

Dear Editor and Reviewers,

We would like to thank the editor and both reviewers very much again for appreciating this work and providing further valuable comments to make this manuscript better. The corresponding comments have been carefully addressed in the revised manuscript accordingly. We hope that with these modifications, this revised manuscript is qualified for publication in the World Journal of Gastrointestinal Surgery.

Comments:

Reviewer 1:

This is an observational study, evaluating the role of diffusion kurtosis imaging (DKI) and DKI-derived metrics in predicting the recurrence and cellular invasion of the peritumoral liver zone of hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (TACE). The authors investigated the characteristics of the DKI-derived metrics between the true progression and pseudo-progression groups. The study is highly original and relevant. The organization & flow of the paper is of high quality. The authors addressed all the limitations of the study properly and despite these limitations, this study has a strength of novelty of describing the DKI with derived functional metrics (including MD, DA, DR, KA, and FAk) as an assessment tool for evaluating the therapeutic response of TACE to HCC, as well as peritumoral zone invasion. Therefore, I recommend to accept this manuscript for publication.

Reply:

We would like to thank this reviewer very much for the confirmation of our work.

Reviewer 2:

1. Pathological examination: Were all cases or selected cases performed? What is the pathological definition of a true progression? What is the pathological definition of pseudo-progression?

Reply:

Thank this reviewer very much for pointing out this issue.

To be honest, only twelve cases in our research were performed pathological examination, for most patients with HCC are diagnosed at the advanced stage and thus lose the opportunity for surgical resection. Four out of twelve cases where pathological results were obtained by puncture results. The remaining pathological results were due to multiple TACE procedures that created the conditions for performing the surgical procedure (the corresponding patients numbers were added to the FIG.1 “flow chart” for better understanding of the inclusion process).

As to the true progression pathologically, there should be viable tumor cells in the foci, including primary liver cancer among the incisions, necrotic material and granulomatous inflammation. For the pseudo-progression, there was no cancer cell infiltration in the operation area, only liver cirrhosis nodules and some fibrous necrosis components. The corresponding part was added to the *subjects* section.

(Emphasize with a yellow background).

2. There were cases TACE was performed more than once. The authors should clearly state the number of times TACE was performed on a tumor.

Reply:

Thank this reviewer very much for pointing out this issue.

Based on initial TACE results of each patient, we evaluated the corresponding mRECIST parameters and decided if further TACE procedure was necessary. Hence,

The number of TACE procedures performed was not identical for all patients, i.e., single or multiple TACE treatments. As requested by the reviewer, we state the number of TACEs in the true vs. pseudo groups in Table 1, including 26 of the 82 cases underwent single TACE, and the rest underwent multiple TACE (4 of the 48 cases underwent single TACE in true progression group, and 22 of the 34 underwent single TACE in the pseudo-progression group, respectively).

3. In Table 1, the authors analyzed AFP with positive or negative values after performing TACE. I think AFP should be analyzed whether the values decrease or not after doing TACE. There are HCC cases without increased AFP.

Reply:

We would like to thank this reviewer for this concern.

According to reports, AFP has a certain positive correlation in patients with HBV infection-related liver cancer. However, AFP values were normal except for liver cancer caused by hepatitis B or some well-differentiated liver cancer.

In addition, for AFP-positive liver cancer treated with TACE or surgery, AFP should be reduced within a certain period of time. In the event of postoperative recurrence or metastasis, AFP re-elevation can occur. However, the recurrence of AFP-positive HCC patients can also be AFP-negative, and the original AFP-negative patients can also be AFP-positive.

Reviewer 3

1). The authors state the strong performance of the method evaluated in the study group. Indeed, this is the most striking aspect of the study. Therefore this finding should be emphasized in the core tip.

Reply:

We would like to thank this reviewer for this comment.

According to the requirements of the reviewer, we have revised and supplemented the core tip regarding the performance of DKI as follows as: “This study demonstrated feasible performance and the advantages in assessing the therapeutic response of the clinical values of DKI metrics (MD, DA, DR, KA, and FAk) in evaluating liver cancer and tumoral cell invasion of peritumoral zone between HCC progressive group and pseudo-progressive group after TACE treatment.” (Emphasize with blue background)

2). Please use words before abbreviations starting from the abstract section.

Reply:

We would like to thank this reviewer for this comment.

As requested, We've double checked and revised whole article starting from the abstract section to make sure words are used before all abbreviations.

3)The lack of pathological examination of tumor changes before and after treatment is another potential limitation of the study. This should be stated in the discussion.

Reply: We would like to thank this reviewer for this comment.

The corresponding part was added to the limitations section with blue background.

“Fourth, the lack of pathological examination of tumor changes before and after TACE treatment. Further researches with more pathologically confirmed cases are required to be conducted.”

4) I suggest that the authors revise and prepare their manuscript according to the guidelines for manuscript submission of the WJGS.

Reply: We would like to thank this reviewer for this concern.

Based on this expert's advice, we have double checked and revised and prepared the manuscript according to the WJGS submission guidelines.