

Peer Review File

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Reviewer A

This manuscript details a study of 13 patients with HCC and cirrhosis and small FLR who underwent PVL with PVE after TACE in order to undergo successful surgical resection.

While the authors should be commended for successfully performing a curative resection for initially unresectable HCC, I have a few concerns regarding this manuscript:

How “experimental” is this method? Everything described in the manuscript is well established and commonly used over the past decade or two.

Reply: We use the term "experimental" because no one has previously reported surgical procedures involving laparoscopic portal vein ligation and portal vein peripheral embolization to increase the volume of the remaining liver, hence it is referred to as an exploratory experiment.

Changes in the text:(see Page 1, line 1-2)

How many patients had this same procedure who were not successfully operated on? We may be seeing a small numerator that is associated with a large denominator of unsuccessful management using this same technique.

Reply: There were totally 13 patients who underwent this procedure, all of whom successfully completed the conversion therapy and received surgical resection.

This is very complex management. The current gold standard is a single treatment of transarterial radioembolization (Y90) which allows for tumor effect (better than TACE) as well as contralateral hypertrophy (of greater extent than PVL/PVE) with the additional benefit of slow defunctionalization of the ipsilateral lobe.

Reply: Thank you for your opinions and suggestions. Since Y90 radioembolization is still in the promotion stage in China, our hospital has not yet routinely carried out this treatment method. Currently, we mainly focus on PVE/PVL and ALPPS treatments, which is also one of the limitations of this article. We will add this point in the discussion section.

Changes in the text:(see Page10, line204-208)

This is a relatively small case series of very minimal impact with only historical value as this is not a standard method of treatment. If the center had access to all of the advanced procedural and medical techniques described in the manuscript, they certainly can have access to the current best treatment method.

Reply: Our research center is capable of performing PVE, PVL, and ALPPS surgeries. However, in clinical practice, we have found that relying on a single method is often insufficient. Therefore, by understanding the principles and pros and cons of the aforementioned methods for promoting liver tissue regeneration, we attempt to combine their advantages through a new laparoscopic technique. This approach also aims to better avoid their drawbacks and adverse reactions. We believe this represents an exploration into new surgical techniques, for which there are currently no similar reports internationally.

Reviewer B

1. Line 29 - prognosis is extremely poor, Line 30 - only curative treatment is surgical -- both these are inaccurate phrases. Prognosis is okay or relatively poor as compared to some other cancers and transplant or ablation (for small lesions) are also curative.

Reply: We have already made modifications in the revised manuscript, thank you for your suggestion.

Changes in the text:(see Page 3, line 52-53)

2. What you have reported is not ALPPS or modified ALPPS. Your technique is a 3-stage process. 1st is TACE. 2nd is PVLPVE. 3rd is Hepatic resection. You CANNOT claim as ALPPS as patient is discharged home between step 2 and step 3. In ALPPS, patient stays in hospital most times and usually is about 5-14 days between the 2 steps of ALPPS. So, to me, your technique is TACE + 2 stage hepatectomy with first stage having PVL + PVE. You should read a review on ALPPS -PMID: 32632388- to understand variations of ALPPS and see if you agree with my comment or criticism that this technique should not be called as ALPPS.

Reply: We agree with your view that this is not a modified ALPPS approach; we prefer to call it a new conversion treatment strategy consisting of three steps: TACE + laparoscopic portal vein ligation and embolization + hepatectomy surgery. We had made revisions in the revised manuscript.

Changes in the text:(see Page 1, line1- 2; page 2, line 27-29)

3. You discuss that ALPPS has good hypertrophy in volume. True. But is this hypertrophied liver truly function? In simple terms - the larger volume does not equate to adequate functional liver. Pls see - PMID: 37064831 - and discuss this important issue that is not widely discussed and reported by many.

Reply: Thank you for your suggestion. We have read the literature you recommended, and we agree with the question you raised. Increased liver volume does not necessarily equate to liver function, and we have included this in the discussion.

Changes in the text:(see Page 8, line 164-168)

4. You rightly discuss the delay in treatment with simply PVE alone and thus doing TACE in your patients. However, your patients had to wait about 2 months before treatment finished (all 3 steps) and this in itself is also considered a bit of delay. Pls discuss - PMID: 38092430-.

Reply: Thank you for your question. We believe that the delay in treatment caused by PVE is due to the fact that isolated PVE is insufficient to completely block the blood flow to the tumor, thus increasing the probability of tumor progression. By performing TACE, we reduce the arterial blood flow, and by combining laparoscopic PVE and PVL, we further block the blood flow from the portal vein, which can further reduce the blood supply to the tumor tissue, thereby lowering the probability of tumor progression. However, this does not guarantee that the tumor will not progress. In the future, we will improve the operation process to try to shorten the waiting time for patients, making the entire process safer.

5. I read that 2 of your patients died within 13 months. Unsure if these deaths were 30 day or

90 day or within 12 months. If the deaths are within 12 months than one can argue that the treatment was futile or wasted from macro point of view. Doing so many intense treatments and patient staying in hospital for so many days, simply dying in 1 year - this patient was better served without surgery but decent quality of life before death - Please discuss these issues - PMID: 35368234.

Reply: Among the 13 patients, the circumstances of the 2 who died were as follows. The first patient experienced intrahepatic recurrence more than 4 months after surgery, and then began treatment with the lenvatinib. The patient died due to a sudden upper gastrointestinal hemorrhage at 6 months post-surgery, not because of tumor progression. The second patient experienced intrahepatic recurrence at 18.5 months post-surgery and died due to widespread systemic metastases at 24.5 months. We express deep regret for the recurrence in the first patient within 1 year post-surgery. This is a new conversion therapy technique, and the patient successfully obtained the opportunity for curative surgery after treatment, but this does not mean that patients will not experience recurrence post-surgery. The quality of life for patients after surgery is still quite good, but unfortunately, the first patient died due to upper gastrointestinal hemorrhage.

6. TACE helps in ischemic preconditioning. This issue is omitted from your report. Please add it as a benefit of TACE procedure.

Reply: Thank you for your opinions and suggestions, we have added this to the revised manuscript.

Changes in the text:(see Page 10, line 196-198)

Reviewer C

This is an interesting study reporting a novel combined surgical/IR approach to increase FLR. This is an interesting and novel approach.

My comments are relatively minor but should be addressed before publication:

1. The conclusion needs to be softened. You cannot claim that this is both safe and effective. It showed good results in this initial small series but there have been no comparative studies and this is a small cohort.

Reply: Thank you for your suggestion, we have modified the conclusion in the revised article.

Changes in the text:(see Page2, line 42-44; page 11, line 226-229)

2. The study does not have a limitations paragraph at all. There are a few sentences that discuss possible procedural limitations but the study itself has limitations (small sample size, retrospective, no comparative group). These limitations don't preclude publication but must be discussed.

Reply: Thank you for your suggestion, we will add a paragraph to discuss the limitations of this article in the final part of the discussion.

Changes in the text:(see Page 11, line 235-239)

3. Could the authors speculate who they feel this procedure is best for? Certainly not all patients need this, with PVE and HVD now most patients would be fine with single stage surgery.

Reply: The criteria for selecting patients mainly involve two aspects. On one hand, from the surgical perspective, patients are not candidates for radical resection due to insufficient residual liver volume. On the other hand, from the oncological perspective, patients have a high likelihood of recurrence post-surgery, such as in cases of vascular invasion, multiple lesions, or excessively large tumor diameters. Of course, we also communicate with patients and their families before surgery, respecting their right to make autonomous decisions.

4. How will this surgery affect those receiving neoadjuvant systemic therapy? Will they have to be off systemic therapy for the whole time between stages?

Reply: Our patients generally suspend systemic treatment during the intervention process and will resume the use of targeted drugs and immunotherapy after assessing the patient's condition post-surgery.

5. The authors only discuss PVE but the new hepatic venous deprivation is a superior technique. That should be discussed relative to this new approach.

Reply: Thank you for your question. Hepatic venous deprivation is a very new technique, and there are not many reports internationally. There is still some controversy about it, and there is no standardized procedure yet. There is also insufficient data on its long-term efficacy. Our center has not yet routinely performed this technique, which is why it was not mentioned in the discussion. Thank you for reminding us, and we will add a discussion about this technique to the discussion.

Changes in the text:(see Page 10, line 200-203)

6. Why do patients get TACE first? Is this for tumor targeting or for actual treatment? We use very little TACE anymore except to enhance radiographic visualization of the tumor. Modern LRT like Y90 seems to have better outcomes. Please discuss why TACE.

Reply: For large hepatocellular carcinoma, the tumor has abundant arterial blood supply. Studies have shown that TACE can achieve good tumor reduction effects and control tumor progression. We use TACE initially to control the arterial blood supply to the tumor, preventing tumor progression during treatment, and on the other hand, to reduce the tumor volume, creating conditions for subsequent surgery. Additionally, some studies report that after blocking the portal vein blood flow, arterial blood flow will compensatorily increase, which is why TACE treatment is necessary to reduce arterial blood flow. Regarding Y90, since this technology is still in its infancy and promotion stage in China, our hospital has not yet started this service.

Changes in the text:(see Page 10, line 204-208)