

Reviewer A

The study compared survival rates for different types of colorectal cancer and their impact on liver metastasis using data from the SEER database. They used statistical methods to identify risk and prognostic factors and found that right-sided colon cancer had a worse prognosis compared to left-sided colon cancer and rectal cancer. They also found that left-sided colon cancer had higher survival rates and rectal cancer had the highest median survival. The study accounted for confounding factors to obtain more reliable results.

However, this article still leaves some shortcomings:

1. There have been many previous studies comparing the prognosis of left-sided colon cancer, right-sided colon cancer, and rectal cancer, but the focus of this study on comparing the survival prognosis of the three is not particularly innovative.

Reply: Yes, multiple studies have suggested that the primary tumor location (PTL) influences the prognosis of patients with advanced CRC, and patients with left-sided colon cancer have a better OS compared with that of patients with R-CCs. However, whether PTL is associated with long-term survival in patients with CRC liver metastases after radical resection of the primary tumor and metastatic tumor remains inconclusive, which still needs to be confirmed. Our study uses data of patients in the SEER database for survival analysis to ensure sufficient quantity. Furthermore, we use propensity score matching method (PSM) to analyze the data to reduce the effect of individual confounding factors and selective propensity on study results, which is a method that can simultaneously match multiple variables to balance baseline differences.

Changes in the text: None

2. The disadvantages of this article include: the narrative order of the article is messy, the table form is not uniform, the picture definition is low, the size of the four charts in Figure 2 is not uniform, and the font is not uniform.

Reply: We have unified the table. And the pictures are replaced with clearer ones. The size of the four charts in Figure 2 are also unified.

3. All tables should be presented in a three-line table format, and boldface should be used consistently for table titles. Larger tables can be separated by background colors for better readability.

Reply: All tables have been revised to a three-line table format, and boldface are used consistently for table titles now. Different background color is also used for tables, which makes the tables better readability now.

4. in line 94, "unresectable colorectal metastases" is incorrect and should be "unresectable liver metastasis."

Reply: It has been revised now. Thank you for your reminder.

Changes in the text: see page 4, line 5.

5. In line 213, "In addition, it is worth noting that the above factors have been

unanimously recognized in terms of all-cause mortality and cancer mortality," please cite relevant literature to support the meaning expressed in the sentence.

Reply: We deleted the sentence. Thanks.

6. In line 270, "patients with rectal primary lesions also having a lower prognostic score," this sentence does not match the study results as rectal cancer had the best survival prognosis curve in Figure 2.

Reply: The wrong description has been revised. Thanks.

Changes in the text: see page 10, line 1

7. In Table 1, the expression "Combined diagnosis-liver" is not clear enough, and it is unclear whether it refers to liver metastasis.

Reply: Yes, it means "with liver metastasis". We have explained it below the Table.

8. Abbreviations used in tables should be explained, such as "Surg Oth Reg/Dis" and "Combined DX-liver," to facilitate quick reading by readers.

Reply: "Surg Oth Reg/Dis" means "having surgical operation on metastatic foci". "Combined DX-liver" has the same meaning with "Combined diagnosis-liver". We have unified the abbreviation and explained them below the Table. Thanks.

Reviewer B

The paper titled "Primary tumor location impacts survival in colorectal cancer patients after primary resection: a population-based propensity score matching cohort study" is interesting. R-CC has a worse survival prognosis compared to L-CC and ReC, and they are fundamentally different tumors that have distinct effects on CRC patients with liver metastases. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What are the factors contributing to this difference? How to determine targeted treatment based on the location of the primary tumor? It is recommended to add relevant content.

Reply: The reason for this discrepancy is the different embryological origins of the left and right colon (the left colon originates from the hindgut and the right colon from the midgut) (8). As for the targeted treatment, researches have reported that gene mutations vary greatly in right-sided and left-sided tumors (37, 38). For example, KRAS mutation and BRAF V600E mutation are predictive markers of resistance to epidermal growth factor-targeted antibodies (39, 40), and BRAF V600E mutation is more common in proximal tumors (41). Furthermore, TP53 mutation frequency is higher in distal tumors (42), and metastatic CRC patients with TP53 mutation have been reported to have shorter survival after receiving chemotherapy (43). These findings indicated that the changes of tumor specific molecules vary with the location of the primary tumor, which may be used for targeted treatment.

Changes in the text: None

2) What are the important factors that affect the long-term survival and quality of life of colorectal cancer patients after primary resection? It is recommended to add relevant content.

Reply: In this study, we found that CRC and CRC with liver metastases subgroup

patients shared several favorable prognostic factors (age <60, married, low LNR, and low TNM stage) and a common unfavorable prognostic factor (R-CC).

Changes in the text: None

3) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Influence of first line chemotherapy strategy depending on primary tumor location in metastatic colorectal cancer, J Gastrointest Oncol, PMID: 34532106”. It is recommended to quote this article.

Reply: Thank you for your advice. The reference is helpful and it is cited now.

Changes in the text: see page 4, line 2

4) There have been many studies on colorectal cancer. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.

Reply: Yes, multiple studies have suggested that the primary tumor location (PTL) influences the prognosis of patients with advanced CRC, and patients with left-sided colon cancer have a better OS compared with that of patients with R-CCs. However, whether PTL is associated with long-term survival in patients with CRC liver metastases after radical resection of the primary tumor and metastatic tumor remains inconclusive, which still needs to be confirmed. Our study uses data of patients in the SEER database for survival analysis to ensure sufficient quantity. Furthermore, we use propensity score matching method (PSM) to analyze the data to reduce the effect of individual confounding factors and selective propensity on study results, which is a method that can simultaneously match multiple variables to balance baseline differences.

Changes in the text: None

5) What type of patients benefit most from the results of this study? What is the author's next research plan? It is recommended to add relevant content to the discussion.

Reply: This population-based propensity score-adjusted analysis of mCRC patients provided compelling evidence that the survival rate of patients with surgically resected liver metastases from CRC varies with the location of the primary tumor. The survival rate of patients with R-CC was significantly lower than that of patients with L-CC or ReC. Whether the patient has an R-CC tumor or L-CC and ReC tumor is an important factor to be considered before surgery for metastatic disease. Targeted treatment strategies based on the location of the primary tumor may improve the prognosis of patients with R-CC.

Changes in the text: None