RESPONSES TO REVIEWERS' COMMENTS

Dear editor:

We are truly grateful to the critical comments and thoughtful suggestions. Based on these comments and suggestions, we have made careful modifications on the original manuscript. All changes made to the text are in red color. Below you will find our point-by-point responses to the reviewers' comments:

1. In introduction section, the authors stated that 'TACE significantly prolongs the survival of patients with HCC who are not candidates for curative treatments', however, a systematic review in Cochrane database showed that there was no evidence supporting the benefits of TAE/TACE for unresectable HCC (doi: 10.1002/14651858.CD004787.pub2).

Response:

The literature commented is of great importance. We agree with your comments for the evaluation of benefits of TACE, though in the later of the same paragraph we stated that 'The heterogeneity…may explain why some randomized, controlled trials of TACE failed to demonstrate prolonged survival in the patients'.

We decided to refer the literature you commented to strengthen our paper and make the following changes 'TACE achieves partial responses in 15-55% of patients with HCC who are not candidates for curative treatments' and 'A systematic review in Cochrane database showed that TACE or transarterial embolisation (TAE) did not significantly increase survival for unresectable HCCs, especially those with bad compensate liver function'.

2. Why the authors used 16-week disease-control rate to evaluated disease control? Was there any

Response:

Disease-control rate at different time point after initial treatment were used by different studies, such as 1 month, 2month, 3 month, 6 months. And 1 month disease-control rate was commonly used. But study indicated that early (1 month) decrease in contrast enhancement and late (6 months) decrease in size could be used to evaluate the antitumor effect of TACE, instead of early decrease in size (Cancer J. 2009 Nov-Dec;15(6):526-32. DOI: 10.1097/PPO.0b013e3181c5214b). So we did not use 1 month DCR.

In addition, previous study suggested that DRC at 2 months was a powerful predictor of subsequent survival and provided an early assessment of subsequent outcome (J Clin Oncol. 2008 Jan 20;26(3):463-7. doi: 10.1200/JCO.2007.13.0344.). But, given that our study is retrospective, not every patient included in our study had image data on 2 months after the initial TACE. So we used a time point which was close to the initial TACE, and about which every patient included got image data.

3. The threshold of 25% for the changes of AFP should be explained.

Response:

It has been suggested that serum AFP change during treatment might serve as a

useful marker for clinical outcome in patients with advanced HCC receiving systemic therapy (Oncologist. 2009 Jul;14(7):717-25. doi: 10.1634/theoncologist. 2009-0038. Epub 2009 Jul 6.). And in this study the patients were separated into three groups based on the change in serum AFP from that at baseline: >50% AFP decline, >50% AFP increase, and <50% change in either direction.

Another study suggested that AFP response was prognostic factors of survival for HCC patients treated with sorafenib. But they chose 20% as threshold (J Hepatol. 2012 Jul;57(1):101-7. doi: 10.1016/j.jhep.2012.02.016. Epub 2012 Mar 10.).

So, we separated patients into three groups and chose 25% as the threshold.

4. As overall survival was the primary outcome, participants without well-document imaging report but was not lost to follow-up should also be included for survival analysis.

Response:

We appreciate the reviewer's suggestion. And we added 29 patients that did not have following-up imaging data into the study. And we collected the clinical characteristics and survival time of these patients, and did all the statistics again. And we re-wrote the text according to the data of those 132 patients.

5. In methods section, the duration that complications were measured should be stated. Does any in-hospital mobility or complications within 30 days after TACE was included?

Response:

The duration that complications were measured was 30 days after TACE. And we are very sorry for our negligence of making this statement clearly in the test.

We make the following change. 'Major complication was defined as events with life-threatening and events with medical importance require inpatient hospitalization or prolongation of existing hospitalization within 30 days after TACE'. We mentioned one death within one month of receiving the second TACE, resulting in a procedure-related mortality rate of 0.76% in the result section.

6. The four patients with lung metastases should be excluded when analysing survival, since they could have significantly poorer prognosis.

Response:

It is true that advance HCC with lung metastasis have a dismal outcome. Systemic treatment provides improved OS for this group of patients, but the survival remains limited.

However, most of these patients die owing to intrahepatic tumor progression or liver failure rather than progression of extrahepatic metastasis. Thus, we assume that delaying intrahepatic tumor progression with TACE has some potential to incur a survival benefit, even in the presence of lung metastasis. And some studies have found some beneficial effects of TACE in patients with exreahepatic metastasis. (Uka K et al, world J Gastroenterol. 2007 Jan 21;13(3): 414-20)(Yoo DJ et al, J Gastroenterol Hepatol. 2011 Jan; 26(1):145-54. doi; 10.1111/j. 1440-1746.2010.06341.x.)(Okusaka

T et al, Hepatogastroenterology. 1997 Jan-Feb; 44(13):251-7.)

So we did not exclude these 4 patients from survival analyzing. And in our everyday clinical work, lung metastasis is not an absolute contraindication.

7. The proportion of patients with cirrhosis should be reported in baseline characteristics. The median and range of follow-up duration should be reported. In addition, post-embolism syndrome needs to be defined.

Response:

We appreciate the reviewer's suggestion. And we are very sorry for our negligence of making this statement clearly in the test.

We added the proportion of cirrhosis in Table 1.

We added 'Median follow-up period was 12.0 months (range, 1.0–48.0).' in the results section.

We added the definition of the post-embolism syndrome to methods section. "Criteria specific for the diagnosis of post-TACE syndrome includes pain, fever, nausea, and vomiting."

8. Since the survival varies in different institutes and population, it should be very cautious to demonstrate 'effective' of this protocol if there was no `comparable control group.

Response:

We made alterations to the conclusion in the text. 'In conclusion, TACE with hepatic infusion of oxaliplatin and 5-fluorouracil and lipiodol embolization might be considered as a safe and promising treatment for patients with HCCs larger than 10 cm in diameter. Although systemic chemotherapy is usually recommended for advanced-stage patients, certain TACE regimens may be considered as adjuvant or sole therapies in a select group of patients.'

9. I would like to see the disease free survival curve, if possible.

Response:

We added the curve in the paper.

At last, we want to thank you again for your time and your good comments. We appreciate your help very much.

Sincerely yours,

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