September 9, 2017

World Journal of Gastroenterology

Dear Editor,

Thank you very much for the letter and decision regarding our manuscript titled, "*Efficacy of Postoperative Adjuvant Transcatheter Arterial Chemoembolization in Hepatocellular Carcinoma Patients with Microvascular Invasion*" (Manuscript No.: 35229). We have addressed the comments point-by-point and incorporated respective changes in the revised manuscript. Regarding the comment from reviewer #2, we speculate that WJG is more suitable than WJH for the current manuscript. After the manuscript is published, we believe there will be increasing attention and citations from potential readers of WJG as the content of manuscript not only provides evidence for hepatic diseases but also for gastrointestinal diseases that might be beneficial to patients worldwide.

We hope the revised text can be judged suitable for publication in *World Journal of Gastroenterology*. We would be glad to answer any further questions that you or the reviewers may have.

With best wishes

Yours sincerely,

Jiazhou Ye

Comments to Author:

Reviewer #1:

1. The study confirms that post-operative TACE could improve OS and RFS. This had been well reviewed in a meta-analysis by Qi X et al on oncotarget 2015. What is the new finding in this study?

Response:

Thanks for you for the comment. The meta-analysis by Qi et al. in Oncotarget 2015 confirm that the post-operative TACE could improve the postoperative OS and RFS in HCC patients based on several pieces of evidence. However, the current study differs from the meta-analysis and those included in the meta-analysis.

1) The meta-analysis from Qi et al. included studies that targeted the population with any type of clinicopathological features. Although the meta-analysis performed stratified analysis based on the macrovascular invasion status to compare the postoperative OS and RFS with or without postoperative TACE, according to the results from the meta-analysis and included studies, they did not perform stratified analysis according to the MVI status. Moreover, the post-operative TACE to HCC without macro-vascular invasion is yet controversial. (As shown below: when the studies and results highlighted in red are excluded, the remaining results indicate converse interpretations).

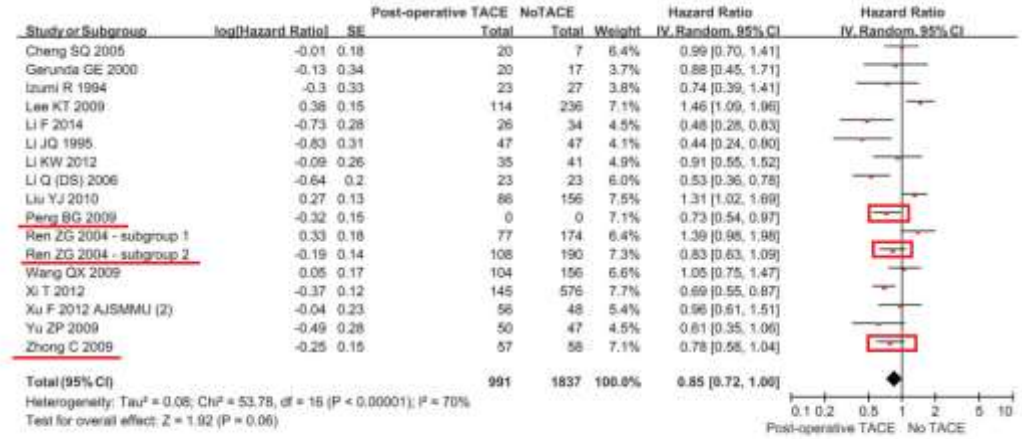

Figure 4: Forest plots comparing the overall survival between hepatic resection with and without post-operative TACE groups.

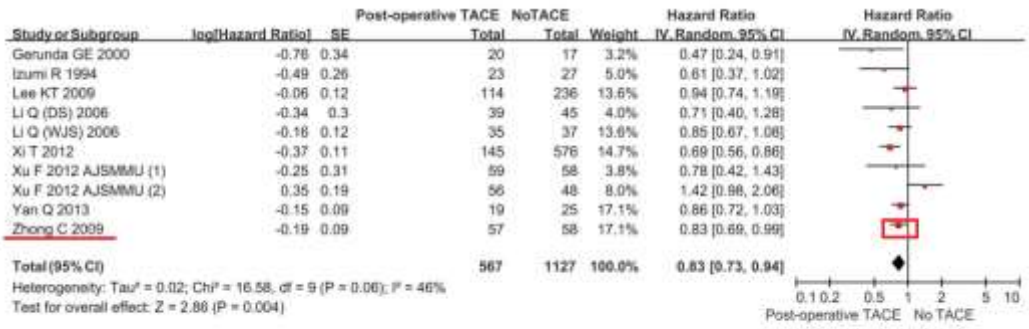

Figure 5: Forest plots comparing the disease-free survival between hepatic resection with and without post-operative TACE groups.

2) Currently, it has been accepted that post-operative TACE effectively improves the postoperative OS and RFS in HCC with macrovascular invasion. However, only a few studies have investigated the efficacy of post-operative TACE in improving the postoperative OS and RFS in HCC with MVI when macrovascular invasion is absent. Thus, whether post-operative TACE could improve postoperative OS and RFS in HCC with MVI remains unclear.

According to the BCLC staging, HCC with macrovascular invasion is at the BCLC advanced stage (BCLC-C). In the current study, only those HCC patients with BCLC early or intermediate disease (BCLC-A or B stages) without macrovascular invasion were included and studied. Our findings confirmed that post-operative TACE should be added only when MVI is present in BCLC early or intermediate stages HCC, supporting clinical decision and strategy.

2. The diagnosis of MVI by histology is an important guide for postoperative TACE. In Table 3, AFP>400 ng/mL, tumor > 5 cm and capsule invasion were important predictors of MVI. The definition of capsule invasion is not found in methodology section. How much cases with MVI can be predicted by these parameters?

Response:

1) Capsule invasion indicates that the capsule of tumor is not complete. Some studies used "incomplete tumor capsule", while others used "tumor capsule invasion". We would use "incomplete tumor capsule" instead of "capsule invasion" for a precise description.

2) In the present study, MVI was found to be positive in 104/168 cases with tumor capsule invasion. We performed multivariate analysis to investigate the predictor of MVI. The number of cases for multivariate analysis of predictor of MVI was not sufficient. Moreover, we speculate that statistical analysis is critical and persuasive to investigate the parameters as predictors or risk factors of MVI rather than the size of samples.

3. In the 2nd paragraph of discussion, the sentence 'A CT study showed that the presence of tumor capsule invasion closely correlated with absence of MVI51.' is confusion and seems to be in the opposite meaning of the reference 51.

Response:

The reference 51 seemed confusing but did not propose an opposite meaning. This study stratified the tumor capsule invasion by 5 rates: ***"Capsule integrity was rated as 5 if it surrounded 80–100% of a nodule; 4 if 60–80%; 3 if 40–60%; 2 if 20–40%; and 1 if <20% or if there was no discernible capsule. To calculate the sensitivity and specificity, we regarded that the capsule was present when this rating was ≥3."*** According to their definition, tumor capsule invasion was explicit in the rates 1-2. Thus, based on the results from this CT study shown in Fig. 6, the presence of microembolism is closely correlated with tumor capsule invasion (36/42 nodules passing capsule with a rating of 1 and 2 showed micro-vascular emboli, P < 0.001, Mann–Whitney test).

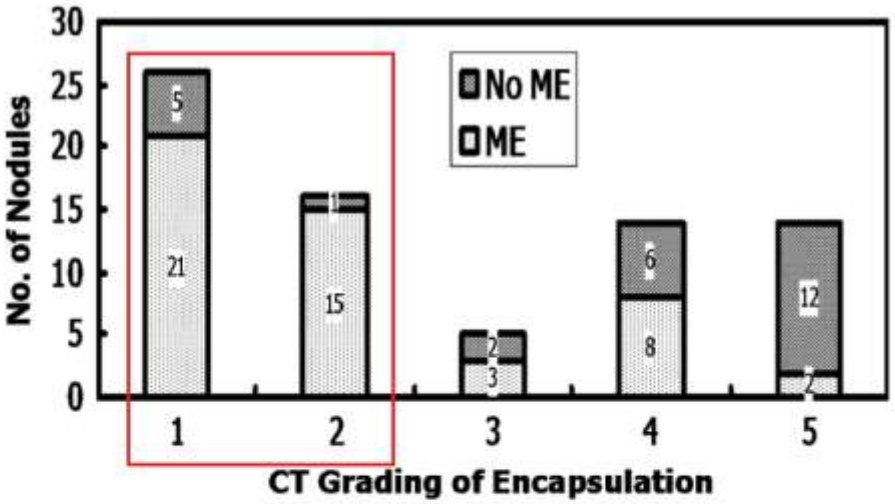

Fig. 6 Relationship between the capsule demonstration on CT (rated from 1 to 5) and the presence of microembolism in histology ($P<0.001$, Mann-Whitney test). Twenty of 33 nodules possessing capsule with a rating of 3, 4, and 5 showed no microvascular emboli, whereas 36 of 42 nodules passing capsule with a rating of 1 and 2 showed microvascular emboli. *ME* microemboli in the surrounding liver parenchyma on histopathologic examination; *No ME* no microemboli in the surrounding liver parenchyma on histopathologic examination

Reviewer #2:

1. The manuscript is interesting and the number of patients in the cohorts is impressive. However, I would suggest to resubmit to World Journal of Hepatology, because Baishideng Publisher has a different journal for

hepatology manuscripts.

Response: We sincerely appreciate the suggestion of reviewer #2. However, we still believe that WJG is more suitable than WJH for the current manuscript as the content not only provides evidence for hepatic diseases but also for gastrointestinal diseases, which may benefit a large number of patients worldwide. Thank you for the consideration.

Reviewer #3:

1. please explain how the deicion was arrived at to offer or not offer PA-TACE to the patients (why had some been given PA-TACE and not others as this as not a trial as such.) Was this based on tumour size for example or AFP perhaps?

Response:

In the current study, decision of PA-TACE was primarily based on the MVI status rather than the tumor size or serum AFP levels.

PA-TACE has been strongly recommended as a safe and effective adjuvant intervention to suppress the incidence and delay the progression of recurrent tumor in patients with residual tumors, including macrovascular invasion, tumor capsule invasion, and multiple or satellite nodules. ***Recently, MVI has been demonstrated as an independent risk factor associated with early tumor recurrence in patients with single HCC without macrovascular invasion, by acting as a "seed" to give rise to micro-metastases in the liver parenchyma, which accounts for approximately 15-60% of HCC patients. However, whether PA-TACE can restrain recurrence and provide the survival benefit to HCC patients with MVI remains unclear.*** Therefore, in this study we recruited HCC patients at BCLC A/B stages without macrovascular invasion. The main purpose was to investigate the effect of PA-TACE to restrain recurrence and prolong survival of HCC patients with MVI, and patients without MVI were used as a parallel control. Thus, no obvious bias of tumor capsule invasion and multiple or satellite nodules between the patients with or without MVI was observed.

2. Please highlight or explain whether there were any complications related to PA-TACE, deaths, liver failure (or even simply a change in Child's or MELD score), side effects, etc

Response:

We add the reports of complications related to PA-TACE at the end of the results section. Owing to PA-TACE as an adjuvant preventive therapy with a low dose of lipiodol (3–5 mL) and chemotherapeutic drugs, lobaplatin (50 mg) and raltitrexed (4 mg), no serious complications were observed in all patients

who received PA-TACE.

3. Are you able to provide info as to what happened to AFP levels after resection and then after TACE and compare to those who didn't receive the PA-TACE (did TACE patients have a further drop in AFP?)

Response:

Thank you for the kind advice. In the present study, we did not evaluate and compare the AFP levels after resection. This was because although it is well accepted that ascending AFP levels are sensitive to HCC recurrence, it is not the only standard for diagnosis of tumor recurrence. The confirmatory diagnosis of HCC recurrence is based on the image examinations in combination with or without ascending AFP levels. In the manuscript, we have defined recurrence on Page 9 Line 6-8 in the follow-up section as follows: "*Recurrent HCC was confirmed by CT or MRI images showing rapid tumor staining in the arterial phase that disappeared in the early venous phase together with an increase in the serum AFP level. DSA was supplemented when tumor lesions were <1 cm.*". Nevertheless, not evaluating AFT is a limitation that could be addressed in further prospective studies. This is added in our limitation on Page 13 Line 26.

4. There remain a few minor grammatical or syntax errors and I would suggest one further proof read of the manuscript 3.

Response:

We re-edited the English language for grammatical and syntax errors and into a concise and easy to read and understand manuscript.