Author's response to reviews

**Title:** Transcatheter arterial chemoembolization combined with radiofrequency ablation delays tumor progression and prolongs overall survival in patients with intermediate (BCLC 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 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 and Zheng-gang Ren

Major revisions

1. The authors mention that ischemia causes reduction of heat dispersion, thus increasing the range of the RFA ablative zone. However, this phenomenon is present when TAE and RFA are performed simultaneously. If you find another paper to prove this, please provide and reference appropriately.

Answer:

Thanks for your suggestion. Indeed, the blood flow is a strong predictor of thermal coagulation volume in RFA (Ann Surg 1998; 227:559–565). Reduction of blood flow before RFA application has been shown to increase the area of coagulation in animal models. (AJR Am J Roentgenol 2001; 176:789–795). It is also well known that TACE through the hepatic artery, especially the injection of lipiodol and gelatin sponge particles, can substantially reduce the blood flow and cause ischaemia in HCC tumors. (Hepatogastroenterology. 1998;45 Suppl 3:1236–1241) Although this embolic effect induced by TACE may not be permanent, in most cases, we believe the reduction of blood flow effect still exists 3-4 weeks after TACE treatment, because lipiodol remains in tumor nodules due to an absence of Kupffer cells inside tumor tissues (Am J Clin Pathol 1988; 90: 536–544.). As a microvascular embolic agent, lipiodol causes the embolic effects on small
tumoral vessels and decreases of tumor blood perfusion. (Korean J Radiol. 2009;10:425-34) However, we did not find published studies directly supporting this viewpoint. According to your concern, we revised the third paragraph in the background section as follows:

RFA has emerged as a new curative treatment owing to its safety and effectiveness for early-stage small HCC.\textsuperscript{9-12} In comparison with TACE, the advantage of RFA is curative local control of small HCC, but it is less favorable for complete tumor necrosis of tumors larger than 5 cm.\textsuperscript{13} The combination of TACE and RFA has several advantages over RFA or TACE alone. First, as a downstage treatment, TACE can reduce tumor burden, decrease viable tumor volume before RFA, thus increasing the possibility of complete thermal ablation. Second, after TACE or repeated TACE procedures, the main artery supplying the tumor may be narrowed or even be occluded, and snaking arterioles may be regenerated from the phrenic, intercostal, gastric and superior mesenteric arteries,\textsuperscript{14} making it difficult to selectively catheterize the feeding artery to control residual tumor cells. While subsequent RFA can directly ablate the refractory tumors. Third, it is generally believed that recurrences after curative treatment for HCC in the early post-treatment period arise, not because of incomplete treatment of the primary tumor but because of pre-existing microscopic tumor foci that are not detected by imaging modalities.\textsuperscript{15} TACE can target undetected these satellite lesions surrounding the main tumor, label the range and size of the tumor, thus providing guidance for RFA.\textsuperscript{16} TACE combined with RFA has been reported to be effective for local control of medium-sized HCC tumors (3-5cm)\textsuperscript{17}. However, whether such combination therapy could provide therapeutic benefits to intermediate HCC unsuitable for RFA monotherapy has not been clarified. The purpose of this study was to evaluate the effectiveness and survival benefit of the TACE+RFA approach to the management of intermediate HCC.

The strategies which author describe in this manuscript are aggressive and worthy of further evaluation. However, according to the fact above, the indications for RFA may be excessive. A large tumor over 5cm with the potential risk of residual tumor, has to be evaluated separately from the point of tumor control. This idea should be included in their discussion.

\textbf{Answer:}
We appreciate your professional suggestion. According to the consensus of RFA guideline, RFA is generally considered as an alternative treatment to partial hepatectomy for early small HCC (≤5cm), especially for patients with impaired liver function. Without combination therapy, RFA should not be indicated in single HCC tumors larger than 5cm. Large HCCs and multiple HCCs exceeding the Milan criteria have been widely treated by TACE for years. However, the efficacy of TACE remains unsatisfactory because it is difficult to achieve complete necrosis of the target tumors by TACE alone. The aim of our study is to evaluate the combination benefits of TACE and RFA in patients with 5-8cm single tumors or multi-nodular intermediate stage HCCs (n ≤ 5, size ≤5cm). We agree with you that our indication of TACE combined RFA is aggressive, however, such explorative study is worthy of investigation because the combination therapy may prolong survival. We also agree with you that tumor control should be carefully evaluated in this study. Therefore, in our revised manuscript, we evaluated local tumor control by tumor control rates as well as tumor progressive rates. The data indicated that combined therapy was significantly superior to TACE alone in terms of tumor control rates and tumor progression rates.

Given that tumor size or tumor number is an important factor impacting treatment efficacy of RFA, different tumor size or tumor number may result in differences in local tumor control and affect survival. We therefore analyzed the differences in tumor control and overall survival between the two subgroups (single tumor group (size: 5-8cm) and multiple tumor group (n≤5 size≤5cm). The results indicated tumor control rate of single-tumor group was slightly lower than that of multiple-tumor group. No significant differences were found (P >0.05), Furthermore, our multivariate analysis confirmed tumor size or tumor number did not impact tumor progression significantly. Taken together, these results suggest RFA provide a favorable local tumor control of intermediate stage HCC tumors. We believe if the tumors can be potentially ablated, local tumor control will not mainly rely on lesion size, but depend
largely on the technique used and the experience of the interventional radiologist who performed the procedure.

3, If the patient condition is suitable for operation (i.e. Child-Pugh A), liver resection, if it is palliative, should become a key part of a multidisciplinary effort. Are there any patients in this study which fit this description?

Answer:
In our institute, the first option for resectable HCC is surgery. All the patients who underwent TACE treatment have been evaluated by experienced surgeons and were excluded the possibility of liver resection or transplantation. Some of the patients with single tumor in this study underwent TACE or combined RFA not because of unresectable lesions but because of refusal of surgery, due to different reasons, such as compromised liver function reverse, tumor location, general clinical status and accompanied systemic diseases. This point has been added in our revised manuscript in the first paragraph of the method section.

4, The authors describe ?viable residual HCC with retained iodized oil after TACE are the candidate of RFA?. However, the enhanced residual tumors still have a chance to undergo another round of TACE.

Answer:
In our study, viable residual HCC with retained iodized oil after TACE is only one prerequisite for RFA, which indicates the target tumors have been partially controlled by TACE (with retained iodized oil) but still need further treatment due to the existence of viable residual tumors. Conventionally, the subsequent treatment should be a repeated TACE, according to the guidelines of the American Society for the Study of Liver Diseases. Our study presents an alternative choice for patients who meet the inclusion criteria of combined RFA therapy. Such new treatment modality may provide potential better tumor control and survival benefits in comparison with TACE alone. Before treatment,
patients will get detailed information about risks, benefits and complications of the two treatment modalities. They make their personal choices and sign informed consent before treatment, irrespective of receiving either TACE or combined RFA.

5, The authors describe ?TACE before RFA can eliminate satellite lesions, which may reduce tumor dissemination after treatment.? TACE can eliminate satellite lesions, but this phenomenon may be noted when the TAE and RFA are performed simultaneously (Ref 14). In the case of undifferentiated carcinomas, the seeding is still a big problem.

Answer:

We agree with you that as a palliative treatment, TACE can’t eliminate all the satellite lesions surrounding the main tumor, even in a combination modality when the TAE and RFA are performed simultaneously. Post-treatment local tumor recurrence or intrahepatic spreading is an inevitable problem to HCC, even after curative liver resection. However, as a palliative treatment, although TACE can’t eliminate all the satellite lesions and achieve a satisfactory tumor control, it can target undetected satellite lesions surrounding the main tumor, label the range of tumor, provide guidance for RFA (Radiology 2009, 252(3): 905-913.)

Here, the expression “eliminate the satellite lesions” is not very proper in describing the advantage of TACE treatment. **So we revised this sentence as follows:**

As a regional treatment, TACE can target undetected satellite lesions surrounding the target tumor, label the range and size of the tumor, thus providing guidance for RFA.¹⁶

6, Please provide more clear pictures, these figures have some suspiciously enhanced lesions, especially in Fig E. (重新编辑图片)

Answer:

Figures have been revised as indicated.
7. The authors use far too many abbreviations. There should be no abbreviations in the abstract. They should limit the abbreviations to RFA, CT, MRI, TACE and HCC. All other abbreviations should be eliminated (e.g. OS, TTP, AFP, US etc.). Once they define an abbreviation they should only use the abbreviation from that point.

**Answer:**

According to your suggestion, we have deleted improper abbreviations in the revised manuscript.

8. The paper is grammatically incorrect with errors on nearly every page that make reading the paper very difficult. The entire paper needs to be edited by someone who can write correct scientific English.

**Answer:**

The revised manuscript has been edited by an expert in English writing. The grammatical errors have been corrected.