

RESEARCH COMMUNICATION

Prognostic Analysis for Treatment Modalities in Hepatocellular Carcinomas with Portal Vein Tumor Thrombi

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Abstract

Objective: To assess prognostic aspects of treatment modalities for cases of hepatocellular carcinoma (HCC) with portal vein tumor thrombi (PVTT). **Method:** 121 treated cases were retrospectively divided into five groups: 1 (liver transplantation); 2 (transcatheter arterial chemoembolization); 3 (hepatectomy plus thrombectomy); 4 (hepatectomy plus thrombectomy combined with adjuvant chemobiotherapy via portal vein); and 5 (conservative treatment). The Kaplan-Meier method with difference in survival estimated by Log-rank test was used to compare between groups. **Result:** Groups 1-5 had a significantly differing median survival times of 7, 7, 10, 16, 3 months ($P<0.05$), respectively. One- and three-year survival rates were 30.0% and 10.0%, 20.0% and 0.0%, 47.0% and 22.0%, 70% and 20%, and 12% and 4%. **Conclusion:** Surgical resection combined with adjuvant chemotherapy via the portal vein is an effective and safe treatment modality for hepatocellular carcinoma with portal vein tumor thrombi.

Keywords: Hepatocellular carcinoma - portal vein tumor thrombus - surgical therapy - treatment modality

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in Asian countries. HCC has a propensity for invading the portal venous system, with an incidence of portal venous tumor thrombi (PVTT) in 62% of autopsies and 14% of surgically treated patients. PVTT indicates an advanced stage of the disease and is associated with risk of esophageal variceal bleeding and liver failure. PVTT is the key factor in intrahepatic invasion and prognostic. Llovet reported a median survival time of 2.7 months for HCC patients with PVTT. Hepatic resection, liver transplantation and transcatheter arterial chemoembolization (TACE) are the common treatment in clinical practice. Some study reported that the postoperative survival rate became increased year by year for the patients who undergo hepatic resection or TACE or liver transplantation, respectively. But the most effective treatment strategy for HCC with PVTT remains to be established. The aim of the present retrospective study was to investigate postoperative prognostic factor and to propose a surgical treatment strategy for the HCC patients with PVTT.

Materials and Methods

Patient selection

From January 2003 to June 2010, 121 patients were performed on HCC patients with PVTT in our institution.

In all patients, preoperative ultrasonography (US) and computed tomography (CT) were performed. From evaluation of these images by more than one experienced radiologist (for CT) or surgeon (for US), PVTT was confirmed macroscopically and microscopically. Of all patients, 114 were male and 7 were female, and their ages ranged from 10 to 86 years (50.0 ± 11.91 years). Hepatitis B surface antigen was positive in 114 cases (94.2%). Increased level of alpha-fetoprotein (AFP) was found in 72 patients (59.5%). Liver cirrhosis occurred in 105 patients (86.8%). The liver tumor was located on the left lobe in 23 patients, on the right lobe in 78 patients, and on bilateral lobes in 20 patients. According to Child-Pugh classification, liver function grade A was shown in 73 patients, grade B was shown in 36 patients, and grade C was shown in 12 patients. Single tumor is shown in 69 patients, and multiple tumors are shown in 52 patients. Tumor thrombus was found on the main trunk in 57 patients, on the first-order branch in 64 patients.

According to the different treatment, all patients were divided into 5 groups: Group1 (liver transplantation), Group2 (transcatheter arterial chemoembolization), Group3 (hepatectomy plus thrombectomy), Group4 (hepatectomy plus thrombectomy combined with adjuvant chemobiotherapy via portal vein), Group5 (conservative treatment). Between the five groups (Table 1), the number of age, gender, Hepatitis B surface, AFP, liver cirrhosis, tumor location, and thrombus location were compared and not considered significant ($P>0.05$). There were

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Table 1. Comparison of the Clinical Data of 5 Groups of HCC with PVTT

Variables	Group1	Group2	Group3	Group4	Group5	P value
Age(years)						
<50	10	5	22	12	10	0.073
≥50	2	5	16	19	20	
Gender						
male	12	10	35	31	26	0.153
female	0	0	3	0	4	
HBV(+)						
yes	12	10	36	30	26	0.300
no	0	0	2	1	4	
AFP(ng/ml)						
<400	4	1	14	16	14	0.172
≥400	8	9	24	15	16	
Liver cirrhosis						
yes	10	9	35	28	23	0.940
no	2	1	3	3	7	
Child-pugh						
A	5	4	27	28	9	<0.001
B	5	6	11	3	11	
C	2	0	0	0	10	
Tumor size						
<5cm	12	8	13	12	12	<0.001
≥5cm	0	2	25	19	18	
Tumor number						
single	4	3	27	20	15	0.039
multiple	8	7	11	11	15	
Tumor location of liver						
left lobe	1	1	8	8	5	0.659
right lobe	9	7	27	17	18	
left and right	2	2	3	6	7	
Thrombus location of PV						
main trunk	6	4	25	12	10	0.068
First-order branch	6	6	13	19	20	

Group1, Liver transplantation group; Group2, TACE group; Group3, Hepatectomy plus thrombectomy group; Group4, Hepatectomy plus group thrombectomy combined with adjuvant chemobiotherapy via portal vein group; Group5, Conservative treatment group

significantly differenceS between Child-Pugh class, tumor size and tumor number($P<0.05$).

Treatment modalities for patients

Liver transplantation: Donors were pathogen-negative and non-heart-beating donors without histories of liver or other major organ disease. We obtained grafts by rapid technique and preserved the grafts following University of Wisconsin solution. The liver grafts' back-table word and the recipients' liver resections were implemented with conventional methods. Selection of surgical procedures depended on the recipients' intraoperative specific situations. Major were classical orthotopic liver transplantation combined with veno-venous bypass. Part was performed with piggyback orthotopic liver transplantation.

Transcatheter arterial chemoembolization (TACE): With the 10 patients under local lidocaine anesthesia and aseptic conditions, the femoral artery was catheterized (Cook Inc, USA) using the Seldinger technique. A 4F to 5F catheter (Cobra, Cook Inc) was introduced into the femoral artery. Under fluoroscopy, the catheter was

manipulated into the celiac axis and superior mesenteric artery. Arteriography was performed to demonstrate the feeding arterials, tumor stain, and thrombus in the portal vein. The dilution of chemotherapeutic agents 5-fluorouracil (500 mg/m²) and adriamycin(30mg/m²) was infused through this catheter. The main artery supplying the tumor was embolized with gelatin sponge particles (1 mm³) after chemotherapy infusion. Super liquefying lipiodol and gelatin sponge particles were used to embolize the end arteries until near complete stasis of blood flow. The course was repeated once every 1 to 2 months for 2 to 5 cycles.

Hepatectomy plus thrombectomy

Hepatectomy plus thrombectomy were preformed in 38 patients. Regular lobectomy or segmentectomy was performed in patients with adequate liver function reserve. Otherwise, limited irregular hepatectomy was performed. Regarding removal of the PVTT, the thrombus was resected together with the liver when the thrombus was confined within the resected liver. In all patients, intraoperative US was performed after PVTT removal to determine whether the tumor thrombus had been removal completely from the portal vein.

Hepatectomy plus thrombectomy combined with adjuvant chemobiotherapy via portal vein

Regular segmentectomy was performed in patients with adequate liver function reserve. Regarding removal of the PVTT, the thrombus was resected together with the liver when the thrombus was confined within the resected liver. Adjuvant chemobiotherapy via portal vein was performed after the thrombectomy. Chemotherapy regimen was as follows: 5-fluorouracil(500mg/m²) and adriamycin(30mg/m²). This procedure was administered in the first year and repeated every 2 months after postoperative 1 year.

Conservative treatment

30 patients who did not agree with the surgical and invasive treatment have taken the conservative treatment which was mainly the drugs protecting liver.

For statistical analysis, postoperative survival curves calculated by the Kaplan-Meier method and log-rank test were used for univariate analysis of prognostic factor, the Cox proportional hazard model was used for multivariate analysis of prognostic factors, and the Pearson Chi-squared test was used to assess the relation between each prognostic factor and the frequency of postoperative sever complications. A value of $p<0.05$ was considered significant. All analyses were performed using SPSS version 16.0 for windows.

Results

Using univariate analysis, possible correlations between survival time and 8 dichotomized variables and 2 trichotomized variables with known values for all 121 patients were evaluated (Table 2). Table 2 shows prognostic factors correlate negatively with survival time: age, gender, positivity for HBV surface antigen, AFP, liver

Table 2. Univariate Analysis of Prognostic Factors

Variables	n	Median survival(months)	P value
Age(years)			
<50	59	8	0.667
≥50	62	7	
Gender			
male	114	8	0.564
female	7	5	
HBV(+)			
yes	7	0	0.248
no	114	8	
AFP(ng/ml)			
<400	49	6	0.618
≥400	72	8	
Liver cirrhosis			
yes	105	8	0.103
no	16	3	
Child-pugh			
A	73	11	0.005
B	36	6	
C	12	3	
Tumor size			
<5cm	57	13	0.017
≥5cm	64	7	
Tumor number			
single	69	9	0.011
multiple	52	7	
Tumor location of liver			
left lobe	23	15	0.377
right lobe	78	7	
left and right	20	12	
Thrombus location of PV			
main trunk	57	13	0.308
First-order branch	64	6	

Prognostic factors correlate negatively with survival time: age, gender, positivity for HBV surface antigen, AFP, liver cirrhosis, tumor location, thrombus location, but Child-Pugh class, tumor size and tumor number remained as independent predictors of poor survival in each group

cirrhosis, tumor location, thrombus location, but Child-Pugh class, tumor size and tumor number remained as independent predictors of poor survival in each group.

Cox proportional hazards model demonstrated that modalities of treatment were independent prognostic factor for cumulative survival, with an odds ratio (OR)

of 2.006 (95%CI=0.604-0.801, $P<0.001$)

Using Kaplan-Meier method and log-rank test, the outcome of survival analysis was obtained: Group1(liver transplantation), Group2(TACE), Group3(hepatectomy plus thrombectomy), Group4 (hepatectomy plus thrombectomy combined with adjuvant chemobiotherapy via portal vein) and Group5(conservative treatment) had a significantly median survival time which were 7,7,10,16,3 months($P<0.05$), respectively. One-, Three-year survival rates were 30.0% and 10.0%, 20.0% and 0.0%, 47.0% and 22.0%, 70% and 20%, 12% and 4%, respectively. In the survival curves (Figure 1), we can see that 5 groups were compared and considered significant ($P<0.05$).

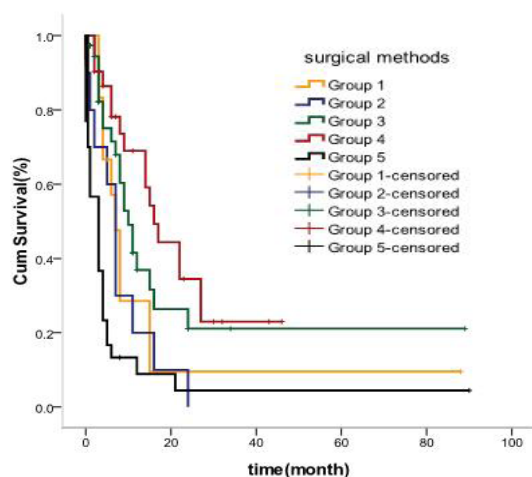
Discussion

In HCC patients with PVTT detected in preoperative imaging, it is quite important to determine a treatment strategy. A previous study found that a substantial number of patients had an extremely poor prognosis (e.g., several months), whereas some patients survived for several years or more. In clinical practice, some investigators found that 60%-90% of late stage HCC had been defined a PVTT. Hepatic resection, liver transplantation and transcatheter arterial chemoembolization (TACE) are the common treatment in clinical practice. The effective treatment of HCC with PVTT still remains a major challenge. In our study, different modalities of treatment led to different prognostic assessment:

Hepatectomy plus thrombectomy: Surgical resection with complete extirpation of tumor gives the best chance of a cure for patients with HCC. Hepatectomy plus thrombectomy can clearly improved the survival of HCC patients with PVTT, especially for the tumor thrombus located in the main trunk of portal vein. The benefits of tumor and thrombus resection en bloc or hepatectomy plus thrombectomy could be summarized as follows: (1) decrease in 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 TACE; and (4) improvement of quality of life and survival rate of the patients. Therefore, surgical resection was an effective therapy that could help to improve the survival for HCC patients with PVTT.

Liver transplantation: Liver transplantation is theoretically ideal because it eliminates not only the existing HCC, but also the precancerous damaged liver itself. With the development of technology and clinical experience, it has been an effective treatment. In our series, estimated survival rates for 1, 3 years were better in liver transplantation (30% and 10%, respectively) than the conservative treatment (12% and 4%, respectively). Significant difference suggests that liver transplantation can improve the survival time of HCC patients with PVTT.

Transcatheter arterial chemoembolization (TACE): Investigators found that TACE could be safely performed even in HCC patients with PVTT as long as good hepatic reserve and collateral circulation around the portal trunk were present. Some studies, as a multimodal treatment for

**Figure 1. Kaplan-Meier Survival Curves**

HCC patients with PVTT, we found TACE treatment can obviously cause the center of tumor and tumor thrombus necrosis. In the procedure, TACE always insure the blood supply. TACE was introduced as a palliative local therapeutic option for the treatment of unresectable HCC. The goal of palliation is to control symptoms, improve life quality and prolong survival. Our study have investigate the predictors of survival after TACE and concluded that the 1, 3 years postoperative survival rate was 20%, 0%.

Hepatectomy plus thrombectomy combined with adjuvant chemobiotherapy via portal vein: Fukuda has reported that hepatectomy plus thrombectomy combined with adjuvant chemobiotherapy via portal vein, the postoperative 3 years survival rate of 19 HCC patients with PVTT was 48.5%, especially 5 cases have survived 5 years. Some study, the median survival time was 6.4 months, which were better than the single hepatectomy plus thrombectomy. Liang et al. (2008) has reported that the median survival time of those HCC patients with PVTT who adjuvant postoperative chemoembolization was 11.5 months, better than the hepatectomy plus thrombectomy. In our study, 1 and 3 years survival rate was 70.0% and 20.0%, respectively, obviously higher than hepatectomy plus thrombectomy, TACE, liver transplantation and conservative treatment.

In conclusion, the results of our study confirmed that surgical removal of the main tumor and PVTT, combining with the adjuvant therapy, significantly improved the survival of HCC patients with PVTT.

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