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Outcomes of liver transplantation to the patients with hepatocellular carcinoma from living donors *versus* transplants from deceased donors

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Summary

Our objective was to compare overall and tumor-free survival for the hepatocellular carcinoma (HCC) patients subjected to liver transplantation from living donor (LDLT) *versus* liver transplantation from deceased donor (DDLT) treated at our center.

Patients and methods

Seventy-three patients underwent liver transplantation for HCC staged according to Milan criteria (MC). The cases have been divided into two groups: (a) forty-four patients transplanted by means of LDLT, and (b) twenty-nine patients underwent DDLT. The patients beyond MC, or those who underwent downstaging locoregional therapy were excluded from the study.

Results

Overall survival outcomes at 5 years were, respectively, 80.3% *vs* 70.4%, in LDLT and DDLT groups whereas tumor-free survival was 79.1% *vs* 76% for LDLT and DDLT cases. LT from living donors showed slightly better patients' survival compared to liver transplantation from deceased donors DDLT (P=0.09). However, the difference in tumor-free survival between both groups was virtually absent (P=0.6).

Conclusion

The present study confirmed that LDLT, while offering a slightly better overall survival, is associated with similar terms of tumor-free survival compared to transplants from deceased donors. This similarity is especially clear when avoiding biases caused by different tumor features and analyzing a perfectly matched cohort of patients presenting with HCC classified according to the Milan criteria.

Keywords

Hepatocellular carcinoma, liver transplant, living donor, deceased donor, survival.

Introduction

Liver transplantation (LT) for hepatocellular carcinoma (HCC) has witnessed a historic change after the milestone article published by Mazzaferro *et al.* [1], who confirmed favorable outcomes for HCC patients similar to outcomes of LT for non-HCC indications. Since then, LT and its main option, the deceased-donor liver transplantation (DDLT) has become a well-established line of treatment with a highly curative profile for cirrhotic patients with HCC, but if only a liver graft is available.

The living-donor liver transplantation (LDLT) was introduced in order to reduce the organ shortage, due to expanding waiting lists for the patients awaiting liver transplant. In some countries, where the number of deceased donor is extremely small, the LDLT has been developed as an

alternative treatment for the end-stage liver diseases, thus becoming an established treatment in HCC cases [2].

Nevertheless, recurrent HCC (rHCC) is still reported in up to 15% of cases following LT. HCC relapse is associated with dismal prognosis and, subsequently, LT failure in most instances [3]. Currently, LT for HCC has increased four-fold since early 2000s [4]. The impact of recurrent HCC is further enhanced by scarcity of liver grafts and fast expansion of LT waiting lists, whereas hepatic resection and other ablative modalities can offer up to 50% patient survival for HCC relapse [5].

Patient survival was shown to be better following LDLT for HCC compared to those transplanted from Deceased Donor (DD) [6, 7]. Many factors were held responsible for such results, including shorter time to transplant, better graft quality with shorter ischemia period.

Moreover, with the accumulation of cases, the impact of LDLT on the rHCC rates after LT has drawn attention of transplant community, since some reports showed higher incidence of rHCC following LDLT [8].

Many pathogenetic mechanisms were considered to explain these reports, including higher cytokine production in regenerating liver grafts and reduced time to transplant that could conceal aggressive tumor biology promoting the HCC recurrence [9-11]. These data were further analyzed to compare rHCC for patients transplanted from LDLT and DDLT source [12-15].

Hence, the aim of our single-center study was to compare overall and tumor-free survival among HCC patients subjected to liver transplantation from living donor (LDLT) *versus* liver transplant from deceased donor (DDLT).

Materials and methods

The study was started after obtaining the approval of Research Ethics Committee at our institution. All the patients were consented for the use of their clinical and pathological data for research purposes in anonymous manner, the patients were also informed that their decision to approve or disapprove the research consent will not influence their clinical management.

The cases of pediatric LT or liver retransplantation were excluded from this study. Finally, 136 patients diagnosed with HCC approved the research consent, being subsequently included in the study. Medical charts of the included patients were retrospectively reviewed. HCC was diagnosed by contrast-enhanced computed tomography (CT) and/or abdominal magnetic resonance imaging (MRI). The disease staging was based on chest CT, cranial CT, and technetium-99m bone scintigraphy, to exclude extra-hepatic disease. The following exclusion criteria were considered absolute contraindications for LT at our center:

- Failed or unfeasible downstaging of HCC originally beyond Milan, or UCSF transplant criteria, i.e., stable disease (SD), progressive disease (PD) according to modified RECIST criteria [16];
- Active extra-hepatic malignancies (excluding non-melanoma skin cancers);
- Untreatable advanced cardiopulmonary disease;
- Active infections e.g., active tuberculosis, uncontrollable sepsis;
- Unstable major psychiatric disorders;
- Disabling extensive intracranial neurological deficit;
- Substance abuse or active alcohol abuse over last 6 months;
- Documented medical non-compliance.

A total of 115 adult patients underwent LT for HCC at our institution between August 2006 and December 2019. LT was performed using either cadaveric, or living donor liver transplantation (LDLT). In LDLT setting, the donors were first- and second-degree relatives of respective patients.

Seventy-three patients conformed with Milan liver transplant criteria (MC) and, for the sake of comparison, they were divided into two groups as follows: Group A included forty-four HCC patients transplanted from living donors (LDLT); Group B consisted of twenty-nine HCC patients who received DDLT.

Fig. 1 illustrates the distribution of HCC patients with respect to decision for LT, and if the transplant was performed as LDLT or DDLT. The patients beyond Milan criteria, or those subjected to downstaging locoregional therapy were excluded from the study.

Details of the transplant procedure were documented; tumor characteristics were based on the pathological findings. HCC size, number of foci, tumor grade, and lymphatic invasion were diagnosed by an experienced pathologist. Demographic data, pre-transplant features, procedure-related variables, pathological findings were retrieved from the patient charts. Triple immunosuppression protocol was applied for the LT recipients including calcineurin inhibitor (CNI), glucocorticosteroids, and mycophenolate mofetil. Clinical and laboratory data were analyzed with t-test and Chi-square test. P-value of <0.05 was considered statistically significant. Kaplan-Meier curves were used to express survival outcomes, and statistical significance was determined by log-rank test. Overall and tumor-free survival were determined during the control contacts and examination of the patients.

Patient survival was calculated from the date of LT to the date of death or the date of the last follow-up for surviving patients. Graft survival was estimated as a death-censored graft survival. It was calculated from the date of transplantation to the date of irreversible graft failure signified by relisting of the patient on liver transplant waiting list, this method was used to avoid estimation of death with a functioning graft as a graft failure. Tumor-free survival was estimated from the date of transplant to the date of confirmed pathological evidence of recurrent HCC.

Results

Seventy-three patients underwent LT between August 2006 and December 2019 at our center for HCC which met MC. Table 1 is summarizing pre-transplant and pathological variables for these patients.

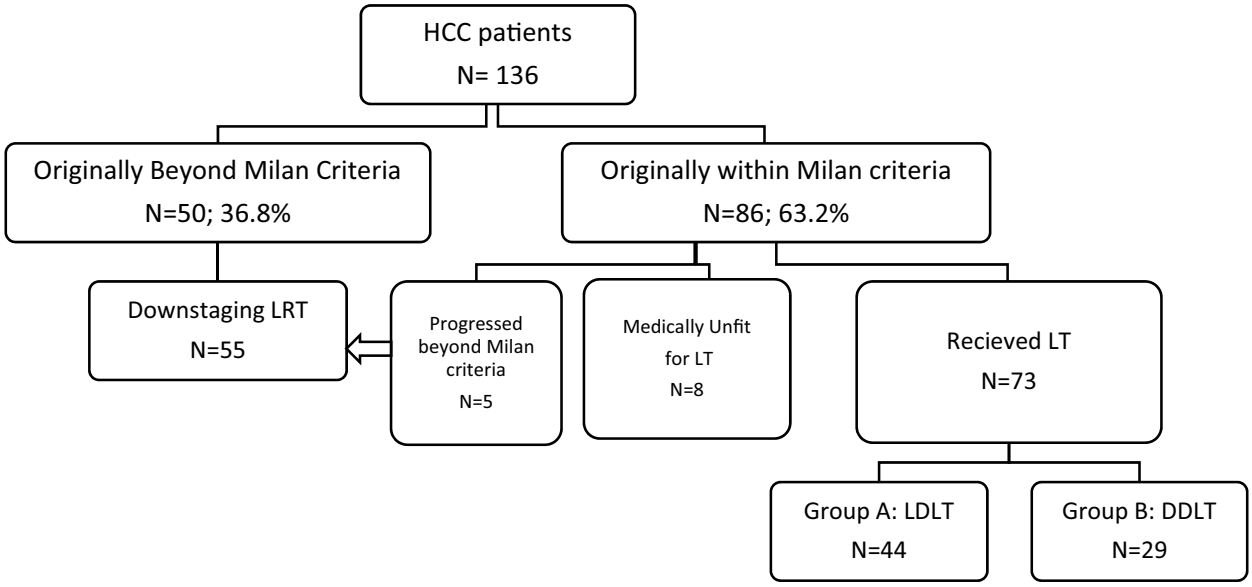

Figure 1. Flowchart of HCC patients enrolled during the study period

Table 1. Comparison of pre-transplant and pathological findings in LDLT and DDLT groups of the patients with hepatocellular carcinoma

Variables			*Group A (LDLT) N=44*		*Group B (DDLT) N=29*		*P value*
			*Number (percent)**	*Mean & SD*	*Number (percent)**	*Mean & SD*	
Patients Demographics	Gender	Female N=33	20 (45.5%)	–	13 (44.8%)	–	1.0
		Male N=40	24(54.5%)		16 (55.2%)		
	Age(years) Range (39-67)		–	61.8±3.5	-	58.1±6.3	0.002
Indication of Transplant	HCV (n=44)		29 (65.9%)	–	15 (51.7%)	–	0.33
	HBV (n=19)		9 (20.5%)		10 (34.5%)		0.28
	Others	Cryptogenic (n=6)	3 (6.8%)		3 (10.3%)		0.68
		Non Alcoholic steatohepatitis (NASH)(n=3)	2 (4.5%)		1 (3.5%)		0.99
		HCV&HBV(n=1)	1 (2.3%)		0		0.99
Child – Turcotte – Pugh (CTP) score Range (6-9 point)			–	8.0±0.9	–	7.7 ±0.6	0.12
Model for end-stage liver disease (MELD) score Range (12-25 points)			–	19 ±5.5	–	17.1 ± 5.4	0.15
Time to Transplant			–	35.8 ±4.5	–	94.7±8.3	<0.0001
Tumor size			–	2.4±0.5	–	2.6±0.7	0.16
Number of lesions			–	1.4±0.7	–	1.6±0.5	0.19
Total Tumor Volume (TTV)			–	109.2±79.7	–	132.2±67	0.2
Tumor Differentiation	Well (n=18)		12 (27.3%)	–	6 (20.7%)	–	0.7
	Moderate (n=44)		24 (54.5)		20 (69%)		
	Poor (n=4)		3 (6.8%)		1 (3.4%)		
	Necrotic (n=7)		5 (11.4%)		2 (6.9%)		
Lympho-vascular invasion (n=6)			4 (9.1%)	–	2 (6.9%)	–	0.99

Time to transplant ranged from 10 to 185 days, patients' age, and time to transplant differed significantly between group A (living donors) and B (deceased donors), (P value, 0.002 and <0.001 respectively). On the other hand, pathological variables did not show significant difference between both groups.

The mean post-transplant follow-up for the studied patients was 46±33.3 months, ranging from 24.3 to 149.9 months. The overall 5-year patient survival, graft survival and tumor-free survival were 78.6%, 90.1% and 86.3% respectively. During the follow-up, a total of six patients manifested with rHCC (8.2%), i.e., four patients (9.1%) developed rHCC in group A, compared to two-cases (6.9%) of rHCC in group B patients, p value was 0.99. With respect to survival outcomes, LDLT group slightly differed from those who received DDLT. The overall patient survival was higher in Group A, at P=0.09 (log-rank test).

Conversely, tumor-free survival was only marginally better in group B, but it did not reach the significance level (P=0.6). On the other hand, graft survival was almost the same in both groups (P=0.99), as seen in Fig. 2 (A, B, C).

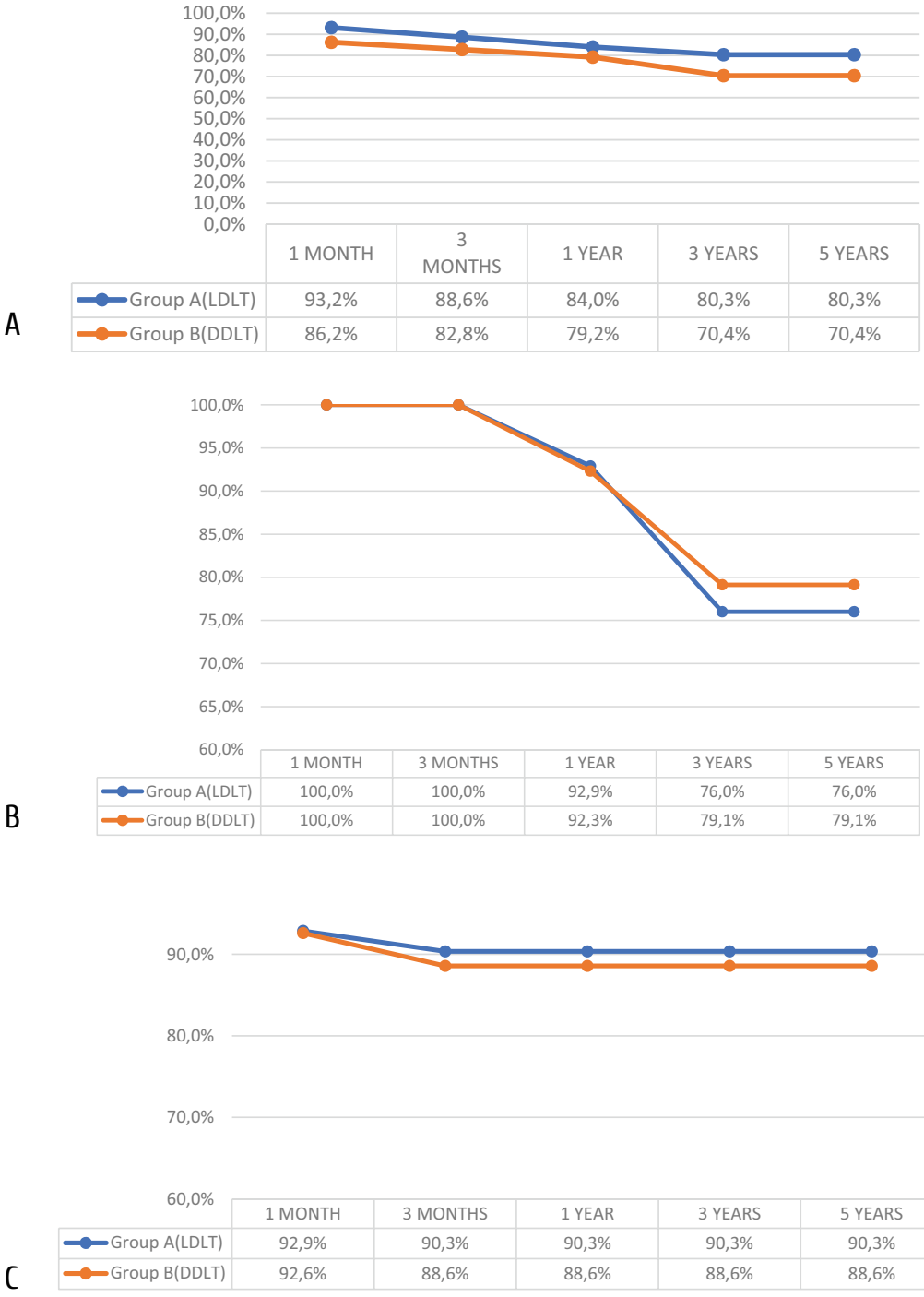

Figure 2. Comparisons for overall survival (A), tumor-free survival (B) and graft survival (C) between the groups A (LDLT) and B (DDLT) using the Kaplan-Meier approach

Discussion

There is a convincing evidence, that LT offers an excellent chance for cure of patients presenting with HCC, especially when their tumor burden is still within Milan criteria. The main concern regarding LT for HCC patients is the issue of liver graft availability and ethical costs to obtain it. Ethical concerns always overshadow the excellent results for LT in HCC patients, especially when allocation system favors HCC patients by the addition of 22 points [3, 4]. Consequently, more liver grafts are being allocated to HCC patients on the expense of patient suffering from liver insufficiency only. Furthermore, the use of LDLT to partially alleviate graft shortage is accompanied by inherent risk for healthy donor. Thus, outcomes of LT for HCC must be at optimal levels, to justify the ethical concerns encountered either in DDLT or LDLT settings. Hence, evaluation of clinical outcomes after LT for HCC in general, and comparative assessment of either LDLT or DDLT advantages over other options is quite important, especially in transplant centers where both LT modes are available.

DDLT is associated with long waiting times and consequently increased mortality and delisting rate while awaiting liver transplant. *Hogen et al.* [17], reported significantly higher waiting list mortality in UNOS regions with long waiting times compared to regions with short waiting times.

One of the main LDLT benefits is its ability to reduce the time to transplant and decrease the waiting list dropout. This is especially vital to the patients with HCC, to avoid tumor progression. *Sandhu et al.* [18], described a significantly shorter waiting time for LDLT compared to DDLT (3.1 *vs* 5.3 months respectively). Similarly, the current study reported significant data from the current study which showed 15% dropout rate for the patients originally presenting with HCC within Milan criteria. More than one third of this dropout rate was due to tumor progression. These patients underwent downstaging protocol using different locoregional neoadjuvant techniques.

The dropout rates vary considerably according to graft allocation policies. In the USA, there is a considerable variability of dropout rate based on the transplant waiting times. *Mehta et al.* [18], compared the dropout risk for HCC patients who received MELD exception points from 2005 and 2014. They described a significantly higher risk for dropout in UNOS regions with long transplant waiting times, the difference was three times higher than in the areas with short transplant waiting times (24% *vs* 8% dropout rate, respectively).

Few studies addressed the question of whether LDLT is associated with higher recurrence rate for HCC compared to DDLT, or not. One of the earliest reports on this issue (*Lo et al.*) described a significantly more common HCC recurrence at their LDLT arm (43 patients), compared to DDLT arm which included 17 patients. The study included heterogenous patient groups, i.e., corresponding the Milan or UCSF criteria, and beyond them. The cases subjected to downstaging locoregional therapy were not excluded from the study [12]. Similar findings were reported by *Fischer et al.* in their large cohort of patients, and they referred to different tumor characteristics, pretransplant locoregional therapies and short time to transplant as the key factors that explain the higher reported rHCC rates following LDLT [13].

On the other hand, *Di Sandro et al.*, reported that LDLT had the same tumor-free survival compared to DDLT in the patients presenting within Milan transplant criteria, when tumor characteristics were kept unified during the study, and MC was recommended as the selection tool for further comparison of both LT modes [14]. Hence, this study reports similar findings, since LDLT was found to be insignificantly different from DDLT regarding tumor-free survival.

Such results were again confirmed by *Sandhu et al.*, where the similar tumor-free survival rates were described in both LDLT and DDLT in a well-matched cohort of patients, especially for the tumor characteristics [15]. *Ogawa et al.*, and *Akamatsu et al.*, described comparable outcomes for both LDLT and DLT [19, 20]. Furthermore, *Zhu et al.*, and *Zhang et al.* in their recently reported meta-analysis concluded that LDLT was not inferior to DDLT regarding overall or tumor-free survival [21, 22].

Conclusion

The results of the current study conclude that LDLT – while offering a slightly better overall survival – has insignificantly shorter tumor-free survival compared to DDLT. This is especially true, when the bias from different tumor characteristics was eliminated by studying a perfectly matched cohort of patients presenting with HCC within MC. Furthermore, LDLT group had a significantly shorter time to transplant compared to DDLT group. Consequently, the resulting decrease in dropout rate should be considered when comparing LLDT and DDLT options.

Conflict of interests

With respect to the current study, the authors declare neither any conflict of interest, nor financial issues to be disclosed.

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Исходы трансплантации печени у пациентов с гепатоцеллюлярной карциномой от живых доноров по сравнению с трансплантацией от погибших доноров

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Резюме

Целью нашей работы было сравнение общей и безопухолевой заболеваемости у пациентов с гепатоцеллюлярной карциномой (ГЦК), леченных в нашем центре, после трансплантации печени от живых доноров (ЖД) и погибших доноров (ПД).

Пациенты и методы

73 пациентам была выполнена трансплантация печени по поводу ГЦК, стадированной по Миланским критериям (МК). Эти пациенты были распределены по 2 группам: (а) 44 больных трансплантированных от ЖД, и (б) 29 пациентов получидли трансплантаты от ПД. Из исследования были искючены больные, не соответствующие Миланским критериям или пациенты после циторедуктивной локорегионарной терапии.

Результаты

5-летняя выживаемость составила, соответственно, 80,3% и 70,4% среди реципиентов печени от ЖД и ПД, тогда как безопухолевая выживаемость составляла 79,1% и 76%, соответственно, в группах больных, трансплантированных от живых и погибших доноров. Трансплантация печени от живых доноров показала несколько лучшие результаты, нежели трансплантация от погибшиз доноров (P=0.09). Однако разница по безопухолевой выживаемости между этими двумя группами не выявлена (P=0.6).

Выводы

Данное исследование подтвердило, что трансплантация печени от живых доноров, при несколько лучшей общей выживаемости, ассоциирована со сходными сроками безопухолевой выживаемости по сравнению с трансплантацией от погибших доноров. Это сходство особенно выражено при устранении возможных факторов, связанных с особенностями опухолей и анализом данных в хорошо сравнимых группах пациентов с ГЦК, классифицированных по Миланским критериям.

Ключевые слова

Гепатоцеллюлярная карцинома, трансплантация печени, живые доноры, погибшие доноры, выживаемость.