



**PEER-REVIEW REPORT**

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 112090

**Title:** Predicting lymph node metastasis in colorectal cancer using case-level multiple instance learning

**Provenance and peer review:** Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer’s code:** 08530878

**Position:** Peer Reviewer

**Academic degree and professional title:** Academic Fellow, Additional Professor, Adjunct Associate Professor, AGAF, Assistant Professor, FRCA, PhD

**Reviewer’s Country/Territory:** China

**Author’s Country/Territory:** China

**Manuscript submission date:** 2025-07-16

**Reviewer chosen by:** AI Editor

**Reviewer accepted review:** 2025-07-17 07:17

**Reviewer performed review:** 2025-07-17 07:38

**Review time:** 1 Hour

<b>Content to be reviewed</b>	<p>Does the manuscript’s content fall within the scope of the journal? <b>Yes</b></p> <p>Is there any Key Word that is not included in the manuscript title? <b>Yes</b></p> <p>Do authors’ affiliations correspond to the content of the manuscript? <b>Yes</b></p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b></p>
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Are the Key Words complete? **No**

Is the content of the Introduction adequate? **No**

Is the content of the Materials and Methods complete?  
**No**

Is the description of the experiments clear and  
complete? **Yes**

Are the experimental data presented in the  
manuscript's biostatistics content reliable? **Yes**

Are the experimental data of the Results true and  
reliable? **Yes**

Are the quality and resolution of the images up to  
standard? **Yes**

Do the selection and design of the figures and tables  
follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the  
manuscript and between the main text and the content  
presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in  
the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **Yes**

Are all references related to the topic of the  
manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?  
**Yes**

Are additional experiments needed for the study? **Yes**



	Does the research scope comply with ethics? <b>Not Applicable</b>
Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade B (Very Good)
Language quality	Grade B (Very good)
Does this manuscript describe a study of the existing knowledge system?	No
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Major revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

### SPECIFIC COMMENTS TO AUTHORS

This study introduces a novel case-level multiple instance learning (MIL) framework to predict lymph node metastasis (LNM) in T3/T4 colorectal cancer (CRC), leveraging whole-slide images (WSIs) and clinical data. The work addresses a clinically significant gap by mimicking pathologists' comprehensive slide-review workflow. While the methodology is innovative and results are promising, several issues require attention to



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enhance clarity, robustness, and clinical relevance.

Major Strengths

Conceptual Innovation:

The case-level MIL approach effectively addresses the sparsity of high-risk histological features (e.g., lymphovascular invasion) by aggregating information across all slides per patient, aligning with pathological practice.

Integration of deep learning (CONCH/UNI2-h) with clinical data (AUC: 0.91) demonstrates synergistic value.

Technical Rigor:

Use of 5-fold Monte Carlo cross-validation prevents data leakage.

Attention mechanisms and unsupervised clustering (UMAP) enable interpretability, linking model decisions to known high-risk histopathological features (Figure 6).

Clinical Relevance:

Model-identified clusters (e.g., micropapillary adenocarcinoma, perineural invasion) align with established prognostic factors, enhancing trustworthiness.

Potential to refine adjuvant therapy decisions in locally advanced CRC.

Major Concerns and Recommendations

1. Study Design and Data

Sample Size and Generalizability:

The cohort ( $n^* = 130$ ) is small for deep learning. While justified as a pilot, the single-center, retrospective design limits generalizability.

Recommendation: Acknowledge this limitation prominently and validate findings in larger, multi-center cohorts. Include demographic diversity in future work.

Temporal Scope:

Cases from 2023–2024 may lack sufficient follow-up for metastasis confirmation.

Recommendation: Clarify follow-up duration and LNM confirmation criteria (e.g.,



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histopathology vs. imaging).

## 2. Methodology

ROI Annotation Paradox:

ROI annotations reduced CONCH v1.5 performance (AUC: 0.90 → 0.84). The hypothesis that stroma contains prognostic signals is intriguing but underdeveloped.

Recommendation: Discuss stromal biology's role in CRC metastasis (e.g., tumor microenvironment interactions) and quantify stromal features in high-attention patches.

Model Selection and Comparison:

CONCH v1.5 (512px tiles) outperformed UNI2-h (256px), likely due to contextual information. However, computational costs/resource requirements are unaddressed.

Recommendation: Report training time, hardware specs, and inference speed to assess clinical feasibility.

## 3. Results and Analysis

Baseline Characteristics (Table 1):

Age stratification shows LNM prevalence drops in 70–79y (35%) vs. <60y (66%), but multivariate analysis (e.g., correcting for stage/location) is absent.

Recommendation: Perform multivariate regression to identify independent LNM predictors.

AUC Variability:

UNI2-c shows high AUC fluctuation (Fold 3: 0.95; Fold 2: 0.61), suggesting instability (Table 2).

Recommendation: Investigate causes (e.g., data imbalance per fold) and report standard deviations for all metrics (beyond AUC).

Clinical Data Integration:

SVM outperforms other models (AUC: 0.91), but feature importance is unclear. Do pathology features dominate predictions?



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Recommendation: Use SHAP/LIME to explain feature contributions (e.g., CEA vs. histology).

#### 4. Figures and Visualization

Figure 2 (Workflow):

Low-resolution TIFF impedes readability of text/diagrams.

Recommendation: Reformat using vector graphics (e.g., SVG) and enlarge labels.

Figures 3–4 (ROC Curves):

Overlapping curves in panels A–E obscure model-specific trends.

Recommendation: Plot mean ROC curves per model across folds with confidence bands.

Figure 6 (Clusters):

Cluster 3 ("complex glandular architecture") lacks CRC-specific prognostic evidence (cited literature focuses on lung cancer).

Recommendation: Replace with CRC references (e.g., tumor budding/grading systems).

#### 5. Discussion and Claims

Pathologist-Level Performance?:

Claims that the model "approaches expert performance" are overstated without direct comparison to pathologists' assessments.



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**Peer-review model:** Single blind

**Reviewer's code:** 02446526

**Position:** Associate Editor

**Academic degree and professional title:** FRCP, MD, MRCP, Professor, Senior Researcher

**Reviewer's Country/Territory:** United Kingdom

**Author's Country/Territory:** China

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<b>Content to be reviewed</b>	Does the manuscript's content fall within the scope of the journal? <b>Yes</b> Is there any Key Word that is not included in the manuscript title? <b>Yes</b> Do authors' affiliations correspond to the content of the manuscript? <b>Yes</b> Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b>
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Conclusion	Minor revision
Re-review	No
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

### SPECIFIC COMMENTS TO AUTHORS

In this pilot study, Zou LF et al. evaluated the predictability of artificial intelligence-based testing systems using utilizing the CONCH v1.5 and UNI2-h deep learning models with a case-level approach to improve Lymph Node Metastasis (LNM) prediction in colorectal cancer at stage 3 and 4. They found that the CONCH v1.5 model achieved a better sensitivity in predicting LNM with a mean area under the curve (AUC) of 0.90, substantially outperforming slide-level training that achieved only a lower AUC



of 0.81. Although this is a relatively small pilot model for common cancer like colorectal cancer, authors used extensive validation of their testing and training sets making the results of the study and the evidence for its performance reasonably robust. I have only few minor points to suggest in making the report better as detailed below:

- Language and style: Mostly OK but minor language polishing is recommended as there are occasional minor syntax errors throughout the paper.
- Title: appropriate for the study
- Abstract: It would be worthy adding the confidence intervals for the AUC which will make the reporting more robust as most viewers on the paper read the abstract while searching the web. This improves the understanding of the statistical validity of the results while searching.
- Introduction: appropriate with adequate appraisal of the current evidence on the topic.
- Methods: Very well described.
- Results: The study flow chart (fig 1) last right-hand box should be changed to “absence of at least 12 LN” to obtain the correct meaning. The figures and tables of this section are good.
- Discussion: This section should start with a short summary of the main points in the results (with appropriate statistical metrics without SD/95% CI etc.) after which authors should compare the evidence compiled with that in existing literature. Authors discuss several important points in the discussion but better to stick on to the above suggestion as most readers view on the abstract and discussion of the study.
- References: appropriate to the paper.



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**Reviewer’s code:** 07483657

**Position:** Peer Reviewer

**Academic degree and professional title:** Assistant Professor, MD

**Reviewer’s Country/Territory:** India

**Author’s Country/Territory:** China

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Does the research scope comply with ethics? **Yes**



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Novelty of this manuscript	Grade A (Excellent)
Creativity or innovation of this manuscript	Grade A (Excellent)
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Conclusion	Minor revision
Re-review	No
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript is well written with description of novel method MIL for identifying LNM in advanced CRC helping in decision making doe adjuvant chemotherapy.

Manuscript needs few grammatical errors correction.

Reference 3,13,23,31,37 needs correction in format.