March 19, 2022

Editors-in-Chief
World Journal of Clinical Cases

Subject: Resubmission of the manuscript, titled "**Preoperative remnant liver evaluation using the indocyanine green plasma clearance rate and 99mTc-GSA SPECT.**"

Manuscript ID number for first submission: **75067, Retrospective Study**

Dear Editors and Reviewers:

Thank you very much for considering our revised manuscript, titled "**Preoperative remnant liver evaluation using the indocyanine green plasma clearance rate and 99mTc-GSA SPECT**" by Iwaki et al, which was originally submitted to the *World Journal of Gastrointestinal Surgery* in January of this year.

In accordance with the Editor's and Reviewers' suggestions, we have answered your comments and modified our manuscript accordingly. The revised parts are shown in with bold font and underlined text again. Modifications and replies to reviewers' comments are specified below.

We believe that we have made our best attempt to revise our paper in accordance with the comments of the reviewers and hope that our revised manuscript is now acceptable for publication.

We are looking forward to hearing from you at your earliest convenience.

Sincerely,

Kentaro Iwaki, MD.,
Department of Surgery, Kobe City Medical Center General Hospital, 2-1-1 Minatojimaminamimachi, Chuo-ku, Kobe 650-0046, Japan
kentaro@kuhp.kyoto-u.ac.jp

Comments

Reviewer #1:

Specific Comments to Authors: Related papers have been published; small sample size

Reply 1:

We appreciate your suggestion. This was a single center retrospective study, and the subject was major liver resection after portal vein embolization. We reviewed records of patients admitted from 2004 to 2019 to increase the sample size. We wrote this limitation in the Discussion section. This study was a small retrospective study; however, we showed a novel remnant liver evaluation system. This evaluation system enabled safe hepatectomy and may extend the number of cases in which hepatectomy is indicated. Although the validity of 99mTc-GSA SPECT was reported in few studies (Reference No [7]-[13]), our study describes a more specific and practical remnant liver evaluation system by using the combination of KICG and 99mTc-GSA SPECT after PVE.

Reviewer #2:

Specific Comments to Authors: English language needs a wide check. The title does not reflect the main subject/hypothesis of the manuscript, neither the kind of the study. Abstract must be shortened and made more concise, focused on the study. In the background it should be highlighted that the value of indocyanine green clearance of the future liver remnant has not been widely validated. The definition of KICG must be written in the methods section, not in the background. Primary endpoint is not clear. Results are not powerful because of the sample size, study design, lack of clearly defined endpoints.

Reply 2:

We appreciate your comments. We had our manuscript proofread again.

We chose this title because our new remnant liver evaluation system was based on the indocyanine green plasma clearance rate and 99mTc-GSA SPECT. This is a functional evaluation.

The value of indocyanine green clearance has been validated in some studies and its safety has been reported (Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg 2006;243:364–372., Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer); however, it was not validated worldwide as you have mentioned. Hence, we revised the text as follows "**An anatomical volume remnant indocyanine green plasma clearance rate (a-rem-KICG: the remnant liver anatomical volume rate×indocyanine green plasma clearance rate [KICG]) of >0.05 is a useful criterion [2,3].**" on page 5 line 6.

We had written the definition of KICG in the Methods section from page 6 line 24 to page 7 line 6. The aim of this study was to analyze the safety of our institution's system for evaluating the functionality of the remnant liver; however, we cannot evaluate our system from only one point. We should know the features of f-rem-KICG. Hence, we showed the features of f-rem-KICG. Second, we defined patients for whom surgery was not indicated by a previous evaluation system (a-rem-KICG) as the marginal group and showed a good postoperative outcome. We added the following sentences "**Outcomes**

First, the perioperative factors and changes in the remnant liver KICGs after PVE were reviewed. Second, we defined the marginal group to be those patients with an a-rem-KICG of <0.05 and an f-rem-KICG of >0.05, and the not-marginal group as those patients with an a-rem-KICG and an f-rem-KICG of >0.05. We then compared the postoperative outcomes between the marginal and not-marginal groups to evaluate the safety of hepatectomy for the marginal group."

in the Patients and Methods section on page 7 line 15.

We wrote about the small sample size in Reply 1 and in the Discussion section.

We revised the Abstract shorter as follows.

Abstract

BACKGROUND

Preoperative evaluation of future remnant liver reserves is important for safe hepatectomy. If the remnant liver is small, preoperative portal vein embolization (PVE) is useful. Liver volume analysis has been the primary method of preoperative evaluation, although functional examination may be more accurate. We performed the functional evaluation of the remnant liver using the indocyanine green plasma clearance rate (KICG) and 99mTc-galactosyl human serum albumin single-photon emission computed tomography (99mTc-GSA SPECT) for safe hepatectomy.

AIM

To analyze the safety of our institution's system of evaluating the remnant liver reserve.

Methods

We retrospectively reviewed the records of 23 patients who underwent preoperative PVE. Two types of remnant liver KICG were defined as follows: anatomical volume remnant KICG (a-rem-KICG), determined as the remnant liver anatomical volume rate×KICG; and functional volume remnant KICG (f-rem-KICG), determined as the remnant liver functional volume rate based on 99mTc-GSA SPECT×KICG. If either of the remnant liver KICGs were >0.05, a hepatectomy was performed. Perioperative factors were analyzed. We defined the marginal group as patients with a-rem-KICG of <0.05 and f-rem-KICG of >0.05 and compared the postoperative outcomes between the marginal and not-marginal (both a-rem-KICG and f-rem-KICG >0.05) groups.

Results

All 23 patients underwent planned hepatectomies. Right hepatectomy, right trisectionectomy, and left trisectionectomy were performed in 16, 6, and 1 case, respectively. The mean blood loss and operative time were 576 ml and 474 minutes, respectively. The increased amount of f-rem-KICG was significantly larger than that of a-rem-KICG after PVE (0.034 vs 0.012, P=0.0273). The not-marginal and marginal groups comprised 17 (73.9%) and 6 (26.1%) patients,

respectively. The complications of Clavian-Dindo classification grade II or higher and post-hepatectomy liver failure were observed in six (26.1%) and one (Grade A, 4.3%) patient, respectively. The 90-day mortality was zero. The postoperative outcomes (prothrombin time, total bilirubin, complication, post-hepatectomy liver failure, hospital stay, and 90-day mortality) were not significantly different between the marginal and not-marginal groups.

Conclusions

Functional evaluation of the remnant liver enabled safe hepatectomy and may extend the indication for hepatectomy after PVE treatment.

Reviewer #3:

Specific Comments to Authors: The authors have conducted this retrospective study to determine the safety of institutional protocol of using anatomical and functional volume remnant KICG for selecting patients for liver resection. However, the sample size of 6 patients in marginal group is too small to draw any meaningful conclusions. I recommend the authors to continue collecting data, update the results and publish the findings when at least 50 patients are present in the marginal group. Other comments regarding the manuscript are as follows: 1. Why only 23 patients who received PVE were selected from the 150 patients operated during the study period? Other patients without PVE satisfying the criteria of marginal group can also be included in this study. 2. What is the benefit of comparing the outcomes of marginal and non-marginal groups? The aim is to study the outcomes of marginal group.

Reply 3:

We wrote about small sample size in Reply 1. This was a single center retrospective study. We reviewed the data of our patients admitted from 2004 to 2019 to increase the sample size. This study may be a small retrospective study; however, we showed a novel remnant liver evaluation system and a new indication for hepatectomy, although further study is needed.

There wer no patient without PVE satisfying the criteria of the marginal group. Therefore, we considered that it would be easier to emphasize the result if we limited it to only PVE cases. In addition, we realized empirically that PVE increased the functional volume of the liver more than the anatomical volume. This was also one of the end points to analyze f-rem-KICG. Hence, we chose 23 patients who received PVE.

The aim is to study the outcomes of the marginal group as you have pointed out. We showed these in Table 3. In addition, we considered that the marginal group might have a poorer postoperative outcome than the not-marginal group. If that is the case, our system (f-rem-KICG) was not a safe evaluation system. Therefore, we compared the outcomes of the marginal and non-marginal groups. There was no significant difference not only in mortality and modality but also in maximum PT-INR and maximum total bilirubin levels. These results suggested that our evaluation system enabled the extension of the indication for hepatectomy, while ensuring safety.

We added a following sentence "**Second, we defined the marginal group to be those patients with an a-rem-KICG of <0.05 and an f-rem-KICG of >0.05, and the not-marginal group as those patients with an a-rem-KICG and an f-rem-KICG of >0.05. We then compared the postoperative outcomes between the marginal and not-marginal groups to evaluate the safety of hepatectomy for the marginal group.**" in the Method section on page 7 line 17.

Reviewer #4:

Specific Comments to Authors: The paper is very interesting. The method for remnant liver functional evaluation provided by authors is interesting, quite simple, and easily reproducible. It will gain interest among the surgeons performing liver resection/transplantation.

Reply 4:

Thank you very much for your kind comments. We hope that, from your journal, many surgeons will be aware of our results to save more lives.

Reviewer #5:

Specific Comments to Authors: In combination with the previous method of evaluating liver function by relying on indocyanine green metabolic rate, this manuscript innovatively proposes to evaluate the preoperative residual liver volume according to the combination of indocyanine green plasma clearance and 99mTc GSA SPECT. Compared with the previous methods, this method is more scientific and has clinical significance. This method not only makes liver surgery more convenient, but also can safely prolong the number of cases of hepatectomy. This makes more patients with advanced liver cancer benefit. However, the number of patients in this study is relatively small, and there are no failure cases as a control. And the rICGK ≧ 0.05 criterion appears to be safe regarding zero mortality, This has not been verified worldwide. More cases are expected to be included in the study.

Reply 5:

We agree with your assessment. We also considered that the limitation of this study was the small sample size and absence of failure cases, as written in the Discussion section and reply 1. We hope to continue collecting data and update the result.

As mentioned in Reply 2, a-rem-KICG>0.05 was reported from Nagoya University (Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg 2006;243:364–372., Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. Br J Surg 2010;97:1260–1268.). This may not be a method used worldwide; however, the previous studies showed its safety. Further studies are needed to investigate the appropriate cut off value of rem-KICG.

Severe PHLF was not observed in this study, suggesting that the safety margin for f-rem-KICG might have been excessive as mentioned in the Discussion section.
We revised the text as follows: "**An anatomical volume remnant indocyanine green plasma clearance rate (a-rem-KICG: the remnant liver anatomical volume rate×indocyanine green plasma clearance rate [KICG]) of >0.05 is a useful criterion [2,3].**" on page 5 line 6.
We revised the text as follows: "**First, severe PHLF was not observed, suggesting that the safety margin for f-rem-KICG might have been excessive.**" on page 10 line 10.

(1) Science editor:

There are many papers published in the literature. Major limitations of this study are: with such small numbers of patients in the retrospective study; it isn't easy to provide a conclusion to the intelligent audience. A comparative prospective study or RCT may help arrive at a definite conclusion. Please address the reviewers' comments.

Reply:

Thank you for your comments. We wrote about thee small sample size in Reply 1. This was a single center retrospective study for major liver resection after PVE. We reviewed the data of our patients admitted from 2004 to 2019 to increase the sample size. This study was a small retrospective study; however, we showed a novel remnant liver evaluation system and a new indication for hepatectomy. We agree with your suggestion. A comparative prospective study or RCT may help arrive at a definite conclusion; however, it is difficult to perform such a study owing to our situation. Hence, we reported our results at this time and let as many surgeons as possible know our findings and re-examine them.
We hope to continue collecting data and update the result for further studies.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Clinical Cases.

Reply:

We appreciate your proposal. We believe that we have made our best attempt to revise our paper in accordance with the publishing standard of World Journal of Clinical Cases. We hope that our manuscript is acceptable for publication.