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Dear Editor,

Title: Perinodular DR/EpCAM loss in small hepatic nodules

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

1 Format has been updated

All paper has been updated.

2 Revision has been made according to the suggestions of the reviewer

(1) Question: At first, the diagnostic accuracy of EpCAM is missing. The sensitivity of DR/EpCAM loss, DR/CK7 loss and DR/CK19 loss in all HCCs (HCC≤3cm and HCC>3cm) was 91.30%, 78.26%, 89.13% and the specificity was 75.76%, 80.30%, 77.27% respectively. What about the negative predictive value (NPV) and the accuracy of the EpCAM?

Answer: the diagnostic accuracy and negative predictive value (NPV) of DR/EpCAM, DR/CK7 and DR/CK19 was added in the result (DR/EpCAM expression compared with DR/CK7 and DR/CK19 expression, page11) respectively .

(2) Question: The same problem is that If 2 or more were positive among DR/EpCAM, DR/CK7 and DR/CK19, this tumor was considered to be DR positive; and if 2 or more were focal/diffuse loss of DR/EpCAM, DR/CK7 or DR/CK19, the tumor was considered to be DR negative. The sensitivity was 91.30% but the specificity was increased to be 98.48%. The specificity of the new group was higher than DR/EpCAM, DR/CK7 or DR/CK19 (u= 3.90, 3.73, 3.39 respectively; P<0.01). Why the author does not present the negative predictive value (NPV) and the accuracy of this method. It is very important to a diagnostic tool.

Answer: the diagnostic accuracy and negative predictive value of combination DR of EpCAM , CK7 and CK19 was added in the result too (DR/EpCAM expression compared with DR/CK7 and DR/CK19 expression, page12) . And then the the diagnostic accuracy and negative predictive value of EpCAM were compared with the combination of DR/EpCAM, DR/CK7 and DR/CK19 in page 12 by u test.

(3) Question: If the evidence of disease progression in this study, is it a linear regression trend on the CIR, CLRN, HGDN, HCC<3cm and HCC>3cm? Missing data to investigate the chronicity of chronic B hepatitis, hepatitis B related liver cirrhosis and hepatoma. Error bar presentation of the DR/EpCAM in the different stage of the disease should be powerful.

Answer: The objects of our study were small hepatic nodules, then the group of CIR,CLRN,HGDN and HCC (≤ 3 cm &> 3 cm)were selected. The chronicity of chronic B hepatitis without nodules in ultrasound scanning or computed tomography were excluded

from the study. So far as I know, error bars are a graphical representation of the variability of data and are used on graphs to indicate the error, or uncertainty in a reported measurement. It give a general idea of how accurate a measurement is, or conversely, how far from the reported value the true (error free) value might be. Error bars often represent one *standard deviation* of uncertainty, one *standard error*, or a *certain confidence interval* (e.g., a 95% interval). That is to say, error bars usually be used in quantitative data. Our data of different clinic group are ordinal variables of count data. Therefore we think that error bars are unfitted for our analysis. But we still hope that the reviewer can give more suggestions to improve our study for our limited knowledge.

(4) Question: In the Table 2, EpCAMDR seems to be not better than those of the CK7DR or CK19DR in the DR presentation of the diagnostic sensitivity. It means that CK7DR and CK19DR are satisfied to predict the disease progression and the evidence of malignant change.

Answer: DR/CK7 and DR/CK19 are really satisfied to predict the disease progression and the evidence of malignant chang. However it still has some ambiguous diagnosis in small hepatic nodules. DR/EpCAM is another marker for this function and be presented to decrease the ambiguous area. DR/EpCAM is not better than those of the DR/CK7 or DR/CK19 alone, however when DR/EpCAM is combined with DR/CK7 and DR/CK19, the diagnostic accuracy and diagnostic specification were both increased. Therefore the study of EpCAM was significant. The combination of DR/EpCAM,DR/CK7 and DR/CK19 can make the diagnosis of HCC more accurate and more specific.

(5) Question: The abbreviation is very confusing such as HCC>3cm and HCC1, HCC<3cm and HCC2 in table 2 and the whole text; and the cirrhosis and CIR in the text 7. The English presentation should be revised such as the follow-up time was 3 to 90mths. No patient was not followed-up….

Answer: we looked through the article and devised both groups of HCC were HCCs $\leqslant$ 3 cm and HCCs > 3 cm.HCC1 and HCC2 were only used in table2 for the uniform of the table and added notes under the table.