Primary tumors of the liver are rarely seen in children, comprising only about 1% of childhood cancers.

Hepatic tumors are the third most common intra-abdominal malignancy in childhood, following Wilms and neuroblastoma. Hepatoblastoma and hepatocellular carcinoma are the two most common hepatic malignancies.

The mean age of children diagnosed with hepatoblastoma is 1 year, while that for children with hepatocellular carcinoma is 11 years. Clinical symptoms of hepatocellular carcinoma appear after age three.

Hepatocellular carcinoma (A – 1) differs from hepatoblastoma not only in age of occurrence, but also in cellular histology, resectability and response to multimodal therapy. Fibrolamellar carcinoma is a variant of hepatocellular carcinoma and is often correlated with good prognosis.

Risk Factors:

Hepatoblastoma is associated with (A – 2) several congenital predispositions and anomalies, such as familial adenomatous polyposis (FAP), inherited overgrowth syndromes such as Beckwith-Weidemann syndrome, and hemihypertrophy. Other anomalies associated with hepatoblastoma include dysplasic kidneys, hernias and Meckel’s diverticulum.

Clinical Signs and Symptoms:

Similar to Wilms tumors, most hepatoblastomas are found incidentally by the caretaker or by a health care provider, presenting as an asymptomatic abdominal mass, associated with abdominal distention and hepatic enlargement that is not often amenable to palpation. Hepatoblastoma is often unifocal with a predilection to the right lobe.

- Asymptomatic abdominal mass
- Pain and/or tenderness, especially in the upper right quadrant of abdomen
Hepatic Tumors: Hepatoblastoma

- Bulkiness or fullness in the upper right quadrant
- Rubbing sensation felt with hand over upper right quadrant
- Anorexia & weight loss
- Vomiting
- Fever
- Rupture or bleeding
- Osteopenia associated with back pain, refusal to walk, pathologic fractures of weight bearing bones.
- Anemia, thrombocytopenia, and leukocytosis.
- Congestive heart failure symptoms in cases of hepatic AV shunting.

**Diagnostic Workup:**

- Complete history of illness including duration, location, and intensity or pain; weight loss; fever; rupture or bleeding, activity levels, especially if osteopenia, anorexia and weight loss are present.
- Physical exam to check for bulkiness or fullness in upper right quadrant; rubbing sensation felt with hand over right-upper quadrant; refusal to walk or gait changes; presence of CHF symptoms if AV shunting is present.
- Abdominal ultrasound to determine whether mass is solid or cystic.
- Doppler evaluation to assess the patency of the inferior vena cava and hepatic veins.
- Abdominal and chest CT to assess extent of tumor involvement and its resectability; and to identify pulmonary metastasis
- MRI to further assess the tumor extent, vascular involvement and response to chemotherapy; more sensitive in assessment of tumor recurrence.
- Liver biopsy to make an accurate tissue diagnosis.
- Measurement of serum alpha-fetoprotein (AFP) level, a tumor marker that is usually highly elevated and that can be used to monitor tumor response to therapy and detect recurrence.
- Measurement of B-hCG, which is elevated in 3% of boys diagnosed with hepatoblastoma.
- Measurement of serum ferritin, which can be elevated with hepatoblastoma.

**Histology:**

Histologic types of hepatoblastoma include:

- Pure fetal: Either fetal or embryonal cells or both
- Epithelial-Mesenchymal: Mesenchymal and epithelial tissue
- Small cell undifferentiated (anaplastic): Sheets of small, undifferentiated cells with minimal cytoplasm and ovoid nuclei, sometimes resembling neuroblastoma cells.
- Macrotrabecular: Cells in this histologic type can be fetal,
Hepatic Tumors: Hepatoblastoma

embryonal or indistinguishable from adult hepatocarcinoma. Often associated with very poor prognosis.

Clinical Grouping of Malignant Hepatic Tumors:

<table>
<thead>
<tr>
<th>Designation</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Complete resection of the tumor</td>
</tr>
<tr>
<td></td>
<td>- wedge resection lobectomy</td>
</tr>
<tr>
<td></td>
<td>- extended lobectomy as initial treatment</td>
</tr>
<tr>
<td>Group II A</td>
<td>Tumors are rendered completely respectable by initial irradiation or chemotherapy</td>
</tr>
<tr>
<td>Group II B</td>
<td>Residual disease confined to one lobe</td>
</tr>
<tr>
<td>Group III</td>
<td>Disease involves both lobes of the liver</td>
</tr>
<tr>
<td>Group III B</td>
<td>Regional node involvement</td>
</tr>
<tr>
<td>Group IV</td>
<td>Distant metastasis, irrespective of the extent of liver involvement</td>
</tr>
</tbody>
</table>

The International Society of Pediatric Oncology (SIOP) developed a (A –3) pretreatment staging system that determines the clinical groups before surgical resection. The involved sectors of the liver are determined using computerized tomography (CT scan) or magnetic resonance imaging (MRI). The sectors are identified by the position of the tumor in relation to the main blood vessels and bile duct. Extra-hepatic lesions are also identified by adding the information to the chart.

Treatment of Hepatoblastoma:

Complete remissions and cures have been documented with combined use of surgery and chemotherapy.

Prior to the advent of efficient chemotherapy agents, the initial treatment included a complete resection of the primary tumor. However, the use of new, more efficient chemotherapy agents with minimal toxicities permits clinicians to delay and/or minimize surgical trauma through adjuvant chemotherapy.

The role of surgery includes open biopsy of the tumor to establish an accurate tissue diagnosis following a complete resection of the tumor. If complete resection is not possible or tumor reduction is necessary, a percutaneous needle biopsy can be performed.

Hepatic resection is often done by a thoraco-abdominal incision, which allows visualization of the structures. A sump tube and/or penrose drains are then placed into the liver bed to accommodate drainage.

In cases of pulmonary metastasis, a wedge resection can be done followed by chemotherapy. Liver transplantation is recommended for patients whose primary tumors are still not amenable to complete resection after preoperative chemotherapy.
Chemotherapy is currently as an adjuvant therapy for hepatoblastoma, both pre-operatively and post-operatively. Pre-operatively, chemotherapy is used to shrink tumors to make them more amenable to surgical resection.

Chemotherapy is usually prescribed 4 weeks after surgery, in cycles 3 to 4 weeks apart, in order to allow adequate regeneration of the liver tissues. Studies have also shown that following chemotherapy, complete regression of documented pre-operative metastatic lesions has occurred.

Effective hepatoblastoma chemotherapy agents include cisplatin (Platinol), vincristine (Oncovin), 5 FU (fluorouracil), doxorubicin (Adriamycin), cyclophosphamide (Cytoxan), carboplatin, and etoposide (VP-16).

Like chemotherapy, radiation therapy also limits liver regeneration, and for that reason, radiation therapy has a limited role as a treatment modality for hepatoblastoma. It may be used for localized field irradiation after resection of microscopic residual disease and in the management of chemo-resistant pulmonary metastasis after wedge resection.

**Prognosis:**

As in any cancer, prognosis and long-term survival can greatly vary among each child. Good prognosis is correlated with aggressive therapy and prompt medical attention. In hepatoblastoma, poor prognosis is associated with:

- Extent (stage) of the disease
  - tumor involves both liver lobes
  - multi-focal disseminated growth pattern in the liver
  - presence of distant metastasis
  - presence of vascular invasion
- Resectability and response of the tumor to therapy
  - no recurrence at least 6 months after primary resection
  - persistent metastatic disease
  - incomplete resection of the tumor/presence of residual disease after surgery
  - rising AFP levels
  - chemo-resistant tumors
- Age and overall health of the child
  - presence of malnutrition and other physiological factors that would compromise treatment efficacy
  - older age
- Intolerance to specific medications, procedures and other therapies

**Recurrent Hepatoblastoma:**

Recurrent cancer usually appears in the liver and the lungs, most often heralded by an increasing serum AFP level. Retreatment should occur immediately with tumor resection and chemotherapy.
Future Directions:

Investigations are aimed at improving concentrations of drugs at the tumor sites. Continuous \textit{(A – 4) intra-arterial infusions} not only increase drug concentrations but also increase the exposure of the tumor to the drug over time. Intra-arterial infusions also minimize the systemic effects of chemotherapy. The procedure has been implemented by investigators from Japan and is known as Transhepatic Arterial ChemoEmbolization (TACE digilander.libero.it/.../casoangio7.htm).

The other focus of research is the use of monoclonal antibodies (MAbs) that will serve as vectors for chemotherapy agents. These MAbs can be directed intracellularly, increasing the cytotoxic ability of the chemotherapy.

The newer, less invasive laparoscopic procedures have been done in cases of hepatic malignancies. The procedure is less invasive and causes much less pain. The role and use of these less invasive procedures should be further investigated.

Further investigations are also underway to determine the efficacy of liver transplantation and non-myeloablative allogeneic hematopoetic stem cell transplantation as a curative modality for hepatoblastoma.
Hepatic Tumors: Hepatoblastoma

Helpful Weblinks:

E-Medicine.com
This website contains a concise description of hepatoblastoma with good diagnostic information – MRIs and CT scans; the second web address provides the information that completes the topic on hepatoblastoma.
http://www.emedicine.com/radio/topic331.htm
http://www.emedicine.com/ped/topic982.htm

St. Jude Children’s Research Hospital, Memphis, TN
This website provides basic public information on hepatoblastoma and news items about the work of St. Jude in this area.
http://www.stjude.org/disease-summaries/

University of Virginia Health System, Charlottesville, VA
This website contains detailed information on hepatoblastoma.
http://www.healthsystem.virginia.edu/uvahealth/peds_oncology/hepato.cfm

Schneider Children’s Hospital, New Hyde Park, NY
This website contains detailed information on hepatoblastoma.
http://www.schneiderchildrenshospital.org/peds_html_fixed/peds/oncology/hepato.htm

Related www.cure4kids.org seminars

Seminar #312 Allogeneic HSCT for Hepatoblastoma
Hiroto Inaba, MD, PhD and Fredric Hoffer, MD
http://www.cure4kids.org/seminar/312

Seminar #118 Hepatoblastoma and Familial Cancer Syndromes
Presenter: Wayne Furman, MD, Robert Sanders, MD, Patricia Gordon, MD, Beth McCarville, MD and Jesse J. Jenkins, III, MD
https://www.cure4kids.org/seminar/118
**Appendix:**

A – 1 Useful Distinctive Features of Hepatic Tumors
(Adapted from Greenberg, M. & Filler, R., Principles and Practice of Pediatric Oncology, Pizzo and Poplack).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hepatoblastoma</th>
<th>Hepatocellular Carcinoma</th>
<th>Fibrolamellar Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of presentation</td>
<td>0 – 3 years</td>
<td>5 – 18 years</td>
<td>10 – 20 years</td>
</tr>
<tr>
<td>Associated congenital anomalies</td>
<td>Dysmorphic- Hemihypertrophy Beckwith-Weideman Syndrome Familial Adenomatous Polyposis</td>
<td>Metabolic – Hereditary tyrosinemia Hepatic fibrosis and cirrhosis G6PD deficiency Viral hepatitis Fanconi’s anemia Ataxia Telangiectasia</td>
<td>None</td>
</tr>
<tr>
<td>Advanced disease at presentation</td>
<td>40% of cases</td>
<td>70% of cases</td>
<td>10% of cases</td>
</tr>
<tr>
<td>Usual site of origin</td>
<td>Right lobe</td>
<td>Right lobe – multi-focal lesions</td>
<td>Right lobe</td>
</tr>
<tr>
<td>AFP elevation</td>
<td>80 – 90%</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>Positive hepatitis serology</td>
<td>Absent</td>
<td>Present in some</td>
<td>Absent</td>
</tr>
<tr>
<td>Abnormal B12-binding protein</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Histology/pathology</td>
<td>Fetal and/or embryonal cells with or without mesenchymal component</td>
<td>Large pleomorphic tumor cells and giant tumor tumor cells</td>
<td>Eosinophilic hepatocytes with dense fibrous stroma</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Cisplatin Vincristine Fluouracil Doxorubicin Etoposide Topotecan Dactinomycin Dacarbazine</td>
<td>Cisplatin Doxorubicin 5 FU VP-16</td>
<td>Cisplatin Doxorubicin 5 FU VP-16</td>
</tr>
<tr>
<td>Surgery- resection</td>
<td>Transabdominal approach</td>
<td>Only 1/3 of cases is resection possible</td>
<td>Same as hepatocellular carcinoma</td>
</tr>
<tr>
<td>5 year Survival</td>
<td>75 – 80 % with tx</td>
<td>35 % with tx</td>
<td>50 – 80 %</td>
</tr>
</tbody>
</table>
Syndromes Associated With Hepatoblastoma

Familial Adenomatous Polyposis (FAC/APC, includes Gardner syndrome): A germline mutation of the adenomatous polyposis gene (ACP); an autosomal dominant inherited disorder, characterized by the presence of numerous multiple precancerous polyps in the colon. Extra colonic manifestations include gastric polyps, dental anomalies, soft tissue tumors, desmoid tumors and associated cancers.

Beckwith-Wiedemann syndrome: An autosomal dominant inherited disorder characterized by exomphalos (abdominal wall defects and muscle weakness), macroglossia (enlarged tongue) and gigantism syndrome (overgrowth). Affected infants are large at birth and their growth remains at or above the 95th percentile (gigantism) until adolescence.

Von Gierke (Glycogen Storage Disease, GSD I): An autosomal-recessive condition characterized by an enzyme (G-6-P) defect blocking the final steps of glycogenolysis and gluconeogenesis, resulting to accumulation of glycogen in the tissues.

Schinzel-Gideon syndrome: A collection of birth anomalies involving the kidneys, heart, brain and skeleton, accompanied by a characteristic flat face. Short lower limbs, nose is short and low, eyes wide-set, and ears low-set, frequently with hearing, vision and mental difficulties.

Simpson-Golabi-Behmel Type I (SGBS BULLDOG SYNDROME): An overgrowth syndrome caused by a mutation in the gene for glypican-3 (GPC3) which maps to Xq26. The syndrome is characterized by large protruding jaws, widened nasal bridge, upturned nasal tip, enlarged tongue, and broad, short hands and fingers.

Hemihypertrophy: An overgrowth syndrome characterized by a greater than 5% difference between the left and right side of the body. The condition can be a benign familial trait or it may occur sporadically with no preceding family history. Children with hemi-hypertrophy tend to develop abdominal tumors.
Hepatic Tumors: Hepatoblastoma

According to this staging system, only children with PRETEXT stage I hepatoblastoma undergo initial resection of the tumor. All the others are treated with chemotherapy prior to attempted resection of the primary tumor. The tumors are staged by interpretation of magnetic resonance imaging with or without additional imaging by computerized tomography or ultrasound.
Transhepatic Arterial Chemo-embolization (TACE)
Hepatocellular Carcinoma before and after TACE

Pre-TACE

Post TACE