Liver transplantation for hepatocellular carcinoma with live donors or extended criteria donors: a propensity score-matched comparison

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Abstract

Background To compare patient survival after liver transplantation (LT) for hepatocellular carcinoma (HCC) from live donors (LD) or extended criteria donors (ECD).

Methods Data from consecutive LT procedures for HCC involving either LD or ECD were reviewed. Patient survival was our primary outcome. Re-transplantation (Re-LT), ischemic type bile lesions (ITBL), and tumor recurrence represented secondary outcomes. The primary outcome was statistically analyzed using Kaplan-Meier estimates and Cox proportional hazards regression; logistic regression analyses were used for statistical analysis of the secondary outcomes. Propensity score was calculated based on patient age, sex, hepatitis C viral infection (HCV), laboratory model for end-stage liver disease (labMELD) score, bridging treatment, Milan criteria, α-fetoprotein levels, and tumor grade.

Results The study evaluated 109 recipients undergoing LT from either LD (n=57) or ECD (n=52). LT procedure (hazard ratio [HR] 2.349, 95% confidence interval [CI] 1.151-4.794, P=0.0190), age (HR 1.075, 95%CI 1.020-1.133, P=0.0074) and labMELD score (HR 1.082, 95%CI 1.021-1.147, P=0.0075) reached significance by Cox proportional hazards regression. After adjustment with the propensity score (stratification with 5 strata), the LT procedure was still significant (HR 2.401, 95%CI 1.114-5.175, P=0.0253). Tumor grade (odds ratio [OR] 9.628, 95%CI 1.120-82.752, P=0.0391), labMELD score (OR 1.224, 95%CI 1.019-1.471, P=0.0306), and Milan criteria (OR 6.375, 95%CI 1.239-32.796, P=0.0267) gained statistical significance by logistic regression analysis for Re-LT, ITBL, and tumor recurrence, respectively.

Conclusions LT for HCC showed superior patient survival with ECD rather than LD grafts. Re-LT, ITBL, and tumor recurrence showed no significant differences between the two groups. However, the diverging criteria for the definition of ECD grafts represent a considerable limitation for the wide application of this policy.

Keywords Liver transplantation, live donors, extended criteria donors, propensity score

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for about 1 million related deaths annually. Its incidence is estimated to have increased by 75% in the United States in the last decade and reflects the increasing prevalence of chronic viral hepatitis [1]. An estimated 372,000 new cases of hepatocellular carcinoma (HCC) are diagnosed each year, constituting 4.6% of all new human cancers [2]. Liver transplantation (LT) is considered to be the treatment of choice for early HCC in patients with end-stage liver failure, but is limited by donor organ availability. Despite recent criticism, the Milan criteria (single tumor up to 5 cm; 2 or 3 tumors, none larger than 3 cm; absence of vascular invasion) are most often used when determining organ allocation for HCC patients being considered for deceased donor LT [3].

In recent years, live donor LT (LDLT) has become the most likely alternative for the expansion of the organ pool for adult patients with HCC [4-10], but its indications and criteria are still subject to debate [11-16]. Extended criteria donors (ECD) represent another reliable alternative. Very limited information, however, is currently available concerning their comparative outcomes, i.e., in the comparison of transplant outcomes using a reduced (about 50%) but "high-quality" liver from a live donor or a whole but "low-quality" liver from an extended criteria donor. The aim of this propensity score-matched study was to compare patient survival after LDLT or ECD-LT for HCC.

Patients and methods

We considered all adult patients who underwent LT in Essen University Hospital, Germany, over a 12-year period. Data were collected prospectively through both the Eurotransplant database and patient records. Recipients with acute liver failure, patients listed with high urgency for re-transplantation, or patients receiving split LT were excluded. All operations were performed using standard surgical techniques. All patients received and signed informed consent at the time of listing. Patients with potential live liver donors were evaluated on a case-by-case basis according to their age, severity of liver disease, α-fetoprotein (AFP) levels, and HCC characteristics at the time of presentation. A very strict evaluation protocol for the potential donors was applied, resulting in only 14% suitability in the adult group in our institution [16].

ECD grafts were offered to HCC patients in an effort to expand the donor pool. ECD grafts were defined according to Eurotransplant Foundation rules, as reported elsewhere [17]. Briefly, during the study period, some of the features that shape the profile of an ECD were the following: donor age >55 years; Intensive Care Unit (ICU) stay >5 days; use of vasopressors; history of cardiopulmonary resuscitation; adiposity (donor body mass index [BMI] >25 kg/m²); peak serum sodium >155 mEq/L; macrovesicular steatosis >30%; elevated levels of aspartate aminotransferase and/or alanine aminotransferase; cold ischemia time >10 h; warm ischemia time >40 min; and risk of disease transmission from the donor to the recipient in the case of: a) viral hepatitis B or C infection; b) sepsis, bacteremia, meningitis; c) history of malignancy; or d) drug abuse. This retrospective, single-center, cohort study was approved by the local ethics committee and conformed to the 1975 Declaration of Helsinki.

All patients were examined using spiral computed tomography technology and intravenous contrast material. Abdominal ultrasonography and bone scintigraphy were additionally performed in all patients. Serial AFP levels were obtained prior to and after LT. The diagnosis of HCC was established according to the consensus statement from the European Association for the Study of the Liver. The clinical classification was based on the morphological description of the tumor according to the radiological findings of 2 independent radiologists.

The following recipient characteristics were evaluated: age, sex, etiology of liver disease, laboratory model for end-stage liver disease (labMELD) score, HCC-specific bridging treatment (radiofrequency ablation or transarterial chemoembolization in most cases), and conformance to the Milan criteria. All explanted livers were examined micro- and macroscopically by an experienced pathologist. The tumor number and size, the occurrence of tumor satellites, the presence of vascular invasion or tumor thrombi, the resection margin, the tumor differentiation, and the classification according to the Milan criteria, were documented. Follow-up data included the need for re-transplantation (Re-LT), the occurrence of ischemic-type biliary lesions (ITBL), the current patient status, recurrent disease and the treatment of recurrence, and the cause of death.

Follow-up studies included CT scans of the abdomen and chest, and measurement of AFP levels every 4 months during the first year after transplantation, every 6 months during the second year, and yearly thereafter. Minimum follow up was either 5 years or until death. No patient was lost to follow up.

Patient survival was our primary outcome. For the secondary outcomes, three major concerns associated with the application of both LD and ECD grafts were explored: 1) rates of Re-LT, which may be the result of small-for-size syndrome after LDLT, or of primary non-function after ECD-LT; 2) rates of ITBL, described as complications in the follow up of both procedures; and 3) tumor recurrence, given that in the setting of LDLT or ECD-LT the Milan criteria are not always strictly followed.

Statistical analysis

Continuous data were expressed as median and range and compared using Student's *t*-test. Categorical data were compared using Fisher's exact test. The primary outcome was statistically analyzed using Kaplan-Meier estimates and Cox proportional hazards regression. Logistic regression analyses were used for statistical analysis of the secondary outcomes. Propensity score was calculated based on patient age, sex, hepatitis C viral infection (HCV), labMELD score, bridging treatment, Milan criteria, AFP levels, and tumor grade. Differences with $P<0.05$ were considered to be statistically significant. Statistical analyses were performed using SAS (SAS Institute).

Results

We reviewed data on 109 consecutive LT for HCC performed in Essen University Hospital, Germany, and which met the inclusion criteria. Of these, 57 used LD grafts and 52 ECD grafts. Patient characteristics and follow-up data are shown in Table 1. Median recipient age was 56 (range 18-69) years. The majority were male (n=79, 72%). the main cause of chronic liver disease was HCV-induced liver cirrhosis (n=42, 39%). Half the patients (n=55) had undergone transarterial chemoembolization or radiofrequency ablation as HCC-specific bridging treatment prior to LT. Fifty-six patients met the Milan criteria at the time of listing. The median value of AFP was 21 ng/mL. Vascular invasion was documented in 21 liver explants (19%). Tumor differentiation was assessed as G1 (n=18), G2 (n=59), G3 (n=13), or Gx (n=10). In 9 instances no living tumor cells were found on pathological examination,

as a consequence of 100% tumor necrosis after successful bridging treatment. Urgent Re-LT with a deceased donor graft was required in 15 cases, in 8 of them following an LDLT. ITBL was documented in 18 patients, of whom the majority (n=11) underwent ECD-LT. Twenty-four patients experienced a post-LT tumor recurrence, 14 after ECD-LT and 10 after LDLT. At the time of the statistical analysis for this study, 73 patients were alive after a median follow up of 36 months. The causes of death in each group are shown` in Table 2.

Extended criteria donors

Donors were classified as ECD according to the following criteria: donor age >55 years, 25 patients; ICU stay >5 days, 20 patients; use of vasopressors, 44 patients; donor BMI >25 kg/m^2, 29 patients; peak serum sodium >155 mEq/L, 19 patients; macrovesicular steatosis >30%, 4 patients; elevated levels of aspartate aminotransferase, 21 patients; alanine aminotransferase, 15 patients; cold ischemia time >10 h, 9 patients; and warm ischemia time >40 min, 11 patients.

Primary outcome

The results of the Cox proportional hazards regression analysis for patient survival are given in Table 3. LT-procedure (hazard ratio [HR] 2.349, 95%Cls 1.151 to 4.794, P=0.019), recipient age (HR 1.075, 95%Cls 1.020 to 1.13, P=0.0074) and labMELD-score (HR 1.082, 95%Cls 1.021 to 1.147, P=0.0075) gained statistical significance. After adjustment with the propensity score (stratification with 5 strata, calculated based on age, sex, HCV, labMELD, bridging-treatment, Milan criteria, AFP and tumor grade), the LT procedure was still significant (HR 2.401, P=0.0253; Table 4). As shown in the Kaplan-Meier survival distribution function, LT for HCC showed superior patient survival with ECD grafts rather than LD grafts (Fig. 1).

Secondary outcomes

The results of the logistic regression analysis for Re-LT, ITBL, and tumor recurrence are presented in Tables 5a, 5b, and 5c, respectively. Tumor grade gained statistical significance for Re-LT (odds ratio [OR] 9.628, P=0.0391), labMELD score for ITBL (OR 1.224, P=0.0306), and Milan criteria for tumor recurrence (OR 6.375, P=0.0267), respectively. However, no statistically significant differences were observed between the two transplant procedures (ECD/LDLT).

Discussion

LT represents the optimal treatment strategy for patients with HCC, as it involves radical oncological resection and

Table 1 Patients' characteristics and follow-up data

Variable	LDLT n=57	ECD-LT n=52
Recipient age (median, range)	55 (18-67)	57 (29-70)
Sex (male)	42	37
Hepatitis-related cirrhosis	35	32
HCV infection	23	19
LabMELD	10	12
Bridging treatment (yes)	22	33
Milan criteria satisfied	24	32
AFP (ng/mL)	26	17
Tumor grade moderate/poor	27/7	32/6
Patients alive in follow up	27	37
Re-LT	8	7
ITBL	7	11
Tumor recurrence	10	14

LDLT, live donor liver transplantation; ECD-LT, extended criteria donor-liver transplantation; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, α-fetoprotein; re-LT, repeat liver transplantation; ITBL, ischemic type bile lesions

Table 2 Causes of death in each group

Cause of death	LDLT	ECD-LT
Primary non-function	0	2
Multi-organ failure	1	3
Pneumonia	2	2
Sepsis	3	3
Graft-versus-host disease	0	1
HCC recurrence	5	1
Small for size	6	0
Pulmonary embolism	4	0
Other	3	0
Total	24	12

LDLT, live donor liver transplantation; ECD-LT, extended criteria donor-liver transplantation; HCC, hepatocellular carcinoma

Table 3 Results of the Cox regression analysis for survival

Variable	Hazard ratio	95% Confidence Interval	P-value
LT-procedure marginal graft (reference)			
LT-procedure LDLT	2.349	1.151-4.794	0.0190
Age	1.075	1.020-1.133	0.0074
Sex	0.752	0.338-1.674	0.4857
HCV	0.609	0.318-1.170	0.1364
LabMELD	1.082	1.021-1.147	0.0075
Bridging	0.536	0.258-1.115	0.0950
Milan	2.115	0.847-5.279	0.1086
AFP	1.000	0.99997-1.0002	0.1912
Tumor grade			
0 (reference)			
1	0.371	0.070-1.952	0.2417
2	0.930	0.297-2.907	0.9003
3	1.780	0.405-7.819	0.4453

LDLT, live donor liver transplantation; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, α-fetoprotein

Table 4 Results of the stratified Cox regression analysis for survival, the propensity score (calculated based on age, sex, HCV, LabMELD, bridging, Milan, AFP and tumor grade) is the stratification variable, with 5 strata

Variable	Hazard ratio	95% Confidence interval	P-value
LT-procedure ECD graft (reference)			
LT-procedure LDLT	2.401	1.114-5.175	0.0253

HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, a-fetoprotein; ECD, extended criteria donor; LDLT, live donor liver transplantation

Table 5 (A) Results of the logistic regression analysis for repeat liver transplantation

Variable	Odds ratio	95% Confidence interval	P-value
LT-procedure ECD graft (reference)			
LT-procedure LDLT	0.527	0.111-2.500	0.4204
Age	1.048	0.944-1.164	0.3815
Sex	1.235	0.201-7.571	0.8195
HCV	1.768	0.393-7.955	0.4574
LabMELD	1.031	0.921-1.155	0.5928
Bridging	2.549	0.481-13.519	0.2716
Milan	0.239	0.039-1.448	0.1194
AFP	0.990	0.975-1.005	0.1806
Tumor grade <3 (reference)			
Tumor grade=3	9.628	1.120-82.752	0.0391

ECD, extended criteria donor; LDLT, live donor liver transplantation; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, a-fetoprotein

Table 5 (B) Results of the logistic regression analysis for ischemic type bile lesions

Variable	Odds ratio	95% Confidence interval	P-value
LT-procedure ECD graft (reference)			
LT-procedure LDLT	6.116	0.824-45.403	0.0766
Age	1.065	0.943-1.203	0.3072
Sex	0.501	0.070-3.569	0.4902
HCV	0.488	0.089-2.678	0.4090
LabMELD	1.224	1.019-1.471	0.0306
Bridging	0.201	0.026-1.533	0.1216
Milan	5.610	0.666-47.224	0.1126
AFP	0.997	0.989-1.005	0.4654
Tumor grade <3 (reference)			
Tumor grade=3	2.157	0.188-24.715	0.5368

ITBL, ischemic type bile lesions; ECD, extended criteria donor; LDLT, live donor liver transplantation; HCV, hepatitis C virus; MELD, model for end liver disease; AFP, α-fetoprotein; re-LT, re-liver transplantation

improves the underlying liver dysfunction. Currently, there are reported 1-year survival rates of up to 80%, 5-year survival rates up to 70%, and recurrence rates of 10-15% in patients fulfilling the Milan criteria [18]. The increasing incidence of HCV-related cirrhosis in the Western world during the past 2 decades has led to a corresponding increase in new HCC-related cases. The potential cohort of new transplant candidates with HCC has grown rapidly. As a result of the scarcity of organs, efforts have focused on expanding the donor pool worldwide, in order to offer LT to more cirrhotic patients [19].

LDLT is an attractive alternative for the expansion of the organ pool for adult patients with HCC and end-stage liver disease [20], and is in part associated with an effort to expand the Milan criteria [21]. In these instances, the strong will to donate among relatives plays a leading role in decision-making [22]. However, the indications for transplantation of HCC patients in the era of LDLT are still being debated. While some centers proposed an expansion of the current listing criteria [4,9], other centers remained conservative [23], emphasizing donor risks as well as a possible return to the suboptimal transplant results of the 1980s. Besides, the overall LDLT setting presupposes an experienced high-volume transplant center and the abovementioned limitations regarding donor safety and long-term oncological results do not allow the wide application of this technique in the western world.

Table 5 (C) Results of the logistic regression analysis for recurrence

Variable	Odds ratio	95% Confidence interval	P-value
LT-procedure ECD graftn(reference)			
LT-procedure LDLT	0.966	0.294-3.170	0.9545
Age	1.000	0.934-1.072	0.9915
Sex	0.886	0.239-3.278	0.8557
HCV	0.556	0.178-1.735	0.3121
LabMELD	1.029	0.928-1.141	0.5827
Bridging	0.391	0.114-1.345	0.1364
Milan	6.375	1.239-32.796	0.0267
AFP	1.000	1.000-1.000	0.2309
Tumor grade<3 (reference)			
Tumor grade=3	1.960	0.344-11.175	0.4485

ECD, extended criteria donor; LDLT, live donor liver transplantation; HCV, hepatitis C virus; MELD, model for end-stage liver disease; AFP, α-fetoprotein
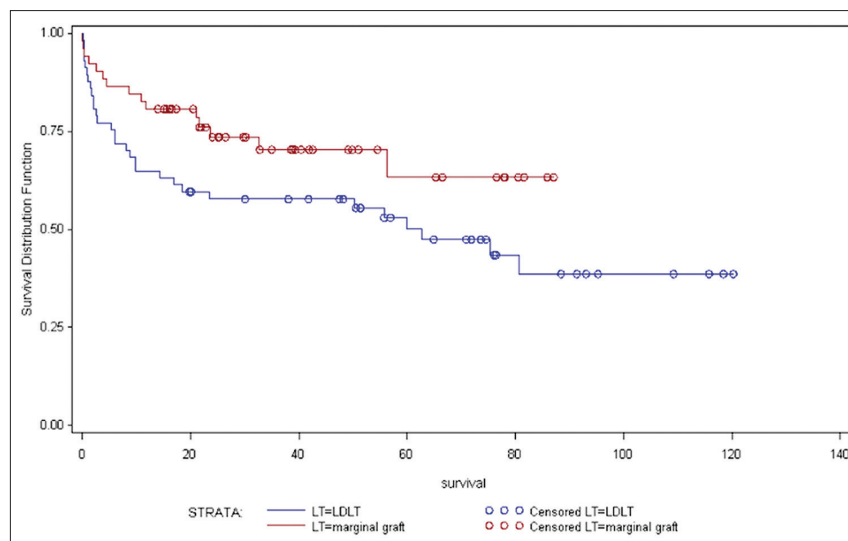
Figure 1 Kaplan-Meier analysis of the two groups

Acceptance of ECD grafts for stable patients with HCC became another potential solution [14,16,24,25]. Its application, however, seems possible mostly in large-volume transplant centers and is limited by local allocation rules. A considerable additional limitation of the ECD transplant policy is the quite heterogeneous donor cohort and the diverging definitions between transplant registries, limiting the comparative analysis of published results.

Although in the present study there were no significant differences in Re-LT, ITBL or tumor recurrence rates between the LDLT and ECD groups, LT for HCC showed superior patient survival with ECD rather than LD grafts. We believe this finding can be attributed to the higher rate of "small-for-size" syndrome manifested in patients receiving an LD graft, which seems to confer a survival benefit inferior to that of a theoretically lower quality ECD graft. Moreover, the timely nature of the operation and the standardized quality of the LD graft should be considered, in contrast to the emergency operation and the vast heterogeneity of ECD grafts.

Our study has some limitations that need to be adressed, the most important being its retrospective single-center design. Moreover, there was vast heterogeneity among the quality of the ECD grafts. Finally the diverging definition criteria of ECD grafts represents another considerable limitation that may affect the generalization of our results to the spectrum of different criteria used by other centers.

Despite the observed survival benefit, the risk–benefit ratio in patients receiving ECD grafts must be evaluated on a case-by-case basis according to the waiting list and the conservative versus expanded policies of each transplant center. It should also be highlighted that the diverging criteria for the definition of ECD grafts represent a considerable limitation to the wide application of this policy. Regardless, developing alternative strategies for the continued expansion of the available organ pool is critical [26]. Thorough and detailed knowledge of the different aspects of liver donation may contribute to further amelioration of donor safety and even recipient outcomes.

Summary Box

What is already known:

- Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with rising incidence
- Liver transplantation (LT) is considered to be the treatment of choice for early HCC in patients with end-stage liver failure, but is limited by donor organ availability
- Live donor LT (LDLT) has become the most promising alternative for the expansion of the organ pool for adult patients with HCC, but indications and criteria are still subject to debate
- Extended criteria donors (ECD) represent a reliable alternative

What the new findings are:

- LT for HCC showed superior patient survival with ECD rather than LD grafts
- Re-LT, ischemic type bile lesions, and tumor recurrence showed no significant differences between groups
- Although LDLT for HCC showed inferior survival results in comparison to ECD-LT, the timely fashion of the operation and the standardized quality of the live donor graft should be considered, in contrast to the emergency operation and the vast heterogeneity of ECD grafts

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