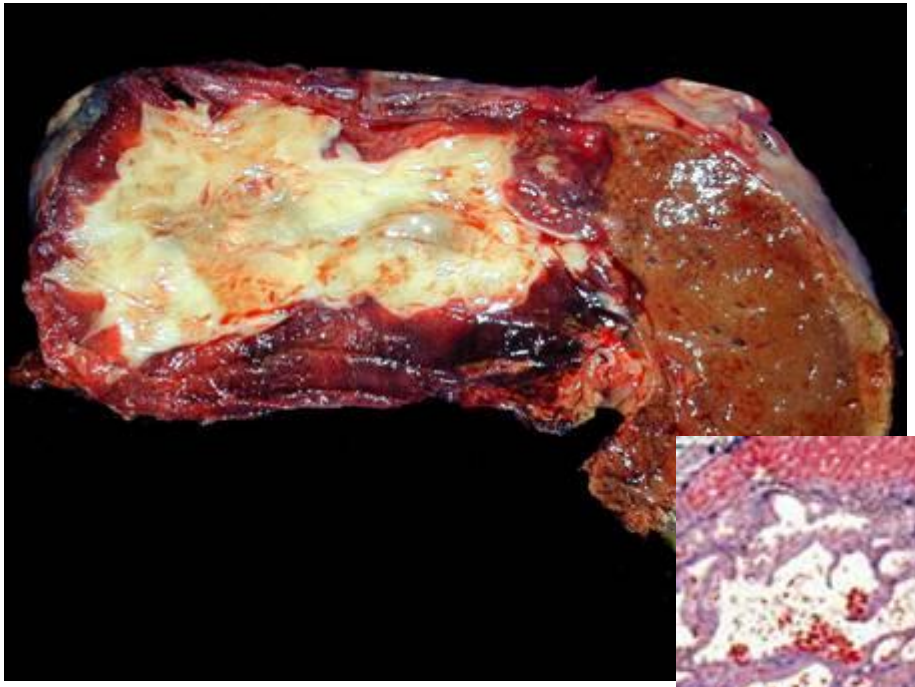
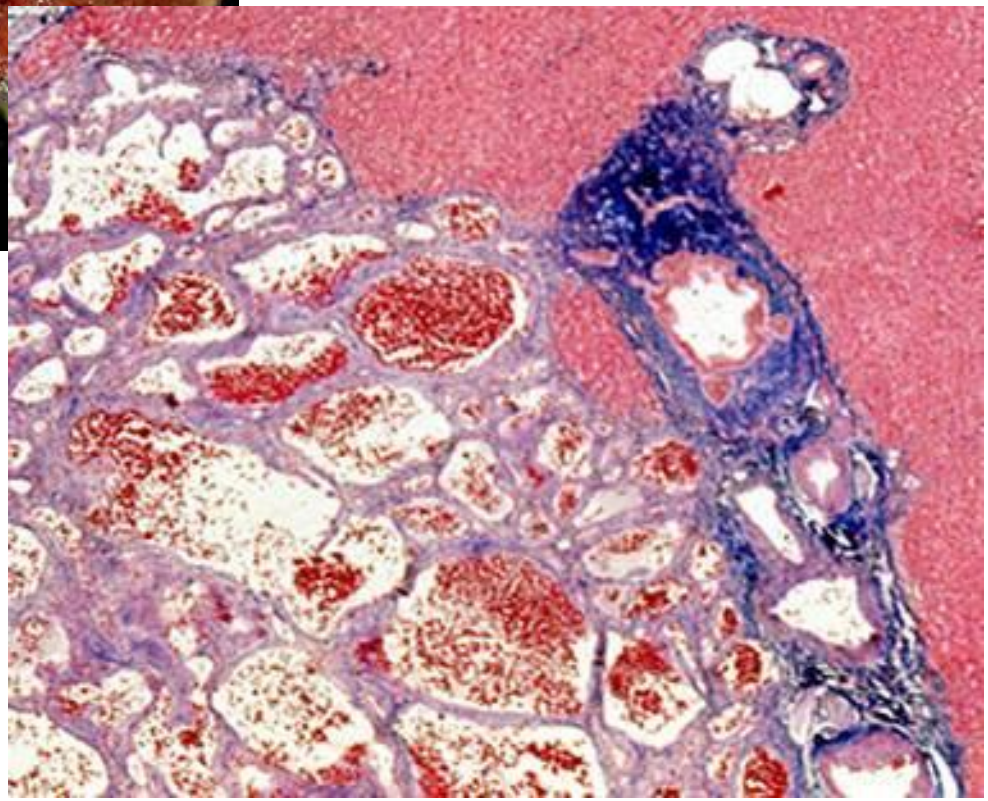
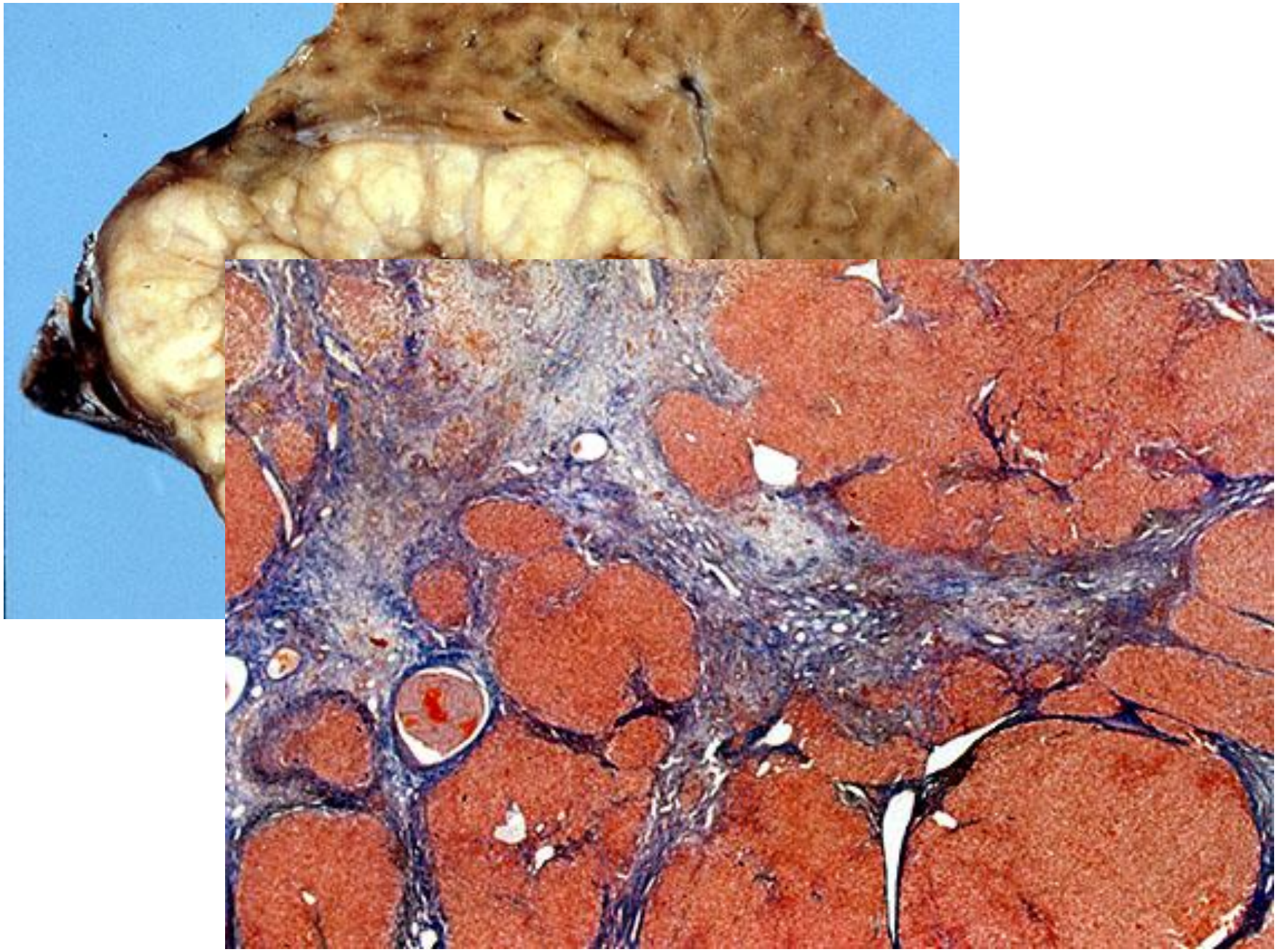
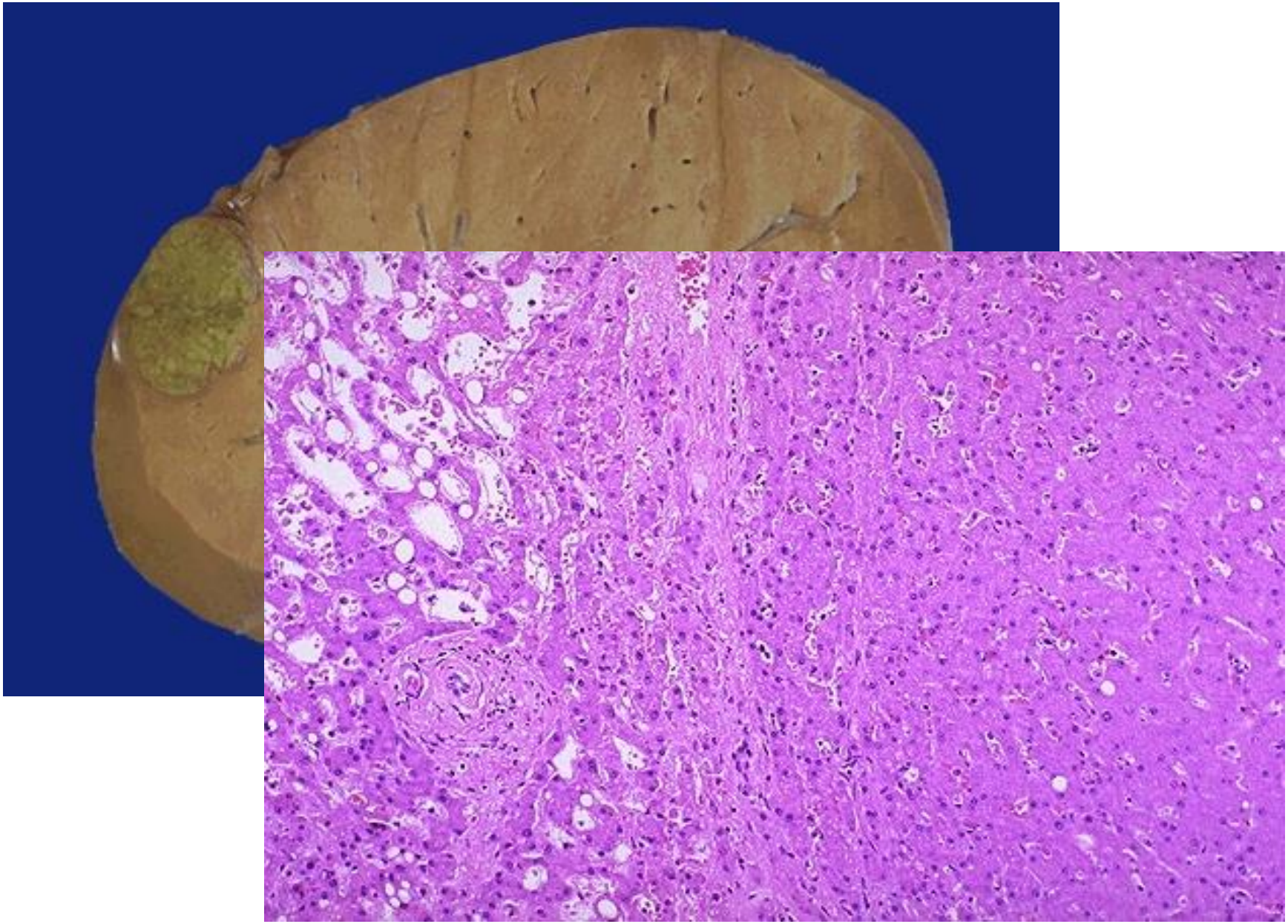
Tumeurs bénignes du foie

- Angiomes
- Hyperplasies nodulaires focales
- Adénomes
- Tumeurs rares
- Pseudo-tumeurs (stéatoses focales, perturbations hémodynamiques)







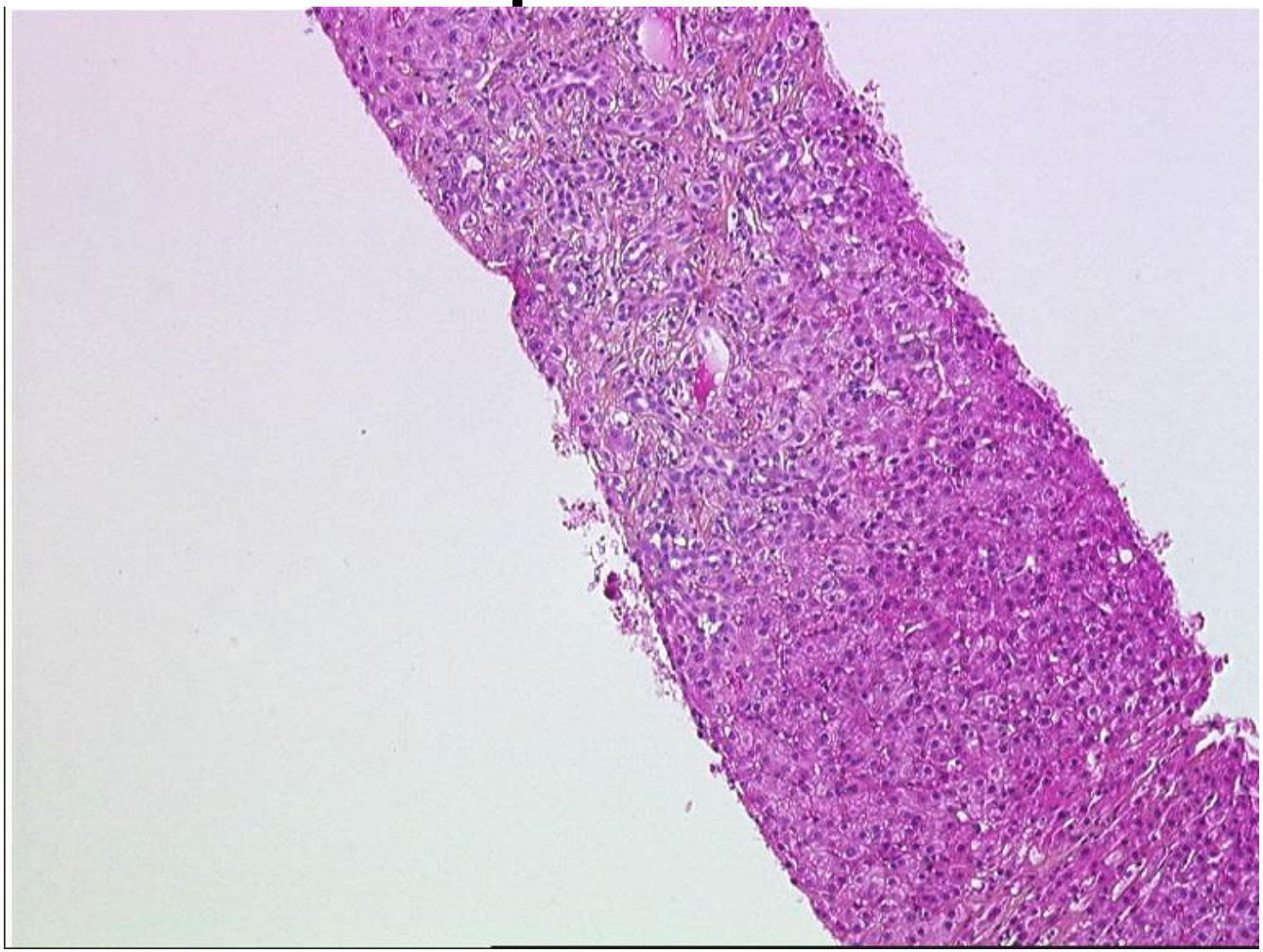


Application à la (ponction-) biopsie

- HNF
  - critères
    - disparition de l'architecture hépatique normale
    - présence de cloisons fibreuses
    - vaisseaux dystrophiques
    - néoductules et inflammation
    - remaniements sinusoïdaux
  - proposition d'un score histologique

Application à la (ponction-) biopsie

- HNF



Application à la (ponction-) biopsie

- Adénome
  - disparition de l'architecture hépatique normale
  - pas de cloison fibreuse
  - travées épaisses formées de «grands» hépatocytes éosinophiles ou stéatosiques
  - nombreuses artérioles

HNF: données nouvelles

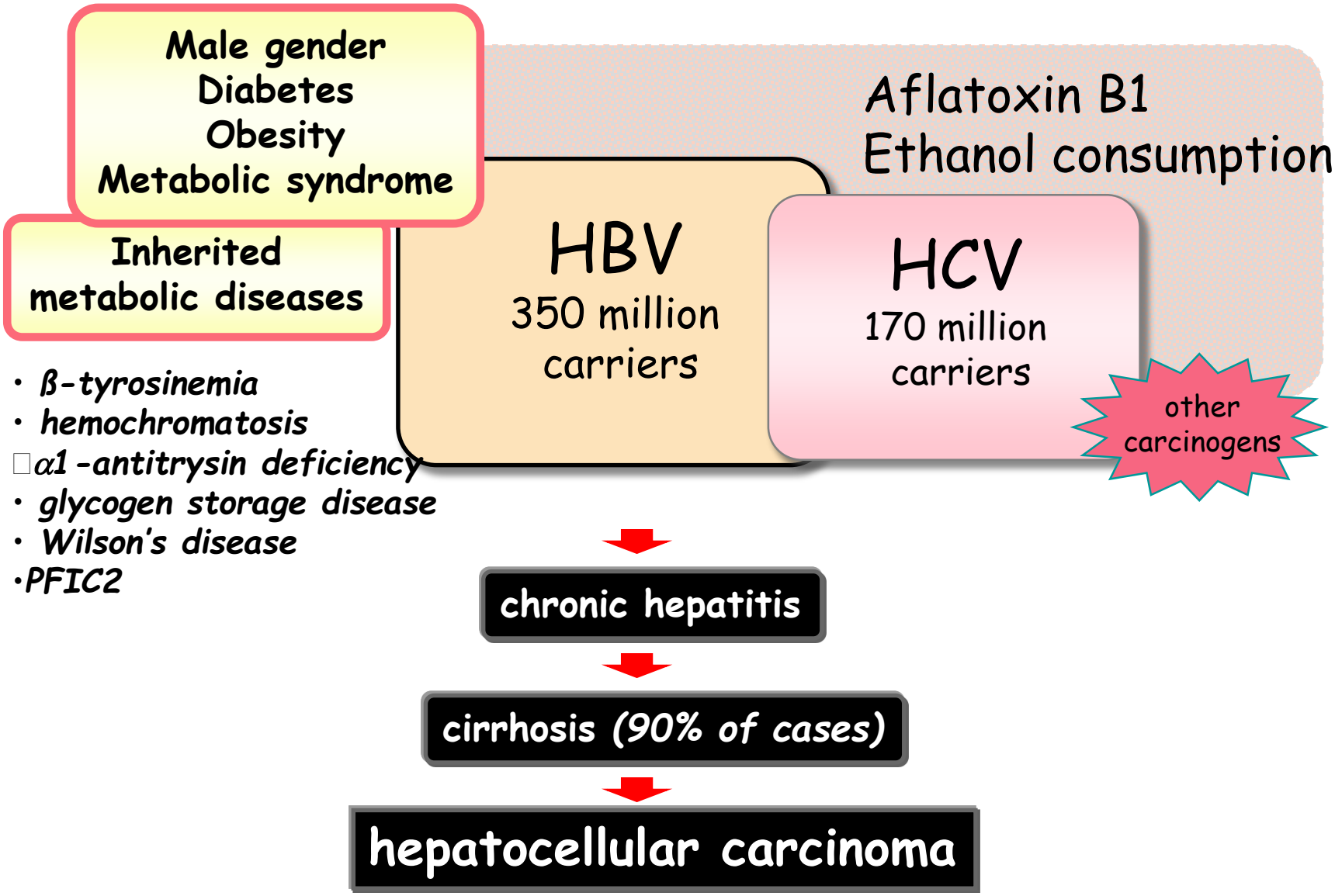
- Physiopathologie
  - hypothèse vasculaire: données cliniques
    - forme primitive: lésion malformative due à un hyperdébit artériel localisé
    - tumeurs HNF-like: secondaires à des pathologies vasculaires
  - hypothèse vasculaire: données moléculaires
    - anomalies d'expression des facteurs angiogéniques (angiopoïétines 1 et 2)
  - rapports avec les oestroprogestatifs

Primary liver cancers

- 4% of all new cancer cases in the world
- Third most common cause of cancer-related death among men and the sixth among women
- 85-90% = **Hepatocellular carcinoma**

Nordenstedt Dig Liver Dis 2010

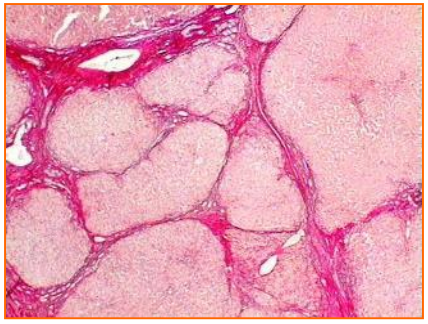
Etiological Factors of Hepatocellular Carcinoma



Hepatocellular carcinoma

IN WESTERN COUNTRIES

90% of HCC on cirrhotic livers



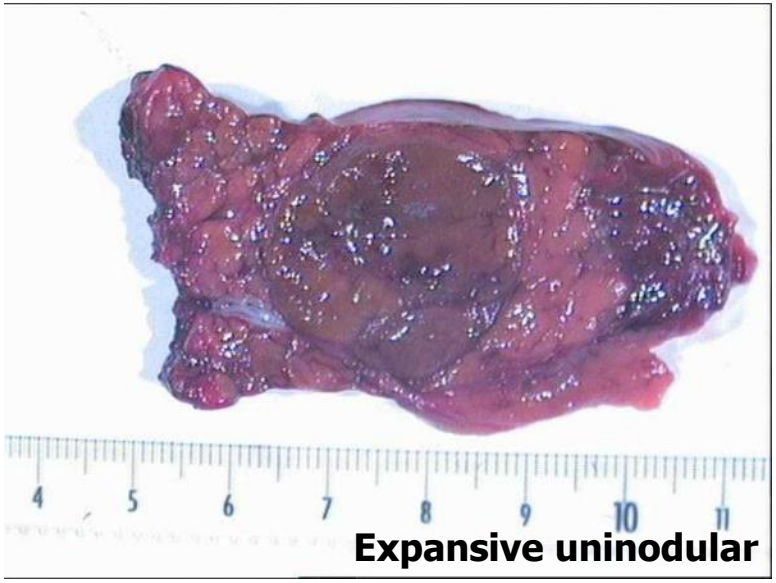
Chronic liver disease

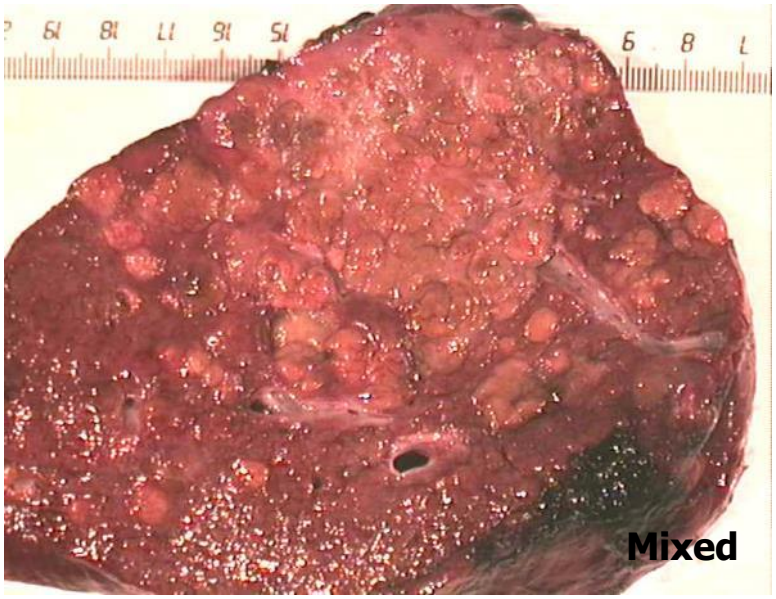
10% of HCC on non cirrhotic livers

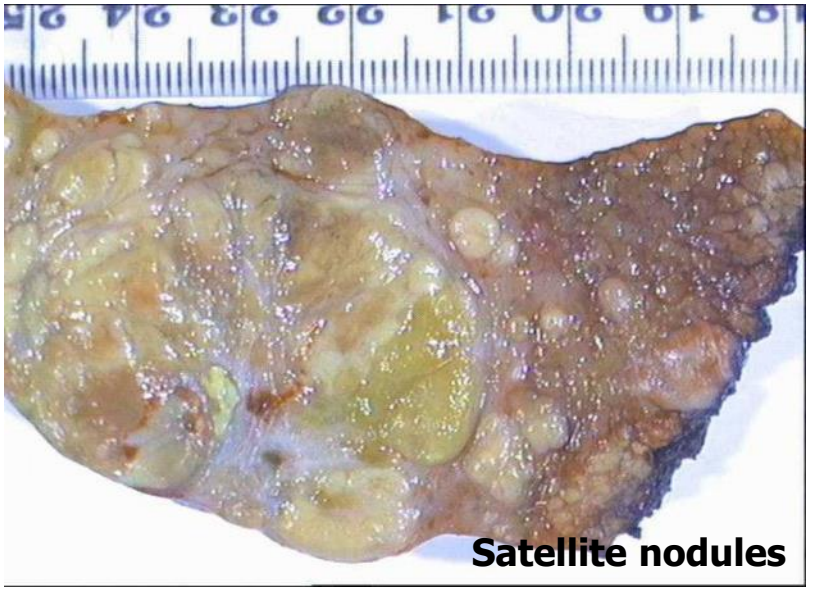
Normal liver

Cirrhosis = pre-cancerous state with an annual incidence of 2- 5% for HCC

Hepatocellular carcinoma: Gross aspect







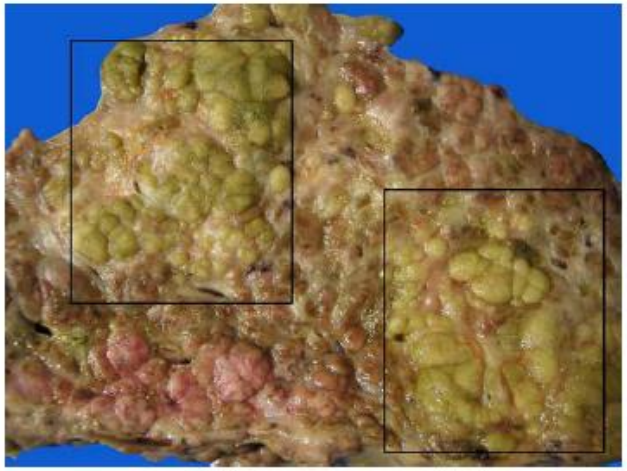
Diffuse cirrhosis-like HCC

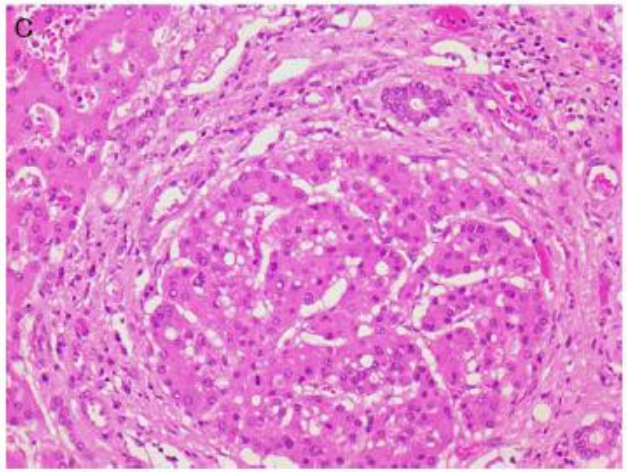
TABLE 1. Summary of Clinical Data

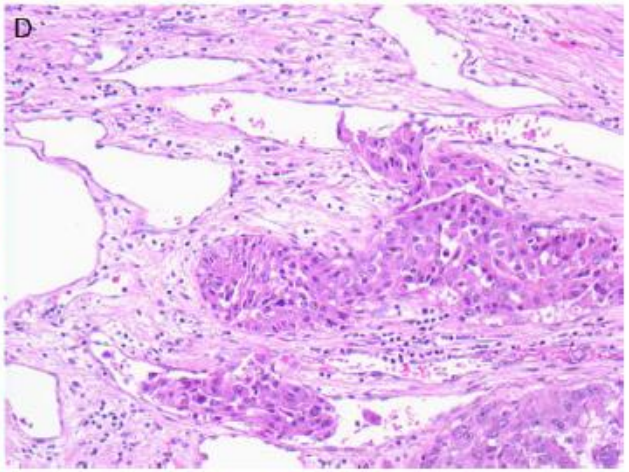
No.	Age (y) and Sex	Cause of Cirrhosis	AFP >20 ng/mL	Pre-OLT >1 cm Mass on Imaging	Follow-up of >3 y
1	62, Male	HCV	No	No	Living, tumor free
2	60, Male	EtOH	No	No	NA
3	80, Male	HCV	144	No	NA
4	73, Male	EtOH	150	No	NA
5	65, Male	HCV	No	No	Living, tumor free
6	59, Male	EtOH	No	No	Living, tumor free
7	35, Male	HBV	No	No	NA
8	60, Male	HCV/HH	No	No	Expired, cardiac HH complications
9	61, Female	AIH	No	No	Expired, tumor recurrence in graft
10	59, Male	HCV/EtOH	252	No	NA

AFP indicates α-fetoprotein; AIH, autoimmune hepatitis; EtOH, alcoholic hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HH, hereditary hemochromatosis; NA, not available; OLT, orthotopic liver transplantation.

Biopsy +

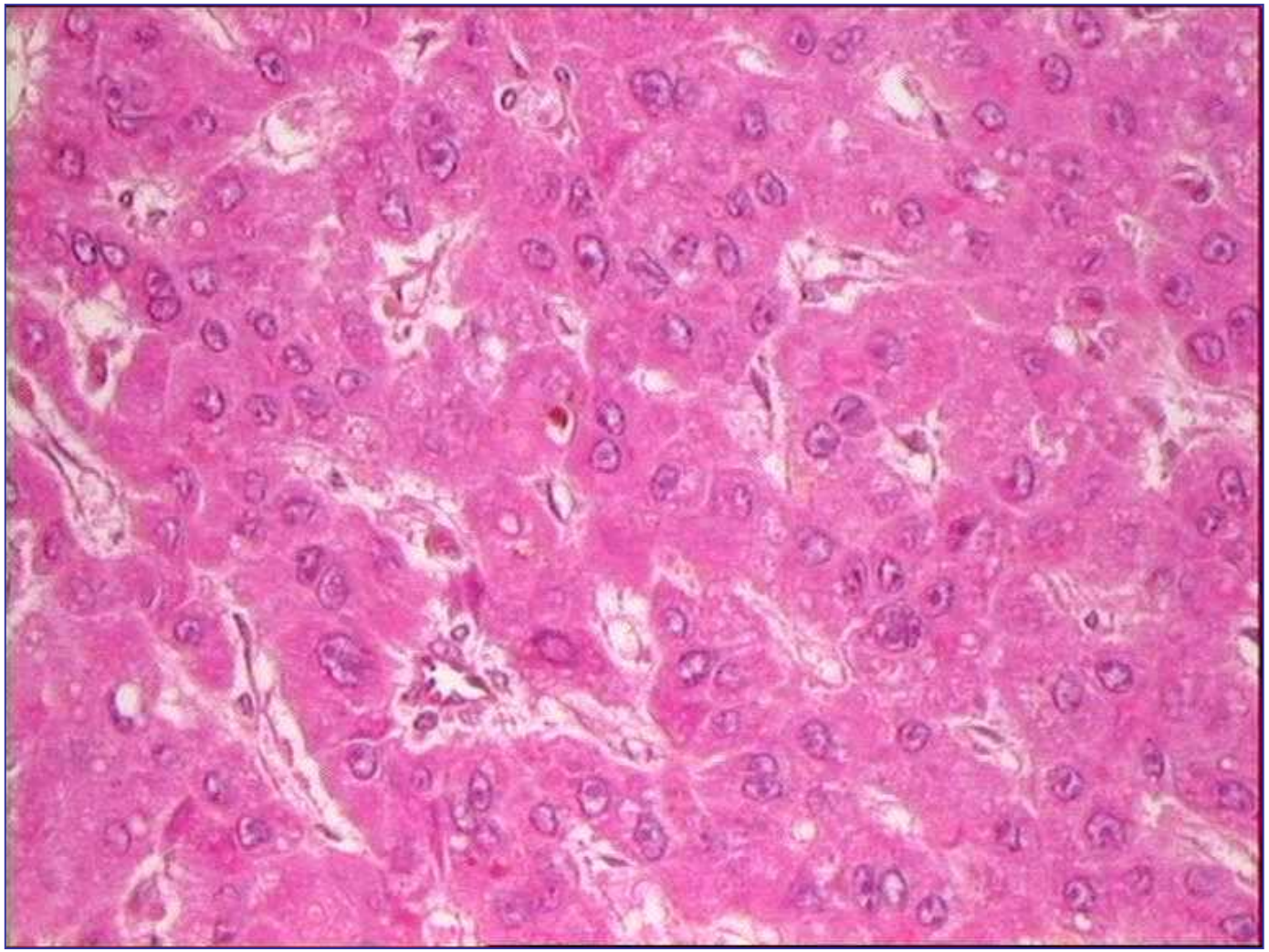






Jakate Am J Surg Pathol 2010

Hepatocellular carcinoma
Classical type



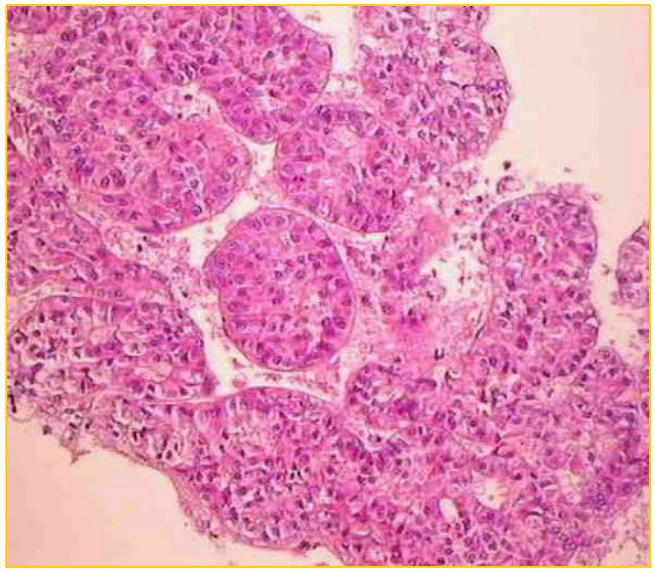
Histological types of Hepatocellular Carcinoma (WHO)

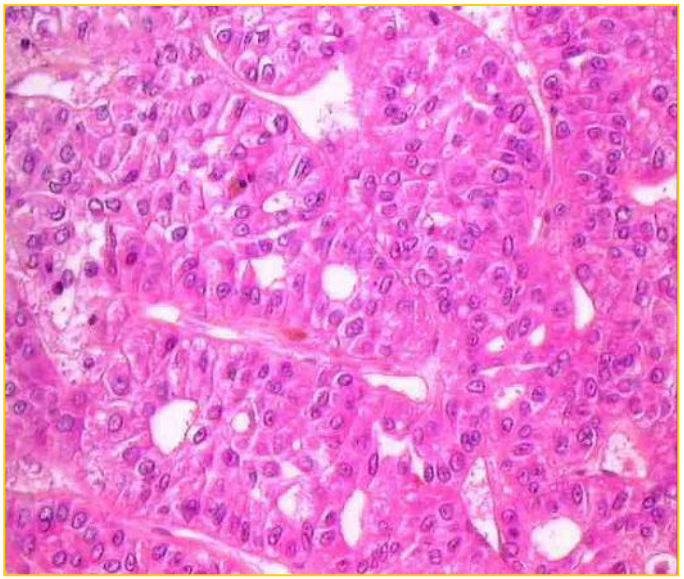
Architecture
- Trabecular
- Pseudoglandular
- Compact
- Squirrhous

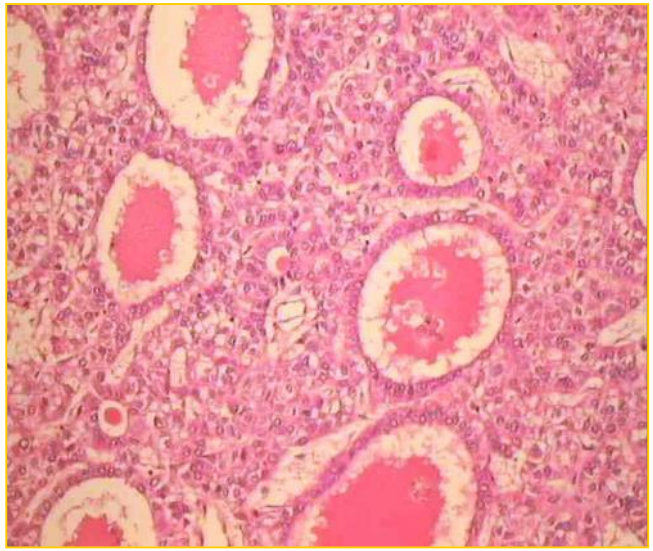
Cytology (variants)
- Pleomorphic
- Clear cells
- Oncocytic
- Sarcomatoid

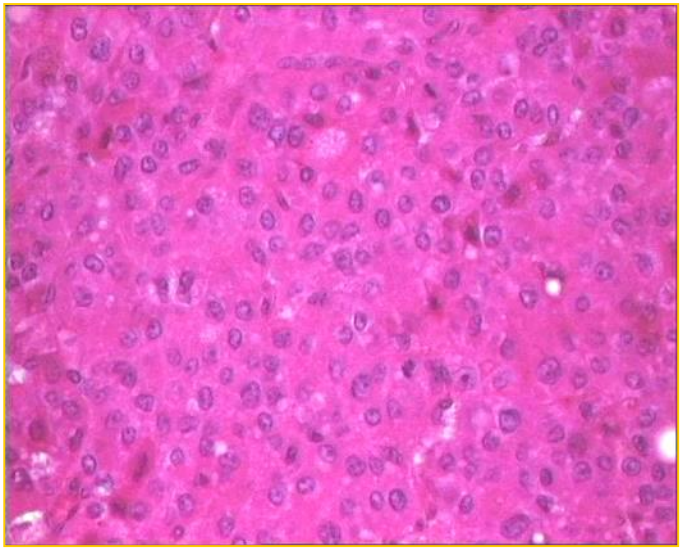
Other aspects
- Bile
- Glycogen
- Steatosis
- Nuclear inclusions
- Hyaline cytoplasmic globules
- Mallory's bodies
- Pale bodies

Hepatocellular Carcinoma: Architecture

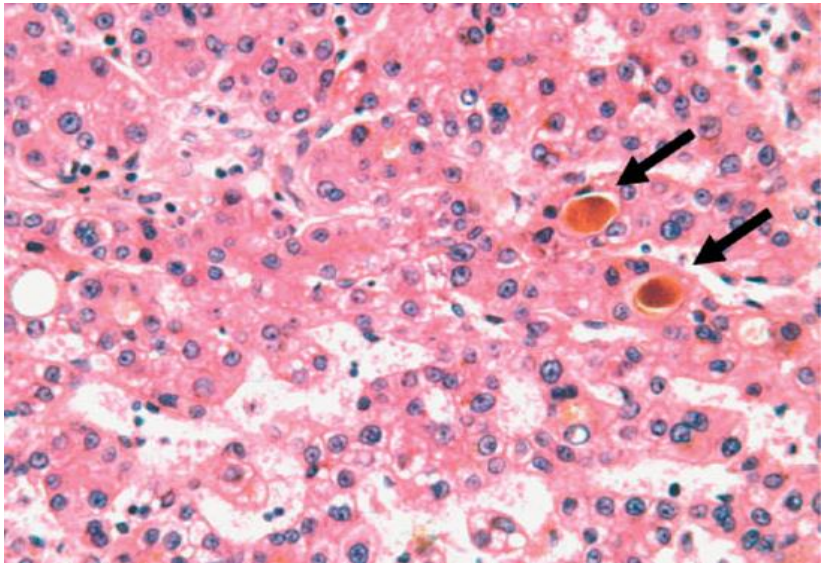


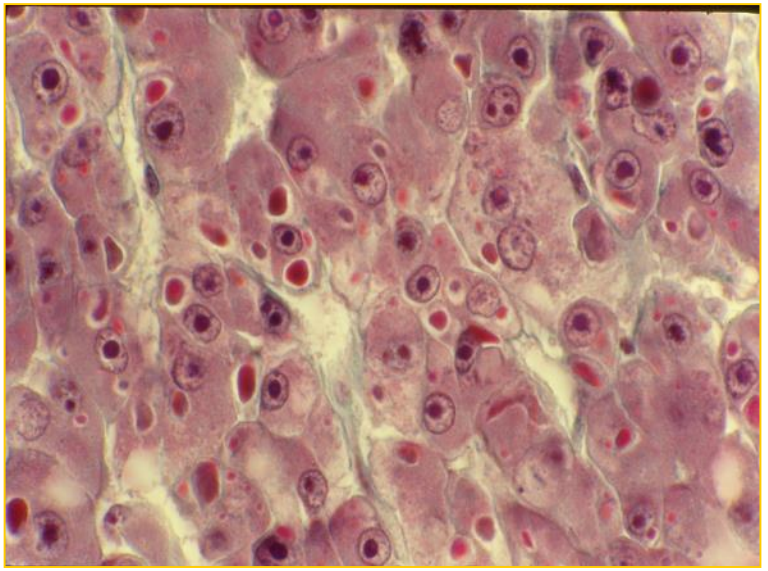


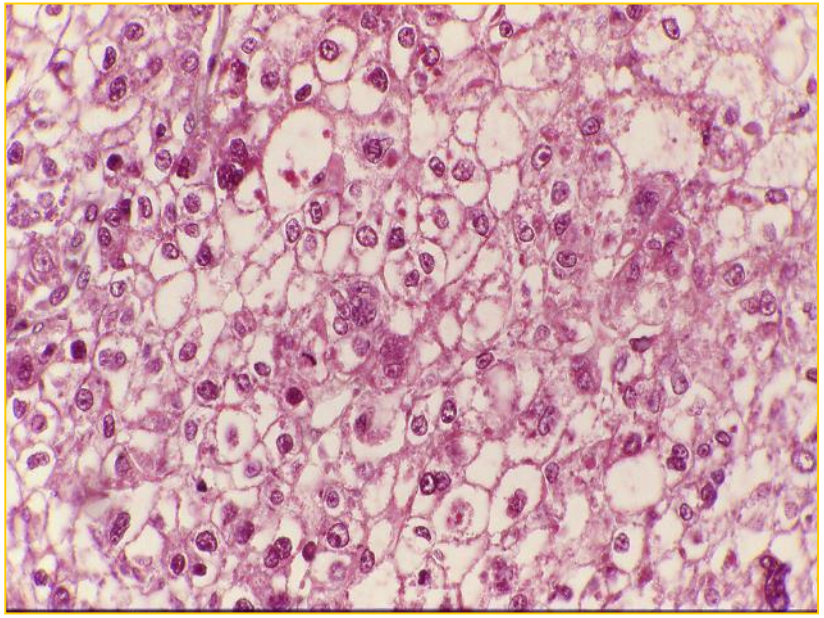


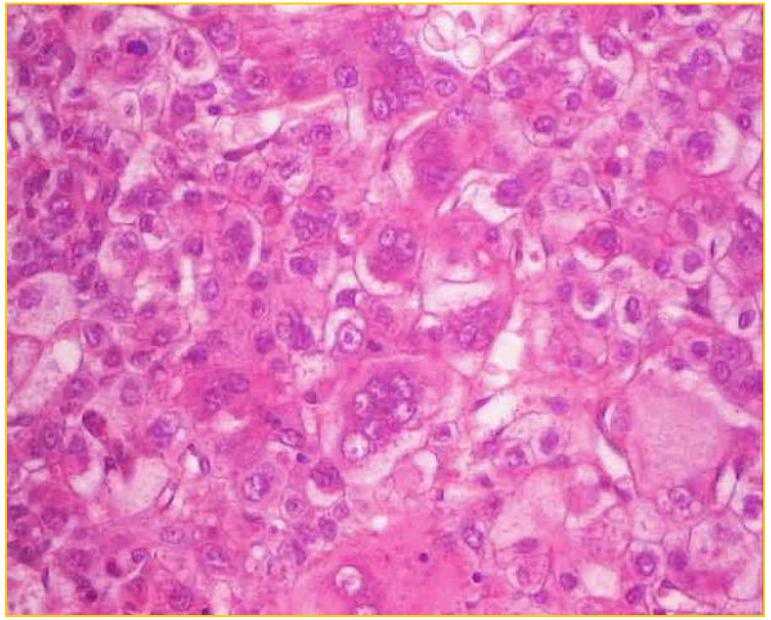


Hepatocellular Carcinoma: Cytological aspects

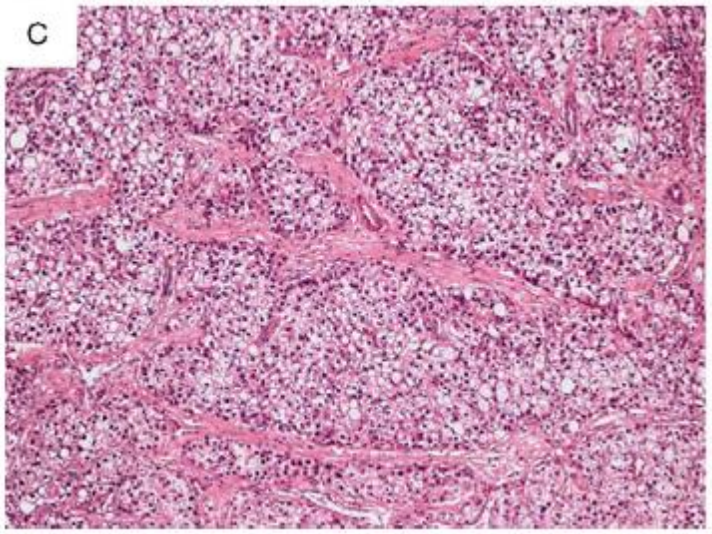






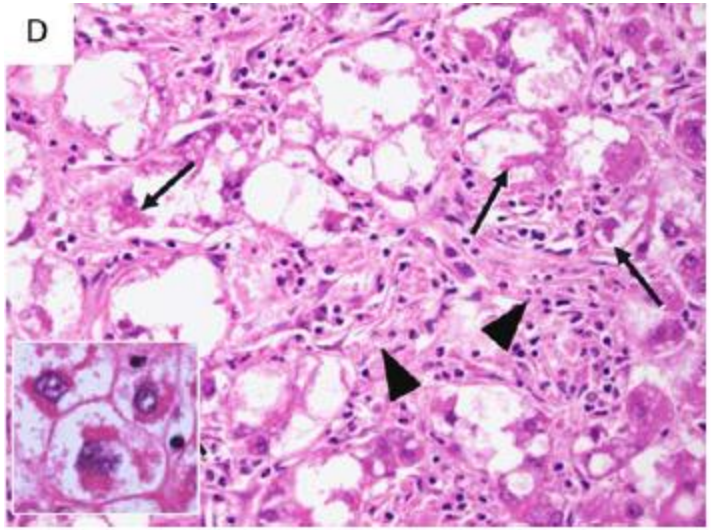


Steatohepatitic hepatocellular carcinoma



22 steatohepatitic HCC (35.5%)
/62 HCC on explant livers with HCV cirrhosis

Steatosis
Mallory bodies
Inflammatory infiltrates
Pericellular or trabecular fibrosis



Risk factors for NALFD/NASH: 63.6%
Steatosis/Steatohepatitis: 63.6% in the non neoplastic liver

Salomao Am J Surg Pathol 2010

HCC ON CIRRHOTIC LIVERS
MOST OFTEN AN EASY DIAGNOSIS
BY IMAGING TECHNIQUES

No need for an histological proof

Diagnosis of HCC on cirrhotic livers: MOST OFTEN AN EASY DIAGNOSIS

- Nodule on cirrhotic liver > 2cm

Diagnosis of HCC by non invasive imaging and laboratory criteria

- Hypervascular arterial supply/portal wash-out
- High serum AFP
- Pathological confirmation is not mandatory. It could be necessary if the imaging data are not typical

- Nodule 1-2 cm

- One or two imaging techniques
- If inconclusive : Biopsy

- Nodule < 1cm

- Repeat US

Ultra-sound guided core biopsy – 16-18G

- Hemorrhagic risk
- Tumor cell seeding on biopsy track (2.7%) – biological glue
- Usefulness of an associated biopsy in non tumor liver +++
- Higher opportunity of immunostaining

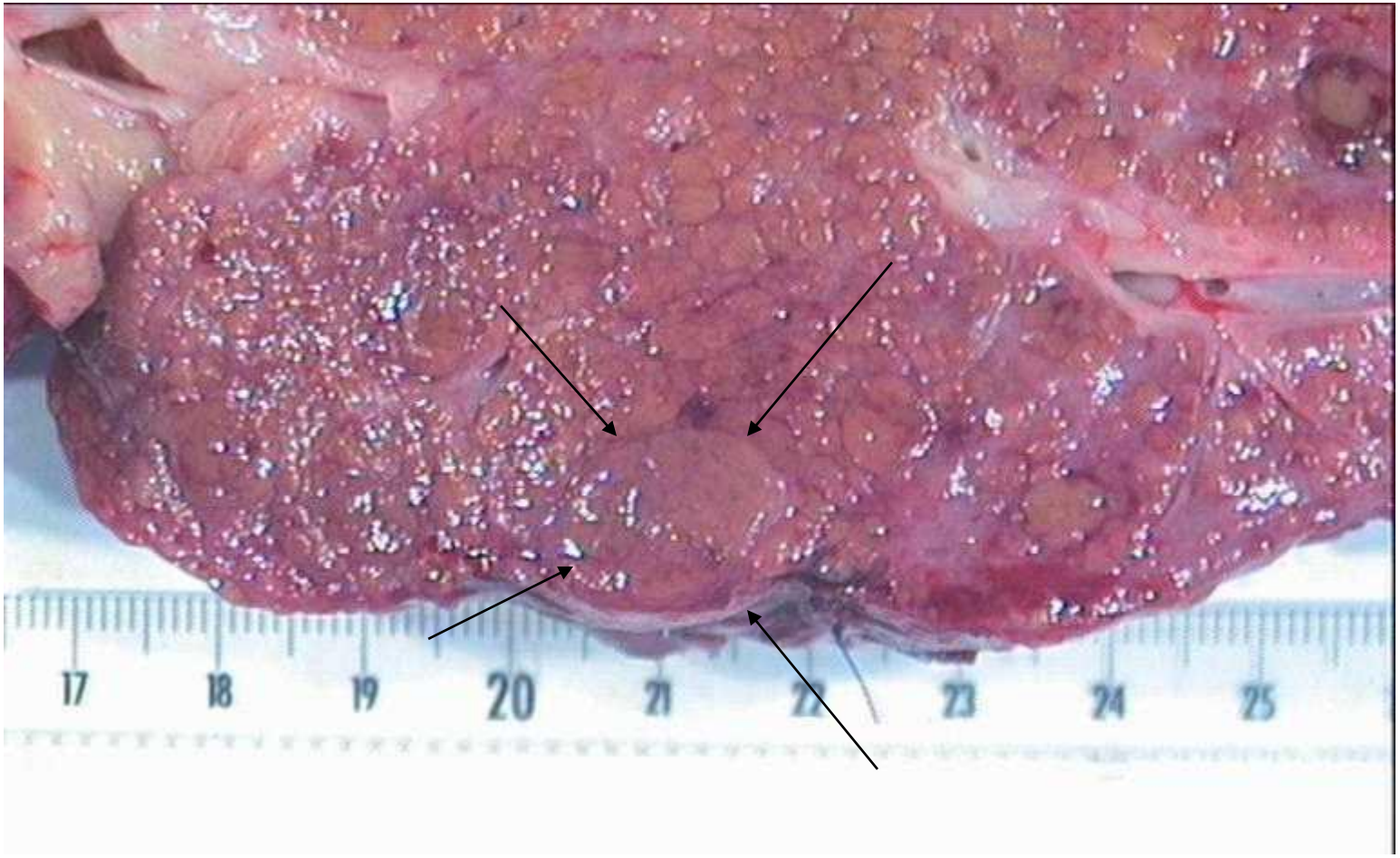
Small Nodules resulting from screening on cirrhotic livers

« Macronodules » : detected by US screening

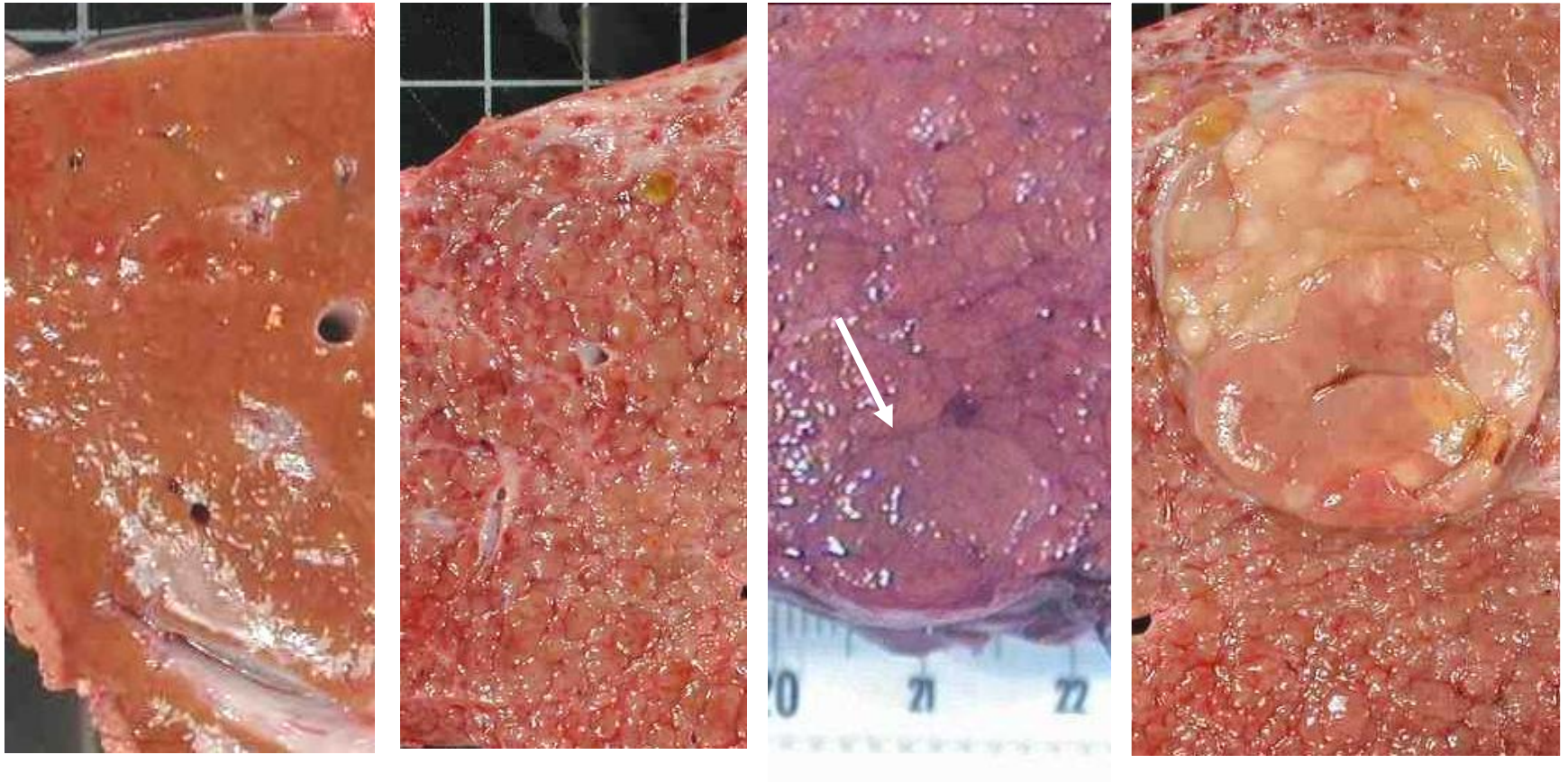
- Macroregenerative nodules
- Low grade dysplastic nodules
- High grade dysplastic nodules
- Small HCC ≤ 2 cm
  - Early HCC
  - Progressed HCC

International working party Hepatology 1995;22:983-993
International Consensus Group for Hepatocellular Neoplasia Hepatology 2009

Macronodule



Hepatocellular carcinoma: Multistep carcinogenesis



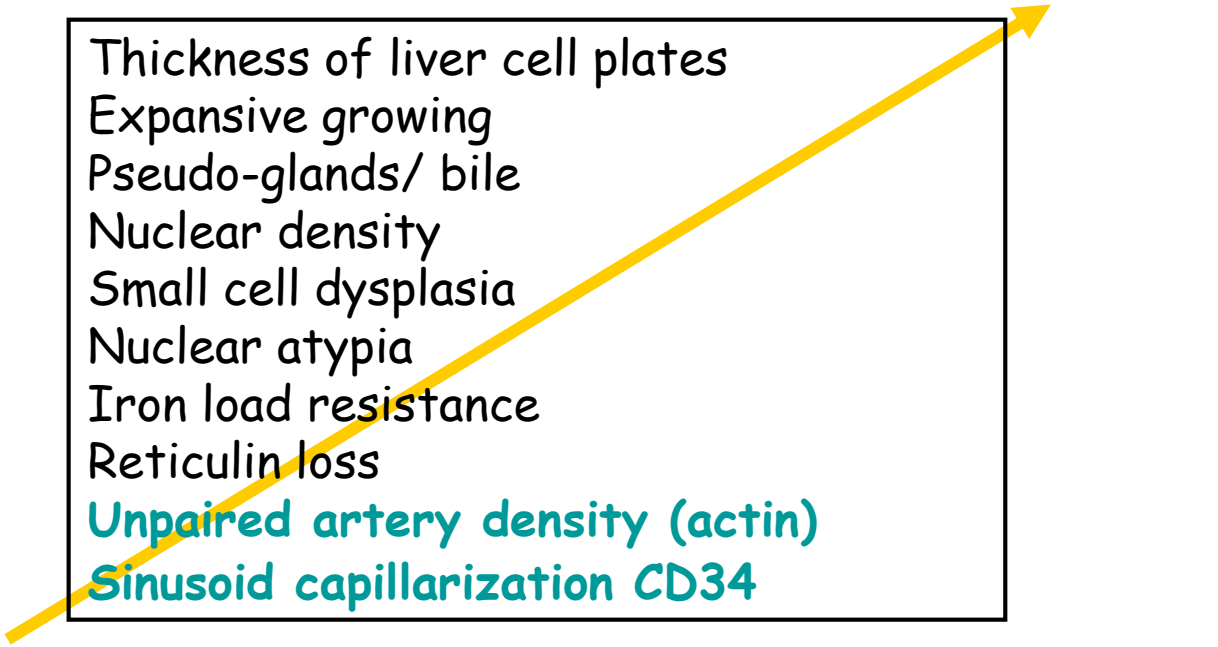
Macronodules on cirrhotic liver

MACROGENERATIVE NODULES

Hyperplastic - Polyclonal - Benign

DYSPLASTIC NODULES

Low grade | High grade | Well differentiated HCC



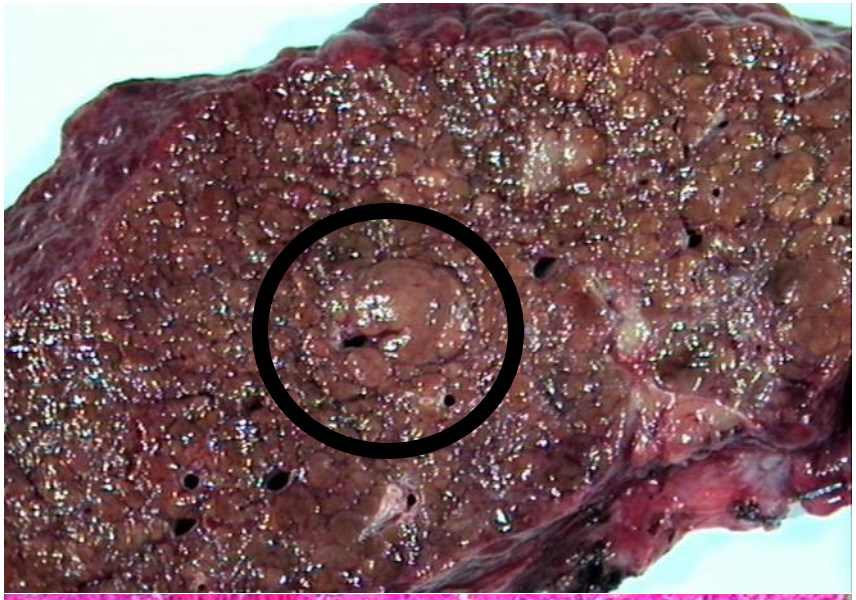
Dysplastic nodules and Hepatocellular carcinoma

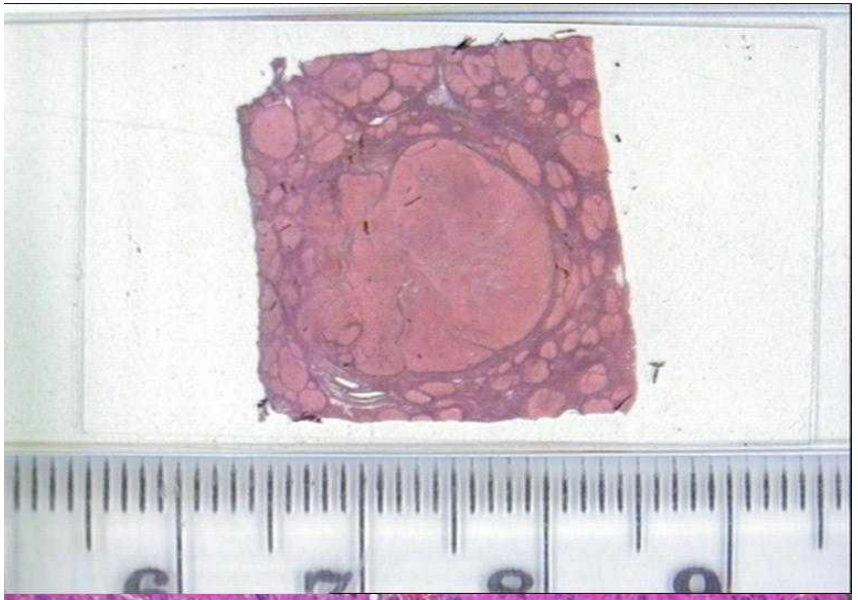
Risk of transformation of dysplastic nodule into HCC

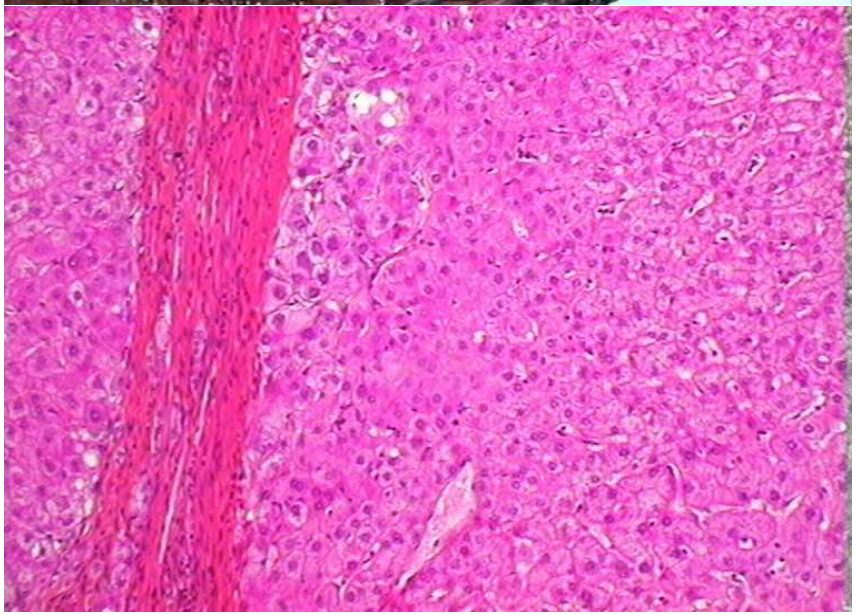
- LGDN: 20%
- HGDN: 20 – 80%

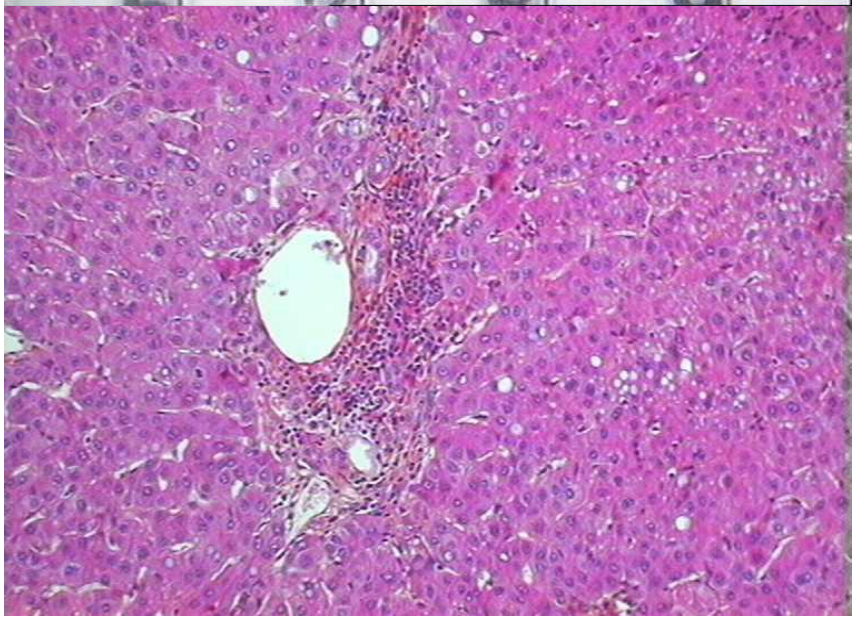
Nault Hepatology 2014

Macroregenerative nodules

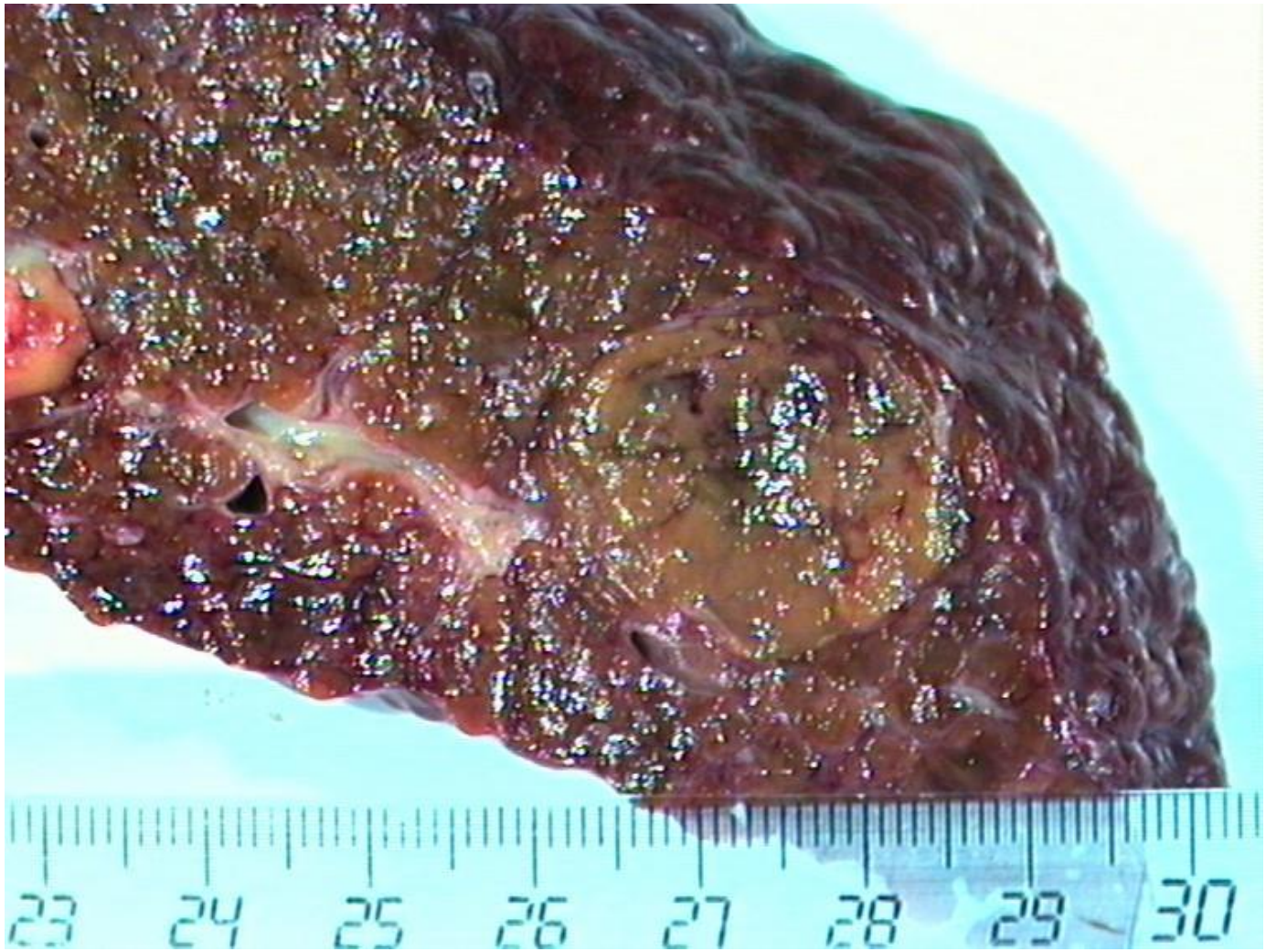


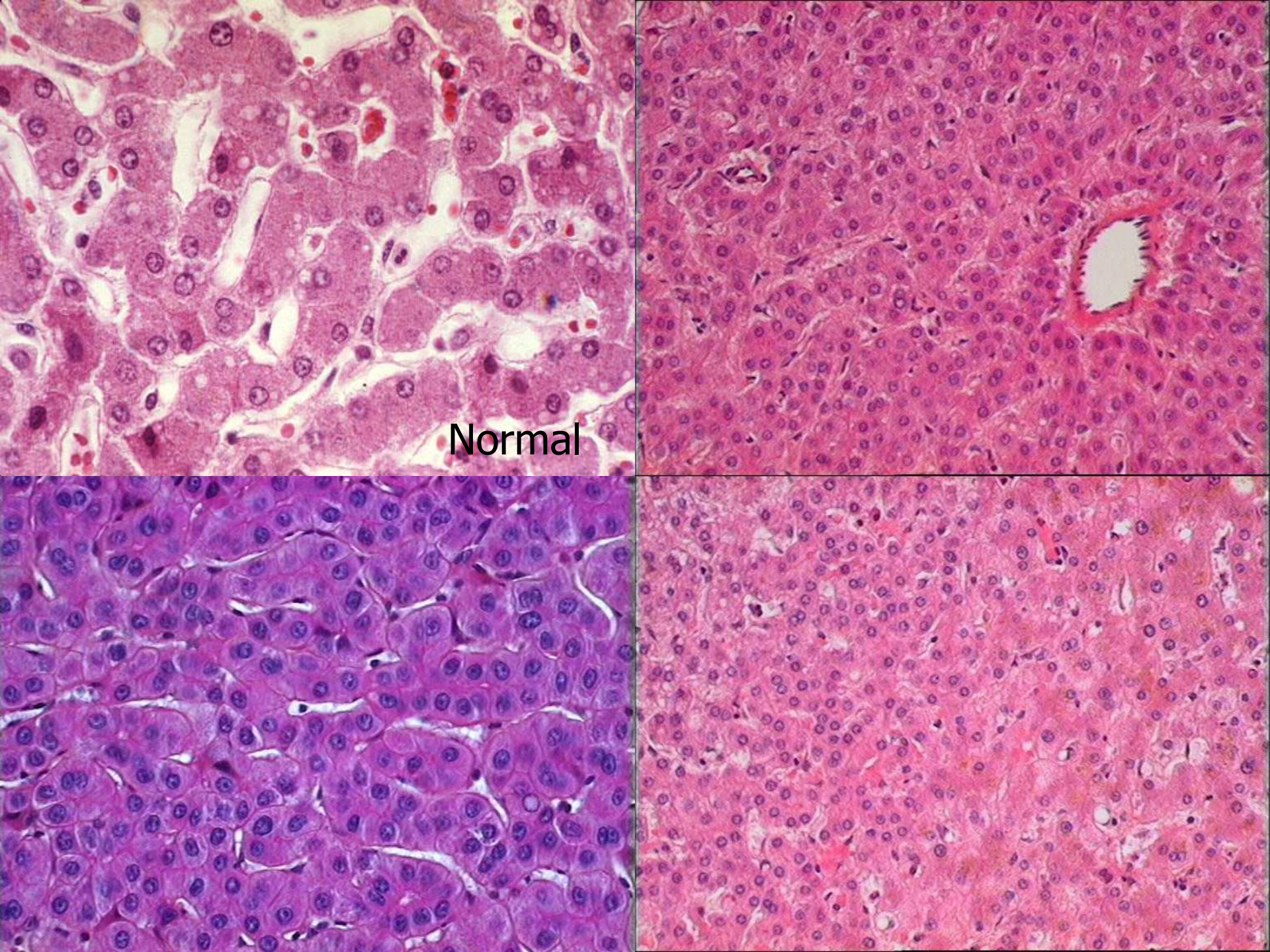


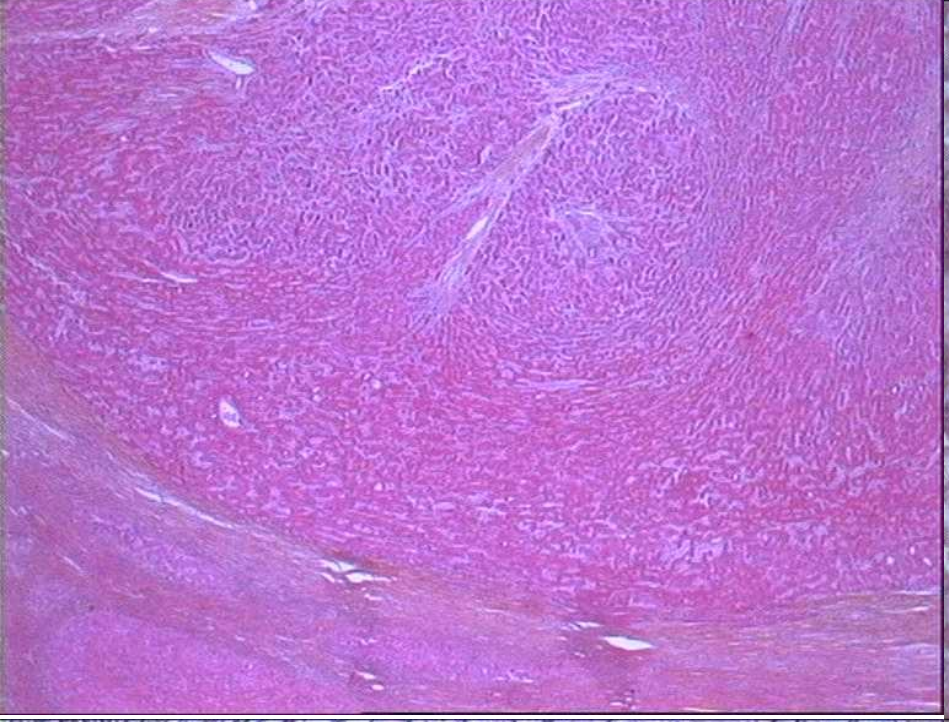


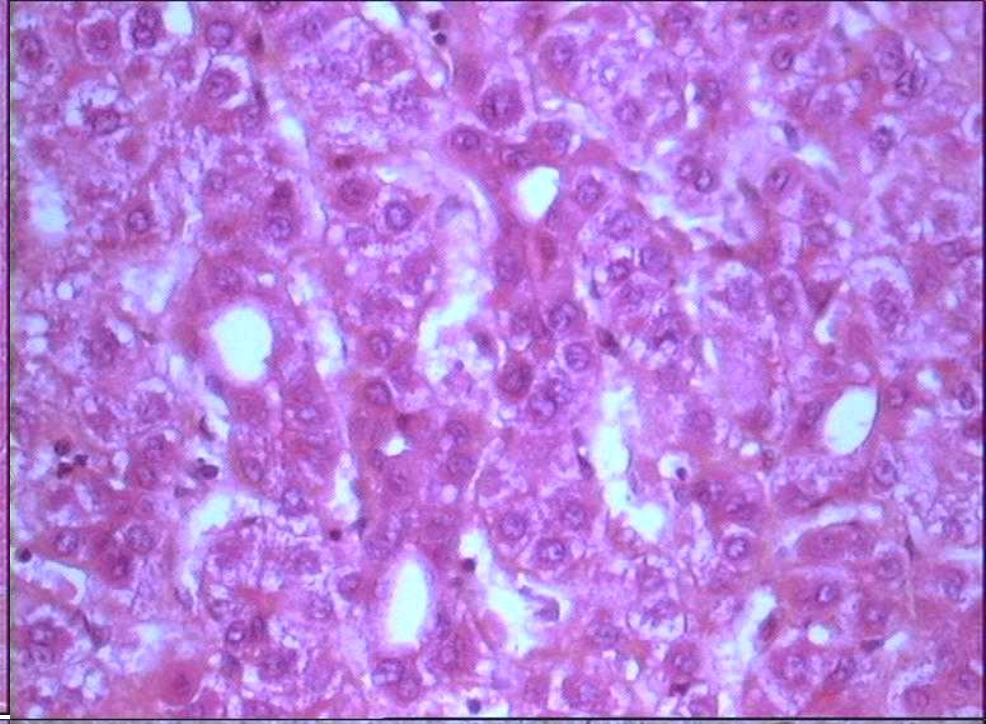


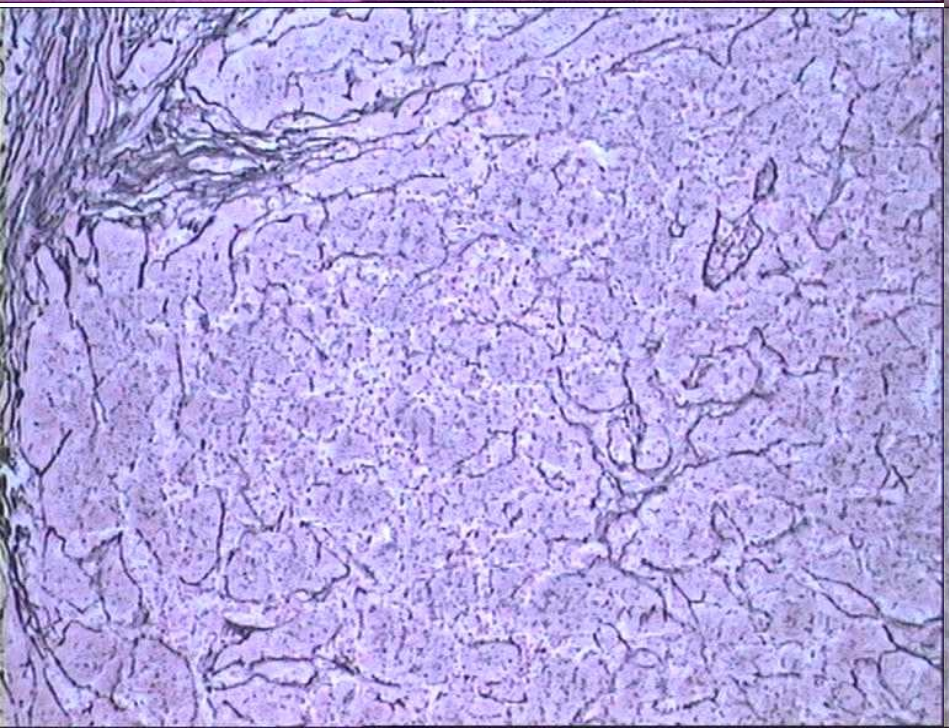
Dysplastic nodule

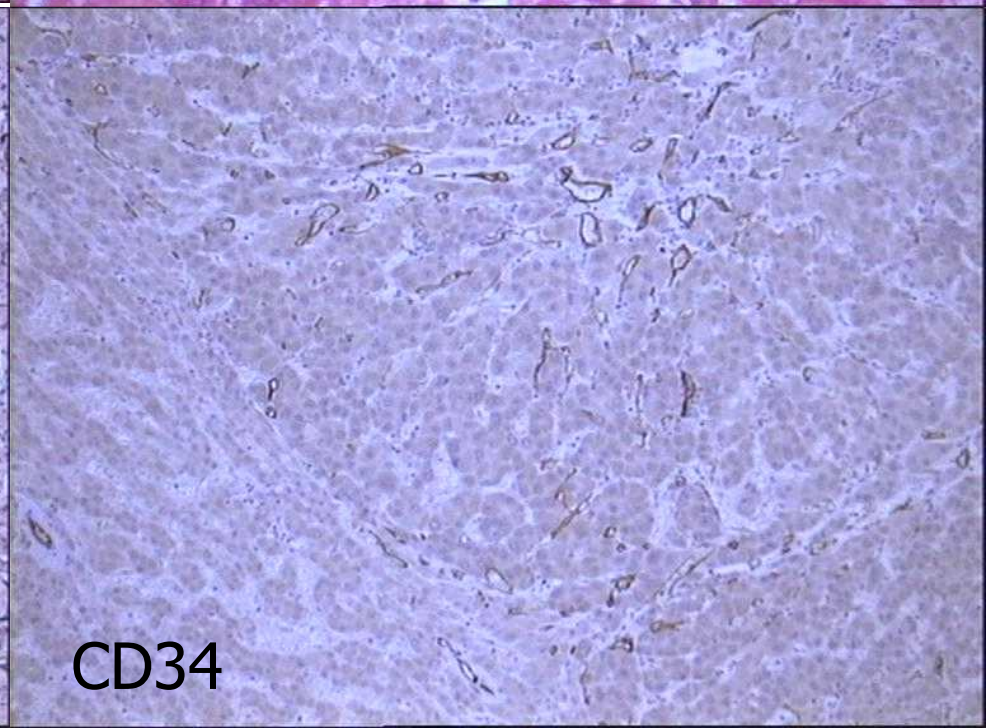



Normal








CD34

Dysplastic Nodules

	Low grade	High grade	Well differentiated HCC
Plate thickness	1 to 2 cells	2 to 3 cells	> 3 cells
Pseudoglands	0	0 ou +	0 ou +
Nodule in the nodule	0 ou +	+ ou 0	+ ou 0
Portal tracts	+	+ ou 0	0
Stromal invasion	0	0	+
Reticulin	+	+/-	-
Unpaired arteries	quelques	+	++
Atypia	mild	+, focal	+
Mitosis (1à 5/ 10 HPF)	-	rares	variable
Dysplasia	Large cell	Large or small cell	-
Clonality	Mono or poly	Mono or poly	mono

Additional diagnostic tools

- Reticulin staining
  Decreased framework in HCC

- Immunostaining
  SMA (smooth muscle actin): unpaired arteries
  CD34: sinusoid capillarization

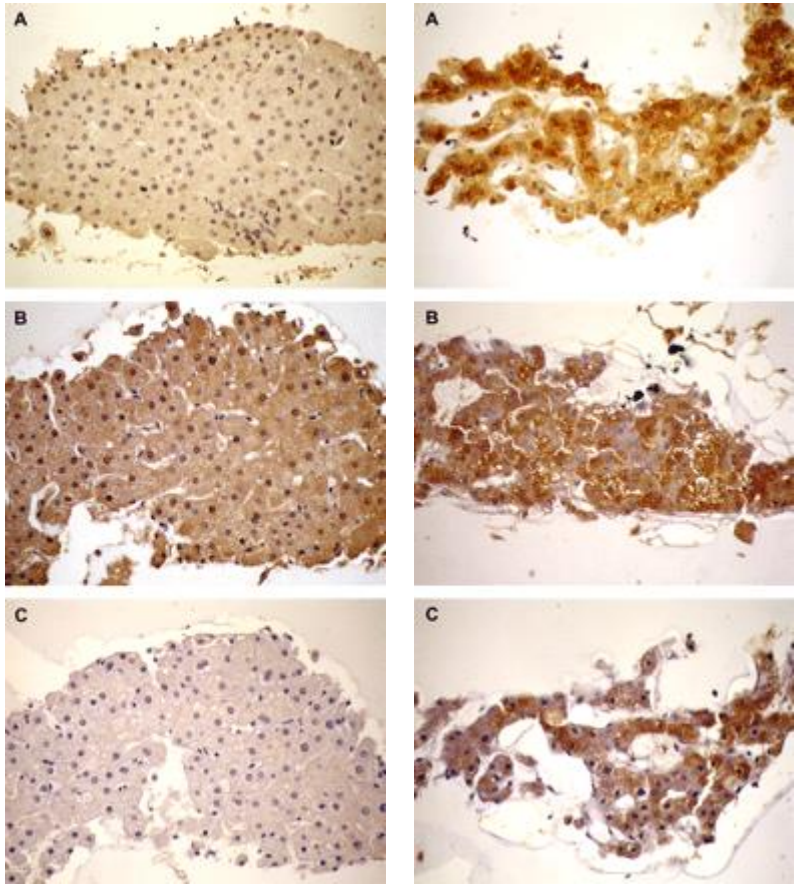
  Glypican3: Fetal oncoprotein
  HSP70: Heat shock protein
  Glutamine synthetase: Glutamine synthesis

International Group recommendations:
2 positive markers/3

Specificity 100% Sensitivity 60% for nodules of 0,5 to 2cm

International Consensus Group for Hepatocellular Neoplasia Hepatology 2009

Prospective validation of an immunohistochemical panel (glypican 3, heat shock protein 70 and glutamine synthetase) in liver biopsies for diagnosis of very early hepatocellular carcinoma



G3

HSP

GS

MRN HCC

Conventional histology

Table 2 Final diagnosis of the 60 nodules according to size at baseline ultrasound (≤10 mm; 11–15 mm and 16–20 mm)

	≤10 mm	11–15 mm	16–20 mm	Total
HCC nodules				
HCC	0	19	21	40
Well-differentiated	0	11	8	19
Moderately-differentiated	0	6	11	17
Poorly-differentiated	0	2	2	4
Non-HCC nodules (dysplastic/regenerative)	6	11	3	20
Total	6	30	24	60

Table 3 Diagnostic accuracy for detection of hepatocellular carcinoma using one, two or three of the markers under study

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
One marker						
GPC3	57.5	95.0	95.8	52.8	11.500	0.447
HSP70	57.5	85.0	88.5	50.0	3.833	0.500
GS	50.0	90.0	90.9	47.4	5.000	0.556
Two markers						
GPC3+HSP70	40.0	100	100	45.5	Inf	0.600
GPC3+GS	35.0	100	100	43.5	Inf	0.650
HSP70+GS	35.0	100	100	43.5	Inf	0.650
Three markers						
At least 1 positive	80.0	70.0	84.2	63.6	2.667	0.285
At least 2 positive	60.0	100	100	55.6	Inf	0.400
All 3 positive	25.0	100	100	40.0	Inf	0.750

GPC3, glypican 3; GS, glutamine synthetase; HSP70, heat shock protein 70; Inf, Infinite; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Tremosini Gut 2012

Small Nodules resulting from screening on cirrhotic livers

EASL-EORTC Clinical Practice Guidelines:
Management of hepatocellular carcinoma ***2012***

Nodule > 2cm ➔Imaging diagnosis (typical features on one imaging technique)
If atypical features ➔Guided biopsy

Nodule < 1cm ➔ Repetition of imaging

Nodule 1cm to 2cm ➔ Imaging diagnosis (typical features on 2* imaging techniques)
If not ➔Guided biopsy

MRN / Dysplastic nodule / HCC ?

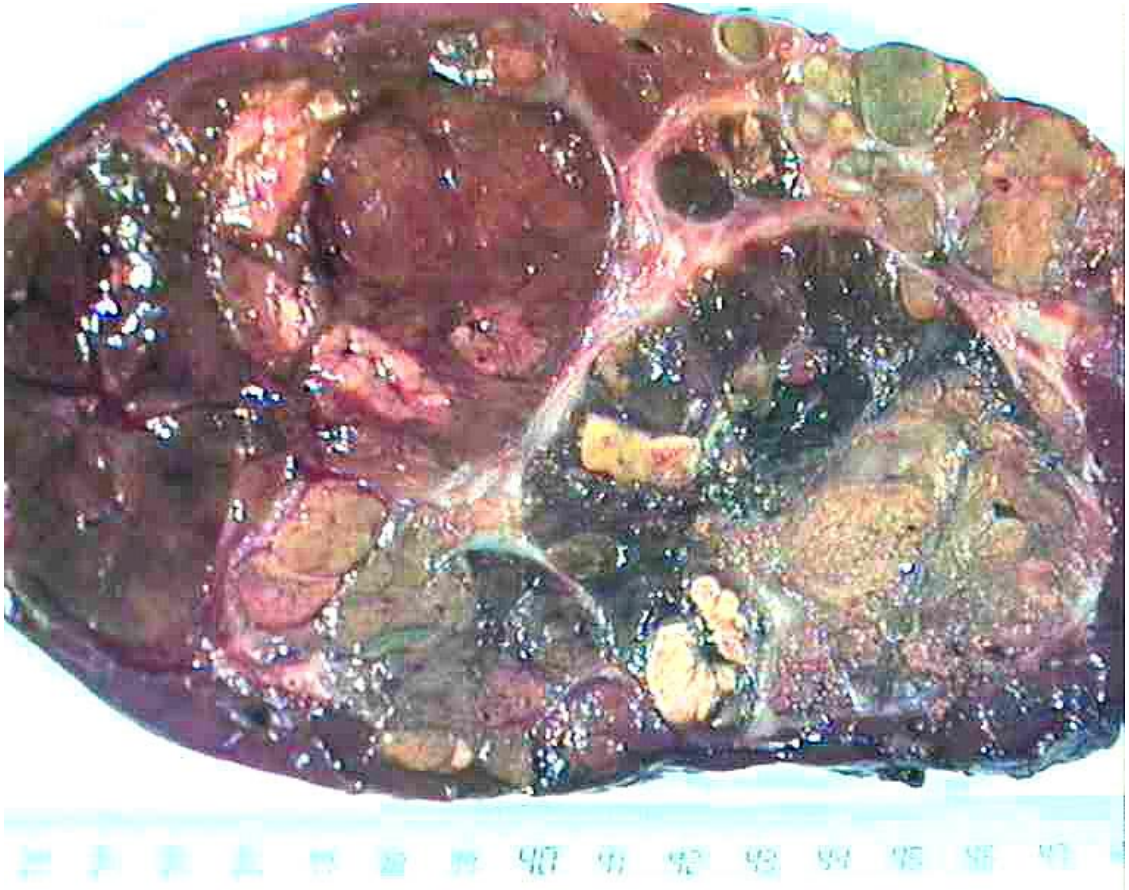
Limits +++
In the nodule?
In the nodule within the nodule?
Low sensitivity for the diagnosis of early HCC?

DIAGNOSIS OF HCC ON NON CIRRHOTIC LIVER

Pathological diagnosis of HCC is recommended for all nodules occurring in non-cirrhotic livers.

EASL-EORTC 2012

Hepatocellular carcinoma on non cirrhotic liver

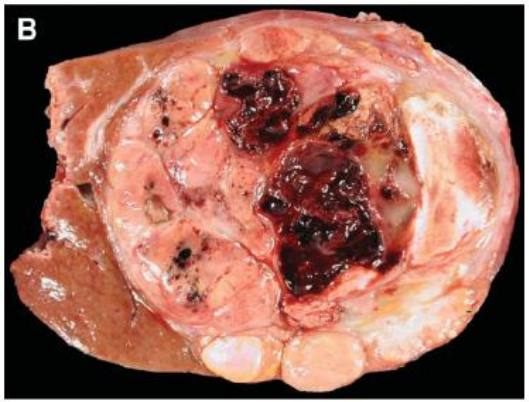


- 10 to 15% of HCC in Western countries
- Large tumors

Metabolic syndrome and HCC

Table 2. Pathological Characteristics of Hepatocellular Carcinoma and Nontumoral Liver in the Three Groups of Patients

	MS Group (n = 31)	CLD Group (n = 81)	CG Group (n = 16)	*P* (MS Versus CLD)
Tumor size (cm)	8.8 ± 6	7.8 ± 6.3	12.8 ± 5.8*	0.06
Bilobar	7 (23%)	5 (6%)	2 (12.5%)	0.03
Number of tumors	1 (1-3)	1 (1-5)	1(1-2)	NS
Capsule	23 (74%)	51 (63%)	7 (44%)†	NS
Macroscopic vascular invasion	6 (19%)	21 (26%)	4 (25%)	NS
Differentiation				
Well	20 (64.5%)	23 (28%)	8 (50%)	
Moderate	11 (35.5%)	47 (58%)	7 (44%)	
Poor	0 (0)	11 (14%)	1 (6%)	<0.001
Microscopic vascular invasion	14 (45%)	52 (64%)	10 (62.5%)	NS
Satellite nodules	11 (35.5%)	36 (44%)	6 (37.5%)	NS
Liver fibrosis				
F0-F2	20 (65.5%)	21 (26%)	12 (75%)	
F3-F4	11 (35.5%)	60 (74%)	4 (25%)	<0.001
Steatosis				
0 (<5%)	6 (19%)	47 (58%)	15 (94%)‡	
1 (5%-33%)	12 (39%)	29 (36%)	1 (6%)	
2 (33%-66%)	11 (35.5%)	3(4%)	0 (0)	
3 (>66%)	2 (6.5%)	2(2%)	0 (0)	<0.001



- Non cirrhotic liver 65%
- Larger tumors
- Well differentiated HCC

Paradis Hepatology 2009

Hepatocellular carcinoma on non cirrhotic liver

Differential diagnosis of hepatocellular tumor (adenoma/ well differentiated HCC)

Fibrous variant of HCC: cholangiocarcinoma, metastasis?

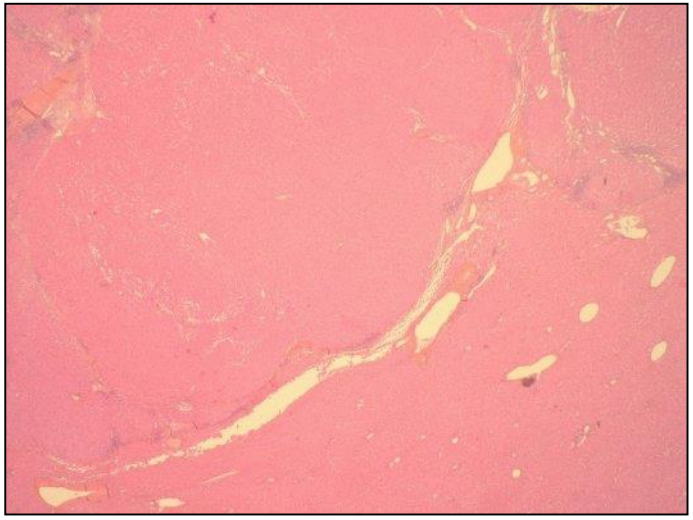
Other rare differential diagnoses: metastasis of Neuroendocrine carcinoma, epithelioid angiomyolipoma

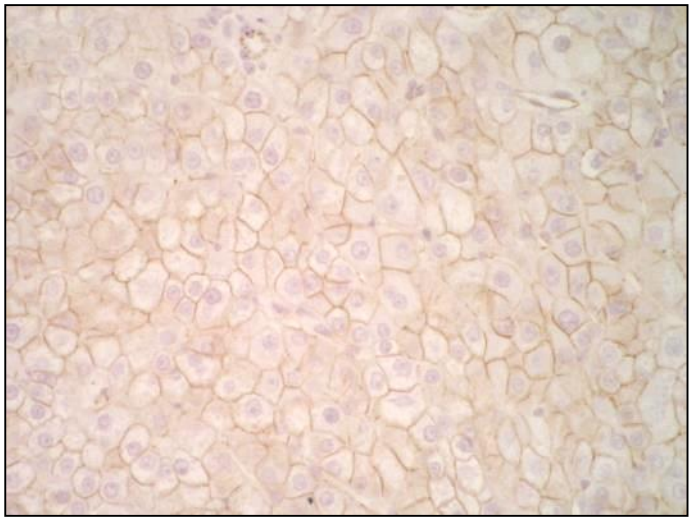
Hepatocellular carcinoma/ Adenoma

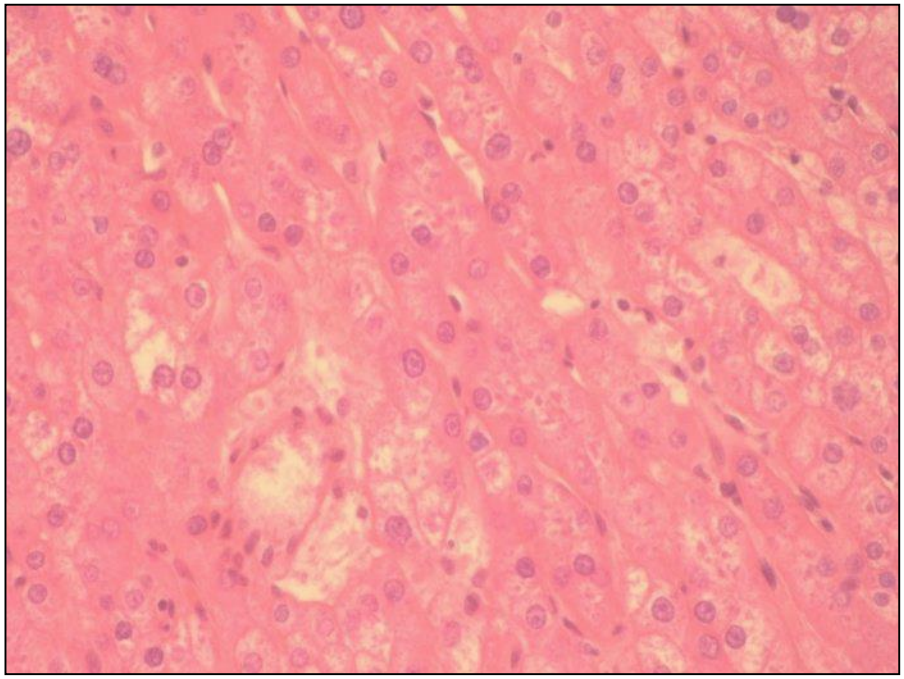
Cellular density
Thickness of liver plates
Pseudoglandular structures
Reticulin staining ++
Cytonuclear atypia, Mitoses
CD34 ??
β-catenin
Glypican 3

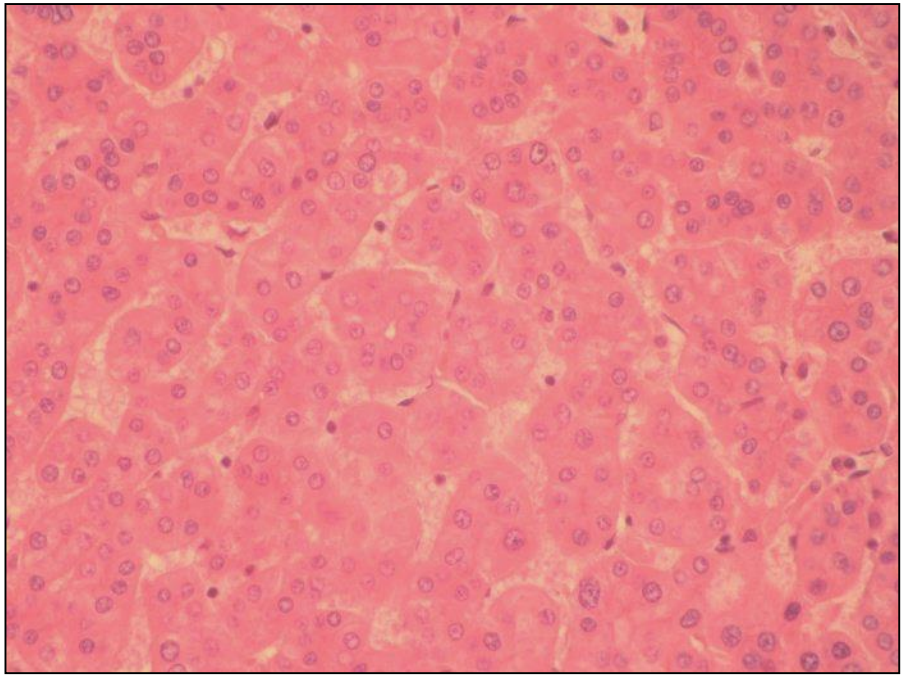
Clinical background +++
Evolution

HCC/ Adenoma

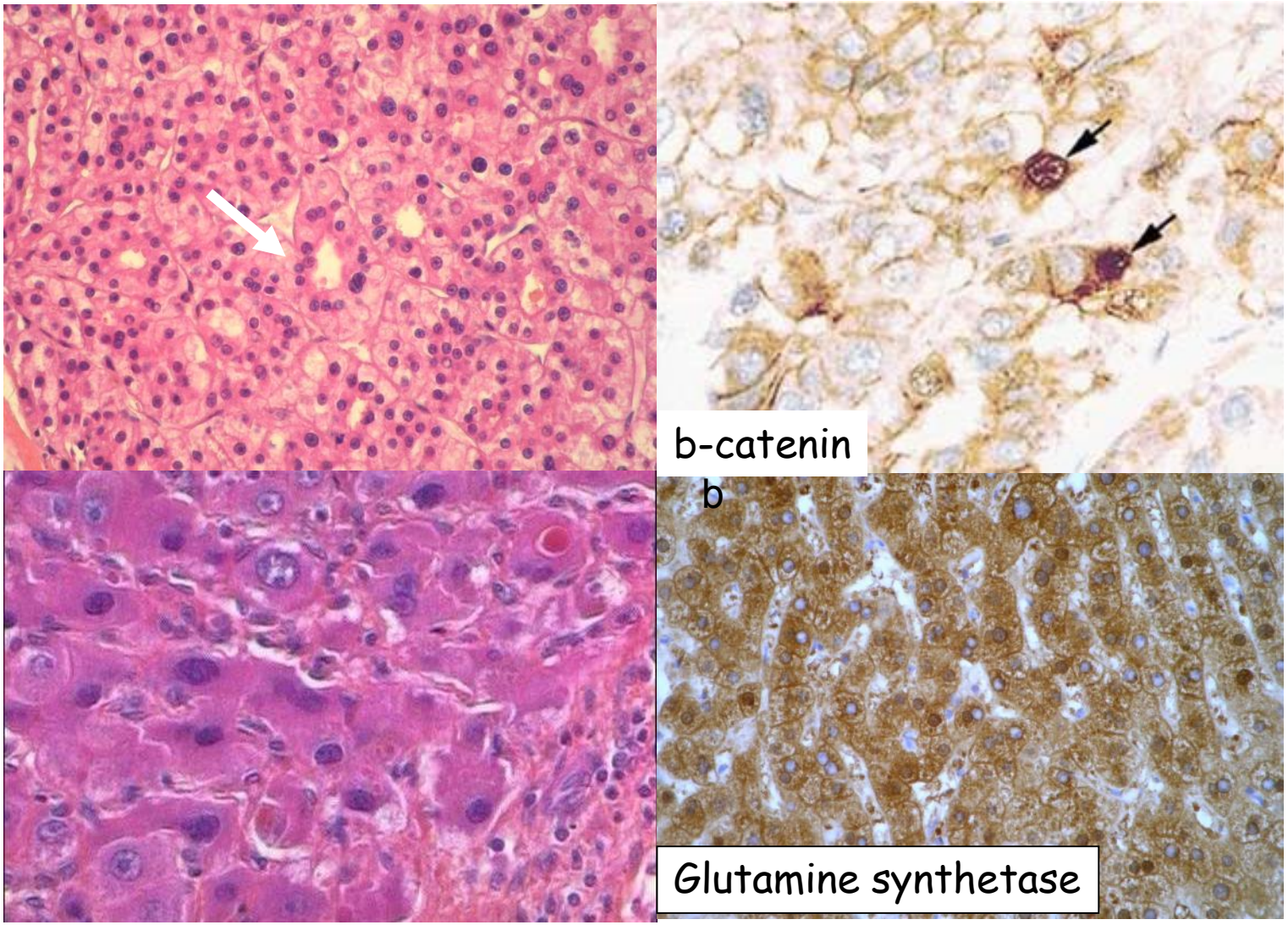






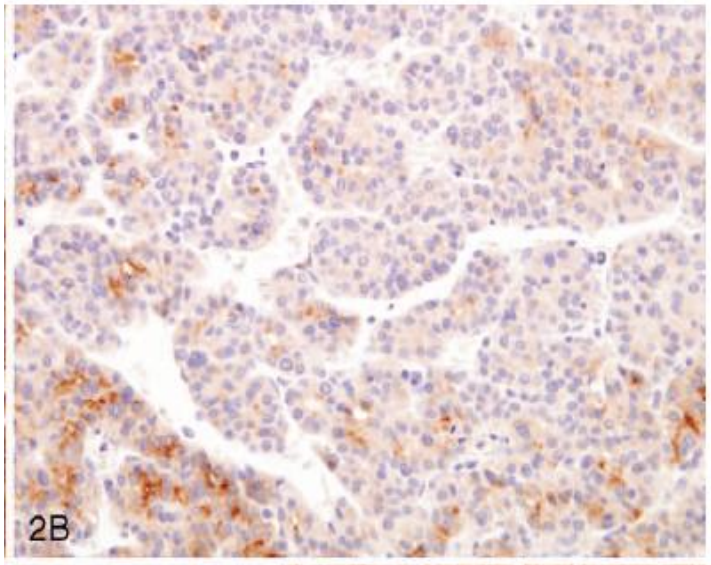


B-catenin mutated adenoma



Risk of transformation++

GLYPICAN 3



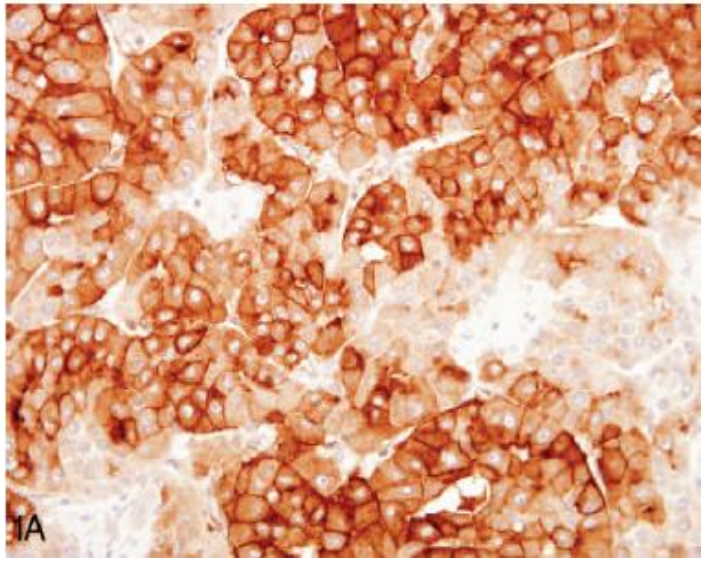


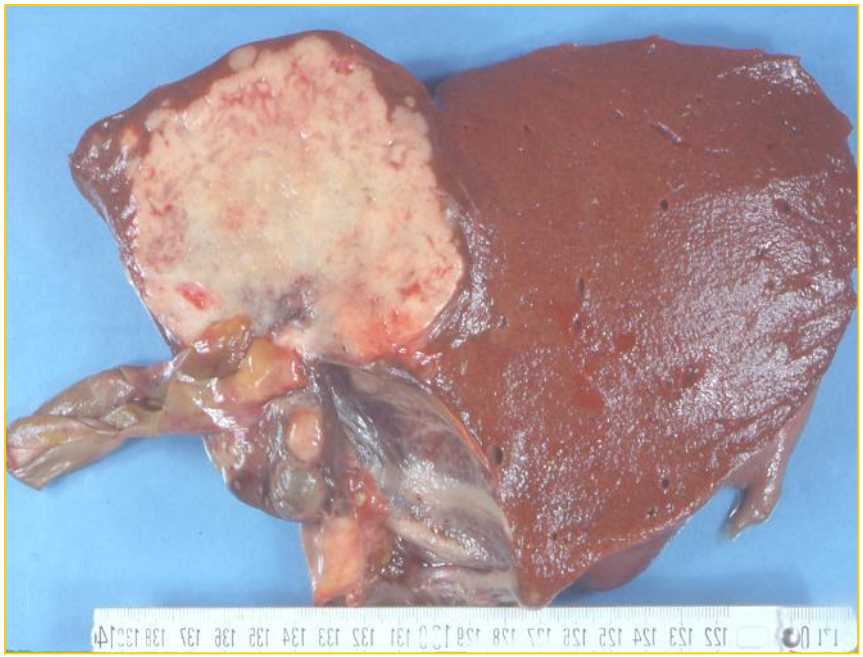
Table 1. Summary of Immunohistochemical Findings of Glypican-3 Expression in Hepatocellular Mass Lesions*

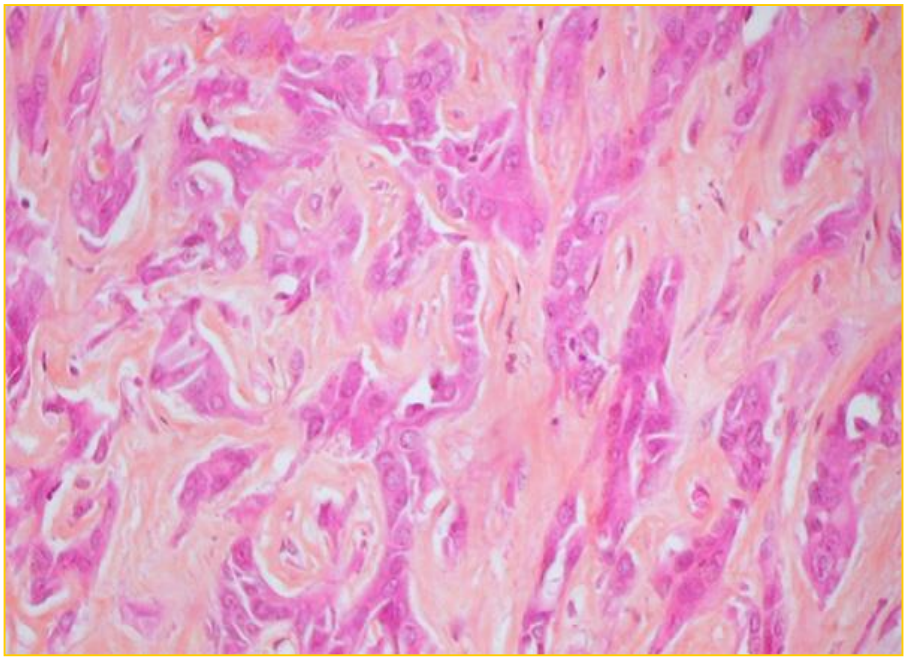
Immunoreactivity (%)	HCC, No. (%) (n = 111)	HCA, No. (%) (n = 48)	FNH, No. (%) (n = 30)	LRN, No. (%) (n = 32)
Negative (<5)	27 (24.3)	48 (100)	30 (100)	32 (100)
Focal (5–50)	23 (20.7)	0	0	0
Diffuse (>50)	61 (55.0)	0	0	0

* HCC indicates hepatocellular carcinoma; HCA, hepatocellular adenoma; FNH, focal nodular hyperplasia; and LRN, large regenerative nodule.

Wang Arch Pathol Lab Med 2008

Hepatocellular carcinoma with fibrous stroma
Sclerosing HCC???





- Abondant fibrous stroma
- Differential diagnosis ⟶ Immunohistochemistry

Immunophenotype of liver tumors

HCC

Hep Par 1 +	73%/ poorly ≠ 63%
Glypican 3	76-79%/ poorly ≠ 89%
AFP +	17% à 62%
CEAp +canalicular	45% à 80%/ CD10
CK8, CK18 +	
CK7*, CK19, CK20 -	
EMA -	

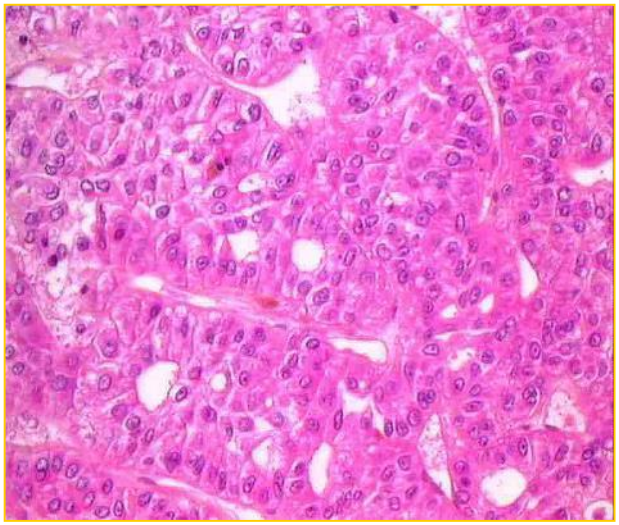
Meta

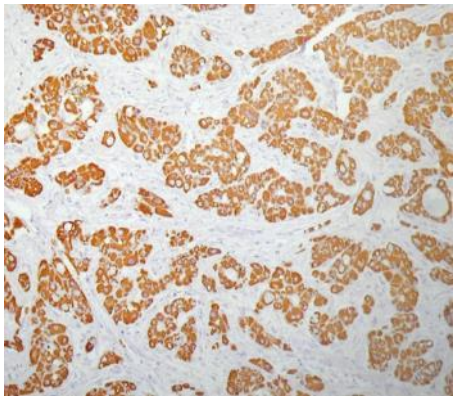
Colorectal : CK7 -, CK20 +
Pancreas/Stomach : CK7 +, CK 20+/-

CC

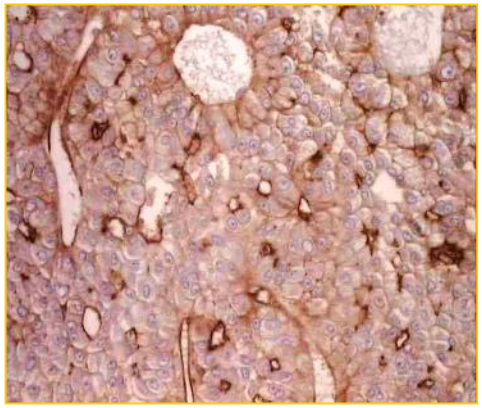
KL1 + Vimentin +
CK7, CK8, CK18,CK19 +
CK20 - or + focal
EMA +
CEAp + apical or cytopl

Immunophenotype of HCC

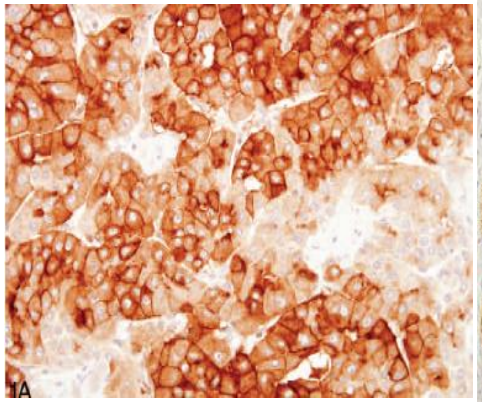




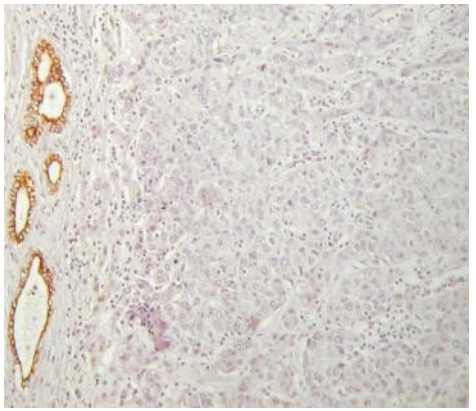
Hep-Par1



CEAp

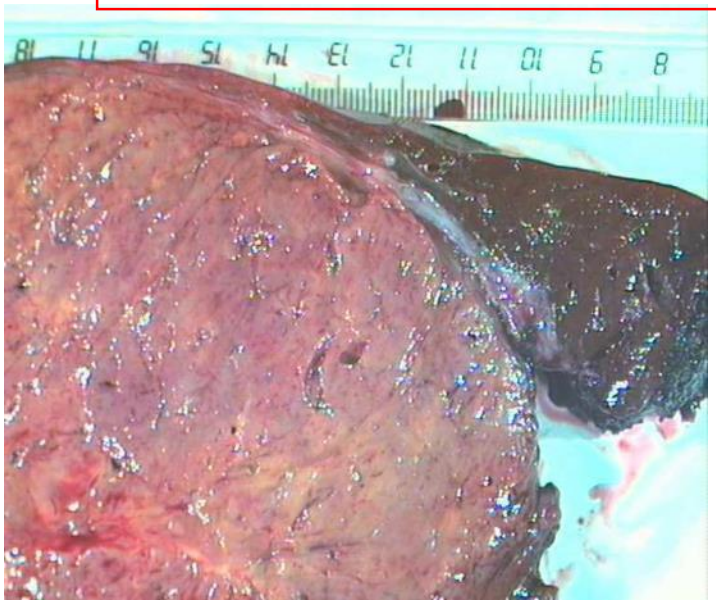


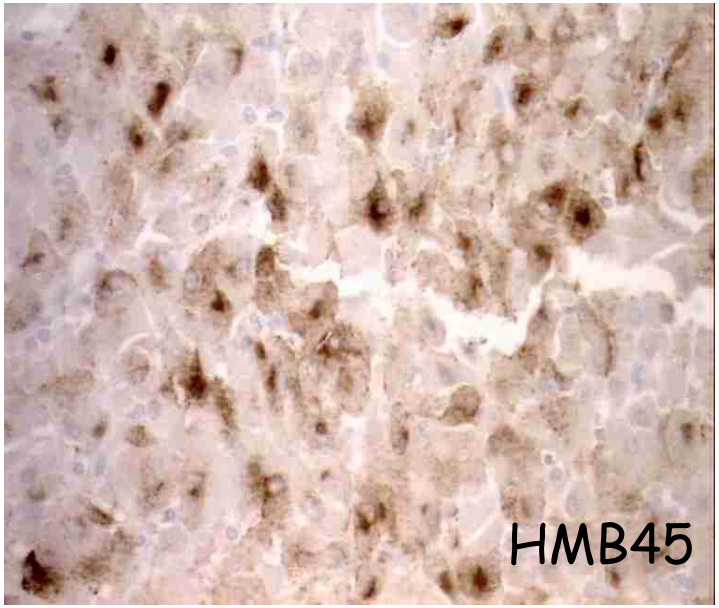
Glypican 3

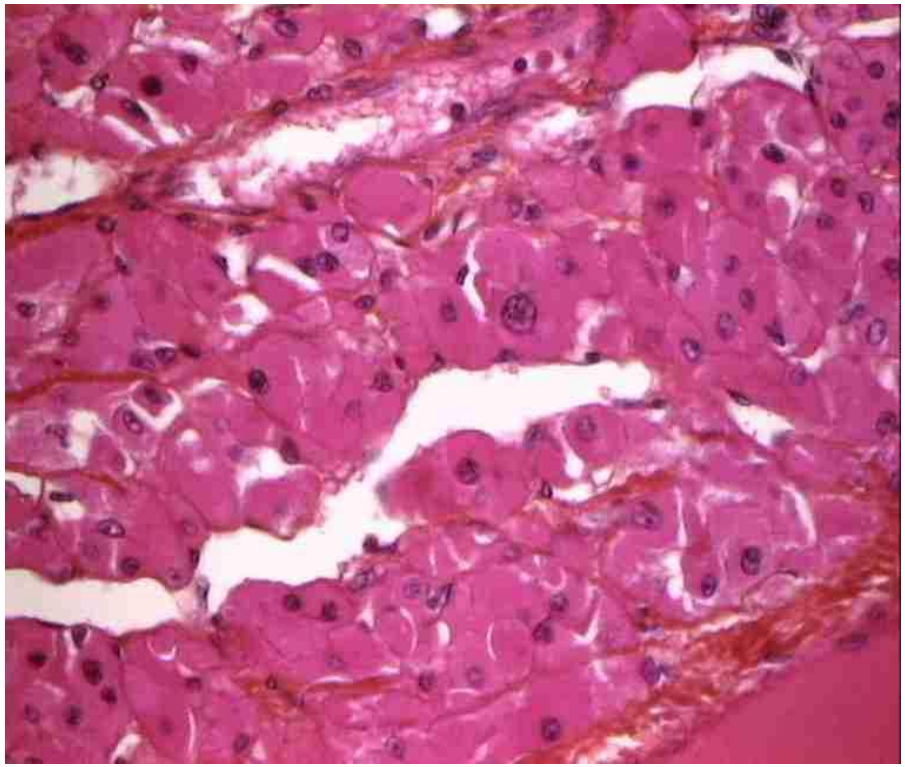


CK19

Epithelioid angiomyolipoma

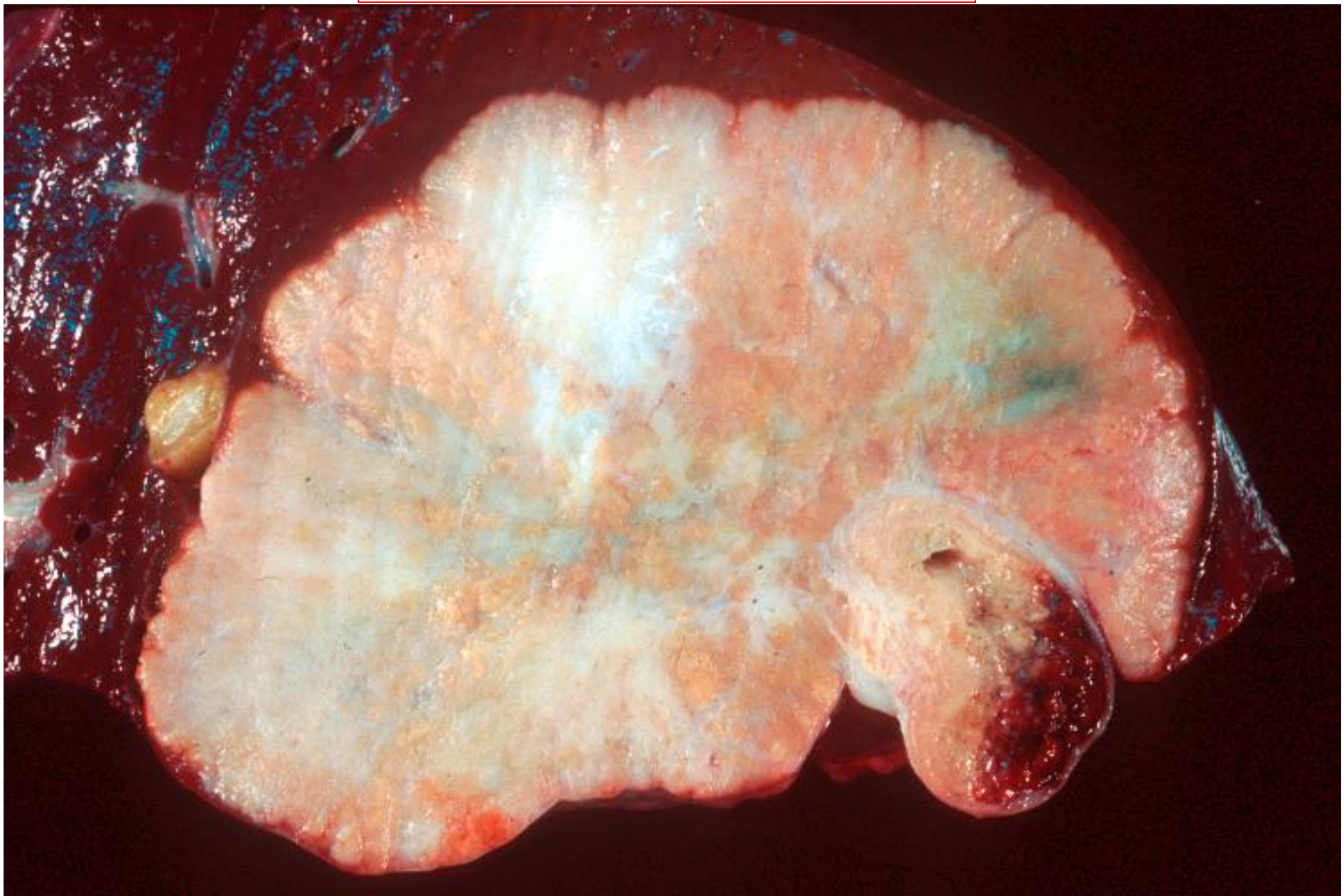






Exclusive monophasic component :
epithelioid cells
⇦ perivascular cells PEC / PECOMA

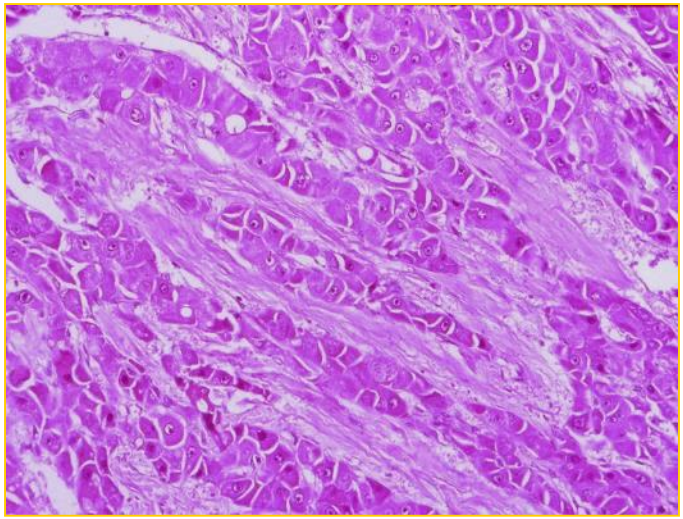
Fibrolamellar carcinoma

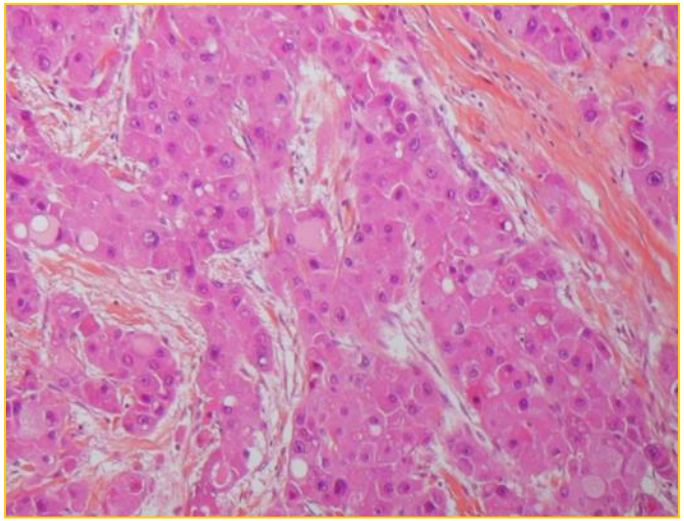


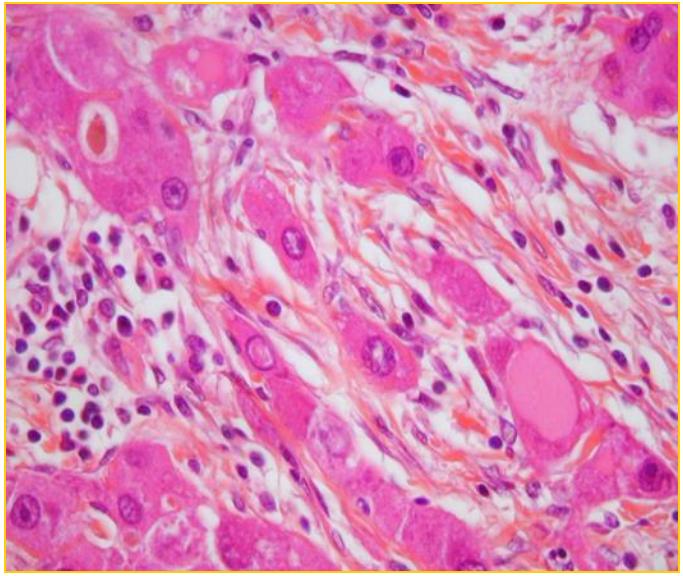
Fibrolamellar carcinoma

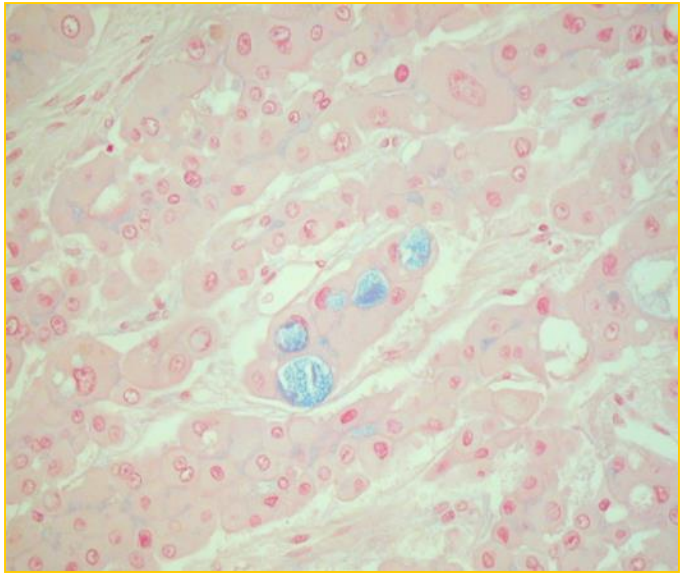
- Rare (<2% of HCC)
- Yound adults and children
- Non cirrhotic liver
- Normal AFP level
- Better prognosis?

Fibrolamellar carcinoma









HepPar1+, CK8 et 18 + / CK7 +, EMA+

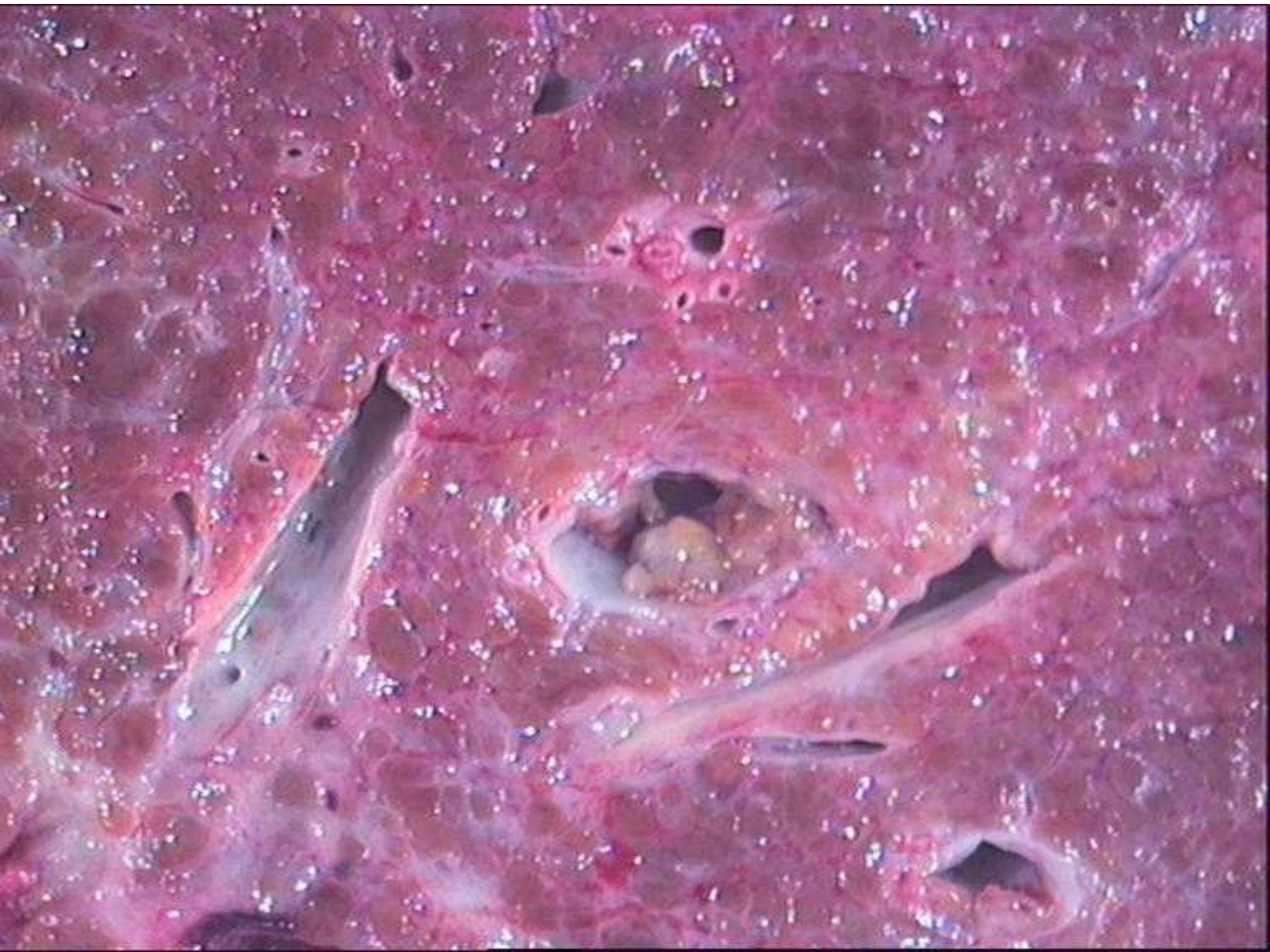
PATHOLOGICAL PROGNOSTIC INDICATORS IN HCC

A résumer (et à regrouper resection/transplantation)

Identification of pathological parameters with predictive efficiency (survival or recurrence) from resection specimens

Gross parameters

- Uninodular > multinodular > massive tumor
- Tumor size
- Capsule
- Satellite nodules
- Macrovascular invasion ++
- Necrosis
- Curative resection

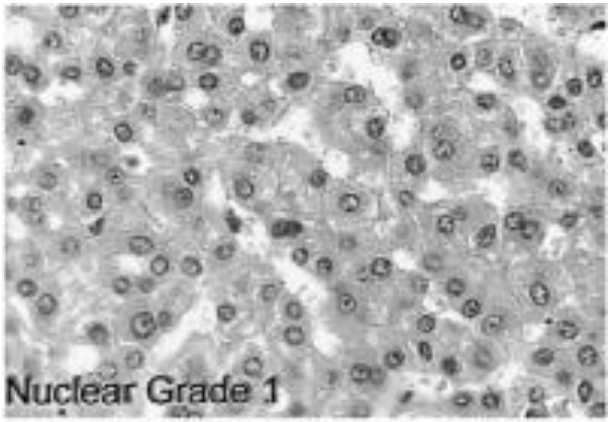


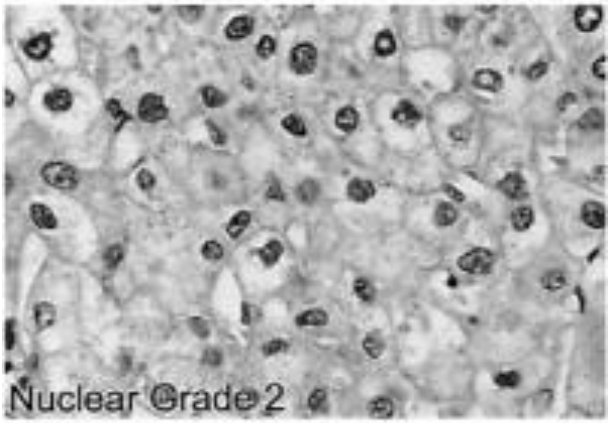
Identification of pathological parameters with predictive efficiency (survival or recurrence) from resection specimens

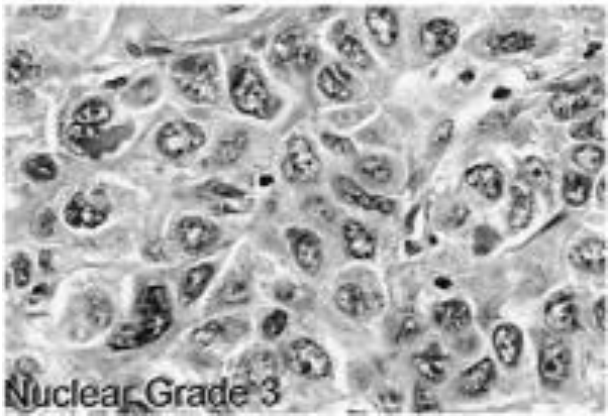
Histological parameters

- Edmonson grading*
- Nuclear grade*
- Mitotic index
- Capsular invasion
- Microvascular invasion*
- Intratumoral inflammation
- Activity and fibrosis in non tumoral liver

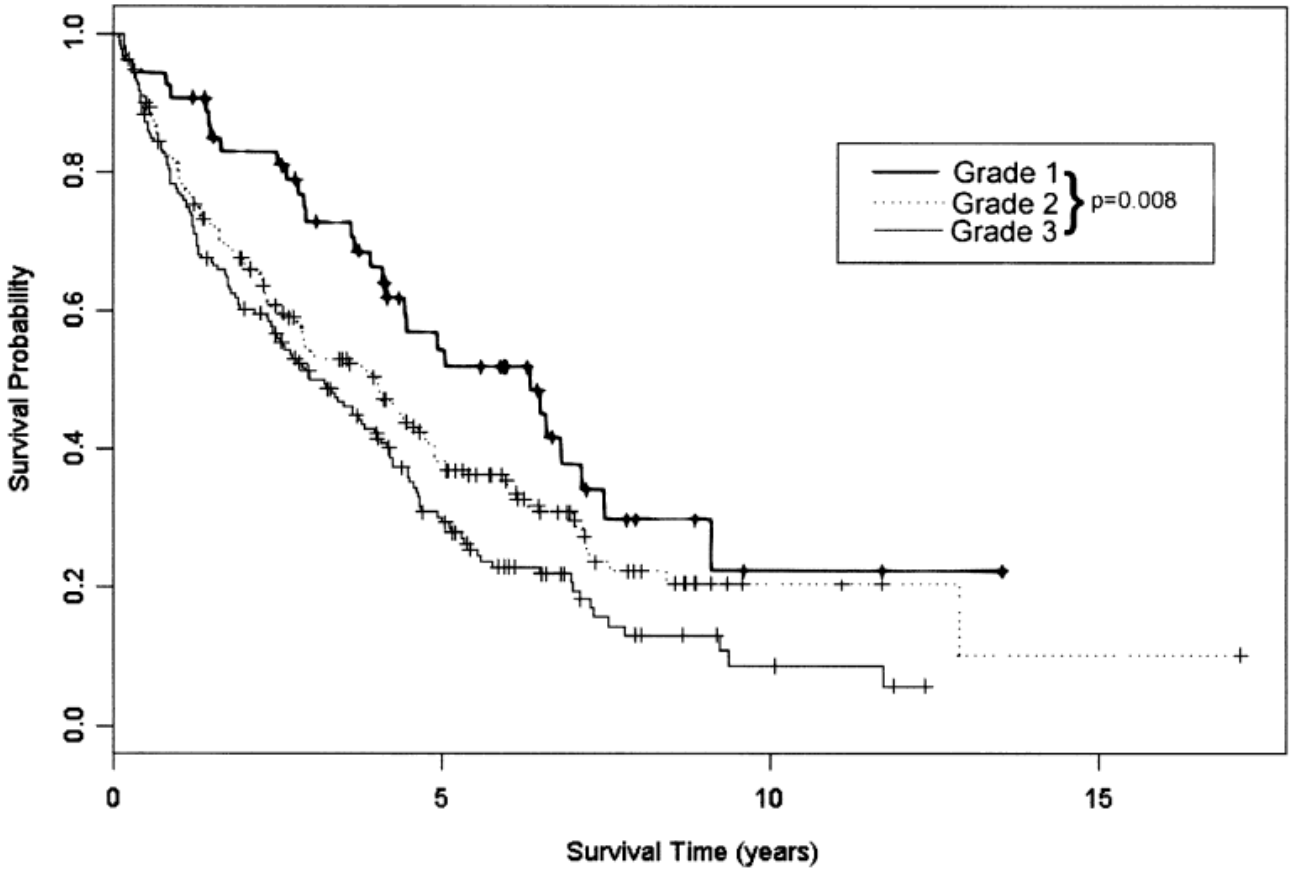
Nuclear grade





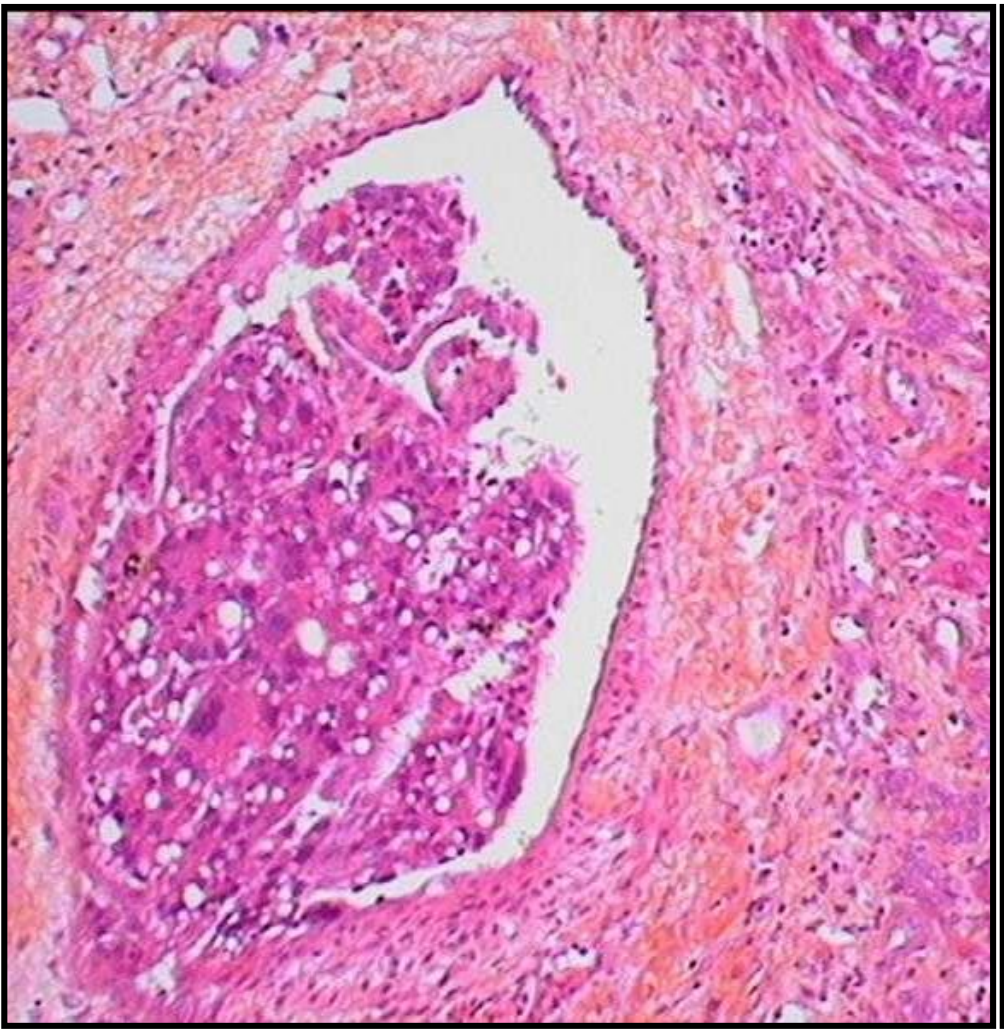


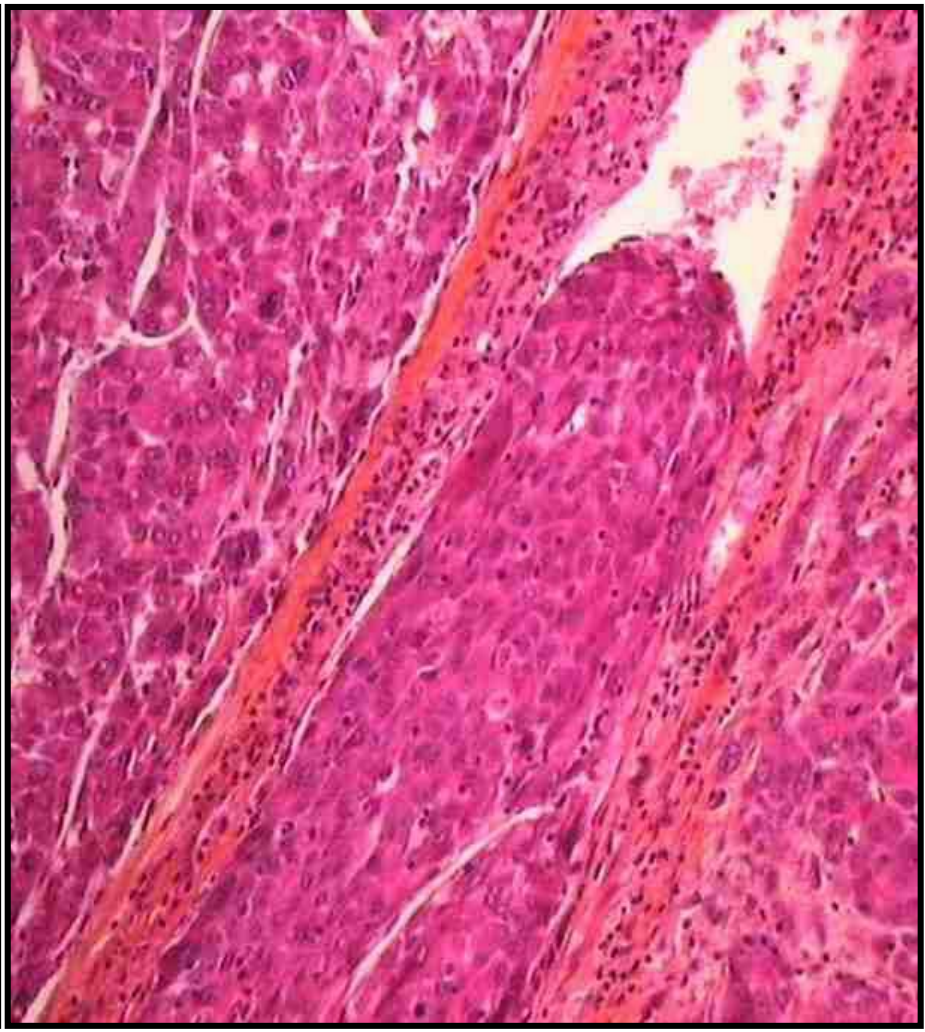
425 curative resections



Am J Surg Pathol 2002; 26: 25-34

Microvascular invasion





Histological grading

WHO

Well differentiated
Moderately differentiated
Poorly differentiated

EDMONSON

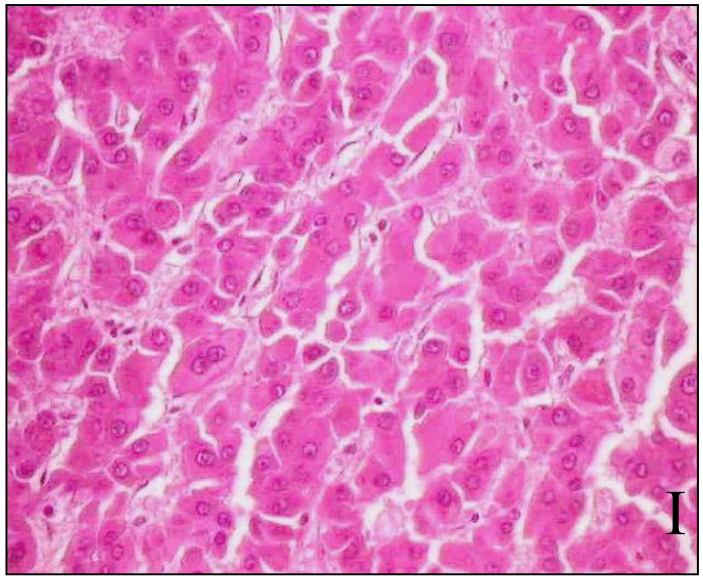
Grade I: Benign appearance - no or slight atypia -
Adenoma? Dysplastic nodule? – Associated with higher grades

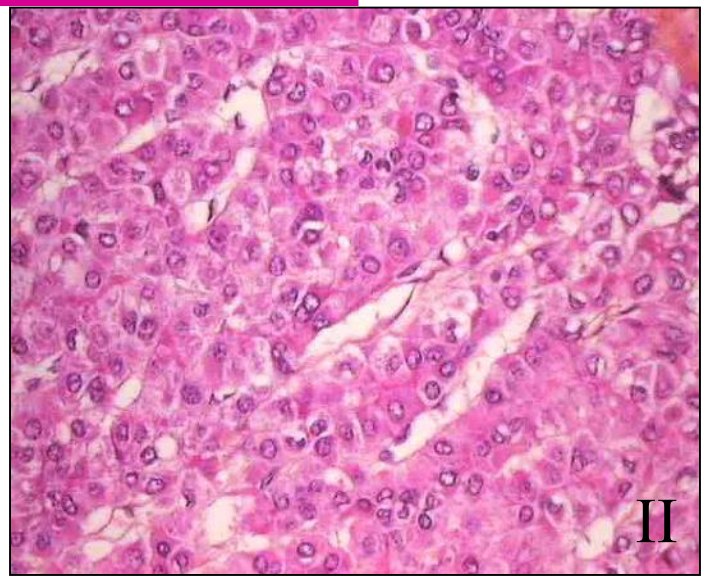
Grade II: Well differentiated – Trabecular or pseudoacinar architecture - Moderate atypia - Bile +

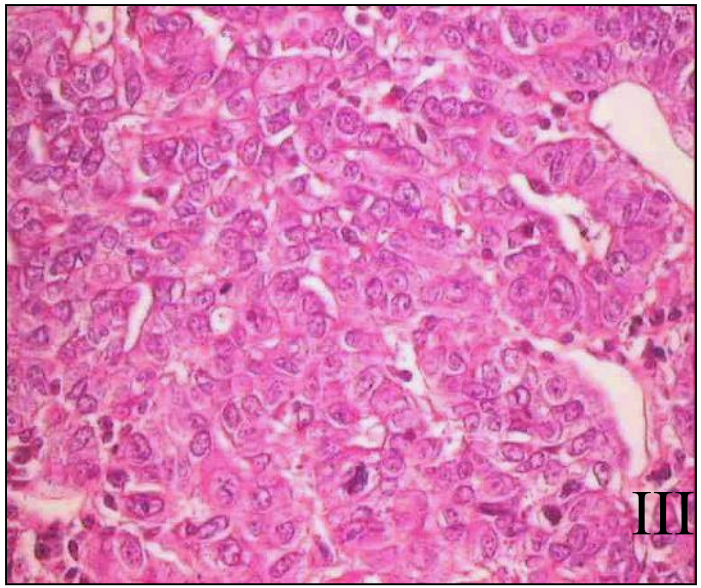
Grade III: Compact architecture - Marked atypia - Syncytial cells

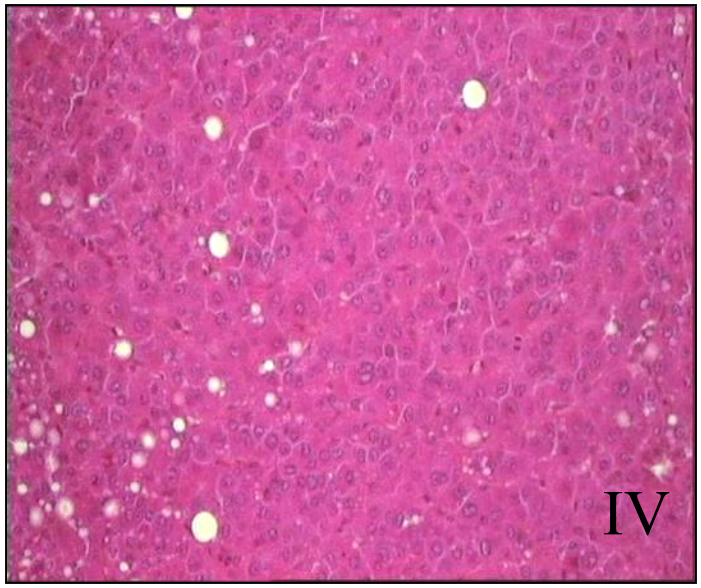
Grade IV: Poorly differentiated - Marked atypia - Small cell or sarcomatoid features

Edmonson's grading

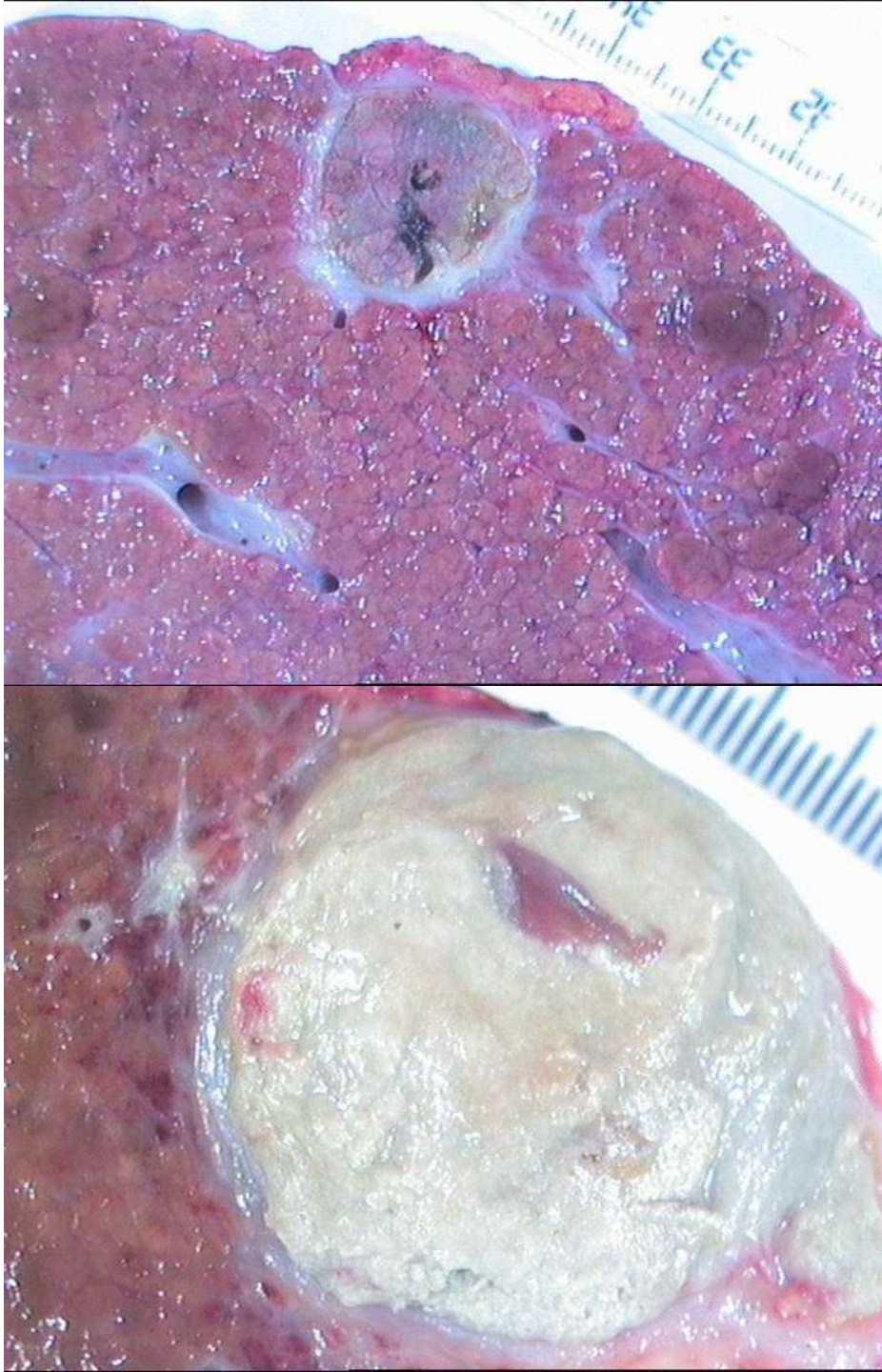




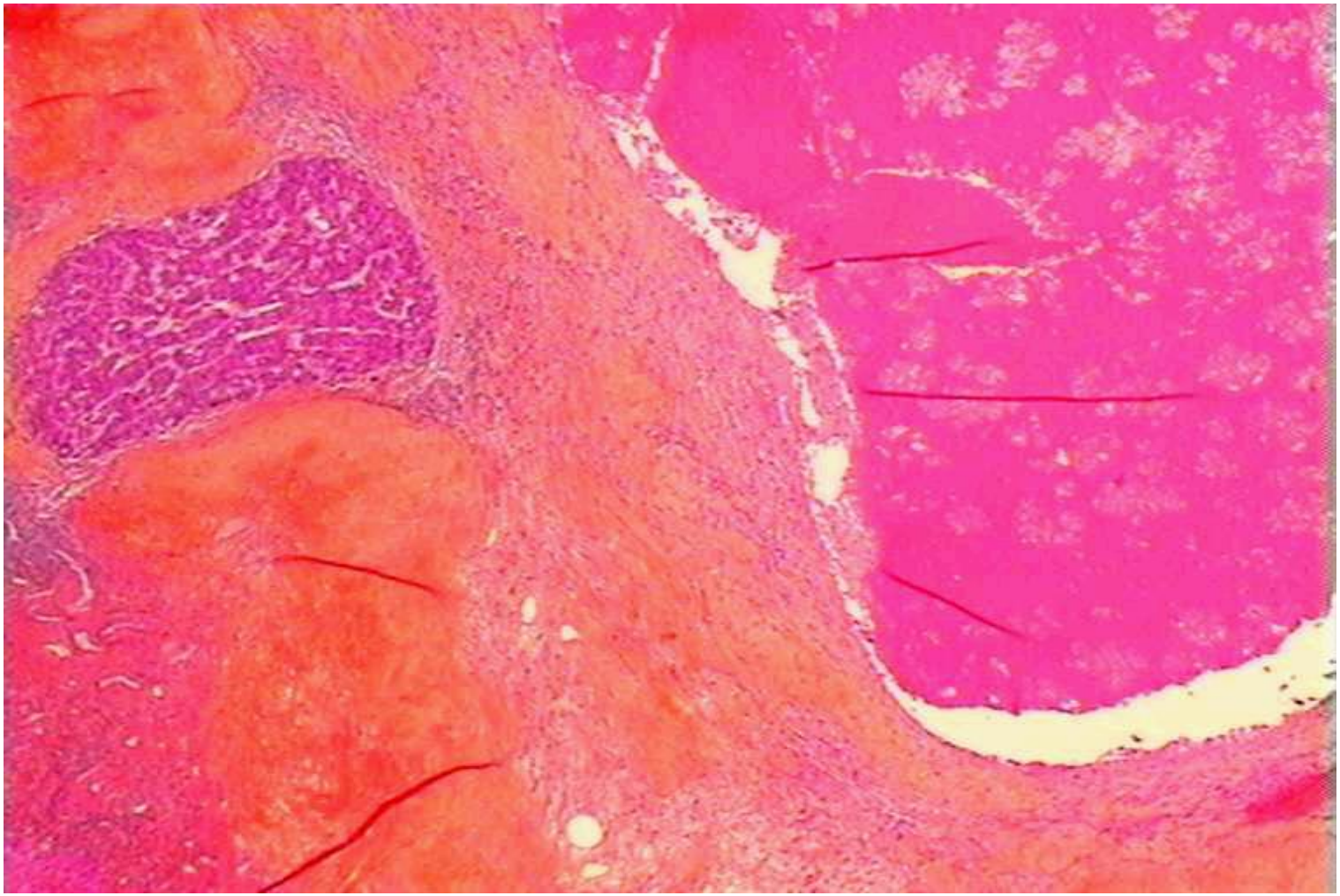




Post-chemoembolization changes



Post-chemoembolization changes



The close future

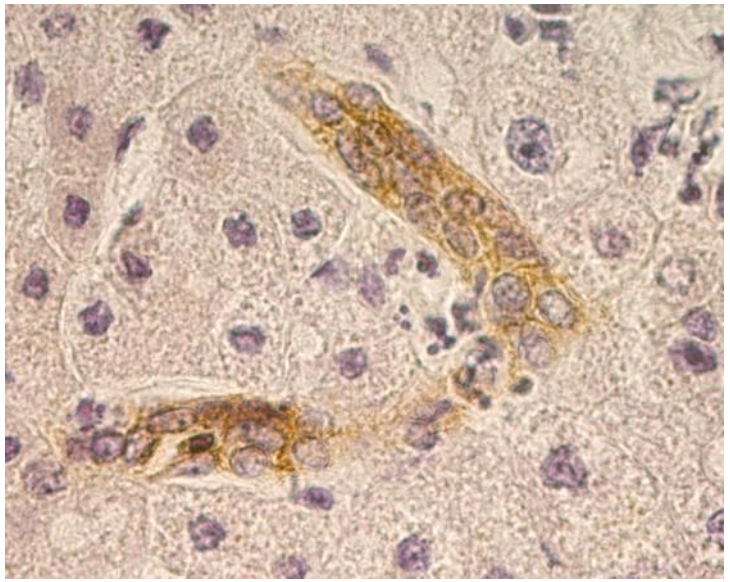
-High-throughput molecular studies: cDNA arrays, CGH arrays, microRNAs, proteome analysis

-Molecular classifications of HCC : Molecular signature with predictive efficiency → IHC markers

-Characterization of signalisation pathways leading to new targeted therapies

EpCAM

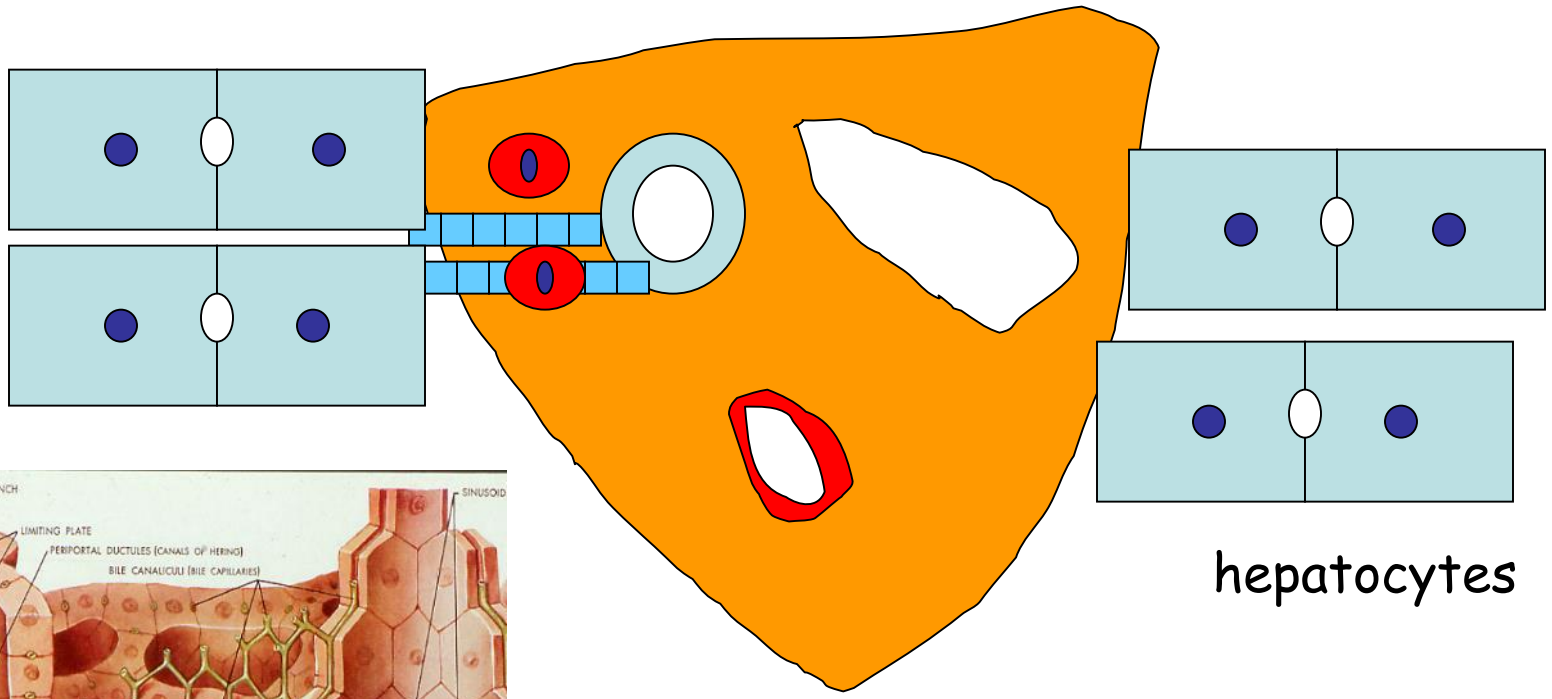
- Epithelial cell adhesion molecule CD326
- *Tumor-associated calcium signal transducer 1* gene
- Liver:
  - Adult liver: bile ducts, ductules
  - Fetal liver: hepatoblasts
- HCC: 35% + for EpCAM



Schmelzer JEM 2007
Yamashita Cancer Res 2008

Progenitor cell of adult liver

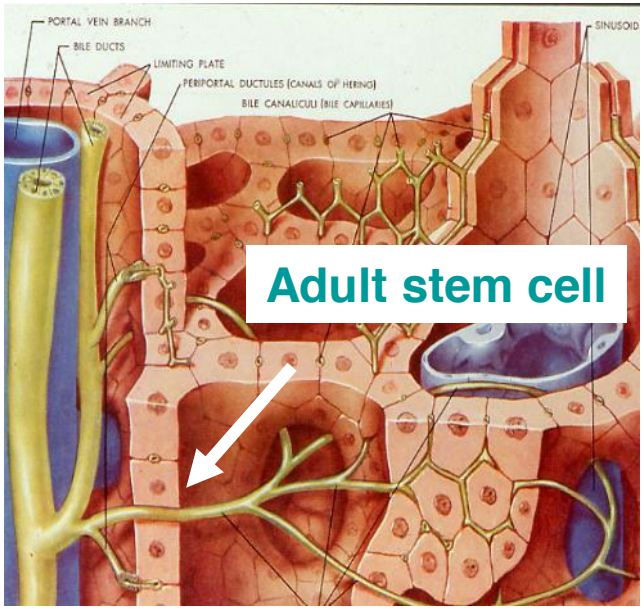
Bipotent progenitor cell of adult liver



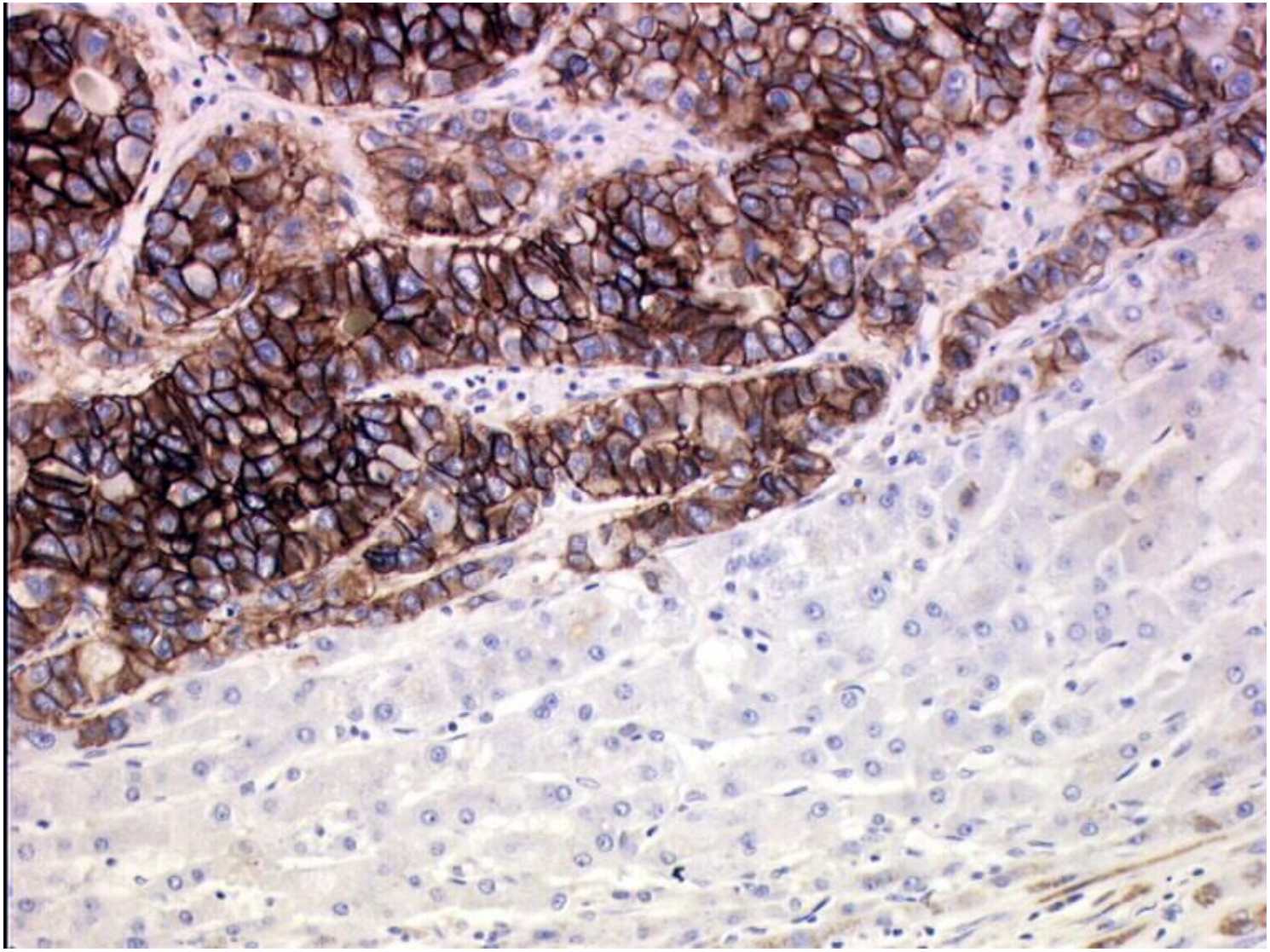
hepatocytes

Portal tract

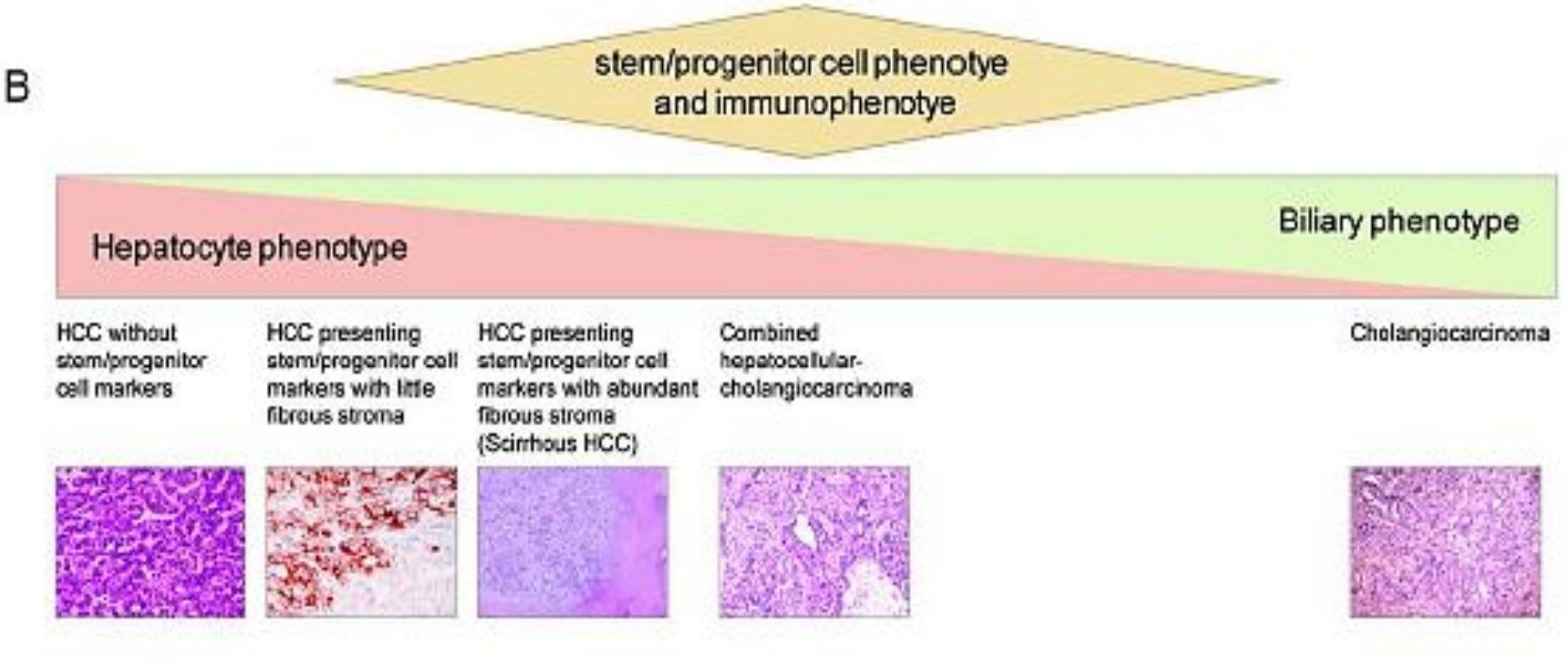
Ductular reaction



EpCAM positive HCC

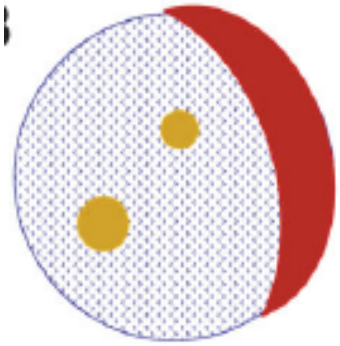


The spectrum of liver cell tumors



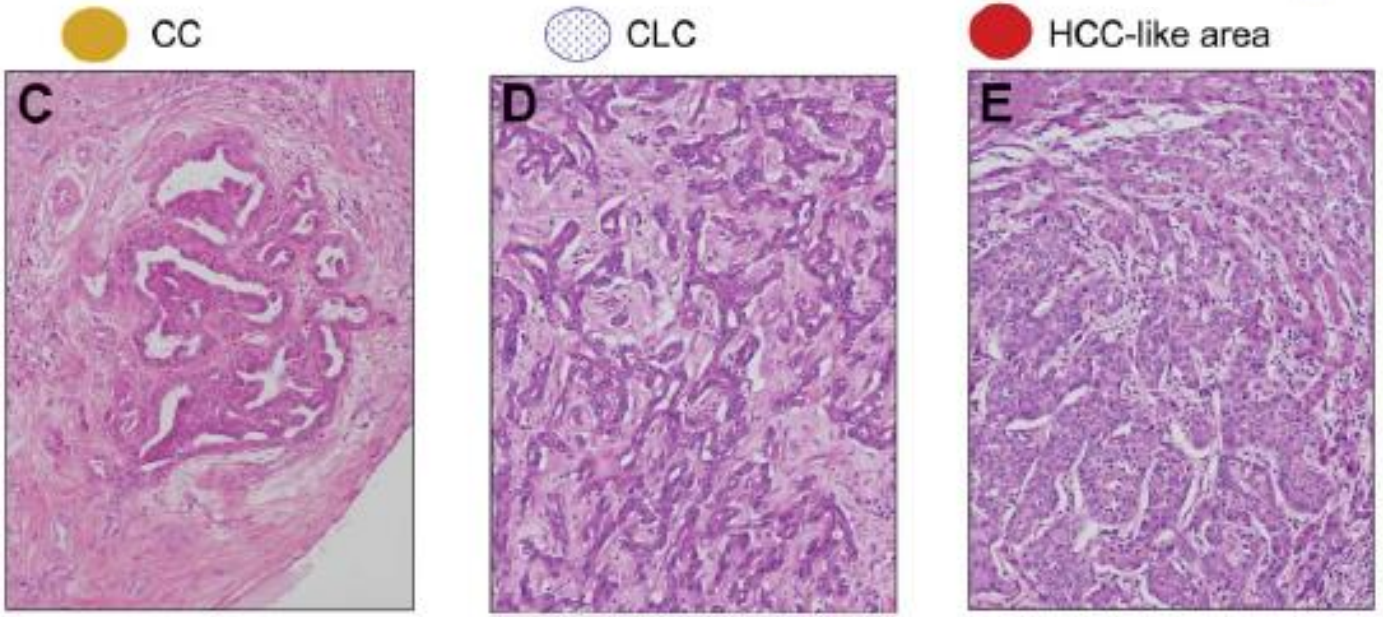
Seok Hepatology 2012

Cholangiolocellular carcinoma



30 cholangiolocellular carcinoma

CLC = phenotypic homology with ductular reaction
(= non tumoral HPCs)

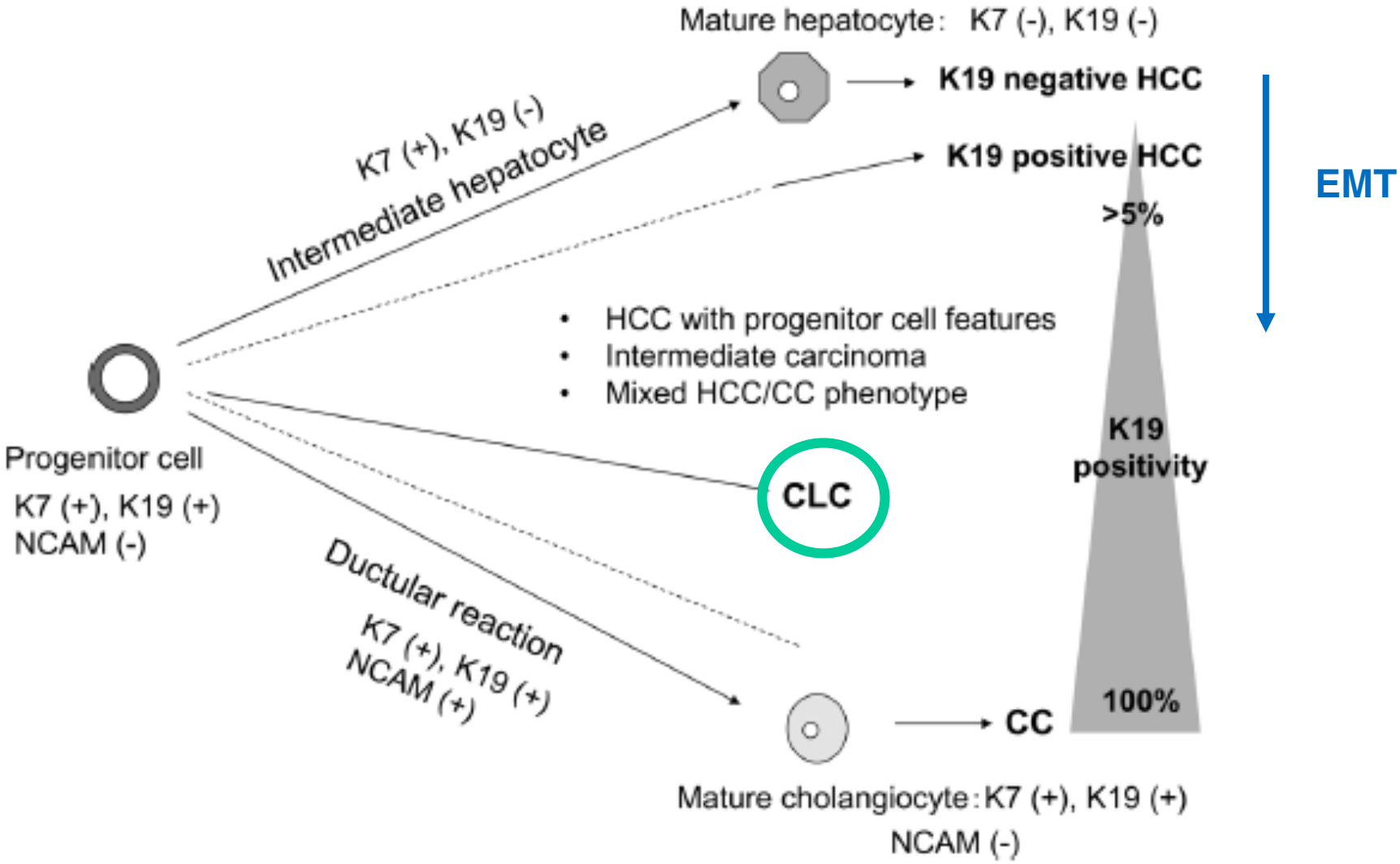


CK19+

-Progenitor cells= target of liver carcinogenesis

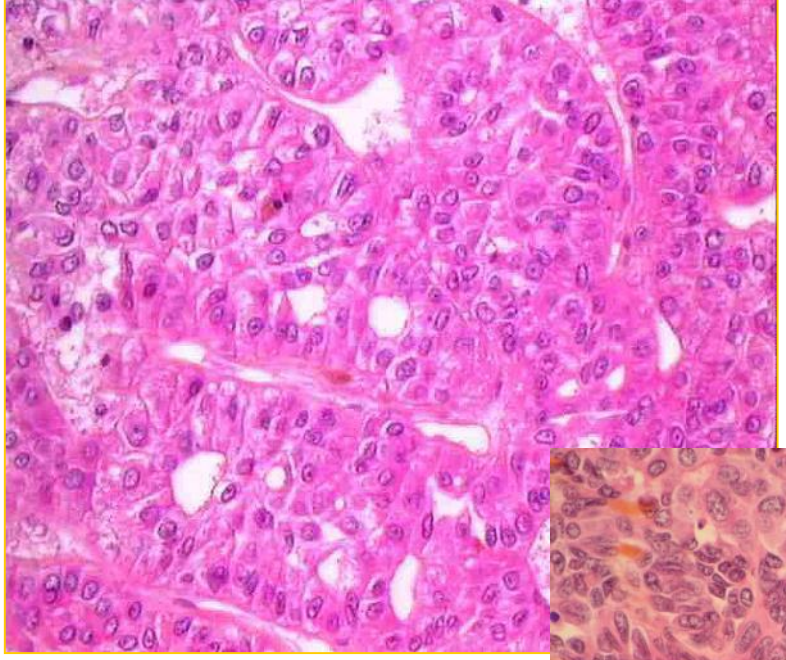
Komuta Hepatology 2008

Lineage of primary liver cancers

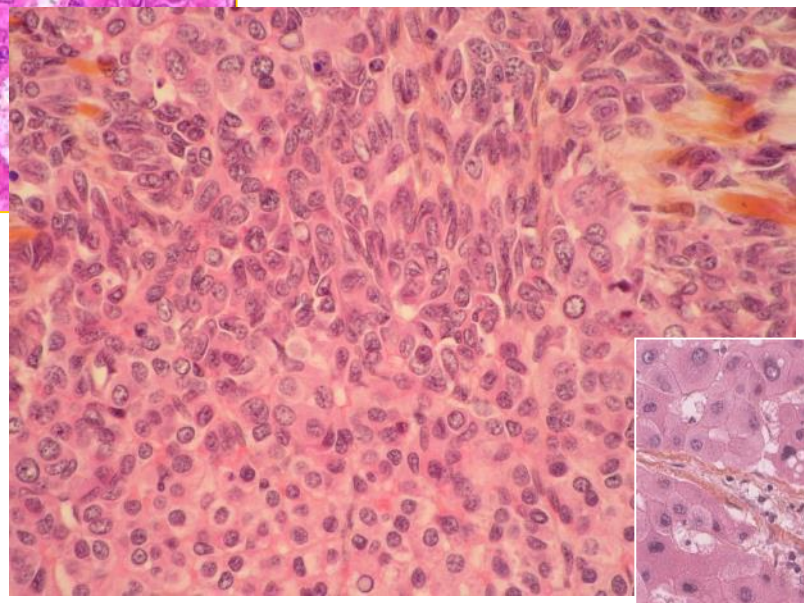


Komuta Hepatology 2008

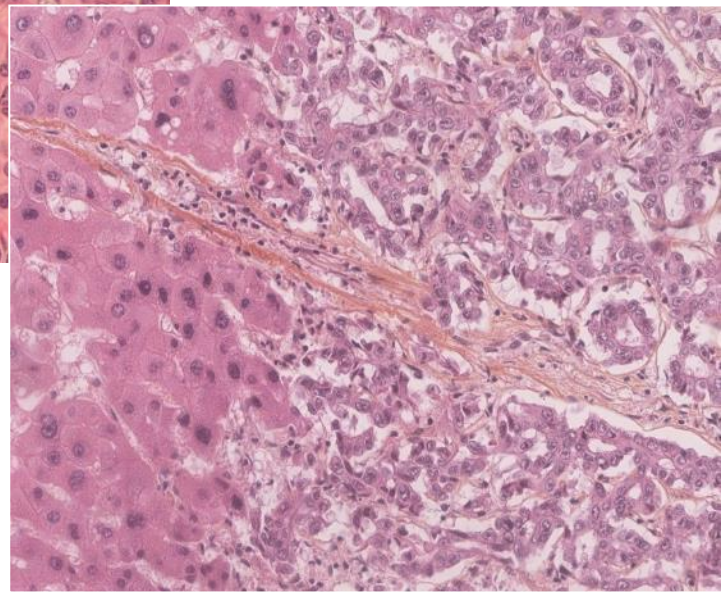
Primary tumors on cirrhotic livers



Classical HCC



Progenitor-like HCC



Cholangiocarcinoma

PROPOSAL OF A NEW PATHOLOGICAL CLASSIFICATION

Early HCC

a/HCC of small size (≤ 2cm), well differentiated (G1), vaguely nodular

Progressed HCC

a/HCC of small size (≤ 2cm), usually moderately differentiated (G2), distinctly nodular type
HCC of not small size (>2cm) single or multiple

b/ HCC with stem/progenitor cell immunophenotype

c/ Mixed hepatobiliary carcinoma, classical type

d/Mixed hepatobiliary carcinoma
with stem/progenitor cell phenotype and immunophenotype

Roncalli Dig Liver Dis 2010

Combined Hepatocellular-Cholangiocarcinomas Classification WHO 2010

TABLE 1. Histologic Features of Combined Hepatocellular-Cholangiocarcinomas According to WHO Classification

Subtypes	Mucin Production	Stroma	Histologic Findings
CHC-classical			
HCC component	None	Scarce	Typical HCC, well to poorly differentiated type
ChC component	Observed	Intermediate-abundant	Typical adenocarcinoma, well to poorly differentiated type
CHC-SC-typical	None	Abundant	Nests of mature looking hepatocytes with peripheral clusters of small cells that have a high nucleus:cytoplasm ratio and hyperchromatic nuclei
CHC-SC-int	None	Intermediate-abundant	Tumor cells show features intermediate between hepatocytes and cholangiocytes. These tumor cells show strands, solid nests and/or trabeculae of small, uniform cells with scant cytoplasm and hyperchromatc nuclei
CHC-SC-CLC	None	Abundant	Tumor is composed of admixtures of small monotonous glands, antler-like anastomosing patterns. Each tumor cell is cuboidal, smaller in size than normal hepatocytes, with high nucleus:cytoplasm ratio, and distinct nucleoli

CHC indicates combined hepatocellular-cholangiocarcinoma; CHC-SC-typical, combined hepatocellular-cholangiocarcinoma, stem cell features, typical subtype; CHC-SC-int, combined hepatocellular-cholangiocarcinoma, stem cell features, intermediate cell subtype; CHC-SC-CLC, combined hepatocellular-cholangiocarcinoma, stem cell features, cholangiolocellular subtype.

Classification relying upon the major component >50%

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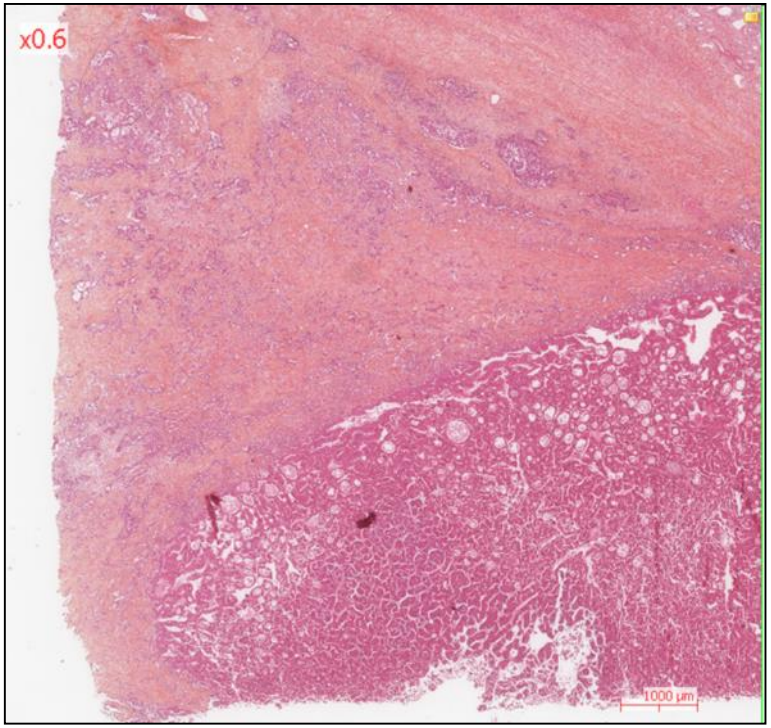
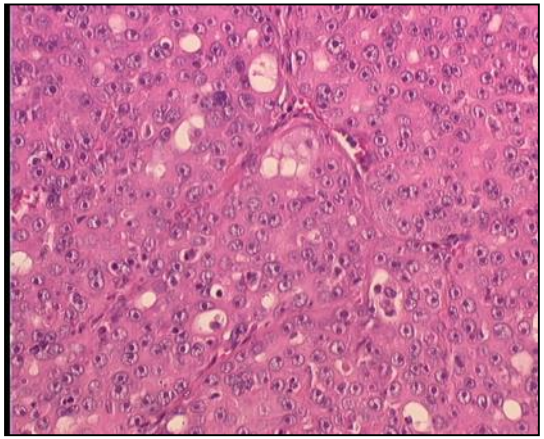
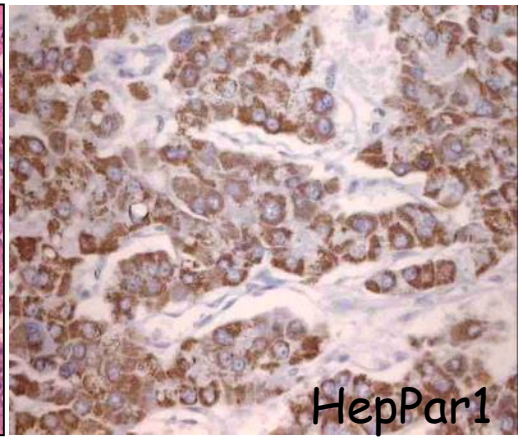
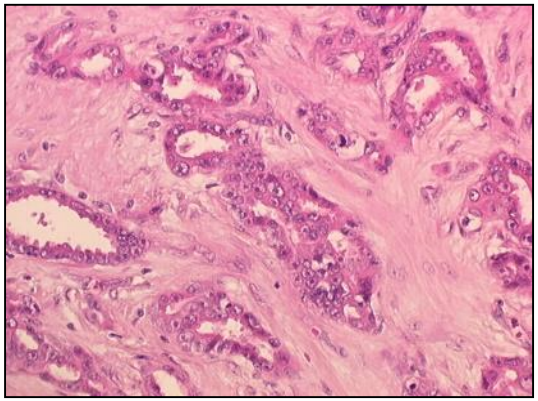
Combined Hepatocellular-Cholangiocarcinomas
Classical type

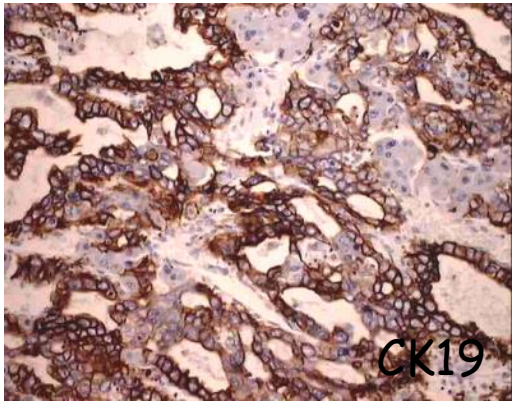
- Two distinct components, hepatocellular carcinoma and cholangiocarcinoma
- Most often observed on chronic liver diseases (HCV, HBV, hemochromatosis)











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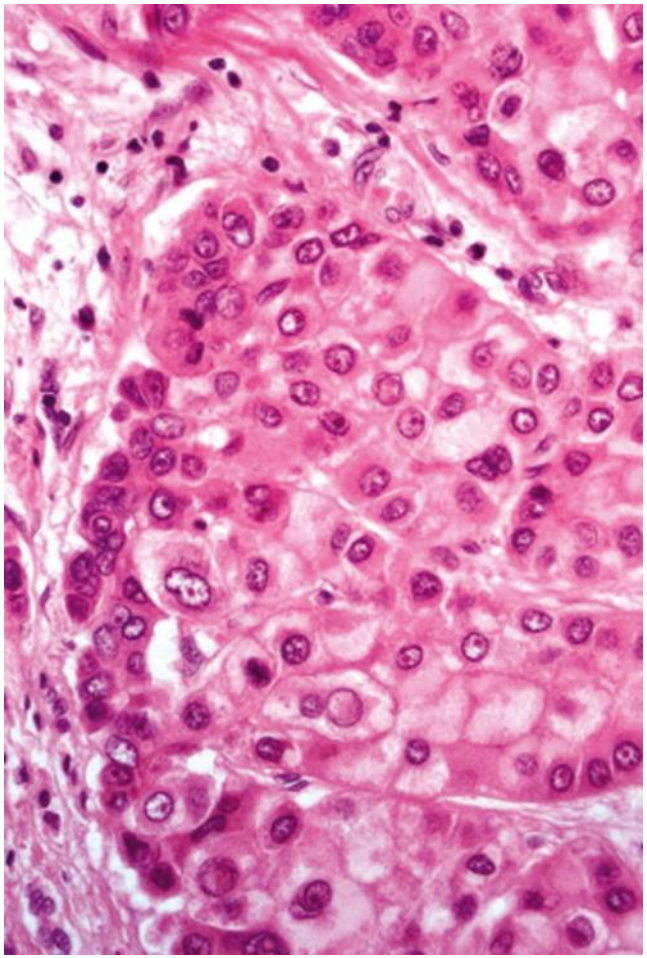
Combined Hepatocellular-Cholangiocarcinoma With Stem cell features – typical type



- Nests of mature hepatocytes
- Peripheral clusters of small stem/ progenitor cells
  CK7+ CK19+ CD56+ c-kit+ EpCAM+
- Fibrous stroma
- Rare

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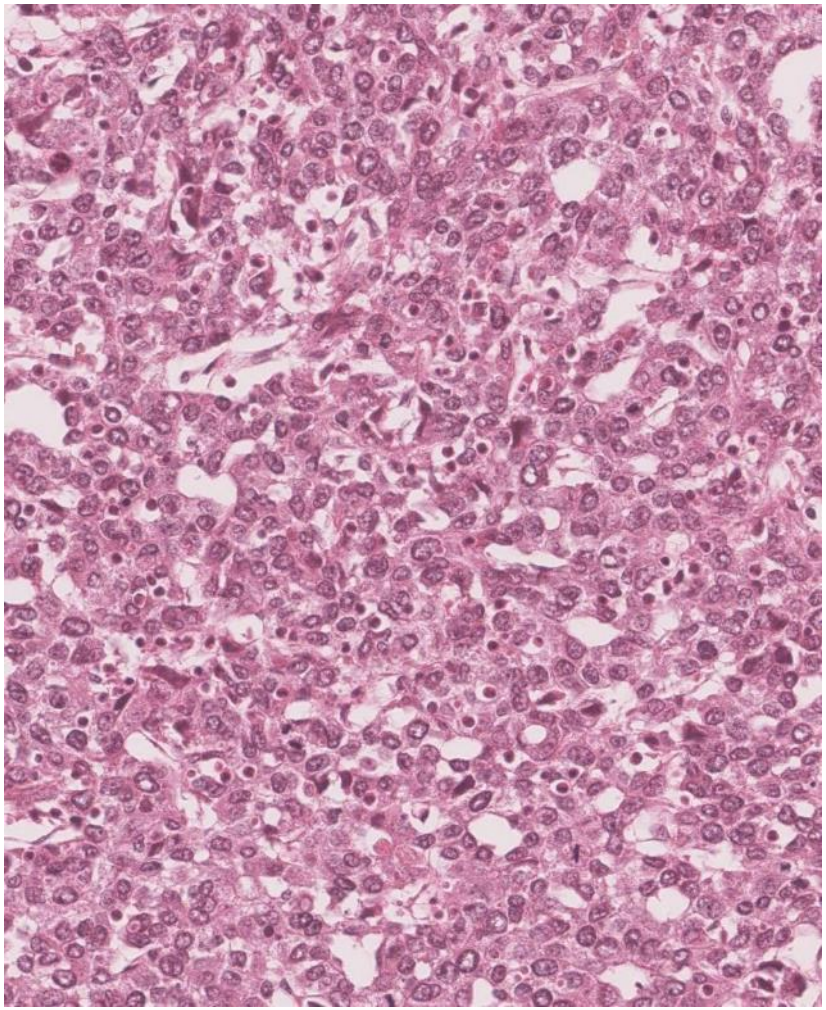
Combined Hepatocellular-Cholangiocarcinoma With Stem cell features – intermediate type



- Cells intermediate between hepatocyte and cholangiocyte
- Strands, solids nests or trabeculae
- HepPar1+, AFP+, CK19+, c-kit+
- Minor components: HCC, CC, cholangiolocellular carcinoma

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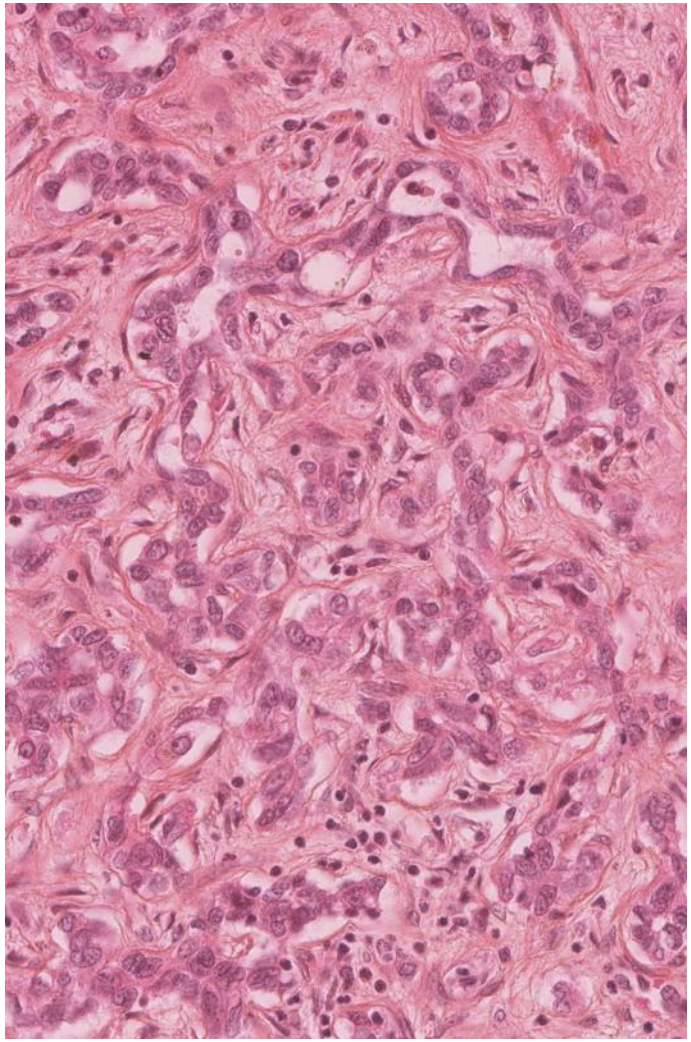
Combined Hepatocellular-Cholangiocarcinoma With Stem cell features – cholangiolocellular type



- Small anastomozing glands with fibrous stroma
- Cuboidal cells
- Coexpression of biliary and progenitor cell markers
- CK19, cKit, NCAM, EpCAM
- Minor components: HCC, CC

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Targeted therapies in HCC?

- Sorafenib
- Tivantinib: c-met receptor?

Conclusion

Cirrhotic liver:

- Diagnosis of small tumors (1 -2 cm)?
- Prognostic factors: Tumor differentiation
  Vascular invasion
  Stem/progenitor cell markers
- New prognosis markers from molecular studies
- A continuous spectrum of liver cell tumors

Non cirrhotic liver:

- Biopsy for differential diagnosis?
- New prognosis markers from molecular studies

New therapies?