Author's response to reviews

Title: Transcatheter arterial chemoembolization combined with radiofrequency ablation prolongs tumor progression and overall survival in patients with intermediate stage (BCLC stage B) hepatocellular carcinoma

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Author's response to reviews: see over
Dear editor:

Thank you very much for the suggestions for our manuscript (Manuscript ID 8813278011026556).

We have revised the manuscript substantially, according to the comments and suggestions of reviewer, and responded point by point to their comments. We wish it can be further reviewed and evaluated.

Looking forward to hearing from you soon.

Sincerely yours

Xin Yin

Comments to the reviewer:

To Hiroyuki Kirikoshi (reviewer 1):

Thank you for your comments for our manuscript. We really appreciated your kind acceptance for our manuscript although it still has some shortcomings. We further revised our manuscript according to the editor and other reviewer. We hope this edition of manuscript is better than the old one.

To Morio Sato(reviewer 2):

We appreciated your careful and kind suggestion. It is very professional and helpful.

According to your suggestion 1, we have revised our manuscript substantially. In our old manuscript, the background of patients is quite different, which may impact the survival results. Therefore, in the revised manuscript, we have adopted new including criteria and excluded patients who have different background. The patient cohort and inclusion and exclusion criteria have been revised as follows:

From January 2005 to December 2011, a total of 747 patients with intermediate stage HCC (BCLC state B) received first line TACE treatment at liver cancer institute, Zhongshan hospital, Fudan University. HCC were confirmed pathologically or clinically according to AASLD criteria. After initial TACE treatment(1-5 sessions), 211 patients who were potential candidates for following RFA treatment were further evaluated and included into this study based on the inclusion criteria: 1) viable residual HCC with retained iodized oil after TACE was found at a follow-up liver CT and/or MRI; 2) in cases with a single viable HCC, the size of tumor was $\leq 8$ cm in diameter( including both viable HCCs and retained iodized oil) ; in cases with multi-nodular HCCs ($n \leq 5$), the size of viable tumor was under 5 cm in diameter ;3) With no portal vein invasion and extrahepatic metastases; 4) Child-Pugh class A or B. Among these patients, 55 patients received combined RFA treatment due to the following criteria: 1) viable residual tumors after TACE was found in follow-up ultrasound; 2) residual tumor can be treated with curative intention by using RFA; 3) absence of severe coagulopathy (i.e., prothrombin time $\leq 16S$ or platelet count $<$
patients consented to receive RFA treatment; Other 156 patients who were not suitable for RFA treatment and received repeated TACE treatment were assigned to TACE alone group, owing to the following reasons: 1) tumors were poorly visible on planning ultrasound; 2) percutaneous RFA was infeasible due to the high risk location of thermal injury or could result in incomplete ablation due to inadequate electrode path; 3) presence of coagulopathy (i.e., prothrombin time >16S or platelet count <50000/mL); 4) residual tumors can be treated with combined TACE and patients were unwilling to receive additional RFA treatment.

As for your question 2: It is strange that the complication rate is significantly higher in TACE alone group than in TACE plus RFA group. We considered this concern is partly resulted from the different background of two groups of patients. In our old manuscript, majority of patients with 8-10cm tumors were included in TACE alone group, these patients are likely to receive more sessions of TACE treatment or more doses of chemical agents than patients with small tumors, which may increase the complication. In our revised manuscript, to make the two cohorts of patients comparable, we revised our inclusion criteria. Only patients who were potential candidates for following RFA treatment were included. Patients with large tumors (8-10cm) tumors which may not be ablated by RFA were excluded. The number of patient included in TACE alone group dropped from 182 to 156. The Major complication observed in TACE patient was decrease to 2.6% (4/156, 2 with liver dysfunction and 2 with upper gastrointestinal bleeding), which was still higher than TACE+RFA group. The difference of complication can be explained. Although the initial background of the two groups is alike, however, they underwent different treatments according to our institutional protocol. Patients in TACE+ RFA group received median 2.0 (range: 1-5) sessions of TACE treatment. While in TACE alone group, patients received median 3.0 (range: 1-9) sessions of TACE treatment. That is, patients in TACE alone group received more TACE treatment than TACE+ RFA group. More sessions of TACE deteriorated liver function, especially for patients with hepatitis background. 2 patients in TACE alone group died from liver dysfunction and none of patients in TACE+RFA group died of liver dysfunction. This differences of complication indicated that the TACE+RFA combined treatment can decrease liver deterioration-related death resulted from TACE alone treatment.