Author’s response to reviews

Title: Intra-arterial ethanol embolization augments response to TACE for treatment of HCC with portal venous tumor thrombus

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Author’s response to reviews:

Dear Prof. Anne Menard and Prof. Dafne Solera,

Thank you very much for your decision letter and advice on our manuscript entitled “Ethanol Delivery for Portal Vein Tumor Invasion using Cone Beam Computed Tomography: A pilot study” (BCAN-D-17-00753). We also thank Prof. Daniel Sze and Prof. Avo Artinyan for the critical comments and suggestions. Accordingly, we have revised the manuscript, and all amendments have been highlighted in red. In addition, point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by Medjaden Bioscience Limited.

We hope that the revision is acceptable for publication in your Journal.

Yours sincerely,

Zhengyin Liao
Editor Comments:

1. We have noted that in the Methods section of your Abstract you have mentioned that this study was “retrospectively registered”. Can you please clarify if this is in relation to a trial registration. If so, please include all the trial registration information, such the registration number, where it was registered, the date it was registered and that it was retrospectively registered after the Conclusion section in the Abstract.

As your study fits the WHO definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes", your study must be registered as a trial. Please do the following:

Response: Our study is currently under registration in the Chinese Clinical Trial Registry (ChiCTR), which was established in 2005 and assigned to be the representative registry of China to join the WHO ICTRP in 2007. The Chinese Clinical Trial Registry is a non-profit organization. We acknowledge that we did not receive the final proved document.

a. Please retrospectively register the trial at one of the WHO approved registries listed in the WHO International Clinical Trials Registry Platform.
http://www.who.int/ictrp/network/primary/en/


b. Add the trial registration number, registration date and the words "retrospectively registered" to the end of the abstract.

Response: The registration number (ChiCTR-OPC-17012179) and date (July 29, 2017) have been added in the revised manuscript.

2. In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to CONSORT guidelines (http://www.consort-statement.org/) for reporting clinical trials. This is so your methodology can be fully evaluated and utilised. Please include a statement within your manuscript to indicate that your study adheres to CONSORT guidelines and include a completed CONSORT checklist as an additional file when submitting your revised manuscript.

Response: We have presented the CONSORT guidelines in the revised manuscript.

3. Please include all information regarding consent in the Ethical approval and consent to participate section, as well as the main text.

Response: This study was approved by the Local Ethics Committee of West China Hospital, Sichuan University. We can provide the approved document, if needed.
4. Please represent authors' names using their full initials, not their full name, in the Authors’ Contributions section. If there are any duplicated initials, please differentiate them to make it clear that the initials refer to separate authors.

Response: We have modified this part accordingly.

5. We would also like to ask for you to provide more justification for the contributions of WHG, TQQ, HJ, ZJF, XZ and Liao Zheng-yin, as currently they do not automatically qualify for authorship.

Response: We have modified this part in the Authors’ Contribution section. Each author in our manuscript provided a significant contribution.

An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. According to the ICMJE guidelines, to qualify as an author one should have:

a) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; AND

b) been involved in drafting the manuscript or revising it critically for important intellectual content; AND

c) given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; AND

d) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Anyone listed as an author must be included in this section. If you choose to change your author list you will need to fill out a change in authorship form and send it by email to the Editorial office to be approved by the Editor. The form can be found here: https://www.biomedcentral.com/getpublished/editorial-policies#authorship.

Anyone who contributed towards the article who does not meet the criteria for authorship can be acknowledged in the ‘ Acknowledgements’ section.

BMC Cancer operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Daniel Sze (Reviewer 1): Review: BMC Cancer
Ethanol Delivery for Portal Vein Tumor Invasion using Cone Beam Computed Tomography: A Pilot Study
BCAN-D-17-00753

Title: Unclear what "ethanol delivery" entails. Cone Beam CT is already standard of care for TACE and other liver-directed therapies, and this is not a new application. Consider changing to "Intra-arterial ethanol embolization augments response to TACE for treatment of HCC with portal venous tumor thrombus."

Response: We thank the reviewer for raising this critical issue. We have modified the title of the revised manuscript.

Abstract: Needs grammatical editing throughout

Response: The language of the whole manuscript has been re-edited.

Keywords: remove "transcatheter ethanol delivery"

Response: The keyword was deleted.

Background:

Page 5 Line 8 5th most common in incidence, 2nd most lethal

Response: We have modified this section, and added a new reference (Page 5, Line 2, Ref. 1 and 2).

Page 5 Line 18 Precipitation of bleeding is from exacerbation of portal hypertension, and is not limited to esophageal and gastric varices. Gastropathy, rectal and duodenal varices are other common complications. In addition, ascites is a common complication.

Response: The correction has been made in the revised manuscript (Page 5, Line 6).

Page 5 Line 43 What is the benefit from sorafenib? Cite statistics.

Response: The correction has been made in the revised manuscript (Page 5, Line 14-16, Ref. 9).

Page 5 Line 48 Add background and reference that PVTT was formerly considered a contraindication to TACE

Response: The correction has been made in the revised manuscript (Page 5, Line 16-19, Ref. 10).

Page 5 Line 54 Avoid abbreviations like "IHL" that are not standard.
Response: The abbreviation “IHL” has been replaced by intrahepatic lesions

Page 6 Line 13 Specify intraarterial, since other applications have involved intra portal

Response: No other applications were applied in these patients.

Page 6 Line 32 "transcatheter ethanol delivery (TED)" is too vague and nonstandard. Consider changing to "intraarterial ethanol embolization."

Response: TED has been changed into intraarterial ethanol embolization without abbreviation in the revised manuscript.

Methods:

Page 7 Line 12 Unclear - the control arm consisted of eligible patients who refused ethanol embolization?

Response: Patients were stratified into two groups according to their willingness. Hence, they chose the group that they themselves want to participate in. We have modified this content in the revised manuscript (Page 7, Lines 6-7).

Page 7 Line 38 What is the definition of "optimal coagulation and liver function"? Child class B could be INR of 5 or bilirubin of 20, which are certainly not optimal coagulation or liver function.

Response: These sentences have been modified in the revised manuscript (Page 7, Lines 18-19).

Page 7 Line 48 Which typical features? Consider using a standard system such as LIRADS, OPTN, or AASLD

Response: We thank the reviewer for the constructive suggestion. According to the global cancer incidence and mortality data, 55% of HCC cases are from China. Hence, we followed the guidelines established in The Expert Consensus on the Treatment Standards for Hepatocellular Carcinoma (the Chinese Consensus), which was published in 2009 by the Chinese Society of Liver Cancer, the Chinese Society of Clinical Oncology, and the Chinese Society of Hepatology Liver Cancer Study Group.

Page 7 Line 51 Why limit to 18 cm?

Response: Although huge HCCs are very common in China, we considered that it would be very dangerous to perform TACE if the diameter of HCC exceeds 18 cm.

Page 7 Line 60 Criterion 9 states patients must refuse sorafenib, but criterion 11 states they must have already been treated by sorafenib and failed - mutually exclusive?
Response: We apologize for this error. Patients who refused sorafenib or failed under sorafenib were included. This part was corrected in the revised manuscript (Page 8, Line 3).

Procedure:

Page 8 Line 49 Spell out FPD and all other abbreviations at first usage

Response: All abbreviations at first usage were checked and defined in the revised manuscript.

Page 8 Line 48 If feeding artery was treated with ethanol until occlusion, how could they embolize with gelatin sponge particles? The artery was already occluded. Figure 2 appears to show gelatin sponge embolization of the parent artery, not the PVTT feeding arteries.

Response: The feeding artery was treated with ethanol until the PVTT-feeding artery was nearly occluded. Figure 2 presents techniques of some special types of PVTT, which had several small tortuous feeding arteries or large arteriovenous fistulas.

Page 9 Line 21 How did authors limit gelatin sponge particles to 0.2-0.5 mm size? Fragmentation through a 3-way stopcock yields a much wider assortment of sizes.

Response: The gelfoam particles were sold by Fukangseng. Co. Ltd., which can provide difference sizes of particles. Emulsified sponge particles can easily pass through the 3-way stopcock and the narrower diameter of the microcatheter.

Page 9 Line 35 No analgesia or sedation?

Response: In general, local anesthesia is enough for TACE. All procedures were performed under local anesthesia at the groin. The patient’s feelings (e.g. pain, cough, palpitation and shortness of breath) were significantly important clinical symptoms during the TACE procedure. Hence, sedation was applied.

Page 9 Line 43 How did the authors decide who needed repeat treatment? Interval imaging? Original PVTT size or extent? Original dose of ethanol? Lipiodol uptake by CBCT? How many patients underwent repeat treatment?

Response: Corrections have been made in the revised manuscript (Page 10, Lines 2-6).

Page 10 Line 18 What tradition? What dose and concentration of epirubicin? What was the epirubicin dissolved in? What ratio of epirubicin solution to lipiodol? What maximum doses of epirubicin and lipiodol? Was gelatin sponge or other embolic mixed with epirubicin/lipiodol emulsion? What was the angiographic endpoint?

Response: These important details were added in the revised manuscript (Page 10, Line 17-20).

Page 10 Line 29 This paragraph is unclear and needs to be rewritten. If the PVTT-feeding artery could not be catheterized, how was "mixture injected in PVTT-feeding artery?" Was
TACE performed to stasis distal to small tortuous feeding arteries, followed by proximal injection of ethanol? Call out Figure 2.

Response: We thank the reviewer for the comment. This section has been modified in the revised manuscript, accordingly (Page 11, Lines 5-6).

Page 10 Line 56 How did the authors catheterize the "distal outflow vein?" Navigate through the PVTT from the arterial end? Direct percutaneous portal access? If blood is flowing away from the PVTT in the vein, how did the authors make the gelatin sponge stay in the vein? The figure illustrates embolizing the artery that feeds the outflow vein, not the outflow vein itself.
Response: This has been corrected in the revised manuscript (Page 11, Lines 12-13).

Page 11 Line 21 Port? What port? Did all these patients have intraarterial ports placed? If so, where was the infusion site - proper hepatic artery? This is certainly not "traditional TACE."
Response: This section has been modified in the revised manuscript.

Page 11 Line 54 Grading system would benefit from a figure and drawings, and additional details. For instance, grade is recanalization - recanalization of what? How complete? If a right lobe PVTT previously protruded into the main PV and retracted after treatment to allow recanalization of the main and left PV but the right PV is still completely occluded, is that grade 3? For grade 2, what degree of decrease is enough? In addition to diameter, is retraction of length measured? Likewise for grade 0, what if diameter is stable but length is increased? Certainly a response system is needed, but the described system is inadequately detailed.
Response: We thank the reviewer for the insightful suggestion. We ignored the length of the PVTT, because the length of the PVTT is usually affected by thrombus, which consists of thrombocytes. We have acknowledged this is an important limitation in the revised manuscript. Furthermore, we modified a section of this assessment system (Page 12, Lines 14-15).

Page 12 Line 24 What if lesion diameter decreased but there was still enhancing tumor?
Response: We considered the procedure to be effective if the diameter decreased by at least 20%, regardless if the tumor was enhanced or not.

Results:

Page 13 Line 5 Maximum of 50 mg epirubicin, or did all patients receive same dose regardless of tumor size? What volume lipiodol for TACE?
Response: The volume of lipiodol was 10 ml and the maximum volume for epirubicin was 50 mg. At our center, we consider that embolization plays a more important role than chemotherapy in patients with tumors exceeding 10 cm. In Europe, the maximal dose of epirubicin can reach 150 mg (Page 13, Lines 19-20). We have modified this section, accordingly.
Page 13 line 16 Did all patients undergo CT 2-7 days after treatment? If so, this should be described in Methods.

Response: These details have been presented in the Methods section of the revised manuscript (Page 12, Lines 20-21).

Page 13 Line 38 Use consistent significant digits.

Response: Inconsistent significant digits have been checked and modified in the revised manuscript.

Page 13 Line 60 Consider using a standard of toxicity, such as CTCAE v. 4.03, and SIR or CIRSE standards of procedural complications.

Response: These standards were not used in the study. These details could not be included at present, because the study has already been completed.

Page 14 Line 24 Stable disease should not be included as "response." Objective response is CR + PR. Adding SD is "Disease control rate."

Response: This section has been modified in the revised manuscript (Page 12, Line 18).

Page 14 Line 29 What is "clinical response rate?" Other response described in this paragraph is radiographic response, not clinical response. Does clinical response mean response by the PVTT grading proposed on page 11?

Response: This refers to the radiographic response. We have modified this section in the revised manuscript.

Discussion:

Page 14 line 54 What were the results of TED for HCC in reference 16?

Response: These results have been added in the revised manuscript.

Page 14 line 60 Stage of disease should have been described in Methods. No new data should be presented in the Discussion. Table 1 does not support claim that test patients had more advanced disease.

Response: We thank the reviewer for the insightful suggestion. The rigorous stage of patients should be assessed by preoperative PET-CT scan. However, since this study has already terminated, it would be impossible to apply such staging. We have modified these related sentences to provide a more precise description.

Page 15 line 57 TACE+TED OS was higher, but TACE alone OS was far lower than other figures published in the literature. Why?
Response: Some patients in the present study failed under sorafenib. Most importantly, a huge tumor size and dispersed nodules were common in our cohort (Page 15, Lines 17-79, 21).

Page 16 line 25 What is meant by control of ethanol doses? Amount of ethanol? Distribution of ethanol?

Response: The dose of ethanol was controlled according to the pain degree of the patient and the distribution of ethanol. This issue has been clarified in both the Methods and Discussion sections (Page 17, Lines 8-9).

Page 16 line 54 Well performed CT and MRI with dynamic imaging provides good flow information. The CTs in the figures appear to be performed with poor contrast bolus and too early timed arterial phase, so it may be true that CT and MRI performed at the authors' institution do not provide good flow information. Contrast-enhanced US can also provide very good PVTT diagnosis. Catheter angiography and CACT should not be relied upon for diagnostic purposes in this day and age.

Response: We acknowledge that our institution could not provide an ideal good flow of information. Among the possible explanations is the considerable daily amount of outpatients (more than 20,000 patients).

Page 17 line 5 The advantages of using CACT for liver-directed therapies has been well documented, and the superficial and incomplete description here could easily be replaced by a few good references.

Response: We have deleted some superficial descriptions and replaced these with new references.

Page 17 line 49 Many authors use other ratios. Why not use lower concentration of lipiodol?

Response: We thank the reviewer for the suggestion. We mainly refer to Gu’s (Ref. 15) viewpoint. He reviewed the ratios of lipiodol and ethanol. Furthermore, several studies have reported good results in treating HCC with transarterial injections of lipiodol:ethanol ratios between 3:1 and approximately 1:3. They have reported that the lipiodol:ethanol ratio can be adjusted according to the type of HCC. For single-nodule HCCs, a relatively high lipiodol ratio (such as 2-3:1) is appropriate. For refractory HCC, a relatively high ethanol ratio is appropriate to inhibit the double blood supply from the hepatic artery and portal vein, which have fistulae in between.

Page 18 line 6 In PVTT, often there is hepatofugal flow in the affected PV, and administration of lipiodol/ethanol passing through sinusoids would result in nontarget portal embolization. The references they describe here are not pertinent.

Response: Reference 15 has been added in the revised manuscript.
Any evidence that it diffuses within tumor cells? Previous paragraph just wrote on mechanism of action of ethanol on vascular endothelium. Authors should not make claim of diffusion unless they have proof or references.

Response: Two old references have proven that ethanol can diffuse from the tumor vasculature to tumor cells (Refs. 29-30).

Why include one sentence on angiogenesis? Did they study this? Are they proposing that angiogenesis is a factor in TED?

Response: We want to express that ethanol is a kind of embolism material that can prevent angiogenesis. We have added References 30 and 31, which provide experimental data that support this viewpoint.

Limitations:

Ethics of randomizing vs sorafenib? Need to review published results of sorafenib. Is repeated TACE cheaper than sorafenib?

Response: The cost for each patient receiving TACE is approximately 14,000 RMB per course (2,074.40 USD). By contrast, the cost of sorafenib is 6,667.90 USD per month. The difference is significant. Moreover, each Chinese individual has free medical care insurance provided by the Chinese government, which fully covers TACE, but does not cover sorafenib. We have added a relevant reference for this issue (Ref. 33).

Table 1

Cirrhosis, ascites can be graded rather than be binary.

Response: We have modified this part in the revised manuscript.

Was tumor size distribution normal? If not, should use median, not mean

"Angiography of PVTT feeding-artery" is not normally reported, and I am not sure what these numbers mean

Response: Many patients are diagnosed with multiple lesions. Hence, we could not measure all the diameters of these lesions. Therefore, we chose the largest one for each patient. We have changed mean size to median size in the revised manuscript.

Table 3

Adverse events should be graded from 0 to 5, not binary.
Response: We thank the reviewer for the suggestion. We acknowledge this limitation. However, all these data could not be retrospectively recorded now.

Figure 2
How does the port fit in to this procedure?
Response: A method similar to TACE was applied. The precision has been indicated in the Figure Legend.

Figure 3
A3: Arterial phase image is very early and does not show PVTT enhancement. Aorta is not very enhanced, suggesting weak bolus.

B2: Any evidence of arteriportal shunting?

C: Any followup imaging of response? Did lipiodol wash out of PVTT faster than from intraparenchymal tumor?
Response: We acknowledge the shortcomings of our Institution regarding the technique of CT scan. For this patient, there was no arteriportal shunting. However, it was present in some of the included patients. Follow-up images have been added in Figure 3 (D1-3).

Avo Artinyan (Reviewer 2): The study by Yang et al. compared the efficacy of TACE+TED vs TACE alone in patients with HCC with portal vein tumor thrombus, a group of patients who are in general poor candidates for resection and transplantation. The study demonstrated a response and survival benefit for TACE+TED compared to TACE alone.

The manuscript in general was well written, well organized. The methodology was well-described, in particular the procedural details which will be useful to readers who wish to replicate the authors' technique. The interpretation and conclusions were mostly valid and appropriate for the results.

Specific criticisms and suggestions follow:

1. The study was not randomized and patients were allowed to select their procedure. The authors recognize this limitation and also point out that the TACE+TED group had more advanced tumors which make their results even more significant. However, the TACE+TED group had a significantly higher proportion of Childs A patients than the TACE alone group. We know that survival in these patients is related not only to the cancer but the underlying cirrhosis. I would ask the authors to provide a stratified analysis in only Childs A patients in addition to the results they have already provided.

Response: We thank for the reviewer for the thoughtful suggestion. To meet this request, we have changed the title into a more precise description. In addition, “TED” was changed into
intraarterial ethanol embolization without abbreviation. It is clear that a higher proportion of Child A patients in the treatment group can favor a longer overall survival. This bias may have been due to the willingness of the patients (Page 19, Lines 16-20). We have added these statements in the limitation section. Furthermore, a subgroup analysis has been added in the Results section (Page 14, Lines 14-16).

2. The number of course of treatment did not appear to be standardized and patients in the TACE+TED group had more courses of treatment. We know from the TACE literature that there is some benefit to repeated TACE in HCC. I think this is a limitation that the authors should discuss.

Response: We thank the reviewer for the constructive suggestion. Clearly, repeated TACE in HCC led to better results. Hence, we added this limitation in the revised manuscript (Page 19, Lines 16-20).