RESEARCH ARTICLE

Treatment Efficacy and Prognostic Factors for Huge HCC Based on Barcelona Clinic Liver Cancer Staging

Zhi-Ming Zhang[1&], Yu-Mei Zhang[2&], Sheng Gao[1], Wei-Ping Yuan[1], Yin-Nong Zhao[1], Bang-De Xiang[1], Fei-Xiang Wu[1], Guo-Bin Wu[1], Jian-Yong Liu[1]*

Abstract

Objective: To explore the most appropriate treatment for patients with hepatocellular cancer (HCC) >10 cm by using the Barcelona Clinic Liver Cancer (BCLC) classification. Materials and Methods: A total of 124 HCC patients undergoing surgery were selected. Disease-free survival (DFS), overall survival (OS) and prognostic factors were respectively assessed. Results: This study showed that the cumulative 1-, 3-, 5-year survival rates were 79.7%, 59.8% and 41.6% in BCLC-A patients, 76.2%, 9.5% and 0% in BCLC-B patients and 44.9%, 0% and 0% in BCLC-C patients, respectively. The 1-, 3-, 5-year DFS rates were 49%, 24.5% and 9.1% in BCLC-A patients, 7.5%, 0% and 0% in BCLC-B patients, respectively. No BCLC-C patients survived 1 year after surgery. Multivariate analysis indicated that hepatitis B surface antigen (HBsAg), vascular invasion, intra-hepatic metastasis, curative resection, tumor rupture and pathologic differentiation were independent prognostic factors. Conclusions: Surgery is effective and safe for patients with HCC >10 cm with sufficient hepatic reserve.

Keywords: Barcelona clinic liver cancer staging - huge hepatocellular carcinoma - hepatectomy - efficacy

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in clinic, whose global incidence increases year by year (625 000 cases/year). Being in the first five malignant tumors, HCC causes nearly 600, 000 deaths per year, whose cancer-related deaths were among the first three (Tsoulfas et al., 2012; Maida et al., 2014; Scaggiante et al., 2014). In China, the liver cancers showed two significant characteristics: firstly, more than 90% were associated with obvious cirrhosis; secondly, the majority of patients have liver cancer treatment when the tumor has grown large enough. It is a large or giant liver cancer accounting for about 75% of patients with clinical diagnosis of liver cancers. The so-called large liver tumor refers to liver tumors with diameter ≥5 cm while the huge one refers to those with diameter >10 cm. Studies have shown that huge liver resection is safe and effective in treating HCC patients (Zhang et al., 2008; Bagi et al., 2012; Yang et al., 2013). Some scholars also believe that the huge and large liver cancers prone to cause enormous metastasis, especially to the small foci liver, which is the main reason for the short-term recurrence after surgery. Other scholars believe that large HCC has relatively unique clinical features, molecular pathological features, reduced invasion and recurrent rate. But the large and huge liver cancers taking over tremendous population of

Chinese has not been recognized by Western countries. So far, barcelona clinical liver cancer staging (BCLC) for treatment is the most popular therapy in Western countries (Graf et al., 2014; Jin et al., 2014; Yang et al., 2014). However, Asia (excluding Japan and Indonesia) and Western countries have a high degree of heterogeneity in HCC, such as etiology, staging, biology malignant behavior, diagnosis and treatment (therapeutic concepts and clinical practice guidelines) and prognosis (Joshita et al., 2010; Chow et al., 2013). Meanwhile, many surgeons in China believe that BCLC staging and therapeutic strategies for the control of surgical indications are too stringent to be suitable for Chinese national conditions and clinical practices (Shin et al., 2010). Based on this, the present studies intend to observe the efficacy of BCLC staging for the treatments of liver cancers and explore a better protocol for the huge selection of liver cancer treatments. This study retrospectively analyzed the data of 124 HCC patients with huge surgeries from January 2004 to December 2010, while surgical patients with HCC were also compared over the same period, and the results were reported as follows.

Materials and Methods

General data

A total of 124 huge HCC patients with surgical

[1]*Department of Hepatobiliary Surgery,* [2]*Department of Chemotherapy, The Affiliated Tumor Hospital of Guangxi Medical University, Nanning, Guangxi, China* [&]*Equal contributors* *For correspondence: ljyljy99@aliyuan.com*

resection diameter >10 cm from January 2004 to December 2010 in Cancer Hospital of Guangxi Medical University were selected in which there were 108 males and 16 females, aged 24~78 years, with median age being 45.0 years; 33.9% (42/124) of patients <40 years, 52.4% (65/124) among 40~60 years, and 13.7% (17/124) ≥60 years; pre-operative liver function: 119 were with Chlid-Pugh grade A and 5 with grade B; the median tumor diameter was 12.6 cm, in which 90 were among 10~15 cm and 30 were ≥15 cm; 77 with tumor growth and 47 without tumor shrinkage; of the patients with intra-hepatic metastasis, 91 with cirrhosis, 50 with portal vein tumor thrombus (PVTT) (naked or radiologically confirmed) and 29 with both cirrhosis and PVTT; 14 patients with ruptured preoperative tumor; of the 7 patients with merging adjacent tissues, 2 with invasion of the gallbladder serosa, 2 with invasion of the peritoneum, 2 with invasion of the diaphragm and 1 with invasion of the right kidney fat sac; 30 patients with high grade and 94 with other differentiation; 91 patients with margin from the tumor ≥1 cm and 33 <1 cm; 32 patients with OK ethanol injection of tumor margins and 47 with the line omentum sustained-release fluorouracil (human fluorine Ann); 67 patients with postoperative blood transfusion, 35 with postoperative prophylactic hepatic transcatheter arterial chemoembolization (TACE), 22 were treated after antiviral treatment and 25 after improved immunity treatment. The clinical data were completed. All patients were pathologically diagnosed with HCC without chemotherapies and radiotherapies before surgeries.

The study was approved by the Ethics Committee of Cancer Hospital of Guangxi Medical University.

Diagnostic and inclusion criteria

Diagnostic criteria: Referring to "Ministry of Health Diagnostic and Therapeutic Practices for Liver Cancers (2011 Edition)".

Inclusion criteria: ①Patients had been implemented with liver resection and the tumor diameter >10 cm; ②Patients were pathologically diagnosed with HCC; ③Patients who had radiotherapies or chemotherapies before inclusion; ④ Patients who had distant tumor metastasis.

Methods

Surgical approach: Of all patients, 65 with radical resection, 59 with palliative resection. Of the 40 patients with routine hepatectomy, 14 were with left liver resection, 15 with right liver resection, 6 with left lateral lobectomy and 5 with right posterior lobectomy. The 84 patients who had non- radical resection were given local excision. Liver resections were based on tumor size and scope of the residual liver function and the liver volume and staging, such as tumor invasion of adjacent organs, the liver resection combined invasion, etc..

Radical resection standard: ①The complete resection of the tumor was visible without residual tumor margins; ②The growth period of tumor ≤2 months on the liver or the leaf; ③No vein trunk and branch level, total liver pipe and a branch of hepatic vein and inferior vena cava tumor thrombus; ④No hilar lymph node metastasis; ⑤No extra-hepatic metastases; ⑥No tumor rupture.
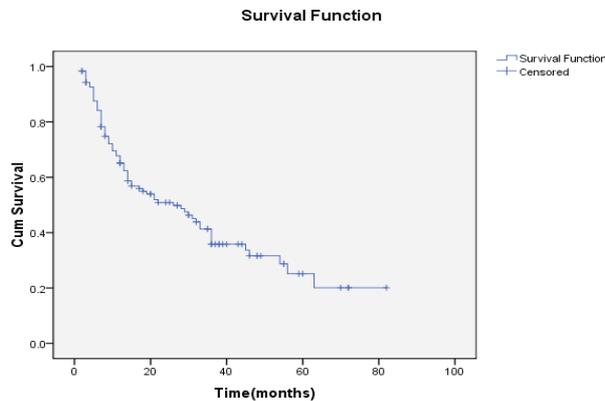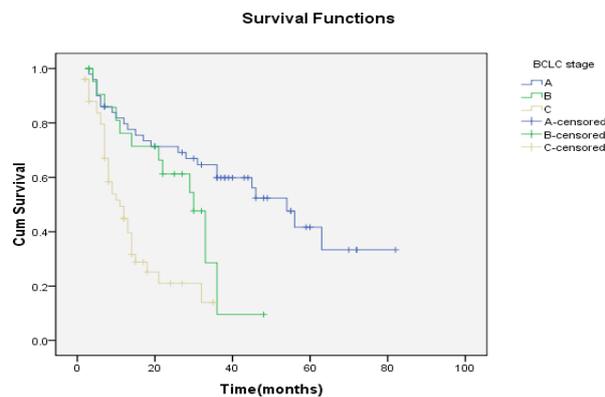
Preventive TACE: Preventive TACE was conducted in the postoperative January and imaged after no clear new or residual lesion was observed. TACE dosage: 5-fluorouracil 1 000~1 500 mg, cisplatin 80~100 mg, or epirubicin 40~60 mg; embolic agents: the amount of iodized oil

Table 1. The Detailed Features of HCC Patients

Factors		The number of cases
Gender	Female	16 (12.9)
	Male	108 (87.1)
Age/years	<60	107 (86.3)
	≥60	17 (13.7)
Abdominal symptoms	Negative	21 (16.9)
	Positive	103 (83.1)
HBsAg	Negative	22 (17.7)
	Positive	102 (82.3)
HCV-Ab	Negative	123 (99.2)
	Positive	1 (0.8)
Preoperative ALT/U·L-1	<40	46 (37.1)
	≥40	78 (62.9)
Preoperative AST/U·L-1	<40	24 (19.4)
	≥40	100 (80.6)
Child-pugh classification	B	5 (4.0)
	A	119 (96.0)
AFP (ng/mL)	<20	29 (23.4)
	≥20	95 (76.6)
Tumor size/cm	10~15	94 (75.8)
	≥15	30 (24.2)
Tumor capsule	No	47 (37.9)
	Damaged	77 (62.1)
Cirrhosis	No	33 (26.6)
	Yes	91 (73.4)
Adjacent tissue invasion	No	117 (94.4)
	Yes	7 (5.6)
Vascular invasion	No	73 (58.9)
	Yes	51 (41.1)
Preoperative tumor rupture	No	109 (87.9)
	Yes	15 (12.1)
Intra-hepatic metastasis	No	95 (76.6)
	Yes	29 (23.4)
Radical resection	No	52 (41.9)
	Yes	72 (58.1)
Routine removal	No	84 (67.7)
	Yes	40 (32.3)
Postoperative complications	No	88 (71.0)
	Yes	36 (29.0)
Distance from the tumor margin/cm	<1	32 (25.8)
	≥1	92 (74.2)
Margin ethanol injection	No	92 (74.2)
	Yes	32 (25.8)
Postoperative blood transfusion	No	57 (46.0)
	Yes	67 (54.0)
Pathologic differentiation	Other differentiation	92 (74.2)
	High-High-moderately differentiation	32 (25.8)
Prophylactic TACE	No	89 (71.8)
	Yes	35 (28.2)
After antiretroviral therapy	No	102 (82.3)
	Yes	22 (17.7)
Postoperative immunotherapy	No	99 (79.8)
	Yes	25 (20.2)
BCLC staging	A	50 (40.3)
	B	23 (18.5)
	C	51 (41.1)

Table 2. Average and Median Survival Time of Patients with BCLC-A, B and C

BCLC staging	Average survival time				Median survival time			
	Time/month	SD	95% CI		Time/month	SD	95% CI	
			Lower limit	Upper limit			Lower limit	Upper limit
A	48.167	4.720	38.917	57.418	54.000	6.534	41.194	66.806
B	26.350	2.991	20.489	32.212	30.000	4.017	22.127	37.873
C	14.663	1.709	11.312	18.013	11.000	2.175	6.737	15.263
Total	34.731	3.113	28.629	40.832	26.000	5.958	14.322	37.678

Figure 1. Survival Curves of 124 Patients

Figure 2. Survival Curves of Huge HCC Patients with BCLC-A, B and C

was 5~10 mL according to the patients' conditions. If the postoperative radiographic lesion was found to be explicit, non-preventive TACE should be considered.

Follow-up

The follow-up was ended on January 20th, 2014. The survival time was recorded monthly with surgery to the time of death or last follow-up as time prevail.

Statistical data analysis

SPSS16.0 statistical software was applied for all statistical analysis. The survival rate was calculated using the Kaplan-Meier method, while the univariate analysis was conducted with Log-rank test. $P<0.05$ was considered to be statistically significant.

Results

Peri-operative mortality and complications

Of the patients without perioperative mortality, postoperative complications accounted for 29.0%
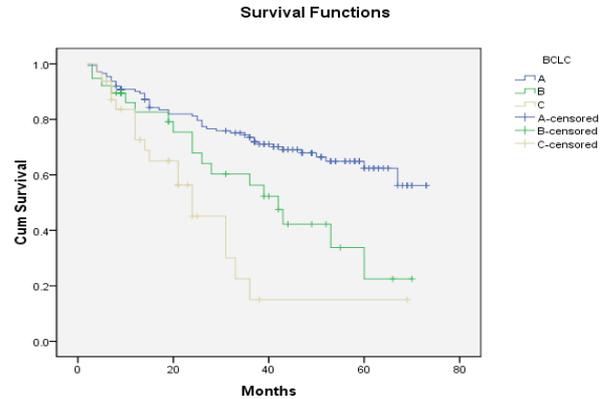
Figure 3. Survival Curves of Patients with HCC BCLC-A, B and C at Same Period

(36/124), in which 28 with pleural effusion pure, 2 with simple subphrenic effusion, 4 with subphrenic effusion and pleural effusion phrenic, 1 with subphrenic infection and 1 with liver dysfunction. The complications were all alleviated after treatment. The detailed features of HCC patients are shown in Table 1.

Huge HCC cumulative survival rate and survival time

Enormous cumulative total HCC survival and overall survival time: Of the 124 HCC patients with surgical treatment, the total 1-, 3- and 5-year survival rates were 65.1%, 35.8% and 25.1% (Figure 1), while the overall average and median survival time were 34.7 months and 26.0 months, respectively (Table 2).

The cumulative survival rate and survival time: The 1-, 3- and 5-year survival rates were 79.7%, 59.8%, 41.6% in patients with huge HCC BCLC-A and 76.2%, 9.5% and 0% in patients with huge HCC BCLC-B, while the 1- and 3-year survival time of BCLC-C patients were 44.9% and 0%, respectively (Figure 2), and the differences were all significant.

The average and the median survival time were 48.2 months and 54 months in patients with huge HCC BCLC-A, 26.4 months and 30 months in those with huge HCC BCLC-B and 14.7 months and 11 months in those with huge HCC BCLC-C, respectively.

Comparisons of the cumulative survival rate and survival time in BCLC-A, B, C patients

The 1-, 3- and 5-year survival rates were 90.1%, 73.5% and 62.4% in BCLC-A patients, 82.6%, 56.3% and 22.5% in BCLC-B patients, respectively and the 1- and 3-year survival rate were 72.7% and 15% in BCLC-C patients respectively (Figure 3).

The average and median survival time was 54.8 months

Table 3. COX Multivariate Analysis Results

Factors	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI	
							Lower limit	Upper limit
HBsAg	0.893	0.373	5.718	1.000	0.017	2.442	1.175	5.077
Tumor shrinkage	-0.352	0.254	1.924	1.000	0.165	0.703	0.428	1.156
Cirrhosis	0.588	0.298	3.883	1.000	0.049	1.800	1.003	3.230
Vascular invasion	0.244	0.639	0.146	1.000	0.703	1.276	0.365	4.463
Intra-hepatic metastasis	-0.690	0.349	3.911	1.000	0.058	0.502	0.253	0.994
Radical resection	-1.135	0.533	4.531	1.000	0.033	0.321	0.113	0.914
BCLC staging	0.223	0.439	0.259	1.000	0.611	1.250	0.529	2.953
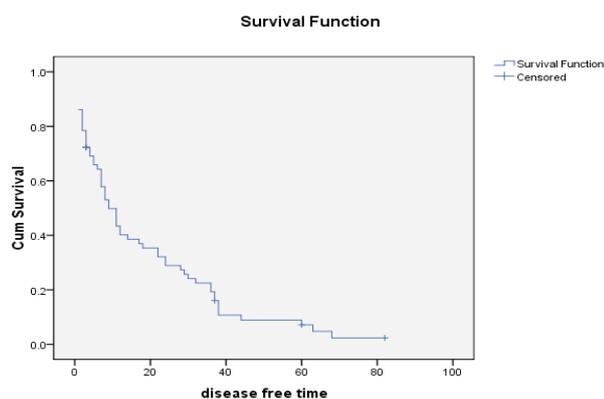
Figure 4. DFS Curves of Patients with Huge HCC

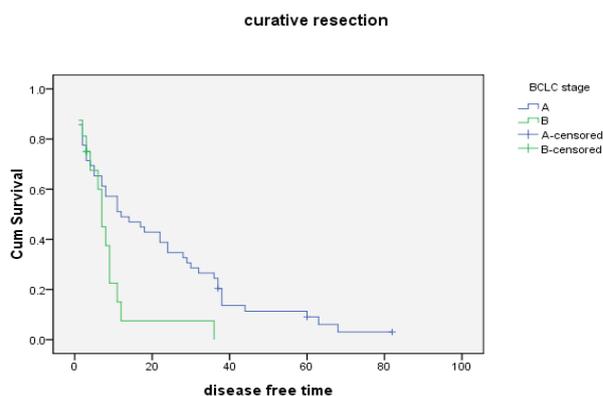**Figure 5. DFS Curves of Patients with Huge HCC BCLC-A and B**

and 54 months in BCLC-A postoperative patients in our department of the same period, 40.7 months and 42.0 months in BCLC-B and 28.2 months and 24.0 months in BCLC-C patients, respectively.

Huge HCC disease-free survival and disease-free survival time

The 1-, 3-, 5-year disease-free survival (DFS) rates of 73 patients with huge HCC radical resection were 40.2%, 19.3% and 7.1% (Figure 4), while the overall mean and median DFS time were 18.6 months and 9.0 months, respectively. However, the 1-, 3-, 5-year DFS rates were 49.0%, 24.5%, 9.1% in patients with huge HCC BCLC-A, while the 1- and 3-year DFS rates were 7.5% and 0% in patients with huge HCC BCLC-B after radical resection, respectively (Figure 5). Additionally, the mean and median DFS time were of huge HCC in BCLC-A 21.2 months and 12.0 months in patients with huge HCC BCLC-A and 8.6 months and 7.0 months in patients with huge HCC BCLC-B, respectively.

Prognostic factors

Univariate analysis showed that the prognosis of patients was closely related with vascular invasion (X^2=7.8065, P=0.0052), intra-hepatic metastasis (X^2=5.433, P=0.020), radical resection (X^2=6.4516, P=0.0111), tumor rupture before surgery (X^2=4.030, P=0.045), tumor shrinkage (X^2=4.165, P=0.041), HBsAg status (X^2=6.560, P=0.010) and cirrhosis (X^2=5.640, P=0.018), but had no association with the routine resection and margin distance. On COX multivariate analysis, the results showed that the HBsAg, cirrhosis and radical resection were the independent influencing factors of HCC patients (Table 3), whose influences on the survival time and DFS were shown in Figure 1~5.

Discussion

The HCC patients in this study were often accompanied by cirrhosis and hepatitis, so huge liver cancers are difficult problems for hepatobiliary surgeons, so how to determine the optimal surgery and surgical methods is dependent on the clinical physicians' experiences and confidences (Ren et al., 2012; Li et al., 2013; Li et al., 2013; Wang et al., 2013; Zhang et al., 2013; Yang et al., 2014). Therefore, in the preoperative selection and evaluation, how to fully anticipate the difficulties and dangers of surgery to prepare vascular repair, maximize the retention of normal liver tissue, make use of the reasonable choice and the hepatic vascular exclusion, and minimize intra-operative bleeding squeeze and reduce surgical mortality and complications of surgical treatment of liver cancer are key points (Hironori et al., 2008; Yang et al., 2010; Yamashita et al., 2011; Zhong et al., 2014).

In this study, no HCC patients with peri-operative mortality was recorded and 36 were with postoperative complications including 28 pleural effusion pure, 2 simple subphrenic effusion, 4 subphrenic effusion and pleural effusion, 1 subphrenic infection and 1 liver dysfunction, which were recovered after treatment before surgery, showing that after a reasonable assessment, the risk of huge liver resection was controllable.

In this study, the univariate analysis showed that with or without vascular huge liver invasion, intra-hepatic metastasis, radical resection, tumor rupture before surgery, tumor shrinkage, HBsAg status and liver cirrhosis were closely related with the prognosis ($P<0.05$), while the routine resection and margin distance had no connection with the prognosis. Before this study, the preoperative 1- and 3-year survival rates of patients with HCC BCLC-C

were 44.9% and 0%, and the average and median survival time were 14.7 months and 11 months respectively, whereas the BCLC-C over the same period of surgical resection were compared (the 1-, 3- and 5-year survival rates of BCLC-C patients were 72.7%, 15% and 0%, and the average and median survival time were 28.2 months and 24 months, respectively). The BCLC-C patients had poor prognosis, which might be associated with different parts of portal vein tumor thrombus, distant cutting edge or liver metastases and so on. In the BCLC staging, the number of tumor lesions was ≤3, if not described in the same liver segment, the tumor might have been transferred to the liver, and the liver cancer lesions were often huge and sometimes merged into multiple nodules. HCC patients sometimes had huge adhesions surrounding organs, sometimes with small parcels bleeding or abdominal hemorrhage. In the present study, these installments in Barcelona were not clearly described. In fact, these factors are likely to have impacts on HCC recurrence. Therefore, in this study, although the comparison with Barcelona staging was performed, the results might be biased since the details of the standard had not been fully refined.

In the present study, the total 1-, 3-, 5-year survival rates were 65.1%, 35.8%, 25.1% in patients with huge HCC, with the average and median survival time being 34.7 months and 26.0 months, respectively. According to BCLC standard restaging, the 1-, 3-, 5-year survival rates were 79.7%, 59.8% and 41.6% in patients with BCLC-A with the average and median survival time being 48.2 months and 54.0 months, respectively, and were 76.2%, 9.5% and 0% in patients with BCLC-B with the average and median survival time being 26.4 months and 30.0 months, respectively. In addition, the 1- and 3-year survival time were 44.9% and 0% in patients with BCLC-C with the average and median survival time being 14.7 months and 11.0 months, respectively. As can be seen from the above comparisons, the clinical efficacy of patients with huge HCC BCLC-A was the best after surgeries, although the 3-year survival rate of those with BCLC-B was low and the 5-year survival rate was 0%, the average and median survival times of were close with those with huge HCC. Although the long-term clinical efficacy of patients with BCLC-C was the worst, the 1-year survival rate was still 44.9%, indicating that as to huge HCC patients with vascular invasion, if the surgery could excise the tumors, the quality of life could also be improved and the short-term efficacy could be satisfactory though the long-term outcome was poor.

From time to tumor recurrence analysis, 1-, 3-, 5-year DFS of huge HCC patients after curative resection were 40.2%, 19.3%, 7.1% in patients with huge HCC. According to BCLC standard restaging, BCLC-A radical resection of patients with the 1-, 3-, 5-year DFS rates were 49.0%, 24.5%, 9.1% in patients with BCLC-A, while the 1- and 3-year ones were 7.5% and 0% in those with BCLC-B, indicating that the majority of huge HCC patients had tumor recurrence. This suggested the need of prophylactic TACE after huge HCC resection and regular review for the early detection of new liver lesions. However, the single factor analysis demonstrated that TACE after huge HCC resection had no association with

prognosis, and it was still unclear whether the case into the group stages was related. It is believed that prophylactic TACE should be recommended to patients with huge HCC after surgeries and the interval between each re-examination should not be too long. Univariate analysis also showed that the prognosis of patients was closely related with vascular invasion, intra-hepatic metastasis, radical resection, tumor rupture before surgery, with or without tumor shrinkage, HBsAg status and cirrhosis, but had no association with the routine resection and margin distance. Additionally, the multivariate analysis showed that the HBsAg, cirrhosis and radical resection were the independent influencing factors for HCC patients, which greatly influenced the survival time and DFS of patients with HCC BCLC A, B and C.

HCC is a brief main classification method in China, compared with the BCLC staging, for the blood vessels invasion (Que et al., 2014). The number of tumor lesion is not required, but the tumor is too large and close to major blood vessels, so few residual livers were left after liver resection with restricted margin (Arai et al., 2014). Surgical resection is difficult to achieve same effect similar to the same staging of BCLC. This study found that nearly half of the patients with huge HCC BCLC-C who had vascular invasion after surgical resection of liver tumors were still alive after 1 year's treatment, and the average and median survival time were 14.7 months and 11.0 months respectively, on which basis it was considered that even if BCLC-C patients, such as the patients who could tolerate surgery to remove the tumor, the surgery should remain as one option, which was supported by many experts (Cheng et al., 2009; Li et al., 2012).

To sum up, the classification of huge HCC has some limitations and the radical resection liver surgery security has been well improved, so it is believed that huge HCC surgery is safe and effective for HCC patients, and long-term survival is significantly better than those with non-surgical treatment, and the cirrhosis, radical resection and BCLC staging were important influencing factors for the diagnosis, treatment and prognosis of patients with huge HCC BCLC.

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