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Review Article

# Insight into Deep Learning for Glioma Medical Image Analysis

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## Abstract

Histopathological images contain rich phenotypic information that can be used to monitor the underlying mechanisms that lead to disease progression and patient survival outcomes. In recent years, deep learning has become the mainstream method of choice for analyzing and interpreting histological images. Histopathological diagnosis of gliomas is a labor-intensive and labor-intensive process. A common method is using deep learning to classify glioma patients or predict prognosis based on histopathological images. However, these technologies still face some key challenges as they move toward clinical application. This review starts with emerging deep learning frameworks and explores how deep learning models based on histopathological images can be applied to gliomas. We focus on multimodal deep learning applications, including genomic, transcriptomic, MRI, and clinical data. We discuss the challenges associated with the use of artificial intelligence and propose potential directions for deep learning based on histopathological images in gliomas.

## Background

Digital pathology includes the process of digitizing histopathology slides using a full scanner and analyzing these digitized whole slide images (WSI) using computational methods. This scanner was introduced two decades ago (1999), but the roots of digital pathology go back to the 1960s when PreWit and Mendelssohn devised a way to scan simple images from the field of microscopy smeared with ordinary blood, which converts optical data into a matrix of optical density values while preserving spatial and grayscale relationships, and then discerns the presence of different cell types based on information in the scanned image [1,2]. The current computational methods for analyzing tissue sections are mainly deep learning (DL). Research has shown that combining deep learning-based methods with human pathologist diagnosis can improve diagnostic accuracy while reducing the human error rate in cancer diagnosis [3,4]. The rapidly growing field of digital pathology is using deep learning-based methods to classify and diagnose digitized images [5-7].

Gliomas are the most common primary malignant brain tumors in adults. Currently, according to the guide of the World Health Organization (WHO), gliomas are classified into grades I-IV by histopathological observation and genetic molecules detection such as IDH, 1p/19q, and ATRX [8-10]. However, histopathological diagnosis of glioma is labor-intensive and time-intensive, which consumes a lot of time and energy for pathologists [11,12]. With the development of artificial intelligence technology, AI must be a better method to assist in the diagnosis of tumors, including glioma.

This article reviews the latest applications of deep learning in classifying and grading gliomas and prognosis prediction. We briefly introduce the current mainstream deep learning methods and then discuss the specific application of deep learning models in glioma. We propose the current challenges and potential directions for research.

## Deep Learning Methods for Digital Pathology

The term digital pathology was originally coined to include the process of digitizing WSI using advanced slide scanning technology, and now also refers to AI-based digitization methods for detecting, segmenting, diagnosing, and analyzing digitized images. A comprehensive study compares diagnostic performance between digital pathology and conventional microscopy [13]. Specimens from 1992 patients with different tumor types were included, involving in 16 surgical pathologists. This study demonstrates that the diagnostic performance of digital WSI is non-inferior to traditional microscope-based methods. DL methods are increasingly used in digital pathology because they do not rely on engineered features and can learn representations directly from raw data, which can also significantly reduce the workload of pathologists. The DL method first involves a set of learned images with relevant class labels, e.g., whether a tumor is benign or malignant [14,15]. The newly entered data is then interrogated without pre-existing assumptions. The whole process involves generating and learning the best image features to accurately separate the classes of interest. In addition to this, the convenience of DL methods (compared to methods of manually delineating features) and high accuracy are also the reasons for their widespread acceptance. Several DL algorithms or models have been developed for the analysis of pathological images.

**Convolutional Neural Networks:** CNN has been widely used in various pathological image analyses [15-17]. A CNN consists of multiple layers that infer an output (usually a class) from an input (such as an image), so it is a deep feed-forward network. The CNN structure is mainly divided into three layers: 1. Convolutional Layer is used to extract features. 2. The Max Pooling Layer can perform down sampling to reduce or reduce the dimension of the feature, but it will not damage the recognition result. 3. The main function of the Fully Connected Layer is to classify. Thus, CNN's work by hierarchically deconstructing images into low-level cues such as edges, curves, or shapes, which are then aggregated to form higher-order structural relationships to identify features of interest [1]. Image-based segmentation and detection tasks typically use CNN DL methods such as identifying and quantifying cells [18,19] (lymphocytes, neutrophils, and blasts), regions of interest [20], and histological features [21]. Conture et al. used CNN analysis of H&E-stained TMA images to determine the histological and molecular subtypes that makeup breast cancer [22]. Nagpal et al used the DL system to automatically assign Gleason scores after detection of cancerous areas in WSI of radical prostatectomy specimens. In a validation set of 331 slides, reference diagnostic criteria were developed by experts in genitourinary pathology who also obtained initial diagnostic comments from previous reviews by at least three general pathologists, and the DL method predicted the Gleason score. The accuracy was 0.70, while the average accuracy of 29 general pathologists was 0.61. In addition, a CNN trained by Jakob Nikolas Kath et al. can identify different tissue types that are abundant in CRC histological images, especially non-tumor tissue types, and then aggregate the abundance of different tissue sections into a prognostic score to become a deep matrix score value for analysis [22]. Prediction of patient survival prognosis. The stroma composition of the depth stroma score itself was moderately correlated with the CAF score (correlation coefficient 0.26, $p < 0.001$) which was higher than the correlation between pathologist annotations and CAF score (correlation coefficient 0.20, $p < 0.001$), suggesting that Neural networks were at least as good as pathologists at detecting stromal components reflected in gene expression analyses.

**Fully Convolutional Network:** It is called a fully convolutional network due to the lack of fully connected layers and a hierarchy containing only convolutional layers. Unlike CNNs, which are used to aggregate information locally for global prediction, FCNs can be used to learn a per-pixel representation, thus making it possible to detect elements or features that may be sparsely present throughout a pathological image. This property enables FCNs to make pixel-level predictions, which may outperform CNNs, which learn from repetitive features present throughout the image. Zhang Jun et al. used a joint learning framework of full and graph convolutional networks to segment tissues/regions of pathological images. They utilize three pathology image datasets (HER2, KI67, and H&E) to show that their proposed joint framework outperforms fully supervised segmentation methods [23] in segmentation performance. Another research team used FCN to train 500 images from 349 patients to detect invasive breast cancer regions on WSI. And the test results were compared with breast cancer pathologists [24].

**Recurrent Neural Network:** RNN is usually used to describe the dynamic time behavior sequence, and the state is circulated in its network, and it can accept a wider range of time series structure input. Different from the feedforward deep neural network, RNN pays more attention to the feedback function of the network. Due to the existence of the connection between the current state and the past state, RNN can have a certain memory function. Current representative recurrent neural networks include traditional RNN models, long short-term memory (LSTM), and GRU (gated recurrent unit) models. Shekoofeh Azizi et al. demonstrated that the LSTM network achieved the highest accuracy in separating cancer and benign prostate tissue and then used RNN to temporally model enhanced ultrasound (TeUS) and found that the combined model could significantly improve PCa detection [25].

**Generative Adversarial Networks:** GANs work by implementing two simultaneous neural networks that play against each other. One network is the generator and produces synthetic data from training examples provided to the network, while the second network evaluates the consistency between the generated data and

the original data. The goal of GAN is to reduce the degree of classification error of the second network so that the generated image is closer to the original image. Currently, Generative Adversarial Networks (GANs) are showing an increasing role in digital pathology [26,27]. A research team used GAN to automatically score PD-L1 expression in images of NSCLC biopsy samples. This approach helps minimize the number of necessary pathologist annotations to compensate for the lack of available tissue in biopsy specimens [28]. Table 1 summarizes the advantages and disadvantages of four different neural network models in medical image applications and typical application scenarios. Choosing the right model often depends on specific task requirements, available data, computing resources, and performance requirements.

| Features/Models | CNN | FCN | RNN | GAN |
|---|---|---|---|---|
| Application scenarios | Image classification, detection, and segmentation, Medical imaging interpretation and diagnosis. | Semantic segmentation, tissue level segmentation, and lesion detection, Organ segmentation, medical image analysis | Time series prediction, text generation, EEG and ECG analysis | Image translation, data enhancement, medical image generation, image restoration, sample amplification |
| Advantages | Strong feature learning ability, pre-trained model usable, efficient calculation | Maintain input and output resolution, end-to-end learning, efficient pixel-level tagging | Processing sequential data, considering contextual information, suitable for continuous data | Generate realistic data, create scarce data, generate multimodal data |
| Disadvantages | Neglecting contextual information, fixed size input images, gradually decreasing feature maps, requiring a large amount of labeled data | Sensitive to input image size, limited by network architecture and hollow convolution, not suitable for variable-length sequence data, limited in capturing detailed information. | Constrained by sequence length, Data-intensive, High computational complexity, Inappropriate for certain tasks, | High training and adjustment complexity, instability in training models, the necessity for meticulous hyperparameter adjustment, and the demand for a large amount of computational resources |

**Table 1:** Advantages and disadvantages of four different neural network models in medical image applications and typical application scenarios.

**Deep learning in gliomas**

Cancer is well known to be diagnosed by histopathology or cytopathology, to confirm the presence of tumor cells in patient samples, evaluate markers associated with cancer, and characterize characteristics such as tumor type, stage, and grade. The process requires that histological images viewed at high magnification (usually 20x or 40x) can reveal millions of subtle cellular features, and deep CNN models are very good at extracting features from high-resolution image data.

**Prognosis and Survival Prediction:** The prognosis of cancer patients is an important part of clinical oncology, as the expected course of disease and likelihood of survival can inform treatment decisions [29,30]. While many morphological features of tumor tissue have prognostic value, DL applied to pathological sections may predict prognosis and patient survival [31-34]. The structure and organization of tumor-infiltrating lymphocytes (TILs) have been found to be prognostic for clinical outcomes. A study using CNNs to detect and quantify the structure of TILs in Cancer Genome Atlas images found this feature to be a prognostic predictor for 13 different cancer subtypes [35]. In addition, Meier et al. identified survival-related features and predicted the risk of cancer-specific death by analyzing HE and immunohistochemically stained organizers [36].

For glioma survival analysis, they used DCNN to classify brain cancer survival by whole-slide histopathology images obtained from H&E stained biopsy tissue sections [33]. They created DeepSurvNet, which allows accurate classification of brain cancer survival directly from WSI, and was validated in an independent local patient cohort. Molecular changes in tumors can cause phenotypic changes in tumor cells and their microenvironment, and routine histopathological sections can reflect such morphological changes. In 2016, the World Health Organization (WHO) proposed that genetic and epigenetic alterations can also be used as criteria for the classification of gliomas based on the histological phenotype of the tumor. While IDH molecular mutations can be used as a criterion for diffuse

glioma [37], Jiangshuai et al. used a deep learning framework trained on full-slide images of a diagnosis of diffuse infiltrating glioma to predict somatic biomarker heterogeneity mutation status of citrate dehydrogenase (IDH) 1/2 [38]. They then used WSI's IDH mutation probability instead of IDH mutation status to predict prognosis, with a model prediction agreement index of 0.739. And due to the relatively small sample size in the study, the number of people lost to follow-up is considerable, making it challenging to develop deep learning frameworks. Recently, researchers developed a survival deep learning (SDL) framework to extract information from H&E-stained tumor tissue images to predict glioma survival [39]. This framework can integrate IDH status and age to obtain different molecular subtypes of glioma patients, thereby delineating different survival risk groups, and its predictive accuracy exceeds that of other methods.

In the above study, IDH mutation status was used as a known glioma survival marker, while Amin Zadeh Shirazi, et al. used a deep convolutional neural network (DCNN) as a semantic segmentation model to analyze different brain tumor regions on the TCGA GBM data. Perform semantic segmentation with matched histopathology images, patient demographics, and gene expression data. Using the results obtained with DCNN, they identified specific markers for each tumor region and assessed their prognostic value in glioblastoma [33]. Researchers are now not only using pathological images for tumor prognosis, but most recent studies combine genomics, clinical data, and histopathology to predict patient survival time. Using genomics and histopathology, Pooya Mobadersany et al. developed survival convolutional neural networks (CNNs), a framework that integrates information from histological images and genomic biomarkers to predict time-to-event outcomes and shows results beyond the current predictive accuracy of a clinical paradigm for predicting overall survival in patients diagnosed with glioma [40]. The combination of deep learning and multi-omics such as transcriptome, histological images, and clinical data can lead to more accurate survival prediction.

**Classification of glioma:** Histopathological diagnosis is a laborious process involving manual inspection of coarse and fine-resolution images covering a large number of tissue samples. Pathologists are also faced with complex classification criteria, which require detailed and exhaustive analysis based on experience. Furthermore, despite well-established grading strategies, analyses of multiple pathologists from the same sample can easily yield inconsistent results, even among experts. Because they have different perceptions and are subject to various biases, this is called inter-observer variability [41-43]. However, with the development of computational pathology, people can use artificial intelligence to help pathologists improve the efficiency and accuracy of diagnosis [44, 45]. Ertosun et al., who first used deep learning for glioma pathological image analysis, used convolutional neural networks to achieve the binary classification of GBM and LGG, as well as to identify LGG grades II and III in a multi-institutional database [46].

However, the accuracy of distinguishing between class II and class III LGGs was only 71%, and the study used predefined features, such as nuclear shape, texture, etc., for classification. Whereas, performing classification tasks using predefined features in convolutional neural networks requires the most informative features of the category. Often, the best features are unknown. Typically, researchers classify glioma nuclei according to various shapes and properties [47]. However, the classification of histological images alone is not satisfactory, so researchers proposed a deep-learning framework for predicting glioma classification by combining radiological and pathological images [48,49]. Among four methods for classifying diffuse gliomas from Computational Precision Medicine (CPM) satellite activity at the 21st International Conference on Computational Medical Image Computing and Computer-Assisted Intervention (MICCAI 2018), investigators used both radiology and histology Multiple deep learning models for images yielded higher classification effect accuracy values than a framework using ensemble learning to combine two different classification models for radiology and histology images [48]. This result demonstrates that the combination of radiographic and histological image information can improve the classification. Pathology is the gold standard for tumor diagnosis [50], and some researchers believe that the fusion of radiology and pathology images destroys the priority of pathology in tumor classification. Therefore, two different CNN frameworks are proposed, one is a 2D CNN based on WSI, and the other is a 3D CNN based on mpMRI. The method mainly focuses on WSI-based results, with mpMRI-based results as a supplementary reference to improve robustness. In 2016, WHO's newly established central nervous system tumor criteria brought the landmark molecules of glioma into people's eyes. Linmin Pei et al used DNN to integrate molecular data for brain tumor types and grading according to 2016 WHO criteria. This work utilizes digital pathology images and four key molecular signatures (IDH1/2, 1p/19q, ATRX, and MGMT) to obtain improved tumor classification and stratification accuracy [51]. The cross-validation classification accuracy of conventional DNN for the classification of high-grade glioma (HGG) and low-grade glioma (LGG) was 93.81%, while the classification accuracy of LGG II and LGG III using Residual Neural Network (ResNet) DNN was accurate the degree of classification was 73.95%, and the classification performance between grades II and III of low-grade gliomas needs to be improved. Liu et al. utilized TERT and ATRX molecular mutations to provide the best LGG grade II and III tumor grading but with a small sample size [52]. The reason for the large difference in the accuracy of LGG grading is not only the different deep learning frameworks used, but also the different combinations of selected

molecular markers, and the molecular subtypes of LGG could not be further subdivided in the above studies. Recently, Jinlei et al. designed a neuropathology diagnostic platform including a slide scanner and deep convolutional neural network (CNN) [53]. The platform is capable of diagnosing five different molecular subtypes of glioma, and the models created employ molecular diagnostics (IDH and 1p/19q) using logic algorithms that integrate deep learning networks for image recognition and logic algorithms for molecular markers together, the diagnostic results will be further improved. Whether it is the combination of MRI and histological images, or the integration of molecular markers and histological images, the accuracy of the network model in classifying and grading gliomas can be well improved. Currently, multimodal deep learning networks for MRI, molecular markers, and histological images are also emerging.

## Challenges and directions of deep learning in glioma pathology

The advent of digital pathology and the development of deep learning have brought exciting opportunities and challenges to the field of oncology. Computational imaging plays a role in the precise treatment and predictive classification of gliomas, but digital pathology-based computer-aided image analysis has a certain degree of difficulty in clinical diagnostic work, and there are many substantial technical and data challenges that need to overcome.

**Data sources and quality:** For digital pathology of glioma, there is still a long way to go. Training of deep learning models requires massive amounts of data, and large WSI datasets for glioma are barren. The datasets currently available to researchers are generally from the TCGA database and the MICCAI CPM-RadPath Challenge, etc., and there is no standardized data repository. For multimodal deep learning models, high-quality cancer datasets that have undergone omics analysis (transcriptome, genome, proteome, etc.) are difficult to obtain in a clinical setting due to cost and sample availability. Transfer learning can pre-train deep learning models for other types of tumors to overcome the lack of large datasets for glioma. However, in practice, large datasets with thousands of samples per class are required to predict clinical outcomes, and there is clinical heterogeneity among patients.

Although histopathological WSI can provide important characterization information, however, the information contained in it can be influenced by a variety of factors. For example, the model of microscope or scanner used for imaging, the size and magnification of the image, and physical color changes caused during tissue section preparation. And because of the WSI's extremely large pixels, researchers need to split the WSI into small modules to fit within the GPU memory to determine the best resolution for their applications and tiles. At this time, the researcher needs to choose information, but this choice will lead to a certain degree of information loss. The most logical data processing approach is minimizing information loss and maximizing architecture utilization.

**Availability of pathological annotations:** The deep learning models based on glioma WSI require pathologists to delineate the features of the images, whether it is the classification of gliomas or the prognosis prediction of glioma patients. Pathological image annotation is difficult for anyone other than pathologists in the field to perform. It also takes a lot of time for pathologists to make annotations, sometimes requiring two to three highly specialized pathologists. Therefore, the availability of pathological annotation data often becomes a hurdle when developing pathological deep learning algorithms. Currently, a pathological adversarial neural network (GAN) can initially capture key tissue features of tumors, and these features have pathological significance. Unsupervised learning of histopathology images using GAN architectures emerges as a way to alleviate the data scarcity of pathology annotations. But currently, most studies focus on MRI rather than pathology datasets, due to the vast amount of publicly available MRI data that far outnumber pathology datasets. Also, GANs typically focus on matching the input image to the target distribution of the image, resulting in extra or misleading features as textures are added or removed for matching.

**Interpretability of Deep Learning:** The interpretability of deep learning models and the uncertainty in their predictions are major challenges for DL in clinical applications. A DL model that is trained rather than explicitly programmed is called a black box, and it is difficult for people to understand the exact underlying functionality of the system. In this context, human acceptance and regulatory approval of DL models are challenging. In the articles reviewed in this article, few researchers addressed this issue. Training physicians to interact with the Cadx system and how to interpret its results to make diagnostic decisions is a technical challenge that may degrade the performance of DL models in practice. In the future, physicians' deeper involvement in the construction of DL models may benefit the interpretability of results.

## Conclusion

In conclusion, DL has the potential to greatly enable precise treatment of glioma patients and improve patient outcomes. This review demonstrates many exciting applications of DL in glioma, including classification, molecular typing, and prognosis. As research matures, multimodal learning is applied to integrate medical images and omics data, resulting in more reliable model predictions or identification of biologically meaningful biomarkers. This biomarker has the potential to be patient-specific and tumor-specific to facilitate the development of precision oncology. An important condition for deep learning to be clinically applied is that DL produces biologically relevant clinical outcomes and rich data for training models. Today, the rapid development of new

technologies such as spatial transcriptomics, proteomics, single-cell technology, and multiplex imaging, as well as the emphasis on data standardization, will greatly improve the availability of medical data. Finally, in order to make DL acceptable to patients and doctors, the interpretability of DL models will receive more attention.

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