

Peer Review File

Article Information: <https://dx.doi.org/10.21037/jgo-23-992>

Reviewer A

Thank you very much for your review of this paper, for your questions and suggestions, all our authors have carried out a detailed discussion, and make out the corresponding responses and modifications, I believe this will further enhance the quality of this paper!

Your text is well structured and easy to read with only a few mistakes. The article is well balanced.

Here are my comments:

Introduction:

Line 64 : You say that TACE represents the predominant therapeutic strategy for HCC. This sentence needs clarification, correction or citation. What do you mean predominant?

Reply: This sentence was inaccurately phrased by us and should have been phrased as being that TACE is a commonly used treatment for patients with unresectable HCC.

Changes in the text: Line 71 we change this sentence to transcatheter arterial chemoembolization (TACE) is the most commonly used method in the treatment of unresectable HCC, demonstrating a definitive survival advantage over supportive care.

Line 67: The ongoing introduction of novel pharmacologic agents, embolic materials, and delivery techniques has enhanced drug delivery efficiency, thereby improving local control rates. This sentence needs citations. If the cited studies show better local control rates for selected patients only, this should be noted.

Reply: We have inaccurately phrased this sentence, which should be phrased as people trying new chemotherapeutic agents, embolic materials, and modes of administration to improve local control rates, and the relevant article has been cited in the article.

Changes in the text: Line 75 we change this sentence to in recent years, more and more scholars have tried to update the chemotherapeutic agents, embolic materials and delivery methods to improve the efficiency of drug delivery and further improve the local control rate.

Line 95: There are also case reports of O TACE for patients with AV shunts notably a series of 11 patients with 8 CR and 3 PR (Lee et al JVIR 2007). This is just a suggestion, you are not obliged to mention it but it would serve as a proof of concept.

Reply: The study by Lee et al demonstrated that temporary balloon occlusion of the hepatic vein in hepatocellular carcinoma with AV shunt allowed completion of TACE using conventional method while preventing pulmonary complications. The content of this study has also been very enlightening and is therefore deliberately illustrated and cited in the text.

Changes in the text: In line 101, we supplement the study of Lee et al.

Materials and methods:

Line 110 : You say that lesions treated had to be in the same hepatic venous drainage area . In the abstract you say same lobe. These are not synonymous. Did you occlude multiple veins at once for some patients?

Reply: Our expression is not accurate enough, and should be the same expression that the lesions confined to the same hepatic venous drainage area.

Changes in the text: Line 28/40 we change this sentence to lesions confined to the same

hepatic venous drainage area.

Line 112 : Patients had preserved liver function Child Pugh A and B. I would be interested to see the score CP among patients characteristics

Reply: All the patients included in this study had the Child-Pugh score of grade A.

Line 128 : Balloon inflated for 2 minutes. I am surprised that two minutes was sufficient for embolization in all cases. Also our experience with hepatic vein occlusion concomitant with portal vein embolization shows that often, collateral veins can be seen very fast in even less than two minutes. Did you encounter such cases? Did you opacify through the fogarty to see if collateral derivation was present during chemoembolization or only in the beginning?

Reply: Hepatic venography was performed only at the beginning of the procedure, and no further venography was performed during infusion and embolization of chemotherapy drugs.

Line 128 : Please describe your technique in detail. Is this arterial chemoinfusion? I am not sure that the term c TACE applies here. Conventional TACE is the injection of an emulsion of lipiodol with a (or multiple) chemotherapeutic agent(s) followed by embolization of the feeding arteries.

Reply: Where we differ from traditional hepatic arterial chemoembolization is that we use a balloon to temporarily block the target hepatic vein before chemoinfusion and embolization, as mentioned by Lee et al JVIR 2007. The specific details of C-TACE were detailed in section 2.2 of the text in line 149.

Line 141,143 The word surgery is not appropriate. I would suggest the word treatment.

Reply: We changed the word surgery to treatment.

Changes in the text: We changed the word surgery to treatment in line 156 and 159.

Line 160 : Systemic therapy is advised for all patients with stage IIb or higher. These guidelines are not very well known outside of China and not in accordance with other guidelines. Please cite at least one major publication that shows a benefit from the combination of TACE and systemic treatment vs systemic treatment alone for this population of patients. Also it is 2022 edition not 2022th

Reply: This statement is incorrect, according to the Standardized Diagnosis and Treatment of Primary Liver Cancer (2022 edition) , systemic therapy is advised for all patients with a diagnosis of stage IIIb or higher, however, patients with stage IIIb and above were not included in this study, so we removed that part.

Changes in the text: we removed that part in line 174.

Results:

Line 179 : ...patients WHO were hepatitis B carriers.....

Reply: We change this sentence to patients with chronic viral hepatitis B.

Changes in the text: We change this sentence to patients who were chronic viral hepatitis B in line 194.

Line 194 : How do you explain the higher CR rate at two and three months? In conventional TACE it is not the case unless an enhancement due to altered hepatic perfusion is mistaken for residual disease.

Reply: CR can be achieved by further necrosis of the residual lesion through multiple embolization.

Line 197 : I do not understand the meaning of this sentence. You mean to say AT ONE month AFTER treatment ?

Reply: This sentence should be changed to one month after treatment.

Changes in the text: This sentence should be changed to one month after treatment in line 213.

Line 199 : post -surgery should be replaced by post intervention

Reply: We change post -surgery to post intervention.

Changes in the text: We change post -surgery post intervention in line 214.

Line 215-217 : These are reductions comparing with values before treatment according to your description above (line 143). An explanation or hypothesis should be provided about why liver function indices would be decreased comparing with pre-treatment values. Unless it is comparing to immediate post treatment values in which case you should do the appropriate corrections.

Reply: Because we improved the patient's liver function by administering hepatoprotective drugs after treatment, the patient's liver function was restored at the re-examination 1 month after treatment.

Discussion:

Line 233 : I believe that the words 'comparing to' are missing after the word notably

Reply: We add the words 'comparing to' after the word notably.

Changes in the text: We add the words 'comparing to' after the word notably in line 251.

Line 233 : I do not see why the comparison with combined treatments is needed here. If you can show that O TACE performs better than 'cTACE' it is enough. This argument would be relevant if you were actually comparing O TACE with a combination of cTACE and thermal ablation.

Reply: What we are trying to say is that we hope to improve the effectiveness of TACE further so that it can be comparable to TACE combined with ablation.

Line 240 : This sentence is not clear. What is it that increases with tumour size?

Reply: It should be the hepatic artery will be increase with tumor size.

Changes in the text: We add 'and the blood supply from hepatic artery is increasing with tumor size' in line 259.

Line 241- 242 hepatic vein.. Did you mean portal vein?

Reply: We change hepatic vein to portal vein.

Changes in the text: We change hepatic vein to portal vein in line 261.

Figures :

Figure 1 I do not think that the term active -inactive / inactivation is suitable. I propose the terms devascularised/devascularisation. Or enhancing non enhancing

Reply: We changed the word inactivation to non enhancing.

Changes in the text: We changed the word inactivation to non enhancing in line 407.

Figure 2 Same

Reply: We changed the word activity to enhancing.

Changes in the text: We changed the word activity to enhancing in line 410.

Figure 6 The word operation should be replaced by treatment or intervention

Reply: We changed the word operation to treatment.

Changes in the text: We changed the word operation to treatment in line 413/416/419/421/425.

Reviewer B

Thank you very much for your review of this paper, for your questions and suggestions, all our authors have carried out a detailed discussion, and make out the corresponding responses and modifications, I believe this will further enhance the quality of this paper!

1. Result: If there are data on procedure time in this study, it would be beneficial to compare the procedure time between the O-TACE and C-TACE groups.

Reply: The procedure time of the patients was not recorded in detail in this study because the additional process of balloon occlusion of the hepatic vein compared to conventional arterial chemoembolization would have been appropriately prolonged, but would not have significantly prolonged the overall procedure time for an experienced interventional radiologist.

2. Discussion (P12 L248): The authors should discuss that transient hypertransaminasemia after TACE is significantly associated with objective radiologic tumor response as recently demonstrated (TRANS-TACE: Prognostic Role of the Transient Hypertransaminasemia after Conventional Chemoembolization for Hepatocellular Carcinoma. *J Pers Med.* 2021 Oct 17;11(10):1041).

Reply: We carefully read this study by Granito et al. who demonstrated that it is possible to predict the local response rate of postoperative lesions by analyzing changes in transaminases after TACE. However, in our study, we only collected preoperative and 1-month postoperative transaminase changes, which did not provide a predictive value for the local response rate of the patients, and we will study the method of Granito et al. to investigate the effect of transaminases on the local response rate of the patients with O-TACE in a subsequent study. We added this part to the discussion and cited the article to prompt us to further refine the subsequent research content.

3. The CR rate in the C-TACE group at 1-month follow-up is lower compared to previous studies. It would be advisable to discuss any specific reasons or speculated causes in the Discussion.

Reply: The CR rate of patients in the C-TACE group was lower than that of previous studies, which may be due to the possible selective bias of fewer patients enrolled in this study on the one hand, and the inclusion of some patients with multiple nodes in this study on the other hand.

Changes in the text: Speculation on the relevant possible causes has been carried out in the discussion section in line 245.

4. The use of arrows or arrowheads for annotation would be helpful to point out specific regions in Figures 1 and 2.

Reply: We have added and modified the article figures within the article accordingly.

Changes in the text: See figures 1 and 2 in the text for details.

5. Uniformly adjusting the length of the bars representing p-values in Figures 3-6 and 8 would make them more visually consistent.

Reply: We have added and modified the article images within the article accordingly.

Changes in the text: See figures in the text for details.

6. Presenting the serum parameters in Figure 8 in a graph that compares data from before the procedure, after the procedure, and at the 1-month follow-up would improve clarity and ease understanding. Please see below for details (*Diseases* 2023, 11(4), 149; <https://doi.org/10.3390/diseases11040149>).

Reply: Since most of the patients were not examined in our hospital one week after treatment, this study failed to obtain relevant serum parameters. The line chart can indeed show the trend of data more clearly, but it seems that the data at only two time points cannot perfectly present this trend, which is also a limitation of this study. We also added this part to the discussion and cited the article to prompt us to further refine the subsequent research content.

Reviewer C

Thank you very much for your review of this paper, for your questions and suggestions, all our authors have carried out a detailed discussion, and make out the corresponding responses and modifications, I believe this will further enhance the quality of this paper!

General comments:

Authors present Efficacy and safety analysis of selective hepatic vein occlusion combined with arterial chemoembolization versus conventional transarterial chemoembolization in the treatment of hepatocellular carcinoma.

1. This novel method is very interesting. However, there are several points to modify in this study. Regarding BCLC stage, patients with stage A were dominant in this study. Accordance with treatment criteria such as Reig M et al's report (BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693.), resection and ablation are recommendable. Although patients in this study declined resection, wasn't ablation applied in such patients? We usually apply TACE for patients with BCLC B. The effectiveness of this method could be limited.

Reply: All patients included in this study refused surgery and local ablation.

2. You discussed the increased velocity after hepatic vein occlusion. At the end of the day, was the amount of the emulsion in O-TACE increased than c-TACE? Please clarify it. Also, large and giant HCC especially in the proximal area near hilar region tends to be less accumulated lipiodol. Was this method effective for such cases?

Reply: During the operation, we did not record in detail the intraoperative dosage of emulsion in the two groups of patients, which is a new inspiration for us, and we will further explore the differences between the two in the subsequent study. This study is only a preliminary exploratory study, and we have little experience in patients with large HCC or giant HCC, especially in the proximal area near hilar region, which is not sufficient to provide substantive proof.

3. What kinds of benefit did the patients who achieved a CR get? The OS between O-TACE and C-TACE shows no differences. For example, was time to TACE progression longer in O-TACE group? Please clarify it.

Reply: Research by Kim et al. indicates that patients with an initial CR exhibit the longest overall survival (OS), notably comparing to those who achieve a CR after multiple sessions or who attain a PR as their best outcome, due to the short follow-up time in our study, none of the patients achieved median OS and median PFS. We will continue to follow up and further clarify in the following articles.

4. Please make a space before parenthesis.

Reply: Corresponding changes have been made in the paper.

Specific comments:

Abstract

No suggestions.

Introduction

No suggestions.

Materials and Methods

5. Page 5, line 110-Page 6, line 111

“Lesions confined...”

If the lesions are located at the watershed of two different hepatic drainage areas, were such cases excluded? How was the hepatic drainage area evaluated? Was it based on the previous report by Murata et al., as written in the O-TACE procedure subsection? Or was retrograde CT hepatic venography used for evaluation?

Reply: The hepatic drainage area was based on the previous report by Murata et al. Patients with lesions in two or more hepatic venous drainage areas were not included in this study.

Page 8, lines 159-164

Systemic subsection

6. Was systemic therapy applied to all patients with a diagnosis of stage IIb or higher? Please clarify. In some cases, I assume that the evaluation of TACE could be unclear. Also, please put a reference number to “the Standardized Diagnosis...”

Reply: This statement is incorrect, according to the Standardized Diagnosis and Treatment of Primary Liver Cancer (2022 edition), systemic therapy is advised for all patients with a diagnosis of stage IIIb or higher, however, patients with stage IIIb and above were not included in this study, so we removed that part.

Changes in the text: we removed that part in line 174.

Results

No suggestions.

Discussion

No suggestions.

Images

7. You discussed that the advantage for O-TACE was higher accumulation of lipiodol. You should demonstrate the CT images just after O-TACE.

Reply: This is an encouraging recommendation, but we did not perform abdominal CT immediately after surgery, and we will further refine this procedure in subsequent studies.

Figure 2

8. This lesion seems to be located in proximal S8. Which hepatic vein did you occlude?

Reply: In this patient we blocked the right hepatic vein.

Tables

9. How was the continuous number expressed (e.g., median (IQR), etc)? Please provide the

details.

Reply: The measurement data meeting the normal distribution were statistically described by mean \pm standard deviation, while the measurement data not meeting the normal distribution were statistically described by median and quartile.