Hepatocellular neoplasia - Recent developments

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• 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)

- F>>M
- Correlation with OC use
- HNF1α gene mutation
- Some inherited cases (adenomatosis, MODY3)

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

Sempoux, World J Hepatol 2014
HNF1α-inactive HCA (H-HCA)

- F>>M
- Correlation with OC use
- HNF1α gene mutation
- Some inherited cases
  - (adenomatosis, MODY3)

Immuno histochemistry:
Loss of Liver Fatty Acid Binding Protein (LFABP)

Sempoux, World J Hepatol 2014
Inflammatory HCA (I-HCA)

- Thick walled arteries
- Haemorrhage
- Inflammation

- Sinusoidal dilatation
- 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)

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

Nault, Gastroenterology 2013
β-catenin mutated HCA (b-HCA)

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

Glutamine Synthetase (GS) β-catenin

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

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

Molecular subtyping (sequencing)

Bioulac-Sage, Hepatology 2007
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

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

Nault, Gastroenterology 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 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

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

HCC: 5th most common cancer and 2nd leading cause of cancer death
2. Hepatocellular carcinoma -
New clinical guidelines
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).
CIRRHOTIC LIVER

Mass/nodule at imaging

<1 cm

Repeat US at 4 mo

Stable****

Growing/changing pattern

Multiphasic contrast-enhanced CT, or multiphasic contrast-enhanced MRI*, or gadoxetic-enhanced MRI**
EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma
Journal of Hepatology 2018 vol. 69 | 182–236

CIRRHOTIC LIVER

Mass/nodule at imaging

-1 cm

Multiphasic contrast-enhanced CT, or multiphasic contrast-enhanced MRI*, or gadoxetic-enhanced MRI**

1 positive technique: HCC imaging hallmarks

No

Use the other modality multiphasic contrast-enhanced CT, or multiphasic contrast-enhanced MRI*, or gadoxetic-enhanced MRI**, or contrast-enhanced ultrasound***

1 positive technique: HCC imaging hallmarks

No

Biopsy

Yes

HCC

- Non-HCC malignancy
- Benign

Biopsy unclear: Consider re-biopsy
Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

A. Vogel1, A. Cervantes2, I. Chau3, B. Daniele4, J. Llovet5,6,7, T. Meyer8,9, J.-C. Nault10, U. Neumann11, J. Ricke12, B. Sangro13, P. Schirmacher14, C. Verslype15, C. J. Zech16, D. Arnold17 & E. Martinelli18, 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
Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

A. Vogel1, A. Cervantes2, I. Chau3, B. Daniele4, J. Llovet5,6,7, T. Meyer8,9, J.-C. Nault10, U. Neumann11, J. Ricke12, B. Sangro13, P. Schirmacher14, C. Verslype15, C. J. Zech16, D. Arnold17 & E. Martinelli18, on behalf of the ESMO Guidelines Committee*

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

Gut 2003;52(Suppl III):iii1–iii8
Current clinical practice in UK:

• ESMO and/or EASL Guidelines
• Histological diagnosis of HCC necessary for patients who are eligible for treatment with sorafenib
Clinical Practice Guidelines: Management of hepatocellular carcinoma

Mass/nodule at imaging

<1 cm

Repeat imaging

<1 cm

Reality

60-90% of HCC:
No biopsy prior to treatment

>1 cm

Contrast-enhanced CT, or contrast-enhanced MRI*, or gadoxetic-enhanced MRI**, or contrast-enhanced ultrasound***

Use the other modality multiphasic contrast-enhanced CT, or multiphasic contrast-enhanced MRI*, or gadoxetic-enhanced MRI**, or contrast-enhanced ultrasound***

1 positive technique: HCC imaging hallmarks

No

- Non-HCC malignancy
- Benign

Yes

Biopsy

HCC
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%

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
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
Fibrolamellar HCC

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

Histological subtyping of HCC

- Personalised treatment with FGFR inhibitors?

Honeyman, Science 2014
Riehle, Mod Pathol 2015
Graham, Mod Pathol 2015
Molecular classification of hepatocellular carcinoma

Main molecular subgroups

**Proliferative subgroup**

- Stem cell (G1, stem cell like, hepatoblast like and S2 subtype)
- Other proliferative HCC (G2-G3, late TGFβ and S1 subgroup)
  - Chromosomal instability

**Gene mutation**

- TP53 and AXIN1 mutations
- FGF19 amplification

**Clinical and histological features**

- CK19 and EPCAM at IHC
- HBV infection
- Macrotrabecular massive HCC
- Poor prognosis

**Non proliferative subgroup**

- Hepatocyte like (G4, interferon and S3 subgroup)
- Wnt/β-catenin (G5-G6, CTNNB1 and S3 subgroup)
  - Chromosomal stability

**Activation of JAK/STAT pathway**

- Steatohepatitic HCC

**CTNNB1 activating mutation**

- Well differentiated HCC with cholestasis
- Glutamine synthase and nuclear B-catenin at IHC

Nault JC, J Hepatol 2018
Novel histological/molecular HCC subtypes

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

Macrotrabecular Massive HCC

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

Calderaro, J Hepatol 2017
Macrotabecular-Massive Hepatocellular Carcinoma: A Distinctive Histological Subtype With Clinical Relevance

Marianne Zio,1,5,6 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,10 Claire Francoz,11 Georges Philippe Pageaux,12 Jeanne Ramos,13 Thomas Decaens,14 Alain Luciani,5,15 Boris Guia,16 Valérie Vilgrain,17 Christophe Aubé,18 Jonathan Derman,19 Cécile Charpy,19 Jessica Zucman-Rossi,19 Nathalie Barget,20 Olivier Seror,21 Nathalie Ganne-Carrié,3,8 Valérie Paradis,4 and Julien Calderaro5,19

Retrospective study of HCC

237 HCC surgical samples
284 HCC liver biopsies from 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

Large size >5 cm

Macrotrabecular architecture correlations:

HBV infection, AFP >100 ng/mL, large size and ….
Macrotrabecular massive HCC subtype correlates with early and overall HCC recurrence even in subgroups according to traditional features of tumour aggressiveness.
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.

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

Quetglas, Best Pract Res Clin Gastroenterol 2014
Integrative HCC Classification

Multiple data platforms
Clinical data

Potential therapeutic targets

- WNT signaling
- MDM4, MET, VEGFA,
- MCL1, IDH1, TERT,
- immune checkpoint proteins CT LA-4, PD-1, and PD-L1.

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

Elizabeth Brunt, Shinichi Aishima, Pierre-Alain Clavien, Kathryn Fowler, Zachary Goodman, Gregory Gores, Annette Gouw, Alex Kagen, David Klimstra, Mina Komuta, Fukuo Kondo, Rebecca Miksad, Masayuki Nakano, Yasuni Nakanuma, Irene Ng, Valerie Paradis, Young Nyun Park, Alberto Quaglia, Massimo Roncalli, Tania Roskams, Michiie Sakamoto, Romil Saxena, Christine Sempoux, Claude Sirlin, Ashley Stueck, Swan Thung, W.M.S. Tsui, Xin-Wei Wang, Aileen Wee, Hirohisa Yano, Matthew Yeh, Yoh Zen, Jessica Zucman-Rossi, and Neil Theise
Combined hepatocellular cholangiocarcinoma - cHCC-CCA
Morphologic variants of “stem/progenitor cell features”

HCC with stem cell/progenitor cell features

Intermediate cell carcinoma

Cholangioloocarcinoma
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**
Mixed hepatocellular cholangiocarcinoma tumors: Cholangiocolocellular carcinoma is a distinct molecular entity

Agrin Moeini¹,², Daniela Sia², Zhongyang Zhang³,⁴, Genis Camprecios², Ashley Stueck², Hui Dong¹, Robert Montal¹, Laura Torrens¹, Iris Martinez-Quetglas¹, M. Isabel Fiel², Ke Hao³,⁴, Augusto Villanueva², Swan N. Thung², Myron E. Schwartz², Josep M. Llovet¹,²,⁵,⁶

Journal of Hepatology 2017 vol. 66 | 952–961

Cholangiocolocellular carcinoma

CLC

Stem-cell

Classical
CLC is a distinct biliary-derived entity associated with chromosomal stability and active TGF-β signaling
Primary Liver Carcinomas With both Hepatocytic and Cholangiocytic Differentiation

• **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 Differentiation

• 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

Courtesy of Peter Schrmacher, Heidelberg, Germany
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
Morpho-molecular Classification Liver Cancer

HCC

'HCC, NOS'
Macro-
Histo-
Cyto-
Pattern

FLC
Chromophobe
Scirrhous
GCSF
Lymphocyte-r
Others?

Molecular Profiling
Morphological
Reanalysis

Morpho-molecular definition of subtypes/variants (~15%)/signature molecular changes!

Other primaries (NET, vascular, other sarcomas, prim. lymphomas etc.)
**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)*
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 $\uparrow$ risk of haemorrhage
  - $\beta$-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 increased 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
  - Cholangioloocarcinoma to be classified as subtype of iCCA
Thank you!
## Differential diagnosis
well differentiated HCC vs HCA

<table>
<thead>
<tr>
<th>Features</th>
<th>Hepatocellular adenoma</th>
<th>Well differentiated hepatocellular carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour architecture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness of cell plates</td>
<td>1-2 cells</td>
<td>variable (&gt;3 cells)</td>
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<tr>
<td>Trabecular growth</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Pseudoglandular structures</td>
<td>no or few</td>
<td>usually yes</td>
</tr>
<tr>
<td>Reticulin framework</td>
<td>retained</td>
<td>decreased</td>
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<td>Invasive growth</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Unpaired arteries</td>
<td>no or few</td>
<td>usually present</td>
</tr>
<tr>
<td><strong>Cytologic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear hyperchromasia</td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Nuclear contour irregularities</td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Nuclear-cytoplasmic ratio</td>
<td>low</td>
<td>often high</td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>absent or rare</td>
<td>absent or present</td>
</tr>
<tr>
<td><strong>Non-lesional liver</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of cirrhosis</td>
<td>no</td>
<td>usually present</td>
</tr>
<tr>
<td><strong>Positive immunostaining</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusoidal CD34</td>
<td>occasional</td>
<td>diffuse</td>
</tr>
<tr>
<td>Glypican 3</td>
<td>negative</td>
<td>75% positive</td>
</tr>
</tbody>
</table>
Differential diagnosis of well differentiated hepatocellular tumours in non-cirrhotic liver

Atypical hepatocellular adenoma–like neoplasms with \(\beta\)-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas.

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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)\textsuperscript{a}
      • Focal architectural atypia (pseudogland formation) in <5% of tumor (1)\textsuperscript{a}
   B. Genetically atypical
      • \(\beta\)-Catenin activated tumors\textsuperscript{b}
   C. Clinically atypical
      • Female >50y or <15y\textsuperscript{a}
      • Male
2. Lesions with features of hepatocellular carcinoma morphologically that can regress with treatment of underlying disease:
   A. Anabolic steroid-induced tumors

\textsuperscript{a} The precise degree of atypia and the age cut-offs are currently not known with certainty and require further study.
\textsuperscript{b} Nuclear/cytoplasmic positivity for \(\beta\)-catenin without other features of atypia is of unknown significance at this time.