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Present challenges and surveillance of artificial intelligence in neuro-oncology

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Abstract

Brain tumors are evaluated, characterized, and monitored using diagnostic imaging. However, because these tumors are so diverse, there are still several difficulties in each group. This might involve differences in the biology of the cancer that are linked to varying intensities of cellular invasion, proliferation, and necrosis, all of which have distinct imaging appearances. Due to these changes, tumor evaluation, including segmentation, surveillance, and molecular characterizations, has become more complex. Even though various rule-based techniques have been put into practice to relate to tumor appearance and size, these techniques naturally reduce the vast quantity of tumor imaging data to a small number of variables. Due to their efficacy in resolving image-based problems, approaches in artificial intelligence, machine learning, and deep learning have found increased use in computer vision tasks, such as tumor imaging. This section aims to provide an overview of some of these developments in tumor imaging.

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INTRODUCTION

With the recent advent of artificial intelligence in neuroimaging, there is a lot of interest in utilizing the potential of novel, intrinsically quantitative computational techniques to measure and categorize brain tumor features on standard and sophisticated magnetic resonance imaging (MRIs) in a non-invasive manner. Machine learning (ML) and deep learning (DL) are two forms of artificial intelligence (AI) that have the potential to automatically identify patterns in images that are invisible to a neuroimager and to outperform human performance in terms of glioma genetics prediction, treatment response prediction, and long-term outcome prediction.

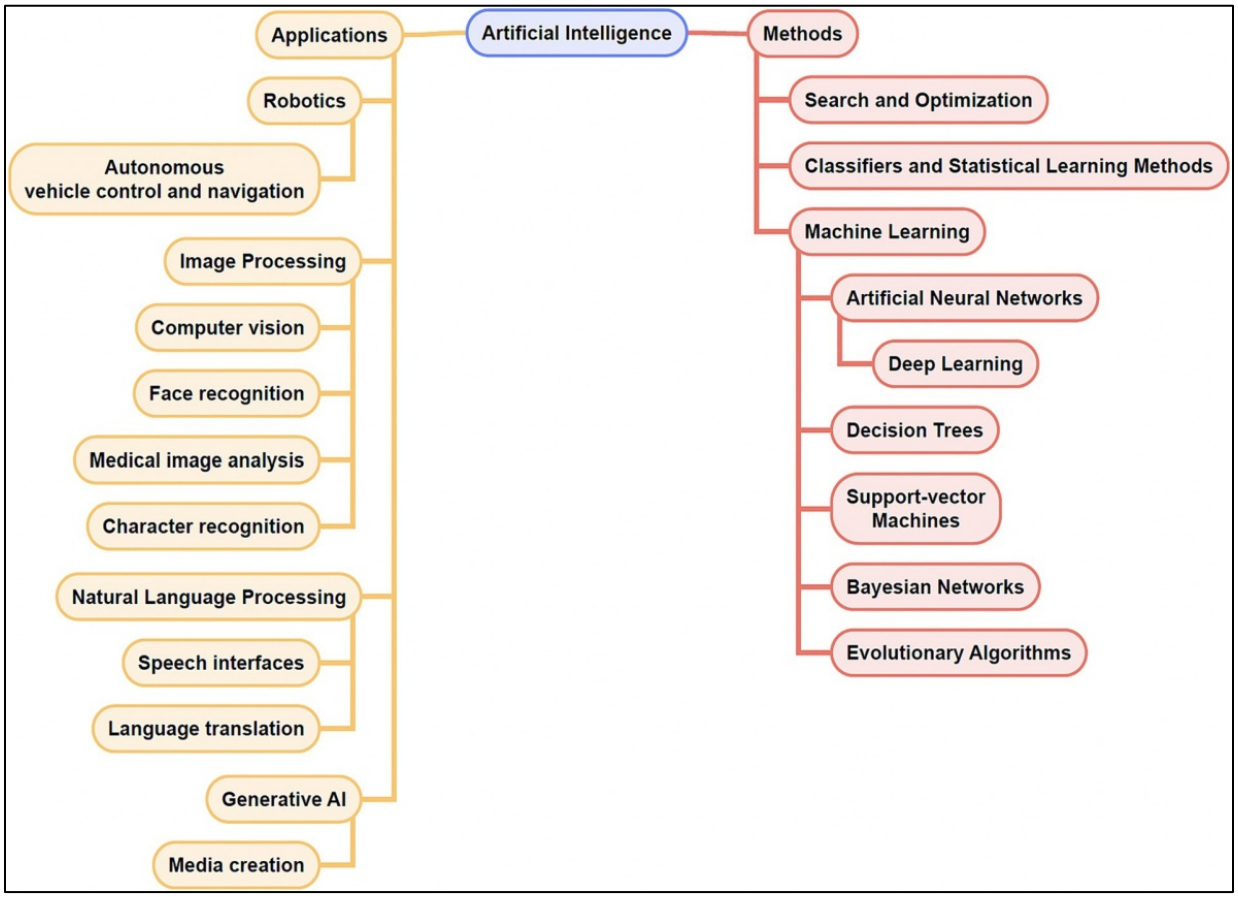

Figure 1 Select artificial intelligence (AI) concept map

In theory, these AI characteristics could help doctors treat patients more quickly and precisely, giving them more value overall. This article will assess the current state of brain tumor imaging, outline possible uses for AI, and provide a brief overview of the epidemiology of primary brain tumors, focusing on gliomas [1].

Artificial intelligence (AI)

Artificial intelligence (AI) is the computational capacity to carry out tasks comparable to those carried out by people to maximize the use of distinctive inputs and produce outputs with a high added value. Medical imaging is one of the most exciting uses of AI at the moment. Radiologists can benefit from using computers when doing routine detection and diagnosis duties. To help radiologists identify and analyze possible lesions, which in turn allows differentiating between lesions, decreasing errors, and boosting radiological efficiency, the goal of promoting Computer-Aided Diagnostic (CAD) systems using state-of-the-art AI techniques was established. As a result, continuous and incremental efforts have been to enhance AI's diagnostic efficiency to be promoted for everyday clinical practice. The creation of artificial neural networks (ANN) in the middle of the past century and their subsequent evolution, which introduced the principles of computational learning models, ML, and DL, is substantially responsible for the progress of AI [2].

Machine learning (ML)

Applications of ML demand a collection of problematic data as input that the machine will utilize for self-training, and such data should always generate the desired output to be expected. There are two types of machine learning (ML): supervised and unsupervised. Supervised ML depends on whether the input was labeled previously by human experts or if the computer performed direct data extraction using various computational methods. The optimal ML model must include the most important features to the outcome (local features) and the most generic ones (global features) with the ability to generalize for new unseen inputs.

Table 1 Applications of AI for neuro-oncology

Study sample (total n)	Task	ML algorithm	Performance
Gliomas graded 2-4 (44 complete tissue slides)	Glioma grade	CNN	96% of GBM vs. LGG and 71% of grade 2 vs. grade 3 Accuracy
Glioma graded 2–4 (323 patients)	Glioma classification	CNN	Accuracy 87.5%
Glioma graded 2–4 (549 patients)	Glioma grade	DNN	Accuracy: 74% grade 2 vs. grade 3; 93.8% HGG vs. LGG
Glioma diffuse (373 patients)	Glioma WHO classification	CNN	93.3% accuracy
Most CNS tumors are classified by the WHO (2801)	CNS Tumor WHO classification	Supervised ML (random forest classifier) and unsupervised ML	12.6% did not match the pathologist, but most subsequently proved correct; 60.4% agreed with the pathologist; 15.5% thought the subclass was better; Eleven percent not classified

Deep learning (DL)

Deep learning (DL) enables automatic dimensionality reduction and more intricate classification procedures by using a hierarchical feature extraction criterion. Convolutional neural networks (CNNs), which incorporate many neural layers between input and output, improve the robustness of deep learning (DL) and enable the training phase to mimic human brain operations. The amount of research on DL has almost skyrocketed in the last few years. Radiomics is a new area of research that has emerged from the ability to relate basic diagnostic patterns and features of radiological scans (with different modalities) to a specific pathological and histological subtyping by combining ML/DL image processing with clinical and, when appropriate, pathological/histological data [3].

Radiomics

Radiomics is a new translational discipline in which a range of properties, including shape, strength, and texture, are identified from radiological pictures to allow for the collection of varied imaging patterns. These patterns may be applied to tumors' staging, grading, and subtyping. In addition, radiology is commonly employed in systems in numerous forms, such as prediction, prognosis, monitoring, and therapy response assessment. Radiomics can be broadly classified into two types: feature-based and deep learning-based. Unlike these clinical evaluations affected by the human reader, the results are more stable, accurate, and reproducible. Radiomics features can be calculated using multiple mathematical algorithms (feature-based) or created statistically from ML-based complex computational models during the training phase (deep learning-based) in an automatic process. Figure 1 depicts the overall framework for radio mics [4].

Neuroradiology applications of AI for neuro-oncology

In neuro-oncology, MRI imaging is essential for diagnosis, radiographic surveillance, and treatment response evaluation. However, interpreting MRIs in patients with brain tumors can occasionally be challenging. Treatment-related changes can mimic the progression of cancer; histologic and molecular features that influence prognosis and treatment choices frequently lack obvious imaging correlates; and estimating tumor size can be difficult in tumors with diverse and infiltrative components [5]. AI techniques like machine learning, deep learning, and radiomics have been used to extract therapeutically useful information from photos that might not be visible to the human eye. Radiomics is taking clinical imaging into quantifiable, mineable data or "features" (such as shape, intensity, and texture). ML techniques frequently use these traits to create models that predict different clinical factors. Machine learning and deep learning have been applied to neuro-

oncology to measure tumor size and kind and predict tumor grade, molecular characteristics, and survival. To provide ground truth for the training of machine learning algorithms, radiologists typically preprocess, standardize, label, and annotate MRI data [6]. These data may undergo additional preprocessing, augmentation, or transformation before being utilized to train machine learning or deep learning algorithms. Frequently, a "test" cohort of patient photos not seen during training is used to evaluate how well these trained algorithms function. Other reviews have examined the technical elements of artificial intelligence in brain tumor imaging.

Brain Tumour Epidemiology:

Primary CNS tumors are a scarce kind of cancer; in adults, the incidence rate is estimated to be 23.8 per 100,000 people. Even though these tumors are uncommon, they account for a sizeable portion of cancer-related morbidity and death. Every year, roughly 10 out of every 100,000 people are diagnosed with a primary brain tumor, and 6 to 7 out of every 100,000 people are diagnosed with a primary malignant brain tumor. The highest incidence of brain cancer is found in North America (age-standardized incidence rate [ASR]: 5.3 per 100,000 individuals), Europe (5.5 per 100,000 persons), Australia, and Western Asia. Gliomas account for about 30% of brain tumors and 80% of all initial malignant brain tumors. Astrocytomas and gliomas are the two most frequent malignant brain tumors in adults after metastasis. Gliomas range in histology from aggressive grade 4 tumors (glioblastoma, GBM) with a high risk of progression and/or recurrence to potentially medically curable grade 1 tumors (pilocytic astrocytoma). To diagnose and generate prognoses accurately, tumors must be accurately classified and characterized [7].

Subtype and staging affect cancer death, and the amount of time survivors survive after diagnosis differs significantly by grade. Molecular and histological markers are used to classify and grade gliomas. GBM is a subtype of Glioma that develops from healthy glial cells. It comprises a variety of tumors with different phenotypes and genetic profiles [8]. With an incidence of 3.2 per 100,000 adults annually, GBM is the most prevalent primary CNS tumor in adults. With a mean diagnostic age of 64 for primary GBM and a peak incidence of 15.2 cases per 100,000 between the ages of 75 and 84, the incidence rises noticeably with age. The occurrence of GBM has been linked to several genetic diseases, such as Li-Fraumeni syndrome, neurofibromatosis type I, and tuberous sclerosis; however, less than 20% of patients with GBM have a strong family history of cancer, and exposure to ionizing radiation is the only known environmental risk factor. Overall, the prognosis and mortality rates for GBM vary greatly depending on the grade and subtype; therefore, techniques to more precisely predict these factors would benefit both treatment and outcomes.

Table 2 Main Primary Central Nervous System Tumors

Malignant	
Astrocytomas	20–25%
Oligodendrogliomas	1–2%
Ependymal tumors	<2%
Other	8%
Non-malignant	
Meningiomas	37%
Pituitary	16%
Nerve sheath	8%
Other	7%

One of the worst malignant solid tumors is still GBM. For freshly diagnosed GBM, the 1-year overall survival rate is 17–30%, while the 5-year survival rate is less than 5%. For GBM, surgical resection combined with chemotherapy and radiation therapy continues to be the standard of care. Chemotherapy response varies, though, and almost all patients experience recurrent illness. Furthermore, the frontal lobe is where these tumors most commonly originate, which causes cognitive and motor impairments that cause many patients to lose their independence. Glioma classification and characterization are increasingly being done using molecular markers. IDH1 mutations, for example, can help differentiate between different glioma subtypes and are a powerful predictor of a good prognosis. More precise diagnosis and prognostication can be achieved by characterizing specific genetic characteristics, such as IDH1 status [9].

Present Challenges with Brain Tumour Imaging:

Segmentation

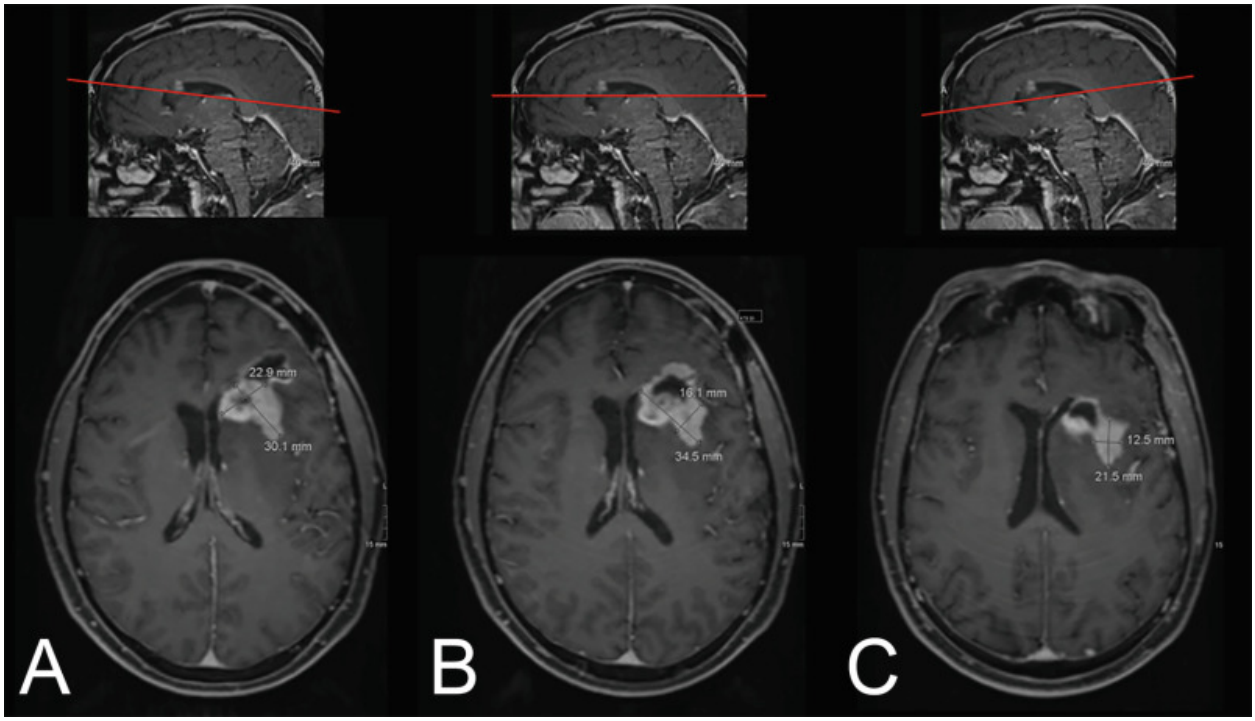

Figure 2 Patient with glioblastoma after resection. Simulation of tilting the patient's head up results in progression of disease (a) while in routine positioning demonstrates stable disease (b), and tilting downward results in partial response (c)

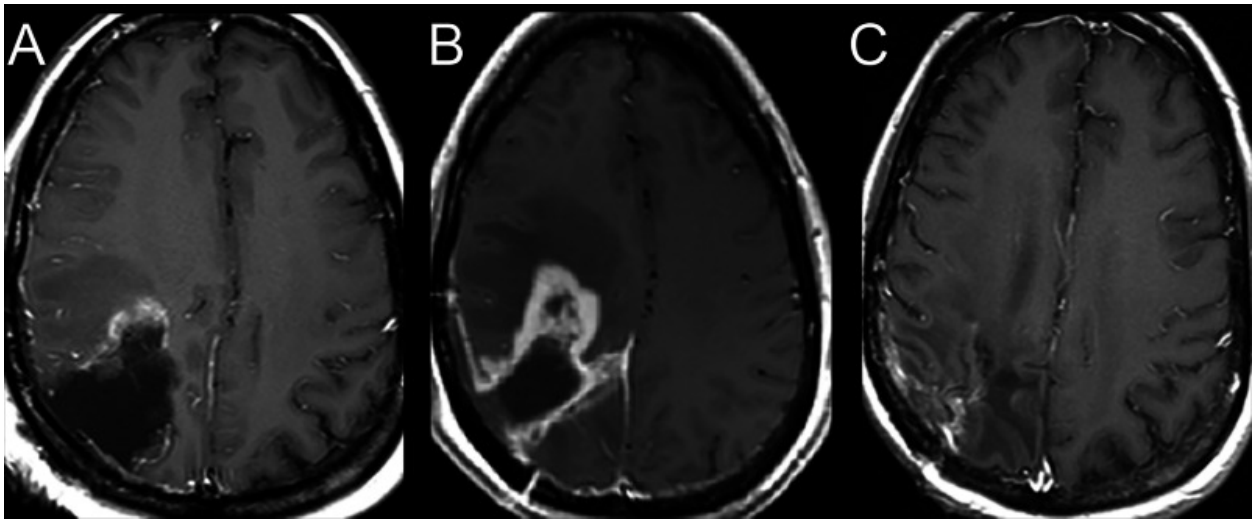

Figure 3 Shortly after resection, axial post-contrast pictures demonstrate minor disease enhancement (a). A month later, a follow-up MRI showed additional thick enhancement (b), which later decreased on images taken a year later (c)

Although neuro-oncology imaging has advanced significantly, there are still several obstacles to overcome before brain tumors can be accurately measured. One current drawback, for instance, is that unidimensional and bidimensional manual measurements are employed in many methods for tumor size monitoring. While this may work for solid tumors with a more spherical shape, the postsurgical cavity and tumors of neuro-oncology patients tend to be highly irregular in shape, which enhances the difficulties in collecting accurate measurements. This is because both the original GBM and its recurrence frequently exhibit irregular and nodular development. Such discrepancies and possible errors could lead patients to label successful treatments as

ineffective or vice versa (Figure 2). Ultimately, this difficulty emphasizes the importance of accurate and repeatable methods for measuring tumor size [10].

Surveillance[11]

Apart from tumor segmentation, radiographic assessment has been a crucial instrument for the ongoing monitoring of patients suffering from brain tumors and has been essential in treatment trials. Historically, imaging markers for treatment response and tumor progression have been associated with increased and decreased tumor size utilizing gadolinium contrast-enhanced sequences. Still, there are drawbacks when using contrast enhancement alone to determine the state of the disease. More specifically, after radiation and temozolomide (TMZ) were added to the standard of care, treatment-related increases in enhancement were seen to resemble progression increasingly. Tumour pseudoprogression, characterized as elevations in edema and contrast enhancement on MRI with or without clinical worsening that subsequently stabilizes or recovers, is seen in 20–60% of patients with TMZ radiation therapy (Figure 3). Furthermore, the incidence has reached 90% in patients with methylation status of the methyltransferase (MGMT) promoter in glioma cells and higher TMZ sensitivity.

Since the precise mechanism is still unclear, the only accepted method for differentiating between treatment-related Parkinson's disease (PD) and proper progression of disease (PD) is invasive tissue sampling, short-interval imaging, or clinical follow-up. However, these methods may cause delays and compromises when managing an aggressive tumor. To address some of these issues, particularly PD, the Response Assessment in Neuro-Oncology (RANO) working group established criteria in 2010. Nonetheless, the assessment of PD is still restricted when using traditional imaging methods. Monitoring GBM patients with PD also presents challenges with other more recent treatments, such as immunotherapies. To prevent labeling effective treatments as ineffective in cases of PD, the immune-related response criteria working group (iRANO) has developed guidelines to address the challenges of radiographic worsening. Nevertheless, the group recognizes that further research and solutions incorporating advanced imaging are required to improve assessment in these patients [12].

Molecular Classification

Impact of Glioma Inter-tumoral Heterogeneity [13]

It has been demonstrated that inter-tumoral genetic variability in Glioma affects prognosis and therapeutic response. For instance, the survival rate of GBMs with isocitrate dehydrogenase (IDH) mutations is noticeably higher than that of GBMs with IDH wild type (31 months as opposed to 15 months). The World Health Organisation (WHO) has placed significant emphasis on integrating molecular markers for its classification systems in its 2021 update, including IDH status, due to its recognition of the significance of genetic information. It is also becoming more apparent that the different genetic characteristics of GBMs lead to varying responses in terms of treatment responsiveness. O6-methylguanine-DNA methyltransferase (MGMT) promoter silencing was one of the first alterations found; it decreases the capacity of tumor cells to repair DNA damage caused by alkylating drugs like temozolomide (TMZ). It was then shown that 45% of GBM patients had MGMT promoter methylation silencing. These patients showed an improvement in survival when treated with TMZ with radiation as opposed to radiotherapy alone (21.7 months versus 15.3 months). To accurately advise personalized therapy and offer prognostic information, it is imperative that future GBM monitoring incorporates genetic and imaging data.

Challenges of Personalized Therapy [14]

With more than 140 clinical studies assessing personalized or targeted medicines for GBMs alone, advancements in genetic profiling have sparked the development of new targeted therapeutics. These treatments are designed to take advantage of therapeutic targets driven by genetics. However, there seems to be a barrier to these tailored strategies: increasing evidence of intra-tumoral heterogeneity in GBM. Using single-cell RNA sequencing. Showed that GBMs are composed of a heterogeneous population of cells with varying gene expression profiles. Similarly, a surgical multisampling method was utilized on 11 GBM patients to find genome-wide variability. For

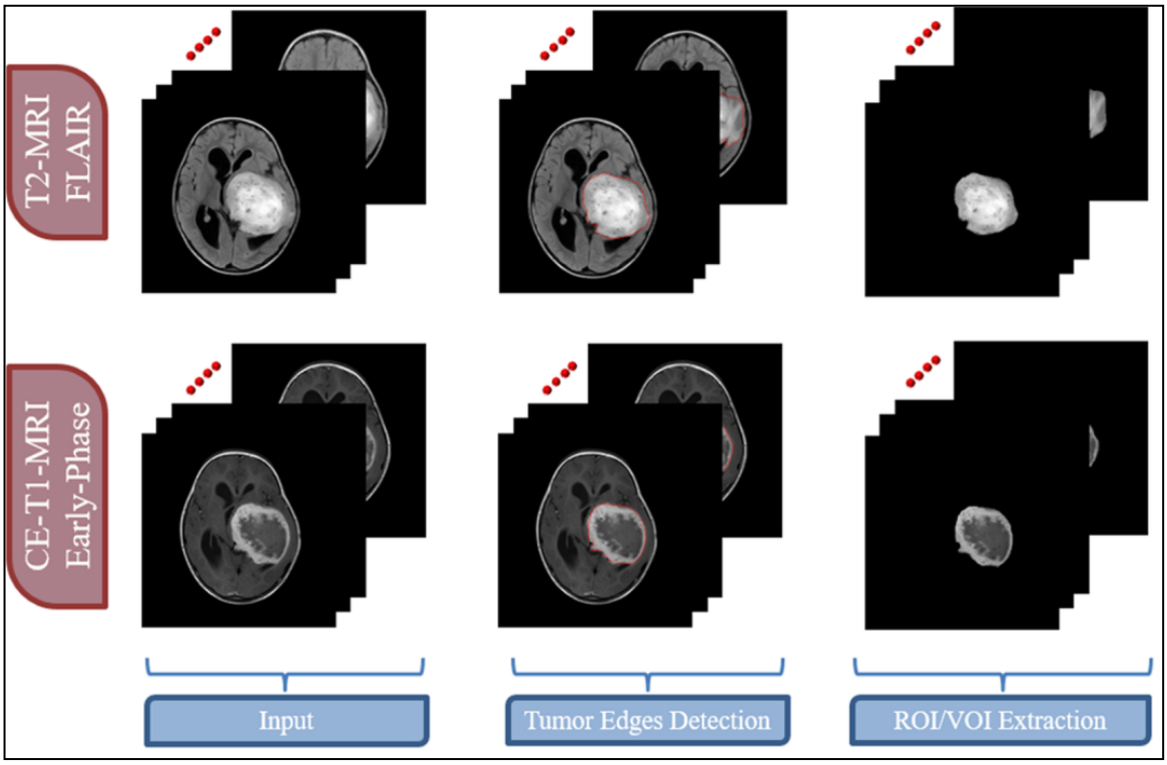

Figure 4 Glioma tumor manual segmentation using two distinct imaging modalities

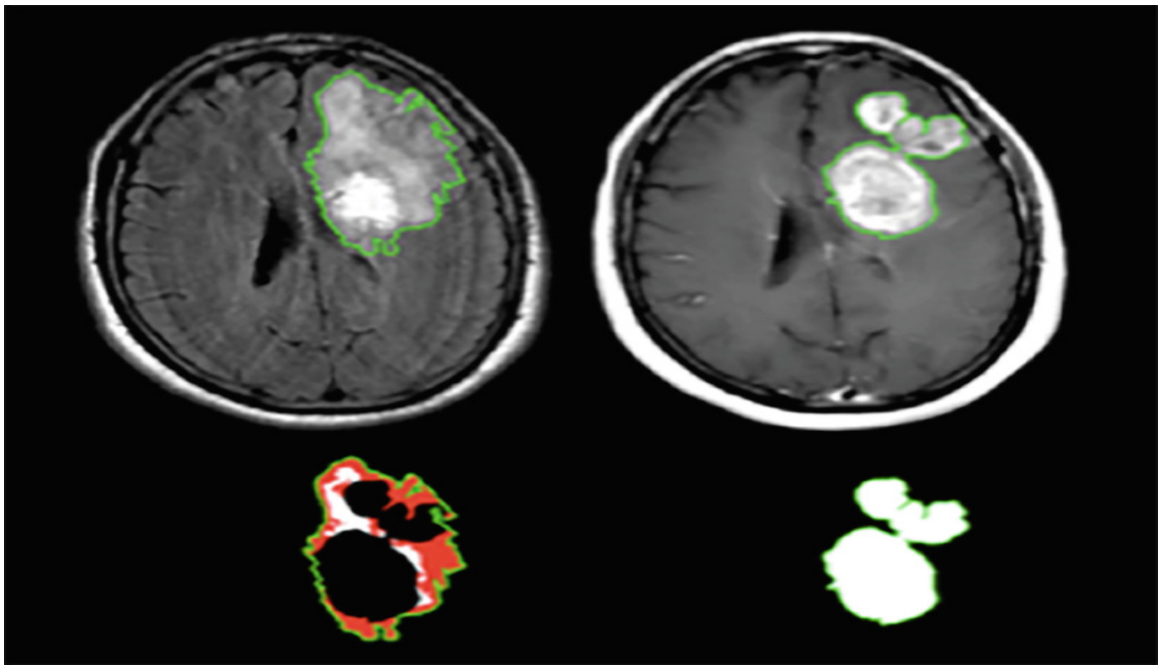

Figure 5 Segmentation of the enhancing tissue (right) and FLAIR edema (left)

this reason, it can be challenging to identify, create, and implement individualized treatment because every brain tumor may represent a variety of distinct tumor habitats, each of which will respond to and reject therapy differently.

MRI Biomarkers of Tumor Biology and Genetic Heterogeneity [15]

Tumor biology is altered due to temporal and geographical variations in genetic expression. These variations include adjustments to angiogenesis, cellular proliferation, apoptosis, and

invasion. These biological alterations then show up as different degrees of edema and augmentation in the varied imaging characteristics of brain tumors. For instance, the blood-brain barrier breaking down causes imaging abnormalities on contrast-enhanced MRI, which can show patches of necrosis as a sign of apoptosis. Furthermore, it has been demonstrated that physiology-based MRI sequences, including perfusion imaging and apparent diffusion coefficient (ADC), correlate with angiogenesis and tumor cellularity.

Moreover, exciting studies have demonstrated that tumors with a smaller cerebral blood volume (CBV) during perfusion have a longer overall lifetime and are more likely to be IDH mutants. With varying degrees of effectiveness, other papers have predicted IDH status using enhancement patterns and ADC. Thus far, based on these MRI findings, there has been inconsistent success in providing molecular categorization for brain tumors. For instance, classifying IDH and MGMT mutant status has shown some success; however, techniques for 1p19q and EGFR have shown less consistency. A "single" tumor may include several distinct mutations inside, and various mutations may exhibit comparable MRI findings. Several methods have been developed to offer glioma visual interpretation that is standardized for tissue classification. As an illustration, the Visually Accessible Rembrandt Images (VASARI) feature set is a rule-based lexicon designed to enhance interpretation repeatability. However, these techniques rely on human visual interpretation, prone to interrater variability and intrinsic subjectivity. Finally, steps must be taken to develop reliable and reproducible methodologies for accurately classifying molecular subtypes a priori.

Potential Applications for Machine Learning:

Segmentation

In oncology, radiographic evaluation is crucial for clinical follow-up and research studies. The RANO criteria currently use subjective evaluation of the FLAIR non-enhancing tumour and 2D measures of the enhancing illness to guide treatment methods. Unfortunately, the postsurgical cavity has a highly uneven form, which could make it more challenging to take repeatable and reliable measurements. Furthermore, linear measures of cystic and necrotic tumors are frequently overstated. It seems logical that 3D segmentation offers a more precise way to measure a tumor's size than linear 2D methods and procedures. Comparing the 3D segmentation to the conventional diameter-based approach, a superior survival prediction is possible.

It has been demonstrated that deep learning, a relatively new area of artificial intelligence, may quickly surpass the imaging benchmarks of previous machine learning techniques for various computer vision applications, including 3D segmentation images. Regarding brain segmentation, the CNN method outperformed other methods such as majority voting, coupled level sets, random forest, and support vector machine (SVM), a conventional linear machine learning methodology. Deep learning techniques for tumor segmentation have proven effective since 2012, as evidenced by the Multimodal Brain Tumour Image Segmentation (BraTS) challenge. Developers can access GBM pictures using this dataset, which currently has over 2000 cases from 37 institutions. Consequently, some teams have created automated brain tumour segmentation tools that use various AI methods to determine lesion margins and offer a more precise estimation of the disease burden (Figure 5). The Sørensen-Dice coefficient scores for the total tumor, tumor core, and augmenting tumor were 88.95, 85.06, and 82.03 respectively [16].

Surveillance

As previously mentioned, RANO criteria cannot consistently identify psPD cases from natural progression, and a recent meta-analysis indicates that up to 36% of cases are underdiagnosed. Invasive tissue sampling and short-term clinical follow-up with imaging are the only recognized ways to differentiate between treatment-related psPD and real PD. However, these procedures may complicate and prolong the therapy of an aggressive tumor.

Radiologic imaging has already been used to characterize psPD using traditional machine learning algorithms. An ideal classifier for psPD was produced using an SVM technique and multi-parametric MRI data. Its sensitivity was 89.9%, and its specificity was 93.7%. While they haven't been used as much, deep learning techniques show promise in differentiating between PSPD

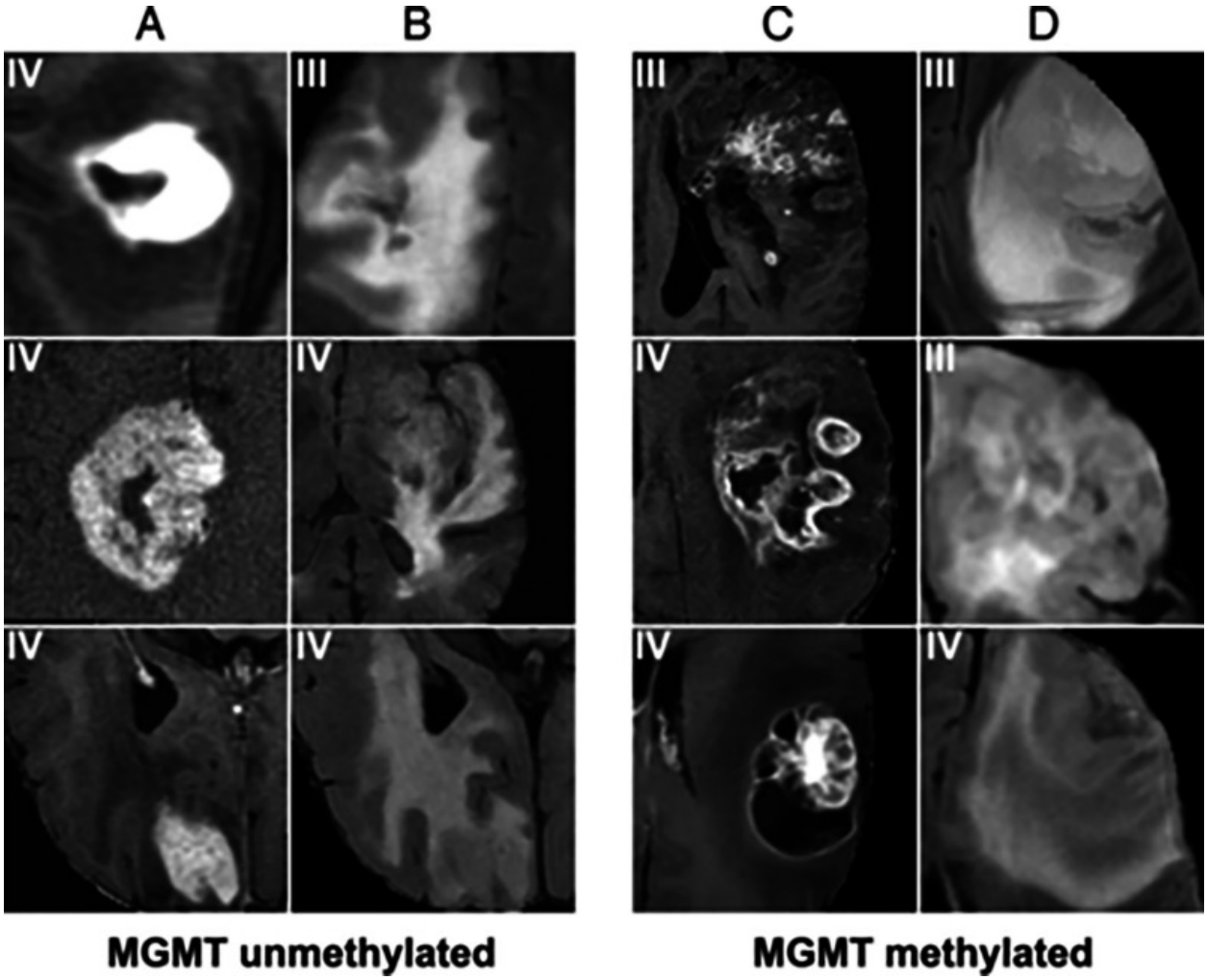

Figure 6 Thick enhancement with central necrosis (a) and infiltrative edema patterns (b) are among the characteristics. However, nodular and heterogeneous enhancement (c) characteristics with mass like FLAIR edema (d) indicate MGMT promoter methylation status

and real PD. A CNN-LSTM (extended short-term memory network paired with a deep learning model) was evaluated to compare tumor PD with psPD in GBM. With 59 patients in the training cohort and 19 in the testing cohort, their dataset included clinical and MRI data from two different institutions. Their CNN-LSTM structure, which used both clinical and MRI data, produced an AUC (area under the curve) of 0.83, an AUPRC (area under the precision-recall curve) of 0.87, and an F-1 score of 0.74, outperforming the two comparison models of CNN-LSTM with MRI data alone and a random forest structure with clinical data alone. More recently, a CNN-STM with an accuracy range of 0.62–0.75 was used to separate PD from PSP. These examples show that when it comes to image analysis, using a deep learning technique can perform better than a more conventional machine learning approach [17].

Molecular Classification [18]

Radio genomics aims to improve diagnosis by establishing connections between gene expression data and medical imaging data to help understand underlying illness causes. The radiological appearance of tissue, including its form and texture, can be computed and observed to exhibit specific molecular and genetic abnormalities. Artificial intelligence has emerged as a crucial component that has contributed significantly to the growth of radio genomics, which uses the interaction between genetic and radiological characteristics in oncology to enhance patient treatment decisions. AI-based radio genomics can potentially improve diagnosis, prognosis, and survival prediction by identifying essential aspects in images that identify genetic properties of disease.

One of the first groups to predict tumoral genetic subtypes from imaging features using neural networks in gliomas. This work used characteristics collected from space-frequency texture analysis on brain MRIs' S-transform to predict the methylation status of the MGMT promoter in patients recently diagnosed with GBM. Levner's team successfully identified 87.7% of the 59 patients, 31 of whom had tumors with MGMT promoter methylation verified by biopsy. In addition to IDH mutation status, residual CNN approaches have been utilized to predict MGMT promoter methylation status. Chang et al., for instance, created a CNN that can accurately and simultaneously categorize the MGMT promoter methylation status, 1p19q codeletion, and IDH1 gene methylation status using imaging data from 259 patients in the Cancer Imaging Archives dataset.

A principal component analysis method was created to separate the last feature layer and identify the elements that have the greatest influence on each categorization (Figure 6). These characteristics mostly coincide with subjective visual assessments of what has been documented in the literature. Used textural analysis to assess glioma heterogeneity and achieved 80% accuracy in differentiating between low- and high-grade gliomas. Furthermore, a textural analysis approach could categorize the MGMT promoter methylation status in glioblastoma patients with 71% accuracy.

CONCLUSION:

In conclusion, the variability of the disease contributes to current challenges in brain tumor imaging and poses issues for disease characterization. However, since novel AI, ML, and DL techniques can reliably and accurately detect imaging patterns beyond human perception, their application to brain tumor imaging seeks to improve several areas. The discipline has also been stimulated by several public competitions (e.g., BraTS), and it has lately started working with several imaging associations, including the RSNA and ASNR. In the end, there is optimism that these instruments will keep producing new opportunities to improve research and treatment in the future.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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