Title

Childrens Oncology Groups 2023 blueprint for research: Liver tumors.

Journal

Medical and pediatric oncology, 70 Suppl 6(Suppl 6)

Authors

ONeill, Allison

Meyers, Rebecka

Katzenstein, Howard

et al.

Publication Date

2023-09-01

DOI

10.1002/pbc.30576

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

Pediatr Blood Cancer. 2023 September ; 70(Suppl 6): e30576. doi:10.1002/pbc.30576.

Children's Oncology Group's 2023 blueprint for research: Liver tumors

Allison F. O'Neill[1], **Rebecka L. Meyers**[2], **Howard M. Katzenstein**[3], **James I. Geller**[4], **Greg M. Tiao**[5], **Dolores López-Terrada**[6], **Marcio Malogolowkin**[7] **on behalf of the Liver Tumor Committee**

[1]Dana-Farber Cancer Institute and Harvard Medical School, Department of Pediatric Oncology, Boston, MA

[2]Division of Pediatric Surgery, University of Utah, Salt Lake City, UT

[3]Nemours Children's Hospital, Wilmington DE

[4]Division of Oncology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati OH

[5]Division of Surgery, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati OH

[6]Department of Pathology & Immunology, Baylor College of Medicine, Texas Children's Hospital and Cancer Center, Houston, TX

[7]University of California Davis Comprehensive Cancer Center, Sacramento, CA

Abstract

Liver tumors account for approximately 1–2% of all pediatric malignancies with the two most common tumors being hepatoblastoma (HB) and hepatocellular carcinoma (HCC). Previous Children's Oncology Group studies have meaningfully contributed to the current understanding of disease pathophysiology and treatment, laying groundwork for the ongoing prospective international study of both HB and HCC. Future work is focused on elucidating the biologic underpinnings of disease to support an evolution in risk categorization, advancements in the multi-dimensional care required to treat these patients, and the discovery of novel therapies.

Keywords

pediatric; liver; hepatoblastoma; hepatocellular; international

INTRODUCTION

Liver tumors account for 1–2% of malignancies occurring in pediatric patients.[1] The two most common liver tumors are hepatoblastoma (HB) and hepatocellular carcinoma (HCC). HB occurs at a median age of 3 years while conventional HCC occurs predominantly in adolescence. A hybrid entity, termed hepatocellular neoplasm not otherwise specified (HCN NOS), occurring in children of intermediate age, can be a challenging histopathologic diagnosis and constitutes an evolving genomic phenotype.[2,3]

Fibrolamellar carcinoma (FLC), previously grouped with conventional HCC, is now recognized as a unique pathologic entity based both on its characteristic histology and a defining *DNAJB1::PRKACA* chimeric fusion.[4,5] While other rare primary tumors arise from the liver in pediatric patients, they are outside the scope of this report.[6] The focus of this manuscript will be on the transformative care of patients with HB and HCC reflective of past and ongoing efforts within the Liver Tumor Committee of the Children's Oncology Group (COG).

STATE OF DISEASE

Epidemiology

Hepatoblastoma occurs with an approximate incidence of 2 cases per million children per year in the United States.[1] Only a minority of patients carry a germline predisposition associated with an increased incidence of HB.[7–10] Low-birth weight confers the highest relative risk of developing HB, particularly for premature infants born at less than 1,000g, although the etiology of this risk remains unclear.[11] The incidence of HB has increased globally over the last decade potentially secondary to the improved survival of premature infants.[12] An elevated serum alpha-fetoprotein (AFP) is a hallmark of HB and has been utilized as a surrogate for disease response to therapy.[13] The three-year overall survival (OS) for patients with non-metastatic HB is currently greater than >90% following receipt of cisplatin-based chemotherapy and complete resection of the primary liver tumor.[14–16] Outcomes for patients with high-risk or metastatic disease have improved only minimally over the last two decades with survival rates ranging from 60–80%.[17,18]

HCC in pediatric patients, in contrast to disease in adults, traditionally arises *de novo* in the context of a normal liver and at a rate of ~1 case per million children per year.[19] The 20% of cases that occur secondary to cirrhosis are often related to hereditary, structural, or metabolic syndromes.[20] AFP is elevated in approximately two-thirds of cases. While 3-year outcomes for patients with resectable disease at diagnosis approach 90%, the majority of patients present with advanced disease and have a dismal outcome of <20%.[20,21] Pediatric HCC, while more chemotherapy-responsive than adult HCC, does not usually respond adequately enough to facilitate primary resection.[20,22] HCN NOS behaves clinically more similar to HCC than HB; outcomes are therefore poor in advanced disease.[3] FLC is a rare subtype of pediatric primary liver cancer. Incidence rates are likely underestimated given lack of disease-specific billing codes, non-familiarity with disease histology, and variable testing for the recently recognized, diagnostic genomic alternation: a *DNAJB1::PRKACA* fusion.[23] Similar to conventional HCC, complete surgical resection is a requisite for cure of FLC. There is no efficacious standard of care for this disease and systemic responses to chemotherapeutics or immunotherapeutics are unpredictable.[5,24]

The last decade of work has been focused on pursuit of a harmonized, global approach to the diagnosis, staging, and risk stratification of pediatric HB and HCC intended to facilitate an international paradigm necessary for the study of these rare diseases. This manuscript describes recently established standards from the COG AHEP0731 trial (NCT00980460), the ongoing COG AHEP1531 trial (NCT03533582), and forthcoming endeavors that will support future study of these uncommon tumors.

RECENT FINDINGS

The Liver Tumor Committee in COG has been conducting prospective trials for pediatric patients with primary liver tumors since the 1970s. In aggregate, these trials demonstrated, for the first time, that prognosis is tied to Evans surgical stage, that resection at diagnosis followed by adjuvant chemotherapy improves outcomes, that cisplatin and doxorubicin are the mainstays of treatment, but that a subset of patients can be cured without use of doxorubicin, and that histology can impact outcome.[25–28] These trials paved the way for conduct of COG AHEP0731, a trial intended to decrease therapy for patients with low-risk tumors resectable at diagnosis, intensify therapy to facilitate surgery for unresectable tumors, and identify novel agents for patients with high-risk, metastatic disease.

Systemic Therapy

AHEP0731 risk-stratified patients with hepatoblastoma into 4 categories based upon surgical resectability, histology, and serum AFP levels at diagnosis. Very low-risk patients (resected at diagnosis, pure fetal histology) were observed following resection without receipt of adjuvant chemotherapy. Outcomes for these patients were excellent (100% 5-year OS) validating similar results from previous small cohort reports.[27,29] Low-risk patients (resected at diagnosis, non-pure fetal histology) received two cycles of cisplatin-containing chemotherapy (cisplatin/5-FU/vincristine; C5V), a reduction compared to the historic 4 cycles, with retained 4-year event-free survival (EFS) of >90%.[15] Patients with intermediate-risk, unresectable disease received a novel regimen of doxorubicin added to the C5V backbone (C5VD) with a resultant improvement in 5-year OS from a historic ~75% to >90%.[14] Patients with metastatic disease or a serum AFP <100 ng/dL received an upfront window therapy of vincristine/irinotecan (VI), with a C5VD backbone to follow. While not powered to study outcomes, results from this stratum demonstrated that VI is an effective anti-tumor combination for patients with advanced disease.[18] Addition of temsirolimus to the VI window (VIT) did not further improve response rates.[30] It is recognized now, in hindsight, that tumors associated with a low AFP level at diagnosis were likely rhabdoid tumors as "low AFP-secreting HB tumors" are exceedingly rare in current HB trials and often reflective of small tumor size.[31] Patients with small cell undifferentiated (SCU) histologic features, of any proportion, were restricted to stratum 3 if fully resected given that this histologic feature was felt to confer a poor prognosis. This theory, surrounding the adverse impact of SCU histology, has now been disproven.[32]

Surgery

Historically, over 60% of children presented with lesions unresectable by conventional surgery. Due to progress in the study of neo-adjuvant chemotherapy, over 75% of these tumors now decrease sufficiently in size to allow for conventional resection.[14] Despite these improvements, significant numbers of patients will still require total hepatectomy and orthotopic liver transplant (OLT) to achieve cure. Approximately 30% of patients on the intermediate-risk arm of AHEP0731 underwent OLT which is perceived to have contributed to improvements in overall survival; however it remains prudent to recognize the association of OLT with lifelong medical therapy, end-organ toxicity, risk for secondary malignancy and the related impacts on quality of life.[14] Future HB treatment strategies will require focus

on alternative tactics to improve tumor responsiveness and facilitate conventional resection. Interventional radiology strategies (i.e., chemo- or radioembolization) may benefit patients with suboptimal responses to chemotherapy, serving as a bridge to conventional resection, but they still require prospective, formal study in pediatric patients.

STRATEGIC APPROACH TO THERAPY

Histology, Staging, and Risk Stratification

Recognizing the need to conduct larger, international studies to power conclusions surrounding chemotherapeutic and surgical interventions, the first step in fostering collaboration was to establish an International Histologic Consensus Classification to be used across consortia. Histopathologic consensus was historically challenged by the rarity and heterogeneity of these neoplasms (Figure 1) as well as a standard in trials, apart from COG, to diagnose these tumors clinically (by age, radiographic findings, and AFP levels) thereby bypassing diagnostic biopsies and tumor banking at enrollment. The first Consensus Classification was drafted in 2011[2], validated using the international CHIC database[33], and is currently in use by international pathology reviewers participating in the current COG AHEP1531/ Paediatric Hepatic International Tumour Trial (PHITT) which will be described further below.

The next step was to arrive at a common denominator for staging and risk stratification. HB risk stratification and treatment in the older COG legacy trials (INT0098 and P9645) were based upon surgical stage, metastasis, and histology and differed from the PRETEXT algorithm used by international colleagues in Japan and Europe. PRETEXT, a radiographically based system, defines the PREtreatment EXtent of disease. The PRETEXT Groups (I, II, III, IV) were first introduced by the Société Internationale d'Oncologie Pédiatrique – Epithelial Liver Tumor Study Group (SIOPEL) group in the 1990s and are defined by the number of contiguous uninvolved sections of liver (Figure 2). The PRETEXT Annotation Factors (V,P,E,F,R,C,N,M) have evolved over time and were revised as "PRETEXT 2017" for global use in AHEP1531/ PHITT (Figure 2).[34]

In the past decade, the pediatric trial groups from the United States, Japan, and Europe formed a cooperative consortium, the Children's Hepatic tumors International Collaboration (CHIC), with the primary objective of developing a common global approach to HB risk stratification. The CHIC unified global risk stratification was developed by statistical interrogation of a large collaborative international dataset for patients treated on eight legacy trials performed by the participating trial groups between 1989 and 2006. PRETEXT group (I,II,III,IV) and metastatic disease (M) were already known to be highly predictive of outcome.[35–38] This was confirmed in the initial CHIC analysis[39], with the stratification algorithm further refined by the addition of AFP and age at diagnosis and the PRETEXT annotation factors VPEFR (Figure 3).[39–41] The discriminatory power of the CHIC stratification is being prospectively validated in the ongoing AHEP1531/PHITT trial, and has recently been validated in a second international dataset that includes contemporary trials (Rangaswami et al., personal communication; Haberle et al. Children's Liver Tumour European Research Network (ChiLTERN) Work-Package-4, personal communication).

There is no validated staging or risk stratification algorithm for pediatric patients with HCC however surgical staging and PRETEXT have been applied. A recent multi-institutional retrospective report identified the presence of an elevated AFP level at diagnosis, multifocality (as an indicator of resectability), and PRETEXT IV as poor prognostic factors.[42] The historical approach of combining the prospective study of patients with HB and HCC on the same trial, with the same regimens, is no longer accepted in the current era thereby resulting in the dedicated study of HCC on the current AHEP1531/PHITT trial.[20,21]

International Collaboration and the AHEP1531/PHITT trial

COG AHEP1531/PHITT (NCT03017326), directly addressed the growing need for a next generation clinical trial for hepatic malignancies, HB and HCC inclusive, incorporating rational reductions in therapy that ameliorate both short and long-term side effects for patients with good prognoses while simultaneously optimizing curative potential with intensification and new agent integration to improve outcomes for those with poor prognoses.[34,40,43,44] AHEP1531/PHITT is the first prospectively designed pediatric international cooperative liver tumors trial in which a consensus approach was established by investigators representing COG, SIOPEL, and the Japanese Children's Cancer Group (JCCG). The study built on treatment strategies established by the most recent trials from the individual consortia (Tables 1 and 2) while proposing new approaches to the study of HB and HCC tumors (FLC inclusive) keeping the aforementioned goals in focus. Candidly, the trial required some compromises from each of the groups and their historical philosophies and tactics. In 2018, the six-arm trial opened across the world and, to date, has enrolled over 970 patients in total. Three of the 4 HB treatment arms have closed to accrual by 2023 and release of outcomes data, specific to these arms, is anticipated in the next two years. The remaining HB arm and the two HCC arms continue to accrue.

Genomics

A critical aim of AHEP1531/PHITT is to bank tumor tissue for both HB and HCC to support the ongoing molecular characterization of these tumors. Historically, genomic characterization of small histologic subsets allowed distinction of three categories of disease: 1) a cohort of aggressive neoplasms initially misdiagnosed as "small cell" hepatoblastomas, known today to represent primary rhabdoid tumors of the liver carrying *SMARCB1* aberrations[45]; 2) an indolent group of very well differentiated HBs with pure fetal histology characterized by a remarkably stable genome[2,27,29,46–48]; and 3) a provisional HCN-NOS category demonstrating higher genomic instability than HB but lower than HCC, and recurrent genetic alterations in cancer pathways such as PI3K-AKT, mTOR, and genes that are commonly mutated in HCC.[3] These and other studies suggest that WNT-driven hepatocellular tumors in children represent a biological and clinical spectrum, and that HCN-NOS tumors are intermediate tumors that are genetically and phenotypically distinct from classical lower-risk HBs and pediatric HCCs, perhaps representing progressed HBs.[3,49,50]

HCCs diagnosed in children represent a heterogeneous clinical and biological group of tumors preliminarily recognized to be different than most HCCs diagnosed in adults.[51] FLC, characterized by a distinct histology associated with the presence of a recurrent

DNAJB1::PRKACA fusion, is one of the only molecularly-defined liver tumor types diagnosed in children and young adults.[4] Otherwise, the molecular characteristics and genomic landscape of pediatric HCCs remain largely heterogeneous and poorly- or under-characterized, including those associated with metabolic disorders and cancer predisposition syndromes. Long-term outcomes remain suboptimal regardless of the HCC phenotype.[50,51]

It is widely recognized that HBs are neoplasms with relatively quiet genomes and a low mutation burden.[46,48–50,52] Despite this, genomic and expression profiling of the first limited series of HBs demonstrated molecular subtypes of potential clinical significance.[46,47,53–58] In addition, HB methylation, epigenetic profiling, and multiomic studies have recently identified novel risk-prognostic clusters, methylation-regulated genes and specific hypomethylated regions of potential prognostic and therapeutic relevance.[48,58,59] Continued banking of clinical specimens and validation of these early molecular findings will inform future prognostication and risk stratification.

Relapse

While the outcomes for patients with HB continue to improve, for the approximately 10–15% of patients with relapsed or refractory disease, standards of therapy for salvage are lacking. The majority of patients with HCC respond sub-optimally and then progress or relapse. Current trials such as the AHEP1531/PHITT trial do not include guidelines or study arms that address this population. While reports have demonstrated that therapy for relapsed/refractory HB can lead to cure in approximately half of such patients, insights on optimal therapy remain elusive and 3-year survival for relapsed HB is estimated at approximately 40%.[26,60] In sum, data support a role for doxorubicin in HB patients who do not receive doxorubicin as upfront therapy[26], a possible role for cisplatin re-treatment in those with initially sensitive disease (Somers et al, personal communication), a role for pulmonary metastatectomy especially for those with late lung relapse[61], and a role for salvage transplant for select patients with intrahepatic relapse.[62] How to combine such therapies, and what to do when such therapies are inadequate, remains unknown. Relapse HCC therapies are predominantly extrapolated from the adult literature without adequate power to determine efficacy in pediatric patients.[63]

On the shoulders of advancing biologic discovery, novel therapy options have emerged for relapsed/refractory HB and HCC, some targeting cell-surface markers such as glypican-3 (GPC) with antibody-based (codrituzumab; NCT04928677) or chimeric antigen-receptor (CAR)-T cell therapies (NCT04093648). Additional targets of interest undergoing clinical study include beta-catenin (tegavivint; PEPN2011; NCT04851119), AFP peptide bound to HLA:A2 (ET140203 T cells; NCT04634357), and a histone deacetylase inhibitor in combination with cisplatin (NCT05756660). Advances in antiangiogenic therapy and immune checkpoint inhibitor-based therapies continue to be explored in pediatric liver tumors, particularly for patients with HCN-NOS and HCC (NCT04134559). New pre-clinical insights in FLC support additional targeted therapies focused on harnessing the immune system or exploiting apoptotic pathways (NCT04134559, NCT04248569).[64]

To address gaps in knowledge, several initiatives have advanced or are set to advance to either retrospectively (RELIVE) or prospectively (https://rrhblregistry.org) amass data on

patients with relapsed/refractory HB and on pediatric patients with HCN-NOS or HCC (https://joincountmein.org/). The RELIVE registry is an international retrospective registry assembling data on >200 children with relapsed/refractory HB and >100 children with HCC via a centralized data capture mechanism. Such data should provide early insight on recent treatments and outcomes for patients with either disease, providing a potential benchmark upon which future trials might be advanced. Participation and leadership in these initiatives by members of the COG Liver Tumor Committee, coupled with ongoing work in the COG early phase trial network, may support the potential incorporation of novel therapies for relapse in the anticipated AHEP1531/PHITT successor trial.

Forthcoming Trials

As outlined above, cisplatin remains the mainstay of therapy predominantly responsible for an improvement in overall survival of patients with HB. However, this benefit comes at the high price of long-term toxicity, particularly ototoxicity. The recently published SIOPEL6 trial demonstrated that use of sodium thiosulfate (STS) with cisplatin monotherapy for patients with standard risk disease maintained previously reported outcomes while achieving a statistically significant decrement in platinum-mediated high-frequency hearing loss.[65] COG study ACCL0431 published in 2017, and updated in 2022, demonstrated that in patients with an array of advanced malignancies, use of STS was associated with an inferior outcome; this may have been related to patient selection or STS administration in this small cohort.[66,67] On the basis of the SIOPEL6 study, sodium STS was granted FDA approval in September 2022 for use in pediatric patients >1 month of age with localized, non-metastatic tumors and is permitted for use in a subset of patients on the AHEP1531/PHITT trial.[68] While it is exciting and important to be able to potentially ameliorate one of the worst toxicities in the HB population, it is not yet proven that use of STS in patients with high-risk disease is safe and maintains the therapeutic efficacy of dose-dense cisplatin. Therefore, a pilot study is under design to evaluate the efficacy and safety of STS in patients with high-risk HB. An additional important area for more immediate study is the exploration of novel therapies for patients with FLC. Most historical databases and survivorship studies have not included pediatric patients with liver tumors. Implementation of formal survivorship protocol(s) to source comprehensive data regarding toxicities beyond oto- and cardiotoxicity are desperately needed and a focus of the COG Liver Tumor Committee.

FUTURE

The past decade has witnessed considerable forward progress in the treatment and outcomes of pediatric patients with HB. The current prospectively enrolling AHEP1531/PHITT trial has set the stage for further advancements in the study of HB, the pursuit of surgical aims, refinement of the PRETEXT staging algorithm, creation of a robust biobank, and above-all, establishment of an international clinical trial network for the successful future study of newly diagnosed and relapsed patients. The study of pediatric HCC has lagged far behind that of HB and outcomes remain very poor for patients unable to undergo upfront resection. AHEP1531/PHITT is the first trial to prospectively collect tissue samples and study dedicated therapies for pediatric patients with HCC addressing this significantly unmet need.

Future initiatives will require ongoing international collaboration and a focus on parallel advances across the many disciplines required for the comprehensive care of patients with both HB and HCC. Specific examples include but are not limited to:

- The genomic characterization of tumor specimens from the AHEP1531/PHITT trial to inform "biologic risk" layered on an evolving interpretation of histopathology, immunohistochemistry, and radiographic PRETEXT staging
- The use of indocyanine-green to guide surgical approach, its sensitivity and specificity, and the role of metastatectomy in patients with lung nodules[69,70]
- The application of pixel-level radiomics to pediatric HB and HCC tumors to further define tumor heterogeneity, as a reflection of tumor histology, and predict response to therapy and overall outcomes
- The exploration of circulating tumor DNA to predict tumor genomic heterogeneity and allow a less invasive approach to prognostication[71–73]
- The tailoring of therapy for patients with co-morbidities secondary to prematurity or other underlying developmental syndromes
- The accessibility of therapy for patients of diverse ethnic and socioeconomic backgrounds
- The discovery of relapse therapies and interventional approaches to local control; and
- The study of constitutional predisposition syndromes and germline associations.[74]

Work by the COG Liver Tumor Committee over the preceding decades has laid a successful foundation for the treatment of HB. Now, in collaboration with international colleagues and consortia, we are working to further innovate and hone the therapeutic approach for HB while advocating for the continued prospective study of pediatric patients with HCC and FLC. An ongoing commitment to bank tumor specimens and prioritize study of the biologic underpinnings of HB, HCN NOS, and HCC will inform the next generation of therapeutic trials. Continued growth of the committee with further inclusion of subspecialty experts and early-career investigators will ensure contributions to the care of pediatric patients with liver tumors for decades to come.

Funding support:

Grant support from the National Institute of Health, U10CA180886, U10CA180899, U10CA098543, U10CA098413, U24CA196173, U24CA114766.

Abbreviations Key:

AFP	Alpha-feto protein
CHIC	Children's Hepatic tumors International Collaboration
ChiLTERN	Children's Liver Tumour European Research Network

CAR	Chimeric antigen receptor
COG	Children's Oncology Group
C5V	Cisplatin/5-FU/vincristine
C5VD	Cisplatin/5-FU/vincristine/doxorubicin
EFS	Event-free survival
FLC	Fibrolamellar Carcinoma
GPC	Glypican-3
HB	Hepatoblastoma
HCC	Hepatocellular carcinoma
JCCG	Japanese Children's Cancer Group
HCN NOS	Hepatocellular neoplasm not otherwise specified
NCI	National Cancer Institute
OS	Overall survival
PHITT	Paediatric Hepatic International Tumour Trial
PRETEXT	Pretreatment Extent of Disease
SIOPEL	Société Internationale d'Oncologie Pédiatrique – Epithelial Liver Tumor Study Group
STS	Sodium thiosulfate
VI	Vincristine/irinotecan
VIT	Vincristine/irinotecan/temsirolimus

REFERENCES

1. Howlander NA KM, et al. eds. SEER Cancer Statistics Review, 1975–2009. National Cancer Institute
2. Lopez-Terrada D et al. Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. Mod Pathol 27, 472–491, doi:10.1038/modpathol.2013.80 (2014). [PubMed: 24008558]
3. Sumazin P et al. Hepatoblastomas with carcinoma features represent a biological spectrum of aggressive neoplasms in children and young adults. Journal of hepatology 77, 1026–1037, doi:10.1016/j.jhep.2022.04.035 (2022). [PubMed: 35577029]
4. Honeyman JN et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. Science 343, 1010–1014, doi:10.1126/science.1249484 (2014). [PubMed: 24578576]
5. O'Neill AF et al. Fibrolamellar carcinoma: An entity all its own. Curr Probl Cancer 45, 100770, doi:10.1016/j.currproblcancer.2021.100770 (2021). [PubMed: 34272087]

6. Finegold MJ et al. Protocol for the examination of specimens from pediatric patients with hepatoblastoma. Arch Pathol Lab Med 131, 520–529, doi:10.5858/2007-131-520-PFTEOS (2007). [PubMed: 17425379]
7. Kim SY et al. Genomic profiles of a hepatoblastoma from a patient with Beckwith-Wiedemann syndrome with uniparental disomy on chromosome 11p15 and germline mutation of APC and PALB2. Oncotarget 8, 91950–91957, doi:10.18632/oncotarget.20515 (2017). [PubMed: 29190888]
8. Hirschman BA, Pollock BH & Tomlinson GE The spectrum of APC mutations in children with hepatoblastoma from familial adenomatous polyposis kindreds. J Pediatr 147, 263–266, doi:10.1016/j.jpeds.2005.04.019 (2005). [PubMed: 16126064]
9. Pereira EM et al. Hepatoblastoma in a mosaic trisomy 18 patient. J Pediatr Hematol Oncol 34, e145–148, doi:10.1097/MPH.0b013e3182459ee8 (2012). [PubMed: 22469941]
10. Aguiar T et al. Unraveling the Genetic Architecture of Hepatoblastoma Risk: Birth Defects and Increased Burden of Germline Damaging Variants in Gastrointestinal/Renal Cancer Predisposition and DNA Repair Genes. Front Genet 13, 858396, doi:10.3389/fgene.2022.858396 (2022). [PubMed: 35495172]
11. Turcotte LM et al. Neonatal medical exposures and characteristics of low birth weight hepatoblastoma cases: a report from the Children's Oncology Group. Pediatr Blood Cancer 61, 2018–2023, doi:10.1002/pbc.25128 (2014). [PubMed: 25044669]
12. Hubbard AK, Spector LG, Fortuna G, Marcotte EL & Poynter JN Trends in International Incidence of Pediatric Cancers in Children Under 5 Years of Age: 1988–2012. JNCI Cancer Spectr 3, pkz007, doi:10.1093/jncics/pkz007 (2019).
13. Van Tornout JM et al. Timing and magnitude of decline in alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Children's Cancer Group. J Clin Oncol 15, 1190–1197, doi:10.1200/JCO.1997.15.3.1190 (1997). [PubMed: 9060563]
14. Katzenstein HM et al. Doxorubicin in combination with cisplatin, 5-flourouracil, and vincristine is feasible and effective in unresectable hepatoblastoma: A Children's Oncology Group study. Cancer 128, 1057–1065, doi:10.1002/cncr.34014 (2022). [PubMed: 34762296]
15. Katzenstein HM et al. Minimal adjuvant chemotherapy for children with hepatoblastoma resected at diagnosis (AHEP0731): a Children's Oncology Group, multicentre, phase 3 trial. Lancet Oncol 20, 719–727, doi:10.1016/S1470-2045(18)30895-7 (2019). [PubMed: 30975630]
16. Perilongo G et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 361, 1662–1670, doi:10.1056/NEJMoa0810613 (2009). [PubMed: 19846851]
17. Zsiros J et al. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. Lancet Oncol 14, 834–842, doi:10.1016/S1470-2045(13)70272-9 (2013). [PubMed: 23831416]
18. Katzenstein HM et al. Upfront window vincristine/irinotecan treatment of high-risk hepatoblastoma: A report from the Children's Oncology Group AHEP0731 study committee. Cancer 123, 2360–2367, doi:10.1002/cncr.30591 (2017). [PubMed: 28211941]
19. Khanna R & Verma SK Pediatric hepatocellular carcinoma. World J Gastroenterol 24, 3980–3999, doi:10.3748/wjg.v24.i35.3980 (2018). [PubMed: 30254403]
20. Czauderna P et al. Hepatocellular carcinoma in children: results of the first prospective study of the International Society of Pediatric Oncology group. J Clin Oncol 20, 2798–2804 (2002). [PubMed: 12065556]
21. Katzenstein HM et al. Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. J Clin Oncol 20, 2789–2797 (2002). [PubMed: 12065555]
22. Schmid I et al. Sorafenib and cisplatin/doxorubicin (PLADO) in pediatric hepatocellular carcinoma. Pediatr Blood Cancer 58, 539–544, doi:10.1002/pbc.23295 (2012). [PubMed: 21922643]
23. Zack T et al. Defining incidence and complications of fibrolamellar liver cancer through tiered computational analysis of clinical data. NPJ Precis Oncol 7, 29, doi:10.1038/s41698-023-00371-2 (2023). [PubMed: 36959495]

24. Kastenhuber ER et al. Road map for fibrolamellar carcinoma: progress and goals of a diversified approach. J Hepatocell Carcinoma 6, 41–48, doi:10.2147/JHC.S194764 (2019). [PubMed: 30951568]
25. Ortega JA et al. Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. J Clin Oncol 18, 2665–2675, doi:10.1200/JCO.2000.18.14.2665 (2000). [PubMed: 10894865]
26. Malogolowkin MH et al. Redefining the role of doxorubicin for the treatment of children with hepatoblastoma. J Clin Oncol 26, 2379–2383, doi:10.1200/JCO.2006.09.7204 (2008). [PubMed: 18467729]
27. Malogolowkin MH et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. J Clin Oncol 29, 3301–3306, doi:10.1200/JCO.2010.29.3837 (2011). [PubMed: 21768450]
28. Katzenstein HM et al. Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. Cancer 115, 5828–5835, doi:10.1002/cncr.24667 (2009). [PubMed: 19813275]
29. Vasudevan SA et al. Outcomes of children with well-differentiated fetal hepatoblastoma treated with surgery only: Report from Children's Oncology Group Trial, AHEP0731. J Pediatr Surg 57, 251–256, doi:10.1016/j.jpedsurg.2022.05.022 (2022). [PubMed: 35810020]
30. Thompson PA et al. Vincristine/irinotecan/temsirolimus upfront window treatment of high-risk hepatoblastoma: A report from the Children's Oncology Group AHEP0731 Study Committee. Pediatr Blood Cancer 70, e30365, doi:10.1002/pbc.30365 (2023). [PubMed: 37073741]
31. Trobaugh-Lotrario AD et al. Outcomes of Patients Treated for Hepatoblastoma with Low Alpha-Fetoprotein and/or Small Cell Undifferentiated Histology: A Report from the Children's Hepatic Tumors International Collaboration (CHIC). Cancers (Basel) 15, doi:10.3390/cancers15020467 (2023).
32. Trobaugh-Lotrario A et al. Small Cell Undifferentiated Histology Does Not Adversely Affect Outcome in Hepatoblastoma: A Report From the Children's Oncology Group (COG) AHEP0731 Study Committee. J Clin Oncol 40, 459–467, doi:10.1200/JCO.21.00803 (2022). [PubMed: 34874751]
33. Cho S, R. S., Alaggio R, Maibach R, Tanaka Y, Inoue T, Leuschner I, Krijger R, Vokuhl C, Krailo M, Malogolowkin M, Meyers R, Czauderna P, Hiyama E, Ansari M, Morland B, Trobaugh-Lotrario A, O'Neill AF, Rangaswami A, Haberle B, Lopez-Terrada D. Pediatric Blood and Cancer. Accepted, Ahead of Print (2023).
34. Towbin AJ et al. 2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT). Pediatr Radiol 48, 536–554, doi:10.1007/s00247-018-4078-z (2018). [PubMed: 29427028]
35. Fuchs J et al. Pretreatment prognostic factors and treatment results in children with hepatoblastoma: a report from the German Cooperative Pediatric Liver Tumor Study HB 94. Cancer 95, 172–182, doi:10.1002/cncr.10632 (2002). [PubMed: 12115331]
36. Aronson DC et al. Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. J Clin Oncol 23, 1245–1252, doi:10.1200/JCO.2005.07.145 (2005). [PubMed: 15718322]
37. Meyers RL et al. Predictive power of pretreatment prognostic factors in children with hepatoblastoma: a report from the Children's Oncology Group. Pediatr Blood Cancer 53, 1016–1022, doi:10.1002/pbc.22088 (2009). [PubMed: 19588519]
38. Maibach R et al. Prognostic stratification for children with hepatoblastoma: the SIOPEL experience. Eur J Cancer 48, 1543–1549, doi:10.1016/j.ejca.2011.12.011 (2012). [PubMed: 22244829]
39. Czauderna P et al. The Children's Hepatic tumors International Collaboration (CHIC): Novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. Eur J Cancer 52, 92–101, doi:10.1016/j.ejca.2015.09.023 (2016). [PubMed: 26655560]

40. Meyers RL et al. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. Lancet Oncol 18, 122–131, doi:10.1016/S1470-2045(16)30598-8 (2017). [PubMed: 27884679]
41. Haeberle B et al. The importance of age as prognostic factor for the outcome of patients with hepatoblastoma: Analysis from the Children's Hepatic tumors International Collaboration (CHIC) database. Pediatr Blood Cancer 67, e28350, doi:10.1002/pbc.28350 (2020). [PubMed: 32383794]
42. Short SS et al. Histologic type predicts disparate outcomes in pediatric hepatocellular neoplasms: A Pediatric Surgical Oncology Research Collaborative study. Cancer 128, 2786–2795, doi:10.1002/cncr.34256 (2022). [PubMed: 35561331]
43. Ranganathan S, Lopez-Terrada D & Alaggio R Hepatoblastoma and Pediatric Hepatocellular Carcinoma: An Update. Pediatr Dev Pathol 23, 79–95, doi:10.1177/1093526619875228 (2020). [PubMed: 31554479]
44. Moroz V, M. B., Tiao G, Hiyama E, Kearns P, Wheatley K. The paediatric hepatic international tumour trial (PHITT): clinical trial design in rare disease. Trials Vol 16, Supplement 2 (2015).
45. Trobaugh-Lotrario AD, Finegold MJ & Feusner JH Rhabdoid tumors of the liver: rare, aggressive, and poorly responsive to standard cytotoxic chemotherapy. Pediatr Blood Cancer 57, 423–428, doi:10.1002/pbc.22857 (2011). [PubMed: 21744471]
46. Sumazin P et al. Genomic analysis of hepatoblastoma identifies distinct molecular and prognostic subgroups. Hepatology 65, 104–121, doi:10.1002/hep.28888 (2017). [PubMed: 27775819]
47. Cairo S et al. Stem cell-like micro-RNA signature driven by Myc in aggressive liver cancer. Proc Natl Acad Sci U S A 107, 20471–20476, doi:10.1073/pnas.1009009107 (2010). [PubMed: 21059911]
48. Nagae G et al. Genetic and epigenetic basis of hepatoblastoma diversity. Nat Commun 12, 5423, doi:10.1038/s41467-021-25430-9 (2021). [PubMed: 34538872]
49. Eichenmuller M et al. The genomic landscape of hepatoblastoma and their progenies with HCC-like features. Journal of hepatology 61, 1312–1320, doi:10.1016/j.jhep.2014.08.009 (2014). [PubMed: 25135868]
50. Hirsch TZ et al. Integrated Genomic Analysis Identifies Driver Genes and Cisplatin-Resistant Progenitor Phenotype in Pediatric Liver Cancer. Cancer Discov 11, 2524–2543, doi:10.1158/2159-8290.CD-20-1809 (2021). [PubMed: 33893148]
51. Haines K et al. Characterization of pediatric hepatocellular carcinoma reveals genomic heterogeneity and diverse signaling pathway activation. Pediatr Blood Cancer 66, e27745, doi:10.1002/pbc.27745 (2019). [PubMed: 30977242]
52. Wheeler DA & Wang L From human genome to cancer genome: the first decade. Genome Res 23, 1054–1062, doi:10.1101/gr.157602.113 (2013). [PubMed: 23817046]
53. Cairo S et al. Hepatic stem-like phenotype and interplay of Wnt/beta-catenin and Myc signaling in aggressive childhood liver cancer. Cancer Cell 14, 471–484, doi:10.1016/j.ccr.2008.11.002 (2008). [PubMed: 19061838]
54. Magrelli A et al. Altered microRNA Expression Patterns in Hepatoblastoma Patients. Transl Oncol 2, 157–163, doi:10.1593/tlo.09124 (2009). [PubMed: 19701500]
55. He J, Guo X, Sun L, Wang N & Bao J Regulatory network analysis of genes and microRNAs in human hepatoblastoma. Oncol Lett 12, 4099–4106, doi:10.3892/ol.2016.5196 (2016). [PubMed: 27895778]
56. Cartier F et al. New tumor suppressor microRNAs target glypican-3 in human liver cancer. Oncotarget 8, 41211–41226, doi:10.18632/oncotarget.17162 (2017). [PubMed: 28476031]
57. Hooks KB et al. New insights into diagnosis and therapeutic options for proliferative hepatoblastoma. Hepatology 68, 89–102, doi:10.1002/hep.29672 (2018). [PubMed: 29152775]
58. Carrillo-Reixach J et al. Epigenetic footprint enables molecular risk stratification of hepatoblastoma with clinical implications. Journal of hepatology 73, 328–341, doi:10.1016/j.jhep.2020.03.025 (2020). [PubMed: 32240714]
59. Wang Q et al. DNMT1-mediated methylation of BEX1 regulates stemness and tumorigenicity in liver cancer. Journal of hepatology 75, 1142–1153, doi:10.1016/j.jhep.2021.06.025 (2021). [PubMed: 34217777]

60. Semeraro M et al. Relapses in hepatoblastoma patients: clinical characteristics and outcome--experience of the International Childhood Liver Tumour Strategy Group (SIOPEL). Eur J Cancer 49, 915–922, doi:10.1016/j.ejca.2012.10.003 (2013). [PubMed: 23146961]
61. Shi Y et al. Relapsed hepatoblastoma confined to the lung is effectively treated with pulmonary metastasectomy. J Pediatr Surg 51, 525–529, doi:10.1016/j.jpedsurg.2015.10.053 (2016). [PubMed: 26607968]
62. Boster JM et al. Predictors of survival following liver transplantation for pediatric hepatoblastoma and hepatocellular carcinoma: Experience from the Society of Pediatric Liver Transplantation (SPLIT). Am J Transplant 22, 1396–1408, doi:10.1111/ajt.16945 (2022). [PubMed: 34990053]
63. Weeda VB, Aronson DC, Verheij J & Lamers WH Is hepatocellular carcinoma the same disease in children and adults? Comparison of histology, molecular background, and treatment in pediatric and adult patients. Pediatr Blood Cancer 66, e27475, doi:10.1002/pbc.27475 (2019). [PubMed: 30259629]
64. Shebl B et al. Targeting BCL-XL in fibrolamellar hepatocellular carcinoma. JCI Insight 7, doi:10.1172/jci.insight.161820 (2022).
65. Brock PR et al. Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. N Engl J Med 378, 2376–2385, doi:10.1056/NEJMoa1801109 (2018). [PubMed: 29924955]
66. Freyer DR et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol 18, 63–74, doi:10.1016/S1470-2045(16)30625-8 (2017). [PubMed: 27914822]
67. Orgel E et al. Sodium thiosulfate for prevention of cisplatin-induced hearing loss: updated survival from ACCL0431. Lancet Oncol 23, 570–572, doi:10.1016/S1470-2045(22)00155-3 (2022). [PubMed: 35489339]
68. FDA approves sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients with localized, non-metastatic solid tumors.
69. Lake CM et al. Indocyanine green is a sensitive adjunct in the identification and surgical management of local and metastatic hepatoblastoma. Cancer Med 10, 4322–4343, doi:10.1002/cam4.3982 (2021). [PubMed: 34117727]
70. Yoshida M et al. Clinicopathological study of surgery for pulmonary metastases of hepatoblastoma with indocyanine green fluorescent imaging. Pediatr Blood Cancer 69, e29488, doi:10.1002/pbc.29488 (2022). [PubMed: 34889497]
71. Jazieh K et al. Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab. J Immunother Cancer 10, doi:10.1136/jitc-2021-003778 (2022).
72. Braman NM et al. Intratumoral and peritumoral radiomics for the pretreatment prediction of pathological complete response to neoadjuvant chemotherapy based on breast DCE-MRI. Breast Cancer Res 19, 57, doi:10.1186/s13058-017-0846-1 (2017). [PubMed: 28521821]
73. Madanat-Harjuoja LM et al. Circulating Tumor DNA as a Biomarker in Patients With Stage III and IV Wilms Tumor: Analysis From a Children's Oncology Group Trial, AREN0533. J Clin Oncol 40, 3047–3056, doi:10.1200/JCO.22.00098 (2022). [PubMed: 35580298]
74. Shahani SA & Marcotte EL Landscape of germline cancer predisposition mutations testing and management in pediatrics: Implications for research and clinical care. Front Pediatr 10, 1011873, doi:10.3389/fped.2022.1011873 (2022). [PubMed: 36225340]
75. Malogolowkin MH et al. Intensified platinum therapy is an ineffective strategy for improving outcome in pediatric patients with advanced hepatoblastoma. J Clin Oncol 24, 2879–2884, doi:10.1200/JCO.2005.02.6013 (2006). [PubMed: 16782927]
76. Haberle B, Bode U & von Schweinitz D [Differentiated treatment protocols for high- and standard-risk hepatoblastoma--an interim report of the German Liver Tumor Study HB99]. Klin Padiatr 215, 159–165, doi:10.1055/s-2003-39375 (2003). [PubMed: 12778356]
77. Becker K, Furch C, Schmid I, von Schweinitz D & Haberle B Impact of postoperative complications on overall survival of patients with hepatoblastoma. Pediatr Blood Cancer 62, 24–28, doi:10.1002/pbc.25240 (2015). [PubMed: 25251521]

78. Brown J et al. Pretreatment prognostic factors for children with hepatoblastoma-- results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. Eur J Cancer 36, 1418–1425, doi:10.1016/s0959-8049(00)00074-5 (2000). [PubMed: 10899656]

79. Perilongo G et al. Hepatoblastoma presenting with lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. Cancer 89, 1845–1853, doi:10.1002/1097-0142(20001015)89:8<1845::aid-cncr27>3.0.co;2-d (2000). [PubMed: 11042582]

80. Pritchard J et al. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach--results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 18, 3819–3828, doi:10.1200/JCO.2000.18.22.3819 (2000). [PubMed: 11078495]

81. Perilongo G et al. Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology--SIOPEL 2. Eur J Cancer 40, 411–421, doi:10.1016/j.ejca.2003.06.003 (2004). [PubMed: 14746860]

82. Zsiros J et al. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 28, 2584–2590, doi:10.1200/JCO.2009.22.4857 (2010). [PubMed: 20406943]

83. Sasaki F et al. Outcome of hepatoblastoma treated with the JPLT-1 (Japanese Study Group for Pediatric Liver Tumor) Protocol-1: A report from the Japanese Study Group for Pediatric Liver Tumor. J Pediatr Surg 37, 851–856, doi:10.1053/jpsu.2002.32886 (2002). [PubMed: 12037748]

84. Murawski M et al. Hepatocellular Carcinoma in Children: Does Modified Platinum- and Doxorubicin-Based Chemotherapy Increase Tumor Resectability and Change Outcome? Lessons Learned From the SIOPEL 2 and 3 Studies. J Clin Oncol 34, 1050–1056, doi:10.1200/JCO.2014.60.2250 (2016). [PubMed: 26811523]

85. Hiyama E et al. A cisplatin plus pirarubicin-based JPLT2 chemotherapy for hepatoblastoma: experience and future of the Japanese Study Group for Pediatric Liver Tumor (JPLT). Pediatric surgery international 29, 1071–1075, doi:10.1007/s00383-013-3399-0 (2013). [PubMed: 24026876]

86. Hishiki T et al. Outcome of hepatoblastomas treated using the Japanese Study Group for Pediatric Liver Tumor (JPLT) protocol-2: report from the JPLT. Pediatric surgery international 27, 1–8, doi:10.1007/s00383-010-2708-0 (2011). [PubMed: 20922397]

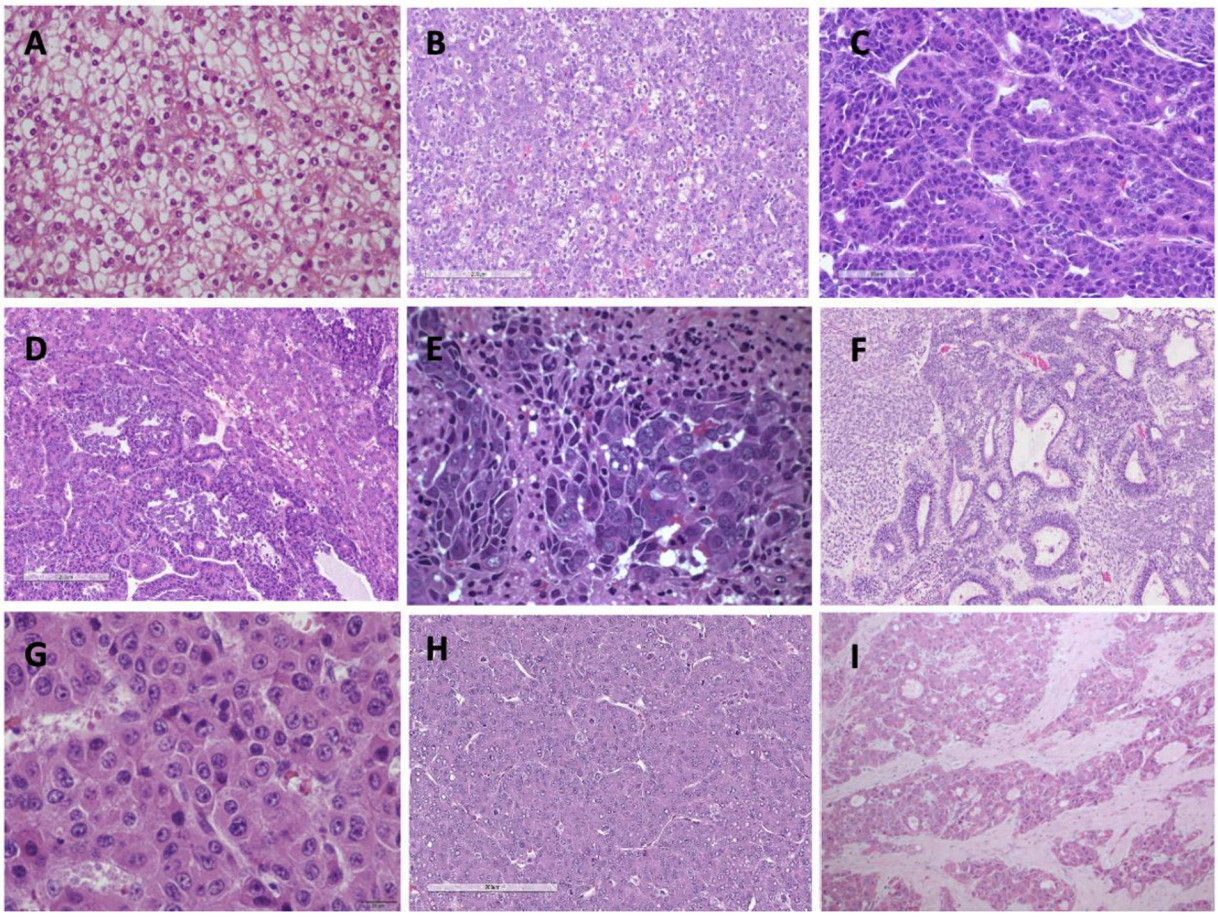
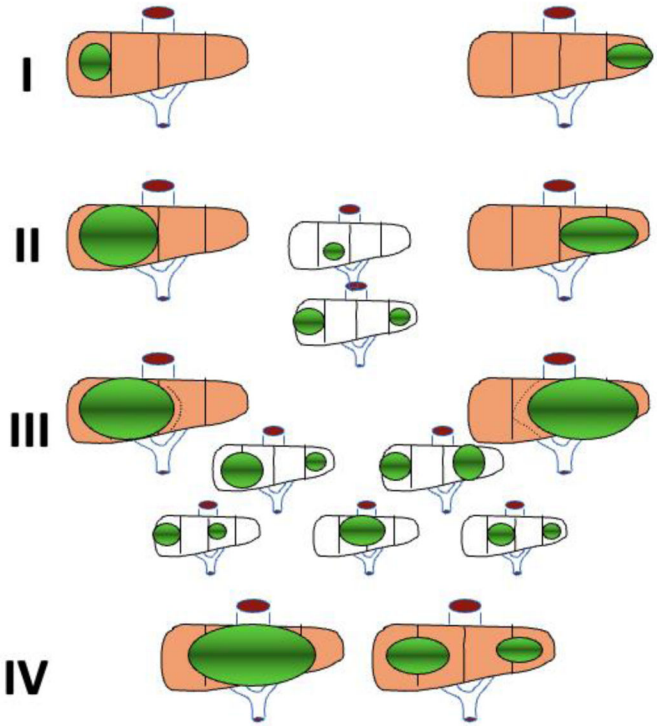


Figure 1:
Pediatric hepatocellular tumor histology: A. Hepatoblastoma, well differentiated fetal (WDF); B. Fetal hepatoblastoma, mitotically active pattern; C. Hepatoblastoma, embryonal pattern; D. Hepatoblastoma, mixed epithelial with fetal, embryonal and small cell components; E. Hepatoblastoma, anaplastic component; D. Mixed epithelial and mesenchymal hepatoblastoma, teratoid variant, with blastema and primitive neuroepithelium. G. Hepatocellular neoplasm, not otherwise specific (HCN-NOS). H. Hepatocellular carcinoma (HCC); I. Fibrolamellar carcinoma.



PRETEXT Group, *Pret*reatment *Ext*ent of Disease
Extent of parenchymal involvement at diagnosis
POST-TEXT Group, *Post*reatment *Ext*ent 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

2017 PRETEXT Annotation Factors[34]
V …involvement all 3 hepatic veins or retrohepatic vena cava and/or tumor thrombus in any one or more of the hepatic veins
P …tumor involvement of the portal bifurcation, both right and left portal veins, and/or tumor thrombus in either the left or right portal
E …contiguous organ involvement such as diaphragm, abdominal wall, colon, stomach
F ….multifocal tumor nodules
R … tumor rupture prior to diagnosis
C …caudate lobe
N … enlarged lymph nodes
M …metastasis, distant extrahepatic tumor (usually lung nodules)

Figure 2:
2017 PRETEXT Group and Annotation Factors[34]

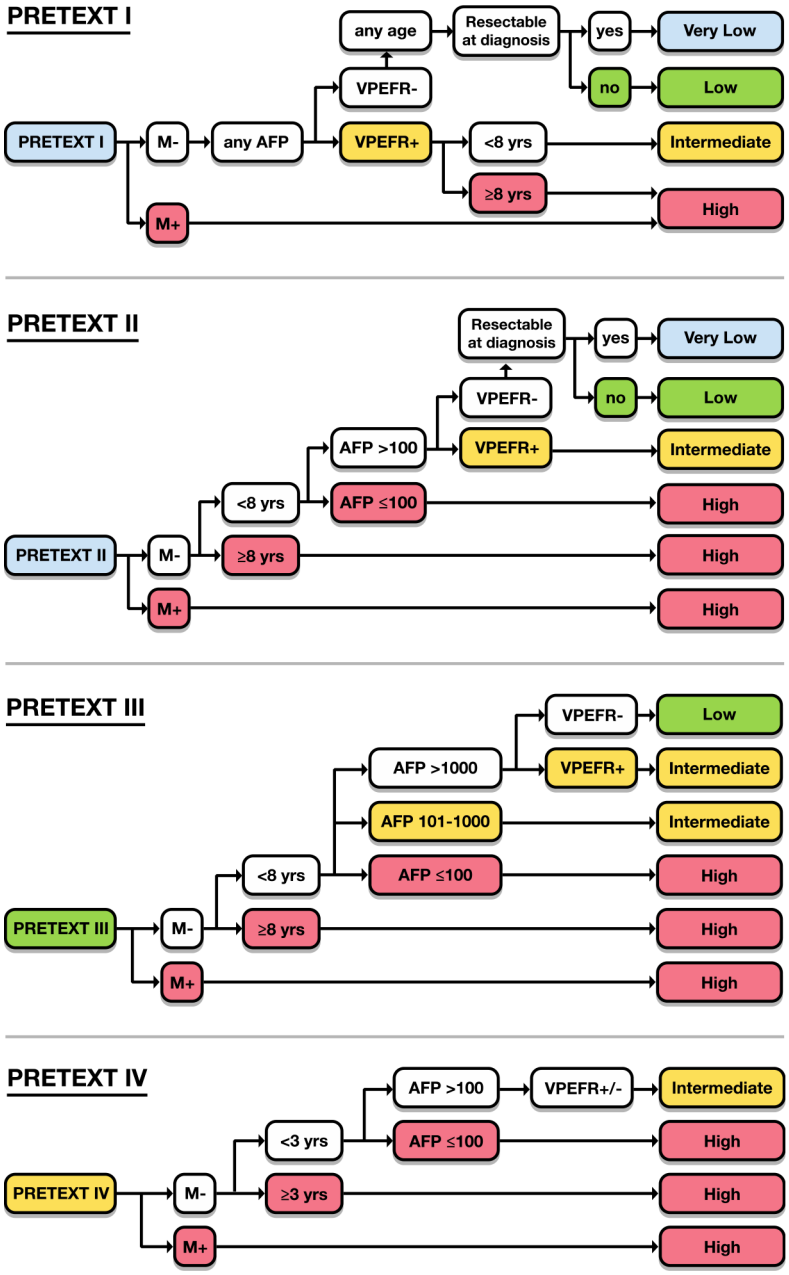


Figure 3: Children's Hepatic tumor International Collaboration (CHIC)- Hepatoblastoma Risk Stratification.

Color highlights of groups within each tree indicate which prognostic factor determined patient assignment to the ultimate group: very low, low, intermediate, or high-risk group.

TABLE 1.

Outcomes of multicenter hepatoblastoma trials over the past four decades.

Study Years conducted Publications	No. Patients by Characteristic Staging System	Chemotherapy Regimen(s)	Outcomes
INT0098 (CCG/POG) 1989–1992[25]	**Stage I/II:** 50	C5V vs. CDDP/Dox	**Stage I/II:** 88%/100% vs 96%/96%
	Stage III: 83		**Stage III:** 60%/68% vs. 68%/71%
	Stage IV: 40		**Stage IV:** 14%/33% vs. 37%/42%
	Evans/Post-surgical		5-year EFS/OS
P9645 (COG) 1999–2002[26–28]	**Stage I/PFH:** 16	**Stage I/PFH:** No chemo	**Stage I/PFH:** 100%/100%
	Stage I/II: 88	**Stage I/II:** C5Vvs. C5V/Ami	**Stage I/II:** 84%/96%
	Stage III/IV: 192	**Stage III/IV:** C5V vs. CDDP/CARBO	**Stage III/IV:** 60%/74% vs. 38%/56%
	Evans/Post-surgical		3-year EFS/OS *
AHEP0731 (COG) 2009–2014 [14,15,18,29,30,32]	**Very low risk:** 8	**Very low risk:** No chemo	**Very low risk:** 100%
	Low risk: 49	**Low risk:** C5V	**Low risk:** > 90%
	Intermediate risk: 102	**Intermediate risk:** C5VD	**Intermediate risk:** 87%/94%
	High risk VI: 30	**High risk VI:** VI + C5VD	**High risk VI:** 49%/62%
	High risk VIT: 36	**High risk VIT:** VIT + C5VD	**High risk VIT:** 47%/67%
	AHEP0731		3–5 year EFS/OS
HB 94 (GPOH) 1994–1997[34]	**Stage I:** 27	**Stages I/II:** IPA	**Stage I:** 89%/96%
	Stage II: 3		**Stage II:** 100%/100%
	Stage III: 25	**Stages III/IV:** IPA +/− VP16/CARBO	**Stage III:** 68%/76%
	Stage IV: 14		**Stage IV:** 21%/36%
	Evans/Post-surgical		5-year EFS/DFS
HB 99 (GPOH) 1999–2008[76,77]	**SR:** 89	**SR:** IPA	**SR:** 91%/94%
	HR: 53	**HR:** VP16/CARBO (IPA if poor response)	**HR:** 51%/62%
	SIOPEL SR/HR		3-year EFS/OS
SIOPEL 1 1990–1994[78–80]			**Overall:** 66%/75%
	PRETEXT I: 6		**PRETEXT I:** 100%/100%
	PRETEXT II: 52		**PRETEXT II:** 83%/91%
	PRETEXT III: 45	PLADO	**PRETEXT III:** 56%/68%
	PRETEXT IV: 39		**PRETEXT IV:** 46%/57%
	PRETEXT		5-year EFS/OS
SIOPEL 2 1994–1998[81]	**SR:** 67	**SR:** CDDP	**SR:** 89%/91%
	HR: 58	**HR:** SUPERPLADO	**HR:** 48%/53%
	SIOPEL SR/HR		3-year EFS/OS

Study Years conducted Publications	No. Patients by Characteristic Staging System	Chemotherapy Regimen(s)	Outcomes
SIOPEL 3 1998–2006[16,82]	**SR:** 255	**SR:** CDDP vs PLADO	**SR:** 83%/95% vs 85%/93%
	PRETEXT I: 18, II: 133, III: 104		
	HR: 151	**HR:** SUPERPLADO	**HR:** 65%/69%
	PRETEXT IV: 74		Metastatic: 57%/63%
	+VPE: 70		
	Metastatic: 70		
	AFP < 100: 12		
	SIOPEL SR/HR		3-year EFS/OS
SIOPEL 4 2005–2009[17]	**HR:** 62		**HR Overall:** 76%/83%
	PRETEXT 1:2, II: 17, III: 27, IV: 16	Blocks A1–3: Weekly CDDP/Dox Blacks B1–3: CARBO/Dox Block C: Higher dose CARBO/Dox	PRETEXT IV: 73%/80%
	Metastatic: 39		Metastatic: 77%/79%
	SIOPEL HR only		3-year EFS/OS
JPLT 1 1991–1999[83]	**Stage I:** 9	**Stages I/II:** Low dose CDDP/ pirarubicin	**Stage I:** 89%/10Q%
	Stage II: 32		**Stage II:** 84%/100%
	Stage IIIa: 43: **Stage IIIb:** 25	**Stages III/IV:** High dose CDDP/pirarubicin	**Stage IIIa:** 68%/77%: **Stage IIIb:** 25/50%
	Stage IV (mets): 20		**Stage IV (mets):** 41%/65%
	JPLT		3-year EFS/OS
JPLT 2 1999–2008[85,86]	**PRETEXT I:** 16	**PRETEXT I:** Low dose CDDP/ pirarubicin	**PRETEXT I:** 78%/100%
	PRETEXT II: 64	**PRETEXT II-IV:** CITA (ITEC if no response)	**PRETEXT II:** 76%/87%
	PRETEXT III: 83		**PRETEXT III:** 72%/89%
	PRETEXT IV: 49		**PRETEXT IV:** 68%/78%
	Metastatic: 35	**Metastatic:** High dose chemo/ stem cell rescue	**Metastatic:** n/a/44%
	PRETEXT		5-year EFS/OS

CCG: Children's Cancer Group; POG: Pediatric Oncology Group; GPOH: German Pediatric Oncology Hematology Group; EFS: event-free survival; OS: overall survival; n/a: not available; SR: standard risk; HR: high risk; PFH: pure fetal histology; AFP: alphafetoprotein;

*Study closed early because of inferior results on the CDDP/CARBO arm.

Chemotherapy Regimens: CDDP: cisplatin; Dox: doxorubicin; CARBO: carboplatin; Ami: amifostine; I: irinotecan; IFOS: ifosfamide; VP16: etoposide; V: vincristine; T: temsirolimus; C5V: cisplatin + 5-fluorouracil (5FU) + vincristine; C5VD: C5V + doxorubicin; IPA: ifosfamide + cisplatin + doxorubicin; PLADO: cisplatin + doxorubicin; SUPERPLADO: cisplatin + doxorubicin + carboplatin; CITA: cisplatin + pirarabicin; 11 EC: ifosfamide + carboplatin + pirarubicin + VP16; JPLT 2 high dose chemo: VP 16 + carboplatin + melphalan

TABLE 2.

Outcomes for pediatric patients with hepatocellular carcinoma treated over the past four decades.

Study Years conducted Publications	No. Enrolled Patients	Chemotherapy Regimen(s)	Outcomes
INT0098 (CCG/POG) 1989–1992[21]	**Stage:** **I:** 3 (C5V). 5 (CD) **III:** 10 (C5V), 15 (CD) **IV:** 7 (C5V), 6 (CD)	C5V vs. CD	**Stage:** **I:** 88% **III:** 23% **IV:** 10% 5-year OS
SIOPEL 1 1990–1994[20]	**PRETEXT:** **I/II:** 15 **III/IV:** 22	PLADO	**PRETEXT:** **I/II:** 44% **III:** 22% **IV:** 8% **Metastatic:** 9% 5-year OS
SIOPEL 2 and 3 1995–2006[84]	**PRETEXT:** **I/II:** 33 **III/IV:** 30 **Metastatic:** 30	SUPERPLADO	**All patients:** 22% **Primary resection:** −50% **Delayed resection:** −40% **Unresectable:** 0% 5-year OS
GPOH 2007–2010[22]	**PRETEXT:** **II:** 5 **III:** 3 **IV:** 4	PLADO + sorafenib	**II:** CR (3, 12–27 mo [1 OLT]), PD (1, 23 mo), DOD (1) **III:** CR (2, 18–32 mo [1 OLT]), SD (1,5 mo) **IV:** CR (1, 12 mo), PD (1, 18 mo), DOD (2) **Metastatic:** CR (1), DOD (1) (PRETEXT staging)

CCG: Children's Cancer Group; POG: Pediatric Oncology Group; GPOH: German Pediatric Oncology Hematology Group; OS: overall survival; CR: complete response, PD: progressive disease, SD: stable disease, DOD: dead of disease, OLT: orthotopic liver transplant.

Chemotherapy regimens: C5V: cisplatin + 5-fluorouracil (5FU) + vincristine; CD: cisplatin + doxorubicin (dosed in INT0098); PLADO: cisplatin + doxorubicin (dosed in SIOPEL); SUPERPLADO: cisplatin + doxorubicin + carboplatin