Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Radiofrequency Ablation Following First-Line Transarterial Arterial Chemoembolization for Patients with Unresectable Hepatocellular Carcinoma Beyond the Milan Criteria” (MS: 6438156869901167).

Those comments are all valuable and very helpful for revising and improving our paper, as well as for further study. We have reviewed the paper according to the reviewer’s comments. Revised portion are marked in red in the paper. The responds to the reviewer’s comments are as followed as below:

Response to DrKirikoshi’s comments:

1. The procedure of combination therapy in this manuscript (RFA is performed within 1-2 months after TACE in patients who has incomplete necrotic tumornodes) considered to be unique and reasonable for the effectiveness treatment. In previous studies including our report (Hepatol Res, 2009; 39: 553-562), RFA was performed for the all HCC lesions as possible, and performed within 1-2 weeks after TACE expecting for larger tumor necrosis due to cooling effect of TACE.

We thanks DrKirikoshi’s very much for the comments about RFA protocol in combination with TACE. We agree to performed RFA ablate all the lesions within 1 to 2 weeks after TACE.

In our study RFA was performed in one or two months after TACE and just
performed in the lesions with contrast enhancement in arterial phase with CT or MRI evaluation with indicating these lesions with tumor activity.

Because the imaging evaluation was performed at 1 month after TACE, disappearance of tumor enhancement in the arterial phase was considered complete necrosis. Mannelli L et al (AJR AM J Roentgenol, 2009,193:1044-52) reported that compared with diffusion-weighted imaging, contrast-enhanced MRI with subtraction technique had more significant correlation with the histopathologic findings in the evaluation of necrosis of HCC after TACE. There was no difference, however, between the two methods in diagnosis of complete tumor necrosis. We deem these necrosis nodules have no need for RFA again. The combined procedure was often used in the patients with multiple nodules, the procedure that ablation in incomplete necrotic lesion not in complete necrotic lesions may be possible to be conducted more safely in clinical practice.

In our study RFA was performed within 1-2 months after TACE. Our study was retrospective as mentioned in the manuscript. The routine imaging evaluation was performed at 1 month after TACE in our department. So the RFA procedure was performed within 1-2 months after TACE. But we also think this procedure has some advantages. In our study, all patients have tumor nodules beyond Milan criteria. These patients always have micro-metastasis which cannot be detected by pre-TACE ultrasonography, CT, or MRI. Lipiodol CT performed 1 month after TACE can detect these small metastasis nodules.

2. There is typos error in the title of the manuscript, “transarterial arterial###”.
Thanks DrKirikoshi very much for the correction and the errors has been revised.
3. Table 1, 2 and 3 are not found in this PDF file (due to error of computer or internet?).

We are very sorry for the mistake. The tables uploaded have been confirmed.

Response to DrNojiri’s comments
1. The author showed the benefit combination therapy of TACE and RFA but there were no novel data and samples were too small to discuss.
It is really true this research has limitations for study design and sample size. This retrospective study revealed the benefits of combination RFA in the patients with tumor beyond Milan criteria while TACE as first line treatment. Further prospective randomized studies are warranted to confirm the efficacy of this promising combination therapy.
2. In the part of Introduction and Discussion there are a lot of same discussions. The author should combine these parts.
We thank DrNojiri’s corrections for introduction and discussion. We have re-written the Introduction and Discussion part according to the Dr. Nojiri’s suggestion.
3. There are many parts that are grammatical mistakes.
The English written has been revised.
We tried our best to improve the manuscript and made some changes in the
manuscript, and hope that the revised manuscript will meet with approval.

Best regard,
Yours Sincerely,
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Zhongshan Hospital,
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