

Liver Transplantation for Adult patients with Hepatocellular Carcinoma in Korea: Comparison Between Cadaveric Donor and Living Donor Liver Transplantations

Shin Hwang,¹ Sung-Gyu Lee,¹ Jae-Won Joh,² Kyung-Suk Suh,³ and Dong-Goo Kim⁴

Current selection criteria of liver transplantation (LT) for patients with hepatocellular carcinoma (HCC) were derived from the outcomes of cadaveric donor LT (CDLT). We tried to assess the applicability of such criteria to living donor LT (LDLT) through a comparative study between CDLT and LDLT. We analyzed the outcomes of 312 HCC patients who underwent LT at 4 Korean institutions during 1992 to 2002. There were no gross differences of tumor characteristics between CDLT group (n = 75) and LDLT group (n = 237). Overall 3-year survival rate (3-YSR) was 61.1% after CDLT and 73.2% after LDLT including 38 cases of perioperative mortality. Comparison of HCC recurrence curves did not reveal any statistical difference between these 2 groups. Patient survival period till 50% mortality after HCC recurrence was 11 months after CDLT and 7 months after LDLT. Significant risk factors for HCC recurrence were alpha-fetoprotein level, tumor size, microvascular invasion, gross major vessel invasion, bilateral tumor distribution, and histologic differentiation in the LDLT group on univariate analysis, and tumor size, gross major vessel invasion, and histologic differentiation on multivariate analysis. Milan criteria were met in 70.4%: Their 3-YSR was 89.9% after CDLT and 91.4% after LDLT with exclusion of perioperative mortality. University of California San Francisco criteria were met in 77.7%: Their 3-YSR was 88.1% after CDLT and 90.6% after LDLT. In conclusion, we think that currently available selection criteria for HCC patients can be applicable to LDLT without change of prognostic power. (*Liver Transpl* 2005;11: 1265-1272.)

Conventional standard treatments of hepatocellular carcinoma (HCC) include surgical resection and nonsurgical treatments such as chemoembolization, ablation, and injection therapy.¹ However, surgical resection has a definite limitation in both tumor resectability and patient safety if hepatic functional reserve is markedly impaired. Nonsurgical treatments often resulted in incomplete tumor control and also revealed high recurrence rate when they were applied to the advanced HCC lesions. On the other hand, liver transplantation (LT) offers a chance to eliminate both tumor and underlying liver cirrhosis at the same time, although there is an additional risk of accelerated tumor recurrence from immunosuppression. If an HCC lesion is

not too far advanced such as to meet the Milan criteria, a satisfactory outcome of LT will be statistically achievable.²⁻⁴ From the viewpoints of quality of life and tumor recurrence, any other treatment modalities cannot achieve such a favorable result comparable to that of LT.

The Milan criteria have been standard eligibility criteria of LT for HCC, but the indication of HCC patients has been prudently expanded in some major LT centers, and their outcomes were also comparably favorable like those within the Milan criteria.^{5,6} We feel that there is a trend toward expanding the selection criteria of LT for HCC beyond the Milan criteria.⁷ At this point, it should be clarified that all of the currently available selection criteria for HCC patients were originally derived from the outcomes of cadaveric donor liver transplantation (CDLT). Contrary to CDLT, regeneration of partial liver graft is an inevitable process during the early postoperative period of adult living donor liver transplantation (LDLT). However, it is not known yet whether or not early graft regeneration and other LDLT-specific features can have any adverse influence on the recurrence of HCC.⁸⁻¹⁰ There was only

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; CDLT, cadaveric donor liver transplantation; LDLT, living donor liver transplantation; 3-YSR, 3-year survival rate; UCSF, University of California San Francisco.

From the ¹Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, ²Department of Surgery, Samsung Medical Center, Sungkyunkwan University, School of Medicine, ³Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, and ⁴Department of Surgery, Gangnam St. Mary's Hospital, Catholic University of Korea, College of Medicine, Seoul, Korea.

Received February 14, 2005; accepted July 5, 2005.

Address reprint requests to: Sung-Gyu Lee, MD, Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 138-736, Korea. Telephone: 82-2-3010-3485; FAX: 82-2-474-9027; E-mail: sglee2@amc.seoul.kr

Copyright © 2005 by the American Association for the Study of Liver Diseases

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lt.20549

1 article of large-volume LDLT for HCC patients, in which the Japanese nationwide experience of 316 HCC cases from 29 LT centers was analyzed.¹¹ Japanese collective data as well as Korean multicenter data of this study were presented at the Korea-Japan Joint Transplant Symposium (Osaka, 2003), in which the outcomes of these 2 studies were very similar each other. As Todo and Furukawa reported the detailed results of HCC after LDLT, we herein report the Korean experience of 312 HCC cases focused on the comparison of HCC recurrence between CDLT and LDLT groups.

Patients and Methods

From August 1992 to December 2002, 1,085 cases of adult LT (341 CDLT cases and 744 LDLT cases) were carried out at the 4 institutions in Korea. This case number accounted for more than 90% of Korean nationwide LTs during the study period. HCC was diagnosed preoperatively or found incidentally in the explanted livers of 312 adult patients (28.8%). Four HCC patients had been excluded from this analysis due to the following reasons: HCC in pediatric patients ($n = 2$), mixed tumor of HCC and cholangiocarcinoma components ($n = 1$), and total tumor necrosis following preoperative therapy ($n = 1$).

For this multicenter study, a questionnaire was sent to each center in late 2003, and additional follow-up surveys were carried out in 2004. We set the timing of final follow-up at the end of 2003. The inquired items included profiles of the recipients (age, sex, cause of liver cirrhosis, viral hepatitis B, viral hepatitis C, serum alpha-fetoprotein, Child-Turcotte-Pugh classification, United Network for Organ Sharing status, donor and LT operation (CDLT, LDLT, and graft type), primary HCC lesion (timing of diagnosis, pretransplant treatment, size, number, microvascular invasion, gross major vessel invasion [hepatic vein and portal vein], tumor distribution, and histologic differentiation), tumor recurrence (timing, site, alpha-fetoprotein, and treatment), and patient survival (perioperative mortality, causes of death, and survival period).

Of the 312 adult recipients, their mean age was 50 ± 8 years (range, 20-67) and 256 were male (82.1%). Viral infection was associated with liver cirrhosis in 310 (99.4%) patients (hepatitis B, $n = 283$ [90.7%]; hepatitis C, $n = 19$ [6.1%]; both hepatitis B and C, $n = 8$ [2.6%]). Nonviral cause was alcoholism ($n = 2$ [0.6%]). These recipients were divided into the Child-Turcotte-Pugh class A ($n = 33$ [10.6%]), class B ($n = 83$ [26.6%]), and class C ($n = 196$ [62.8%]) according to the Child-Turcotte-Pugh classification. They were also classified as United Network for Organ Sharing status 1 ($n = 4$ [1.3%]), status 2A ($n = 35$ [11.2%]), status 2B ($n = 220$ [70.5%]), and status 3 ($n = 43$ [13.8%]).

Thirty-nine patients were incidentally diagnosed as HCC after detection of HCC lesions at the explanted livers. Of the 273 patients who had been preoperatively diagnosed with

HCC, 61 (22.3%) did not receive any specific treatment because of poor liver function or prescheduled LDLT operation. Another 212 patients underwent transarterial chemoembolization ($n = 183$ [67%]), radiofrequency ablation ($n = 22$ [8.1%]), surgical resection ($n = 14$ [5.1%]), percutaneous ethanol injection ($n = 8$ [2.9%]), systemic chemotherapy ($n = 5$ [1.8%]), and other therapy ($n = 20$ [7.3%]).

The tumor extents of HCC lesions were classified as T1 ($n = 150$ [48.1%]; 25 were incidentally detected), T2 ($n = 121$ [38.8%]; 14 incidental cases), and T3 ($n = 41$ [13.1%]; no incidental cases) according to the new pathologic staging system (American Joint Committee on Cancer/International Union Against Cancer, 6th edition).^{3,12} Tumor characteristics are summarized in Table 1 and Table 2. In the explanted livers with incidental HCC, the diameter of single or largest lesion was 13.8 ± 6.4 mm (range, 5-29 mm). The number of incidental HCC lesions was single ($n = 25$), 2 ($n = 6$), 3 ($n = 2$), and 4 or more ($n = 6$).

Seventy-five patients received cadaveric liver grafts (whole liver, $n = 74$; split right trisegment, $n = 1$) and 237 patients received living donor partial grafts (left lobe with/without caudate lobe, $n = 34$; right lobe with/without middle hepatic vein trunk or reconstruction, $n = 188$; dual grafts, $n = 15$). There were 2 cases of retransplantation due to primary non-function of the first graft (CDLT to CDLT, $n = 1$; CDLT to LDLT, $n = 1$). One patient underwent cadaveric kidney transplantation simultaneously. Preoperative care, surgical techniques, and postoperative management as currently practiced were similar center to center and have been described elsewhere.¹³⁻¹⁵

The degree of liver cirrhosis and extent of HCC lesions were routinely investigated before LDLT or CDLT operation. The primary reason for LT in HCC patients with liver cirrhosis of Child-Turcotte-Pugh class C was treatment of the liver cirrhosis itself; for patients with Child-Turcotte-Pugh class A, the primary reason was treatment of the unresectable or refractory HCC lesion. All 4 LT centers had a consensus on exclusion of extrahepatic metastasis and major vascular invasion in principle. However, the Milan criteria were not applied strictly, and some patients with advanced HCC lesions were selected on a case-by-case basis, especially for LDLT. When there was any suspicion of extrahepatic tumor spread, the recipient operation was initiated first to confirm the suitability of LT before laparotomy of a living donor.¹⁶

Perioperative mortality was defined as patient death of any cause within 3 months after LT. Mean values with standard deviation and median values with ranges were used for numeric data. The significance of differences was assessed by chi-square, *t*-test, and analysis of variance. Survival curves were estimated by the Kaplan-Meier method and compared with log-rank test and Gehan's Wilcoxon test (especially for short-term follow-up). Patient death unrelated to HCC recurrence was regarded as censored case during the statistical analysis of HCC recurrence. Regression analysis was performed with the Cox proportional hazard model. Differences of $P < 0.05$ were considered to be statistically significant.

Table 1. Demographic Data of the Patients with HCC who Underwent CDLT or LDLT

	CDLT	LDLT	P Value
No. of patients	75 (24%)	237 (76%)	
Age (mean $\pm$ SD, years)	49 $\pm$ 7	50 $\pm$ 8	0.599
Sex			0.595
Male	60 (80%)	196 (82.7%)	
Female	15 (20%)	41 (17.3%)	
Child-Turcotte-Pugh classification			0.005
A	4 (5.3%)	29 (12.2%)	
B	13 (17.3%)	70 (29.5%)	
C	55 (73.4%)	138 (58.3%)	
Serology			0.458
Hepatitis B	68 (90.7%)	215 (90.7%)	
Hepatitis C	6 (8%)	13 (5.5%)	
Hepatitis B & C	0	8 (3.4%)	
None	1 (1.3%)	1 (0.4%)	
Pathologic tumor stage			0.767
T1	34 (45.3%)	116 (49.0%)	
T2	25 (33.3%)	96 (40.5%)	
T3	16 (21.3%)	25 (10.5%)	
T4	0	0	
Milan criteria			0.694
Within	53 (70.7%)	173 (73%)	
Beyond	22 (29.3%)	64 (27%)	
Perioperative mortality < 3 months	14 (18.7%)	24 (10.1%)	0.048
No. of discharged patients	61 (81.3%)	213 (89.9%)	
Follow-up period (Median [range], months)	45 (4-101)	26 (4-80)	<0.001

Results

Recipient Profiles

Demographic data and operation profiles of the 75 CDLT and 237 LDLT recipients are described at Table 1. These data revealed that there were no gross differences in the general characteristics of patient and tumor profiles between the 2 groups, but LDLT has been often carried out for the patients with less severe liver cirrhosis.

Patient Survival

Of the 61 discharged CDLT recipients, HCC recurred in 11 (18%), and 7 of the patients died from HCC recurrence during the median follow-up of 45 months. Another 10 recipients died of various causes other than HCC recurrence. On the other hand, HCC recurred in 33 (15.5%) of 213 discharged LDLT recipients during the median follow-up of 26 months, and 27 of the patients died from HCC recurrence. Another 5 recipients died of various causes other than HCC recurrence. Cumulative 3-year survival rate (3-YSR) was 61.1% after CDLT and 73.2% after LDLT ($P = 0.043$; Fig. 1).

HCC Recurrence

Data on 274 recipients were used for analysis of HCC recurrence after exclusion of 38 cases of perioperative mortality. Patients who died without evidence of HCC recurrence were regarded as censored cases.

Recurrence-free survival curves of CDLT and LDLT groups are compared in Figure 2. Comparison of the cumulative recurrence curves did not reveal any significant difference between these 2 groups ($P = 0.884$). All of the HCC recurrence occurred only in the preoperatively diagnosed HCC patients. Recurrence-free survival curves were analyzed again after exclusion of patients with incidental HCC. There was also no significant difference between the 2 groups ($P = 0.765$), but the survival rates were slightly lowered: 1-year and 2-year recurrence-free survival rates were 88.3% and 81.6% in CDLT and 82.9% and 79.7% in LDLT, respectively, without incidental HCC cases ($n = 235$), but 89.9% and 87.7% in CDLT and 85.1% and 80.27% in LDLT, respectively, with incidental HCC cases ($n = 274$).

The common sites of initial HCC recurrence were the graft liver itself ($n = 25$), lung ($n = 19$), bone ($n =$

Table 2. Univariate Analyses of 2-Year Tumor Recurrence in 274 Patients With HCC who Underwent CDLT or Living LDLT

	CDLT			LDLT		
	Case No.	2-Year Recurrence-Free Survival Rate	P Value	Case No.	2-Year Recurrence-Free Survival Rate	P Value
Preoperative alpha-fetoprotein			0.044			<0.001
≤20 ng/mL	25	91.7%		96	91.4%	
>20 ng/mL, ≤200 ng/mL	23	82.3%		69	92.3%	
>200 ng/mL, ≤1000 ng/mL	3	—		16	86.7%	
>1000 ng/mL	6	66.7%		25	41.4%	
Tumor size			0.417			<0.001
≤2 cm	26	95.9%		87	97.6%	
>2 cm, ≤5 cm	29	88.7%		109	82.2%	
>5 cm	6	60.0%		17	39.8%	
Tumor number			0.403			0.101
1	34	83.7%		125	88.4%	
2	11	90.9%		37	86.4%	
3	4	75.0%		17	82.4%	
≥4	12	83.3%		34	71.4%	
Microvascular invasion			0.083			0.011
No	53	87.9%		177	87.6%	
Yes	8	86.7%		36	70.0%	
Gross major vessel invasion			0.65			<0.001
No	52	91.7%		199	87.7%	
Yes	9	64.7%		14	40.9%	
Tumor distribution			0.321			<0.001
Unilobar	50	83.3%		160	90.8%	
Bilobar	11	68.8%		53	66.6%	
Histologic differentiation			0.019			0.001
Well	30	95.7%		115	91.5%	
Moderate/poor	27	83.7%		87	74.0%	

11), peritoneum ($n = 8$), and brain ($n = 7$). Multimodality treatments of the recurred HCC lesions included systemic chemotherapy ($n = 22$), chemoembolization ($n = 18$), radiotherapy ($n = 11$), lung metastasectomy ($n = 5$), liver resection ($n = 4$), or other therapy ($n = 5$). However, the survival periods till 50% mortality after HCC recurrence were 11 months after CDLT and 7 months after LDLT (Fig. 3, $P = 0.095$).

Risk Factor Analysis for Posttransplant HCC Recurrence

Univariate analysis was carried out on each group with exclusion of perioperative mortality cases. Significant risk factors were preoperative serum alpha-fetoprotein level, tumor size, microvascular invasion, gross major vessel invasion, bilateral tumor distribution, and histologic differentiation in LDLT group (2-year data, Table 2). However, the patterns of HCC recurrence in CDLT group seemed to be similar to those of the LDLT group, but they were not fully evaluated, due to the small sample numbers. We also carried out multivariate anal-

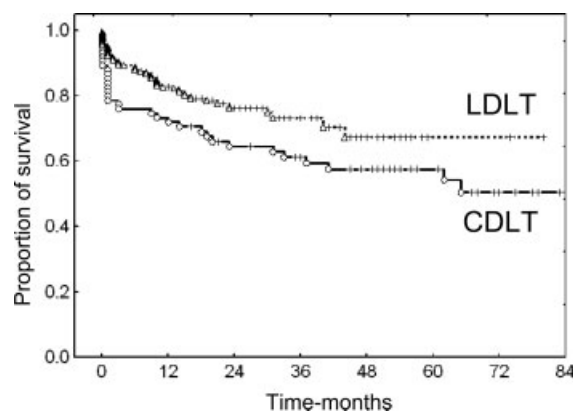


Figure 1. Cumulative survival curves of the patients with hepatocellular carcinoma after CDLT ($n = 75$) and LDLT ($n = 237$). A significant difference of the cumulative survival curves occurred since the early posttransplant period ($P = 0.024$) due to the different rates of perioperative mortality. This discrepancy was maintained throughout the follow-up period ($P = 0.043$). Solid line indicates CDLT.

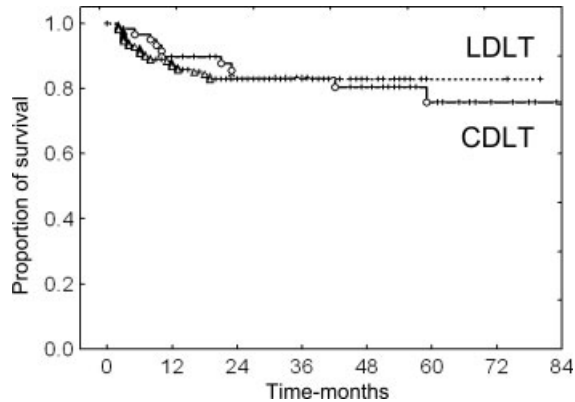


Figure 2. Cumulative recurrence-free survival curves of the patients with hepatocellular carcinoma after CDLT ($n = 61$) and LDLT ($n = 213$). There was no statistical difference of the recurrence-free survival curves all along ($P = 0.884$). The solid line indicates CDLT.

ysis with the data of LDLT and CDLT altogether ($n = 274$), by which the tumor size, gross major vessel invasion, and histologic differentiation were proven as the independent risk factors (Table 3).

Patient Selection Criteria

These survival analyses were also carried out with exclusion of perioperative mortality cases. Of the 274 survived recipients, 193 (70.4%) met the Milan criteria.² The patients who met or exceeded the Milan criteria revealed 3-YSR as 89.9% and 66.4% after CDLT ($P = 0.181$) and 91.4% and 62.6% after LDLT ($P < 0.001$), respectively.

When the University of California San Francisco

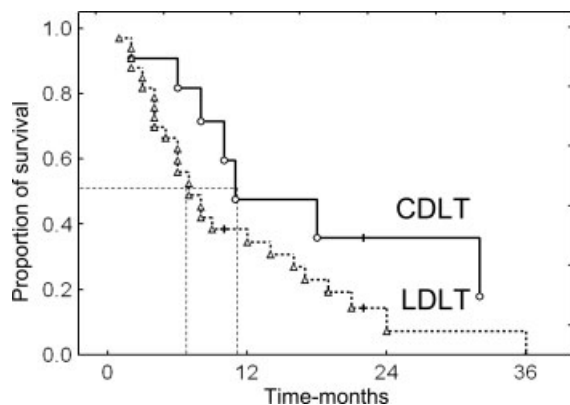


Figure 3. Cumulative survival curves after the first detection of hepatocellular carcinoma recurrence in CDLT and LDLT groups. The CDLT group seemed to reveal a longer survival period at the level of 50% mortality (dashed boxes), but there was no statistically significant difference ($P = 0.095$). Solid line indicates CDLT.

Table 3. Multivariate Analysis of the Independent Risk Factors for Tumor Recurrence in 274 Patients With HCC

Risk Factors	Relative Risk	P Value
Preoperative alpha-fetoprotein	—	0.957
Microvascular invasion	—	0.181
Tumor distribution	—	0.225
Gross major vessel invasion	2.5	0.049
Histologic differentiation	2.6	0.012
Tumor size	3.4	<0.001

(UCSF) criteria were applied, 213 (77.7%) recipients met the selection criteria. It could expand the indication population by 7.3% comparing with the Milan criteria. Their 3-YSR within or beyond the UCSF criteria were 88.1% and 68% after CDLT ($P = 0.199$) and 90.6% and 58.5% after LDLT ($P < 0.001$), respectively.⁴

When only gross invasion of the major vessel was excluded, 248 (90.5%) recipients were indicated. It could expand the indication population by 20.1% and 12.8% comparing with the Milan and UCSF criteria, respectively. Their 3-YSR without or with major vessel invasion were 86.9% and 64.7% after CDLT ($P = 0.466$) and 86.9% and 35.7% after LDLT ($P < 0.001$), respectively.

Sophisticated analyses of the patient survival curves after CDLT revealed that lack of statistical significance might originate in the small sample numbers rather than true difference of the survival rates. Detailed results according to the different eligibility criteria for HCC patients are described collectively (Fig. 4).

Annual Trends of the Perioperative Mortality and 1-Year HCC Recurrence Rate

Yearly perioperative mortality rate was close to 15% before 1999, but it steadily decreased to 7% in 2002. HCC recurrence rate during the first 12 months post-transplant was also analyzed and found to be 11% in 1999, 19% in 2000, 15% in 2001, and 13% in 2002.

Discussion

The patient profiles and results of this study disclosed every aspect of LT on HCC patients. The affirmative side of LT included the restoration of normal life and the high probability of prolonged survival. Conversely, perioperative mortality and early HCC recurrence belonged to LT's negative side. The Milan and UCSF groups suggested that LT can offer a chance of prolonged survival when the HCC lesion does not

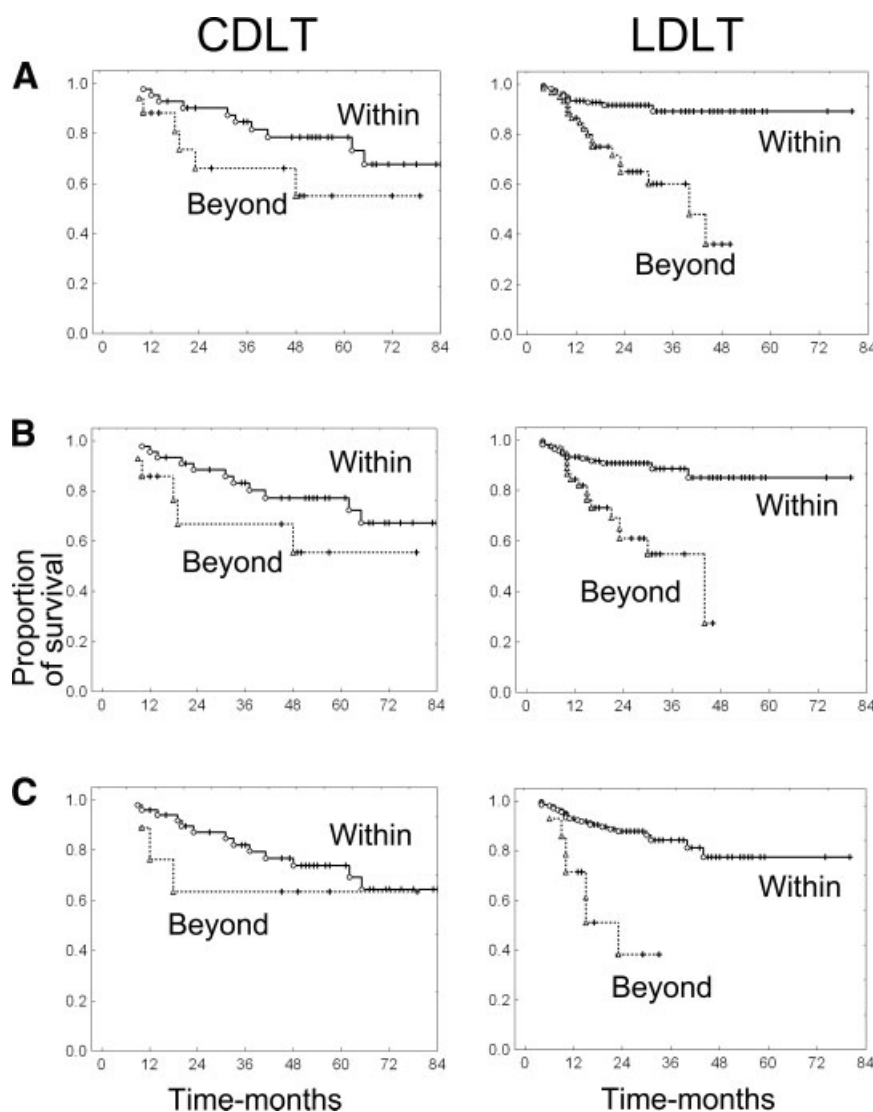


Figure 4. Comparison of the cumulative survival curves according to the 3 different selection criteria of patients with HCC after CDLT and LDLT. (A) The Milan criteria was applied to the CDLT group (within, $n = 42$, 3-YSR 89.9%; beyond, $n = 19$, 3-YSR 66.4%; $P = 0.181$) and the LDLT group (within, $n = 151$, 3-YSR 91.4%; beyond, $n = 62$, 3-YSR 62.6%; $P < 0.001$). (B) The UCSF criteria was applied to the CDLT group (within, $n = 46$, 3-YSR 88.1%; beyond, $n = 15$, 3-YSR 68%; $P = 0.199$) and the LDLT group (within, $n = 167$, 3-YSR 90.6%; beyond, $n = 46$, 3-YSR 58.5%; $P < 0.001$). (C) Exclusion of the gross major vessel invasion was applied to the CDLT group (within, $n = 51$, 3-YSR 86.9%; beyond, $n = 10$, 3-YSR 64.7%; $P = 0.466$) and the LDLT group (within, $n = 197$, 3-YSR 86.8%; beyond, $n = 16$, 3-YSR 35.7%; $P < 0.001$). Solid lines indicate the survival curve within the corresponding criteria.

exceed their proposed eligibility criteria.^{2,4,5} Before allocation of the cadaveric liver grafts to HCC patients, the potential risk of HCC recurrence has been investigated for the patients themselves and for the efficient sharing of organs. On the other hand, for LDLT, living-donor-specific factors that are different from the efficiency of organ sharing should be taken into account. A living donor is uniquely matched to a certain recipient in most of the LDLT situations. From the recipient's standpoint, this special relationship between the donor and recipient can give a patient the chance to undergo LT even in some suboptimal conditions of advanced HCC. Reversely, such high probability of tumor recurrence can evoke some ethical issues from the viewpoint of the living donor. In reality, as a small proportion of patients with advanced HCC have survived several

years after LT, such an advanced lesion itself cannot always be absolutely contraindicated for LT. These dilemmas about the efficiency of cadaveric donor organ allocation, perioperative mortality, tumor recurrence, and living-donor-specific factors were intrinsically dispersed in the raw data of this study, but we concentrated on the risk-outcome sequences.

There are many publications on the outcomes of CDLT for HCC patients, but only a few noticeable LDLT series for HCC have been reported to date.^{6,10,11} There was still no large-volume comparative study of CDLT and LDLT on the prognosis of HCC patients as far as we knew. It was the background reason why we carried out this comparative study after dividing the patient population into CDLT and LDLT groups.

The primary purpose of this study was to confirm

the applicability of the CDLT-based selection criteria of HCC to the field of LDLT. We recognized that the follow-up periods or case numbers in the CDLT group were somewhat insufficient to carry out totally reliable analyses, but they might be evincive enough to perform this comparative analysis.

Although the general features of HCC lesions were not exactly case-controlled in the CDLT and LDLT groups, we observed that the characteristics of HCC recurrence after LDLT were not statistically different from those after CDLT. At first, it had been supposed that rapid graft regeneration could be associated with an acceleration of tumor cell growth, but such an adverse effect was not demonstrated in this study. After a living donor liver graft has been regenerated, there would be no difference of tumor biology between CDLT and LDLT. Therefore, the crude risk of HCC recurrence may be the same following either CDLT or LDLT. As a result, the similar outcomes of HCC recurrence will be achievable after LDLT if the Milan or UCSF criteria are applied like in CDLT.

At this point, we have to comment on the recurrence of small HCC lesions. We encountered a LDLT recipient who showed unexpectedly early recurrence of HCC after only 3 months, in whom the HCC lesion was only a 1-cm single mass and incidentally detected. However, we excluded the case from this study because the liver pathology was compatible to the mixed HCC tumor. Unless there was such an exceptionally aggressive pathology, small incident lesions of HCC would have very low risk of recurrence. The data of this study demonstrated that there was no recurrence of HCC in the patients with such HCC on the median follow-up of 29 months.¹⁴ It implies that there is no pressing need to worry about the prognosis of incidentally detected HCC.

The tumor characteristics of this study were based on the pathology of explanted livers, which enabled us to include the incidental HCC lesion during the prognosis analysis. The correlation between the preoperative diagnosis and final pathologic stage of HCC lesions was evaluated by using the data of 1 institution ($n = 157$). It was found that recent preoperative assessment of HCC between the years of 2001 and 2002 (90 cases including 8 incidental HCC lesions), carried out by the updated high-resolution imaging study machines, could reliably predict the real extent of intrahepatic HCC lesions if the lesion was not too small. Considering the low recurrence risk of incidentally detected HCC, preoperative diagnosis of tumor extent can be reliably used for patient selection in spite of some potential risk of underestimation.^{11,14,17}

Our results of CDLT and LDLT on HCC recurrence within the Milan or UCSF criteria were comparatively similar not only to their original results of CDLT but also to the Japanese results of LDLT.^{2,4,11} It may imply that the selection criteria of HCC patients for CDLT can be equally applicable to LDLT. On the other hand, it should be pointed out that the indication expansion from the Milan criteria to the UCSF criteria increased the indication population by only 7.3% in this series. Such a small increase in the study population is likely to make little difference in the outcome unless the total population volume is enough large. The broadest criteria such as exclusion of major vessel invasion resulted in the 3-YSR of 86.8% with exclusion of perioperative mortality (Fig. 4). It expanded the indication population by 20.1% compared with the Milan criteria and the prognostic influence from the favorable patients (within the Milan criteria) would be diminished compared with that of the UCSF criteria. Achievement of recurrence-free 3-YSR close to 87% in both CDLT and LDLT must be an encouraging result for HCC patients without gross vascular invasion although it did not include perioperative mortality. However, gross vascular invasion definitely resulted in a disappointing outcome. Considering the efficient organ sharing in CDLT and donor ethics in LDLT, HCC patients with suspicious major vessel invasion should be prudently selected for LT. Highly suspicious invasion of major vessels is usually not indicated for LT.

In LDLT, the safety of the living donor is of the utmost importance. Fortunately there is no mortality of living donors in Korea to date, but we have never ignored the real incidence of serious donor complications, not to mention of the real occurrence, of living donor mortality.^{13,18,19}

In this multicenter study, both early HCC recurrence and perioperative mortality played major roles in lowering the overall survival rate. The yearly rate of perioperative mortality has decreased after the learning curve period in each LT center, and that of LDLT decreased to near 5% in 2003.^{13,20} However, the perioperative mortality of CDLT has still remained over 10% in Korea. Scarcity of cadaveric donors resulted in relatively high probability of severe graft dysfunction and extremely low possibility of retransplantation. Contrarily, it is still hard to think that the yearly rates of HCC recurrence during the first 12 months would show a decreasing tendency. In fact, the actual selection criteria of HCC patients have been steadily expanded during the last several years especially in the fields of LDLT. However, to date, there is no effective adjuvant therapy to reduce early HCC recurrence as far as we

know. Some prophylactic regimens, such as postoperative systemic chemotherapy or administration of the vitamin K, retinoid, and anti-angiogenetic agent, have been tried, but we could not find any beneficial effects yet.

Multimodality tumor control was usually performed on the recurred HCC lesions. We have often observed extensive tumor dissemination even during such treatments. This aggressive pattern of HCC recurrence seems to be associated with the unfavorable tumor biology (i.e., low histologic grade) and inevitable immunosuppression. Early HCC recurrence was closely related to the more shortened survival period after its recurrence.

Based on these multicenter data, the independent risk factors of HCC recurrence were large-size tumor (exceeding 5 cm in diameter), gross invasion of major hepatic vessels, and low-grade histologic differentiation. The first 2 factors should be included for establishment of eligibility criteria of HCC patients in both CDLT and LDLT. Grade of histological differentiation must be another important prognostic factor, but this item cannot be included in the routine pretransplant protocol for assessment of HCC.^{11,21,22}

In conclusion, LT can achieve acceptable survival in the HCC patients, even if liver cirrhosis is severe or HCC is uncontrollable by conventional treatments. In this Korean multicenter study, the timing, patterns, and risk factors of HCC recurrence were not different between the CDLT and LDLT groups. Therefore, we think that the selection criteria of CDLT for patients with HCC can be equally applicable to LDLT without significant change of prognostic power.

References

1. Bruix J, Llovet J. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002;35:519-524.
2. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinoma in patients with cirrhosis. *N Engl J Med* 1996;334:693-699.
3. Marsh JW, Dvorchik I, Bonham CA, Iwatsuki S. Is the pathologic TNM staging system for patients with hepatoma predictive of outcome? *Cancer* 2000;88:538-543.
4. Yao FY, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl* 2002;8:765-774.
5. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394-1403.
6. Kaihara S, Kiuchi T, Ueda M, Oike F, Fujimoto Y, Ogawa K, et al. Living-donor liver transplantation for hepatocellular carcinoma. *Transplantation* 2003;75(Suppl):S37-S40.
7. Yao FY, Roberts JP. Applying expanded criteria to liver transplantation for hepatocellular carcinoma: too much too soon, or is now the time? *Liver Transpl* 2004;10:919-921.
8. Efimova EA, Glanemann M, Liu L, Schumacher G, Settmacher U, Jonas S, et al. Effects of human hepatocyte growth factor on the proliferation of human hepatocytes and hepatocellular carcinoma cell lines. *Eur Surg Res* 2004;36:300-307.
9. von Schweinitz D, Faundez A, Teichmann B, Birnbaum T, Koch A, Hecker H, et al. Hepatocyte growth-factor-scatter factor can stimulate post-operative tumor-cell proliferation in childhood hepatoblastoma. *Int J Cancer* 2000;85:151-159.
10. Gondolesi GE, Roayaie S, Munoz L, Kim-Schluger L, Schiano T, Fishbein TM, et al. Adult living donor liver transplantation for patients with hepatocellular carcinoma: Extending UNOS priority criteria. *Ann Surg* 2004;239:142-149.
11. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: Experience in Japan. *Ann Surg* 2004;240:451-459.
12. Pawlik TM, Esnaola NF, Vauthey JN. Surgical treatment of hepatocellular carcinoma: similar long-term results despite geographic variation. *Liver Transpl* 2004;10(Suppl):S74-S80.
13. Moon DB, Lee SG. Adult-to-adult living donor liver transplantation at the Asan Medical Center. *Yonsei Med J* 2004;45:1162-1168.
14. Choi SH, Lee HH, Lee DS, Choi JH, Heo JS, Lee KW, et al. Clinicopathological features of incidental hepatocellular carcinoma in liver transplantation. *Transplant Proc* 2004;36:2293-2294.
15. Hwang S, Lee SG, Ha TY, Ahn CS, Park KM, Kim KH, et al. Simplified standardized technique for living donor liver transplantation using left liver graft plus caudate lobe. *Liver Transpl* 2004;10:1398-1405.
16. Sugiyama M, Sakahara H, Torizuka T, Kanno T, Nakamura F, Futatsubashi M, et al. 18F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. *J Gastroenterol* 2004;39:961-968.
17. Libbrecht L, Bielen D, Verslype C, Vanbeckevoort D, Pirenne J, Nevens F, et al. Focal lesions in cirrhotic explant livers: Pathological evaluation and accuracy of pretransplantation imaging examinations. *Liver Transpl* 2002;8:749-761.
18. Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, et al. Operative morbidity of living liver donors in Japan. *Lancet* 2003;362:687-690.
19. Lo CM. Complications and long-term outcome of living liver donors: A survey of 1,508 cases in five Asian centers. *Transplantation* 2003;75(Suppl):S12-S15.
20. Fan ST, Lo CM, Lui CL, Yong BH, Wong J. Determinants of hospital mortality of adult recipients of right lobe live donor liver transplantation. *Ann Surg* 2003;238:864-870.
21. Tamura S, Kato T, Berho M, Misiakos EP, O'Brien C, Reddy KR, et al. Impact of histological grade of hepatocellular carcinoma on the outcome of liver transplantation. *Arch Surg* 2001;136:25-30.
22. Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001;33:1080-1086.