

ANSWERING REVIEWERS

Name of the journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40129

TITLE: Ampulla of Vater carcinoma: molecular landscape and clinical implications

Dear Editors and Reviewer, *World Journal of Gastrointestinal Oncology*

We sincerely thank you for your constructive comments and suggestions, as well as for the words of praise about our paper, also giving us the possibility to send a revised version of our manuscript. Here we present our answers, point by point, to all your evaluable questions. All changes in the text of the revised manuscript have been highlighted in **yellow**.

REVIEWER 1.

Comment 1. I would like to know how different mutations impact outcomes in AVC. Is there a poor prognostic group that should undergo more radical surgery or surgery can be deferred completely in some patients?

Answer. Thanks a lot for raising such comment. We have added a paragraph about this topic in the revised manuscript (the last paragraph in the section "Genetic Landscape" of the revised manuscript). We have highlighted that *TP53* and *KRAS* represent independent poor prognostic predictors regardless of histological subtypes. After discussing in that paragraph also the importance of the Wnt-pathway, we have also indicated that mutations affecting *SMAD4* and *CDKN2A* usually occur at later stages of tumor growth. We have also presented, as suggested, the impact of the mutational status of these genes in influencing current and future therapeutic approaches, also commenting the potential roles of microsatellite instability and immunotherapy.

Comment 2. Management of dysplasia in this region should also be considered since many

a times dysplasia progresses to AVC and is a management dilemma.

Answer. Thank you for this observation. We have added a paragraph in the revised manuscript to better describe this interesting topic (2nd paragraph in the section “Endoscopic vs. surgical treatment – Endoscopic Papillectomy”). In this paragraph, we have discussed above all the importance of correct indications for papillectomy vs. surgery, and the issue of surgical margins in these types of procedures.

REVIEWER 2.

Comment 1. In the manuscript, frequent mutated AVC genes in different histotypes are discussed in detail. However, its prognostic values are introduced within relatively short space. Further information should be added to help in better understanding the inner association.

Answer. Thank you for this consideration. This is very similar to the comment 1 of Reviewer #1. We have provided further information about this topic in the last paragraph of the section “Genetic Landscape” of the revised manuscript. Following your evaluable suggestion, we have discussed the most important molecular alterations in this tumor type.

Comment 2. There are a few spelling and grammatical errors that should be checked carefully and corrected throughout the manuscript.

Answer. We have checked and corrected typos and grammatical errors. Thanks.

Concluding, we want to thank the Editors and the Reviewers for the possibility to send a revised version of our manuscript. Thanks to the important suggestions received, we hope that now the revised manuscript has been improved, becoming also acceptable for publication on World Journal of Gastrointestinal Oncology.

Thank you. Yours sincerely,

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