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INTERVENTIONAL RADIOLOGY

Alpha-fetoprotein assessment for hepatocellular carcinoma after transarterial chemoembolization

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Abstract

Purpose To evaluate whether AFP classification criteria correlate with tumor response measured using the European Association for the Study of the Liver (EASL) and predicate survival in patients with hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE).

Methods Data from 143 consecutive patients with unresectable HCC and elevated AFP (> 20 ng/mL), who underwent TACE as initial treatment between January 2011 and December 2015 were collected, retrospectively. AFP response was classified as follows: complete response, normalization of AFP; partial response, > 50% decrease from baseline; stable disease, − 50 to + 30% change from baseline; or progressive disease, > 30% increase from baseline. Response rates according to AFP and EASL criteria were compared, and associations between the AFP response and overall survival (OS) were evaluated.

Results The *k* value for agreement between AFP criteria and EASL criteria was 0.52 (moderate), with response rates of 42.7% and 41.3%, respectively ($P = 0.811$). The OS of responders was significantly longer compared with non-responders for both AFP (21 vs. 6 months, $P < 0.001$) and EASL (23 vs. 6 months, $P < 0.001$). Multivariate analysis revealed that the AFP response (hazard ratio [HR], 0.430, 95% CI, 0.233–0.794; $P = 0.007$), EASL response (HR, 0.343; 95% CI, 0.176–0.666; $P = 0.002$), and macroscopic vascular invasion (HR, 2.104; 95% CI, 1.403–3.154; $P < 0.001$) were significantly associated with OS.

Conclusions The defined AFP classification criteria was moderate correlated with EASL criteria and predicted the outcome in patients with HCC who underwent TACE.

Keywords Alpha-fetoprotein · Transarterial chemoembolization · Hepatocellular carcinoma · Assessment · Radiology · Survival

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related death worldwide [1]. In developed countries, HCC incidence is increasing and is particularly high in endemic areas such as Southeast Asia and China [1–3]. Liver resection, liver

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transplantation, and percutaneous ablation are the main radical treatments for HCC. However, only 30–40% of early-stage patients are amenable to curative therapies, > 50% of HCCs are diagnosed at the unresectable stage [2–4]. Based on the proven survival benefits, transarterial chemoembolization (TACE) is a valuable and commonly applied treatment for patients with unresectable HCC [2–7].

Conventionally, the response of HCC tumors to TACE is assessed radiologically. The World Health Organization [8] and Response Evaluation Criteria in Solid Tumors (RECIST) [9] criteria focus on tumor size, to assess radiological tumor response. Whereas, because they include radiologically enhanced criteria, the European Association for the Study of the Liver (EASL) [10] and modified RECIST (mRECIST) [11] criteria can reliably predict survival outcome in patients with HCC undergoing local ablation or TACE [12–14]. Therefore, the radiologically enhanced criteria are widely used to assess the tumor response in patients with HCC undergoing TACE.

Changes in serum tumor markers are also important for monitoring anticancer treatment responses. Alfa-fetoprotein (AFP), a glycoprotein, is secreted by ~ 70% of HCCs and is a universally recognized tumor marker for HCC [15]. The diagnostic and prognostic role of AFP in HCC patients has been confirmed [16–25], and AFP has been included in several prognostics scores for HCC patients treated with TACE [26–29]. However, there are no universally accepted AFP criteria for the assessment of patients with HCC who undergo TACE.

In the present study, to assess the treatment response in patients with unresectable HCC and elevated serum AFP (> 20 ng/mL) who underwent TACE, we defined AFP response criteria and compared them with radiologic responses to determine whether the AFP response was correlated with the radiologic response. We also evaluated whether the AFP response was a superior predictor of survival compared with the radiologic response.

Patients and methods

Patient selection

The study protocol was approved by the ethics committees of the institution. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Patients with unresectable HCC who underwent TACE as initial treatment at our center, between January 2011 and December 2015, formed the cohort. The HCC diagnosis was made according to the EASL guidelines [3].

The inclusion criteria were: (a) age, 18–75 years; (b) Barcelona Clinic Liver Cancer stage B or C; (c) Child-Pugh class A or B; (d) Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2; (e) no previous treatments; (f) HCC with elevated baseline AFP (> 20 ng/mL); and (g) availability of radiologic imaging and serum AFP data. Patients were excluded for any of the following: HCC with normal baseline serum AFP (< 20 ng/mL), extrahepatic metastasis, complete main portal vein obstruction, Child-Pugh class C or massive ascites, secondary malignancy, and missing data.

Methods

TACE procedure

TACE was performed as described previously [30]. Briefly, 10–20 mL lipiodol (Guerbet, Paris, France) was mixed with 20–40 mg epirubicin (Pfizer, New York, USA) to create an emulsion. Depending on the tumor size and liver function, 2–20 mL of the emulsion were infused into the liver tumor via a catheter. Subsequently, Gelfoam embolization was performed. When blood flow slowed, or a vascular cast was observed, the injection was discontinued. The bilobar or multiple tumors were concurrently treated in one session of TACE. Depending on the tumor distribution, the lobar, segmental, or subsegmental tumor-feeding artery was targeted, preferentially. In patients with normal liver function, repeated TACE was indicated if viable residual tumors or new lesions were evident on contrast-enhanced computed tomography (CT) images.

Pre- and post-TACE investigations

Before the initial TACE session, patients underwent laboratory tests, including a liver function test, serum AFP assay, and a hepatitis serologic test. Patients also underwent dynamic liver CT. To evaluate treatment response, all examinations, except the hepatitis test, were repeated at 1 month after TACE. In patients who achieved a complete response (CR), follow-up including the above evaluations was performed every 2 months for the first 2 years, then every 6 months for 2 years thereafter, and then every 12 months for a further 5 years.

Assessments

Serum AFP levels were measured using a microparticle enzyme immunoassay (Abbott Laboratories, Chicago, IL). AFP response was classified as follows: CR, normalization of AFP; partial response (PR), > 50% decrease from baseline; stable disease (SD), − 50 to + 30% change from baseline; or progressive disease (PD), > 30% increase from baseline. Tumor response evaluation criteria were based on radiologic evaluation according to the EASL

guidelines [10]. All measurements were performed by an independent observer (M.T. with > 10 years of experience in diagnostic radiology) who was blinded to the clinical data to minimize the possibility of false categorizations. Whenever response categorization was not obvious, final classification was made by consensus (M.T. and J.L. who had > 20 years of experience).

Because the initial response is a robust predictor of favorable outcome, treatment response was evaluated after one TACE sessions [31, 32]. Objective response was defined as the sum of CR and PR, whereas non-response was defined as the sum of SD and PD. Overall survival (OS) was defined as from the date of treatment initiation until the date of death or last follow-up.

Statistical analyses

All statistical analyses were performed using SPSS software (SPSS version 16.0, SPSS, Chicago, IL). For baseline characteristics, continuous variables are described as medians ± standard deviations and categorical variables are expressed as frequencies and percentages. Intermethod agreement between the two methods was assessed using Cohen's kappa (k) coefficient. A k coefficient >0.75 represented excellent intermethod agreement and a k coefficient of <0.21 represented poor intermethod agreement [33]. The Kaplan–Meier method and log-rank test were used to calculate and compare survival differences, respectively. Univariate analyses were performed using the log-rank test. Variables with a P value < 0.1 were entered into a multivariate analysis using the Cox proportional hazards model to identify risk factors associated with OS. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Study population

Among 536 consecutive newly diagnosed patients with unresectable HCC who underwent TACE as initial treatment, 393 were excluded because they had normal serum AFP (n = 106), extrahepatic metastasis (n = 85), complete main portal vein obstruction (n = 64), Child-Pugh class C HCC or massive ascites (n = 48), or secondary malignancies (n = 8). In addition, 82 patients were excluded because their data were not available. The analysis cohort included 143 patients. The baseline characteristics of all patients are shown in Table 1.

Table 1 Baseline patient characteristics

Characteristics	Number (%)
Age (years)[a]	51.3 ± 11.2
Sex	
Male	138 (96.5)
Female	5 (3.5)
Etiology	
Hepatitis B	136 (95.1)
Hepatitis C	1 (0.7)
Other	6 (4.2)
Cirrhosis	
Present	111 (77.6)
Absent	32 (22.4)
No. of tumors	
1–5	68 (47.6)
> 5	75 (52.4)
Size of main tumor (cm)*	10.2 ± 3.9
≥ 10	76 (53.1)
< 10	67 (46.9)
ECOG	
0	31 (21.7)
1–2	112 (78.3)
Child-Pugh class	
A	134 (93.7)
B	9 (6.3)
MVI	
Absent	59 (41.3)
Present	84 (58.7)
AFP (ng/mL) (range)	24–999,999
≤ 400	40 (15.7)
> 400	103 (84.3)

AFP, alpha-fetoprotein; MVI, macroscopic vascular invasion; ECOG, Eastern Cooperative Oncology Group

[a]Data represents mean ± SD

The mean follow-up duration was 15.3 months (range 3–63 months).

AFP response in correlation with radiologic response

According to the AFP criteria, 24 patients had a CR, 37 had a PR, 37 had SD, and 45 had PD. The AFP response rate was 42.7%. According to the EASL criteria, 11 patients had a CR, 48 had a PR, 15 had SD, and 69 had PD. The EASL response rate was 41.3%. The response rates between the two criteria were comparable (Pearson, P = 0.811). Intermethod agreements between the two methods are shown in Table 3. The k value between the AFP criteria and EASL criteria was 0.52 (moderate, $P < 0.001$).

Overall survival stratification according to, AFP criteria, EASL criteria and macroscopic vascular invasion (MVI)

The median OS times between the AFP responders and non-responders were 21 (95% CI, 17.5–24.4) and 6 (95% CI, 5.2–6.8) months, respectively ($P < 0.001$; Fig. 1A). The median OS times between the EASL responders and non-responders were 23 (95% CI 19.4–26.6) and 6 (95% CI 5.1–6.9) months, respectively ($P < 0.001$; Fig. 1B). The median OS times for HCC patients with and without MVI were 7 (95% CI 5.4–8.6) and 21 (95% CI 16.2–25.8) months, respectively ($P < 0.001$).

AFP response for stratification of EASL PD patients

Of the 69 patients with EASL PD, according to AFP criteria, 26 (37.7%) had a PR ($n = 5$) or SD ($n = 21$), and 43 (62.3%) had PD. In a subgroup analysis, the median OS in patients with EASL PD alone was 9 (95% CI 6.5–11.5) months, whereas in those with both AFP PD and EASL PD it was 5 (95% CI 3.8–6.2) months ($P < 0.001$; Fig. 2 and Table 2).

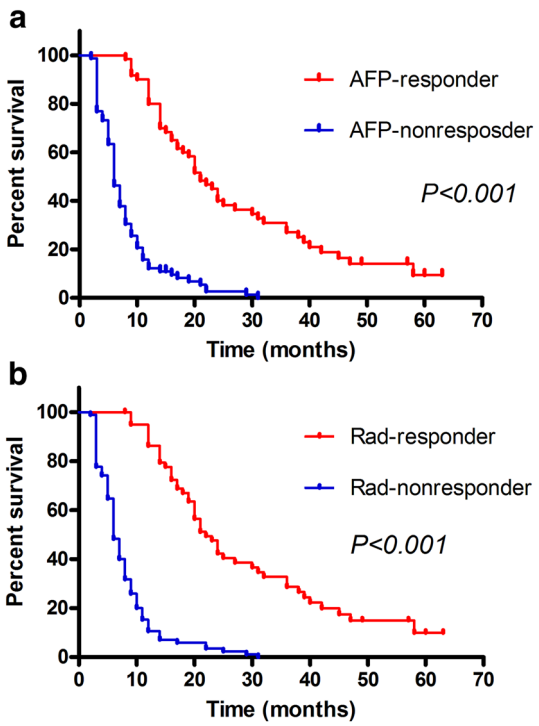

Fig. 1 Kaplan–Meier curves showing median overall survival (OS). **A** The median OS times in AFP responders and non-responders were 21 and 6 months, respectively ($P < 0.001$). **B** The median OS times in EASL responders and non-responders were 23 and 6 months, respectively ($P < 0.001$)

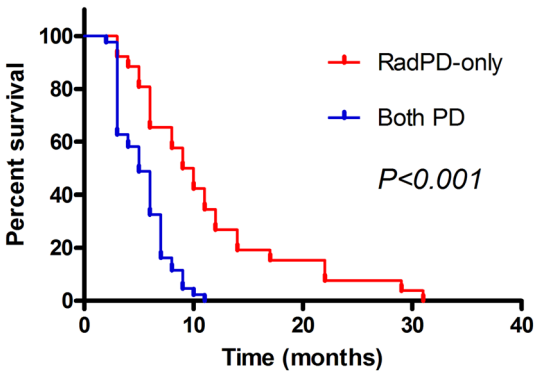

Fig. 2 Kaplan–Meier curves showing median overall survival (OS) according to AFP and non-AFP progressive disease (PD) regarding EASL PD. The median OS times in patients with EASL PD, in the AFP and non-AFP PD groups were 5 and 9 months, respectively ($P < 0.001$)

Serum AFP predicted the response rate after TACE

For patients with AFP ≤400 ng/mL, the objective response rate was 60.0% (24/40). For those with AFP 400–1000 ng/mL, the response rate was 50.0% (7/14). For patients with AFP 1000–10,000 ng/mL, the response rate was 43.8% (14/32). For those with AFP 10,000–100,000 ng/mL, the response rate was 29.6% (8/27). For patients with AFP > 100,000 ng/mL, the response rate was 26.7% (8/30). Twelve patients with the maximum AFP level (> 999,999 ng/mL) did not respond to TACE.

Independent risk factors for survival

On univariate analysis, tumor number, tumor size, AFP level, MVI, being an EASL responder, and being an AFP responder were significantly associated with OS. On multivariate analysis, being an AFP responder (HR 0.430; 95%

Table 2 Intercriterion agreement between AFP and EASL criteria

	AFP response				
	CR	PR	SD	PD	Total
EASL					
CR	9	2	0	0	11
PR	14	29	4	1	48
SD	1	1	12	1	15
PD	0	5	21	43	69
Total	24	37	37	45	143

The k value for agreement between AFP criteria and EASL criteria was 0.52 ($P < 0.001$)

AFP, alpha-fetoprotein; EASL, European Association for the Study of the Liver; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

CI 0.233–0.794; $P = 0.007$), being an EASL responder (HR 0.343; 95% CI 0.176–0.666; $P = 0.002$), and MVI (HR 2.104; 95% CI 1.403–3.154; $P < 0.001$) were independent prognostic factors for OS (Table 3).

Discussion

For the assessment of HCC treatment, the size and enhancement criteria on radiological imaging are reliable predictors of therapy response and survival, and its role in treatment strategies is irreplaceable. However, the radiologic criteria present some limitations including interobserver subjectivity, variable enhancement, increased patient exposure to radiation, and misinterpretation because of regenerative or dysplastic nodules, or perfusion abnormalities [24]. Therefore, AFP response, which can be characterized objectively without interobserver variability might provide a simple, reproducible, and potentially less subjective method to assess tumor response.

We proposed that AFP criteria could be used to assess tumor response, and found that, in patients with unresectable HCC undergoing TACE, the AFP response was highly associated with the EASL response, and was a good predictor of OS. These findings are congruent with those concluded in previous studies [18–25]. Moreover, we found that different serum AFP levels could predict the tumor response rate after TACE. The higher the serum AFP level, the lower response rate, with a complete lack of response to TACE when the AFP level was > 999,999 ng/mL, indicating that TACE would be ineffective in such patients. This might not be surprising because higher AFP levels are correlated with advanced tumor stage, large tumor burden, portal vein tumor thrombosis, and poor outcome [15, 16, 18]. In addition, we identified a subgroup of patients with EASL PD alone, who had superior OS compared to those with both AFP PD and EASL PD. There are two likely explanations for this. First, TACE is a local treatment that can cause chemoembolization-mediated hypoxia in tumors and the surrounding liver tissues. Ischemic injury after TACE can induce upregulation of circulating vascular endothelial growth factor, which could lead to tumor growth and metastasis [34]. Second, serum AFP level has been closely associated with tumor burden and activity. Based on EASL criteria, if new lesions or enlarged non-target lesions were detected, the overall response was classed as PD, ignoring any primary tumor response. Although a new lesion or enlarged non-target lesion might have appeared as a result of TACE, the primary tumor might have shown an objective response, therefore decreasing tumor burden, and, in parallel, decreasing or stabilizing serum AFP. Therefore, the EASL PD situation might not accurately reflect the effectiveness of TACE in treating the primary lesions, and such patients underwent subsequent therapy to treat any new lesions. For example (Fig. 3), in a 40-year-old male patient with multiple HCC lesions and elevated serum AFP (24113 ng/mL), contrast-enhanced liver

Table 3 Univariate and multivariate analyses of prognostic factors

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Tumor size			0.012	–	–	NA
≥ 10 cm	1.000					
< 10 cm	1.596	1.107–2.302				
Tumor number			< 0.001	–	–	NA
> 5	1.000					
≤ 5	2.250	1.543–2.957				
AFP level (ng/mL)			0.015	–	–	NA
> 400	1.000					
≤ 400	2.222	1.541–2.904				
MVI			< 0.001			< 0.001
Absent	1.000			1.000		
Present	2.800	2.098–3.502		2.104	1.403–3.154	
AFP response			< 0.001			0.007
Non-responder	1.000			1.000		
Responder	0.136	0.089–0.209		0.430	0.233–0.794	
EASL response			< 0.001			0.002
Non-responder	1.000			1.000		
Responder	0.111	0.072–0.171		0.343	0.176–0.666	

AFP, alpha-fetoprotein; MVI, macrovascular invasion; CI, confidence interval; EASL, European Association for the Study of the Liver

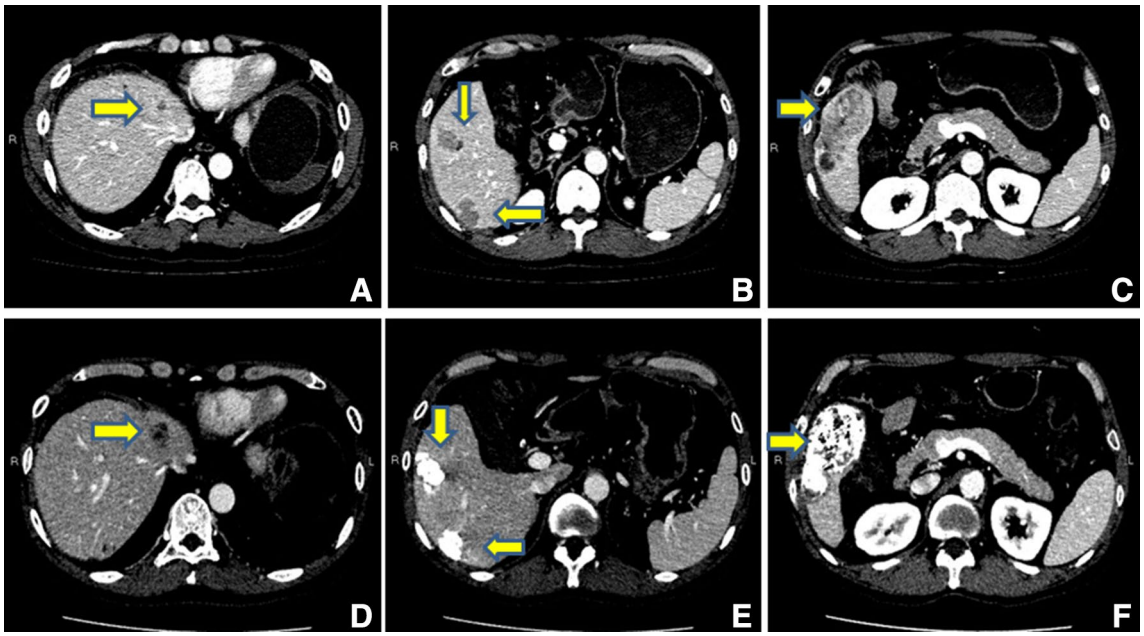

Fig. 3 Comparison of AFP and EASL tumor response assessment: a case example. **A–C** pretreatment axial computed tomography (CT) images show multiple HCC lesions (washout in the portal venous phase) in segments IV, V, and VI (serum AFP level was 24495 ng/mL). **D–F** CT images at 1-month post-TACE follow-up showing the target lesion in segment V and VI obtained a partial response, while the non-target lesion in segment IV had enlarged, the overall radiologic response was PD according to EASL. However, his serum AFP level (3520 ng/mL) had decreased significantly; consequently, the AFP response was PR

CT performed 1-month after TACE showed dense accumulation of iodized oil in the target segment V and VI lesions with a PR response. The non-target segment IV lesion had enlarged significantly. Consequently, the overall radiologic response was PD. However, his serum AFP (3570 ng/mL) had decreased significantly, giving a PR AFP response. It is obvious that TACE is effective for this population and could prolong the survival time. Therefore, patients with EASL PD alone showed a response to TACE suggesting that to some extent, the presented AFP PD criteria covered the shortfalls of the EASL PD criteria.

Previous studies [19–22], in patients undergoing systemic therapy, have used a decrease in AFP of > 20% from baseline as the AFP response. In the present study, which examined the response to TACE, we defined patients with a > 50% decrease in baseline AFP as an AFP responder. As an exploratory value, this showed that the number of patients who were AFP responders was almost equivalent to the number of EASL responders. By contrast, if we had used a >20% decrease as an AFP responder, there would have been more AFP responders than EASL responders (73 vs. 59). Occasionally, we found that response evaluation according to radiologic criteria alone was not accurate. However, this might depend on radiologists' experience or the imaging equipment used. For example (Fig. 4), in a 55-year-old male patient with multiple HCC lesions and elevated serum AFP (7237 ng/mL), contrast-enhanced liver CT performed 1-month after TACE showed dense accumulation of iodized oil in the target segment IV lesion without enhancement during the arterial phase. This lesion was assessed as CR according to EASL. However, his serum AFP increased slightly (8290 ng/mL), so his AFP response was classed as SD. Follow-up CT obtained 2 months later showed the target segment IV lesion had enlarged, leading to a PD response. At the same time, serum AFP level had further increased to 9814 ng/mL, giving an equivalent AFP response of PD. Therefore, in this case, the AFP response reflected the tumor response more accurately. Although magnetic resonance imaging could be used to assess response with greater accuracy than CT [35, 36], it is prohibitively expensive and not always available. Therefore, CT remains the most commonly used radiological method for HCC assessment.

The present study has several limitations. First, this study was performed retrospectively. Second, HCC with positive AFP occurred in ~ 70% of patients; therefore, universal applicability of AFP as a tumor response marker in all patients with HCC would not be feasible. Third, about 50% of the cohort had advanced HCC, and according to the Barcelona Clinic Liver Cancer therapy strategy, TACE is not a recommend standard treatment for this population. Nevertheless, TACE significantly improves survival and is commonly used in patients with unresectable HCC [5, 6]. Prothrombin induced by vitamin K absence-II (PIVKA-II, des-gamma carboxyprothrombin) is a tumor marker used

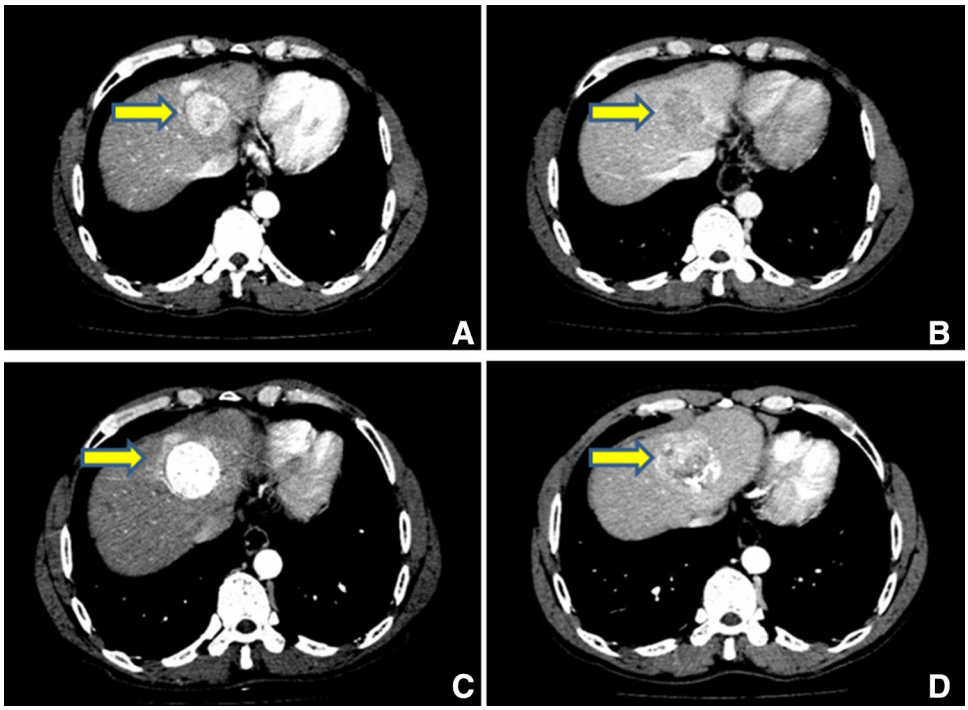

Fig. 4 Comparison of AFP and EASL tumor response assessment: a case example. **A**, **B** pretreatment axial computed tomography (CT) images show the target lesion (hypervascular in the arterial phase with washout in the portal venous phase). **C** A CT image at 1-month post-TACE showing the target lesion with no arterial enhancement (complete response [CR] according to EASL and stable disease [SD] according to AFP criteria). **D** A CT image obtained 3 months post-TACE, showing an enlarged target lesion that was PD according to both EASL and AFP criteria

for surveillance of at-risk patients and HCC diagnosis. Compared with AFP, PIVKA-II has been shown to possess greater sensitivity and specificity for early HCC diagnosis [37]. In the present study, we did not evaluate PIVKA-II, and it might be useful in future studies, to compare the utility of AFP and PIVKA-II as treatment response markers.

In conclusion, the AFP response, defined by our criteria, showed a moderate correlation with EASL response in HCC patients after TACE. Serum AFP level could predict the tumor response rate and survival in these patients. For patients with EASL PD, the AFP criteria might identify those with expected OS superiority, which, to some extent, covers the shortfalls of the radiologic PD criteria.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Jemal A, Siegel R, Ward E, et al. (2008) Cancer statistics, 2008. CA Cancer J Clin 58:71–96
2. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
3. European Association for the Study of The Liver (2012) European Organisation For Research and Treatment of Cancer EASL-EORTC clinical practice guidelines management of hepatocellular carcinoma. J Hepatol 56:908–943
4. Forner A, Reig ME, de Lope CR, et al. (2010) Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30:61–74
5. Lo CM, Ngan H, Tso WK, et al. (2002) Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164–1171
6. Omata M, Lesmana LA, Tateishi R, et al. (2010) Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 4:439–474
7. Llovet JM, Bruix J (2003) Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 37:429–442
8. Miller AB, Hoogstraten B, Staquet M, et al. (1998) Reporting results of cancer treatment. Cancer 47:207–214
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
10. Bruix J, Sherman M, Llovet JM, et al. (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 35:421–430
11. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30:52–60
12. Jung ES, Kim HJ, Yoon EL, et al. (2013) Comparison of the methods for tumor response assessment in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. J Hepatol 58:1181–1187
13. Gillmore R, Stuart S, Kirkwood A, et al. (2011) EASL and mRECIST response are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial chemoembolization. J Hepatol 55:1309–1316
14. Shim JH, Lee HC, Kim SO, et al. (2012) Which response criteria best help predict survival of patients with hepatocellular

carcinoma following chemoembolization? A validation study of old and new models. Radiology 262:708–718
15. Mclntire KR, Vogel CL, Princler GL, et al. (1972) Serum alpha-fetoprotein as a biochemical marker for hepatocellular carcinoma. Cancer Res 32:1941–1946
16. Tangkijvanich P, Anukulkarnkusol N, Suwangool P, et al. (2000) Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. J Clin Gastroenterol 31:302–308
17. Baig JA, Alam JM, Mahmood SR, et al. (2009) Hepatocellular carcinoma (HCC) and diagnostic significance of alpha-fetoprotein (AFP). J Ayub Med Coll Abbottabad 21:72–75
18. Zhang YQ, Jiang LJ, Jia Wen, et al. (2018) Comparison of alpha-fetoprotein criteria and mRECIST for the prediction of overall survival of hepatocellular carcinoma patients after transarterial chemoembolization. J Vasc Interv Radiol 29:1654–1661
19. Chan SL, Mo FK, Johnson PJ, et al. (2009) New utility of an old marker: serial alpha-fetoprotein measurement in prediting radiologic response and survival of patients with hepatocellular carcinoma undergoing systemic chemotherapy. J Clin Oncol 27:446–452
20. Personeni N, Bozzarelli S, Pressiani T, et al. (2012) Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. J Hepatol 57:101–107
21. Yau T, Yao TJ, Chan P, et al. (2011) The significance of early Alpha-fetoprotein level changes in predicting clinical and survival benefits in advanced hepatocellular carcinoma patients receiving sorafenib. Oncologist 16:1270–1279
22. Shao YY, Lin ZZ, Hsu C, et al. (2010) Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. Cancer 116:4590–4596
23. Liu L, Zhao Y, Jia J, et al. (2016) The prognostic value of alpha-fetoprotein response for advanced-stage hepatocellular carcinoma treated with Sorafenib combined with transarterial chemoembolization. Sci Rep 6:19851
24. Memon K, Kulik L, Lewandowski RJ, et al. (2012) Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with transarterial therapies: a subgroup analysis. J Hepatol 56:1113–1120
25. Riaz A, Ryu RK, Kulik LM, et al. (2009) Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. J Clin Oncol 27:5734–5742
26. Kadalayil L, Benini R, Pallan L, et al. (2013) A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 24:2565–2570
27. Pinato DJ, Arizumi T, Allara E, et al. (2015) Validation of the hepatoma arterial embolization prognostic score in European and Asian populations and proposed modification. Clin Gastroenterol Hepatol 13:1204–1208
28. Park Y, Kim SU, Kim BK, et al. (2016) Addition of tumor multiplicity improves the prognostic performance of the hepatoma arterial-embolization prognostic score. Liver Int 36:100–107
29. Xu L, Peng ZW, Chen MS, et al. (2015) Prognostic nomogram for patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. J Hepatol 63:122–130
30. Zhang Y, Fan W, Wang Y, et al. (2015) Sorafenib with and without transarterial chemoembolization for advanced hepatocellular carcinoma with main portal vein tumor thrombosis: a retrospective analysis. Oncologist 20:1417–1424
31. Kim BK, Kim SU, Kim KA, et al. (2015) Complete response at first chemoembolization is still the most robust predictor for favourable outcome in hepatocellular carcinoma. J Heaptol 62:1304–1310
32. Wang W, Zhao Y, Bai W, et al. (2015) Response assessment for HCC patients treated with repeated TACE: The optimal time-point is still an open issue. J Hepatol 63:1530–1531
33. Viera AJ, Garrett JM (2005) Understanding interobserver agreement: the kappa statistic. Fam Med 37:360–363
34. Shim JH, Park JW, Kim JH, et al. (2008) Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. Cancer Sci 99:2037–2044
35. Kim HD, Lim YS, Han S, et al. (2015) Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. Gastroenterology 148:1371–1382
36. Ozkavukcu E, Haliloglu N, Erden A (2009) Post-treatment MRI findings of hepatocellular carcinoma. Diagnostic and interventional radiology 15:111–120
37. Pote N, Cauchy F, Albuquerque M, et al. (2015) Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. J Hepatol 62:848–854