Author's response to reviews

Title: Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma

Authors:

Yanming Zhou (zhouyms@yahoo.com.cn)
Yanfang Zhao (zhyf715@126.com)
Bin Li (Binl1962@yahoo.com.cn)
Donghui Xu (thk579@sina.com)
Zhengfeng Yin (yinzfk@yahoo.com.cn)
Feng Xie (hunanxiefeng@yahoo.com.cn)
Jiamei Yang (yjm.1952@yahoo.com.cn)

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Author's response to reviews:

Dear Dr. Hans Zauner:

Thank you for your kindness to review our manuscript (MS: 1678670284339794). Following the criticisms from you and reviewers, we have revised our paper. The point to point answers to three reviewers are supplemented at the end of this letter. It is important to note that the name of my hospital was changed to “The First affiliated Hospital of Xiamen University” a week ago.

With best wishes
Dr. Yanming Zhou
Department of Hepato-Biliary-Pancreato-Vascular Surgery
The First affiliated Hospital of Xiamen University,
Xiamen 361003, Fujian Province
China

Reviewer 1: Guy J Maddern
a) On page 6, second line: RFA has been incorrectly described as FRA. This is a correction that would need to be made prior to the manuscript being published.

answer: We have revised FRA to RFA.

b) In a number of places within the manuscript some spelling errors have occurred.

Answer: We have carefully read our manuscript again and corrected some spelling errors.

c) The topic of radiofrequency ablation versus hepatic resection remains controversial and the discussion is an important one to have. It is unfortunate that only one randomised controlled trial exists. It may be useful if the authors were
able to at least look at the different outcomes that occurred with laparoscopic and percutaneous radiofrequency ablation versus open radiofrequency ablation. This would be an important area to segment and assess whether or not there were different outcomes associated with the procedures that have greater difficulty in assessing disseminated involvement within the liver. This would certainly add further weight to the study.

Answer: RFA can be performed by percutaneous, laparoscopic or open approaches. Just as we described in part of Discussion “Laparoscopic and open approaches increase the chance of detection of unknown intrahepatic and extrahepatic tumors because they allow complete abdominal exploration and intraoperative ultrasound assessment. The additional advantages of open and laparoscopic approaches are the accurate placement of electrodes and the possible treatment of tumors in percutaneously inaccessible areas of the liver and tumors in close proximity to or invading the adjacent organs”. According to your suggestion, we performed electronic searches on the PubMed and Medline database, unfortunately, we failed to find any study that compared the outcomes of different approaches and RFA systems on therapy efficacy of HCC. Thus, we were not able to assess the influence of these factors. We have addressed this concern in discussion.

Reviewer 2: Kazutaka Kurokohchi

Major concern: As everyone knows at present, adaptation of RFA is considered to be suitable for HCC within 3 nodules and 3 cm in diameter in the liver. It is important to treat HCCs within 3 nodules, 3cm in diameter in the liver and those over 3 nodules, 3 cm separately. Thus, in case comparing the therapeutic effects of HR and RFA for HCC, the number and size of HCCs should be adjusted between HR and RFA. In this manuscript, authors show there was no significant difference in overall and disease-free survival between HR and RFA groups for patients with tumors < 3cm. Therefore, content of conclusions can not be accepted as it is in this manuscript. Analysis and conclusions should be changed according to the tumor number and size in the liver.

Answer: Thank you very much for your revision and pointing out the questions. I have revised our manuscript according to your suggestions by adding “For tumors # 3 cm HR did not differ significantly from RFA for survival, as reported in three NRCTs” in the Results of Abstract and by revising original conclusion to “HR was superior to RFA in the treatment of patients with small HCC eligible for surgical treatments, particularly for tumors > 3 cm.”

Reviewer 3: Linda M Wong

Major Compulsory Revisions:

1. The authors have studied 10 trials of liver resection vs RFA for hepatocellular cancer and performed a meta-analysis to try to determine which of the two therapies is superior. The problem and the question posed by the authors are well defined however the inclusion and exclusion criteria are not so clear. Was there a tumor size criteria for inclusion or exclusion? Did this exclude any patient that may have been rescued by liver transplant for failure of the initial therapy? Were they all cirrhotics? Differences in viral hepatitis? Patients undergoing these
two treatments may be rather heterogeneous which is why it is so difficult to conduct a randomized clinical trial.

Answer: Than you very much for your revision. Your suggestions are instructive and very important for improving the quality of our manuscript. I have revised our manuscript as you suggested. The details are as follows:

For inclusion in the meta-analysis, a study had to fulfil the following criteria: 1) compare the initial therapy effects of RFA and HR for the treatment of small HCC, regardless of the etiology of liver disease, cirrhotics status, or differences in viral hepatitis; 2) report on at least one of the outcome measures mentioned below; 3) clearly document indications for RFA and HR; 4) In dual (or multiple) studies were reported by the same institution and/or authors, either the one of higher quality or the most recent publication was included in the analysis. The primary endpoints were overall survival at 1, 3, and 5 years, and local recurrence. The secondary endpoints were disease-free survival at 1, 3, and 5 years, morbidity, and mortality.

Small HCC are defined according to the criteria developed by Yao et al. [11] from the University of California, San Francisco, a single HCC nodule of up to 6.5 cm, or with up to 3 lesions, the largest of which is no larger than 4.5 cm.

Abstracts, letters, editorials and expert opinions, reviews without original data, case reports and studies lacking control groups were excluded. The following studies were also excluded: 1) those dealing with unresectable HCC or HCC recurrence after hepatectomy; 2) those with no clearly reported outcomes of interest; 3) those evaluating patients with cholangiocellular carcinomas or liver metastases.

2. The data is sound and they do mention the limitations in the discussion. However, could they expand more on the populations of the trials – in terms of age, tumor number, tumor size, Child–Pugh score etc. This appears to be on the supplemental table but this is not discussed in the results section or the discussion.

Answer: We have discussed what you mentioned in the results section as follows:

84.7% of patients were in Child-Pugh class A. Most patients (91.0%, 1139/1251) had a single tumor. The median/ mean tumor size (cm) ranged from 1.98 to 3.65. Median/ mean duration of follow-up ranged from 21.9 to 43 months (Table 1).

3. Although the meta-analysis suggests that there is no difference in the early survival at 1 and 3 years, there is a survival advantage at 5 yrs for hepatic resection. Is this because the liver resection patients were younger, had better liver function, were not cirrhotic, had smaller tumors or something else? It’s not clear that a meta-analysis would be able to sort this out, but they should at least comment on this.

Answer: We have commented this in the paragraph 6 of Discussions.

4. The title and abstract seem to convey what has been found and the writing is acceptable, but perhaps they need to say that this is a meta-analysis of RFA vs HR for small HCC, if that is their inclusion criteria otherwise the reader is just not
sure what this study covers.

Answer: We have replaced the original HCC with small HCC in the title and abstract according to your suggestion.