COMMENTARY

A new paradigm for cytology-based artificial intelligence-assisted prediction for cancers of unknown primary origins

Hongrui Li,[1] Shun Wang,[1] Yi Zhang,[1] and Wenbin Li[1,*]

[1]Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

*Correspondence: liwenbin@cicams.ac.cn

Received: May 30, 2024; Accepted: August 6, 2024; Published Online: August 22, 2024; https://doi.org/10.59717/j.xinn-life.2024.100086

Citation: Li H., Wang S., Zhang Y., et al., (2024). A new paradigm for cytology-based artificial intelligence-assisted prediction for cancers of unknown primary origins. The Innovation Life **2(3)**: 100086.

The study by Tian et al. trained a multitask neural network model for tumor origin differentiation using cytological histology (TORCH) by integrating attention- and transformer-based multiple-instance learning methods, which can identify malignancy and predict the origin of cancer of unknown primary (CUP) simply by analyzing cytopathological images.[1] In this commentary, we highlight the model development and validation process and provide our insights into the role of deep learning (DL) in predicting tumor origin in CUP, aiming to further explore the potential of TORCH as a clinically assisted diagnostic tool (Figure 1).

CUP is a group of heterogeneous tumors with clinically proven metastatic and undetermined primary anatomical sites of tumor origin, which is characterized by difficult diagnosis, multiple organ involvement and poor prognosis. In recent years, advances in precision medicine targeting tumor genomic mutations have significantly improved outcomes for cancer patients;

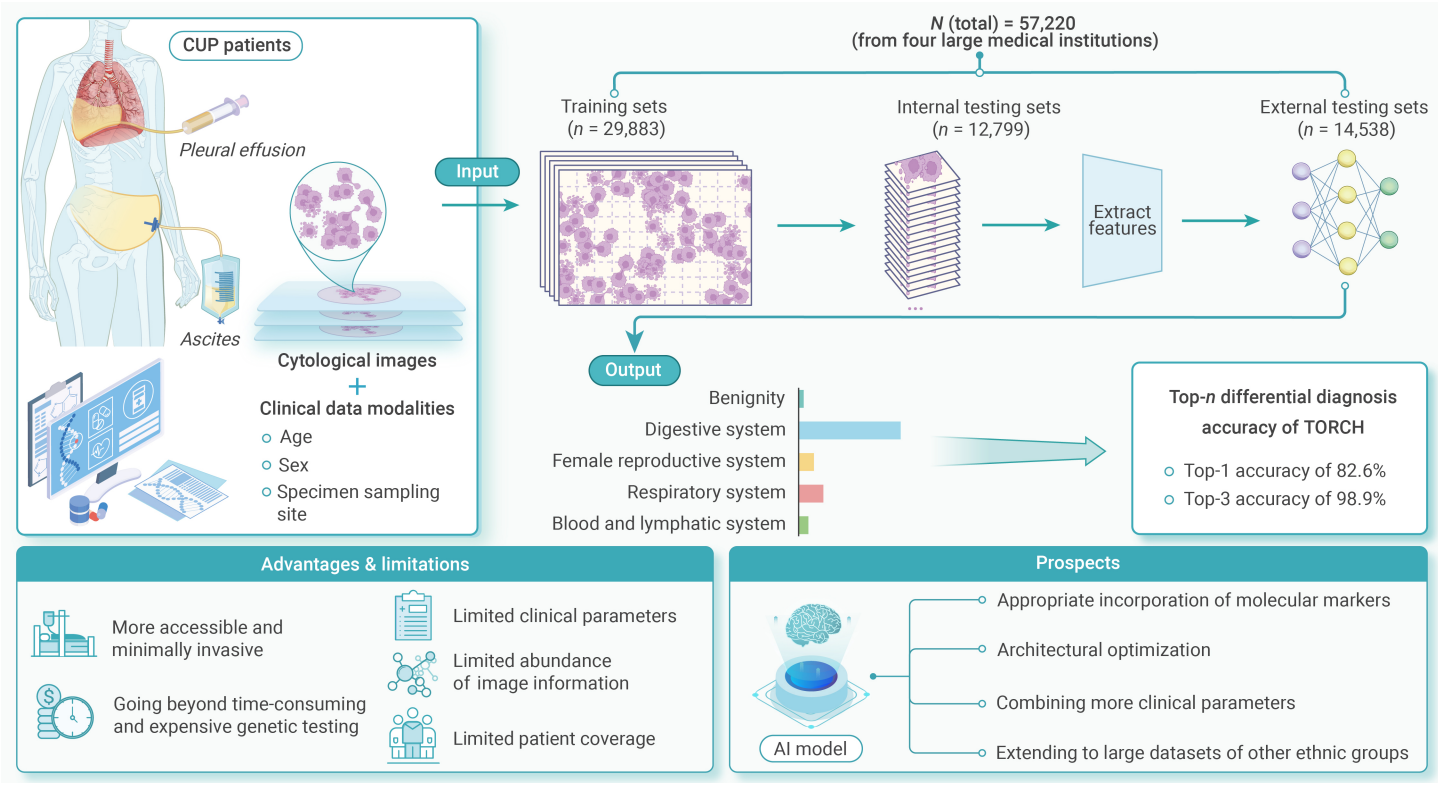

Figure 1. TORCH workflow, advantages, limitations and prospects The model input included cytological imaging data and clinical parameters (age, sex, and specimen sampling site). TORCH was trained and validated on datasets from four large medical institutions. With ResNet50 extracting features, the model was trained using attention- and transformer-based multiple-instance learning, and finally assembled into a multitask neural network model by averaging the prediction probabilities. The model output included the identification of malignancy and the classification of primary tumor origin. Finally, top-*n* differential diagnosis accuracy was used to evaluate the performance of TORCH. The advantages, limitations and prospects of the model are shown at the bottom.

however, identification of tumor origin remains critical to guide treatment options for CUP cases. Clinical manifestations and routine histological diagnosis are used to describe specific subgroups of CUP to suggest the primary site, but only 15-20% of patients respond.[2] For an unfavourable subset of CUP, molecular detection and artificial intelligence (AI) methods are emerging as promising tools. AI-based methods for analyzing molecular and imaging data have been attempted to guide the inference of tumor origin. For example, Nguyen et al. developed a random forest classifier based on somatic driver and passenger mutations utilizing whole-genome sequencing data from primary and metastatic tumors, which could improve the classification of CUP origin.[3] Similarly, Darmofal et al. described a DL model that relies on targeted panel sequencing to demonstrate the potential application of AI-based molecular profiling in CUP origin prediction from a perspective close to clinical implementation.[4] However, considering the high economic and time costs of genetic testing, DL methods for pathology image analysis offer new opportunities.

DL algorithms, a subset of machine learning, have emerged as potent tools in pathological image analysis due to their ability to capture nonlinear and multi-layer image features, showing great potential in clinical oncology research. By analyzing extensive digital histopathology images and extracting valuable morphological features from them, DL models can help pathologists improve diagnostic accuracy and speed, and provide valuable insights for prognostic prediction, ultimately benefiting patient outcomes. Therefore, under the limitations of existing methods, the use of DL methods to predict

CUP origin has a wide range of applicability and facilitates the development of a new paradigm of AI-assisted tumor pathology diagnosis. In a groundbreaking study published in 2021, Lu et al. trained a weakly supervised model, Tumor Origin Assessment via Deep Learning (TOAD) on a large whole-slide image (WSI) dataset spanning 18 common origins of primary cancer, which can predict whether a tumor is metastatic and assign a differential diagnosis for the origin of the primary tumor.[5] When evaluated using top-*k* differential diagnosis accuracy, TOAD achieved a top-3 accuracy of 93.4% in the external test cohort and 94.9% in the difficult cases of metastatic tumors cohort. Meanwhile, researchers are actively exploring more rapid and effective auxiliary examination methods, given the intolerability of surgery in patients with late-stage CUP. Notably, many cases of CUP present with pleural or peritoneal metastasis, and cytological examination by fine-needle aspiration may provide evidence of tumor origin sites. In this article, Tian et al. proposed TORCH, a cytology-based DL model, which achieved a top-1 accuracy of 82.6% and a top-3 accuracy of 98.9% in predicting the primary system origin of tumors. Unlike the common use of histopathological images as input for model feature extraction, the AI-assisted diagnosis of tumor origin by liquid-based smear containing malignant cells overcomes the difficulties of visual diagnosis caused by the scarce number and morphological heterogeneity of tumor cells in pleural effusion and ascites, demonstrating the potential of TORCH in this clinical oncology task. In addition, predictions of TORCH can help CUP patients select more appropriate treatment strategies, such as tumor type-specific therapy rather than empirical chemotherapy—often the former showing a better prognosis. In conclusion, with its high performance, the model demonstrates diagnostic accuracy beyond pathologists, laying the foundation for future human-machine collaborative integration into clinical diagnostic tasks.

During model development, The Cancer Genome Atlas (TCGA) database and cytological smear images from three independent training sets were used for feature extraction, and three internal cohorts and two external cohorts were used to validate the model. Tian et al. developed TORCH by integrating neural network models trained on different types of input, which demonstrated high performance and relatively reliable generalization in predicting tumor origin in both internal and external testing sets. They also compared the predictive performance of TORCH with that of pathologists, showing that TORCH outperformed pathologists (diagnostic score of 1.677 versus 1.265, $P < 0.001$) in accuracy, sensitivity, and precision for the task of cytology-based differentiation of benign diseases from malignant tumors, which has significant expert variability. Subsequently, the authors tested the performance of junior pathologists assisted by TORCH and found that while they made better predictions compared to before AI assistance, they were still lower overall than the performance of TORCH itself and senior pathologists. In addition, the researchers embedded clinical variables into multidimensional vectors obtained from the image feature extractor to train the model. The overall performance of the model decreased significantly after removing clinical parameters such as age, sex and specimen sampling site from the input of TORCH. The results of ablation studies and random perturbations showed that the clinical parameters in the input modalities had an important impact on the predictive ability of TORCH, particularly the specimen sampling site. Further survival analysis linked TORCH predictions to better clinical outcomes in CUP patients, with those who received treatment consistent with TORCH-predicted cancer origin having significantly better overall survival (27 versus 17 months, $P = 0.006$). This finding reveals the clinical significance of TORCH in oncology research.

The analysis of false results indicated that the overall false-positive rate of TORCH in differentiation between malignancy and benignity was 11.0% (1,171 of 10,635) and the overall false-negative rate was 5.4% (904 of 16,702), mainly due to the misdiagnosis caused by the similarity of cell morphology and tissue structure as well as the quality control problems during smear preparation. Furthermore, the model interpreted the prediction results by highlighting the histomorphological features of regions with high diagnostic value and generating attention heatmaps. In contrast to previous studies, the innovation of this study lies in predicting CUP origin from cytological images, which is particularly useful for patients with effusions, especially those with late-stage CUP. In this context, more accessible cytology samples can provide rapid results in a minimally invasive manner, which is not only critical for timely diagnostic decisions, but also spares late-stage patients with poor tolerance from unnecessary surgery.

The research team highlighted the great potential of TORCH in predicting the tumor origin of CUP while also acknowledging several limitations of the study. First, the model development process considered only a few quantifiable parameters in clinical practice, neglecting other variable factors of patients such as medical history and metastatic site. Second, the cytology samples from hydrothorax and ascites were insufficient to cover all CUP patients, leaving the model unable to provide effective predictive support for tumor types with non-thoracoabdominal metastases. Third, compared to histological images that can provide information on organizational structures and cellular interactions, the limited abundance of cytological image information allows TORCH to localize tumor origins only at the organ-system level, thus to some extent limiting more detailed treatment guidance. Additionally, given the heterogeneity of CUP, models incorporating molecular markers may provide meaningful predictions for different CUP subsets and help to enhance considerations for tumor type-specific therapy and biomarker-guided therapy. However, this combined strategy must strike a balance between improving prediction accuracy and maintaining the efficiency and cost-effectiveness of the detection to achieve technical synergies. Future models can explore the integration of clinical parameters through architectural optimization and be extended to large datasets of other ethnic groups to enhance the clinical usefulness of the model.

Overall, the study proposes a highly accurate and generalized DL model, TORCH, which combines clinical parameters and cytological images to predict the origins of metastatic free tumor cells in pleural and peritoneal serous effusions. It is worth noting that previous studies generally focused on histopathological images, but driven by advances in AI technology and patients' demand for early cancer screening, more and more studies have begun to focus on biopsy samples and even cell samples. Tian et al. highlighted the feasibility of cytological samples in the field of AI-assisted pathological image analysis and provided a new perspective on the application of DL models to predict tumor origin.

REFERENCES

1. Tian, F., Liu, D., Wei, N., et al. (2024). Prediction of tumor origin in cancers of unknown primary origin with cytology-based deep learning. Nat. Med. **30**: 1309–1319. DOI: 10.1038/s41591-024-02915-w.
2. Rassy, E. and Pavlidis, N. (2020). Progress in refining the clinical management of cancer of unknown primary in the molecular era. Nat. Rev. Clin. Oncol. **17**: 541–554. DOI: 10.1038/s41571-020-0359-1.
3. Nguyen, L., Van Hoeck, A., and Cuppen, E. (2022). Machine learning-based tissue of origin classification for cancer of unknown primary diagnostics using genome-wide mutation features. Nat. Commun. **13**: 4013. DOI: 10.1038/s41467-022-31666-w.
4. Darmofal, M., Suman, S., Atwal, G., et al. (2024). Deep-learning model for tumor-type prediction using targeted clinical genomic sequencing data. Cancer Discov. **14**: 1064–1081. DOI: 10.1158/2159-8290.Cd-23-0996.
5. Lu, M.Y., Chen, T.Y., Williamson, D.F.K., et al. (2021). Ai-based pathology predicts origins for cancers of unknown primary. Nature **594**: 106–110. DOI: 10.1038/s41586-021-03512-4.

FUNDING AND ACKNOWLEDGMENTS

This work was supported by grants from Beijing Nova Program (Grant No. 20220484210), Beijing Hope Run Special Fund of Cancer Foundation of China (LC2022L02), Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2023-JKCS-07) and Capital's Funds for Health Improvement and Research (2024-2-40211). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Hongrui Li and Wenbin Li conceived the original idea and provided critical revisions. Hongrui Li wrote the manuscript and designed the figures. Shun Wang and Yi Zhang supervised the whole process and revised the manuscript. All authors read and approved the manuscript before submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.