RESEARCH COMMUNICATION

Long-term Prognosis in Hepatocellular Carcinoma Patients after Hepatectomy

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Abstract

Background: The hepatocellular carcinoma is very common in China. Our aim in this report was to investigate clinical and pathological factors based on the current decade data that could influence prognosis of HCC patients after hepatectomy. Methods: Between 2002 and 2009, all patients undergoing hepatectomy for HCC were followed up and reviewed retrospectively. Prognostic factors were studied by univariate and multivariate analysis, with Kaplan-Meier and Cox multivariate survival analyses. Results: Complete clinicopathologic and follow-up data were available for 114 patients. The estimated cumulative survival rates at 1, 3, and 5 yr were 84.6%, 60.2% and 51.8%, respectively. On univariate analysis, key prognostic factors were AFP level, GGT level, tumor size, number of tumors, portal vein invasion, liver cirrhosis status and TNM stage. In the multivariate analysis, tumor size, GGT level, liver cirrhosis status and portal vein invasion were significantly associated with patients' prognosis. Conclusion: Through follow-up of a relatively large cohort of Chinese patients, tumor size, GGT level, liver cirrhosis status, portal vein invasion were revealed as important factors for long-term survival after hepatectomy. Early diagnosis for tumor and the improvement of liver function before surgery are important ways to improve the prognosis.

Keywords: Hepatocellular carcinoma - hepatectomy - multivariate analysis - prognosis

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in China (Peng et al., 2010). Since HCC is insensitive to the radiotherapy and chemotherapy, surgical resection is one important curative treatment for HCC (Jarnagin, 2010). With earlier diagnosis and tumors detected at an early stage, there is substantially increased survival and curative surgical resection possible. However, long-term survival remains unsatisfactory. The 5-year overall survival rates for patients with HCC after operation reminds lower than 50% (Altekruse et al., 2009). This article aims to explore the factors which influent HCC patients' prognosis after operation based on a retrospective analysis on the common clinicopathologic parameters from114 HCC patients.

Materials and Methods

Patient Selection

From January 2002 to December 2009, 114 primary lesions of HCC that were resected from patients in the first affiliated hospital of Xi'an Jiaotong University. Follow-up after hepatic resection was performed for all patients. The data of patients suffering from diseases seriously affect health during perioperative period, the data of those who has died because of other nonsurgical reasons and the data of insufficient clinical and follow-up record were excluded from the analysis of the cumulative survival rate.

Clinicopathologic parameters measurements

In the data base, 22 clinicopathologic and biologic variables were used to survey patients with HCC. Patients were then stratified by gender, age, history of blood transfusion, HBsAg status (hepatitis B virus surface antigen), HCV-Ab status (hepatitis C virus antibody), liver cirrhosis status, preoperative serum AFP (α-fetoprotein), γ-GGT (γ-glutamyltransferase) level, serum bilirubin level, serum albumin level, prothrombin activity, maximal tumor dimension, number of tumors, intrahepatic extent of tumor, extrahepatic metastasis (including lymph node metastasis indicated in the preoperative imaging studies or operative findings), pathologic types, capsular formation, portal vein invasion, hepatic vein invasion, bile duct invasion, surgical curability of liver resection, free surgical margins. The adjuvant therapies after operation include DDS (drug delivery system), TACE (transcatheter arterial chemoembolization) and so on. The classification of surgical modes, (1) Pathologically curative resection: no more than 2 tumor nodules intrahepatic and no

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Table 1. Single-factor Analysis of Prognosis of Operation on 114 HCC Patients

Variables	No.of patients	Survival rate(%)			P value
		1Yrs	3Yrs	5Yrs	
Tumor size					
≤3 cm	36	86.0	75.2	42.3	0.009
3~5 cm	36	68.6	48.1	24.6	
>5 cm	42	66.0	31.6	13.3	
AFP					
<200	48	80.3	68.6	47.1	0
200~400	29	68.9	45.2	27.4	
≥400	37	55.4	26.5	11.4	
GGT					
≤50	51	81.1	67.1	40.3	0
50~100	30	84.0	50.2	34.8	
>100	33	52.7	28.4	13.7	
Tumor numbers					
Solitary	81	79.2	55.3	38.5	0.039
Multiple	33	59.1	35.4	22.7	
Portal vein invasion					
Present	14	71.3	52.5	23.6	0.011
Absent	100	85.4	72.6	30.1	
Cirrhosis status					
Normal	27	82.4	62.1	41.3	0.017
Small nodule	14	80.1	50.2	31.6	
Big nodule	73	71.5	39.1	19.6	
TNM stage					
I	59	84.4	56.4	31.2	0.025
II	17	67.8	46.5	28.4	
III	38	58.1	35.2	16.5	

extrahepatic metastasis; no clinical and histologic invasion to hepatic vein and the first branches of the portal vein or more proximal portion; completely resect the tumor and resected stump with a margin more than 1 cm from the edge of the tumor (2) Clinically curative

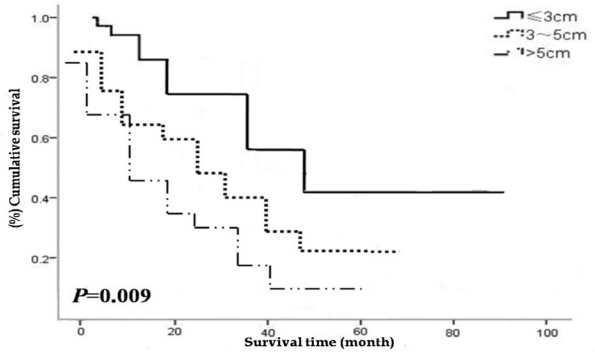

Figure 1. Kaplan-Meier Analysis of Tumor Size and Prognosis

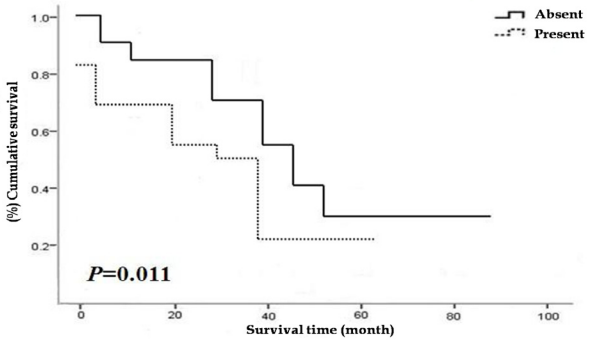

Figure 2. Kaplan-Meier Analysis of Portal Vein Tumor Thrombi and Prognosis

Table 2. Multiple-factor Analysis of Prognosis of Operation on 114 PLC Patients

Variables	Regression coefficient	S.E.	Wald	P value	Risk Ratio
Cirrhosis status	0.174	0.046	10.21	0.006	1.209
GGT	0.003	0.001	11.82	0.001	1.303
Portal vein invasion	0.009	0.054	11.58	0.007	1.107
Tumor size	0.187	0.053	12.47	0.000	1.506

resection: according to the literature, the criterion between pathologically curative resection and palliative resection (3) Palliative resection: the first branches of portal vein or more proximal portion have tumor thrombus; AFP level higher than normal after operation (Ryder, 2003). TNM stage use the latest six edition made by UICC/AJCC. Complications after operation include gastrointestinal hemorrhage, obstinate ascites, liver failure, etc.

Statistical analysis

All the databases were input the computer and classified as the standards. Overall, cumulative survival rates were obtained using the Kaplan–Meier method. The differences in survival between the groups were compared using the log-rank test. Cox's proportional hazards model was used for the multivariate analysis. The starting point for calculating survival was the date of surgery, and the endpoint was the date of death. Patients who remained alive on March 20, 2011, were censored. P values < 0.05 were considered statistically significant. Statistical analysis was carried out using SPSS16.0 software.

Results

Patient characteristics

Follow-up ended on March 20, 2011. The median survival time of all 114 cases is 36 months and a woman after initial operation keeps alive and enjoys the longest survival time of 91months. The overall 114 cases consisted of 89 male (78.1%) and 25 female cases ranged in age from 19 to 74 years (mean, 53.08±11.10 years). 25 cases were found by the way of physical examination, while other patients were discovered by outpatient examination when their symptoms emergence. Among them, 83 cases with positive HBs-Ag status and 87 cases with cirrhosis. In addition, 39 HCC patients were undergone pathologically curative resection, the other 48 and 27 cases were operated clinically curative resection and palliative resection respectively, and 14 cases were found portal vein invasion during operation. 24.6% of patients are with tumor in the left liver, 64% in the right, the rest in both left and right. All the tumor specimens were confirmed by the Department of Pathology, and the distance between cut surface and tumor edge in the resected specimen were ranged from 0.05 to 3.5 cm (mean, 0.68cm). Until the endpoint, 8 of 114 patients were noted to have recurrence (4 intrahepatic, 4 extrahepatic). The 1,3,5-year survival rates were 84.6%, 60.2% and 51.8%.

Prognostic factors for overall survival

In the univariate analysis, there were significant differences in survival among the groups stratified by

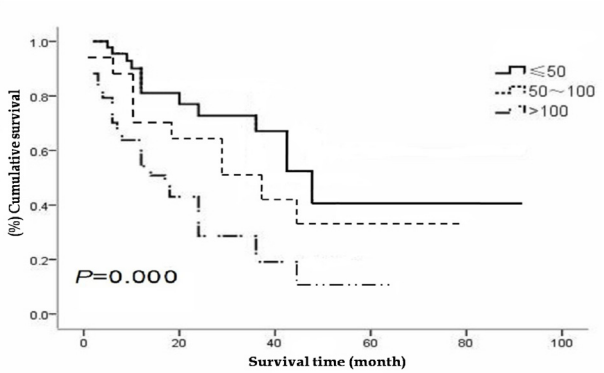

Figure 3. Kaplan-Meier Analysis of GGT Level and Prognosis

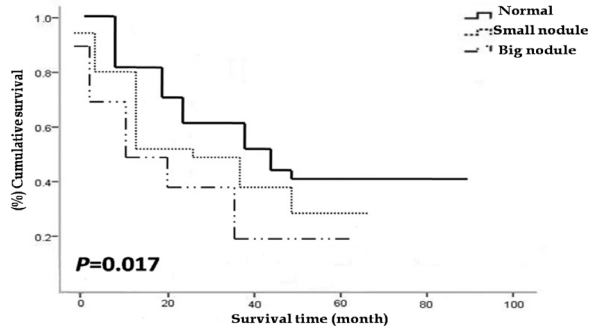

Figure 4. Kaplan-Meier Analysis of Liver Cirrhosis Status and Prognosis

tumor size, number of tumors, TNM stage, liver cirrhosis status, portal vein invasion, serum level of AFP and GGT level (Table 1and Figures 1-4). There were no significant differences in survival between patients with gender, age, capsular formation, free surgical margin, etc. A multivariate analysis using a stratified Cox proportional hazards model according to associated liver disease indicated that tumor size, GGT level, liver cirrhosis status and portal vein invasion were independent prognostic predictors for patients with HCC (Table 2).

Discussion

Advances in the diagnosis and surgical treatment of hepatocellular carcinoma have improved the prognosis for patients with HCC who undergo liver resection. In the current study, we analyzed patients with HCC from 2002 to 2009, during which the 5-year survival rate improved to 51.8%. The number of patients increased obviously during the last decade, and the patients' profiles have changed. Therefore, prognostic factors for patients with HCC should be further exploration.

Recently, most studies identify the risk factors for HCC patients' prognosis main from four facts: degree of liver damage, tumor characteristic, surgical-related elements and the adjuvant therapy after operation (Ryder, 2003; Schiffman et al., 2010). In the univariate analysis for the current study, 7 of 22 factors showed significant differences; and the multivariate analysis, which was stratified by associated liver disease, found that 2 tumor factors (tumor size and hepatic vein invasion) and 2 clinical factors (status of liver cirrhosis and GGT level) were independent prognostic factors for overall survival. Thus, tumor size, status of liver cirrhosis and portal vein invasion are well known prognostic factors in patients with HCC.

Patients who had tumors that measured ≤ 3 cm had a significantly better prognosis compared with patients who had tumors that measured 3–5 cm and >5cm. A survival analysis was done for 1073 cases, which indicated the relations between tumor size and prognosis, that is, the bigger tumor size, the more probable coexistence of vessel invasion, and the lower tumor grade (Pawlik et al., 2005). We think that the tumor size can reflect on patients liver storage ability and limit surgical-related factors (e.g. surgical mode, operation time, portal blockage).

It is well known that portal vein invasion is the main reason for intrahepatic metastasis and tumor recurrence after operation (Eguchi et al., 2011). Recently, clinical studies come to emphasize on the affection that microvascular invasion on HCC patients prognosis (Colombo et al., 2011).There is literature shows that microvascular invasion is a risk factor for disease-free survival rate, the 5-year disease-free survival rate in groups with and without microvascular invasion are 20.8% and 52.6%, respectively (Sumie et al., 2008). Therefore, in the recent six edition TNM classification system proposed by the UICC/AJCC revise T1 stage as single tumor without vascular invasion and dispose the standard that tumor size ≤2cm.

The HCC patients median survival time in groups GGT levels ≤50, 50-100 and > 100 are 64, 52 and 42 months, respectively (P<0.05), in accordance with previous study (Ju et al., 2009). The survival rate curves in Figure 3 also can show differences in groups. GGT is a membrane-bound enzyme which is highest in embryo livers and decreases rapidly to the lowest levels after birth. GGT is re-expressed during the development of HCC and can be divided into several subfractions. The HS-GGT is a part of total GGT activity that can only be found in sera of HCC patients, and has been confirmed a useful specific HCC marker (Yao et al., 2007). Besides, the overexpression of GGT in HCC may be related to the hypomethylational status of CCGG sites of GGT genes (Yao et al., 2000). We consider that GGT level is also an important factor for HCC patients prognosis.

HCC patients with cirrhosis are common in China. Cirrhosis always not only can restrict the resection margin, but also decline liver function, limiting patients' treatment and prognosis. In our report, 76.3% of all 114 cases correlate with cirrhosis. The results show that the median survival time of normal liver, small nodule and big nodule groups are 54 , 30 and 23 months, respectively (P<0.05). Figure 4 shows the different survival rate in groups. Either univariate analysis or multivariate analysis shows cirrhosis play an important role in HCC patients' prognosis, in accordance with previous researches, implicating the importance of cirrhosis treatment and liver function reformation.

In summary, the results of the current study, in which we reevaluated prognostic factors for patients who underwent liver resection using a recent, large-scale data base, will provide useful information for clinic

study. For patients with HCC, it is important to select adequate therapeutic options based on a reliable prognostic preoperative assessment using imaging studies and clinical data. According to the factors, we could detect tumor foci as early as possible; improve liver function as well as preoperative management. Besides, our group will continue to follow-up the enrolled and new patients in order to the next stage study.

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