Liver Transplantation for Hepatocellular Carcinoma: Further Considerations on Selection Criteria

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The selection criteria in liver transplantation for HCC are a matter of debate. We reviewed our series, comparing two periods: before and after 1996, when we started to apply the Milan criteria. The study population was composed of patients with a preoperative diagnosis of HCC, confirmed by the pathological report and with a survival of >1 year. Preoperative staging as revealed by radiological imagining was distinguished from postoperative data, including the variable of tumor volume. After 1996 tumor recurrences significantly decreased (6 out of 15 cases, 40% vs. 3 out of 48, 6.3%, $P < .005$) and 5-year patient survival improved (42% vs. 83%, $P < .005$). Not meeting the Milan criteria was significantly related to higher recurrence rate (37.5% vs. 12.7%, $P < .05$) and to lower 5-year patient survival (38% vs. 78%, $P < .005$%) in the preoperative analysis, but not in the postoperative one. The alfa-fetoprotein level of more than 30 ng/dL and the preoperative tumor volume of more than 28 cm^3 predicted HCC recurrences in the univariate and mutivariate analysis ($P < .005$ and $P < .05$, respectively). The ROC curve showed a linear correlation between preoperative tumor volume and HCC recurrence. Milan criteria significantly reduced tumor recurrences after liver transplantation, improving long-term survival. In conclusion, the efficacy of tumor selection criteria must be analyzed with the use of preoperative data, to avoid bias of the postoperative evaluation. Tumor volume and alfa-fetoprotein level may improve the selection of patients. (*Liver Transpl 2004;10:1195–1202.*)

Since liver transplantation (LT) was first proposed for patients with hepatocellular carcinoma (HCC), three distinct periods can be identified. In the first there was no patient selection and the results obtained were disappointing.[1–3] In 1996, the Milan criteria (MC) were proposed[4] and gradually included in the selection options of liver transplant centers, with remarkably improved results. Unfortunately, many patients do not meet the MC and are excluded from any therapeutic strategy. This is the main reason why some authors suggest that these criteria should be expanded.[5,6]

Several papers have appeared in the literature, including results obtained with patients transplanted because of HCC and not meeting the MC. In these reports, the authors included postoperative (post-op) tumor features in their analysis, which have a substantial chance of being different from the preoperative (pre-op) evaluation.[4,6–14]

At the time of inclusion on the waiting list for LT, the possibility of predicting HCC recurrence in the individual patient is usually evaluated by the MC, which only include the number and diameter of the HCC, since other HCC biological features have not proven to be of clinical usefulness.[15] The introduction of selection criteria based on these parameters has led to a rate of tumor recurrence (TR) lower than 20%, but these criteria envisage only two groups of patients: a low risk of TR after LT and a risk which is not low. The clinicopathological variables related to the outcome of LT are multiple and a more specific scoring system to assay the risk of TR is advisable.

We retrospectively reviewed our series focusing on the bias between pre-op and post-op data and investigating the variables effective in adding a specific risk of TR to patients after LT.

Materials and Methods

Study Population

From November 1986 to August 2001, 657 LTs were performed at the Department of Surgery and Transplantation of the University of Bologna. One hundred and six (16%) had an HCC found in the surgical specimen but only 70 of them

Abbreviations: LT, liver transplantation; HCC, hepatocellular carcinoma; MC, Milan criteria; post-op, postoperative; pre-op, preoperative; TR, tumor recurrence; AFP, alfa-fetoprotein level; TACE, transarterial chemoembolization; TV, tumor volume; ROC, receiver operating characteristic; RR, risk ratio; CI, confidence interval.

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Table 1. Clinico-Pathological Variables of the Study Population of 36 Patients Divided

Variables		Total 63 Patients	Before 1996 15 Patients	After 1996 48 Patients	χ^2
Gender	Male	56 (88.9%)	13 (86.7%)	43 (89.6%)	N.S.
Age (yr; mean 52 ± 7; range 32–64)	>50 years	39 (61.9%)	8 (53.3%)	31 (64.6%)	N.S.
Child-Turcotte-Pugh class	A	8 (12.7%)	4 (26.7%)	4 (8.3%)	<0.05
	B	32 (50.8%)	9 (60%)	23 (47.9%)	
	C	23 (36.5%)	2 (13.3%)	21 (43.8%)	
Etiology of cirrhosis	HCV-positive	35 (55.6%)	8 (53.3%)	27 (56.3%)	N.S.
Waiting time (days; mean 163 ± 178; range 15–877)	>180 days	18 (29%)	6 (40%)	12 (25.0%)	N.S.
Pre-op treatments	Yes	38 (60.3%)	9 (60%)	29 (60.4%)	N.S.
Pre-op selective criteria	Not meeting MC	8 (12.7%)	5 (33.3%)	3 (6.3%)	<0.05
Pre-op HCC number (mean 1.6 ± 0.8; range 1–4)	Multiple	24 (38.1%)	4 (26.7%)	20 (41.7%)	N.S.
Pre-op HCC diameter (cm; mean 3.1 ± 2.1; range 0.8–16)	>5 cm	3 (4.8%)	3 (20%)	0	<0.05
Pre-op tumor volume (cm^3; mean 54 ± 270; range 0.5–2144)	>28 cm^3	19 (30.2%)	10 (66.7%)	9 (18.7%)	<0.001
Alfa-fetoprotein level (ng/dL; mean 53 ± 113; range 1–546)	>30 ng/dL	19 (30.2%)	6 (40%)	13 (27.1%)	N.S.
Tumor vascular invasion	Presence	25 (39.7%)	6 (40%)	19 (39.6%)	N.S.
Edmondson grade	III°–IV°	30 (47.6%)	11 (73.3%)	19 (39.6%)	<0.05
Satellite nodules	Present	13 (20.6%)	7 (46.7%)	6 (12.5%)	<0.005
Peritumoral capsule	Present	14 (22.2%)	3 (20%)	11 (22.9%)	N.S.

had a pre-op diagnosis of HCC and were thus included in this study.

In the most recent series of LT for HCC, the percentage of death unrelated to TR varies between 35% and 90%.[4,6–14] Furthermore, almost all authors analyze the effectiveness of the post-op variables on survival and they transfer their clinical application on the pre-op selection criteria, without considering the differences between pre-op and post-op data and the rate of patients with incidental HCC. Patients with incidental HCCs were excluded from this study.

The correlation between tumor features and TR was instead investigated only in those patients with a survival of more than one year (63 cases), the minimum time to develop most TRs, considering pre-operative and post-operative data.

Starting from 1996 our evaluation protocol included the MC, which indicated a maximum diameter of the tumor up to 5 cm if the tumor appeared to be single and up to 3 cm in the case of 2 or 3 nodules.[4] Our study population was therefore modified over this period as reported in Table 1.

Diagnosis, Waiting Time, and Follow-Up

The radiological work-up for patients with HCC changed over time, according to the development of new imaging techniques over these 15 years.[16] Before inclusion on the waiting list, almost all patients underwent abdominal CT, liver ultrasound, and determination of alfa-fetoprotein blood level. Patients with HCCs were included on the ordinary waiting list and they did not have any definitive priority over other patients. When in 1997 our Center started to routinely utilize donors older than 60,[17,18] patients with HCCs were considered more frequently for the use of these marginal organs, to reduce their waiting time.[19]

Liver ultrasound and the measurement of alfa-fetoprotein level (AFP) were performed every three months during the waiting time.

Treatments for HCC while awaiting LT included transarterial chemoembolization (TACE), percutaneous ethanol injection, and radiofrequency ablation, and they were decided on a case-by-case basis in a multi-disciplinary tumor meeting, according to the current indications in the scientific literature.[20–22] After LT, no patient received adjuvant chemotherapy; chemotherapies were administered only in patients with HCC recurrence and with individual protocols.

The immunosuppression strategy in almost all cases included calcineurin inhibitors and steroids; 10% of these patients received different protocols for a variety of clinical problems.

Histology and Tumor Features

The diseased liver was examined by two experienced histopathologists (W.G. and A.D.).

The HCC parameters investigated were the following: number and diameter of nodules, presence of a peritumoral capsule, satellite nodules, tumor vascular invasion detected histopathologically, and differentiation degree according to Edmondson's classification.[23]

We also calculated the tumor volume (TV), considering the nodules as sphere-shaped, with the expression: $TV = (4/3)\pi r^3$; in patients with multiple lesions, the total volume was calculated as the sum of the volume of each HCC.[24,25]

Number, diameter, and volume of nodules were first evaluated pre-op by radiological imaging and then post-op in the explanted liver.

Statistical Analysis and Criteria of Analysis

The results were expressed as mean ± standard deviation. The survival rates were obtained by the Kaplan-Meier method and the differences were compared by the log-rank test. Survival was considered from the day of surgery to the day of death or to the most recent follow-up visit. After univariate analysis, only variables that emerged as significant were used in the multivariate analysis using Cox's proportional hazard model.

Chi-square analysis was performed to evaluate categorical variables in relation to TR. The recurrence rate was computed from the day of surgery to the first follow-up visit at which TR was noticed. Multiple logistic regression analysis with the maximum likelihood estimation was performed with the risk factors significant at the univariate analysis.

Continuous variables were transformed into binary variables and the cutoffs were chosen, according to previous studies.

To improve the selection criteria based on number and diameter of HCC, we measured the TV. The cutoff of TV, a variable never investigated before in LT, was established by applying the polynomial logistic regression (Hosmer-Lemeshow *P* value: 7503) with subsequent receiver operating characteristic (ROC) analysis[26–28] on pre-op TV. The response variable was the appearance of HCC recurrence. The subsequent ROC analysis showed a cutoff of 28 cm^3 to be effective for pre-op TV.

The value of 28 cm^3 approximately corresponds to (1) a single nodule 4 cm in diameter, (2) two nodules with a diameter of 3 cm, (3) seven nodules with a diameter of 2 cm.

Statistical analysis was carried out with SPSS (SPSS Base 8.0, Application Guide, SPSS Inc., Chicago, IL) and Stata (Stata Corporation, College Station, TX).

Results

Impact of the Selection Criteria on the Study Population

The main change in the policy of HCC treatment with LT at our Center occurred in 1996, when we started to apply the MC. This change in policy was confirmed while cross tabulating MC and tumor size, before and after 1996.

Child-Turcotte-Pugh class, Edmondson grade, and presence of satellite nodules also differed between the two periods (Table 1).

This policy led to improved results in tumor recurrence and patient survival. After 1996 there were only 3 HCC recurrences in 48 patients (6.3%), while before 1996 we had 6 recurrences in 15 patients (40%), $P<0.005$.

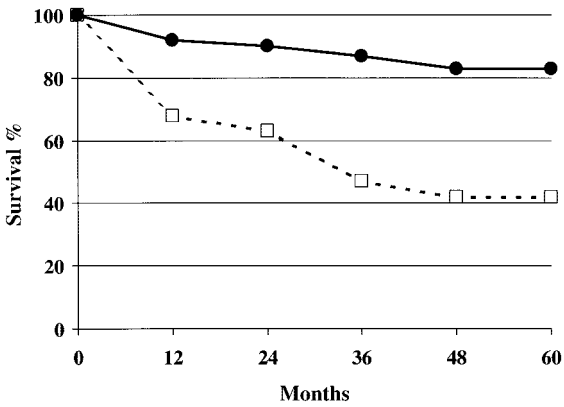

Figure 1. Overall survival of patients according to the year (□ before 1996 and ● after 1996).

Patient survival and recurrence rate changed over the two periods: after 1996 3- and 5-year survival was 87% and 83%, while before it was 47% and 42%, respectively $P<0.005$ (Figure 1).

Preoperative Analysis

Preoperative analysis showed that selection criteria and tumor size affected TR and patient survival, as did AFP level and year of transplant.

There were 8 patients (12.7%) not meeting the MC pre-op and 3 of them (37.5%) developed HCC recurrence compared to 6 out of 55 (10.9%) in the group meeting the MC pre-op ($P = .05$). TV over 28 cm^3 and AFP level over 30 ng/dL were strongly related to HCC recurrence ($P<0.005$ and $P<0.05$ respectively). Seven (36.8%) out of 19 patients with a TV over 28 cm^3 developed TR, compared to 2 (4.5%) out of 44 in the group with a lower volume. Furthermore, ROC analysis showed that considering the presence of HCC recurrence as the event to be predicted, the cutoff of 28 cm^3 pre-op was able to correctly classify 82% of patients (specificity 60%, sensitivity 85%) and there was a linear relation between TR and TV (Figure 2).

Six (31.6%) out of 19 patients with AFP more than 30 ng/dL developed TR, compared to 3 (6.8%) out of 44 in the other group (Table 2).

At the logistic regression analysis only AFP over 30 ng/dL and TV over 28 cm^3 remained independently related to TR: $P < .005$ (relative risk [RR] = 13.9, 95% CI = 2.2-87.6), and $P < .05$ (RR = 7.4, 95% CI = 1.3-42.5), respectively.

The univariate analysis of patient survival confirmed

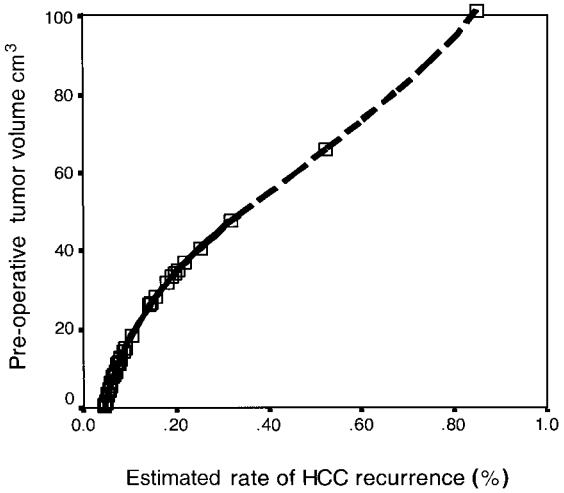

Figure 2. Estimated rate of HCC recurrence according to the preoperative tumor volume.

the results of TR. At the Kaplan-Meyer analysis the following variables were related to a lower overall survival: not meeting the MC ($P < .005$), TV greater than 28 cm^3 ($P < .05$), AFP more than 30 ng/dL ($P < .001$), and year of LT before 1996 ($P < .001$), as reported in Table 2. In the Cox regression analysis only AFP more than 30 ng/dL and year of LT before 1996 significantly reduced survival: $P < .005$ (RR = 4.9, 95% CI = 1.8–13.5) and $P < .05$ (RR = 4.1, 95% CI = 1.6–10.8), respectively.

Postoperative Analysis

The analysis based on the histological features of the HCCs did not reveal any correlations with TR and patient survival (Table 3). Unlike the pre-op results, the selection criteria and the tumor size were not able to predict HCC recurrence and patient outcome.

The rate of patients not meeting the MC post-op was significantly higher than pre-op: 28.6% (18 cases) and 12.7% (8 cases), respectively ($P < .05$). This post-op over-staging according to the MC was due to the presence of small additional nodules, not detectable before surgery, as demonstrated by the significantly increased number of nodules: the mean number of HCCs post-op was 2.1 ± 1.8 versus 1.6 ± 0.8 pre-op ($P < .05$). These small nodules did not significantly change the rate of patients with a TV greater than 28 cm^3, remaining close to 30% pre-op and post-op.

The TR of patients not meeting the MC decreased from 37.5% pre-op to 16.7% post-op (Table 4). The analysis of survival showed similar results: the 5-year survival of patients not meeting the MC pre-op increased from 38% to 67% in patients not meeting the MC post-op (Fig. 3A and 3B). Therefore the MC were effective in predicting TR and patient survival when applied pre-op but not post-op.

Discussion

We retrospectively reviewed our experience in the treatment of HCCs with LT in order to evaluate the impact on the outcome of the selection criteria, applied since 1996, and to analyze the prognostic role of the clinical-pathological variables investigated.

When we started to apply the MC after 1996, tumor recurrences fell drastically and overall patient survival consequently improved. The policy of applying the MC led our center to perform LTs for HCCs with a lower tumor size than in the past and with a lower recurrence rate. The MC evaluated pre-op by radiological imagining were effective in predicting HCC recurrence and patient survival. On the other hand, they were ineffective when elaborated post-op, confirming the relevant clinical bias between pre- and post-op data.

The AFP level and the tumor volume, a variable never formerly investigated, were significantly related to tumor recurrence and patient survival in the pre-op analysis, suggesting their possible application in improving selection criteria and determining a specific risk of recurrence.

We started our study because some authors[5,6] suggested expanding the MC, reporting an acceptable survival in patients not meeting the MC. The major criticism regarding these reports and those with the most numerous clinical series are: (1) the set of data varies from paper to paper; (2) the effectiveness on survival and on HCC recurrence of the variables evaluated post-op are transferred onto the pre-op selection criteria, without considering the differences between pre- and post-op data and the presence of incidental HCCs; (3) the minimum period of time for detecting HCC recurrence is not considered, although the percentage of deaths unrelated to recurrence varies between 35% and 90%.

The main aim of our analysis was thus to define a precise study population that could correctly represent a suitable cohort of patients for the statistical observation of our defined end-point: impact of the variables available pre-op on HCC recurrence and survival.

We selected only cases with a pre-op diagnosis of

Table 2. Preoperative Analysis of Tumor Recurrence and Patient Survival

Variables	No. Patients	No. Recurrences (Rate)	*P* Value	5-Year Survival %	*P* Value
Gender					
Male	56	8 (14.3%)	N.S.	71	N.S.
Female	7	1 (14.3%)		67	
Age (yr)					
0–50 years	24	4 (16.7%)	N.S.	70	N.S.
>50 years	39	5 (12.8%)		69	
Etiology of cirrhosis					
HCV-negative	28	6 (21.4%)	N.S.	60	N.S.
HCV-positive	35	3 (8.6%)		79	
Child-Turcotte-Pugh class					
A	8	3 (37.5%)	<0.05	65	N.S.
B–C	55	6 (10.9%)		71	
Waiting time					
0–180 days	45	7 (15.5%)	N.S.	62	N.S.
>180 days	18	2 (11.1%)		84	
Pre-op treatments					
No	25	3 (12%)	N.S.	67	N.S.
Yes	38	6 (15.8%)		73	
Selection criteria*					
Meeting MC	55	6 (10.9%)	<0.05	78	<0.005
Not meeting MC	8	3 (37.5%)		38	
HCC number*					
Single	39	6 (15.4%)	N.S.	73	N.S.
Multiple	24	3 (12.5%)		66	
HCC diameter*					
0–5 cm	60	8 (13.3%)	N.S.	72	N.S.
>5 cm	3	1 (33.3%)		50	
Tumor volume*					
0–28 cm^3	44	2 (4.5%)	<0.005†	82	<0.05
>28 cm^3	19	7 (36.8%)		46	
Alfa-fetoprotein level					
0–30 ng/dL	44	3 (6.8%)	<0.05†	85	<0.001‡
>30 ng/dL	19	6 (31.6%)		37	
Year					
Before 1996	15	6 (40%)	<0.005	42	<0.001‡
After 1996	48	3 (6.3%)		83	

* Based on radiological imaging.
† Independently related to TR on the multivariate regression analysis.
‡ Independently related to patient survival on the multivariate Cox analysis.

HCC, subsequently proven on the samples, and the analysis of tumor recurrence was performed in cases with at least one year of survival. Each variable was also analyzed with the data detected pre-op by the radiological imagining and post-op by the histological evaluation, in order to reduce the statistical bias, which we criticize in past reports.

The most convincing results, concerning the effectiveness of our statistical method, were related to the MC. The post-op analysis based on the histological tumor features, as reported by almost all studies,[8–10,29] did not find any relation between patient outcome and MC. The results were completely different in the pre-op analysis based on the radiological imaging: MC influenced tumor recurrence and patient survival in the univariate analysis, suggesting its relevant role in the selection of patients.

The statistical bias between pre-op and post-op data was caused by the small multiple nodules not detected pre-op, which moved patients within MC pre-op to outside MC post-op, without affecting the recurrences. The number of patients not meeting MC post-op were higher than pre-op, but the HCC recurrences were the same; the recurrence rate was therefore lower and the

Table 3. Postoperative Analysis of Tumor Recurrence and Patient Survival

Variables	No. Patients	No. Recurrences (Rate)	*P* Value	5-Year Survival %	*P* Value
Tumor vascular invasion					
Presence	38	8 (21.1%)	N.S.	69	N.S.
Absence	25	1 (4%)		72	
Edmondson grade					
I°–II°	33	3 (9.1%)	N.S.	76	N.S.
III°–IV°	30	6 (20%)		62	
Satellite nodules					
Presence	13	3 (23.1%)	N.S.	68	N.S.
Absence	50	6 (12%)		77	
Peritumoral capsule					
Presence	14	2 (14.3%)	N.S.	68	N.S.
Absence	49	7 (14.3%)		73	
Selection criteria*					
Meeting MC	45	6 (13.3%)	N.S.	73	N.S.
Not meeting MC	18	3 (16.7%)		67	
HCC number*					
Single	36	5 (13.9%)	N.S.	68	N.S.
Multiple	27	4 (14.8%)		74	
HCC diameter*					
0–5 cm	58	8 (13.8%)	N.S.	72	N.S.
>5 cm	5	1 (20%)		54	
Tumor volume*					
0–28 cm^3	46	5 (10.9%)	N.S.	77	N.S.
>28 cm^3	17	4 (23.5%)		57	

Abbreviations: HCC, hepatocellular carcinoma; MC, Milan criteria.
* Based on histological sample.

efficacy to predict recurrence was lost, as reported in Table 4.

Additional data in favor of the MC emerged from the analysis performed over fifteen years of experience. In the first period, when our center did not apply any selection criteria, patient outcome was very poor. Although improvements in medical care contributed to increase patient survival in the second period independently of any oncological causes, selection criteria significantly changed our study population concerning the tumor features: HCCs had a smaller size, better differentiation degree and less satellite nodules. The tumor recurrences were consequently reduced, favoring better patient survival.

The MC led our center to perform LT for HCCs in their early stage, but they selected only two groups of patients: low risk of recurrence vs. a risk that is not low. Since the variables related to the outcome of LT are multiple, a more specific scoring system to assay the risk of tumor recurrence is mandatory and our study suggested the evaluation of the AFP level and the tumor volume as being effective for this purpose.

The tumor volume synthesizes the variables of HCC number and diameter, adding more statistical relevance

Table 4. Statistical Bias of the Milan Criteria (MC) Evaluated With Pre-op and Post-op Data

	Selection Criteria	No. Patients (Rate)	No. Recurrences (Rate)	*P* Value	5-Year Survival %	*P* Value
Pre-op analysis based on radiological imaging	Meeting MC	55 (87.3%)	6 (10.9%)	<0.05	78%	<0.05
	Not meeting MC	8 (12.7%)	3 (37.5%)		38%	
Post-op analysis based on histological samples	Meeting MC	45 (71.4%)	6 (13.3%)	N.S.	73%	N.S.
	Not meeting MC	18 (28.6%)	3 (16.7%)		67%	

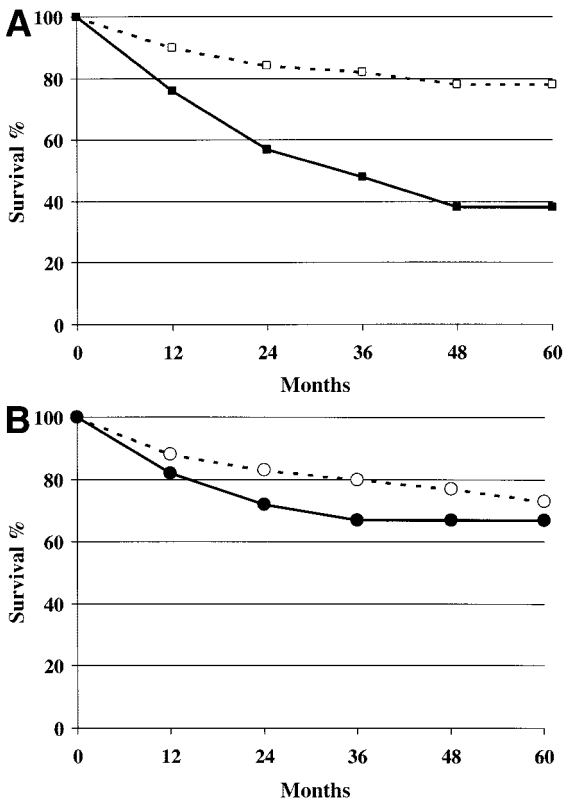

Figure 3. (A) Overall survival of patients according to the preoperative Milan criteria (□ meeting Milan criteria and ■ not meeting Milan criteria). (B) Overall survival of patients according to the postoperative Milan criteria (○ meeting Milan criteria and ● not meeting Milan criteria).

to the diameter, which is related to the vascular support of the tumor and to its tendency to spread into the blood.[10]

The pre-op tumor volume predicted the HCC recurrences and the patient outcome, while the ROC analysis showed a linear correlation between the increasing level of tumor volume and the higher rate of recurrences (Fig. 2). The knowledge of the risk of HCC recurrence for each value of tumor volume permits a comparison with the other clinical variables and it may help in choosing the most appropriate treatment. Once the limit of tumor recurrence acceptable by liver transplant centers has been established, the ROC curve could indicate the corresponding value of tumor volume to select patients. Using the 28 cm^3 cutoff emerging from our study, which was designed to be added to the MC rather than to replace them, we would be more restrictive with a single nodule (4 cm in diameter instead of 5) and with nodules with a 3 cm diameter (two nodules instead of three), but we would expand the selection criteria for patients with small multiple nodules with a diameter of less than 2 cm (less than 7 instead of 3).

The results of our study suggest extending the indication for LT without increasing recurrences toward small multiple HCCs with a volume less than 28 cm^3. These tumors, nowadays staged better pre-op thanks to the radiological improvements, have an aggressive biological behavior, but they probably have a lower risk of spreading into the blood than large single nodules and therefore a better outcome after LT.

As far as the AFP level was concerned, this predicted HCC recurrence and patient survival in the univariate and multivariate analysis. This variable is the same pre- and post-op, it can be accurately measured and its role in improving the selection criteria of patients is absolutely justified.

As regards the correlation with tumor recurrence of the variables detected in the histological samples, like tumor vascular invasion and the Edmondson grade, previously found to be related to tumor recurrence,[8,10,11,15,30,31] they were not the subject of our study since they are not available pre-op for the selection of patients and are consequently not discussed in further detail.

In conclusion, the evaluation of two periods in our experience without and with the MC, the pre-op analysis of selection criteria and the correlation between tumor volume and HCC recurrence by ROC curves suggest that the pretransplant policy to extend the MC advocated by many authors will increase recurrences. Patient survival will be the same, if the deaths unrelated to tumor recurrence are reduced, selecting recipient and donor features.

The assessment of the AFP level and the tumor volume may improve the pre-op evaluation of patients and it allows the selection of HCCs with a corresponding risk of recurrence. Therapeutic strategies, such as liver transplantation from living donors,[32–35] may consequently be applied by establishing the acceptable risk of tumor recurrence.

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