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AI Neuropathologist: an innovative technology enabling a faultless pathological diagnosis?

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See the article by Jin et al. pp. 44–52.

Interobserver variability in the typing and grading of gliomas based on histological criteria has been a significant issue in the World Health Organization (WHO) classification of tumors of the central nervous system. The grading scheme comprising a 4-tiered system with atypia, mitosis, microvascular proliferation, and necrosis can pose a challenge in evaluation because of each subjective definition. Even after several revisions of the WHO classification, the grading scheme itself has essentially not changed.[1,2]

Computational pathology, a new discipline critical to the future of the practice of pathology and medical practice in general, has been proposed,[3] using computation to interpret multiparameter data. Its practical working definitions include an approach that incorporates raw data sources such as pathology imaging and laboratory data to make the best possible medical decisions. However, clinically applicable methods to determine the glioma grading (ie, the biological malignancy scale of gliomas) have not been implemented.

Convolutional neural networks (CNNs) are a new generation of deep learning techniques by artificial intelligence (AI) that allow a practical application to recognition tasks, such as diagnostic imaging, in clinical practice. Recent achievements using CNNs include the detection of dysmorphic cells in peripheral blood smears[4] and the dermatologist-level classification of skin cancer,[5] with high sensitivity and specificity.

In this issue of *Neuro-Oncology*, using CNNs, Jin et al developed a quick and automatic platform named "AI Neuropathologist," which can provide an unbiased histological diagnosis on whole-slide images of hematoxylin and eosin (H&E)–stained sections.[6] This platform successfully demonstrated a patch-level accuracy of 86.5% and a patient-level accuracy of 87.5% in the diagnosis of 5 major histological types of diffuse gliomas (glioblastoma [GBM], anaplastic astrocytoma, diffuse astrocytoma, and oligodendroglioma [the types principally corresponded to those in the WHO 2007 classification]). In this system, the use of 2 molecular markers (isocitrate dehydrogenase [IDH] mutation and 1p/19q codeletion) could further amplify the histopathological diagnoses to incorporate the current WHO 2016 classification.

Although this study's overall accuracy seems sufficiently high, the number of each category after incorporation with genetic data was not; for instance, the number of patients with "GBM with IDH-mutation" was 16, and that of "GBM with IDH-wildtype" was 39. These numbers of patients are generally considered inadequate for a deep learning platform.[7] The histopathological images were obtained from H&E-stained slides of 323 classified glioma patients without any adjustment by patient age. Nonetheless, the gliomas in children and adolescents are genetically and biologically distinct from their adult counterparts[8]; they should be separately classified as "pediatric-type gliomas," although both types are histologically indistinguishable with the human eyes. Such an acquisition process of digital data that combines genetically heterogeneous tumors into the same category may weaken the training dataset's teaching power. Furthermore, 2 pathologists determined the designated pathological types on H&E slides without genetic information before random spitting of patch images into the training and validation sets; this approach might be challenging to avoid interobserver variability. To escape such possibility, the digital images for the training dataset should be obtained from H&E sections that are molecularly characterized, not only by IDH mutations and 1p/19q codeletion but also by comprehensive molecular and methylation profiling.

The quality of an AI diagnosis heavily depends on the quality and quantity of the training dataset. Recent studies using CNNs to diagnose diffuse gliomas that took a similar approach to Jin's analysis did not reach sufficient accuracy to make it readily applicable to daily practice.[9,10] The fundamental disadvantage of this type of approach (ie, data acquisition based on a histology-driven diagnosis) lies in the inaccuracy of pathological diagnosis without genetic information. Gliomas represent a rare cancer composed of tremendously heterogeneous tumor types and subtypes, reflecting distinctive genotypes. Each genotype shares nonspecific, overlapping histological features on H&E sections, making it difficult to give a proper pathological diagnosis. The scarcity of each type and subtype of gliomas also constricts the adequate learning processes of CNNs. Taken together, gliomas

are not the most suitable subject for an AI diagnosis when the approach—as mentioned earlier—is applied. Alternatively, the disadvantage of CNNs to a "real" neuropathologist is that the neural network, which is composed of multiple convolutional and pooling layers, becomes a complete black box that is technically unable to provide informative feedback to a "real" neuropathologist. The platform does not use the 4-tiered system. The basis of the assessment for tumor typing and grading is unknown, preventing the neuropathologists from verifying its interpretation and results. Backup with molecular data may well be required. A novel technology that can visualize the basis of AI assessment for the human eyes would be a genuine aid for the integrated neuropathological diagnostic workflow for gliomas.

In conclusion, although there may be several practical barriers to the implementation of a clinically applicable AI Neuropathologist, with respect to the digital data acquisition methods and the collection of adequate numbers of rare molecularly defined types and subtypes of gliomas, Jin et al demonstrated that AI using deep learning on histology is a feasible method for the nonbiased neuropathological diagnosis of gliomas. The next step in their projects is anticipated.

Keywords

artificial intelligence | deep learning | diffuse gliomas | neuropathology | WHO 2016 classification

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