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Professor Ze-Mao Gong

Science Editor, Editorial Office

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Dear Professor Gong,

Revised manuscript (Manuscript NO. 19172)

Enclosed is our revised manuscript entitled, “Preoperative portal vein embolization for hepatocellular carcinoma.” A point-by-point response to the comments made by the reviewers, is also enclosed. We have also revised the manuscript according to the “Guidelines and Requirements for Manuscript Revision: Topic Highlight”. As a result, we have added the “Core tip” and one more key word in the manuscript.

I hope our replies to the various comments are satisfactory and that our manuscript is now acceptable for publication.

Sincerely yours,

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Point-by-point replies to the comments made by the reviewers.

Reviewer #1 Comment 1

- According to the title the author states that the aim of the article will be a review about preoperative vein embolization for hepatocellular carcinoma. This aim is insufficiently developed during the manuscript leading a poor discussion about how to manage future liver remnant for different liver tumors, therefore the aims of this article are not fulfilled.

The topic that we are dealing with in this manuscript is PVE for cases of HCC with underlying cirrhosis. Actually, PVE is widely used for patients with hilar cholangiocarcinoma, and especially those with colorectal liver metastases, but here, we focus on the indications of PVE for HCC patients with underlying chronic liver disease.

Reviewer #1, Comment 2

- Through the article the growing of the FLR in terms of percentage is never mentioned. When addressing any type of major liver resection particularly in patients with HCC in cirrhotic livers, the specific growth of the FLR must be detailed.

Thank you for this significant comment of the reviewer. The indication for major hepatic resection is judged by the ratio of the volume of the future liver remnant (FLR) to the total liver volume, but we have not referred to the interval between the PVE and hepatectomy or to the hypertrophy rate of the FLR. Therefore, we have added a new paragraph as follows:

Page 10, lines 7-14, (new)

Clinically, the percent increase in the volume of the FLR in cirrhotic livers within the first 2-3 weeks after PVE is reported to in the range of 5 to 10%[10-12], and the hypertrophy ratio of the FLR has also been reported to be approximately 1.3 to 1.5[10, 11, 13]. Others have reported a rate of hypertrophy in cirrhotic livers of 9cm^2/day at 2 weeks[14]. These figures are significantly smaller than those reported in non-cirrhotic livers[14-17]. Nevertheless, most previous reports have documented the safety of the PVE procedure and of subsequent major hepatic resection even in cases with a cirrhotic liver[18-20].

Reviewer #1, Comment 3

- In the segment “Clinical implications of PVE”. In the first paragraph the author states ¨ it may be deduced that PVE may not have an adverse effect on oncogenesis in the FLR ¨. There is enough evidence (by authors like Elias, Kokudo and Van Gulik) supporting that portal vein embolization is associated with increased tumor growth rate and new tumor appearance in the FLR. In a different paragraph of the same segment the authors claim an adverse effect of PVE on tumor growth, therefore contradicting themselves.

We admit that the description was misleading. In the paragraph in question, we referred to the risk of recurrence of a tumor after hepatic resection. As the recurrence-free and overall survival rates between the PVE+ and PVE- groups were similar, we speculated that the tumor recurrence pattern and treatment after recurrence may not differ significantly between the two groups. To convey our actual intended meaning, we have added the following explanation in the revised manuscript:

Page 10, lines 19-21 (new)

It may be deduced that PVE does not have any adverse effect on the risk of oncogenesis (i.e., intrahepatic HCC recurrence or development of new primary lesions) in the FLR after hepatic resection.

Reviewer #1, Comment 4

- The sub-segment “Sequential TACE and PVE and two-staged hepatectomy” starts by describing tumor growth after PVE. Even more the author mentions that a recent meta-analysis reported that about 15% of patients could not undergo curative resection after PVE, and about half of these patients showed severe tumor progression or extrahepatic tumor spread. This manuscript already has a sub-segment for this information called “tumor growth after PVE” All this information should be written in this segment. In addition regarding tumor growth the author only mentions the meta-analyses by the group of Long R. Jiao publish in the Annals of Surg in which they report that half of the 15 % of patients with PVE could not undergo curative resection for tumor progression. However there is broad evidence supporting that tumor progression after PVE can reach up to 30% of patients (Van Gulik et al in the Annals of surgery in 2012) and this strong evidence should also be presented here.

We appreciate the reviewer’s critical comments. According to the reviewer’s recommendation, we have organized the descriptions concerning tumor growth after PVE in the appropriate section. Of course, we have read the report of Hoekstra LT and van Gulik (Ann Surg 2012). Unfortunately, most papers dealing with this issue have investigated tumor growth after PVE mainly in patients with colorectal liver metasatses. On the other hand, in our study, the subjects were HCC patients. Thus, some HCC

patients with cirrhosis may have dropped out because of intrahepatic tumor progression, some because of worsening of the liver functional reserve, and some because of the absence of any beneficial effect of PVE. We speculate that the circumstances may differ between HCC patients and patients with colorectal liver metastases.

We have revised the manuscript as follows:

Page 12, lines 5-8 (old)

Several previous reports have addressed this issue, however, concluded conflicting results have been reported;[26-29] however, accumulating evidence suggests an adverse effect of PVE on tumor growth.

Page 11, lines 12-16(new)

Several previous reports have addressed this issue. Despite some conflicting results, accumulating evidence suggests an adverse effect of PVE on tumor growth[34-38], although most previous studies investigating the risk of tumor growth after PVE have dealt with patients having colorectal liver metastases.

Page 11, lines 17-21 (the paragraph has been transferred)

Tumor growth after PVE, especially tumor growth in the nonembolized FLR and/or extrahepatic tumor progression, may preclude curative resection. Indeed, a recent meta-analysis reported that about 15% of patients could not undergo curative resection after PVE, and about a half of these patients showed severe tumor progression or extrahepatic tumor spread[19].

Page 12, lines 1-3 (new)

As mentioned above, the risk of tumor growth after PVE may counteract the beneficial effect of PVE. Therefore, measures to prevent tumor growth during the waiting period before hepatectomy should be considered.

REFERNCES (new)

38 **Hoekstra LT,** van Lienden KP, Doets A, Busch OR, Gouma DJ, van Gulik TM. Tumor progression after preoperative portal vein embolization. Ann Surg 2012; 256: 812-817 [DOI: 10.1097/SLA. 0b013e3182733f09.]

Reviewer #1, Comment 5

- The sub-segment “Sequential TACE and PVE and two-staged hepatectomy” Though I find a good contribution to the manuscript the mentioning of two publications in which TACE plus PVE for HCC had good results, the author lefts unmentioned the risk of embolizing portal and arterial flow in the same hepatic area and this for me is considered paramount when discussing new techniques.

Thank you for the critical comment. As the reviewer has correctly pointed out, liver infarction is a potential concern. However, our previous study confirmed that necrosis of the non-cancerous liver parenchyma was minimal. We speculate that recanalization of the hepatic artery may abrogate the possible adverse effect of dual embolization. We think that this discussion is very important, and have referred to this issue as follows:

Page 12, lines 20-24 (new)

A potential concern of sequential TACE and PVE is infarction or necrosis of the non-cancerous liver parenchyma. Our previous results showed, however, that necrosis of the non-cancerous liver parenchyma in the resected specimens was minimal. Possibly, recanalization of the hepatic artery abrogates the possible adverse effect of dual embolization.

Reviewer #1, Comment 6

-The Segment “basic aspects of PVE” should be located before “clinical implications of PVE”. The whole distribution of the segments should be revised.

According to the recommendation of the reviewer, we have re-arranged the sections. As a result, “basic aspects of PVE” has been placed ahead of “clinical implications of PVE.” The arrangement of the references has also been revised.

Reviewer #1, Comment 7

- In the sub-segment ”PVE vs PVL vs ALPPS” second row of second paragraph the author misspells ALLPS instead of ALPPS. ALLPS does not exist in the abbreviation paragraph and I assume the authors referred to the ALPPS procedure.

Thank you - we have corrected the typographic error.

Reviewer #1, Comment 8

- The article is a review of PVE for HCC but the author left unmentioned Child score or the specifics indications and contraindication of the PVE in this kind of patients.

PVE is a preoperative treatment carried out prior to major hepatic resection. Therefore, this procedure is contraindicated in Child-Pugh class B/C patients.

We have appropriately revised the text in the manuscript as follows:

Page 7, lines 7-11 (old)

The indications of PVE for HCC are determined by the relationship between the liver functional reserve (indocyanine green retention rate at 15 minutes [ICG-R15]) and the volumetric ratio of the FLR (Figure 1).[4] An ICG-R15 value of >20% is generally a contraindication for major hepatic resection and therefore not an indication for PVE.

Page 7, lines 1-8 (new)

The indications for PVE in cases of HCC is determined by the relationship between the liver functional reserve and the volumetric ratio of the FLR to the total liver volume. In general, major hepatic resection is contraindicated in Child-Pugh class B or C patients; these patients are therefore also not suitable candidates for PVE. In addition, Child-Pugh class A patients should undergo assessment by the indocyanine green retention rate at 15 minutes [ICG-R15]. An ICG-R15 value of >20% is generally considered as a contraindication for major hepatic resection and therefore also for PVE (Figure 1)[4].

Reviewer #1, Comment 9

-Also the article disregards PVE in condition of hiperbilirrubinemia and the recommendation of chemotherapy during the interval period between the PVE and the hepatic resection. This could be a great addition to this article.

Again, we are focusing on PVE for HCC patients, and not for patients with colorectal liver metastases or hilar cholangocarcinoma, in our present manuscript. In general, chemotherapy is not administered as a bridge therapy between PVE and subsequent hepatic resection in HCC patients. Besides, HCC patients with poor liver functional reserve, as reflected by hyperbilirubinemia, are not suitable candidates for major hepatic resection.

Reviewer #2, Comment 1

-I totally agree that data supporting ALPPS in HCC with cirrhosis are still very weak; however, a few reports have been published specifically on the matter, and I would suggest to cite at least the paper by Vennarecci et al, Eur J Surg Oncol 2014.

We gratefully appreciate the reviewer's comment. Indeed, some papers have reported that ALPPS could be safely performed in HCC patients with cirrhosis. Therefore, we have revised the relevant text in the manuscript as follows:

Page 14, lines 12-15 (new)

The ALPPS series included some patients with HCC (about 10% of the patients), and some recent papers have documented that ALPPS can be safely performed in HCC

patients with cirrhosis; however, no detailed data are available because of the small number of patients[5, 6, 39].

Reviewer #2, Comment 2

-The authors states at the end of the introduction that alternatives to PVE would be discussed, however only ALPPS is effectively discussed. I would suggest to add a small paragraph about radioembolization, as at least one paper exist specific to HCC (Edeline et al, Ann Surg Oncol 2013), and another paper make an interesting comparison with PVE (Garlipp et al, Hepatology 2014).

Thank you for the kind recommendations. According to the reviewer's suggestion, we have added a paragraph describing radioembolization as an alternative to PVE. We have revised the relevant teext as follow:

Page 13, line 7(new)

Alternatives to PVE

Page 14, lines 18-Page 15, line 4 (new)

2. Radioembolization

Our group has applied a combination of preoperative TACE and PVE to prevent tumor progression during the waiting period before surgery. An alternative to this strategy is

radioembolization, which treats the tumor in the embolized lobe along with induction of contralateral hypertrophy. An increase in the size of the non-embolized lobe by 42% after radioembolization has been reported in cirrhotic livers[49]. A comparison of PVE and radioembolization in non-cirrhotic livers has shown that PVE induces a greater degree of hypertrophy of the FLR than that radioembolization[50]. Nevertheless, this novel procedure is promising, as it enables both embolization and treatment of the tumor(s) in a single step.

Reviewer #2, Comment 3

-A strange sentence at the end of 1st paragraph page 12: “Several previous reports have addressed this issue, however, concluded conflicting results have been reported; 26-29 however, accumulating evidence suggests an adverse effect of PVE on tumor growth.” Suggestion to modify this for “Several previous reports have addressed this issue. Despite some conflicting results, accumulating evidence suggests an adverse effect of PVE on tumor growth.”?

We appreciate the reviewer’s comment. According to the recommendation, we have revised the relevant sentence as follows:

Page 12, lines 5-7(old)

Several previous reports have addressed this issue, however, concluded conflicting results have been reported; [26-29] however, accumulating evidence suggests an adverse

effect of PVE on tumor growth.

Page 11, lines 12-16(new)

Several previous reports have addressed this issue. Despite some conflicting results, accumulating evidence suggests an adverse effect of PVE on tumor growth[34-38], although most previous studies investigating the risk of tumor growth after PVE have dealt with patients having colorectal liver metastases.