

Acta Med. Okayama, 2012  
Vol. 66, No. 2, pp. 131–141

Copyright©2012 by Okayama University Medical School.

Acta Medica  
Okayama

<http://escholarship.lib.okayama-u.ac.jp/amo/>

Original Article

## Prognosis of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Assessment Based on Clinical and Computer Tomography Characteristics

Lizhong Jia<sup>a,c\*</sup>, Shigeru Kiryu<sup>b</sup>, Takeyuki Watadani<sup>a</sup>, Hiroyuki Akai<sup>a</sup>,  
Hideomi Yamashita<sup>a</sup>, Masaaki Akahane<sup>a</sup>, and Kuni Ohtomo<sup>a</sup>

<sup>a</sup>Department of Radiology, Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan,

<sup>b</sup>Department of Radiology, Institute of Medical Science, University of Tokyo, Minato-ku, Tokyo 108-8639, Japan, and

<sup>c</sup>Department of Radiology, First Affiliated Hospital, Kunming Medical University, Kunming city 650032, China

Patients with hepatocellular carcinoma (HCC) complicated by portal vein tumor thrombus (PVTT) have an extremely poor prognosis. It is important to select adequate therapeutic options based on reliable prognostic factors using imaging studies and clinical data. Prognostic factors were analyzed in patients with HCC with PVTT in the first branch or main trunk of the portal vein. From 2000 to 2007, 107 consecutive patients with HCC with PVTT in the major portal vein were reviewed, and diagnostic images and clinical characteristics were retrospectively observed. Thirty-eight possible prognostic factors for survival were analyzed by the log-rank test and multivariate analysis using Cox's proportional hazards model. Median overall survival was 14 months following PVTT diagnosis. Survival rates at 6 months, 1, 2, and 3 years were 72.1%, 52.6%, 32.6%, and 29.6%, respectively. Independent prognostic factors for longer survival included: patient age < 65 years, Child-Pugh classification A/B, PVTT treatment, accumulation of Lipiodol in the PVTT after TACE, initial radical treatment for HCC, HCC located in a single lobe of the liver, and no invasion of HCC to the hepatic vein or bile duct. Survival was associated with liver function, tumor extension, and treatment for HCC and PVTT.

**Key words:** hepatocellular carcinoma, portal vein tumor thrombus, prognostic factors

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. In recent years, the development of imaging techniques has facilitated the detection of HCC at early stages [1–4]. The introduction of new therapeutic modalities such as percutaneous ethanol injection (PEIT), radiofrequency ablation (RFA), and liver transplantation have provided various options for the treatment of

HCC, and have markedly improved the prognosis for this disease [5–7]. Despite this marked progress in medical science, the prognosis of advanced HCC remains poor, particularly in patients with tumor thrombus in the portal vein (PV).

HCC has a high frequency of PV invasion, which is reportedly observed in 11% to 42% of patients with HCC [8–11]. Portal vein tumor thrombus (PVTT) is a crucial factor that can worsen the prognosis of HCC because it can lead to the wide dissemination of tumors throughout the liver and cause a marked deterioration of hepatic function. Previous

Received August 16, 2011; accepted November 17, 2011.

\*Corresponding author. Phone: +81-3-5800-8666; Fax: +81-3-5800-8935

E-mail: jialzmsn@hotmail.com (L. Jia)

studies have reported that the median survival time of patients with PV invasion was 2.7 to 4 months if left untreated, whereas the median survival time in those without PV invasion was 24.4 months [12, 13]. However, the authors of one previous study found that a substantial number of patients with PVTT had an extremely poor prognosis (several months), whereas some of these patients survived for several years or more [14].

Various treatments have been applied to improve the short-term prognosis of patients with PV invasion of HCC, but the management of HCC with PVTT in the major branches is complicated and controversial. No standard treatment has been established for such patients. Tumor thrombus is generally assumed to develop during the terminal stage of HCC. To improve outcomes in these patients, it is important to evaluate potential prognostic factors for the elucidation of treatment strategies. Diagnostic imaging is an important tool in the clinical setting to select the treatment and to evaluate the efficacy of the treatment once delivered. However, to our knowledge, few studies have evaluated the prognostic factors including diagnostic image factors for HCC with PVTT.

In this retrospective study, prognostic factors were analyzed in patients with HCC with tumor thrombosis in the first branch or main trunk of the PV. Imaging characteristics that affected survival were evaluated, and the effects of the location and extent of PVTT were evaluated in association with long-term outcomes.

## Patients and Methods

During the 8-year period from January 2000 to September 2007, 3,408 patients with HCC were admitted to the University of Tokyo Hospital in Japan. Of these, 107 (3%) patients were included in this study because they had gross PVTT in the first branch or/and the main trunk of the PV. Diagnosis of HCC was confirmed either by histopathological examination or by clinicopathological findings from biopsy specimens, ultrasonography, computed tomography (CT), or angiography. The tumor thrombus was diagnosed using contrast-enhanced CT in all patients. On contrast-enhanced CT, PVTT was identified by the presence of an intraluminal filling defect with generalized enhancement, intrathrombus

neovascularity, accompanying portal venous expansion, or direct invasion of the PV [15]. Among those patients, 14 had PVTT demonstrated by histopathology following surgery.

CT was performed with multi-detector CT (MDCT) systems (LightSpeed QX/I, LightSpeed Ultra, GE, USA; TOSHIBA Aquilion, Toshiba, Japan; Somatom Plus 4, Siemens, Germany). In all cases, non-enhanced and contrast-enhanced CT (2.5- to 5.0-mm slice thickness, 120 kVp, 200–400 mAs with 5-mm axial reconstructions) was performed. Enhanced images were obtained after power injection of 100–120 ml iodinated contrast medium at a rate of 3 ml/sec. The ensuing average start time for the hepatic arterial phase was 30 sec. For the portal venous and equilibrium phases, scans were acquired at 60 sec. and 180 sec, respectively. All CT images were evaluated by 2 trained radiologists by consensus.

A series of demographic, biochemical, and clinical data were collected at the time of diagnosis of the presence of PVTT and included age, gender, presence of cirrhosis etiology (hepatitis B virus surface antigen or hepatitis C virus antibody), presence of liver cirrhosis, presence of ascites or hepatic encephalopathy, serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum albumin, prothrombin time (%), platelet count, and serum  $\alpha$ -fetoprotein (AFP), protein induced by vitamin K absence or antagonist II (PIVKA-II) levels, the initial therapeutic approach for HCC treatment, and the main PVTT therapy. The degree of liver damage was assessed by Child-Pugh grade.

Imaging characteristics of the tumor were evaluated. For HCC, 2 phases of data were recorded which included the initial period and the time PVTT was diagnosed. Characteristics included the number of lesions, gross lesion type, lobar distribution, diameter of the largest nodule, and presence of extrahepatic metastasis. For the PVTT, recorded characteristics included location, type, maximal diameter of the PVTT, enhancement, A-P shunt, and the presence of hepatic vein or bile duct invasion. The accumulation of Lipiodol was checked in patients who underwent transcatheter arterial chemoembolization (TACE). The effects of location, treatment for PVTT, and the initial HCC therapy were analyzed with regard to associations with patient survival.

**Statistical analysis.** Overall, cumulative sur-

vival rates were obtained using the Kaplan-Meier method. The starting point for calculating survival was the date PVTT was diagnosed, and the endpoint was the date of death. Patients who were still alive through December 31, 2008, were censored. Each continuous variable was transformed into a binary variable divided by a median value. All possible prognostic factors for survival were analyzed by the log-rank test. Independent factors associated with the survival rate were assessed using Cox's proportional hazard regression model, where significant variables in a univariate analysis were included in a multivariate analysis. A value of  $p < 0.05$  (two-tailed) was considered to represent statistical significance. Statistical analyses were performed using JMP 9 (SAS Institute, Inc., Cary, NC, USA) software.

## Results

**Patient characteristics.** The study population included a total of 107 patients (84 males and 23 females; ratio: 3.7 : 1) with a mean age of  $65.3 \pm 10.4$  years (range, 27–88 years). In these patients, the etiology of the background liver disease was hepatitis C virus (HCV) in 68 patients (64%, with 1 patient also positive for HBV), hepatitis B virus (HBV) in 21

patients (20%), and non-B non-C hepatitis in 9 patients (8%). Non-liver disease was found in only 9 patients (8%). A total of 50 patients (47%) were classified with Child-Pugh class A disease, 39 (36%) with Child-Pugh class B disease, and 18 (17%) with Child-Pugh class C disease when PVTT was diagnosed. A total of 51 patients (48%) patients had PVTT in the first branch and 56 (52%) in the main trunk of the PV. The mean of the maximum diameter of the intrahepatic HCC was  $62.4 \pm 38.8$ mm (range, 5.5–213mm). Clinical and imaging characteristics are summarized in Table 1 and 2.

**Survival periods.** The average duration of follow-up was 18 months (range, 1 to 71 months). Forty-six patients were alive, and 61 patients had died (58%) at the end of the follow-up period. Ten patients (9%) died within 30 days. The causes of death were tumor progression in 59 patients, upper gastrointestinal bleeding in 2 patients, and cardiac failure in 1 patient. The cumulative survival curve for all patients is shown in Fig. 1. Median overall survival was 14 months following PVTT diagnosis. Survival rates at 6 months, 1 year, 2 years, and 3 years were 72.1%, 52.6%, 32.6%, and 29.6%, respectively. Only 1 patient was alive for more than 5 years of follow-up.

**Table 1** Univariate analysis of clinical characteristics potentially predictive of survival in 107 patients with hepatocellular carcinoma complicated by portal vein tumor thrombosis

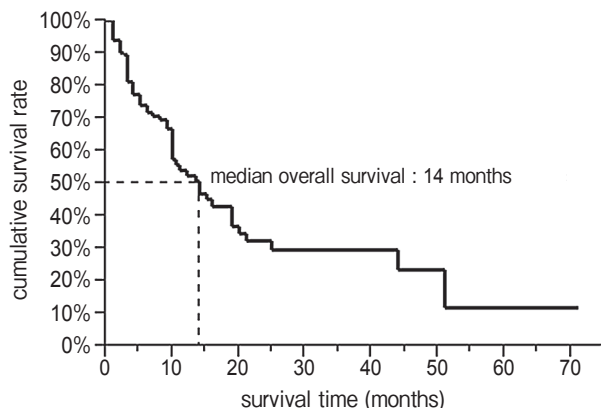
Variables	Category	Number	Median survival time (month)	p-value (log-rank)
gender	female/male	23/84	13.25/14	0.7817
age	<65 y/≥65 y	46/61	17.5/10.25	0.0465*
hepatitis virus	positive/negative	89/18	13.75/14.5	0.7752
ascites	absence/presence	69/38	17.5/3.75	0.0018*
hepatic encephalopathy	absence/presence	102/5	14.5/1.5	0.0002*
AST	<54/≥54 (IU/l)	31/76	20.5/9.5	0.0173*
ALT	<54/≥54 (IU/l)	63/44	17.5/9.5	0.0625
Albumin	<3.5/≥3.5 (g/dL)	59/48	9.5/17.5	0.0028*
total bilirubin	<2.0/≥2.0 (mg/dl)	84/23	15.5/7.5	<0.0001*
prothrombin time	<70%/≥70%	55/52	11.5/17.5	0.1111
platelet count	<10/≥10 ( $\times 10^4/\mu\text{l}$ )	29/78	8/17.5	0.0084*
AFP	<400/≥400 ng/ml	57/50	13.75/9.5	0.1264
PIVKA- II	<40/≥40 (mAU/ml)	23/84	16/12.25	0.4292
PVTT Child-Pugh	A, B/C	89/18	19/3	<0.0001*
PVTT treatment	treatment/support	92/15	16/4	<0.0001*
HCC initial Child-Pugh	A, B/C	99/8	15/3	0.0002*
HCC initial treatment	radical/conservative treatment <sup>a</sup>	59/42	20/10	0.0059*

<sup>a</sup>radical treatment: surgical resection, RFA, PEIT; conservative treatment: TAE, TAI.

**Table 2** Univariate analysis of CT characteristics potentially predictive of survival in 107 patients with hepatocellular carcinoma complicated by portal vein tumor thrombosis

Variables	Category	Number	Median survival time(month)	p-value (log-rank)
PVTT location	main trunk/first branch	56/51	11.5/13.5	0.8985
PVTT type	Vp3/Vp4 <sup>a</sup>	46/61	13.5/11.5	0.8519
PVTT arterial-enhancement	yes/no	11/96	13.25/10.5	0.0754
PVTT venous-hypodense	yes/no	11/96	13.25/10.5	0.0754
PVTT max-diameter	<16·18 mm/≥16·18 mm <sup>b</sup>	84/30	13.25/15.5	0.6329
AP-shunt	presence/absence	17/90	11.5/24.5	0.2321
other invasion <sup>c</sup>	presence/absence	22/85	7.5/17.5	0.0010*
accumulation of lipiodol	presence/absence	39/20	17.5/9.5	0.0082*
Initial HCC No. of nodules	solitary/multiple	31/70	16.5/11.5	0.3444
Initial HCC size	<20/≥20 mm	14/85	16/12.75	0.9678
	<50/≥50 mm	62/37	12.5/11.25	0.7661
Initial HCC location	R/L/both lobe <sup>d</sup>	38/15/49	17/9.5/9.75	0.3984
	R, L/both lobe	53/49	17.5/9.75	0.0722
Initial HCC extrahepatic metastasis	presence/absence	12/95	13.75/14.5	0.4615
HCC No. of nodules	solitary/multiple	13/92	17/10.25	0.1386
HCC size	<20 mm/≥20 mm	8/97	15/11.5	0.3164
	<50 mm/≥50 mm	50/55	13.75/10.25	0.6769
HCC location	R, L/both lobe	36/69	17.5/9.5	0.0004*
HCC extrahepatic metastasis	presence/absence	35/72	9.75/13.75	0.4207

<sup>a</sup>Vp3, PVTT in first-order branches; Vp4, PVTT in main trunks or/and both first branches; <sup>b</sup>PVTT, max-diameters were categorized by 16mm which in the right first branches and 18mm which into the left first portal brunch or main trunks; <sup>c</sup>other invasion, hepatic vein or bile duct invasion; <sup>d</sup>R/L, right or left lobe.

**Fig. 1** Overall survival of 107 patients with hepatocellular carcinoma and portal vein tumor thrombus (Kaplan-Meier method).

### Univariate and multivariate analysis.

Possible associations between survival and the clinical and imaging variables were evaluated with univariate analysis using the Kaplan-Meier method for all 107 patients. Fourteen factors were found to have a sig-

nificant negative association with survival in the log-rank test (Table 1 and 2). The biochemical and clinical variables (11 variables) were: age < 65 years, presence of ascites, presence of hepatic encephalopathy, AST < 54 IU/l, albumin ≥ 3.5 g/dl, total bilirubin < 2.0 mg/dl, platelet count ≥ 10 × 10<sup>4</sup>/μl, Child-Pugh classification grades for the PVTT and initial HCC, HCC initial radical treatment, and PVTT treatment. The imaging variables (3 variables) were: HCC located in a single lobe, no invasion of HCC to hepatic vein or bile duct, and accumulation of Lipiodol in the PVTT after TACE.

The remaining variables analyzed were not found to have predictive prognostic value in the univariate analyses: gender, hepatic virus, ALT, prothrombin time ≥ 70%, AFP ≥ 400 ng/ml, PIVKA-II ≥ 40 mAU/ml; for HCC: number of nodules, size, extrahepatic metastasis; for PVTT: type, location, enhancement, diameter, presence of AP-shunt.

To evaluate the prognostic factors for the survival of HCC patients with PVTT, we dichotomized the

**Table 3** Multivariate analysis of prognostic factors by the Cox proportional hazard model

Factor	Category	Hazard ratio	95%CI	p-value
age	< 65y/≥65y	1.3734	0.9997–1.8868	0.0471*
AST	< 54UI/≥ 54UI	0.9537	0.2563–3.5487	0.0923
PLT	≥ 10/ < 10 ( $\times 10^4/\mu\text{l}$ )	1.1199	0.8375–1.4975	0.4475
PVTT Child-Pugh	A, B/C	1.3609	1.0065–1.8404	0.0444*
PVTT treatment	treatment/support	1.6219	1.1023–2.3865	0.0183*
HCC initial Child-Pugh	A, B/C	0.8316	0.1547–4.4707	0.1825
HCC initial treatment	radical/conservative treatment <sup>a</sup>	1.8874	1.3582–2.6229	< 0.0001*
accumulation of lipiodol	presence/absence	1.3508	0.9922–1.8391	0.0490*
other invasion	absence/presence	1.5269	1.1091–2.1022	0.0145*
HCC location	R, L/both lobe	1.7257	1.1937–2.4947	0.0024*

<sup>a</sup>radical treatment: surgery resection, RFA, PEIT; conservative treatment: TAE, TAI.

**Table 4** Survival comparison according to location of the portal vein tumor thrombosis

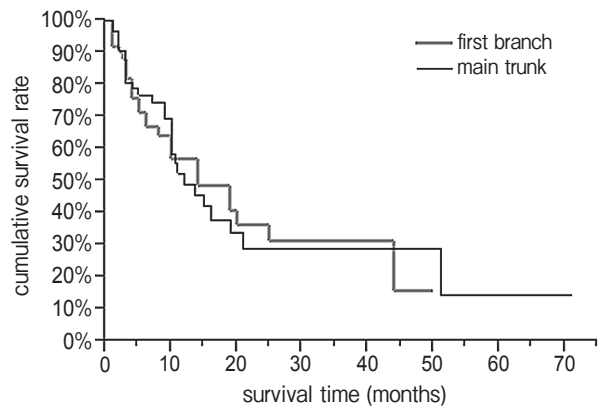
Category	Number	Median survival time (month)	p-value (log-rank)
R/L/M/B <sup>a</sup>	23/23/46/15	14/14/13.5/10	0.8634
main trunk/first branch	51/56	14/12	0.8985
Vp3/Vp4 <sup>b</sup>	46/61	14/12	0.8519
R/L	23/23	14/14	0.5389
M/B	46/15	13.5/10	0.5303

<sup>a</sup>R, right first branch; L, left first branch; M, main trunk; B, both first branch.

<sup>b</sup>Vp3, PVTT in first-order branches; Vp4, PVTT in main trunks or/and both first branches.

factors with a significant negative association with survival listed above and used Cox's proportional hazard model for multivariate analysis (Table 3). The analysis revealed that the following variables were independent predictors for longer survival: patient age < 65 years, PVTT Child-Pugh classification grade A/B, PVTT treatment, accumulation of Lipiodol in PVTT after TACE, initial radical treatment for HCC, HCC located in a single lobe, and no invasion of the hepatic vein or bile duct. A platelet count of  $\geq 10 \times 10^4/\mu\text{l}$  was not identified to be a prognostic factor by Cox's proportional hazard model.

The effect of the extent of the PVTT on survival was evaluated in terms of association with the curative strategy for PVTT and the initial treatment for HCC (Tables 4–6). The evaluation showed a non-significant negative association with invasion of the major branches of the portal trunk (Fig. 2). Treatment for PVTT was associated with better survival than supportive care alone (Fig. 3). Especially, surgical resection was seen to be associated with better outcomes (Fig. 4). Radiotherapy also had a positive



**Fig. 2** Comparison of survival rates between patients with PVTT located at the main trunk of the portal vein and at the first branch of the portal vein. There was no significant difference ( $p = 0.8985$ ; log-rank test).

association with outcome (Fig. 5). Concerning HCC initial treatments and prognosis, radical therapies were better than conservative treatment, hepatectomy was better than TACE/transcatheter arterial infusion

**Table 5** Survival comparison according to the main treatment for portal vein tumor thrombosis

Category	Number	Median survival time (month)	<i>p</i> -value (log-rank)
OPE/RT/TACE/TAI/support <sup>a</sup>	14/18/35/25/15	44/14/15/10/4	<0.0001*
treatment/support	92/15	16/4	<0.0001*
OPE/RT	14/18	44/14	0.0699
OPE/TACE	14/35	44/15	0.0825
OPE/TAI	14/25	44/10	0.0380*
OPE/support	14/15	44/4	<0.0001*
RT/TACE	18/35	14/15	0.9610
RT/TAI	18/25	14/10	0.3940
RT/support	18/15	14/4	0.0003*
TACE/TAI	35/25	15/10	0.4423
TACE/support	35/15	15/4	<0.0001*
TAI/support	25/15	10/4	0.0341*

<sup>a</sup>OPE, surgical resection; RT, radiotherapy; TACE, transcatheter arterialchemoembolisation; TAI, transcatheter arterial infusion.

**Table 6** Survival comparison according to the initial treatment for hepatocellular carcinoma

Category	Number	Median survival time (month)	<i>p</i> -value (log-rank)
OPE/RFA/PEIT/TACE/TAI/support <sup>a</sup>	30/18/11/29/13/6	21/20/19/10/6/1.5	<0.0001*
radical/conservative treatment <sup>b</sup>	59/42	20/10	0.0059*
OPE/RFA	30/18	21/20	0.8163
OPE/PEIT	30/11	21/19	0.8158
OPE/TACE	30/29	21/10	0.0247*
OPE/TAI	30/13	21/6	0.0265*
RFA/PEIT	18/11	20/19	0.8329
RFA/TACE	18/29	20/10	0.1673
PEIT/TACE	11/29	19/10	0.1536
TACE/TAI	29/13	10/6	0.4134
TAI/support	13/6	6/1.5	0.0060*

<sup>a</sup>OPE, surgical resection; PEIT, percutaneous alcoholinjection; RFA, radiofrequency ablation; TACE, transcatheter arterialchemoembolisation; TAI, transcatheter arterial infusion.

<sup>b</sup>radical treatment, surgical resection, RFA; PEIT conservative treatment, TAE, TAI.

(TAI), and TACE/TAI was better than supportive care.

## Discussion

HCC patients with PVTT have an extremely poor prognosis. It is important to evaluate potential prognostic factors for the elucidation of treatment strategies. Even after concomitant partial liver resection and thrombectomy, the postoperative 5-year survival rate has been reported to be only 10–30% [14]. The most effective treatment strategy for HCC with PVTT remains to be established. It is important to choose adequate therapeutics based on reliable prog-

nostic factors, including both imaging studies and clinical data for such patients.

In this study, the univariate analysis revealed significant differences for 14 of 33 factors; multivariate analysis found that 4 clinical factors (age, PVTT Child-Pugh classification grade, radical vs. conservative initial HCC treatment, PVTT treatment vs. supportive care) and 3 imaging factors (intrahepatic extent of HCC, hepatic vein or bile duct invasion, accumulation of Lipiodol in the PVTT after TACE) were independent prognostic factors for overall survival.

Age < 65 years was the only significant prognostic factor in the patient background category in this study.

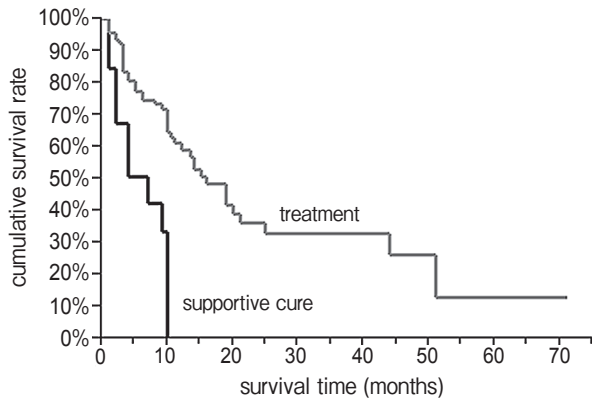


The risk of HCC is known to be age dependent, but the influence of age on prognosis is controversial. Age was not found to be a prognostic factor in some previous studies performed on HCC patients with PVTT [16, 17]. However, the present data may conform to the generally accepted theory that younger patients need to be treated in order to gain longer survival, and that these patients should be treated with a posi-

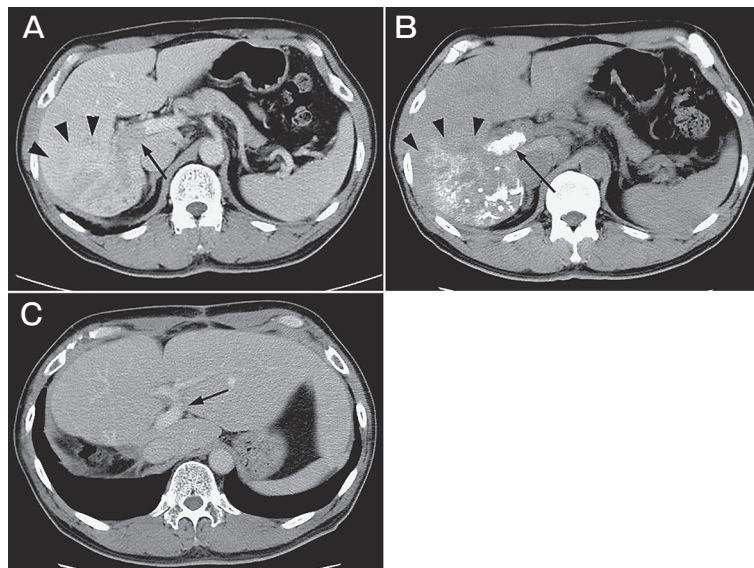
tive, radical approach if possible.

Among measurements of liver function, factors significantly associated with prognosis were AST, albumin, and total bilirubin. The presence of ascites and hepatic encephalopathy were also associated with significant differences in survival by univariate analysis. Except for the level of AST, other parameters are used in the Child-Pugh classification system. Child-Pugh grading was an independent factor with a significant influence on overall survival based on both univariate and multivariate analyses. Poor overall survival rates in the present study were strongly associated with liver function. In patients with Child-Pugh grade C, the survival rate at 6 months was 32.4%, and no patients survived longer than 10 months. There was no significant difference in the survival of Child-Pugh grade C patients between the treated and the untreated groups. Similar results have been previously reported [18]. Therefore, it might be that Child-Pugh class C patients with PVTT should not be subjected to active treatment.

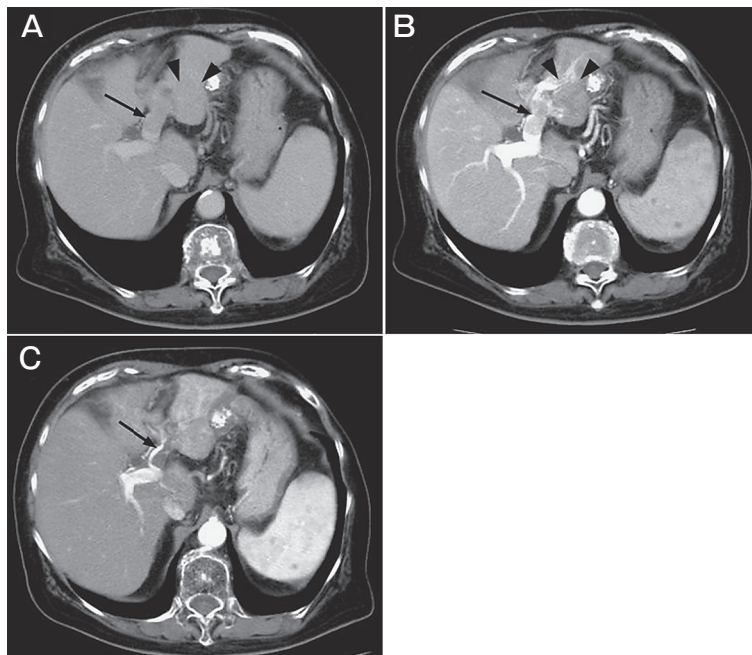
Applied treatment was another major factor predictive of survival. Both univariate and Cox's multivariate analyses showed that the strategy of treatment for HCC and PVTT were positive prognostic factors.



**Fig. 3** Comparison of survival rates between treatment and supportive care alone for HCC patients with PVTT. A significant difference in survival rate was observed ( $p < 0.0001$ ; log-rank test).



**Fig. 4** A 57-year-old man. Survival time was 41 months. CT findings after combination therapy of preoperative TACE and hepatic resection. **A**, Portal-dominant phase dynamic CT showed a solitary HCC in segment 8 (arrowhead) with portal vein tumor thrombus in the right first branch (arrow); **B**, On the plain CT taken 3 weeks after TACE, an iodized oil (Lipiodol) accumulated in the nodule of the HCC (arrowhead) and portal vein tumor thrombus located at the right first branch (arrow); **C**, Arterial-dominant phase dynamic CT 8 weeks after hepatic resection. HCC and tumor thrombus disappeared, and the portal blood flow in the left liver was normal (arrow).



**Fig. 5** An 85-year-old woman. Survival time was 27 months. CT findings after radiation therapy. **A, B**, Arterial-dominant phase and portal-dominant phase dynamic CT show a HCC in segment 2 (arrowhead) with portal vein tumor thrombus in the left first branch (arrow); **C**, Dynamic CT 7 weeks after radiotherapy shows a reduction in the size of the tumor thrombus and improved portal blood flow in the left liver (arrow).

Curative initial treatment for HCC was an independent prognostic factor. The cumulative survival rate for locoregional curative treatments for HCC (including liver resection, PEIT, and RFA) were better than conservative treatments (including TACE, TAI). The survival rates at 6, 12, and 24 months for locoregional curative treatments were 82.3%, 69.9%, and 45.6%, respectively, and for conservative treatments were 64.9%, 31.9%, and 17.1%, respectively. The present cases also had large differences in survival between the treated and untreated groups (with supportive care alone). The median survival time was 16 months for the treatment group, whereas the median survival time for the supportive care group was 4 months. The survival rates at 6, 12, and 24 months for the treated group were 76.6%, 60.5%, and 37.5%, respectively, and for the untreated group were 36.4%, 0%, and 0%, respectively.

Among the treatment strategies, surgical resection was the most effective therapy. Therefore, surgical resection may be regarded as the only potentially curative treatment for HCC with PVTT. Hepatic resection is usually not suitable for patients who have

HCC with a tumor thrombus in the main trunk or major branches of the portal vein. Patients need to have good liver function and performance status for surgical treatment. Moreover, the volume of resected liver tends to be large, resulting in a high frequency of postoperative complications and tumor recurrence [19, 20]. In the present study only a few (13%, 14/107) patients received resection surgery. The survival rates at 1, 2, 3, and 5 years for surgical treatments were 83.9%, 73.4%, 58.7%, and 0%, respectively.

Several nonsurgical modalities can be used for patients who have HCC with PVTT, such as TACE, TAI (including continuous hepatic arterial infusion chemotherapy, CHAIC), and radiotherapy (RT). TACE is usually contraindicated in patients with portal obstruction because of the high risk of hepatic insufficiency. Recently, Lee *et al.* reported that TACE can be safe for patients who have HCC with PVTT if sufficient collateral circulation around the portal trunk were established [21]. In the present retrospective series, 59 patients received TACE, and the accumulation of iodized oil (Lipiodol) not only in HCC nodules



but also in PVTT was seen in the vast majority of patients (66%, 39/59). Similar results have been reported by Minagawa *et al.*, that necrosis of the PVTT was detected by pathologic examination [22]. It seems reasonable to suppose that TACE can impair the rapid growth of PVTT.

In recent years, RT has been reported to be used for HCC patients with major PV invasion. RT has limited benefit for patients with HCC owing to the low tolerance of the whole liver to radiation [23, 24]. Combined treatment for liver tumors consisting of 3-D CRT for PVTT and TACE was reported to have a response rate from 40% to 60% and a median survival time from 7 to 10 months [25, 26]. In the present study, 18 patients received RT in the form of 3-D CRT. The mean radiation dose was 52 Gy (range 10–60 Gy) delivered a mean of 26 times (range 5–30 times), depending on the tolerance and the functional reserve of the liver. A response was observed in 15 of 18 patients; the response rate was 83%, and the median survival time was 14 months.

Because the present study design was retrospective, tumor characteristics were different between the treatment groups. Thus, the exact difference in survival between these groups could not be compared. Therapeutic procedures for patients who have HCC with PVTT are limited and controversial, and new treatment strategies are required.

With regard to imaging characteristics, the tumor size, number, and extent are well known to be prognostic factors after treatment in patients with HCC [27]. The present study recorded two-phase data for HCC, including the initial period and the time PVTT was diagnosed. Of those factors, only the extent of HCC was seen to be a significant and independent determinant of survival. The present study had many patients with multiple HCC; 69 patients (64%) had HCC that had spread to both lobes. On the other hand, in 22 patients only the right lobe was affected, and in 14 patients only the left lobe was affected. The median survival times of these 3 groups were 9.5 months, 17 months, and 15.5 months, respectively. There were no significant differences in survival between the groups with HCC distributed in the right or left lobe, but there were significant differences in survival between patients with HCC in both lobes compared with patients with HCC in only 1 lobe ( $p = 0.0004$ ). For advanced HCC, prognosis should be

even worse if the HCC has spread to both lobes.

HCC often involves the intrahepatic portal vein, but sometimes hepatic venous or bile duct invasion is present. Although the rate of hepatic venous invasion is only 9% [10], and it is a less common finding compared to portal venous invasion, it is thought to be an important prognostic factor regulating recurrence and survival after surgical resection in HCC patients [28, 29]. It was reported that the 5-year survival rate after hepatectomy was 54.1% in the absence of hepatic venous invasion, but it was 33.7% in the presence of hepatic venous invasion [10]. In the present data, 12 patients (11%) were found to have hepatic venous invasion when the PVTT presented (10 of those patients had inferior vena cava involvement). The median survival time for those patients was 5.0 months, and the survival rates at 1, 2, and 3 years were 30.9%, 15.4%, and 0%, respectively.

Bile duct invasion occurs even less frequently than does hepatic venous invasion, with a rate of only 4% [10]. Tumor invasion into the bile duct sometimes causes obstructive jaundice. Ikenaga *et al.* reported that the median survival time after hepatectomy was 56.1 months for patients without bile duct invasion, but it was 11.4 months for patients with bile duct invasion [30]. In the present study, 10 patients (9%) were found to have bile duct invasion simultaneously present with PVTT. For those patients the median survival time was 7 months, and the survival rate at 1 year was 23% and at 2 years was 0%.

According to the present data, other vascular invasion along with portal vein invasion, including hepatic vein, IVC (inferior vena cava), and bile duct invasion was 20.6% (22/107 patients) overall. There was a significant difference in the median survival time between patients with and without other vascular invasion ( $p = 0.001$ ), 7.5 months and 17.5 months, respectively. Other vascular invasion along with portal vein invasion was an independent prognostic factor and therefore should receive full attention during diagnostic imaging.

As reported above, significant factors for prognosis of HCC with PVTT were evaluated. Some factors that have been thought to affect prognosis did not appear to be associated with significant differences in survival in the present study. For example, high levels of the serum tumor markers AFP and PIVKA-II were believed to predict a worse prognosis. Inves-

tigators of the Cancer of the Liver Italian Program also reported that AFP was an independent prognostic factor [31]. However, we couldn't find significant association between levels of AFP or PIVKA-II with survival in the present study. It is possible that because only HCC patients with PVTT were enrolled in our study, the population was differed from that of the previous studies that enrolled patients with HCC with or without PVTT.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the 2 most important etiologic agents of HCC. The long-term survival of patients with HCC who have different hepatitis viral infections has been controversial [32–34]. In the present study, there was no significant difference in survival stratified by either hepatitis B or hepatitis C serology.

Extrahepatic metastases have been reported as a poor prognostic factor for HCC patients. The median survival period of patients with HCC with extrahepatic metastases was just 5 to 8 months [35, 36]. But in the present study, extrahepatic metastasis, to either distant organs or lymph nodes, was not associated with prognosis. We suspect this is because the patients in this study were limited to those with advanced HCC complicated with PVTT at the major portal vein, and thus our study population was different from those of previous studies.

In conclusion, prognostic factors were analyzed for HCC patients with tumor thrombosis in the major portal vein. Survival was associated with variables reflecting liver function, as assessed by Child-Pugh classification, by treatments for HCC and PVTT, and also by tumor extension. All treatments influenced patient outcomes, although only in the advanced stages. The results of treatments for patients with this disease remain unsatisfactory. Further prevention, early diagnosis, and development of new treatment strategies are required for such patients.

## References

- Saar B and Kellner-Weldon F: Radiological diagnosis of hepatocellular carcinoma: *Liver Int* (2008) 28: 189–199.
- Mita K, Kim SR, Kudo M, Imoto S, Nakajima T, Ando K, Fukuda K, Matsuoka T, Maekawa Y and Hayashi Y: Diagnostic sensitivity of imaging modalities for hepatocellular carcinoma smaller than 2cm. *World J Gastroenterol* (2010) 16: 4187–4192.
- Martie A, Sporea I, Popescu A, Sirli R, Dănilă M, Serban C, Ardelean M, Bota S, Sendroiu M and Chisevescu D: Contrast enhanced ultrasound for the characterization of hepatocellular carcinoma. *Med Ultrason* (2011) 13: 108–113.
- Haradome H, Grazioli L, Tinti R, Morone M, Motosugi U, Sano K, Ichikawa T, Kwee TC and Colagrande S: Additional value of gadoxetic acid-DTPA-enhanced hepatobiliary phase MR imaging in the diagnosis of early-stage hepatocellular carcinoma: Comparison with dynamic triple-phase multidetector CT imaging. *J Magn Reson Imaging* (2011) 34: 69–78.
- Bouza C, López-Cuadrado T, Alcázar R, Saz-Parkinson Z and Amate JM: Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol* (2009) 29: 502–510.
- Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y and Zeng Y: A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* (2010) 252: 903–912.
- Zarrinpar A, Kaldas F and Busuttil RW: Liver transplantation for hepatocellular carcinoma: an update. *Hepatobiliary Pancreat Dis Int* (2011) 10: 234–242.
- Adachi E, Maeda T, Kajiyama K, Kinukawa N, Matsumata T, Sugimachi K and Tsuneyoshi M: Factors correlated with portal venous invasion by hepatocellular carcinoma: univariate and multivariate analyses of 232 resected cases without preoperative treatments. *Cancer* (1996) 77: 2022–2031.
- Stuart KE, Anand AJ and Jenkins RL: Hepatocellular carcinoma in the United States: Prognostic features, treatment outcome, and survival. *Cancer* (1996) 77: 2217–2222.
- Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, Nakanuma Y, Okita K, Omata M, Takayasu K and Yamaoka Y: Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. *Cancer* (2004) 101: 796–802.
- Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA and Giulini SM: Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg* (2006) 243: 229–235.
- Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J and Bruix J: Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* (1999) 29: 62–67.
- Villa E, Moles A, Ferretti I, Buttafoco P, Grottoia A, Del Buono M, De Santis M and Manenti F: Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival. *Hepatology* (2000) 32: 233–238.
- Minagawa M and Makuuchi M: Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* (2006) 12: 7561–7567.
- Tublin ME, Dodd GD 3rd and Baron RL: Benign and malignant portal vein thrombosis: differentiation by CT characteristics. *AJR Am J Roentgenol* (1997) 168: 719–723.
- Ikai I, Hatano E, Hasegawa S, Fujii H, Taura K, Uyama N and Shimahara Y: Prognostic index for patients with hepatocellular carcinoma combined with tumor thrombosis in the major portal vein. *J Am Coll Surg* (2006) 202: 431–438.
- Cho SJ, Yoon JH, Hwang SS and Lee HS: Do young hepatocellular carcinoma patients with relatively good liver function have poorer outcomes than elderly patients? *J Gastroenterol Hepatol* (2007) 22: 1226–1231.
- Takizawa D, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, Katakai K, Kojima A, Matsuzaki Y and Mori M: Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteris-

- tics, prognosis, and patient survival analysis. *Dig Dis Sci* (2007) 52: 3290-3295.
19. Kondo K, Chijiwa K, Kai M, Otani K, Nagaike K, Ohuchida J, Hiyoshi M and Nagano M: Surgical strategy for hepatocellular carcinoma patients with portal vein tumor thrombus based on prognostic factors. *J Gastrointest Surg* (2009)13: 1078-1083.
  20. Chen XP, Qiu FZ, Wu ZD, Zhang ZW, Huang ZY, Chen YF, Zhang BX, He SQ and Zhang WG: Effects of location and extension of portal vein tumor thrombus on long-Term outcomes of surgical treatment for hepatocellular carcinoma. *Ann Surg Oncol* (2006) 13: 940-946.
  21. Lee HS, Kim JS, Choi IJ, Chung JW, Park JH and Kim CY: The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. *Cancer* (1997) 79: 2087-2094.
  22. Minagawa M, Makuuchi M, Takayama T and Ohtomo K: Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. *Ann Sur* (2001) 233: 379-384.
  23. Lewin K and Millis RR: Human radiation hepatitis. A morphologic study with emphasis on the late changes. *Arch Pathol* (1973) 96: 21-26.
  24. Stillwagon GB, Order SE, Guse C, Leibel SA, Asbell SO, Klein JL and Lechner PK: Prognostic factors in unresectable hepatocellular cancer: Radiation Therapy Oncology Group Study 83-01. *Int J Radiat Oncol Biol Phys* (1991) 20: 65-71.
  25. Yamada K, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E, Matsumoto S, Soejima T and Sugimura K: Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* (2003) 57: 113-119.
  26. Yoon SM, Lim YS, Won HJ, Kim JH, Kim KM, Lee HC, Chung YH, Lee YS, Lee SG, Park JH and Suh DJ: Radiotherapy Plus Transarterial Chemoembolization for Hepatocellular Carcinoma Invading the Portal Vein: Long-Term Patient Outcomes. *Int J Radiat Oncol Biol Phys* (2011) May 26. [Epub ahead of print]
  27. Tandon P and Garcia-Tsao G: Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. *Liver Int* (2009) 29: 502-510.
  28. Lauwers GY, Terris B, Balis UJ, Batts KP, Regimbeau JM, Chang Y, Graeme-Cook F, Yamabe H, Ikai I, Cleary KR, Fujita S, Flejou JF, Zukeberg LR, Nagorney DM, Belghiti J, Yamaoka Y, Vauthey JN and International Cooperative Study Group on Hepatocellular Carcinoma: Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. *Am J Surg Pathol* (2002) 26: 25-34.
  29. Yang Y, Nagano H, Ota H, Morimoto O, Nakamura M, Wada H, Noda T, Damdinsuren B, Marubashi S, Miyamoto A, Takeda Y, Dono K, Umeshita K, Nakamori S, Wakasa K, Sakon M and Monden M: Patterns and clinicopathologic features of extrahepatic recurrence of hepatocellular carcinoma after curative resection. *Surgery* (2007) 141: 196-202.
  30. Ikenaga N, Chijiwa K, Otani K, Ohuchida J, Uchiyama S and Kondo K: Clinicopathologic characteristics of hepatocellular carcinoma with bile duct invasion. *J Gastrointest Surg* (2009) 13: 492-497.
  31. The Cancer of the Liver Italian Program Investigators: A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators *Hepatology* (1998) 28: 751-755.
  32. Yamanaka N, Tanaka T, Tanaka W, Yamanaka J, Yasui C, Kuroda N, Takada M and Okamoto E: Correlation of hepatitis virus serologic status with clinicopathologic features in patients undergoing hepatectomy for hepatocellular carcinoma. *Cancer* (1997) 79: 1509-1515.
  33. Wu CC, Ho WL, Chen JT, Tang JS, Yeh DC and P'eng FK: Hepatitis viral status in patients undergoing liver resection for hepatocellular carcinoma. *Br J Surg* (1999) 86: 1391-1396.
  34. Yano Y, Yamashita F, Sumie S, Kuwaki K, Yamamoto H, Toyoda N, Ando E, Tanaka M and Sata M: Clinical significance of antibody against hepatitis B virus core antigen in patients with hepatitis C virus-related hepatocellular carcinoma. *Liver Int* (2003) 23: 227-231.
  35. Uka K, Aikata H, Takaki S, Shirakawa H, Jeong SC, Yamashina K, Hiramatsu A, Kodama H, Takahashi S and Chayama K: Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* (2007) 13: 414-420.
  36. Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, Goto T, Omata M, Yoshida H and Koike K: Hepatocellular carcinoma with extrahepatic metastasis: Clinical features and prognostic factors. *Cancer* (2011) 117: 4475-4483.