Efficacy and Safety of Conventional Transarterial Chemo-embolization for Patients with Advanced Stage Hepatocellular Carcinoma

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Background: *Transarterial chemo-embolization (TACE) is the standard care for patients with intermediate stage hepatocellular carcinoma (HCC); however, in real-world practice, TACE is sometimes utilized in patients with more advanced stage HCC, including those with portal vein thrombosis/invasion (PVT) and/or extrahepatic metastasis. The efficacy and safety data of TACE in these contingencies are limited.*

Objective: *To evaluate the efficacy and safety of TACE in patients with intermediate (BCLC-B) and advanced (BCLC-C) stages HCC as defined by Barcelona Clinic Liver Cancer (BCLC) staging system.*

Material and Method: *Data of consecutive patients with intermediate and advanced HCC who underwent TACE between January 2008 and December 2012 in the single tertiary center (Rajavithi Hospital, Bangkok) were retrospectively reviewed. HCC patients with BCLC-B were classified as the "standard TACE criteria" (S-TACE) group, whereas patients with BCLC-C were classified as the "extended TACE criteria" (E-TACE) group. The primary endpoint was the overall survival (OS). Secondary endpoints were safety data and objective tumor response of TACE. Outcomes of patients with HCC BCLC-B/C who refused TACE for personal reasons and received only supportive care (BSc cohort) were compared with those patients who underwent TACE.*

Results: *A total of 110 HCC patients were included in the analysis: mean age 54 years, 53% hepatitis B positive, 23% Child-Pugh B and 89% tumor size ≥5 cm. There was no significant difference in OS between the E-TACE group (n = 54) and S-TACE (n = 56): OS 7.7 vs. 9.6 months; p = 0.535, respectively. Progressive disease by mRECIST criteria was more common in the E-TACE group (31.5% vs. 10.7%, p = 0.007). Pre-treatment MELD score, PVT and TACE-related complications were independent predictors for OS in multivariate analysis. The OS of patients with PVT (n = 40) was significantly lower than that of those without it (5.6 vs. 11.2 months, p<0.001). There was no difference in OS between patients with (n = 31) and without extrahepatic metastases (9.6 vs. 8.5 months, p = 0.784). TACE-related complications were uncommon and similar in the two groups (p<0.05). The OS in the TACE cohort was significantly better than in the BSC cohort (n = 24) (8.8 vs. 3.1 months, p<0.001).*

Conclusion: *The overall median survival and adverse events following TACE were similar in HCC patients with BCLC stage B and C, and were better than those patients who received only supportive care. This finding supports the use of TACE in selected patients with advanced HCC, including in those with extrahepatic metastasis.*

Keywords: *Hepatocellular carcinoma, Cirrhosis, Transarterial chemoembolization, Portal vein thrombosis, Advanced stage*

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Hepatocellular carcinoma (HCC) is a major global health problem. It is the third most common cause of cancer-related death worldwide and is currently the most common indication for liver transplantation in the USA[1,2]. Most HCCs develop in patients with chronic liver disease and/or cirrhosis and its incidence varies across the world (>80% of HCCs develop in Asian and African countries, where 40% to 90% of HCCs are attributable to chronic hepatitis B (HBV), whereas the incidence of HCC in the US and Europe is relatively low and up to two-thirds of HCCs in these regions are attributable to chronic hepatitis C[2].

The Barcelona Clinic Liver Cancer (BCLC) staging system has been the most widely used and validated system that links HCC stages with a potential treatment algorithm and is endorsed by Western guidelines[3-6]. Curative therapies with surgical resection, liver transplantation and radiofrequency ablation (RFA) are recommended for patients with early-stage HCC (BCLC-0 and BCLC-A) with satisfactory

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outcomes (expected median survival >60 months; 5-years survival: 40% to 70%)[3]. Unfortunately, the majority of HCC patients are diagnosed with intermediate (BCLC-B) and advanced stages (BCLC-C) accounting for 60% to 70% of HCC patients in developed countries and more in developing countries where patient awareness and surveillance programs are suboptimal[2,3]. Therefore, most HCC patients in Thailand are not eligible for potentially curative therapy due to large tumor size, vascular invasion or distant metastasis, and are associated with poorer prognosis. Available treatment options in these patients include palliative locoregional therapy, chemotherapy and, in those with poor liver function and physical performance, best supportive care.

Transarterial chemoembolization (TACE) is a recommended locoregional treatment option for patients with intermediate stage HCC defined by single large or multifocal HCC with preserved liver function and without vascular invasion or extrahepatic spread. Expected median survival in this group of patients is 8 to 15 months without treatment, whereas treatment with TACE has shown to improve median survival to 20 (14 to 45) months and has a 2-year survival rate of 31% to 63%[3,7-10]. Advanced stage HCC (BCLC-C) includes symptomatic patients who have some limited performance status and/or aggressive tumor with vascular invasion or extrahepatic spread. These patients have short life expectancy, with median survival of 5 to 10 months and 20% to 35% survival at 1 year, and are candidates for systemic therapy such as sorafenib[3,7-10]. According to two phase III randomized placebo-controlled studies, sorafenib increased overall survival from 7.9 months to 10.7 months ($p<0.05$) in the international SHARP study (Europe, America and Australia)[11] and from 4.2 months to 6.5 months ($p = 0.017$) in the Asia-Pacific SHARP study[12]. Notably, portal vein invasion or thrombosis (PVT) was an important negative prognostic factor affecting survival in unresectable HCC patients who underwent TACE, mainly due to increased risk of post-TACE liver decompensation, so that TACE is not generally recommended in patients with advanced stage HCC apart from some exceptions such as ruptured HCC[3,4,13]. In addition, modifications of conventional TACE techniques, such as chemo-embolization with drug-eluting beads and radio-embolization with microspheres containing Yttrium-90, have been evaluated and have shown promising early results in patients with advanced HCC in terms of increasing treatment efficacy and reducing post-TACE complications[3,14,15]. However, in developing countries, sorafenib and novel TACE techniques are available only in a very few centers and are also associated with very high cost, so the majority of HCC patients do not have access to these treatments. Thus, many physicians perceive that locoregional therapies are more effective than systemic chemotherapy or conservative treatment. Therefore, conventional TACE has commonly been utilized in patients with advanced stage HCC in developing countries although the data on efficacy and safety of TACE in this setting are limited[13,16,17].

In the present study, we aimed to evaluate the overall survival rates, as well as tumor response rates, of conventional TACE in patients with advanced stage HCC compared to those with intermediate stage.

Material and Method

Study design and patients selection

Adult patients with unresectable HCC who underwent TACE at a single tertiary center (Rajavithi Hospital, Bangkok, Thailand) between January 2008 and December 2012 were included in the analysis. The diagnosis of HCC was based on the American Association Study of Liver Disease (AASLD) criteria: a persistently elevated serum alpha-fetoprotein (AFP) level >200 ng/dL and typical features on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) that were consistent with the diagnosis of HCC (showing early arterial enhancement with a rapid venous wash-out). Liver histopathology was required to confirm the diagnosis of HCC in those patients who did not meet the clinical criteria[4].

The exclusion criteria were patients who: (a) underwent surgical resection, liver transplantation, percutaneous ablation or radiation therapy before or after TACE; (b) underwent TACE as an emergency treatment for bleeding/ruptured HCC; (c) had nearly-complete to complete main portal vain occlusion (either by tumor invasion or thrombus) identified by imaging techniques; (d) had Child-Pugh class C cirrhosis; and (e) had severe medical comorbidities that significantly affected their chances of survival.

All clinical, laboratory and radiological data were reviewed from the paper and electronic records including demographic data, performance status, staging of HCC, clinical details and severity of liver disease and other comorbidities, liver function test, renal function test, coagulogram, complete blood count, AFP level, radiological features of the tumor (s), evidence of portal vein and IVC invasion from the

tumors, and metastases of the tumors to extra-hepatic organs.

In this study, patients with intermediate HCC (BCLC-B), which included asymptomatic patients with single large HCC and those with multifocal HCC who had preserved liver function and did not have vascular invasion or extrahepatic spread, were classified as the "standard TACE criteria" group (S-TACE), and patients with advanced HCC (BCLC-C), which included symptomatic patients who had limited performance status (ECOG performance scale 1 to 2) and/or aggressive tumor with vascular invasion or extrahepatic spread, were classified as the "extended TACE criteria" group (E-TACE). Some patients with unresectable HCC whose characteristics nearly matched the study inclusion/exclusion criteria and who were advised to undergo TACE by the multidisciplinary hepatopancreatobiliary tumor (MDT) conference decided to refuse TACE, as well as other locoregional therapy, chemotherapy or radiotherapy; instead, after being informed of risks/benefits, they opted, for personal reasons (e.g. fear of procedure, financial concerns, inability to attend frequent visits), to receive only supportive care (BSC group). The data of this group were recorded to compare their survival rates with those of the study population.

This study protocol was reviewed and approved by the Medical Ethics Committee of Rajavithi Hospital (No. 046/2557 and No. 105/2558).

Procedure and technique

At Rajavithi Hospital, the management of all new patients with HCC is decided by diagnoses made by different departments of Rajavithi Hospital or by those sent from other hospitals from which they have been referred. Treatment is guided by the consensus of the MDT conference which includes a panel hepatologists, hepatobiliary surgeons, oncologists, interventional and nuclear radiologists. The common reasons for unresectability were tumors in both lobes of liver or in one lobe but with inadequate predicted residual liver volume and functions (calculated by CT volumetry and/or indocyanine green retention test); decompensated liver disease (e.g. total bilirubin level >2 mg/dL; uncontrolled ascites; hepatic encephalopathy); major vessel involvement; or extra-hepatic metastases. The selection of locoregional treatment modality, including TACE, radiofrequency ablation and percutaneous ethanol injection, was generally based on size, number and location of the tumor (s). TACE was performed by three experienced interventional radiologists at the Department of Radiology in accordance with the same standard protocol. Chemo-embolization was performed as selectively as possible via the lobar, segmental, or subsegmental arteries, depending on the tumor distribution and each patient's hepatic functional reserve, under sterile technique with local anesthesia and fluoroscopic guidance. Amoxycillin/Clavulanate 1.2 gram was used as a prophylactic antibiotic (single dose intravenously before the procedure). The right common femoral artery was punctured and replaced with a 5-French sheath. Visceral angiogram was then performed in the celiac and superior mesenteric arteries with 5-French Simmon-1 catheter. When the location of the feeding vessel of the tumor was identified, lipiodol 10 ml mixed with mitomycin-C 20 mg was injected to the vessel, and then pieces of gelfoam were used to embolize the artery.

Follow-up period and outcome measurement

Post-TACE complications such as post-TACE syndrome (manifested by fever, malaise, right upper quadrant pain, nausea, and vomiting), liver decompensation, GI bleeding, and liver abscess, were recorded. Computed tomography scan and serum alpha fetoprotein (AFP) levels were performed within 4 to 6 weeks after TACE to evaluate the tumor response, and the next TACE was scheduled 4 to 8 weeks after the previous one. The objective tumor response was assessed based on the mRECIST criteria: Complete response (CR) = Disappearance of any intratumoral arterial enhancement; Partial response (PR) = At least a 30% decrease in the sum of the diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions in all target lesions; Stable disease (SD) = Any cases not qualifying for either PR or PD; and Progressive disease (PD) = An increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since treatment started[3]. Patients who had residual viable tumors or recurrent tumors on follow-up CT/MRI, received repeat TACE session (s) if there was no contra-indication. The primary endpoint of the study was overall survival (OS) and 2-year survival. Secondary endpoints were other safety and efficacy parameters of TACE including objective tumor responses.

Statistical analyses

All statistical analyses were performed

using SPSS, version 17.0 (IBM statistics). To determine significant differences between the two groups, the continuity correction and independent-samples t, Pearson χ^2, and Fisher exact tests were used. Survival curves were calculated for the two groups using the Kaplan-Meier methods. Univariate analyses were performed with the log-rank test, and variables with a *p*-value of less than 0.05 at univariate analysis were entered into a multivariate analysis. Multivariate analyses were performed with a Cox proportional hazard regression model, and Wilcoxon signed-rank test was used to determine the difference in liver function test values before and after treatment. All statistical tests were two-tailed and $p = 0.05$ indicated a significant difference.

Results

Data were reviewed of 671 consecutive patients with HCC who underwent TACE during the study period. Five hundred and sixty-one patients were excluded due to incomplete data (n = 243); having had prior surgery (n = 172); being under BCLC stage A (n = 92); having had prior RFA/PEI (n = 48); or having had other malignancy (n = 6). A total of 110 patients, who met the inclusion criteria, were included in the analysis: 56 (50.9%) patients were classified as the S-TACE group, and the other 54 (49.1%) were classified as the E-TACE group.

Of these 110 patients, 90 (81.8%) were male and the mean age was 56.2±11.2 years. The most common underlying etiologies of HCC were HBV (51.6%) and alcohol (36.4%). Severity of liver disease was classified as Child-Pugh class A in 85 (86.4%) patients and class B in the other 25 (15.6%). Baseline demographic data and liver disease-related parameters that were significantly different between the 2 groups included age, smoking, hypertension, serum aspartate aminotransferase (AST) levels and estimated glomerular filtration rate (eGFR) (Table 1). Most patients had large (≥5 cm) and multiple HCC (more than one lesion). The number of HCC was not significantly different between the 2 groups, but size of tumor (the

Table. 1 Baseline demographic data and liver disease-related parameters (n = 110)

Parameters	S-TACE (n = 56)	E-TACE (n = 54)	*p*-value
Male	45 (80.4)	45 (83.3)	0.686
Age (years)	58±11	54±11	0.047*
≥50 years	46 (82.1)	36 (66.7)	0.063
Alcohol	31 (55.4)	39 (72.2)	0.066
Smoking	19 (33.9)	32 (59.3)	0.008*
Etiology			
HBV	30 (53.6)	28 (51.9)	0.857
HCV	12 (21.4)	14 (25.9)	0.579
Alcohol	19 (33.9)	21 (38.9)	0.589
Hypertension	20 (35.7)	7 (13.0)	0.006*
BMI (kg/m^2)	21.1±3.1	20.9±3.3	0.677
Child-Pugh score	6 (5-8)	6 (5-9)	0.926
Child-Pugh class A	45 (80.4)	40 (74.1)	0.432
Child-Pugh class B	11 (19.6)	14 (25.9)	0.432
MELD score	9 (8 to 10)	9 (8 to 11)	0.400
MELD ≥15	2 (3.6)	3 (5.6)	0.618
AFP (ng/dl)	9.7±16.7	13.8±21.0	0.238
Total bilirubin (mg/dl)	1.1±0.8	1.2±0.7	0.369
AST (U/L)	116±116	143±121	0.021*
ALT (U/L)	66±75	65±50	0.291
Albumin (g/dl)	3.5±0.6	3.5±0.5	0.965
INR	1.1±0.1	1.2±0.1	0.237
Platelets ($cells/mm^3$)	229,179±146,079	250,315±113,378	0.398
eGFR (ml/min)	73.2±24.7	87.6±31.3	0.008*

HBV = Hepatitis B virus, HCV = Hepatitis C virus, BMI = Body mass index, AFP = Alfa-fetoprotein, AST = aspartate aminotransferase, ALT=Alanine aminotransferase, INR = International ratio, eGFR = Estimated glomerular infiltration rate
Values are represented as n (%), Mean±SD, Median (Min-Max), * = Significant at $p<0.05$

maximal diameter of the largest HCC) was significantly greater in the E-TACE groups. Presence of PVT, IVC invasion and extra-hepatic metastasis was documented in 74.1%, 18.5%, and 57.4% of patients respectively in the E-TACE group compared to none (0.0%) in the S-TACE group (Table 2).

The median number of TACE was 2 (1 to 3) sessions in both groups. Objective tumor response was more commonly seen in the S-TACE than in the E-TACE group (62.5% vs. 25.9%, respectively; $p = 0.001$). The incidence of post-TACE syndrome (79.6 to 83.9%) and TACE-related complications were not significantly different in the 2 groups. Five (4.6%) patients (2 in the S-TACE group and 3 in the E-TACE group; $p = 0.618$) died of causes related to the TACE procedure; the causes of death were acute liver failure (4 patients) and

Table. 2 Tumor characteristics (n = 110)

Parameters	S-TACE (n = 56)	E-TACE (n = 54)	*p*-value
Tumor number			0.605
Single lesion	16 (28.6)	13 (24.1)	
2-3 lesions	11 (19.6)	8 (14.8)	
>3 lesions	29 (51.8)	33 (61.1)	
Tumor size (cm.)	9.7±4.3	12.5±4.8	0.002*
≥5 cm	48 (85.7)	50 (92.6)	0.247
Portal vein invasion	0 (0.0)	40 (74.1)	NA
Left or right	0 (0.0)	35 (64.8)	
Main (partial)	0 (0.0)	5 (9.3)	NA
Inferior vena cava invasion	0 (0.0)	10 (18.5)	NA
Metastasis	0 (0.0)	31 (57.4)	NA
Lymph node	0 (0.0)	18 (33.3)	NA
Lung	0 (0.0)	7 (13.0)	NA
Bone	0 (0.0)	6 (11.1)	NA
Adrenal gland	0 (0.0)	3 (5.6)	NA

Values are represented as n (%), Mean±SD, * = Significant at $p<0.05$

Table. 3 Objective tumor responses and adverse events after TACE (n=110)

Parameters	S-TACE (n = 56)	E-TACE (n = 54)	*p*-value
No. of TACE session(s)	2 (1-3)	2 (1-3)	0.762
Tumor response			
Complete response (CR)	3 (5.4)	4 (7.4)	0.660
Partial response (PR)	32 (57.1)	10 (18.5)	0.001*
Stable disease (SD)	13 (23.2)	18 (33.3)	0.238
Progressive disease (PD)	6 (10.7)	17 (31.5)	0.007*
Objective response	35 (62.5)	14 (25.9)	0.001*
Non-response	19 (33.9)	35 (64.8)	0.001*
Disease control	48 (85.7)	32 (59.3)	0.002*
Post-TACE syndrome	47 (83.9)	43 (79.6)	0.559
TACE-related complications			
Acute kidney injury	5 (8.9)	5 (9.3)	0.952
Liver abscess	1 (1.8)	0 (0.0)	0.324
GI bleeding	2 (3.6)	5 (9.3)	0.222
Liver decompensation	17 (30.4)	16 (29.6)	0.934
Liver failure	1 (1.8)	3 (5.6)	0.291
Death	2 (3.6)	3 (5.6)	0.618

Objective response = CR+PR, Non-response = SD+PD, Disease control = CR+PR+SD
Values are represented as n (%), * = Significant at $p<0.05$

sepsis (1 patient) (Table 3).

The median OS was 8.79 months (95% CI: 7.33 to 10.25) during the median follow-up duration of 11.3 (1-24) months. In the S-TACE group, 1- and 2-year survival was 44.6% (95% CI: 31.4 to 57) and 14.3% (95% CI: 6.2 to 25.7), respectively. In the E-TACE group, 1- and 2-year survival was 38.9% (95% CI: 26 to 51), and 15.2% (95% CI: 7.0 to 26.5), respectively. There was no statistically significant difference in OS between the S-TACE and E-TACE group (9.57 months (95% CI: 6.49 to 12.66) vs. 7.74 months (95% CI: 5.73 to 9.75), respectively; $p = 0.535$) (Fig. 1). Patients with PVT were associated with shorter OS than those without it (5.61 months (95% CI: 3.88 to 7.33) vs. 11.18 months (95% CI: 7.85 to 14.51), respectively; $p<0.001$) (Fig. 2). There was no statistically significant difference in OS between patients with and without extrahepatic metastasis (9.57 months (95% CI: 4.27 to 14.88) vs. 8.49 months (95% CI: 6.83 to 10.16), respectively; $p = 0.784$) (Fig. 3).

Univariate analysis showed that the significant predictors for survival were age, male gender, MELD score, presence of PVT, progressive disease and TACE-related complications. Multivariate analysis revealed that the significant predictors for survival were MELD score, presence of PVT and TACE-related complications (Table 4).

Median survival in the E-TACE group was significantly better than in the best supportive care (BSC) cohort (8.8±0.8 vs. 3.1±0.7 months, $p<0.001$). The 3-, 6- and 12-month survival rates for the TACE and the BSC groups were 88.2%, 66.4% and 41.0% vs. 50.0%, 25.0% and 12.5%, respectively (Table 5).

Discussion

Because there are several barriers to the use target therapy in developing countries, a considerable proportion of patients with advanced HCC have undergone conventional TACE as a main palliative treatment option, despite the fact that this does not follow the international guidelines, and that the supportive evidence for its use is quite weak. In the present study, we reported the efficacy and safety outcomes of conventional TACE in a cohort of 54 patients with advanced HCC. Although objective tumor responses appeared to be better in patients with intermediate HCC (S-TACE) than in those with the advanced stage (E-TACE), OS and TACE complications they were not significantly different between the 2 groups. In addition, treatment with TACE was associated with a significantly better OS (almost double) when compared to those partially-matched patients

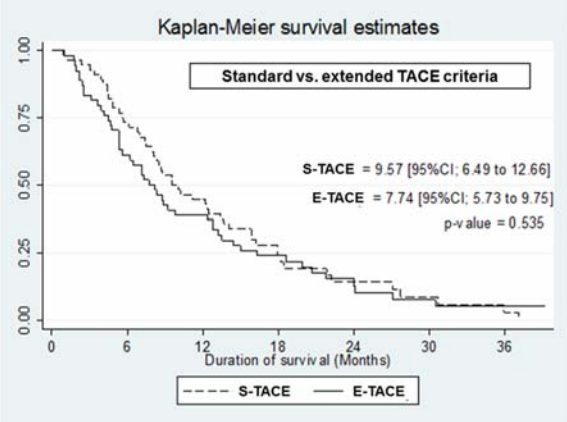

Fig. 1 Kaplan-Meier survival curve in the TACE groups (standard vs. extended criteria).

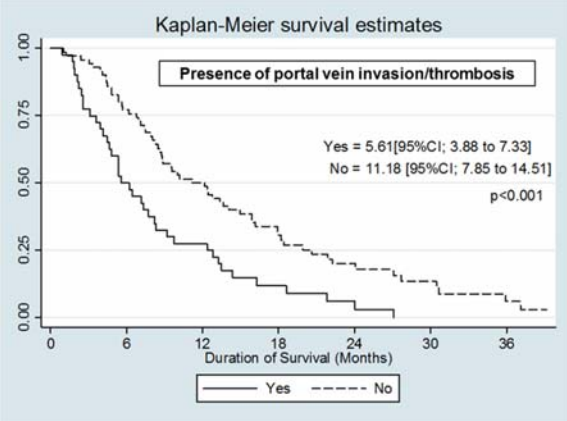

Fig. 2 Kaplan-Meier survival curve showing the presence of portal vein invasion/thrombosis.

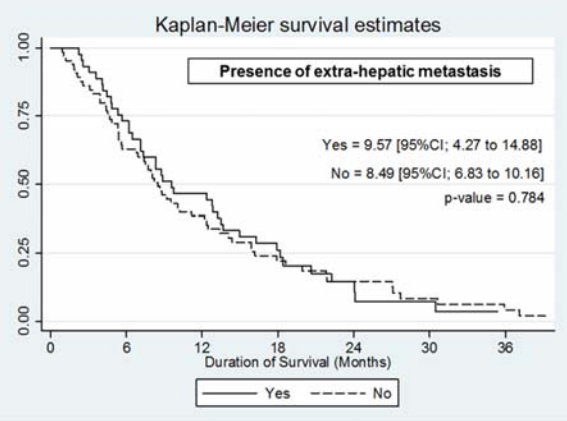

Fig. 3 Kaplan-Meier survival curve showing the presence of extra-hepatic metastasis.

Table. 4 Univariate and multivariate analyses of prognostic factors for survival

Factor	HR (95%CI)	*p*-value
Univariate analysis		
BCLC-B vs. BCLC-C	1.13 (0.76 to 1.68)	0.536
Age	0.97 (0.95 to 0.99)	0.003*
Male	1.86 (1.1 to 3.14)	0.020*
Alcohol	1.46 (0.96 to 2.22)	0.076
Child-Pugh score	1.27 (1.0 to 1.61)	0.051
MELD score	1.14 (1.06 to 1.23)	0.001*
Albumin	1.1 (0.8 to 1.52)	0.568
Tumor size >5 cm	1.45 (0.77 to 2.72)	0.248
Portal vein invasion/thrombosis	2.11 (1.39 to 3.19)	0.001*
Inferior vena cava invasion	0.75 (0.37 to 1.51)	0.420
Metastasis	0.95 (0.63 to 1.42)	0.784
Progressive disease	2.51 (1.56 to 4.06)	0.001*
TACE-related complications	2.45 (1.57 to 3.84)	<0.001*
Multivariate analysis factor		
MELD score	1.1 (1.02 to 1.19)	0.018*
Portal vein invasion	3.37 (1.63 to 6.98)	0.001*
TACE-related complications	1.95 (1.21 to 3.15)	0.006*

BCLC = Barcelona clinic Liver Cancer staging
Values are represented as Median (Min-Max), * = Significant at $p<0.05$

with intermediate/advanced HCC receiving BSC. These findings suggest that conventional TACE may be also a reasonable treatment option in patients with advanced HCC.

Similar to the findings of previous studies, significantly negative prognostic factors affecting OS among HCC patients undergoing TACE were high pre-treatment MELD score, PVT and TACE complications. Presence of PVT is known to be one of the worst prognostic indicators in HCC patients. In the present study, we performed TACE in 40 patients with PVT (left, right or partially main portal vein). Serious adverse events following TACE in patients with PVT were uncommon, but the benefit of using TACE in this group was questionable since OS did not seem significantly better than BSC (just 5 to 6 months). Interestingly, according to the international guidelines, HCC patients with extrahepatic metastasis are typically precluded from having locoregional treatment; however, the presence of extrahepatic metastasis did not significantly affect OS among patients who underwent TACE in the present study, and this supports the role of TACE as a palliative option to control intra-hepatic tumor which may prolong survival in this subgroup of patients.

The efficacy outcomes of conventional TACE in the present study appear to be considerably lower than those of previous reports, particularly for patients with intermediate HCC (OS 9.6 months in this study, compared to 14 to 45 months in previous reports)[3,7-10]. This may be due to several factors such as unmatched patient population, operator experience, stringency of TACE schedule, patient self-care of cirrhosis or publication bias. Nevertheless, the OS in patients with advanced HCC who underwent TACE (7.7 months in this study) does not seem different from previous reports (BSc: OS 5 to 10 months and sorafenib: OS 7 to 11 months)[3,7-10,17]. In terms of safety outcomes, the incidence of TACE-related complications was similar in the S-TACE and E-TACE groups. The development of liver decompensation (32.1% to 35.2%) and death (3.6% to 5.6%) following TACE were uncommon, with somewhat similar rates compared to those of previous reports[9,13,17].

The present study had several limitations including its retrospective nature, limited number of patients, heterogeneity of the study population and some missing data. However, we believe that our data may represent the real-world population and practices regarding TACE in Thailand.

In conclusion, OS in patients with advanced stage HCC who underwent conventional TACE was similar to that of those patients with intermediate stage without increment of TACE-related complications. This finding supports the use of TACE as an alternative

Table. 5 Characteristics and outcomes among HCC patients who underwent TACE and those who received best supportive care (n = 134)

Parameters	TACE group (n = 110)	BSC group (n = 24)	*p*-value
Male	90 (81.8)	18 (75.0)	0.568
Age (years)	56.2±11.2	57.8±12.9	0.580
Alcohol	70 (63.6)	11 (45.8)	0.106
Etiology			
HBV	58 (52.7)	14 (58.3)	0.618
HCV	26 (23.6)	4 (16.7)	0.458
BMI (kg/m^2)	21±3.18	21.99±3.22	0.172
Child-Pugh classification			0.021*
Class A	85 (77.3)	13 (54.2)	
Class B	25 (22.7)	11 (45.8)	
MELD score	9.5 (6-21)	10.4 (6-22)	0.054
AFP (ng/dl)	11.7±19.0	21.0±50.5	0.644
Total bilirubin (mg/dl)	1.7±0.8	3.0±5.4	0.277
AST (U/L)	129±119	122±84	0.651
ALT (U/L)	66±64	77±62	0.191
Albumin (g/dl)	3.5±0.5	3.6±0.6	0.779
INR	1.14±0.11	1.15±0.11	0.790
Platelets ($cells/mm^3$)	239,555±130,883	255,541±143,583	0.576
eGFR (ml/min)	80.3±28.9	90.7±20.4	0.042
Tumor number			<0.001*
Single lesion	294 (26.4)	15 (62.5)	
2 to 3 lesions	19 (17.3)	8 (33.3)	
>3 lesions	62 (56.4)	1 (4.2)	
Tumor size ≥5 cm	98 (89.1)	21 (87.5)	0.732
Portal vein invasion/thrombosis	40 (36.4)	6 (25.0)	0.288
Inferior vena cava invasion	10 (9.1)	1 (4.2)	0.688
Metastasis	45 (40.9)	11 (45.8)	0.658
Lymph node	18 (16.4)	5 (20.8)	
Lung	7 (6.4)	6 (25.0)	
Bone	6 (5.5)	2 (8.3)	
Adrenal gland	3 (2.7)	0 (0.0)	
Overall median survival (months)	8.8±0.8	3.1±0.7	<0.001*
3-month survival rate	97 (88.2)	12 (50.0)	<0.001*
6-month survival rate	73 (66.4)	6 (25.0)	<0.001*
12-month survival rate	45 (41.0)	3 (12.5)	<0.001*

HBV = Hepatitis B virus, HCV=Hepatitis C virus, BMI = Body mass index, AFP = Alfa-fetoprotein, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, INR = International ratio, eGFR = Estimated glomerular infiltration rate
Values are represented as n (%), Mean±SD, Median (Min-Max), * = Significant at $p<0.05$

treatment option in selected patients with advanced HCC, particularly in those with extrahepatic metastasis. Further prospective or randomized studies with larger samples size are required to determine survival benefits and the safety of TACE in this group of patients.

What is already known of this topic?

TACE is considered as a standard care modality to prolong survival in patients with intermediate stage HCC.

TACE can be associated with complications, such as liver failure, when performed in patients with advanced stage HCC, especially in those with PVT.

What this study adds?

TACE is reasonably safe and likely to prolong survival (when compared to supportive care) in patients with advanced stage HCC and relatively preserved liver functions.

TACE can be considered as an alternative

treatment option in selected patients with advanced HCC, particularly in those with extrahepatic metastasis.

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Potential conflict of interest

None.

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