Peer Review File

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Reviewer A:

Comment 1: Inclusion criteria: regarding the characteristics of enrolled patients an important issue to take into account is to specify whether patients had received previous HCC treatments (surgery, transarterial, systemic, etc) since it is well-known that the impact of previous treatment might have a significant impact on the liver functional reserve that has a prognostic impact in HCC patients.

Reply 1：Patients with previous HCC treatments were excluded from the exclusion criteria (please see page 3, line 64-65).

Comment 2: Therapeutic procedure: could the Authors expand the description of the TACE procedure? Selective/superselective?

Reply 2: The TACE procedure is superselective.

Reviewer B:

Comment 1: The statement "We recommend combination treatment because ..." (line 48-49). Who are we?

Reply 1: The sentence was inaccuracy and has been deleted.

Changes in the text: We have modified our text as advised (see Page 3, line 49).

Comment 2: For the entire manuscript, I feel like what the authors really wanted to compare is localized chemoinfusion using FOLFOX with or without embolization, right? I think using the word TACE combined with HAIC versus HAIC alone is confusing, TACE stands for transarterial chemoembolization which includes chemoinfusion in the term already. If the difference between the procedure in your study and the conventional TACE is the chemotherapeutic agent regimen, please clarify that, but refrain using the term TACE plus HAIC, I personally think it did not make sense. [If I understand this incorrectly, please feel free to let me know].

Reply 2: We used a mixture of lipiodol and idarubicin, chemotherapeutic drugs have little effect, mainly by embolism caused tumor necrosis to play a role.

Comment 3: Why the authors choose a cutoff of 5 cm as a large HCC? is there any ref? the RCT in ref 19 choose 7 cm, why do you choose the different cutoff?

Reply 3: Liver tumor larger than 5cm was classified as “large HCC”, which cited from “Chang YJ, Chung KP, Chang YJ, Chen LJ. Long-term survival of patients undergoing liver resection for very large hepatocellular carcinomas. Br J Surg. 2016 Oct;103(11):1513-20. doi: 10.1002/bjs.10196. ”. Also because the cases were limitted, choosing 7cm as the cutoff value would further narrow the sample datas.

Comment 4：The size of >5 cm was not contraindicated for surgery, how the authors defined that these patients were unresectable?

Reply 4：The patients enrolled were those who lost surgical excision indication.

Changes in the text: We have modified our text as advised (see Page 3, line 62-63).

Comment 5: Have the author calculalated the sample size, if so, please state.
Reply 5: Excuse me, do you say the size of tumor. We caculate the mean size of all as 9.7cm.

Comment 6: Although the authors stated that there is no difference in baseline characteristics between the two groups, but if we looked at table 1 closedly, the patients in HAIC group had more ascites, more multiple HCC, and even lower albumin and higher T.bilirubin. The statistically significant level was not reached for the comparison might be from the small sample size but the differences in proportion between two groups might be meaningful. And these could make the HAIC alone group predisposed to the lower overall survivals. This should be mentioned in the discussion and the conclusion that TACE is superior than HAIC is a very dangerous conclusion.
Reply 6: This section has been added at limitations part.
Changes in the text: We have modified our text as advised (see Page 10, line 201-205).

Comment 9: I don't understand the paragraph line 185-191, please check whether the writing is correct.
Reply 9: This is the answer to the experts whether there were any residual tumor activity after TACE, and it is also a difficult problem for the future research in this paper.

Reviewer C:
Title:
Comment 1: recommend indicate that this is a comparative study.
Changes in the text: We have modified the title.

Abstract:
Comment 1: Line 21 and 22: please list p values for OS and PFS comparisons.
Changes in the text: We have modified our text as advised (see Page 1-2, line 23-24).

Comment 2: Line 24: “neither was statistically significantly significant”. Recommend listing p values instead.
Changes in the text: We have modified our text as advised (see Page 2, line 26).

Introduction:
Comment 1: Line 33: HCC diagnosis is different between USA and Asia countries given etiology difference. In the US, HCC can be diagnosed at an early stage due to cirrhosis and screening programs.
Reply 1: We carefully considered and revised the relevant content.
Changes in the text: We have modified our text as advised (see Page 2, line 35-36).

Comment 2: Line 47: evidence does not support HAIC as curative option.
Reply 2: We provide new evidence.
Changes in the text: We have modified our text as advised (see Page 3, line 47-49).

Methods:

Comment 1: Line 55: please indicate prospective or retrospective. If clinical trial, please include registration or published protocol if available.

Reply 1: This was a retrospective study which was indicated in the text.

Comment 2: Line 65: authors excluded patients receiving sorafenib or levatinib. How aboutu other immunotherapy and other systemic treatment? Are included pateints treatment naive?

Reply 2: This study excluded the patients received other immunotherapy and other systemic treatment.

Changes in the text: We have modified our text as advised (see Page 3, line 66).

Comment 3: were HAIC done outpatient? What is the hospital stay per session?

Reply 3: HAIC were done in the ward which can be seen at page 5, line 90. The hospital stay per session about three to five day.

Results

Comment 1: Please report etiology of tumors ie HBV, HCV.

Reply 1: The patients with Hepatitis enrolled were all positive for HBsAg.

Changes in the text: We have modified the table.

Comment 2: How many people had cirrhosis?

Reply 3: A total of 41 patients had cirrhosis, among whom 18 patients in TACE-HAIC group and 14 patients in HAIC alone group. This can be found in Table 1.

Comment 3: Line 120: what's the p value between follow-up times?

Changes in the text: We have modified our text as advised (see Page 6, line 122).

Comment 4: Line 122: please report p value of average treatment.

Changes in the text: We have modified our text as advised (see Page 6, line 123).

Comment 5: Line 126-130: when was tumor response measured? At 3month? Or best response?

Reply 5: The tumor response was measured at best response.

Changes in the text: We have modified our text as advised (see Page 5, line 99).

Comment 6: Line 130: please list specific p values.

Changes in the text: We have modified our text as advised (see Page 6, line 131).

Comment 7: Line 140: it appears that authors selected several cutoff for regression analyses. Please indicate so in the manuscript.

Changes in the text: We have modified our text as advised (see Page 7, line 140-144).

Discussion

Comment 1: Line 186: it should be "on one hand" insetead of "in the one hand"

Changes in the text: We have modified our text as advised (see Page 9, line 185).

Reviewer D:

ABSTRACT:

Comment 1: What is the size definition of "large HCC"?

Reply 1: Liver tumor larger than 5cm was classified as “large HCC”, which cited from “Chang YJ, Chung KP, Chang YJ, Chen LJ. Long-term survival of patients undergoing liver resection for very large hepatocellular carcinomas. Br J Surg. 2016 Oct;103(11):1513-20. doi: 10.1002/bjs.10196. ”.

Comment 2: The definition of "the two groups " should be described in Materials and Methods.

Reply 2: The definition of "the two groups " had been described in Materials and Methods.

Changes in the text: We have modified our text as advised (see Page 1, line 14-15).

Comment 3: How did the authors analyze the data? Which statistics method?

Reply 3: Overall survival (OS), progression-free survival (PFS), tumor response, and adverse events were used to evaluate the efficacy and safety of the two groups by using log-rank test. The independent factors of OS of large HCC patients were investigated by Cox regression model.

Changes in the text: We have modified our text as advised (see Page 1, line 18-19).

Comment 4: The information on the age and sex of the patients should be described.

Changes in the text: We have modified our text as advised (see Page 1, line 20).

Comment 5: There were no p values for comparison of OS, PFS, ORR, DCR.

Reply 5:

Changes in the text: We have modified our text as advised (see Page1-2 , line23-24,26).

MATERIALS AND METHODS:

Comment 1: What is the endpoint of TACE? Were there any residual viable tumors after TACE? The residual viable tumors after TACE are very important for determining the objective tumor response.

Reply 1: The endpoint of TACE was that arteriography showed the stasis of tumor’s blood flow.

Changes in the text: We have modified our text as advised (see Page 4, line 81-82).

Comment 2: What was the level of HAIC or where was the location of the catheter tip? Subsegmental, segmental, lobar, or entire liver?

Reply 2: The location of the catheter is not fixed and should be combined with arteriography to ensure that the drug at the microcatheter site can cover the tumor’s major blood vessel.

Comment 3: Who performed HAIC or TACE, experienced interventional radiologists?

Reply 3: The operations were performed by Xianfu Shang and Junbiao Li whom are experienced interventional radiologists and also the authors of the article.

Changes in the text: We have modified our text as advised (see Page 4, line 74).

Comment 4: What were the selection criteria for the two treatments?

Reply 4: This was a retrospective study. In the early stage, we mainly used HAIC to treat large liver cancer, but later we found that TACE combined with HAIC might more effective, so we gradually

tried to adopt combination regime.

RESULTS

Comment 1: (Line 128-129) The ORR and DCR for the TACE-HAIC group were significantly higher…: Since p value is not more than 0.005, the expression of “significantly” is not proper.
Changes in the text: We have modified our text as advised (see Page 6, line 131).

Comment 2: In the section of Survival Analysis, there were no p values for PFS and OS.
Changes in the text: We have modified our text as advised (see Page7 , line 136,138).

Comment 3: I think the univariate and multivariate Cox regression analyses must be different. However, the authors described them together. Two analyses should be described separately in the figure as well as in the manuscript.
Changes in the text: We have modified our text as advised (see Page 7 , line 140-144).

FIGURE:

Comment 1: I could not find Figure 2 (B).
Reply 2: We have reuploaded Figure 2(B).

Comment 2: In Figure 3, OS is not “over survival”.
Changes in the text: We have modified our text as advised (see Page 14, line 291).