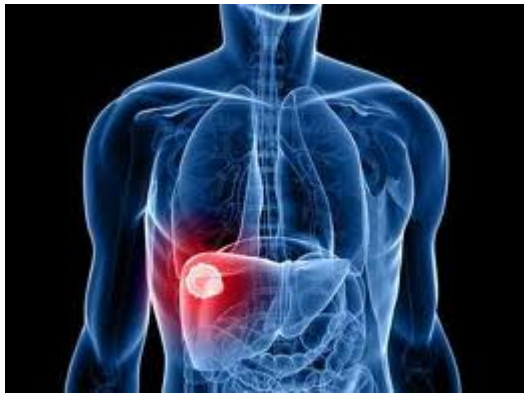


FRCPath Course

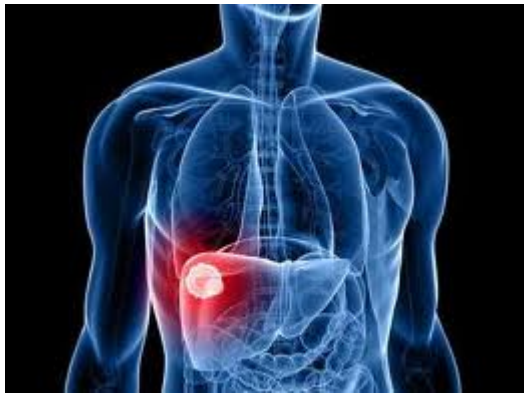
Algorithmic approach to the diagnosis of solid and cystic liver lesions

Dr Tu Vinh Luong
Consultant Histopathologist

Wednesday 16th September 2020

UCLPartners
Academic Health Science Partnership

Royal Free London NHS
NHS Foundation Trust



Acknowledgments

Some images and cartoons are from Dr Neil Theise's presentation downloaded from SlideShare.net and Neil Theise's and Romil Saxena's chapter in the Odze and Goldblum Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas book.

WHO 2019 Classification

WHO 2019 Classification

WHO classification of tumours of the liver and intrahepatic bile ducts

Benign hepatocellular tumours
8170/0 Hepatocellular adenoma
- *HNF1A*-inactivated hepatocellular adenoma
- Inflammatory hepatocellular adenoma
- B-catenin-activated hepatocellular adenoma
- B-catenin-activated inflammatory hepatocellular adenoma

Malignant hepatocellular tumours and precursors
8170/3 Hepatocellular carcinoma NOS
8171/3 Hepatocellular carcinoma, fibrolamellar
8172/3 Hepatocellular carcinoma, scirrhous
8174/3 Hepatocellular carcinoma, clear cell type
- Hepatocellular carcinoma, steatohepatitic
- Hepatocellular carcinoma, macrotrabecular massive
- Hepatocellular carcinoma, chromophobe
- Hepatocellular carcinoma, neutrophil-rich
- Hepatocellular carcinoma, lymphocyte-rich

8970/3 Hepatoblastoma NOS

Benign biliary tumours and precursors
8160/0 Bile duct adenoma
9013/0 Adenofibroma NOS
8148/0 Biliary intraepithelial neoplasia, low grade
8148/2 Biliary intraepithelial neoplasia, high grade
8503/0 Intraductal papillary neoplasm with low-grade intraepithelial neoplasia
8503/2 Intraductal papillary neoplasm with high-grade intraepithelial neoplasia
8503/3 Intraductal papillary neoplasm with associated invasive carcinoma
8470/0 Mucinous cystic neoplasm with low-grade intraepithelial neoplasia
8470/2 Mucinous cystic neoplasm with high-grade intraepithelial neoplasia
8470/3 Mucinous cystic neoplasm with associated invasive carcinoma

Malignant biliary tumours
8160/3 Cholangiocarcinoma
- Large duct intrahepatic cholangiocarcinoma
- Small duct intrahepatic cholangiocarcinoma

8020/3 Carcinoma, undifferentiated, NOS
8180/3 Combined hepatocellular carcinoma and cholangiocarcinoma
8240/3 Neuroendocrine tumour NOS
8240/3 Neuroendocrine tumour, grade 1
8249/3 Neuroendocrine tumour, grade 2
8249/3 Neuroendocrine tumour, grade 3
8246/3 Neuroendocrine carcinoma NOS
8013/3 Large cell neuroendocrine carcinoma
8041/3 Small cell neuroendocrine carcinoma
8154/3 Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)

These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2) (1378A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

This classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

WHO classification of tumours of the digestive system. 5th Edition 2019

Changes since previous WHO

- Hepatocellular adenoma subtypes:
  - HNF1A-inactivated
  - Inflammatory
  - Beta-catenin-activated
  - Beta-cateinin-activated inflammatory
- Hepatocellular carcinoma subtypes:
  - Steatohepatitic
  - Clear cell
  - Macrotrabecular/massive
  - Scirrhous
  - Chromophobe
  - Fibrolamellar
  - Neutrophil-rich
  - Lymphocyte-rich
- Benign biliary precursors (two-tiers grade system):
  - Biliary intraepithelial neoplasia, low grade
  - Biliary intraepithelial neoplasia, high grade
  - Intraductal papillary neoplasm with low-grade dysplasia
  - Intraductal papillary neoplasm with high-grade dysplasia
  - Mucinous cystic neoplasm with low-grade dysplasia
  - Mucinous cystic neoplasm with high-grade dysplasia
- Malignant biliary tumours
  - Cholangiocarcinoma: - large duct and small duct Icca
- Combined HCC and CCA (no subtypes)
- Classification of NETs

The diagnosis of a liver tumour is facilitated by 4 vital pieces of clinical and radiological information

- Age
- Solid vs cystic
- Single vs multicentric
- Underlying fibrotic chronic liver disease

Diagnostic clues from the clinical picture

- Age
- Sex
- Anamnestic data: contraceptive pills, drugs, dismetabolic disorders, hematologic diseases.
- Biological markers: viral serology, oncofetal markers (AFP, CEA).

Case scenario:

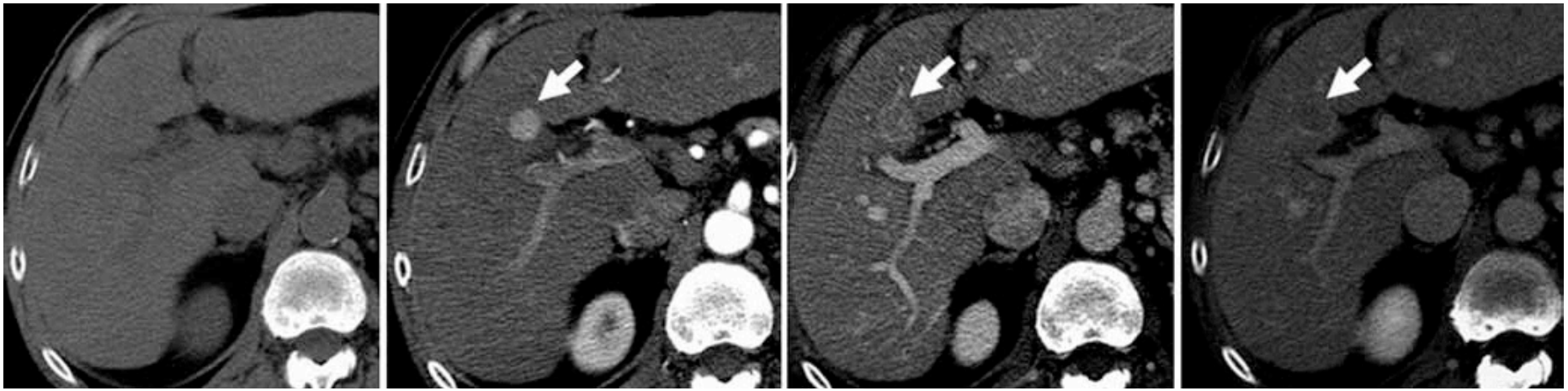
- A young woman taking contraceptive pills who presents with acute abdominal haemorrhage is most likely to have a hepatocellular adenoma
- The presence of underlying chronic liver disease, especially when there is advanced fibrosis or cirrhosis, represents high odds for the presence of HCC

Age < 2 years
Infantile haemangioma
Mesenchymal hamartoma
Hepatoblastoma
Hepatic malignant rhabdoid tumour
Rhabdomyosarcoma
Age > 2 years
Focal Nodular Hyperplasia
Hepatocellular adenoma
Fibrolamellar carcinoma
Hepatocellular carcinoma
Transitional liver cell tumour
Calcifying nested epithelial stromal tumour
Undifferentiated embryonal sarcoma

Diagnostic clues from the radiological information

- Solid vs cystic
- Single vs multicentric
- Imaging pattern and its variation during follow-up
- Underlying fibrotic chronic liver disease

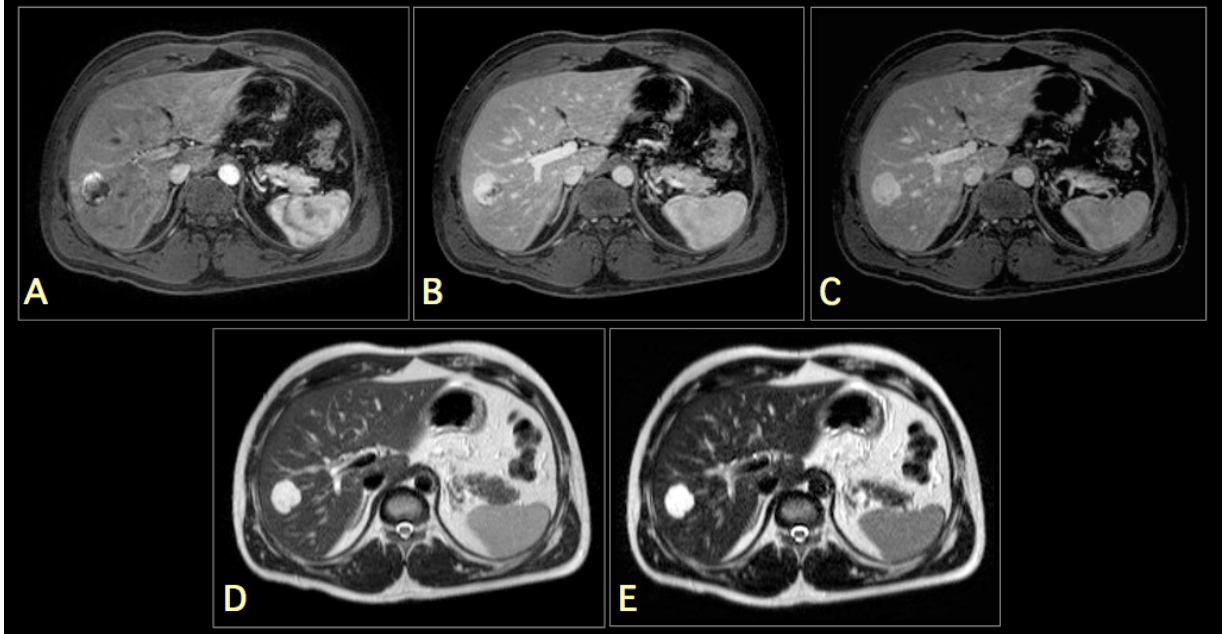
HCC at contrast-enhanced spiral CT



Baseline | Arterial phase | Venous phase | Delayed phase

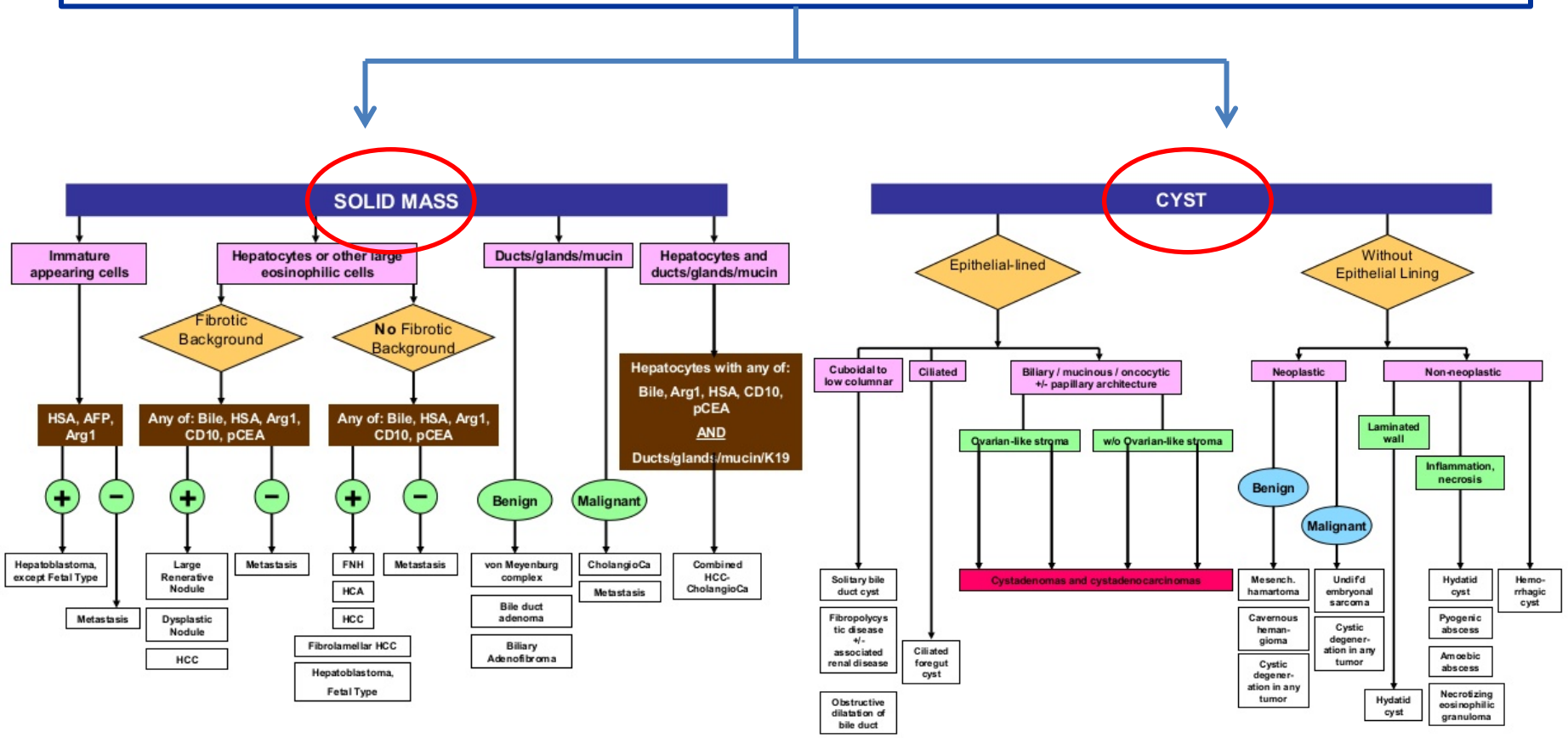
The HCC lesion in segment IV is barely visible at baseline scan (A), shows clear-cut enhancement in the arterial phase (B, arrow) and rapid wash-out in the portal venous (C, arrow) and delayed phases (D, arrow).

Hepatic Cavernous Hemangioma

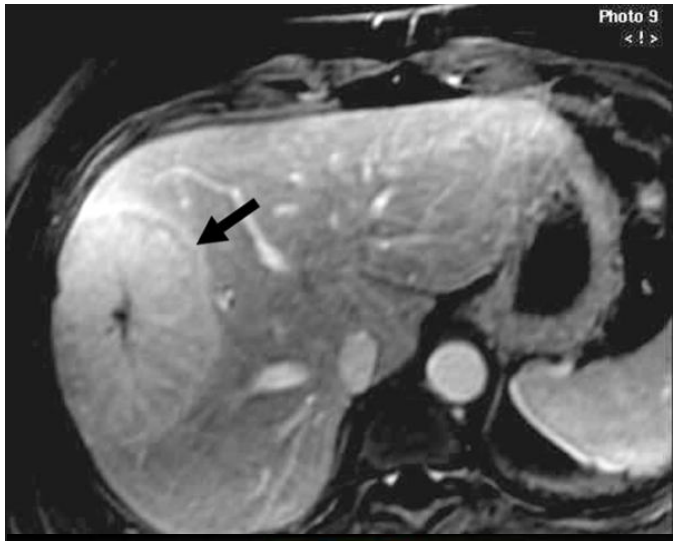


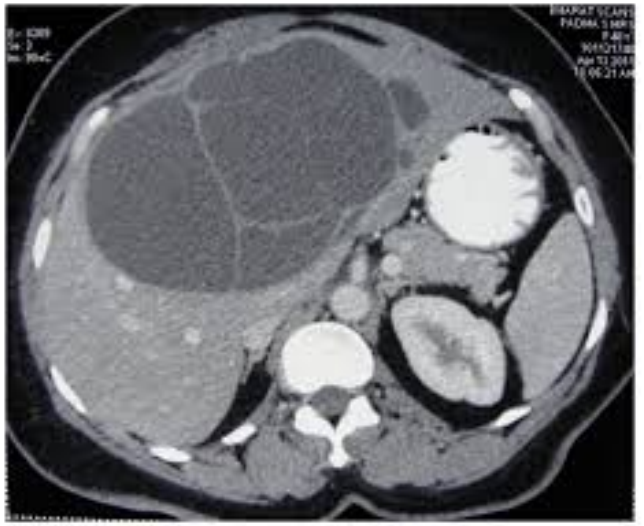
CE 3D FS T1W GRE in arterial (A), venous (B) and delayed phases (C) demonstrate characteristic peripheral pooling or puddling enhancement with centripetal fill in over time. This pattern is pathognomonic for benign cavernous hemangioma. T2W images show the lesion to be as bright as CSF at both echo times, 80 msec (D) and 140 msec (E). This excludes the possibility of hepatoma which may be hyperintense on less heavily T2W images of TE=80 msec.

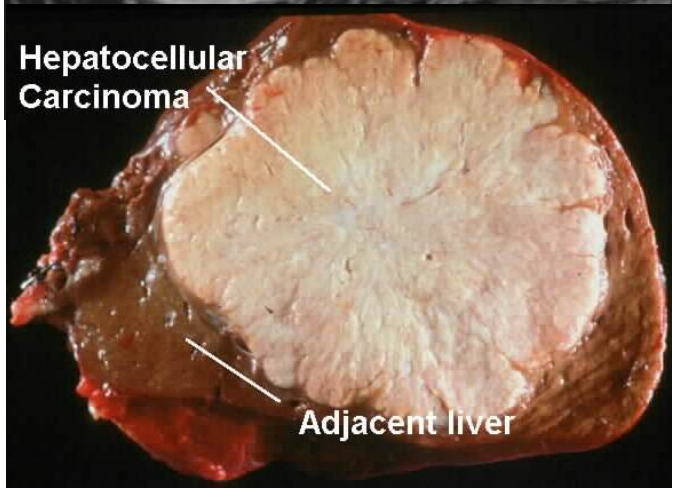
Diagnostic algorithm of liver lesions

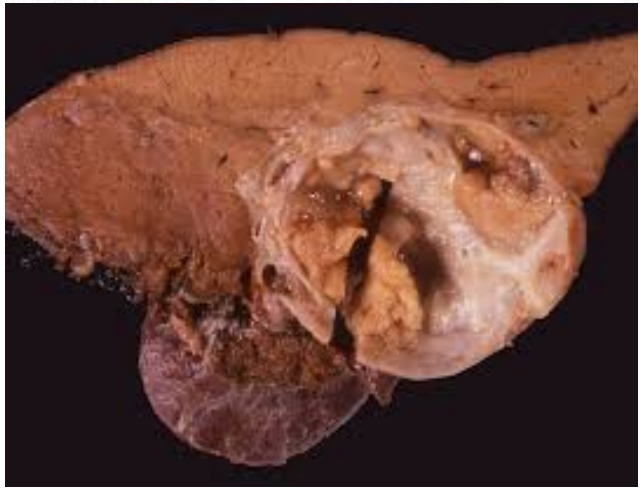


First step – Diagnostic algorithm
Gross appearance

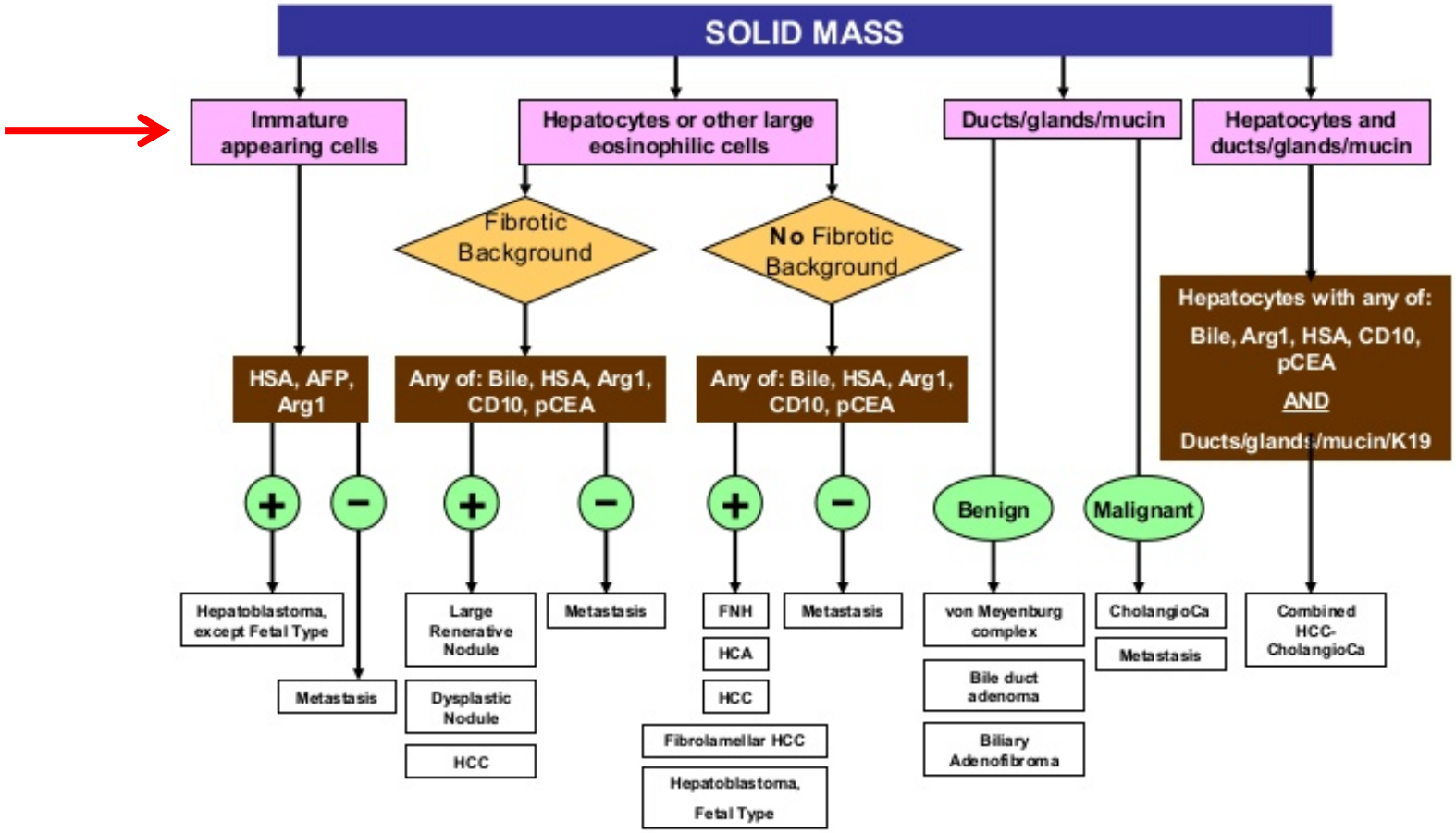


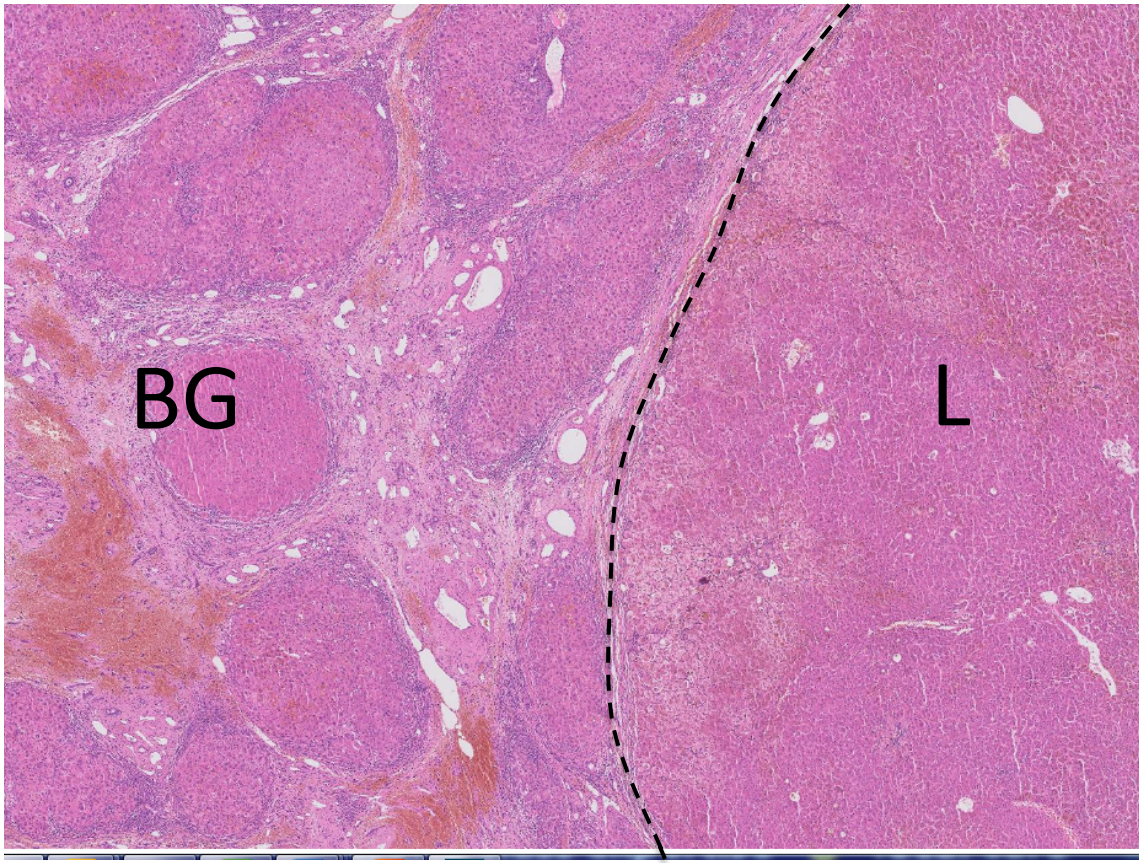




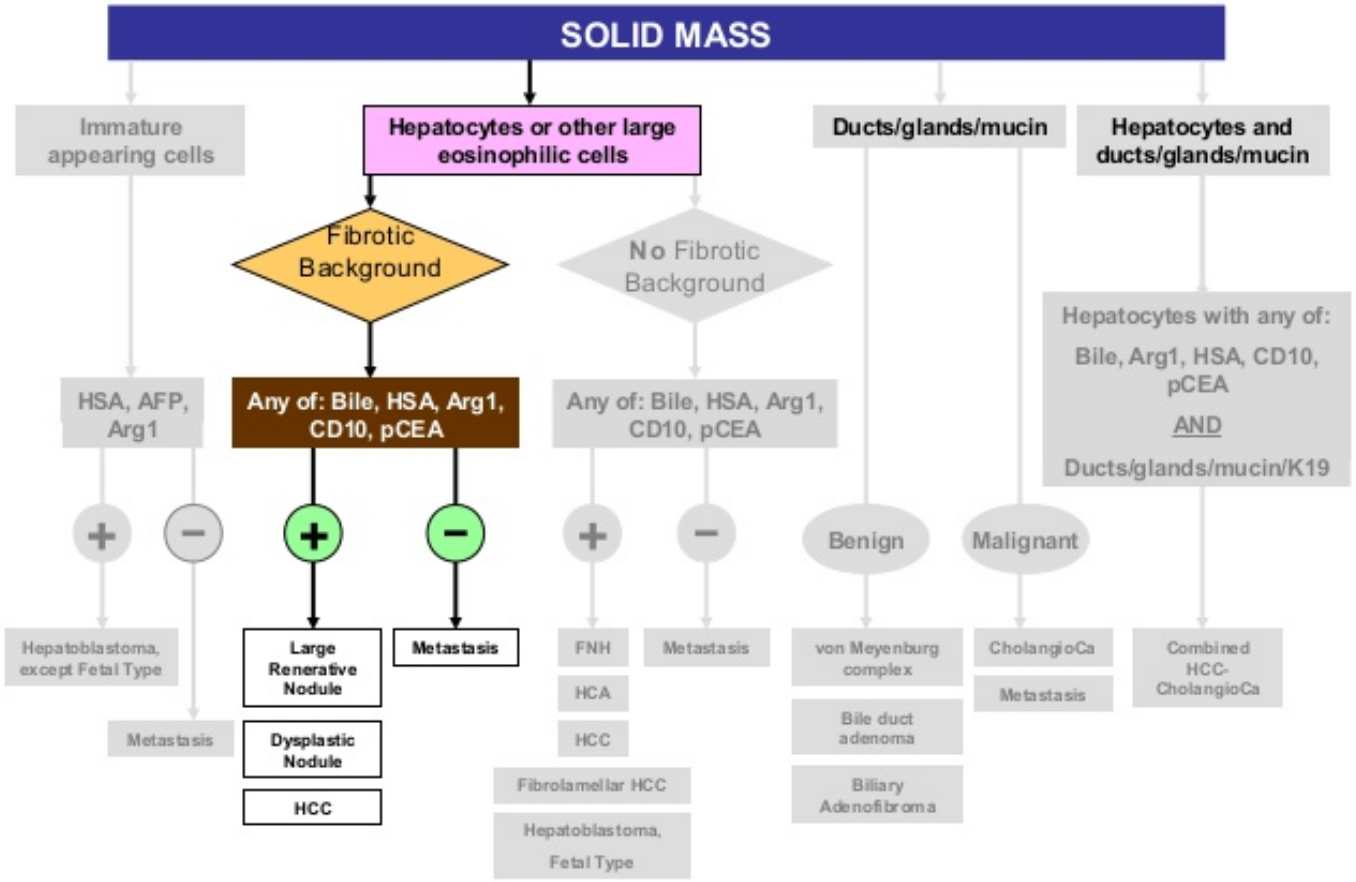


Diagnostic algorithm of liver lesions with solid mass

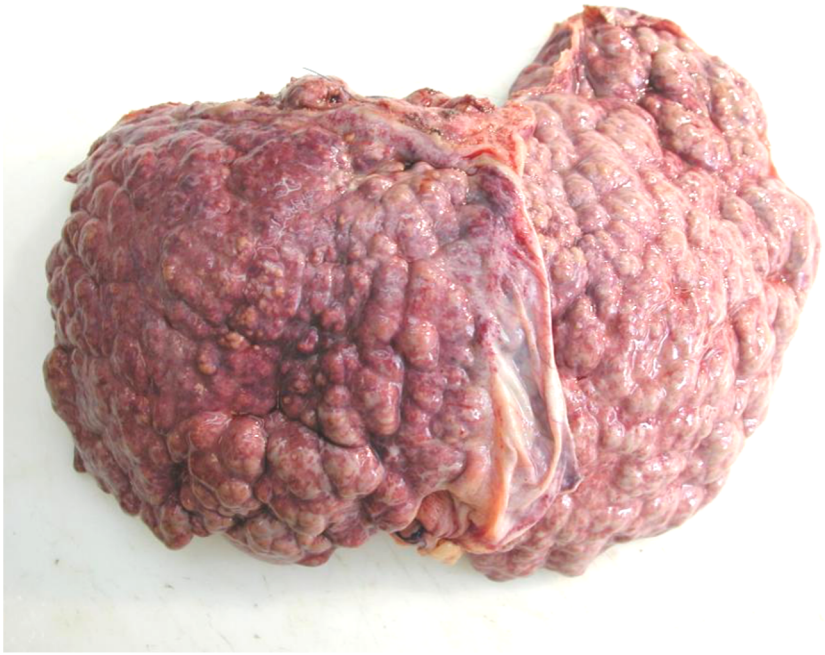



BG
L

Diagnostic algorithm of liver lesions with solid mass



Solid lesions in fibrotic background



- Macroregenerative nodule
- Dysplastic nodule
- Hepatocellular carcinoma

Key diagnostic features: architectural elementary lesions

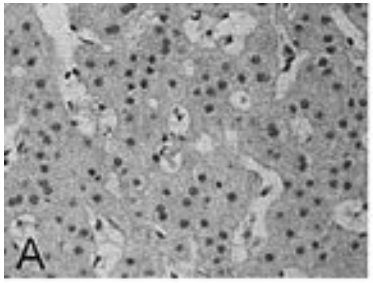
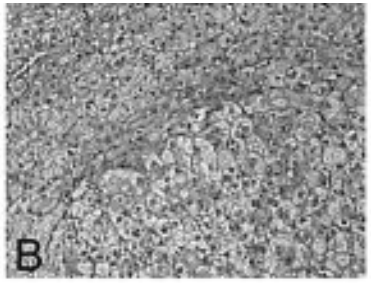
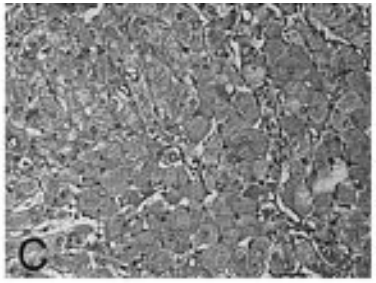


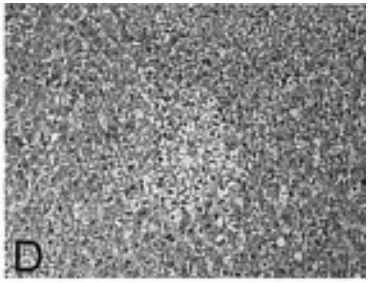
Plate thickening



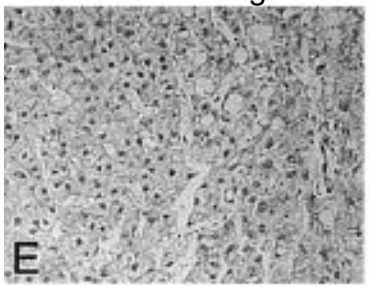
Clonal growth: bulging



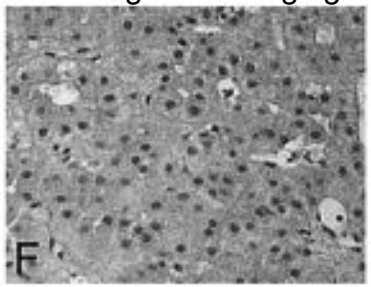
Clonal growth: map-like



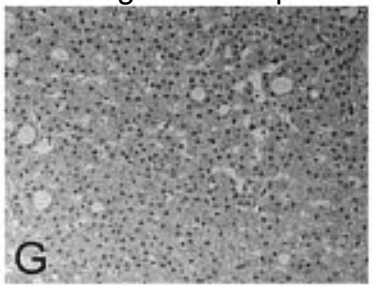
Clear cell type



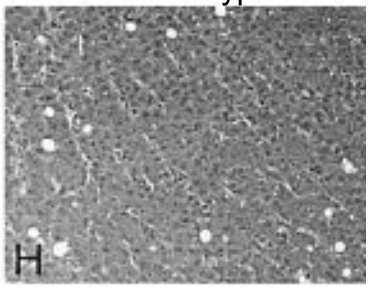
Iron-free type



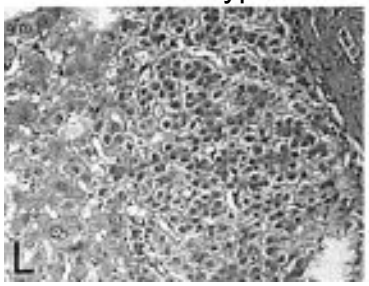
Small cell change



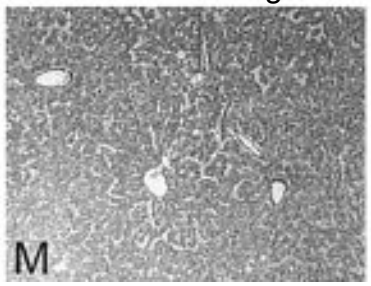
Pseudoglands



Sinusoidal nuclear alignment



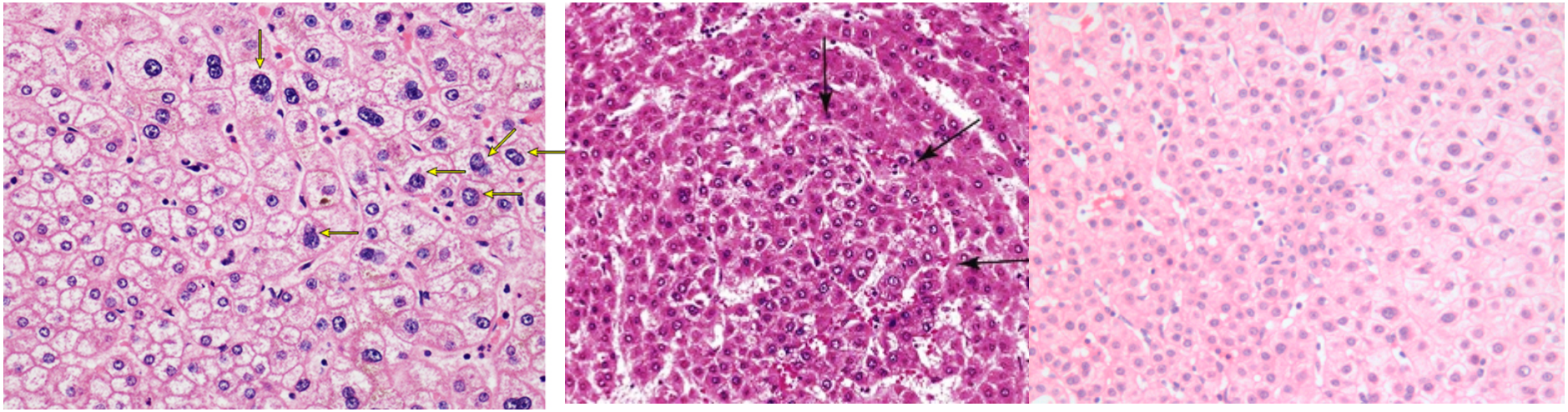
Nuclear crowding



Non accompanied arteries

Liver Transplantation Volume 10, Issue S2, pages S9-S15, 30 JAN 2004 DOI: 10.1002/lt.20047
http://onlinelibrary.wiley.com/doi/10.1002/lt.20047/full#fig1

Key diagnostic features: cytological elementary lesions

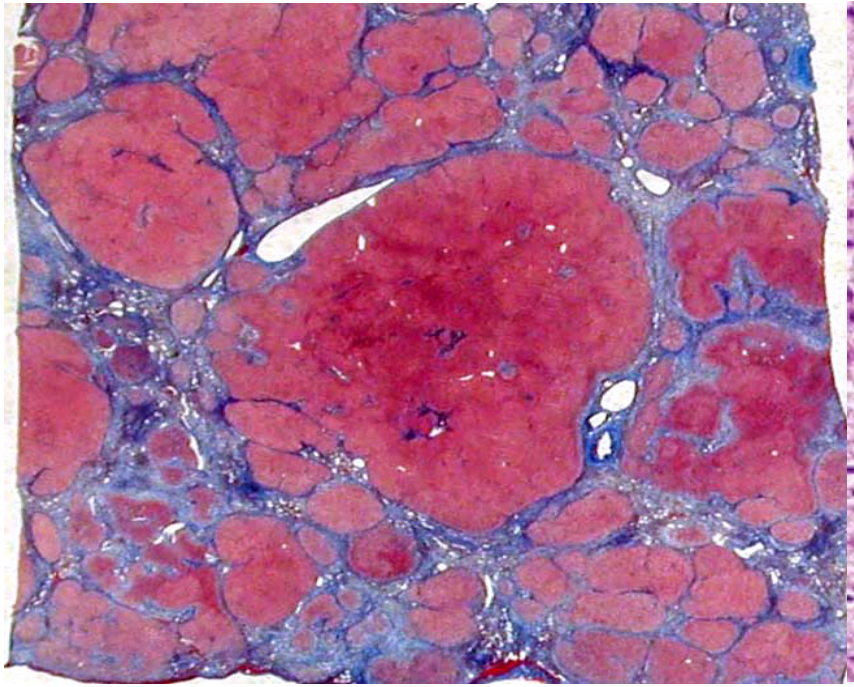


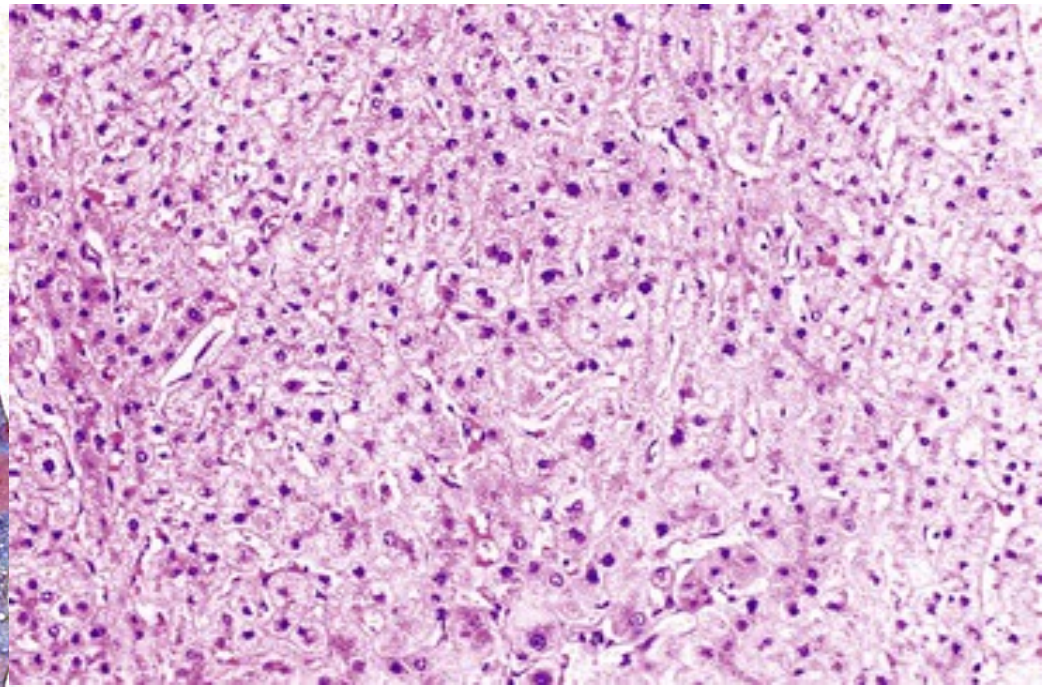
Large cell change
(preserved N/C ratio)

Small cell change
(increased N/C ratio)

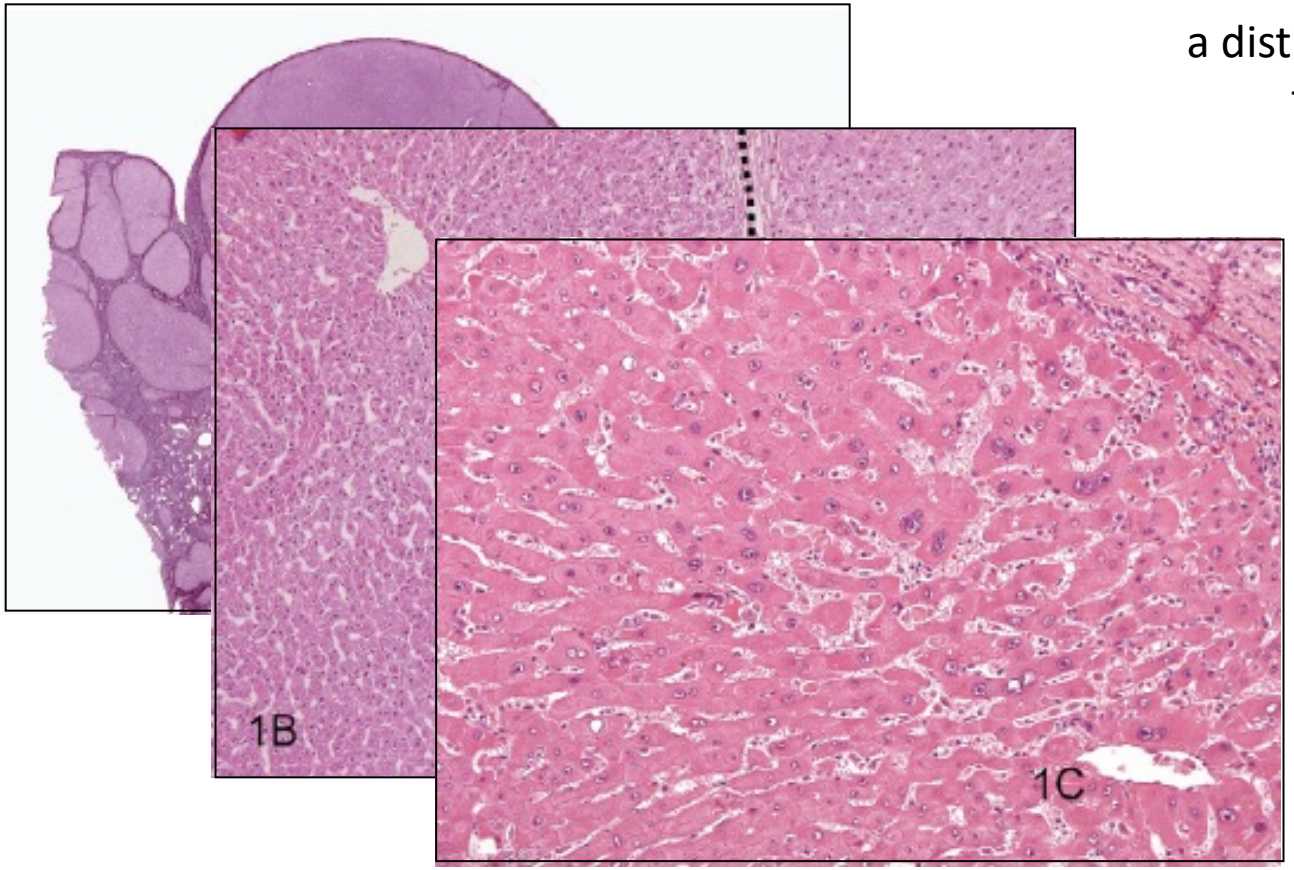
Liver Transplantation Volume 10, Issue S2, pages S9-S15, 30 JAN 2004 DOI: 10.1002/lt.20047
http://onlinelibrary.wiley.com/doi/10.1002/lt.20047/full#fig2

Macroregenerative nodule





Low grade dysplastic nodule (LGDN)

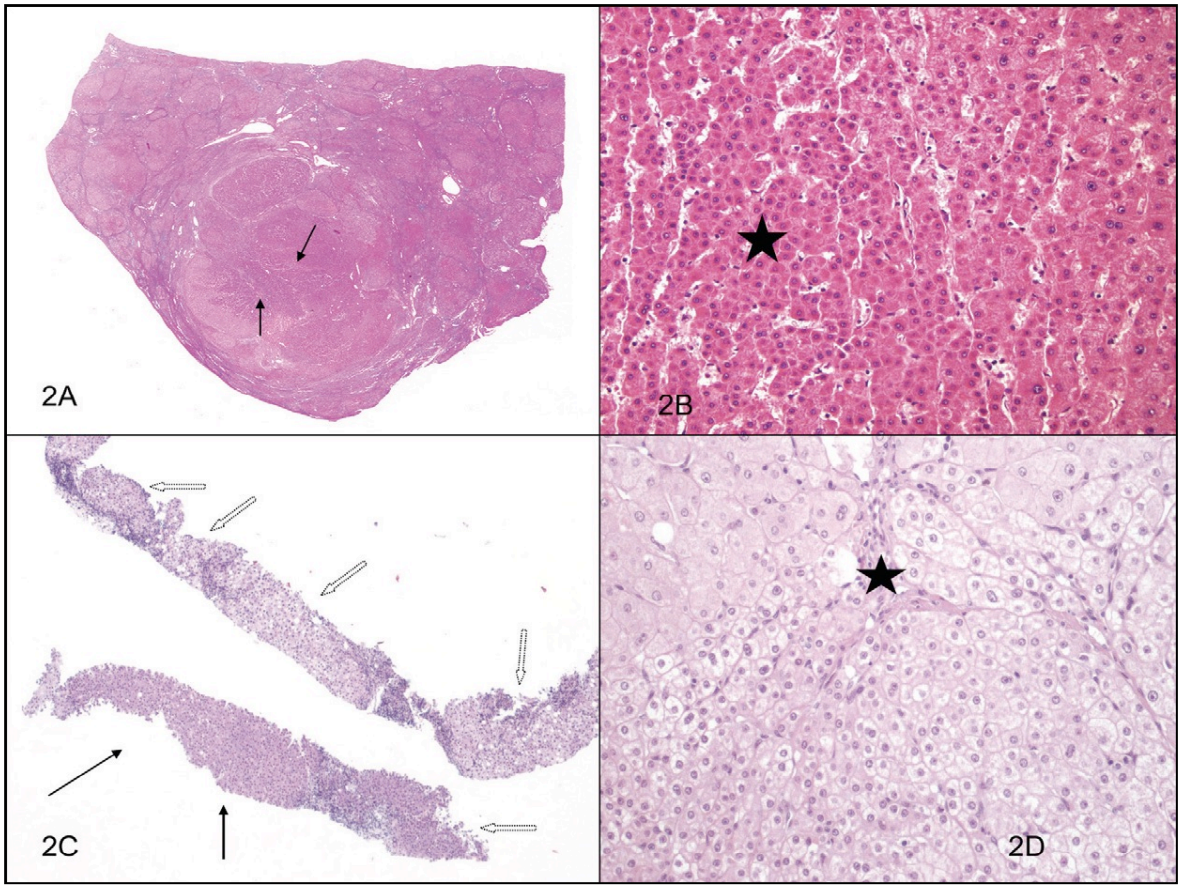


a distinctly nodular lesion that differs from the surrounding liver parenchyma

Normal cytology or
Large cell change only
No architectural atypia

Digestive and Liver Disease 43S (2011) S361–S372

High grade dysplastic nodule (HGDN)



- **Cytologic atypia**

e.g. small cell change

- **Architectural atypia**

e.g. plate thickening, nuclear crowding, pseudogland formation

- **Clone-like domains**

e.g. fatty or clear cell change, iron resistance etc.

- **Nodule-in-nodule expansile growth**

Digestive and Liver Disease 43S (2011) S361–S372

Nomenclature of small (< 2 cm) hepatocellular lesions (international consensus 2009)

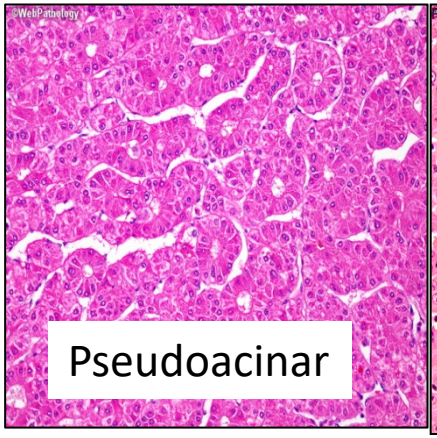
Dysplastic foci (only seen under microscope)
Microscopic features: cluster of hepatocytes, <1 mm, characterized by small (SCC) or large cell (LCC) changes.

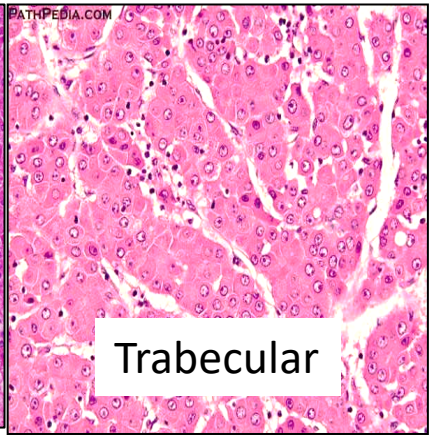
Dysplastic nodule
Gross features: a distinctly nodular lesion that differs from the surrounding liver parenchyma with regard to size, colour, texture and degree of bulging of the cut surface.
Microscopic features: distinguished into two categories:
1. low grade (LGDN): a (clonal) cell population lacking architectural atypia with mild increase in cellularity as compared to surroundings; portal tracts detectable within;
2. high grade (HGDN): frank cytological and architectural atypia as compared to surroundings but insufficient for a diagnosis of malignancy; portal tracts detectable within.

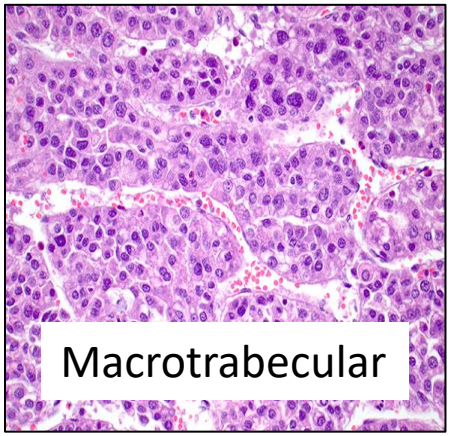
Small HCC (<2cm)
According to gross and microscopic features it is differentiated into:
1. early HCC: a vaguely nodular lesion with indistinct margins with a well differentiated histology which may require careful distinction from HGDN; a few portal tracts detectable within;
2. progressed HCC: a distinctly nodular lesion with well (G1) to moderately (G2) differentiated histology in which malignancy is recognized at first glance; no portal tracts detectable within.

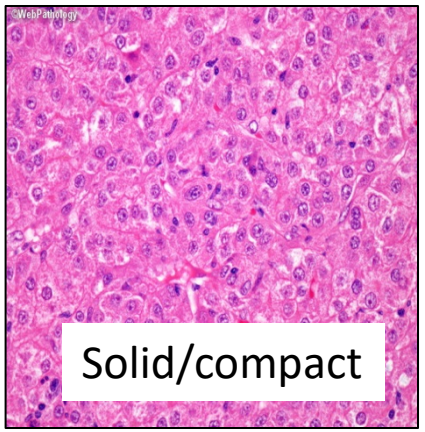
M. Roncalli et al. / Digestive and Liver Disease 43S (2011) S361–S372

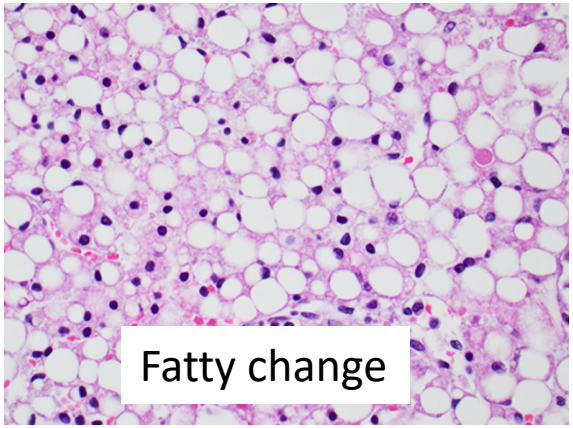
HCC

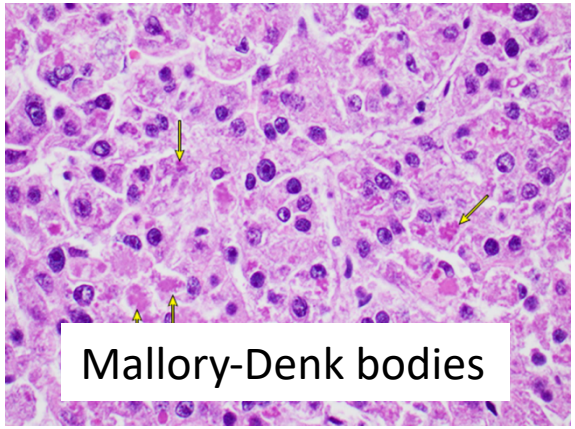

Pseudoacinar

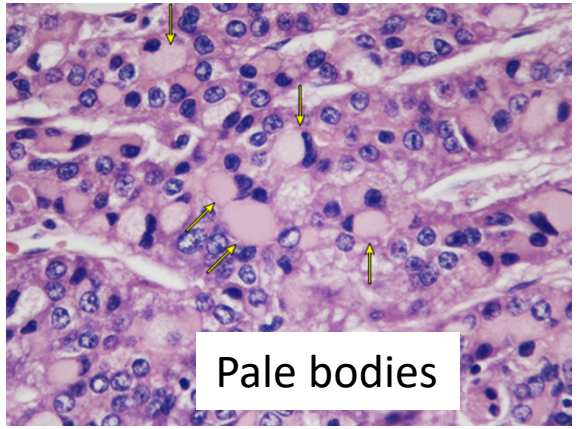

PATHPEDIA.COM
Trabecular


Macrotrabecular

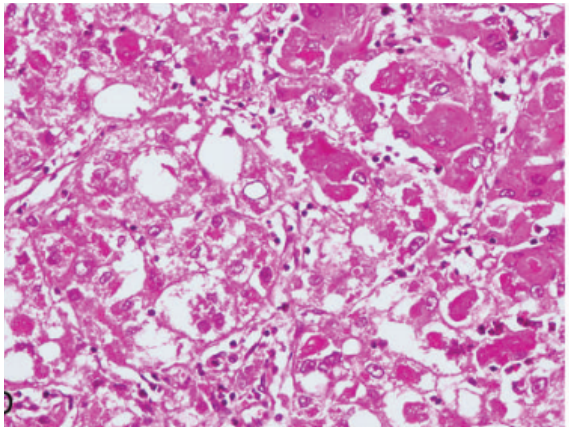

Solid/compact

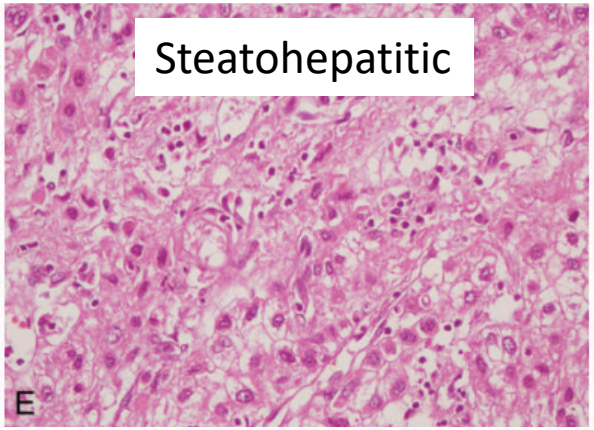

Fatty change

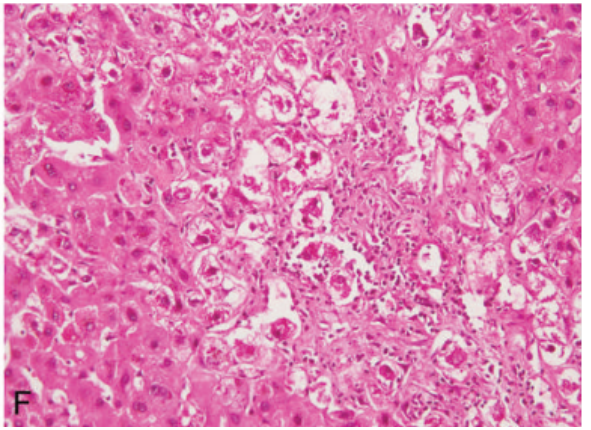

Mallory-Denk bodies

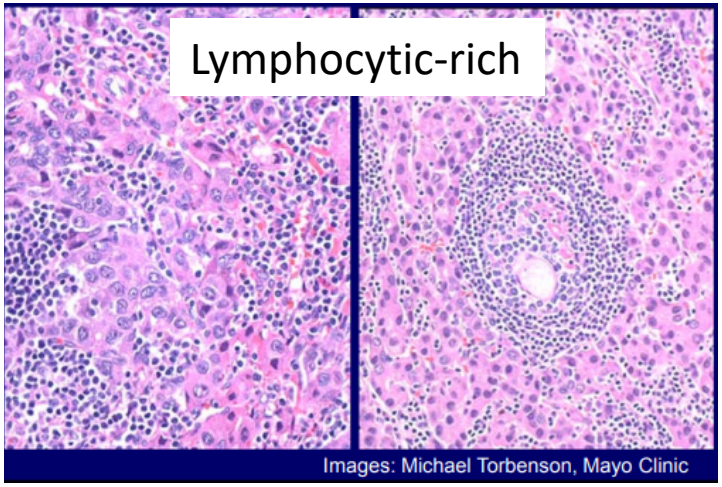

Pale bodies

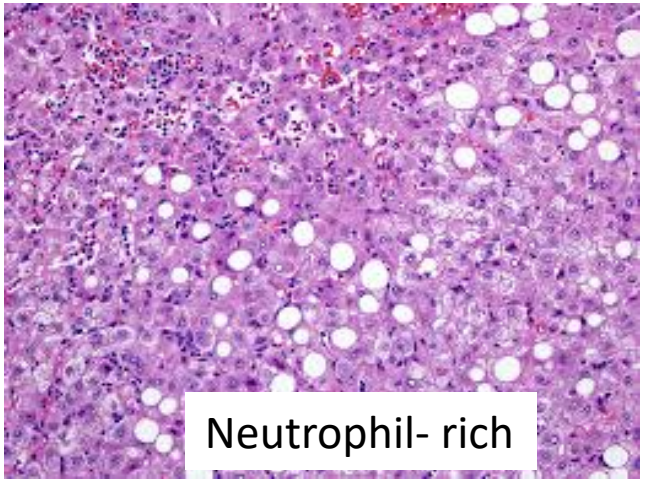
HCC – Subtypes



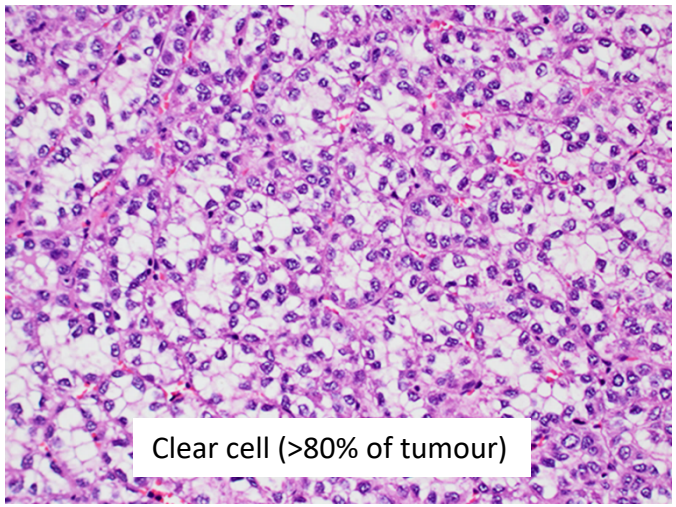




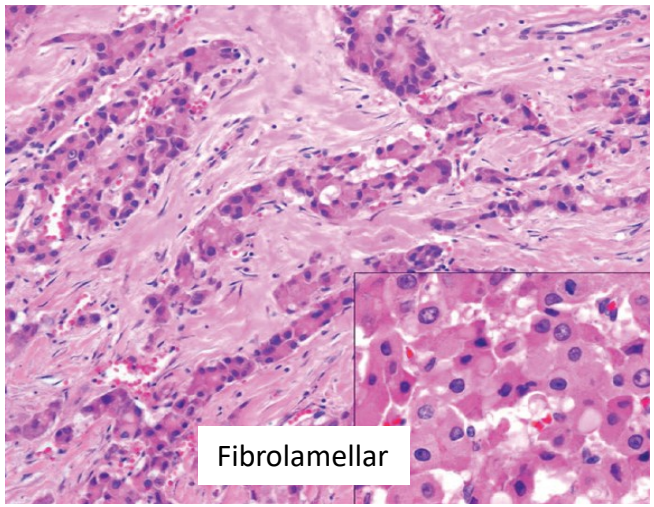




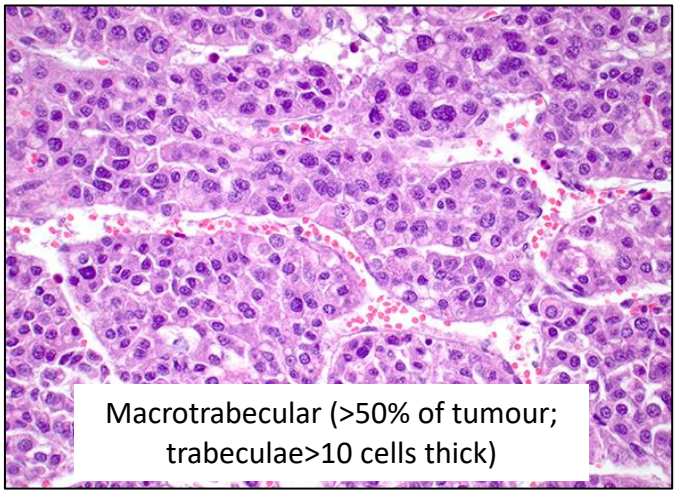
HCC – Subtypes



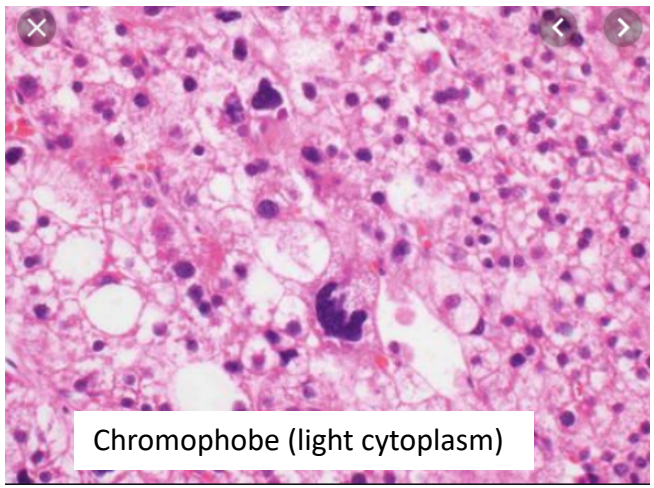
Clear cell (>80% of tumour)



Fibrolamellar



Macrotrabecular (>50% of tumour; trabeculae>10 cells thick)



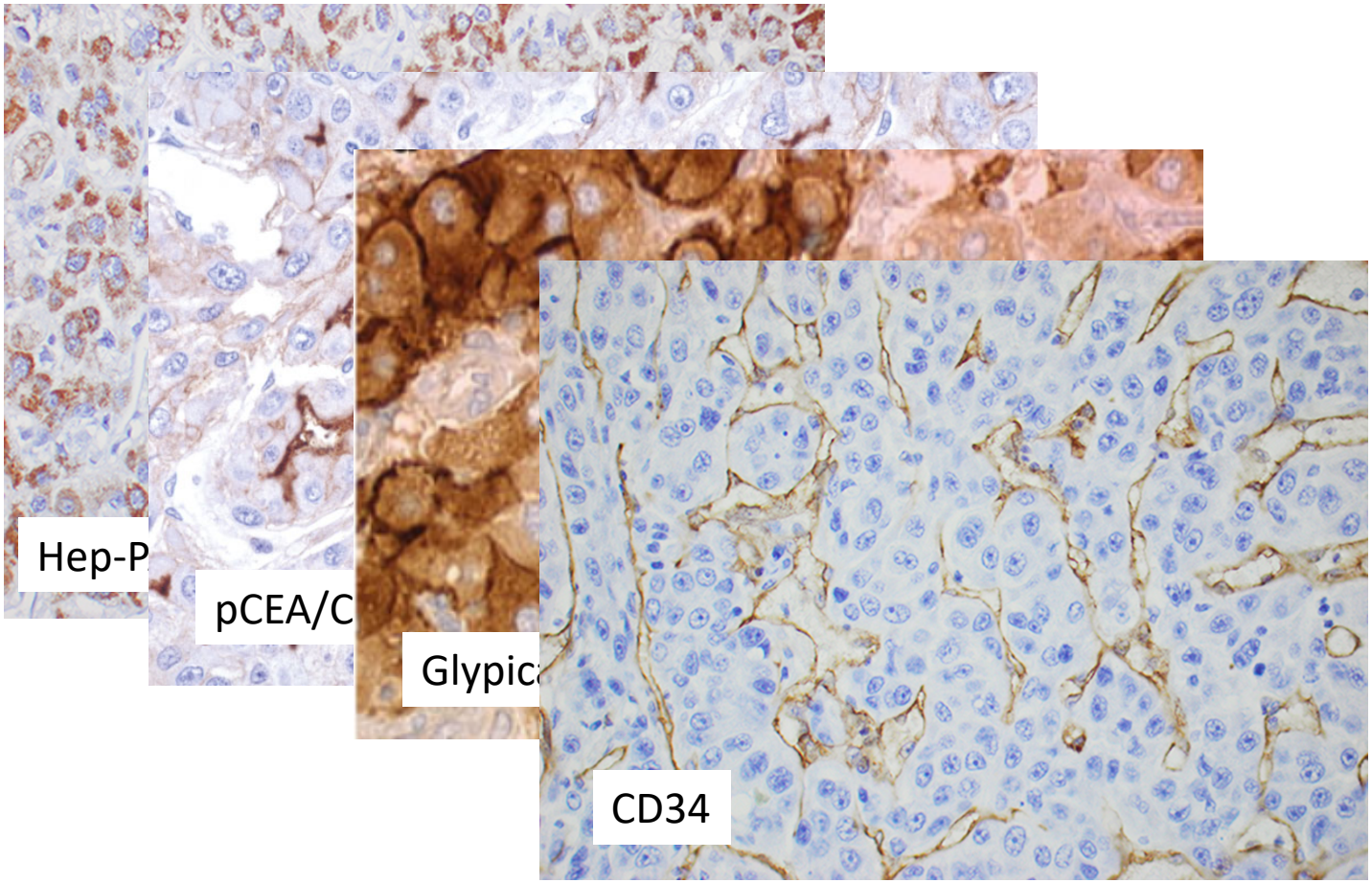
Chromophobe (light cytoplasm)

Tumour grading

Three-point grading system:

- Well-
- Moderately-
- Poorly-differentiated

HCC - Immunohistochemistry



Sensitivity of commonly used hepatocellular markers

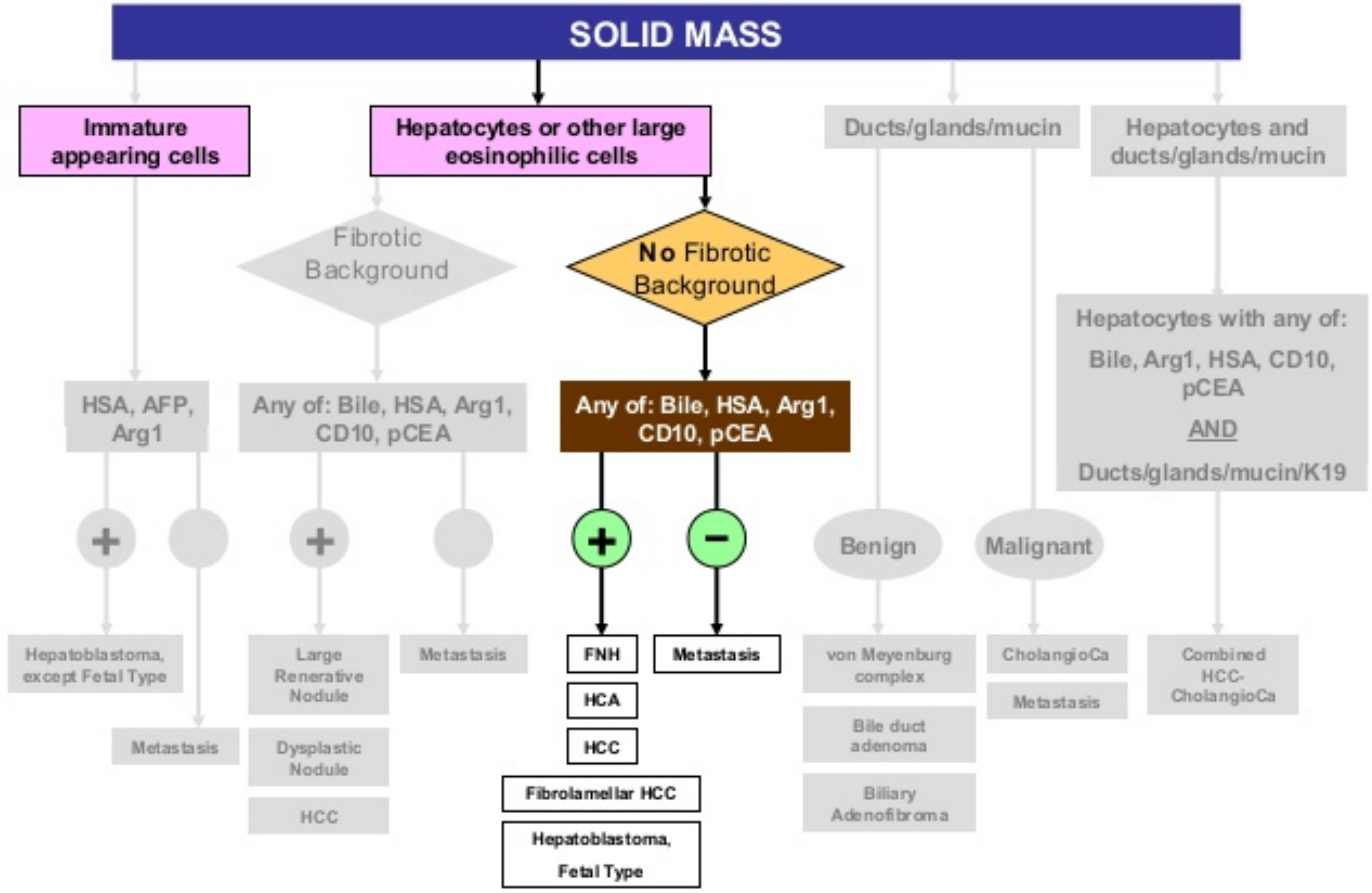
	WELL-DIFF	MODERATELY-DIFF	POORLY-DIFF
Hep-PAR1	100%	98%	63%
pCEA/CD10	92%	88%	60%
Glypican-3	62%	83%	86%
Arginase-1	100%	100%	97%

Philips/Kakar, Arch Path Lab Med 2015

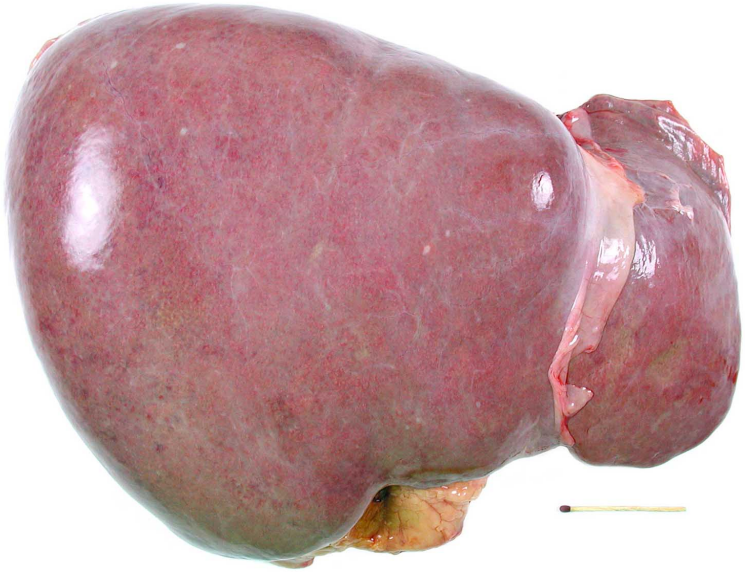
TNM staging of HCC

	UICC/AJCC 7th	UICC/AJCC 8th
T1	Solitary tumour without vascular invasion	**T1a** Solitary tumour 5 cm or less in greatest dimension without vascular invasion **T1b** Solitary tumour >5cm without vascular invasion
T2	Solitary tumour with vascular invasion or multiple tumours, none >5cm	Solitary tumour with intrahepatic vascular invasion or multiple tumours, with or without vascular invasion
T3	Multiple tumours any >5cm or tumour involving a major branch of portl or hepatic veins T3a Multiple tumours any >5cm T3b Tumour involving a major branch of portl or hepatic veins	Tumour perforating the visceral peritoneum
T4	Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	Tumour involving local extrahepatic structures by direct hepatic invasion
N1	Regional LN mets	Regional LN mets (histological examination of 6 or more lymph nodes)
M1	Distant metastasis	Distant metastasis

Diagnostic algorithm of liver lesions with solid mass



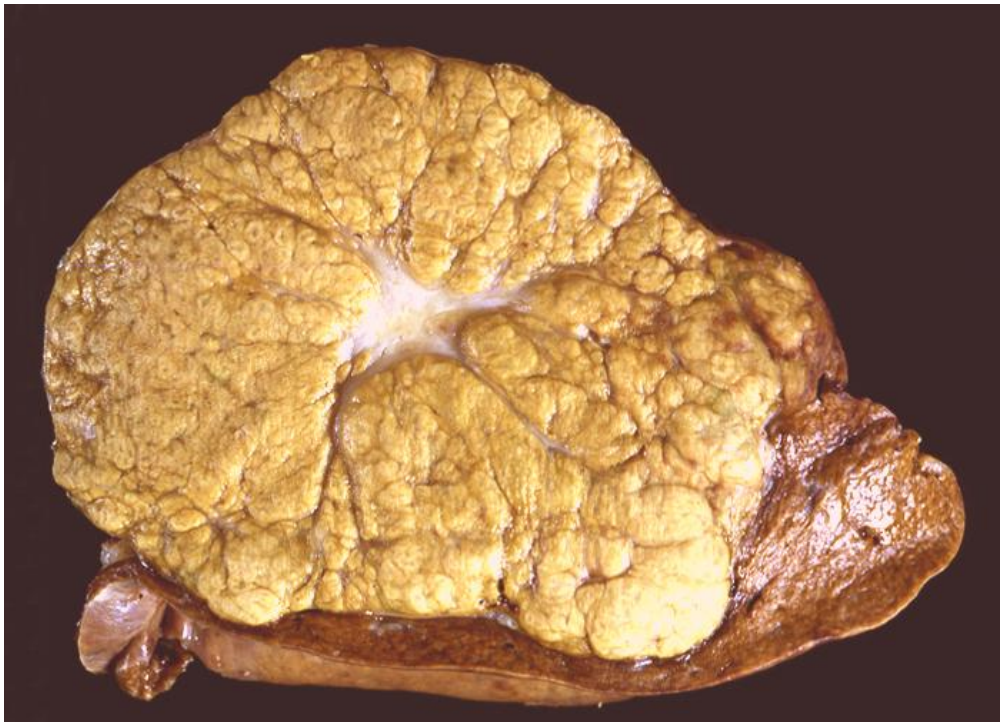
Solid lesions in non-fibrotic background



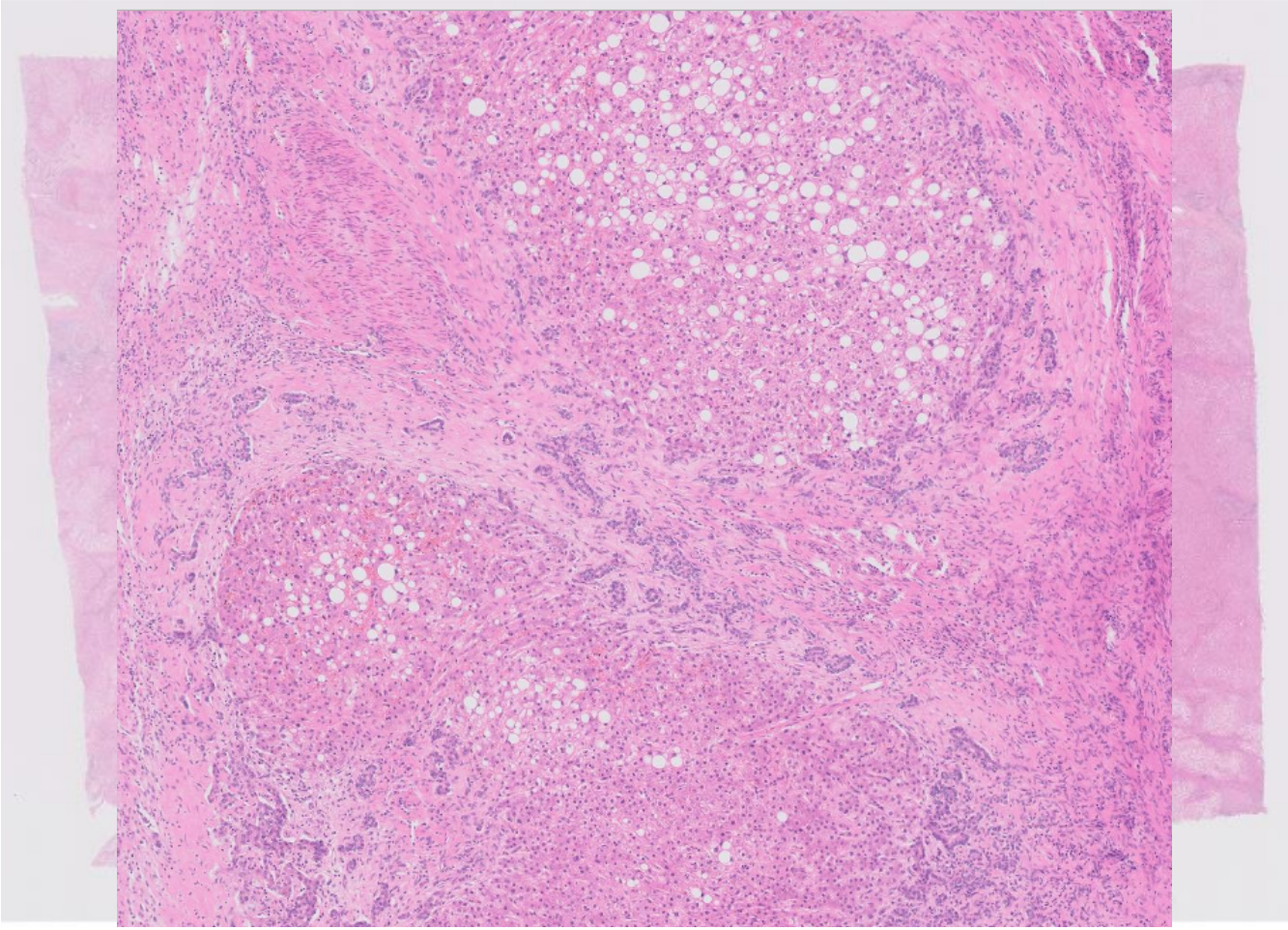
- Focal nodular hyperplasia (FNH)
- Hepatocellular adenoma (HCA)
- Hepatocellular carcinoma (HCC)
- Fibrolamellar carcinoma
- Hepatoblastoma
  Fetal type

CASE

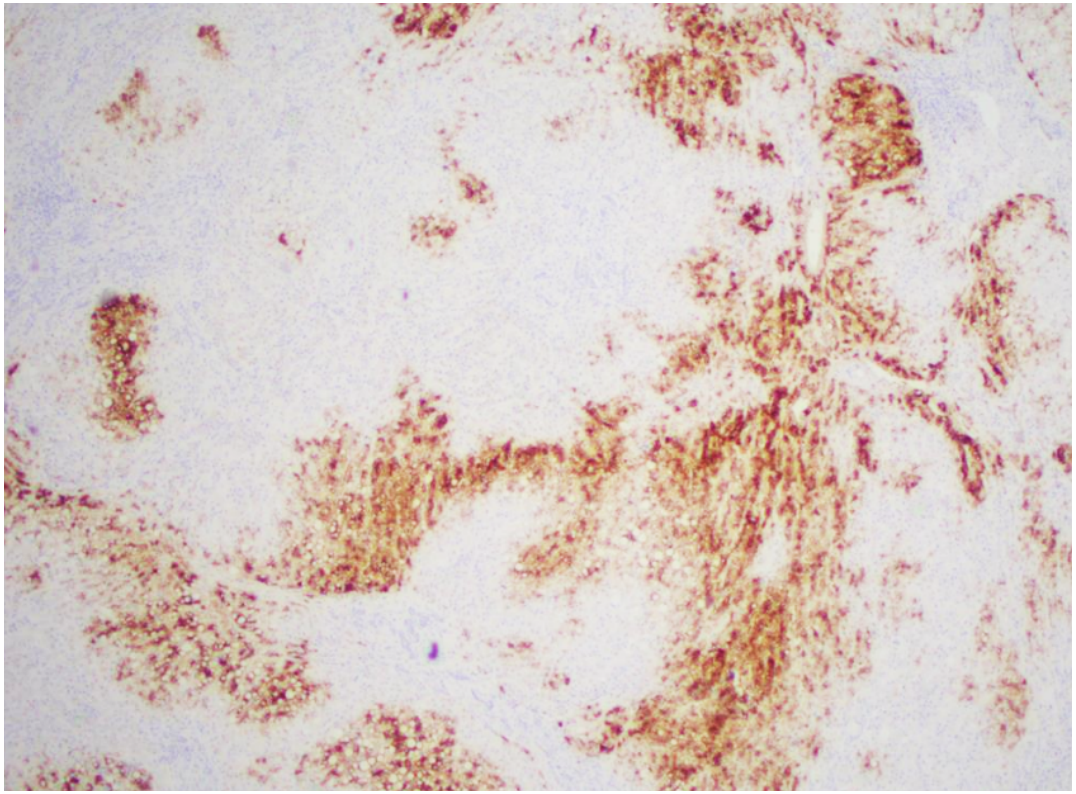
- **Specimen type**: Right hepatectomy
- **Clinical details**: 35 year old lady with a liver lesion.
- **Macroscopic description**: Non cirrhotic liver with a circumscribed, cream coloured and lobulated nodule, measuring 46 x 35 x 52 mm. A central scar is noted.



Histology

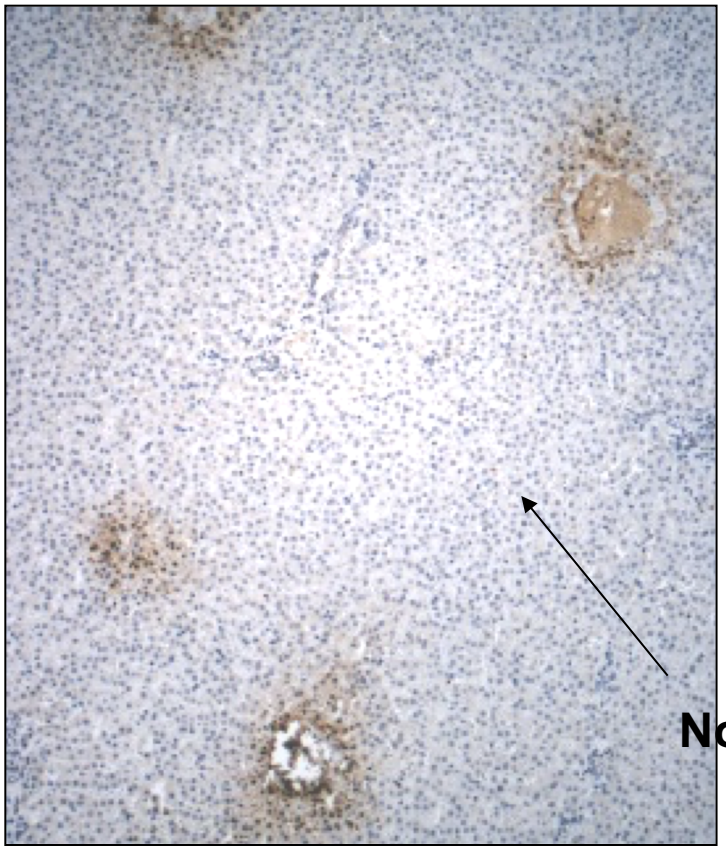


Immuno for GS

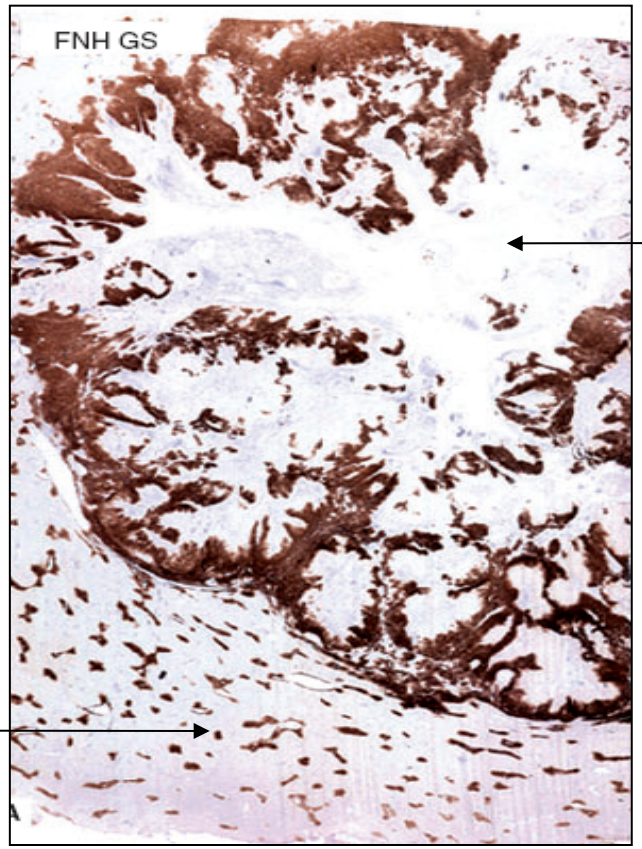


Glutamine synthetase

Glutamate + ATP + NH3 → Glutamine + ADP + phosphate



Normal



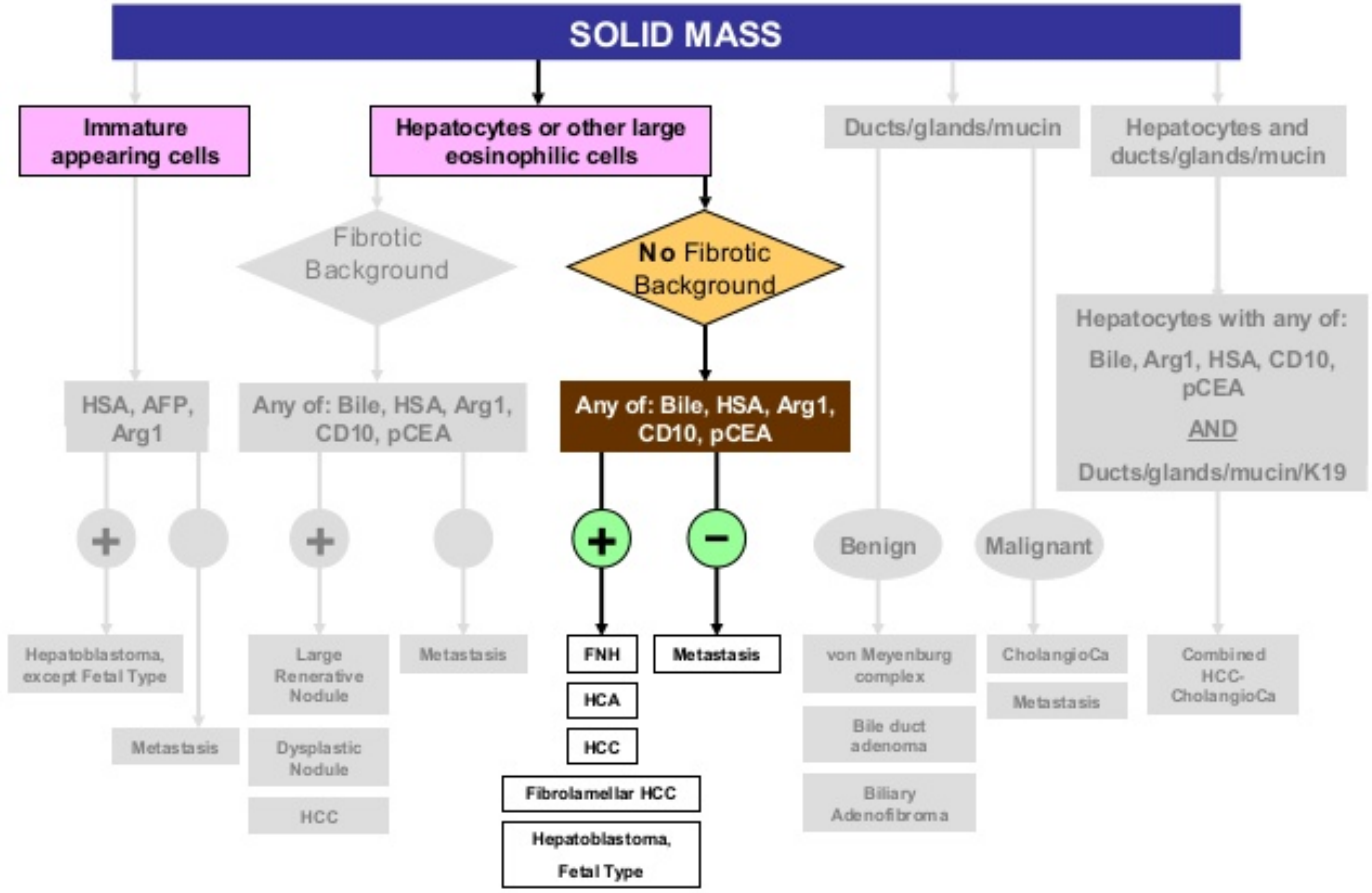
FNH

Histopathology 2013, 62, 431-445. DOI: 10.1111/his.12011

Diagnosis

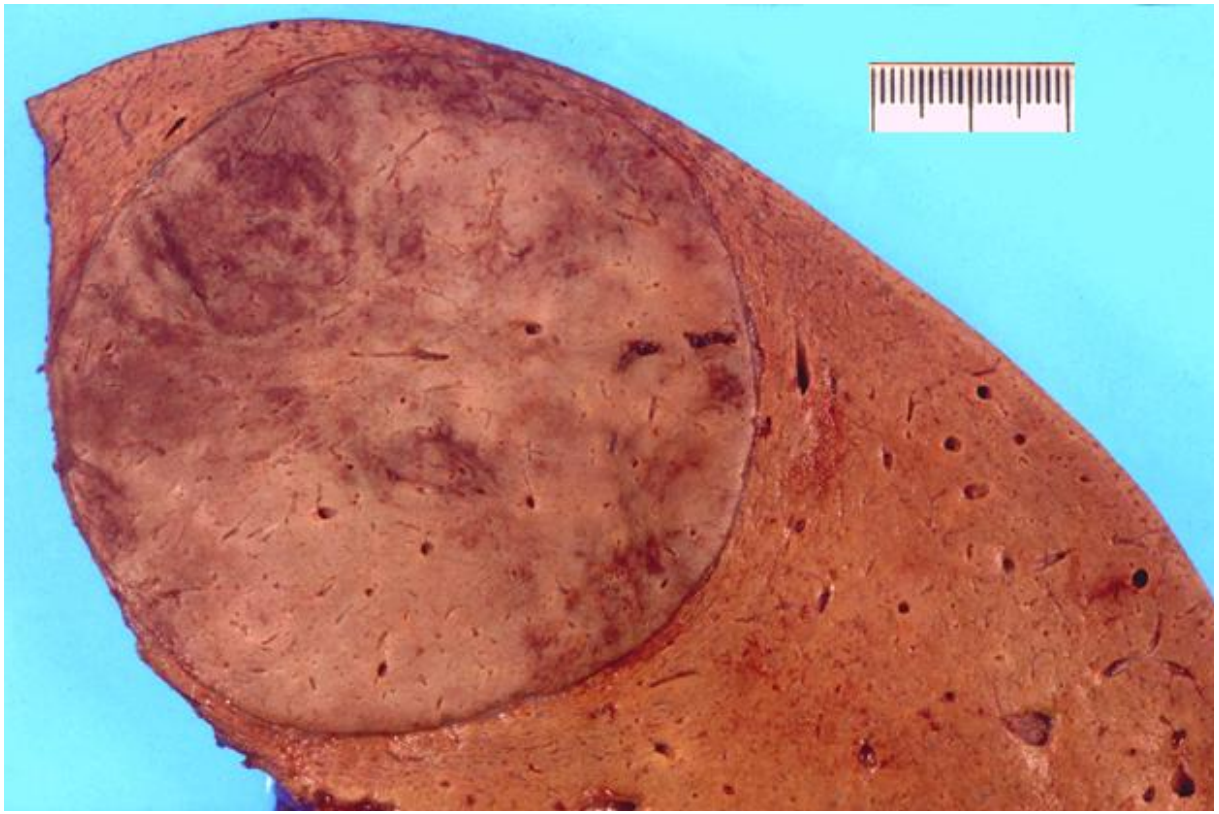
Focal Nodular Hyperplasia (FNH)

Diagnostic algorithm of liver lesions with solid mass

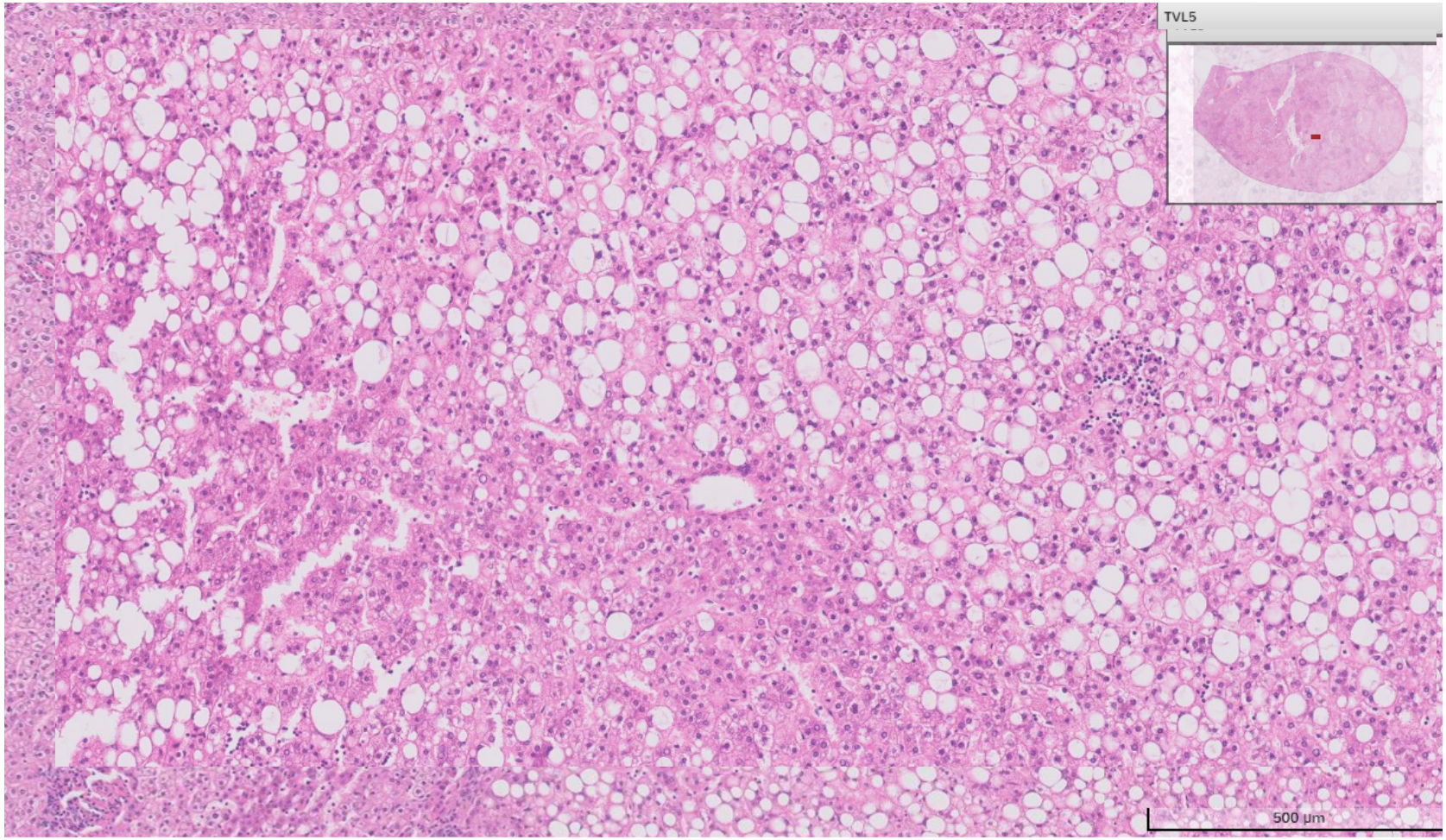


CASE - Macroscopic

- **Specimen type**: Segment 5 liver resection
- **Clinical details**: 30 year old lady with an incidental finding of and isolated, undefined, liver lesion. AFP normal.
- **Macroscopic description**: Non cirrhotic liver with a circumscribed, pale tan coloured nodule, measuring 15 x 13 x 15 mm.



Histology



HCA: Heterogenous entity subclassified into 3 groups according to genotype and phenotype

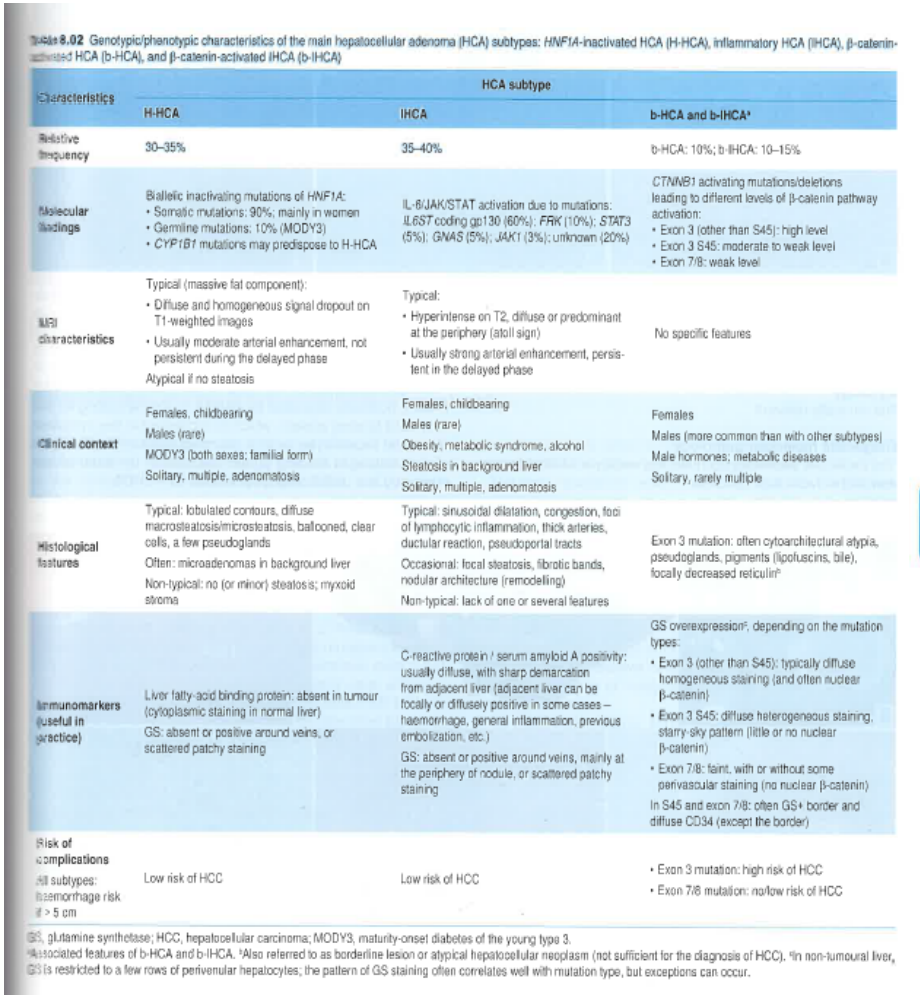


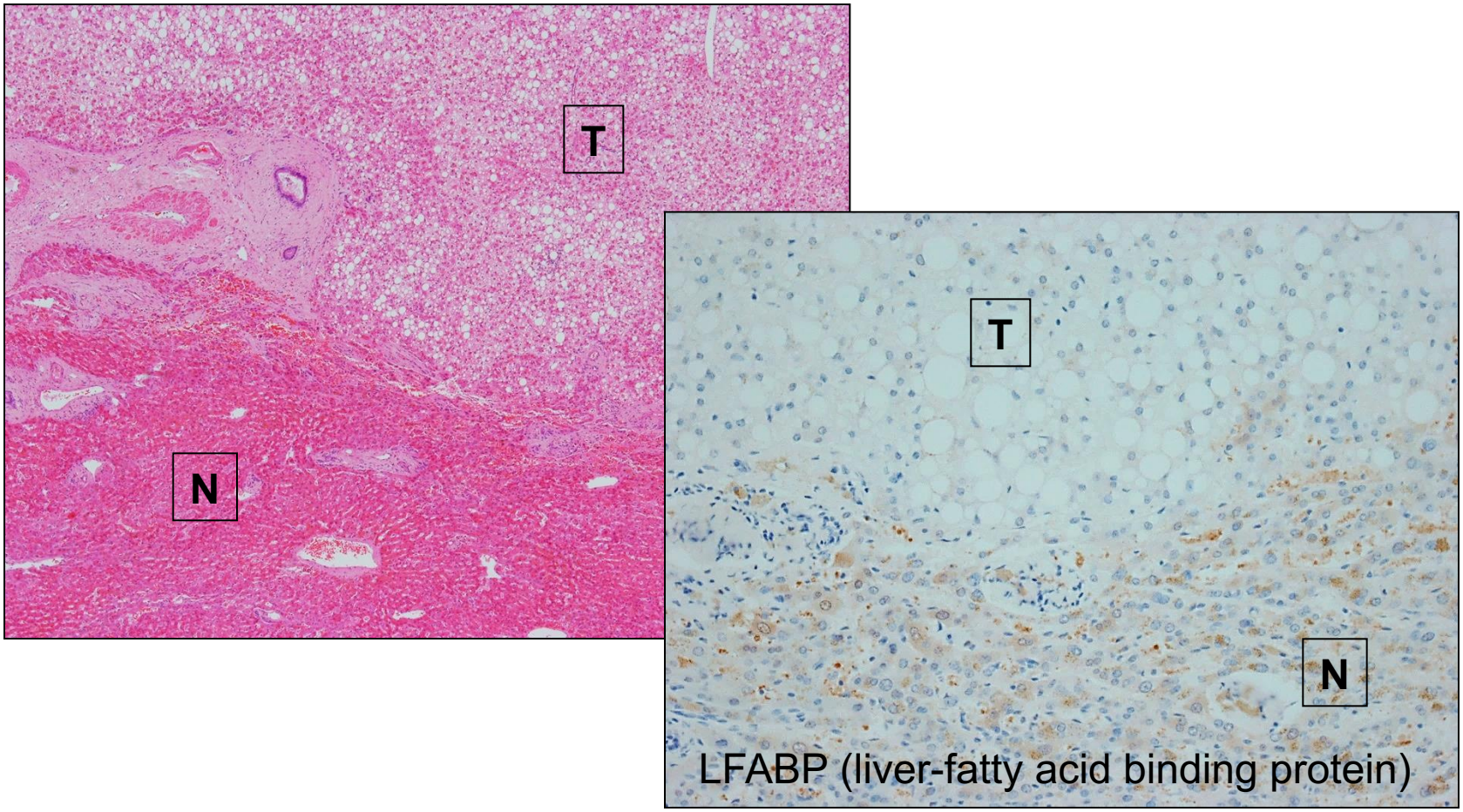
Table 8.02 Genotypic/phenotypic characteristics of the main hepatocellular adenoma (HCA) subtypes: *HNF1A*-inactivated HCA (H-HCA), inflammatory HCA (IHCA), β-catenin-activated HCA (b-HCA), and β-catenin-activated IHCA (b-IHCA)

Characteristics	HCA subtype		
	H-HCA	IHCA	b-HCA and b-IHCA[a]
Relative frequency	30–35%	35–40%	b-HCA: 10%; b-IHCA: 10–15%
Molecular findings	Biallelic inactivating mutations of *HNF1A*: • Somatic mutations: 90%; mainly in women • Germline mutations: 10% (MODY3) • *CYP1B1* mutations may predispose to H-HCA	IL-6/JAK/STAT activation due to mutations: *IL6ST* coding gp130 (60%); *FRK* (10%); *STAT3* (5%); *GNAS* (5%); *JAK1* (3%); unknown (20%)	*CTNNB1* activating mutations/deletions leading to different levels of β-catenin pathway activation: • Exon 3 (other than S45): high level • Exon 3 S45: moderate to weak level • Exon 7/8: weak level
MRI characteristics	Typical (massive fat component): • Diffuse and homogeneous signal dropout on T1-weighted images • Usually moderate arterial enhancement, not persistent during the delayed phase Atypical if no steatosis	Typical: • Hyperintense on T2, diffuse or predominant at the periphery (atoll sign) • Usually strong arterial enhancement, persistent in the delayed phase	No specific features
Clinical context	Females, childbearing Males (rare) MODY3 (both sexes; familial form) Solitary, multiple, adenomatosis	Females, childbearing Males (rare) Obesity, metabolic syndrome, alcohol Steatosis in background liver Solitary, multiple, adenomatosis	Females Males (more common than with other subtypes) Male hormones; metabolic diseases Solitary, rarely multiple
Histological features	Typical: lobulated contours, diffuse macrosteatosis/microsteatosis, ballooned, clear cells, a few pseudoglands Often: microadenomas in background liver Non-typical: no (or minor) steatosis; myxoid stroma	Typical: sinusoidal dilatation, congestion, foci of lymphocytic inflammation, thick arteries, ductular reaction, pseudoportal tracts Occasional: focal steatosis, fibrotic bands, nodular architecture (remodelling) Non-typical: lack of one or several features	Exon 3 mutation: often cytoarchitectural atypia, pseudoglands, pigments (lipofuscins, bile), focally decreased reticulin[b]
Immunomarkers (useful in practice)	Liver fatty-acid binding protein: absent in tumour (cytoplasmic staining in normal liver) GS: absent or positive around veins, or scattered patchy staining	C-reactive protein / serum amyloid A positivity: usually diffuse, with sharp demarcation from adjacent liver (adjacent liver can be focally or diffusely positive in some cases – haemorrhage, general inflammation, previous embolization, etc.) GS: absent or positive around veins, mainly at the periphery of nodule, or scattered patchy staining	GS overexpression[c], depending on the mutation types: • Exon 3 (other than S45): typically diffuse homogeneous staining (and often nuclear β-catenin) • Exon 3 S45: diffuse heterogeneous staining, starry-sky pattern (little or no nuclear β-catenin) • Exon 7/8: faint, with or without some perivascular staining (no nuclear β-catenin) In S45 and exon 7/8: often GS+ border and diffuse CD34 (except the border)
Risk of complications All subtypes: haemorrhage risk if > 5 cm	Low risk of HCC	Low risk of HCC	• Exon 3 mutation: high risk of HCC • Exon 7/8 mutation: no/low risk of HCC

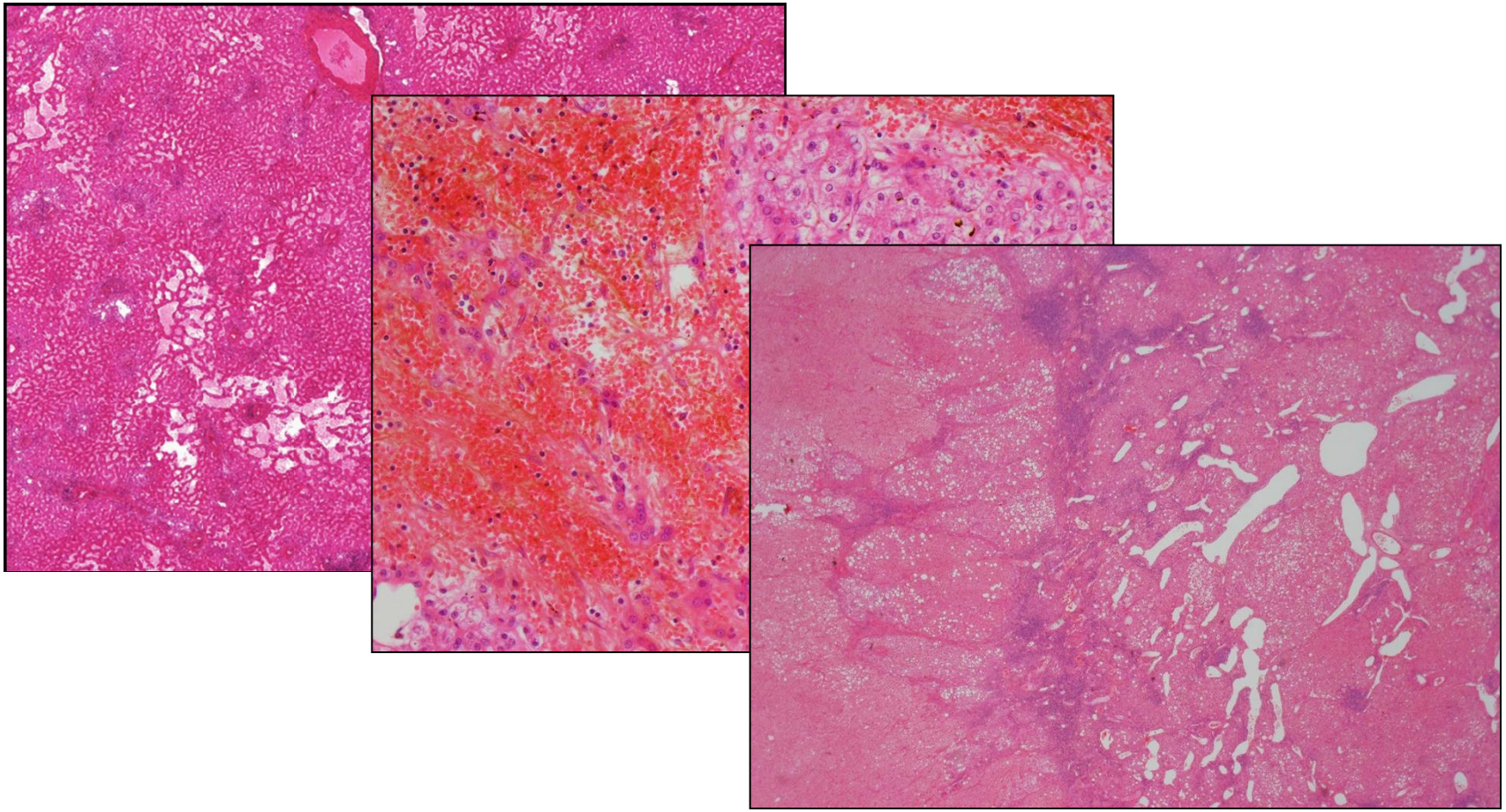
GS, glutamine synthetase; HCC, hepatocellular carcinoma; MODY3, maturity-onset diabetes of the young type 3.
[a]Associated features of b-HCA and b-IHCA. [b]Also referred to as borderline lesion or atypical hepatocellular neoplasm (not sufficient for the diagnosis of HCC). [c]In non-tumoural liver, GS is restricted to a few rows of perivenular hepatocytes; the pattern of GS staining often correlates well with mutation type, but exceptions can occur.

WHO classification of tumours of the digestive system. 5th Edition 2019

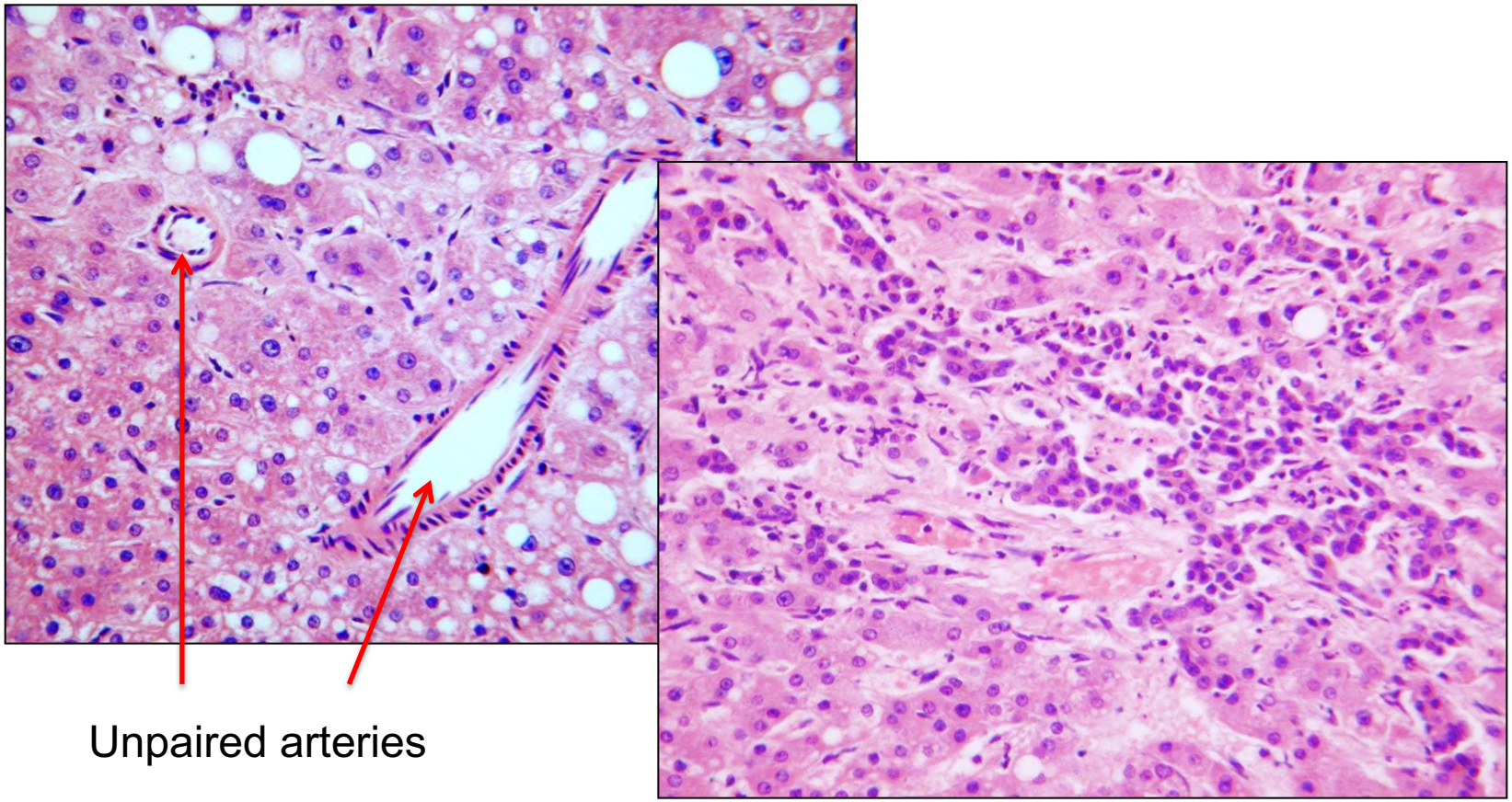
Diagnosis: HNF-1a inactivated Hepatocellular Adenoma (30-35%)



Inflammatory type Hepatocellular Adenoma (35-40%)

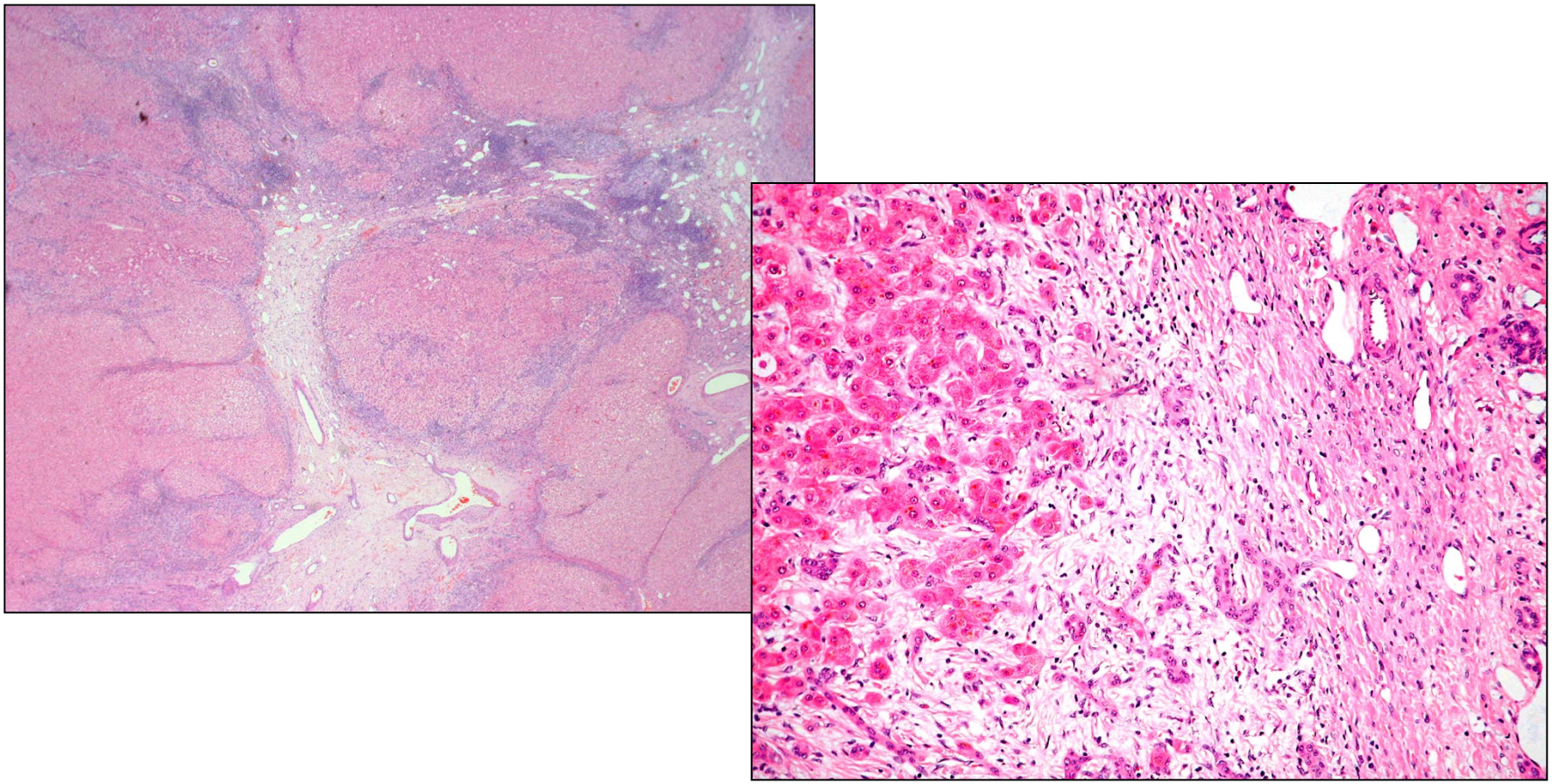


Inflammatory type Hepatocellular Adenoma

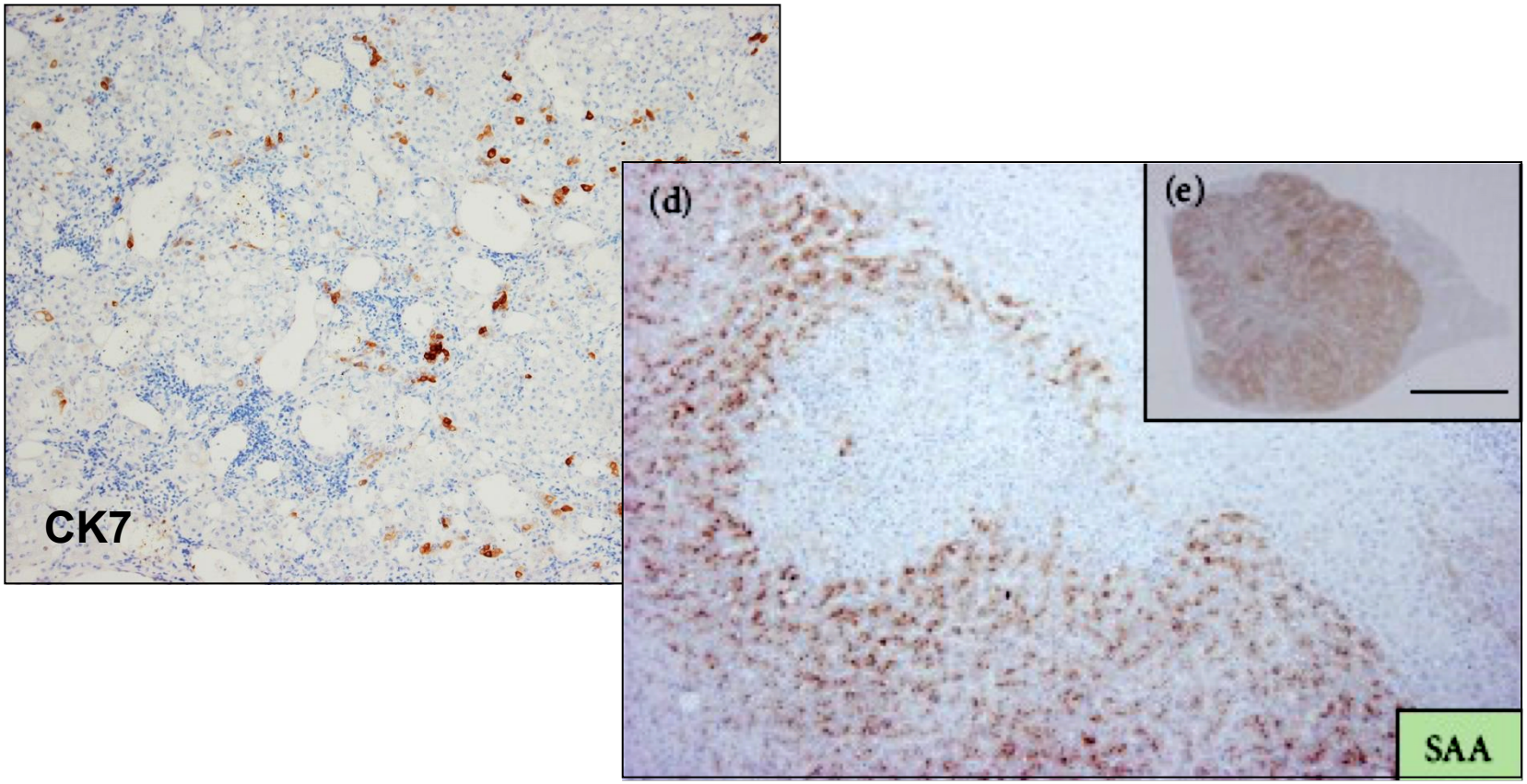


Unpaired arteries

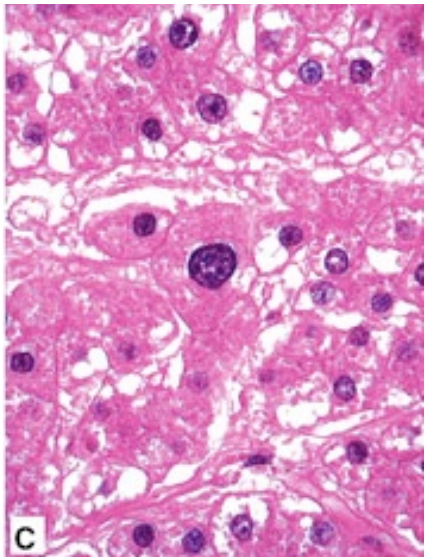
FOCAL NODULAR HYPERPLASIA



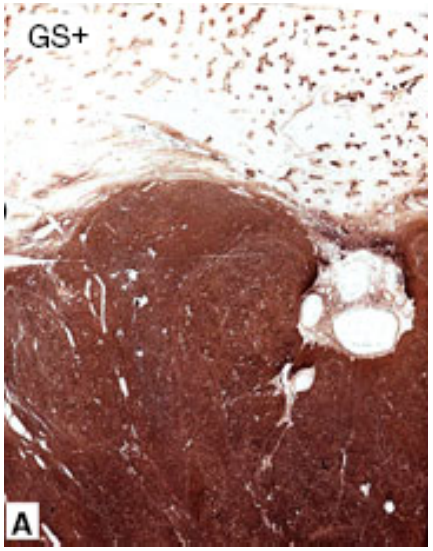
Inflammatory type Hepatocellular Adenoma



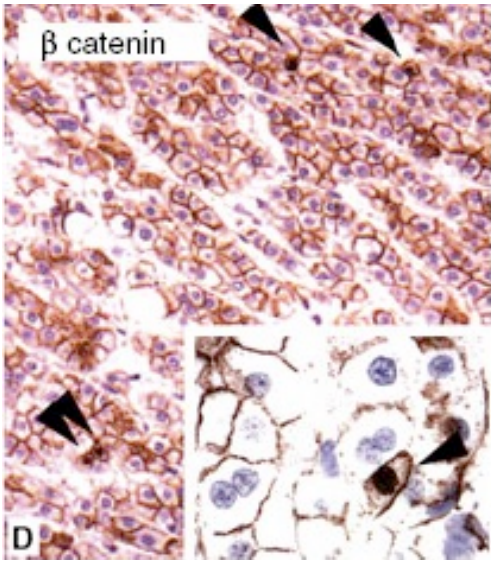
Beta-catenin mutated HCA (10%) and beta-catenin mutated IHCA (10-15%)



Exon 3 mutation
High risk of HCC



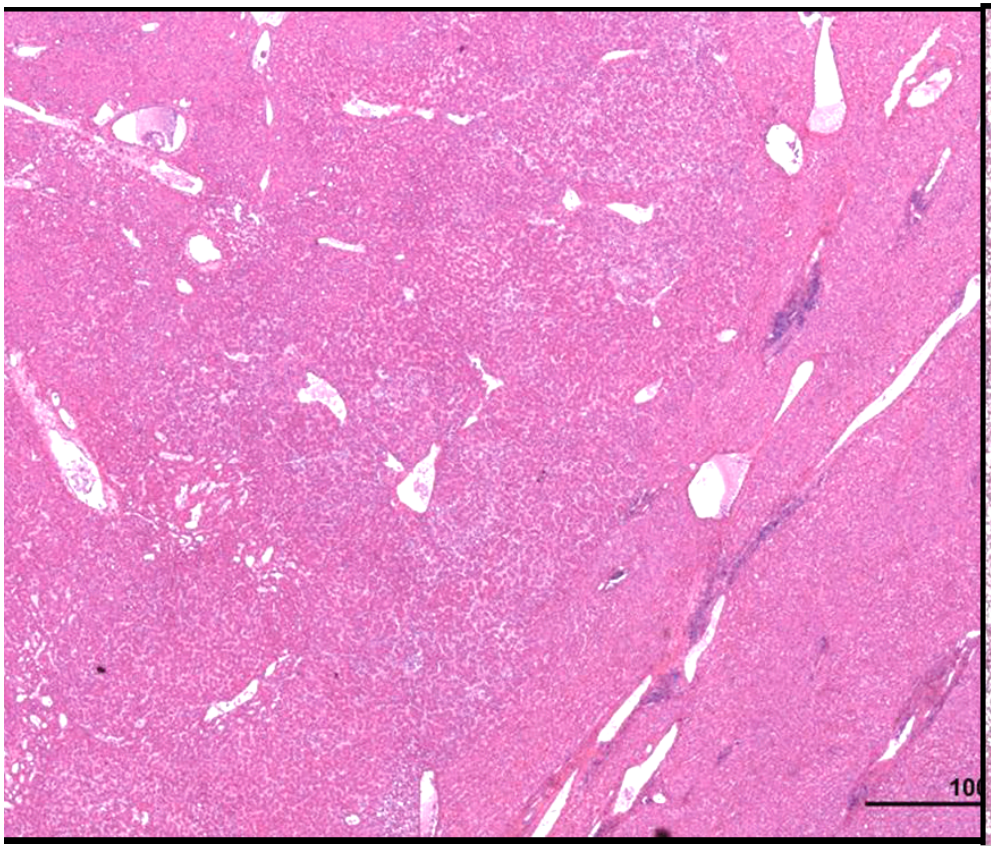
GS overexpression depends on the mutation type:
- Exon 3 (other than S45): diffuse
- Exon 7/8: faint (low risk of HCC)



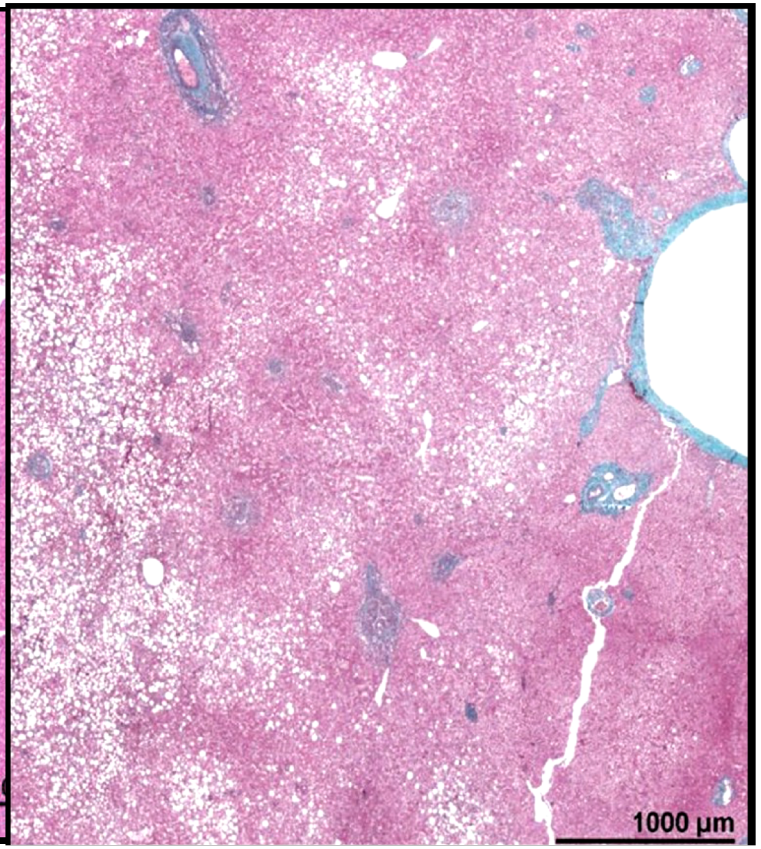
Nuclear expression depends on the mutation type:
- Exon 3 (other than S45): often+
- Exon 7/8: negative (low risk of HCC)

Pictures from Histopathology 2013, 62, 431-445. DOI: 10.1111/his.12011

Limits of morphology

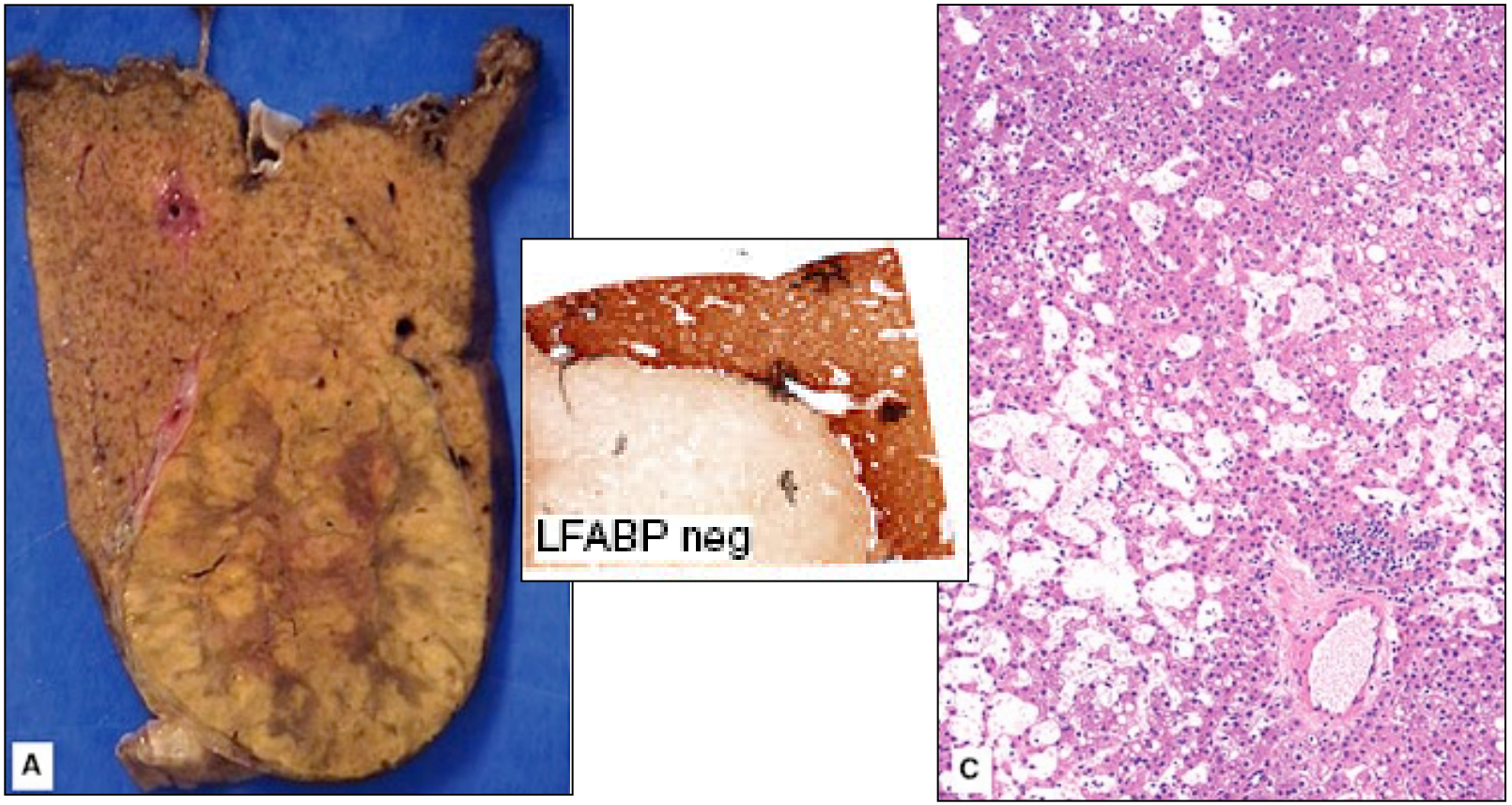


H-HCA



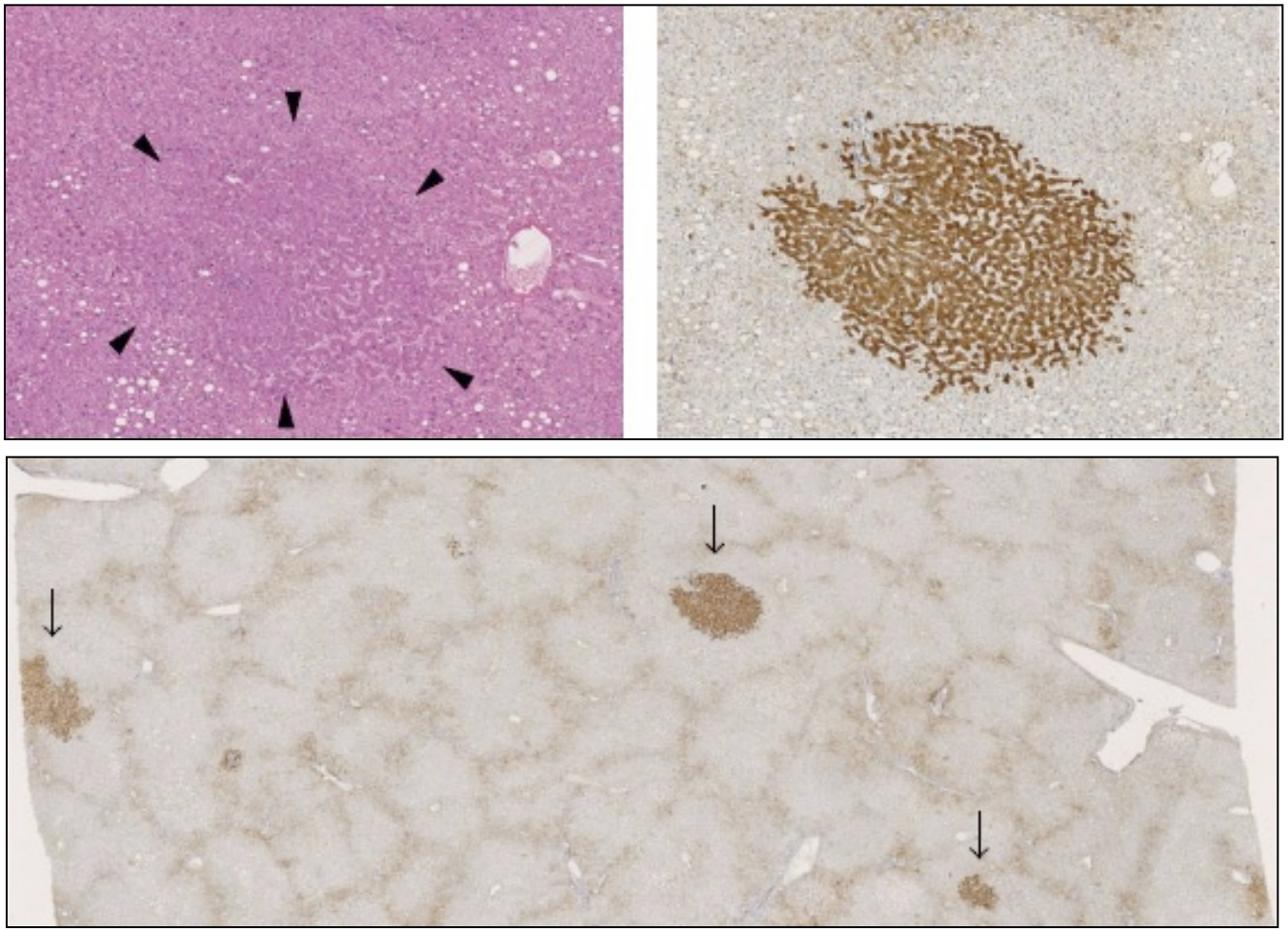
I-HCA

Immunohistochemistry utility



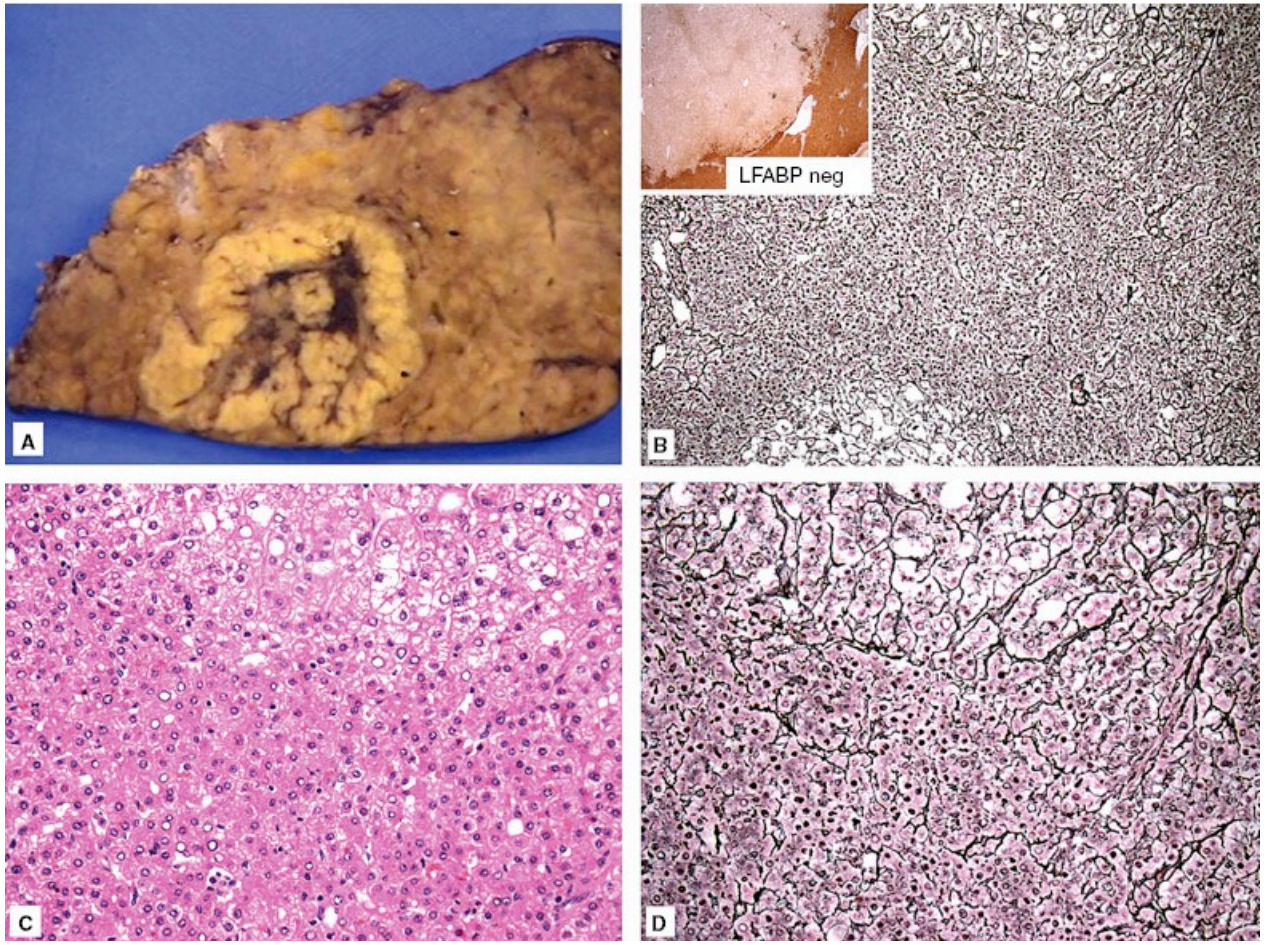
Histopathology 2013, 62, 431-445. DOI: 10.1111/his.12011

Immunohistochemistry utility
CRP



International Journal of Hepatology Volume 2012, Article ID 805621, 8 pages

Malignant transformation

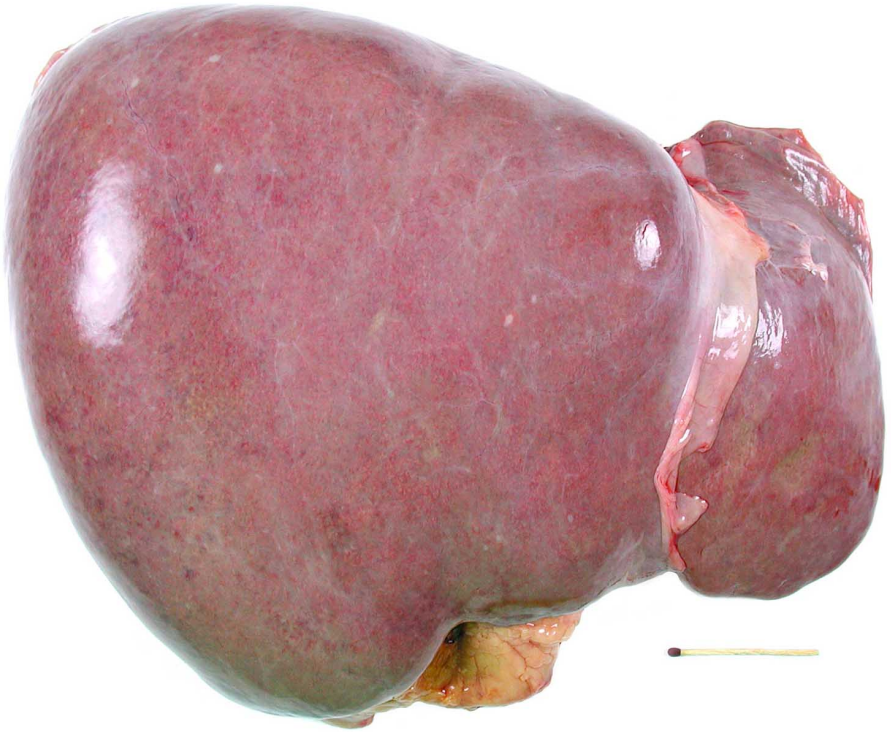


Histopathology 2013, 62, 431-445. DOI: 10.1111/his.12011

Solid tumours in non-fibrotic liver

NON FIBROTIC LIVER:

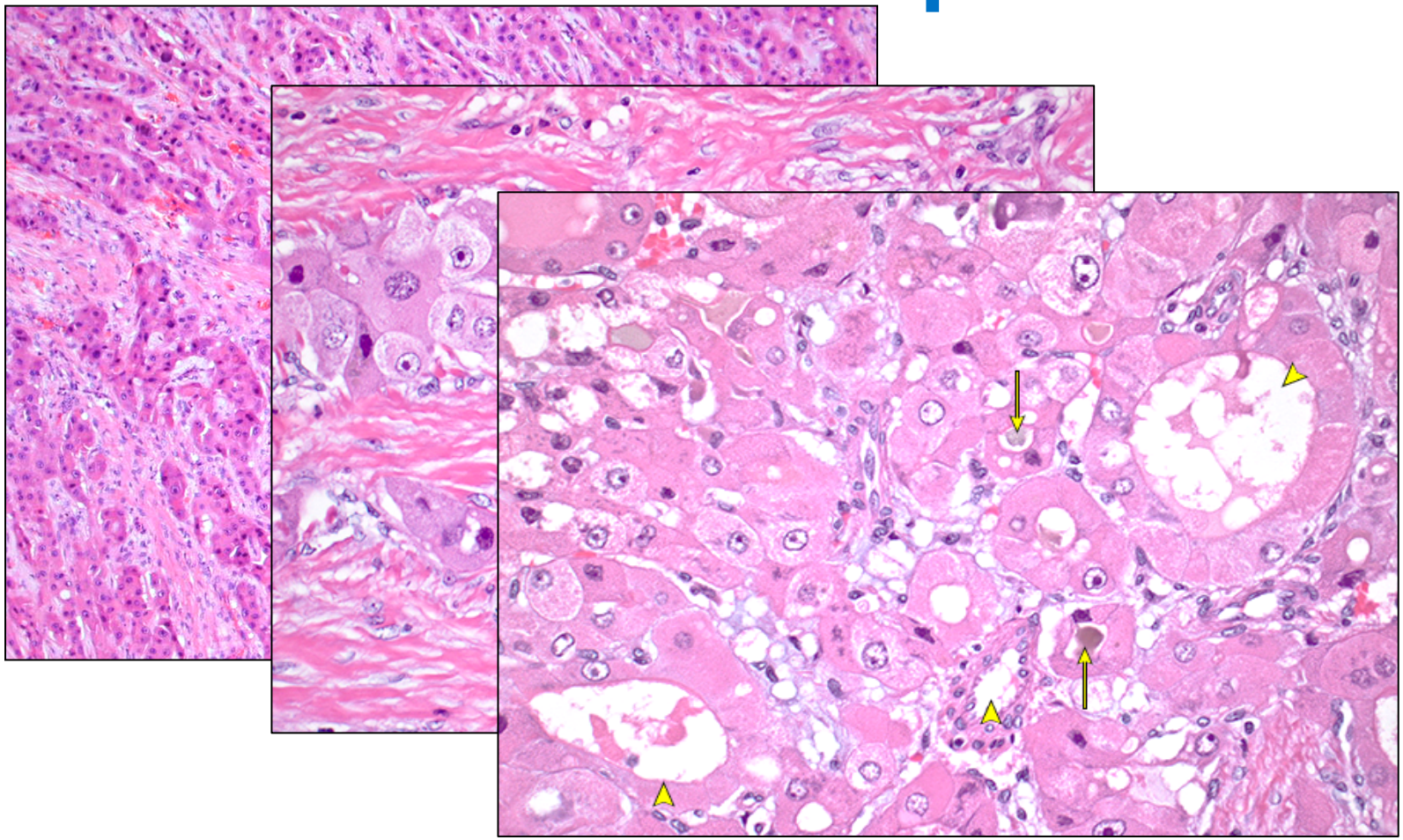
- Focal nodular hyperplasia
- Hepatocellular adenoma
- Hepatocellular carcinoma
  - NOS
    - Steroids
    - Elderly
  - Fibrolamellar variant



Fibrolamellar Carcinoma

- Distinctive liver cancers of children and young adults (median age: 25 years) that differ from classical HCC at the clinical, histological and molecular levels
- Key molecular features: activation of PKA via a DNJB1-PRKACA fusion gene)
- FLC arises in non-cirrhotic liver; normal AFP
- Etiology and risk factors are not known
- Two thirds involve the left lobe. A central scar may be found in about 75% of cases

Fibrolamellar Carcinoma microscopic



Main diagnostic problems in non-fibrotic liver

1. Focal nodular hyperplasia vs Hepatocellular adenoma

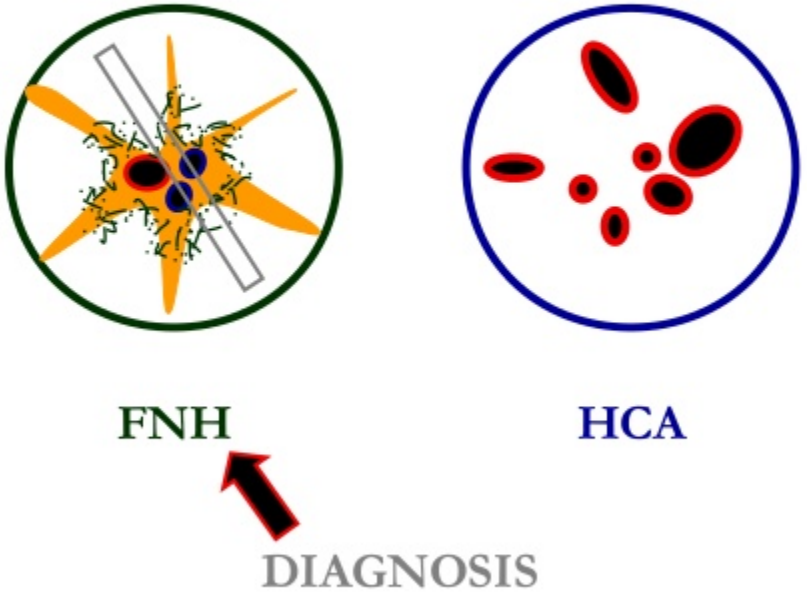
2. Hepatocellular adenoma vs well-differentiated hepatocellular carcinoma

20th CENTURY APPROACH: NON-IMMUNO

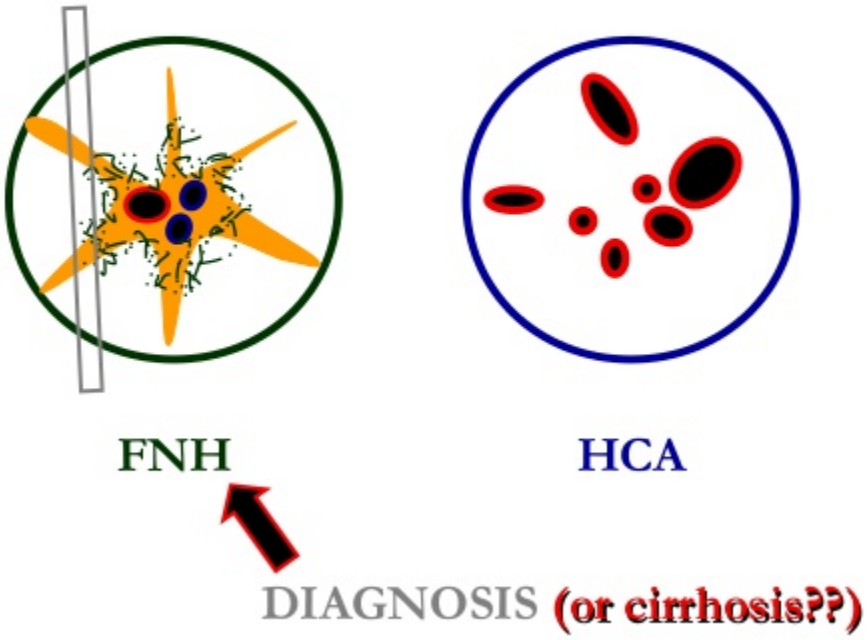
FNH

HCA

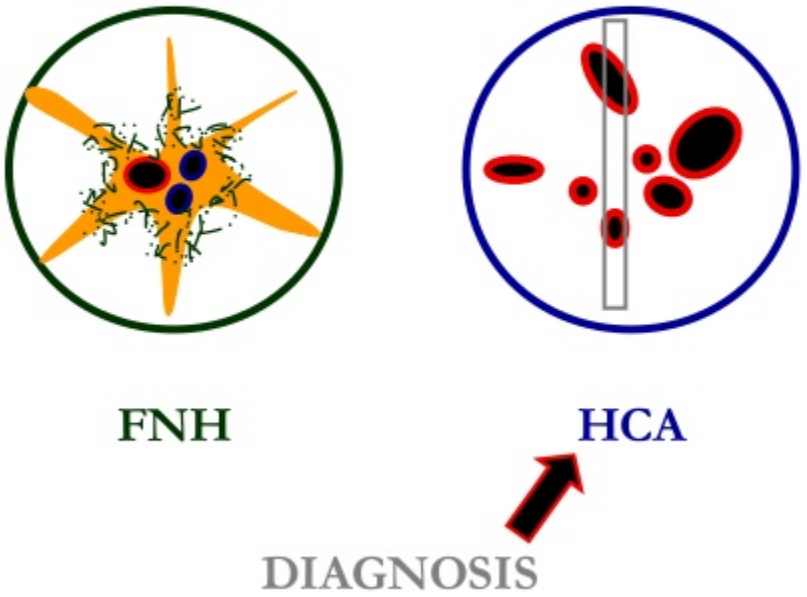
Diagnosis: Benign hepatocellular lesion, favour FNH



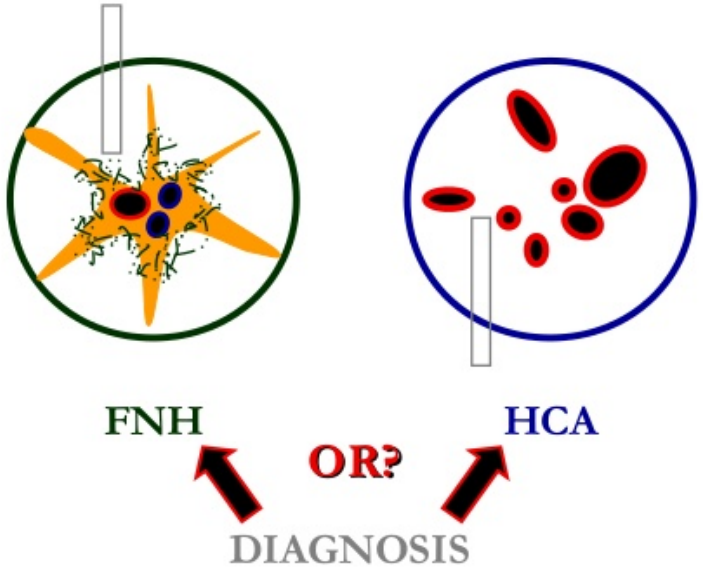
Diagnosis: Benign hepatocellular lesion, suggestive of FNH



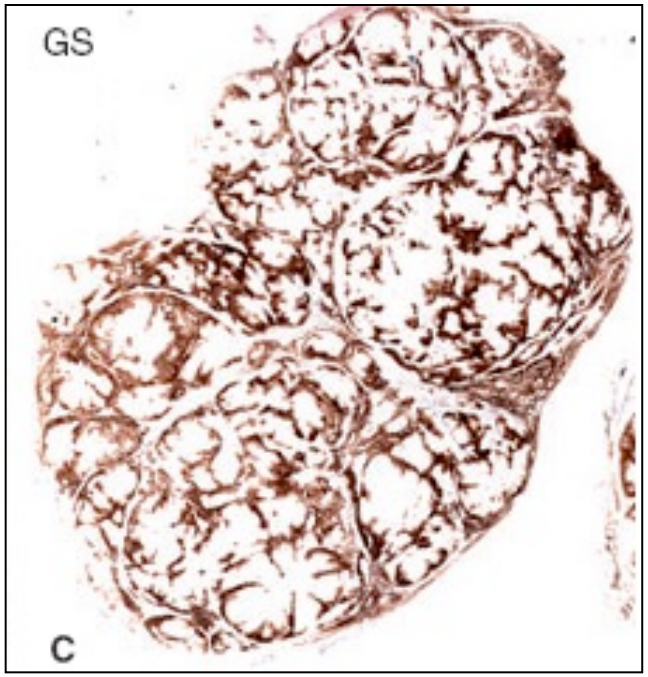
Diagnosis: Benign hepatocellular lesion, favour HCA

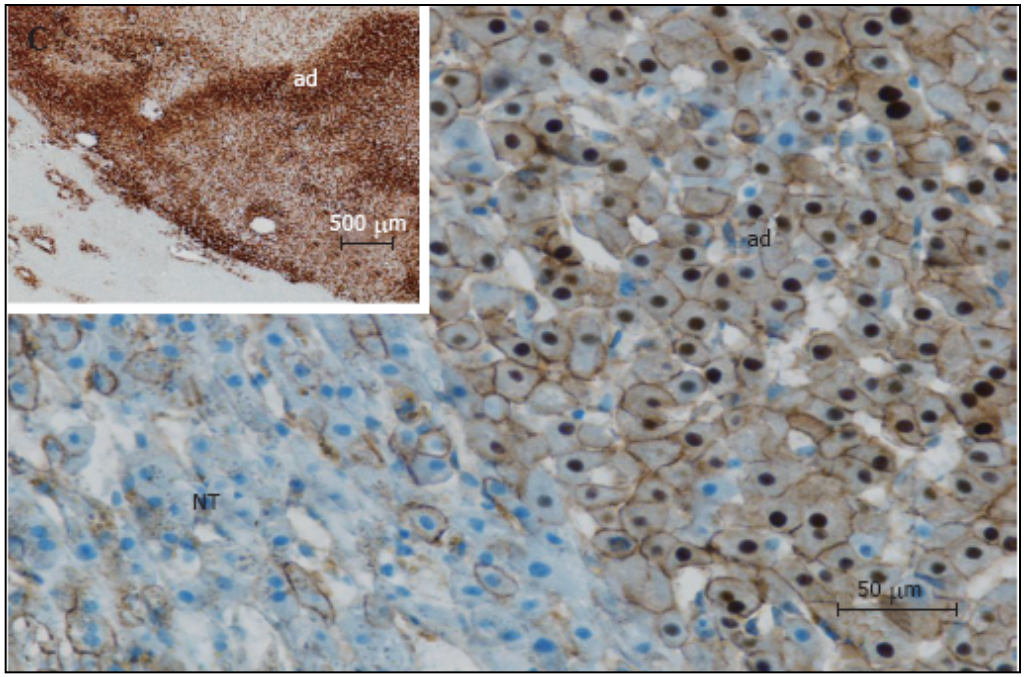


Diagnosis: Benign hepatocellular lesion, ? FNH vs HCA

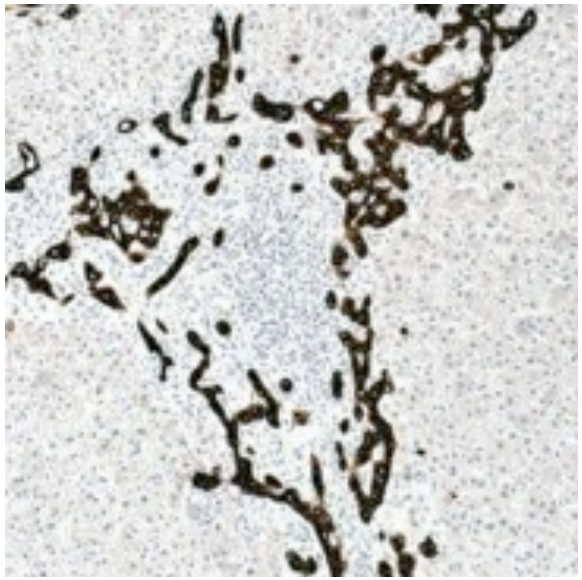


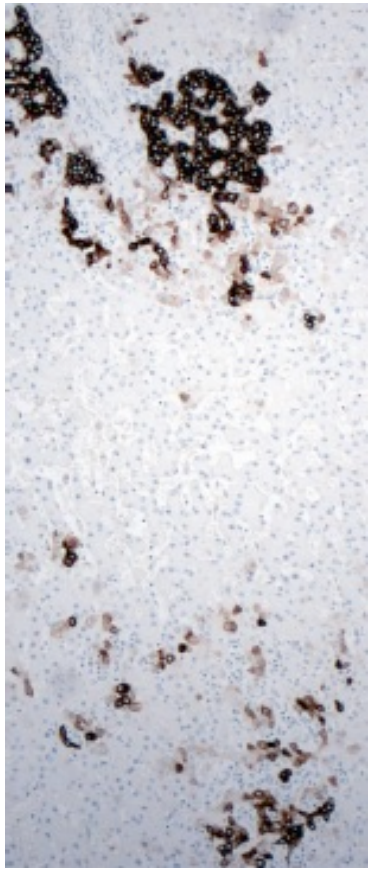
FNH vs HCA
21th century approach: GS





FNH vs HCA : CK7



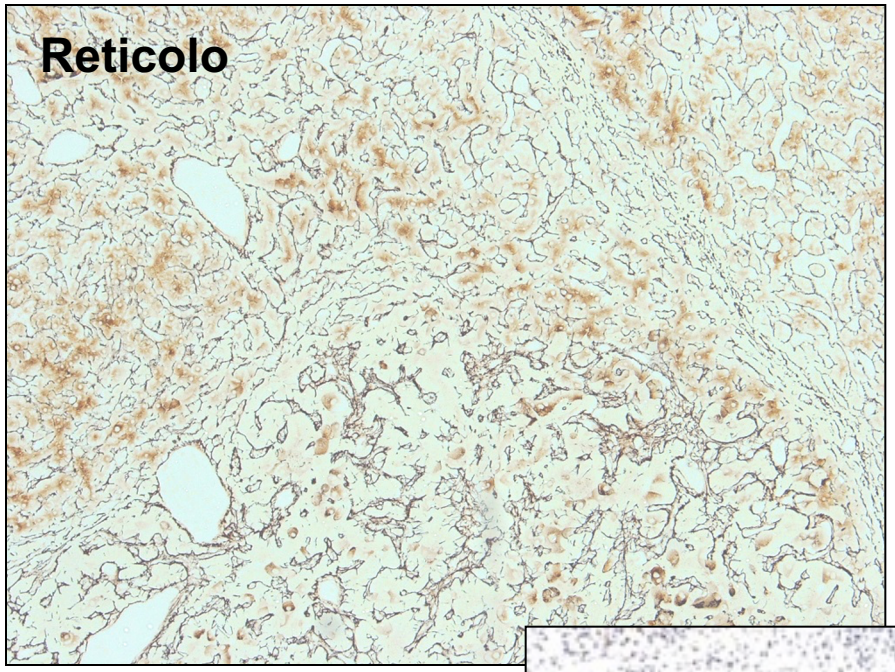


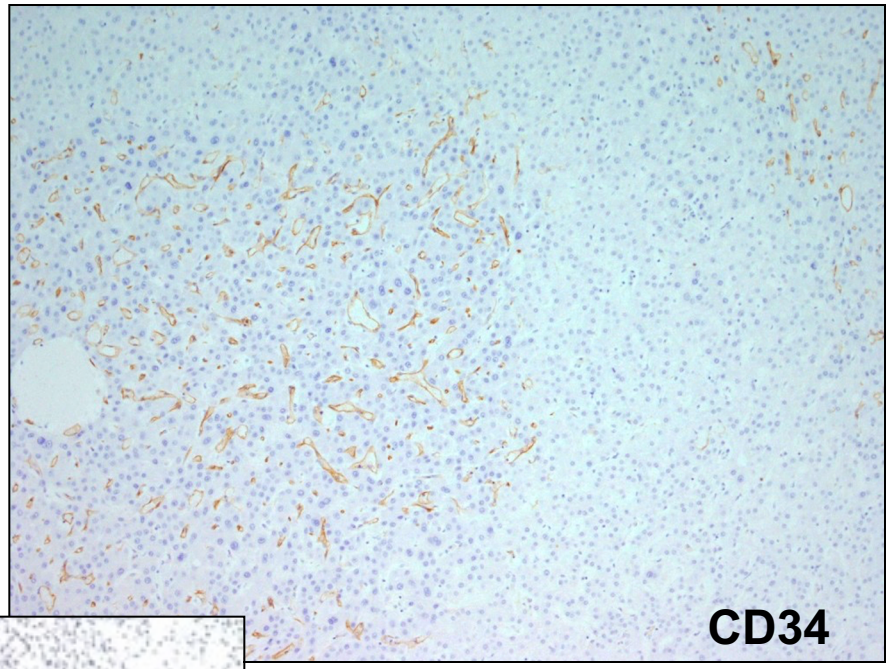
Main diagnostic problems in non-fibrotic liver

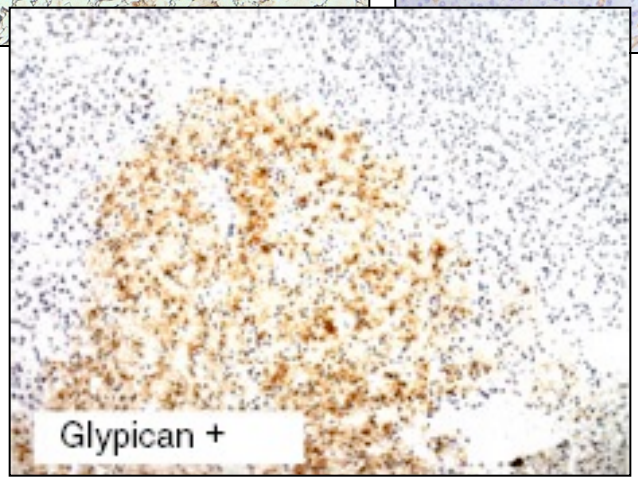
1. Focal nodular hyperplasia vs Hepatocellular adenoma

2. Hepatocellular adenoma vs well-differentiated hepatocellular carcinoma

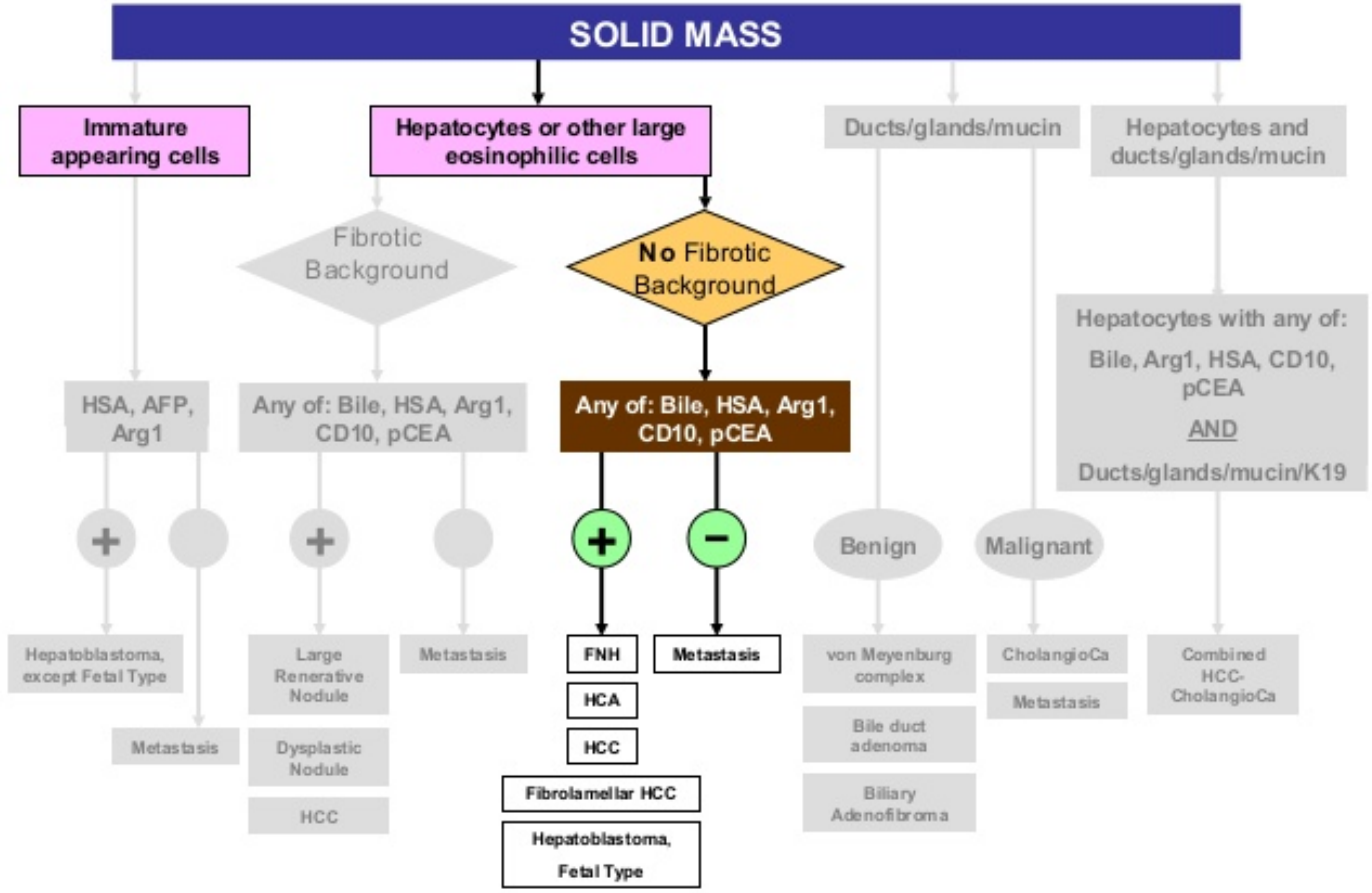
HCA vs e-HCC





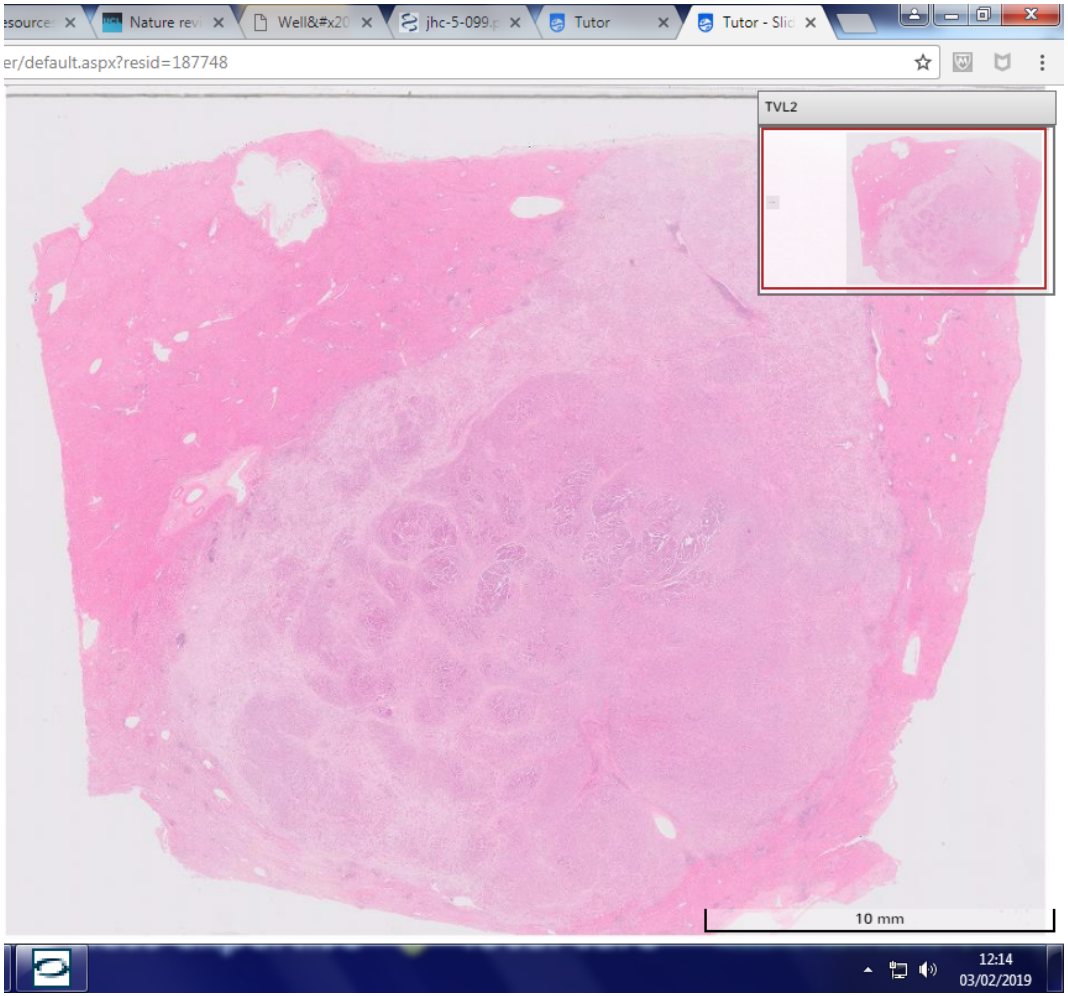


Diagnostic algorithm of liver lesions with solid mass



CASE

From liver lobectomy of 76 y-old female. On sectioning 7 tumours are identified.



Histology

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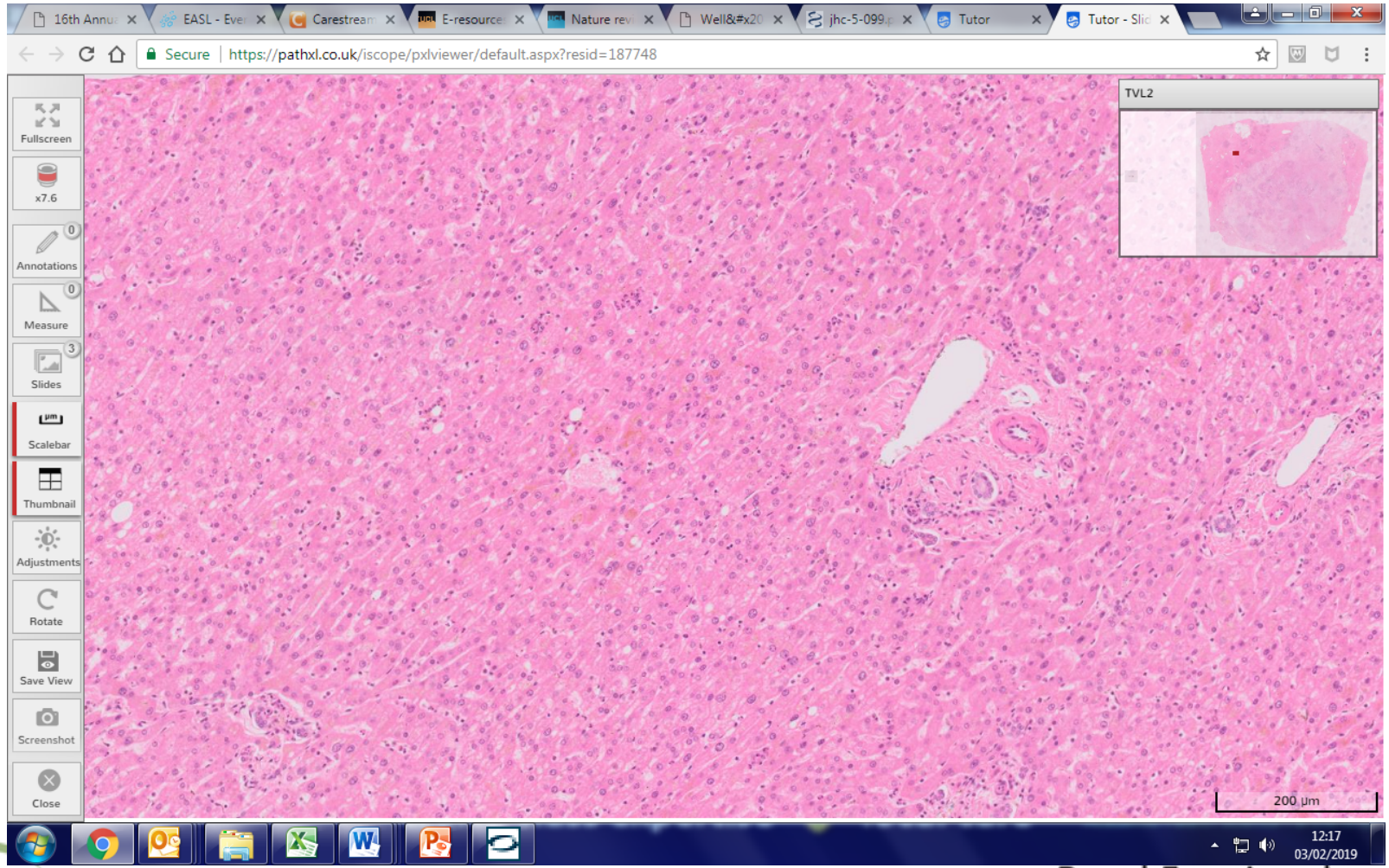
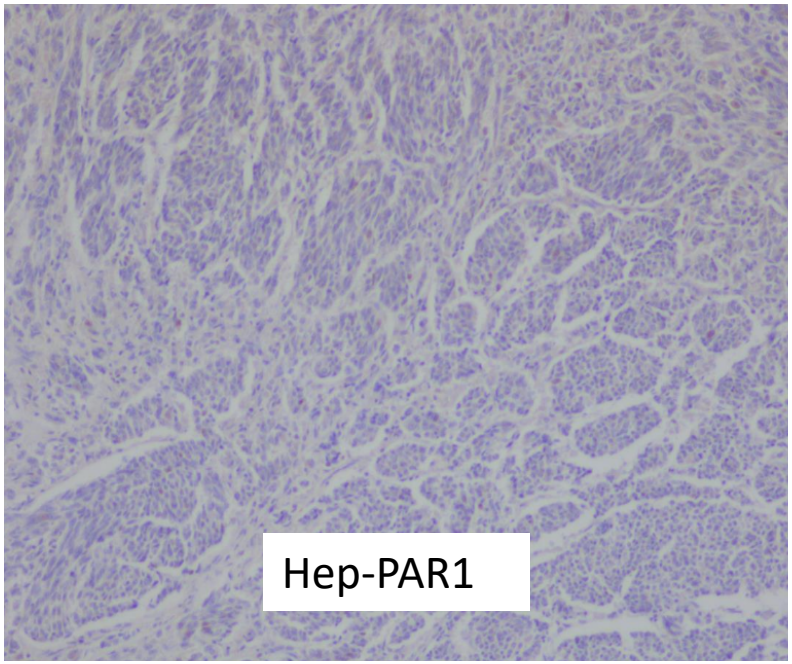
Background

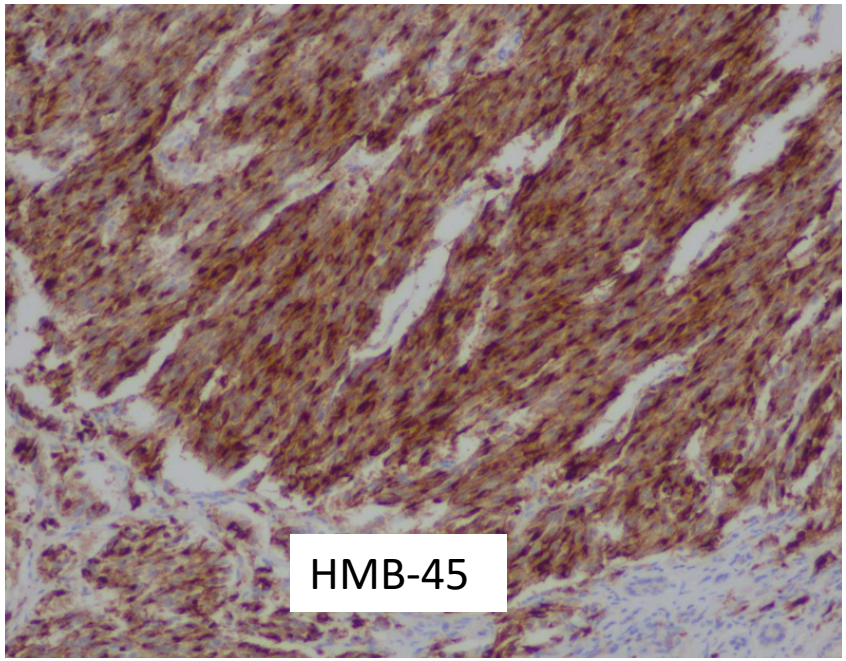


UCLPartners
Academic Health Science Partnership

Royal Free London
NHS Foundation Trust
NHS

CASE N.8



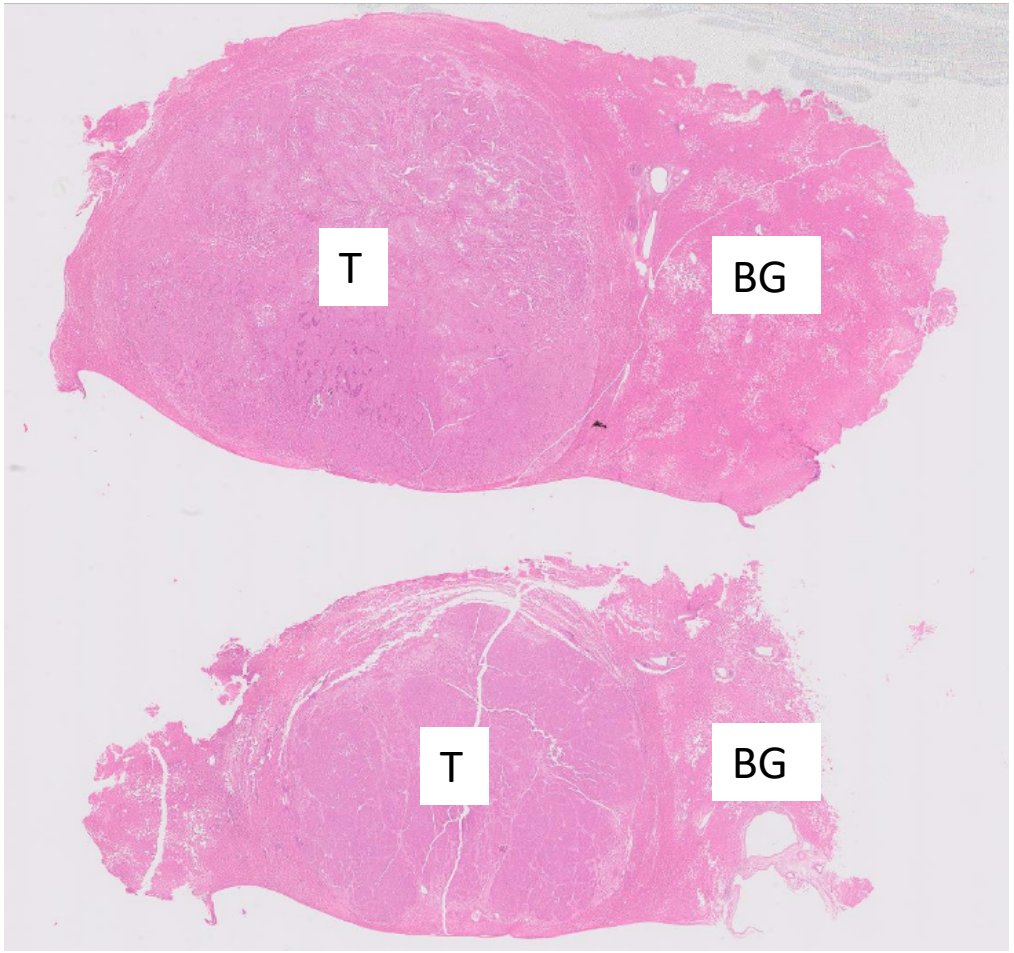


Diagnosis

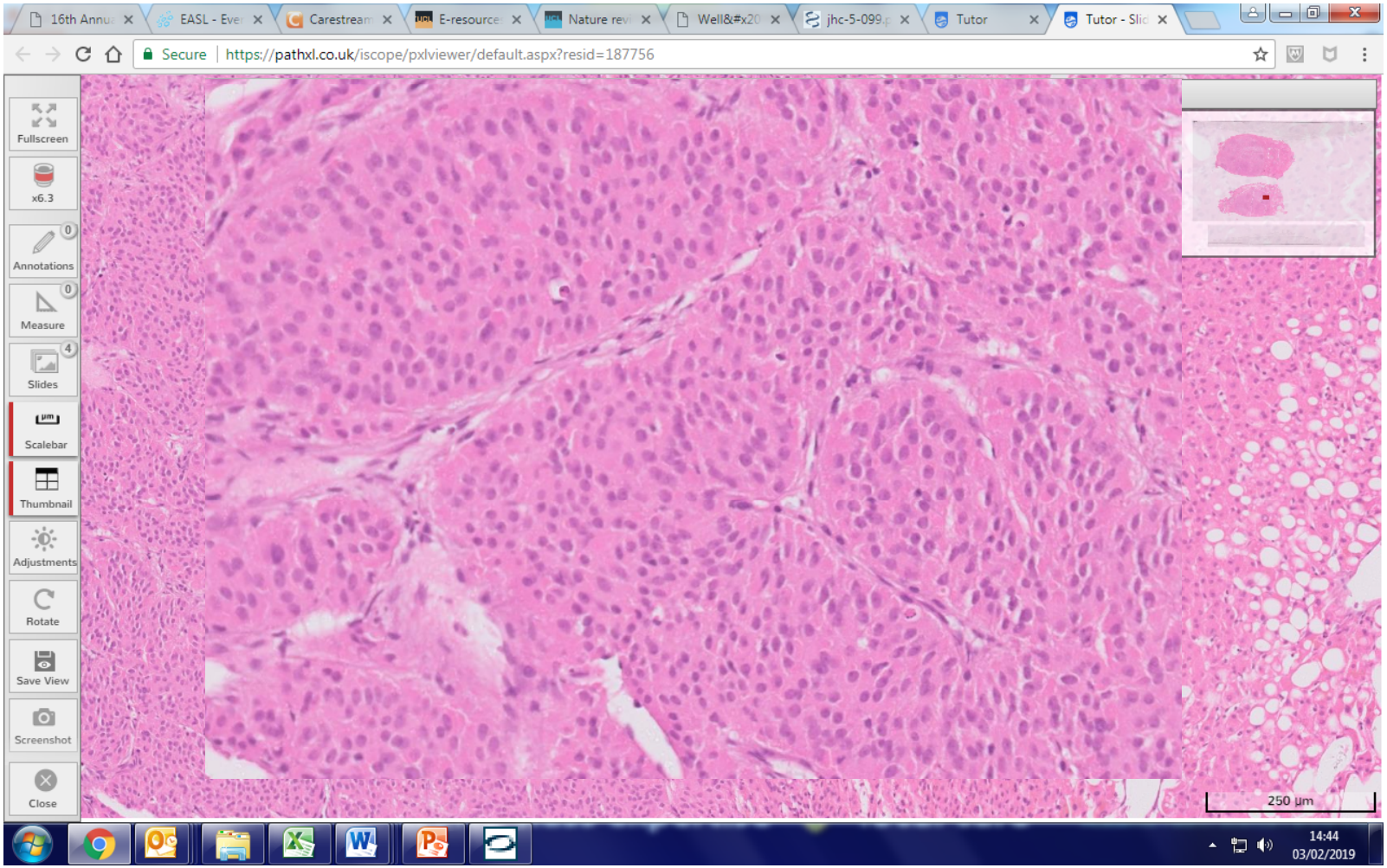
Metastatic melanoma

CASE N.10

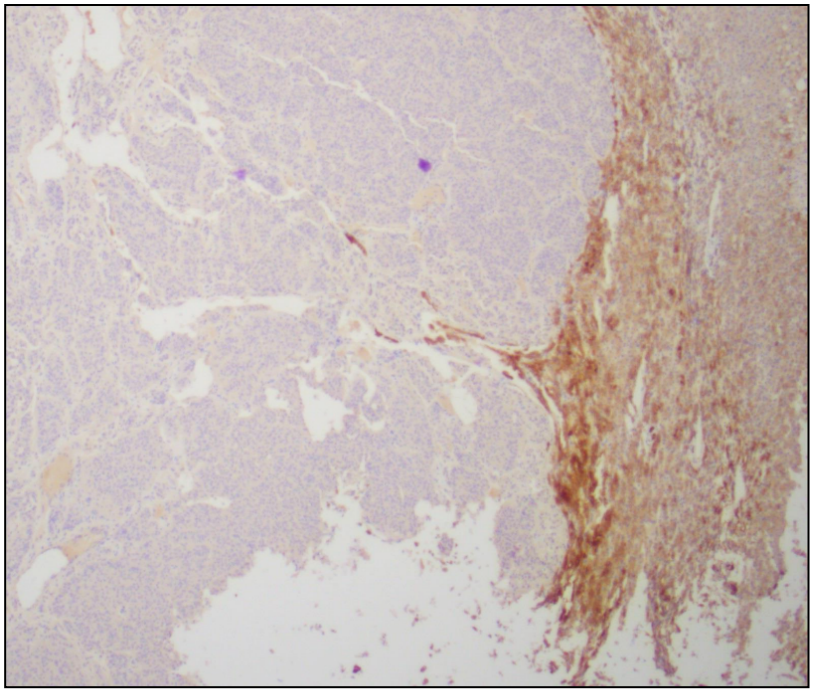
Specimen type: Liver wedge resection.
Clinical details: 51 year old gentleman referred from Cyprus with liver lesion.



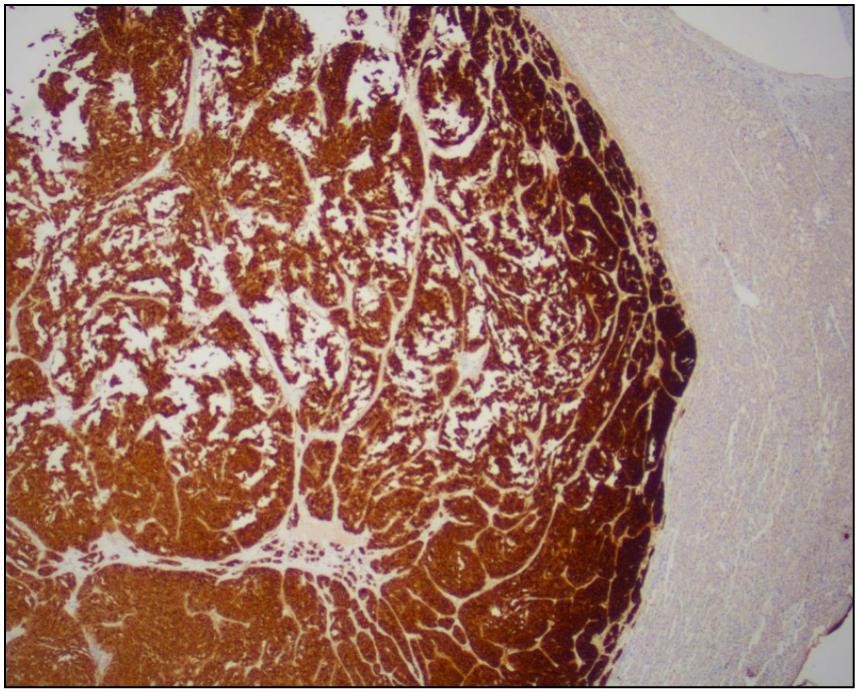
CASE N.10


Secure
https://pathxl.co.uk/iscope/pxlviewer/default.aspx?resid=187756
Fullscreen
x6.3
Annotations
Measure
Slides
Scalebar
Thumbnail
Adjustments
Rotate
Save View
Screenshot
Close
250 µm
14:44
03/02/2019

CASE N.10



CAM5.2



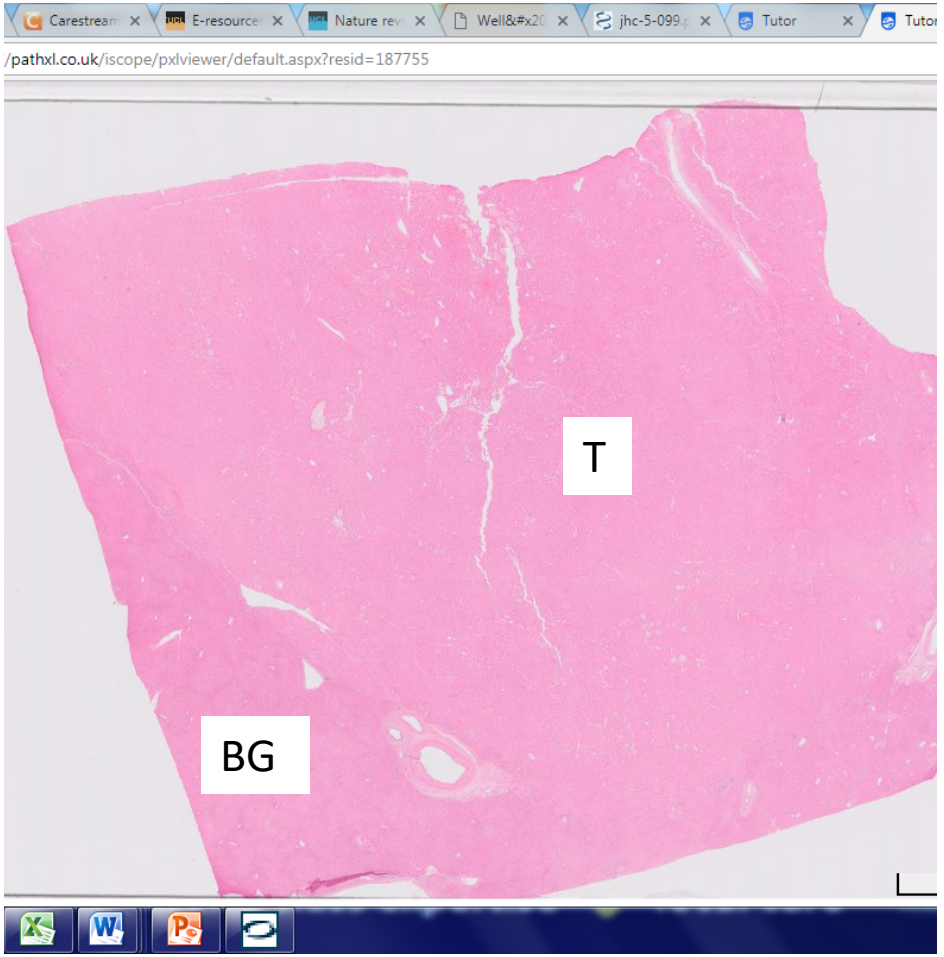
Inhibin
synaptophysin

Diagnosis

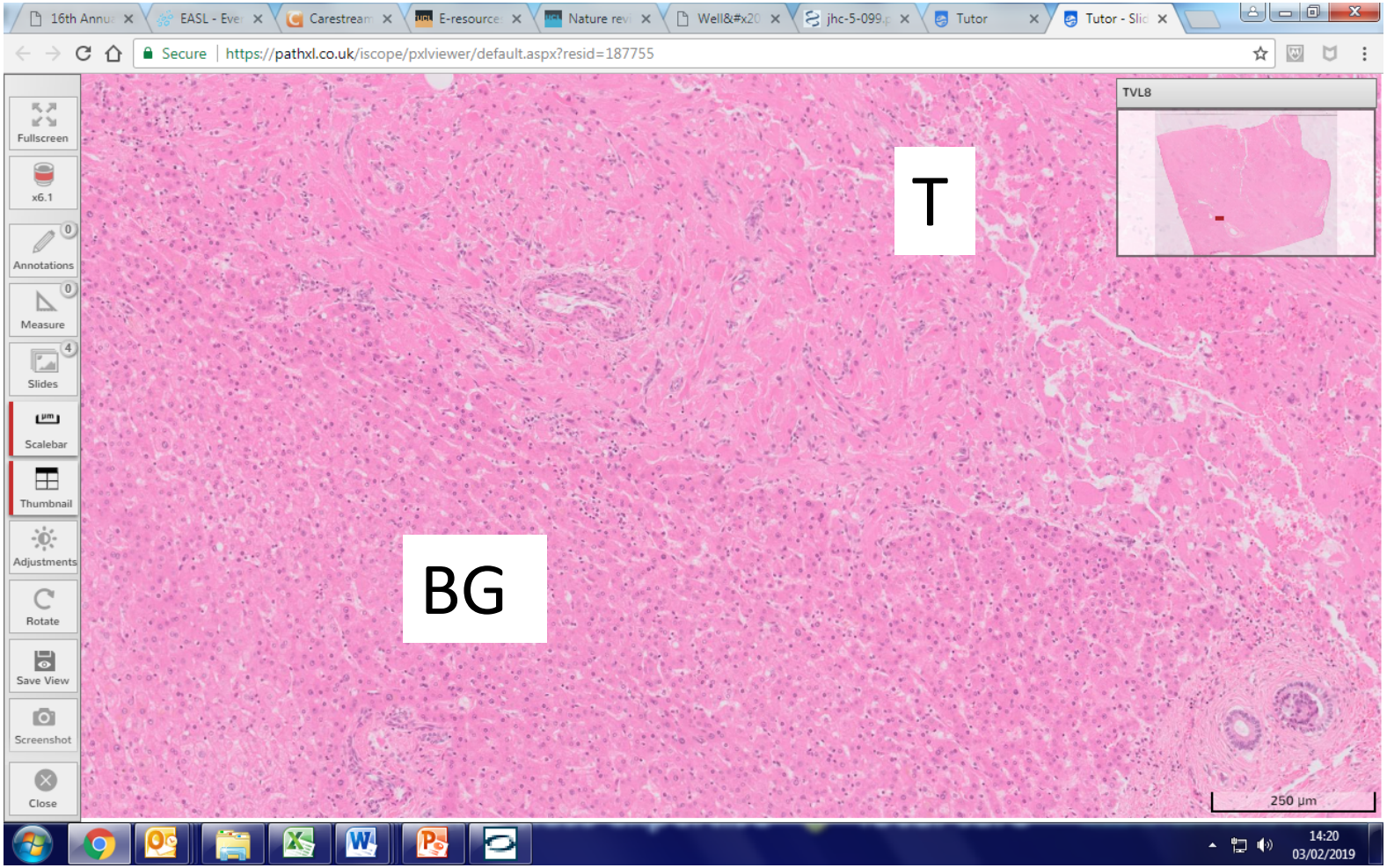
Metastatic adrenocortical carcinoma

CASE N.11

Specimen type: Central hepatectomy.
Clinical details: 66 year old lady with large liver mass
Macroscopic description: Non cirrhotic liver with a well circumscribed, pale tan coloured mass, measuring 80 x 50 x 64mm.



CASE N.11



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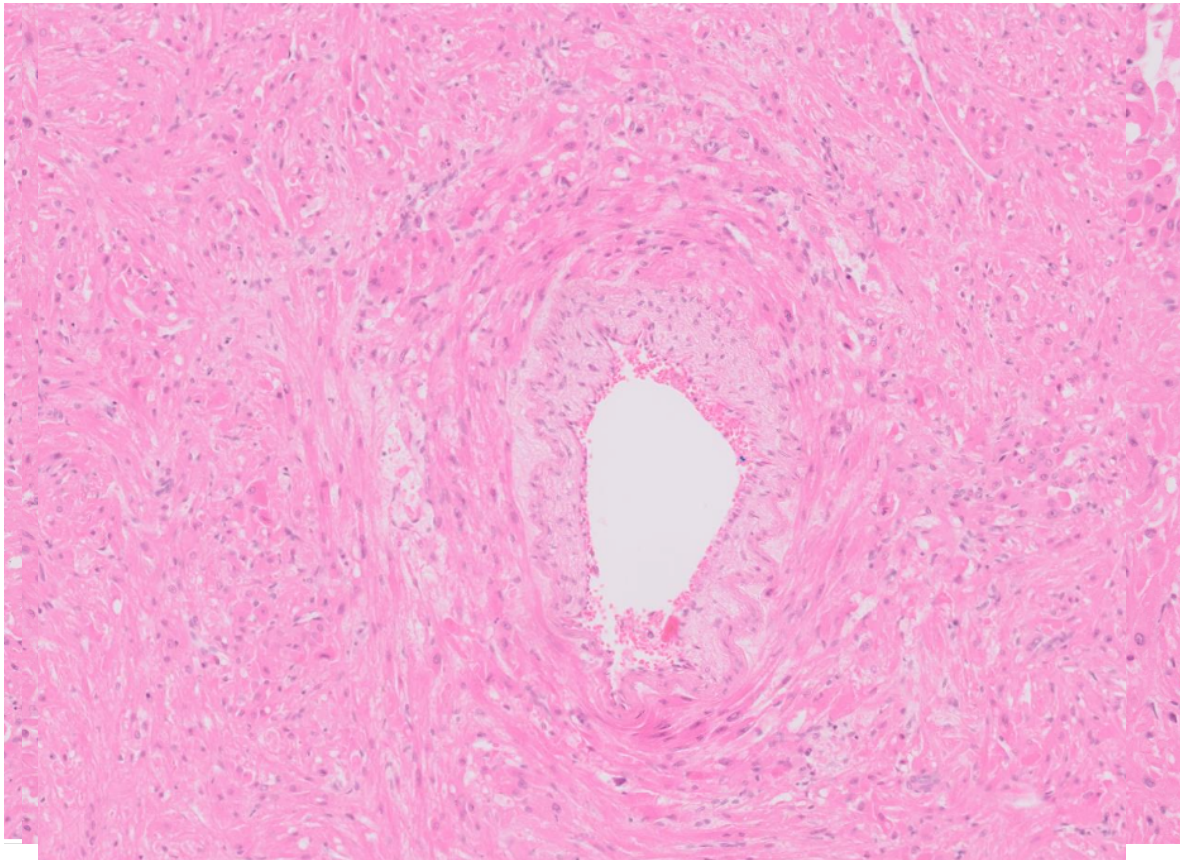
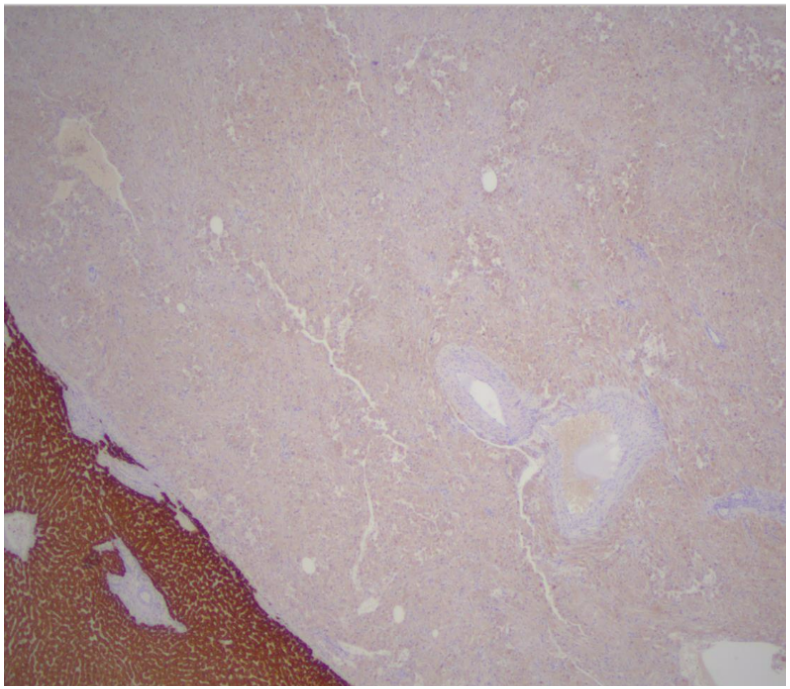
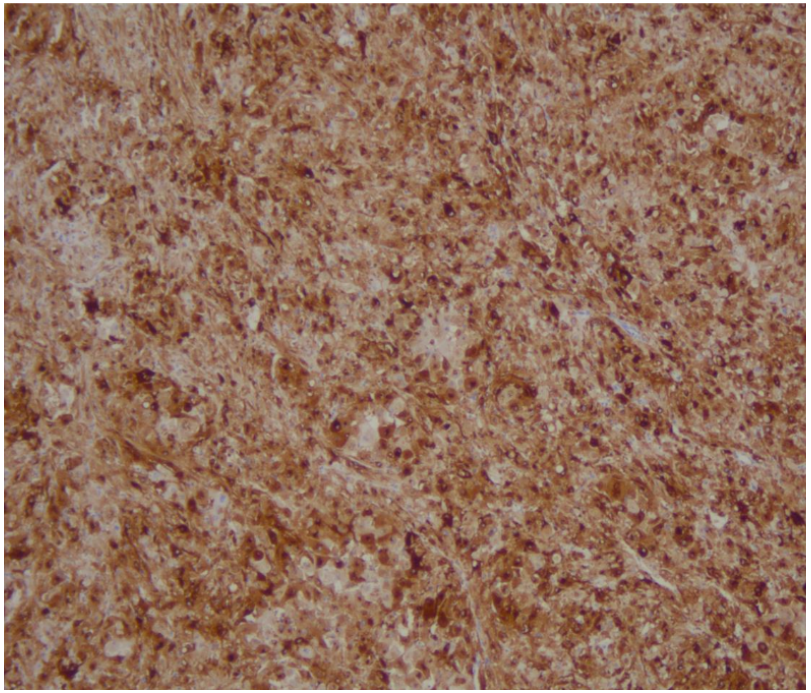
CASE N.11



CASE N.11



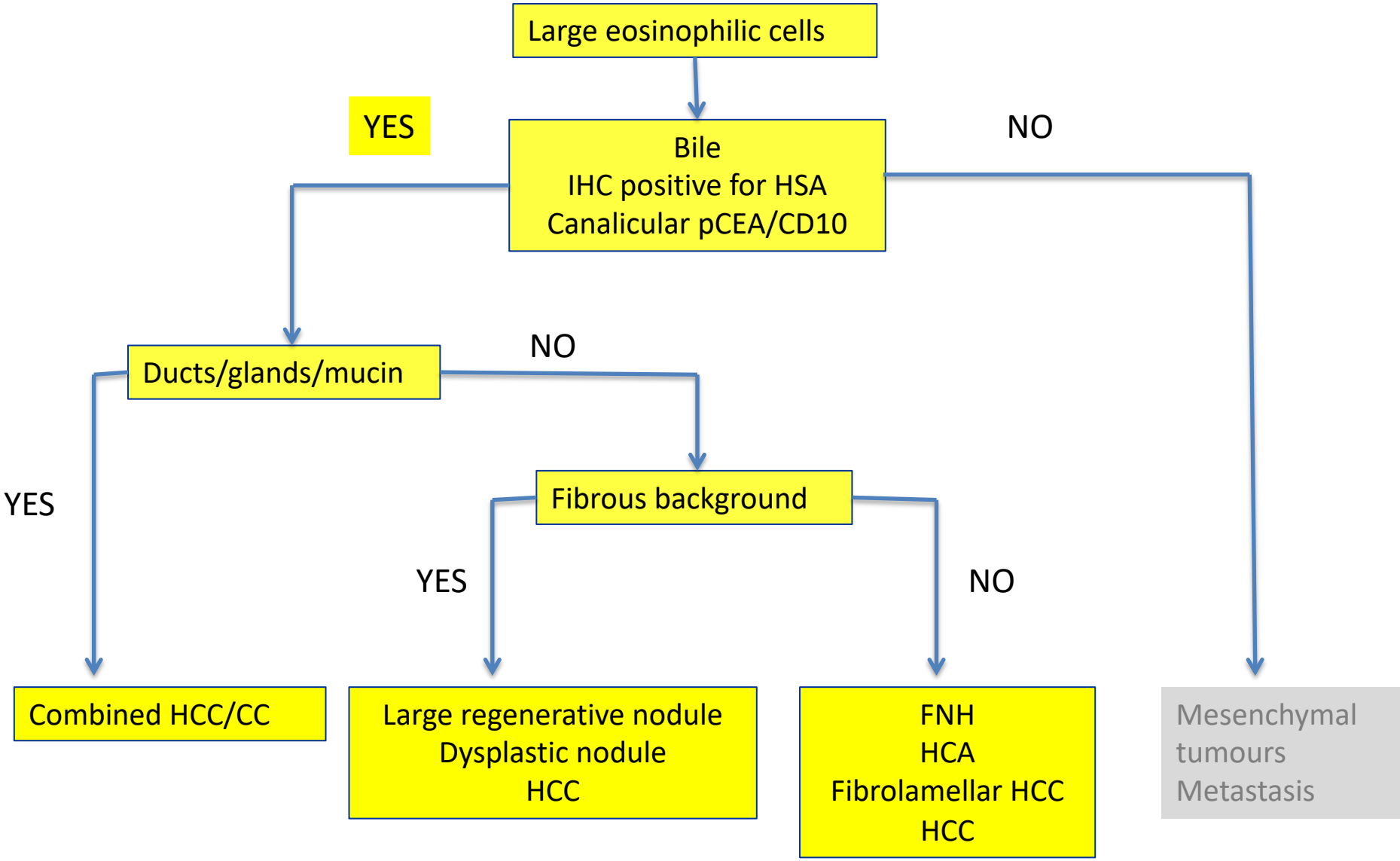
Hep-PAR1

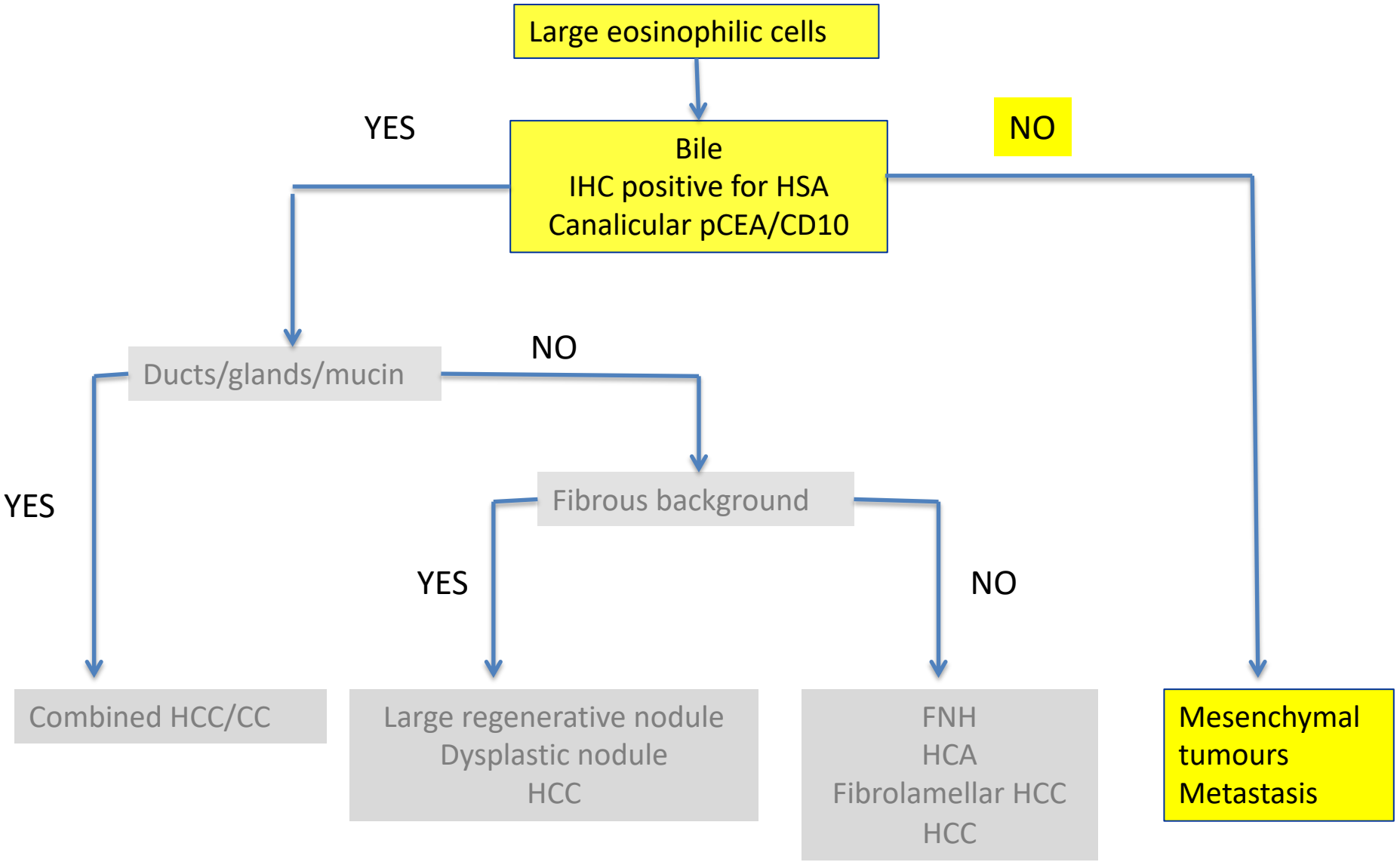


HMB-45
SMA

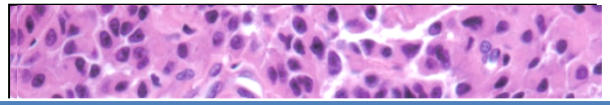
Diagnosis

Angiomyolipoma


Large eosinophilic cells
YES
Bile
IHC positive for HSA
Canalicular pCEA/CD10
NO
Ducts/glands/mucin
NO
YES
Fibrous background
YES
NO
Combined HCC/CC
Large regenerative nodule
Dysplastic nodule
HCC
FNH
HCA
Fibrolamellar HCC
HCC
Mesenchymal tumours
Metastasis

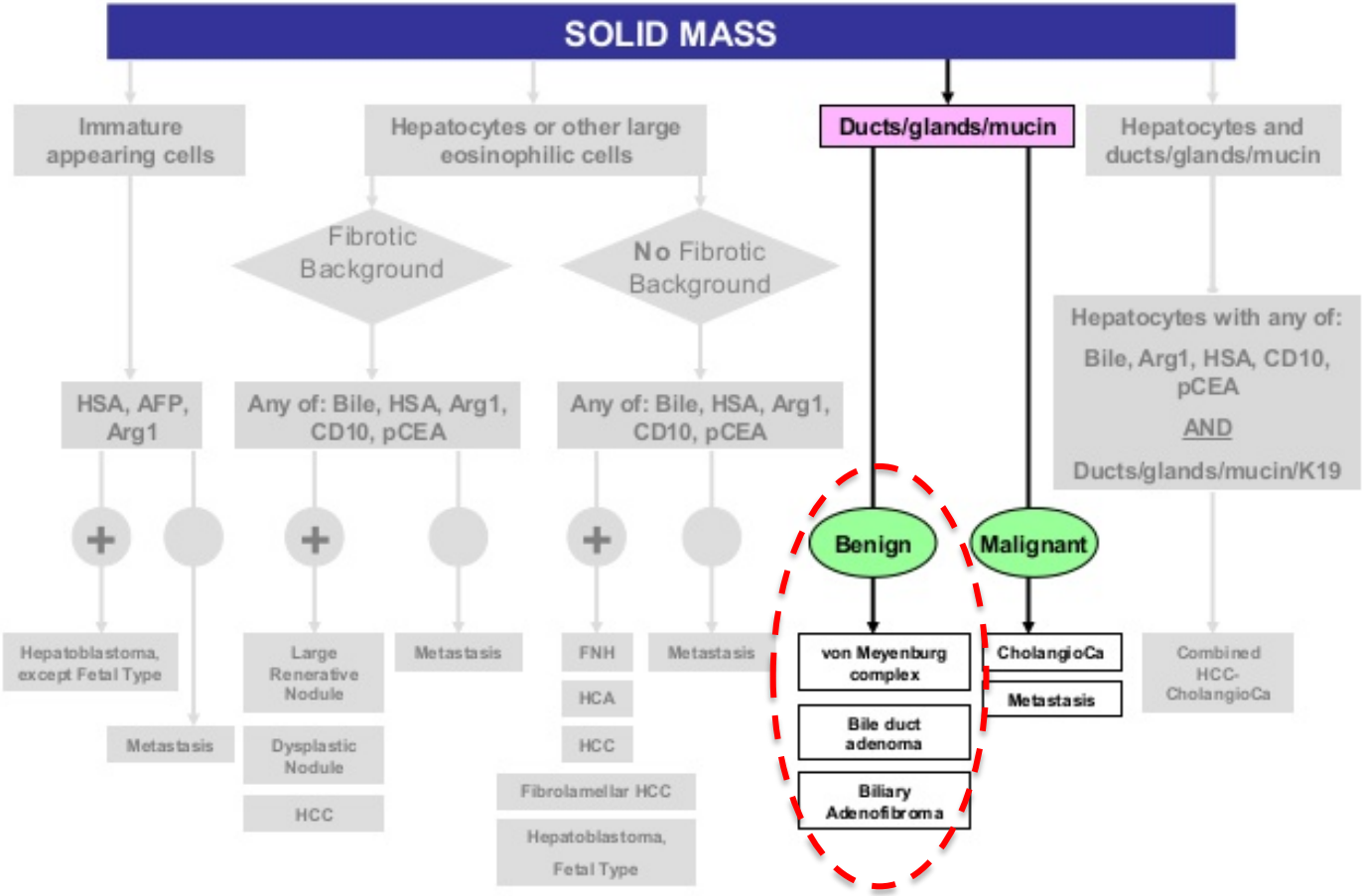


Tumours with large eosinophilic cells (HCC/HCA mimickers)

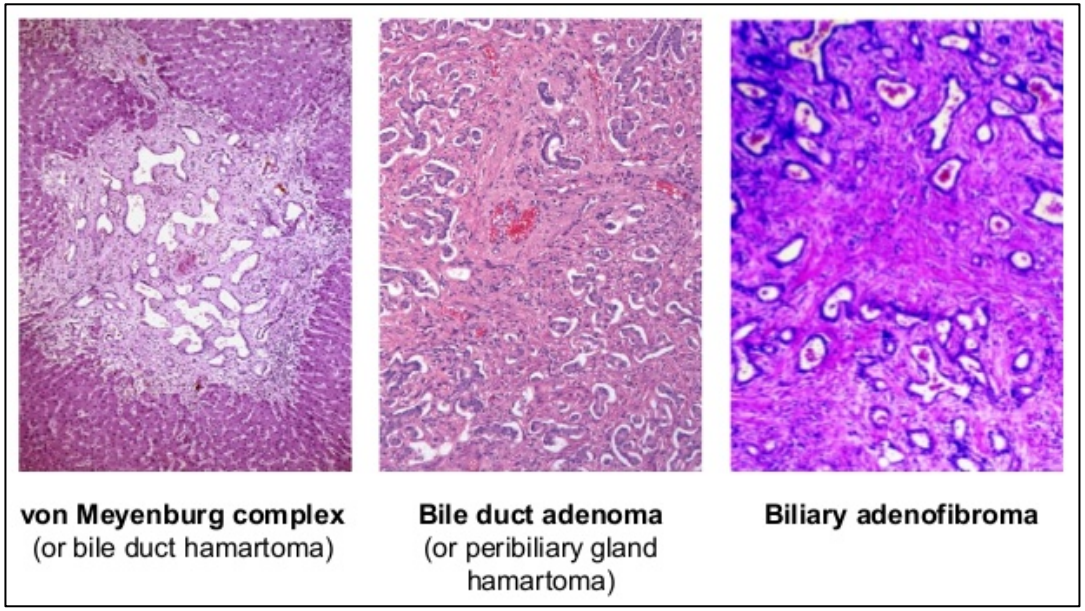


Diagnosis	Helpful immuno-markers
HCC	HSA, canalicular CD10/pCEA, arginase1, CK18
Adrenocortical carcinoma	Inhibin, Melan-A, calretinin, vimentin, synaptophysin
RCC	PAX8, CD10 (membranous), vimentin, carbonic anhydrase IX, glutamine-S-transferase-a
NET	CAM5.2, chromogranin, synaptophysin
Angiomyolipoma	HMB-45, Melan-A, SMA
Melanoma	Melan-A, HMB-45, S-100
GIST (epithelioid)	CD117, DOG1

Diagnostic algorithm of liver lesions with solid mass



Solid benign biliary and gland-forming lesions



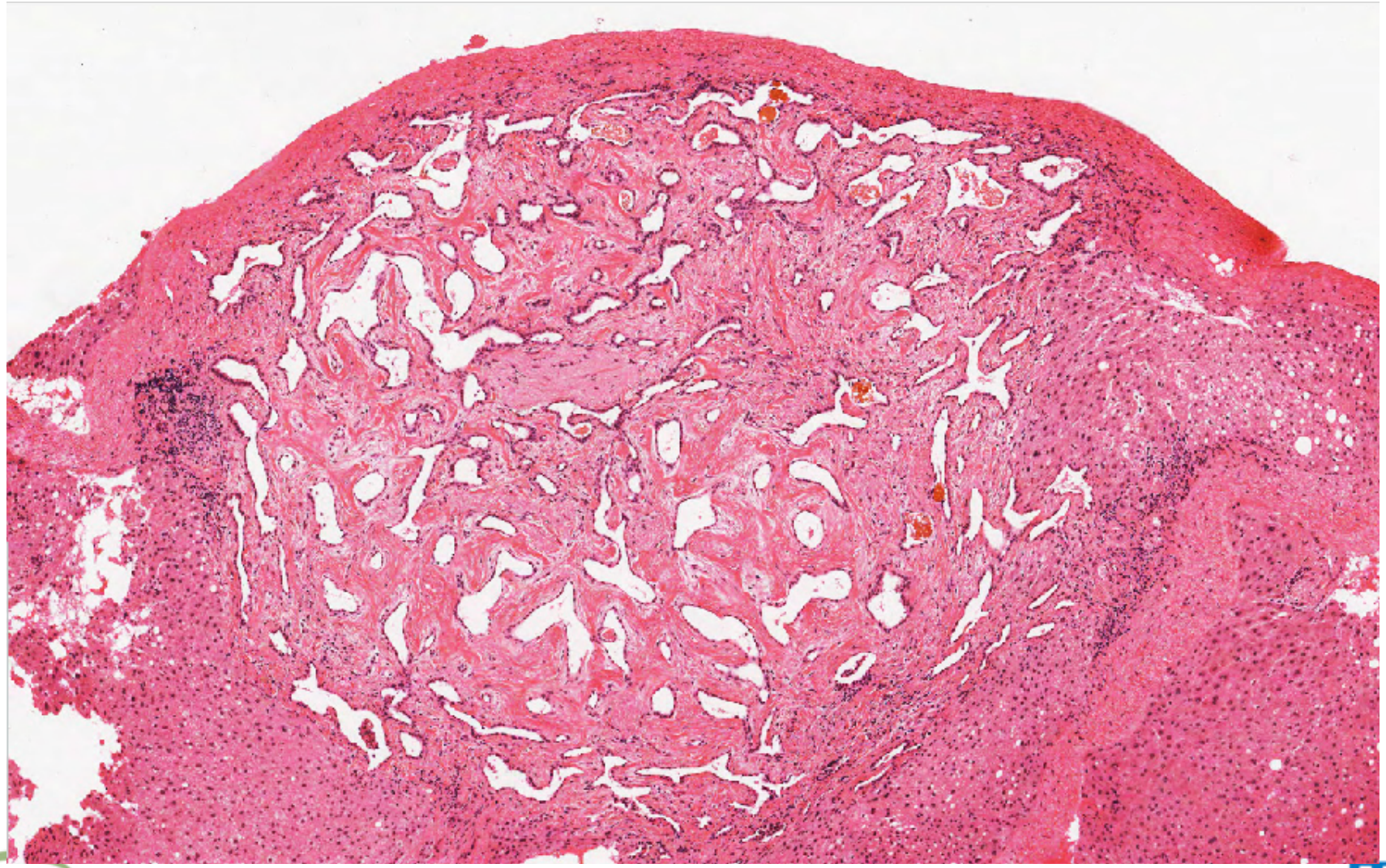
von Meyenburg complex (or bile duct hamartoma)

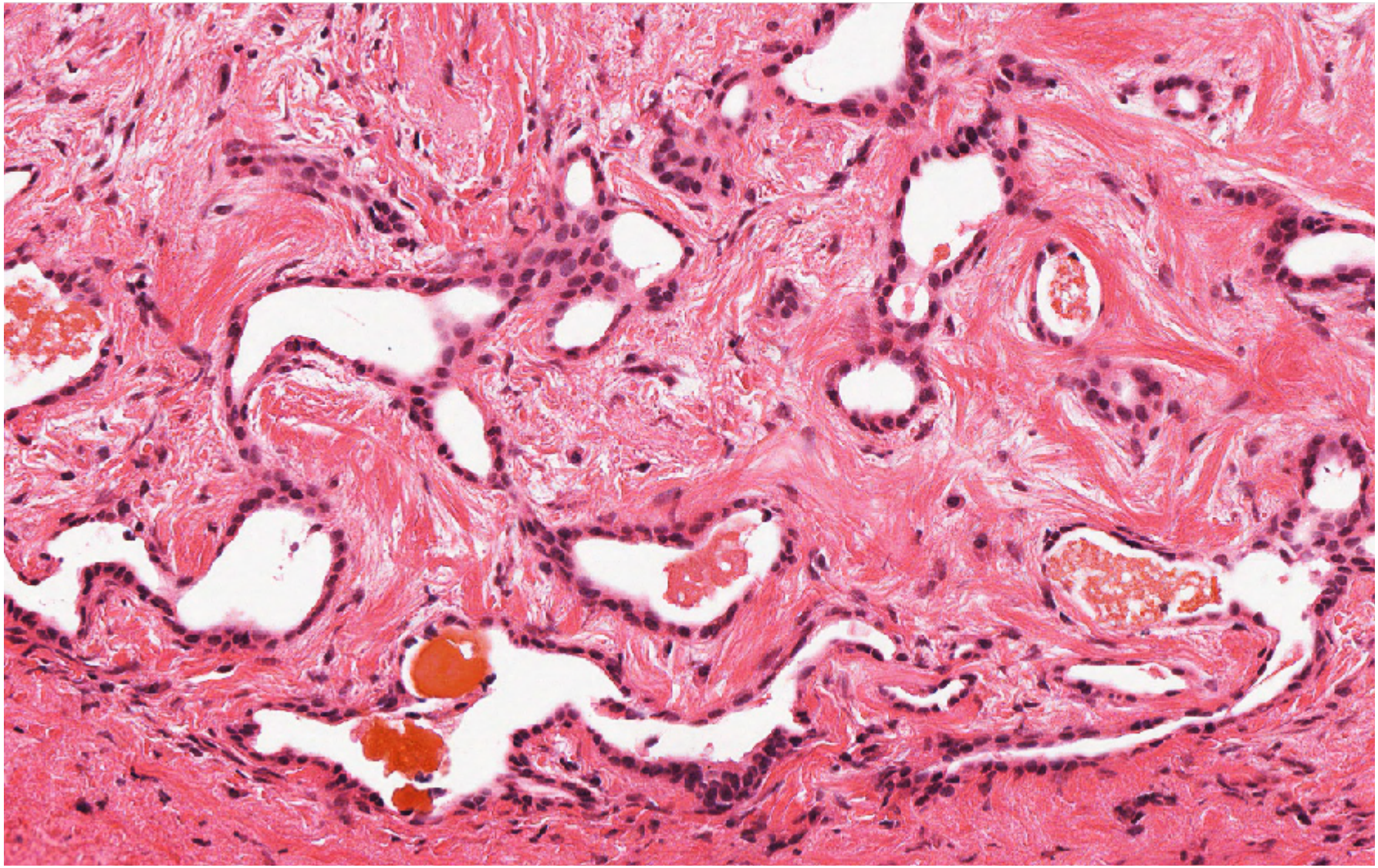
Bile duct adenoma (or peribiliary gland hamartoma)

Biliary adenofibroma

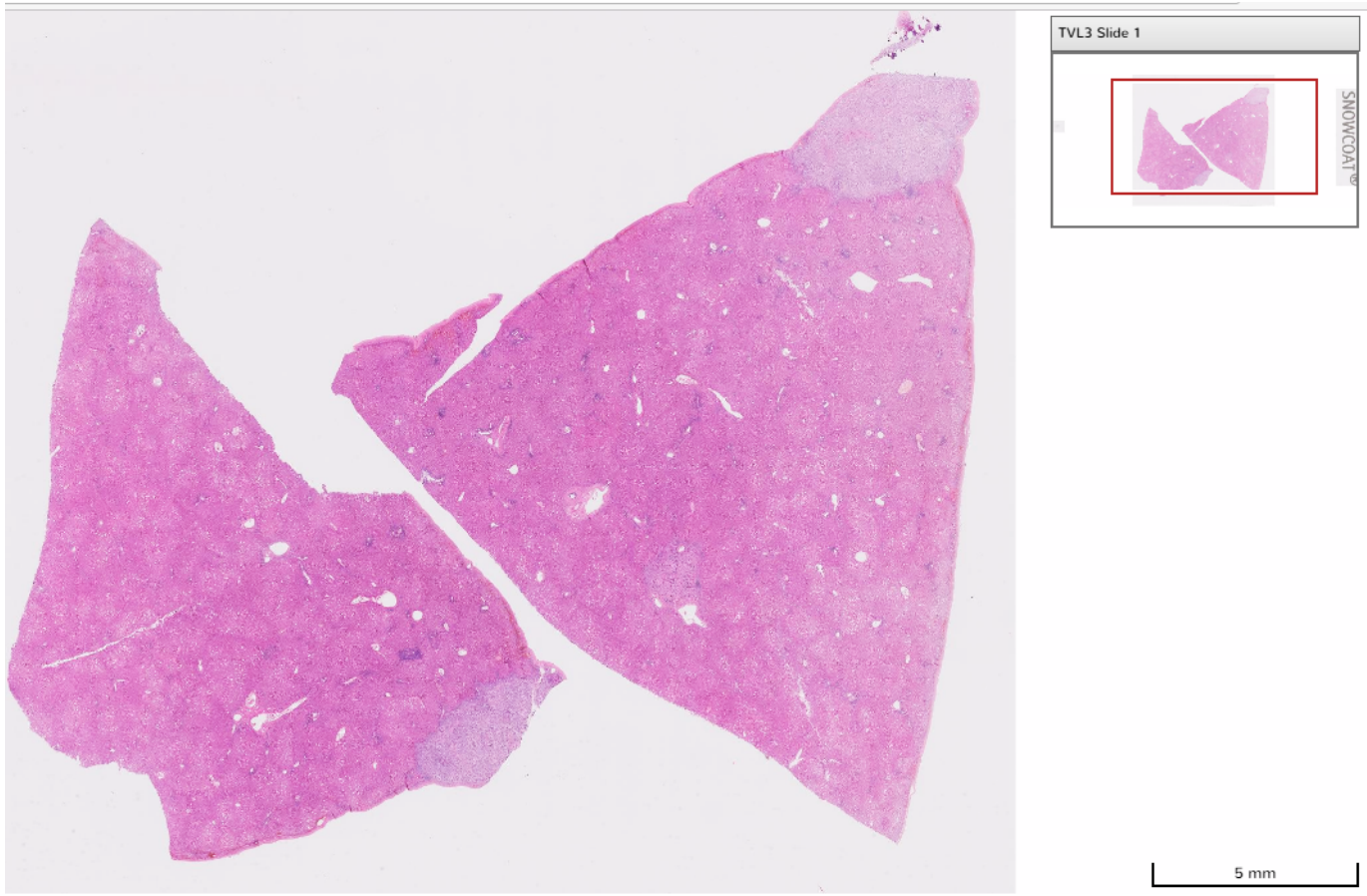
Solid glandular lesion	Gross characteristics	Histological/Immunohistoch. characteristics
Von Meyenburg complex	Multiple discrete nodules, related to portal tracts; may contain bile; usually <0.5 cm	Irregular or rounded ductal structures lined by flattened or cuboidal epithelium; lumina may contain proteinaceous fluid or bile; dense fibrous stroma; usually portal or periportal; CK7+/CK19+
Bile duct adenoma	Solitary subcapsular, whitish firm discrete nodule; usually < 2cm	Small, round tubules, lined by cuboidal epithelium, may contain mucin; often contains normal portal tracts; CK7+/CK19+
Biliary adenofibroma	Circumscribed whitish tumour, with microcystic areas, may be as large as 16 cm	Complex tubulo-cystic sructures with complex branching, single-layered biliary epithelium, sometimes with mitotic activity; lumina may contain cellular debris; abundant fibroblastic stroma and/or ares of hyalinisation; CK7+/CK19+

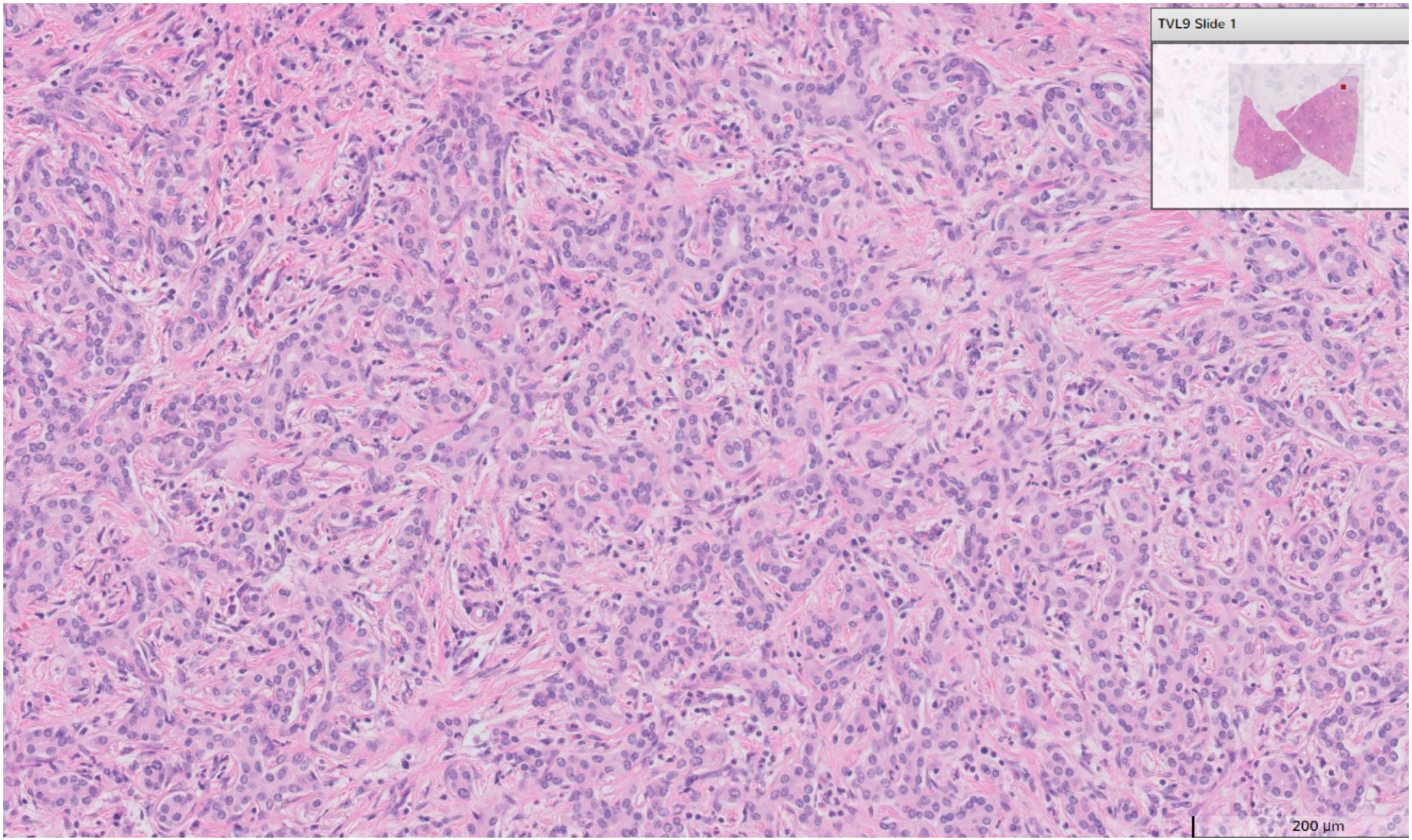
Von-Meyenburg



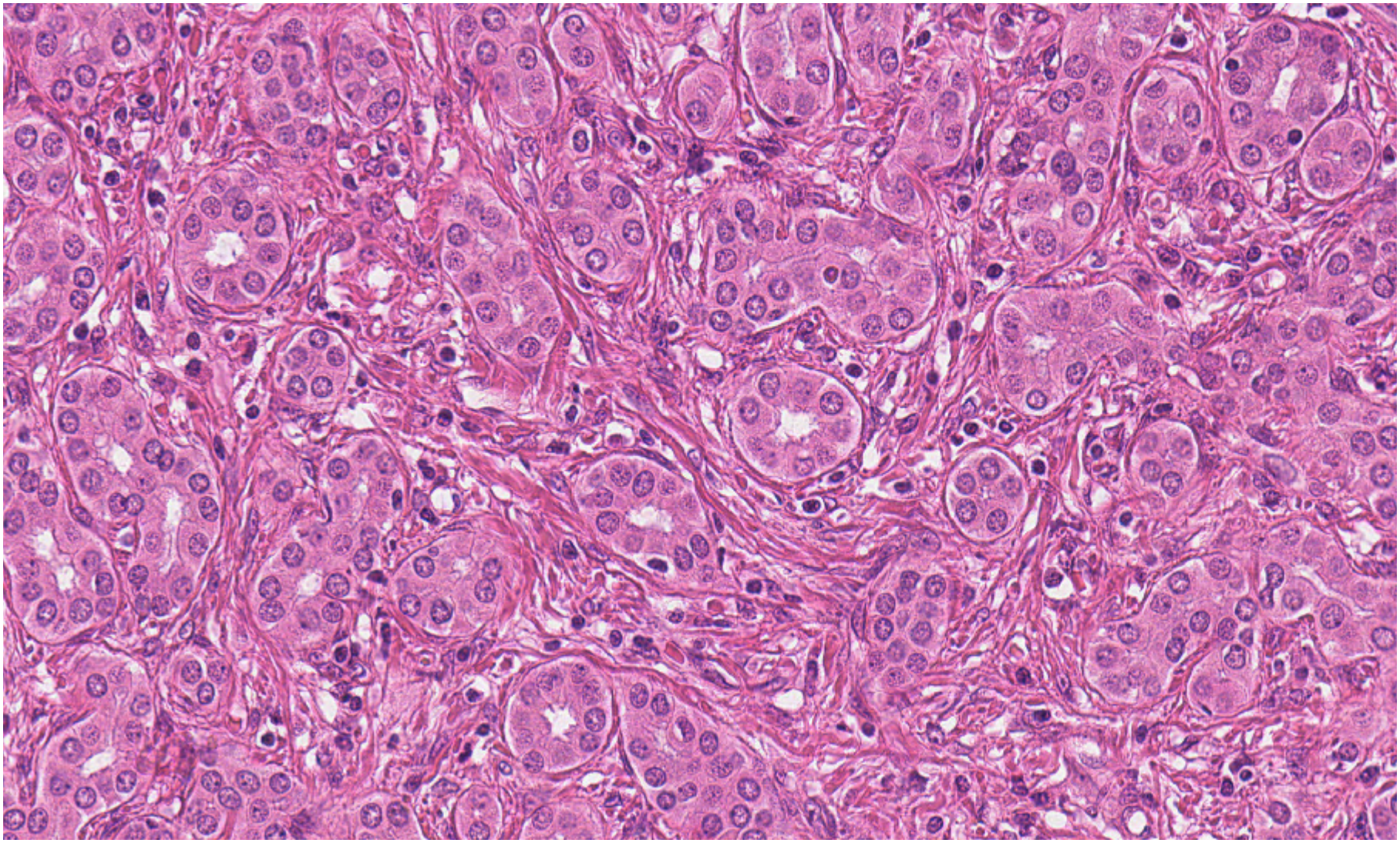


Bile duct adenoma





The ductules are relatively evenly spaced and form small, curvilinear glandular structures, separated by fibrous tissue. The cytology of the ductules is unremarkable.



The ductules are usually uniform in size, are not dilated. They have a tubular or curvilinear shape and are lined by cuboidal cells with bland, round to oval nuclei. No mitosis.

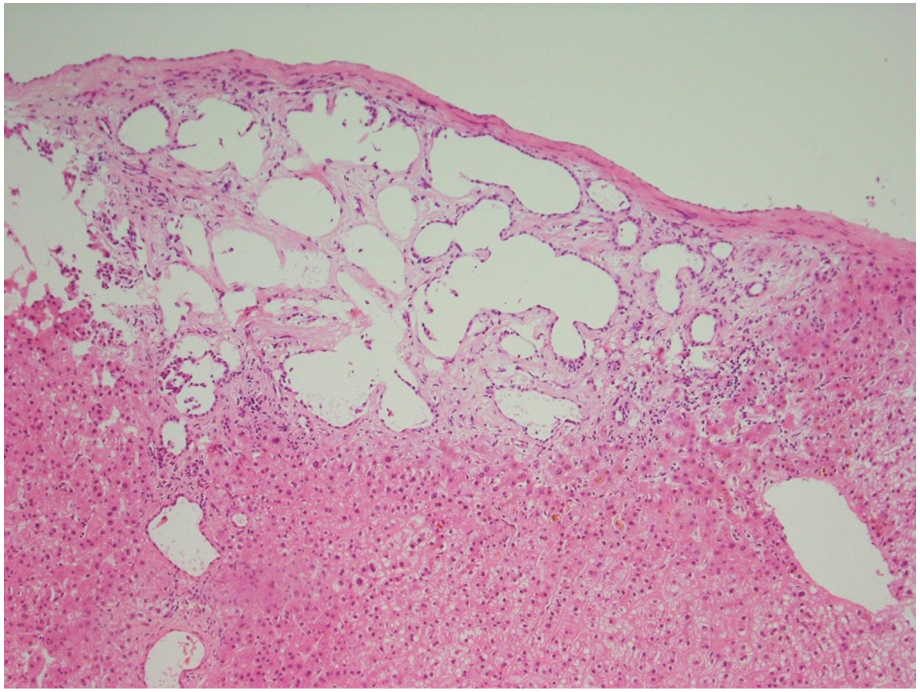
Differential diagnosis

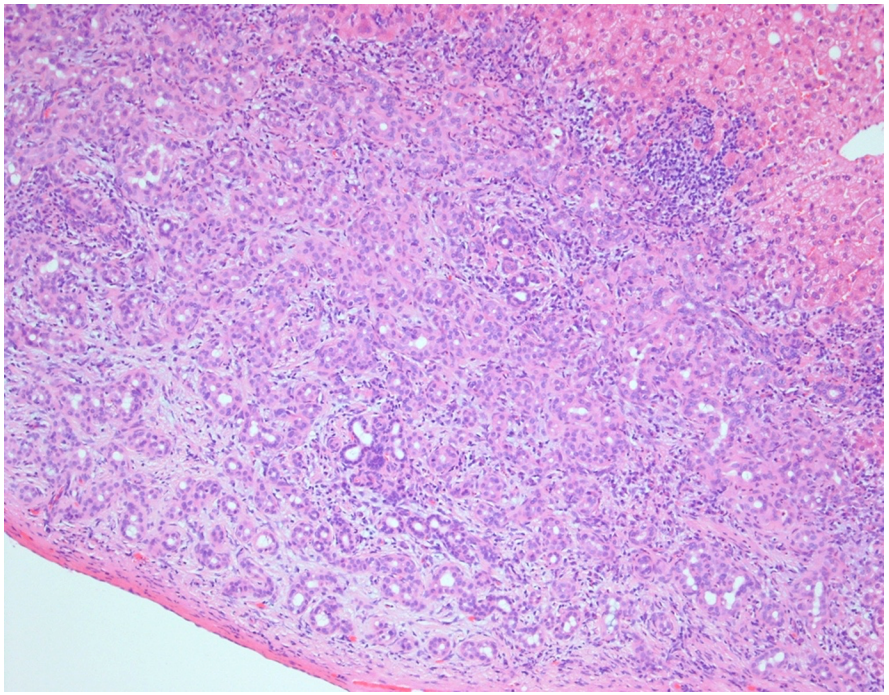
White spots on liver capsule (laparoscopy/tomy)

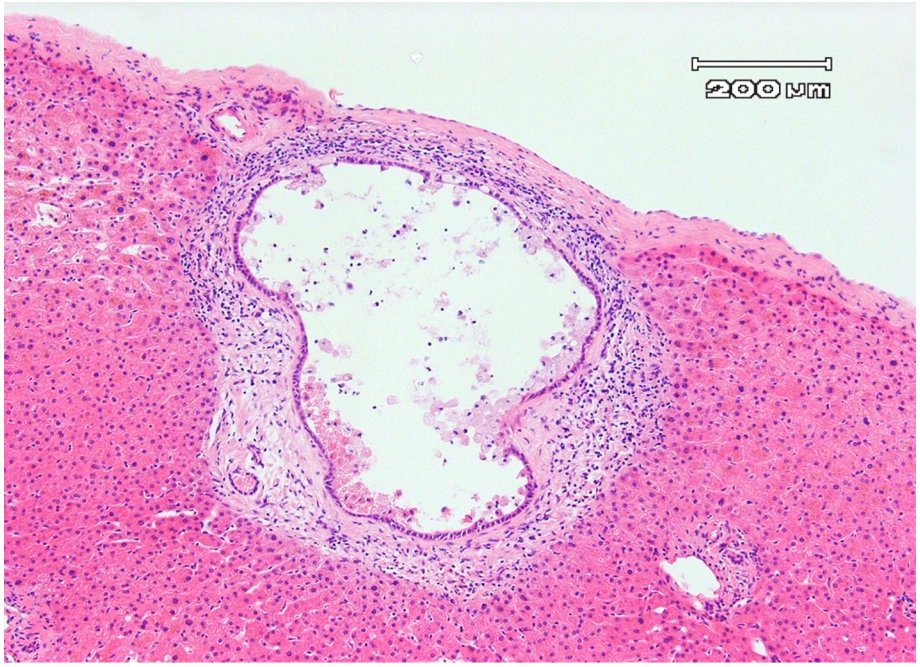
- Metastasis
- Bile duct hamartoma
- Bile duct adenoma
- Simple cyst
- Abscess
- Fibrous calcified nodule
- FNH
- Steatosis
- Primary malignant liver tumour

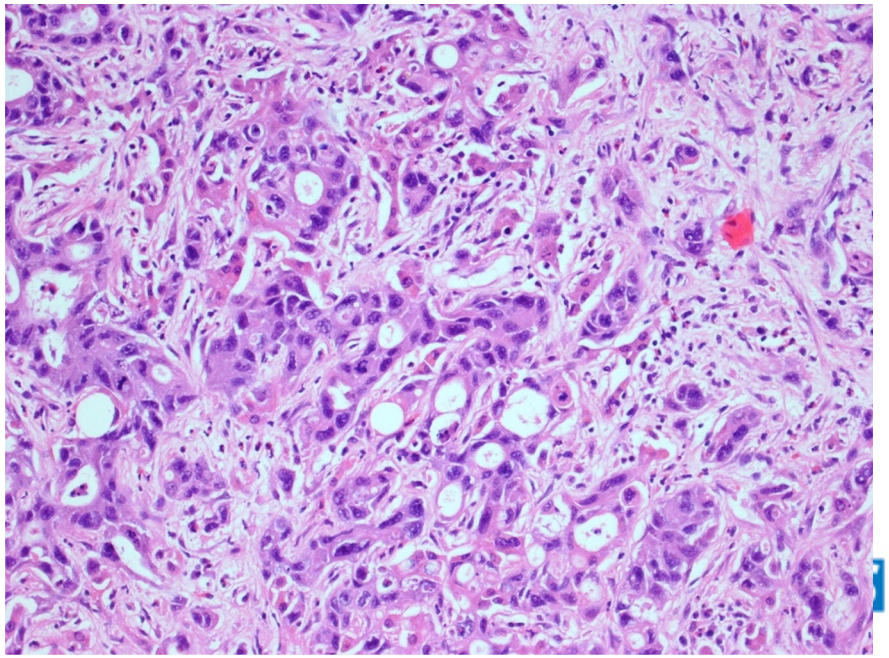
Biliary-like lesions

- Metastasis
- Bile duct hamartoma
- Bile duct adenoma
- Simple cyst
- Cholangitis/abscess
- Cholangiocarcinoma

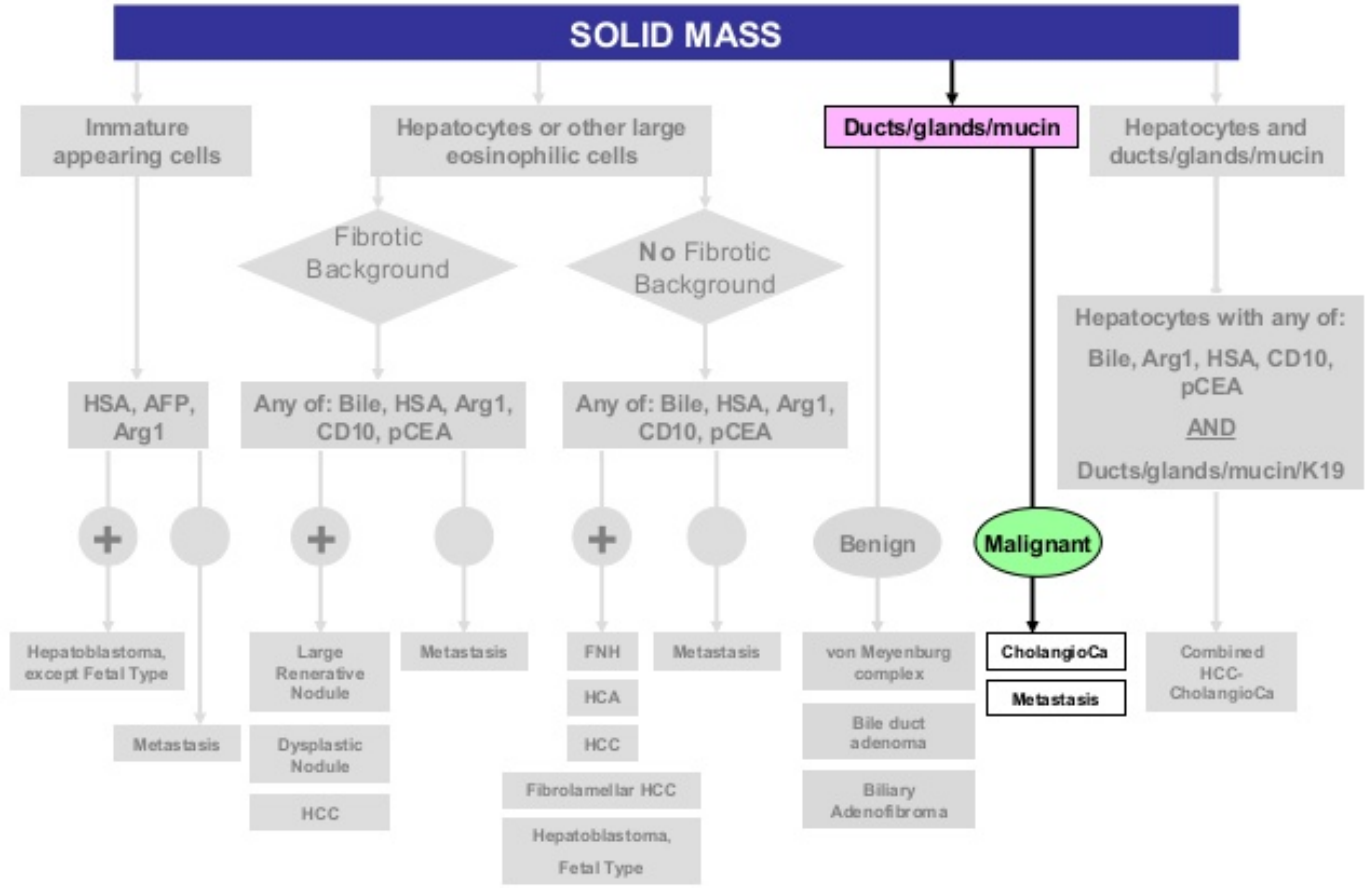




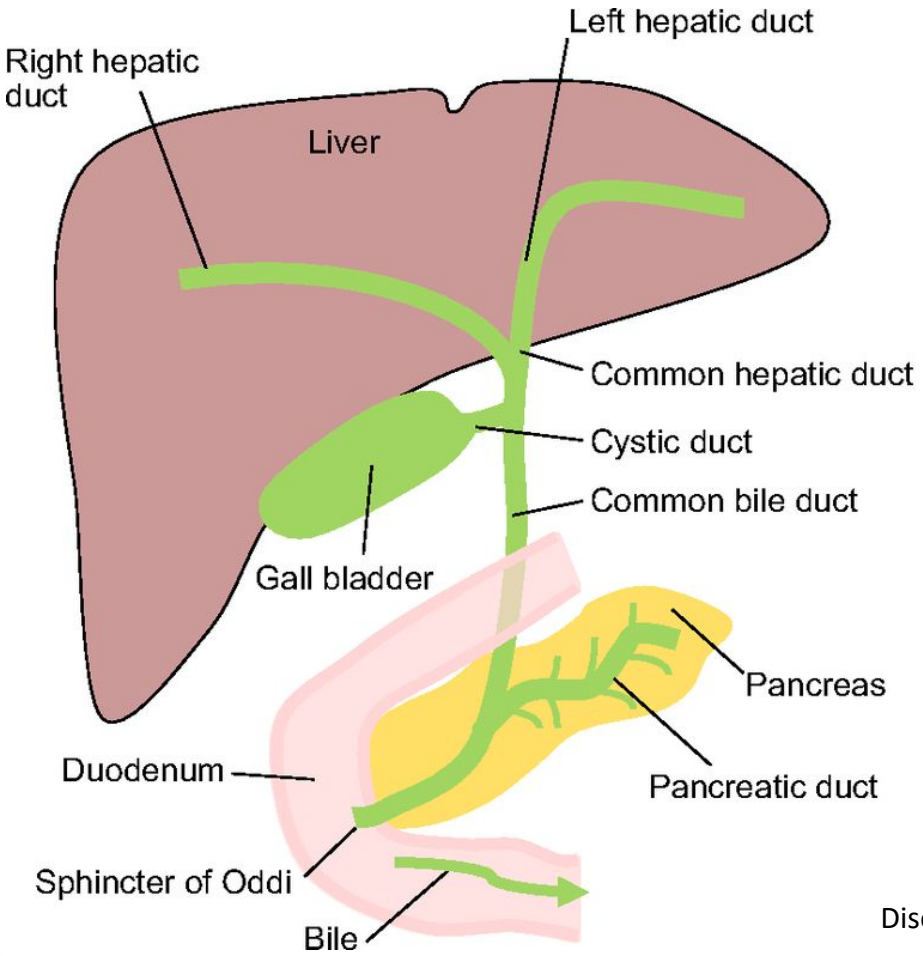

200 µm

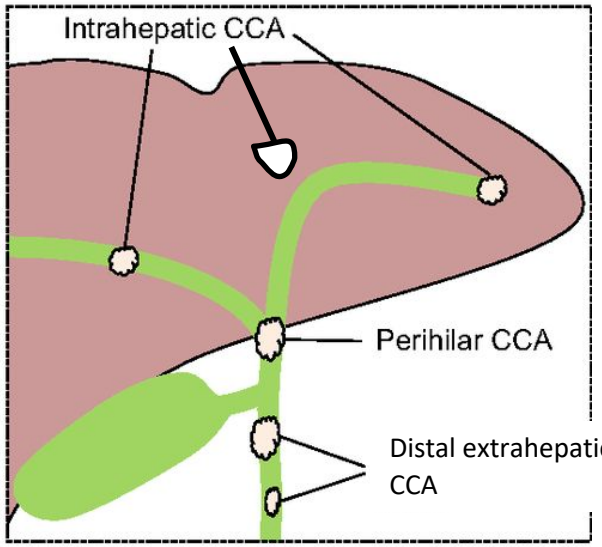


Diagnostic algorithm of liver lesions with solid mass



Cholangiocarcinoma
WHO 2019-TNM UICC 8th

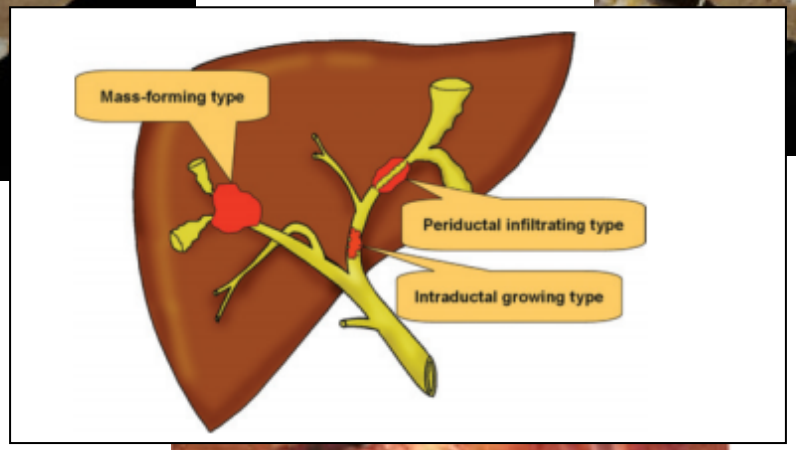


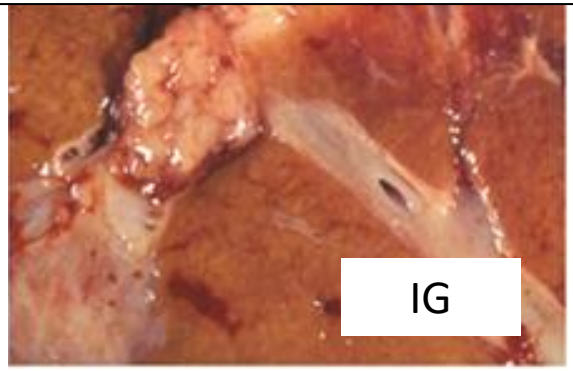


Disease Models & Mechanisms 2013 6: 281-292

Three main macroscopic patterns of growth

Liver Cancer Study Group of Japan





Srinagarind Medical Journal,Faculty of Medicine, Khon Kaen University.

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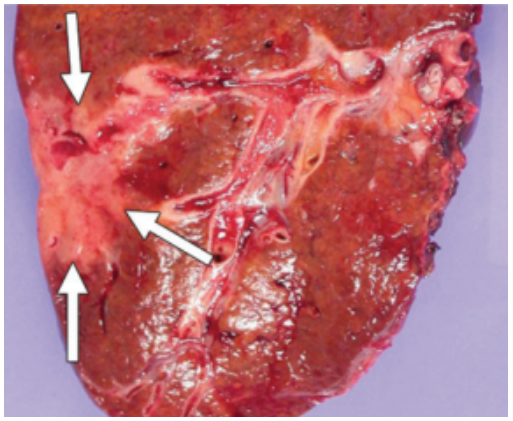
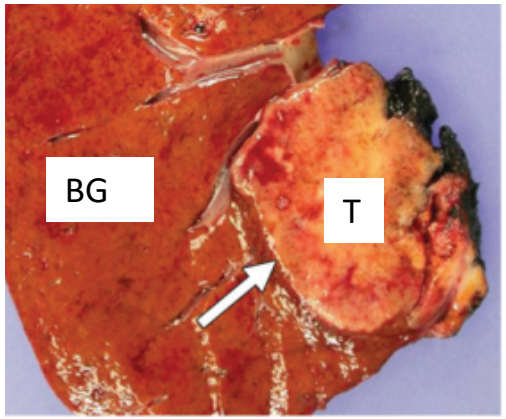
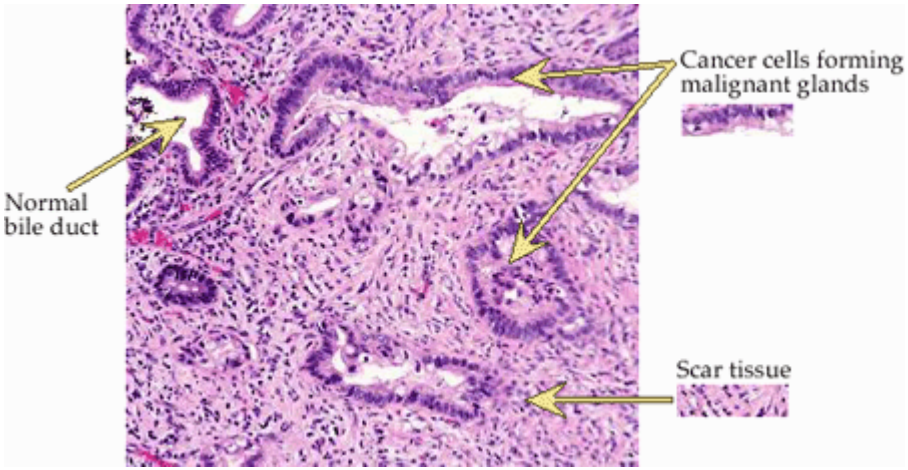
Intrahepatic cholangiocarcinoma

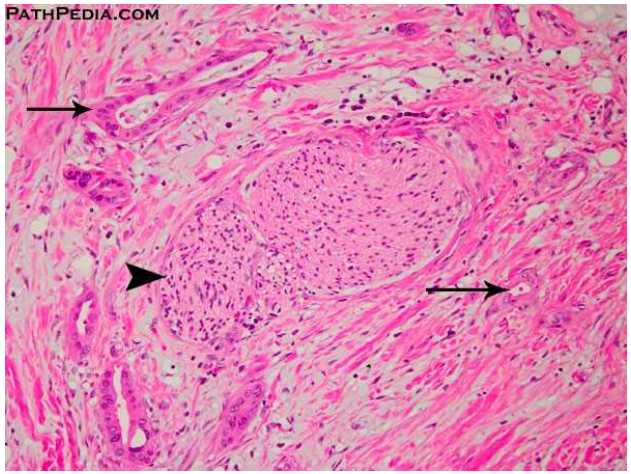
- Intrahepatic biliary tree between segmental ducts and ductules
  - Right and left bile duct tumours considered hilar
- Two main subtypes:
  - Large duct (close to the liver hilum, proximal to right and left hepatic ducts, preferentially periductal infiltrating pattern)
  - Small duct (located in the hepatic periphery, primarily mass-forming pattern)
- Differential diagnosis: metastasis, bile duct adenoma, biliary adenofibroma, microhamartomas, peribiliary glands lesions, HCC





Solid malignant biliary and gland-forming lesions





Solid glandular lesion	Gross characteristics	Histological/Immunohistoch. characteristics
Intrahepatic cholangiocarcinoma	Variable appearance, any size: • Single firm nodule • Multiple nodules • Diffuse growth • Irregular periductal thickening • Intraductal polypoid mass • Any combination of above	Adenocarcinoma, often with abundant desmoplastic stroma, perineural invasion and/or mucin secretion. Immunoprofile: CK7+/CK19+/EMA+/CEA+. In 20% of cases CK20+
Metastatic pancreatobiliary ductal carcinoma	Single or multiple firm nodules of any size	Adenocarcinoma indistinguishable from cholangiocarcinoma either by morphology or by immunohistochemistry. Need radiological data.
Metastatic colorectal adenocarcinoma	Single or multiple nodules of any size, often with central necrosis	Adenocarcinoma, of the with garland patern and central dirty necrosis. Immunoprofile: CK20+/CDX2+/CK7-
Metastatic adenocarcinoma from other sites	Single or multiple of any size	Adenocarcinoma with variable appearance Immunoprofile: first segregate according to pattern of CK7 and CK20, then apply markers according to the suspected primary site

Differential diagnosis of unknown primary cancers based upon immunostaining for cytokeratin (CK) 7 and 20

CK7+ CK20+	CK7+ CK20-	CK7- CK20+	CK7- CK20-
Urothelial tumors	Non-small cell lung cancer	Colorectal cancer	Hepatocellular cancer
Mucinous ovarian cancer	Small cell lung cancer	Merkel cell cancer	Renal cell cancer
Pancreatic or biliary cancer	Breast cancer		Prostate cancer
	Endometrial cancer		Squamous cell lung cancer
	Nonmucinous ovarian cancer		Head and neck cancer
	Mesothelioma		
	Squamous cancer of cervix		
	Pancreatic or biliary cancer		

Modified from: Dabbs D. Diagnostic Immunohistochemistry, 2nd ed, Churchill Livingstone, 2006.

Sensitivities for various immunohistochemical markers in differentiating hepatocellular carcinoma, cholangiocarcinoma, and metastatic adenocarcinoma

	HCC	CC	MA
Hep Par 1	86-96%	0-12.5%	0-14%
GPC3	75-88%	0-19%	0-6%
pCEA	50-96%	100%	93-96%
MOC 31	0-14%	67-100%	66-100%
CK7	7-21%	78-100%	3-36%
CK8/18	70%	20%	
CK19	0-10%	44-80%	29-64%
CK20	0-5%	10-11%	30-74%
CD34	94-95%		

Original figure modified for this publication. Chan ES, Yeh MM. The use of immunohistochemistry in liver tumors. Clin Liver Dis 2010; 14:687.

TNM staging of intrahepatic CCA

(applied to intrahepatic CCA, cholangiocellular carcinoma and combined HCC/CCA)

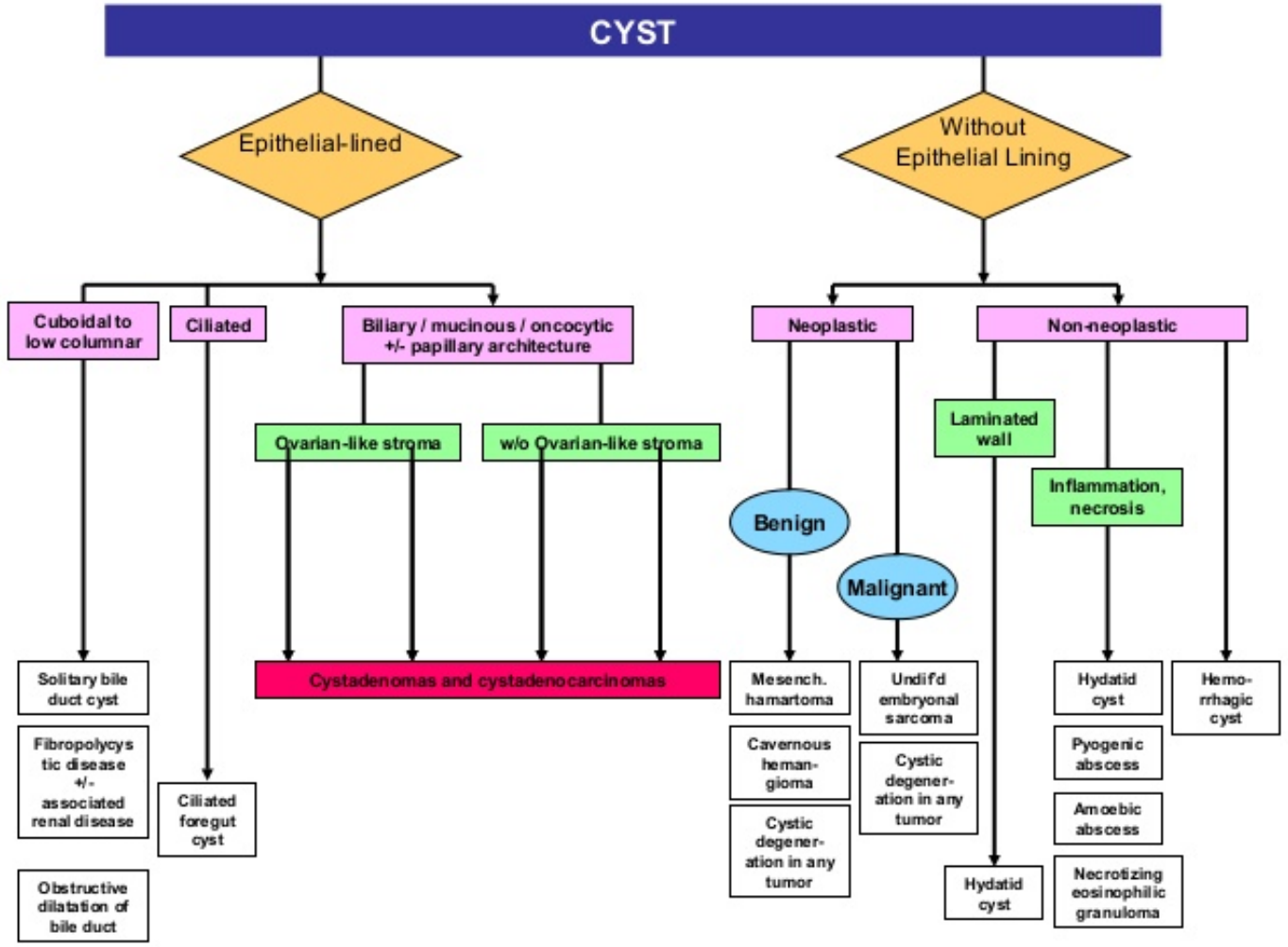
	UICC/AJCC 7th	UICC/AJCC 8th
T1	Solitary tumour without vascular invasion	**T1a** Solitary tumour 5 cm or less in greatest dimension without vascular invasion **T1b** Solitary tumour >5cm without vascular invasion
T2	**T2a** Solitary tumour with vascular invasion **T2b** Multiple tumours with or without vascular invasion	Solitary tumour with intrahepatic vascular invasion or multiple tumours, with or without vascular invasion
T3	Tumour perforates the visceral peritoneum or directly invades adjacent extrahepatic structures	Tumour perforating the visceral peritoneum
T4	Tumour with periductal invasion (periductal growth pattern)	Tumour involving local extrahepatic structures by direct hepatic invasion
N1	Regional LN mets	Regional LN mets (histological examination of 6 or more lymph nodes)
M1	Distant metastasis	Distant metastasis

TNM staging of perihilar CCA

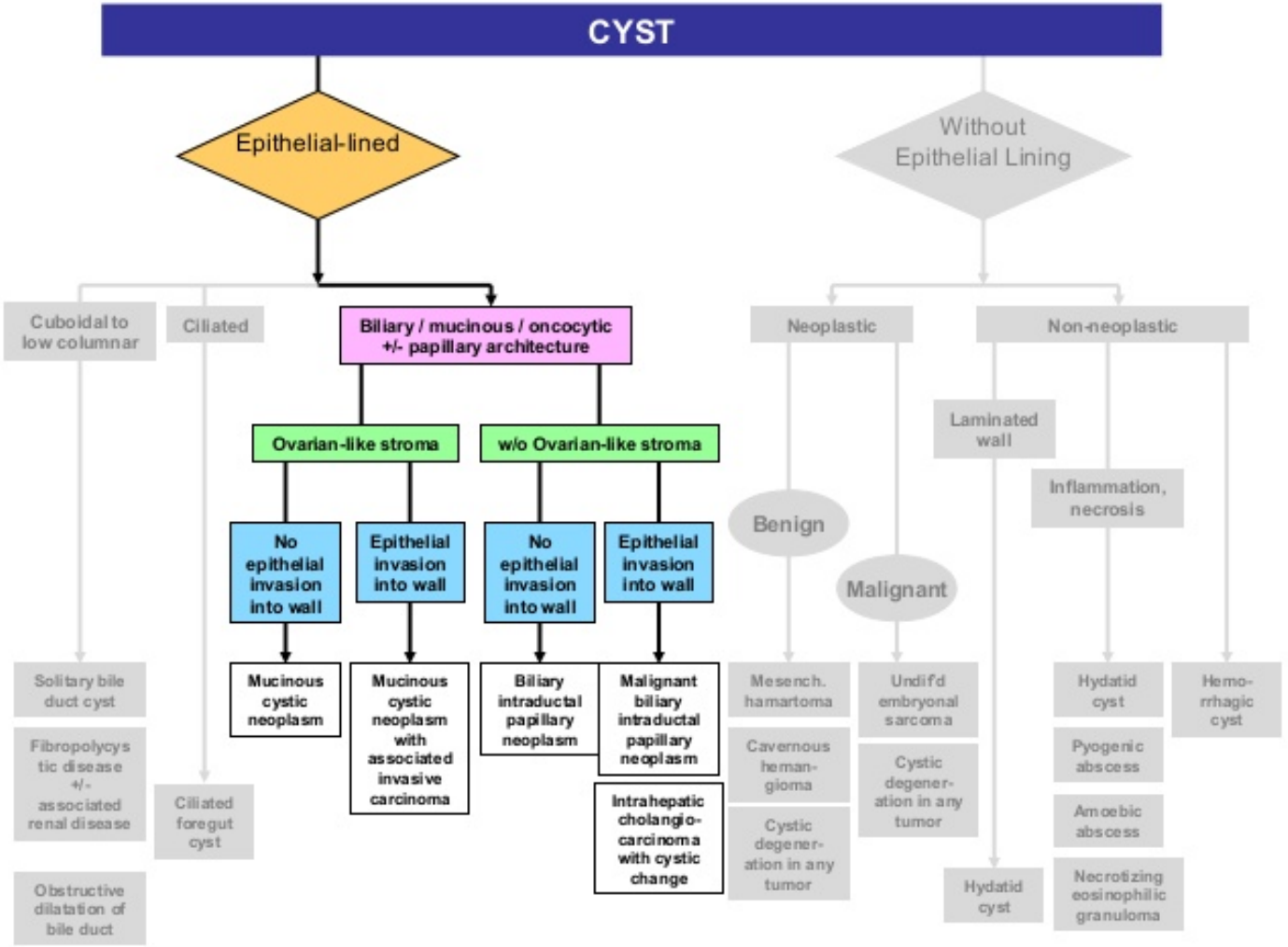
(applied to extrahepatic bile ducts of perihilar localisation (Klatskin tumours). Included are the right, left and the common hepatic ducts

	UICC/AJCC 7th - 8th
T1	Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	**T2a** Tumour invades beyond the wall of the bile duct to surrounding adipose tissue **T2b** Tumour invades adjacent hepatic parenchyma
T3	Tumour invades unilateral branches of the portal vein or hepatic arery
T4	Tumour invades the main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
N1	Regional LN mets
M1	Distant metastasis

Diagnostic algorithm of cystic lesions of the liver



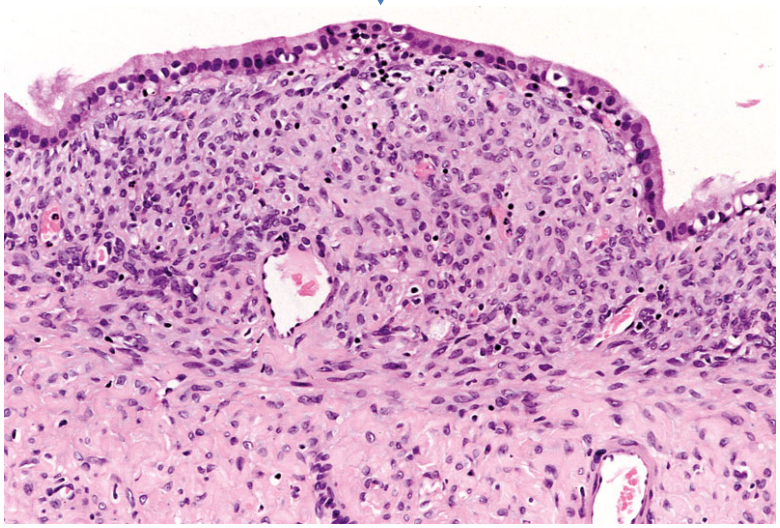
Diagnostic algorithm of cystic lesions of the liver



Cystic neoplasms
Truly cystic-epithelium lined

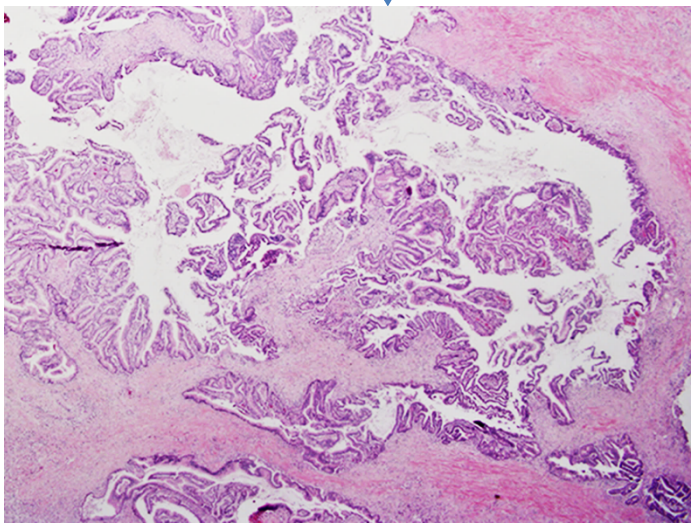
Ovarian-like stroma

YES



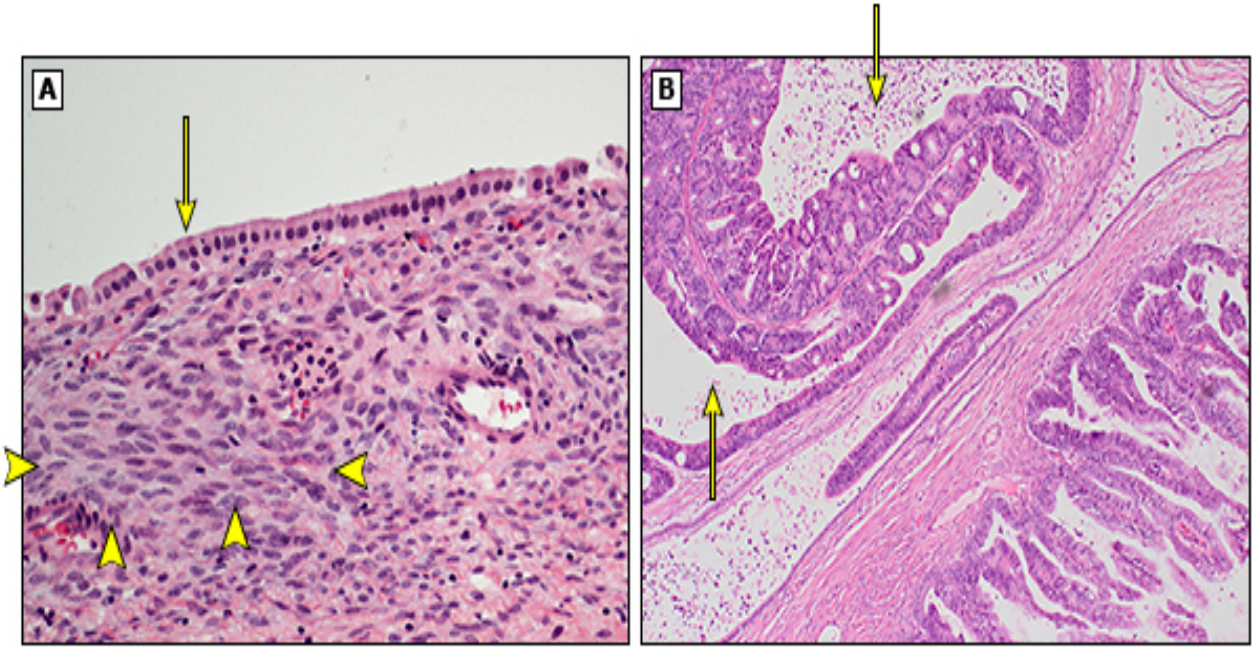
Mucinous cystic neoplasm (ex biliary cystadenoma)

NO



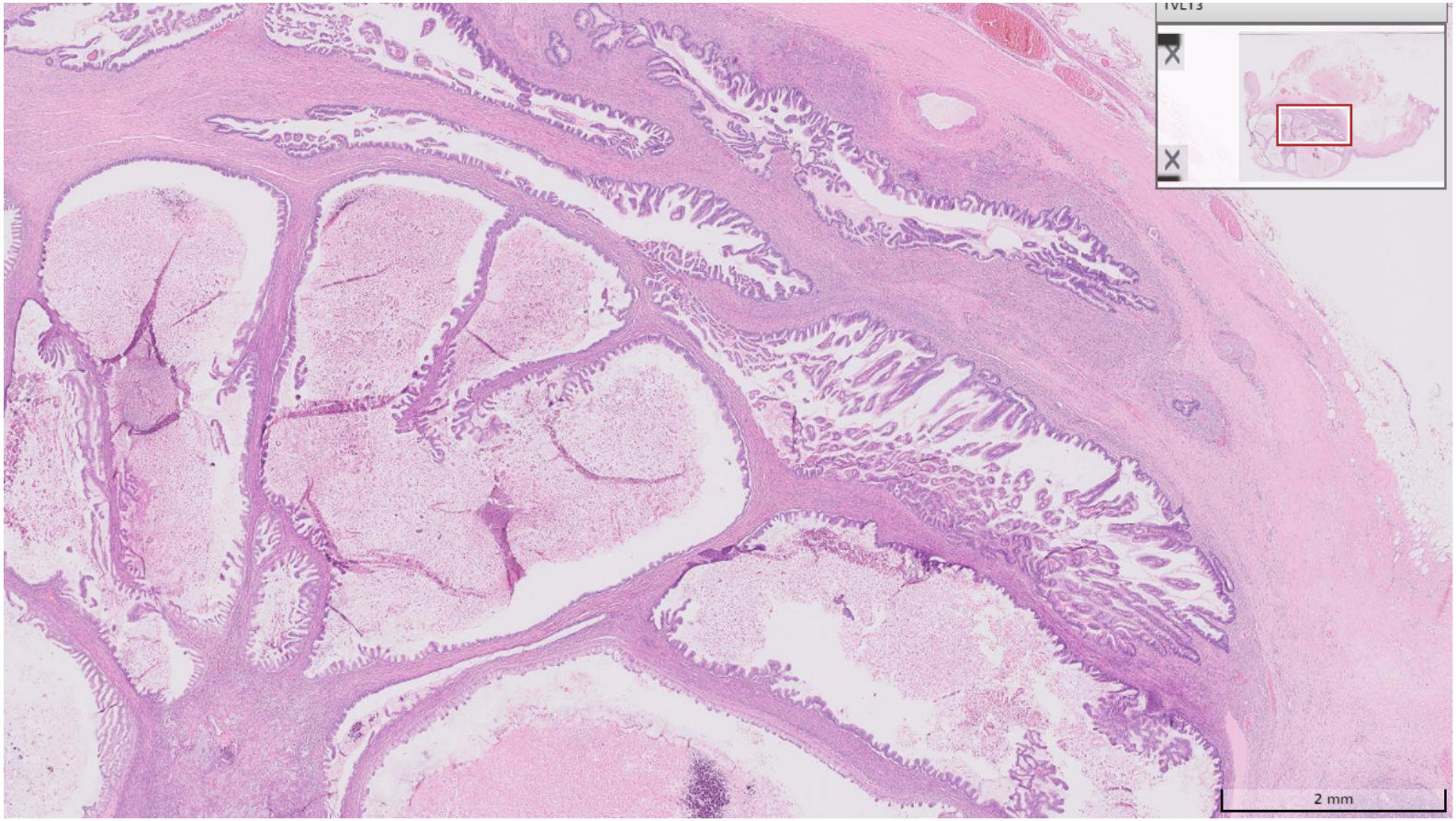
Intraductal papillary neoplasm of the bile duct (IPN-B)

Mucinous cystic neoplasm (ex biliary cystadenoma)

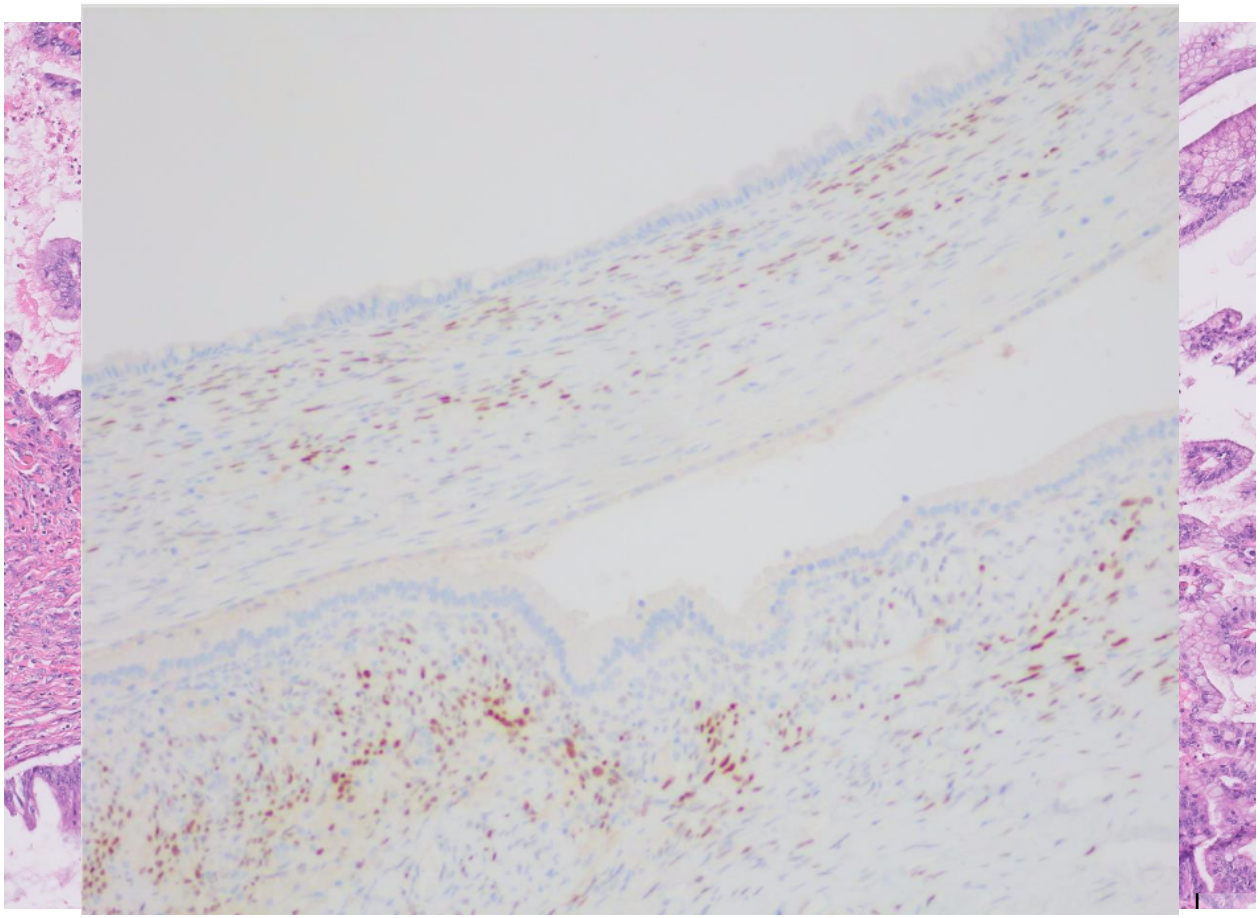


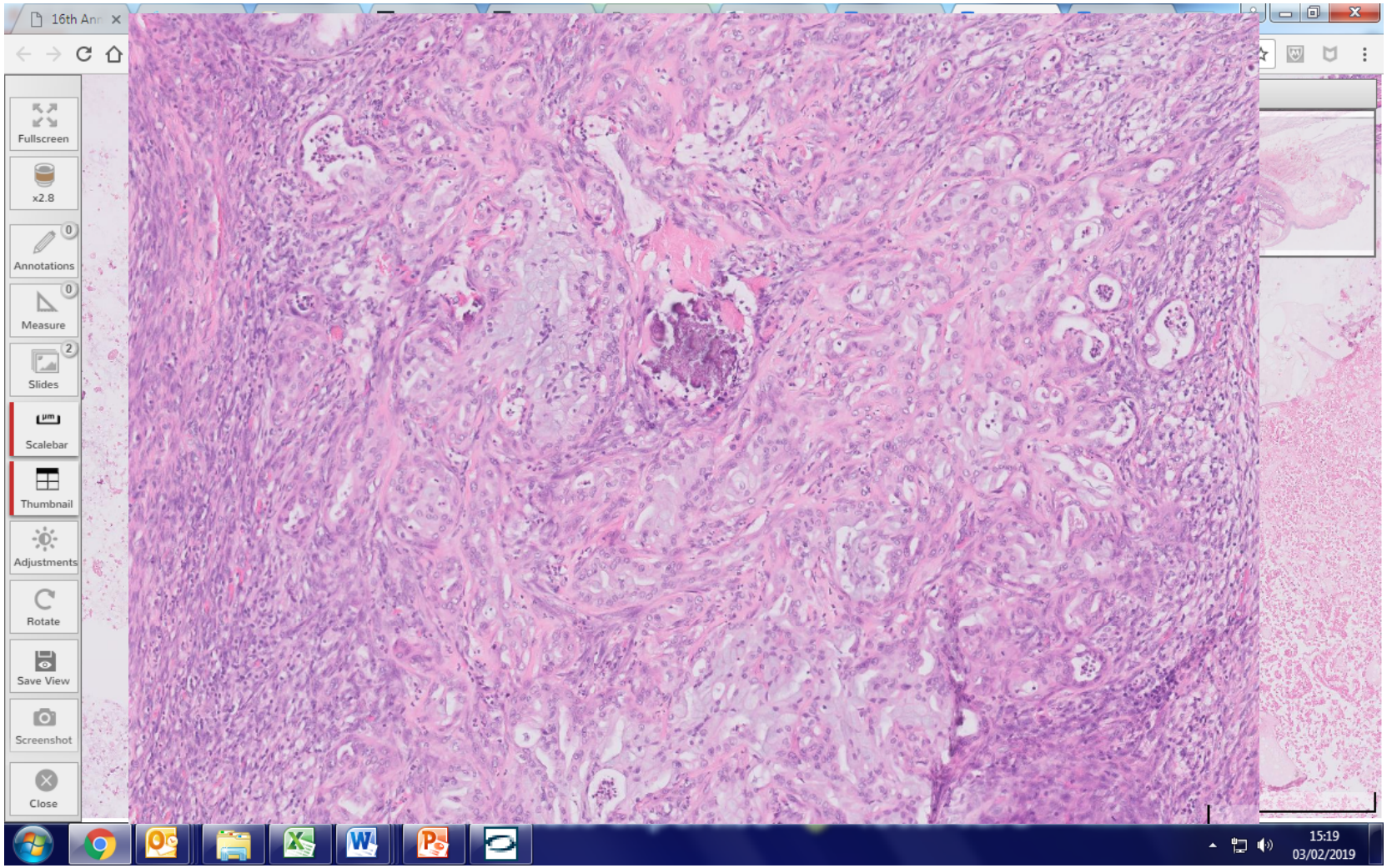
A) Low-grade showing bland neoplastic epithelial cells (arrow) and underlying compact spindle-cell "ovarian-type" stroma (arrowheads).
B) High-grade composed of multiloculated cysts (arrows) that are lined by pleomorphic neoplastic cells with cribriform pattern.

CASE N.15



CASE N.15

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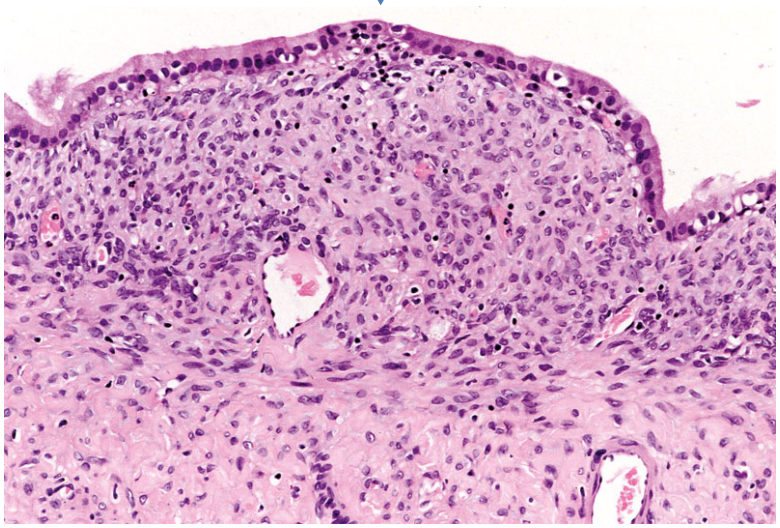
Cystic neoplasms
Truly cystic-epithelium lined

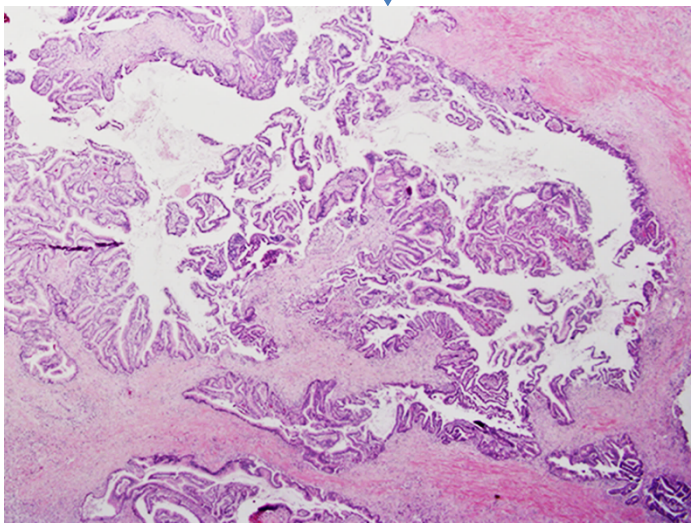
Ovarian-like stroma

YES



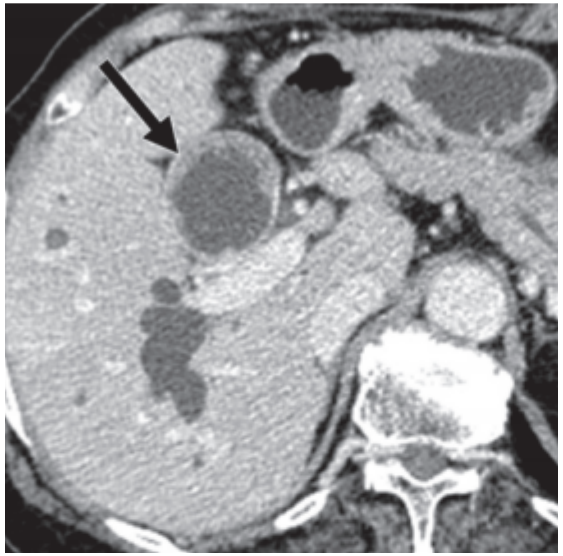
Mucinous cystic neoplasm (ex biliary cystadenoma)

NO

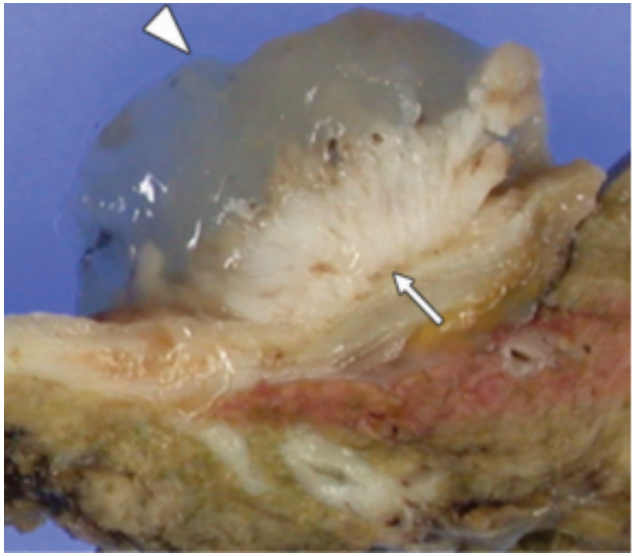


Intraductal papillary neoplasm of the bile duct (IPN-B)

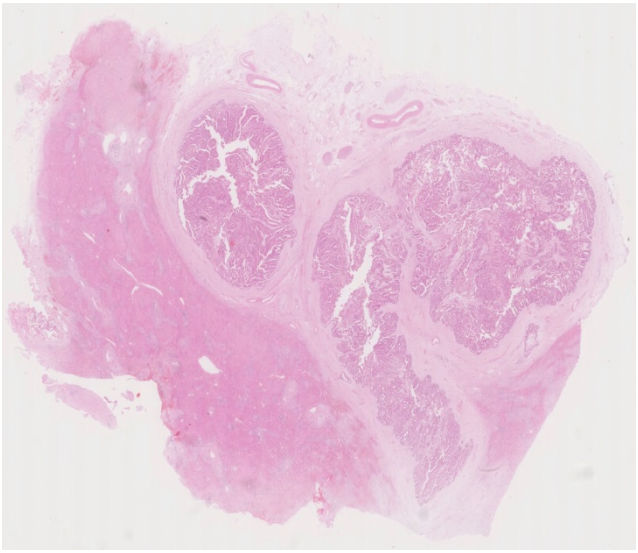
Intraductal papillary neoplasm of the bile duct (IPN-B)



CT scan shows a markedly dilated intrahepatic duct with mural nodules or irregular wall thickening (arrow).



The gross specimen reveals an intraductal greyish polypoid friable tumour (arrow) and mucin (arrowhead).



Histology shows an intraductal papillary biliary neoplasm

RadioGraphics 2009; 29:683–700

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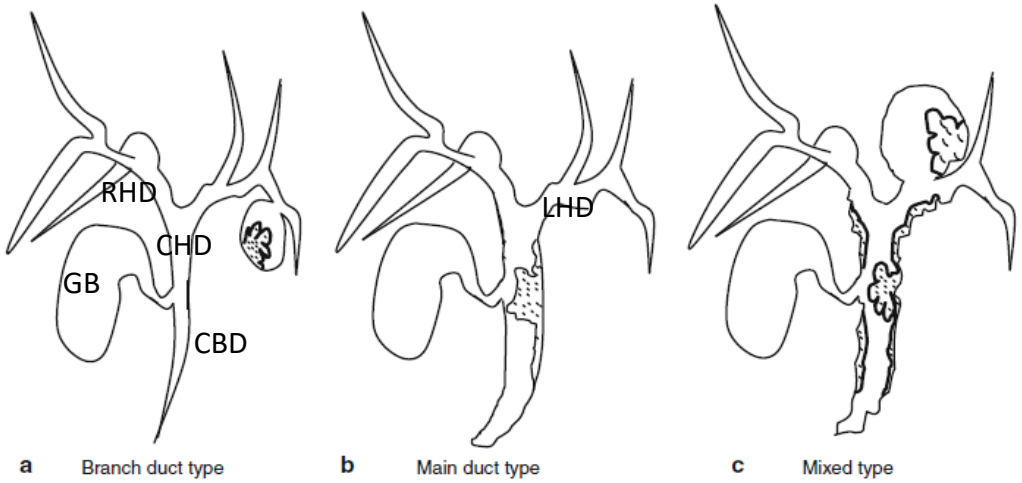
Intraductal papillary neoplasm of the bile duct (IPN-B)

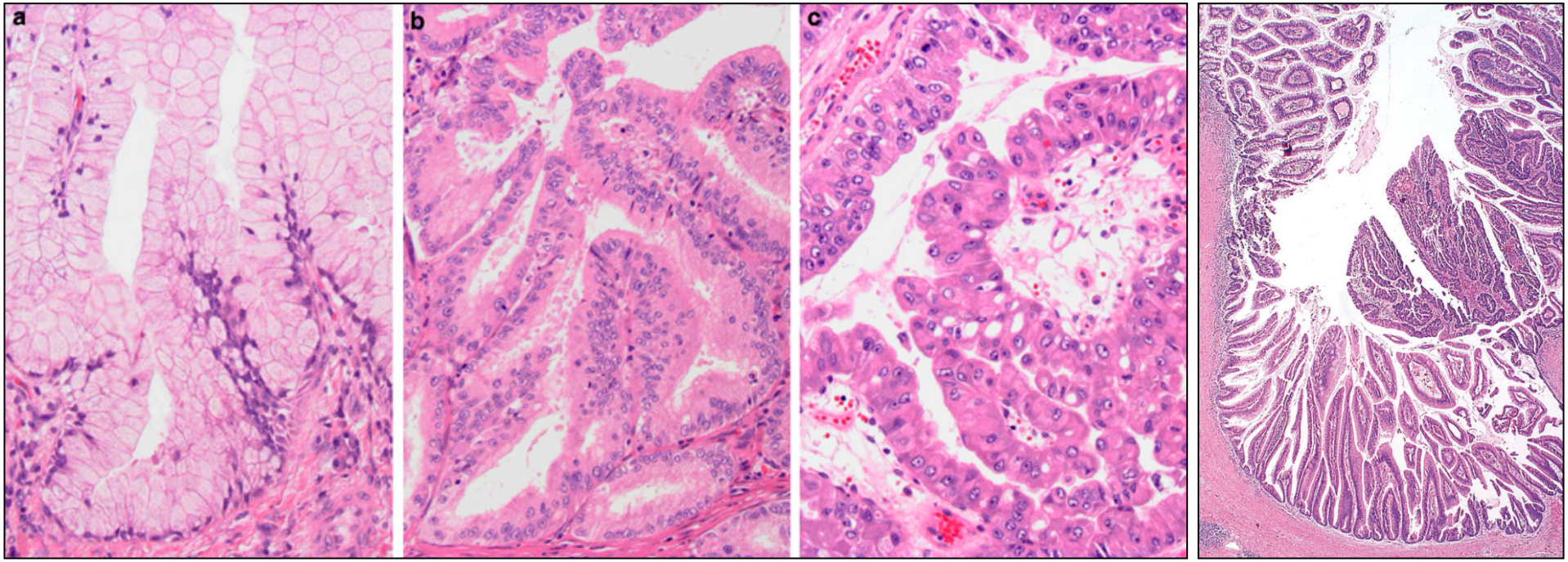


A) Branch duct type IPN-B: an ectatic lesion of the intrahepatic bile duct, which includes the proximal bile duct of second order biliary radicals, without dilatation of the extrahepatic bile duct.

B) Main duct type IPN-B: lesion involving the extrahepatic bile duct, which includes the right hepatic duct, left hepatic duct, hilar bile duct and common bile duct.

C) Mixed type IPV-B had the characteristics of both branch duct and main duct types

Intraductal papillary neoplasm of the bile duct (IPN-B)



Gastric type | Pancreatobiliary type | Oncocytic type | Intestinal type

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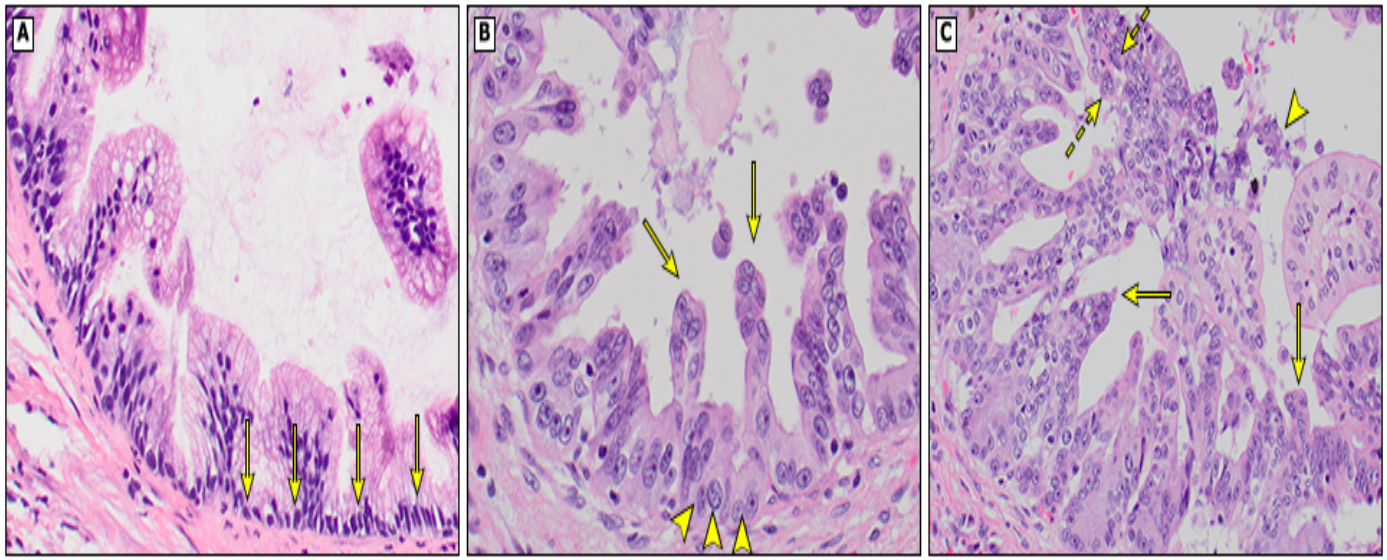
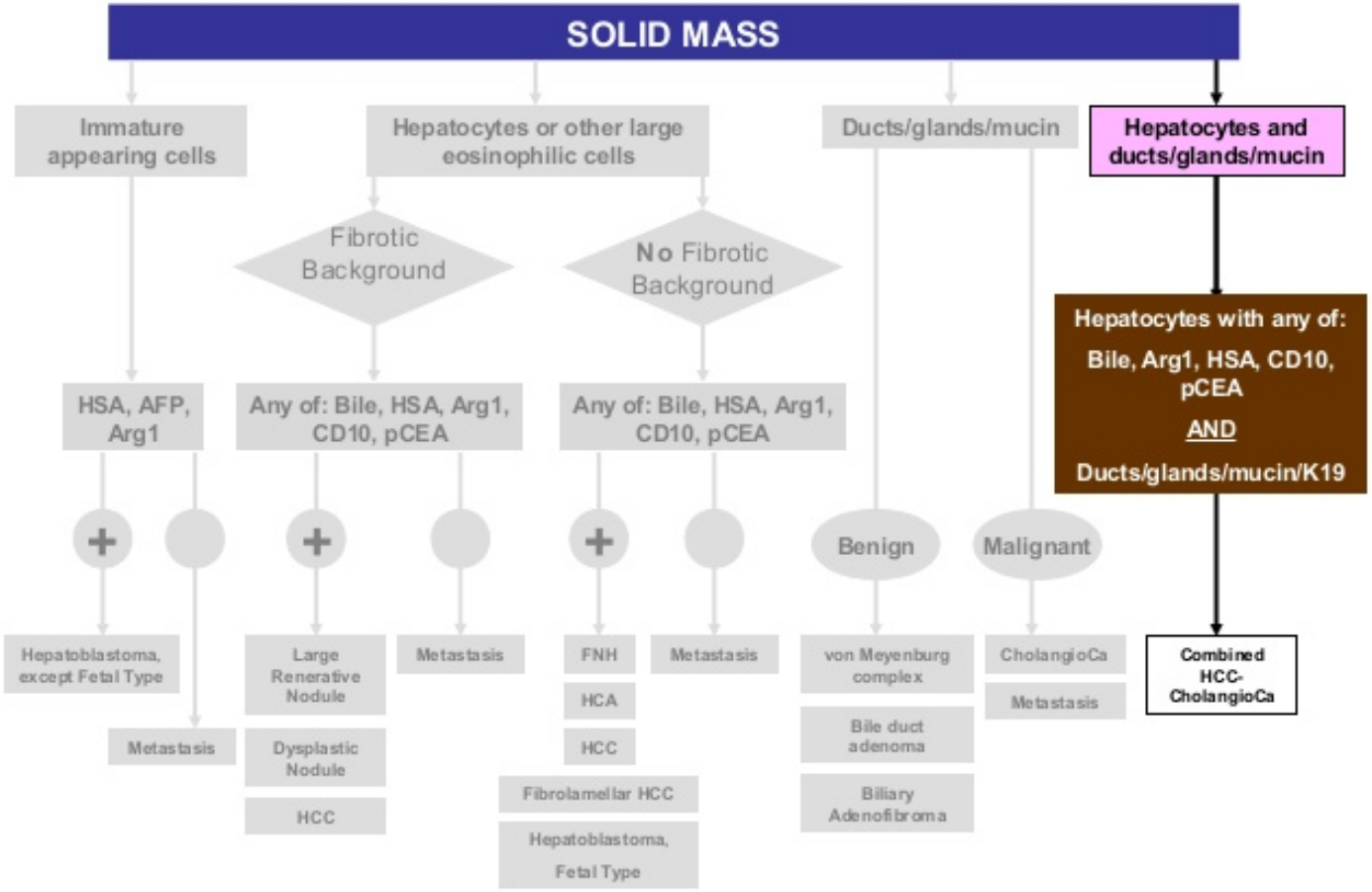
Bile duct premalignant lesions

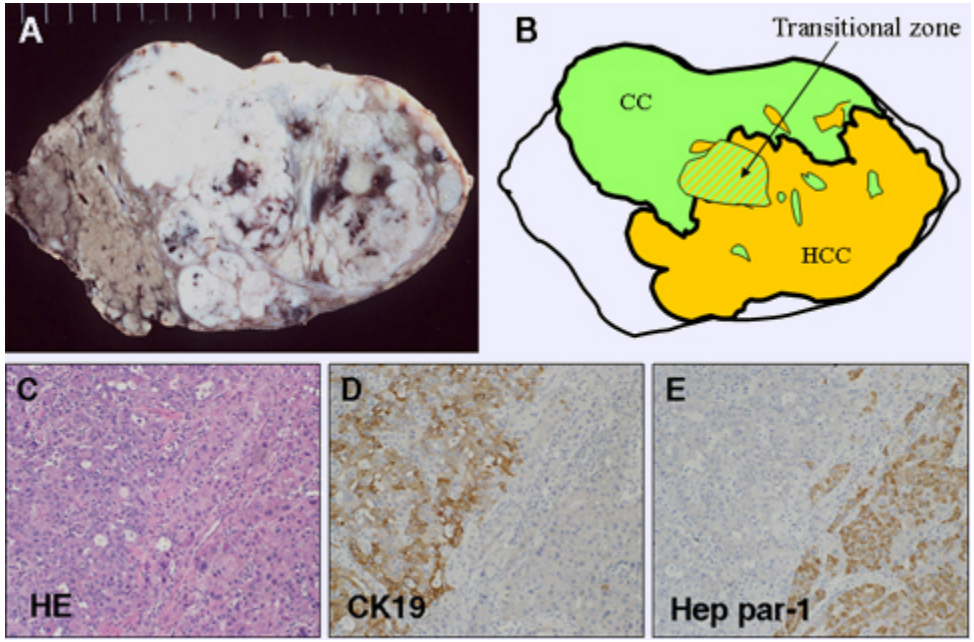


	Premalignant lesion	Morphology
Low-grade	Bil-IN1	Flat or micropapillary architecture with basally located and relatively uniform nuclei (arrows).
	Bil-IN2	Pseudopapillary or micropapillary architecture with nuclear pseudostratification reaching the luminal surface (arrows). The nuclei demonstrate dysplastic nuclear changes, including enlargement, hyperchromasia, and irregular nuclear membrane. Some variations in nuclear sizes and shapes are seen (arrowheads).
High-grade	Bil-IN3	Pseudopapillary lesion, cytologically resembling carcinoma, but invasion through the basement membrane is absent. Loss of nuclear polarity resulting in cellular piling at luminal surface (arrows) and "budding off" of small clusters of cells in the lumen (arrowhead). The cells have cytologically malignant features with hyperchromasia, nuclear membrane irregularities, and large nuclei (dashed arrows).

Diagnostic algorithm of liver lesions with solid mass



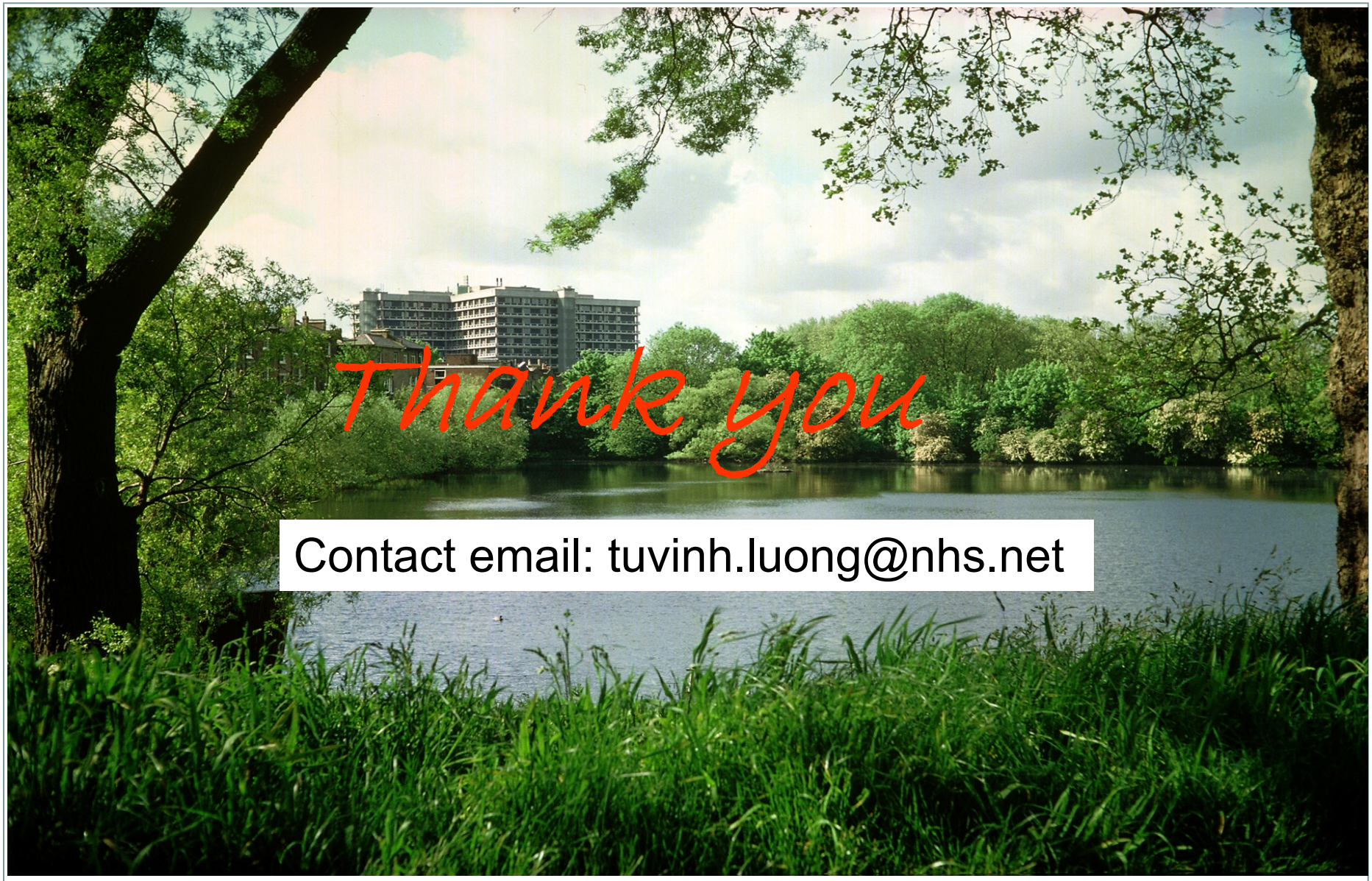
COMBINED HC/CC



C-E: Border zone between HCC and CC. Moderately differentiated HCC (right) with vague grandular component (left). The glandular tumour cells are positive for CK19 and HCC component is positive for Hep par-1.

Exceptions to the simplified algorithmic scheme

- **Rare neoplasms**
  (microcystic adenoma, transitional liver cell tumour)
- **Mesenchymal tumours**
  (angiomyolipoma, epithelioid hemangioendothelioma and others)
- **Carcinoma with mixed epithelial-mesenchymal tumours**
  (calcifying nested stromal epithelial tumour…)



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