

Dear Editorial officer

Please review the feedback on the issues raised by the peer review highlighted with yellow color.

Reviewer #1:

Specific Comments to Authors: This paper covers very interesting topics. Contents are generally okay but some points are missing. After improving the contents, this paper can be very useful. Specific comments are below. This review still lacks important factors. In a new short section, the author should discuss environmental, dietary, and life habit factors which influence metabolism, cell survival, tumor progression and metastasis. The authors should discuss these points, influence of those factors on tumor biology, metastasis, and clinical outcome. These factors may influence molecular pathology in each patient differentially. Along with the same context, research on environment, diet, lifestyle, life course, and other factors should be integrated with analyses of personalized molecular biomarkers in tumor. Revised the manuscript and added external lifestyle factors including BMI, dietary, life habit. And discuss those factors on tumor biology, metastasis and clinical outcome which could influence molecular pathology.

The authors should discuss molecular pathological epidemiology research that can investigate those factors in relation to molecular pathologies, metastasis, and clinical outcomes. Molecular pathological epidemiology research has been discussed in the literature, eg, Ann Rev Pathol 2019, Gut 2022, and can be a promising direction. This will also significantly add novelty to this article.

Totally agreed with the peer's opinion and we are close to complete another manuscript which explain the molecular pathologies especially for the mCRC patients. The authors expect to communicate again with peer reviewer when the manuscript is accepted by the journal.

Please write TP53, TP53 mutation, TP53 gene, TP53 protein, etc. (not p53).

See www.genenames.org

Already revised manuscript accordingly.

Reviewer #2:

Specific Comments to Authors: .- Conclusion: Minor revisions. So, I encourage authors to improve the manuscript with these suggestions, at least in enumeration of bibliographical citations, to be evaluated for publication.

Checked all the citations and revised some of them accordingly.