### WHO Classification3 of tumours of the liver and intrahepatic bile ducts

**Epithelial tumours: hepatocellular**

- **Benign**
  - Hepatocellular adenoma 8170/0
  - Focal nodular hyperplasia

- **Malignancy-associated and premalignant lesions**
  - Large cell change (formerly “dysplasia”)
  - Small cell change (formerly “dysplasia”)
  - Dysplastic nodules
    - Low grade
    - High grade

- **Malignant**
  - Hepatocellular carcinoma 8170/3
  - Hepatocellular carcinoma, fibrolamellar variant 8171/3
  - Hepatoblastoma, epithelial variant 8970/3
  - Undifferentiated carcinoma 8020/3

**Epithelial tumours: biliary**

- **Benign**
  - Bile duct adenoma (peribiliary gland hamartoma and others) 8160/0
  - Microcystic adenoma 8020/0
  - Biliary adenofibroma 9013/0

- **Premalignant lesions**
  - Biliary intraepithelial neoplasia, grade 3 (BILIN-3) 8168/2*
  - Intraductal papillary neoplasm with low- or intermediate-grade intraepithelial neoplasia 8503/0
  - Intraductal papillary neoplasm with high-grade intraepithelial neoplasia 8503/2*
  - Mucinous cystic neoplasm with low- or intermediate-grade intraepithelial neoplasia 8470/0
  - Mucinous cystic neoplasm with high-grade intraepithelial neoplasia 8470/2

- **Malignant**
  - Intrahepatic cholangiocarcinoma 8160/3
  - Intraductal papillary neoplasm with an associated invasive carcinoma 8503/3*
  - Mucinous cystic neoplasm with an associated invasive carcinoma 8470/3

**Malignancies of mixed or uncertain origin**

- Calciﬁying nested epithelial stromal tumour 8975/1*
- Carcinosarcoma 8860/3
- Combined hepatocellular-cholangiocarcinoma 8180/3
- Hepatoblastoma, mixed epithelial-mesenchymal 8970/3
- Malignant rhabdoid tumour 8963/3

**Mesenchymal tumours**

- **Benign**
  - Angiomyolipoma (PEComa) 8860/0
  - Cavernous haemangioma 9121/0
  - Intense haemangioma 9131/0
  - Inflammatory pseudotumour 9170/0
  - Lymphangiomia 9170/0
  - Lymphangiomyomatosis
  - Meconchymal hamartoma
  - Solitary fibrous tumour 6515/0

- **Malignant**
  - Angiosarcoma 9120/3
  - Embryonal sarcoma (undifferentiated sarcoma) 8891/3
  - Epithelioid haemangiopericytoma 9133/3
  - Kaposi sarcoma 9140/3
  - Leiomyosarcoma 8890/0
  - Rheboidiomysarcoma 8900/3
  - Synovial sarcoma 9040/3

**Germ cell tumours**

- Teratoma 9080/1
- Yolk sac tumour (endodermal sinus tumour) 9081/3

**Lymphomas**

**Secondary tumours**
Lesion in a patient with chronic liver disease?
Lesion in a patient without chronic liver disease?
Patients with cirrhosis

- Liver: 77%
- Stomach: 4%
- Colon: 4%
- Pancreas: 2%
- Lung: 7%
- Other: 6%

Melato M et al, *Cancer*, 1989
Malignant Neoplasms in the Liver - Site of Origin

Liver 2%
Lung 23%
Colon 13%
Pancreas 18%
Breast 7%
Stomach 10%
Other 27%
No Liver Disease

Melato M et al, Cancer, 1989
Global cause of death

- Global annual number of deaths: 52M

- Top 20 global causes of death

<table>
<thead>
<tr>
<th>Position</th>
<th>Cause</th>
<th>Global 1990</th>
<th>Global 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ischaemic heart disease</td>
<td>1.0 (1 to 1)</td>
<td>35 (29 to 39)</td>
</tr>
<tr>
<td>2</td>
<td>Stroke</td>
<td>2.0 (2 to 2)</td>
<td>26 (14 to 32)</td>
</tr>
<tr>
<td>3</td>
<td>COPD</td>
<td>3.4 (3 to 4)</td>
<td>-7 (~12 to 0)</td>
</tr>
<tr>
<td>4</td>
<td>Lower respiratory infections</td>
<td>3.6 (3 to 4)</td>
<td>-18 (~24 to 11)</td>
</tr>
<tr>
<td>5</td>
<td>Lung cancer</td>
<td>5.8 (5 to 10)</td>
<td>48 (24 to 61)</td>
</tr>
<tr>
<td>6</td>
<td>HIV/AIDS</td>
<td>6.4 (5 to 8)</td>
<td>396 (323 to 465)</td>
</tr>
<tr>
<td>7</td>
<td>Diarrhoea</td>
<td>6.7 (5 to 9)</td>
<td>-42 (~49 to ~35)</td>
</tr>
<tr>
<td>8</td>
<td>Road injury</td>
<td>8.4 (5 to 11)</td>
<td>47 (18 to 86)</td>
</tr>
<tr>
<td>9</td>
<td>Diabetes</td>
<td>9.0 (7 to 11)</td>
<td>93 (68 to 102)</td>
</tr>
<tr>
<td>10</td>
<td>Tuberculosis</td>
<td>10.1 (8 to 13)</td>
<td>-18 (~35 to ~3)</td>
</tr>
<tr>
<td>11</td>
<td>Malaria</td>
<td>10.3 (6 to 13)</td>
<td>21 (~9 to 56)</td>
</tr>
<tr>
<td>12</td>
<td>Cirrhosis</td>
<td>11.8 (10 to 14)</td>
<td>33 (25 to 41)</td>
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<tr>
<td>13</td>
<td>Self-harm</td>
<td>14.1 (11 to 20)</td>
<td>32 (8 to 49)</td>
</tr>
<tr>
<td>14</td>
<td>Hypertensive heart disease</td>
<td>14.2 (12 to 18)</td>
<td>48 (39 to 56)</td>
</tr>
<tr>
<td>15</td>
<td>Preterm birth complications</td>
<td>14.4 (12 to 18)</td>
<td>-28 (~39 to ~17)</td>
</tr>
<tr>
<td>16</td>
<td>Liver cancer</td>
<td>16.9 (14 to 20)</td>
<td>63 (49 to 78)</td>
</tr>
<tr>
<td>17</td>
<td>Stomach cancer</td>
<td>17.0 (13 to 22)</td>
<td>-2 (~10 to 5)</td>
</tr>
<tr>
<td>18</td>
<td>Chronic kidney disease</td>
<td>17.4 (15 to 21)</td>
<td>82 (65 to 95)</td>
</tr>
<tr>
<td>19</td>
<td>Colorectal cancer</td>
<td>18.5 (15 to 21)</td>
<td>46 (36 to 63)</td>
</tr>
<tr>
<td>20</td>
<td>Other cardiovascular and circulatory</td>
<td>19.7 (18 to 21)</td>
<td>46 (40 to 55)</td>
</tr>
</tbody>
</table>

Lozano et al, Lancet 2012
Mongolia has the world’s highest incidence of liver cancer, with 78 cases per 100,000 inhabitants (8 times the global average). Underlying risk factors are HBV and HCV infection, and alcohol consumption.

China
Approximately 54% of HCCs can be attributed to HBV infection, which affects 400 million people globally. The prevalence of HBsAg in the Chinese population is 9%.

Sudan
Dietary exposure to aflatoxin B1 is an important cofactor for HCC development in Sub-Saharan Africa and Southeast Asia. An estimated 60% of liver cancer cases have aflatoxin B1 as a cofactor in Sudan.

United States
In the United States, NASH associated with obesity and/or diabetes is emerging as a risk factor for HCC. In 2014, 35% of the US adult population was obese.

Egypt
HCV is responsible for 31% of liver cancer cases. The prevalence of HCV infection rose from 122 to 185 million individuals from 1990 to 2005 globally. Egypt has the highest prevalence of HCV in the world, estimated at 14.7%.

Age-standardized liver cancer rates per 100,000 people:
- >9.2
- 5.4–9.1
- 4.2–5.3
- 3.1–4.1
- <3.0
- No data
## Risk factors

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>AAIR M/F</th>
<th>Risk factors</th>
<th>Alcohol (%)</th>
<th>Others (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HCV (%)</td>
<td>HBV (%)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>6.7/2.3</td>
<td>60-70</td>
<td>10-15</td>
<td>20</td>
</tr>
<tr>
<td>Southern</td>
<td>10.5/3.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>4.1/1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>6.8/2.3</td>
<td>50-60</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Asia and Africa</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Asia</td>
<td>21.6/8.2</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>China</td>
<td>23/9.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>20.5/7.8</td>
<td>70</td>
<td>10-20</td>
<td>10</td>
</tr>
<tr>
<td>Africa</td>
<td>1.6/5.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WORLD</td>
<td>16/6</td>
<td>31</td>
<td>54</td>
<td>15</td>
</tr>
</tbody>
</table>
Histopathological progression and molecular features of HCC

Farazi PA, Nat Rev Cancer, 2006
1. Expansive (nodular)
2. Infiltrative
3. Mixed Expansive and Infiltrative
4. Diffuse
5. Pedunculated
The most common type. Typically seen in association with cirrhosis.
The lesion is poorly circumscribed with ill-defined invasive borders. This pattern is seen more commonly in non-cirrhotic livers.
Diffuse HCC/cirrhotomimetic
The outstanding histological feature is the resemblance of the tumor cells to normal hepatocytes

1. Trabecular (sinusoidal) pattern
2. Pseudoglandular (acinar) pattern
3. Compact (solid) pattern
Tumor cells grow in cords of variable thickness separated by prominent sinusoids lined by flat endothelial cells.
Pseudoglandular pattern

A variety of gland-like structures may be seen.
Bile production: the most specific marker of hepatocellular differentiation!
The pattern is basically trabecular but the tumor cells apparently grow in solid masses and the sinusoids are rendered inconspicuous by compression.
Grading WHO

**Well differentiated**
Most common in small early stage tumors of < 2cm, mild atypia, increased nucleus-to-cytoplasm ratio

**Moderately differentiated**
Most common in tumors of > 3cm, mainly trabecular growth. Tumor cells with abundant eosinophilic cytoplasm and round nuclei.

**Poorly differentiated**
Rare in small tumours, mainly solid pattern, marked pleomorphism.
Grading Edmondson

**Grade I**: Best differentiated, simulates normal liver plates

**Grade II**: Larger nucleus, prominent nuclei, eosinophilic and granular cytoplasm

**Grade III**: Nuclei more enlarged and hyperchromatic, angulated nuclei, less abundant cytoplasm

**Grade IV**: Marked pleomorphism, hyperchromaticia, scanty cytoplasm, anaplasia loss of trabecular pattern

Edmondson HA and Steiner PE, Cancer, 1954
Diagnosis of HCC

1) HE

2) Reticulin stain

3) Immunohistochemistry

4) (Molecular pathology)
The reticulin framework is preserved in the non-neoplastic liver (left part of image), but the tumor shows substantial loss of reticulin
# Table 1. A Panel of Immunomarkers Helpful in Confirming Hepatocellular Differentiation

<table>
<thead>
<tr>
<th>Markers</th>
<th>Staining Pattern</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARG1</td>
<td>Cytoplasmic and nuclear</td>
<td>80–95</td>
<td>95–100</td>
</tr>
<tr>
<td>HepPar1</td>
<td>Cytoplasmic</td>
<td>70–80</td>
<td>~80</td>
</tr>
<tr>
<td>GPC3</td>
<td>Cytoplasmic</td>
<td>50–80</td>
<td>~95</td>
</tr>
<tr>
<td>pCEA</td>
<td>Canalicular</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>CD10</td>
<td>Canalicular</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>CD34</td>
<td>Sinusoidal</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Abbreviations: ARG1, arginase 1; GPC3, glypican 3; HepPar1, hepatocyte paraffin 1; n/a, not available; pCEA, polyclonal carcinoembryonic antigen.
Cave: Poorly-differentiated tumours often have aberrant staining patterns

- Edmondson grade:
  - grade I-II: 100%
  - grade III: 84%
  - grade IV: 50%
Differential diagnosis:

- Adrenocortical carcinoma
- Angiomyolipom
- Renal cell carcinoma
- Clear cell carcinoma
- Melanoma
- Large cell neuroendocrine carcinoma
Special Types of HCC

Fibrolamellar carcinoma
Scirrhous HCC
Undifferentiated carcinoma
Lymphoepithelioma-like carcinoma
Sarcomatoid carcinoma
Mainly in children and young adults (Ø 25 years old) 
0.5%-9.0% of primary liver cancers

Arises in non-cirrhotic liver 
Etiology and risk factors are unknown

Large polygonal cells with abundant eosinophilic (oncocytyic) cytoplasm, large vesicular nuclei and large nucleoli

Lamellar fibrosis
Fibrolamellar HCC
### precursor lesions for HCC

**Macrogenenerative Nodule**

- **LGDN**

**HGDN**

**Early HCC**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low-grade dysplastic nodule (LGDN)</th>
<th>High-grade dysplastic nodule (HGDN)</th>
<th>Well-differentiated HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical change</td>
<td><img src="image" alt="Anatomical change" /></td>
<td><img src="image" alt="Anatomical change" /></td>
<td><img src="image" alt="Anatomical change" /></td>
</tr>
<tr>
<td>Clinico-pathological</td>
<td>Premalignant</td>
<td></td>
<td>Early HCC</td>
</tr>
</tbody>
</table>
Precursor lesions for HCC

**Macoregenerative Nodule/Low grade dysplastic nodule**
Tumor-like hepatocellular mass
Well demarcated and surrounded by condensed connective tissue
Clonal cell population without architectural atypia
Portal tracts (artery and bile duct), ductular reaction
Clonal cell population with architectural atypia,
No stromal invasion
Increased cell density
Some portal tracts (artery and bile duct),
Some aberrant unpaired arterioles
Ductular reaction

Tommaso L et al 2013
Early HCC <2cm Ø

Slowly growing tumor of vaguely nodular appearance
Higher cell density
Often fatty changes
Stromal invasion
Increased cell density

Tommaso L et al 2013
## Genes/Proteins Upregulated in Early HCC

<table>
<thead>
<tr>
<th>Genes/Proteins</th>
<th>Functions and Characteristics</th>
<th>Immunohistochemistry (criteria for positivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glypican-3</td>
<td>Heparan sulphate proteoglycan, Promotes growth of HCC by stimulating Wnt signalling</td>
<td>Cytoplasmic/membranous (&gt; 5-10% of cells)</td>
</tr>
<tr>
<td>HSP 70</td>
<td>Chaperone stress protein, Potent anti-apoptotic survival factor</td>
<td>Cytoplasmic/nuclear (&gt; 5-10% of cells)</td>
</tr>
<tr>
<td>Glutamine Synthetase</td>
<td>Target gene for beta-catenin, GS overexpressed with activation/mutation of beta-catenin, Involved with hepatocyte regeneration &amp; proliferation</td>
<td>Cytoplasmic (diffuse &gt; 50%, unrelated to vessels)</td>
</tr>
</tbody>
</table>
IHC for early HCC

Di Tommaso L et al, 2009
### IHC for early HCC

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat shock protein 70</td>
<td>78%</td>
<td>95%</td>
</tr>
<tr>
<td>Glutamine synthetase</td>
<td>59%</td>
<td>86%</td>
</tr>
<tr>
<td>Glypican 3</td>
<td>69%</td>
<td>91%</td>
</tr>
<tr>
<td><strong>When 2 of them are positive</strong></td>
<td><strong>72%</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Di Tommaso L, Hepatology, 2007  
Bruix J, Hepatology, 2011
## Table 1 | Major recurrent molecular aberrations observed in advanced HCC

<table>
<thead>
<tr>
<th>Pathway(s)</th>
<th>Gene(s)</th>
<th>Alteration</th>
<th>Frequency in HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telomere maintenance</td>
<td>TERT</td>
<td>Promoter mutation</td>
<td>54–60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amplification</td>
<td>5–6%</td>
</tr>
<tr>
<td>Cell cycle control</td>
<td>TP53</td>
<td>Mutation or deletion</td>
<td>12–48%</td>
</tr>
<tr>
<td></td>
<td>RB1</td>
<td>Mutation or deletion</td>
<td>3–8%</td>
</tr>
<tr>
<td></td>
<td>CCND1</td>
<td>Amplification</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>CDKN2A</td>
<td>Mutation or deletion</td>
<td>2–12%</td>
</tr>
<tr>
<td>WNT–β-catenin signalling</td>
<td>CTNNB1</td>
<td>Mutation</td>
<td>11–37%</td>
</tr>
<tr>
<td></td>
<td>AXIN1</td>
<td>Mutation or deletion</td>
<td>5–15%</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>NFE2L2</td>
<td>Mutation</td>
<td>3–6%</td>
</tr>
<tr>
<td></td>
<td>KEAP1</td>
<td>Mutation</td>
<td>2–8%</td>
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<tr>
<td>Epigenetic and chromatin remodelling</td>
<td>ARID1A</td>
<td>Mutation or deletion</td>
<td>4–7%</td>
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<tr>
<td></td>
<td>ARID2</td>
<td>Mutation</td>
<td>3–18%</td>
</tr>
<tr>
<td></td>
<td>KMT2A (MLL1), KMT2B (MLL4), KMT2C (MLL3) and KMT2D (MLL2)</td>
<td>Mutation</td>
<td>2–6%</td>
</tr>
<tr>
<td>AKT–mTOR–MAPK signalling</td>
<td>RPS6KA3</td>
<td>Mutation</td>
<td>2–9%</td>
</tr>
<tr>
<td></td>
<td>TSC1 and TSC2</td>
<td>Mutation or deletion</td>
<td>3–8%</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>Mutation or deletion</td>
<td>1–3%</td>
</tr>
<tr>
<td></td>
<td>FGF3, FGF4 and FGF19</td>
<td>Amplification</td>
<td>4–6%</td>
</tr>
<tr>
<td></td>
<td>PI3KCA</td>
<td>Mutation</td>
<td>0–2%</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>VEGFA</td>
<td>Amplification</td>
<td>3–7%</td>
</tr>
</tbody>
</table>

Llovet et al Nat Rev Dis Prim 2016
Rare, benign liver neoplasm

Strongly associated with oral contraceptive use and androgen steroid therapy, also in patients with glycogen storage disease, diabetes mellitus

3-4 per 100’000 in long term OC users

Can become symptomatic and lead to bleeding

A small subset have the potential for malignant transformation
Solitary, with size to 30cm

Soft white to brown and delineated with little or no fibrous capsule, heterogeneous areas of necrosis or hemorrhage
Molecular classification of HCA

- HNF1α inactivated (TCF1 gene mutated) (30%-35%)
  - β-Catenin mutated (10%-15%)
- Inflammatory (50%)
- Unclassified (10%)

<table>
<thead>
<tr>
<th>HA Subtype</th>
<th>Frequency Range, %</th>
<th>Molecular Findings</th>
<th>Pathologic Features</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-H</td>
<td>35–40</td>
<td>Somatic mutations of (85%) TCF1 (HNF1A) gene; heterozygous germline mutations (&lt;5%) of CYP1B1 gene</td>
<td>Steatosis, lack of inflammation, and cytologic atypia</td>
<td>Decreased or absent L-FABP in neoplastic hepatocytes, compared with nonneoplastic liver; patchy CD34 expression; focal, interspersed CK7 positivity in small hepatocytes</td>
</tr>
<tr>
<td>HA-B</td>
<td>15–19</td>
<td>β-catenin gene-activating mutations</td>
<td>Pseudoacinar pattern, cytologic atypia, steatosis, and/or lack of inflammation</td>
<td>Increased nuclear β-catenin protein expression; strong diffuse glutamine synthetase positivity</td>
</tr>
<tr>
<td>HA-I</td>
<td>30–35</td>
<td>Gain-of-function mutations of the IL6ST gene; 10% with coexisting β-catenin gene mutations</td>
<td>Pseudoportal tracts with thick-walled arteries and lack of bile ducts or veins; inflammatory infiltrate; ductular reaction; sinusoidal dilatation; and peliosis</td>
<td>Diffuse, strong serum amyloid-A and C-reactive protein expression; CD34 reactivity around pseudoportal tracts; diffuse glutamine synthetase positivity if associated with β-catenin mutation</td>
</tr>
<tr>
<td>HA-U</td>
<td>10</td>
<td>No specific mutations</td>
<td>No distinctive morphology</td>
<td>No specific protein expression</td>
</tr>
</tbody>
</table>
HNF1α inactivated
β-Catenin mutated

5a β-catenin

5b glutamine synthetase
Inflammatory/teleangiectatic HCA

Serum amyloid precursor protein
### Table 2. Immunohistochemistry Markers and Staining Patterns in Different Types of Hepatocellular Adenoma

<table>
<thead>
<tr>
<th></th>
<th>LFABP</th>
<th>SAA/CRP</th>
<th>GS</th>
<th>β-Catenin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1α inactivation</td>
<td>Negative</td>
<td>Negative</td>
<td>Central vein</td>
<td>Membranous</td>
</tr>
<tr>
<td>β-Catenin activated</td>
<td>Positive</td>
<td>Negative</td>
<td>Diffusely positive</td>
<td>Nuclear</td>
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<tr>
<td>Inflammatory</td>
<td>Positive</td>
<td>Positive</td>
<td>Central vein</td>
<td>Membranous or nuclear</td>
</tr>
<tr>
<td>Unclassified</td>
<td>Positive</td>
<td>Negative</td>
<td>Central vein</td>
<td>Membranous</td>
</tr>
<tr>
<td>FNH</td>
<td>Positive</td>
<td>Negative</td>
<td>Irregular anastomosing</td>
<td>Membranous</td>
</tr>
<tr>
<td>Normal liver</td>
<td>Positive</td>
<td>Negative</td>
<td>Central vein</td>
<td>Membranous</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; FNH, focal nodular hyperplasia; GS, glutamine synthetase; HNF1α, hepatocyte nuclear factor 1α; LFABP, liver fatty acid binding protein; SAA, serum amyloid-associated protein.
HCA vs HCC

Favoring HCC: thickened cell plates, loss of reticulin network, cytological atypia, mitosis, pseudoacinar architecture

<table>
<thead>
<tr>
<th>Markers</th>
<th>Malignant</th>
<th>Benign</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPC3</td>
<td>Positive</td>
<td>Negative</td>
<td>40–60</td>
<td>95–100</td>
</tr>
<tr>
<td>HSP70</td>
<td>Positive</td>
<td>Negative</td>
<td>40–60</td>
<td>95–100</td>
</tr>
<tr>
<td>GS</td>
<td>Diffuse positive</td>
<td>Patchy/focal</td>
<td>~80</td>
<td>~50</td>
</tr>
<tr>
<td>PCNA or Ki-67</td>
<td>High</td>
<td>Low</td>
<td>~90</td>
<td>~60</td>
</tr>
</tbody>
</table>

Abbreviations: GPC3, glypican 3; GS, glutamine synthetase; HSP70, heat shock protein 70; PCNA, proliferative cell nuclear antigen.
Focal nodular hyperplasia (FNH)

10 times more common than HCA

Women between 30-50 years of age

Develop in the context of hepatic venous outflow obstruction including Budd-Chiari syndrome

Macroscopy shows solitary, discrete, rounded mass, pale, with well-deliniation from background normal liver

Frequently with central scar
Macroscopy FNH

Solitary, discrete, rounded mass, pale, with well-delination from background normal liver, frequently with central scar
Microscopy FNH

Fibrous septa contain often large, dystrophic arteries with thick walls

Benign hepatocellular nodules arranged in plates no more than two cell thick

Maplike pattern of glutamine synthetase
Advances precancerous lesions in the liver
Tommaso L et al., Best Practice and Research Clinical Gastroenterology, 2013


Hepatocellular Carcinoma