



Published in final edited form as:

*J Pediatr Surg*. 1992 March ; 27(3): 292–297.

## Resection, Including Transplantation, for Hepatoblastoma and Hepatocellular Carcinoma: Impact on Survival

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### Abstract

Long-term survival in children with primary hepatic malignancies can not be expected without complete tumor resection. In the last ten years we have treated 21 children with hepatocellular carcinoma (HCC) and 21 children with hepatoblastoma (HEP), with tumor extirpation our surgical goal. Operative treatment included partial hepatectomy ([PH] 20), either primary (10) or delayed (following chemotherapy) (10), total hepatectomy and orthotopic liver transplantation ([OLT] 13), or upper abdominal exenteration and multiple organ transplantation (2). Two patients had both PH and subsequent total hepatectomy and OLT. Overall survival was 48% (20/42), with 9 patients dying of progressive disease prior to removal of their tumor. HEP patient survival was 67% (14/21), including 2 of 6 who underwent primary PH, 7 of 8 who had delayed PH, and 5 of 6 who underwent OLT. Survival for the children with HCC was 29% (6/21), including 1 of 4 after primary PH, 1 of 2 following delayed PH, 3 of 7 following OLT, and 1 of 2 after exenteration and multiple organ transplantation. Preoperative chemotherapy facilitated removal of 10 initially unresectable tumors (8 HEP, 2 HCC) at a second-look procedure. Total hepatectomy and OLT markedly improved survival in patients with disease unresectable by standard methods. Partial hepatectomy, either primary or delayed, should be attempted in all children with hepatic malignancies. Total hepatectomy and OLT appears to be a viable adjunct in the treatment of childhood malignancies, and should be used for otherwise unresectable tumors as part of a carefully planned protocol.

### INDEX WORDS

Hepatoblastoma; hepatocellular carcinoma; liver transplantation

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Childhood liver tumors continue to have a poor prognosis despite increasingly sophisticated diagnostic methods, aggressive surgical techniques to achieve complete resection, and more effective systemic chemotherapy. Total surgical removal remains the mainstay of treatment, although there are rare reports of long-term survivors achieved with chemotherapy alone. Preoperative chemotherapy has increased the number of patients undergoing potentially curable resections.<sup>1</sup> However, a large proportion of children, especially with hepatocellular carcinoma (HCC), are not resectable by standard methods. Total hepatectomy and orthotopic liver transplantation (OLT), the only alternative for unresectable tumors, is still controversial due to the high incidence of tumor recurrence.<sup>2</sup>

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Presented at the 22nd Annual Meeting of the American Pediatric Surgical Association, Lake Buena Vista, Florida, May 15–18, 1991.

We have treated 42 children with HCC or hepatoblastoma (HEP) in the last 10 years, many of whom were evaluated elsewhere and felt to be unresectable. A retrospective review of their treatment courses is the basis for this report. Tumor resection, either by partial hepatectomy (primary or delayed) or total hepatectomy and OLT, was accomplished whenever possible.

## MATERIALS AND METHODS

### Demographics

Fifty-six children with primary liver tumors were evaluated and treated at Children's Hospital of Pittsburgh from 1980 to 1990: HEP (21), HCC (21), sarcoma (5), anaplastic tumor (1), and incidental HCC (8). Mean ages for the 21 HEP and 21 HCC patients were  $3.2 \pm 0.8$  years and  $9.9 \pm 1.0$  years, respectively ( $P < .001$ ). There were 24 boys and 18 girls. All but 5 of the 42 patients presented with an abdominal mass. Associated diseases were common, especially in HCC: tyrosinemia (4), hepatitis B (2), complex congenital heart disease (2), and neonatal hepatitis (1). Two patients with HEP had the Beckwith-Wiedemann syndrome.

### Laboratory

Platelet counts averaged  $775,000/\text{mm}^3$  and  $359,000/\text{mm}^3$  for HEP and HCC, respectively (normal,  $150,000/\text{mm}^3$  to  $450,000/\text{mm}^3$ ;  $P < .003$ ).  $\alpha$ -Fetoprotein was elevated in 18 of 21 (86%) HEP children and 11 of 17 (65%) with HCC ( $P = .26$ ), ranging from 215 to 4,528,000 ng/mL. Mean SGOT was 137 IU/L and 71 IU/L (normal,  $<50$  IU/L) and gamma glutamyl transpeptidase was 241 IU/L and 113 IU/L (normal,  $<44$  IU/L) in HCC and HEP children, respectively. Four HCC patients but no HEP children had bilirubins greater than 3 mg/dL (normal,  $<1.2$  mg/dL).

### Imaging Studies

Computed tomography was used in 40 patients, ultrasound examination in 36 patients, and magnetic resonance imaging in 5 patients. Hepatic angiography was performed in 14 children; 10 were studied to determine resectability. Four patients underwent angiography for possible intraarterial chemotherapy: one child had a replaced left hepatic artery and intraarterial chemotherapy was not administered while the other three patients underwent two (2) or three (1) courses.

### Staging

Tumor stage was determined at initial diagnosis according to current Children's Cancer Study Group (CCSG)/Pediatric Oncology Group (POG) Intergroup study protocol: stage I, complete resection; stage II, microscopic residual; stage III, gross residual or nodal involvement; stage IV, metastatic disease. Patients underwent operative biopsy if they had not been staged elsewhere. Percutaneous needle biopsy was used in three patients with obvious metastatic disease.

### Transplantation

Transplantation was performed an average of 6 months following initial presentation. Immunosuppression included cyclosporine and prednisone in the first 9 patients and FK506 in the last 6. Thirteen patients underwent total hepatectomy and celiac/pyloric lymphadenectomy. Two patients underwent upper abdominal exenteration (cluster procedure): removal of their liver, pancreas, stomach, spleen, duodenum, and proximal jejunum.<sup>3</sup> OLT was performed in all children and the 2 cluster patients also had pancreatic islet cell transplantation. Islets were isolated from the donor pancreas, purified by a COBE 2991 cell separator (COBE Laboratories, Lakewood, CO), resuspended in Hank's solution with 10% albumin, and infused through the portal vein into the newly engrafted liver.<sup>4</sup>

## Chemotherapy

Seven patients received adjuvant chemotherapy following complete primary tumor resection. Thirty-five patients received chemotherapy to treat residual disease following initial resection (3) or biopsy (32). Most children were treated on CCSG protocols, in which Adriamycin and cisplatin predominate. Cytosin, vincristine, bleomycin, 5-fluorouracil (5-FU), and VP-16 were also used, particularly in treatment failures. Three transplant patients received preoperative intraarterial infusion of Adriamycin and cisplatin conjugated with Lipiodol, ie, chemoembolization, followed by postoperative systemic 5-FU, folinic acid, and interferon.

## Statistics

Descriptive analyses were by unpaired Student's *t* tests, with mean  $\pm$  SEM. Distributions were compared using the  $\chi^2$  test of proportions or Fisher's exact test where appropriate.  $P < 0.05$  was considered significant.

## RESULTS

### Staging

Results for HEP patients included: stage I (5), stage II (1), stage III (10), and stage IV (5). HCC staging included: stage I (2), stage II (2), stage III (12), and stage IV (5). Twenty-two patients (14 HCC and 8 HEP) were initially treated elsewhere and subsequently transferred, 20 of whom were felt unresectable by the referring surgeons and 2 who had residual disease following resection. Of the 20 "in-house" patients there were stage I (7), stage II (1) and stage III/IV (6 each).

### Pathology

Seventeen of the 21 HEPs were classified into subtypes: mixed (8), epithelial (6: 2 fetal and 4 embryonal), teratoid (2), and anaplastic (1). There were three fibrolamellar variants and three cases of cirrhosis in the HCC patients.

### Initial Operation

Ten patients (6 HEP, 4 HCC) underwent primary resection and 32 children had biopsy alone (29 operative, 3 percutaneous) (Table 1). Estimated blood loss (EBL) for resections was 145 mL for HEP and 4,000 mL for HCC patients ( $P < .05$ ). Pathology confirmed negative margins in 5 of 6 HEP and 2 of 4 HCC children. There was one HCC operative death following left lobectomy with a 10,000-mL EBL. Both HCC patients who underwent trisegmentectomy developed subphrenic abscesses, which progressed to an empyema and bronchopleural fistula in one, necessitating a right lower lobectomy of the lung. There were no complications in the six primarily resected HEP patients.

### Second-Look Procedure

Sixteen children (10 HEP, 6 HCC) had sufficient response to chemotherapy to warrant a second-look exploration an average of 5 months following diagnosis. Eight HEP patients underwent resection (EBL, 1,100 mL), which included 6 trisegmentectomies, whereas only 2 HCC children could undergo resection (Table 1). Resection margins were negative for tumor in 9 of 10 patients (exception was HCC trisegmentectomy). One HEP patient suffered an intraoperative cardiac arrest from arrhythmia and subsequent death following right trisegmentectomy. One HCC patient and one HEP patient developed a biliary fistula that closed without operative intervention and one HEP child experienced a wound infection.

## Transplantation

Eighteen children underwent laparotomy for potential total hepatectomy and OLT. Three children had widespread intraabdominal metastases. Thirteen children underwent total hepatectomy and OLT and 2 children underwent the cluster procedure. Three children were returned to the operating room within 48 hours of their transplant for bleeding (2) or suspected intestinal perforation (1). Eleven children experienced acute rejection episodes requiring immunosuppressive changes and one child required retransplant for chronic rejection. Bacterial and viral infections were common: coagulase-negative staphylococcal bacteremia (3), cytomegalovirus hepatitis (2), respiratory syncytial virus (2), *Candida* peritonitis (1), and *Cryptosporidium* (1).

## Survival

Overall survival for HEP patients was 14 of 21 (67%), with a follow-up of  $2.4 \pm 2.6$  years (Table 2). Six HEP patients underwent primary resection: two died during adjuvant chemotherapy, one died of metastatic disease, and one required OLT for tumor recurrence. Thus, 2 of 6 (33%) patients are alive with no evidence of disease (NED) at 10.5 and 4.5 years following primary resection. Eight patients underwent delayed resection; 7 (87%) are alive with NED at  $1.5 \pm 1.1$  years ( $P = .06$  v primary resection). Two patients died of progressive disease having undergone biopsy alone.

Overall survival for HCC was 6 of 21 (29%) ( $P < .05$  v hepatoblastoma) (Table 2). Four children underwent primary excision: one is alive (7.5 years). Two children underwent delayed resection: one is alive with NED (3.2 years) and the other died following OLT and subsequent tumor recurrence. Seven patients died of progressive disease prior to tumor resection.

Nine of 15 (60%) transplanted children are presently alive with NED ( $1.9 \pm 0.5$  years), including 5 of 6 (83%) HEP children ( $1.3 \pm 0.9$  years) and 4 of 9 (44%) HCC children ( $2.3 \pm 1.2$  years). One child who underwent a cluster procedure for HCC is alive with NED (off all exogenous insulin) at 14 months posttransplant. All six transplant deaths were due to malignancy. One HCC child died of severe lymphoproliferative disease (Burkitt's lymphoma) 8 years posttransplantation. The remaining five deaths were secondary to recurrence of the initial tumor in the transplanted liver (1), distant site (3), or both (1). Prognostic factors for recurrence (vascular invasion, lymph node involvement, intraabdominal metastases) were evaluated in all transplant patients. Four of six HEP patients had at least one poor prognostic factor, but three of those four are alive with NED. Six of nine HCC patients had at least one factor present, and two of those six are presently alive with NED (Table 3).

## Chemotherapy

Three of seven children (43%) who received adjuvant chemotherapy following primary tumor resection survived. Preoperative chemotherapy converted 10 of 32 (31%) initially unresectable tumors (8/15 HEP, 2/17 HCC) to removable at a second-look procedure; only one (HCC) had a positive margin for tumor. Three deaths were directly attributable to chemotherapy. Two children died of sepsis during a pancytopenic period while receiving adjuvant therapy. One child died as the result of an intraoperative cardiac arrhythmia ascribed to Adriamycin toxicity and another child developed nonlethal Adriamycin cardiotoxicity. Restrictive lung disease developed in one patient following bleomycin therapy.

All children developed nausea and vomiting following chemoembolization; one also had significant elevation of her liver transaminases. There were no technical complications related to angiography for chemoembolization.

## DISCUSSION

In their classic 1967 monograph Ishak and Glunz were the first to classify childhood epithelial liver neoplasms into hepatoblastoma and hepatocarcinoma.<sup>5</sup> They reviewed 47 such cases from the Armed Forces Institute of Pathology, reporting that 0 of 12 HCC children and 10 of 35 (29%) HEP patients survived. They particularly noted that 9 of 10 (90%) of the survivors had undergone resection. Subsequently, a 1974 survey of the Surgical Section of the American Academy of Pediatrics reported survival rates of 35% (45/129) for HEP and 13% (12/98) for HCC.<sup>6</sup> Importantly, no HCC or HEP patient survived who did not undergo resection. Thus, it became apparent that resection was required to cure malignant liver tumors in children.

However, primary standard hepatic resection is feasible only in a minority of patients.<sup>7</sup> Various surgical techniques have been used to increase the percentage of resectable tumors: profound hypothermia and circulatory arrest,<sup>8</sup> hemodilutional anesthesia,<sup>9</sup> total hepatic vascular exclusion,<sup>10</sup> and concomitant liver and inferior vena cava resection.<sup>11</sup> However, none of these techniques have reliably increased the number of liver tumors amenable to partial hepatectomy. Efforts using chemotherapy to increase the percentage of children able to undergo resection were not initially encouraging.<sup>5</sup> It wasn't until 1982, when Evans et al<sup>12</sup> reported the results of a cooperative CCSG and Southwest Oncology Group (SWOG) study, that combination chemotherapy was shown to affect a significant percentage (12/27) of unresectable liver malignancies. In that same year, Weinblatt et al<sup>13</sup> reported that 7 of 8 (87%) unresectable childhood hepatic malignancies treated with chemotherapy exhibited a pronounced clinical response; four HEP children were able to have complete surgical excision of residual disease and one HCC patient had complete disappearance of all disease without surgery. More recently, continuous-infusion Adriamycin and cisplatin facilitated delayed hepatic resection in 20 of 34 (59%) initially unresectable liver tumors.<sup>1</sup> In the present series preoperative chemotherapy facilitated removal of 8 of 15 HEP but only 2 of 17 HCC tumors (one with positive margins) by delayed resection.

The present data also indicated that those patients with HEP undergoing primary resection fared worse (2/6 NED) than those who underwent initial biopsy, chemotherapy, and second-look procedure (7/8 NED), although follow-up lengths were not comparable. A similar result was also seen at Children's Hospital of Los Angeles, where mean and 2-year survival for initially resected tumors were 23 months and 37.5%, respectively, versus 4 years and 100% for those initially undergoing chemotherapy.<sup>14</sup> However, this has not been a universal finding, and in the CCSG/POG experience, survival following delayed resection and primary resection was 41% and 58%, respectively.<sup>1</sup>

This apparent improvement in survival by delayed resection has been accompanied by a definite increase in operative morbidity. In our series, EBL for primary versus delayed HEP resection of was 143 mL versus 1,100 mL ( $P < .05$ ). Similarly, there was one intraoperative death, one biliary fistula, and one wound infection in the eight HEP patients undergoing delayed resection, whereas there were no complications in the six children who were primarily resected. The recent CCSG/POG intergroup prospective study reported similar findings, with morbidity rates of 8% and 25% for primary and delayed resection.<sup>1</sup>

Partial hepatectomy, either primary or delayed, was considered first for all patients in this series. Twenty patients were initially evaluated elsewhere, felt to be unresectable, and were then referred for OLT. Our transplant team, which has one of the world's largest experiences with partial hepatic resection,<sup>15</sup> performed partial hepatectomies whenever possible. However, because overall resectability rates for primary liver malignancies rarely exceed 30% to 40%, total hepatectomy and liver replacement is a logical alternative to achieve complete resection.<sup>16</sup> Total hepatectomy and OLT was used only when standard resection was not possible.

The data cautiously support the role of transplantation in pediatric hepatic malignancies. Five of 6 (83%) patients transplanted for HEP are presently alive with NED (1.3 years). Four of 9 children (44%) with HCC are presently alive and NED (2.3 years), including a 15-year-old girl who is over 1 year postoperation from upper abdominal exenteration, OLT, and islet cell transplantation. Obviously, longer follow-up periods will be required before this optimism can be substantiated, but a recent 10-institution report on 12 children who underwent OLT for HEP found 50% survival at 24 to 70 months without recurrence.<sup>17</sup>

Many of the early successes in liver transplantation were obtained in patients with hepatic tumors. However, the tumors frequently recurred, often in the first 2 years. In 1985, Iwatsuki et al reported tumor recurrence in 5 of 6 (83%) children who received liver replacement for unresectable hepatic malignancies.<sup>18</sup> Israel Penn, in a recent review of the Cincinnati (previously Denver) Transplant Tumor Registry, evaluated overall recurrence rates and 2- and 5-year tumor-free survivals in 597 patients (both adult and children) transplanted for hepatic malignancies.<sup>2</sup> Best results were seen in incidental hepatoma (15% recurrence, 21% and 11% 2- and 5-year follow-up), HEP (40%, 32%, and 7%, respectively), and fibrolamellar hepatoma (42%, 32%, and 6%, respectively). HCC had a 41% recurrence with 2- and 5-year survivals of 7% and 3%.

Factors that help predict tumor recurrence are poorly understood at the present time. Ringe et al,<sup>19</sup> in a retrospective analysis of 95 patients transplanted for malignancy, found a better prognosis in earlier disease stages and in recipients without lymph node involvement. Iwatsuki et al found similar results in HCC patients; vascular invasion, tumor number, tumor shape, and lymph node invasion were found to be significant independent factors affecting survival.<sup>20</sup> However, in a review of 28 patients transplanted for hepatic malignancies (primary and metastatic) at UCLA, no specific prognostic factors correlating with survival or recurrence could be elucidated.<sup>21</sup> Adult patients made up the vast majority of cases in those three reports, and there are little data on children transplanted for hepatic malignancies. Of our 15 transplanted children, 10 (4 HEP and 6 HCC) had at least one of the proposed prognostic factors for tumor recurrence. Five of those 10 are currently alive with NED, from 5 to 36 months posttransplant. Included in the survivors are a 2-year-old child who had omental involvement and vascular invasion (follow-up 3 years) as well as several children who had tumor thrombus removed from their portal vein.

Complete tumor extirpation remains the primary goal when treating pediatric hepatic malignancies. Primary resection, if done without excessive morbidity and mortality, should be accomplished whenever possible. Preoperative chemotherapy has allowed resection for previously unresectable disease, particularly in HEP patients. Although it is unclear whether primary resection offers superior survival rates to delayed resection, operative morbidity is increased in delayed procedures. Total hepatectomy and OLT improves survival in those who are unresectable following chemotherapy and is potentially a valuable adjunct in the treatment of childhood malignant liver tumors. However, due to the shortage of available donor organs and the unanswered questions regarding tumor recurrence, OLT for hepatic malignancy should be performed only at transplant centers that use carefully planned protocols.

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**Table 1**

## Standard Hepatic Resections Performed, Including Both Primary and Delayed Procedures

Primary Resection (no.)	Delayed Resection (no.)
HEP	
Left lobectomy (2)	Left lobectomy (1)
Right lobectomy (2)*	Left trisegmentectomy(1)
Right trisegmentectomy (1)	(1) Left lateral segmentectomy (1)
Right anterior segmentectomy (1)	Right trisegmentectomy (5)
HCC	
Left lobectomy (2)*	Right lobectomy (1)
Right trisegmentectomy (2)*	Right trisegmentectomy (1) <sup>†</sup>

Abbreviations: HEP, hepatoblastoma; HCC, hepatocellular carcinoma.

\* One of the cases had margins of resection positive for tumor.

<sup>†</sup> Margins of resection positive for tumor.



**Table 2**

Overall Treatment Results for Hepatoblastoma and Hepatocellular Carcinoma Patients

	Overall Survival	Primary Resection	Delayed Resection	OLT	Cluster	Biopsy
HEP	14/21* (67%)	2/6 <sup>‡</sup> (33%)	7/8 (87%)	5/6 (83%)	—	0/2 (0%)
HCC	6/21* (29%)	1/4 (25%)	1/2 <sup>‡</sup> (50%)	3/7 (44%)	1/2 (50%)	0/7 (0%)

Abbreviations: HEP, hepatoblastoma; HCC, hepatocellular carcinoma; OLT, total hepatectomy and orthotopic liver transplantation.

\*  $P < .05$ .

<sup>‡</sup> One of the two survivors is status post OLT.

<sup>‡</sup> The child who died did so following tumor recurrence, OLT, and subsequent tumor re-recurrence.

**Table 3**  
 Prognostic Factors Associated With Tumor Recurrence and Survival Following Transplantation

	Case No.	Vascular Invasion	Lymph Node	Metts	Outcome*	Follow-Up (mo)
HEP	1	+	-	-	Alive	5
	2	+	+	+	Dead	1
	3	-	+	-	Alive	13
	4	+	+	+	Alive	36
HCC	1	+	-	+	Dead	6
	2	+	-	-	Dead	30
	3	+	-	-	Alive	32
	4	+	+	-	Dead	14
	5	+	+	-	Alive	13
	6	+	-	-	Dead	7

Abbreviations: HEP, hepatoblastoma; HCC, hepatocellular carcinoma; Mets, intraabdominal metastases.

\* None of the patients who are alive have recurrent disease.