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Liver Transplantation for Hepatoblastoma

The American Experience

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The current role of liver transplantation in treating malignant tumors of the liver is uncertain, except for select histologic types. Pooled data on the results of liver transplantation in 12 children with hepatoblastoma is presented here. One half of the children are alive 24 to 70 (44 ± 19) months after transplantation with no evidence of recurrence. Three patients (25%) died of tumor recurrence and three (25%) died of other causes. Unifocal and intrahepatic tumors were associated with better prognosis compared to the multifocal tumors and tumors with extrahepatic spread (p = 0.04 and 0.13). Microscopically vascular invasion and the predominance of embryonal and/or anaplastic epithelium were associated with a poor prognosis compared to the tumors with no vascular invasion and with predominantly fetal epithelium (p = 0.08 and 0.1). It is concluded that continued efforts to treat unresectable hepatoblastomas by liver transplantation is justified and the role of adjuvant chemotherapy in improving the results needs to be better defined.

AT THE TIME of the initial trials of clinical liver transplantation, the ideal indication was perceived to be a malignant tumor confined to the liver that could not be removed with partial hepatic resection.[1,2] However efforts to apply this concept were disillusioning because the incidence of recurrence after orthotopic liver transplantation was very high.[3] Nevertheless some malignant tumors in adults have been treated effectively with total hepatectomy and replacement of the liver.[4–7]

The possibility that hepatoblastoma should be considered in a special category was suggested by anecdotal accounts of children surviving for long periods after liver replacement for this indication. However there are no reports of a significant number of cases as to the long-term results of liver transplantation for hepatoblastoma.[7] We report here observations in 12 children with hepatoblastomas who were treated by liver transplantation in the United States.

Case Material

As of August 1988, 12 children had received 13 liver grafts for hepatoblastoma in 10 different medical centers in the United States. Data were collected on all patients regarding age, sex, previous liver resection, chemotherapy before and after the transplant, extent of gross disease at the time of transplant, recurrence after the transplant, and the patients' current clinical status (Table 1). Information on the histologic features of the tumors was obtained through review of the surgical pathology reports and, when necessary, by direct contact with the examining pathologists.

The 12 children were aged from 6 months to 11 years (42 ± 33 months); 6 were girls. Four underwent a hepatic resection 9 to 20 months before their transplant in an attempt to control the tumor. All children had markedly elevated serum alpha-feto-protein levels at the time of their transplantation. Only 1 of the 12 children had cirrhosis.

Extent of Gross Disease at Transplantation

The disease was entirely intrahepatic in six patients. Although another three patients had intrahepatic tumor, a tumor thrombus was also present in the main portal vein. The remaining three patients were thought to have direct extrahepatic tumor invasion at the time of surgery. However, in one of these patients, the excised portion of the right hemidiaphragm was merely adherent to the tumor with no histologic invasion. In seven patients with multifocal tumors the largest of the nodules measured 2.5 to 9.0 (m = 5.4) cm. Five patients had unifocal tumors infiltrating both lobes and/or the hilum of the liver. The size of these tumors varied form 5 to 18 (m = 12) cm in diameter.

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TABLE 1. *Patients with Hepatoblastoma Treated by Liver Transplantation*

Age, Sex	Prior Hepatic Resection	Pre-TX Chemo.	Gross Disease	Histologic Features	Post-TX Chemo.	Recurrence	Status
1.75 yrs. M	Yes	Yes	IH Unifocal	Predominantly F No vascular invasion	No	No	Died of Pneumocystis Pneumonitis; 9 mos.
4.5 yrs. M	Yes	Yes	IH + TT Multifocal	F + E Vascular invasion+	Yes	Yes Peritoneum; brain	Died of recurrence; 23 mos.
5 yrs. F	Yes	Yes	IH + TT Multifocal	Predominantly E Vascular invasion+	No	No	Died of hepatic artery thrombosis; 15 days
0.5 yrs. M	No	No	IH; Unifocal	E + A; No vascular invasion	No	No	Died of hepatic artery thrombosis; 4 mos.
1.5 yrs. F	No	No	IH; Unifocal	F; No vascular invasion	No	No	Alive; 66 mos.
4 yrs. M	Yes	Yes	IH Multifocal	E; Vascular invasion+	No	Yes Lungs; liver	Died of recurrence; 4 mos.
11 yrs. F	No	Yes	IH; Unifocal	F + E; No vascular invasion	Yes	No	Alive; 30 mos.
5 yrs. M	No	Yes	IH Multifocal	A; Vascular invasion+	No	No	Alive; 43 mos.
3 yrs. F	No	Yes	IH + TT Unifocal	Predominantly F Vascular invasion+	Yes	No	Alive; 32 mos.
2.5 yrs. F	No	No	EH Multifocal	F + E; Vascular invasion+	Yes	No	Alive; 24 mos.
2 yrs. F	No	Yes	EH + Multifocal	F + E + A Vascular invasion+ Lymph node+	No	Yes Brain; lungs	Died of recurrence; 35 days
2.3 yrs. M	No	Yes	IH Multifocal	E + A; Vascular invasion+	Yes	Yes Pulmonary 7 mos.	Alive; 70 mos.

IH, intrahepatic; EH, extra hepatic extension; TT, tumor thrombus in the main portal vein; F, fetal epithelium; E, embryonal epithelium; A, anaplastic epithelium.

Histologic Characteristics

In nine (75%) patients, the tumors contained only epithelial elements. In three (25%), a variable amount of mesenchymal components also were present. Three patients had a purely or predominantly fetal epithelium. Embryonal and anaplastic epithelial patterns predominated in two patients each. There was an admixture of two or three epithelial patterns with no pattern predominating in five (42%) patients. Anaplastic epithelium was a component in three of these latter five patients.

Vascular invasion was evident microscopically in eight patients, including all three with tumor thrombii in the main portal vein. Only one child in the group of 12 had lymph node metastases and positive hepatic resection margins. Her tumor extensively infiltrated the rectus sheath, diaphragm and the pericardium.

Chemotherapy

Nine patients received chemotherapy before and five after the transplant under different protocols (Table 1).

Statistical Analysis

The median patient survival rate was calculated among the various groups and a nonparametric test (log rank test) was used to assess the statistical significance of the differences in the length of survival. A p value of 0.05 or less was considered significant.

Results

Survival

Six of the twelve children with hepatoblastoma died after transplant. Three died due to recurrent disease at 35 days, 4 and 23 months after transplantation. All three had multiple sites of recurrence. Two children died of allograft hepatic artery thrombosis, one despite retransplantation, 15 days and 4 months after operation, respectively. The sixth child died of Pneumocystis pneumonitis 9 months after transplantation. Autopsies performed in the latter two patients did not reveal any evidence of tumor.

The remaining six children are alive 24 to 70 (44 ± 19) months after transplantation with no evidence of malignancy. The longest surviving child developed a solitary pulmonary metastasis 7 months after his transplant despite adjuvant post-transplant chemotherapy. This was resected and he remains tumor free with 70 months of follow-up. All survivors have had good allograft function. One patient developed a lymphoproliferative disorder 2 years after transplantation that resolved with the reduction of cyclosporine.

The deaths due to recurrent disease and the duration of survival have been analyzed further in relation to the factors listed below.

(1) Previous liver resection: two of the four patients (50%) who underwent hepatic resection before the transplant died of recurrent tumor compared to one of the eight patients (13%) without a previous resection.

(2) Extent of gross disease (Table 2): in children with unifocal tumors, no deaths occurred due to recurrent disease and they survived significantly longer than did those children with multifocal tumors ($p = 0.04$). Similarly intrahepatic tumors had a better prognosis than did tumors manifesting portal vein tumor thrombus or direct extrahepatic invasion. The difference in their median survival times, however, did not reach statistical significance ($p = 0.13$). The child with lymph node involvement died of cerebral metastases 35 days after the transplantation.

(3) Histology (Table 2): microscopic evidence of vascular invasion and the presence of embryonal and/or anaplastic epithelium in the tumors were associated with poor prognosis. These differences, however, did not reach statistical significance ($p = 0.08$ and 0.1, respectively).

(4) Chemotherapy: three of the nine children who received chemotherapy before transplantation died of recurrence. One of the five (20%) children who received post-transplant chemotherapy and two of the seven (28%) who did not receive chemotherapy died as a result of recurrent tumor.

Discussion

Hepatoblastoma is the most common primary malignant liver tumor in children younger than 5 years.[8,9] Partial hepatic resection is the standard form of curative therapy. In recent years preoperative chemotherapy has allowed resection of previously unresectable tumors.[10–12]

Total hepatectomy and orthotopic liver transplantation becomes a rational choice for tumors that are unresectable by conventional means. Application of this concept to treat unresectable hepatocellular carcinoma has had a high incidence of recurrence and death after transplantation.[2–7] Long-term survival after transplantation for hepatoblastoma previously has been reported only for one patient surviving 6 years after transplantation.[7]

The results of liver transplantation for hepatoblastoma in this series is inferior compared to the overall survival rate of pediatric liver recipients (58% *versus* 71% 2-year survival rate).[13] However this compares favorably to the 20% to 30% 2-year survival rates reported after transplantation for hepatocellular carcinoma.[3,7]

Children who had a hepatic resection before transplantation appeared to have worse prognoses compared to the children who did not. The reason is unknown but might be due to the more aggressive nature of the recurrent tumors. Various clinicopathologic correlations have been made to identify prognostic factors that affect survival in children with hepatoblastoma. The size of the tumor alone has not been shown to be significant as long as it is resectable.[9,14] In this series the unifocal tumors were generally much larger than the multifocal tumors (d = 12 cm *versus* 5.4 cm) but had a significantly better prognosis. Extent of gross disease evident at surgery appears to have a definite impact on survival after transplantation. Patients with only intrahepatic tumors had better survival rates compared to the patients with extrahepatic extension.

Kasai and Watanabe[15] and subsequently other authors[8,14,16–18] reported the favorable prognosis associated with fetal epithelium in the tumors compared to that for the embryonal and anaplastic types. In this series also, patients with pure or predominantly fetal epithelial tumors did better. Vascular invasion had a negative impact on survival. The percentage of tumors containing mesenchymal elements varies among various reports and their prognostic significance is uncertain.[15,18,19] In this study the presence of mesenchymal elements in the tumors did not appear to affect the prognosis.

Reduced rates of recurrence have been reported with combination chemotherapy following a curative resection for hepatablastoma.[12] However our observations regarding the role of chemotherapy are inconclusive because of the small number of patients in each group and also because of the different protocols used.

In conclusion liver transplantation should be considered for nonmetastatic unresectable hepatoblastoma. The future role of pre- and post-transplant chemotherapy in improving the results remains to be defined.

TABLE 2. *Extent of Gross Disease and Histologic Features Correlated to the Outcome*

Prognostic Tumor Characteristics	Deaths Due to Recurrent Disease	Median Survival in Months	
Extent of Disease at Surgery			
Unifocal	0/5	30	p = 0.04
Multifocal	3/7 (43%)	5	
Intrahepatic	1/7 (14%)	30	p = 0.13
Extrahepatic	2/5 (40%)	5	
Histologic Characteristic			
Vascular invasion			
Present	3/8 (38%)	14.5	p = 0.08
Absent	0/4	19.5	
Type of epithelium			
Fetal	0/3	32	p = 0.10
Nonfetal or mixed	3/9	5	

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