



המרכז הרפואי ת"א ע"ש סוראסקי

המכון למחלות דרכי העיכול והכבד
Department of Gastroenterology and Hepatology

05/05/2019

Dear Jia-Ping Yan,

Science Editor

World Journal of Gastroenterology

Manuscript NO: 47845

Title: Hepatocellular Carcinoma in The Post-HCV Era: Should We Change the Paradigm?

We would like to thank you and all the reviewers for their valuable comments and the opportunity to revise our work accordingly. We have addressed and corrected the manuscript in accordance to each point raised. We hope that the revisions in the manuscript and our accompanying responses will be to your satisfaction.

Please find attached a revised version of our manuscript. Revisions in the text are highlighted in yellow.

Yours sincerely,

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Reviewer #1:

Comment: *A useful and timely review that is well written and gives a good overview on the current situation on HCC. The English could be improved by a native speaker. The authors should consider to include a brief discussion on the issue of HCV diagnosis and treatment options in developing/Asian/Eastern countries, which will be one of the major obstacles on the road to eradication.*

Response: We greatly appreciate the positive feedback from the reviewer. We agree that despite the breakthrough of DAA, there are still many barriers to overcome HCV especially in Asian countries. We added a short discussion regarding it as suggested by the reviewer (Page 4, line 6)

Reviewer #2:

Comment: *Good paper. HBV is necessary to mention, as one hundred million people in China were infected with the HBV and with a high risk for the development of HCC.*

Response: We thank the reviewer for his appreciation and the insightful comment. As suggested, we added a sentence regarding HBV (Page 4, line 26)

Reviewer #3

Comment: *This review article discusses a common disease hepatocellular carcinoma (HCC). A series of reviews on this topic have been published recently. Given that new progresses have been made in this field at a rapid pace, this topic will be still one of great interests for the readers. In this manuscript the authors made a good attempt to summarize relevant literature on the risk of HCC occurrence and recurrence in the Post-HCV era. The writing is smooth and the figures are appropriate. I would recommend it for publication if the authors could discuss more updated literature, in particular for this literature: El-Emshaty HM, Saad EA, Gouida MS, Elshahawy ZR (2018) Associations between CD133, CK19 and G2/M in cirrhotic HCV (genotype-4) patients with or without accompanying tumor. Biocell 42(2):55–60*

Response: We are thankful for the reviewer's comment. The article by El-Emshaty HM et al supports the possible role of biomarkers to confirm progression of liver disease-associated with

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HCV to HCC. We added a brief discussion regarding blood based biomarkers to discriminate early HCC (page 10, line 2)

Reviewer #4

Comment: *The authors should be congratulated for this well-written review article. It is thorough, reads well, and addresses an important issue in Hepatology. I have no major concerns. MINOR COMMENTS 1. As authors mention, all most international guidelines recommned continuing surveillance even after the achievement of sustained virological response (SVR). Would surveillance be required in patients who are proved to have marked reduction in fibrosis either through repeat liver biopsy or FibroScan years after achieving SVR? Is there any evidence to support discontinuation of surveillance in this group of patients? 2. Figure 2B: according to Figure 2B, authors recommned 3-4 monthly surveillance following curative therapy for HCC. Given that the risk of HCC recurrence is high in the first 2 years, should this not be 2 years? 3. Title is somewhat misleading. This review is about the risk factors and screening/surveillance of HCC and not about the treatment of it. Therefore the title 'Managing HCC....' is somewhat misleading. I would recommned simplying removing the word 'Managing' and leave the title as 'Hepatocellular Carcinoma in the'. 4. Page 4, line 9, which starts as 'use even in patients with advanced liver disease' should be changed to 'use even in patients with decompensated liver disease'.*

Response: We thank the reviewer for his highly insightful feedback and the constructive comments on the manuscript. We addressed each comment in details as follows:

- Reply to comment1: Whether fibrosis regression translate into a reduced HCC risk beyond the benefit of achieving SVR is an important issue we added a comment addressing it (page 8, line 28).
- Reply to comment 2: We agree with the reviewer's comment and the figure was corrected accordingly
- Reply to comment 3: Title was simplified as suggested
- Reply to comment 4: Rephrasing has been done.



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Reviewer #5:

Comment: *The manuscript of Meringer et al. is a nice and complete review on the recent past and new frontiers of Hepatocellular Carcinoma. It summarizes the main recent literature on the topic offering an easy and exhaustive narrative review to the reader. The only concern regards the two figures which should be eliminated since they do not add any useful message and contain generic data.*

Response: We thank the reviewer for the positive feedback. The figures represent our view based on the recent data and aim to visually summarize the narrative for the reader.