

July 24<sup>th</sup>, 2013



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3765-review.doc).

**Title:** Added value of hepatobiliary phase gadoxetic acid-enhanced MRI for diagnosis of hepatocellular carcinoma in high-risk patients.

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 3765

The manuscript has been improved according to the suggestions of reviewers:

1. Manuscripts has been edited by the English language editing companies (American Journal Experts)
2. Format has been updated and revision has been made according to the suggestions of the reviewer.
3. Reviewer comments that need to clarify as below;

Reviewer#02438768

(1) It is not clear why the authors use 3 different standards for diagnosis of HCC in the Methodology. Could this affect the reliability of different study groups? Please clarify.

Response: First of all, this study is a retrospective study. Therefore, there is a limitation to control the reference standard, **which is already stated in the manuscript**. Three standards for diagnosis of HCC that used in this study, however, are generally accepted in clinical practice. Pathologic study by surgical specimen or percutaneous biopsy has no doubt for its standard. While, diagnosis of HCC based on typical enhancement pattern (rapid arterial enhancement and rapid washout) is recommended by AASLD guideline for diagnosing HCC without tissue biopsy and underwent TACE as a non-surgical treatment option. Contrary, the nodules that are not suspected HCC on the first imaging study, it is unethical to get tissue in this

circumstance. We believe that the reliability of different study groups is acceptable by the fact that the result of this study reflects the real clinical practice for making diagnosis of HCC.

(2) In this study, 46 benign nodules did not contain precancerous lesions such as dysplastic nodules( DN)s; Nor were pathological grades of HCC included. Therefore, information in Methods is incomplete.

Response: We already stated in the manuscript that “28 of 46 benign nodules were hepatocyte in origin (i.e. cirrhotic nodule), in which three nodules pathologically confirmed RN and cirrhotic nodule”. While pathological grades of HCC are not included in the result owing to the aim was not to demonstrate the relationship of pathological grade and behavior of hepatocyte-specific contrast uptake by nodule.

(3) Is Gd-EOB-DTPA-enhanced MRI urgently required by the 100 patients selected in the study? Have the authors considered cost-effectiveness as far as the patients who didn't need Gd-EOB-DTPA-enhanced MRI are concerned?

Response: One hundred patients that included in this study are not urgently required using Gd-EOB-DTPA. The contrast selection in each patient was based on radiologist's judgment at the performed date. **We realized that this is one of the limitations.** About the cost-effectiveness issue, it is beyond the scope of this study. However, to my knowledge, there are few studies going on, in which they are studying based on Cost-effectiveness model.

(4) Should there be patients among the 100 that are suffering from renal impairment, can Gadoteric acid be safely used in this group?

Response: There is an on-going multi-institutions trial conducted by the company on using Gadoteric acid contrast in patients with renal impairment. So far, there have not been reported on serious adverse effect including NSF. **However, all patients in this study were counseling and were aware of those possible complications. None have serious side effect.**

(5) In the Introduction, the authors stated” Owing to difference in the population together with the nature of disease, we set out a study to figure out the added value of Gd-EOB-DTPA-enhanced hepatobiliary phase MRI for diagnosis HCC in the setting of high-risk patients at Ramathibodi Hospital.” Therefore, any conclusion in this study should have been drawn with great caution.

Response: This study was conducted by the single institution within the country (Thailand), therefore, demographics and natural history of cirrhosis of Thai population may be different from the others. It might not be possible to make direct comparison to the others. However, the diagnostic accuracy is improved same as other previous works.

(6) In the Discussion, the authors stated "The significant improvement was obtained in the small lesion (1-2 cm in diameter) , in particular. No significant difference was found in the lesion larger than 2 cm in diameter." That is to say those that have small lesions (smaller than 1 cm in diameter) were not investigated in the study. Why not?

Response: The lesions smaller than 1 cm in diameter were not included into the study population because almost all were follow up, which is recommended by APASL guideline adopted in our hospital. We also cannot differentiate between true nodules and pseudolesions when they are smaller than 1 cm. Moreover, the nodule smaller than 1cm that suspicious of malignancy, the interventionists at our hospital have had a hard time to get the tissue biopsy. With all these limitations, we decided not to include the lesion smaller than 1 cm. **We added this limitation into the manucrypt.**

Reviewer#02438650

(1) All(100) patients were registered between January 2010 and July 2010, the follow-up CT or MRI were performed at least 6 months in your study. How many times of follow-up CT or MRI scan for each one?

Response: We enrolled patients from January 2010 to July 2010, in order to have at least 6 months follow-up period at the time of study. All patients have at least one follow-up MRI or CT scan. For those who do not have pathologically proven HCC or not undergo TACE, the CT or MRI follow up must have at lest one follow-up CT or MRI performed at least 6 months after initial imaging.

(2) How about the prevalence of HCC in Thais?

Response: So far, there is no nationwide prevalence of HCC reported. However, the data that came from cancer registry of the institutions, the prevalence of HCC was 6.8 in 100,000 of male and 1.6 in 100,000 of female.

(Vatanasapt V, Parkin DM, Sriamporn S. Epidemiology of liver cancer in Thailand. In: Vatanasapt V, Sripa B, editors. Liver Cancer in Thailand, Epidemiology, Diagnosis and Control. Khon Kaen: Siriphan Press 2000; 3-6.)

(3) Statistical analysis: For the different standard for diagnosis of HCC in your study, how about the data's homogeneity of variance of different study groups?

Response: Even though, this study used three different standards to confirm diagnosis of HCC. But, they are combined into one group as the gold standard. This study tested the accuracy between conventional MRI and

conventional MRI plus hepatobiliary phase, which they both tested against the same gold standard group. Therefore, the variances of two populations are equal.

(4) Why the observer in your study only recorded the possibility of HCC lesion no less than 1 cm in diameter? “----for each dominant lesion (defined by size criterion 1 cm or larger”

Response: The lesions smaller than 1 cm in diameter were not included into the study population because almost all were follow up as recommendation by APASL guideline which is adopted in our hospital. We also cannot differentiate between true nodules and pseudolesions when they are smaller than 1 cm. Moreover, the nodule smaller than 1cm that suspicious of HCC, the interventionists at our hospital have a hard time to get the tissue biopsy. With all these limitations, we decided not to include the lesion smaller than 1 cm. **We added this limitation into the manuscript.**

(5) How about the diagnostic accuracy of gadoxetic acid for diagnosis HCC smaller than 1 cm in diameter in your study?

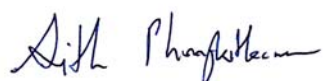
Response: We do not have result on diagnostic accuracy for diagnosis HCC smaller than 1 cm in diameter. This is beyond the scope of the study. Again, this is almost impossible to get the accurate accuracy, except the gold standard is explanted liver or surgical resection.

4. References and typesetting were corrected.

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

Sincerely yours,

Best Regards,



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