Living donor liver transplantation for hepatocellular carcinoma: Milan criteria versus University of California San Francisco

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Introduction
Hepatocellular carcinoma (HCC) is the most common primary liver cancer and most patients with HCC also suffer from coexisting cirrhosis. HCC recurrence is a major concern after liver transplant. The Milan criteria was accepted after a good 5 years survival but was criticized for being so restricted and this criticism promoted the appearance of more expanded criteria like the University of California San Francisco (UCSF). Our study compares the results of both Milan and UCSF criteria and the risk factors for recurrence.

Patients and methods
This study included 60 patients had living donor liver transplantation for HCC between January 2011 and December 2016 in Ain Shams Center for Organ Transplantation. They were divided into two groups. Group A: transplanted within the Milan criteria; and group B: transplanted while beyond Milan but within the UCSF criteria. Both groups are compared as regards the recurrence, survival, and risk factors for recurrence.

Results
There is no statistically significant difference between the two groups as regards the survival and recurrence. The 1 and 3 years survival were 86.5 and 71.9% for the Milan group and 81.7 and 61.4% in the group of patients beyond Milan (statistically nonsignificant, P=0.348). Seven (15.1%) patients from the Milan group had recurrence while in the beyond Milan group four (28.6%) patients had recurrence (statistically nonsignificant, P=0.258). There were no statistically significant difference in microvascular invasion (P=0.388), tumor grade (P=0.207), and α-fetoprotein (P=0.112) between both groups.

Conclusion
Milan criteria can be safely expanded to UCSF with comparable results if responding well to downstaging and with low α-fetoprotein.

Keywords:
beyond Milan criteria, hepatocellular carcinoma, living donor liver transplantation, Milan criteria

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Introduction

Hepatocellular carcinoma (HCC) constitute about 80–90% of all liver malignancies [1]. Although there are different modalities for HCC treatment, liver transplant is considered a superior modality as it does not only remove the tumor from the body, but also remove the whole diseased organ and provide the patient with a new liver specially in patients with liver cell failure. HCC recurrence is always a concern and prediction of the recurrence is always a challenge. The appearance of the Milan criteria was mainly to predict the outcome after liver transplant and to find the group of patients who will have a survival benefit from transplant with less recurrence rates. The Milan criteria was criticized by many literatures because of its selectivity as it being restricted to small group of patients. Many literatures showed that the Milan criteria can be safely expanded with comparable results but still the Milan criteria is widely used in many different center all over the world.

This study aims at assessment of the outcome of living donor liver transplantation (LDLT) for patients with HCC within the Milan criteria and beyond Milan criteria but within University of California San Francisco (UCSF).

Patients and methods

This is a retrosepctive study analyzing the clinical data from 60 consecutive adult patients who had LDLT between January 2011 to December 2016 for having HCC in Ain Shams Centre for Organ Transplantation. Our study included 60 patients who met our criteria and transplanted for HCC out of total 254 patients who were transplanted during the previously mentioned period of

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time. After approval by the ethical committee in Ain Shams university, Patients were divided in two groups; (group A) represents patients whom underwent liver transplantation for HCC within Milan's criteria.

The patients were divided in two groups: group A represents patients who underwent liver transplantation for HCC within the Milan criteria, while group B represents patients who underwent liver transplantation for HCC beyond the Milan criteria but within UCSF. Both groups were compared as regards the recurrence, survival (1 and 3 years survival), tumor grade, microvascular invasion, largest tumor size, and the total tumor burden (the total tumor diameter for patients with multiple tumor nodules was calculated as the sum of the maximal diameter of each lesion in centimeters).

The patients were followed up after transplantation with clinical, laboratory [liver function tests, α-fetoprotein (AFP), and lab for routine post-transplant follow-up, e.g. kidney function tests, etc.) and radiological [abdominal ultrasound every month and abdominal triphasic computed tomography (CT) every 6 months]. If CT scan showed hepatic focal lesion with HCC criteria or elevated AFP, metastatic work-up (i.e. CT chest and bone scan or total body positron emission tomography scan) was done.

Our inclusion criteria include patients with HCC without extra hepatic metastasis and no macrovascular invasion. Patients included in this study were either within the Milan criteria or beyond Milan but within UCSF with good response to downstaging (child A, early B) (most of group B patients) or test of time (child late B, C) patients. Downstaging was done for patients exceeding Milan but within the UCSF criteria. Bridging treatment [ablation or transarterial chemoembolization (TACE)] was done for patients within Milan if transplantation will be delayed for any reason.

We consider downstaging was successful when:

(1) The tumor size and number were stationary.
(2) AFP <decreasing to be less than 200.
(3) Adequate radiological response with no enhancement in 1 and 3 months follow-up imaging (triphasic CT or MRI).

Protocol of immunosuppression

The standard is a combination of the two drugs calcineurin inhibitors (CNIs) and steroids. High-dose intravenous corticosteroids are used in the immediate perioperative and postoperative period and then tapered accordingly. In patients without renal dysfunction post-transplantation, CNIs are the mainstay of therapy with the long-term goal of low levels of immunosuppression and minimization of medication. In patients with renal insufficiency, a combination of low-dose CNI therapy and Mycophenolic ascid (MFAs) or a switch to mammalian target of Rapamycin (mTOR) inhibitors to preserve graft function and prevent further renal deterioration. Patients are weaned off corticosteroids within 3 months, providing they do not have evidence of autoimmune disease or recurrent episodes of rejection.

Results

The Milan group had 46 patients, 44 were men and two patients were women and the beyond Milan group had 14 patients, 13 men and one women patient. There is no statistically significant difference between the two groups as regards the sex distribution. Also the age was nearly comparable. The Milan group mean age was 53 years, ranging between 38 and 66 years, while in the beyond Milan group the mean age was 51 years with a range between 30 and 60 years. There is no statistically significant difference between the two groups as regards age (Table 1).

As regards the model for end-stage liver disease score, the mean model for end-stage liver disease for the Milan group was 16.98 and for the beyond Milan was 15.86 (statistically nonsignificant, P=0.152).

The etiology of the liver disease was mainly due to hepatitis C cirrhosis in both groups 95.7 and 92.9 for the Milan and beyond Milan. Each group has one case of cryptogenic cirrhosis and one case in the Milan group had hepatitis B virus infection (statistically nonsignificant, P=0.575).

As regards the liver functions, the Milan group had four (8.7%, child A) cases, and 15 (32.6, child B) cases, and 27 (58.7%, child C) cases and for the beyond Milan group there were six (42.9%, child A) cases, and five (35.7%, child B) cases, and three (21.4%) cases were child C (statistically significant, P=0.005).

Survival

We compared the 1 and 3 years survival for both groups and we did not find statistically significant difference in survival between the two groups (P=0.348). The overall 1 and 3 years survival were 88.2 and 69.5% with a mean survival of 44.9 months for the whole group. The 1 and 3 years survival were 86.5% and versus 85.7% and 61.4% with a mean survival of 37.3 months for patients within the UCSF and beyond Milan (Fig. 1, Tables 2 and 3).

Table 1 Preoperative data

	Milan group (*n*=46) [*n* (%)]	Beyond Milan group (*n*=14) [*n* (%)]	Test value	*P* value	Significance
Sex					
Female	2 (4.3)	1 (7.1)	0.177[a]	0.674	NS
Male	44 (95.7)	13 (92.9)			
Age					
Mean±SD	53.09±6.50	51.07±9.07	0.922[b]	0.360	NS
Range	38–66	30–62			
MELD score					
Mean±SD	16.98±2.66	15.86±1.99	1.453[b]	0.152	NS
Range	12–21	13–19			
Child					
A	4 (8.7)	6 (42.9)	10.528[a]	0.005	HS
B	15 (32.6)	5 (35.7)			
C	27 (58.7)	3 (21.4)			
Etiology					
Cryptogenic	1 (2.2)	1 (7.1)	1.108[a]	0.575	NS
HBV	1 (2.2)	0 (0.0)			
HCV	44 (95.7)	13 (92.9)			

HBV, hepatitis B virus; HCV, hepatitis C virus; HS, highly significant; MELD, model for end-stage liver disease; S, significant; [a]χ^2-test; [b]Independent *t*-test; [c]Mann–Whitney test.

Table 2 Overall survival and mean survival for each group

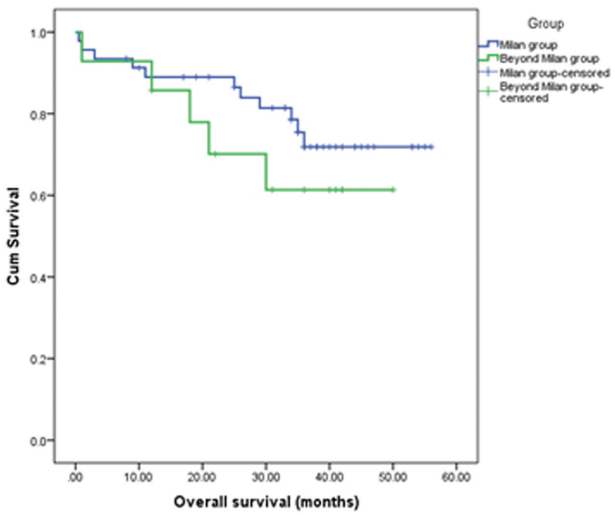
	Overall survival (months)		Log-rank test		1 year (%)	3 year (%)
	Mean	SE	χ^2	*P* value		
Milan group (*n*=46)	46.160	2.668	0.880	0.348	86.5	71.9
Beyond Milan group (*n*=14)	37.279	4.700			85.7	61.4
Overall survival (*n*=60)	44.945	2.431			88.2	69.5

Table 3 Hepatocellular carcinoma recurrence

	Milan group (*n*=46) [*n* (%)]	Beyond Milan group (*n*=14) [*n* (%)]	Test value	*P* value	Significance
HCC recurrence					
No recurrence	39 (84.8)	10 (71.4)	1.278	0.258	NS
Recurrence	7 (15.2)	4 (28.6)			

HCC, hepatocellular carcinoma.

Figure 1



Overall survival in months.

Recurrence

As regards recurrence, seven patients from the Milan group had recurrence with a recurrence rate of 15.1%, while for the beyond Milan group, four (28.6%) patients had recurrence with no statistically significant difference between the two groups (*P*=0.258).

Bridging and downstaging

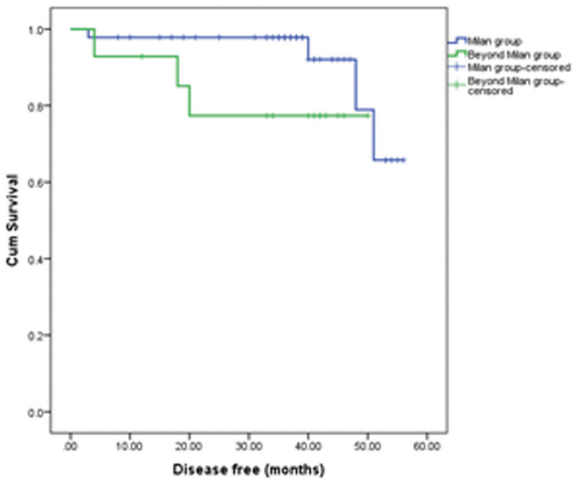
Only six patients from the Milan group needed intervention before transplant as a bridge to avoid tumor progression (Table 4). Two (4.3%) patients had TACE and four (8.7%) patients had radiofrequency ablation (RfA), while on the other hand in the beyond Milan group eight (51%) patients had TACE before transplant and two (14.3) patients had RfA and one (7.1) patient had microwave ablation (statistically highly significant, *P*<0.000) (Figs 2 and 3).

Table 4 Tumor characters, bridging, and downstaging in both groups

	Milan group (*n*=46) [*n* (%)]	Beyond Milan group (*n*=14) [*n* (%)]	Test value	*P* value	Significance
Bridging and downstaging					
N	40 (87.0)	3 (21.4)	28.002[a]	0.000	HS
Microwave	0 (0)	1 (7.1)			
RfA	4 (8.7)	2 (14.3)			
TACE	2 (4.3)	8 (57.1)			
Largest tumor size (cm)					
Mean±SD	2.73±0.90	4.39±0.85	6.119[b]	0.000	HS
Range	1.5–5	3.5–6			
Total tumor burden (cm)					
Mean±SD	3.60±1.15	6.82±1.05	9.339[b]	0.000	HS
Range	1.5–6	5.5–8.5			
AFP					
Median (IQR)	10.3 (4.61–76.6)	16.33 (10.8–46)	−1.590[c]	0.112	NS
Range	1.96–989	5.88–899			
Microvascular invasion					
No	32 (69.6)	8 (57.1%)	0.745[a]	0.388	NS
Yes	14 (30.4)	6 (42.9%)			
Tumor grade					
No	2 (4.3)	1 (7.1)	4.560[a]	0.207	NS
I	24 (52.2)	5 (35.7)			
II	18 (39.1)	5 (35.7)			
III	2 (4.3)	3 (21.4)			

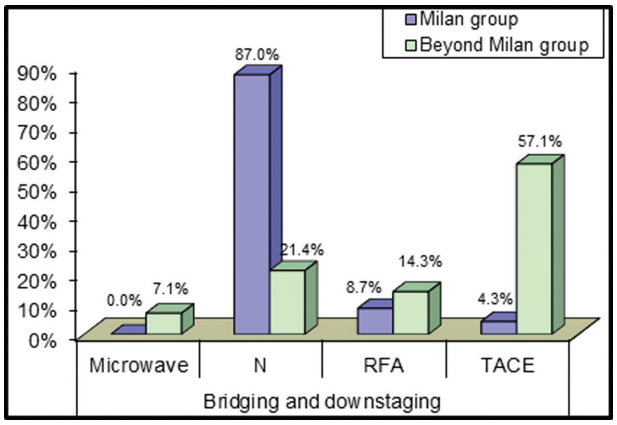
AFP, α-fetoprotein; HS, highly significant; IQR, interquartile range; RfA, radiofrequency ablation; S, significant; TACE, transarterial chemoembolization; [a]χ^2-test; [b]Independent *t*-test; [c]Mann–Whitney test.

Figure 2



Disease-free survival.

Figure 3



Bridging and downstaging (statistically highly significant, *P*=0.000).

Tumor character

In our study, the mean of the largest tumor size in the Milan group was 2.7±0.9 cm ranging between 1.5 and 5 cm, while the mean largest tumor size for the beyond Milan was 4.39± 0.85 cm ranging between 3.5 and 6 cm, which was highly significant (statistically highly significant, *P*<0.000) (Fig. 4).

Also the total tumor burden for the Milan group was 3.6 cm and for the beyond Milan was 6.82 cm which was highly significant (statistically highly significant, *P*<0.000) (Fig. 4).

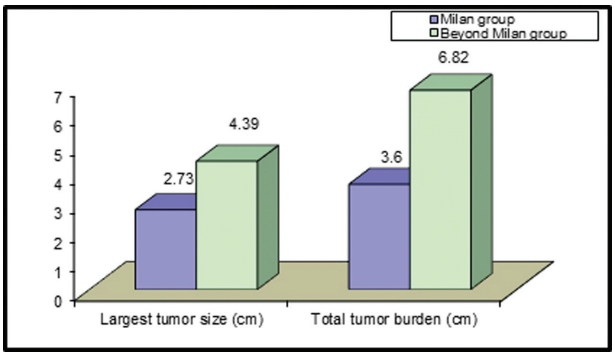
Microvascular invasion

Fourteen patients from the Milan group had microvascular invasion (MVI) which constitute 30% of the cases while in the beyond Milan group six (42.8%) patients showed MVI (statistically no significant, *P*=0.388).

Tumor grade

In our study, 52% of the patients in the Milan group had grade I (well-differentiated) tumor by pathology,

Figure 4



Largest tumor size and total tumor burden (statistically highly significant, *P*=0.000).

39% grade II, and 4.3% grade III and only two (4.3%) cases could not be assessed due to good ablation. For the other group of patients (beyond Milan group), five (35.7%) cases had grade I tumors, five (35.7%) cases had grade II, and three (21/4%) cases had grade III. Only one case could not be assessed due to severe tumor necrosis (statistically nonsignificant, *P*=0.207).

α-Fetoprotein

The median for AFP at the time of transplantation for the Milan group was 10.3, while for the beyond Milan group it was 16.33 (statistically nonsignificant, *P*=0.112).

Discussion

It is well known that HCC recurrence affects survival postliver transplantation; that is why the selection of a suitable candidate for liver transplant with HCC is crucial in order to avoid wasting of the resources especially at a time of marked organ shortage all over the world.

Following the Milan criteria the liver transplant showed good results for HCC patients with a 5-year survival of 79%, but was criticized for being so restrictive which promoted the appearance of many expanded criteria like UCSF, Tokyo criteria, Hangzhou criteria, and the up to seven criteria [2].

Tokyo criteria that involve the 5–5 rule (tumors not >5 cm and not >5 lesions) showed 3 years survival of 94% compared with 50% in patients outside the criteria [2]. The up to seven criteria by Mazaferro (the sum of the tumor number and the size of the largest tumor (in cm) was not larger than 7) showed that the 5-year survival was 71.25. Also the UCSF criteria showed that the 5-year survival was 64%, *P*=0.61 [3].

In this study, we compared the results of the LDLT for HCC patients who are within Milan and the beyond Milan but within the UCSF criteria as regards the survival, recurrence, and possible risk factors for recurrence. Our study showed that the survival is comparable in both groups. The 1 and 3 years survival was 86.5 and 71.9% for the Milan group, respectively, and 85.7 and 61.4% for the beyond Milan group. Although the 3 years survival in the beyond Milan group is slightly lower, it is not statistically significant with a *P* value of 0.348.

As regards the tumor size, it has been shown in any literature that the size of the tumor is an important preoperative variable and the Milan criteria is mainly dependent on the tumor size, but Ito *et al.* [4] have shown that there is no difference in survival in patients within and beyond Milan in his study (71% in patients within Milan compared with 64% in patients beyond Milan). In our study, the mean of the largest tumor size in the Milan group was 2.7 cm, ranging between 1.5 and 5 cm, while the mean largest tumor size for the beyond Milan was 4.39, ranging between 3.5 and 6 cm which was a highly significant difference between the two groups ($P<0.05$); also the total tumor burden for the Milan group was 3.6 cm and for the beyond Milan was 6.82 cm which was highly significant ($P<0.05$). There was no statistically significant difference as regards the difference between the two groups as regards the largest tumor size and total tumor burden and the overall survival and recurrence which confirm that the tumor size alone is not the only predictor for recurrence.

MVI has been shown in different studies that it is associated with high recurrence rates and poor survival. Unfortunately, it is a postoperative finding and cannot be assessed by the preoperative biopsy. Many studies are trying to find a preoperative marker for MVI.

Also the histologic grade is an important factor affecting recurrence and survival after liver transplant for HCC. Poorly differentiated tumors were previously considered as a contraindication for liver transplant. High-grade tumors have been correlated in some studies to increase the size of the tumor. A study by Mazaffero *et al.* [3] showed that the increase in tumor size and number together with the microvasular invasion goes in parallel relation with the high-grade tumors.

In our study, there is no statistically significant difference between the two groups as regards MVI and tumor grade. This finding may be explained by proper patient selection due to acceptance only for patients with HCC within the UCSF if responding

to downstaging or test of time. The absence of significant difference in MVI and grade between both groups may be the main cause of absence of significant difference in overall and recurrence-free survival.

AFP is an important marker for diagnosis and follow-up in patients with HCC. The high levels of AFP before transplant were correlated to poor prognosis and high recurrence rate. Also the AFP level is important to monitor the response after locoregional therapy and the persistent high levels of AFP after locoregional therapy may predict either inadequate treatment or distant metastasis. Unfortunately, AFP is not always high in recurrence. In a study done by Hsieh *et al.* [5], 23% of patients demonstrated normal AFP levels at the time of HCC recurrence. The AFP levels in these patients were initially high. Those patients with inconsistent AFP levels had a longer recurrence interval and worse recurrence-to-death survival rate than other patients in the study which may be because of the delay of the recurrence diagnosis [5].

In our study, the median for AFP at the time of transplantation for the Milan group was 10.3, while for the beyond Milan group it was 16.33. There was no statistically significant difference between the two groups as regards the AFP level.

Many authors have shown that downstaging can decrease recurrence rate and the dropout of the waiting list. Mazzaferro *et al.* [3] reported no dropouts in 50 patients within the Milan criteria treated with RFA. Some studies reported no dropouts in patients within Milan treated by TACE and a short waiting time (178 days), while others documented a probability of dropout of 15% at 6 months and 25% at 12 months. Cumulative results show that RFA achieves the highest rates of complete necrosis (12–55%) compared with TACE (22–29%). Complete necrosis is best achieved with percutaneous ablation in tumors less than 3 cm in diameter [3,6].

Only six patients from the Milan group needed intervention before transplant as a bridge to avoid tumor progression. Two (4.3%) patients needed TACE and four (8.7%) patients needed RfA, while on the other hand the beyond Milan group had eight (51%) patients who had TACE before transplant and two (14.3) patients had RfA and one (7.1%) patient had microwave ablation. The difference in selection were mostly related to tumor character (size, site, diffuse, or well localized, in relation to major vascular or biliary structure).

Conclusion

Although the Milan criteria were used as the standard criteria for the selection of patients with HCC eligible for LDLT, it seems to be too restrictive. The Milan criteria can be safely expanded to UCSF with comparable results if responding well to downstaging and with low AFP.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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