Title

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Journal

Journal of Clinical Oncology, 40(5)

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Publication Date

2022-02-10

DOI

10.1200/JCO.21.00803

Peer reviewed

original reports

Small Cell Undifferentiated Histology Does Not Adversely Affect Outcome in Hepatoblastoma: A Report From the Children's Oncology Group (COG) AHEP0731 Study Committee

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abstract

PURPOSE Small cell undifferentiated (SCU) histology in hepatoblastoma (HB) tumors has historically been associated with a poor prognosis. Tumors from patients enrolled on Children's Oncology Group (COG) study AHEP0731 underwent institutional and central pathologic review for identification of SCU histology.

PATIENTS AND METHODS Patients with SCU histology identified at the local treating institution who had otherwise low-risk tumors were upstaged to the intermediate-risk treatment stratum, whereas those only identified by retrospective central review were treated per the local institution as low-risk. Patients with otherwise intermediate- or high-risk tumors remained in that treatment stratum, respectively. Central review was to be performed for all tissue samples obtained at any time point. Treatment was per local review, whereas analysis of outcome was based on central review.

RESULTS Thirty-five patients had some elements (1%-25%) of SCU identified on central review of diagnostic specimens. All but two patient tissue sample retained nuclear INI1 expression. The presence of SCU histology did not correlate with age, alpha-fetoprotein level at diagnosis, or sex. The presence of SCU did not affect event-free survival (EFS). EFS at 5 years for patients with low-risk, intermediate-risk, and high-risk with SCU HB was 86% (95% CI, 33 to 98), 81% (95% CI, 57 to 92), and 29% (95% CI, 4 to 61), respectively, compared with EFS at 5 years for patients without SCU enrolled with low-risk, intermediate-risk, and high-risk of 87% (95% CI, 72 to 95), 88% (95% CI, 79 to 94), and 55% (95% CI, 32 to 74; $P = .17$), respectively.

CONCLUSION The presence of SCU histology in HB does not appear to adversely affect outcome. Future studies should be able to treat patients with SCU HB according to risk stratification without regard to the presence of SCU histology.

J Clin Oncol 40:459-467. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Sharing Statement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 1, 2021 and published at ascopubs.org/journal/jco on December 7, 2021: DOI https://doi.org/10.1200/JCO.21.00803

INTRODUCTION

In relatively small series and anecdotal reports, hepatoblastoma (HB) tumors with any identifiable components of small cell undifferentiated (SCU) histology have been previously described to have a poor prognosis.[1-4] However, the definition of SCU has not been universally accepted or reproducible and was therefore part of an international pathology consensus conference in 2011 intended to establish uniform pathologic criteria for all pediatric liver tumors.[5] SCU cells are undifferentiated cells with scant cytoplasm and round lightly chromatic nuclei with inconspicuous nucleoli.[1] These cells usually are discohesive and do not form tubules, and typically infiltrate the liver while sparing bile ducts and sometimes invading venous structures. When comprising a portion of an otherwise typical HB with epithelial and mesodermal derivatives, areas of SCU cells are identified as discrete small nests most often associated with embryonal elements. Immunohistochemically, they may pose a diagnostic dilemma by their similarity to rhabdoid tumor cells with biphenotypic expression of cytokeratin and vimentin intermediate filaments, albeit without abundant eosinophilic cytoplasm of the typical rhabdoid cell.[6] Previous descriptions of SCU tumors have included liver tumors predominantly composed of this component with associated rhabdoid cells.

These SCU tumors have also often been previously described to present with a low or even normal serum

CONTEXT

Key Objective

The AHEP0731 included an objective to determine whether tumors with small cell undifferentiated (SCU) elements had a different prognosis than tumors without SCU elements. Patients with stage I and II tumors with locally identified SCU tumors had their treatment intensified, whereas intermediate- and high-risk tumors were treated the same regardless of whether SCU tumor elements were present.

Knowledge Generated

With the regimens used, there was no difference in event-free survival or overall survival for patients with SCU tumor elements regardless of their treatment stratification.

Relevance

SCU histology had historically been considered an adverse prognostic factor. The AHEP0731 trial does not demonstrate that this is the case. This difference from previous literature is likely largely to be related to improved immunostaining and cytogenetic techniques that can better differentiate a hepatoblastoma with SCU elements from a rhabdoid tumor. SCU at this time is no longer considered to be a prognostic variable in hepatoblastoma.

alpha-fetoprotein (AFP) level.[2,7,8] However, since AFP levels are usually elevated in HB, this leads one to question whether or not these previously reported low AFP tumors were truly HB or potentially were rhabdoid or other non-HB tumors.[2]

In 1998, rhabdoid tumors were identified to result from homozygous inactivating mutations of the *SMARCB1*/hSNF5-INI-1 gene located in the chromosomal region 22q11.2.[9] This *SMARCB1* inactivation may result from mutations, deletions, or unbalanced translocations, and has been observed in tumors from all locations where rhabdoid tumors occur, including brain, kidney, and liver.[10] Along with cytogenetic evaluation, immunohistochemical staining for INI1 is now considered as standard practice in pathologic evaluation of these tumors to help establish a definitive and accurate diagnosis.[11]

Children's Oncology Group (COG) Protocol (online only) AHEP0731 stratified patients as very low, low, intermediate, or high risk based upon COG surgical stage,[12] histology, and AFP level. Patients with resected tumors with SCU identified at the local treating institution were to be upstaged to receive additional cycles of intensified therapy, whereas patients with unresectable, nonmetastatic SCU tumors were to receive the same intensified therapeutic regimen. Herein, we report the characteristics and outcomes of these patients.

PATIENTS AND METHODS

Study Patients

Patients were eligible for study if they were < 21 years of age and had newly diagnosed, previously untreated biopsy-proven HB of any clinical stage and met all organ function requirements. Patients who were deemed clinically unstable for biopsy could be enrolled if they met all other requirements and if subsequent collection of tissue confirmed the diagnosis.

The National Cancer Institute, the Pediatric Central IRB, and the institutional review boards of the participating institutions approved the Protocol. Informed consent was obtained for all patients before treatment.

Staging

Patients were to be staged for risk classification using COG staging guidelines before the initiation of chemotherapy: stage I, complete gross resection with clear margins; stage II, gross total resection with microscopic residual disease at the margins of resection or preoperative or intraoperative tumor rupture; stage III, gross total resection with nodal involvement or incomplete resection with gross residual intrahepatic disease; and stage IV, metastatic disease with either complete or incomplete resection. PRETEXT grouping was also to be done for all patients at diagnosis and at any time when subsequent abdominal scans were performed preoperatively. All diagnostic and follow-up tissue samples were to be centrally reviewed by both study pathologists (M.J.F. and S.R.).

Risk Classification

Patients were classified as very low-risk if their tumor was completely resected at diagnosis and rapid central pathologic review confirmed 100% pure fetal histology with low mitotic activity. These patients were then to be observed with no further therapy. Patients were classified as low-risk if they had their tumor completely resected at diagnosis and were not 100% pure fetal histology and did not have SCU components identified by the local pathologists at the treating institution. Patients with stage I SCU, stage II SCU, and stage III disease of any histology who had SCU identified by the local pathologists at the treating institution were upstaged and considered intermediate-risk. Patients were classified as high-risk if they had either metastatic disease or a serum AFP level of < 100 ng/mL, regardless of stage.

Chemotherapy

Low-risk patients were to receive two cycles of (C5V), which consisted of cisplatin (100 mg/m^2/dose or 3.3 mg/kg/dose for children $<$ 10 kg) intravenously over 6 hours on day 1; fluorouracil (600 mg/m^2/dose or 20 mg/kg/dose for $<$ 10 kg) intravenous push on day 2; and vincristine (1.5 mg/m^2/day or 0.05 mg/kg/day) intravenous push on days 2, 9, and 16 as detailed elsewhere. Intermediate-risk patients were to be treated with six cycles of (C5VD), which consisted of cisplatin (100 mg/m^2/dose or 3.3 mg/kg/dose for $<$ 10 kg) intravenously on day 1; doxorubicin (30 mg/m^2/dose or 1 mg/kg/dose for $<$ 10 kg) intravenously on days 1 and 2; fluorouracil (600 mg/m^2/dose or 20 mg/kg/dose for $<$ 10 kg) intravenously on day 2; and vincristine (1.5 mg/m^2/day or 0.05 mg/kg/day) intravenously on days 2, 9, and 16. Dexrazoxane (300 mg/m^2/dose or 10 mg/kg/dose for patients $<$ 10 kg) intravenous push was given before doxorubicin during the last two cycles of C5VD. High-risk patients were to receive vincristine (V), 1.5 mg/m^2/day (0.05 mg/kg/day) intravenously, on days 1 and 8 in combination with irinotecan (I), 50 mg/m^2/day (1.67 mg/kg for patients $<$ 10 kg), intravenously over 90 minutes, days 1-5 (VI) as detailed elsewhere. Repeat imaging and AFP measurements were performed after two cycles to assess response to VI. Patients who were considered responders according to local assessment were intended to receive two additional cycles of VI intermixed with six cycles of C5VD as above. Chemotherapy cycles were to occur every 21 days.

Surgery

Study patients could have primary tumor resection at any point during therapy, either by surgical resection or total hepatectomy followed by orthotopic liver transplant, irrespective of PRETEXT stage. Delayed resection optimally was intended per protocol after cycle #4 in intermediate-risk patients and for high-risk patients after cycle #7 of 10 in responders or after cycle #6 of eight in nonresponders. Metastatic lesions were to be addressed surgically at the discretion of treating physicians.

Pathology

Central histologic review was to be performed for all biopsied and resected specimens (liver and/or lung) to assess tumor histology. If patients were deemed too sick to undergo biopsy at diagnosis, they were still eligible for enrollment if they met HB criteria including elevated AFP.

For treatment purposes, SCU tumors were defined as tumors with any amount of SCU cells detected at the local treating center. For evaluation of outcome, SCU tumors were considered as those identified by central review at diagnosis. The percentage of SCU cells was calculated using the fraction of viable tumor that conformed to SCU morphology estimated in all of the sections submitted for review at 100× magnification in hematoxylin-eosin–stained slides. After defining the SCU with dual positivity for Pan-cytokeratin (Millipore AE1/AE3 at 1/20,000) and Vimentin (Dako Vim 3B4 at 1/300), immunostaining for the presence of the INI1 protein (using BD 25 clone 612110 at 1:25) was performed on all tumors as part of the central pathologic review. The pathologists examined the samples independently and met to reconcile any differences and established consensus in each case.

Evaluation of Response

Baseline physical examinations, organ function, AFP levels, and imaging studies (including a computed tomography [CT] or magnetic resonance imaging of the abdomen, ultrasound of the liver, and CT of the chest) were performed

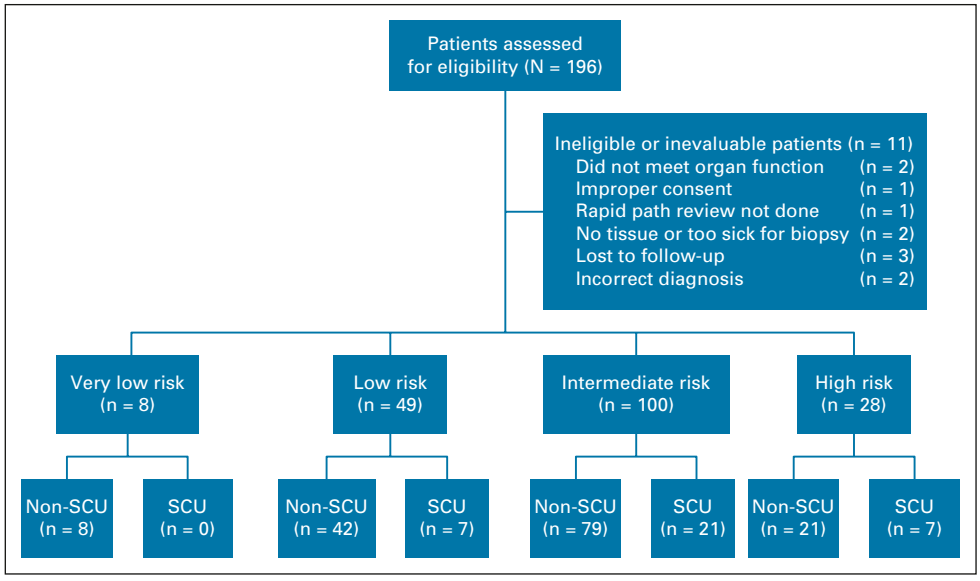

FIG 1. CONSORT diagram. SCU, small cell undifferentiated.

TABLE 1. Baseline Characteristics for the 177 Patients With Central Review

Characteristic	SCU From Central Review: Yes (N = 35)	No (N = 142)	Overall (N = 177)	*P*
Age at enrolment, months				
Mean (SD)	19.9 (15.9)	25.7 (29.2)	24.6 (27.1)	.47
Median (min, max)	17.0 (4.00, 78.0)	18.0 (0, 189)	17.0 (0, 189)	
Sex, No. (%)				.68
Female	12 (34.3)	54 (38.0)	66 (37.3)	
Male	23 (65.7)	88 (62.0)	111 (62.7)	
Race, No. (%)				.19
White	22 (62.9)	99 (69.7)	121 (68.4)	
Black or African American	1 (2.9)	15 (10.6)	16 (9.0)	
Asian	4 (11.4)	9 (6.3)	13 (7.3)	
Unknown	8 (22.9)	19 (13.4)	27 (15.3)	
Ethnicity, No. (%)				.16
Not Hispanic or Latino	20 (57.1)	103 (72.5)	123 (69.5)	
Hispanic or Latino	13 (37.1)	33 (23.2)	46 (26.0)	
Unknown	2 (5.7)	6 (4.2)	8 (4.5)	
Stage, No. (%)				.09
I	12 (34.3)	35 (24.6)	47 (26.6)	
II	4 (11.4)	7 (4.9)	11 (6.2)	
III	12 (34.3)	79 (55.6)	91 (51.4)	
IV	7 (20.0)	21 (14.8)	28 (15.8)	
Stratum, No. (%)				.47
2	7 (20.0)	42 (29.6)	49 (27.7)	
3	21 (60.0)	79 (55.6)	100 (56.5)	
4	7 (20.0)	21 (14.8)	28 (15.8)	
Initial AFP (ng/mL), No. (%)				.12
100-1,999	0 (0)	13 (9.2)	13 (7.3)	
1,000-999,999	30 (85.7)	119 (83.8)	149 (84.2)	
> 999,999	4 (11.4)	10 (7.0)	14 (7.9)	
Missing	1 (2.9)	0 (0)	1 (0.6)	
Percentage SCU				
Mean (SD)	3.71 (5.28)			
Median (min, max)	2.00 (1.00, 25.0)			

Abbreviations: AFP, alpha-fetoprotein; SCU, small cell undifferentiated; SD, standard deviation.

before initiating therapy. Repeat imaging studies (CT or magnetic resonance imaging of the abdomen) were performed in intermediate-risk patients after every two cycles of C5VD and in high-risk patients after two cycles of VI and then after every two cycles of C5VD. AFP levels were obtained before beginning each cycle.

For the purpose of this study, a complete response was considered to be the disappearance of all lesions and a normal AFP level. A partial response was considered as either (1) a ≥ 30% decrease according to RECIST; or (2) a serum AFP level concentration decline of ≥ 90% (≥ 1 $\log_{10}$) after two cycles in the absence of disease progression.

Statistical Design and Analysis

Event-free survival (EFS) was measured from the time of patient enrollment until the last follow-up or an analytic event was observed, whichever occurred first. Analytic events for this cohort were (1) progression of disease or occurrence of disease at new sites; (2) death from any cause before disease progression; or (3) diagnosis of a second malignancy. Overall survival (OS) was defined from the time of enrollment until death from any cause or last follow-up, whichever came first. The proportion of patients who were event-free or alive as a function of time since enrollment was estimated using the Kaplan-Meier method, and 95% CIs were estimated by the log-log method. The multivariate Cox model was fitted to assess differences in EFS for SCU group versus non-SCU group. Hazard ratios with adjustment of treatment or stratum were reported. Chi-square tests (or Fisher's exact tests as appropriate) were used to evaluate the association between patient categorical characteristics and presence of SCU histology. Wilcoxon tests were used to evaluate the association between patient continuous characteristics and presence of SCU histology. Statistical significance was set at a two-sided *P* value of .05.

RESULTS

All Patients

A total of 188 low-, intermediate-, and high-risk patients were enrolled on the study between September 2009 and May 2014. Eleven patients were deemed ineligible for this analysis including six patients who did not meet organ function requirements or not have consent signed before beginning therapy, two patients who were too sick to biopsy and so did not have pathology for review, and three patients whose status was unknown (CONSORT diagram, Fig 1). Outcome current to March 31, 2020, was used in this analysis. The median age at diagnosis was 17 months (range, 0-189 months). There were 111 males and 66 females. The 177 evaluable patients for this analysis therefore included 49 low-risk patients, 100 intermediate-risk patients, and 28 high-risk patients. The median initial AFP at enrollment was 106,483 ng/mL (104-5,036,000 ng/mL). The median follow-up for patients who did not experience an event was 8 years.

Patients With SCU HB

SCU was noted in a total of 35 patients by central review at diagnosis summarized in Table 1. The median percentage of SCU was 2% (range, 1%-25%). The median age at diagnosis for patients with tumors with SCU was 17 months (range, 4-78 months). There were 23 males and 12 females.

TABLE 2. Outcome of 35 Patients With Hepatoblastoma With SCU Histology at Diagnosis From Central Review

Strata	Stage (I/II/III/IV)	Central Review (N)	Local Review (N)	% SCU (central review)	No. of EFS-type Events	No. of Deaths
Low risk	6/1/0/0	7	0	1-10	1	0
Intermediate risk	6/3/12/0	21	8	1-25	4	3
High risk	0/0/0/7	7	1	1-10	5	2

Abbreviations: EFS, event-free survival; SCU, small cell undifferentiated.

The median initial AFP at enrollment in the patients with SCU was 194,823 ng/mL (range, 3,124-2,538,300 ng/mL). The presence or percentage of SCU did not appear to correlate with age, stage, or the initial AFP level. Thirty-three of the 35 patients with SCU identified at diagnosis were INI1-positive or retained. The two patients whose tumors demonstrated focal loss of integrase interactor 1 (INI) staining included one patient with stage II disease at diagnosis who relapsed and died of disease 8 months later, and one stage III patient who remains disease-free 99 months from diagnosis.

Seven additional patients who did not have SCU detected at diagnosis had some SCU elements (1%-10%) detected at second look surgery, all on central review only, all with retained INI staining and only one of these patients has had disease recurrence.

Concordance between local and central review of the presence of SCU histology at diagnosis was poor and agreed in only 9 of 35 patients (26%) summarized in Table 2. Interestingly, this was not different in 4 of 16 (25%) specimens obtained from a complete upfront

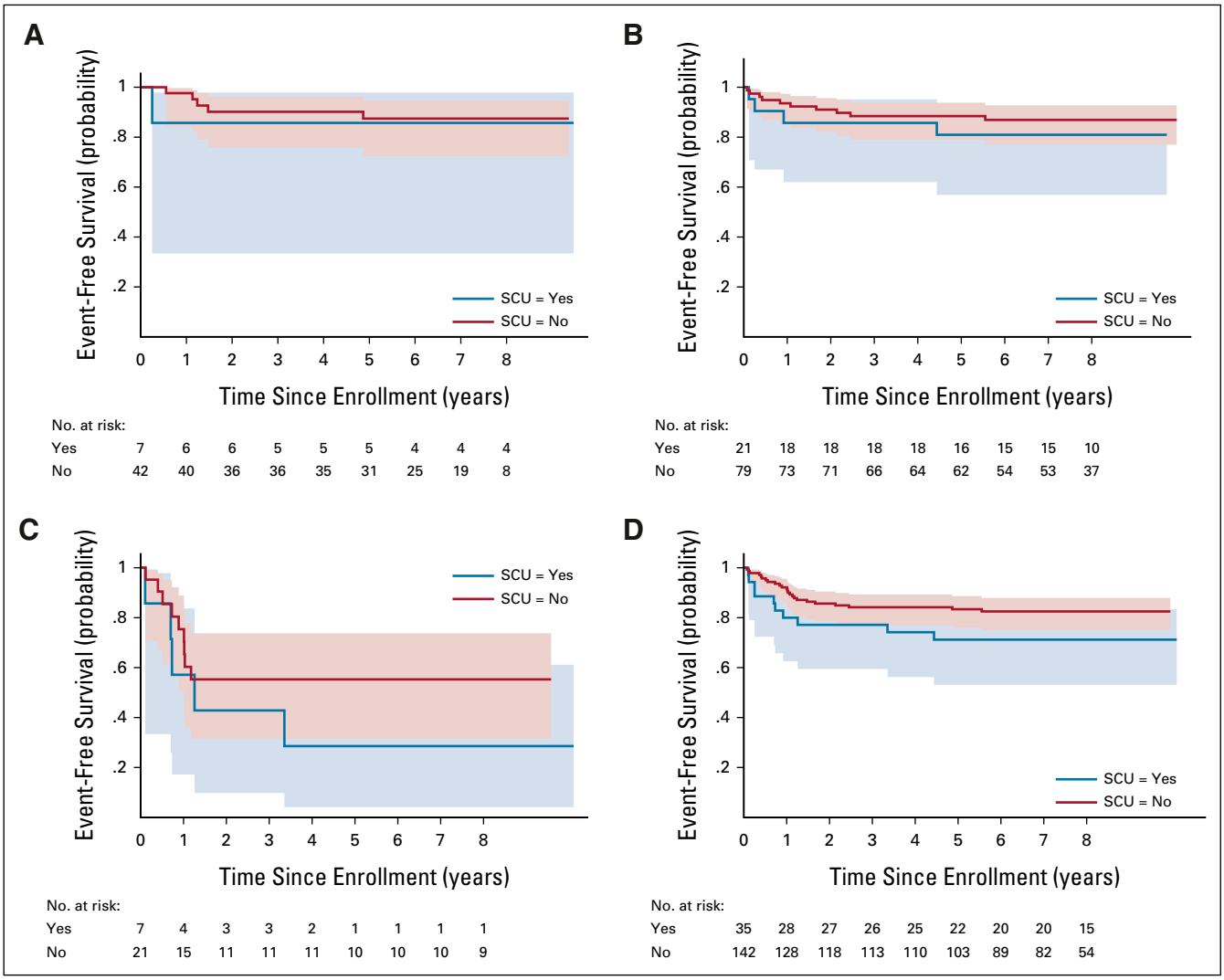

FIG 2. Event-free survival of patients with (A) low-, (B) intermediate-, and (C) high-risk hepatoblastoma, and (D) SCU elements. SCU, small cell undifferentiated.

resection or 5 of 19 (26%) specimens resulting from a diagnostic biopsy.

Twenty-five patients had tumors with < 5% SCU (seven relapsed and one secondary malignancy), eight patients had tumors with 5%-10% SCU (two have relapsed), and two patients had tumors with > 10% SCU (both disease-free without recurrence).

Outcome

The presence of the SCU elements at diagnosis was not significantly associated with the EFS adjusting for treatment (*P* value = .17). The 5-year EFS was 71% (95% CI, 53 to 83) for patients with SCU compared with 83% (95% CI, 76 to 89) for patients with non-SCU tumors shown in Figure 1. The 5-year OS was 86% (95% CI, 69 to 94) for the patients with SCU compared with 90% (95% CI, 83 to 94) for the patients with non-SCU tumors, as shown in Figure 2. The details of SCU patients with events are detailed in Table 3.

Low-risk. Of the seven patients who were identified with SCU by central review, only one with 2% SCU cells has recurred and remains alive and disease-free 97 months after relapse. This patient had a bile leak and bowel perforation following initial resection. The 5-year EFS for low-risk SCU tumors was 86% (95% CI, 33 to 98) compared with 87% (95% CI, 72 to 95) for non-SCU tumors, as shown in Figure 2A. The 5-year OS for low-risk SCU tumors was 100% and was 92% (95% CI, 78 to 97) for low-risk non-SCU tumors, as shown in Figure 3A.

Intermediate-risk. Of the 21 patients with SCU, three have recurred and are dead of disease. One additional patient with Beckwith-Wiedemann had a second tumor and is alive in remission from both tumors. The 5-year EFS for intermediate-risk tumors was 81% (95% CI, 57 to 92) and was 88% (95% CI, 79 to 94) for non-SCU tumors, as shown in Figure 2B. The 5-year OS for SCU tumors was 86% (95% CI, 62 to 95) and OS for intermediate-risk patients with SCU tumors compared with 95% (95% CI, 87 to 98) non-SCU tumors, respectively, as shown in Figure 3B.

High-risk. Of the seven high-risk patients with SCU, five have recurred and three remain alive 61, 110, and 114 months after relapse. The 5-year EFS for high-risk SCU tumors was 29% (95% CI, 4 to 61) versus 55% (95% CI, 32 to 74) for SCU tumors, as shown in Figure 2C. The 5-year OS of high-risk patients with SCU tumors was 71% (95% CI,

TABLE 3. Patients With Hepatoblastoma With Events

#	Age (months)	Sex	Stage	PRETEXT	Strata	AFP at Diagnosis	% SCU	INI Staining	Resection	Event	Complications	Outcome
1	24	M	2	2	Low risk	113,765	2	POS	Yes	Liver 3 months	Bowel perforation	NED/CR2 100 months
2	13	M	2	3	Std risk	320,437	1	NEG	Yes	Liver 1 month	No	DOD 8 months
3	22	M	2	2	Std risk	2,538,300	2	POS	Yes	Liver, lung 11 months	Blood loss at surgery	DOD 29 months
4	17	M	3	2	Std risk	414,091	5	POS	Yes	Liver, Lung 3 months	Bowel perforation	DOD 8 months
5	14	M	4	2	High risk	610,640	10	POS	Not on protocol	Lung 1 month	No	NED/CR2 115 months
6	16	M	4	3	High risk	111,268	2	POS	Yes	Lung 8 months	No	NED/CR2 118 months
7	78	M	4	4	High risk	60,500	2	POS	No	Bone, lung 15 months	No	DOD, 21 months
8	36	M	4	3	High risk	1,597,904	1	POS	Yes	Lung, brain 40 months	No	DOD, 40 months
9	41	F	4	3	High risk	58,228	1	POS	Yes	Lung 9 months	No	NED/CR2 70 months
10[a]	4	F	3	2	Std risk	630,000	2	POS	Yes	Second malignancy, 53 months	No	NED 111 months
A[b]	50	M	3	3	Std risk	520	1	POS	Yes	Lung 13 months	No	Alive with disease, 19 months

Abbreviations: AFP, alpha-fetoprotein; CR2, second complete remission; DOD, dead of disease; NA, not applicable; NED, no evidence of disease; NEG, no INI1 staining; POS, positive for retained INI1 staining; SCU, small cell undifferentiated; Std risk, standard risk.

[a]Patient with Beckwith-Wiedmann syndrome.

[b]Tumors identified with SCU elements following postchemotherapy resection.

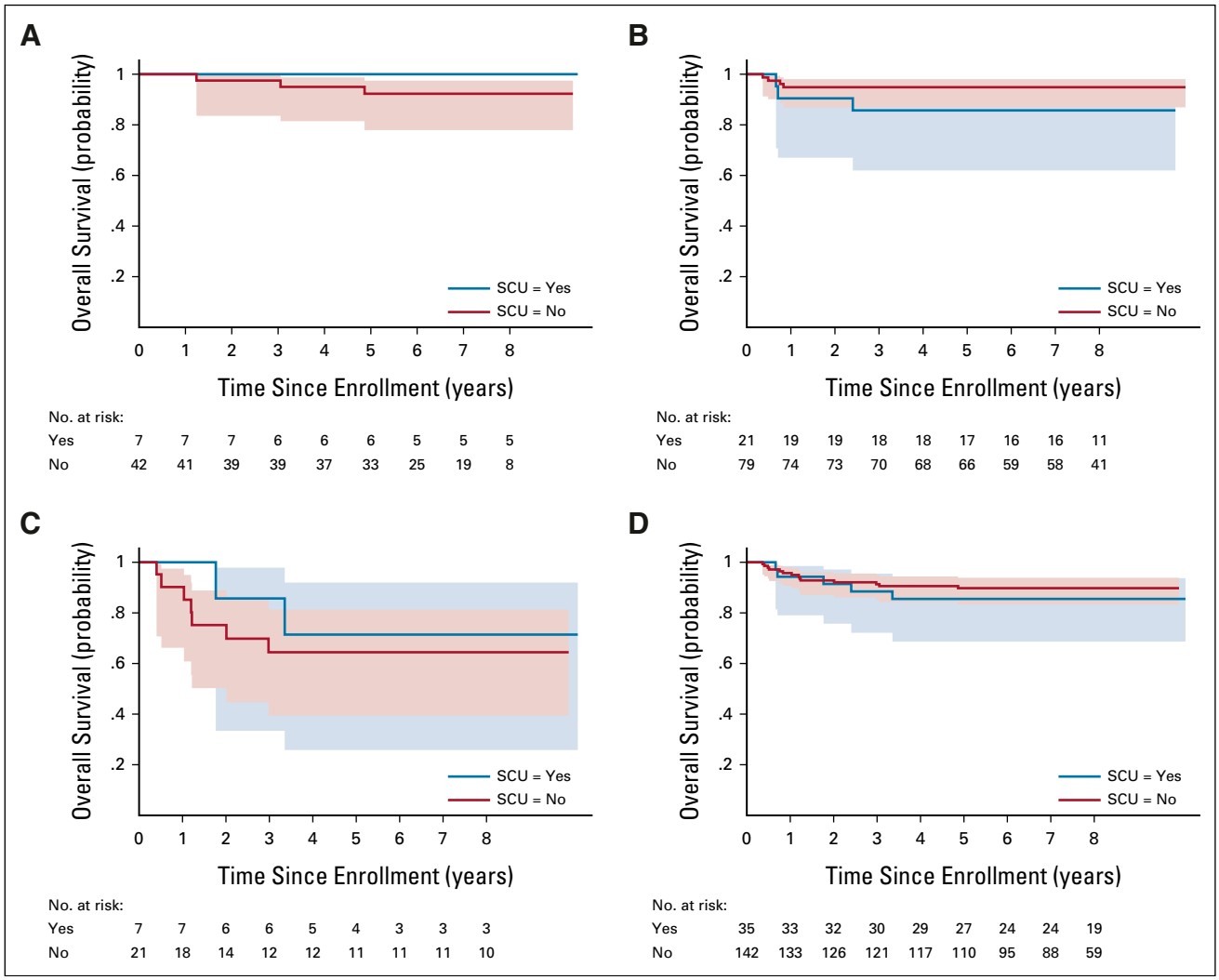

FIG 3. Overall survival of patients with (A) low-, (B) intermediate-, and (C) high-risk hepatoblastoma, and (D) SCU elements. SCU, small cell undifferentiated.

26 to 92) and 64% (95% CI, 39 to 81), as shown in Figure 3C.

DISCUSSION

The results of AHEP0731 failed to demonstrate that the presence of SCU histology was associated with an adverse outcome. To our knowledge, this is the largest single series of prospectively treated and evaluated HB patients with SCU features. Our data are in contrast to what has previously been reported in the literature.[2,6,13] It is likely that the findings in this current series are a result of this being a refined cohort of patients with true HB with SCU elements and that previous reports may have included other diagnoses, most specifically rhabdoid tumors because of the lack of INI staining and cytogenetics being performed in many previous studies. There has been a concentrated effort over the past few years to develop international consensus on the pathologic classification of pediatric liver tumors.[5] The results of those efforts appear to be evident in this study. In contrast to other series, no patient with a tumor with SCU components in this trial had a low AFP level (< 100 ng/mL) at diagnosis. In addition, all SCU tumors, except for two patients in our series, retained INI1 staining, which has not been the case in the majority of previous reports. The patients with INI1-negative cells had only 1% and 2% SCU elements. Seven patients in this series had SCU elements identified on post-therapy resection specimens that were not seen on diagnostic biopsies. Whether this is because of sampling issues or whether these pathologic features denote a more aggressive or resistant phenotype is difficult to discern because of the small numbers here.

Recently, a subset of patients with SCU HB were described with tumors found to be INI1-negative, as in rhabdoid tumors.[13] In addition, one HB tumor in that report was found to exhibit cytogenetic and molecular abnormalities

similar to those described in rhabdoid tumors. None of the 11 patients with SCU HB described in that series survived. All six patients tested were INI1-negative, and AFP levels were normal in four of the five patients who had available data.

The presence of SCU tumor elements was rarely identified by local pathologists in our study, and there was poor concordance between local and central pathologic review. This may be in part because of the fact that the majority of tumors with SCU features had only small amounts (< 5%) of SCU present. Central review of pathologic specimens as part of cooperative group protocols for patients with liver tumors, as well as other rare pediatric tumors, may be helpful especially when feasible and when affecting stratification or treatment. The data here also suggest that cytogenetic evaluation for mutations in the *SMARCB1* hSNF5/INI-1 gene and INI1 staining should be routinely performed in any patient with HB who has an AFP level < 100 ng/mL to confirm an accurate diagnosis as the treatment and outcome for rhabdoid tumors is dramatically different than that for HB. Since the majority of patients in this series had retained INI1 staining in their tumors, the need for cytogenetic testing for those patients is not definitively necessary and should be evaluated in future studies.

The presence of SCU histology in HB in the setting where INI1 expression is retained does not appear to adversely affect outcome but must be considered within the limitations of the study, which include study size and the treatment regimens used. SCU histology is not being used for stratification of treatment in the current AHEP1531: Pediatric Hepatic Malignancy International Therapeutic Trial (PHITT).

Refinements of the pathologic classification of liver tumors have appeared to result in improved classification of tumors and the ability to deliver the appropriate risk-based therapy. The data here suggest that future studies should incorporate risk stratification and treatment without regard to the presence of SCU histology.

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EQUAL CONTRIBUTION

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SUPPORT

NCTN Operations Center Grant U10CA180886. NCTN Statistics & Data Center Grant U10CA180899, St Baldrick's Foundation. NIH/NCI U10 CA29511, Quality Assurance Review Center (QARC). NIH/CI U24 CA180803, Imaging and Radiation Oncology Core (IROC).

CLINICAL TRIAL INFORMATION

NCT00980460

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00803.

DATA SHARING STATEMENT

Children's Oncology Group Data Sharing Statement: The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase III studies, individual-level deidentified data sets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non–phase 3 studies, data are available following the primary publication. An individual-level deidentified data set containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use.
For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical or biotechnology company must comply with the data sharing terms of the binding collaborative and contractual agreement and must receive the proper approvals.

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ACKNOWLEDGMENT

The study team is indebted to Fran Laurie, Karina Rossi-Toole, Sandy Kessel, Richard Hanusik, Brandon Davis, and the rest of the staff of the Quality Assurance Review Center for collection of scans, compilation of data, and facilitation of central review sessions.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Small Cell Undifferentiated Histology Does Not Adversely Affect Outcome in Hepatoblastoma: A Report From the Children's Oncology Group (COG) AHEP0731 Study Committee

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No other potential conflicts of interest were reported.