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Review

Applications of Machine Learning in Histopathology: From Diagnostic Accuracy to Prognostic Insights

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ABSTRACT

Background: Histopathological examination remains the gold standard for evaluating morphological alterations in tissues and plays a pivotal role in both disease diagnosis and therapeutic decision-making. With the exponential growth of digital pathology, the integration of artificial intelligence (AI), particularly machine learning (ML) algorithms, has emerged as a transformative approach to optimize histopathological workflows. **Objective:** This review aims to systematically evaluate recent advances in ML applications within histopathology, focusing on their roles in enhancing diagnostic precision and enabling prognostic stratification across various malignancies. **Methods:** A comprehensive literature analysis was conducted, encompassing peer-reviewed studies that investigate the implementation of ML models in histopathological image interpretation, classification, segmentation, and outcome prediction. Emphasis was placed on convolutional neural networks, and ensemble learning techniques. **Findings:** Machine learning-based approaches demonstrate high sensitivity and specificity in the detection and classification of neoplastic lesions, particularly in breast, colorectal, thyroid, gastric, and head and neck cancers. These tools facilitate intraoperative consultation, mitotic figure quantification, and tumor grading, thereby improving diagnostic accuracy and reproducibility. Moreover, emerging prognostic models incorporating histopathological features show potential in predicting disease recurrence, overall survival, and treatment response, supporting the paradigm shift toward personalized medicine. **Conclusions:** The incorporation of ML into histopathological practice holds substantial potential to revolutionize diagnostic and prognostic processes. As algorithmic models continue to evolve and validate in clinical settings, their integration may redefine standard-of-care practices and bridge the gap between pathology and computational medicine.

Keywords—*Artificial intelligence, Histopathology, Cancer diagnosis, Digital pathology, Personalized treatment.*

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INTRODUCTION

Histopathology, as a diagnostic method, constitutes a fundamental aspect of modern medicine by analyzing structural and cellular changes at the tissue level, playing a crucial role in the diagnosis and treatment of various conditions, including cancer.[1] The integration of artificial intelligence (AI) into healthcare holds significant potential to enhance both volume of histomorphological assessments and precision of histopathological diagnoses.[2]

The application of AI technologies in histopathology could revolutionize the diagnosis and treatment of diseases, such as cancer, by improving accuracy and introducing a new dimension to personalized medicine. Recent studies have demonstrated that advances in AI have significantly transformed the processes of disease diagnosis and classification.[3] AI methodologies, utilized in tasks such as object recognition, detection, and segmentation play a significant role in driving advancements within histopathological practice.[4,5] Current literature clearly highlights the efficacy of AI-based methods in enhancing diagnostic accuracy and expediting workflows in histopathology.[6] It is stated that the future research will further expand the applications of AI in this field.

THE WORKING PRINCIPLE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence is associated with significant advancements in various fields, particularly pathology, by enabling advanced data analysis.[7] AI equips machines with cognitive abilities through computational networks (neural networks) that mimic biological nervous systems.[8] In a traditional algorithm, the computer executes predefined, explicitly programmed instructions each time it encounters a trigger. In contrast, AI can modify algorithms in response to learned inputs without human intervention. Machine learning (ML), a subset of AI, focuses on developing algorithms that use statistical analysis to make inferences by processing input data without explicit programming. Deep learning (DL), an evolution of ML algorithms, employs artificial neural networks in a hierarchical manner to extract higher-level features gradually from raw input.[9] In this context, the use of AI in healthcare holds significant potential in histopathology, offering high accuracy in the diagnosis and prognosis of diseases, such as cancer.

Machine learning algorithms form the core of AI by transforming input data into actionable outputs through coded instructions. As a subset of AI, ML applies statistical and mathematical modeling techniques to analyze large datasets rapidly and generate predictions or decisions with varying levels of autonomy.[10]

Machine learning can be categorized into supervised, unsupervised, and reinforcement learning, based on how models interpret data. In supervised learning, algorithms learn from labeled datasets to predict outcomes, whereas unsupervised learning involves identifying hidden structures in unlabeled data. Reinforcement learning, on the other hand, enables models to learn optimal actions through a feedback system of rewards and penalties.[11]

Deep learning, a subset of ML, utilizes multi-layered neural networks to extract hierarchical features from data and can operate in supervised, unsupervised, or semi-supervised settings. Deep learning approaches typically require extensive, high-quality datasets for effective training and are tightly linked to big data methodologies, leading to substantial demands on storage and computational resources.[12] These advancements collectively enable AI to efficiently process complex medical data, making it a powerful tool for clinical decision support and precision diagnostics in cancer.

APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN HISTOPATHOLOGY

Artificial Intelligence in Diagnosis and Classification in Oncopathology

Artificial Intelligence is utilized to predict prognosis and treatment responses based on histological features.[13] In this regard, directly correlating various tumor characteristics, the surrounding microenvironment, and genetic profiles with survival outcomes and treatment responses to adjuvant/neoadjuvant therapy can provide valuable insights. Additionally, the use of AI in histopathological diagnosis and classification processes can enhance accuracy and precision in clinical applications.

In a 2024 study, ML was used to predict malignancy in thyroid nodules. The logistic regression model based

on backward stepwise regression demonstrated high discrimination, with Area Under the Curve (AUC) values of 0.83 and 0.80 during the training and validation phases, respectively. AUC is a performance metric that measures the ability of a model to distinguish between classes, with higher values indicating better discrimination.[14] The nomogram developed with this model aims to reduce unnecessary surgeries and improve clinical decision-making by providing personalized risk assessments. In another study, AI-assisted Raman histology was used for intraoperative tissue diagnosis. High accuracy was achieved for meningiomas and gliomas, with an AUC value of 0.93 reported for predicting isocitrate dehydrogenase (IDH) mutations.[15] In this context, AI can enhance accurate intraoperative diagnoses, thereby improving surgical decision-making.

Artificial Intelligence-based research in histopathology has conducted analyses focusing on the differentiation of atypical and typical mitoses in breast and colon cancers. In the breast cancer study, AI models achieved an F1 score of 94.49% for detecting invasive carcinoma (the F1 score is a performance metric that combines precision and recall, offering a single measure of a model's accuracy in datasets where class distribution may be imbalanced). In the mitosis project, F1 scores were reported as 80.18% for mitosis, 97.40% for atypical mitosis, and 97.68% for typical mitosis layers. For the colon cancer study, the models achieved the overall F1 scores of 90.02% for invasive carcinoma, 94.81% for the submucosal layer, and 98.02% for vessels and lymph nodes.[16]

Additionally, Yoshida et al. developed the "e-Pathologist" software for classifying carcinoma, adenoma, and malignant lesions in gastric biopsies, achieving 90% sensitivity and 50% specificity.[17] In 2023, Wibawa et al. introduced an AI-based model for whole-slide analysis of head and neck cancers, particularly nasopharyngeal carcinoma.[18] This system accurately evaluated the spatial distribution and density of tumor-infiltrating lymphocytes (TILs: immune cells that migrate into the tumor microenvironment and play a critical role in the immune response against tumors). By assessing TIL distribution with high precision, the model provided significant prognostic information to guide personalized treatment strategies.[17,18] The literature also highlights that ML models can serve as valuable tools for assessing malignancy risk in oral lesions and for detecting and grading malignant lesions.[19,20] Collectively, these studies demonstrate the substantial potential of AI-based analyses in advancing cancer diagnosis and treatment planning.

The deep learning-based system developed by Lan et al. significantly reduced error rates of pathologists and diagnosis period for the analysis of 2020 gastric slide images.[21] Similarly, another study trained a neural model based on the Inception-v3 framework to classify whole-slide images of gastric biopsies into three categories: adenocarcinoma, adenoma, and non-neoplastic. The model was validated using a test cohort of 45 whole-slide images, achieving an accuracy of 95.6% and an AUC of 0.924.[22] These studies highlight the potential of AI to enhance both accuracy and efficiency of pathological diagnosis.

In 2019, Jeyaraj et al. achieved an accuracy of 91.4% (sensitivity: 0.94; specificity: 0.91) in the early diagnosis of oral cancer and in classifying malignant tumors and normal tissues using a dataset of 100 images.[23] These results demonstrated that AI-based models performed with high accuracy in histopathological analyses and were particularly effective in detecting invasive carcinoma, mitotic types, submucosal layer, and vascular and lymph node structures in breast and colon cancers.[24]

Artificial Intelligence holds significant potential for accelerating diagnostic processes and improving accuracy in these areas. By expediting diagnoses and enhancing clinical accuracy in cancers, such as breast, colon, and thyroid cancers, AI can contribute to improved surgical decision-making and personalized risk assessments.

Artificial Intelligence in Cancer Metastasis and Recurrence Prediction

Artificial Intelligence significantly contributes to survival analysis and clinical decision-making by predicting the risk of metastasis and recurrence in cancer patients. In 2024, AI-based models provided personalized survival predictions for patients with advanced non-small cell lung cancer (NSCLC) based on clinical and radiological features. The Random Survival Forest (RSF) model successfully distinguished poor survivors treated with pembrolizumab because of high programmed death-ligand 1 (PD-L1) expression and patients receiving targeted

therapy for driver oncogenes.[25] In another study, a deep learning model was developed to predict lymph node metastasis in lung squamous cell carcinoma. The model demonstrated high performance using the ExtraTrees algorithm, achieving AUC values of 0.941 in the training set and 0.788 in the test set.[26]

Wang and colleagues trained a ML model using nuclear orientation, nuclear shape, tissue, and tumor architecture from hematoxylin and eosin (H&E)-stained tissue microarray (TMA) slides to predict recurrence in early-stage NSCLC.[27] Their model achieved accuracy rates of 82% and 75% in two independent early-stage NSCLC cohorts. These findings suggest that deep learning-based approaches have clinical value in predicting metastasis and survival outcomes in lung cancer. Studies indicate that AI-based approaches can guide survival analyses and clinical decision-making by predicting metastasis and recurrence risks in cancer treatment.

Prediction of Mutations Using Artificial Intelligence in Histopathology

Histopathology plays a crucial role in elucidating the molecular mechanisms of diseases by providing insights into the effects of mutations at cellular level. In this context, the potential of AI to detect subtle or hidden features that pathologists might overlook is highly compelling. Studies have reported that driver gene mutations or microsatellite instability can be predicted from H&E-stained images of certain cancer types.[28]

In a 2018 study, a deep convolutional neural network (DCNN, Inception-V3) was developed to classify lung cancer into adenocarcinoma, squamous cell carcinoma, and normal lung tissue. Additionally, the platform was trained to predict the most common mutations in 10 genes from histopathological images of lung adenocarcinoma. The predicted genes (STK11, EGFR, FAT1, SETBP1, KRAS, and TP53) exhibited AUC values ranging from 0.733 to 0.856.[29]

Although the sensitivity and specificity of this approach have not yet reached clinically significant levels, future advancements could significantly contribute to areas such as pre-sequencing sample selection, clonality assessment, and evaluation of tumor heterogeneity. Further studies utilizing advanced techniques such as laser capture microdissection to analyze genetic signatures in heterogeneous tumor foci may help to validate these findings.

Integration of Histopathology with Artificial Intelligence in Non-Cancer Fields

Histopathology plays a crucial role in diagnosing and understanding the pathogenesis of various inflammatory, infectious, and degenerative diseases, in addition to cancer, by enabling detailed examination of cellular changes. This capability guides both clinical practice and research. In this context, AI-assisted analyses significantly enhance the accuracy and efficiency of clinical decision support systems by facilitating an in-depth evaluation of cellular morphology in non-cancerous diseases.

In 2018, a convolutional neural network (CNN) model was developed to detect clinical heart failure using H&E-stained endomyocardial biopsies. The study utilized biopsy samples from 104 patients for model training and from an independent cohort of 105 patients for testing. The model achieved an AUC of 0.97 in detecting heart failure from H&E-stained whole tissue sections, surpassing the evaluations of two expert pathologists (AUC: 0.75).[30]

Similarly, a 2019 study developed a neural network model to distinguish between celiac disease, nonspecific duodenitis, and normal tissues. The model was trained and optimized on a dataset of 1018 duodenal biopsy images and later validated on an independent cohort comprising biopsies from 212 different patients. The performance of model was benchmarked against the evaluations of three gastrointestinal pathologists. The deep learning model achieved a high performance with an AUC > 0.95 for slide-level classification across all categories.[31]

Artificial Intelligence-assisted histopathological analyses have demonstrated significant advancements in diagnosing and prognosticating non-cancerous diseases. By enabling comprehensive evaluation of cellular morphology, these technologies contribute to the improvement of clinical diagnostic systems.

DISCUSSION

This review indicates the potential applications of AI in histopathology and highlights innovative developments in the field. AI holds significant promise, particularly in identifying and analyzing subtle or complex pathological features that may be challenging for pathologists to distinguish.[32] ML can be applied to various tasks in histopathological

interpretation, including cancer classification, tumor grading, genetic mutation prediction, cell classification, treatment planning, and survival prediction.[33]

The integration of AI into healthcare has a significant potential to accelerate early diagnosis, provide more accurate diagnoses, uncover novel insights into human biology, and advance personalized patient care. In the field of histopathology, AI-based tools promise groundbreaking innovations in both clinical practice and research. High-quality histopathological analysis is a cornerstone of clinical studies and medical research, offering deeper insights into tumor biology and disease mechanisms. However, the limitations of AI must also be considered. Traditional ML algorithms heavily depend on the quality of training data and may experience performance degradation when faced with new datasets. Additionally, the lack of transparency in the decision-making processes of these systems presents a major challenge to their clinical integrainte.[34]

In order for AI-based models to be safely implemented in healthcare, it is essential to improve data quality, enhance the generalizability of models, and increase the explainability of decision-making processes. Addressing issues of transparency and interpretability in deep learning approaches could facilitate the broader adoption of these technologies. It is important to consider AI not only as a diagnostic tool but also as a platform that can be used to understand disease mechanisms and support innovative therapeutic approaches. Additionally, data derived from H&E-stained slides provide a rich resource for deep learning models to identify nuanced patterns in tumor morphology and develop precise risk stratification criteria.[35] Furthermore, integrating histopathology with "omics" sciences, such as transcriptomics, proteomics, and metabolomics, could support a better understanding of diseases and the development of personalized treatment strategies.[36,37] The ability of AI to combine such datasets can not only improve diagnostic accuracy but also contribute to the development of prognostic and predictive models.

One of the most impressive capabilities of AI is its ability to detect rare or ambiguous histopathological patterns. AI has been shown to out perform traditional methods, particularly in areas such as the detection of micrometastases.[38] However, AI techniques based on traditional ML algorithms have limitations, including dependence on the quality of training data and a lack of transparency. To overcome these challenges, new approaches are needed.[39,40]

In addition, pathologists should adopt AI-integrated workflows in diagnostic environments while paying attention to ethical considerations and quality assurance. The increasing use of AI methods requires a better understanding of their roles in cancer cytopathology.[41,42] In addition to diagnosis, providing supplementary information, such as prognostic indications and predictions of treatment effects, is more suitable for clinical needs. Such integrated pathological diagnoses may become feasible in the future. The development of integrated AI methods has been reported in the literature.[43,44] In this context, the adoption of AI-integrated workflows by pathologists will enhance the accuracy of diagnostic processes and improve the quality of healthcare services by providing valuable prognostic and treatment guidance.

In line with the growing demand for personalized cancer approaches, AI must provide more accurate biomarker evaluations and quantitative histopathological analyses. In this context, pathologists require new methodologies and tools to enhance diagnostic sensitivity and specificity. It is clear that AI is the next step toward precision pathology. However, for these technologies to be applied effectively and safely in healthcare, addressing technical, ethical, and clinical limitations, as well as increasing healthcare professionals' trust in these systems, is of critical importance.

RESEARCH GAPS AND FUTURE OPPORTUNITIES

The successful implementation of AI in healthcare relies heavily on the engagement of clinicians, patients, and investors. A major obstacle remains the skills gap among healthcare professionals and their hesitation in adopting unfamiliar technologies, highlighting the need for tailored training programs and user-friendly AI interfaces.[45] Patient acceptance is often hindered by limited exposure to AI tools and concerns about reliability and deviation from traditional care norms. For investors, the rapid pace of technological evolution poses uncertainty, leading to cautious or inconsistent funding in AI-driven healthcare solutions.[46] Hence, despite notable progress in AI-based cancer diagnostics, challenges remain in the generalizability of models because of limited dataset diversity and lack of

multi-center validation studies. The future research should focus on developing explainable and ethically transparent algorithms that can be seamlessly integrated into clinical workflows. Moreover, expanding AI applications to rare cancers and addressing regulatory and infrastructural barriers is critical for widespread clinical adoption.

Data Privacy and Ethical Considerations

The implementation of AI in cancer diagnostics raises significant concerns regarding patient data privacy and ethical governance. Histopathological images and associated clinical metadata often contain sensitive and identifiable information, making secure data handling a critical requirement. Traditional anonymization techniques may be insufficient in safeguarding complex biomedical datasets, particularly when combined with external data sources.[47] Therefore, the future research should prioritize the development of privacy-preserving ML frameworks, such as federated learning and differential privacy, to facilitate collaborative model training without compromising patient confidentiality. Establishing clear ethical guidelines and robust institutional policies are also essential to ensure responsible AI integration in clinical practice.

Clinical Validation and Regulatory Challenges

Despite the growing body of research highlighting the diagnostic accuracy of AI-based systems in histopathological image analysis, their translation into routine clinical practice remains limited. Securing regulatory approval demands comprehensive assessment of algorithmic safety, generalizability, and seamless integration into existing clinical infrastructures.[48] Overcoming these hurdles necessitates sustained interdisciplinary collaboration among computational scientists, pathologists, healthcare providers, and regulatory authorities to ensure both clinical relevance and compliance with ethical and legal standards. Also, the majority of AI research in histopathology is focused on common cancers, such as breast and colorectal carcinoma. Rare tumors and histological subtypes remain largely underrepresented in datasets and in model development. Expanding research to encompass these less frequent but clinically significant conditions could improve diagnostic equity and enable earlier detection strategies.

AUTHOR CONTRIBUTIONS

Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Writing–Original Draft Preparation, Writing–Review & Editing, Project Administration: D.Z. The sole author, Doğanyiğit Züleyha, contributed to all aspects of the work, and have read and agreed to the published version of the manuscript.

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The authors declare they have no competing interests.

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