

## **Clinical prognosis observation and complications of hepatocellular carcinoma complicated with portal hypertension after hepatectomy.**

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### **Abstract**

**Objective:** To analyse the clinical curative effect and complications of primary hepatocellular carcinoma complicated with portal hypertension treated with hepatectomy.

**Methods:** The clinical data of 489 patients undergoing hepatectomy in our hospital were retrospectively analysed. Among them, 68 patients were complicated with portal hypertension (13.91%), and the remaining 421 patients were as control group without portal hypertension (86.09%). The postoperative complications, mortality, clinical baseline data, and survival rates were evaluated in two groups of patients, and the factors affecting survival were analysed with the Cox regression risk model.

**Results:** (1) Postoperative complications: observation group of 20.59% and control group of 13.54% ( $\chi^2=7.19$ ,  $P<0.05$ ). The mortality of the two groups was compared within the postoperative 30 d ( $\chi^2=2.91$ ,  $P>0.05$ ) and within 90 d after the operation ( $\chi^2=5.35$ ,  $P<0.05$ ); (2) The gender, age, tumor size, alpha-fetoprotein level, tumor histology, and margin of the two groups had no statistical difference ( $P>0.05$ ), while the difference of total bilirubin level, number of foci, cased of Child-PughB grade and albumin level were statistically significant ( $P<0.05$ ), using the Cox regression risk model, we found that only the number of cancer foci (OR=1.17, 95% CI: 0.90-1.732) and the diameter of tumor (OR=1.27, 95% CI: 0.984-1.844) were the independent risk factors ( $P<0.05$ ) affecting the mortality after hepatectomy in HCC patients with cirrhosis. (3) The survival rates of the control group at 1<sup>st</sup>, 2<sup>nd</sup>, 5<sup>th</sup> and 6<sup>th</sup> year after operation were 91.1%, 79.2%, 56.21% and 41% respectively, while 84.9%, 69.3%, 48.2% and 22.3% of the observation group. The two groups were statistically significant ( $P<0.05$ ).

**Conclusion:** Portal hypertension is not the absolute contraindication of radical resection of primary hepatocellular carcinoma. Small lesion hepatocellular carcinoma complicated with portal hypertension can choose the corresponding hepatectomy.

**Keywords:** Primary liver cancer, Portal hypertension, Hepatectomy, Survival rate, Risk factor.

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### **Introduction**

Primary Liver Cancer (PLC) ranks as the second leading cause of cancer death worldwide, among which HCC is one of the most lethal malignancies because of its high morbidity and mortality, as well as aggressiveness. An estimated 782500 new PLC cases and 745500 deaths occurred worldwide during 2012, with China alone accounting for about 50% of the total number of cases and deaths [1]. On the basis of the International Cancer Society survey in 2009, about 80% of patients with primary liver cancer are associated with hepatitis B virus [2,3]. The latest epidemiological survey demonstrated that more than 90% of patients with liver cancer had liver cirrhosis [4,5] 10% to 15% of patients with portal hypertension

[6]. Because the portal vein blood cannot flow back to the inferior vena cava through the liver, the effect of hepatectomy was directly affected. Some studies reported that synchronous hepatectomy and splenectomy should consider a choice of operation for PLC accompanied portal hypertension and hypersplenism. It may be safe with indication properly chosen and well treatment during the peri-operative period [7]. Another study showed that the patients with PLC undergoing simultaneous operation could acquire curative effect as compared with those who underwent hepatectomy. This operation is beneficial to the patients with poor liver function [8]. However, Barcelona stage (BCLC) clearly pointed out that venous hypertension is contraindicated in hepatectomy, the

recent breakthrough in this restricted area caused controversy. In this study, a number of 489 patients with hepatocellular carcinoma and liver cirrhosis underwent hepatectomy were analysed. Therefore, we aimed at analyzing the clinical curative effect and complications of primary hepatocellular carcinoma complicated with portal hypertension treated with hepatectomy.

## Clinical Treatment and Methods

### General data

489 patients with hepatocellular carcinoma and liver cirrhosis treated with hepatectomy in our hospital from January 2006 to January 2011 were enrolled in this study, including 298 males and 191 females, aged from 19 to 80 y old (average of  $49 \pm 6.9$ ). According to Child-Pugh, 301 cases were in A grade, 187 cases of B grade, and there were no Child-Pugh C grade patients. All patients were divided into control group (421 cases without portal hypertension) and observation group (68 patients with portal hypertension).

### Exclusion criteria

Patients will be excluded due to autoimmune, genetic metabolic liver disease, alcohol fatty liver, coronary heart disease, kidney disease, rheumatism, and diabetes. Patients who have received TACE (Trans-Catheter Arterial Chemo-Embolization) or recurred after liver resection, were combined with severe heart and brain n disease, and refused to sign informed consent will also be excluded [6].

### Inclusion criteria

1. Radical resection of liver cancer, and postoperative pathology confirmed liver cancer; 2. Not receive any new adjuvant therapy before surgery; 3. No heart and brain and other major organ disease; 4. No other malignancies 5 y before surgery and when liver cancer diagnosed; 5. Signed informed consent [4].

### Judgment standard for portal hypertension

Spleen is big, platelet count is less than  $10 \times 10^{10}/L$ , portal vein pressure and hepatic vein impaction pressure are 5 mmHg more than the inferior vena cava pressure; Hepatic Vein Pressure Gradient (HVPG) is more than 5 mmHg.

### Follow-up and observation indicators

All patients were reviewed 1 time a month within 3 months after discharge, then 1 time every 3 months. The diagnosis of recurrence was made by means of 2 imaging modalities or 1 imaging modalities combined with serum Alpha Fetoprotein (AFP), and the location and number of recurrences were recorded. Registration means the occurrence of death within 30 and 90 d after operation.

**Observation indicators:** Serum Alpha-Fetoprotein (AFP), liver color Doppler ultrasound, liver function. TACE was

performed 30 d after liver resection for patients with multiple lesions, small hepatocellular carcinoma, and visually impaired blood vessels. The follow-up period was 1 month to 8 y, with a median follow-up time of 3.4 y.

### Ethical consideration

The study was carried out in compliance with the Declaration of Helsinki of the World Medical Association, and according to a protocol approved by the Ethical Committee of Zigong Third People's Hospital, the approval number is 2006003. The objectives of the study were explained to the study participants and verbal consent was obtained before interviewing each participant.

### Statistical methods

SPSS18.0 was used for data analysis, measurement data was present as ( $\bar{x} \pm s$ ). The data were analysed by  $\chi^2$  test or t-test. The Shapiro-Wilk test and Levene test were employed for analysis of normal distribution and homogeneity of variance distribution. The group data was compared with  $\chi^2$  test or t-test. The cumulative survival rate was analysed with Kaplan-Meier,  $P < 0.05$  as the statistically significant difference, and the factors affecting P value were evaluated with Cox regression model.

## Results

### Postoperative complications and mortality

The Clavien-Dindo scoring system was used to determine the postoperative complications. There were 14 cases with complications (20.59%) in the observation group and 57 cases (13.54%) in the control group, with  $\chi^2 = 7.19$  and  $P = 0.04 < 0.05$ . The Statistics also found that only the complication of ascites ( $> 800$  ml/d) had significant difference with liver related diseases ( $P < 0.05$ ), the rest (pleural effusion, infection of incision, peritoneal effusion/abscess) had no significant difference between two groups ( $P > 0.05$ ). For 30 d mortality rate after surgery, 3 cases in the observation group were dead (4.41%); while 17 cases of death in the control group (4.04%), without significant difference between the two groups ( $\chi^2 = 2.91$ ,  $P = 0.18 > 0.05$ ); for 90 d mortality rate after operation, 8 cases in the observation group were dead (11.76%); while 21 cases of death in the control group (4.04%), with significant difference between the two groups ( $\chi^2 = 5.35$ ,  $P = 0.02 < 0.05$ ).

### Comparison of clinical data baseline of the two groups

There were no significant differences in gender, age, tumor size, alpha-fetoprotein level, tumor histology and margin of the two groups ( $P > 0.05$ ), while the total bilirubin level, the number of foci, the number of Child-Pugh B cases and albumin level had a significant difference ( $P < 0.05$ ). The Cox regression risk model was used to evaluate the difference in the number of foci and tumor diameter, which were independent risk factors

## Clinical prognosis observation and complications of hepatocellular carcinoma complicated with portal hypertension after hepatectomy

for mortality after hepatectomy in HCC patients with cirrhosis ( $P < 0.05$ ) (Tables 1 and 2).

**Table 1.** Comparison of clinical and pathological data of the two groups.

Factors	Control group		Observation group		$\chi^2$ value	P value
	Cases	%	Cases	%		
Male/female	259/162	61.52/38.48	39/29	57.35/42.65	3.72	0.18
$\geq 55$ y old/ $<55$ y old	113/308	26.84/73.16	18/50	26.47/73.53	4.09	0.32
HBsAg+/-	387/34	91.9/8.1	62/6	91.2/8.8	2.91	0.53
Child-Pugh A/B grade	386/35	92.4/7.6	66/2	97.06/2.94	2.11	0.02
Total bilirubin $>20$ $\mu\text{mol/L}$	162	38.48	11	16.17	5.54	0.04
Albumin $<35$ g/L	98	23.23	6	8.82	3.29	0.001
Liver resection range $>1$ segment of the liver	147	34.92	24	35.29	2.98	0.092
Diameter of tumor $\geq 5$ cm	138	32.78	30	44.12	3.92	0.035
AFP $>20$ ng/ml	86	20.43	23	33.82	5.23	0.29
High histologic differentiation of tumor	49	11.64	8	11.76	6.16	0.78
Incisal margin $>0.5$ cm	262	62.23	43	63.24	2.16	0.63
Number of cancer foci ( $\geq 3$ / $<3$ )	273/148	64.85/35.15	59/9	86.76/13.24	4.32	0.018
Splenectomy	80	19		22	32.35	0.028

**Table 2.** Analysis of factors affecting survival.

Factors	P value	RR (95% CI)	OR value
Child-Pugh A/B grade	0.63	1.27 (0.959-1.674)	2.35
Total bilirubin $>20$ $\mu\text{mol/L}$	0.56	1.98 (1.634-2.731)	1.92
Albumin $<35$ g/L	0.24	1.17 (0.90-1.732)	2.11
Tumor diameter $\geq 5$ cm	0.04	1.27 (0.984-1.844)	2.35
Number of cancer foci ( $\geq 3$ / $<3$ )	0.02	1.15 (0.933-1.673)	3.29
Splenectomy	0.12	1.19 (0.931-1.654)	2.96

### Comparison of survival rates in the two groups

The survival rates of the control group in the first, second, fifth and sixth year after surgery were 91.1%, 79.2%, 56.21% and 41% respectively, while in the observation group were 84.9%, 69.3%, 48.2% and 22.3%, with statistically significance ( $P < 0.05$ ).

### Discussion

Domestic and foreign studies [9,10] confirmed the value of hepatectomy in the treatment of primary liver cancer, but the 2005 US Liver Disease Research Association modified that BCLC clear HCC with portal hypertension was a contraindication to liver resection, the conclusion by BRUIXJ [11] limited the development of liver surgery, "anatomy of the restricted area" of hepatic surgery has also been breakthrough one by one.

The results of this study showed that there is no difference in the incidence of complications between the two groups, only complications of ascites and liver-related diseases were statistically significant ( $P < 0.05$ ). The divergent factors were analysed by Cox regression risk model, it was found that only the number of foci and the diameter of tumor were independent risk factors of death of HCC patients with liver cirrhosis after hepatectomy, indicating that portal hypertension is not a risk factor for prognosis of patients with hepatectomy. Yan et al. showed that the diameter of tumor  $<5$  cm had a good prognosis [12], which was consistent with our results. Therefore, we conclude that isolate HCC patients with portal hypertension and tumor diameter  $\leq 5$  cm can receive hepatectomy. For patients with primary liver cancer who have abnormal liver function and have more than 3 cancer foci or have a tumor size of more than 5 cm, the risk of complications will increase after hepatectomy, resulting in poor prognosis. The radiofrequency ablation or even liver transplant should be considered.

In all kinds of complications, esophageal variceal rupture and postoperative liver failure are the main complications. If the esophageal variceal rupture and postoperative liver failure can be in effective control, 90 d survival rate in patients will be greatly improved.

It has been confirmed that the coagulation dysfunction caused by hyperthyroidism is the direct cause of death in patients with primary liver cancer. According to the Cox risk model, it is found that splenectomy does not affect the prognostic risk factors. We believe that this is mainly when liver cancer occurs, apoptosis of spleen can synthesize large amounts of

tumor destruction factor is released into the blood to promote cancer cells, when splenectomy the blood tumor destruction factor still plays an antitumor immune function [13,14].

This study demonstrated that portal hypertension is not a contraindication of primary liver cancer patients receiving hepatectomy, but most of the complications are liver-related. The preoperative evaluation is very important to avoid postoperative liver-related complications to increase surgical safety and success, and patients of small lesion primary liver cancer complicated with portal hypertension can choose the corresponding liver resection.

### Limitations

Several limitations of this study should be considered. Firstly, this research was a cross-sectional study; the mechanism involved in the interactive effect is still unclear. Further studies are needed to unravel this. Secondly, the sample size is not big enough. However, the study setting is a modern, high level comprehensive medical institution with sophisticated clinical diagnosis facilities and medical record management. Thus, the data used can be deemed reliable.

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