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Editorial

Deep learning applications in neuro-oncology

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ABSTRACT

Deep learning (DL) is a relatively newer subdomain of machine learning (ML) with incredible potential for certain applications in the medical field. Given recent advances in its use in neuro-oncology, its role in diagnosing, prognosticating, and managing the care of cancer patients has been the subject of many research studies. The gamut of studies has shown that the landscape of algorithmic methods is constantly improving with each iteration from its inception. With the increase in the availability of high-quality data, more training sets will allow for higher fidelity models. However, logistical and ethical concerns over a prospective trial comparing prognostic abilities of DL and physicians severely limit the ability of this technology to be widely adopted. One of the medical tenets is judgment, a facet of medical decision making in DL that is often missing because of its inherent nature as a “black box.” A natural distrust for newer technology, combined with a lack of autonomy that is normally expected in our current medical practices, is just one of several important limitations in implementation. In our review, we will first define and outline the different types of artificial intelligence (AI) as well as the role of AI in the current advances of clinical medicine. We briefly highlight several of the salient studies using different methods of DL in the realm of neuroradiology and summarize the key findings and challenges faced when using this nascent technology, particularly ethical challenges that could be faced by users of DL.

Keywords: Deep learning, Glioma prognostication, Machine learning, Neuro-oncology

INTRODUCTION

Amidst contemporary shifts in the global “smart-tech” arena, there has been a parallel shift in the dynamics of technological integration in health care and its rapidly growing role in supplementing traditional methods of patient care.^[36] An integral aspect of this global movement is the marriage of artificial intelligence (AI) with vast databases as a tool to assist physicians to not only diagnose but also subsequently manage the ever-growing burden of disease.

The realm of AI contains within itself machine learning (ML), as well as a further subset known as deep learning (DL). ML takes use of statistical models to enable these algorithms to improve as more data are introduced to them [Figure 1].^[28] DL is also a process by which computers glean patterns from past experiences and large amounts of data to generate algorithms designed to make increasingly accurate predictions about future events.^[3,5] What further specializes it from ML is the multilayered neural networks used to train on vast amounts of data. Neural networks much like the brain use nodes of information (neurons) that are arranged in layers. Each

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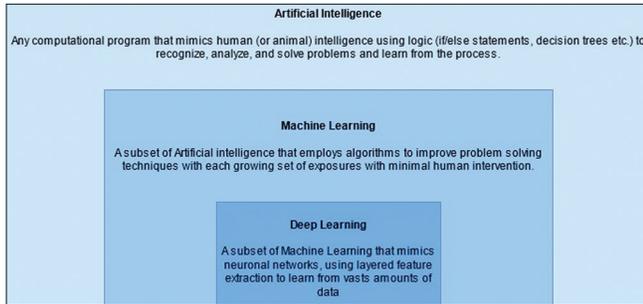


Figure 1: The subsets of artificial intelligence.

neuron uses data from the training set (or previous neuronal connections) and calculates a new piece of datum using weightage and bias factors before communicating the new piece to neuron(s) in the next layer, eventually generating an outcome.^[39]

DL algorithms may then function when provided sets of parameters to evaluate a plethora of aspects of clinical importance in medicine, including screening, diagnosis, and treatment efficacy. Each algorithm must first be assessed by the relevant performance metrics of the extracted patterns when extrapolating beyond the model dataset.^[39] In practice, however, the presence of unknown confounders and imprecise measurements endows a random component to our estimates that varies from individual to individual and population to population.^[5] As a result, the diversity of a training dataset will enable the DL algorithm to learn “better,” which, in turn, would allow for greater and more valid generalizability of predicted patterns on a wider range of populations.^[5,39]

Consequently, this generalizability requires a revolution in data mining to generate large volumes of data from which this subset of AI technology can learn. This is vital to overcome the challenges of data sparsity, multicollinearity, and overfitting, and therefore, to effectively minimize internal bias in the model developed.^[38]

Based on a subtle balance between use and limitations, DL promises to play a crucial role in healthcare, allowing us to find a niche between generalized practice guidelines and personalized patient-centric care. These algorithms have already shown a high level of diagnostic performance based on imaging data for conditions including diabetic retinopathy, skin cancer, and pneumonia.^[36] Salim *et al.*, for example, have recently commented on the rates of diagnostic capabilities of AI (92% area under the receiver operating curve [AUROC] for three different commercially available computer-aided detection [CADE] algorithms) in assessments of screening mammograms, with one algorithm demonstrating comparable sensitivity (81.9%) to those of first-reader (77.4%) and second-reader (80.1%) radiologists given that the AI and radiologists’ readings were equally

probable to rule in the disease (at the same specificity).^[30] Other applications include but are not limited to the ability to predict genomic features such as clinically relevant mutations, to predict and build models of regulatory and enhancing elements in the DNA replication and transcription, and to predict patterns of disease based on population statistics such as infectious disease epidemics and pandemics.^[38]

Amidst these enhancements in health care across disciplines, the realm of prediction and management in oncology stands to benefit greatly from such technologies.^[26] In 2014, Louis *et al.* published an update on behalf of the International Society of Neuropathology stating that non-tissue-based information (e.g. clinical and radiological information), could be of clear utility to aid in reaching a diagnosis. This support from an international body has led neuroradiology to play an increasingly important role in the potential treatment of neuro-oncological patients, with promises of AI-enhanced readings further elevating the importance of neuroradiology.^[24] As such, our paper, as summarized in [Figure 2], aims to assess the state of DL algorithms in their efficacy and precision of pre-, peri-, and post-operative decision-making in neuro-oncology, using gliomas as an oncologic model.

DIAGNOSIS, GRADING, AND CLASSIFICATION OF GLIOMAS

The clinical course of a neoplasm is dependent on the efficacy of several stages of medical intervention including the recognition of clinical manifestations, initial screening of the lesion (employing imaging or laboratory testing), the decision to observe or treat, postscreening histopathological assessment/gold standard confirmation, and predicting morbidity and mortality outcomes. ML can be used to aid this paradigm of medical intervention at several of these levels [Figure 3].^[28]

As mentioned before,^[38] the strength of ML as a tool to evaluate radiological screening independently or augmentatively is yielding promising results, with this excitement not only limited to mammography but also in the realms of lung cancer, prostate cancer, and brain metastases with the use of CADE and computer-aided diagnoses techniques.^[2,7,35] Prospectively, ML may be able to correlate radiological imaging detailing the extent of disease with genomic data of the lesion such as mutations and gene expressions and histopathological findings to establish an accurate diagnosis in an emerging field known as imaging genomics.^[4]

The promise of ML in the field of oncology in addition to the growing recognition of an integrated approach to neuropathology lends optimism to the treatment of a subset of neuro-oncological entities known as gliomas. These tumors are difficult to render an exact judgment on, due to

TAKE HOME MESSAGE

Deep Learning Applications in Neuro-Oncology

ARTIFICIAL INTELLIGENCE

The realm of Artificial Intelligence contains within itself Machine Learning (ML), as well as a further subset known as Deep Learning (DL). ML uses statistical models to enable these algorithms to improve as more data is introduced to them

APPLICATIONS OF AI IN NEURO-ONCOLOGY

In 2014, Louis *et al.* published an update on behalf of the International Society of Neuropathology stating that non-tissue-based information (e.g., clinical, radiological information), could be of clear utility to aid in reaching a diagnosis.

ETHICAL CONSIDERATIONS

- Lack of autonomy for patients in "black box" algorithms
- Lack of accountability
- Comprises Patient-Physician relationship

FUTURE OF ML

A prospective trial on glioma patients, using a previously trained CNN based on an accurate model, to help prognosticate or diagnose a patient is sorely needed. Until we overcome challenges in implementation and their exact use in clinical decision-making processes becomes apparent, they will remain promising research ventures.

Figure 2: The take-home message.

similarity of cellular structures among lower grade lesions; with estimations varying due to inter-reader variability depending on the professional experience of histopathologists and radiologists, introducing an element of subjectivity.^[37] Although the simple grading of these tumors is not a principle bottleneck in their treatment paradigm, some difficulties remain in the presence of standardization efforts, such as the use of objective classification criteria, the most prevalent of which is the WHO classification.^[34] Furthermore, although histopathological and molecular analysis remains the gold

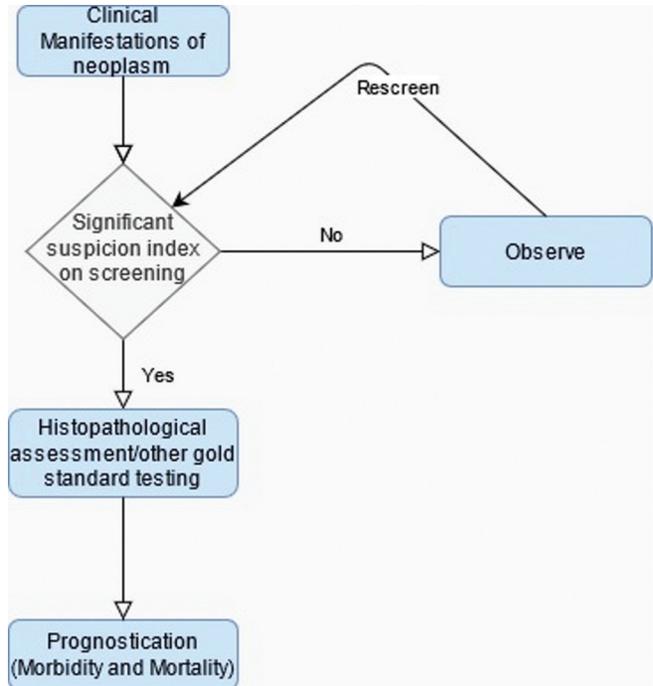


Figure 3: Levels of entry for deep learning applications in neuro-oncology.

standard for the diagnosis of gliomas, the very notion of a biopsy raises a few concerns. There are many inherent risks with this method of diagnosis, with inevitable errors due to inadequate sampling and time inefficiency.^[43] Thus, the need for elimination of subjectivity and improvement of sensitivity and timeliness of histopathological diagnosis as well as the growing logistical feasibility of ML imparts a growing confidence in the use of such technology in the diagnosis of gliomas.

Broadly, ML techniques can be divided into those that learn to predict outcomes based on input-output paired training, termed supervised learning, or those that find patterns within input data itself without preset outcomes, termed unsupervised learning. Supervised learning itself can be achieved through several techniques such as support vector matrixes (SVMs) which aim to delineate a function that separates two sets of data.^[33]

Previously, studies have demonstrated that gliomas can be classified according to their clinical grade using linear SVMs which were trained on descriptive features such as amount of mass effect of blood supply. The limitation of these studies, such as one by Li *et al.*, is that these quantitative features were estimated by domain experts and the definition of these features was limited to expert opinion and hence not reproducible.^[23] Two other studies subsequently used other parametric features to improve accuracy; Devos *et al.* used MR intensities with spectroscopy using linear discriminant

analysis, linear and nonlinear least squares SVMs (AUROC of 0.94 in distinguishing low-grade vs. high-grade gliomas),^[11] whereas Rajendran made use of association rule mining (specifically pruned association rule), a technique in ML that aims to predict certain characteristics of a set based on other characteristics, to categorize CT scan brain images as simply either normal, benign, or malignant with a 96% sensitivity and 93% accuracy.^[29]

It stands to reason from this discussion that the beginnings of ML in neuropathology must be the generation of a dataset from which newly developed AI can learn. For gliomas, radiological evidence in addition to matched clinical, genetic, and pathological data collections reside in the Cancer Imaging Archive and Genomics Data Commons Data Portal respectively, as a joint effort between the National Cancer Institute and the National Human Genome Research Institute from 2006 onward.^[13] Since 2012, ML and DL techniques applied to carefully selected data subsets from these archives have already generated numerous algorithms related to tumor segmentation (delineating the location and extension of a lesion from surrounding tissue) under the brain tumor segmentation challenge.

At present, algorithms generated by ML have shown promise in accurate recognition of characteristics used to define gliomas. Noninvasive neuroimaging tools for glioma grading using a multitude of quantitative parameters obtained from advanced magnetic resonance imaging (MRI) techniques, such as dynamic contrast-enhanced MRI, arterial spin labeling, and diffusion-weighted imaging, are currently being utilized in many ML/DL models.^[40] Skogen *et al.* were able to discriminate high-grade gliomas from low-grade gliomas using MRI texture analysis with a fine texture scale resulting in a sensitivity and specificity of 93% and 81%, out of a total of 95 glioma patients, but fared worse at differentiating within those grades.^[32]

The emerging field of radiogenomics breaks the restrictions of applying AI technology to segmentation only. Advancement in our understanding of key molecular differences in tumor cells in comparison to normal cells and how these differences drive changes in the microenvironment of the lesions now lends itself to radiological patterns that can more accurately identify a tumor. For example, certain glioma varieties exhibit differences in isocitrate dehydrogenase (IDH), a key enzyme in the Krebs cycle. Gliomas that potentiate the activity of certain genotypes can drive the production of 2-hydroxyglutaric acid, vascular endothelial growth factor, and hypoxia-induced factor-1 α . The activity of these molecules may, in turn, produce characteristic radiological findings such as alterations in histogram analysis.^[21]

In fact, the current literature supports the idea of using radiological imaging to predict the presence of such biomolecular differences. Specifically in the context of

gliomas, studies have been conducted on IDH mutations, O6-methylguanine methyltransferase (MGMT) hypermethylation, epidermal growth factor receptors (EGFRs), and 1p/19q chromosomal codeletions.

Zhang *et al.* were able to generate a predictive model for IDH genotypes (of which genotypes 1 and 2 predict good response to therapy) within high-grade glioma lesions based on clinical data and radiological features obtained through conventional MRI with an AUROC of 0.9231 in a validation cohort.^[41] The radiological features considered included anatomical location, texture, and shape, among others. An analogous non-AI-assisted study conducted by Zhou *et al.* was also able to generate a similar algorithm to predict IDH1 mutation (AUROC 0.86 \pm 0.01), 1p/19q codeletion status (conferring increased survival) (AUROC of 0.96 \pm 0.01), and histological grade (AUROC 0.86 \pm 0.01).^[42] In contrast, a convolution neural network (CNN), a form of DL especially suited to image recognition, developed by Chang *et al.* demonstrated a high degree of accuracy in predicting IDH genotypes from MRI features in Grade II–IV gliomas in a validation test (AUROC 0.95).^[8] Chang *et al.* also developed a neural network predictive of several factors, of which its accuracy in predicting IDH1 mutation status was 94%.^[9]

Similarly to IDH, MGMT hypermethylation is an important identifying marker due that also happens to predict higher response to treatment with combination temozolomide and radiation.^[17] Korfiatis *et al.* evaluated three residual deep neural network architectures in their ability to predict the MGMT methylation status. The three 18, 34, and 50 layered architectures were able to achieve an accuracy of 76.75% (\pm 20.67%), 80.72% (\pm 13.61%), and 94.90% (\pm 3.92%), respectively, lending credibility to higher-order processing providing better results.^[22] Similarly, Han and Kamdar obtained a 67% accuracy on their validation set exploring MGMT methylation status from MRI scans obtained from glioblastoma multiforme (GBM) (Stage IV glioma) patients in the TCIA/TCGA archives.^[16] Chang *et al.* developed a neural network from data for 259 patients from the TCIA/TCGA archives, showing 83% accuracy in predicting methylation status.^[9]

Other studies have also shown the ability of ML to detect 1p19q chromosomal codeletion (recognized as predictor of chemotherapeutic response in gliomas), and EGFR amplification status, another avenue for targeted therapy. The aforementioned neural network developed by Chang *et al.* manages to predict 1p19q codeletion status at an accuracy of 92%.^[9] A multiscale CNN developed by Akkus *et al.* similarly predicts the codeletion at an 87.7% accuracy.^[11] Kickingreder *et al.* set out to use ML techniques to identify a myriad of molecular characteristics including MGMT hypermethylation and hallmark copy number variations. Of these, they managed to develop a model that predicted EGFR with a 63% accuracy.^[21]

With such exciting advancements, comparable outputs to traditional methods of algorithmic generation, and a yet unmet ceiling for improvement, it is thought that in the near future, with the increasing availability of high-quality data, CNNs will be the mainstay in both diagnosing and prognosticating cancer, using widely available imaging modalities.

PROGNOSIS PREDICTION

While ML can be useful in predicting prognosis based just on imaging characteristics before surgery, we have more information after surgical resection of the tumor that can be incorporated in making extensive ML algorithms. Along with imaging characteristics, the cumulative biopsy and clinical data such as tumor markers can help generate ML algorithms for estimating prognosis, complications, and other outcomes. It can also overcome challenges such as the correct recognition of tumor progression versus pseudoprogression, a transient MRI finding mimicking progression with eventual improvement. One such study aiming to delineate the two conducted by Jang *et al.* developed a CNN model with an AUROC of 83% that was trained on 59 individuals and tested on 19 (Seoul National University Hospital dataset).^[19] Repeat model development by Jang *et al.* on the Korean Radiation Oncology Data ($n = 182$) yielded a model with an AUROC of 86%.^[20] The necessity to develop a second model shall be discussed in the section on ML and challenges.

Conventionally, prognosticating for GBM involves accounting for a multitude of independent risk factors impacting overall survival (OS) such as male gender, age >60 years), poor preoperative Karnofsky scores of <70, Caucasian ethnicity, advanced tumor with partial resection, and surgery without adjuvant chemoradiation.^[35] Using several of these factors, Gittleman *et al.* developed an independently validated nomogram with a concordance index (equivalent to AUROC for the censored data used in the study) of 0.657.^[14] Notably, however, this study was conducted on a Caucasian majority sample and utilizes only MGMT hypermethylation as a prognostic factor of the molecular characteristics seen in gliomas.

A study by Nie *et al.* demonstrated that through a 3D CNN, they were able to train a support vector machine to predict a long or short OS time. Their experimental results were able to achieve 89.9% accuracy through their methods.^[27] They were able to feed single-channel (T1 MRI) multi-channel (fMRI and DTI) data through a binary classifier (e.g. SVM) to produce a framework for high-level brain tumor prognosis. The study elucidates the incredible potential application that a neural network possesses in prognosticating neuro-oncological patients based on just imaging alone. Similarly, a study by Sanghani *et al.* was able to produce comparable results on GBM patients based on routinely acquired MR

images alone. MR image derived texture features, tumor shape, and volumetric features, and patient age was obtained for 163 patients, which after put through a similar SVM, was capable of producing 2-class and 3-class OS group prediction accuracy of 98.7% and 88.95%, respectively.^[31]

Another study by Zhou *et al.* utilized nonquantitative spatial-correlated features from MRI defined tumor subregions (termed habitats) in developing a computational framework. This framework was able to use intratumoral grouping and spatial mapping to identify GBM tumor subregions and yield habitat-based features. After separating data sets into those that underwent resection with GBM (32 patients), and those that did not (22 patients), they were able to achieve 87.50% and 86.36% accuracies for survival group prediction, respectively.^[44]

The role of computational networks in prognosticating overall long- and short-term survival is one that has been evaluated through dozens of studies in low- to mid-grade tumors, yielding similar results when applied to high-grade tumors as well.^[14,19,20,27,31,35,44] These networks are capable of functioning on routinely acquired data, as demonstrated by Sanghani *et al.*, but also provide considerable information to both the health-care provider and the patient. Eventually, these systems are thought to be able to augment a neuro-oncologist's decision-making ability, however, it would not be long before they are potentially able to surpass human performance in terms of prognostication.

CHALLENGES AND LIMITATIONS

Ethical considerations

ML, like any early adopted technology, is not without its potential drawbacks in terms of ethical dilemmas.^[10] ML applied in other fields has already shown some biases, with the problem stemming from the fact that algorithms may mirror human biases. These biases may be introduced into a medical setting where patients receive notably different treatment regimes leading to an unoptimized approach and potential harm.

There is an incredibly urgent need for ethical guidelines for medical practitioners to use these advancing AI and machine learning technologies. Time-constrained consultants are expected to understand the inner workings of these insular programs, as without knowing the data sets they are built on, the technology can progress into a black box leading to ethically gray outcomes. The lack of transparency inherent with these systems may lead to physicians doubt either the algorithm, or themselves, when their decision is conflicting with one made by a machine.

It is also important to recall that the foundation of the current medical system in many nations was based on a

patient-doctor relationship, not a patient-health-care system relationship. Many doctors (and patients) feel uneasy at the growing rate at which we are adopting these machines into our health-care decisions. One study showed that over 63% of adults in the United Kingdom felt uncomfortable with AI replacing the conventional decision-making process.^[12] Their lack of acceptance of AI is, to some degree, warranted. In many fields, such as engineering, AI and ML represent efficiency and will play an important role in the future. However, one of the basic ethical tenets of medicine is autonomy, which requires physicians to have a deeper understanding of the clinical validation of ML in studies. Health-care professionals operate on their own basis of expertise and clinical acumen. When their decision-making skills are infringed upon, by blindly accepting a prognosis, diagnosis, or route of treatment provided by an AI or algorithm, they could be seen as violating their Hippocratic oath: *primum non nocere* (“first, do no harm”).^[10] It is this lack of transparency and explainability that is vital in the role of medicine that limits its use when compared to its role in business or engineering. Autonomy and nonmaleficence are ethical principles grounded in “consequentialist” ethical theory, which holds that the moral quality of an action depends on its consequences. If the consequences of choosing an AI favored diagnosis over a physician diagnosis, whether for a high- or low-grade tumor, have the possibility (however *minute* as shown by the accurate results of ML) of resulting in an increased mortality – should we still use this technology?^[12]

Finally, the laws and rules of ethics are a worldwide debate but enforced by national laws. Ethical laws on the potential of AI and ML in medicine have been hotly contentious but are virtually absent in low- and middle-income countries.^[15] This is not based on a lack of acceptance of AI/ML, as most health-care professionals are in favor of their use (despite ethical dilemmas), rather it is contingent on lack of infrastructure, high cost, and lack of training in the region.^[18]

Another reason for the impediment in widespread adoption, and perhaps the most important one, is a lack of accountability.^[12] Allocation and grounds for liability for adverse events related to the ML tools used with actual patients need to be clarified by a national/international ethical body. There is currently no conceivable method to predict how these tools, along with other ML models in medicine, will expose hospitals, physicians, and patients to liability.

Other logistical drawbacks to the use of AI in medicine include the scale of computational power required to develop useful algorithms and prioritization of resource allocation toward more pragmatic algorithms to maximize their effects.

Specifically in the field of radiological AI interpretations, a major drawback in considering findings and pattern

recognition in any image modality is a lack of consensus on which features would add most value to a preoperative diagnosis, whether from a histogram parameters or image texture attributes.^[6] Attribute selection is a concept that aims to remedy this challenge. It revolves around choosing a division with the chosen least number of variables providing the highest accuracy, alongside the most informative attributes. The rigorous selection process searches through possible combinations of attributes to find a particular subset that can reliably predict outcomes, resulting in an algorithm that is characterized by the method used to define the predictive value of each subset of attributes (feature evaluator) and the method determining the search over the attributes (search method).^[40]

A prospective trial on glioma patients, using a previously trained CNN based on an accurate model, to help prognosticate or diagnose a patient is sorely needed. Until, we overcome challenges in implementation and their exact use in clinical decision-making processes becomes apparent, they will remain promising research ventures.

CONCLUSION

The use of AI to augment the clinical judgment and practice of a physician is an exciting prospect, specifically in the field of neuro-oncology where neuroradiology and neuro-radiogenomics are prime candidates for the use of the algorithmic learning in order. In a noninvasive manner, these tools can predict the presence of several factors that can be helpful in the diagnosis and prognostication of gliomas. Current literature already demonstrates a high sensitivity and accuracy of individual learning techniques in determining genetic markers and radiological features. The challenge lies in creating algorithms that are applicable on much larger scale, with greater amounts of learning and practice sets for AI learning techniques to be tested on, while still remaining logistically feasible to be run within the strict timeframes within which health-care systems operate. In addition, there are ethical considerations to be made regarding the use of AI within the clinical realm and their impact on a physician’s decision-making.

Declaration of patient consent

Patient’s consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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