COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Pediatric Patients With Hepatoblastoma

Protocol applies to hepatoblastoma. Other malignant primary hepatic tumors are not included.

No AJCC/UICC TNM Staging System
The Children's Oncology Group Staging System is recommended

Protocol web posting date: October 2013

Procedures
• Hepatectomy, Partial or Complete

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

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CAP Hepatoblastoma Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Hepatoblastoma 3.1.1.0

Summary of Changes
The following changes have been made since the November 2011 release.

Resection

Macroscopic Extent of Tumor was moved from a subcategory of "Margins" to a standalone data element, and "Cannot be assessed" was added as follows:

+ Macroscopic Extent of Tumor at Operation (select all that apply)
+ ___ Tumor extends into adjacent organ(s)
+ ___ Tumor extends into adjacent soft tissue
    + ___ Diaphragm
    + ___ Abdominal wall
    + ___ Other (specify): _____
+ ___ Intraoperative tumor spill
+ ___ Cannot be assessed

Important Note

First priority should be given to formalin-fixed tissues for morphologic evaluation. The second priority for tissue processing is snap-freezing up to 1 g (minimum of 100 mg) of tumor from grossly different regions for molecular studies, as well as viable sterile tumor for cytogenetic studies (see Explanatory Note A). Samples from the same foci should be collected for histology, with appropriate identification. Samples of nontumoral liver should be collected for snap-freezing as well.

For more information, contact: The Children's Oncology Group Biopathology Center;
Phone: (614) 722-2890 or (800) 347-2486.

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

HEPATOBLASTOMA (PEDIATRIC LIVER): Resection

Select a single response unless otherwise indicated.

Procedure (Note A)
___ Right lobectomy
___ Extended right lobectomy
___ Medial segmentectomy
___ Left lateral segmentectomy
___ Total left lobectomy
___ Explanted liver
___ Other (specify): _____
___ Not specified

Tumor Site
___ Right lobe
___ Left lobe
___ Right and left lobes
___ Other (specify): _____
___ Not specified

Tumor Size (specify for each nodule)
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be assessed (see Comment)

+ Tumor Focality (within liver)
+ ___ Unifocal
+ ___ Multifocal
+ ___ Indeterminate
+ ___ Cannot be assessed

+ Macroscopic Extent of Tumor at Operation (select all that apply)
+ ___ Tumor extends into adjacent organ(s)
+ ___ Tumor extends into adjacent soft tissue
    + ___ Diaphragm
    + ___ Abdominal wall
    + ___ Other (specify): _____
+ ___ Intraoperative tumor spill
+ ___ Cannot be assessed

+ Data elements preceded by this symbol are not required. However, these elements may be
   clinically important but are not yet validated or regularly used in patient management.

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Histologic Type (Note B)
___ Hepatoblastoma, epithelial type, fetal pattern (mitotically inactive)
___ Hepatoblastoma, epithelial type, fetal pattern (mitotically active)
___ Hepatoblastoma, epithelial type, fetal and embryonal pattern
___ Hepatoblastoma, epithelial type, macrotrabecular pattern
___ Hepatoblastoma, epithelial type, small cell undifferentiated pattern
        + Percentage of tumor with this histologic feature: _____
___ Hepatoblastoma, mixed epithelial and mesenchymal type without teratoid features
___ Hepatoblastoma, mixed epithelial and mesenchymal type with teratoid features
___ Hepatoblastoma, rhabdoid type
___ Hepatoblastoma, other (specify): _____

Histologic Grade (Note C)
___ Favorable (purely epithelial, fetal subtype, mitotically inactive with ≤2 mitoses in 10 X40 objective fields; stage I)
___ Less favorable (all subtypes other than those designated "Favorable" or "Unfavorable")
___ Unfavorable (small cell undifferentiated or rhabdoid as the predominant or sole histopathologic subtype; any stage)

Margins (select all that apply) (Note D)

Resection Margin
___ Cannot be assessed
___ Uninvolved by invasive tumor
        Distance of invasive tumor from closest margin: ___ mm *OR* __cm
        Specify margin(s): _____
___ Involved by invasive tumor
        Specify margin(s) _____

Capsular Surface
___ Cannot be assessed
___ Uninvolved by invasive tumor
        Distance of invasive tumor from closest surface: ___ mm *OR* __cm
        Specify margin: _____
___ Involved by invasive tumor

+ Lymph-Vascular Invasion (select all that apply)
+ ___ Not identified
+ ___ Portal vein invasion present
+ ___ Hepatic vein invasion present
+ ___ Present within tumor nodules
+ ___ Present in vessels of parenchyma outside of tumor nodules
+ ___ Indeterminate

Lymph Nodes (Note E)
___ Cannot be assessed
___ Regional lymph node metastasis not identified
___ Regional lymph node metastasis present
        Specify location, if known: _____
Specify: Number of lymph nodes examined: ___
        Number of lymph nodes involved by tumor: ___

+ Data elements preceded by this symbol are not required. However, these elements may be
  clinically important but are not yet validated or regularly used in patient management.

Distant Metastases
___ Not applicable
___ Distant metastasis present (includes metastasis to lymph nodes in the following locations: inferior
     phrenic, distal to hilum, hepatoduodenal ligament, or caval region)
          + Specify site(s), if known: _____

Staging (Children's Oncology Group) (select all that apply) (Note F)
___ Stage I   Complete resection, margins grossly and microscopically negative for tumor
___ Stage II   Microscopic residual tumor present
                 ___ Microscopic residual tumor present at hepatic resection margin
                 ___ Microscopic residual tumor present at extrahepatic resection margin
                 ___ Intraoperative tumor spill
___ Stage III   Gross residual tumor present
                 ___ Macroscopic tumor visible at resection margin(s)
                 ___ Lymph node metastasis present
___ Stage IV   Metastatic disease present
                 ___ Primary tumor completely resected
                 ___ Primary tumor not completely resected

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Cirrhosis/fibrosis
+ ___ Iron overload
+ ___ Hepatitis (specify type): _____
+ ___ Other (specify): _____

+ Other (specify) (Notes G, H, I)
+ Specify: _____

+ Comment(s)

+ Data elements preceded by this symbol are not required. However, these elements may be
  clinically important but are not yet validated or regularly used in patient management.

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Explanatory Notes

A. Submission of Tissue

Use of intraoperative frozen sections should be avoided unless the operative procedure will be altered by the result. Biopsies of pediatric liver tumors present significant potential for diagnostic error, even on permanent sections. First priority should be given to formalin-fixed tissues for morphologic evaluation. For resection specimens, sections should be prepared from each major tumor nodule, with representative sampling of smaller nodules, if macroscopically different in appearance. The total number of sections taken should be equal to or greater than the greatest dimension of the tumor in centimeters, to better assure detection of areas of unfavorable (eg, small cell undifferentiated) histopathologic features. Sections from inked margins of resection and portal vein or hepatic vein–inferior vena cava involvement should also be submitted if this feature is seen grossly. Documentation should include gross vascular invasion versus intravascular growth found only microscopically, and whether it is within the tumor mass or outside of it.

The second priority for tissue processing includes snap-freezing up to 1 g (minimum of 100 mg) of tumor from regions of different appearance for future molecular studies; viable sterile tumor should be submitted for cytogenetic studies whenever possible. Samples of nontumoral liver should be collected for snap-freezing as well.

Primary diagnosis by cytology (fine-needle aspiration) may be misleading because of difficulties in distinguishing well-differentiated hepatocellular malignancy from regenerative changes and benign proliferations, and because of the variability of histologic features in hepatoblastoma.

B. Histologic Type

Primary malignant tumors of the liver account for approximately 1% of all childhood cancer. The most common type is hepatoblastoma, which has an annual incidence of 0.9 per 1 million children. Not only are hepatoblastomas rare, but their diversity significantly limits the experience of any one center and pathologist. A classification scheme for hepatoblastoma[1] that divides the more frequently or prognostically influential features from infrequent or inconsequential (minor) components is presented in Table 1, based on a study of tumor resection specimens.

Table 1. Classification of Hepatoblastoma

Major Categories
    Epithelial
        Fetal, well-differentiated (mitotically inactive with minimal mitotic rate of
           ≤2 mitoses per 10, X40 objective fields)
        Fetal, mitotically active (>2 mitoses per 10, X40 objective fields)
        Embryonal
        Macrotrabecular
    Small cell, undifferentiated
    Rhabdoid
    Mixed stroma having osteoid features; rarely striated muscle, cartilage or minor
     components as follows:
        Cholangioblastic (ductal)
        Intestinal glandular epithelium (teratoid)
        Neuroid-melanocytic (teratoid)
        Rhabdomyoblastic
        Chondroid
        Blastemal

There is no relationship between the age of the child and the predominant cell type in hepatoblastoma.[1] Of all cases at all ages, 85% to 90% contain both fetal and embryonal derivatives in variable proportions; 20% have stromal derivatives. Because these histologic types tend to be randomly intermingled, both fine-needle aspiration and biopsies may capture a nonrepresentative sample of tumor.

Distinguishing well-differentiated (mitotically inactive) fetal hepatocytic tumor cells from normal liver in an infant can be difficult. The fetal tumor cells are larger than normal fetal hepatocytes and have a higher nuclear-to-cytoplasmic ratio. The nuclei are regular and round with little discernible mitotic activity (≤2 mitoses per 10 high-power [X40 objective] fields) in the well-differentiated variety. Fetal tumor cells grow in cords, as in normal liver, or in nests or nodules. Clusters of normoblasts (extramedullary hematopoiesis) are commonly seen, as in fetal liver. The cytoplasm of the fetal tumor cells varies from eosinophilic to clear, depending on the amount of glycogen content. Fetal tumor cells may also contain abundant lipid, producing vacuolization. In well-differentiated fetal tumors, bile secretion may be observed.

The embryonal cellular component of hepatoblastoma is less well differentiated than its fetal hepatocytic counterpart, with cells that are small and have a high nuclear-to-cytoplasmic ratio with ovoid nuclei and that may assume a tubular or rosette-like configuration. Purely embryonal tumors are almost never encountered and invariably show some fetal areas.

A macrotrabecular pattern of hepatoblastoma growth is one in which fetal or embryonal cells number 20 or more within a cord or cluster, as opposed to the usual 2- to 6-cell-thick cords or plates.

Some histopathologic subtypes of hepatoblastoma have prognostic and therapeutic importance. Well-differentiated (mitotically inactive) fetal histology was superior to embryonal differentiation in long-term survival; therefore, the current Children's Oncology Group (COG) study is treating stage I well-differentiated fetal hepatoblastoma (with low mitotic rate) with surgery alone.[1,2] An urgent research need is to identify more effective medical therapy for both small cell undifferentiated hepatoblastoma and rhabdoid hepatoblastoma, the most aggressive forms of this malignancy.[1]

When first distinguished from embryonal epithelium, small undifferentiated cells in hepatoblastoma were noted to resemble neuroblastoma, to have a low mitotic rate, and were called *anaplastic*, consistent with the dictionary definition, characterized by imperfect development. Because anaplastic was redefined by Faria et al[3] for Wilms tumor as nuclear enlargement to 3 times that of typical tumor cells, hyperchromasia, and atypical mitoses, the small cell undifferentiated component is no longer designated as anaplastic. Beckwith-type anaplasia does occur rarely in hepatoblastoma, and its significance is unknown. The small cells have been considered putative hepatic progenitor cells on the basis of immunohistochemical and electron microscopic studies. When present in a significant fraction of the hepatoblastoma (75%), or as the sole cell type, the small cell type is typically found in infants younger than 1 year; they have a poor prognosis, with poor response to current therapy. The prognostic significance of smaller proportions of the small cell undifferentiated type is still undetermined. Rhabdoid tumor cells have the characteristic eccentric pink cytoplasmic inclusions (periodic acid-Schiff/diastase positive, vimentin or cytokeratin positive) with vesicular nuclei and fibrillar inclusion bodies by electron microscopy. They may be associated with the small cell component in otherwise typical hepatoblastomas or as the exclusive cell type, in which case they occur in infancy and are associated with a poor prognosis.

Often, mixed hepatoblastomas contain epithelial membrane antigen (EMA)-positive nests of squamous epithelium. The osteoid component of mixed hepatoblastomas is found to be a matrix of collagen surrounding cells expressing EMA and having ultrastructural features of epithelium rather than osteoblasts. Hepatoblastomas may contain other stromal derivatives, including cartilage and rhabdomyoblasts. There is no prognostic significance to the presence of mixed histologic features.

Several other variant (stromal) histologic patterns in hepatoblastoma are placed into a "minor category" on the basis of infrequency of the cell type or the lack of measurable prognostic consequence. Multinucleated tumor giant cells are found in rare hepatoblastomas, sometimes associated with human chorionic gonadotropin (HCG) production and clinical virilization. Teratoid hepatoblastoma was initially depicted as having intestinal, neural, and melanocytic elements. These are distinguished from true teratomas, which can also occur in the livers of children, on the basis of organoid differentiation and even greater diversity of tissue elements in the teratomas.

Postchemotherapy resection specimens often show eradication of the embryonal cells and more prevalent osteoid-like foci. Heifetz et al[4] reported that vascular invasion, amount of mesenchyme, persistence of embryonal epithelium, extent of tumor necrosis, and mitotic activity of the epithelial component have predictive value in this type of specimen. This has yet to be confirmed, but the items should be documented, as should the presence of any small undifferentiated cells, which are known to negatively affect prognosis but may have been missed in the initial biopsies of stage III and IV lesions.

Typical Hepatoblastoma Histologic Types
Epithelial, fetal, well differentiated (with minimal mitotic rate of ≤2 per 10, X40 objective fields) (7%)
Epithelial, fetal, mitotically active pattern (>2 mitoses per 10, X40 objective fields) (11%)
Epithelial type, fetal and embryonal pattern only (39%)
Epithelial type, macrotrabecular pattern (12%)
Small cell undifferentiated pattern (5.6%)
Mixed epithelial and mesenchymal type without teratoid features (20%)
Mixed epithelial and mesenchymal type with teratoid features (4%)

Immunohistochemistry for hepatocyte antigen, α-fetoprotein, and, in some instances, ß-catenin may be useful in the diagnosis of hepatoblastoma, mostly for tumors with favorable and unfavorable histologies. There is no immunostain to differentiate hepatocellular carcinoma from hepatoblastoma. Possible genetic markers (trisomies for chromosomes 2, 20, and 8, abnormalities of chromosome 1p) are being

investigated and may help differentiate these two entities, but only in approximately 35% to 40% of hepatoblastomas that carry the abnormalities.[1]

C. Histologic Grade: Grading for Hepatoblastoma (see Note B and Table 1)
Tumors with favorable histopathologic features are purely fetal, well-differentiated lesions defined as mitotically inactive with a minimal mitotic rate of 2 or fewer mitoses per 10, X40 objective fields. When these tumors are also stage I they are treated with surgery alone.

Tumors with unfavorable histopathologic features have either undifferentiated small cell or rhabdoid subtypes, or both. When present in a significant fraction of the hepatoblastoma (75%) or as the sole cell type, the small cell undifferentiated subtype is typically found in infants younger than 1 year, with poor prognosis regardless of stage or therapy. When this subtype is present in lesser proportions, the prognostic implications remain undetermined. When the rhabdoid cell type is the exclusive histopathology, it is also found typically in infants and has a poor prognosis.

Less favorable histopathologies include all other tumor subtypes not mentioned above, although they may be associated with favorable prognosis if stage I and are usually treated with multimodal therapy.

D. Margins
The evaluation of margins for total or partial hepatectomy specimens depends on the method and extent of resection. It is recommended that the surgeon be consulted to determine the critical foci within the margins that require microscopic evaluation. The transection margin of a partial hepatectomy may be large, rendering it impractical for complete examination. In this setting, grossly positive margins should be microscopically confirmed and documented. If the margins are grossly free of tumor, judicious sampling of the cut surface in the region closest to the nearest identified tumor nodule is indicated. In selected cases, adequate random sampling of the cut surface may be sufficient. If the neoplasm is found near the surgical margin, the distance from the margin should be reported. For multiple tumors, the distance from the nearest tumor should be reported.

E. Lymph Nodes
Histologic examination of a regional lymphadenectomy specimen usually involves examination of 3 or more lymph nodes. The regional lymph nodes of the hepatic region include the hilar, hepatoduodenal ligament, and caval lymph nodes. Nodal involvement of the inferior phrenic lymph nodes or other lymph nodes distal to the hilar, hepatoduodenal ligament, and caval lymph nodes is considered distant metastasis.

F. Staging of Hepatoblastoma
Staging in the United States combines imaging with surgical judgment about resectability.[5] Computed tomography and magnetic resonance imaging are used exclusively in the SIOPEL (Societé Internationale D'Oncologie Pediatrique Liver Tumor Study Group) protocol[6,7] to determine the location and extent of hepatic involvement of hepatoblastoma preoperatively; tumors sparing the left medial and right anterior sectors are primarily resected.

Dissemination of hepatic malignancies occurs within portal veins and follows the expected ready access of infiltration into hepatic veins, with frequent lung involvement. Further spread to the brain may occur. Hilar lymph node metastases are relatively infrequent, but capsular rupture of subcapsular masses either before or during surgery can upstage an otherwise resectable malignancy.

The Children's Oncology Group staging system is recommended for hepatoblastomas[5] (staging is performed at diagnosis, prior to any form of therapy).

Stage I (favorable histologic type) tumors are completely resected and have typical histologic features of a purely fetal well-differentiated histologic pattern (minimal mitotic index of 2 mitoses per 10 high-power [X40 objective] fields).

Stage I (other histologic type) tumors are completely resected, with a histologic picture other than purely fetal, well-differentiated pattern.

Stage II tumors are grossly resected with evidence of microscopic residual tumor. Such tumors are rare, and patients with this stage have not fared differently from those with stage I tumors in previous protocols. Resected tumors with preoperative (intraoperative) rupture are classified as stage II.

Stage III (unresectable) tumors are those that are considered by the attending surgeon not to be resectable without undue risk to the patient. These include partially resected tumors with measurable tumor left behind. They do not include grossly resected tumors with microscopic disease at the margins or resected tumors with preoperative/intraoperative rupture. Lymph node involvement is considered stage III disease and may require evaluation with second laparotomy after an initial 4 courses of chemotherapy.

Stage IV tumors are those that present with measurable metastatic disease to the lungs or other organ.#

Nodal involvement of the inferior phrenic lymph nodes or other lymph nodes distal to the hilar, hepatoduodenal ligament, or caval lymph nodes are considered distant metastases.

Resectability is the key prognostic feature for all liver malignancies, with the possible exception of rhabdomyosarcoma (see separate College of American Pathologists protocol for rhabdomyosarcoma[8]). Unfortunately 67% of hepatoblastomas were not amenable to primary surgery (48% stage III and 19% stage IV) in the 16 years of Pediatric Oncology Group/Children's Oncology Group accessions.[1]

G. Associated Environmental and Genetic Factors

Hepatoblastoma occurs in association with several well-described environmental factors and cancer genetic syndromes (see Table 2); however, not all of these associations are necessarily of statistical significance. Environmental factors and prenatal exposure to different agents have been implicated in hepatoblastoma.[1]

An increased incidence of hepatoblastoma—from 0.4 to 1.0 per million between 1971 and 1983—has been observed at a Children's Tumour Registry in Manchester, United Kingdom.[9] Data from the US National Cancer Institute Surveillance, Epidemiology, and End Result (SEER) program revealed an average annual increase of 5.2% in the incidence of hepatoblastoma from 1973 to 1992.[10] This change might be explained by hepatoblastoma occurring in surviving premature infants. Hepatoblastomas in Japan accounted for 58% of all malignancies in children who weighed less than 1000 g at birth.[11] Further analysis of the Japanese Children's Cancer Registry data revealed that 15 of 303 (5%) hepatoblastomas between 1985 to 1995 occurred in infants with history of prematurity and weight less than 1500 g at birth.[12] This rate was greater than 10 times that for all live births. The relative risk for hepatoblastoma for children who weighed less than 1000 g at birth was 15.64 compared with 2.53 for those 1000 g to 1499 g and 1.21 for children weighing 2000 g to 2499 g at birth. Of 77 children with hepatoblastoma in the German registry, 3 (4%) were premature infants who required parenteral nutrition, a treatment that has been lifesaving for many small premature infants but has been reported to lead to cirrhosis in many survivors. It has not been previously associated with hepatoblastoma. The histologic features of hepatoblastoma after prematurity are indistinguishable from those of other hepatoblastomas.

The Children's Cancer Group has evaluated environmental or drug exposure. Seventy-five sets of parents of children with hepatoblastoma were compared with the parents of age-matched controls. In the group of children with hepatoblastoma, there was a significant excess of maternal exposure, before and during pregnancy, to metals used in welding and soldering, lubricating oils, and protective greases.[13] Paternal exposure to metals was also greater. At 23 weeks, a congenital hepatoblastoma was found in a stillborn fetus whose mother was an artist exposed to volatile hydrocarbons.[14]

Table 2. Clinical Syndromes, Congenital Malformations, and Other Conditions Associated With Hepatoblastoma

Congenital Malformations

    Absence of left adrenal gland
    Bilateral talipes
    Duplicated ureters
    Dysplasia of ear lobes
    Cleft palate
    Fetal hydrops
    Hemihypertrophy
    Heterotopic lung tissue
    Horseshoe kidney
    Inguinal hernia
    Intrathoracic kidney
    Macroglossia
    Meckel diverticulum
    Persistent ductus arteriosus
    Renal dysplasia
    Right-sided diaphragmatic hernia
    Single coronary artery
    Umbilical hernia

Syndromes

    Beckwith-Wiedemann syndrome
    Beckwith-Wiedemann syndrome with opsoclonus, myoclonus
    Budd-Chiari syndrome
    Familial adenomatous polyposis syndrome
    Li-Fraumeni cancer syndrome
    Polyposis coli families
    Schinzel-Geidion syndrome
    Trisomy 18

Table 2. Clinical Syndromes, Congenital Malformations,
and Other Conditions Associated With Hepatoblastoma

Metabolic / Pathophysiologic Abnormalities

       Cystathioninuria

       Glycogen storage disease types Ia, III, and IV

       Hypoglycemia

       Heterozygous a_1-antitrypsin deficiency

       Isosexual precocity

       Prematurity

       Total parenteral nutrition

       Very low birth weight

Environmental / Other

       Alcohol embryopathy

       Human immunodeficiency virus or hepatitis B virus infection

       Maternal clomiphene citrate or Pergonal

       Oral contraceptive, mother

       Oral contraceptive, patient

       Osteoporosis

       Synchronous Wilms tumor

Karyotyping of hepatoblastomas has revealed a recurrent pattern of chromosomal abnormalities.[15,16] The most common karyotypic changes are extra copies of entire chromosomes (trisomies), sometimes in conjunction with other complex structural changes and often in association with double-minute chromosomes. Trisomies of chromosomes 2 and 20 have each been reported most commonly,[15,16] and each of these trisomies has been reported as a sole karyotypic event, suggesting that they may represent an early stage of tumor evolution. Trisomy of chromosome 20 and duplication of the long arm of chromosome 20 have also been observed in rhabdomyosarcoma, suggesting a link between these 2 embryonal tumors, both of which are also associated with losses at the Beckwith-Wiedemann syndrome locus.[17] Trisomy of chromosome 8 is also common; other trisomies are seen with lesser frequency. Occasional losses of entire chromosomes are seen, and these, too, are not random. The clinical significance of trisomies is unknown at present, although a recent study using comparative genomic hybridization has suggested that chromosomal gains at chromosomes 8 and 20 may be associated with an adverse prognosis.[18] A unique translocation has been reported in undifferentiated small cell hepatoblastoma,[19] a variant associated with a poor prognosis, although this cytogenetic variant has not been reported in other cases.

Numerous recent studies have documented molecular genetic abnormalities in hepatoblastomas (see Table 3) and other hepatic tumors. Several genetic changes are shared with other embryonal tumors, such as loss of heterozygosity at chromosome 11p15, also described in rhabdomyosarcomas and Wilms tumors. Acquired mutations of the *APC* gene and the *ß-catenin* gene, both members of the Wnt signaling pathway, have also been reported in hepatoblastoma.[20,21] The high frequency of *ß-catenin* mutations in hepatoblastomas and the increased incidence of hepatoblastomas in familial adenomatous polyposis families suggest the important role of an overactivation of wingless/Wnt pathway in the pathogenesis of hepatoblastoma. Collection of fresh or frozen hepatoblastoma tumor material as well as nontumoral liver tissue from these patients will be of great importance to the further investigation of the clinical relevance of these and other molecular genetic abnormalities in predicting the prognosis and clinical behavior of these tumors.

Table 3. Constitutional Genetic Disease Associated With Hepatoblastoma			
Disease	Tumor Type	Chromosomal Locus	Gene
Familial adenomatous polyposis	Hepatoblastoma, hepatocellular carcinoma or adenoma, biliary adenoma	5q21.22	A*PC*
Beckwith-Wiedemann syndrome	Hepatoblastoma, hemangioendothelioma	11p15.5	*p57KIP2*, others
Li-Fraumeni syndrome	Hepatoblastoma, undifferentiated sarcoma	17p13	*TP53*
Trisomy 18	Hepatoblastoma	18	—
Glycogen storage disease types Ia, III, IV	Hepatocellular adenoma or carcinoma, hepatoblastoma	17	*Glucose-6-phosphatase*; *debrancher* and *brancher* enzymes

H. Tumor Markers

Serum α-fetoprotein (αFP) is the most useful indicator of hepatocellular neoplasia. Levels of serum αFP are markedly elevated in 80% to 90% of hepatoblastomas and in 60% to 70% of hepatocellular carcinomas.[16] Lesser degrees of elevation in infants can be due to variations in the rate of decline after birth or to secretion from regenerating hepatocytes adjacent to hemangioendotheliomas or mesenchymal hamartomas. Therefore, it is unacceptable practice to institute chemotherapy for mass lesions of the liver based solely on imaging studies and serum αFP levels. αFP also can be elevated in yolk sac tumors, which may occur as primary tumors in the liver or together with hepatoblastoma. On the contrary, αFP levels will not be increased when hepatoblastomas are primarily composed of the small cell undifferentiated type or in most fibrolamellar carcinomas, but even some typical fetal hepatoblastomas have failed to produce detectable increases in serum αFP levels. Following the αFP level in patients with unresectable hepatoblastoma after chemotherapy had prognostic value in a retrospective analysis of 31 patients in a Children's Cancer Group series from 1986 to 1989.[1]

There are many other proposed blood assays for the detection of hepatic malignancies. Other than αFP and human chorionic gonadotropin (HCG), none is used widely thus far because of relatively low specificity and predictive value. Occasionally, hypercholesterolemia is found in patients with hepatoblastoma, especially in infants with fetal histology, and all those with high levels died.[22,23] Precocious puberty secondary to HCG or testosterone secretion has been observed in 6% of boys with hepatoblastoma.[24] Thrombocytosis has been present in 25% to 65% of patients with hepatoblastoma.[25]

I. Clinical Features and Differential Diagnosis

The presenting symptom of virtually all liver tumors in children is abdominal swelling secondary to hepatomegaly. When confronted with this symptom, it is useful to consider the age at which liver tumors tend to occur (see Table 4). Exceptions are frequent, but age can serve as a guide when the presenting symptoms lack specificity. In the Pediatric Oncology Group series from 1986 to 2002,[1] 66% of hepatoblastomas were manifest by the second year, and 11% before 6 months of age. Approximately 50% of those in infants were congenital, given their size when discovered by 2 to 3 months of age; 6% of hepatoblastomas occurred after 5 years of age. Hepatocellular carcinomas have been observed as

early as 6 months of age. Seven examples of mixed hepatoblastomas and hepatocellular carcinomas have been observed at a mean age of 8.5 years; perinatally acquired hepatitis B virus was responsible in three instances. Yolk sac tumors are more common in early childhood, but they also occur rarely in older adults. Systemic malignancies and metastatic disease must be considered at all ages because hepatomegaly due to megakaryoblastic leukemia, Langerhans cell histiocytosis, and neuroblastoma are important sources of confusion with hepatoblastoma in infancy, as are intra-abdominal desmoplastic small round cell tumors later in childhood.

Table 4. Tumors of the Liver in Children: Usual Age of Presentation		
Age	**Benign**	**Malignant**
Infancy (0-1 y)	Hemangioendothelioma Mesenchymal hamartoma Teratoma	Hepatoblastoma, especially small cell undifferentiated Rhabdoid tumor Yolk sac tumor Langerhans cell histiocytosis Megakaryoblastic leukemia Disseminated neuroblastoma
Early childhood (1-3 y)	Hemangioendothelioma Mesenchymal hamartoma	Hepatoblastoma Rhabdomyosarcoma Inflammatory myofibroblastic (pseudo) tumor
Later childhood (3-10 y)	Perivascular epithelioid cell tumors (PE-Comas), including angiomyolipoma in liver and clear cell tumor of ligamentum teres / falciform ligament	Hepatocellular carcinoma Embryonal (undifferentiated) sarcoma Angiosarcoma Cholangiocarcinoma Endocrine (gastrin) carcinoma
Adolescence (10-16 y)	Adenoma Focal nodular hyperplasia Biliary cystadenoma	Fibrolamellar hepatocellular carcinoma Hodgkin lymphoma Leiomyosarcoma

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