

Format for ANSWERING REVIEWERS



April 25, 2015

Dear Editor,

Please find enclosed the edited manuscript in a Word format (file name: 17535-review.doc).

Title: A novel 3-dimensional virtual hepatectomy simulation combined with real-time deformation

Author: Yukio Oshiro, Hiroaki Yano, Jun Mitani, Sangtae Kim, Jaejeong Kim, Kiyoshi Fukunaga, Nobuhiro Ohkohchi

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17535

We would like to thank the reviewers for their careful and thorough reading of this manuscript and for their thoughtful comments and constructive suggestions, which have helped us improve the quality of this manuscript. Our responses follow (the reviewer's comments are in italics).

According to the reviewers' comments, I have revised my manuscript. The yellow highlighted parts are additional sentences, references, and reference numbers. The green highlighted parts throughout the manuscript refer to the questionnaires regarding the Liversim, as Reviewer 2 suggested, and include additional sentences, figure 5, and the legend for figure 5.

(1) Reviewed by 00058443

Comments to Authors

Please have my humble comments. Virtual hepatectomy by using 3-dimentional imaging can provide precise visual contact and will play key role during liver surgery. Comprehensive understanding of liver anatomy, detailed pre-operative dynamic image study, and intra-operative Doppler ultrasound are still the standard methods in hepatectomy. The Liversim would be more useful for complex hepatectomy, non-anatomical hepatectomy and laparoscopic hepatectomy. Hepatectomy without aid of 3-D virtual hepatectomy simulation combined real time deformation would generate same outcome in this case series. But, it does not indicate that the method described in this manuscript is not useful. On the contrary, new innovative softwares in virtual system will be created step by step in the future, and should not be the reason to reject this paper. This paper is worth to be accepted and published in World Journal of Gastroenterology.

Response to reviewer

I appreciate your insightful comments about my manuscript. I agree that new innovative virtual software, such as our Liversim software system, should be developed for hepatobiliary surgery and to serve humankind in the future. Although Liversim is still in the preliminary stages, we will improve it to a high quality level in the near future.

As you pointed out, there were unfortunately no significant differences in the perioperative outcomes between the SYNAPSE VINCENT group and the Liversim group. However, we indeed felt able to perform a useful, comfortable hepatectomy of safe duration using Liversim, and although our sample of Liversim cases included only 11 patients, an accumulation of the Liversim cases may affect the difference in the preoperative outcomes between the two groups in the future. Furthermore, we think that Liversim was not clinically inferior to SYNAPSE VINCENT and that Liversim is useful for educating surgical residents and medical students about performing a safe hepatectomy. Additionally,

the primary advantage of Liversim was that the surgical team was able to use visual information that was identical to the patient's liver anatomy to determine the appropriate surgical procedure.

(2) Reviewed by 03261278

Comments to Authors

The authors developed a novel 3D virtual hepatectomy simulation software "Liversim" that enables real-time deformation of the liver intraoperatively and described its utility in 11 patients. Although the images appear accurate and intuitive, the presentation requires some refinements.

1. The authors aimed to evaluate the "usefulness" of Liversim in this study; however, it is unclear in the paper. Figures 4A and 4B and the video does demonstrate the similarity between the created images and the actual transection plane. If the authors wanted to show that there were no discrepancies between simulation and actual surgery by using Liversim, they should have presented images of other cases as well. If the authors' aim was to demonstrate its usefulness in surgical education (as mentioned in Discussion), they should have invited residents or medical students Liversim in the study and attempts should have been made to compare their level of understanding liver surgery with and without the use of Liversim. Moreover, the authors stated that their team was "able to discuss several critical points" by the Liversim images during hepatectomy: Please describe those critical points because that might be the heart of their presentation. My impression is that Liversim may not add much to experts because they can foresee most of the time, without the aid of Liversim, which portal pedicle or hepatic branch would show up after any given parenchymal dissection. I agree that Liversim has several advantages in clinical practice but what is the most striking point that the authors want to tell the readers?

Response to reviewer

I appreciate your insightful comment and fully agree with you. I think that Liversim may not be necessary for experts or skilled surgeons such as you. In our experiences with Liversim, during the ongoing resection process, there were no large discrepancies (such as the emergence of 4th branches of the portal vein covered in Glisson's sheath or the hepatic vein or the depth and direction of the resection line) between our simulation and the actual surgery. Therefore, we were able to determine the intrahepatic vessels preoperatively. Accordingly, Liversim can be useful for young hepatic surgeons and medical students to help them understand the liver anatomy in preparation for hepatectomy, as you pointed out. The questionnaires about the usefulness of the Liversim were distributed to the surgical residents and medical students to assess their understanding of liver surgery using the Liversim. Therefore, we added information about the questionnaires to the manuscript (the parts highlighted in green in the abstract; the introduction, methods, results, and discussion sections; and Figure 5). If you feel that this additional information is not necessary, I will remove it.

Unfortunately, there were no significant differences in the perioperative outcomes between the SYNAPSE VINCENT group and the Liversim group. However, there were only 11 cases in the Liversim group, and the accumulation of Liversim cases may impact the differences in preoperative outcomes between the two groups in the future. Furthermore, we think that Liversim was not clinically inferior to SYNAPSE VINCENT.

As you indicated, the creators of 3D liver models are not able to detect the invisible small branches of the hepatic vein or Glisson's sheath on the CT because, as you know, not all branches in each patient were visualized on the CT. Our Liversim software is still in the preliminary stage, so unfortunately, we can only cut straight lines in the liver. Accordingly, we were only able to perform simple liver resections, such as the lateral sectionectomy and the extended left hepatectomy (Figure 4). In the near future, we will improve the Liversim to cut complex lines in the liver.

Liversim imaging during hepatectomy helped our team discuss several critical points. Regarding the reviewer's comment, several critical points include the surgical margin and the relationship between the tumor and the hepatic vein and Glisson's sheath. We added the "(i.e., the surgical margin and the relationship between the tumor and the hepatic vein and Glisson's sheath)" (highlighted in yellow) on P13, line 19. We are able to project the Liversim images on a large display in an operating room for aid in surgical navigation. Thus, Liversim allowed us to share anatomical images with the surgical staff

during the actual hepatectomy.

Finally, the most striking point that we want to convey to readers is that Liversim, our novel liver surgery simulation software, combined with real-time deformation is thought to be helpful for performing a safe hepatectomy and for the surgical education of surgical residents and medical students. Although Liversim is currently in the preliminary stage, we are currently improving its sophisticated simulation.

2. In relation to the above question, the authors admit that they were not able to prevent accidental injury by using Liversim when compared with SYNAPSE VINCENT. This is probably because both software miss small vessels anyways. If this problem gets solved, the software may indeed become useful for experts. Is it just a matter of the resolution level of the CT? Isn't it dependent on the operator, who creates the Liversim or SYNAPSE VINCENT images from the CT?

Response to reviewer

Thank you for your thoughtful comment. As stated earlier, unfortunately, there were no significant differences in the perioperative outcomes between the two groups. Because we used Liversim with only 11 patients, the future accumulation of Liversim cases could make differences in the preoperative outcomes of the two groups. You pointed out that both software programs may miss small vessels, and I entirely agree that this might lead to an absence of significant differences between the two groups. As mentioned above, the creators of 3D liver models from CT scans cannot detect the invisible small branches of the hepatic vein or Glisson in CT images. It is my understanding that this matter may depend on the resolution level of the CT and not the skill of the person creating the 3D liver model.

3. There is an overlap between the period of SYNAPSE VINCENT and Liversim. What was the patient selection criteria?

Response to reviewer

At present, our Liversim program is still in the preliminary stages; consequently, we can only cut the liver straight. Accordingly, we selected simple liver resections, such as sectionectomies or hemihepatectomies. In the near future, we will consult with system engineers to improve the Liversim to allow the cutting of complex resection lines.

(3) Reviewed by 00225294

Comments to Authors

This is a very original and technical sound support to reveal 3D changes during liver surgery. The text is well organized in describing the changes depicted in the figs and in the accompanying video. Open access to all this info will significantly provide support to surgeons and professionals in this field.

Response to reviewer

We appreciate the reviewer's positive review.

(4) Reviewed by 00068443

Comments to Authors

Liversim system provides specialized functions for liver surgery planning. This function enables us to represent the real time motion and display an estimated vascular territory of segments. The paper is clearly written and contains valuable information. Publishing it would be of great value for surgeons.

Response to reviewer

We appreciate the reviewer's positive review.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, reading 'Yukio Oshiro', on a light yellow rectangular background.

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