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# Clinical Outcomes of Living Donor Liver transplantation for Hepatocellular Carcinoma in Egypt

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**Background:** Over the last decade, there has been considerable improvement in the outcome of liver transplantation in patients with Hepatocellular carcinoma (HCC).

Aim: To evaluation the prognosis of living donor liver transplantation (LDLT) as a definitive treatment of HCC in patients who met criteria of transplantation including the recurrence of HCC in Egypt.

**Methods:** We retrospective analysed preoperative, operative, post-operative and follow-up records of liver transplanted patients' attending hepato-pancreato-biliary (HPB) surgery department at International Medical Center (IMC), Egypt from April 1, 2013 to the December 31, 2016. During this period, 53 patients underwent LDLT and hepatic focal lesions (FLs) were the indication of liver transplantation in all the cases. Descriptive and analytical statistics were applied to summarize the findings and Kaplan-Meier survival analysis was performed to investigate the survival rates in LDLT recipients. A *p*-value <0.05 was considered statistical significant.

**Results:** Of 53 LDLT recipients, 50 (94.3%) were male, mean age of 52±7.64 years and a majority (86.8%) of the patients were HCV positive. However, nearly three-forth (73.6%) of the patients have comorbidities at the time of transplantation and the mean model for end-stage liver disease (MELD) score was 17.3± 6.1 (range: 8 – 35). Nineteen (35.8%) patients developed recurrent HCV after transplantation and nine (17%) had faced transplant rejection. After one year of LDLT, 64.1% of recipients survived, 58.49% for three years, and 39.6% for five years. One year mortality was 35.8% (19 cases), 41.5% (22 cases) in three years and on five years it reached to 60.3% (32 cases).

**Conclusion:** This studies identified that the success of LDLT in HCC patients rely on a stepwise approach that incorporates morphological and biological criteria of the tumor. Major vascular invasion, massive infiltrative type, ruptured HCC and distant metastasis are to be considered as absolute contraindications for transplant.

**Keywords:** hepatocellular carcinoma, liver transplantation, living donor liver transplantation, survival, mortality, Egypt.

## 1 Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the second leading cause of cancer-related deaths worldwide [1]. Over the last decade, there has been considerable improvement in the outcomes in the HCC patients by Liver transplantation. However, prognostic factors such as vascular invasion and tumor differentiation are the utmost important indicators in predicting recurrence in liver transplant survivals [2]. In addition, radiological parameters such as tumor size and number are still regarded as the best selection criteria for patients with HCC to undergo liver transplant in clinical practice [3]. For >10 years since the "Metroticket concept" described by the Milan selection criteria have remained as gold stand for selection of HCC patients for liver transplantation remained as gold standard [4]. Further extension, University of California at San Francisco (UCSF) criteria have been proposed to expand the tumor number–size limits to solitary tumor up to 6.5 cm or a maximum of 3 tumor nodules each up to 4.5 cm, and a total tumor diameter not exceeding 8 cm, without compromising patient survival [5]. Currently, the Milan and UCSF criteria are the most popular reference criteria in deciding the candidacy of patients with HCC for liver transplantation.

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Liver transplantation in HCC patients currently represents 20-30% of the indications for liver transplantation in United States of America (USA) and Europe [6,7]. With a limited number of liver grafts, the need to obtain organs that are available has prompted the maintenance of selection criteria has prolonged the waiting period. This results in tumor progression to an extent beyond the transplantable criteria, leading to a patient's removal or dropout from the waiting list. In most countries, liver donor living transplantation (LDLT) has been suggested due to shortage of organ availability and increased waiting time [8]. The strong benefit with LDLT would be shorten recipients' time to surgery and thereby preventing disease progression. Further it also reduces the reducing the number of recipients on the deceased donor waiting list. Several previous studies have reported conflicting results with respect to recurrence rates and overall survival after LDLT in HCC patients [9-13]. Two meta-analysis examined the outcomes including patient survival, recurrence-free survival, and recurrence rates at defined time points in HCC patients receiving a LDLT or a deceased donor liver transplantation (DDLT) [12,13]. In the first meta-analysis, no significant difference in the overall survival rates, recurrence-free survival rates and 5-year recurrence rates between LDLT and DDLT recipients [12]. These findings suggests that LDLT represents an acceptable option that does not compromise patient survival or increase HCC recurrence that DDLT. Second meta-analysis identified lower disease free survival after LDLT in patients with HCC compared with DDLT. However, HCC patients selected for LDLT may worse tumor biology than DDLT [13].

In Egypt, the incidence of HCC has been nearly doubled over the past decade and plagued with highest prevalence of HCV in the world, ranging from 6%-28% [14]. The prevalence of HCV infection in patients with HCC is nearly 80%. However, uncertainty regarding the outcomes of patients with HCC in LDLT is unclear. Therefore, we aimed to investigate the prognosis of LDLT as a definitive treatment of HCC in patients who met criteria of transplantation including the recurrence of HCC.

## 2 Methods

This is a retrospective analysis of liver transplanted patients in the department of hepato-pancreato-biliary (HPB) surgery, International Medical Center (IMC), Egypt from April 2013 to December 2016. During this period, 53 patients underwent LDLT. Hepatic focal lesions (FLs) were the indication of liver transplantation in all the cases. Preoperative records, operative data records, postoperative patients' files and from follow-up records of all the transplanted patients were collected. All their clinical and laboratory data documented in the charts were also collected.

1. *Preoperative data*: Demographic details of patients, disease indications, comorbidities, viral markers (HCV, HBV), blood group, abdominal ultrasound (number of focal lobes, size and site), Child-Pugh score, and model of end stage liver disease (MELD) score.

2. *Pre-transplant selection criteria for patients with HCC*: Milan criteria (single tumor ≤ 5 cm; or ≤ 3 tumors each ≤ 3cm; no vascular invasion and no distant metastases), UCSF criteria (single tumor ≤ 6.5 cm; or ≤ 3 tumors, none > 4.5 cm and total diameter ≤ 8 cm, no vascular invasion).

3. *Operative data*: size and number of hepatic FLs, size of FLs, vascular invasion, portal vein thrombosis (PVT)-thrombactormy or venous graft, hepatic adhesions, type of anastomosis, use of venous graft of recipient liver, graft weight, graft recipient weight ratio (GRWR) (< 0.8, or > 0.8), cold ischemia time (CIT), warm ischemia time (WIT) and total operative time (TOT).

4. *Post-operative data*: Cytology of ascetic fluid, number, size and distribution of focal lobes, presence or absence of tumor capsule, histological differentiation of cancer cells, microvascular invasion, standard immunosuppressive, steroids, anticoagulants and other postoperative drugs.

5. *Follow up after transplantation*: Patients were followed up regularly in IMC hospital. Routine laboratory investigations, abdominal ultrasound, computed tomography of abdomen and Doppler ultrasonography were performed regularly, liver biopsy (if necessary), post-transplant complications, and HCC recurrence rates were retrospectively reviewed. Special attention was given to recording the complications, total survival and tumor free survival, and cause of mortality in LDLT recipients.

## 3 Statistical analysis

Data were collected in a specialized data collection form and entered in the Statistical package for social sciences (SPSS, version 22.0; SPSS Inc., Chicago, IL, USA) for windows. Data were expressed as mean with standard deviations (SD) and range, and frequencies as appropriate. Chi-square test and student t-test were used to measure the association between the quantitative variables. Multinomial logistic regression model was used to give adjusted odds ratio (OR) and 95% confidence interval to investigate the effect of different factors on the recurrence of the malignancy. Kaplan-Meier analysis was done to measure the patients' survival rates. A *p*-value of <0.05 was considered statistically significant.

## 4 Results

### *4.1 Sociodemographic data of the recipients*

From April 2013 to December 2016, 53 patients underwent LDLT in the International Medical Center, Cairo, Egypt. The mean age of the patients 52.9± 57 (ranged from 40 – 63.2 years), more than ninety percent were male (94.3%) and with mean BMI of 24.5±3 (range: 19-32). Nearly three-forth (73.6%) had comorbidities such as Diabetes (n=16), regular

sclerotherapy of the malignant nodules (n=9) and diabetes with bronchial asthma was noticed in two patients. The baseline characteristics of the LDLT recipients were summarized in Table 1.

**Table 1:** Baseline characteristics of the HCC patients underwent living donor liver transplantations (LDLT) (N=53)

| | **No (%)** |
|---|---|
| **Age (mean ± SD)** | 52.9± 57 (range: 40 – 63.2) |
| **Sex (male)** | 50 (94.3%) |
| **Weight (mean ± SD)** | 79 ± 10.6 (range: 58 – 104) |
| **Height (mean ± SD)** | 173.8 ± 6.2 (range: 160-187) |
| **BMI (mean ± SD)** | 24.5±3 (range: 19-32) |
| ***Donor-recipient relation*** | |
| **Unrelated** | 43 (81.1%) |
| **Related** | 10 (18.9%) |
| ***Comorbidites (n=39)*** | |
| **Diabetes mellitus** | 16 (30.2%) |
| **Regular sclerotherapy (RST) of the malignant nodules** | 9 (16.9%) |
| **Diabetes and RST** | 6 (11.3%) |
| **Diabetes with bronchial asthma** | 2 (3.8%) |
| **Diabetes with hypertension and RST** | 1 (1.9%) |
| **Diabetes with hypothyroidism** | 1 (1.9%) |
| **Diabetes with RST and bronchial asthma** | 1 (1.9%) |
| **Portal vein thrombosis** | 1 (1.9%) |
| **RST and bronchial asthma** | 1 (1,9%) |

*HCC: hepatocellular carcinoma; SD: standard deviation

**Table 2:** Pretransplant Clinical and laboratory data of the recipients (N=53)

| ***Clinical features*** | ***No (%)*** |
|---|---|
| *Viral markers* | |
| Hepatitis C virus | 46 (86.8%) |
| Hepatitis B virus | 1 (1.9%) |
| Hepatitis C + Hepatitis B virus | 6 (11.3%) |
| *Blood group* | |
| A | 19 (35.8%) |
| B | 13 (24.5%) |
| AB | 7 (13.2%) |
| O | 14 (26.4%) |
| *Donor blood group* | |
| Identical | 33 (62.3%) |
| Compatible | 20 (37.7%) |
| ***Laboratory features*** *(mean± SD)* | |
| Total bilirubin (mg/dl) | 3.0± 3.4 (range: 0.8 - 21.9) |
| AST (u/l) | 88.8 ± 63.1 (range: 20 – 492) |
| ALT (u/l) | 59.5 ± 45.8 (range: 13 – 367) |
| Albumin (g/dl) | 2.8 ± 0.6 (range: 1.6 – 4.4) |
| INR | 1.5 ± 0.4 (range: 1 - 2.6) |
| Creatinine (mg/dl) | 0.8 ± 0.3 (range: 0.3 – 1.8) |
| Ascites (yes) | 40 (75.4%) |
| AFP (ng/ml) | 350.9 ± 920.6 (range: 0.35- 3218) |
| *Child-Pugh score* | |
| A | 9 (17%) |
| B | 22 (41.5%) |
| C | 22 (41.5%) |
| *MELD score* | 17.3± 6.1 (range: 8 – 35) |
| <20 | 34 (64.2%) |
| ≥20 | 19 (35.8%) |

AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR:

international normalization ratio; AFP: alfafetoprotein; MELD: model for end-stage liver disease.

**Table 3:** Operative details of the LDLT recipients (N=53)

| Characteristics | n (%) |
|---|---|
| ***Type of graft*** | |
| **Right lobe** | 52 (98.1%) |
| **Right lobe + MHV** | 1 (1.8%) |
| ***Graft weight (gm)**** | 1200 ± 300 (range: 800 – 1800) |
| ***GRWR (%)**** | 1.2 ± 0.3 (range: 0.8- 1.8) |
| ***Number of hepatic vein anastomosis*** | |
| **1** | 28 (52.8%) |
| **2** | 17 (32.1%) |
| **3** | 8 (15.1%) |
| ***Number of portal vein anastomosis*** | |
| **1** | 45 (84.9%) |
| **2 (y-shaped graft)** | 8 (15.1%) |
| ***Portal vein thrombosis*** | 8 (15.1%) |
| ***Hepatic artery anastomosis*** | |
| **1** | 49 (92.5%) |
| **2** | 4 (7.5%) |
| ***Number of bile duct anastomosis*** | |
| **1** | 31 (58.5%) |
| **2** | 20 (37.7%) |
| **3** | 2 (3.7%) |
| ***Anhepatic phase (h)**** | 4 ± 1.1 (range: 2 – 7) |
| ***CIT (min)**** | 60.8 ± 25 (range: 20 – 120) |
| ***WIT (min)**** | 53.3 ± 15.5 (range: 30 – 95) |
| **Total operative time (h)*** | 14.8 ± 2.5 (range: 8 – 23) |
| **Blood transfusion (unit)*** | 5.8 ± 6.4 (range: 0 – 28) |
| **Plasma transfusion (unit)*** | 8.4 ± 10.7 (range: 0 – 53) |

MHV- middle hepatic vein; GRWR- graft-recipient weight ratio; *mean± standard deviation; CIT: cold ischemia time; WIT- warm ischemia time.

## *4.2 Pretransplant clinical and laboratory data*

The clinical and laboratory investigations performed before 24 hours of transplantation were summarized in Table 2. HCV was identified as dominant viral marker (86.8%) of LDLT transplants, and have identical donar donor blood group (62.3%). Majority of the LDLT recipients are of Child-Pugh score B and C, and more than three-fifth (64.2%) were with MELD scores <20.

## *4.3 Operative details*

Data regarding the operative details and the pathology of the explanted liver includes right lobe graft in almost all LDLT recipients except one patients with a mean graft recipient weight of 1200 ± 300 grams ranging from 800 – 1800 grams and the mean graft-recipient weight ratio of 1.2 ± 0.3%. Twenty eight patients (52.8%) underwent at least one hepatic vein anastomosis, one portal vein anastomosis in forty five patients (89.9%), single hepatic artery anastomosis considered in 92.5% LDLT recipients and at least one bile duct anastomosis was performed in 58.5% of patients. The mean operative time was 14.8 ± 2.5 hours and an average of 5.8 ± 6.4 units of blood and 8.4 ± 10.7 units of plasma transfused during LDLT (Table 3).

**Table 4:** Findings of post-operative specimens in LDLT recipients

| Characteristics | n (%) |
|---|---|
| ***Histopathological liver nodules*** | |
| Well-diff HCC | 43 (81.1%) |
| Mod-diff HCC | 1 (1.9%) |
| Dysplastic nodule | 6 (11.3%) |
| Complete focal necrosis | 1 (1.9%) |
| Partial focal Necrosis | 2 (3.8%) |
| ***Site of hepatic focal lesions*** | |
| Right | 36 (67.9%) |
| Left | 7 (13.2%) |
| Both | 10 (18.9%) |
| ***Number of hepatic focal lesions*** | |
| Single lesion | 26 (49.1%) |
| Two lesions | 22 (41.5%) |
| Three lesions | 5 (9.4%) |
| ***Size of hepatic focal lesions*** | |
| < 3 cm | 18 (34%) |
| ≥ 3 cm | 35 (66%) |
| ***Size of hepatic focal lesions at 5 cm*** | |
| <5 cm | 47 (88.7%) |
| ≥ 5 cm | 6 (11.3%) |
| ***Milan criteria*** | |
| Within | 42 (79.2%) |
| Beyond | 11 (20.8%) |
| ***Tumor grade of liver nodules*** | |
| Grade I | 13 (24.5%) |
| Grade II | 24 (45.3%) |
| Grade III | 6 (11.3%) |
| Complete necrosis | 10 (18.9%) |

**Table 5:** Major post-operative complications in LDLT recipients

| Complications | n (%) |
|---|---|
| ***Transplant rejection*** | |
| **acute** | 3 (5.7%) |
| **chronic** | 6 (11.3%) |
| **Biliary** | 4 (7.5%) |
| ***Infection*** | |
| **wound sepsis** | 2 (3.8%) |
| **chest** | 1 (1.9%) |
| ***Vascular*** | |
| **MHV thrombosis** | 1 (1.9%) |
| **Bleeding** | 1 (1.9%) |
| **Intracranial hemorrhage** | 1 (1.9%) |
| **HCV recurrence** | 19 (35.8%) |
| **HCC recurrence** | 7 (13.2%) |

MHV- middle hepatic vein; HCV- hepatitis c virus; HCC- hepatocellular carcinoma.

## *4.4 Explanted liver findings*

Histopathological examination revealed well-differentiated hepatocellular carcinoma in forty-three (81.1%) LDLT recipients, 68% had right side hepatic focal lesions, and nearly ninety percent (88.7%) had hepatic focal lesions less than 5 cms and were within-Milan criteria (79.2%) (Table 4).

**Table 6:** Survival and mortality rates in LDLT recipients

| Survival rate | n (%) |
|---|---|
| **One year** | 34 (64.1%) |
| **Three years** | 31 (58.5%) |
| **Five years** | 21 (39.6%) |
| **Mean survival duration (months)** | 71.7 (95% CI: 55-88.5) |
| **Median survival duration (months)** | 52 (95% CI: 9.25-94.6) |
| **Mortality** | |
| ***After one year*** | **19 (35.8%)** |
| **Hepatic cause** | 6 (11.3%) |
| **Non-hepatic cause** | 13 (24.5%) |
| ***After three years*** | **22 (41.5%)** |
| **Hepatic cause** | 8 (15%) |
| **Non-hepatic cause** | 14 (26.4%) |
| **After five years** | **32 (60.3%)** |
| **Hepatic cause** | 14 (26.4%) |
| **Non-hepatic cause** | 18 (34%) |

95% CI: conference interval

### *4.5 Post-operative complications in LDLT recipients*

The most frequently encountered post-operative complications in LDLT recipients are presented in Table 5. A fraction of patients (n=3) faced acute transplant rejection, three developed infections and another three experienced vascular complications. However, nineteen (35.8%) of LDLT recipients had recurrence HCV and HCC was reoccurred in seven (13.2%) LDLT recipients.

### *4.6 Survival and mortality in LDLT recipients*

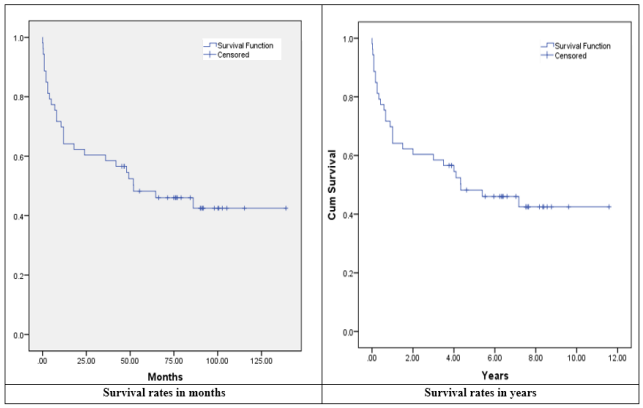


**Figure 1:** Kaplan-Meier survival plot showing Overall survival after liver transplantation

Nineteen patients (35.8%) died within one year after surgery, after three years twenty two patients died (41.5%) and another thirty two patients died after five years of LDLT (Table 6). The mean survival time was 71.7 (95% CI: 55-88.5) months and median survival duration was 52 (95% CI: 9.25-94.6). The cumulative survival rates in LDLT recipients were shown in Figure 1.

## 5 Discussion

HCC is one of the few major cancer showing unfavorable trends in several parts of the world and the mortality was two-to five-folds higher in North Asia [15]. Liver transplantation remained as the only effective and available therapy for patients with end-stage liver disease. The current shortage of organ and absence of DDLT program in Egypt had led to a consequent increase in the number seeking LDLT. With a higher incidence of HCC cases in Egypt (25.6/100,000) and the most HCV-related HCC cases has raised dramatically in Egypt [16,17]. The clinical outcomes of the 53 patients reported in this study may provide a strong source of evidence of patients with HCC undergoing LDLT in Egypt.

The knowledge and understanding obtained from outstanding clinical studies have paved the way to the creation of the criteria for liver transplantation and guidelines that are used today. In the present study 62.3% of the patients were within imaging Milan criteria and remaining were beyond-Milan criteria according to pre-transplant imaging study. So patients that were within-Milan criteria in the present study were less than what was reported by *Mazzaferro et al.* [4] study in 1996, that 43 patients (81.1% of the total patients) whom met the predetermined

criteria for the selection of small hepatocellular carcinomas at pathological review of the explanted liver. Hence, international recommendations also recommended Milan criteria as the benchmark not only for selecting HCC patients for liver transplantation, but also for future comparisons of expanded selection criteria and refinements.

The prognostic evaluation of HCC patients includes both disease extent assessment and other relevant prognostic variables such as liver functions. In *Yang et al.* study [18], they discussed the revised scoring system which includes tumor size, tumor number, and pre-transplant serum AFP level as prognostic factors. They defined that HCC patients with 3 to 6 points and 7 to 12 points were transplantable and non-transplantable respectively with overall 1 and 5 year survival rates of 81.3% and 67.0%, respectively. By application of this scoring system in the present study, it revealed that 7 patients had scores ≥7 so, they should have been non-transplantable according to this revised scoring system, and 44 patients had scores ≤ 6 so, they were transplantable. The described scoring criteria [18] could be used effectively to expand liver transplantation selection criteria for patients with HCC without adversely affecting outcome in the LDLT setting, and the described scoring criteria predict tumor recurrence better than the Milan or UCSF criteria. However, because the sample size used in this study was relatively small, the described scoring system requires further verification by a large-scale study.

The main concern after liver transplantation for HCC is the risk of tumor recurrence; in our study seven patients developed HCC recurrence. HCC recurrence was seen mainly in first 2 years with range (17-29 months) postoperatively; they had a median total survival of 2.5 years, and less than 1 year survival from the time of diagnosis. Similar results were noticed in *Hollebecque et al.* study [19], where HCC recurrence occurred in 8–20% of LDLT recipients and HCC recurrence seen within the first 2 years after liver transplantation, and is associated with a median survival of less than 1 year (7–18 months) from the time of diagnosis. However, several findings showed that most recurrences are associated with systemic tumor dissemination, thus retransplantation is not indicated [20-22]. In that minority of cases where localized recurrence is detected, however, direct treatment by surgery or ablation warrants consideration.

The total survivors after 1 year in our sample were 34 (64.15%) patients, after 3 years 31 (58.49%), and after 5 years were 21 (39.62%). Previous studies have reported conflicting results with respect to recurrence rates and overall survival after LDLT. Several studies comparing deceased donor liver transplantation (DDLT) and LDLT for HCC. Despite higher recurrence rates in these three studies [23-25], the overall survival rates of LDLT for HCC compared to DDLT in all studies were not inferior. One could argue that this difference would eventually translate into a lower long-term survival in the LDLT groups. A recent analysis of 60 Egyptian adult patients underwent right lobe LDLT for cirrhosis complicated by HCC revealed, the median follow-up was 39.5 months. Overall 1-, 3-, and 5-year survival rates were 98.3%, 93.5%, and 71.4%. Overall disease-free survival rates at 1, 3, and 5 years were 96.6%, 93.5%, and 64.2% [26]. Efforts need to be focused to decrease posttransplant liver HCV recurrence rates and to further improve overall survival in LDLT for HCC.

## 6 Conclusion

Through this study we identified that the success of LDLT in HCC patients rely on a stepwise approach that incorporates morphological and biological criteria of the tumor. Major vascular invasion, massive infiltrative type, ruptured HCC and distant metastasis are to be considered as absolute contraindications for transplant

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