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ORIGINAL ARTICLE

Hepatocellular carcinoma and macrovascular tumor thrombosis: treatment outcomes and prognostic factors for survival

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Abstract

Purpose To determine the treatment outcome and prognostic factors for survival in patients with hepatocellular carcinoma (HCC) and macrovascular tumor thrombosis (MTT).

Methods Between January 2010 and December 2018, 66 patients diagnosed with HCC and MTT, who received specific treatment were included. Various clinical and imaging data, treatment methods, outcomes, prognostic factors, and overall survival were evaluated. Outcomes were compared with those of 24 patients treated with supportive care.

Results Most patients with HCC and MTT showed disease progression (80.3%) and a low 5-year survival rate. The median survival time after treatment was 13 months (vs. supportive care group 3 months, $p < 0.001$). Main branch MTT ($p = 0.036$), extent of tumor thrombus > 1 segment ($p = 0.039$), presence of ascites ($p = 0.009$) and among treatment methods, systemic therapy alone ($p = 0.007$), and supportive care ($p < 0.001$) compared with combined local with systemic therapies were prognostic factors for poor survival.

Conclusions Although most patients with HCC and MTT showed disease progression, median survival time was significantly longer than that with supportive care. Main branch and > 1 segment involvement of MTT and presence of ascites were significant prognostic factors for poor survival. Combined local and systemic therapy over systemic therapy alone are recommended for patients with these advanced stage HCCs.

Keywords Hepatocellular carcinoma · Macrovascular invasion · Tumor thrombosis · Treatment outcome · Survival

Introduction

Tumor macrovascular invasion of the hepatic and/or portal vein branches occurs frequently during the natural course of hepatocellular carcinoma (HCC) [1]. It has been reported that approximately 10–40% of patients with HCC have portal vein tumor thrombus at the time of diagnosis [2]. HCC with macrovascular tumor thrombosis (MTT) is associated with a poor prognosis and significantly reduces the median survival compared with HCC without MTT [3]. A combination of factors including the intrinsic aggressiveness of tumor; large tumor size, high tumor grade, high serum alpha-fetoprotein (AFP) concentration, increased portal vein pressure, increased risk of tumor spread, and reduced tolerance to treatment may ultimately result in poor survival outcomes ranging from 2 to 4 months after supportive care [4, 5].

The Barcelona Clinic Liver Cancer (BCLC) staging system, endorsed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver (EASL) 2018 guidelines, classifies HCC with MTT as advanced HCC (stage C) [6, 7]. Although antiangiogenics are currently the only evidence-based therapeutic option for patients with HCC and MTT, studies have shown a poor response rate and a slightly increased median overall survival of 3.1–6.0 months in response to antiangiogenic treatment [8, 9]. Locoregional therapies including transarterial chemoembolization (TACE) are more commonly performed in the clinical practice in the Asia–Pacific region. Therefore, TACE and/or radiation therapy (RT) are suggested as an alternative or first-line treatment in patients

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with MTT and no extrahepatic metastasis in the clinical practice guidelines of the Asian Pacific Association for the Study of the Liver (APASL) [10], the Japan Society of Hepatology (JSH) guidelines, the Hong Kong Liver Cancer staging system [11, 12], and the Korean Liver Cancer Study Group-National Cancer Center (KLCSG-NCC) [13]. HCC with MTT is a heterogeneous group of diseases with variable prognosis; the choice of treatment is based on the extent of MTT, presence of extrahepatic metastasis, background liver cirrhosis, and the patients' performance status [6]. Therefore, the optimal treatment for advanced-stage HCC is still controversial. Individualized management strategies should be investigated beyond the established recommendations to broaden the treatment options including surgery, locoregional therapy, and systemic therapy.

In this study, we attempted to evaluate the outcomes of various individualized treatment strategies and to determine the prognostic factors for the survival outcome of patients with HCC and MTT.

Materials and methods

Study population

This study was approved by our institutional review board and the requirement for informed consent was waived because of the retrospective nature of the study. Between January 2010 and December 2018, 183 patients diagnosed with HCC and MTT in the liver dynamic computed tomography (CT) and magnetic resonance imaging (MRI) with liver-specific contrast agent (Gadolinium ethoxybenzyl-diethylenetriamine pentaacetic acid; Gd-EOB-DTPA, Primovist, Bayer Schering Pharma, Berlin, Germany) were enrolled in the study. MTT was defined as a visually identified tumor thrombosis involving the major vessels of liver such as the portal vein (PV), hepatic vein (HV), and inferior vena cava (IVC). Among them, 116 patients were excluded because of (1) supportive care without specific treatment ($n = 61$), (2) no identifiable macroscopic tumor thrombus ($n = 15$), (3) presence of bland thrombosis only ($n = 21$), (4) transfer to other hospital without treatment ($n = 5$), (5) no follow-up imaging data after treatment ($n = 6$), (6) death without treatment ($n = 4$), (7) other malignant tumor confirmed by biopsy ($n = 3$), and (8) intraductal thrombus only ($n = 1$). Finally, a total of 66 patients with HCC and MTT were included in this study after excluding one patient who underwent hepatic resection, as resection is considered a curative treatment, which is beyond the scope of this study (Fig. 1). In addition, of the 61 patients who did not receive a specific treatment, after excluding 37 patients (28 patients without follow-up data after diagnosis, five who died immediately after diagnosis, three without identifiable tumor thrombosis, and one with biopsy-proven cholangiocarcinoma), 24 patients were classified into a supportive care group. These patients only received conservative management according to the symptoms without a specific treatment for HCC and MTT.

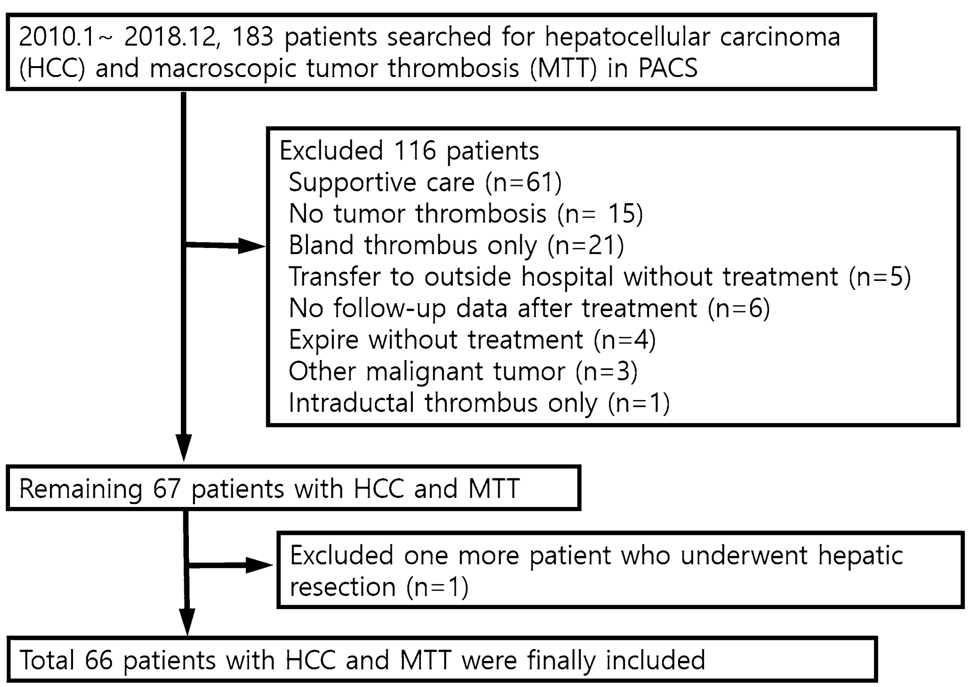

Fig. 1 Flowchart of patient selection

Clinical data analysis

Patients' clinical characteristics were evaluated, including age, sex, presence of chronic hepatitis, etiology of the hepatitis, history of alcohol consumption, presence of co-morbidities, Child–Pugh class, modified Union for International Cancer Control (mUICC) stage, presence of lymphadenopathy, timepoint of developing tumor thrombosis (whether at the time of initial diagnosis or recurrence in the posttreatment period), and presence of extrahepatic metastasis. Serum AFP, protein induced by vitamin K absence or antagonist-II (PIVKA-II), albumin, bilirubin levels, and the albumin–bilirubin (ALBI) grade were also determined.

Various treatment methods were evaluated and the median survival time after treatment was calculated by month unit. The treatment outcomes were classified into four categories; progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR) and were evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [14]. The sum of enhancing tumor portions was indicated, as target lesions and MTT was indicated as a non-target lesion. Axial images were mainly used to measure the long diameter of target lesions. We reviewed the baseline images at the time of diagnosis, serial images during follow-up period and the last follow-up images, and determined the outcome among four categories.

Selection of treatment methods

Transarterial chemoembolization (TACE) was performed in the patients with (1) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (2) Child–Pugh class A or B, (3) platelet count ≥ 75,000/mm^3, and (4) tolerable hepatic function with a total bilirubin level ≤ 2 mg/dL, and serum aspartate aminotransferase (AST)/alanine transaminase (ALT) ≤ threefold limit of the normal range regardless of the extent of MTT. However, patients with a poor general condition such as (1) ECOG performance status 3 or 4, (2) Child–Pugh class C, (3) serum creatinine ≥ 1.5 mg/dL, or (4) extensive extrahepatic disease (e.g., lymphadenopathy or distant metastases) were not considered candidates for TACE. Regarding the procedure, superselection of the feeding arteries of the hyperstaining main tumor and MTT was performed and a mixture of 50–75 mg doxorubicin (Adriamycin, IldongPharm., Seoul, Korea) and 10 mL iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) was infused, followed by embolization with gelatin sponge (Gelix, Medical Impact Inc., Korea) 150–350 µm, 350–510 µm, 500–700 µm according to the size of the feeding arteries until a near stasis of arterial flow. Immediately after TACE, lipiodol CT was performed to evaluate the lipiodolization status of the tumor mass and MTT. Follow-up CT or MR was usually performed at 2–3 months after the procedure to evaluate the result of TACE, and if a viable tumor remained, repeat TACE would be additionally performed. In case if multiple TACEs were planned for large tumors prior to the initial treatment, repeat TACEs were performed with 1–2 month interval.

Radiation therapy (RT) was performed in patients who underwent TACE or were treated with antiangiogenics as a palliative treatment. Patients who showed a poor response or progression after TACE or antiangiogenics, or had a symptomatic condition, such as bile duct invasion, were selected for RT. RT was performed with a total dose of 3750–6100 cGy during 15–20 fractions depending on the tumor burden. Systemic chemotherapy was usually administered with antiangiogenics in patients with metastatic HCC and MTT, and the regimen at our institution was doxorubicin plus cisplatin.

Imaging data analysis

Two reviewers (5 years and 11 years of experience in abdominal radiology, respectively) reviewed the imaging data obtained by liver dynamic CT and MRI with liver-specific contrast agent. Any disagreement was resolved by a consensus. In case of multiple tumors in the liver, the largest or/and relevant tumor mass leading to tumor thrombus (TT) was indicated as the main tumor. The characterization of the main tumor included the tumor location (central, peripheral, or both); the largest diameter of the tumor measured in centimeters; tumor size (< 3 cm, 3–5 cm, > 5 cm); total number of tumors; and type of morphology (nodular, infiltrative, or bilobar). Regarding the tumor location, central location was defined if the tumor was located at the level of the main and first-order PV in the vicinity of hepatic hilum. Peripheral location was defined if the tumor was located at the level of second or distal to the second-order PV branches near the periphery and subcapsular portion of liver. In addition, the locations of TT, PV, and HV (central, peripheral, or both) were investigated. Central location of TT was defined as involvement of the main and first order branch of PV, IVC, and the major branch of HV. Peripheral location of TT was defined as involvement of a second- and third-order branch of the PV and HV. The presence of co-existing tumor thrombosis in other vessels, extent of portal vein tumor thrombus (PVTT), presence of bile duct invasion by TT, and co-existing bland thrombosis was also investigated. The extent of PVTT was defined according to the liver cancer study group of Japan classification: Vp1 (third-order branch), Vp2 (second-order branch), Vp3 (right or left, first-order branch), and Vp4 (main or contralateral portal vein) [15]. Among the four segments of the PV (main, first-, second-, and third-order branches) and three segments of the HV (IVC, main, and peripheral branches), involvement of more than one segment with TT was defined as a longer extent > 1 segment. Liver conditions (normal, fatty liver, chronic liver disease, or liver cirrhosis) and pattern of the liver parenchyma in the hepatobiliary phase (HBP) of MRI (normal, mild-to-moderate dysfunctional, or severe dysfunctional pattern) were also evaluated. Chronic liver disease was defined as the presence of hepatomegaly, hepatic angle blunting on liver dynamic CT, or reticular pattern of the parenchyma in the HBP of liver MRI. Liver cirrhosis was defined as the presence of marginal serration. Regarding the parenchymal pattern in the HBP, the absence of reticular pattern in the parenchyma and a distinct vascular marking was defined as 'normal'; the presence of a mild reticularpattern in the parenchyma, a slightly indistinct vascular marking and mildly reduced parenchymal enhancement, was defined as 'mild-to-moderate' dysfunctional pattern, and the presence of a severe reticular pattern in the parenchyma, an indistinct vascular marking, and a reduced parenchymal enhancement was defined as 'severe' dysfunctional pattern.

Statistical analysis

The numerical data were presented as mean and standard deviation and the categorical data were presented as percentages. Univariate and multivariate analyses using the Cox proportional hazard ratio were performed to determine the prognostic factors for survival. Kaplan–Meier curves were generated to determine the survival rates during the follow-up period. Log-rank test was performed to evaluate the differences in the survival curves among the several categories. All statistical analyses were performed using statistical software (SPSS, version 21; Chicago, IL, USA) and two-sided p values < 0.05 were considered statistically significant.

Results

Clinical characteristics and the imaging findings of the study population

The clinical characteristics of the patients and imaging data are presented in Tables 1 and 2. The mean age was 59.4 ± 10.9 years, and the majority were male patients (n = 58, 87.9%). Most of the patients had chronic hepatitis (95.5%); the etiology of the hepatitis was mostly viral hepatitis B (82.8%) and C (6.3%). Near half of the patients had co-morbidities (n = 28, 42.4%). Most of the patients were Child–Pugh class A (74.2%) and the mUICC stages were 3, 4a, and 4b. Eight (12.1%) patients had lymph node metastasis, 12 (18.2%) had extrahepatic metastasis (8 lung, 2 bone, 2 adrenal, and 1 peritoneal carcinomatosis), and 10 (15.2%) patients had ascites. The median serum AFP was 554.3 ng/mL and ALBI grade was mostly grade 1 (54.5%) and 2 (42.4%). The mean largest diameter of the main tumor was 7.2 ± 4.1 cm, and most of the tumors (84.8%) were > 3 cm. A single tumor was presented in 37.9% of the patients; however, 28.8% of patients had multiple tumors more than three. Central location of the main tumor was observed in 40.9% of the patients. The type of morphology of the tumors was mainly nodular (56.9%) followed by infiltrative (41.5%). Most of the TT were in the PVs (96.9%) and two patients had TT in the HVs. Central location of TT was observed in 60.6% of patients. Ten patients (15.2%) had a co-existing TT in other vessels such as HVs, IVC, and PVs. Among the four categories of the extent of PVTT, first-order branch involvement was the most common (42.2%) followed by second-order branch involvement (25.0%). Nine patients (13.6%)

Table 1 Clinical information of patients who received specific treatments (n = 66)

	Number of patients (n = 66)
Age (years old, mean ± SD)	59.4 ± 10.9
Male gender, n (%)	58 (87.9)
Chronic hepatitis, n (%)	63 (95.5)
Etiology of hepatitis, n (%)	
HBV	52 (82.5)
HCV	4 (6.3)
Alcoholic	13 (20.6)
Child–Pugh class, n (%)	
A	49 (74.2)
B	13 (19.7)
C	4 (6.0)
Alcohol history, n (%)	31 (47)
Timepoint of developing tumor thrombosis	
Initial diagnosis	44 (66.7)
Recurrence	22 (33.3)
Co-morbidity, n (%)	28 (42.4)
Diabetes mellitus (DM)	9 (32.1)
Hypertension (HTN)	10 (35.7)
DM + HTN	9 (32.1)
Others (congestive heart failure, chronic renal disease, stroke)	4 (14.3)
mUICC stage	
Stage 3	19 (28.8)
Stage 4a	41 (62.1)
Stage 4b	6 (9.0)
AFP (ng/mL, median, range)	554.3 (60,498.65)
AFP ≥ 200 ng/mL, n (%)	38 (57.6)
PIVKA II (mAI/mL, median, range)	711.0 (74,984)
ALBI (Albumin-Bilirubin) grade	
Grade 1	36 (54.5)
Grade 2	28 (42.4)
Grade 3	2 (3.0)
Extrahepatic lymphadenopathy, n (%)	8 (12.1)
Extrahepatic metastasis, n (%)	12 (18.2)

Table 2 Imaging findings of patients with HCC and macrovascular tumor thrombosis (MTT) who received specific treatments

	Number of patients ($n=66$)
Location of main tumor (HCC), *n* (%)	
Central	19 (28.8)
Peripheral	38 (57.6)
Both	8 (12.1)
The largest diameter of main tumor (cm, mean ± SD)	7.2 ± 4.1
3 cm >	10 (15.4)
3–5 cm	14 (21.5)
5 cm <	41 (63.1)
Number of tumors, *n* (%)	
1	25 (37.9)
2–3	22 (33.3)
4–6	9 (13.6)
7–10	10 (15.2)
Tumor type, *n* (%)	
Nodular	37 (56.9)
Infiltrative	27 (41.5)
Bilobar	1 (1.5)
Location of tumor thrombosis	
Central	12 (18.2)
Peripheral	26 (39.4)
Both	28 (42.4)
Co-existing tumor thrombosis in other vessels, *n* (%)	10 (15.2)
Extent of portal venous tumor thrombosis (PVTT)[a]	
VP1 (third-order branch)	10 (15.6)
VP2 (second-order branch)	16 (25.0)
VP3 (right or left first portal vein)	27 (42.2)
VP4 (main portal vein)	11 (17.2)
Bile duct invasion of tumor thrombosis, *n* (%)	20 (30.3)
Co-existing bland thrombosis, *n* (%)	9 (13.6)
Ascites, *n* (%)	10 (15.2)
Background liver: liver cirrhosis	58 (87.9)
Parenchymal pattern of liver on hepatobiliary phase	
Normal	3 (4.9)
Mild-to-moderate dysfunctional pattern	44 (72.1)
Severe dysfunctional pattern	14 (23.0)

[a]According to liver cancer study group of Japan classification

had a co-existing bland thrombosis and 20 patients (30.3%) showed bile duct invasion by the TT. Liver background was mostly liver cirrhosis (87.9%). Mild-to-moderate dysfunctional pattern (72.1%) was the most common parenchymal type in the HBP of liver MRI.

Treatment outcomes

Overall, 36.8% of the patients were treated with transarterial chemoembolization (TACE), 13.2% were treated with TACE with radiation therapy (RT), 11.9% were treated with TACE with RT and antiangiogenics, 5.9% were treated with RT and antiangiogenics, 4.5% were treated with TACE and antiangiogenics, 4.4% were treated with antiangiogenics and chemotherapy, and 20.6% were treated with antiangiogenics alone. Most of the patients showed disease progression (80.3%). The median survival time after treatment was 13 months (95% CI 9.7–16.3). The 6-month, 1-year, 3-year, and 5-year survival rates were 77%, 55%, 34%, and 7%, respectively (Table 3, Figs. 2, 3).

Table 3 Treatment outcomes of the patients with HCC and MTT

	Number of patients ($n=66$)
Methods of treatment	
TACE	25 (37.8)
TACE + RT	9 (13.6)
TACE + RT + antiangiogenics	7 (10.6)
TACE + antiangiogenics	4 (6.0)
RT + antiangiogenics	4 (6.0)
Antiangiogenics + CTX	3 (4.5)
Antiangiogenics	14 (21.2)
Outcomes of treatment	
Progressive disease	53 (80.3)
Stable disease	4 (6.1)
Partial response	8 (12.1)
Complete response	1 (1.5)
Survival rate (%)	
6 month	77
1 yr	55
3 yr	34
5 yr	7
Median survival time after treatment (months, 95% CI)	13.0 (9.7–16.3)

TACE transarterial chemoembolization, *RT* radiation therapy, *CTX* chemotherapy, *yr* year, *CI* confidence interval

Comparison with the supportive care group

The clinical, imaging data, and the median survival time of supportive care group compared with those of treated group are presented in Supplementary Table 1. The supportive care group showed a more advanced Child–Pugh class, ALBI grade ($p<0.001$), and mUICC stage ($p=0.013$) than the treated group. The tumor masses were larger in size (11.9 ± 4.7 vs. 7.2 ± 4.1), more frequently multiple (91.7% vs. 62.1%), and with central location (87.5% vs. 40.9%) in the supportive care group. Longer extent of TT (more than 1 segment, 91.7% vs. 65.2%), main PV involvement with TT (75% vs. 17.2%), and as cites (91.7% vs. 15.2%) were more common in the supportive care group. The median survival time was 3 months (95% CI 2.4–3.6) which was significantly

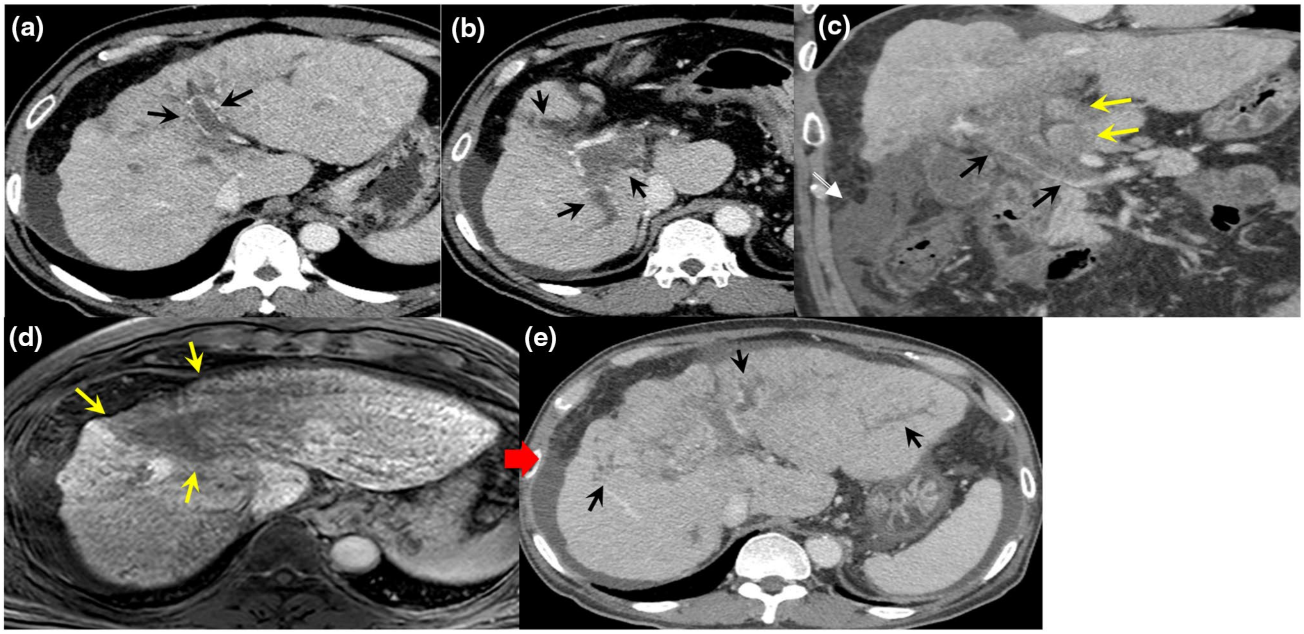

Fig. 2 56-year-old male with HCC and macrovascular tumor thrombosis (MTT) showing disease progression. **a**–**c** Initial contrast-enhanced CT images in the portal phase show a long segmental tumor thrombosis in the main-, first-, second-, and third-order branches of the portal vein. There were metastatic LAP in the porta hepatis (yellow arrows) and ascites (double lined arrow). **d** Initial liver MRI in the hepatobiliary phase shows an infiltrative tumor in the liver S4 segment (yellow arrows). Note the indistinct vascular markings and marked reticular pattern of the background liver. **e** Although he was treated with antiangiogenics, bile duct invasion by the tumors and the ascites progressed. The patient died 5 months after the systemic treatment

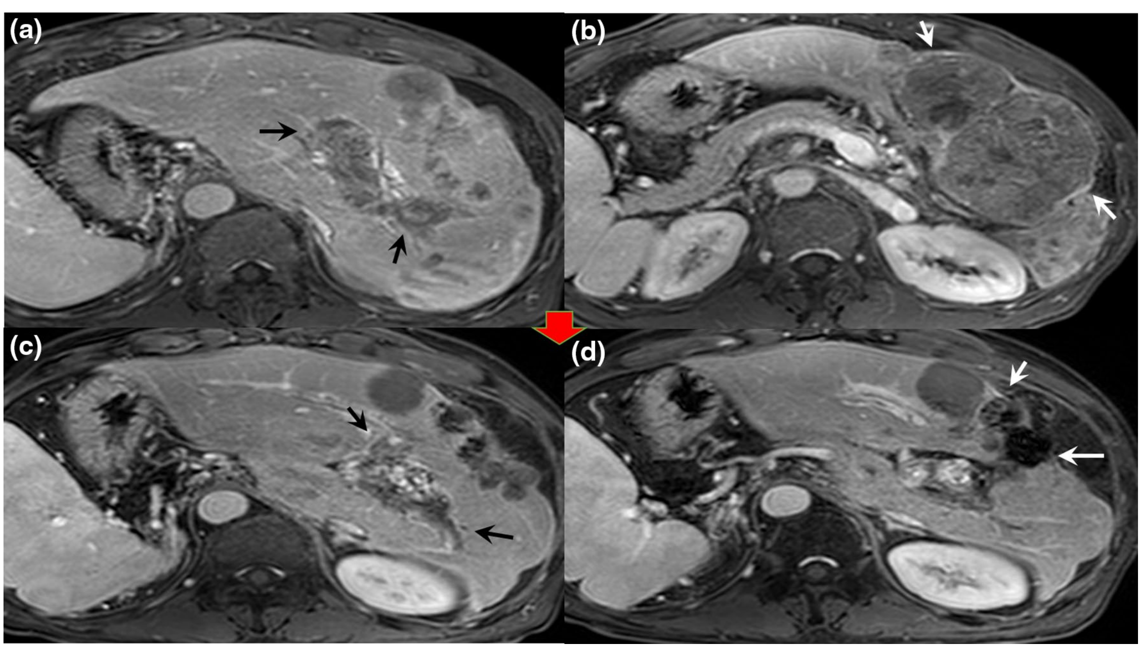

Fig. 3 59-year-old male with HCC and MTT showing improvement after treatment. **a**, **b** Pretreatment MRI in the portal phase shows tumor thrombosis in both first-order portal veins and multinodular HCC masses in the right anterior and left medial segments. This patient had situs inversus totalis. **c**, **d** After TACE with RT, the main tumor and the tumor thrombosis markedly decreased with lipiodolization. He is alive after 8 months of follow-up

shorter than that of the treated group (13 months, 95% CI 9.7–16.3, $p<0.001$).

Prognostic factors for survival

The prognostic factors for survival are listed in Tables 4, 5 and the Kaplan–Meier curves are presented in Fig. 4.

In the univariate analysis, mUICC stage 4b was significantly related to the survival among clinical variables. Main portal vein involvement with TT (Vp4) among four categories of PVTT, longer extent of TT > 1 segment, presence of other intrahepatic tumor, and presence of ascites were significant prognostic factors for survival. Regarding the treatment strategies, supportive care and systemic therapy alone were significant prognostic factors for poor survival compared with local and combined local with systemic therapies.

Multivariable Cox regression analyses confirmed that main portal vein involvement with TT (Vp4, HR 5.46; 95% CI 1.12–26.71; $p=0.036$), longer extent of TT > 1 segment (HR 3.24; 95% CI 1.06–9.89; $p=0.039$), and presence of ascites (HR 3.95; 95% CI 1.40–11.14; $p=0.009$) were significant prognostic factors for poor survival. The supportive care group was included in the categories of treatment methods, and systemic therapy alone (HR 3.48; 95% CI 1.40–8.61, $p=0.007$) and supportive care (HR 11.25; 95% CI 4.08–31.04, $p<0.001$) were associated with a poor overall survival compared with two other groups, i.e., local therapy, and combined local with systemic therapies.

Discussion

In our study, the majority of the patients showed disease progression (80.3%) and a low 5-year overall survival (OS). However, the 1-year OS of our study population was slightly better than those of the previous studies (56% vs.

Table 4 Univariate Cox regression analysis of prognostic factors for survival

	Univariate analysis		
	Hazard ratio	95% CI	*p* value
Number of tumor (multiplicity, ≥ 2)	1.82	0.88–3.77	0.109
Tumor size (cm, mean ± SD)	1.06	0.99–1.13	0.118
Infiltrative tumor type	1.56	0.78–3.12	0.211
Bilobar tumor type	5.14	0.65–40.58	0.121
ARBI (Albumin–bilirubin) grade 3	5.99	0.75–47.67	0.091
Child–Pugh class C	2.27	0.48–10.80	0.303
mUICC stage 4b	**8.90**	**2.80–28.33**	**0.001 >***
Central location of TT	1.53	0.72–3.25	0.270
Extent of PVTT			
Vp1	1		
Vp2	2.64	0.69–10.03	0.153
Vp3	2.31	0.66–8.12	0.192
Vp4	**5.16**	**1.28–20.77**	**0.021***
Long extent of TT (> 1 segment)	**2.96**	**1.22–7.21**	**0.016***
Co-existing bland thrombus	1.54	0.55–4.36	0.411
Presence of tumor thrombus in other vessels	1.40	0.57–3.43	0.460
Presence of other intrahepatic tumor	**2.18**	**1.03–4.58**	**0.041***
Background liver: Cirrhosis	2.09	0.63–6.97	0.228
Parenchymal pattern on HBP: severe dysfunctional	2.40	1.00–5.76	0.050
Presence of extrahepatic LAP	2.57	0.98–6.78	0.056
Presence of extrahepatic metastasis	1.05	0.43–2.58	0.910
Ascites	**5.85**	**2.39–14.32**	**0.001 >***
Methods of treatment			
Local tx	1		
Local with systemic tx	1.27	0.51–3.16	0.611
Systemic tx	**3.18**	**1.45–6.96**	**0.004***
Supportive care	**15.34**	**6.59–35.72**	**0.001 >***

p value < 0.05 was considered significant

PVTT portal vein tumor thrombosis, *TT* tumor thrombosis, *HBP* hepatobiliary phase, *LAP* lymphadenopathy, *tx* treatment, *SD* standard deviation, *CI* confidence interval

Table 5 Multivariate Cox regression analysis of prognostic factors for survival

	Multivariate analysis		
	Hazard ratio[a]	95% CI	*p* value
Number of tumor (multiplicity, ≥ 2)	1.74	0.78–3.86	0.176
Tumor size (cm, mean ± SD)	1.06	0.97–1.16	0.218
Extent of PVTT			
Vp1	1		
Vp2	2.54	0.57–11.23	0.219
Vp3	2.80	0.69–11.22	0.147
Vp4	**5.46**	**1.12–26.71**	**0.036***
Long extent of TT (> 1 segment)	**3.24**	**1.06–9.89**	**0.039***
Presence of tumor thrombus in other vessels	1.83	0.69–4.91	0.227
Presence of other intrahepatic tumor	2.03	0.91–4.56	0.085
Background liver: Cirrhosis	3.42	0.76–15.44	0.110
Parenchymal pattern on HBP: severe dysfunctional	2.37	0.89–6.33	0.085
Presence of extrahepatic LAP	3.84	0.36–40.75	0.264
Presence of extrahepatic metastasis	1.40	0.49–3.95	0.521
Ascites	**3.95**	**1.40–11.14**	**0.009***
Methods of treatment			
Local tx	1		
Local with systemic tx	1.01	0.36–2.85	0.983
Systemic tx	**3.48**	**1.40–8.61**	**0.007***
Supportive care	**11.25**	**4.08–31.04**	**0.001 >***

p value < 0.05 was considered significant

[a]Adjusted for age, sex, Child–Pugh class, ARBI grade, and mUICC stage

17.8–30.9%) [16, 17]. This difference in the survival might stem from the heterogeneous study population of each study. A similar study from Taiwan reported that the worst OS and the study population consisted of patients with PVTT solely in the main and first-order branches [16]. Conversely, Kim et al. reported an even better 5-year OS compared with that in our study (12% vs. 7%), probably due to the fact they only included patients with segmental PVTT [18]. However, in another study, Luo et al. included all patients with PVTT of both main and segmental branches similar to our study, and they reported a slightly lower 1-year OS (56% vs. 30.9%) [17]. This result may be attributed to the different treatment methods applied in each study; the previous study included only TACE, whereas we included various kinds of treatment. The median survival time of the supportive care group was 3 months in our study, which was significantly lower than that of the treated group and comparable to that in the previous reports [4, 19].

HCC with MTT is more common in tumors of larger size and higher histologic grade [20]. The mean tumor size in our study was 7.2 cm, which is slightly smaller than that in the previous studies (9.8–11.1 cm) [17, 18]; however, 84.8% of the tumors were > 3 cm. Previous reports indicated the tumor size as one of the prognostic factors for survival [16, 21]; however, the tumor size was not a significant factor for survival in this study as demonstrated by the univariate and multivariate analyses. This result can be explained by the intrinsic aggressiveness of tumors with MTT showing mostly large size in this study population.

The extent of MTT was the common significant factor for both unfavorable treatment and survival outcome, consistent with the findings of the previous reports [16, 17, 19, 21, 22]. In other words, main branch involvement with PVTT and IVC involvement were related to significantly worse OS and treatment response than those of segmental PVTT (second- and third-order branches). Therefore, our study supports the need for further stratification of BCLC stage C according to the extent of PVTT corresponding to findings of the previous reports [19]. In addition to the extent of MTT, a longer extent > 1 segment of MTT was additional prognostic factor for poor survival. Thus, along with the main branch involvement, the longer extent of MTT > 1 segment should be considered during patient selection.

Ascites was a prognostic factor for poor survival despite the adjustment of various clinical and laboratory variables. However, there is some controversy regarding ascites as a significant factor for survival. Ajit et al. also reported ascites as a prognostic factor along with Child–Pugh class, a response to TACE [24]. However, although ascites was a significant factor in the univariate analysis, it was excluded from the multivariate analysis in other studies [16, 25]. Instead, serum bilirubin was suggested as a significant

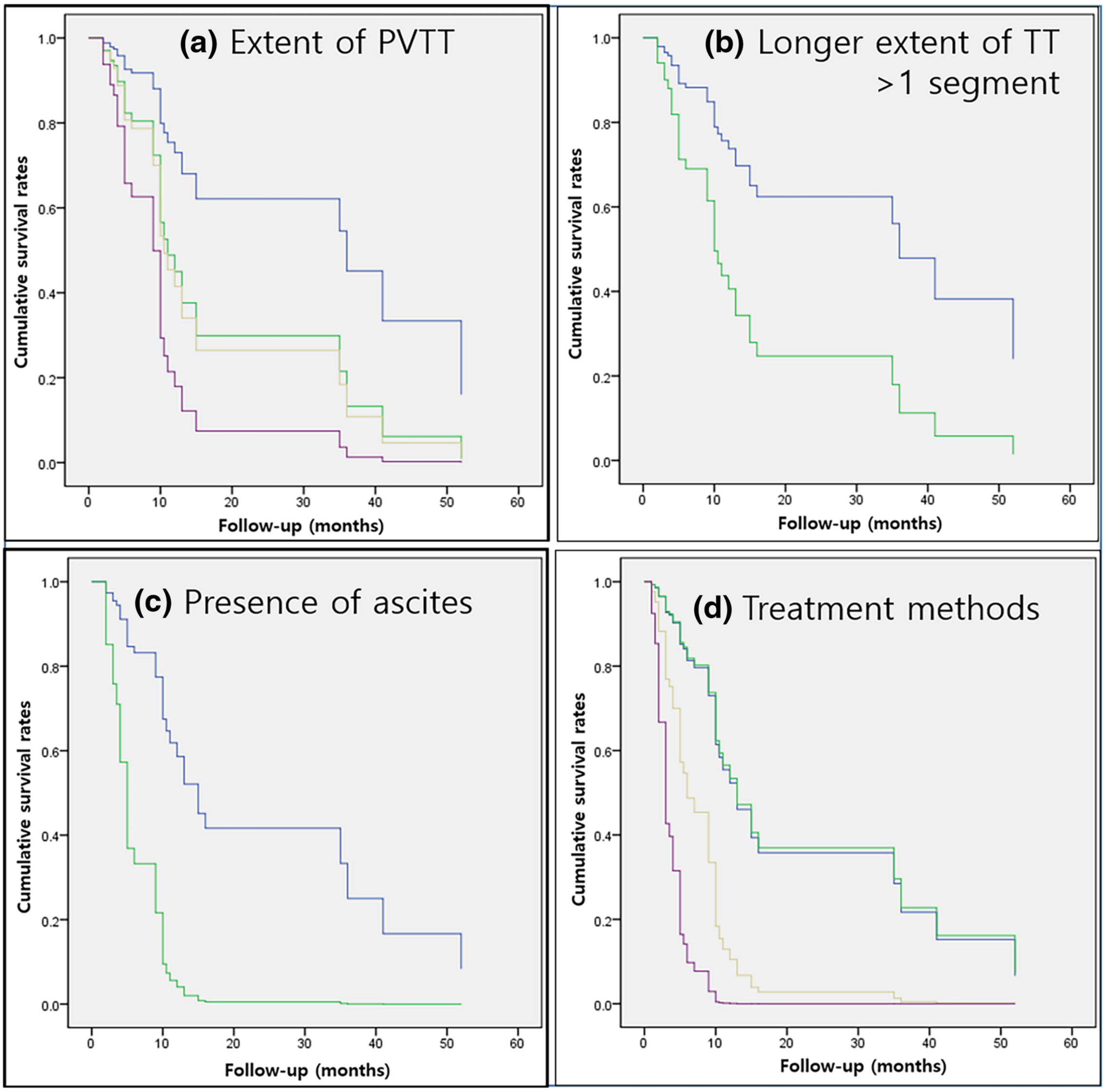

Fig. 4 Kaplan–Meier curves show the patients' survival rates according to several prognostic factors. **a** Location of PVTT. The median survival time is significantly lower with main branch TT (purple line) than that with a third-order branch TT (blue line, $p=0.036$). **b** Long extent of tumor thrombosis, more than one segment. The median survival time with a longer TT (green line) is significantly lower than that with a one segment TT (blue line, $p=0.016$). **c** Presence of ascites. The median survival time is significantly lower with ascites (green line, $p<0.001$) (**d**) treatment methods. The median survival time is significantly lower with systemic therapy alone (yellow line, $p=0.004$) and supportive care (purple line, $p<0.001$) than that with local therapy (blue line) and combined local with systemic therapies (green line)

prognostic factor [17, 25]. Conversely, serum bilirubin was not a significant factor in this study, because the levels were mostly < 2 mg/dL, except in five patients, and the mean serum bilirubin level was only 1.08 mg/dL, which is within normal limits. Serum bilirubin level is a good representative of the hepatic function. It is included in the Child–Pugh classification and may be related to imaging parameters such as parenchymal pattern of the liver background on HBP. In this context, the presence of a severe dysfunctional pattern showing decreased biliary excretion of liver specific agent (Gd-EOB-DTPA) was investigated. This imaging parameter was a significant factor for the survival only in the univariate analysis and not in the multivariate analysis. Ascites and ALBI grade are additional representatives of the liver function. Several reports demonstrated that the ALBI grade is an important predictor for the treatment outcome and survival [26, 27], although ALBI grade was not a significant factor for survival in this study. However, when combining supportive care and treated groups, the ALBI grade turned out to be a significant prognostic factor for survival (HR 4.48, $p=0.017$, Suppl. Table 2). The small difference in ALBI grades among the treated patients and the small size of the study population can be limitations for the analysis of ALBI grade as a prognostic factor. Serum AFP is one of the reliable biomarkers for HCC and is related to the tumor size, vascular invasion, and prognosis of HCC [28]. A recent report demonstrated that radiologic ascites, total bilirubin, and AFP were all related to short-term survival during the post-hepatectomy period in HCC and PVTT group [23]. However, AFP was not a significant factor for OS in our study. Comparing the two studies, the mean serum AFP in our study was much higher than that shown by Huo et al. (7703 vs. 1210 ng/mL). This discrepancy might be due to the fact that the majority of HCCs in their report were solitary (about 90%), which can be candidates for surgery [23]. They also indicated the extent of PVTT as a significant prognostic factor for the long-term survival.

In this study, we compared the three groups, i.e., local therapy alone, combined local with systemic therapies, and systemic therapy alone, and the systemic therapy alone group demonstrated a worse median survival than that of the combined locoregional with systemic therapy group and was associated with a poor prognosis. Hence, we recommend a treatment strategy of combining locoregional and systemic therapies even for patients with advanced stage HCCs with MTT according to the patient's condition.

As previously mentioned, the current clinical practice guidelines recommend antiangiogenics for the treatment of HCC with MTT. However, HCC with MTT is a heterogeneous group of diseases; therefore, various treatment strategies might be applied including surgical resection for resectable cases [29, 30]. Studies on the efficacy of aggressive locoregional therapies are actively undergoing. There are several studies demonstrating good treatment outcomes of TACE [18, 21, 31–33], TACE combined with RT [34–37], and TACE combined with antiangiogenics [38, 39]. Other alternative treatment strategies including radioembolization [40] and hepatic arterial infusion chemotherapy [8, 41] can also be suggested based on the patient's condition. Yttrium-90 trans-arterial radioembolization (TARE) is an emerging treatment strategy for advanced-stage, unresectable HCC. The reported median survival time of TARE-treated patients is 9.7 months [42], and the 6-month, 1-year OS are 76% and 47%, respectively [43], comparable to our results (13 months, and 77% and 55%, respectively). On the other hand, several studies continue to support antiangiogenics for the treatment of advanced-stage HCC, because alternative treatment modalities lack the high-quality evidence [44, 45]. Recently, a randomized clinical trial demonstrated a better treatment outcome and survival benefit for patients treated with TACE and RT compared with those of patients treated with antiangiogenics [46], thereby supporting the results of the previous observational studies [37, 35]. Therefore, individualized multidisciplinary management planning is necessary for patients with advanced-stage HCC. Considering several prognostic factors such as main branch involvement, longer extent of MTT, and presence of ascites, appropriate selection of patient for a more aggressive treatment, and subdivision and stratification of patients according to the prognosis would be possible.

There are several limitations in this study. First, a relatively small number of patients were analyzed. Second, the retrospective design could have incorporated selection bias and inherent flaws in the data analysis. Third, not all patients were with treatment-naïve HCC. Previously treated HCC cases that developed MTT at the time of recurrence were also included. Fourth, heterogeneous treatment strategies were all analyzed resulting in few cases with a rarely applied treatment. To overcome the lack of data in some group, we simplified the various treatment methods into three groups for the comparative analysis. Fifth, there were several missing data in the clinical and imaging variables. Sixth, not all HCC masses were pathologically confirmed in this study. Seventh, six patients were lost to follow-up due to transfer to other hospitals. These patients' data were considered as censored data when calculating OS using the Kaplan–Meier method.

In conclusion, the majority of HCC with MTT cases showed disease progression after a specific treatment and a low 5-year survival rate. Main branch involvement, longer extent of MTT, and presence of ascites were the prognostic factors for the patient's survival. Although patients with HCC with MTT are in the advanced stage, specific treatment such as aggressive locoregional therapy combined with systemic therapy over systemic therapy alone would be recommended according to the patient's condition such as the extent and location of the MTT and the presence of ascites.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical statement This study was approved by our institutional review board and informed consent was waived, because this is a retrospective study using pre-existing data. We declare that all human studies have been performed in accordance with the ethical standards laid down in the 1964 Helsinki declaration and its later amendments.

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