

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Different treatment strategies and molecular features between right-sided and left-sided colon cancers

Author: Hong Shen, Jiao Yang, Qing Huang, Meng-Jie Jiang, Yi-Nuo Tan, Jian-Fei Fu, Li-Zhen Zhu, Xue-Feng Fang, Ying Yuan

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated according to the Format for Topic Highlight. All the identify statistical probability (P) used the special font and style "P"

2 Revision has been made according to the suggestions of the reviewer

1) Reviewed by 03062291 Comments To Authors

Current review aims at summarizing the differences in-between these cancer types with respect to various therapeutic strategies. The manuscript is well written and does not require significant improvement. However, I would like to see more clear differences for the patients with RCC and LCCC. For instance - where is the higher median age at diagnosis, the age-dependent prognosis (especially as a risk factor for post-surgical recurrence). It would be also helpful to include abbreviations for uncommon terms.

Answer to Reviewer 03062291:

Thank you for your advice. Because this paper is mainly focused on the survival and molecular features, it has just mentioned that "The incidence of RCC is associated with a number of risk factors, for example female, old age, previous cancer history or insulin resistance" in "Introduction: Line 9". Most studies found that patients with RCC have higher median age at diagnosis than LCC, for example, it's 73 years old versus 69 years old in Meguid's paper[Reference 5]. Benedix's study[2] revealed a linear correlation between age and tumor location. The further tumor was from ileocecal valve, the younger median age of patients was, from 71.6 years to 68.3 years ($P < 0.001$) [Reference 10]. Namely, the CRC translated from left to right as age increased. Actually, we have written another manuscript focused on the different risk factors of RCC and LCC, which has been accepted in a Chinese magazine.

2) Reviewed by 03088461 Comments To Authors

The authors reviewed the molecular and genetic background of right colon cancer and left colon cancer. The outcome of the CRC patients differs according to the site and molecular biological characteristics. I think the bare bones of the theme is well written. It would be accepted with minor revision.

1.1 Radical surgery: Line 9: "Mortain's study" > Is "Moritani's" correct? 1.1 Radical surgery: Line 12: "Later in 1990s, published studies reported that differences emerged in 5-year OS rates of RCC and LCC, of which were 56.3% versus 59.7% (p<0.01)[5]," > This data is not seen in the reference 5. Please cite the correct paper. There are two abbreviations for "metastatic colorectal cancer", such as "MCC" and "metastatic CRC". The authors had better use one term in order to avoid confusion. "P53" should be described as "p53". Both are used in the text. Proximal CRC and Distal CRC, RCC and LCC, Are these relationships (the borderline) the same? If these are the same, please describe it in the text.

Answer to Reviewer 03088461:

Thank you for your detailed review.

- 1) In "Radical surgery: Line 9", the correct word is "Moritani's".
- 2) For "Radical surgery: Line 12", the correct reference should be "5 Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N. Is there a difference in survival between right- versus left-sided colon cancers? *Annals of Surgical Oncology* 2008;15(9):2388-2394[PMID: 18622647 DOI: 10.1245/s10434-008-0015-y]". The survivals of patients with colon cancers in 1988-2003 were analyzed with such result that "Survival for left-sided colon cancers was 59.7% at 5 years, 41.9% at 10 years, and 29.5% at 15 years. For right-sided colon cancers, survival was 56.3% at 5 years, 37.8% at 10 years, and 24.5% at 15 years. Survival of left- and right-sided colon cancer subjects was significantly different at all three of these time points (P<.001)." (at the second paragraph, in Page 2392).
- 3) The former "metastatic colorectal cancer" includes metastatic cancers derived from colon and rectum, while the "MCC" means metastatic colon cancers. They are two different groups. In several studies, rectal cancers were integrated into left colorectal cancers. They made comparisons among right colon cancers and left colorectal cancers. We couldn't extract independent data of left colon cancers, so that two abbreviations were used.
- 4) All the "P53" were changed into "p53".
- 5) In my opinion, the borderlines for "Proximal CRC and Distal CRC" and "RCC and LCC" are the same. In other words, "Proximal CRC" and "RCC" are the same group, but "Distal CRC" contains LCC and rectal cancers.

3) Reviewed by 03086186 Comments To Authors

The authors have made a review on the differences between right-sided and left-sided colon cancers in regard of treatment strategies and molecular features. The review is comprehensive on these aspects and is expected to draw interest from the reader. However, I expect more citation of works from China.

Answers to Reviewer 03086186:

Thanks for your advice. There are few credible Chinese works on this theme, either for small sample size or publication in Chinese magazine. We have added another citation of works from China in "2.4 RAS: Line 24". In addition, the conclusion in "2.4 RAS: Line 9" is also a Chinese work.

3. According to the advices in "**16676** Edited.PDF", such changes have been made:

Word version document was submitted

4. Conflict-of-interest statement in PDF format was added.

5. Copyright Assignment form in PDF format was added