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Prognostic Value of Alpha-Fetoprotein in Patients Who Achieve a Complete Response to Transarterial Chemoembolization for Hepatocellular Carcinoma

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Purpose: Alpha-fetoprotein (AFP) is a prognostic marker for hepatocellular carcinoma (HCC). We investigated the prognostic value of AFP levels in patients who achieved complete response (CR) to transarterial chemoembolization (TACE) for HCC.
Materials and Methods: Between 2005 and 2018, 890 patients with HCC who achieved a CR to TACE were recruited. An AFP responder was defined as a patient who showed elevated levels of AFP (>10 ng/mL) during TACE, but showed normalization or a >50% reduction in AFP levels after achieving a CR.
Results: Among the recruited patients, 569 (63.9%) with naïve HCC and 321 (36.1%) with recurrent HCC after complete resection were treated. Before TACE, 305 (34.3%) patients had multiple tumors, 219 (24.6%) had a maximal tumor size >3 cm, and 22 (2.5%) had portal vein tumor thrombosis. The median AFP level after achieving a CR was 6.36 ng/mL. After a CR, 473 (53.1%) patients experienced recurrence, and 417 (46.9%) died [median progression-free survival (PFS) and overall survival (OS) of 16.3 and 62.8 months, respectively]. High AFP levels at CR (>20 ng/mL) were independently associated with a shorter PFS [hazard ratio (HR)=1.403] and OS (HR=1.284), together with tumor multiplicity at TACE (HR=1.518 and 1.666, respectively). AFP non-responders at CR (76.2%, n=359 of 471) showed a shorter PFS (median 10.5 months vs. 15.5 months, HR=1.375) and OS (median 41.4 months vs. 61.8 months, HR=1.424) than AFP responders (all *p*=0.001).
Conclusion: High AFP levels and AFP non-responders were independently associated with poor outcomes after TACE. AFP holds clinical implications for detailed risk stratification upon achieving a CR after TACE.

Key Words: Carcinoma, hepatocellular; alpha-fetoprotein; prognosis; treatment outcome; transarterial chemoembolization

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INTRODUCTION

A significant portion of patients with intrahepatic hepatocellular carcinoma (HCC) are not suitable candidates for curative treatments, such as local ablation, surgical resection, and liver transplantation, due to decreased liver function, large tumor burden, and vascular invasion.[1-3] The majority of these patients receive single or multiple rounds of transarterial chemoembolization (TACE), which takes advantage of the hypervascularized nature of HCC with increased arterial enhancement and rapid washout on imaging studies.[1,3-5]

Recent studies have shown that response evaluation according to enhancement criteria, such as European Association for the Study of the Liver and modified response evaluation criteria in solid tumor (mRECIST) criteria, holds prognostic implications in patients with HCC,[1,6] and a complete response (CR) has been found to be an independent predictor of overall survival (OS) among patients with inoperable HCC after TACE.[7-9] Thus, to ensure better outcomes, achieving a CR after TACE according to enhancement criteria is most important in patients with HCC.[5-7] However, CR achievement does not always guarantee total necrosis of the tumor or the absence of small intrahepatic metastases, and thus, a considerable portion of these patients experience recurrence that needs further treatments.[8,10-12]

Serum alpha-fetoprotein (AFP) is a well-recognized biomarker that is overexpressed in the majority of human HCCs. AFP is usually low in adult serum because mature hepatocytes usually lose their ability to synthesize AFP. However, liver cancer cells can regain the ability to produce AFP, a phenomenon that is known to be correlated with tumor burden and poor differentiation.[13,14] Previous studies have revealed that AFP levels are associated with prognosis after loco-regional treatment of HCC,[15] and post-treatment changes in AFP levels are also known to be good prognostic factors for HCC, even after TACE.[16,17] However, the prognostic value of AFP in patients who achieve a CR after TACE has not been investigated.

Therefore, we aimed to investigate whether changes in AFP levels between TACE and achieving a CR and absolute AFP levels upon achieving a CR have prognostic implications in patients with HCC.

MATERIALS AND METHODS

Patient eligibility

Patients who achieved a CR after one or more sessions of TACE as the first-line treatment were recruited using a retrospective review of patient databases at nine tertiary medical centers in Korea (Severance Hospital, Yonsei University College of Medicine; Samsung Medical Center, Sungkyunkwan University School of Medicine; Ewha Womans University College of Medicine; CHA Bundang Medical Center, CHA University; Ajou University School of Medicine; Inje University Haeundae Paik Hospital; Pusan National University Yangsan Hospital; Yeungnam University Medical Centre; and Kyungpook National University). The study population included patients treated for naïve HCC and recurrent HCC after curative resection.

The exclusion criteria were 1) under 19 years of age; 2) metastatic liver mass from other cancers; 3) co-existing extrahepatic tumor; 4) no measurement of AFP before TACE and at the time of confirming CR; 5) significant extrahepatic disease representing an imminent life threatening outcome; 6) uncontrolled medical comorbidity; 7) mortality of unknown cause that was not due to illness; 8) mortality that was absolutely due to procedure-related complications, rather than liver failure after TACE; 9) follow-up loss within 2 months after the TACE date after which the first CR was achieved; and 10) additional local therapies, such as radiofrequency ablation and intraarterial chemoinfusion, before the first CR.

The study protocol was in accordance with the 1975 Declaration of Helsinki guidelines. The need for written informed consent was waived because of the retrospective nature of this study. The Institutional Review Board, Yonsei University Health System, Severance Hospital approved the study procedure (IRB No. 4-2019-1272).

HCC diagnosis

HCC was diagnosed histologically or clinically according to the guidelines proposed by the Korea Liver Cancer Study Group. A positive finding for typical HCC on dynamic computed tomography or magnetic resonance imaging (MRI) was described as increased arterial enhancement followed by decreased enhancement, compared to the liver (washout), in the portal or equilibrium phases.[4] Recurrent HCC was defined as the presence of newly appeared lesions strongly suspected for HCC rather than other malignancies in imaging studies after CR confirmation.

Barcelona Clinic Liver Cancer (BCLC) stage was classified based on the extent of the primary lesion, performance status according to each patient's medical record, and portal vein tumor thrombosis.[18] Since this study excluded patients with extrahepatic lesions, patients with BCLC stage C were classified according to portal vein tumor thrombosis and performance status.

Treatment modality

Before TACE, angiography of the superior mesenteric and hepatic arteries was performed to assess portal vein patency, vascular anatomy, and tumor vascularity. During TACE, a mixture of 5 mL of iodized oil contrast medium, lipiodol, and 25–75 mg of adriamycin was infused selectively at the level of a sub-segmental branch (if possible) or a segmental branch of the feeding arteries. Thereafter, embolization was performed using gelatin sponge particles. In cases of residual or recurrent viable tumor seen on liver dynamic computed tomography

(LDCT) or MRI, sequential TACE was scheduled at 6- to 8-week intervals and on an 'on-demand' basis until CR achievement, provided that the patients' clinical and laboratory findings permitted this and if there was no evidence of extrahepatic spread or major portal vein invasion without appearance of extrahepatic metastases, major portal vein invasion, or deterioration in the clinical status or laboratory values.

Assessment of treatment responses using mRECIST

The treatment responses were assessed 3–4 weeks after TACE sessions using LDCT or MRI. In cases where there was no viable portion of the tumor after TACE, patients underwent LDCT or MRI within 2–3 months until recurrence. Two or more independent radiologists in each institution analyzed the images to minimize the possibility of false categorizations.

The mRECIST guidelines, which define viable tumors according to the uptake of contrast material in the arterial phase of dynamic CT, were used in this study; tumors retaining iodized oil, as well as necrotic lesions without intratumoral arterial enhancement, were regarded as necrotized tumor foci. Up to two target lesions (selected in the order of the maximum baseline diameter to represent the entire tumor burden) in the liver were assessed using one-dimensional measurements according to previous investigations on the 'optimal number of target lesions' for the mRECIST guidelines on HCC treated with TACE.[6] This study focused on the acquisition of a CR, defined by complete disappearance of viable lesions after TACE, and recurrence or progression, defined as a newly developed lesion from previously treated lesions or other sites.

Definitions

The time point of CR achievement after TACE was set as the baseline to investigate the prognostic value of AFP upon achieving a CR after TACE. The time point of TACE (at TACE) was defined as the time point of the last TACE just before obtaining a CR. An AFP responder was defined as a patient with elevated AFP levels (>10 ng/mL) at TACE, but with >50% reduction in AFP or AFP ≤10 ng/mL at CR. In contrast, AFP nonresponders were defined as patients with AFP >10 ng/mL at TACE, ≤50% reduction in AFP, and elevated AFP >10 ng/mL at CR.

Statistical analysis

Considering the time interval between TACE and CR achievement, progression-free survival (PFS) was assessed from the date of achieving CR after TACE until the date of first recurrence or death. OS was calculated as the time interval between TACE and either death or final follow-up. PFS and OS were estimated by the Kaplan-Meier analysis, and survival differences between subgroups were assessed by log rank test. The Cox proportional hazards model was used for univariate and multivariate analyses of PFS and OS. All variables found to be significant in univariate analysis were included in the multivariate model. A $p<0.05$ was considered statistically significant, with a confidence interval (CI) of 95%. Statistical analyses were conducted using IBM SPSS Statistics software, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

From 2005 to 2018, a total of 890 patients with naïve or recurrent HCC after curative surgery who achieved a CR after single or multiple sessions of TACE as a front-line therapy were re-

Table 1. Baseline Characteristics of the Study Population after Achieving a Complete Response after TACE (n=890)

Variables	Values
Demographic variables	
Age (yr)	61.4 (55.0–69.4)
>70	208 (32.4)
Male gender	695 (78.1)
Body mass index (kg/m²)	24.0 (22.1–25.9)
Hypertension	248 (27.9)
Diabetes mellitus	185 (20.8)
Viral infection	750 (84.3)
Hepatitis B virus/Hepatitis C virus	621/135
Alcoholic etiology	103 (11.6)
Liver cirrhosis	671 (75.4)
Laboratory variables	
Aspartate aminotransferase (IU/L)	37.0 (28.0–53.0)
Alanine aminotransferase (IU/L)	25.0 (16.0–41.0)
Serum albumin (g/dL)	3.9 (3.5–4.2)
Total bilirubin (mg/dL)	0.8 (0.6–1.1)
Prothrombin time (INR)	1.09 (1.02–1.17)
AFP (ng/mL)	6.36 (3.13–15.64)
>10	303 (34.0)
>20	196 (22.0)
Tumor variables at TACE	
AFP (ng/mL)	11.85 (4.10–80.30)
>10	471 (52.9)
>20	366 (41.1)
Recurrent HCC after complete resection	321 (36.1)
Disease-free period from resection (months)	19.2 (9.4–40.9)
BCLC stage 0/A/B/C	253 (28.4)/472 (53.0)/ 112 (12.6)/53 (6.0)
Multiple tumors	305 (34.3)
Maximal tumor size (cm)	2.0 (1.4–2.9)
>3 cm	219 (24.6)
Portal vein tumor thrombosis	22 (2.5)

TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; INR, international normalized ratio; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer.
Values are expressed as a median (interquartile range) or n (%).

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viewed in this retrospective, multicenter, cohort study.

Baseline characteristics of the patients with a CR are summarized in Table 1. The median age of 695 (78.1%) male patients and 195 (21.9%) female patients was 61.4 [interquartile range (IQR), 55.0–69.4] years. Among all patients, 569 (63.9%) with naïve HCC and 321 (36.1%) with recurrent HCC after complete resection were treated with TACE. Hepatitis B virus infection was identified in 621 (69.8%) patients, and 671 (75.4%) patients were diagnosed with liver cirrhosis. At TACE, 165 (18.6%) patients had intermediate and advanced stage HCC according to BCLC. Tumor multiplicity was identified in 305 (34.3%) patients, and the maximal tumor size was over 3 cm in 219 (24.6%) patients. A total of 53 (6.0%) patients had BCLC stage C HCC due to portal vein tumor thrombosis (n=22) and poor performance status (n=29).

AFP levels and changes after CR achievement following TACE

The median AFP level was 11.85 (IQR, 4.10–80.30) ng/mL, and elevated AFP levels (>10 ng/mL) were identified in 471 (52.9%) patients at TACE. The median AFP level at CR was 6.36 (IQR, 3.13–15.64) ng/mL, and the AFP value at CR was still elevated >10 ng/mL in 303 (34.0%) patients and >20 ng/mL in 196 (22.0%) patients. Of 471 patients with elevated AFP at TACE (>10 ng/mL), 112 (23.8%) patients were AFP non-responders (Tables 1 and 2).

Prognosis after CR

During the median follow-up period of 35.2 (IQR 20.5–67.5) months after TACE, 630 (70.8%) patients experienced HCC recurrence, and 417 (46.9%) patients died. Median PFS was 16.3 (IQR 7.9–41.6) months, and median OS was 62.8 (IQR 34.9–103.6). Among 471 patients with AFP >10 ng/mL at TACE, median PFS was 13.7 (IQR 7.3–36.5) months, and median OS was 56.1 (IQR 31.5–95.6) months (Table 2 and Supplementary Fig. 1, only online).

Better outcomes in patients with low AFP values and AFP responders at CR

Among the study population, patients with an elevated AFP value >20 ng/mL at CR (n=196, 22.0%) showed significantly shorter PFS (median 11.2 months vs. 17.7 months, p<0.001) and OS (median 50.5 months vs. 70.2 months, p=0.003) than those with AFP below 20 ng/mL at CR. In the subgroup with an elevated AFP level >10 ng/mL at TACE (n=471), AFP responders showed a significantly longer PFS (median 15.5 months vs. 10.5 months, p=0.001) and OS (median 61.8 months vs. 41.4 months, p=0.001) than non-responders (Table 2 and Fig. 1).

Independent predictors of shorter PFS at CR

Univariate analysis revealed that four variables were significantly associated with shorter PFS: BCLC stage B and C (vs. stage 0 and A), multiple tumors, low serum albumin, and an AFP value >20 ng/mL at CR (Supplementary Table 1, only online). Multivariate analysis showed that AFP >20 ng/mL at CR [hazard ratio (HR)=1.403] and tumor multiplicity (HR=1.518) were significantly associated with shorter PFS (Table 3). In a subgroup with an AFP level >10 ng/mL at TACE (n=471), AFP non-responders were independently associated with shorter PFS (HR=1.375), together with BCLC stage B/C (vs. 0/A, HR=1.377) and tumor multiplicity (HR=1.317) (Table 3 and Supplementary Table 1, only online).

Independent predictors of shorter OS at CR

An elevated AFP value (>20 ng/mL) at CR significantly predicted a shorter OS in univariate analysis with several other variables (Supplementary Table 2, only online). Multivariate analysis showed that AFP >20 ng/mL at CR (HR=1.310), tumor multiplicity at TACE (HR=1.614), and higher total bilirubin level at CR (HR=1.429) were significantly associated with a shorter OS. Previous history of complete HCC resection was independently associated with longer OS (HR=0.713) (Table 4). In a subgroup with AFP >10 ng/mL at TACE, AFP non-responders

Table 2. PFS and OS after TACE

Patient group	Survival			AFP ≤20 ng/mL at CR (n=694, 78.0%)	AFP >20 ng/mL at CR (n=196, 22.0%)	p value
Overall patients (n=890)	PFS	Mean (95% CI)	34.4 (31.1–37.6)	36.7 (32.8–40.5)	25.4 (19.8–30.9)	<0.001
		Median (IQR)	16.3 (7.9–41.6)	17.7 (9.1–46.4)	11.2 (6.5–26.9)	
	OS	Mean (95% CI)	77.8 (73.0–82.5)	80.4 (74.8–85.9)	67.3 (58.6–75.9)	0.003
		Median (IQR)	62.8 (34.9–103.6)	70.2 (38.4–105.8)	50.5 (28.2–89.3)	
	Survival			AFP responder* (n=359, 76.2%)	AFP non-responder† (n=112, 23.8%)	p value
Patients with AFP >10 ng/mL at TACE (n=471)	PFS	Mean (95% CI)	30.1 (26.1–34.0)	33.0 (28.2–37.7)	18.3 (14.7–21.9)	0.001
		Median (IQR)	13.7 (7.3–36.5)	15.5 (7.7–39.6)	10.5 (6.7–20.8)	
	OS	Mean (95% CI)	71.7 (65.9–77.4)	76.3 (69.6–83.1)	53.1 (45.4–60.9)	0.001
		Median (IQR)	56.1 (31.5–95.6)	61.8 (35.7–103.6)	41.4 (26.1–75.8)	

TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; CR, complete response; PFS, progression-free survival; OS, overall survival; CI, confidence interval; IQR, interquartile range.

*AFP responder: patients with AFP >10 ng/mL at TACE and a >50% reduction in AFP or AFP ≤10 ng/mL at CR, †AFP non-responder: patients with AFP >10 ng/mL at TACE and a ≤50% reduction in AFP and AFP >10 ng/mL at CR.

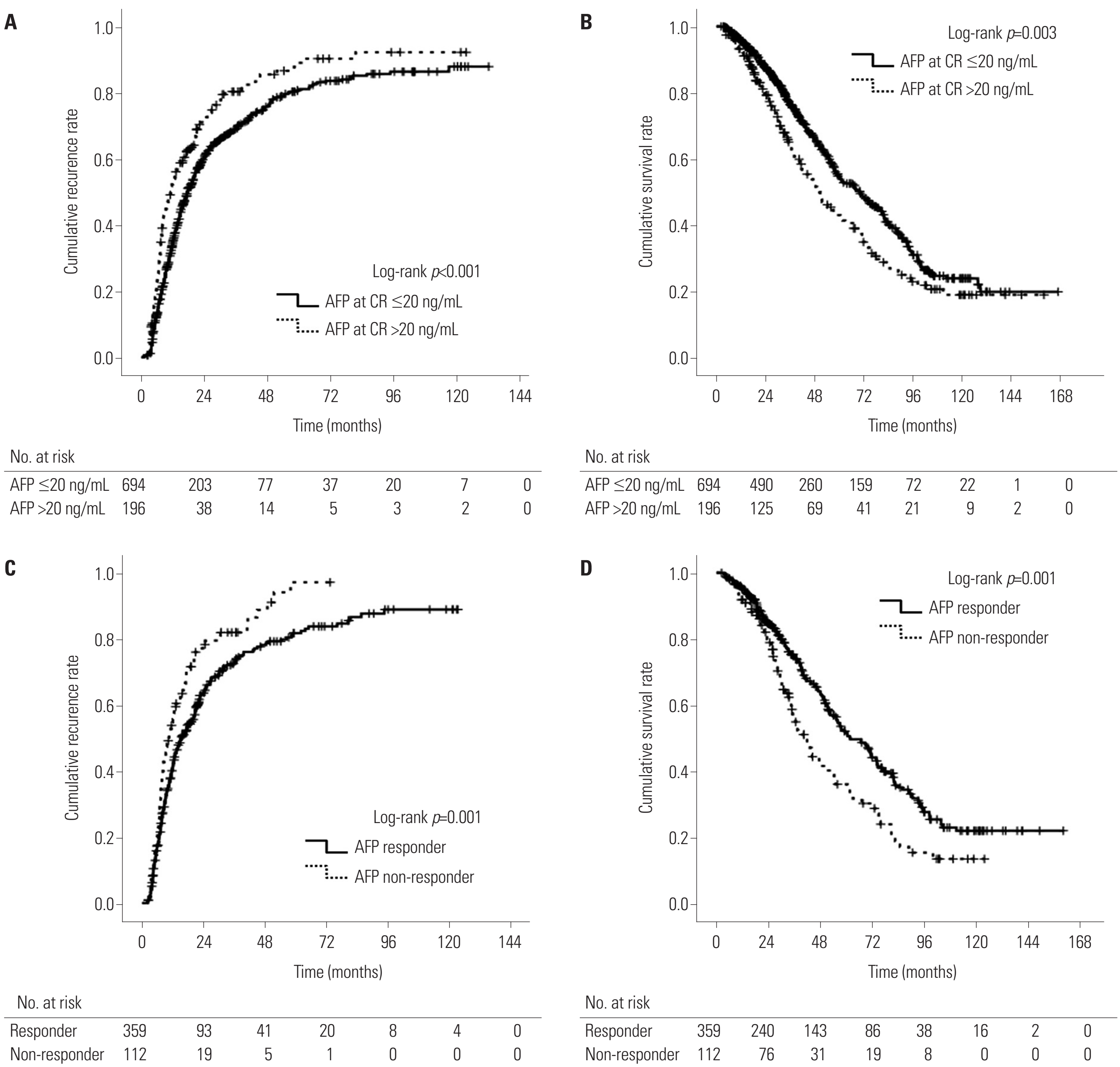

Fig. 1. Kaplan-Meier analysis for the subgroup by AFP at CR (>20 ng/mL) for PFS (A) and OS (B), and for the subgroup by AFP responder for PFS (C) and OS (D). AFP, alpha-fetoprotein; CR, complete response; PFS, progression-free survival; OS, overall survival.

were independently associated with shorter OS (HR=1.406), together with tumor multiplicity at TACE (HR=1.463) and higher total bilirubin level at CR (HR=1.485). Previous HCC resection was still associated with longer OS (HR=0.761) in this subgroup (Table 4 and Supplementary Table 2, only online).

Subgroup analysis in patients with BCLC stage B HCC

When 112 patients with BCLC stage B HCC were selected (Supplementary Table 3, only online), patients with elevated AFP levels at CR (>20 ng/mL, n=80, 71.4%) showed shorter PFS (median 6.5 months vs. 13.5 months, p=0.002) and OS (median 28.2 months vs. 52.4 months, p=0.142), whereas AFP responders (n=42, 59.8%) did not have longer favorable PFS and OS, compared to non-responders (n=25, 37.3%, p=0.277 and 0.882) (Supplementary Table 4, only online). Multivariate analysis showed that high AFP at CR (>20 ng/mL) was independently associated only with shorter PFS (HR=2.287, p<0.001) (Supplementary Tables 5 and 6 only online).

DISCUSSION

In this study, we evaluated whether AFP levels at CR achievement after TACE have prognostic value, based on the fact that

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Table 3. Multivariate Analysis to Identify Independent Predictors for Shorter Progression-Free Survival after Achieving a CR after TACE

Variables	Univariate *p* value	Multivariate *p* value	Multivariate Hazard ratio (95% CI)
All (n=890)			
BCLC stage B/C vs. 0/A	<0.001	0.053	1.252 (0.997–1.572)
Tumor multiplicity	<0.001	<0.001	1.518 (1.262–1.827)
Serum albumin, g/dL	0.004	0.096	0.875 (0.748–1.024)
AFP >20 ng/mL at CR	<0.001	<0.001	1.403 (1.167–1.686)
Subgroup with AFP level >10 ng/mL at TACE (n=471)			
BCLC stage B/C vs. 0/A	<0.001	0.033	1.377 (1.027–1.847)
Tumor multiplicity	<0.001	0.033	1.317 (1.022–1.697)
AFP non-responder*	0.001	0.011	1.375 (1.077–1.756)

CR, complete response; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization.
*AFP non-responder: patients with AFP >10 ng/mL at TACE and a ≤50% reduction in AFP and AFP >10 ng/mL at CR.

not all patients who achieve radiological CR show AFP levels in the normal range. To this aim, we retrospectively analyzed 890 patients with HCC who achieved CR after TACE. Compared with previous studies that recruited mostly HCC patients with elevated AFP levels,[16,17,19,20] our study population had relatively small tumors (median 2.0 cm) with mostly BCLC stage 0 and A tumors (81.4%), which might be associated with the higher rate of CR achievement after TACE. In addition, among patients with elevated AFP levels at TACE, 359 (76.2%) showed AFP response, which is similar or higher to the results from previous studies.[20-24] In multivariate analysis, patients with elevated AFP at CR and AFP non-responders were independently associated with poor outcomes (HR=1.403 and 1.375 for shorter PFS, and HR=1.310 and 1.406 for shorter OS, respectively).

Our study has several clinical implications. First, we showed that both absolute AFP levels at CR and changes in AFP levels between TACE and CR achievement have a prognostic role in predicting disease progression and OS. To date, AFP has been shown to be quantitatively correlated with tumors and to be associated with aggressive behavior and microvascular invasion.[25] Accordingly, AFP has been used as a biomarker for HCC, having both diagnostic and prognostic roles. Further, post-treatment AFP response has also been found to predict prognosis.[15-17,20,26-32] In the present study, although the median AFP level at CR achievement after TACE was within the normal range (6.36 ng/mL), approximately 22% of the patients (n=196 of 890) still had elevated AFP (>20 ng/mL) even after achieving a CR. This could be explained by the presence of residual or satellite cancer cells resistant to TACE that were not detected by conventional imaging studies, thus leading to early recurrence with aggressive tumor behavior.

Second, our finding that post-treatment AFP response was a favorable predictor of longer PFS and OS is supported by other studies, which defined post-treatment AFP response differently: reduction of 20% to 50% in AFP levels from baseline according to the characteristics of cancer and treatment modalities among patients with elevated AFP level prior to treatments.[16,17,20,31] Regardless of the varying study designs, patients with an AFP response consistently showed better survival outcomes than their counterparts. However, this definition might have some disadvantage in that it is difficult to apply directly to patients with low baseline AFP levels, and the effect of minor AFP changes on prognosis could be ignored. Therefore, we evaluated the impact of AFP normalization as an additional definition of AFP response. In our study, AFP response was defined not only as a 50% reduction in AFP levels from baseline, but also as its normalization (<10 ng/mL) at CR achievement. Similar with previous studies, using this definition, we found that patients with an AFP response showed better outcomes of prolonged PFS (median 15.5 months vs. 10.5 months) and OS (median 61.8 months vs. 41.4 months), compared to patients with no AFP response. An unfavorable AFP response might represent insufficient tumor necrosis by hypoxic damage through TACE more sensitively than post-treatment imaging studies, especially when imaging studies cannot provide any

Table 4. Multivariate Analysis to Identify Independent Predictors for Shorter Overall Survival after Achieving a CR after TACE

Variables	Univariate *p* value	Multivariate *p* value	Multivariate Hazard ratio (95% CI)
All (n=890)			
Age >70 (yr)	0.016	0.127	1.222 (0.944–1.582)
Hepatitis B	0.010	0.281	0.844 (0.619–1.150)
Hepatitis C	0.020	0.903	1.023 (0.713–1.468)
Liver cirrhosis	0.034	0.951	1.008 (0.794–1.279)
Recurrent HCC after complete resection	<0.001	0.003	0.713 (0.569–0.893)
BCLC stage B/C vs. 0/A	0.017	0.943	1.010 (0.762–1.340)
Tumor multiplicity	<0.001	<0.001	1.666 (1.348–2.058)
Aspartate aminotransferase (IU/L)	0.004	0.589	1.000 (0.999–1.001)
Serum albumin (g/dL)	<0.001	0.077	0.820 (0.658–1.021)
Total bilirubin (mg/dL)	<0.001	<0.001	1.441 (1.268–1.638)
Prothrombin time (INR)	0.001	0.480	1.269 (0.655–2.460)
AFP >20 ng/mL at CR	0.003	0.027	1.284 (1.028–1.604)
Subgroup with AFP level >10 ng/mL at TACE (n=471)			
Recurrent HCC after complete resection	0.001	0.002	0.761 (0.608–0.951)
BCLC stage B/C vs. 0/A	0.003	0.965	0.992 (0.696–1.415)
Tumor multiplicity	0.003	0.006	1.463 (1.113–1.923)
Serum albumin (g/dL)	0.003	0.586	0.924 (0.696–1.228)
Total bilirubin (mg/dL)	<0.001	<0.001	1.485 (1.291–1.708)
Prothrombin time (INR)	0.001	0.654	0.809 (0.320–2.046)
AFP non-responder*	0.001	0.015	1.424 (1.070–1.895)

CR, complete response; CI, confidence interval; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; INR, international normalized ratio; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization.
*AFP non-responder: patients with AFP >10 ng/mL at TACE and a ≤50% reduction in AFP and AFP >10 ng/mL at CR.

more information regarding tumor viability.[33]

Third, along with AFP levels at CR and changes therein from baseline, tumor multiplicity was also independently associated with prognosis, in spite of CR achievement. To date, various tumor-staging systems have already incorporated tumor multiplicity, which has also been studied as a part of a prognostic scoring systems for TACE in several studies.[32,34-36] In our study, the predictive value of tumor multiplicity at the time of TACE was maintained even after CR achievement. This might be due to a higher possibility for remnant viable tumors in the treated lesion, which were undetected using radiological assessment, or small intrahepatic tumors. In addition, BCLC stage B and C tended to be associated with shorter PFS, compared to BCLC stage 0-A (HR=1.252, p=0.053).

Fourth, based on the results of our study, we cautiously suggest that further advanced surveillance strategies are required, even after CR achievement after TACE. To date, various scoring systems have been proposed to stratify patients with different prognoses after TACE. While it might be clinically infeasible to use complex scoring systems, using post-treatment AFP levels and changes therein as a biologic response surrogate after TACE, even after CR achievement, could be a simple and more intuitive way of aiding clinical decision-making. For patients with elevated AFP or poor AFP response after CR, surveillance using MRI,[37] scheduled secondary angiography,[10] and additional therapy, such as ablation or stereotactic radiotherapy, might be helpful for early detection of hidden lesions.[38,39]

Although we focused on the time point of CR after one or several TACEs as our baseline, we collected additional information regarding the number of TACE sessions to achieve CR status. Most patients achieved CR through one (83.5%) or two TACE sessions (14.0%). Patients who achieved CR after multiple sessions of TACE had a significantly shorter OS than those with one TACE session (HR=1.730, p=0.002), which was supported by a previous study showing that CR at first TACE was the most robust predictor for favorable OS.[8] However, single or multiple TACE sessions did not influence PFS (p=0.177), probably due to the significantly skewed distribution of the number of TACE sessions to achieve CR.

Several unresolved issues remain in our study. First, since most HCC diagnoses lacked histologic evaluations according to the current guidelines,[1,4] the correlations between tumor differentiation and AFP levels were not identified.[33] Second, the retrospective setting of the present study limited the evaluation of other potential risk factors, such as recurrent type of HCC (intrahepatic vs. intrahepatic and extrahepatic) and des-gamma carboxyprothrombin (DCP), which is another well-demonstrated serum marker for HCC prognosis. Although a previous study noted the poor performance of DCP response on prognosis after TACE,[20] identifying its efficacy in patients with a CR may be of additional value for clinicians. Third, due to the retrospective nature of our study, it remains unclear why most patients with early HCC did not receive resection or ablation in our study. Old age, comorbidity, or preference to receive non-surgical treatment might be potential reasons for this. Indeed, in our institute, a significant proportion of patients with early stage HCC received TACE, instead of resection or ablation.[2] Fourth, AFP and its response showed an insufficient association with outcomes in a subgroup with BCLC stage B, probably due to the skewed distribution of BCLC stages in our study. High AFP level was significantly associated with PFS among patients classified as BCLC stage B [n=112 (12.6%)]. However, AFP and its response were insufficiently associated with OS, while serum bilirubin still was found to influence the outcome. The significantly small distribution of this subgroup probably biased the association, especially in patients with AFP level >10 ng/mL at TACE [n=67 (7.5%)]. Fifth, this study could not evaluate the effect of disease progression after HCC relapse and subsequent treatments on patient prognosis. Finally, the influence of detailed technical variables, such as origin of the feeding vessel and procedure time, were not investigated.

In conclusion, high AFP and AFP non-responder were independently associated with poor outcomes after achieving a CR after TACE. Thus, assessment of AFP levels after achieving a CR after TACE might provide further detailed prognostication, even when radiological CR is achieved.

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