Pathological classification of Hepatobiliary tumors

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Tumours of the liver and intrahepatic bile ducts: Introduction

Epithelial tumours

Benign hepatocellular tumours
- Focal nodular hyperplasia of the liver
- Hepatocellular adenoma

Malignant hepatocellular tumours and precursors
- Hepatocellular carcinoma
- Hepatoblastoma

Benign biliary tumours and precursors
- Bile duct adenoma
- Biliary adenofibroma
- Biliary intraepithelial neoplasia (See chapter 9)
- Intraductal papillary neoplasm of the biliary ducts (See chapter 9)
- Mucinous cystic neoplasm of the liver and biliary system

Malignant biliary tumours
- Intrahepatic cholangiocarcinoma
- Combined hepatocellular-cholangiocarcinoma and undifferentiated primary liver carcinoma
- Hepatic neuroendocrine neoplasms

9. Tumours of the gallbladder and extrahepatic bile ducts

Tumours of the gallbladder and extrahepatic bile ducts: Introduction

Epithelial tumours

Benign epithelial tumours and precursors
- Pyloric gland adenoma of the gallbladder
- Biliary intraepithelial neoplasia
- Intracholecystic papillary neoplasm (formerly intracytic / intraductal papillary neoplasm)
- Intraductal papillary neoplasm of the biliary ducts

Malignant epithelial tumours
- Carcinoma of the gallbladder
- Carcinoma of the extrahepatic bile ducts
- Neuroendocrine neoplasms of the gallbladder and bile ducts
Inflammatory myofibroblastic tumour

Mesenchymal tumours

Leiomyoma
Leiomyosarcoma
Rhabdomyosarcoma

Smooth muscle and skeletal muscle tumours

Haemangioma
Epithelioid haemangioendothelioma
Kaposi sarcoma
Angiosarcoma

Vascular and perivascular tumours

PEComa, including angiomyolipoma
Mesenchymal hamartoma of the liver
Calcifying nested stromal-epithelial tumour
Embryonal sarcoma of the liver

Leukaemia and myeloproliferative disease

Acute leukaemias
Hairy cell leukaemia
Chronic leukaemias
Chronic myeloproliferative disorders and myelodysplastic syndromes
Myelomatosis/multiple myeloma

Lymphomas and lymphoreticular neoplasms

Hodgkin lymphoma
Non-Hodgkin lymphoma
B-cell lymphomas
T-cell lymphomas
Primary hepatic lymphomas
Hepatosplenic T-cell lymphoma
Follicular dendritic cell tumours
Other primary hepatic lymphomas

Metastatic tumours
Focal Nodular Hyperplasia (FNH)

- In 80% of cases, young women, rarely in men or children
- Solitary in 80% of cases
- Most are asymptomatic, incidental findings
- Presence of unusually large vessels suggests that FNH is a nonspecific response to focally increased blood flow
- Outflow obstruction/congestive injury: parenchymal collapse and fibrosis, arteriovenous shunting, and loss of portal veins and ducts
- Increased ANGPT1:ANGPT2 ratio
- β-catenin pathway is activated
Focal Nodular Hyperplasia (FNH)
Hepatocellular adenoma (HCA)

- Benign, Monoclonal
- About 85% of HCAs occur in women of childbearing age
- Rare in children, men, > 65 years.
- Abdominal pain, palpable mass, or hemorrhage; incidental
- Single or multiple
- ≥ 10, known as adenomatosis
- Transformation to hepatocellular carcinoma (HCC) is uncommon (4–8%) and occurs mainly in men
- Risk varies with HCA subtype and is higher in some clinical settings (glycogenosis, AAS use, vascular diseases)

<table>
<thead>
<tr>
<th>Subtype (frequency, %)</th>
<th>Molecular</th>
<th>Characteristic features</th>
<th>Histopathological</th>
<th>Immunohistochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1A-inactivated HCA</td>
<td>HNF1A inactivating mutations (germinal 10%, somatic 90%)</td>
<td>Female, obesity, MODY3, adenomatosis</td>
<td>Diffuse steatosis</td>
<td>L-FABP expression loss</td>
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<tr>
<td>Inflammatory HCA</td>
<td>gp130/L6ST, FRK, STAT3, GNAS, JAK1 mutations</td>
<td>Obesity, metabolic syndrome, alcohol, oral contraceptives</td>
<td>Sinusoidal dilatation, Vascular proliferation</td>
<td>SAA, CRP expression</td>
</tr>
<tr>
<td>β-catenin-activated HCA (10%)</td>
<td>CTNNB1 exon 3 activating mutations</td>
<td>Male, young age, anabolic steroids, glycogen storage disease, increased risk of HCC transformation</td>
<td>Cytological and architectural atypia</td>
<td>Nuclear β-catenin expression</td>
</tr>
<tr>
<td>β-catenin (exon 3)-activated HCA (7%)</td>
<td>CTNNB1 exon 7 or 8 activating mutations</td>
<td>Low risk of HCC transformation</td>
<td></td>
<td>Absent/rare nuclear β-catenin expression</td>
</tr>
<tr>
<td>β-catenin (exon 7,8)-activated HCA (3%)</td>
<td>gp130/L6ST, STAT3, FRK, GNAS, JAK1 mutations + CTNNB1 exon 3 or 7/8 mutations</td>
<td>Similar to inflammatory HCA</td>
<td>Similar to inflammatory HCA</td>
<td>SAA, CRP expression</td>
</tr>
<tr>
<td>β-catenin-activated inflammatory HCA (5%–10%)</td>
<td>INHBE-GLI1 fusion, resulting in sonic hedgehog pathway activation</td>
<td>Obesity, hemorrhage</td>
<td>Hemorrhage</td>
<td>PTGDS, ASS1</td>
</tr>
<tr>
<td>Unclassified HCA (&lt;7%)</td>
<td>Unknown</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

HCA, hepatocellular adenoma; MODY3, maturity-onset diabetes type 3; L-FABP, liver fatty acid binding protein; SAA, serum amyloid A; CRP, C-reactive protein; HCC, hepatocellular carcinoma; GS, glutamine synthetase; PTGDS, prostaglandin D2 synthase; ASS1, argininosuccinate synthase 1.
• HNF1A-inactivated HCA with loss of LFABP
• Diffuse strong glutamine synthetase suggesting strong β-catenin activation
  • SAA staining
Hepatocellular carcinoma (HCC)

- Incidence is increasing steadily over the past two decades
- Currently ranks fifth most common cancer in men and seventh in women
- Major risk factors: HBV, HCV, chronic alcohol consumption, and NAFLD
- Majority detected at a clinically advanced stage
- Hepatocarcinogenesis is a multistep process of malignant transformation of hepatocytes through the sequential accumulation of multiple genomic and epigenomic alterations.
- HCC is a histologically and genetically diverse cancer
- Several new pathologic subtypes have been reported recently and new underlying genetic alterations have been described.
- Histological growth patterns are related to molecular alterations and oncogenic pathways.
International consensus group for hepatocellular neoplasia classification of small hepatocellular lesions

- **Small Hepatocellular lesions**
  - Dysplastic foci (<1mm)
    - Large cell change
    - Small cell change
  - Dysplastic nodules
    - Low grade dysplastic nodule
  - Small HCC (≤2cm)
    - Early HCC
    - Progressed HCC
Trabecular growth pattern
Pseudoacini growth pattern
Solid sheets with pleomorphism and steatosis
Macrotrabecular-Massive (MTM-HCC)

- HBV
- High AFP levels
- Very aggressive phenotype
- Frequent satellite nodules and vascular invasion
- Angiogenesis activation is a hallmark feature
- Both angiopoietin 2 and VEGFA overexpression
Lymphoepithelioma-like Hepatocellular Carcinoma (LEL-HCC)/Lymphocyte rich hepatocellular carcinoma
- Well to moderately differentiated
- Upregulation of interleukin-6
- C-reactive protein
CK19 Positive HCC (Proginator subtype)
CTNNB1 encodes b-catenin
- Key transducer Wnt signaling pathway
- Regulates liver physiology
- Inhibited
- Mutations, stabilization and nuclear accumulation
- Enhance proliferation and survival
Sarcomatoid HCC
Vessels Encapsulating Tumor Clusters (VETC) Is a Powerful Predictor of Aggressive Hepatocellular Carcinoma

Salvatore Lorenzetti Renne 1,2, Ha Young Woo 2, Larisa Miele 2, Natalia Rezimi 1, Hiroshi Yone 2, Matteo Donadus 3,4, Luca Vigano 2,5, Jun Akita 3, Hye Sun Lee 3, Byungjin Rhee 2, Young Myun Park 2, Massimo Roccia 2,5, Luca Di Tommaso 1,5

Vessels That Encapsulate Tumor Clusters (VETC) Pattern Is a Predictor of Sorafenib Benefit in Patients with Hepatocellular Carcinoma

Jian-Hong Feng 1, Li Xu 2, Li-Pu Shang 2, Chi Shu Peng 2, Jia Cong 2, Yuan-Qing Tang 2, Hai Liu 3, Chao Xiong Lu 3, Jie Lin Zheng 3, Yan-Lin Zhang 3, Zheng-Guo Zhou 2, Jing Xu 2, Lin Lin Zheng 2, Min-Shen Chen 2, Shi-Mei Zhuang 3, 4, 5
Clinical, biological, pathological and molecular features of main HCC subtypes

Most frequent alterations: TERT promoter, CTNNB1 and TP53 mutations

Molecular and histological correlations in liver cancer

Julien Calderaro 1, Marianne Ziol 2, Valerie Paradis 3, Jessica Zucman-Rossi 4
Molecular subclasses and oncogenic pathways of hepatocellular carcinoma (HCC) with clinicopathological correlates
Fibrolamellar HCC (FL-HCC)

- Rare and unique histologic subtype with a predilection for adolescent and young adults
- Without underlying liver disease
- Mostly solitary, large and well circumscribed grossly, with a yellow tan to greenish coloured cut surface and areas of central scarring
- Tumour cells are large polygonal with abundant eosinophilic granular cytoplasm, centrally located nuclei with vesicular chromatin, and prominent nucleoli
- Dense bands of intratumoral fibrosis arranged in lamellar (parallel arrangement) pattern separates the trabeculae and clusters of tumour cells
- Recurrent-specific translocation PRKACA-DNAJB1
- Immunophenotyping: Positivity of CD68 and CK-7 (biliary lineage) apart from markers of hepatic differentiation (Arginase 1, Hep-par1 and albumin mRNA as detected by in situ hybridization).
- Both FISH or RT-PCR are available now to detect DNAJB1-PRKACA fusion
Fibrolamellar HCC
Fibrolamellar HCC
Cholangiocarcinoma

• Heterogeneous group of highly aggressive cancers
• May arise anywhere within the biliary tree
• Wide geographical variation
• Most cases (70%) are sporadic, occurring without any probable or known risk factors
• Intrahepatic, perihilar and distal based on their anatomical location
• Significant turning point in iCCA treatment: identification of IDH mutations and FGFR fusions
• Can be targeted with currently available therapies.

Mass forming Intrahepatic Cholangiocarcinoma
<table>
<thead>
<tr>
<th></th>
<th>Large duct type</th>
<th>Small duct type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Proximal to hepatic hilum</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Risk factors</td>
<td>PSC, Liver fluke infection, Hepatolithiasis</td>
<td>Chronic liver disease, viral hepatitis</td>
</tr>
<tr>
<td>Gross features</td>
<td>Periductal infiltrating, Mixed pattern</td>
<td>Mass forming</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>BilIN, IPNB, ITPN</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pathology</td>
<td>Large, widely spaced glands, Columnar with mucin production, desmoplastic stroma</td>
<td>Small tubules, fused or anastomosing glands, cuboidal to low columnar; central scarring, minimal to no mucin</td>
</tr>
<tr>
<td>Perinipheral invasion</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Lymphovascular invasion/lymph node metastases</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Tumour border</td>
<td>Infiltrative</td>
<td>Expansile or pushing, rarelyinfiltrative</td>
</tr>
<tr>
<td>Immunohistochemical features</td>
<td>S100P and TFF1</td>
<td>CD56, N-cadherin, CRP</td>
</tr>
<tr>
<td>Molecular alterations</td>
<td>KRAS and GNAS mutations, COX2 upregulations</td>
<td>IDH1/IDH2 and BRAF mutations, FGFR2 fusion</td>
</tr>
</tbody>
</table>

BilIN: Biliary intraepithelial neoplasia; CRP: C-reactive protein; IPNB: Intraductal papillary neoplasm of the bile duct; ITPN: Intraductal tubulopapillary neoplasms; PSC: Primary sclerosing cholangitis.

**Ivosidenib, an IDH1 inhibitor**

**Infigratinib, an FGFR2 inhibitor**

Adenosquamous carcinoma

Neuroendocrine tumours

• Extremely rare
• 0.01%
• Small (generally < 2 cm)
• Greyish-white or yellow submucosal nodules
• Prognostic data is highly limited because of the rarity of these tumours;
• Prognosis seems to be similar to that of NETs in the GI tract
Combined hepatoccholangiocarcinoma

- Both hepatocytic and biliary differentiation.
- Pathological definition has evolved over time.
- Primarily based on morphology using routine staining.
- Molecular evidence supports clonal nature of cHCC-CCA.
- Genetic alterations observed in HCC and/or iCCA.
- Morphological diagnosis of cHCC-CCA is challenging.
- cHCC-CCA’s cell of origin remains an area of active research.
- Prognosis is generally worse than HCC, and similar to that of iCCA.
- Resection with lymph node dissection is unfortunately the only curative option for patients with cHCC-CCA.

Intermediate cell carcinoma
PRECURSORS LESIONS OF CHOLANGIOCARCINOMA
Biliary epithelial neoplasia
Intraductal papillary neoplasms of the bile duct

• Uncommon tumours
• Incidence of IPNB ranges widely by geographic locations—singular or multiple
• Polypoid, exophytic masses arising in dilated bile ducts
• IPNBs can be classified into subtypes based on the nature of the neoplastic epithelium: pancreatobiliary-type, intestinal-type, gastric-type, and oncocytic-type
• High risk of malignancy, with studies reporting an invasive component in up to 80% of cases
• Type 1, or pancreatic type
• Type 2, or nonpancreatic type

Hum Pathol. 2021 Jun;112:70-83
Intraductal papillary neoplasms of the bile duct
• IPNB-associated cholangiocarcinoma with mucinous (colloid) morphology
Intraductal tubulopapillary neoplasms of the bile duct
Mucinous cystic neoplasm
Bile duct adenoma
Paediatric Malignant Liver Tumours

- Extremely rare accounting for only 1% of all pediatric malignancies
- >60% are hepatoblastomas (HBs), remaining HCCs and the very rare embryonal sarcomas of liver
- Recent increase in the incidence of HBs, probably in relation with the increased survivors of premature birth
- Predisposition to develop HB with birth weight lower than 1500 g
- HB are typical of the first 3 years of life and can be congenital.
- Most are sporadic
- Subset of HB occurs in the context of familial syndromes, such as Beckwith–Weidemann syndrome, Simpson–Golabi–Behmel syndrome, Sotos syndrome, familial APC, and trisomy 18
Hepatoblastoma (HB)

- Primary hepatoblast or undifferentiated multipotent progenitor cells
- Wnt/beta catenin signaling pathway
- Two subclasses identified in gene expression profiling
- Genetically stable and unstable
- Single (80%) or multiple nodules
- Cut surface appearance depends on tumor character (Tan, soft, gritty)
- Epithelial and mixed epithelial and mesenchymal components
- Hemorrhage, necrosis
- HB mimics the developing fetal or embryonal liver histologically

Fetal Epithelial pattern
Hep-par1 & Glypican 3, Glutamine synthetase, Cyclin D1
Crowded fetal (CF) HB
(mitotically active fetal)
Embryonal HB

- Embryonic stage of liver (6-8 weeks) development.
- Cells have high N/C ratio, scant cytoplasm with indistinct borders, and a large, angulated to oval nucleus with a prominent nucleolus.
- Cell density is also increased.
- Frequent mitoses.
- Necrosis may be seen.
- Glandular, acinar or pseudorosette.
- Serpentine and microcystic pattern can be seen.
- Myxoid change may be noted in the microcystic areas.

Macrotrabecular (MT) HB

- <5%, Thick trabeculae ($\geq 5$-to $\geq 20$-cell-thick –trabeculae)
- The cells can show fetal or embryonal morphology or pleomorphic cells or cells resembling HCC
Small cell undifferentiated (SCUD)
Post chemotherapy
Hepatocellular Neoplasm-NOS

- New provisional category that includes tumours previously designated as transitional cell liver tumours
- Represent lesions with intermediate or combined biology
- Histological features of both HBL and carcinoma (HCC)
- Tumour cells may also be monotonous and resemble crowded fetal cells.
- May have macrotrabecular arrangement
- HCN-NOS carry β-catenin (CTNNB1) mutations as well as other mutations seen in HCC, such as TERT promoter mutations,
- Poor prognosis
- More frequent in children older than 8 years
- Aggressive associated with poor outcome.
- Currently treated as Group D high-risk HBL
Pediatric HCC

~20% of all malignant pediatric liver tumors

Clinically challenging

Often presenting as large, unresectable lesions, typically in older children/adolescents.

2 groups

One is associated with underlying metabolic and/or genetic diseases

HT, BSEP, MDR 3 & TJP2 deficiency, and less often in BA and viral hepatitis.

Other group with no evidence of chronic liver disease
Pediatric HCC
Hepatocellular Carcinoma in Paediatric Patients with Alagille Syndrome: Case Series and Review of Literature

Joseph J. Valentine, Narasir Srinivasan, Mukul Vij, Mettu Srinivas Reddy, Mohamed Reis

Paediatric hepatocellular carcinoma in tight junction protein 2 (TJP2) deficiency

Mukul Vij, Narasir Srinivasan, Mettu Srinivas Reddy, Srinivas Sathararajasekar, Mohamed Reis

Hepatocarcinogenesis in multidrug-resistant P-glycoprotein 3 deficiency

Mukul Vij, Narasir P. Srinivasan, Mettu Srinivas Reddy, Sanjay Govil, Mohamed Reis
Malignant Rhabdoid tumour (MRT)

• Rare aggressive malignancies most commonly found in kidneys and central nervous system.
• MRT involving liver is extremely rare with dismal prognosis
• MRT of the liver most commonly occurs in infancy (median age 8 months)
• Characterized by mutations involving loss/deletions in SMARCB1/INI1 gene encoding the SWI/sucrose non-fermenting ATP dependent chromatin remodeling complex, involved in tumor suppression
• Varying micro architectural patterns including myxoid, myxohyaline, cord-like stranding, pseudo-alveolar, vague spindling, clear-cell and small cell undifferentiated varieties
• Kohashi et al reclassified pediatric rhabdoid tumors into conventional type, atypical teratoid/rhabdoid type, and small cell types
• Heterogenous immune profile, with the expression of neural, mesenchymal, and epithelial markers
Hepatic Rhabdoid tumour
Cavernous Hemangioma
Hepatic haemangioma (HCH & HIH)
Epithelioid haemangioendothelioma

- Rare vascular tumor
- Epithelioid and histiocytoid vascular endothelial cells in myxoid or fibrotic stroma
- Can arise in multiple locations
- In liver, presents on imaging as an incidental finding of multifocal, heterogeneously enhancing nodules in both lobes
- Presents clinically with nonspecific abdominal symptoms.
- Stains positive for vascular markers, factor VIII–related antigen, CD31, and CD34
- CAMTA1-WWTR1 fusion, most common genetic abnormality
- YAP-TFE3 fusions rare

Epithelioid haemangioendothelioma

Mesenchymal hamartoma

- Benign tumour
- Well-circumscribed, multilocular or multicystic mass
- Third most common hepatic tumour in childhood
- 85% of affected children present before the age of 3 years
- Chromosomal rearrangements involving chromosome 19q13.4
- Loose connective tissue and epithelial bile ducts in varying proportions arranged in lobulated islands

Hepat Oncol. 2020 Apr 7;7(2):HEP19.
Embryonal sarcoma

- Malignant mesenchymal tumour
- Heterogeneous morphology and no specific differentiation pattern
- Chromosome 19 microRNA cluster (C19MC), a potential oncomir
- Variable cellularity
- Medium to large spindle and stellate cells embedded in a myxoid stroma
- Bizarre cells
- t(11;19)(q13;q13.4) translocation
- TP53 mutation

Hepat Oncol. 2020 Apr 7;7(2):HEP19.
INFLAMMATORY MYOFIBROBLASTIC TUMOUR (IMFT)

• Distinctive fibroblastic/myofibroblastic neoplasm of intermediate biological potential
• Prominent inflammatory infiltrate, chiefly lymphocytes and plasma cells
• TKR gene rearrangements, most often involving the ALK locus at 2p23, with diverse fusion partners
• ~5% of IMFTs harbour ROS1 gene fusions; other rare gene fusions involve NTRK3, PDGFRB, and RET
• ALK-negative tumours may have a higher risk of metastases
Hepatobiliary Rhabdomyosarcoma

• Rare lesion
• 0.5% of pediatric RMS and 0.04% of all pediatric malignancy
• Commonly misdiagnosed
• Most common malignant cause of obstructive jaundice in pediatric patients
• Biliary tract had been classified as “favorable site” in recent Children’s Oncology Group (COG) studies
• Assumed to have a better prognosis, thus requiring a less aggressive therapy

Front Oncol. 2021 Sep 30;11:701400.
PEComa/Angiomyolipoma

- Mesenchymal neoplasm
- Composed of distinctive, predominantly epithelioid cells
- Angiomyolipoma (PEComa subtype) that also contains adipocytes and thick-walled, tortuous blood vessels
- Variable expression of smooth muscle and melanocytic markers
- AML mostly sporadic; 5–10% with tuberous sclerosis
- TSC2 mutations
- TFE3 gene rearrangements
Epstein Barr Virus Associated Smooth Muscle Tumor (EBV-SMT)

Thank you