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Factors Associated with Disease Survival after Surgical Resection in Chinese Patients with Hepatocellular Carcinoma

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Abstract

Objective: The aim of this cohort study was to investigate clinical outcome and prognostic factors after surgical resection for hepatocellular carcinoma (HCC).

Materials and Methods: A total of 1,157 HCC patients undergoing hepatic resection between 1998 and 2003 were included in this study. Univariate and multivariate analyses were performed to examine factors affecting clinical outcome and recurrence.

Results: Surgical procedures consisted of 1,011 (87.4%) anatomical resections, including 205 (17.7%) extended hepatectomies, 324 (28.0%) hemihepatectomies, 482 (41.7%) segmental resections, and 146 (12.6%) local resections. The results suggest that 56.6% of patients had a recurrence of HCC during the study period and the main recurrence type was intrahepatic (542; 83.1%). The median survival time was 45 months. The 1-, 3- and 5-year overall disease-free survival rates for the study population were 74%, 47%, and 39% respectively.

Conclusions: The results of proportional hazard analyses suggest that tumor size, number of nodules and vascular invasion were significant predictors for poor survival rates.

Hepatocellular carcinoma (HCC) is one of the few cancers in which incidence is on the rise in western countries,[1] despite a downward trend observed over the past 2 decades in developing countries. HCC remains one of the leading causes of cancer-related deaths in China.[2] HCC is the most common primary cancer of the liver and accounts for 90% of all primary liver malignancies.[3] Although the overall survival for liver cancer patients has improved in China,[4] the 5-year survival rate remains low.[5] Liver resection is an important clinical procedure for treating liver cancer patients; previous research reports that liver resection is associated with lower mortality and improved survival rate as well as quality of life.[6] However, one of the important factors affecting long-term survival in post-resectional liver cancer patients is the recurrence of tumors.[7] Previous studies suggest that the long-term results after hepatic resection for this malignancy are far from satisfactory as 5-year survival rates are still as low as 30% in patients with underlying cirrhosis.[7–10] In China, a large number of patients undergo liver resectional operation, yet studies examining survival and cancer recurrence in this population are scant. The objective of this study is to examine survival rates of liver cancer patients by investigating clinical outcome and prognostic factors after surgical resection for HCC using a hospital-based cohort in China.

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PATIENTS AND METHODS

The participants of this study were 1,157 patients receiving curative hepatic resection for HCC at the Tianjin

Medical University Cancer Hospital (TMUC) between January 1998 and December 2003. Diagnosis of liver cancer was determined prior to surgery using at least 2 of the following 4 diagnostic procedures: ultrasonography (US), plain or enhanced computed tomography (CT), magnetic resonance imaging (MRI), and angiography. A Child-Pugh classification was used to evaluate cirrhotic patients with impaired liver function. Post-hoc pathological verification was performed in all cases. Curative surgery was defined as complete resection of all macroscopic and microscopic tumors.

Tumor staging was pathologically performed in accordance with the American Joint Commission on Cancer (AJCC) staging system (6th edn).[11] When clusters of cancer cells were present within the portal vein, hepatic vein or microvascular embolism, vascular invasion was considered to be present. In all selected patients, we obtained histopathologic information regarding tumor size and number, portal vein or hepatic vein invasion, microvascular embolism, presence of capsule formation, and cirrhotic change in background liver.

Patients given liver resection were followed up at the outpatient clinic every 3 months with measurement of the serum alpha-fetoprotein level and hepatic ultrasonography, and every 6 months with chest X-ray. When recurrence was suspected, further evaluations were made by abdominal CT scan and/or angiography of the celiac trunk with lipiodol injection and, if necessary, by ultrasound-guided biopsy to confirm the diagnosis. Study follow-up ended on 31 March 2005.

Statistical Analysis

In preliminary data analyses, all selected variables of this study were first explored in terms of means (continuous variables) and proportions (categorical variables). Disease-free survival rates were evaluated in the patients with curative resection who were discharged from the hospital from the date of surgery to the time of recurrence, end of the study or the date of death. Variables were selected for their potential relation to recurrence based on previous studies or on our own clinical experience. The variables chosen were cirrhosis, diameter of the main nodule, number of nodules, tumor capsule, intraoperative blood transfusion, and vascular invasion. Kaplan–Meier survival curves were produced for selected variables and log-rank tests were performed for statistical differences in bi-variate survival analyses. Based on the exploratory analyses, a proportional hazard was used to assess the independent impact for selected variables. Differences associated with P values less 0.05 were considered significant. Statistical analysis was carried out using SPSS 13.0.

RESULTS

Patient Characteristics

There were 1,013 men and 144 women among the 1,157 patients, with ages ranging between 16 and 85 years. About 89.02% of patients were HBsAg-positive, 72.08% had an alpha-fetoprotein higher than 20 μg/l, and 80.12% of patients also had liver cirrhosis, including 29.1% in Child-Pugh A, 55.9% in Child-Pugh B, and 15.0% in Child-Pugh C. Complications due to liver cirrhosis were present in 80.12% of the patients. Although patients were similarly distributed among the T1 and T2 subgroups, there was a slight predominance of patients in the T3 subgroup (40.7%; Table 1). In contrast, only 8.04% had T4 disease.

Surgical Outcome and Survival

In the 1,157 patients, 87.4% of the surgical procedures were anatomical resections. Of those resections, there were 17.7% extended hepatectomies, 28.0% hemihepatectomies, 41.7% segmental resections, and 12.6% local resections. Mean perioperative blood loss was 330.4 ± 265.5 ml (range: 80–2,550 ml). Postoperative complications developed in 3.72% of patients, including intra-abdominal hemorrhage (n = 7), multiple organ dysfunction syndrome (MODS; n = 15), and severe ascites (n = 21); 1.03% of the 1,157 patients were classed as having perioperative deaths (Table 1). Perioperative death was defined as a death during the operation or within 30 days of surgery. The median survival time is 44.87 months. The 1-, 3-, and 5-year overall survival and disease-free survival rates of the patients treated with hepatic resection were 85%, 54% and 47%, and 74%, 47% and 39% respectively.

Recurrence of HCC

Among the 1,157 patients, 652 experienced recurrence of HCC. The types of recurrence were mainly intrahepatic (83.1%). Of the intrahepatic recurrences, 40.4% were multi-segmental and 49.5% of patients had solitary recurrence in the remnant liver. Extra-hepatic recurrence was found in 14.0% of patients, while 2.9% of patients had both intra- and extra-hepatic recurrence.

Table 1.
Clinicopathological and surgical features of liver cancer patients (1998–2003, Tianjin, China)

Variable	Category	N	%
Sex	Male	1,013	87.6
	Female	144	12.4
Age in years	<45	259	22.4
	45–54	298	51.7
	55–64	206	17.8
	>64	94	8.1
Child-Pugh classification	Child-Pugh A	337	29.1
	Child-Pugh B	647	55.9
	Child-Pugh C	173	15.0
HBsAg	Positive	1,030	89.0
	Negative	127	11.0
AFP(+) ≥ 20 ng/ml		834	72.1
Cirrhosis (histologically confirmed)		927	80.1
AJCC T category	T1	231	20.0
	T2	362	31.3
	T3	471	40.7
	T4	93	8.0
Diameter of main nodule	≤5 cm	480	41.5
	>5 cm	677	58.5
Number of nodules	Single	841	72.7
	Multiple	316	27.3
Anatomical resections	Extended hepatectomies	205	17.7
	Hemihepatectomies	324	28.0
	Segmental resections	482	41.7
Local resections		146	12.6
Perioperative average blood loss		330.4 ± 265.5 ml	(range 80–2,550 ml)
Perioperative deaths		12	1.0

Table 2.
Disease-free survival rates of hepatocellular carcinoma (HCC) patients after hepatectomy (1998–2003, Tianjin, China)

		Disease-free survival rate (%)			
	Number of patients	1-year	3-year	5-year	*P* value
Cirrhosis					
Yes	927	70.7	40.3	36.9	0.001
No	230	76.7	59.1	50.1	
Diameter of main nodule					
≤5cm	480	80.6	62.2	55.9	0.001
>5cm	677	65.2	36.5	27.9	
Number of nodules					
Single	841	78.6	57.4	49.6	0.000
Multiple	316	53.2	17.9	9.7	
Tumor capsule					
Absence	430	68.0	38.7	28.4	0.002
Presence	727	73.8	51.4	45.2	
Intraoperative transfusion					
Yes	187	72.3	49.3	41.4	0.001
No	970	67.9	36.3	29.3	
Vascular invasion					
Absence	692	79.1	62.5	58.1	0.000
Presence	465	60.6	24.7	21.4	

The exploratory analysis (Table 2) was used to identify prognostic factors for disease-free survival rates in patients with HCC after hepatectomy. Statistical analysis revealed that a tumor diameter ≥5 cm, the presence of multiple nodules, the absence of capsule formation, vascular invasion, cirrhosis, and intraoperative blood

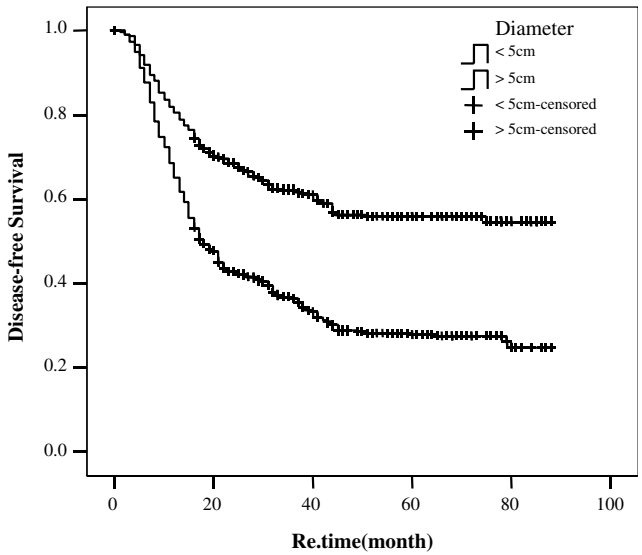

Figure 1. Disease-free survival rates after surgery based on initial tumor size.

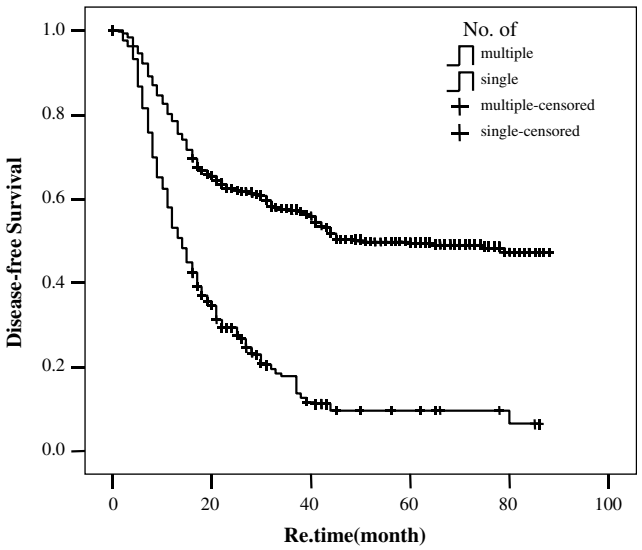

Figure 2. Disease-free survival rates after surgery comparing initial number of tumor nodules.

transfusion were all significant predictors of poor survival. Whereas the 5-year disease-free survival rate of the patients with tumors measuring ≥5cm was 27.9%, it was 55.9% (P = 0.001) in those with tumor diameters of <5 cm (Fig. 1). Similarly, the presence of multiple nodules was a powerful predictor of survival; the 5-year disease-free survival in patients with multiple tumor nodules was significantly shorter than that of patients with a single nodule (P =0.000; Fig. 2). The presence of vascular invasion was a significant predictor of survival. The 5-year disease-free survival in patients with vascular invasion was 2.14%, whereas it was 58.1% in those without vascular invasion (P = 0.000; Fig. 3).

The results from the multivariate proportional hazard analysis are largely consistent with the bi-variate analyses. As shown in Table 3, the size of the tumor (RR = 2.21, 95% CI: 1.85–2.63), number of nodules (RR = 2.69, 95% CI: 2.22–3.24), vascular invasion (RR = 2.72, 95% CI: 2.31–3.29), and absence of capsule formation (RR=1.67, 95% CI: 1.40–1.99) were all significantly associated with poor survival rates. However, there were no statistically significant impacts on survival rates for age, sex, and cirrhosis.

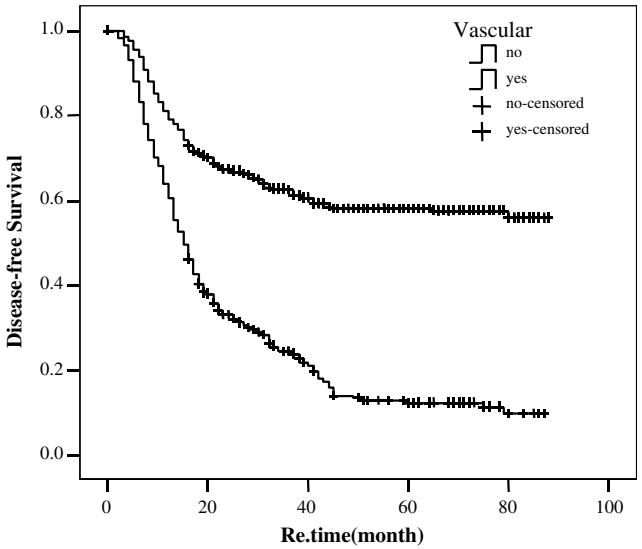

Figure 3. Disease-free survival rates after surgery with and without vascular invasion.

DISCUSSION

Hepatic resection has remained the standard therapy for HCC.[12] Many clinical and non-clinical factors can affect the short- and long-term clinical outcomes. Using a clinical cohort of post-resectional liver cancer patients, this study described factors affecting liver cancer recurrence. To our knowledge, this is one of the most comprehensive studies conducted from China.

In most institutions, the reported surgical mortality rate is less than 10%; in many centers of excellence, major hepatic resections are undertaken with no mortality.[13] The fear of uncontrolled hemorrhage was a major impediment to the evolution of hepatic resection as an effective form of therapy.[14,15] While bleeding remains a concern, surgical techniques have improved greatly, and experienced centers have achieved significant reductions in blood loss and transfusion requirements, even after major resections.[16] Portal-triad clamping reduces hepatic

Table 3.
Proportional hazard analyses of liver cancer patients surgically treated between 1998 and 2003, Tianjin, China

Variable	Category	Relative risk	95% CI
Age	<45	1	
	Over 10-year increase	0.99	0.88, 1.12
Sex	Male	1	
	Female	1.12	0.88, 1.43
Diameter of main nodule	<5 cm	1	
	5 cm or bigger	2.21	1.85, 2.63
Number of nodules	1	1	
	2 or more	2.69	2.22, 3.24
Tumor capsule	Presence	1	
	Absence	1.67	1.40, 1.99
Vascular invasion	Absence	1	
	Presence	2.72	2.31, 3.20
Cirrhosis	Absence	1	
	Presence	1.46	1.13, 1.87

arterial and portal venous bleeding, but does not address the hepatic veins, which are usually the major sources of blood loss.[17,18] Our approach to hepatic resection involves inflow and outflow vascular control before parenchymal transection, low central venous pressure anesthesia to minimize hepatic venous bleeding, and anatomically based resections. Using these approaches, we have reduced the mean blood loss to less than 500 ml and the proportion of patients requiring transfusion to less than 20%. At the same time, anatomically based partial hepatectomy is the best way to achieve a negative margin. Wedge resections are usually inadequate and potentially dangerous, especially for large tumors, and are often associated with greater blood loss and a greater incidence of positive histological margins.[19] Anatomic segmental resections are much more controlled and are generally superior to wedge resections. We believe that these clinical procedures are associated with the low postoperative mortality in this cohort.

A large body of literature suggests that postoperative recurrence is the single most important factor affecting survival rate in liver cancer patients. Thus, examining the associated contributing factors has attracted substantial research interest in the past few decades.[20–22] Tumor size,[21,23] multiple nodules,[21,23–25] vascular invasion,[22,23,26–29] cirrhosis,[30] and absence of capsule formation[22,23,31] have been found to be significant predictors of recurrence. Most of the factors involved in recurrence are related to the tumor characteristics, which are likely due to intrahepatic metastasis or to multicentric carcinogenesis, the presence of satellite nodules.[21,22,26,32] These findings are consistent with previous studies and underscore the importance of early clinical intervention. Another group of established risk factors are related to surgery, such as intraoperative blood transfusion. This has been shown to be associated with increased intrahepatic recurrence.[33,34] In our study, we found that intraoperative blood transfusion was a significant factor related to survival. The application of improved medical imaging technology to detect liver cancer at an early stage may significantly enhance the overall survival. However, as clinical diagnostic tests are often invasive and expensive, they are particularly relevant in predisposing factors for liver cancer, such as cirrhosis, multiple nodules, vascular invasion, etc.

A large sample size and a low rate of patients lost to follow-up (3.46%) are the primary strengths of this study. Nevertheless, liver resection was the only surgical intervention explored, although there are a number of other clinical interventions and adjuvant therapies available. These interventional factors are expected to be associated with disease-free survival and it is important for these issues to be addressed in future studies. In this study, survival was chosen as a sole outcome measurement. Evaluations on quality of life assessment for liver cancer patients receiving surgical resection should also be considered in future research. Lastly, patients in this study were followed up to a maximum of 6 years; more convincing clinical insights could be acquired from a longer follow-up.

In conclusion, surgical resection has generally been accepted as the first treatment of choice for HCC. Improvements in imaging methods and surgical techniques have made it possible to increase the number of patients in whom treatment is aimed at being curative. At the same time, based on a large clinical cohort of liver cancer patients assembled in a Chinese cancer hospital, this study shows that tumor-related, as opposed to per-

sonal, factors are significant predictors for disease-free survival. This finding has important implications for early detection in those at a high risk of this disease.

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