

HANDBOOK FOR CHILDREN WITH LIVER TUMORS

Updated Spring 2014

This handbook is created for the clinician treating children with liver tumors. Material is taken from the biology protocol ABTR01B1, clinical protocol AHEP0731, and epidemiology study AEPI04C1 (which closed 2012). It represents a synthesis of surgically relevant information from which to organize pertinent data information in treating your patient.

This handbook begins with a One Minute Review, which outlines bare minimum facts for the surgeon in the OR, including stage, surgical guidelines, and tissue handling. There follow several sections, including abstract, background, details of PRETEXT and POSTTEXT groupings for staging and assessment of resectability, surgical guidelines and operative details, tissue and pathology requirements, treatment and follow-up guidelines, epidemiologic implications of hepatoblastoma, and surgeon responsibilities.

What's New:

- Surgical resectability will be determined by PRETEXT grouping, a European concept of Pretreatment Extent of Disease, and based on imaging of tumor location and surrounding structure involvement.
- Treatment groups will be based on COG operative staging and histopathology.
- Treatment groups will include very low, low, intermediate, and high risk, with intent to decrease therapy for favorable tumors, and try new agents for unfavorable tumors.
- Liver transplantation will be considered as a primary treatment option for unresectable tumors rather than as a salvage therapy. Timely referrals and surgeries are emphasized.
- Enrollment on ABTR01B1 encouraged not mandated to enroll on AHEP0731.
(POG9346 closed)

This document should make life easier for the surgeon and facilitate maximal compliance with protocol guidelines. Surgery Study members are listed below, and should be contacted for questions. Any and all suggestions for improvement are welcome. The Chair of the Liver Tumor Surgery Steering Committee is Rebecka Meyers.

Surgery Study Members:

Rebecka Meyers, Chair	(801) 662-295	rebecka.meyers@hsc.utah.edu
Eugene McGahren	(434) 924-5643	edm6k@virginia.edu
Max Langham, Jr	(901) 572-3300	mlangham@utmem.edu
Stephen P. Dunn	(302) 651-5999	sdunn@nemours.org
Gregory Tiao	(513) 636-4371	greg.tiao@cchmc.org

Colleen Fitzpatrick
John J. Doski
UTHSC San Antonio
jjdoski@gmail.com

ONE MINUTE REVIEW

Resectability determined by PRETEXT (PreTreatment Extent of Disease) or POSTTEXT (PostTreatment Extent of Disease) groupings.

- PRETEXT1** Tumor in 1 liver section, 3 adjoining free of tumor
 2 Tumor in 2 adjoining sections, 2 adjoining free of tumor
 3 Tumor in 3 adjoining sections or 2 nonadjoining, 1 free or 2 nonadjoining free
 4 Tumor involves all 4 liver sections, no section free

*Any Pretext group can be annotated with following modifiers:

- +V Involvement of IVC or all 3 hepatic veins
- +P Involvement of portal bifurcation or both right/left portal veins
- +C Involvement of caudate lobe
- +E Extrahepatic contiguous tumor
- +M Distant metastatic disease

SURGICAL GUIDELINES

Primary resection for PRETEXT 1 or PRETEXT 2 with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or portal bifurcation (V,P).

Initial Tumor biopsy for PRETEXT 2 with **less than** 1 cm radiographic margin for V,P, PRETEXT 3, PRETEXT 4, or metastatic disease. Biopsy technique at discretion of institution- percutaneous tru-cut, laparoscopic tru-cut (3 tru-cut cores) laparoscopic wedge, or open. Larger biopsies better to evaluate for heterogeneous foci of small-cell undifferentiated (SCU) tumor- worse prognosis.

Following Chemotherapy:

Primary resection for POSTTEXT 1, 2 with >1cm margin on V,P after 2 cycles

Primary resection for POSTTEXT 3 and no major venous invasion. (Margin <1cm ok)

Liver transplant referral after 2 cycles for PRETEXT 3 with venous invasion, multifocal PRETEXT3, and PRETEXT 4. Transplant within 4 wks of completion 4th cycle.

OPERATIVE STAGE

- I Completely resected. (Requires rapid pathology review prior enrollment)
- II Grossly resected, microscopic margin positive, or pre/intraop rupture. (Requires rapid pathology review prior enrollment)
- III Unresectable, partially resected; abdominal lymph node involvement
- IV Metastatic disease to lungs, other organs or sites distant from the abdomen

TISSUE HANDLING

All tissue obtained in OR sent fresh to pathologist.

Abstract/Overview

This study will classify newly diagnosed children with hepatoblastoma into low, intermediate and high-risk treatment groups and therapy based upon the risk classification. Children with low-risk disease that can undergo tumor resection at diagnosis and do not have any unfavorable biologic features have a very good outcome (90% survival). This study will test whether this outcome can be maintained with a reduction in therapy from 4 cycles to 2 cycles of standard chemotherapy with cisplatin, 5-fluorouracil, and vincristine (C5V). Patients with tumors that are completely resected upfront and have pure fetal histology have been shown to have an excellent outcome with surgery alone (approaching 100% survival) and will continue to be treated with surgery only. Children with tumors that can not be removed at diagnosis and do not have evidence of metastatic disease can only be resected and ultimately cured in 50-70% of patients following treatment with chemotherapy. This study will attempt to improve resection rates and survival with the addition of doxorubicin, an agent well documented to have efficacy in hepatoblastoma, to the C5V chemotherapy regimen. In addition, as surgical resection is essential for cure in this disease, this study will explore the feasibility of timely referral for liver transplant consultation. Patients with metastatic disease and with a low AFP (< 100 ng/ml) at diagnosis have a poor outcome. Novel agents to treat hepatoblastoma have been difficult to identify due to low numbers of relapsed hepatoblastoma patients entered onto phase I and II trials. This study will therefore incorporate a novel drug (irinotecan), into an upfront window to determine its anti-tumor efficacy and whether it is able to improve survival.

This study will also attempt to: 1) study the affect of histologic subtypes (macrotrabeclar, small cell undifferentiated) on outcome, 2) determine the effect of biologic and pathologic features (microscopic positive surgical margins, multi-focal tumors, microscopic vascular invasion, and AFP < 100 ng/ml at diagnosis) on outcome, 3) incorporate the use of the PRETEXT system, determine its utility, and validate its usefulness as a prognostic variable, 4) study the surgical treatment of pulmonary metastases and determine if there is a correlation of treatment with outcome 5) foster the collection of tumor samples for biologic studies (the presence of Trisomy 2, 8 and 20 or the translocation of the NOTCH2 gene) and determine if there is a correlation with outcome.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Hypotheses:

- 1.0 A risk-based treatment approach will maintain or improve event-free survival (EFS), decrease acute and long-term chemotherapy toxicity, and identify new agents in the treatment of children with hepatoblastoma.
 - 1.1 Stage I hepatoblastoma (non-PFH), non-SCU (small cell undifferentiated) and Stage II (non-SCU) is a highly curable disease with two cycles of adjuvant cisplatin, 5-fluorouracil, and vincristine (C5V).
 - 1.2 The addition of doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma will be feasible and associated with acceptable levels of toxicity.
 - 1.3 The use of vincristine and irinotecan in an upfront window for children with high-risk, metastatic hepatoblastoma will improve the response rate in this group of children.
- 2.0 Referral for orthotopic liver transplant (OLT) is feasible in a cooperative group setting in children with hepatoblastoma designated as potentially unresectable following central surgical review and staging according to the PRETEXT staging system
- 3.1 Primary Objectives:
 - 3.1.1 To estimate the EFS in children with Stage I (non-PFH, non-SCU) and Stage II (non-SCU) hepatoblastoma treated with two cycles of C5V.
 - 3.1.2 To determine the feasibility and toxicity of adding doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma.
 - 3.1.3 To estimate the response rate to vincristine and irinotecan in previously untreated children with high-risk, metastatic hepatoblastoma.
 - 3.1.3 To determine whether timely (after second cycle of chemotherapy) consultation with a treatment center with surgical expertise in major pediatric liver resection and transplant can be achieved in 70% of patients with potentially unresectable hepatoblastoma.
 - 3.1.5 To determine the frequency of the presence of Trisomy 2, 8 and 20 or the translocation of the NOTCH2 gene and associated outcome in this patient population in order to provide data on planning parameters for the subsequent clinical trial.
- 4.2 Secondary objectives:
 - 4.2.1 To determine the feasibility and toxicity of adding doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma.
 - 4.2.2 To determine whether OLT can be accomplished after successful referral and completion of four courses of initial chemotherapy.
 - 4.2.3 To estimate the 2-year EFS for patients once identified as candidates for possible OLT, the 2-year EFS for patients referred to a transplant center that are resected without OLT, and the 2-year EFS for patients referred to a transplant center who receive OLT.

- 4.2.4 To register children with hepatoblastoma who receive OLT with PLUTO (Pediatric Liver Unresectable Tumor Observatory), an international cooperative registry for children transplanted for liver tumors.
- 4.2.5 To determine if PRETEXT grouping can predict tumor resectability.
- 4.2.6 To monitor the concordance between institutional assessment of PRETEXT staging and PRETEXT staging as performed by expert panel review.
- 4.2.7 In Stage IV patients, to estimate the proportion of patients who have surgical resection of metastatic pulmonary lesions.
- 4.2.8 To determine the proportion and estimate the EFS of patients with potential poor prognostic factors including microscopic positive surgical margins, multi-focal tumors, microscopic vascular invasion, macrotrabecular histologic subtype, SCU histologic subtype, and AFP < 100 ng/ml at diagnosis.

2.0 BACKGROUND

Hepatoblastoma is the most common malignant liver neoplasm in children. Although surgical resection is the mainstay of curative therapy for children with hepatoblastoma, only one-third to one-half of newly diagnosed patients with hepatoblastoma can be expected to have resectable disease at presentation.^{1,2} The main determinants of clinical outcome in patients with hepatoblastoma are the presence or absence of metastatic disease, and tumor resectability.³ In addition, unique histologic variants of hepatoblastoma, such as small cell undifferentiated (SCU) histology, have also been shown to adversely affect survival.^{4,5}

Patients who undergo a primary complete resection of their tumor have an excellent prognosis (90% event-free survival) in several series.^{3,6,7} The use of chemotherapy has improved survival in patients with unresectable hepatoblastoma by increasing the number of patients whose tumors can be resected.^{6,8} Cisplatin (CDDP) has been identified as the most active agent for the treatment of hepatoblastoma.^{9,10} Doxorubicin (DOX) appears to be the next most active agent. There is relatively little information on the efficacy of other single agents such as ifosfamide (IFOS), etoposide (VP), vincristine (VCR), 5-fluorouracil (5-FU), cyclophosphamide (CYC), and carboplatin (CARBO) in the treatment of hepatoblastoma as most of these agents have been used in combination.^{2,11,12} Cooperative group studies from around the world performed in the late 1980s and early 1990s demonstrated the effectiveness of chemotherapy in increasing rates of surgical resection and survival in initially unresectable patients.^{13,14} However, more recent trials over the last decade have failed to significantly improve upon these survival numbers. Therefore, the current event-free survival for the entire group of patients with non-metastatic, unresectable hepatoblastoma at diagnosis remains suboptimal (< 70%) and warrants novel treatment approaches. The survival of patients with metastatic disease at diagnosis remains poor (20-30%) and also requires consideration of novel therapeutic strategies.^{2,15}

For patients without metastatic disease, delayed tumor resection has been associated with survival rates comparable to the survival rates observed in patients who undergo a primary resection at the time of diagnosis.² However, only approximately 2/3 of patients with unresectable tumors at diagnosis become resectable with chemotherapy² leaving too many children with gross residual disease. There is no good marker or method to predict which tumors considered unresectable initially will eventually become amenable to resection. Orthotopic liver transplantation (OLT) is sometimes the only option that may result in complete tumor removal and therefore greatly increasing the individual's chance for cure.

In addition, biologic factors may be able to help predict tumor phenotype. These biologic variables may help to result in better identification of disease-risk and therefore yield additional refinement criteria to risk-stratified therapy. This could decrease toxicity by limiting therapy in the most favorable groups and maximize therapeutic options for the most aggressive tumor phenotypes. Hepatoblastoma has been characterized by several genetic markers, including chromosomal numerical and structural aberrations, in particular specific trisomies of chromosome 2, 8, and 20 and translocations with breakpoints at chromosome 1q12. The correlation of these genetic markers in response to treatment and outcome has been only minimally studied. We have recently determined that translocation of the *NOTCH2* gene on chromosome 1 may be an important component to the development of some cases of hepatoblastoma. In this study, we will characterize these genetic markers with respect to their association with outcome. Systematic evaluation of tumor biology may allow for refining risk stratification and for developing more targeted therapy for this childhood cancer.

Pathologic Considerations

Patients with Stage I PFH hepatoblastoma have been considered as a “favorable” subtype and have been treated with surgical resection without adjuvant chemotherapy on the P9645 study. The rationale for this approach was based upon reports of selected patients who fared well with surgery alone.¹⁶ Stopping rules for the failure of this hypothesis have not been met on the current P9645 study and no events have been observed in the 15 patients enrolled on the study to date.¹⁷ This suggests that surgical resection alone provides adequate therapy for this selected subset of children with hepatoblastoma. This approach will limit unnecessary and harmful exposure to various chemotherapeutic regimens, such as cisplatin, vincristine, 5-fluorouracil, and doxorubicin in the approximately 4% of all children with stage I PFH hepatoblastoma.

The presence of SCU components in the resection specimen is an unfavorable histologic variant and has been previously associated with a trend towards an increased risk for an adverse event ($p=0.15$). However, the number of patients with SCU tumors reported in the literature is relatively small.⁵ In this largest previous report, Haas and colleagues described the presence of SCU elements in 16 patients with stage I tumors. A much higher than expected relapse rate for stage I patients was observed in this cohort with recurrences in ten of the 16 patients.⁵ Relapses and death were seen even in patients with a small focus of SCU, including one patient who ultimately died from disease and had only one microscopic SCU focus among eight slides examined. These observations warrant further study. The adverse prognostic impact of SCU in the reported cases

warrants that the presence of any SCU elements must be considered as significant. In an analysis of data from CCG trial CCG-881, survival was 70% in stage I patients without SCU (n=30) vs. 50% in stage I patients with SCU (n=4). In a similar analysis of the INT-0098 study, recurrence was observed in 9% of non-SCU, non-PFH stage I patients (n=35) compared to a 38% recurrence rate in stage I patients with SCU (n=8). The presence of SCU elements has also been recently identified and correlated with the presence of a low AFP level (< 100ng/ml), another poor prognostic variable, and has been observed in all stages of hepatoblastoma.¹⁸ Previous cytogenetic reports have demonstrated that SCU hepatoblastomas have chromosome aberrations involving chromosome 22q11.^{19,20} A deletion of the rhabdoid associated gene, hSNF5/INI1 gene, has been observed in tumor tissue from one patient with SCU histology studied in the hepatoblastoma biology study, POG 9346.

Chemotherapy Considerations

Over the last two decades, the chemotherapeutic regimen cisplatin/5-fluorouracil/vincristine (C5V) has been utilized and studied within COG trials and has been adopted as the standard treatment regimen by COG because of its similar activity and favorable toxicity profile when compared to doxorubicin containing regimens.

Low-risk patients

Low-risk patients will include those patients who have grossly resected tumors (stage I and II) AND lack any unfavorable biologic feature (any SCU elements or a low diagnostic AFP level < 100ng/ml)

Approximately 20-30% of children with hepatoblastoma can be expected to be classified as low-risk. In the POG 8696/8697, INT-0098, and P9645 these patients received four adjuvant cycles of C5V and their 5-year EFS was 84% and survival was 96% in patients treated with this approach.⁶ This approach has used the most active compound, cisplatin, as the integral component of therapy and has avoided exposure to anthracyclines and ifosfamide and their associated short and long-term toxicities in the 15-30% of low-risk patients diagnosed with hepatoblastoma and treated on COG studies. The five-year EFS for stage I patients with non-PFH is 91% and survival is 98% in patients treated with this approach.⁶ Cumulative grade 3-4 toxicities associated with four cycles of this regimen on P9645 include: anemia (45%), neutropenia (75%), thrombocytopenia (11%), anorexia (10%), vomiting (14%), febrile neutropenia (16%), and stomatitis (2%). Noticeable hearing loss (> 40 dB at any freq from 3-5 kHz or > 20 but <= 40 dB at 2 kHz) as a measure of ototoxicity occurred in 2 of 21 evaluable patients (10%). This therapy has a significant impact on both the short-term and long-term quality of life in these children. Therefore, the history of the successful use of the C5V regimen within COG studies over the last twenty years has lead to the point where a reduction in chemotherapy appears justified in the subset of patients with non-PFH, non-SCU hepatoblastoma who have an excellent prognosis. In addition, the successful reduction in therapy for stage I PFH patients treated with surgery alone helps to justify the reduction in therapy for this group of stage I non-PFH, non-SCU patients who comprise about 20-25% of all hepatoblastoma patients. Strict monitoring criteria and stopping rules will be utilized to ensure patient safety and that excellent EFS is maintained.

While cisplatin has been the backbone of hepatoblastoma therapy, the additional agents used in combination with cisplatin have differed among the various cooperative groups. It is somewhat difficult to compare the results of COG studies with that of international groups as different staging criteria have been used and therefore comparison groups are not necessarily equivalent. COG and the German Cooperative Pediatric Liver Tumor Studies have used a surgical staging system. SIOPEL has classified patients using radiographic criteria as part of the PRETEXT system and has categorized standard-risk patients as those with tumors that are either PRETEXT I, II, or III.³ This standard risk group is fairly similar to the stage I and II COG patients classified in this trial as low-risk. The most recent published results of SIOPEL-2 have focused on the use of CDDP monotherapy for these standard-risk patients who received a total of 6 cycles of CDDP at 80 mg/m² for a cumulative dose of 480 mg/m².³ This is more than the total cumulative dose given during the 4 cycles of CDDP at 100 mg/m² used for resected stage I and II patients on COG studies such as P9645. In the German Cooperative Group HB studies, resected patients received two to three cycles of DOX (60 mg/m²) and IFOS (3500 mg/m²) in addition to CDDP (20mg/m² x 5) exposing these patients to much more toxic chemotherapy than in resected stage I and II COG patients.^{7,21} The further reduction in this proposal to 2 cycles of CDDP for low-risk patients should reduce both associated toxicity and medical costs. A comparison of survival rates in several recent studies are summarized in Table 1. Survival rates among COG and SIOPEL groups are comparable with SIOPEL-2 standard-risk patients having a 3-year progression-free survival (PFS) of 89 ± 7% compared to 88 ± 6% for low-risk COG patients treated with C5V on INT-0098 and 86 ± 6% for COG patients treated with C5V without amifostine on P9645.³ However, results of the SIOPEL-2 trial must be interpreted with caution for several reasons: 1) the study uses any tumor shrinkage or decrease in AFP as a response, which is far less stringent than the 50% decrease in tumor size used as response criteria on COG studies; 2) twenty-three of the 77 standard-risk patients (30%) who were classified as standard-risk were not treated according to protocol and received additional, more intense, therapy with doxorubicin and carboplatin making the SIOPEL-2 results difficult to interpret. When chemotherapy administration in violation of protocol was considered as an event in the SIOPEL-2 study, the 3-year EFS was substantially inferior to COG studies at only 73 ± 11% for the standard-risk patients.³

Table 1. Treatment and Survival of Resectable and Non-Metastatic Hepatoblastoma Patients in Recent Studies

Study	Treatment	Number of patients	Stage	EFS	S
P9645 ¹⁷	CDDP/5-FU/VCR	55	I/II	84%*	96%*
INT-0098 ⁶	CDDP/5-FU/VCR	26	I/II	88%*	100%*
	CDDP/DOX	24	I/II	96%*	96%*
SIOPEL-2 ³	CDDP	6 36 25	I,II,III (PRETEXT)	73% [#]	91% [#]
SIOPEL-1 ¹⁴	CDDP/DOX	6	I	100% ^{&}	100% ^{&}
		52	II	83% ^{&}	91% ^{&}
		45	III (PRETEXT)	56% ^{&}	68% ^{&}
HB-94 ⁷	CDDP/DOX/IFOS	27	I	89%	96%
		3	II	100%	100%
HB-89 ²¹	CDDP/DOX/IFOS	21	I	100%	
		6	II	50%	

* = 4-year EFS or S; & = 5-year EFS and S; # = 3-year EFS and S

While the roles of vincristine and 5-fluorouracil used in COG studies are not entirely clear, indirect evidence suggests that these two agents are active against hepatoblastoma and may be synergistic with CDDP. COG results compare favorably with those reported in the SIOPEL studies using the PLADO regimen (CDDP and DOX) and with the three drug IPA regimen (IFOS, CDDP, DOX) used in the HB (German Cooperative Pediatric Liver Tumor) studies. If vincristine and 5-fluorouracil were entirely inactive than it would be expected that both the PLADO and IPA regimens should be superior to C5V but the results of SIOPEL and German trials have been either equivalent or inferior to COG studies (Table 1) despite more intense chemotherapy exposure in the international studies. In addition, in the most recent COG study P9645, the experimental arm of intensified platinum-based therapy with CDDP and CARBO that was administered to advanced-stage patients proved to be inferior to the C5V regimen suggesting that the addition of vincristine and 5-fluorouracil may add to the activity of single agent CDDP. Since CDDP is the main cause of chemotherapy-related toxicity in low-risk patients, the best strategy to decrease toxicity may be to decrease the total dose of CDDP that is administered. The continued use of vincristine and 5-fluorouracil and their potential synergy with CDDP may be a significant contributor to the safe reduction in the total cumulative dose of CDDP delivered to low-risk patients. The toxicity associated with vincristine and 5-fluorouracil is mild with little to no expected long-term toxicity as compared to the significant short and long-term toxicities often associated with DOX, IFOS, or ETOP.

This data demonstrates that low-risk COG patients (stage I non-PFH, stage II patients): 1) have excellent survival with the current COG standard therapy C5V, 2) have equivalent, if not better, survival with C5V when compared to other cooperative group regimens; 3) have potential for diminished toxicity when using regimen C5V compared with other regimens by avoiding the use of anthracyclines and ifosfamide; 4) have potential for salvage in the event of relapse with the administration of doxorubicin when it is excluded from initial treatment. For these reasons, C5V is the optimal treatment for the 20-25% of patients with non-PFH, low-risk disease.

Intermediate-risk patients

Intermediate-risk patients will include those patients with: 1) gross residual disease/unresectable disease; or 2) grossly resected disease with any SCU elements but who do not have metastatic disease and do not have a low diagnostic AFP level < 100ng/ml.

The Pediatric Intergroup Study INT-0098 randomized patients with hepatoblastoma to receive treatment with either C5V [CDDP (90mg/m²), 5-FU (600 mg/m²), and vincristine (1.5 mg/m²)], or CD [cisplatin and doxorubicin (80mg/m²)]. Resected patients received 4 courses whereas initially unresected patients received 6 or 8 cycles totaling a maximum of 720 mg/m² of CDDP and 640 mg/m² of doxorubicin.⁶ Three patients treated with CD developed congestive heart failure, two of whom died. No significant renal toxicity was reported and information on ototoxicity was not specifically measured or reported. Five-year EFS was 64% for 83 stage III patients and 25% for 40 stage IV patients. Survival for children with localized hepatoblastoma was approximately 70%, while for those with metastatic disease at diagnosis, survival was approximately 35%. Although there was no significant difference in outcome between the two treatment arms, they differed regarding the types of events observed. Tumor progression accounted for 86% of the events among patients treated with C5V, but only 50% of the events for those treated with CD. Therefore, COG adopted treatment with C5V as the standard for the treatment of patients with hepatoblastoma. While the doxorubicin arm was associated with a greater number of toxic events and deaths, these results do suggest some improved tumor response for patients receiving doxorubicin. This proposal will evaluate if the addition of doxorubicin can improve EFS in children with intermediate and high-risk disease. In patients with unresectable and metastatic disease at diagnosis, no published treatment regimen has demonstrated clearly superior results (Table 2). Therefore, it is reasonable to consider the use of C5VD as a novel therapeutic strategy to improve EFS for intermediate and high-risk patients. The addition of doxorubicin to the C5V regimen will intensify this regimen in an attempt to improve the outcome for this group of patients. This trial proposes to determine the feasibility and toxicity of adding doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma.

The administration of doxorubicin in the majority of previous trials has been by continuous infusion.^{6,14,21} However, there are no data that establish continuous infusion doxorubicin as more efficacious than bolus administration. Prolonged administration of doxorubicin requires hospitalization and results in more mucositis and myelosuppression. In addition, there is no documented evidence that continuous infusion doxorubicin results

in diminished cardiac toxicity.²²⁻²⁴ The incidence of significant cardiac toxicity in INT-0098 was relatively small with 3 patients (4%) developing congestive heart failure among 81 patients who were intended to receive either 320mg/m² (n=24) or 640 mg/m² (n=57) of doxorubicin.⁶ In an older study CCG-823F, > 400 mg/m² of doxorubicin was given to 30 patients with no cardiac dysfunction reported.¹³ Cisplatin was also given in that study at 100 mg/m² for a total of 4 or 8 courses depending upon the timing of resection. Magnesium wasting occurred in 13% of patients but no other permanent renal dysfunction was reported. Since the EFS in patients with stage III and IV disease is less than desirable at 64% and 25% respectively,⁶ the relatively small risk of cardiac toxicity with a maximum cumulative dose of 360 mg/m² is reasonable. No data has been established to suggest that the administration of dexrazoxane has impaired survival in pediatric malignancies. Therefore, the cardioprotectant dexrazoxane will be incorporated into treatment postoperatively for all patients (when the doxorubicin dose has exceeded 240 mg/m²). In this study, doxorubicin will be administered as a short infusion over 2 hours on 2 consecutive days.

The HB studies from the German Cooperative Pediatric Liver Group have used a slightly different treatment strategy and have incorporated ifosfamide (IFOS) and etoposide (ETOP) along with cisplatin and carboplatin (CARBO). In HB-89, patients were treated with IFOS (3.5 gm/m²), DOX (60 mg/m²), and CDDP (20 mg/m² x 5) per course. Twenty-one stage I patients received 3 cycles and had 100% disease-free survival (DFS), six stage II patients received 4 cycles and had only 50% DFS. DFS was 71% in thirty-eight stage III patients and only 29% for the seven stage IV patients.²¹ A separate report from the HB-89 study reported on a total of thirty-seven patients with unresectable or metastatic disease. However, the number of chemotherapy courses was not standardized as twenty-one patients received 2 courses, five patients received 3 courses, seven patients received 4 courses, three patients received 5 courses, and one patient received 6 courses.²⁵ Therefore, the efficacy of the IPA regimen in inducing resectability and survival is not assessable because it was not administered in a consistent manner. In HB-94 a total of sixty-nine patients with hepatoblastoma were treated according to a complex treatment schema with CDDP/DOX/IFOS and with additional CARBO and ETOP administered to 46% of patients with poor responses. It is again difficult to discern the number of cycles different patients received but EFS was 89% for twenty-seven stage I patients, 100% for three stage II patients, 68% for twenty-five stage III patients and 21% for fourteen stage IV patients which is no different and no better than that observed in COG studies.⁷

A summary review of the results from the most recent COG, SIOPEL, and German studies are listed in Table 2. These results demonstrate that there is no obviously superior regimen when comparing the largest international trials. Overall survival for patients treated on P9645 was greater than that observed in SIOPEL-2 and may reflect the ability to salvage patients with the use of doxorubicin.

Table 2. Treatment and Survival of Unresectable and Metastatic Hepatoblastoma Patients in Recent Studies

Study	Treatment	Number of Patients	Stage	EFS	S
P9645 ¹⁷	CDDP/5-FU/VCR	38	III	63%*	88%*
		10	IV	50%#	67%#
INT-0098 ⁶	CDDP/5-FU/VCR CDDP/DOX	45	III	60%*	68%*
		21	IV	14%*	33%*
		38	III	68%*	71%*
		19	IV	37%*	42%*
SIOPEL-2 ³	CDDP/DOX/CARBO	21	IV,	48%#	61%#
		25	Metastatic (PRETEXT)	(combined)	44%#
SIOPEL-1 ¹⁴	CDDP/DOX/IFOS	39	IV	46%&	57%&
		31	Metastatic (PRETEXT)	28%&	57%&
HB-94 ⁷	CDDP/DOX/IFOS VP/CARBO	25	III	68%	76%
		14	IV	21%	36%
HB-89 ²¹	CDDP/DOX/IFOS	38	III	71%	Not provided
		7	IV	29%	

* = 4-year EFS or S; & = 5-year EFS and S; # = 3-year EFS and S

Xenograft studies have been performed using DOX, CDDP, CARBO, ETOP, and IFOS.²⁶ Reduction in tumor size and declines in AFP values were only seen following CDDP and DOX. IFOS, CARBO, and ETOP caused a slightly lower rate of tumor growth when compared to controls. This xenograft study concluded that as single agents, CDDP and DOX are most effective, IFOS is effective in some, CARBO is moderately effective and ETOP is ineffective. This xenograft report followed the completion of HB-94 which incorporated all of these agents. Previous phase II studies have evaluated the response of IFOS in 3 patients with hepatoma, all three of which did not respond.

High-risk patients

High risk patients include any patient with metastatic disease and any patient with a low diagnostic AFP level < 100 ng/ml.

The optimal dose of CDDP to administer to patients with unresectable and metastatic disease is unclear. However, the EFS of 40-70% for unresectable patients and 20-40% for metastatic patients remains suboptimal in multiple cooperative group studies (Table 2). In addition, CDDP is the most active agent suggesting that intensification of CDDP therapy may be beneficial in this disease. The dose of CDDP proposed for intermediate and high-risk patients in this trial exceeds doses used in other trials. However, SIOPEL administers an additional 3 grams of platin based therapy with CARBO to patients who receive 320 mg/m² of CDDP. SIOPEL-4, the current study for high-risk patients includes CDDP (570mg/m²), DOX (300-350 mg/m²) and 2-3 courses of CARBO. The German HB studies administer 12 grams/m² of ifosfamide. The following table provides a dose comparison of the cumulative chemotherapy dosing for intermediate and high-risk patients being used in current studies:

Table 3 Cumulative Dosage of Chemotherapy in Advanced-Stage Patients According to Treatment Regimen

Study	CDDP	DOX	IFOS	CARBO	VCR	5-FU
COG (AHEP0731)	600	360	0	0	33-39	3600
P9645	600	0	0	0	0	0
SIOPEL-2	320	360	0	3000	0	0
SIOPEL-4	570	300-350	0	2-3 courses	0	0
HB-GPOH	400	240	12000	0	0	0

*chemotherapy dosing is mg/m²

Chemotherapy is an important part of the therapy for patients with hepatoblastoma. However, since the introduction of platinum agents as part of the chemotherapy for hepatoblastoma, no new agents with activity have been identified. Since most pediatric phase I and II studies usually include less than two patients with liver tumors, identification of new effective agents against these tumors has been and will continue to be a challenge. Children with metastatic hepatoblastoma account for 25% of all cases of this disease. However, the outcome for these patients over the last 30 years has remained poor, despite intensive chemotherapy with the best available agents including cisplatin and doxorubicin (PLADO) as given by SIOPEL or COG, or with C5V as developed by POG and compared in INT-0098.⁶ All of these studies show similar unacceptable outcomes with < 40% 5-year EFS.^{3,6,7} Although these patients often respond well initially, these early responses have not translated into cures. For example, Katzenstein et al observed initial partial responses (PRs) to carboplatin alone in 55% of advanced-stage patients although the 5-yr EFS of stage IV patients was still only 27%.² New agents for this high-risk group of children are urgently needed.

Irinotecan is a topoisomerase I inhibitor with significant antitumor activity against human tumor xenografts.²⁷⁻²⁹ Irinotecan, with or without doxorubicin, is currently being administered to relapsed patients in a SIOPEL trial which has yet to release results and has been accruing patients slowly. Anecdotal data in the literature^{30,31} and from members of the Liver Tumor committee exist for a total of approximately 10 patients with

recurrent or progressive hepatoblastoma who have been treated with irinotecan (personal communication, *O Beatty*). Of the 10 patients, six patients achieved a PR lasting 3 to 12 months. Two patients with lung metastases had complete disappearance of the lung nodules and normalization of AFP levels (6 and 11 months). The remaining 2 patients showed no response to therapy. Overall therapy was well tolerated with myelosuppression and diarrhea as the most common side effects. PRs in six of these very heavily pretreated patients suggest that irinotecan may be an active drug in this disease and justifies its evaluation in a group of patients who have a 70% chance of eventually succumbing to their disease with “standard therapy.”

This study will estimate the response rate associated with two cycles of vincristine and irinotecan (VI) when administered as “up-front” window therapy for the treatment of high-risk children with metastatic hepatoblastoma (Stage IV). This regimen has been piloted in phase I/II studies within the COG (P9971, D9802). Patients who develop frank progression after the first course of VI will proceed directly to therapy with C5VD. Responders will alternate treatment with VI and C5VD and will receive a total of 4 cycles of VI and 6 cycles of C5VD. Following treatment of an initial cohort of 25 patients, additional agents will be considered for inclusion in this upfront window.

Prognostic Variables

The decline of AFP levels after 4 cycles of chemotherapy and prior to surgical resection of the tumor has been shown to have prognostic value.³² No data has been reported that suggests that the initial rate of decline or that the magnitude of decline of AFP after each cycle can be used to guide therapy. Data analyzed from INT-0098 and P9645 do not support AFP decline as a useful tool in low-risk patients (personal communication, *M Malogolowkin*). Initial AFP < 100ng/ml has been described as being associated with an adverse outcome. While older reports of liver tumors with low AFP levels may include some misdiagnoses with other malignant liver disorders, recent reports continue to suggest that AFP < 100ng/ml is associated with worse prognosis in hepatoblastoma. Data from SIOPEL reported 3-year EFS of 13% in patients with a low AFP.¹⁸ Therefore, patients in this study with a low AFP at the time of initial diagnosis will be considered to be high-risk and treated accordingly.

Additional risk factors including histologic subtype, especially macrotrabecular and small cell undifferentiated,^{33,34} PRETEXT group,³⁵ surgical margin,^{36,37} surgical complications,^{38,39} and diffuse multifocal tumors⁴⁰ have been reported to have potential prognostic value in hepatoblastoma and should be investigated further in a prospective, multi-group setting. It would be particularly advantageous to collaborate with our international colleagues in the collection of these potential prognostic variables enabling the data to be pooled in the future into an international cooperative database, thereby increasing the statistical power to make subtle, or rare, observations.

Surgical Considerations

When the proportion of Stage I patients in INT-0098 is compared with P9645, it appears that over the 1990's there was a trend away from upfront resection by some surgeons. Stage I patients accounted for 28% (51/182) of the total in INT-0098 and 23% (40/175) of the total in P9645. However, as the data below suggest this phenomenon occurred prior to the start of P9645 and is now static. Recent anecdotal trends in hepatoblastoma treatment within COG institutions have suggested a possible decrease in the numbers of Stage I patients and an increase in the number of Stage III patients reflecting a possible paradigm shift towards the SIOPEL strategy using pre-operative chemotherapy to shrink tumors, increase resectability, and decrease surgical morbidity associated with resection. However, one potential result of this practice is an overall increase in the amount of chemotherapy that patients receive. In the most recent COG study P9645, patients who only had an initial biopsy performed received a total of 6 cycles of therapy which is two more cycles of chemotherapy than patients who underwent primary resection and received a total of 4 cycles of treatment. These additional cycles of chemotherapy result in increased short-term and long-term toxicity. In addition, "extra" cycles of chemotherapy are often administered by treating physicians and surgeons to make a tumor resectable. However, a review of data from INT-0098 indicates that 4 more cycles of therapy did not increase the likelihood of tumor resectability in patients who were not resected after the initial four cycles of chemotherapy.

The reported incidence of surgical morbidity and mortality on previously conducted COG studies has historically been extremely low. However, as a recent retrospective analysis of INT-0098 revealed (personal communication, *R. Meyers and M. Malogolowkin*), this issue has not been rigorously investigated in prior studies. With the current available advanced surgical and radiologic techniques, it would be expected that current surgical morbidity and mortality rates could be even lower. We have developed, specific surgical guidelines using PRETEXT criteria have been developed in an attempt to minimize surgical risk. It is expected that these guidelines would maximize the number of patients with localized PRETEXT I and II tumors that are most appropriately resected at diagnosis (Stage I), and minimize the number of patients with PRETEXT III and IV tumors where attempts at resection at diagnosis would lead to increased surgical risk. It is interesting and important to note that the most recent publication of SIOPEL-2 reported 4 surgical related deaths in patients treated pre-operatively with chemotherapy.³ This is more than reported in any previous COG study. A surgically related death was reported in only 1 of the 182 patients with hepatoblastoma treated on INT-0098.⁶ In the HB-89 study, surgical complications occurred in 15% of patients who had a primary resection and 21% of patients who had a resection following chemotherapy failing to validate the hypothesis that pre-operative chemotherapy will diminish the incidence of surgical morbidity.²¹ Although these numbers might suggest that upfront resection carries less risk of surgical morbidity, it is important to note that the PRETEXT classification of these tumors is not known. It would be expected to observe much greater surgical morbidity in PRETEXT III and IV tumors, the very tumors that are most likely to have been treated with neoadjuvant chemotherapy. The ultimate question is whether the risk of upfront surgical morbidity and mortality exceeds that of the additional chemotherapy administered to patients who have delayed resections. Various cooperative groups have

established different criteria for diagnoses in part because of concerns with biopsy related surgical morbidity. The SIOPEL group has treated patients on study without a diagnostic biopsy as was done in nearly 20% of patients on SIOPEL-1. Within COG, up to this point in history, a diagnostic sample has been required of all patients treated on study.

This study proposes to provide specific guidelines for surgical approaches to hepatoblastoma since surgery is the critical component necessary for obtaining a cure. Patients with PRETEXT I and PRETEXT II tumors that have a clear radiographic 1 cm margin CT or MRI imaging at diagnosis should have a resection performed as soon as possible after the diagnosis of hepatoblastoma is confirmed.. The surgical strategy for patients with more advanced PRETEXT-stage disease is described in the surgical guidelines.

No patient with stage IV will be offered a liver transplant unless all metastatic extrahepatic disease had been radiographically documented to have disappeared on neoadjuvant chemotherapy or has been surgically removed.

The historical barrier of “unresectability” can be redefined with the concept of “total liver resection” and salvage orthotopic liver transplantation (OLT). Interestingly, although one of the first long-term survivors of liver transplantation was a child with hepatoblastoma, the role of liver transplantation in the treatment of pediatric hepatoblastoma has never been fully defined. Because liver transplant has not historically been offered to these children as part of a planned treatment algorithm, the optimal timing of transplantation and the potential role of post-transplant adjuvant chemotherapy remain unclear. Largely due to negative experience with liver transplant in the treatment of adult hepatocellular carcinoma, liver transplant for the treatment of hepatic malignancy developed an early reputation as a dreaded, last resort, heroic, and even potentially ethically inappropriate intervention. But the biology of pediatric hepatoblastoma has proven to be very different from that of adult hepatocellular carcinoma, and experience with liver transplantation for hepatoblastoma has been far more favorable.

In study after study, complete surgical resection has been the most important predictive factor of survival.^{6,32,41-43} There are 11 studies reporting outcome after liver transplantation for unresectable hepatoblastoma that have been published in the past decade.^{44,45} All but one of these studies are single institution studies, with small numbers of highly selected patients. Factors thought to contribute to these improved survival rates include complete resection as soon as possible after completing planned induction chemotherapy (usually 4 cycles), avoiding excessive cycles (>4-6) of pre-transplant chemotherapy, and a favorable response to chemotherapy. In Birmingham, England, 5-year disease free survival was 100% when primary transplant was performed in patients with a good response to chemotherapy, 60% after primary transplantation in patients with a poor response to chemotherapy, only 50% in patients with transplant as a second option or “rescue transplantation”, and 0% in patients not undergoing surgery.⁴⁶ In SIOPEL 1, overall survival at 10 years was 85% with a primary transplant but only 40% for the children who underwent a “rescue transplant.”⁴⁷ In a collaborative report of the world experience of liver transplantation for hepatoblastoma⁴⁵ overall survival rate at six years

was 82% for 106 patients who received a “primary transplant” but only 30% for 41 patients who underwent a “rescue transplant”. This data stresses the importance of facilitating primary transplant as it appears to be far superior to a “rescue” transplant in yielding long term survival.

The current UNOS (United Network of Organ Sharing) policy for liver allograft allocation in children with pediatric hepatoblastoma gives the patient an automatic PELD priority score of 30. This places the hepatoblastoma patient near the top of the PELD (Pediatric End Stage Liver Disease) scoring system, the system which is used to determine liver allograft distribution priority in children. A similar scoring system called MELD is used in adults. A PELD/MELD score of 30 places the patient near the top of the list and takes priority over all other listed patients, except Status I. For non-cancer patients, Status I means the patient is dying from liver failure, in an intensive care unit, with a life expectancy < 7 days. Cancer patients may occasionally be listed as Status I, even though they are not in liver failure in an ICU, under the condition that they have not received a liver allograft within 30 days of listing on the PELD system. Average waiting time as a Status I is 3-7 days. Alternatively, additional PELD points may be awarded by the local UNOS review board as “exception” points. The verbatim policy is quoted below:

UNOS Policy 3.6.4.4.1, November 19, 2004. Pediatric Liver Transplant Candidates with Hepatoblastoma: A pediatric patient with non-metastatic hepatoblastoma who is otherwise a suitable candidate for liver transplantation may be assigned a PELD (less than 12 years old) or MELD (12-17 years old) score of 30. If the candidate does not receive a transplant within 30 days of being listed with a PELD/MELD of 30, then the candidate may be listed Status I.

Hepatoblastoma patients who are identified as candidates for liver transplant and identified to UNOS, therefore, have a good chance of receiving a cadaveric donor liver. This modality, therefore, may present a viable method of obtaining complete extirpation of the tumor when conventional surgery is not possible. The current study will assess the feasibility of identifying appropriate hepatoblastoma patients in the context of the current health care system.

SIOPEL 1 introduced the PRETEXT (Pretreatment Extent of Disease) system to the pediatric liver tumor community as an anatomic definition of the extent of liver involvement by the tumor, and the PRETEXT system depends upon accurate radiologic imaging and review.⁴⁸ The PRETEXT system aims to predict surgical resectability and prognosis. However, the PRETEXT system has not been fully validated. Results published on PRETEXT in the SIOPEL-I study reported that postoperative pathologic evaluation demonstrated that preoperative PRETEXT staging was accurate in only 51% of patients and that 37% of patients were overstaged and 12% of patients were understaged using PRETEXT.³⁵ While this recent report claimed that PRETEXT was superior to the COG staging system, the validity of this conclusion is in question as the study excluded patients who failed neoadjuvant therapy and only included the selected group of patients whose tumors were able to be resected. The number of surgically staged metastatic patients in this study who survived was > 90%.³⁵ This questions the

reliability of this study as the survival of this cohort is so significantly superior and discordant from all other series in the literature. The more recent SIOPEL-2 study did not fully validate PRETEXT either as patients were categorized and treated as either high or low-risk.³ These high and low-risk groups consisted of several PRETEXT stages within each of these categories. No EFS data was provided for patients according to individual PRETEXT stages as is indicated in Tables 1 and 2 above. In addition, PRETEXT IV was not predictive of overall survival. So while the PRETEXT system has shown potential utility as a tool to compare treatment results between different multi-center trials, and as a tool to objectively quantify response to neoadjuvant chemotherapy and predict surgical resectability, defining its precise role and validating its use is still required and therefore will be a secondary aim of this study.

Therefore, in order to validate PRETEXT central surgical and radiology review of CT scans must be performed to validate the PRETEXT staging done at the local institutions. This review will be performed on a yearly basis. CT scans reviewed will include those obtained at diagnosis, and repeat scans performed after the second and fourth cycles of chemotherapy in patients with Stage III and Stage IV tumors. PRETEXT will be interrogated to determine its effectiveness at determining surgical resectability, and to determine its utility in objectively quantifying the chemotherapy response (PRETEXT “downstaging”). The PRETEXT definition of potential unresectability is defined: PRETEXT III extensive multifocal; PRETEXT III +V; PRETEXT III +P; or any PRETEXT IV. For complete and precise resection criteria, refer to surgical guidelines below.

Recent studies have reported long-term survival and cure in patients with known microscopic residual disease. SIOPEL-1⁴⁷ reported that positive microscopic surgical resection margins had no effect on the rate of survival.^{38,47} The implications of microscopic margins are thus poorly understood and have never been evaluated prospectively in the any hepatoblastoma trial. Microscopic positive margins have been repeatedly shown to increase the risk of local relapse, metastatic relapse, and death in patients with hepatocellular carcinoma. However, the implications of microscopically positive margins on the recurrence and survival of patients with hepatoblastoma remains unclear will be studied as a secondary aim within this study. We hypothesize that microscopic margins may be of increasing importance in those tumors shown to be poor responders to chemotherapy

The most common site of metastasis for hepatoblastoma is the lung. The therapeutic approach and prognosis for patients with pulmonary metastases remains somewhat uncertain. A recent review of the INT-0098 data revealed that 18 patients who had previously achieved complete tumor clearance experienced subsequent pulmonary relapse of their tumor (12 Stage-I,-II, or-III, 6 Stage-IV). All 18 pulmonary relapse patients had salvage chemotherapy, 11 also had thoracotomy and pulmonary metastectomy (7) or thoracotomy and tumor biopsy (4). Only 2/11 were long-term survivors, both were Stage I relapse patients. For the 38 patients with metastatic disease at diagnosis, nine of these 38 underwent thoracotomy and pulmonary metastectomy either before (2), simultaneous (5), or after (2) resection of their primary liver tumor. Six of

these 9 patients with metastectomy were long-term survivors. This data demonstrates that there is much variation in the surgical approach to pulmonary metastasis in hepatoblastoma and that thoracotomy may have limited utility in the management of pulmonary relapse, but appears to be important in the management of metastases that persist following neoadjuvant chemotherapy. Other reports indicate that patients with metastatic disease, who are rendered free of gross disease by resection of the primary tumor, as well as resection of pulmonary metastases, may experience cure or long-term survival.^{47,49} In SIOPEL-1, all four of the 22 patients with pulmonary metastases at diagnosis in whom a metastectomy was performed survived without residual disease.⁴⁷ Results were not as promising in SIOPEL-2 in which eight out of 25 patients had surgery for lung metastases and only three of these patients are alive.³ The difference in outcomes for patients who achieve a clinical remission of pulmonary metastases as a result of surgical resection and for those who achieve clinical remission in response to chemotherapy remains unknown and needs to be defined. A better understanding of hepatoblastoma metastases isolated to the lung(s) would help guide therapy and predict prognosis more appropriately and reliably. It is therefore critical to attempt to adopt a uniform strategy to pulmonary metastatic lesions as the data do suggest that significant numbers of patients do exist that make this study question important and feasible. The impact of surgical resection of metastatic pulmonary lesions on survival will therefore be evaluated as a secondary aim within this study.

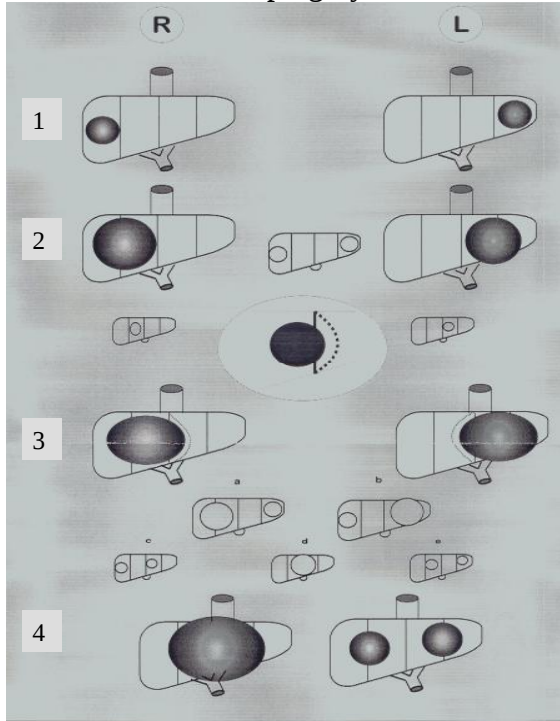
This study functionally divides patients into low-, intermediate-, and high-risk cohorts. It seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients. This study builds on the results of the last 20 years of hepatoblastoma clinical trials. There are no competing trials.

Since hepatoblastoma is a disease that is dependent upon surgical resection for curative potential, this study will ask several surgical questions that address several key concepts in treatment and may be used to guide therapy in future trials. Survival rates are much better with “primary transplant” than after a “rescue” or “salvage” transplant. Unfortunately, too many children continue to be referred for transplant after having received additional undue chemotherapy and/or after a failed initial attempt at resection. Some concepts remain unclear. What is the optimal timing of transplantation? What, if any, is the role of post-transplant chemotherapy? The Children’s Oncology Group Liver Tumor Subcommittee would ultimately like to study these questions with a randomized protocol. However, unless we can ensure that appropriate patients will be referred to appropriate transplant centers in a timely fashion embarking upon a randomized protocol is likely doomed to failure. The current, too commonly encountered factors of undue pre-surgical chemotherapy and “rescue” transplant would seriously muddle and confound the results.

Therefore, we propose a study to determine the feasibility of studying transplantation in a cooperative group setting. For future randomized study to be a reasonable option, we need to see if it is possible to capture at least 70% of eligible (potentially unresectable) patients and get them referred in a timely fashion to a surgical center that offers surgical expertise in major pediatric liver resection and liver transplantation.

RESECTABILITY ACCORDING TO PRETEXT/POSTTEXT GROUPING

A. PRETEXT Grouping System



PRETEXT

or
POST-TEXT if assigned after
chemotherapy

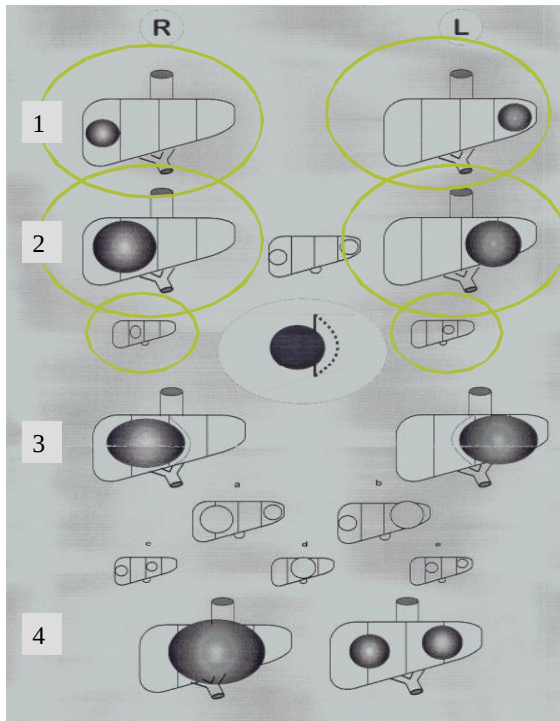
- 1 3 contiguous free sections
- 2 2 contiguous free sections
- 3 1 contiguous free section
- 4 no free sections

Any group may have

involvement of:

- V vena cava or all 3 hepatic veins
- P main portal or portal bifurcation vein
- C caudate
- E extrahepatic, contiguous
- M distant metastatic

B. LESIONS FOR PRIMARY RESECTION



AHEP 0731 Surgical Resection Guidelines

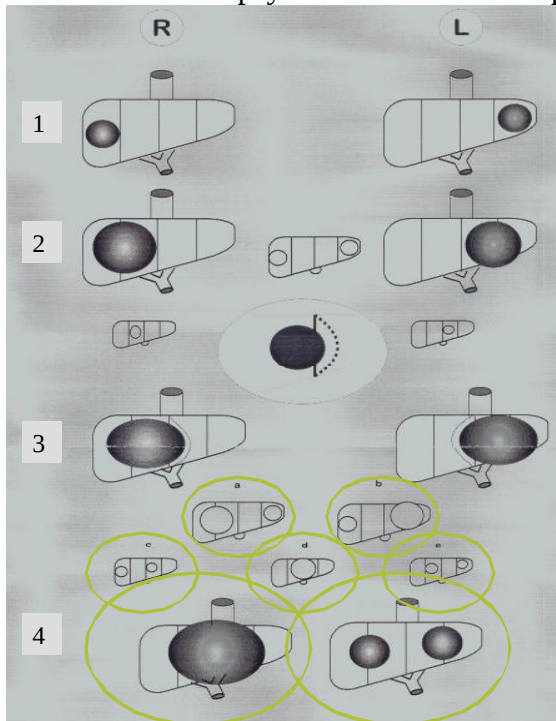
Resect at Diagnosis

Easy lobectomy with > 1 cm
margin:

- PRETEXT 1
- PRETEXT 2

Diagnosis CT shows unifocal
tumor with at least 1cm clear
radiographic margin from middle
hepatic vein and portal bifurcation

C. Tumors to Biopsy and Refer to Liver Specialty Center at Diagnosis



AHEP 0731 Surgical Resection Guidelines

Biopsy and Refer to liver specialist at diagnosis or during first two cycles of chemotherapy

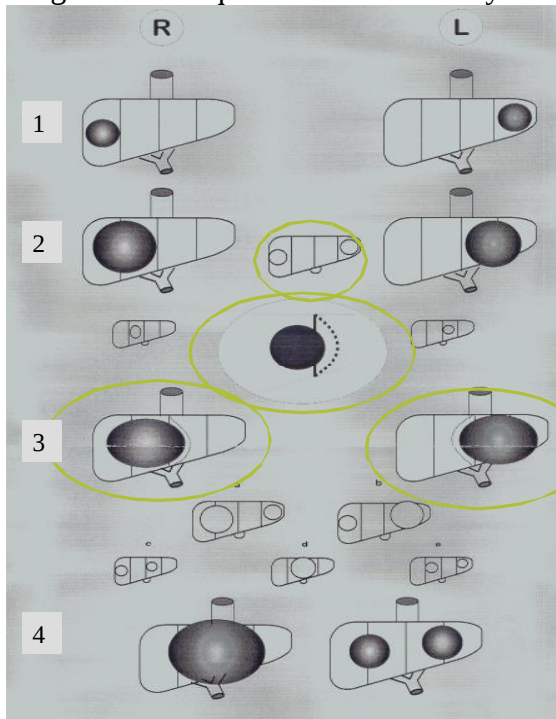
Tumor expected to require liver transplantation or complex liver resection

- multifocal PRETEXT 3
- PRETEXT 3 +V, +P
- any PRETEXT 4

Consultation with liver program to complete transplant evaluation and listing with goal of complex resection or transplant on or before completion of four cycles neoadjuvant chemotherapy

CureSearch
Children's Oncology Group

D. Tumors to Biopsy at Diagnosis and Resect by Conventional Surgical Techniques after 2nd or 4th Cycle of Neoadjuvant Chemotherapy



AHEP 0731 Surgical Resection Guidelines

Biopsy at Diagnosis
Neoadjuvant Chemotherapy

POST-TEXT => Repeat CT Scan after 2nd cycle chemotherapy

* Resect after 2nd cycle chemo

- POST-TEXT 1
- POST-TEXT 2

** Resect after 4th cycle chemo

- POST-TEXT 3

*** Refer to liver center

- POST-TEXT 3 +V, +P

Consultation with liver program to complete transplant evaluation and listing with goal of transplant on or before completion of four cycles neoadjuvant chemotherapy

CureSearch
Children's Oncology Group

13.0 SURGICAL GUIDELINES

13.1 Surgical Resection Guidelines

Surgical resection guidelines will be determined according to the PRETEXT grouping system, which was designed specifically for patients with liver tumors. Terminology for PRETEXT grouping at diagnosis is “PRETEXT”. PRETEXT assignment AFTER chemotherapy is referred to as “POST-TEXT”.

13.1.1a Tumors Considered Resectable at Diagnosis

Non-Extreme Resection

- PRETEXT 1.
- PRETEXT 2 with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or the portal bifurcation.

13.1.1b Tumor Biopsy Only at Diagnosis (Stage III)

- PRETEXT 2 with **less than** 1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, and the portal bifurcation.
- PRETEXT 3.
- PRETEXT 4.
- Biopsy technique at the discretion of the treating institution may be a percutaneous tru-cut, laparoscopic tru-cut or wedge, or open biopsy. Minimum biopsy size is 3 tru-cut cores of tissue. Larger biopsies, however, are strongly recommended where feasible to evaluate for the possibility of heterogenous foci of small-cell undifferentiated (SCU) tumor.

13.1.2 Tumors Considered Resectable After First 2 Cycles of C5VD Neoadjuvant Chemotherapy

Non-Extreme Resection

- Tumors with POST-TEXT 1.
- Tumor with POST-TEXT 2 with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or the portal bifurcation.

13.1.3 Tumors With Potential Need for Liver Transplant or Extreme Resection

- Definition of potential candidate for liver transplant or extreme resection:
 - Major Venous Invasion: Unifocal PRETEXT 3 with tumor invasion of all 3 hepatic veins or the retrohepatic vena cava (V), or both main branches of the portal vein (P). The distinction between major venous “invasion” by tumor vs major venous “displacement” or “extrinsic compression” by tumor can be radiographically very difficult. Clinicians are encouraged to err on the side of “possible invasion” and refer patient for transplant evaluation if this distinction is very difficult to make.
 - Unifocal PRETEXT 4
 - Multifocal PRETEXT 3 and 4
- **Refer to surgical center with expertise in pediatric liver transplant and “extreme” liver resection at diagnosis if possible and no later than just after the first 2 cycles of C5VD neoadjuvant chemotherapy have been completed.** Resection planning is to be completed before completion of the 4th cycle of chemotherapy. Transplant or “extreme”

resection is to occur within 4 weeks of completing the 4th cycle of chemotherapy.

13.1.4 Tumors Considered Resectable Within 4 weeks of Completing 4th Cycle of Chemotherapy

Non-Extreme Resection

- Tumors with POST-TEXT 3 and no major venous invasion. The surgeon must anticipate the ability to achieve a negative surgical margin on the right/left hepatic vein, retrohepatic IVC, or portal bifurcation. Margin may be less than 1 cm if the surgeon feels a complete resection will be feasible without transplant and patient has completed 4 cycles of C5VD chemotherapy.

13.1.5 Tumors Presenting with Metastatic Disease (Stage IV)

- Complete 2 cycles of upfront experimental window chemotherapy.
- Repeat radiographic imaging after completing upfront window therapy
- Resect (non-extreme) tumors POST-TEXT 1 or 2 with > 1 cm radiographic margin on the middle hepatic vein, retrohepatic IVC, and portal bifurcation
- For all others, proceed with 2 cycles of C5VD
- Repeat radiographic imaging after completing first 2 cycles of C5VD
- Resect (non-extreme) tumors downstaged to PRETEXT Group 1, 2, or 3 tumors with >1 cm radiographic margin on right/left hepatic vein, retrohepatic IVC, and portal bifurcation.
- For patients potentially needing liver transplant/extreme resection (see definition in Section 13.1.3), refer to surgical center with expertise in pediatric liver transplant and “extreme” liver resection at diagnosis if possible and no later than end of Cycle #4 (after 2 cycles of C5VD). Resection planning is to be completed before completion of Cycle #7 in high risk responders and before completion of Cycle #6 in high risk non-responders. Transplant or “extreme” resection is to occur within 4 weeks of completing the 7th cycle of chemotherapy in high risk responders and the 6th cycle of chemotherapy in high-risk non-responders.
- Repeat chest CT scan must demonstrate complete clearance of pulmonary metastatic disease within 1 week prior to liver transplant.
- Those patients with persistent extrahepatic disease, may be resected (not transplanted) at the discretion of the surgical center with expertise in pediatric liver transplant and “extreme” liver resection.
- Those patients with persistent extrahepatic disease who are not anatomically resectable without transplantation will continue chemotherapy.

13.1.6 Optional Central Assistance to Aid in Determination of Tumor Resectability

If the treating physicians/surgeons desire assistance with their clinical decision making this will be available from one of the study surgeons on the Surgical Review Committee with expertise in the treatment of pediatric liver tumors. Clinical consultation is NOT REQUIRED. However, at least one of these surgeons will be available AT ALL TIMES for emergent consultation. The local treating institution is ultimately responsible for making the treatment decision regarding resectability with the full backup of the OPTIONAL consultation. The consulting surgeon on call can be reached by contacting the surgical study chair or the study chair.

13.2 Central Surgical Review

For purposes of evaluating clinical predictive value and reproducibility of the PRETEXT system, central review will be completed for all scans obtained at diagnosis (PRETEXT) and after the 2nd cycle of chemotherapy (POST-TEXT). The central surgical review will be performed yearly by the team of study surgeons. This review will be coordinated through QARC and completed by the team of surgeons and radiologists.

13.3 Surgical Management of Pulmonary Metastasis

Patients presenting with pulmonary metastatic disease (Stage IV) will receive the “up-front” window chemotherapy described above for high-risk patients. If metastases disappear with chemotherapy, no pulmonary surgical intervention will be performed. If metastases are persistent after 4 total cycles of C5VD chemotherapy and the patient is considered a candidate for liver transplant at that time, metastases are to be resected to render the patient free of extrahepatic disease prior to transplant. Transplant may then be undertaken.

If the liver tumor can be primarily resected after either Cycles 4 or 7 in high risk responders and after Cycles 4 or 6 in high-risk non-responders without transplant, this should be performed and the final cycles of chemotherapy should be administered. If the metastases are still present, they should then be resected. Pulmonary metastectomy may be performed earlier in the course of therapy if it can be done without resulting in delays in the administration of scheduled chemotherapy.

13.4 Liver Transplant or Extreme Liver Resection

Two distinct cohorts of unresectable patients are expected. Patients identified as potentially unresectable based on preoperative radiographic imaging that are either: 1) successfully referred for evaluation at a transplant center in a timely fashion, or 2) not successfully referred for evaluation at a transplant center in a timely fashion. Within the first cohort there are further possible subgroups: 1a) prove to be resectable at the time of surgery; 1b) remain unresectable and primary transplant performed, 1c) remain unresectable, no surgery performed due to persistent metastatic disease unresponsive to chemotherapy or surgical resection, or 1d) do not proceed to surgery because of refusal or deteriorating patient condition.

Post surgery/transplant chemotherapy will be based on the chemotherapy received preoperatively. For patients with disease confined to the liver, 2 additional post operative/transplant cycles of the same chemotherapy given preoperatively (4 cycles) will be given postoperatively for a total of 6 cycles. For patients with metastatic disease, additional cycles of the same chemotherapy given pre-operatively will be given post-operatively. The number of post operative cycles may vary depending upon the point in treatment during which resection occurred for a total of 8 cycles for patients who did not respond to window therapy and a total of 10 cycles for patients who did respond to window therapy.

Patient management guidelines will follow the same format that has been discussed and agreed upon by an international committee of liver transplant surgeons in the preparation of the Pediatric Liver Unresectable Tumor Observatory (PLUTO). All patients treated by liver transplantation will be asked to sign a consent within one month post transplant giving permission for registration on the PLUTO multi-center international cooperative database for children who receive a liver transplant for hepatoblastoma or hepatocellular carcinoma. The database collects information about type of liver tumor, tumor size, number and location of tumors in and outside of the liver, involvement of blood vessels, chemotherapy medications used, lymphocyte blood count, immunosuppression medications used after transplant, side effects of the medications, at what point in the treatment was the transplant performed, complications from the transplant surgery, and outcome of the transplant and the disease free survival. This database can be accessed via the PLUTO Registry Website: <http://pluto.cineca.org/access.htm>. In order to be authorized to use the transplant database, it is necessary to register with PLUTO. The link to the required participation form is found using the same PLUTO access link provided above.

SURGICAL STAGING OF PRIMARY TUMOR AT TIME OF INITIAL SURGERY

Patients are staged for risk classification and treatment using COG staging guidelines as listed below:

Stage I: completely resected tumors.

Note: all Stage I tumors require rapid pathology review prior to enrollment.

Stage II: grossly resected tumors with evidence of microscopic residual.

Resected tumors with microscopic positive margins or pre-operative (intra-operative) rupture.

Note: all Stage II tumors require rapid pathology review prior to enrollment.

Stage III: unresectable tumors

Partially resected tumors with measurable tumor left behind or patients with abdominal lymph node involvement.

Stage IV: metastatic disease to lungs, other organs or sites distant from the abdomen.

PFH tumors are entirely composed of a purely fetal histologic pattern with a low mitotic index defined as

≤ 2 mitoses/10 high power fields

SCU tumors are tumors with any amount of small cell undifferentiated cells detected.

14.2 Biology Studies

The submission of tissue for biologic studies is strongly encouraged. Please submit biology specimens using P9346, its successor biology study or ABTR01B1 or other appropriate study.

ABTR01B1 A Children's Oncology Group Protocol for Collecting and Banking Pediatric Research Specimens Including Rare Pediatric Tumors

2.0 BACKGROUND AND RATIONALE

Although tremendous improvement in the treatment of childhood cancer has resulted from use of the empiric clinical trial mechanism it is clear that additional significant progress will require a better understanding of the molecular pathogenesis of pediatric malignancies as well as the specific alterations which underlie resistance to current therapies. In addition, the COG has recognized that the merger of the pediatric legacy groups provides a unique opportunity to prospectively study adequate numbers of patients with rare tumors within the context of a multi-institutional collaborative group effort. To facilitate the acquisition of pathologic materials for patients with infrequently encountered childhood tumors, the Rare Tumor Committee of the COG will use this protocol as a mechanism to obtain these rare tumor specimens. This mechanism is designed to optimize the acquisition of specimens from rare and other pediatric tumors (benign or malignant) and will likely impact on the prioritization and design of biologic and therapeutic trials for rare tumors. The Biopathology Center (BPC) along with other approved COG sites will serve as repositories for banking tumor and other biological specimens from pediatric patients. The BPC and/or other repositories will make tissue available to COG investigators and to other investigators who apply through the COG. All proposals for research using banked tissue will be reviewed and prioritized by the appropriate Disease Committee(s). Details concerning the application process for specimen retrieval are available on the COG and BPC websites and in Section 8.0 of this protocol.

4.2.1

Biological specimens, including solid tumors and leukemias, must be available for submission. Eligible diagnoses include those having an ICD-O Morphology Code ending in 1, 2 or 3 as listed in the *International Classification of Diseases for Oncology, Third Edition*. The minimum requirements for eligibility are listed below:

4.2.1.1 Solid Tumors:

- Snap frozen primary tumor *or* OCT embedded primary tumor *or* formalin fixed (block or tissue in formalin) primary tumor, **and**
- At least 10 unstained paraffin slides **must be** submitted for NIH Mandated QC in addition to the minimum required primary tumor listed above. IF primary tumor is submitted in formalin or as a paraffin block, the QC slides can be obtained from that material; otherwise QC slides must be cut from the diagnostic pathology blocks retained by the institution. If the tumor has undergone central pathology review as part of a COG protocol, that review will suffice for this quality control.

- If the patient has a rare tumor, slides for pathology review are required instead of the slides for QC. See Section 5.3 for the pathology review requirements and a list of rare tumor diagnoses.

4.2.1.2 Pleural Fluid or Cytologic Specimens:

- If pleural fluid or cytologic specimens are submitted, send at least 1 mL of fluid in a purple top (EDTA) tube. In addition, at least 2 unstained cytopsin slides must be submitted for QC. Note that if the fluid is diluted prior to making the cytopsin, the diluting ratio (e.g. 4 diluent, 1 fluid or 4:1) must be written on the specimen shipping form. If the fluid is too thick for making cytopsin slides, then 2 unstained smears should be provided. If the patient has a rare tumor then slides for pathology review as outlined in Section 5.3 are required instead of the slides for QC.

4.2.1.3 ALL/AML:

- 3-6 mL of bone marrow aspirate and 10 mL of whole blood

4.2.2 Age

Patients < 30 are eligible for enrollment.

4.2.3

Patients must not be eligible for enrollment on an open COG trial with biology or banking components.

4.2.4

Patients are eligible at the time diagnosis of their primary neoplasm or at the time of development of a second malignant neoplasm. Enrollment must occur within 30 working days of one of these two events. Patients should be enrolled only once on the study, but specimens may be sent at multiple (serial) time points such as at the time of second look surgery, at the time of relapse or recurrence, and at the time of autopsy. If a patient is enrolled on ABTR01B1 and later found to be eligible for and enrolled on ARAR0331 (nasopharyngeal carcinoma) or ARAR0332 (adrenocortical tumor), specimens can be transferred. Enrollment on the tumor specific studies ARAR0331 and ARAR0332 protocols is encouraged for all eligible cases. Additional pathology materials may need to be submitted per directions in the therapeutic protocol.

5.0 PROCUREMENT, PREPARATION AND SHIPMENT OF SPECIMENS AND RELATED MATERIALS

Specimen procurement kits are provided upon request by the BPC. The kits include foil for frozen tissue, sealable plastic baggies, truncated embedding molds for tumor frozen in OCT, formalin containers for fixed tissue, and vials for frozen sera. Also included with each kit are complete instructions, an Exempt Human Specimens sticker, a dry ice label, two sets of secondary shipping envelopes with absorbent material and a Federal Express form (pre-billed to the BPC). Tissue culture media for the fresh tumor tissue is not included in the kit, but is available upon request. Please use these kits when sending tissue to the BPC. To obtain a specimen procurement kit, call the BPC at 1-800-347-CHTN (2486) during regular business hours on Monday-Friday from 8:30AM-5:00PM EST.

5.1 Procurement of Specimens and Related Materials

5.1.1

Operating Room personnel should not put the tissue into fixative. The specimen should be brought to the Pathology Department quickly (by special messenger if necessary). It may be

appropriate to hold occasional meetings of surgical, laboratory, and clinical personnel to emphasize the urgency of processing these specimens rapidly, preferably within twenty minutes.

5.1.2

Tissues should be as clean as possible. After the necessary tissues are obtained for local institutional diagnosis and research, the remaining tissue should be submitted.

5.1.3

Submission documentation

Send the following documentation to the BPC with EACH shipment:

- A surgical pathology report and operative report, if available, **within 30 working days** of diagnostic or other subsequent surgical procedure(s).
- A specimen shipping form

5.2 Preparation of Specimens

Promptly following removal of tissue or cells specimens should be prepared as described below.

5.2.1 Tissue Specimens For Translational Research **Please submit solid tissue (malignant and normal) in as many of the following formats as possible but do so in this order of priority:**

5.2.1.1 Snap Frozen Cut at least one specimen from the primary (if present) and metastatic areas (if present) into 1 gram aliquots (send as much tissue as available), wrap in foil and snap freeze in liquid nitrogen or cold isopentane. Using a waterproof marker, label baggies as "primary" and/or "metastatic" and also with the BPC Number, specimen type, and date obtained. If available, submit normal tissue in addition to the tumor tissue. This can be any normal tissue, e.g. muscle or skin. Send as much normal tissue as possible but do not exceed the amount of tumor tissue being submitted. Wrap in foil, snap freeze, and label baggie as "normal". Also label it with the BPC Number, specimen type, and date obtained. If not shipped immediately, these samples can be kept adequately in a -70° C freezer until shipped. A regular freezer (- 20° C) is not adequate. Foil will be provided in the specimen procurement kit. Place the snap frozen tissues in the appropriate baggies (primary, metastatic, or normal) and, using a waterproof marker, label the baggie with the BPC Number, specimen type, and the date obtained.

5.2.1.2 OCT Embedded

One truncated mold is provided in the specimen procurement kit for primary tumor. Use a *CryoMarker* or *Securline Superfrost* Marker to label the mold with the BPC Number and, if possible, the date obtained. Cover the bottom of the mold with OCT embedding medium. Using forceps, place the mold over (not in) liquid nitrogen until the OCT appears to lose its transparency. Place up to 1 gram of tissue in this thickened gel, pushing the specimen to the bottom of the mold. Add additional OCT to completely cover the tumor and fill until approximately three-fourths full. Gradually immerse the entire mold into liquid nitrogen until completely solid. Place the OCT mold in the "primary" tumor plastic baggie along with the snap frozen primary tumor tissue. Using a waterproof marker, assure the baggie is labeled with the BPC Number, specimen type, and date obtained. Store the mold with the snap frozen specimens (in dry ice if

short term or in a -70° C freezer if long term) until shipment.

5.2.1.3 Formalin Fixed

Obtain tissue sections ("cassette sized") adjacent to the sample of tumor, and normal tissue if available, for evaluation of histology. Place the tissue sections in the appropriately labeled formalin jars that are provided in the specimen procurement kit. Using a waterproof marker, label the jars with the BPC Number, specimen type, and the date obtained. If not shipped immediately, the formalin jars should be kept at room temperature. These should be shipped as soon as convenient since excessive fixation reduces the usefulness of the tissue.

5.2.2 Liquid Specimens

Blood, bone marrow or sera specimens are of value for biologic studies either as normal tissues or from patients with leukemia. Pre-treatment specimens are most valuable. Pleural fluid or cytologic specimens from hematopoietic or solid tumors are also eligible. Please collect at least 1 mL of pleural and/or cytologic fluid in EDTA (purple top) tubes. Label with the BPC Number, specimen type and date obtained. Ship fluid at room temperature. If not shipped immediately, store at 4° C (refrigerator) until shipment.

5.2.2.1 Bone Marrow and Blood

Collect three to six mLs of bone marrow aspirate and five to ten mLs of whole blood, anticoagulated with EDTA (purple top tubes which are not provided in the specimen procurement kit) and keep at room temperature. If patient is an infant, follow institutional guidelines regarding maximal amount of blood permissible to be drawn. Using a waterproof marker, label the tubes with the BPC Number, specimen type and the date obtained. Saturday delivery is available for blood and bone marrow collected on Fridays. Please mark *For Saturday Delivery* on the Federal Express air bill and contact the BPC with the Federal Express tracking number before shipment. If for any reason the blood and/or bone marrow cannot be shipped the day of collection, please store at 4° C (refrigerator) and ship on the next working day. Upon receipt at the BPC, these specimens will be routinely processed by Ficoll Hypaque centrifugation for isolation and snap freezing of the nucleated cell pellet. In the case of "dry taps" marrow may be obtained by biopsy which should be snap frozen.

5.2.2.2 Serum

Prior to surgery or other therapy, collect 6 mLs of blood in a red top tube (which is not provided in the specimen procurement kit), spin for 10 minutes at 2500 rpm at 4° C and transfer in 1 mL aliquots to the vials provided in the specimen procurement kit. Using a waterproof marker, label the tubes with the BPC Number, specimen type and the date obtained and place the tubes in the baggie labeled "serum"; also label the plastic baggie with the BPC Number. Store the sera with the snap frozen specimens (in dry ice if short term, or in a -70° C freezer if long term) until shipment.

5.4 Shipment of Specimens

Specimen procurement kits should be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday. Blood and bone marrow that are collected on Friday can be shipped for Saturday delivery. Please refer to Section 5.2.2.1 for details.

The specimen procurement kit is constructed to allow shipment of frozen (**on dry ice**) and ambient temperature tissues in the same container. **Dry ice may be placed in either compartment of the kit, but should not be put in both.**

1. Any snap frozen and OCT embedded tissues, as well as the pretreatment sera **must** be sent on dry ice (approximately 4 lbs. total). Layer 1/2 the dry ice on the bottom of the compartment, place the baggies in the plastic secondary biohazard envelope with absorbent material followed by placing the biohazard envelope into the Tyvek pressure-proof secondary envelope. The secured specimens can then be placed in the compartment and filled with dry ice. Place the Styrofoam cover on top.
2. Place any slides, glutaraldehyde-fixed blocks or tissues, pleural or cytologic fluid, pretreatment bloods, and bone marrows in the other plastic biohazard secondary envelope with absorbent material and then into the Tyvek envelope before placing specimens into the second compartment. Place the Styrofoam insert on top of the specimen box to secure specimens during shipment.
3. Include the specimen shipping form, a copy of the signed informed consent, and pathology report (if available at the time) with the shipment. Put these forms in the plastic bag that contained the kit instructions and place the bag on top of the Styrofoam kit box. As stated in Section 5.13, the surgical pathology report must be submitted when it becomes available.
4. Seal the kit **securely** with filament or other durable sealing tape. Complete the pre-printed Federal Express airbill, insert into the plastic pouch and attach the pouch to the top of the kit. Complete the dry ice label (UN 1845) and stick this label and the Exempt Human Specimens label to the side of the box.
5. Arrange for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355. When requesting pick-up, be sure to give the account number (1290 2562 0) on the preprinted air-bill, but **stress** that pick-up is at your institutional address.

Send the Specimens to:

Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, Room WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
For questions call: (800) 347-2486

*The room number is required. Packages not listing the room number will be denied and returned to the sender.

IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

There are 2 study radiologists: Dr. Beth McCarville and Dr. Keith White.

15.1 Primary Site Imaging

The same modality used at baseline should be used for all follow-up imaging.

15.1.1 Primary Site Computed Tomography

1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle) that allow optimal image quality.
2. CT slice *acquisition* thickness should be 1.5 mm or less.
3. Post-contrast IV enhanced portal venous phase abdominal and pelvic CT should be performed from just above the diaphragm to the symphysis pubis. Dual phase (arterial and portal venous) abdominal CT is strongly recommended.
4. Oral contrast is strongly recommended.

15.1.2 Primary Site Magnetic Resonance Imaging

Axial images and coronal images of the liver tumor should be acquired with at least two pulse sequences, including T1 and either fat-suppressed T2, STIR, or fat-suppressed fast/turbo imaging. Gadolinium should be given if appropriate and if there is normal renal function. After contrast administration T1W, fat-suppressed, axial images should be obtained. Based on patient age, images may be non-breath-hold or breath-hold, including respiratory triggered or respiratory gated.

Dual phase MRI may be performed at the discretion of the local radiologist. To perform dual phase MR, gadolinium-enhanced imaging is performed in combination with dynamic gradient echo sequences. After contrast agent injection, images are obtained through the liver during the arterial phase (20 to 30 seconds post injection), portal venous phase (60 to 80 seconds after injection), and at equilibrium (3 to 5 minutes after injection). Delayed images can be obtained if needed for further lesion characterization.

15.2 Metastatic Site Imaging

Chest CT is required to evaluate metastatic disease. Chest CT may be performed without intravenous contrast material. The diameter of a "measurable" nodule should be at least twice the reconstructed slice thickness. Smaller nodules are considered detectable, but will be counted as "non-measurable. Bone scan is not required but should be considered in symptomatic patients with bone pain or bone lesions. Metastatic disease to bone and bone marrow is extremely rare and should only be considered if the patient is symptomatic with unexplained bone pain or unexplained cytopenias.

15.3 Timing of Imaging

All patients with initial resection will have initial diagnostic CT studies (with and without contrast) **AND** diagnostic ultrasound (to evaluate the IVC and portal vein) if reconstructed CT MIP or VRT images of the portal vein are inadequate to exclude thrombus. These studies should be submitted to QARC **within 1 month of diagnosis**. No

additional radiographic studies need to be submitted for very low-risk patients who undergo primary resection. Low-Risk patients are required to have imaging repeated at the end of therapy.

All patients with tumors that are only biopsied initially will have CT scans performed at diagnosis, after Cycles #2 and #4 in intermediate-risk patients, after Cycles #2, #4 and #7 in high-risk responders and after Cycles #2, #4 and #6 in high-risk non-responders, and at end of therapy. These patients will all have abdominal ultrasounds performed at diagnosis (to evaluate the IVC and portal vein) if reconstructed CT MIP or VRT images of the portal vein are inadequate to exclude thrombus. Patients with tumor/thrombus in blood vessels at diagnosis should have repeat examinations using the same confirmatory imaging modality after Cycles #2 and #4 of C5VD. All CT scans and ultrasounds will be submitted to QARC **within 1 month** of each set of scans. Additionally, high-risk patients will also have a CT scan and ultrasound after Cycle #2 of VI.

15.4 Image Submission and Review

All scans will be submitted to the Quality Assurance Review Center (QARC). No hard copies can be submitted. Digital studies should be in Dicom format. These files should be burned onto a CD for submission. Institutions with PACS systems may contact QARC regarding installation of the COG Dicommunicator software that manages e-mailing of studies to QARC.

CT images will be distributed from QARC to the study radiologists on a monthly basis for review and determination of PRETEXT. Central radiologic review will be completed on an annual basis at a minimum, by the central review panel. The central radiologic review will include the following:

- PRETEXT at diagnosis (to establish concordance between local and central grouping)
- POST-TEXT for Stage III and IV patients after 2nd and 4th cycles of chemotherapy (to compare concordance between local and central grouping and compare with surgical/pathologic staging)
- RECIST at baseline and end of window for patients receiving up-front window therapy

4.1 Overview of Treatment plan

Chemotherapy regimen:

- T** Cisplatin, 5 fluorouracil, Vincristine (C5V) for 2 cycles
F Cisplatin, 5 fluorouracil, Vincristine Doxorubicin (C5VD) for 6 cycles
W Vincristine/Irinotecan x 2 upfront, then
Responders: C5VD for 6 cycles, with VI 1 cycle between each 2 cycles
Nonresponders: C5VD for 6 cycles

Stage	Histology	AFP	Risk Stratification	Regimen	Response	Cycles (Total)
I	PFH	>100 ng/ml	Very Low	Surgery only		0
I	Non-PFH, Non-SCU	>100 ng/ml	Low	T		2
I	SCU	>100 ng/ml	Intermediate	F		6
II	Non-SCU	>100 ng/ml	Low	T		2
II	SCU	>100 ng/ml	Intermediate	F		6
III	Any	>100 ng/ml	Intermediate	F		4-6*
IV	Any	Any	High	W/WR	Yes	4W + 6F
IV	Any	Any	High	W/WNR	No	2W + 6F
Any	Any	<100 ng/ml	High	W/WR	Yes	4W + 6F
Any	Any	<100 ng/ml	High	W /WNR	No	2W + 6F

AEPI04C1 Low Birth Weight & Other Risk Factors for Hepatoblastoma

2.1 Protocol Abstract

Hepatoblastoma (HB) accounts for over 65% of all liver cancer diagnosed in children under 15 years of age in the United States.¹ It is most common in infancy and early childhood. The overall rate is about 1 case per million children under the age of 15 years, which translates into approximately 100 cases per year in the U.S. While rare, HB is among the less treatable childhood cancers. Moreover, our recent analysis indicates that the incidence rates for HB in the U.S. have *doubled* between 1975 and 1999.² Due to its rarity, the epidemiological literature regarding HB is sparse. Case reports have suggested links between HB and fetal alcohol syndrome, oral contraceptive use during pregnancy, and maternal liver transplantation, but anecdotes such as these are not conclusive.³⁻⁶ A few small (< 100 cases) case-control studies have suggested

associations with maternal smoking,⁷ parental occupation,⁸ and genetic susceptibility.⁹ Importantly, recent evidence from case series in Japan and the United States provides support for an increased risk of HB in low (LBW: 1,500-2,500 grams), and especially very low (VLBW: < 1,500 grams), birth weight infants.^{2,10-14} A recent case-control study has also confirmed the increased risk of HB among LBW and VLBW infants.¹⁵ Using the resources from the Children's Oncology Group, we propose to conduct the largest, most comprehensive case-control study of HB yet undertaken. The aims of the study are to: 1) investigate the role of treatment for prematurity in the risk of hepatoblastoma among low birth weight children, 2) examine parental occupation and maternal lifestyle during pregnancy among cases and controls, 3) investigate polymorphisms in candidate susceptibility genes in children, 4) investigate polymorphisms in candidate susceptibility genes in mothers, and 5) describe the pattern of IGF-2 imprinting in HB cases. A total of 600 cases (including an estimated 120 with birth weights less than 2500 grams) diagnosed at United States COG institutions between 1/1/2000 and 12/31/2008 will be enrolled. A total of 720 sex and birth weight-matched population controls will be enrolled from state birth registries. Exposure data will be collected through telephone interviews of mothers and through abstraction of medical records of low birth weight participants. DNA will be obtained from the cheek cells of mothers and children for genotyping. Lastly, HB tumor specimens will be collected for analyses of genomic imprinting.

3.1 Introduction: Why study hepatoblastoma?

Historically, the study of rare tumors has led to major findings in our understanding of cancer etiology. Examples of these cancers include retinoblastoma, angiosarcoma, and vaginal clear cell carcinoma. We believe that the study of HB can also offer unique insight into the process of carcinogenesis. Uniquely among childhood cancers, there has been a marked rise in incidence of HB in recent years that does not appear to be artifactual. At the same time low birth weight has emerged as a strong risk factor for HB. These circumstances suggest a prime opportunity to elucidate a carcinogenic mechanism. We hypothesize that it is not low birth weight *per se*, but rather the panel of treatments for the same, which increases risk of HB. We also surmise that other candidate risk factors for HB are of minor etiologic importance among low birth weight children given the presentation of low birth weight cases at older ages and more advanced stages, the strength of the association between low birth weight and HB, and the genotoxic potential of treatment for prematurity. There is also a paucity of epidemiologic studies of HB apart from low birth weight. Candidate risk factors such as maternal lifestyle during pregnancy, parental occupation, and genetic susceptibility that have been suggested previously by single, small studies will be comprehensively evaluated in this study of HB, the largest one to date. The study, as the largest case series to examine genetic imprinting in HB, will also shed light on the natural history of the disease.

3.2 Incidence, mortality, and trends

We recently evaluated hepatoblastoma (HB) incidence and trends among children aged 0-4 years in the United States from 1975 through 1999 in the nine reporting areas of SEER.^{2,16} The overall incidence rate of HB in this age group rose from 2.59 (95% CI: 1.70-3.93) per million in 1975-79 to 5.27 (95% CI: 4.03-6.88) in 1995-99, which

represented a statistically significant 3.9% annual rise in incidence (Figure 1). The rate of HB among infants (< 12 months of age) was at least double that among older children for each quinquennium (Table 1). For instance, in 1995-99 the rate of HB among infants was 9.3 (95% CI: 5.96-14.64) per million and 4.3 (95% CI: 3.06-5.93) among children aged 1-4 years. However, the rate of HB among older children increased more notably (5.3% per annum; 95% CI: 2.35-8.25), than did the rate among infants (2.2% per annum; 95% CI: -0.10-5.54). The rate of HB was slightly higher in males compared to females and in blacks compared to whites. There was a significant annual rise in incidence for males, females and whites.² The average annual percent change (AAPC) for blacks suggested a rise in incidence but was not significant. The incidence of HB is vanishingly small, 0.3 cases per million or less, at ages older than 4 years.¹⁶ The five-year survival rate for children with hepatoblastoma was 60.6% for the period 1985-1999 in SEER, with infants experiencing better survival (67.3%) than children ages 1-4 years (55.7%). These figures mark HB as one of the least treatable childhood cancers, with only acute myeloid leukemia, primitive neuroectodermal tumors, and some gliomas having lower 5-year survival rates among 0-14 year olds.

3.3 Genetic Syndromes and HB

Several cases of HB have been reported in children with Familial Adenomatous Polyposis (FAP)¹⁷ and Beckwith-Wiedemann Syndrome (BWS)¹⁸ which, due to the rarity of these conditions, supports a causal association. *Familial Adenomatous Polyposis*: FAP involves inheritance of a defective copy of the APC tumor suppressor gene. Carriers of this autosomal dominant gene develop adenomatous colorectal polyps at young ages.¹⁷ In addition, carriers are at a vastly increased risk of developing HB. Incidence of HB among children ages 0-4 years in the Johns Hopkins Polyposis registry was 847 (95% CI: 230-2168) times the incidence in the SEER population. *Beckwith Wiedemann Syndrome*: BWS is an “overgrowth” syndrome, characterized by gigantism, macroglossia, omphalocele, hemihypertrophy, and neonatal hypoglycemia.²⁰ The rate of HB among children ages 0-4 years in a BWS registry was 2280 (95% CI: 928-11,656) times that of the U.S. population of the same age.²¹ Children with BWS appear to be conceived using assisted reproductive technology (ART) more often than the general public.²²⁻²⁴ It would be reasonable to speculate that conception by ART may be a risk factor for HB, even apart from increasing the risk of BWS, given the propensity for such procedures to cause abnormal imprinting.

3.4 Low birth weight and HB

Recent observations regarding HB and low birth weight offer compelling evidence of an association. A Japanese report first noted that the percentage of HB cases that weighed 1500 grams or less at birth increased significantly between the late 1980's and the early 1990's, when survival of very low birth weight babies improved.²⁵ Subsequent studies confirmed that the proportion of low birth weight among U.S. HB cases was unusually high¹⁴ and that the rate of HB was significantly higher among very low birth weight babies compared to those with normal birth weight in Japan.²⁶ We recently confirmed that the rise in HB incidence in the United States was consistent with the rise in the proportion of births with very low birth weight. Low birth weight cases are diagnosed at

more advanced stages in one study²⁷ and at older ages²⁸ than are cases with normal birth weight. Identification of a subgroup of cancer cases with differing characteristics can indicate a differing etiology. Children with low birth weight are routinely exposed to an array of medical treatments to which other children are not. Therefore, we hypothesize that the intensity and duration of treatment for prematurity are risk factors for hepatoblastoma among children with low birth weight. Two small studies (12 cases, 75 controls²⁹ and 5 cases, 285 controls.) have suggested that HB in VLBW infants may be related to the length of therapy for prematurity. In particular, Oue et al reported that the mean durations of mechanical ventilation, oxygen inhalation, and hospitalization during the perinatal period were significantly longer than in patients compared to birth weight matched controls. Lastly, a recent case-control study from California collected information from birth certificates. The study estimated the relative risk of HB in low birth weight infants more precisely than had been done using case series data. The researchers found that the rate of HB among VLBW infants was 50-fold that of infants weighing 2,500-3,999 grams (OR = 50.6; 95% CI: 6.6-388.0).

3.5 Other risk factors for hepatoblastoma

There are few epidemiological studies of HB and in their absence risk factors have tentatively been suggested by case reports. HB has been reported in single instances in association with fetal alcohol syndrome, oral contraceptive use during pregnancy, sterility treatment, and maternal liver transplantation with immunosuppressive therapy. An exploratory study that consisted of 75 cases and 75 controls found that mothers of children with HB were significantly more often occupationally exposed to metals, petroleum products, and paints and pigments before or during pregnancy, while fathers of children with HB were significantly more often occupationally exposed only to metals. The study did not find evidence of hypothesized associations of HB with hepatitis viruses, maternal alcohol consumption, or maternal smoking. A recent study of all childhood cancers and smoking included 28 cases of HB as well as 7,581 controls. Alone among specific types of childhood cancer, parental smoking significantly increased risk of HB. In addition to a borderline significant trend with the mother's daily number of cigarettes preconception ($p = 0.058$), there was a significant association with having both parents smoke (OR = 4.74; 95% CI: 1.68- 13.35). Upon further examination it appeared that the association between HB and smoking was independent of low birth weight, which can be caused by maternal smoking while pregnant and which, as described above, appears to be a risk factor for HB. A second British study also found an association of HB with parental smoking.

3.6 Genetic susceptibility and hepatoblastoma

Due to its rarity, few studies have explored genetic susceptibility with respect to population polymorphisms and risk of HB. It is important to consider genes that are most active during fetal development,³³ as well as consider maternal genes that may be relevant in the context of the fetus.³⁴ We have extensively reviewed the literature to identify genes that may be of interest. Below, we describe these selected genes in the context of potential mechanisms and pathways (e.g. Phase II) that may make them important in the genesis of hepatoblastoma. We expect that additional genes will be investigated as pathways and relevant haplotypes become more clearly defined.

3.7 Genomic imprinting and hepatoblastoma

Genomic imprinting is the differential expression of a gene depending on the parent of origin. Several genes are known to be imprinted, including insulin-like growth factor-2 (IGF2) and H19. In most healthy tissues, humans have monoallelic expression of these genes; humans only express the father's copy of the IGF2 gene and the mother's copy of the H19 gene. One exception is liver, in which biallelic expression of IGF2 is the normal state after the age of about 1 year.⁵¹ Biallelic expression of IGF2 and H19 has been demonstrated in several pediatric and adult malignancies, including Wilms' tumor, Ewing sarcoma, embryonal rhabdomyosarcoma, germ cell tumors, lung cancer, esophageal cancer, glioma and renal cell carcinoma (reviewed in⁵²). In contrast, for HB, monoallelic expression of IGF2 has generally been reported, with biallelic expression observed in only a minority of cases. In our recent study, for all HB cases tissue was examined (including both malignant and normal adjacent liver tissue), H19 was monoallelically expressed,⁵² suggesting that dysregulation of H19 is unlikely to contribute to HB development. In contrast, variable patterns of allele-specific expression at IGF2 were observed. The majority (10/13) of informative tumors demonstrated monoallelic expression of IGF2. Three tumors demonstrated biallelic expression of IGF2, which were diagnosed in children aged 10 months, 18 months and 9 years. In two cases diagnosed at ages 18 months and 2 years normal adjacent liver tissue showed biallelic expression of IGF2, while expression was monoallelic in the tumor tissue. However, two others (diagnosed at ages 13 months and 2 years) showed monoallelic IGF2 expression in tumor tissue and in adjacent normal liver tissue. In our study, the observation of monoallelic IGF2 expression in HB tissue at ages when normal liver expresses IGF2 biallelically may indicate a failure to follow the normal sequence of change in promoter usage (e.g., increased usage of P1). In such cases, it is possible that carcinogenesis is initiated at an earlier developmental timepoint than in cases in which normal progression to biallelic usage is seen. Importantly, at least one study suggests that HB cases that develop in association with low birth weight tend to occur at later ages.^{12,28} We will explore whether biallelic expression of IGF2 occurs more often in low birth weight cases.

3.8 Summary

HB, though rare, has been increasing in incidence over the past three decades. Meanwhile, evidence that HB is associated with LBW, and especially VLBW, is convincing. Low birth weight cases appear to be diagnosed at older ages and perhaps in more advanced stages than HB cases of normal birth weight, which suggests that etiology may differ between the two groups. An obvious difference between low and normal birth weight babies is treatment for prematurity, which can include supplemental oxygen, total parenteral nutrition, red cell transfusions, and phototherapy. We hypothesize that the duration and intensity of these treatments modulates risk of HB. Other risk factors for HB, including parental occupation and maternal lifestyle during pregnancy, have been described. We hypothesize that any association with these exposures will be specific to children with normal birth weight. Polymorphisms in genes that affect the ability to detoxify environmental toxins may contribute to genetic susceptibility to HB. Since many cases of HB are presumed to originate *in utero* maternal genotype as well as child's

genotype may be important. Lastly, it appears that HB, like other embryonal tumors, displays abnormally retained imprinting of the insulin-like growth factor-2 (IGF-2) gene, which may be a window into the natural history of HB.

Surgeon Responsibilities:

Dictated Operative Report including:

- Demographics (name, date, surgeon, pre and postoperative diagnosis, operation)

- Clinical Summary (age, sex, symptoms and brief outline, PRETEXT group, preoperative treatments, indications and objectives of surgery)

- Operation-narrative summary (incision, general observations, description of procedure, extent of spread/spill/rupture, presence of gross tumor residual, all specimens taken, staging biopsies, and blood loss)

- Operative Stage