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# Multimodality treatment in hepatocellular carcinoma patients with tumor thrombi in portal vein

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**Subject headings** carcinoma, hepatocellular/therapy; neoplasm circulating cells; portal vein; antineoplastic agents; combined modality therapy; chemoembolization, therapeutic

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## Abstract

**AIM To compare the therapeutic effect and significances of multimodality treatment for hepatocellular carcinoma (HCC) with tumor thrombi in portal vein (PVTT).**

**METHODS HCC patients (*n* = 147) with tumor thrombi in the main portal vein or the first branch of portal vein were divided into four groups by the several therapeutic methods. There were conservative treatment group in 18 out of patients (group A); and hepatic artery ligation (HAL) and/or hepatic artery infusion (HAI) group in 18 patients (group B), in whom postoberative chemoembolization was done periodically; group of removal of HCC with PVTT in 79 (group C) and group of transcatheter hepatic arterial chemoembolization (TACE) or HAI and/or portal vein infusion (PVI) after operation in 32 (group D).**

**RESULTS The median survival period was 12 months in our series and the 1-, 3-, and 5-year survival rates were 44.3%, 24.5% and 15.2%, respectively. The median survival times were 2, 5, 12 and 16 months in group A, B, C and D, respectively. The 1-, 3- and 5-year survival rates were 5.6%, 0% and 0% in group A; 22.2%, 5. 6% and 0% in group B; 53.9%, 26.9% and 16.6% in group C; 79.3%, 38.9% and 26.8% in group D, respectively. Significant difference appeared in the survival rates among the groups (*P*<05).**

**CONCLUSION Hepatic resection with removal of tumor thrombi and HCC should increase the curative effects and be encouraged for the prolongation of life span and quality of life for HCC patients with PVTT, whereas the best therapeutic method for HCC with PVTT is with regional hepatic chemotherapy or chemoemblization after hepatic resection with removal of tumor thrombi.**

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## INTRODUCTION

Hepatocellular carcinoma (HCC) with tumor thrombi in the main trunk or the first branch of the portal vein would be considered to be advanced stage of liver cancer[1], which often results in intrahepatic metastasis and can only be treated with conservative or non-operative methods such as per oral chemotherapy, biotherapy, traditional Chinese medicine, etc. In China, some patients even give up all the therapeutic methods for HCC. The majority of those patients usually die of liver failure or bleeding of the upper digestive tract within several months[2,3]. In recent decade, the active therapeutic measure for HCC with tumor thrombi in portal vein (PVTT) was performed at the Liver Cancer Institute of Shanghai Medical University, i. e., hepatic resection with removal of PVTT. After the operation, some patients obtained satisfactory curative effects through transcatheter chemotherapy or transcatheter hepatic arterial chemoembolization (TACE), or hepatic artery infusion (HAI) and/or portal vein infusion of chemotherapeutic agents (PVI).

## MATERIALS AND METHODS

### *Patients*

By December 1996, 147 patients with pathologically proven HCC with tumor thrombi in the main trunk or the first branch of the portal vein had been treated at the Liver Cancer Institute of Shanghai Medical University. Among them, 144 were males and 3 females, the median age was 48. 2 years (ranged from 20 to 70 years). Serum hepatitis B surface antigen was found positive in 123 cases (83.7%). Coexisting cirrhosis was found in 138

cases (93.9%): macronodular cirrhosis (cirrhotic nodule >3 mm) in 81 patients and micronodular cirrhosis (cirrhotic nodule ⩽3 mm) in 57 patients. Alpha-fetoprotein (AFP) levels were elevated (21-16 000 μg·L$^{-1}$) in 120 cases (81.6%). The tumors were situated in the left lobe in 53 cases, the right lobe in 61 and both lobes in 33.

### Groups of patients

One hundred and forty-seven patients were divided into 4 groups. Group A: conservative treatment group, receiving only oral medications of chemotherapy or Chinese herbal decoction and supporting treatment, 18 cases; Group B: hepatic artery ligation (HAL) and/or HAI or PVI (postoperative chemotherapy through hepatic artery or portal vein, and periodical chemoembolization through hepatic artery), 18 cases; Group C: removal of HCC with PVTT in 79 cases; among them, 5 patients were lost to follow-up. The tumors and tumor thrombi were resected simultaneously or tumor thrombi were extracted from the portal vein after removal of the tumors for the HCC patients with PVTT; Group D: Intrahepatic arterial chemoembolization or chemotherapy and/or intraportal chemotherapy by catheterization or TACE were periodically performed after resection of HCC with PVTT in 32 cases; among them, 3 cases were lost to follow-up.

### Location of tumor thrombi

Fifty-one cases had tumor thrombi in left branch of portal vein, 47 in right branch, 10 in both branches, 14 in left branch extending to the main portal vein, 9 in right branch extending to the main trunk of portal vein, and 16 in both branches and the main portal vein.

### Comparison of clinical data in different groups in HCC patients with PVTT

These data are shown in Table 1, indicating that there were no statistical differences between groups.

**Table 1 Comparison of several treatments groups for HCC with PVTT**

| | Group A ($n$ = 18) | Group B ($n$ = 18) | Group C ($n$ = 74) | Group D ($n$ = 29) | $P$ |
|---|---|---|---|---|---|
| Tumor diameter | | | | | |
| <10 cm | 2 | 5 | 39 | 14 | NS |
| ⩾10 cm | 16 | 13 | 35 | 15 | |
| Tumor number | | | | | |
| Single | 7 | 13 | 46 | 18 | NS |
| ⩾2 | 11 | 5 | 28 | 11 | |
| Encapsulation | | | | | |
| Well | 1 | 3 | 16 | 5 | NS |
| Poor | 17 | 15 | 58 | 24 | |
| PVTT in main trunk | | | | | |
| - | 6 | 12 | 58 | 24 | NS |
| + | 12 | 6 | 16 | 5 | |

NS: no significance statistically.

### Resection of HCC and catheterization after resection

Resection of left lateral lobe was performed in 18 cases, resection of left lateral lobe and partial right hepatic resection in 3, left hemihepatectomy in 40, left trilobectomy in 9, resection of hepatic medial lobe in 3, right hemihepatectomy in 4 and right partial hepatectomy in 34. PVI was followed by resection in 5 cases, HAI in 7 and HAI + PVI in 9. The catheters were cannulated into the hepatic artery and portal vein, and the ports were completely implanted beneath the abdominal wall.

### Treatment methods for PVTT

For the tumor thrombi in left branch of portal vein, the right branch of portal vein was detached at first and then ligated by using a cotton ribbon or a fine rubber tube. The purpose was to prevent spreading of cancer cells of tumor thrombi from the left branch of portal vein to the right lobe during the resection or PVTT removal. After resection of left lateral lobe or left hemihepatectomy, the tumor thrombi were taken out from the stump of left branch of portal vein and irrigation was done with physiological saline, then the stump of portal vein was sutured and the ligature of the right branch of portal vein was released.

For tumor thrombi in the right branch of portal vein, the treatment for HCC with PVTT was similar to that in the left branch.

For the tumor thrombi in both branches of portal vein, the stump of one branch of portal vein was exposed after resection of liver cancer in left or right lobe, the hepatoduodenal ligament was ligated to block the blood flow entering the liver, and then the tumor thrombi were sucked or taken out through the stump.

For the tumor thrombi in the left or right branch of portal vein extending to the main trunk, the liver cancer in left or right lobe was removed first after detaching and ligating the right or left branch of portal vein, the stump of portal vein was clipped, then the main portal vein over the duodenum was gently held by the thumb and index finger. While the stump was being loosened, the tumor thrombi would flow out with the on-going portal blood flow.

For the tumor thrombi in both branches and the main trunk of portal vein, the tumor thrombi were sucked through the stump of one branch of portal vein, while pressing the opposite branch with an index finger for preventing dissemination of tumor cells. If the tumor thrombi were difficult to be sucked or taken out, the main portal vein should be detached. A longitudinal incision of 1.5 to 2.0 cm was made on anterior or right vascular wall of the main trunk of portal vein, and then the tumor thrombi were taken out directly. After the operation, B-mode ultrasonography was performed to make out whether the tumor thrombi had been

removed completely from the portal vein.

### *Chemotherapy after operation*

Group D: After operation, 11 patients received 1 to 3 times of TAI or TACE (median 1.5 times) and other 21 patients received 2 to 4 times (median 2.5 times) of HAI and/or PVI or hepatic arterial chemoembolization (HAE). Group B: All patients were treated by HAI or HAE and/or PVI 1 to 4 times (median 2 times). The dosages of chemotherapy in HAI or TAI and/or PVI were 5-fluorouracil (5-Fu) 1 000 mg, mitomycin (MMC) 12 to 20 mg and cisplatin or carborlatinum 80 mg, and lipoidal 5 mL in group D to 20 mL in group B of lipiodol was used in the TACE or HAE.

### *Statistical method*

All the data were calculated with the digital Cox model and the limit of significant difference was $P<0.05$.

## RESULTS

### *Curative effects of several therapeutic methods for HCC patients with PVTT*

Among the series, the follow-up survey was lost in 8 cases. The median survival period of the 139 patients was 12 months, and the 1-, 3 and 5- year survival rates were 44.3%, 24.5% and 15.3% respectively. The median survival period and the 1, 3 and 5- year survival rates in different groups are shown in Table 2.

**Table 2 Survival time and rates of patients with PVTT**

| | Group A ($n$ = 18) | Group B ($n$ = 18) | Group C ($n$ = 74) | Group D ($n$ = 29) |
|---|---|---|---|---|
| Median survival periods (months) | 2.0 | 5.0 | 12.0 | 16.0 |
| Survival rates | | | | |
| 1-year(%) | 5.6 | 22.2 | 53.9[a2] | 79.3[a1] |
| 3-year (%) | 0 | 5.6 | 26.9[a2] | 38.9[a1] |
| 5-year(%) | 0 | 0 | 16.6[a2] | 26.8[a1] |

[a1]$P<0.05$, *vs* Group C, B and A; [a2]$P<0.05$, *vs* Group B and C.

**Table 3 Survival time and rates of patients with the tumor thrombi in the main trunk and the first branch of portal vein**

| | Tumor thrombi in the main trunk | | | | Tumor thrombi in the first branch | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr.A ($n$ = 12) | Gr.B ($n$ = 6) | Gr.C ($n$ = 16) | Gr.D ($n$ = 5) | Gr.A ($n$ = 6) | Gr.B ($n$ = 12) | Gr.C ($n$ = 58) | Gr.D ($n$ = 24) |
| MST* (months) | 2.0 | 5.5 | 8.0 | 16.0 | 2.0 | 5.0 | 13.0 | 16.5 |
| Survival rate | | | | | | | | |
| 1-year(%) | 8.3 | 33.3 | 29.4 | 80.0 | 0 | 16.7 | 59.7 | 79.2 |
| 3-year (%) | 0 | 0 | 14.3 | 20.0 | 0 | 8.3 | 27.4 | 54.6 |
| 5-year(%) | 0 | 0 | 11.1 | 0 | 0 | 0 | 8.8 | 42.0 |

* MST: median survival time.

### *Curative effects between PVTT in the main trunk and the first branch*

Table 3 shows the results of multimodality treatment in patients with tumor thrombi in the main trunk and the first branch of portal vein. It indicates that the results of treatment in patients with PVTT in the first branch were better than that in patients with PVTT in the main trunk in groups C and D.

### *Curative effects and factors influencing the prognosis of the patients*

after resection of HCC with PVTT (Table 4) The results of resection followed by chemotherapy or chemoembolization in patients with a diameter of tumor mass less than 10 cm, without tumor thrombi in the main portal vein were better than those in patients with diameter of more than 10 cm, with tumor thombi in the main portal vein and without chemotherapy or chemoembolization after resection.

**Table 4 Curative effects and factors influencing the prognosis of patients after removal of HCC with PVTT**

| | Patients | 1-year(%) | 3-year(%) | 5-year(%) | $P$ |
|---|---|---|---|---|---|
| Removal of PVTT | 103 | 61.7 | 32.3 | 22.4 | |
| Tumor diameter | | | | | |
| <10 cm | 53 | 64.2 | 41.5 | 27.0 | 0.014[a1] |
| ⩾10 cm | 50 | 59.7 | 25.2 | 19.3 | |
| PVTT in main trunk | | | | | |
| - | 82 | 66.3 | 36.9 | 26.1 | 0.027[a2] |
| + | 21 | 42.9 | 14.3 | 8.6 | |
| Encapsulation | | | | | |
| Well | 21 | 75.6 | 30.9 | 8.6 | 0.928 |
| Poor | 82 | 58.4 | 32.9 | 26.7 | |
| Chemotherapy or chemoembolization after operation | | | | | |
| No | 74 | 53.9 | 26.9 | 16.6 | 0.012[a3] |
| Yes | 29 | 79.3 | 38.9 | 26.8 | |
| Tumor number | | | | | |
| Single | 64 | 59.4 | 27.7 | 18.7 | 0.561 |
| ⩾2 | 39 | 65.4 | 38.7 | 27.7 | |

[a1]$P<0.05$ *vs* ⩾10 cm group; [a2]$P<0.05$ *vs* PVTT in main trunk (+) group; [a3]$P<0.05$ *vs* chemotherapy or chemoembolization after operation (yes) group.

## DISCUSSION

HCC with tumor thrombi in the main trunk or the first branch of the portal vein is considered to be a late stage of liver cancer, lacking in ideal therapeutic measures. The treatment was often given up in former times. As the majority of the patients with HCC have been in advanced stage when first seen, a large probortion of the patients are associated with tumor thrombi in the main trunk or the first branch of the portal vein. Therefore, it is very important to explore effective therapeutic methods for HCC with PVTT and to raise the survival rates of these patients.

Until now, the treatments for HCC with PVTT are limited. In the medical literaures about the treatments of HCC with PVTT, there were the following methods: TACE, PVI, percutaneous ethanol injection in tumor thrombi, TACE + radiotherapy and surgical removal of tumor thrombi etc. Chung *et al*[4] reported that the 1 and 2-year survival rates were 30% and 18% respectively in 110 HCC patients with PVTT by TACE. Katsumori *et*

*al*[5] reported that the 3-year survival rate was 44% in 9 cases of tumor thrombi in the main portal vein by hepatic arterial chemotherapy through the implanted ports beneath the abdominal wall. It was also reported that the percutaneous ethanol injection in PVTT and TACE + radiotherapy gave satisfactory curative effects for PVTT[6-8]. There were only a few papers about the resection of HCC with removal of tumor thrombi in the main trunk or the first branch of the portal vein[9,10]. Yamaoka *et al*[9] adopted 5 resection modes for PVTT. The operative mortality of 29 patients with PVTT was 11%, and the 1, 2 and 3-year survival rates after operation were 52.2%, 23. 2%, and 11.6%, respectively. Four different procedures were used for the patients with PVTT in our series, and the results revealed poor efficacy in the conservative treatment group. The median survival time was only 2 months (group A). The best curative effect was in group of removal of HCC with PVTT + HAI and/or PVI or TACE (group D). The median survival time was 16 months and the 5-year survival rate was 26.8%. For this reason, if the tumors with PVTT are limited in the left or right lobe of liver and liver function as evaluated is able to tolerate the operation, we should adopt active therapeutic procedure. The best try should be made for removal of HCC with PVTT and hepatic regional chemotherapy or chemoembolization are periodically performed after operation. This procedure can further raise the treatment efficacy and prolong the survival for the HCC patients with PVTT.

The conservative treatment (only per oral chemotherapy or Chinese herbal decoctions) can not inhibit or kill cancer cells in the HCC patients with PVTT. Rapid progression of liver cancer will result in death in a short time due to liver failure or portal hypertension, with vigorous variceal bleeding. Among 18 patients undergoing conservative treatment, 12 cases died of vigorous bleeding of upper digestive tract within 3 months and only one case had the longest survival of 13 months. Although the survival time of 18 patients treated with HAL and/or HAI were shorter, the curative efficacy was better than that of conservative treatment group. The 1-year survival rate was 22.2%. Perhaps the periodical hepatic artery chemotherapy or chemoembolization can inhibit the tumor growth in various degrees and result in partial necrosis of tumor thrombi. The results of Katsumori[5] and Ando[11] also support this viewpoint. The result in the group of removal of HCC and PVTT (Group C) was evidently better than those of Groups A and B, the median survival time being 12 months and the 1, 3 and 5-year survival rates being 53.9%, 26.9%, 16.6% respectively. If HCC is limited to one lobe and the residual liver is estimated to be functionally efficient, we should first choose surgical resections for the patients with PVTT. The residual cancer and residual tumor thrombi are primary factors influencing the survival of the HCC patients with PVTT. According to patient's conditions, periodical HAI/PVI or TACE are effective methods to improve the survival rate after operation. In the group of HAI/ PVI or TACE after resection of HCC with PVTT (group D), the median survival time was 16 months and the 1, 3, and 5-year survival rates were 79.3%, 38.9%, 26.8% respectively. The result was better than the other three groups. These results indicate that the best therapeutic method is sequential regional hepatic chemotherapy or TACE after surgical removal of HCC and PVTT. Table 3 shows curative effects in HCC patients with tumor thrombi in the main trunk of portal vein were inferior to those in patients with tumor thrombi in the first branch. The tumor thrombi in the main trunk represent the disease in advanced stage, which is often accompanied with tumor thrombi in both branches and disseminated foci in the opposite side of liver. Moreover, the resection of thrombi in the main trunk of portal vein may lead to cancer cell dissemination or incomplete extermination and rapid formation of thrombi in the main trunk after operation. The above factors cause the poor efficacy for HCC patients with tumor thrombi in the main trunk of portal vein, and poor quality of life than those with tumor thrombi in the first branch.

It has been convinced that the factors influencing curative effects for HCC with PVTT such as location of tumor thrombi (in the main trunk or the first branch of portal vein), tumor size and regional hepatic chemotherapy, etc. To our experience, the treatment methods for removal of tumor thrombi are closely related to the efficacy. Before operation, we must find out the scope of tumorthrombi with ultrasonography, CT or magnetic resonance angiography (MRA). During resection, we should block the blood flow of portal vein into liver or blood flow of the opposite branch, suck the tumor thrombi completely as far as possible and not break it. Then, we scrape off with curet the residual tumor thrombi attached on the vascular wall, and perform repeated irrigation and exsuction with physiological saline. Furthermore, anticoagulant injections through the portal vein during several postoperative days may also be an effective procedure to prevent and reduce the rapid recurrence of thrombi in the portal vein[12,13].

The therapeutic methods for HCC with PVTT are still at the investigative stage. Such patients occupy a considerable proportion in the liver cancer clinic. As PVTT is an important factor resulting in intrahepatic metastasis and recurrence after operation, it will be very valuable to study the mechanism of the PVTT formation in HCC patients and to explore more effective treatment measures for prolonging survival and improving their quality of life.

## REFERENCES


1 Mitsunobu M, Toyosaka A, Oriyama T, Okamoto E, Nakao N. Intrahepatic metastases in hepatocellular carcinoma: the role of the portal vein as an efferent vessel. *Clin Exp Metastasis*, 1996; 14:520-529

2 Yu YQ, Xu DB, Zheng YX, Zhang BH. Resection of hepatocellular carcinoma with tumor thrombi for the patients with hepatocellular carcinoma-report of 25 cases. *Zhongguo Shiyong Waike Zazhi*, 1994;14:18-19

3 Pirisi M, Avellini C, Fabris C, Scott C, Bardus P, Soardo G, Beltrami CA, Bartoli E. Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy study. *J Cancer Res Clin Oncol*, 1998;124:397-400

4 Chung JW, Park JH, Han JK, Choi BI, Han MC. Hepatocellular carcinoma and portal vein invasion: results of treatment with transcatheter oily chemoembolization. *Am J Roentgenol*, 1995;165:315-321

5 Katsumori T, Fujita M, Takahashi T, Satoh O, Ichijima S, Nakamura T, Morishita H, Ohno K, Nakano Y, Maeda T. Effective segmental chemoembolization of advanced hepatocellular carcinoma with tumor thrombus in the portal vein. *Cardiovasc Intervent Radiol*, 1995;18:217-221

6 Livraghi T, Grigioni W, Mazziotti A, Sangalli G, Vettori C. Percutaneous alcohol injection of portal thrombosis in hepatocellular carcinoma: a new possible treatment. *Tumori*, 1990;76:394-397

7 Chen SC, Lian SL, Chang WY. The effect of external radiotherapy in treatment of portal vein invasion in hepatocellular carcinoma. *Cancer Chemother Pharmacol*, 1994;33:S124-127

8 Raoul JL, Guyader D, Bretagne JF, Heautot JF, Duvauferrier R, Bourguet P, Bekhechi D, Deugnier YM, Gosselin M. Prospective randomized trial of chemoembolization versus intra-arterial injection of $^{131}$I-labeled-iodized oil in the treatment of hepatocellular carcinoma. *Hepatology*, 1997;26:1156-1161

9 Yamaoka Y, Kumada K, Ino K, Takayasu T, Shimahara Y, Mori K, Tanaka A, Morimo to T, Taki Y, Washida M, Manaka D, Hayashi M, Fujita T, Ozawa K. Liver resection for hepatocellular carcinoma (HCC) with direct removal of tumor thrombi in the main portal vein. *World J Surg*, 1992;16:1172-1177

10 Tanaka A, Morimoto T, Yamaoka Y. Implications of surgical trea tment for advanced hepatocellular carcinoma with tumor thrombi in the portal vein. *Hepatogastroenterology*, 1996;43: 637-643

11 Ando E, Yamashita F, Tanaka M, Tanikawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. *Cancer*, 1997;79: 1890-1896

12 Gurgey A, Buyukpamukcu M, Baskut C, Yalcin B, Gogus S.Portal vein thrombosis in association with factor V Leiden mutation in a patient with hepatocellular carcinoma. *Med Pediatr Oncol*, 1997; 29:224-225

13 Engelberg H. Actions of heparin that may affect the malignant process. *Cancer*, 1999;85:257-272


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