Aliment Pharmacol Ther 2003; 17 (Suppl. 2): 119–129.

Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre

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SUMMARY

Background: Differences in risk factors for survival and recurrence after liver resection for hepatocellular carcinoma (HCC) in patients with or without cirrhosis are not fully clarified.

Aim: To review a single-centre experience of curative liver resections for HCC in order to evaluate clinicopathologic features and the long-term outcome of cirrhotic and noncirrhotic patients.

Methods: From 1981 to 2002, 308 curative liver resections for HCC on cirrhosis (Group 1) and 135 for HCC without cirrhosis (Group 2) were performed. The main demographic, clinicopathologic and operative parameters, as well as early results were analysed and compared. Overall and disease-free survival were evaluated. Prognostic factors for survival and for tumour recurrence were studied by univariate and multivariate analysis.

Results: Group 1 had worse preoperative liver function and higher frequency of hepatitis C virus infection. In Group 2, HCC showed larger mean tumour diameter ($P < 0.001$), poorer differentiation ($P < 0.05$) and more frequent macrovascular invasion ($P < 0.05$). Although more extended resections were performed in Group 2 ($P < 0.001$), there were no differences in blood transfusions, while post-operative complication rate was higher in Group 1 ($P < 0.005$). After 1992, in-hospital mortality was 2.9% in Group 1 and 1.1% in Group 2 ($P =$ N.S.). The 3- and 5-year overall survival was 63.7% and 42.2% in Group 1, and 67.9% and 51% in Group 2 ($P < 0.05$). The 3- and 5-year disease-free survival was 49.3% and 27.8% in Group 1, and 58% and 45.6% in Group 2 ($P < 0.005$). Serum bilirubin level > 1.2 mg/dL, multiple nodules, micro and macrovascular invasion, diaphragm infiltration and blood transfusions independently affected survival in Group 1. Blood replacement was the only negative prognostic factor in Group 2. Independent risk factors for tumour recurrence were satellite nodules and resection performed before 1992 in Group 1, and age < 60 in Group 2.

Conclusions: Despite a more aggressive behaviour, HCC without cirrhosis led to better overall and disease-free survival compared to HCC with cirrhosis after curative liver resection. Age and intra-operative blood transfusions are the only predictors of outcome in patients without cirrhosis. The impact of the latter on long-term survival in both our groups outlines the importance of surgical technique on the results of hepatectomies.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the more common malignancies and its frequency is increasing in Western countries.[1–3] For patients carrying tumours at

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an early stage and with a preserved hepatic function, liver resection is the best therapeutic choice.

The recent improvements in preoperative selection of patients, in surgical techniques and in post-operative care yield very low operative mortality rates in the most experienced centres.[4–6] Furthermore, in the last few years the same institutions have reported increasing long-term results, with a 5-year survival of around 50% or even higher.[6, 7] In spite of this, the rate of tumour recurrence after hepatectomy remains high, ranging from 60% to 100% in the long-term.[7–11]

Factors related to tumour recurrence and survival in cirrhotic patients undergoing liver resection have been extensively studied.[7–15] In patients without cirrhosis (i.e. those with chronic hepatitis or a morphologically healthy liver), however, knowledge on the variables with an impact on long-term outcome and tumour recurrence is more limited, with only a few studies addressing this issue reported in the literature.[16, 17]

We retrospectively reviewed our experience of liver resections for HCC in order to verify the differences in clinicopathologic characteristics and outcome of patients with and without cirrhosis. We also assessed the influence of patient and tumour-related factors on survival and recurrence of HCC in these two different populations.

PATIENTS AND METHODS

From March 1981 to June 2002, a total of 443 curative hepatic resections for HCC were performed at the Department of Surgery and Transplantation, University of Bologna, Italy. A resection was defined as curative when it was possible to remove the entire neoplastic mass with a histologically proven tumour-free surgical margin. The results of most hepatectomies performed in cirrhotic patients have been reported in an already published report.[6]

The present series included 308 liver resections for HCC on cirrhosis (69.5%, Group 1) and 135 liver resections for HCC in noncirrhotic livers (30.5%, Group 2), considering in this latter group either patients without liver fibrosis ($n = 68$, 50.4%) or patients with chronic hepatitis with fibrosis up to stage III[18] ($n = 67$, 49.6%). There were 339 males (76.5%) and 104 females (23.5%). Mean age was 62.3 ± 9.7 years (ranging from 13 to 82 years).

Surgical treatment was indicated when the complete removal of the tumour was considered possible, in accordance with the volume of the remnant liver, the technical feasibility (based on size and location of the lesion) and the preoperative liver function, which was assessed with the Child–Pugh score[6] and subsequently with the lignocaine (lidocaine) (MEGX) test.[19]

After discharge, patients were followed-up with dosage of serum α-fetoprotein (AFP) level and hepatic ultrasonography every 3 months, and with chest X-ray every 6 months. In the case of suspected tumour recurrence, abdominal computed tomography and/or angiography of the celiac trunk with Lipiodol injection and, if necessary, liver biopsy was carried out.

The results for the treatment of tumour recurrence have already been reported.[6]

End-points

The primary aim of this study was to examine and compare demographic and clinicopathologic characteristics, early results (in terms of in-hospital mortality and complication rate), long-term survival and disease-free survival of the two groups of patients. Secondarily, factors with a possible impact on patient survival and tumour recurrence were separately analysed in the two study groups.

The following 21 variables were evaluated in a univariate and multivariate analysis: sex, age, symptoms related to tumour mass-effect or rupture at presentation, presence of ascites, total serum bilirubin level, Child–Pugh score; aetiology (viral, alcoholic or other), hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibodies (anti-HCV) status, AFP level; tumour histological features (maximum tumour diameter, number of nodules, presence of capsule, presence of satellite nodules, micro and macrovascular invasion, Edmonson's grade of differentiation); liver resection performed before 1992 or starting from 1992, type of hepatectomy (wedge resection, resection of one or two liver segments, or more than two liver segments, according to the Couinuad's classification[20]), diaphragm infiltration, and intra-operative packed red blood cells consumption.

The year 1992 was chosen as the cut-off value because the improvements in clinical assessment, surgical technique, anaesthesiology support and post-operative care were definitely introduced since that date, as reported elsewhere.[6]

Statistical analysis

Results were expressed as median ± standard deviation. Differences between continuous and categorical variables were evaluated with the Student's *t*-test and with the χ^2 test, respectively. The Kaplan–Meier method was used for the analysis of prognostic factors for patient survival and disease-free survival, and the differences between the groups were compared by the log-rank test. Survival was considered from the day of surgery to the day of death or the last follow-up visit. Recurrence rate was computed from the day of surgery to the date of detection of tumour recurrence. Disease-free survival was computed by combining the two mentioned variables, considering the date of death or the date of tumour recurrence as the terminal events. Variables achieving statistical significance at the univariate analysis of survival were put in the multivariate analysis, performed with the Cox's proportional hazard model. Variables with significant impact on tumour recurrence at the univariate analysis were used in the multivariate analysis with the Cox regression model. A *P*-value < 0.05 was considered statistically significant. Statistical analysis was carried out with the SPSS software packaging (SPSS Inc., Chicago, IL).

RESULTS

Clinicopathologic profiles (Table 1)

Group 1 and Group 2 were comparable as regards sex and age distribution, documented alcoholic habit, HBsAg

Table 1. Clinicopathologic profiles of cirrhotic and noncirrhotic patients

	Cirrhotic patients ($n = 308$)	Noncirrhotic patients ($n = 135$)	*P*-value
Sex (M/F)	239/69	100/35	N.S.
Age (years)	62 ± 8 (22–81)	62 ± 12 (13–82)	N.S.
Alcoholic habit	67 (21.7%)	29 (21.5%)	N.S.
Tumor-related symptoms	54 (17.5%)	69 (51.1%)	< 0.001
Ascites	23 (7.5%)	–	< 0.001
Albumin level (g/dL)	3.8 ± 0.4 (2–5.2)	4.0 ± 0.4 (2.9–5.1)	< 0.001
Total bilirubin level (mg/dL)	1.1 ± 0.6 (0.3–6.6)	0.9 ± 0.5 (0.3–4)	< 0.001
Child-Pugh score			
A	248 (80.5%)	125 (92.6%)	< 0.01
B or C	60 (19.5%)	10 (7.4%)	
Etiology			
Viral	216 (70.1%)	47 (34.8%)	< 0.001
Alcohol	11 (3.6%)	9 (6.7%)	
Other	81 (26.3%)	79 (58.5%)	
HBsAg+	46 (14.9%)	17 (12.6%)	N.S.
HCV+	182 (56.8%)	33 (24.4%)	< 0.001
α-fetoprotein (ng/mL)	885 ± 7070 (1–105 000)	4374 ± 19 455 (1–130 000)	N.S.
Maximum tumour diameter (cm)	4.3 ± 2.1 (0.5–15)	7.9 ± 4.6 (1.3–20)	< 0.001
Number of nodules			
Single	282 (91.6%)	118 (87.4%)	N.S.
Multiple	26 (8.4%)	17 (12.6%)	
Tumor capsule			
Complete	111 (36%)	42 (31.1%)	N.S.
Incomplete or absent	197 (64%)	93 (68.9%)	
Satellite nodules			
Present	46 (14.9%)	22 (16.3%)	N.S.
Absent	262 (85.1%)	113 (83.7%)	
Microvascular invasion			
Present	154 (50%)	72 (53.3%)	N.S.
Absent	154 (50%)	63 (46.7%)	
Macrovascular invasion			
Present	8 (2.6%)	11 (8.1%)	< 0.05
Absent	300 (97.4%)	124 (91.9%)	
Edmonson grade 3–4	168 (54.5%)	81 (60%)	< 0.05

status, mean preoperative AFP level, number of cases with multiple nodules, absent or incomplete tumour capsule, satellite nodules and microvascular thrombosis.

Conversely, noncirrhotic patients presented with tumour-related symptoms in more than half of cases, and with a tumour diameter larger than 5 cm in almost 60% of cases. Cirrhotics were usually diagnosed to carry smaller HCCs during monitoring of liver disease.

There was a higher incidence of viral aetiology (70%) and HCV+ patients (57%) in cirrhotic patients, whose preoperative clinical conditions were significantly worse than in noncirrhotic patients, resulting from higher preoperative albumin and bilirubin levels, higher Child–Pugh score and presence of ascites. In both groups the number of patients belonging to Child C and B classes was very low, according to our policy of selecting patients with a normal liver function.[6]

Pathological features of HCC in noncirrhotic patients were a lower tumour differentiation and a higher incidence of macrovascular thrombosis compared to cirrhotics.

Operative parameters and early results (Table 2)

Approximately two-thirds of surgical procedures were carried out after 1992 in both groups.

Although the better hepatic function in patients of Group 2 allowed the removal of a greater portion of liver parenchyma, as a result of the higher proportion of resection of more than two segments in this population (45% of cases), the number of patients receiving intra-operative packed red blood cells and fresh-frozen plasma transfusions was similar. On the other hand, Group 1 patients more frequently experienced post-operative complications (42% vs. 26% of cases), as expected by the presence of cirrhosis. No significant differences were observed in proportion of cases with diaphragm infiltration.

The post-operative hospital stay and the in-hospital mortality rates were also similar. The in-hospital mortality showed a clear decrease in the more recent years in both study groups.

Patient survival, recurrence rate and disease-free survival

The median follow-up was 28.4 months (range: 0–241). A total of 169 patients from Group 1 and 48 from Group 2 died (54.9% and 35.6%, respectively). The 1-, 3- and 5-year overall survival rates were 86.1%, 63.7% and 42.2% in Group 1, and 84%, 67.9% and 51% in Group 2, respectively. Patient survival was significantly worse ($P < 0.05$) in cirrhotic patients (Figure 1).

Table 2. Operative data and early outcome of cirrhotic and noncirrhotic patients

	Cirrhotic patients ($n = 308$)	Noncirrhotic patients ($n = 135$)	*P*-value
Time of surgery			
Before 1992	102 (33.1%)	44 (32.6%)	N.S.
1992 or later	206 (66.9%)	91 (67.4%)	
Type of resection			
Wedge	108 (35.1%)	17 (12.8%)	< 0.001
1–2 segments	176 (57.3%)	62 (45.9%)	
> 2 segments	24 (7.8%)	56 (42.1%)	
Anatomical resections			
Yes	200 (64.9%)	117 (86.7%)	< 0.001
No	108 (35.1%)	18 (13.3%)	
Diaphragm infiltration	9 (2.9%)	8 (5.9%)	N.S.
Packed red blood cells transfusions			
Yes	116 (37.7%)	53 (39.2%)	N.S.
No	192 (62.3%)	82 (60.7%)	
Fresh-frozen plasma transfusions			
Yes	106 (34.4%)	34 (25.2%)	N.S.
No	202 (65.6%)	101 (74.8%)	
Post-operative complications	129 (41.9%)	35 (25.9%)	< 0.005
Hospital stay (days)	11 ± 23 (4–94)	10 ± 34 (4–64)	N.S.
Hospital mortality	15 (4.9%)	4 (3.0%)	N.S.
Hospital mortality after 1992	6 (2.9%)	1 (1.1%)	N.S.

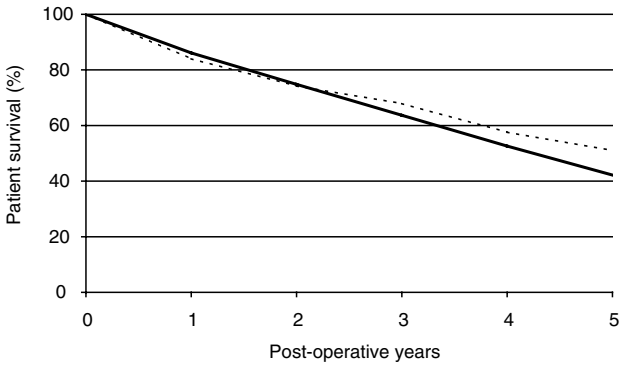

Figure 1. Overall survival of cirrhotic patients ($n = 308$, continuous line) and noncirrhotic patients ($n = 135$, dotted line) undergoing liver resection for HCC ($P < 0.05$).

Tumour recurrence was observed in 120 (39%) patients from Group 1 and 41 (30.4%) patients from Group 2 ($P =$ N.S.). For patients with a follow-up of at least 1 year, tumour recurrence was the cause of death in 75% of patients in Group 1 and 88.2% of patients in Group 2.

The 1-, 3- and 5-year recurrence rates were 15.2%, 33.1% and 50.5% in Group 1, and 17.3%, 32.8% and 39.7% in Group 2, respectively ($P =$ N.S.). The 1-, 3- and 5-year disease-free survival rates were 76%, 49.3% and 27.8% in Group 1, and 77.6%, 58% and 45.6% in Group 2, respectively ($P < 0.005$) (Figure 2).

In Group 2, 17 patients with chronic hepatitis (25.4%) and 31 patients without chronic hepatitis died (45.6%). The 1-, 3- and 5-year overall survival of these subgroups of patients were almost significant in favour of patients with chronic hepatitis (93%, 76.5% and 57.4% vs. 75.3%, 59.8% and 45.5%, respectively, $P = 0.053$).

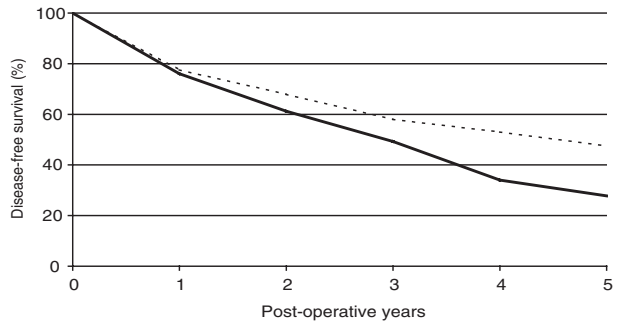

Figure 2. Disease-free survival of cirrhotic patients ($n = 308$, continuous line) and noncirrhotic patients ($n = 135$, dotted line) undergoing liver resection for HCC ($P < 0.005$).

For both groups, the 1-, 3- and 5-year overall survival was significantly better for patients operated on in 1992 or later than for those operated on before 1992 (Group 1: 91.6%, 70.7% and 48.6% vs. 76.5%, 52.9% and 33.3%, $P < 0.01$; Group 2: 90.4%, 78.9% and 64.1% vs. 72.7%, 52.3% and 36.4%, $P < 0.005$).

Univariate analysis of variables affecting overall survival and tumour recurrence

By the univariate analysis, factors negatively affecting survival in Group 1 were tumour-related symptoms at presentation, presence of ascites, total serum bilirubin > 1.2 mg/dL, Child–Pugh score B or C, AFP level > 20 ng/mL, multiple nodules, absent or incomplete capsule, presence of satellite nodules, macrovascular and microvascular invasion, resection performed before 1992, diaphragm infiltration, and necessity of intra-operative blood transfusions. In Group 2, variables predicting poorer survival were tumour-related symptoms, presence of satellite nodules, surgery before 1992, and intra-operative blood transfusions (Table 3).

In Group 1, tumour recurrence was significantly correlated with male sex, liver disease other than viral or alcoholic, presence of satellite nodules, surgery before 1992, and blood transfusions, while in Group 2 it was associated with age < 60 years, macrovascular infiltration and surgery before 1992 (Table 4). The higher recurrence in patients without viral or alcoholic disease is probably due to the fact that many patients were undiagnosed as having HCV viral infection before 1990.

Multivariate analysis of variables affecting overall survival and tumour recurrence

At multivariate analysis, only total bilirubin level > 1.2 mg/dL, presence of multiple nodules, micro- and macrovascular infiltration, diaphragm infiltration and intra-operative blood transfusions were independently correlated to survival in cirrhotic patients. Necessity of packed red blood cells transfusion was found as the only independent predictive factor of lower survival of noncirrhotic patients.

Tumour recurrence was correlated with presence of satellite nodules and surgery performed before 1992 in Group 1, and only with patient's age below 60 years in Group 2 (Table 5).

Table 3. Univariate analysis of factors affecting survival. *P = N.S.

	Cirrhotic patients (n = 308)		Noncirrhotic patients (n = 135)	
Variables	5-years surv.	P-value	5-year surv.	P-value
Age				
0–60 years	45.5%	*	44%	*
> 60 years	42.2%		54.8%	
Sex				
Male	41.4%	*	55.5%	*
Female	53.6%		41.6%	
Tumor-related symptoms				
Present	34.2%	< 0.05	40.4%	< 0.05
Absent	45.5%		63.9%	
Preoperative ascites				
Present	14.9%	< 0.001	Not evaluable	
Absent	46.3%			
Total bilirubin level				
0–1.2 mg/dL	50.4%	< 0.01	48.6%	*
> 1.2 mg/dL	32.1%		56.2%	
Child–Pugh				
A	48%	< 0.01	51.9%	*
B–C	28%		28.6%	
Etiology				
Viral	47.1%	*	47.7%	*
Alcohol	34.3%		80%	
Other	38%		48.8%	
HBsAg+				
Positive	35.7%	*	37.7%	*
Negative	46.1%		54.3%	
HCV+				
Positive	52.4%	*	53.1%	*
Negative	43.3%		68%	
α-FP				
0–20 ng/mL	52.2%	< 0.01	49.3%	*
> 20 ng/mL	32.4%		50.8%	
Tumour diameter				
0–5 cm	45.1%	*	57%	*
> 5 cm	40.1%		58%	
Multiple nodules				
Single	46.7%	< 0.001	52.1%	*
Multiple	13.2%		42.7%	
Tumour capsule				
Complete	51%	< 0.05	44.5%	*
Absent/incomplete	40%		50.9%	
Satellite nodules				
Present	26%	< 0.01	29.8%	< 0.05
Absent	47.3%		56.9%	
Microvascular invasion				
Present	35.7%	< 0.05	58.5%	*
Absent	51.4%		42.2%	
Edmonson's grade				
1–2	44.8%	*	58.3%	*
3–4	42%		44.3%	
Year of surgery				
Before 1992	34%	< 0.01	36.4%	< 0.01
1992 and after	50%		64.1%	

Table 3. Continued

	Cirrhotic patients ($n = 308$)		Noncirrhotic patients ($n = 135$)	
Variables	5-years surv.	*P*-value	5-year surv.	*P*-value
Type of surgery				
Wedge	42.9%	*	29.1%	*
1–2 segments	44.4%		57%	
> segments	40%		44.8%	
Macrovascular infiltration				
Present	0%	< 0.001	45.7%	*
Absent	44.5%		51.1%	
Diaphragm infiltration				
Present	15.2%	< 0.01	85.7%	*
Absent	44.4%		54.4%	
I.o. packed red blood cells transfusions				
Yes	34.9%	< 0.001	34.7%	< 0.001
No	50.2%		69.5%	

Table 4. Univariate analysis of factors affecting recurrence. *P = N.S.

	Cirrhotic patients ($n = 308$)		Noncirrhotic patients ($n = 135$)	
Variables	Recurrence	*P*-value	Recurrence	*P*-value
Age				
0–60 years	42%	*	49%	< 0.01
> 60 years	37%		24%	
Sex				
Male	42%	< 0.05	31%	*
Female	27%		31%	
Tumor-related symptoms				
Present	40%	*	38%	*
Absent	39%		23%	
Preoperative ascites				
Present	48%	*	Not evaluable	
Absent	38%			
Total bilirubin level				
0–1.2 mg/dL	39%	*	31%	*
> 1.2 mg/dL	40%		29%	
Child–Pugh				
A	39%	*	32%	*
B–C	40%		17%	
Etiology				
Viral	36%	< 0.01	28%	*
Alcohol	9%		22%	
Other	54%		33%	
HBsAg+				
Positive	47%	*	35%	*
Negative	37%		29%	
HCV+				
Positive	33%	*	22%	*
Negative	28%		27%	
α-FP				
0–20 ng/mL	39%	*	33%	*
> 20 ng/mL	42%		27%	

Table 4. Continued

Variables	Cirrhotic patients ($n = 308$) Recurrence	*P*-value	Noncirrhotic patients ($n = 135$) Recurrence	*P*-value
Tumour diameter				
0–5 cm	40%	*	21%	*
> 5 cm	37%		33%	
Multiple nodules				
Single	39%	*	31%	*
Multiple	52%		39%	
Tumour capsule				
Complete	33%	*	26%	*
Absent/incomplete	43%		34%	
Satellite nodules				
Present	59%	< 0.01	42%	*
Absent	37%		30%	
Microvascular invasion				
Present	39%	*	33%	*
Absent	41%		26%	
Edmonson's grade				
1–2	37%	*	39%	*
3–4	43%		31%	
Year of surgery				
Before 1992	57%	< 0.001	37%	*
1992 and after	31%		28%	
Type of surgery				
Wedge	35%	*	13%	< 0.05
1–2 segments	42%		25%	
> segments	33%		45%	
Macrovascular infiltration				
Present	38%	*	64%	< 0.05
Absent	39%		27%	
Diaphragm infiltration				
Present	44%	*	0%	*
Absent	39%		33%	
I.o. packed red blood cells transfusions				
Yes	51%	< 0.001	39%	*
No	31%		25%	

Table 5. Multivariate analysis of factors affecting survival and tumour recurrence. s.e. = standard error. HR = hazard ratio

	Variables	Coefficient	s.e.	HR	*P*-value
Group 1 – Overall survival	Bilirubin level > 1.2 mg/dL	−0.4520	0.1827	0.6364	< 0.05
	Multiple nodules	−1.1034	0.2907	0.3317	< 0.001
	Microvascular invasion	−0.5226	0.1949	0.5930	< 0.01
	Macrovascular infiltration	−1.4023	0.4507	0.2460	< 0.005
	Diaphragm infiltration	−1.1747	0.4401	0.3089	< 0.01
	I.o. packed red blood cells transfusions	−0.6113	0.1855	0.5426	< 0.001
Group 2 – Overall survival	I.o. packed red blood cells transfusions	−1.2681	0.3475	0.2814	< 0.001
Group 1 – Tumour recurrence	Satellite nodules	0.7911	0.3483	2.2058	< 0.05
	Surgery before 1992	0.9893	0.2694	2.6895	< 0.001
Group 2 – Tumour recurrence	Age < 60 years	1.0880	0.4209	2.9682	< 0.01

DISCUSSION

The first aim of this study was to assess the clinicopathologic differences between the groups of patients with and without cirrhosis. We found noncirrhotic patients to be similar to cirrhotic ones as regards age, gender, alcoholic habit and number of HBsAg+ cases. These findings are partially in contrast with those reported in a recent study comparing patients with and without liver fibrosis undergoing hepatectomy for HCC,[21] where the nonfibrotic group had higher prevalence of men, alcoholic abuse and lower prevalence of positive HBsAg. In a cohort of patients almost double that in the above-mentioned report, we could not even confirm the data of previous studies showing that HCC arising in a noncirrhotic liver affects subjects younger and more frequently female than HCC with cirrhosis.[22, 23] It must be taken into consideration that our series includes only patients already selected for surgery and this could lead to a bias in the study of the demographic characteristics. With the limitation given by the impossibility of determining HCV infection before 1990, the less frequent viral aetiology and positive HCV status, and the better preoperative liver function of noncirrhotic patients were consistent with previous data.[21]

One interesting finding of the present study was the tendency of HCC to be more aggressive in patients without cirrhosis, having a larger diameter, a poorer differentiation, a higher incidence of macrovascular invasion than HCC with cirrhosis, and being encapsulated in only 30% of cases. While the first two characteristics are commonly reported in HCC in the absence of cirrhosis,[21, 23, 24] portal vein thrombosis and absence of capsule were more frequently found in cirrhotics than in noncirrhotics in a large patient series.[24] This data might have predicted a worse outcome, but this does not come out from statistical analysis of overall and disease-free survival.

Patients without cirrhosis underwent resection of larger portions of the liver, with intra-operative packed red blood cells consumption similar to that required by cirrhotic patients. The complication and the in-hospital mortality rates were lower in the former group. The early mortality of less than 3% (1% in noncirrhotic patients) and the significantly better results obtained in both groups in the more recent years confirms the increasing success of the surgical approach to HCC,[6] which should be taken into consideration especially when considering cirrhotic patients for possible treatment.

The analysis of long-term outcome showed lower results in cirrhotic than in noncirrhotic patients. A lower survival and a higher tumour recurrence should be expected in patients carrying high grade liver fibrosis (i.e. cirrhosis) compared to those with chronic hepatitis and less advanced fibrosis,[15] however when evaluating all patients without cirrhosis, consideration should be given to the possibility that it is a inhomogeneous group of different conditions, from chronic hepatitis with stage III fibrosis[18] to a morphologically healthy liver. A correct methodological approach would therefore be to distinguish different subgroups and to separately assess the prognosis in each of them. Even if we did not compare the clinical and pathologic features of noncirrhotic patients according to specific liver diseases, we found overall survival to be similar in subjects carrying or not carrying chronic hepatitis. The importance of liver fibrosis on intrahepatic tumour recurrence has been recently pointed out,[25] unfortunately without a differentiation in prognostic reliability among stages II, III and IV of fibrosis. On the other hand, a further multicentric study showed that the presence or absence of cirrhosis itself is able to predict long-term survival.[15]

In our study, the survival of patients with HCC with cirrhosis was correlated to clinical (abnormal preoperative bilirubin level), histological (presence of multiple nodules, micro- and macrovascular invasion) and surgical variables (intra-operative blood transfusions and diaphragm infiltration, which probably reflected the complexity of the procedure without predisposing to tumour recurrence). Predictors of tumour recurrence in the same group were the presence of satellite nodules and resection performed before 1992. These prognostic factors have been already reported and discussed by others.[7, 8, 11, 12, 14, 15] Conversely, the only independent variables correlated to patient survival and tumour recurrence in noncirrhotic patients were the need for intra-operative blood transfusions and age less than 60 years, respectively. The few studies aiming to evaluate prognostic factors in patients undergoing liver resection for HCC without cirrhosis based their conclusions on less numerous series than the present one and showed a number of variables significantly affecting survival (i.e. blood losses, surgical resection margin, tumour size, capsular invasion, presence of intrahepatic

metastases, portal vein invasion and extent of resection) and tumour recurrence (i.e. tumour size, portal vein invasion and HCV infection).[16, 17] Our experience suggests that the outcome of patients with noncirrhotic liver remains rather difficult to evaluate using the clinicopathologic criteria of categorization commonly adopted.[7, 8, 11, 12, 14, 15] Recent studies have outlined that HCC tends to recur more frequently in patients with a high necro-inflammatory activity, which makes serum transaminases a reliable method of stratification,[26, 27] probably more promising than the histological assessment alone.

Our study also confirms the importance of avoiding intra-operative blood losses, which mostly depends on the surgical technique.[7] The experience gained by our group determined a significant minimization of the intra-operative use of blood transfusions in recent years,[6] which means a direct positive impact on long-term results.

Surgery represents a consolidated therapy for HCC arising both with and without cirrhosis. The improved long-term survival and the reduction in early mortality give this procedure added value. The analysis of clinical variables leading to higher survivals still lacks strong and unanimously accepted indicators. Today, however, it is possible to identify groups at higher risk of failure in which surveillance must be extremely strict.

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