Complete Surgical Resection Is Curative for Children With Hepatoblastoma With Pure Fetal Histology: A Report From the Children's Oncology Group

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ABSTRACT

Purpose

Children with pure fetal histology (PFH) hepatoblastoma treated with complete surgical resection and minimal adjuvant therapy have been shown to have excellent outcomes when compared with other patients with hepatoblastoma. We prospectively studied the safety and efficacy of reducing therapy in all children with stage I PFH enrolled onto two consecutive studies.

Patients and Methods

From August 1989 to December 1992, 9 children with stage I PFH were treated on the Intergroup Hepatoblastoma study INT-0098 and were nonrandomly assigned to receive chemotherapy after surgical resection with single-agent bolus doxorubicin for 3 consecutive days. From March 1999 to November 2006, 16 children with stage I PFH enrolled onto Children's Oncology Group Study P9645 were treated with observation after resection. Central confirmation of the histologic diagnosis by a study group pathologist was mandated. The extent of liver disease was assigned retrospectively according to the pretreatment extent of disease (PRETEXT) system and is designated "retro-PRETEXT" to clarify the retrospective group assignment.

Results

Five-year event-free and overall survival for the 9 patients treated on INT-0098 were 100%. All 16 patients enrolled onto the P9645 study were alive and free of disease at the time of last contact, with a median follow-up of 4.9 years. Retro-PRETEXT for the 21 patients with available data revealed seven patients with stage I disease, 10 patients with stage II disease, and four patients with stage III disease.

Conclusion

Children with completely resected PFH hepatoblastoma can achieve long-term survival without additional chemotherapy. When feasible, surgical resection of hepatoblastoma at diagnosis, without chemotherapy, can identify children for whom no additional therapy is necessary.

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INTRODUCTION

Hepatoblastoma is the most common pediatric liver malignancy.¹ Surgical resectability and the presence of metastatic disease are critical prognostic factors.^{2,3} However, biologic and pathologic factors that might predict tumor response to therapy, resectability, and outcome are less well described. Small series have suggested that low alpha fetoprotein (AFP) levels, rate of decline of AFP, and tumor histology may also offer prognostic information that could guide therapy.⁴⁻⁶

Early studies by Evans et al⁷ demonstrated that tumor resectability was the most significant prognostic factor for patients with hepatoblastoma and on the basis of this observation, they established a

staging system that was based on tumor resectability and extent of disease. Subsequent clinical trials have shown that cisplatin-based chemotherapy improves survival by increasing tumor resectability, treating metastatic disease, and reducing the incidence of local and distant relapse.⁸⁻¹² In the prechemotherapy era, Kasai and Watanabe¹³ reported that among children with resectable tumors, there was a higher rate of survival for children with fetal histology than for those with anaplastic or poorly differentiated small-cell histology. Weinberg and Finegold¹⁴ similarly reported long-term survival for six children who had completely resected tumors of pure fetal histology (PFH), whereas only two of 10 patients with other histologic cell types survived. Haas et al¹⁵ confirmed these results in a larger series that

demonstrated that patients with completely resected PFH tumors have significantly improved event-free survival (EFS) when compared with all other patients. Of the five histologic subtypes—PFH, embryonal, mixed epithelial, mesenchymal/macrotrabecular, and small-cell undifferentiated (SCU)—PFH was associated with the most favorable prognosis. This data suggested that this subgroup of patients was appropriate for a tailored, monitored reduction in therapy. This article describes the results of two consecutive studies from the Children's Cancer Study Group and the Pediatric Oncology Group (INT-0098) and the Children's Oncology Group (P9645) that were designed to reduce the chemotherapy for children with completely resected stage I PFH tumors.

PATIENTS AND METHODS

Patients

From August 1989 to December 1992, 182 children with previously untreated hepatoblastoma were enrolled onto Intergroup Hepatoblastoma Study INT-0098 (Children's Cancer Study Group [CCG] 8881; Pediatric Oncology Group [POG] 8945). Details of the study design and requirements for eligibility have been described previously.¹¹ Patients with stage I non-PFH (unfavorable histology), stage II, stage III, and stage IV hepatoblastoma were randomly assigned between two cisplatin-based chemotherapy regimens. Patients with stage I PFH were nonrandomly assigned to receive four cycles of chemotherapy with single-agent doxorubicin (regimen C).

Between March 1999 and November 2006, the Children's Oncology Group study (P9645) enrolled 289 children with untreated hepatoblastoma. Details of this study have also been described previously.¹⁶ Patients with stage I PFH were nonrandomly assigned to observation without additional chemotherapy after surgical resection.

The National Cancer Institute and the institutional review boards of the participating institutions approved the protocols. Informed consent was obtained from parents, patients, or both, as deemed appropriate according to Department of Health and Human Services guidelines.

Staging

Evans stage of disease was determined by surgical and histologic criteria at the initial surgical intervention before the initiation of chemotherapy. Stage I was defined as complete gross resection with clear margins, stage II as gross total resection with microscopic residual disease at the margins of resection or preoperative/intraoperative tumor rupture, stage III as gross total resection with nodal involvement or tumor spill or incomplete resection with gross residual intrahepatic disease, and stage IV as metastatic disease with either complete or incomplete resection. Central review of the imaging studies was not required by either of these studies.

Our international colleagues rely on PRETEXT rather than on Evans stage for risk stratification (Fig 1).¹⁷ To enhance the international comparability of our data and to determine whether PRETEXT correlates with upfront tumor resectability, the extent of liver involved by tumor at the time of diagnosis was assigned retrospectively, according to the definitions used in the PRETEXT system (designated as retro-PRETEXT to clarify the retrospective method of group assignment). Given that all patients underwent resection at diagnosis, retrospective assignment was possible because there was no possibility of preoperative tumor shrinkage by neoadjuvant chemotherapy before surgery. The retro-PRETEXT was assigned by analysis of the radiographic computed tomography reports, operative reports, anatomic drawings included in the on-study surgical checklist completed by the operating surgeon, and pathology reports. The assignment was made only if the available documentation was of sufficient detail to be certain that the assignment was accurate (R.L.M. and M.H.M.).

Pathology

Rapid central review was required from the study pathologists (INT-0098, J.H. and M.J.F.; P9645, M.J.F. or J.M.R.) within 7 days for all patients

Fig 1. Pretreatment extent of disease (PRETEXT) classification of liver tumors. I, 3 contiguous sectors of liver tumor free and invasion of all three hepatic veins; II, two contiguous sectors of liver tumor free and invasion of main portal vein; III, one contiguous sector of liver tumor free and invasion of extrahepatic organ; IV, no contiguous sector of liver tumor free, as well as distant metastatic disease and involvement of the caudate lobe. Reprinted with permission.¹⁷

Fig 2. Well-differentiated fetal hepatoblastoma (A) without mitoses and (B) with two mitoses in one high-power field (circles).

with stage I tumors. Institutional pathology and surgery reports were also used to confirm diagnosis and staging. The protocols for sampling in both studies called for the institutional pathologist to harvest one section of the tumor for each centimeter of maximum tumor diameter, with each section measuring approximately 2.5×1.5 cm, and additional sections of the same size from the margin of surgical resection. The number of slides reviewed per case ranged from two to 31 (mean, 12) and depended largely on the size of the specimen.¹⁸ Patients with stage I disease were classified as having PFH, defined as PFH with minimal mitotic activity (≤ 2 mitoses per 10 high-power microscopic fields; $\times 400$ magnification), or as having unfavorable histology, which included all other histologic subtypes. Well-differentiated fetal cells are illustrated in Figure 2A. Tumor cells are generally smaller than host hepatocytes and have a slightly higher nucleus/cytoplasmic ratio, showing minimal variation in size, shape, and chromatin content, and relatively inconspicuous nucleoli. The cytoplasm varies from clear to amphophilic or eosinophilic, depending on the cellular glycogen content, and is sometimes vacuolated as a result of the presence of lipid. This can produce a pattern of light or pale cells alternating with dark, more compact cells. When mitotic activity is present, it tends to occur in the more compact areas and is usually associated with larger nuclei having slightly more pleomorphism (Fig 2B). Tumor cells also tend to grow in slender cords, like the host liver, or in tubules or clusters. In these cases, the hepatoblastomas were always well-circumscribed although nonencapsulated, and there was no invasion of hepatic veins. Portal vein invasion within the primary tumor mass was found rarely but not specifically quantified or noted. The distance from the edge of the tumor to the resection margin was not uniformly measured or noted in every report, but it ranged from 0.8 to 2.8 cm. The capsule of the liver overlying the tumor was often attenuated but never penetrated. Regional lymph nodes were not resected as part of the protocol, but they were reviewed when sampled, and no metastases were detected. There were no instances of disagreement between the institutional pathologists and reviewers in this series.

Chemotherapy

Patients enrolled onto INT-0098 with stage I PFH were nonrandomly assigned to receive treatment with four cycles of bolus doxorubicin (20 mg/m^2 per dose intravenously for 3 consecutive days). Each cycle was given ≥ 3 weeks apart, depending on recovery of peripheral neutrophil and platelet counts to $1,000 \text{ cells}/\mu\text{L}$ and $\geq 100,000 \text{ cells}/\mu\text{L}$, respectively. Initial chemotherapy was delayed for at least 2 weeks for any patient in whom $\geq 50\%$ of the liver was resected. In P9645, study patients with stage I PFH were nonrandomly assigned to observation without chemotherapy after surgical resection.

Statistical Design and Analysis

Study design. Details of the study design and planned patient enrollment for INT-0098 and P9645 have been described previously.^{11,16} The primary outcome measures for this study were event-free survival (EFS) and overall survival (OS).

Outcome definitions. EFS was defined as the period from the date of surgery until evidence of an event (progressive disease, death, diagnosis of a second malignant neoplasm) or last contact, whichever occurred first. OS was

defined as the period from the date of surgery until death or last contact, whichever occurred first. A patient who died was considered to have experienced an event regardless of the cause of death. Patients who did not experience an event were censored on the date of last contact.

Statistical methods. Life-table estimates of survival time were calculated according to the method of Kaplan and Meier.¹⁹ Standard deviation of the Kaplan-Meier estimate of the survivor function at selected points was calculated by using Greenwood's formula.²⁰

RESULTS

A total of 182 children with hepatoblastoma were enrolled onto the INT-0098 study and 270 were enrolled onto the P9645 study. Nine patients (5%) on INT-0098 and 16 patients (6%) on P9645 were confirmed by central pathology review as having stage I PFH.

With a median follow-up of 5.1 years (range, 3.8 to 6.3 years) for patients on INT-0098 and 4.9 years (range, 9 months to 9.2 years) for patients on P9645, the 5-year EFS and OS were both 100% for patients with stage I PFH. There was one patient on the P9645 study who had a follow-up of only 9 months who was alive with no evidence of disease at the time of last follow-up and was withdrawn from additional follow-up at the request of the parents.

We compared the outcome of all patients with incompletely resected tumors (stage II through IV) with PFH at time of diagnosis, as determined by examination of the materials submitted to the review pathologists (M.J.F. and J.M.R.), with the outcomes of patients with other histologic types. The presence of PFH was not associated with a reduced EFS (data not shown).

Sufficiently detailed data were available to assign the retro-PRETEXT group for all patients with stage I PFH enrolled onto INT-0098 and for 12 of 16 patients enrolled onto P9645. Table 1 shows the retro-PRETEXT and surgical procedure of the study patients. Four patients enrolled onto P9645 had insufficient data available to assign a PRETEXT group with confidence. There were seven children with PRETEXT stage I, 10 children with PRETEXT stage II, and four children with PRETEXT stage III. In INT-0098, two patients underwent segmentectomies, five children underwent lobectomies, and two others underwent trisegmentectomies; whereas, on P9645, five patients underwent wedge resection, two patients underwent segmentectomies, four patients received lobectomies, and one patient underwent a trisegmentectomy.

Three patients experienced postoperative events (bile leak, $n = 1$; reoperation for bleeding, $n = 1$; and reoperation for positive

Table 1. PRETEXT Stage and Type of Surgical Resection in Patients With Stage I Pure Fetal Histology Hepatoblastoma

PRETEXT Stage	INT-0098		P9645	
	Total No. of Patients	Type of Surgery	Total No. of Patients	Type of Surgery
I	3	Lobectomy (n = 1); segmentectomy (n = 2)	4	Wedge resection (n = 2); segmentectomy (n = 2)
II	4	Lobectomy (n = 4)	6	Wedge resection (n = 2); lobectomy (n = 4)
III	2	Trisegmentectomy (n = 2)	2	Wedge resection (n = 1); trisegmentectomy (n = 1)

Abbreviation: PRETEXT, pretreatment extent of disease.

microscopic margin, n = 1). No patients with stage I PFH on INT-0098 study experienced any significant cardiotoxicity (grades 3 and 4) from doxorubicin.

DISCUSSION

We have identified a cohort of children with stage I PFH hepatoblastoma that can be cured with primary surgical resection; this cohort represents approximately 6% of patients with hepatoblastoma in the two studies. Both studies were conducted with rapid central pathology review and strict monitoring criteria and stopping rules to safely test the strategy. Criteria for diagnosis of PFH included a low mitotic rate of no more than two mitoses per 10 high-power microscopic fields ($\times 400$ magnification) per the report by Weinberg and Finegold.¹⁴ The PFH criteria were rigidly defined and strict because of the known benefit of cisplatin-based chemotherapy despite its toxicity. The ultimate goal is to maintain cure and reduce acute and long-term toxicity. COG has continued this strategy in its current trial AHEP0731. In this study, we have reduced chemotherapy for all well-differentiated stage I fetal histology tumors regardless of mitotic rate.

In 1970, Kasai and Watanabe¹³ were the first to show a relationship between histopathology and outcome in children with hepatoblastoma. Gonzalez-Crussi et al²¹ explored histologic subtypes and reported on five patients of total fetal histology. In their study, two patients were cured with resection alone, two patients had extrahepatic disease and did not survive, and one patient was found to have an incidental tumor noted at autopsy after death that was related to complications of Down syndrome. Lack et al²² reported on a series of 54 patients and suggested a more favorable outcome in patients with a predominantly fetal pattern. Interestingly, eight of 11 patients treated with resection alone survived, although specific follow-up and the specific histologies of these tumors were not provided. Weinberg and Finegold¹⁵ reported on 27 patients with hepatoblastoma, including six of eight patients with PFH who were without disease for more than 4 years from diagnosis. These authors refined the criteria for PFH to require ≤ 2 mitoses per 10 high-power ($\times 400$ magnification) fields and stipulated that the entire tumor exhibit fetal histology. Douglass et al¹⁰ reported on four patients with stage I PFH tumors who survived with resection alone in the Pediatric Oncology Group Studies 8696 and 8697.

Haas et al¹⁵ have conducted the most extensive analysis of fetal histology. In a series of 168 patients with hepatoblastoma, ninety patients were described as having PFH, 28 of whom were resected at diagnosis, 46 had nonmetastatic and nonresectable disease, and 16 had metastatic disease. Twenty-five patients (89%) with resected PFH were free of disease at 4 years, whereas those with unresected or

metastatic PFH had no survival advantage. In this study, the number of mitoses per high-power field was not specifically evaluated.

In addition to the United States data from Haas et al¹⁵, studies from England²³ and Germany³ have also suggested an improved outcome for patients PFH. The International Childhood Liver Tumours Strategy Group (SIOPEL) trials 1 and 2 have not specifically addressed this issue.^{2,9} Uniform criteria in diagnosing, describing, centrally reviewing, and treating patients with fetal histology have been not used. The diagnostic criteria for the determination of PFH has varied, and perhaps most importantly, the SIOPEL studies have not had access to tissue from untreated tumors for analysis. Brown et al² did not identify PFH as having an improved outcome, probably because this study relied on needle biopsy tissue with potential sampling error and an inability to reflect the entirety of the tumor. Others have based the analysis on predominant fetal histology,^{15,22,24} a term that is not equivalent to the PFH criteria used in this study as established by Weinberg and Finegold.¹⁴

When feasible and safe, the COG strategy has favored primary resection for hepatoblastoma in an attempt to minimize total chemotherapy exposure in the approximately 30% of newly diagnosed patients who can undergo resection at diagnosis. In a philosophy designed to decreased surgical morbidity and truncate time to chemotherapy, in contrast, SIOPEL has favored upfront chemotherapy for all patients. This study suggests that mandatory neoadjuvant chemotherapy may result in potentially unnecessary exposure to chemotherapy and potentially unnecessary chemotherapy toxicity. In a small but real cohort of patients, upfront surgical resection leads to the identification of favorable histology features that may identify some patients for whom no chemotherapy is necessary. Modern imaging techniques and application of the PRETEXT system provide us with the means to identify patients whose tumors should be safe to resect at diagnosis.

The data reported here demonstrates that clinical and pathologic features can predict outcome in hepatoblastoma and that PRETEXT can be used to predict surgical resectability.¹⁷ The one patient who underwent reoperation for resection of a microscopic positive margin was a trisegmentectomy patient who would not have met the guidelines for upfront resection in our current protocol. The surgical guidelines in our contemporary COG hepatoblastoma study (AHEP0731) recommend upfront resection in PRETEXT 1 tumors and in PRETEXT 2 tumors with a clear radiographic margin on the middle hepatic vein and portal venous bifurcation, in which margin negative resection can be anticipated by simple segmentectomy or lobectomy.

In contrast to PFH, it appears that tumors with SCU elements have an unfavorable prognosis and require more aggressive therapy.^{25,26} The proportion of small cells cannot be adequately evaluated

from a small biopsy, and when chemotherapy is given before surgery, the histopathologic constituents of the original neoplasm may be altered. In the various series from the United States and Germany, the error rate in diagnosis of SCU from an initial pathologic reading has ranged from 10% to 16%.^{27,28} The errors reflect mimicry of the radiologic appearance of hepatoblastoma by some benign vascular tumors (eg, infantile hemangioma) and mesenchymal hamartomas. Biopsy is often needed because serum alpha protein may be elevated in some of the benign tumors. Alternatively, low AFP is seen in a small subset of hepatoblastoma in which the tumor is either a well-differentiated fetal hepatoblastoma, a poorly differentiated SCU hepatoblastoma or a rhabdoid tumor.^{26,27,29}

The molecular pathogenesis of hepatoblastoma is slowly but progressively being elucidated. Activation of the canonical Wnt pathway is present in 70% to 90% of hepatoblastoma.^{30,31} B-Catenin (*CTNNB1*) mutations have been identified in all hepatoblastoma subtypes. The relationship of *CTNNB1* mutation type to histologic type was statistically significant ($P = .003$) in a report by Lopez-Terrada et al.³² Aberrant activation of the Notch pathway has also been documented in hepatoblastoma. Lopez-Terrada et al have recently demonstrated that Wnt activation is prevalent in hepatoblastoma, most significantly in predominantly embryonal and mixed histologic subtypes, whereas Notch activation was highest in PFH hepatoblastoma. Examination of Wnt versus Notch activation may be useful in the future to stratify different hepatoblastoma subtypes and identify patients for whom no additional therapy or alternative is necessary. Correlation between recently reported prognosis-associated gene ex-

pression signatures in histologic subtypes of hepatoblastoma may also be potentially useful for patient stratification.³³

In summary, PFH has been identified as a good prognostic factor, and we propose that chemotherapy not be given to this group of patients with stage I disease. These results stress the importance of our continued research focus on investigating hepatoblastoma tumor biology and pathology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

- Bulterys N, Goodman M, Smith M, et al: Hepatic tumors, in Ries L, Smith M, Gurney J, et al (eds): Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. Bethesda, MD, National Cancer Institute, 1999, pp 91-98
- Brown J, Perilongo G, Shafford E, 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, 2000
- von Schweinitz D, Hecker H, Schmidt-von-Arndt G, et al: Prognostic factors and staging systems in childhood hepatoblastoma. *Int J Cancer* 74:593-599, 1997
- Meyers RL, Rowland JR, Krailo M, 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, 2009
- Van Tornout JM, Buckley JD, Quinn JJ, 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, 1997
- De Ioris M, Brugieres L, Zimmermann A, et al: Hepatoblastoma with a low serum alpha-fetoprotein level at diagnosis: The SIOPEL group experience. *Eur J Cancer* 44:545-550, 2008
- Evans AE, Land VJ, Newton WA, et al: Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 50:821-826, 1982
- Ortega JA, Krailo MD, Haas JE, et al: Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: A report from the Children's Cancer Study Group. *J Clin Oncol* 9:2167-2176, 1991
- Perilongo G, Shafford E, Maibach R, 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, 2004
- Douglass EC, Reynolds M, Finegold M, et al: Cisplatin, vincristine, and fluorouracil therapy for hepatoblastoma: A Pediatric Oncology Group study. *J Clin Oncol* 11:96-99, 1993
- Ortega JA, Douglass EC, Feusner JH, 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, 2000
- von Schweinitz D, Byrd DJ, Hecker H, et al: Efficiency and toxicity of ifosfamide, cisplatin and doxorubicin in the treatment of childhood hepatoblastoma: Study Committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society for Paediatric Oncology and Haematology. *Eur J Cancer* 33:1243-1249, 1997
- Kasai M, Watanabe I: Histologic classification of liver-cell carcinoma in infancy and childhood and its clinical evaluation: A study of 70 cases collected in Japan. *Cancer* 25:551-563, 1970
- Weinberg AG, Finegold MJ: Primary hepatic tumors of childhood. *Hum Pathol* 14:512-537, 1983
- Haas JE, Muczynski KA, Krailo M, et al: Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. *Cancer* 64:1082-1095, 1989
- Malogolowkin MH, Katzenstein H, Krailo MD, et al: Intensified platinum therapy is an ineffective strategy for improving outcome in pediatric patients with advanced hepatoblastoma. *J Clin Oncol* 24:2879-2884, 2006
- Aronson DC, Schnater JM, Staalman CR, 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, 2005
- Finegold MJ, Lopez-Terrada DH, Bowen J, et al: Protocol for the examination of specimens from pediatric patients with hepatoblastoma. *Arch Pathol Lab Med* 131:520-529, 2007
- Kaplan EL, Meier P: Nonparametric estimations from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
- Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, NY, Wiley, 1980
- Gonzalez-Crussi F, Upton MP, Maurer HS: Hepatoblastoma: Attempt at characterization of histologic subtypes. *Am J Surg Pathol* 6:599-612, 1982
- Lack EE, Neave C, Vawter GF: Hepatoblastoma: A clinical and pathologic study of 54 cases. *Am J Surg Pathol* 6:693-705, 1982
- Stringer MD, Hennayake S, Howard ER, et al: Improved outcome for children with hepatoblastoma. *Br J Surg* 82:386-391, 1995
- Conran RM, Hitchcock CL, Wacławski MA, et al: Hepatoblastoma: The prognostic significance of histologic type. *Pediatr Pathol* 12:167-183, 1992
- Haas JE, Feusner JH, Finegold MJ: Small cell undifferentiated histology in hepatoblastoma may be unfavorable. *Cancer* 92:3130-3134, 2001

26. Trobaugh-Lotrario AD, Tomlinson GE, Finegold MJ, et al: Small cell undifferentiated variant of hepatoblastoma: Adverse clinical and molecular features similar to rhabdoid tumors. *Pediatr Blood Cancer* 52:328-334, 2009
27. Finegold MJ: Chemotherapy for suspected hepatoblastoma without efforts at surgical resection is a bad practice. *Med Pediatr Oncol* 39:484-486, 2002
28. von Schweinitz D, Gluer S, Mildenerberger H: Liver tumors in neonates and very young infants: Diagnostic pitfalls and therapeutic problems. *Eur J Pediatr Surg* 5:72-76, 1995
29. Tsuchida Y, Ikeda H, Suzuki N, et al: A case of well-differentiated, fetal-type hepatoblastoma with very low serum alpha-fetoprotein. *J Pediatr Surg* 34:1762-1764, 1999
30. Koch A, Denkhau D, Albrecht S, et al: Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the beta-catenin gene. *Cancer Res* 59:269-273, 1999
31. Park WS, Oh RR, Park JY, et al: Nuclear localization of beta-catenin is an important prognostic factor in hepatoblastoma. *J Pathol* 193:483-490, 2001
32. Lopez-Terrada D, Gunaratne PH, Adesina AM, et al: Histologic subtypes of hepatoblastoma are characterized by differential canonical Wnt and Notch pathway activation in DLK+ precursors. *Hum Pathol* 40:783-794, 2009
33. Cairo S, Armengol C, De Reynies A, 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, 2008

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