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Predictors of Refractoriness and Survival following Transarterial Chemoembolization for Hepatocellular Carcinoma: Outcomes from a Southeast Asian Cohort

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Abstract

Purpose Patients with hepatocellular carcinoma (HCC) become refractory to repeated sessions of transarterial chemoembolization (TACE). The aim of this study was to identify predictors associated with overall survival and refractoriness following repetitive TACE of HCC among patients in Southeast Asia.

Methods The clinical and laboratory characteristics and radiologic response of 39 patients treated with conventional TACE (range 2 to 5) with mitomycin from January 2012 to June 2018 were retrospectively analyzed. Patients were mostly male with a median age of 59 years and belonged to the BCLC B stage with a median tumor size of 7.5 cm.

Results The median overall survival was 23.2 months and the overall mortality at 5 years was 36%. Multivariate Cox regression analysis revealed that Child–Pugh (CP) score (hazard ratio [HR] = 3.47, $p = 0.044$), AST (HR = 7.6, $p = 0.021$), tumor size (HR = 5.47, $p = 0.033$), progressive disease on Choi criteria (HR = 5.47, confidence interval [CI] 1.15–25.99, $p = 0.033$), neutrophil-lymphocyte ratio (HR = 1.25, $p = 0.049$), and nodular enhancement on follow-up computed tomography (CT; HR = 1.98, $p = 0.034$) were independent risk factors for poor survival. ALT ($p = 0.005$), enhancement ($p = 0.003$), CP score ($p = 0.010$), and progressive disease on Choi criteria ($p = 0.022$) were predictive of TACE refractoriness/failure.

Conclusion Elevated liver enzymes, CP score, and progressive disease on Choi criteria accurately predict TACE refractoriness and failure, allowing early identification of patients who might benefit from other therapies.

Keywords
- TACE
- liver cancer
- response
- survival

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cancer in the Philippines in both sexes, where its high incidence is largely attributed to the high endemicity of hepatitis B-related cirrhosis. It is the second leading cancer among men and ninth among women. HCC ranks as the fifth most common malignancy and the third leading cause of cancer-related deaths worldwide.[1]

In the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is considered the treatment of choice for intermediate-stage HCC.[2] TACE, when repeated, may lose its efficacy at some point and patients enter the so-called state of TACE failure/refractoriness.[2] Reduced survival time is usually the consequence of extrahepatic spread and the damage caused by repeated TACE.[2] Treatment modalities should be switched before patients enter this state.[3]

Treatment guidelines also do not offer specific criteria for repetitive TACE treatments for cases other than complete response after the initial TACE. This highlights the impetus for studies to identify the predictors of TACE refractoriness among patients undergoing retreatment with TACE.

This study aims to identify prognostic factors for TACE refractoriness/failure and survival, as treatment guidelines currently lack adequate criteria to guide clinicians in making the decision to switch or adjust treatment after initial TACE. Prediction of refractoriness to TACE early in the course of therapy enables earlier changes in treatment strategy, such as combination therapy with molecular-targeted agents or switching to other therapeutic modalities.

Materials and Methods

This study was approved by the local institutional review board. This study is a retrospective analysis as described in ►**Fig. 1**. It conforms to the standards of practice set by the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) checklist.

Study Subjects

Records of all HCC patients above 18 years of age and belonging to the BCLC B stage and had undergone TACE from January 2012 to June 2018 were retrieved from the medical records of a tertiary referral and transplant center in the Philippines. The diagnosis of HCC was based on the enhancement pattern consistent with HCC on dynamic liver imaging, such as computed tomography (CT) or magnetic resonance imaging, in conjunction with an elevated level of serum a-fetoprotein, according to the criteria set by the European Association for the Study of the Liver (EASL) and were then classified as intermediate-stage HCC according to the BCLC criteria. None of these patients had histologic tissue diagnosis.

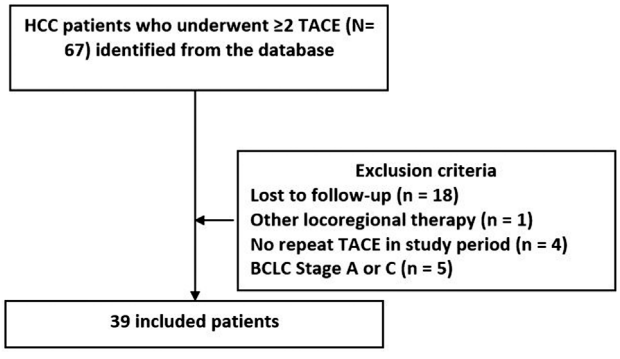

Fig. 1 Flow chart of the methodology

A total of 67 patients with HCC who underwent repeat ($\geq$ 2) TACE sessions were identified. In all, 28 patients were excluded due to the following reasons: (a) lost to follow-up ($n = 18$), (b) other locoregional therapy (ablation, $n = 1$), (c) other incomplete data ($n = 4$) and were either staged as BCLC Stage A or C ($n = 5$). Three patients with severe comorbidities (all with congestive heart failure) were also excluded to avoid confounding effects of poor prognosis in this group of patients. After TACE sessions, a repeat CT/MR imaging was performed within 12 weeks to assess tumor response and laboratory tests to assess liver function.

Patient Characteristics and Data Collection

►**Table 1** summarizes the baseline patient characteristics of 39 patients. Most patients were male (81.5%) with a median age of 59 years. The majority of patients (51.3%) had an ECOG (Eastern Cooperative Oncology Group) performance status of 1, while 46.2% of patients had an ECOG PS of 0. Hypertension was present in 14 patients (35.9%) and diabetes in 7 (17.9%) patients. Hepatitis B infection was the most common cause of liver disease (56.4%). The majority of patients (82%) had compensated liver disease, belonging to the Child–Pugh Class A.

Baseline imaging at least 1 week before TACE and all follow-up CT imaging were reviewed. Baseline tumor characteristics are summarized in ►**Table 2**. The tumor size ranged from 3.8 cm to 16.0 cm in cumulative size for patients with multiple tumors, with 48.7% of patients having tumors larger than 7 cm. Most patients had unilobar involvement (59.0%), with most HCC tumors observed in the right lobe.

Treatment Scheme and Evaluation

A conventional TACE was performed according to our institutional protocol by two experienced and board-certified interventional radiologists. Inter-operator variability and technical factors influencing the study outcome were performed by the same two interventional radiologists performing all procedures. An emulsion containing mitomycin C 20 mg with 10 mL of iodized oil (Lipiodol; Guerbet) was infused through a microcatheter (2.8- or 3-Fr) placed into tumor-feeding arteries. The amount of emulsion injected was based on the tumor size and uptake characteristics during the procedure. The same dose regimen was used in succeeding TACE procedures. Depending on the portal vein status, embolization was accomplished using absorbable gelatin sponge particles (Gelfoam) following the injection of the emulsion.

Repeated sessions of TACE were considered if residual viable or newly developed tumors were identified after the previous TACE, and were performed on an "on-demand"

Table 1 Baseline characteristics of patients with HCC ($n = 39$)

		Number	Percentage
Sex	Male	32	82.1
	Female	7	17.9
Age (median, range)		59 (51–85)	
ECOG functional status	0	18	46.2
	1	20	51.3
	2	1	2.5
	3	0	0
	4	0	0
	5	0	0
Comorbid conditions	None	5	12.8
	Hypertensive	14	35.9
	diabetic	7	17.9
	Hypertensive and diabetic	6	15.4
	diabetic and others	2	5.2
	Hypertensive and others	5	12.8
Etiology	Hepatitis B	22	56.4
	Hepatitis C	1	2.5
	NASH	9	23.1
	Alcoholic	5	12.8
	Cryptogenic	2	5.2
Child–Pugh class (baseline)	A	32	82.0
	B	7	18.0
	C	0	0

basis depending on individual tumor response and liver function. The median time period between TACE sessions was 8 weeks, as adjudged by the referring clinician.

Target lesion response was assessed using the mRECIST (modified Response Evaluation Criteria in Solid Tumors) criteria and CHOI response criteria. These criteria categorized the tumor as having complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) with the CHOI response criteria also evaluating residual enhancement.[3,4] TACE failure/refractoriness and stage progression was classified according to the Liver Cancer Study Group of Japan 2014 criteria update.[5] In this criteria, TACE failure/refractoriness is defined as follows: (1) intrahepatic lesion showing two or more consecutive insufficient responses (e.g., SD or PD) of the treated tumor, (2) two or more consecutive progressions in the liver, (3) continuous elevation of tumor markers immediately after TACE despite the slight transient reduction, (4) new vascular invasion, and (5) new extrahepatic spread. Patients were followed up after 2 to 3 months or as clinical concerns arose and up to their most recent admission and/or until the time of their death. Contrast-enhanced triphasic CT of the liver was used to assess imaging response.

Table 2 Baseline characteristics of HCC tumors

		Number	Percentage
Tumor number	Single	23	59.0
	Multiple	16	41.0
Tumor size	<5 cm	9	23.1
	5–7 cm	11	28.2
	>7 cm	19	48.7
Lobar involvement	Right	22	56.4
	Left	4	10.3
	Bilobar	13	33.3

Tumor sizes and contrast attenuation values (HU) were individually measured and compared on the follow-up scans on a Siemens Syngo Via workstation, according to the standard protocol described in the mRECIST and the CHOI response criteria.

Statistical Analysis

Patient demographics and clinical characteristics before the first TACE as well as baseline tumor characteristics are presented using descriptive statistics. All valid data from evaluable subjects were included in the analysis. In all, 18 patients had incomplete data while 8 patients were non-evaluable. A listwise deletion approach was used to exclude incomplete datasets from the analysis.

For univariate analysis, the Kaplan–Meier method with log-rank test was used to calculate survival and determine significance. Variables with $p < 0.20$ in the univariate analysis were entered into a stepwise Cox regression model (conditional backward selection).

Multiple binary logistic analysis using the conditional backward selection was also done to identify prognostic factors that may correlate with TACE refractoriness.

All statistical analyses were performed using the IBM SPSS Statistics 22 (Armonk, NY, USA). Reported two-tailed p-values were considered significant at less than 0.05 at a 95% confidence interval.

Spearman rho was used to test if there was a significant correlation between the number of TACE sessions and the patient's state of refractoriness.

Results

TACE Failure/Refractoriness

The mean and median number of TACE sessions received by the patient was 3 (range, 2–5). Using the Liver Cancer Study Group of Japan 2014 criteria update definition, TACE failure/refractoriness was observed in 44% of patients, characterized mainly by the presence of macrovascular invasion or extrahepatic spread based on the latest imaging. There was no significant correlation between the number of TACE sessions and the patient's refractoriness/failure using Spearman's rho ($e = 0.274$, $p = 0.92$).

Overall Survival and Univariate Analysis of Prognostic Factors

During the study period of 72 months, 14 patients (36%) died. The median overall survival was 23.2 months (range, 4–66 months). Potential variables based on a prior literature search were included in the univariate analysis. On univariate analysis, refractory status ($p = 0.007$), age ($p = 0.088$), Child–Pugh score ($p = 0.200$), neutrophil–lymphocyte ratio ($p = 0.154$), AST ($p = 0.004$), AFP ratio of 1.85 above the baseline ($p = 0.189$), tumor size ($p = 0.004$), enhancement on post-TACE CT scan ($p = 0.036$), radiologic response using CHOI criteria ($p = 0.011$), and ART score ($p = 0.068$) were associated with survival (►**Table 3**).

Multivariate Analysis

Potential relevant covariates from the univariate analysis were placed in the multivariate Cox regression analysis. AST and ALT are markers of liver function and were included because of their ability to change in the acute setting. The composite marker Child–Pugh score (composed of total bilirubin, serum albumin, international normalized ratio, ascites, and hepatic encephalopathy) was chosen as a marker of chronic liver disease because of its importance in selecting candidates for TACE. After one-at-a-time stepwise removal of the covariates with $p > 0.05$ until all significant regression coefficients remained. Child–Pugh B score (hazard ratio [HR] = 3.47, confidence interval [CI] = 1.31–9.15, $p = 0.044$), elevated AST (HR = 7.6, CI = 1.36–46.61, $p = 0.021$), tumor size greater than 7.2 cm (HR = 5.47, CI = 1.15–25.99, $p = 0.033$), progressive disease on radiologic follow-up using CHOI criteria (HR = 5.47, CI = 1.15–25.99, $p = 0.033$), elevated neutrophil–lymphocyte ratio (HR = 1.25, CI = 1.19–9.86, $p = 0.049$) and significant enhancement on follow-up CT imaging (HR = 1.98, CI = 1.05–3.72, $p = 0.034$) were independent risk factors for poor survival. Significant enhancement was indicated by the enhancement of more than 20 HU between the non-enhanced phase and the arterial phase.

Multiple binary logistic analysis using conditional backward selection also showed that ALT ($p = 0.005$), significant enhancement ($p = 0.003$), elevated Child–Pugh score ($p = 0.010$), and progressive disease on radiologic follow-up using CHOI criteria ($p = 0.022$) were predictive of TACE refractoriness/failure.

Discussion

Repetition of TACE increases tumor response and prolongs survival[6]; however, it is necessary to differentiate between patients, who may not benefit from TACE and transition them to other treatments for improved outcomes. This necessitates the identification of predictors for TACE refractoriness and survival of these patients. In the current study performed in the Southeast Asian setting, we explored predictive factors for survival and TACE refractoriness/failure in a country where most patients have primarily viral hepatitis B-related HCC. We also evaluated the utility of neutrophil–lymphocyte ratio and the ART score in this patient population.

The most common cause of HCC was viral in almost 60% of patients, composed mainly of hepatitis B. This compares to most studies done in Asia[6,7] survival of patients who underwent TACE was also comparable to previous studies with a range of 23.1 to 26.0 months.[7,8]

Predicting which subset of patients benefits from repeat TACE sessions is paramount in developing a treatment plan. Patients with TACE refractoriness or failure may benefit from an early shift in treatment protocol to include combination therapy, Yttrium 90 radioembolization, or systemic chemotherapy. Therefore a composite prediction tool was developed, entitled Assessment for Retreatment with Transarterial chemoembolization or ART.[9] The ART score depends on the Child–Pugh score, AST, and radiologic tumor response[9]. The ART score demonstrated a significant predictive value in overall survival and clinical adverse events during two initial cohort studies. Later studies, however, in other European and Asian countries were not able to replicate the predictive success of the ART score.[7,8] Such disparity was attributed to differing etiologies of HCC in their subset of patients, i.e., studies in Italy[8] and Taiwan[7] where the prevalent cause of HCC was viral etiology, rather than alcoholic liver cirrhosis. Previous studies are largely conflicting.[7–9] Differences in the predictive capability of various clinical, laboratory, and radiologic parameters were attributed to differences in patient demographics and the etiologic agent of liver cirrhosis.

The current study shows that a high Child–Pugh B score, elevated AST, tumor size, progressive disease on radiologic follow-up, elevated neutrophil–lymphocyte ratio, and significant enhancement on follow-up CT imaging were independent risk factors for poor survival. These findings are similar to a previous Korean study where tumor size, AFP ratio, AST > 95 U/L, AST increase > 25%, and poor radiologic tumoral response emerged as significant predictors for poor prognosis.[6]

The effectiveness of the ART score was not proven in three further studies[6–8] where viral hepatitis was the predominant cause of HCC. These findings are similar to the current study, where viral hepatitis related to hepatitis B was the predominant cause of HCC. The ART score was not shown to be effective in the current study where it was not related to survival and refractoriness.

The current study also found some predictive value of the neutrophil-lymphocyte ratio (elevated when above 2.2 in this study), a novel serum marker for poor prognosis among HCC patients[10] and[11] it was posited that the neutrophil–lymphocyte ratio reflected a pro-inflammatory state associated with poorer outcomes among hepatocellular patients. An ideal cut-off has yet to be determined.[12]

Identification of risk factors for TACE failure/refractoriness allows for more accurate prognostication of patients. Early identification of TACE failure/refractoriness allows patients to be initiated earlier on combination therapy with locoregional ablative methods, Yttrium-90, and immunotherapy or to shift treatment strategies. Meanwhile, patients with risk factors for poor survival can also be prognosticated more accurately, allowing more realistic goal-setting and initiation of more intensified treatment strategies.

Table 3 Overall survival and univariate analysis of prognostic factors

Variables	*n*	OS (months)	95% CI		*p*-Value
		Mean			(log-rank)
Refractory status					
Refractory	17	44	54	66	0.007*
Non-refractory	22	60	31	56	
Age					
< 60 years	21	58	50	66	0.088*
≥ 60 years	18	47	35	59	
Etiology					
Non-viral	14	50	38	63	0.932
Viral	25	54	46	63	
Child–Pugh score					
A	7	61	54	69	0.200*
B	32	51	43	59	
Neutrophil–lymphocyte ratio					
Non-significant < 2.2	22	58	50	66	0.154*
≥ 2.2	17	46	34	58	
ALT					
< 95	33	55	47	62	0.349
≥ 95	6	43	24	62	
AST					
< 95	29	58	51	64	0.004*
≥ 95	10	39	21	57	
AST increase 25%					
Absent	28	53	45	62	0.946
Present	11	52	39	64	
AFP ratio of 1.85 above baseline					
Absent	32	54	47	56	0.189*
Present	7	46	29	66	
Tumor size					
< 7.2 cm	20	61	53	69	0.004*
≥ 7.2	19	44	33	55	
Tumor number					
Unifocal	24	52	42	53	0.762
Multifocal	15	54	44	64	
Enhancement on post-TACE study					
Absent	17	47	37	57	0.036*
Present	22	60	51	69	
Child–Pugh score increase					
Absent	8	55	47	64	0.324
Increase	6	48	35	60	
mRECIST criteria					
Stable disease	34	54	47	61	0.249
Partial response	4	50	24	76	
Progressive disease	1	26	26	26	
CHOI criteria					

(*Continued*)

Table 3 (*Continued*)

Variables	*n*	OS (months)	95% CI		*p*-Value
		Mean			(log-rank)
Stable disease	16	56	47	66	0.011*
Partial response	14	60	53	67	
Progressive disease	9	35	17	53	
ART score					
Non-significant (<2.5)	26	58	50	65	0.068*
Significant (≥2.5)	13	43	30	57	

This study, however, is neither definitive nor exhaustive and is limited by the retrospective nature of the methodology. The study is also limited by the small sample size and the single center enrolled in this study While most of the enrolled patients had hepatitis B as an etiologic risk factor for the development of HCC, more than one-third also had non-alcoholic steatohepatitis and alcoholic cirrhosis as etiology, which are important emerging causes for HCC. Nevertheless, hepatitis B remains the world's most common serious liver infection and the most common cause of HCC, despite worldwide efforts to boost vaccination against hepatitis B.[13] Differences in prognosis and TACE efficacy according to the etiologic agent are however poorly understood.

Conclusion

High Child-Pugh score, elevated AST, tumor size, progressive disease on radiologic follow-up, elevated neutrophil-lymphocyte ratio, and significant enhancement on follow-up CT imaging were independent risk factors for poor survival. Meanwhile, ALT, significant enhancement, elevated Child–Pugh score, and progressive disease on radiologic follow-up using Choi criteria were predictive of TACE refractoriness/failure in this model. The ART score was not applicable in our cohort of mostly viral hepatitis-related HCC etiology. Identification of these laboratory and radiologic parameters allows the identification of patients at risk for TACE failure, allowing the early decision to shift treatment strategies or initiate combination therapies. Further studies, preferably in a multicenter set-up, can be designed to identify specific laboratory values or create dedicated composite clinical risk scores that may serve as a cut-off for identifying patients at risk for TACE refractoriness and poor survival.

Ethical Approval

This work is an original research work of the authors and has been approved by the Research Ethics Committee of the National Kidney and Transplant Institute, Philippines. It follows international guidelines on the ethical conduct of research, including the Declaration of Helsinki and the Committee on Publication Ethics.

Conflict of Interest

None declared.

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