Living Donor Liver Transplantation for Hepatocellular Carcinoma

B. Isik, V. Ince, K. Karabulut, C. Kayaalp, and S. Yilmaz

ABSTRACT

Background. Liver transplantation is a widely accepted modality in the treatment of hepatocellular carcinoma (HCC). In our center, patients with HCC limited to the liver without macrovascular invasion are accepted as candidates for living donor liver transplantation (LDLT). The aim of this study was to describe the patient characteristics and outcomes at a single institution to analyze the impact of our criteria on the survival of HCC patients.

Patients and Methods. We reviewed the medical records of all HCC (n = 105) patients who underwent liver transplantation in our institution. We excluded deaths in the early postoperative period and deceased donor liver transplantation (DDLT) patients, leaving 74 subjects (65 males and 9 female). Their median age was 53 years (range, 19–69). Univariate Kaplan-Meier and multivariate Cox proportional hazards models were used to analyze overall and disease-free survivals.

Results. Thirty-two (43%) patients were within the Milan criteria, and 42 (57%) exceeded them. One- and 2-year overall survival rates for patients within versus exceeding the Milan criteria were 72% versus 68% and 61% versus 58%, respectively. One- and 2-year disease-free survival rates for patients within versus exceeding the Milan criteria were 72% versus 68% and 60% versus 55%, respectively ($P > .05$). Tumor recurrence rates for patients within versus exceeding the Milan criteria were 0% versus 36%, respectively ($P = .0002$). Alpha-fetoprotein level was the only predictor of overall survival; alpha-fetoprotein level and tumor differentiation were predictors of disease-free survival.

Conclusion. Although higher recurrence rates have been observed among patients exceeding the Milan criteria, LDLT is the only treatment option for the patients in countries with limited sources of cadaveric organs. As a general principle, we believe that the use of cadaveric donor liver grafts is not suitable for patients who exceed these criteria.

HEPATOCELLULAR carcinoma (HCC) one of the most common malignancies, causes about 1 million deaths annually. Orthotopic liver transplantation (OLT) is a generally accepted treatment modality for HCC. In recent years, the indications of living donor liver transplantation (LDLT) in adults include hepatitis B virus (HBV) hepatitis C virus (HCV)–related cirrhosis with carcinoma. LDLT plays an important role to treat early malignant hepatic tumors.[1] In our center, we perform OLT for patients with HCC within the Milan criteria. Additionally, we reserve the LDLT option for subjects without macrovascular invasion whose tumor cannot be treated or downstaged by other treatments. In this study, we sought to describe patient characteristics and outcomes at a single institution and to analyze the effect of our criteria on survival of HCC patients.

PATIENTS AND METHODS

We reviewed medical records of all HCC (n = 105) patients who underwent liver transplantation at our institution between April 2006 and August 2011 mostly including 91% LDLT. Early postoperative death and deceased donor liver transplantation (DDLT) patients were excluded we retrospectively reviewed the remaining 74 patients. In our center, patients with HCC limited to the liver without macrovascular invasion were accepted as LDLT candidates. Preoperative workup included computed tomography (CT) scans, alpha-fetoprotein (AFP) levels, liver function tests, complete

From the Department of Surgery and Liver Transplantation Institute, Inonu University, Malatya, Turkey.

Address reprint requests to Cuneyt Kayaalp, Department of Surgery and Liver Transplantation Institute, Inonu University, 44315, Malatya, Turkey. E-mail: cuneytkayaalp@hotmail.com

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Table 1. Clinical and Demographic Parameters of the Patients

Parameter	
Age (y)	53 (19–69)
Gender	
Female	9 (12%)
Male	65 (88%)
Dominant tumor size	
Mean ± SEM	5.2 ± 0.5
Median (range)	4 (0.3–20)
No. of tumors	
<10	63 (85%)
≥10	11 (15%)
Cirrhotic/non-cirrhotic	69 (93%)/5 (7%)
Child class	
A	22 (30%)
B	35 (47%)
C	17 (23%)
MELD score	13 (6–41)
Milan (+)	32 (43%)
AFP (IU/mL)[11]	
<200	53 (74%)
>200	19 (26%)

Abbreviations: SEM, standard error of the mean; MELD, model for end-stage liver disease.

blood counts, and coagulation parameters. AFP tests were repeated monthly in the follow-up period. Tri-phasic liver CT scans were obtained for patients with high AFP levels.

We evaluated demographic data, tumor characteristics, liver functions, and survival parameters. Univariate Kaplan-Meier and multivariate Cox proportional hazards model were used to analyze overall and disease-free survivals. The level of statistical significance was set at $P < .05$.

RESULTS

Demographic and clinical parameters of the patients are shown in Table 1. Sixty-five (88%) patients were males and 9 (12%) were females. Median age was 53 years (range, 19–69). The most common etiologic factor for HCC was HBV (n = 61; 83%). There was hepatitis delta virus (HDV) co-infection in 20% of HBV(+) patients. The other etiologic factors were cryptogenic (7%; n = 5), HCV (5%; n = 4), fibrolamellar HCC (3%; n = 2), alcohol (1%; n = 1), and Wilson disease (1%; n = 1). HCC was diagnosed incidentally in 4 (5%) patients. The median follow-up duration was 12 months (range, 3–52). Preoperative AFP level was <200 IU/mL in 74% of patients. Preoperative AFP level was unknown in 2 patients. Thirty-two (43%) patients were within the Milan criteria, whereas 42 (57%) exceeded them. Recurrence was diagnosed in 16 patients; it was hepatic (n = 3; 19%), extrahepatic (n = 2; 12%), or both hepatic and extrahepatic (n = 11; 69%).

One-, 2-, and 3-year overall and disease-free survival rates were 66%, 62%, and 56% and 65%, 60%, and 54%, respectively. One- and 2-year overall survival rates for the patients within versus exceeding the Milan criteria were 72% versus 68%, and 61% versus 58%, respectively. One- and 2-year disease-free survival rates for the patients within versus exceeding the Milan criteria were 72% versus 68%, and 60% versus 55%, respectively ($P > .05$). Tumor recurrence for patients within versus exceeding the Milan criteria were 0% versus 36%, respectively ($P = .0002$; Fig 1 and Fig 2).

On univariate analysis AFP level was the only predictor of overall survival, AFP level and tumor differentiation were predictors of disease-free survival (Fig 3). On multivariate analysis, AFP level was the only independent predictor of both overall and disease-free survival ($P = .01$ and .006, respectively; Table 2).

Mortality was due to nononcologic reasons in 52% of patients who died in the follow-up period. Forty-seven patients are still alive; 24 (51%) of them exceeded the Milan criteria. Tumor recurrence occurred in only 2 of these 24 patients.

DISCUSSION

The increased incidence of HCC reflects the increasing prevalence of chronic viral hepatitis.[1] OLT is considered the treatment of choice for early HCC patients with end-

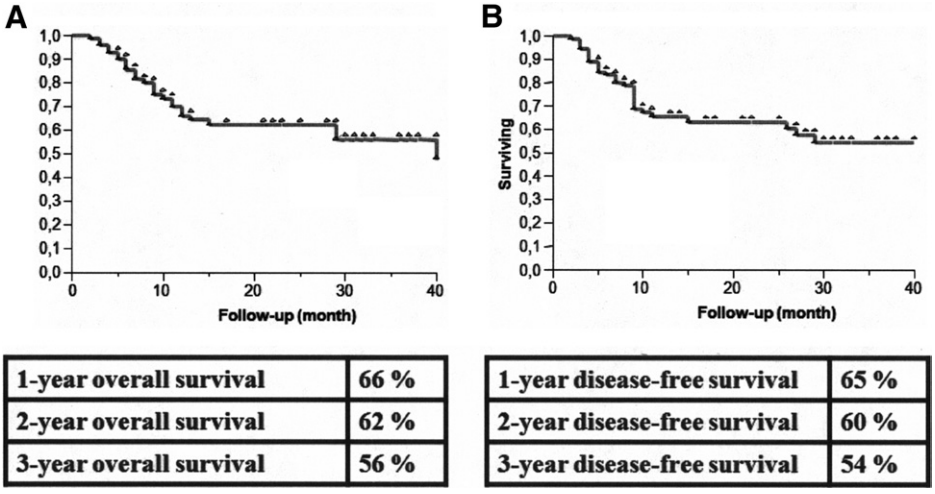


Fig 1. Kaplan-Meier overall survival and disease-free survival graphs: **(A)** Overall survival; **(B)** Disease-free survival.

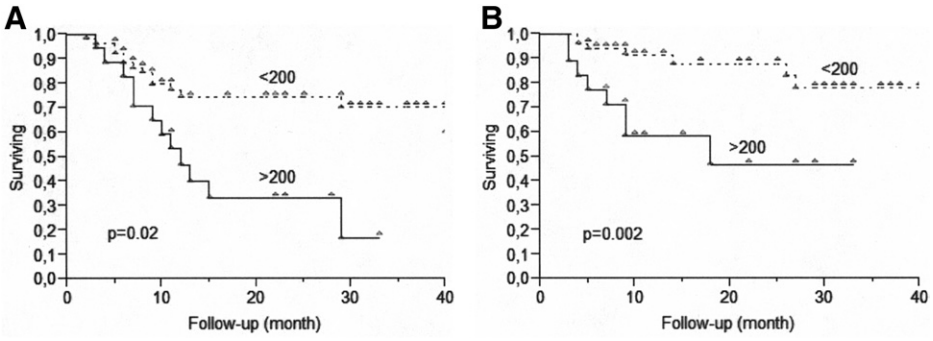


Fig 2. Kaplan-Meier overall survival and disease-free survival based on Milan criteria: **(A)** Overall survival; **(B)** Disease-free survival.

stage liver failure, but its availability is limited by the donor organs. In recent years, LDLT has been an alternative to DDLT for patients with HCC.[2–4]

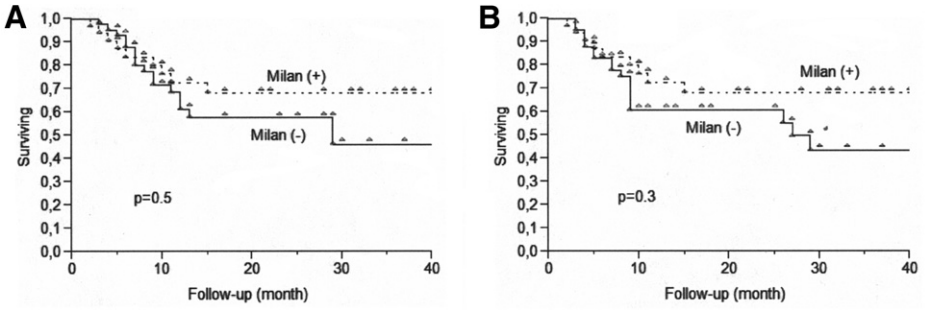
Organ donation rate in our country is 3–4 per million population. Cadaveric grafts are a poor source of donor organs. According to the legislation, transplant candidates are determined by The National Coordination Center.

In our country, the Milan criteria are used for DDLT for patients with HCC. We believe that these criteria are not suitable for LDLT. A living donor graft should be considered as an individual gift, not as a public domain like deceased donor grafts. Our transplantation program is mainly based on LDLT. Patients with HCC limited to the liver without macrovascular invasion are accepted as candidates for LDLT. In our study we observed that neither being within nor exceeding the Milan criteria had a significant effect on overall or disease-free survival rates, similar to the results in the literature.[5]

In the literature, MELD score and preoperative serum AFP levels have been reported to be independent risk factors for survival. AFP level, tumor size, vascular invasion, and bilobar distribution have been reported to be independent risk factors for HCC recurrence.[6] But in our study, we observed only AFP level as an independent risk factor for overall survival; AFP level and degree of differentiation were independent risk factors for disease-free survival.

The reported 1- and 3-year overall survival rates in the literature range between 70% and 77% and 66% and 69%; the 1- and 3-year disease-free survival rates range between 72% and 82% and 64%, respectively.[7–10] But in our study, 1- and 3-year overall survival rates were 66% and 56%; 1- and 3-year disease-free survival rates were 65% and 54%, respectively. Our survival results are lower than those reported in the literature because the numbers of patients who died due to nononcologic reasons were much greater than the tumor-related cases.

In conclusion, AFP level was the only predictor of overall survival. AFP level and tumor differentiation were the predictors of disease-free survival. In terms of recurrence the results are worse among patients exceeding the Milan criteria as expected, but we believe that LDLT is the only treatment chance for these patients who live in countries with poor sources of cadaveric organs. As a general principle, we believe that the use of



	Milan (+) %	Milan (-) %	p
1-year overall survival	72	61	> 0.05
2-year overall survival	68	58	> 0.05
1-year disease-free survival	72	60	> 0.05
2-year disease-free survival	68	55	> 0.05
Recurrence	0	36	0.0002*

Fig 3. Kaplan-Meier overall survival and disease-free survival based on AFP: **(A)** Overall survival; **(B)** Disease-free survival.

Table 2. Overall and Disease-Free Survival on Multivariate Analysis

Parameters	Overall Survival			Disease-Free Survival		
	P	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI
AFP (IU/mL) >200 vs <200	.01*	3.1	1.3–7.5	.006*	3.4	1.4–8.3
Milan (−) vs (+)	.2	1.8	0.8–4.4	.1	1.9	0.8–4.8
MELD >14 vs ≤14	.8	1.1	0.4–2.7	.7	1.2	0.5–2.8
Age >55 vs <55	.1	2.1	0.8–4.9	.3	1.7	0.7–3.9

Abbreviation: CI, confidence interval.

cadaveric liver grafts is not suitable for patients exceeding the milan criteria.

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