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

By Edward P. Tagge, Derya U. Tagge, Jorge Reyes, Andreas Tzakis, Shunzaburo Iwatsuki, Thomas E. Starzl, and Eugene S. Wiener

Pittsburgh, Pennsylvania

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 (IPH 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.

Copyright © 1992 by W.B. Saunders Company

INDEX WORDS: Hepatoblastoma; hepatocellular carcinoma; liver transplantation.

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. 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.

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 ± 0.8 years and 9.9 ± 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/mm³ and 359,000/mm³ for HEP and HCC, respectively (normal, 150,000/mm³ to 450,000/mm³; P < .003). a-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.\(^1\) 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.\(^1\)

**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. Cytoxan, 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, folic acid, and interferon.

**Statistics**

Descriptive analyses were by unpaired Student's t tests, with mean ± 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 “inhouse” 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 \((P < 0.05)\). 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.

**Table 1. Standard Hepatic Resections Performed, Including Both Primary and Delayed Procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Primary Resection (no.)</th>
<th>Delayed Resection (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lobectomy (2)</td>
<td>Left lobectomy (1)</td>
<td></td>
</tr>
<tr>
<td>Right lobectomy (2)*</td>
<td>Left trisegmentectomy (1)</td>
<td></td>
</tr>
<tr>
<td>Right trisegmentectomy (1)</td>
<td>Left lateral segmentectomy (1)</td>
<td></td>
</tr>
<tr>
<td>Right anterior segmentectomy (1)</td>
<td>Right trisegmentectomy (5)</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lobectomy (2)*</td>
<td>Right lobectomy (1)</td>
<td></td>
</tr>
<tr>
<td>Right trisegmentectomy (2)*</td>
<td>Right trisegmentectomy (1)*</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HEP, hepatoblastoma; HCC, hepatocellular carcinoma.
*One of the cases had margins of resection positive for tumor.
†Margins of resection positive for tumor.
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 ± 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 ± 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 ± 0.5 years), including 5 of 6 (83%) HEP children (1.3 ± 0.9 years) and 4 of 9 (44%) HCC children (2.3 ± 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.

---

**Table 2. Overall Treatment Results for Hepatoblastoma and Hepatocellular Carcinoma Patients**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Vascular Invasion</th>
<th>Lymph Node</th>
<th>Mets</th>
<th>Outcome</th>
<th>Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEP 1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Alive</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dead</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Alive</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Alive</td>
<td>36</td>
</tr>
<tr>
<td>HCC 1</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Dead</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Alive</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Alive</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Alive</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
<td>7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Vascular Invasion</th>
<th>Lymph Node</th>
<th>Mets</th>
<th>Outcome</th>
<th>Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEP 1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Alive</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Dead</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Alive</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Alive</td>
<td>36</td>
</tr>
<tr>
<td>HCC 1</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Dead</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Alive</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Alive</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Alive</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
<td>7</td>
</tr>
</tbody>
</table>

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

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

In their classic 1967 monograph Ishak and Glunz were the first to classify childhood epithelial liver neoplasms into hepatoblastoma and hepatocarcinoma. 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. 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. Various surgical techniques have been used to increase the percentage of resectable tumors: profound hypothermia and circulatory arrest, hemodilutional anesthesia, total hepatic vascular exclusion, and concomitant liver and inferior vena cava resection. 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. It wasn't until 1982, when Evans et al 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 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. 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. 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.

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.

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, 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. 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.

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. 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. Best results were seen in incident hepatic carcinoma (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., 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. 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. 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.

REFERENCES

16. Starzl TE, Koep LJ: Surgical approaches for primary and metastatic liver neoplasms, including total hepatectomy with orthotopic liver transplantation. Prog Clin Cancer 7:181-193, 1978
Discussion

**D.R. King (Columbus, OH):** This is a very interesting and provocative report and I just want to caution all of you to read the paper very carefully. You really have to dig into the paper to understand it well and I think that resection is the treatment for hepatoblastoma and hepatocellular carcinoma and transplant should be appropriately reserved for a few patients. I have some concern with the data. The overall survival for your stage I and II disease patients is 40%, whereas patients with stage III and IV disease had a 50% survival. You did better with the worse patients. Can you explain that to me? The answer to me, for one reason, would be that the data are not mature. The majority of these patients seem to have been followed for less than 2 years and many of them may have been off chemotherapy for less than 6 to 12 months. As an example, of the 15 children who underwent OLT there was a total follow-up of 28 patient years. However, one of the survivors lived 7 years, so that's a bit troublesome and to report these survivals as percentages when the follow-up has been so short may not be particularly meaningful. Do you have any survival curves that might help elucidate for us in a better statistical fashion what's happening to these patients? Were any of the OLT survivors patients who had incidental tumors? What were the selection criteria for orthotopic liver transplantation? Certainly the patient whose CT scan you showed seemed to have been a candidate for primary resection. It's interesting that surgical therapies seem to follow the interests of the organization. For instance, at Pittsburgh you've got a relatively low primary resection rate—25% as compared with 40% to 50% where those of us who don't do transplants perhaps might labor a little harder in the vineyard of resection. You also seem to have a low secondary resection rate in the CCSG study of continuous infusion. In other words, of the patients treated with chemotherapy, 60% of them underwent a secondary resection successfully, whereas your resection rate was only a third. And it's interesting in the CCSG study of the continuous-infusion doxorubicin, there was an overall 46% survival at 29 months but this is only taking patients in stages II, III, and IV, whereas in this study the survival is about the same and includes a significant percentage of patients with stage I disease. So, again, you and the institution are to be congratulated on a very successful transplant program but I think transplant needs to be kept in perspective and it is not treatment for these tumors, it is treatment for a small minority of these tumors. Perhaps for those with unresectable hepatocellular carcinoma, it could be considered more as a primary mode of therapy, which I think would be appropriate.

**Edward P. Tagge (response):** I thank Dr King for his comments. We do agree that this is a preliminary report and that the data, particularly for the transplanted patients, are not mature. However, Saul Penn recently presented data of some 600 liver transplants done for malignancy at the Central Surgical Society. In his study recurrence of the primary tumor occurred within the first 2 years in the vast majority (85%) of patients. Regarding our resection rate, it is not as good as the CCSG study that was presented last year, but certainly is in line with many other reports concerning primary resection for hepatic malignancies. In addition, half of our patients were referred from other institutions with "unresectable" disease. Thus, there was a significant bias toward advanced stage disease, which I think may help explain why primary resection was not more frequently performed.

These data did not include the 8 children with incidental tumors who have undergone liver transplantation. All 8 are alive with no evidence of disease at the present time.

Standard partial hepatic resection was the initial goal of both the pediatric surgery and transplant surgery services. Our transplant surgeons have one of the world's largest experiences with partial hepatectomies and, thus, transplantation was not considered until the child was felt to be unresectable by standard methods. If the patient was unresectable aggressive chemotherapy, including chemoembolization, was used prior to and following total hepatectomy and orthotopic liver transplantation.