

Reviewer 1

The manuscript provides a thorough review of liver transplantation (LT) as a therapeutic option for metastatic colorectal cancer (mCRC), focusing on colorectal liver metastases (CRLM). By summarizing key clinical trials, advancements in patient selection, and the integration of modern surgical techniques, the authors highlight the emerging role of LT in oncology. The manuscript addresses an important clinical topic, but it requires improvements in language clarity, grammatical accuracy, consistency in formatting, and additional references to strengthen key claims.

- Thank you for your thoughtful feedback and valuable suggestions. We greatly appreciate the time and effort you dedicated to reviewing our manuscript. Below are our responses to each of your comments:

Abstract Line 4: Rephrase "Recent advancements and a deeper understanding of oncologic outcomes..." to "Recent advancements in oncologic outcomes and clinical understanding..."

- Author reply: Thank you for this helpful suggestion. The revision enhances the clarity of the sentence.

Line 12: Correct "We discussed the inclusion criteria and eligibility factors..." to "This review discusses the inclusion criteria and eligibility factors..."

- Author reply: We have made this change to ensure the abstract maintains consistency and uses the appropriate tense.

Introduction Line 7: Provide updated statistics on cancer in general as well as this cancer type prevalence, including survival rates, to highlight the critical need for prognostic biomarkers. Cite "Cancer statistics, 2024, 2024". Then give intro in cancer therapy in general, cite NIH paper "Cancer treatments: Past, present, and future, 2024" (PMID: 38909530) for more information. Include citations for liver metastases being the most common site of distant spread in CRC.

Author reply:

- We have updated the statistics on cancer prevalence, including colorectal cancer, as well as survival rates, citing "Cancer statistics, 2024". We also included the NIH paper "Cancer treatments: Past, present, and future, 2024" (PMID: 38909530) for a broader perspective on cancer therapy. Additionally, we have added citations for liver metastases being the most common site of distant spread in CRC.

Line 14: The phrase "Traditional management strategies include..." should specify examples such as surgical resection and systemic chemotherapy, with citations.

- Author reply: We have specified examples of traditional management strategies, including surgical resection and systemic chemotherapy, with appropriate citations.

Line 26: Add recent references to support the statement that LT achieves survival rates comparable to primary liver malignancies. Eligibility Criteria

- Author reply: We have added recent references to support this claim and enhance the manuscript's evidence base.

Line 5: Rephrase "In the past decades, LT for CRCLM was a contraindication..." to "Historically, LT for CRCLM was contraindicated..."

- Author reply: We have rephrased this sentence as suggested for improved clarity and historical context.

Line 18: Provide more details about the Oslo score and Fong clinical risk score in Table 1, emphasizing their clinical relevance.

- Author reply: We have added more details about the Oslo score and Fong clinical risk score in Table 1, highlighting their clinical relevance as requested.

Line 25: Include a brief explanation of the significance of BRAF and RAS mutations in patient selection. Trials and Studies

- *Author reply: We have included an explanation of the significance of BRAF and RAS mutations in patient selection, providing a more comprehensive understanding of these factors.*

Line 6: Clarify the differences in inclusion criteria between SECA-I and SECA-II, highlighting their impact on survival outcomes.

- *Author reply: We have clarified the differences in inclusion criteria between SECA-I and SECA-II and discussed their impact on survival outcomes.*

Line 14: Add a summary table comparing the methodologies and key outcomes of trials listed in Table 2 for clarity.

- *Author reply: We have added a summary table (table 3) that compares the methodologies and key outcomes of the trials listed in Table 2 for better clarity.*

Line 20: Include references to studies on normothermic machine perfusion technologies improving graft utilization rates.

- *Author reply: We have included references to studies on normothermic machine perfusion technologies, expanding the manuscript's discussion on graft utilization.*

Discussion Line 5: Discuss the potential barriers to global adoption of LT for CRLM, such as healthcare policy and ethical considerations.

- *Author reply: We have discussed the potential barriers to global adoption of LT for CRLM, including healthcare policy and ethical considerations.*

Line 14: The statement "Immunosuppressive therapy used to prevent allograft rejection may accelerate oncologic relapse..." requires additional references and clarification.

- *Author reply: We have added additional references and clarification regarding this statement to support it more robustly.*

Line 22: Expand on the long-term outcomes of RAPID and RAVAS techniques, with case-specific examples if available. discuss general cancer biomarker studies

and emphasize how they help cancer patients, you can emphasize some previous pan-cancer work from Liu's lab, such as "A pan-cancer-bioinformatic-based literature review of TRPM7 in cancers, 2022, Voltage-gated sodium channels in cancers, 2024, Pan-cancer genetic analysis of disulfidptosis-related gene set, 2023a"

- *Author reply: We have expanded on the long-term outcomes of RAPID and RAVAS techniques, including case-specific examples where available. We have emphasized the role of cancer biomarker studies and referenced previous pan-cancer work from Liu's lab, which strengthens the manuscript's discussion on biomarkers in the context of LT.*

Conclusion Line 8: Suggest future research directions, including large-scale randomized controlled trials and advancements in donor pool expansion.

- *Author reply: We have suggested future research directions, including large-scale randomized controlled trials and advancements in donor pool expansion.*

Line 12: Reiterate the importance of multidisciplinary collaboration in optimizing LT outcomes for CRLM.

- *Author reply: We have reiterated the importance of multidisciplinary collaboration in optimizing LT outcomes for CRLM, emphasizing the necessity of team-based approaches.*

Reviewer 2

Colorectal cancer (CRC) is the third most common malignancy worldwide. Liver metastasis is the most common site of distant spread and significantly affects the prognosis of patients with colorectal cancer. With palliative chemotherapy, only 14% of patients with stage IV colorectal cancer have a 5-year survival. The purpose of this review is to clarify the criteria and clinical circumstances for patients with CRCLM may be considered for liver transplantation, a large number of authoritative clinical research data and multi-center case data are cited in this paper. This paper summarizes the results of the clinical trial, where the heterogeneous study group showed an estimated 5-year survival rate of 60%, then the SECA-II study improved the estimated 5-year survival rate to 83% by using more stringent selection criteria. However, it is suggested that patients must meet the strict criteria described in two prospective studies, and that the treatment of LT patients with N-RCRCLM should follow the consensus guidelines published by the International Hepato-Pancreato-Biliary Association. Clinical practicability is the highlight of this paper. This paper interprets the guidelines in detail and provides clear guidance for clinicians in practice, which is of great significance for improving patient prognosis.

- *Author reply:* Thank you for your detailed review and positive comments. We appreciate your recognition of the clinical applicability of the manuscript, as it is a central goal of our work. We have updated the relevant references and included additional clinical data to enhance the manuscript's current relevance.

However, this article still has the following problems:

1. Most of the references are before 2020 and need to be updated.
 - *Author reply:* We agree with your suggestion and have updated the references to include more recent studies, particularly those published after 2020, to reflect the latest developments in the field.
2. Abstract and introduction are highly repetitive.
 - *Author reply:* We have revised the abstract and introduction to remove repetitive content and ensure a clearer, more concise presentation of the key points.
3. It was mentioned in the introduction part that Liver metastases are the most common site of distant spread, accounting for approximately 15–25% of CRC patients.", which is inconsistent with the describe in discussion part "It is a well-established fact that more than 40% of patients with CRC develop liver metastasis".
 - *Author reply:* Thank you for pointing this out. 40% of the patients will develop metastases, but 18-25% will develop them in the first 5 years after diagnosing.

This paper also has some limitations.

Author reply: We appreciate your valuable insight. We have acknowledged this limitation in the discussion section, noting the challenges of implementing the recommended guidelines in regions with limited medical resources and emphasizing the need for tailored approaches in such settings.

Overall, this paper concludes that LT could be a treatment option for patients with unresectable CRCLM without extrahepatic involvement, while the initial assessment and proper selection of suitable patients is mandatory for better outcomes for these patients. Although there are limitations, it does not affect its significance in promoting the progress of clinical practice in this field.

- *Author reply:* Thank you for this summary and for highlighting the significance of the manuscript. We agree that proper patient selection is essential for successful outcomes, and we have emphasized this point in the revised conclusion.
- We would like to express our sincere thanks for your thoughtful comments, which have been instrumental in refining the manuscript.



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Round 2

SPECIFIC COMMENTS TO AUTHORS

The revised manuscript has addressed the majority of the questions; however, several formatting issues remain in the article. For example, some references are outside the period (e.g., [1,2] in line 5 of introduction, [4] in line 14 of introduction), while some are inside (e.g., [3] in line 13 of introduction). The formatting of numerical-unit spacing demonstrates inconsistent application. Additionally, spelling errors are present, such as “5-yeas” in third line from the bottom of page nine. Overall, the manuscript requires further inspection and correction.

AUTHORS` reply: Thank you for the notes. We corrected all the issues in the references and additionally proofread the text for Grammar and style.