

Dear Editor,

World Journal of Gastrointestinal Endoscopy

Regarding Manuscript # 36681: *Utility of Endoscopy, ERCP and Endoscopic Ultrasound (EUS) in diagnosis and management of Hepatocellular Carcinoma and its complications*

The authors wish to extend our deepest gratitude to the editors and reviewers for the time they spent to review our important article, to provide their invaluable suggestions. And thank you Dr. Cui for allowing us extra time till December 11<sup>th</sup> 2017, to submit our response.

Please find attached our reply to reviewer's comments.

***Reviewer # 03529777:***

The paper " Utility of Endoscopy, ERCP and Endoscopic Ultrasound (EUS) in diagnosis and management of Hepatocellular Carcinoma and its complications" is is an interesting review about the management of the utility of hepatocellular carcinoma. It is a very complete and well written review that addresses the most important topics. The present study is a review on a topic not much described in the literature and very heterogeneous with little evidence. The endoscopic approach in HCC is an alternative for diagnosis and to resolve some complications as well as in centers that do not have interventional radiology. Nevertheless, this type of approach must be developed further with more prospective randomized trials since it can be used only in selected cases. However, the present study is limited in the methodology. 1. If the authors present this paper as a systematic review they should include a systematic review based on recommendations of PRISMA, STROBE and AMSTAR. They should include the information sources and database searching, quality assessment, data extraction and data synthesis about the review. In the current format this study should be presented as a monography rather than as a review. 2. Authors should change the title "Utility of EUS and Endoscopy in diagnosis and staging of HCC" because the text refers more to recommendations on imaging tests than just the utility of EUS and endoscopy. 3. There is a grammatical error:

the authors should change demonstrated by demonstrated. 4. In the manuscript the authors should choose either numbers or letters but not both. 5. In the section “potential advantages of EUS in the management algorithm” the text does not describe complications and the therapeutic roles. They should be mentioned before the section of potential advantages of EUS. 6 In the section “Utility of ZEUS and endoscopy in treatment of HCC” the role of microwaves and radioembolization should be discussed. 7. Authors should remove Figure 1 and should include an algorithm of the diagnostic role of EUS in the diagnosis and management of HCC. They should also include a table with the articles reviewed and the main topics developed in the text. 8. The authors should include in the bibliography and in the discussion these two revisions: - Shah KN1, Clary BM2. Endoscopic and percutaneous approaches to the treatment of biliary tract and primary liver tumors: controversies and advances. *Surg Oncol Clin N Am*. 2014 Apr;23(2):207-30. doi: 10.1016/j.soc.2013.10.003. Epub 2013 Dec 27. - Minami Y1, Kudo M. Hepatocellular carcinoma with obstructive jaundice: endoscopic and percutaneous biliary drainage. *Dig Dis*. 2012;30(6):592-7. doi: 10.1159/000343087. Epub 2012 Dec 13.

***Authors' Reply:*** The authors wish to thank you for recognizing that our topic is not much described in the literature and is very heterogeneous with little evidence, yet you found our review article to be complete and well-written, which we wholeheartedly appreciate.

The authors completely agree with you that given heterogeneous evidence in this field, more prospective randomized trials are needed before adoption of endoscopic approach in HCC (in select cases), and especially at centers with limited interventional radiology (IR) services. Our purpose of submitting this manuscript is not to promote utility of endoscopic approaches over IR, but to bring forward the recent advances in this field, for readers to be aware about the growing field of endohepatology.

- 1) This article is not intended as a systematic review, given very limited and very heterogeneous evidence in this field. We agree with you that this is more of a monography, and we have changed the submission category to reflect that on the

cover page. As stated previously, our manuscript puts forward the recent advances in this field, for readers to be aware about the growing field of endohepatology.

- 2) Thank you for the suggestion of a new title, which we have changed to “*Utility of Endoscopic Ultrasound (EUS) and Endoscopy in diagnosis and management of Hepatocellular Carcinoma and its complications: What does EUS offer above and beyond conventional cross-sectional imaging?*”
- 3) The grammatical errors have been carefully corrected in the revised manuscript, including “demonstrated”.
- 4) We have edited the numbers/letters to keep manuscript consistent. We have removed the alphabets, and replaced with bullet points, to reflect transition of different major sections of the manuscript.
- 5) The sequence of EUS complications and advantages has been changed, per your suggestion. We have now included potential EUS advantages as a part of Figure-1 algorithm, as per your suggestion in point # 7.
- 6) We have added detailed discussions regarding role of microwaves, and radioembolization, as per your suggestion, to further strengthen the discussion.
- 7) We have omitted Figure-1 per your advise, and replaced with an algorithm to demonstrate potential role of EUS in diagnosis and management of HCC. The key messages of the studies reviewed have been included in the text at appropriate junctures, and an additional table would mean repetition of the same data. However, if you still feel it is necessary, and the journal allows publication of large supplemental files, we are more than happy to comply and provide a table.
- 8) The suggested two references have been added to the bibliography as references 111 and 112.

**Reviewer # 00013213:**

Your review article reviewing the use of endoscopic procedures in diagnosis and treatment of HCC is attractive, albeit there are some remarks that need your response: 1- The use of upper endoscopy and ERCP in various situations related to HCC is a daily practice and need not to be reviewed and it will be more appropriate to restrict your review on the recent and add on uses of EUS in the diagnosis and management of HCC. 2- You have not presented any mention about the diagnostic criteria of HCC nodular lesions as detected by EUS that makes it more superior in detection of smaller lesions than other modalities. 3- In each study enlisted at your review, you have to mention its data for accuracy of the EUS in the diagnosis of HCC compared to a gold standard that the study has used. 4-Also, it is better to refer to the rate of occurrence of adverse events in each cited study. 5-Major language revision is required.

**Authors' Reply:** The authors wish to thank you for your supportive comments.

1. We acknowledge that use of upper endoscopy and ERCP are standard in management of various situations related to HCC. Our intent was to present a one stop-shop article discussing all the aspects of use of endoscopic techniques in HCC, and moreover with the expanding field of endohepatology, these details were presented to engage the readers.

However, per your suggestion, we have significantly shortened our discussion of endoscopy and ERCP, and expanded more on the potential uses of EUS, by including role of contrast-enhances EUS, microwave ablation, as well as TARE. The remaining endoscopic discussion pertains to esophageal and gastric varices, and we use that as segway to discuss emerging roles of EUS guided varices treatments. Thank you for the suggestion.

2. The only established EUS criteria for liver nodular lesions pertains to the study by Fujii-Lau et al. published in GIE in 2015, which helps distinguish benign from malignant nodular lesions, but are not specific for HCC.

However, we appreciate the suggestion, and have included this article in our discussion.

3. We have extensively discussed the diagnostic accuracy of EUS-FNA over conventional diagnostic modalities, which are considered conventional gold standard, under the topic “EUS and EUS-FNA vs. other imaging techniques (US, CT and MRI)” Please refer to the paragraph, “*MRI with angiography has been shown to be better than CT for diagnosis of HCC, the benefit being mostly for detection of nodules between 10-20 mm<sup>22-23</sup>. At present, it is considered the gold standard for staging of HCC prior to surgery<sup>22,24</sup>. The accuracy of EUS alone for accurate diagnosis of liver lesions may only be 65%, but it increases to ~ 94% when combined with FNA which is similar to that of MRI<sup>19</sup>. However, in the same study EUS was found to detect a significantly higher number of nodular lesions than MRI ( $p = 0.04$ )<sup>19</sup>.*”
4. Regarding the rate of occurrence of adverse events: After your query, a careful re-review of HCC-EUS literature was performed and we observe that the data available in HCC specific studies pertains to overall complications of all the EUS-related interventions, and not clear about individual adverse events.  
These available details on overall complications of EUS-FNA have been added to our revised manuscript as a separate paragraph, per your suggestion.
5. The language and grammatical errors have been carefully corrected in the revised manuscript.

The authors hope that after resolution of all concerns raised by the reviewers, in a point-by-point fashion, our important manuscript will be accepted into your journal for publication.

Sincerely,

Mohit Girotra, Kaartik Soota, Amaninder S Dhaliwal, and co-authors.