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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Advances in Pediatric Liver Tumors

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Abstract
Purpose of Review Hepatoblastoma and hepatocellular carcinoma are rare pediatric tumors. We review the significant advances in hepatoblastoma and pediatric hepatocellular carcinoma prognosis and treatment.
Recent Findings International pathologic classification and risk stratification have been extensively reviewed and redefined for hepatoblastoma via international collaborative analyses of an international hepatoblastoma database. International trials have identified patients for whom (1) no adjuvant chemotherapy is indicated, (2) neoadjuvant chemotherapy improves resectability and survival, and (3) intensified therapy improves survival (for patients with metastatic disease). Hepatocellular carcinoma studies highlight the poor prognosis for patients with nonlocalized disease emphasizing the need for future collaborative efforts exploring molecular characteristics and novel therapeutics.
Summary Recent advances have significantly improved treatment of hepatoblastoma by implementing a consensus international pathologic classification and risk stratification and identification of higher risk biological features. Advances in pediatric hepatocellular carcinoma treatment lag behind hepatoblastoma. The Pediatric Hepatic International Tumor Trial (PHITT) will focus on decreasing long-term toxicity, improving outcomes, providing surgical guidelines, and advancing the knowledge of the biology of hepatoblastoma and hepatocellular carcinoma.

Keywords Pediatric · Liver tumor · Hepatoblastoma · Hepatocellular carcinoma · Staging · Risk stratification · Therapy · Biology

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Introduction

Liver tumors comprise approximately 1% of all pediatric malignancies [1, 2]. Hepatoblastoma (HB) accounts for greater than two thirds of these liver tumors, while hepatocellular carcinoma (HCC) is the second most common pediatric liver tumor. Other less common pediatric primary malignant liver tumors include undifferentiated sarcoma and angiosarcoma. Pediatric patients with HB or HCC typically present with an enlarged abdomen, palpable abdominal mass, and elevated alpha-fetoprotein (AFP). Liver tumors can directly extend through the portal or hepatic vasculature. Distant metastases most frequently occur in the lung. Diagnostic imaging focuses on the evaluation of the liver parenchyma, typically with magnetic resonance imaging (MRI) with the use of hepatocyte-specific contrast agent for increased specificity and noncontrast spiral computed tomography (CT) of the lungs [3, 4]. Definitive diagnosis is typically made by biopsy with the pretreatment acquisition of tissue becoming more important as genomic studies become increasingly incorporated into clinical trials.

Premature infants with very low birth weight have been shown to be at substantially higher risk of developing HB

[5]. Others at risk for HB include patients with familial adenomatous polyposis and a germline adenomatous polyposis (*APC*) gene mutation, Beckwith-Wiedemann syndrome, and a history of maternal tobacco exposure [6–8]. HCC has been linked to hepatitis B or C infection, the former less common following the institution of widespread vaccination programs, and other more rare hereditary syndromes predisposing to liver disease (e.g., glycogen storage disease, biliary atresia, and alpha-1-antitrypsin deficiency) [9–11]. Substantial advances have been made in the treatment of HB over the last decade, with an 80–100% 5-year event-free survival (EFS) for patients with localized disease and a 30–80% survival for those with extensive liver disease and/or distant metastases [12, 13, 14••]. Patients with HCC, however, fare poorly with a less than 25% 5-year EFS [15, 16]. We will focus on novel developments in the diagnosis and the molecular biology of these tumors as well as the treatment of pediatric patients with HB and HCC highlighting important aspects to the management of these patients and future directions in their care.

Pathology and Biology

HB is an embryonal tumor believed to arise from a hepatocyte precursor cell and often recapitulates various stages of liver development. These tumors usually show a combination of epithelial, mesenchymal, undifferentiated, and rarely other histologic components (Table 1) [17••]. The most common epithelial variant is the embryonal type in which tumor cells resemble hepatocytes at 6 to 8 weeks of gestation, with a high nuclear-to-cytoplasmic ratio as well as angulated nuclei, forming primitive tubules and that are commonly accompanied by extramedullary hematopoiesis. In contrast, fetal HB contains cells with centrally placed, small and round nuclei and finely stippled chromatin with either clear or eosinophilic cytoplasm. Other rare epithelial variants include small cell undifferentiated, cholangioblastic, and epithelial macrotrabecular patterns. In addition, 20 to 30% of HBs contain stromal components including spindle cells, osteoid, skeletal muscle, and cartilage and are designated teratoid HBs when the mixture of heterologous components includes elements such as endoderm, neuroectodermal derivatives, melanin-containing cells, and others.

Like other embryonal tumors in children, HB is believed to partly arise as a result of aberrant activation of developmental and cancer pathways (Fig. 1). The Wnt signaling pathway plays a crucial role regulating embryonic liver development and hepatocellular tumorigenesis. Germline mutations of the *APC* gene or sporadic mutations in canonical Wnt pathways genes, such as beta-catenin (*CTNNB1*) and *AXIN2*, lead to the abnormal activation of Wnt signaling. Sequentially aberrant overexpression and nuclear translocation of beta-catenin turns on the transcription of downstream genes such as *CYCLIN D1* invariably resulting in uncontrolled neoplastic cell proliferation and the inhibition of cell differentiation, thereby leading to tumorigenesis. Beyond driving mutations in Wnt signaling pathways, recent studies using genomic signature and RNA expression profiling demonstrate molecular biomarkers that may be useful to improve HB risk classification and improve risk stratification and patient-specific treatment [18••].

Table 1 Pediatric primary malignant liver tumor classification

- Epithelial tumors
  - Hepatocellular
    - Hepatoblastoma
      - Epithelial variants
        - Pure fetal with low mitotic activity
        - Fetal, mitotically active
        - Pleomorphic, poorly differentiated
        - Embryonal
        - Small cell undifferentiated (SCU)
          - INI1-negative
          - INI1-positive
        - Epithelial mixed (any/all above)
        - Cholangioblastic
        - Epithelial macrotrabecular pattern
      - Mixed epithelial and mesenchymal
        - Without teratoid features
        - With teratoid features
    - Hepatocellular carcinoma (HCC)
      - Classic HCC
      - Fibrolamellar HCC
    - Hepatocellular neoplasm, not otherwise specified (NOS)
  - Biliary
    - Cholangiocarcinoma
    - Combined hepatocellular and cholangiocarcinoma
- Mesenchymal tumors
  - Embryonal sarcoma
  - Rhabdomyosarcoma
  - Vascular tumors
    - Epithelioid hemangioendothelioma
    - Angiosarcoma
- Other malignancies
  - Malignant rhabdoid tumor
    - INI1-negative
    - INI1-positive
  - Nested epithelial stromal tumor
  - Germ cell tumors
    - Teratoma
    - Yolk sac tumor
  - Desmoplastic small round cell tumor (DSRCT)
  - Peripheral primitive neuroectodermal tumor (pPNET)

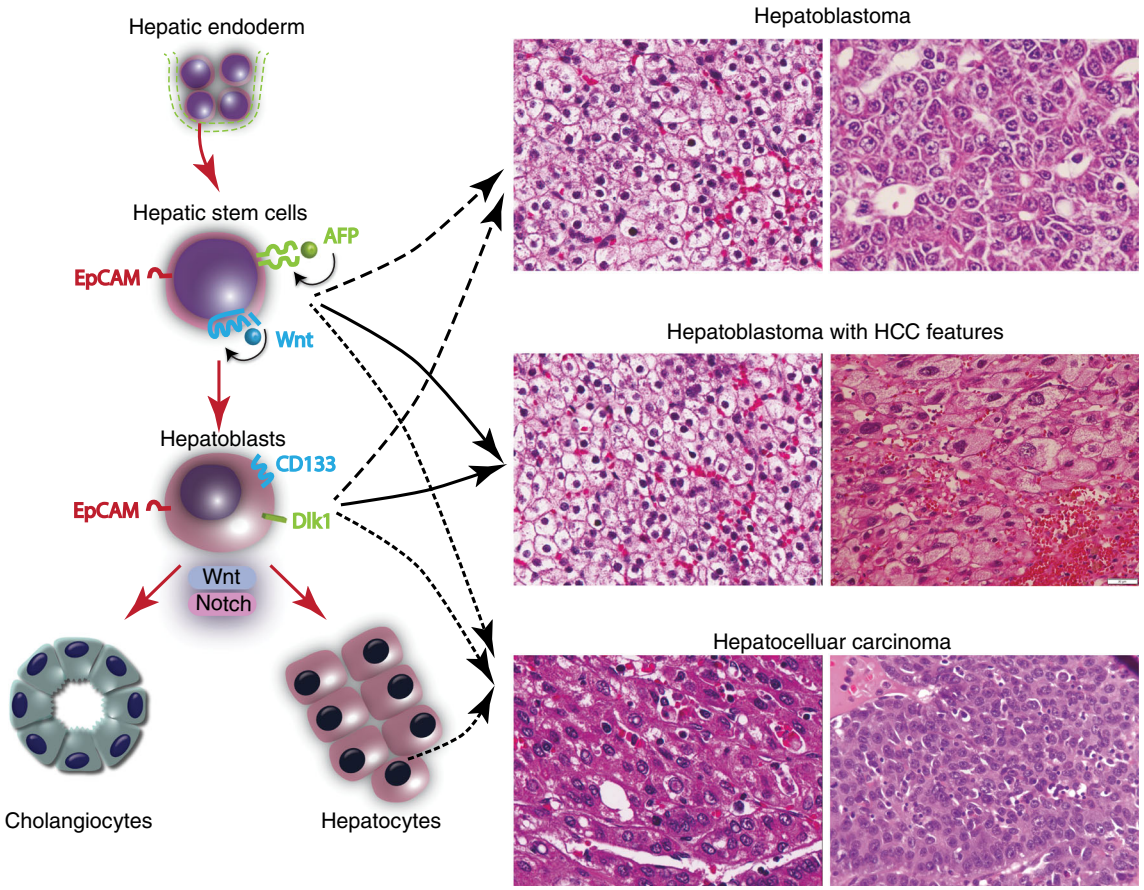

Fig. 1 Histologic and biologic characterization: tumorigenesis of hepatoblastoma and hepatocellular carcinoma. Wnt signaling pathway is essential for embryonal hepatocyte development where the hepato-endoderm gives rise to hepatic stem cells with the ability to self-renew and differentiate into multiple cell lineages. Hepatic stem cells in turn develop into hepatoblasts which further differentiate into either hepatocytes or cholangiocytes. Hepatoblastomas are considered to derive from hepatic stem cells and hepatoblasts and often show phenotypic similarities to fetal liver cells with great histologic heterogeneity. Hepatocellular carcinomas, in contrast, are derived from cells at the early stage of development: hepatic stem cells or dedifferentiation of mature hepatocytes

Cytogenetic abnormalities, both numerical and structural, are found in approximately half of all HB. Trisomies of chromosomes 2 and 20 are the most commonly reported abnormalities followed by trisomy 8 and rare translocations although the overall clinical significance of these cytogenetic abnormalities in HB remains unclear [16].

Rare hepatocellular tumors in older children and adolescents show an unusual phenotype with a distinct aggressive clinical behavior and poor response to systemic chemotherapy. These tumors show overlapping phenotypic features of HB and HCC including significant cytologic atypia or focal anaplasia (Fig. 1). These HB with HCC features, previously designated as "transitional liver cell tumors," represent a distinct group of lesions. Like classical HB, most HBs with HCC features have *CTNNB1* mutations/deletions and corresponding aberrant nuclear expression by immunohistochemistry. In contrast, *TERT* promoter hotspot mutations G228A and G250A, and other rare mutations seen in HCC, only appear to occur in HB with HCC features, but not in classical HB. In addition, higher genomic instability and increased number of DNA gains and losses than in conventional HB are also observed in HB with HCC features [19, 20].

The two histologic subtypes of pediatric HCC are fibrolamellar and classic types. *DNAJB1-PRKCA* and *GLIS3-CLPTM1L* fusion transcripts have recently been reported in most, if not all, cases of fibrolamellar HCC [21•]. The *DNAJB1-PRKCA* fusion transcript leads to the overactivation of cAMP-dependent protein kinase A (PKA) signaling and elevated phosphor-CREB levels with resultant oncogenesis. In addition, the *GLIS3-CLPTM1L* fusion transcript promotes cancer phenotypes in human HCC cell lines. In contrast to fibrolamellar HCC, no single disease defining mutations or characteristic cytogenetic abnormalities have been identified in the classic HCC type, and although aberrant activation of WNT signaling pathway is seen in approximately one third of cases, it is unclear whether aberrations in other driving oncogenic pathways seen in HCC diagnosed in adults are also present in pediatric HCC [20]. Karyotypic abnormalities are uncommon in fibrolamellar HCC beyond the translocation description above, and unlike adult HCC in which

complex karyotypes are often seen, the overall genomic instability remains unrevealed [20]. Multiple lesions, intravascular spread, and metastases are more common in HCC than in HB.

Radiology

Over the past two decades, there has been an increased reliance on imaging to diagnose, stage, and treat hepatic malignancies. This trend has been pervasive across all imaging modalities. However, its effect is best illustrated through two key examples: MRI with hepatocyte-specific contrast agent (gadoxetate sodium) and hepatic arterial-directed therapies. As imaging advances over the next decade, the potential of radiogenomics brings with it the promise of precision medicine.

Several factors have contributed to help make MRI the preferred imaging modality for pediatric liver tumors. These factors include the concern of radiation exposure from CT, the superior soft tissue resolution of MRI, and the advent of hepatocyte-specific contrast agents for MRI. The combination of superior soft tissue resolution and hepatocyte-specific contrast agents has allowed radiologists to identify more lesions, to diagnose liver tumors with greater specificity, and to have more confidence in their diagnosis [3, 22, 23•]. What this means practically is that radiologists are better able to define tumor boundaries for pretreatment extent of disease (PRETEXT) staging, better able to distinguish focal nodular hyperplasia (FNH) from adenomas or metastases, and better able to identify targets for biopsy [3, 22, 23•, 24–26].

Targeted therapies for liver tumors were first described nearly two decades ago [27–29]. At that time, the predominant mode of therapy was intrahepatic arterial chemoembolization. Over the past decade, the number of therapeutic options has increased and includes Y-90 radioembolization, bland embolization, and targeted tumor embolization (radiofrequency ablation, cryoablation, and microwave ablation) [30, 31]. Because of continued improvement in the primary therapeutic modalities (chemotherapy and surgical resection), the interventional radiology-directed therapies have been limited mostly to patients with advanced disease and poor surgical candidates. To date, there have been no comparative trials evaluating the different imaging-guided therapeutic options.

Radiogenomics is based on the hypothesis that tumor heterogeneity on imaging can be explained by tumor genetics [32, 33••]. Currently, radiologists perform this task in a crude manner. They identify the MRI imaging characteristics on a number of various sequences to make a specific tumor diagnosis. For example, FNH is slightly hypointense to isointense on T1W images and isointense to slightly hyperintense on T2W images, enhances avidly on the hepatic arterial phase, becomes isointense to slightly hyperintense on the portal venous phase, and retains contrast on the hepatocyte phase. As we move into the machine era of image analysis, computers will help radiologists analyze each pixel of imaging data. Even though age and clinical history are usually the only pieces of information needed to distinguish between hepatoblastoma and hepatocellular carcinoma, the hope is that this radiomic data will allow radiologists to reliably predict tumor histology and even tumor genetics in order to allow oncologists and surgeons to treat the specific subtypes of liver tumors more precisely. While this type of image analysis has shown promise in the diagnosis and characterization of adult brain tumors, prostate carcinoma, and breast cancer, there has been no published research regarding the utility of this technique in the setting of liver malignancies [34–36].

Staging and Risk Stratification

Clinical stage and histologic subtype impact prognosis for patients with HB and HCC. For treatment and prognostic purposes, risk stratification in HCC is characterized by histology and by disease extent (localized/resectable or nonlocalized/unresectable). Recent advances in staging and risk stratification have allowed for better defined risk groups in HB. In North America, the staging of pediatric liver tumors has been traditionally based on the extent of disease at the time of surgical resection; however, in Europe, staging has been recently based on PRETEXT with groups assigned based on the number of liver sectors involved and the presence (or absence) of annotation factors, i.e., metastasis, multifocality, extrahepatic disease, tumor rupture, and vascular involvement (Fig. 2) [37]. Furthermore, through an international cooperative effort (Children's Hepatic tumors International Collaboration [CHIC]), a complete, retrospective, multicooperative group review of decades of collaborative HB data was performed and established stratification criteria according to the risk for adverse disease outcome by EFS and classified patients into very-low-, low-, intermediate-, and high-risk groups (Table 2) [38••, 39••]. Patients with localized disease resected at diagnosis have very low-risk disease. Patients with low-risk features (AFP >100 ng/mL, age <8 years, negative annotation factors) have low-risk disease. Patients with metastatic disease, age ≥8 years, or AFP ≤100 ng/mL have high-risk disease. All others fall into the intermediate-risk group.

Surgery in Hepatoblastoma

Surgery is the therapeutic cornerstone for achieving cure in pediatric patients with liver tumors. Be it a conventional extirpative procedure or a transplant operation, rendering the patient free of disease is the goal of treatment.

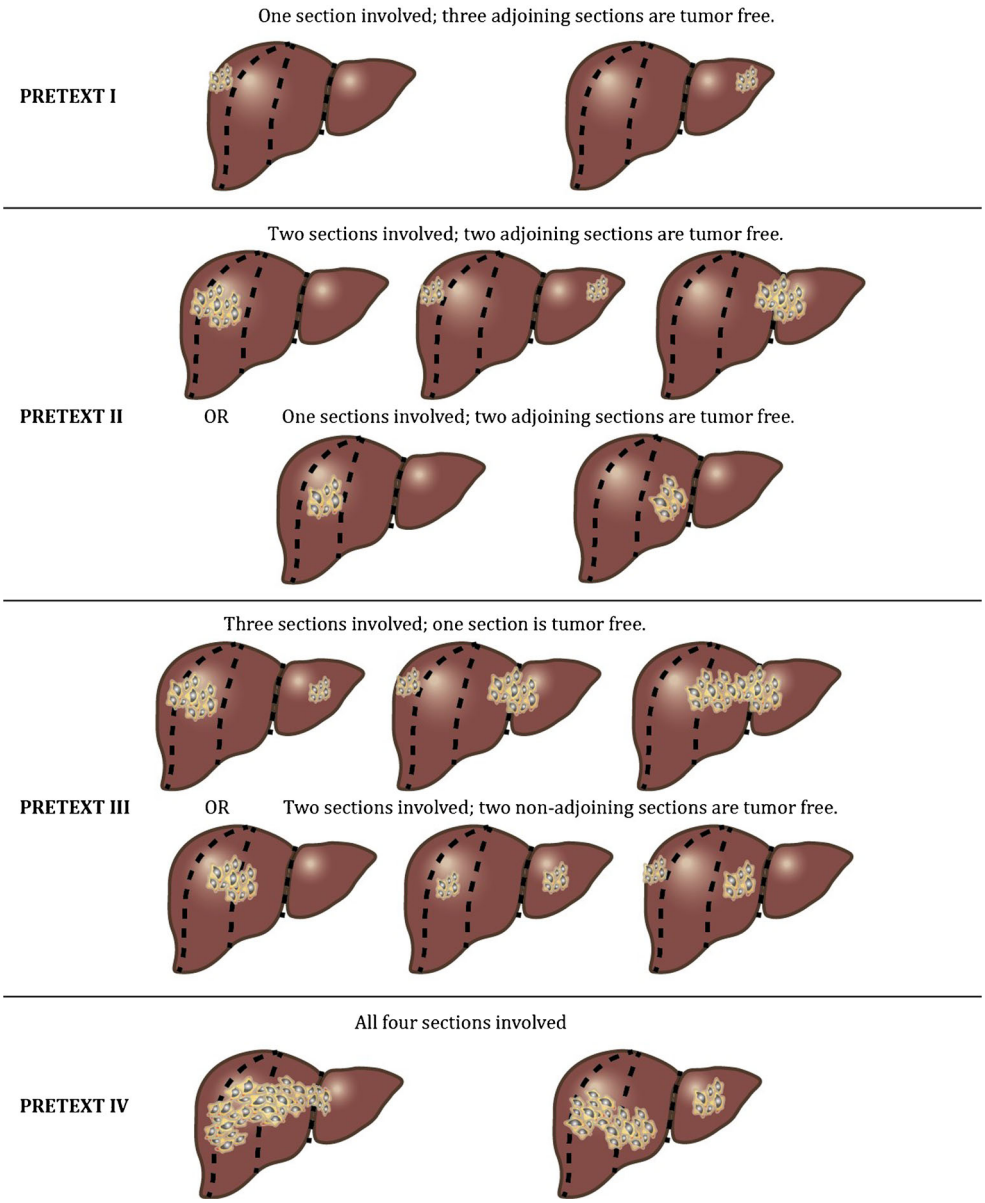

Fig. 2 Radiologic characterization: hepatoblastoma PRETEXT grouping system

For patients with HB, only 40% of patients present with tumors amenable to resection at diagnosis [40]. The advent of effective adjuvant chemotherapy regimens has made once unresectable tumors resectable. The determination of when to apply surgery during treatment and what operation to utilize is defined by the expertise of the surgeon and treating center, the anatomic extent of disease as determined by radiographic analysis (PRETEXT), and the suitability of the patient for surgery. Consensus agreement regarding the terminology employed to describe these operations is lacking, but Strasberg put forth and described the modern standard most widely accepted [41].

Table 2 Pediatric hepatoblastoma risk-based classification based on the CHIC analysis

Risk	Classification criteria
Very low	Resected at diagnosis without high-risk features
Low	Not resected at diagnosis with low risk features (negative annotation factors, age < 8 years and AFP>100 ng/mL)
Intermediate	Not resected at diagnosis with intermediate risk features (positive annotation factors, age < 8 years and AFP > 100 ng/mL)
High	Metastatic disease, age ≥8 years or AFP level ≤100 ng/mL

Data and tradition in North American trials have traditionally favored upfront surgery where feasible to reduce or even eliminate the need for adjuvant chemotherapy, especially with tumors that are smaller and not multifocal that can be resected without a significant risk of perioperative morbidity (PRETEXT I/II tumors) [42]. This fact is evident in the report from the Children's Oncology Group (COG) that documented that patients with HB with pure fetal histology had an EFS and overall survival (OS) of 100% with resection alone, and this premise is being further actively pursued in the current COG hepatoblastoma trial (AHEP 0731) where PRETEXT I/II patients who underwent complete extirpation at diagnosis of HB with pure fetal histology received no postoperative chemotherapy [43]. This ongoing trial has also instituted a reduction from four to two cycles of neoadjuvant therapy for other histopathological subtypes of HB that are PRETEXT I/II tumors prior to resection. Though ongoing and complete data analyses are lacking in both trial arms mentioned above, it should be noted that the stopping rules have not been met to date for either arm. Furthermore, based on these data, the forthcoming multicooperative group Pediatric Hepatic International Tumor Trial (PHITT) will be assessing the feasibility of further chemoreduction for specific groups of children (Greg Tiao, personal communication).

In the event that a tumor is locally advanced or centrally located (PRETEXT III/IV) with or without the presence of metastatic disease, neoadjuvant chemotherapy is employed with serial imaging after two and four cycles to determine tumor response and likelihood of complete extirpation at these time points. For those tumors that do not respond or respond poorly where conventional extirpative approaches will not result in complete removal, orthotopic liver transplantation (whole or split organ, deceased or live donors) is strongly recommended as the primary mode of local control in lieu of attempted surgical resection and subsequent rescue transplantation procedures [44, 45]. Ultimately, the decision of conventional surgery versus transplantation is determined by the treating center and its physicians, but the rise of advanced imaging techniques and computer-aided anatomical models has allowed for a more exhaustive preoperative evaluation about the extent of the resection required and, hence, the possible and likely benefit of which patients truly need transplant referral [46].

Chemotherapy in Hepatoblastoma

When surgically indicated for patients with HB, resection at diagnosis is preferable; however, approximately two thirds of patients present with tumors that are unresectable at diagnosis [47]. Treatment of HB is based on resection of all measurable disease when possible. Treatment advances have been made over the last 40 years (Table 3) [13, 14••, 17••, 38••, 43, 47–58]. Neoadjuvant and adjuvant chemotherapy is administered to render tumors amenable to resection, eradicate gross and microscopic metastatic disease, and decrease metastatic spread of tumor with the curative goal of achieving remission and avoiding tumor recurrence or progression (Table 3). Treatment varies for patients depending on their clinical presentation and is affected by multiple different factors affecting risk stratification including age, degree of AFP elevation, PRETEXT group, and histology; nonetheless, approach to treatment is dependent on several different clinical groupings: (1) patients with tumors that can be cured by resection alone, (2) patients with tumors that can be cured using chemotherapy but without inclusion of doxorubicin, (3) patients with tumors amenable to resection with or without liver transplantation following multi-agent neoadjuvant chemotherapy (including doxorubicin), and (4) patients with tumors that have metastasized or have other poor risk features for which new agents or new timing of agents is being sought.

- *Resection alone*. Patients with tumors of pure fetal histology with low mitotic activity (PFH) that are resectable at diagnosis are cured following complete resection and do not require any chemotherapy treatment [43].
- *Chemotherapy without doxorubicin*. The majority of patients with non-PFH tumors that are resectable at diagnosis can be cured with cisplatin alone or with cisplatin, 5-fluorouracil, and vincristine and therefore avoid the cardiotoxicity associated with the use of doxorubicin [47, 57].
- *Multi-agent neoadjuvant chemotherapy followed by conventional surgical approach or by liver transplantation*. Most patients with localized tumors that are not resectable at diagnosis are able to undergo resection of their primary liver tumors following multi-agent neoadjuvant chemotherapy that includes cisplatin and doxorubicin [51, 56]. Importantly, incorporation of liver transplantation (orthotopic or living donor related) when conventional resection is not feasible has significantly improved the survival of this group of patients [14••].
- *Tumors that have metastasized or have other poor risk features for which new agents or new timing of agents is being sought*. For patients with metastatic disease or other poor risk features, a recent pilot study of cisplatin dose compression has improved the chance of cure significantly [14••]. Still, further therapeutic studies incorporating new regimens as well as newer targeted agents are warranted in this high-risk patient population.

Table 3 Landmark studies in the treatment of hepatoblastoma

Advance in approach to HB	Significance	Study/studies	Year of publication	Outcomes	Reference
Resection instead of palliative care	Resection utilized to successfully cure children with embryonal hepatoma and hepatoblastoma	Case reports, CCG 831	1961, 1975, 1982	– First report of 1 child alive 5 years post liver tumor resection – 58% survival in patients post complete resection – 36% survival in patients post complete resection – 0% survival without complete resection	[48–50]
Neoadjuvant and adjuvant chemotherapy	Chemotherapy improves survival by increasing resectability and decreasing risk of recurrent metastatic disease	CCG831, CCG823F, POG8697, HB-89, INT0098, SIOPEL 1	1982, 1991, 1993, 1997, 2000, 2000	– 17.5% survival in patients without complete resection at diagnosis – ~28% survival in patients without complete resection at diagnosis – 91% 5 year EFS in patients with complete resection at diagnosis – 29% >2 year EFS in patients with metastatic disease – 25% 5 year EFS in patients with metastatic disease – 28% 5 year EFS in patients with metastatic disease	[13, 47, 50–53]
Radiologic grouping system	PRETEXT grouping predictor of survival	SIOPEL 1	2000	– 100% 5 year EFS for PRETEXT I – 83% 5 year EFS for PRETEXT II – 56% 5 year EFS for PRETEXT III – 46% 5 year EFS for PRETEXT IV	[13]
Risk stratification	Intensified treatment (often with doxorubicin) for patients with high-risk disease resulted in improved survival in these patients	INT0098, SIOPEL 2, P9645, SIOPEL 3 HR	2000, 2004, 2008, 2010	– 37% 4 year EFS for patients with metastatic disease – 44% 3 year OS for patients with metastatic disease – 56% 3 year EFS for patients with metastatic disease – 50% 3 year EFS for patients with metastatic disease	[47, 54–56]
Cisplatin monotherapy for lower risk HB	Less intense treatment for patients with lower risk HB did not impact high survival rate in these patients	SIOPEL 3 SR	2009	– 83% 3 year EFS for cisplatin monotherapy (85% for cis/doxo)	[57]
Resection alone for PFH	Tumors with PFH histology can be cured with resection alone	P9645	2011	– 100% 5 year EFS for 16 patients with PFH with resection alone	[43]
Treat INI1-negative SCU HB as rhabdoid tumors	Tumors with SCU histology should be tested for INI1 and, if negative, should be treated as rhabdoid tumors	INT0098	2009	– 0% survival for 11 patients with SCU histology. Six of 6 patients tested were INI1 negative.	[58]
Liver transplantation for higher risk HB	Utilization of liver transplantation increases the resection rate for patients with higher risk HB	SIOPEL 3 HR	2010	– 76% of patients had complete resection (21% by LT)	[56]
Cisplatin dose compression for higher risk HB	Increase in survival in patients with metastatic disease with dose-compressed cisplatin	SIOPEL 4	2013 2014	– 3 year EFS 76% for all patients – 77% 3 year EFS for patients with metastatic disease	[14••] [17••]

Table 3 (continued)

Advance in approach to HB	Significance	Study/studies	Year of publication	Outcomes	Reference
International collaboration on pathologic definitions	International consensus on pathologic definitions of pediatric liver tumors allows for improved comparison study among international groups of treating physicians	International Pathology Symposium		– 22 pathologists and experts in pediatric liver tumors defined criteria for pediatric liver tumor classification	
International collaboration on advanced risk stratification	International collaboration to study risk factors in HB results in clinically significant risk stratification data for use on future prospective therapeutic trials	CHIC	2016	– 1605 patients in database studied – Decreased survival in patients with higher PRETEXT group, vascular involvement, extrahepatic disease, multifocal tumor, tumor rupture at diagnosis, age ≥8 years, AFP <100 ng/mL, and/or metastatic disease	[38••]

HB hepatoblastoma, *EFS* event free survival, *OS* overall survival, *cis* cisplatin, *doxo* doxorubicin, *PFH* pure fetal histology with low mitotic activity, *SCU* small cell undifferentiated, *LT* liver transplantation, *AFP* alpha-fetoprotein

Surgery in Hepatocellular Carcinoma

For HCC, effective adjuvant chemotherapeutic regimens remain elusive. As such, surgery's role in delivering a cure is (possibly) even greater than in children with HB. However, the number of children in whom surgery can be performed at diagnosis is at best 30%, and hence, the utilization of adjuvant therapies (chemotherapy alone or in combination with catheter-directed intra-arterial chemotherapy with or without the addition of embolization) is a critical first step [59]. If possible, conventional resection (regardless of the extent of the procedure proposed) should be entertained first with the use of liver transplantation reserved for those with unresectable, localized tumors. The application of transplantation as bound by the Milan criteria (single tumor ≤5 cm or ≤3 nodules [each ≤3 cm]; no macrovascular invasion; no extrahepatic disease) is less clear in pediatric patients. Furthermore, the initial Milan criteria have been expanded to encompass larger and/or more tumors ("rule of 7" [largest tumor diameter in cm plus the total number of lesions cannot exceed 7]) in adult patients, but their strict applicability in pediatric patients has been called into question, especially in those children in whom neoadjuvant therapies have been successful in reducing both local-regional and metastatic disease. In addition, by UCSF criteria, the size limits are expanded to include solitary tumor ≤6.5 cm or ≤3 nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm [60]. An excellent point-counterpoint manuscript by Gupta and colleagues explores this topic (among others with pediatric HCC) in great detail [61]. Most telling in this report, however, is the reiteration of the basic tenet in pediatric HCC that without local control surgery by some means (conventional resection or transplant), mortality is 100%. Hence, a treating center must appraise critically the suitability of each pediatric HCC patient who responds to neoadjuvant therapy for liver transplant if required for local control regardless of what criteria are met (or not) and by what standard they are measured (Milan, expanded Milan, UCSF, Toronto, others). Furthermore, available data would indicate that strict adherence to "adult" criteria for pediatric patients with HCC may not be appropriate [62, 63]. But as in the case of HB, refractory, progressive, and/or uncontrolled disease (especially metastatic) disavows transplant listing.

Chemotherapy in Hepatocellular Carcinoma

While publications abound detailing patient characteristics, treatment regimens, and outcomes for patients with HB, there is a paucity of literature examining treatment of HCC in the pediatric population (Table 4) [15, 16, 64, 65]. This is secondary to small patient numbers and the collaborative efforts required to study such a rare disease. It is theorized that pediatric HCC carries a phenotype distinct from adult HCC on the basis of a divergent pathogenesis and up to a 50% response rate to chemotherapy.

Table 4 Landmark studies in the treatment of hepatocellular carcinoma

Advance in approach to HCC	Significance	Study/ studies	Year of publication	Outcomes (5-year OS)	Reference
Neoadjuvant and adjuvant chemotherapy (PLADO or C5V)	Completely resected patients receiving adjuvant therapy achieved reasonable outcomes	INT-0098 SIOPEL 1	2000	INT-0098 (COG staging): I = 88% III = 23% IV = 10% SIOPEL 1 (PRETEXT): I/II = 44% III = 22% IV = 8% Metastatic = 9%	[15, 16]
Neoadjuvant and adjuvant chemotherapy (SuperPLADO)	Overall survival remains poor even with treatment intensification; 50% or fewer patients achieve resection	SIOPEL 2 and 3	2006	All patients = 22% Primary resection = ~50% Delayed resection = ~40% Unresectable = 0%	[64]
Neoadjuvant and adjuvant chemotherapy (PLADO + sorafenib)	Addition of a biologic agent affords only a modest improvement in survival	GPOH	2012	(PRETEXT) II: CR (3, 12–27 months (1 OLT)), PD (1, 23 months), DOD (1) III: CR (2, 18–32 months, (1 OLT)), SD (1, 5 months) IV: CR (1, 12 months), PD (1, 18 months), DOD (2) Metastatic: CR (1), DOD (1)	[65]

PLADO cisplatin/doxorubicin, *C5V* cisplatin/5-fluorouracil/vincristine, *SuperPLADO* cisplatin/doxorubicin/carboplatin, *CR* complete remission, *OLT* orthotopic liver transplantation, *PD* progressive disease, *DOD* died of disease, *SD* stable disease

Historically, pediatric HCC patients have been treated on protocols designed for patients with HB. Results of these trials have conclusively demonstrated a moderate 50–88% 5-year OS for patients with resectable disease [12, 15, 16]. However, despite upfront responses to chemotherapy, these studies consistently show a devastatingly poor outcome (less than 20% 5-year OS) for patients with unresectable disease underscoring the importance of surgical resection for cure. Recently designed HCC-dedicated treatment efforts have therefore focused on more targeted therapies or introduction of interventional approaches (transarterial chemoembolization, radiofrequency ablation, yttrium-90) intended to increase response rates as a bridge to resection. Liver transplantation for pediatric HCC has demonstrated great promise for patients with nonmetastatic PRETEXT III or IV tumors; however, this category of patients is rare and disease control prior to receipt of an organ is challenging [66]. For patients with upfront-resectable disease, the need for adjuvant chemotherapy remains debated. For patients with unresectable disease, recent chemotherapeutic efforts have built upon prior drug backbones (cisplatin + doxorubicin) with the addition of sorafenib, based upon the adult experience, with modest overall effect [65, 67]. Treatment regimens designed for patients with fibrolamellar HCC, developed at Memorial Sloan Kettering Cancer Center, have focused either on estrogen deprivation given a known hormonal role in tumor growth or protein kinase A inhibition (the latter postulated to be unregulated secondary to the DNAJB1-PRKACA chimeric fusion transcript) [68]. Results from the first trial (estrogen deprivation) were disappointing (results not published), while the latter trial remains ongoing. Checkpoint inhibition has been shown, in the adult literature, to impact disease growth for patients with tumors harboring genomic instability or a high burden of silent mutations [69]. Use in adult HCC has preliminarily proven promising; pediatric investigators have trialed the agent (nivolumab) off-study, but a larger, collaborative effort is warranted to assess efficacy [70].

Interventional Radiology/Other Techniques

Interventional techniques including transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have been utilized in adult patients with HCC for the purposes of primary tumor response as a bridge to transplant or for palliative care. The translation of these techniques to pediatric patients has been slower due to the delayed development and approval of new devices for children, size limitations, and a hesitation to test novel treatment approaches in children [71]. While TACE and RFA have been trialed in pediatric patients with HB, there are only anecdotal cases of use in HCC and few publications [72–74]. The use of transarterial radioembolization with yttrium-90 or external beam

radiotherapy (both to the primary and for lung metastases), while more routinely pursued in the adult community, is rarely utilized in pediatric patients with the former only being studied in the palliative setting [31].

Conclusions

In the past 40 years, we have seen significant advances in the diagnosis, imaging, and treatment (surgery and chemotherapy) of children with liver tumors, and these have led to a continued improvement in the outcome of children with hepatoblastoma. The advent of open multicooperative group international communication with the subsequent pooling and interrogation of information and data has led to the development of an internationally derived, pediatric liver tumor pathology consensus classification, the establishment of CHIC, the identification of prognostic factors, and the development of a new risk stratification schema for children with hepatoblastoma [17••, 38••, 39••].

The upcoming Pediatric Hepatic International Tumor Trial (PHITT) is a worldwide, multicooperative group collaborative clinical trial designed by the COG, Société Internationale D'Oncologie Pédiatrique Epithelial Liver Tumor Study Group (SIOPEL), Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH), and the Japanese Study Group for Pediatric Liver Tumors (JPLT). The trial has been designed utilizing a new pathologic classification (Table 1) and new risk stratification for HB generated from the CHIC collaboration, and it will have an arm dedicated to the study of potential new chemotherapeutic approaches for HCC [17••, 38••, 39••]. Furthermore, the study will provide surgical and interventional guidelines for HB/HCC in addition to collecting data regarding global outcomes. The aims of the study include decreased treatment intensity for low-risk patients with HB/HCC with goals to diminish long-term toxicity and treatment intensification for high-risk patients with HB/HCC with the goal of improving outcomes. Finally, it will aim to assemble the world's largest biorepository of pediatric HB and HCC specimens to date. As we approach the next decade, the chemotherapeutic, surgical, and interventional approaches to the treatment of HB and HCC will continue to evolve as will targeted therapies taking into account genomic risk stratification and tumor classification.

Compliance with Ethical Standards

Conflict of Interest Angela D. Trobaugh-Lotrario, Allison F. O'Neill, Peng Li, Christopher Weldon, Dolores López-Terrada, and Marcio H. Malogolowkin each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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