Update from the 2019 Gnomes Meeting - Rochester, Minnesota June 19-22

Primary Malignant Epithelial Neoplasms of the Liver
Chief Gnome – Michael Torbenson

Stefan Hübscher,
Institute of Immunology and Immunotherapy, University of Birmingham
Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham

Annual Meetings of the International Liver Study Group

- First meeting, July 1968, University of Zürich (Martin Schmid)
- Currently 14 circulating members (7 Europe, 5 North America, 2 Australia)

- Cases circulated prior to meeting (2/person) to cover particular theme
- Suggested diagnoses submitted prior to meeting and collated by local organiser

- Cases presented and discussed further at meeting (2 days)
- Aim to reach consensus and provide summary/guidelines
  - **2019 – "Primary Malignant Epithelial Neoplasms of the Liver"**

Classification of Primary Epithelial Neoplasms of the Liver

(Introduction - M Torbenson)

Variant Definition

First proposed Laennec 2012 (Heidelberg)

1. A unique morphology that can be recognized on H&E
2. Immunohistochemical studies that can then confirm the H&E impression
3. Unique and consistent molecular findings
4. Clinical correlates

PMID: 23640129

AFIP fascicle

Motto for meeting

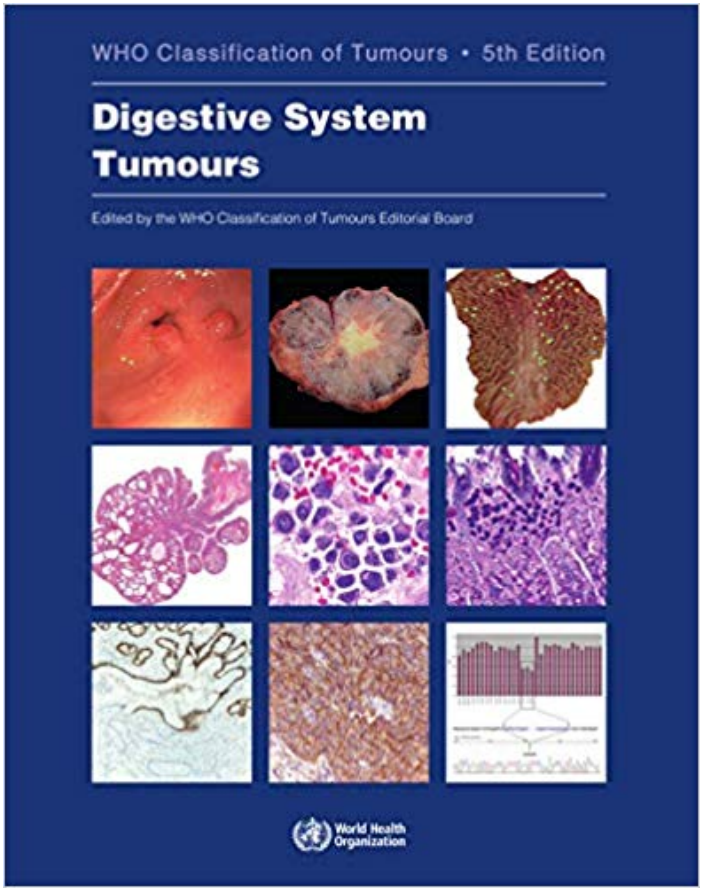
Esse quam videri

(To be rather than to seem)

WHO Classification of Tumours – 5th Edition – Digestive System Tumours

Chapter 8: Tumours of the liver and intrahepatic bile ducts

Edited by: Paradis V, Fukayama M, Park YN, Schirmacher P



Published July 2019

Summary of Presented Cases

Gnomes 2019

Rochester

HCC Variants

HCC with inflammation

Lymphocyte rich HCC

- Athens A
- St Louis C
- Washington A, HCC with anaplastic giant cells
- Washington B, plus granulomas

Lymphoepithelioma-like carcinoma

- Basel A
- St Louis B

Athens A/2019 (Dina Tiniakos)

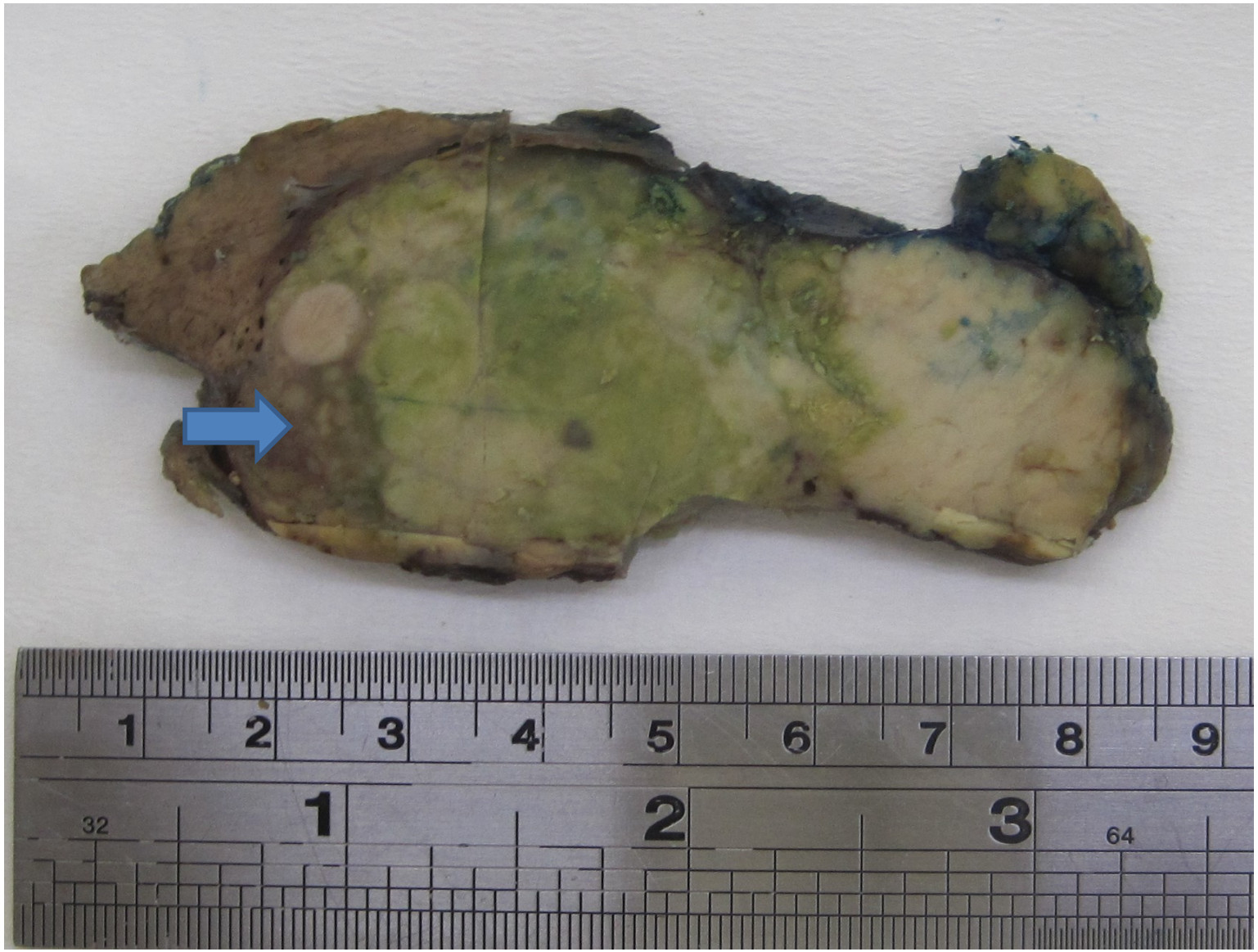
76-year-old woman

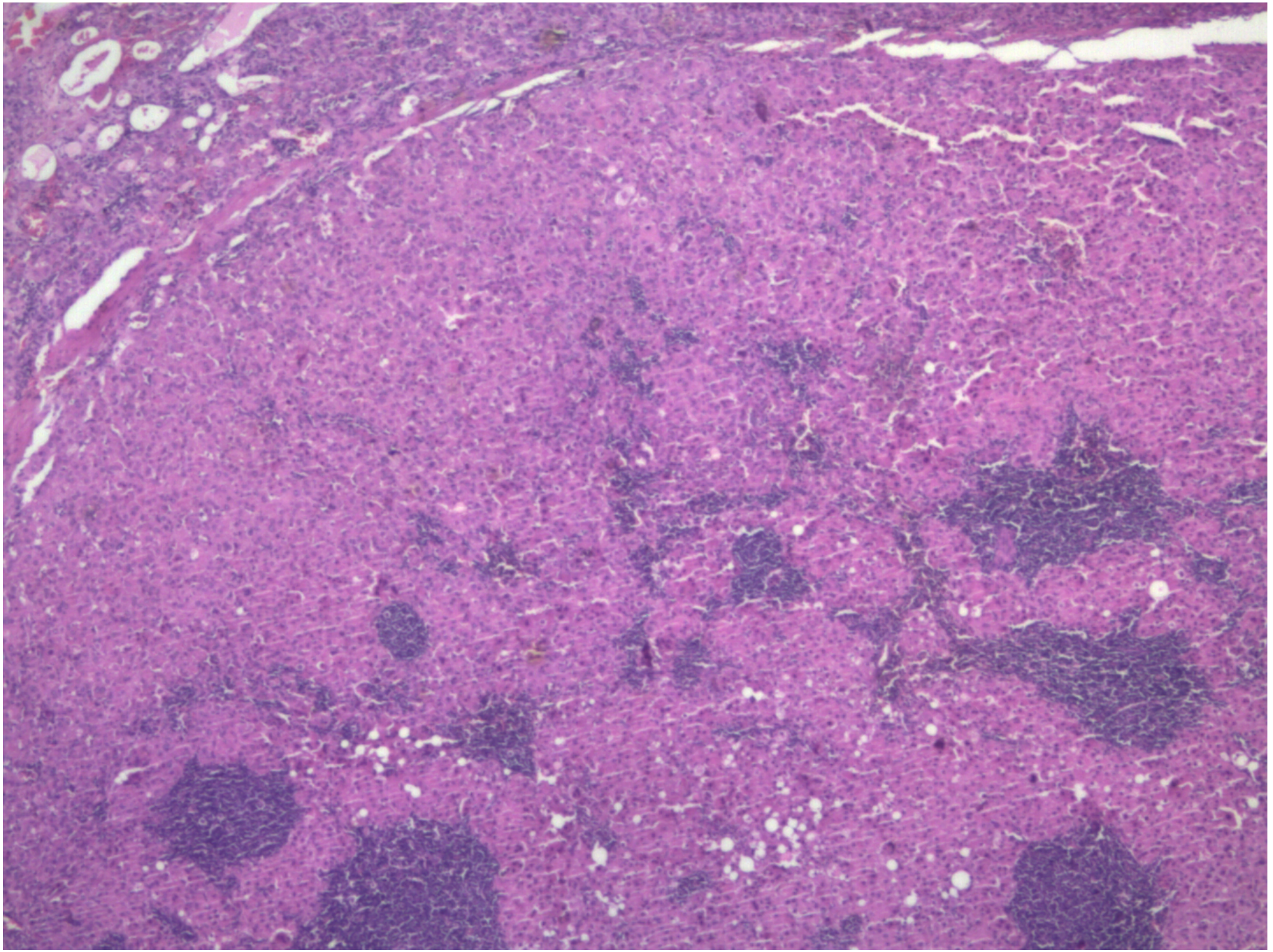
- No significant past medical history
- Normal BMI, no signs of metabolic syndrome
- No alcohol use
- Viral screen and autoantibodies negative
- Examined for abdominal discomfort

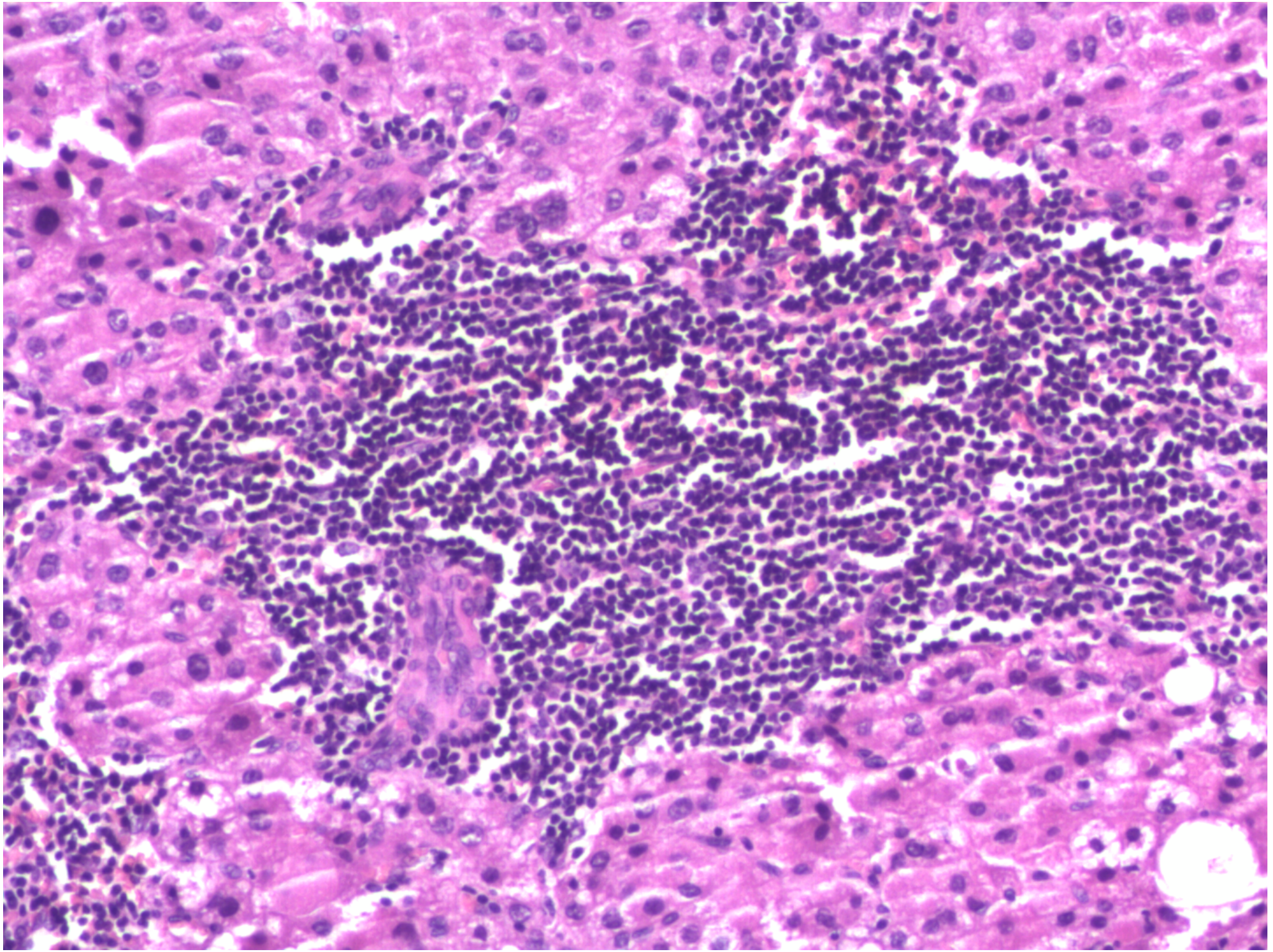
- **CT scan**: hypodense tumour 5.7x 4.7 cm, caudate lobe extending to segments V & VI
- Serum AFP 1888 ng/mL
- Surgical resection was performed

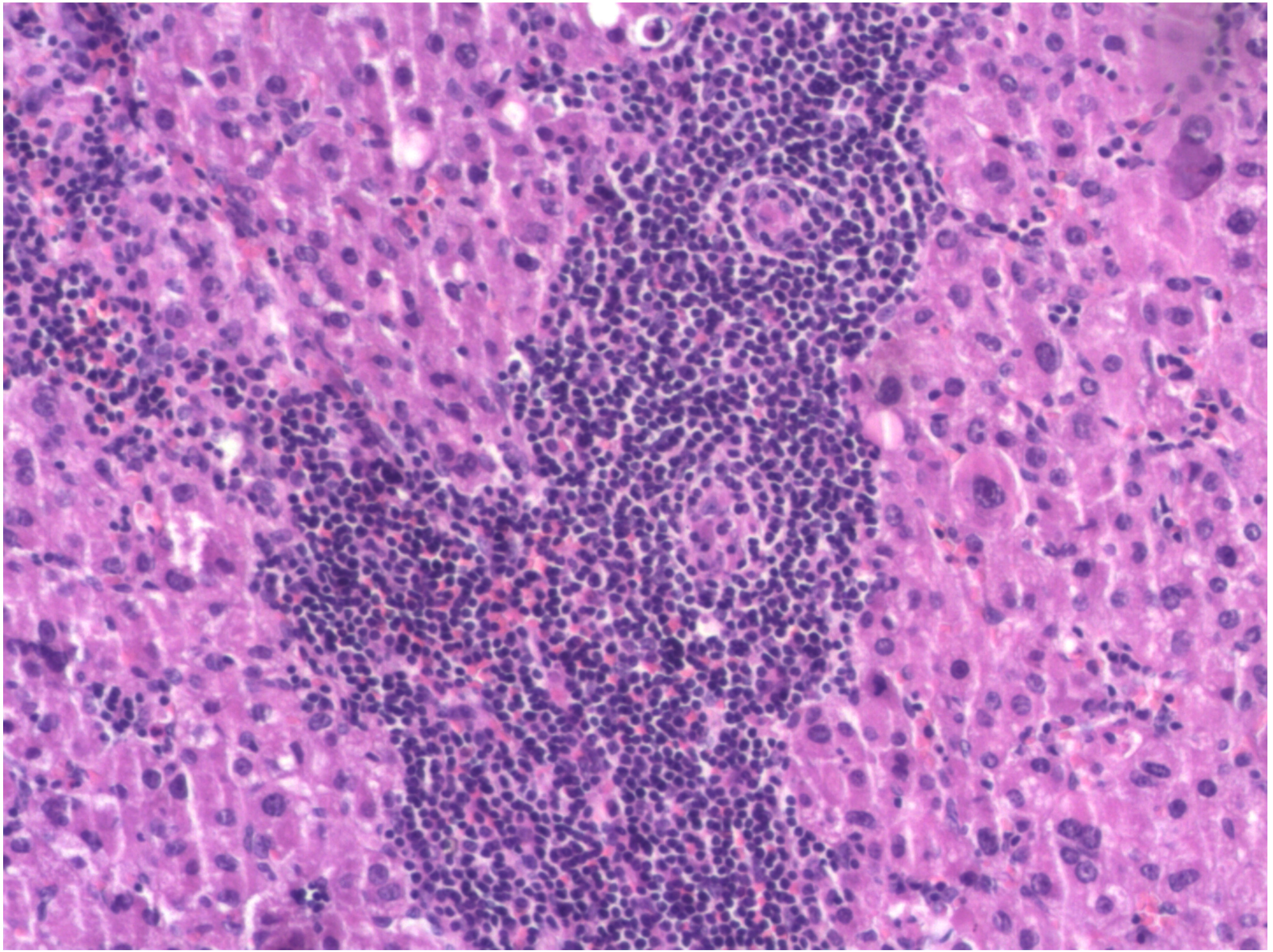
Caudate lobe resection

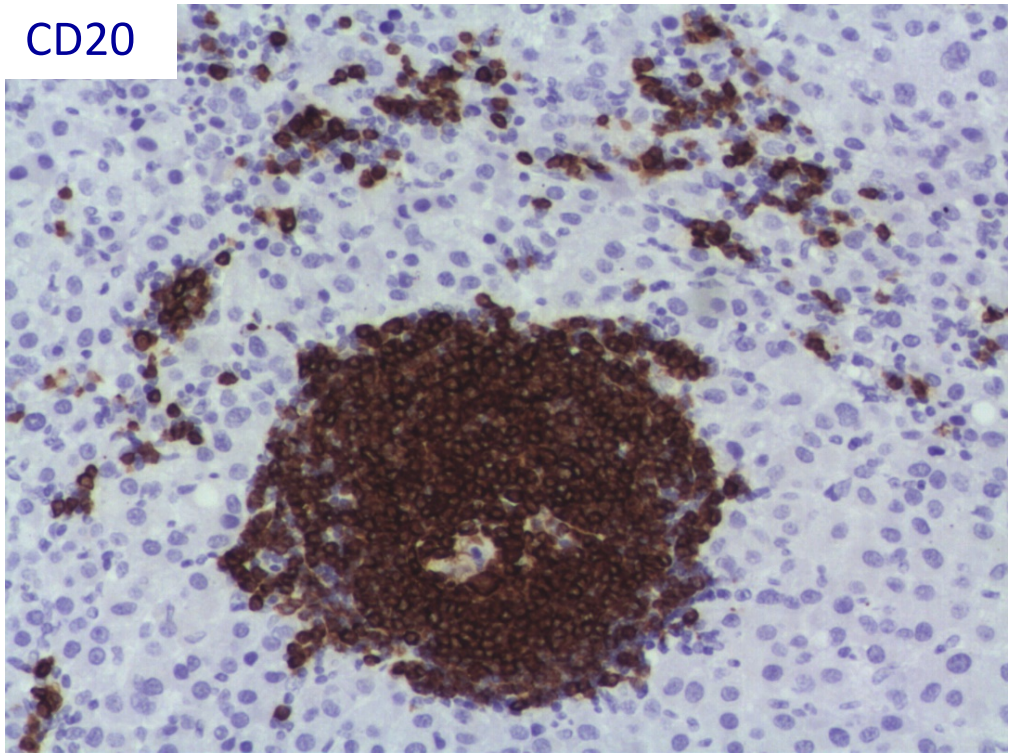
- 6.7 cm multinodular tumour
- Heterogeneous gross appearance
- 1cm tan nodule with whitish foci at tumour periphery







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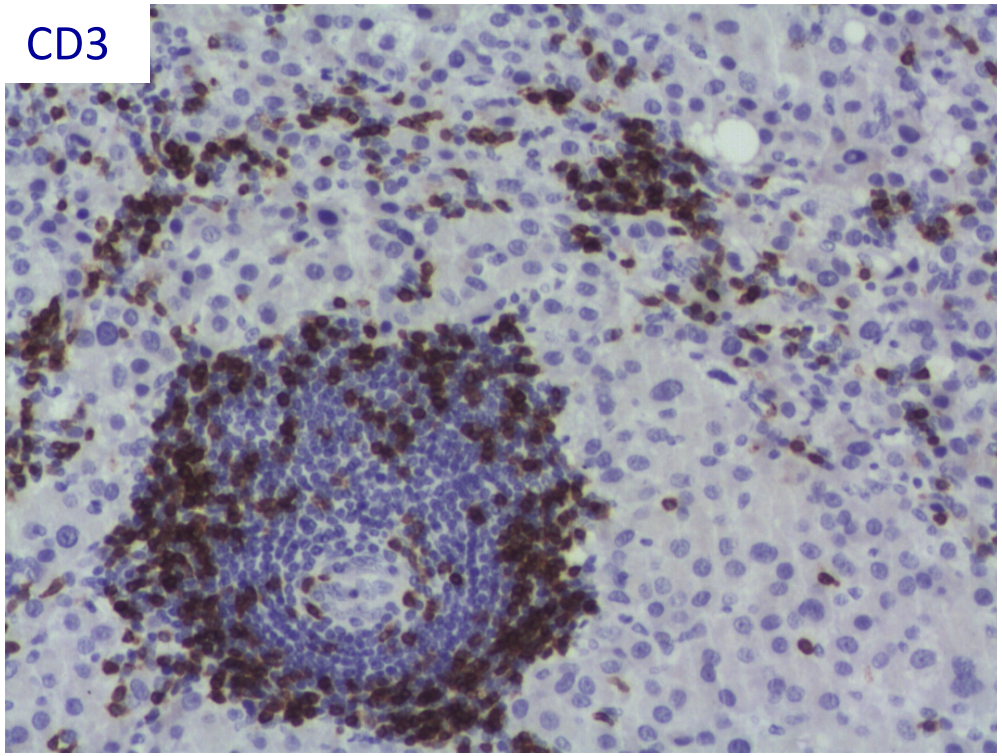
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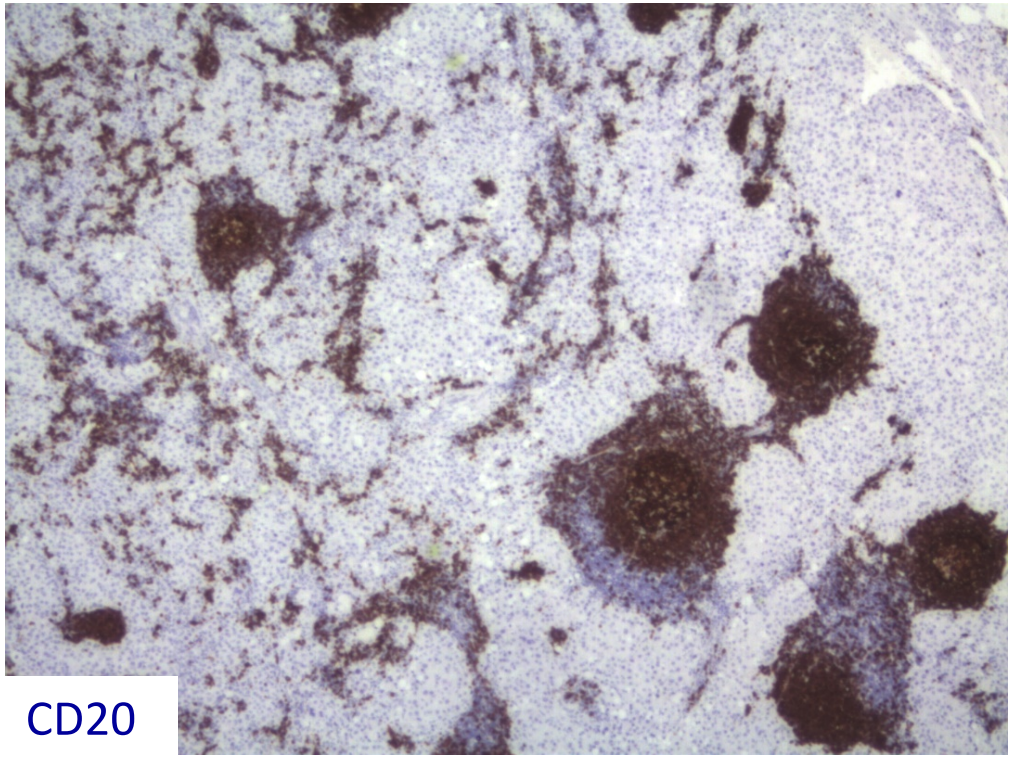
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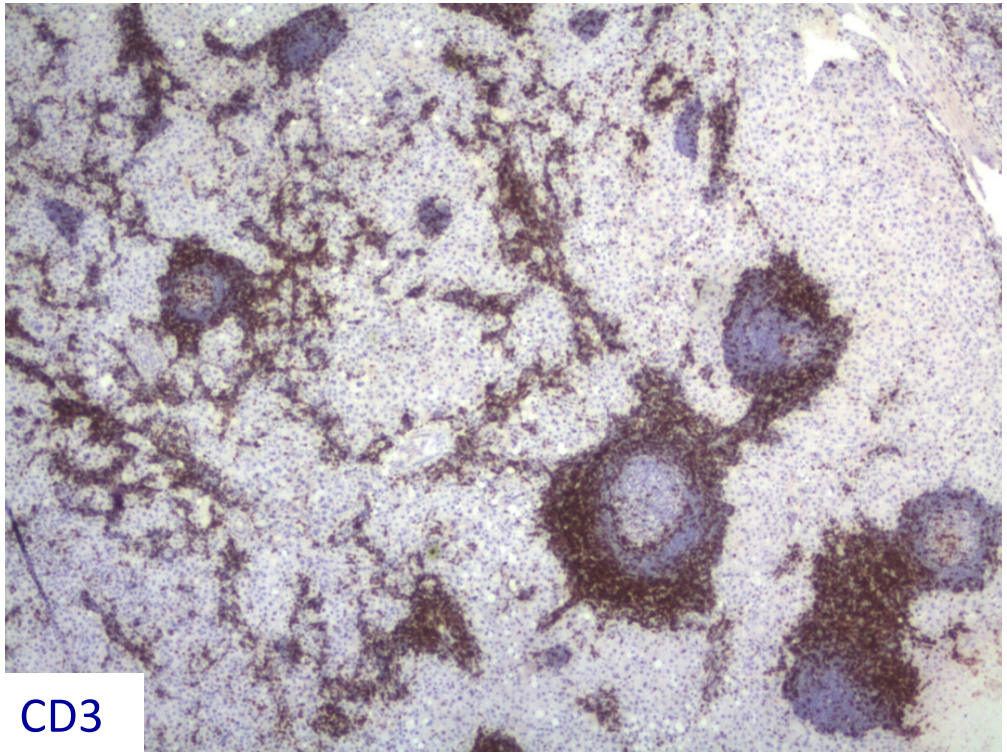
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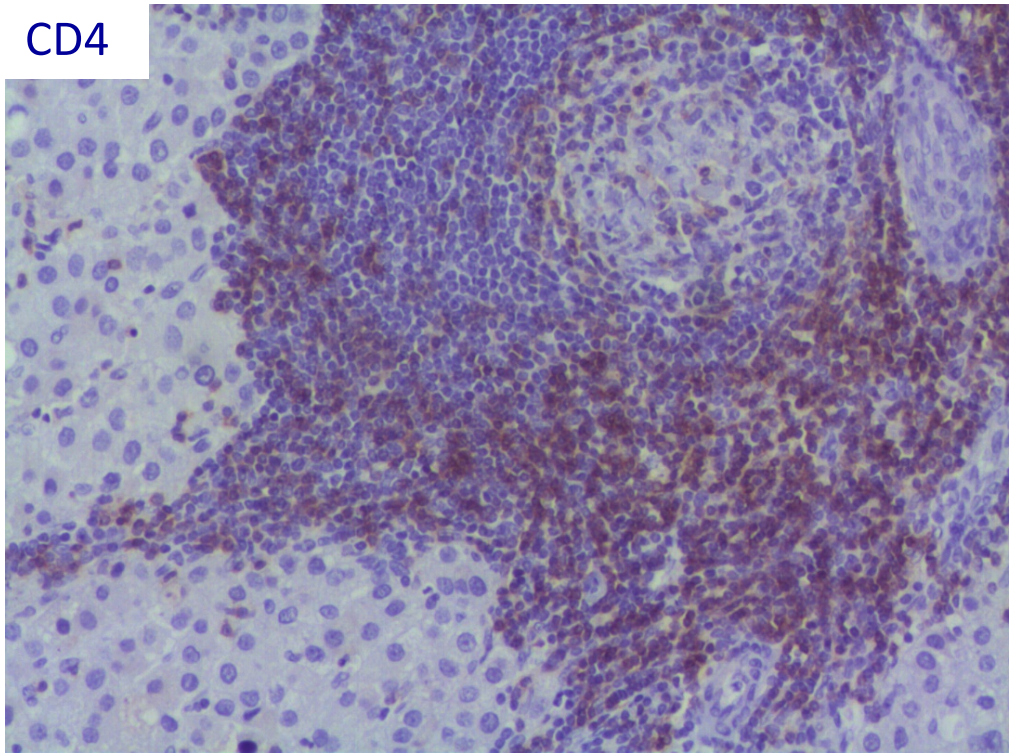
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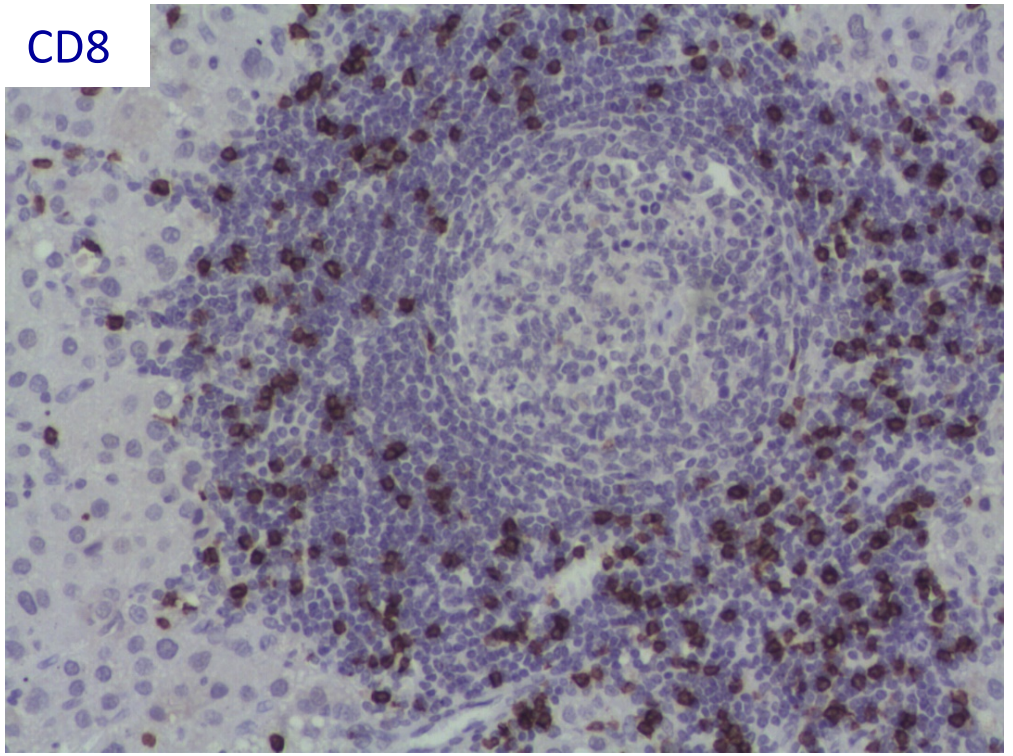
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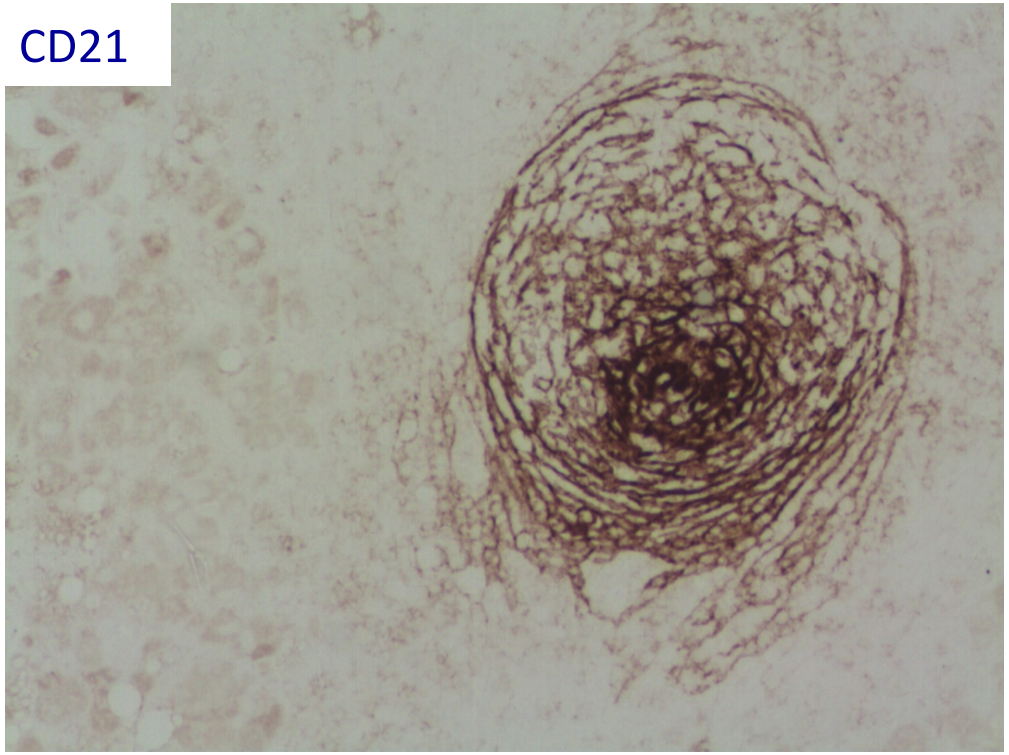
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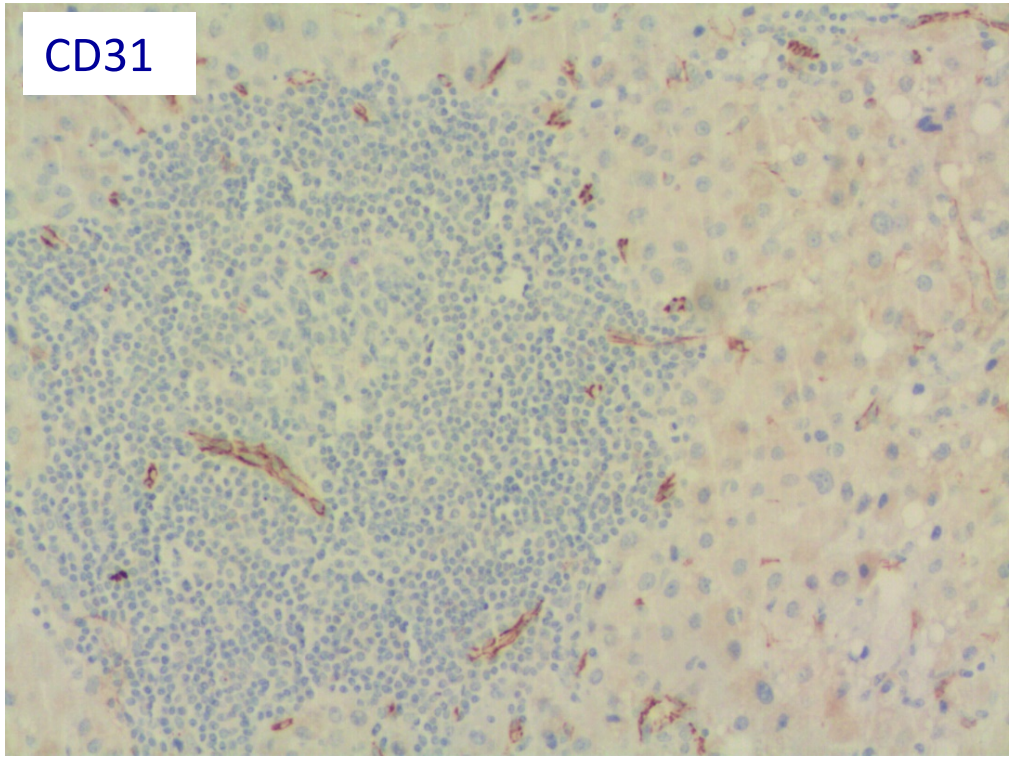
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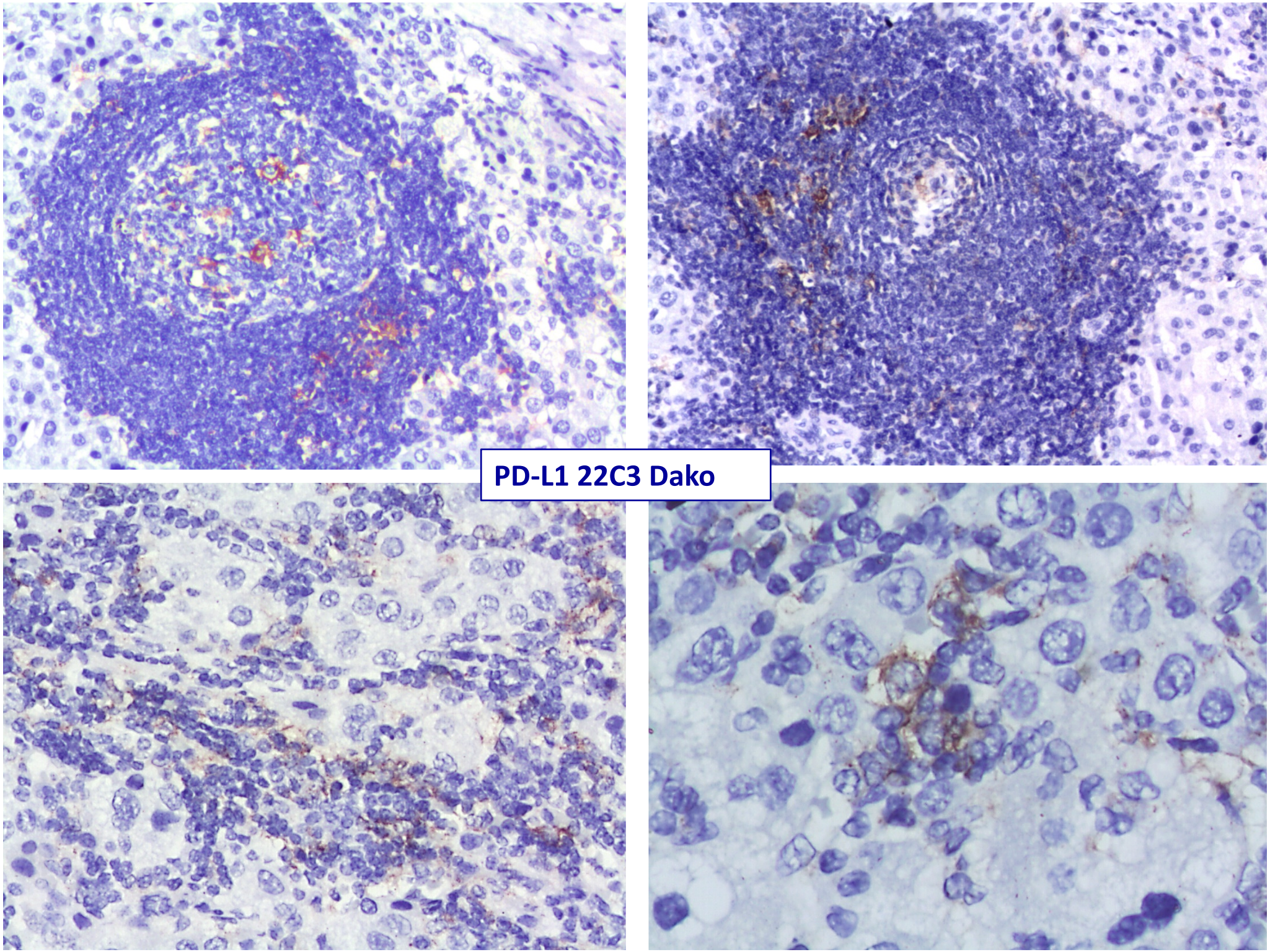
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Athens A/2019

HCC with lymphocyte-rich areas

HCC with tertiary lymphoid structures

Tertiary lymphoid structures

- Collections of immune and stromal cells confined within an organ or tissue
- Structures of varying organization: simple clusters of lymphocytes to sophisticated, segregated lymphoid structures (secondary lymphoid organ-like)
- Form at localized sites of microbial infection or chronic inflammation
- Noted in many autoimmune diseases and in cancer

Colbeck et al, Front Immunol 2017

Detection, prognostic and predictive impact of tertiary lymphoid structures in human cancers

Tumour type	Number of patients investigated	Method of TLS detection	% of patients[a]	TLS location	Prognostic value	Correlation with tumour progression	Predictive impact of TLSs
Lung	74	IHC (CD20)	NA	Tumour stroma and invasive margin	Favourable	NA	NA
Lung	151	IHC (DC-LAMP and CD8 markers)	NA	Tumour and invasive margin	Favourable	NA	After neoadjuvant chemotherapy
Lung	362	IHC (DC-LAMP)	54	Tumour	Favourable	NA	NA
Lung squamous	138	H&E	>95	Tumour periphery	Favourable	NA	Prognostic impact lost in patients treated by neoadjuvant chemotherapy; TLSs decrease upon corticosteroi treatment
Melanoma	82	IHC (DC-LAMP and CD3 markers)	NA	NA	Favourable	NA	NA
Melanoma	225	HEV	NA	NA	NA	HEV density decreases in higher tumour stages	NA
Metastases of melanoma	10	12-Chemokine signature	42	Peri-tumoura tissue	Favourable	NA	NA
Oral (squamous)	80	IHC	21	Tumour periphery	Favourable	NA	NA
Metastases of ovarian	172	IHC	20	Tumour stroma	Favourable association of plasma cells with TLSs	NA	NA
Metastases of ovarian	147	IHC (DC-LAMP and CD20 markers)	50	Tumour stroma	Favourable	NA	NA

Sautes-Fridman C, Nature Rev Cancer 2019

Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma☆

Julien Calderaro[1,2,3,4,*], Florent Petitprez[4,5], Etienne Becht[4,5], Alexis Laurent[6], Théo Z. Hirsch[7], Benoit Rousseau[2,3,8], Alain Luciani[2,3,9], Giuliana Amaddeo[2,3,10], Jonathan Derman[1], Cécile Charpy[1], Jessica Zucman-Rossi[7,11,12], Wolf Herman Fridman[4,13,†], Catherine Sautès-Fridman[4,13,†]

Journal of Hepatology **2019** vol. 70 | 58–65

n=273 resected HCC

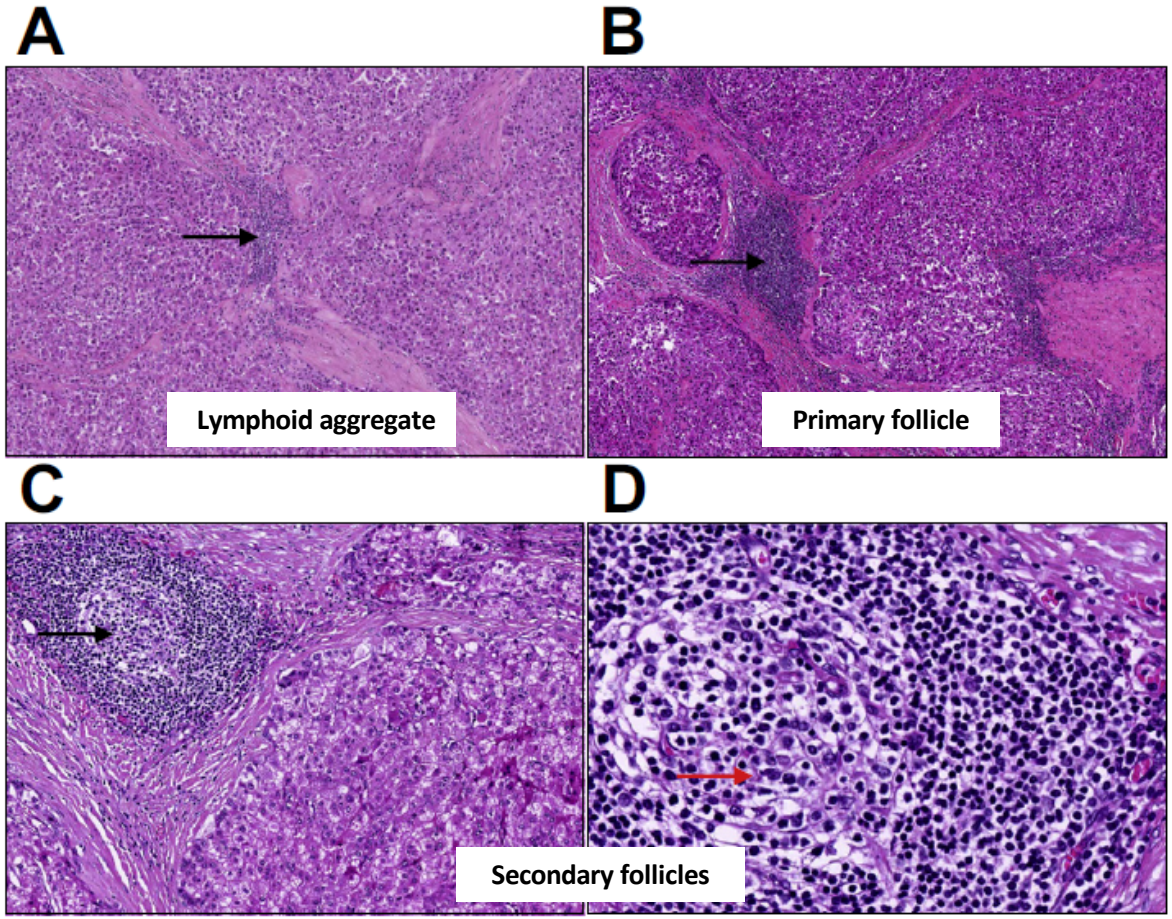
Male 82%, >60 yo 58%

Aetiology:

- HBV 29%
- Alcohol 27%
- HCV 25%
- NASH 14%

47% had TLS

- 26% lymphoid aggregates
- 16% primary follicles
- 5% secondary follicles



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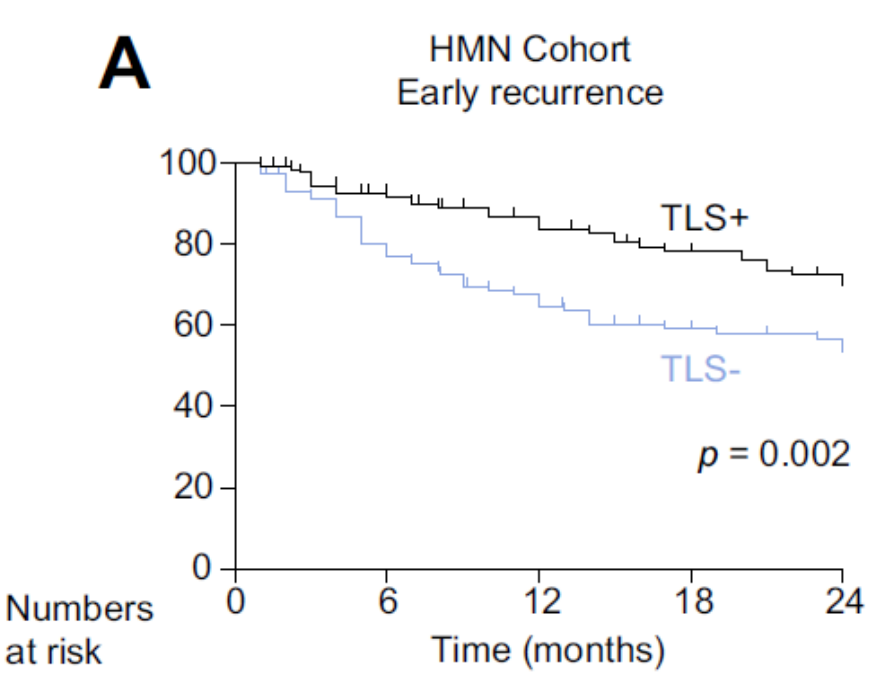
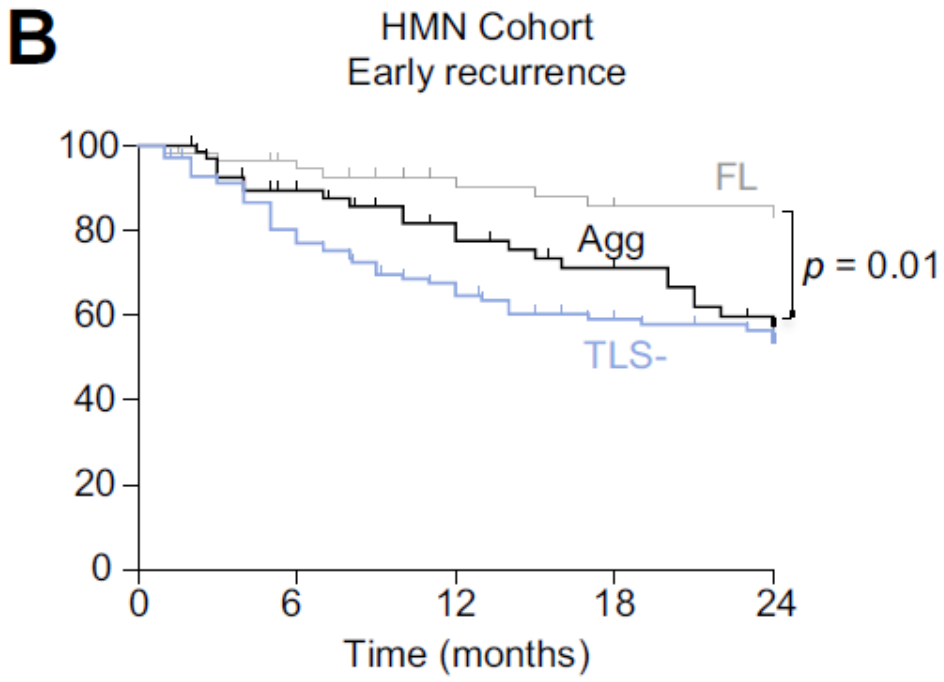


Lower risk of recurrence in cases with TLS (any)



Lower risk of recurrence in cases with 1^{O} or 2^{O} follicles (vs lymphoid aggregates)

HCC with inflammation

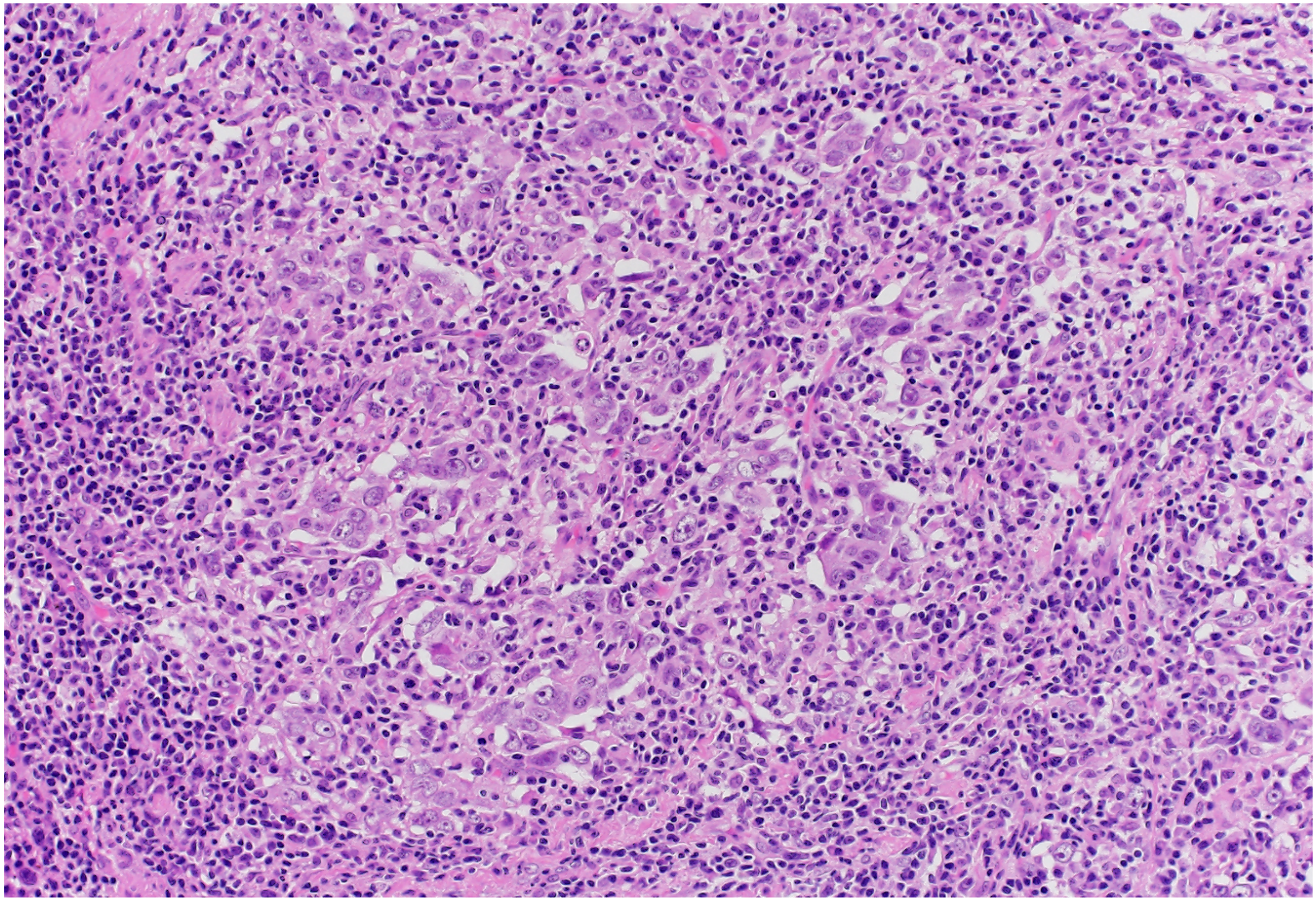
Lymphocyte rich HCC

- Athens A
- St Louis C
- Washington A, HCC with anaplastic giant cells
- Washington B, plus granulomas

Lymphoepithelioma-like carcinoma

- Basel A (LEL cholangiocarcinoma)
- St Louis B (LEL HCC)

Lymphoepithelioma-like Carcinoma in the Liver
Basel A/2019 (Luigi Terracciano)

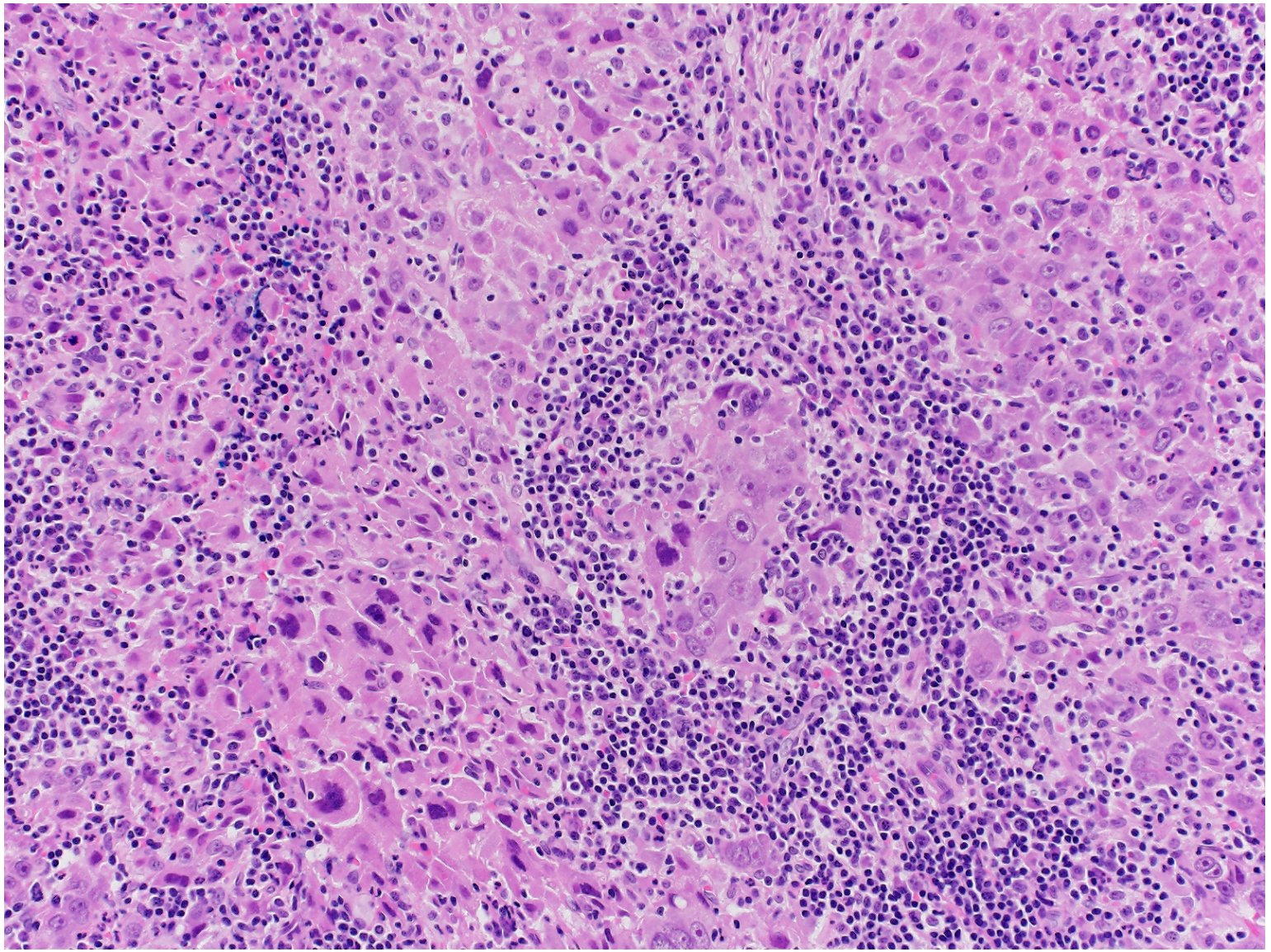


Large undifferentiated cells, poorly cohesive, with indistinct cell borders intermingled with abundant lymphocytes and plasmacells

Lymphoepithelioma-like Carcinoma in the Liver

B16.48004

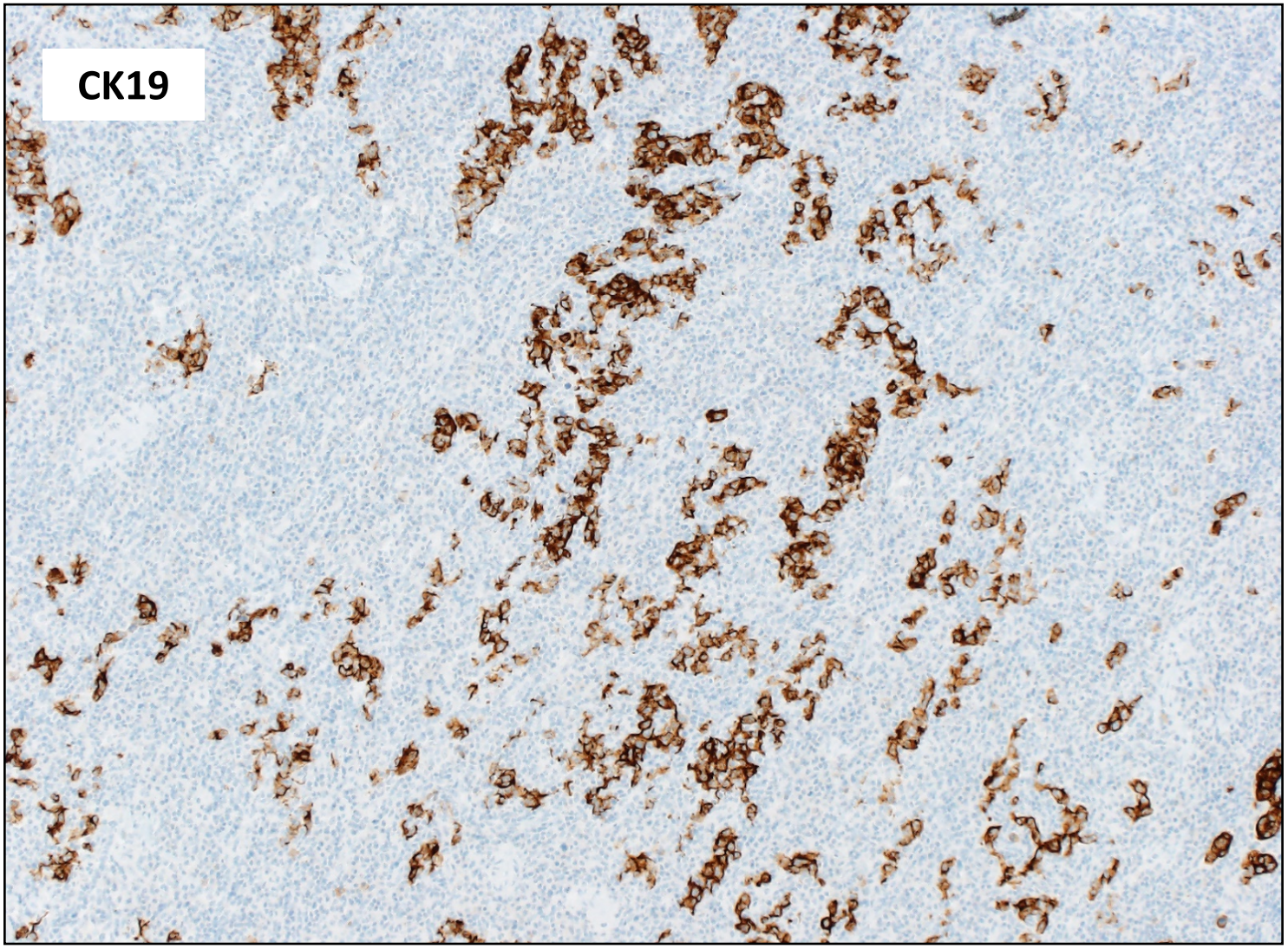
Basel A/2019 (Luigi Terracciano)



Large undifferentiated cells, with pleomorphic nuclei, prominent nucleoli and moderately abundant eosinophilic cytoplasm

Universitätsspital Basel

Lymphoepithelioma-like Carcinoma in the Liver
Basel A/2019 (Luigi Terracciano)

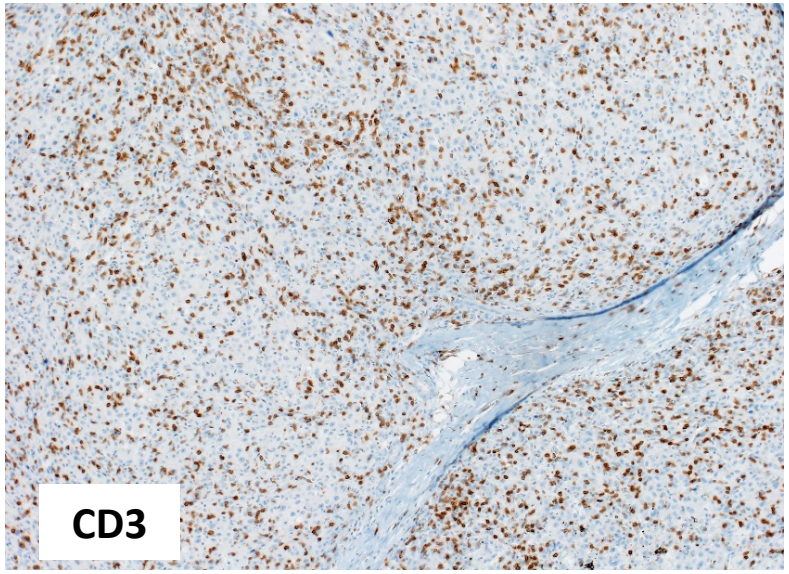


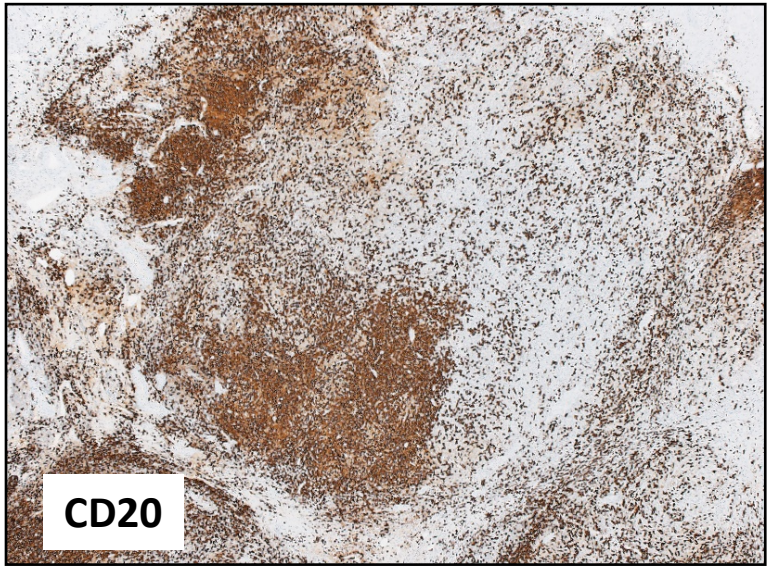
- Tumour cells express CK19 (and CK7)
- Negative for Arginase 1, Hep Par1, pCEA,

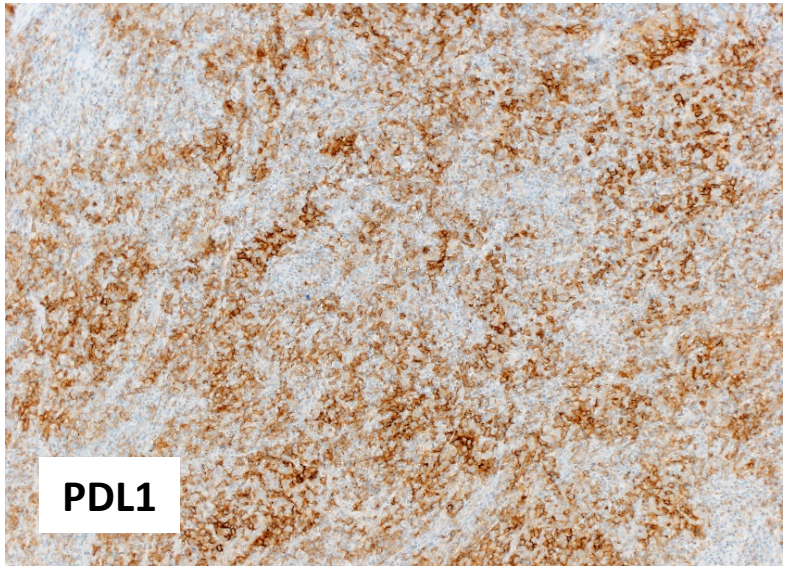
Lymphoepithelioma-like Carcinoma in the Liver

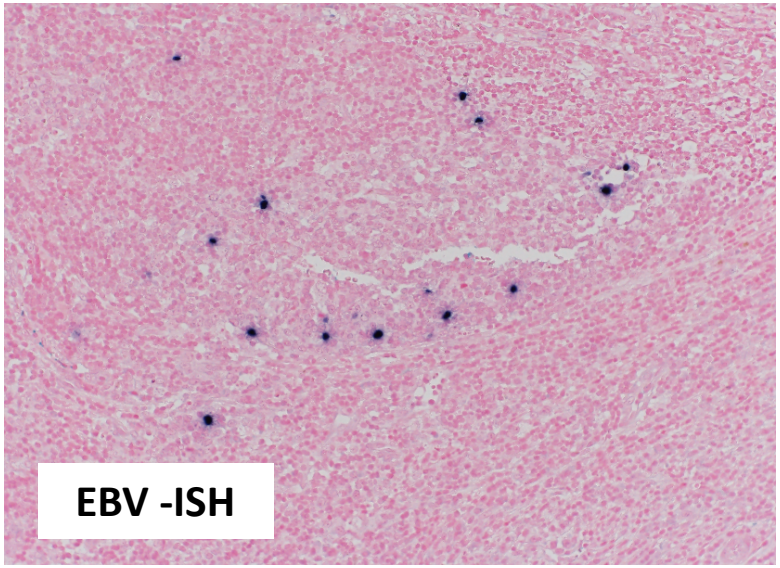
Basel A/2019 (Luigi Terracciano)

B16.48004







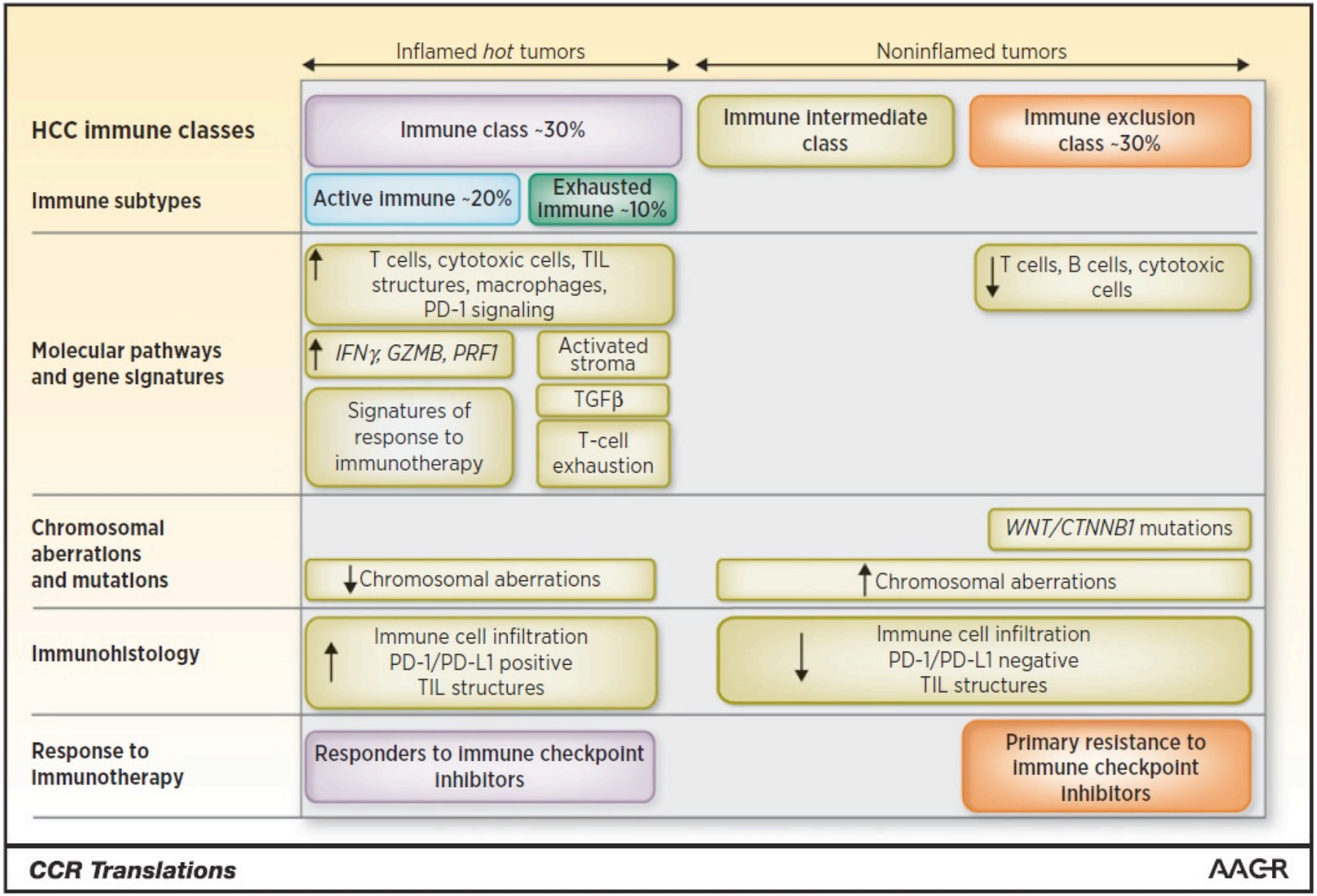


Lymphoepithelioma-like (LEL) Carcinoma in Liver

- Rare: 66 cases of LEL-HCC , 27 cases of LEL-CC (Labgaa, Am J Pathol 2017).
- LEL-HCC poorly-differentiated (contrasting with lymphocyte-rich HCCs, which are typically well- or moderately differentiated).
- Immunohistochemistry required to prove hepatocytic differentiation (versus LEL-cholangiocarcinoma and metastatic LEL-carcinoma).
- EBV positivity seen consistently in LEL-CC, very rare in LEL HCC (1/66 cases reviewed by Labgaa 2017).
- LEL-HCC has better prognosis than conventional HCC

- **Lymphocyte-rich HCC recognised as subtype in WHO 2019 Classification**
  - **Rare (<1%)**
  - **“Lymphocytes outnumber tumour cells in most fields“**

Classification of HCC based on Immune Status of Tumour Microenvironment Possible Implications for Treatment



Pinyol, Clin Cancer Res 2019

Steatohepatitic HCC

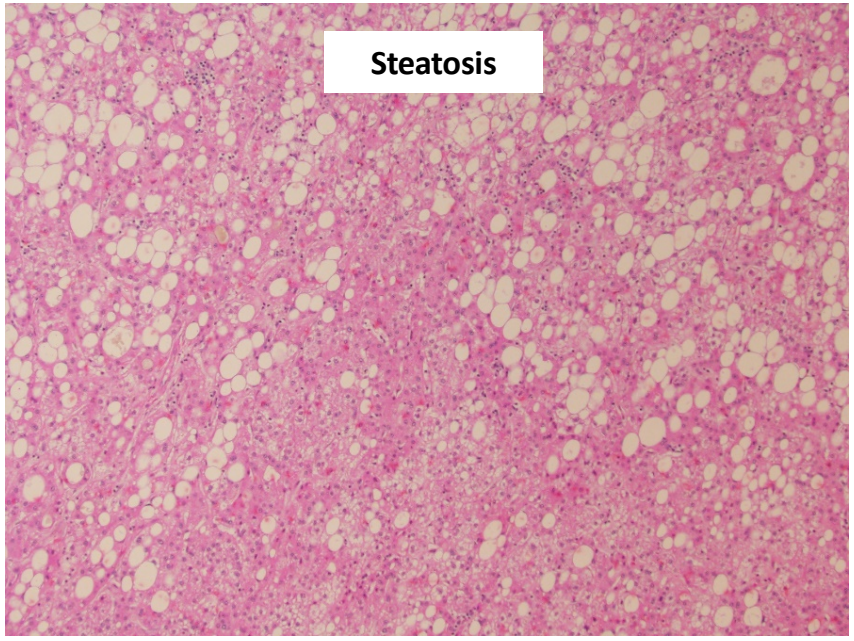
- Athens 1A (second nodule)
- Bethesda A
- Birmingham A (in HCC component of mixed HCC-cholangiocarcinoma)
- Brisbane B
  - Also with foci mimicking cholangiocarcinoma
  - Emphasis on under-recognition by pathologists (Quality assurance data from Australia)
- Heidelberg 1C
  - vs Hepatic adenoma, in patient with glycogen storage disease type 1.
- Heidelberg 2b

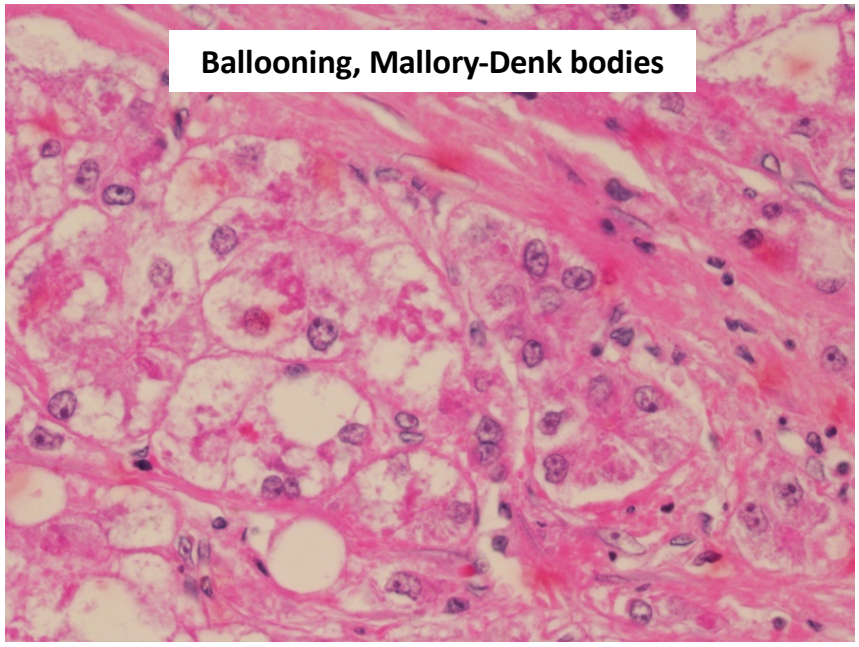
Bethesda A/2019 (David Kleiner)

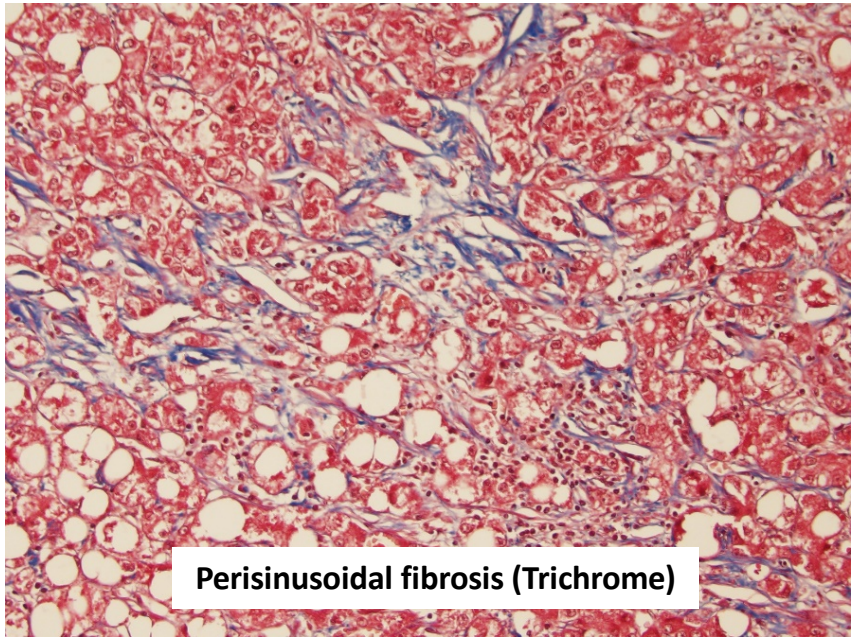
75 yo Asian male

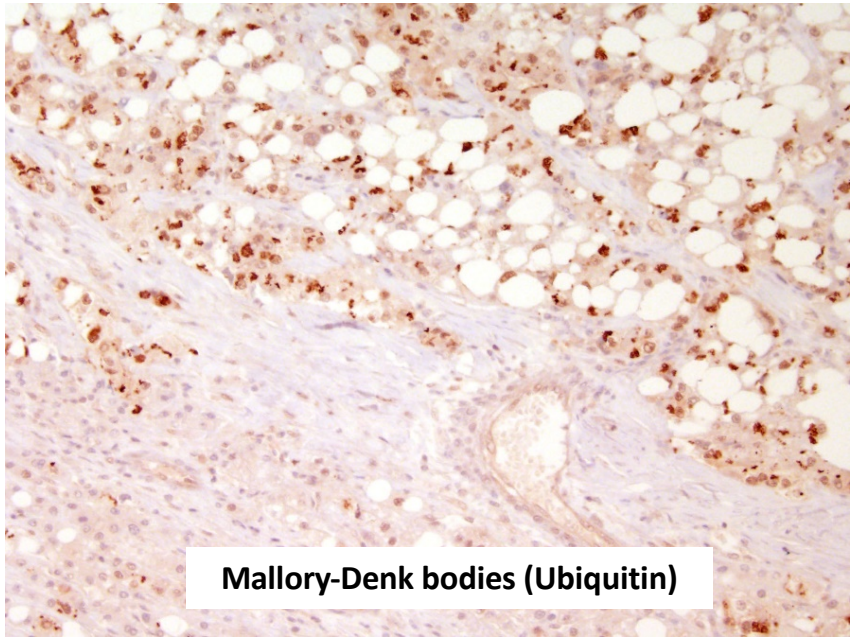
- Several month history of weight loss and fatigue
- History of HBsAg (+), HBeAg (-) active chronic HBV infection (apparently untreated) and a 10 year history of DM.
- CT/MRI at showed a 3.2 cm lesion suspected to be HCC. Background liver looked cirrhotic.
- This lesion was resected.
- A section of this resection was sent for review (no macroscopic images)
- He is alive and without disease 1 year later.

Bethesda A/2019 (David Kleiner)
Histological Features









Steatohepatitic variant of hepatocellular carcinoma

(Salamao 2010, Salamao 2012, Shibahara 2014, Yeh 2015, Tan 2016, Calderaro 2017)

- Variably defined, but later studies use 50% cut-off of involvement by SH component

- SH-HCC tended to be smaller, lower grade, less vascular invasion or bile duct invasion
- Disease-free but not overall survival better in SH-HCC

- Great majority of cases associated with metabolic syndrome and/or fatty liver disease in non-tumoral liver
  - Steatohepatitic features could be an epiphenomenon related to general metabolic-syndrome milieu

- Recent studies suggest that there may be distinctive chromosomal, mutational and transcriptional differences between SH-HCC and other subtypes

Steatohepatitic HCC (WHO 2019 Classification)

- Recognised as a variant of HCC, prevalence of 5 -20%
- Tumour shows histological features of steatohepatitis

Molecular studies:

- Lack of *CTNNB 1* and *TP53* mutations
- High frequency of pro-inflammatory IL6/JAK/STAT activation
  - ➢ Expression of CRP and SAA
  - ➢ Also express SHH (Ando 2015)

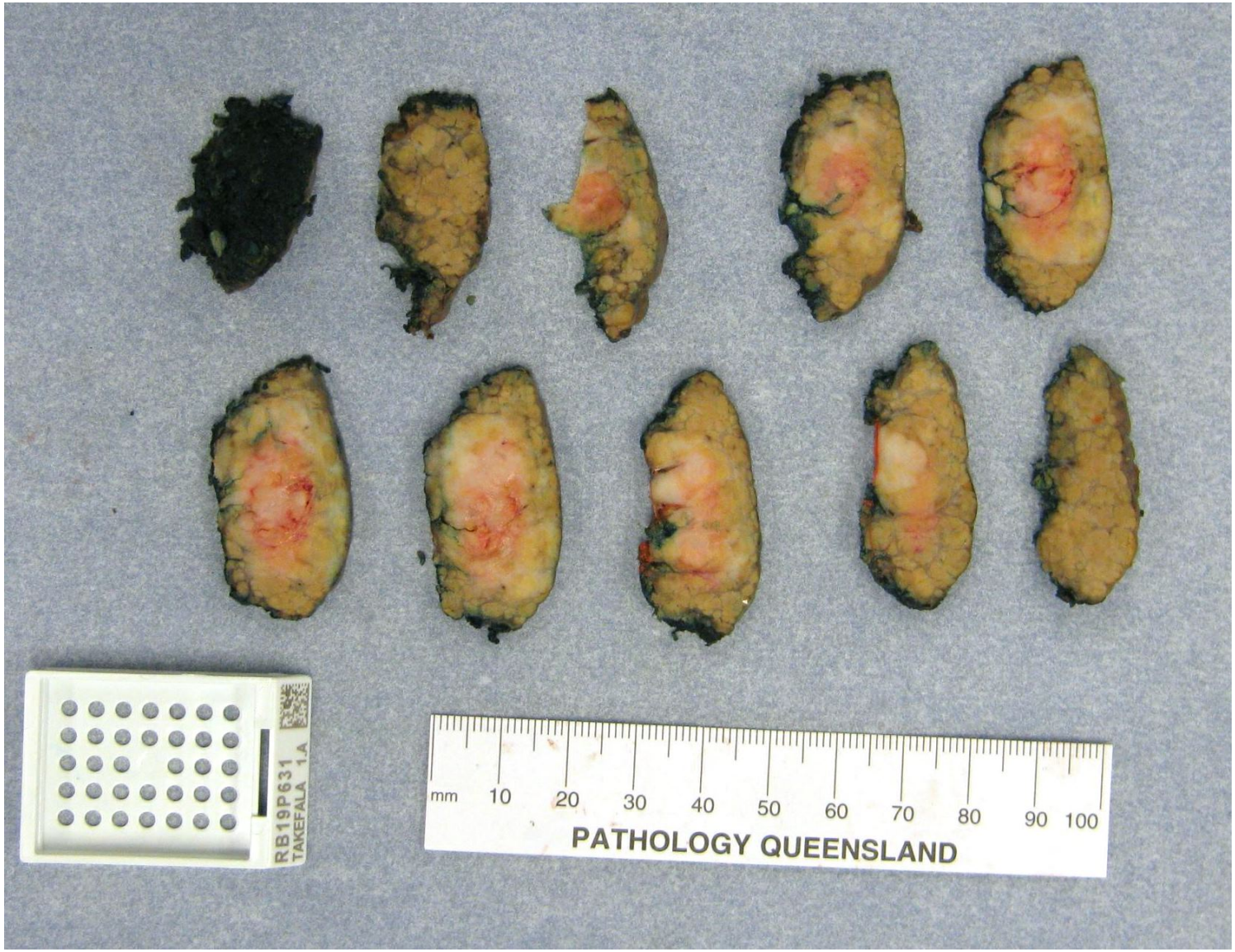
Steatohepatitic HCC

- Athens 1A (second nodule)
- Bethesda A
- Birmingham A (in HCC component of mixed HCC-cholangiocarcinoma)
- Brisbane B (Andrew Clouston)
  - Also with foci mimicking cholangiocarcinoma
  - Emphasis on under-recognition by pathologists (Quality assurance data from Australia)
- Heidelberg 1C
  - vs Hepatic adenoma, in patient with glycogen storage disease type 1.
- Heidelberg 2b

Brisbane B/2019 (Andrew Clouston)

- 54 yo male of Pacific Islander extraction
- chronic hepatitis C cirrhosis

- developed tumour
- resected tumour 24 mm diam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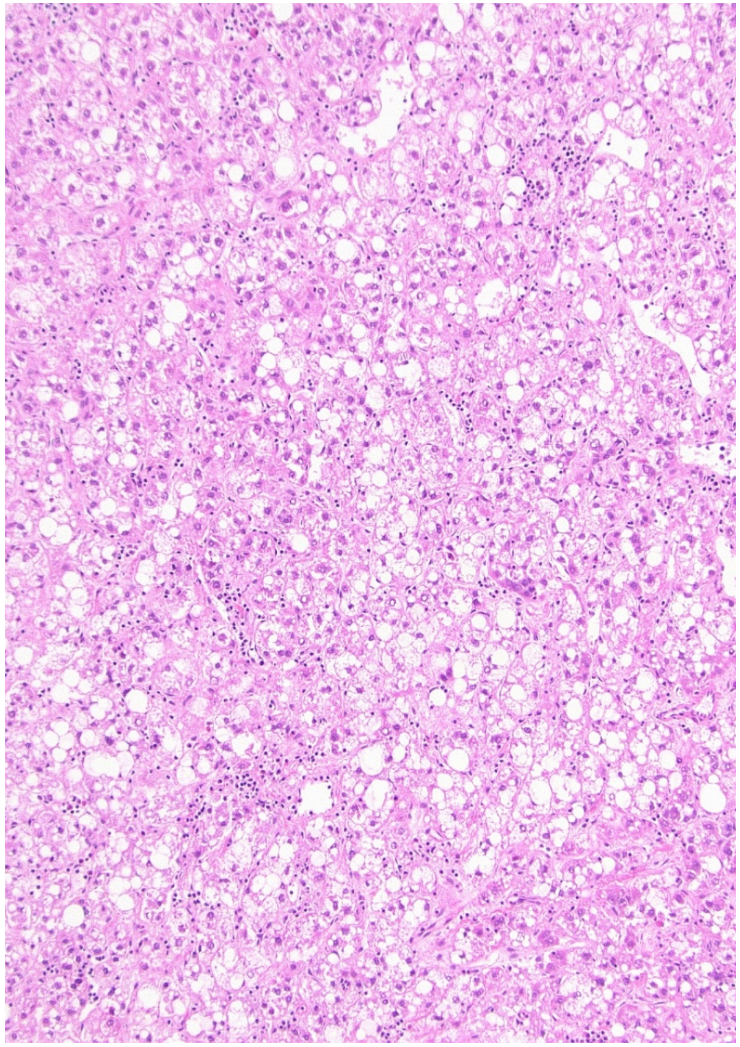
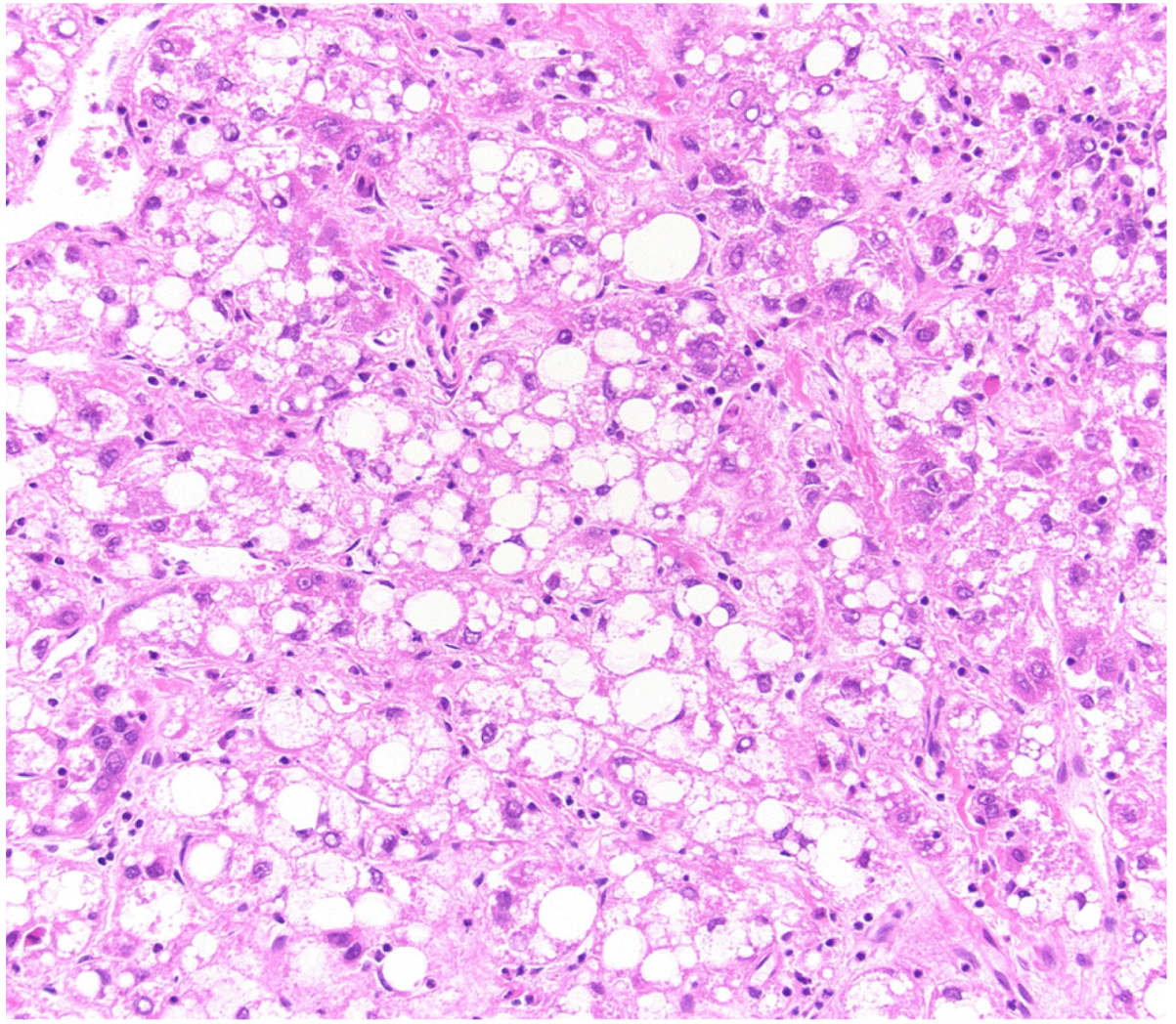
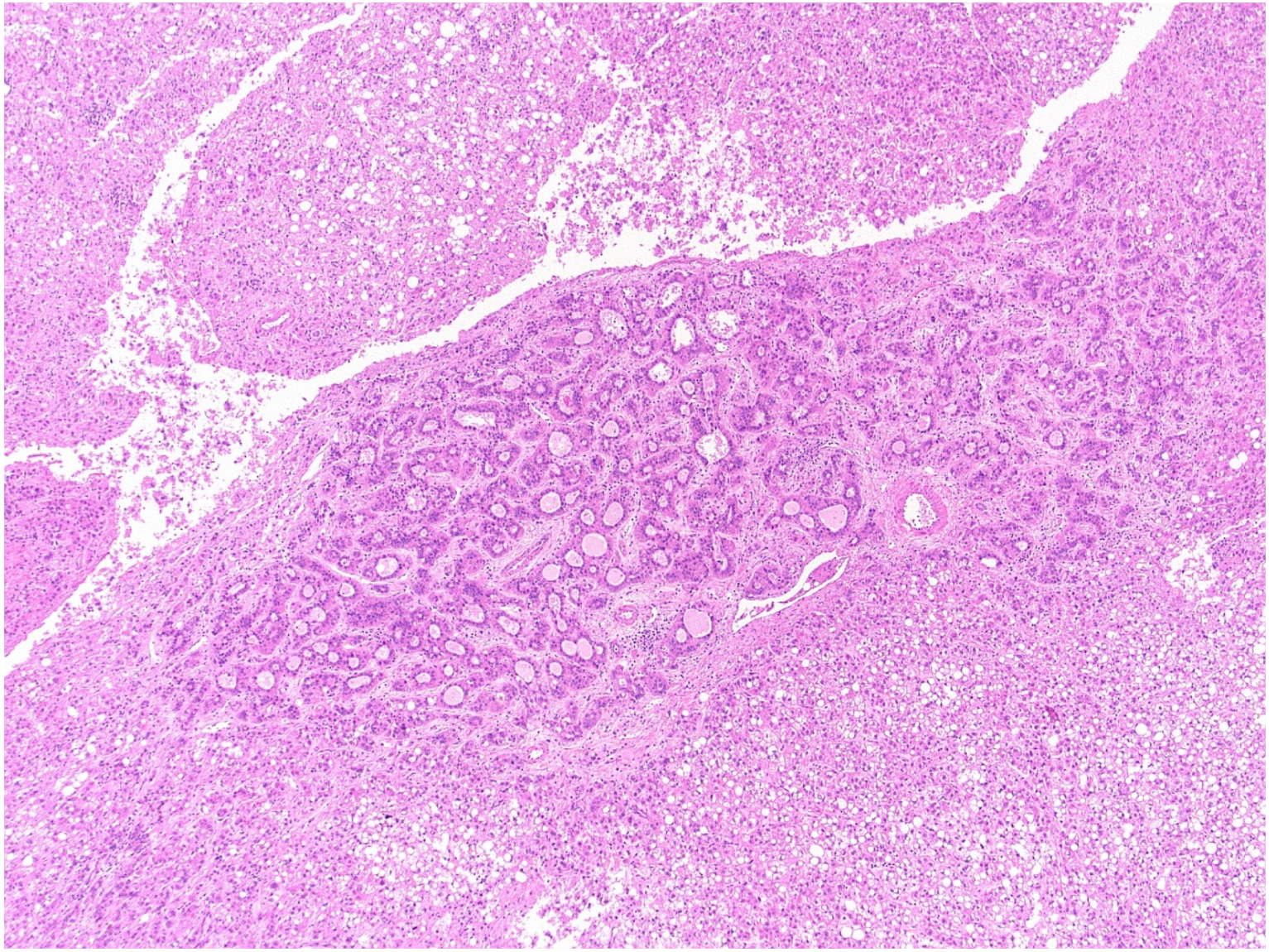
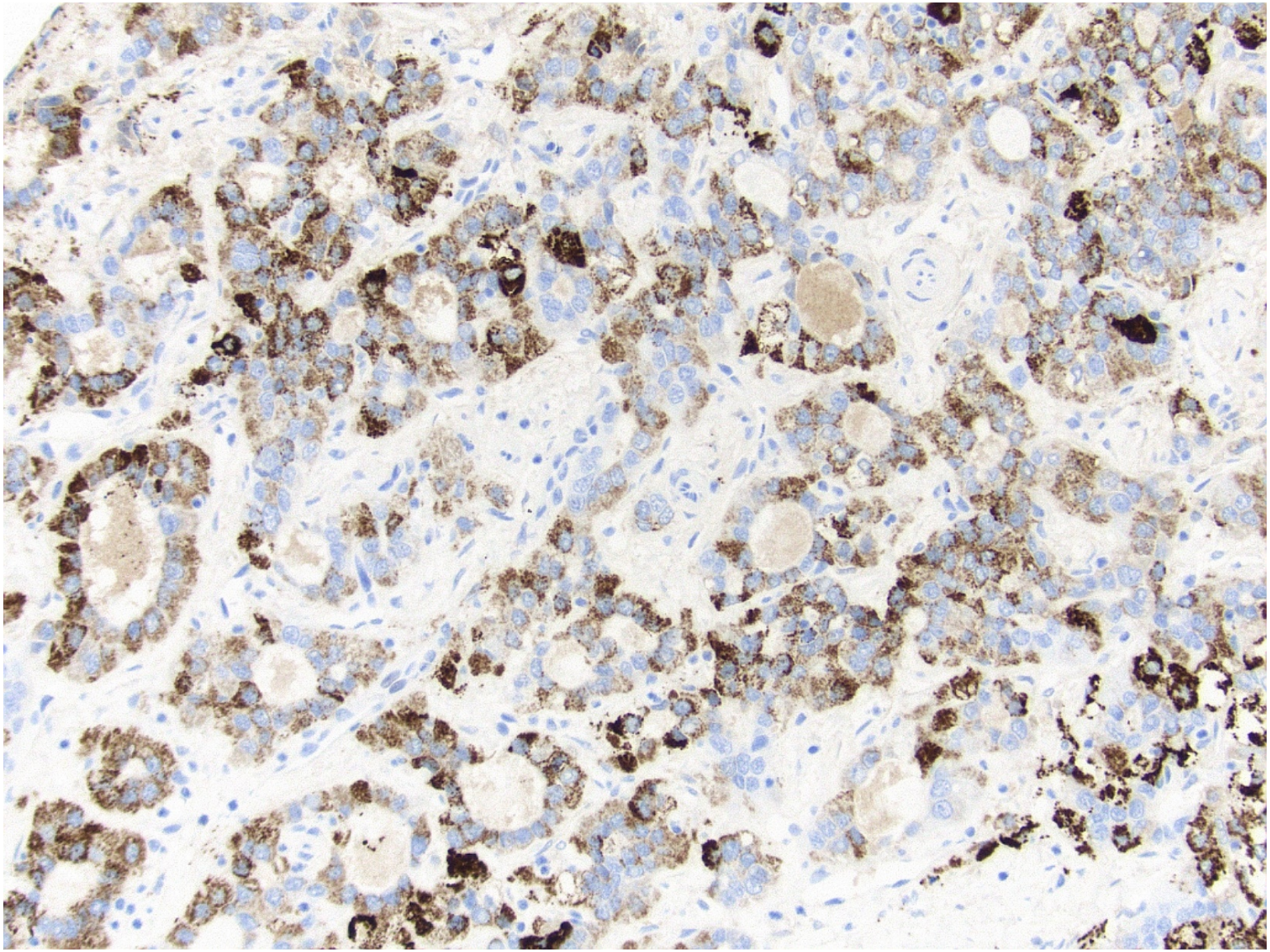
mm 10 20 30 40 50 60 70 80 90 100
PATHOLOGY QUEENSLAND

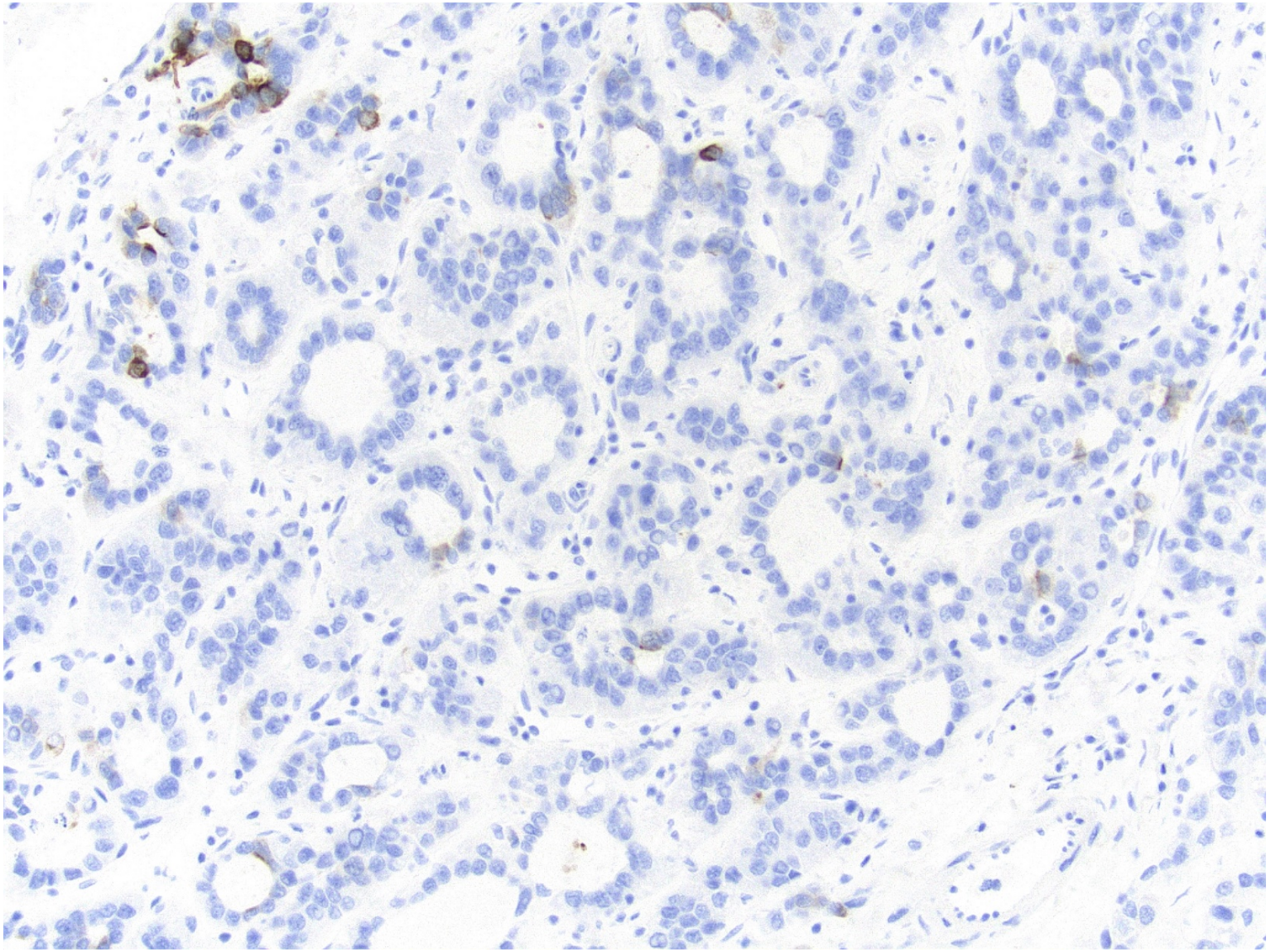




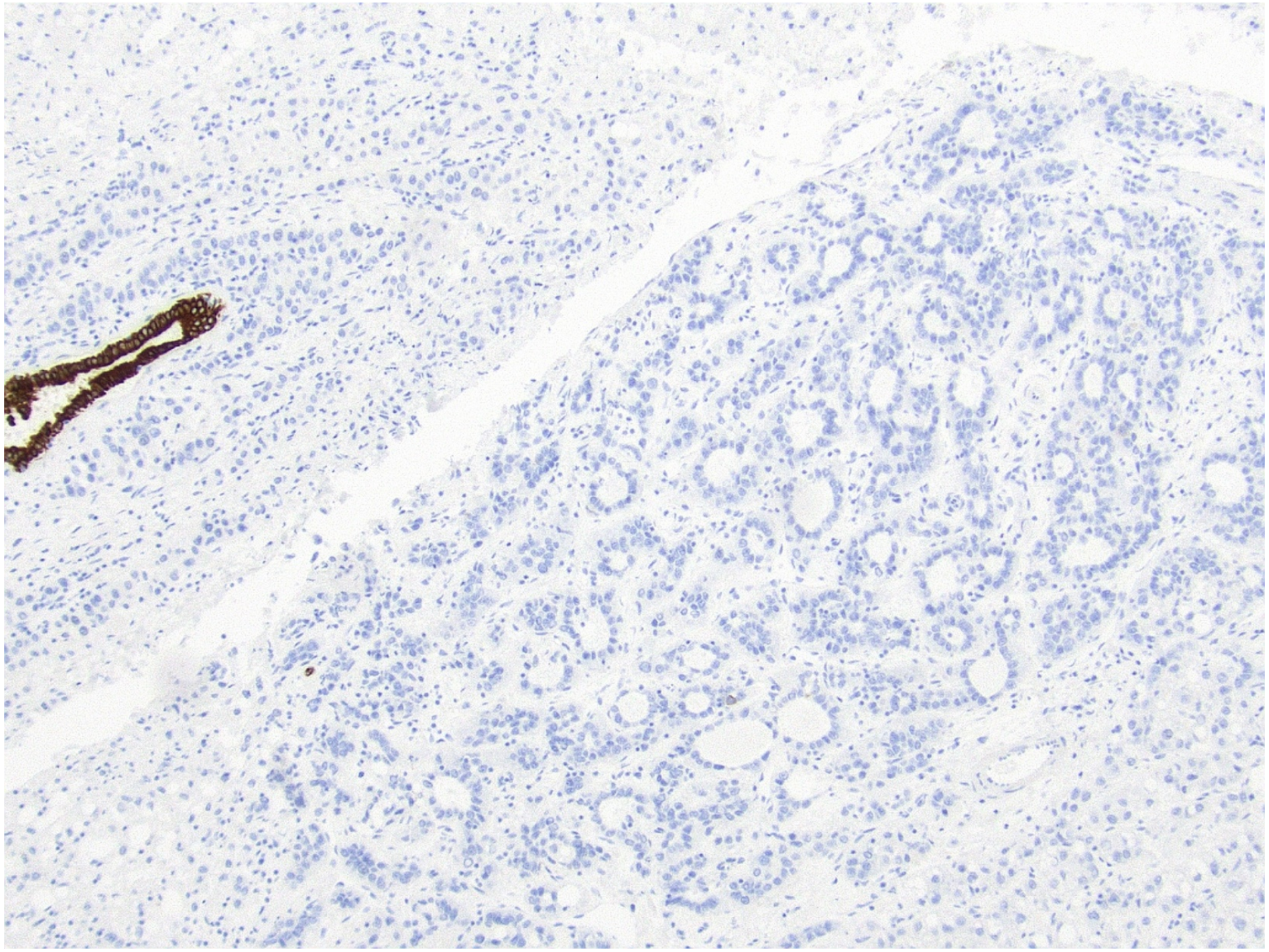




HepPar



CK7



CK19

Steatohepatitic HCC - Prone to be mis-diagnosed

RCPAQAP

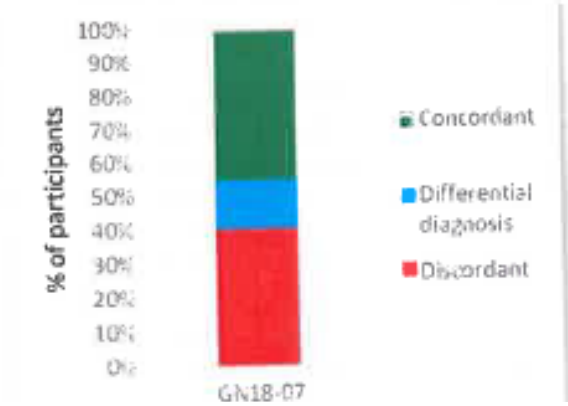
QAP identifier	EX17-164
Specimen	Segment 6 liver lesion.

Final target diagnosis
Well to moderately differentiated hepatocellular carcinoma.

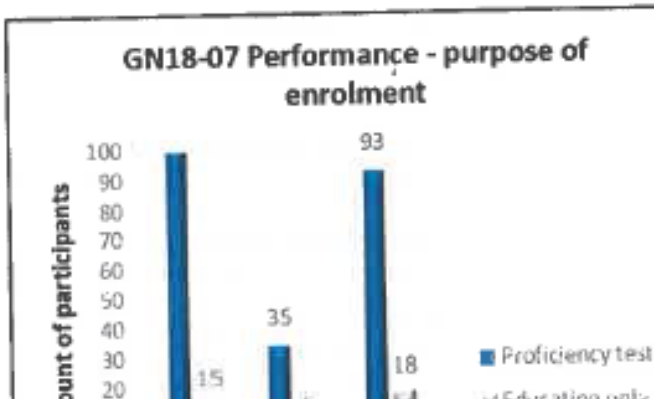
clear cell tumour, adrenal cortical carcinoma, metastatic clear cell tumour and metastatic liposarcoma.

Responses
273 responses were assessed as:

Concordant	44%
Differential diagnosis	15%
Discordant	41%



Participant performance
Case GN18-07 had the highest discordance rate and the lowest concordance rate for survey GN2018-1. Performance has been categorised against purpose of enrolment (Figure 17).



Practice Point:

- Steatohepatitic HCCs are usually well- or moderately-differentiated
- Immunohistochemistry for hepatocyte markers may be useful to confirm hepatocellular nature of tumour

Combined HCC - Cholangiocarcinoma

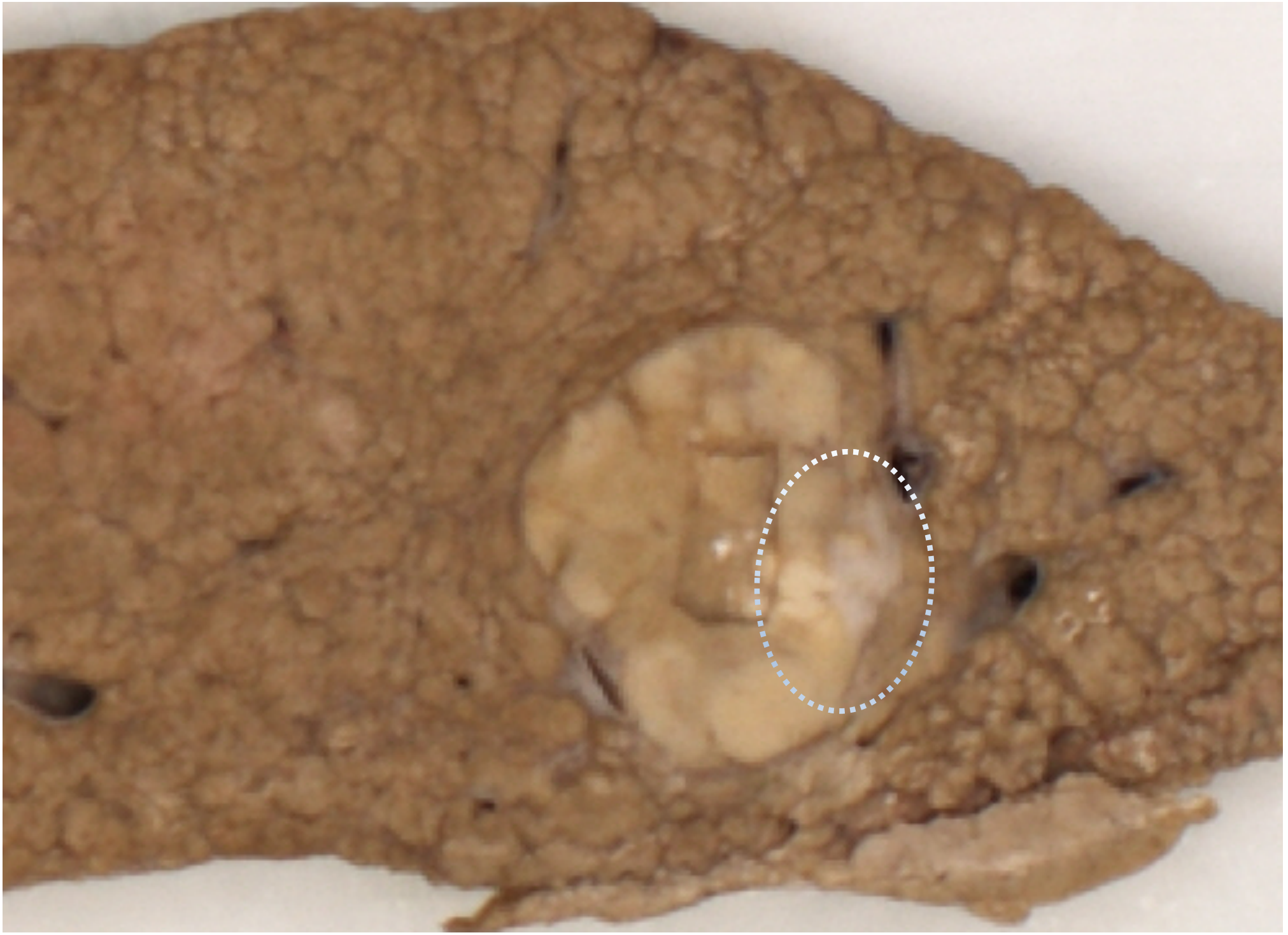
- Athens B
- Basel B, with stem cell features
- Birmingham A
- Groningen A, with intermediate features
- Groningen B

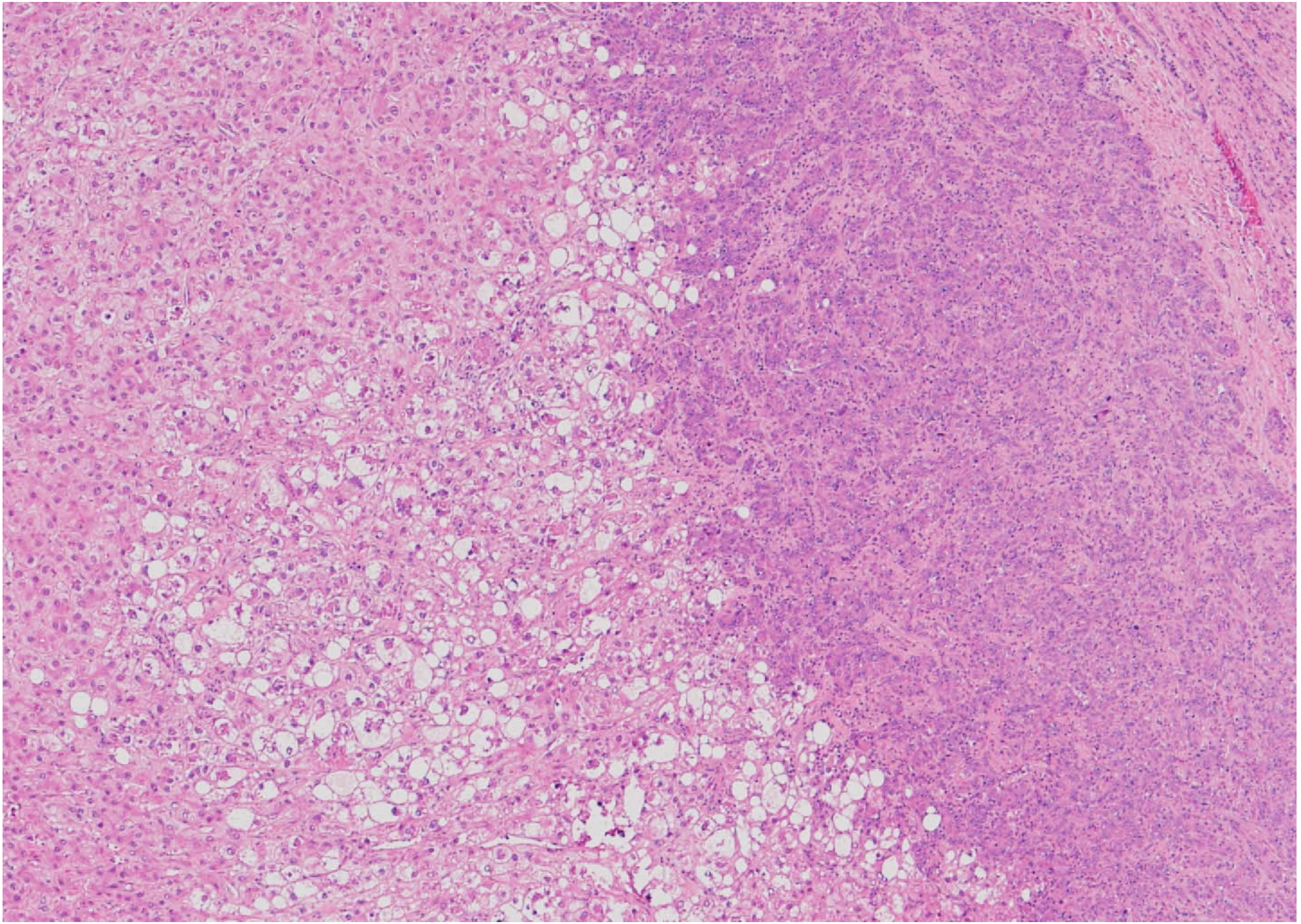
Birmingham A/2019 (Stefan Hubscher)

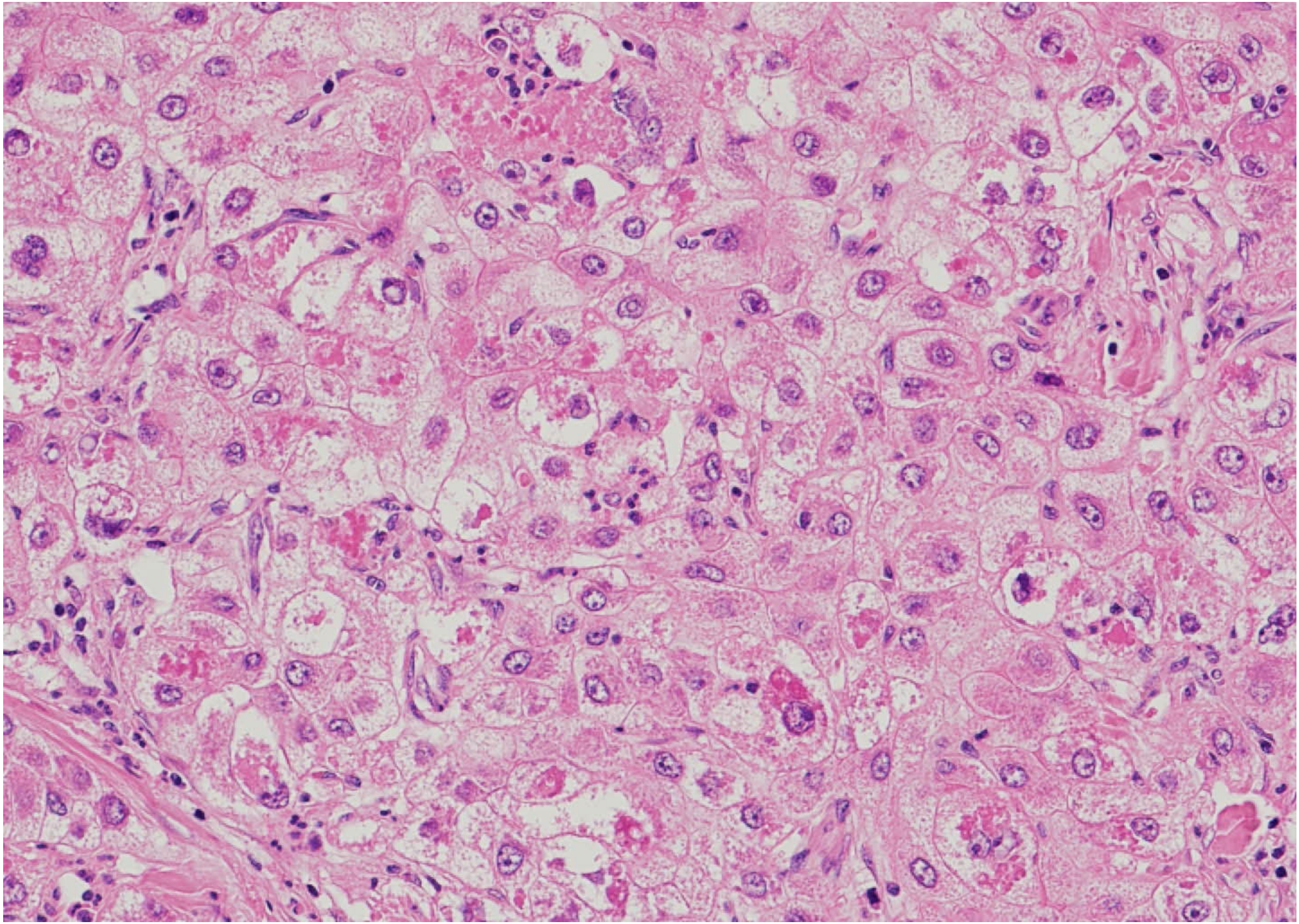
Female, age 66.

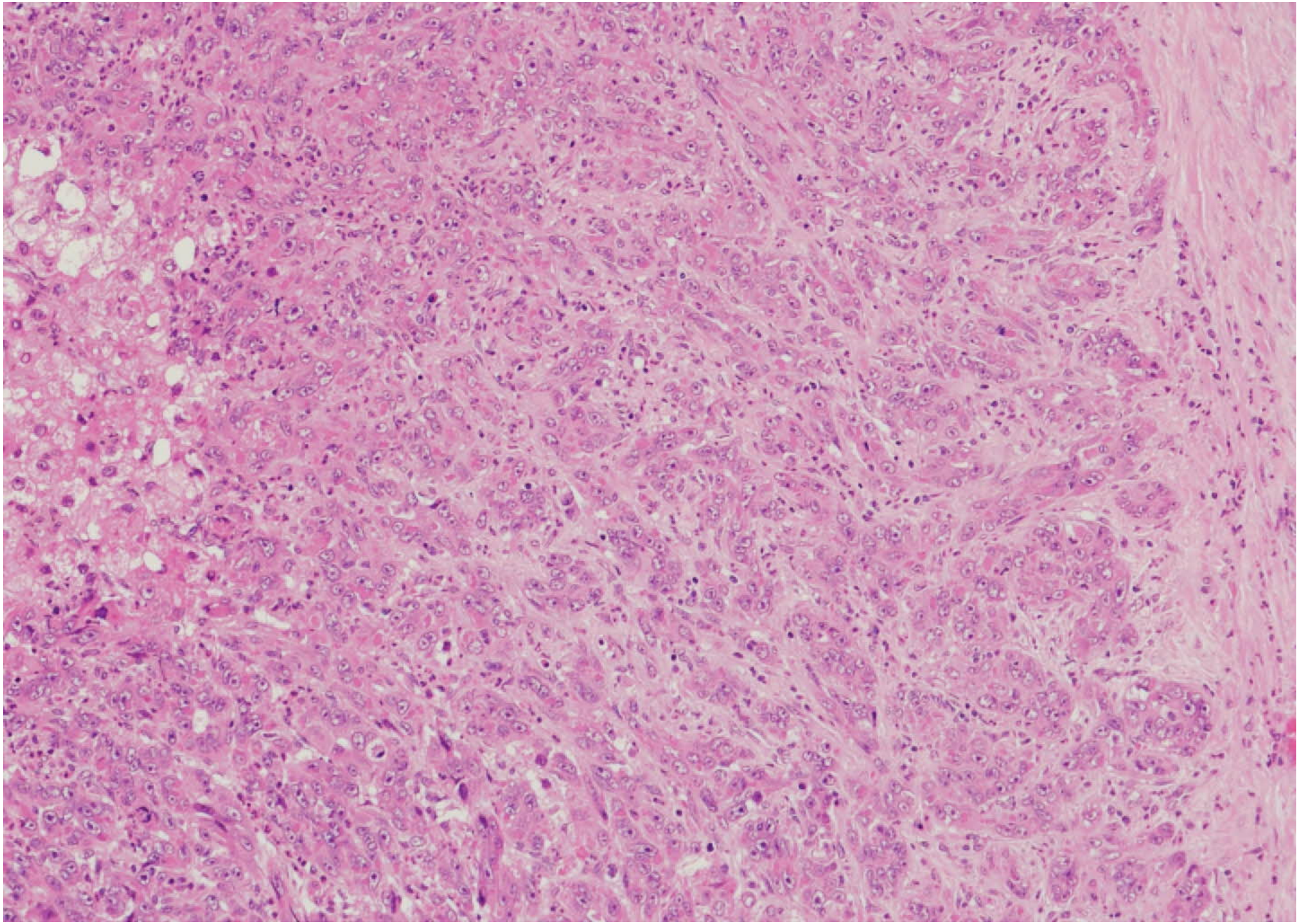
- Liver transplant for NASH cirrhosis + HCC.
- Pre-transplant imaging studies had shown a 2.5cm lesion in segment 3.
- Hepatectomy specimen contained a 2.8cm nodule in left lobe.

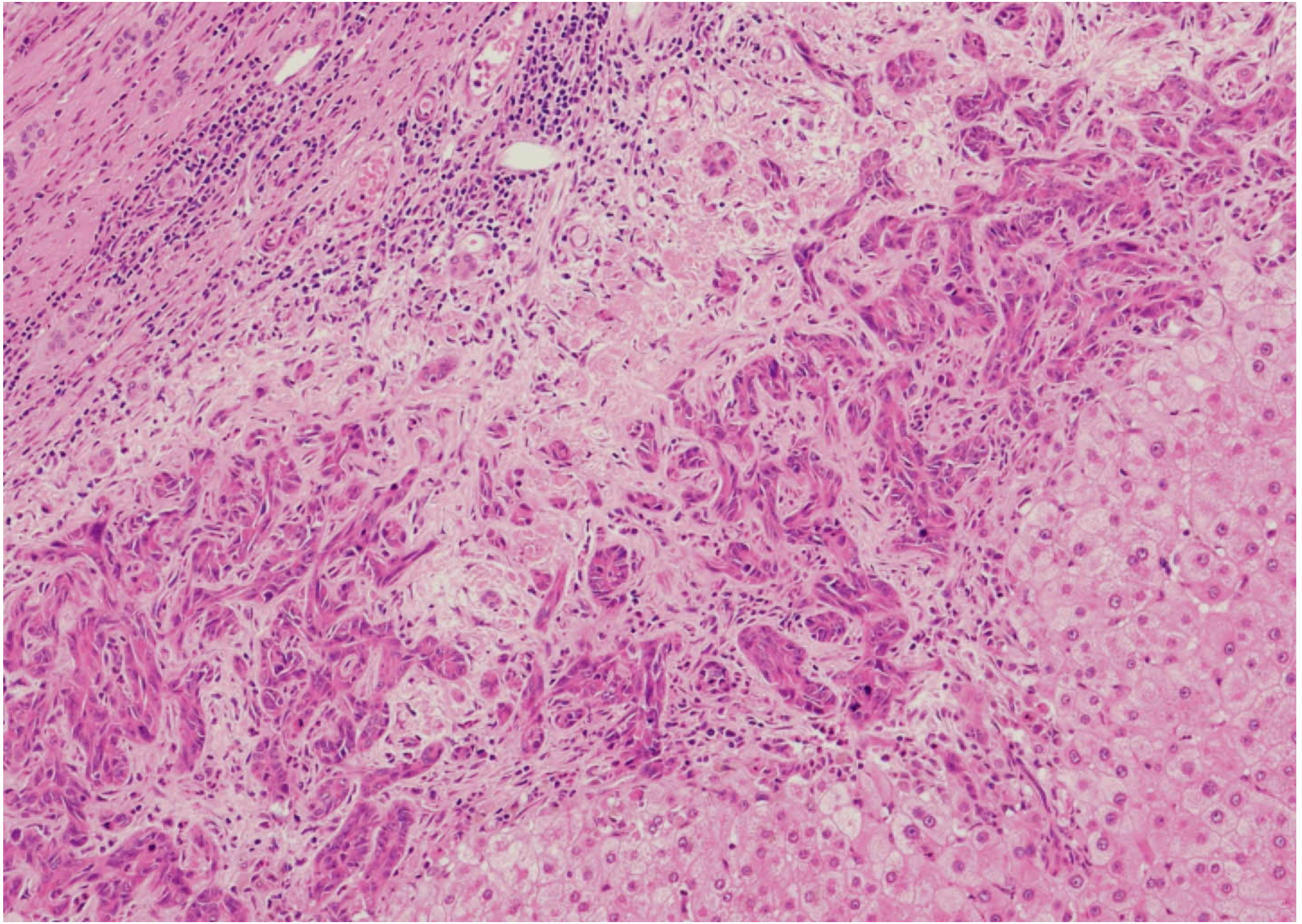

20 mm

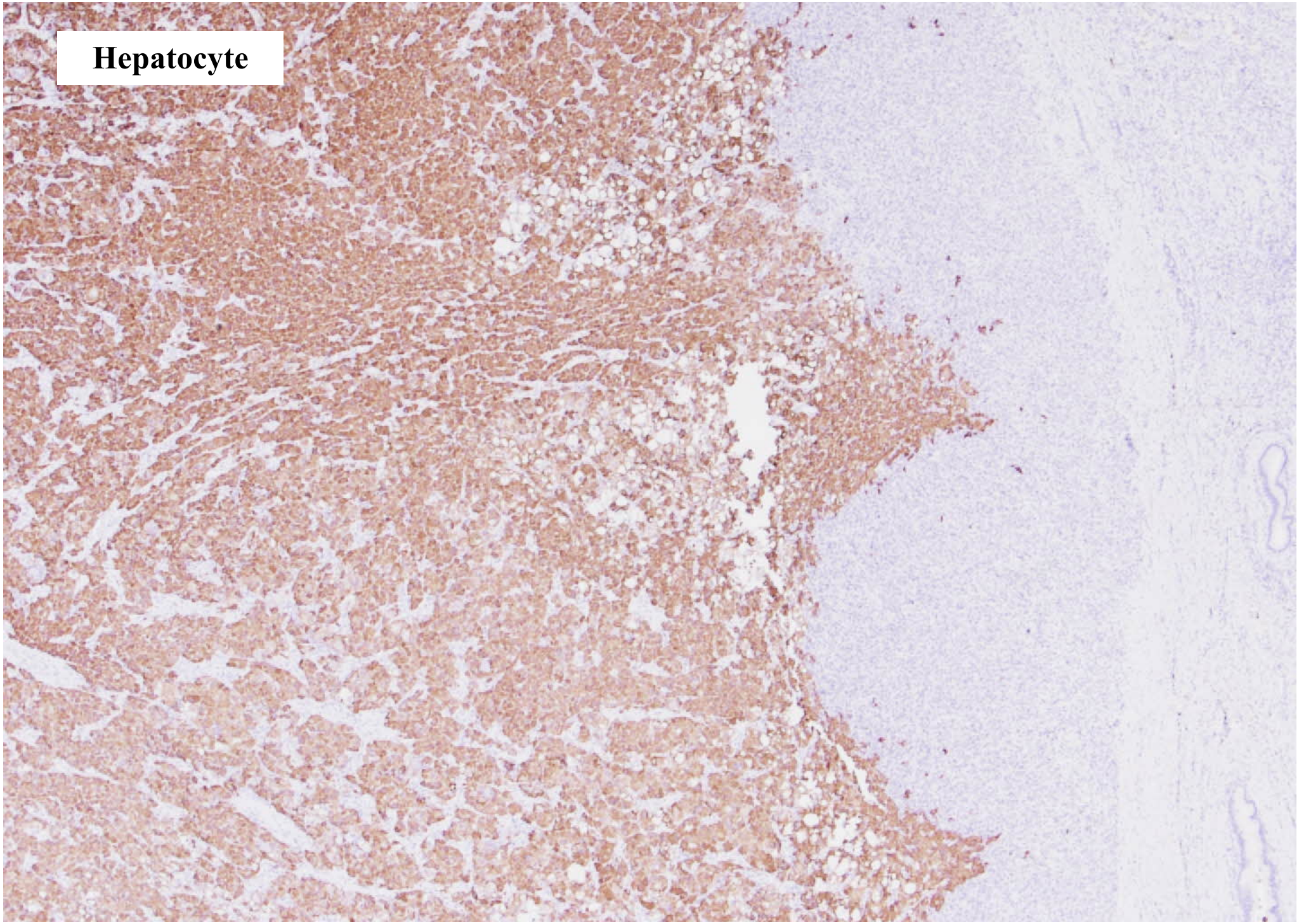


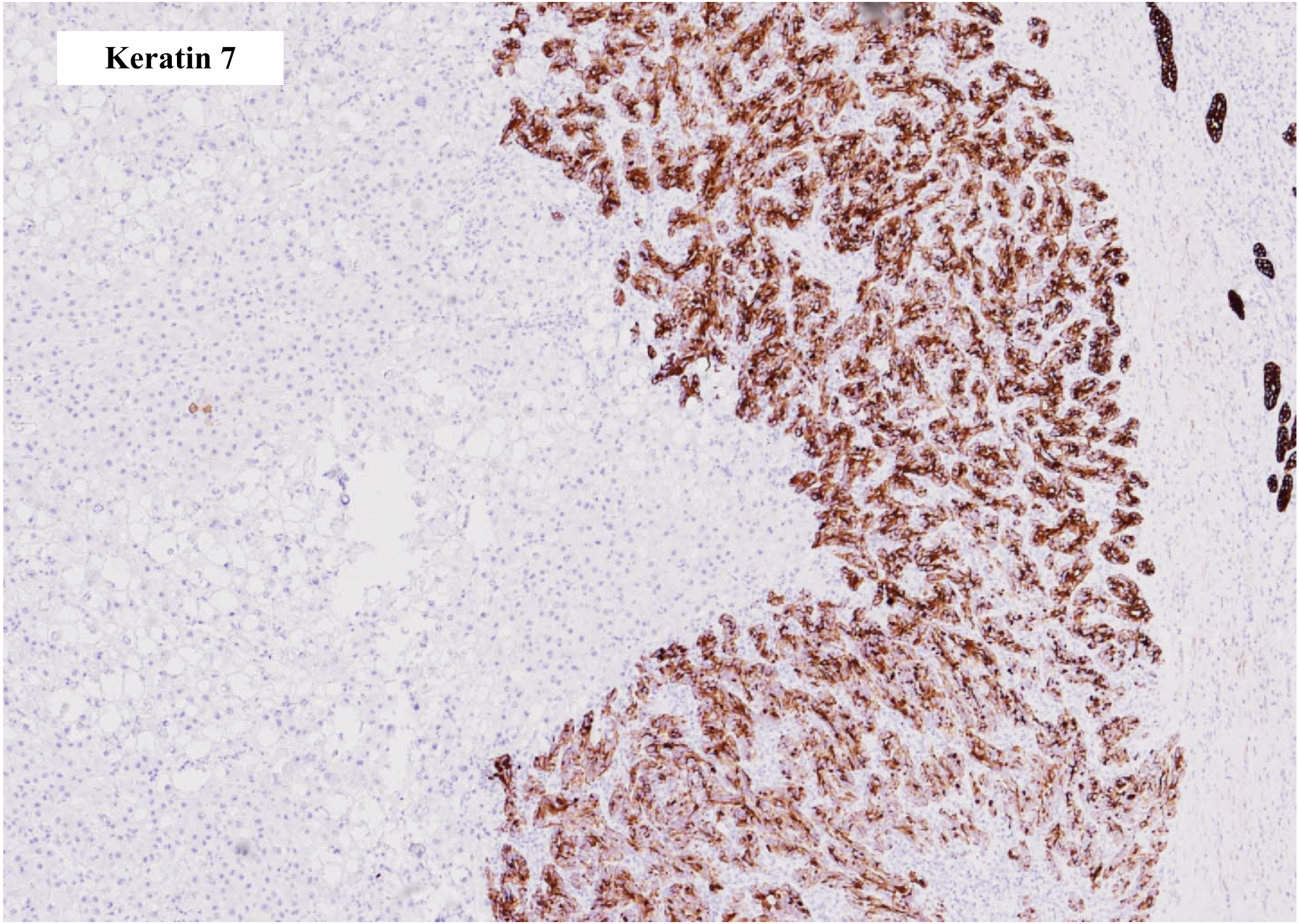


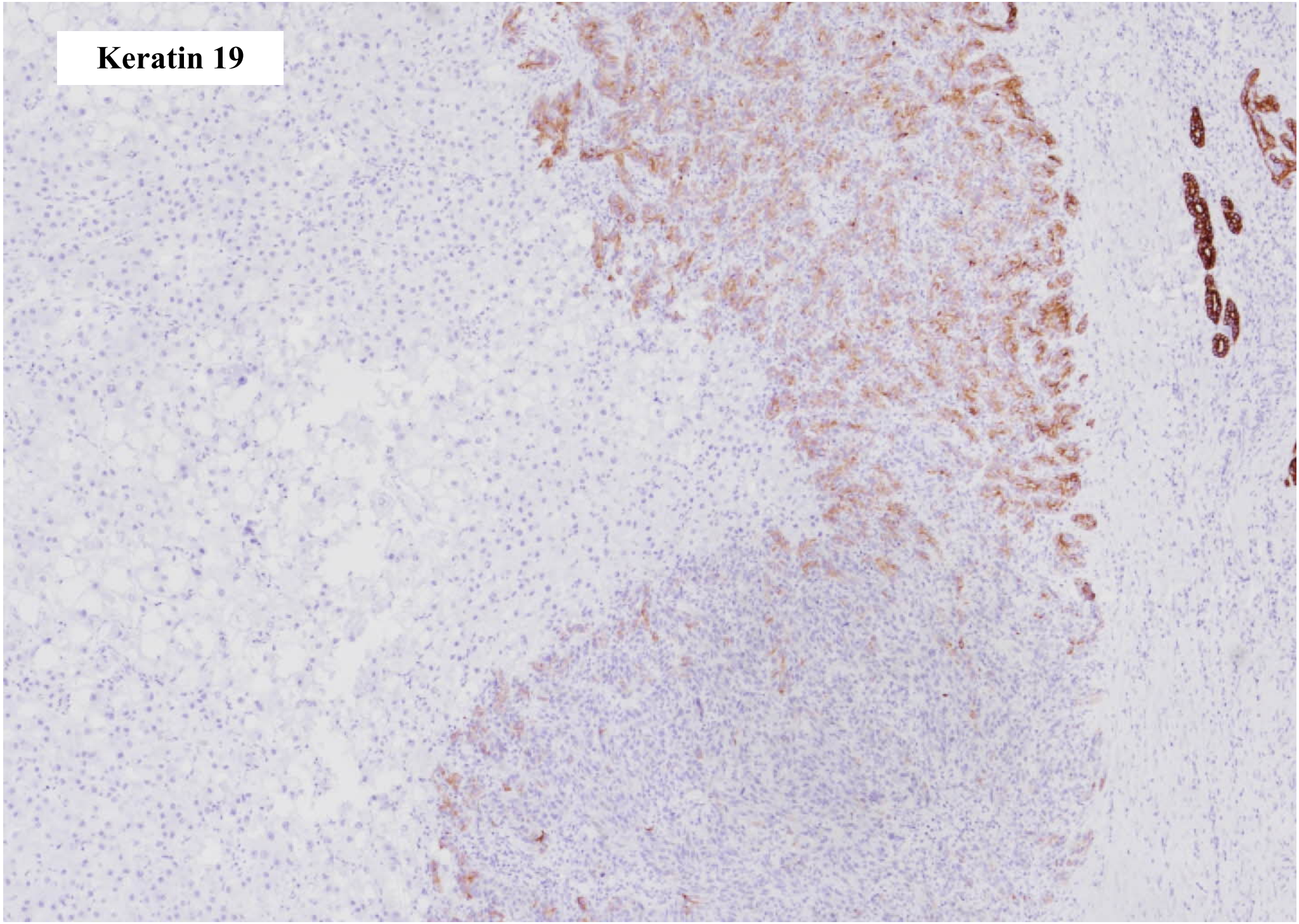




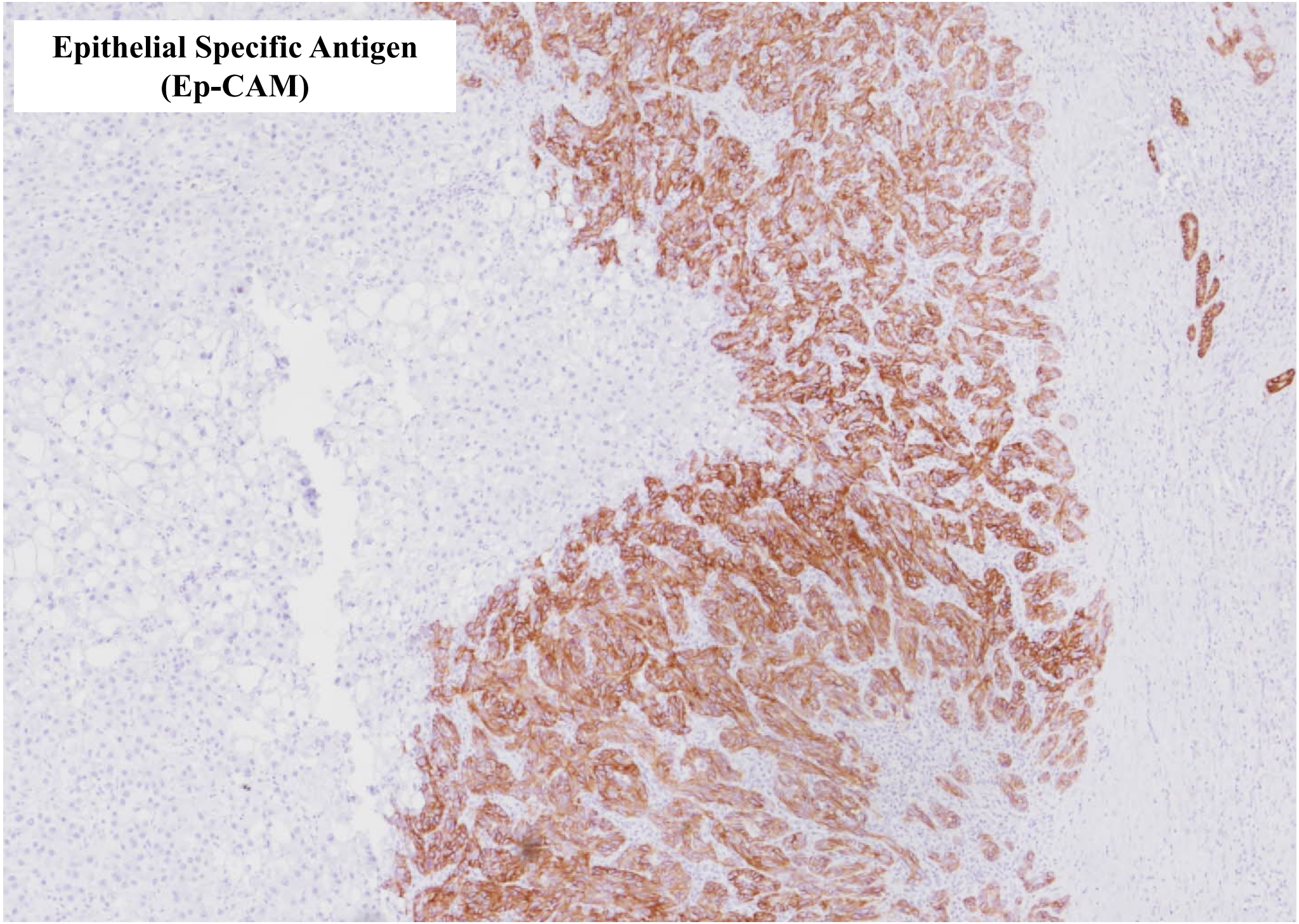


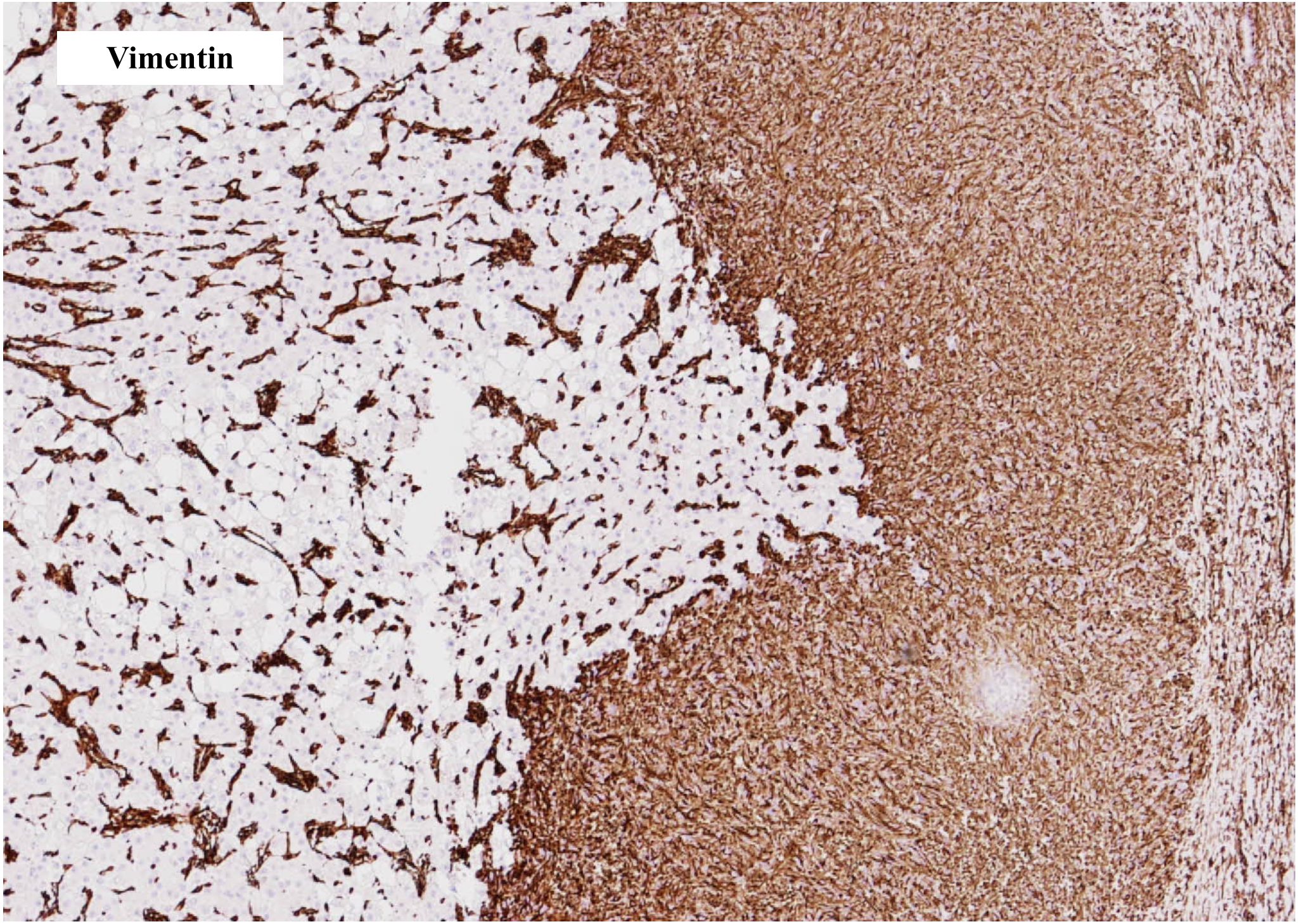

Hepatocyte


Keratin 7


Keratin 19

Epithelial Specific Antigen (Ep-CAM)




Vimentin

Birmingham A/2019 - Diagnosis

Combined HCC – Cholangiocarcinoma (Classical Type)

NASH Cirrhosis

Combined HCC – Cholangiocarcinoma Classification

(Theise - WHO Classification, 4th Edition 2010)

1. **Combined hepatocellular-cholangiocarcinoma, classical type**

2. **Combined hepatocellular-cholangiocarcinoma with stem cell features:**
   - Typical
   - Intermediate cell
   - Cholangiolocellular

cHCC-CCA: Consensus Terminology for Primary Liver Carcinomas With Both Hepatocytic and Cholangiocytic Differentation

Elizabeth Brunt,[1] Shinichi Aishima,[2] Pierre-Alain Clavien,[3] Kathryn Fowler,[4] Zachary Goodman,[5] Gregory Gores,[6] Annette Gouw,[7] Alex Kagen,[8] David Klimstra,[9] Mina Komuta,[10] Fukuo Kondo,[11] Rebecca Miksad,[12] Masayuki Nakano,[13] Yasuni Nakanuma,[14] Irene Ng,[15] Valerie Paradis,[16] Young Nyun Park,[17] Alberto Quaglia,[18] Massimo Roncalli,[19] Tania Roskams,[20] Michiie Sakamoto,[21] Romil Saxena,[22] Christine Sempoux,[23] Claude Sirlin,[24] Ashley Stueck,[25] Swan Thung,[26] W.M.S. Tsui,[27] Xin-Wei Wang,[28] Aileen Wee,[29] Hirohisa Yano,[30] Matthew Yeh,[31] Yoh Zen,[32] Jessica Zucman-Rossi,[33] and Neil Theise[34]

(HEPATOLOGY 2018;68:113-126)

Combined HCC-CCA, Classical Type - Diagnostic Criteria

(Brunt, Hepatology 2018)

Essential features:

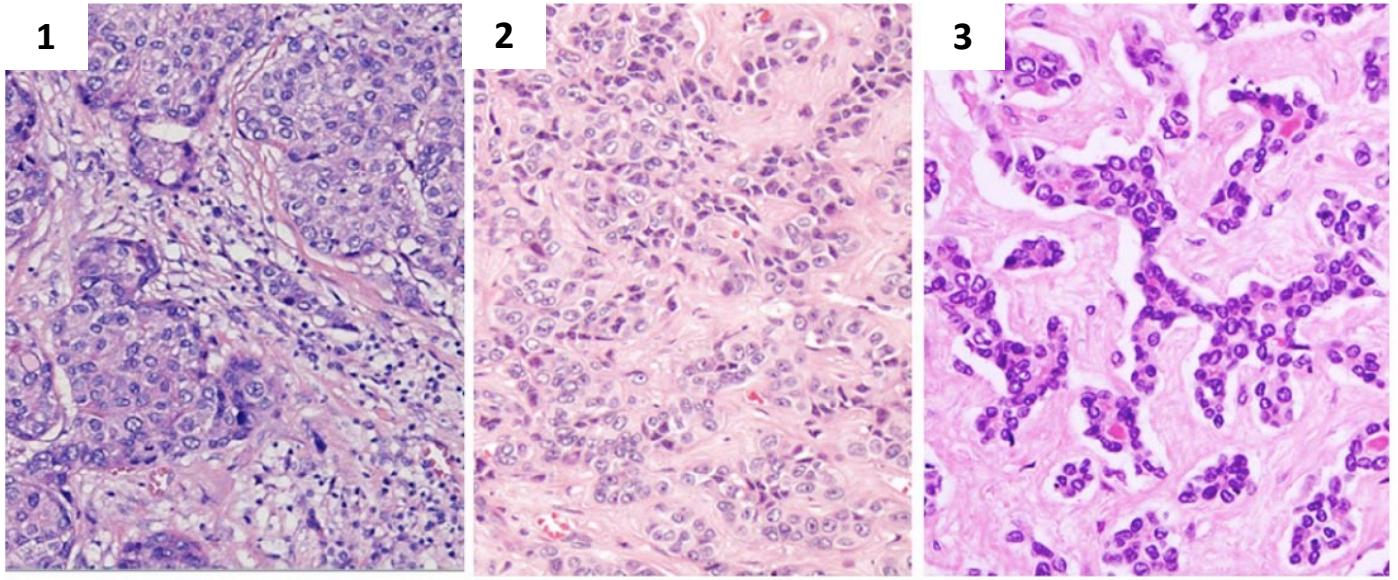
- Areas of typical HCC and typical CC, **based on H & E appearances**
- Two components should be in direct contact with each other (not separate "collision tumours")
- Frequently have a transition / interface zone in which two components are intimately intermingled

Immunohistochemistry:

- Immunostains helpful to confirm hepatocellular and biliary phenotypes
- Commonly used antibodies are:
  - Hep Par 1, Arginase-1, CD10, pCEA, Glypican 3, AFP (hepatocellular)
  - Keratin 7 & 19, EpCAM (biliary)
- IHC should be used as an adjunct to routine microscopy and **not** as a primary defining feature. For example
  - Conventional HCCs often show focal expression of CK7 or CK19
  - Typical iCCAs may show focal expression of Hep Par 1 (or albumin mRNA)

Combined HCC-CCA with Stem Cell Features

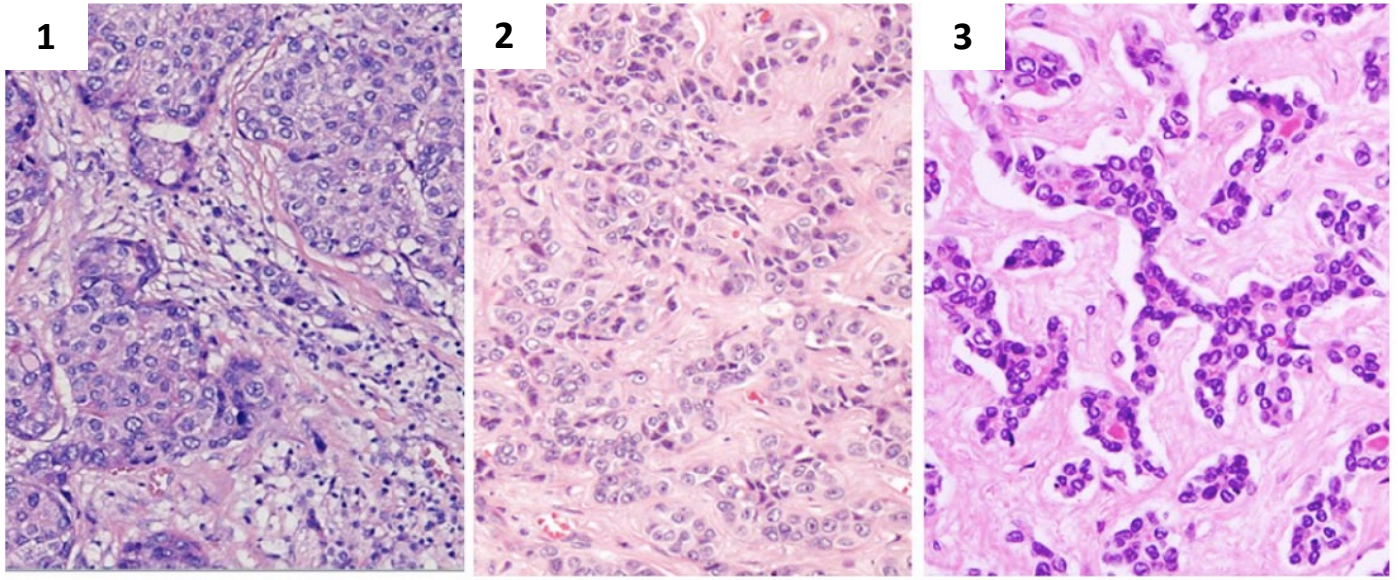
(Theise ND, Nakshima O, Park YN, Nakanuma Y, WHO 4th Ed, 2010, 225-227)



Subtype	Histological Features
1. Typical	Nests of cells with hepatocellular morphology with peripheral clusters of smaller cells resembling stem cells
2. Intermediate	Cells with features intermediate between hepatocytes and cholangiocytes, without clear gland formation, often in a desmoplastic stroma.
3.Cholangiolocellular	Small cells resembling cholangioles, growing in a tubular, cord-like, anastomosing ("antler-like") pattern within a dense stroma

Combined HCC-CCA with Stem Cell Features

(Theise ND, Nakshima O, Park YN, Nakanuma Y, WHO 4th Ed, 2010, 225-227)



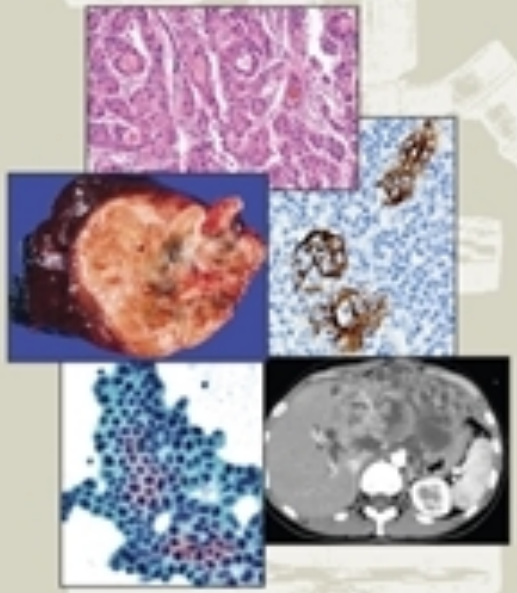
Subtype	Histological Features	Change in classification (Brunt 2018: WHO 5th Ed 2019
1. Typical	Nests of cells with hepatocellular morphology with peripheral clusters of smaller cells resembling stem cells	Now regarded as a variant of HCC
2. Intermediate	Cells with features intermediate between hepatocytes and cholangiocytes, without clear gland formation, often in a desmoplastic stroma.	Remains as a distinct subtype, which is neither HCC nor CCA **(intermediate cell carcinoma)**
3.Cholangiolocellular	Small cells resembling cholangioles, growing in a tubular, cord-like, anastomosing ("antler-like") pattern within a dense stroma	Now regarded as a subtype of intrahepatic cholangiocarcinoma **(Cholangiolocarcinoma)**

27

AFIP ATLAS OF TUMOR PATHOLOGY
Series 4

Tumors of the Liver

Michael Torbenson, MD
Yoh Zen, MD, PhD, FRCPath
Matthew M. Yeh, MD, PhD



AFIP

ARP

Ceremonial Transfer of the Gnomes Hat

Gnomes Meeting, Washington DC, 6th – 9th May 2020
Chief Gnome – Zack Goodman
Theme: "Fatty Liver, NASH and related topics: Controversies and variant lesions"