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To

Prof. Shui Qiu  
Editor-in-Chief  
World Journal of Radiology

Subject: Revision of Manuscript No 24392

Dear Prof. Shui Qiu

We thank the reviewers for the revision of our manuscript and for the helpful comments. Below, please find our point-by-point answers to the reviewer's comments and suggestions for improvement of the manuscript.

We would be more than happy if you would consider the revised version of our manuscript worthy of publication in your much appreciated journal.

Sincerely

Gerd Grözinger MD

Marius Horger MD

## **Response to the comment of Reviewer No. 00068723**

1. This study showed that arterial blood supply dominated in HCC. This is a well-known phenomenon, which was the basis of HPI. Authors should clearly show the significance of the study and potential application to clinical practice.

We thank the reviewer and agree with this statement. We rephrased the first paragraph of the discussion section in order to clarify the additional value of perfusion CT to reliably detect tumor arterialization, even in the case of unclear MR signal constellation or contrast kinetics.

2. Introduction of VPCT is required in "Introduction" section.

We added a brief section in the Introduction section introducing the technique of VPCT.

3. Discussion. Some parts were suitable for Introduction and redundant.

We agree with the reviewer and rearranged the discussion, added the suitable parts to the introduction and removed redundant parts.

4. Discussion should focus on the significance of the study. "In summary" seemed long. Conclusion sentences should be compact.

We thank the reviewer for this comment. The discussion was significantly shortened. The sentence starting with "in summary" was shortened to be more compact.

Figure 1 B. C showed that wash-in was unclear. D showed clear wash-in. How did the author speculate this discrepancy? Was contrast-medium different? Perfusion speed different? Timing of image acquiring different?

We agree with the reviewer that this is an interesting question. In figure 1B we show an example of atypical MR morphology and signal constellation. As stated by the reviewer the MR image shows no clear wash-in on arterial phase MRI whereas VPCT depicted a clear arterialization of the lesion.

Of course for VPCT, contrast agent containing iodine was used (Ultravist 370). This was injected at a high flow rate (5ml/s). The MR contrast agent was injected at much lower speed (Gadovist, 2ml/s). However to our opinion this does not fully explain the missing arterialization (wash-in) on MR images. This finding can be explained by two possible

reasons: First, the exact time of peak wash-in in MR could have been missed due to suboptimal timing which is a common problem in MR imaging. This is often the case due to variable circulatory time of the patient. This pitfall is omitted in VPCT due to repetitive short interval scanning of the volume which ensures an optimal time-resolved scanning of the volume. Second, the infiltrative, diffuse growth pattern without clear tumour margins of the lesion might be a reason for the lower visibility of the arterial wash-in in MRI. Thirdly, the wash-in effect depends on the contrast agent used for MRI. Although not used in this case, in our experience hepatocellular contrast media like Primovist lack a clear early enhancement in DCE-MRI contrary to other agents.

Figure 1 A. Explanation of F is lacking.

We rephrased the description to clarify the image and added a description on F.

Figure 2 and 3. What is the red line?

Red line indicates the mean value of HPI and ALP. This was added in the description.

Figure 4 and 5. What are Green line, box, and bar?

The red Boxes indicate the box-and-whisker plots indicating the upper and lower quartiles. The Box plots have lines extending vertically from the boxes indicating variability outside the upper and lower quartiles. We added a brief description in the figure legend.

## **Response to the comment of Reviewer No. 00032726**

### **COMMENTS TO AUTHORS**

1. In the background, please introduce a little more details of VPCT and other treatment and diagnostic technology.

We introduced a brief section on VPCT in the introduction section. Furthermore we added the stage-dependent treatment options in the first sentence of the introduction. One sentence about contrast-enhanced ultrasound was added.

2. The manuscript may try to avoid repeating the same meaning and reduce the case of the original intention.

We agree with the reviewer and shortened the manuscript significantly. Accordingly the manuscript is now more concise.

3. There are a lot of problems in the charts, such as Figure 2-5 didn't explain the means of the red line and green line and the format of statistical charts is not correct.

We agree with the reviewer and improved the description of each figure in order to state their meaning more clearly. We added a description of the red and green lines.

4. Whether the level of assessment of different gender groups should not be the same? Different gender groups should have different assessment results

According to our experience, the values of HCC-perfusion parameters did not differ depending on patient's gender, neither did the surrounding liver parenchymal perfusion differ significantly in different gender. Furthermore we did not find a hint in the current literature suggesting a principal difference in the functional perfusion parameters for male or female HCCs.

#### **Response to the comment of Reviewer No. 00069297**

##### **COMMENTS TO AUTHORS**

This manuscript written by Dr. Gerd et al. has perfectly determined if functional perfusion parameters by means of VPCT differ in HCC lesions with typical and atypical MR pattern including enhancement patterns and the correlation with histology. They found hepatic perfusion index (HPI) measured with help of VPCT was very high in all HCC lesions and the ALP decreased with increasing tumor dedifferentiation. The conclusion seems to be fair. The contents would give significant information.

We thank the reviewer for this encouraging notice.

#### **Response to the comment of Reviewer No. 00068107**

##### **COMMENTS TO AUTHORS**

The references are not appropriate and up-to-date.

We thank the reviewers for this hint and added the following recent publication in the field of HCC imaging.

*Kaufmann S, Horger T, Oelker A, Kloth C, Nikolaou K, Schulze M, Horger M. Characterization of hepatocellular carcinoma (HCC) lesions using a novel CT-based volume perfusion (VPCT) technique. European journal of radiology 2015; 84(6): 1029-1035 [PMID: 25816994 DOI: 10.1016/j.ejrad.2015.02.020]*

*Schraml C, Kaufmann S, Rempp H, Syha R, Ketelsen D, Notohamiprodjo M, Nikolaou K. Imaging of HCC-Current State of the Art. Diagnostics 2015; 5(4): 513-545 [PMID: 26854169 PMCID: 4728473 DOI: 10.3390/diagnostics5040513]*

*Zheng SG, Xu HX, Liu LN. Management of hepatocellular carcinoma: The role of contrast-enhanced ultrasound. World journal of radiology 2014; 6(1): 7-14 [PMID: 24578787 PMCID: 3936208 DOI: 10.4329/wjr.v6.i1.7]*

*Duran R, Chapiro J, Scherthaner RE, Geschwind JF. Systematic review of catheter-based intra-arterial therapies in hepatocellular carcinoma: state of the art and future directions. The British journal of radiology 2015; 88(1052): 20140564 [PMID: 25978585 PMCID: 4651391 DOI: 10.1259/bjr.20140564]*