

Ulm, July 28th 2021

Shu-You Peng

Editor-in-Chief
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Response to the reviewer

Dear Prof. Peng,
Dear reviewer,

Please find our response to the reviewer's comments below:

The authors wrote a quite interesting review on colo-rectal cancer. This is generally of interest. Following things should be addressed and the authors should improve the paper. Prevention should be the top topics. It is currently hidden in the middle. The authors should discuss more prevention and early detection as main topics since they are important in reducing the cancer burden much more effectively than treatment. The authors should discuss the importance of diet and lifestyle for not only prevention but also survivorship. Indeed there are many environmental, dietary, and lifestyle factors that influence the microbiome (in both intestine and other tissue), immune system, pathogenic mechanisms. The authors should discuss factors other than diet too, eg, smoking, alcohol, obesity, diabetes, bowel habits, etc. There are also influences of germline genetic variations on both immune system and microbiota. Gene-by-environment interactions should be discussed. In these lines, research on dietary / lifestyle factors, microbiome, immunity, and personalized molecular biomarkers in tumor is needed for prevention and treatment research. The authors should discuss molecular pathological epidemiology research that can investigate those factors in relation to microbiome, molecular pathologies, immunity, and clinical outcomes. Molecular pathological epidemiology research can be a promising direction. Strengths and challenges of molecular pathological epidemiology (J Pathol 2019, Ann Rev Pathol 2019, Curr Colorectal Cancer Rep 2017, etc.) should be discussed. Currently, despite use of the term "multidisciplinary", the authors mainly discuss surgery and oncology only. The authors should discuss epidemiology, nutrition, pathology, genetics, microbiology, immunology, gastroenterology, and integration of these fields.

We thank the reviewer for pointing out the importance of preventive measures in reducing the burden of colon and rectal cancer.

We do agree that primary prevention can overall be more effective than secondary prevention. We've included some highly interesting literature on the exogenous and endogenous risk factors for the development of CRC. We believe that, by addressing these individual risk factors, the trend of personalizing medicine can not only be included in therapeutics but also in prevention.

However, the first measures taken by our interdisciplinary group were to increase the outcome of surgical patients. For those, obviously, merely preventive measures are

several years late. Nevertheless, our team succeeded in improving overall survival even in far progressed cases. We believe these efforts to be a central part of our paper.

Still, we realized that surgery alone will not solve the burden that CRC puts on patients and clinicians. By including highly motivated and skillful colleagues from several professional directions, we were also able to include both preventive as well as best supportive care measures for patients, all-in-all in order to improve our patient's quality of life.

We hope that were able to address your comments to your satisfaction.

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