Peer Review File

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Reviewer Comments

This is an interesting study on the predictive impact of ΔAFP following HCC resection. There are some important issues that have to be clarified:

Major comments:

1. The authors should add data on preoperative AFP level and liver function (Child, MELd, ALBI score).

Reply 1: Thank the reviewer for the comment. Preoperative AFP and liver function scores (Child-Pugh, MELD and ALBI scores) were added to Table 1. At the same time, the corresponding content is added in the method and result part of the manuscript.
Change in the text: Preoperative AFP and liver function scores (Child-Pugh, MELD and ALBI scores) were added to Table 1. At the same time, the corresponding content is added in the method and result part of the manuscript.

2. What kind of resections are we Talking of? How many atypical, typical resections, Major/minor resections?

Reply 2: Thank the reviewer for the comments. There were 702 patients with atypical resections, 1144 patients with typical resections, 937 patients with major resections and 909 patients with minor resections.
Change in the text: None.

3. When comparing the predictive value of AFP versus ΔAFP regarding early / late HCC recurrences, the authors should add statistical test.

Reply 3: Thank the reviewer for the comment. We have performed statistical test and the results have been added to our manuscript (see page 6, line 1).
Change in the text: We have performed statistical test and the results have been added to our manuscript (see page 6, line 1).

4. For better understanding: please better describe how you finally concluded ΔAFP to be faster in indicating HCC reclapse than other imaging techniques such as MRI and CT. AFP determination and radiography are perormed at the same post-resectional time points. So, for example, how many patients demonstrated ΔAFP exceeding cut-off value with negative radiopraphy and when, during follow-up, CT/MRI was able to detect HCC recurrence.

Reply 4: Thank the reviewer for the comment. 174 of 950 patients with recurrence

exhibited ΔAFP exceeding cut-off value before clinical diagnosis of tumor recurrence, as determined by CT or MRI.

Change in the text: We have described the result of ΔAFP to be early detect liver cancer recurrence than CT or MRI and the results have been revised in the manuscript (see page 6, line 6-10).

5. What would be the clinical consequwences of your data regarding treatment Options? Please specify your modified therapeutical strategy based on ΔAFP.

Reply 5: Thank the reviewer for the comment. If △ AFP exceeds the cut-off value after liver cancer surgery, we suggest that patients should increase the frequency of reexamination or add other part of examination such as chest CT or bone scan. So that, we can find the recurrence and metastasis of liver cancer patients as early as possible and increase the opportunity to get curative treatment such as second resection, radiofrequency ablation. Finally, it can improve the prognosis of patients with liver cancer

Change in the text: We have modified our text as advised (see page 8-9, line 30-31/1-2).

6. Probably, a multivariate analysis on overall survival including ΔAFP might be useful.

Response: Thank the reviewer for the comment. Our study focused on the role of Δ AFP in monitoring the recurrence of liver cancer after surgery. The results showed that Δ AFP was more sensitive than AFP in detecting recurrence of liver cancer. It was also found that Δ AFP exceed cut-off value indicated worse prognosis. Because part of patients lost follow-up after the diagnosis of recurrence, the statistics of death cases had deviation. In addition, this study focus on Δ AFP is more sensitive in predicting the recurrence and metastasis of liver cancer. Therefore, we did not supplement the multivariate analysis of overall survival in the manuscript. The table of multivariate analysis is attached to the response letter.

Change in the text: None.

Table. Univariate and multivariate analysis of overall survival in the liver cancer

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Sex, male/female	0.792(0.509-1.233)	0.302		
Age, ≤50/>50, year	0.804(0.611-1.060)	0.122		
Smoking history, yes vs. no	1.123(0.851-1.482)	0.412		

Alcohol history, yes vs. no	0.838(0.616-1.140)	0.260		
Etiology, HBV vs. others	1.026(0.680-1.549)	0.902		
Etiology, HCV vs. others	0.494(0.184-1.330)	0.163		
Cirrhosis, yes vs. no	0.819(0.385-1.741)	0.604		
TNM stage				
I vs. II	0.259(0.114-0.588)	**0.001**		
II vs. III	0.418(0.276-0.632)	**0.000**		
Tumor diameter, cm				
3-5 vs. <3	0.448(0.274-0.733)	**0.001**		
>5 vs. <3	0.545(0.402-0.739)	**0.000**		
Differentiate, poor vs. well	1.648(1.248-2.176)	**0.000**		
Microscopic vascular invasion, yes vs. no	2.302(1.745-3.037)	**0.000**		
Macroscopic vascular invasion, yes vs. no	3.928(2.712-5.688)	**0.000**		
Tumor multiplicity, yes vs. no	1.593(1.154-2.197)	**0.005**		
Neuro invasion, yes vs. no	2.683(1.189-6.050)	**0.017**		
Child-Pugh, stage A vs. B	1.535(0.215-10.957)	0.669		
ΔAFP, exceed cut-off value vs. no	5.289(3.940-7.100)	**0.000**	6.550(3.692-11.622)	**0.000**
AFP level before hepatecotemy(ug/L)				
<20 vs. 20-400	0.726(0.511-1.031)	0.073		
20-400 vs. >400	0.843(0.601-1.181)	0.321		

Abbreviations: AFP, α-fetoprotein; HBsAg, hepatitis B virus surface antigen; HCVAg, hepatitis C virus antigen; CI, confidence interval; HR, Hazard ratio;