Influence of Tumor Characteristics on the Outcome of Liver Transplantation Among Patients With Liver Cirrhosis and Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) may recur after liver transplantation (LT), mainly in patients with multinodular and large tumors. However, factors predictive of outcome after LT in patients with small tumors remain ill defined. We investigated which factors were related to mortality or tumor recurrence among 47 liver transplant recipients with liver cirrhosis and HCC and compared them with 107 patients with liver cirrhosis without tumor who underwent LT in the same period. Patients with HCC were older ($P < .001$), more frequently had cirrhosis of a viral origin ($P < .001$), and had lower Child-Pugh scores ($P < .001$) than patients without tumor. Survival of patients with and without tumor was not significantly different ($P = .20$). Among patients with HCC, those with lower recurrence-free survival rates had liver cirrhosis of a viral origin, vascular invasion, bilobar disease, and tumor-node-metastasis (TNM) stage IV. At multivariate analysis, the only factor associated with mortality or recurrence was TNM stage IV ($P = .02$). Our results suggest that in patients with HCC and TNM stage IV, LT might be contraindicated. (*Liver Transpl 2001;7:631-636.*)

The role of liver transplantation (LT) in the treatment of hepatocellular carcinoma (HCC) has evolved. In the early ages, LT was indicated in all cases of unresectable HCC without known extrahepatic spread.[1,2] Long-term survival was poor among patients with advanced disease because of a high incidence of tumor recurrence.[3] In the 1990s, several series showed that early HCC seldom recurred after LT and survival was similar in patients with cirrhosis with or without HCC.[2,4-6] Some prefer LT over resection in these patients.[2,6-8]

Several studies investigated which factors predispose to HCC recurrence after LT. Several investigators studied which factors are related to post-LT outcome.[2,5,8-11] Llovet et al[5] did not find any factor predictive of post-LT outcome. In other series, poor differentiation, vascular invasion, greater number of tumor nodules, and greater tumor size were related to lower survival or disease-free survival rates,[2,8,9,11] but most series were based on unselected groups of patients and included a considerable proportion of patients with large nodules.

The present study investigates factors associated with mortality and tumor recurrence among 47 patients with HCC who underwent LT according to well-defined selection criteria in a single center.

Patients and Methods

Between 1991 and June 2000 in our center, 160 adult patients with liver cirrhosis underwent a first LT. Forty-seven of these patients also had HCC diagnosed before LT, 6 patients had incidental HCC, and 107 patients had liver cirrhosis without HCC. Patients with incidental HCC were excluded from this retrospective study.

Patients with HCC were selected for LT if they had a single nodule not exceeding 60 mm in diameter or 2 or 3 tumors, none exceeding 50 mm in diameter, assessed by computed tomographic (CT) scan. Patients in whom vascular invasion or extrahepatic spread was evident preoperatively were excluded. LT was considered the treatment of choice for all patients with HCC if they fulfilled these criteria and did not have a contraindication for LT. Patients with HCC did not have a priority for LT compared to other patients with cirrhosis. During this period, only 2 patients were excluded from the LT waiting list 6 and 7 months after their listing because of progressing HCC.

As well as ultrasonography and CT scan, hepatic angiography was generally performed before LT. When HCC had been detected or suspected and it was technically feasible, hepatic angiography was followed by selective transarterial chemoembolization and lipiodol injection into both hepatic lobes. A postlipiodol CT scan was repeated 2 to 3 weeks later if the patient had not undergone LT by that time. If hepatic angiography had been performed before referral for LT, transarterial chemoembolization was performed only if the expected waiting period before LT was longer than 3 months. Preoperative staging of HCC included CT scan in all 47 cases, ultrasound in 45 cases, hepatic angiography in 43 cases, and postlipiodol CT scan in 37 cases. Extrahepatic spread was

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ruled out by bone scintigraphy, thoracic and abdominal CT scan, and brain magnetic resonance imaging.

Two patients had an HCC resected 1 and 8 years previously and underwent LT because of tumor recurrence. Thirty-two patients were treated while on the waiting list by either percutaneous ethanol injection (5 patients) radiofrequency ablation (3 patients), or transarterial chemoembolization (24 patients).

Fine-needle aspiration biopsy was performed in 18 patients, resulting in the diagnosis of HCC in 12 patients. In the remaining 6 patients, LT was indicated despite a cytological specimen negative for malignancy because the diagnosis of HCC was highly probable on the basis of imaging techniques. In 5 of these 6 patients, pathological examination of the liver confirmed the diagnosis of HCC (in 1 patient, complete necrosis of the nodule was observed after transarterial chemoembolization). In another 29 patients, preoperative diagnoses of HCC were based on radiological examination. Pathological examination of the liver confirmed the diagnosis in 24 patients (in 5 patients with single nodules, preoperative treatment achieved total necrosis of the tumor).

The number, site, and size of all tumor nodules found in the explanted liver, histological differentiation grade according to criteria of Edmonson and Steiner,[12] and the presence of vascular invasion were obtained from pathological records. The presence of tumor capsule was not considered for analysis because preoperative treatment achieved complete necrosis in 11 of the patients with solitary nodules.

Immunosuppressive therapy consisted of cyclosporine or tacrolimus, azathioprine, and prednisone. Patients who underwent LT for chronic hepatitis B virus infection were administered prophylaxis with intravenous hepatitis B immune globulin. Patients with a postoperative diagnosis of vascular invasion and/or more than 10 tumor nodules were considered for adjuvant chemotherapy with doxorubicin (60 mg/m^2 intravenously, every 4 weeks for 4 cycles) starting within the first postoperative month after serum bilirubin levels were less than 3 mg/dL. The 3 patients with more than 10 tumor nodules and 7 of 9 patients with vascular invasion underwent such therapy. In 2 patients, chemotherapy was not started because of postoperative complications.

Screening for tumor recurrence was by measurements of alphafetoprotein, abdominal ultrasound, and chest radiograph every 6 months and when clinically indicated. Diagnosis of HCC recurrence was based on pathological examination in all cases.

Patients were followed up until February 20, 2000, a follow-up for survivors of at least 8 months.

Statistical Analysis

Epidemiological and laboratory values are expressed as mean and interquartile range. Length of follow-up is shown as median and range.

Patients with HCC diagnosed before LT and patients without HCC were compared for age, sex, Child-Pugh status,[13] cause of liver cirrhosis (viral *v* nonviral), and time on the waiting list before LT by using 2-tailed Student's *t*-test for continuous variables and Chi-squared test and Fisher's exact test, as appropriate, for categorical variables. Kaplan-Meier method was used to obtain actuarial survival rates, and both curves were compared using the log-rank test.

The influence on recurrence-free survival of the following variables was assessed: age (>60 *v* <60 years), sex, viral liver disease, biopsy of the tumor before LT, Child's class (A versus B or C), Okuda's stage[14] (I or II *v* III), Cancer of the Liver Italian Program stage[15] (0 or 1 *v* ≥ 2), Barcelona Clinic Liver Cancer stage[16] (A *v* B, C, or D), alphafetoprotein level (>10 *v* <10 ng/mL and >100 *v* <100 ng/mL), preoperative tumor treatment, graft rejection, and pathological characteristics of the tumor, including number of tumor nodules (solitary *v* multinodular and 1 to 3 *v* >3 nodules); tumor diameter (>30 *v* ≤ 30 mm and >40 *v* ≤ 40 mm); unilobar or bilobar tumor; pathological tumor-node-metastasis (pTNM) stage[17] (stage I, II, or III *v* IV); vascular invasion, and degree of differentiation (Edmonson's grade I or II *v* III). Statistical significance of Kaplan-Meier estimates was analyzed by log-rank test, and variables with *P* less than .05 were entered in a multivariate Cox model. Multivariate Cox proportional hazard regression models were performed to estimate the adjusted ratios for risk factors of mortality and tumor recurrence.

Results

Basal characteristics of patients with and without HCC are listed in Table 1. Patients with HCC were older and had better liver function than patients without HCC, and their liver disease was more frequently of viral origin.

Ten patients in the HCC group and 15 patients in the non-HCC group died after a median follow-up of 33 months (range, 2 to 116 months) and 51 months (range, 0 to 119 months), respectively. Cause and time of death of patients in both groups are listed in Table 2. Main causes of death in both groups were infectious diseases. Two patients died of tumor recurrence 7 and 9 months after LT. Actuarial survival (Fig. 1) was not significantly different between the groups.

Clinical staging and main radiological and pathological tumor characteristics are listed in Table 3.

Accuracy of Liver Imaging

CT staging was compared with pathological findings. Radiological assessment had a trend to underestimate the number of tumor nodules; 14 of 31 patients (45%) with solitary HCC assessed by imaging techniques were found to bear additional nodules. Radiological TNM staging underestimated pTNM in 23 cases (49%) and overestimated it in 2 cases (4%). The upgrade of pTNM staging was caused by the detection of vascular invasion in the liver explant in 4 cases.

Table 1. General Characteristics of Patients With and Without HCC

	HCC (n = 47)	Without HCC (n = 107)	*P*
Sex (men/women)	37/10	76/31	NS
Age (yr)	60.74 (55-67)	53.57 (48-62)	<.001
Cause of cirrhosis			
Viral	31 (66%)	32 (30%)	<.001
Hepatitis C virus	28 (60%)	27 (25%)	
Alcoholic	12 (26%)	47 (44%)	
Others	4 (8%)	28 (26%)	
Child's class			<.001
A	15 (30%)	3 (3%)	
B	22 (49%)	56 (52%)	
C	10 (21%)	48 (45%)	
Child-Pugh score	7.91 (6-9)	9.48 (8-11)	<.001
Time waiting for LT (d)	117.28 (20-209)	118.05 (25-193)	NS

Abbreviation: NS, not significant.

Recurrence

Tumor recurred in 6 patients at 5, 9, 16, 17, 32, and 33 months after LT. Sites of recurrence were lung (5 cases), liver (2 cases), bone (1 case), chest wall (1 case), and lymph nodes (1 case). Patients' main baseline characteristics are listed in Table 4. Two patients died of tumor recurrence 7 and 9 months after LT, another patient with tumor recurrence died of an unrelated cause (biliary complications secondary to hepatic artery thrombosis) 18 months after LT, and 3 patients are currently alive 42, 50, and 63 months after LT. Figure 2 shows the actuarial recurrence-free survival curve.

Analysis of Factors Predictive of Disease-Free Survival

Table 5 lists 1-, 2-, and 3-year actuarial disease-free survival rates in the HCC group for those variables reaching significance in univariate analysis. Patients with viral liver disease, bilobar tumor, pTNM stage IV, and microscopic vascular invasion had poorer disease-free survival than patients with nonviral liver disease; unilobar HCC; pTNM stages I, II or III; and without microscopic vascular invasion. In multivariate analysis, the only factor independently associated with mortality or recurrence was pTNM stage IV compared with stages I, II, and III (adjusted relative risk, 3.91; 95% confidence interval, 1.26 to 12.13; $P = .02$).

Table 2. Causes of Death for Patients With and Without HCC

HCC	N	Without HCC	N
Infections	3	Infections	8
Tumor recurrence	2	De novo neoplasia	3
Recurrent hepatitis B	1	Postoperative bleeding	1
Bleeding after liver biopsy	1	Central myelinolysis	1
Biliary complications	1	Cerebral hemorrhage	1
Sudden death	1	Chronic renal failure	1
De novo neoplasia	1	Biliary complications	1

Discussion

Results of the present study confirm that selected patients with liver cirrhosis and HCC may undergo LT with excellent results. In our center, LT was considered in patients with solitary HCC with a maximum diameter of 60 mm and those with 2 or 3 nodules up to 50

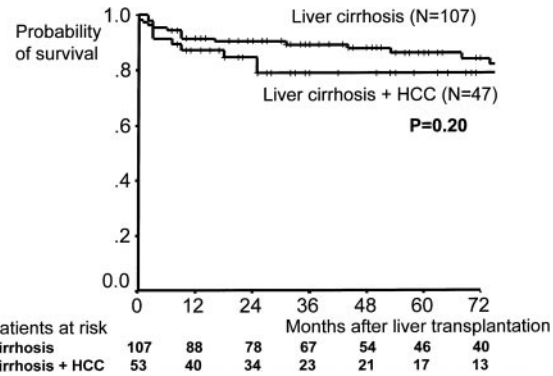

Figure 1. Actuarial patient survival after orthotopic LT in 47 patients with HCC diagnosed before LT and 107 patients with liver cirrhosis without HCC.

Table 3. Tumor Characteristics of 47 Liver Transplant Recipients With HCC

Alphafetoprotein (<10/10-100/>100 ng/mL)	29/11/6
Clinical staging	
Okuda (I/II/III)	15/22/10
CLIP (0/1/2/>2)	6/16/19/6
BCLC (A/B/C/D)	24/11/1/11
Radiological staging (CT scan)	
No. of nodules (0/1/2/3)	4/31/7/5*
Maximum diameter (mm) (n = 43)†	33.07 (20-40)
1-30	27
31-40	7
41-50	4
>50	5
Lobar involvement (unilobar/bilobar)	37/6
TNM (0/I/II/III/IV)	4/7/24/6/6
Pathological staging	
No. of nodules (1/2/3/>3)	21/8/6/12
Maximum diameter (mm)	31.47 (22-36)
1-30	26
31-40	13
41-50	6
51-60	2
Lobar involvement (unilobar/bilobar)	34/13
TNM (I/II/III/IV)	4/15/14/14
Microscopic vascular invasion	9‡ (17%)
Differentiation degree§ (I/II/III)	6/15/19

Abbreviations: CLIP, Cancer of the Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer.
* Four cases were detected by computed tomography (CT), but were detected preoperatively by ultrasonography (3 cases) and hepatic angiography (4 cases).
† Patients with tumors not detected on CT scan were not included.
‡ Two patients also had macroscopic vascular invasion.
§ Not available in 7 patients because of complete necrosis.

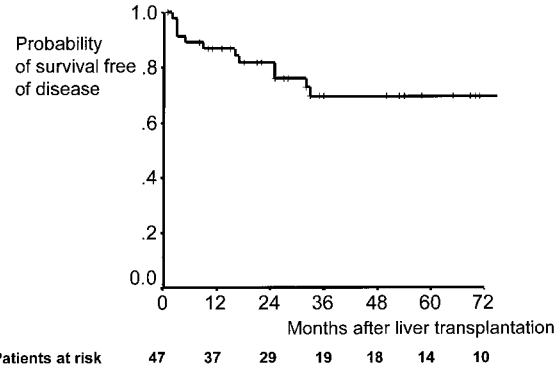

Figure 2. Actuarial survival free of tumor recurrence after orthotopic LT in 47 patients with HCC.

mm. Using these selection criteria, survival rates of patients with and without HCC were similar. One-, 3-, and 5-year survival estimates for patients with HCC were 87%, 79%, and 79%, and 1-, 2-, and 3-year actuarial recurrence-free survival rates rates were 87%, 82%, and 70%, respectively. These results are similar to those of previous series of liver transplant recipients with HCC at an early stage.[2,4-6]

In previous reports of selected series of LT recipients with HCC, Mazzaferro et al[4] found that survival was higher in patients with correct preoperative staging within their inclusion criteria than in patients with more advanced disease, and Figueras et al[6] found that patients with tumor nodules greater than 5 cm and macroscopic vascular invasion had a greater mortality rate. Conversely, Llovet et al[5] did not find a correlation between tumor characteristics and patient outcome, but in this series, 12% of the patients had incidental HCC. In our study, patients with cirrhosis of viral origin, microscopic vascular invasion, bilobar disease, and pTNM stage IV did worse than patients with non-

Table 4. Baseline Characteristics of 6 Patients With Recurrent HCC After LT

Age (yr)	67	68	64	61	73	68
Sex	Female	Female	Male	Male	Male	Male
Cause of cirrhosis	Hepatitis C	Hepatitis C	Hepatitis C	Hepatitis C	Alcohol	Hepatitis C
Waiting time (d)	14	226	52	63	255	22
Alphafetoprotein (ng/mL)	1,900	11	198	1	6	6
No. of tumors	1	3	2	6	>10	2
Vascular invasion	Yes	Yes	Yes	Yes	No	No
pTNM	IV	III	IV	IV	IV	III
Differentiation grade	III	III	III	III	III	III
Preoperative treatment	TAE	No	No	No	TAE	TAE
Postoperative treatment	Yes	Yes	Yes	Yes	Yes	No

Abbreviation: TAE, transarterial chemoembolization.

Table 5. Prognostic Variables Related to Recurrence-Free Survival After LT in 47 Patients With HCC

	No. of Patients	Actuarial Survival (%) 1-Yr	2-Yr	3-Yr	*P*
Viral disease					.03
No	16	100	93	93	
Yes	31	80	76	57	
Lobes involved					.03
Unilateral	40	91	87	82	
Bilateral	13	77	69	46	
pTNM					.007
I-III	33	94	90	84	
IV	14	71	64	43	
Vascular invasion					.02
No	38	89	86	79	
Yes	9	78	67	25	

viral cirrhosis, no vascular invasion, unilobar disease, or pTNM stages I to III. The only factor independently predictive of recurrence or mortality was pTNM stage IV, suggesting that LT should be questioned in patients with HCC and pTNM stage IV, as suggested in series of unselected liver transplant recipients with HCC. Unfortunately, only 6 of 14 patients (43%) with pTNM stage IV were correctly staged on a CT basis, and when the worst stage of a combination of imaging techniques was used, only 8 of 14 patients (57%) were correctly identified. Conversely, no patient was misdiagnosed as TNM stage IV on a CT basis. The use of iodized-oil CT scan has been reported to be very useful in the preoperative staging of HCC, with an agreement of 96% between radiological and pathological staging,[18] but in the present series, such agreement was not found.

The possible role of adjuvant chemotherapy in this group of patients with a high risk for tumor recurrence remains unclear. Encouraging results have been obtained with the use of doxorubicin[19] and the combination of doxorubicin and cisplatin.[20] In our series, postoperative doxorubicin was administered to patients believed to have a high risk for tumor recurrence, but half these patients had tumor recurrence. All but one of the patients with HCC with recurrence had been administered adjuvant chemotherapy. However, whether adjuvant chemotherapy may have influenced the time to recurrence in these patients could not be determined.

We could not ascertain whether pre-LT treatment might reduce the risk for post-LT HCC recurrence. Pre-LT treatment achieved complete tumor necrosis in 11 cases. None of them had post-LT recurrence. Conversely, only 1 of 15 patients with a single nonnecrotic nodule had recurrence.

In summary, patients with small HCCs who undergo LT have a survival similar to that of patients with liver cirrhosis without HCC and an acceptable recurrence-free survival rate. pTNM stage IV helps distinguish a subset of patients with a poor oucome, but imaging techniques are not accurate enough to predict pTNM stage because they miss a significant proportion of patients with pTNM stage IV. Radiological TNM stage IV might be considered a contraindication for LT.

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