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Should Hepatomas Be Treated with Hepatic Resection or Transplantation?

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BACKGROUND. The aim of this collaborative study was to compare the long term results of hepatic resection (Hx) with those of orthotopic liver transplantation (OLTx) in large numbers of cirrhotic patients with hepatocellular carcinoma (HCC) and to delineate the roles of these two surgical treatments.

METHODS. The databases of the National Cancer Center Hospital in Japan and the University of Pittsburgh Medical Center in the U. S. were exchanged and 294 cirrhotic patients who underwent curative Hx and 270 cirrhotic patients who underwent curative OLTx were selected for comparison.

RESULTS. The mortality rate within 30 days and that within 150 days after Hx were significantly lower than those after OLTx ($P = 0.001$ and $P = 0.00007$, respectively). Overall survival was similar between the Hx group and the OLTx group ($P = 0.40$). When compared in the HCC patients without macroscopic vascular invasion and lymph node metastases, the overall survival rate after OLTx was significantly higher than that after Hx ($P = 0.006$). However, this difference was not significant between the patients with Child-Pugh Grade A tumors in the Hx group and all patients (majority with Child-Pugh Grade C tumors) in the OLTx group ($P = 0.25$). Tumor free survival after OLTx was significantly higher than that after Hx ($P < 0.0001$), particularly in HCCs measuring ≤5 cm, unilobarly distributed tumors, and HCCs with either no or only microscopic vascular invasion. In HCCs measuring > 5 cm and those with macroscopic vascular invasion, the tumor free survival rate was similar between the Hx group and the OLTx group.

CONCLUSIONS. In the face of organ shortage, HCC developing in a well compensated cirrhotic liver initially may be treated with Hx. However, the authors believe OLTx should be applied selectively to those patients with tumor recurrence and/or progressive hepatic failure. *Cancer* **1999;86:1151–8.**

KEYWORDS: hepatocellular carcinoma, cirrhosis, treatment, survival, recurrence.

Several effective therapeutic options for hepatocellular carcinoma (HCC) have become available in recent years. Among them are regional chemoembolization,[1] percutaneous alcohol injection,[2] cryosurgical[3] or microwave ablation,[1] subtotal hepatectomy (hepatic resection),[5-11] and total hepatectomy with liver replacement (orthotopic liver transplantation).[12-16]

The outcome after hepatic resection (Hx) for HCC and that of orthotopic liver transplantation (OLTx) have been debated in several reports but without definite conclusions regarding the difference in long term survival.[17-20] In addition, each report contained only a limited number of early stage HCC tumors in patients with cirrhotic livers treated by Hx because of the small numbers of such cases in the Western countries. Therefore, the database of the National Cancer Center Hospital (Tokyo, Japan) and that of the University of Pitts-

burgh Medical Center (Pittsburgh, PA) were exchanged to compare the long term overall and tumor free survival rates between Hx and OLTx in a large number of cirrhotic patients with HCC.

MATERIALS AND METHODS

Hepatic Resection Group

Between 1985 and 1994, 723 patients underwent primary Hx for the treatment of HCC at the National Cancer Center Hospital (NCCH), Tokyo, Japan. Portions of this experience were reported previously.[10,21] Among these 723 patients, 403 (55.7%) had histologically proven concomitant cirrhosis. Resection of the tumor(s) was incomplete in 109 patients (27.0%) (58 patients had microscopic exposed tumors, 5 patients had positive surgical margins at the tumor thrombus in the portal vein, 45 patients underwent debulking resection due to limited liver function, and 1 patient had extrahepatic disease that was not removed). The remaining 294 cirrhotic patients (72.9%) who underwent complete resection of the tumors were selected for this study. The range of the follow-up period was 0.23–140 months (median, 46.0 months). The preoperative level of serum α-fetoprotein ranged from 0.1–376,200 ng/mL (mean, 2094 ng/mL). The surgical procedure was comprised of 2 trisegmentectomies (0.7%), 8 bisegmentectomies (2.7%), 30 segmentectomies (10.2%), 57 subsegmentectomies (19.4%), and 197 nonanatomic limited resections (less extensive than subsegmentectomy) (67.0%). The details of the surgical techniques were reported previously.[10] During the same period, no liver transplantation was performed at either NCCH or in Japan.

Orthotopic Liver Transplantation Group

Between 1981–1997, 307 patients underwent OLTx in the presence of HCC at the University of Pittsburgh Medical Center (Pittsburgh, PA). Portions of this experience were reported previously.[18,22] Of the 307 transplanted patients, 283 (92.1%) had concomitant cirrhosis. Thirteen of the 283 patients (4.6%) had microscopic positive margins due to extrahepatic extension of the tumor. The remaining 270 cirrhotic patients who underwent complete removal of the tumor(s) by OLTx were selected for the study. The follow-up period ranged from 3–201 months (median, 36.6 months). Eighty-seven patients (32.2%) had HCCs that were undetected preoperatively. Cyclosporine and steroids were used as immunosuppressive therapy between 1981–1989; tacrolimus replaced cyclosporine beginning at the end of 1989. Immunosuppressive therapy and the OLTx technique were described previously.[23,24] One hundred and one patients underwent hepatic resection for HCC between 1980–1997 at Pittsburgh University Hospital.

Patient Characteristics

The patients' characteristics are shown in Table 1. The mean age of the patients was lower in the OLTx group and the incidence of viral hepatitis as the etiology of the cirrhosis was higher in the Hx group. Although there was no significant difference in the mean tumor size ($P = 0.08$), tumors measuring ≤2 cm and those measuring >5 cm in greatest dimension were more frequent in the OLTx group than in the Hx group. The OLTx patients had significantly more bilobar tumors compared with Hx patients. The overall incidence of vascular invasion was similar between the two groups; however, macroscopic vascular involvement was observed more frequently in the OLTx group (17.7%) than in the Hx group (7.2%). With regard to the histologic differentiation of HCC, the Hx group contained more patients with poorly differentiated tumors than the OLTx group. When stratified according to the pTNM staging system,[25] >66% of the Hx patients were classified as Stage II and Stage IIIA, whereas patients in the OLTx group were evenly distributed into Stage I, Stage II–IIIA, and Stage IVA. The OLTx group included more patients with poor hepatic functional reserve (Child-Pugh Grade C) than the Hx group.

Statistical Analysis

The Statistical Package for Social Science software (SPSS, Inc., Chicago, IL) was used for data analysis. The Kaplan–Meier product-limit method with the log rank test was used to evaluate tumor free and patient survival rates for various prognostic factors. Results were reported as the mean ± the standard error of the mean (SE). Significance levels were set at $P < 0.05$.

RESULTS

Surgical Mortality and Short Term Results

Four patients in the Hx group died within 1 month after surgery (surgical mortality rate: 1.4%) and an additional 8 patients died during the initial hospital stay (in-hospital mortality rate: 4.1%). Nine patients (3.1%) died of hepatic failure, 2 patients (0.7%) died of cardiopulmonary complications, and 1 patient (0.3%) died of tumor recurrence. A total of 17 patients (5.8%) died within 150 days after resection.

In the OLTx group, 22 patients died within 1 month of transplantation (surgical mortality rate: 7.8%). Forty-nine patients (17.3%) died within 150 days after transplantation of various complications not related to HCC.

TABLE 1
Characteristics of the Patients Who Underwent Hepatic Resection and Those of Patients Who Underwent Liver Transplantation

Factor	Hepatic resection (n = 294)	Liver transplantation (n = 270)	*P* value[a]
Age (yrs)			
Mean ± SE	59.7 ± 7.5	54.5 ± 11.6	< 0.001[b]
≤60	171 (58.2%)	178 (65.9%)	0.06
>60	123 (41.8%)	92 (34.1%)	
Gender			
Male	219 (74.5%)	202 (74.8%)	0.93
Female	75 (25.5%)	68 (25.2%)	
Etiology of cirrhosis			
Hepatitis B	50 (17.0%)	57 (21.1%)	
Hepatitis C	145 (49.3%)	17 (6.3%)	
NonA, NonB[c]	36 (12.2%)	77 (28.5%)	
Alcoholic		46 (17.0%)	
Metabolic diseases		20 (7.4%)	
Others	63 (21.4%)	53 (19.6%)	
Size of tumor (cm)			
≤2 cm	71 (24.1%)	125 (46.3%)	< 0.00001
2–5 cm	183 (62.3%)	96 (35.6%)	
>5 cm	40 (13.6%)	49 (18.1%)	
No. of tumors			
Single	165 (56.1%)	144 (53.3%)	0.51
Multiple	129 (43.9%)	126 (46.7%)	
Lobar involvement			
Unilobar	286 (97.3%)	197 (73.0%)	< 0.00001
Bilobar	8 (2.7%)	73 (27.0%)	
Vascular invasion			
Absent	171 (58.2%)	160 (59.3%)	0.00004
Microscopic	110 (37.4%)	72 (26.7%)	
Macroscopic	13 (4.4%)	38 (14.1%)	
Histologic differentiation[d]			
Well	26 (10.4%)	55 (23.2%)	< 0.00001
Moderate	166 (66.4%)	166 (70.0%)	
Poor	58 (23.2%)	16 (6.8%)	
Lymph node metastases			
Absent (N0)	293 (99.7%)	265 (98.1%)	0.07
Present (N1)	1 (0.3%)	5 (1.9%)	
pTNM Stage			
I	44 (15.0%)	85 (31.5%)	< 0.00001
II	85 (28.9%)	47 (17.4%)	
IIIA	133 (45.2%)	51 (18.9%)	
IIIB	1 (0.3%)	2 (0.7%)	
IVA	31 (10.5%)	85 (31.5%)	
Child classification			
A	193 (65.6%)	10 (3.7%)	< 0.00001
B	97 (33.0%)	19 (7.0%)	
C	4 (1.4%)	241 (89.3%)	

SE: standard error.

[a] The significance of the difference was tested for each parameter by the Mantel–Haenszel chi-square test.

[b] The average ages were compared by a two-tailed Student *t* test for paired data.

[c] These patients included those with viral hepatitis before the test for the hepatitis C virus was available.

[d] The data regarding histologic differentiation of the hepatocellular carcinomas were not available for 44 patients (14.9%) in the hepatic resection in 33 patients (12.2%) in the orthotopic liver transplantation group.

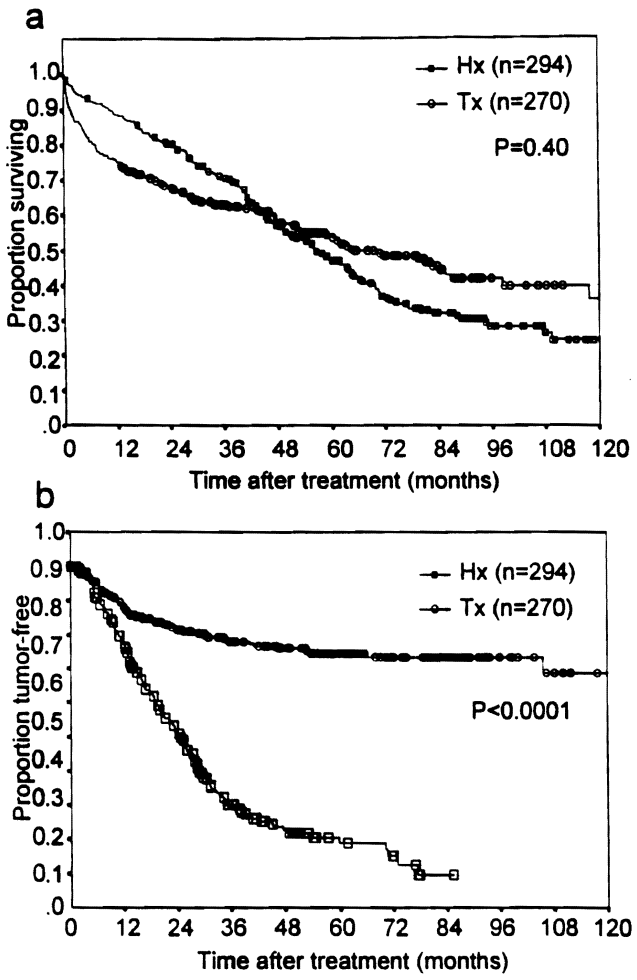

FIGURE 1. (a) Overall patient survival rates were similar between the hepatic resection (Hx) group (n = 294) and the orthotopic liver transplantation (Tx) group (n = 270) (p =0.40) but (b) tumor free survival rates were significantly higher in the Tx group compared with the Hx group ($P < 0.0001$).

Overall Patient Survival and Tumor Free Survival Rates

The 1-year, 3-year, 5-year, and 10-year overall cumulative survival rates after Hx were 88.7%, 70.8%, 47.1%, and 24.4%, respectively, and were 75.6%, 63.1%, 54.5%, and 36.2%, respectively, after OLTx (Fig. 1a). There was no significant difference in overall survival ($P = 0.40$).

During the follow-up period, 176 of 294 patients in the Hx group (59.9%) and 53 of 270 patients in the OLTx group (19.6%) developed tumor recurrence. Cumulative 1-year, 3-year, 5-year, and 7-year tumor free survival rates in the OLTx group were 75.2%, 63.1%, 53.9%, and 44.4%, respectively, and were 67.8%, 24.1%, 14.3%, and 7.2%, respectively, in the Hx group (Fig. 1b). The difference was statistically significant ($P < 0.0001$).

Prognostic Factors

The influence of various prognostic factors on overall and tumor free survival is shown in Table 2. The overall survival rate was significantly better in the OLTx group than in the Hx group for solitary tumors, unilobarly distributed tumors, and for tumors with microscopic vascular invasion. The overall survival rate of the OLTx group also was significantly higher than that of the Hx group with regard to patients with pTNM Stage II tumor(s) or those with fair liver function (Child-Pugh Grade B). However, survival after Hx was significantly higher for the patients with tumors with macroscopic vascular invasion.

The tumor free survival rate of the OLTx group was significantly higher than that of the Hx group for tumors measuring ≤5 cm, unilobarly distributed tumors, tumors with no or only microscopic vascular invasion, and tumors of well or moderate histologic differentiation (Table 2). However, when the tumors measured >5 cm or had macroscopic vascular invasion or poorly differentiated histology, there was no statistically significant difference in tumor free survival between the Hx and the OLTx groups. Lymph node status could not be analyzed because lymph node metastasis was so rare for both groups (one case in the Hx group and five cases in the OLTx group).

Specific Comparisons

The majority of liver transplantation centers no longer consider patients for OLTx if the HCC invades the major vascular branches or regional lymph nodes or if the patient has distant metastases. Overall and tumor free survival rates for the patients with tumors without macroscopic vascular invasion, regional lymph node metastases, or distant metastases were compared between 287 patients in the Hx group and 230 patients in the OLTx group (Figs. 2a and 2b). In this subgroup of patients both the overall and tumor free survival rates in the OLTx group were significantly higher than those in the Hx group.

Liver transplantation primarily is the treatment of hepatic failure. Should HCC in those patients with well compensated cirrhosis be treated with transplantation? To answer this question, 193 patients in the Hx group with good hepatic function (Child-Pugh Grade A) without macroscopic vascular invasion, regional lymph node metastases, or distant metastases were selected. The overall and tumor free survival rates of 193 patients in the Hx group was compared with that of 230 patients in the OLTx group (all Child-Pugh grades) with the same tumor characteristics (i.e., no macroscopic vascular invasion, regional lymph node metastases, or distant metastases). As shown in Fig-

TABLE 2
Univariate Analysis of Prognostic Factors for Patient and Tumor Free Survival Rates

Factor	Patient survival (mean in months ± SE)			Tumor free survival (mean in months ± SE)		
	Hepatic resection (n = 294)	Liver transplantation (n = 270)	P value[a]	Hepatic resection (n = 294)	Liver transplantation (n = 270)	P value[a]
Age (yrs)						
≤60	70.6 ± 3.9	99.6 ± 8.4	0.69	32.1 ± 2.2	140.7 ± 9.5	<0.0001
>60	60.9 ± 4.5	58.7 ± 5.2	0.80	32.3 ± 3.0	93.2 ± 4.8	<0.0001
Gender						
Male	71.4 ± 3.6	76.9 ± 5.7	0.40	33.4 ± 2.2	114.5 ± 7.3	<0.0001
Female	53.0 ± 4.4	114.2 ± 12.6	0.002	29.9 ± 3.2	164.6 ± 10.5	<0.0001
Size of tumor (cm)						
≤2	69.9 ± 5.6	85.5 ± 6.2	0.14	35.5 ± 3.4	131.4 ± 6.4	<0.0001
2-5	68.1 ± 3.9	105.4 ± 10.4	0.29	30.6 ± 2.1	140.7 ± 10.4	<0.0001
>5	55.2 ± 7.2	48.0 ± 8.7	0.09	32.9 ± 6.1	65.2 ± 12.9	0.76
No. of tumors						
Single	71.4 ± 4.0	118.2 ± 10.4	0.02	37.7 ± 2.6	175.4 ± 9.1	<0.0001
Multiple	62.9 ± 4.8	69.1 ± 7.1	0.31	25.7 ± 2.5	108.1 ± 8.7	<0.0001
Lobar involvement						
Unilobar	67.2 ± 3.1	112.0 ± 8.1	0.01	32.8 ± 1.9	173.6 ± 7.1	<0.0001
Bilobar	72.5 ± 18.7	42.9 ± 4.5	0.22	21.6 ± 4.4	49.3 ± 5.6	0.23
Vascular invasion						
Absent	76.2 ± 4.0	113.5 ± 9.0	0.19	37.7 ± 2.3	180.6 ± 8.2	<0.0001
Microscopic	56.3 ± 4.7	89.7 ± 10.8	0.05	26.2 ± 2.9	121.6 ± 11.2	<0.0001
Macroscopic	39.9 ± 9.0	20.4 ± 4.0	0.04	13.4 ± 2.5	19.0 ± 4.5	0.51
Histologic differentiation[b]						
Well	6.37 ± 0.52	6.52 ± 0.62	0.98	3.22 ± 0.38	8.75 ± 0.25	<0.0001
Moderate	5.62 ± 0.33	6.09 ± 0.44	0.92	2.47 ± 0.18	8.64 ± 0.45	<0.0001
Poor	4.08 ± 0.42	5.65 ± 1.79	0.55	2.90 ± 0.38	8.08 ± 2.36	0.24
pTNM Stage						
I	74.6 ± 6.2	82.2 ± 5.9	0.38	39.7 ± 4.3	113.8 ± 3.3	<0.0001
II	70.4 ± 4.9	133.8 ± 14.4	0.02	35.5 ± 3.1	[c]	<0.0001
IIIA	62.2 ± 4.6	100.8 ± 12.1	0.11	30.9 ± 3.0	142.3 ± 12.0	<0.0001
IIIB	[d]	2.38 ± 2.0	0.23	[e]	4.4 ± 1.1	
IVA	55.0 ± 8.7	40.5 ± 4.0	0.28	22.0 ± 4.4	46.0 ± 5.1	0.006
Child classification						
A	75.8 ± 4.0	112.3 ± 26.7	0.72	37.5 ± 2.5	119.2 ± 29.2	0.06
B	51.2 ± 3.9	83.1 ± 12.5	0.03	23.8 ± 2.1	100.2 ± 12.3	<0.0001
C	35.4 ± 12.9	93.4 ± 7.2	0.13	13.5 ± 3.5	148.8 ± 7.7	<0.0001

SE: standard error.

[a] The significance of the difference was tested for each subgroup by the log rank test.

[b] Analyses were performed for the patients with data available regarding histologic differentiation.

[c] Value could not be computed because all observations were censored at a maximum of 201 months (i.e., no recurrence occurred).

[d] Included only 1 case and could not be computed because all observations were censored at a maximum of 65.3 months (i.e., no patient died).

[e] Included only 1 case and could not be computed because all observations were censored at a maximum of 65.3 months (i.e., no recurrence occurred).

ures 3a and 3b, overall survival after Hx in this subgroup was similar to that after OLTx ($P = 0.25$), although the tumor free survival rate was significantly lower in the Hx group ($P < 0.0001$).

DISCUSSION

Subtotal hepatectomy or hepatic resection is used to treat HCC of limited number and size in patients with compensated cirrhosis. Total hepatectomy and liver replacement or OLTx primarily is the treatment of choice for hepatic failure although it can be used to treat HCCs of any number and size even in patients with decompensated cirrhosis. The prognosis of patients with advanced stage HCC (HCC with macroscopic vascular invasion, lymph node involvement, and distant metastases) is very poor after either hepatic resection or transplantation.[17,18,26,27]

In this study, two large series of HCC patients with cirrhosis treated by different surgical strategies at institutions in Japan and the U. S. were compared ret-

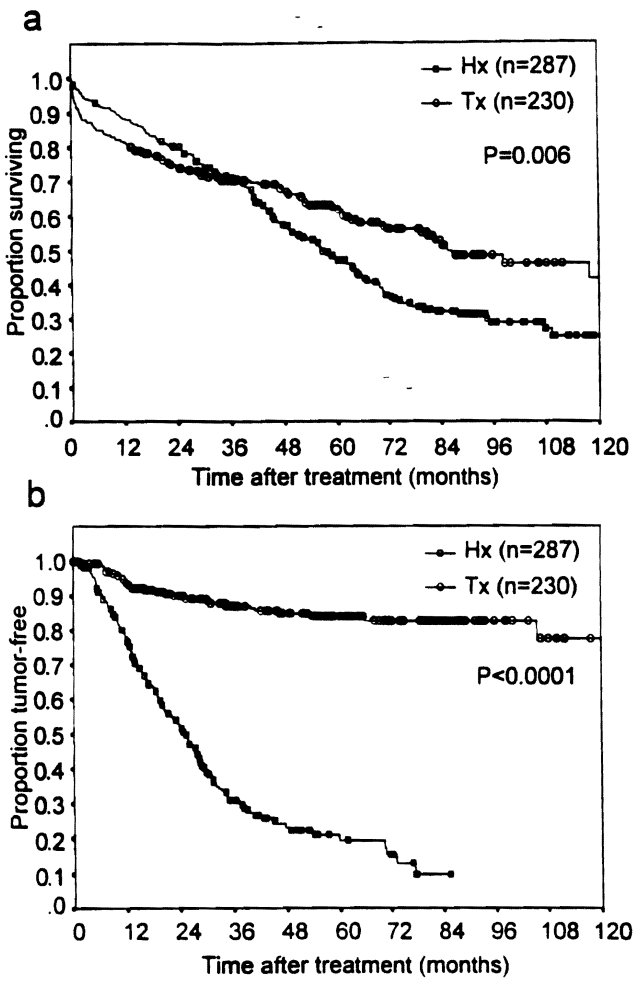

FIGURE 2. Both (a) patient survival rates and (b) tumor free survival rates were significantly higher in orthotopic liver transplant (Tx) group compared with the hepatic resection (Hx) group ($P = 0.006$ and $P < 0.0001$, respectively) when the patients with good risk hepatocellular carcinoma (pTNM Stages I, II, IIIA, and IVA without macroscopic vascular invasion) were selected.

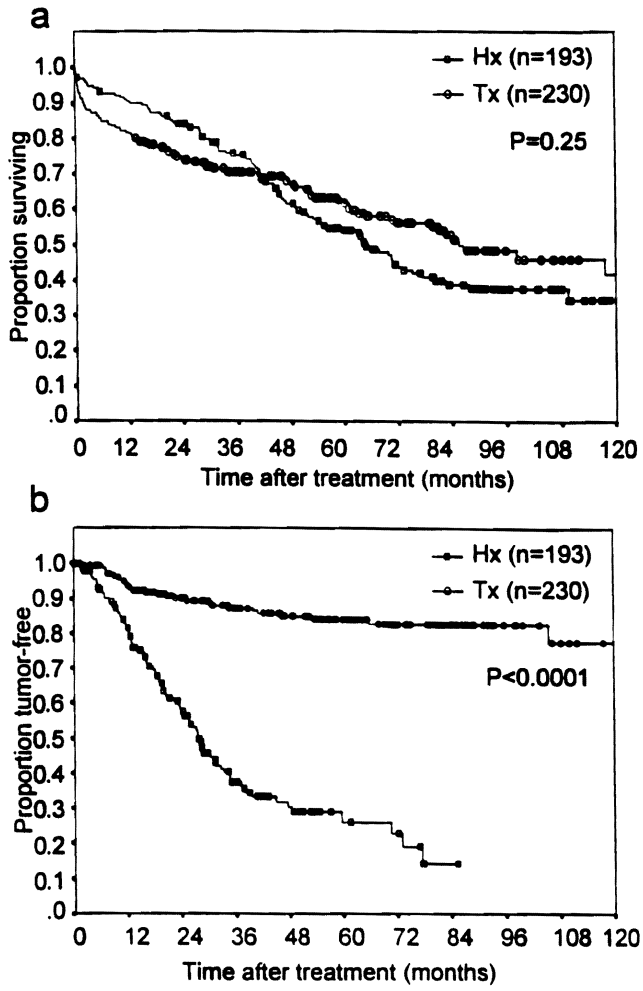

FIGURE 3. (a) Patient survival rates of patients with Child-Pugh Grade A disease in the hepatic resection (Hx) group (n = 193) were similar ($P = 0.25$) to those of the patients with mostly Child-Pugh Grade C disease in the orthotopic liver transplantation (Tx) group (n = 230) when patients with good risk hepatocelluar carcinoma were selected, but (b) the tumor free survival rates were significantly higher in Tx group compared with the Hx group ($P < 0.0001$).

rospectively. There was a difference in the etiology and hepatic functional reserve between the two groups. The OLTx group was comprised more of early stage and advanced stage tumors than the Hx group based on the comparison of maximum tumor size, vascular invasion, and pTNM stage. As mentioned earlier, OLTx can be used to treat HCCs of any number and size. OLTx patients treated for end-stage liver disease occasionally have early stage tumors undetected by preoperative examination. When the patients are selected according to established criteria for appropriate treatment in one institution, there should be no overlapping of patients between each treatment group. In Western nations, transplantation has been chosen for many cirrhotic patients with HCC, for whom major hepatic resection was impossible due to limited liver function. Among 101 patients treated by hepatic resection at Pittsburgh University Hospital during the same period, 69 patients (68.3%) had noncirrhotic livers, 51 patients (50.5%) had pTNM Stage III tumors, and 38 patients (38%) had pTNM Stage IV tumors. In addition 82 patients (81.1%) underwent major hepatic resection. However, in Asian countries, especially Japan, in which early stage HCC is diagnosed through routine physical examination for those patients with chronic liver disease, resection has been performed widely for cirrhotic patients with tumors by limited liver resection. Thus, Japanese patients with HCC and cirrhosis who are treated by hepatic resec-

tion should overlap with those Western patients with similar diseases treated by transplantation.

Our study reconfirmed the findings of other reports that in patients with early stage HCC (HCC without macroscopic vascular invasion, lymph node involvement, or distant metastases), hepatic resection can provide excellent survival for those patients with good liver function,[8,10,11] but the incidence of tumor recurrence after resection is extremely high when compared with that after transplantation.[14-19] Should this then lead to the conclusion that all early stage HCC patients should be treated with transplantation regardless of hepatic function? As indicated in this study and others,[13,17] surgical and perioperative mortality is significantly higher after transplantation than after hepatic resection. The overall survival rate actually was higher for the initial 3–4 years after hepatic resection than transplantation (Fig. 3a), despite the higher incidence of tumor recurrence after resection (Fig. 3b).

In the Hx group the patients with recurrent HCC were treated effectively with reresection (20 patients), ethanol injection (18 patients), and chemoembolization (87 patients), or a combination thereof. Conversely, the recurrent tumors in the OLTx group were widespread and rarely could be treated by regional therapy. The mean survival after tumor recurrence was 31.6 ± 21.5 months (mean ± SE) in the Hx group and 15.3 ± 14.5 months (mean ± SE) in the OLTx group ($P < 0.001$). Tumor growth under immunosuppression appeared to be accelerated.[28]

Within 5 years, 143 patients died after resection and 114 patients died after transplantation. One hundred of the 143 patients (69.9%) died with tumor recurrence after resection, and 41 of the 114 patients (36.0%) patients died after transplantation. After 5 years, 35 patients died after resection and 17 patients died after transplantation. Ten of the 35 patients (28.6%) in the Hx group and 13 of the 17 patients (76.5%) patients in the OLTx group died free of tumor. Thus, the incidence of death unrelated to HCC was significantly higher in transplantation group than in the resection group both within and after 5 years ($P < 0.00001$ and $P = 0.001$, respectively). The cirrhotic HCC patients who were treated by hepatic resection most often died with HCC or of the complications of hepatic failure and portal hypertension. When those patients were treated by liver transplantation, the deaths related to HCC or cirrhosis could be avoided either largely or entirely. However, the mortality inherent to transplantation, such as death due to infection and rejection, still affected the survival rates.

Liver transplantation should be avoided in HCC patients with macroscopic vascular invasion, lymph node involvement, or distant metastases.[18,19] Hepatic resection for HCC in patients with concomitant cirrhosis should be limited to patients with good hepatic function. Tumor recurrence should be monitored very closely after resection, and recurrent tumors should be treated aggressively with reresection, chemical or thermal ablation, and/or arterial chemoembolization. With this approach the survival of patients with good hepatic function should be as good as that of patients who undergo liver transplantation, as indicated in this study. When liver function begins to deteriorate and/or when the recurrent tumors appear to be better treated by liver replacement, liver transplantation may be considered. Longitudinal therapeutic planning (hepatic resection followed by aggressive regional therapy as described earlier and liver transplantation) may improve survival further for the patients with HCC with compensated cirrhosis. We believe patients with fair or poor liver function are best treated with liver transplantation, providing the HCC does not invade major branches of hepatic vessels and does not have lymph node or distant metastases. In the face of organ shortage, the use of liver transplantation for HCC should be limited to good risk patients as indicated in this study and others.[14-20]

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