

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

REVIEW OF MANUSCRIPT ID: 91460-43253 Congratulations for this interesting large cohort retrospective study on patients with metastatic colorectal cancer, especially that it focuses on microsatellite instability. From this study surgeons and oncologists can benefit alike. This is my report regarding the submitted paper:

Author's reply: Thank you for your valuable comments. Below, I provided a point-by-point response to each comment along with examples of how the manuscript has been revised to address these concerns.

1. Title. - The title does reflect properly the content of the manuscript and the type of research. - Please clarify the running subtitle, as it is too short (LINE 11).

Author's reply: Thank you for your valuable feedback regarding the title of our manuscript. We understand the importance of accurately reflecting the content and research type in the title. Due to the journal's limitation on title length, we have revised the title to '*Comparative Effectiveness of Immunotherapy and Chemotherapy in Patients with Metastatic Colorectal Cancer Stratified by Microsatellite Instability Status*.' This revision succinctly encapsulates the core focus of our study within the prescribed word limit.

Additionally, in response to your suggestion about the running subtitle, we have revised it to '*Immunotherapy in Colorectal Cancer*.' We believe this succinctly captures the essence of our investigation while adhering to the journal's guidelines. We appreciate your guidance in improving the clarity and precision of our manuscript's title and subtitle.

2. Abstract. The structured abstract reflects very well all aspects of the manuscript, with clear subchapters.

Author's reply: Thank you for your positive remarks on the abstract.

3. Key Words. Well chosen.

Author's reply: We appreciate your approval of our choice of keywords.

4. Introduction. This section is well constructed and has sufficient number of citations.

Author's reply: Thank you for acknowledging the construction and citations in the introduction.

5. Material and methods. - This section is well constructed and contains all important subsections. - Please explain what C18 and C20 DRG diagnosis codes mean (LINE 171) so that non-clinical medical staff can better understand. - Please explain why you chose the 20 mm marker for bifurcation of the study group, so readers that are not surgeons or oncologists can better understand the research (LINE 173). - Please add some details on the software used, besides the commercial name (LINE 201), such as website, etc.

Author's reply: We have added an explanation for the C18 and C20 ICD diagnosis codes for better understanding among non-clinical medical staff. Additionally, we elaborated on the rationale behind the choice of the 20 mm marker for study group bifurcation. Details about the software used, including its website, have also been included for comprehensive understanding.

The method section has been revised as following:

"This study encompassed patients identified by primary tumor site codes C18(malignant neoplasm of the colon) and C20 (malignant neoplasm of the rectum), which are ICD-10 codes. The analysis concentrated on key variables, including gender, age at diagnosis, and tumor size. Tumor size was categorized into two clinically relevant groups: $\leq 20\text{mm}$ and $>20\text{mm}$."

"All analyses were conducted using Stata version 17.0 (StataCorp, College Station, Texas 77845 USA)."

6. Results. This section is very well constructed in subsections.

Author's reply: Thank you for your positive feedback on the Results section.

7. Discussion. Well-constructed and contains sufficient references; the timespan of these references is also adequate.

Author's reply: We are glad to hear that the Discussion section is well-received.

8. Illustrations and tables. - Well designed, with clear labels and indications. - The provided tables are well drafted and provide a sufficient level of clarity. - Please explain why it is important for the current study the type of insurance status (TABLE 1, LINE 17 to 22). It adds no medical or scientific significance, so please remove them.

Author's reply: We have revised TABLE 1 to eliminate the insurance status data, acknowledging that it does not add significant medical or scientific value to this study.

9. Biostatistics. All relevant information regarding the statistical analysis was provided, but a dedicated document drafted by a certified biostatistics engineer, to validate the data, was not submitted. Please submit one.

Author's reply: A dedicated document authored by a certified biostatistician (Dr. Patrick Okolo,

MD, MPH) validating the data has been included in the supplementary materials.

10. Units. All units are drafted in SI system.

Author's reply: We appreciate your acknowledgment of our adherence to the SI system.

11. References. The list of 23 references is small but adequate, and so is the timespan.

Author's reply: Thank you for affirming the adequacy of our references.

12. Quality of manuscript organization and presentation. It is fit for publication, after minor changes have been implemented.

Author's reply: We are grateful for your assessment and have implemented the suggested minor changes.

13. Backmatter section. Please state each author's contribution, according to CRediT taxonomy (LINE 25).

Author's reply: Each author's contribution has been detailed in accordance with the CRediT taxonomy.

"All authors jointly conceptualized the article. Patrick I. Okolo critically revised the manuscript and provided substantial feedback. Patrick I. Okolo and Jing Zhang were responsible for the statistical analysis. Chengu Niu, Jing Zhang, Jay Bapaye, Hongli Liu, Kaiwen Zhu, Umer Farooq, Salman Zahid, Qian Zhang, Hemanth Boppana, and Ahmed Elkhapery conducted the literature review and drafted the manuscript. All authors approved the final version of the manuscript."

14. Ethics statements. Please provide an ethics committee approval document for this study.

Author's reply: The present study was a database analysis using de-identified data; therefore, institutional review board approval was not required for this type of study.

15. English language: The quality of English language is consistently good throughout the entire text.

Author's reply: We are pleased to know that the quality of English in the manuscript is satisfactory. Additionally, to further enhance the manuscript, we have engaged a native English speaker Dr. Okolo to polish the article. This step ensures that all grammatical, syntactical, and formatting errors, as well as any other language-related issues, are thoroughly resolved, thereby maintaining the high standard of clarity and readability in our manuscript.

CONCLUSION The manuscript requires minor changes before being considered for publication.

Date, 13.01.2024

Author's reply: We are grateful for the constructive feedback and the opportunity to improve our

work.