ESPS Manuscript Number: 1751

Manuscript Title: **CT/99mTc-GSA SPECT fusion images demonstrates different function in the two liver lobes**

Dear Editor

 Thank you for your letter and the referee’s comments concerning our manuscript entitled “**CT/99mTc-GSA SPECT fusion images demonstrate different functions for the liver lobes**”.

We found the referee’s comments most helpful and have revised the manuscript.

We hope that the paper in its revised form will be acceptable.

Sincerely yours,

Tatsuaki Sumiyoshi MD

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**List of Revisions Made to ESPS Manuscript No. 1751**

***Reviewer No.00214251***

We agree excellent referee’s comments. Our paper was revised according to these helpful comments.

Comments

As you mentioned, we added the haemodynamic data.

However, We have to apologize that we couldn’t submit data of Doppler ultrasound examination because that examination had not been performed before the surgery in this study.

Instead, we measured the diameter of the right portal vein (RPV) and left portal vein (LPV) on enhanced CT examination as　the parameter of the portal flow. Of cause, although diameter of the portal vein can’t directly indicate the portal flow volume, it is one of two factors which define the blood flow volume. Furthermore, a portal flow decrease without an arterial flow change can cause significant regional function decreases,although the liver receives a dual blood supply from the portal vein and the hepatic artery. In this study, the LPV-to-RPV diameter ratio showed a significant correlation with the function-to-volume ratio in both lobes, indicating that portal flow significantly influences the function of the 2 lobes.

Underline page 15 line 2 to line 15

Underline page 19 line 7 to line 15

2.

As you mentioned, we rephrased the title as follows.

**Title: CT/99mTc-GSA SPECT fusion images demonstrate different functions for the liver lobes**

***Reviewer No. 02353650***

We agree excellent referee’s comments. Our paper was revised according to these helpful comments.

Comments

1. How the liver parenchyma was evaluated as normal on CT.

We added following sentences to prove the normality of the 2 liver lobes.

All these 30 patients underwent 4-phase multidetector-row computed tomography (1 unenhanced image and 3 contrast-enhanced images) preoperatively, which confirmed that none of them had anatomical abnormalities, such as portal venous occlusion, hepatic artery stenosis, or intrahepatic biliary stenosis. Furthermore, it was also confirmed that there was no heterogeneous hepatic parenchymal enhancement in 3 contrast-enhanced images from each patient.Underline

page 8 line 6 to line 11

All values of the serum liver function tests were within the reference ranges for all

patients (Table. 1).

Underline page 13 line 3 to line 4

1. The reason for exclusion of cirrhotic patients is unclear.

As you mentioned, we added the reason of exclusion.

Cirrhotic patients were not included in this study because it is well known that the hemodynamics of bilateral portal flow and the bilateral lobe volumes are clearly different between non-cirrhotic and cirrhotic livers[23, 24]. These differences might greatly influence the function of each lobe function, and therefore, we investigated only non-cirrhotic livers in the current study.

Underline page 7 line 5 to line 9

1. The degree of hepatic fat deposition or chronic hepatitis should be clarified because these factors may affect the uptake of GSA in hepatocytes.

As you mentioned, we investigated the degree of hepatic fat deposition and the number of hepatitis patients.

Serum liver function tests, including albumin level, bilirubin level, platelet count, prothrombin time, and the presence or absence of hepatitis virus were investigated in all patients. Two other parameters that might influence 99mTc-GSA accumulation in the liver were also measured on CT images. The first parameter is the degree of fat deposition, which was assessed by measuring the CT attenuation values (in Hounsfield units [HU]) on unenhanced CT images[26, 27]. We delineated 12 regions of interest (ROIs) of 1 cm diameter within the liver. One ROI was defined in 4 sectors (right posterior, right anterior, left medial, and left lateral) at 3 representative levels. The levels consist of the confluence of the right hepatic vein, the umbilical portion, and the right posterior portal vein. While defining ROIs, special attention was placed on excluding cystic areas and the vessels. The mean attenuation value of 6 ROIs in the right posterior and right anterior sectors was defined as the attenuation value of the right lobe, and that of the 6 ROIs in the left medial and lateral sector was defined as the attenuation value of the left lobe.

Underline page 11 line 11 to page 12 line 4

Hepatitis B virus antigen and hepatitis C virus antibody were positive in 1 and 5 patients, respectively. However, none of them were associated with active hepatitis, and none of them showed clinical symptom of hepatitis. There were no cases of non-B, non-C hepatitis.Underline

Underline page 13 line 4 to line 6

Degree of fat depositon in each lobe

The attenuation value of the right lobe ranged from 35.0 to 70.5 HU (median, 56.3 HU), and that of the left lobe ranged from 39.5 to 73.0 HU (median, 57.5 HU). Only 2 of 30 patients showed severe fatty change with an attenuation value of <40 HU. There were no significant differences between the attenuation values of the 2 lobes.

Underline page 13 line 8 to line 12

1. The use of cardiac or respiratory synchronization should be clarified.

As you mentioned, we added the explanatory text as follows.

Cardiac and respiratory synchronization were not used in this modality. Instead, to minimize the possibility of artifacts due to cardiac pulsation and respiratory motion, the patients were encouraged to rest and take a small, slow breath before image acquisition.

Underline page 9 line 9 to line 12

1. “The correlations between the %Function/%Volume ratio and ICG R15 values for each lobe were also determined.” This sentence should be located in the statistical analysis section.

As you described, the sentence was moved to the stastical analysis.

(We deleted “ICG R15” and added “LPV to RPV diameter ratio”.)

1. Authors should show threshold or criteria to decide surgical procedure. Discussion section.

As you described, we added our indication for surgery as follows.

Although this scintigraphic examination is not yet widely used worldwide, it is recognized as a useful modality for preoperative liver function assessment in Japan, and we have decided the surgical indication on the vasis of the estimated remnant liver function ratio measured by this modality. The plasma clearance rate of indocyanine green (ICG K) was measured preoperatively in each patient, and a patient with a future liver remnant ICGK value (ICGK × remnant liver function ratio) of >0.05 was considered a candidate for hepatectomy[29].

Underline page 16 line 3 to line 8

1. The conspicuity of liver vessels can be unclear when the fat deposition is present in the liver. Therefore the presence of fatty liver in subjects must be described.

As you described, we measured the CT attenuation values on unenhanced CT, and only 2 of 30 cases showed severe fatty change with CT attenuation value less than 40.

Underline page 13 line 10 to line 11

1. The artifact caused by cardiac pulsation or respiratory motion has been reported.

As you mentioned, there can be the artifact caused by cardiac pulsation or respiratory motion. To minimize the possibility of the artifact caused by cardiac pulsation and respiratory motion, the patients were encouraged to rest and take a small, slow breath before image acquisition in our institution.

Underline page 9 line 9 to line 12

1. Authors should show the evidence that the portal laminar flow changes between the patients with normal and diminished liver function to support their hypothesis.

As you mentioned, there was no direct evidence of the effect of portal laminar flow.

We could not prove the evidence of it, and deleted the sentences with reference to the portal laminar flow.

1. The artifact from tracer accumulation at adjacent organ on SPECT has been reported.

As you mentioned, the effect of tracer accumaulation at heart chamber should be investigated. To confirm the presence or absence of the artifact from tracer accumulation at heart chamber, we checked all SPECT images of all 30 patients, and no apparent artifact could be confirmed.

We added the sentence as follow.

Second, the effect of tracer accumulation at the heart chamber: to confirm the presence or absence of artifacts from tracer accumulation at the heart chamber, we checked all SPECT images of all 30 patients, and no apparent artifact could be confirmed.

Underline page 18 line 1 to line 4

***Reviewer No.00181304***

We agree excellent referee’s comments. Our paper was revised according to these helpful comments.

Comments

1. As you mentioned, we sent our revised manuscript to the expert in English language for the proof reading.
2. As you described, we rephrased the title within 12 words as follows: **CT/99mTc-GSA SPECT fusion images demonstrate different functions for the liver lobes.**
3. As you mentioned, we replaced the term ‘%Function/%Volume ratio’ with ‘function-to-volume ratio’.
4. As you described, we drop the Child-Pugh classification, and added the results of serum liver function tests in Table. 1
5. As you mentioned, we omitted the description on the post-hepatectomy clinical course.
6. The method is not generally accepted as a “golden standard” and has not gained any clinical use outside of Asia and the statement should be rephrased.

If GSA scintigraphy reflects the number of hepatocytes, lower function in the left lobe should indicate fewer hepatocytes/volume unit?

We agreed your comment, and deleted the following sentences.

“99mTc-GSA scintigraphy has been reported to be the ideal modality for evaluating liver function because the liver is the only uptake site for 99mTc-GSA. 99mTc-GSA is an agent that binds to the asialoglycoprotein receptors on the surface of hepatocytes, and the number of the receptors reflects the number of functioning hepatocytes.”

Instead, we added the following sentence.

“Although this scintigraphic examination is not yet widely used worldwide, it is recognized as a useful modality for preoperative liver function assessment in Japan,”

Underline page 16 line 3 to line 4

1. The authors also state that the portal perfusion of the left lobe is lower than that of the right due to anatomical properties of the portal vein. There is no reference to support this statement and this is only speculative.

We agreed your comment, and deleted the following sentence.

“The left lobe is supplied with blood only from the left portal vein, and the flow is less than that of right portal vein because of the 90° orifice into the left portal vein.”

To investigate the correlation between the portal flow and the function-to-volume ratio, we measured the diameter ratio of left portal vein to the right portal vein (LPV to RPV diameter ratio). As the results, the function-to-volume ratio showed significant correlation between the LPV to RPV diameter ratio in both lobes.

1. The statement that this is the first report about the functional differences of the right and left lobes is not correct and should be rephrased.

We agreed your comment, and deleted the following sentence.

“This appears to be the first report to describe functional differences between the 2 lobes in patients with apparently homogeneous livers. A few reports on liver scintigraphy using other agents, 99mTc-dimethyliminodiacetic acid for biliary scintigraphy and radiolabeled colloids for depiction of the reticuloendothelial system, have also shown the lower uptake in the left liver lobe than in the right lobe [25, 26]. Although these results might also indicate functional differences between the 2 liver lobes, unlike 99mTc-GSA scintigraphy, these scintigraphy are not the established modalities for the liver function assessment and the correlation between the result of these scintigraphy and the liver function is unclear.”

Instead, we added the following sentence.

This appears to be the first report to describe the functional differences between the 2 lobes by using 99mTc-GSA scintigraphy. A few reports on liver scintigraphy with other agents, such as 99mTc-dimethyliminodiacetic acid for biliary scintigraphy and radiolabeled colloids for depiction of the reticuloendothelial system, have also shown lower uptake in the left liver lobe than in the right lobe[30, 31].

Underline page 17 line 3 to line 7