

Determinants of Survival of Ablation Treatment for Portal Vein Tumor Thrombus in Patients With Hepatocellular Carcinoma

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Abstract. *Background/Aim:* The prognosis of hepatocellular carcinoma (HCC) complicated with portal vein tumor thrombus (PVTT) is extremely poor. This study investigated whether local ablation—a curative treatment similar to resection—could improve the prognosis of patients with Child-Pugh B/C PVTT. *Patients and Methods:* Between January 2020 and December 2023, 25 patients with Child-Pugh B/C PVTT HCC were enrolled, and their overall survival with radiofrequency ablation treatment and the associated drivers were investigated. *Results:* Overall survival (median 282 days) differed between the group treated with transarterial chemoembolization (TACE, 285 days) and the group without it (159 days, $p=0.0151$). The median survival in the esophagogastric variceal exacerbation group (120.5 days) was shorter than that in the non-exacerbation group (284.0 days, $p=0.00964$). In multivariate analysis, concomitant TACE had a hazard ratio (HR) of 0.121 ($p=0.0097$), and the exacerbation of esophagogastric varices had a HR of 6.761 ($p=0.01$). *Conclusion:* Local ablation for PVTT may promote patient survival specifically by inhibiting the exacerbation of portal hypertension in patients with hepatocellular carcinoma.

Hepatocellular carcinoma is a highly vascular invasive disease that often develops portal vein tumor thrombus (PVTT) at an early stage (1). PVTT-related complications are difficult to treat due to the exacerbation of portal hypertension (PHT) and

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are an important prognostic factor: patients with PVTT have a very poor prognosis of 2-3 months if left untreated (2, 3).

Surgical resection is the only curative treatment for hepatocellular carcinoma (HCC) with PVTT (4, 5). According to the internationally accepted Barcelona Clinic Liver Cancer Staging Classification, HCC is unresectable when the liver reserve is limited by cirrhosis and multiple bilobar lesions, and early recurrence is common due to intrahepatic metastasis (6, 7). However, the Japanese guidelines for the treatment of HCC consider surgery indicated up to Vp3, considering the natural course of the disease and lack of indications for other treatment methods (8). PVTT may promote residual liver recurrence, making its control an important clinical issue. Various treatment options, including hepatic artery infusion chemotherapy, transarterial chemoembolization (TACE), and radiotherapy of the tumor thrombus, have been reported; however, their therapeutic efficacy is low, and no standard treatment exists for PVTT. Treatment for this condition is further limited by esophagogastric variceal hemorrhage associated with progressive PHT, which is often fatal. Therefore, treatment strategies that prevent progression of short-term PHT are urgently needed.

Although recent advances in systemic therapy have shown promise for PVTT treatment (9, 10), systemic therapy is indicated only in Child A cases, whereas most PVTT cases have non-compensated Child classifications owing to the progression of PHT. In contrast, locoregional therapy for HCC offers excellent local control, is the second most curative treatment after hepatic resection, and can be performed even in patients with impaired liver function. Radiofrequency ablation (RFA) has been widely used for the treatment of HCC during the last decade. As it is minimally invasive and potentially curative, RFA is currently considered the best option for patients with HCC who are not eligible for surgical intervention (11, 12). However, few reliable studies have investigated the safety and efficacy of local RFA treatment against Child B/C PVTT in HCC.

This study investigated the performance of RFA treatment in patients with HCC complicated with PVTT.



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Table I. Demographic and clinical characteristics of 25 patients with unresectable hepatocellular carcinoma with portal vein tumor thrombus.

Demographic variables	Mean±SD	Range
Age (years)	69.88±8.47	53-85
Sex (Male:Female)	24:1	
Etiology (HBV/HCV/NonHBVNonHCV)	3:5:17	
AFP (ng/ml)	5,467.34±18,328.45	2.60-90,742.00
DCP (mAU/ml)	7,163.75±15,920.38	130.00-75,000.00
Child-Pugh Score (7/8/9/11)	15/5/4/1	
TACE (With: Without)	21:4	

SD: Standard deviation; HBV: Hepatitis B virus; HCV: hepatitis C virus; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; TACE transarterial chemoembolization.

Patients and Methods

Ethics approval and informed consent. This study was approved (E17-27) by the Institutional Review Board of Saiseikai Niigata Hospital and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Participants. This retrospective study included 25 patients with Child B/C HCC with PVTT who underwent PVTT-targeted RFA using a unipolar needle electrode between January 2020 and December 2023 at the Saiseikai Niigata Hospital (Niigata, Japan). HCC was diagnosed using dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging. The participant selection criteria were as follows: 1) PVTT identified in ultrasonography for cases up to Vp3; 2) no extrahepatic metastases observed during pre-therapy imaging; and 3) a normal prothrombin time and platelet count >50,000. The exclusion criteria were as follows: 1) systemic therapy had been administered, 2) no follow-up CT was performed, 3) no follow-up gastrointestinal endoscopy was performed, and 4) patient was eligible for systemic therapy in Child-Pugh class A.

RFA was conducted using the arfa® (Japan Lifeline Co. Ltd., Tokyo, Japan) RF Ablation System with an adjustable electrode needle device, equipped with variable electrodes and a 30 mm cautery electrode. All RFA sessions were performed percutaneously under ultrasound guidance (LOGIQ E9, XDclear 2.0, GE Healthcare, Chicago, IL, USA). RFA was performed under intravenous conscious sedation and vital signs were continuously monitored. The treatment protocol employed a linear mode, starting with a power of 40 W and 5 W increments at 30 s intervals, and ablation was completed in one session.

For concomitant TACE, the femoral artery was punctured using the Seldinger technique, a 5F introducer was inserted, 5F catheter was inserted, and 3F microcatheter (Attendant, Terumo, Tokyo, Japan) was advanced to the subregion or further peripheral nutrient vessels using the coaxial technique, and TACE was performed. Treatment outcomes and factors contributing to survival were investigated.

Statistical analysis. The sex ratio was compared using Fisher's exact test, while background disease and T-factors were analyzed using the χ^2 test. The Child-Pugh score, nodal size, total bilirubin, platelet count, prothrombin time, alpha-fetoprotein (AFP), and des-gamma-

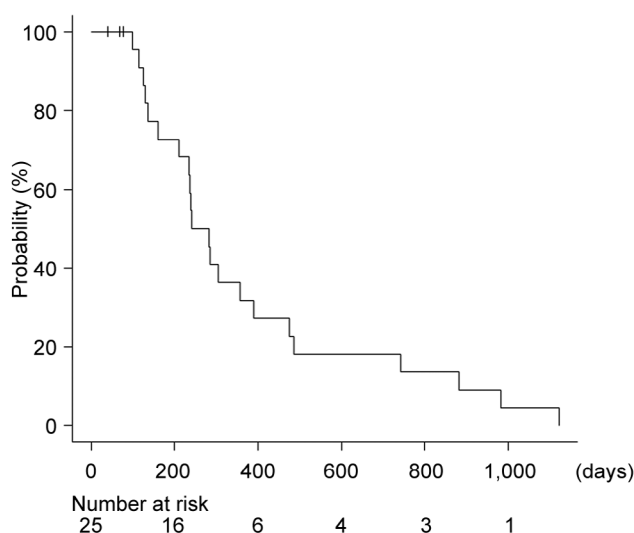


Figure 1. Kaplan-Meier curve demonstrating overall survival of hepatocellular carcinoma with portal vein tumor thrombus after radiofrequency ablation.

carboxy prothrombin (DCP) were assessed using the Mann-Whitney *U*-test. Overall survival during the follow-up period was compared using the Kaplan-Meier method and evaluated using the log-rank test. A *p*-value <0.05 was considered significant. Multivariate analysis was performed to identify independent prognostic factors, and the Cox proportional hazards model was used to calculate adjusted hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) (13).

Results

The clinical backgrounds of all patients are shown in Table I. The mean age was 69.88±8.47 years, with a sex ratio of 24 men to 1 woman. The ratio of background liver factors for hepatitis B virus: hepatitis C virus: Non-B Non-C was 3:5:17. The AFP value was 5,467.344±18,328.45 ng/ml and DCP value was 7,163.752±15,920.38 mAU/ml. The Child-Pugh Scores were 7/8/9/11, distributed as 15/5/4/1, respectively.

The median overall survival (OS) was 282 days after RFA (Figure 1). The OS in the TACE group (*n*=21) was significantly better than that in the non-TACE group (*n*=4; 285 days vs. 159 days, *p*=0.0151; Figure 2).

Five patients experienced exacerbations of esophagogastric varices, while 20 patients had no exacerbations of PHT, likely due to the use of RFA. The median survival in the esophagogastric variceal exacerbation group (120.5 days) was shorter than that in the non-exacerbation group (284.0 days, *p*=0.00964; Figure 3). No significant differences were observed in survival according to background liver factors,

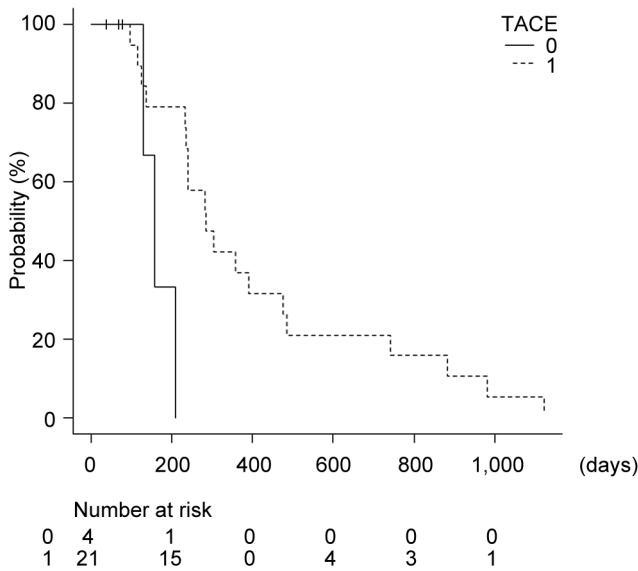


Figure 2. Kaplan-Meier curve demonstrating overall survival of hepatocellular carcinoma with portal vein tumor thrombus after radiofrequency ablation in the transarterial chemoembolization (TACE) group and no-TACE group ($p=0.0151$). 0: No TACE group, 1: with TACE group.

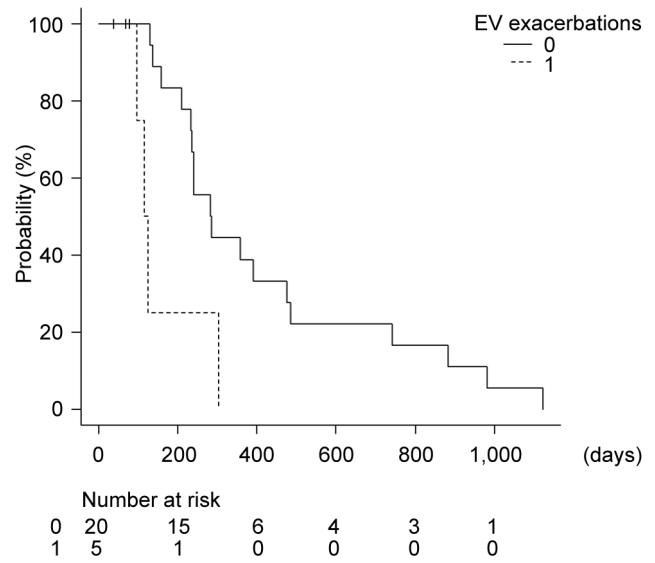


Figure 3. Kaplan-Meier curve demonstrating overall survival of hepatocellular carcinoma with portal vein tumor thrombus after radiofrequency ablation in the esophagogastric variceal exacerbation group and in the non-exacerbation group ($p=0.00964$). 0: the non-exacerbation group, 1: esophagogastric variceal exacerbation group.

AFP or DCP levels, sex, or age. In the multivariate analysis, the hazard ratio was 0.121 ($p=0.0097$) for concomitant TACE and 6.761 ($p=0.01$) for exacerbation of esophagogastric varices (Table II).

Discussion

HCC with PVTT has the poorest prognosis among HCC cases, with a reported mean survival of 2.7 months in the absence of therapeutic intervention (2). In particular, the prognosis of Vp3 cases is extremely poor, with a reported mean survival of approximately 5 months with transarterial embolization or chemotherapy alone (2, 3, 8). However, only a few reports have investigated long-term survival in cases of multidisciplinary treatment combining surgery and radiotherapy.

HCC with PVTT is preferably treated using hepatic resection, including TACE; however, resection may be complicated by various factors, such as reduced liver function, presence of distant metastases, and degree of progression in tumor thrombus. In the 2021 Guidelines for the Treatment of Liver Cancer (8), the recommended treatments for HCC with vascular invasion are systemic pharmacotherapy, and TACE, with no recommendations for radiotherapy. According to data from the National Primary Liver Cancer Follow-up Report, the median survival of CP-A patients with portal tumor thrombus who underwent resection (Vp1: 42.7%, Vp2: 25.2%, Vp3: 22.3%, Vp4: 9.8%) was 34 months (14). As for systemic

Table II. Prognostic factors related to overall survival determined by multivariate analysis using Cox proportional hazard model.

Variables	Categories	HR	95%CI	p-Value
AFP	Decrease	1.06	0.39-2.86	0.91
	Increase	1		
DCP	Decrease	1.221	0.34-3.61	0.72
	Increase	1		
TACE	With TACE	0.121	0.02-0.59	0.0097
	Without TACE	1		
EV exacerbations	Yes	6.761	1.56-28.73	0.01
	No	1		
Age	≥ 70	0.96	0.90-1.02	0.2
	< 70	1		

HR: Hazard ratio; CI: confidence interval; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; TACE: transarterial chemoembolization; EV exacerbations: esophagogastric variceal exacerbations.

pharmacotherapy, the IMbravel50 trial reported median survival rates of 14.2 and 9.7 months in the atezolizumab plus bevacizumab and sorafenib alone arms, respectively (15).

However, systemic therapy is reserved for Child-Pugh class A cases, and most patients with advanced-stage HCC and PVTT have a reduced liver reserve under Child-Pugh class B or higher. Furthermore, these treatments require time for tumor thrombus necrosis or regression, during which there is a high risk of varix rupture due to the rapid progression of PHT. As systemic therapy, lenvatinib

treatment may lead to more favorable outcomes compared with those of sorafenib for advanced HCC patients with PVTT in Child Pugh A (16).

Furthermore, it has been reported that chemoembolization may be effective in controlling tumor thrombi in the IVC or right atrium when there is major vascular invasion (17). Ablation is also not recommended for treating HCC with PVTT, but it is highly curative and may show short-term efficacy when combined with resection. Notably, percutaneous intravascular RFA is technically feasible (18).

In HCC with PVTT (especially at tumor diameters >5 cm and grade Vp3), TACE combined with percutaneous ethanol injection (PEI) is safe and has been associated with improved survival outcomes (19). Moreover, nodule treatment with RFA and portal tumor thrombosis treatment with ethanol injection is effective and safe, and the rate of complications is low (20-22).

In the present study, we investigated the performance of local ablation treatment in patients with PVTT who were not eligible for pharmacological treatment based on hepatic reserve status. Our results indicated a high median survival rate in patients with non-compensated hepatic reserves after targeted treatment of the PVTT, confirming the efficacy of the local RFA treatment. Patients treated with TACE had a significantly higher median survival rate than patients not treated with TACE, emphasizing the applicability of concomitant TACE in treating PVTT. Overall, concomitant TACE and no exacerbation of esophagogastric varices with RFA treatment contributed greatly to the improved prognoses, with no effects associated with fluctuations in tumor markers or liver reserve status. Proton beam radiotherapy has also demonstrated comparable local control with acceptable toxicity to RFA (23).

Although the relevance of RFA as a local treatment modality for PVTT has been reported, few coherent studies have been performed. PVTT causes PHT *via* an arterial portal vein short circuit or shunt, which induces refractory ascites, exacerbation of esophagogastric varices, and bleeding, further worsening the prognosis. We previously reported that control of PHT by portal stenting in PVTT improved prognosis and RFA may prevent the exacerbation of esophagogastric varices by suppressing PVTT invasion. Notably, in the present study, patients without exacerbation of esophagogastric varices had significantly improved survival rates, likely due to reduced gastrointestinal bleeding.

Study limitations. First, the sample size was relatively small. Second, the study lacked a comparison of patients with various disease stages. Third, the retrospective design may have introduced bias in the selection of patients. Finally, it only considered data from a single center. Future prospective clinical trials with larger sample sizes and varied multicenter patient populations are needed to verify our findings.

Conclusion

Various types of locoregional treatment are performed in patients with PVTT not amenable to pharmacological treatment. RFA for PVTT may effectively ameliorate PHT exacerbations in short-term applications, though a larger scale prospective study is required to confirm these findings.

Funding

None.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: Toru Ishikawa; Data Curation: Toru Ishikawa; Formal Analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Ryo Sato, Ryo Jimbo, Yuji Kobayashi, Toshifumi Sato, Akito Iwanaga, Tomoe Sano, Junji Yokoyama, Terasu Honma; Methodology: Toru Ishikawa; Project Administration: Toru Ishikawa; Resources: Toru Ishikawa; Software: Toru Ishikawa; Visualization: Toru Ishikawa; Writing – Original Draft: Toru Ishikawa; Writing – Review & Editing: Toru Ishikawa, Ryo Sato, Ryo Jimbo, Yuji Kobayashi, Toshifumi Sato, Akito Iwanaga, Tomoe Sano, Junji Yokoyama, Terasu Honma

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