

Comparison of liver resection and living donor liver transplantation in patients with hepatocellular carcinoma within Milan criteria and well-preserved liver function

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Abstract

Background and Aim: Liver resection (LR) and liver transplantation (LT) are curative treatments for hepatocellular carcinoma (HCC). The main purpose of this study was to compare the survival of LR and LDLT in patients with HCC within the Milan criteria.

Materials and Methods: The results of the LR (n=67) and LDLT (n=391) groups were compared for overall survival (OS) and disease-free survival (DFS). Twenty-six of the HCCs in the LRs met the Milan and Child A criteria. Also, 200 of the HCC patients in the LDLTs met the Milan criteria, of which 70 also met the Child A criteria.

Results: Early mortality was higher in the LDLT group (13.9% vs 1.47%; p=0.003). The 5-year OS was higher in the LDLTs than the LRs, but not statistically significant (84.6% vs 74.2%; p=0.287). However, 5-year DFS was better in the LDLT group (96.8% vs 64.3%; p<0.001). When the LRs (n=26) and the LDLTs (n=70) that met both Milan and Child A criteria were compared, 5-year OS was similar (81.4% vs 74.2%; p=0.512), but DFS was better in the LDLTs (98.6% vs 64.3%; p<0.001).

Conclusion: LR can be justified as the first-line treatment for HCC patients who meet Milan and Child A criteria in terms of early mortality and OS.

Keywords: Hepatocellular carcinoma; liver resection; liver transplantation.

Introduction

Although liver resection (LR) and liver transplantation (LT) are considered the only potentially curative treatments for hepatocellular carcinoma (HCC), LT is the best theoretical option because it cures both

the HCC and the underlying cirrhotic liver disease. However, LT can be performed in a limited number of patients due to insufficient organ donation. For this reason, there is renewed interest in LR for HCC in countries like Turkiye, where organ donation is extremely low.^[1-3] In fact, LR for HCC can achieve overall 5-year survival rates comparable to those of LT in early HCC. Despite this, underlying liver disease is associated with HCC recurrence. Therefore, lower disease-free survival (DFS) is found after LR compared to LT. However, LR preserves the possibility of salvage LT. Additionally, histopathologic features of the LR specimen can be used as a guide for selecting LT candidates.^[4-6]

We believe that LR results for HCC will be better due to greater familiarity with intrahepatic anatomy in experienced living donor liver transplantation (LDLT) centers. Although there are many publications comparing the results of LR and cadaver donor liver transplantation (DDLTL) in studies published so far,^[6-8] we have found very few studies comparing LR and LDLT in terms of overall survival (OS) and DFS in HCC within the Milan criteria.^[9,10] Additionally, we think the selection of only the group within the Milan criteria is insufficient to compare the LR and LT results in HCC. LR cannot be performed for every patient with HCC included in the Milan criteria, due to both the anatomical distribution of the tumors and the degree of liver function deterioration. Therefore, when LDLT is performed on HCC cases within the Milan criteria, it is necessary to select and compare the cases suitable for LR in this group. In this study, we formed the study groups by considering these features. The aims of this study are to analyze OS and DFS after LR and LDLT in HCC patients within the Milan criteria but suitable for LR, with special reference to DFS, recurrence, and salvage LT.

Materials and Methods

In this study, the database of patients who underwent LR or LDLT for HCC was acquired from a prospectively collected and retrospectively analyzed source. Between January 2009 and December 2022, all patients with partial or total hepatectomy whose explants were reported as containing HCC in our liver transplant institute were reviewed. Mixed tumors that included a cholangiocarcinoma component were excluded. In this period, 534 patients with HCC underwent surgery, of which 68 underwent LR with complete excision of the tumor, and 466 underwent LDLT. The cases that died in the first 3 months after surgery were considered early mortality. Mortality rates were compared between the two

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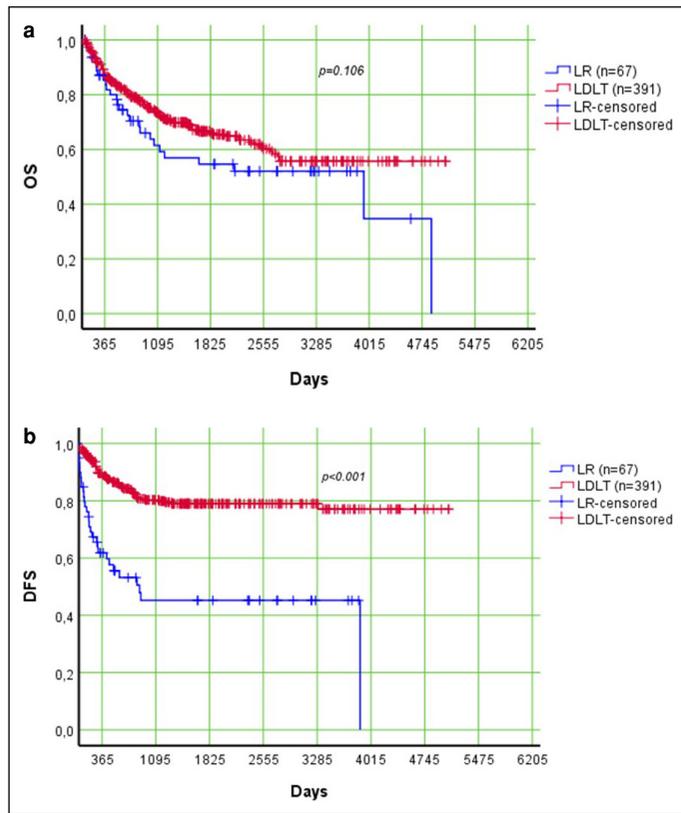


Figure 1. Kaplan-Meier survival curves of overall (a) and disease-free survival (b) analysis of HCC patients treated with LR and LDLT.

groups, but mortal cases were not taken into account in the evaluation of survival to reveal oncologic survival. As a result, the log-rank test was used for the results of LR versus LDLT in a cohort of 458 HCC patients regarding patient demographics, overall survival (OS), and disease-free survival (DFS) rates. Sixty-seven patients had LR, whereas 391 patients had LDLT as the first surgical modality. In the LR group, 26 patients were within the Milan criteria. In the LDLT group, 200 patients were within the Milan criteria, but only 72 were eligible for resection (Child A and tumor suitability for resection).

The following demographic and clinical characteristics of HCC patients were analyzed for this study: age, gender, pre-transplant last alpha-fetoprotein (AFP) level, locoregional therapies (trans-arterial chemoembolization, trans-arterial radioembolization, radiofrequency ablation, etc.), and factors related to tumor pathologic characteristics (tumor size, number of tumors, histopathologic grade, presence of microvascular invasion) were reviewed for the risk factor analysis for HCC recurrence. The primary objective of this study was to compare the survival of both groups after LR and LDLT in patients with HCC within the Milan criteria in conditions where both treatment modalities were possible.

The study protocol was approved by the ethical committee of the Inonu University institutional review board (IRB) for non-interventional studies (No: 2023-4253) and conducted in adherence to the Declaration of Helsinki. Informed consent was obtained from all participants before the LR and LT procedures.

In our Liver Transplant Institute, the decision to resect or transplant a patient with HCC is always made in a multidisciplinary staff meeting attended by transplant surgeons, hepatologists, medical oncologists, ra-

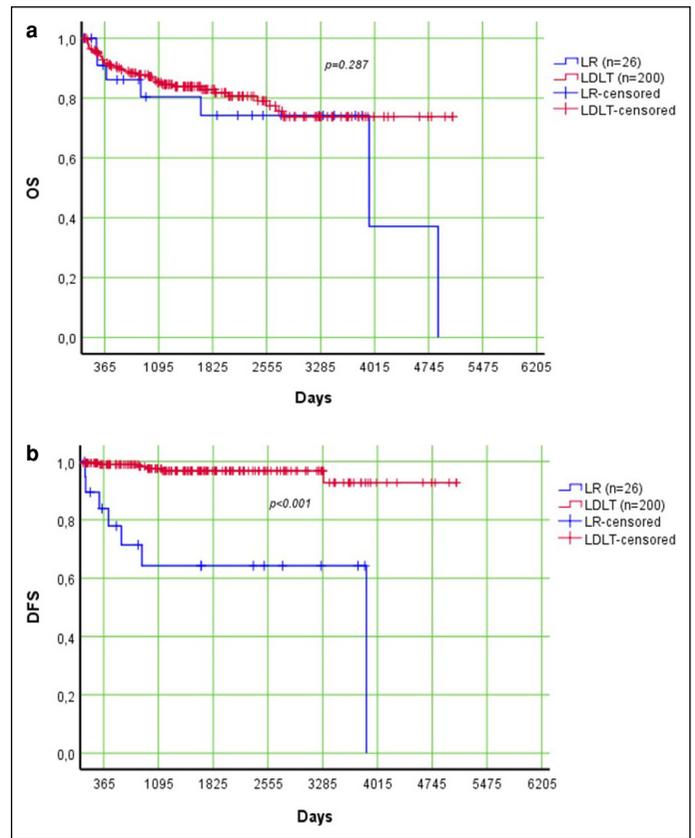


Figure 2. Kaplan-Meier survival curves of overall (a) and disease-free survival (b) analysis of HCC patients in the LR group who met the within Milan criteria were compared with those in the LDLT group.

diologists, radiation oncologists, nuclear medicine specialists, and pathologists. HCC diagnosis was based on preoperative CT and MR images, tumor marker levels, and clinical profiles. Our general approach is to offer LR as a first-line treatment modality to an HCC patient with Child A cirrhosis. However, LDLT is offered to patients with HCC whose LR is not suitable for surgical technique or with impaired liver function. Candidates for LR were patients with good general status (availability of Indocyanine green retention testing enabling LR) and a feasible, complete, safe resection (Child-Pugh score class A) of the liver tumor with no identified extrahepatic disease. Anatomic resection with complete removal of at least one Couinaud’s segment, including the tumor area fed by portal branches, was attempted. If anatomic resection was not technically possible, we tried to obtain an appropriate margin. Complete excision of the tumor with a safe margin was confirmed by pathologic examination in all LR patients. Follow-up included liver function tests, alpha-fetoprotein, dynamic CT, and liver-specific MR at 3-month intervals during the first year and every 6 months after the first year.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences for Windows version 25.0 (SPSS; New York; USA). Qualitative variables were presented as numbers and percentages (%). Quantitative variables were given as median and 95% confidence interval (CI). The Shapiro-Wilk test of normality was applied to the variables containing quantitative data. Pearson’s chi-square test, Yates’

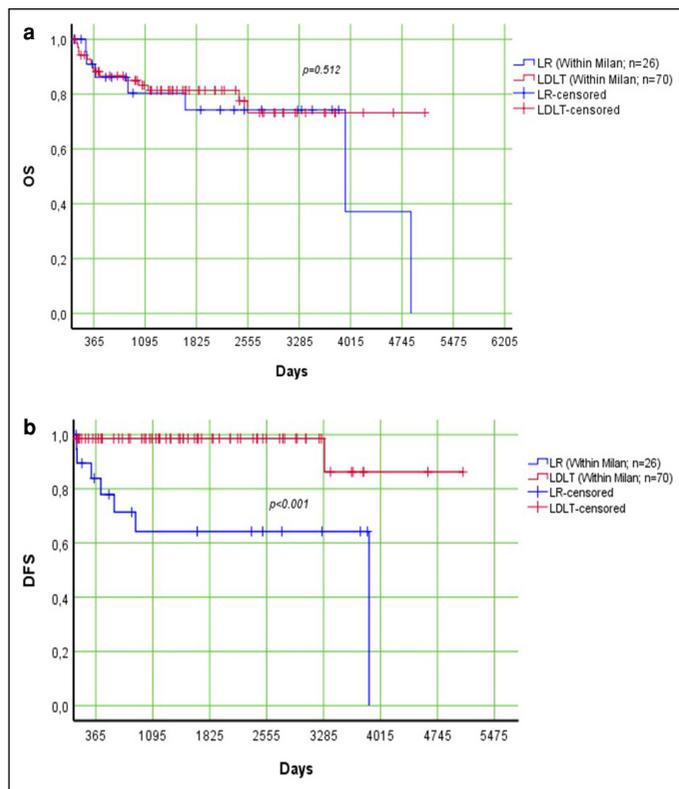


Figure 3. Kaplan-Meier survival curves of overall (a) and disease-free survival (b) analysis of HCC patients in the LR group who met the within Milan criteria and Child A were compared with those in the LDLT group.

correction for continuity, or Fisher's exact test were used where appropriate for the comparison of categorical variables. The Mann-Whitney U test was used in the evaluation of quantitative data. A $p < 0.05$ level was accepted as significant in all evaluations. Overall survival (OS) was defined as the time from the date of liver transplantation or liver resection to the date of death from any cause, regardless of loco-regional recurrences, distant metastases, and second primary cancer. DFS was defined as the time from LT or LR to the first loco-regional recurrence, distant metastases, or death from any cause. Salvage LDLT (sLDLT) was defined as LT performed for HCC recurrence or liver failure after primary LR. However, all sLDLT cases included in this study were due to HCC recurrence.

Results

In this study, we first compared the cases with early mortality in the LR and LDLT groups. This rate was 1.47% in the LR group and 13.9% in the LDLT group ($p = 0.003$, OR:10.8). The high mortality in the LDLT group is due to the high mortality rates in the early years of the study. In the last 5 years, the mortality rate in the LDLT group is less than 5%. We did not consider mortality cases when evaluating oncological survival. As a result, of the 458 patients with HCC, 67 were in the LR group and 391 were in the LDLT group. The median follow-up period of 458 patients included in the study was 7.5 years (95% CI= 4.8-10.2).

Overall Survivals

Comparing 67 HCC patients who underwent LR and 391 HCC patients who underwent LDLT, the 5-year OS rates were similar (54.6% for LR

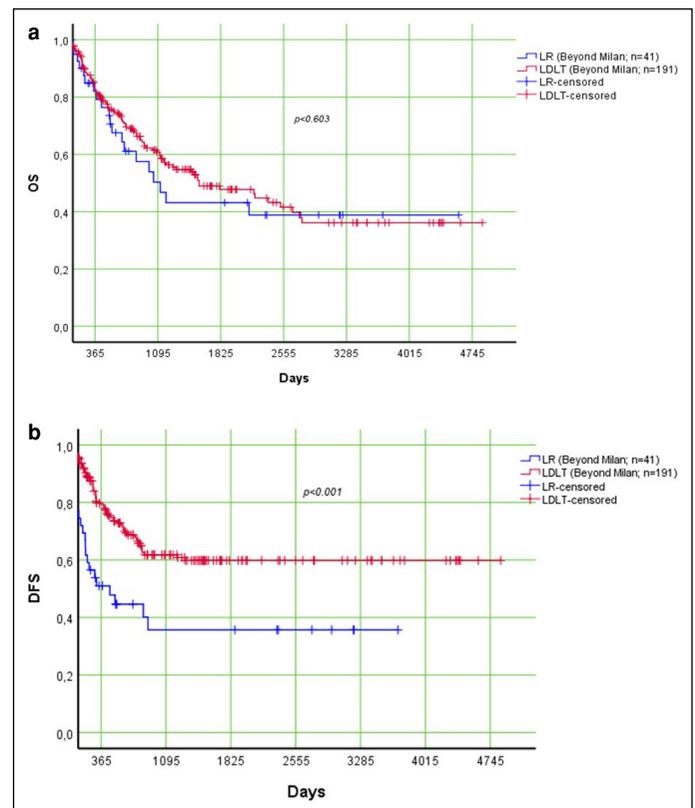


Figure 4. Kaplan-Meier survival curves of overall (a) and disease-free survival (b) analysis of HCC patients in the LR group who met the beyond Milan criteria and Child A were compared with those in the LDLT group.

vs 69% for LDLT, $p = 0.106$). However, 5-year DFS rates were better in the LDLT group (45.2% for LR vs 79% for LDLT, $p < 0.001$) (Fig. 1a, b). The reason why 5-year DFS rates were higher than OS in the LDLT group was that patients in this group died from other causes without HCC recurrence. In parallel with these results, recurrence rates were higher in the LR group (47.6% for LR vs 17.9% for LDLT, $p < 0.001$, OR: 4.16).

Survivals within Milan Criteria

Patients who underwent LR and LDLT were divided into subgroups based on Child A and within Milan criteria, and patients who met these criteria were compared. Although all of the HCC patients who underwent LR met Child A, only 26 of them met the "within Milan criteria". On the other hand, 70 of the HCC patients who underwent LDLT met both Child A and "within Milan criteria". Statistically significant differences were found between groups in terms of differentiation, vascular invasion, recurrence, MELD score, platelets, total bilirubin, GGT, albumin, and maximum tumor size. The results are summarized in Table 1 and Table 2.

In terms of overall survival (OS), 26 patients in the LR group and 200 patients in the LDLT group, who were within the Milan criteria, were compared. The 5-year OS rate was 74.2% in the LR group and 84.6% in the LDLT group, with no statistical difference ($p = 0.287$). However, 5-year DFS rates were better in the LDLT than the LR group (64.3% for LR vs 96.8% for LDLT, $p < 0.001$) (Fig. 2a, b). In the continuation of this comparison, 26 HCC patients who underwent LR within the Milan criteria and 70 HCC

Table 1. Comparison of LR and LDLT groups (Child A) meeting “within Milan criteria” in terms of qualitative variables

Parameters	LR (n=26)		LDLT (n=70)		OR (95% CI)	p
	n	%	n	%		
Gender					NS	0.541
Male	21	80.8	60	85.7		
Female	5	19.2	10	14.3		
Number of tumor					NS	0.545
1	23	88.5	57	81.4		
>1	3	11.5	13	18.6		
Differentiation					8.2 (1.9-34.5)	0.004
Well	19	73.1	67	95.7		
Poor	7	26.9	3	4.3		
Vascular invasion					3.9 (1.5-10.2)	0.008
No	12	46.2	54	77.1		
Microvascular	14	53.8	16	22.9		
Bridging treatment					NS	1.000
Yes	3	11.5	10	14.3		
No	23	88.5	60	85.7		
Recurrence					12.5 (2.4-66.6)	0.001
Yes	19	73.1	68	97.1		
No	7	26.9	2	2.9		
Outcome					NS	0.652
Alive	19	73.1	56	80.0		
Dead	7	26.9	14	20.0		

LR: Liver resection; LDLT: Living donor liver transplantation; OR: Odd ratios; CI: Confidence interval; NS: Not significant.

patients who were within the Milan criteria who underwent LDLT but also met the LR (Child A and anatomically suitable tumor distribution for resection) were compared. Although the 5-year OS rates were similar (74.2% vs 81.4%, respectively, $p=0.512$), DFS rates were higher in the LDLT than the LR group (64.3% vs 98.6%, respectively, $p<0.001$) (Fig. 3a, b).

Survivals Beyond Milan

Patients who underwent LR and LDLT and were beyond the Milan criteria were also compared for survival. The overall 5-year survival of 41 patients who underwent LR and 191 patients who underwent LDLT was lower than those within the Milan group, but there was no statistically significant difference between the groups (43.1% for LR vs 48.9% for LDLT, $p=0.603$). As in other comparisons, 5-year DFS rates were better in the LDLT group (35.7% for LR vs 59.8% for LDLT, $p<0.001$) (Fig. 4a, b).

Survival for Salvage and Primary LT

Finally, 5-year OS and DFS rates of 10 patients who underwent LR and subsequently underwent salvage LDLT (sLDLT) for HCC recurrence were analyzed from two different perspectives. LR was performed for HCC, which was within the Milan criteria in 4 of the 10 patients who had sLDLT, and in 6 of them who were beyond the Milan criteria. First, 10 patients with sLDLT were compared with 200 patients within the Milan criteria who underwent primary LDLT.

Table 2. Comparison of LR and LDLT groups (Child A) meeting “within Milan criteria” in terms of quantitative variables

Parameters	LR (n=26)		LDLT (n=70)		p
	Med.	95% CI	Med.	95% CI	
Age	57	50-61	54	52-58	0.302
MELD	7	7-8	8	8-10	0.002
AFP	17	4-400	11	7-24	0.490
Platelets	192	139-208	120	98-137	0.002
WBC	5.9	5.3-6.2	5.9	5.1-6.3	0.902
Neutrophil	3.3	3.0-3.5	3.1	2.7-3.7	0.808
Lymphocyte	1.8	1.6-2.0	1.7	1.3-1.9	0.316
Bilirubin	0.7	0.6-1.0	1.0	0.9-1.2	0.026
GGT	37	25-46	76	52-106	<0.001
Albumin	4.0	3.8-4.3	3.6	3.6-3.7	<0.001
Maximum tumor size (mm)	35	30-45	25	20-27	0.004
Follow-up	1295	534-2504	1486	1168-1948	0.704

LR: Liver resection; LDLT: Living donor liver transplantation; Med: Median; OR: Odd ratios; CI: Confidence interval; AFP: Alpha-fetoprotein; MELD: Model for end-stage liver disease; WBC: White blood cell; GGT: Gama glutamil transferaz.

The 5-year OS rates were similar (65.6% for sLDLT vs 84.6% for pLDLT; $p=0.067$), but 5-year DFS was better in the primary LDLT

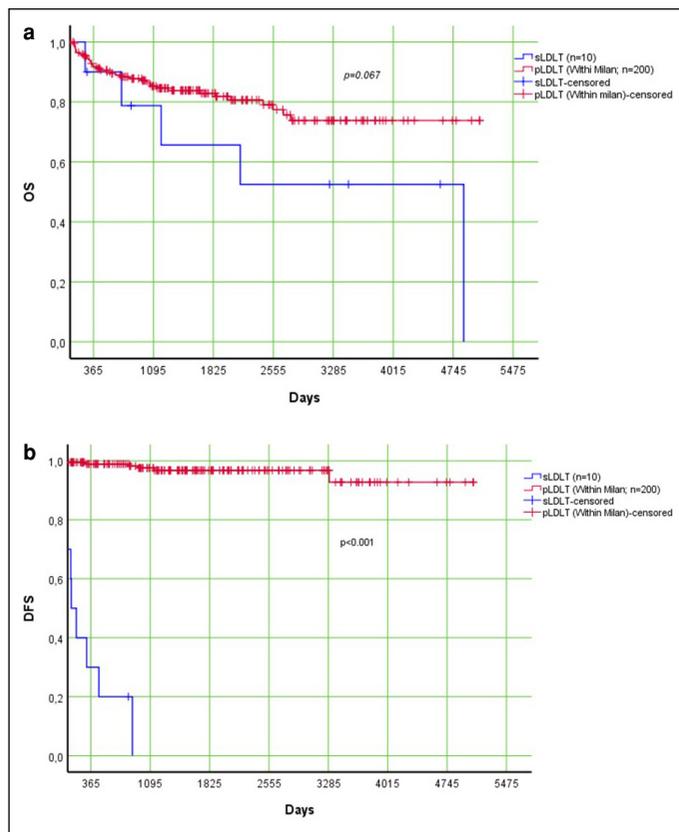


Figure 5. Kaplan-Meier survival curves of overall (a) and disease-free survival (b) analysis of HCC patients with sLDLT were compared with HCC patients within the Milan criteria who underwent primary LDLT.

group (20% for sLDLT vs 96.8% for pLDLT; $p<0.001$) (Fig. 5a, b). Then, 10 patients with sLDLT were compared with 70 HCC patients who underwent primary LDLT, and those not only within the Milan criteria LDLT but also met the LR. Similar 5-year OS (65.6% for sLDLT vs 81.4% for primary LDLT; $p=0.161$) and 5-year DFS (20% for sLDLT vs 98.6% for primary LDLT; $p<0.001$) rates were obtained here (Fig. 6a, b).

Discussion

This study focused on the long-term results after LR and LDLT in patients with HCC within the Milan criteria, but who had preserved liver function, Child-Pugh class A. Although previous studies have reported low survival and high recurrence rates after LR of HCC within the Milan criteria,^[9-11] there are also favorable results on the outcomes of LR in patients with preserved liver function and HCC within the Milan criteria.^[12-14] Major society guidelines recommend LR when the hepatic function is preserved and sufficient remnant liver volume is maintained.^[15-17] Our results show that LR of Child-Pugh class A patients with HCC within the Milan criteria can be performed with a low death rate of 1.47% and a 5-year overall survival rate of 74.2%. Therefore, in terms of overall survival rate, LR can be justified as the first-line treatment for patients with HCC within the Milan criteria and with preserved liver function. However, the 5-year DFS rate in this cohort of patients was 64.3%, whereas the corresponding DFS rate after LDLT for similar patients was about 98.6%. The lower tumor recurrence rate has been the main argument for advocating LT

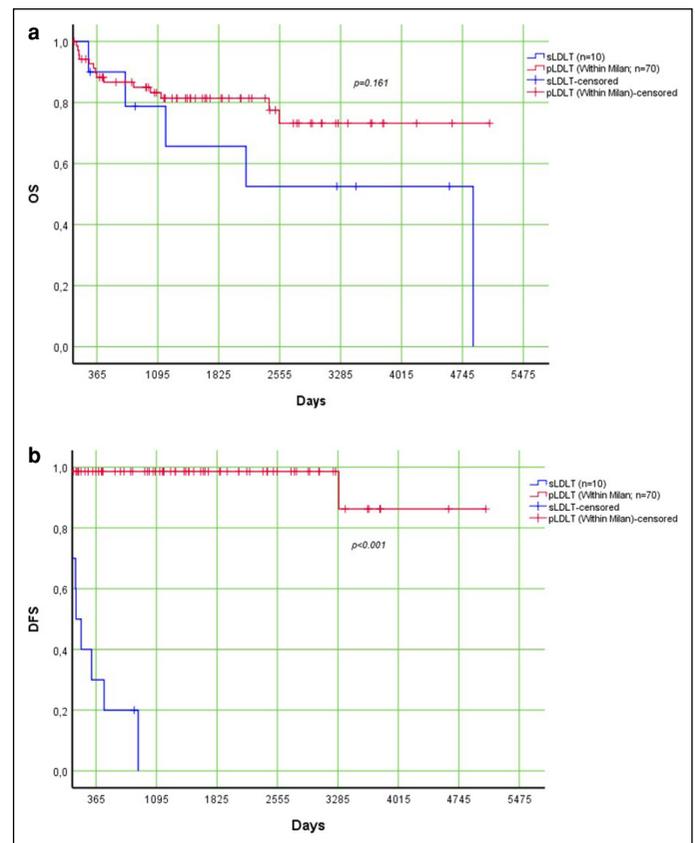


Figure 6. Kaplan-Meier survival curves of overall (a) and disease-free survival (b) analysis of HCC patients with sLDLT were compared with HCC patients within the Milan criteria and Child A who underwent primary LDLT.

for HCC within the Milan criteria and Child-Pugh class A patients.^[7,10] We think that a 74.2% 5-year OS is quite a good level in the LR group. Although the OS rate obtained in the LDLT group was 84.6%, it was not a statistically significant difference. DFS rates are better in the LT group, but we think that the LR results obtained without using a living donor and with low mortality rates are valuable.

The most striking point in publications on this subject is the comparison of LR and LT in patients with HCC within the Milan criteria.^[9,11,14] There is nothing to criticize in the evaluation of patients within the Milan criteria in the LR group. Because LR can only be performed in HCC cases with well-preserved liver function and who are anatomically suitable. We think that it is not an accurate comparison to compare the LR group with the LT group selected in this way in terms of survival since not every case within the Milan criteria undergoing LT is suitable for LR. In some cases with impaired liver function, in some cases, the tumor or tumors are not in a location suitable for resection anatomically, even if they are within the Milan criteria. In this study, patients in the LT group were selected as the LDLT group if they were within the Milan criteria and their liver functions and tumor localization were suitable for LR. Therefore, the tumor characteristics and liver functions of the patients in both groups are similar.

LR group patients had larger tumors, and LDLT group patients had less preserved liver parenchymal function. To briefly mention the demographic characteristics that were different between the 2 groups, the poorer differentiation and microvascular invasion in the LR group were due to the resection of larger HCCs in this group. This is because there

was a tendency to resect larger tumors in the LR group, even within the Milan criteria. We think that the high MELD score, bilirubin and GGT levels, and low platelet and albumin levels are due to greater hepatic parenchymal dysfunction in the LT group.

The LT group in this study included only patients who underwent LDLT. LDLT is the treatment of choice for patients with early HCC who have moderate to severe cirrhosis. The role of LDLT for an early HCC patient with resectable disease remains uncertain due to the potential morbidity and mortality of healthy live donors. The mortality in the LDLT group is due to the high mortality rates in the first years of the study. In the last 5 years, the mortality rate in the LDLT group is less than 5%. LDLT is a very complicated operation compared to LR. But, LDLT has advantages such as absence of waiting time, removal of the underlying diseased liver, which is potentially a source of future (recurrent) tumors, and the use of healthy grafts. In addition, surgeons in highly experienced LDLT centers are more familiar with intrahepatic anatomy. The low mortality of 1.47 % in the LR group in our study can be interpreted with this perspective. Although tumor recurrence is much less a problem after LT, there are other complications specific to LT that can compromise long-term survival, such as graft rejection, opportunistic infections, and the development of other malignancies as a result of immunosuppression.

In this study, in 67 patients including HCC patients within and beyond Milan criteria, 5-year OS rates of 54.6% were obtained with LR. Forty-one patients beyond the Milan criteria had 5-year OS rates of 43.1% with LR. These results show that the chance of LR is an option that can be offered to patients in resectable HCCs that are not suitable for LT. The 5-year OS was 65.6% in the sLT group, which included 10 patients. Our limited data suggest that LR followed by sLT for recurrence or deterioration of liver function may be a rational approach.

The study has a few limitations. One of them is the retrospective analysis of the cases. Although the data were collected prospectively, a randomized cohort study would be better in this aspect. The second limitation is the relatively lower number of patients within the Milan Criteria, in the resection arm (n=26).

In conclusion, this study shows that LR can be performed safely with an overall 5-year survival rate of 74.2% in patients with HCC who had Child-Pugh class A and were within the Milan criteria. A considerable proportion of patients may survive disease-free or with recurrences for 5 or even 10 years. The patients who underwent LDLT exhibited a significantly lower HCC recurrence rate compared to LR. Our data related to sLT for recurrent HCC is limited, but our long-term results are encouraging.

Ethics Committee Approval: The Inonu University Clinical Research Ethics Committee granted approval for this study (date: 24.01.2023, number: 2023/4253).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SY; Design – VI; Supervision – BIC; Materials – ANA; Data Collection and/or Processing – SK; Analysis and/or Interpretation – SA; Literature Search – YD; Writing – SY; Critical Reviews – RK.

Conflict of Interest: The authors have no conflict of interest to declare.

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