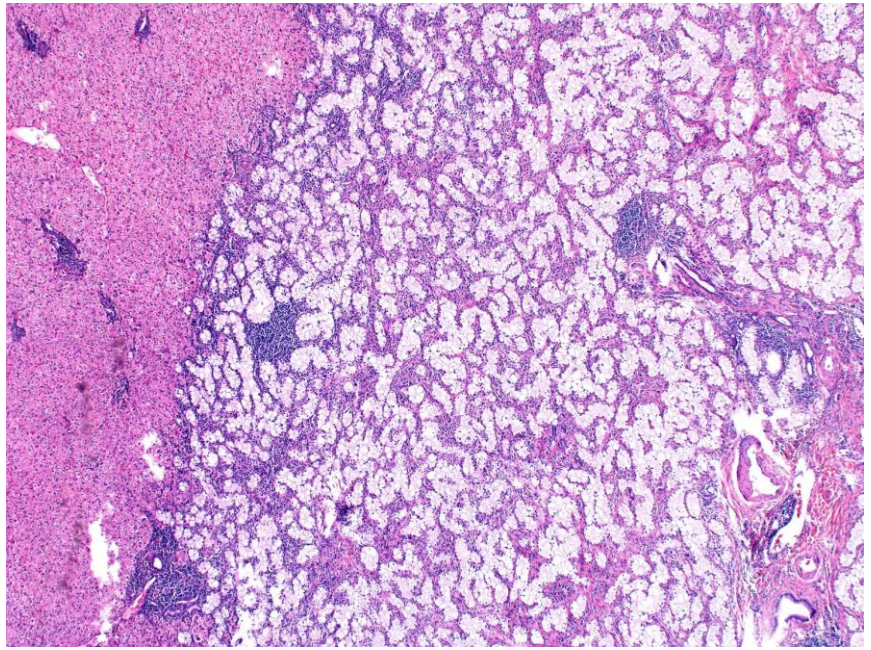
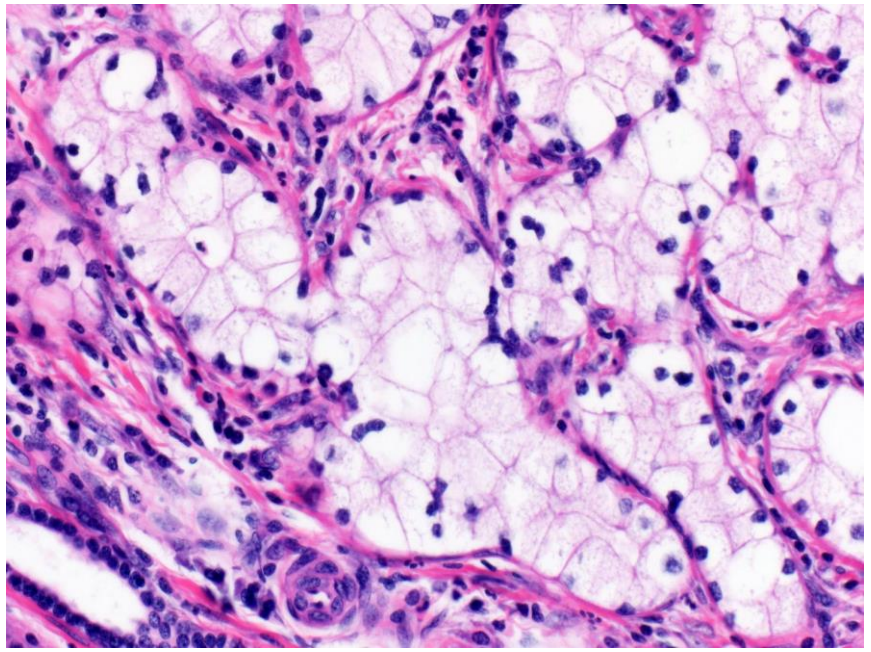
Unusual liver tumours

Alastair Burt
Newcastle University

Rochester A

- 36-year-old woman with history of metastatic papillary thyroid carcinoma.
- Imaging identified a liver lesion that was biopsied and diagnosed as adenocarcinoma.
- Commercial molecular assay reported a 96% probability for pancreatic or biliary origin.
- Lesion subsequently resected





Mike Torbenson

Clear cell bile duct adenomas

- Tumour cells have abundant clear cytoplasm
- Tubules and nests; mild stromal fibrosis
- 25-64 years
- Relatively well demarcated but some “infiltration” at edges
- One case with lymphocytic inflammation in stroma

The American Journal of Surgical Pathology 25(7): 956–960, 2001

Atypical Bile Duct Adenoma, Clear Cell Type

A Previously Undescribed Tumor of the Liver

Jorge Albores-Saavedra, M.D., Mai P. Hoang, M.D.,
Linda A. Murakata, M.D., Prasanna Sinkre, M.D., and Hadi Yaziji, M.D.

A variable proportion of bile duct adenomas of the liver are still confused with metastatic well-differentiated adenocarcinoma by surgeons and pathologists. We present here three examples of previously undescribed primary hepatic bile duct tumors that were composed almost entirely of clear cells that closely mimicked metastatic renal cell carcinoma. They were interpreted as atypical bile duct adenomas and occurred in two males and one female whose ages ranged from 25 to 64 years. All three tumors were incidental findings and measured from 0.8 to 1.1 cm. The clear neoplastic cells showed mild nuclear atypia and no mitotic activity. They were arranged in tubules and nests that focally infiltrated the hepatic parenchyma. For comparison, a case of clear cell cholangiocarcinoma and 13 conventional bile duct adenomas were examined. The clear cell cholangiocarcinoma was larger (6.0 cm) and had the tubular pattern of conventional cholangiocarcinoma and an abundant desmoplastic stroma. The clear cells of this tumor exhibited greater nuclear atypia and increased mitotic activity. All three atypical bile duct adenomas expressed cytokeratin (CK) 7, p53 protein, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA); they were negative for CK20, vimentin, Hep Par 1, chromogranin, and prostatic specific antigen (PSA) and exhibited less than 10% of Ki-67-positive nuclei. One atypical bile duct adenoma displayed luminal immunoreactivity for villin. With the exception of Ki-67 reactivity, the 13 conventional bile duct adenomas and the clear cell cholangiocarcinoma had essentially a similar immunohistochemical profile as that of the atypical clear cell bile duct adenomas. The absence of an extrahepatic primary tumor, the histologic features, the immunohistochemical profile, and the fact that all patients are symptom-free 2 months to 18 years after wedge liver biopsy support the interpretation of atypical clear cell bile duct adenoma. The differential diagnosis with clear cell hepatocellular carcinoma and metastatic clear cell carcinomas is discussed.

Key Words: Atypical bile duct adenoma—Clear cell type—Immunohistochemistry.

Am J Surg Pathol 25(7): 956–960, 2001.

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Two types of intrahepatic benign bile duct proliferations have been characterized: bile duct hamartomas (also called von Meyenburg complexes) and bile duct adenomas.[4,5] The former lesion is frequently multiple and composed of dilated bile ducts that often contain bile. The latter lesion is characterized by a disordered proliferation of noncystic ductules lined by cuboidal biliary cells without nuclear atypia or mitotic activity. This lesion is still confused by both surgeons and pathologists with metastatic adenocarcinomas during frozen sections performed in patients with known adenocarcinomas. In approximately one third of the cases of bile duct adenomas published by Allaire et al.[5] the diagnosis of adenocarcinoma was made or was seriously considered.

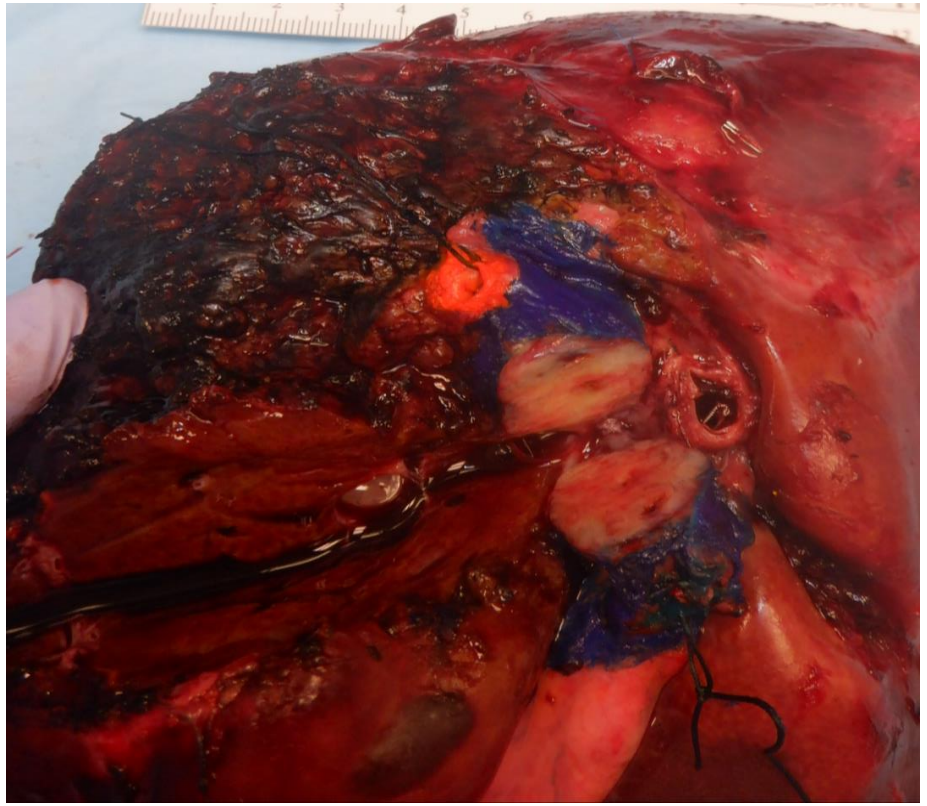
We present here three examples of primary hepatic tumors interpreted as atypical bile duct adenomas composed almost exclusively of clear cells that closely resemble metastatic renal cell carcinoma. These atypical clear cell bile duct adenomas are compared with a clear cell cholangiocarcinoma and 13 conventional bile duct adenomas, and their similarities and differences are emphasized. To our knowledge, this unusual type of bile duct adenoma, atypical clear cell type, has not been previously described.

MATERIALS AND METHODS

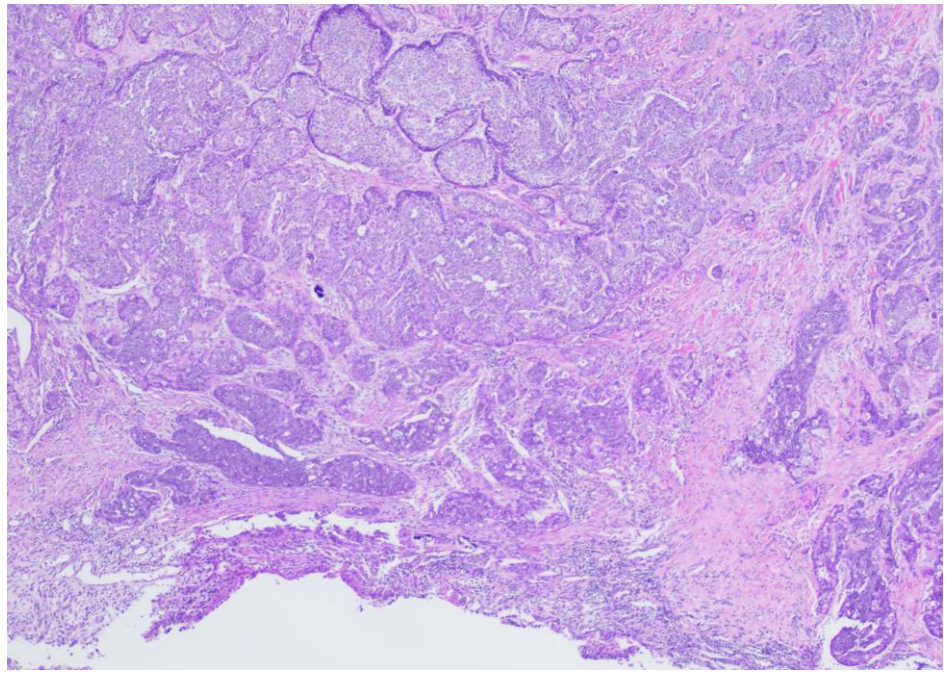
Sections of the four hepatic tumors were fixed in 10% buffered formalin and embedded in paraffin. The lesions of cases 1, 2, and 3 were entirely submitted. Hematoxylin and eosin, alcian blue stain, and periodic acid-schiff (PAS) stains were performed. Additional sections were obtained from the paraffin blocks for immunohistochemical studies, which were performed on a Biotek Solutions Tech Mate 1000 automated immunostainer (Tucson, AZ, USA) using the standard avidin-biotin peroxidase technique. The list of primary antibody sources and dilutions appears in Table 1. For comparative purposes immunohistochemical studies were also performed on 13 conventional bile duct adenomas. The clinical history was

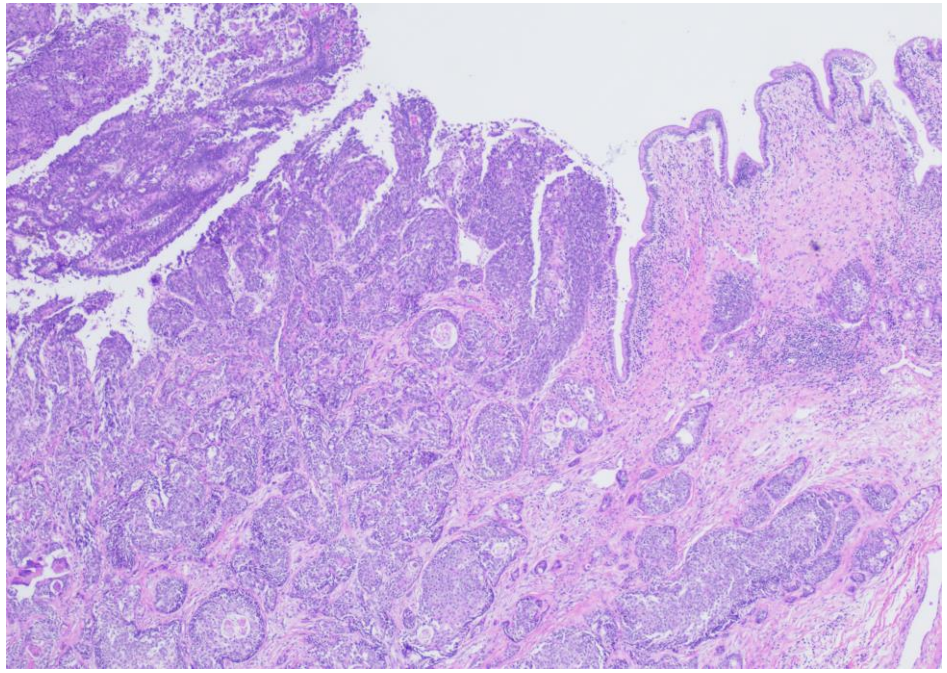
New York B

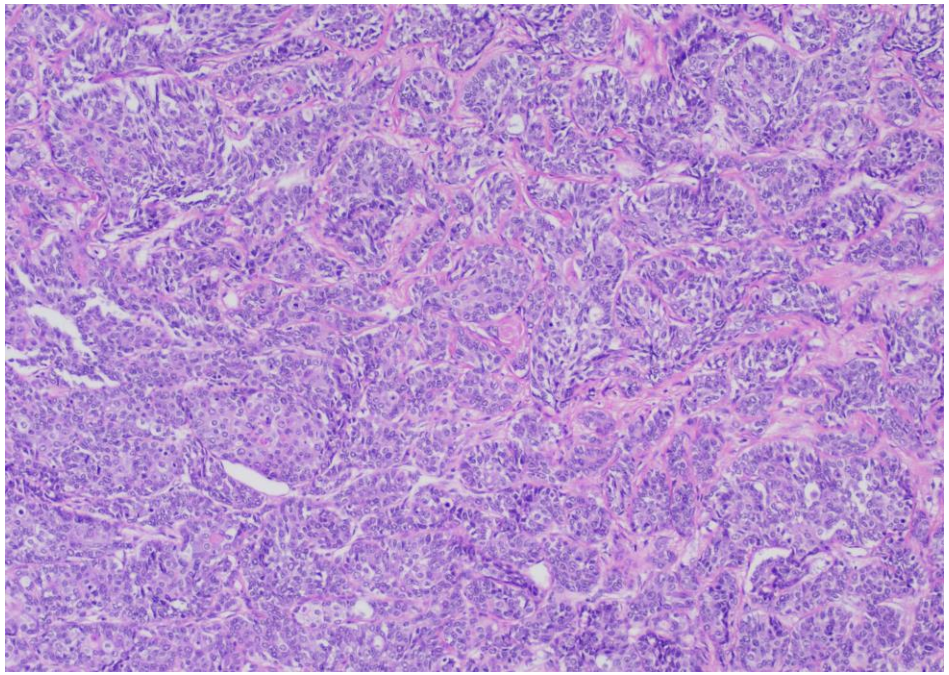
- 35-year-old female presented with abdominal pain, jaundice, itching, and fever.
- Ultrasound showed intrahepatic biliary dilatation with numerous cysts in the liver.
- MRCP demonstrated diffuse intrahepatic bile duct dilatation secondary to a stricture at the biliary confluence.
- ERCP with biopsy showed invasive poorly-differentiated carcinoma.

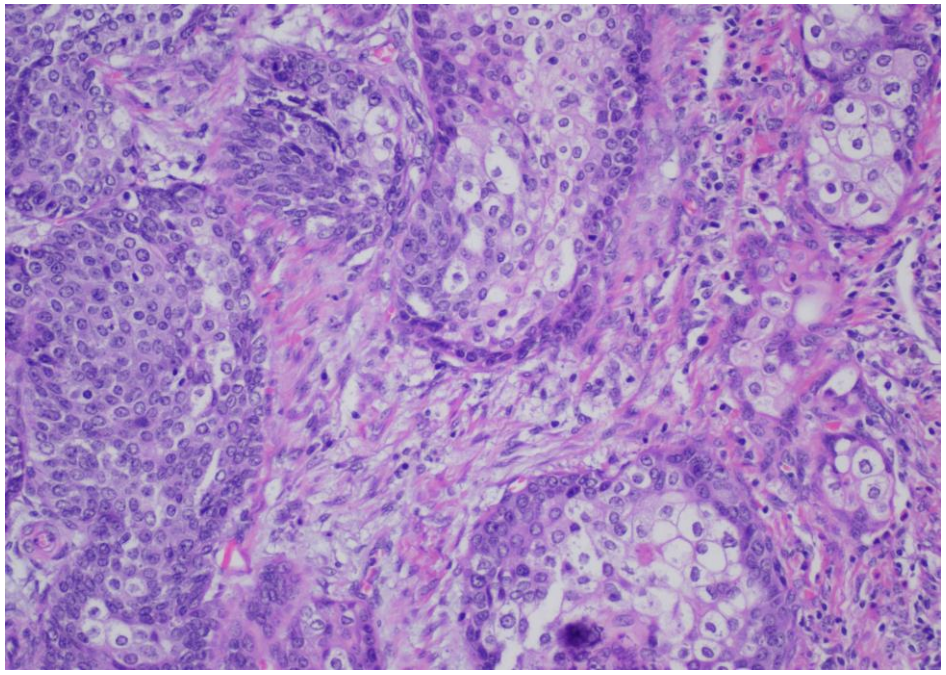


Isabel Fiel

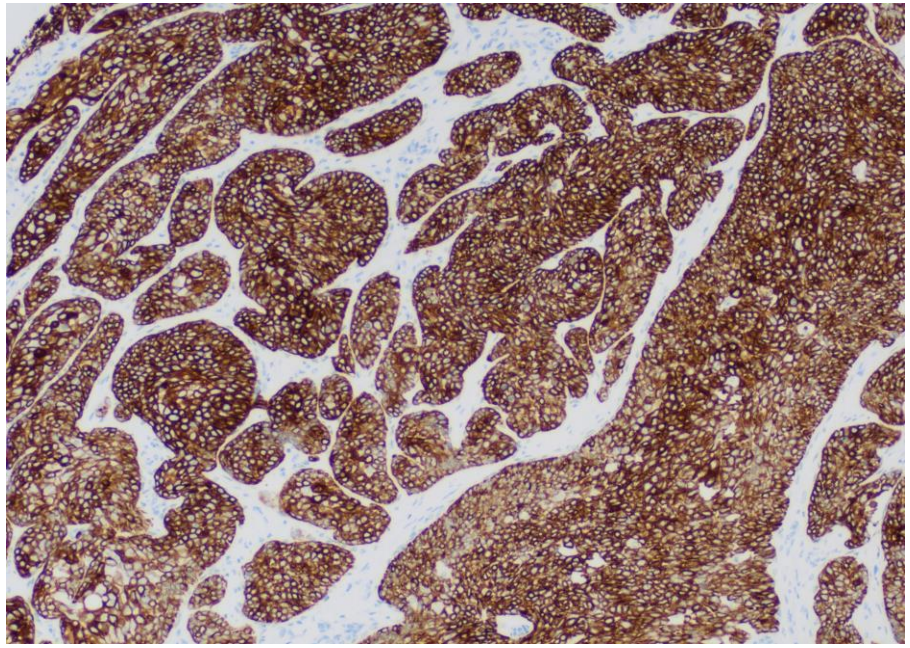


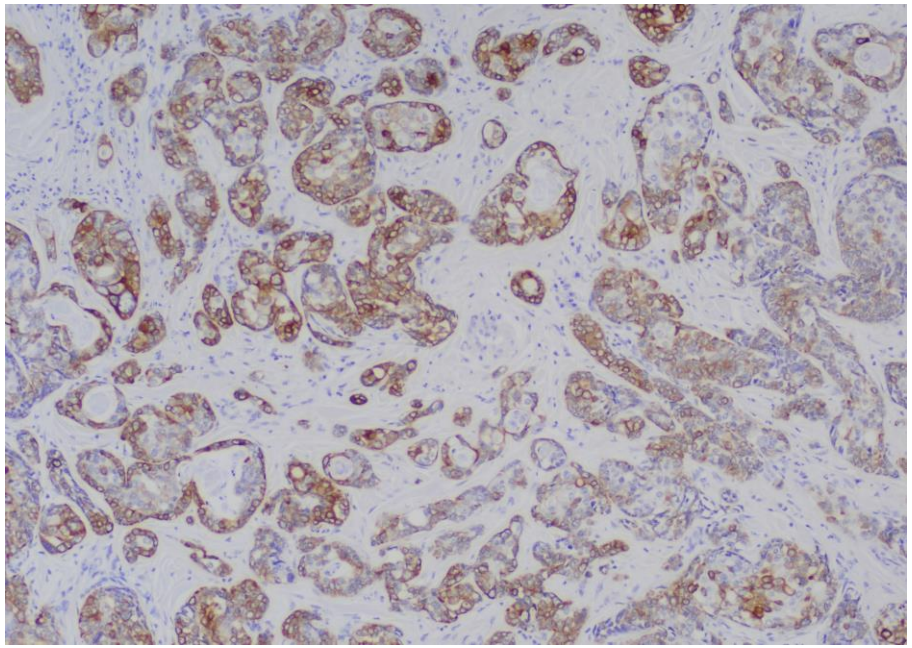






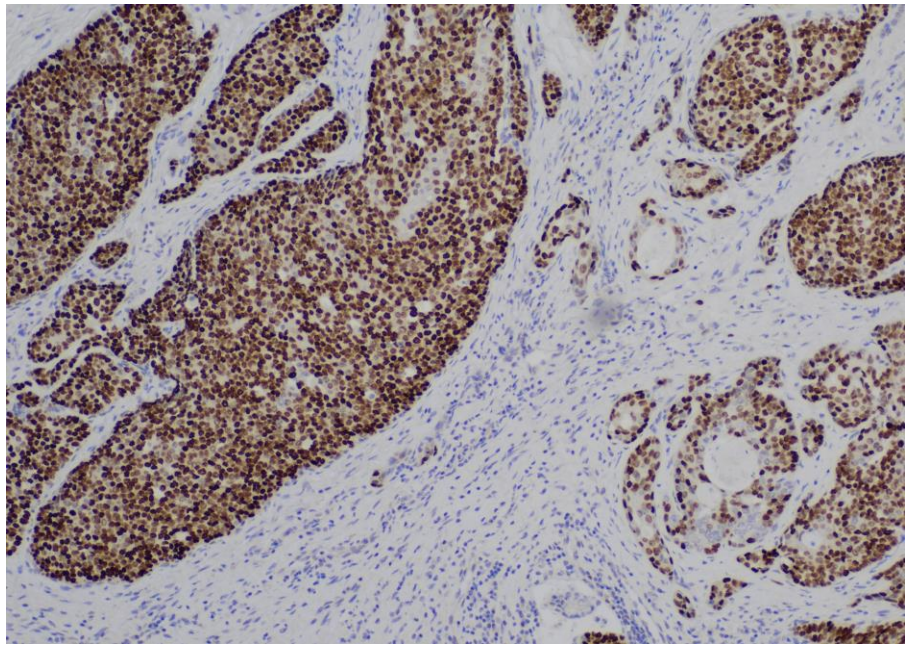
CK7

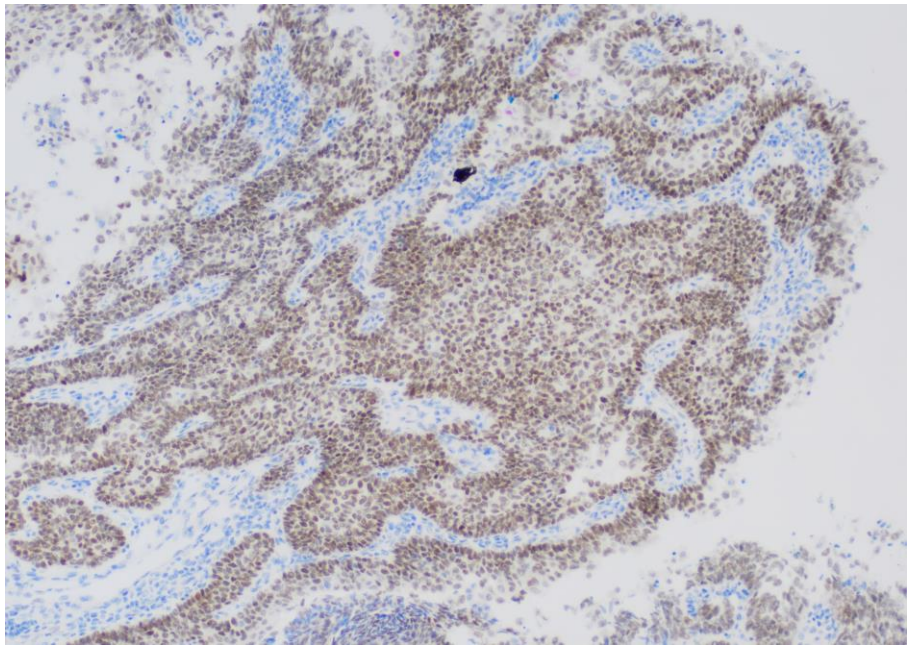




CK19

P63





NUT

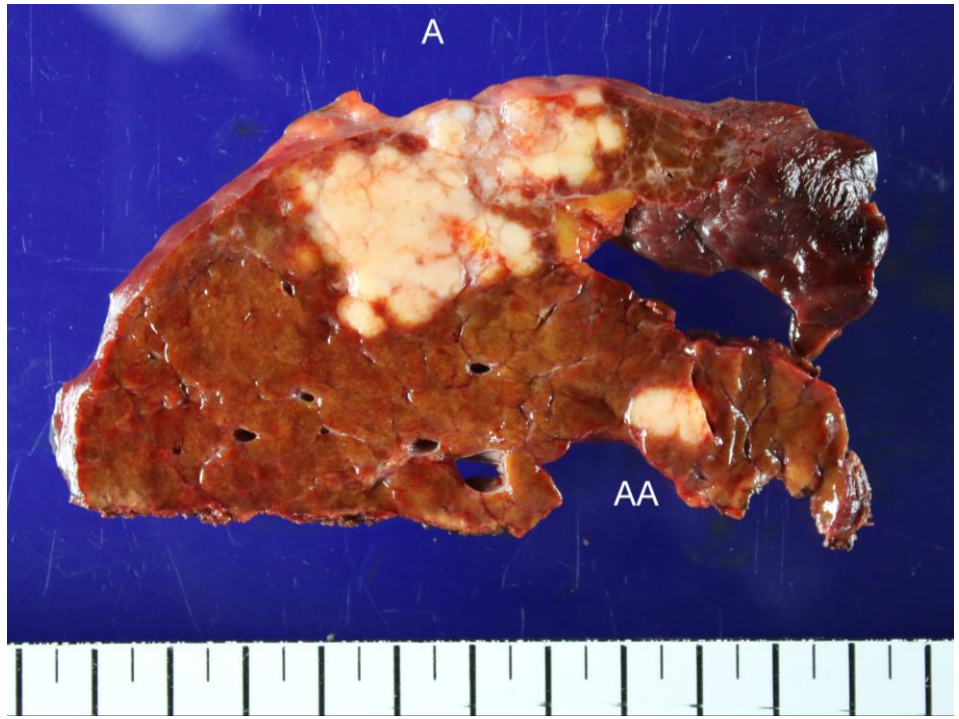
NUT carcinoma

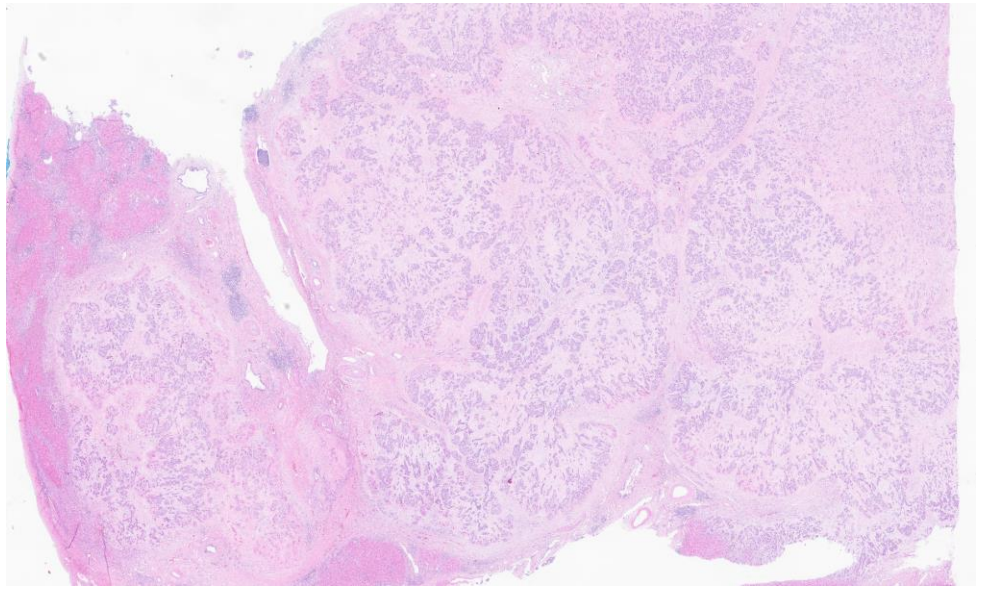
- Nuclear protein in testis (NUT)
- Relatively new entity that may likely be unrecognized and under-diagnosed
  - *BRD4-NUTM1* fusion gene identified resulting from this translocation (2003)
  - *NUTM1*-rearranged carcinoma described as a distinct entity (2004)
- Rare, sporadic, aggressive tumours: initially identified in NUTM1-midline carcinoma but subsequently identified in non-midline locations
- Primarily affects children, adolescents and young adults
- Diagnosis can be made by immunohistochemistry: Clone C52B1, 1:45, Cell Signaling Technology - 87% sensitivity, 100% specificity

Kubonishi Cancer Res 1991; French C et al, Cancer Res 2003; French C et al, J Clin Oncol 2004

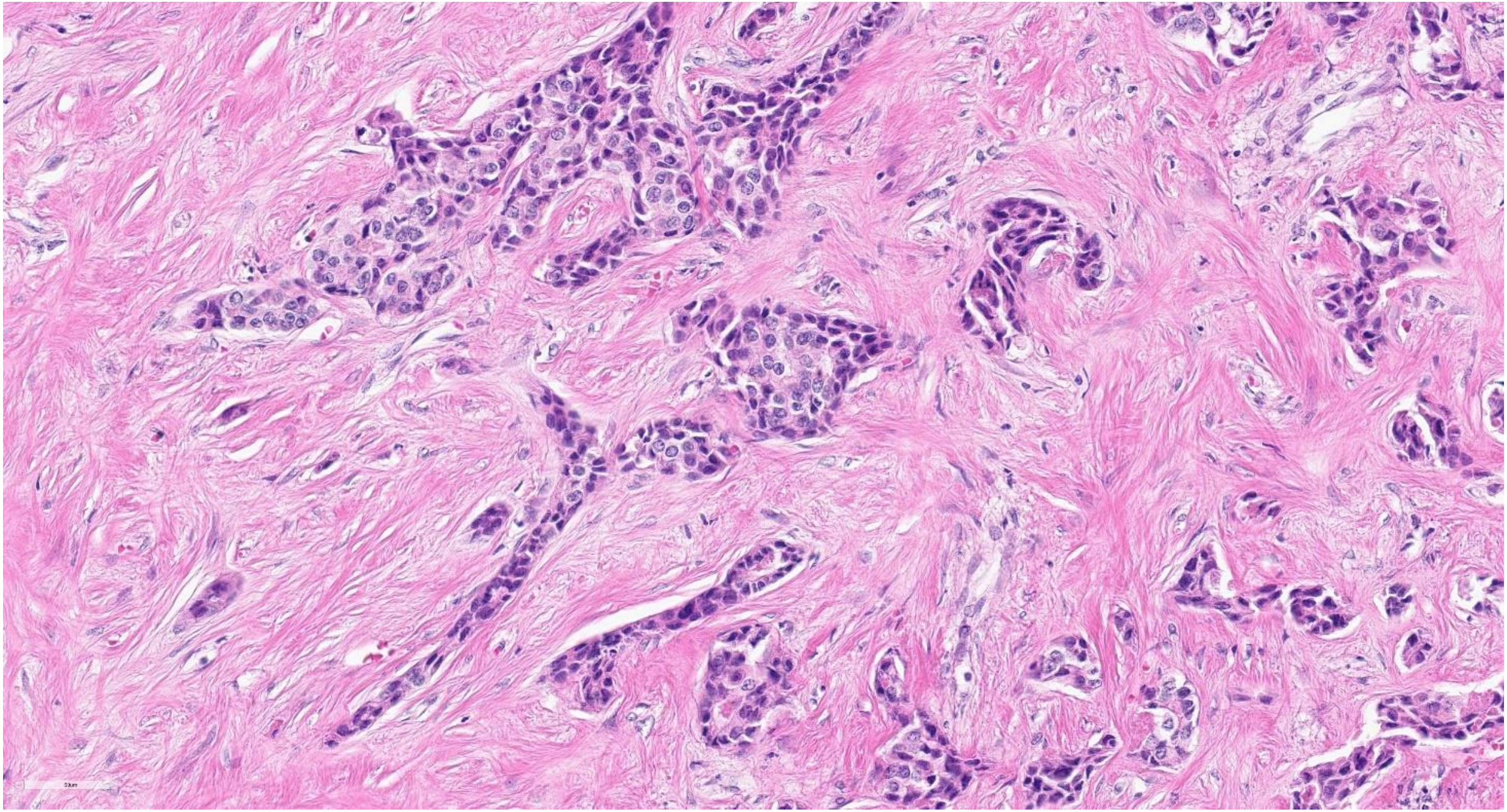
Seoul A

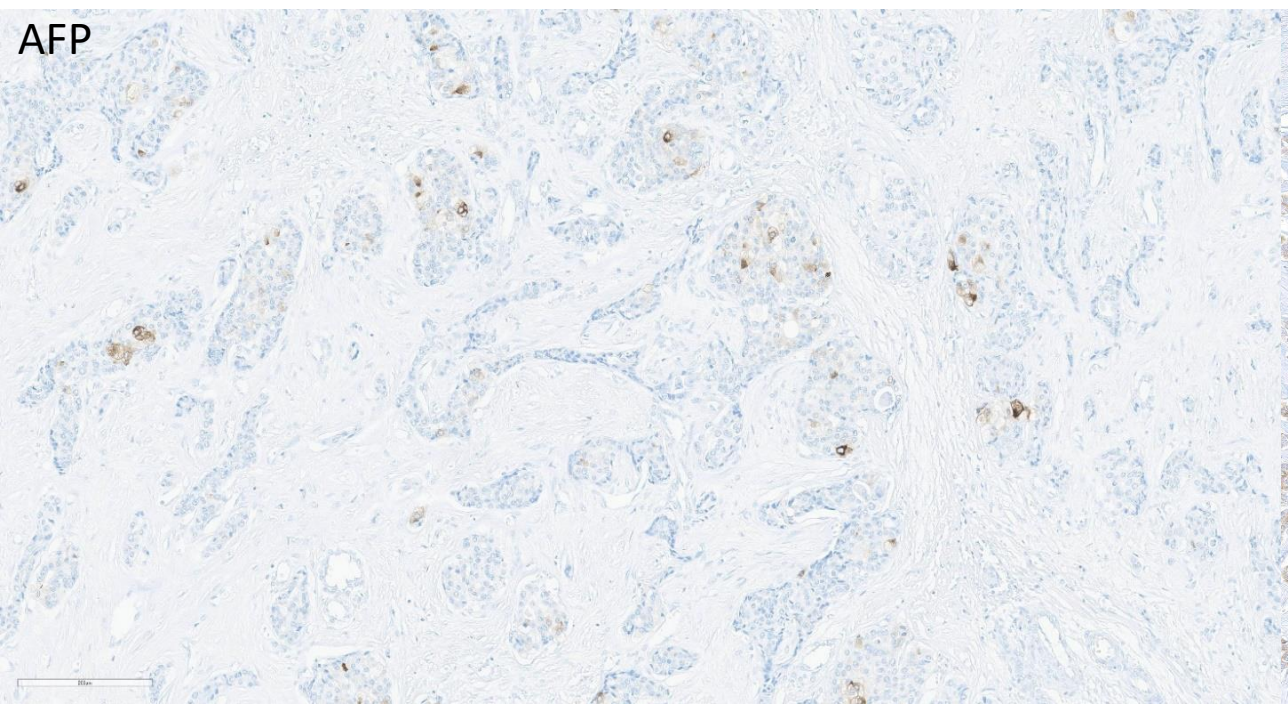
- 67 year old man - HBV carrier
- Fasting glucose 113 (Nr, 70-110 ng/dL), AFP isoenzyme-L3 56.5 ng/ml, AFP-L3 85.8% (Nr, 0-10 %),
- MRI: primary hepatic malignancy (LR-M) (5.9cm) in S4/8 and S5. ? HCC-CCA, cholangiocarcinoma, poorly differentiated HCC.

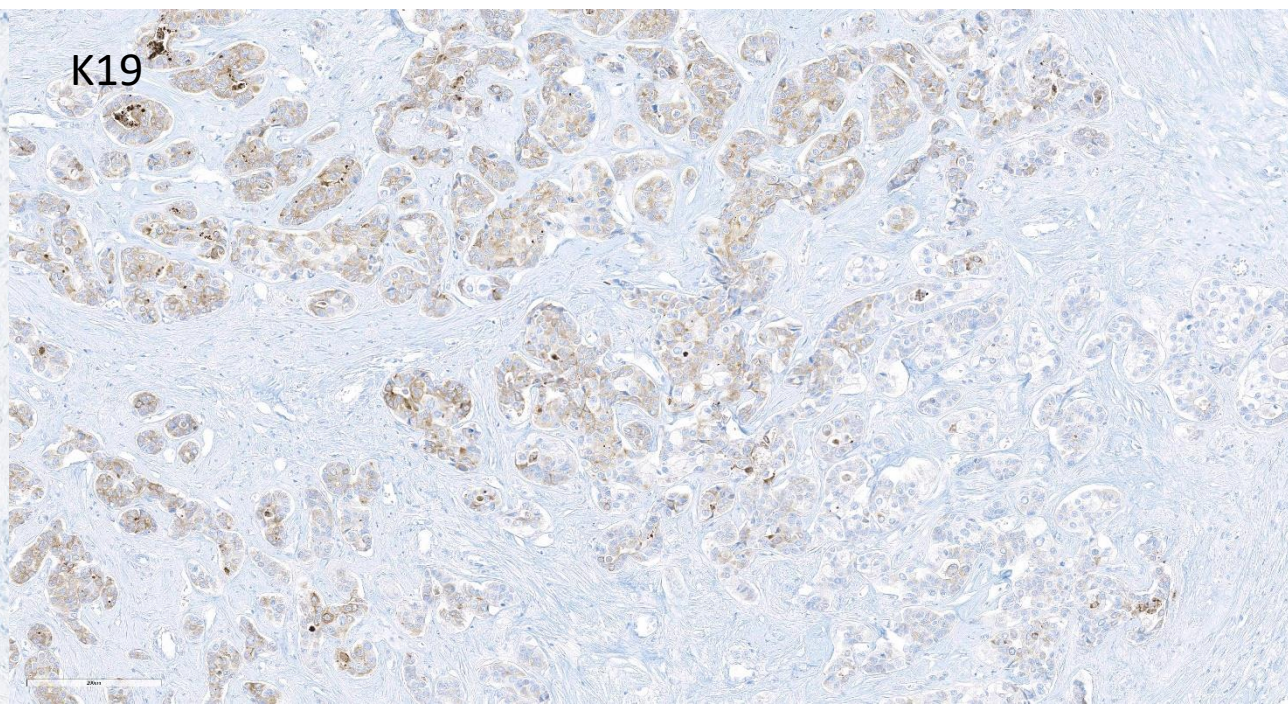


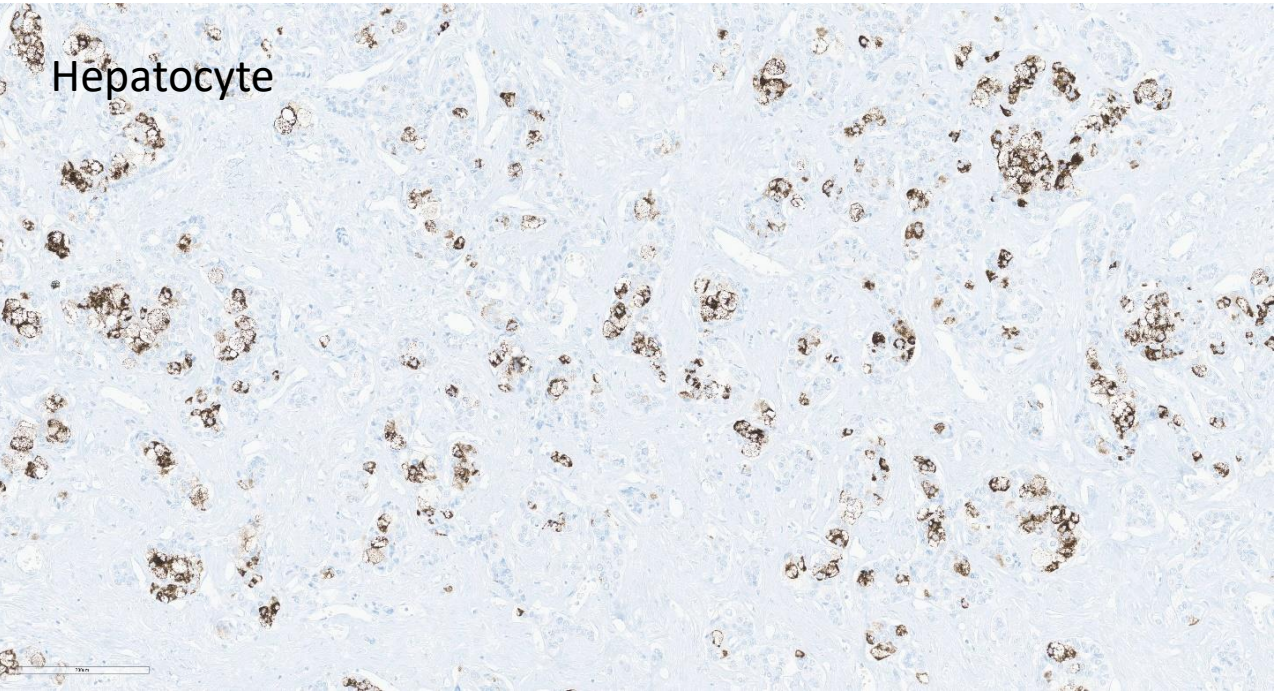


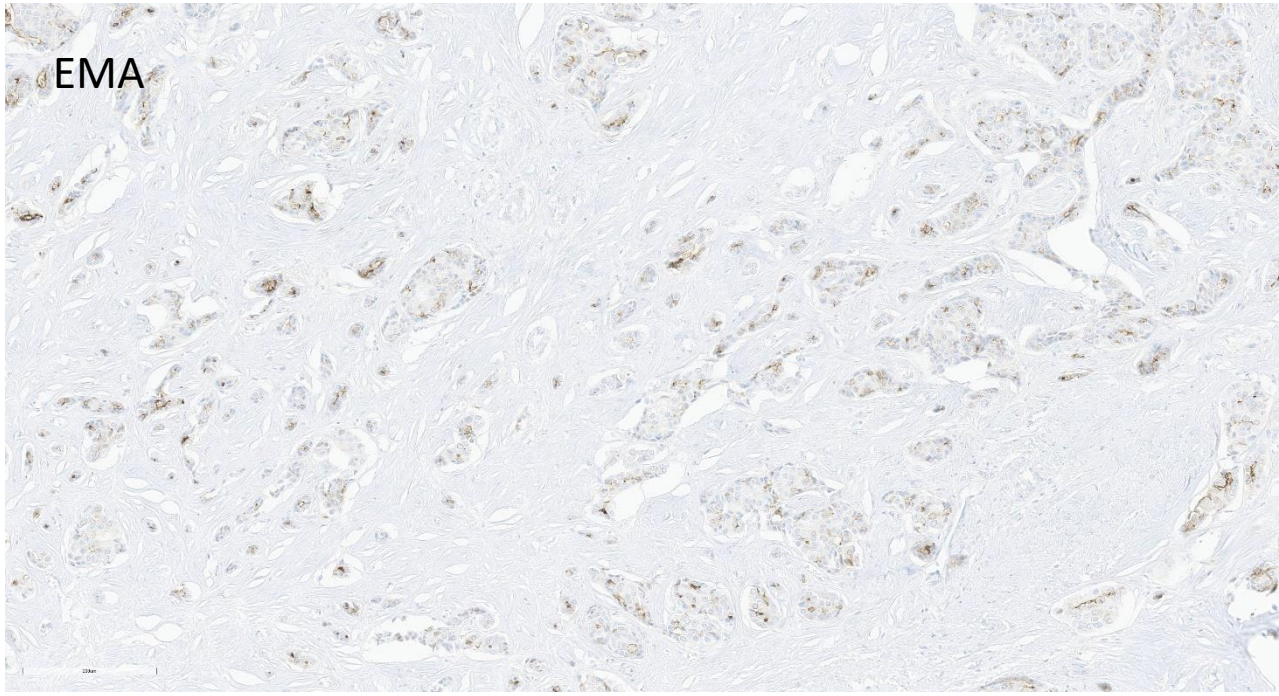
Young Nyun Park




AFP


K19


Hepatocyte


EMA

Nomenclature

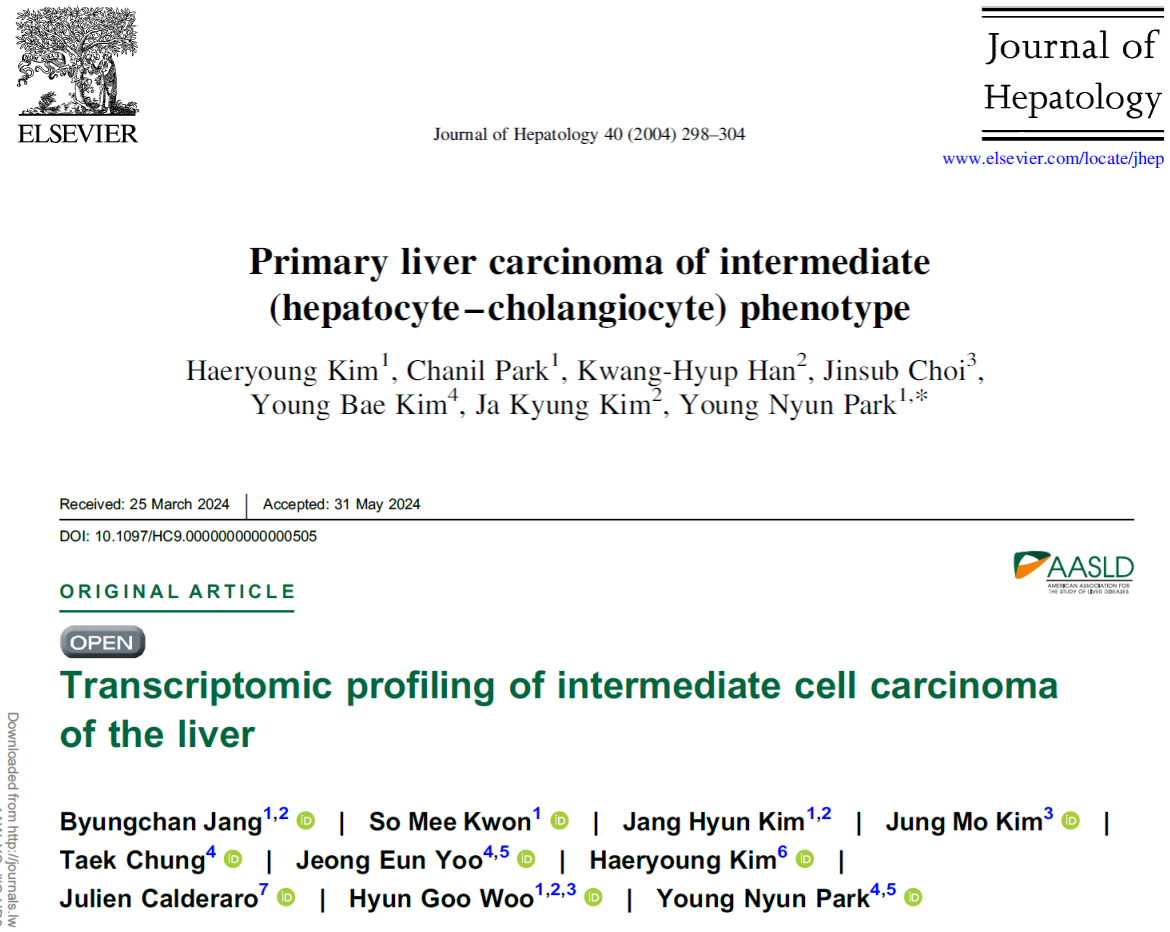
Type of cHCC-CCA	Microscopic features	Immunohistochemistry features
Classical	Unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumour: • all architectural and cytological differentiation patterns described for HCC and Icca are possible • no minimum cut-off amounts of each component Possible identification of cancer stem cells in various proportions: small uniform cells with scant cytoplasm and inconspicuous nucleoli	Confirmation of both differentiations by immunohistochemical markers: • Hepatocytic differentiation: Glypican, AFP, Hepar-1, Arginase-1, Polyclonal CEA and CD10 • Cholangiocytic differentiation: CK7, CK19, EpCAM Identification of stem-cell features: CK19, EpCAM, CD56, CD117, CD133
Intermediate cell carcinoma	Biphenotypic differentiation: • Tumour cells have a morphology intermediate between a hepatocyte and a cholangiocyte • Monotonous tumour cells with scant cytoplasm arranged in strands in an abundant fibrous stroma	Expression by tumour cells of both hepatocytic and cholangiocytic markers.

cHCC-CCA: combined hepatocellular-cholangiocarcinoma, HCC: hepatocellular carcinoma, iCCA: intrahepatic cholangiocarcinoma.

Beaufrere A, J Hep 2022

Intermediate cell carcinoma

- Monotonous morphological features intermediate between those of hepatocytes and cholangiocytes
- The tumour cells are small with scant cytoplasm, and arranged in cords, strands, trabeculae, and occasional gland-like structures in an abundant fibrous stroma.
- Dual expression of hepatocytic and cholangiocytic markers in the tumour cells supports an intermediate hepatobiliary cell phenotype.
- Intermediate cell carcinoma has unique and distinct molecular features, strikingly different from both HCC and iCCA.



ELSEVIER

Journal of Hepatology 40 (2004) 298–304

Journal of Hepatology

www.elsevier.com/locate/jhep

Primary liver carcinoma of intermediate (hepatocyte–cholangiocyte) phenotype

Haeryoung Kim[1], Chanil Park[1], Kwang-Hyup Han[2], Jinsub Choi[3], Young Bae Kim[4], Ja Kyung Kim[2], Young Nyun Park[1,*]

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DOI: 10.1097/HC9.0000000000000505

AASLD

ORIGINAL ARTICLE

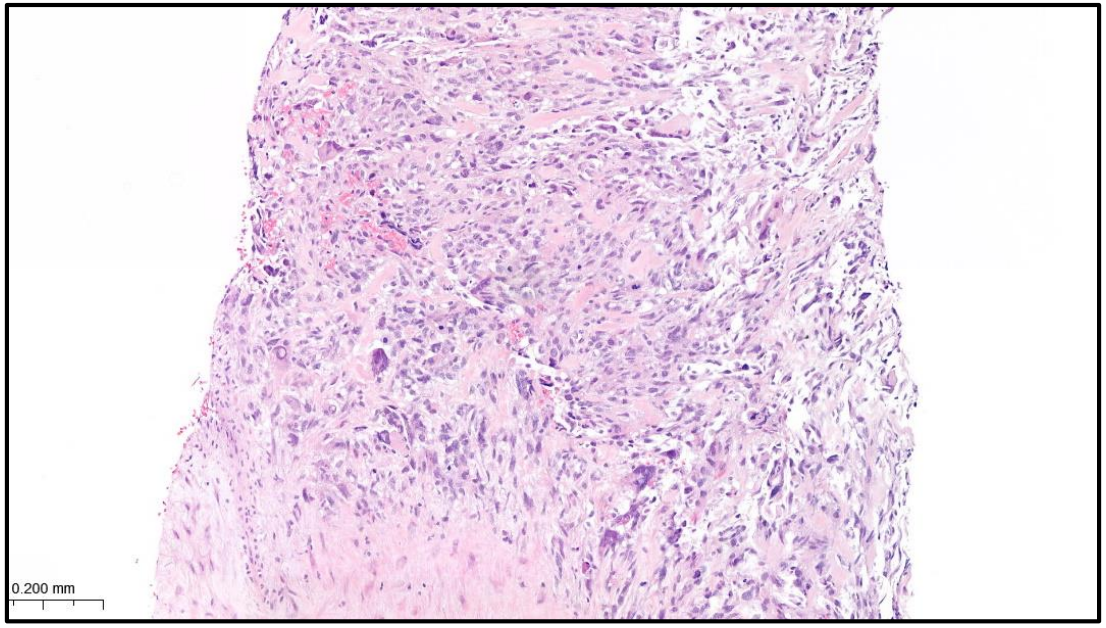
OPEN

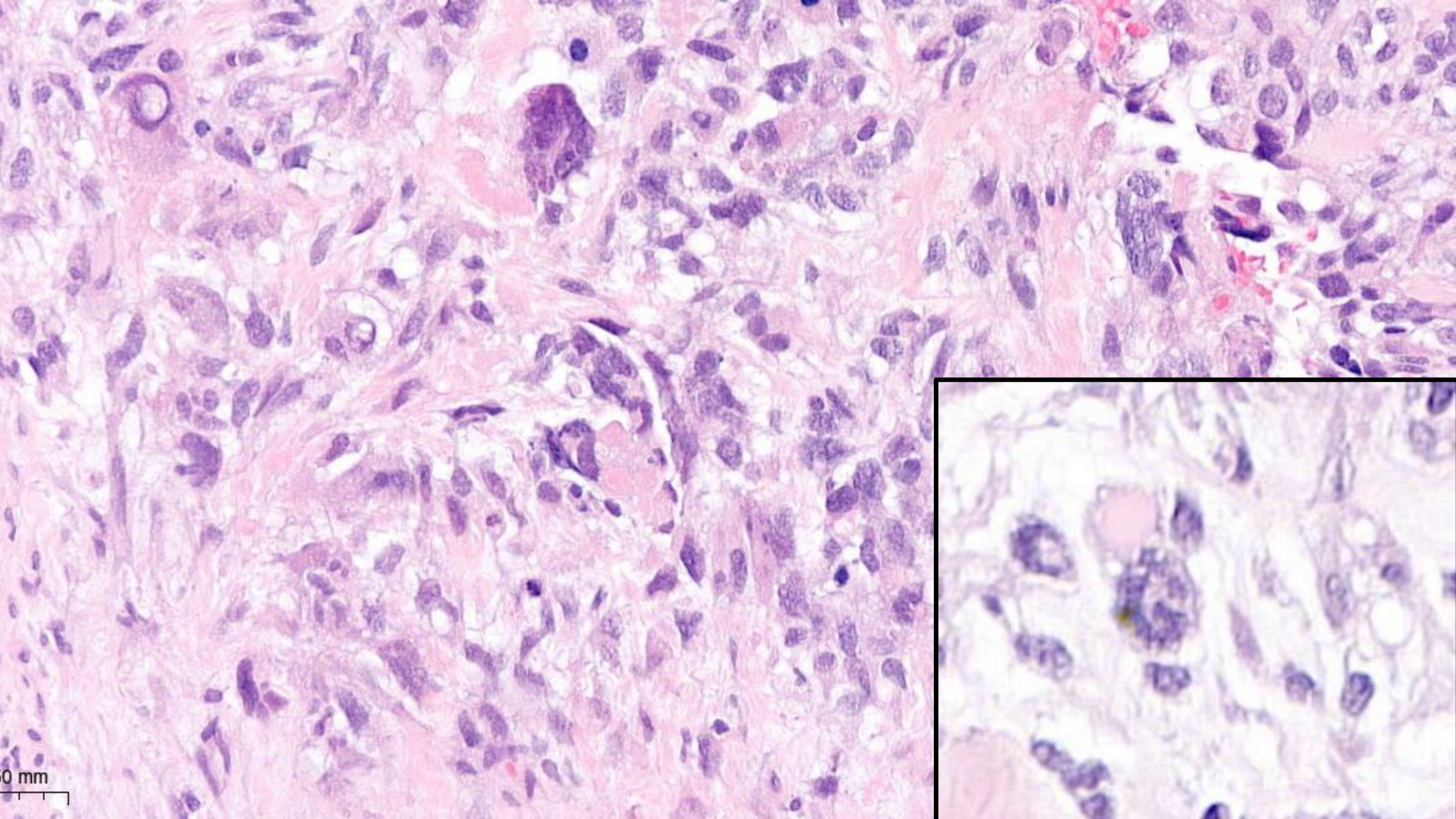
Transcriptomic profiling of intermediate cell carcinoma of the liver

Byungchan Jang[1,2] | So Mee Kwon[1] | Jang Hyun Kim[1,2] | Jung Mo Kim[3] | Taek Chung[4] | Jeong Eun Yoo[4,5] | Haeryoung Kim[6] | Julien Calderaro[7] | Hyun Goo Woo[1,2,3] | Young Nyun Park[4,5]

Newcastle A

- 9-year-old female who was previously well
- Presented with one week history of distended and tender RUQ
- Noticed lump in this area which progressively enlarged over several days
- MRI showed a large right lobe mass which was biopsied. The mass occupied most of the right lobe with some peripheral sparing of segments VI and VII
- No metastases were found.

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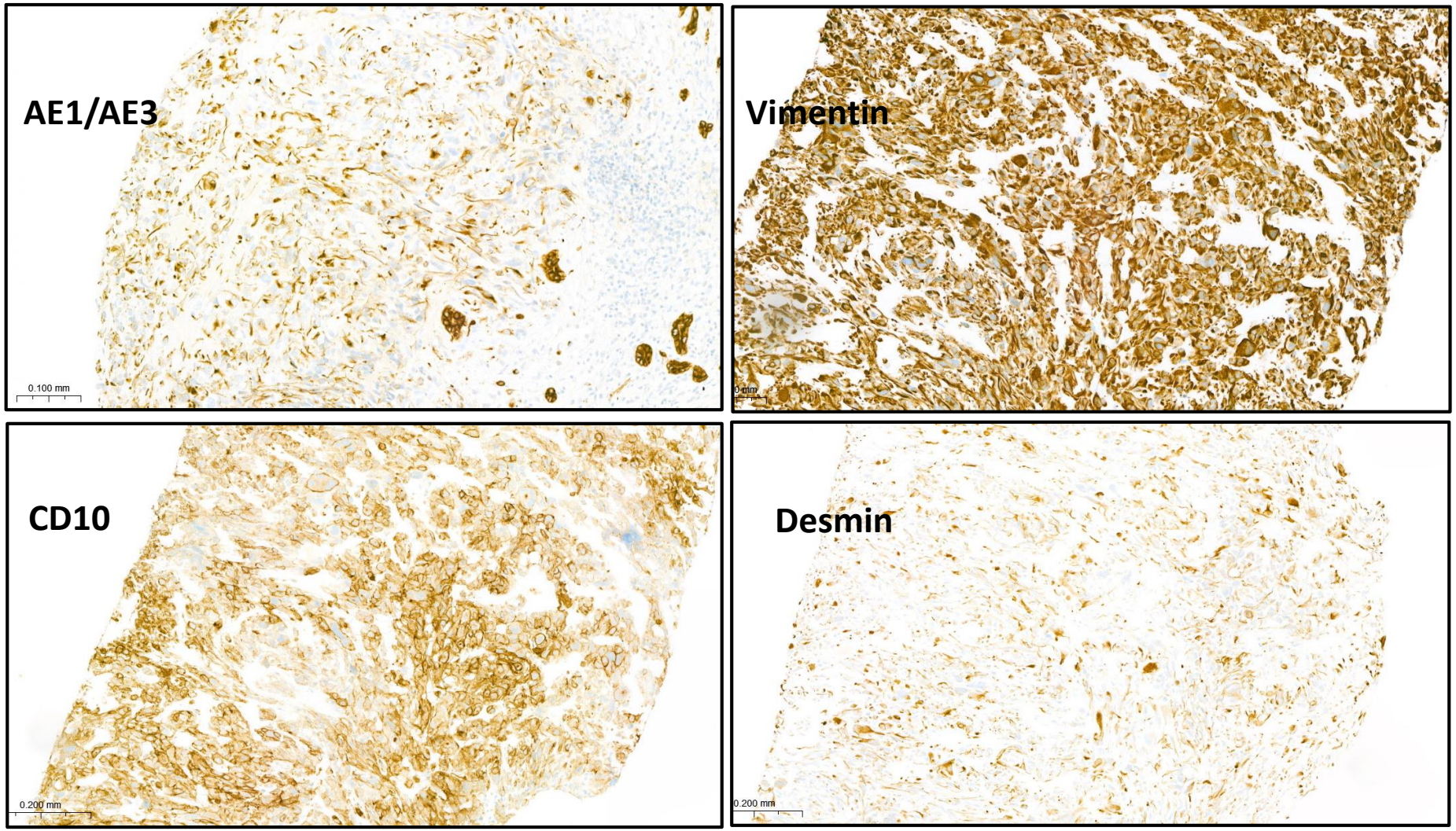
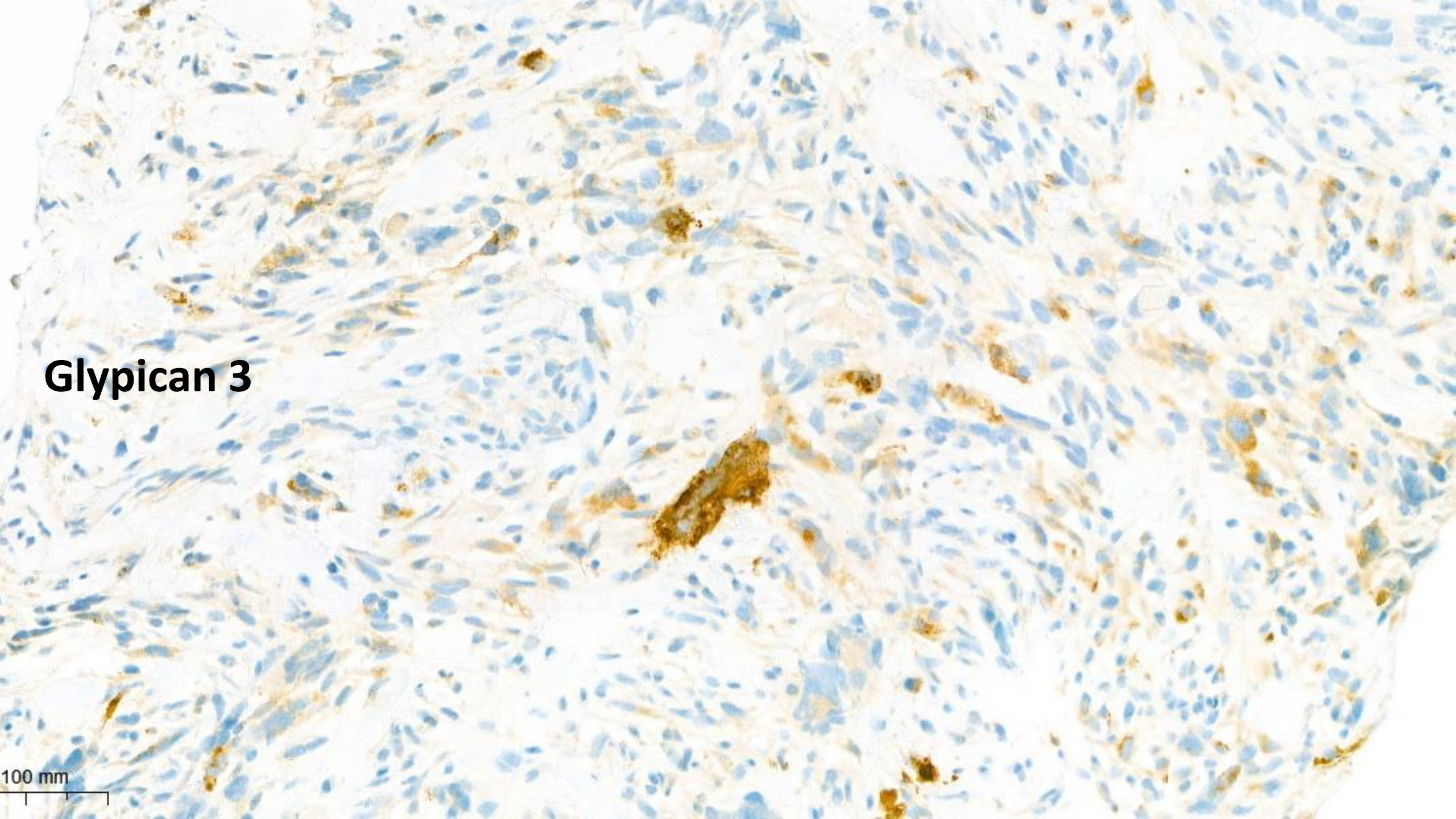
Newcastle A




Glypican 3
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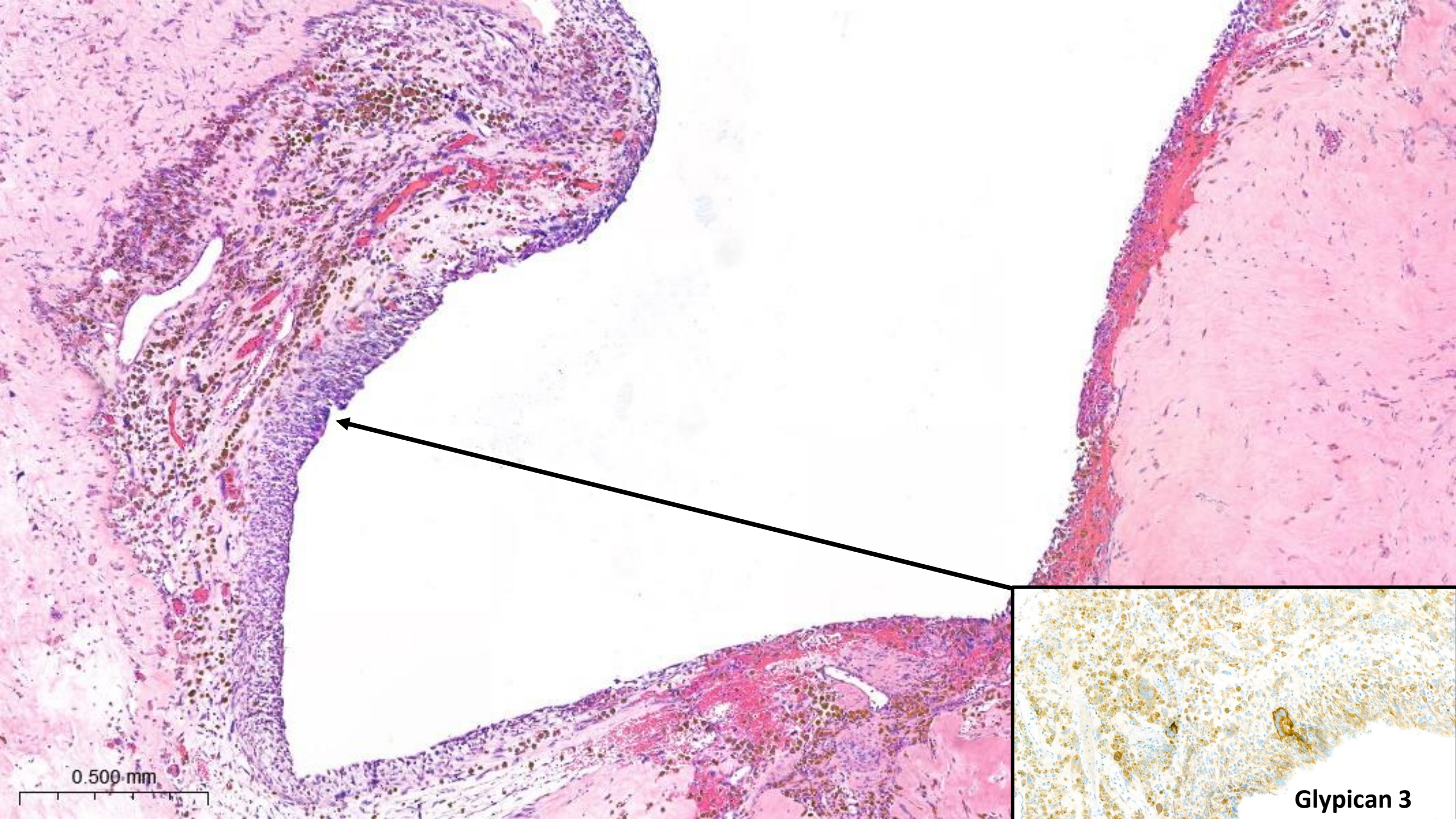

0.500 mm
Glypican 3

Virchows Archiv (2025) 486:23–47
https://doi.org/10.1007/s00428-024-03985-4

REVIEW

"Update on pediatric primary liver tumors"

Dolores López-Terrada[1] · Jens Stahlschmidt[2] · Antonio R. Pérez-Atayde[3]

Received: 28 August 2024 / Revised: 14 November 2024 / Accepted: 15 November 2024 / Published online: 21 January 2025

Mixed Epithelial/Mesenchymal or Uncertain Origin

Hepatoblastoma mixed
- Epithelial and mesenchymal
- Teratoid hepatoblastoma

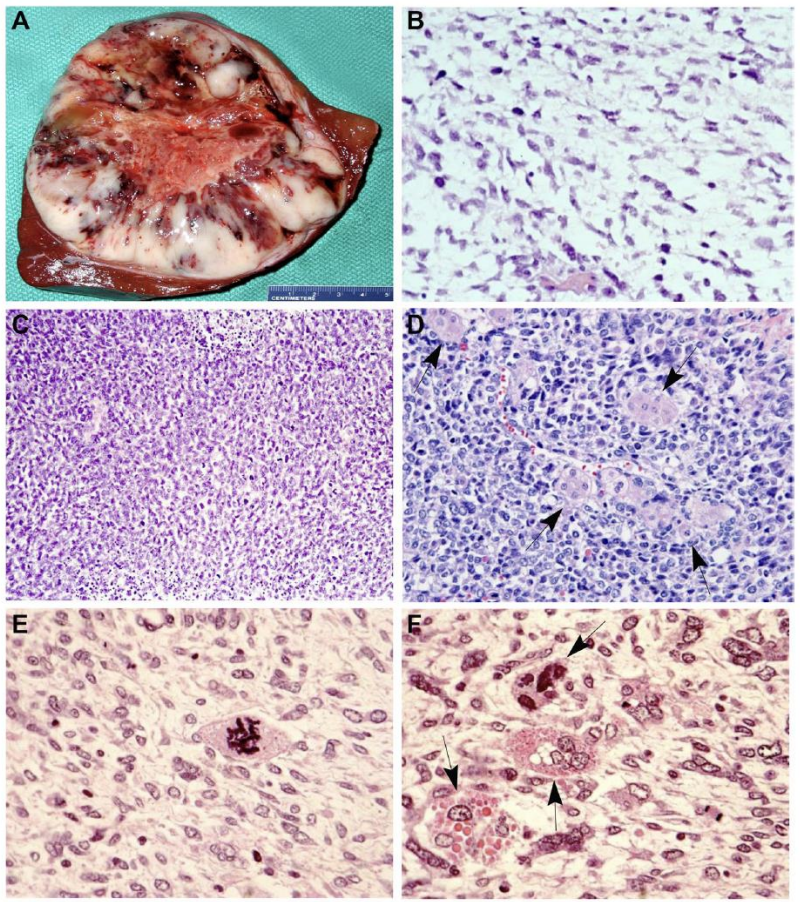
Malignant rhabdoid tumor
- INI1– (documented *INI1* mut)
- INI1+

Nested epithelial–stromal tumor

Mesenchymal Tumors

Malignant
- Embryonal sarcoma
- Rhabdomyosarcoma
- Epithelioid hemangioendothelioma
- Angiosarcoma (adult type)
- Synovial sarcoma
- Other (including DSRCT, PNET, NUT carcinoma)

Benign
- Infantile hemangioma
- Cavernous hemangioma
- Mesenchymal hamartoma



UNDIFFERENTIATED (EMBRYONAL) SARCOMA OF THE LIVER

Report of 31 Cases

J. THOMAS STOCKER, MAJOR, USAF, MC,* AND KAMAL G. ISHAK, MD, PHD

Thirty-one cases of undifferentiated (embryonal) sarcoma of the liver are presented. The tumor is found predominantly in the pediatric age group, the majority of patients (51.6%) being between 6 and 10 years of age. An abdominal mass and pain are the usual presenting symptoms. Radiographic examination is nonspecific except to demonstrate a space-occupying lesion of the liver. The tumors are large, single, usually globular and well demarcated, and have multiple cystic areas of hemorrhage, necrosis, and gelatinous degeneration. Histologic examination shows a pseudocapsule partially separating the normal liver from undifferentiated sarcomatous cells that, near the periphery of the tumor, surround entrapped hyperplastic or degenerating bile duct-like structures. Eosinophilic globules that are PAS positive are usually found within and adjacent to tumor cells. Areas of necrosis and hemorrhage are prominent. The prognosis is poor, with a median survival of less than 1 year following diagnosis.

Cancer **42:336–348, 1978.**

TABLE 1. Age at Diagnosis of 31 Patients with Undifferentiated Sarcoma of Liver

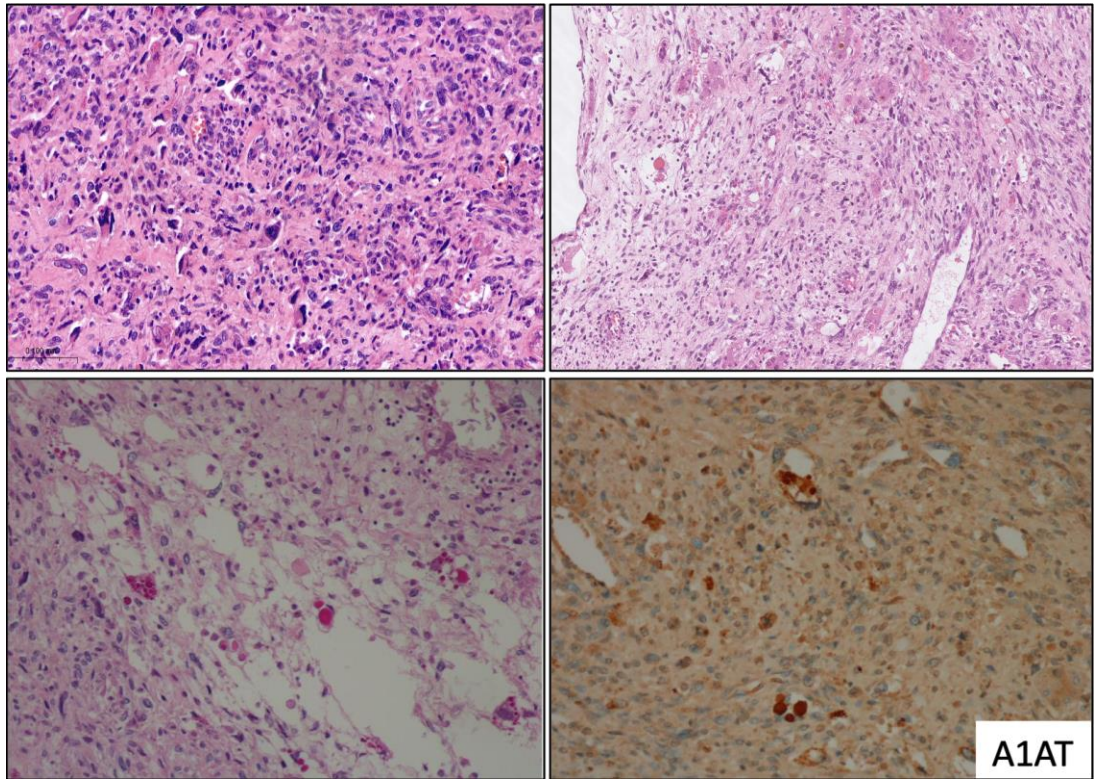
Age	Number of cases	Percent
0–5	5	16.1
6–10	16	51.6
11–15	6	19.4
16–20	2	6.5
>20	2	6.5
TOTAL	31	100.1

TABLE 2. Presenting Symptoms of 31 Patients with Undifferentiated Sarcoma of the Liver

Presenting complaint	Number of cases
Abdominal mass only	12
Abdominal pain only	10
Abdominal mass and pain	6
Fever only	3
TOTAL	31

Newcastle A1

- 21-year-old female nurse
- Presented with abdominal distension
- Ultrasound demonstrated large cystic lesion in right lobe (segments 8, 6, 7 and 5)
- Underwent right hemihepatectomy
- Necrotic, multicystic tumour with mucoid and solid white components 30cm greatest diameter



Newcastle A1

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- Underwent right hemihepatectomy
- Necrotic, multicystic tumour with mucoid and solid white components 30cm greatest diameter

Undifferentiated Embryonal Sarcoma of the Liver in Adults

Frank Lenze, MD[1]
Traute Birkfellner, MD[1]
Philipp Lenz, MD[1]
Kais Hussein, MD[2]
Florian Länger, MD[2]
Hans Kreipe, MD[2]
Wolfram Domschke, MD[1]

[1] Department of Medicine B, University of Muenster, Muenster, Germany.

[2] Institute of Pathology, Hannover Medical School, Hannover, Germany.

BACKGROUND. Undifferentiated embryonal sarcoma of the liver (UESL), a rare tumor that predominantly affects children, generally has been considered an aggressive neoplasm with an unfavorable prognosis. More recent reports have indicated that modern multimodal treatment and supportive care improve the survival of children with UESL. Data regarding the treatment and survival of adults have not been reviewed comprehensively, and only a few adult patients with UESL have been reported in the literature.

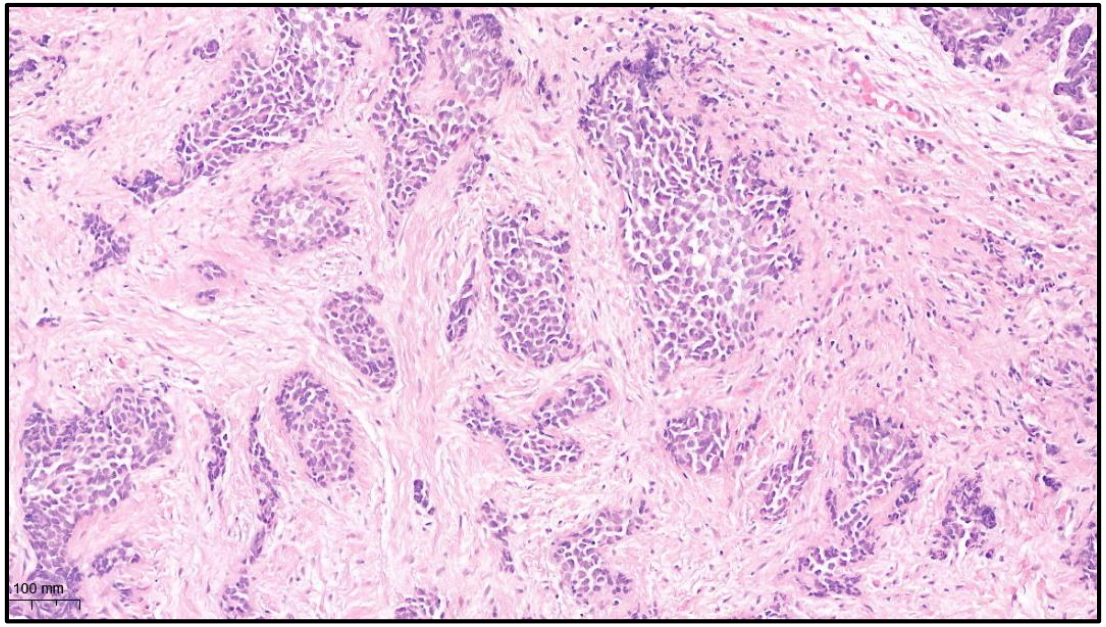
METHODS. The authors analyzed demographics, treatment, and actuarial survival of all reported cases of UESL in patients aged ≥15 years (n = 67 patients). In addition, 1 case is presented of a patient with UESL who was treated successfully at the authors' institution.

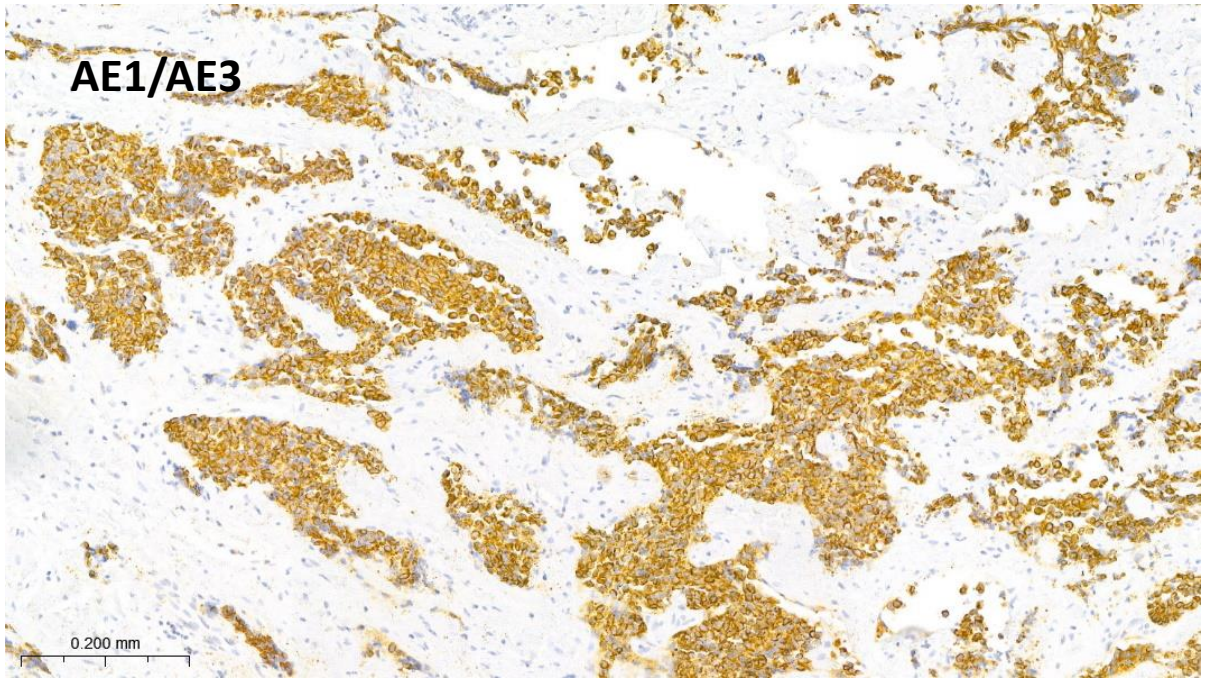
RESULTS. The median survival of all patients with UESL who were analyzed was 29 months. Patients who underwent complete tumor resection followed by adjuvant chemotherapy survived over a median follow-up of 28.5 months and had significantly better survival compared with patients who underwent surgical treatment alone. Patients who underwent an incomplete tumor resection had a tendency toward poorer outcomes.

CONCLUSIONS. To the authors' knowledge, this is the first report to demonstrate a significant effect on survival for adjuvant chemotherapy after complete surgical resection of UESL in adults. The role of neoadjuvant chemotherapy was not evaluated in this study. In the case study presented herein, combined therapy with surgery and chemotherapy led to a complete, sustained remission that has lasted for >6 years to date. ***Cancer*** **2008;112:2274–82.** © *2008 American Cancer Society.*

Newcastle B

- 36-year-old male who presented with mass in RUQ and in area of hepatic flexure
- Large tumour noted on imaging with major intrahepatic component
- Subsequently underwent right hemicolectomy, omentectomy, liver resection and portocaval node resection




AE1/AE3
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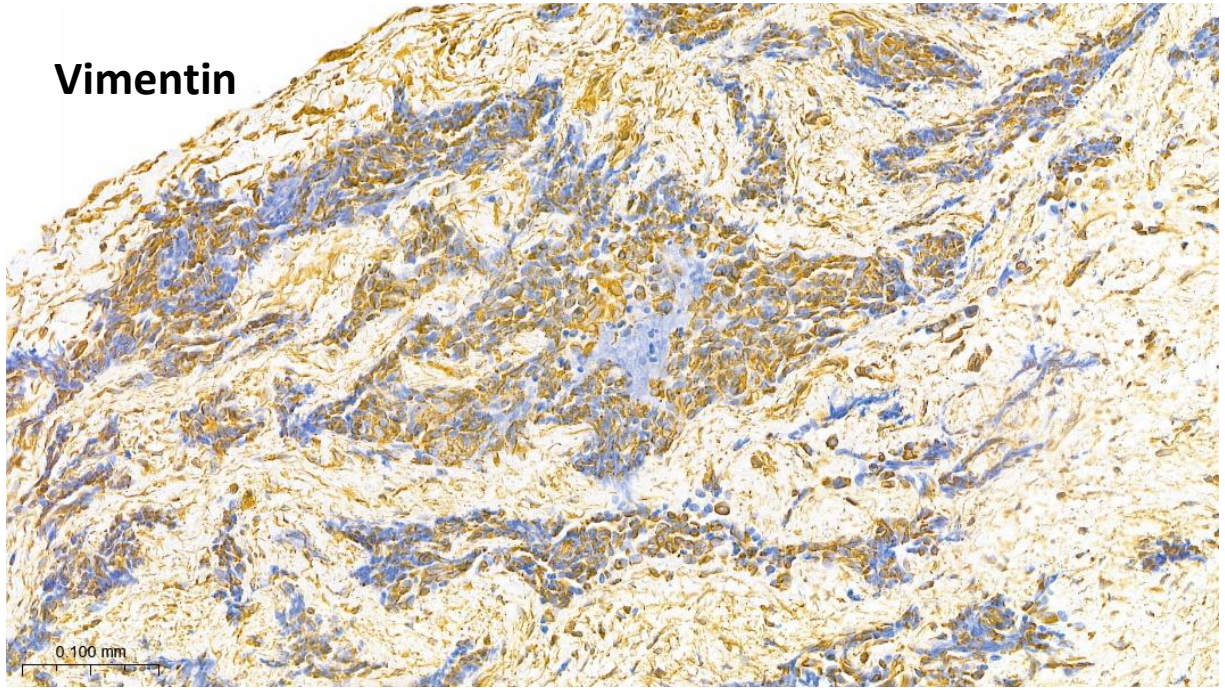
Vimentin
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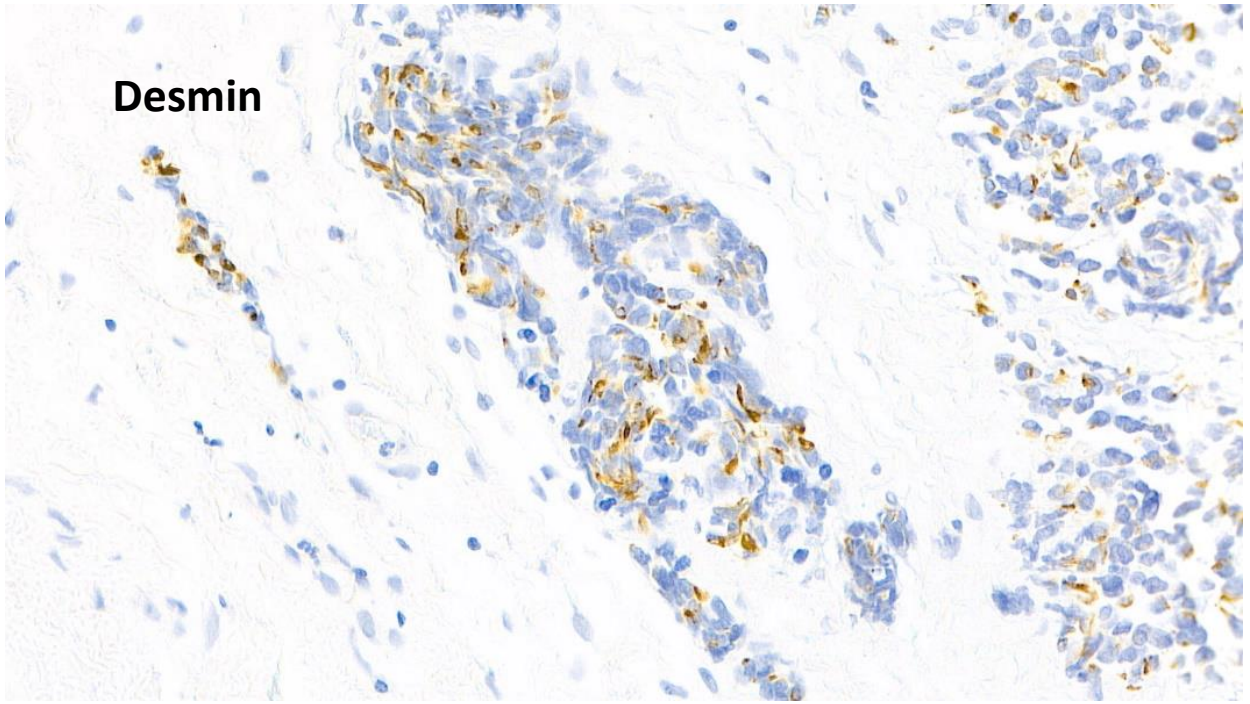
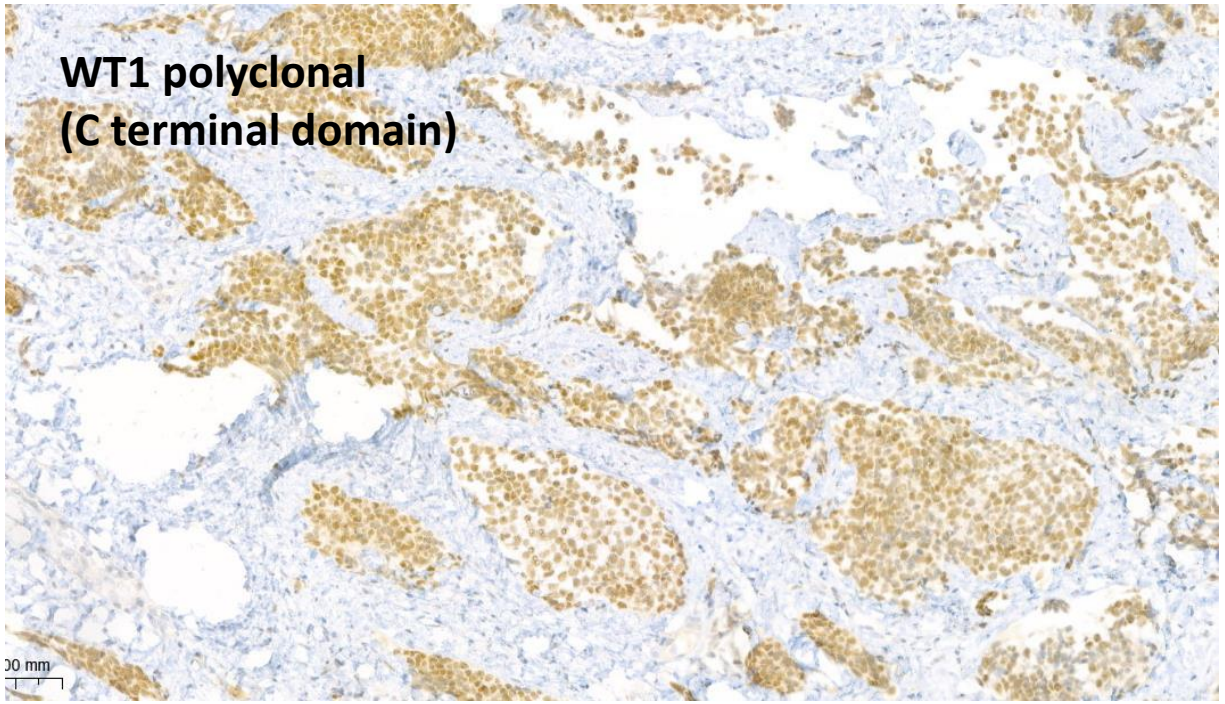
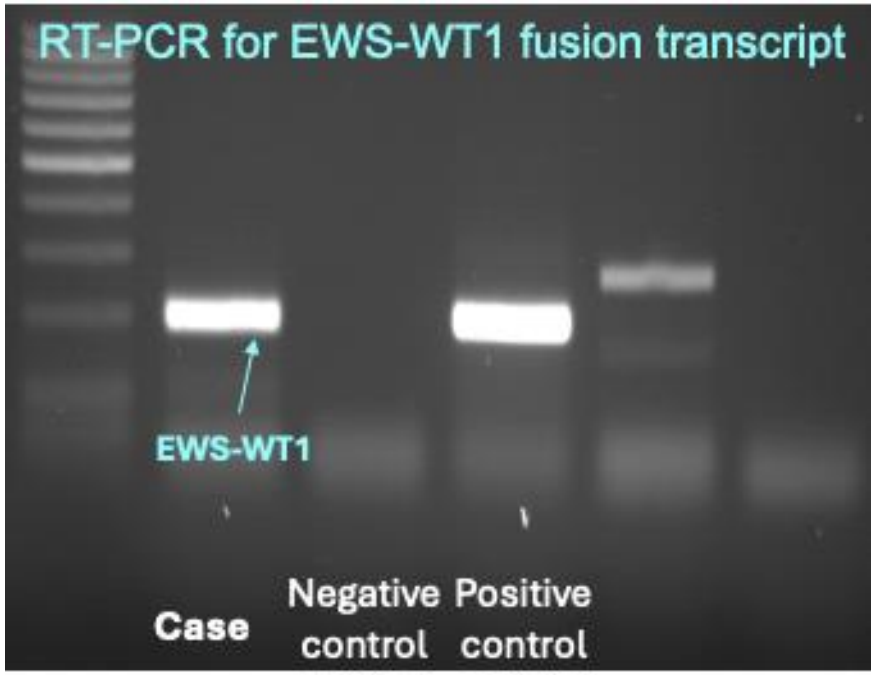

Desmin


WT1 polyclonal
(C terminal domain)

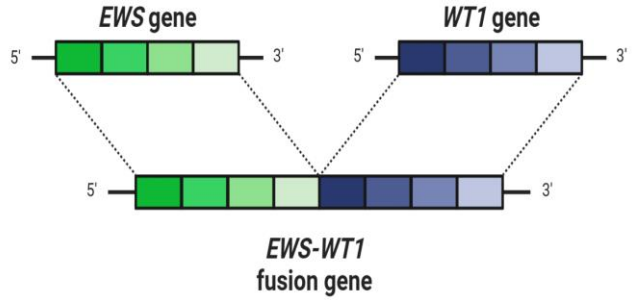
Newcastle B

- Cytogenetic analysis performed using RT-PCR with EWS and WT1 primers demonstrated fusion transcript implicating translocation t(11;22)(p13;q12) (note historical case)
- Diagnosis of desmoplastic small round cell tumour (DSRCT)
- Complete resection achieved but recurrent tumour within 6 months
- Multiple rounds of VIDE chemotherapy but died after 18 months



Desmoplastic small round cell tumour

- First described by Gerald & Rosai in 1989
- Predominantly adolescent/young adult males
- Fusion protein driver with pleotropic effects: up-regulation of PDGFα, IGF-1R, NTRK3 and VEGF (*Mello et al, 2021*)
- Proteomic studies show over-expression of AR and EGFR
- Often multiple tumours and synchronous liver lesions
- Median survival 25 months
- Mainstay of treatment: chemoradiotherapy and resection ((Ewing sarcoma regimen generally given – VDC/IE)

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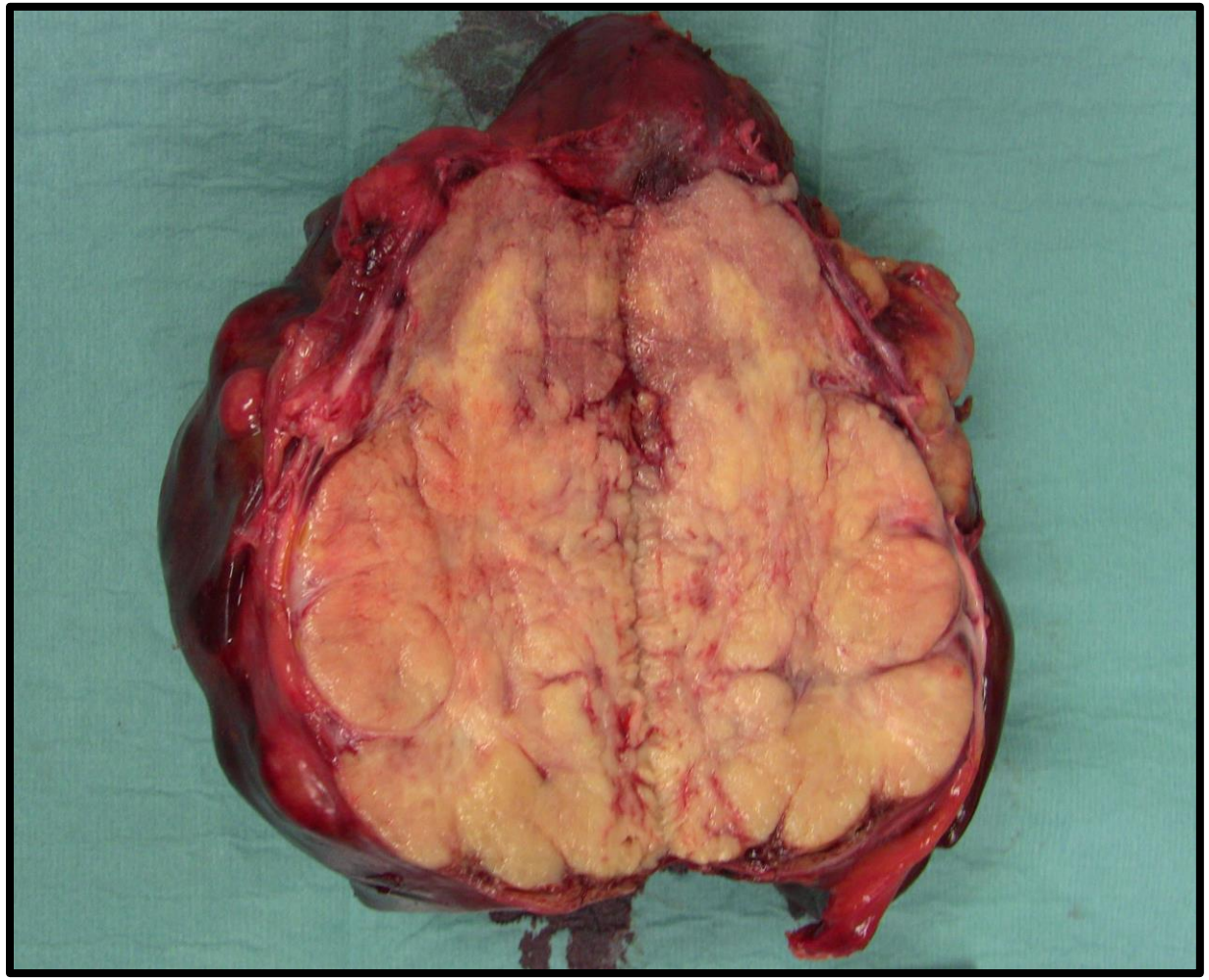
Molecular profiling in desmoplastic small round cell tumours

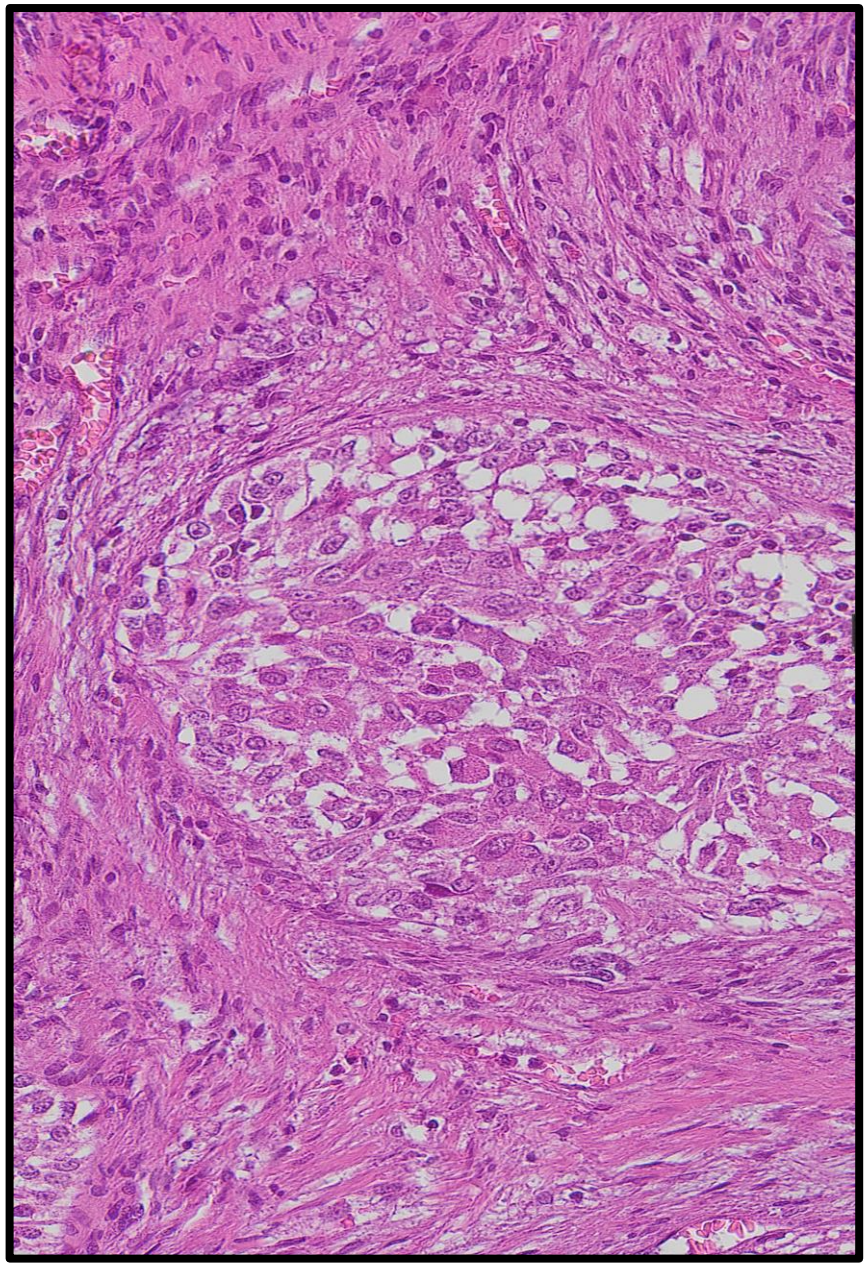
Yuen Bun Tam [a], Robin L. Jones [b,c], Paul H. Huang [a,*]

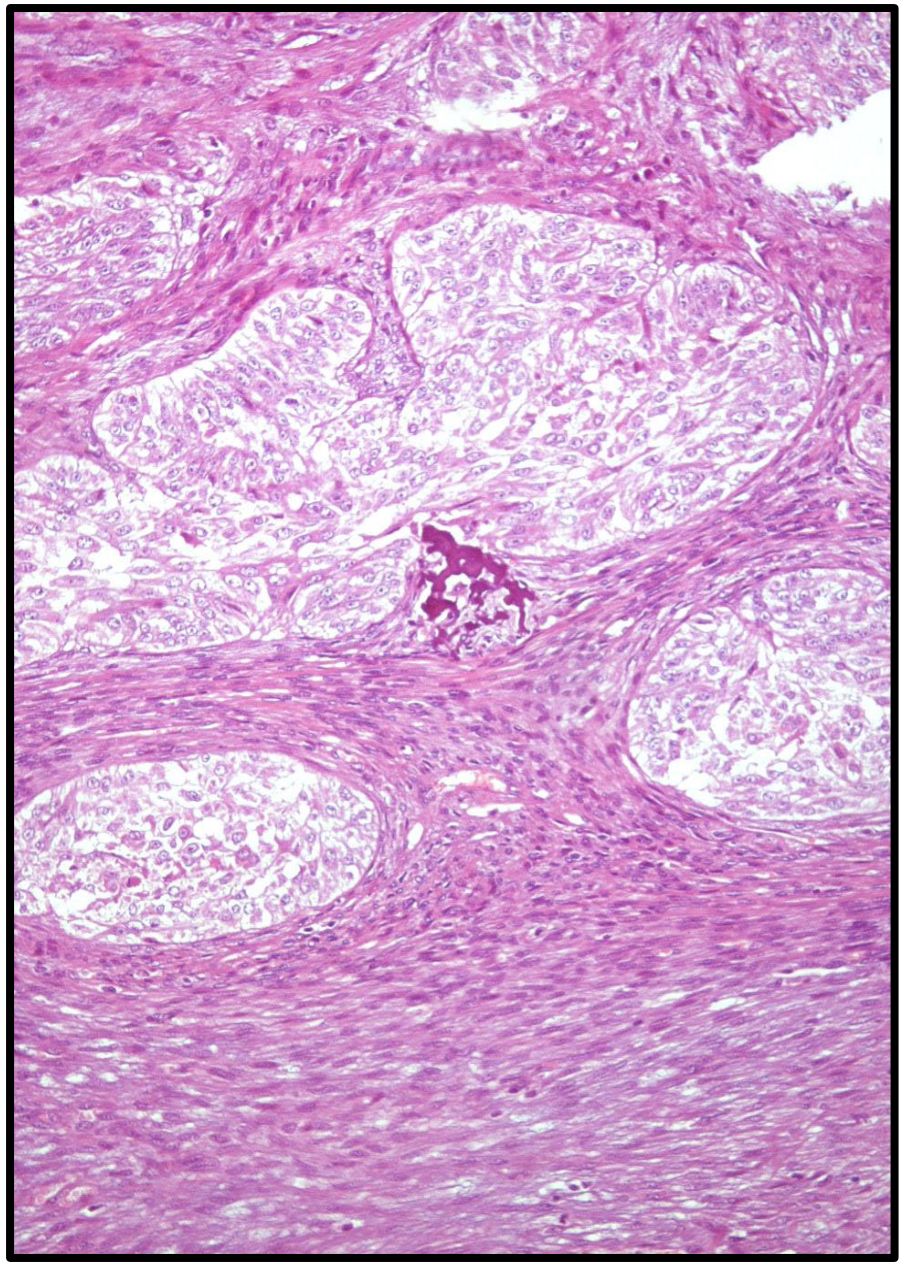
Milan B

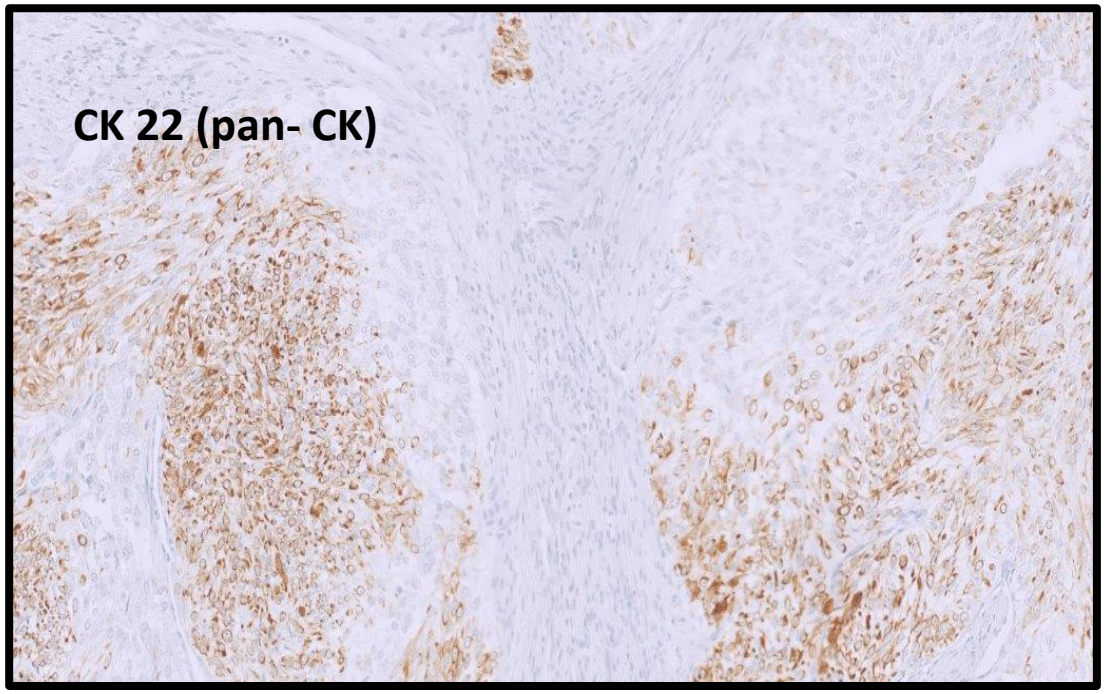
- 23 year-old female referred for recurrent dull abdominal pain, abdominal distension and dyspepsia.
- Past history of oral contraceptive use for previous 5 years.
- On physical examination, a palpable mass in the upper abdomen was revealed. No Cushingoid or other clinical features were evident.
- AST (36 IU/L), ALT (297 IU/L), and gamma-GT (285 IU/L).

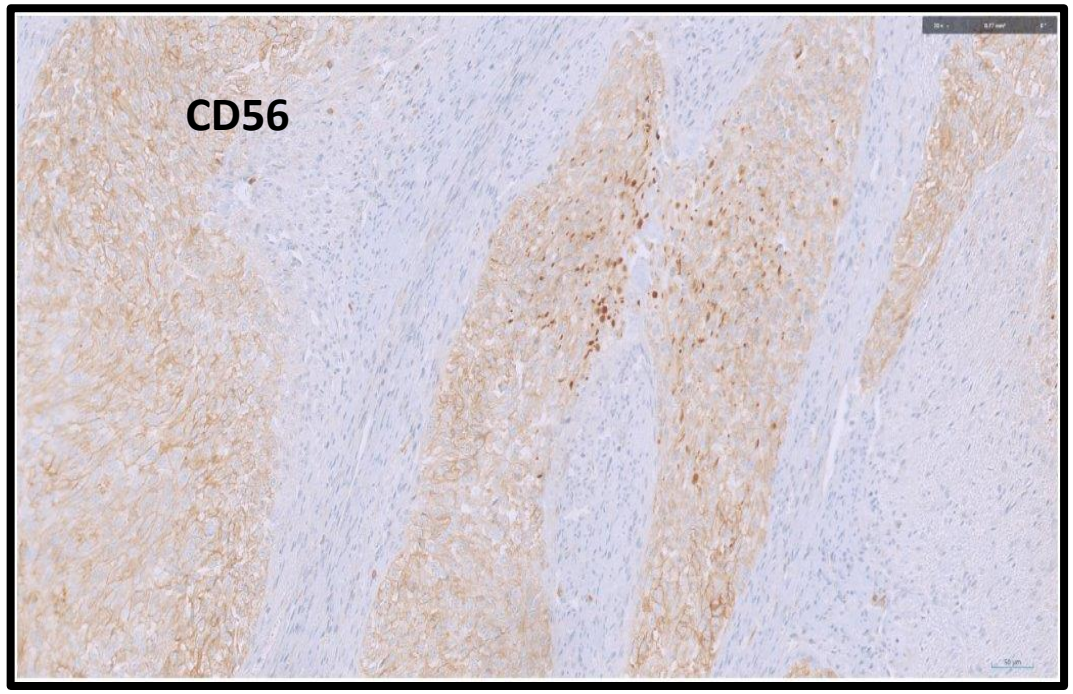


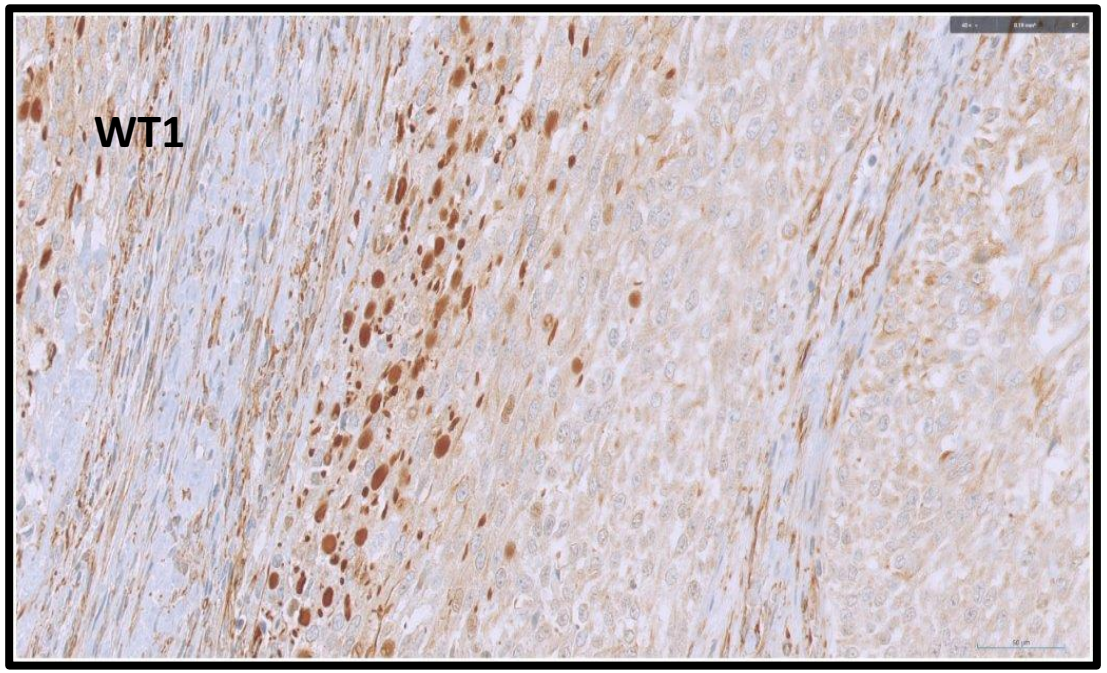
Luigi Terracciano











CTNNB1: deletion exon 3 (p.D32_k63del)
TERT promoter hotspot mutation: point mutation T41A

Calcifying nested stromal-epithelial tumour

- First description by Ishak et al. in 2001
- Age range : 2- 34 years; predominantly in young women (71%); more frequent in the right lobe (65%)
- Most occur sporadically; some cases linked to Beckwith –Weidemann syndrome
- Low-grade non-hepatocytic and non-biliary tumour composed of nests of epithelioid and spindle cells with an associated desmoplastic myofibroblastic stroma and variable calcification ± ossification
- Tumour cells positive for broad spectrum CK, WT1, and b-catenin (nuclear and cytoplasmic) . Occasionally positive for CD56,EMA, NSE, CD99 CD57, CD56, CD117; Stromal spindle cells positive for SMA
- Uncertain histogenesis: epithelial origin with differentiation toward a mesenchymal origin or vice versa? hepatic mesenchymal precursor?

Benedict M, Arch Pathol Lab Med, 2019