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**Manuscript Type:** Letter to Editor

**Radiomics and Machine Learning for Predicting Metachronous Liver Metastasis in Rectal Cancer**

We thank the reviewers for their thoughtful feedback. We greatly appreciate your insights on how to improve our manuscript. We have carefully revised the manuscript to address each of your concerns and recommendations. We revised the manuscript title to more closely reflect the letter's focus. Below is a detailed response to each point raised:

<b>Question #</b>	<b>Reviewer Comment</b>	<b>Answer as Response to the comment</b>
<b>Reviewer #1:</b>		
1.	The letter written by the authors, who have sufficient knowledge to make such an assessment, is valuable.	We sincerely thank the reviewer for recognizing our expertise in assessing this topic and for highlighting the value of our letter. Your encouragement inspires us to further contribute meaningfully to this field.
2.	The title chosen by the authors, who work in important centers, is also very appropriate. It is a text from which scientists working in this field can benefit and which will inspire future studies.	We are thankful for your positive feedback on the title of our manuscript and its alignment with the study's focus. It effectively reflects the scope and objectives and your acknowledgment that this work can inspire future studies and benefit scientists in this domain. I intend to provide a foundation for advancements in this critical area.
3.	Keywords have been chosen to reflect the scope of the main content. The manuscript has a good logical flow and gives sufficient space to each element discussed.	Thank you for noticing the appropriateness of the keywords and carefully selecting them to encompass the core aspects of the manuscript and ensure broader discoverability.

4.	<p>The limitations of the study are also discussed in detail and details are included to strengthen the reader's perspective. The conclusions section is written realistically and line with the text. The text is reinforced by the use of up-to-date and appropriate references. I would like to congratulate the authors on the absence of bias in the references, the absence of unnecessary underlining of their work, and the observance of ethical rules.</p>	<p>Thank you for recognizing the detailed discussion of the study's limitations and the realistic conclusions that align with the findings. The manuscript was aimed to provide a balanced perspective.</p> <p>Thank you so much for your comments on the appropriate use of up-to-date references and compliance with ethical standards. The manuscript was aimed to ensure objectivity and avoid unnecessary emphasis on our prior work.</p>
5.	<p>I consider the article to be grammatically and punctuationally correct, with appropriate use of abbreviations</p> <p>Both the reviewed study and this letter to the editor will contribute meaningfully to ongoing efforts to improve the early detection and management of metachronous liver metastases in rectal cancer patients. I believe that the development of the non-invasive predictive models discussed will open new horizons in clinical decision-making and may improve patient outcomes.</p>	<p>Thank you for taking the time to provide valuable feedback regarding our work, particularly concerning grammatical accuracy, punctuation, and the correct application of abbreviations.</p> <p>Your perspective reinforces our belief that this research can potentially motivate a wider acceptance of predictive models in different geographical regions and among various patient populations. We share your enthusiasm and optimism that this work will pave the way for innovative approaches in clinical practice.</p>
6.	<p>The recommendations discussed have the potential to form the basis for future studies and have the potential to improve predictive models. As stated promoting collaboration among radiologists, oncologists, surgeons, and data scientists will augment the model's development and implementation. Interdisciplinary approaches will foster a comprehensive understanding of rectal cancer and its metastasis, ensuring that the</p>	<p>Thank you for your insights; I believe that promoting interdisciplinary collaboration among radiologists, oncologists, surgeons, and data scientists is important for improving the development and implementation of healthcare models. I am dedicated to encouraging these collaborative approaches in our future research efforts.</p>

	<p>predictive model is clinically relevant and effective. I hope that this development will be implemented in a short period and the next step will be the use of these models in different centres and we will have knowledge of different geographies and different patient populations.</p>	
<b>Reviewer #2:</b>		
1.	<p>This is an excellent article that systematically and comprehensively evaluates the study by Long ZD et al. The authors acknowledges the innovative predictive model developed by Long ZD et al to predict metachronous liver metastasis from rectal cancer, The predictive model for metachronous liver metastasis as evidenced by the area under the curve (AUC) of 0.919 in the training cohort and 0.901 in the validation cohort, highlighted its potential clinical utility.</p>	<p>We sincerely thank you for acknowledging the thorough assessment of the predictive model developed by Long ZD et al.</p> <p>Your review emphasizes clinical utility, particularly the impressive AUC values observed in the training and validation cohorts, which underscore why we are valued. It reinforces the model's value in real-world clinical applications and highlights its potential impact on improving patient outcomes in practice.</p>
2.	<p>The model could potentially help clinically improve prognosis through personalised monitoring and treatment. The development of non-invasive predictive models like the one presented here has the potential to revolutionize clinical decision-making and improve patient outcomes. The suggestions aimed to address these challenges; future studies can refine predictive models. Ongoing research in this domain can potentially improve clinical outcomes and the quality of care for RC patients.</p>	<p>We appreciate your recognition of the model's potential to improve prognosis through personalized monitoring and treatment. We also share your optimism regarding the transformative impact of noninvasive predictive models on clinical decision-making and patient outcomes. Future studies will focus on addressing the identified challenges to improve predictive capabilities further.</p>
3.	<p>However, the authors also identified a several</p>	<p>We appreciate you acknowledging the predictive model's</p>

	remaining inadequacies in the work of the research.	shortcomings and agree that addressing these challenges is important for refining its utility.
4.	Firstly, the model has not include genomic markers like KRAS/NRAS mutations, future studies need to integrate non-invasive genomic or liquid biopsy markers to improve the model accuracy and clinical applicability.	<p>I concur with your suggestion to integrate non-invasive genomic markers.</p> <p>The omission of genomic markers like KRAS/NRAS mutations is a significant limitation. Incorporating non-invasive genomic or liquid biopsy markers in future studies will improve model accuracy and broaden clinical applicability.</p>
5.	Secondly, this is a retrospective research work, which may be subject to potential selective bias, and the need for external validation in different patient populations.	<p>Thank you for agreeing with our observation about the potential selection bias inherent in retrospective studies. To mitigate this, prospective studies and external validation across diverse patient populations will be prioritized in future research.</p>
6.	Finally, and very importantly, this was a single-centre study with a limited number of patients and insufficient external inflammation, which further restricted the model's usefulness for clinical applications. authors also give specific directions for future research.	<p>Thank you for agreeing with our point about the limitations of a single center with a relatively small sample size.</p> <p>It is important to expand this research by incorporating multicenter studies that involve a diverse and larger patient population to improve the reliability and applicability of the findings,</p> <p>Addressing these limitations effectively improves the model's generalizability, making it more suitable for clinical applications across various settings.</p>
7.	Based on the above review, I recommend that the letter	We appreciate your suggestion for acceptance without any

	undergo acceptance with no changes before being considered for publication. I unreservedly recommend this article for publication.	changes. This supportive feedback for our work validates our efforts and motivates us to continue making valuable contributions to advancements in this field.
<b>Reviewer # 3:</b>		
1.	The letter has made some comments on a recently published study about a radiomics-based predictive model for predicting metachronous liver metastasis in newly diagnosed rectal cancer patients. The authors first acknowledged the potential clinical value of the predictive model, highlighting its potential in non-invasive risk assessment. Besides, they proposed several limitations of the study, such as its single-center, retrospective design, the exclusion of genomic and other omics data, and the lack of external validation et al. Finally, the authors provided some suggestions for future research. Overall, the letter has made some good points about the study.	<p>We thank the reviewer for their insightful suggestions for improving our manuscript.</p> <p>We have carefully addressed all comments and incorporated the recommended changes into the revised version.</p>
2.	A few questions for authors that may benefit from mentioning in the manuscript: 1. The authors mentioned that “future studies could benefit from incorporating non-invasive genomic or liquid biopsy markers to improve the model's predictive accuracy and clinical applicability”. However, the available data through liquid biopsy remains quite limited, and due to the lack of standardized testing platforms, it is difficult to draw consistent conclusions. Plus, the AUC of the radiomics-based predictive models in the study has already exceeded 0.9. Whether integrating liquid biopsy data can improve predictive efficacy? More	<p>We appreciate the reviewer's concern about the limited data availability and standardized testing methods for liquid biopsies. Although liquid biopsy technologies are still developing, recent studies indicate they can complement radiomics by offering dynamic, tumor-related insights.</p> <p>As noted in the manuscript, the study by Di Sario et al. showed that a multi-omics approach, including liquid biopsy, has significant clinical potential. However, larger datasets are needed for validation. Despite the AUC exceeding 0.9 in the current study, integrating liquid biopsy markers may not necessarily improve predictive</p>

	related data needs to be shown. Additionally, the costs of liquid biopsy tests are generally not covered by insurance, and the potential benefits in terms of cost-effectiveness remain to be further investigated.	efficacy but enhance interpretability and clinical decision-making in cases where radiomics features alone may be insufficient. Additionally, we agree that evaluating the cost-effectiveness of these integrations is essential, and we recommend that future research investigate the economic feasibility of including liquid biopsy tests in clinical practices.
3.	The authors suggested integrating multi-omics data and conducting large-scale, multi-center validations.	Multicenter studies ought to focus on diverse patient groups, covering differences in tumor stage, genetic backgrounds, and treatment plans. Furthermore, prospective cohort studies implementing uniform imaging and annotation methods can reduce variability and improve reproducibility. We suggested forming partnerships with prominent cancer centers to combine resources and data, facilitating strong external validation of predictive models.
4.	Are there more specific guiding directions for this? For instance, is there any previous studies reported data involving the combination of radiomics data with other types of omics? Or is there any related clinical trial ongoing?	Taking into account of reviewer's feedback, we suggested investigating the combination of radiomics data with proteomics, metabolomics, and genomic datasets. Research like that of Lipkova et al. has demonstrated that AI models can effectively merge multimodal datasets, including radiomics and genomic attributes, to enhance prediction accuracy. Furthermore, Langlotz et al. (2019) presented a path for implementing AI in radiology, emphasizing the importance of workflow integration and prospective clinical trials. Hence, examining the integration of MRI-radiomics with proteomics data could yield significant insights into this combination. We recommended emphasizing genomic changes (such as KRAS mutations) or metabolomic profiles pertinent to

		rectal cancer metastasis.
5.	<p>In general, the authors have proposed several promising directions for future research, such as conducting multicenter studies and integrating genomic, proteomic, and metabolomic data. It would be better to provide more specific guidance to enhance the feasibility of future studies.</p>	<p>Based on reviewer's suggestion, we highlighted the significance of conducting longitudinal studies incorporating dynamic changes in radiomic and clinical parameters over time. This approach could facilitate the innovation of adaptive predictive models that can progress alongside the disease. In addition, although advanced imaging techniques like PET/MRI showed promise, their implementation in clinical practice requires precise cost and clinical outcomes advantages. In addition, efforts should also train radiologists and clinicians to interpret complex multi-omics and radiomics data effectively, ensuring their integration into clinical workflows.</p>