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Original article

Prognostic factors after resection of hepatocellular carcinoma in the non-cirrhotic liver: Presentation of 51 cases☆

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A B S T R A C T

Background: Clinical presentation, treatment and prognosis of hepatocellular carcinoma depend on the presence or absence of cirrhosis. In the literature there are few reports of hepatocellular carcinoma in non-cirrhotic patients.

Objective: To describe a consecutive series of resected patients with hepatocellular carcinoma in non-cirrhotic liver and to identify prognostic factors of recurrence and survival.

Material and methods: Between 1990 and 2006, 51 patients were operated on. Data were collected retrospectively until 2001 and prospectively from then on. The results of surgery were assessed. Single and multivariate analyses were performed to identify factors associated with survival and disease-free survival.

Results: Thirty-three patients were male, median age 49.8 years. A major hepatectomy was performed in 72%. Morbidity was 43% and mortality was 0%. One-, two- and three-year survival rates were 90%, 75%, and 67%, respectively. One-, two- and three-year disease-free survival rates were 65%, 41%, and 37%, respectively. Presence of vascular invasion and of positive nodes was statistically significant for survival in univariate analysis but had no statistical significance in multivariate analysis.

Conclusions: Major hepatic resection is a safe treatment for hepatocellular carcinoma in non-cirrhotic patients. Both vascular invasion and presence of positive nodes were associated with poor survival. However, neither of them represented an independent variable.

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Factores pronósticos del hepatocarcinoma en el hígado no cirrótico tras su resección: presentación de 51 casos

Palabras clave:
Carcinoma hepatocelular
Hepatectomía
Hígado no cirrótico
Factores pronósticos

RESUMEN

Introducción: La presentación, el tratamiento y el pronóstico del hepatocarcinoma dependen de la presencia o la ausencia de cirrosis. Existen pocos estudios de hepatocarcinoma en pacientes sin cirrosis.

Objetivo: Analizar una serie consecutiva de pacientes operados por hepatocarcinoma en hígado no cirrótico e identificar los factores de pronóstico de la recidiva y la supervivencia.

Material y método: Se operó a 51 pacientes entre 1990 y 2006. Se organizó una base de datos retrospectiva hasta el año 2001 y prospectiva desde esa fecha. Se evaluaron los resultados de la cirugía. Se realizaron análisis univariado y multivariado para identificar los factores asociados con la supervivencia y el tiempo libre de enfermedad.

Resultados: Treinta y tres pacientes eran de sexo masculino (mediana de edad de 49,8 años). Al 72,5% se le realizó una hepatectomía mayor. La mortalidad intrahospitalaria fue del 0% y la morbilidad del 43%. El tiempo de supervivencia fue del 90, el 75 y el 67% a uno, a 2 y a 3 años. El tiempo libre de enfermedad fue del 65, el 41 y el 37% a uno, a 2 y a 3 años. En el análisis univariado, la invasión vascular y la infiltración ganglionar fueron estadísticamente significativas para la supervivencia, pero ninguna de éstas fue significativa en el estudio multivariado.

Conclusiones: La resección hepática mayor es un tratamiento seguro para el tratamiento del hepatocarcinoma en el hígado no cirrótico. Tanto la presencia de invasión vascular como la infiltración ganglionar están estadísticamente relacionadas con la supervivencia, pero no se identificaron como factores pronósticos independientes de ésta.

Introduction

Hepatocellular carcinoma is one of the most common malignant tumours, affecting half a million people a year worldwide and it is the third cause of cancer death.[1]

Independent of its aetiology, cirrhosis is considered a preneoplastic condition,[2] but between 10-49% of hepatocellular carcinomas develop in non-cirrhotic livers.[3-7]

The clinical presentation, treatment and prognosis of hepatocellular carcinoma depend on the presence or absence of cirrhosis. There are many publications about the characteristics, treatment and prognosis of hepatocellular carcinoma in cirrhotic livers. However, very few studies have been performed into this disease in non-cirrhotic livers.[4,5,7-13]

The aim of this paper is to describe a consecutive series of resected patients with hepatocellular carcinoma in a non-cirrhotic liver and to identify prognostic factors of recurrence and survival.

Material and methods

Between July 1990 and March 2006, 51 patients with hepatocellular carcinoma in a non-cirrhotic liver underwent a curative operation in our hospital. These patients represent 40% of those with hepatocellular carcinoma who underwent surgical treatment (resection or liver transplant) during that period. The patients who underwent palliative treatment were excluded.

The absence of cirrhosis was confirmed with postoperative anatomical pathology.

Data were gathered retrospectively until 2001 and prospectively from then on, and pre-, intra- and postoperative data were collected.

The preoperative studies for the diagnosis and staging of the hepatocellular carcinoma included biochemical parameters of liver function, alpha fetoprotein, viral serology, an abdominal ultrasound and a TC scan of the chest and abdomen; also, a splenic angiogram with splenoportography was performed in selected cases.

All the patients under study were assessed with intraoperative ultrasound, and underwent liver resection with early ligation of the vascular pedicles and liver parenchyma dissection with an ultrasonic dissector, the Kelly clamp technique or an electronic scalpel, depending on the preference of the surgeon.

Major liver resection was considered to be the resection of at least 3 segments. Postoperative complications were grouped according to the Dindo et al classification.[14]

All the anatomical pathology studies recorded data about tumour size, number of tumours, microscopic vascular invasion, surgical margin and the presence of positive nodes. The stage of the tumour was ranked according to the TNM classification.[15] The degree of differentiation of the tumour was grouped according to the Edmondson and Steiner classification.[16] We considered as non-cirrhotic diseased livers those with steatosis or fibrosis in the anatomical pathology study.

Follow-up was performed by analysing the patients' medical histories as inpatients and outpatients or by a face-

to-face or telephone interview. All the patients underwent laboratory alpha-fetoprotein analysis, as well as ultrasound and CT scans of the abdomen every 4 months during follow-up.

We used the Kaplan-Meier method to calculate survival and the Log-Rank test for the univariate analysis. The prognostic factors which were statistically significant (P<.1) in the univariate analysis underwent a multivariate analysis using the Cox regression model. A P<.05 value was considered statistically significant.

Results

Study population

Table 1 shows the characteristics of the 51 patients in the study.

Ten of the patients who were transferred to our hospital had already undergone a punction biopsy of the tumour. Right portal embolisation (by ligation) was performed on one patient in order to hypertrophy the future remaining liver as it was calculated to be insufficient for the patient's weight.

Surgical and postoperative results

Thirty-eight major and 13 minor hepatectomies were performed (Table 1).

The median operating time was 4 h (range: 2-11 h) using Pringle's manoeuvre on 14 patients, with a mean of 30 min (range: 15-80 min).

The total length of the hospital stay was between 5 and 17 days (median 8 days) with between 1 and 10 days (median 2 days) in the intensive care unit.

Intrahospital mortality was 0% and morbidity 43%. We recorded 33 complications in total in 22 patients: Degree i: 36%, degree ii: 24%, degree iii: 15%, degree iv: 22%, degree v: 0% (Table 2).

Results of anatomical pathology studies

In one patient who had undergone preoperative chemical embolisation (and had a positive preoperative biopsy), no tumour was evidenced in the anatomical pathology study.

Table 3 shows the other anatomopathological characteristics.

Results of survival and recurrence

The follow-up period lasted between 2-148 months (median 21 months). Thirty-one patients suffered recurrence (liver [22], lung [12], spine [one], peritoneal metastatic carcinoma [4], stomach [one], left adrenal gland [one] mediastinal nodes [one]). Two patients underwent re-resection of the liver (one of them 2 re-resections). Seven patients underwent chemical embolisation of the recurrent tumour and had a subfrenic abscess or hepatic abscess as complications (both treated with percutaneous drainage). During follow-up, 2 patients died of unrelated causes. Overall one-, two- and three-year survival rates were 90%, 75% and 67%, respectively. One-, two- and three-year disease-free survival rates were 65%, 41% and 37%, respectively (Figure).

Table 1 – Patient and surgery characteristics[a]

Total patients, n 51	n[a]
Sex	
Female	18
Male	33
Age, median (range)	49.8 (12-77)
Alpha fetoprotein	
Normal	15
High	25 b50 (1.8-35 000)
Not measured	11
Ac Anti HBV	4
Ac Anti HBV + alcohol	1
Ac HCV	3
Alcohol consumption	2
Preoperative treatment	
Chemical embolisation	3
Portal vein ligation	1
Tumour biopsy	10
Type of resection	
Right hepatectomy	15
Right trisectionectomy	12
Left hepatectomy	7
Left trisectionectomy	4
Central hepatectomy	2
Right anterior sectionectomy	2
Right posterior sectionectomy	1
Left lateral sectionectomy	1
Segmentectomy	6
Tumourectomy	1
Associated procedure (n=10)	
Staging laparoscopy	2
Radiofrequency thermal ablation	1
Ganglion removal	7
Right adrenalectomy	2
Subtotal gastrectomy	1
Hepaticojejunostomy	2
Intraoperative transfusions (n=30)	
RBC	27 [b]2 U (1-6)
FFP	18 [b]2 U (1-7)
Total blood	2 [b]1.5 U (1-2)
Postoperative transfusions (n=14)	
RBC	13 [b]2 U (1-11)
FFP	8 [b]2 U (2-13)
Total blood	1-2 U

Ac anti HBV: hepatitis B virus, anti-core antibodies; Ac anti HCV: hepatitis C virus, antibody; FFP: fresh frozen plasma; RBC: red blood cells.
[a]Information expressed in whole numbers, except where clarified.
[b]Median (range).

Analysis of prognostic factors

Thirteen factors were assessed to determine their importance in relation to survival and disease-free survival. The univariate

Table 2 – Postoperative complications

Complication	Patients, n	Treatment
Liver failure	6	Medical
Acute renal failure	2	Medical
Ascites	4	Medical
Intraabdominal abscess[a]	2	Percutaneous drainage
Encephalopathy	3	Medical
Pleural effusion	3	Pleural drainage: 1
Wound abscess	4	Drainage
Biliary fistula	3	Percutaneous drainage: 1 Rehepaticojejunostomy 1[b]
Haemoperitoneum	1	Reoperation (laparotomy + hemostasis)
Pneumonia	2	Medical
Difficult-to-treat DBT	1	Medical
CHF	1	Medical
Fever without source	1	Medical
Total complications	33	

CHF: congestive heart failure; DBT: diabetes.
[a]Patient with sepsis.
[b]Readmission for biloma, treated with percutaneous drainage.

Table 3 –Anatomical pathology characteristicsa (n: 50)[a]

	n[b]	%[b]
Tumour diameter, range (median)	10-240 mm (80 mm)	
Margin, range (median)	0-30 mm (12 mm)	
Margin under 10 mm	20	40
Fibromellar carcinoma	7	14
Single nodule	45	80
Invasive growth	19	37
Microscopic vascular invasion	15	30
Glisson's capsule invasion	8	16
Encapsulated	13	26
Satellite nodule	4	8
Positive nodes	7	14
TNM		
E I	20	40
E II	8	16
E IIIa	5	10
E IIIb	9	18
E IIIc	7	14
E IV	1	2
Edmondson		
I-II	18	36
III-IV	14	36
No information	18	28
Remaining liver (n: 51)		
Healthy	29	57
Steatosic	4	8
Active chronic hepatitis	1	2
Fibrous	17	33

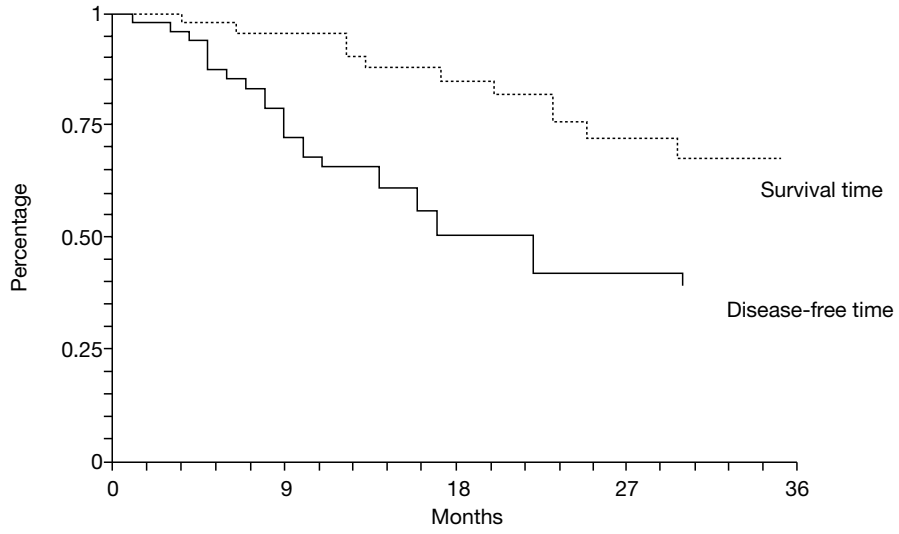
E: Edmonson; TNM: tumour, adenopathy, metastasis.
[a]In one patient the anatomical pathology study (with chemical embolisation) did not reveal a tumour.
[b]Information expressed in whole numbers and percentages, except where clarified.

analysis showed no factors were statistically significant for disease-free survival time. As for survival, both the presence of positive nodes and microscopic vascular invasion were statistically significant associated factors. However, when a multivariate analysis was performed on these 2 data, neither of them was significant (Table 4).

Discussion

The absence of cirrhosis is confirmed in 10%-49% of patients with hepatocellular carcinoma in the western world.[3-7] The aetiological factors involved in hepatocellular carcinomas in non-cirrhotic livers are not clear. In a histological study assessing the non-tumour parenchyma of these patients, some kind of histopathological change was found in every case (fibrosis, hepatitis, steatosis, iron accumulation or areas of dysplasia). It was shown that an abnormal histological environment, particularly with an accumulation of iron and areas of dysplasia, was an underlying reason behind the formation of this tumour.[17] In our series, 41% of the patients evidenced histopathological changes in the non-tumour area of the liver parenchyma. However, no significant differences were found regarding disease-free survival time and survival among these patients when compared with patients with a histologically normal liver.

The role of hepatitis B and C has been highlighted in several studies.[7,18,19] Nagasue et al[7] report a higher recurrence rate in patients with hepatitis C. We found no significant differences regarding either survival or disease-free time in patients with or without hepatitis B or C infection. This may be due to the small number of patients with this disease in our series. Recent studies show that both obesity and diabetes are major risk factors for developing hepatocellular carcinoma in a non-cirrhotic liver.[20,21] Furthermore, Verhoef et al stated



Exposed	51	49	46	44	44	40	35	29	28	26	22	20	18	18	17	Survival time
						1 a				2 a					3 a	
	51	48	44	40	36	33	30	28	21	20	18	15	15	14	14	14	Disease-free time
							1 a				2 a					3 a	

Figure – Survival time and disease-free time.

that helicobacter colonisation in the stomach is associated with the development of hepatocellular carcinoma, either by direct colonisation or indirectly by the secretion of toxins by bacteria living in the stomach.[22]

Similar to other studies,[4,5,10,11] the size of the tumours in our series (median 80 mm) seems larger than is usually reported for cirrhotic livers.[10,23,24] This is because, in cases with a non-cirrhotic liver, the diagnosis is generally made later and the tumour has become quite large when symptoms are finally evidenced. This results in a high percentage of major liver resections, which can be performed with low morbidity and mortality. Seventy-two point five per cent of our resections were major; morbidity was 43% and mortality was 0%.

Traditionally, anatomical, not local, resections are recommended for hepatocellular carcinoma associated with cirrhosis as they result in lower levels of recurrence without increasing morbidity and mortality.[25] However, there are no studies assessing the type of resection performed (anatomical versus local) in non-cirrhotic livers. Recent studies have shown that it is not necessary to perform a major hepatectomy if there is a positive tumour-free margin, since this is an independent factor for recurrence.[12,26,27]

Despite the larger tumours at the time of diagnosis and treatment, survival rate results seem to be better in non-cirrhotic livers than the results reported in the resection of non-selected cases of hepatocellular carcinoma in cirrhotic livers.[10,26,28,29] Table 5 shows the results of the best-known series of resections for hepatocellular carcinoma in non-cirrhotic livers.

Despite the 3 year survival rate being between 38%-86%, the recurrence rate remains high (over 50% at 3 years in most series). Many authors have studied the prognostic factors for survival and recurrence after resection for hepatocellular carcinoma, including patients with and without cirrhosis. In cirrhotic patients, long term survival after liver resection basically depends on the basal disease rather than the hepatocellular carcinoma, so the results cannot be compared.[28] Results vary in studies performed with only non-cirrhotic livers. Bismuth et al[8] found that the size of the tumour and the presence of capsules were prognostic factors for survival, but only tumour size was a significant factor for recurrence. On the other hand, Nagasue et al[7] obtained the following independent survival factors: blood loss, resection margin, the presence of intrahepatic metastases and portal vein invasion. However, the only prognostic factors for intrahepatic recurrence were vascular invasion and hepatitis C virus infection. Other authors[5,11,12] published similar results, but added the absence or disruption of the tumour capsule, the number of positive nodules and the presence of satellite nodules as prognostic factors. In our study we performed a univariate analysis for 13 prognostic factors and found that only microscopic vascular invasion and the presence of positive nodes were statistically significant with regard to poor survival. But the multivariate analysis showed that neither of these was an independent factor for survival. This could possibly be due to the study population being heterogeneous and that there is interaction between the many biological variables. When we tried to homogenise the sample, the number of cases was very limited so we do not think it is valid to draw conclusions from it.

Table 4 – Univariate and multivariate analysis of prognostic factors of disease-free time and survival

Variable	Groups n	DFT	Survival
Univariate analysis			
Sex	Male: 33 Female: 18	P=.325	P=.704
Age	Under 65: 33 Over 65: 18	P=.528	P=.214
HBV+	No: 46 Yes: 5	P=.807	P=.287
HCV+	No: 48 Yes: 3	P=.726	P=.688
Alpha fetoprotein[a]	<100 ng/ml: 28 >100 ng/ml: 12	P=.621	P=.169
RBC transfusion	No: 24 Yes: 27	P=.442	P=.428
Tumour diameter[b]	<8 cm: 23 >8 cm: 27	P=.477	P=.531
Number of nodules[b]	One: 45 Several: 5	P=.209	P=.163
Microscopic vascular invasion[b]	No: 35 Yes: 15	P=.85	P=.008
Capsule[b]	No: 37 Yes 13	P=.088	P=.305
Free margin[b]	<5 mm: 37 >5 mm: 13	P=.858	P=.949
Ganglions+[b]	No: 43 Yes: 7	P=.388	P=.032
Remaining liver	Healthy: 29 Diseased: 22	P=.226	P=.347
Multivariate analysis[c]			
Microscopic vascular invasion	No: 35 Yes: 15		P=.075
Lymph nodes +	No: 43 Yes: 7		P=.416

DFT: disease free time; HBV: hepatitis B virus; HCV: hepatitis C virus, antibody; RBC: red blood cells.
[a]Measured in only 40 patients.
[b]Anatomical pathology characteristics of 50 patients.
[c]The factors were examined by univariate analysis with p value of 0.1 considered statistically significant.

Table 5 – Results of resection of hepatocellular carcinoma in non-cirrhotic livers

Reference	Non-cirrhotic liver, n, %	Overall survival			Disease-free survival		
		1 year	3 years	5 years	1 year	3 years	5 years
Bismuth et al, 1995[8]	79 (36)	74	52	40	71	43	33
Fong et al, 1999[9]	123 (30)	83	58	42	–	–	–
Nagasue et al, 2001[7]	126 (36)	97	76	50	79	38	31
Verhoef et al, 2004[4]	40 (22)	96		68	86		59
Chang et al, 2004[10]	223 (50)	97	86	70	85	65	54
Lang et al, 2005[11]	33	76	38	–	–	–	–
Laurent et al, 2005[12]	108	–	55	43	–	43	29
Dupont-Bierre et al, 2005[5]	84 (41)	77	55	44	73	49	49
Xu et al, 2008[13]	96	84	62	18	56	40	33
This study	51 (40)	90	67	–	65	37	–

To conclude, hepatocellular carcinomas in non-cirrhotic livers are generally diagnosed when they are large and they require major resections. This can be performed very safely, independent of whether the liver has any degree of fibrosis, although the recurrence rate is high. Different factors have been studied to identify the group of patients with the highest risk of relapse. The results obtained have been very heterogeneous, and further studies are needed to determine which group of patients benefit from undergoing a resection and which could be potential candidates for a liver transplant.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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