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• *BRIEF REPORTS* •

Efficacy of different treatment strategies for hepatocellular carcinoma with portal vein tumor thrombosis

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Abstract

AIM: To evaluate the efficacy of different treatment strategies for hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) and investigate factors influencing prognosis.

METHODS: One hundred and seventy-nine HCC patients with macroscopic PVTT were enrolled in this study. They were divided into four groups and underwent different treatments: conservative treatment group (n = 18), chemotherapy group (n = 53), surgical resection group (n = 24) and surgical resection with postoperative chemotherapy group (n = 84). Survival rates of the patients were analyzed by the Kaplan-Meier method. A log-rank analysis was performed to identify group differences. Cox's proportional hazards model was used to analyze variables associated with survival.

RESULTS: The mean survival periods of the patients in four groups were 3.6, 7.3, 10.1, and 15.1 mo respectively. There were significant differences in the survival rates among the groups. The survival rates at 0.5-, 1-, 2-, and 3-year in surgical resection with postoperative chemotherapy group were 55.8%, 39.3%, 30.4%, and 15.6% respectively, which were significantly higher than those of other groups (P<0.001). Multivariate analysis revealed that the strategy of treatment (P<0.001) and the number of chemotherapy cycles (P = 0.012) were independent survival predictors for patients with HCC and PVTT.

CONCLUSION: Surgical resection of HCC and PVTT combined with postoperative chemotherapy or chemoembolization is the most effective therapeutic strategy for the patients who can tolerate operation. Multiple chemotherapeutic courses should be given postoperatively to the patients with good hepatic function reserve.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with the highest incidence in Asia and Africa[1]. HCC tends to invade the intrahepatic vasculature, especially the portal vein. Portal vein tumor thrombosis (PVTT) can be detected in 30.0% to 62.2% of patients with HCC[2-4]. Macroscopic tumor thrombus in portal vein appears to be the terminal stage of HCC, and is associated with the threat of bleeding of the esophageal varices, or liver failure[5,6]. The natural history of untreated HCC with PVTT is very poor. The median survival of such patients was reported to be 2.7 mo, whereas survival in those without PVTT was 24.4 mo[7,8]. Furthermore, it has been proved that portal vein invasion is correlated with intrahepatic metastasis and recurrence after treatment. The presence of tumor thrombus is correlated with poor prognosis[9-11]. The management of HCC with portal vein tumor thrombosis is complicated and controversial. PVTT was considered a relative or absolute contraindication to surgical resection. Only conservative and palliative treatments were available. With the improvement of surgical techniques and chemotherapy, many strategies have been used to treat HCC with PVTT. Some therapies have been reported to achieve promising results[3,12-16]. However, little has been done to assess the efficacy of different therapeutic strategies. In this study, we compared the clinical outcomes of different treatment strategies and investigate prognostic factors of patients with HCC and PVTT at our institution.

MATERIALS AND METHODS

Patients

The eligibility criteria were: (1) HCC with tumor thrombus in the first branch and/or main trunk of the portal vein confirmed by preoperative investigations or intraoperative exploration; (2) solitary or multiple tumors mainly located

in one lobe of the liver, and the PVTT can be removed together with the tumors in preoperative assessment; (3) no distant metastasis; (4) good or moderate hepatic function (Child-Pugh A or B); and (5) no contraindication to laparotomy.

From January 1997 to December 2002, 198 HCC patients with PVTT who met the eligibility criteria were treated at the Liver Cancer Institute, Digestive and Interventional Department of Zhongshan Hospital, Fudan University, China. Nineteen patients who were lost to follow-up were excluded. The remaining 179 were enrolled in the current study. There were 160 men and 19 women with a mean age of 47.46±10.8 years (range, 26-75 years). Serum hepatitis B surface antigen (HBsAg) was positive in 146 patients (81.6%), and hepatitis C antibody was positive in 5 patients. The α-fetoprotein (AFP) level was elevated in 149 cases (83.2%). Most of the patients had underlying cirrhosis (87.6%). According to the Child-Pugh classification, 135 patients (75.4%) were Child-Pugh A, 44 patients (24.6%) were Child-Pugh B. The tumor size was 10.5±3.2 cm (range, 3.0-22.0 cm) in diameter. Tumor thrombi involved in the first branch or extended to main trunk of portal vein. Written informed consent was obtained from all of the patients. Patients were followed until January 2004, or until the time of death.

Study design

One hundred and seventy-nine patients were divided into four groups and received different strategies of treatment: (1) conservative treatment group: traditional Chinese medicine or combined with immunotherapy was prescribed in 18 patients; (2) chemotherapy group: TACE or intraoperative hepatic artery ligation (HAL) combined with hepatic artery infusion (HAI) or portal vein infusion (PVI) were performed in 53 patients. Postoperative chemotherapy was performed through the hepatic artery or portal vein, and periodical chemoembolization through hepatic artery; (3) surgical resection group: tumors and PVTT were resected en bloc or thrombi were extracted from the portal vein after removal of the tumors in 24 patients; and (4) surgical resection combined with adjunctive chemotherapy group: hepatic arterial infusion chemotherapy (HAIC) and/or portal vein infusion chemotherapy (PVIC), transcatheter hepatic arterial chemoembolization (TACE), or selective percutaneous portal vein chemotherapy (SPVC) were performed in 84 patients after hepatectomy and thrombectomy.

Surgical procedure

Left lateral segmentectomy was performed in 7 patients, left hemi-hepatectomy in 20, left trilobectomy in 3, right partial hepatectomy in 43, right hemi-hepatectomy in 13, right trilobectomy in 2, partial median lobectomy in 5, combined left and right partial hepatectomy in 6, combined hepatic segmentectomy in 7, and complete caudate lobe resection and extended left lateral segmentectomy in 2 patients. PVTT was taken out in all cases underwent resection. Extrahepatic bile duct tumor thrombus was removed simultaneously in 6 patients, hepatic vein tumor thrombus in 5, the inferior vena cava tumor thrombus in 3, and superior mesenteric vein tumor thrombus in 1. The technique for tumor thrombus removal was as described previously[17].

Chemotherapy regimen

Each course of chemotherapy consisted of 1 000-1 500 mg 5-fluorouracil (5-FU), 80-100 mg cisplatin (CDDP), 8-20 mg mitomycin (MMC) or 40-60 mg epiadriamycin and 5-20 mL lipiodol. For TACE or SPVC, the drugs were administered in bolus injection. For HAIC and/or PVIC, they were administered via a subcutaneously implanted injection port either by intermittent injection or by a continuous infusion pump. Lipiodol was administered through hepatic artery. This procedure was repeated at one-month intervals according to patients' liver function and response to treatment. The number of chemotherapy cycles varied from 1 to 7.

Statistical analysis

Differences in clinicopathologic variables among the four groups were compared by the χ^2 test. Survival of the patients was analyzed by the Kaplan-Meier method, and comparison of the group differences was made by the log-rank test. Cox's proportional hazards model was used to analyze the variables associated with survival. Statistical analysis was carried out with SPSS software. $P<0.05$ was considered significant.

RESULTS

The clinical characteristics of 179 HCC patients with PVTT are summarized in Table 1. The clinicopathologic variables of the four groups were not statistically significant in terms of gender, age, Child-Pugh classification, tumor location, tumor size, tumor number, or location of tumor thrombus ($P>0.05$).

Survival periods

The survival of the four groups is presented in Table 2. The mean survival times of patients in conservative treatment group, chemotherapy group, surgical resection group, and surgical resection combined with adjunctive chemotherapy group were 3.6, 7.3, 10.1, and 15.1 mo respectively. The overall 0.5-, 1-, 2- and 3- year survival rates of the patients in the surgical resection combined with adjunctive chemotherapy group were 55.8%, 39.3%, 30.4%, and 15.6% respectively, which were the highest among the four groups ($P<0.001$). Survival periods of surgical resection group were significantly longer than those of conservative treatment group ($P = 0.001$). In addition, a statistically significant difference was found between surgical resection group and chemotherapy group ($P = 0.019$).

Factors influencing the survival after surgical resection

In the univariate analysis, variables that showed significant differences in survival for 108 patients who underwent surgical resection were tumor size and number of chemotherapy cycles (Table 3). None of the other variables, including number of tumors, tumor capsules, and location of tumor thrombus were significantly associated with

survival. Multivariate analysis with Cox's proportional hazards model identified only number of chemotherapy cycles was an independent prognostic factor for a favorable prognosis ($P = 0.008$), while tumor size was not.

Table 1 Clinical characteristics of 179 HCC patients with PVTT

Clinical characteristics	Conservative treatment ($n = 18$)	Chemo-therapy ($n = 53$)	Surgical resection ($n = 24$)	Surgical resection with chemotherapy ($n = 84$)	P
Gender					0.522
Male	15	49	20	76	
Female	3	4	4	8	
Age (yr)					0.510
<45	8	28	9	45	
⩾45	10	25	15	39	
Child-Pugh Class					0.731
A	12	39	18	66	
B	6	14	6	18	
Tumor location					0.351
Left lobe	3	6	5	22	
Right lobe	10	33	13	51	
Left and right lobe	4	13	6	9	
Caudate lobe	1	1	0	2	
Tumor size					0.430
<10 cm	6	25	13	45	
⩾10 cm	12	28	11	39	
Tumor number					0.715
1	11	33	14	58	
⩾2	7	20	10	26	
Tumor thrombus location					0.639
Left branch	3	7	4	18	
Left branch extending to main trunk	1	2	2	7	
Right branch	6	23	12	41	
Right branch extending to main trunk	4	10	4	11	
Left, right branch and main trunk	4	11	2	7	

Table 2 Survival periods and rates of different groups

Groups	Mean survival periods (mo)	0.5-yr survival rate (%)	1-yr survival rate (%)	2-yr survival rate (%)	3-yr survival rate (%)
Conservative treatment	3.6	5.5	0	0	0
Chemotherapy	7.3	34.6	11.8	0	0
Surgical resection	10.1	46.8	22.7	9.8	0
Surgical resection with chemotherapy	15.1	55.8	39.3	30.4	15.6

Table 3 Variables influencing postoperative survival of patients with HCC and PVTT

Influent variables	Survival periods (mo) mean±SD	P
Tumor size		
<10 cm	19.2±3.26	0.037
⩾10 cm	12.8±2.47	
Number of chemotherapy cycles		
0	8.6±1.68	0.006
1	11.9±2.24	
2	16.7±2.98	
⩾3	23.1±4.32	

Prognostic factors for PVTT patients

Pretreatment and treatment variables of all 179 patients with PVTT were analyzed by the Cox's proportional hazards model. Multivariate analysis showed that the strategy of treatment ($P<0.001$) and the number of chemotherapy cycles ($P = 0.012$) were independent survival predictors for patients with HCC and PVTT.

DISCUSSION

Efficacy of surgical resection for HCC with PVTT

Prognosis is extremely poor in patients with HCC complicated with PVTT[7,8]. Different treatments have been tried, to improve the survival of those patients. Some investigators reported the safety and efficacy of TACE for HCC with portal vein tumor thrombosis; however, the 5-year survival rate of the patients was only 0-16.8%[18,19]. These data indicate that TACE is not effective in treating portal vein tumor thrombosis. It was suggested that surgical resection provided more satisfactory results. Ohkubo *et al*[3] presented the report of surgical resection for 47 patients with PVTT. The postoperative 1-, 3-, and 5-year survival rates were 53.9%, 33.2%, 23.9% respectively. The prognosis was better if the tumor was less than 10 cm and had no intrahepatic metastases. Minagawa *et al*[20] also reported the efficacy of surgical treatment in HCC patients with PVTT. The mean survival time of the 18 patients who underwent surgical resection was 3.4±2.7 years, and postoperative 1-, 3- and 5-year survival rates were 82.0%, 42.0% and 42.0% respectively, whereas the mean survival time of 27 patients of chemotherapy group was 0.36±0.26 years. Multivariate analysis indicated that surgical resection is a positive prognostic factor. We previously reported that hepatic resection combined with thrombectomy was performed in 79 patients with HCC and PVTT at our institute, and the median survival time was 12 mo, while the median survival time of 18 patients in HAI or TACE group was 5 mo. The postoperative 1-, 3-, and 5-year survival rates were 53.9%, 26.9% and 16.6% in surgical resection group *vs* 22.2%, 5.6% and 0% in the HAI or TACE group respectively[17]. These results were in agreement with those of others. In this study, patients of surgical resection group and surgical resection combined with adjunctive chemotherapy group had higher survival rates than those of conservative treatment group or chemotherapy group. Cox's multivariate analysis also showed that the strategy of treatment was an independent survival predictor for patients with HCC and PVTT. We believe that the benefits of tumor and thrombus resection en bloc or hepatectomy plus thrombectomy are as follows: (1) decrease of portal vein pressure and prevention of intractable ascites and esophageal varices bleeding; (2) recovery of blood flow of portal vein and improvement of liver function; (3) reducing the tumor burden and increasing the efficacy of postoperative multimodality treatments such as HAI, PVI, TACE and biotherapy; and (4) improvement of quality of life and survival rate of the patients[13,21,22]. Therefore, surgical resection is an effective therapy for HCC with PVTT.

Necessity of postoperative chemotherapy

The major cause of postoperative death in the patients with

PVTT was cancer recurrence in the remnant liver[3,20,23]. The possible causes of HCC recurrence after surgical resection include invisible intrahepatic metastases present preoperatively in the remnant liver, dissemination of tumor cells during surgical manipulation, and multicentric origin of the tumor. It is widely accepted that intrahepatic metastasis, by the portal venous system, is an important mechanism for intrahepatic recurrence[9,24,25]. Adjuvant chemotherapy after hepatic resection may effectively kill residual microscopic tumor cells in the remnant liver and circulation. Lipiodol was also used because of its selective accumulation in tumors when delivered intraarterially and being a carrier for anticancer drugs[10,18,26]. Recent reports have presented favorable results of using adjunctive chemotherapy or chemoembolization after operation for PVTT patients. In our previous study, we reported that 58 patients with HCC with tumor thrombus in the first branch of portal vein underwent surgical resection and 24 patients received operation combined with periodical PVI and/or HAI, chemoembolization or TACE. The median survival time of the first group was 13 mo, and the postoperative 1-, 3- and 5-year survival rates were 59.7%, 27.4%, 8.8% respectively, whereas the median survival time of the second group was 16.5 mo and 1-, 3- and 5-year survival rates were 79.2%, 54.6% and 42.0% respectively; the difference between the two groups was significant[27]. Similar results have been published by Fukuda *et al*[23]. He reported that the overall 3-year survival rate was 48.5% for 19 HCC patients with tumor thrombi in the main portal vein, inferior vena cava and extrahepatic bile duct, who had received postoperative hepatic arterial infusion chemotherapy, and 5 patients survived more than 5 years after the operation. In the present study, the overall 0.5-, 1-, 2- and 3-year survival rates of the patients in the surgical resection combined with adjunctive chemotherapy group were 55.8%, 39.3%, 30.4% and 15.6% respectively. However, the overall 0.5-, 1-, 2- and 3- year survival rates of patients underwent surgical resection alone were 46.8%, 22.7%, 9.8% and 0% respectively. Our results indicate that postoperative adjunctive chemotherapy can reduce recurrence and is indispensable to prolonging survival. Thus, adjunctive chemotherapy should be recommended after operation in attempts to eliminate micrometastases that might be present at the time of operation or malignant cells shed during surgical manipulation of the tumor.

Prognostic factors related to survival of patients with HCC and PVTT

In this study, multivariate analysis with Cox's proportional hazards model identified the strategy of treatment and the number of postoperative chemotherapy cycles were independent prognostic factors for a favorable prognosis of patients with HCC and PVTT. The strategy of treatment influencing the survival had been well discussed above. Multiple chemotherapy courses also prolonged the survival of the patients with HCC and PVTT. We believe that the explanation for this phenomenon is that the cytotoxic effects of chemotherapy drugs usually follow log cell kill kinetics[28]. Cell killing, therefore, is proportional. Tumor cells cannot be eliminated by only one course of chemotherapy. If multiple treatments cycles are given, the opportunity to kill the residual tumor cells will increase, and the better prognosis may achieve. However, chemotherapy or chemoembolization may damage the remnant liver parenchyma, especially in cirrhotic patients, which result in impairment or deterioration of liver function[29,30]. Consequently, the number of the chemotherapy cycles will be decided according to patients' hepatic function and response to the treatment. With careful monitoring, repeated chemotherapy or chemoembolization is safe and effective.

In conclusion, surgical resection combined with postoperative adjunctive chemotherapy is the most effective therapeutic strategy for HCC patients with PVTT when liver function is compensative. If hepatic reserve is permitted, repeated adjunctive chemotherapy or chemoembolization after operation could be recommended to prolong the survival of the patients. Further prospective randomized controlled studies with large case numbers are required to support our findings.

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