LIVER TRANSPLANTATION FOR THE TREATMENT OF SMALL HEPATOCELLULAR CARCINOMAS IN PATIENTS WITH CIRRHOSIS

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Abstract *Background.* The role of orthotopic liver transplantation in the treatment of patients with cirrhosis and hepatocellular carcinoma is controversial, and determining which patients are likely to have a good outcome after liver transplantation is difficult.

Methods. We studied 48 patients with cirrhosis who had small, unresectable hepatocellular carcinomas and who underwent liver transplantation. In 94 percent of the patients, the cirrhosis was related to infection with hepatitis B virus, hepatitis C virus, or both. The presence of tumor was confirmed by biopsy or serum alpha-fetoprotein assay. The criteria for eligibility for transplantation were the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinomas and no more than three tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors. Twenty-eight patients with sufficient hepatic function underwent treatment for the tumor, mainly chemoembolization, before transplantation. After liver transplantation, the patients were followed prospectively for a median of 26 months (range, 9 to 54). No anticancer treatment was given after transplantation.

Results. The overall mortality rate was 17 percent. After four years, the actuarial survival rate was 75 percent and the rate of recurrence-free survival was 83 percent. Hepatocellular carcinoma recurred in four patients (8 percent). The overall and recurrence-free survival rates at four years among the 35 patients (73 percent of the total) who met the predetermined criteria for the selection of small hepatocellular carcinomas at pathological review of the explanted liver were 85 percent and 92 percent, respectively, whereas the rates in the 13 patients (27 percent) whose tumors exceeded these limits were 50 percent and 59 percent, respectively ($P = 0.01$ for overall survival; $P = 0.002$ for recurrence-free survival). In this group of 48 patients with early-stage tumors, tumor–node–metastasis status, the number of tumors, the serum alpha-fetoprotein concentration, treatment received before transplantation, and 10 other variables were not significantly correlated with survival.

Conclusions. Liver transplantation is an effective treatment for small, unresectable hepatocellular carcinomas in patients with cirrhosis. (N Engl J Med 1996;334:693-9.)

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THE value of orthotopic liver transplantation in the treatment of hepatocellular carcinoma has often been debated. Although liver replacement could be curative for patients with tumors confined to the liver, the long-term results of liver transplantation in patients with hepatocellular carcinoma have been disappointing, with an overall five-year survival rate ranging from 30 to 40 percent.[1-9]

In recent years, revisions of the tumor–node–metastasis (TNM) classification system[9] and other systems for determining the stage of hepatocellular carcinoma[10] have made possible a more detailed, retrospective analysis of treatment in these patients. In several studies, tumor stage before transplantation was directly related to the rate of recurrence of cancer after liver transplantation. Moreover, in patients with early-stage hepatocellular carcinoma, liver transplantation was more effective than resection of the liver.[11-15] To examine further the efficacy of transplantation, we undertook a prospective cohort study of patients with cirrhosis who had unresectable hepatocellular carcinomas and who received liver transplants; in this study we also assessed the influence of characteristics used to select patients for transplantation on the recurrence of cancer and on survival.

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METHODS

Study Design

Between January 1991 and December 1994, 295 patients with hepatocellular carcinoma who were seen at the Division of Gastrointestinal Surgery of the National Cancer Institute in Milan, Italy, were judged to have cancer that was unresectable because of the location of the tumor in the liver, because the tumor was multifocal, or because the patient had advanced hepatic insufficiency related to cirrhosis. Among those 295 patients, 60 who had histologically proved cirrhosis (20 percent) were eligible for the present study because their tumors were at an early stage. The diagnosis of hepatocellular carcinoma was confirmed in all patients either by biopsy of the tumor or by a serum alpha-fetoprotein measurement above 300 ng per milliliter.

For patients with a single hepatocellular carcinoma to be eligible for the study, the tumor could not exceed 5 cm in diameter. In patients with multiple tumors, there could be no more than three tumors, none exceeding 3 cm in diameter. Patients in whom tumor invasion of blood vessels or lymph nodes was evident or suspected preoperatively were excluded.

Forty-eight patients received transplants during the study period, 1 patient died while awaiting transplantation, and 11 others were still awaiting transplantation on September 30, 1995. Once patients were accepted as candidates for transplantation, preoperative treatment of their tumor was scheduled, depending on their Child–Pugh class (indicating the adequacy of liver function) at that time (Table 1). Patients in Child–Pugh class A (12 patients) or class B (21 patients) received anticancer treatment before transplantation (hepatic-artery chemoembolization in 26 patients, percutaneous injection of alcohol in 1 patient, and hepatic resection three years before liver transplantation in the single patient with the fibrolamellar variant of hepatocellular carcinoma). The five remaining patients who were otherwise eligi-

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ble for chemoembolization were not treated for technical or anatomical reasons. The 15 patients with Child–Pugh class C hepatic insufficiency received no treatment before surgery.

Because liver transplantation was considered the keystone of treatment, it was performed whenever a compatible liver became available, regardless of any scheduled anticancer therapy. So that the influence of the tumor stage before transplantation on patients' survival could be assessed, neither medical therapy nor radiation treatment was given after transplantation unless recurrence of the cancer was detected. In addition to regular post-transplantation follow-up, the tumor stage was determined every three months (by ultrasonography, chest radiography, and measurement of serum alpha-fetoprotein) in all patients; abdominal and thoracic computed tomographic (CT) scans were obtained every six months, and radionuclide bone scans were obtained every eight months. The study protocol was approved by the ethics committee of the institute, and all the patients gave informed consent for the procedures.

Characteristics of Patients and Staging Procedures

Of the 48 patients, 38 were men and 10 were women, with a median age of 52 years (range, 39 to 60). Forty-five patients had cirrhosis caused by chronic viral hepatitis (hepatitis B virus [HBV] in 11 patients, hepatitis C virus [HCV] in 32, and both HBV and HCV in 2). In all patients, viral status was assessed before and after transplantation with the latest-generation antibody-detection techniques and was confirmed by the identification of HBV DNA, HCV RNA, or both in serum. Only three patients had no evidence of hepatitis at the time of transplantation; one had a multifocal fibrolamellar hepatocellular carcinoma, and the other two had alcoholic or cryptogenic cirrhosis. All the patients were judged to have unresectable cancer because the tumor was centrally located in the liver (5 patients) or multifocal (7 patients) or because the patient had advanced cirrhosis (36 patients).

Assessment of the tumor before transplantation consisted of hepatic angiography and liver CT scanning performed during the period of portal venous flow after the arterial injection of contrast material (CT arterial portography).[17] Iodized oil (Lipiodol) was then injected into the hepatic artery, and transarterial chemoembolization was performed in 26 patients.[18] Four weeks later, the intrahepatic retention and distribution of iodized oil were measured, and a map of the apparent distribution of tumor within the liver was prepared. For chemoembolization, 14 patients received iodized oil plus doxorubicin (35 mg per square meter of body-surface area), and 12 patients received iodized oil plus mitoxantrone (14 mg per square meter). The treatments were repeated every six to eight weeks, with a median of two cycles per patient (range, one to four). There were no deaths related to chemoembolization; nevertheless, seven of these patients had deterioration in liver function.

Table 1. Child–Pugh System for Grading the Severity of Liver Disease.*

Variable	Points Scored
Encephalopathy†	
None	1
1–2	2
3–4	3
Ascites	
Absent	1
Slight	2
Moderate	3
Serum bilirubin (mg/dl)‡	
1.0–2.0	1
2.1–3.0	2
≥3.1	3
Serum albumin (g/liter)	
>35	1
28–35	2
<28	3
Prolongation of prothrombin time (sec)	
1–3	1
4–10	2
>10	3

*Child–Pugh class A (a total of 5 to 6 points) indicates good hepatic function; class B (7 to 9 points), intermediate hepatic function; and class C (10 to 12 points), poor hepatic function.

†Graded according to the system of Trey et al.[16]

‡To convert values for bilirubin to micromoles per liter, multiply by 17.1.

Table 2. Causes of Death after Liver Transplantation among Eight Patients with Small Hepatocellular Carcinomas and Cirrhosis.

Cause of Death	Time after Transplantation
Intraoperative bleeding, graft failure	2 days
Adult respiratory distress syndrome, sepsis	1 mo
Pulmonary embolism, hypertension	1 mo
HBV hepatitis in graft, sepsis after retransplantation	9 mo
Recurrence of carcinoma in lungs	18 mo
Post-transplantation lymphoproliferative disease	25 mo
Chronic rejection, aspergillosis	35 mo
Recurrence of carcinoma in liver and bone	35 mo

Tumor staging was completed a median of 143 days (range, 2 to 294) before liver transplantation. During that period, only one patient who was originally considered eligible for liver transplantation was removed from the waiting list because of disease progression (she died six months later).

Liver transplantation was performed with an average of 8 units of packed red cells (range, 0 to 98). Venovenous bypass was used in 22 patients; in the remaining 26 patients, the recipient's inferior vena cava was preserved.[19] The livers removed at the time of total hepatectomy were fixed in formalin and were cut into slices 1 cm thick (the same thickness as the "slices" of a CT scan). The number, diameter, anatomical location, and microscopical appearance of each tumor were recorded (T stage), as well as the possible presence of tumor-capsule or microvascular invasion. The lymph nodes of the hepatic hilum were removed and studied separately for possible tumor spread (N stage). An autopsy was always performed in patients who died after transplantation, and the possible recurrence of cancer was investigated.

The immunosuppressive regimen after liver transplantation consisted of cyclosporine, azathioprine, and corticosteroids. Azathioprine was stopped after one month. The dose of corticosteroids was progressively tapered, and administration was stopped altogether after six months. Cyclosporine monotherapy was maintained successfully thereafter in 40 of the 45 long-term survivors. Three patients received tacrolimus at various times after liver transplantation because of rejection resistant to treatment with corticosteroids and cyclosporine.

Statistical Analysis

The cumulative overall and recurrence-free survival rates were calculated by the Kaplan–Meier method.[20] Data on three patients who died within one month after transplantation were included in the calculations of recurrence-free survival on the assumption that the patients did not survive long enough for recurrent tumors to develop. The survival curves were compared by means of the log-rank test.[21] All statistical tests were two-tailed. Analyses were performed with the SAS statistical package, with the inclusion of 15 variables related to the patients, their cirrhosis, and their tumors, including treatment before transplantation and the criteria used for the selection of patients.

Results

As of September 30, 1995, the median follow-up for the 48 patients with cirrhosis and unresectable hepatocellu-

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lar carcinomas who underwent liver transplantation was 26 months (range, 9 to 54). Among these patients, two required retransplantation because of recurrent viral hepatitis (one with HBV and one with HCV). Three patients died perioperatively (6 percent). Altogether, eight patients died after transplantation (17 percent), with recurrent cancer accounting for only two of the deaths (Table 2). Four patients had recurrent cancer a median of 3 months after transplantation; two of them died, and a third patient with metastases to the lung was still alive 26 months after transplantation. The fourth patient had a single subcutaneous mass of hepatocellular carcinoma detected along the needle track of the percutaneous liver biopsy performed before transplantation; that tumor was surgically removed, and the patient was free of disease 14 months later. In three of the four patients with recurrent cancer, the tumor stage assigned preoperatively was lower than that of the resected tumor (two patients had more than three tumors, and one patient's tumor was more than 5 cm in diameter). The fourth patient (who had the subcutaneous recurrence) had a single tumor 2.8 cm in diameter. The overall actuarial four-year survival was 75 percent, and the recurrence-free survival at four years was 83 percent, with three-year standard errors of 5.8 percent and 5.9 percent, respectively (Fig. 1). After three years, recurrence-free survival became higher than overall survival, because recurrence of cancer was excluded at autopsy in some patients who died or because data were censored earlier in the calculation of recurrence-free survival.

The influence of several variables on overall and recurrence-free survival is shown in Table 3. Survival was not affected by the patient's age or sex or by common markers of chronic liver disease, such as the type of hepatitis virus and the Child–Pugh stage at the time of transplantation. Of particular importance was the fact that, as long as all liver cancers were removed at an early stage, even classic prognostic factors such as the T stage, number of tumors, serum alpha-fetoprotein concentration, and presence or absence of a capsule were not statistically significant predictors of survival (with so few recurrences, however, these analyses had very low power).

In this selected group of patients with small tumors, preoperative chemoembolization proved ineffective (Fig. 2), even though this treatment was not randomly assigned but, rather, was used only if liver function was not seriously impaired. In the 28 pretreated patients (58 percent of the total) four-year survival was 79 percent and recurrence-free survival was 87 percent. Similarly, 69 percent of the 20 patients who received no treatment before transplantation were alive and 78 percent were free of recurrence after the same period of follow-up.

The selection of patients (and tumors) was the main factor affecting survival after transplantation, as was confirmed by the small number of recurrences (in four patients) and by pathological examination of the explanted livers, which revealed a median of 2 tumor masses per liver (range, 1 to 11) and a median diameter of 1.5 cm per tumor (range, 0.2 to 6). With respect to TNM stage, neither vascular invasion nor lymph-node metastases were detected, and the number and size of the tumors in each liver were not significantly different at various T stages. Fifteen patients had single tumors of 2 cm or less in diameter (stage T1); 18 patients had a median of 1 tumor 2 cm or less in diameter (stage T2); and 13 patients had multiple tumors (range, 2 to 10) 2.2 cm in diameter (stage T3). Finally, only two patients had multiple tumors (range, 2 to 10) that were 2.5 cm or more in diameter diffused to both lobes of the liver (stage T4). The size, number, and location of tumors were the only

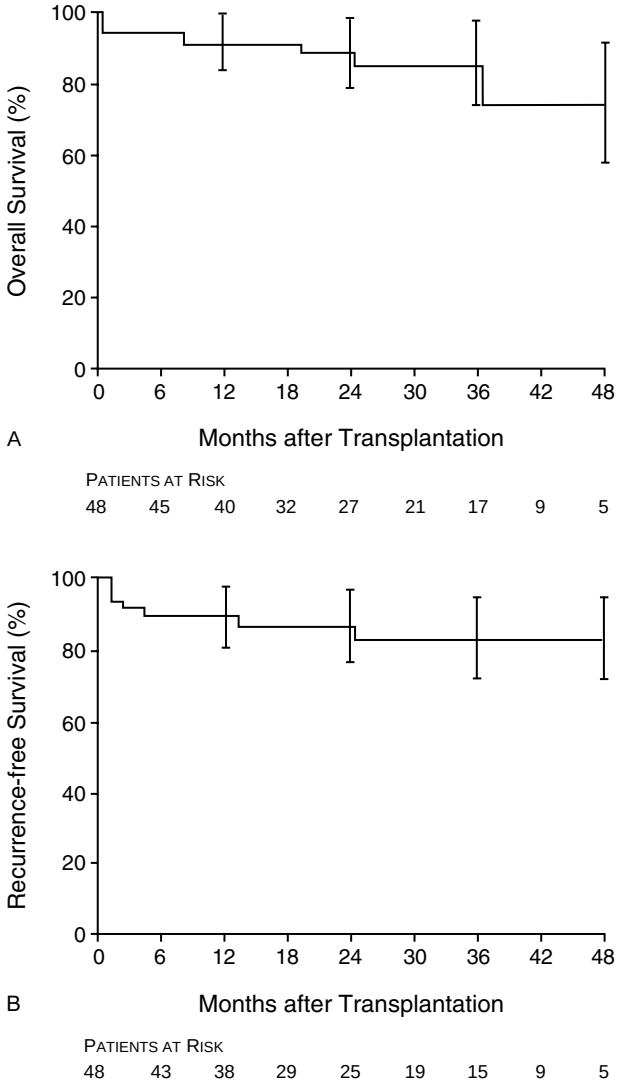

Figure 1. Overall Survival (Panel A) and Recurrence-free Survival (Panel B) after Liver Transplantation in 48 Patients with Small Hepatocellular Carcinomas and Cirrhosis.

Data on the three patients who died within one month after transplantation were included in the calculation of recurrence-free survival. The three-year standard errors are 5.8 percent for overall survival and 5.9 percent for recurrence-free survival; 95 percent confidence intervals (bars) are shown at one-year intervals.

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variables that affected the TNM stage; there was no macroscopic or microscopic vascular invasion and no lymph-node or distant metastasis.

Since an early tumor stage at the time of transplantation was the critical factor associated with greater rates of recurrence-free survival, we attempted to define more exactly the small cancers (either single or multiple) that could be cured by liver transplantation. Although there were no differences in overall or recurrence-free survival after transplantation between patients who had single tumors and those with multiple tumors (Table 3), the particular criteria for tumor stage that we used in recruiting patients proved effective in predicting outcome after transplantation (Fig. 3). On pathological examination of the explanted livers, 35 patients (73 percent) were found to have tumors that met the predetermined selection criteria (i.e., single tumors ≤5 cm in diameter or no more than three tumors ≤3 cm in diameter), whereas 13 patients (27 percent) had tumors that exceeded those limits and were in fact assigned too low a stage before surgery.

The actuarial four-year survival rate among the 35 patients in whom preoperative staging was correct, as determined by post-transplantation pathological examination, was 85 percent, and the rate of recurrence-free survival was 92 percent. In contrast, the four-year rates of survival and recurrence-free survival among the 13 patients whose tumors were not correctly identified as to stage before transplantation were 50 and 59 percent, respectively. Comparisons between the two groups showed a significant advantage for the patients who had tumors at earlier stages ($P=0.01$ for overall survival and $P=0.002$ for recurrence-free survival) (Fig. 3).

Table 3. Prognostic Variables Related to Survival and Recurrence of Cancer after Liver Transplantation in 48 Patients with Small Hepatocellular Carcinomas and Cirrhosis.*

Variable	No. of Patients/ No. of Recurrences	Actuarial Survival					
		Overall			Recurrence-free		
		1 yr	3 yr	4 yr	1 yr	3 yr	4 yr
		percent					
Demographic							
Age							
≤52 yr	23/2	96	86	69	96	85	85
>52 yr	25/2	92	85	85	84	84	84
Sex							
Male	38/4	92	89	76	89	82	82
Female	10/0	90	90	60	90	90	90
Cirrhosis-related							
Virus							
HCV	32/4	97	87	66	91	81	81
HBV	11/0	91	81	81	91	91	91
HCV and HBV	2/0	100	100	100	100	100	100
Other	3/0	67	67	67	100	67	67
Child-Pugh class at transplantation†							
A	12/1	93	74	74	86	86	86
B	21/2	89	89	72	89	79	79
C	15/1	93	93	80	93	86	86
Tumor-related							
T stage‡							
T1 and T2	33/3	97	77	77	94	85	86
T3 and T4	15/1	79	69	69	80	80	80
No. of tumor nodules							
1	25/1	96	90	79	92	81	81
≥2	23/3	86	78	69	94	89	86
Capsule							
Present	16/3	100	100	85	100	84	84
Absent	30/1	86	74	65	83	83	83
Unknown	2/0	100	100	100	100	100	100
Serum alpha-fetoprotein§							
≤300 ng/ml	40/3	92	85	73	92	85	85
>300 ng/ml	8/1	87	87	87	75	75	75

*Data on the three patients who died within one month after transplantation were included in the calculation of recurrence-free survival. For each variable, the difference between the survival curves (overall and recurrence-free) was nonsignificant by the log-rank test.

†Child–Pugh class A indicates good hepatic function, class B intermediate hepatic function, and class C poor hepatic function.

‡In the TNM system, T1 indicates a single tumor ≤2 cm in diameter; T2 indicates a single tumor ≤2 cm with vascular invasion, a single tumor >2 cm without vascular invasion, or multiple single-lobed tumors ≤2 cm without vascular invasion; T3 indicates a single tumor >2 cm with vascular invasion, multiple single-lobed tumors >2 cm without vascular invasion, or multiple single-lobed tumors of any size with vascular invasion; T4 indicates multiple two-lobed tumors of any size, with or without vascular invasion. None of the patients had positive lymph nodes, metastases, or vascular invasion; their tumors were therefore classified as N0 and M0.

§Normal range in adults, 0 to 10 ng per milliliter.

Using the same statistical analysis, we tested seven other variables: duration of the waiting period before transplantation, variation in the Child–Pugh class over time, extent of donor–recipient HLA cross-matching, incidence of graft rejection, type of immunosuppressive regimen, perioperative use of blood products, and surgical technique used in graft implantation. None of these variables were significantly related to recurrence of the tumor or survival of patients.

Discussion

Patients with cirrhosis are at substantial risk for hepatocellular carcinoma; the yearly incidence in such patients is 3 percent.[22] The prognosis for patients with the disease is poor, because the number of new cases roughly equals the number of deaths per year, and cirrhosis itself may be a preneoplastic condition,[23] even though the incidence of hepatocellular carcinoma is not related to the severity of liver disease.[13,22,23] In fact, about one third of our patients with hepatocellular carcinoma underwent liver transplantation although they had good hepatic function (Child–Pugh class A); those patients could not be treated without transplantation because their cancer was multiple or centrally located in the organ.

The length of follow-up in this study (median, 26 months) is notable, because most recurrences of cancer occur within 2 years after transplantation.[11-13,24] The overall results (four-year

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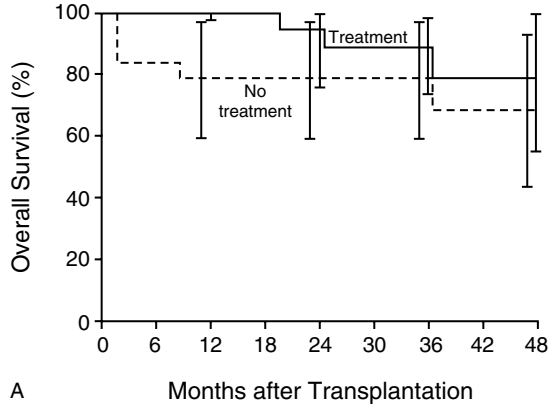
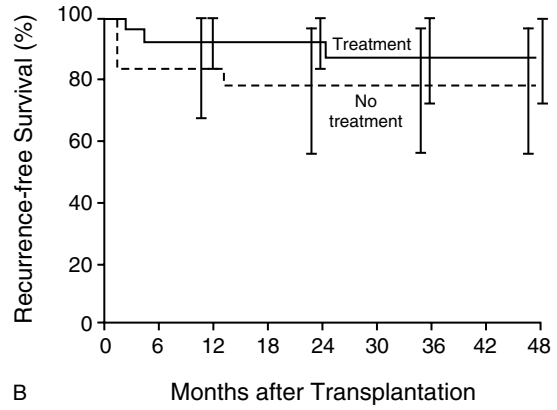


PATIENTS AT RISK

Treatment	28	28	26	21	17	11	9	4	3
No treatment	20	19	14	11	11	10	8	5	3



PATIENTS AT RISK

Treatment	28	27	24	19	16	10	8	5	3
No treatment	20	16	14	10	10	9	8	5	3

Figure 2. Effect of Anticancer Treatment before Transplantation on Overall Survival (Panel A) and Recurrence-free Survival (Panel B) in 48 Patients with Cirrhosis and Hepatocellular Carcinomas.

Data on the three patients who died within one month after transplantation were included in the calculation of recurrence-free survival. Ninety-five percent confidence intervals (bars) are shown at one-year intervals.

actuarial survival, 75 percent; recurrence-free survival, 83 percent) are encouraging when compared with the natural history of small, untreated hepatocellular carcinomas in patients with cirrhosis, in whom the three-year survival rate is only 25 percent.[25] The survival of our patients after transplantation is quite similar to the 70 percent reported after four years in patients with cirrhosis alone who underwent transplantation.[26]

Such good results were first predicted 10 years ago, when an excellent survival rate after liver transplantation was reported in patients with incidentally detected hepatocellular carcinomas (tumors ≤5 cm in diameter discovered by pathological examination in resected livers not originally thought to contain tumors[27]). Today, because of the high rate of diagnosis of liver carcinoma, incidentally detected tumors in patients with cirrhosis are mainly less than 2 cm in diameter.

With very few exceptions,[15] a diameter of 5 cm is still the generally accepted upper limit for small intrahepatic tumors. That cutoff was used in selecting patients for the present study; moreover, patients with multiple tumors (up to three tumors, none exceeding 3 cm in diameter) were considered eligible for transplantation. These criteria for the selection of patients were significant predictors of good survival rates after liver transplantation (Fig. 1 and 3).

At this early stage of tumor development, there were no other factors (such as the TNM stage, serum alpha-fetoprotein concentration, or the presence or absence of capsule) that had prognostic value. Recognized indicators of poor prognosis, such as lymph-node spread, vascular invasion, or metastases, were not detected in this study, confirming that in Western patients the clinical and pathological progression of hepatocellular carcinoma is usually slow and is related to tumor size.[28]

At the time of diagnosis, 20 to 60 percent of small hepatocellular carcinomas are multifocal.[23,25,29] We found that 27 percent of small tumors in patients with cirrhosis were assigned too low a stage before transplantation, despite extensive preoperative evaluation. Nevertheless, survival after transplantation was similar in patients with a single tumor and those with multiple tumors.[14] (The TNM classification does not distinguish among patients with multiple hepatocellular carcinomas on the basis of the number of tumors, although a limit of three tumors is probably important with respect to better patient survival after liver replacement.[14]) In fact, since patients with multifocal hepatocellular carcinomas (48 percent of our patients) are currently not considered for transplantation, the procedure should be proposed only if the patient has no more than three small tumors.

If our results are confirmed by others, the optimal treatment for patients with cirrhosis who have single hepatocellular carcinomas no more than 5 cm in diameter — resection or transplantation — may become a subject of debate. Retrospective analysis has shown that patients with cirrhosis who have stage T1 or T2 tumors do better after transplantation (five-year survival, 67 to 75 percent) than after hepatic resection (0 to 56 percent).[11,12] Furthermore, the five-year rate of recurrence-free survival after the resection of single, small (≤5 cm) hepatocellular carcinomas is practically zero.[30] Our study does not address the issue of liver transplantation for patients with small, resectable hepatocellular carcinomas. None of the tumors in the patients we studied were considered resectable; indeed, this was a requirement for entering the trial. Consequently, as long as the number of donors remains limited and until the results of randomized studies become available, liver transplantation should be proposed only for patients with cirrhosis who have small hepatocellular carcinomas that cannot be resected.

There have been reports of detrimental effects of immunosuppression in patients with cancer who undergo sol-

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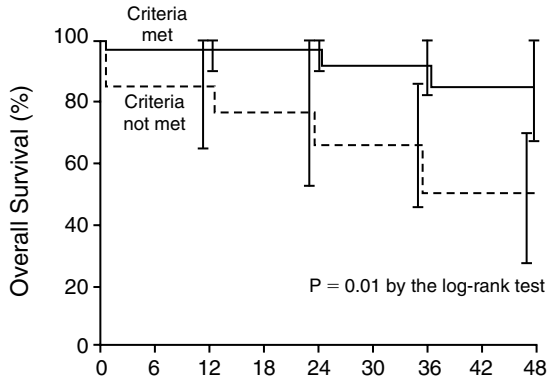
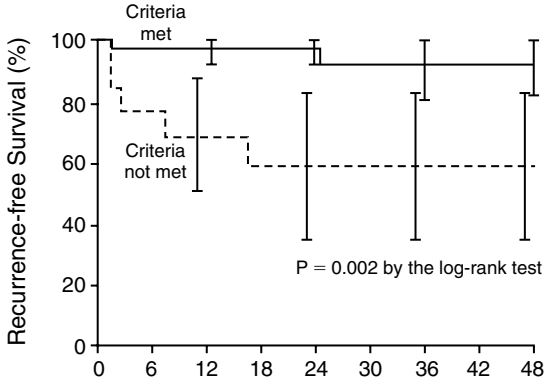


PATIENTS AT RISK

Criteria met	35	34	31	24	21	16	13	6	3
Criteria not met	13	13	11	8	6	6	4	4	3



PATIENTS AT RISK

Criteria met	35	34	31	24	21	15	12	6	3
Criteria not met	13	10	9	5	5	5	4	3	3

Figure 3. Correlation of Post-Transplantation Pathological Confirmation of Early-Stage Hepatocellular Carcinoma with Overall Survival (Panel A) and Recurrence-free Survival (Panel B) among 48 Patients with Cirrhosis.

Data on the three patients who died within one month after transplantation were included in the calculation of recurrence-free survival. Before transplantation, all the patients were estimated to have either a single hepatocellular carcinoma ≤5 cm in diameter or no more than three tumors each of which was ≤3 cm in diameter. After transplantation, the explanted livers were examined pathologically, and the patients whose tumors actually met the predefined criteria were compared with those whose tumors did not meet those criteria. Ninety-five percent confidence intervals (bars) are shown at one-year intervals.

id-organ transplantation.[31] Most of our patients were treated with a cyclosporine-based immunosuppressive regimen, with corticosteroids discontinued after six months in most cases. The risk of recurrence among patients who continue to receive corticosteroids may be as much as four times higher than the risk in patients in whom the corticosteroid is discontinued soon after transplantation.[32] Our results confirm previous experience[2] and may lead to further studies of the influence of different immunosuppressive regimens on the development of cancer after transplantation, with particular reference to the corticosteroid-sparing properties of tacrolimus and the possible reduction in the dosage of immunosuppressive agents under favorable conditions.[33]

In the past, it was tempting to conclude that liver transplantation for hepatocellular carcinoma was futile.[5,24] However, as documented in this study, long-term survival can be achieved with liver transplantation in carefully selected patients.

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