

October 25, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 22204-Revised manuscript.doc).

Title: Latest developments in precancerous lesions of hepatocellular carcinoma

Author: Zhao-Shan Niu, Xiao-Jun Niu, Wen-Hong Wang and Jing Zhao

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 22204

The manuscript has been improved according to the suggestions from You and Reviewers:

1. Format has been updated
 - Copyright agreement was uploaded
 - A copy of signed Conflict-of-interest statement was uploaded
 - Audio core tip was uploaded
 - Language certificate was uploaded
 - Blank space between reference number and the before words in the paper had been deleted.
2. Revision has been made according to the suggestions of the reviewers. **The changes in the revised manuscript are outlined in red.**

(1)Reviewer: 00227134

This comment is not part of a manuscript review.

Response: The authors greatly appreciate the reviewer's comment.

(2)Reviewer: 02447122

In the present article, authors summarized the current knowledge on the characteristics of liver preneoplastic lesions based on clinical, pathological, molecular genetics and radiological studies. Authors have done a very good work in gathering and presenting critical recent findings related to a major problem for clinicians, which is the differentiation of dysplastic lesions from early HCC. This review is detailed, well-organized, and clearly written. In my opinion, it should be published. I have only one suggestion that will be helpful for readers. Authors could prepare a table, with references, making comparisons among the different studies that allow distinguishing microscopic dysplastic foci from macroscopic dysplastic nodules, and showing the evidence that support the idea that high-grade dysplastic nodules are precancerous lesions of HCC.

Response: We thank this reviewer for his excellent suggestion along with his positive comments. According to reviewer's suggestion, such a table (Table 1) has been added to the revised manuscript. "The main pathological, molecular genetic and radiological features of distinction between LGDNs and HGDNs are summarized in Table 1."(Page 10, Section -DYSPLASTIC NODULES (DNs), 2nd paragraph, lines 5-7).

(3)Reviewer: 00625524

Latest Developments in precancerous lesions of hepatocellular carcinoma Zhao-Shan Niu, et al. This article is a review on an important area of precancerous lesions in hepatocellular carcinoma. The authors have exhaustively reviewed literature pertaining this area. Authors also have published a few articles related to this field. I have a few suggestions regarding better presentation of the review. The authors conclude that there is a need for development of biomarkers to detect precancerous lesions at an early stage and existing imaging techniques are inadequate. Therefore the review may be reorganized in following manner. 1. After reviewing development in histopathology, literature related to imaging techniques may be reviewed. 2. Immunohistochemistry and molecular biology techniques may be grouped under I common heading "Biomarkers". 3. Literature related to immunohistochemistry can be the following topic. 4. Sub-heading changes in "DNA methylation" may be put under molecular biology.

Response: Thank you very much for the excellent and valuable suggestions regarding better presentation of our manuscript. The revised editorial has

been reorganized according to reviewer's suggestions.

The structural order of the original manuscript is as follows: “.....

Histopathologic features → Immunohistochemical studies[VEGF、Glypican-3 (GPC3)、Micronucleus (MN)] → Changes in DNA methylation (DNMT3A、RASSF1A) → Molecular biology and genetic studies[Allelic losses (loss of heterozygosity, LOH)、Telomerase reverse-transcriptase (TERT)、MicroRNAs (miRNAs)] → Imaging differences between HGDNs and LGDNs,”

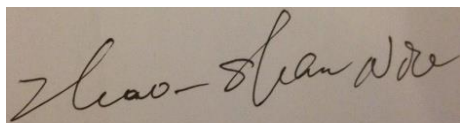
The structural order of the revised manuscript is as follows: “.....

Histopathologic features → Imaging differences between HGDNs and LGDNs → Biomarkers for the discrimination between LGDNs and HGDNs {Molecular Genetic Biomarkers [Allelic losses (loss of heterozygosity, LOH)、Telomerase reverse-transcriptase (TERT)、MicroRNAs (miRNAs) 、Changes in DNA methylation (DNMT3A、RASSF1A)]}→ Immunohistochemical Biomarkers[VEGF、Glypican-3 (GPC3)、Micronucleus (MN)] ,”

4. References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink on a light-colored background. The signature is written in a cursive, flowing style and appears to read 'Zhao-Shan Niu'.

Zhao-Shan Niu, MD
Lab of Micromorphology
Medical College of Qingdao University
Shandong Province, China
E-mail: niu miao1993@hotmail.com