



## Original Research

# Salvage Living Donor Liver Transplantation for Best Supportive Care Patients with Advanced HCC

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### Abstract

**Objectives:** Patients with advanced stage hepatocellular carcinoma (HCC) and liver decompensation have been suggested to receive best supportive care (BSC) according to BCLC algorithm and these patients have a median estimated survival of only 3 months (1). By contrast, living donor liver transplantation (LDLT) performed in a subgroup of BSC patients may not cure the advanced cancer, but it can cure the liver dysfunction. Thus, even if the tumor recurs after transplantation, patients can be treated with local or systemic therapies due to their good liver function, with potential for longer survival. The aim of this study was to compare the survival of BSC patients versus salvage LDLT (sLDLT).

**Methods:** The data of 492 LT patients with HCC were analyzed retrospectively from our databank, which is recorded prospectively and sequentially (2). Among these LDLT patients, those with Child class C and advanced stage HCC [beyond Expanded Malatya criteria] (3) without extrahepatic metastasis aged between 18-60 years were included in the study as the sLDLT group. The data of non-transplant HCC patients were also reviewed and BSC patients were included as BSC group. The survival of sLDLT and BSC groups was then compared.

**Results:** sLDLT group had 17 patients and BSC group had 48 patients. Median survivals were 1020 days (291.6 – 1748.4, 95% CI) in sLDLT group and 40 days (30.9 – 49.1, 95% CI) in BSC group. Hospital mortality (<90 days) in sLDLT group was 2 patients (11.7%), and in BSC group was 81.3% (39/48). Post-LDLT recurrence rate was 66.7% (10/15) and 3-year overall survival (OS) was 50%. We then dichotomized the LDLT group into >2 years and <2 years survival, patients who survive >2 years had significantly lower MTD (2.5 vs 7.5 cm,  $p=0.036$ ) and lower platelet levels (60.5 vs 93,  $p=0.027$ ).

**Conclusion:** No palliative treatment could result in 50% 3-year OS in the BSC patients. However, we could achieve 3-year OS of 50% in selected patients in the BSC group (No extrahepatic metastasis, Child C and ages between 18-60) by LDLT.

**Keywords:** BSC, Palliative, LDLT, live donor, macrovascular invasion

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Liver transplantation (LT) is a potentially curative treatment for HCC, while palliative treatments are not curative. These 2 terms should not be used together in a single

sentence. However, as surgeons, we operate on tumor patients for 2 main goals. The first goal is to cure the cancer which means long term and tumor free survival, and the

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second goal is to ensure that patients have some quality of life for the rest of their lives. Based on the second goal, the question arose as to whether we can use living donor liver transplantation (LDLT) as a palliative treatment in patients with advanced hepatocellular carcinoma (HCC).

Patients with advanced stage HCC and liver decompensation have been suggested to only be eligible for best supportive care (BSC) according to the BCLC algorithm and these patients have only a median 3 month estimated survival.<sup>[1]</sup> On the other hand, LDLT in a subgroup of BSC patients, may not cure advanced cancer, but it can normalize the liver function. Thus, even if the tumor recurs after transplantation, patients can be treated with local or systemic therapies due to good liver function post-transplant with potential for a longer life.

The aim of this study was to compare the survival of BSC patients with salvage LDLT (sLDLT).

## Methods

### Ethics

This study has been approved by Inonu University Ethics Committee with approval no: 2024/6410. Due to this study having a retrospective design, informed consent from patients was not necessary.

### Study Population

Between March 2002 and July 2024, 592 LTs were performed at the Liver Transplantation Institute of Inonu University for patients with HCC.<sup>[2]</sup> We retrospectively analyzed the data of LT patients with HCC from the database which is recorded prospectively and sequentially.

Patients beyond Expanded Malatya Criteria<sup>[3]</sup> were reviewed and the patients who met the inclusion criteria were analyzed.

### Inclusion Criteria

1. Child-Pugh class C.
2. HCC limited in the liver (no extrahepatic spread).
3. Age between 18 and 60.

Data of BSC patients were reviewed from the whole HCC council databank of the Liver Transplantation Institute of Inonu University.

Patient demographics, tumor morphology (according to explant pathology report), etiology of the underlying liver disease, pre-transplant laboratory values, Child-Pugh class, MELD Na score, graft to recipient weight ratio (GRWR), overall survival (OS) years and post-transplant recurrence rate were recorded.

## Surgical Technique and Management of Immunosuppressive Treatment

Our patient selection criteria, surgical method in LT for HCC, and immunosuppressive treatment protocol have been described in our previous studies.<sup>[4-8]</sup>

### Statistical Analysis

Normality of the quantitative data was assessed by Shapiro-Wilk test and summarized by median and interquartile range (IQR). Mann-Whitney U test was used to compare two independent groups. The distribution of the qualitative data was presented by count and percentage. Exact chi-square tests were used for comparisons according to categorical data. The two-sided significance level was considered as 0.05 in all analysis.

Survival analyses were performed using the Kaplan-Meier method, Log-Rank test, and Cox regression analysis. The two-tailed significance level was set at 0.05. Overall survival defined as the time between the transplant day and death and calculated as years and death patients were censored by Kaplan-Meier method. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

## Results

There were 17 patients who met the inclusion criteria in the sLDLT group, and 48 in the BSC group. Patient demographics were summarized in Table 1.

### Patient Demographics

sLDLT and BSC groups were statistically different in terms of age, MELD score, liver function tests, and AFP levels but were similar in terms of BMI, BSA, MTD, number of nodules, etiology and gender. The 62.5% (30/48) of the BSC patients were metastatic.

The median age, MELD Na score, AFP, MTD and number of nodules in sLDLT group were 53 years (41 – 59), 21 (16-34), 184ng/ml (2.0-14560), 4.5 cm (2.0-20), 4 (1-11), respectively.

The median age, MELD Na score, AFP, MTD and number of nodules in BSC group were 64 years (37 – 84), 14 (6 – 25), 1000 (1.67 – 97248), 11 cm (1.8 – 25), 2 (2-11), respectively.

In the sLDLT group, 82.4% of patients were male and the major etiology was HBV cirrhosis in 58.8%, while in the BSC group, male gender was 91.7% and HBV was 35.4%. Patient demographics were summarized at Table 1.

### Patient Mortality Rates

Two patients in the sLDLT group died in the early post-LDLT period due to sepsis. Hospital mortality rate (<90 days) in the sLDLT was 11.7% (2/17).

**Table 1.** Demographics of the patients

Parameters	pLDLT (n=17) Median (min-max)	BSC (n=48) Median (min-max)	p
Age	53 (41 – 59)	64 (37 – 84)	<0.001
MELD score	21 (16 – 34)	14 (6 – 25)	<0.001
BMI	24.7 (19.1 – 35.6)	24.0 (17 – 50)	0.727
BSA	1.96 (1.55 – 2.25)	2.00 (1.53 – 2.82)	0.523
GRWR (%)	1.06 (0.77 – 1.87)		
Albumin	2.4 (1.2 – 3.6)	3 (1.7 – 3.9)	0.012
Total Bilirubin	5.15 (2.1 – 16.7)	3 (0.5 – 27.1)	0.049
INR	1.52 (1.25 – 3.19)	1 (0.9 – 1.8)	<0.001
Platelet	84 (23 – 197)	169 (11.2 – 405)	<0.001
AST	176 (57 – 7789)	134 (38 – 397)	0.402
ALT	98,5 (38 – 3535)	55 (24 – 226)	0.001
GGT	100.5 (29 – 192)	234 (37 – 1179)	<0.001
ALP	148 (28 – 2327)	231 (74 – 1649)	0.003
AFP	184 (2.0 – 14560)	1000 (1.67 – 97248)	0.018
WBC	4.5 (1.8 – 29.3)	8 (2.5 – 28.6)	0.014
MTD (cm)	4.5 (2.0 – 20.0)	11 (1.8 – 25)	0.126
Number of nodules	4 (1 – 11)	2 (2 -11)	0.766
NLR	6.66 (1.62 – 35.3)	4.24 (0.94 – 16.6)	0.510
PLR	110 (38.05 – 252.5)	161.5 (16 – 876.6)	0.130
CRP	2.35 (0.3 – 41.7)	3 (0.38 – 17.1)	0.522
	<b>n (%)</b>	<b>n (%)</b>	<b>p</b>
Gender			
Female	3 (17.6)	4 (8.3)	0.287
Male	14 (82.4)	44 (91.7)	
Differentiation			
Well	1 (5.9)		
Moderate	8 (47.1)		
Poor	8 (47.1)		
Venous invasion			
None	2 (11.8)		
Micro (+)	8 (47.1)		
Macro (+)	7 (41.2)		
Recurrence			
Yes	10 (58.8)		
No	7 (41.2)		
Extrahepatic disease			
Yes	0 (0)	30 (62.5)	<0.001
No	17 (100)	18 (37.5)	
Etiology			
Cryptogenic	4 (23.5)	19 (39.6)	0.129
HBV	10 (58.8)	17 (35.4)	
HBV+HDV	2 (11.8)	1 (2.1)	
HCC	1 (5.9)	10 (20.8)	
HCV	0 (0)	1 (2.1)	
GRWR, %			
≥0.8	16 (94.1)		
<0.8	1 (5.9)		
TTD, cm			
≤8	6 (35.3)		
>8	11 (64.7)		

All patients died in the BSC group before 1 year. Mortality rate within 90 days in the BSC group was 81.3% (39/48).

### Patient Overall Survival

Median overall survival (OS) for the sLDLT group (n=17) was 1020 days (almost 3 years) (62.0 – 1977.9 days, 95% CI), and for the BSC group was 40 days (30.9 – 49.1 days, 95% CI)  $p<0.001$  (Fig. 1).

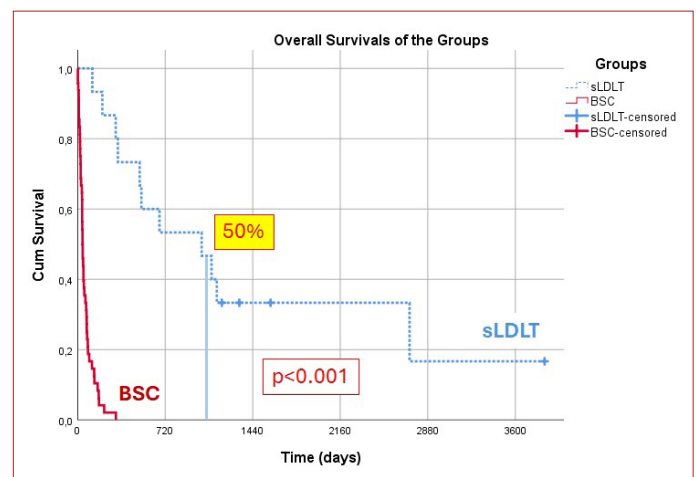
3-year OS rate was 50% and post-Tx recurrence rate was 66.7% (10/15) in the sLDLT group.

### Post-Transplant Recurrence

Post-transplant recurrence was detected in 10 patients in the sLDLT group. One patient had only hepatic recurrence which is unresectable treated by systemic chemotherapy, 4 patients had only extrahepatic disease (1 bilateral lungs treated by systemic chemotherapy, 2 had vertebra treated by Radiotherapy and Cyber knife, 1 brain metastases treated by surgical resection), and 5 patients had both hepatic and extrahepatic disease treated by systemic chemotherapy. In Türkiye, immune check point inhibitors are not covered by the government so, only tyrosine kinase inhibitors (sorafenib as first line) are reimbursement by Ministry of Health. Only the patient who had brain metastasis treated by surgical resection is still alive since 1714 days from transplantation (4.7 years), 653 days from the recurrence (1.8 years), remaining all recurrent patients were died.

### Subgroup Analysis of the sLDLT Patients

The LDLT group was subsequently dichotomized into >2 years and <2 years survival groups, patients who survive >2 years had significantly lower MTD (2.5 vs 7.5 cm,  $p=0.036$ ) and lower platelet levels (60.5 vs 93,  $p=0.027$ ) (Table 3).



**Figure 1.** Overall survivals of the groups.

**Table 2.** Comparison of treatment modalities for advanced HCC

Study, year	BSC	ICI	TKI	TACE	LDLT	p
Xia J, et al, 2021						
Median survival, months	1.3	3.3	3.1			<0.05
Fulgenzi CAM, et al, 2024						
Median survival, months	4.04	7.5				<0.001
Akarapatima K, et al, 2022						
Median survival, months	8.2			21.4		<0.001
Xiang X, et al, 2019						
Median survival, months	6			9		0.007
Llovet JM, et al, 2008						
Median survival, months	7.9		10.7			<0.05
Yau T, et al, 2019						
Median survival, months		16.4	14.7			0.752
Cheng AL, et al, 2022						
Median survival, months		19.2	13.4			<0.001
Malatya experience, 2024*						
Median survival, months	1.3				36	<0.001

BSC: Best supportive care; LDLT: living donor liver transplantation; ICI: Immun-check point inhibitors; TKI: tirosin kinaz inhibitors; TACE: Transarterial chemoembolization; \*: current study.

## Discussion

Best supportive care has been suggested for HCC patients with terminal stage (D) disease, according to the updated Barcelona Clinic Liver Cancer Staging System in 2022 with an estimated survival of only 3 months for these patients.<sup>[1]</sup> The BCLC Stage D is defined as patients with any tumor burden and end stage liver function and ECOG performance score 3-4.<sup>[1]</sup> We have a weekly liver tumor board in our center and we discuss all tumor patients in a multidisciplinary manner.<sup>[9]</sup> HCC patients beyond the Expanded Malatya criteria with macrovascular invasion and age >70 years with Child class C cirrhosis and/or extrahepatic spread are normally suggested to be offered only BSC by our tumor board. The 62.5% of the BSC patients had extrahepatic disease and the rest of them had macrovascular portal vein and/or hepatic vein tumor thrombosis with decompensated liver functions.

As a result of the accumulated LDLT experience in our center, we have seen that the LDLT outcomes of some patients who were suggested for BSC were encouraging. So, we reviewed our transplant-HCC databank and generated the sLDLT group. LDLT patients with Child class C and advanced stage HCC (beyond Expanded Malatya criteria) without extrahepatic metastasis and ages between 18-60 years were included into the sLDLT group. The data of non-transplant HCC patients were also reviewed and BSC patients were included as the BSC group. We found remarkable survival differences between the groups. The median survival time in the BSC group was 40 days, while the 3-year overall survival

rate in the sLDLT group was 50%. However, the recurrence rate after Tx was very high at 66.7% as expected, but these patients were able to receive local or systemic treatments due to their good liver function resulting from their liver transplantation.

### Can LDLT be Used as a Palliative Treatment in Selected Patients within the BSC Group?

LDLT has some advantages and disadvantages. In the LDLT procedure, the graft is a personal gift from the recipient's family, so there is no harm to those on a transplant wait list. Quality of the graft used in LDLT and LDLT gives a chance of saving or improving the life of their beloved recipients for the donors. Centers in Türkiye are very experienced on LDLT. On the other hand, LDLT has some disadvantages. There is donor risk in LDLT procedure and risks a life to save another life. What should be the minimum recipient survival that would be worth risking the donor? According to the transplant community, minimum expected (acceptable) recipient survival to cover these risks should be >50% at 5 years.<sup>[10, 11]</sup> In a study on donor candidates from Canada, donor candidates agree to be a donor if the recipient's life expectancy after LDLT will be extended by at least 11±22 months on average.<sup>[12]</sup> Basic ethical principles of LDLT are autonomy, altruism, utilitarianism, beneficence, non-maleficence and justice. The basis of live donation is a selfless gift to others, without donor coercion, voluntarily, without any payment, and solidarity between donor and recipient. To prevent coercion, we established a "plausible deniability" mechanism. Donors have the chance to opt out of LDLT confidentially at four stages during screening, making them ineligible if they choose to opt out. When a donor is declared ineligible for LDLT/LPE, whether due to opting out or any other reason, only the donor is informed about the cause of their ineligibility. Written informed consent for procedures and anesthesia is obtained from each individual.<sup>[13]</sup> In light of these ethical principles, they donate in order to benefit their loved ones. Therefore, minimum donor risk and maximum recipient benefit must be targeted.

According to our results, donor complications are acceptable<sup>[14, 15]</sup> and sLDLT patients have a 3-year overall survival of 50%. In addition, hospital mortality (<90 days) in sLDLT was 11.7%, while in BSC it was 81.3%. Based on these results, LDLT can be considered as a palliative method for selected patients in the BSC group.

There are numerous studies comparing treatment modalities with BSC in terms of survival for advanced HCC, as shown in Table 2.<sup>[16-22]</sup> In fact, these comparisons are not appropriate, because on the one side there are BSC patients who cannot receive any treatment due to impaired liver function, and on the other side there are patients with

**Table 3.** Subgroup analysis of the pLDLT group (n=17)

	Survival ≤2 years (n=9)		Survival >2 years (n=8)		p
	n	Median (IQR)	n	Median (IQR)	
Age at Tx date	9	54 (8.5)	8	50.5 (9.5)	0.423
MELD score	9	24 (11)	8	20 (6.75)	0.743
BMI	9	25.7 (4.59)	8	23.81 (4.25)	0.606
BSA	9	1.97 (0.27)	8	1.86 (0.4)	0.370
GRWR (%)	9	1.04 (0.55)	8	1.16 (0.39)	0.673
Albumin	8	2.4 (1.17)	8	2.4 (0.93)	0.878
Total Bilirubin	8	5.67 (7.1)	8	4.95 (6.27)	0.798
INR	8	1.52 (0.44)	7	1.56 (0.7)	0.955
Platelet	9	93 (71.5)	8	60.5 (53.25)	0.027*
AST	8	210.5 (172)	7	144 (191)	0.397
ALT	8	122.5 (152)	8	83 (83.75)	0.279
GGT	8	141 (115)	8	56 (96)	0.234
ALP	8	127 (106)	8	158.5 (89.25)	0.195
AFP	9	227.9 (5408.95)	8	26.7 (416.47)	0.093
WBC	9	6.72 (8.25)	8	4.39 (1.06)	0.277
RDW	8	16.8 (4.92)	8	17.3 (4.95)	0.959
MTD (cm)	9	7.5 (5.25)	8	2.5 (2.5)	0.036*
Number of nodules	9	3 (9)	8	4 (8)	1.000
NLR	8	5 (4.68)	8	7.37 (9.33)	0.574
PLR	8	99.1 (79.61)	8	124.17 (159.74)	0.959
MPV	8	10.9 (2.02)	8	10.1 (3.53)	0.645
CRP	4	5.34 (30.64)	6	2.22 (4.54)	0.171
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>	<b>p</b>
Gender					
Female	1	(11.1)	2	(25)	0.576
Male	8	(88.9)	6	(75)	
Differentiation					0.798
Well	0	(0)	1	(12.5)	
Moderate	5	(55.6)	3	(37.5)	
Poor	4	(44.4)	4	(50)	
Venous invasion					0.440
None	0	(0)	2	(25)	
Micro (+)	5	(55.6)	3	(37.5)	
Macro (+)	4	(44.4)	3	(37.5)	
Recurrence					0.637
Yes	3	(33.3)	4	(50)	
No	6	(66.7)	4	(50)	
AFP, ng/ml					0.153
≤200	3	(33.3)	6	(75)	
>200	6	(66.7)	2	(25)	
GGT, IU/L					0.619
≤104	3	(37.5)	5	(62.5)	
>104	5	(62.5)	3	(37.5)	
Etiology					1.000
Cryptogenic	2	(22.2)	2	(25)	
HBV	5	(55.6)	5	(62.5)	
HBV+HDV	1	(11.1)	1	(12.5)	
HCC	1	(11.1)	0	(0)	
GRWR, %					1.000
≥0.8	8	(88.9)	8	(100)	
<0.8	1	(11.1)	0	(0)	
TTD, cm					0.335
≤8	2	(22.2)	4	(50)	
>8	7	(77.8)	4	(50)	



preserved liver function who can receive local or systemic treatments. Consequently, patients who can receive any palliative treatment live longer than BSC patients, but no palliative treatment can result in 50% 3-year survival, except sLDLT.

Post-transplant recurrence rate were high in the sLDLT as 66.7%. Fifty percent of recurrences were both hepatic and extrahepatic disease, 40% (4/10) of recurrence were only extrahepatic disease and local treatments such as surgical resection, radiotherapy were used for this patients. All recurrent patients who had systemic disease or can not treat locally had sorafenib as a systemic chemotherapy. One patient whose brain metastasis treated by surgical resection is still alive for 1714 days from the LDLT, 653 days from the recurrence time. Immune check point inhibitors are not reimbursement yet in Türkiye, but in 2025 it will be covered by the social insurance. Oncologic treatments are developing quickly, so future treatments can offer better survival for these patients, and sLDLT can add extra years for selected BSC patients.

We divided the sLDLT group into 2 subgroups, namely those who survived more than 2 years and those who survived less than 2 years and we then examined the characteristics of those who survived longer in terms of tumor and laboratory parameters. Patients who survive >2 years had significantly lower MTD (2.5 vs 7.5 cm,  $p=0.036$ ) and lower platelet levels (60.5 vs 93,  $p=0.027$ ) (Table 3). This finding can help explain the survival difference.

Limitations of this study are the retrospective design and the small patient numbers, absence of quality-of-life data but the strength of this study is that it is the first report on this subject, which is promising.

## Conclusion

We could achieve 3-year OS 50% in selected patients from the BSC group (no extrahepatic metastasis, Child C cirrhosis and ages between 18-60) by LDLT, although the post-Tx recurrence rate was 66.7%. No palliative treatment could achieve 50% 3-years overall survival in BSC patients other than LDLT.

## Disclosures

**Ethics Committee Approval:** This study has been approved by Inonu University Institutional Review Board (Approval no: 2024/6410).

**Peer-review:** Externally peer-reviewed.

**Data Availability:** The raw data used to support the findings of this study are available from the corresponding author upon request.

**Informed Consent:** No informed consent was requested from patients since this is a retrospectively designed study.

**Author Contributions:** Concept – V.I., F.O.; Design – V.I., F.O., S.U., B.I.C., S.Y.; Supervision – B.I.C., B.I., S.Y.; Funding – None; Materials – None; Data Collection and/or Processing – V.I., F.O., S.U.; Analysis and/or Interpretation – H.G.B, V.I., S.U.; Literature Review – V.I., F.O., B.I.C.; Writing – V.I., F.O.; Critical Review – B.I.C., B.I., S.Y.

**Declaration of Interests:** The authors have no conflict of interest to declare.

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