

## Peer Review File

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### Review Comments

This study aimed to develop a nomogram model integrating carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and preoperative spectral computed tomography (CT) parameters to predict liver metastasis after colorectal cancer (CRC) surgery. Using a retrospective analysis of 100 CRC patients, the study identified venous-phase spectral CT parameters (iodine concentration, spectral slope  $\lambda$ HU, and CT40 keV) as independent predictors, alongside CEA and CA19-9. The model demonstrated high predictive accuracy with an AUC of 0.9078 in the training set and 0.9502 in internal validation, supported by good calibration and clinical utility via decision curve analysis. However, limitations include the small single-center sample size, lack of external validation, potential selection/information bias inherent in retrospective designs, and variability in CA19-9 expression, which may affect generalizability. Further multicenter validation is needed to confirm its clinical applicability.

**Reply 1: Thank you very much for your valuable suggestion. Limitations of the study have been added in the discussion section.**

**Changes in the text: See Page 13, line 404 to 409.**

Comment 2: The title needs to indicate the development and validation of a prediction model and both biological makers and spectral CT features used.

**Reply 2: Thank you very much for your valuable suggestion. We have modified the title as advised.**

**Changes in the text: See Page 1, line 3-4.**

Comment 3: The abstract needs some revisions. The background did not indicate the current knowledge gap on the prediction model of liver metastasis and why the combination of both biological makers and spectral CT features could be potentially accurate for the prediction of liver metastasis, the methods did not describe the inclusion criteria, diagnosis criteria of liver metastasis, generation of training and validation samples, the results did not describe the patient sample characteristics, and the current conclusion did not have comments for the clinical implications of the findings.

**Reply 3: Thank you very much for your valuable suggestion. The gaps in knowledge concerning liver metastasis prediction models, as well as why the combination of biomarkers and spectral CT features can potentially provide accurate predictions of liver metastasis, have been elaborated in the background. Inclusion criteria and diagnostic criteria for liver metastasis are detailed in the methods section of the main text, as the abstract requires brevity and thus these details are not presented there. The generation of training and validation samples has been supplemented in the methods**

section. To maintain the conciseness of the abstract, detailed sample characteristics of the patients are described in the main text. The conclusion section has been revised. Thank you again.

Changes in the text: page 3-4/line 66-102.

Comment 4: The introduction of the main text is poor. The authors need to review what has been known on the prediction models of liver metastasis following CRC surgery including their predictors, and have comments on their limitations and predictive accuracy to indicate the clinical needs for new prediction models. The authors need to further explain why the combination of biological makers and spectral CT features is potentially accurate for the prediction of liver metastasis. It is problematic to emphasize spectral CT features only.

Reply 4: Thank you very much for your valuable suggestion. We have modified Introduction as advised.

Changes in the text: See Page 4 to 5, line 126-159.

Comment 5: In the methodology, the authors need to correctly describe the clinical research design, sample size estimation, follow up procedures, and diagnosis of liver metastasis.

Reply 5: Thank you very much for your valuable suggestion. The clinical study design, sample-size estimation, follow-up process, and diagnosis of liver metastases have been described in the Methods section.

Changes in the text: See Page 5 to 6, line 174-197.

Comment 6: The sample size is too small to generate training and validation samples and the authors did not describe how the training and validation samples were generated. In statistics, please ensure  $P < 0.05$  is two-sided, as well as the calculation of sensitivity and specificity.

Reply 6: Thank you very much for your valuable suggestion. The content of the Statistical Analysis section has been modified.

Changes in the text: See Page 8, line 243-252.

Comment 7: Please cite several related papers: 1. Xing Y, Yu G, Jiang Z, Wang Z. Development of prediction models for liver metastasis in colorectal cancer based on machine learning: a population-level study. *Transl Cancer Res* 2024;13(11):5943-5952. doi: 10.21037/tcr-24-1194. 2. Zhou B, Sun M, Yang M, Cui W, Yang H. The current status and reflections on 3D in vitro modeling of liver metastasis in colorectal cancer. *Hepatobiliary Surg Nutr* 2024;13(1):180-183. doi: 10.21037/hbsn-24-13. 3. Peng W, Wan L, Zhao R, Chen S, Dong S, Li L, Zhang H. Novel biomarkers based on dual-energy computed tomography for risk stratification of very early distant metastasis in

colorectal cancer after surgery. Quant Imaging Med Surg 2024;14(1):618-632. doi: 10.21037/qims-23-861.

Reply 7: Thank you very much for your valuable suggestion. The recommended literature has been cited.

Changes in the text: reference 4,5,11.

Comment 8: Inconsistent terminology (e.g., "spectral CT" sometimes referred to as "spectral computed tomography" without consistent abbreviation)

Reply 8: Thank you very much for your valuable suggestion. The full text has been checked to ensure that the full name is provided only when it first appears, and the abbreviation "spectral CT" is used uniformly thereafter.

Changes in the text: The full text has been checked.

Comment 9: Awkward phrasing (e.g., "exhibited good clinical value" instead of "showed strong clinical utility"),

Reply 9: Thank you very much for your valuable suggestion. We have modified our text as advised.

Changes in the text: See Page 2, line 44.

Comment 10: Grammatical inconsistencies (e.g., "patients were categorized into two groups based on the incidence of liver metastasis occurring within 2 years after surgery" could be rephrased for clarity).

Reply 10: Thank you very much for your valuable suggestion. We have modified the sentence as advised.

Changes in the text: See Page 3, line 78.

Comment 11: Some sentences are overly redundant (e.g., "The model derived from these parameters yielded an area under the curve...") and lack precision in scientific reporting.

Reply 11: Thank you very much for your valuable suggestion. We have modified our text as advised.