

# Transarterial chemoembolization extends long-term survival in patients with unresectable hepatocellular carcinoma

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## Abstract

The long-term survival benefit of treating unresectable hepatocellular carcinoma (HCC) patients with transarterial chemoembolization (TACE) rather than conservative treatment remains controversial. This retrospective case-control study evaluated the survival of patients with unresectable HCC treated with TACE, relative to that of patients who received best supportive care.

From January 2002 to December 2010, 522 of 2386 consecutive patients with unresectable HCC were enrolled. Patients were treated with TACE ( $n = 347$ ) or best supportive care (non-TACE;  $n = 175$ ). A survival analysis compared the survival of the 2 groups, as well as only those at Barcelona Clinic Liver Cancer Classification (BCLC)-C and Child-Pugh-B (39 TACE, 61 non-TACE). The median follow-up was 5 months (0.15–106 months).

The overall median survival of the TACE group (8.0 months) was significantly longer than that of the non-TACE (2.0 months;  $P \leq .01$ ). Of the patients at BCLC-C and Child-Pugh-B, the overall median survivals of the TACE and non-TACE patients were 6.0 and 2.0 months, respectively ( $P \leq .01$ ); and the 1, 2, 3, 5, and 8-year overall survival rates were significantly superior in the TACE group ( $P \leq .01$ ). For all the patients, the independent predictors of survival were treatment modalities, portal vein tumor thrombosis, alpha-fetoprotein, and BCLC stage. Regarding the TACE patients, contributors to prognosis were portal vein tumor thrombosis, alpha-fetoprotein level, and the number of TACE procedures.

TACE for unresectable HCC was associated with longer survival compared with best supportive care, especially for patients at BCLC-C and Child-Pugh-B.

**Abbreviations:** AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer Classification, HCC = hepatocellular carcinoma, PVTT = portal vein tumor thrombosis, TACE = transarterial chemoembolization.

**Keywords:** conservative treatment, hepatocellular carcinoma, prognosis, survival, transarterial chemoembolization

## 1. Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide and the third leading cause of cancer-related mortality in China.<sup>[1,2]</sup> The HCC prognosis is very poor, most likely because of late-stage diagnosis and limited access to timely and standard treatments.<sup>[3,4]</sup> About 80% to 90% of patients with HCC at diagnosis are considered not eligible for any of the available curative treatments, especially liver resection or transplantation. In this setting, the treatment modalities have not been standardized.<sup>[3,4]</sup> For these patients, the available treatment options are transarterial chemoembolization (TACE),

radiofrequency ablation, hepatic arterial infusion chemotherapy, sorafenib, and best supportive care. In actual practice, the choice among these is determined by the clinical situation.<sup>[5]</sup>

TACE has been proposed for a long time as the criterion standard for palliative treatment of unresectable HCC,<sup>[6,7]</sup> and has been reported to improve the survival of these patients, compared with supportive treatment.<sup>[8,9]</sup> According to Barcelona Clinic Liver Cancer (BCLC) tumor staging and management, TACE is recommended as the first-line therapy for unresectable intermediate stage HCC (stage B).<sup>[10]</sup> Although BCLC guidelines have been extensively validated, a heterogeneous population of patients with intermediate-stage HCC or with advanced-stage HCC has consistently raised issues in clinical practice. Because multiple variables affect the clinical course of HCC,<sup>[11]</sup> the number of studies comparing TACE to conservative management remains limited.<sup>[12,13]</sup>

These data prompted us to analyze retrospectively the long-term follow-up of 522 consecutive HCC patients. This study compared the overall survival and survival rates of patients with unresectable HCC who were given either TACE or best supportive care, and assessed the factors that influenced the overall survival of these patients.

## 2. Materials and methods

The Ethics Committee of the Fourth Hospital of Hebei Medical University approved the study (No. 2014MEC020), which was registered in the Chinese Clinical Trial Registry (ChiCTR-IPC-14005432). Written consent was obtained from each patient.

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The authors report no conflicts of interest.

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## 2.1. Patients

A consecutive cohort of 2386 patients, who were admitted to the Fourth Hospital of Hebei Medical University from January 2002 to December 2010, was investigated. We retrospectively enrolled 522 patients who underwent TACE ( $n=347$ ) or conservative management ( $n=175$ ) as initial treatment in our hospital. The HCC diagnosis was confirmed by histological or cytological examination or on the basis of the domestic standard criteria of clinical diagnosis and staging<sup>[14]</sup> (Guangzhou, 2001) and the domestic clinical guidelines (Zhejiang, 2011).<sup>[15]</sup> Patients were excluded if they had other locoregional or systemic therapy, or previous or current malignancy aside from HCC. The choice of treatment was made at the patients' request after a full discussion with our multidisciplinary treatment team, which included radiologists, surgeons, hepatologists, and oncologists.

## 2.2. TACE procedure

TACE was performed using the Seldinger technique. The whole procedure was performed under fluoroscope. A selective catheter was used and visceral angiography was performed to assess the feeding arteries, tumor type and size, tumor number, arterial tumor supply, portal vein tumor thrombus, and arteriovenous fistula. Then the tip of the catheter was advanced into the right or left hepatic artery, or tumor-feeding branches. After safe positioning of the catheter, an emulsion of lipiodol and anticancer agents was infused.

The treatment regimen consisted of iodized oil (10–30 mL), tropisetron (5 mg), and tegafur (1.0 g). Embolization was then performed with injection of absorbable gelatin sponge particles through the angiographic catheter to reach stasis in a tumor-feeding artery. The dose of embolic agents depended on tumor size and blood supply of the hepatic artery. Depending on the patient's situation, 3 kinds of antineoplastic agents were injected into the hepatic artery, among them fluorouracil, doxorubicin, mitomycin, theraurubicin, cisplatin, oxaliplatin, or hydroxycarbamide. The specific dose of antineoplastic agents depended on the patient's body surface area and general condition.

## 2.3. Conservative management

During the same study period, 175 patients with HCC received best supportive care measures including hepatic protectors, analgesics, Chinese medicine, nutritional support, and management of HCC complications.

## 2.4. Follow-up

The clinical, laboratory, and radiological data of all the patients were retrospectively reviewed. The survival status and subsequent treatments were followed. The differences in therapeutic efficacy between the 2 groups were evaluated by comparing overall survival and survival rates. Overall survival was a primary endpoint, defined as the time from the date of HCC diagnosis until the date of death from any cause, or the date of the most recent follow-up, and was expressed in months. The follow-up deadline was April 2015.

## 2.5. Statistical analysis

All statistical analyses were conducted using SPSS 17.0 software (SPSS Inc, Chicago, IL). Continuous variables were compared

using Student *t* test and the  $\chi^2$  test was used for categorical variables. Survival was calculated with the Kaplan-Meier method and compared statistically using the log-rank test. To identify the independent factors for survival and prognosis, variables that were associated with survival and prognosis in univariate analysis were subsequently included in the multivariate analysis, using the Cox proportional hazard model. A 2-tailed *P* value  $<.05$  was considered statistically significant.

## 3. Results

### 3.1. Patient baseline characteristics

A total of 522 patients were recruited in this study, from January 2002 to December 2010 (Table 1). Of them, 347 patients (66.5%) received TACE treatment (TACE group), and 175 (33.5%) received best supportive care (conservative or non-TACE group). Men were predominate (439, or 84.1%). Patients' ages ranged from 18 to 94 years.

No statistical differences were observed between the 2 groups in terms of general condition, preoperative liver function, tumor features, age, sex, hepatitis B virus infection, presence of cirrhosis, or alpha-fetoprotein (AFP) levels (Table 1). However, some hematological indexes were statistically different between the TACE and non-TACE groups, such as leucocyte count ( $P<.05$ ) and hemoglobin values ( $P<.05$ ).

Liver dysfunction was more pronounced in the TACE group, as shown by liver function tests and Child-Pugh scoring. In the TACE group, 265 (76.4%), 77 (22.2%), and 5 (1.4%) were in the Child-Pugh A, B, and C categories, respectively, compared with 44 (25.1%), 75 (42.9%), and 56 (32.0%) in the non-TACE group ( $P<.05$ ). In the TACE group, 64.0% of patients displayed 1 lesion, compared with 44.6% in the conservative group ( $P<.05$ ). The ratio of patients with portal vein tumor thrombosis (PVTT) to patients without PVTT was 32.3% in the TACE group, and 115.0% in the non-TACE group ( $P<.05$ ). According to BCLC,<sup>[16]</sup> significantly more patients in the TACE group were at BCLC stages B or C ( $P<.05$ ).

In the TACE group, the mean number of TACE procedures was  $2.3\pm 1.8$ . In all, 155 patients received TACE only once (44.7%), and the other 192 patients received  $>1$  TACE procedure (range, 2–12). TACE was performed every 1 to 3 months.

### 3.2. Comparison of overall survival in the TACE and conservative groups

The median follow-up duration was 5 months (range, 0.15–106 months), specifically 8 months in the TACE group and 2 months in the conservative group. By the end of the study period, 489 patients (317 TACE, 172 non-TACE) had died. The mortality rates of the TACE and non-TACE groups were 91.4% and 98.3%, respectively. The mean survival periods were  $17.3\pm 1.4$  months and  $5.2\pm 0.7$  months ( $P<.05$ ).

The overall median survival period for the 522 patients was 5.0 months, and was significantly longer in the TACE group (8.0 months) than the conservative (2.0 months);  $P<.05$ ; Fig. 1). The overall survival rates at 1, 2, 3, 5, and 8 years were each significantly higher in the TACE group than the non-TACE group ( $P<.05$ , all). Specifically, in the TACE group, the overall survival rates at 1, 2, 3, 5, and 8 years were 39.4%, 20.1%, 9.5%, 6.9%, and 4.9%, respectively, and in the non-TACE group, the rates were 9.1%, 2.3%, 1.7%, 1.7%, and 1.7%.

**Table 1**

**Baseline characteristics of the entire patient group (n=522) with unresectable HCC\*.**

		TACE	Conservative	$t/\chi^2$	P
Subjects, n		347	175	—	—
Sex, male/female		290/57	149/26	0.21	.64
Age, y		58.2±10.6	58.4±10.7	-0.18	.86
HBsAg, positive/negative/not clear		211/86/50	119/35/21	2.60	.27
Liver cirrhosis, yes/no		311/36	159/16	0.20	.66
Lesions, single/multiple/not defined		222/113/12	78/71/26	30.50	.00
PVTT, yes/no/NA		84/260/3	92/80/3	43.73	.00
Distant metastasis, presence/absence		33/314	20/155	0.47	.49
Alpha-fetoprotein, µg/L				3.45	.18
	<400	160	71		
	≥400	170	89		
	NA	17	15		
PT, s		13.5±5.4	14.5±2.6	-2.15	.03
WBC, ×10 <sup>9</sup> cells/L		6.6±3.0	7.8±5.3	-3.18	.02
HGB, g/L		132.8±20.5	117.6±25.5	7.23	.00
ALB, g/L		35.4±5.5	29.1±6.7	11.49	.00
TBIL, µmol/L		18.8±8.6	57.1±76.4	-9.22	.00
Child-Pugh				161.60	.00
	A	265	44		
	B	77	75		
	C	5	56		
BCLC				149.77	.00
	A	43	0		
	B	158	26		
	C	141	93		
	D	5	56		

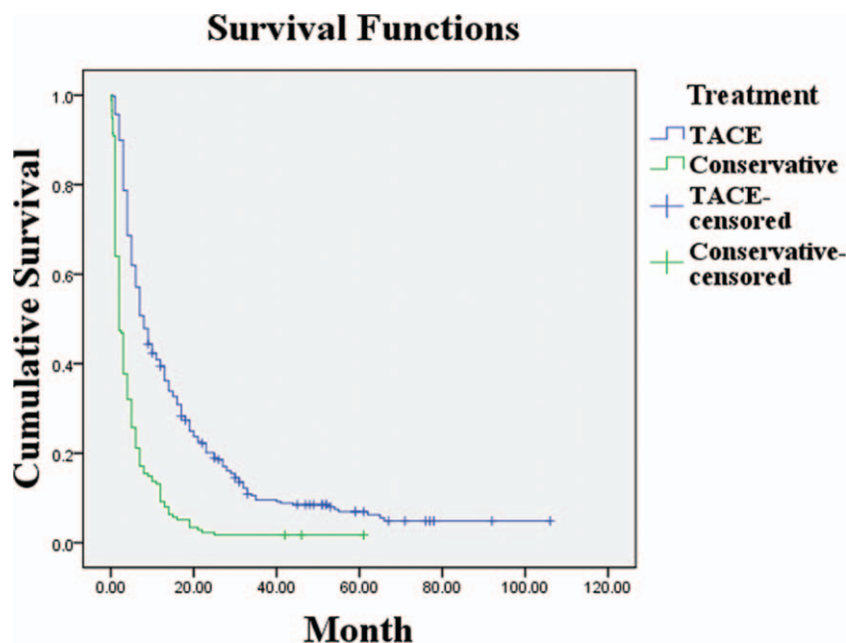
ALB = albumin, BCLC = Barcelona Clinic Liver Cancer Classification, HBsAg = hepatitis B virus surface antigen, HCC = hepatocellular carcinoma, HGB = hemoglobin, NA = not available, PT = platelet, PVTT = portal vein tumor thrombosis, TACE = transarterial chemoembolization, TBIL = total bilirubin, WBC = white blood cells.  
\* n, unless indicated otherwise.

**3.3. Subgroup analysis of patients with BCLC-C stage and Child-Pugh-B class**

Considering the lack of homogeneity in baseline characteristics of the 522 patients, a subgroup analysis was performed. One hundred consecutive patients with both stage BCLC-C and Child-Pugh-B were enrolled (Table 2). The TACE and non-TACE

patients who met this criterion of homogeneity were comparable in all baseline features, including lesion number and presence of PVTT.

The mean survival times in this subgroup were 10.7±1.8 months for the TACE patients, and 4.7±0.6 months for the non-TACE (P < .05). The overall median survival of the TACE group



**Figure 1.** Survival rates of the TACE and conservative treatment groups (P < .05). TACE=transarterial chemoembolization.

**Table 2****Baseline characteristics of the patient subgroup (n=100)\*.**

	TACE	Conservative	# $\chi^2$	P
Subjects, n	39	61	—	—
Sex, male/female	31/8	52/9	0.56	0.46
Age, y	57.8±8.6	58.3±10.6	-0.28	0.78
HBsAg, positive/negative/NA	26/5/8	40/12/9	1.13	0.57
Liver cirrhosis, yes/no	38/1	56/5	0.53	0.47
Lesions, single/multiple/NA	24/12/3	31/21/9	1.58	0.45
PVTT, yes/no/not defined	20/19	40/21	2.03	0.16
Distant metastasis, yes/no	6/33	8/53	0.10	0.75
Alpha-fetoprotein, $\mu\text{g/L}$			1.77	0.41
	<400	25		
	≥400	26		
	NA	10		
WBC, $\times 10^9$ cells/L	6.4±3.2	8.5±7.2	-1.66	0.10
HGB, g/L	115.9±17.7	114.0±27.9	0.41	0.69

NA=not available or not clear, HBsAg=hepatitis B virus surface antigen, HGB=hemoglobin, PVTT=portal vein tumor thrombosis, TACE=transarterial chemoembolization, WBC=white blood cells.  
\*n, unless indicated otherwise.

was 6.0 months, and that of the non-TACE was 2.0 months ( $P < .05$ ; Fig. 2). The survival rates at 1, 2, 3, 5, and 8 years were significantly higher in the TACE than the non-TACE group. Specifically, the survival rates of the TACE group at 1, 2, 3, 5, and 8 years were 33.3%, 11.1%, 5.6%, 5.6%, and 5.6%. The survival rates of the non-TACE group at 1 year were 8.2% and 0% after this (Fig. 3).

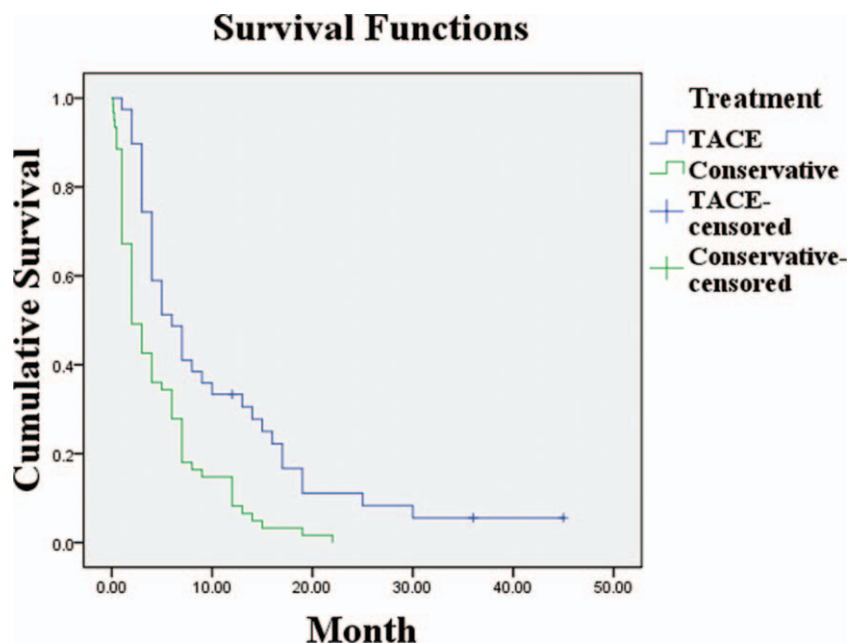
### 3.4. Survival and prognostic factors

The univariate analysis showed that the following were significantly associated with overall survival: Child-Pugh classification, presence of PVTT, BCLC stage, AFP level, treatment mode, and some hematological indexes ( $P < .05$ ; Table 2). According to the multivariate analysis, only treatment mode, PVTT, AFP level, and BCLC stage remained as independent predictors of survival (Table 3).

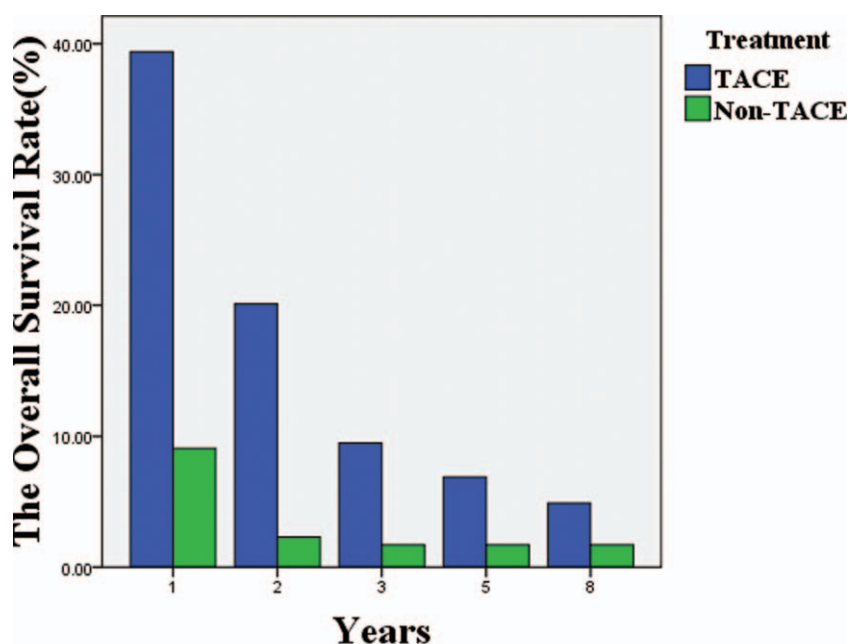
The univariate analysis revealed the following potential prognostic factors in the TACE group: PVTT, AFP levels, BCLC stage, and number of TACE procedures (Table 4). Results of the multivariate analysis indicated that the following were independent factors affecting the efficacy of TACE treatment: portal vein tumor thrombosis, AFP levels, and number of TACE procedures (Table 4).

### 4. Discussion

The annual incidence of HCC in China is estimated to be 50% that of the world.<sup>[1]</sup> In our experience, a majority of HCC patients do not receive surgical treatment, mostly because of tumor extension, liver dysfunction, or poor general condition. In contrast, TACE has been widely accepted for HCC treatment.<sup>[17]</sup> We present herein a large-sample retrospective study, evaluating the efficacy of TACE for prolonging survival, compared with best



**Figure 2.** Survival rates of the TACE and conservative treatment groups in 100 patients with unresectable hepatocellular carcinoma of BCLC-C stage and Child-Pugh-B class ( $P < .05$ ). TACE=transarterial chemoembolization.



**The Survival Rate of TACE vs. Non-TACE on Year 1,2,3,5,8**

**Figure 3.** Survival rates of the TACE and non-TACE groups at 1, 2, 3, 5, and 8 years ( $P < .05$ ). TACE=transarterial chemoembolization.

supportive care alone. The results revealed that TACE was an effective treatment option and improved the overall survival for patients with unresectable HCC.

For assessing the efficacy of TACE, the usual evaluated data are imaging, biological response, and quality of life.<sup>[5,17,18]</sup> However, the ultimate goal of HCC treatment is to prolong survival, and overall survival is therefore the best parameter for evaluating the benefit of TACE. In 2002 in Spain, a randomized controlled trial of patients with unresectable HCC of Child-Pugh class A or B and Okuda stage I or II showed that chemoembolization provided a

survival benefit compared with conservative treatment (for death, hazard ratio [HR]=0.47 [95% confidence interval, CI 0.25–0.91],  $P=.025$ ). Survival rates at 1 and 2 years were 75% and 50% for embolization, 82% and 63% for chemoembolization, and 63% and 27% for the control (chemoembolization compare/ vs (cf.) control,  $P=.009$ ).<sup>[8]</sup> Moreover, a small randomized, controlled trial from Hong Kong, China, reported that the survival benefit of chemoembolization was significant (relative risk of death=0.49; 95% CI 0.29–0.81;  $P=.006$ ), with a better actuarial survival (1 year, 57%; 2 years, 31%; 3 years, 26%) than

**Table 3**

**Multivariate analysis of prognostic variables affecting the survival of the HCC patients (n=522).**

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, ≤58 y/>58 y	1.00 (0.99–1.00)	.27		
Sex, male/female	1.12 (0.88–1.43)	.35		
HBsAg, positive/negative/NA	1.05 (0.91–1.22)	.47		
Liver cirrhosis, yes/no/NA	0.85 (0.64–1.15)	.30		
Lesions, single/multiple/NA	1.05 (0.93–1.18)	.47		
PVTT, yes/no/NA	1.68 (1.42–1.98)	.00	1.40 (1.11–1.76)	.00
Distant metastasis, yes/no	1.30 (0.98–1.73)	.08		
Alpha-fetoprotein, <400/≥400 μg/L	1.27 (1.11–1.47)	.00	1.17 (1.01–1.36)	.04
PT, 10–14 s cf. otherwise	1.26 (1.04–1.53)	.02		
WBC, (4.0–10.0 × 10 <sup>9</sup> cells/L cf. otherwise	1.12 (0.92–1.36)	.27		
HGB, 120–160 g/L cf. otherwise	1.27 (1.05–1.53)	.01		
ALB, 35.0–55.0 g/L cf. otherwise	1.51 (1.26–1.81)	.00		
TBL, 3.4–20.1 μmol/L cf. otherwise	1.27 (1.06–1.52)	.01		
PLT, 100–300 × 10 <sup>9</sup> /L cf. otherwise	1.01 (0.82–1.24)	.93		
Child-Pugh, A/B/C	1.60 (1.40–1.82)	.00		
BCLC, A/B/C/D	1.71 (1.52–1.93)	.00	1.30 (1.11–1.51)	.00
Treatment mode, TACE/conservative	1.14 (1.11–1.18)	.00	1.10 (1.06–1.14)	.00

ALB=albumin, BCLC=Barcelona Clinic Liver Cancer Classification, cf.=compare/ vs, CI=confidence interval, HBsAg=hepatitis B virus surface antigen, HCC=hepatocellular carcinoma, HGB=hemoglobin, HR=hazard ratio, NA=not available or not clear, PLT=platelet, PVTT=portal vein tumor thrombosis, TACE=transarterial chemoembolization, TBL=total bilirubin.

**Table 4****Multivariate analysis of prognostic variables affecting the survival of patients with TACE treatment (n = 347).**

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, ≤58 y/>58 y	1.00 (0.99–1.00)	.52		
Sex, male/female	1.29 (0.96–1.73)	.09		
HBsAg, positive/negative/NA	1.06 (0.88–1.27)	.55		
Liver cirrhosis, yes/no/NA	0.87 (0.60–1.24)	.44		
Lesions, single/multiple/NA	1.08 (0.91–1.27)	.38		
PVTT, yes/no/NA	1.54 (1.23–1.92)	.00	1.54 (1.20–1.97)	0.00
Distant metastasis, yes/no	1.35 (0.93–1.94)	.11		
Alpha-fetoprotein, <400/≥400 μg/L	1.27 (1.06–1.52)	.01	1.24 (1.03–1.49)	0.02
PT, 10–14 s cf. otherwise	1.03 (0.80–1.32)	.83		
WBC, 4.0–10.0 × 10 <sup>9</sup> cells/L cf. otherwise	0.94 (0.73–1.22)	.65		
HGB, 120–160 g/L cf. otherwise	1.12 (0.88–1.42)	.37		
ALB, 35.0–55.0 g/L cf. otherwise	1.20 (0.96–1.50)	.10		
TBIL, 3.4–20.1 μmol/L cf. otherwise	0.99 (0.79–1.25)	.95		
PLT, 100–300 × 10 <sup>9</sup> cells/L cf. otherwise	0.93 (0.73–1.19)	.56		
Child-Pugh, A/B/C	1.07 (0.85–1.35)	.57		
BCLC, A/B/C/D	1.44 (1.23–1.68)	.00		
Number of TACE procedures	0.79 (0.74–0.84)	.00	0.80 (0.74–0.85)	.00

ALB = albumin, BCLC = Barcelona Clinic Liver Cancer Classification, cf. = compare/ vs, HBsAg = hepatitis B virus surface antigen, HGB = hemoglobin, NA = not available or not clear, PLT = platelet, PT = platelet, PVTT = portal vein tumor thrombosis, TACE = transarterial chemoembolization, TBIL = total bilirubin.

in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%;  $P = .002$ ).<sup>[19]</sup> In a recent retrospective comparative study from Guangzhou, China, of a cohort of 287 patients, the 12- and 24-month overall survival rates for the TACE group (18.5% and 2.3%, respectively) were significantly higher than those of the conservative treatment group (12.1% and 0%).<sup>[12]</sup> However, in the above studies, both the number of patients and the follow-up duration were limited.

Few reports have documented the long-term survival associated with the TACE procedure,<sup>[19]</sup> and the reported 5-year survival rates of HCC patients after TACE have ranged from 1% to 8%.<sup>[19,20]</sup> Our present study enrolled 522 patients without previous or current malignancy except for HCC, and included 347 consecutive HCC patients in the TACE group and 175 patients in the conservative group. The longest follow-up was 8.9 years. In agreement with the above studies, TACE treatment offered a survival benefit for patients with unresectable HCC, compared with conservative treatment. The overall median survival was significantly longer in the TACE group, as well as the survival rates at 1, 2, 3, 5, and 8 years ( $P = .00$ ). It has been observed previously that the overall survival and survival rates were lower in Eastern than in Western HCC patients. These differences may be related to the higher prevalence of hepatitis B virus infection in Eastern countries, which increases the risk of developing HCC.<sup>[21]</sup>

Because of the significant differences between the treatment groups with regard to prognostic variables such as PVTT, Child-Pugh grade, BCLC stage, and tumor number, we performed a case-control subgroup analysis of the 100 HCC patients graded at BCLC-C and Child-Pugh-B. In this subgroup, there were no significant differences in baseline characteristics between the patients who received TACE and those with conservative care, but the survival outcomes were significantly better for the patients who received TACE.

According to BCLC staging, TACE is recommended for BCLC-B and sorafenib for BCLC-C as standard treatments.<sup>[22]</sup> However, because of the heterogeneity of patients with advanced-stage HCC and to the short median survival time associated with sorafe-

nib,<sup>[5,23]</sup> TACE is still used to treat selected HCC patients with vascular invasion or extrahepatic metastases.<sup>[24–28]</sup> Our present results with TACE indicated a survival benefit which was consistent with previous controlled trials in advanced HCC with PVTT.<sup>[25–27]</sup> A meta-analysis of 6 studies showed that TACE significantly improved the 6-month overall survival (HR, 0.41; 95% CI: 0.32–0.53;  $z$ , 6.28;  $P = .000$ ) and 1-year overall survival (HR, 0.44; 95% CI: 0.34–0.57;  $z$ , 6.22;  $P = .000$ ) of patients with PVTT, compared with conservative treatment.<sup>[25]</sup> In another study, Yoo et al<sup>[28]</sup> reported that patients with advanced HCC treated with TACE alone (without systemic therapy) showed an improved overall median survival of 13.4 months, noting however that patients with advanced HCC (BCLC stage C) did not obtain similar benefits from TACE in the patient subgroup with extrahepatic metastases (median, 8.3 cf. 19.1 months;  $P = .001$ ). That study suggested that TACE may be an alternative treatment for advanced HCC, particularly for patients with portal vein invasion without extrahepatic metastases.

The main factors affecting survival prognosis are considered the extent of the tumor and severity of hepatic dysfunction.<sup>[29–31]</sup> Our results show that treatment modality, PVTT, AFP levels, and BCLC were independent survival predictors. Based on the multivariate analysis, the Child-Pugh grade was not an independent prognostic factor. In the TACE group, portal vein tumor thrombosis, AFP levels, and number of TACE procedures were significant prognostic indicators. Another study showed that HCC patients with type I PVTT, Child-Pugh B class, and extrahepatic metastasis may be poor candidates for TACE.<sup>[32]</sup> Many studies have evaluated the prognostic factors associated with TACE treatment, but the data remain controversial.<sup>[7]</sup> Therefore, further studies are required for defining the real indications and prognostic factors of TACE.

#### 4.1. Limitations of the study

There were some limitations in our study. First, it is a retrospective, nonrandomized, single-center study, and heterogeneity in the baseline characteristics of the whole cohort exposed

the results to a major bias risk. However, this drawback was, at least partly, counteracted by adopting a subgroup analysis strategy focusing on BCLC-C and Child-Pugh-B patients. Second, the study population comprised patients administered TACE alone; patients with other therapies, such as sorafenib and cytotoxic drugs, were excluded by the study design. Sorafenib is recommended as a current standard treatment for BCLC stage C patients, and TACE-based multimodal treatments have been reported as more beneficial than conservative management.<sup>[11]</sup> Whether combining TACE with systemic therapy would further enhance the survival of patients with advanced HCC deserves further study. Third, patients were only treated with TACE or best supportive care, so that few patients had histopathological data, and in uni- and multivariate analyses, these data were not included as variables. Fourth, in the TACE group, the administered antineoplastic agents and their doses varied. To the best of our knowledge, no standardized protocols exist with regard to the choice of chemotherapeutic agent, dosage, dilution, rate of injection, and optimal retreatment strategy.<sup>[33]</sup> Moreover, there is no conclusive evidence for TACE superiority over transarterial embolization.<sup>[34]</sup> Therefore, the influence of this factor in our study is likely to be very small.

## 5. Conclusion

The present study suggests that TACE significantly improved the survival of patients with unresectable HCC, especially in those graded BCLC-C and Child-Pugh-B. However, because of the study's limitations, prospective, randomized studies are needed before this therapeutic approach can be recommended in clinical practice.

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