

Prognostic Factors of Recurrence and Survival After Living-donor Liver Transplantation for Hepatocellular Carcinoma: Mansoura Experience

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ABSTRACT

Abbreviations:

LDLT: living-donor liver transplantation;
HCC: hepatocellular carcinoma;
 α -FP: alpha-feto protein;
ICU: Intensive Care Unit.

Background: To evaluate our center experience of living-donor liver transplantation (LDLT) in hepatocellular carcinoma (HCC) patients regarding recipients' mortality and morbidity and study the various prognostic factor affecting tumor recurrence and its impact on patients' survival.

Methods: This is a retrospective study including patients who underwent LDLT for HCC complicating liver cirrhosis in period from 2004 to 2020.

Results: The study included 252 patients. The mean age was 52 ± 6 years. All patients had underlying liver cirrhosis with hepatitis C virus in 241 patients (95.6%). The mean MELD score was 14 ± 4 and mean alpha-feto protein (α -FP) 73 ± 178 ng/ml. 138 patients (54.8%) subjected to preoperative loco-regional therapy. The patients received right hemi-liver graft without the middle Hepatic vein. The mean graft weight was 911 ± 181 gm and mean GRWR 1.9 ± 0.3 . Morbidity occurred in 86 patients (34.1%). Mortality occurred in 71 patients (28.1%). The mean follow-up duration ranged from 6 – 173 months. The 1-, 3-, and 5-year disease-free survival rate was 93%, 85%, and 78%, respectively. Multivariate analysis shows that the only significant factor for tumor recurrence are vascular invasion α -FP > 200 ng/ml.

Conclusion: LDLT solve the problem of organ shortage and dropout of the list, however, recurrence of the tumors, still a major problem affecting recipients' survival.

Key words: hepatocellular carcinoma, living-donor liver transplantation, tumor recurrence

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the 3rd leading cause of mortality worldwide (1,2). The incidence is

increasing worldwide ranging between 3-9% annually. This is attributed to increase prevalence of hepatitis virus B & C infection. In Egypt, about 7.2 % of chronic liver disease patients due to hepatitis C virus develop HCC (3). Males are more commonly affected by HCC with male : female ratio of 5 : 1 (4).

Liver transplantation now becomes the standard therapy for patient with early stage HCC. Liver transplantation can treat both tumor with the underlying liver disease. In 1996, Mazzafero et al proposed Milan criteria that restrict liver transplantation to patient with single tumor < 5 cm or 2-3 tumors < 3 cm without major vascular invasion or extra hepatic spread. With this careful selection, liver transplantation achieved good survival rates with 4 years patient survival of 75% and recurrence rate <10 % which is nearly equal to patients transplanted without HCC (5).

Despite the good results achieved with the application of Milan criteria, it is so restrictive and many patients who can get benefit from transplantation are unfairly excluded (5).

In the era of living-donor liver transplantation (LDLT) many high-volume transplantation centers used to extend the criteria beyond the Milan criteria as UCSF, Tokyo criteria (5-5 rule) & up to 7 criteria (6). Also, many Japanese centers used to transplant patients with tumors of any size, any number, provided that no vascular invasion or extra hepatic spread (7). Such expansion of the criteria has shown good outcomes in selected patients. Also, it helps to solve the problem of organ shortage with available donors, so decrease the waiting time and prevent progression of the disease (8).

The aim of the current study is to evaluate our center experience of LDLT in HCC patients regarding recipients' mortality and morbidity and study the various prognostic factor affecting recurrence of the tumor and its impact on patients' survival.

MATERIALS AND METHODS

This is a retrospective study conducted on patients who underwent LDLT for HCC complicating liver cirrhosis at Gastro-Intestinal Surgery Center, Mansoura University in period from January 2004 to January 2020.

Preoperative assessment

Preoperative workup had been described elsewhere (9,10). To summarize, potential recipients were evaluated in four consecutive phases. The first phase

included laboratory and radiological evaluation, and consultation for anesthetic fitness. The second phase included cardiological and neurological evaluation, and disease specific evaluation as autoimmune markers and magnetic resonance cholangio-pancreatography. The third phase included endoscopic evaluation. The final phase included routine consultations to excluded possible hidden septic foci.

All patients underwent contrast enhanced computerized axial tomography with revision of the tumor burden with expert radiologist as regards the number and the size of each nodule. Patients who underwent locoregional therapy were included in the study and the tumor burden was calculated without deduction of the ablated areas. Patients with extrahepatic metastases or macrovascular invasion to the main portal vein or its first order branches were not accepted for transplantation. Patients with tumors beyond Milan criteria (3) were accepted on a case-by-case basis. Patients with large HCC more than 6.5 cm, either solitary or part of multifocal HCC, were not accepted unless downstaged with good response for 3 months prior to transplant. Good response was judged based on drop of alpha-feto protein (α FP) levels and absence of newly developed lesions.

Postoperative care

Intensive care unit care

After the surgical procedure, all recipients were transferred to the intensive care unit (ICU) for monitoring of the laboratory and radiological findings. Recipients were encouraged to start oral fluids and ambulation on the third postoperative day. Afterwards, recipients were transferred to the ward on the fifth postoperative day or afterwards depending upon the postoperative clinical improvement.

Radiological Evaluation

Doppler ultrasound evaluation was performed routinely once daily during the first postoperative week, day after other during the second and third weeks and before hospital discharge. After discharge, doppler ultrasound was performed once weekly during the following 2 months.

Follow-up

The recipients were followed up in the outpatient clinic after discharge. Follow up visits were more focused during the first 3 months then on monthly basis afterwards or on patient's demand.

Follow-up visit included detailed clinical evaluation, detailed laboratory evaluation including trough level of immunosuppression drugs, and evaluation of hepatic vasculature by doppler ultrasound.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS) software (IBM, Chicago, IL, USA, version 20). Categorical variables were addressed as number and percentage, while continuous variables were addressed as median and range. Survival outcomes were calculated by the Kaplan-Meier method, and comparison between the different groups was done by Log-rank test. A p value less than 0.05 was considered statistically significant.

RESULTS

Our study included 252 patients transplanted for HCC out of total 750 patients transplanted during the study period.

Patients demographic data

The study included 230 males (91.3%) and 22 females (8.7%). The mean age was 52 ± 6 years (range: 32 - 65). All patients had underlying liver cirrhosis with hepatitis C virus in 241 patients (95.6%), hepatitis B virus in 6 patients (2.4%), both in 4 patients (1.6%), and cryptogenic cirrhosis in one patient (0.4%). Most of the patients belong to child B and C cirrhosis as shown in *table 1*.

Tumor characteristics

65.5% of the patients fulfill the Milan criteria, 16.7% within the extended Milan criteria, and 17.8% beyond both Milan and extended Milan criteria. MELD score ranged from 6-27 with mean 14 ± 4 . α -FP ranged from 1.2 - 1283 ng/ml with mean 73 ± 178 ng/ml as shown in *table 1*. 138 patients (54.8%) subjected to preoperative loco-regional therapy in form of radio-frequency ablation, trans-arterial chemo-embolization, or both either for downstaging of the tumor or to stop progression of the tumor during waiting period. The mean interval between loco-regional therapy and liver transplantation was 6 ± 5 weeks (range: 1.5 – 39 weeks) as shown in *table 1*.

Graft type and volumetry

The patients received right hemi-liver graft without the middle Hepatic vein. The mean graft weight was 911 ± 181 gm (range: 498 – 1521 gm). The mean graft to

Table 1 - Demographic data and Tumor characteristics

Variable	Data
Age (years)	52 ± 6 (32 - 65)
Sex	
• Male	230 (91.3%)
• Female	22 (8.7%)
Etiology of liver cirrhosis	
• HCV	241 (95.6%)
• HBV	6 (2.4%)
• Both	4 (1.6%)
• Cryptogenic	1 (0.4%)
Child Pugh Classification	
• A	54 (22%)
• B	109 (43%)
• C	89 (35%)
MELD score	14 ± 4 (6 – 27)
Alpha feto protein (ng/ml)	90 ± 204 (1.2 – 1283)
Tumor size	
Mean $\pm$ SD (Range) (cm)	4.8 ± 3 (1 – 15.5)
• Less than 5 cm	166 (65.9%)
• More than 5 cm	86 (34.1%)
Tumor criteria	
• Milan	165 (65%)
• Extended Milan	42 (16%)
• Beyond both	45 (17%)
Previous treatment	138 (54.8%)
• RFA	22 (15.5%)
• TACE	82 (59%)
• Both	28 (20 %)
• Liver resection	6 (4.3 %)
• None	114 (46.2%)

recipient weight ratio (GRWR) 1.9 ± 0.3 gm (range: 0.81 – 1.99).

Morbidity and mortality

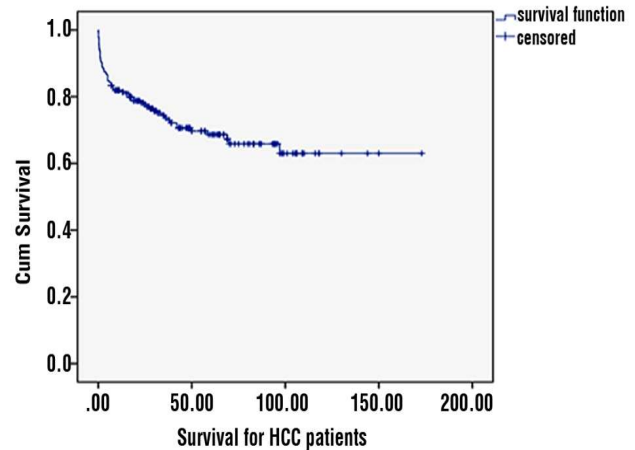
No morbidities occurred in 95/252 patients (37 %). Morbidity occurred in 86 patients (34.1%) as shown in *table 2*. Biliary complication represents the most common complication and occurred in 38 patients (15.1%) in the form of leak, biloma, and stricture. Bilomas are treated with tube drainage or ERCP& stent, while strictures are treated either with endoscopic balloon dilatation & stenting if failed surgical reconstruction can be done. Mortality from biliary complication occur in 2 patients (5.3%).

Other complications as acute cellular rejection renal impairment, recurrent HCV are responding to conservative medical treatment with no long-term morbidity.

Mortality occurred in 71 patients (28.1%). Early mortality occurred in 31 patients (12.4%), while late mortality occurred in 40 patients (16.1%) mostly related to tumor recurrence which occurred in 33 patients in a period ranging from 4 month to 6 year. Mortality from recurrence occurred in 21/33 patients (63.9%).

Table 2 - Morbidities after liver transplantation

Variable	Data
Biliary complications	38 (15.1%)
Acute rejection	14 (5.5%)
Recurrence HCV	8 (3.2%)
Renal impairment	6 (2.4%)
Neuro toxicity	6 (2.4%)
Metabolic syndrome (obesity)	1 (0.4%)
Pleural & Pericardial Effusion	2 (0.8%)
Incisional hernia	1 (0.4%)
Chronic rejection	1 (0.4%)
Hepatic artery thrombosis	1 (0.4%)
Chest infection	6 (2.4%)
Portal vein thrombosis	1 (0.4%)
Bleeding varices	1 (0.4%)
Acute myocardial infarction	1 (0.4%)

**Figure 1 - Disease free survival of all study cases**

Tumor recurrence

The mean follow-up duration ranged from 6 – 173 months. The 1-, 3-, and 5-year disease-free survival rate was 93%, 85%, and 78%, respectively as shown in *fig. 1*.

Factors affecting the tumor recurrence

Multiple factors are evaluated for their impact on tumor recurrence:

- Single & multiple tumor:

Multiple tumor had significant higher rate of recurrence 24.5% compared to 7.3% in single tumor as shown in *Table 3*.

- Milan criteria:

Also, tumor beyond Milan had significant Higher rate of recurrence 21.5% compared to 11.3% recurrence rate within Milan as shown in *table 3*.

- Pathology grading:

Post-transplant pathological grading recurrence rate was 12.1% in grade I tumors while it was 26.2% in grade II as shown in *table 3*.

- Micro-vascular invasion:

Micro-vascular invasion is a postoperative finding and its presence micro-vascular invasion is associated with high incidence of tumor recurrence 33 % compared to 9.7 % in patient without micro-vascular invasion as shown in *table 3*.

- Alpha-feto protein:

Also, in this study pre transplant α -FP > 200 ng/ml associated with high rate of recurrence as shown in *table 3*.

- Loco-regional therapy:

In this study 138 patients who treated with pre-

Table 3 - Prognostic factors affecting the tumor recurrence

Factors	No recurrence	Recurrence	P value
Number			0.004
• Single	123 (48.8%)	9 (6.2%)	
• Multiple	98 (38.8%)	24 (24.5%)	
Tumor character			0.001
• Within Milan	142 (56.3%)	16 (11.5 %)	
• Within UCSF	37 (14.7%)	2 (5.4 %)	
• Beyond both	42 (16.7%)	15 (35.7%)	
Tumor grade			0.04
• I	175 (69.4%)	21 (8.3%)	
• II	41 (16.2%)	11 (4.4%)	
• III	4 (1.6%)	1 (0.4%)	
Microvascular invasion			0.002
• Negative	177 (70.2%)	17 (6.7%)	
• Positive	44 (17.4%)	15 (5.9%)	
Alpha feto-protein			0.001
• Less than 200	200 (79.3%)	23 (9.1%)	
• More than 200	21 (8.3%)	10 (3.9%)	

operative loco-regional therapy have higher rate of tumor recurrence compared to 114 patients not receive loco regional treatment as shown in *table 3*.

Multivariate analysis shows that the only significant factor for tumor recurrence are vascular invasion α -FP>200 ng/ml

Survival

Also, we study the various factors that have impact on the survival rate:

- Milan criteria:

Patients beyond Milan criteria have a significant lower median survival as shown in *table 4*.

- Tumor size:

166 patients with tumor less than 5 cm have a better median survival (112 ± 69 m) compared to 88 patients with tumor > 5 cm which have lower median survival (80 ± 6.7 m) but the P. value is statistically insignificant ($P = 0.543$) as shown in *table 4*.

- Tumor number

Median survival is nearly equal and not statistically significant between single and multiple tumor as shown in *table 4*.

- Tumor differentiation

195 patients with grade I tumor have statistically better median survival, compared to undifferentiated tumor (GII & GIII) as shown in *table 4*.

- Micro vascular invasion

Post-transplant micro vascular invasion was +ve in 44 patients, with statistically lower median survival 66 ± 2 m compared to 208 patients with -ve micro

vascular invasion which have statistically better median survival 124 ± 7 m, ($P = 0,002$) as shown in *table 4*.

- Alpha Feto-protein

23 patients with pre transplant α FP level more than 200 ng/ ml have statistically lower median survival 30 ± 6 M compared to 128 ± 9 M median survival in 229 patients with α FP level < 200 ng/ml, ($P=0.001$) as shown in *table 4*.

- Local regional Treatment

In the current study 138 patients subjected to per operative loco regional treatment as a bridge to transplantation does not achieve increase in survival rate compared to untreated group as shown in *table 4*.

DISCUSSION

Hepatocellular carcinoma is a major health problem worldwide and it is one of the major indications for liver transplantation as it eliminates tumor & cure the underlying liver disease. However, the main concern after liver transplantation is the risk of tumor recurrence and its impact on survival, it is estimated that the rate of recurrence occurred in 8-20 % (11) and usually occurred in the first 2 years (7 – 18 month) & 5 years survival reported to be 63 – 80 % (12,13). So, every effort must be made to decrease recurrence rate and improve the survival. In this study, we discussed the various prognostic factors that affect the rate of recurrence and its impact on survival and compare them with other current literature.

Table 4 - Prognostic factors affecting survival

Factors	Number (Percentage)	Median survival (month)	P value
Tumor character			0.048
• Within Milan	142 (56.3%)	139 ± 7	
• Within UCSF	37 (14.7%)	114 ± 12	
• Beyond both	42 (16.7%)	64 ± 7	
Tumor size (cm)			0.876
• Less than 5 cm	166 (65.9%)	112.2 ± 6.9	
• More than 5 cm	86 (34%)	80.2 ± 6.7	
Number			0.157
• Single	141 (56%)	125 ± 6	
• Multiple	111 (44%)	122 ± 9	
Tumor grade			0.037
• I	195 (78%)	111.5 ± 5.4	
• II	50 (20%)	78 ± 15	
• III	5 (2%)	48 ± 82	
Microvascular invasion			0.002
• Negative	44 (17.5%)	63 ± 9	
• Positive	208 (82.5%)	124 ± 6	
Alpha feto-protein			0.001
• Less than 200	229 (90.9%)	125 ± 6	
• More than 200	23 (9.1%)	43 ± 2	

In our study multiple tumor had significant higher rate of recurrence and this is in concern with Zavaglia et al 2005 who proved that the number of tumor more than two & located in one lobe has a good curative effect early after liver transplantation, but the recurrence and metastasis of the tumor will greatly affect the long term survival (14). Also, Mazzafero et al 2009 and many transplant centers proved that the size and numbers of the tumor have a combined effect on tumor recurrence after transplantation (15). Germani et al 2011 analysis of fifteen study over 4575 patients evaluating the impact of number of tumor nodule on overall survival, disease free survival & recurrence after liver transplantation concluded that patients with > 3 tumor have a high risk of death when compared to those with < 3 tumor, as the number and distribution of the tumor reflect the biological behavior of malignant tumor invasion in certain extent (16). Also, in our study patient beyond Milan criteria has a significant higher rate of recurrence & low median survival.

Although expansion of the Milan criteria has shown a good outcome in selected individuals and many high-volume centers in Japan & Hongkong have changed them criteria, before 2002 radiological Milan criteria were used. From 2002-2005, the selection criteria were expanded to much, the radiological university of California San Francisco (tumor < 6.5 cm or 2-3 tumor < 4.5 cm & total No < 8 cm). From 2006 onward the selected patient with more advanced HCC were enrolled for living-donor liver transplantation according to the following exclusion criteria, no vascular invasion, no evidence of distant metastasis or diffuse HCC (17). However this extended criteria which include size & number of the tumor are devoid of biological marker and pathological differentiation of liver tumor which accurately had reflection on the prognosis. Until 2006 where the transplantation in Zhejans University proposed the Hangzhou criteria which defined as tumor < 8 cm with no portal vein thrombosis, or tumor < 8 cm and α -FP < 400 mg/ ml & there tumor biopsy grade I & II Hangshow criteria considered the biological behavior of HCC and expand size of the tumor and proved that tumor achieve these criteria has no significant difference from Milan criteria (18). In our study multivariate analysis show that the only significant factor for tumor recurrence was vascular invasion and α -FP > 200 ng/ ml and also associated with statistically lower median survival, therefore α FP is well established surrogate for tumor biology as it correlates with Histological grading and vascular invasion.

Normal level of α -FP generally less than 20 ng/ml. In patients with primary hepatocellular carcinoma the

level may significant increase & this may be due to the ability of primary liver malignant tumor to restore synthesis of α -FP. Many different researches report different value of α -FP as 100, 200, 400 & 1000 ng/ml (19). However, more report studies show the pre-operative α -FP > 400 ng/ml was independent risk factor for tumor recurrence (20).

Also, Xu et al 2008 in his study over 96 patients was found that HCC recipient with pre transplant α -FP > 400 ng/ml were associated with high incidence of tumor recurrence. So pre transplant α -FP level should be seriously considered before liver transplantation (21), and a large number of studies have highlighted the importance of increased α -FP value for recurrence risk and it is importance to note that increase α -FP is not the only risk factor not only for patient beyond, but also in patient within Milan criteria. Also, patient with persistent elevation of α -FP level (>15 ng/ml) after loco-regional therapy should be considered contraindication for liver transplantation even in patient within Milan criteria (22,23).

Numerous recent studies have confirmed that poor differentiation & microvascular invasion are associated with recurrence in patients within and beyond various transplant criteria (24-26). Mazzafero et al 2009 proved that 5 years survival is 33 % in patient with post-transplant micro-vascular invasion companied to 64 % with negative micro-vascular invasion (15).

So, absence of this risk factor may justify liver transplantation in patient with large tumor as shown by Toronto experience which allow liver transplantation for patient with any number, any size of HCC lesion provided no vascular invasion or extra hepatic spread (27). However, micro-vascular invasion is a post-operative finding since biopsy is rarely performed for hepatic focal lesion in cirrhotic patient for fear of bleeding, leak or tumor spread. Also, assessing tumor grading & micro vascular invasion is not always available even if biopsy is performed as tumor differentiation & micro-vascular invasion can be missed in multi-locular tumor. Therefore α -FP protein level is a good indicator for tumor biology as it correlates with histological grading and vascular invasion (20,23) and if micro-vascular invasion is found in post-explant liver. Immune suppressive therapy should be modified to minimize tumor recurrence (28).

In our study, micro-vascular invasion detected in 44 post explants recipient and associated with significant high recurrence rate and lower medical survival.

Loco-regional therapy used to stop progression of the disease and prevent dropout the list during waiting period which reported to be 20% (29), also for down staging of the tumor that allow many patient to get

benefit from exceeding Milan criteria (30), and patient with complete response to loco-regional therapy has overall survival of 5 years 64% (31). However, patient with Milan but not responding to loco-regional therapy has poor prognosis compared to patient beyond Milan criteria but responding to loco-regional therapy (32). Also, Pompili et al shows that tumor progressing during the waiting period which should be at least 3 months despite loco-regional therapy is a strong predictor for HCC recurrence even if tumor stage is within Milan criteria (33).

Our study shows that group of patients subjected to LRT have a higher rate of recurrence than untreated patients also the treated group does not achieve any increase in overall survival, also there is no randomized study to prove any benefit for pre-operative LRT in prevention or reduction of post liver transplant recurrence (34). A recent study by Le Surtel et al 2006 did not show any benefit for preoperative LRT, regarding post-operative LT survival (35). and a recent report shows that slope increase in AFP 15ng/ml per month is an indication of poor prognosis (36). Also recipient with elevated AFP who were treated with LRT but not decrease less than 15 ng/ml has increased risk of post transplantation tumor recurrence (37) and this could be attributed to the group subjected to loco-regional therapy have a large size with progressive tumor biology which is dictated by histological differentiation & micro-vascular invasion & both are strong predictors for tumor recurrence.

CONCLUSION

Hepatocellular carcinoma is the most common prevalent disease worldwide and carry high mortality rate. Surgical resection is a standard good line of treatment but only suitable for small numbers of patients, so liver transplantation is the only hope for cure of both tumor and underlying disease. LDLT solve the problem of organ shortage and dropout of the list, However, recurrence of the tumors, still a major problem reflected on overall survival. So, we need more studies of the biology of tumors in cirrhosis. Also, vascular invasion which have surrogate on tumor recurrence cannot be determined except after explants, so we need more pre-operative markers for the biological behavior of the tumor that able to predict the risk of recurrence & in order to get better selection of the recipient with less incidence of tumor recurrence and better survival.

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Conflicts of interest

All authors declare no conflicts of interest.

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Ethical statement

This study was approved by institutional review board and local ethical committee at the Faculty of Medicine, Mansoura University.

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