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Original Article

Surgical management and survival analysis of patients with hepatocellular carcinoma beyond BCLC recommendation

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Abstract: Purpose: To analyze the prognosis and risk factors of the patients with Barcelona clinical liver cancer (BCLC) B or C stage after hepatectomy. Methods: 908 HCC patients who underwent surgical management in Cancer Institute and Hospital, Chinese Academy of Medical Sciences from 1999 to 2010 were included in our study. Survival analysis was performed. Results: Beyond BCLC group was consisted of 149 BCLC stage B or C cases and control group was of 759 BCLC stage A cases. For the beyond group, the median OS was 26 months, and 1-, 3-, 5-year OS were 54%, 31% and 14%; the median DFS was 12 months, and the 1-, 3-, 5-year DFS were 33%, 26% and 15%. Both the median OS and DFS were significantly shorter than the control group (OS: *P*=0.000, DFS: *P*=0.000), Survival analysis showed that OS was significantly associated with solitary mass, extrahepatic spread, vascular invasion and performance status. DFS was associated with only extrahepatic spread. Patients with any of the risk factors (single lesion, extrahepatic involvement, vascular invasion & tumor embolus and clinical symptoms) were classified as the high-risk group (n=96) and the others as the low-risk group (n=53). For the high-risk group, the median OS was 21 months, and the 1-, 3-, 5-year OS were 45%, 18% and 8%; the median DFS was 8 months, and the 1-, 3-, 5-year DFS were 26%, 16% and 8%. Both were significantly shorter than the low-risk group (OS: *P*=0.000, DFS: *P*=0.040), Large tumor size was more commonly seen in high-risk group. Conclusion: On condition that the operation indication is strictly grasped, surgical management of HCC with BCLC stage B or C could bring favorable survival benefits.

Keywords: Hepatocellular carcinoma, BCLC staging, hepatectomy, prognosis

Introduction

Hepatocellular carcinoma (HCC) has been one of the most dangerous cancers in the world, and ranks 5th in the global incidence of malignant tumors, ranks 2nd in the cause of death [1]. There have been a variety of staging systems for HCC, among which BCLC staging has been widely accepted because of its capability of indication of prognosis as well as recommendation of treatments [2-4]. However BCLC staging has its own shortcomings-with the development of surgical technology, the safety of hepatectomy is greatly improved and perioperative care becomes more perfect, therefore some of the patients who were previously regarded inappropriate to surgery according to the BCLC staging can have operations and achieve a better prognosis now. At present, there is still a lack of reports of the outcomes of surgical management for BCLC B and C patients, and whether some of them may benefit from operations is unknown. Therefore, this study aims to explore the prognosis and risk factors of patients who underwent surgical management beyond the BCLC staging recommendations, so as to provide some guidance for clinical work in the future.

Patients and method

General information

A total of 908 HCC patients who received curative hepatectomy in Cancer Hospital, Chinese Academy of Medical Sciences from January 1999 to December 2010 were included in our study. The diagnoses of all patients were confirmed pathologically and the follow-up were

Table 1. The baseline information and clinic feature for control and BCLC beyond groups

		Control group		BCLC beyond group		
		Number	%	Number	%	*P* value
Total		759		149		
Gender	Male	653	86.0%	132	88.6%	0.404
	Female	106	14.0%	17	11.4%	
Age	≥60	267	35.2%	45	30.2%	0.242
	<60	492	64.8%	104	69.8%	
Etiology	HBV	674	88.8%	127	85.2%	0.217
	Others	85	11.2%	22	14.8%	
Child-Pugh	A	740	97.5%	104	69.8%	0.000*
	B	19	2.5%	45	30.2%	
Tumor number	Single	727	95.8%	28	18.8%	0.000*
	Multiple	32	4.2%	121	81.2%	
Tumor Size	Diameter ≥5 cm	263	34.7%	90	60.4%	0.000*
	Diameter <5 cm	496	65.3%	59	39.6%	
Vascular invasion or tumor embolus	Yes	57	7.5%	23	15.4%	0.002*
	No	702	92.5%	126	84.6%	
Lymphatic metastasis	Yes	1	0.1%	31	20.8%	0.000*
	No	758	99.9%	118	79.2%	
Extrahepatic metastasis	Yes	13	1.7%	20	13.4%	0.000*
	No	746	98.3%	129	86.6%	
Clinical symptoms	Yes	321	42.3%	82	55.0%	0.004*
	No	438	57.7%	67	45.0%	
AFP	≥400 ng/ml	183	24.1%	56	37.6%	0.001*
	<400 ng/ml	576	75.9%	93	62.8%	
CEA	≥5	47	6.2%	10	6.7%	0.811
	<5	712	93.8%	139	93.3%	
ALP	Normal	680	89.6%	130	87.2%	0.399
	Abnormal	79	10.4%	19	12.8%	
PT	≥80%	520	68.5%	113	75.8%	0.075
	<80%	239	31.5%	36	24.2%	

*P<0.05.

perfectly performed. There were 759 patients with BCLC staging A, who served as control group and a total of 149 cases with BCLC staging B and C (including 106 cases with BCLC B and 43 cases with BCLC C) served as beyond BCLC group. The baseline information and clinic feature for control and BCLC beyond groups are shown in **Table 1**. Among the beyond BCLC group, there were 132 males and 17 females, with the median age of 55 (19-85) years old. 127 cases had a history of hepatitis B. There were 104 cases with Child-Pugh grade A, and 45 with grade B. 28 cases had single lesion and 121 had multiple lesions. The tumor size was equal to or greater than 5 cm, in 90 patients and less than 5 cm in 59 patients. There were 30 cases with carcinoma cell embolus, 31 with lymph node involvement and 20 with extrahepatic involvement. 56 cases had positive alpha-fetoprotein (AFP, serum AFP ≥400 ng/ml). (See **Table 2**) Based on the statistic results, patients with any of the risk factors (single lesion, extrahepatic involvement, vascular invasion & tumor embolus and clinical symptoms) were classified into the high-risk group (n=96) and the others were into the low-risk group (n=53).

This study was approved by the Regional Ethics Committee of cancer hospital, Chinese Academy of Medical Sciences and all patients signed informed consents.

Table 2. Effects of various clinicopathologic features on OS and DFS

			Overall Survival (%)				Disease-free Survival (%)			
		No (%)	1st year	3rd year	5th year	*P* value	1st year	3rd year	5th year	*P* value
Total		149	54	31	15		33	26	15	
Gender	Male	132 (88.6%)	55	31	15	0.928	32	25	14	0.859
	Female	17 (11.4%)	43	32	0		39	39	0	
Age	≥60	45 (30.2%)	46	26	9	0.228	31	27	4	0.134
	<60	104 (69.8%)	58	33	18		34	26	22	
Etiology	HBV	127 (85.2%)	53	30	18	0.596	34	25	15	0.963
	Others	22 (14.8%)	59	36	8		30	30	15	
Child-Pugh	A	104 (69.8%)	54	32	15	0.530	33	26	15	0.922
	B	45 (30.2%)	50	0	0		33	0	0	
Tumor number	Single	28 (18.8%)	26	6	0	0.007*	13	0	0	0.253
	Multiple	121 (81.2%)	59	35	17		36	29	16	
Tumor Size	Diameter ≥5 cm	90 (60.4%)	54	25	12	0.486	30	22	8	0.165
	Diameter <5 cm	59 (39.6%)	54	38	17		37	31	22	
Vascular invasion or tumor embolus	Yes	23 (15.4%)	28	14	0	0.001*	11	0	0	0.143
	No	126 (84.6%)	58	34	17		35	28	16	
Lymphatic metastasis	Yes	31 (20.8%)	60	42	35	0.444	38	29	20	0.464
	No	118 (79.2%)	52	28	10		31	25	14	
Extrahepatic metastasis	Yes	20 (13.4%)	25	0	0	0.000*	0	0	0	0.001*
	No	129 (86.6%)	58	35	16		37	30	17	
Clinical symptoms	Yes	82 (55.0%)	25	11	0	0.019*	26	16	8	0.249
	No	67 (45.0%)	60	45	22		39	36	23	
AFP	≥400 ng/ml	56 (37.6%)	48	21	14	0.093	30	25	15	0.433
	<400 ng/ml	93 (62.4%)	57	37	15		34	27	15	
CEA	≥5	10 (6.7%)	60	38	0	0.588	33	33	0	0.723
	<5	139 (93.3%)	54	34	27		32	27	21	
ALP	Normal	130 (87.2%)	55	34	18	0.535	33	26	15	0.560
	Abnormal	19 (12.8%)	48	18	4		29	29	14	
PT	≥80%	113 (75.8%)	56	29	13	0.358	37	27	11	0.072
	<80%	36 (24.2%)	41	26	26		23	23	23	

*P<0.05.

Follow-up

All the patients who underwent hepatectomy were followed up in outpatient clinic regularly every 3 months after surgery. The followed-up included clinical examination, liver function tests, tumor markers and imaging examinations. If recurrence or metastasis were observed, treatments as surgery, transcatheter arterial chemoembolization, chemotherapy and targeted drug therapy were applied according to the specific situation. The deadline of follow-up was December 31, 2010 or the date of death, and the median follow-up time was 28 (rang 1-144) months.

Statistical analysis

SPSS17.0 software was used for statistical analysis of the data in our study. t-test and chi-square test was used to compare the clinical and pathological features; overall survival and disease-free survival was carried out with the Kaplan-Meier method and Cox regression model. Death or relapse was regarded as end-point for disease-free survival. $P<0.05$ was considered statistically significant.

Results

Overall survival

For the control group, the median survival time was 83 months, and the 1-, 3-, and 5-year survival rates were 86%, 69% and 42%. For the beyond BCLC group, the median survival time was 26 months, and the 1-, 3-, and 5-year survival rates were 54%, 31% and 14%, respectively, which were significantly lower than the control group ($P=0.000$, See **Figure 1A**).

Disease-free survival

For the control group, the median disease-free survival was 46 months, and the 1-, 3-, and

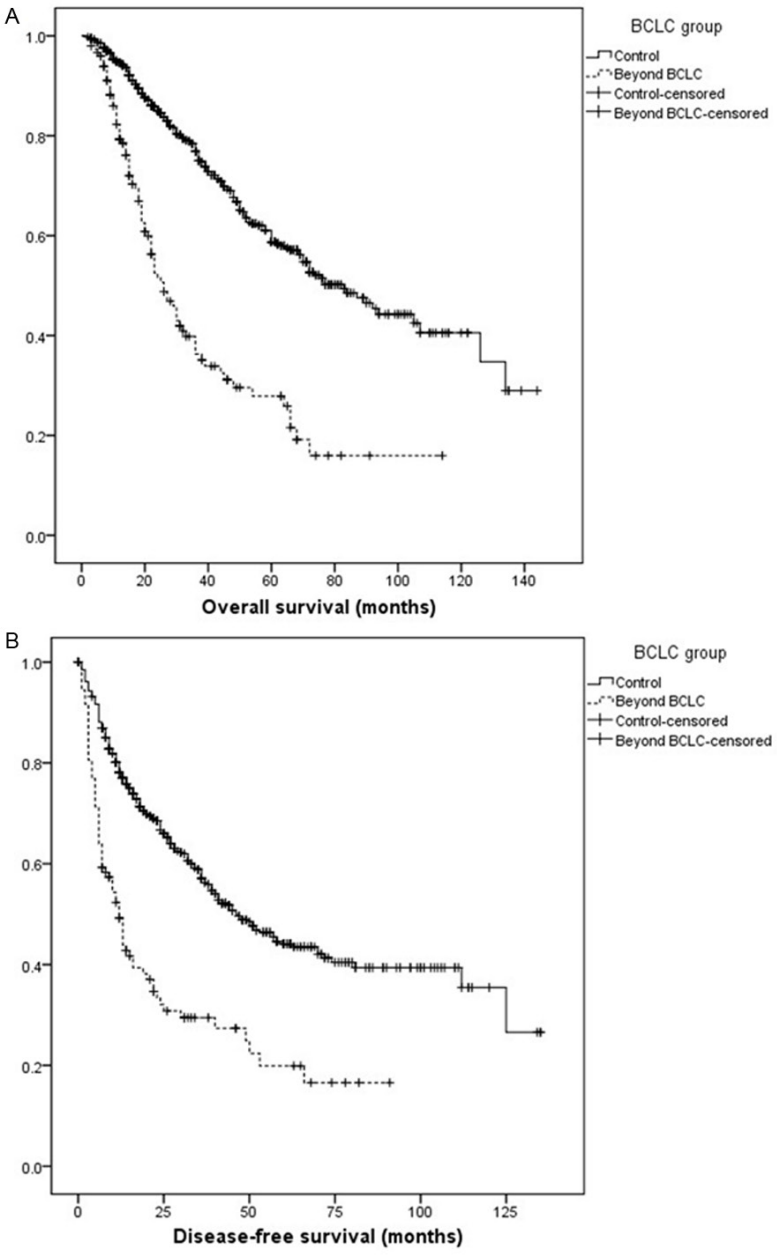

Figure 1. Comparison of Overall Survival (A) and Disease-free Survival (B) between beyond BCLC group and control group.

5-year disease-free survival rates were 68%, 49% and 36%. For the beyond BCLC group, the median survival time was 12 months, and the 1-, 3-, and 5-year disease-free survival rates were 33%, 26% and 15%, respectively, which were significantly lower than the control group (*P*=0.000, See **Figure 1B**).

Survival analysis of beyond BCLC group

Overall survival and disease-free survival analysis were performed for the 149 patients in the beyond BCLC group. Univariate survival analysis showed that factors predicting poor outcomes included single lesion, extrahepatic involvement, vascular invasion & tumor embolus and clinical symptoms (ECOG PS 1-2). Only extrahepatic involvement was associated with disease-free survival. Multiple survival analysis did not show an independent risk factor for OS or DFS (See in **Table 2**).

Risk classification of the beyond BCLC group

The results showed that the median overall survival was 21 months in the high-risk group and 54 months in the low-risk group, and the difference had statistical significance (*P*=0.000). The 1-, 3-, and 5-year overall survival rate of the high-risk group were 45%, 18%, 8%, which were significantly lower than the 69%, 54%, and 27% of the low-risk group. The disease-free survival of high-risk group was 8 months which was lower than 14 months of low-risk group with statistic significance (*P*=0.040). The 1-, 3-, and 5-year disease-free survival rates of high-risk group were 26%, 16%, 8%, which were significantly lower than 41% 38% and 24% of the low-risk group (See **Figure 2A**, **2B** and **Table 3**).

Comparison of clinicopathological features between high-risk group and low-risk group

We compared the clinicopathological features and laboratory indicators between the high-risk group and the low-risk group, and the results showed that only tumor size was larger in high-risk group and no other significant difference were observed between the two groups (See **Table 4**).

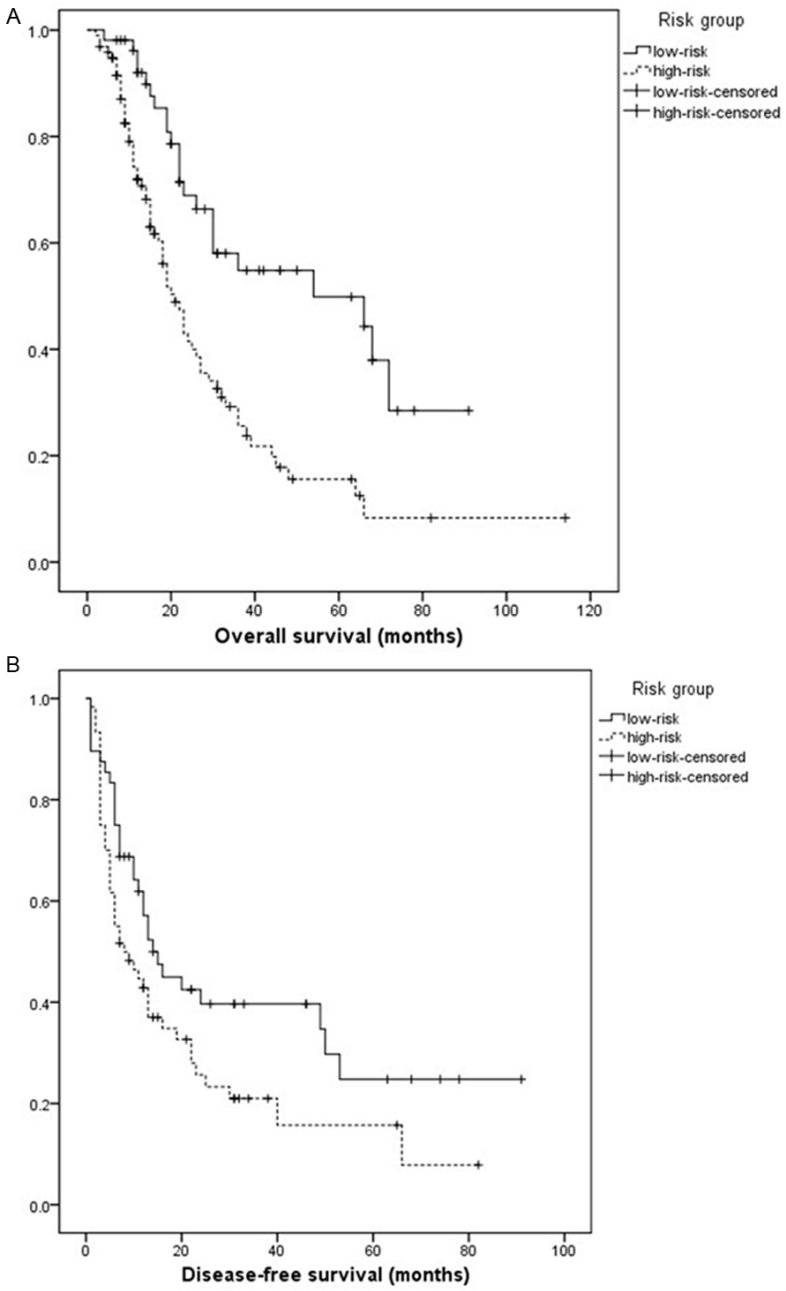

Figure 2. Comparison of Overall Survival (A) and Disease-free Survival (B) between high-risk group and low-risk group.

Discussion

Hepatocellular carcinoma ranks 2nd in mortality among all kinds of cancers in China, and is one of the most dangerous threats to the people's health. Currently, surgery is still the primary treatment for HCC patients, which can lead to good prognosis. However, the indication of the hepatectomy remains controversial. The BCLC staging had been confirmed effective in Europe and the United States [2, 3, 5], as it can well predict the prognosis of HCC patients, which is consistent with the result of Chinese population in our study. Nevertheless the strict requirements for the indication of hepatectomy greatly limit the number of HCC patients who are able to receive surgical management. In recent years, with the development of surgical techniques and perioperative management, many scholars have proposed that the recommendations of the treatments in BCLC staging should be re-evaluated [6-9].

In this article we retrospectively analyzed the prognosis of BCLC staging B and C patients after hepetectomy. The results showed the beyond BCLC group had a median overall survival of 26 months, and the 1-, 3-, and 5-year survival rates were 54%, 31% and 14%. Survival analysis showed that risk factors in this group included single lesion, extrahepatic involvement, vascular invasion & tumor embolus and clinical symptoms. Patients with any of the risk factors were classified into high-risk group, of which the median overall survival was 21 months and median disease-free survival was eight months. Both the OS and DFS of high-risk group were significantly lower than of the low-risk group (median OS: 54 months; median DFS: 14 months).

Invasion of intrahepatic vessels is one of the biologic characteristics of hepatocellular carcinoma, and involvement of portal vein is most common. A number of studies have found that vascular invasion or tumor embolus is a signifi-

Table 3. Comparison of OS and DFS between high-risk group and low-risk group

Groups	No (%)	Overall Survival (%)				Disease-Free Survival (%)			
		1st year	3rd year	5th year	*P* value	1st year	3rd year	5th year	*P* value
High-risk group	96 (64.4%)	45	18	8	0.000	26	16	8	0.040
Low-risk group	53 (35.6%)	69	54	27		41	38	24	

Table 4. Comparison of clinicopathologic features between high-risk group and low-risk group

		High-risk group No (%)	Low-risk group No (%)	*P* value
Gender	Male	86 (89.6%)	46 (86.8%)	0.601
	Female	10 (10.4%)	7 (13.2%)	
Age	≥60	27 (28.1%)	18 (34.0%)	0.463
	<60	69 (71.9%)	35 (66.0%)	
Etiology	HBV	77 (80.2%)	43 (81.1%)	1.000
	Others	18 (19.8%)	10 (18.9%)	
Child-Pugh	A	92 (95.8%)	53 (100%)	0.297
	B	4 (4.2%)	0 (0%)	
Tumor Size	Diameter ≥5 cm	69 (71.9%)	21 (39.6%)	0.000*
	Diameter <5 cm	27 (28.1%)	32 (60.4%)	
Lymphatic metastasis	Yes	17 (17.7%)	14 (26.4%)	0.215
	No	79 (82.3%)	39 (73.6%)	
AFP	≥400 ng/ml	38 (39.6%)	18 (34.0%)	0.597
	<400 ng/ml	58 (60.4%)	35 (66.0%)	
CEA	≥5	6 (2.7%)	8 (15.1%)	0.077
	<5	90 (97.3%)	45 (84.9%)	
ALP	Normal	82 (85.4%)	48 (90.6%)	0.448
	Abnormal	14 (14.6%)	5 (9.4%)	
PT	≥80%	69 (71.9)	38 (71.7%)	0.982
	<80%	27 (28.1%)	15 (28.3%)	

*P<0.05.

cant risk factor of postoperative recurrence and extrahepatic metastasis [10, 11], which agrees with the result in our research. Many scholars thought R0 resection of cancer embolus at 1st or 2nd branches of the portal vein and the primary liver lesion could benefit the prognosis, but Liu etc. [12] reported that the 1-year recurrence rate after this management was close to 100% with unsatisfactory survival time. Therefore, in consideration of surgical management of the BCLC staging B or C, vascular invasion and tumor embolus should been taken into account and carefully evaluated.

Previous studies have shown that multiple lesions is a risk factor for poor prognosis of the HCC patients, but in our study, single lesion becomes the risk factor for poor outcomes instead for BCLC staging B and C patients. There might be two reasons: First, the single tumor tends to be larger in diameter than the multiple ones, as 78.6% of single lesion was larger than 5 cm, which is obviously higher than 57.0% of multiple lesions. And several studies have pointed out that the larger the tumor is, the higher risk is that the tumor have microvascular invasion, which will lead to a poor prognosis [13, 14]. Secondly, with the development of surgical techniques, he-patectomy has been able to significantly improve the prognosis of patients with multifocal HCC when the indication of operation is strictly controlled [15, 16]. This study indicates that the single lesion might be a potential predictor of poor prognosis of patients with BCLC B and C grade, but due to the small number of cases, further clinical studies are necessary to discuss this issue.

With insidious onset, there are usually no obvious clinical symptoms on early stage of HCC and typical manifestations such as abdominal pain or jaundice merely occur on advanced stage. Therefore a number of previous studies found that ECOG score is a risk factor for HCC prognosis, and more attention should be paid for the HCC patients with clinical symptoms [17, 18], which the results of this study are consistent with. On the other hand, some scholars suggested that HCC patients in China often have a history of hepatitis B and cirrhosis, which may lead to clinical symptoms earlier and

weaken its predicting capability for prognosis [19]. So whether clinical symptoms are associated with prognosis of HCC patients needs further validation.

In conclusion, this study found that single lesion, extrahepatic involvement, vascular invasion & tumor embolus and clinical symptoms are risk factors for poor prognosis of patients beyond the BCLC recommendation after hepatectomy. However, under the premise of strict control of the indications for operation, some of BCLC B and C patients can benefit from surgical management and achieve a satisfactory prognosis. The BCLC staging system needs to be further evaluated and adjusted with regard to Chinese population.

Disclosure of conflict of interest

None.

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