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March 13, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 24393-revised manuscript.doc).

Title: Primary hepatic epithelioid angiomyolipoma: a malignant potential tumor which should be recognized

Author: Jie Liu, Cheng-Wu Zhang, De-Fei Hong, Ran Tao, Yuan Chen, Min-Jie Shang, Yu-Hua Zhang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 24393

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

Reviewer 1

The study describes a rare disease. It helps to enhance the knowledge in this field by concisely summarizing the findings of the last few years and comparing them to cases the authors investigated themselves. Minor language revision is needed before publication. The authors should consider if giving mean and/or median of four values is necessary.

Respond: Thanks to your comments. Language had been revised and

amended. We had added the mean data of four patients in manuscript.

Reviewer 2

Very nice work for this uncommon hepatic tumor.

Respond: Thanks to your comments.

Reviewer 3

1. Primary hepatic epitheloid angiomyolipoma(AML) is a benign hepatic tumor, even though there are several case reports showing potential malignancy. Authors reviewed 4 cases experienced of the AML in their own institution and reviewed 80 cases reported in the medical literature. The authors' review of their own cases and other reports so far is very informative. **Authors concluded proposed that AML has malignant potential after review of the papers.** However the analysis going reality is to be proved more, in terms of image, pathology and final diagnosis of the suspicious recurrent or metastatic masses.

Respond: Thanks to your comments. We want to emphasize that we did not concluded that **AML has malignant potential, but HEAML has.**

Although HEAML belong to the AML, HEAML has malignant potential just like Renal EAML. For prove this, we collected 81 cases of HEAML in world and found 8 cases in these patients had local recurrence or metastasis after surgery. As we know, poor outcome is considered when necrosis, mitotic figures, plastic nucleus or a cytological atypia are observed in pathological studies. The presence of 3 or more features above was highly predictive of malignant behavior. In our four patients, mitotic figures, necrosis, cytological atypia and liver invasion were all observed in pathology in two cases. And our pathologist considered this as low malignant tumor.

2. After analysis of the 80 cases, authors concluded that 10%(8/80) of the cases had recurrence or metastasis after surgery. However the authors in the reference 14(Xu) described characteristics of image **only in recurrence, no pathology and prognosis described**, the authors of the reference 26(Xu et al.) described that the biologic behavior of the AML is benign. Need clarify of these cases review.

Respond: we extract the following from the reference

14(Xu) "Recurrent hepatic lesions were found in one patient, **pubic**

bone destruction and metastatic nodule in body soft tissue were proved with biopsy in another”.

“There is clinical evidence of aggressive behavior such as recurrence and metastases beyond the liver, for two cases in these 10 Epi-AML cases. Therefore, although most HAMLs are biologically benign, this tumor should be considered to have malignant potential, especially for Epi-AML. So resection and careful follow-up are recommended.”

We extract the following from the reference 26(Xu et al.)

31 个月)。在获得随访资料的 21 例中, 2 例 (9.5%) 出现了手术后的局部复发, 无远处转移和

Translation: 2 cases had local recurrence after surgery.

3. The imaging of the AML in the CT and MRI shows strong enhancement in arterial phase and wash out in the portal phase, which is mimic to hepatocellular carcinoma (stronger enhancement in arterial phase than HCC) and focal nodular hyperplasia (similar strong arterial enhancement but no wash out in FNH). In the MRI finding in the figure 2, the finding of 20 minute delay phase is absent, that finding may be



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important differentiation point. Adding of the 20 minutes delay image will be appreciated.

Respond: we had added the 20 minutes delay image in the figure 2.

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

Sincerely yours,

A handwritten signature in blue ink that reads 'CHENG WU ZHANG'.

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