Neuro-Oncology
23(2), 182–183, 2021 | doi:10.1093/neuonc/noaa294 | Advance Access date 8 January 2021

IDH glioma radiogenomics in the era of deep learning

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See the article by Choi et al, pp. 304–313.

Genomic information has become increasingly vital to the evaluation of infiltrating gliomas, both as part of establishing an integrated diagnosis and for prognosis. Perhaps most important is isocitrate dehydrogenase (IDH) mutation status, as this is a key event that occurs early in gliomagenesis and a defining characteristic for classification with broad implications for patient prognosis and potential targeted therapies. Investigators have embarked on many different imaging strategies to determine IDH-mutant status, including 2HG spectroscopy, pH-sensitive chemical exchange saturation transfer (CEST), and diffusion imaging.[1–3] The simplest strategy—which requires only visual inspection of standard-of-care images—is recognition of the T2-fluid attenuated inversion recovery mismatch sign. The mismatch (T2 hyperintense signal and FLAIR hypointense signal aside from a hyperintense peripheral rim) is reproducible and highly specific for IDH-mutant astrocytoma with perfect or near-perfect specificity and positive predictive value.[2] Nevertheless, the limited sensitivity at 51% leaves much room for improvement.

Accelerating advances in machine learning continue to reshape our society, both overtly (eg, emerging self-driving cars) and more subtly (eg, web searches, social media, and targeted advertising).[4] There is great promise for machine learning to transform the practice of medicine, particularly by potentially increasing the speed and accuracy of diagnosis in radiologic and pathologic images. Image classification, detection, and segmentation have historically been difficult computer vision tasks. Following the initial success of AlexNet on the ImageNet image classification challenge in 2012[5]; however, improvements in deep convolutional neural networks (CNNs) have been able to overcome previously very difficult challenges by learning high-dimensional representations of imaging data. These improvements in machine learning models and techniques can be applied to elucidate the distinctive imaging phenotypes of IDH-mutant and wild-type gliomas.

In this issue, Choi et al. created fully automatic segmentation and classification models that incorporated raw imaging data using a residual deep CNN as well as demographic information and radiomic features extracted from automatic tumor segmentation.[6] Examining n = 1166 patients with gliomas (n = 353 IDH-mutant, n = 813 IDH wild-type) from Severance Hospital (n = 856), Seoul National University Hospital (n = 107), and The Cancer Imaging Archive (n = 203), their models were applied to n = 727 internal development (n = 596 training and n = 131 tuning), and n = 439 internal and external validation sets. They examined T2-weighted, FLAIR, and contrast T1-weighted 2D images and extracted radiomic 3D shape (n = 13) and loci (n = 6) features. In addition to performing well on their internal dataset (area under the receiver operating characteristics curve [AUROC] 0.96 for per patient diagnosis), their model performed well on the two external test datasets (AUROC 0.94 and 0.86, respectively). By selectively evaluating each part of their model separately (also known as an "ablation study"), they demonstrated that each component of their model contributed to the overall model performance, with patient age contributing the least. In addition, they performed saliency mapping on their CNN—a way of visualizing which voxels were contributing the most to the classification in the neural network—that confirmed the model was weighing the enhancing and non-enhancing tumor voxels and immediate surrounding parenchyma most heavily in choosing a genotype, much like a human radiologist would. In combination, these results are a promising advance toward further generalizability and interpretability of machine learning for prediction of infiltrating glioma IDH mutation status.

Although they can be very powerful, deep CNN models are vulnerable to overfitting to their given training dataset. Without testing against additional external holdout datasets, the generalizability of the models can remain dubious. Multicenter studies like the one reported by Choi et al. in this issue[6] are essential to overcome these limitations by testing against both internal and external data. Their work builds upon prior articles in *Neuro-Oncology*. Earlier this year, Bangalore Yogananda et al. reported their own fully automated MRI-based deep learning technique to predict IDH mutation status.[7] Examining n = 214 patients with gliomas (n = 94 IDH-mutant, n = 120 IDH wild-type) from The Cancer Imaging Archive, they trained T2-net (T2-weighted images only) and TS-net (T2-weighted + FLAIR + contrast T1-weighted images) networks using 3D

Dense-UNets for voxel-wise dual-class segmentation of the whole tumor. The T2-net and the TS-net achieved comparable mean cross-validation accuracy of 97%, specificity 97%-98%, and sensitivity 97%-98%, indicating that deep learning of FLAIR and contrast T1-weighted images did not improve performance over using just the T2-weighted images. Last year, Choi et al. applied an explainable recurrent neural network (RNN) to dynamic susceptibility contrast (DSC) perfusion images from n = 463 patients with gliomas (125 IDH-mutant, 338 IDH wild-type), divided into n = 18 test, n = 395 training, and n = 50 validation cohorts.[8] The (R)-2HG oncometabolite produced by IDH-mutant gliomas leads to decreased hypoxia-inducible factor 1-α, which is a potent driver of hypoxia-induced tumor angiogenesis and provides the impetus for perfusion imaging. The RNN is a deep learning model that can learn sequential patterns or temporal dependencies in dynamic time-series data and model the effects of tumor perfusion and permeability. The bidirectional convolutional long short-term memory (LSTM) network with attention mechanism RNN analysis of raw DSC data obviated the traditional extended Tofts-based DSC postprocessing that is dependent on arterial input function and leakage correction algorithms. They achieved 92.8% accuracy, 93.1% specificity, and 92.6% sensitivity.

Novel, fully automated postprocessing analyses of standard and advanced MR images are clearly rapidly approaching. These fully automated analyses are especially appealing because they provide unbiased evaluations independent of local operator training or experience. Thorough understanding of the principles of deep and machine learning is necessary, however, to best develop and then apply these techniques to clinical practice while wary of potential pitfalls. Although unlikely to replace tissue sampling in the near future, the continued improvement in model performance and consistency across diverse imaging datasets brings us closer to a "virtual biopsy." Perhaps in the not-too-distant future, when tumor genomic analysis is not feasible or available, these methods may offer prognostic considerations or additional therapeutic options for our patients without surgery.

Funding

None declared.

Conflict of interest statement. R.J.Y. has served as a consultant for Agios, Puma, ICON, and NordicNeuroLab, and received grant funding from Agios, unrelated to this work. D.C.G. has no conflict of interest to report.

Author contributions. Both authors co-wrote, edited, and approved this editorial. The text is the sole product of the authors and no third party gave input or support to its writing.

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