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ORIGINAL ARTICLE

Liver Transplantation in Patients with Hepatocellular Carcinoma Across Milan Criteria

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Milan criteria are the most frequently used limits for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC), but our previous experience with expanded criteria showed encouraging results. The aim of this study was to investigate whether our expanded Clinica Universitaria de Navarra (CUN) criteria (1 nodule up to 6 cm or 2-3 nodules up to 5 cm each) could be used to select patients with HCC for LT. Eighty-five patients with HCC fulfilling CUN criteria were included as candidates for LT. Survival of transplanted HCC patients was compared with survival of patients without HCC (n = 180). After the exclusion of 2 patients with tumor seeding of the chest wall due to pre-LT tumor biopsy, survival and recurrence rates were compared according to tumor staging. Twenty-six out of 85 (30%) patients exceeded Milan criteria. Twelve patients had tumor progression on the waiting list. Patients exceeding Milan criteria had a higher dropout rate due to tumoral progression. One-, 3-, 5-, 7-, and 10-year survival rates of the 73 transplanted HCC patients were 86%, 74%, 70%, 61%, and 50%, respectively. Survival of patients with HCC was significantly lower than that of patients without HCC, but by multivariate analysis, HCC was not associated with lower survival. Tumor recurrence and survival rates were similar for patients fulfilling Milan and CUN criteria. Pathological staging showed 55 patients within Milan criteria, 7 patients exceeding them but within CUN criteria, and 9 patients exceeding CUN criteria. Tumor recurrence rates were 2/55 (4%), 0/7 (0%), and 4/9 (44%) in each of these groups, respectively. In conclusion, following CUN criteria could increase the number of HCC patients who could benefit from LT, without worsening the results. Because of the short number of patients in this series, these data need external validation. ***Liver Transpl 14:272-278, 2008.*** © **2008 AASLD.**

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Liver transplantation (LT) is the best treatment option for patients with hepatocellular carcinoma (HCC) and liver cirrhosis, unless they have excellent liver function and minimal portal hypertension.[1] Early experience of LT for patients with HCC was poor because tumoral recurrence was very frequent.[2] In 1996, Mazzaferro et al.[3] reported encouraging results in patients with a single tumor of up to 5 cm in diameter or 2-3 lesions of up to 3 cm. These Milan criteria were adopted by the United Network for Organ Sharing and by most transplant centers as selection guidelines for LT in patients with HCC.

However, recent data suggest that Milan criteria may be too conservative. Yao et al.[4] reported their results with a moderate expansion of these criteria [the so-called University of California at San Francisco (UCSF) criteria]. Patients selected with these expanded criteria had disease-free survival that was comparable to survival of patients selected with Milan criteria.

We published the results of our own series of LT for patients with HCC in 2001.[5] Our selection criteria for LT were 1 nodule of up to 6 cm in diameter or 2-3 nodules of up to 5 cm. Tumor recurrence rates were comparable to those obtained by other groups that used the stricter Milan criteria.

Abbreviations: CI, confidence interval; CT, computed tomography; CUN, Clinica Universitaria de Navarra; HCC, hepatocellular carcinoma; HR, hazard ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MR, magnetic resonance; NS, not significant; UCSF, University of California at San Francisco.

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In this article, we update the results of our series of LT for HCC using our expanded criteria. We have also analyzed the possible impact on survival and tumor recurrence rates of these criteria in comparison with Milan criteria according to preoperative staging.

PATIENTS AND METHODS

Criteria for LT and Preoperative Follow-Up

Patients with unresectable HCC were considered potential candidates for LT if they fulfilled the Clinica Universitaria de Navarra (CUN) criteria (1 tumoral nodule not larger than 6 cm in diameter or 2-3 nodules of up to 5 cm each). Both dynamic computed tomography (CT) and magnetic resonance (MR) scans were obtained for each patient, and the largest tumor size on either study was used for indicating LT. Macroscopic vascular invasion and extrahepatic spread were excluded with thoracic and abdominal CT, cerebral MR, and bone scintigraphy. After inclusion in the waiting list, treatment of HCC (usually transarterial chemoembolization) was used or not according to the criteria of the patient's physician (based on the expected waiting time for LT and the hepatic function of the patient). Hepatic CT/MR imaging scan was repeated at least every 3 months while the patient was on the waiting list. Patients were excluded from the waiting list if at any time staging exceeded the aforementioned criteria because of tumor progression.

Patients

All patients with HCC on the waiting list for LT between 1991 and 2005 were included (8 patients with incidental tumors transplanted in that period of time were not included in the study). Pathological records of the specimens of the explant were reviewed. In order to detect HCC recurrence, alpha-fetoprotein, chest X-ray film, and abdominal ultrasound were repeated every 6 months after transplantation or when clinically indicated in order to detect HCC recurrence. Causes of death of deceased patients were recorded.

Statistical Analyses

Tumor progression exceeding CUN criteria was studied in all the patients who were initially considered for LT. The risk of progression of patients who fulfilled Milan criteria when they were included on the waiting list was compared with the risk of those who exceeded these criteria.

Survival of patients transplanted for HCC who fulfilled CUN criteria was compared with survival of all the patients transplanted for liver cirrhosis without HCC between 1991 and 2005. The potential influence of donor and recipient age and sex, Child-Pugh status at transplantation, HCC, and etiology of liver cirrhosis (hepatitis C virus versus other causes of cirrhosis) on survival was studied. Variables with $P < 0.2$ in the univariate analysis were included in a multivariate analysis of survival.

To compare Milan and expanded criteria, we excluded 2 patients who had HCC recurrence due to tumor seeding caused by pre-LT tumor biopsy. Actuarial rates of survival and tumor recurrence were compared according to radiological maximum staging. Intention-to-treat actuarial rates of survival were compared according to radiological staging at listing.

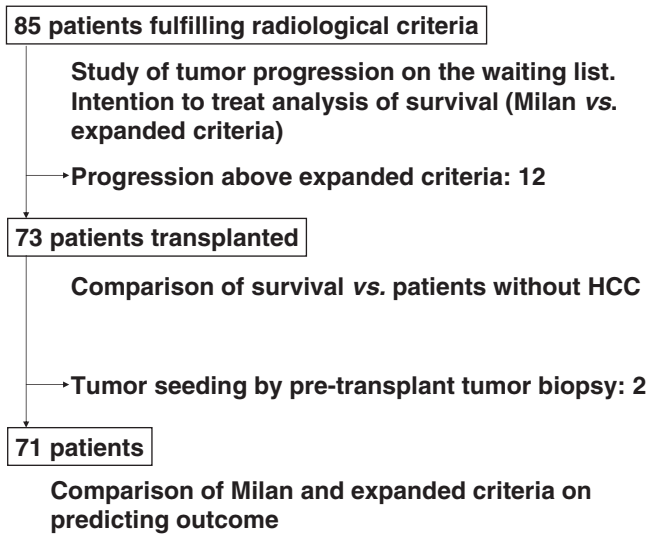

Figure 1. Evolution of patients considered for liver transplantation for hepatocellular carcinoma (HCC).

Statistical Methods

Categorical variables are expressed as absolute number (%). Continuous variables are expressed as median (interquartile range). Comparison of groups was done by the chi-square method (categorical variables) or Mann-Whitney U test (continuous variables).

Actuarial rates of survival and tumor recurrence and their 95% confidence intervals were obtained with the Kaplan-Meier method. Comparisons between curves were done with the long-rank test (categorical variables) and univariate Cox regression model (continuous variables). Multivariate analysis of survival was done with the multivariate Cox model.

Differences were considered significant if P values were below 0.05.

RESULTS

Between 1991 and 2005, 85 patients fulfilling our criteria were included on the waiting list for LT. Twelve patients exceeded these criteria during regular restaging while on the waiting list (Fig. 1). The remaining 73 patients transplanted for HCC were compared with 178 patients transplanted for cirrhosis without HCC. Finally, the comparison between the CUN criteria and the Milan criteria in terms of survival and tumor recurrence after LT was studied after the exclusion of 2 patients who had tumor recurrence due to cutaneous seeding by pre-LT tumor biopsy.

Analysis of Progression

Of the 85 patients included on the LT waiting list for HCC, 59 fulfilled the Milan criteria, and 26 (30%) did

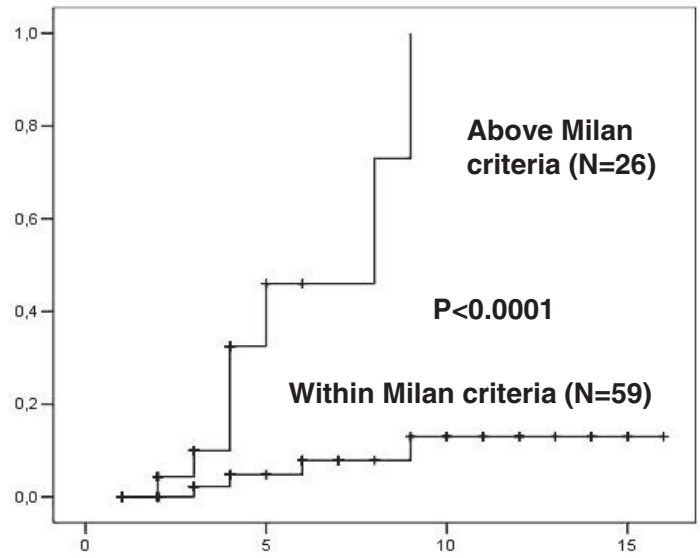

Figure 2. Tumoral progression while patients were on the waiting list for transplantation according to whether or not the patients fulfilled Milan criteria.

TABLE 1. Comparison of Liver Transplant Recipients With or Without Hepatocellular Carcinoma

	Hepatocellular Carcinoma (n = 73)	No Hepatocellular Carcinoma (n = 178)	*P*
Hepatitis C	40(55%)	47(26%)	<0.001
Female sex	13(18%)	48(27%)	NS
Female donor sex	28(39%)	70(40%)	NS
Child status			<0.001
A	26(36%)	7(4%)	
B	32 (44%)	92 (52%)	
C	15 (20%)	79 (44%)	
MELD at listing	13 (10-16)	16 (14-20)	<0.001
MELD at transplant	12 (10-16)	16 (14-21)	<0.001
Age (years)	60.8 (54.9-67.4)	55.05 (47.5-62.0)	<0.001
Donor age (years)	47 (26-64)	44 (25-59)	NS

Abbreviations: MELD, Model for End-Stage Liver Disease; NS, not significant.

not. Dropout from the waiting list due to tumor progression occurred in 4 patients (7%) within the Milan criteria and in 8 patients (30%) exceeding them at the time of inclusion on the list. The actuarial risk of progression was significantly higher for patients who exceeded the Milan criteria at diagnosis (Fig. 2). The risk of progression was not significantly lower among patients receiving antitumoral therapy while on the list. Currently, 6 of these patients are alive (5 of them after transplantation according to expanded criteria).

Comparison of Patients With HCC Versus Patients Without HCC

General characteristics of both groups of patients are given in Table 1. Patients with HCC had a significantly higher frequency of hepatitis C virus infection, were significantly older, and had less severe liver cirrhosis as assessed by the Child-Pugh status or the Model for End-Stage Liver Disease score. One-, 3-, 5-, 7-, and 10-year actuarial (95% confidence interval) survival rates were 86% (78%-94%), 74% (68%-84%), 70% (59%-81%), 61% (48%-74%), and 50% (35%-65%), respectively, for patients with HCC and 91% (87%-99%), 88% (83%-93%), 84% (78%-90%), 80% (74%-87%), and 76% (68%-83%), respectively, for patients without HCC. The difference in actuarial survival between both groups was statistically significant ($P = 0.002$; Fig. 3). Other variables associated with lower survival were hepatitis C virus infection, donor age (above 60 years), and higher recipient age (Table 2). By multivariate analysis, only higher recipient age was independently associated with a lower survival. The association between survival and HCC was close to statistical significance but did not reach it. Causes of death in both groups are detailed in Table 3.

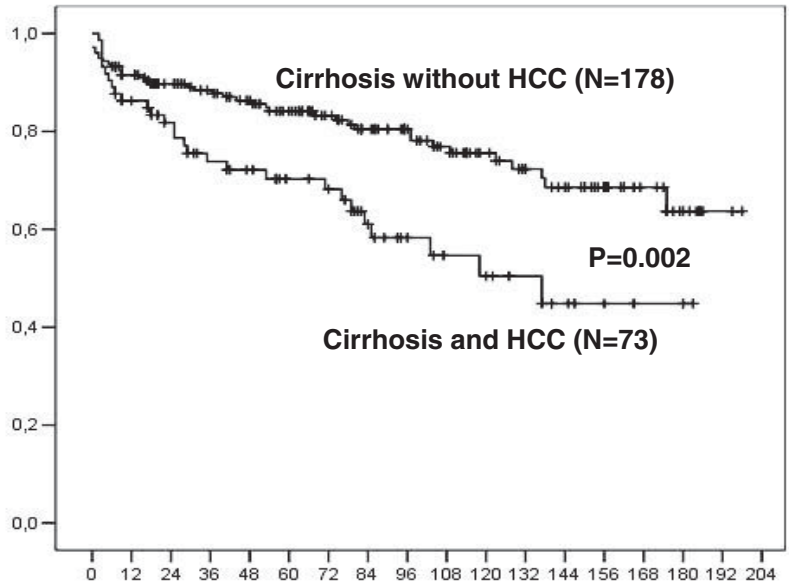

Figure 3. Survival after liver transplantation of patients with liver cirrhosis with or without hepatocellular carcinoma (HCC).

TABLE 2. Variables With Influence on Survival in 251 Patients Transplanted With Liver Cirrhosis (73 Patients With Hepatocellular Carcinoma and 178 Without Tumor)

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)	1.064 (1.033-1.095)	<0.001	1.051 (1.019-1.084)	0.002
Donor > 60 years	1.913 (1.096-3.339)	0.022	1.559 (0.887-2.739)	0.122
Hepatitis C	1.620 (1.000-2.623)	0.05	1.236 (0.744-2.053)	0.413
Hepatocellular carcinoma	2.097 (1.287-3.419)	0.003	1.589 (0.942-2.679)	0.082

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3. Causes of Death of Patients Transplanted for Liver Cirrhosis With or Without Hepatocellular Carcinoma

	Hepatocellular Carcinoma [28/73 (38%)]	Cirrhosis Without Tumor [39/178 (22%)]
Infection	5 (18%)	7 (18%)
De novo neoplasia	6 (21%)	17 (44%)
Recurrent hepatocellular carcinoma	8 (29%)	0
Recurrent viral hepatitis	4 (14%)	1 (2%)
Other complications	5 (18%)	14 (36%)

Impact of the Expanded Criteria

Of the 73 patients transplanted, 47 patients were within Milan criteria, and 26 (35%) exceeded them. Two patients exceeding Milan criteria were excluded from this analysis because they had HCC recurrence due to tumor seeding by pre-LT tumor biopsy. Tumor recurred in 4 patients (8%) fulfilling the Milan criteria and in 2 patients exceeding them (8%). Tumor recurrence and survival were not significantly different between these 2 groups. One-, 3-, 5-, 7-, and 10-year actuarial survival rates (95% confidence interval) were 83% (72%-94%), 73% (60%-85%), 70% (56%-84%), 70% (56%-84%), and 43% (17%-69%), respectively, for patients fulfilling the Milan criteria and 92% (82%-100%), 78% (61%-95%), 73% (55%-92%), 56% (35%-76%), and 56% (35%-76%), respectively, for patients exceeding them (Fig. 4).

Intention-to-treat survival of the 26 patients who exceeded the Milan criteria when they were included on the waiting list was compared with survival of those who fulfilled Milan criteria (n = 59). One-, 3-, 5-, 7-, and 10-year actuarial survival rates (95% confidence interval) were 88% (80%-96%), 73% (61%-85%), 66% (53%-79%), 66% (53%-79%), and 49% (30%-69%), respectively, for patients fulfilling the Milan criteria and 88% (76%-100%), 72% (55%-90%), 68% (49%-86%), 52% (31%-73%), and 52% (31%-73%), respectively, for pa-

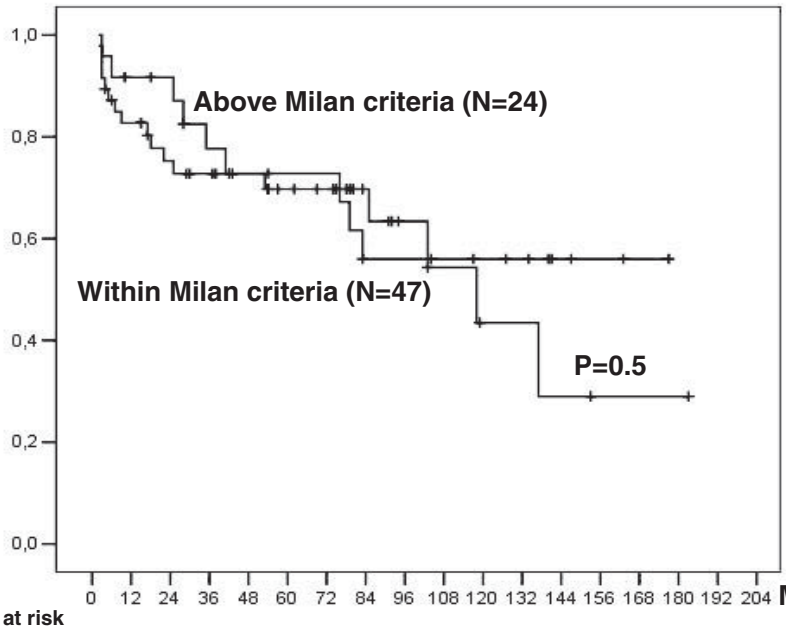

Figure 4. Survival after liver transplantation of patients transplanted according to expanded criteria comparing patients that fulfilled and exceeded Milan criteria.

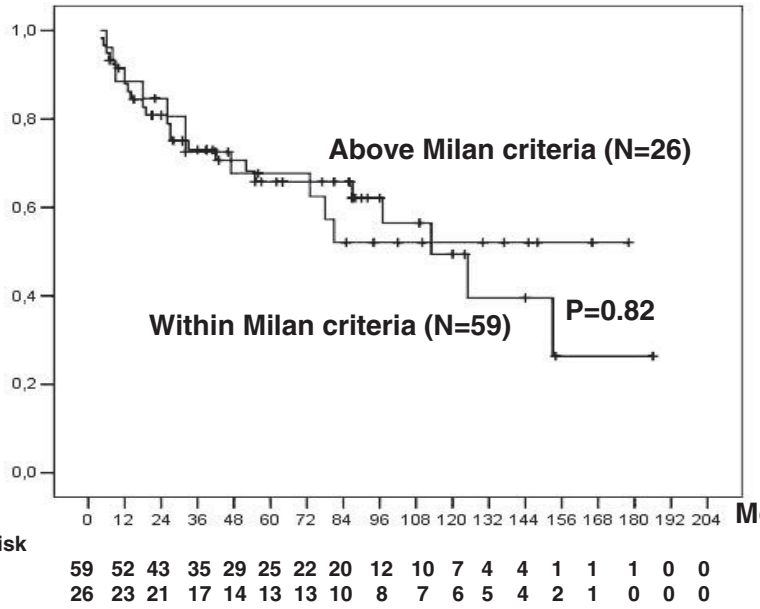

Figure 5. Survival of patients with hepatocellular carcinoma who were listed for liver transplantation comparing patients that fulfilled and exceeded Milan criteria at listing.

tients exceeding them (Fig. 5). Differences between both groups were not significant.

Pathological staging after LT disclosed that 55 patients (77%) were within Milan criteria, 7 patients (10%) exceeded them but fulfilled the expanded criteria, and 9 patients (13%) exceeded the latter. Tumor recurrences were diagnosed in 2/55 (4%), 0/7 (0%), and 4/9 (44%) in each of these groups, respectively. Tumor recurrence rates were significantly higher in patients who exceeded CUN criteria than in the other 2 groups (Fig. 6).

Vascular invasion, the single factor most frequently associated with tumor recurrence, was also associated with a higher rate of recurrence in this series. Recurrence was diagnosed in 3/11 (27%) patients with vascular invasion and 3/60 (5%) patients without vascular invasion. Our criteria and the Milan criteria (radiological or pathological) were not associated with a different rate of vascular invasion.

DISCUSSION

The most relevant finding of this article is the confirmation that the Milan criteria could be expanded without

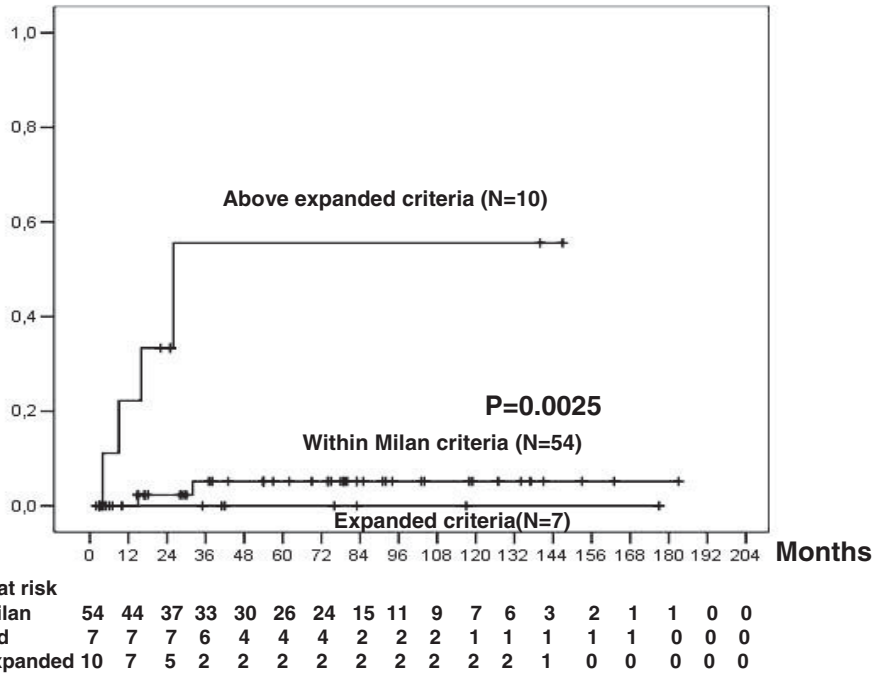

Figure 6. Tumor recurrence after liver transplantation of patients transplanted for hepatocellular carcinoma according to their pathological staging (within Milan criteria, above Milan criteria but within expanded criteria, and above expanded criteria).

worsening the results of LT in patients with HCC, as suggested by other groups.[4] With the Milan criteria as the limit for LT, 26/73 (35%) patients would not have been transplanted, and this would have precluded their access to the only potentially curative option for them. Because these patients had survival and recurrence rates comparable to those of patients fulfilling the Milan criteria, there seems to be no objective reason for denying LT to these patients.

Mazzaferro et al.[3] found that patients with pathological tumoral staging exceeding the Milan criteria had a higher recurrence rate than patients fulfilling them. Yao et al.[6] had similar findings: patients fulfilling their UCSF criteria had better prognosis than patients with higher tumoral burden. Similarly, we have found that patients exceeding our criteria at the examination of the pathological specimen had higher recurrence rates and lower survival rates. Recently, in a large multicenter series, Onaca et al.[7] found that patients fulfilling Milan criteria at the examination of the liver explant have survival similar to that of patients with 1 nodule of up to 6 cm or 2-4 nodules smaller than 5 cm. Patients exceeding these limits have significantly lower survival. Anyway, the indication or contraindication for LT must be based on radiological staging, and unfortunately, radiological staging does not have a good correlation with the pathological examination.[8] In our series, the discrepancy between radiological and pathological staging has 2 causes. Radiological techniques occasionally missed tumor nodules. Additionally, radiological techniques found some lesions to be larger than in the pathological specimen; this may be due in part to the effect of pre-LT treatment.

Establishing a limit for LT among patients with HCC is the consequence of the scarcity of available grafts. The parameter most frequently associated with the risk of recurrence is vascular invasion,[5,9-11] but the presence or absence of microscopic vascular invasion is difficult to ascertain solely on the basis of the number and size of tumor nodules. In our series, the risk of vascular invasion was similar in patients within or above the Milan criteria, albeit if CUN criteria were fulfilled. Probably other markers of tumor behavior such as the grade of histological differentiation could better reflect the risk of recurrence. Other markers such as cell-cycle modulators[12] or the detection of bone marrow micrometastases[13] are better related to vascular invasion and could be useful predictive factors of tumor recurrence, but their clinical role needs to be evaluated in larger studies.

In conclusion, the Milan criteria, currently used in most centers as the limit for LT in patients with HCC, seem to be too restrictive. Patients transplanted according to the expanded criteria presented herein (1 nodule not bigger than 60 mm or 2-3 nodules up to 50 mm) have survival and recurrence rates that do not differ from those fulfilling the Milan criteria. Patients exceeding Milan criteria have a higher rate of dropout from the waiting list for transplantation that could lead to a lower intention-to-treat survival. Future studies with higher numbers of patients and longer follow-up need to confirm these results before these criteria become the standard limits for LT in patients with HCC.

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