22 November 2018

Hepatocellular neoplasia - Recent developments

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Speaker Declarations

Dina Tiniakos

This presenter has the following declarations of relationship with industry

- Personal payments/honoraria/fees: Allergan, Intercept
- Educational grants: Histoindex

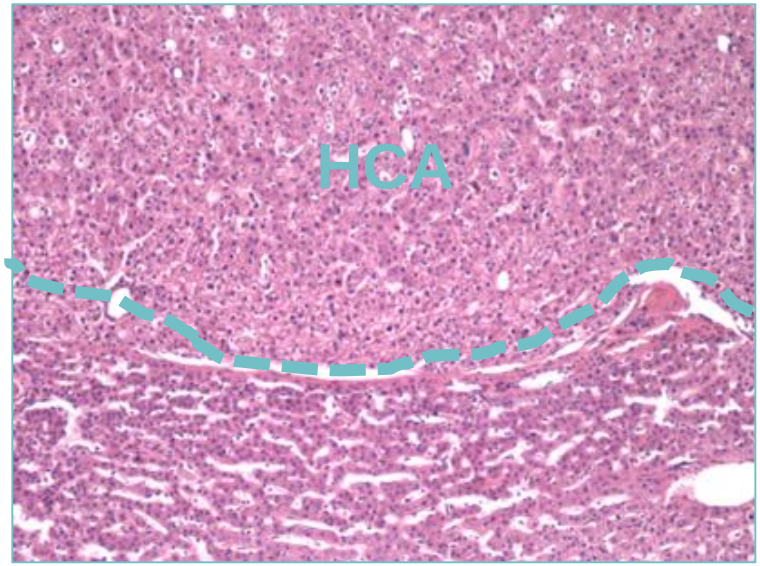
22-11-2018

1. Hepatocellular adenoma - Recent developments

Hepatocellular adenoma (HCA)

- Rare neoplasm
- Typically, women 15-45 y
- **Non-cirrhotic liver**
- Strong aetiological correlation with steroid use
  - 80% oral contraceptives (OC)
  - anabolic/androgen steroids (men, Fanconi anaemia)
- Correlation with glycogen storage disease I & III (multiple HCA)
- Correlation with diabetes MODY3 (TCF1 mutation)

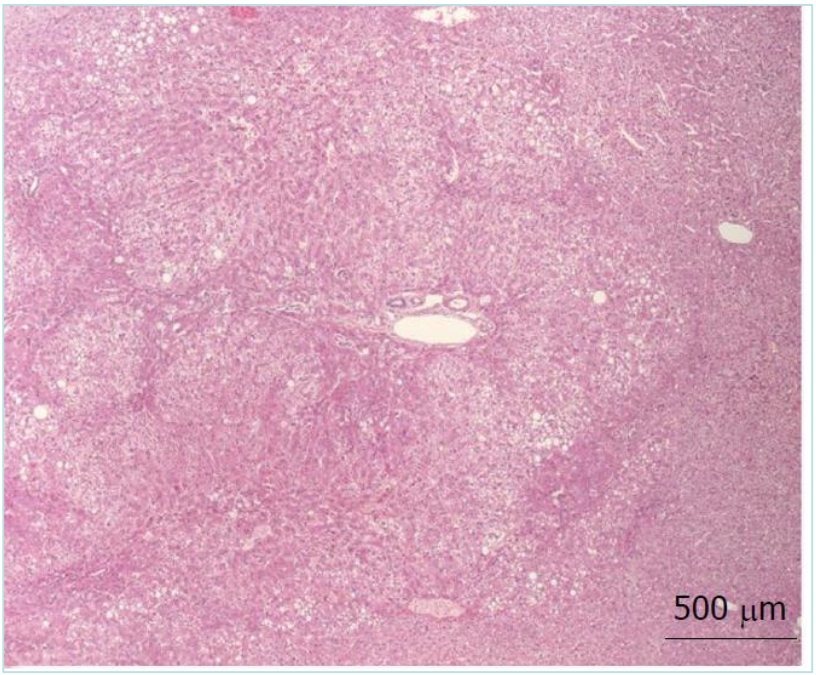
Hepatocellular adenoma (HCA)

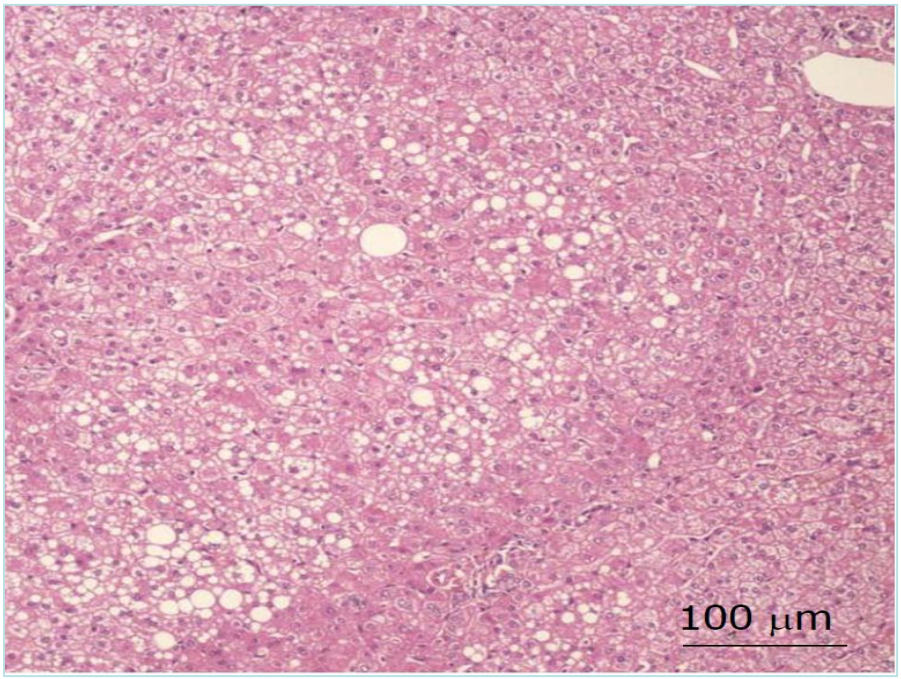


Subtyping – Molecular Classification of HCA 2018

- HNF1α-inactive HCA
- Inflammatory HCA
- β-catenin mutated HCA
- Sonic hedgehog HCA
- Unclassified HCA

HNF1α-inactive HCA (H-HCA)



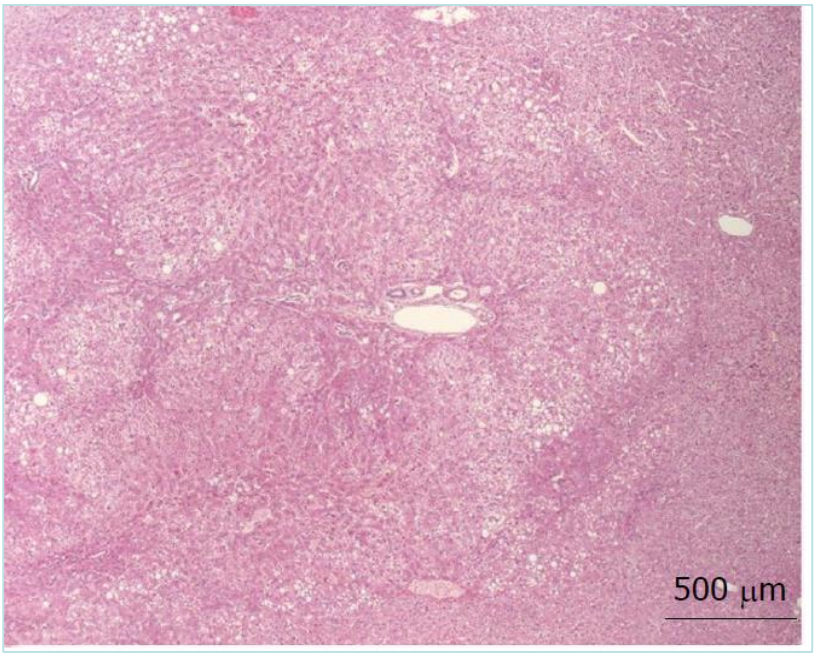


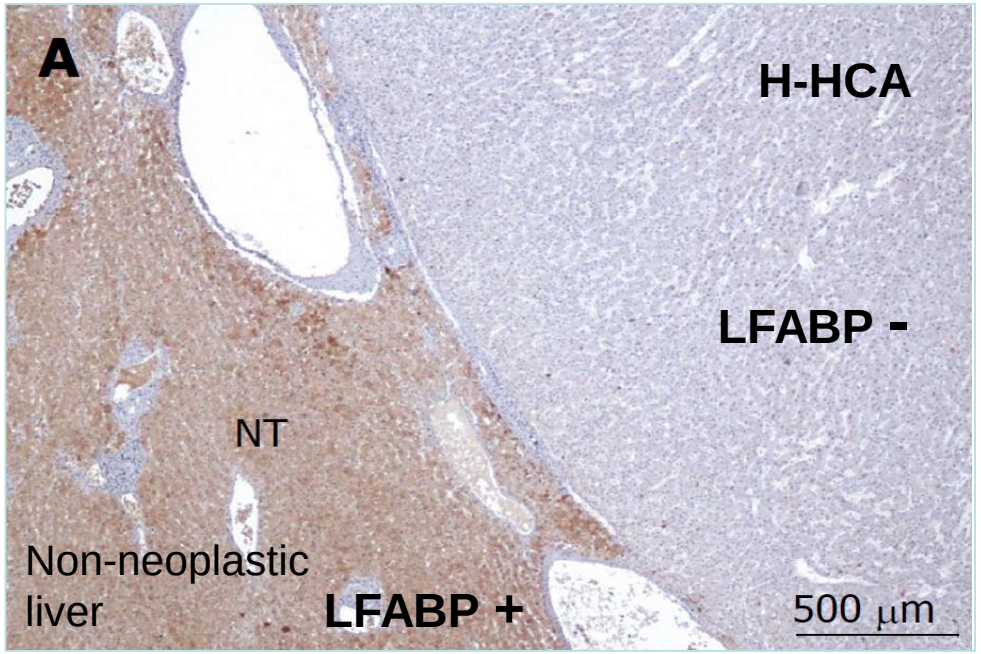
Sempoux, World J Hepatol 2014

- F>>M
- Correlation with OC use
- HNF1a gene mutation
- Some inherited cases (adenomatosis, MODY3)

- Classic morphology
- Steatosis is common
- Transformation very rare
- Adenomatosis

HNF1α-inactive HCA (H-HCA)





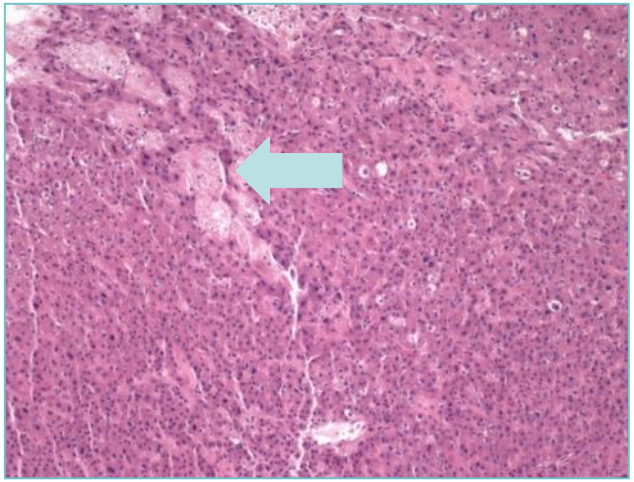
Sempoux, World J Hepatol 2014

- F>>M
- Correlation with OC use
- HNF1a gene mutation
- Some inherited cases
- (adenomatosis, MODY3)

Immunohistochemistry:
Loss of Liver Fatty Acid Binding Protein (LFABP)

Inflammatory HCA (I-HCA)

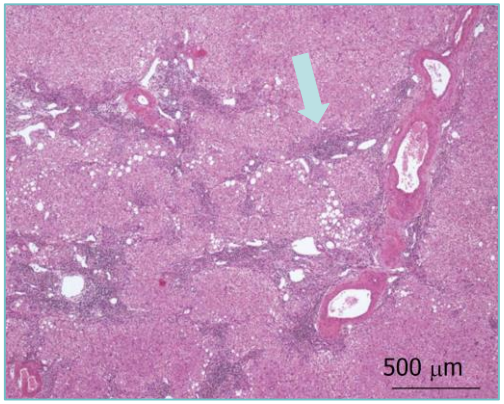
Haemorrhage

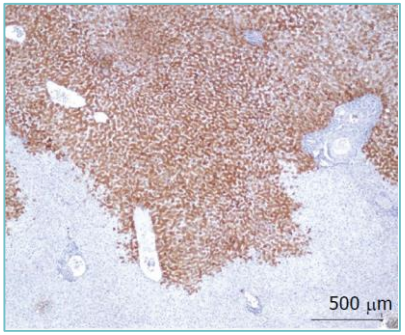


Sinusoidal dilatation

Thick walled arteries

Inflammation



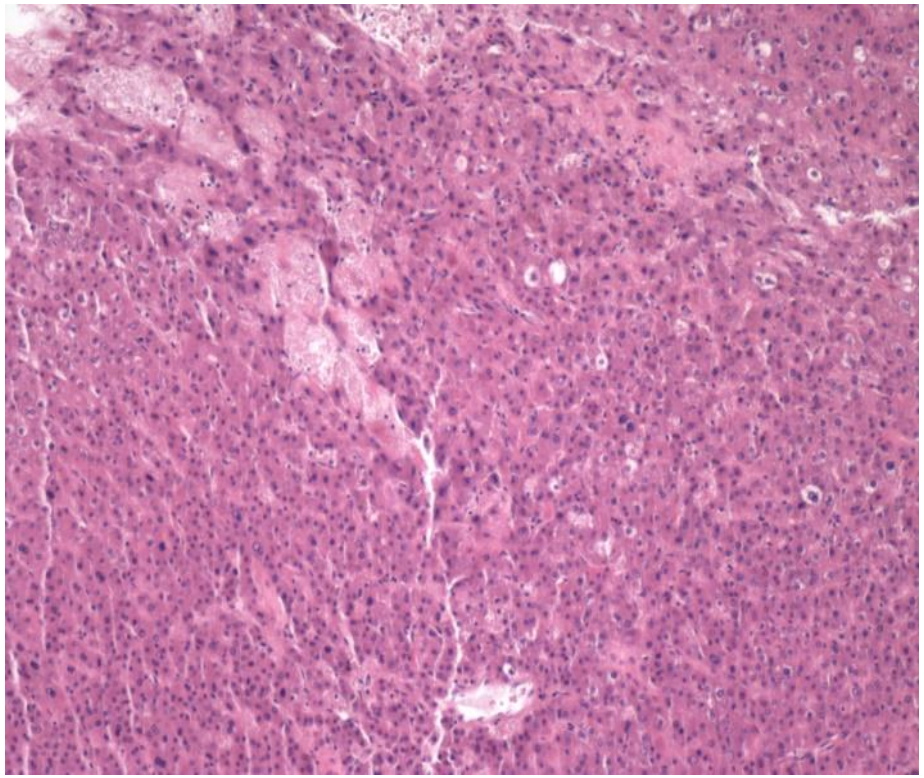


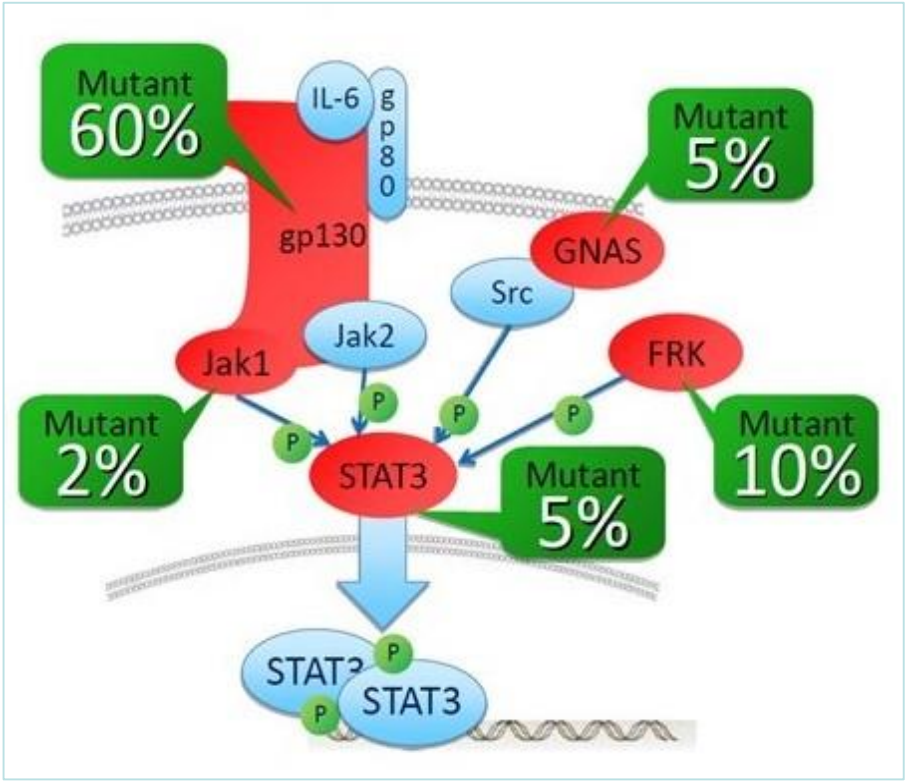
SAA/CRP + immunostain

- M>F (West), M=F (East)
- Correlation with OC (West)
- Single or multiple

- Rarely: glycogen storage disease, FAP, vascular diseases
- Very rarely in cirrhotic liver
- Serology: ↑CRP

Inflammatory HCA (I-HCA)

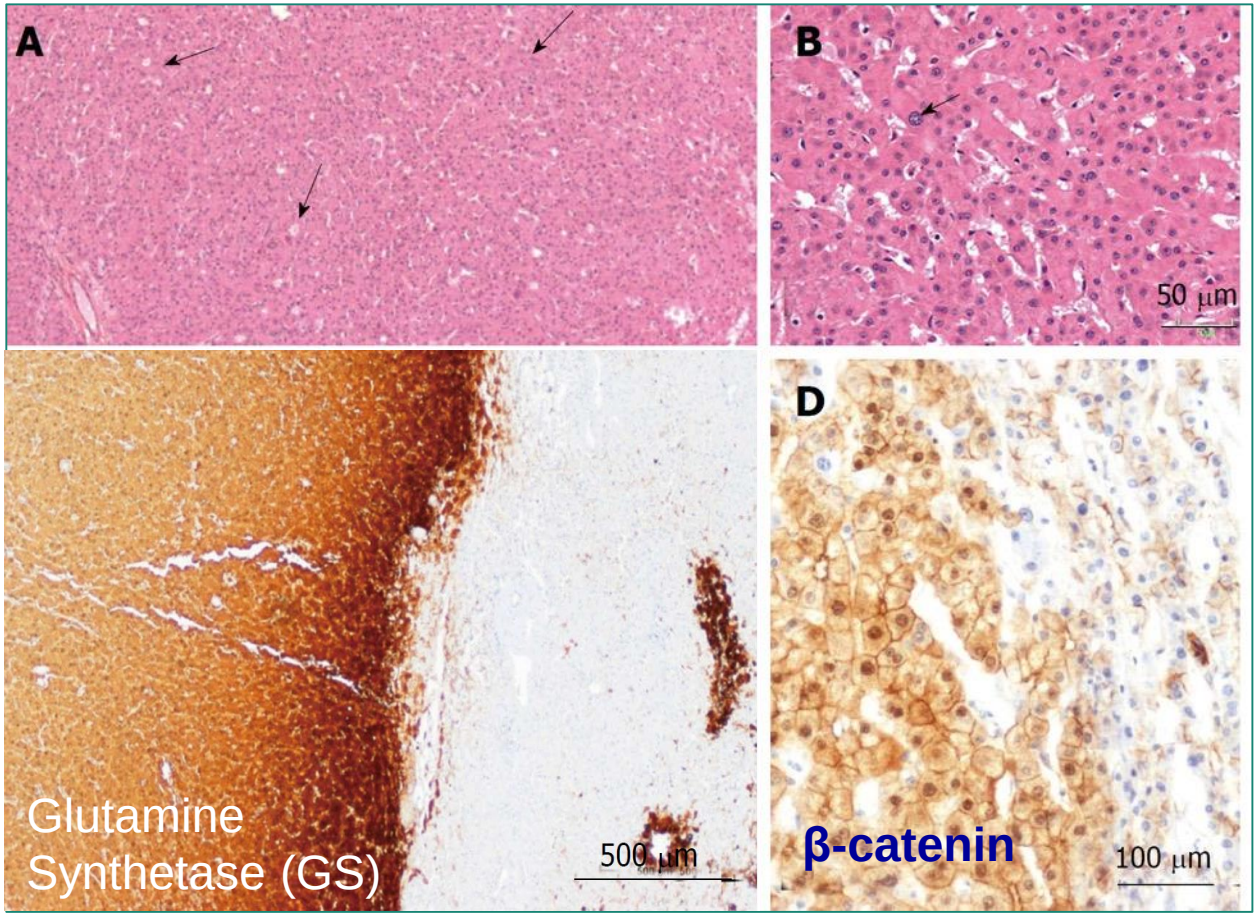




Nault, Gastroenterology 2013

I-HCA: Mutations in genes of the IL6/JAK/STAT signalling pathway (82%)

β-catenin mutated HCA (b-HCA)



Bioulac-Sage, Hepatology 2007

- mainly men
- drugs/steroids
- cellular atypia
- pseudoglands

Molecular subtyping (sequencing)

Exon 3 mutation: ↑ GS, nuclear β-catenin
↑ transformation risk

Exon 7/8 mutation: ~ GS, membranous β-cat
↓ transformation risk

Gastroenterology 2017;152:880–894

BASIC AND TRANSLATIONAL—LIVER

Molecular Classification of Hepatocellular Adenoma Associates With Risk Factors, Bleeding, and Malignant Transformation

Jean-Charles Nault, ···· and Jessica Zucman-Rossi

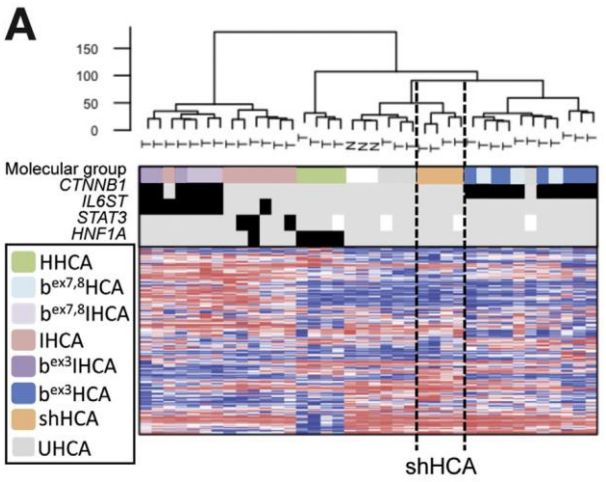
28 centres mainly in France, 2000-2014

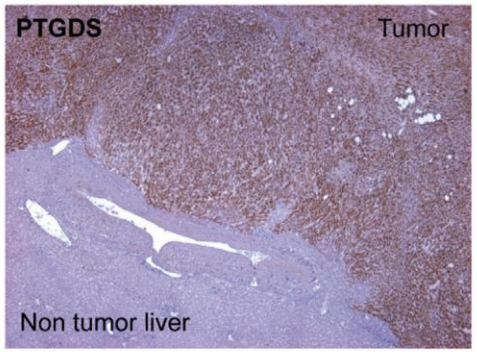
533 HCAs from 411 patients

- histology
- immunohistochemistry
- gene expression profile
- RNA sequencing
- whole exome and genome sequencing

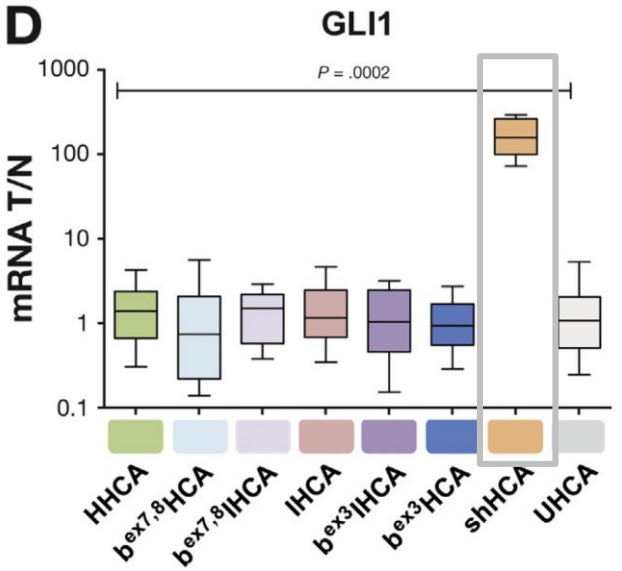
New subtype of HCA: Sonic Hedhehog HCA

Estrogen +++ → Obesity → **ShHCA** 4% of HCA → Frequent symptomatic bleeding





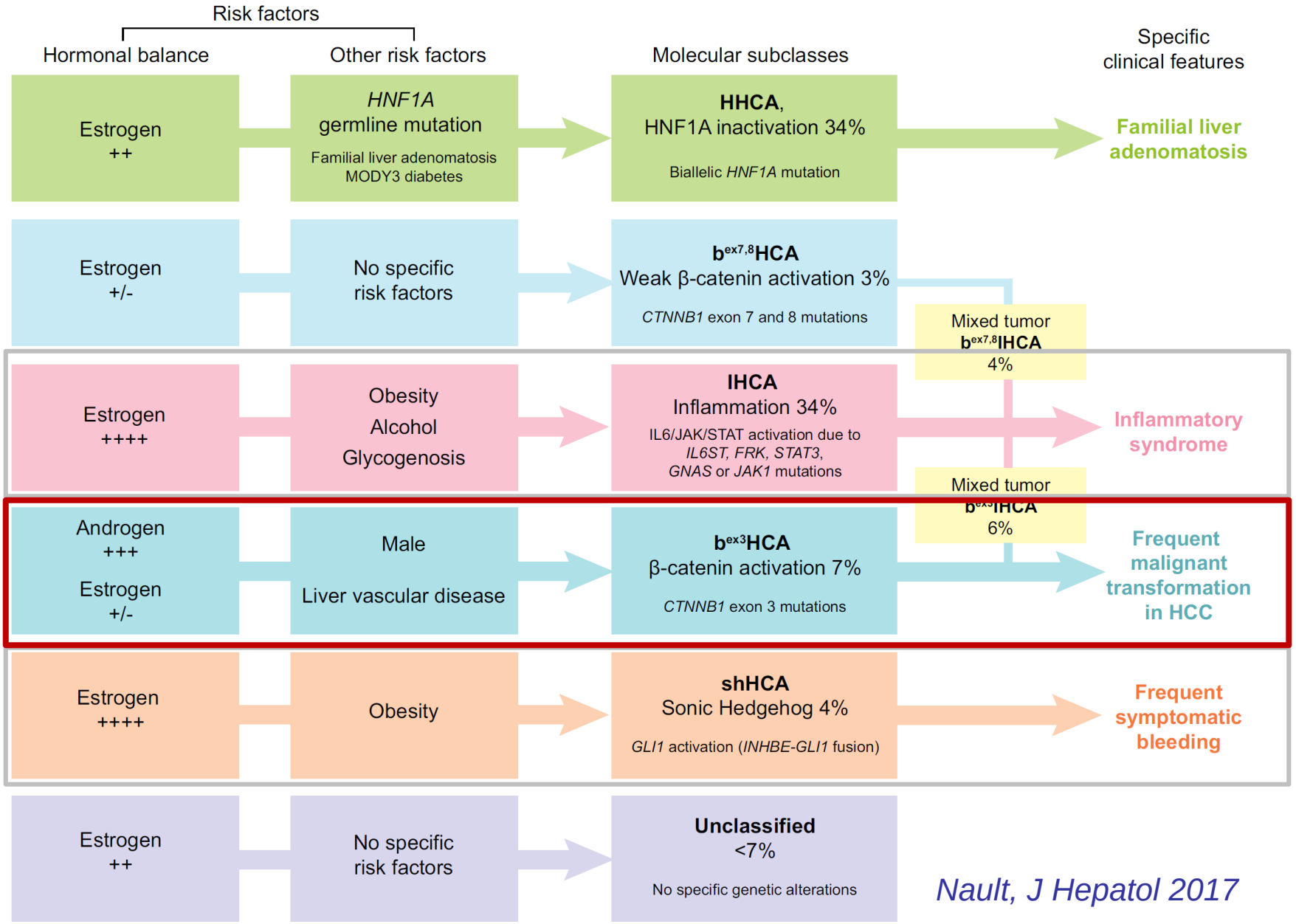
Prostaglandin D synthetase immunostain



HCA molecular subtypes correlate with specific imaging, histological and clinical features

Nault, Gastroenterology 2017

Genotype/phenotype classification of HCA



Nault, J Hepatol 2017

Value of liver biopsy in HCA

- **Diagnosis-Differential diagnosis** (i.e. vs FNH, HUMP, HCC)
- **HCA subtyping**
  - Bleeding risk (Sonic hedgehog HCA)
  - Assessment of malignant transformation (β-catenin exon 3)
  - Follow-up (adenomatosis, mixed types)

To biopsy or not to biopsy a liver nodule suspicious for HCA ?

EASL JOURNAL OF HEPATOLOGY

2016

EASL Clinical Practice Guidelines on the management of benign liver tumours☆

Whether the risk of haemorrhage or malignant transformation attributed to β-catenin activation in HCA is independent of the identified clinical risk factors (sex, size, rate of change) is presently unknown. There is no justification therefore to recommend histopathology or molecular subtyping of HCA as routine clinical practice. As evidence accumulates and methodologies improve with respect to risk and sensitivity, this may change.

Biopsy may be considered within a benign liver tumour

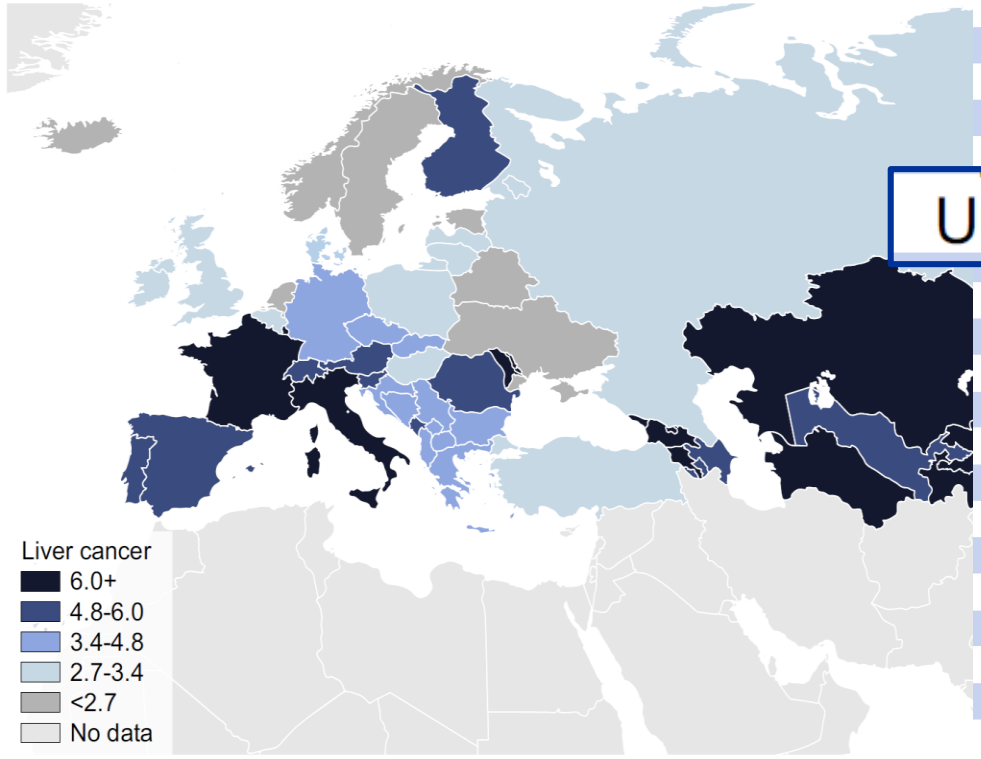
MDT at a reference centre to exclude malignancy

If biopsy, HCA subtyping is necessary

2. Hepatocellular carcinoma - Recent developments

Incidence rates of primary liver cancer according to country in Europe

Total numbers/country and age-adjusted incidence rates/100,000, 2012



Population numbers

Italy	10,733	The Netherlands	475
Germany	9,202	Croatia	466
France (metropolitan)	8,332	Republic of Moldova	448
Russian Federation	6,812	Slovakia	398
United Kingdom	4,186		
Romania	2,214	Denmark	311
Poland	1,998	Ireland	239
Ukraine	1,567	Slovenia	216
Greece	1,054	Norway	190
Portugal	1,004	Lithuania	175
Austria	955	Albania	171
Czech Republic	919	Latvia	154
Switzerland	811	FYR Macedonia	135
Serbia	799	Luxembourg	68
Belgium	645	Estonia	64
Bulgaria	640	Cyprus	56
Hungary	630	Montenegro	51
Finland	620	Malta	19
Sweden	490	Iceland	10

HCC: 5th most common cancer and 2nd leading cause of cancer death

EASL HCC Guidelines, J Hepatol 2018
Forner et al, Lancet 2018

2. Hepatocellular carcinoma -

New clinical guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY 2018

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

Journal of Hepatology **2018** vol. 69 | 182–236

Diagnosis

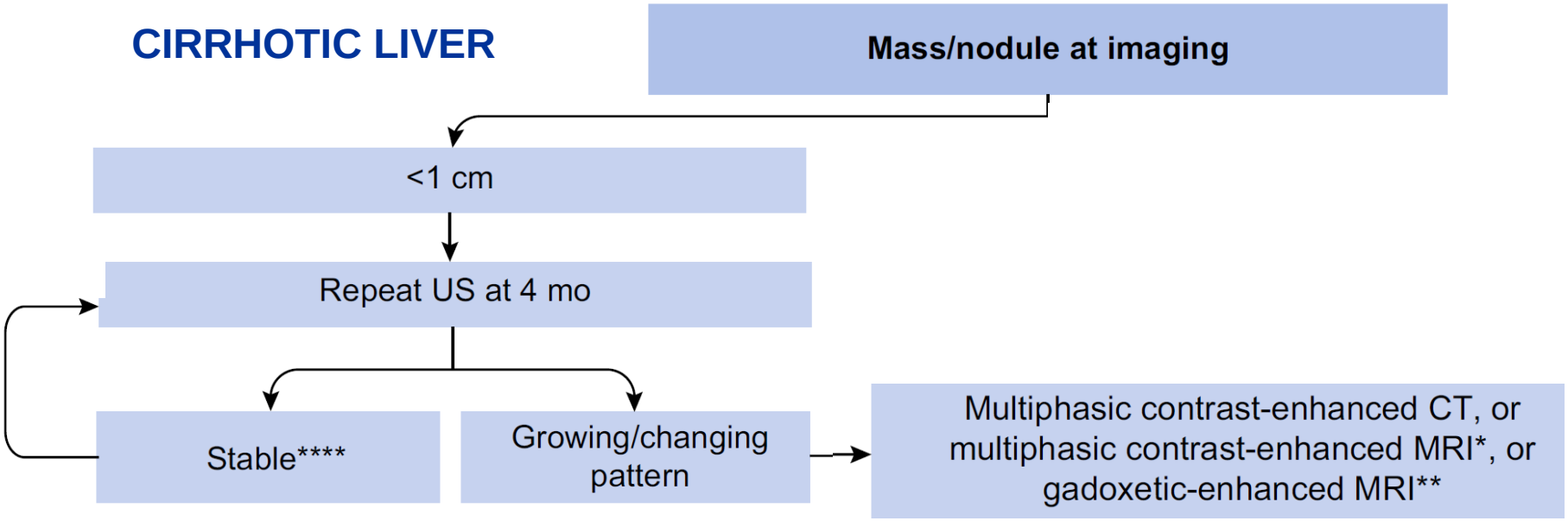
Recommendations

- Diagnosis of HCC in cirrhotic patients should be based on non-invasive criteria and/or pathology (**evidence high; recommendation strong**).
- In non-cirrhotic patients, diagnosis of HCC should be confirmed by pathology (**evidence moderate; recommendation strong**).
- Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistological analyses (**evidence high; recommendation strong**).

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

Journal of Hepatology **2018** vol. 69 | 182–236



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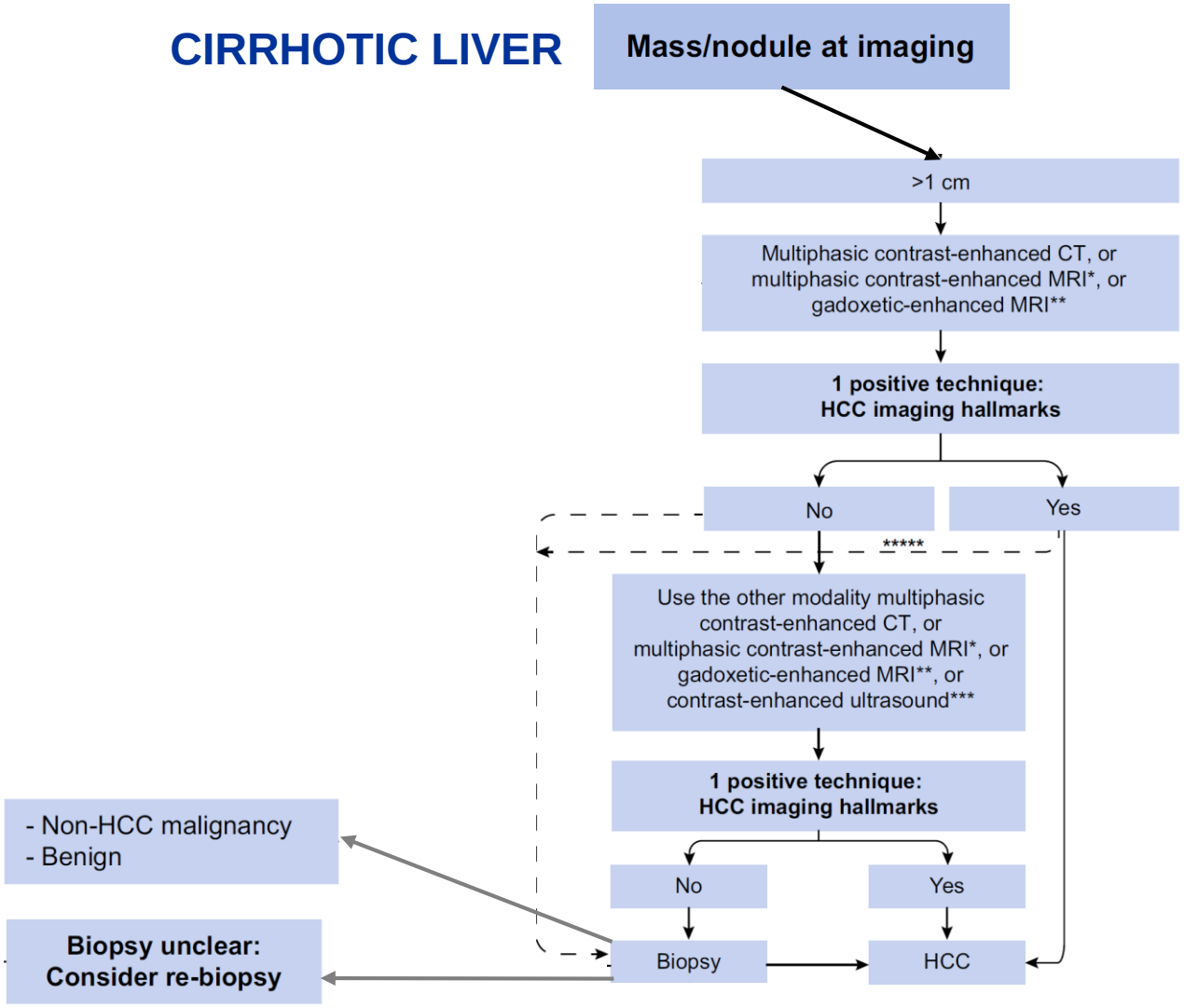
EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

Journal of Hepatology **2018** vol. 69 | 182–236

CIRRHOTIC LIVER



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv238–iv255, 2018

Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

A. Vogel[1], A. Cervantes[2], I. Chau[3], B. Daniele[4], J. Llovet[5,6,7], T. Meyer[8,9], J.-C. Nault[10], U. Neumann[11], J. Ricke[12], B. Sangro[13], P. Schirmacher[14], C. Verslype[15], C. J. Zech[16], D. Arnold[17] & E. Martinelli[18], on behalf of the ESMO Guidelines Committee*

Tumour biopsy

Useful for nodules with non-diagnostic at imaging

Required to diagnose HCC in non-cirrhotic liver

Should be carried out according to national or institutional policy in all clinical trials and may support centre-based innovative treatment approaches

Ideally, should evaluate tumour and non-tumour tissue when used for scientific purposes

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv238–iv255, **2018**

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It is now well accepted that the potential risks of tumour biopsy, bleeding and needle track seeding, are infrequent, manageable and do not affect the course of the disease or overall survival (OS) and, therefore, should not be seen as a reason to abstain from diagnostic liver biopsy.

BRITISH SOCIETY OF GASTROENTEROLOGY

BSG guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults

Gut 2003;52(Suppl III):iii1–iii8

BRITISH SOCIETY OF GASTROENTEROLOGY

Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

A. Vogel, et al. Annals of Oncology 29 (Supplement 4): iv238–iv255, 2018

BSG Guidelines

HCC

Current clinical practice in UK:

- ESMO and/or EASL Guidelines
- Histological diagnosis of HCC necessary for patients who are eligible for treatment with sorafenib

NICE National Institute for Health and Care Excellence

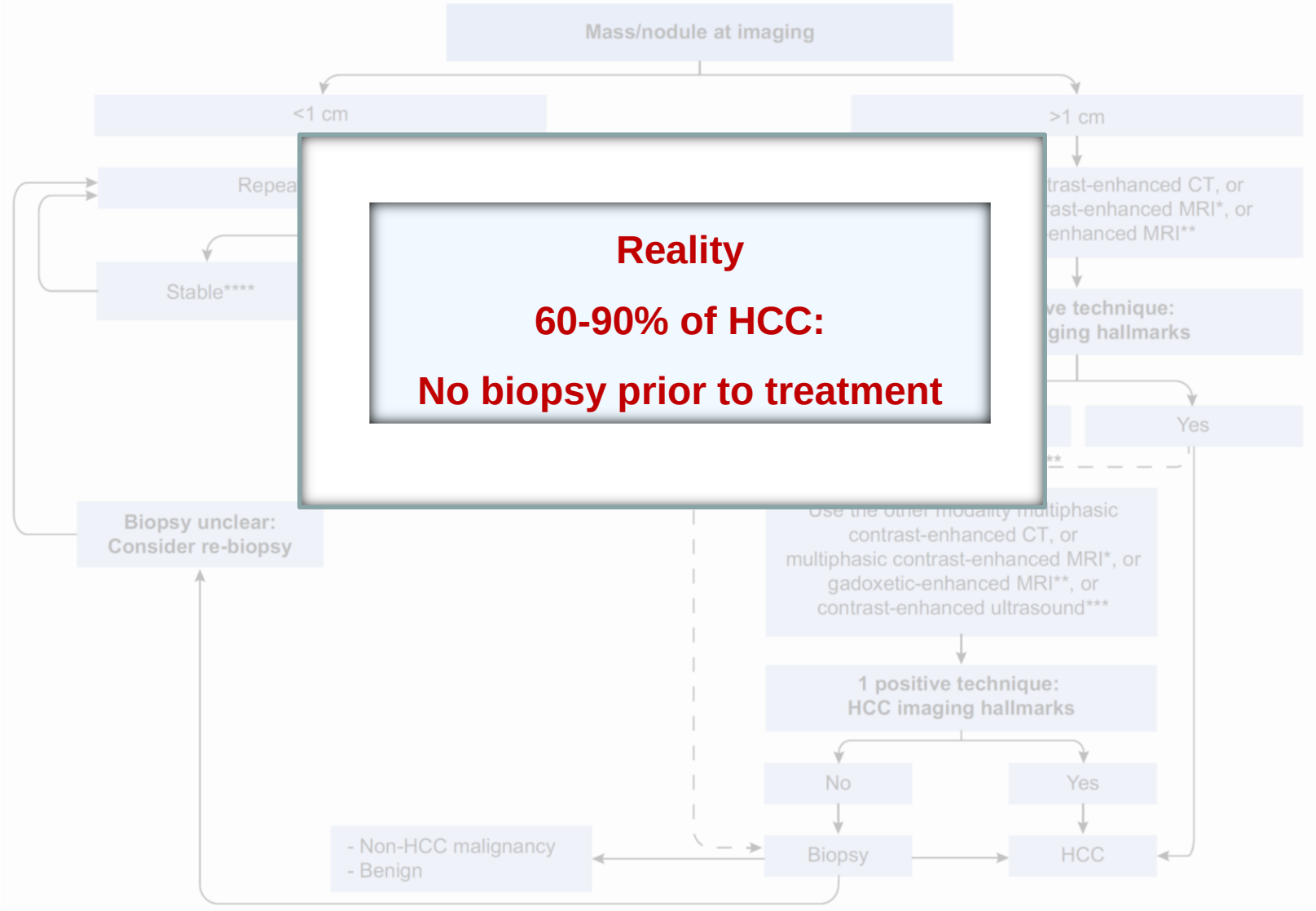
Sorafenib for treating advanced hepatocellular carcinoma

Technology appraisal guidance [TA474] Published date: 06 September 2017

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

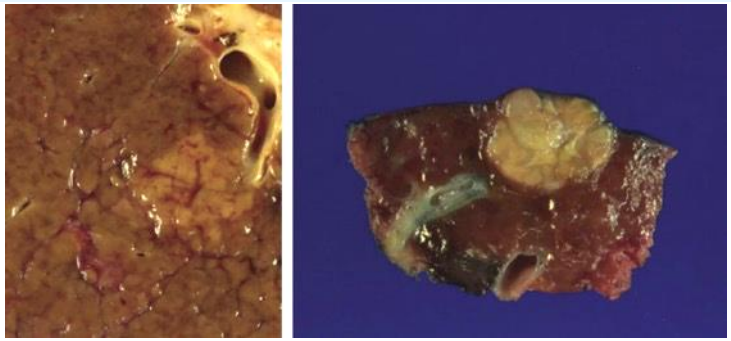


Reality

60-90% of HCC:

No biopsy prior to treatment

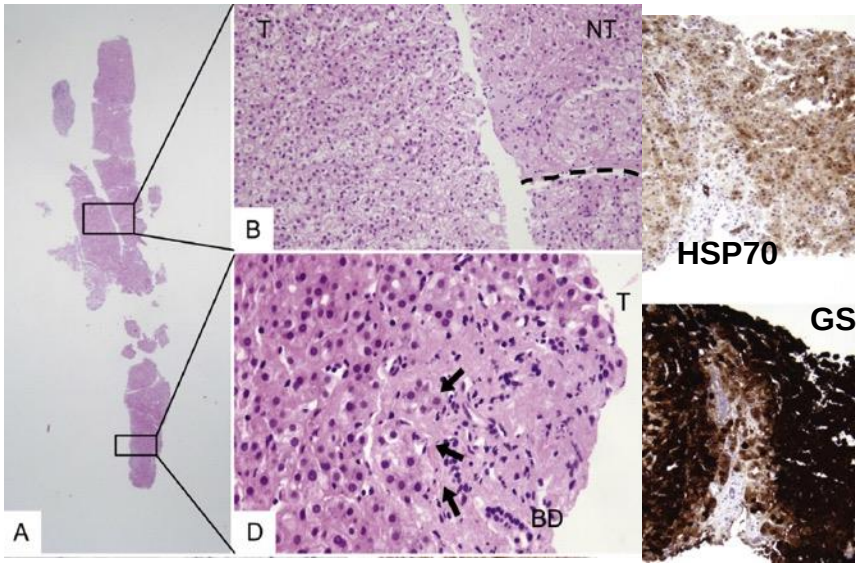
Accuracy of liver biopsy for diagnosis of HCC



Kim & Park, Best Pract Res Clin Gastro 2014

Very early HCC in cirrhosis

- Additional value of immunohistochemistry
- Glypican 3, heat shock protein 70, glutamine synthetase



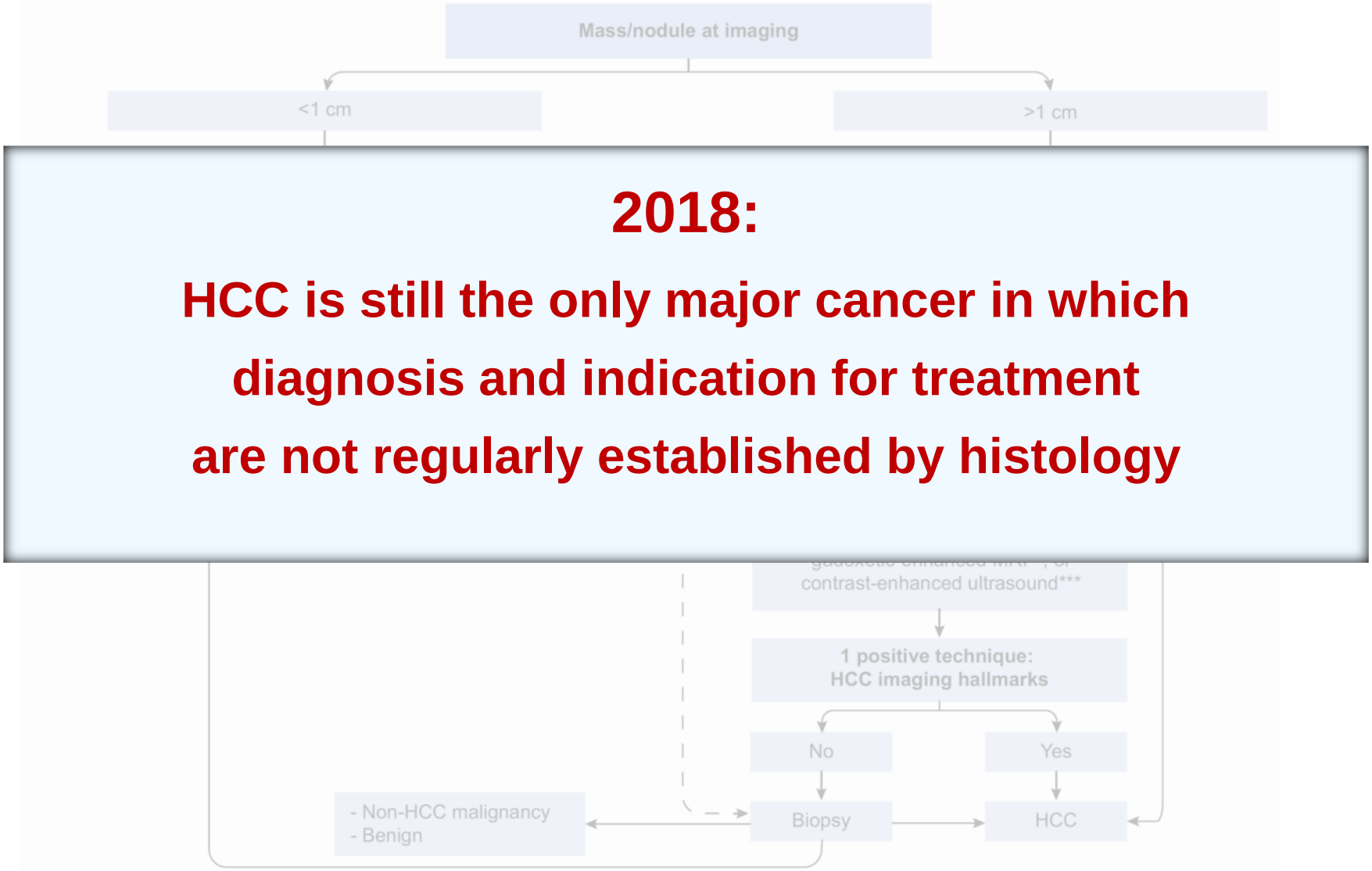
≥ 2 positive markers	
Sensitivity	60-72%
Specificity	100%

Di Tommaso, J Hepatol 2009
Tremosini, Hepatology 2014

Pre-operative liver biopsy in cirrhotic patients with early hepatocellular carcinoma represents a safe and accurate diagnostic tool for tumour grading assessment

Colecchia Journal of Hepatology **2011** vol. 54 | 300–305

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY



2018:

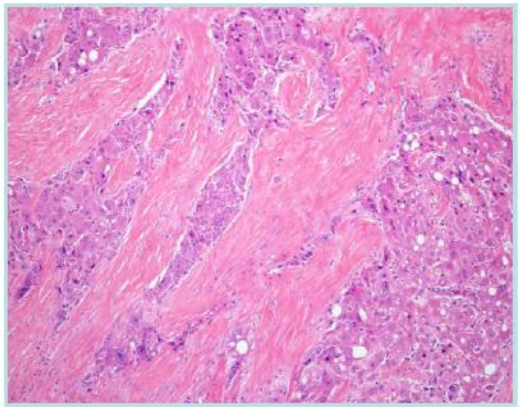
HCC is still the only major cancer in which diagnosis and indication for treatment are not regularly established by histology

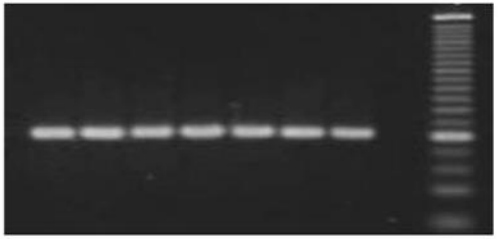
2. Hepatocellular carcinoma -

Molecular signatures

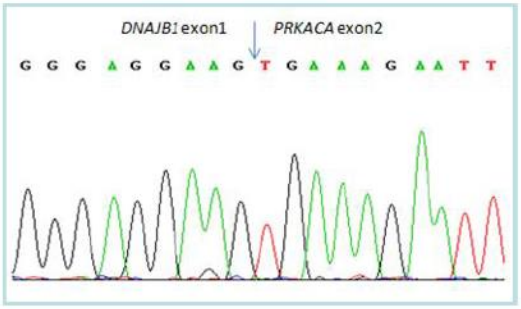
for HCC subtypes

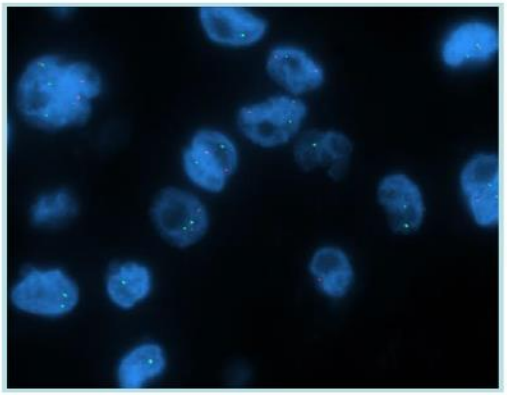
Histological subtyping of HCC





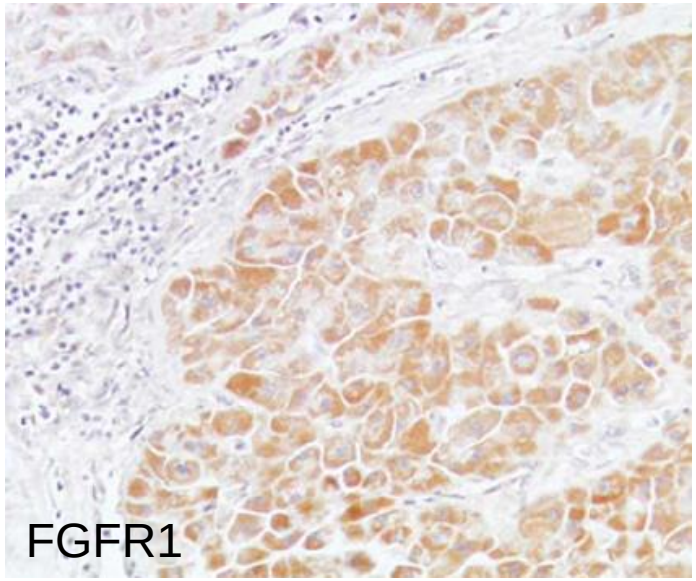
PGK (126 bp)





Fibrolamellar HCC

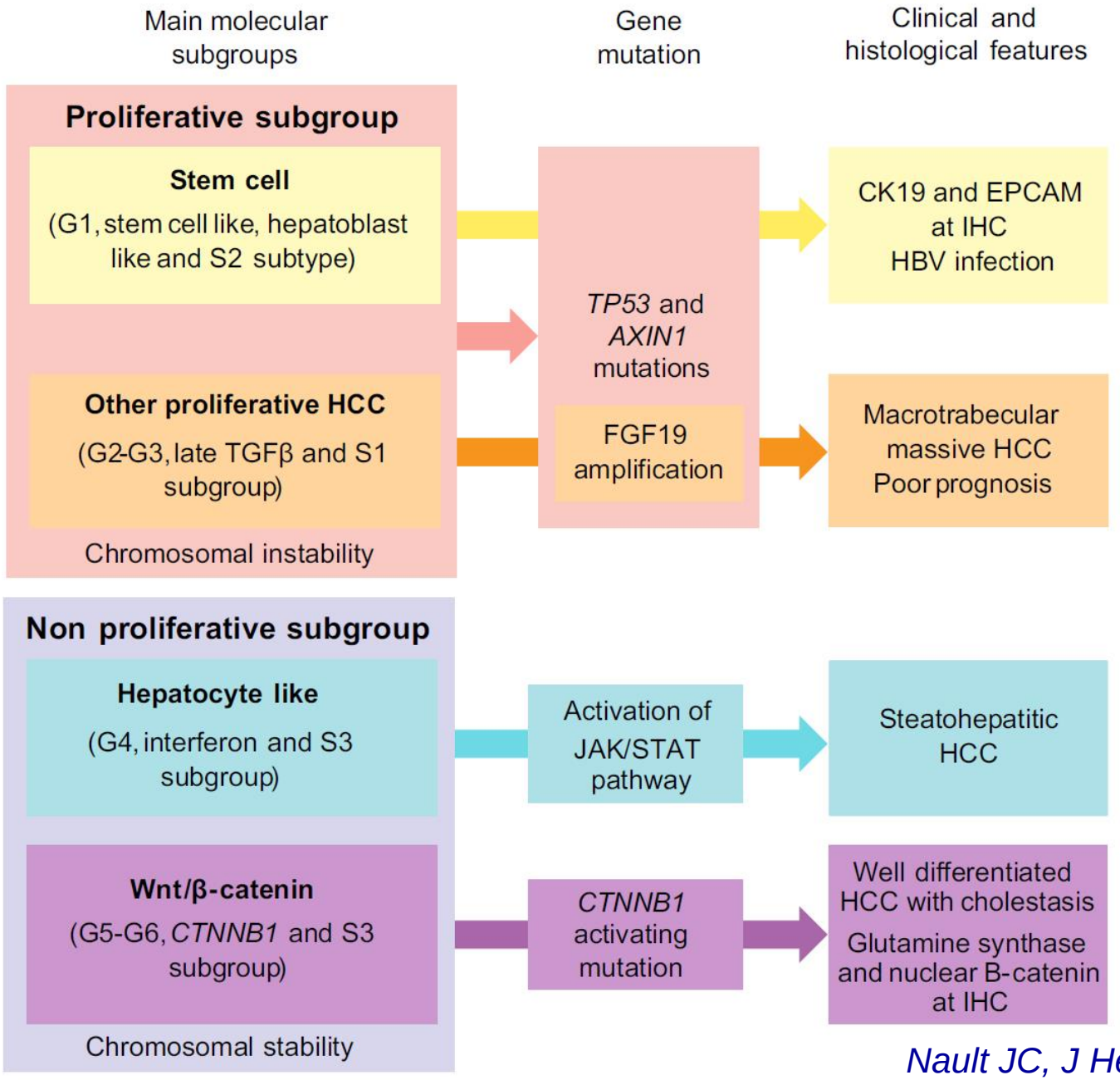
- Unique fusion transcript DNAJB1/PRKACA
- Interaction with FGF pathways
- Overexpression of FGFR1



- **Personalised treatment with FGFR inhibitors ?**

Honeyman, Science 2014
Riehle, Mod Pathol 2015
Graham, Mod Pathol 2015

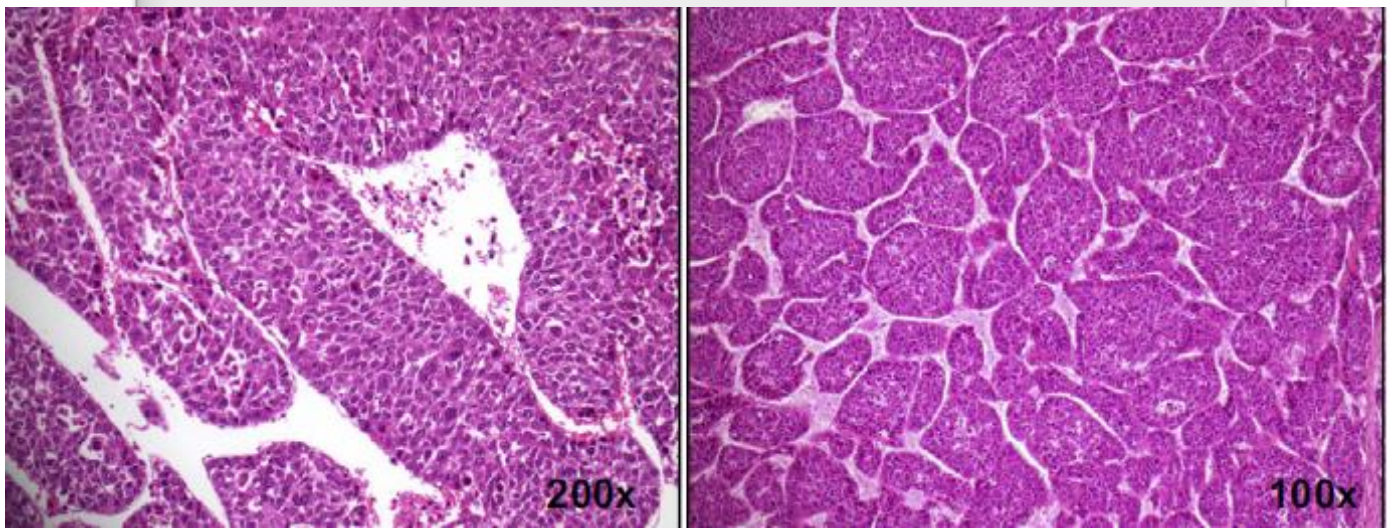
Molecular classification of hepatocellular carcinoma



Nault JC, J Hepatol 2018

Novel histological/molecular HCC subtypes

Macrotrabecular Massive HCC



- 5-10% HCC
- Younger patients
- ↑ serum AFP
- Poor prognosis
- 100% vascular invasion

Molecular features

- p53 mutations
- FGF19 amplification
- Activation of angiogenic factors (Ang2, VEGFA)

Calderaro, J Hepatol 2017

HEPATOLOGY, VOL. 68, NO. 1, **2018**

Macrotrabecular-Massive Hepatocellular Carcinoma: A Distinctive Histological Subtype With Clinical Relevance

Marianne Ziol,[1-3] Nicolas Poté,[4] Giuliana Amaddeo,[5,6] Alexis Laurent,[5,7] Jean-Charles Nault,[2,3,8] Frédéric Oberti,[9] Charlotte Costentin,[6] Sophie Michalak,[10] Mohamed Bouattour,[11] Claire Francoz,[11] Georges Philippe Pageaux,[12] Jeanne Ramos,[13] Thomas Decaens,[14] Alain Luciani,[5,15] Boris Guiu,[16] Valérie Vilgrain,[17] Christophe Aubé,[18] Jonathan Derman,[19] Cécile Charpy,[19] Jessica Zucman-Rossi,[2] Nathalie Barget,[20] Olivier Seror,[21] Nathalie Ganne-Carrié,[3,8] Valérie Paradis,[4] and Julien Calderaro[5,19]

Retrospective study of HCC

237 HCC surgical samples

284 HCC liver biopsies ftom pts treated with resection and RFA

Male 81% HCV (32%), HBV (25%), Alcoholic (23%) & other aetiology

Macrotrabecular architecture in >50% tumour

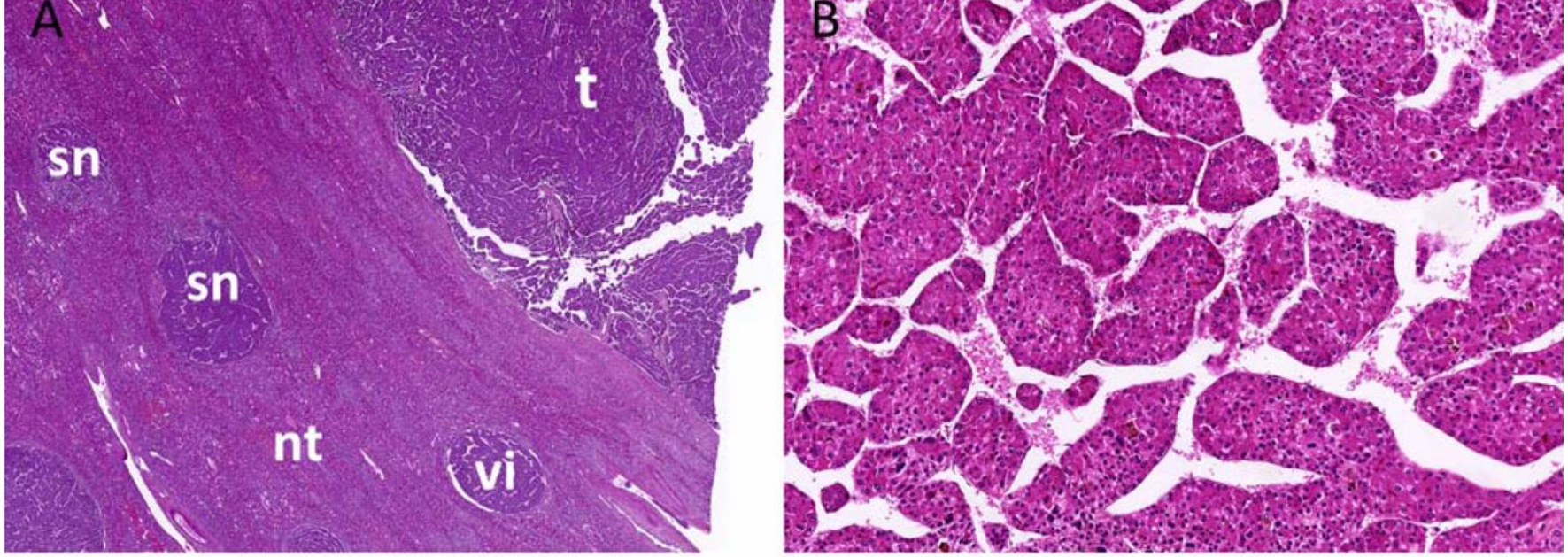
6-cell thick trabeculae

Overall Frequency
12%

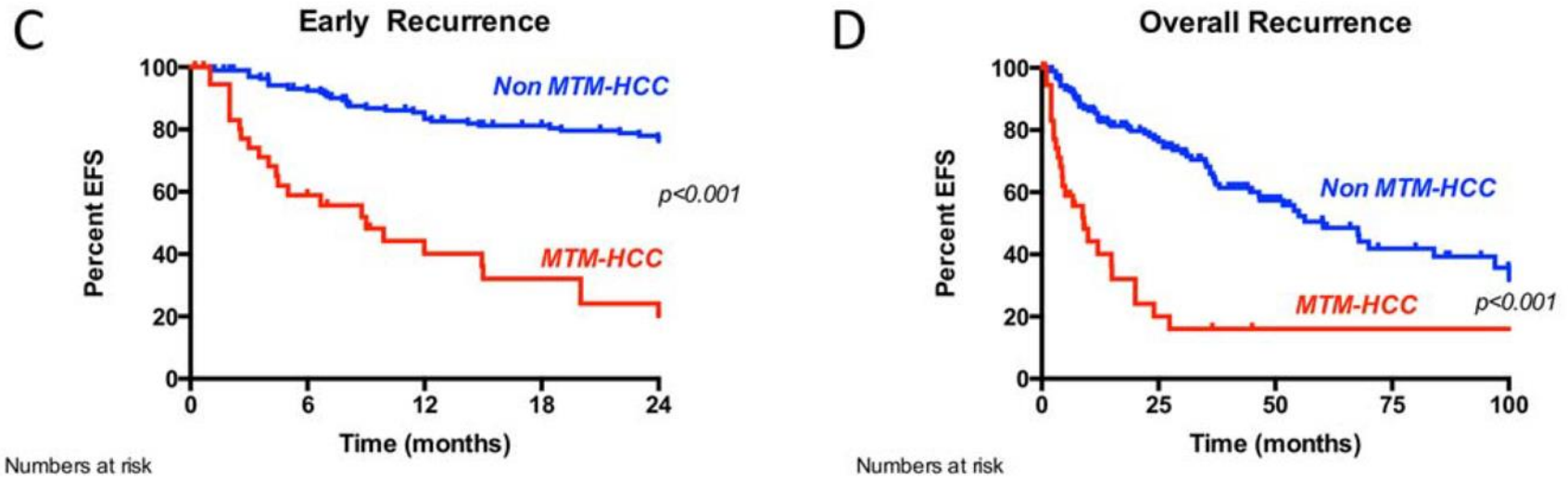
Large size >5 cm

Macrotrabecular architecture correlations:

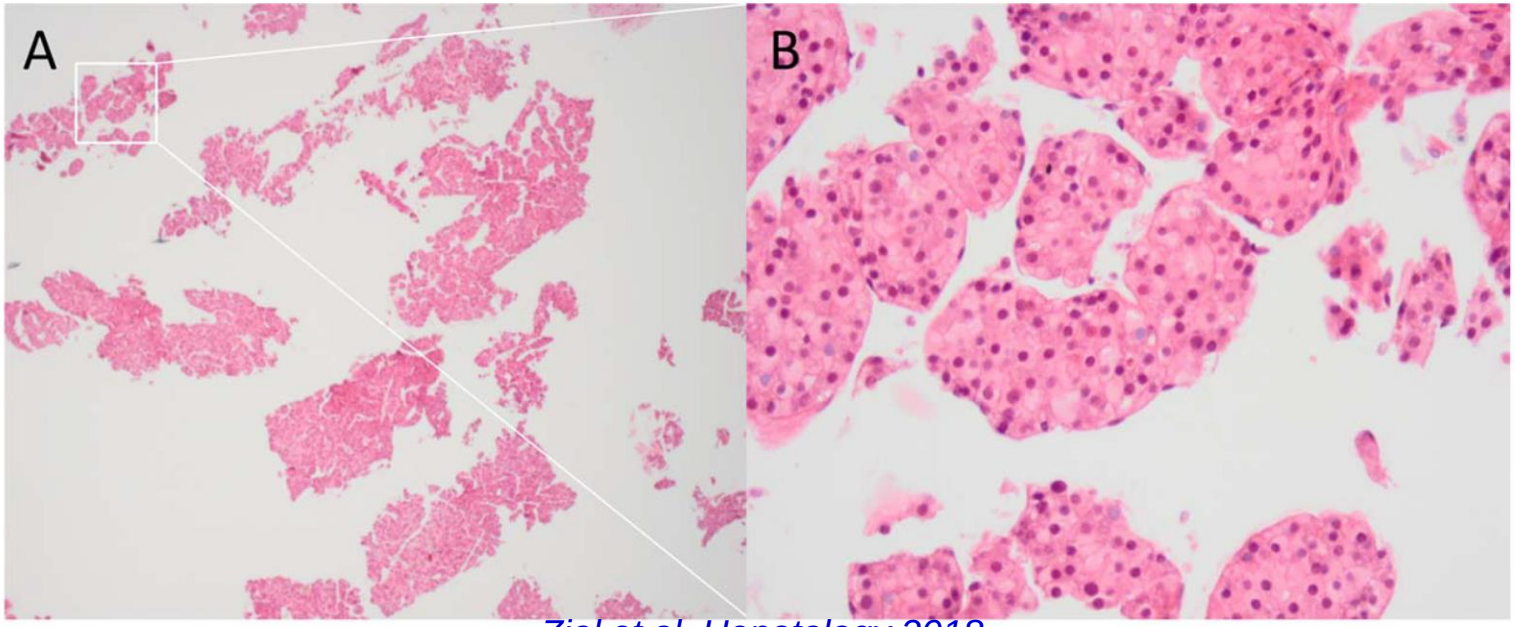
HBV infection, AFP >100 ng/mL, large size and …..



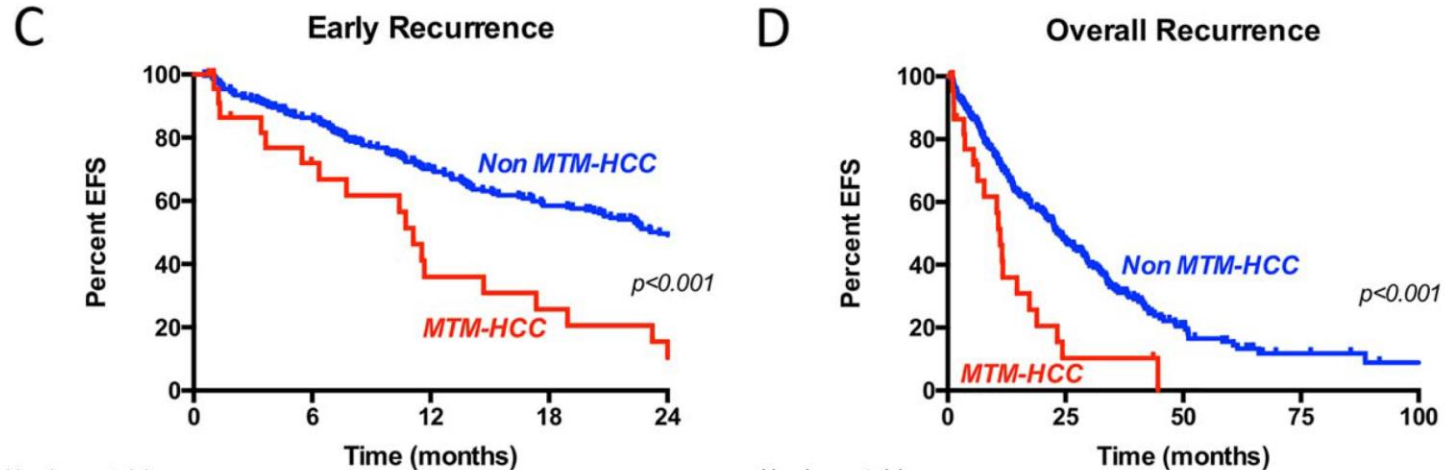
Ziol et al, Hepatology 2018



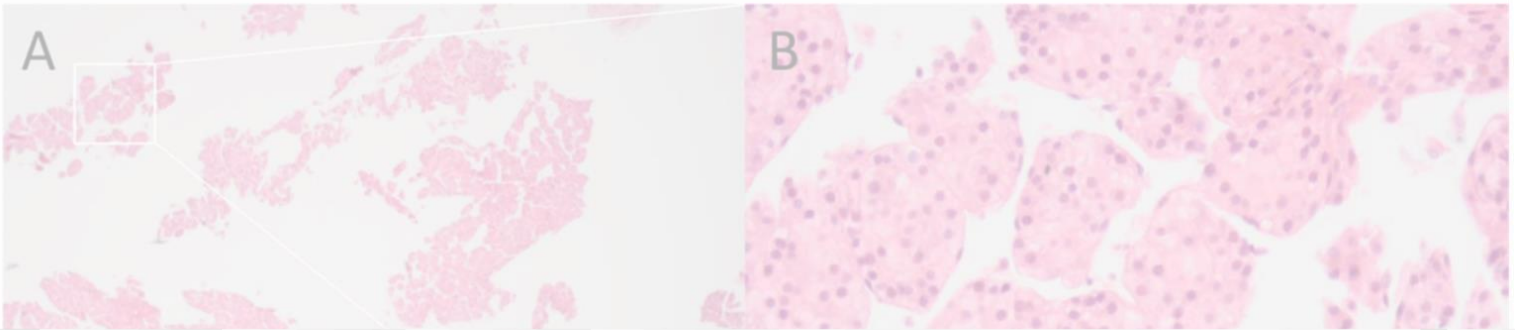
Macrotrabecular massive HCC subtype correlates with early and overall HCC recurrence even in subgroups according to traditional features of tumour aggressiveness



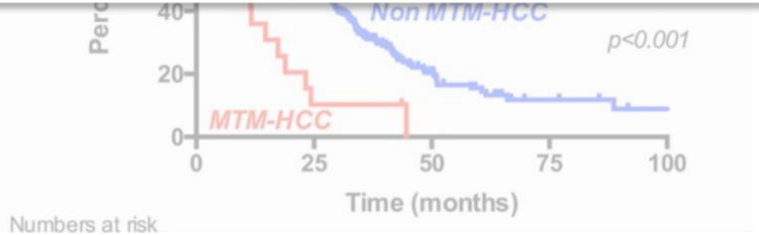
Ziol et al, Hepatology 2018



Macrotrabecular massive HCC subtype correlates with early and overall HCC recurrence in biopsy samples of tumours treated with RFA

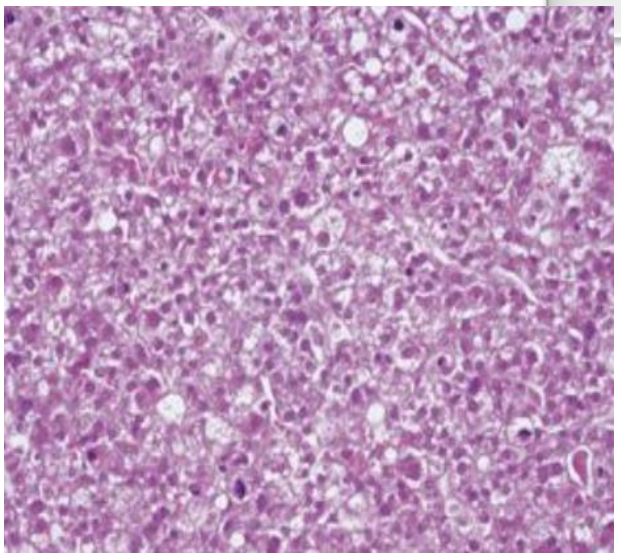


- Identification of the MacroTrabecular Massive (MTM) HCC subtype during pre-treatment workup has strong prognostic implications
- Patients with this MTM-HCC subtype may benefit from adjuvant therapies and/or upfront registration on liver transplant waiting lists after resection or RFA
- Strong argument **pro-liver biopsy in the diagnosis of HCC**

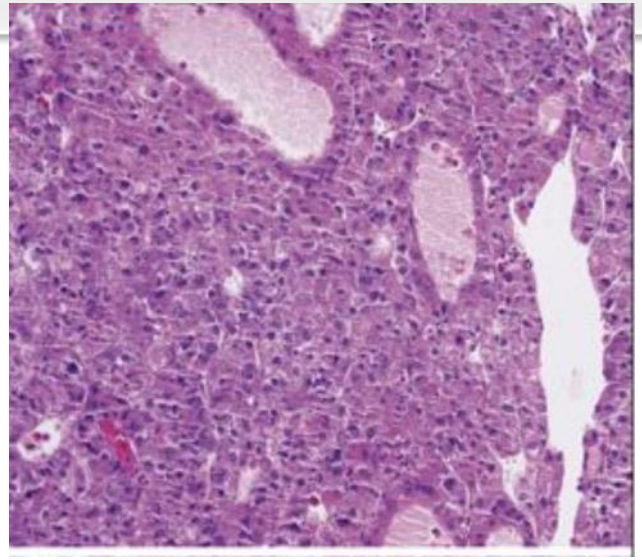


Novel histological/molecular HCC subtypes

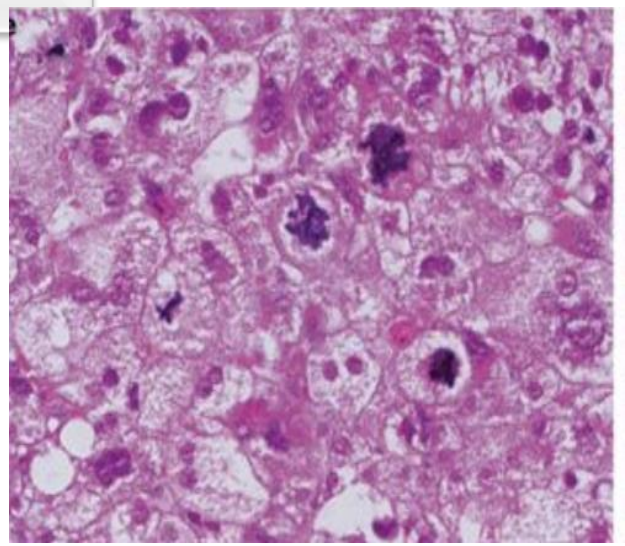
Chromophobe HCC



Chromophobic cytoplasm

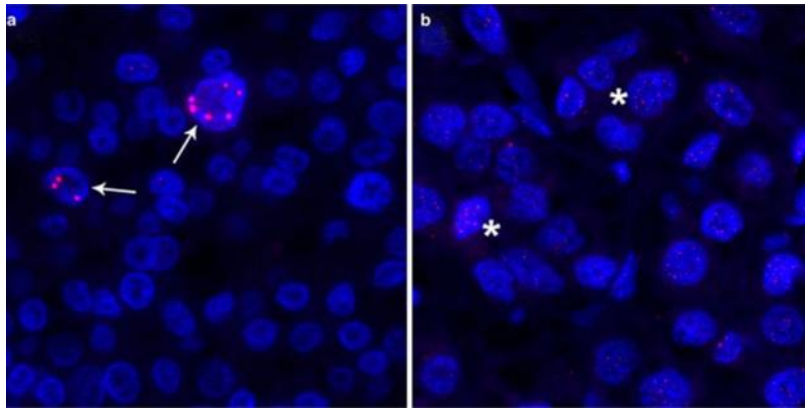


Abrupt focal nuclear anaplasia



Microscopic pseudocysts

- 5% HCC
- HBV-related (50%)
- Alternative lengthening of telomere (ALT) by telomere FISH



Wood, Mod Pathol 2013

Gene expression signatures

Signatures potentially useful for HCC management. The most relevant gene expression signatures with reported HCC risk assessment, diagnostic and prognostic power from tumour and adjacent tissue are listed. HGDN = high grade dysplastic nodules; HBV = hepatitis B virus; HCV = hepatitis C virus; Y = yes; N = no.

Signature	Tissue source where signature was generated	Aetiology of patients	Genomic data	Number of genes	Validation cohort
Signatures for HCC risk assessment					
Poor survival signature [6,21]	Adjacent tissue (FFPE)	HBV, HCV, alcohol	mRNA	186	Y
Signatures for HCC diagnosis					
3 Gene-diagnostic signature [29]	HGDN and HCC	HCV	mRNA	3	Y
13 Genes-diagnostic signature [28]	Normal liver, cirrhotic and HCC	HBV, HCV, alcohol	mRNA	13	N
Signatures for HCC prognosis					
Immune response signature [20]	Adjacent tissue (FF)	HBV	mRNA	17	Y
Poor survival signature [6,21]	Adjacent tissue (FFPE)	HBV, HCV, alcohol	mRNA	186	Y
Metastasis inclined microenvironment signature [40]	Adjacent tissue	HBV	mRNA	153	Y
Multicentric HCC signature [45]	Adjacent tissue	HCV	mRNA	36	N
HCC metastatic signature [41]	HCC	NA	mRNA	153	N
Intrahepatic recurrence signature [42]	HCC	HBV and HCV	mRNA	12	Y
Early recurrence signature [43]	HCC	HBV and HCV	mRNA	172	Y
Tumour recurrence signature [44]	HCC	HBV and HCV	mRNA	20	Y
Vascular invasion signature [46]	HCC	HBV, HCV, alcohol	mRNA	35	Y
Proliferation subclass [48]	HCC	HCV	mRNA	400	N
G3 class [49]	HCC	HBV, HCV, alcohol	mRNA	248	Y
Class A [50]	HCC	HBV and HCV	mRNA	406	Y
Class S1 (WNT/TGF-β) [51]	HCC	HBV, HCV, alcohol	mRNA	237	Y
Hepatoblast signature [54]	HCC	HBV and HCV	mRNA	795	Y
EPCAM signature [55]	HCC	HBV	mRNA	59	Y
Human CK19 signature [56]	HCC	HBV, HCV, alcohol	mRNA	265	Y
5 Gene-prognostic signature [59]	HCC	HBV, HCV, alcohol	mRNA	5	Y
19-miRNA signature [60]	HCC	HBV and HCV	miRNA	19	N
20-miRNA signature [61]	HCC	HBV	miRNA	20	Y
Cholangiocarcinoma-like	HCC, CC, and CHC	HBV	mRNA	251	Y

Quetglas, Best Pract Res Clin Gastroenterol 2014

Integrative HCC-Classification

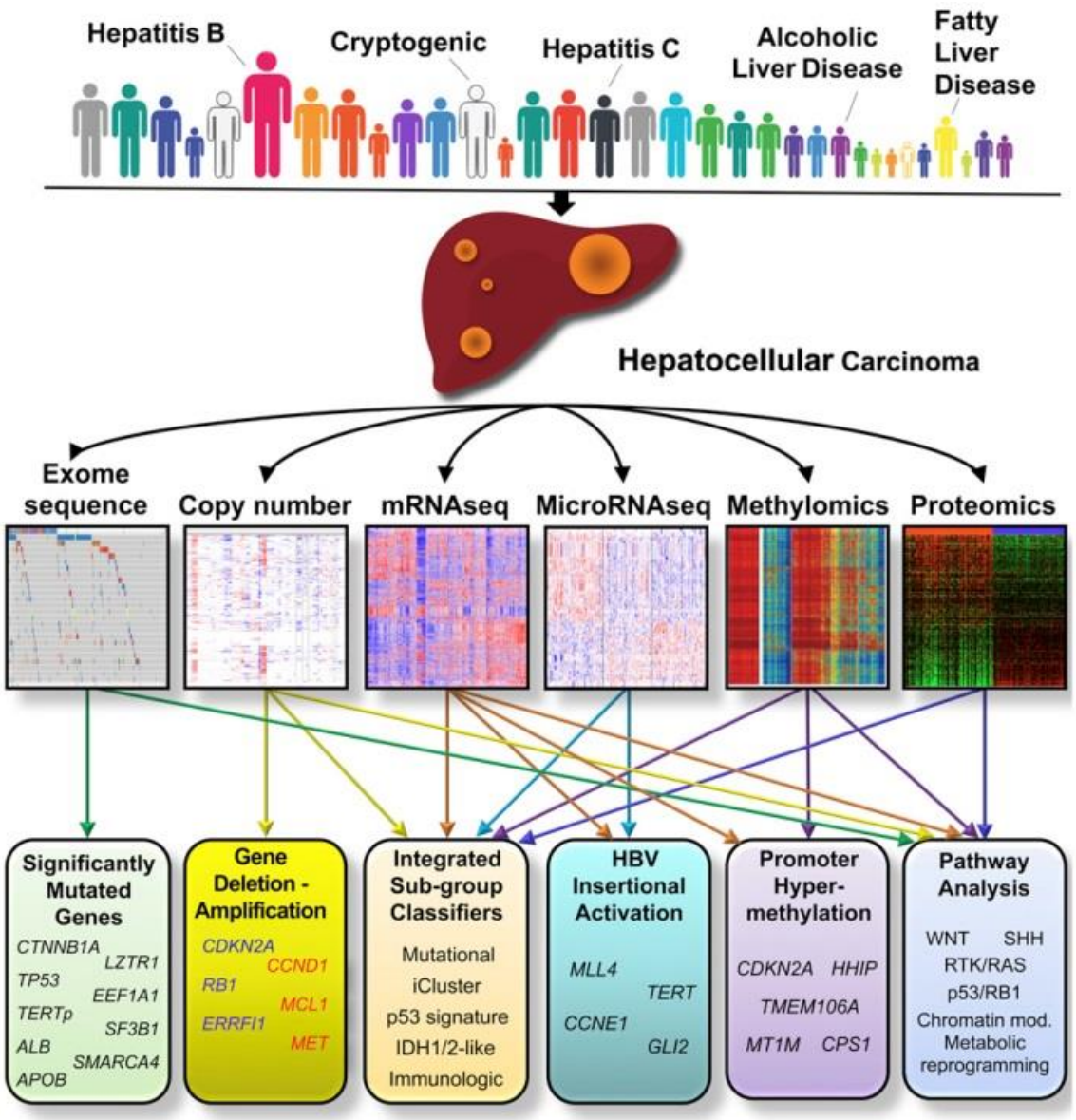
Multiple data platforms
Clinical data

e

Potential therapeutic targets

- WNT signaling
- MDM4, MET, VEGFA,
- MCL1, IDH1, TERT,
- immune checkpoint proteins

  CTLA-4, PD-1, and PD-L1.



The Cancer Genome Atlas Research Network,
Cell 169: 1327-43, 2017

3. Hepatocellular carcinoma - Combined HCC-CC

WHO 2010 Classification of Combined HCC-CC

- **Combined hepatocellular-cholangiocarcinoma, classical type**
  - Has a border between the two types
  - Formerly known as "collision tumor"

- **Combined hepatocellular-cholangiocarcinoma, with stem cell features**
  - ***Typical subtype***: HCC nodules with "stem cell" cancer cells at periphery
  - ***Intermediate subtype***: tumor nodules are comprised of cells that express hepatocyte and biliary markers
  - ***Cholangiolocellular subtype***: tubules, antler-like, in desmoplastic stroma; cells express hepatocyte and biliary markers

Theise, Nakashima, Park, Nakanuma in WHO 2010, p225-227

Brunt EM, Laennec Liver Society Meeting 2018

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

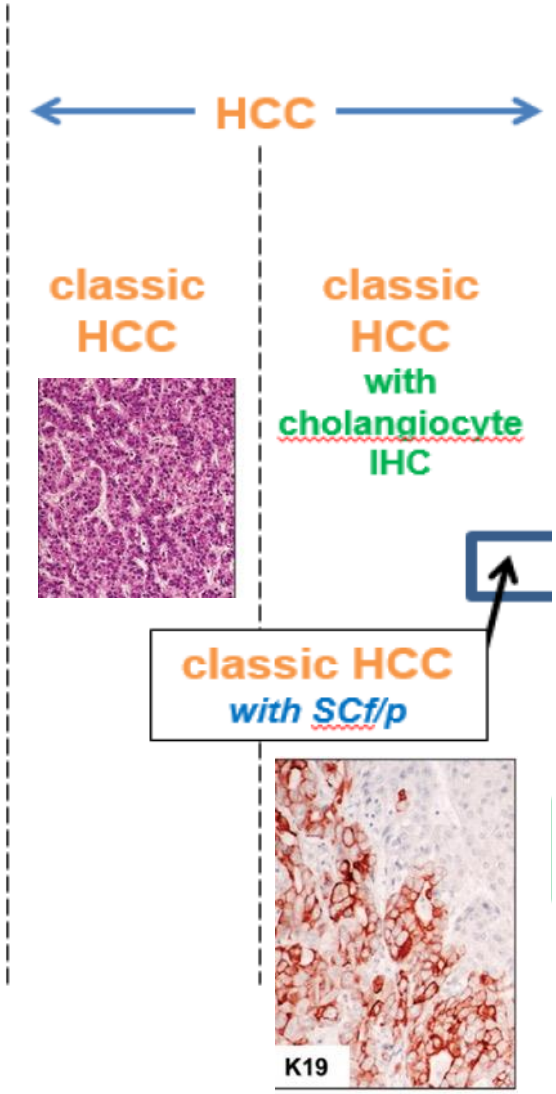
HEPATOLOGY, VOL. 00, NO. 00, 2018

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

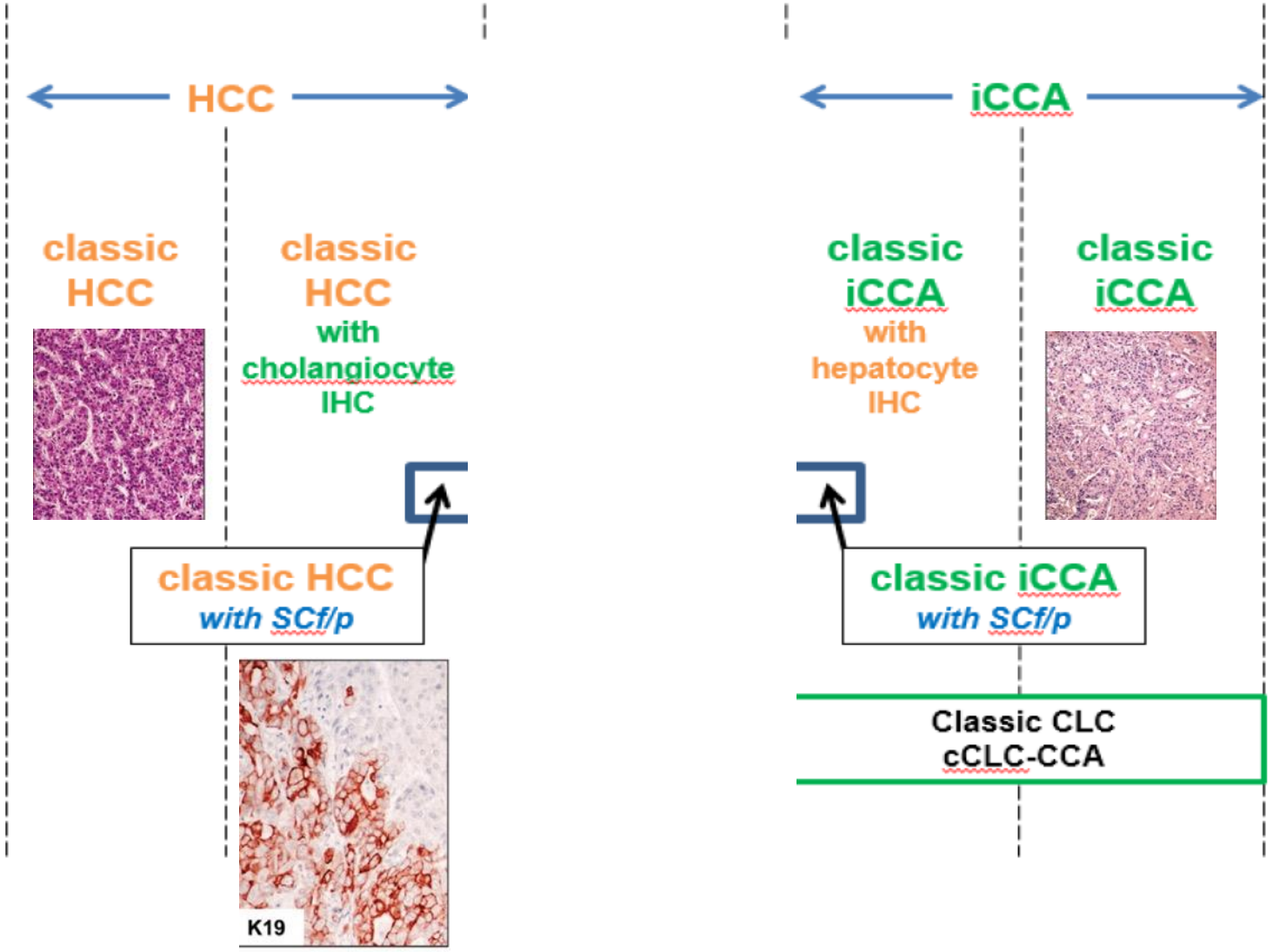
Elizabeth Brunt,[1] Shinichi Aishima,[2] Pierre-Alain Clavien,[3] Kathryn Fowler,[4] Zachary Goodman,[5] Gregory Gores,[6] Annette Gouw,[7] Alex Kagen,[8] David Klimstra,[9] Mina Komuta,[10] Fukuo Kondo,[11] Rebecca Miksad,[12] Masayuki Nakano,[13] Yasuni Nakanuma,[14] Irene Ng,[15] Valerie Paradis,[16]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

International Multidisciplinary Proposal 2018

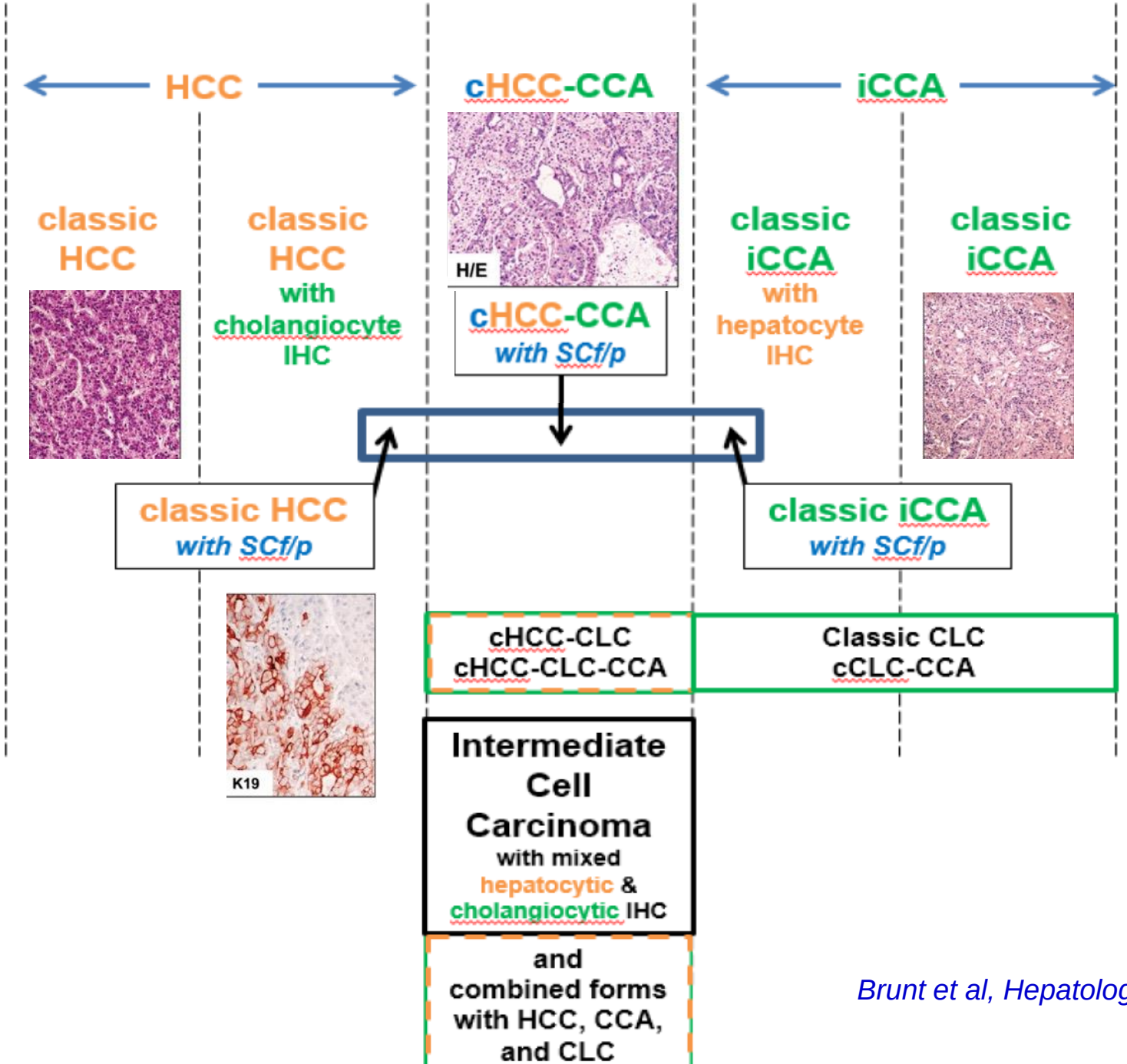
Pathology, Radiology, Hepatology, Molecular Biology



Brunt et al, Hepatology 2018

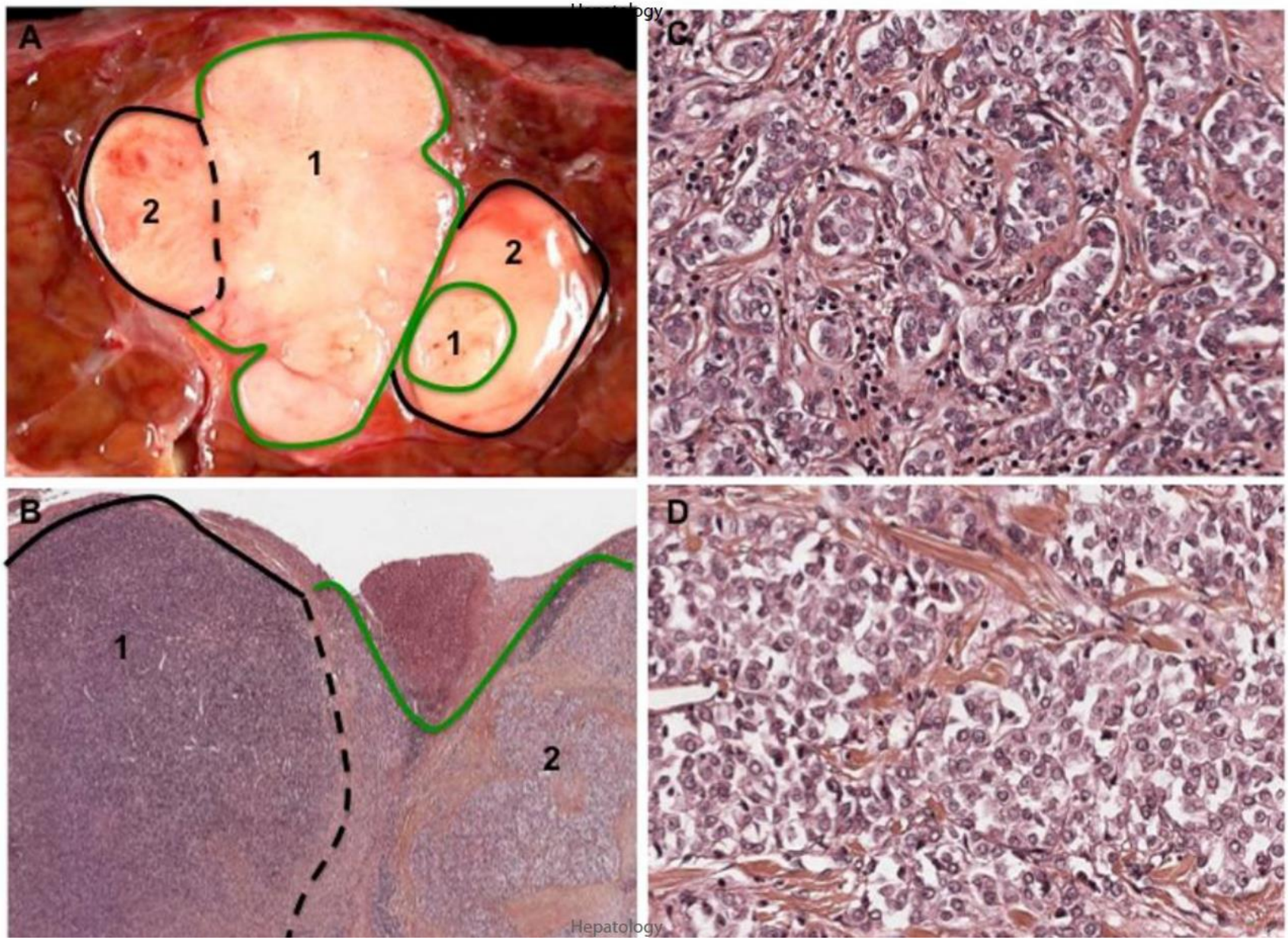


Brunt et al, Hepatology 2018



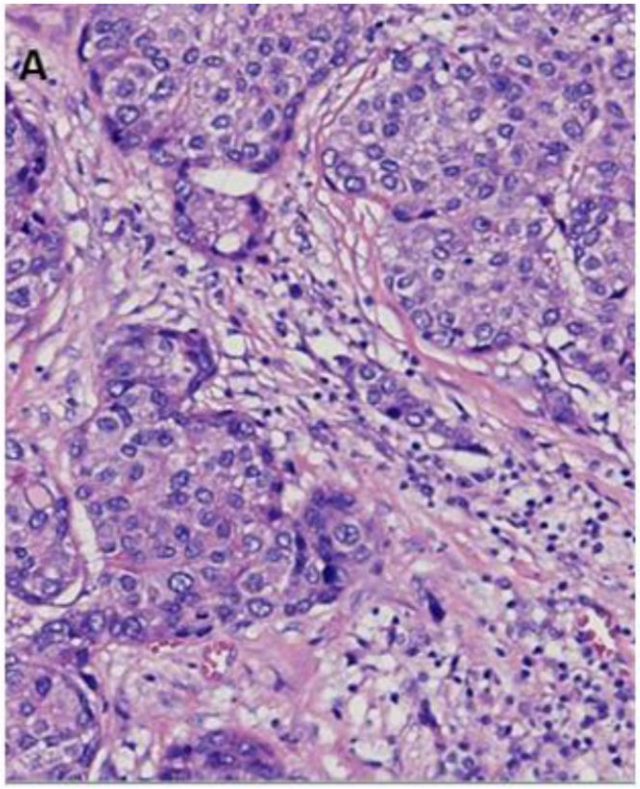
Brunt et al, Hepatology 2018

Combined hepatocellular cholangiocarcinoma - cHCC-CCA

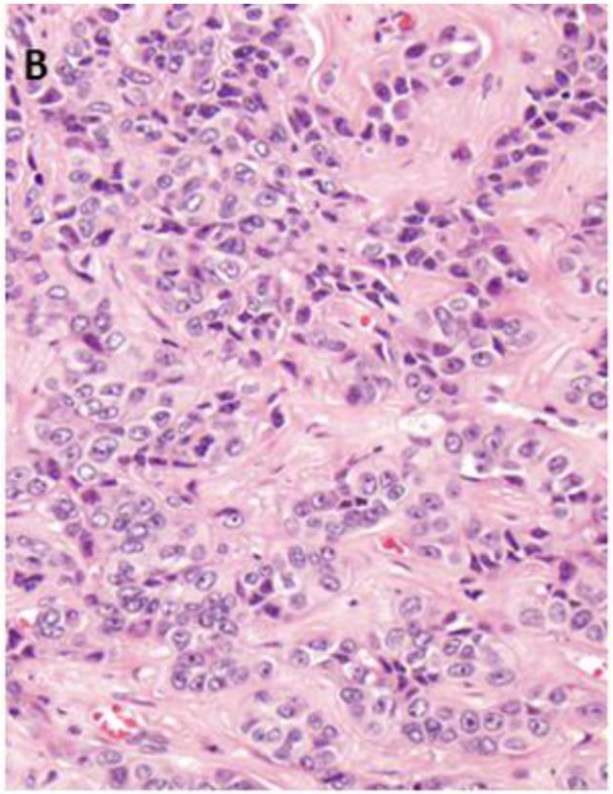


Brunt et al, Hepatology 2018

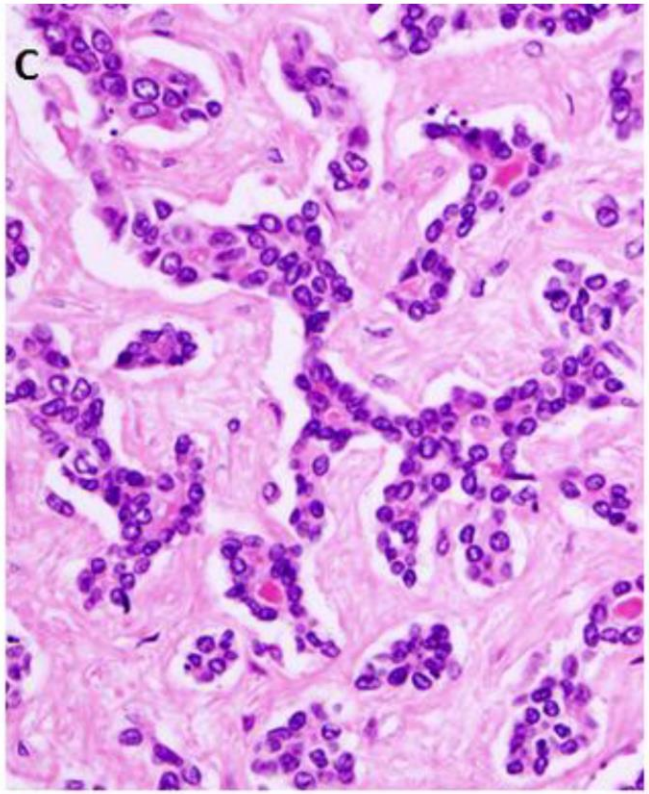
Morphologic variants of “stem/progenitor cell features”



HCC with stem cell/progenitor cell features



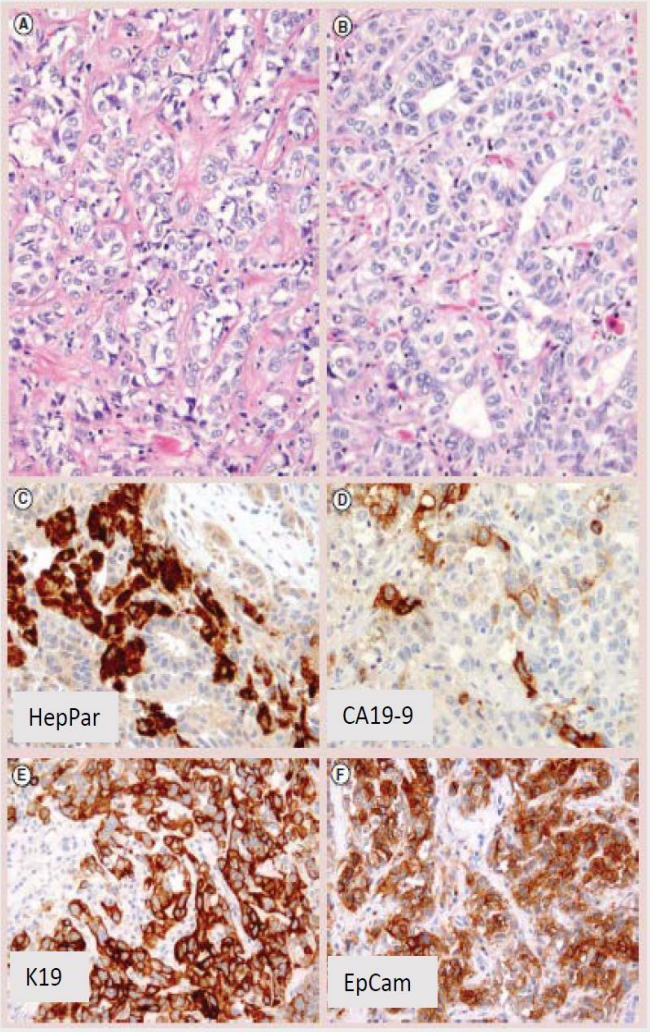
Intermediate cell carcinoma



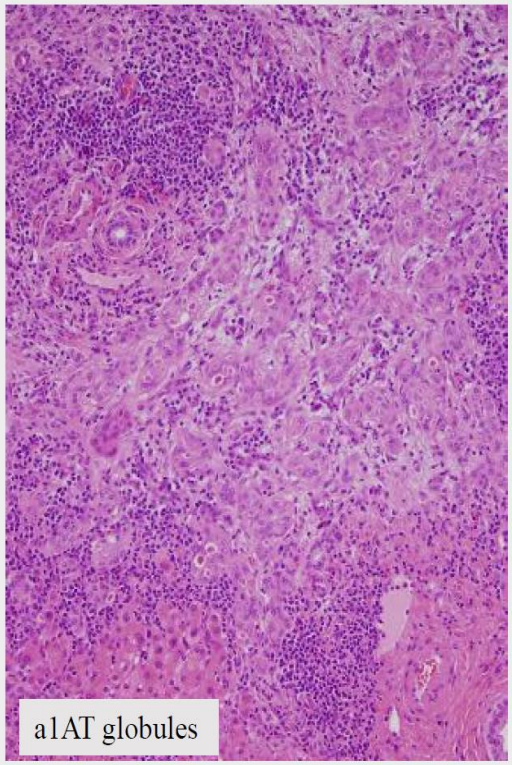
Cholangiolocarcinoma

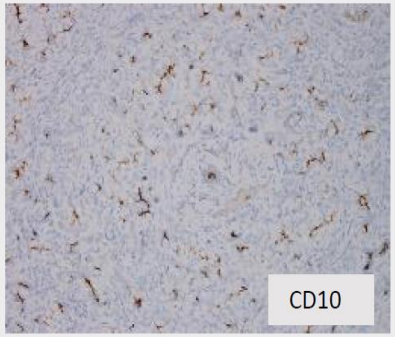
Intermediate Cell Carcinoma

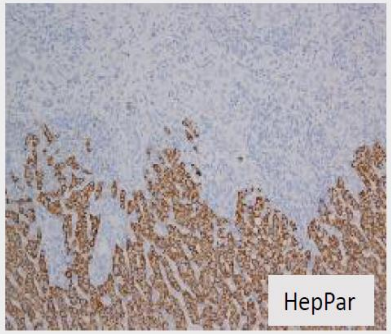
- **Monomorphic tumor** of cells of size intermediate b/w hepatocytes and cholangiocytes; wide histologic diversity between tumors
- Cords, trabeculae, no true glands
- +/- stroma
- Of all the subtypes, **this is the one most often confused for iCCA**

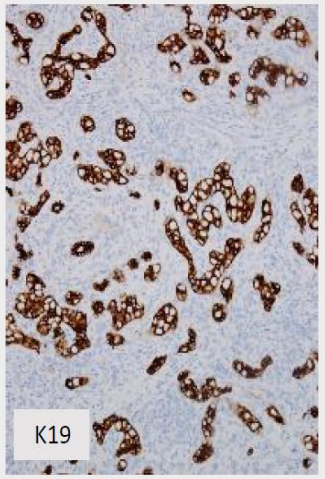


Brunt, Paradis, Sempoux, Theise, Hepatic Oncol 2015;2:255-273







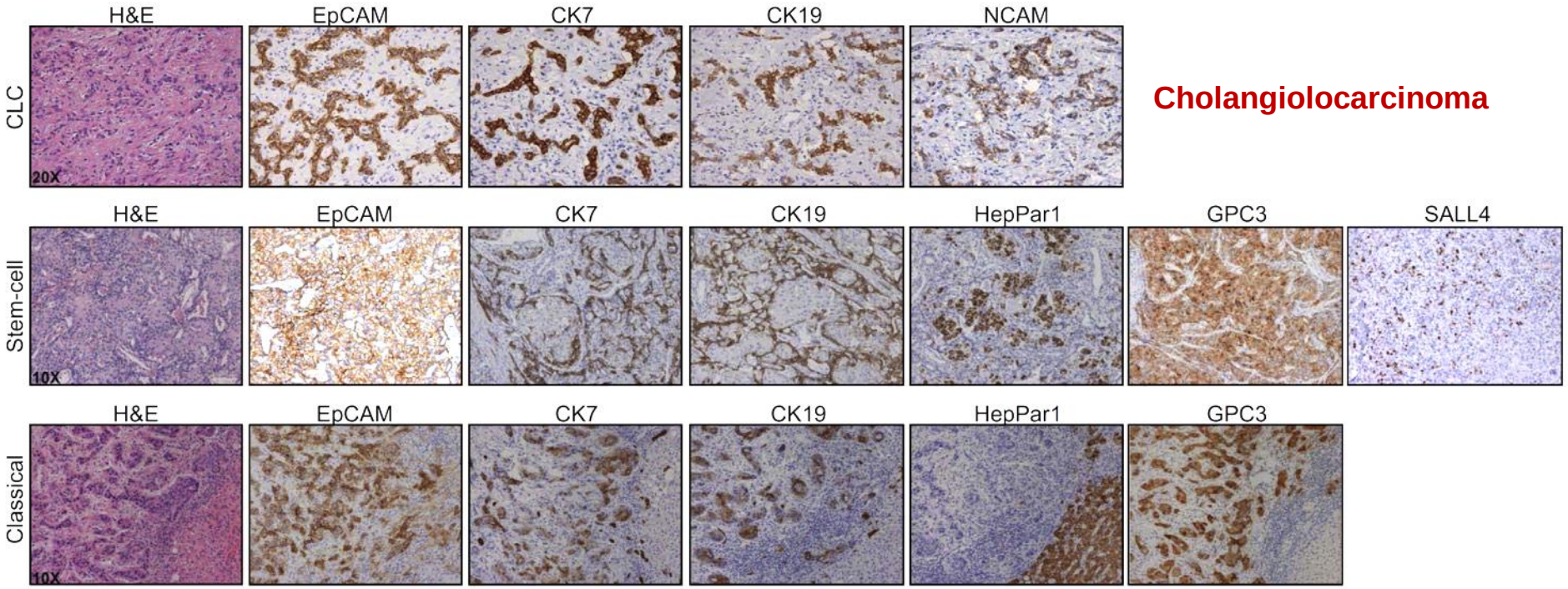


Brunt EM, Laennec Liver Society Meeting 2018

Mixed hepatocellular cholangiocarcinoma tumors: Cholangiolocellular carcinoma is a distinct molecular entity

Agrin Moeini[1,2], Daniela Sia[2], Zhongyang Zhang[3,4], Genis Camprecios[2], Ashley Stueck[2], Hui Dong[1], Robert Montal[1], Laura Torrens[1], Iris Martinez-Quetglas[1], M. Isabel Fiel[2], Ke Hao[3,4], Augusto Villanueva[2], Swan N. Thung[2], Myron E. Schwartz[2], Josep M. Llovet[1,2,5,*]

Journal of Hepatology **2017** vol. 66 | 952–961



Cholangiolocarcinoma

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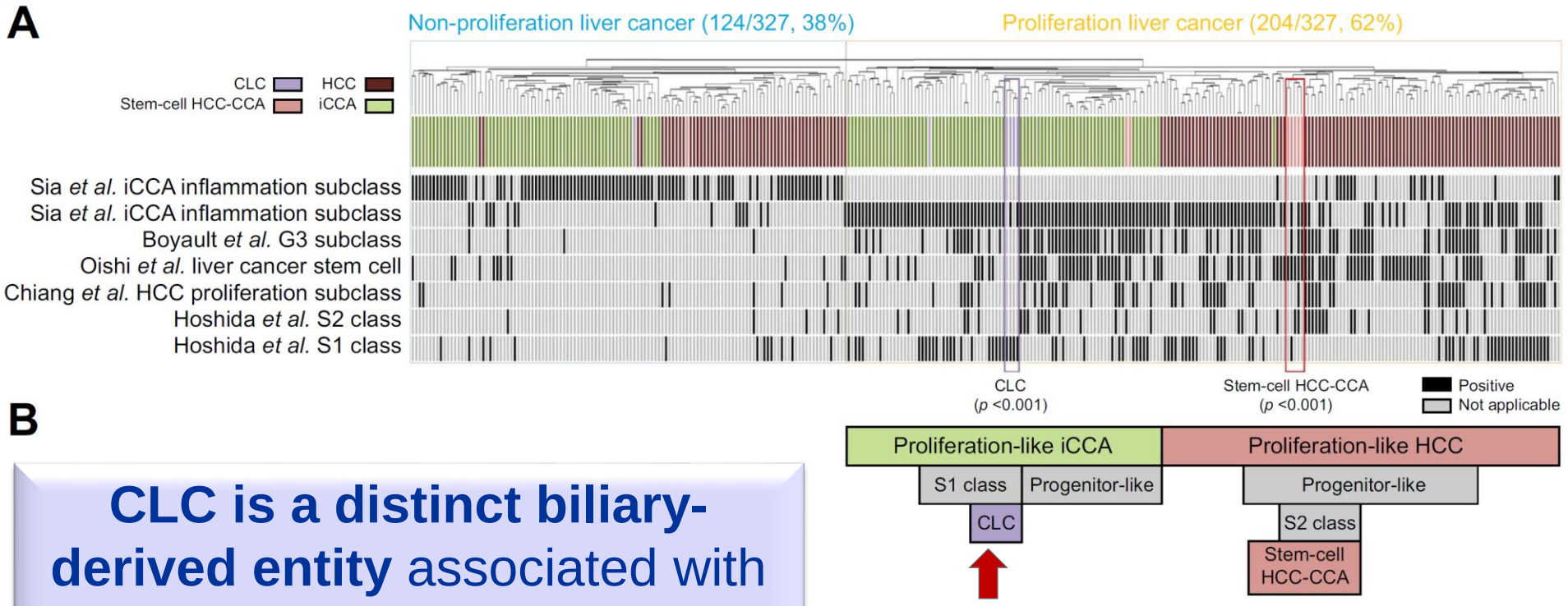
Journal of Hepatology **2017** vol. 66 | 952–961

Integrative genomic analysis of HCC-CCA with HCC and iCCA



CLC is a distinct biliary-derived entity associated with chromosomal stability and active TGF-b signaling

Primary Liver Carcinomas With both Hepatocytic and Cholangiocytic Differentation

- **Combined HCC-CCA: cHCC-CCA**
  - With or without stem cell/progenitor cell features
  - Not including Keratin 19+ HCC or iCCA with hepatocytic markers
  - Not including collision tumours
- **Intermediate Cell Carcinoma**
- **Cholangiolocarcinoma** (CLC)
  - aka cholangiolocellular carcinoma

  This is now considered as subtype of iCCA

Primary Liver Carcinomas With both Hepatocytic and Cholangiocytic Differentation

- **Diagnosis of cHCC-CCA relies on routine stains**
  Immunohistochemistry is only supplemental!

- **Stem cell phenotypes/features may exist within cHCC-CCA, and can be noted in a descriptive report**
  No separate subclassification!

- Radiology of cHCC-CCA to date indicate features between HCC and iCCA, but often not specific for either
  Biopsy confirmation may be indicated

- Impact on patient management

- Establish an international registry with centralized pathology and radiology for further clinical study

4. Hepatocellular carcinoma - New WHO blue book Update

Courtesy of Peter Schrmacher, Heidelberg, Germany

LCCH
Liver Cancer Center
Heidelberg

IPH
Institute of Pathology Heidelberg

Important New Aspects

- Scanned slides in addition to photomicrographs
- Online version
- Shorter chapters (word limits)
- Standardized formats across entities
- Restrict to confirmed published evidence
- Concentrate on (independently) confirmed evidence; not case-based/personal opinions
- GI is frontrunner of 5th edition !!
- General description of organ-non-specific entities (sarcomas, hematolymphatic taken out)

WHO BB Layout (5th Series) DRAFT

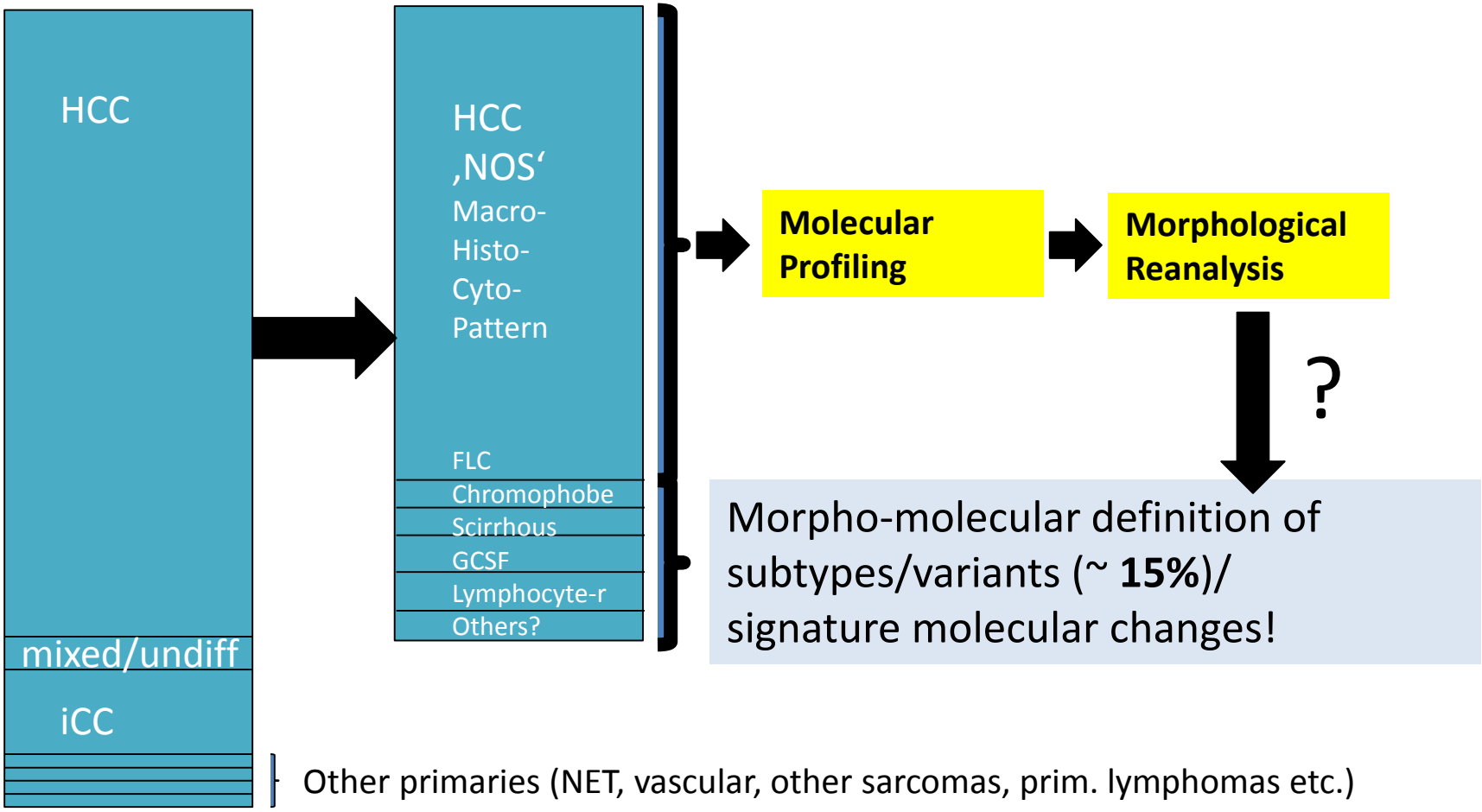
- Definition
- ICD-O and ICD11 Codes
- Synonyms
- Variants - list
- Localization
- Clinical features and Radiology
- Epidemiology
- Etiology
  - Causes
  - Predisposition (Genetics)
- Pathogenesis
- Histopathology
  - Macroscopic appearance
  - H&E appearance
  - Immune response & Microenvironment
  - Vascularity
  - Invasion (e.g. PNI)
  - Immunohistochemistry
  - Differential diagnosis
- Cytology
- Molecular pathology
  - Somatic genetics
  - Gene expression
  - Protein expression
  - Tumour markers
- Diagnostic criteria – essential and desirable
- Staging (UICC TNM)
- Prognosis and Prediction
  - Prognostic factors
  - Predictive biomarkers
- Links to other resources
  - ICCR reporting guidance
  - TNM (UICC)

Courtesy of I. Cree

LCCH
Liver Cancer Center
Heidelberg

IPH
Institute of Pathology Heidelberg

Morpho-molecular Classification Liver Cancer



HCC – some aspects

- **Aetiology update:** Including NAFLD/NASH
- **Molecular pathology diagnostics:**
  - Comprehensive profiling data on mutational landscape (but some discrepancies)
  - New subtypes (PRKCA-TL in FLC (incl. diagnostic test),
    ALT in chromophobe; AFP in massive/macrotrabecular, etc
  - Molecular correlations with pattern
  - Predictive targets tested – so far unsuccessful (KRAS, MET; no significant MSI)
  - Markers for treatment response to sorafenib suggested (VEGF-A amp, pATF2), but not validated prospectively
  - Additional markers for malignant transformation (H-TERT-promoter mutation, β-catenin)
  - Predictive markers for TACE response

HCC – some aspects

- **Histopathology**
  - New subtypes (chromophobe, *massive macrotrabecular – high AFP; Steatohepatitic, Granulocyte Colony Stimulating Factor-producing?)*
  - Distinction of HCC *and combined HCC/CC*
  - Undifferentiated HCC (?) should be removed from HCC

- ***Staging***
  - *Modified BCLC – staging; Milan/San Francisco criteria (LTx)*

- ***Others***
  - *Tumour biopsy issue? (misclassification, center issues, risks)*

LCCH
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Heidelberg

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Problems

- **Strict formal approach does not fit all entities equally well**
- **No more Liver chapters for „overarching“ entities**
  - **Secondary tumours are only described for whole GI**
    (liver peculiarities are not reflected adequately)
  - **Mesenchymal tumors described for whole GI**
    (no specific chapter for hepatic vascular tumours!!)
  - **Neuroendocrine**
  - **Haematolymphatic (referencing)**

Summary

- **Revised subtyping of hepatocellular adenoma**
  - inclusion of Shh-activated subtype with ↑ risk of haemorrhage
  - β-catenin mutated subtypes (exon 7 & 8 **or** exon 3 mutations)

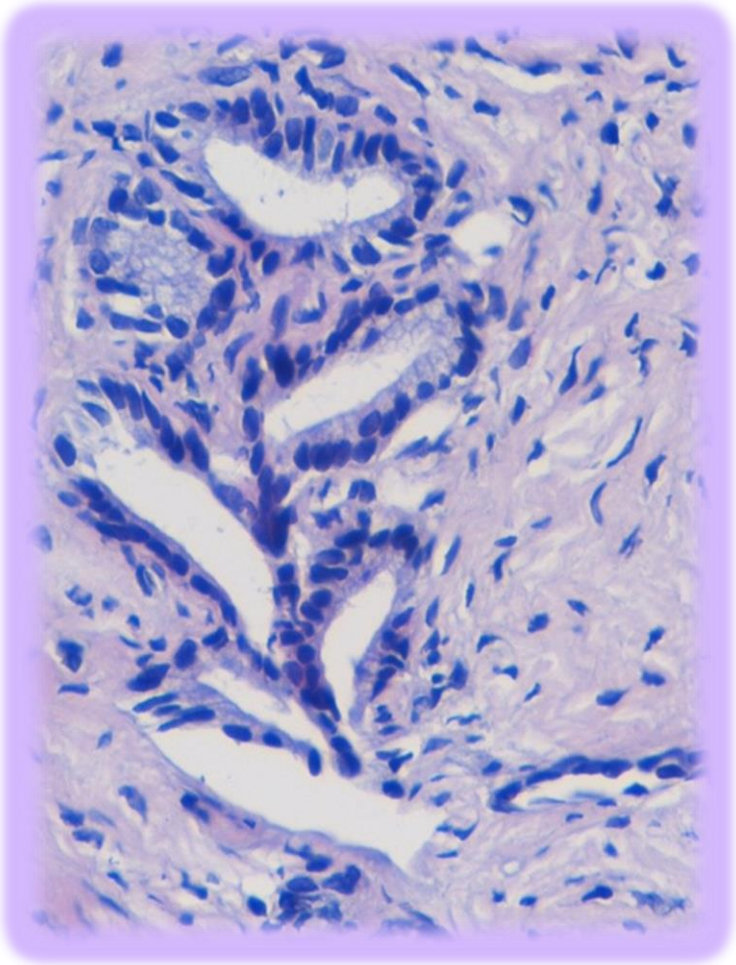
- **New HCC management clinical guidelines** (EASL, ESMO) **2018**
  - Role of liver biopsy for HCC diagnosis to be revisited
  - Still non-invasive imaging diagnosis for the majority of HCC in cirrhotic liver

Summary

- **HCC histological subtypes are closely related with specific oncogenic pathways and molecular alterations**
  - 15-20% of HCC have identifiable and possibly targetable molecular alterations
  - Macrotrabecular massive HCC has ↑ recurrence risk and poor prognosis

Summary

- **HCC histological subtypes are closely related with specific oncogenic pathways and molecular alterations**
  - 15-20% of HCC have identifiable and possibly targetable molecular alterations
  - Macrotrabecular massive HCC has ↑ recurrence risk
- **New consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentiation**
  - Diagnosis based on morphology not immunohistochemistry
  - Stem cell/progenitor cell features do not define specific histological subtypes of cHCC-CCA
  - Intermediate Cell Carcinoma separate from cHCC-CCA
  - Cholangiolocarcinoma to be classified as subtype of iCCA



Thank you!

Differential diagnosis well differentiated HCC vs HCA

Features	Hepatocellular adenoma	Well differentiated hepatocellular carcinoma
Tumour architecture		
Thickness of cell plates	1-2 cells	variable (>3 cells)
Trabecular growth	no	yes
Pseudoglandular structures	no or few	usually yes
Reticulin framework	retained	decreased
Invasive growth	no	yes
Unpaired arteries	no or few	usually present
Cytologic features		
Nuclear hyperchromasia	uncommon	common
Nuclear contour irregularities	uncommon	common
Nuclear pleomorphism	uncommon	common
Nuclear-cytoplasmic ratio	low	often high
Mitotic figures	absent or rare	absent or present
Non-lesional liver		
Evidence of cirrhosis	no	usually present
Positive immunostaining		
Sinusoidal CD34	occasional	diffuse
Glypican 3	negative	75% positive

Differential diagnosis of well differentiated hepatocellular tumours in non-cirrhotic liver

Atypical hepatocellular adenoma–like neoplasms with β-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas☆,☆☆

Kimberley J. Evason MD, PhD[a], James P. Grenert MD, PhD[a], Linda D. Ferrell MD[a], Sanjay Kakar MD[a,b,*]

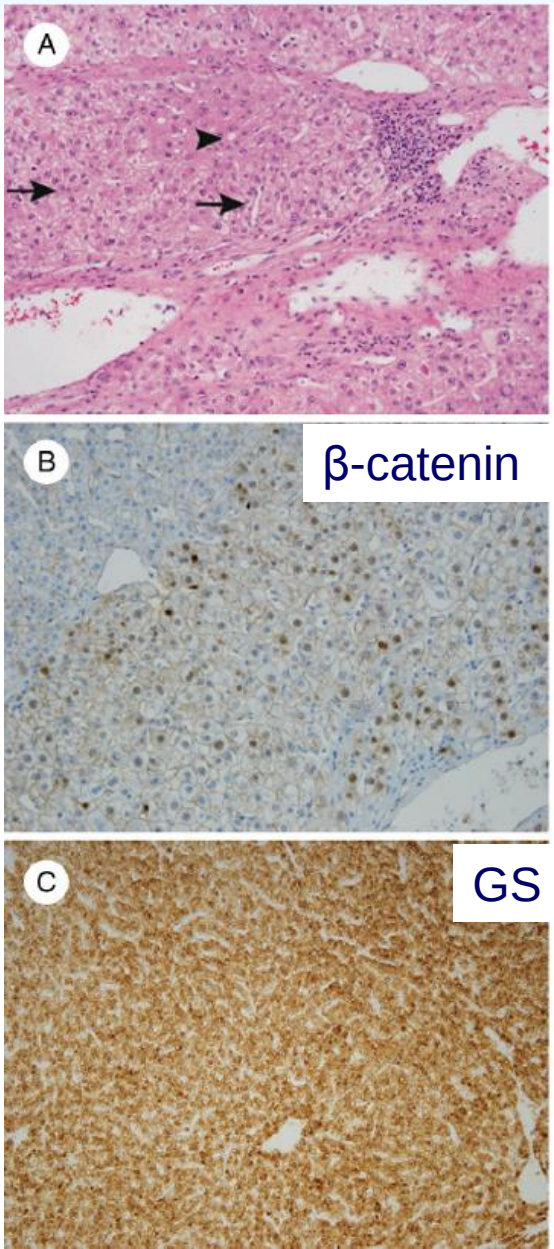
[a]Department of Pathology and Liver Center, University of California, San Francisco, CA 94143, USA
[b]VA Medical Center, San Francisco, CA 94121, USA

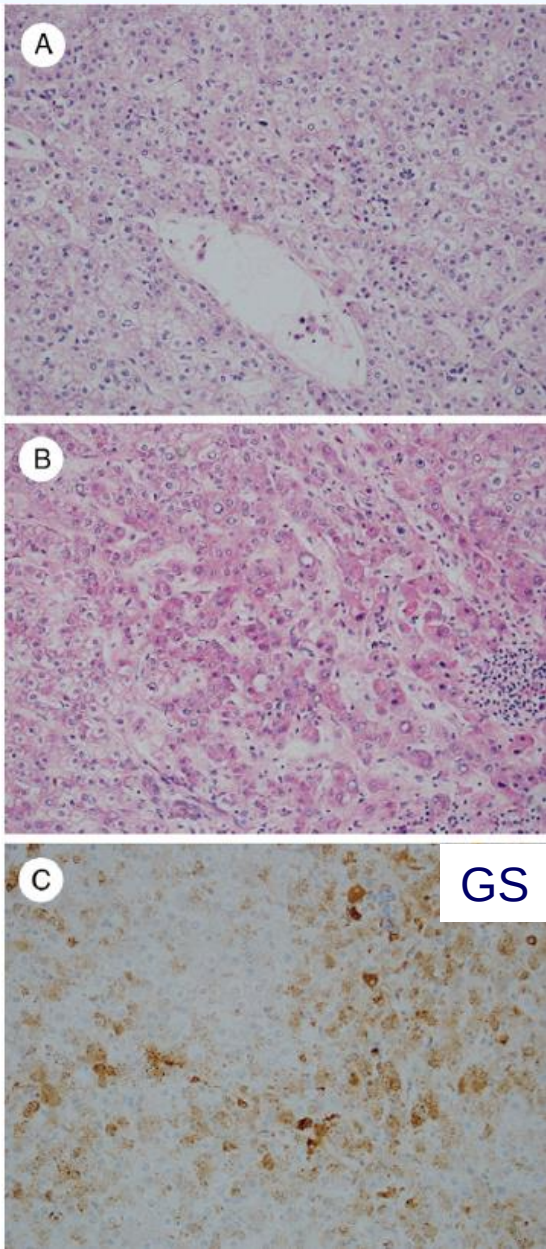
Human Pathology (2013) **44**, 750–758

HCA-like neoplasms with atypical features

Unusual clinical settings
- men
- women <15 y, >50 y

Atypical morphology
- focal cytologic atypia
- focal architectural atypia





Differential diagnosis of well differentiated hepatocellular tumours in non-cirrhotic liver

HCA-like neoplasms with atypical features
Evason et al, Human Pathol 2013

HCA-borderline lesions
Balabaud, Int J Hepatol 2013

Well differentiated Hepatocellular neoplasm of Uncertain Malignant Potential (HUMP)
Bedossa et al (Gnomes), Human Pathol 2014

β-catenin activation significantly more common in atypical hepatocellular neoplasms compared to typical HCA

Similarity in morphologic and cytogenetic features of β-catenin–activated HCA–like tumours and HCC

?

extremely well-differentiated variant of HCC

Choi & Kakar, Adv Anat Pathol 2018

Well-differentiated hepatocellular neoplasm of uncertain malignant potential: proposal for a new diagnostic category

Human Pathology (2014) 45, 657–663

Table Proposed entities considered to represent well differentiated HUMP

1. Lesions with features of hepatocellular adenoma morphologically, but:

A. Focally histologically atypical

- Focal reticulin loss
- Focal cytological atypia (small cell change, nuclear atypia) in <5% of tumor (1)[a]
- Focal architectural atypia (pseudogland formation) in <5% of tumor (1)[a]

B. Genetically atypical

- β-Catenin activated tumors[b]

C. Clinically atypical

- Female >50y or <15y[a]
- Male

2. Lesions with features of hepatocellular carcinoma morphologically that can regress with treatment of underlying disease:

A. Anabolic steroid-induced tumors

[a] The precise degree of atypia and the age cut-offs are currently not known with certainty and require further study.

[b] Nuclear/cytoplasmic positivity for β-catenin without other features of atypia is of unknown significance at this time.