Original Article

Prognostic Score Predicting Overall Survival of Patients with Intermediate Stage of Hepatocellular Carcinoma after Transcatheter Transarterial Chemoembolization

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Background: Except benefits, patients with intermediated stage of hepatocellular carcinoma undergoing Transcatheter arterial chemoembolisation (TACE) might be dealt with TACE-related adverse events, especially liver decompensation. The aim of this study is to develop a prognostic score for avoiding unnecessary retreatment with TACE.

Materials and Methods: A retrospective cohort study between January 2007 and December 2012 at Siriraj Hospital, Mahidol University including 216 patients with intermediate stage of HCC undergoing consecutive TACE within 90 days. We investigated the effect of baseline characteristics, liver function, and dynamic tumor response after TACE session on the median overall survival.

Results: Five independent parameters impacted on overall survival (OS) with statistical significance in multivariate analysis. These factors were baseline Child-Pugh score (CTP) class B (hazard ratio [HR] 1.77, p = 0.04), the Barcelona Clinic Liver Cancer (BCLC) stage B (HR 1.95, p = 0.001), increased CTP score (+1 [HR 2.29], +2 [HR 11.74], p<0.001], baseline AFP level ≥200 and <50% reduction after TACE (HR 2.07, p = 0.003) as well as radiologic response (HR 1.56, p = 0.01). The new prognostic score was developed and divided into 2 groups (<3 point and ≥3 point) with different prognosis (median OS 26.3 months vs. 10.7 months, p<0.001). Furthermore, prognostic score of ≥3 point was associated with higher TACE related liver decompensation with relative risk 20.2 (p<0.001).

Conclusion: Patients with prognostic score ≥3 point prior second TACE had poor prognosis and high rate of major complication. Retreatment with TACE should be avoided.

Keywords: Hepatocellular carcinoma, TACE, Chemoembolization, Prognosis

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide, especially in Asia[1,2]. The prognosis is poor because curative treatment e.g. partial hepatectomy, radiofrequency ablation and liver transplantation is applicable to a small proportion of patients. According to the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of Liver (EASL) guidelines, transcatheter transarterial chemoembolization (TACE) is recommended as a first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (intermediate HCC)[3-7]. Furthermore, TACE can be applied to patients in the early stage, who are ineligible for surgery due to poor residual liver function or multiple co-morbidities.

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Overall, the median survival for patients with intermediate HCC is expected to be approximately 16 months, while the median survival for patients receiving TACE treatment is about 20 months[5]. However TACE treatment is not the only factor to determine overall survival. Several studies showed that baseline tumor characteristics such as size of tumor or extension of disease, tumor staging, alpha-fetoprotein (AFP) level, baseline Child-Turcotte-Pugh score (CTP) and biochemical lab, presence of ascites, tumor-related dynamic change after TACE e.g. CTP score change, radiologic (mRECIST and EASL criteria) and biochemical (AFP) responses were associated with overall survival (OS) of patients with HCC[8-14]. Except benefit of TACE, adverse events such as TACE-related liver decompensation, acute renal failure, and post TACE syndrome might be occurred and suffered patient's quality of life[8,15].

Recently, there was ART score (Assessment for Retreatment with Transarterial chemoembolization), which was calculated based on 3 parameters measured just before the second TACE session, including CTP score increase from

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baseline, aspartate transaminase (AST) increase >25% from baseline, and radiologic evidence of tumor response after a previous TACE session. It was shown that a score of at least 2.5 identified patients with a dismal prognosis who may not profit from further TACE sessions[16]. Therefore, we aimed to develop a new prognostic tool including both clinical and radiological factor for preventing TACE-related adverse events and avoiding unnecessary TACE.

Materials and Methods

Study design

A retrospective cohort study was approved by the Ethics Committees of Siriraj Hospital, Mahidol University. We searched electronic database using ICD 10 code C220 (hepatocellular carcinoma) and procedure code 9925 (angiography) or 8847 (chemoinfusion) from 1 January 2007 to 31 December 2012 at Siriraj Hospital. Data were prospectively collected until 31 December 2014 or dates of last follow-up.

Inclusion criteria

HCC was diagnosed by using histology criteria or dynamic imaging (computed tomography [CT]/magnetic resonance imaging [MRI]) criteria according to the AASLD/EASL guidelines. HCC patients with BCLC stage A or B and preserved liver function (CTP A or B) who received at least 2 TACE sessions within 90 days were included. Types of TACE were either conventional TACE (cTACE) or TACE with drug-eluting beads (DEB-TACE). All patients were more than 18 years old at the time of the first TACE session.

Exclusion criteria

Patients received TACE before curative treatment or previous TACE from other hospital were excluded. Patients with decompensated cirrhosis (CTP C), BCLC stage C and ruptured HCC at presentation who received TACE were ineligible. Additionally patients who had incomplete survival data were also excluded.

Data collection

Baseline characteristic, laboratory data including AFP level and baseline liver function e.g. CTP score and Model for End-stage Liver Disease (MELD) score at 1 day before first and second TACE session were collected. HCC was classified according to BCLC classification and tumor node metastasis (TNM) classification. Baseline imaging (triphasic CT or MRI scan) and radiologic tumor response was reviewed by SS using mRECIST and EASL criteria. Dynamic change parameters including AST, alanine transaminase (ALT), alpha-fetoprotein (AFP), CTP and MELD score were determined. TACE related adverse events that occurred within 4 weeks after TACE were documented according to the Common Terminology Criteria for Adverse Events v. 3.0 (CTCAE).

Definitions

Radiologic response was defined as partial response (PR) after TACE; whereas, no radiologic response was defined as stable disease (SD) and progressive disease (PD) after TACE. AFP changes were classified in to 2 groups: AFP response was defined as initial AFP ≥200 U/L and decrease ≥50% after TACE and AFP no response was defined as initial AFP ≥200 U/L and decrease <50% after TACE. CTP change after TACE was defined as CTP score increase 1 or more. Overall survival was defined as the time from the day of first TACE session until death or last follow-up or 31 December 2014.

TACE procedure

All procedures were performed by fellows and staffs at radiointervention unit, Siriraj Hospital. Most patients were performed under local anesthesia. TACE technique e.g. super selected branch or no selected branch was used individually upon intervention radiologist. The standard emulsion consisted of 500 mg of 5-fluorouracil (5-FU) and 20 mg of mytomicin C mixed with 10 ml of lipiodol. However, some physicians preferred using one drug or half dose of combination drug. Embolization was subsequently performed with gelatin-sponge (gelfoam) particles.

Statistical analysis

Baseline patient characteristics prior to first TACE session were performed with descriptive analysis. The Chi-squared test or Fisher's exact test were used to compared quantitative outcome between groups. Survival curves were analyzed using the Kaplan-Meier method. Median OS and 95% confidence interval (95% CI) were presented.

The log-rank test was used to analyzed the effects of variable including baseline characteristic before first TACE, dynamic liver function, laboratory (AST, ALT, platelets and AFP level) and radiologic change (mRECIST and EASL criteria). All variable with $p<0.05$ in the univariate analysis were included into multivariate analysis using stepwise Cox regression model (likelihood ratio backward selection). Hazard ratio (HR) and *p*-value were reported. Statistical analyses were performed using IBM SPSS v.20.0 (SPSS, Armonk, NY) and SAS 9.3 (SAS Institute, Cary, NC).

Results

Total 1,880 TACE sessions in 1,258 HCC patients were performed between 2007 and 2012. Approximately 57% (216/376 patients) with consecutive TACE treatment within 90 days were included into these cohort as Figure 1.

Baseline characteristics in this cohort were shown in Table 1. Most patients were male (75%), infected with HBV infection (53%), and well preserved liver function (CTP A, 89.3%). Approximately 70% were in BCLC stage B. Most of patients (82.9%) were treated with TACE as the first line therapy; whereas, the remaining had received prior treatment before first TACE (partial hepatectomy 10.6%, RFA 6.5%). There were only 32.5% of patient had AFP level more than 200 U/L. All patients had received conventional TACE therapy except 2 patients received TACE with DEB. Most

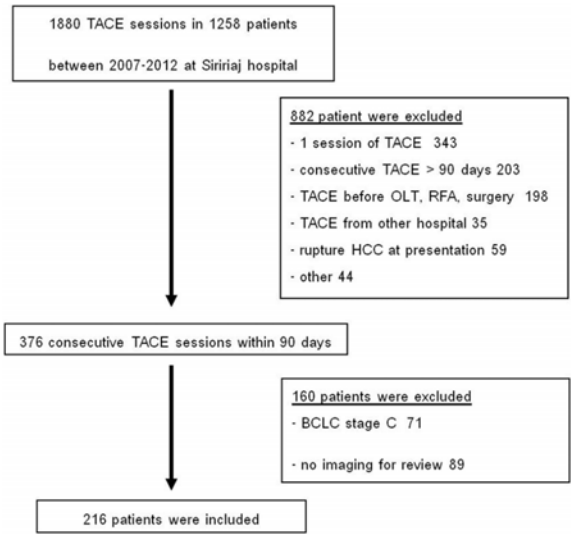

Figure 1. Patient selection.

of TACE sessions (92.6%) used super selection technique. Physicians were preferred full dose and combination of drugs at 80.6% and 85.2% respectively. Forty-five and 4 patients had increase 1 and 2 point of CTP score, respectively; while, 167 patients had no change in CTP score. The median time interval between the first and second TACE was 62.24 days (23 to 90).

Univariate analysis of prognostic factors

One hundred ninety-four (89.8%) patients died during period between January 2007 and December 2012, and 10.2% of patients (n = 22) were still alive. The median OS in cohort was 24.04 months (95% CI, 20.75 to 27.33).

Several baseline characteristics' variable showed significant impacts on OS such as CTP score, MELD score, tumor size, tumor extent, tumor number, and both BCLC and TNM staging (Table 2). Moreover, tumor dynamic change variables such as CTP score change (median OS: no change vs. increase 1 point vs. increase more than 1 point: 26.4 vs. 15.9 vs. 5.2 months (95% CI 22.5 to 30.4 vs. 12.4 to 19.3 vs. 3.4 to 7.0 months, p<0.001), AFP response (median OS: <200, ≥200 and decrease ≥50%, >200 and decrease <50%: 26.1 vs. 22.8 vs. 16.5 months, p = 0.03), and radiological response (median OS: response vs. no response: 27.2 vs. 18.0 months, p = 0.005) were associated with a OS (Table 2). We evaluated the impact of TACE procedures including super selected branch technique, combination or single drug used and half or full dose of chemotherapy used on median OS illustrated that there were no clinically significant.

Multivariate analysis of prognostic factors

Ten significant variables in univariate analysis were entered into Cox Regression model (step backward LR). There were 5 factors that remained significant predictor of OS (Table 3). The calculated regression coefficients (B-values) were multiplied times 2 and rounded in order to simplify the calculation of prognostic score.

Table 1. Baseline characteristics of patients prior to the first TACE session

Variables	Value
Age (years), mean (SD)	59.15 (11.5)
Male, n (%)	162 (75)
Underlying disease, n (%)	
Diabetes mellitus	81 (37.5)
Hypertension	102 (47.2)
Hyperlipidemia	33 (15.3)
Chronic kidney disease	7 (3.2)
Etiology, n (%)	
Hepatitis B	115 (53.2)
Hepatitis C	46 (21.3)
Alcohol	17 (7.9)
Nonalcoholic fatty liver disease	16 (7.4)
Cryptogenic	20 (9.3)
Child-Pugh score, n (%)	
A	193 (89.3)
B (score 7)	18 (8.3)
B (score ≥8)	5 (2.4)
MELD, mean (SD)	8.75 (1.98)
Tumor size (cm), mean (SD)	7.98 (5.26) (1 to 37.5)
Tumor extent, n (%)	
Unilobar	135 (62.5)
Bilobar	80 (37.5%)
Tumor number, n (%)	
Unifocal	85 (39.4)
Multifocal	130 (60.6)
BCLC staging, n (%)	
A	65 (31)
B	149 (69)
TNM staging, n (%)	
I	53 (24.5)
II	106 (49.1)
III	55 (25.4)
Previous treatment, n (%)	
Partial hepatectomy	23 (10.6)
Radiofrequency ablation	14 (6.5)
No	179 (82.9)
AFP level (kU/L), n (%)	
≥200	70 (32.6)
≥400	61 (28.2)

AFP = alpha-fetoprotein, MELD = Model for End-stage Liver Disease

Internal validation of prognostic score

Prognostic score varied from 0 to 9.5 point. We calculated the prognostic score for all patients who had all 5 variables from these cohort (n = 165). We divided patients into 2 groups. First group, patients with score <3, had a median OS of 26.3 months (95% CI 22.4 to 30.2 months). Second group, patients with score ≥3, had a median OS of 10.7 months (95% CI 8.5 to 12.8 months; p<0.001) (Figure 2). We performed subgroup analysis according to BCLC staging, baseline CTP, tumor size and extent, MELD score and AFP level. The prognostic score (cut point at 3)

Table 2. Univariate analysis of prognostic factors of HCC patients after TACE

Variables	Total (n)	Death (n)	Overall Survival (months)		*p*-value
			Median	95% CI	
Age (years)					
<65	140	125	25.1	20.8 to 29.4	0.52
≥65	76	69	21.8	20.8 to 27.3	
Sex					
Male	162	146	22.3	19.3 to 25.3	0.67
Female	54	48	25.0	18.5 to 31.5	
Etiology					
Hepatitis B	101	94	21.2	17.5 to 24.8	0.21
Others	115	100	25.3	20.8 to 29.7	
Previous treatment					
Yes	37	35	21.7	15.0 to 28.4	0.42
No	179	159	23.8	20.5 to 27.3	
Child-Pugh score					
A	192	170	25.3	21.7 to 29.0	0.001
B	24	24	14.0	10.5 to 17.5	
MELD score					
<10	155	137	26.1	22.1 to 30.2	0.007
≥10	56	52	17.8	13.7 to 21.8	
Tumor size (cm)					
<6.5	93	78	29.2	24.0 to 34.4	<0.001
≥6.5	101	95	17.6	15.0 to 20.1	
Tumor extent					
Unilobar	135	116	27.8	23.3 to 32.4	<0.001
Bilobar	80	77	16.5	13.8 to 19.1	
Tumor number					
Unifocal	85	74	27.1	22.2 to 32.0	0.02
Multifocal	130	119	22.2	18.1 to 26.4	
Portal vein thrombosis					
No	198	176	24.7	21.1 to 28.3	0.40
Yes	18	18	19.4	14.1 to 24.8	
BCLC staging					
A	65	54	29.8	24.5 to 35.2	<0.001
B	149	139	19.5	16.6 to 22.5	
TNM staging					
I	53	44	31.2	25.4 to 37.0	<0.001
II	106	95	22.1	17.9 to 26.3	
III	55	54	15.8	13.3 to 18.4	
Dose of chemotherapy					
Full dose	174	158	23.2	19.5 to 26.8	0.07
Decrease dose	42	36	26.6	20.7 to 27.3	
Single drug					
No	184	184	21.1	18.8 to 23.5	0.99
Yes	32	32	21.0	16.4 to 25.6	
Super selected branch technique					
Yes	200	200	21.3	19.2 to 23.4	0.64
No	16	16	19.1	7.5 to 30.7	
Thrombocytopenia (per uL)					
≥100,000	158	144	23.6	19.9 to 27.3	0.53
<100,000	58	50	23.6	18.6 to 28.6	
AFP level (kU/L)					
<200	145	127	24.7	20.9 to 28.5	0.06
≥200	70	67	19.4	15.9 to 22.9	
AFP response					
<200	144	126	26.1	21.7 to 30.5	0.03
>200, ≥50% reduction	37	33	22.8	17.2 to 28.5	
>200, <50% reduction	32	32	16.5	11.7 to 21.4	

Table 2. Cont.

Variables	Total (n)	Death (n)	Overall Survival (months)		*p*-value
			Median	95% CI	
AST response					
No	178	159	25.0	21.3 to 28.8	0.36
Yes	38	35	19.1	14.3 to 23.8	
ALT response					
No	189	168	24.5	20.8 to 28.2	0.79
Yes	27	26	20.9	16.0 to 25.8	
Child-Pugh score change					
0	167	148	26.5	22.5 to 30.4	<0.001
+1	45	42	15.9	12.5 to 19.3	
+2	4	4	5.2	3.4 to 7.1	
Radiologic response**					
Yes	74	66	27.2	22.2 to 32.2	0.005
No	94	87	18.1	15.1 to 21.0	

AFP = alpha-fetoprotein, ALT = alanine transaminase, AST = aspartate transaminase, MELD = Model for End Stage Liver Disease, RFA = radiofrequency ablation
** 48 missing data

Table 3. Multivariate analysis of prognostic factors in HCC patients after first TACE session

Variables	Overall survival			Score point*	*p*-value
	Hazard ratio	95% confidence interval	B		
Baseline CTP score					
A	Reference				
B	1.77	1.01 to 3.07	0.57	1	0.04
BCLC staging					
A	Reference				
B	1.95	1.30 to 2.93	0.67	1	0.001
AFP change (kU/L)					
<200	Reference				
>200, <50% reduction	2.07	1.28 to 3.33	0.73	1.5	0.003
Child-Pugh score change					
0	Reference				
+1	2.29	1.49 to 3.51	0.83	1.5	
+2	11.74	3.20 to 43.00	2.46	5	<0.001
Radiologic response					
Partial response	Reference				
Stable, progressive disease	1.56	1.09 to 2.24	0.45	1	0.01

AFP = alpha-fetoprotein, PR = partial response, SD = stable disease, PD = progressive disease
* The regression coefficients(B) were multiplied by 2 and adjusted in order to simplify to calculation

remained prognostic significant (Figure 3).

Adverse events

Eight (3.7%) patients had 30-days procedure related liver decompensation after first TACE, 3 of them died. Patients who got prognostic score ≥3 had a 30-days procedure related liver decompensation more than those who got prognostic score <3 significantly with RR 20.2 (95% CI 2.3 to 183.1, $p<0.001$). After TACE procedures, patients developed fever (47.2%), abdominal pain (15.3%), and nausea-vomiting (7.4%).

Discussion

TACE is considered the appropriate treatment of patients with intermediate stage of HCC or who are not suitable for curative therapy[4,5]. Many studies revealed repeating TACE effected on prolonged survival. Nevertheless, treatment guidelines did not specify the criteria

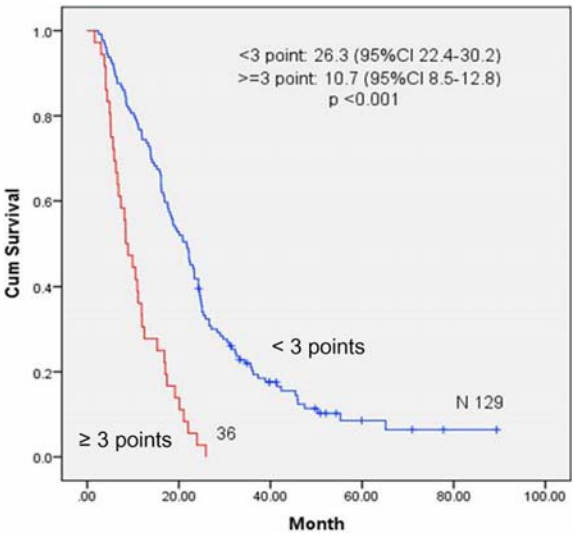

Figure 2. Kaplan-Meier curve showed prognosis between patients who had score ≥3 and those who had <3 (dark line).

for repeating or stopping TACE[8]. In real life practice, TACE was discontinued due to patients had suffering from TACE-related adverse events or liver decompensation or progression of tumor assessed by mRECIST or EASL criteria. Previous studies showed many predictive factors; however, there was not the best factor to predict treatment outcome. The combination of both clinical and radiological factor should be the most important factor to make treatment decision in those patients.

In this cohort study, the authors included 216 patients with intermediated HCC receiving consecutive TACE sessions within 90 days. Result showed that our studied patients had HCCs larger than previous studies possibly because of the lack of awareness in patients with high-risk of HCC. Also, our study had many patients who were in BCLC stage Adue to unavailable of curative treatment because we had low rate of liver transplantation (104 patients with HCC over 12 year). Most common etiology was HBV infection. The median overall survival was 24 months. HCC patients with BCLC stage B had median OS of 19.5 months; whereas, HCC patients with BCLC stage A that were not suitable for curative treatment had a good prognosis with OS of 29.8 months.

Our study showed that 5 clinical patient's parameters were associated with a poor prognosis after TACE session composing of baseline characteristic (CTP B and BCLC stage B), dynamic change factors (baseline AFP >200 and decrease less than 50% as well as radiologic tumor response) and deterioration of liver function (CTP score increase after TACE). Prognostic score was developed and had internal validated. These score identified 2 separated groups of different prognosis and was a significant predictor of OS in multiple subgroups of patients. Patients who got score <3 had an OS of 10.7 months and increase risk of TACE-related liver decompensation with RR 20.2. So we should label this group of patient as TACE failure that has no clinical benefit and increase risk of major adverse events after retreatment with TACE, another treatment regimen such as targeted therapy should be considered.

There are some limitations of the present study, first bias was occurred the retrospective nature. Second we could not perform external validation because no remaining data at Siriraj Hospital. However, we had plan of co-investigation with other medical university. Third, we had incomplete data in 77.8% of dynamic radiologic response parameter. However, these variables achieved the statistical significant with enough number.

Conclusion

Non-invasive prognostic scores composing of both clinical and radiological responses for patients with intermediate stage HCC was developed. Patients with ≥3 points in these prognostic scores prior to the second TACE, had poor prognostic outcomes and higher incidence of procedure-related to liver decompensation, than retreatment with TACE and should be avoided. Our results will be confirmed in external validation and prospective clinical study.

What is already known of this topic?

TACE is recommended as a first-line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (intermediate stage). Common complications after TACE are liver decompensation, acute renal failure, and post TACE syndrome which may affect patient's survival and quality of life. ART score composing both clinical and radiological response ≥2.5 prior the second TACE can identify patients with a dismal prognosis who may not profit from further TACE sessions.

What this study adds?

Five factors determining poor prognosis included baseline Child-Turgot Pugh B, baseline BCLC stage B, baseline AFP more than 200 with less than 50% reduction after TACE, Child-Turgot-Pugh change after TACE, and mRECIST showing stable or progressive disease after TACE. The new score using 5 parameters has been developed. HCC patients with score <3 before the second TACE had a median OS of 26.3 months, whereas, patients with score ≥3, had a median OS of 10.7 months. Repeated TACE should be avoided in HCC patients who had score ≥3 before second TACE.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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