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Growth velocity of the portal vein tumor thrombus accelerated by its progression, alpha-fetoprotein level, and liver fibrosis stage in patients with hepatocellular carcinoma

Hidetoshi Gon, MD, PhD[a,*], Masahiro Kido, MD, PhD[a], Motofumi Tanaka, MD, PhD[a], Hisoka Kinoshita, MD, PhD[a], Shohei Komatsu, MD, PhD[a], Daisuke Tsugawa, MD, PhD[a], Masahide Awazu, MD, PhD[a], Hirochika Toyama, MD, PhD[a], Ippei Matsumoto, MD, PhD[b], Tomoo Itoh, MD, PhD[c], Takumi Fukumoto, MD, PhD[a]

[a] Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan
[b] Department of Surgery, Kindai University, Faculty of Medicine, Osaka-Sayama, Osaka, Japan
[c] Division of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

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ABSTRACT

Background: Progression of portal vein tumor thrombus directly affects the prognosis and treatment for patients with hepatocellular carcinoma; there are no data on the growth velocity of portal vein tumor thrombus. We analyzed the growth velocity of portal vein tumor thrombus and its risk factors to propose the best timing of surgical treatment for hepatocellular carcinoma with portal vein tumor thrombus.
Methods: We retrospectively collected data on 57 hepatocellular carcinoma patients with portal vein tumor thrombus who underwent computed tomography twice preoperatively and hepatectomy between 2005 and 2015. To calculate the growth velocity of portal vein tumor thrombus, migration lengths of portal vein tumor thrombus were divided by the number of days. To identify risk factors for rapid growth of portal vein tumor thrombus, patients were classified according to the velocity: rapid ($\geq$ 1.0 mm/day, $n = 23$) and slow ($<$ 1.0 mm/day, $n = 34$).
Results: Median survival times of patients with portal vein tumor thrombus that invaded the ipsilateral second portal branch, ipsilateral first portal branch, and portal trunk were 42.9, 11.7, and 12.3 months, respectively. The average growth velocity of portal vein tumor thrombus was 0.9 $\pm$ 1.0 mm/day. Median estimated times required from ipsilateral second portal branch to ipsilateral first portal branch and ipsilateral first portal branch to portal trunk were 8.2 and 11.5 days, respectively. Liver fibrosis, alpha-fetoprotein, and extent of portal vein tumor thrombus were independent risk factors for rapid progression of portal vein tumor thrombus. Proteins induced by vitamin K absence or antagonist II, extent of portal vein tumor thrombus, and liver fibrosis, not rapid growth of portal vein tumor thrombus, were independent prognostic factors.
Conclusion: An understanding of the rapid progression of portal vein tumor thrombus and its risk factors can be helpful in deciding an appropriate timing of surgical treatment for hepatocellular carcinoma with portal vein tumor thrombus.

Background

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide.[1] In the patients with advanced HCC, portal vein tumor thrombus (PVTT) is one of the most serious factors associated with poor prognosis, which easily accelerates growth of intrahepatic and extrahepatic metastases.[2–4] In addition, PVTT extending into the main portal vein aggravates portal vein hypertension and causes a life-threatening sequence of events, such as massive ascites or variceal hemorrhage. These complications sometimes hamper effective treatments. As a result, the natural history of patients with HCC and PVTT reveal a median survival time of only 9 to 10 weeks.[2,5]

Although the current standard treatment for the patients with HCC and PVTT (Barcelona clinic liver cancer stage C) is target

* Corresponding author: Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Graduate School of Medicine, Kobe University, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.
E-mail address: hidetoshi541128@gmail.com (H. Gon).

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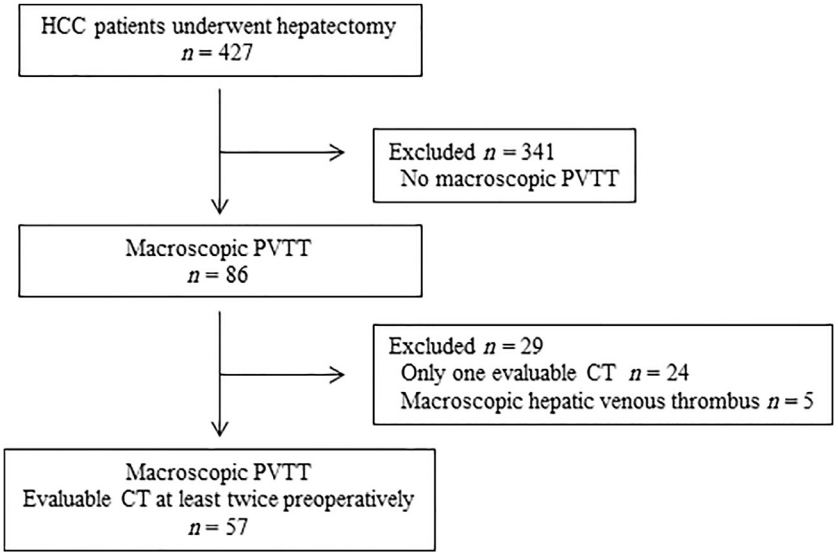

Fig. 1. Flow sheet of the study population. *CT*, computed tomography; *HCC*, hepatocellular carcinoma; *PVTT*, portal vein tumor thrombus.

therapy with sorafenib based on the results of randomized, controlled trials,[6–8] increasing data suggest that some patients with this type of refractory HCC might benefit from surgical treatment.[9–15] If the radical resection of tumors and PVTT can be achieved macroscopically, the 3-year survival rates after complete resection range from 17% to 33%.[10,12–14] A recent large cohort study of more than 2,000 patients with HCC in 10 hepatobiliary tertiary referral centers (3 Asian centers, 3 American centers, and 4 European centers) revealed that about 50% of these patients underwent liver resection against European Association for the Study of the Liver/American Association for the Study of Liver Diseases guidelines.[9] In particular, 264 patients underwent liver resection, even though they were staged as Barcelona clinic liver cancer C, and 38% had a 5-year survival rate. These data suggest that certain patients with HCC and PVTT can benefit from surgical treatment rather than sorafenib monotherapy.

The extent of PVTT is an important factor in deciding the operability and surgical procedure in patients with HCC and PVTT. PVTT in the ipsilateral portal branch can be extirpated in an *en bloc* manner at the time of a right or left hemihepatectomy. PVTT in the portal vein bifurcation or the portal trunk was also resected, using peeling-off techniques or thrombectomy.[16] Surgical treatment for PVTT beyond these stages is challenging and usually considered as a contraindication for surgical treatment,[17] so systemic chemotherapy with molecular target therapy with sorafenib is selected. Therefore, the time required for the growth velocity of PVTT is an important factor in deciding the optimum treatment and the timing of operation. However, little is known about the growth velocity of PVTT in patients with HCC.

The aim of this study was to determine the growth velocity of PVTT and factors associated with it to determine the optimal timing of treatment.

Methods

A total of 427 patients with HCC underwent hepatectomy at Kobe University hospital between October 2005 and February 2015. Among them, 86 patients were complicated with macroscopic PVTT. All patients underwent computed tomography (CT) for diagnosis in the referring hospital. After referral to our hospital, patients underwent CT for operation. In addition, recent patients underwent an additional CT examination just before the operation at our hospital because of rapid PVTT progression. Therefore, all patients underwent preoperative CT at least twice. A total of 62 of 86 patients, who had at least two evaluable CT scans, were enrolled in this study. The remaining 24 cases were excluded because of the low quality of the CT images obtained from the referring hospital. Furthermore, 5 patients were excluded because they were diagnosed as having HCC with PVTT and hepatic venous thrombus extending into the inferior vena cava. A total of 57 patients were enrolled in this study (Table 1, Fig. 1). We reviewed the clinical, pathologic, and preoperative laboratory data of all patients retrospectively. All patients were followed until their death or until December 2016.

Liver functional reserve was assessed by serum biochemical data (albumin level, total bilirubin level, and prothrombin time), and the patients were categorized according to the severity of liver disease based on Child-Pugh stages.[18] The preoperative diagnosis of HCC was confirmed by imaging studies, such as ultrasonography, CT, angiography, or magnetic resonance imaging (MRI), and by serum levels of tumor markers, such as the serum alpha-fetoprotein (AFP) level and proteins induced by vitamin K absence or antagonist II (PIVKAII). Routine angiography included celiac, superior mesenteric, and selectively proper hepatic arteriography, using the Seldinger method.

The present study was approved by our institutional ethics committee (number 170123) and conducted in accordance with the ethical standards set forth by the Declaration of Helsinki. All patients provided general informed consent.

Treatment strategy for the patients with HCC and PVTT

We typically perform hepatectomy and thrombectomy for patients with HCC and PVTT without neoadjuvant treatment. However, some patients underwent preoperative therapy before referral to our hospital. In this study, 4 (7%) and 3 (5.3%) patients underwent preoperative transcatheter arterial chemoembolization and hepatic artery infusion, respectively. When there were residual lesions in the remnant liver, additional adjuvant treatment including transcatheter arterial chemoembolization, hepatic arterial infusion therapy, and radiotherapy was considered, depending on the patient's disease status.

Staging of PVTT

The extent of PVTT was macroscopically determined according to the Japan Liver Cancer Study Group Criteria:[19] The tip of

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