Effect of delta α-fetoprotein on the detection of liver cancer recurrence

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Background: We explored the ability of delta α-fetoprotein (ΔAFP) to detect recurrence in patients with liver cancer treated with hepatectomy.

Methods: A total of 1,846 patients diagnosed with local liver cancer who underwent hepatectomy at Sun Yat-sen University Cancer Center were enrolled in the present study. Receiver operating characteristic curve analysis was used to determine the cutoff value of ΔAFP at the last follow-up or recurrence.

Results: Recurrence occurred in 51.5% (950/1,846) of liver cancer patients. The cutoff value of ΔAFP was 1.295 ng/mL in our model. Sensitivity in our model was higher than the normal range for AFP level for detecting recurrence (59.8% *vs.* 43.8%), but specificity was similar (98.4% *vs.* 99.8%). ΔAFP in preoperative AFP-positive patients (77.16% *vs.* 63.28%) and AFP-negative patients (31.20% vs. 11.70%) was more sensitive than normal AFP. ΔAFP was superior to AFP in the early (78.13% *vs.* 63.75%) or late recurrence (56.08% *vs.* 39.75%) of liver cancer. Moreover, in 18.3% of patients with recurrence (174/950), ΔAFP detected recurrence earlier than computed tomography/magnetic resonance imaging by 158.33 days. ΔAFP during follow-up indicated a worse prognosis after hepatectomy.

Conclusions: The cutoff value of ΔAFP is more sensitive for monitoring recurrence than a normal AFP level in liver cancer patients.

Keywords: Liver cancer; hepatectomy; delta α-fetoprotein (ΔAFP); recurrence

Introduction

Hepatectomy is the only potential curative therapy for liver cancer without distant metastasis (1); however, the high incidence of tumor recurrence and metastasis is the main reason for mortality after surgery (2). Therefore, monitoring after hepatectomy is crucial for the early detection of recurrence and the subsequent determination of whether these patients who experience recurrence are eligible for additional therapy, such as repeat hepatectomy and liver transplant (3). Patients who undergo second

and third hepatectomies after tumor recurrence have a 5-year survival rate of 60% and 43%, respectively (4,5). Computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used methods for detecting disease recurrence after hepatectomy, but they have the disadvantage of being expensive, and are therefore unavailable in many hospitals. They also lack sensitivity and specificity for the early detection of recurrence.

α-Fetoprotein (AFP) is an embryo protein produced by the yolk sac and fetal liver during fetal development. It is

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the most widely used tumor biomarker currently available for the detection of liver cancer (6,7), and is therefore often used to diagnose and monitor liver cancer in patients (8,9). It has been shown that 60–70% of patients with liver cancer, especially hepatocellular carcinoma (HCC), have elevated AFP levels, which are lower in patients with intrahepatic cholangiocarcinoma (ICC) and mixed-type HCC (10,11). AFP for liver cancer diagnosis currently has unsatisfactory sensitivity in clinical practice (12), and previously published studies have demonstrated that higher AFP levels result in worse overall survival (OS) in HCC patients after hepatectomy (12,13), whereas its effects on the prognosis of other histological types of liver cancer (ICC or mixed-type HCC) are not clear. Moreover, it has been shown that normal AFP levels have low sensitivity and specificity for monitoring recurrence (13), especially in preoperative AFP-negative liver cancer (14). A previously published study showed that there was an upward trend in AFP levels during liver cancer recurrence (15). The results suggest that a slight rise in serum AFP may be sensitive for detecting the recurrence of liver cancer. In another study, elevated carcinoembryonic antigen (CEA) was found to be highly sensitive and specific for predicting the recurrence of colorectal cancer after surgery (16). The results showed that changes in traditional tumor biomarkers, such as CEA or AFP, are potentially useful for monitoring tumor recurrence with high sensitivity and specificity. However, the effects of serum delta AFP (ΔAFP) on the detection of treatment outcomes and on the prediction of prognosis in HCC patients after hepatectomy are unknown.

In the present study, we evaluated the effects of ΔAFP on detecting recurrence and predicting prognosis in patients with liver cancer treated with hepatectomy and without distant metastasis. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1874).

Methods

Patient enrollment

We retrospectively analyzed patients who underwent liver tumor resection without lymph node or distant metastasis at Sun Yat-sen University Cancer Center between January 2012 and September 2017. The inclusion criteria were a diagnosis of liver cancer and the availability of complete clinical and follow-up data. Data collected included sex, age, smoking history, history of alcohol consumption, Child-Pugh score, model for end-stage liver disease (MELD) score, albumin-to-bilirubin (ALBI) score, tumor-node-metastasis (TNM) stage, tumor size, tumor differentiation, vascular invasion, tumor multiplicity, neural invasion, hepatitis virus infection, liver cirrhosis, preoperative AFP level, postoperative AFP level, surgery date, recurrence date, and last follow-up date. The Child-Pugh, MELD, and ALBI scores according to formulas (17-19). The TNM stage in the present study was defined according to the AJCC Cancer Staging Manual, 8th edition, for liver cancer. The exclusion criteria were relapse-free patients re-examined after hepatectomy fewer than two times, tumor recurrence at the first re-examination after hepatectomy, diagnosis with secondary primary cancer, and lymph node metastasis or organ invasion found by pathological examination. Patients' baseline characteristics are summarized in *Table 1*. The present study was approved by the Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center (No. B2019-019-01). All procedures were strictly in accordance with the appropriate version of the Declaration of Helsinki (as revised in Brazil 2013). Individual consent for this retrospective analysis was waived.

Laboratory measurements

The AFP level was tested with the collected serum samples that were stored at room temperature and centrifuged at 3,500 ×g/min for 8 minutes. A Roche E-170 automatic electrochemistry analyzer was used to measure the lipid level.

Follow-up

After curative hepatectomy, patients underwent follow-up and examinations, including AFP serum test, CT scan, and MRI, in the first month after surgery and then every 3 months during the first 2 years after hepatectomy and every 6 months thereafter. Recurrence was determined by CT, MRI, and medical records. The research end-points were disease-free survival (DFS) and OS.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0. Pearson's χ^2-test or Fisher's exact test was chosen for evaluating the correlation between liver cancer recurrence and the clinical characteristics and pathological results. Survival curves were constructed using the Kaplan-Meier

Table 1 Association of clinical features with liver cancer recurrence

Variables	Recurrence	No recurrence	P value
No. patients	950	896	
Age (years)	51.35±11.87	52.59±11.36	0.220
Sex, n (%)			0.000
Male	853 (89.8)	742 (82.8)	
Female	97 (10.2)	154 (17.2)	
Smoking history, n (%)			0.676
Ever	370 (39.0)	334 (37.3)	
Forever	500 (52.6)	490 (54.7)	
Cessation	80 (8.4)	72 (8.0)	
Alcohol history, n (%)			0.229
Ever	200 (21.5)	176 (19.6)	
Forever	709 (74.6)	695 (77.6)	
Cessation	37 (3.9)	25 (2.8)	
HBsAg, n (%)			0.284
Positive	814 (85.7)	783 (87.4)	
Negative	136 (14.3)	113 (12.6)	
HCVAg, n (%)			0.250
Positive	14 (1.5)	8 (0.9)	
Negative	936 (98.5)	888 (99.1)	
Cirrhosis, n (%)			0.156
Yes	932 (98.1)	870 (97.1)	
No	18 (1.9)	26 (2.9)	
Child-Pugh score	5.06±0.29	5.03±0.22	0.000
Class			0.197
A	939 (98.8)	890 (99.3)	
B	11 (1.2)	6 (0.7)	
C	0	0	
MELD score	4.48±2.65	3.92±2.98	0.001
ALBI score	−2.90±0.32	−2.96±0.30	0.018
TNM stage, n (%)			0.000
IA	65 (6.8)	143 (16.0)	
IB	307 (32.3)	426 (47.5)	
II	372 (39.2)	264 (29.5)	
IIIA	96 (10.1)	32 (3.6)	
IIIB	110 (11.6)	31 (3.5)	

Table 1 (*continued*)

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Variables	Recurrence	No recurrence	P value
Histological type, n (%)			0.897
HCC	899 (94.6)	847 (94.5)	
Intrahepatic cholangiocarcinoma	30 (3.2)	31 (3.5)	
Mixed-type HCC	21 (2.2)	18 (2.0)	
Tumor size (cm)	5.94±3.49	4.52±2.84	0.000
Differentiation, n (%)			
Well-moderate	471 (49.6)	513 (57.3)	0.001
Poor-undifferentiated	479 (50.4)	383 (42.7)	
Microscopic vascular invasion, n (%)			
Yes	434 (45.7)	252 (28.1)	0.001
No	516 (54.3)	644 (71.9)	
Macroscopic vascular invasion, n (%)			
Yes	99 (10.4)	28 (3.1)	0.000
No	851 (89.6)	868 (96.9)	
Tumor multiplicity, n (%)			
Single	727 (76.5)	793 (88.5)	0.000
Multiple	223 (23.5)	103 (11.5)	
Neuro invasion, n (%)			
Yes	18 (1.9)	8 (0.9)	0.068
No	932 (98.1)	888 (99.1)	
AFP level before hepatectomy (ng/mL)	7,658.31±23,754.66	4,507.02±20,042.67	
Follow-up time (months)	4.07±2.68	6.75±4.08	0.000

AFP, α-fetoprotein; HBsAg, hepatitis B virus surface antigen; HCVAg, hepatitis C virus antigen; MELD, model for end-stage liver disease; ALBI, albumin-to-bilirubin.

method and log-rank test. ΔAFP was equal to AFP at current re-examination minus AFP at the last re-examination after hepatectomy. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff value of the ΔAFP level. Comparisons of sensitivity and specificity of AFP and ΔAFP were analyzed using Pearson's χ^2-test. $P<0.05$ was considered statistically significant.

Results

Patients' clinical characteristics

A total of 1,846 patients who underwent hepatectomy were enrolled in the present study. Of these, 51.5% (950/1,846) had experienced tumor recurrence by the last follow-up. The median follow-up time was 31 months (range, 1.2–79.5 months). The relationship between tumor recurrence and patients' clinical characteristics is summarized in *Table 1*. Tumor recurrence was correlated with male sex, higher Child-Pugh score, higher MELD score, higher ALBI score, higher TNM stage, larger tumor size, poorly differentiated tumors, microscopic vascular invasion, macroscopic vascular invasion, and tumor multiplicity ($P<0.05$) (*Table 1*). Age, smoking history, history of alcohol consumption, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, liver cirrhosis, histological type, and neural invasion were not statistically different between patients with and without recurrence ($P>0.05$).
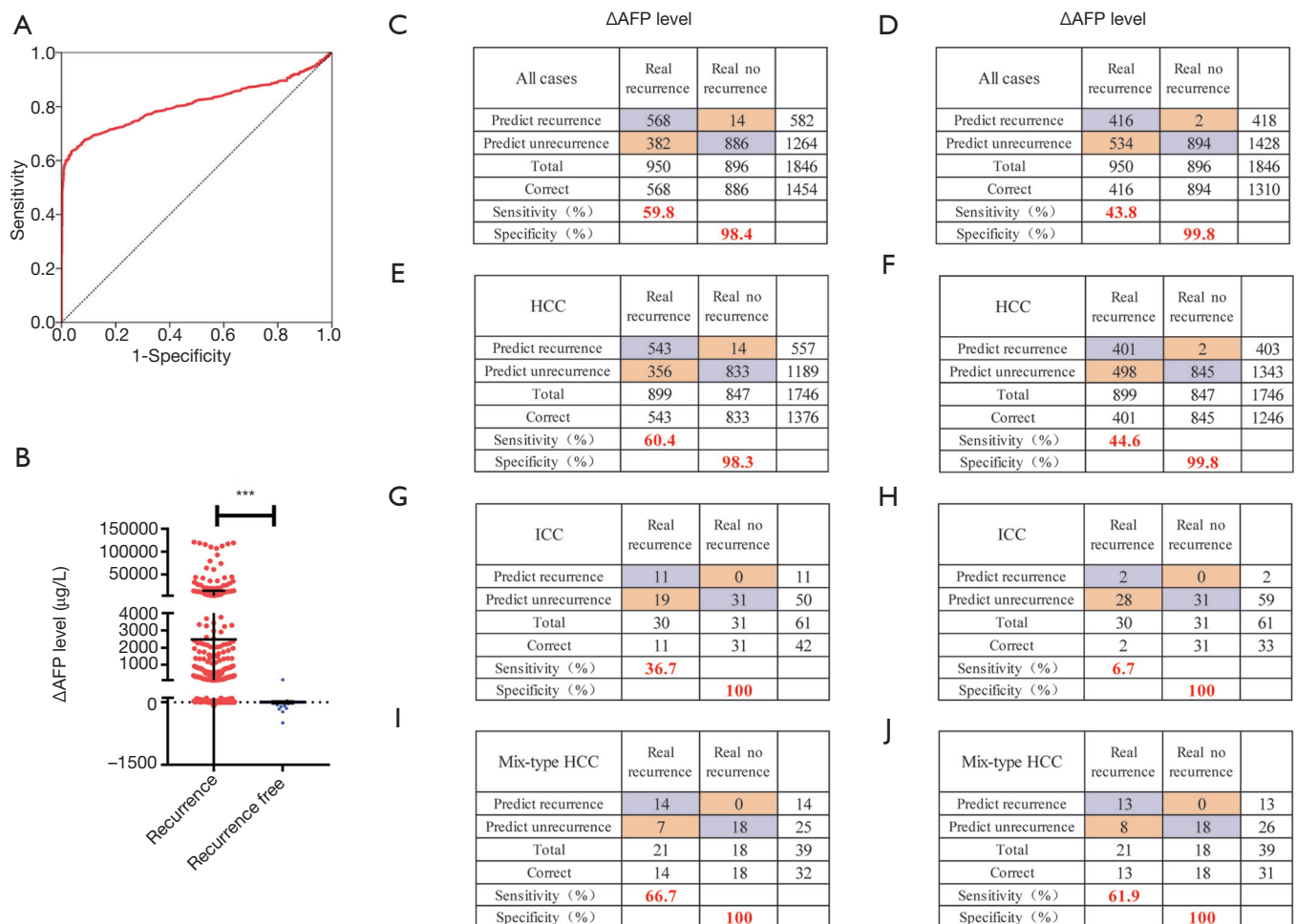
Figure 1 Delta α-fetoprotein (ΔAFP) cutoff level was compared to normal AFP level to detect recurrence (A). ΔAFP cutoff value was obtained from the receiver operating characteristic curve. ΔAFP was significantly higher in patients with than without recurrence at last follow-up (B). ΔAFP level was used to detect tumor recurrence in liver cancer (C). ΔAFP level in hepatocellular carcinoma (HCC) (E), intrahepatic cholangiocarcinoma (ICC) (G), and mixed-type HCC (I) was more sensitive than AFP level in liver cancer (D); HCC (F), ICC (H), and mixed-type HCC (J). ***, P<0.001. AFP, α-fetoprotein; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

ΔAFP in the detection of liver cancer recurrence

The ΔAFP cutoff value of 1.295 ng/mL for detecting recurrence was generated using ROC curve analysis (*Figure 1A*). The ΔAFP level was significantly higher in patients with tumor recurrence than in those without (P<0.05) (*Figure 1B*). There was no difference between normal AFP and ΔAFP at recurrence or last follow-up regarding sex, smoking history, history of alcohol consumption, HBV surface antigen, HCV antigen, cirrhosis, or histology type (*Table 2*). However, there was a significant difference between normal and ΔAFP levels in patients with recurrent liver cancer (*Table 3*). Compared to

AFP in the normal range, ΔAFP showed more sensitivity (59.8% *vs.* 43.8%), but similar specificity (98.4% *vs.* 99.8%) for monitoring liver cancer recurrence after liver resection. In the three main histological subtypes of liver cancer, ΔAFP also showed more sensitivity and similar specificity as AFP (*Figure 1C,D,E,F,G,H,I,J*). ΔAFP was more sensitive than normal AFP in both preoperative AFP-positive and preoperative AFP-negative patients. In AFP-positive patients, ΔAFP was more sensitive than normal AFP (77.16% *vs.* 63.28%), and specificity was similar (98.30% *vs.* 99.58%); the area under the curve (AUC) of the ROC curve was 0.877 and 0.814, respectively. In AFP-negative patients, ΔAFP was more sensitive than normal AFP

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Table 2 α-Fetoprotein (AFP) and delta AFP (ΔAFP) levels associated with clinical characteristics

Variables	AFP at recurrence/last follow-up	P value	ΔAFP at recurrence/last follow-up	P value
Sexual (ng/mL)		0.237		0.234
Male	1,301.39±8,945.53		1,155.50±8,373.60	
Female	4,463.75±42,092.62		4,305.16±41,695.66	
Smoking history (ng/mL)		0.746		0.738
Ever	1,858.86±11,141.38		1,690.66±10,479.14	
Forever	1,801.14±22,105.20		1,651.22±21,783.53	
Cessation	686.50±3,614.10		649.27±3,551.21	
Alcohol history (ng/mL)		0.806		0.836
Ever	2,179.41±12,949.95		1,989.78±12,164.40	
Forever	1,648.93±19,013.13		1,507.32±18,699.41	
Cessation	852.18±5,426.92		826.12±5,398.97	
HBsAg (ng/mL)		0.404		0.423
Positive	1,438.97±10,006.45		1,304.80±9,415.4	
Negative	3,606.73±40,751.70		3,372.93±40,468.18	
HCVAg (ng/mL)		0.667		0.681
Positive	175.47±706.13		79.35±299.10	
Negative	1,750.14±17,722.92		1,601.90±17,345.79	
Cirrhosis (ng/mL)		0.853		0.821
Yes	1,719.51±17,728.82		1,569.53±17,350.87	
No	2,217.20±1,865.87		2,166.18±12,141.83	
Histological types (ng/mL)		0.628		0.665
HCC	1,825.90±18,110.81		1,670.34±17,725.87	
ICC	4.86±5.70		1.42±4.50	
Mixed-type HCC (ng/mL)	199.62±738.88		182.43±683.53	

HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; HCVAg, hepatitis C virus antigen; ICC, intrahepatic cholangio-carcinoma.

Table 3 A-Fetoprotein (AFP) and delta AFP (ΔAFP) levels associated with recurrence and clinical characteristic

Variables	AFP level	P value	ΔAFP level	P value
At recurrence (ng/mL)	3,361.29±24,453.40	0.000	3,079.15±23,946.13	0.000
At last follow-up (no recurrence) (ng/mL)	3.23±5.64		−1.76±20.98	
Type of recurrence (ng/mL)		0.000		0.000
Intrahepatic recurrence only (n=767)	2,242.85±12,052.48		1,993.86±11,264.97	
Intra- and extrahepatic recurrence (n=63)	11,449.77±28,982.30		10,626.11±27,260.61	
Extrahepatic recurrence only (n=120)	6,263.55±57,834.24		6,053.75±57,638.38	

(31.20% *vs.* 11.70%), and specificity was similar (99.03% *vs.* 100.00%); the AUC of the ROC curve was 0.649 and 0.558, respectively (*Figure 2A,B*).

ΔAFP performed well for monitoring recurrence for liver cancer patients with early and late recurrence after resection. Early recurrence refers to recurrence within 1 year after hepatectomy, and late recurrence refers to recurrence >1 year after hepatectomy. The results showed that ΔAFP could predict 78.13% (125/160) and 56.08% (443/790) of early and late liver cancer recurrence, respectively. In comparison, AFP was found to predict 63.75% (102/160) and 39.75% (314/790) of early and late liver cancer recurrence, respectively (P<0.05).

ΔAFP showed a low false-positive rate when predicting recurrence

To validate the false-positive rate of the ΔAFP cutoff value during follow-up, we measured ΔAFP levels in recurrence-free patients (896/1,846), who had an average of 6.75±4.08 re-examinations after hepatectomy. The false-positive rates were 2.86%, 2.90%, 1.49%, and 4.13% for liver cancer, HCC, ICC, and mixed-type HCC, respectively (*Figure 2C*). However, 174 of 950 patients with recurrence exhibited ΔAFP exceeding the cutoff value before the clinical diagnosis of tumor recurrence, as determined by CT or MRI. In these patients, the time predicted by ΔAFP was 158.33 days for liver cancer, 159.25 days for HCC, 124.50 days for ICC, and 149.33 days for mixed-type HCC compared with CT or MRI (*Figure 2D*).

ΔAFP and liver cancer prognosis after hepatectomy

We analyzed the effect on prognosis between patients who exceeded the ΔAFP cutoff value more than once (exceeded group) and those who never exceeded the cutoff value (never-exceeded group) after hepatectomy. The median DFS for the never-exceeded and exceeded groups was 74.71±8.01 and 11.27±0.62 months, respectively. Kaplan-Meier survival analysis showed that liver cancer patients who never exceeded the ΔAFP cut-off value after hepatectomy had a longer DFS (P<0.001) and OS (P<0.001) than those who exceeded the cutoff value more than once (*Figure 3A,B*). The subtype analysis of patients by histological type showed better DFS in the never-exceeded group compared with the exceeded group (HCC group: P<0.001; ICC group: P=0.007; mixed-type HCC: P=0.007). OS was significantly different between the never-

exceeded and exceeded groups in HCC patients (P<0.001), but not in ICC (P=0.365) and mixed-type HCC (P=0.649) patients (*Figure 3C,D,E,F,G,H*). In the Cox regression analyses, the adjusted hazard ratios (HRs) for DFS revealed significant differences between the exceeded and never-exceeded group in all cases [HR: 4.209, 95% confidence interval (CI): 3.672–4.824, P<0.001] and in the three main histological types of liver cancer (HCC group, HR: 4.329, 95% CI: 3.760–4.984, P<0.001; ICC group, HR: 2.580, 95% CI: 1.257–5.297, P=0.010; mixed-type HCC group, HR: 3.403, 95% CI: 1.316–8.800, P=0.012). In the survival analyses, the adjusted HRs showed a significant association with exceeding the cutoff value of ΔAFP after hepatectomy in liver cancer patients (HR: 3.792, 95% CI: 2.786–5.160, P<0.001). Subtype analysis of patients by histological type showed better OS in HCC patients in the never-exceeded group (HR: 4.201, 95% CI: 2.901–5.575, P<0.001), but no significant difference in ICC and mixed-type HCC patients (ICC group, HR: 1.825, 95% CI: 0.488–6.832, P=0.372; mixed-type HCC group, HR: 1.485, 95% CI: 0.268–8.217, P=0.651).

Discussion

AFP level plays an important role in liver cancer diagnosis, prognosis, recurrence monitoring, and treatment response, but the effects of ΔAFP on liver cancer prognosis and surveillance are unclear. In the present study, we evaluated the ability of ΔAFP in recurrence detection and prognosis based on a cutoff value. We found that a ΔAFP cutoff value was more sensitive for detecting recurrence than AFP based on the normal range, and exhibited an upward trend before CT or MRI examination. However, liver cancer patients who exceeded this cutoff value more than once during follow-up had a worse prognosis after hepatectomy.

AFP level is commonly used as an indicator to monitor recurrence after hepatectomy in patients with liver cancer, especially HCC (14,20). The 2018 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Hepatobiliary Cancers, version 3, recommends that HCC patients after hepatectomy have serum AFP levels checked every 3 months for 2 years, and then every 6–12 months after 2 years; however, a definitive cutoff AFP value to predict recurrence and detect a change of recurrence risk level with a monitoring strategy remains unknown (21). Chang *et al.* reported that the best cutoff AFP value was 5.45 µg/L based on the last follow-up/ recurrence AFP level of 72 HCC patients treated with

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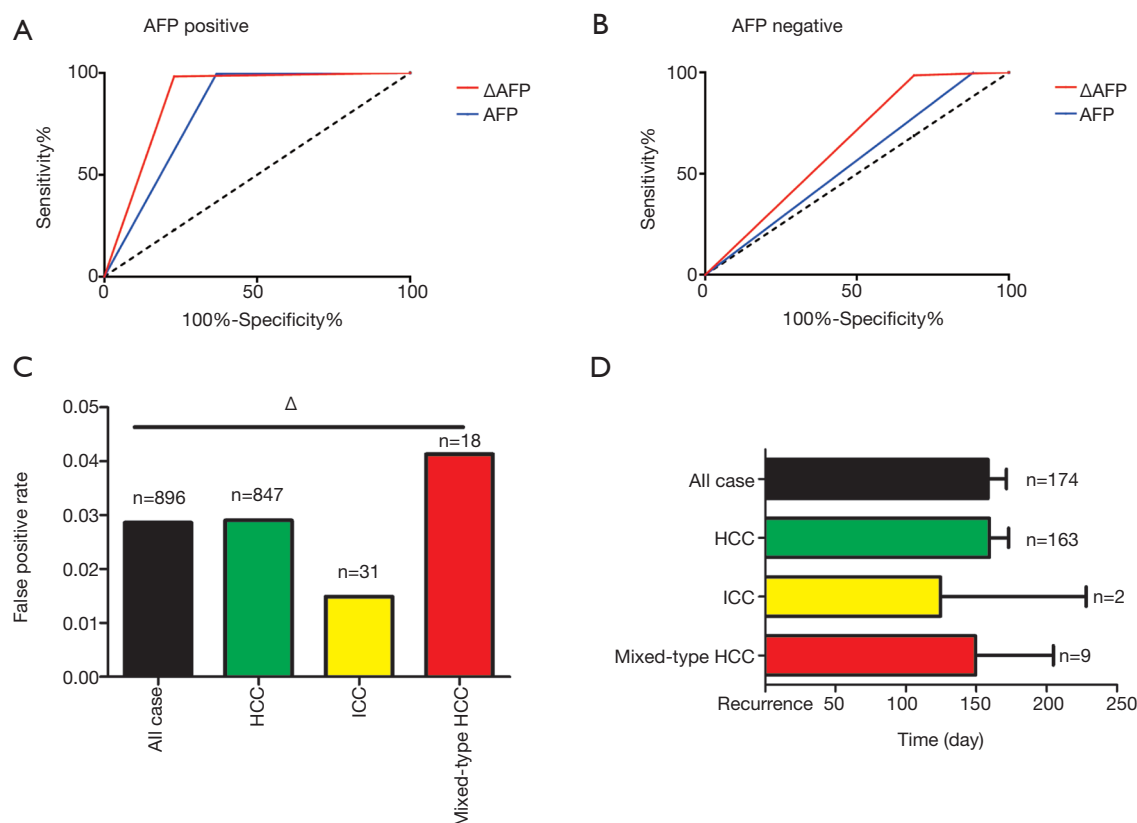
Figure 2 Subtype analyses of delta α-fetoprotein (ΔAFP) cutoff value in the detection of liver cancer recurrence. ΔAFP showed more sensitivity in detecting tumor recurrence in preoperative AFP-positive (A) and AFP-negative (B) patients. ΔAFP best cutoff value in patients with no recurrence showed high specificity, and each histological subtype showed no statistical difference (C). A total of 174 patients had ΔAFP level exceed the cutoff value before recurrence, and the average time was earlier than that measured with computed tomography/magnetic resonance imaging (D). Δ, P>0.05. AFP, α-fetoprotein; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

hepatectomy and liver transplantation (15). This value was sensitive to AFP levels based on the normal range (84.8% *vs.* 62.5%), but its specificity was lower (77.1% *vs.* 94.3%). For liver transplantation, Nörthen *et al.* suggested best cut-off AFP values of 7, 6, and 6 μg/L at 1, 3, and 5 years after liver transplantation in 63 HCC patients with a diagnostic sensitivity of 79%, 81%, and 77%, and a specificity of 82%, 79%, and 69% (22). Previous studies have indicated that a cutoff value depends on AFP level after treatment with high sensitivity but low specificity, possibly due to the focus on AFP level without taking into account the variation of AFP values. Chang *et al.* found that some patients with recurrence exhibited an upward trend in AFP level before tumor recurrence, suggesting that the minor variable of AFP could be a sensitive biomarker in detecting liver cancer recurrence (15). However, the effect of ΔAFP level on liver cancer patients after hepatectomy is not yet clearly

understood. In our study, 568 of 950 patients (59.8%) had an upward trend for the prediction of tumor recurrence. The cutoff ΔAFP level was more sensitive than the AFP level based on the normal range of 0–25 ng/mL (59.8% *vs.* 43.8%), but the specificity between these values was similar (98.4% *vs.* 99.5%). Our study also showed that this ΔAFP cutoff level may be useful for detecting ICC and mixed-type HCC after hepatectomy. The sensitivity was 36.7% in ICC patients and 66.7% in mixed-type HCC patients, while that yielded by the normal range was 6.7% and 61.9%, respectively. Specificity was 100% for all histological types and methods. About 40% of liver cancer patients were AFP-negative preoperatively, and had different biologic characteristics than those with AFP-positive liver cancer (23). Previous studies have found that AFP-positive liver cancer is associated with a worse prognosis compared with AFP-negative liver cancer (24). However, in current
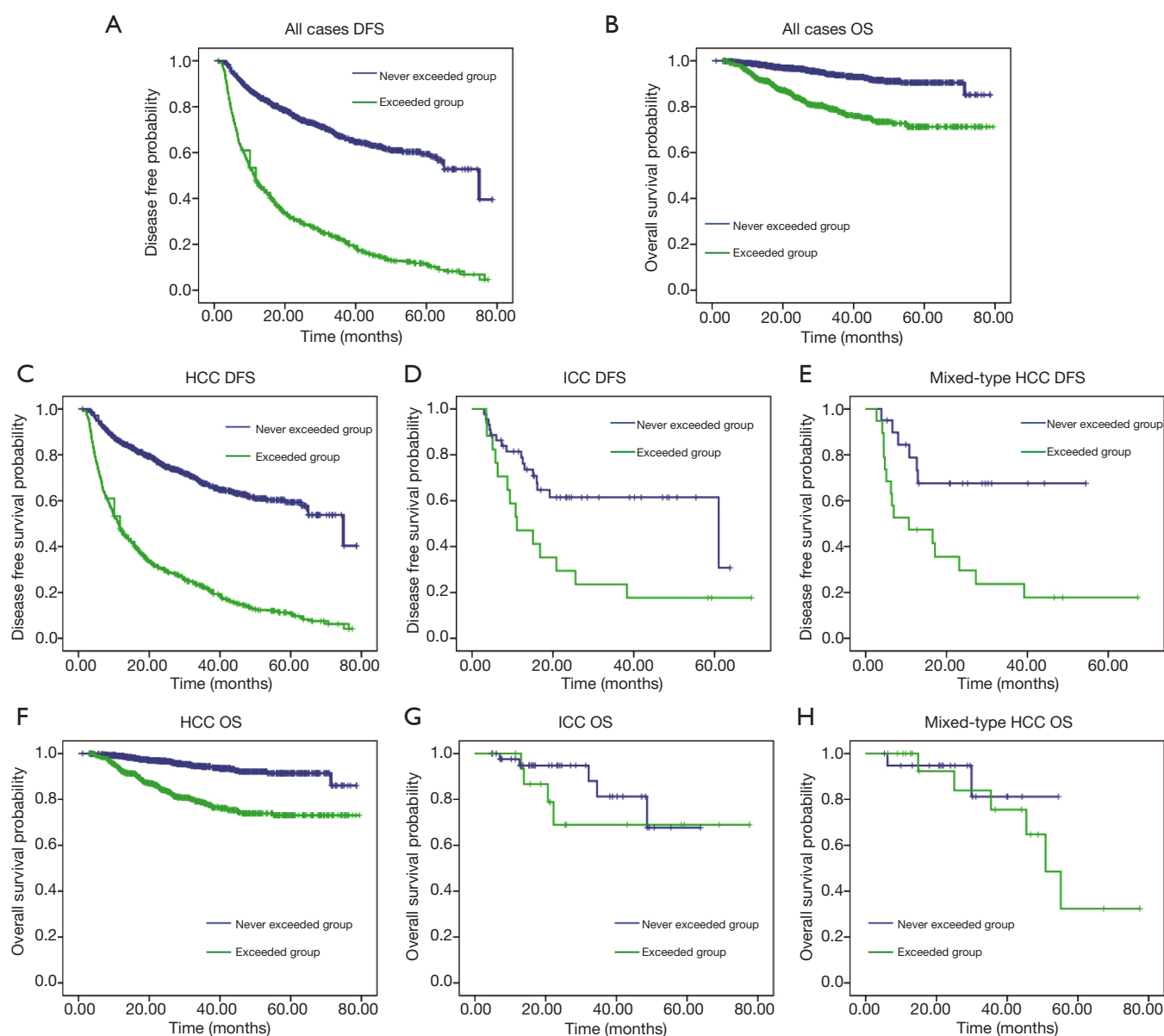
Figure 3 Delta α-fetoprotein (ΔAFP) level predicts prognosis in hepatocellular carcinoma (HCC) patients. Kaplan-Meier analyses showed differences in recurrence probabilities among all cases. (A,C,D,E) Liver cancer (P<0.001) (A), HCC (P<0.001) (C), intrahepatic cholangiocarcinoma (ICC) (P=0.007) (D), and mixed-type HCC (P=0.007) (E) patients that exceeded the cutoff value more than once and those that never exceeded the value. Overall survival probabilities between liver cancer (P<0.001) (B) and HCC (P<0.001) (F) showed significant difference between the exceeded and never-exceeded groups, but ICC (P=0.365) (G) and mixed-type HCC (P=0.649) (H) showed no difference between the two groups. AFP, α-fetoprotein.

clinical practice, there is a lack of appropriate indicators for detecting recurrence of liver cancer after hepatectomy among liver cancer patients. Our findings suggest that ΔAFP is more sensitive than AFP in detecting recurrence among AFP-negative patients (31.2% *vs.* 11.7%). In addition, the ΔAFP cut-off level showed high specificity in 896 recurrence-free patients. The false-positive result might have been due to benign conditions after surgery, such as liver inflammation and cirrhosis (25). However, we found that 174 of 950 patients with recurrence had exceeded ΔAFP cutoff levels before recurrence was detected by MRI or CT scan, which likely means that tumor recurrence was below the level of detection on CT or MRI, but which might have led to increased AFP levels. These data suggest that the ΔAFP cutoff level may not only be used for detecting liver cancer postoperatively, but could also have potential for the early prediction of recurrence after hepatectomy (26).

In the survival analysis, we found that liver cancer patients who had exceeded ΔAFP cut-off levels during follow-up exhibited worse DFS and OS than patients who had never exceeded ΔAFP cutoff levels. This finding suggests that an exceeded ΔAFP cut-off level during follow-up is a prognostic indicator of liver cancer after hepatectomy. There was no difference in OS between the exceeded group and never-exceeded group in ICC and mixed-type HCC patients, but there was a significant difference in HCC patients. One reason for this difference may be due to the small sample size of patients with ICC and mixed-type HCC. Another reason may be that ICC and mixed-type HCC express lower levels of AFP than HCC (11,27,28). Several studies have reported that preoperative AFP level is a prognostic indicator in HCC patients (27-30). Although previous studies have reported that changes in AFP levels between pre- and post-hepatectomy can predict surgical outcomes (14,31,32), the effects of variations in AFP after hepatectomy remain unclear. The results of our study provide a new indicator for the real-time monitoring of recurrence and the evaluation of the prognosis of liver cancer after hepatectomy. If the ΔAFP exceeds the cutoff value during the postoperative monitoring of liver cancer patients, it is suggested that the frequency of re-examination is increased, or that additional examinations, such as chest CT or isotope bone scan, are undertaken for the early detection of metastatic and recurrent lesions to improve the prognosis of liver cancer.

The results of the present study showed that the ΔAFP cutoff level was sufficiently sensitive for monitoring recurrence after liver cancer hepatectomy, and patients with recurrence exhibited an upward trend with ΔAFP compared to MRI. However, the present study has some limitations. We excluded patients with metastasis and recurrence 1 month after surgery; therefore, subsequent studies are needed to validate and explore the ΔAFP cutoff level in all liver cancer patients, including those with inoperable cancer. In addition, as a retrospective study, we were not able to monitor AFP levels in a strict manner with regular frequency, which may have affected the observed fluctuations in AFP level. Finally, different institutions may have different values for the normal range. Therefore, further prospective studies are required to further explore and validate the detection ability of the ΔAFP cutoff level.

Footnote

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