

Subject: Re: World Journal of Gastroenterology Manuscript review of Manuscript NO: 113550

Dear Editors and Reviewers,

Thank you for the opportunity to revise our manuscript, "Prevention is better than cure: Combining locoregional therapy with capecitabine maintenance for lung oligometastases from colorectal cancer" (Manuscript NO: 113550). We are grateful to the reviewers for their insightful and constructive comments, which have helped us significantly improve the quality and scholarly contribution of our letter.

We have thoroughly revised the manuscript to address all points raised. The key revisions include:

1. **Providing a deeper, more critical appraisal** of the Li et al. study, including a dedicated limitations section discussing selection bias, unmeasured confounders, and generalizability issues.
2. **Adding novel discussion points** on the dissociation between PFS and OS, the biological mechanism of the RFA/capecitabine synergy, and the practical aspects of patient selection and toxicity management.
3. **Enhancing the letter's originality** by incorporating a new table (Table 1) that synthesizes key international evidence on combined modality therapy and by offering a fresh interpretation of the clinical implications.
4. **Restructuring the abstract and the letter's body** to be more concise and analytical, in line with the expected format for a Letter to the Editor, and adopting a more objective tone throughout.
5. **Changing the title** to "Capecitabine Maintenance after RFA: A Preventive Strategy for Lung Oligometastases from Colorectal Cancer" to better reflect the core message.

Below, we provide a point-by-point response to the reviewers' specific comments.

Response to Reviewer #1:

- **1. Comment on lack of originality and critical depth:** We agree that a Letter to the Editor must extend beyond summary. Our revision now provides a critical appraisal of the Li et al. study's limitations, including selection bias and generalizability concerns. We also introduce a novel discussion on the intriguing dissociation between PFS and OS, hypothesizing that capecitabine may "modify the disease trajectory" by making recurrences more treatable. Furthermore, the addition of Table 1 synthesizes broader evidence, enhancing the letter's scholarly contribution.
- **2. Comment on superficial critique of limitations:** We have significantly expanded the critique. A new paragraph explicitly details limitations such as the potential for selection bias by multidisciplinary boards, unmeasured confounders, and limited generalizability due to the study's conduct in two Chinese centers.
- **3. Comment on stylistic and structural shortcomings:** We have shortened the abstract to a concise, single paragraph and removed the IMRAD structure. The tone has been revised throughout to be more objective and analytical, replacing promotional language with scholarly critique.
- **4. Comment on reference and discussion:** We have added a sentence summarizing the baseline characteristics from Li et al. and have incorporated a dedicated limitations section, as requested, which also addresses the potential for patient selection bias.

Response to Reviewer #2:

- **1. Comment on title relevance:** We have changed the title to "Capecitabine Maintenance after RFA: A Preventive Strategy for Lung Oligometastases from Colorectal Cancer" to be more direct and accurately reflect the letter's content.
- **2. Comment on references and purpose:** We have expanded the references (now 30 items) to provide a more comprehensive context, including studies on mechanism, safety, and real-world application. The purpose of our letter—to critically appraise and contextualize the findings of Li et al.—is now clearer in the introduction and throughout the text.
- **3. Comment on multi-center evidence:** We have added a new table (Table 1) that summarizes key international multi-center studies and randomized trials (e.g., EORTC 40983, SABR-COMET, de Baère et al.), placing the findings of Li et al. within a broader, more robust evidence base.
- **4 and 5. Comment on safety, alternatives, and mechanism:** We have added a detailed paragraph on the safety and toxicity profile of capecitabine, including management strategies and references to real-world data. We briefly discuss the biological rationale for the combination, citing the immune-modulatory effects of RFA and the cytotoxic action of capecitabine. While we focus on CRC lung metastases, we now briefly speculate on the applicability of the strategy to other sites and cancers.
- **6 and 7. Comment on patient characteristics and limitations:** We have added a sentence summarizing the baseline characteristics from Li et al. and have incorporated a dedicated limitations section, as requested, which also addresses the potential for patient selection bias.

We believe the revised manuscript is now substantially strengthened and provides the critical depth, originality, and scholarly contribution expected for publication in the *World Journal of Gastroenterology*. Thank you for your time and consideration.

Sincerely,

Francesco Giangregorio, MD