

Recurrence of Hepatocellular Carcinoma After Liver Transplant: Patterns and Prognosis

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Very little is known about the natural history, effects of therapy, and survival after recurrence of hepatocellular carcinoma (HCC) after liver transplantation. All adult patients undergoing liver transplant from September 19, 1988, until September 19, 2002, were reviewed. Only patients with histologically proven HCC in the explant who subsequently developed recurrence were included in further analysis. The endpoints analyzed were survival from time of transplant and survival from time of recurrence. Recipient demographics and laboratory values, technique of transplant (whole cadaver, split, or living donor), and tumor characteristics were analyzed. The time to, location of, and any medical or surgical treatment of recurrences also were considered. Of the 311 patients with HCC in the explant, 57 (18.3%) eventually were diagnosed with recurrent tumor after transplant. Median time to recurrence was 12.3. Five-year survival was significantly lower for patients with recurrence (22%) than for patients without recurrence (64%) ($P < 0.0001$). Multivariate analysis demonstrated that the size and differentiation of the original tumor, as well as the presence of bone recurrence, were independently associated with survival from transplant in patients with recurrence. When survival from the time of recurrence was analyzed, multivariate analysis showed that the absence of bone metastases, recurrence more than 12 months from transplant, and surgical treatment of the recurrence were independently associated with significantly longer survival. In conclusion, recurrence of HCC significantly shortens survival after transplant. Nonetheless, some patients with recurrence can be expected to live for a considerable period of time. Recurrent disease should be treated surgically when possible, because surgery is independently associated with longer survival. (*Liver Transpl* 2004;10:534–540.)

Hepatocellular carcinoma (HCC) has been well studied with the aim of determining which characteristics predict recurrence and survival after liver transplant.^{1–3} Analysis of the data from the International Registry of Hepatic Tumors in Liver Transplantation has demonstrated that 25.5% of the 422 patients transplanted with HCC have had recurrence of their tumor.¹ More recent studies using better patient selection still demonstrate recurrence in 8–11% of patients.^{2,3}

Since adoption of the Model for End-stage Liver Disease (MELD) system for organ allocation in February of 2002, patients with HCC meeting the United Network of Organ Sharing criteria have been afforded priority for cadaver liver allografts. During the first 12 months of the MELD allocation system, 979 patients with HCC were transplanted in the United States (personal communication from D. Tripp, United Network of Organ Sharing research department, April 7, 2003). This represents nearly a 3-fold increase from same period the year MELD during which only 369 patients with HCC were transplanted (personal communication from D. Tripp, United Network of Organ Sharing research department, April 7, 2003). Consequently, we can expect to see an increasing number of patients with recurrent HCC after liver transplant over the next few years.

Very little has been reported regarding the natural history, effects of medical or surgical treatment, and predictors of survival in patients who develop recurrence of HCC after transplant.⁴ This study reports on 57 patients from a single institution who developed recurrent HCC after liver transplant.

Abbreviations: HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

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Experimental Procedures

Data on all adults undergoing primary liver transplant between September 19, 1988, and September 19, 2002, was entered prospectively and reviewed retrospectively. All cirrhotic patients were followed with serial computed tomography scans of the abdomen every 6 months as surveillance for development of HCC while on the waiting list. Patients with known or suspected HCC were followed for tumor progression and extra-

Table 1. Patient and Tumor Characteristics

	All Patients Transplanted With HCC (n = 311)	Patients With Recurrent HCC (n = 57)
Age (mean $\pm$ SD)	56.9 $\pm$ 8.8	55.6 $\pm$ 11.6
Underlying liver disease		
Hepatitis C	188 (60.5%)	32 (56%)
Hepatitis B	54 (17%)	6 (11%)
Alcohol	26 (8%)	8 (14%)
Cryptogenic	21 (7%)	5 (9%)
Other	22 (7%)	6 (11%)
Liver allograft		
Whole cadaver	267 (86%)	50 (88%)
Split cadaver	6 (2%)	0
Living donor	36 (12%)	7 (12%)
Domino	2 (<1%)	0
Median number tumors	1	2
Mean size of largest tumor (cm; mean $\pm$ SD)	3.6 $\pm$ 2.4	5.4 $\pm$ 3.0
Grade		
Well	53%	33%
Moderate	37%	44%
Poor	10%	22%
Vascular invasion present	48%	88%

hepatic spread every 3 months with computed tomography scans of the chest and abdomen as well as a single bone scan. All explanted livers were cut into serial 1-cm thick sections and examined for tumor nodules. Only patients with histologically proven HCC in their explants were included in this study. These patients were followed for recurrence with computed tomography scans of the chest and abdomen every 3 months for the first year, every 6 months for the next year, and then annually. Patients also had measurement of alpha fetoprotein every 6 weeks for the first year, every 3 months for the next year, and then biannually.

Patients with a rising alpha fetoprotein level and a hepatic mass that enhanced on arterial phase imaging were considered to have a recurrence without the need for a biopsy. All other patients had tissue obtained for histologic confirmation of recurrent HCC. Patients with recurrence that could be surgically treated for cure underwent resection or ablation of their tumors. All others were referred for medical therapy.

Variables analyzed included recipient age; underlying liver disease; highest preoperative alpha fetoprotein; type of liver allograft used; and primary tumor characteristics, including size and number of tumors, differentiation, and the presence and extent of vascular invasion. Also included in the analysis were the time from transplant to recurrence, the location of the recurrence, and any medical or surgical treatment of the recurrence. Time to recurrence was compared among groups using

an independent sample *t* test or analysis of variance. Survival was calculated using the Kaplan–Meier method and compared using the log-rank test. All variables found to be significant on univariate analysis ($P < 0.05$) were entered into a backward step-down Cox proportional hazard regression analysis. Survival from the time of transplant and survival from the time of recurrence were analyzed as independent endpoints.

Results

Between September 19, 1988, and September 19, 2002, 1674 primary liver transplants were performed on adults. Of these patients, 311 (18.6%) were found to have HCC in their explanted livers on histologic examination. Of the 311 transplanted with HCC, 57 (18.3%) were eventually diagnosed with a recurrence, and these were the patients included in the study.

Patient and tumor characteristics for those transplanted with HCC, as well as those developing recurrence, are given in Table 1. There was a wide range in the time from transplant to the diagnosis of recurrence, with the median being 12.3 months (range 1.5–60.3 months, Fig. 1). The recipient's underlying liver disease, as well as size and differentiation of the primary tumor, correlated significantly with time to recurrence (Table 2). Recurrence was limited to the liver in 9 patients, was extrahepatic in 30 patients, and was both intrahepatic and extrahepatic in 18 patients. Sites of

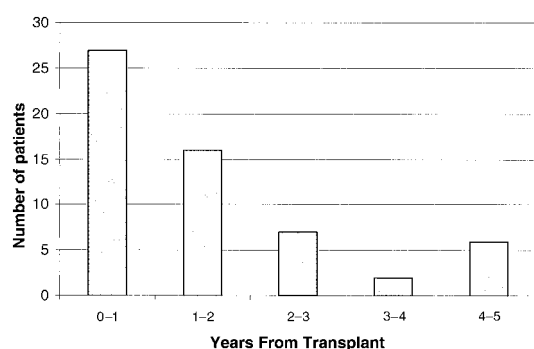


Figure 1. Time from transplant to recurrence of hepatocellular carcinoma.

recurrence included the liver ($n = 27$), lung ($n = 25$), bone ($n = 19$), and other sites ($n = 14$). Median follow-up was 51.9 months for all patients transplanted with HCC and 21.8 months for those with recurrence.

Eighteen patients underwent resection or ablation of recurrent HCC. Surgical treatment included resection

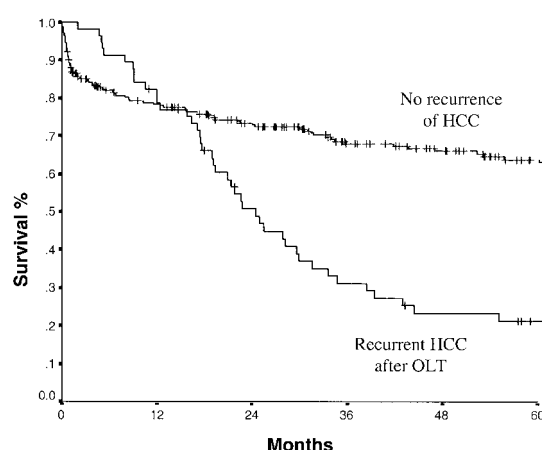


Figure 2. Survival from transplant based on recurrence of hepatocellular carcinoma after transplant ($P < 0.0001$).

of the transplanted liver ($n = 5$), lung resection ($n = 7$), radiofrequency ablation of hepatic lesions ($n = 3$), adrenalectomy ($n = 2$), and resection of a chest wall recurrence at a pretransplant tumor biopsy site ($n = 1$). Of the 18 patients treated surgically, 12 ultimately died with tumor, 3 are alive with tumor, and 3 are alive and free of disease.

All of the remaining patients were referred for medical treatment of their recurrence. Three patients with unresectable recurrence confined to the liver received transarterial chemoembolization. Fifteen patients received systemic chemotherapy with doxorubicin. Four patients received external beam radiation. The remaining 17 patients were not treated because of poor cardiac function, poor hepatic function, or patient refusal.

Survival From Transplant

Median survival from the time of transplant was 24.5 months for patients with recurrence. Survival for patients with recurrence was significantly shorter than for patients transplanted with HCC that did not recur (Fig. 2). Nevertheless, 5-year actuarial survival in patients with recurrent HCC was 22%. At the time of this analysis, 8 patients were alive more than 5 years from transplant.

Primary tumor characteristics included a solitary lesion, maximum tumor diameter less than 5 cm, and well-differentiated histology correlated with longer posttransplant survival (Figs. 3A–C). The presence of bone metastases, irrespective of other metastatic disease, was a significant predictor of shortened survival from the time of transplant (Fig. 3D). Patients who

Table 2. Recipient, Primary Tumor, and Transplant Characteristics Versus Time to Recurrence

	n	Time to Recurrence (mo)	P
Underlying liver disease			0.043
Hepatitis C	32	17.1 ± 14.2	
Hepatitis B	6	13.5 ± 19.7	
Alcohol	8	33.3 ± 18.3	
Cryptogenic	5	12.5 ± 8.7	
Other	6	13.3 ± 8.6	
AFP			0.931
≥ 1000 ng/ml	19	19.1 ± 17.4	
< 1000 ng/ml	38	18.7 ± 15.2	
Number of tumors			0.235
Solitary	10	12.9 ± 7.4	
Multiple	47	19.4 ± 16.6	
Tumor size			0.008
≥ 5 cm	26	12.7 ± 10.6	
< 5 cm	31	23.5 ± 17.5	
Grade			0.018
Well	19	26.5 ± 17.3	
Moderate	25	16.0 ± 15.7	
Poor	13	11.0 ± 7.6	
Vascular invasion			0.628
Macrovascular	15	16.3 ± 15.1	
Microvascular	35	18.1 ± 15.2	
Absent	7	23.1 ± 19.6	
Liver allograft			0.082
Whole cadaver	50	19.6 ± 16.0	
Living donor	7	8.7 ± 5.7	

Values expressed as mean ± SD.

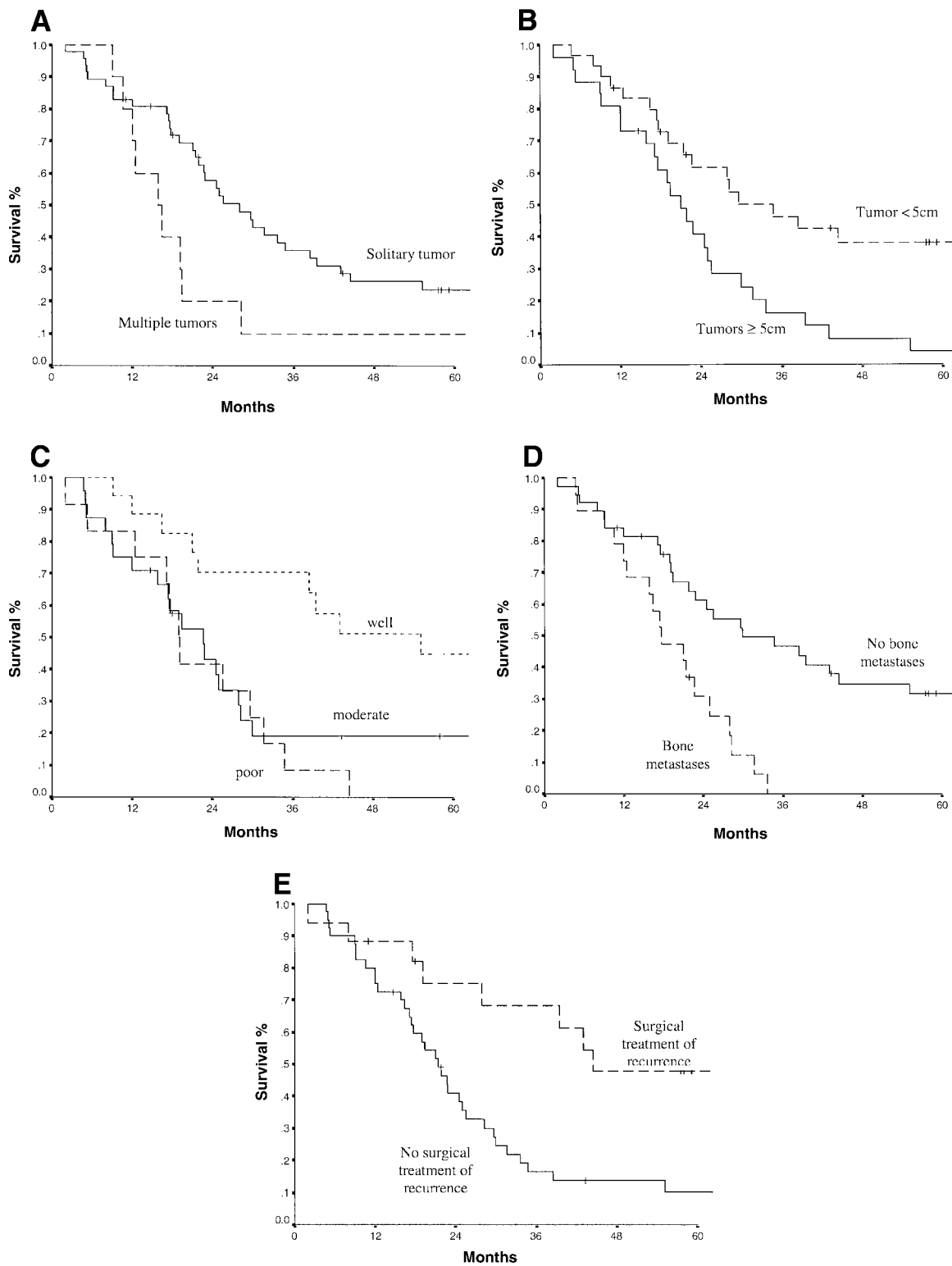


Figure 3. Survival from transplant based on (A) multiple vs. solitary tumor before transplant ($P = 0.0273$), (B) size of tumor before transplant ($P = 0.0041$), (C) differentiation of tumor before transplant ($P = 0.015$), (D) presence of bone metastases ($P = 0.00015$), and (E) surgical treatment of recurrence ($P = 0.006$).

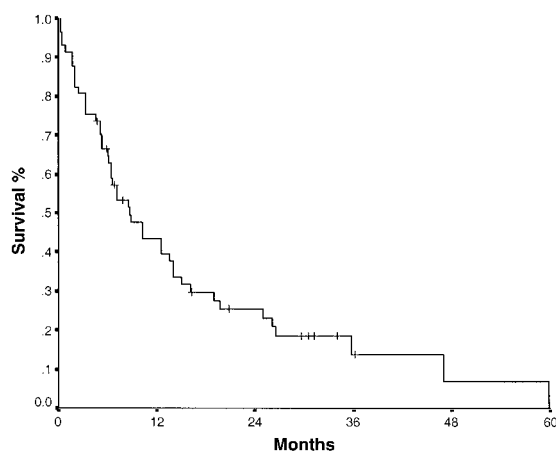


Figure 4. Survival from diagnosis of recurrent hepatocellular carcinoma after transplant.

underwent surgical treatment of their recurrence had significantly longer survival than those who did not, with 47% alive at 5 years from transplant (Fig. 3E). Multivariate analysis revealed that tumor size, differentiation, and the presence of bone metastases were all independent predictors of survival from the time of transplant (Table 3).

Survival From Recurrence

Median survival from the time of recurrence was 8.7 months (Fig. 4). Among primary tumor characteristics, only well-differentiated histology correlated with significantly longer survival from time of recurrence (Fig. 5A). Patients who recurred more than 1 year after transplant, as a group, lived significantly longer after recurrence than did those whose recurrence was diagnosed during the first year (Fig. 5B). The presence of bone metastases, irrespective of other metastases, correlated with significantly shorter survival from the time of recurrence (Fig. 5C). Surgical treatment of recurrence was associated with significantly longer survival from the time of recurrence (Fig. 5D). Multivariate analysis showed that bone metastases, the time from transplant to recurrence, and surgical treatment of recurrence were independent predictors of survival from the time of recurrence (Table 3).

Discussion

It is not surprising that recurrence of HCC after transplant shortens survival. Nevertheless, in this study, posttransplant survival in patients with recurrent HCC was 22% at 5 years. This is similar to the 23% survival

in such patients at 4 years reported by Regalia et al.⁴ Although most recurrences present within 2 years, approximately 10% of patients in this study were first diagnosed with recurrence more than 4 years after transplant, suggesting that surveillance must be maintained for an extended period.

The data from this study also demonstrate that tumor factors associated with a high likelihood of recurrence after transplant (such as tumors ≥ 5 cm in diameter and poor differentiation) also correlate with earlier recurrence and shorter survival from the time recurrence is diagnosed. One explanation for earlier recurrence in these patients is that metastases, although occult at the time of transplant, began earlier and were further along in their development. Shorter survival from the time of diagnosis of recurrence, however, implies that these tumors are also biologically more aggressive. This is consistent with the fact that HCC becomes less well differentiated and tumor doubling time decreases with increasing tumor stage.⁵ The fact that vascular invasion did not correlate with time to recurrence or with survival after recurrence is likely because nearly all patients with recurrence (88%) had vascular invasion. Although vascular invasion correlates strongly with recurrence, its presence or extent in the original tumor does not help predict survival once recurrence has occurred. The presence of bone metastases, irrespective of other sites of metastasis, was an independent predictor of poor outcome in this study. The reason for this is not clear, but given the poor prognosis, we plan to treat these patients more aggressively using zoledronic acid, which has shown significant clinical benefits in patients with bone metastases from other solid tumors.^{6,7}

Table 3. Results of Multivariate Analyses

	<i>P</i>	Exp(B)*	95% CI Exp(B)†
Survival from transplant			
Diameter	0.017	1.117	1.020–1.223
Grade	0.012		
Grade (moderate)		2.540	1.086–5.942
Grade (poor)		4.058	1.611–10.223
Bone metastases	0.002	0.329	0.162–0.668
Survival from recurrence			
Bone metastases	0.021	0.541	0.268–1.092
Surgical treatment	0.016	2.512	1.079–5.847
Time to recurrence	0.002	0.963	0.937–0.990

*Natural exponent of Beta.

†95% confidence interval for Exp (B).

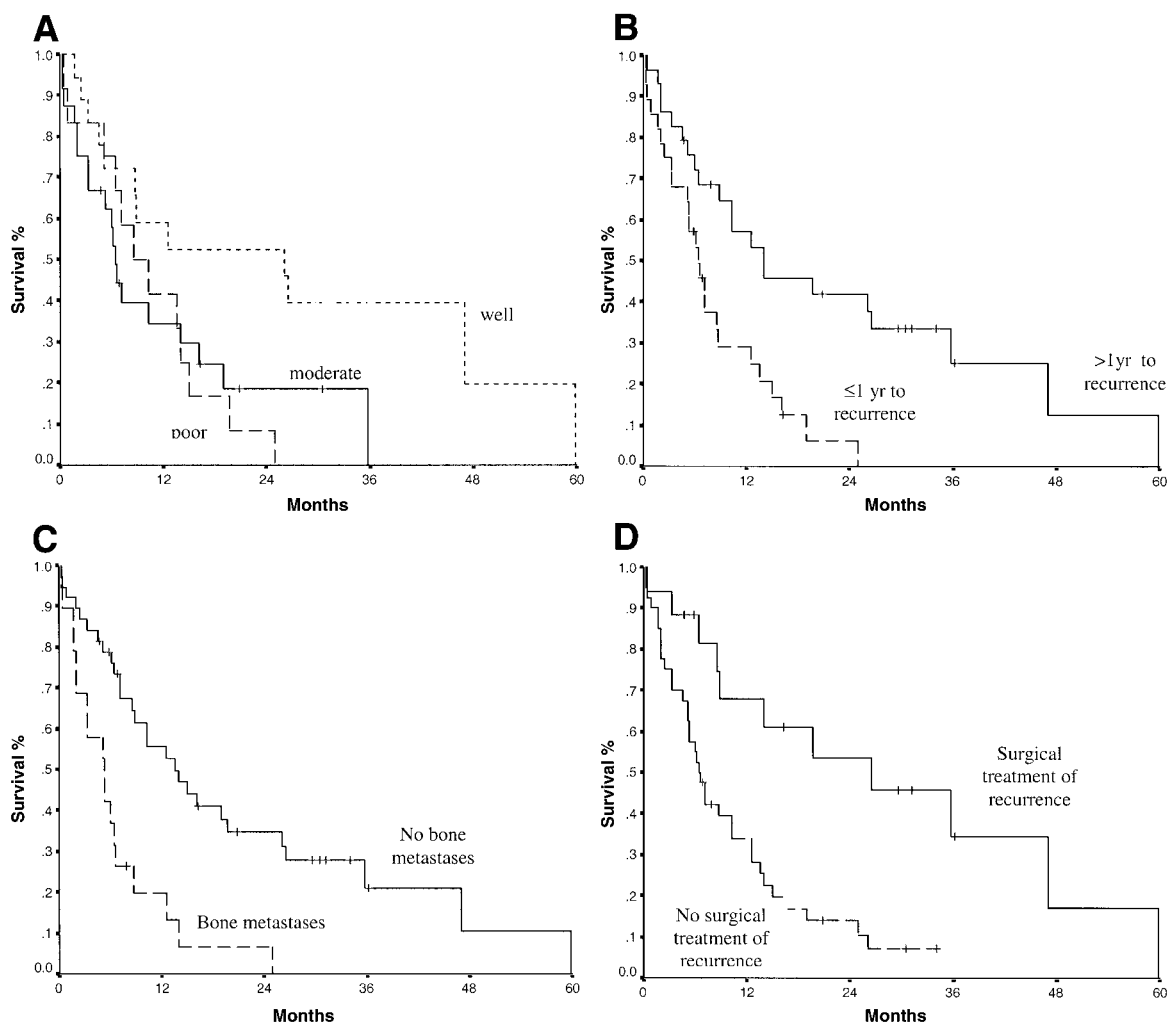


Figure 5. Survival from diagnosis of recurrence based on (A) differentiation of tumor before transplant ($P = 0.04$), (B) time from transplant to recurrence of hepatocellular carcinoma ($P = 0.0015$), (C) presence of bone metastases ($P = 0.002$), and (D) surgical treatment of recurrence ($P = 0.0015$).

It is impossible to determine from this study whether surgical treatment of recurrence prolongs survival or whether patients who are amenable to surgical treatment are a more favorable group. Surgical treatment of recurrence rarely results in complete eradication of HCC. In our series, 15 of the 18 surgically treated patients eventually developed re-recurrence of their HCC. Nonetheless, posttransplant survival of surgically treated patients was 47% at 5 years. Again, this figure is consistent with the 57% survival at 4 years reported for similar patients by Regalia et al.⁴ The fact that patients undergoing resection or ablation of a recurrence also had significantly longer survival from the time of recurrence suggests that surgery does indeed prolong survival, even if it does not result in a cure.

Therapeutic options for recurrent HCC that is not amenable to surgery are limited. Hepatic artery chemoembolization can prolong survival in primary HCC; however, its use in posttransplant situations is limited both by higher potential for biliary necrosis and the high prevalence of extrahepatic disease in this population.^{8,9} Systemic or intra-arterial chemotherapy has been shown to prolong survival in recent series.^{10,11} Significant responses from chemotherapy are nonetheless infrequent, and there is enhanced potential for serious toxicity in patients with hepatic or renal dysfunction.^{12,13} In our series, there was no difference in survival among patients who received medical therapy and those that did not.

In summary, recurrence of HCC after transplant

results in significantly diminished survival. However, there is significant variation in the time to and survival after recurrence. Patients with advanced tumors before transplant, who have a high likelihood of recurrence, will have a worse prognosis after recurrence. The presence of bone metastases is an indicator of poor survival and may require more aggressive medical management. Patients with recurrence amenable to surgical treatment should be resected or ablated, as this appears to prolong survival.

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