

Dear Editors and Reviewers,

Thank you for the comments concerning our manuscript entitled "Contrast-enhanced ultrasound of histologically proven hepatic epithelioid hemangioendothelioma" (WJG-24138). The comments have been important and helpful to improve our paper. Please find the revision of our manuscript according to the comments and a point-to-point reply below.

We are hoping that after careful revision our paper deserves publication in WJG.

Cordially

Christoph F Dietrich

Corresponding author

### **Editors' comment:**

1. Institutional review board statement, informed consent statement must be signed by the corresponding author and provided in a PDF format.

Due to the retrospective study analysis character of our current paper, we do not have the institutional review board statement or informed consent statement.

2. Conflict-of-interest statement and data sharing statement must be signed by the corresponding author and provided in a PDF format.

Thank you for your good suggestions. We will upload those files in our revision paper.

3. Please reformat all the reference numbers. Please check throughout.

Thank you for your good suggestions. We had made this change with our current paper.

4. Please write the COMMENTS section.

Thank you for your good suggestions. We had added this part in our current revised paper.

5. Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.

Thank you for your good suggestions. We had put our original pictures as a word format in our current revised paper.

### **Reviewers' comment:**

#### **Reviewer #1:**

1. Why the authors use ALK and CD68 as markers of endothelial cells? How do you explain the positivity of ALK and CD68. Though the authors can get all the pathology information from pathology report, it is better have at least one pathologist included in this study to explain the pathological features.

Thank you for your good comments and suggestions. However, as this pathological

issue is not important related to our topic, we had removed it from our paper with the aim to avoid causing confusion.

2. The authors tried to CEUS to differentiated HEHE and FNH/hemangioma. It is difficult to differentiate HEHE from malignant angiosarcoma. It is better that authors include several cases of liver angiosarcoma in this study. In this way, the authors can compare the vascular lesion from pure benign (FNH/hemangioma), intermediate (HEHE) and malignant (angiosarcoma).

Thank you for your good comments and suggestions. Previously, we had made some research about the malignant angiosarcoma of liver, please refer to our published paper in JCU (Trojan J, Hammerstingl R, Engels K, Schneider AR, Zeuzem S, Dietrich CF. Contrast-enhanced ultrasound in the diagnosis of malignant mesenchymal liver tumors. J Clin Ultrasound 2010; 38(5):227-231).

However, due to shortage of time and also with the aim to avoid diffusion information of our current paper, we do not include the malignant angiosarcoma of liver in our current paper.

**Reviewer #2:**

1. Since HEHE imitates malignant metastasis, if it was possible to add on CEUS findings of this group. this will allow to calculate sensitivity and specificity of each features.

Thank you for your good comments and suggestions. Previously, we had made some research about the malignant angiosarcoma of liver, please refer to our published paper in JCU (Trojan J, Hammerstingl R, Engels K, Schneider AR, Zeuzem S, Dietrich CF. Contrast-enhanced ultrasound in the diagnosis of malignant mesenchymal liver tumors. J Clin Ultrasound 2010; 38(5):227-231).

There might be of too many information in our purely retrospective study. This might be referred to a future prospective study including metastasis, malignant angiosarcoma, etc., to compare such features mainly in the arterial phase.

2. Table 4 can be included in table 3.

Thank you for your good comments and suggestions. We had made this change with our current paper.

**Reviewer #3:**

1. Authors should be used another malignant lesion like HCC or metastatic lesion as control groups. Arterial hypervascularization and washout during portal phase are characteristic findings of HCC.

As mentioned above, previously, we had made some research about the malignant angiosarcoma of liver, please refer to our published paper in JCU (Trojan J, Hammerstingl R, Engels K, Schneider AR, Zeuzem S, Dietrich CF. Contrast-enhanced ultrasound in the diagnosis of malignant mesenchymal liver tumors. J Clin Ultrasound 2010; 38(5):227-231).

Thank you for your good comments and suggestions. It will be very interesting topic

for future prospective study to analyse certain defined criteria using CEUS.

2. Material and methods section should be written more comprehensively.

Thank you for your good comments and suggestions. We had edited our material and methods part in our current paper according to the suggestions of reviewers.

3. Author report that all patients asymptomatic and laboratory findings almost normal. This is not plausible for clinician

Due to the retrospective study analysis, including patients with oncological background, the almost normal laboratory findings only referred to the group of analyzed HEHE, but not to the comparative group. Therefore, we deleted the information because of confusion.

4. Why they perform biopsy for hemangioma. Because, a great majority of hemangioma don't require biopsy. Therefore, there is some ethics concerns.

In all patients with hemangioma, the reason for biopsy was oncological reasons and patients at risk. We totally agree with the ethics concerns. According to the study design as our hepatology paper. (Dietrich CF, et al. Contrast-enhanced ultrasound of histologically proven liver hemangiomas. Hepatology 2007;45(5):1139-1145)