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Research Article

Recurrence of HCC after living donor liver transplantation, retrospective cohort study of a single centre experience.

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Abstract

Background: Hepatocellular carcinoma is a prominent reason of mortality on a global scale. The occurrence of this condition is high in Egypt, & it is on the rise as a result of infection with HCV. Liver transplantation provides the dual benefit of managing the carcinoma & replacing the cirrhotic liver in cases with hepatocellular carcinoma & hepatic cirrhosis. Consequently, transplantation of the liver is generally considered the optimal management, particularly for cases with end-stage liver disease. Regrettably, tumor recurrence is a prevalent occurrence, & there is much debate regarding the natural history, therapeutic effects, & survival rates following the recurrence of hepatocellular carcinoma (HCC) following transplantation of the liver. **Methods:** Between 2010 & 2016, patients who presented with hepatocellular carcinoma with or without end stage liver disorder and treated with liver transplantation were retrospectively analyzed to assess for recurrence & its prognostic factors. **Results:** Fifty-nine (n=59) with hepatocellular carcinoma were managed by transplantation of liver & included in the study. Recurrent HCC detected in 15 patients (25.4 percent) of 59 cases & was most common in the liver in the first two years. Among cases with recurrent disease, the rate of death was sixty percent. It was 94.9 percent, 78 percent, & 74.5%, respectively, for the overall survival at one year, three years, & five years. At one year, three years, & five years, the cumulative recurrence-free survival rate was 88.1%, 64.5 percent, & 62.7 percent, respectively. A multivariate Cox hazard model demonstrated that the presence of AFP ≥ 400 nanogram per milliliters, microvascular invasion in the explanted liver & preoperative ablative therapy were statistically independent prognostic factors. Patients with AFP level < 200 nanogram per milliliter were having better recurrence free survival than patients with ≥ 200 ng /ml. Milan Criteria was statistically insignificant regarding recurrence or overall survival. **Conclusions:** Hepatocellular carcinoma recurrence is a frequent occurrence following transplantation of the liver, & the prognosis isn't favorable. The occurrence of high preoperative AFP & microvascular invasion are adverse prognostic factors. Preoperative ablative therapy seems to improve recurrence free survival but not overall survival. Milan criteria should be validated and a new model for selection of cases suffering from HCC for liver transplantation; considering not only the morphological features of the tumor but additionally its biological behavior, should be developed.

Keywords: survival, resection, hepatitis c

Introduction

Hepatocellular carcinoma is the 3rd most frequent cause of cancer-related death & the 5th most prevalent form of tumors globally. Hepatocellular carcinoma frequently happens in the background of cirrhosis of liver. The geographic distribution of death is comparable

to that of occurrence, & cancer of the liver has a high rate of death. The occurrence of hepatitis viruses in the populations is likely to be a contributing factor to the variations in the age-, sex-, & race-specific rates of Hepatocellular carcinoma in various geographic regions [1].

in Egypt, hepatocellular carcinoma is the 2[ed] most prevalent tumor among males & the sixth most prevalent tumor among females. The elevated incidence of hepatitis C virus (HCV) & its complications is the cause of the increasing occurrences [2].

Hepatocellular carcinoma diagnosis may be difficult & frequently demanding the utilization of one or more imaging modalities. To ensure that all management options are available, it is recommended that tumors be identified at a size of about two centimeters. [3]

Tumors might appear as a single mass lesion or as diffuse growth, which might be difficult to distinguish from the regenerating liver nodules & the adjacent cirrhotic liver tissue in imaging investigations. The presentation might be partially due to a mass impact that may result in obstruction of the biliary system or any location that affects the hepatic vasculature. The median survival period following diagnosis is approximately six to twenty months. A poor result is correlated with a large tumor size, vascular invasion, nodal metastases & poor functional status.[4]

High-risk cases who have hepatocellular carcinoma & either have serum AFP levels that are greater than or equal to 200 nanograms per milliliter or a triphasic CT-scan abdomen that demonstrates standard criteria for hepato-cellular carcinoma must be diagnosed with hepatocellular carcinoma. (NB*: The radiological criteria for hepatocellular carcinoma appear as early enhancement during the arterial phase, followed by rapid contrast elimination in the delayed phase*.) [4].
If surgical resection or liver transplantation (LT) is offered to the patients, it is up to the surgical team to continue further assessment to ensure the feasibility of either treatment. For example, low platelets & presence of oesophageal varices are used as surrogate markers for the occurrence of portal hypertension & preclude surgical resection[4].

There is no consensus on the most effective staging system for predicting the survival of cases suffering from hepatocellular carcinoma. In general, pathologic staging systems, like the AJCC TNM staging system, are more accurate in predicting prognosis compared to clinical systems, especially when evaluating the results of resection. In cases with advanced hepatocellular carcinoma who are undergoing nonsurgical treatment & have poor liver function, Okuda, Barcelona, & CLIP are more beneficial for predicting result [5].

The consensus of the American Hepato-Pancreato Biliary Association (updated in 2010) reasserts the requirement for utilizing various systems for various. The TNM system is recommended for the prediction of outcomes following resection or liver transplantation in their consensus statement, while the BCLC scheme is recommended for cases with advanced hepatocellular carcinoma who aren't candidates for operation [6].

In 1996, landmark research has been published by Mazzaferro. The world of liver transplan-tation for hepatocellular carcinoma has entered a completely new era as a result of the widespread adoption of the so-called Milan criteria. The rate of survival of cases who fulfilled the Milan criteria following under-going liver transplantation was nearly identical to that of cases who had benign liver disease. Subsequently, LT for hepatocellular carcinoma progressively progressed in the right way [7].

Post-transplantation therapy for cases suffering from hepatocellular carcinoma is primarily composed of three components: (i) The treatment of an efficient immunosuppression protocol that achieves a balance among the prevention of the immune system from rejecting the allograft & the promotion of cancer growth; (ii) The screening of cases for hepatocellular carcinoma recurrence following transplantation; (iii) the management of hepatocellular carcinoma recurrence [8].
Recurrence of cancer subsequent to surgical intervention is the primary obstacle to

prolonged survival. Numerous authors recommend that the occurrence of hepato-cellular carcinoma recurrence is significantly greater after resection of liver compared to following transplantation. The recurrence of a tumor following liver resection is primarily intrahepatic. In contrast, recurrent hepato-cellular carcinoma following OLT may manifest at multiple locations, such as the transplanted allograft, bone, lung, & brain. Recurrent tumors typically manifest within a short period of time following the initial transplant. This indicates that recurrent disease is the result of microscopic metastasis that occurs either preoperatively or intraoperatively. Regrettably, the phenotypic distinctions between the metastatic lesions & primary tumor aren't clearly identified. Nevertheless, it is conceivable that these recurrent lesions are biologically more aggressive or inadequately distinguished [9].

The discovery that small, incidentally discovered hepatocellular carcinoma in explanted livers didn't adversely impact the survival of cases having liver transplantation for other conditions, in contrast to cases whose livers didn't contain a malignancy, led to a shift in the philosophy of transplantation for hepatocellular carcinoma. Additionally, a rising number of retrospective investigations indicated that liver transplantation was as efficient as & potentially more effective compared to alternative treatments in carefully selected subgroups of cases [10].

However, the Milan criteria might be excessively strict & efforts to expand them in a safe manner remain continuing. Living donor liver transplantation (LDLT) for hepatocellular carcinoma is advancing swiftly due to the scarcity of reduced donor livers. [11]

The management of hepatocellular carcinoma tumors before to liver transplantation involves the following: transarterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), resection of liver, & cryoablation & microwave coagu-lation. A reduced recurrence rate following liver transplantation is correlated with treatment before transplantation for hepato-cellular carcinoma [12].

Patients and Methods

Maadi Armed Forces Medical Compound electronic databases were the main sources of information used while gathering data for this investigation.

Initial staging of the primary liver tumour has been made on the basis of radiological imaging. Throughout the duration of this investigation, the treatment protocol at our centre has been standardized according to the international guidelines with some limited modifications to comply with Egyptian patients.

Inclusion criteria were adults over the age of eighteen years; referred to our hepatobiliary & liver transplant centre for consideration of adult-to-adult living donor liver transplantation during the period of time from 2004 to 2012. cases with hepatocellular carcinoma as the primary indication for LDLT or postoperative pathological discovery were identified to form the main study population.

Our approach towards patients' selection

In general, we adopt conservative view of patient selection based on Milan criteria & AFP level less than 1000 nanogram per milliliters.
The rationale behind this policy comes from the fact that we care about the valuable living donor, & we do not want to waste his or her sacrifice in vain by selecting poor recipients based on weak evidence & waiting for good results.

On the other hand, some donors are very enthusiastic & self-motivated to donate to their relatives without consideration of the evidence especially in borderline cases & argue with us fiercely to go for the procedure & give them a chance.

We now see it can backfire in either case; as we can overestimate a case based on our conservative policy & waste a good chance for better survival. On the other face of the coin, we may underestimate a case based on the relative's pressure & lack of scientific thinking 7 go through dangerous territories with unnecessary procedures, putting both donor & recipient under great harm with no clear or tangible benefit.

STUDY DESIGN

From January 2004 to January 2012, cases who presented with hepatocellular carcinoma have been retrospectively recognized from the MDT database at Maadi hepatobiliary & liver transplant center. Initial staging has been made on the basis of radiological imaging. Patients who did have LDLT were included & retrospectively analyzed to assess the main complication of such patients, namely recurrent HCC, & assessment of the risk factors as the primary endpoint.

MEASUREMENTS AND CALCULATIONS

The overall survival (OS) has been determined from the date of diagnosis to the date of mortality or the most recent follow-up. The disease-free survival (DFS) has been determined from the date of transplantation until the date of recurrence, mortality, or the last follow-up for those who didn't recur.

STATISTICAL ANALYSIS

IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL) has been utilized to analyze the data. Numerical data has been presented as the standard deviation & mean or range & median, as appropriate. Frequency & percentage were the metrics utilized to represent qualitative data. The Kaplan-Meier method has been utilized to conduct the analysis of survive, & the log-rank test has been utilized to compare the two survival curves. The Hazard ratio (HR) was calculated using the Cox-regression method, & the ninety-five percent confidence interval (CI) has been used to estimate the risk. All tests were two-tailed. A p-value lower than 0.05 has been regarded as statistically significant.

Result

A total of fifty-nine case have been included in the investigation group: - 53 (89.8%) males & 6 (10.2%) females. Cases had a mean age of fifty-two years (41-61). Infection with hepatitis C was the only reason of cirrhosis in 54 (91.6%) patients. Hepatitis B & mixed infection HCV & HBV were detected in 4 (6.8%) & 1 (1.7%) patient respectively.

38 patients (64.4%) had Child score A where Child B & C score were detected in 17 (28.8%) & 4 patients (6.8%) respectively.

However, MELD score is not used for patients' stratification; it has been calculated in all patients. None of the patients exceeded 19 & 95% of the patients had a score of 15 or less.

Preoperative cancer number & size have been utilized to put the case on the waiting list of transplantation according to Milan criteria. In thirty patients (50.8 percent), a solitary lesion was identified, while in eighteen case (30.5 percent), two lesions were identified. Ten cases (16.9 percent) & one case (1.7 percent) had three & four lesions, respectively. The mean size of the solitary Hepatocellular carcinoma lesion or the largest lesion in multiple cancer was 3.5 centimeters, with a range of 1.5 to six centimeters.

Preoperative Milan criteria were met in 42 patients (71.1%) & 17 (28.9%) of the patients were deemed outside Milan; one patient had 4 small lesions & the other 16 were outside because of tumour size.

Preoperative locoregional management was done in 25 patients (42.3%) in the form of TACE either once or more in 20 patients (33.9%), RFA in 2 (3.4%) & both TACE & RFA in 3 patients (5.1%).

Preoperative AFP level in 39 patients (66.1%) was less than 200ng/ml & was greater than 200 nanogram per milliliter in 20 cases (33.9%). When a cutoff level of 400 nanogram per milliliters is used; forty-nine cases (83.1 %) were less than 400 nanogram per milliliters & ten cases (16.9 %) were more than 400 nanogram per milliliters. Three cases showed levels more than 1000 nanogram per milliliters.

Mean duration of operation was 10 +/- 2.1 hours (range: 6.5- 15 hours) It has been affected throughout time due to a learning curve.

Graft size ranged from 690 grams to 920 grams with a median weight of 785 grams. Graft recipient weight ratio (GRWR) median was 0.85 with a minimum of 0.7 and a maximum of 1.0. (the standard is > 0.8) CIT (Cold Ischaemia Time) mean was 41+/- 6 minutes WIT (warm Ischaemia Time) median was 45 minutes (range 25- 110 minutes).

Transfusion of blood & fresh frozen plasma was given to all the 59 patients. Blood units'

median was 6 (range: 2 to 24 units). FFP transfusion mean, & standard deviation was 12.8 & 7.5 respectively.

Morbidity

Postoperative pathological findings showed some differences in HCC lesions number & size. Single lesion was found in 24 patients (40.7%) while 24 patients (40.7) & 11 patients (18.6%) had 2 or 3 lesions respectively. One patient with preoperative 4 lesions had only one lesion identified as a dysplastic nodule, in the postoperative pathology report.

Postoperative assessment of the patients regarding Milan criteria showed that 37 patients (62.7%) were within the standard criteria where 22 patients (37.3%) were outside. 18 of the patients who are postoperatively outside MC had multiple lesions (81.1 %) & none of the lesions exceeded 4 cm. The sum of the lesions was between 8 & 9 cm in eight patients. Only 4 patients had single lesion that measured 5.2, 5.3, 5.5 & 5.7 cm.

In the 24 patients with a single HCC lesion; a capsule was detected after histopathologic examination of the explanted liver in 5 cases only. Also, a capsule was detected in 12 lesions out of the 82 multiple lesions in the rest of the study group & this was in 9 cases only.

Microvascular invasion has been identified in the explanted liver in sixteen cases (27.1 percent) while forty-three cases (72.9 percent) were free. Lymph node metastasis wasn't identified in any case.

Twenty-five (42.3%) patients had ablative treatment before surgery for hepatocellular carcinoma. After the pathological investigation of explanted liver, nine cases (36%) have been ablated with no residual tumour activity; while the other 16 patients (64%) demonstrated incomplete tumour ablation with ongoing tumor activity.

Methylprednisolone, in conjunction with calcineurin inhibitors (CNI) like tacrolimus & mycophenolate mofetil, was the primary immune suppressant protocol following surgery. If complications arose as a result of tacrolimus; other immunosuppressants was utilized like the mammalian target of rapamycin (m-TOR) inhibitors (sirolimus or everolimus). There was a lot of heterogeneity in the regimen used for each patient therefore we removed the immunosuppression as a prognostic variable from this study.

Recurrence and Survival

A total of fifty-nine cases with a mean age of fifty-two years, have been subjected to long-term monitoring for the recurrence of hepatocellular carcinoma. There were fifty-three men cases & six women cases. In order to follow up, none of them were lost.

Overall survival at one year, three years & 5 years was 94.9%, 78% & 74.5% respectively. Disease free survival at one year, three years and five years was 88.1%, 64.5% & 62.7% respectively.

The overall survival (OS) has been determined from date of diagnosis to date of mortality or the most recent follow-up. The disease-free survival has been determined from the date of transplantation until the date of recurrence, mortality, or the last monitoring for those who didn't recur.

Fifteen (25.4 %) patients had HCC recurrence throughout the duration of the investigation; all were male cases suffering infection with from hepatitis C virus. hepatocellular carcinoma recurrence has been observed mainly in the 1st two years with a range among 8 & 39 months postoperatively. The mean time of recurrence was 21.7 months following transplantation.

The pattern of HCC recurrence was as follow:

- Intrahepatic only in 10 patients (66.7%)
- Extrahepatic only in two cases (13.3 ercent); one bone & one lung metastasis
- Mixed intra & extrahepatic in three cases (twenty percent)

2 cases had recurrence twice & one case had recurrence three 3 after resection of the first intrahepatic recurrence.

Management was as follows:

- Resection once in three cases (20%)
- Resection three times in one case (6.7%)
- transarterial chemoembolization & resection in one case (6.7)
- Open radiofrequency ablation in one case (6.7%)

- Radiotherapy to bone metastasis in one case (6.7%)
- Sorafenib or Nexavar in one case (6.7%)
- Palliation in 7 patients (46.7%)

There were 17 deaths; nine (52.9) of them were related directly to HCC recurrence & eight cases (47.1%) were due to other different causes listed in the table.

Cox regression analysis of many prognostic factors & their effect on overall survival showed that:

- Preoperative AFP concentration is an independent risk factor affecting overall survival in cases suffering from hepatocellular carcinoma receiving liver transplant. (*p-value*< 0.001)
- Microvascular invasion that could found in the explanted liver is also independent risk factor. (*p-value*= 0.009)
- Other proposed factors failed to demonstrate any significance, specifically the Milan criteria status of the patient. (*p-value* = 0.786)

Cox regression analysis to the same variables regarding recurrence free survival showed again that both pre-operative AFP concentration & microvascular invasion are independent risk factors that negatively affect recurrence free survival following transplantation in HCC cases. Though, pre-operative therapy showed no statistical significance as a risk factor to improve outcome (*p-value* = 0.061), it could be of great clinical impact.

Survival analysis showed that overall survival was clearly affected by the level of AFP at a cutoff of more than 400 ng /ml (p-value < 0.001) but not affected at cutoff level of 200 ng /ml (p-value = 0.079). Also, microvascular invasion negatively affected overall survival (p-value = 0.005). Again, preoperative ablation with TACE & or RFA failed to show statistical significance (p-value = 0.097).

Survival analysis regarding recurrence free survival showed that pre-operative AFP at 400 & 200 ng /ml increased HCC recurrence post-transplant with a p-value less than 0.001 & 0.01 respectively. Also, microvascular invasion increased the risk of early recurrence (p-value < 0.001). management before operation was very close to be significant with a p-value of 0.053.

Table (1): Baseline characteristics of the study population

	Study group (n = 59)		***Study group (n = 59)***
Age		***MELD score***	
<60	52 (88.1)	***<10***	10 (16.9)
>=60	7 (11.9)	***>=10***	49 (84.1)
		>=19	1 (1.7)
Gender		***Milan Criteria (Pre-Op)***	
Male	53 (89.8)	***In***	42 (71.2)
Female	6 (10.2)	***Out***	17 (28.8)
Viral status		***Preoperative management***	
HCV	54 (91.5)	***TACE***	20 (33.9)
HBV	4 (6.8)	***RFA***	2 (3.4)
Both	1 (1.7)	***Both***	3 (5.1)
		None	34 (42.4)
Child score		***Preoperative AFP***	
A	38(65.5)	***<200 ng/ml***	39 (66.1)
B	17 (28.8)	***>=200 ng/ml***	20 (33.9)
C	4 (6.8)	***>=1000 ng/ml***	3 (5.1)

Table (2): Operative and pathological findings

	Study group (n = 59)		*Study group (n = 59)*
Operative time		***FFP transfusion***	
≤ 10 hours	23 (39)	***≤10 units***	32 (54.2)
> 10 hours	36 (61)	***> 10 units***	27 (45.8)
CIT		***Milan Criteria (Post-Op)***	
25-40 min	36 (61)	***In***	37 (62.7)
41-55 min	23 (39)	***Out***	22 (37.3)
WIT		***Capsule***	
25-60 min	40 (67.8)	***Yes***	14 (23.7)
61-110 min	19 (32.2)	***No***	35 (76.3)
Blood transfusion		***Microvascular Invasion***	
2-7 units	30 (50.1)	***Yes***	16 (27.1)
≥ 8 units	29 (49.9)	***No***	43 (72.9)

Table (3): Management of recurrence

Management		
	Frequency	**Percent**
Supportive	7	46.7%
Resection (once)	3	20%
Resection (three)	1	6.7%
Open RFA	1	6.7%
TACE & Resection	1	6.7%
RTx	1	6.7%
Nexavar	1	6.7%

Table (4): Causes of deaths in the study group

Causes of death		
	Frequency	**Percent**
Biliary complications	3	17.6%
Myocardial infarction	1	5.9%
Primary non function	1	5.9%
Rejection	1	5.9%
Stroke	1	5.9%
Fungal infection	1	5.9%
Recurrence	9	52.9%

Table (5): Cox Regression analysis of overall survival

	B	SE	p-value	HR	95.0% CI for HR	
					Lower	Upper
Age	-.006	.055	.919	.994	.893	1.107
MELD	.056	.103	.584	1.058	.865	1.294
Preop.HCC (N)	.142	.285	.620	1.152	.659	2.014
Preop. HCC size	-.072	.220	.743	.931	.605	1.432
Postop. HCC (N)	-.016	.328	.961	.984	.518	1.871
Postop. HCC size	-.096	.242	.690	.908	.565	1.459
Preop.AFP	.001	.000	***<0.001***	1.001	1.001	1.002
Op time	.064	.117	.584	1.066	.847	1.343
Graft size	.002	.005	.604	1.002	.994	1.011
GRWR	-1.277	2.747	.642	.279	.001	60.788
Blood Transfusion	-.102	.066	.120	.903	.794	1.027
PlasmaTransfusion	-.027	.027	.321	.973	.923	1.027
CIT	-.006	.038	.871	.994	.922	1.072
WIT	.003	.017	.856	1.003	.970	1.038
Gender	.550	1.031	.594	1.734	.230	13.084
Viral status	.536	1.031	.603	1.709	.227	12.897
Child BC vs A	.272	.493	.581	1.313	.500	3.451
Milan	.138	.508	***.786***	1.148	.424	3.105
Microvascular invasion	1.272	.487	***.009***	3.567	1.374	9.266
Preop. Management	.720	.533	***.177***	2.055	.723	5.843

Table (6): Cox Regression analysis of recurrence free survival

	B	SE	p-value	HR	95.0% CI for HR	
					Lower	Upper
Age	-.001	.048	.982	.999	.910	1.096
MELD	.010	.093	.911	1.010	.842	1.212
Postop. HCC no	.053	.249	.831	1.055	.647	1.718
Preop. Size	-.046	.186	.805	.955	.664	1.374
Postop. HCC no	.103	.269	.702	1.108	.654	1.879
Postop. Size	.006	.207	.978	1.006	.670	1.509
Preop.AFP	.001	.000	***<0.001***	1.001	1.001	1.002
Op. Time	.084	.098	.393	1.088	.897	1.319
Graft size	-.002	.004	.639	.998	.990	1.006
GRWR	-1.988	2.310	.390	.137	.001	12.686
Blood Transfusion	-.040	.047	.397	.961	.876	1.054
Plasma Transfusion	-.008	.020	.710	.992	.954	1.033
CIT	-.036	.033	.276	.965	.904	1.029
WIT	.012	.013	.378	1.012	.986	1.039
Gender	.986	1.023	.335	2.680	.361	19.898
Viral status	.879	1.023	.390	2.408	.324	17.867
Child	.045	.438	.918	1.046	.443	2.468
Milan	.349	.421	***.407***	1.418	.621	3.237
Microvascular Invasion	1.858	.435	***0.000***	6.411	2.732	15.045
Preop.Management	.893	.476	***.061***	2.443	.961	6.209

Table (7): Overall survival analysis

	n = 59	OS at one year	OS at three years	OS at five years	P value
Whole group	59	94.9 %	78 %	74.5	
Gender					
Male	53	96.2 %	77.4 %	73.5 %	0.589
Female	6	100 %	83.3 %	83.3 %	
Age					
≤ 60	52	94.2 %	75 %	73.1 %	0.347
>60	7	98.1 %	85.7 %	85.7 %	
Viral status					
HCV	54	84.4 5	75.9 %	74.1 %	0.598
HBV	5	100 %	80 %	80 5 %	
Child score					
A	38	97.4 %	81.6 %	76.1 %	0.579
B &C	21	95.2 %	71.4 %	71.4 %	
MELD score					
≤ 10	28	92.9 %	82.1 %	74.6 %	0.381
> 10	31	96.8 %	74.2 %	69.8 %	
Milan					
In	37	94.6 %	78.4 %	75.7 %	0.786
Out	22	92.9 %	77.3 %	72.1 %	
Preoperative AFP					
≤ 400 ng/ml	49	98 %	83.7 %	81.6%	***0.001***
> 400 ng/ml	10	90.1 %	80 %	40.5%	
< 200 ng/ml	39	97.4 %	82.1 %	79.5%	
≥ 200 ng/ml	20	95 %	70 %	59.2%	***0.079***
Preop. Management					
Yes	25	96 %	92 %	84 %	***0.167***
No	34	94.1 %	70.6 %	67.6 %	
Operative time					
≤10 hours	23	95.7 %	78.3 %	73.9 %	0.395
> 10 hours	36	94.4 %	77.8 %	71.9 %	
GRWR					
<0.8	22	90.9 %	59.1 %	54.5 %	0.296
≥0.8	37	86.5 %	67.6 %	64.6 %	
Blood Transfusion					
≤ 8 units	24	97.1 %	78.4 %	71.4 %	0.142
> 8units	25	95.8	72.8 %	68.2 %	
CIT (min)					
≤ 40	36	88.9 %	66.7 %	61.1 %	0.265
>40	23	87.2 %	73.9 %	69.6 %	
WIT (min)					
≤60	29	86.2 %	65.1 %	61.2 %	0.555
>60	30	86.7 %	63.4 &	60.5 %	
HCC lesions					
Single	30	93.3 %	73.3 %	66.7%	0.326
Multiple	29	82.8 %	62.1	58.6	
HCC size					
<5 cm	45	95.6 %	73.3 %	71.1 %	0.171
≥ 5 cm	14	100 %	92.9 %	85.7 %	
Microvascular invasion					
Yes	16	75 %	37.5 %	18.8 %	***0.005***
No	43	93.7 %	81.4 %	79.1 %	

Table (8): Recurrence free survival analysis

	n=59	DFS at one year	DFS at three years	DFS at five years	P-value
Whole group	59	88.1 %	62.7 %	61 %	
Gender					
Male	53	88.7 %	60.4 %	58.5%	0.316
Female	6	83.3 %	83.3 %	83.3%	
Age					
≤ 60	52	86.5 %	61.5 %	59.6 %	0.496
>60	7	100 %	85.7 %	71.4%	
Viral status					
HCV	54	87 %	61.1%	59.3%	0.375
HBV	5	100 %	80 %	80%	
Child score					
A	38	86.8 %	63.2 %	60.5 %	0.618
B &C	21	90.5 %	61.9 %	61.9 %	
MELD score					
≤ 10	28	92.9 %	64.3 %	64.3 %	0.113
> 10	31	83.9 %	61.3 %	58.1 %	
Milan					
In	37	91.9 %	67.6 %	64.9 %	0.404
Out	22	81.8 %	54.9 %	54.9 %	
Preoperative AFP					
≤ 400 ng/ml	49	91.8%	73.5%	73.5%	***< 0.001***
> 400 ng/ml	10	70 %	20 %	0.0 %	
< 200 ng/ml	39	92.3%	76.9%	76.9%	
≥ 200 ng/ml	20	80 %	35 %	30%	***<0.001***
Preop. Management					
Yes	25	88 %	76 %	76 %	***0.053***
No	34	88.2 %	52.9 %	50 %	
Operative time					
≤10 hours	23	91.3 %	65.2 %	60.9 %	0.979
> 10 hours	36	86.1 %	61.1 %	61.1 %	
GRWR					
<0.8	22	90.9 %	54.5 %	54.5 %	0.296
≥0.8	37	86.5 %	67.6 %	64.9 %	
Blood Transfusion					
≤ 8 units	24	94.3 %	74.3 %	74.3 %	0.115
> 8units	25	81.2 %	65.8 %	61.7 %	
CIT (min)					
≤ 40	36	88.9 %	55.6 %	55.6 %	0.285
>40	23	87 %	73.9 %	69.6 %	
WIT (min)					
≤60	29	86.2 %	62.1 %	62.1 %	0.595
>60	30	90 %	63.3 %	60 %	
HCC lesions					
Single	24	91.7 %	70.8 %	66.7%	0.524
Multiple	35	85.7 %	57.1 %	57.1%	
HCC size					
<5 cm	45	87.2 %	61.7 %	59.6 %	0.137
≥ 5 cm	14	91.7 %	66.7 %	66.7 %	
Microvascular invasion					
Yes	16	75 %	18.8 %	12.5 %	***< 0.001***
No	43	93 %	79.1 %	79.1 %	

Table (9): Previous studies from literature

Source	No of Patients	% of Recurrence	Study description/outcome
Marsh et al	178	40	Artificial neural network model to predict the likelihood of HCC recurrence following OLT
Schlitt et al	69	56.5	Vascular invasion, tumor size and number, cirrhosis associated with tumor recurrence
Regalia et al	132	15.9	Tumor size, Milan criteria, and capsular invasion associated with HCC recurrence
Roayaie et al	311	18.3	> 1 y to recurrence, without bone metastasis, surgical treatment of metastasis associated with longer survival
Shimoda	67	16.4	Pre-OLT TACE, adjuvant Chemotherapy associated with reduced risk of death following OLT
Hemming et al	112	9.8	Vascular invasion is an independent risk factor for HCC recurrence
Margarit et al	103	14.5	Vascular invasion is the only independent risk factor for HCC recurrence
Zavaglia et al	155	6.4	HCC recurrence is associated with grade and macroscopic vascular invasion
Yoo et al	985	7.6	five-year survival for patients with HCC was 42.3 percent and 71.7 percent in patients without HCC (from UNOS data set)
Leung et al	144	15.3	AFP greater than ten milligrams per milliliters and pathologic UCSF criteria are predictors of recurrence-free survival
Mazzaferro et al	48	8	Milan Criteria developed

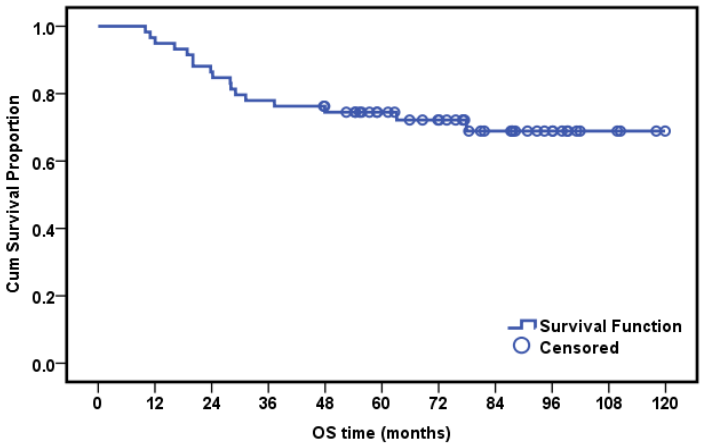

Figure 1: ***Overall survival Kaplan-Meier curve***

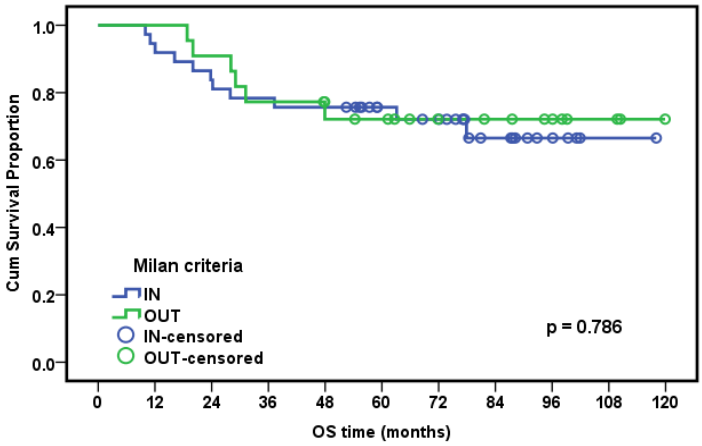

Figure 2: ***Kaplan Meier curve of OS in patients within and ouside MC***

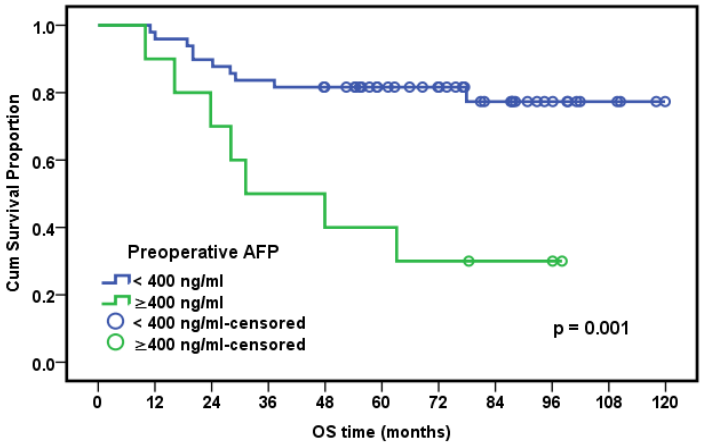

Figure3: Kaplan Meier curve of *Overall survival* in relation to preoperative AFP at 400 ng/ mlas a cutoff level

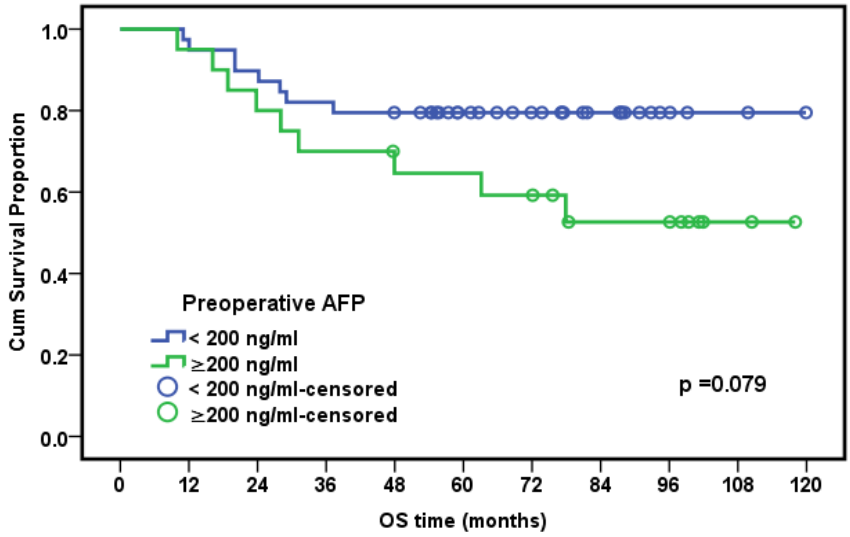

Figure 4: Kaplan Meier curve of *Overall survival* in association with AFP at a cutoff level of 200 ng/ ml

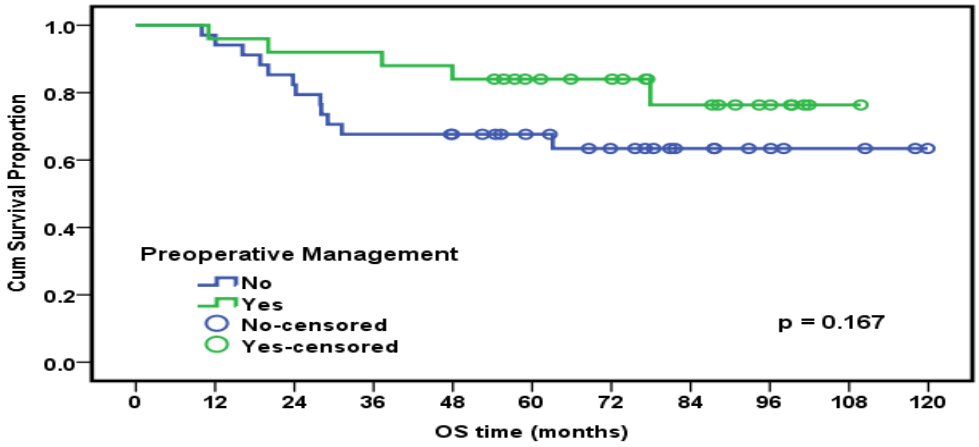

Figure 5: Kaplan Meier curve of *Overall survival* in association with preoperative treatment

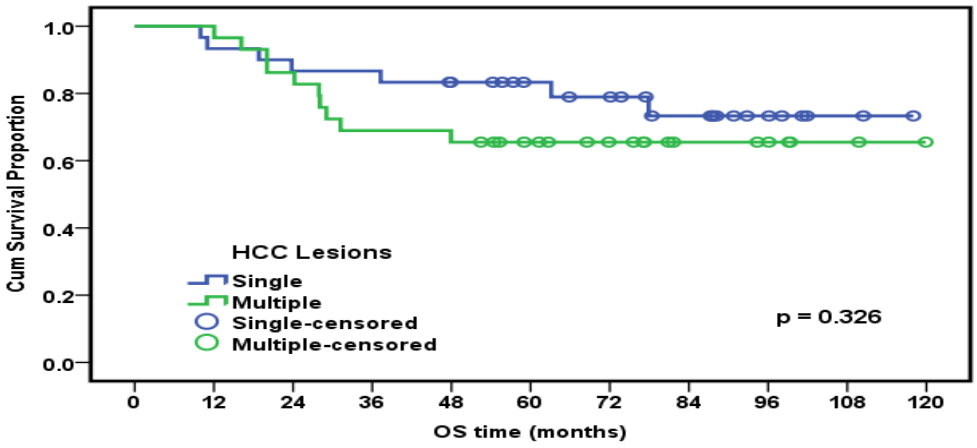

Figure 6: Kaplan Meier curve of *Overall survival* in association with HCC being single or multiple

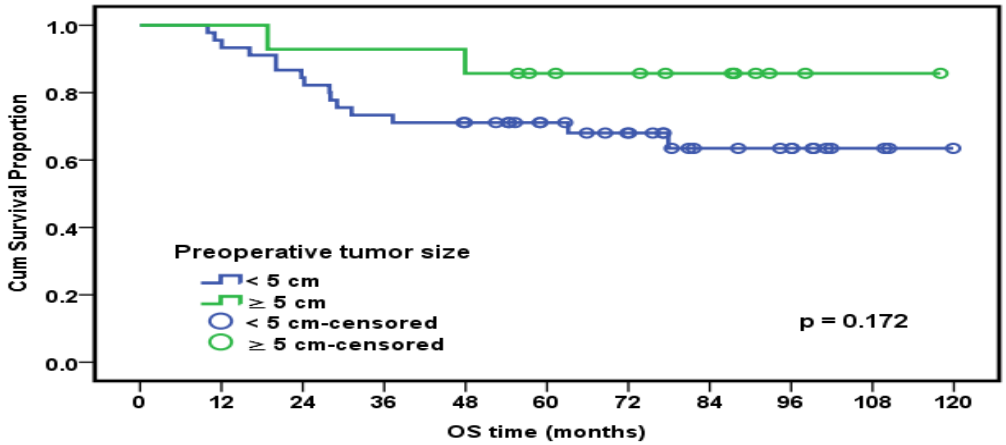

Figure 7: Kaplan Meier curve of *Overall survival* in association with biggest HCC lesion size

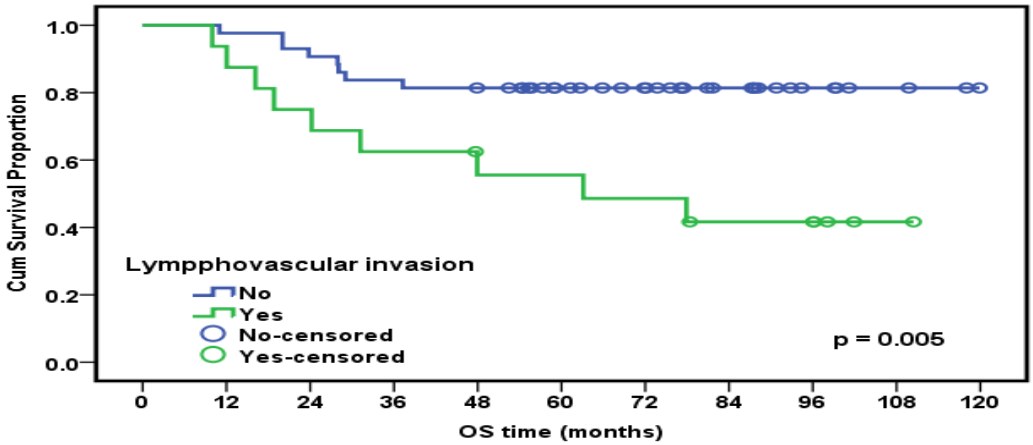

Figure 8: Kaplan Meier curve of *Overall survival* in association with microvascular invasion

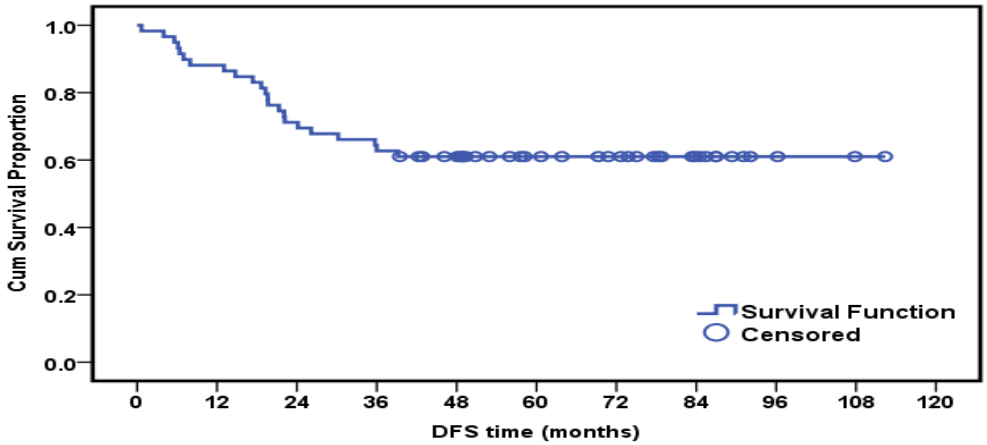

Figure 9: Kaplan Meier curve of DFS to the whole group

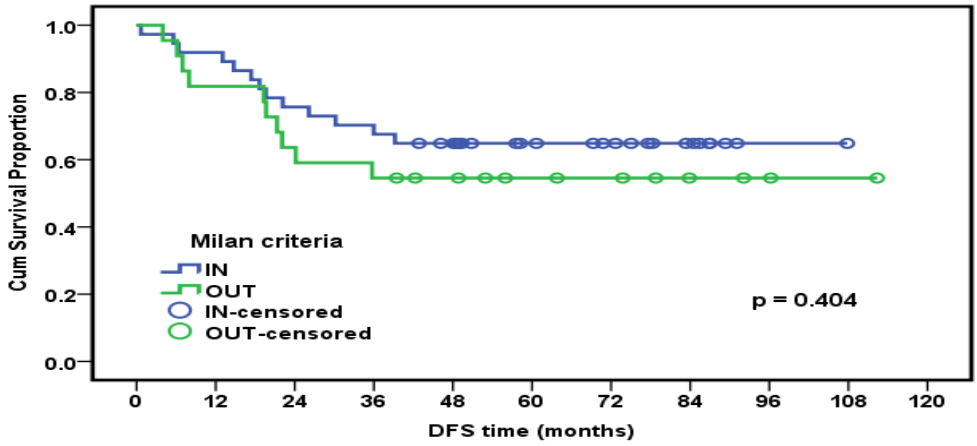

Figure 10: Kaplan Meier curve of DFS association with to MC

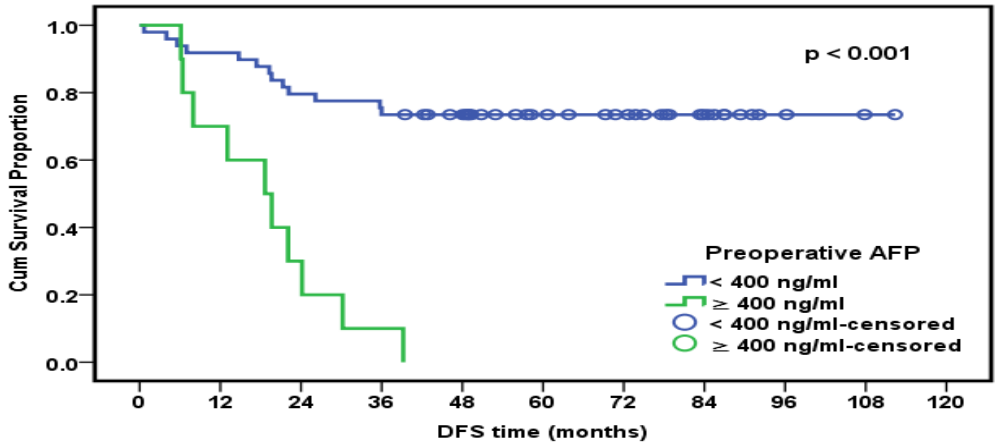

Figure 11: Kaplan Meier curve of DFS in association with preoperative AFP at 400 ng

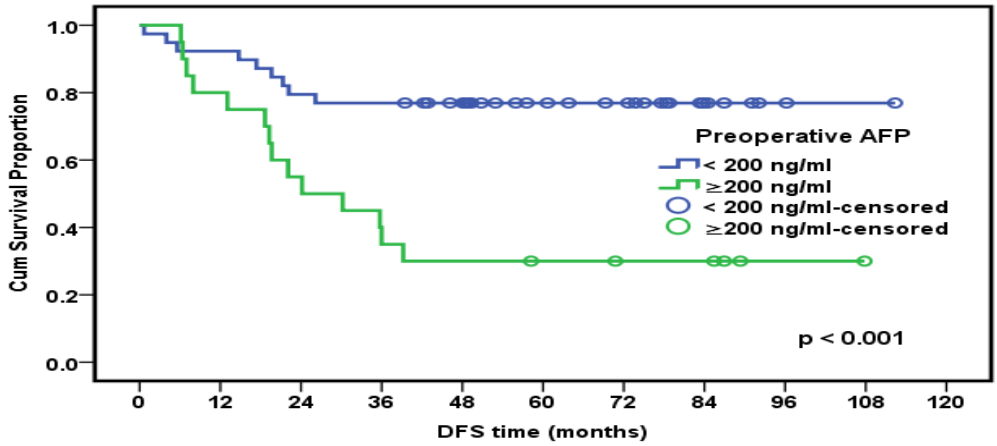

Figure 12: Kaplan Meier curve of DFS in association with preoperative AFP at 200ng

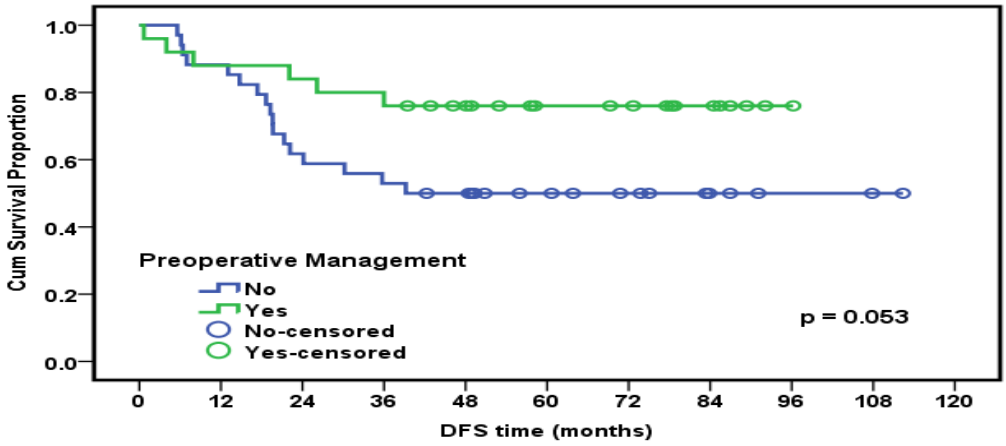

Figure 13: Kaplan Meier curve of DFS in association with preoperative management

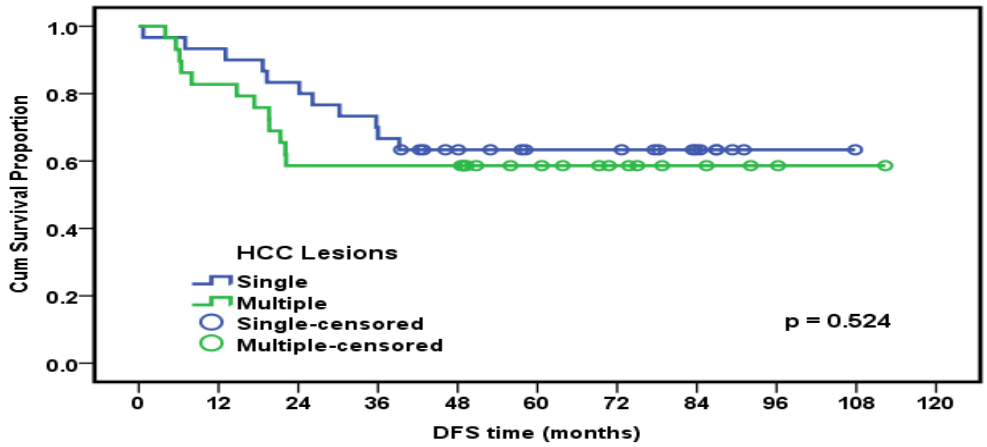

Figure 14: Kaplan Meier curve of DFS in association with HCC lesion being single or multiple

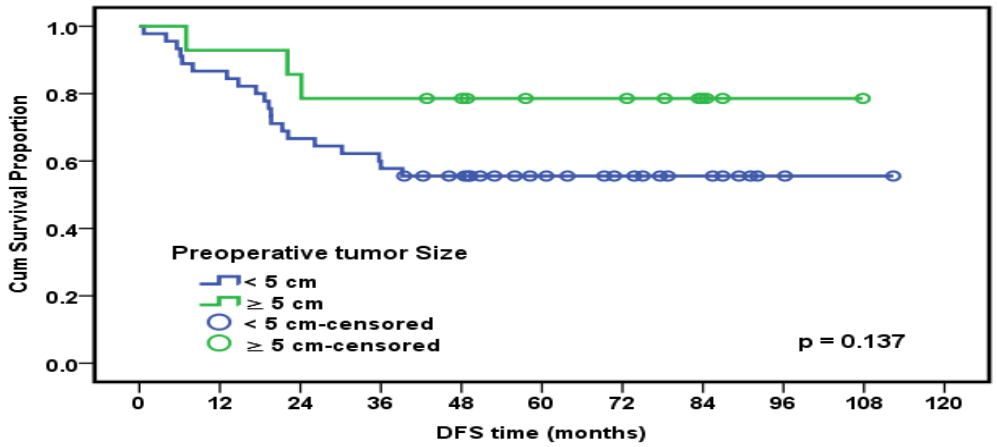

Figure 15: Kaplan Meier curve of DFS in relation size of biggest lesion

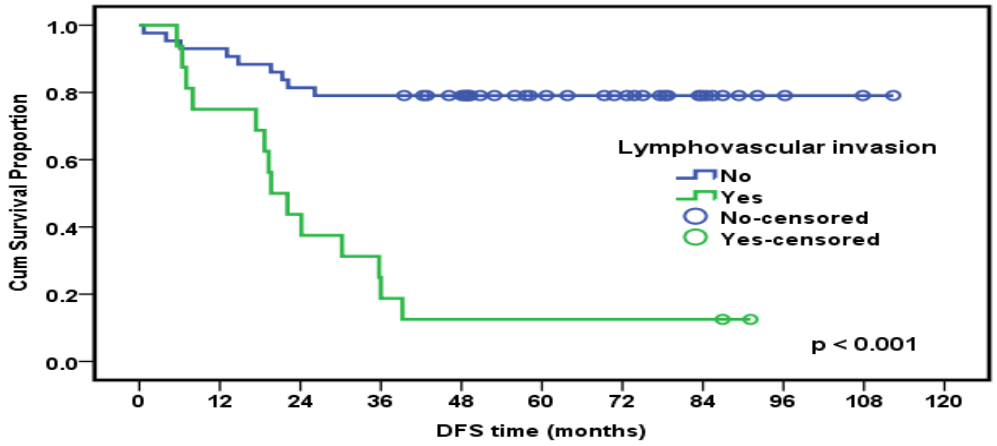

Figure 16: Kaplan Meier curve of DFS in association with microvascular invasion

Discussion

In the context of post-transplant hepatocellular carcinoma recurrence, the paradox of the "two hundred % death rate" is frequently referenced. This paradox not only pertains to the cases who ultimately succumbs to tumour recurrence following transplantation, but additionally to another possible liver recipient who didn't receive the same graft [13].

The adoption of strict macro-morphological selection criteria (number & size of nodules) has resulted in a remarkable enhancement in rate of survival for transplanted hepatocellular carcinoma cases over the past numerous years. However, a number of recent investigations have demonstrated the limitations of such criteria in terms of their ability to predict the patient's long-term prognosis [9].
cases who have cirrhosis are at an elevated possibility for developing hepatocellular carcinoma; a yearly occurrence of this condition seen in cases with cirrhosis is three percent. The prognosis for cases suffering from the illness is poor, as the number of new cases is approximately equivalent to the number of mortality [14].

The choice of cases with hepatocellular carcinoma for liver transplantation has consistently been a topic of debate. The prolonged outcomes of liver transplantation in hepatocellular carcinoma cases were greatly enhanced by the strict selection criteria that clinicians established in response to the frustrating experiences of the early days of LT with advanced cancer.

A recurrence following transplantation may manifest in 2 different situations: Initially, when an extra-hepatic metastasis was missed (or undetectable) during the pre-transplant work-up. Secondly, a recurrence may additionnally result from the engraftment & growth of circulating hepatocellular carcinoma cells in a target organ throughout the duration before transplantation. Following transplantation, it is predicted that such recurrences will manifest earlier due to the higher initial tumors load of the first mechanism. The detected bimodal distribution of recurrences, with the majority occurring within the first eighteen months of life & a few, more indolent, being diagnosed up to ten years following transplantation, may be explained by these two mechanisms [15].

In the current study the overall survival result at one, 3, five -years was 94.9 percent, 78% & 74.5% respectively. The recurrence free survival at one, three, & five years was 88.1%, 64.5% & 62.7% respectively. The overall survival in cases who had recurrence was less than 40 % but was 81.8 % in patients who had not experienced recurrence. All patients with recurrence & still alive represent a big challenge in their management & health financial budget. Also, the health care related quality of life in those cases is dramatically affected giving another bad face to hepatocellular carcinoma recurrence after LT.

Compared to the natural history of untreated hepatocellular carcinomas in cases suffering from cirrhosis, where the 3-year rate of survive for cases with cirrhosis & untreated hepatocellular carcinomas is nearly zero percent, transplantation is the sole life-saving treatment for cases with unresectable hepato-cellular carcinomas & cirrhosis [16].

Roayaie & colleagues documented an eighteen percent occurrence of tumor recurrence in over 300 cases who underwent transplants for hepatocellular carcinomas. The five-year survival rate was significantly lower in cases with recurrence (twenty-two percent) compared to those without (sixty-four percent). Vascular invasion was observed in the majority of cases (eighty-eight percent) with recurrent tumor [17].

The important research of Mazzaferro in 1996, demonstrated that the total death rate was seventeen percent. Following four years, the rate of survival was seventy-five percent , & the rate of recurrence-free survival was eighty-three percent [14].
Hepatocellular carcinoma recurred in 4 cases (eight percent). The overall & recurrence-free survival rates at 4 years were eighty-five percent & ninety-two percent, respectively, for the thirty-five cases (seventy-three percent of the total) who met the predetermined criteria for the selection of small HCC at pathological review of the explanted liver. In contrast, the rates for the thirteen cases (twenty-seven percent) whose cancers exceeded these limits were fifty percent & fifty-nine percent, respectively (P -value less than 0.01 for overall survival; P-value less than 0.002 for recurrence-free survival) [14].

The recurrence of HCC in our study was 25.4 % (15 out of 59) which is close to the mean rate of all reported studies in literature (around 20%). However, it is not optimal, & this can be attributed to the following: Firstly, we are entirely reliant on living donation, & occasionally we have succumbed to family pressure & transplanted unsuitable cases. Secondly, we might have a different form of Hepatocellular carcinoma compared to other regions due to our distinctive infection with HCV. This finding might motivate the transplant community in Egypt to develop novel criteria depend on results drawn from our cases.

Recurrence of hepatocellular carcinoma still occurs in ten to twenty percent of cases within the 1st five years following liver transplantation, despite the Milan criteria, which are regarded the benchmark for the selection of candidates for liver transplantation, being based on cancer number & size. It has become increasingly apparent that post-transplant outcomes are greatly affected by factors other than the number & size of Hepatocellular carcinomas. An area of intense research interest has been the detection of cancers & biologic markers that can successfully predict cancer recurrence or microvascular invasion [18].

Felga et al., conducted 130 OLT for unresectable Hepatocellular carcinoma within the Milan Criteria. Nine cases (6.9 percent) experienced tumor recurrence. In five (55.6 percent) & two (22.2 percent) cases, respectively, microvascular & macrovascular invasion have been detected. Recurrence has been observed in the liver (number = three; 33.3 percent), lung (number = three; 33.3 three), brain, peritoneum, & adrenal gland (number = one each; 11.1 percent each) 23.1 ± 14.3 months following OLT. Hepatocellular carcinoma recurrence can happen following OLT, despite the strict candidate selection criteria, which has significant effects on post-transplant results. To optimize outcomes, it is necessary to refine candidate selection & establish a well-defined, cost-effective post-OLT surveillance protocol [19].

In the current investigation, there was a recurrence of Hepatocellular carcinoma after transplantation in 15 cases, 7 of them (46.7 %) met the widely adopted Milan criteria for patients' selection. 37 patients (62.7 %) were within the limits of MC where 22 patients (37.3 %) were considered outside with recurrence free survival of 64.9 % & 56.5% respectively (p = 0.404).

In order to exclude cases with tumors from OLT with an elevated probability of relapse, Milan criteria have been established. However, multiple investigations have shown that size &

number of tumors have a restricted ability to predict the prognosis of OLT. This is due to the fact that a significant number of cases who didn't meet the Milan criteria exhibited a favorable long-term disease-free survival [20].

Roayaie et al., conducted one of the earliest investigations to query the MC. Eighty cases have been included; thirty-seven percent were ultimately excluded, primarily due to progression of the illness while on the list of waiting, & forty-three underwent a LT. The mean pathologic tumor diameter was 5.8 ± 2.7 centimeters the median follow-up period for transplanted cases who survived was 55.1 ± 24.9 months. 2 (4.7 percent) deaths before operation. The median overall survival of transplanted cases was significantly greater (49.9 ± 10.42 months) compared to that of those who have been excluded (6.83 ± 1.34 months). At five years, the total & recurrence-free survival rates of transplanted cases were forty-four percent & forty-eight percent respectively. Recurrence was significantly associated with a tumor size bigger than seven centimeters & the presence of vascular invasion. The thirty-two cases with tumors measuring between five & seven centimeters (fifty-five percent) had a significantly greater recurrence-free survival rate at five years of age than twelve cases with tumors larger than seven centimeters (thirty-four percent). A significant proportion of cases with hepatocellular carcinoma that is five centimeters or larger can attain prolonged survival following liver transplantation. cases with tumors that are between five & seven centimeters in size have significantly longer recurrence-free survival [21].

On the other hand, Mazzaferro et al., conducted the initial systematic review to evaluate the efficacy of the MC as an independent prognostic factor that impacts the results of liver transplant for the management of hepatocellular carcinoma. It has been established that hepatocellular carcinoma that meet the MC are a distinct prognostic category that has been related to good results following liver transplant (a five-year survival rate of at least seventy percent). This has resulted in the worldwide assimilation of the MC into transplant indications, staging systems, & prioritization policies. [22].

However, the present study failed to demonstrate any significance for MC as enlisting tool for transplantation in hepatocellular carcinoma, it is not wise to take this as a conclusion to abandon it entirely. The analysis depended on numbers & we have seen single tumor measured 5.1 cm & this considered outside MC & on the other hand a single tumor measured 5 cm & this considered within MC. The debate could be about; should we expand it & for what extent.

Historically, the serum a-fetoprotein (AFP) concentration has been utilized to screen high-risk groups for hepatocellular carcinoma & to confirm the diagnosis. It is no longer recommended to be used in these clinical settings due to its inadequate diagnostic capabilities. However, serum a-fetoprotein is presently playing an increasingly significant role as a biomarker of tumor biologic aggressiveness. The prognostic significance of serum a-fetoprotein before surgery in resection of liver & liver transplant has been confirmed by a multitude of research. Nevertheless, there is no consensus regarding the most suitable criterion for serum a-fetoprotein when choosing hepatocellular carcinoma cases for liver transplant [23].

One of the major outcomes of the current investigation is that Cox regression analysis of the data collected support the rationale of including serum a-fetoprotein in the existing criteria are in accordance with the outcomes in previous reports. Notably, serum a-fetoprotein less than 200 nomogram per milliliters was independent predictor of tumor recurrence (p - value less than 0.001), whereas the number of tumors did not (p = 0.326).
It is worth mentioning that in Egypt, the significant AFP cutoff level used to diagnose HCC is 200 nanogram per milliliters (in cases with hepatic focal lesion in cirrhotic liver) due to high occurrence of hepatitis C virus infection and HCC.

The existing & already popular selection criteria have been utilized to identify the optimal serum a-fetoprotein cutoffs then utilized to develop a protocol for their modification. These cutoffs have been determined using prediction curves that were

derived from Kaplan-Meier recurrence-free survival estimates. We examined the two most frequently used cutoffs: 200 nanogram per 7milliliters & 400 nanogram per milliliters. Hepatocellular carcinoma recurrence and survival following LT were significantly correlated with serum a-fetoprotein levels of ≥ 400 nanogram per milliliters (p-value less than 0.001). AFP levels with a cutoff at ≥ 200 ng /ml showed no significant correlation (p = 0.071) with overall survival though it was an important predictor of recurrence (p = 0.001). This finding could be of great clinical significance if interpreted on individual basis for each patient where we can use any AFP cutoff level to gain the maximal benefit for individual patient.

Serum a-fetoprotein has been observed to reflect biological malignancy in early Hepatocellular carcinoma. It isn't expressed in well-differentia7ted Hepatocellular carcinoma && is correlated with intrahepatic metastases & vascular invasion. Despite the fact that the prognostic significance of serum a-fetoprotein in non-transplant cases has been established, the prognostic value of serum a-fetoprotein concentration in Hepatocellular carcinoma transplant candidates & their effect on liver transplant outcomes have been a debate. Decreased post-transplantation survival has been related to pre-transplantation levels exceeding 1000 nanogram per milliliters 13 or 300–400 nanogram per milliliters. Nevertheless, there is still a lack of consensus in terms of serum a-fetoprotein thresholds that can accurately predict a poor prognosis, & the prospective validation of the a-fetoprotein level in the choice of Hepatocellular carcinoma candidates hasn't been conducted [24].

Duvoux et al., also assessed the concept of integrating serum a-fetoprotein with the morphologic characteristics of the tumor. The authors of that highly pertinent report developed a predictive model for recurrence of tumor that surpasses the Milan criteria in terms of its capability to classify cases into low- & high-risk groups. This model depends on the number of tumor nodules, the size of the cancer, & the serum a-fetoprotein concentration. The outcomes of the current research suggest that the Milan criteria may be slightly expanded without adversely affecting the possibility of recurrence, in contrast to the intriguing proposal of replacing them entirely with a new risk index [25].

In an investigation that involved ninety-two cases who underwent liver transplants for hepatocellular carcinoma, Yaprak et al., discovered that the a-fetoprotein concentration can be used to differentiate between those at low- & high-risk of cancer recurrence [26].
It is important to note that the findings of the current research suggest that the optimal cutoffs might vary substantially among cases within & beyond specific selection criteria. This is a reasonable conclusion, given the association among a-fetoprotein & tumor size. In addition, the findings of the present investigation underscore the inverse correlation among the possibility of recurrence & a-fetoprotein, which may be beneficial in clinical practice regardless of whatever the proposed expansion of selection criteria.

A cohort of 158 consecutive adult cases who have liver transplant for hepatocellular carcinoma at the Rome Inter- University Consortium for Organ Transplantation from January 1999 to November 2008 was retrospectively analyzed. Twelve recurrences (7.6 percent) have been identified. At the multivariate analysis, the most significant predictors of recurrence were alpha-fetoprotein >400 nanogram per milliliters (odds ratio [OR] 8.4, p-value less than 0.01) & total tumor diameter (TTD) above eight centimeters (OR 7.4, p -value equal 0.01). The AFP-TTD criteria caused a 22.2 percent rise in the number of LT & a low rate of five-year recurrence (4.9 percent) in comparison to the MC. The five-year disease-free survival rate in cases who met the AFP-TTD criteria was 74.4 percent, with greater efficacy in stratifying the cohort based on the MC. Total tumor diameter & a-fetoprotein are both reliable independent predictors of the recurrence of Hepatocellular carcinoma. Their combination appears to improve the choice of candidates for liver transplant without compromising cases survival & recurrence rates. This approach enables a rise in the number of cases who may be eligible for transplantation [27,28,29].

An investigation from University of Tokyo, Tokyo, Japan among January 1996 & December 2012; 124 cases have been identified as having Hepatocellular carcinoma throughout the pretransplant work-up & have been invstigated in detail. The maximal a-fetoprotein value is a critical factor in the prognosis of cases who are undergoing liver transplantation for Hepatocellular carcinoma. Incorporating this tumor marker with conventional indication criteria may facilitate the more accurate stratification of cases with a high probability of recurrence of tumor & a poor prognosis [30].

Several selection criteria using a-fetoprotein have been proposed to date, as the Seoul criteria, total tumor volume/AFP (TTV/AFP) criteria & Hangzhou criteria. The Seoul criteria have been established as the greatest cancer size being no more than five centimeters & hepatocellular carcinoma levels being less than 400 nanograms per milliliter, regardless of the number of cancers. The authors of the Hangzhou criteria suggested an identical cutoff. They suggested that liver transplantation may be considered appropriate for all cases with well- or moderately differentiated cancers & an a-fetoprotein concentration of less than 400 nanogram per milliliters [31].

De Mattos et al carried out a retrospective investigation of 768 cases undergoing liver transplantation among 1997 & 2010 (206 with a histological diagnosis of hepatocellular carcinoma). The most prevalent cause of cirrhosis was additionally hepatitis C. cases have been monitored for a maximum of 173 months (mean 549.8 months). The survival rates of liver transplantation recipients were 78.5 percent, 65.4 percent, 60.5 percent, & 38.7 percent at years one, three, five & fourteen respectively. AFP concentration has been related to recurrence of tumor, & the survival rate was greater in the recurrence-free group compared to in cases with recurrence of hepatocellular carcinoma (P-value less than 0.001). The rate of hepatocellular carcinoma recurrence in cases with a-fetoprotein levels less than fifty nanogram per milliliters was 13.1 percent at the 5-year post-transplant follow-up. The rates were 29.4 percent for a-fetoprotein concentration of fifty to two hundred nanogram per milliliters & 36.7 percent for a-fetoprotein concentration greater than two hundred nanogram per milliliters (P50.002). A hazard ratio (HR) of 3.85 [ninety-five percent confidence interval (CI)51.66-8.93, P50.002] was observed for a-fetoprotein levels exceeding 200 nanogram per milliliters in a univariate analysis of risk factors for hepatocellular carcinoma recurrence. Additional risk factors for recurrence included the number of tumors (HR51.37, ninety-five percent CI51.20-1.56, P-value less than 0.001), the degree of differentiation (HR52.28, 95% CI51.18-4.39, P50.014), vascular invasion (HR54.82, 95% CI52.08-11.17, P-value less than 0.001), & the occurrence of satellite nodules (HR53.33, 95% CI51.66-6.68, P50.001). Only a-fetoprotein levels exceeding 200 nanogram per milliliters were recognized as a risk factor in a multivariate analysis, with a hazard ratio of 3.32 (ninety-five percent CI 51.40-7.91, P50.007). It is believed that the limited number of cases who meet this criterion & the requirement for a more stringent standard for organ allocation make very high levels of a-fetoprotein (>1000 nanogram per milliliters) restrictive, despite the wide range of values identified in the literature [33].

In the current investigation, we demonstrated that the a-fetoprotein concentration at listing was an independent predictor of recurrence following transplantation for hepatocellular carcinoma & additionally predicted survival following transplantation. The a-fetoprotein values at listing are now combined with the standard criteria of cancer size & quantity, based on this. In comparison to the Milan criteria alone, this practice significantly enhances the prediction of hepatocellular carcinoma recurrence. Decreased post-transplantation survival has been related to pre-transplantation levels exceeding 400 nanogram per milliliters. Nevertheless, no consensus has been reached regarding a-fetoprotein thresholds that could accurately predict a poor prognosis. This could be due to difference in HVC prevalence which affects the sensitivity & specificity of the test & it is a good practice to tune the cutoff according to the centre experience & outcome to achieve the optimum level to assess any patient to enlist for transplantation.

Macroscopic vascular invasion is another strong predictor of hepatocellular carcinoma recurrence & an independent prognostic parameter. After the exclusion of cases with macroscopic vascular invasion & inadequate hepatocellular carcinoma differentiation, it was feasible to increase the tumor size beyond the five centimeters threshold without compromising survival. In addition, molecular signatures are currently being assessed as surrogate markers of predictors of recurrence of tumor & tumor biology [34]

Bismuth et al., were the 1st to demonstrate that the surgical strategy for the management of hepatocellular carcinoma in cirrhosis in the early era of liver transplantation had been based on a misconception, which involved the selection of cases with advanced, & consequently unresectable, tumors as transplant candidates. However, the most favorable outcome was observed in small hepatocellular carcinoma foci, which are frequently suitable for resection. Nevertheless, the current state of pretransplantation & intraoperative diagnostic imaging has still not been able to reliably differentiate among cases with hepatocellular carcinoma in cirrhosis & those without a vascular infiltration. Unfortunately, the issue of microscopic tumor cell dissemination is particularly significant in liver transplantation, as posttransplantation immunosuppression appears to modify the kinetics of tumor cells [35].

Recent investigations demonstrate the importance of microscopic vascular invasion as an independent prognostic factor for hepatocellular carcinoma cases having resection or transplantation, but this histopathologic variable can't be utilized for choosing before surgery because it is only measurable by histopathology on the explanted liver. According to certain investigations, the histologic grade of the hepatocellular carcinoma is the primary predictor of microvascular invasion. This grade can be identified prior to surgery through percutaneous needle biopsy [36].

However, the pre-OLT fine-needle biopsy has been demonstrated to have a weak correlation with the grading of the tumor & the occurrence of microvascular invasion in comparison to the post-OLT histopathologic examination of the resected hepatocellular carcinoma [37].

However, cases who underwent preoperative liver biopsy exhibited a nearly eightfold increased possibility of recurrence of extrahepatic cancer following OLT, with a median risk of 2.3 percent for cancer propagation. The issue of cancer sampling error is another caveat of tumor biopsy, as it may not include a representative sample of tumor tissue. In order to avoid fine-needle biopsy, it is necessary to identify surrogate markers of vascular invasion (e.g., cancer size) & cancer malignancy (e.g., cancer growth rate). It has been documented that the possibility of recurrence of tumor is correlated with the extent of the cancer, rather than the number of tumor nodules, & with vascular invasion.

Additionally, the survival rate wasn't significantly impacted by the number of hepatocellular carcinoma nodules [38].

Furthermore, because of the possibility of sampling error, non-invasive methods for recognizing cancer microvascular invasion are currently being investigated. For example, des-gamma-carboxy thrombin was identified as a promising surrogate marker; however, additional research is required to verify these findings [34].

Quirino et al., recently published a paper that discusses a novel and straightforward prognostic score that is derived from the combination of pre-operatively available variables in cases with hepatocellular carcinoma who are awaiting liver transplantation. Recent research has demonstrated that the possibility of intention-to-treat (ITT)-recurrence & death is significantly influenced by the extent of radiological response to loco-regional therapies, inflammatory markers, duration of the waiting period & the alpha-fetoprotein modification. The training set consisted of 179 hepatocellular cancer cases who were listed for liver transplantation from January 2000 to December 2012, while the validation set consisted of 110 cases who were listed from January 2005 to December 2014. The most accurate predictor of microvascular invasion was the Time-Radiological-response-Alpha-fetoprotein-INflammation (TRAIN) score that has been proposed. In terms of ITT & recurrence survivals, both the investigated populations

were admirably stratified by a TRAIN score >=1.0. The proposed score enabled the acquisition of an increase in the number of potentially transplantable cases (+8.9 percent in the training set & 24.6 percent in the validation set) without additive recurrence possibilities when contrasted with Milan criteria [39].

The current investigation concentrated on the variables that predicted the recurrence of HCC in a cohort of fifty-nine cases, both pre-transplant & post-transplant. We discovered that microvascular invasion, which was detected following the explanted liver & been examined, was linked to the recurrence of hepatocellular carcinoma & was additionally one of the independent predictors of survival following transplantation. In sixteen cases, vascular invasion has been identified, & fourteen of them experienced recurrence. The DSF rate was adversely impacted (p-value less than 0.0001). Additionally, the presence of vascular invasion resulted in a dismal overall survival rate (p-value = 0.005). The Hazard ratio of 3.567 (ninety-five percent % CI 1.374-9.266) & p-value of 0.009 indicated a significant negative effect of vascular invasion in the Cox regression analysis.

Our data are supporting the growing evidence that microvascular invasion has a negative effete on outcome following transplantation. Macrovascular invasion could be detected during the pretransplant workup. On the other hand, microvascular invasion is a histopathologic diagnosis that can't be determined before the liver specimen is &. Due to the significant impact of microvascular invasion on survival and recurrence following transplantation, numerous studies are currently being conducted to identify surrogate markers or methods for predicting microvascular invasion during the pretransplant period.

In recent years, the use of transarterial chemoembolization & radiofrequency ablation techniques as neoadjuvant bridging therapies before LT have become more prevalent [201, 202]. In the present day, transarterial chemoembolization is the locoregional standard of care for LT candidates in cases where resection of liver isn't possible. Several investigations & evaluations have provided information on the efficacy & technique of transarterial chemoembolization up to the present day. Conversely, there were substantial disparities in the nature of the research, the number of cases included, the intended therapies, the criteria for identifying LT, & the percentage of cases who dropped out due to their tumors. The exact prognostic effect of transarterial chemoembolization in the context of liver transplantation for Hepatocellular carcinoma is still unknown [8].

In an evidence-based analysis, Lesurtel et al., carried out an electronic search on Medline database (1990–2005) to find relevant research evaluating the role of pre-transplant transarterial chemoembolization. The authors found that there is currently insufficient evidence to suggest that transarterial chemoem-bolization as a bridging treatment provides any benefit for LT cases with early or advanced Hepatocellular carcinoma , either in terms of result following transplantation or in terms of predicting pretransplant drop-out, based on this analysis [40].

The validity of this study was heavily criticized due to lack of randomised controlled trials which is not easy to conduct in HCC patients for ethical & technical reasons.
An investigation was conducted to examine the impact of transarterial chemoembolization on the prolonged survival of 116 cases with hepatocellular carcinoma who have been listed for liver transplantation. The drop-out rate was twenty percent in cases with Hepatocellular carcinoma that exceeded the MC, whereas none of the cases meeting the MC have to be removed from the waiting list. The early-stage Hepatocellular carcinoma group experienced a post-transplant hepatocellular carcinoma recurrence rate of 2.4 percent, while the advanced Hepatocellular carcinoma population experienced a rate of thirty percent. The authors determined that transarterial chemoembolization is a viable neoadjuvant management option for cases with hepatocellular carcinoma who meet the criteria, but it is not effective for those who exceed the MC [41].

In an intent-to-treat analysis of the effect of clinical response of cancer to transarterial chemoembolization (estimated on computed tomography scans) on overall survival, a total

of 116 cases have been involved in an investigation. The intent-to-treat analysis revealed that cases who experienced a complete (no vital tumor on control computed tomography) or partial (devascularization ≥ thirty percent on control computed tomography) response to transarterial chemoembolization had a significantly better one-, two, & five-year survival rate (hundred percent, 93.2 percent, & 85.7 percent, respectively) than those who didn't have an adequate response or even cancer progression under transarterial chemoembolization (82.4 percent, 50.7 percent, & 19.3 percent). Finally, one hundred & six cases have undergone liver transplantation. Similarly, cases who experienced a complete or partial response to transarterial chemoembolization had a significantly improved result following transplantation than those who did not (Millonig et al., 2007).

A group from Royal Free hospital reported the benefit of pre-transplant transarterial chemoembolization on a group of 150 patients

& concluded that Pre-transplant transarterial chemoembolization significantly decreases hepatocellular carcinoma recurrence following transplantation in cases within the Milan criteria[43].

In contrast, many recent investigations have been able illustrate the beneficial role of transarterial chemoembolization in the selection an&d treatment of LT cases with hepatocellular carcinoma beyond MC.
Otto et al., documented on 96 consecutive liver transplant cases with hepatocellular carcinoma who had recurrent transarterial chemoembolization procedures [208]. 63 of them demonstrated hepatocellular carcinoma that exceeded the MC on clinical staging. Ultimately, fifty cases underwent liver transplantation; thirty-four of them were beyond MC at the time of pretransplant clinical staging. The five-year survival rate of the entire research group (*n*umber= ninety-six) was 51.9 percent. The freedom from recurrence after five years was 94.5 percent in cases (*n*umber= 39) with progression-free transarterial chemoembolization & 35.4 percent in those with tumor progression despite transarterial chemoembolization (*n*umber= 11; *P* -value equal to 0.0017). The rate of recurrence-free survival five years following liver transplantation was similar among cases who met the minimum criteria (93.8percent) & those who exceeded it (74.5%; *P*-value equal to 0.421). The authors decided that the successful transplantation of even large & multifocal hepatocellular carcinoma can be achieved by utilizing a sustained response to transarterial chemoembolization as a biological collection criterion [44].

It has been established that progression of Hepatocellular carcinoma during locoregional bridging treatment is one of the independent risk factors for Hepatocellular carcinoma recurrence following transplantation. The prognostic significance of post-interventional cancer necrosis in the context of liver transplantation for advanced cancer has also been documented [20].

Numerous other trails have recently confirmed the exceptional prognostic value of cabcers necrosis/nonviable hepatocellular carcinoma on explant histopathology for attaining recurrence-free prolonged findings [45].

In the current investigation, twenty-five cases (42.4 percent) underwent locoregional interventions before transplantation, with the majority of them receiving transarterial chemoembolization for a variety of indications. The results of the Cox regression analysis indicate that interventions before transplantation have a hazard ratio of 2.443 (ninety-five percent confidence interval: 0.965–6.209) & a p-value of 0.061. Additionally, this variable has a more positive impact on recurrence-free survival than on overall survival in the context of survival analysis, with a p-value of 0.053 & 0.107, respectively. The figures aren't statistically significant, but they were extremely nearby. This can be attributed to the sample size's low power.

In an international consensus conference held in 2010 in London, the recent practice of liver transplantation in cases with hepatocellular carcinoma has been re-evaluated & internationally accepted statements have been developed. A total of seventy-seven statements have been established, which addressed all aspects of

liver transplantation in cases suffering from HCC. Of these, five statements addressed the treatment of cases on the waiting list. Although the level of evidence is still limited, locoregional treatment might be appropriate for cases with hepatocellular carcinoma within the MC. Although there is no recommendation for the utilization of bridging treatments in cases with advanced hepatocellular carcinoma, there are raising indicators of the value of transarterial chemoembolization as a biological choice apparatus prior to liver transplantation [46]

However, the result of our study regarding the issue of pre-transplant management is not supporting its use on regular basis to improve the findings of LT as a management for hepatocellular carcinoma, it is very encouraging to do further researches in that topic.

It has been illustrated that pharmacologic immunosuppression, traditionally based on calcineurin inhibitors (CNI), represents an independent risk factor for hepatocellular carcinoma recurrence; by using Sirolimus (SRL) which acts as a primary immune-suppressant or antitumor agent, exposure to calcineurin inhibitors might be diminished, dropping the possibility of hepatocellular carcinoma recurrence[47].
Zhou et al., retrospectively evaluated seventy-three consecutive cases who underwent OLT for hepatocellular carcinoma that exceeded the Milan criteria. Twenty-seven cases have been received treatment with Sirolimus-based immunosuppressive protocols following OLT, while forty-six cases have been managed with an FK506-based protocol. The intent-to-treat method was employed to conduct the statistical analysis. The Sirolimus group had a mean overall survival of 594 ± 35 days, while the FK506 group had a mean overall survival of 480 ± 42 days (P _.011). The Sirolimus group had a mean disease-free survival duration of 519 ±43 days, while the FK506 group had a mean disease-free survival duration of 477 ±48 days (P_.234). They determined that the SRL-based immunosuppressive protocol enhanced the total survival of cases with hepatocellular carcinoma that exceeded the Milan criteria following OLT. This improvement was likely achieved by delaying recurrence & enhancing tolerability [48].

The same conclusion was obtained in another investigation conducted by Toso et al., who discovered that sirolimus-based immune-suppression correlated with enhanced cases survival following liver transplantation for hepatocellular carcinoma. They believed that these findings would be beneficial in the management of hepatocellular carcinoma cases during transplantation. This will involve the integration of a balanced selection of candidates with expected good results & a adjuvant therapy following transplantation that includes suitable & efficient immune-suppression with anticancer properties [15].

There is RCT underway comparing sirolimus-containing versus mTOR inhibitor-free immune-suppression in cases undergoing LT for HCC & waiting its outcomes [49].ff
In the current study we did not include immunosuppression protocols in the final assessment because we did not start using sirolimus till recently. However, so far, we have 6 patients surviving with HCC recurrences in the study group & all of them receiving sirolimus based immunosuppression.
There are many contradicting reports in literature about the prognostic effect of recipient & donor age, operative time, extent of transfusion, graft size, length of both cold & warm ischaemia time, MELD score & Child class. We could not find any statistical significance to any one of these variables however; this statement shouldn't be taken as a definite conclusion giving the retrospective nature of our investigation & the limitations it has. These variables are still in need for further assessment for better patient selection & outcome.

Most cases with recurrent hepatocellular carcinoma following liver transplantation in the present research had extrahepatic metastasis & multifocal lesions (66.7 percent). Consequently, local therapy may not be an effective management for recurrent hepatocellular carcinoma following liver transplantation. Additionally, cases who have been administered immunosuppressants to prevent allograft rejection may experience decreased tolerance to systemic chemotherapy. This has made many clinicians hesitate to begin chemotherapy, although some reports have

demonstrated the effectiveness & safety of chemotherapy in cases who have undergone a transplant. Furthermore, the efficacy of liver-directed therapy, including hepatic resection, radiofrequency ablation, or trans-catheter arterial chemoembolization/infusion (TACE/I), in the context of isolated intrahepatic relapse following LT has not been established. However, the advantages of local treatment in other clinical settings for hepatocellular carcinoma are well-established. The natural history & most effective management protocol for relapsed hepatocellular carcinoma following liver transplantation are not well-documented [50].

Surgical management as rejection of transplanted liver or metastatic lesion has been documented as an independent predictor of survival [51].
However, evaluation of various therapies of recurrence is beyond the scope of our research; five cases received surgical metastasectomy. Their overall survival was relatively lengthier than that of previous investigations; three individuals were still alive at the time of analysis. Nevertheless, it was challenging to determine whether surgical management of recurrence extended the survival of cases & to identify the characteristics of cases who are more probable to benefit from surgical therapy. Other modalities such as TACE or RFA are feasible if resection is not possible & the recurrences are still in the confinement of the transplanted liver.

The preliminary findings indicate that sorafenib is a safe & efficacious management for recurrent hepatocellular carcinoma following OLT. Utilization of sorafenib before liver transplantation doesn't raise the possibility of surgical complications, even when used until the day of the operation [52].
A recent meta-analysis regarding the role of sorafenib in recurrence of hepatocellular carcinoma following liver transplantation concluded that further data from multicenter perspective research is necessary to definitively determine whether sorafenib is a safe & acceptable management for recurrence of hepatocellular carcinoma after liver transplant. However, it is advisable to avoid its correlation with m-Tor inhibitors [53].

Conclusion

This retrospective investigation determined that LDLT is a viable management option for cases with hepatocellular carcinoma, with appropriate morbidity (provided that the data is available) & favorable five-year overall & DFS rates. We discovered that the presence of microvascular invasion & a pre-operative AFP concentration (>400 nanogram per milliliters) were independent risk factors for overall survival, while the presence of microvascular invasion & a pre-operative AFP concentration (>200 nanogram per milliliters) were independent risk factors for DES. The patient's Milan criteria status did not accurately predict their overall or disease-free survival.
Our data suggests that the Milan criteria alone should not be used for the decision of whether to transplant HCC patients. The number & size of cancers may not be as important as other factors such as pre-operative AFP concentration in predicting disease recurrence. However, further prospective multi-centred investigation is needed before our current practice is changed.

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