

## ORIGINAL ARTICLE

# Actual 10-year survival following hepatectomy for hepatocellular carcinoma

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## Abstract

**Objectives:** This study was conducted to compare 10-year survivors with patients who survived <10 years in a large Western series of patients submitted to hepatectomy for hepatocellular carcinoma (HCC).

**Methods:** A retrospective review of a series of hepatic resections conducted in a referral centre for HCC between January 1987 and October 2002 was conducted.

**Results:** A total of 176 patients were analysed. Twenty-eight patients survived  $\geq 10$  years (Group A) and were compared with the 148 patients who did not (Group B). Group A had smaller tumours (5.7 cm versus 8.2 cm;  $P = 0.001$ ) and a lower incidence of microvascular invasion (18.5% versus 37.1%;  $P = 0.004$ ). Recurrence did not differ significantly (Group A 18/28, 64.3% versus Group B 94/148, 63.5%). Median time to recurrence was longer in Group A (70 months versus 15 months;  $P < 0.0001$ ), and more patients in Group A were able to undergo curative treatment for recurrence (88.8% versus 40.4%;  $P < 0.0001$ ). Multivariate analysis showed that lack of vascular invasion ( $P = 0.020$ ), absence of perioperative transfusion ( $P = 0.014$ ), and recurrence at  $>2$  years after primary resection ( $P = 0.045$ ) were significantly associated with 10-year survival.

**Conclusions:** Ten-year survival after liver resection for HCC can be expected in approximately 15% of patients. Recurrence does not preclude longterm survival. Recurrence at  $>2$  years after resection, absence of vascular invasion, and absence of perioperative transfusion are independently associated with 10-year survival.

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## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most frequent cause of cancer-related deaths worldwide.<sup>1</sup> Hepatic resection remains the treatment of choice for single HCC in patients with preserved liver function.<sup>2</sup> Clinically significant portal hypertension and high total bilirubin ( $\geq 1.0$  mg/dl) are generally regarded as contraindications for resection.<sup>3</sup> According to these criteria, only about 20% of patients with HCC would be considered ideal candidates for resection.

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Despite a large number of series reporting outcomes of hepatic resection for HCC, actual 10-year follow-up and survival data are seldom reported.<sup>4–7</sup> A recent meta-analysis of 14 retrospective series found that only 303 actual 10-year survivors had been reported in the world literature over a 20-year span. This translated into an actual 10-year survival rate of only 7%.<sup>8</sup>

A high rate of recurrence after resection is thought to be the major impediment to longterm survival. In large series of resections performed for HCC, recurrence is generally reported to exceed 60% at 5 years and survival at 5 years is reported to be between 40–50%.<sup>4–7</sup> Recurrence most commonly occurs during the first 2 years and has been shown to be mostly attributable to true metastases from the resected tumour during this early period.<sup>9,10</sup> *De novo* tumours, accounting for the majority of late

recurrences, arise in patients with underlying liver disease and their incidence increases with time.<sup>10,11</sup>

The aim of this study was to identify and characterize patients who have survived for  $\geq 10$  years after primary hepatic resection for HCC and to identify the variables associated with 10-year survival.

## Materials and methods

This study was approved by the study centre's institutional review board. Subsequently, data for all primary liver resections performed for HCC from January 1987 to October 2002 were collected from a prospectively maintained database and reviewed retrospectively. Follow-up was complete until October 2012, allowing for a 10-year follow-up of all survivors. Patients lost to follow-up were excluded from the study. Patients were divided into two groups; Group A included only patients who survived  $\geq 10$  years after resection and Group B comprised those who died at  $< 10$  years. The terms '10-year survivors' and 'longterm survivors' will be used interchangeably.

### Criteria for primary resection

Patients were required to have a single tumour on imaging and the absence of extrahepatic spread. Inclusion criteria for resection also required patients to demonstrate Child–Pugh class A liver function. Prior to 1995, a few patients with Child–Pugh class B liver function were offered resection. Evidence of portal hypertension on imaging or a platelet count of  $< 100\,000/\mu\text{l}$  was not a contraindication for resection prior to 2002. A transjugular portocaval gradient of  $>10$  mmHg was considered to contraindicate surgery after 2002 and was measured in patients with low platelet counts and no radiographic signs of portal hypertension (splenomegaly or variceal veins) and in those with previous splenectomy in whom platelet count cannot be used as a surrogate for portal hypertension. Gross vascular invasion was not considered a contraindication to resection as long as the main portal vein and the branch to the remaining portion of the liver were patent. Barcelona Clinic Liver Cancer (BCLC) staging was used to guide decision making, but resection was not limited to class A patients because segmental vascular involvement and tumours measuring  $>5$  cm were not considered to contraindicate surgery.<sup>12</sup> Patients were discussed weekly in a multidisciplinary conference as suggested by American Association for the Study of Liver Disease (AASLD) guidelines.<sup>3</sup>

### Follow-up protocol

Patients were followed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and non-contrast CT of the chest every 3 months during the first year after resection, every 4 months during the second year, and every 6 months subsequently. Serum alpha-fetoprotein (AFP) was measured at the same intervals.

The diagnosis of intrahepatic recurrence was based on imaging alone if the tumour displayed enhancement characteristics typical of HCC. Extrahepatic tumours and those with atypical imaging characteristics were biopsied to confirm HCC.

### Variables studied

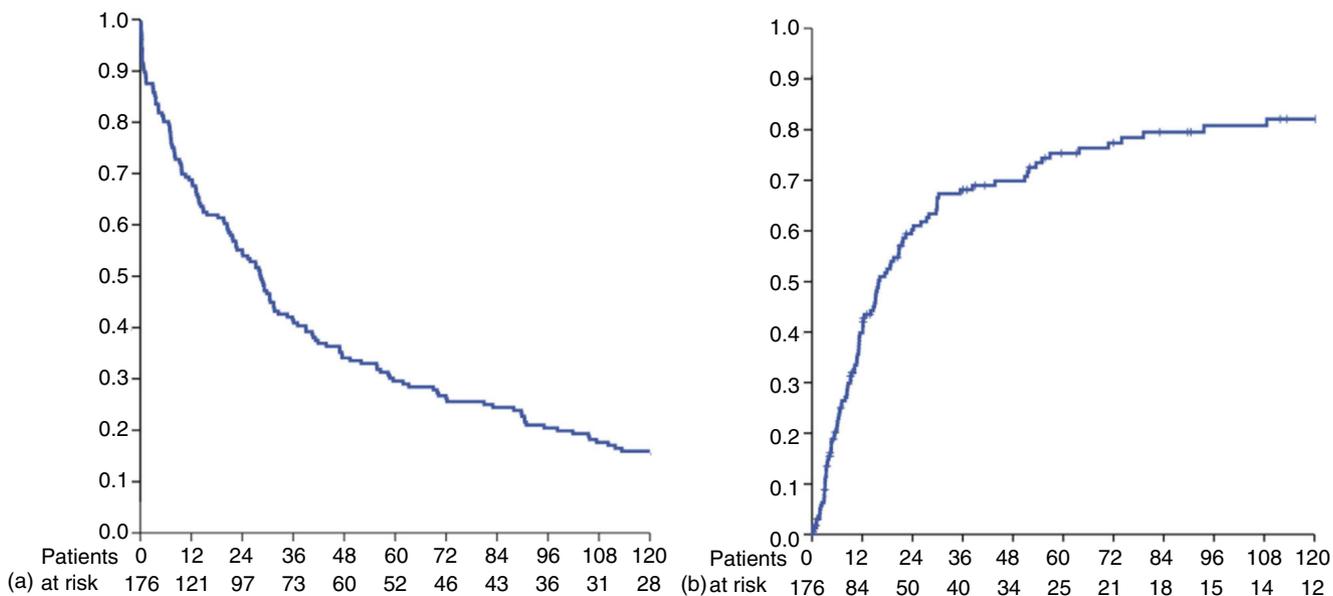
Twenty-two variables divided into four subgroups were identified. Preoperative variables included age, gender, BCLC classification, portal hypertension (on axial imaging and/or based on a platelet count of  $< 100\,000/\mu\text{l}$ ), AFP levels, and underlying liver disease [including hepatitis B and C viruses (HBV, HCV), alcoholic liver disease and other conditions (haemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis and cryptogenic cirrhosis)]. Perioperative variables included major resection (three or more segments), need for transfusion and portal thrombectomy. Pathological variables were identified through the systematic review of specimens for the presence and degree of fibrosis (Scheuer fibrosis stage), largest tumour diameter, tumour differentiation, degree of vascular invasion, presence of satellites, and positive margin status (defined as tumour cells on the cut surface of the resection). Postoperative variables were concentrated mainly in recurrence data and included the number of liver tumours at recurrence, AFP level and BCLC class at recurrence, site of recurrence, time to recurrence and treatment of recurrence. Treatment options after recurrence included potentially curative treatments, such as a second resection, liver transplant, ablation (radiofrequency or ethanol ablation), and non-curative treatments, including transarterial embolization (bland or chemoembolization) and other treatments (systemic chemotherapy and/or external beam radiation).

### Statistical analysis

Descriptive statistics are reported as the percentage or as the mean  $\pm$  standard deviation (SD). Categorical data were compared using the chi-squared test. Continuous data were analysed with *t*-tests. Survival was calculated in months from the time of initial hepatectomy until the last clinical or telephone encounter, or death. Clinically relevant variables that were significant on univariate analysis were entered into a multivariate binary logistic Cox regression model to identify independent predictors of outcome. Recurrence and time to recurrence were included to evaluate their impact on survival. Overall survival and recurrence curves were generated using the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed using IBM SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, NY, USA). *P*-values of  $\leq 0.05$  were considered to indicate statistical significance.

## Results

During the time period under study, 210 patients with HCC underwent hepatic resection as primary treatment, of whom 34 (16.2%) were lost to follow-up. The study population comprises the remaining 176 patients.



**Figure 1** Kaplan–Meier curves showing (a) overall survival and (b) recurrence in the entire cohort of 176 patients submitted to hepatectomy for hepatocellular carcinoma

Of these 176 patients, 28 (15.9%) survived  $\geq 10$  years and were labelled as Group A. The remaining 148 (84.1%) patients survived for  $< 10$  years and represent Group B. The mean length of follow-up in the entire series was 28 months. All survivors were followed for  $\geq 10$  years. Overall survival and recurrence curves are shown in Fig. 1.

Baseline characteristics are displayed in Table 1. Perioperative variables and pathological data are shown in Table 2. Variables related to recurrence are recorded in Table 3. The absolute rates of recurrence were almost identical in the two groups [18 of 28 patients (64.3%) versus 94 of 148 patients (63.5%);  $P = 0.938$ ]. However, Kaplan–Meier analysis and the log-rank test indicated that recurrence was significantly higher in Group B ( $P = 0.001$ ) as shown in Fig. 2. Early recurrence was far more common in Group B. Median time to recurrence was 70.8 months in Group A and 12.1 months in Group B ( $P < 0.0001$ ). Recurrence within 2 years was observed in six of 18 Group A patients and 80 of 94 Group B patients ( $P < 0.0001$ ). Patients in Group A showed significantly better BCLC scores at the time of recurrence, which increased their eligibility for curative treatment. All 18 patients in Group A were treated for their recurrence as noted in Table 3, whereas 10 of the 94 patients in Group B received only supportive care.

Multivariate analysis showed the absence of perioperative transfusion, the absence of vascular invasion and recurrence at  $> 2$  years to be independently associated with 10-year survival (Table 4).

## Discussion

This study presents a large series of patients submitted to resection for HCC with actual 10-year survival data; these longterm survi-

vors are the focus of the paper. Few series, particularly in the West, are large enough and have long enough follow-up to provide robust actuarial outcomes for HCC patients 10 years after resection, much less actual survival data. A recent meta-analysis found an actual 10-year survival rate of 7.2%.<sup>8</sup>

Although hepatic resection is considered a potentially curative treatment for HCC, approximately 70% of patients will develop recurrence within 5 years. The present study confirms this: Kaplan–Meier curves for the entire cohort show that 75.3% of patients experienced recurrence within 5 years and 82.1% did so within 10 years. Of note, recurrence was as common among 10-year survivors as it was in those who died within 10 years of resection in absolute numbers, but, when calculated using the Kaplan–Meier method, the rate of recurrence was statistically higher in Group B. This, however, represents an anomaly of the Kaplan–Meier method. The rate of recurrence is calculated based on the number of patients at risk at a certain time-point. Thus, as none of the patients in Group A died, the denominator in this group remained constant. As patients in Group B died, the denominator in this group became progressively smaller and the proportion of the remaining population at risk increased. Thus, although absolute rates of recurrence were the same in both groups, Kaplan–Meier analysis showed the percentage of patients experiencing recurrence to be higher in Group B.

The most substantial differences between longterm survivors and the rest of the HCC resection population pertained to the ‘when, where and how’ aspects of recurrence rather than the ‘if’. On univariate analysis, 10-year survivors were found to experience recurrence later, were more likely to have a single recurrence in the liver, had a better BCLC score at recurrence and received

**Table 1** Baseline characteristics of patients submitted to resection for hepatocellular carcinoma who did (Group A) and did not (Group B) survive for  $\geq 10$  years after resection ( $n = 176$ )

Preoperative characteristics	Group A ( $n = 28$ , 15.9%)	Group B ( $n = 148$ , 84.1%)	P-value
Age, years, mean $\pm$ SD	60.8 $\pm$ 12.1	57.5 $\pm$ 11.4	0.191
Male gender, $n$ (%)	19 (67.9%)	107 (72.3%)	0.633
Underlying liver disease, $n$ (%)			0.012
Hepatitis B virus	15 (53.6%)	30 (20.3%)	
Hepatitis C virus	9 (32.1%)	59 (39.9%)	
Other	1 (3.6%)	23 (15.5%)	
None	3 (10.7%)	36 (24.3%)	
Stage 3–4 fibrosis, $n$ (%)	15 (53.6%)	89 (60.1%)	0.517
Platelets $<100\,000/\mu\text{l}$ (Missing data: 12, 6.8%)	5 (21.0%)	21 (15.2%)	0.489
AFP, mean $\pm$ SD (Missing data: 28, 15.9%)	7567 $\pm$ 33 070	6903 $\pm$ 60 350	0.926
AFP of $>400$ ng/ml, $n$ (%)	7 (29.2%)	40 (32.3%)	0.766
BCLC class at presentation, $n$ (%) (Missing data: 12, 6.8%)			0.378
A	18 (66.7%)	68 (48.9%)	
B	3 (11.1%)	26 (18.7%)	
C	6 (22.2%)	43 (30.9%)	

SD, standard deviation; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

**Table 2** Perioperative and pathological factors affecting longterm survival in patients submitted to resection for hepatocellular carcinoma who did (Group A) and did not (Group B) survive for  $\geq 10$  years after resection ( $n = 176$ )

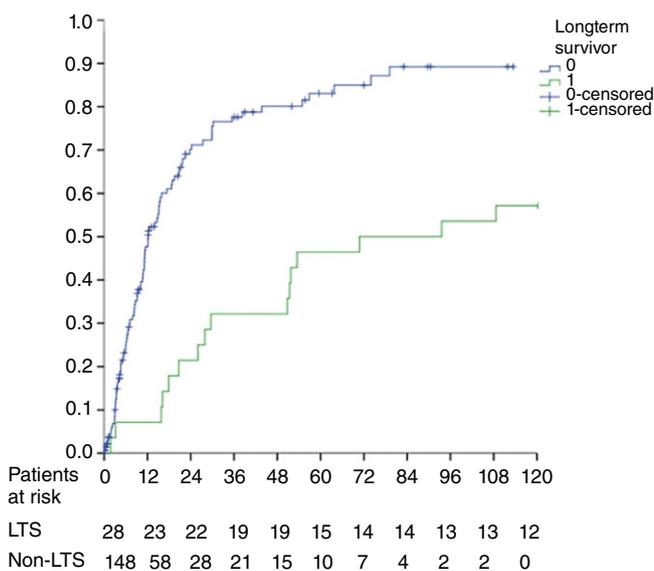
Factors	Group A ( $n = 28$ , 15.9%)	Group B ( $n = 148$ , 84.1%)	P-value
Perioperative factors			
Major resection ( $>3$ segments), $n$ (%)	11 (39.3%)	77 (52.0%)	0.204
Portal thrombectomy, $n$ (%)	1 (3.6%)	19 (12.8%)	0.154
Required transfusion, $n$ (%) (Missing data: 5, 2.8%)	8 (28.6%)	82 (57.3%)	0.005
Pathological factors			
Largest diameter, cm, mean $\pm$ SD (Missing data: 6, 3.4%)	5.7 $\pm$ 3.1	8.2 $\pm$ 5.2	0.001
Largest diameter $>5$ cm, $n$ (%)	11 (40.7%)	92 (64.3%)	0.021
Tumour differentiation, $n$ (%) (Good/moderate/poor) (Missing data: 25, 14.2%)	10 (38.5%)/12 (46.2%)/4 (15.4%)	42 (33.6%)/59 (47.2%)/24 (19.2%)	0.851
Margin positive resection, $n$ (%) (Missing data: 9, 5.1%)	1 (3.6%)	9 (6.5%)	0.581
Satellites, $n$ (%) (Missing data: 8, 4.5%)	8 (28.6%)	68 (48.6%)	0.075
Vascular invasion, $n$ (%) (Missing data: 6, 3.4%)			0.001
None	15 (55.6%)	34 (23.8%)	
Micro	5 (18.5%)	53 (37.1%)	
Gross	7 (25.9%)	56 (39.2%)	

SD, standard deviation.

**Table 3** Postoperative factors affecting longterm survival in patients submitted to resection for hepatocellular carcinoma who did (Group A) and did not (Group B) survive for  $\geq 10$  years after resection ( $n = 176$ )

Factors	Group A ( $n = 28$ , 15.9%)	Group B ( $n = 148$ , 84.1%)	P-value
Recurrence, $n$ (%)	18 (64.3%)	94 (63.5%)	0.938
Intrahepatic/intra-extra/extrahepatic, $n$ (Missing data: 1, 0.5%)	16/2/0	54/26/13	0.049
Single recurrence, $n$ (Missing data: 16, 14.3%)	13/18	30/94	0.009
Recurrence at < 2 years, $n$	6/18	80/94	<0.001
BCLC class A/B/C/D, $n$ (Missing data: 19, 17.0%)	12/0/2/0	27/9/39/4	0.006
AFP at recurrence, ng/ml, mean $\pm$ SD (Missing data: 28, 25.0%)	7340 $\pm$ 26 219	4723 $\pm$ 21 964	0.702
AFP >400 ng/ml, $n$ (%)	2 (15.4%)	15 (21.1%)	1.000
Type of treatment after recurrence, $n$ (%) (Missing data: 11, 9.8%)	18 (64.3%)	94 (63.5%)	0.010
Re-resection	5/18	8/94	
Transplant	8/18	14/94	
Radiofrequency ablation	3/18	16/94	
Transarterial chemoembolization	1/18	19/94	
Other (chemotherapy and/or radiation)	1/18	16/94	
Supportive care	–	10/94	

BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; SD, standard deviation.



**Figure 2** Kaplan–Meier curves for recurrence in patients who did and did not achieve 10-year survival after hepatectomy for hepatocellular carcinoma. LTS, longterm survivors

curative treatment for recurrence (second resection, transplant or radiofrequency ablation) more frequently.

Tumour size has been linked repeatedly to recurrence and survival across multiple studies. A direct relationship between the size and degree of vascular invasion is also well known, and vascular

**Table 4** Multivariate analysis of factors affecting longterm survival in all patients submitted to resection ( $n = 176$ )

	P-value
Pathological factors, $n$ (%)	
Vascular invasion, yes	0.020
Tumour diameter of >5 cm	0.192
Intraoperative factors, $n$ (%)	
Blood transfusion (yes/no)	0.014
Recurrence-related factors, $n$ (%)	
Recurrence in < 2 years	0.045

invasion is, by itself, a well-defined predictor of poor outcome.<sup>13–15</sup>

In this study, the mean tumour size in both groups was relatively large (>5 cm.). Longterm survivors in this study had significantly smaller tumours and were less likely to have vascular invasion on univariate analysis. Microvascular invasion was found to be significantly different in univariate analysis ( $P = 0.004$ ), but remained independently associated with 10-year survival on multivariate analysis only when clustered together with gross vascular invasion. Another known predictor of poor outcome is need for transfusion; Group A had significantly less need for transfusion on univariate and multivariate analyses.<sup>4,16</sup> Although it was not statistically significant, a trend toward higher percentages in Group B emerged in relation to thrombectomy and the presence of satellite nodules, both of which are regarded as ominous.<sup>17,18</sup>

The distribution of underlying liver disease in this series reflects the heterogeneity of the population. Univariate analysis showed

that significantly more patients with HBV were longterm survivors in this series, suggesting that HCC in association with HBV may have a more favourable prognosis. Conflicting results have emerged in previous research pertaining to this association, including a large multicentre study by Pawlik *et al.*<sup>19–22</sup> Other preoperative factors that have been reported to impact prognosis, such as the presence of stage III–IV fibrosis and low platelet count (a surrogate for severe fibrosis),<sup>23</sup> did not differ between the groups in this study.

In this series only 35.7% (10 of 28) of longterm survivors remained recurrence-free at 10 years. A recent Japanese study showed that 14 of 74 (18.9%) patients who were disease-free at 10 years after resection for HCC eventually developed recurrence, prompting the authors to suggest lifelong follow-up.<sup>24</sup> Delayed recurrence in longterm survivors is likely to represent *de novo* HCC rather than the progression of occult metastatic disease.<sup>10,11</sup>

## Conclusions

Ten-year survival after liver resection for HCC is possible and can be expected in approximately 16% of patients. Recurrence alone does not preclude longterm survival. Lack of vascular invasion, absence of perioperative transfusions and time to recurrence of >2 years were independent factors associated with 10-year survival.

## Conflicts of interest

None declared.

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