

## **Curative effects and safeties of excision and interventional therapy as treatments for early intrahepatic recurrence and metastasis after primary hepatocellular carcinoma operation.**

**Yu-Jun Shi<sup>1</sup>, Wei Hu<sup>2\*</sup>, Lu-Jun Wang<sup>1</sup>, Jia-Fu Liu<sup>1</sup>**

<sup>1</sup>Department of General Surgery, People's Hospital of Anji, Huzhou, Zhejiang, PR China

<sup>2</sup>Department of Critical Care Medicine, Hangzhou First People's Hospital, Hangzhou, Zhejiang, PR China

### **Abstract**

**Objective:** This study aims to compare the effects of excision with those of interventional therapy on early postoperative intrahepatic recurrence and metastasis of primary hepatocellular carcinoma.

**Method:** A total of 80 patients with early postoperative intrahepatic recurrence and metastasis of primary hepatocellular carcinoma who were treated in our hospital from January 2012 to 2013 were equally divided into the operation group (n=40) and the intervention group (n=40) according to random number table method. The patients in the operation group were subjected to reoperation excision, whereas those in the intervention group were subjected to embolotherapy. The curative effects of the operation group were then compared with those of the intervention group.

**Results:** The one-, two-, and three-year survival rates of the patients in the observation group were significantly higher than those in the control group (P<0.05). No significant difference was observed between the White Blood Cell (WBC) and Alpha-Fetoprotein (AFP) levels of the two groups before treatment (P>0.05). The patients in the observation group had significantly higher WBC levels than the control group (P<0.05) after their respective treatments. Meanwhile, the AFP levels had opposite results (P<0.05). The liver fiber indexes in the observation group were significantly lower than those in the control group (P<0.05). Furthermore, no significant difference was observed between the occurrence rates of adverse reactions of the two groups (P>0.05).

**Conclusion:** Excision can improve the WBC and AFP levels of patients with early postoperative intrahepatic recurrence and metastasis of primary hepatocellular carcinoma. This method can also decrease the extent of fibrosis effectively and increase survival rate.

**Keywords:** Excision, Interventional embolization, Primary hepatocellular carcinoma.

*Accepted on April 1, 2017*

### **Introduction**

Primary hepatocellular carcinoma as a common malignant tumor occurring in China, causing high morbidity and mortality rates [1]. Although excision is often preferred for primary hepatocellular carcinoma treatment, it results in residual tumor cells and thus causes postoperative intrahepatic recurrence and metastasis. To date, the main therapeutic methods for recurrent hepatocellular carcinoma are mainly reoperation and interventional therapy [2,3]. The former can radically excise recurrent tumor tissues but causes great trauma to the patient. The latter exhibits fewer traumas to the patient but has adverse effects on normal hepatic cells and causes halfway embolism [4]. Therefore, the different effects of excision and interventional therapy performed as treatments for intrahepatic recurrence and metastasis in early postoperative period of primary hepatocellular carcinoma were compared and analysed in this study to provide reference for clinical treatment.

### **General Data and Method**

#### **General data**

A total of 80 patients were selected for the study. These patients were treated in our hospital from January 2012 to 2013 and exhibited early postoperative intrahepatic recurrence and metastasis of primary hepatocellular carcinoma. All the patients satisfied diagnostic criteria according to the computed tomography and pathological examination results. Patients with chronic diseases, mental diseases, and perceptual disorders were excluded. Permissions from Medical Ethics Committee of our hospital and informed consent forms were also signed by the patients. Random number method was used to equally divide patients into the operation and intervention groups (40 patients in each group). The observation group was composed of 25 male and 15 female patients with an average age of  $49.97 \pm 11.39$  years (range, 34-71 years). Its postoperative transfer time is within 3 and 24 months, with an

average transfer time of  $16.24 \pm 2.75$  months. The control group comprises 24 male and 16 female patients with an average age of  $49.25 \pm 12.44$  (range, 34-69 years). Its postoperative transfer time is within 4 and 22 months, with an average transfer time of  $16.77 \pm 2.68$  months. The differences between the two groups in terms of general data, such as gender, age, and transfer time, were non-significant ( $P > 0.05$ ).

### Therapeutic method

The patients in the operation group were subjected to reoperation therapy. The positions of recurrence and metastasis foci were observed. Primary incision or chevron offside incision below the dual-costal margins was adopted. Liver surface was freed. Adhesions between the liver and peritoneum and between the liver and omentum majus were separated to sufficiently expose the focus. The first porta hepatis was freed and placed in the sebific duct. Cancer focus excision was used to excise the central focus in the liver parenchyma. Irregular hepatic lobe excision and B-ultrasonic localization were also used in the operation.

The patients in the intervention group underwent interventional embolotherapy. After puncturing with Seldinger method, a 4ERH catheter was placed in the common hepatic artery. Then, 30 ml of nonionic contrast medium was injected at a flow velocity of 10 ml/s on the basis of the digital subtraction angiography of the entire liver. The 4FRH catheter was inserted to the left and right hepatic arteries, and then 1.0 g of 5-fluorouracil, 150 mg of oxaliplatin, 50 mg of azithromycin, 1.6 g of gemcitabine hydrochloride, and ultrafluid iodized mixture were instilled for chemoembolization. The treatment was performed five times at an interval of five weeks.

### Observation indexes

The observation indexes were as follows: post-treatment one, two, and three-year survival rate; WBC and AFP levels before and after treatment; liver fiber indexes (Laminin (LN), Hyaluronic Acid (HA), Hydroxyl-Propyl Cellulose III (HPC-III)), and Hydroxyl-Propyl Cellulose IV (HPC-IV); and occurrence of adverse reactions.

**Table 2.** Comparison between WBC and AFP levels before treatment and those after treatment.

Group	WBC ( $\times 10^9/L$ )		AFP (ug/L)	
	Before treatment	After treatment	Before treatment	After treatment
Observation Group (40)	$5.76 \pm 1.24$	$5.15 \pm 0.77$	$879.37 \pm 80.34$	$211.27 \pm 65.14$
Control Group (40)	$5.79 \pm 1.32$	$3.28 \pm 0.65$	$914.38 \pm 82.32$	$434.86 \pm 73.74$
$\chi^2$	0.105	11.737	1.925	14.372
P	0.917	0.000	0.058	0.000

### Statistical analysis

SPSS 22.0 was used for data analysis, and  $\bar{x} \pm S$  represents the measurement data. A t-test was conducted between the groups, and “%” represents the enumeration data. Then, a  $\chi^2$  test was performed. A difference with P value of  $< 0.05$  was considered statistically significant.

### Results

#### Comparison between the two groups in post-treatment survival rate

The one-, two-, and three-year survival rates of patients in the observation group were significantly higher than those in the control group ( $P < 0.05$ , Table 1).

**Table 1.** Comparison between the two groups in post-treatment survival rate.

Group	One year	Two years	Three years
Observation group (40)	31 (77.5%)	21 (50.5%)	12 (30%)
Control group (40)	23 (57.5%)	8 (20%)	5 (12.5%)
$\chi^2$	9.117	20.378	9.150
P	0.000	0.000	0.002

#### Comparison between the two groups in WBC and AFP levels before and after treatment

Differences between the two groups in WBC and AFP levels before and after treatment were not significant without statistical significance ( $P > 0.05$ ). WBC level of patients in the observation group after treatment was significantly higher than that in the control group ( $P < 0.05$ ). Meanwhile, AFP level in the observation group was significantly lower than that in the control group as seen specifically in Table 2.

*Curative effects and safeties of excision and interventional therapy as treatments for early intrahepatic recurrence and metastasis after primary hepatocellular carcinoma operation*

**Comparison between the two groups in liver fiber index**

Liver fiber indexes of patients in the observation group were significantly lower than those in the control group ( $P < 0.05$ , Table 3).

**Comparison between the two groups in adverse reaction**

In the observation group, four patients felt pain, three suffered bleeding, and five had intra-abdominal infection. The

occurrence rate of adverse reactions was 30%. In the control group, two patients suffered emesis, four had fever, two felt nausea, and two were infected with oesophagitis. The occurrence rate of adverse reactions being 25%. The occurrence rates of adverse reactions of the two groups had no significant difference ( $\chi^2 = 0.428$ ,  $P > 0.05$ ) (Table 4).

**Table 3.** Comparison between the two groups in liver fiber index.

Group	HA (ug/L)	HPC-III (ug/L)	HPC-IV (ug/L)	LN (ug/L)
Observation Group (40)	278.54 ± 67.24	219.82 ± 62.43	109.39 ± 37.31	118.68 ± 21.93
Control Group (40)	345.31 ± 73.41	283.27 ± 61.45	161.47 ± 39.29	156.72 ± 32.87
T	4.242	4.581	6.079	6.089
P	0.000	0.000	0.000	0.000

**Table 4.** Comparison between the two groups in adverse reactions.

Group	Pain	Bleeding	Intra-abdominal Infection	Emesis	Nausea	Oesophagitis	Fever	Occurrence rate of adverse reactions
Observation group (40)	4	3	5	0	0	0	0	30%
Control group (40)	0	0	0	2	2	2	4	25%
$\chi^2$	/	/	/	/	/	/	/	0.428
P	/	/	/	/	/	/	/	>0.05

**Discussion**

In recent years, morbidity rates caused by primary hepatocellular carcinoma in China have presented a rising tendency and thus the health of Chinese people is seriously threatened [5]. The clinical symptoms of primary hepatocellular carcinoma are extremely nontypical and often subtle. In fact, 70% of small hepatocellular carcinomas below 5 cm show no symptom, and approximately 70% of asymptomatic subclinical hepatocellular carcinomas are categorized as small hepatocellular carcinomas [6]. Therefore, the presence of symptoms indicates a large tumor. In such case, the disease tendency is generally rapid, and the disease usually presents cachexia within several groups. Moreover, affected patients often die of hepatic failure within several months or one year. The clinical manifestations of hepatocellular carcinoma are mainly lesions in the following aspects: manifestations of liver cirrhosis, such as occurrence of ascites and collateral circulation, hematemesis, and limb edema, and symptoms, such as weight loss, lack of strength in the entire body, hepatalgia, and liver swelling, which are generated by the tumor itself [7,8]. As found in any area across the world, chronic liver disease caused by any of these factors can play a

significant role in the occurrence and development of hepatocellular carcinoma.

To date, the most effective therapeutic method for hepatocellular carcinoma is excision as radical treatment. However, several studies have proven that operative treatment of primary hepatocellular carcinoma results in residual tumor cells and cancer cell metastasis within half a year or one year after the operation [9]. Among the complications of this treatment, intrahepatic reoccurrence and metastasis of primary hepatocellular carcinoma is the most common. Moreover, excision affects the curative effect of patients and decreases their survival rate after operation. The main therapeutic methods of recurrence and metastasis after radical operative treatment of primary hepatocellular carcinoma are excision, interventional embolization, radiotherapy, and microwave ablation [10]. Reoperation and interventional embolization are also the main clinical choices. The latter is a non-radical treatment method. The therapeutic mechanism mainly involves the interdiction of the blood supply for hepatoma cells and the subsequent administration of chemotherapeutics to kill the hepatoma cells. This procedure is the optimal therapeutic method when treatment cannot be tolerated. Thus, different effects of excision and interventional therapy used for the

treatment of early postoperative intrahepatic recurrence and metastasis of primary hepatocellular carcinoma were analysed in this study.

The following results were obtained in this study: the one-, two-, and three-year survival rates of the patients in the observation group were significantly higher than those in the control group ( $P < 0.05$ ). No significant difference was observed between the WBC and AFP levels of the two groups before treatment ( $P > 0.05$ ). After treatment, the WBC levels in the observation group were significantly higher than those in the control group ( $P < 0.05$ ). Meanwhile, the AFP levels had an opposite result ( $P < 0.05$ ). The liver fiber indexes in the observation group were significantly lower than those in the control group ( $P < 0.05$ ). The difference between the occurrence rates of adverse reaction of the two groups was non-significance ( $P > 0.05$ ). These results indicated that re-excision has a minimal effect on WBC level and can decrease AFP level. Furthermore, it can radically excise intrahepatic recurrence and metastasis foci. Meanwhile, although interventional embolization can also block the blood supply for the carcinoma cells, it cannot radically kill these cells because of the newly formed collateral circulation. Meanwhile, the present study was limited by the few number of observed cases and short duration of follow-up visit.

## Conclusion

Excision can improve the WBC and AFP levels of patients with intrahepatic recurrence and metastasis in early postoperative period of primary hepatocellular carcinoma. This treatment can also effective decrease the fibrosis level and increase the survival rates of the patients. However, some patients cannot tolerate operation and thus prefer interventional embolotherapy.

## References

- Miyoshi Y, Iwao K, Nagasawa Y, Aihara T, Sasaki Y. Activation of the beta-catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. *Cancer Res* 1998; 58: 2524-2527.
- Hu N, Hu Y, Zhu XF. Synthesis and evaluation of tetrahydroisoquinoline derivatives against human hepatoma carcinoma cell lines. *Lat Am J Pharm* 2017; 36: 192-195.
- Peng Y, Xu W. Assessment of right ventricular contraction by speckle tracking echocardiography in pulmonary hypertension patients. *Biomed Res Ind* 2017; 28: 173-177.
- Feitelson MA, Zhu M, Duan LX, London WT. Hepatitis B x antigen and p53 are associated in vitro and in liver tissues from patients with primary hepatocellular carcinoma. *Oncogene* 1993; 8: 1109-1117.
- Vanitha L, Suresh GR, Chandrasekar M, Punita P. Development of four stress levels in group stroop colour word test using HRV analysis. *Biomed Res Ind* 2017; 28: 98-105.
- Cui J, Zhou XD, Liu YK, Tan ZY, Zile MH. Abnormal  $\beta$ -catenin gene expression with invasiveness of primary hepatocellular carcinoma in China. *World J Gastroenterology* 2001; 7: 542-546.
- Bai X, Guan B, Liu M, Zhu Q, He Y, Wang P, Wang Y, Li Q. The antitumor effect of hederagenin on tumors growth of hepatocarcinoma (H22) tumor-bearing mice. *Lat Am J Pharm* 2017; 36: 142-150.
- Cong WM, Wu MC, Zhang XH, Chen H, Yuan JY. Primary hepatocellular carcinoma in women of mainland China. A clinicopathologic analysis of 104 patients. *Cancer* 1993; 71: 2941-2945.
- Jiang XW, Ge CX, Ge SF, Li WL. Potential bisphenol af-irinotecan interaction during the treatment of renal cell carcinoma. *Lat Am J Pharm* 2016; 35: 2036-2040.
- Sebastin AJS, Seldev C, Jereesha MSJ. Novel watermarking scheme with watermark encryption for copyright protection. *Biomed Res Ind* 2017; 28: 51-57.

## \*Correspondence to

Wei Hu

Department of Critical Care Medicine

Hangzhou First People's Hospital

PR China