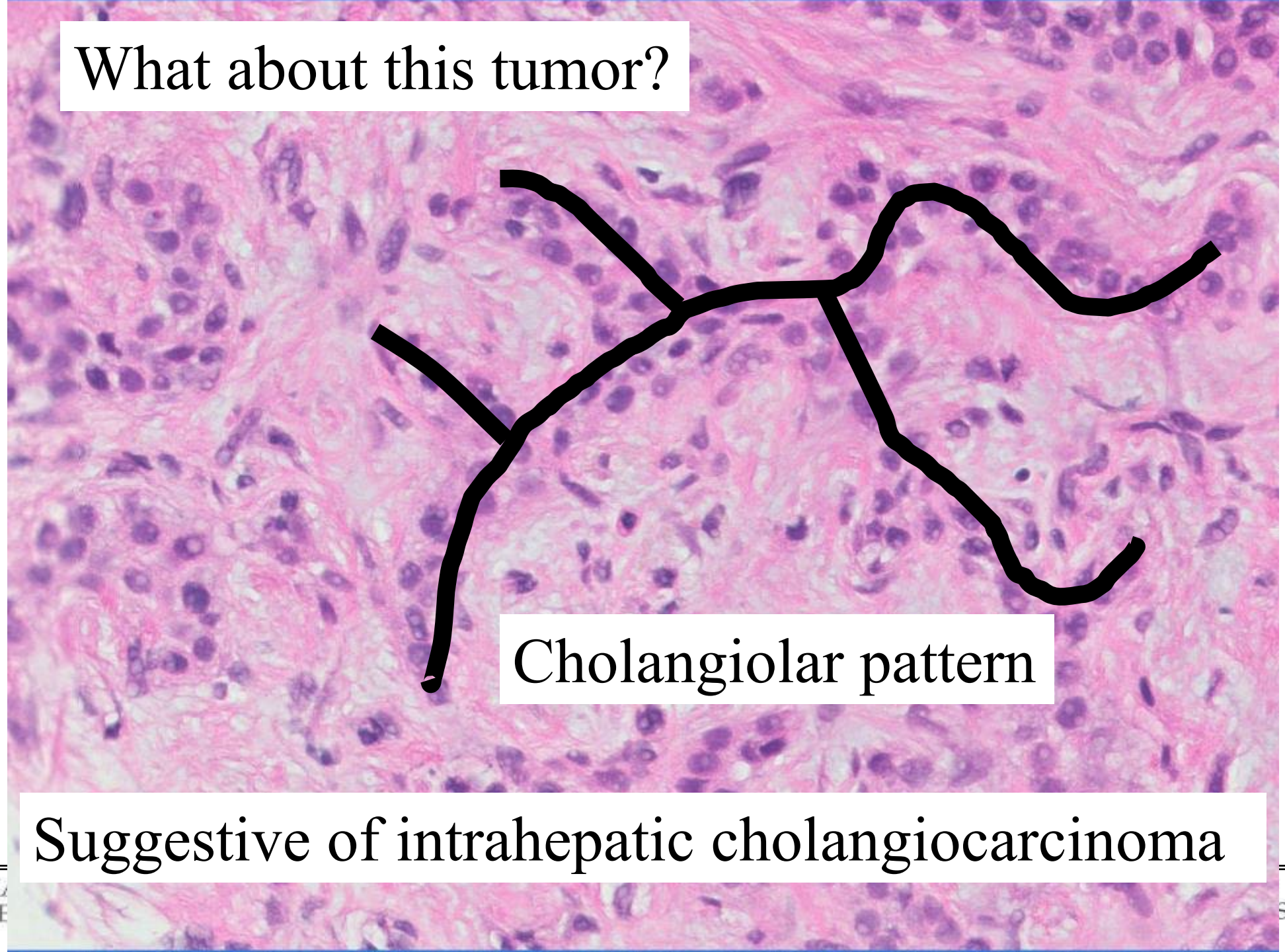
Cholangiolar pattern

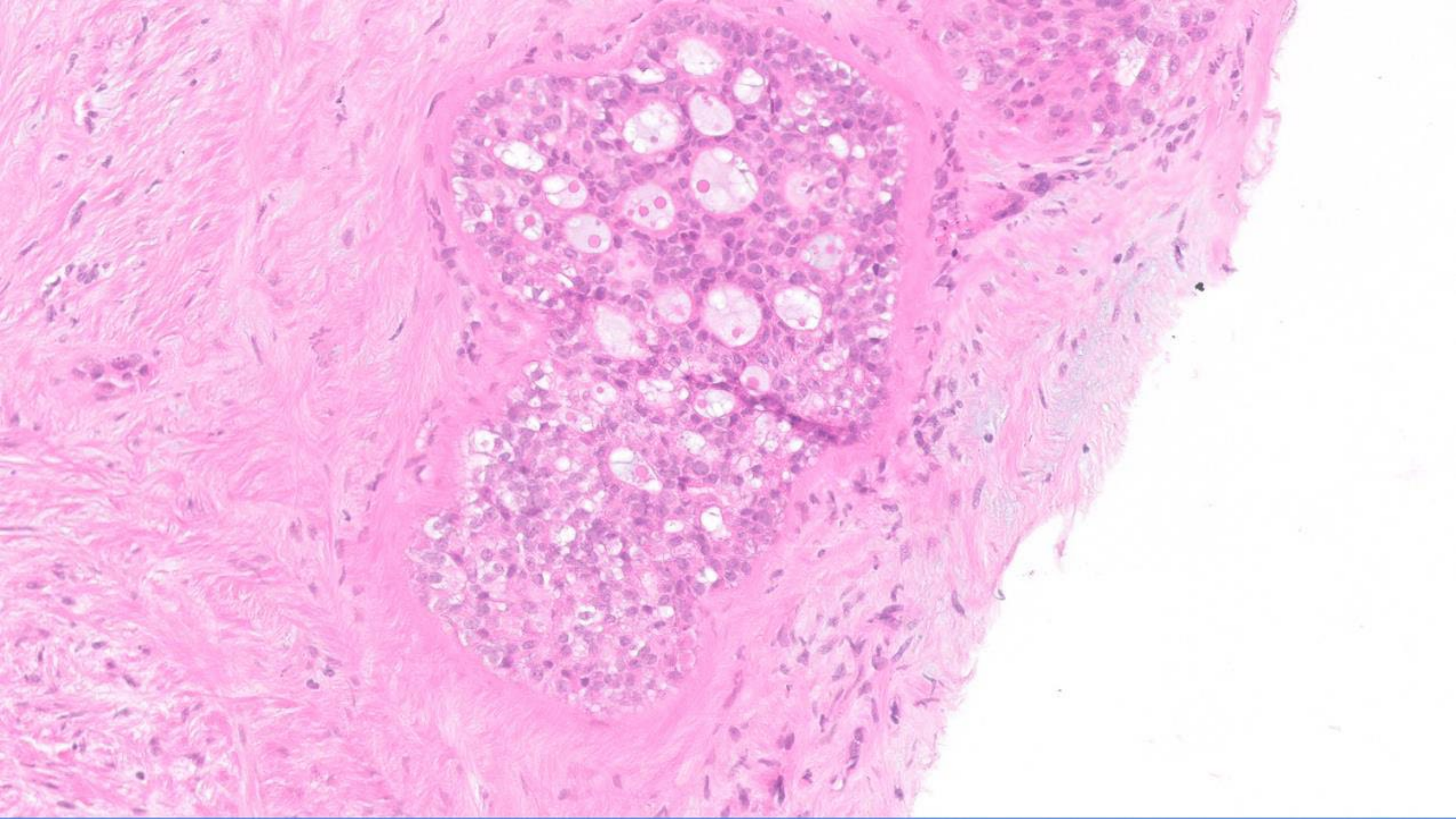
Histologic Patterns of CC

- Cholangiolar

Highly suggestive of cholangiocarcinoma

- Tubular
- Nested- neuroendocrine-like
- Large duct
- Undifferentiated


What about this tumor?
Cholangiolar pattern
Suggestive of intrahepatic cholangiocarcinoma

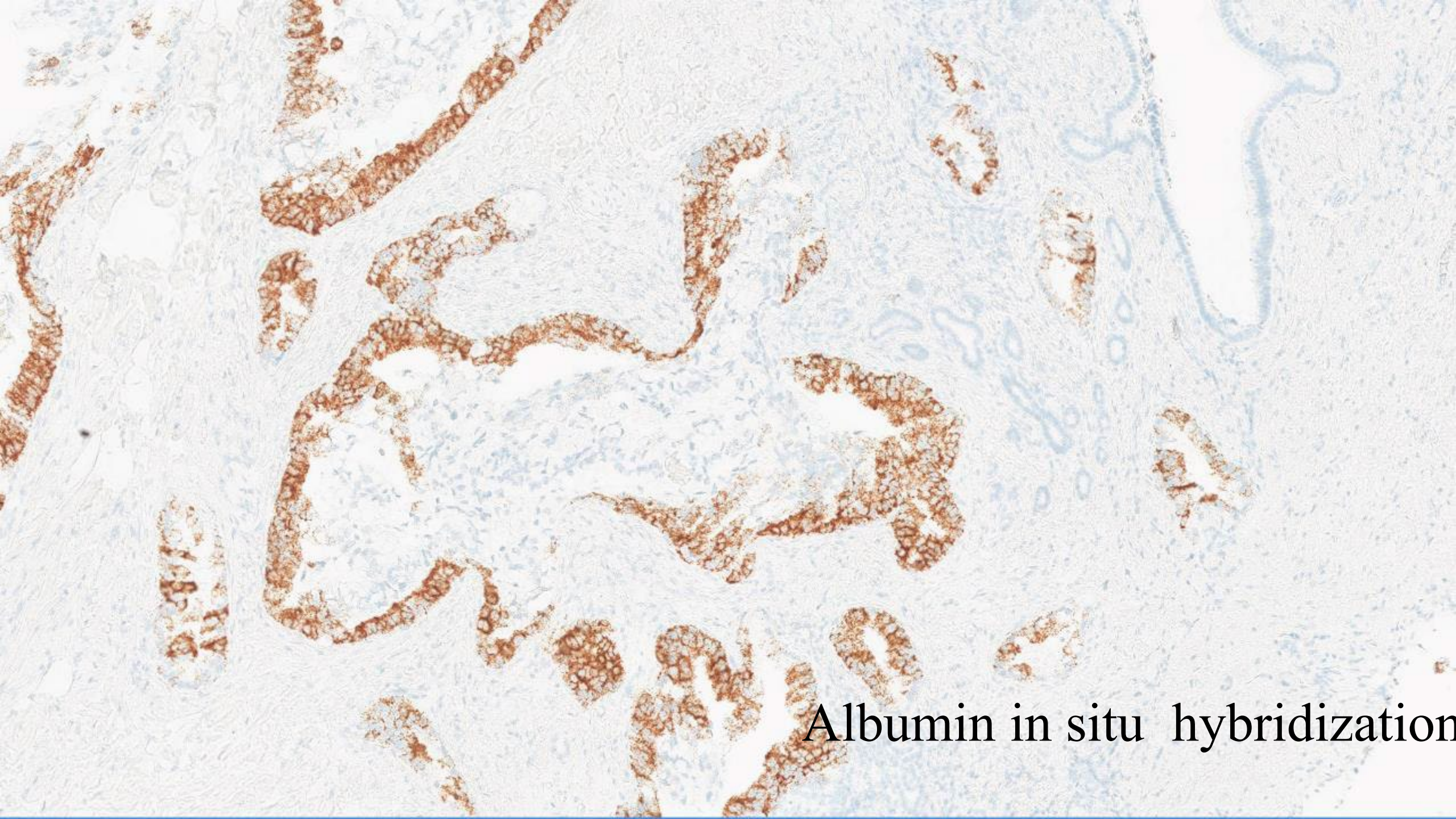


What about this tumor?

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

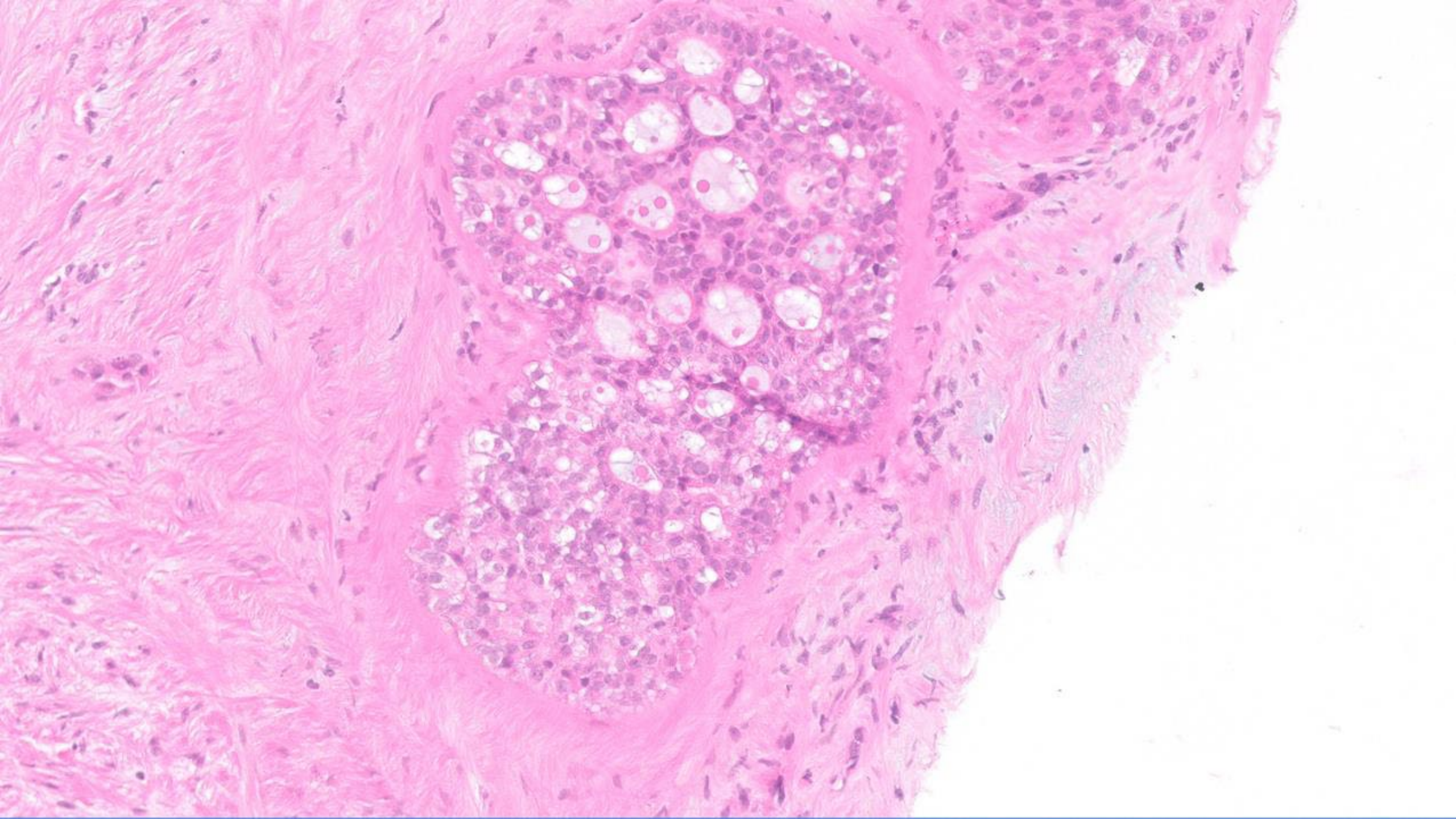
Diagnostic Histopathology 2022

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

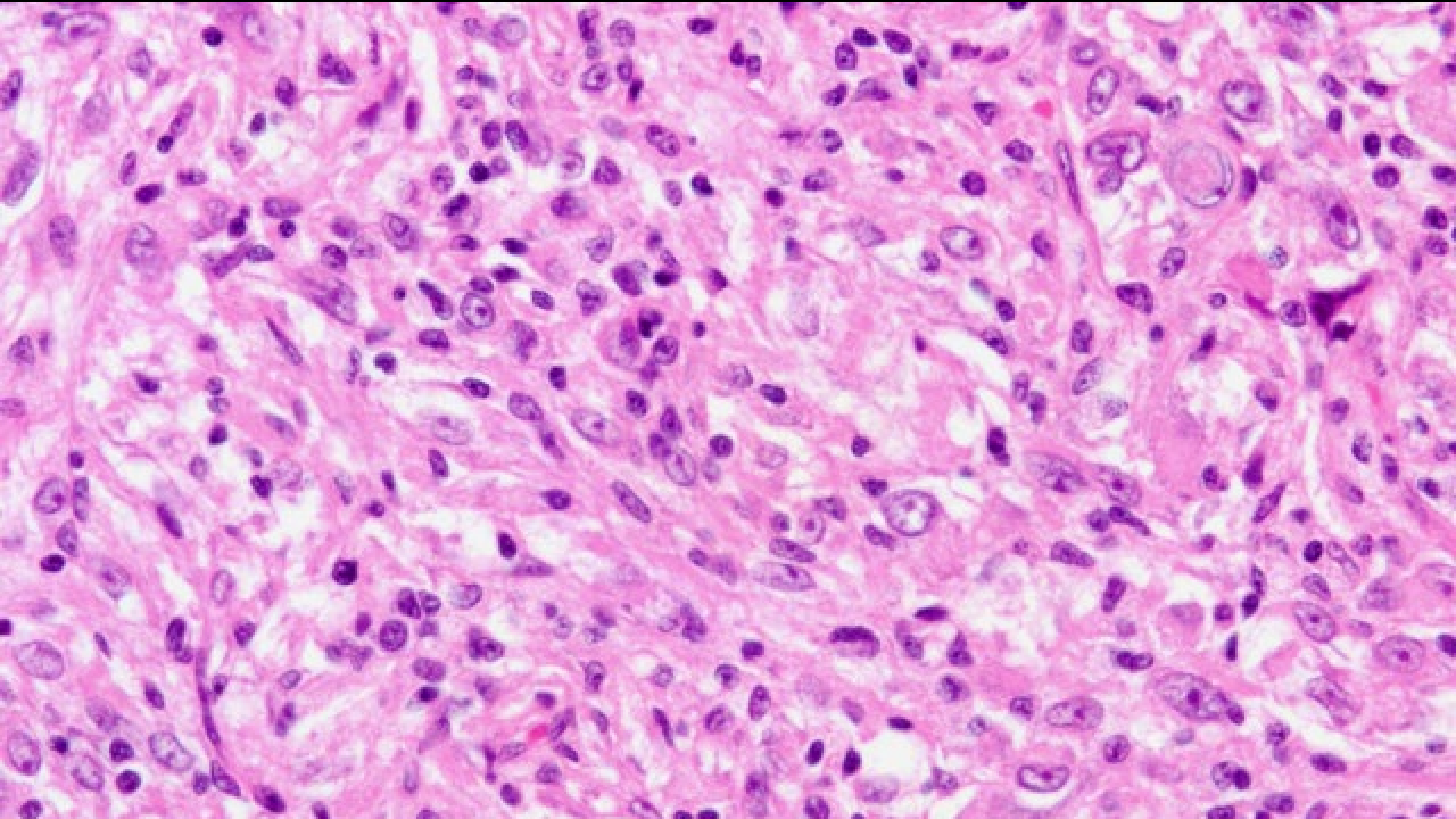
Conclusions – Cholangiocarcinoma Diagnosis

- Use limited immunohistochemical panel
- Keratin 7/19, TTF-1, CDX2

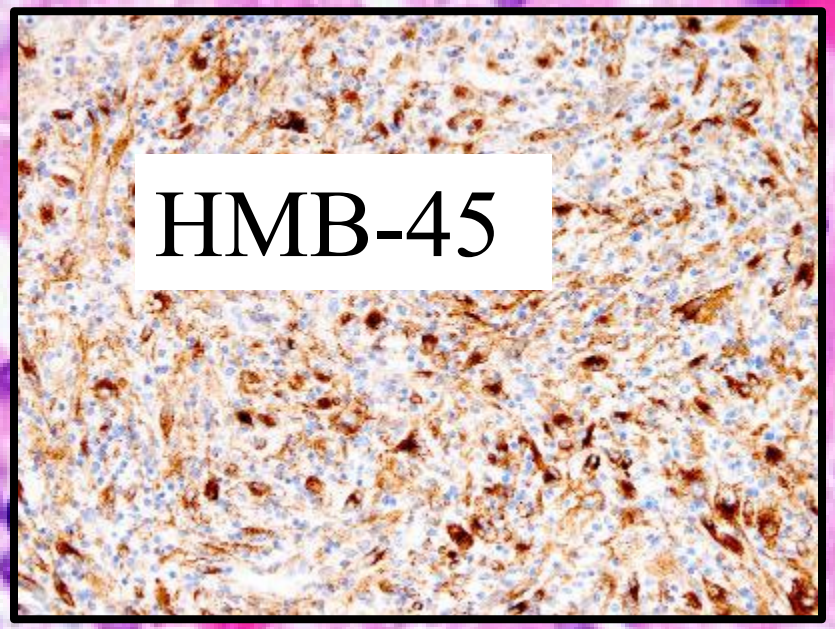
- Cholangiolar histology

- Save tissue for molecular studies

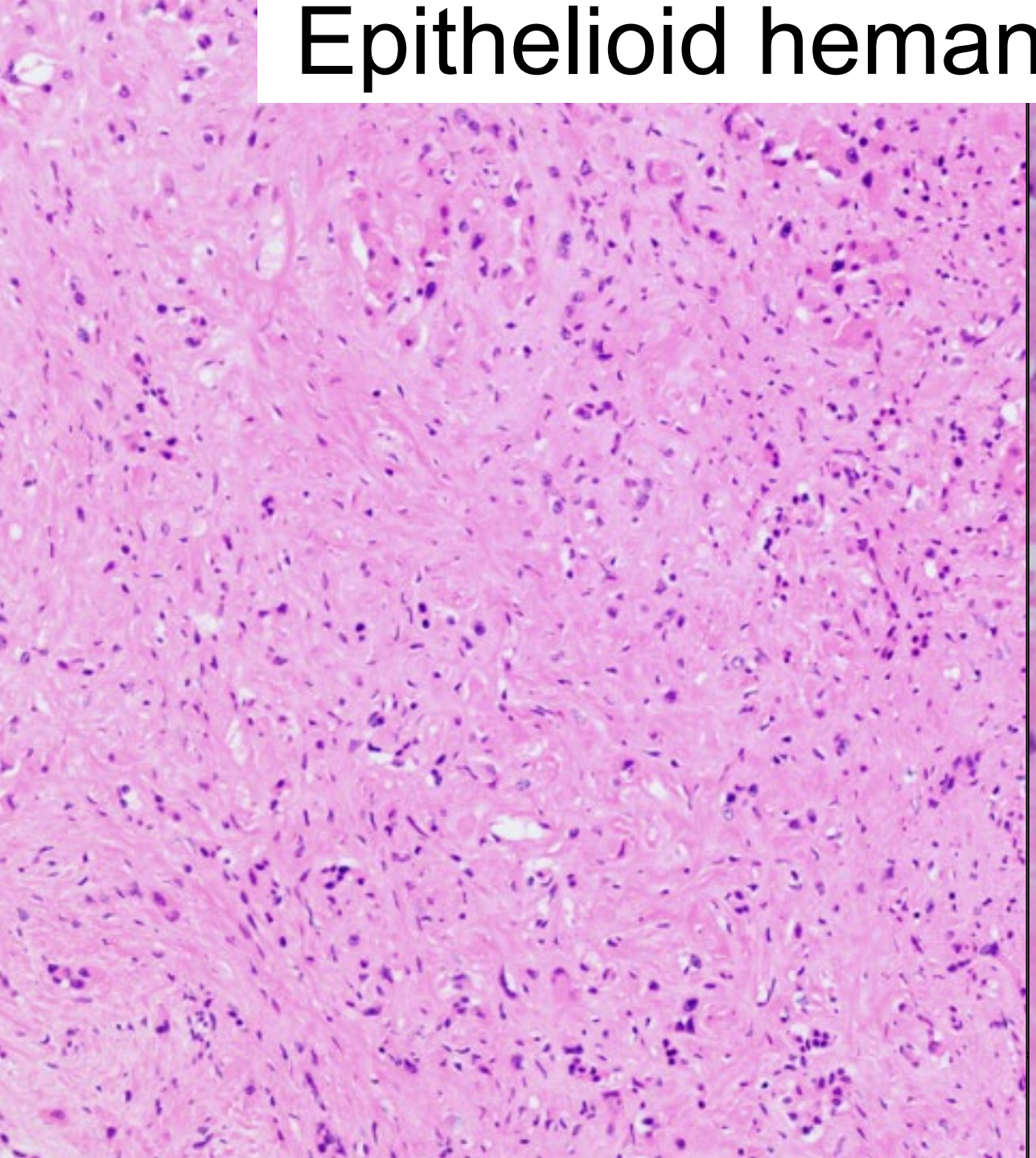
Question 6: Sure, looks hepatocellular carcinoma, but could I be missing something?

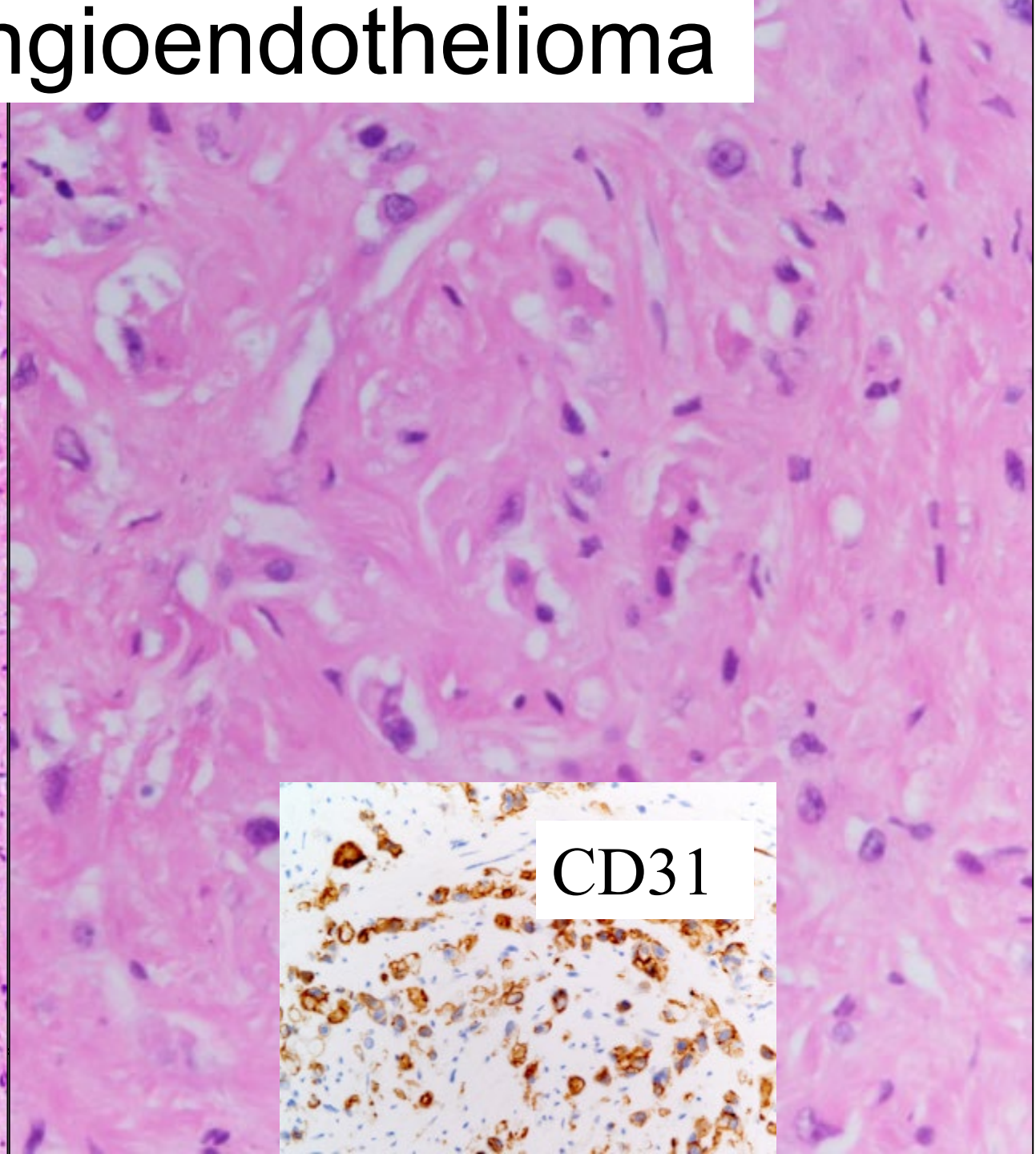


PEComa (Epithelioid angiomyolipoma)

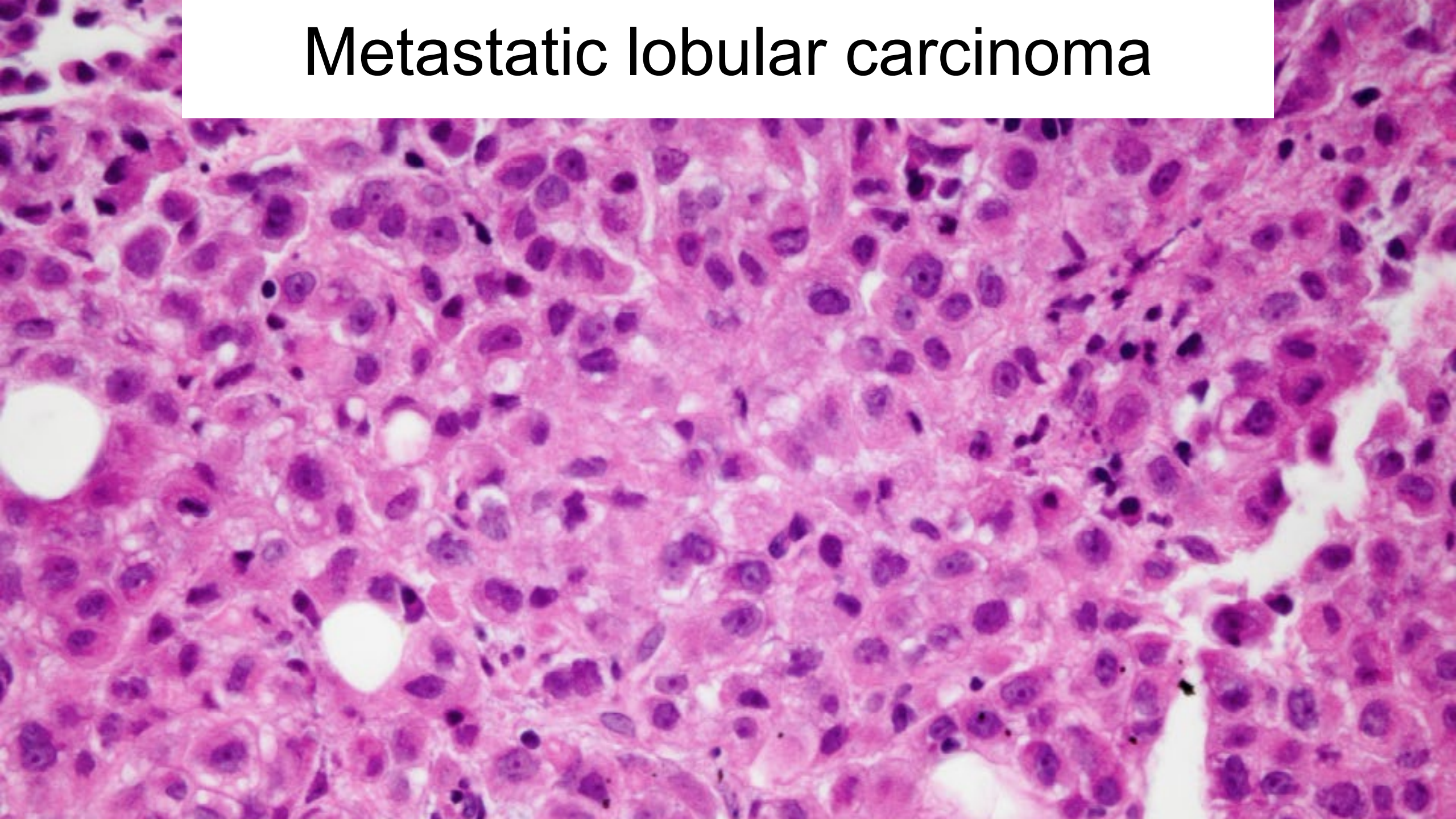


Epithelioid hemangioendothelioma

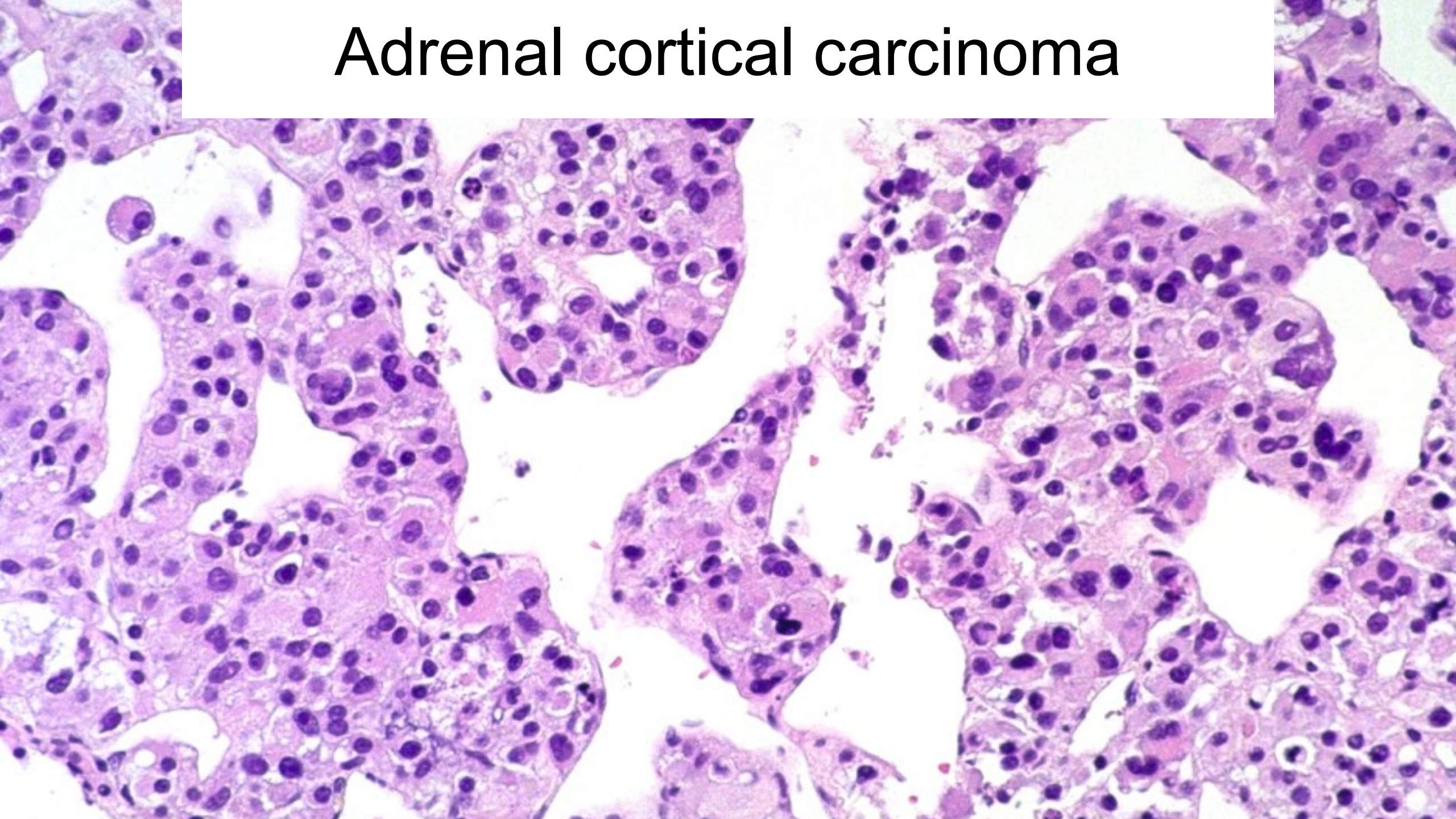




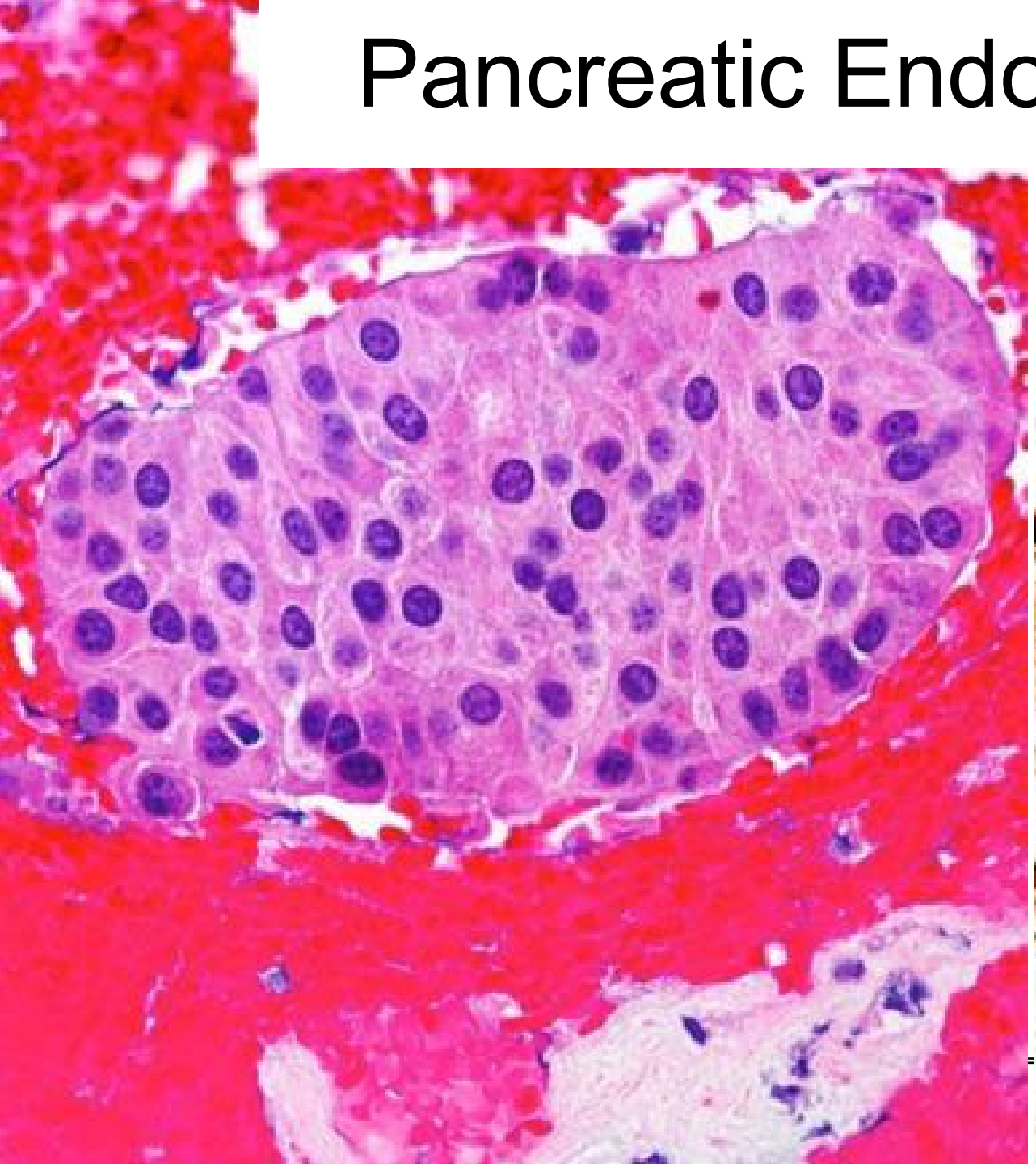
Metastatic lobular carcinoma

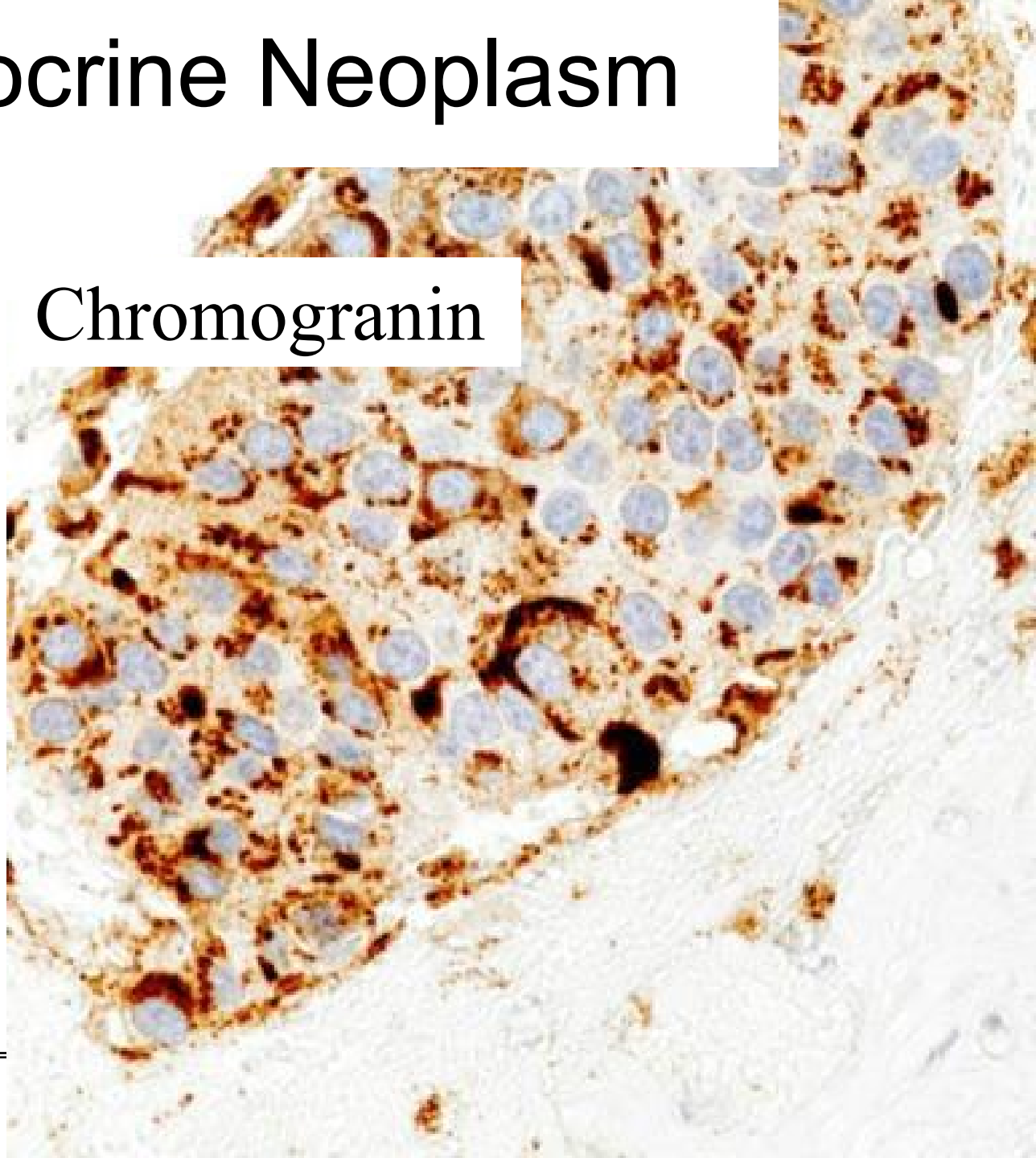


Adrenal cortical carcinoma

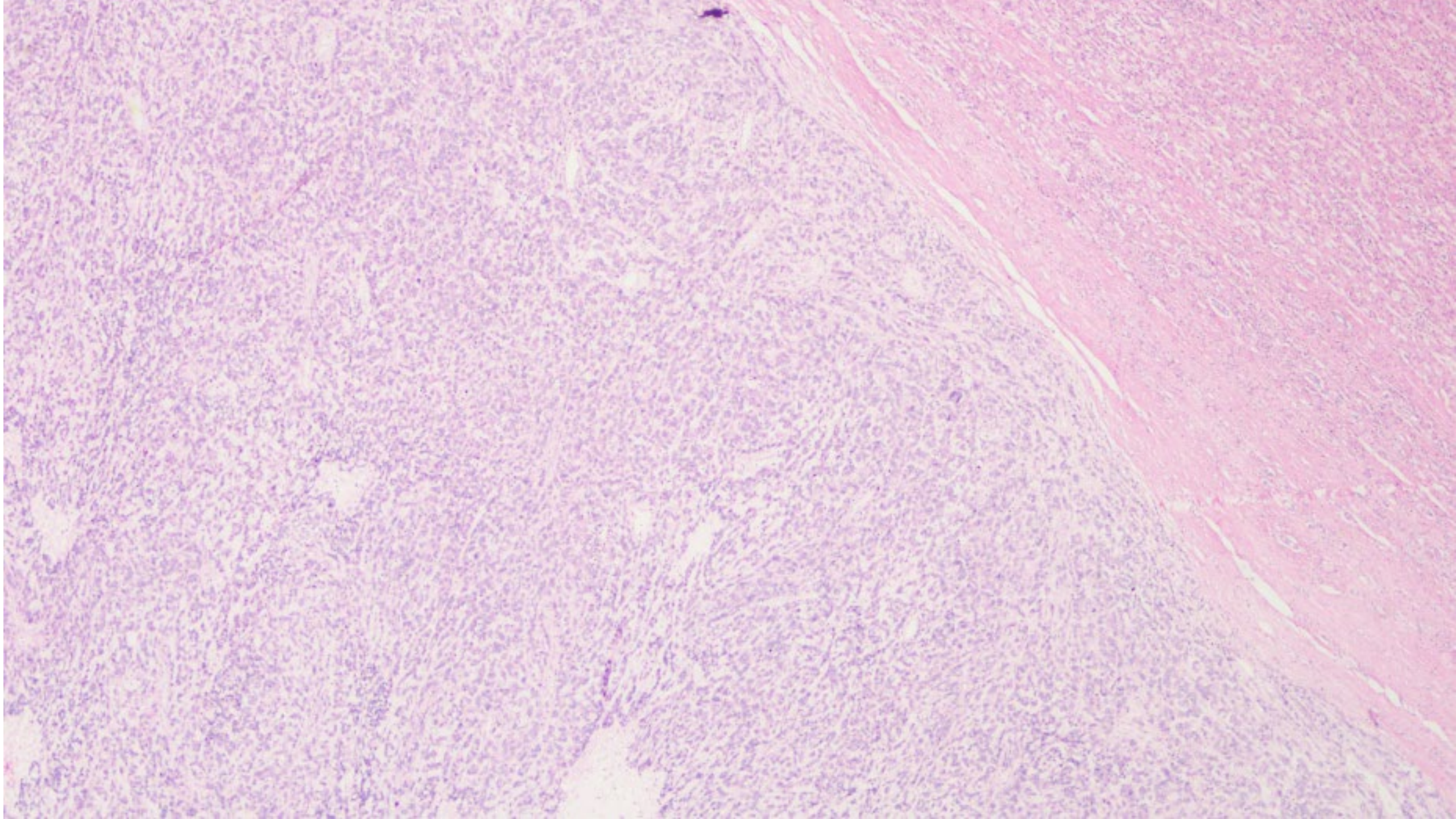


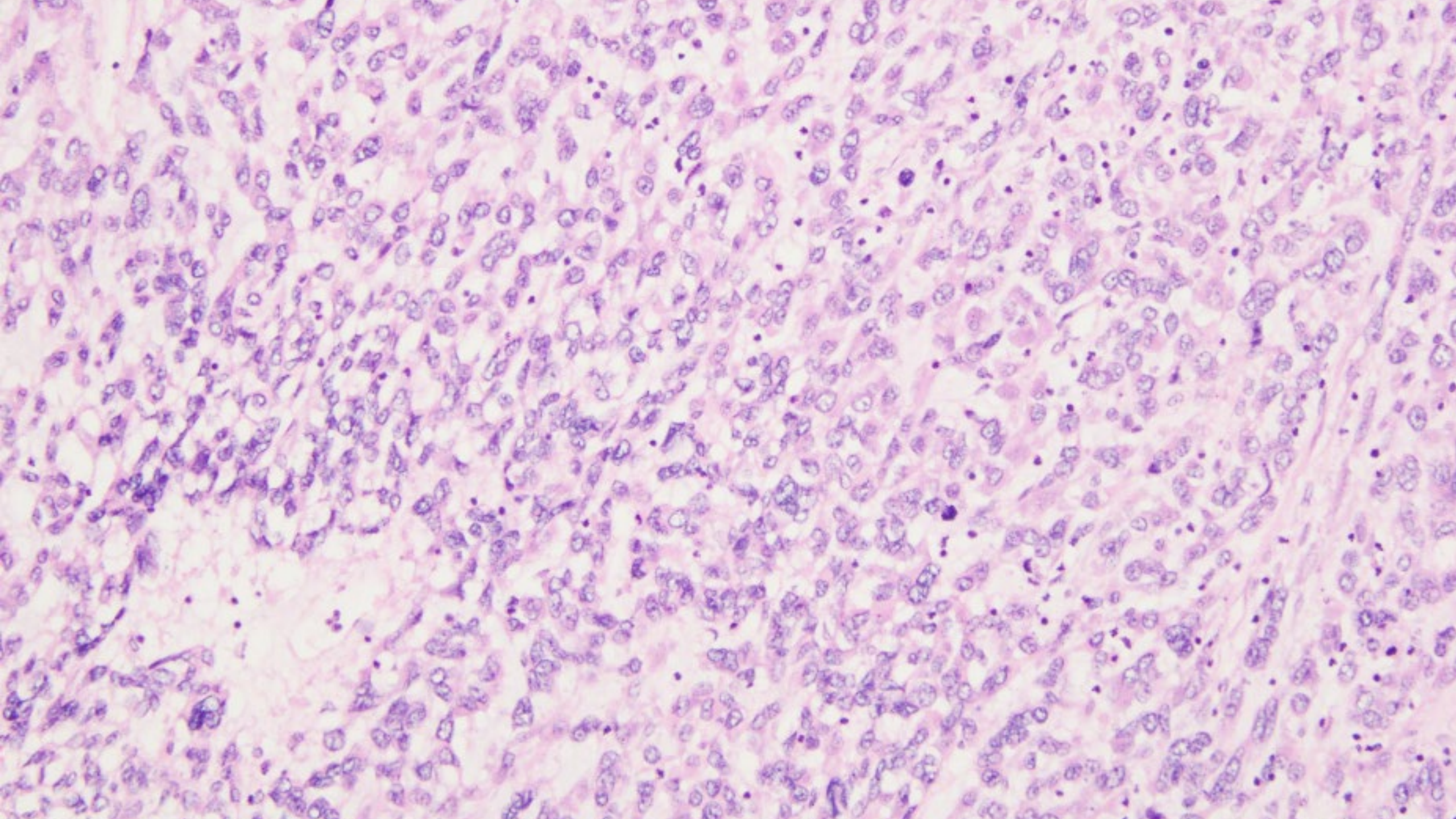
Pancreatic Endocrine Neoplasm

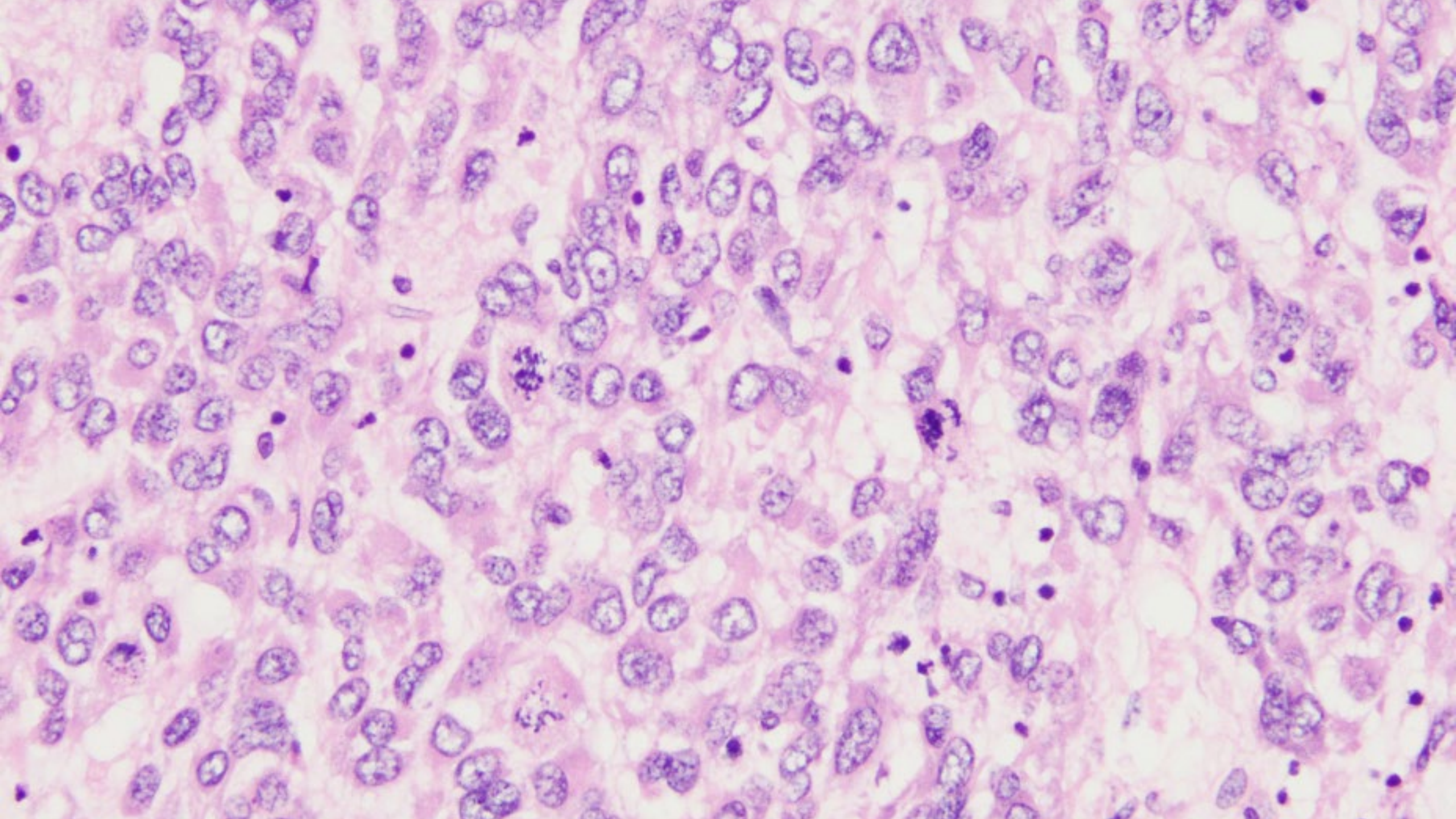


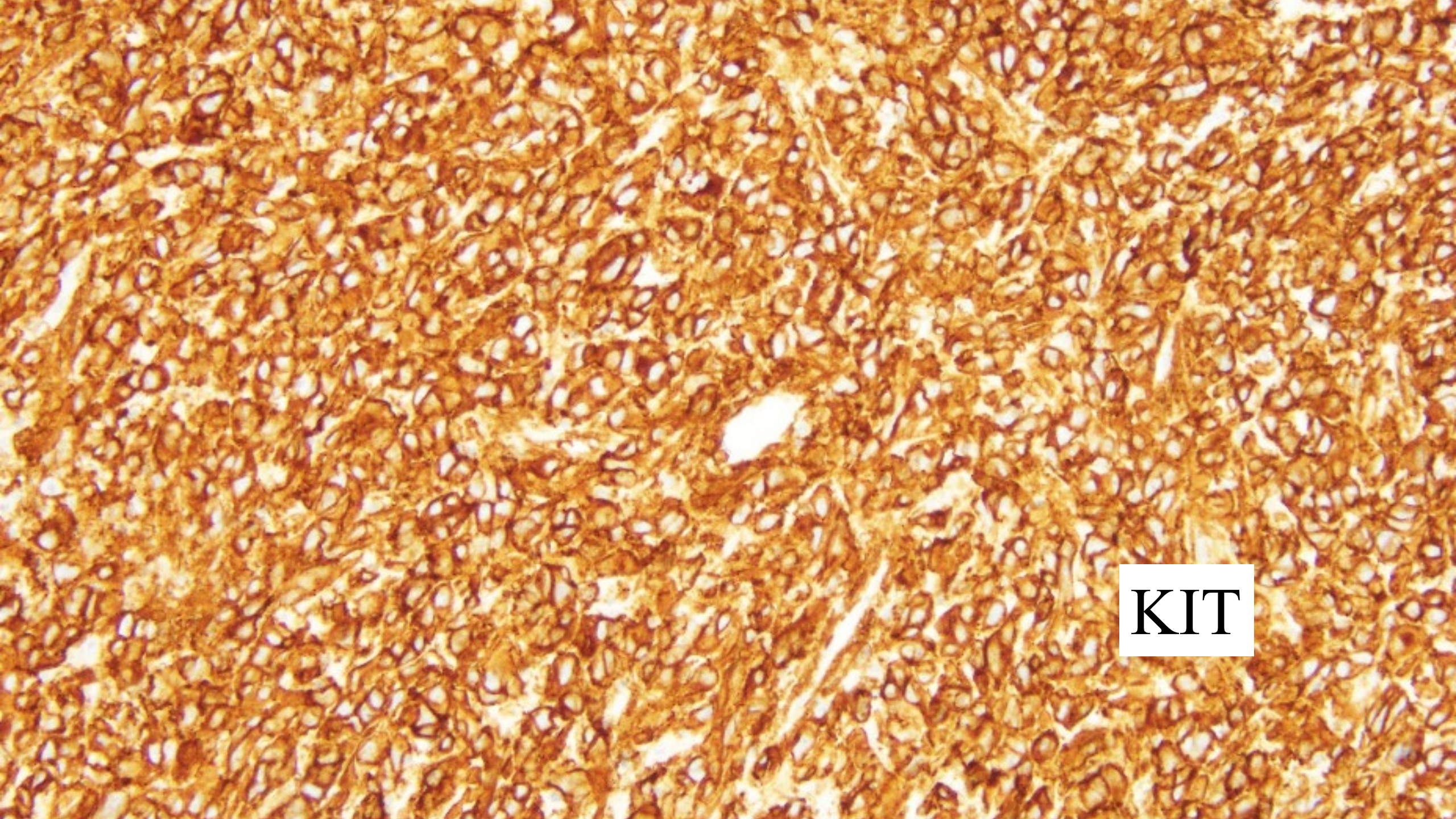


Chromogranin





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