Liver transplantation in the management of unresectable hepatoblastoma in children

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1. ABSTRACT

Complete surgical resection is essential to long-term survival in children with hepatoblastoma. We present the guidelines from the Children's Oncology Group (COG), liver tumor study group of the Societe Internationale Oncologie Pediatrique (SIOPEL), and German Pediatric Oncology Group (GPOH) for early referral of children with potentially unresectable hepatoblastoma to a specialty center with expertise in "extreme resection" and liver transplantation. Patients who will become candidates for liver transplantation should receive chemotherapy following the same protocols as for children undergoing a partial hepatectomy. The Pediatric Liver Unresectable Tumor Observatory (PLUTO) is an international prospective database established to collect data and make future recommendations on controversial issues regarding the use of transplant in hepatoblastoma including: 1) What is the optimal treatment of multifocal tumors? 2) What is the role of "extreme resection" vs. liver transplant in patients with major venous involvement? 3) What is the role of transplant in patients who present with lung metastasis? 3) Should patients with tumor relapse be offered a "rescue" transplant? 4) What is the role of pre- and post- transplant chemotherapy?

2. INTRODUCTION

In the treatment of hepatic malignancy, liver transplantation has a checkered past, a vibrant present, and a potentially spectacular future. Initial long-term results, especially in adult hepatocellular carcinoma prior to the full understanding and adoption of strict selection criteria, were too often disappointing due to tumor recurrence. With this early experience reaping a high rate of post-transplant tumor recurrence, transplant was relegated to the role of a salvage therapy; something to try after everything else had been tried and failed. However, as our experience evolved and we began to understand the importance of strict selection criteria, survival rates improved. Once these selection criteria for different tumor types and circumstances were clearly established, survival rates soared. Concomitant advances in liver surgery brought techniques such as in-flow occlusion, total vascular exclusion, in-situ flush with preservation solution, and complex venous resection and reconstruction of the vena cava. As these advanced surgical techniques matured, extensive liver resection, without transplantation, became safer. A new term began to appear in the literature describing these heroic liver resections as "extreme liver resection". These "extreme liver resections" are not

Table 1. Summary results recent hepatoblastoma multicenter cooperative trials

Study	Chemotherapy	Number of Patients	Outcome
INT-0098 (56)	C5V vs. CDDP/Doxo	Stage:I/II: 50; Stage III: 83; Stage IV: 40	4-year EFS/OS: I/II = 88%/100% vs. 96%/96% III = 60%/68% vs. 68%/71% IV = 14%/33% vs 37%/42%
P9645 (COG) (43)	C5V vs. CDDP/CARBO	Stage:I/II: *pending publication* Stage III=38; Stage IV=50	1-year EFS* : Stage III/IV: C5V 51%;CDDP/Carbo 37% *study closed early due to inferior results CDDP/CARBO arm
HB 94 (GPOH) (44)	I/II: IFOS/CDDP/DOXO III/IV: IFOS/CDDP/DOXO + VP/CARBO	Stage: I: 27; II: 3; III: 25; IV: 14	4-year EFS/OS: I = 89%/96%;II = 100%/100%; III = 68%/76%IV = 21%/36%
HB 99 (GPOH) (45)	SR: IPA HR: CARBO/VP16	SR: 58 HR: 42	3-year EFS/OS: SR: 90%/ 88% HR: 52%/55%
SIOPEL 2 Perilongo (36)	SR: PLADO HR:CDDP/CARBO/DOXO	PRETEXT: I= 6; II=36; III=25; IV=21; Mets: 25	3-year EFS/OS: SR: 73%/91% HR: IV: 48%/61% HR Mets: 36%/44%
SIOPEL 3 (46) (4)	SR: CDDP vs PLADO HR: SUPERPLADO	SR: PRETEXT I=18;II=133; III=104 HR: PRETEXT IV=74; +VPE=70; mets=70; AFP<100=12	3-year EFS/OS: SR: CDDP 83%/95%; PLADO 85%/93% HR: overall 65%/69%; mets 57%/63%
JPLT1 (47)	I/II: CDDP(30)/THPA-DOXO III/IV: CDDP(60)/THPA-DOXO	Stage: I: 9; II: 32; IIIa:48, IIIb 25; IV: 20	5-year EFS/OS: I = ? /100%;II = ? /76%; IIa = ? /50%; IIIb = ? /64%; IV = ?/ 77%

C5V=Cisplatin, 5FU, Vincristine ; CDDP = Cisplatin ; DOXO = Doxorubicin ; IFOS= Ifosfamide ; IPA= Ifosfamide,cisplatin,adriamycin/doxorubicin ; PLADO = Cisplatin and Doxorubicin ; SUPERPLADO= intensified cisplatin delivery (more frequent cycles) ; CARBO= Carboplatin ; THPA-Doxo = Doxorubicin

necessarily safer than transplantation, but as they push the limits of technical feasibility they make us more clearly reflect on the potential risks and benefits of the different options (1). In some cases an increase in surgical risk of "extreme resection" might be justified when balanced against the alternative of transplantation and lifetime immunosuppression. But many questions remain regarding hepatic insufficiency, limits on hepatic regeneration in children on chemotherapy, and the potential for increased risk of tumor recurrence, especially in the case of multifocal tumors. This review will focus on the role of transplantation in the treatment of the most common pediatric liver tumor, hepatoblastoma. We conclude with a plea to all clinicians treating children with potentially unresectable liver tumors to contribute to the international prospective database, PLUTO (Pediatric Liver Unresectable Tumors Observatory). Collection of comprehensive data should provide future refinement in our knowledge of which children with unresectable liver tumors should have an attempt at aggressive resection and which patients should proceed to transplantation.

3. TREATMENT OF HEPATOBLASATOMA IN COOPERATIVE GROUP TRIALS

Cases of "unresectable" liver tumors due to involvement of the entire liver, extensive multifocality, or extensive hepatic venous or portal venous involvement comprise 10 – 20% of all hepatoblastomas treated in multicenter cooperative group trials. Hepatoblastoma is a rare malignancy which nevertheless accounts for 75% of primary liver tumors in children. The five year survival rate of children affected by hepatoblastoma and treated with combination cisplatin-based chemotherapy and complete surgical resection is now in the range of 80-90%, which represents at least a doubling of the survival rate

reported in the early 1980s (2). Despite these exciting results epidemiologists estimate the 5-year disease free survival in the USA to be no higher than 50% suggesting that many children are not receiving optimal contemporary care (3). We speculate that the differences between the results reported in the best cooperative group trials and overall results seen in the population as a whole may be due to excessive surgical morbidity and poor survival in children with unresectable tumors. These cases of unresectable liver tumors are due to involvement of the entire liver, extensive multifocality, or extensive hepatic venous or portal venous involvement. Together such tumors comprise 10-20% of all hepatoblastomas treated on multicenter cooperative group trials. Comparative survival outcomes of the different cooperative study groups over the past two decades are shown in Table 1. One major problem in comparing the results of these different groups is the use of different staging systems. The staging system used in North American trials, INT-0098 and P9645, is often referred to as the COG (previously the CCG & POG legacy groups) or Evan's staging system and does not attempt to define the anatomic extent of tumor in the liver at diagnosis (Table 2). Instead the North American trials have historically relied on the judgment of the individual surgeon in defining which tumors are resectable at diagnosis, which tumors receive neoadjuvant chemotherapy, and which tumors are referred for a liver transplant. In neither of the two most recent North American trials, INT-0098 nor COG P9645, was liver transplantation included in the protocol or recommended in any systematic way. The current Children's Oncology Group (COG), trial, AHEP0731 has abandoned the historic ad hoc approach to decisions about surgical resection and adopted the *Pret*reatment *Ext*ent of Disease (PRETEXT) grouping system to specifically define surgical resectability and to help clinicians determine which tumors need to be referred to a specialty liver program early in the course of

Table 2. Staging and risk stratification or hepatoblastoma

Former COG (Evans)	Current COG North American	SIOPEL (European, International)	JPLT (Japanese)	GPOH (German)
I. Tumor completely resected at diagnosis by segmentectomy or standard anatomic lobectomy, recommended for PRETEXT I and PRETEXT II tumors with clear vascular margins on preoperative imaging	Very Low Risk: Pure fetal histology resected at diagnosis, PRETEXT I or II		Very Low Risk: PRETEXT I Primary Resection	
II. Complete gross resection at diagnosis with microscopic residual	Low risk: Any Histology resected at diagnosis, PRETEXT I or II	Standard Risk: PRETEXT I, II, III	Low risk: PRETEXT II Limited preop chemo	Standard Risk: PRETEXT I, II, III
III. Biopsy only at diagnosis, or, gross total resection with nodal involvement or tumor spill or incomplete resection with gross intra-hepatic disease	Intermediate Risk: PRETEXT III and IV Extrahepatic tumors (+VPE) ; SCU		Intermediate Risk: PRETEXT III and IV Extrahepatic tumor (+VPE)	
IV. Distant metastatic disease at diagnosis, irrespective of local extent of tumor	High Risk: Metastatic disease at diagnosis, AFP < 100 at diagnosis	High Risk: PRETEXT +VPEM, IV, metastasis at diagnosis, SCU histology, AFP <100 at diagnosis	High Risk: Metastatic disease Stem Cell Transplant	High Risk: PRETEXT +VPEM, IV, metastasis at diagnosis, SCU histology, AFP <100 at diagnosis

their treatment for consideration of either an extreme resection or total hepatectomy and liver transplantation (Figure 1).

The PRETEXT grouping system (*Pret*reatment *Ext*ent of disease), originally developed by the Societe Internationale Oncologie Pediatrique (SIOP) liver tumor study group (SIOPEL), has been used by SIOPEL for many years as a tool for risk stratification. In SIOPEL trials PRETEXT I, II, and III tumors have been treated as "standard risk" (SR), and PRETEXT IV, +M (metastatic), and those with AFP <100 have been treated as "High Risk" (HR). Results for Standard Risk (SR) and High Risk (HR) hepatoblastoma in the SIOPEL 2 and SIOPEL 3 trials are shown in Table 1. The recommendations for liver transplant used in the recent trial, SIOPEL 3 were as follows: *"The commonest reasons for a tumor being deemed "unresectable" (except via total hepatectomy) are: (a) tumor clearly involving all four sections of the liver as judged by MRI scan +/-angiography; or (b) location so close to the main vessels at the hilum of the liver that it is unlikely that a tumor-free excision plane will be achieved. These patients should be identified at diagnosis and their clinical course and imaging followed closely throughout their initial chemotherapy, in conjunction with a liver transplant surgeon."* The results of the High Risk (HR) arm of SIOPEL 3 are shown in Table 1 and reveal an improvement in HR outcome in SIOPEL 3 when compared to SIOPEL 2 (4). . One possible explanation for the improved outcome of HR tumors in SIOPEL 3 is the increased use of liver transplant for unresectable tumors.

Contemporary treatment protocols define as potentially unresectable those tumors designated as central PRETEXT III tumors with involvement of all three major hepatic veins (+V) or both branches of the portal vein (+P) and all PRETEXT IV tumors (5-7). The PRETEXT group (Figure 1) is based upon division of the liver into four parts, called sectors or, most recently, "sections" (8). The sections correspond to the traditional surgical division of the liver into left lateral and medial segments, and right

anterior and posterior segments. PRETEXT system designates the following: (1) left lateral (Couinaud segments 2 and 3); (2) left medial (Couinaud segment 4) (3) right anterior (Couinaud segments 5 and 8); and (4) right posterior (Couinaud segments 6 and 7). Couinaud segment 1, the caudate lobe, was originally not included in PRETEXT but in a recent published revision of the PRETEXT system caudate lobe involvement is now denoted by an annotation of "C1" (8). The liver tumor is classified into one of the following four PRETEXT groups depending on the number of *contiguous sections that are free of tumor:* PRETEXT I, three adjacent sections free of tumor; PRETEXT II, two adjacent sections free of tumor (or one section in each hemi-liver); PRETEXT III, one section free of tumor (or two sections in one hemi-liver and one nonadjacent section in the other hemi-liver); and PRETEXT IV, no tumor free sections. Extrahepatic growth is indicated by adding one or more of the following:"V", vena cava or all three hepatic veins involved; "P", main portal or both portal branches involved; "E", extrahepatic contiguous growth (e.g., diaphragm or stomach);"C" Caudate; and "M", distant metastases (mostly lungs, otherwise specify).

Early referral to a specialty liver center with transplant capability is currently recommended by COG, SIOPEL, and GPOH for PRETEXT III extensive multifocal tumors, PRETEXT III +V+ P tumors, and all PRETEXT IV tumors.

4. OUTCOME OF LIVER TRANSPLANT FOR HEPATOBLASTOMA: PUBLISHED LITERATURE

In 1968 Starzl reported the first long-term survivor of liver transplantation, a child with a liver tumor. From that time until the cluster of papers published by Al-Qabandi, Reyes, Pimpalwar, Molmenti and Srivastin in 1999-2002 (9-13), most descriptions of the use of transplant in hepatoblastoma were anecdotal case reports (Table 3). Largely due to negative experience with liver transplant in the treatment of adult hepatocellular

Table 3. Published literature: Liver transplant for hepatoblastoma in children

References	Number of Patients	Percent Survival	Follow-Up (years)
(48)	18	50%	?
(49)	12	50%	2 – 6
(50)	6	83%	0.5 – 2
(51)	3	66%	2
(52)	1	100%	11
(53)	1	100%	1.3
(1)	3	66%	1 – 5
(54)	2	100%	3.5
(55)	2	50%	2 - 3
(9)			?
(10)	12	83%	0.1 – 15.4
(11)	12	83%	0.1 – 9.2
(12)	9	55%	0.5 – 16
(13)	13	85%	0.1 – 9
(15)	4	75%	1.1 – 2
(16)	7	57%	0.2 – 9
(17)	106	82%	?
(17)	41	30%	?
(18)	9	80%	?
(19)	10	70%	3.7 - 18
(21)	14	71%	3.5 +/- ?
(22)	7	85%	0.6 – 18
(23)	11	82%	1 – 14
(24)	135	69%	?
(25)	8	75%	0.6 – 4.4
(26)	15	86%	3.3 +/- 3.5
(27)	25	78%	0.9 – 14.9
(20)	14	71%	3.8 +/-?
(28)	6	66%	?

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 (14).

The biology of pediatric hepatoblastoma has proven to be very different from that of adult hepatocellular carcinoma, with cisplatin based chemotherapy proven to be of significant value in a number of randomized trials (Table 1). This availability of effective chemotherapy led credence to the statement by Reyes *et al* say in their landmark paper in 2000 (10), "in these children with unresectable tumors, the historical barrier of "unresectability" can be redefined with the concept of "total liver resection" and salvage orthotopic liver transplantation (OLT)". Thus, beginning in 2000 liver transplantation was offered to some children as part of a planned treatment algorithm with efforts made to define the optimal timing of transplantation and the potential role of post-transplant adjuvant chemotherapy and the experience with liver transplantation in children with hepatoblastoma blossomed.

In the past decade more than a score of reports have appeared in the literature championing the potential role of liver transplant in the treatment of unresectable pediatric hepatoblastoma (Table 3) (9-13,15-29). These studies establish the beneficial role of liver transplantation in children who previously would have succumbed to progressive disease. Transplant, although potentially life-saving, carries attendant consequences including perioperative morbidity and mortality and the subsequent need for life-time immunosuppression. What remains to be determined is who most will benefit from transplantation. A report from the group in Birmingham, UK shed some

light on this question when they found that 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 (11). 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" (17,30). In a collaborative report of the world experience of liver transplantation for hepatoblastoma (17) 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". The timing of chemotherapy, the timing of transplantation, and the use of post-transplant chemotherapy varied too much between centers to be evaluated separately with confidence. A new benchmark was achieved in the most recent series reported from Cincinnati OH at the American Pediatric Surgical Association Meeting in 2009 (29). This series includes 16 patients who underwent both primary and rescue liver transplantation for hepatoblastoma with an overall survival of 100%.

5. GUIDELINES FOR LIVER TRANSPLANTATION IN UNRESECTABLE HEPATOBLASTOMA

Hepatoblastoma patients who respond to chemotherapy but have unresectable tumors and no evidence of persistent extrahepatic disease should be considered for orthotopic liver transplantation. As shown in the simplified flow diagram in Figure 3, the following criteria are currently used by COG and SIOPEL to select potential candidates for transplant.

Multifocal PRETEXT IV, multifocal tumor in all four liver sections at diagnosis

Unifocal PRETEXT IV, with neoadjuvant chemotherapy often these tumors will "downstage" to a Post-treatment Extent of Disease (POST-TEXT) III and become amenable to conventional resection by trisegmentectomy

PRETEXT III +V, proximity of the tumor to the vena cava or all three major hepatic veins makes adequate tumor clearance doubtful.

PRETEXT III+P, proximity of the tumor to the portal venous bifurcation or both major branches of the portal vein makes adequate tumor clearance doubtful

Intrahepatic relapse or residual tumor after previous attempt at resection..."rescue transplant"

Although these guidelines are very useful, some uncertainty and controversy remains regarding the management of multifocal tumors, patients with venous involvement who might be candidates of "extreme resection", patients who present with pulmonary metastasis, and patients who are referred with relapse or residual tumor and require "rescue" transplant
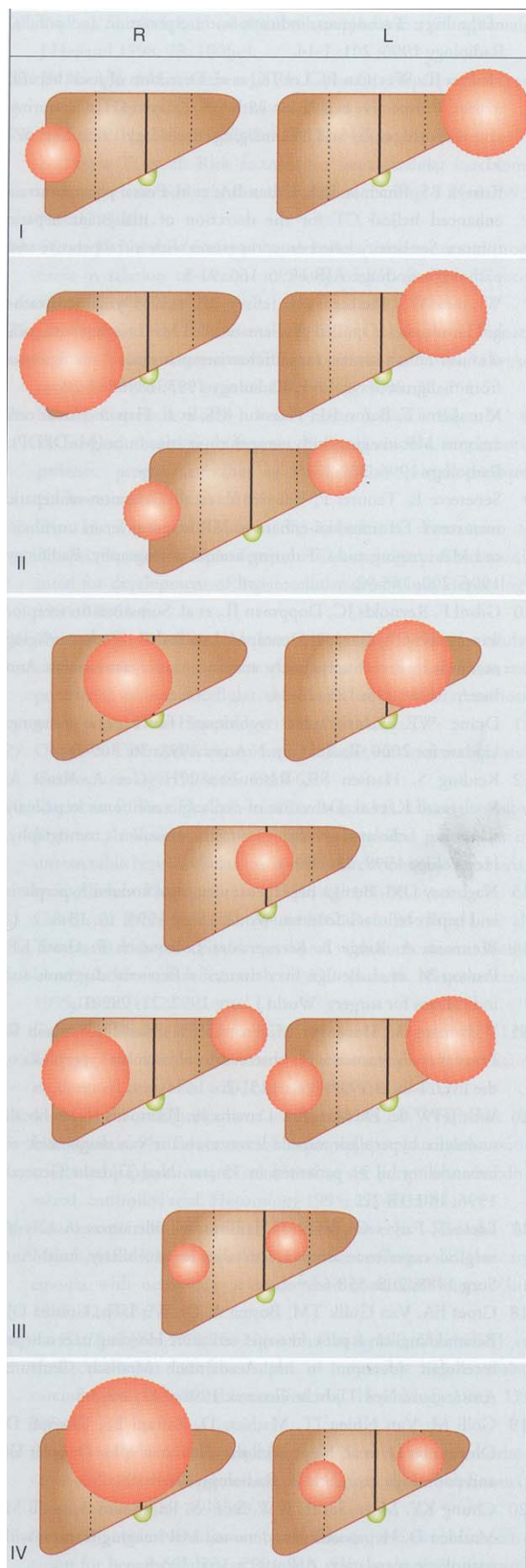
Figure 1. Pretreatment Extent of Disease = PRETEXT.

6. MULTIFOCAL TUMORS

Both COG and SIOPEL currently recommend that all patients with multifocal PRETEXT IV tumors should undergo liver transplantation, even if one of the liver sections is apparently clear of tumor nodules after pre-operative chemotherapy (5-7, 31). In support of this are reports of the presence of viable tumor foci within areas of total hepatectomy specimens despite the apparent disappearance of tumor nodules from these areas after preoperative chemotherapy (32). In addition, multiple series have shown excellent results from primary transplant and poor results from rescue transplant (11,17,20,23,25). In a more recent series from Padova, predictors of failed conservative therapy included multifocality (33). Patients who had multifocal lesions and those who had an alpha-fetoprotein level <100ng/ml survived only if they underwent transplantation.

These recommendations may remain controversial for the near future. Over the years there have been patients with multifocal tumors in the large multicenter trials who survived with conventional resection (35,36). Excellent responses to chemotherapy with disappearance of pulmonary metastases are usually taken to indicate their eradication. Why multifocal liver nodules which resolve should behave differently is unknown (34). Better definition of the tumor biology including response to chemotherapy may be critical in deciding the optimal surgical management. It is clear that our current understanding of hepatoblastoma does not allow specific risk stratification. Given this uncertainty, most transplant surgeons active in this field recommend that *all* multifocal PRETEXT IV tumors should be treated with transplantation (6,7) regardless of the chemotherapy response. Response to chemotherapy may be the critical factor in deciding the optimal surgical management where good responders might become candidates for partial hepatectomy but poor responders may be better treated by total hepatectomy and transplant (34). Caution is given that the pediatric oncologist should resist the temptation of intensifying chemotherapy in vain efforts to avoid transplantation.

7. VENOUS INVOLVEMENT: TRANSPLANT VS EXTREME RESECTION

Resections less than total hepatectomy with transplantation as reconstruction have been successful in patients with tumor encroachment on the vena cava, the portal vein bifurcation, and all three hepatic veins. These types of heroic resections depend upon vascular reconstruction, must be planned carefully and should not be performed if a negative surgical margin cannot be reasonably anticipated. There is insufficient data to determine whether such resections have benefit over transplantation. Poorly planned or executed operations risk excessive bleeding, post-operative vascular obstruction, biliary leakage or stricture, cholangitis, and/or hepatic insufficiency. Some of the confusion or controversy in these cases has resulted from the observation that a microscopic "positive" margin does not necessary mean

Table 4. Transplant for hepatoblastoma: Pulmonary metastasis at diagnosis (1,4,9,10,23,25,29,30,36,41)

Pulmonary Metastasis at Diagnosis	N =	Post-transplant Pulmonary Relapse	Alive without evidence of tumor	Died of other causes
Lung lesions disappeared with chemotherapy	24	9 (38%)	14 (58%)	1 (4%)
Pretransplant Pulmonary Metastasectomy	8	3 (38%)	5 (62%)	
TOTAL	32	12 (37%)	19 (60%)	1 (3%)

residual malignant tumor because of the electrocautery artifact often present at the resected margin of liver. In fact, microscopic residual tumor was NOT a reliable predictor of tumor relapse in SIOPEL 1 or 2 (30,37). Here again it is likely that the chemosensitivity of the tumor is of paramount importance in achieving event free survival in the presence of possible microscopic residual. It would be an error to extrapolate these observations to assume that a positive surgical margin or an incomplete resection because of encroachment on a major vascular structure is satisfactory—it is not. It is our opinion that it is inappropriate to embark on a resection where tumor clearance is doubtful and patients with extensive venous involvement are often be best treated by primary liver transplantation.

Some surgeons recommend that the retrohepatic vena cava should be removed en bloc with the liver during the transplant in these patients. The cava can then be reconstructed using either donor iliac vein (cadaveric donor) or autologous jugular vein (live donor) (15). In cases where the vena cava has been completely obliterated by tumor prior to transplant, it may be that no vena cava reconstruction is necessary at all (38).

Future decisions as to the role of "extreme" resections will require more data. Despite the potential for excellent tumor free survival, liver transplant does carry some lifelong risk. Tiao et al reported rejection in 50% of patients transplanted for HB (18) and Mejia et al reported a 70% incidence of rejection (19). In both of these series there was a preponderance of cadaveric grafts. Whether living donor grafts might require less immunosuppression as suggested by Gras (39), or whether alternative immunosuppression using Rapamycin (Sirolimus), a drug with both antineoplastic and immunosuppressive properties will have any impact in children with hepatoblastoma remains to be seen.

While most agree that "extreme" resection of tumors without liver transplant will avoid the need for long-term immunosuppression (5,15,32,40), outcomes with these techniques have not been rigorously reported. At least 3 patients treated in the INT-0098 suffered from life-threatening venous outflow obstruction after attempted resection of tumors with venous involvement. Two of the three ultimately did not survive (35). Current recommendations for referral of high risk patients with hepatoblastoma to centers that have the ability to do both extreme resections and liver transplant should result in an improved ability to compare the outcomes of these two approaches (33,40).

8. PULMONARY METASTASIS AT DIAGNOSIS

An absolute contraindication to liver transplant is persistent pulmonary metastases non-responsive to neoadjuvant chemotherapy and not amenable to surgical resection. The tumor should show at least a partial response to chemotherapy (decrease in tumor size, decrease in serum AFP, decrease in size or disappearance of pulmonary nodules). Stable or progressive disease is a relative contraindication to transplant (6,7,15,34). Lung metastases that disappear completely with chemotherapy with or without surgical resection do not pose a contraindication, yet the risk of post-transplant pulmonary relapse is substantial and therefore the use of liver transplantation for children with metastatic disease remains controversial. Table 4 shows the accumulated cases in the literature and presented at national and international meeting over the past 10 years (1,4,9,10,23,25,29,30,36,41). Overall survival appears to be about 60% with no large difference in outcome when lung metastasis cleared completely on chemotherapy vs pulmonary metastasectomy. Interpretation of this data must be done with some caution as this is a highly selected group of patients from centers who have a strong commitment to transplantation. Some techniques that have been suggested to ensure the clearance of lung metastasis prior to transplantation include the use or irinotecan pre-transplant, AFP imaging pre-transplant, PET-CT pre-transplant, median sternotomy with manual palpation of both lungs pre-transplant, lobectomy rather than metastasectomy if lung have more than 4 nodules in same lobe (42).

9."RESCUE" TRANSPLANT FOR RELAPSE OR PERSISTENT TUMORS

Multiple series have shown superior outcome after primary transplant (about 80% overall survival) when compared to "rescue" transplant (about 30-40% overall survival) (11,17,20,23,25). The basis for this is undoubtedly multifactorial, but two important reasons are the likelihood of chemotherapy resistance in relapse tumors, and the debilitated state of the patients when transplanted in the face of end-stage disease. Potential candidates for transplant not only require careful evaluation of their tumor but also a thoughtful consideration of their ability to tolerate the physiologic stress of transplant. Doxorubicin is cardiotoxic and both doxorubicin and cisplatin are nephrotoxic. A detailed echocardiogram and assessment of renal function is essential prior to transplant, especially a "rescue" transplant. After months, sometimes years of failed therapy, the child's nutritional status may be compromised rendering them more susceptible to infectious complications.

In Otte's review of the world literature (17) the survival was only 30% for "rescue" transplant. It is reasonable to presume that these patients would have died without transplant. For this reason it has been argued that it would potentially be unethical to deny transplantation when

it is the only hope for survival in these children. This rationale is commonly espoused in the treatment of several other pediatric cancers where similar life threatening therapies, e.g., bone marrow transplant, are routinely performed for children with survival chances in the range of 30%. What is different here is that transplantation of a cadaveric liver graft means that another patient who may have a better chance of survival might be denied an opportunity for transplantation if the donor organ is allocated to such a child. Some have advocated using exclusively live-donor transplants in this setting but this too is controversial because of the potential that if a live-donor allograft were to fail (e.g. portal vein or hepatic artery thrombosis), the child could require a deceased donor (cadaveric) retransplatation..

It is most appropriate to conclude a discussion of "rescue"transplant by emphasizing the need to avoid this situation wherever possible. The strategy, first recommended by the Birmingham UK group (11) of avoiding any attempt at resection when a complete and safe resection seems difficult or unlikely (17) and timely referral of these children for primary transplantation will reliably result in a far better survival rate.

10. POST-TRANSPLANT CHEMOTHERAPY

Post transplant chemotherapy will depend on the timing of the transplant and the pretransplant chemotherapy received by the child. Current COG and SIOPEL protocols both recommend that liver transplant patients receive the same pre-operative and post-operative chemotherapy given to patients treated with conventional resection--no more, no less. Success of this strategy will depend importantly on the ability to provide a transplant at the appropriate time in the child's chemotherapy regime.

In his 2005 review of the World literature, Otte reported 65 of 147 patients received post-transplant chemotherapy with no statistically significant difference in overall survival rates between those who did (77%) and those who did not (70%) receive post-transplant chemotherapy (17). When combined with post-transplant immunosuppression, many have worried that the risks of chemotherapy might be potentiated. This has led some groups to recommend no post-transplant chemotherapy in patients who have negative tumor margins at the time of transplant and have no history of metastatic disease (22). Other groups have advocated chemotherapy when the tumor burden is at its lowest, i.e., immediately post-transplant, arguing that reported morbidity with this approach in actually very low (27). With such small number of patients in each of the individual series reported to date, it is not possible to make a clear recommendation at this time. Such controversial issues may be better answered in the future when the PLUTO database matures.

11. PEDIATRIC LIVER UNRESECTABLE TUMOR OBSERVATORY (PLUTO)

At present, the SIOPEL study group together with support from COG, GPOH, and the Study of Pediatric Liver Transplantation (SPLIT) has established a worldwide electronic registry for liver transplant in childhood liver tumors (hepatoblastoma, hepatocellular carcinoma, and diffuse infantile hemangioma). All patients treated by liver transplantation will be asked to sign a consent 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. 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. Anyone having difficulty accessing the website is encouraged to contact the website support staff at www.cineca.org whose number is available on the website.

12. CONCLUSION

Total hepatectomy and liver transplantation should be considered an integral part of the contemporary treatment of high risk hepatoblastoma. Reliance on chemotherapy to reduce the size or extent of tumors in these children places them at risk for excess morbidity from chemotherapy, a higher tumor recurrence rare, or death before or during resection. While alternative therapy with "extreme" surgery has been reported with good results in some hands, it remains dependent upon specialized surgical skills and surgical teams with extensive experience. It is these very specialized surgical teams who are best positioned to make a decision regarding transplantation vs. complex resection with a transplant safety-net. Patients who present with metastatic disease may still benefit from transplantation but significant questions remain about their optimal treatment. We strongly urge all physicians and surgeons involved in the care of these high risk patients to enroll them on available group studies and to register them with the PLUTO registry.

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Abbreviations: COG: Children's Oncology Group; SIOPEL: Liver tumor study gorup of the Societe Internationale Oncologie Pediatrique; GPOH: German Pediatric Oncology Group; PLUTO: Pediatric Liver Unresectable Tumor Observatory; CCG: Children's

Cancer Group; POG: Pediatric Oncology Group; PRETEXT; Pretreatment Extent of Disease; AFP; alpha feto-protein; SPLIT; Study of Pediatric Liver Transplantation

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