

18 July 2023

Respected Sir/Madam

**Reference#: 85686**

**Title:** Systemic treatment for metastatic colorectal cancer

I am hereby giving points response to your comments;

### Reviewer #1

**Comment #1:** As immunotherapy has achieved significant efficacy and acceptable toxicity in both first-line and second-line treatment of advanced EC, neoadjuvant immunotherapy has become a research hotspot in resectable locally advanced EC currently. In this paper, the latest research progress and some limitations of neoadjuvant immunotherapy in locally advanced resectable EC were reviewed. The feasibility, safety and efficacy of neoadjuvant immunotherapy still need to be further verified by large randomized clinical studies.

**Author answer:** Thank you very much for your valuable comments. I do agree with the comments.

### Reviewer #2

**Comment #1:** The authors wrote a quite interesting review on esophageal cancer and treatment. This is generally of high interest. There are big research gaps. Foods and other factors are known to influence the gut microbiome, which in turn affect tumorigenesis. At least, they should discuss interactions if foods are not main themes. There is a widely open opportunity that is currently missed. These facts should be discussed. The authors should discuss gaps and opportunities such as research on dietary / lifestyle factors including alcohol, smoking, medications, microbiome, and personalized molecular biomarkers, which is needed for further research. The authors should discuss molecular pathological epidemiology research that can investigate diet, microbiota, immune and other factors in relation to molecular pathologies and clinical outcomes. Molecular pathological epidemiology research can be a promising direction (eg, Annu Rev Pathol 2019; Gut 2022; etc.) and should be discussed in this paper.

**Author answer:** Thank you very much for the important comments and advice. I already added a paragraph to improve understanding about the role of diet and microbiota in EC.

### Reviewer #3

**Comment #1:** This paper has some significance for clinicians and researchers working. However, it has some major issues: 1. This minireview paper is by far too long, it should be significantly shortened. Do not review the subject extensively.

**Author answer:** Thank you for your comment, however, I try to write this manuscript concisely.

**Comment #2:** 2. The authors should produce 2-3 figures and tables and so that paper is easier to read and data can be presented in a compact manner.

**Author answer:** Thank you for your advised. I already inserted 1 table for a better understanding.

**Comment #3:** 3. The author might need to add more information about the mechanisms of immune checkpoint inhibitors for resectable esophageal cancer treatment.

**Author answer:** Thank you for the suggestion. The molecular mechanisms of immune checkpoint inhibitors were already mentioned in the former paragraph of the manuscript.

Best regards,

W. Leowattana

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