Review of outcomes of primary liver cancers in children: Our institutional experience with resection and transplantation

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Background. Operative intervention plays an important role in the management of primary liver cancers in children. Recent improvements in diagnostic modalities, pre- and postoperative chemotherapy, and operative technique have all led to improved survival in these patients. Both hepatic resection and orthotopic liver transplantation are effective operations for pediatric liver tumors; which intervention is pursued is based on preoperative extent of disease. This is a review of our institution’s experience with operative management of pediatric liver cancer over an 18-year period.

Methods. A retrospective chart review from 1990 to 2007 identified patients who were ≤18 years old who underwent operative intervention for primary liver cancer. Demographics, type of operation, intraoperative details, pre- and postoperative management, as well as outcomes were recorded for all patients.

Results. Fifty-four patients underwent 57 operations for primary liver cancer, 30 of whom underwent resection; the remaining 27 underwent orthotopic liver transplantation. The mean age at diagnosis was 41 months. Twenty patients had stage 1 or 2 disease and 34 patients had stage 3 or 4 disease. Forty-eight (89%) patients received preoperative chemotherapy. Postoperative chemotherapy was given to 92% of patients. Mean overall and intensive care unit duration of stay were 18 and 6 days, respectively. About 45% of patients had a postoperative complication, including hepatic artery thrombosis (n = 8), line sepsis (n = 6), mild acute rejection (n = 3), biliary stricture (n = 2), pneumothorax (n = 2), incarcerated omentum (n = 1), Horner’s syndrome (n = 1), and urosepsis (n = 1). Only 6 patients had a recurrence of their cancer, 5 after liver resection, 3 of whom later received a transplant. There was only 1 recurrence after liver transplantation. There was 1 perioperative mortality from cardiac arrest. Overall survival was 93%.

Conclusion. Operative intervention plays a critical role in the management of primary liver cancer in the pediatric population. Neoadjuvant chemotherapy can be given if the tumor seems unresectable at diagnosis. If chemotherapy is unable to sufficiently downstage the tumor, orthotopic liver transplantation becomes the patient’s best option. Our institution has had considerable experience with both resection and liver transplantation in the treatment of pediatric primary liver cancer, with good long-term outcomes. (Surgery 2010;148:778-84.)

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Primary liver neoplasms are relatively uncommon in children. The most common pediatric liver cancer is hepatoblastoma which has an incidence of about 1 per 1 million children.1,2 Hepatocellular carcinoma is even less common with an incidence of <0.5 per 1 million children. Improvement in pediatric liver transplant outcomes as well as better chemotherapeutic regimens has led to a much improved prognosis for pediatric liver tumors.3-6 Prospective multicenter studies have shown a long-term survival of 70–80% for children with hepatoblastoma. Several recently published studies have reviewed outcomes of treatment for pediatric liver cancers.7-10 The current study is among the largest in the number of cases reviewed, but also the only such study to present a nearly equal
representation of resection and transplantation for the treatment of pediatric liver cancers.

MATERIALS AND METHODS

After obtaining institutional review board approval (#7070164), we retrospectively reviewed the charts of all patients who underwent an operation for a liver cancer over an 18-year period at the Children’s Hospital of Pittsburgh of the University of Pittsburgh Medical Center. Any patient who underwent operative intervention for a pediatric liver cancer was included.

Charts were reviewed for patient age; preoperative evaluation (alpha-fetoprotein [AFP] level, size and location of the neoplasm on computed tomography [CT], and presence of metastases); preoperative chemotherapy; operative data (resection versus transplant, estimated blood loss [EBL], fluid volume given, and duration of operation); tumor characteristics (stage, size, and margins); and outcomes (duration of stay, 30-day morbidity, 30-day mortality, graft survival, recurrence, and overall survival).

The group of patients who underwent operative intervention for liver cancers were analyzed on the whole and also as 2 separate groups—those undergoing liver resection and those receiving a liver transplant. Differences between the transplant and resection groups were evaluated using either the Chi-square or Fisher’s exact tests for categorical variables and the Mann-Whitney U test for continuous variables using SPSS software (version 15.0; SPSS Inc., Chicago, IL). A 2-sided P value of < .05 was considered significant.

RESULTS

Our database search yielded 54 patients who underwent 57 operations. There were 30 liver resections and 27 liver transplants. Three patients first underwent a resection and later received a liver transplant after the liver cancer recurred. The mean age of patients undergoing operative intervention for liver cancer was 41.2 months (range, 2–189). There was no difference in patient age between the children undergoing liver resections and those receiving a liver transplant. Forty-two children had hepatoblastomas, 6 had hepatocellular carcinoma, and 6 neoplasms were of different histology, including undifferentiated sarcoma, embryonal sarcoma, and yolk sac tumor.

Mean tumor size as assessed on preoperative CT was 740 cm³ (range, 3–8,372). Tumor size was not different between the 2 groups. Mean EBL was 1,060 mL (0–15,000) with almost no difference in blood loss between the resection and transplant groups. Duration of stay in the intensive care unit (ICU) was 6.4 days (range, 0–64) with a mean overall duration of 18 days (range, 5–120). Both ICU and overall durations of stay were significantly greater in the transplant group (10 vs 3 days [P < .001] and 27 vs 9 days [P < .001]). The mean AFP level was 113,008 ng/mL (range, 1–972,000). There was no difference in AFP level between the transplant and resection groups.

Almost all patients underwent preoperative chemotherapy. Six patients did not and these were all in the liver resection group. Five out of 6 of these patients had stage 1 or 2 disease. One patient had a stage 4 yolk sac liver neoplasm. Accordingly, nearly all patients also underwent postoperative chemotherapy with no predilection to postoperative chemotherapy in either the resection or the transplant group. Six patients had a positive margin. One patient who had a positive margin later required a transplant.

Most children undergoing liver resection had stage 1 or 2 disease (18/29 patients), whereas those undergoing transplant most commonly had stage 3 or 4 disease (23/25; P < .001). Overall survival for all patients was 93%. Overall survival in the hepatoblastoma group was 95% (40/42 patients). Of the patients with hepatoblastoma, 21 underwent a resection and 23 underwent liver transplantation, 2 of which were for recurrence after resection. Overall survival in the hepatocellular carcinoma group was 67% (4/6 patients). Of the patients with hepatocellular carcinoma, 5 underwent resection and 2 underwent liver transplantation, 1 of which was for recurrence after resection. Of patients who underwent liver resection, overall survival was 90% (27/30 patients). Overall survival was 93% in patients undergoing liver transplantation (25/27). There were 6 patients who developed recurrence of disease, 5 from the resection group, 3 of whom later had a transplant, and only 1 from the transplant group. One of the patients who had a transplant after the tumor recurred died. Twenty-six patients (46%) had a postoperative complication, 8 in the resection group (27%), including urosepsis, line sepsis, Clostridium difficile, Horner’s syndrome, pneumothorax, and pulmonary congestion, and 18 in the transplant group (67%), including hepatic artery thrombosis, biliary stricture, cholangitis, wound dehiscence, ascites, chest hematoma, C. difficile, pancreatic injury, hemotorax, and line sepsis (Table 1).

The incidence of hepatic artery thrombosis (8/27; 30%) is consistent with previously published data which report that this complication may complicate as many of 42% of pediatric liver transplants.11
DISCUSSION

The prognosis for children with hepatoblastoma has improved over the last few decades. This finding is likely due to improvements in both operative technique and chemotherapy.\textsuperscript{12-14} Recent studies have shown the ability of preoperative chemotherapy to convert unresectable neoplasms into operable lesions\textsuperscript{15} and the importance of a complete resection. A complete resection only requires a margin of a few millimeters.\textsuperscript{12,13,16,17} The conclusions of those important studies have led to improved long-term survival in recent prospective and retrospective trials. The SIOPEL-1 study,\textsuperscript{4} the Japanese Study Group for Pediatric Liver Tumor-1,\textsuperscript{18} and the German Cooperative Pediatric Liver Tumor Study\textsuperscript{12,14} have all shown long-term survival rates of 75–78%. These studies have examined largely the results of hepatic resection for primary liver neoplasms after administration of preoperative chemotherapy, with very few patients treated with liver transplantation.

Currently, liver transplantation has become a very effective treatment strategy for certain children with primary liver cancer. Patients who respond to chemotherapy but have unresectable cancers with no evidence of persistent extrahepatic disease or have minimal metastatic disease such as a solitary pulmonary metastasis are potential candidates for liver transplantation.\textsuperscript{19} Neoplasms that are stable or grow despite appropriate chemotherapy are a relative contraindication to liver transplantation.\textsuperscript{20,21} The criteria established by SIOPEL recommend that liver transplantation should be considered in patients with the following characteristics: neoplasms in all 4 liver sections, tumor extension into the vena cava or all 3 hepatic veins, invasion of the main and/or left and right portal veins, or recurrent disease after resection (rescue transplant).\textsuperscript{22} Applying these criteria, multiple studies have shown a long-term survival of 50–88%.\textsuperscript{19,20,23-27}

<table>
<thead>
<tr>
<th>Total (n = 57)</th>
<th>Liver resection (n = 30)</th>
<th>Transplant (n = 27)</th>
<th>P value</th>
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<tr>
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<td>Preoperative CT size (cm\textsuperscript{3})</td>
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<td>Preoperative chemotherapy</td>
<td>48 (89%)</td>
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<td>30-day morbidity</td>
<td>26 (46%)</td>
<td>8 (27%)</td>
<td>18 (67%)</td>
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<tr>
<td>Recurrence</td>
<td>6 (12%)</td>
<td>4 (17%)</td>
<td>1 (4%)</td>
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<tr>
<td>Survival</td>
<td>47/52 (90%)</td>
<td>25/26 (89%)</td>
<td>24/26 (92%)</td>
</tr>
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*Statistically significant.
|Some patients were lost to follow-up.

AFP, Alpha-fetoprotein; CT, computed tomography; ICU, intensive care unit; LOS, length of stay.

Table I. Demographics, tumor stage, preoperative treatment, operative details, and outcomes for pediatric liver tumors with comparison of resection and transplant groups.
Most of our patients (42/54) had hepatoblastomas; very few had hepatocellular carcinoma (Table II). Given the less aggressive nature and improved prognosis of hepatoblastoma, this finding may account for our excellent overall survival rate (93%). Overall survival was much better in our patients with hepatoblastoma (95%) than in those with hepatocellular carcinoma (67%), consistent with data published previously. Aggressive use of preoperative chemotherapy and liver transplantation may also be responsible for our survival rate.

Tumors in the transplant group tended to be larger than in the resection group (860 vs 669 cm$^3$; not significant); the trend is not surprising given that transplants are reserved typically for children with extensive bilobar or locally advanced disease. Accordingly, patients undergoing resection typically had a lesser stage of disease. Of 29 resection patients who had a documented stage, 18 had either stage 1 or 2 disease at diagnosis, whereas only 2 of 25 stage-documented patients who underwent transplantation were stage 1 or 2 at diagnosis.

Children are more vulnerable to blood loss than adults during liver surgery. The EBL ranged from 0 to 15,000 mL (median, 325) in all patients. One patient with stage 4 hepatocellular carcinoma died from exsanguination during liver resection. This patient required 15 L of blood. Many of our hepatic resections were extensive and, therefore, EBL was no different between the resection and transplant groups.

All but 6 patients underwent preoperative chemotherapy. These 6 patients underwent liver resection, and all but 1 had stage 1 or 2 disease. One patient had a stage 4 yolk sac liver cancer. Nearly all patients underwent postoperative chemotherapy, and 3 of the 4 who did not undergo a liver transplant for a stage 3 liver cancer.

Mean overall duration of stay was 16 days (range, 5–120) with an average ICU stay of 5.9 days (range, 0–64). Not surprisingly, patients who underwent liver transplantation had significantly greater duration of stay overall and in the ICU, likely owing to greater operative times, a slightly greater rate of complications, and more complex immediate postoperative care.

We had a complication rate of 46% after operative intervention for primary liver cancer at our institution. Our morbidity was slightly greater than recent studies, which have shown a complication rate of 16–29%. This observation is explained by our much greater representation of patients treated with liver transplantation. In this study, patients had a significantly greater morbidity after liver transplant (67%) as compared with resection. Our observed morbidity after liver resection (27%) is very similar to the complication rate shown in these recent studies.

Primary liver cancers are rare neoplasms of childhood. Hepatoblastomas are the most common histology for pediatric primary liver cancers. Recent advancements in operative techniques, chemotherapeutic regimens, and liver transplantation have contributed to improved prognosis for primary liver cancers of childhood. These improvements are most evident for hepatoblastoma. The current study showed a very good long-term survival rate of 90% with an even better survival rate when specifically looking at children with hepatoblastoma (95%). Aggressive management of these patients with neoadjuvant chemotherapy, radical resection, and/or liver transplantation for locally advanced disease or for recurrence can lead to excellent outcomes for primary liver cancers in children.

### REFERENCES

with hepatoblastoma—results from the International Society of Paediatric Oncology (SIOP) study SIOPEL. 1. Eur J Cancer 2000;36:1418-25.


**DISCUSSION**

Dr Benedict Nwomeh (Columbus, OH): To my knowledge, no other institution has reported performing nearly as many transplantations as primary resections for this disease. And, in fact, fully half of your patients received liver transplantation as you reported. Here is my first question: Do you believe that transplantation should be used more as primary treatment than as a rescue procedure? My second question is in regard to your use of neoadjuvant chemotherapy. As you know, in many centers neoadjuvant chemotherapy is considered to be used primarily as a means of downstaging unresectable tumors. Yet I observed that nearly all your patients received neoadjuvant chemotherapy, perhaps more in line with the SIOPEL recommendations. Can you briefly explain your institutional philosophy toward chemotherapy for primary tumors? Finally, have you performed a pulmonary resection for mets from hepatoblastoma, and, if so, would you consider transplantation in a patient with an isolated pulmonary metastasis?

Dr Marcus Malek (Pittsburgh, PA): Thank you very much, Dr Nwomeh, for your discussion and questions. Your first question, just to repeat it, essentially you are asking if we think that transplantation should be used more often specifically as a primary method of therapy as opposed to a rescue transplant after recurrence of disease. I think that is one of the very important things that the PRETEXT staging system allows us to do. The data do, in fact, show that kids do much better if they receive a primary transplant than they do if they are resected first, followed by a rescue transplant.

If we can identify the kids who are not going to be resectable even with chemotherapy, and will require a transplant, rather than resecting them and seeing how
they do, they actually do much better. So I would say, yes, we need to be very critical in our imaging preoperatively, and having an understanding that not to be afraid, particularly because our numbers were so good, to proceed with a liver transplant primarily as opposed to a rescue transplant. So I feel that certainly that is important.

Your second question was about the use of neoadjuvant chemotherapy. As you said, our institution did, in fact, use neoadjuvant chemotherapy in most cases, and that is in concordance with the SIOPEL study. A number of these international groups, including the SIOPEL group, the German cooperative group that has been very involved in looking at chemotherapy in these kids, they do tend to recommend neoadjuvant chemotherapy in all cases. Some institutions will go ahead in a stage 1 or 2 that seems very easily resectable to do it first. We sort of look to those large studies, many of which are prospective, randomized trials. We fall under their recommendations and we tend to give preoperative chemotherapy to nearly all the kids. There are a few—5 out of the 6 that did not have stage 1 or 2 disease only—and those were kids that we felt could be resected early on. And that is the reason why we did it in those kids. For the most part, we do give neoadjuvant chemotherapy.

Your third question was about kids with pulmonary metastases and whether we would proceed with liver transplantation in those kids. That is certainly an issue, an area of some debate. I believe that it certainly depends on the extent of pulmonary metastases. I think if you have a solitary module near the periphery that would be easy to resect near the time of your primary operation, I believe that you can proceed with a liver transplantation in those kids, if you are sure that that is the total extent of disease. But that is one of those gray areas where you need to be very careful, because you certainly do not want to transplant a kid who you think has a number of metastases, or who is obviously going to recur because of the tumor load throughout the body.

Dr Dennis Lund (Madison, WI): A very interesting group of patients. But right now, I would say our rate of primary resections versus transplants for primary liver tumors in children is running about 4 to 1, nowhere near 1 to 1 where you are. I wonder if your referral pattern is such that you are having a lot of patients who are treated primarily at outside institutions then referred in as unresectable patients, primarily for liver transplantation. And I wonder if you looked at whether these are kind of internal referrals or external referrals.

You commented about neoadjuvant use. In your 18 years in your study, actually the practice in the United States around neoadjuvant therapy has changed. And despite the fact you did not see any difference in survival in your first 8 years versus your second 10 years, did you see any difference in the neoadjuvant use in those 2 periods of time?

I am just interested in who is actually doing the liver resections in your institution in children. Are they hepatobiliary surgeons, are they transplant surgeons or are they pediatric surgeons?

Finally, any experience using ablative therapy like cryoablation or radiofrequency ablation in patients who have a closed resection margin?

Dr Marcus Malek (Pittsburgh, PA): To go 1 by 1, I appreciate your commentary on how many transplants the institution is doing. It certainly is quite a high number and the 1-to-1 ratio was surprising to all of us when we reviewed it. But in terms of internal versus external referrals, I believe that because I was the one who actually sat and reviewed the data I can comment on that. We did not actually look at that as part of our study. There were a fair number of external referrals, and these were typically kids that were pretty fraught with disease, had pretext 4 or had invasion of the vasculature. So, probably, part of the reason why our numbers are inflated somewhat is that we were getting referrals from outside institutions, who then went on to primary liver transplants.

We also did get a number of referrals from outside institutions where the tumor had recurred after primary resection. I think part of it is that as a whole the institution is relatively aggressive in terms of liver transplantation. Just to follow that up quickly with your third question in terms of who is doing them. Currently Dr George Mazariégos is very involved and Rakesh Sindhi is doing them. They are both liver transplant surgeons at Children’s Hospital in Pittsburgh.

Then, in terms of the chemotherapy, what has changed? The regimens have changed from decade to decade. Initially, we were using more 5-FU, more doxorubicin, I think cisplatin has been used throughout. Recent studies have shown that cisplatin monotherapy is probably just as good as cisplatin with doxorubicin. For the most part, our institution is using cisplatin doxorubicin. And before that was using a little bit of vincristine and 5-FU as well.

Your final question about ablative therapy, you were asking about kids who recurred, who had close margins. We did not really use ablative therapy in those kids.

Dr Frederick Rescorla (Indianapolis, IN): It looks like by your numbers at least 14 of the 20 stage 1 or 2s received preoperative chemotherapy, a group that most of us would probably consider amenable to primary resection. And I think it is important to at least recognize that some stage 1 tumors that have favorable histology may not need chemotherapy. So by administering preoperative chemotherapy, you may actually overtreat many of these children. Also by doing preoperative chemotherapy, you really upstage the patient and really commit them to further chemotherapy and perhaps even more chemotherapy than they needed. My question is if you saw someone now that might be amenable to a lobectomy or even a trisegmentectomy, would you give them preoperative chemotherapy? Would you ever consider upfront resection?

Dr Marcus Malek (Pittsburgh, PA): I think that sort of gets to one of the most controversial issues right now in pediatric liver tumors, particularly hepatoblastomas, and that is do you give neoadjuvant chemotherapy to everyone? Or in the population of kids that you mentioned, that exact population, do you go ahead and resect...
them, and then perhaps give postoperative chemotherapy? In our institution for the most part, we are giving preoperative chemotherapy. That being said, other institutions have shown very good outcomes within the same 5-year survival rates as those large studies without doing neoadjuvant chemotherapy in those kids. If I saw a kid with favorable histology with a PRETEXT 1 or 2 tumor, particularly a PRETEXT 1, that I felt would be easily resectable, obviously no metastases, I would go ahead and resect it and then give chemotherapy postoperatively.