

# Transarterial chemoembolization of hepatocellular carcinoma with segmental portal vein tumour thrombus

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## Abstract

**Objectives** To evaluate the clinical outcome and safety of transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) with segmental or subsegmental portal vein tumour thrombus (sPVTT) in patients with preserved hepatic function, and to address the efficacy of additional chemoinfusion after TACE (TACE+CI).

**Methods** From January 2003 to December 2012, TACE was conducted on 81 patients with Child-Pugh score  $\leq 7$  who had HCC with sPVTT. Thirty-one of them underwent TACE+CI. The overall survival (OS) and serious adverse events (SAEs) were evaluated. The efficacy of TACE+CI was appraised after adjustment with inverse probability of treatment weighting (IPTW).

**Results** The OS after TACE (median, 15.5 months) was significantly related with aspartate aminotransferase (hazard ratio [HR], 1.011), modified Barcelona Clinic Liver Cancer (BCLC) stage D (HR, 2.841), extrahepatic spread (HR, 4.862), and TACE+CI (HR, .367). The SAE incidence was

significantly associated with modified BCLC stages (HR, 10.174 [proper-C] and 24.000 [D]). After IPTW adjustment, TACE+CI significantly improved OS ( $p = .028$ ; HR, .511), but the SAE incidence was not significantly altered ( $p = .737$ ; HR, .819).

**Conclusions** TACE can be an effective and safe treatment option for HCC with sPVTT in patients with preserved hepatic function. Furthermore, additional chemoinfusion can enhance the therapeutic efficacy while maintaining the safety.

## Key Points

- TACE is effective and safe for treating HCC with sPVTT.
- Modified BCLC stages can stratify the risk and benefit of TACE.
- Additional chemoinfusion can enhance the therapeutic efficacy while maintaining the safety.

**Keywords** Hepatocellular carcinoma · Portal vein tumour thrombus · Transarterial chemoembolization · Chemoinfusion · Barcelona Clinic Liver Cancer Stage

This study has not been presented or accepted for presentation at any scientific meetings.

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## Abbreviations

TACE	Transarterial chemoembolization
HCC	Hepatocellular carcinoma
BCLC	Barcelona Clinic Liver Cancer
ECOG	Eastern Cooperation Oncology Group
PVTT	Portal vein tumour thrombus
sPVTT	Segmental or subsegmental portal vein tumour thrombus
CT	Computed tomography
cTACE	Conventional transarterial chemoembolization
TACE+CI	Transarterial chemoembolization plus additional transarterial chemoinfusion
CSPH	Clinically significant portal hypertension
EHS	Extrahepatic spread

MELD	Model for End-stage Liver Disease
OS	Overall survival
AE	Adverse event
CTCAE	Common Terminology Criteria for Adverse Events
SAE	Serious adverse event
IPTW	Inverse probability of treatment weighting
CI	Confidence interval
AST	Aspartate aminotransferase
HR	Hazard ratio

## Introduction

Transarterial chemoembolization (TACE) has been widely used as a palliative treatment option for hepatocellular carcinoma (HCC) [1, 2]. According to the Barcelona Clinic Liver Cancer (BCLC) staging system [3], TACE is regarded as the first-line treatment in patients with multinodular HCCs, Child-Pugh class A or B, and Eastern Cooperation Oncology Group (ECOG) performance status 0 (i.e., BCLC stage B). Recently, however, criticism of the BCLC indication for TACE has been raised by some investigators, as stage B includes patients with very heterogeneous conditions [4–6]. In addition, several studies have reported promising outcomes of TACE in patients beyond BCLC stage B [7–9]. Hence, patient selection for initiating TACE is becoming a key issue to achieve favourable outcomes in HCC patients [10].

Some investigators have extended the indication for TACE, asserting the safety and efficacy of TACE for HCC with portal vein tumour thrombus (PVTT) [8, 11, 12]. Under the current BCLC system, HCC patients with macrovascular invasion are considered to be stage C, regardless of the extent of tumour thrombus (subsegmental, segmental, lobar, or main portal vein). Therefore, the patients are contraindicated to TACE [1–3]. For stage C patients, sorafenib is considered to be the first-line treatment option [13], allowing about 8.1 months of median survival in HCC patients with macrovascular invasion [14]. In this context, HCC with segmental or subsegmental PVTT (sPVTT) in patients with preserved hepatic function are placed in a grey-zone between stages B and C. Given that sorafenib is not a tumoricidal therapy and that sPVTT is quite an early stage of vascular invasion, a more potent treatment may need to be considered for these patients. However, there is only limited knowledge about survival outcomes of TACE for HCC with sPVTT in patients with preserved hepatic function. In addition, little is known about which TACE technique is optimal for these patients. While diverse TACE protocols have been applied for HCC patients with macrovascular invasion, Kim et al. [7] reported a survival benefit of additional chemoinfusion (cisplatin) following TACE in HCC patients with hepatic vein invasion.

Therefore, this retrospective study was conducted to evaluate the clinical outcome and safety of TACE, and to address the efficacy of additional chemoinfusion, for HCC with sPVTT in patients with preserved hepatic function.

## Materials and methods

### Patients

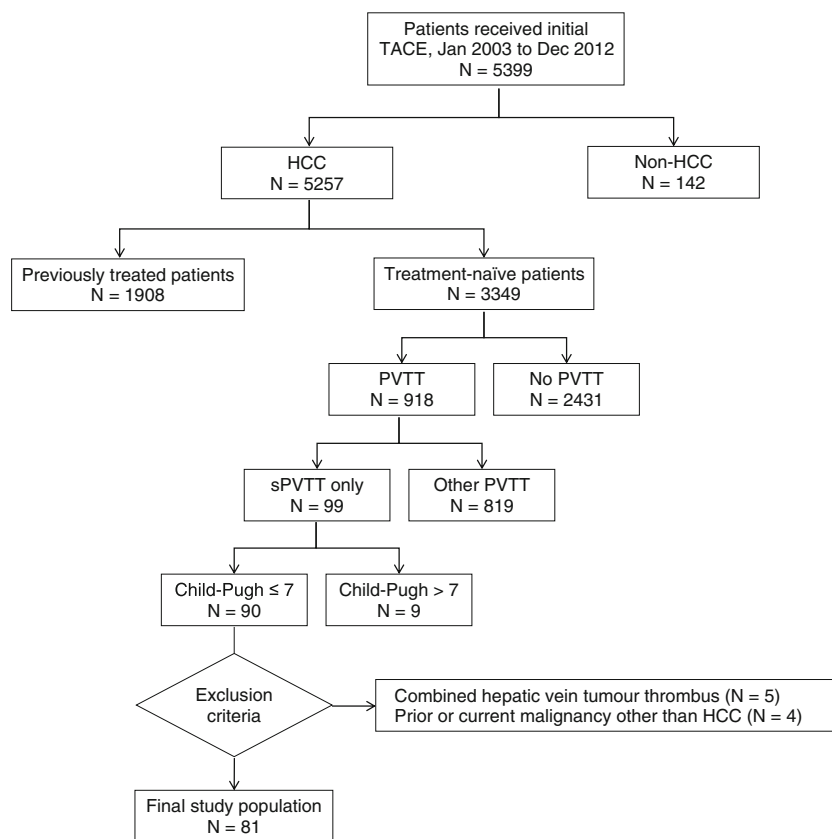
The institutional review board approved this retrospective study, and permitted the waiving of informed consent. From January 2003 to December 2012, a total of 5399 patients received initial TACE at our institution. The inclusion criteria for this study consisted of: 1) HCC diagnosis by biopsy or American Association for the Study of Liver Diseases imaging criteria [1]; 2) treatment-naïve HCC patients who received TACE as first-line therapy; 3) radiologic evidence of sPVTT on dynamic computed tomography (CT) or magnetic resonance images [15–17]; and 4) preserved liver function with Child-Pugh score  $\leq 7$  [5, 18]. The exclusion criteria were: 1) patients having PVTT beyond the segmental portal vein; 2) patients with hepatic vein tumour thrombi; and 3) prior or current malignancy other than HCC.

A total of 81 HCC patients with sPVTT (69 men and 12 women) were finally included in this study (Fig. 1). Their mean age was  $58.0 \pm 9.1$  years (range, 41 to 78 years). Fifty patients (61.7 %, 50/81) were treated with conventional TACE (cTACE) and the remaining 31 patients (38.3 %, 31/81) were managed by TACE plus additional transarterial chemoinfusion (TACE+CI). Twenty-four out of the 81 patients (29.6 %) had clinically significant portal hypertension (CSPH) at the time of initial TACE. CSPH was determined to be present when a patient had one or more of following: 1) varix on upper endoscopy; 2) unequivocal gastric or oesophageal varix on CT imaging; 3) ascites requiring diuretic treatment; or 4) splenomegaly ( $>12$  cm on the largest dimension) with thrombocytopenia (platelet count  $< 100,000/\text{mm}^3$ ) [1, 19–21].

### Pre-procedural evaluation

Multi-detector CT images were obtained within a week prior to TACE, and an experienced radiologist (H.C.K.) evaluated tumour type (nodular, infiltrative), tumour extent (unilobar, multilobar), extrahepatic spread (EHS; present, absent), extent of sPVTT (single, multiple), and ascites (present, absent). Tumour size (cm) was measured for nodular tumours. EHS referred to both distant metastasis and lymph node involvement [13]. Within three days prior to the procedure, blood sampling was conducted to evaluate liver function, coagulation function, serum creatinine, and alpha-fetoprotein. The Model for End-stage Liver Disease (MELD) score was calculated based on the laboratory findings. The BCLC staging system was

**Fig. 1** Flowchart of selecting the study population



modified for detailed analyses: quasi-C was defined as patients with Child-Pugh class A, performance status of ECOG 0, no EHS, and HCC with sPVTT [5]. BCLC stage C patients who did not fulfil the quasi-C criteria were classified as proper-C. Because this study analysed patients during a long period of 10 years, the procedure date was dichotomized (2003 to 2009 years, 2010 to 2012 years), in order to consider whether recent advances in care, if any, may have affected the outcomes.

### Transarterial chemoembolization and additional chemoinfusion

TACE was performed by using 2–12 mL of iodized oil (Lipiodol; Andre Guerbe, Aulnay-sous-Bios, France) mixed with 10–60 mg of doxorubicin hydrochloride (Adriamycin RDF; Ildong Pharmaceutical, Seoul, Korea) as an emulsion. The amount of emulsion administered was determined based on the tumour burden in each tumour-feeding artery. Afterwards, gelatine sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA, or Cutanplast; Mascia Brunelli, Milano, Italy) soaked with 2 mg of mitomycin C (Mitomycin-10; Kyowa Hakko Kogyo, Tokyo, Japan) or 20 mg of doxorubicin hydrochloride solution were used to embolize tumour-feeding arteries. A 2.0-Fr-tip microcatheter (Progreat 2.0; Terumo, Tokyo, Japan) or a 2.4-Fr-tip microcatheter

(MicroFerret; Cook, Bloomington, IN) was advanced into tumour-feeding arteries as selectively as possible, and embolization was conducted until the point when the injected contrast agent was not washed away from a tumour-feeding artery within five heartbeats [7].

The need for additional chemoinfusion was determined by each operator's opinion. For patients in the TACE+CI group, cisplatin solution (Cisplan; Dong-A Pharmaceutical, Seoul, Korea) was administered through arteries supplying sPVTT, after near-complete embolization using gelatine sponge particles. It was surmised that this sequence may enhance cisplatin exposure to HCCs during the first pass and may reduce systemic toxicity. A three-way stopcock was assembled to a microcatheter, then connected by a contrast agent-loaded syringe and by a cisplatin infusion line, in each side. The total dose of cisplatin was 0.7 mg/kg per patient with Child-Pugh class A5 and A6, and it was reduced by 70 % in patients with Child-Pugh class B7 (i.e., 0.49 mg/kg). Cisplatin was prepared as a solution at a concentration of 0.5 mg/mL and administered by an infusion pump at a rate of 4–10 mL/min, depending on the size of the target artery. A weak antegrade flow during chemoinfusion was intermittently checked by the injection of contrast agent. In cases of sPVTT supplied by multiple arteries, the cisplatin solution was divided based on the tumour burden of each artery, and was administered separately.

## Clinical efficacy

Overall survival (OS) was measured from the date of the initial TACE until death from any cause. Because current imaging response criteria are unsuitable for assessing treatment responses of infiltrative HCCs, i.e., non-measurable lesions, and determining the progression of PVTT [22, 23], OS was the only estimate regarding clinical efficacy in this study. The death dates were acquired from the Korean Ministry of Public Administration and Security, which registers the death dates for all citizens, thus follow-up loss did not exist in this study population. The data of survivors were censored at March 2015, and the median follow-up period was 12.7 months (range, 1.0 to 143.9 months).

## Safety

All treatment-emergent adverse events (AEs) were archived from the institutional medical record database and graded according to version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). In terms of postembolization syndrome, i.e., non-infectious fever, nausea, vomiting, fatigue, and/or abdominal pain after the procedure [24], CTCAE grading followed the classification of surgical and medical procedures, and it was not separately evaluated by each symptoms/signs. In contrast, other AEs, such as infectious conditions, followed the classification of a specific set of symptom/signs. Blood sample testing was routinely conducted one month after discharge, which was compared with pre-procedural samples. Because patients with underlying chronic liver disease frequently had abnormal laboratory findings even prior to TACE, the AEs were classified according to the gradient of increase from the pre-procedural to post-procedural CTCAE grades [25].

Treatment-related serious adverse events (SAEs) were defined as those that were immediately life-threatening, resulted in death within 30 days, resulted in permanent or significant disability or incapacity, or extended hospitalization or required unplanned hospitalization [26, 27]. Relatedness to the treatment was determined by an investigator (J.W.C) who was blinded to the treatment protocols (cTACE, TACE+CI).

## Statistical analysis

Baseline characteristics and post-procedural hospitalization periods of the cTACE group and TACE+CI group were compared using the chi-square test or Fisher's exact test for categorical variables, and compared by the independent t-test or Mann-Whitney test for numerical variables.

The Kaplan-Meier method and log-rank test were used to compare the OS depending on a modified BCLC stage and on the treatment protocols (cTACE, TACE+CI). To identify factors affecting OS and SAEs, baseline characteristics and

treatment protocols were evaluated using the Cox proportional hazard and logistic regression analyses, respectively. Type I errors of multiple comparisons on the univariate analyses were corrected using the Bonferroni method with a correction factor of 23 [28]. Thereafter, variables with a Bonferroni-adjusted  $p$ -value  $\leq .10$  were subjected to multivariate Cox proportional hazard or logistic regression analyses [29].

To minimize the effect of potential selection bias between the cTACE group and TACE+CI group, inverse probability of treatment weighting (IPTW) was utilized. Propensity scores were calculated using a logistic regression model to predict the probability of each patient receiving TACE+CI on the basis of 22 baseline characteristics, including pre-procedural CT findings, laboratory findings, and procedure date. According to the propensity scores, stabilized weight, i.e., marginal probability of the observed treatment divided by the conditional probability of the observed treatment, was applied so that inverse probability weighting was not to be overwhelmed by a few severely imbalanced variables. After the adjustment by means of IPTW, the OS and incidence of SAEs between the two treatment groups were compared using the Cox proportional hazard and logistic regression analyses, respectively.

A  $p$ -value of less than .05 was considered to indicate a statistical significance. All statistical analyses were performed using commercial statistics software (MedCalc, version 15.4; MedCalc Software, Ostend, Belgium).

## Results

### Baseline characteristics

The baseline characteristics of our study patients are summarized in Table 1. The TACE+CI group patients had significantly more non-viral aetiology ( $p = .024$ ), lower MELD score ( $p = .004$ ), better Okuda stage ( $p = .044$ ), more infiltrative tumour ( $p = .020$ ), more recent procedure date ( $p = .003$ ), lower serum total bilirubin ( $p = .004$ ), and lower serum creatinine ( $p = .039$ ) compared to the patients who underwent cTACE.

### Technical feasibility

TACE was performed in all included patients without immediate AEs during the procedure. Tumour-feeding arteries of sPVTT were selectively catheterized at the level of the segmental or subsegmental arteries in all patients, and TACE was conducted at the same level (Fig. 2). In patients who underwent TACE+CI, a planned dose of cisplatin was tolerable during the procedure, and was infused through all identified tumour-feeders.

**Table 1** Baseline characteristics of the 81 hepatocellular carcinoma patients with segmental or subsegmental portal vein tumour thrombus

Variable	Overall ( <i>n</i> = 81)	cTACE ( <i>n</i> = 50)	TACE+CI ( <i>n</i> = 31)	Unadjusted <i>p</i> -value	Adjusted <i>p</i> -value*
Sex				.521	.566
Male	69 (85.2)	44 (88.0)	25 (80.6)		
Female	12 (14.8)	6 (12.0)	6 (19.4)		
Age, mean ± SD (year)	58.0 ± 9.1	57.7 ± 9.9	58.6 ± 7.8	.675	.870
Aetiology				.024	.498
Viral	63 (77.8)	43 (86.0)	20 (64.5)		
Non-viral	18 (22.2)	7 (14.0)	11 (35.5)		
CSPH†				.926	.930
Absent	57 (70.4)	35 (70.0)	22 (71.0)		
Present	24 (29.6)	15 (30.0)	9 (29.0)		
Ascites				.292	.264
Absent	77 (95.1)	46 (92.0)	31 (100.0)		
Present	4 (4.9)	4 (8.0)	0 (0.0)		
Child-Pugh class				.292	.276
A	77 (95.1)	46 (92.0)	31 (100.0)		
B	4 (4.9)	4 (8.0)	0 (0.0)		
MELD score, mean ± SD	8.5 ± 1.9	9.0 ± 2.1	7.8 ± 1.2	.004	.106
AST, mean ± SD (IU/L)	61.1 ± 42.3	55.5 ± 32.3	70.1 ± 54.1	.186	.157
ALT, mean ± SD (IU/L)	49.3 ± 39.7	42.3 ± 26.4	60.5 ± 53.5	.292	.159
Albumin, mean ± SD (g/dL)	3.7 ± 0.4	3.7 ± 0.5	3.8 ± 0.4	.085	.131
Total bilirubin, mean ± SD (mg/dL)	1.0 ± 0.4	1.1 ± 0.5	0.8 ± 0.3	.004	.240
INR, mean ± SD	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	.239	.724
Platelet, mean ± SD (billion/L)	164.0 ± 82.9	161.0 ± 75.8	168.8 ± 94.4	.973	.662
Creatinine, mean ± SD (mg/dL)	1.0 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	.039	.206
Modified BCLC stage‡				.091	.323
Quasi-C	38 (46.9)	22 (44.0)	16 (51.6)		
Proper-C	36 (44.4)	21 (42.0)	15 (48.4)		
D	7 (8.6)	7 (14.0)	0 (0.0)		
Okuda stage				.044	.149
I	70 (86.4)	40 (80.0)	30 (96.8)		
II	11 (13.6)	10 (20.0)	1 (3.2)		
Tumour type				.020	.217
Nodular	42 (51.9)	31 (62.0)	11 (35.5)		
Size <sup>  </sup> , mean ± SD (cm)	5.8 ± 3.1	5.8 ± 3.2	5.8 ± 2.8		
Infiltrative	39 (48.1)	19 (38.0)	20 (64.5)		
Tumour extent				.053	.405
Unilobar	55 (67.9)	30 (60.0)	25 (80.6)		
Multilobar	26 (32.1)	20 (40.0)	6 (19.4)		
sPVTT extent				1.000	.506
Single segment	74 (91.4)	46 (92.0)	28 (90.3)		
Multiple segments	7 (8.6)	4 (8.0)	3 (9.7)		
EHS				.776	.762
Absent	64 (79.0)	39 (78.0)	25 (80.6)		
Present	17 (21.0)	11 (22.0)	6 (19.4)		
AFP,				.413	.583
≤ 200 ng/mL	36 (44.4)	24 (48.0)	12 (38.7)		
> 200 ng/mL	45 (55.6)	26 (52.0)	19 (61.3)		
Procedure date				.003	.214
2003 to 2009 year	48 (59.3)	36 (72.0)	12 (38.7)		
2010 to 2012 year	33 (40.7)	14 (28.0)	19 (61.3)		

Abbreviations.—cTACE, conventional TACE; TACE+CI, TACE with adjuvant chemoinfusion; SD, standard deviation; CSPH, clinically significant portal hypertension; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio of prothrombin time; sPVTT, segmental or subsegmental portal vein tumour thrombus; EHS, extrahepatic spread; AFP, alpha-fetoprotein

Note.—Numbers in parenthesis are percentages in a column

\* Adjusted *p*-value by inverse probability of treatment weighting

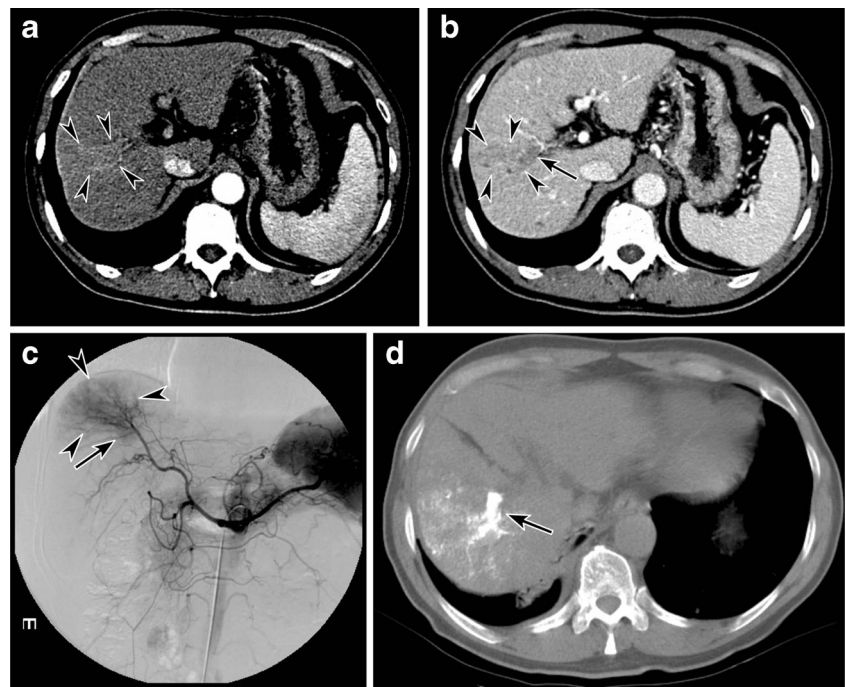
† CSPH was defined as follows: 1) varix on upper endoscopy, 2) unequivocal gastric or oesophageal varix on CT imaging, 3) ascites requiring diuretic treatment, or 4) splenomegaly (>12 cm) with thrombocytopenia (platelet count < 100,000/mm<sup>3</sup>)

‡ Quasi-C was defined as follows: Child-Pugh class A, performance status of 0, no extrahepatic spread, and HCC with sPVTT

The patients had Eastern Cooperation Oncology Group performance status > 2

<sup>||</sup> Tumour size was measured in nodular tumours

**Fig. 2** A 66-year-old-man who had HCC with sPVTT and preserved hepatic function. **a** An axial CT image on the arterial phase showing enhancing, infiltrative HCC (arrowheads) in the right lobe of the liver. **b** An axial CT image on the portal phase presenting infiltrative HCC (arrowheads) with sPVTT (arrow) in the segment VIII portal vein. **c** Digital subtraction angiography demonstrating an enhancing lesion (arrowheads) with sPVTT (arrow) in the segment VIII portal vein. **d** An unenhanced, axial CT image, obtained one month after TACE, showing compact iodized oil uptake (arrow) in the segment VIII portal vein



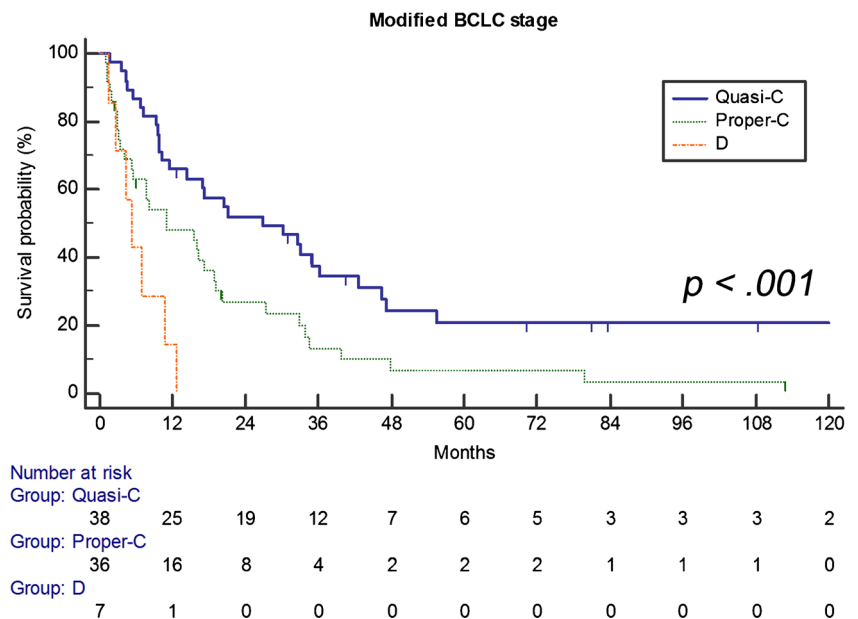
**Clinical efficacy**

The median OS of HCC patients with sPVTT after TACE was 15.5 months (95 % confidence interval [CI], 9.8 to 20.1) (Suppl. Fig. 1). According to modified BCLC stages, the median OS of stage quasi-C, proper-C, and D were 26.9 months (95 % CI, 14.2 to 42.6), 11.0 months (95 % CI, 5.4 to 18.9), and 5.3 months (95 % CI, 2.7 to 10.6), respectively; and they significantly differed ( $p < .001$ ) (Fig. 3). Regarding the treatment protocols, the TACE+CI group (median, 32.7 months; 95 % CI, 17.2 to 46.4) showed significantly longer OS than

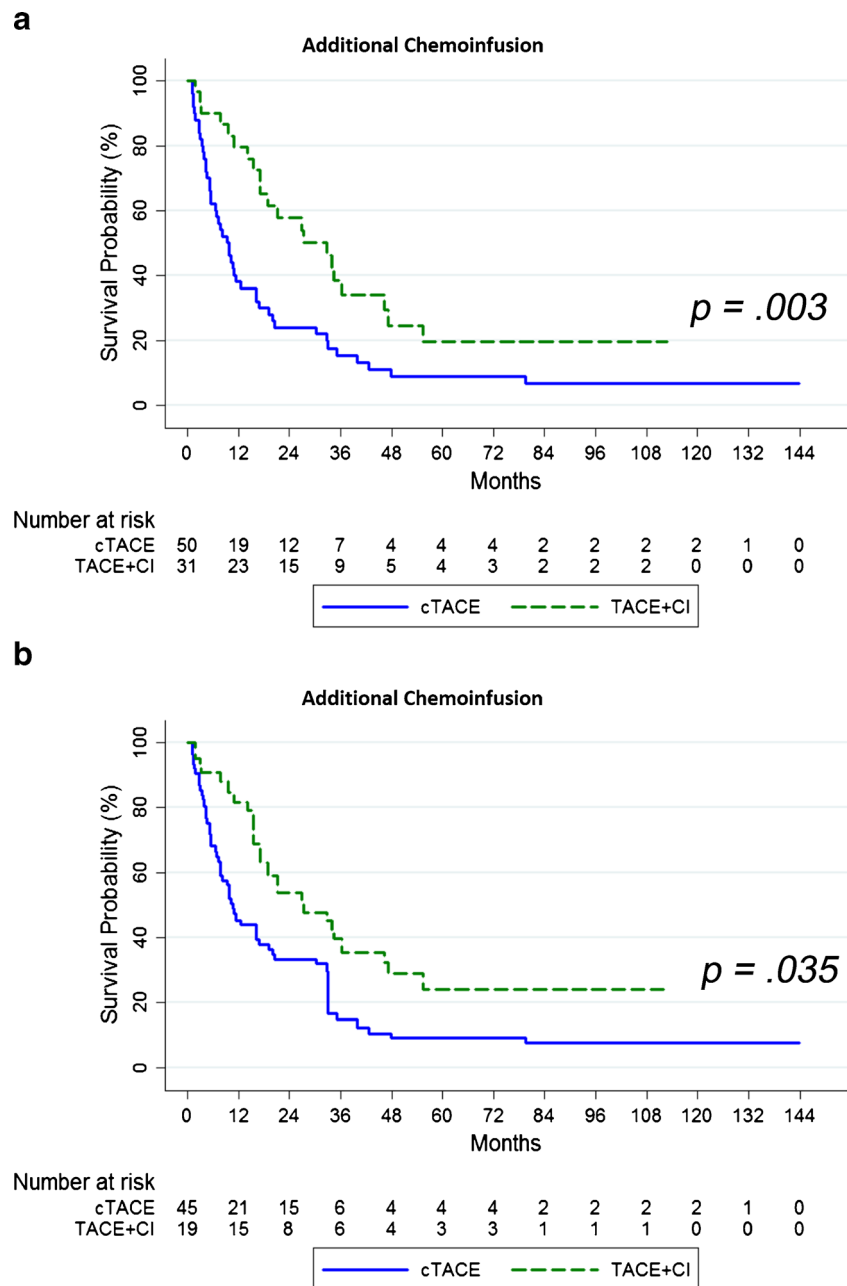
that of the cTACE group (median, 9.4 months; 95 % CI, 5.4 to 12.6) ( $p = .003$ ) (Fig. 4a).

In univariate analyses, aspartate aminotransferase (AST), international normalized ratio of prothrombin time, modified BCLC stage, extrahepatic spread, and treatment protocol were possible predictors of OS (Suppl. Table 1). Multivariate analysis revealed that a high AST level ( $p < .001$ ; hazard ratio [HR], 1.011; 95 % CI, 1.005 to 1.017), modified BCLC stage of D ( $p = .038$ ; HR, 2.841; 95 % CI, 1.063 to 7.592), and extrahepatic spread ( $p < .001$ ; HR, 4.862; 95 % CI, 2.246 to 10.526) were significantly related with shorter OS, and that

**Fig. 3** Kaplan-Meier curves of overall survival after TACE, depending on modified BCLC stage (log-rank test for trend,  $p < .001$ ). Quasi-C: Child-Pugh class A, performance status of 0, no extrahepatic spread, and HCC with sPVTT. Proper-C: BCLC stage C patients who did not fulfil quasi-C criteria



**Fig. 4** Kaplan-Meier curves of survival after TACE, depending on the application of additional chemoinfusion. **a** Cumulative overall survival curves in patients of cTACE and TACE+CI groups (log-rank test,  $p = .003$ ). **b** Cumulative overall survival curves after inverse probability of treatment weighting adjustment, in patients of cTACE and TACE+CI groups (log-rank test,  $p = .035$ )



additional chemoinfusion ( $p = .002$ ; HR, .367; 95 % CI, .195 to .692) was significantly associated with longer OS (Suppl. Table 1).

### Safety

Patients were discharged a median three days after TACE (range, 1 to 25 days). As post-procedural events other than postembolization syndrome, liver abscess, ascites and pleural effusion requiring diuretics, secondary bacterial peritonitis, and erythema multiforme due to doxorubicin hypersensitivity occurred in two, two, one, and one patients, respectively. All

treatment-emergent AEs depending on the treatment groups are summarized in Table 2.

Treatment-related SAEs occurred in 19 out of 81 patients (23.5 %). There were no patients who obtained permanent adverse sequelae or who died within 30 days. The incidences of SAEs were 5.3 % (2/38), 36.1 % (13/36), and 47.1 % (4/7) in stage quasi-C, proper-C, and D patients, respectively. Regarding the treatment protocols, the incidences were not significantly different between the cTACE group (26.0 %, 13/50) and TACE+CI group (19.4 %, 6/31) ( $p = .677$ ).

From the results of regression analyses, poor modified BCLC stage (proper-C;  $p = .004$ ; HR, 10.174; 95 % CI, 2.100 to 49.295) (D;  $p = .003$ ; HR, 24.000; 95 % CI, 3.041

**Table 2** Treatment-emergent adverse events graded according to version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)

Adverse Events	Level of increase in CTCAE grade					
	Overall ( <i>n</i> = 81)		cTACE ( <i>n</i> = 50)		TACE+CI ( <i>n</i> = 31)	
	Any increase	3–4 grades increase	Any increase	3–4 grades increase	Any increase	3–4 grades increase
Postembolization syndrome*	35 (43.2)	14 (17.3)	18 (36.0)	10 (20.0)	17 (54.8)	4 (12.9)
Other post-procedural event <sup>†</sup>						
Any event	6 (7.4)	5 (6.2)	4 (8.0)	3 (6.0)	2 (6.5)	2 (6.5)
Liver abscess	2 (2.5)	2 (2.5)	1 (2.0)	1 (2.0)	1 (3.2)	1 (3.2)
Ascites/pleural effusion	2 (2.5)	2 (2.5)	2 (4.0)	2 (4.0)	0 (0.0)	0 (0.0)
Secondary bacterial peritonitis	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.2)
Hypersensitivity	1 (1.2)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lab investigation						
Any abnormality	56 (69.1)	14 (17.3)	34 (68.0)	6 (12.0)	22 (71.0)	8 (25.8)
Hypoalbuminemia	30 (37.0)	0 (0.0)	22 (44.0)	0 (0.0)	8 (25.8)	0 (0.0)
Bilirubin increased	25 (30.9)	2 (2.5)	13 (26.0)	2 (4.0)	12 (38.7)	0 (0.0)
INR increased	21 (25.9)	0 (0.0)	13 (26.0)	0 (0.0)	8 (25.8)	0 (0.0)
AST increased	33 (40.7)	10 (12.3)	18 (36.0)	4 (8.0)	15 (48.4)	6 (19.4)
ALT increased	42 (51.9)	10 (12.3)	24 (48.0)	3 (6.0)	18 (58.1)	7 (22.6)
Creatinine increased	4 (4.9)	0 (0.0)	4 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations.—INR, international normalized ratio of prothrombin time

Note.—Numbers in parenthesis are percentages per group population

\* Postembolization syndrome was defined as non-infectious fever, nausea, vomiting, fatigue, and/or abdominal pain after the procedure

to 189.441) was the only significant risk factor for SAEs (Suppl. Table 2).

### Clinical efficacy and safety of additional chemoinfusion after inverse probability of treatment weighting

After IPTW adjustment, all confounding variables were well-balanced between the two treatment groups (Table 1). In subsequent analyses, the TACE+CI group showed significantly improved OS compared to the cTACE group (adjusted  $p = .028$ ; HR, .511; 95 % CI, .281 to .929). The adjusted median OS of the TACE+CI and cTACE groups were 27.3 months (95 % CI, 15.5 to 55.4) and 10.6 months (95 % CI, 6.9 to 20.1), respectively. The adjusted 1-year, 3-year, and 5-year OS rates were 81.4 %, 39.7 %, and 23.8 % for the TACE+CI group, and 45.3 %, 14.7 %, and 9.0 % for the cTACE group, respectively (Fig. 4b). In addition, the occurrence of treatment-related SAEs in the TACE+CI group was not significantly different than that of the cTACE group (adjusted  $p = .737$ ; HR, .819; 95 % CI, .255 to 2.630). The adjusted incidences of treatment-related SAEs were 19.4 % and 26.0 % for the TACE+CI group and the cTACE group, respectively.

### Discussion

This study demonstrated that TACE achieved a median OS of 15.5 months, which could be stratified according to the modified BCLC stages, for HCC with sPVTT in patients with preserved hepatic function. Furthermore, additional chemoinfusion had 16.7 months of adjusted median OS benefit, as compared with that of cTACE. The overall incidence of treatment-related SAEs was 23.5 %, and it was not increased by additional chemoinfusion, but was affected by modified BCLC stages.

Bolondi et al. [5] recently proposed the stage quasi-C as an overlap between BCLC stage B and C, and recommended sorafenib as the first treatment option, followed by TACE and radioembolization. However, there is limited evidence supporting the use of sorafenib treatment for these patients because sorafenib's survival outcome has been proven to be significantly worse in cases of macrovascular invasion [14]. Radioembolization may be a promising option, because it induces minimal embolic effects during internal radiation [30]. Although several studies are underway to evaluate the efficacy and safety of radioembolization in HCC with PVTT, until now, this novel technique has been performed on a limited number of patients compared to TACE, which has more than three decades of experience.



In contrast, TACE has been widely used for these patients, particularly in Asian countries [11, 31]. Luo et al. [32] claimed that the efficacy of TACE for HCC with sPVTT, in patients with Child-Pugh class A and ECOG 0–1, and presented a median OS of 10.2 months compared to 5.2 months in the conservative management group. Concordantly, our study demonstrated a reproducible result regarding 10.6 months of IPTW adjusted median OS in the cTACE group. The median OS of 15.5 months in our study may be considered to be between the survival outcomes of stage B patients and stage C patients in general [5, 33]. In particular, the median OS of 26.9 months of stage quasi-C patients came close to that of stage B patients [6]. These findings suggested that TACE can be regarded as a useful option for quasi-C patients.

Additional chemoinfusion significantly improved patients' OS (adjusted HR, .511; 95 % CI, .281 to .929), while it did not elevate the incidence of treatment-related SAEs. Concordantly, Kim et al. [7] claimed that additional chemoinfusion can enhance the OS of HCC patients with hepatic vein invasion. Although the number and kind of chemotherapeutic agents mixed with iodized oil are regarded as not considerable in the outcome of TACE [34, 35], the effect of additional chemoinfusion has not been sufficiently validated until now. According to the results of our study, additional chemoinfusion may safely provide additional anticancer effects in patients with preserved hepatic function. The combination of anticancer drugs with different mechanisms theoretically enhances tumoricidal effects, leading to longer patient survival. However, the amount of chemotherapeutic agents in a tolerable dose of iodized oil was strikingly limited, which inevitably restricts the efficacy of the combination therapy. In contrast, additional chemoinfusion can administer a chemotherapeutic agent as much as can be effective, if the patient is tolerant. In other words, additional chemoinfusion may be particularly useful in HCC patients, who require a potent treatment and who also have preserved hepatic function, such as stage quasi-C patients. Meanwhile, additional chemoinfusion did not increase the incidence of SAEs in our study, which implies that patients with preserved hepatic function, even having sPVTT, are able to tolerate more potent treatments. Noticeably, no patients demonstrated a remarkable increase in creatinine in the TACE+CI group (Table 2), although renal toxicity is a well-known side effect of cisplatin.

With regard to the TACE+CI protocol, we hypothesized that slow chemoinfusion following TACE could potentially carry highly concentrated drugs without dilution and extend the drug-exposure time to the tumour. When chemotherapeutic agents are infused via the untreated artery, the drug is immediately diluted by arterial inflow and then rapidly passed through the tumour bed. Alternatively, preceding TACE may allow minimal, sluggish arterial inflow, which could slowly deliver highly concentrated drugs by subsequent chemoinfusion.

The median OS as well as the incidence of SAEs were significantly stratified using the modified BCLC stages. Although Bolondi et al.'s [5] subclassification of BCLC stage B is being validated by many researchers, their proposal of stage quasi-C has rarely been evaluated. The results of this study imply that the interposed stage may be used to predict clinical outcome and to select a treatment strategy.

The incidence of treatment-related SAEs was 23.5 %, and all SAEs were properly managed without any permanent adverse sequelae. This can be regarded as an acceptable safety profile, considering the known rates of SAEs or complications, depending on the definition in each study, after TACE [18, 26]. Selective catheterization may contribute to this phenomenon. As the microcatheter was advanced as distally as possible, chemoembolic agents were able to be administered selectively, which in turn minimized unintended chemoembolization of the normal liver and reduced systemic toxicity. Interestingly, the incidence of liver abscess (2.5 %) was not remarkably high in our study [24]. This was discordant with a common belief that TACE frequently induces liver abscesses in cases of PVTT.

There are a few limitations in this study. Although IPTW adjusted baseline characteristics of the cTACE and TACE+CI groups, the results may, nevertheless, have been due to selection bias. Therefore, added benefit and safety of TACE+CI compared to cTACE should be validated by prospective, randomised studies. The outcomes of TACE were not compared with alternative options, such as sorafenib, radioembolization, or surgical resection [36, 37], because the number of patients who underwent the treatments, introduced comparatively late, were limited until now. In addition, this study evaluated patients who were archived for about ten years. Although this study analysed almost all of the possible prognostic factors and roughly adjusted the time-effect by including the procedure dates in those, there might be still potentially confounding variables that could affect clinical outcomes. For example, the sensitivity and specificity of HCC diagnosis may be improved by the use of magnetic resonance imaging and liver-specific contrast agents. The quality of supportive care may also have been enhanced during this period. Lastly, our hypothesis regarding the sequence of TACE+CI (i.e., preceding TACE followed by chemoinfusion) does not have sufficient evidence to assure its anticancer mechanism. The process, which has resulted in the superior outcome of the TACE+CI group, needs to be further evaluated in future pre-clinical and clinical studies, in order to optimize the protocol as well as to understand its therapeutic effectiveness.

In conclusion, TACE can be an effective and safe treatment option for HCC with sPVTT in patients with preserved hepatic function. Furthermore, additional chemoinfusion can enhance the therapeutic efficacy while maintaining the safety of the procedure.

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Methodology: retrospective, observational, performed at one institution.

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