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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 67202

Title: The emerging role of long noncoding RNAs in recurrence hepatocellular carcinomas

Reviewer's code: 00073640
Position: Editorial Board
Academic degree: PhD
Professional title: Associate Research Scientist
Reviewer's Country/Territory: Slovenia
Author's Country/Territory: China

Manuscript submission date: 2021-04-18
Reviewer chosen by: AI Technique
Reviewer accepted review: 2021-04-21 05:29
Reviewer performed review: 2021-04-30 09:43
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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript is topical and interesting. It summarizes the current knowledge about the role of long non-coding RNA in hepatocellular carcinoma. This topic and knowledge is currently of interest and needed. However, in the introduction section there are misleading and incorrect statements that needs to be properly corrected. The authors wrote : » The recurrence of intrahepatic HCC is caused by two different mechanisms: i) intrahepatic metastasis (IM) descending from the primary cancer; and ii) independent carcinogenesis leading to multicentric occurrence (MO), also known as multicentric carcinogenesis. Treatment options for recurrent intrahepatic HCC include repeat liver resection and ablative therapy.[5] (Fig 1)« . The origin of multifocal hepatocellular carcinoma is uncertain, and cannot be determined solely by histologic features. However, previous studies have shown that clarification of the relationship among multiple tumors may be clinically important. Some investigators believe that multifocal hepatocellular carcinomas result from intrahepatic metastasis of a primary tumor, a view that is supported by the unique drainage system of the liver, frequent finding of vascular invasion, and histologically similar tumors. Satellite lesions were frequently observed surrounding the larger tumor lesion in our cases. Other investigators suggest that multifocal tumors in patients with chronic liver disease represent clonally independent tumors arising as a consequence of field effect. It is important to note that neither mechanism is mutually exclusive; both intrahepatic metastasis and field effect may play important roles in the pathogenesis of multifocal hepatocellular carcinoma. However, useful clinical information may be gained through detailed genetic characterization and comparison of clonality between separate tumors. Thus, I strongly suggest authors to correctly state the current patohistological knowledge and state citation. The authors wrote: »MO is characterized as follows: a large body of nodules of well-differentiated

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carcinoma; nodules of well-differentiated carcinoma accompanying less-differentiated carcinoma, with higher differentiation than the primary tumors that have been resected; and without of vascular involvement.[6] IM is usually distributed in a gradient or to a separate tumor near the largest lesion that is significantly smaller than the largest lesion and is histologically similar to or less differentiated than the largest lesion.[7] The "invasion-metastasis cascade" describes the method of recurrence, which starts with separation from tumor cells and migration out of the primary tumor and invasion into the surrounding tissue.[8] After reaching the "destination", these cells either enter a long-term dormant state as a single diffuse tumor cell, or multicellular micrometastases eventually form a macrometastasis.[9] ». These statements are patohistologicaly incorrect and misleading - authors inappropriately reform statements from article they cite. If authors want to provide correct patohistological description of such lesions than I strongly suggest reading proper literature and providing citation from the literature from the field of patohistological classification of HCC tumors and their characteristics or to copy-paste statement from the article they cite. The author wrote: »Histopathological analysis still the most convenient strategy, but it is subjective and limited in accuracy.« Such statement are incorrect and shows that authors do not understant the histopatological characteristics and pathogenesis of HCC. Patients with HCC frequently have multiple anatomically separate tumors, which may have both clinical and biological implications. Two distinct biological processes can lead to multifocal HCC. First, 1 primary HCC can spread to additional locations in the liver, representing intrahepatic metastasis (IM). In addition, because HCC frequently occurs in the background of underlying liver disease, multifocal HCC can also represent multiple independent cancers, also known as multicentric carcinogenesis (MC). Although these 2 possibilities are conceptually quite distinct, they cannot be reliably distinguished based on routine clinical and pathological analyses. Therefore, multiple previous studies have

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attempted to distinguish IM and MC based on molecular alterations, and these studies have reported widely disparate frequencies of these 2 possibilities. Pathology is a specialisation, where a diagnose is based on tissue and cell morphology alterations (this is not subjective!!!!!). In the case of HCC, there are no significant morphological alterations that could be used as a diagnostic markers, therefore various molecular markers are under investigation, including lncRNA.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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SPECIFIC COMMENTS TO AUTHORS

The authors followed suggestions and corrected and improved their manuscript.