Round-1

MODIFY DESCRIPTION

Dear Editor:

We appreciate the reviewers and you for carefully reading and thoughtful comments on this draft. Those comments are all valuable and helpful for revising and improving our paper, as well as the important guiding significance to our research. We have carefully taken the comments into consideration in preparing our revision. Minor language polishing has been proofed. The following summarizes our response.

Thanks for all the help.

Best wishes,

Xuan-Hui Yan

Peer-review report

Reviewer #1:

1) it will be much better if you conduct a control study comparing your results with the results of standard of care therapy or TIPS without planting seeds;

This is a good advice, and we envisioned designing a control study before the study began. But there is no standard treatment paradigms for patients with mPVTT and CPH in clinical practice. If without treatment, they would die within a few months, so we can not take a blank control and it is not medically ethical. Performing TIPS without planting seeds means that there is no effective PVTT suppression after the operation, and the incidence of postoperative complications including shunt stenosis, recurrence of portal hypertension and distant metastasis of tumor would be greatly increased, so we adopted what we considered was the most effective treatment for the majority of patients, and the patients who rejected the seeds implantation did not reach the effective sample size. Because tumor related studies can use survival time as "gold standard" of evaluation, we finally took a single-arm retrospective cohort study with historical control.

2) in figure 2a, the site of thrombosis should be indicated with an arrow.

I have revised the corresponding part of the figure. Thanks for your advice.

3) in figure 2g it is not clear where the thrombus is located;

I have appropriately readjusted the location and figure annotation. Because in the operation the PVTT in the vessel was grabbed and aspirated as much as possible, there was few residual PVTT in the vessel. Thanks for your comment.

4) the introduction or discussion section should better describe the mechanism of action of the seeds.

In discussion section, I have already described some of the mechanism of the seeds. Apart from that, I have made appropriate additions to the description. Thanks for your suggestion.

Reviewer #2:

1) In particular, neither the Introduction nor the Discussion alludes to outcomes for other treatments in patients with mPVTT, such as radioembolization, radiation, or systemic therapy, with the understanding that TIPS might be required as an adjunct.

Thanks for your considerable comment. For the treatment of mPVTT, our patients only received radioactive seed strand implantation and some of them received targeted therapy such as sorafenib or lenvatinib. In consideration of some high-quality studies[1-3] which showed that sorafenib did not achieve satisfactory outcomes in the treatment of HCC with PVTT, our article removed the analysis of targeted therapy. However, this is our thoughtlessness and negligence, and now I have added the description and analysis of targeted therapy in the methods, results and discussion section accordingly. Apart from that, our patient did not receive other treatments such as radioembolization or radiation. By the way, TIPS is an adjunct treatment for mPVTT, but an important and effective treatment for decompensated CPH.

I have made the corresponding revision. Thanks again.

References:

1. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific

region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25-34. doi:10.1016/S1470-2045(08)70285-7
2. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol*. 2012;57(4):821-829. doi:10.1016/j.jhep.2012.06.014
3. Zhu K, Chen J, Lai L, et al. Hepatocellular carcinoma with portal vein tumor thrombus: treatment with transarterial chemoembolization combined with sorafenib--a retrospective controlled study. *Radiology*. 2014;272(1):284-293. doi:10.1148/radiol.14131946

2) How was refractory variceal bleeding defined? Had patients failed prior medical and/or endoscopic therapy?

This may be an ambiguity in my description of method section. One of the indications for the procedure is failure of prior conservative treatment for cirrhosis-related decompensated events such as EGVB or refractory ascites/hydrothorax. Prior conservative treatments include medical and/or endoscopic therapy. I have revised it accordingly. Thanks for your comment.

3) How was recurrent CPH defined?

The recurrence of CPH was determined as recurrent EGVB or hepatic ascites/hydrothorax, which principally resulted from shunt or intra-stent stenosis. I have made description in the study design section. Thanks for your comment.

4) I am not sure that the denominators for rates of recurrent CPH and for shunt stenosis at 1 year and beyond are correct, since half of the patients at that point were alive. Please reconsider how to calculate these outcomes.

Both the rate of shunt stenosis and the recurrence rate of CPH are cumulative. The denominator of the rates is the total number (83) of patients at baseline. I have made the corresponding revision. Thanks for your comment.

5) It is interesting that BCLC Stage D patients were treated, since they are typically considered for supportive care only. The authors may wish to comment on their median survival (which appears to be 6 months) and whether they really benefitted

from any intervention.

BCLC stage D means Child-Pugh grade C, with very poor liver function. These patients typically receive supportive care only, but we treat them according to their condition and wishes. As we know, Child-Pugh grade C is not a contraindication for TIPS. In HCC patients with PVTT the median survival is only 2.7–4.0 months without treatment, and poor liver function and cirrhosis-related decompensated events would accelerates the death. Although patients with BCLC stage D had a median survival of 6 months from the survival curve, we hope them to benefit from treatment and further relevant studies are warranted to follow and expand. Thanks for your comment.

6) It is interesting that radioembolization was not used in any of the cases. Is this a practice choice at the author's institution?

Radioembolization was approved in China only last year, and has yet to gain much practice in China. Our institution has not performed any practice about radioembolization. Thanks for your comment.

Science editor:

1) It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

I have revised the references according to the above suggestion. Thanks.

2) The site of thrombosis should be indicated by an arrow.

I have revised the corresponding part of the figure. Thanks for your advice.

Round-2

MODIFY DESCRIPTION

Dear Editor:

Many thanks to science editor and peer reviewers. This considerable comment is not only of great help to improve our paper, but also of guiding significance to our future clinical management. Careful revision with highlight in red font was taken in our manuscript. The following summarizes our point-by-point response.

Thanks for all the help.

Best wishes,

Xuan-Hui Yan

Re-review report

Reviewer #1:

1) I have no additional comments.

Thanks for your great help with our paper.

Reviewer #2:

1) The manuscript has been considerabley improved by the revisions. It would be helpful to point out in the Discussion that radioembolizaton was not approved during the time of the study, but it could considered for combination treatment in the future.

Thanks for your recognition and considerable comment. It is our shortcoming and regret that we failed to apply radioembolization in our study and clinical management. I have added the corresponding description in the limitation part of the Discussion with highlight in red font. Thanks again.