

## Single HCC with Compensated Liver: Best Surgical Strategy

H. Said<sup>1</sup>, Ahmed Khalil<sup>1</sup>, Ahmed Fathy Hilal<sup>2</sup>

<sup>1</sup>General Surgery Department, Faculty of Medicine, Ain Shams University

<sup>2</sup>Tropical Medicine Department, Faculty of Medicine, Ain Shams University

### ABSTRACT

**Aim of the work:** comparison of 1 year overall and recurrence free survival and complication between patients offered Living Donor Liver Transplantation (LDLT) and patients offered Liver Resection (LR) in management of single Hepatocellular carcinoma (HCC) less than 5cm in well compensated cirrhosis. **Type of study:** cohort prospective study. **Patients and method:** This study includes 36 patients who had surgical intervention for HCC between June 2013 and June 2016, sixteen patients underwent LDLT and 20 patients underwent LR. They were then followed for up to 1 year with record the outcomes and complications. This study was done in Ain Shams University Hospitals and Egypt Air Hospital. **Results:** Recurrence of HCC in the resection group occurred in 4 patients (20%) These were managed by radiofrequency (RF), Trans-arterial Chemoembolization (TACE), re-resection and best supportive care. In the transplant group, there was 1 case (6.2%) of HCC recurrence that was managed by sorafenib (P-value = 0.0431). Mortality in the transplant group occurred in 2 cases (12.5%), [ 3<sup>rd</sup> week and 10<sup>th</sup> month]. In the resection group, there was 1 mortality (5%) [4<sup>th</sup> week] (P-value = 0.418). The overall complication rate between LDLT and LR was nearly similar, but with a different pattern. In the transplantation group there were more vascular (12.5% Vs 0%) and biliary (18.8% Vs 5%) complications and also complications related to immune-suppressant like chest infection (18.8% Vs 5%) and renal impairment (6.2% Vs 5%). In resection group the main complications were related to liver decompensation (25% Vs 0%), hepato-renal syndrome, and biliary leak in major hepatectomy. **Conclusion:** LDLT is better than LR for single HCC < 5 cm regarding Disease free survival (DFS) with no difference in overall survival (OS) in short term follow up. Postoperative morbidity is nearly similar for both strategies as regard overall incidence but with a different pattern.

**Key Words:** Single HCC, Compensated Liver, Strategy

### INTRODUCTION

The diagnosis and treatment of HCC has progressed remarkably in the last years. Of the treatment options now available (alcoholization, radiofrequency ablation, chemoembolization, hepatic resection, and hepatic transplantation), only resection and transplantation, by theoretically removing all tumor tissue, can offer the chance of long-term survival or cure. Although both of them were applied with varying results in recent years, the optimal surgical treatment of hepatocellular carcinoma on well-compensated cirrhosis is still controversial. It is not yet possible to say which of them provides the better option in each individual case. The aim of this work is to compare 1 year overall and recurrence free survival and perio-operative complication in patients offered LDLT and those offered liver Resection in management of single HCC < 5cm in well compensated cirrhosis.

### MATERIAL AND METHOD

#### Patients:

This study is a cohort prospective analysis of 36 patients underwent surgical intervention for HCC between June 2013 and June 2016, sixteen of them underwent LDLT while the other 20 patients underwent liver resection. They were all followed for up to 1 year with recording the outcome and complications. This study was done at Ain Shams University Hospitals and Egypt Air Hospital

#### Inclusion criteria:

- The transplantation group includes patients with single HCC less than 5 cm.
- The resection group includes patients with single HCC between 3 and 5 cm or less than 3 cm not feasible for radiofrequency ablation.
- Patients with early stage liver disease, Child A or MELD score < 9.

**Exclusion criteria:**

- Patients with multiple HCC or single lesion larger than 5 cm.
- Patients with Child B or C or MELD score > 9.
- AFP more than 400 or rising titre
- Vascular invasion
- Patients with portal vein thrombosis (benign or malignant).
- Patients with combined liver-kidney transplant. -
- Patients with significant portal hypertension and need for major hepatectomy

**Preoperative work up:****Patients for transplant were subjected to:**

1. Full clinical assessment.
2. Laboratory investigations: CBC, coagulation profile, liver function tests, kidney function tests, lipid profiles, diabetes profile, serum electrolytes, viral markers and tumor markers, laboratory investigations for bilharzias, autoimmune and for metabolic liver disease.
3. Radiological investigations: Tri-phasic pelviabdominal CT with portography venography and arteriography, bone scan, and chest CT scan.
4. Endoscopy: upper GI and colonoscope.
5. Medical consultations: cardiological, chest, psychological, ENT, dental, gynecological consultations and others according to the patient's condition.
6. Calculation of MELD and Child score.

**Patients for resection were subjected to:**

1. Full clinical assessment.
2. Laboratory investigations: CBC, coagulation profile, liver function tests, kidney function tests, lipid profiles, diabetes profile, serum electrolytes, viral markers and tumor markers.
3. Radiological investigations: Tri-phasic pelviabdominal CT with portography, bone scan and chest CT scan.
4. Calculation of MELD score and Child classification.

**Post-operative workup:****Post-operative workup for transplantation:****Early work up:(1<sup>st</sup> 3 months):**

- Follow up labs and Doppler US daily for two weeks, then twice weekly for 2 weeks, then once weekly for 2 months.

**Later:(After 3 months):**

- Follow up labs and US every 2-4 weeks according to patient's condition.
- Follow up tumor markers every 3 months and Abdominal C.T. every 6 months.

**Post-operative workup for liver resection:****Early work up:(1st 3 months):**

- Follow up full labs first 3 days, then every other day for a week then weekly for a month then once every month for the next 2 months.

**Later:(After 3 months):**

- Follow up labs every month.
- Follow up tumor markers and US every 3 months and Abdominal C.T. every 6 months

**Stratification of patients between both group:**

- After discussion with patients and their families about advantages and disadvantages of living donor liver transplantation(LDLT) and liver resection (LR) patients had to decide to proceed in either way according to:
  - Acceptance of risk for the patient with liver resection and for recipient and donor with LDLT
  - If a medically and ethically accepted donor is available or not
  - Financial issues (this was an obstacle in early cases, but this issue was solved later on)

**Management of HCC pretransplant:**

A bridge therapy for HCC before transplantation was done only if prolonged waiting time was expected to avoid tumor progression. This was in the form of transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave or combined

**Protocol of immunosuppression:**

Immunosuppression: the standard is a combination of 2 drug groups calcineurin inhibitors (CNIs) and steroids.

High-dose intravenous corticosteroids were used in the immediate peri- and post-operative period and then tapered accordingly. In patients without renal dysfunction post-transplantation, CNIs were the mainstay of therapy with the long term goal of low levels of immunosuppression and minimization of medication. In patients with renal insufficiency, combination of low-dose CNI therapy and MFAs or a switch to mTOR inhibitors was done to preserve graft function and prevent further renal deterioration. Patients were

weaned off corticosteroids within 3 months, providing they do not have evidence of autoimmune disease or recurrent episodes of rejection.

This study involves follow up of 36 patients who underwent LDLT or LR at Ain-shams university hospitals and Egypt Air Hospital. These patient were classified into two groups:

1. Transplantation group
2. Resection group

Comparison between the 2 groups :

- Pre-operative data
  - Demographic data
  - Associated comorbidities
- Operative data
  - Biliary complications: stricture, leak
  - Vascular complications: thrombosis, stenosis
  - Systemic complications: cardiac, pulmonary, renal, psychological and neurological.
  - Need for re-operation
  - Post-operative infection
- Long term results
  - Overall survival
  - HCC Recurrence free survival

#### Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The comparison between the two groups with qualitative data was

done by using *Chi-square test* and/or *Fisher exact test* was used instead of Chi-square test when the expected count in any cell was found less than 5.

The comparison between two independent groups regarding quantitative data with parametric distribution was done by using *Independent t-test*.

The comparison between two independent groups regarding quantitative data with non-parametric distribution was done by using *Mann-Whitney test*.

*Kaplan Mayer survival analysis* was used to compare between the two studied groups regarding recurrence, mortality and perioperative mortality using *Log-Rank test*.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as follows:

- P > 0.05: Non-significant.
- P < 0.05: Significant.
- P < 0.01: Highly significant.

## RESULTS

This study compares between 16 cases having single HCC < 5cm who underwent transplantation and 20 cases having same disease who underwent liver resection.

**Table (1): Comparison between demographic data of the patients:**

		Trans-plantation group	Resection group	Independent t-test	
				T	P-value
Age	Mean ± SD	55.19 ± 6.48	56.20 ± 8.10	-0.406	0.687
	Range	38 – 65	40 – 69		
HBV	No	15 (93.8%)	18 (90.0%)	0.164	0.686*
	Positive	1 (6.2%)	2 (10.0%)		
HCV	No	2 (12.5%)	7 (35.0%)	3.531	0.171*
	Positive	14 (87.5%)	13 (65.0%)		
Alpha FP	Median (IQR)	16.4 (9.3 – 49.5)	20 (8.5 – 134)	-0.239	0.811•
	Range	6.5 – 220	4.7 – 378		

\*: *Chi-square test*

•: *Mann-Whitney test*

This table shows no statistically significant differences between the two groups as regard age, virology and Alpha FP.

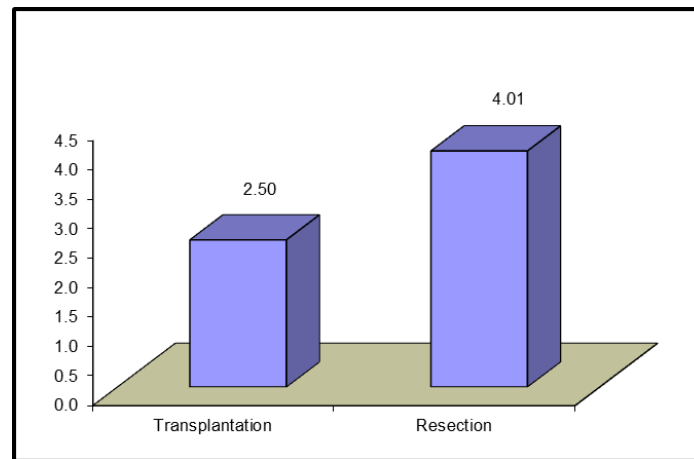


Fig. (1): Comparison between tumor size in both groups (P-value = 0.000).

The tumor size was significantly larger ( $P=0.000$ ) in cases of resection ranging between 2.9 cm to 5 cm ( $4.01 \pm 0.63$ ) in comparison to 1 – 5 cm ( $2.50 \pm 1.08$ ) in the

group of liver transplantation because there is a tendency to treat lesions smaller than 3 cm with RF instead of resection if feasible (fig 1).

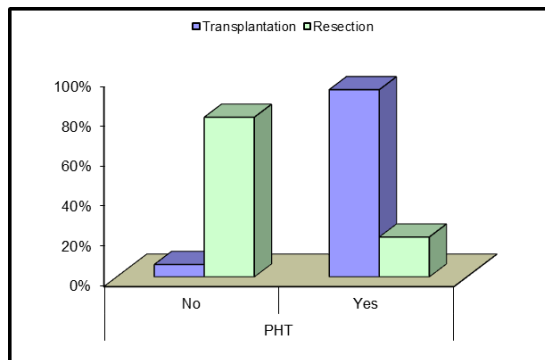
Table (2): Preoperative portal hypertension (PHT) and associated comorbidities in both groups:

		Trans-plantation group		Resection group		Chi-square test	
		No.	%	No.	%	X <sup>2</sup>	P-value
PHT	No	1	6.2%	16	80.0%	19.399	0.000
	Yes	15	93.8%	4	20.0%		
Associated Comorbidities	No	15	93.8%	15	75.0%	2.250	0.134
	Yes	1	6.2%	5	25.0%		
Cardiology	Free	16	100.0%	20	100.0%	NA	NA
Chest	Free	15	93.8%	18	90.0%	1.286	0.257
	Yes	1	6.2%	2	10.0%		
Psychology	Free	16	100.0%	-	-	NA	NA
ENT	Free	16	100.0%	-	-	NA	NA
Dental	Free	16	100.0%	-	-	NA	NA
Metabolic	DM	0	0.0%	3	15.0%	2.618	0.106
	Free	16	100.0%	17	85.0%		

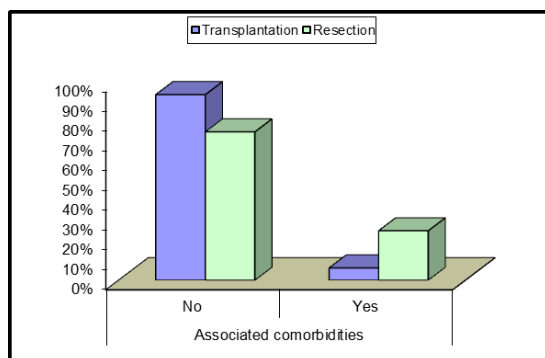
NA: Not applicable

This table shows statistically highly significant difference between both groups in PHT due to exclusion of patients with significant portal hypertension in resection group if major

hepatectomy was needed but statistically no significant difference in associated comorbidities (table2, fig 2,3).



**Fig. (2):** Comparison between both groups regarding PHT (P-value = 0.000).



**Fig. (3):** Comparison between associated comorbidities in both groups ((P-value = 0.134).

Regarding postoperative complications no statistically significant difference between both groups (*table 3, Fig 4*); the most important are the biliary complications, they occurred in 3 cases (18.8%) in the transplant group, one of them was biliary leakage which occurred in 1st postoperative week and was managed conservatively, the leakage stopped after 2 weeks. The other 2 cases were biliary stricture which occurred in the 8th week and 3rd month, both were managed successfully by ERCP. In the resection group, there was one case of biliary leakage after left lateral hepatectomy, it occurred 1st day postoperative and was managed conservatively for 2 weeks till it stopped.

As for the vascular complications, they occurred in 2 cases (12.5%) in the transplant group, one of them was decreased flow in the portal vein to 20mm/sec in the 5th day that was managed conservatively by therapeutic dose of anticoagulation and stopping glypressin, while the other one was stenosis in the hepatic vein after 1 month, that was managed by stenting. In the resection group, there were no vascular complications.

Cardiac complications occurred in 2 patients (10%) in the resection group in the form of arrhythmias which occurred intraoperative in one case and in the 5th postoperative day in the second case. that was controlled in both cases with medications.

Renal complications occurred in 1 case (6.2%) in transplantation group in the form of acute renal injury induced by immunosuppressive drugs that occurred 10 days postoperative with failure of medical treatment that lead to patient death after 3 weeks post operative. In the resection group, transient renal impairment occurred in 1 patient (5%) in the 1st week that was managed with fluid therapy, Glypressin and Albumin.

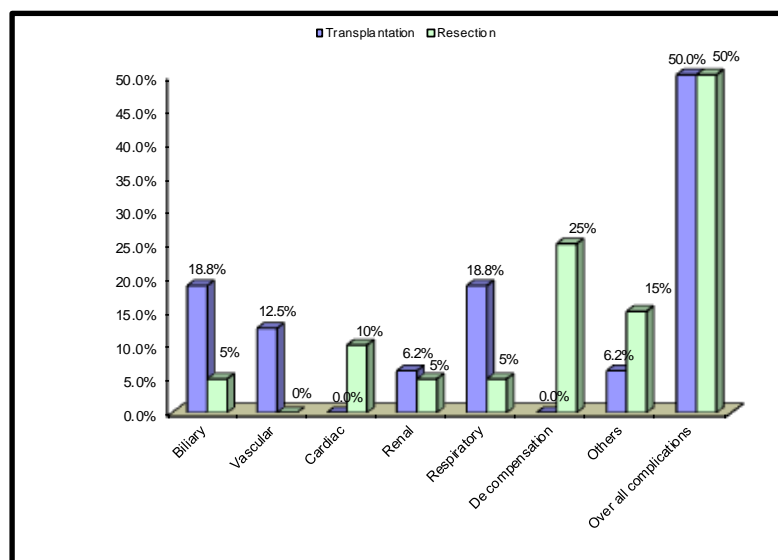
Respiratory complications occurred in 3 cases (18.8%) in the transplant group in the form of chest infection that was managed by antibiotics, chest physiotherapy in 2 patients with addition of antifungal medication in the 3<sup>rd</sup> one. In the resection group, 1 case (5%) of chest infection occurred in the 1<sup>st</sup> postoperative week and was managed medically.

Liver decompensation (ascitis, bilirubin > 5 after 1<sup>st</sup> week) occurred in 5 cases (25%) in the resection group, 4 of them were managed successfully but the 5<sup>th</sup> had sever decompensation in the 2nd week that led to death after 1 month of operation. No cases of small for size occurred in the transplantation group.

Other complications in the transplant group were sepsis from unknown cause in 1 case (6.2%) after 10 month that led to septic shock and death of the recipient within 8 days. In the resection group 2 cases had incisional hernias and 1 patient had an attack of adhesive intestinal obstruction that was managed conservatively.

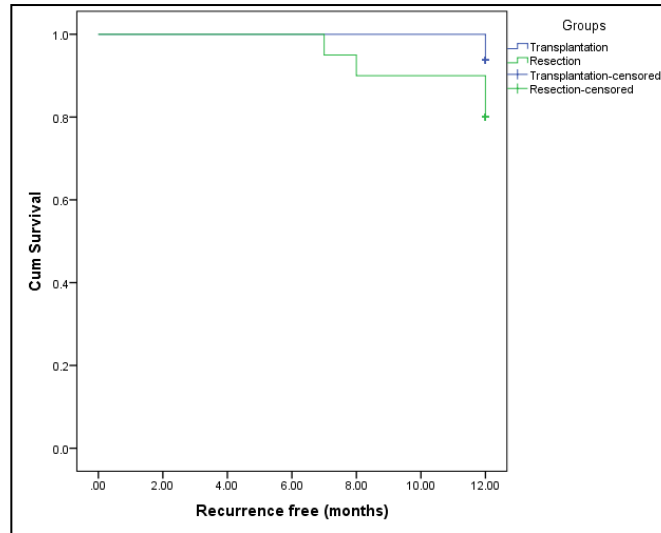
**Table (3): Comparison between the complications in both groups:**

		Transplantation		Resection		Chi-square test	
		No.	%	No.	%	X <sup>2</sup>	P-value
Biliary	No	13	81.2%	19	95.0%	1.702	0.192
	Yes	3	18.8%	1	5.0%		
Vascular	No	14	87.5%	20	100.0%	2.647	0.104
	Yes	2	12.5%	0	0.0%		
Hematologic	No	16	100.0%	20	100.0%	NA	NA
Cardiac	No	16	100.0%	18	90.0%	1.694	0.193
	Yes	0	0.0%	2	10.0%		
Metabolic	No	16	100.0%	20	100.0%	NA	NA
Renal	No	15	93.8%	19	95.0%	0.823	0.364
	Yes	1	6.2%	1	5.0%		
Respiratory	No	13	81.2%	19	95.0%	NA	NA
	Yes	3	18.8%	1	5.0%		
Neurological	No	16	100.0%	20	100.0%	NA	NA
Decompensation or small for size	No	16	100.0%	15	75.0%	4.645	0.031
	Yes	0	0.0%	5	25.0%		
Others	No	15	93.8%	17	85.0%	0.689	0.406
	Yes	1	6.2%	3	15.0%		
Overall complications	No	8	50.0%	10	50.0%	0.00	1
	Yes	8	50.5%	10	50.0%		

**Figure (4) : Comparison between both groups in postoperative complications.**

Recurrence of HCC in the resection group occurred in 4 patients (20%) in 7,8,12 and 12 months, these were managed by RF, TACE, re-resection and best supportive care, respectively. In the transplant group, there was 1 case (6.2%) of

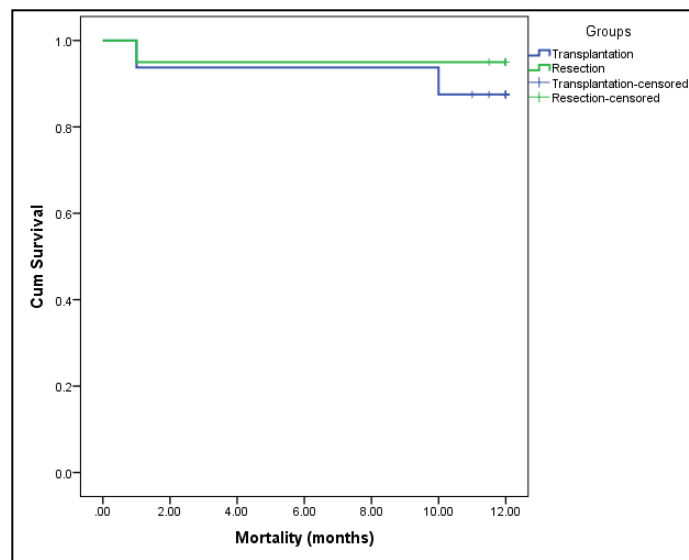
HCC recurrence which occurred hepatic and left supraclavicular Lymph node in the 11<sup>th</sup> months, that was managed by sorafenib (*statistically significant*  $P= 0.0431$ ) (*fig 5*).



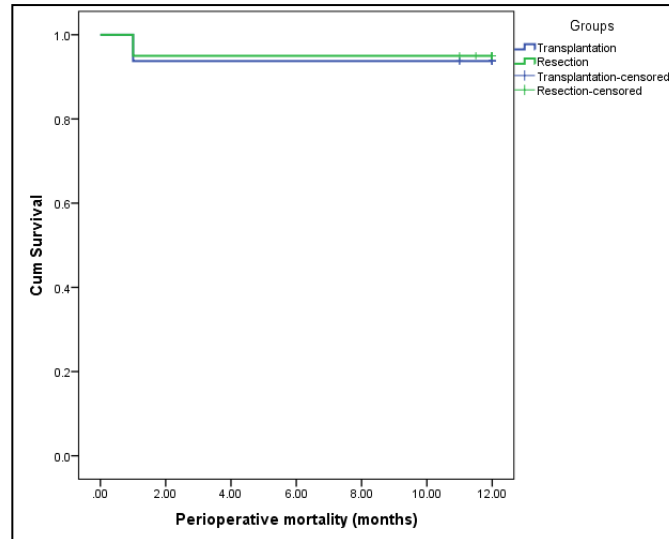
**Fig. (5): Kaplan Mayer analysis comparing the two studied groups regarding recurrence ( $P = 0.0431$ ).**

Mortality in the transplant group occurred in 2 cases (12.5%), 1 of them occurred perioperatively in the 3<sup>rd</sup> week due to renal failure and the other mortality occurred in the 10<sup>th</sup> month due to sepsis.

In the resection group, there was 1 mortality that occurred perioperatively in the 4<sup>th</sup> week due to sever decompensation (**fig 6,7**).



**Figure (6): Kaplan Mayer analysis comparing the two studied groups regarding mortality ( $P = 0.365$ ).**



**Fig. (7): Kaplan Mayer analysis comparing the two studied groups regarding peri-operative mortality ( $P = 0.791$ ).**

## DISCUSSION

### HCC recurrence:

Squires et al. in their study stated that the recurrence rate for HCC was not only significantly greater for patients within MC undergoing resection versus transplantation (49% vs. 11%,  $P < 0.001$ ), but increased recurrence was directly translated into significantly worse survival for patients treated with resection. Of the 20 resection patients, 14 had recurrent HCC at the time of their death. <sup>(2)</sup>

Jiang et al. showed that a high recurrence rate is a major drawback of LR as a curative therapy. According to their data, the 5-year recurrence-free survival was only 19.8%, which was significantly lower than that of the patients who underwent LDLT (72.0%). They suggested that the high recurrence rate in the resection could be partly contributed to the underlying liver diseases, such as viral hepatitis and cirrhosis. <sup>(3)</sup>

Bigourdan et al study and Margarit et al reported that tumor recurrence was higher in the liver resection group, but extrahepatic recurrences predominated after LT and were associated with a rapid tumor growth, and suggested that due to a deleterious effect of immunosuppression on host immunity. <sup>(4,5)</sup>

In our study, follow up for 1 year showed recurrence of HCC in the resection group

occurred in 4 patients (20%) in 7,8,12 and 12 months, these were managed by RF, TACE, re-resection (hepatic recurrence) and best supportive care (due to distant spread with decompensated liver), respectively. In the transplant group, there was 1 case (6.2%) of HCC recurrence which occurred hepatic and left supraclavicular lymph node in the 11<sup>th</sup> months that was managed by sorafenib ( $P$ -value = 0.0431).

### Overall Survival and morbidity:

Jiang et al. showed that the 1-, 3- and 5-year overall survival (OS) rate was higher in LDLT group than that in LR group (94.1%, 91.2% and 76.5% vs. 84.8%, 64.0% and 51.2%, respectively,  $P = 0.046$ ), so they claimed that LDLT might offer better long-term survival and lower HCC recurrence rates than LR; Moreover, no differences existed in perioperative death and major complications between LDLT group and LR group. <sup>(3)</sup>

A recent meta-analysis by Lim et al. of outcomes for patients undergoing hepatic resection of HCC meeting MC concluded that resection in patients with preserved liver function produced good outcomes, with a 5-year OS of 67% (range, 27– 81%), but was associated with a substantial risk of disease recurrence (5-year RFS: 37%; range, 21–57%) <sup>(6)</sup>

In our study, Mortality in the transplant group occurred in 2 cases (12.5%), 1 of them occurred perioperatively in the 3<sup>rd</sup> week due to acute renal



injury, and the other mortality occurred in the 10<sup>th</sup> month due to sepsis. In the resection group, there was 1 mortality that occurred perioperatively in the 4<sup>th</sup> week due to liver cell failure (P-value = 0.418).

The overall complication rate between LDLT and liver resection was nearly similar but with a different pattern. In the transplantation group there was more vascular (12.5% Vs 0%) and biliary complications (18.8% Vs 5%) and complications related to immunosuppressant like chest infection (18.8% Vs 5%) and renal impairment (6.2% Vs 5%). In resection group the main complications were related to liver decompensation (25% Vs 0%), hepato-renal syndrome and biliary leak in major hepatectomy.

## CONCLUSION

Living Donor Liver Transplantation is better than liver resection for single HCC less than 5 cm regarding recurrence free survival with no difference in overall survival in short term follow up. Postoperative morbidity is nearly equal for both strategies regarding overall incidence but with different pattern.

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