### Hepatocellular Lesions

**Note:** All of these lesions stain with Hepatocellular stains (Hepar-1 and Arginase)!
Also, canalicular staining with CD10 and pCEA. Cytoplasmic TTF-1. Negative MOC-31.

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#### Macregenerative Nodule

An unusually large regenerative nodule (often >1 cm) that develops in the setting of **cirrhosis**.

Hyperplastic liver parenchyma. Plates may be slightly thickened (usu. 1-2 cells thick, maybe focally 3). Have **normal constituents** (bile ducts, arteries, veins, etc...). **No atypia** (Unless dysplastic).

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#### Focal Nodular Hyperplasia (FNH)

**Not a true neoplasm; “Focal Cirrhosis”**

Regenerative hyperplastic response of hepatocytes secondary to vascular abnormalities

Very common

Well-circumscribed with **central stellate scar** with fibrous septae with entrapped vessels, bile ducts, and inflammatory cells

Normal plate thickness. No true portal tracts.

“Map-like” staining with glutamine-synthetase

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#### Glutamine Synthetase IHC:

- **Normal, pericentral staining**

**Strong “Map-like” staining**

**Note:** In cirrhosis it shows weak, patchy periseptal staining.

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#### Hepatocellular Adenoma

**Subtypes:**

- **Inflammatory/Telangiectatic** (~45%) → Stain with serum amyloid A and CRP; associated inflammatory infiltrate, peliosis, and bile ductular reaction in fibrous septae. Transformation to HCC occurs.

- **B-catenin activated** (~15%) → Nuclear B-catenin (focal), Diffuse, strong glutamine synthetase. Highest risk of malignant transformation

- **HNF1α-inactivated** (~30%) → Loss of LFABP staining. Associated with adenomatosis (>10 adenomas). Very low risk of transformation.

- **Unclassified** (~10%) → None of the above (~10%)

**Benign liver neoplasm.**

Assoc. with oral contraceptives/steroids.

**Risk of transformation to HCC and/or bleeding/rupture**

Benign-appearing hepatocytes, No significant atypia.

**Normal plate thickness (1-2 cells thick)**

Unpaired arteries, absent bile ducts

No mitoses

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**Unpaired arteries**

**Normal Liver**
**Hepatocellular Lesions**

### Hepatocellular Carcinoma

**Malignant** tumor with hepatocellular differentiation

- Often occurs in setting of **cirrhosis** (associated with chronic liver damage such as viral hepatitis, EtOH, and NASH)
- **Dx** often made **clinically** (Radiology + ↑ AFP = HCC)
- Treat often with embolization, resection, or transplant

**Widening of hepatic plates (>2 cells thick)**

- Absent portal tracts, often unpaired arteries.
- Architecture and cytologic atypia varies and includes pseudoacini/pseudogland formation and wide trabeculae. Often bile production by tumor cells.

**Staining:**

- **Reticulin** → Widening of hepatic plates
- **CD34** → Diffuse sinusoidal (“capillarization”)
- **Glypican-3** → +/- (but negative in benign liver, Positive staining supports malignancy)

### Variants:


Classically thought to be better prognosis, but this is likely mostly due to demographics (younger, non-cirrhotic patients)

**Steatohepatitic HCC** → Assoc with Hep C with NASH.

Macrovesicular steatosis, ballooning degeneration, M-D bodies. Can be hard to recognize on biopsy (esp. if background NASH)!

**Macrotrabecular-Massive HCC** → Thick trabeculae coated by endothelial cells and surrounded by vascular space. Aggressive subtype with high AFP and TP53 mutations or FGF19 amplification.

### Hepatoblastoma

**Most common liver tumor in Children.**

**Malignant.** Assoc. w/ Beckwith-Wiedmann

- Shows a variety of epithelial (e.g., fetal and embryonal) and mesenchymal cell types (“teratoid”) recapitulating hepatic ontogenesis.

- Frequent β-Catenin mutations
- Nuclear localization by IHC → worse prognosis
Biliary Lesions

Note: The epithelium in all of these lesions stain with CK7, CK19, and MOC31 (among other stains). These lesions are negative for hepatocellular stains (Hepatitis-1, Arginase, and Glypican-3).

**Bile Duct Adenoma**

Benign bile duct proliferation
Usu. <1 cm, subcapsular, and well-circumscribed.
Small, uniform, small ducts with cuboidal cells and regular nuclei.
Biliary adenofibroma → more complex epithelial growth with abundant fibroblastic stromal components
Clinically, may mistake intraoperatively for a metastasis

**Bile Duct Hamartoma**

aka Von Meyenburg Complex

Benign, may be multiple.
Usu. small (several mm)
Irregular to round bile dilated bile ducts
Associated with fibrous/hyalinized stroma
Lumens contain bile and proteinaceous material

**Adenocarcinoma arising from intrahepatic bile ducts**

Inflammatory disorders can predispose (e.g., PSC or liver fluke infection). Must clinically distinguish from metastasis as overlap.
Usu. tubular pattern. Sometimes large ducts. Often sclerotic center.
Non-specific IHC profile, but (+) Albumin ISH supports intrahepatic

**Cholangiocarcinoma**

**Combined Hepatocellular - Cholangiocarcinoma**

A single tumor with morphologically distinct areas of HCC (Arginase and Hepar +) and Cholangiocarcinoma (CK7+).
Treated and prognosis similar to cholangiocarcinoma (Worse than HCC, No transplantation).

**Additional DX:**

**Intraductal Papillary Neoplasms** → Similar to IPMNs in the Pancreatic duct. Can progress to cholangiocarcinoma.

**Mucinous Cystic Neoplasms** → Just like in the pancreas! Ovarian-type stroma surrounding mucinous epithelium.
Vascular Lesions

Note: All of these lesions stain with endothelial markers, including CD31, ERG, and FLI-1.

**Cavernous Hemangioma**

*Most common benign tumor of the liver.*
Thought to be malformations and non-neoplastic.
*Often asymptomatic and diagnosed radiographically.*
More common in females
Fibrous septae lined by single layer for flat endothelial cells.
Can thrombose and calcify.

**Epithelioid Hemangioendothelioma**

Endothelial tumor of **low-grade malignancy**.
Eosinophilic, slightly epithelioid cells with **signet ring-like** features representing intracytoplasmic lumina (often contain RBCs). Associated dense fibrous stroma.
Often have intravascular papillary growth and infiltrate sinusoidal spaces at edge of lesion
Translocation: **WWTR1-CAMTA1 fusion**
Sometimes focally positive for cytokeratins by IHC

**Angiosarcoma**

*Malignant* endothelial tumor. Most common liver sarcoma.
Spindled to epithelioid cells. **Variously atypical** endothelial cells with **multilayering and mitoses**. Anastomosing spaces.
Like to grow along pre-existing vascular spaces.
Usually **large and/or multifocal**.
Assoc. with exposure to Vinyl Chloride or Thorothrast.
Poor prognosis.

**Other Tumors:**

**PEComa/Angiomyolipoma** → *Benign* tumors, just like in the kidney! Think of this if you see **fat**.

**Embryonal Sarcoma** → Malignant tumor composed of undifferentiated mesenchymal cells. Usu. older children. Loose myxoid tissue with immature and giant cells. Characteristic **eosinophilic intracellular hyaline globules**. Can rupture. Previously bad prognosis, but improving.