

LIVING-DONOR LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

SATOSHI KAIHARA,¹ TETSUYA KIUCHI,¹ MIKIKO UEDA,¹ FUMITAKA OIKE,¹ YASUHIRO FUJIMOTO,¹ KOHEI OGAWA,¹ KOICHI KOZAKI,¹ AND KOICHI TANAKA^{1,2}

In cadaveric liver transplantation, the Milan criteria have been accepted as the selection criteria for hepatocellular carcinoma (HCC) patients in considering organ allocation. However, the situation is different in living-donor liver transplantation (LDLT), in which the donor has a strong preference for altruism. The authors describe herein their experience with LDLT for HCC patients using their patient selection criteria. From February 1999 to March 2002, right lobe LDLT was performed in 56 patients with HCC. The authors' exclusion criteria included only those with extrahepatic metastasis or vascular invasion detected during preoperative evaluation. Thirty patients (54%) were in tumor, node, metastases stage IVa and 25 patients (45%) did not meet the Milan criteria at the time of LDLT. The follow-up period was 1 to 39 months (median, 11 months). The overall survival rates at 1 and 3 years were 73% and 55%, respectively, and the latter was significantly lower than that of adult right lobe LDLT without HCC (71% at 3 years). Fourteen patients died because of postoperative complications without tumor recurrence. Thirty-six patients survived without recurrence and six patients had recurrence. Among the six patients with recurrence, four had survived for 11 to 36 months after LDLT. In the analysis of patients who survived longer than 3 months after transplantation, 19 of 20 within the Milan criteria survived without recurrence. However, 15 of 20 patients beyond the criteria also survived without recurrence for 3 to 33 months (median, 12 months) and three of five patients with recurrence were alive for 11 to 36 months (median, 20 months). Histopathologic grading and microscopic portal venous invasion had significant negative impact on tumor recurrence. LDLT was an effective treatment for uncontrollable hepatocellular carcinoma. Because many patients who did not meet the Milan criteria survived without tumor recurrence after transplantation, different patient selection criteria are necessary in LDLT to save those with advanced HCC.

One million patients suffer from hepatocellular carcinoma (HCC) each year worldwide, accounting for approximately 1 million deaths annually (1, 2). More than 80% of HCC arises in cirrhotic patients, with a 1% to 6% annual incidence (3). In recent years, however, progress has been achieved in the treatment of HCC, and an increasing number of patients can survive with many therapeutic modalities including transcatheter arterial chemoembolization, percutaneous ethanol

injection, radiofrequency cytoablation, and liver resection. Liver transplantation is another excellent treatment for HCC patients because this procedure is able to cure not only the tumor but also the underlying cirrhosis.

Initially, liver transplantation was suggested for extensive unresectable HCC, but had unsatisfactory results because of a high rate of tumor recurrence (4–9). However, 5-year survival rates have reached 70% in well-selected candidates, and a consensus on patient selection criteria for cadaveric transplantation (the Milan criteria) has been reached in considering organ allocation (10–13).

Because living-donor liver transplantation (LDLT) has been a successful and fully accepted treatment for adult patients with end-stage liver disease, interest in this modality as the treatment for HCC has arisen. Some institutions have already started LDLT programs for HCC patients, with satisfactory results (14–16). The Milan criteria are based on organ allocation. The situation is quite different in LDLT, where the donor has a strong preference for self-giving and dedication. Therefore, other criteria for patient selection are necessary in LDLT. We describe herein our experience with LDLT for HCC patients under our own patient selection criteria. The aim of the present study is to analyze the multiple factors that affect the outcome of LDLT for HCC and to establish new patient selection criteria for LDLT in HCC patients.

PATIENTS AND METHODS

Patients with HCC who were considered for LDLT fell into three categories: (1) HCC patients with decompensated hepatic failure, (2) patients with HCC not suitable for resection or local ablative therapy because of tumor spreading or poor liver function reserve, and (3) patients with repeated tumor recurrence after previous treatment. All patients were evaluated for the extent of tumor involvement with abdominal ultrasonography; brain, chest, and bone scintigraphy; and occasionally hepatic angiography by the same radiologist in our institute. Number and size of tumor were not reasons for exclusion. Transplantation was performed with the approval of the ethics committee at Kyoto University.

From February 1999 to March 2002, 122 patients with HCC were referred to our department for consideration of LDLT and 56 LDLT have been performed. The remaining 66 cases did not undergo LDLT in our program for various reasons: contraindication in 32 patients, donor or family problems in 17 cases, other treatment in three cases, transplantation at other institutions in eight patients, and on the waiting list in six cases (Fig. 1). The demographic data of the recipients are shown in Table 1. Most patients had virus-associated liver cirrhosis as the underlying disease. Thirty-three patients were classified as Child-Pugh A or B and 23 were Child-Pugh C just before transplantation. Thirty patients (54%) were in tumor-node-metastases (TNM) stage IVa and 25 patients (45%) had tumors beyond the Milan criteria. Before transplantation, most patients had received various forms of treatment for HCC, including transcatheter arterial chemoembolization in 39 cases, percutaneous ethanol injection or

¹ Department of Transplantation and Immunology, Graduate School of Medicine, Kyoto University, Japan.

² Address correspondence to: Koichi Tanaka, M.D., Department of Transplantation and Immunology, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8057, Japan. E-mail: koichi@kuhp.kyoto-u.ac.jp.

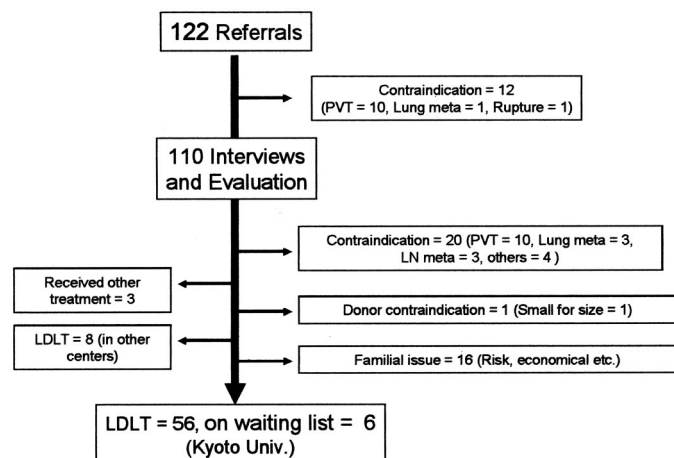


FIGURE 1. One hundred twenty-two HCC patients were referred to our department and 56 LDLT were performed under our patient selection criteria. Sixty cases did not receive LDLT in our program because of various reasons and six patients are on our waiting list.

radiofrequency cytoablation in 24 cases, liver resection in eight cases, and irradiation in one case.

All patients received right lobe (right hemiliver) grafts from living donors. After laparotomy, tumor localization was confirmed again and, if there was any lesion suspected of being metastatic, the tumor was resected and processed for frozen section examination. Ascites was also collected and sent for cytologic study to rule out tumor dissemination. During hepatectomy, hepatic inflow was dissected first to prevent tumor spreading in the succeeding steps of the procedure. In some cases, a portosystemic shunt was created temporarily between the portal vein and the inferior vena cava to prevent the adverse effects of portal hypertension.

For immunosuppression, patients were administered tacrolimus orally from the next morning and the dosage was adjusted to maintain a trough level of 10 to 15 ng/mL. Methylprednisolone was administered only immediately after reperfusion at 1 mg/kg. Patients who experienced an acute rejection were treated with a 10-mg/kg bolus of methylprednisolone for 3 days. The patients who were diagnosed with TNM stage III or IVa disease before transplantation received epirubicin infusion at 10 mg/m² during the anhepatic period without any critical adverse effects. After transplantation, chemotherapy was continued using the same drug and dose weekly for 10 weeks, for those with p-TNM stage III or IVa disease when their general condition allowed.

RESULTS

Fourteen patients (25%) died because of posttransplant complications, sepsis, or recurrence of hepatitis C virus hepatitis from 3 weeks to 11 months after transplantation. Two patients died of tumor recurrence at 17 and 31 months after transplantation. The overall survival rates at 1 and 3 years were 73.1% and 54.6%, respectively (Fig. 2), and the latter was significantly lower than that of the patients who received right lobe grafts for reasons other than HCC during the same period (3-year survival, 70.5%).

Recurrence of HCC occurred in six patients (11%) from 3 to 25 months after transplantation, and the tumor-free survival rates at 1 and 3 years were 85.4% and 68.3%, respectively (Fig. 2). The incidences of recurrence according to various tumor-related parameters are shown in Table 2. The sites of recurrence were the lung in three patients; the adrenal

TABLE 1. Demographic data of HCC patients who underwent LDLT

	HCC patients (n=56)
Age (years)	21.8–69.2 (median, 53.8)
Case	
Right lobe graft (with MHV)	4
ABO incompatible	6
Follow-up period (mo)	1–39 (median, 11)
Child-Pugh score	
A	14
B	19
C	23
Pretransplant indication	
HBV-LC	21
HCV-LC	25
PBC	2
Alcoholic	2
Unknown	2
HBV plus HCV	1
Biliary atresia	1
Congenital biliary dilatation	1
Citrulinemia	1
TNM stage	
I	8
II	13
III	5
IVa	30
Milan criteria	
Within	31
Beyond	25
Previous therapy	
TACE	39
Cytoablation	24
Liver resection	8
Irradiation	1
No previous therapy	13

MHV, middle hepatic vein; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; PBC, primary biliary cirrhosis; TACE, transcatheter arterial chemoembolization.

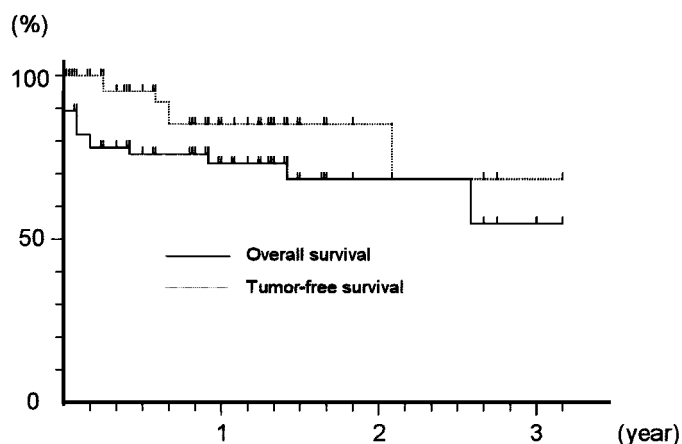


FIGURE 2. Overall and tumor-free survival of 56 HCC patients after LDLT.

gland, diaphragm, and retroperitoneal cavity in two patients; and the brain, the bone, and the liver graft in one patient. Treatment for the recurrent tumor included tumor resection in five patients, systemic chemotherapy in three patients, and transarterial chemotherapy and irradiation in two pa-

TABLE 2. Relationship between various factors and HCC recurrence

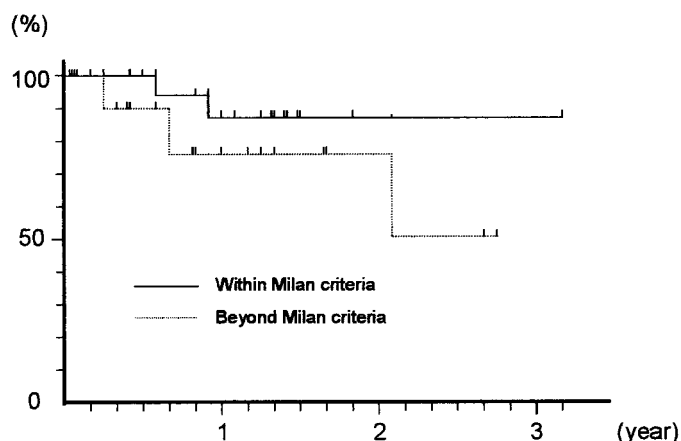
	Total	Recurrence (positive)	p value (Fisher's test)
TNM stage			
I-III	15	1	0.38
IVa	25	5	
Pre-Tx therapy			
Positive	33	6	0.57
Negative	7	0	
Pre-Tx AFP			
<100	27	2	0.07
>100	13	4	
Pre-Tx PIVKA-II			
Within normal limit	18	3	>0.99
Over normal limit	20	3	
Pre-Tx tumor diameter ^a			
<5 cm	33	4	0.28
>5 cm	7	2	
Pre-Tx tumor number ^a			
≤3	27	2	0.07
>3	13	4	
Milan criteria			
Within	20	1	0.19
Beyond	20	5	
p-TNM stage			
I-III	10	0	0.31
IVa	30	6	
Histologic grade			
Well, moderately	31	1	<0.01
Poorly	9	5	
Microvascular invasion			
Positive	12	5	<0.01
Negative	28	1	
Adjuvant chemotherapy			
Positive	7	3	0.055
Negative	33	3	
Post-Tx tumor diameter ^b			
<5 cm	33	4	0.28
>5 cm	7	2	
Post-Tx tumor number ^b			
≤3	21	1	0.08
>3	19	5	

^a On pretransplant imaging studies.^b On pathologic examination of explants.Tx, Transplant; AFP, α -fetoprotein; PIVKA-II, protein induced by vitamin K absence-II.

tients each. With these treatments, four patients were still alive at 6 to 12 months after their recurrence and two patients died at 14 and 23 months after their recurrence.

The risk for HCC recurrence was analyzed for 13 pre- and posttransplant factors in 40 patients who survived longer than 3 months after transplantation (Table 2). In univariate analysis, none of the preoperative factors showed significant risk for tumor recurrence. Among the posttransplant factors, the histologic grade and the existence of microvascular invasion showed a significant correlation with recurrence.

Five of six patients with recurrence did not meet the Milan criteria, and tumor-free survival of the patients within and beyond the Milan criteria at 2 years was 87.4% and 76.2%, respectively (Fig. 3). However, among the patients who did not meet the Milan criteria, 15 had no tumor recurrence and

**FIGURE 3. Comparison of tumor-free survival in patients within and beyond the Milan criteria.**

18 were alive for 1 to 36 months (median, 13 months) after transplantation.

DISCUSSION

Liver transplantation is now acknowledged as the treatment of choice for patients with early, unresectable HCC, and the Milan criteria have been widely accepted in the selection of HCC patients for transplantation (11, 12). Our data also supported the significance of the Milan criteria for selecting patients with a low risk of recurrence, because only 1 of 20 patients within the Milan criteria had recurrence after transplantation, and tumor-free survival was 87% at 2 years. However, the other 20 patients with tumors beyond the Milan criteria showed tumor-free survival as high as 76% at 2 years and 15 patients were alive for 1 to 36 months (median, 13 months). These results clearly demonstrated that many HCC patients who would have been excluded by the Milan criteria could survive for a long period after transplantation. The same results were published by Yao et al. (13), and they reported that the Milan criteria specifications for tumor size might be modestly expanded while still preserving excellent survival. In this study, LDLT was performed under our own patient selection criteria, and the overall and tumor-free survival rates were 54.6% and 68.3%, respectively, at 3 years. These were lower than those after orthotopic liver transplantation under the Milan criteria; however, we consider that our results were acceptable because most of the patients could not have survived for 3 years without transplantation. Likewise, if we had applied the Milan criteria to our patients, we would have denied many patients who were alive after transplantation. The Milan criteria are derived from cadaveric organ allocation, but the situation is quite different in LDLT, in which the donor has a strong will for dedication. Other criteria for patient selection are, therefore, necessary in LDLT.

In univariate analysis of the relationship between various factors and the incidence of HCC recurrence, only histologic type and the existence of microvascular invasion had a significant positive impact on HCC recurrence after transplantation. However, these factors and some other posttransplant factors with a positive correlation with tumor recurrence were retrospective factors and could not be applied before

transplantation. Among the pretransplant factors, TNM stage, α -fetoprotein level, maximal diameter and total number of tumors, and the Milan criteria tended to be associated with tumor recurrence; however, none of them were statistically significant.

In this study, all HCC patients were evaluated for tumor distribution with brain, chest, and abdominal computed tomographic scan, ultrasonography, and scintigraphy within 2 months before transplantation. However, the findings in pretransplant imaging studies did not correspond to the pathologic findings in many patients. For example, 21 patients (37.5%) were correctly evaluated for their tumor number before transplantation, and the remaining 35 patients were wrongly assessed (nine were overestimated and 26 were underestimated). This disparity cannot be neglected because the pretransplant evaluation directly influences the indication for transplantation for HCC patients. We need to build a new protocol to achieve consistent and reliable methods for evaluation of HCC patients.

CONCLUSION

Although long-term follow-up is needed to assess fully the benefits of LDLT for uncontrollable HCC patients, this study demonstrated favorable results in the patients chosen by our extended patient selection criteria. However, to achieve a survival rate as high as that of LDLT for non-HCC patients, other preoperative factors need to be considered in the patient selection criteria. The Milan criteria do not seem to be suitable for selecting HCC patients for LDLT.

REFERENCES

- DiBisceglie AM, Rustgi VK, Hoofnagle HH, et al. Hepatocellular carcinoma. *Ann Intern Med* 1988; 108: 390.
- Munoz N, Bosch X. Epidemiology of hepatocellular carcinoma. In: Okuda K, Ishak KG, eds. *Neoplasms of the liver*. Tokyo, Springer 1989, p 3.
- Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer* 1985; 56: 918.
- Ringe B, Wittekind C, Bechstein WO, et al. The role of liver transplantation in hepatobiliary malignancy: A retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. *Ann Surg* 1990; 211: 246.
- Iwatsuki S, Gordon RD, Shaw BW, et al. Role of liver transplantation in cancer therapy. *Ann Surg* 1985; 202: 401.
- O'Grady JG, Polson RJ, Rolles K, et al. Liver transplantation for malignant disease: Results in 93 consecutive patients. *Ann Surg* 1988; 207: 373.
- Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993; 218: 145.
- Michel J, Suc B, Montpeyroux F, et al. Liver resection or transplantation for hepatocellular carcinoma? Retrospective analysis of 215 patients with cirrhosis. *J Hepatol* 1997; 26: 1274.
- Calne R, Yamanoi A, Oura S, et al. Liver transplantation for hepatocarcinoma. *Surg Today* 1993; 23: 1.
- Mozzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334: 693.
- Llovet JM, Bruix J, Fuster J, et al. Liver transplantation for treatment of small hepatocellular carcinoma: The TNM classification does have prognostic power. *Hepatology* 1998; 27: 1572.
- Bismuth H, Majno PE, Adem R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999; 19: 311.
- Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; 33: 1394.
- Cheng SJ, Pratt DS, Freeman RB, et al. Living-donor versus cadaveric liver transplantation for non-resectable small hepatocellular carcinoma and compensated cirrhosis: A decision analysis. *Transplantation* 2001; 72: 861.
- Sarasin FP, Majno PE, Llovet JM, et al. Living donor liver transplantation for early hepatocellular carcinoma: A life-expectancy and cost-effectiveness perspective. *Hepatology* 2001; 33: 1073.
- Gondolesi G, Munoz L, Matsumoto C, et al. Hepatocellular carcinoma: A prime indication for living donor liver transplantation. *J Gastrointest Surg* 2002; 6: 102.