Liver Tumors in Pediatric Patients

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KEYWORDS

- Hepatoblastoma • Hepatocellular carcinoma • PRETEXT
- Undifferentiated embryonal sarcoma of the liver • Biliary rhabdomyosarcoma
- Malignant rhabdoid tumor of the liver • Mesenchymal hamartoma
- Focal nodular hyperplasia • Infantile hemangioma

KEY POINTS

- The most common liver tumors by age are benign congenital and infantile hemangiomas in newborns/infants, malignant hepatoblastoma in an infants/toddlers, and malignant hepatocellular carcinoma in teenagers.
- Hepatoblastoma is usually chemosensitive and with surgical resection has a favorable prognosis.
- Hepatocellular carcinoma occurs most commonly as a de novo tumor in an otherwise healthy liver.
- Hepatocellular carcinoma is relatively chemoresistant; therefore, complete surgical resection is central to achieving favorable outcomes.
- The Pediatric Hepatic International Tumor Trial is a collaborative multicenter trial prospectively investigating all stages of pediatric hepatoblastoma and pediatric hepatocellular carcinoma.

INTRODUCTION

In contrast with adults, about two-thirds of hepatic tumors in children are malignant. The 2014 international consensus classification of pediatric liver tumors is shown in **Box 1** (International Consensus Classification Pediatric Liver Tumors). The differential diagnosis includes epithelial tumors, mixed epithelial and mesenchymal tumors, and

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Box 1
Pediatric tumors of the liver, international consensus classification

EPITHELIAL TUMORS
- **Hepatocellular**
  - Benign and tumor like conditions
    - Hepatocellular adenoma (adenomatosis)
    - Focal nodular hyperplasia (FNH)
    - Macroregenerative nodule
  - Premalignant lesions
    - Dysplastic nodules
  - Malignant
    - Hepatoblastoma, HB (epithelial variants)
      - Pure Fetal with low mitotic activity
      - Fetal, mitotically active
      - Pleomorphic, poroly differentiated
      - Embryonal
      - Small cell component, IN1-negative/ INI1-positive
      - Epithelial mixed (any/all above)
      - Cholangioblastic
      - Epithelial macrotrabecular pattern
      - Mixed Epithelial and Mesenchymal
      - With teratoid features
      - Without teratoid features
    - Hepatocellular Carcinoma, HCC
      - Classic HCC
      - Fibrolamellar HCC
    - Hepatocellular Neoplasm, not otherwise specified (HcN-NOS), HB with HCC features
- **Biliary**
  - Benign
    - Bile duct adenoma, hamartoma, other
  - Malignant
    - Cholangiocarcinoma
    - Combined (hepatocellular cholangiocarcinoma)

MESENCHYMAL TUMORS
- **Benign**
  - Vascular tumors (Infantile hepatic hemangioma, Rapidly involuting congenital hemangioma)
  - Mesenchymal hamartoma
  - Pecoma
- **Malignant**
  - Embryonal Sarcoma
  - Rhabdomyosarcoma
  - Vascular (Epithelioid hemagnioendothelioma, Angiosarcoma)

OTHER MALIGNANCIES
- **Tumors of uncertain origin**
  - Malignant rhabdoid tumor of the liver (INI-1 negative)
  - Nested epithelial stromal tumor
  - Other
    - Germ cell tumors
    - Desmoplastic small round cell tumor (DSRCT)
    - Peripheral primitive neuroectodermal tumor (pPNET)
- **Metastatic (and Secondary)**
  - Metastatic solid tumors (Neuroblastoma, Wilms, other)
  - Hepatic Involvement Hematologic Malignancy (Acute Myeloid Leukemia, Megakaryoblastic Leukemia (M7), Hemophagocystic Lymphohistiocytosis (HLH), Langerhahn's Cell Histiocytosis (LCH))

Data from Lopez-Terrada D, Alaggio R, DeDavila MT et al. Towards an international pediatric liver tumor consensus classification: Proceedings of the Los Angeles COG International Pathology Pediatric Liver Tumors Symposium. Modern Pathology, 2014; 26; 19-28 PMID: 24008558.

mesenchymal tumors, including some rare sarcomas, germ cell tumors, and metastatic or secondary tumors.[1] The 2 most common malignant primary hepatic tumors are hepatoblastoma (HB) and hepatocellular carcinoma (HCC), with HB accounting for 90% of malignant tumors in children younger than 5 years of age.[2] Curiously, although the incidence of HB has doubled from about 0.1 in 100,000 in the 1980s to about 0.2 in 100,000 in 2008, the incidence of HCC in children in the United States has remained constant at 0.5 in 100,000.[3] Occasional epithelial liver tumors are seen in intermediate age children with histologic heterogeneity and features of both HB and HCC.

Malignant mesenchymal tumors of the liver are more rare than epithelial liver tumors with malignant rhabdoid tumor of the liver seen in infants, whereas biliary rhabdomyosarcoma and undifferentiated embryonal sarcoma of the liver (UESL) are seen in school age children.[4] Angiosarcomas are exceedingly rare.

Over the last 4 decades, effective chemotherapeutic regimens have been introduced and, in combination with modern surgical techniques, have resulted in significant improvement in the prognosis. HB risk stratification and treatment in the legacy trials of the pediatric trial groups were based on different risk classifications for stage, metastasis, and histology.[5] In the past decade, the 4 major trial groups formed a cooperative consortium, the Children's Hepatic tumors International Collaboration (CHIC), which had a primary objective of developing a common global approach to risk stratification. In 2018, based on these consensus definitions and staging, the Pediatric Hepatic International Tumor Trial (PHITT) opened to international enrollment.

PATIENT EVALUATION OVERVIEW

Diagnosis

The most common signs of a pediatric liver tumor are abdominal distension and a palpable mass. In the rare case of prediagnosis tumor rupture there will be peritoneal irritation and anemia. Serum alpha-fetoprotein (AFP) is the most important clinical marker for HB, and is monitored both as a response to treatment and for relapse.[6–8] Malignant rhabdoid tumors do not express AFP and have a worse prognosis.[9,10] Elevated AFP may be associated with germ cell tumors and benign liver tumors, such as mesenchymal hamartoma and infantile hemangioma, but in these situations the AFP elevation is less pronounced.[11]

Radiographic Imaging

Imaging is either by contrast-enhanced abdominal computed tomography (CT) scan or by MRI. MRI enhanced by hepatocyte specific contrast agents (eg, Eovist) may improve differential diagnosis and are especially helpful in the detection of small multifocal nodules not reliably seen with a CT scan[12] (**Fig. 1**); MR with Eovist showing multifocal nodules). Metastases when present are usually to the lungs and diagnosed by a chest CT scan. In 1990, the European based International Childhood Liver Tumors Strategy Group (SIOPEL) introduced radiology based staging called PRE-Treatment EXTent of disease (PRETEXT). The PRETEXT groups (I, II, III, and IV) have remained constant; however, the PRETEXT Annotation Factors (V, P, E, F, R, C, N, and M) have evolved over time[12,13] (**Fig. 2**). Definitions of a positive annotation factor for the PHITT study are detailed in Towbin and colleagues[12] (2018) as follows: Positive V = tumor involvement of all 3 hepatic veins or retrohepatic vena cava and/or tumor thrombus in any 1 or more of the main hepatic veins; positive P = tumor involvement of the portal bifurcation, both right and left portal veins, and/or tumor thrombus in either the left or right portal; positive E = contiguous organ involvement such as the diaphragm, abdominal wall, colon, and stomach; positive F = multifocal tumor

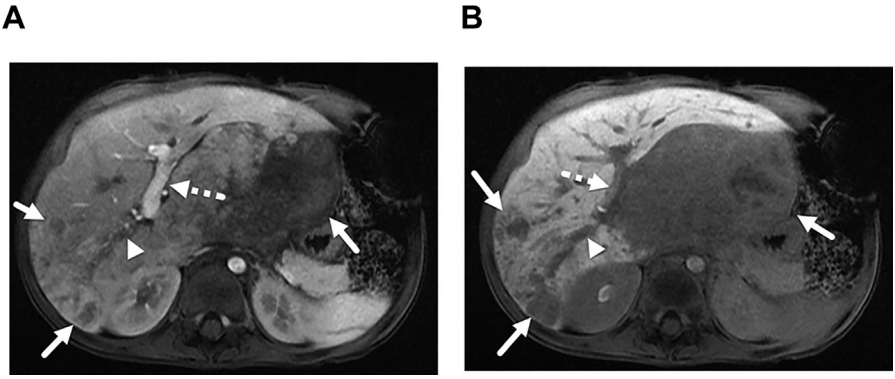

Fig. 1. HB, PRETEXT II, positive P and F. (*A*) Hepatocyte specific contrast enhanced MRI, axial T1-weighted image obtained in the portal venous phase of enhancement after administration of a hepatocyte specific contrast agent shows enhancement of the left portal vein (*dashed arrow*), thrombosis of the right portal vein (*arrowhead*), and multifocal tumor (*arrows*). (*B*) The multifocal tumor is seen better on the hepatocyte phase of imaging (annotations point to the same landmarks).

nodules; positive R = tumor rupture before diagnosis; positive N = enlarged lymph nodes; positive C = tumor involvement of the caudate lobe; and positive M = distant metastatic, usually lung nodules.

Biopsy

For tumors that are not clearly benign or resectable at diagnosis, the recommended approach is image-guided, coaxial core needle biopsy with embolization of the biopsy tract.[14,15]

HEPATOBLASTOMA

Risk Stratification

The PRETEXT/POST-TEXT groups (I, II, III, and IV) and metastatic disease (M) have been shown to be highly predictive of outcome.[16–19] Building on this foundation, the CHIC unified global risk stratification was developed, which adds other risk factors including AFP level, patient age at diagnosis, and the PRETEXT annotation factors VPEFR[5,10,20] (**Fig. 3**). A recent single institution series validated the discriminatory power of the CHIC stratification.[21] Accurate PRETEXT grouping (I, II, III, or IV) and PRETEXT annotation factor (VPEFR/M) assessment is vital for patient assignment to the appropriate risk group.[12]

Chemotherapy

Contemporary chemotherapy regimens have all been variations on a backbone of cisplatin and sometimes doxorubicin. The evolution of these chemotherapeutic approaches has shown a decrease in toxicity for localized disease and an increased intensity for high-risk tumors.[4,11,22] Details and outcomes of the most recently published studies are presented elsewhere in this article, under the discussion of outcomes.

Surgical Guidelines and Interventional Treatment Options

Although new, uniform, PRETEXT-based, international surgical guidelines are now in place, historically the recommended timing of surgical resection of HB has varied

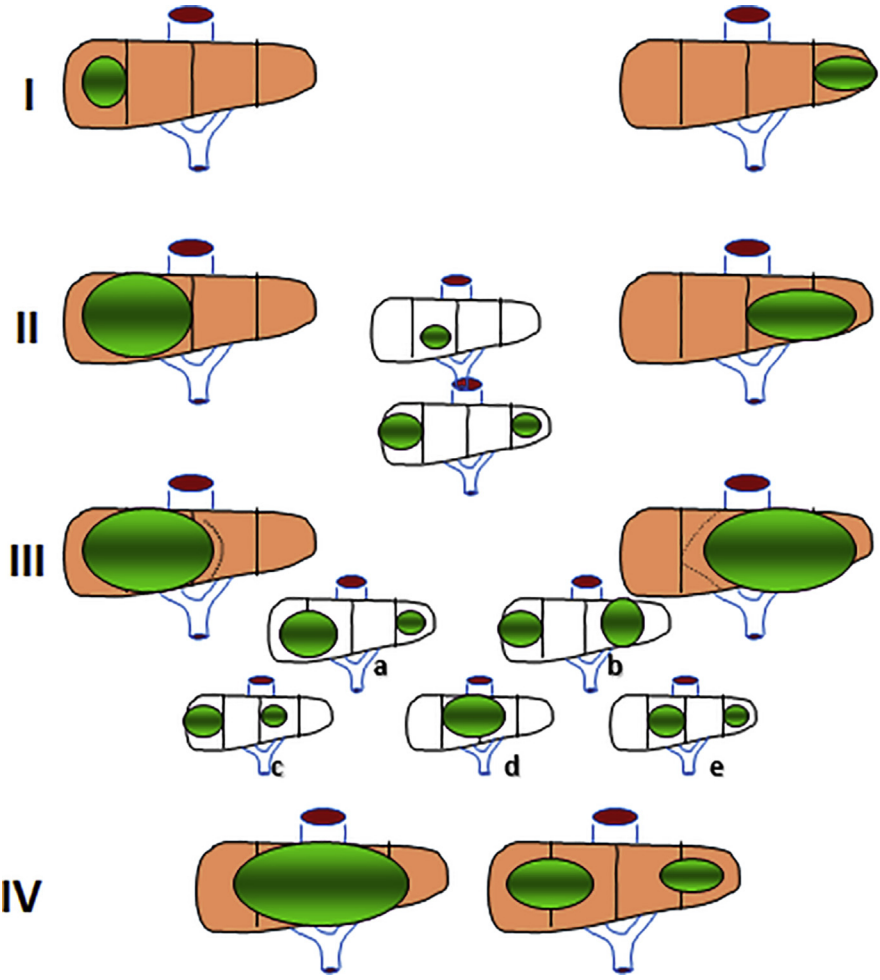

Fig. 2. PRETEXT group, pretreatment extent of disease. Extent of parenchyma involvement at diagnosis. POST-TEXT Group, Posttreatment Extent of Disease, Extent of parenchyma involvement after chemotherapy. I, 3 contiguous sections tumor free; II, 2 contiguous sections tumor free; III, 1 contiguous sections tumor free; IV, no contiguous sections tumor free. In addition, any group may have 1 or more. Annotation factors: V, involvement vena cava, all 3 hepatic veins; P, involvement portal bifurcation, both R and L; E, contiguous extrahepatic tumor; F, multifocal tumor; R, tumor rupture before diagnosis; C, caudate lobe; N, lymph node involvement; M, metastasis, distant extrahepatic tumor.

among the major trial groups.[4,23,24] In North America, consideration for surgical resection of tumors at diagnosis resulted in a surgical-based staging system: stage 1 successfully resected at diagnosis, stage 2 resected at diagnosis with microscopic residual, stage 3 unresectable at diagnosis, or gross residual/rupture/biopsy only, and stage 4, metastatic disease. In Europe since 1990 all children received preoperative chemotherapy and staging has been based on PRETEXT.

Resection rates have increased over time through intensification of chemotherapy for high-risk tumors and an increased use of vascular reconstruction and liver

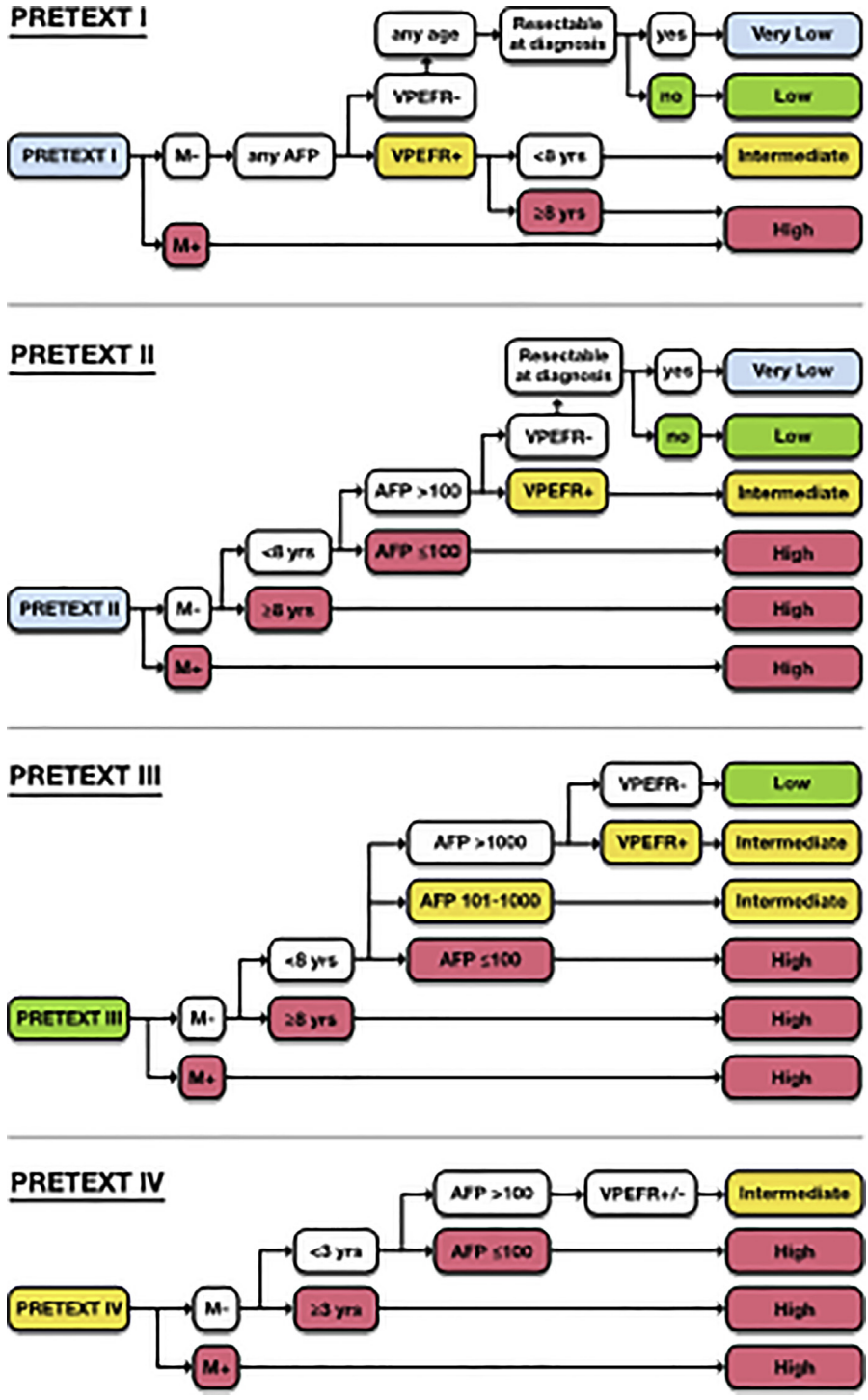

Fig. 3. Children's Hepatic tumor International Collaboration (CHIC) hepatoblastoma risk stratification. Color highlights of groups within each tree indicate which prognostic factor determined patient assignment to the ultimate group assignment: very low, low, intermediate, or high-risk group.

transplantation for unresectable tumors[25–27] (Table 1). One important observation has been that the majority of the chemotherapy response occurs in the first few cycles and continuing chemotherapy beyond this point induces drug resistance genes and increased toxicity.[28,29]

The PHITT trial introduced common, international, PRETEXT-based, surgical resection guidelines.[4,29] Resection is recommended at diagnosis for PRETEXT I and II tumors, with negative VPEFR/M annotation factors, if preoperative radiographic imaging shows 1 cm or more of uninvolved parenchyma between the tumor and the middle hepatic vein, inferior vena cava, and remaining portal vein. Resection at diagnosis should not require extension across Cantlie's line. Trial guidelines recommend that PRETEXT II, III, and IV tumors with less than 1 cm of a radiographic margin from the middle hepatic vein, and/or a positive VPEFR/M annotation factor, be biopsied and receive preoperative chemotherapy. Early communication with a transplant-capable liver center is encouraged for tumors with anticipated POST-TEXT unresectable vascular involvement and POST-TEXT IV multifocal tumors.

Extreme resections required in large central tumors with major vascular involvement of all 3 hepatic veins, the retrohepatic vena cava, and/or both portal veins are done by experienced liver surgeons as a potential alternative to orthotopic liver transplantation. This point is especially important for patients with extensive tumors and chemoresistant metastatic disease in which orthotopic liver transplantation cannot be offered.[30,31] When the surgical resection is performed after a confirmed effective chemotherapy response, SIOPEL experience suggests that a positive microscopic resection margin may not portend a worse prognosis.[32] Most investigators agree that POST-TEXT IV multifocal tumors require transplantation to prevent local relapse from occult nodules. It is important for all treating teams to realize that children who present with unresectable tumors may become resectable with neoadjuvant chemotherapy and careful POST-TEXT oncologic reevaluation is needed before deciding on the resection strategy.[22,29,31]

Surgical Complications

Intraoperative complications may include hemorrhage, air embolism and subsequent cardiac arrest. The most common postoperative complications are bleeding, impairment of blood flow in or out of the liver remnant, bile blockage or bile leak, liver failure, infection and ileus.[4] The potential causes of postoperative liver failure include a small

Table 1
HB increased surgical resection rates over time

	Years	Patient Group	Resection Rate (%)	Liver Transplantation, n (%)
INT-0098	1988–1992	Children's Oncology Group stage III/IV	57	0 (0)
SIOPEL 1	1989–1994	High risk[a]	53	6 (5)
SIOPEL 2	1994–1998	High risk[a]	67	7 (12)
SIOPEL 3HR	1998–2006	High risk[a]	74	34 (21)
SIOPEL 4	2005–2009	High risk[a]	97	16 (27)
AHEP-0731	2009–2012	Intermediate risk[b]	96	33 (32)

[a] PRETEXT IV or any PRETEXT with +VPEM or SCU histology.
[b] PRETEXT III with +V + P or any PRETEXT IV.
Data from Refs.[4,23,106]

liver remnant, liver devascularization, interruption of hepatic venous drainage, excessive liver warm ischemia owing to prolonged vascular occlusion or massive bleeding, major bile duct obstruction, halogenated anesthetic agents, viral infections, and drug reactions. Bile leak occurs in 10% to 12% of cases and its frequency has not decreased over the years. The prevention of bile leak requires a detailed anatomic knowledge of the potential variations in biliary anatomy, avoiding extensive dissection at the hepatic hilum and a low threshold for performing an intraoperative cholangiogram.

Surgical Management of Lung Metastasis

Children's Oncology Group (COG) studies have shown pulmonary metastectomy to be an effective strategy to achieve complete remission for lesions that fail to resolve on chemotherapy.[33,34] The Japanese trial experience suggests that metastatectomy for residual pulmonary nodules after chemotherapy is effective provided the primary liver tumor can be resected completely.[35] The role of metastatectomy for relapse is less definitive but the bulk of evidence supports surgical resection as a safe and, in the context of multimodal therapy, efficacious approach to manage pulmonary relapse.[8,36] Recently, preoperative intravenous indocyanine green (ICG) has been used to localize occult nodules at the time of metastatectomy and may enhance our ability to clear the lungs of metastatic disease.[37,38]

Transarterial Chemoembolization and Radioembolization

Transarterial chemoembolization or transarterial radioembolization are occasionally used to increase resectability in children who are not liver transplant candidates owing to uncontrolled metastatic disease.[39,40] It has also been used to maintain disease control for those patients who have completed protocol systemic chemotherapy but for whom a donor organ is not yet available.

Hepatoblastoma Outcomes and Combination Therapies

The most recent published trial results for each of the major multicenter trial groups involved in the study of HB are shown in **Table 2**. The most contemporary results for SIOPEL are SIOPEL 4 and 6. SIOPEL 6 was able to decrease ototoxicity and maintain good outcomes in standard risk tumors using 6 cycles cisplatin monotherapy randomized with or without the otoprotectant sodium thiosulfate.[41] SIOPEL 4 study used a neoadjuvant induction of weekly, dose-compressed cisplatin and 3-weekly doxorubicin in high risk (either PRETEXT IV or metastatic) with event-free survival and overall survival of 76% and 83%, respectively, the best results to date for patients presenting with metastatic disease.[42] Results for COG AHEP-0731, which enrolled 225 eligible patients from 2009 to 2018, by treatment strata were as follows: (a) very low risk and low risk, PRETEXT I and II tumors resectable at diagnosis, maintained excellent outcomes with reductions in chemotherapy, (b) intermediate risk showed improved survival and surgical resection rates, compared with historic controls, by adding doxorubicin to their historic regimen and encouraging early involvement of liver specialty surgical centers[43]; and (c) high risk, patients with metastatic disease were randomized to upfront experimental window chemotherapy of either vincristine–irinotecan[44] or vincristine–irinotecan–temsirolimus. There was response to the upfront experimental therapy, but this response was not superior to the C5VD backbone. The Japanese JPLT 2 study, which enrolled 361 patients from 1999 to 2012, showed inferior outcome in the ruptured at diagnosis subset of the low-risk group when ruptured tumors were resected before chemotherapy. This Japanese study achieved outstanding results for cisplatin + pirarubicin responders and did not support intensified chemotherapy or stem cell transplantation for cisplatin + pirarubicin nonresponders.[45] Cross-study

Table 2
Most recently published HB multi-center cooperative trials

Study	Chemotherapy	Patients and PRETEXT	Outcomes
AHEP-0731 2009–2012[25,43,44]	Very low risk: none Low risk:C5V postop Intermediate risk (SCU or stage III) C5VD Mets: VIwindow; VIT Window[a]	n = 225 Very low risk/PRETEXT I/II = 8 Low risk PRETEXT I/II = 47; III = 2; Intermediate risk PRETEXT: I/II = 34; III = 54; IV = 14; MetsVI: 30 Mets/VIT[a]: 36 (to be published)	5-Year EFS/OS Very low risk: 100%/100% Low risk: 91%/97% Intermediate risk: 87%/95% MetsVI: 49%/62%
HB 99 (GPOH) 1999–2004[24]	SR: IPA; HR: CARBO/VP16	n = 100 SR: 58 HR: 42	3-Year EFS/OS SR: 90%/88% HR: 52%/55%
SIOPEL 4 2005–2009[42]	HR: Block A: Weekly CIS + 3 weekly DOXO; Block B CARBO/DOX	n = 62 PRETEXT: I = 2; II = 17; III = 27; IV = 16; Mets: 39	3-Year EFS/OS HR all:76%/83% PRETEXTIV = 75%/88% Mets: 77%/79%
SIOPEL 6 2007–2014[41]	SR: CIS vs CIS + STS	n = 109; CIS PRETEXT: I/II = 31; III = 21 CIS + STS PRETEXT: I/II = 41; III = 16	3-Year EFS/OS CIS: 79%/92% CIS + STS: 82%/98%
JPLT 2 1999–2012[45]	1: low-dose CITA postop only 2: low-dose CITA 3: CITA full dose 4: high dose ± SCT	n = 361; Course 1 PRETEXT I/II rxn@ dx; Course 2 PRETEXT I/II preoperative chemotherapy; Course 3 PRETEXT III/IV; Course 4 metastatic or CITA nonresponder	5-Year EFS/OS 1: 74%/90% 2: 85%/91% 3: 77%/87% 4: 37%/53%

Abbreviations: AFP, alpha fetoprotein; C5V, cisplatin + 5-flurouracil (5FU) + vincristine; C5VD, cisplatin + 5-flurouracil (5FU) + vincristine + doxorubicin; CARBO, carboplatin; CIS, cisplatin; CITA, cisplatin + pirarubicin; DOXO, doxorubicin; EFS, event-free survival; HR, High Risk; IPA, Ifosfamide + cis + adriamycin; OS, overall survival; PFH, pure fetal histology; SCT, Stem Cell Transplant; SCU, Small Cell Undifferentiated; SR, standard risk; STS, sodium thiosulfate otoprotectant; VIT, vincristine–irinotecan–temsirolimus; VP16, etoposide.

[a] VIT window enrolled 2013 to 2016, not yet published.

group comparisons are complicated by the fact that PRETEXT IV nonmetastatic patients were considered intermediate risk by COG and JPLT and high risk by SIOPEL.

Hepatoblastoma with Features of Hepatocellular Carcinoma and Hepatocellular Neoplasm Not Otherwise Specified

Occasionally with expert pathologic review, a consensus diagnosis for histologic subtype cannot be reached because of a variable heterogenous mix of HB, HCC, and undifferentiated histologies. The international consensus conference called these tumors hepatocellular neoplasm, not otherwise specified,[1] although since then they are more often referred to as HB with HCC features. Prokurat and associates[46] and Zhou and coworkers[47] have also reported such tumors, which they respectively called "transitional liver cell tumors" and hepatocellular malignancies not otherwise specified. The median age is about 7 years (range, 4–15 years), AFP is elevated, and response

to chemotherapy is common. Historically, there has been no consensus on whether to treat these tumors according to either HB or HCC protocols; the PHITT study protocol recommends that they be treated as HB.

New Developments

Biology

As our understanding of the tumor biology has increased, poor molecular prognostic factors such as NFR2 mutation and a 12-gene signature have been identified.[48,49] Genetic and epigenetic analysis has included Wnt pathway and gene expression analysis, DNA methylation profiling, and *TERT* promoter mutations. Nuclear and cytoplasmic accumulations of β-catenin, whose oncogenic mutations lead to chromosomal instability and aberrant Wnt/β-catenin signaling, are seen in almost all patients with HB and may contribute to tumorigenesis.[48–50]

Indocyanine green navigation surgery

The technique relies on the intravenous administration of ICG before surgery and the intraoperative illumination of the surface of the organ by an infrared camera that simultaneously induces and collects the fluorescence[37,38] (**Fig. 4**). With ICG navigation, tumor nodules otherwise not visible may be seen by green fluorescence at the time of surgery. Usually, ICG (0.5 mg/kg) is injected 24 hours before pulmonary metastatectomy. For the detection of nodules in the liver a higher dose is given several days before surgery because ICG is secreted in the bile and requires time to clear the normal liver. The sensitivity for viable tumor cells is 95%, but the specificity is only about 80% owing to the false-positive fluorescence of inflammatory cells. A limitation of ICG navigation is the inability to detect nodules deep in the parenchyma (deeper than 10–15 mm).

HEPATOCELLULAR CARCINOMA

Most pediatric HCC are de novo tumors and develop in normal livers without underlying chronic liver disease. These de novo HCC include conventional HCC, fibrolamellar HCC, and foci of HCC histology occurring in HB. Comparing pediatric with adult HCC, it has been debated whether pediatric de novo HCC is the same disease as

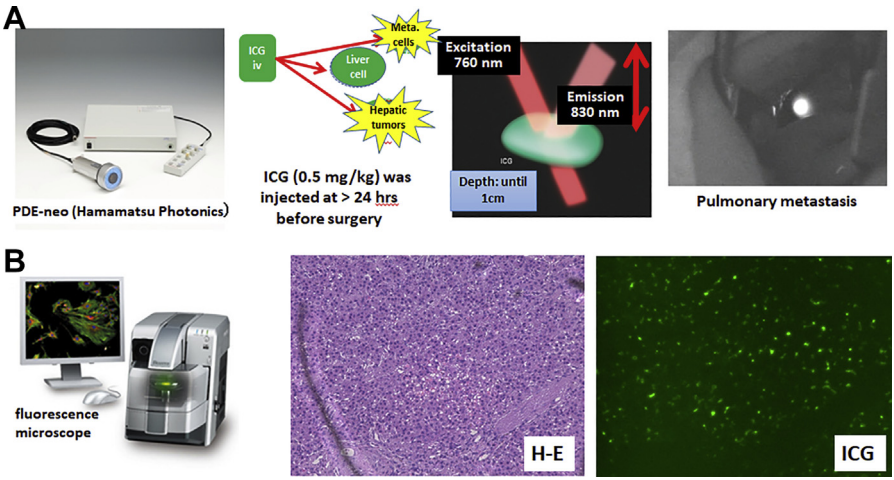

Fig. 4. (*A*) Indocyanine green (ICG) navigation surgery. (*B*) ICG for pulmonary metastasectomy.

HCC in adult cirrhotic livers.[51–53] From a cytogenetic and molecular viewpoint, it seems most likely that the type of HCC and its molecular changes are more important than the age group at which HCC is diagnosed.[53] In a minority of cases of pediatric HCC, the tumor occurs in the background of cirrhosis. Cirrhosis in children is caused by variety of disorders and those with cancer predisposition include tyrosinemia, progressive familial intrahepatic cholestasis syndromes, primary sclerosing cholangitis, congenital portosystemic shunts, glycogen storage disease types I to IV, Fanconi syndrome, and ataxia telangiectasia.[54] As in adults, children with chronic liver disease–induced cirrhosis require surveillance for tumor.

Localized Hepatocellular Carcinoma

In the case of localized, nonmetastatic disease, surgical resection at diagnosis, even by extreme resection or orthotopic liver transplantation, should be considered.[55,56] Contrary to HB, where lymph node metastases are rare, the lymph nodes must be sampled in HCC. In adult HCC, liver transplantation may be restricted to the Milan criteria (single tumor <5 cm; $\leq$3 tumors <3 cm). Milan criteria were originally derived in the context of HCC in adult cirrhotic livers and organ shortage, thus aimed to select patients for optimal success. However, in children it is more common to have large de novo tumors in healthy livers, which, although outside of Milan criteria, have been shown to have a good prognosis with orthotopic liver transplantation.[52] Recent reports show good survival rates of in the range of 75% to 80% at 5 years in selected patients.[56–58] Data from 2 separate Surveillance, Epidemiology, and End Results registry database studies reported that, in children presenting with nonmetastatic HCC, regardless of tumor size, the 5-year survival rate was better after liver transplantation than after resection.[55,57] Although the Surveillance, Epidemiology, and End Results registry data do not include important staging information, the favorable survival suggests that liberalized transplant criteria in children is warranted.

Neoadjuvant Chemotherapy

Various chemotherapy regimens have been used, although the role of chemotherapy in this relatively chemoresistant tumor remains unclear. Results of the SIOPEL-1 study, using neoadjuvant cisplatin and doxorubicin (PLADO), could not be improved in the SIOPEL-2 and -3 studies using neoadjuvant intensified platinum and doxorubicin (SUPER-PLADO), with both studies showing dismal survival rates of 28% and 22% at 5 years.[51,52] Patients who underwent primary surgery or those with complete resection at delayed surgery showed overall survival rates of 40%.[52] The German trial group used ifosfamide, cisplatin, and doxorubicin in the HB-89 trial and carboplatin and ifosfamide in HB-94.[59] The overall survival rates were 33% and 32%, respectively. The more recent HB99 trial showed better (overall survival and event-free survival) 3-year survival rates of 89% and 72%, respectively, in patients with resectable tumors followed by 2 cycles of carboplatin and etoposide. However, in those with metastatic disease or nonresectable tumors, the survival rates were disappointing at 20% and 12%, respectively.[59] These results are in line with a small COG study showing that upfront resections had good survival (5-year event-free survival 88%) with postoperative chemotherapy and the outcome was uniformly poor for advanced stage disease (5-year event-free survival of 10%–23%).[60] Tumor-free margins been have shown to be a strong predictor of favorable outcome,[52] whereas lymphovascular invasion, extrahepatic tumor, and metastatic disease precluding complete resection are poor prognostic factors (5-year event-free survival of 10%).[51] Common pathways for target are vascular endothelial growth factor receptor (sorafenib, bevacizumab, brivanib, sunitib), epidermal

growth factor (erlotinib), mammalian target of rapamycin (everolimus, tyrosine kinase receptor for hepatocyte growth factor, cMET [tivantinib]), combined vascular endothelial growth factor and cMET (carbozantinib) and programmed cell death receptor (nivolumab).[53,54] Sorafenib has been used by the German pediatric group in combination with PLADO, which showed tumor regression in a small number of patients with unresectable tumors.[59]

Metastatic Hepatocellular Carcinoma

In children with metastatic HCC, the prognosis is grim. Although there is increasing experience with first- and second-line chemotherapy in adult patients, none of these regimen have translated into prolonged survival. They include treatment with gemcitabine plus oxaliplatin, 5-fluoracil (5-FU) plus cisplatin, cape-citabine plus cisplatin, 5-FU plus mitomycin, 5-FU plus oxaliplatin, gemcitabine plus cisplatin, 5-FU plus interferon, and monotherapy with sorafenib.[54] In the SIOPEL experience the partial tumor response rate to cisplatin and doxorubicin was 33-49%, however many of these patients never became resectable.[52] Only scarce data on the use of gemcitabine plus oxaliplatin in pediatric patients with HCC is available. Some investigators have hypothesized that pediatric HCC is more responsive to chemotherapy than adult HCC, but whether this finding is true for all de novo HCC types in children, or specifically for the hepatocellular neoplasm, not otherwise specified type (HB with HCC features), remains open.[52] Ablative therapies like radiofrequency ablation, percutaneous ethanol ablation, or transarterial chemoembolization, hepatic arterial infusion chemotherapy, and transarterial radioembolization have been widely used in adults, mostly for downstaging to comply with Milan criteria and for bridging to transplantation; however, the experience in children is limited.[61,62] The role of a palliative resection of the primary tumor with the goal to preserve quality of life or even prolong survival is unclear.[62]

Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar HCC is most common in adolescents and young adults and has a slight female preponderance. AFP is usually normal, although the level of transcobalamin I may be elevated.[54] At diagnosis, 35% of patients have vascular invasion and 60% have extrahepatic disease.[63] Although fibrolamellar HCC seems to have a more favorable prognosis in adults, this does not seem to be the case in children.[63–65] A review of SIOPEL fibrolamellar HCC cases showed 31% partial response to super-PLADO, 42% complete resection, and 3-year event-free survival and overall survival rates of 22% and 42%, respectively, which were comparable with conventional pediatric HCC.[65] A recent finding of an RNA transcript and protein incorporating *DNAJB1* and *PRKACA* may provide the basis for a diagnostic marker and could be a future target for therapeutic interventions.[66]

OTHER MALIGNANT LIVER TUMORS IN CHILDREN

Pediatric Hepatic Sarcomas

- *Undifferentiated Embryonal Sarcoma of the Liver (UESL).* UESL is the third most common malignant pediatric liver tumor usually presenting around 6 to 10 years, it can occur in both younger and older children.[67–69] It has been reported to arise within mesenchymal hamartomas sharing genetic features.[70] UESL has cystic and solid components and the myxoid cystic components may hemorrhage or rupture at diagnosis or with biopsy attempts[68] (**Fig. 5**A). A biopsy should be undertaken with ultrasound guidance to the more solid areas of the tumor and/or a biopsy of a metastatic lesion. Complete resection is crucial and most neoplasms are treated according to the embryonal sarcoma regimens for other pediatric soft

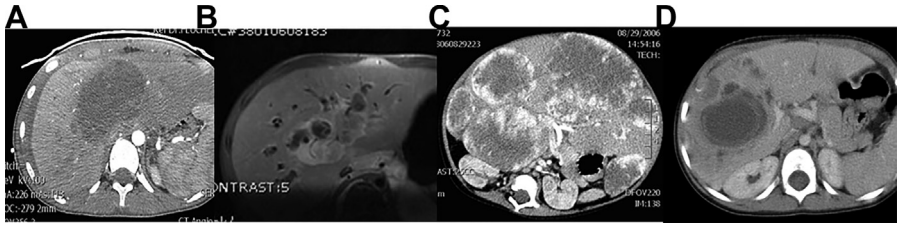

Fig. 5. Radiographic appearance of pediatric liver tumors. (*A*) Undifferentiated embryonal sarcoma (UESL) with a mixture of cystic/myxoid and solid components. (*B*) Biliary rhabdomyosarcoma, presentation with biliary tract obstruction is common. (*C*) Multifocal or diffuse subtype of infantile hepatic hemangioma can involve the entire liver with significant hepatomegaly. (*D*) Mesenchymal hamartoma presents as a multicystic mass with thick vascular sepatae.

tissue sarcoma anatomic sites. Response to multimodal therapy has improved and the overall survival rate is now about 70%.[67–69]

- *Biliary rhabdomyosarcoma.* Biliary rhabdomyosarcoma accounts for less than 1% of rhabdomyosarcoma in children; the median age at diagnosis is 3 years.[71] The typical presentation is with jaundice and biliary obstruction, occasionally cholangitis.[71] Imaging shows hypoechoic intraductal or periductal cystic solid mass with dilation of a partially obstructed biliary tract (**Fig. 5**B). Often, imaging is misdiagnosed as a choledochal cyst.[72] Biopsy can be either percutaneously or by endoscopic retrograde cholangiopancreatography.[73] Neoadjuvant chemotherapy and radiation therapy will decrease the mass effect and improve the biliary obstruction. Most tumors are localized and hence resectable, but complete resection can be challenging when located in the hilum. The reported 5-year survival for patients with local–regional disease is 50% to 78%. Metastatic disease is often fatal.[74]
- *Angiosarcoma.* A handful of pediatric cases have been reported, some of which seemed to be a malignant transformation of infantile hepatic hemangioma.[75–77] Infantile hepatic hemangioma and angiosarcoma can both have positive GLUT-1; hence, it is difficult to determine if angiosarcoma emerged from the infantile hepatic hemangioma or in association with the infantile hepatic hemangioma.[77] Refractory metastatic disease is common and the prognosis is poor, with a median survival of 14 to 18 months and an overall survival at 5 years of 20% to 35%.[75–77]
- *Malignant rhabdoid tumor of the liver.* Rhabdoid tumors are aggressive with poor survival. The typical age at diagnosis is 0 to 3 years and, although most common in the kidney, they can occur anywhere in the body; the liver is the fourth most common site. Some patients with an AFP of less than 100 in older HB trials may have been malignant rhabdoid tumors of the liver, which would explain their poor survival.[78] Malignant rhabdoid tumors of the liver are defined by lack of INI-1 tumor suppressor gene; therefore, the diagnosis requires immunohistochemistry.[79–82] Treatment is with aggressive chemotherapy combined with complete resection, but these are often metastatic neoplasms with a poor survival.[80–84]
- *Other malignant liver tumors in children.* A nested stromal epithelial tumor is a recently described rare neoplasm showing nests of spindled epithelioid cells with a potential for calcification.[83,84] Surgical resection is the treatment of choice, after which Cushing syndrome, when present, will resolve.

Cholangiocarcinoma is rarely seen in the pediatric population. If diagnosed before adulthood, it can be associated with choledochal cysts, primary sclerosing cholangitis, biliary atresia and other biliary anomalies, human immunodeficiency virus infection, and radiation therapy.[85,86] A primary yolk sac tumor of the liver is extremely rare, but has been reported in young children. It is easily confused with HB owing to age and high AFP so histologic examination is essential for diagnosis.[87] A primary hepatic lymphoma is a lymphoproliferative disorder confined to the liver, whereas non-Hodgkin's lymphoma may involve the liver as a secondary manifestation. The liver is the third most common abdominal organ with lymphoma involvement.[88] Liver disease may be focal, but more commonly shows multiple small ultrasound hypoechoic nodules.[89] Hepatomegaly is a common presentation in many pediatric hematologic malignancies including hemophagocytic lymphohistiocytosis, Langerhans cell histiocytosis, and acute megakaryoblastic leukemia. Many pediatric abdominal solid tumors can spread to the liver and metastatic liver tumors should always be considered in the differential diagnosis of any child with a neoplastic liver process. During the first year of life, liver metastases can be found in neuroblastoma. In older children, germ cell tumors, neuroendocrine pancreatic tumors, pancreatoblastoma, gastrointestinal stromal tumor, desmoplastic small round cell tumor, and Wilms' tumor can metastasize to the liver.[4]

Benign Liver Tumors in Children

- *Congenital hemangioma.* Congenital hemangiomas proliferate in utero and generally reach peak size before or at birth. Diagnosis may occur on prenatal imaging or through evaluation of a mass or heart failure in the newborn. Congenital hemangiomas are high-flow vascular lesions and may have intratumoral bleeding, thrombocytopenia, hypofibrinogenemia, and high-output cardiac failure. A newborn may present with significant anemia, thrombocytopenia, and mild hypofibrinogenemia. They are GLUT-1 negative and typically follow 1 of 3 clinical patterns: rapidly involuting congenital hemangioma), partially involuting congenital hemangioma, and noninvoluting congenital hemangioma.[90]
- *Infantile hemangioma.* Infantile hemangioma are GLUT-1 positive and continue to proliferate until approximately 6 to 12 months of age, with gradual involution until 3 to 9 years of age. Like congenital hemangiomas, they may be high flow, but the vascular symptoms will develop later during the postnatal proliferation period as shunting increases. Acquired consumptive hypothyroidism is specific for hepatic infantile hemangioma. Focal tumors may be silent clinically; however, multifocal or diffuse tumors may develop into abdominal compartment syndrome and failure to thrive.[90]
- *Multifocal or diffuse infantile hepatic hemangioma* (**Fig. 5**C). The treatment of symptomatic diffuse lesions is in conjunction with a multidisciplinary team well-versed in the natural history of these lesions and familiar with the medical treatment and percutaneous embolization approaches in children.[91]
- *Focal nodular hyperplasia.* These neoplasms are uncommon in children, but can occur in specific subgroups of patients with abnormal hepatic circulation, patients with a history of chemotherapy for a nonliver malignancy, and adolescent females.[92] MRI can be diagnostic showing isointense to hypointense on T1-weightged imaging, and isointense to mildly hyperintense on T2-weighted sequences.[93,94] In equivocal cases, a biopsy may be needed.[92]
- *Mesenchymal hamartoma.* These tumors, usually in a preschool age child, tend to be large with multiloculated cysts separated by thick vascularized septae[95,96]

(Fig. 5D). The differential diagnosis is sometimes challenging and includes UESL, simple hepatic cysts, teratoma, ciliated foregut cysts, echinococcal abscess, and purulent abscess. Occasionally, the AFP may be elevated.[97] Treatment usually consists of complete surgical resection with negative margins given a genetic association with UESL.[98,99]

- *Hepatocellular adenoma*. In children, the mean age of diagnosis is 14 years with rare cases in younger children.[100] Usually, they are solitary, although multiple adenomas may be seen in children with predisposing conditions such as glycogen storage disease. Apart from the special circumstance of glycogen storage disease, surgical excision has been recommended for lesions greater than 5 cm, dysplastic foci, enlarging size, features of malignant change on imaging, β-catenin activation, or male gender.[101]
- *Rare benign tumors*. Rare benign tumors include inflammatory myofibroblastic tumor,[102] teratoma,[103] intrahepatic bile duct adenoma,[104] and macroregenerative nodules.[105]

SUMMARY, DISCUSSION, AND FUTURE DIRECTIONS

The survival of children with liver tumors, especially HB, has improved significantly after the introduction of effective chemotherapeutic regimens and appropriate surgical approaches, including liver transplantation, resulting in an increase in the number of patients undergoing definitive tumor resection and a decrease in the incidence of postsurgical recurrences. With improvements in survival, decreasing late effects such as ototoxicity, secondary malignancies, and the long-term complications of transplantation should be an increased focus of our research effort. Future trials should investigate risk-based strategies for management of metastatic and refractory disease and minimizing treatment-related complications and long-term toxicities. Moreover, further histologic and biological studies are necessary in moving toward the individualization of therapy.

CLINICS CARE POINTS

- Screening of a palpable abdominal mass in a child is with ultrasound. When ultrasound shows liver mass in a young child diagnosis of HB includes elevated AFP, contrast-enhanced CT scan or MRI of the liver, and a chest CT scan.
- Radiographic staging of the pretreatment extent of the tumor (PRETEXT) includes PRETEXT group (I, II, III, and IV), depending on number of anatomic liver sections free of tumor, and PRETEXT annotation factors (VPEFRM), which denote extent of major vessel involvement and extraparenchymal tumor extension (see Fig. 2).
- Treatment protocols for HB depend on the PRETEXT group (I, II, III, or IV), PRETEXT annotations factors (VPEFR), metastasis (M), patient age, and AFP level (see Fig. 3).
- The survival of children with HB has improved significantly after the introduction of cisplatin-based chemotherapeutic regimens, which resulted in an increase in the number of patients ultimately undergoing complete tumor resection and a decrease in the incidence of postsurgical recurrences.
- Complete tumor resection remains the cornerstone of curative therapy for both HB and HCC.
- New developments in HB include the international collaborative multicenter trial (PHITT), sodium thiosulfate to protect against cisplatin ototoxicity, ICG navigation surgery, and increasing identification of biologic markers for prognosis.

- Long-term follow-up after treatment for HB is needed for late effects of therapy, such as ototoxicity, cardiotoxicity, renal toxicity, growth delay, and secondary malignancies.

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DISCLOSURE

The authors have nothing to disclose.

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