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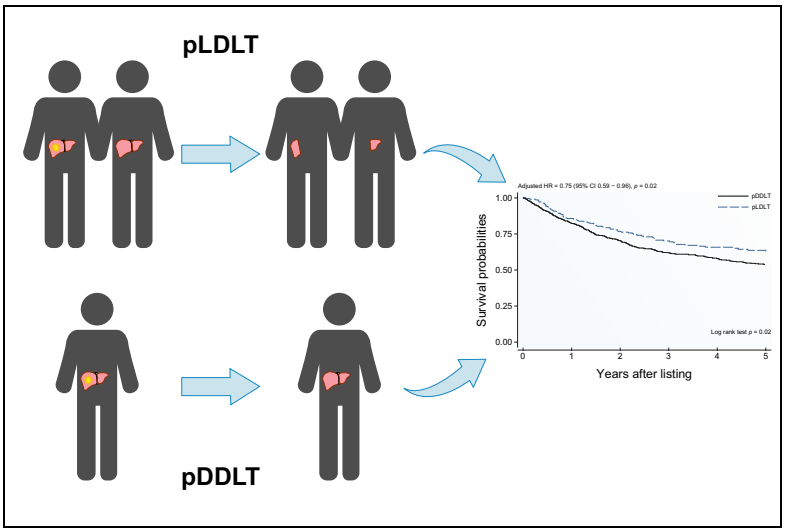
Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival *vs.* deceased donation

Graphical abstract



Highlights

- The dropout rate is lower for patients listed for liver transplantation with a potential live donor.
- The waiting time is shorter for patients listed for liver transplantation with a potential live donor.
- These 2 advantages of live donation result in a survival benefit for patients with HCC listed with a potential live donor.

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Lay summary

Liver transplantation (LT) offers the best chance of survival for patients with hepatocellular carcinoma and can be performed using grafts from deceased donors or live donors. In this work, we aimed to assess the differences in survival after live donor LT when compared to deceased donor LT. We studied 219 patients listed for live donor LT and 632 patients listed for deceased donor LT. Patients who had a potential live donor at the time of listing had a higher survival rate. Therefore, being listed for a live donor LT was a protective factor against death.

http://dx.doi.org/10.1016/j.jhep.2018.12.029
 J. Hepatol. 2019, 70, 666–673

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Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival *vs.* deceased donation

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Background & Aims: There are conflicting reports on the outcomes after live donor liver transplantation in patients with hepatocellular carcinoma (HCC). We aimed to compare the survival of patients with HCC, with a potential live donor (pLDLT) at listing *vs.* no potential donor (pDDLT), on an intention-to-treat basis.

Methods: All patients with HCC listed for liver transplantation between 2000–2015 were included. The pLDLT group was comprised of recipients with a potential live donor identified at listing. Patients without a live donor were included in the pDDLT group. Survival was assessed by the Kaplan-Meier method. Multivariable Cox regression was applied to identify potential predictors of mortality.

Results: A total of 219 patients were included in the pLDLT group and 632 patients in the pDDLT group. In the pLDLT group, 57 patients (26%) were beyond the UCSF criteria whereas 119 patients (19%) in the pDDLT group were beyond ($p = 0.02$). Time on the waiting list was shorter for the pLDLT than the pDDLT group (4.8 [2.9–8.5] months *vs.* 6.2 [3.0–12.0] months, respectively, $p = 0.02$). The dropout rate was 32/219 (14.6%) in the pLDLT and 174/632 (27.5%) in the pDDLT group, $p < 0.001$. The 1-, 3- and 5-year intention-to-treat survival rates were 86%, 72% and 68% in the pLDLT *vs.* 82%, 63% and 57% in the pDDLT group, $p = 0.02$. Having a potential live donor was a protective factor for death (hazard ratio [HR] 0.67; 95% CI 0.53–0.86). Waiting times of 9–12 months (HR 1.53; 95% CI 1.02–2.31) and ≥12 months (HR 1.69; 95% CI 1.23–2.32) were predictors of death.

Conclusion: Having a potential live donor at listing was associated with a significant decrease in the risk of death in patients with HCC in this intention-to-treat analysis. This benefit is related to a lower dropout rate and a shorter waiting period.

Lay summary: Liver transplantation (LT) offers the best chance of survival for patients with hepatocellular carcinoma and can be performed using grafts from deceased donors or live donors. In this work, we aimed to assess the differences in survival after live donor LT when compared to deceased donor LT. We studied 219 patients listed for live donor LT and 632 patients listed for deceased donor LT. Patients who had a potential live donor at the time of listing had a higher survival rate. Therefore, being listed for a live donor LT was a protective factor against death.

Introduction

Live donor liver transplantation (LDLT) improves survival compared to deceased donor liver transplantation (DDLT) when analyzed from the time of listing (intention-to-treat [ITT] analysis) in patients with end-stage liver disease.[1,2] However, this benefit has never been shown in patients with hepatocellular carcinoma (HCC). Initial experiences with LDLT for HCC had suggested a higher HCC recurrence rate and a decreased survival after transplantation when compared to DDLT.[3–6] Concerns have been raised regarding liver regeneration after LDLT, the potential of suboptimal oncological resection since the inferior vena cava is not removed, and the fact that some patients with more aggressive tumor biology might be "fast tracked" to LT.[3] More recent studies have reported similar outcomes for LDLT and DDLT for patients with HCC.[7,8] To the best of our knowledge, only 2 studies have compared the outcomes between LDLT and DDLT for HCC on an ITT analysis.[7,8] Both studies had a limited number of patients undergoing LDLT (36 and 79) and showed no survival differences between LDLT and DDLT.[7,8]

The lack of data supporting the benefit of LDLT for patients with HCC, leaves 2 very important questions unanswered: ii) should all patients with HCC awaiting LT be encouraged to

Keywords: Living donor; Deceased donor; Intention-to-treat; Hepatoma; Liver cancer.
Received 28 July 2018; received in revised form 14 December 2018; accepted 18 December 2018; available online 8 January 2019
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consider LDLT? and ii) when should LDLT be performed in a patient with HCC? We hypothesized that patients with HCC who are listed for LT with a potential live donor would have a survival benefit. The aim of this study was to compare outcomes between LDLT and DDLT for patients with HCC, from the time of listing. We also aimed to identify potential risk factors for death after inclusion on the LT waiting list (WL).

Patients and methods

The present study was approved by the Research Ethics Board of the University Health Network (CAPCR #15-9989).

Study design

Using our prospectively collected database, we retrospectively analyzed all patients with HCC diagnosis listed for LT between January 1st, 2000 and December 31st, 2015 at the Multi-Organ Transplant Program at the University of Toronto. Patients that had been listed and thereafter refused LT or had their tumors controlled with bridging therapies were excluded. For the ITT analysis, patients were divided into 2 groups according to the presence of a potential live donor (pLDLT) at the time of listing. We defined pLDLT as an individual who: i) had stepped forward for live donation, ii) had been suitable for donation after the screening phase and, iii) had undergone imaging assessment.[9,10] All patients who had a pLDLT at the time of listing were included in the pLDLT group. Otherwise, patients were included in the deceased donor liver transplantation (pDDLT) group. Of note, patients whose potential live donors were deemed unsuitable for donation before proceeding to imaging assessment (*i.e.* a donor with evident medical comorbidity) were included in the pDDLT group.

HCC diagnosis and waiting list practices

HCC diagnosis was made following international guidelines.[11] We recorded the length of time between the HCC diagnosis and the date of listing. The maximum tumor burden, at any time point from diagnosis to transplant, was used for tumor staging purposes. Alpha-fetoprotein (AFP) was measured at the time of diagnosis, listing, and preceding LT.

All patients within Milan criteria were included on the WL. Until December 2012, patients exceeding the Milan criteria were included in the WL as long as they fulfilled the Extended Toronto Criteria (ETC).[12] According to the ETC, patients are selected for LT proven they do not have extrahepatic disease, cancer-related symptoms or poorly differentiated tumors regardless of the tumor size and number. After January 2013, patients beyond Milan criteria who did not have a live donor were included in the WL proven they had a total tumor volume (TTV) ≤115 cm^3 and a serum AFP ≤400 ng/ml.[13] Importantly, for LDLT candidates, the ETC was accepted during the entire study period. The decision to remove a patient from the WL was done at multidisciplinary meeting. Patients were delisted if they presented macrovascular invasion or extrahepatic disease on computed tomography (CT) or magnetic resonance imaging (MRI). If patients progressed beyond a TTV of 115 cm^3 and/or an AFP >400 ng/ml and did not have a live donor available, they were placed on hold and treated with further locoregional therapy aimed at downstaging.

Live donor selection practices

As part of the University of Toronto LDLT listing practices, irrespective of the model for end-stage liver disease (MELD) score and disease severity, LDLT is encouraged in all patients included on the WL. All donations were voluntary and altruistic. Detailed descriptions of our live donor evaluation process, surgical techniques, and donor outcomes have been previously described.[9,10]

Patients' characteristics

Patient demographics, clinical and tumoral characteristics were recorded at the time of listing. The tumor burden was assessed based on the size of the biggest lesion, the total number of lesions and the TTV. The TTV was calculated by the sum of the volume of all tumors. The volume of each tumor was defined by the formula $4/3\pi r^3$.[14] All patients were staged according to the Milan criteria, the University of California San Francisco (UCSF) criteria, and the ETC.[12,15,16]

Time on the waiting list and bridging therapies

WL time was defined as the time between date of inclusion on the WL and the delisting date. Dropout from the WL was realized upon patient death, or removal from the WL due to i) tumor progression exceeding the transplant criteria, or ii) complications from liver decompensation. The probability of dropout was estimated and compared between the 2 study groups.

All patients with an expected WL time longer than 3 months and in the absence of decompensated cirrhosis were treated with transarterial chemoembolization (TACE), ablation or stereotactic body radiotherapy (SBRT) as bridging therapy. The decision to treat and the type of treatment were discussed in a weekly multidisciplinary conference.[17] There was no difference in the indication of bridging therapies between patients waiting for an LDLT or DDLT.

While waiting, all patients were re-assessed every 3 months clinically, with AFP level and either CT of the chest and abdomen, or MRI, to rule out tumor progression or need for further bridging therapies.

Explant pathology analysis

Explant pathology from all patients who underwent LT were available for analysis. Patients with completely necrotic tumors (*i.e.* successfully ablated tumor) were considered as having "zero" tumors and the degree of differentiation as "no viable tumor".

Follow-up after LT

An MRI and/or a thoraco-abdominal CT, and AFP measurement, were performed every 6 months for the first 2 years after LT. Thereafter, CT was performed annually or if clinically indicated. Diagnosis of tumor recurrence was based on imaging. A biopsy was performed if the image was non-conclusive.

Intention-to-treat analysis

For the ITT analysis, the primary outcome was overall survival (OS). Survival time was defined as the time from listing date to death, last visit, or the end of study (December 31st, 2017). To assess the potential impact of waiting time on the study outcome, we considered waiting time (divided into 5 strata: <3 months, 3–6 months, 6–9 months, 9–12 months and ≥12 months) as a time-varying covariate. bridging therapies were also recorded as time-varying. The rationale for this was to allow an estimation of each of the variables' impact on the OS that were not defined at the study starting-point in an ITT analysis. To expand the external validity of the study results, we performed a sensitivity analysis among patients who were

within Milan criteria, and those who were beyond UCSF criteria but within the ETC at the time of listing.

Analysis from the time of LT

In Toronto, every patient who is offered an LDLT is placed on the WL for deceased organs.[9] Given that it is possible that some patients initially included in the pLDLT group were finally transplanted with a deceased donor graft and vice versa, we did an analysis of post-transplant outcomes (as treated analysis), based on the type of graft received. Patients were divided between those who actually underwent LDLT (aLDLT) and those who actually underwent DDLT (aDDLT). The outcomes were post-transplant survival (PTS) and disease-free survival (DFS). PTS was defined as the length of time between the date of LT and death, last visit, or the end of study. DFS was defined as the length of time between the date of LT, HCC recurrence, last visit, or the end of study. The serum AFP dynamics during the waiting time were assessed amongst those patients who underwent LT. This was calculated by the difference between the serum AFP at transplant and the serum AFP at listing divided by the waiting time.[18] The AFP dynamics was categorized at the cut-off of 5 ng/ml/-month. This was defined applying the Youden index.[19]

Statistical analysis

Categorical data were expressed as proportions and compared by the Chi-squared test with Fisher's correction. Continuous variables were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney *U* test. Dropout was considered a time-to-event variable and its occurrence probabilities were calculated by the Kaplan-Meier method for failure probabilities and compared by the log-rank test. Survival probabilities were also assessed by the Kaplan-Meier method and compared by the log-rank test. A univariable Cox regression was applied to identify potential outcome predictors. Variables with a p <0.10 in the univariable analysis were included in the multivariable Cox regression. For the analysis of DFS, we accounted for the competing-risks between HCC recurrence and death not related to HCC.[20] Results of multivariate analysis were expressed as hazard ratios (HR) with 95% CIs. The proportional hazard assumption for the Cox modeling was not violated as assessed through Schoenfeld residuals and related global tests. A p <0.05 was considered statistically significant. All statistical analyses were performed using STATA 15.0 (Stata Corp., College Station, TX).

Results

Between January 1st, 2000 and December 31st, 2015, 893 patients with HCC diagnosis were listed for LT at our center. Among those, 42 patients refused LT or had their tumors controlled with bridging therapies and were de-listed. These patients were excluded from the analysis. Therefore, the study population included 851 patients. Of those, 219 (25.7%) constituted the pLDLT group. The remaining 632 (74.3%) patients composed the pDDLT group. Fig. 1 shows the study flowchart. The median follow-up for the entire series was 3.1 (IQR 1.4–7.5) years. No differences were detected between both groups (pLDLT 3.3 [IQR 1.5–7.5] years and pDDLT 3.1 [IQR 1.4–7.3] years, p = 0.52).

Intention-to-treat analysis

Patient characteristics

Patient characteristics are summarized in Table 1. At the time of listing, 143 patients (65.3%) in the pLDLT group and 449 patients (71.0%) in the pDDLT group were within the Milan criteria (p = 0.11). While 57 patients (26.0%) in the pLDLT group were beyond the UCSF criteria, 119 (18.8%) in the pDDLT where beyond this definition (p = 0.02). As expected, the WL time was significantly shorter for patients in the pLDLT *vs.* the pDDLT group (4.8 [2.9–8.5] months *vs.* 6.2 [3.0–11.4] months, respectively, p = 0.02).

Dropout and survival

While on the WL, 32 (14.6%) patients in the pLDLT group and 174 (27.5%) in the pDDLT group dropped out (p <0.001). Among these, in the pLDLT group 21/32 (65.6%) patients dropped out because of HCC progression and 11/32 (34.4%) patients died while waiting. Likewise, in the pDDLT group 115/174 (66.1%) patients dropped out because of HCC progression and 59/174 (33.1%) died while waiting (p = 0.96). Out of the 32 patients who dropped out in the pLDLT, 11 recipients had a donor ready at dropout and 21 live donations were precluded because of donor anatomy (16 donors) or persistent obesity/steatosis (5 donors). Dropout probabilities between the study groups are presented (Fig. 2).

The 1-, 3- and 5-year actuarial survival rates from the time of listing were 86% *vs.* 82%, 72% *vs.* 63% and 68% *vs.* 57% for the pLDLT and the pDDLT groups, respectively (p = 0.02) (Fig. 3).

In the multivariate regression analysis, having a live donor available was a protective factor for death (HR 0.67; 95% CI

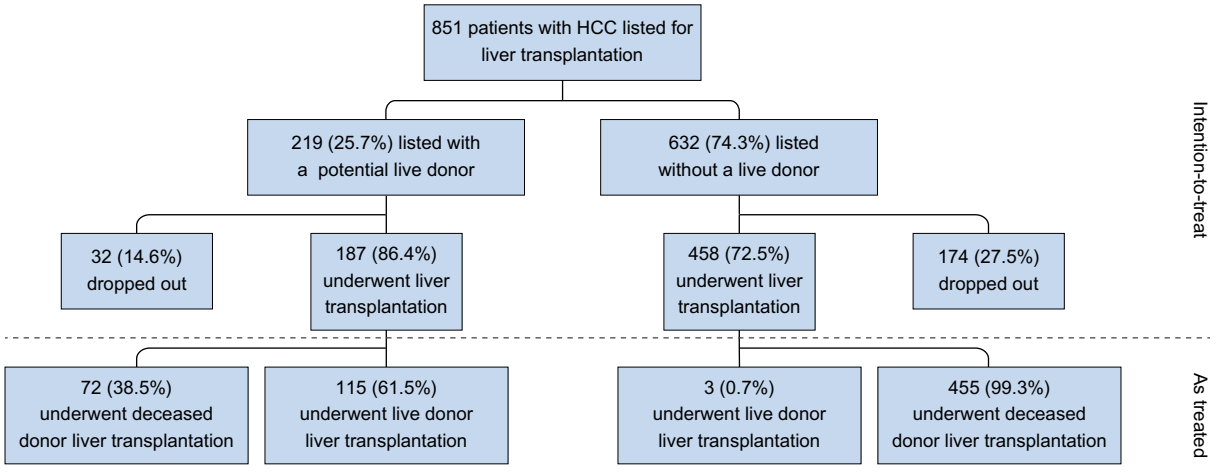


Fig. 1. Study flowchart. HCC, hepatocellular carcinoma.

Table 1. Characteristics of study patients at the time of listing.

Variable	Overall n = 851	Study groups		
		pLDLT n = 219	pDDLT n = 632	*p* value
Sex, male (%)	698 (82.0)	176 (80.4)	522 (82.6)	0.46
Median age, years (IQR)	59 (53–63)	58 (53–63)	59 (53–63)	0.81
Median BMI, kg/m^2 (IQR)	26.9 (24.2–30.4)	27.4 (24.4–30.8)	26.7 (24.0–30.1)	0.24
Etiology of liver disease (%)				<0.001
Hepatitis C	438 (51.5)	122 (55.7)	316 (50.0)	
Hepatitis B	179 (21.0)	21 (9.6)	158 (25.0)	
Alcohol	114 (13.4)	32 (14.6)	82 (13.0)	
NASH	54 (6.3)	20 (9.1)	34 (5.4)	
Cryptogenic	21 (2.5)	6 (2.7)	15 (2.4)	
PSC	14 (1.6)	6 (2.7)	8 (1.3)	
Other	31 (3.6)	12 (5.5)	19 (3.0)	
Median calculated MELD score (IQR)	11 (8–14)	11 (8–14)	10 (8–14)	0.22
Median size of the largest tumor, cm (IQR)	2.7 (1.9–3.9)	2.9 (1.8–4.5)	2.7 (1.9–3.8)	0.10
Median number of tumors (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.98
Median TTV, cm^3 (IQR)	18.8 (6.4–3.6)	24.4 (5.6–118.8)	18.8 (7.2–69.4)	0.18
Staging (%)				
Within Milan	592 (69.6)	143 (65.3)	449 (71.0)	0.11
Within UCSF	675 (79.3)	162 (74.0)	513 (81.2)	0.02
Median serum AFP, ng/ml (IQR)	12 (5–42)	11 (5–52)	12 (5–42)	0.82
<20	524 (61.6)	132 (60.3)	392 (62.0)	0.14
20–99	195 (22.9)	46 (21.0)	149 (23.6)	
100–999	98 (11.5)	27 (12.3)	71 (11.2)	
≥1,000	33 (3.9)	14 (6.4)	19 (3.0)	
Bridging therapy, yes (%)	553 (65.0)	125 (57.1)	428 (67.7)	0.01
Bridging type (%)[¶]				0.01
Ablation	386 (69.8)	79 (63.2)	307 (71.7)	
TACE	142 (25.7)	36 (28.8)	106 (24.8)	
SBRT	25 (4.5)	10 (8.3)	15 (3.5)	
Median time from HCC diagnosis to listing, months (IQR)	4.9 (2.3–9.5)	4.1 (1.3–7.7)	5.2 (2.5–11.5)	0.001
Median time on the waiting list, months (IQR)	5.9 (3.0–0.4)	4.8 (2.9–8.5)	6.2 (3.0–11.4)	0.02
Waiting–time categories (%)				0.03
<3 months	220 (25.9)	60 (27.4)	160 (25.3)	
3–6 months	210 (24.7)	67 (30.6)	143 (22.6)	
6–9 months	164 (19.3)	43 (19.6)	121 (19.1)	
9–12 months	77 (9.0)	16 (7.3)	61 (9.7)	
≥12 months	180 (21.2)	33 (15.1)	147 (23.3)	

Categorical data expressed as proportions and compared by the Chi-squared test with Fisher's correction. Continuous variables expressed as median and IQR and compared by the Mann-Whitney *U* test. AFP, alpha-fetoprotein; BMI, body mass index; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; pLDLT, potential live donor liver transplantation; pDDLT, potential deceased donor liver transplantation; PSC, primary sclerosing cholangitis; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TTV, Total tumor volume; UCSF, University of California San Francisco.
[¶] Among 553 patients.

0.53–0.86). Waiting times of 9–12 months (HR 1.53; 95% CI 1.02–2.31) and ≥12 months (HR 1.69; 95% CI 1.23–2.32) were associated with an increase in the hazard of death (Table 2).

ITT subgroup analysis

We performed a subgroup ITT analysis in patients fulfilling the Milan criteria and those beyond Milan. We also performed an analysis on those patients that had tumors beyond the conventional criteria, but within the ETC. In those patients within the Milan criteria, the waiting time was shorter, and the dropout rate was lower in the pLDLT group. There was no difference between pLDLT and pDDLT regarding the waiting time and dropout rate in those patients that were beyond the Milan criteria. The results of these subgroup analyses are presented (Table S1).

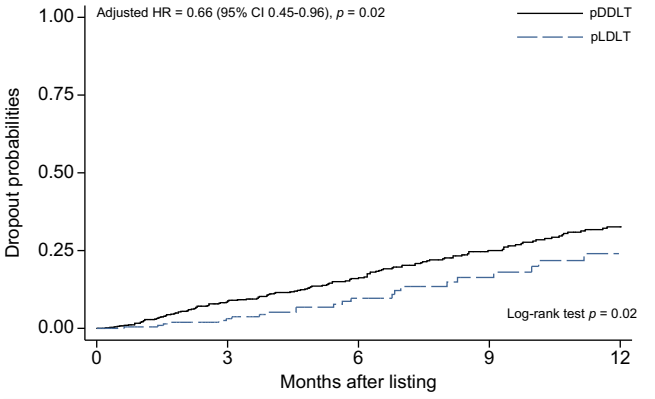
The survival benefit appeared to be predominantly in patients whose tumors fulfilled the Milan criteria: among the 592 patients within the Milan criteria, 143 were in the pLDLT group and 449 in the pDDLT group. The 1-, 3- and 5-year actuarial survival rates were 87%, 76% and 70% in the pLDLT group and 82%, 61% and 53% in the pDDLT group ($p = 0.002$). Among the 259 patients beyond Milan criteria, 76 were included in the pLDLT group and 183 in the pDDLT group. The 1-, 3- and 5-year survival rates were 84%, 66% and 62% for those beyond Milan in the pLDLT group and 84%, 67% and 62% for those beyond Milan in the pDDLT group ($p = 0.98$). The survival curves for these subgroups are provided (Fig. 4).

In this study, 176 patients were beyond the UCSF criteria at the time of listing but within the ETC (pLDLT group: 57 *vs.* pDDLT group: 119). The 1-, 3- and 5-year rates of OS were similar on an ITT basis: 86%, 65% and 60% in the pLDLT group *vs.* 82%, 61% and 56% in the pDDLT group, $p = 0.72$. The multivariable regression for predictors of mortality among subgroups is presented (Table S2).

Analysis from the time of LT (as treated analysis)

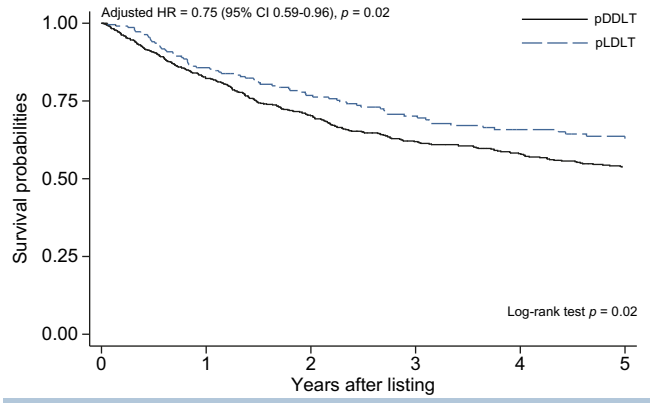
Study population

At the time of transplant, 72 (38.5%) out of 187 patients who were initially listed for LDLT, underwent LT with a deceased donor graft. Whereas, 3/632 (0.7%) patients initially included



N° at risk					
pDDLT	632	474	330	208	148
pLDLT	219	162	92	49	33

Fig. 2. Dropout probabilities between the pLDLT group and the pDDLT group. HR, hazard ratio; pDDLT, potential deceased donor liver transplantation; pLDLT, potential live donor liver transplantation.



N° at risk						
pDDLT	632	515	419	321	272	237
pLDLT	219	182	147	118	96	82

Fig. 3. Intention-to-treat overall survival between patients listed for pLDLT and pDDLT. HR, hazard ratio; pDDLT, potential deceased donor liver transplantation; pLDLT, potential live donor liver transplantation.

in the DDLT group were finally transplanted with a live donor graft. Therefore, of the initial 851 patients in the study, a total of 118 (13.2%) patients underwent aLDLT and 527 (59.0%) patients aDDLT (Fig. 1).

The clinical and pathological characteristics of these patients are presented (Table S3). At the time of transplant, patients who underwent aLDLT had higher MELD scores than those who underwent aDDLT. The number of patients receiving bridging therapies was significantly higher in those receiving aDDLT (aLDLT recipients: 64 (54.2%) *vs.* aDDLT recipients: 380 (72.1%); p <0.001). The WL time was shorter for patients receiving an aLDLT transplant (LDLT 3.6 [2.5–6.5] months *vs.* aDDLT 6.3 [3.2–11.2] months; p <0.001). The median time between the HCC diagnosis and the LT was 6.8 (4.7–12.3) months for patients who received an aLDLT graft and 11.5 (7.1–18.4) months for patients who received an aDDLT graft (p <0.001).

Survival

The median follow-up for this subgroup was 4.1 (1.8–8.3) years, with no differences between groups (aLDLT 4.0 (1.7–8.2) years *vs.* aDDLT 4.3 (2.0–9.0) years; p = 0.84). During the follow-up, 17 (14.4%) aLDLT recipients and 97 (18.4%) aDDLT recipients experienced HCC recurrence, p = 0.30. The 1-, 3- and 5-year actuarial DFS rates were 85% *vs.* 88%, 80% *vs.* 76% and 78% *vs.* 72% for the aLDLT and the aDDLT recipients, respectively (p = 0.24) (Fig. 5-A). Similarly, the 1-, 3- and 5-year actuarial PTS rates were 90% *vs.* 93%, 81% *vs.* 81% and 79% *vs.* 76% for the aLDLT and the aDDLT recipients, respectively (p = 0.34) (Fig. 5-B). In the multivariable regression model, serum AFP progression >5 ng/ml/month, tumor size, number of lesions, presence of microvascular invasion and poorly differentiated tumors were predictors of tumor recurrence. Tumor size, number of lesions, presence of macrovascular invasion and poorly differentiated tumors were related to increased risk of post-transplant death (Table 3 and Table S4). Neither the transplant type nor the time on the WL were associated with the outcomes. We compared the OS between patients listed for a pLDLT who underwent DDLT (72 patients) with patients listed for a pLDLT who underwent LDLT. There was no statistical difference between both groups in PTS (p = 0.15) or DFS (p = 0.22).

Discussion

The present study demonstrated that patients listed with a potential live donor had a 33% reduction in the risk of death from the time of listing. To our knowledge, this is the largest study comparing LDLT to DDLT in patients with HCC and the first to demonstrate a survival benefit for live donation. Moreover, our as treated analysis showed no difference in post-transplant outcomes between LDLT and DDLT.

The reasons for the improved survival in the ITT analysis were the shorter waiting time and the decreased dropout risk. Patients in the pLDLT had a relative reduction of 47% in their risk of dropout. Since pLDLT patients do not have to wait for an organ, they were not affected by graft scarcity. The reasons for dropout were similar, indicating that LDLT provides an absolute benefit in the dropout rate. The dropout rate in the pLDLT group was the lowest possible dropout rate among patients listed with HCC.

The wait-time for patients with a potential live donor was equivalent to the donor and recipient work-up time. Nevertheless, some patients in the pLDLT group still had relatively long waiting times (>180 days). This happens when donor schedules do not permit a straightforward assessment, when extra time is required to work-up donors with mild clinical issues that do not preclude donation but take time to be managed (*e.g.* obesity and/or steatosis); and our policy to perform sequential work-ups which only yield a donor in one-third of candidates.

Interestingly, even with a small difference in the length of waiting time (1.4 months), patients with a pLDLT had a ~50% lower dropout rate. Our dropout rate among pLDLT is in contrast to previous studies that have reported 0% dropout in the LDLT groups.[7,8] The reason for this difference may rely on the fact that, in Toronto, potential donors are not fully evaluated until the recipient is listed, and every patient with a live donor is also included and "active" on the deceased donor WL until their living donor's evaluation is completed and their LDLT surgery is booked. Finally, because of our study design (ITT), some patients who had a pLDLT at the time of listing ended up crossing over to the DDLT group. We believe the results presented here reflect the reality of other centers performing LDLT for HCC.

Table 2. Intention-to-treat univariate and multivariate Cox regression analysis for overall survival in patients with HCC after listing for liver transplantation.

Variable	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Sex (ref.: male)	0.89 (0.69–1.14)	0.37	–	–
Age (years)	1.01 (0.99–1.02)	0.10	–	–
BMI (kg/m^2)	1.01 (0.99–1.03)	0.20	–	–
Etiology liver disease (ref.: Hepatitis C)			–	–
Hepatitis B	0.62 (0.47–0.81)	<0.001	0.61 (0.47–0.77)	<0.001
Alcohol	0.99 (0.74–1.32)	0.93	0.96 (0.67–1.21)	0.49
NASH	1.05 (0.69–1.61)	0.80	0.91 (0.61–1.39)	0.68
Cryptogenic	0.99 (0.53–1.88)	0.99	0.85 (0.45–1.61)	0.62
PSC	0.41 (0.13–1.28)	0.12	0.37 (0.12–1.17)	0.09
Other	0.93 (0.56–1.55)	0.79	0.87 (0.50–1.51)	0.62
Calculated MELD score	1.03 (1.01–1.05)	0.01	1.03 (1.01–1.06)	0.01
Size of the largest tumor (cm)	1.06 (1.02–1.11)	0.01	1.07 (1.03–1.12)	0.01
Tumor number (lesion)	1.00 (0.94–1.07)	0.99	–	–
TTV (per 100 cm^3)	1.00 (0.98–1.02)	0.89	–	–
Milan in (ref.: out)	0.99 (0.80–1.22)	0.92	–	–
UCSF in (ref.: out)	0.85 (0.67–1.08)	0.19	–	–
AFP (ng/ml, ref.: <20)			–	–
20–99	1.21 (0.96–1.53)	0.13	1.18 (0.93–1.49)	0.17
100–999	1.37 (1.02–1.84)	0.04	1.43 (1.07–1.90)	0.01
>1,000	2.59 (1.70–3.95)	<0.001	2.61 (1.72–3.96)	<0.001
Bridging therapies (ref.: yes)	0.82 (0.67–1.00)	0.05	–	–
Time on waiting list (ref.: <3 months)			–	–
3–6	1.05 (0.77–1.43)	0.76	1.06 (0.77–1.46)	0.71
6–9	0.98 (0.70–1.38)	0.92	1.05 (0.74–1.48)	0.79
9–12	1.46 (0.98–2.19)	0.06	1.53 (1.02–2.31)	0.04
≥12	1.67 (1.22–2.28)	0.01	1.69 (1.23–2.31)	0.001
Type of graft intended at listing (ref.: potential deceased donor)				
Potential live donor	0.75 (0.59–0.96)	0.02	0.67 (0.53–0.86)	0.01

AFP, alpha-fetoprotein; BMI, body mass index; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; TTV, Total tumor volume; UCSF, University of California San Francisco.

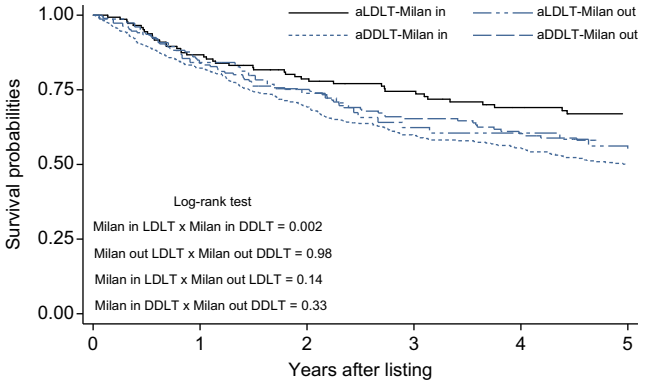


Fig. 4. Comparison between subgroups of patients with HCC listed for live donor liver transplantation and diseased donor liver transplantation according to Milan criteria. HCC, hepatocellular carcinoma; pDDLT, potential deceased donor liver transplantation; pLDLT, potential live donor liver transplantation.

One of the main concerns when offering LDLT to patients with HCC is the risk of "fast-tracking" patients to transplant and a potential increase in the risk of post-transplant recurrence.[3,21,22] Previous studies have shown that shorter waiting times may be associated with higher post-transplant recurrence.[23,24] To address this, the United Network for Organ Sharing has implemented a mandatory waiting time of 6 months before patients with HCC can accrue exception points.[25] This policy is mainly designed for DDLT, but should patients with an available live donor wait before being transplanted? Our study indicates that waiting times shorter than 9 months are not detrimental. This result is in accordance with others.[21,22] In our opinion patients with an available live donor should not wait beyond the work-up time for transplant. Importantly, in a region like Ontario, without a centralized HCC referral system, patients wait ~5 months from cancer diagnosis to listing. This "waiting time" will already be acting as a "test of time" in this population. It is likely that this is true for many other jurisdictions around the globe. One of the limitations with this information is that we cannot report the number of patients that started evaluation but dropped out for tumor progression and were never listed. Interestingly, our study also demonstrates that a longer waiting time is detrimental for patients; waiting over 9 months increased the risk of death by more than 50%. Given the smaller sample size compared to other studies in this field,[24] we believe that these findings should be interpreted with caution.

Two previous studies compared the outcomes from the time of listing in patients with HCC who underwent either LDLT or DDLT. Bhangui *et al.* in 2011[8] compared 36 patients that underwent LDLT to 147 listed for DDLT. They demonstrated that patients in the LDLT group had a faster access to transplant with shorter WL times and reduced dropout rates compared to the DDLT group. However, OS from the time of listing was similar between both groups. In 2017, a French multicenter study compared 79 patients listed for LDLT to 782 patients listed for DDLT.[7] In this study, the OS was similar between groups. Two other studies from China also failed to show the survival benefit of live donation.[26,27] Our results, differ from these studies since for the first time we were able to demonstrate a survival benefit with LDLT for patients with HCC. Most likely, the relatively small sample size of the previous studies, compared to ours, contributed to their failure to find a significant difference

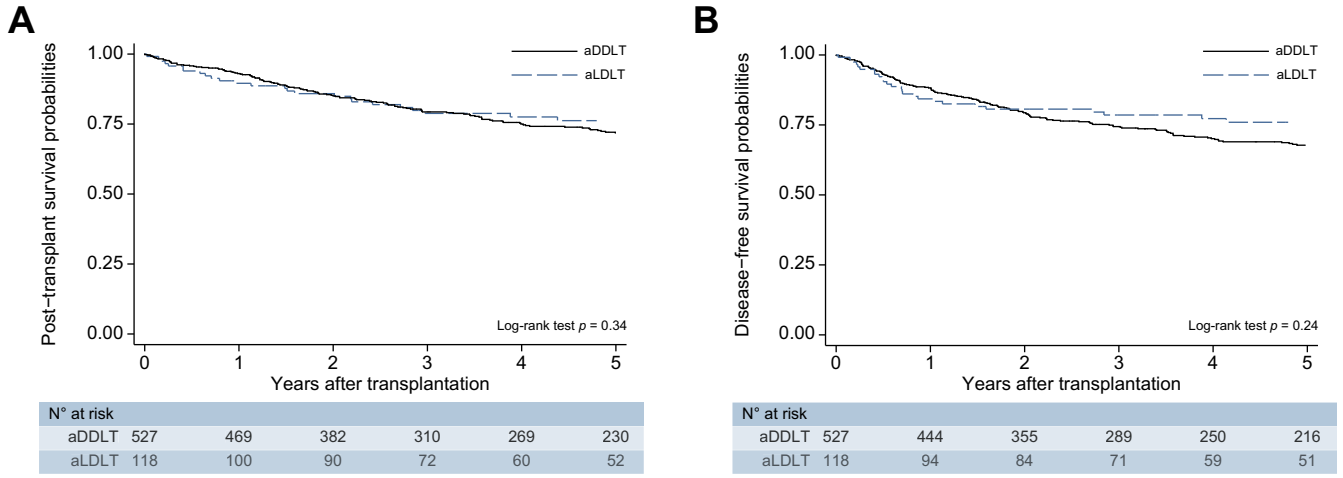


Fig. 5. Post-transplant patient and graft survival according to graft type in patients that underwent liver transplantation. (A) Post-transplant survival probabilities according to graft type in patients that underwent liver transplantation. (B) Disease-free survival among patients who underwent liver transplantation according to the type of graft. aDDLT, actual deceased donor liver transplantation; aLDLT, actual live donor liver transplantation.

Table 3. Multivariate Cox regression analysis for DFS and PTS in patients with HCC after liver transplantation.

Variable	DFS		PTS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Etiology liver disease (ref.: Hepatitis C)				
Hepatitis B	–	–	0.51 (0.35–0.75)	0.001
Alcohol	–	–	0.86 (0.57–1.31)	0.49
NASH	–	–	0.79 (0.40–1.57)	0.51
Other	–	–	0.64 (0.28–1.44)	0.28
Cryptogenic	–	–	0.63 (0.20–1.98)	0.43
PSC	–	–	0.32 (0.04–2.34)	0.26
AFP trend, ref.: stable				
Decrease > 5 ng/ml/mo	1.45 (0.74–2.86)	0.28	1.13 (0.68–1.89)	0.63
Decrease ≤ 5 ng/ml/mo	1.59 (0.92–2.74)	0.10	1.05 (0.71–1.55)	0.80
Increase ≤ 5 ng/ml/mo	1.22 (0.67–2.22)	0.52	1.03 (0.68–1.55)	0.89
Increase > 5 ng/ml/mo	2.06 (1.11–3.83)	0.02	1.47 (0.96–2.24)	0.07
Biggest size at explant, cm	1.13 (1.07–1.20)	<0.001	1.09 (1.05–1.14)	<0.001
Lesion number at explant	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	0.001
Microvascular invasion (ref: no)	2.68 (1.67–4.31)	<0.001	1.58 (1.15–2.17)	0.004
Macrovascular invasion (ref.: no)	1.06 (0.56–2.01)	0.85	–	–
Poorly differentiated, (ref.: not)	2.60 (1.52–4.44)	<0.001	1.84 (1.23–2.75)	0.003

AFP, alpha-fetoprotein; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; PSC, primary sclerosing cholangitis; PTS, post-transplant survival.

between groups. Our study also demonstrates that even with a potential live donor there is still a risk of tumor progression and dropout that must be considered.

In 2007, the A2ALL research study group compared the outcome of patients with HCC undergoing LDLT (n = 58) *vs.* DDLT (n = 34).[3] There was a higher HCC recurrence rate in those patients receiving a live donor graft (29% *vs.* 0%). However, the higher recurrence rate was probably a result of more advanced tumors at the time of transplant.[4] Our post-transplant outcomes are consistent with reports demonstrating no differences when comparing different types of grafts.[7,8] Theoretically, patients who had a pLDLT might have benefited from a greater family support or a better socioeconomic status. We performed a comparison between patients who had a potential live donor and underwent LDLT or DDLT. In accordance with our previous results, we did not identify any PTS differences between groups. We identified that patients who presented with AFP progression during the waiting time had an increased risk of HCC recurrence. This finding is in agreement with previous reports.[18,28,29] Furthermore, patients who had a significant decrease (<5 ng/ml/month) in their serum AFP had the same risk of tumoral relapse as patients with stable serum AFP.[29] A pre-transplant serum AFP >1,000 ng/ml was not identified as a predictor of tumor recurrence or PTS, likely due to the number of patients (24 [3.7%] patients).

Our study has several limitations. The retrospective study design and inherent limitations of a non-randomized study could result in missing confounding factors that favor the outcome in patients undergoing LDLT. However, given a prospective trial comparing LDLT *vs.* DDLT for patients with HCC will not be feasible, the results presented here might be the best possible evidence. Another potential weakness of this study might be that OS was analyzed from the time of listing and not from the time of diagnosis of the disease. Due to the nature of our health system, many patients are referred for transplantation late in the course of their disease and the true impact of both transplant approaches might be underestimated. However, we compensate for these shortcomings by providing a well-defined, large, single- center patient population that was treated following well-established and consistent criteria. Moreover, reviewing patients' outcomes, not only from the time of LT but also from the time of listing, allowed us to assess the real benefit of LDLT for the treatment of this disease.

In conclusion, based on our findings, patients with HCC listed for LT who have an available live donor experience significantly higher OS rates than patients that wait for a deceased donor graft. In this study, the superiority of outcomes in the LDLT group derived from shorter WL times and reduced dropout rates. Therefore, transplant programs around the world should encourage patients with HCC who are listed for LT to consider LDLT, so that they have faster access to transplants and better survival outcomes.

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

NG, AG and GS contributed to study design, data collection and analysis, drafted the manuscript and approved the final version. AD, KT, and WZ contributed to data collection and approved the manuscript's final version. BEH contributed with statistical analysis and approved the manuscript's final version. AG, LL, MC, ZG, MS, MB, MS, IM, PDG and DRG contributed to data analysis and interpretation, critical appraisal of the manuscript, and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.029.

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Author names in bold designate shared co-first authorship.

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