Primary malignant liver tumors

**Hepatocellular**

- Hepatoblastoma (HB) (epithelial variants)
- Hepatocellular carcinoma (HCC)
- Premalignant lesions
  - Dysplastic foci, characterized by cytological small cell change.
  - Dysplastic nodules (low grade and high grade)

**Biliary**

- Cholangiocarcinoma
- Premalignant lesions

**Mixed hepatocellular and biliary**

- Combined hepatocellular cholangiocarcinoma

**MIXED EPITHELIAL/MESENCHYMAL OR UNCERTAIN ORIGIN**

- Hepatoblastome (HB) mixed Epithelial and mesenchymal
- Teratoid HB
- Malignant rhabdoid tumor
  - INI– (documented INI mut)
  - INI+
- Nested epithelial–stromal tumor

**MESENCHYMAL TUMORS**

**Germ Cell Tumor (GCT)**

- Yolk sac tumor

**Liver cysts**

- Congenital
- Acquired: bacterial, hydatid, amoebic.
- Blood: hematoma
- Bile: biliary atresia, inspissated bile lake
Wnt/B-catenin signaling

- **B-catenin protein** is encoded by CTNNB1 gene.
- **B-catenin has a dual function protein:**
  - Regulate the coordination of cell-cell adhesion
  - Gene expression.

- Mutation and overexpression of B-catenin are associated with many cancers (HCC, breast, colorectal, lung, ovarian and endometrial cancers).
- **Coding at exon 3** of CTNNB1 is responsible for Wnt ligand-binding site.
  - Wnt ligand-binding site is required for **B-catenin degradation**.
- **Mutations** or **deletions** clustered in exon 3 of CTNNB1 → B-catenin cytoplasmic accumulation.
### Histologic Subtypes Hepatoblastoma

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<thead>
<tr>
<th>Epithelial</th>
<th>Subtype/Definition</th>
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<tbody>
<tr>
<td>- <strong>Fetal</strong></td>
<td>Well differentiated with minimal mitotic activity</td>
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<tr>
<td></td>
<td>Crowded or mitotically active</td>
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<td>Pleomorphic, poorly differentiated</td>
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<tr>
<td></td>
<td>Anaplastic, abnormal mitosis</td>
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<tr>
<td>- <strong>Embryonal</strong></td>
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<td>- <strong>Macrotrabecular</strong></td>
<td>Fetal or embryonal growing in clusters of &gt;5 cells between sinusoids</td>
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<td>- <strong>SCU “Small cell undifferentiated”</strong></td>
<td>Poor prognosis, especially in infants, low serum AFP, fail to express INI</td>
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<td>- <strong>Cholangioblastic</strong></td>
<td>The epithelial cells resemble bile duct components</td>
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### Mixed

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<tr>
<td>- <strong>Stromal derivatives</strong></td>
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<tr>
<td>- <strong>Teratoid</strong></td>
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### Clinical picture

- Asymptomatic right hypochondriaum or epigastric mass.
- Pain due to tumor rupture.
- Constitutional symptoms (weight loss).
- Obstruction of hepatic veins (ascites), portal veins (portal hypertension), biliary tree (jaundice).
**Indications:**

Unresectable HB due to Multifocal PRETEXT IV (+F, -M)

- It is a clear indication for liver transplantation especially in the presence of extensive multifocality regardless of results of neoadjuvant chemotherapy.

- Avoid the temptation to intensify chemotherapy to avoid transplant.

- Radiographic clearance of tumor nodules from one liver section should not distract from transplant because of a high probability of persistent microscopic viable neoplastic cells.

**Solitary PRETEXT IV (-F, -M)**

- Large solitary PRETEXT IV → neoadjuvant chemotherapy → if
  - POST-TEXT II → extended hemihepatectomy.
  - POST-TEXT IV (-M) → liver transplant

**PRETEXT III (+P, +V)**

- Tumor location so close to both main portal vessels at the hilum of the liver and/or all three hepatic veins that it is unlikely that a tumor free excision plane will be achieved without risking life-threatening hemorrhage.

- If major vascular invasion doesn’t clear with neoadjuvant chemotherapy → liver transplant.
**With metastasis at diagnosis**

*Chemotherapy* followed by reassessment of surgical resectability.

- If the primary tumor and extrahepatic disease is *resectable* after chemotherapy, *surgical resection* followed by *additional chemotherapy*.
- If extrahepatic disease is *in complete remission* after chemotherapy and/or surgery, but the primary tumor remains unresectable, *orthotopic liver transplantation*.
- If extrahepatic disease is *not resectable* or the patient is *not a transplant candidate*, *additional nonstandard chemotherapy* such as irinotecan, high-dose cisplatin/etoposide, or continuous-infusion doxorubicin have been used; [Level of evidence: 3iiA], TACE, or radiation therapy.

The standard combination chemotherapy regimen is *four courses* of cisplatin/vincristine/fluorouracil or doxorubicin/cisplatin followed by *attempted complete tumor resection*. If the tumor is completely removed, *two postoperative courses* of the same chemotherapy are usually given.

High-dose chemotherapy with stem cell rescue *does not* appear to be more effective than standard multiagent chemotherapy.

The outcome for metastatic HB at diagnosis is grim, but long-term survival and cure is possible. Survival rates at 1-5 years range from *20% to 60%*.  

**Evidence**

1. The SIOPEL-1 study employed a well-tolerated regimen of doxorubicin/cisplatin chemotherapy.
   - About *50%* of patients with metastases at presentation survived 5 years after diagnosis. Half of these survivors developed progressive disease that was successfully treated with surgery and other interventions.

2. In rare cases, chemotherapy has eradicated pulmonary metastases and eliminated multinodular tumor foci in the liver. In the SIOPEL-3HR study, patients with metastatic disease were treated with intensive platinum- and doxorubicin-based multidrug chemotherapy.
   - This regimen induced complete regression in approximately *50%* of patients, with subsequent 3-year EFS of *56%*.

3. A prospective feasibility trial (SIOPEL-4 [NCT00077389]) of dose-dense, cisplatin-based chemotherapy and radical surgery evaluated 62 patients with high-risk hepatoblastoma.[Level of evidence: 3iiDi]
   - This treatment regimen resulted in a 3-year EFS of **76%** and 3-year OS of **83%**.
   - Of 37 patients with distant metastases on the study, 27 (78%) were disease free at 3 years.
No staging or grading system has been found that accurately predicts prognosis in pediatric HCC.

Prior trials in USA have used the traditional Evans staging system.

Current discussions describing the extent of tumor involvement of the liver are based upon PRETEXT.

The overall survival of children with HCC remains low.

Surgical resection is the most important prognostic factor.

Higher rate of tumor response to chemotherapy was seen in pediatric patients more than adults (this may be due to de novo tumors that develop in livers without cirrhosis).

Chemotherapy:

- Neoadjuvant:
  - Aim: to ↑ rate of resectability.
  - Types: cisplatin, carboplatin, doxorubicin

- Adjuvant:
  - For stage I→ unknown benefit.

- Gemcitabine and oxaliplatin are effective in adult patients.

- Anti-angiogenesis (sorafenib) in combination with doxorubicin.
  - ↑ time to tumor progression (median 5.5 months vs 2.8m).
  - ↑OS (10.7 months vs 7.9 months).
- **Indications**: (bridge – conversion – palliation)

  - A bridge to liver transplantation (waiting for a donor).
  - An attempted conversion of no operable & systemically chemo resistant tumors to resectable one.
  - Palliation in children with large symptomatic tumors and uncontrolled metastatic disease.

**Portal venous embolization:**

- **Way**: the portal venous branch on the side of the tumor is cannulated percutaneously and polyvinyl alcohol & coils are inserted to induce portal vein occlusion.

- **Indications**: large tumors

- **Aim**:

  - Thrombosis of the embolized tumor
  - Compensatory hypertrophy of unharmed opposite liver lobe.

**Percutaneous ablative therapies** *(not well studied in children)*

- **Available methods**:

  - Percutaneous radiofrequency ablation (RFA)
  - Percutaneous ethanol injection (PEI)
  - Cryotherapy (cold injury by cryoprobe delivery of liquid nitrogen)

- **Indications**: for smaller-size tumors (<4cm)

- **Aim**: palliation than cure in advanced cases.

- **complications**: pain, fever, bleeding, tumor seeding, GIT perforation.
Pediatric rhabdoid tumors are more common in the kidney & brain.
Liver, mediastinum, and soft tissue do occur.
If the primary rhabdoid in the liver, difficult to distinguish histologically from SCU variant of HB (need INI1 expression evaluation).
It is a rare and locally aggressive tumor of the younger children.
The median age is 8 months.
It is chemo resistant (Vincristine, doxorubicin, cyclophosphamide, and ifosfamide)
The most important treatment goal is complete surgical excision.

It is a rare disease (30 cases have been reported).
Other names: ossifying stromal-epithelial tumor & desmoplastic nested spindle cell tumor.
Age range from 2 to 34 years (mostly in teens or early 20s).
65% of them were females.