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Liver transplantation for hepatocellular cancer: should the current indication criteria be changed?

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Abstract Liver transplantation (LTx) is the best treatment for hepatocellular carcinoma (HCC), but should be offered only to selected patients. The usual procedure is to transplant only for small and unilobular tumors. The aim of this paper is to verify whether the actual indication criteria are still justified. The details of 121 patients with HCC who were submitted to LTx from 1985 to 2000 were analyzed. Age, gender, liver disease, Child class, α-fetoprotein (AFP) level, presence of tumor capsule, vascular invasion, size and number of nodules, histological grade, and pTNM were considered. The 5- and 10-year actuarial survival rates were 61.7% and 53.1%. Freedom from recurrence was 85.9% and 85.9%, respectively. At univariate analysis, size, presence of capsule, AFP levels, vascular invasion, grade, pTNM, transarterial chemoembolization (TACE), Child class, and age were all significantly related to survival and/or cancer recurrence. Presence of capsule, AFP levels, and viral cirrhosis were independent variables in Cox's analysis for survival, whereas histological grade, AFP levels, and vascular invasion were significant independent variables for recurrence. In conclusion, a strict selection should be made to optimize graft allocation while size and multifocality should probably no longer be considered a contraindication for LTx. Histological grade, AFP levels, and vascular invasion, as indicator of tumor behavior, more likely reflect the risk of recurrence.

Keywords Liver transplantation · Hepatocellular carcinoma · Indication criteria · Transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is one of the world's most common malignant tumors and usually develops against a background of chronic inflammatory liver disease [1]. For this reason HCC is, in most cases, a problem of two diseases, the malignancy itself and cirrhosis. Because of the strict correlation between HCC and liver cirrhosis, therapy by surgical intervention is still a matter of debate. Indeed, the possibility of performing liver resection (LR) is limited by the severity of cirrhosis, and tumor recurrence is a frequent event in the cirrhotic liver remnant, which maintains its potential to generate new tumors.

Liver transplantation (LTx) is the only option for treating tumor and cirrhosis at the same time. Its wide application in neoplastic diseases, however, is hampered by the risks of local and systemic tumor recurrence, which may be accelerated by the immunosuppressive treatment associated with organ transplantation [17, 25]. Moreover, it cannot be applied to all patients with HCC, since the limited number of donors worldwide demands that organs be allocated to candidates with better chances of long-term survival. Nevertheless, excellent

results after LTx were reported in the past decade, provided that patients with certain tumor characteristics were strictly selected before transplantation. In these cases, LTx is recognized to be the best therapy for HCC [6, 15, 17, 21]. It is now of crucial importance to verify whether, after 10 years, this philosophy of treatment should be confirmed or whether the selection made was too restrictive, thus excluding from LTx many patients with good chances of survival.

The Department of Surgery and Transplantation of Niguarda Hospital in Milan has wide experience both in liver resection and transplantation (545 LRs for benign and malignant diseases and 605 LTxs since 1985). This study presents retrospectively the results obtained in a large series of patients with HCC who underwent LTx in the same surgical facility with a long follow-up (up to 15 years). Our aim was to investigate the impact of various tumor characteristics and related risk factors on immediate and long-term results and re-evaluate the criteria upon which an appropriate selection policy for LTx can be based.

Patients and methods

Patients

At our department, 121 patients with HCC were submitted to LTx with curative intention from December 1985 to December 1999. A curative operation was defined as absence of tumor outside of the liver in the pre-operative stage and no evidence of tumor anywhere but in the liver during surgery. All patients were staged by ultrasound (US) and CT scans, and celiac-mesenteric angiography. Patients on the waiting list for LTx had US scans and α-fetoprotein (AFP) analysis performed every 6 months: CT, MRI, or angiography were repeated only when required. The enlistment of patients ended on December 1999 in order for there to be more than 18 months of follow-up in all surviving patients. Age, gender, presence of cirrhosis or chronic liver disease, etiology of liver disease (viral or not), Child-Pugh classification, and AFP level were considered. After surgery, the pathologists were requested to define in a questionnaire the following points: (1) presence, absence, or infiltration of a tumor capsule; (2) micro- or macrovascular invasion; (3) size and number of the nodules; (4) tumor-free margins; (5) histological grade (modified Edmondson criteria, I: well differentiated; II: moderately differentiated; III: poorly differentiated HCC); (6) pTNM (this staging was revisited according to the recently modified TNM classification) [2, 26]. The stratification of the patients' characteristics is represented in Table 1.

Diagnosis of HCC was always confirmed by biopsy in the vast majority of patients: biopsy was not performed only in seven patients (5.7%) with advanced cirrhosis and, therefore, at high risk of bleeding, and in 28 other patients (23.1%) who were serendipitously diagnosed as having HCC when their native liver was dissected. In these incidental cases the diameter of the nodule ranged between 1 and 12 cm (median: 2.3 ± 2.1 cm). In the entire series of transplantation patients, the diameter ranged between 1 and 14 cm (median: 3.7 ± 2.5 cm). Follow-up was completed in all patients (mean follow up: 3.9 ± 3.3 years, range: 1–5, 108 days).

Survival rates and tumor recurrence were the end point of this analysis. Tumor recurrence was defined as a lesion in the liver or other organs that presented CT features of HCC (hypervascular lesion with rapid contrast enhancement in the arterial phase, hypodense aspect without contrast in the venous phase) and with or without (less frequently) histological confirmation or increase in AFP. The majority of these lesions were treated, when possible, with systemic chemotherapy, transarterial chemoembolization (TACE), ethanol injection and, more recently, radio-frequency ablation.

Table 1 Characteristics of patients and tumors

Characteristic	LTx $n = 121$
Age	51.06 ± 7.1 years
Gender (M/F)	104/17
Cirrhosis/chronic active hepatitis	118/3
Child-Pugh classification	
No cirrhosis	3
A	18
B	49
C	51
pTNM	
pTx[a]/pT1	40
pT2	29
pT3	26
pT4	26
TNM	
Tx[b]/T1	33
T2	55
T3	17
T4	16
Tumor size	
≤ 3 cm	63
> 3 cm	58
≤ 5 cm	98
> 5 cm	23
Number of nodules	
$n = 1$	72
$n = 2$	29
$n > 2$	20
Tumor capsule	
Absent	42
Infiltrated	36
Complete	43
Vascular invasion	
Microscopic	17
Macroscopic	9
Absent	95
α-Fetoprotein	
≤ 20 ng/ml	61
> 20 ng/ml	60
Histological grade	
Well differentiated	45
Moderately differentiated	59
Poorly differentiated	17

[a]Eleven patients with a completely necrotic nodule
[b]Twenty-eight patients with incidental tumor

Treatment

LTx was generally offered as a treatment for HCC to cirrhotic patients aged less than 60 years in whom the tumor could not be removed by resection, or when advanced cirrhosis was an indication for LTx per se. At the beginning of our program, large or multifocal tumors were frequently treated by LTx. From 1989, indication for transplantation, as defined in our previous papers [3, 6, 19] and, conclusively, by a cooperative study in Milan in 1994

[14], tended to be limited either to a single HCC nodule with a diameter of less than 5 cm or to multiple nodules (not more than three), each one having a diameter of less than 3 cm, corresponding to pTNM stage 2.

With the intention of having progression of the tumor limited, 60 patients (49.5%) underwent loco-regional therapy for their HCC while still on the transplant waiting list [8, 10]. In all these cases, HCC was histologically ascertained before treatment. Loco-regional therapy included TACE (56 patients), radio-frequency ablation (two patients), and ethanol injection (two patients). This policy of treatment was introduced into our protocol in 1992; before this date eight of 34 patients (23.5%) had TACE before LTx, while in the last 8 years 52 of 87 patients (59.7%) were treated for their HCC before LTx ($P < 0.05$). TACE was performed via an ultraselective technique by the introduction of a microcatheter on the distal branches of the hepatic artery, thus reducing the risk of hepatic decompensation. Patients with advanced Child-C cirrhosis and bi-lobar or incidental tumors were not submitted to this procedure for evident reasons. In 44 patients (73%) loco-regional therapy induced nodular necrosis ranging from 30% to 100% of the nodules. In 11 patients (18.3%) the nodule in the removed liver was entirely necrotic.

The median waiting time (247 days, range 32–545 days) varied according to AB0 blood group (182 days for group A, 315 days for group 0, and 492 days for groups B and AB). The median waiting time increased from 88 days (1985–1992: 55 patients, two deaths while on the waiting list) to 394 days (1993–1999); during this latter period, eight of the 76 patients who presented a tumor at preoperative assessment were excluded while on the waiting list (351 days, range 189–410 days) because they had died (three patients) or because of an evident progression of the disease (five patients) far beyond the indication criteria (well-documented increase in number or size of the tumor or appearance of vascular neoplastic thrombosis). In a consistent number of patients, however, the progression of the tumor failed to be detected during the waiting period and transplantation was nevertheless performed.

Statistical analysis

A first analysis was performed to determine the risk of death or recurrence within 5 years after the operation. This 5-year interval was arbitrarily selected in order to deal with statistically relevant cohort sizes in each group. Moreover, no patient had recurrence beyond 3 years from LTx and so the influence of the different risk factors seems of little importance at over 5 years after the operation. Indeed, 10–15 years after the operation the number of surviving patients is too small to have any statistical meaning.

Univariate analysis was performed to determine the influence of the quoted parameters on survival as well as on tumor recurrence. For the evaluation of the rate of recurrence-free patients, only recurrence was regarded to be an event in Kaplan-Meier estimates. When freedom from recurrence was considered, patients who had died 3 months after surgery were excluded from analysis. Correlation among the variables was tested with the Spearman correlation rank test. Overall survival (including early and late mortality rates), according to the covariates, was calculated by the Kaplan-Meier method. Statistical significance of the Kaplan-Meier curves was analyzed by the log-rank test and the Mantel-Haenzel test. Variables showing a statistically significant association with 5-year survival and disease recurrence in the univariate analysis ($P < 0.05$) were included in a multivariate analysis performed with the Cox proportional hazard regression model. Multivariate analysis (SAS PHREG procedure) was performed by a stepwise approach, which included step 1: individual test score for all the covariates (χ^2 score); step 2: forward stepwise sequence of χ^2 statistics in the order of greater increase to the overall test statistics; and step 3: inclusion in the final model of the covariates with significant ($P < 0.05$) χ^2 increment. Regression coefficients were expressed as relative risk (RR) with 95% confidence interval (CI). All data were analyzed with the Statistical Analysis System Package (SAS Institute, Cary, N.C.) release 6.11 and with the statistical software Prism 2.01, which also allowed the data to be plotted. Moreover, a second analysis was performed on long-term survival and disease-free interval (i.e., over the entire 15-year period of the study), which compared the curves of different groups of patients with different types of variables according to the log-rank and the Mantel-Haenzel test.

Results

Mortality and recurrence

Actuarial survival and freedom from recurrence were 61.7% and 85.9%, respectively, at 5 years and 53.1% and 85.9% at 10 years (Fig. 1). The distribution of survival rates and freedom from recurrence over the entire period is depicted in Fig. 2. Of the 121 transplant-recipients, 22 (18.1%) died within the first 3 months after surgery. Mortality and recurrence in the entire series of patients are reported in Table 2. Of these early

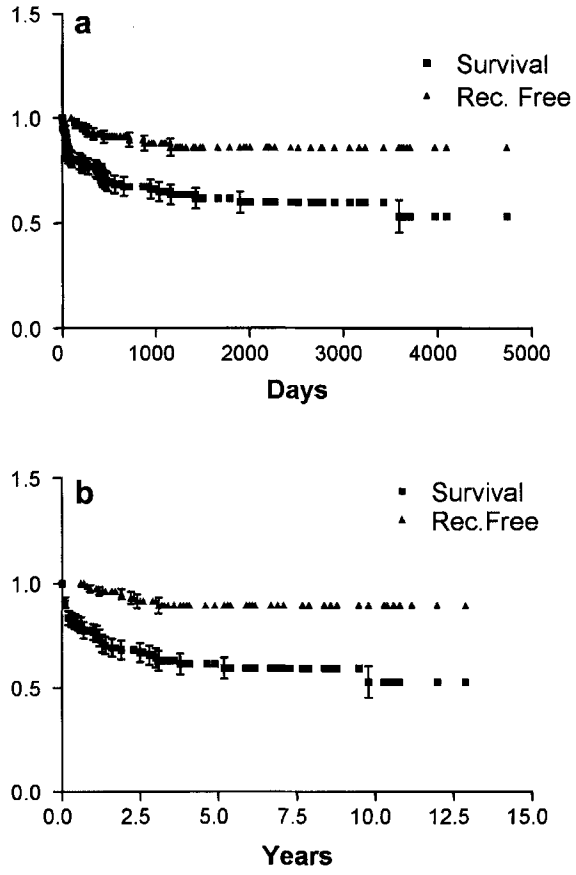

Fig. 1 Overall actuarial survival rate and freedom from recurrence curves after LTx for HCC. When recurrence rate was analyzed, early mortality (< 3 months) was eliminated

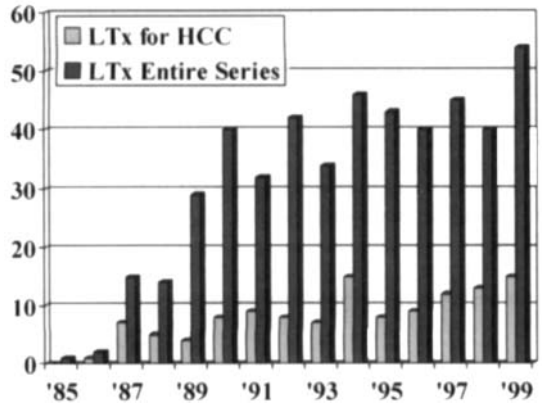

Fig. 2 Distribution of patients per year over the study period (1985–1999). The whole series of patients is compared with the patients who underwent LTx for HCC

Table 2 Mortality and recurrence after LTx for HCC (*MOF* multiple organ failure, *PGNF* primary graft non-function, *PTLD* post-transplantation lymphoproliferative disorder)

Parameter	*n*
Early mortality (< 90 days)	22 (18.1%)
Sepsis	5
MOF/PGNF/liver failure	6
Vascular complications	4
Hemorrhagic shock	3
Cerebrovascular/myocardial accident	3
Rejection	1
Late mortality unrelated to tumor recurrence	12/99 (12.1%)
Recurrent hepatitis/cirrhosis	4
Chronic rejection	2
Cerebrovascular/myocardial accident	3
PTLD/De novo tumor	1
Other	2
Late mortality related to tumor recurrence	10/99 (10.1%)
Number of patients with recurrence	11/99 (11.1%)
Intra-hepatic	3
Intra/extra-hepatic	6
Extra-hepatic	2
Alive with recurrence	1

mortality cases, nine patients were of Child-C status, 11 were B, one was A, and one had chronic active hepatitis (CAH). During the successive postoperative course, 12 of the remaining 99 patients (12.1%; mean survival 740 days, range 94–3,591 days) died of causes unrelated to neoplasm recurrence.

Recurrence occurred in 11 of the 99 patients (11%) who survived for more than 3 months (mean recurrence time 427 days, range 129–1,161 days; median 274 days). Recurrence leading to death occurred in ten cases (10.1%; mean survival 686 days, range 279–1,423 days). At the end of the follow-up, one patient (2,643 days) is alive with HCC recurrence, having experienced different therapeutic strategies on the recurrent disease (TACE, radio-frequency ablation, systemic chemotherapy).

Univariate and multivariate analysis

At univariate analysis, tumor size, presence of capsule, vascular invasion, histological grade, pTNM stage, AFP level, Child status, viral etiology, and loco-regional treatment were significantly correlated with survival, whereas only capsule, vascular invasion, AFP, grade, and age were significantly correlated with freedom from recurrence.

Multivariate analysis allowed us to conclude that presence of capsule, AFP level, and viral cirrhosis are significantly correlated with survival, whereas AFP level, vascular invasion, and grade showed an independent influence upon freedom from recurrence. Comparison of curves by log-rank test, showing the influence of histological grade and vascular invasion, are depicted in Fig. 3.

Discussion

The debate over the optimal treatment for HCC in patients with cirrhosis who are eligible for surgery cannot be easily resolved as long as randomized controlled trials are lacking. Such trials require large numbers of cases to generate an even distribution of patients within the different stages of the disease. Retrospective studies, when conducted on large numbers of patients, may provide information on the roles of different variables in survival and recurrence after surgical treatment. This might help to identify new criteria for treatment of patients with HCC [4, 5, 20].

LTx may be considered the most rational treatment for HCC in cirrhosis because it addresses the multifocal potential of HCC in many patients, which limits the success of other treatment options, and also treats the underlying liver disease. This way, tumor and cirrhosis are treated together with a single procedure. However, in the literature, good results were reported only when restricted indication criteria for transplantation were adopted [5, 15, 19]. These criteria principally involved the extent and size of the tumor, as these characteristics are evident at pre-LTx assessment and were based on empiric and very restrictive observations that stated that tumors incidentally discovered during pathological dissection of the removed liver gave, surprisingly, results comparable with non-neoplastic diseases. Because these tumors were solitary and smaller than the tumors that were usually considered as indication for LTx, the concept that only patients with small uni-focal tumors could undergo successful transplantation became popular. However, findings that many transplant patients who had tumors exceeding the pT2 criteria may have good results, with a low recurrence rate at long-term follow-up, were recently reported [9, 11, 18, 26]. In fact, there is no clear consensus on the greatest tumor diameter for solitary or multifocal lesions for

Table 3 Five-year survival and freedom from recurrence after LTx for HCC. Stratification according to prognostic parameters. Univariate analysis

Parameters	*n*	Survival (%)	*P*	*n*	Recurrence-free (%)	*P*
Gender (M/F)	104/17	60.8/67.9	0.8	86/13	85.2/90.9	0.1
Age						
≤ 55 years	77	74.5	0.08	60	79.6	0.03
> 55 years	44	54.6		39	96.9	
Viral cirrhosis						
Yes	94	64.8	0.005	83	92.8	0.4
No	27	49.7		16	84.8	
Child class						
0–A	21	54.3	0.4	19	69.6	0.02
B–C	100	63.8		80	89.9	
Number of nodules						
1	72	70.6	0.06	59	74.2	0.1
> 1	49	46.9		40	55.1	
Size						
≤ 3 cm	63	73.1	0.01	54	90.5	0.1
> 3 cm	58	47.7		45	80.3	
Vascular Invasion						
No	95	70.7	0.002	79	93.8	0.001
Yes	26	26.4		20	53.3	
Capsule						
Yes	43	85.9	0.001	39	100.0	0.004
No	78	48.6		60	74.3	
pTNM						
x–1–2	69	72.3	0.05	58	92.3	0.1
3–4	52	45.8		41	78.2	
α-Fetoprotein						
≤ 20 ng/ml	61	77.5	0.002	52	100.0	0.002
> 20 ng/ml	60	45.8		47	71.3	
Histological grade						
Well/moderately differentiated	104	72.1	0.002	87	89.4	0.02
Poorly differentiated	17	28.5		12	41.3	
Chemoembolization						
No	61	49.4	0.05	46	57.5	0.5
Yes	60	68.3		53	66.9	

Table 4 Independent variables in the Cox analysis for 5-year survival and freedom from recurrence after LTx for HCC

Parameter	Variable	Risk ratio	Confidence interval	*P*
Survival	Capsule	2.466	0.992/6.130	0.05
	α-Fetoprotein	2.323	1.109/4.864	0.02
	Viral cirrhosis	2.260	1.108/4.607	0.02
	Histological grade	2.220	1.067/5.001	0.03
Freedom from recurrence	Vascular infiltration	11.108	2.855/43.216	0.0005
	α-Fetoprotein	2.675	2.131/8.584	0.0001
	Histological grade	2.978	2.456/9.751	0.0002

which LTx can be performed with an acceptably low risk of HCC recurrence. In addition, there are still uncertainties regarding some histological features, namely grade and the presence of vascular invasion, as determinants of a dismal outcome after LTx [5, 9].

In this study, a large group of patients submitted to LTx for HCC in cirrhotic liver were considered. Indication criteria tended to exclude patients with advanced age or tumor; for different reasons, however, a consistent number of patients with advanced-stage tumor were given transplants, and this permitted an analysis that included tumors with different characteristics.

The early mortality rate after LTx (18.1%) was high, partly because all our experience was considered, including the initial learning curve, and partly because the stage of cirrhosis and the general condition of the patients had a great impact on the peri-operative period. This rate has been improving with time down to 6% between 1995 and 2000. This is, of course, the consequence of improved logistical facilities as always occurs when new surgical technology is implemented together with proper selection of candidates.

Late mortality unrelated to tumor recurrence was mainly a consequence of hepatitis relapse or cardiovas-

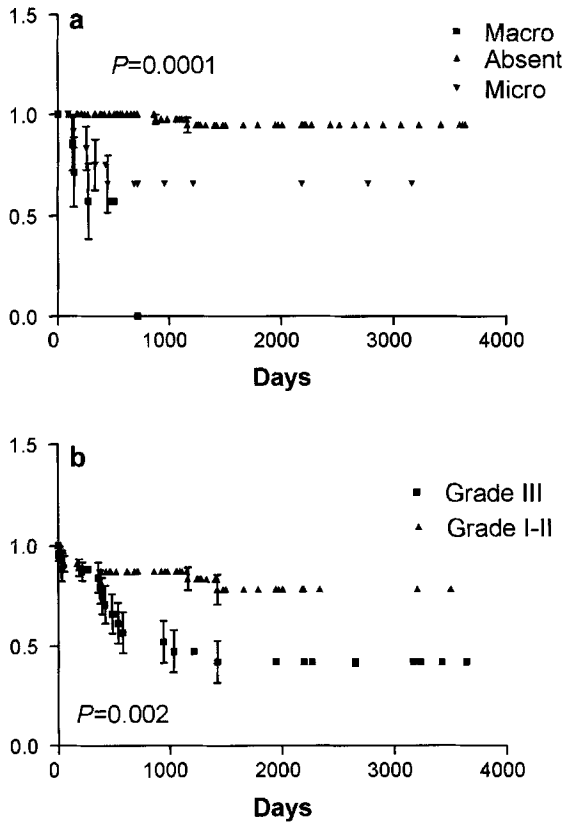

Fig. 3 **a** Freedom from recurrence after LTx for HCC according to vascular invasion. The difference between the curves is significant in the log-rank test. **b** Significance is again evident when survival rates are compared according to different histology

cular accidents. Late mortality related to tumor recurrence and overall tumor recurrence rate were 10% and 11%, respectively, and it is a low recurrence rate when the fact is considered that a number of large and multinodular tumors were present in the transplant recipients. A particular aspect of this study is the observation that no patient had a recurrence beyond 3 years after LTx, even at a very long-term follow-up; it seems that after this period LTx patients may be considered reasonably cured from HCC. This statement may appear too strong, and more studies are needed to ascertain this. Indeed, the present series, which included different types of tumors in a large number of patients, seems to confirm this hypothesis.

An important aspect of the interpretation of the data is that in this study all the tumor parameters entered into the analysis were obtained from operative specimens. For hepatic tumors, pre- and intra-operative findings are known to differ considerably. Therefore, decisions before surgery are at least partially based on unreliable data. In fact, there were 28 patients with incidental tumors, and this had to be somehow taken into account in the analysis because the indication for LTx was a consequence only of the severity of cirrhosis. Our decision to include these patients in the study was justified by the fact that tumor features in this subgroup were similar to the ones of the other transplanted patients. It turned out that the long-term results of these incidental patients did not show any significant difference [11, 13, 21]. The high number of incidental tumors in our series and, in some cases, the great size of the tumors discovered, is a consequence of the long waiting time on our list, which permitted growth of the neoplasm, and of the low accuracy of the radiological approach (mainly US scans) while patients were on the waiting list. The accuracy of pre-operative staging is crucial when LTx in neoplastic disease is considered. In the literature, it is to be found that the radiological procedures generally underestimate the size or the multifocality of the neoplasm in more than 25% of cases. Satellite lesions are detectable with US scans and MRI in only 34–42% of cases [7, 11]. Our experience, by comparing pre-operative TNM and pTNM, confirm these data (Table 1). This lack in sensitivity of the pre-operative assessment also explains why many patients in our series underwent transplantation even when the size and extent of their tumor had exceeded the indication criteria. The improvement in imaging techniques in recent years (contrast MRI, multidetector multiphase CT) has provided more sensitivity for the detection of both the main HCC lesion and the satellite nodules, and the chance of underestimating HCC stage is lessening.

Univariate analysis indicates that the characteristics of the tumor play an important role in survival rate, and this is in accordance with what was reported in the literature [4, 15, 20]. Size, number of nodules, and pT stage, together with presence of capsule, vascular invasion, AFP level, and histological grade appeared to be determinant prognostic factors. Viral etiology and Child status both had influence on survival, reflecting the high recurrence rate of hepatitis of the new liver and the impact of the advanced cirrhosis on early results. Surprisingly, Cox analysis did not entirely confirm the results, because only factors linked to the aggressiveness of the neoplasm rather than to its morphology acquired relevance. The presence of a capsule, AFP level, and histological grade were, in fact, significant, but not the size of the neoplasm or the number of nodules.

When freedom from recurrence is considered, some characteristics of the tumor (presence of a capsule, vascular infiltration, histological grade, and AFP) were significant prognostic factors at univariate analysis. Vascular invasion, histological grade, and AFP were independent variables at Cox multivariate analysis. Tumor size and multifocality were not significant, either in uni- or multivariate analysis, and this is in contrast with current literature on LTx. Of course, the selection we performed pre-operatively may be biased; however, the

fact that these variables were strongly related to recurrence seems to indicate that the intrinsic behavior of the neoplasm rather than the static characteristics of the tumor are crucial for its prognosis.

Some consideration should be given to the different risk factors. AFP levels lower than 20 appeared to be a predictor of better outcome: this level is based on the results of our statistical analysis and ROC curve and demonstrates that higher levels of AFP in our population correlate with death or recurrence; however, our study could not evaluate the exact levels of risk of recurrence. Grade was a significant prognostic factor for recurrence and survival. As for other types of neoplasm, cellular differentiation appeared to be an important prognostic determinant. This is to be taken into account when one is considering the necessity of performing diagnostic pre-operative biopsies. Indeed, the advantage of having a reliable pre-operative prognostic factor when indicating a patient to a surgical procedure is crucial in the setting of these surgical candidates and balances the risk associated with performing biopsies.

In our center, candidates for LTx remain on the waiting list from 6 to 15 months before undergoing LTx, and patients with HCC are only minimally favored with respect to other patients with advanced cirrhosis. For this reason, loco-regional therapy is usually performed in order to limit the progression of the disease. In our series, TACE and other alternative pre-operative treatments were performed in 60 out of 121 patients (49.5%), but when only individuals with a biopsy-proven HCC are considered, this percentage approximates 70% of the transplant patients (60 out of 86). TACE showed only limited influence on survival or recurrence in the LTx group, despite good results obtained in terms of tumor necrosis at radiological controls and at pathological examination (20% of cases with complete regression of the tumor). Also, in this case, our impression is that it depended mainly on the low number of patients considered and on the low recurrence rate in this group of patients. Indeed, the lack of significance of TACE in reducing the rate of recurrence may be due to different behaviors of the tumor: patients with slowly progressing tumors may be virtually cured by TACE, as results from the relatively high rate of necrotic nodules present in our series; indeed, other tumors show rapid progression despite repeated TACE, suggesting that the mechanism of cellular replication may be up-regulated in the whole cirrhotic liver and, thus, less susceptible to treatments which aim at limiting progression of the disease [22, 23]. As this behavior is difficult to foresee, TACE is strongly recommended if patients are maintained on the waiting list for a long time [8, 12, 16]. A strict follow-up is advised. The policy of excluding patients who showed a rapidly progressing disease is in accord with the concept that the behavior of the tumor and not its characteristics determine the prognosis.

From an oncological point of view, the HCCs most suitable for resection are the same tumors that should have the best results when treated by transplantation, i.e., small localized tumors with low AFP levels. At the same time, the inability to offer LTx as an immediate treatment jeopardizes the outcome in many patients. Our policy is to reserve LTx for younger patients (< 50 years) who have a longer life expectancy and in whom cirrhosis is more likely to progress to a severe disease over time. Other patients with similar tumor characteristics are best treated by LR, as identical 5-year survival rates can be achieved. Adult, living-donor liver transplantation (LDLT) is emerging as a therapeutic option in these cases since it can be offered by passing the waiting list, significantly reducing the time lapse between diagnosis and treatment [25]. In our experience five out of 73 patients were excluded from LTx as a consequence of an evident growth of the neoplasia beyond predefined criteria. This appears to be an important prognostic factor if an intention-to-treat analysis is done, as these dropped patients should be considered as having died, thus influencing the survival curve [11].

An argument favoring LTx is the high rate of cancer recurrence in the remnant cirrhotic liver after partial hepatectomy. Hepatitis C virus (HCV)-related cirrhosis, however, is now the main indication for LTx worldwide, and the graft, despite antiviral treatment, almost invariably becomes infected with the HCV. Therefore, the opinion that LTx removes the malignant potential of the cirrhotic liver may loose its validity [25].

In conclusion, LTx appears to offer satisfying long-term survival and freedom from recurrence in patients with HCC, provided that the time from diagnosis to operation is kept as short as possible. The shortage of organs worldwide and, especially, in Italy limits the possibility of offering this therapy to every patient with HCC. A strict selection should be made to optimize the allocation of organs for transplantation, but probably the actual criteria are too restrictive and based on unproven data. Our impression is that size and multifocality are not, per se, signs of aggressive behavior of the tumor and should not be considered a contraindication for LTx. Other parameters, such as AFP, vascular invasion, histological grade, and aggressive behavior during the waiting period, more likely reflect the risk of recurrence of the disease and should be considered when one is indicating a patient for LTx [9, 25, 26]. Maybe other parameters reflecting high proliferation indices of the tumoral mass will be available in the future [22, 23, 24]. Indeed, criteria for transplantation may be somewhat widened, to include larger tumors in young patients, but the length of waiting time and the appropriateness of organ allocation limit this procedure only to selected cases [11].

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