Review of Contemporary Philosophy
ISSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
Pp 2396 - 2412

Gliomas: An Advanced MRI Techniques for the Preoperative Diagnosis and Imaging.

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Abstract:

Background: Gliomas are primary brain tumors originating from glial cells and are classified based on histological and molecular markers. The WHO 2021 updated classification system has integrated genetic factors such as IDH mutations and 1p/19q co-deletion, refining glioma subtyping. Advanced magnetic resonance imaging (MRI) techniques have emerged as promising non-invasive tools for assessing glioma characteristics, including their molecular subtypes, without the need for biopsies.

Aim: This review aims to explore the application of advanced MRI techniques in preoperative glioma diagnosis, highlighting their role in characterizing tumor molecular subtypes and aiding clinical decision-making.

Methods: The review synthesizes recent advancements in MRI technologies, including perfusion imaging, diffusion MRI, and magnetic resonance spectroscopy (MRS). It also evaluates the validation and clinical applications of methods such as dynamic contrast-enhanced (DCE) MRI, arterial spin labeling (ASL), and MR elastography (MRE), based on expert consensus and available literature.

Results: Various MRI modalities, including DSC-MRI for cerebral blood volume (rCBV) measurement and MR spectroscopy, have shown promise in non-invasively predicting glioma subtypes as per the 2021 WHO classification. These advanced techniques can enhance tumor characterization, helping to identify glioma grades and predict patient outcomes. However, the clinical integration of these methods faces challenges such as standardization, validation, and the need for specialized equipment and expertise.

Conclusion: Advanced MRI techniques offer significant potential for the preoperative assessment of gliomas. They can non-invasively predict molecular subtypes and tumor behavior, facilitating more precise treatment planning. However, widespread clinical adoption is hindered by the need for further validation, standardized protocols, and overcoming practical barriers related to equipment and operator expertise.

Keywords: Gliomas, MRI, advanced imaging, glioma subtypes, molecular diagnostics, preoperative assessment, neuro-oncology, dynamic susceptibility contrast (DSC) MRI.

Received: 05 october 2023 **Revised:** 19 November 2023 **Accepted:** 02 December 2023

Introduction:

With an age-adjusted incidence rate of 6.03 per 100,000 people, gliomas are a diverse group of neuroepithelial tumors that arise from glial cells [1]. Traditionally, a four-step grading system is used to classify these tumors; higher grades indicate more malignant traits and are linked to a generally bad prognosis. The WHO Classification of Tumors of the Central Nervous System (CNS) 2021 edition significantly updated the World Health Organization's (WHO) grading system, which has traditionally depended on histological inspection [2]. Compared to the previous 2016 edition, this updated classification offers better prognostic predictions by incorporating molecular diagnostics into the glioblastoma classification and grading process [3, 4]. Unlike the 2016 guidelines, the WHO 2021 classification includes a wider range of molecular changes, classifying gliomas as ependymal tumors, glioneuronal and neuronal tumors, circumscribed astrocytic gliomas, pediatric-type diffuse low-grade (LGG) and high-grade gliomas (HGG), and adult-type diffuse gliomas. Isocitrate dehydrogenase (IDH) 1 and 2 mutations, 1p/19q co-deletion, H3F3A changes, ATRX gene mutations, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, CDKN2A loss, epidermal growth factor receptor (EGFR) amplification, combined gain of chromosome 7 and loss of chromosome 10, and TERT promoter mutations are now important genetic markers used for glioma classification. The word "glioblastoma" is now used only to describe IDH-wildtype tumors in adults, which are consistently rated as grade 4, whereas IDH-mutant astrocytomas constitute a separate condition, with grades varying from 2 to 4 as the illness worsens. Additionally, oligodendrogliomas are now categorized independently from astrocytomas, with grades ranging from 2 to 4, because they show both IDH mutations and 1p/19q co-deletion. Since gliomas' metabolic pathways and phenotypic behavior are influenced by their genetic makeup, sophisticated magnetic resonance imaging (MRI) techniques may offer a viable, noninvasive means to anticipate the types and behaviors of gliomas. Glioma localization, tumor volume, infiltration characteristics, compressive effects on surrounding structures, and associated consequences are all made possible by preoperative MRI. With particular slice thicknesses and b-values, standard structural imaging procedures at 3T usually include T1-weighted imaging (both before and after contrast), T2-weighted imaging (after contrast), T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging, and diffusion-weighted imaging (DWI) [5].

Glioma molecular subtypes can now be noninvasively characterized in accordance with the 2021 WHO classification because to improvements in MRI sequences that enable quantitative imaging of different pathophysiological characteristics in gliomas and adjacent tissues [6, 8]. Preoperative advanced MRI may help clinical decision-making and allow for tailored treatment based on tumor-specific features, even though tissue-based genotyping via neurosurgical biopsy or tumor removal is still the gold standard [6, 9]. However, for preoperative glioma assessment, only conventional MRI is used in many clinical settings. A number of obstacles have prevented new MRI techniques from reaching their full potential and from being incorporated into standard clinical practice. Despite suggestions to speed up the development of imaging biomarkers in oncology, one of the main obstacles is the lack of validation of sophisticated MRI-derived biomarkers and the absence of regulatory standards and guidelines for their application [10–13]. Furthermore, modern imaging modalities are time-consuming and rely on specially designed processing pipelines since they frequently call for specific hardware, software, and knowledge for acquisition, processing, and interpretation [14]. By describing the procedures and possible advantages of several MRI modalities for preoperative glioma assessment, this review seeks to increase knowledge of sophisticated MRI techniques and ease their practical implementation. The review is broken down into two sections. The

first discusses perfusion imaging methods, such as arterial spin labeling (ASL), dynamic contrast-enhanced (DCE) MRI, and dynamic susceptibility contrast (DSC) MRI, as well as diffusion MRI, vascular imaging, and relaxometry. MR spectroscopy, chemical exchange saturation transfer (CEST), susceptibility-weighted imaging (SWI), MRI-PET, MR elastography (MRE), MR-based radiomics, and artificial intelligence (AI) applications are among the more sophisticated methods included in the second section.

Data Analysis and Methodologies:

This review was initiated as part of the European Cooperation in Science and Technology (COST) Glioma MR Imaging 2.0 (GliMR) initiative, which convened a multidisciplinary group of clinicians, engineers, and physicists specializing in advanced MRI techniques for brain tumor imaging. These experts participated in a series of virtual and onsite meetings from July 2020 to September 2022 [10]. The review is aimed at clinicians, such as neuroradiologists, neurosurgeons, and neuro-oncologists, as well as researchers who seek to enhance their knowledge of advanced MRI techniques for brain tumor imaging. The GliMR consortium's technical expertise was leveraged to compile available evidence and assess the validation level of cutting-edge MRI methods, along with the information that can be derived from these techniques. The advanced MRI techniques reviewed enable semi-quantitative imaging of various tumor characteristics, including composition, metabolism, physiology, and mechanical properties, which are not captured by routine clinical protocols. The review specifically focuses on acquisition, reconstruction, and postprocessing methods that have already demonstrated pilot results in brain tumor imaging. While this review does not encompass all literature, topical experts selected recent peer-reviewed publications indexed in the MEDLINE database, focusing on reviews that present techniques with the highest potential impact. Each topic includes a brief technological introduction and serves as the foundation for evaluating the methodological readiness of preoperative advanced MRI techniques for future clinical implementation.

The review examines multiple MRI methodologies and contrasts, categorized into two parts. The first part covers techniques such as dynamic contrast-enhanced (DCE) MRI, dynamic susceptibility contrast (DSC) MRI, arterial spin labeling (ASL), diffusion MRI, vessel imaging, and magnetic resonance fingerprinting (MRF). The second part discusses magnetic resonance spectroscopy (MRS), chemical exchange saturation transfer (CEST), susceptibility-weighted imaging (SWI), MR-PET, MR elastography (MRE), and MR-based radiomics, including applications in artificial intelligence (AI). The reviews of these sequences are structured to provide an overview of each technique, its clinical application in glioma imaging (with a focus on glioma subtypes according to the 2021 WHO classification), the level of clinical and technological validation, and the recommended clinical use. An expert panel assessed the validation level of each technique. A survey was distributed to all experts, which included questions on the acquisition, processing, and clinical evidence of each method for pre-treatment glioma characterization. In cases of discordance, the expert panel reviewed recent literature. After multiple consensus meetings, the validation level of each technique, which included relevant literature references.

For each method, validation was assessed across multiple dimensions, including test-retest repeatability, cross-vendor reproducibility, and multi-site reproducibility. Clinical evidence was evaluated in terms of proof-of-concept in patients, the evaluation of the method in clinical studies (including single-center and multi-center studies), meta-analysis results, diagnostic accuracy, and established criteria for glioma differentiation. The review also highlights the acceptance of these techniques, including whether method guidelines have been established, if the methods are included in national imaging guidelines, and their application in clinical trials and international guidelines. The clinical use of these methods in brain tumor imaging, particularly for gliomas, was assessed, along with the implementation of specific sequences and post-processing software availability. Additionally, the ease of data acquisition, post-processing, and interpretation was evaluated from the perspective of the scanner operator, clinical department, and clinician. The methodologies, parameters, and associated molecular markers are summarized for each technique, referencing key studies that support the use of advanced MRI techniques for glioma characterization and grading. In conclusion, while many advanced MRI techniques demonstrate significant potential in preoperative glioma imaging, their clinical implementation remains contingent on continued

validation, the development of standardized protocols, and overcoming the challenges of equipment and expertise availability. The expert consensus and the detailed review of each technique offer valuable insights into the current state and future direction of advanced MRI in brain tumor diagnostics.

Dynamic Susceptibility Contrast-Enhanced Magnetic Resonance Imaging (DSC-MRI):

Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI) involves the acquisition of T2 or T2*-weighted images with high temporal resolution, during which a gadolinium-based contrast agent (GBCA) is injected as a bolus. A gradient-echo echo planar imaging (GRE-EPI) sequence, typically heavily T2*-weighted, is most commonly employed. When the GBCA is confined to the vessels in the brain with an intact blood-brain barrier (BBB), a gradient of susceptibility between intra- and extravascular tissues is induced, resulting in a transient shortening of the dynamic T2*-weighted signal (S(t)). This signal is converted into the relaxation rate change ($\Delta R2 \times (t)$), which, when integrated, provides a voxel-wise estimate of the relative cerebral blood volume (rCBV) in comparison to other regions of the brain. Additionally, voxel-wise cerebral blood flow (CBF) can be estimated by separately measuring the arterial input function (AIF) from large arteries, in conjunction with the tissue-specific $\Delta R2 \times (t)$. rCBV is the most commonly utilized DSC-MRI parameter for evaluating brain tumors [15-17]. However, estimation of rCBV can be confounded by the extravasation of GBCA through a disrupted BBB, a frequent occurrence in brain tumors. While this leakage effect compromises the assumption of GBCA vascular compartmentalization, DSC-MRI can still be effectively used to estimate rCBV in brain tumors if this leakage effect is adequately considered. A recent consensus on DSC-MRI acquisition for brain tumors has led to two recommended approaches [18]. The first approach involves a pre-dose of GBCA to minimize T1 leakage effects that could arise during the subsequent DSC-MRI acquisition. The second, which does not require a pre-dose, uses a low (30°) or intermediate (60°) flip angle with field-strength-dependent echo times (TEs), with values ranging from 40-50 msec at 1.5T and 25-35 msec at 3T. For both methods, a repetition time (TR) of 1000-1500 msec is recommended, and the inclusion of a contrast-agent leakage correction method is essential. The Boxerman-Schmainda-Weiskoff (BSW) method is widely used for leakage correction, though other techniques have been proposed [19-21].

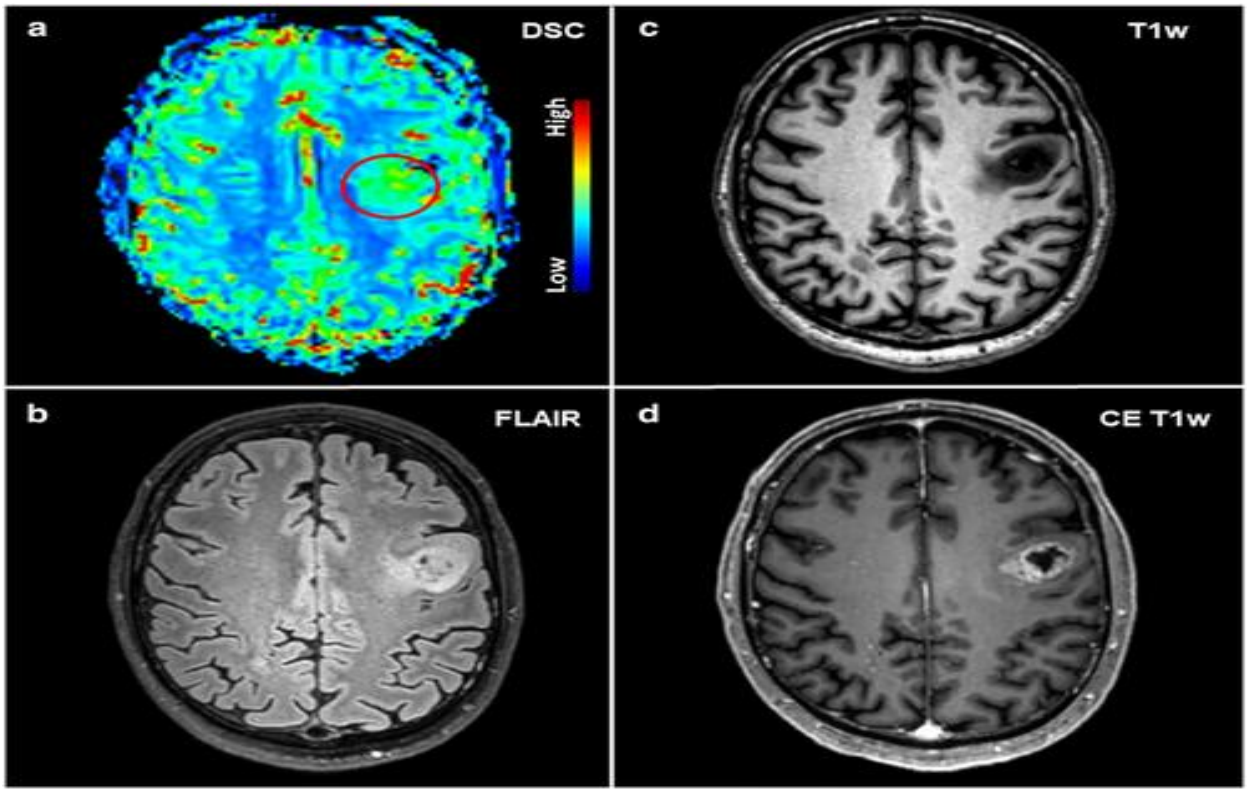

Figure 1: Dynamic Susceptibility Contrast Magnetic Resonance Imaging (DSC-MRI).

CLINICAL APPLICATION:

In addition to classifying patients into low, intermediate, and high-risk categories, studies have shown that rCBV ratios can predict glioma grade [15, 22–24] and that a greater rCBV is associated with a shorter survival [25]. It has been demonstrated that both intra-tumoral and peri-tumoral rCBV can accurately and consistently distinguish between low-grade gliomas (LGG) and high-grade gliomas (HGG) with great sensitivity [26]. Furthermore, it was discovered that pre-operative rCBV "habitats," which indicate regions of low, intermediate, and high vascularity in both the peritumoral and contrast-enhancing regions, were highly predictive for patients receiving standard-of-care treatment [27].

Because glioma heterogeneity can result in undergrading and misdiagnosis, one of the most important uses of pre-operative rCBV is its ability to ensure proper diagnosis. By directing the selection of the best biopsy sites, rCBV has been helpful in preventing such misdiagnoses [28] or in detecting them after the fact [25]. Tissue from regions with low rCBV correlated with non-tumor histopathological diagnoses, while tissue from regions with high rCBV exhibited early and aggressive recurrence, according to a recent case report [29] that used rCBV class maps, which identify regions of varying vascularity (low, intermediate, and high). Therefore, for an appropriate diagnosis and subsequent treatment planning, it is essential to comprehend spatial variation in rCBV, both in resected and residual tissue. The success of the 2016 World Health Organization (WHO) categorization, which now include molecular markers, may also be significantly influenced by pre-operative rCBV. Molecular markers from a single tumor specimen are usually used for treatment and patient stratification, despite the fact that there is substantial heterogeneity at both the cellular and molecular levels. However, despite advances in the area, this method frequently underutilizes the potential of genetic profiling, which may account for the limited gains in patient outcomes [30]. In comparison to tumor background tissue, hypercellular, hypervascular microfoci display higher expression of markers such Ki-67, HIF-1a, CD31, and EGFR [31], and rCBV has been demonstrated to predict differences in IDH1 mutation and MGMT status [32]. As a result, rCBV can inform biopsy choices and offer a more precise foundation for genetic and histopathological studies.

VALIDATION:

The usefulness of rCBV as an essential supplement to conventional MRI is supported by the available data. However, the lack of consistency has hindered the clinical adoption of rCBV, which could explain the variation in reported rCBV thresholds [33]. However, recent research indicates a high degree of technological readiness for rCBV due to its great repeatability, cross-site consistency, and market availability. rCBV was demonstrated to be highly repeatable in a study involving DSC-MRI data taken twice in 8 days in individuals with HGG [34]. A standardization technique, which does not require a user-defined reference region to normalize rCBV to normal brain values, further decreased the coefficient of variance within individuals. Standardized rCBV demonstrated higher repeatability than normalized rCBV, and similar outcomes were observed in a multi-site clinical trial with outstanding rCBV repeatability [35].

High-grade and low-grade gliomas were consistently differentiated by rCBV in a multi-site analysis of a shared DSC-MRI dataset utilizing various processing tools [36]. Additionally, a single threshold that applied to all platforms was found, emphasizing that variations in patient demographics, image acquisition settings, or data pre-processing may have contributed to a large portion of the prior heterogeneity in reported thresholds. Results became more consistent once these variables were fixed. Consistency in rCBV data and the criteria used to differentiate tumor grades could be greatly improved by the broad implementation of the suggested acquisition technique [18]. As confirmed by spatially matched biopsies, two separate sites employing identical acquisition and post-processing techniques were able to determine the same threshold for differentiating between tumor and therapy effects [37, 38]. Platforms for rCBV analysis that have received FDA clearance and CE marking are currently widely accessible. The usefulness of rCBV in forecasting patient outcomes in clinical trials has been highlighted by studies comparing platforms, which have shown how simple they are to use and how well they can gather and interpret multi-site rCBV data [35, 41, 42].

However, there are still issues with DSC-MRI optimization. For example, in places close to bone, resection cavities, or air-tissue interfaces, GRE-EPI sequences may suffer signal dropout, making tumor evaluation more difficult. It is vital to make technical advancements to improve spatial resolution and lessen susceptibility effects. Additionally, the evaluation of tumor-specific vascularity is made more difficult by GRE-EPI's strong sensitivity to big normal arteries. Combining the GRE-EPI and SE-EPI sequences could be a viable option, providing pictures with different levels of sensitivity to vessel size and a more thorough understanding of the vascularity of the tumor [15, 17, 24, 43]. Nevertheless, there are currently no clinically available combinations of these sequences. Furthermore, whole-brain imaging is frequently not possible due to the high temporal resolution needed for DSC-MRI; however, developments in parallel and multi-slice imaging may provide an alternative [44]. Glioma diagnosis and therapy management have benefited greatly from the relatively simple collecting of pre-operative DSC-MRI data, especially by rCBV mapping. By resolving previous concerns about standardization, current consensus guidelines for data collecting and the convergence of analysis methods can speed up full clinical adoption. To further increase the clinical relevance of DSC-MRI, there are still issues to be resolved, such as enhancing picture quality and coverage.

DCE Overview

A perfusion imaging method called dynamic contrast-enhanced MRI (DCE-MRI) monitors the T1-shortening effect of gadolinium-based contrast agents (GBCA) in tissue and blood plasma, especially when leakage happens. The recorded signal is especially helpful for describing the tumor microvasculature since it offers conflicting information about blood perfusion, artery permeability, and the fraction of extracellular extravascular space (EES). By assessing variables like contrast arrival time, time to peak, maximum intensity, area under the curve, wash-in slope, and wash-out rate, semi-quantitative signal analysis can be carried out. As an alternative, tracer kinetic models can be used to perform quantitative analysis. According to the extended Tofts model, which is the most widely used model in tumor assessment, the contrast tracer is dispersed throughout the intravascular space and the EES and exchanges in both directions across the blood vessel wall. The volume fraction of plasma (Vp), the volume fraction of EES (Ve), the reflux exchange rate from the EES to the blood plasma (Kep), and the volume transfer constant between the blood plasma and the EES (Ktrans) can all be numerically estimated using this model. The most often utilized DCE metric in glioma research is Ktrans, which measures vascular permeability. Numerous papers have compiled general recommendations for using DCE imaging in preclinical research (45, 46, 48, 49, 50).

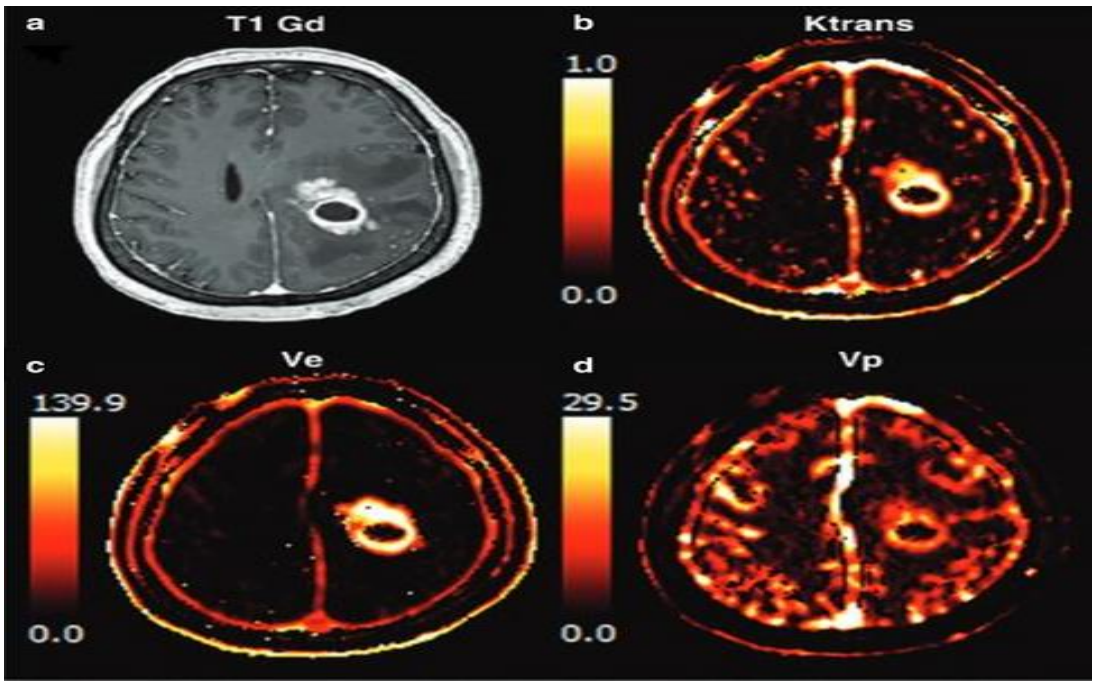

Figure 2: DCE Imaging.

Clinical Application

Significant angiogenesis is a characteristic of malignant gliomas, which results in aberrant blood flow, increased vascular permeability, and irregular vascular structures. DCE-derived metrics are used in tumor monitoring and have been found to be possible indicators of angiogenic activity in gliomas. Based on DCE parameters, a thorough review (52) combined 14 research that distinguished between low-grade gliomas (LGGs) and high-grade gliomas (HGGs) and five studies that distinguished between primary central nervous system (CNS) lymphomas and HGGs. With an area under the curve (AUC) of 0.96 for separating LGGs from HGGs and an AUC of 0.86 for separating primary CNS lymphomas from HGGs, the research showed high diagnostic accuracy. Furthermore, it has been demonstrated that DCE parameters can forecast molecular traits such isocitrate dehydrogenase (IDH) and O6-methylguanine-DNA methyltransferase (MGMT) methylation that are essential for classifying gliomas. Notably, Hu et al. (53) found that IDH-mutated and wild-type gliomas differed statistically significantly in the Ktrans and Ve histogram parameters. Additionally, MGMT-methylated glioblastomas had noticeably higher Ktrans values, according to Zhang et al. (48). This suggests that MGMT methylation is connected to glioma-associated angiogenesis that is marked by increased endothelial permeability. Furthermore, the predictive potential of DCE parameters has been investigated in a number of studies; the results show a correlation between lower overall survival (OS) and greater Ktrans and Ve values. Notably, Ulyte et al. (54) showed that in patients with HGG, higher Ve consistently predicted worse OS and progression-free survival (PFS).

Validation

For more than 30 years, DCE-MRI has been the focus of intensive research, with multiple studies demonstrating its value in glioma diagnosis, prognosis, and therapeutic monitoring. However, a significant obstacle that makes cross-center comparisons more difficult is the variation in DCE values among various imaging suppliers and systems. Variations in field strength, imaging methods, sequence settings, and analysis software are some of the factors that contribute to this variability. Kim (55) has talked about these causes of variability and offered some possible ways to lessen them. Nevertheless, in order to incorporate this method into conventional clinical practice, several facilities must agree on standardized DCE imaging protocols. Furthermore, the DCE parameters are greatly impacted by the pharmacokinetic model selection. Compared to simpler models that impose inappropriate limits and may introduce bias, complex models tend to be more physiologically correct since they make fewer assumptions. Nevertheless, the implementation of sophisticated models is more difficult due to their increased susceptibility to noise (56). Quantitative DCE-MRI parameters have shown promise as imaging biomarkers for gliomas in both preclinical and clinical trials. However, differences in scanners, sequences, and software prevent DCE-MRI from being widely used in clinical settings. Enhancing the quality of obtained DCE images would make it easier to employ more intricate models, which provide a more accurate depiction of pathological situations and, consequently, more accurate and dependable DCE parameters.

ASL Overview

An inversion pulse applied proximal to the imaging region is used in the arterial spin labeling (ASL) technique to magnetically label arterial blood water. The influx of inverted spins in the blood is reflected in an image that is acquired in the brain following a small lag known as the post-labeling delay. The volume of labeled blood delivered to each voxel can be measured by subtracting the tissue signal from an unlabeled picture. This separates the signal from the incoming blood. The measurement needs to be made several times in order to get a strong enough signal. Without the need for intravenous contrast chemicals, this technique enables the absolute measurement of cerebral blood flow (CBF). Particularly for certain patient groups, including as toddlers, gadolinium-allergic patients, and people with renal failure, for whom GBCA administration is contraindicated, ASL's non-invasive nature makes it appropriate for repeated assessments and inclusion into normal MR protocols. Both within and between sessions spaced out by days or months, ASL-MRI has shown good reproducibility.

Clinical Application

The use of ASL in glioma diagnosis, grading, and preoperative planning has been confirmed by numerous investigations (58). ASL has shown promise in differentiating gliomas from primary CNS lymphoma, metastases, and other non-neoplastic brain lesions. It can also identify increased blood flow in gliomas (59, 60). According to meta-analyses, ASL can be helpful in distinguishing between high-grade gliomas (HGGs) and low-grade gliomas (LGGs). The highest discrimination performance is shown by the maximum tumor blood flow in relation to contralateral healthy tissue (61, 62). An above-average ASL signal is typically seen in HGGs due to increased vascularity and perfusion, which is correlated with the tumor's high metabolic activity. On the other hand, although there are certain outliers, including pilocytic astrocytoma and ganglioglioma, LGGs usually exhibit lower-than-normal blood flow (58, 60). Additionally, it has been demonstrated that ASL can predict certain molecular markers, such as p53 status (related with lower perfusion), MGMT promoter methylation (associated with higher perfusion), and IDH1 (63, 64). ASL has also been linked to vascular endothelial growth factor (VEGF) expression (66) and tumor microvascular density (65). Notwithstanding these results, more investigation is needed to improve the ASL classification of gliomas (59). Last but not least, ASL can predict the malignant progression of grade 2 gliomas and has prognostic value in patients with glioblastoma, with poor perfusion associated with longer OS and EFS (64,67).

Validation

Standardizing ASL procedures for clinical brain imaging was the goal of the 2015 ISMRM Perfusion Study Group ASL recommendations (57). Adopted by all major scanner suppliers, the guidelines—which include using a 3D pseudo-continuous sequence with background suppression—remain the best option for ASL in glioma imaging. A labeling length of 1800 msec, a post-labeling delay of 2000 msec, a simple subtraction computation, and normalization to contralateral gray matter (GM) values are among the suggested parameters. To confirm the effectiveness of multiple post-labeling delays in improving ASL ability, more research is needed (68). Strong correlations have been found between ASL-derived CBF and DSC-measured relative cerebral blood volume (rCBV) in gliomas (69), despite the fact that ASL images generally have a lower signal-to-noise ratio than dynamic susceptibility contrast (DSC) imaging. Velocity-selective ASL has even shown better results than conventional pseudo-continuous ASL (70). The inability to read ASL images is a serious restriction, though, and it continues to be a major obstacle to its practical use. To prove that ASL is a trustworthy substitute for DSC, radiologists must receive more thorough training and do additional validation research. ASL is technically prepared for clinical use and enables the absolute measurement of tumor blood flow without the need of exogenous contrast ants. The method circumvents the problems linked to blood-brain barrier (BBB) leakage seen in post-contrast T1-weighted images and has a strong correlation with tumor histology, grade, and microvascular density. To prove the worth of ASL in comparison to DSC, more multi-center research is necessary, and precise diagnostic standards must be set for its clinical use.

Diffusion MRI in Neuro-Oncology: A Comprehensive Overview

Diffusion MRI is a sophisticated imaging method that attenuates signals according to the direction and amplitude of water molecule movement by using motion-sensitizing magnetic field gradients (b-values). The microstructure of the tissue affects the Brownian motion, which is reflected in this attenuation. Since the movement of water is greatly impacted by a number of microstructure-affecting parameters, including cellular density, viscosity, and the tortuosity of the extracellular space, the measurement of diffusion can be used as a marker of pathological alterations. In neuro-oncology, diffusion MRI is being utilized more and more for preoperative and diagnostic evaluations since it provides insightful information on tissue properties.

Due to its quick acquisition and accessibility, the diffusion-weighted echo-planar imaging (EPI) pulse sequence is the most widely used technique for diffusion measurement. However, some of the drawbacks of EPI, such as geometric distortions in areas with susceptibility variations, like the interfaces between soft tissue and bone, can be addressed by non-EPI techniques like steady-state free precession or turbo spin-echo (SE) imaging. The apparent diffusion coefficient (ADC), which eliminates T2-weighting

effects and condenses multi-directional diffusivity into a single value, is commonly used to evaluate water diffusion resistance. Diffusion tensor imaging (DTI), which provides quantitative measures like mean diffusivity (MD) and fractional anisotropy (FA), is also widely employed in clinical practice. A number of 0 represents isotropic diffusion, while a value close to 1 indicates highly anisotropic conditions, like those found in densely packed white matter (WM) fibers. FA quantifies the directional dispersion of diffusion. Like ADC, MD represents the average diffusion in all directions and measures the total diffusion inside a particular volume. Diffusion kurtosis imaging (DKI) and intravoxel incoherent motion (IVIM) imaging are two further diffusion MRI methods. DKI provides information about the non-Gaussian behavior of biological tissues by quantifying the diffusion's departure from a Gaussian distribution. Mean kurtosis (MK), axial kurtosis, and radial kurtosis are important metrics obtained from DKI that offer important information about tissue microstructure, especially when b-values are larger. Contrarily, IVIM imaging uses numerous b-values to distinguish between pure diffusion and perfusion components, offering information on tissue microcirculation and diffusion characteristics. This method allows for the creation of maps for diffusion coefficients, pseudo-diffusion, and microvascular volume fractions and is especially helpful in differentiating between the effects of diffusion and perfusion.

Clinical Application

In the preoperative assessment of gliomas, diffusion MRI is essential because ADC values can reveal details about the cellularity and load of the tumor. For example, according to a meta-analysis of 15 studies, ADC values have been successfully used to distinguish between low-grade gliomas (LGG) and high-grade gliomas (HGG), with reported sensitivities and specificities of 0.85 and 0.80, respectively, and an area under the curve (AUC) of 0.90 [71]. Additionally, IDH1-mutated gliomas had considerably higher ADC values than IDH1-wild-type gliomas [72]. Taking into account both the 2007 and 2016 WHO classifications, ADC has also been linked to several histologic and genetic kinds of WHO grade II-III diffuse gliomas, namely for 1p/19q co-deletion and IDH1 mutant status [73]. Furthermore, EGFR amplification status of IDH-wild-type WHO grade II-III gliomas has been accurately predicted using ADC values in a multi-center investigation; lower mean ADC and the lower 5th percentile of ADC values may be imaging biomarkers for EGFR amplification [74]. ADC values were significantly higher in tumor tissue compared to marginal tumor areas for patients with IDH-mutated tumors, according to additional research on the evaluation of ADC values in different parenchyma and brain tumor regions. In contrast, no significant differences were found between tumor and marginal areas for IDH-wild-type tumors [75]. The mean ADC value in H3 K27M histone-mutant diffuse midline glioma was $0.84 \pm 0.15 \times 10{-}3$ mm^2/s, according to ADC evaluation [76]. Likewise, normal ATRX expression was linked to reduced ADC values in diffuse midline glioma non-enhancing regions [77]. It has been demonstrated that, in contrast to LGG, where infiltration without disruption is more common, maximal and/or mean FA values are generally higher in HGG, possibly as a result of both infiltration and fiber disruption [78]. However, in WHO grade II and III gliomas, the reverse trend has been noted. This is probably because tumor infiltration, rather than aberrant cellularity, dominates FA values and disturbs the neuronal, axonal, and glial architecture [79]. Studies have looked into FA's capacity to distinguish between tumors according to the presence or absence of an IDH mutation, in addition to differentiating gliomas using WHO grading.

Oligodendroglial tumors with and without IDH mutations showed significant changes in maximal FA values and the ratio of maximal FA to contralateral normal FA, with AUCs of 0.79 and 0.82, respectively [80]. In addition, a group of HGG patients showed a favorable association between MD and IDH1 status [81]. In WHO grade II gliomas, whole-tumor histograms and textural analysis of FA maps have also demonstrated potential in predicting the presence of 1p/19q co-deletion and IDH1 mutations [82]. Furthermore, assessing FA in the peritumoral area could provide information about possible baseline spatial recurrence patterns [83]. Preoperative imaging in neuro-oncology has also made use of more sophisticated diffusion MRI methods, such as DKI and IVIM imaging. greater glioma malignancy has been demonstrated to increase MK values derived from DKI, and HGG had greater axial and radial kurtosis values than LGG. These findings support the use of MK for grading (WHO grades II–IV) and predicting Ki-67, a marker associated with cellularity [84][85]. Additional research has shown that MK values are substantially greater in HGG than in

LGG, and intrinsic tumoral heterogeneity, as manifested by varied intravoxel kurtosis features, has been connected to DKI's capacity to predict the presence of IDH mutations [86][87]. In addition to predicting survival and treatment responses in newly diagnosed HGG patients, IVIM imaging has demonstrated significant promise in differentiating between HGG and LGG [88][89].

Validation

In the context of gliomas, diffusion MRI is a potential method for assessing tissue microstructure; yet there are difficulties due to the variety of available sequences and processing methods. Due to their quick acquisition times, single-shot EPI methods are used by many centers for diffusion sequences. However, because of their limited spatial resolution and susceptibility to artifacts, these methods can have an impact on both qualitative and quantitative analyses, particularly at tissue interfaces. Eddy currents in EPI-based techniques can also skew pictures, making it more difficult to evaluate diffusion parameters. Another major concern is motion artifacts, especially with multi-directional DTI acquisitions that might take several minutes and are susceptible to head motion distortions. Combining prospective and retroactive motion-correction approaches may be necessary to enable overall distortion correction, even if there are a variety of processing tools available to address residual motion artifacts. Perfusion effects can also affect DWI sequences; in highly vascular tumors, water movement in the capillary network may cause ADC readings to be overestimated. However, the IVIM approach can successfully distinguish between diffusion and perfusion effects, giving glioma imaging more precise information. Diffusion-weighted imaging (DWI), which supplements traditional structural imaging, is still one of the most commonly used sequences in preoperative imaging. The capacity of fundamental measurements like ADC and FA to distinguish between different glioma subtypes and, more recently, to forecast molecular subtypes of gliomas has been the subject of much research. Although EPI-based and DTI approaches have dominated clinical practice, the diffusion of MRI's clinical value in glioma diagnoses is enhanced by more sophisticated techniques like DKI and IVIM imaging, which are becoming more widely available and provide more subtle insights into tissue microstructure.

Vessel Imaging

Overview

- **MR Angiography (MRA)**:
  - **Technique**: The principal method used for MRA is Time-of-Flight (TOF) angiography, also known as inflow angiography. This technique does not require gadolinium-based contrast agents (GBCA) and instead visualizes arteries by utilizing the magnetically unsaturated spins of flowing blood, which provide more signal than the surrounding tissue.
  - **Clinical Application**: MRA is useful for detecting pathological neovascularization, and it is primarily used for neurosurgical planning. Studies show that TOF angiography is able to make arterial vessels visible and quantifiable, showing more and denser vessels in glioblastoma compared to normal tissue. A newer analysis method to measure vessel orientation angles is also being explored to differentiate normal from abnormal tumor vessels.
- **Vessel-Architectural Imaging (VAI)**:
  - **Technique**: This technique combines gradient echo (GRE) and spin echo (SE) echo-planar imaging (EPI) sequences during an intravenous GBCA injection. It is used to estimate vessel calibers in gliomas and to differentiate between different vessel types. The GRE signal is highly sensitive to blood vessels of all calibers, while SE is sensitive mainly to microscopic vessels or capillaries.
  - **Clinical Application**: VAI has demonstrated successful differentiation of glioma types based on histology, including distinguishing gliomas by IDH mutation. It can provide insight into the heterogeneity of glioma microvasculature, which is a hallmark of the tumor's angiogenic activity. VAI maps have proven valuable in delineating gliomas from peripheral edema and early detection of neovascularization.

Validation

- **MR Angiography**:
  - MR Angiography (TOF) has been compared to conventional angiography methods like digital subtraction angiography (DSA) and contrast-enhanced MRA (CEMRA). While TOF angiography is non-invasive and does not require external contrast agents, it is less accurate than these conventional techniques, especially on clinical scanners (≤3T). Ultra-high-field 7T scanners show improved quality and contrast in TOF angiography, but clinical applicability remains limited due to scanner availability and artifacts.
- **Vessel-Architectural Imaging**:
  - VAI faces challenges in clinical validation, mainly due to the complexity of imaging parameters, the need for specialized post-processing software, and the expertise required for data interpretation. Furthermore, VAI's ability to discriminate between tumor types or predict treatment outcomes remains uncertain due to the overlapping distributions of vessel calibers across tumor types.

Summary

- **MR Angiography**:
  - TOF angiography is non-invasive and does not require contrast agents, making it advantageous over conventional angiography. However, its limited accuracy in glioma analysis and its main application in surgical planning or morphologic vascular analysis currently restrict its broader use in clinical practice.
- **Vessel-Architectural Imaging**:
  - VAI provides an attractive tool for glioma diagnosis and monitoring due to its ability to assess angiogenesis, but it suffers from a lack of clinical validation, and its clinical utility remains limited due to technical challenges. Nonetheless, with ongoing research and improvements, VAI could become more widely available outside of research settings.

Relaxometry and MR Fingerprinting (MRF)

Overview

- **MRF Technique**:
  - Magnetic Resonance Fingerprinting (MRF) allows for rapid and simultaneous mapping of T1 and T2 relaxation times using a sequence with pseudo-randomly varying acquisition parameters. The resulting signals, or "fingerprints," are compared to a pre-calculated dictionary to obtain voxel-wise parameter values, enabling the construction of quantitative maps. This technique allows for faster acquisition of T1 and T2 data, which are crucial for tumor characterization.
- **Biological Relevance of T1 and T2 Mapping**:
  - T1 and T2 relaxation times are influenced by tissue properties such as lipid content, protein concentration, and water content. In gliomas, T1 and T2 relaxation times are typically longer than surrounding healthy tissue due to increased hydration from intra-tumoral edema caused by leaky blood vessels from neovascularization. These relaxation times provide insights into tumor cellularity and microstructure.

Clinical Application

- **Tumor Grading and Differentiation**:
  - T1 and T2 relaxation times have been found to vary significantly between glioma types, with lower-grade gliomas (LGGs) and high-grade gliomas (HGGs) showing distinct relaxation time profiles. Studies have shown that T1 and T2 values can also correlate with IDH mutation status in gliomas, which can be a useful biomarker for tumor grading and prognosis.

- **MRF Mapping**: Quantitative mapping using MRF provides additional insights into tumor invasion, particularly into peritumoral regions, which is often not detectable on conventional imaging. T1 and T2 maps derived from MRF have demonstrated the ability to detect subtle tumor infiltration and the surrounding edema in gliomas.

Validation

- **MRF Feasibility and Reliability**: Although MRF is a promising technique, its clinical validation is still in the early stages. Few studies have been conducted with small patient cohorts, and the results have shown varying degrees of tumor characterization success. There is a need for larger, more robust studies to establish repeatability and reliability, as well as to assess its clinical impact on glioma diagnosis and treatment.

Summary

- **MRF**: MRF holds promise for rapid and non-invasive quantitative T1 and T2 mapping in glioma characterization. However, its clinical application is still limited by small cohort sizes, inconsistent results across different types of dialects, and the need for further validation. With more extensive research, MRF could potentially revolutionize the way gliomas are imaged, particularly by providing detailed insight into tumor invasiveness and tumor microstructure.

Overview: Level of Clinical Validation

This review provides a summary of the clinical utility of advanced MRI techniques for glioma characterization, focusing on the need for further validation and development of implementation guidelines.

- **DWI (Diffusion Weighted Imaging)** is widely used in glioma imaging, primarily due to its easy implementation and availability. However, advanced diffusion sequences such as IVIM (Intravoxel Incoherent Motion) and DKI (Diffusion Kurtosis Imaging) are less frequently used due to their lower availability and more complex data processing requirements.
- **DSC (Dynamic Susceptibility Contrast)** has seen successful clinical translation, with substantial work invested into validating the technique, especially for glioma assessment. The introduction of consensus recommendations has paved the way for clinical adoption. However, such consensus guidelines are still lacking for most other advanced MRI techniques.

In conclusion, advanced MRI techniques like MRA, VAI, and MRF hold great promise for glioma diagnosis and monitoring. However, challenges such as limited clinical validation, technical complexity, and the need for standardized protocols hinder their widespread implementation in clinical settings. Continued research and validation are crucial to making these advanced techniques a routine part of glioma management.

Conclusion:

Advanced MRI techniques have revolutionized the preoperative imaging of gliomas, allowing clinicians to gain valuable insights into the molecular characteristics and behavior of these tumors. The integration of genetic markers, such as IDH mutations and 1p/19q co-deletion, into glioma classification has provided a more accurate and detailed approach to diagnosing and grading these tumors. Conventional MRI, while still widely used, has limitations in characterizing the molecular and metabolic characteristics of gliomas. This review emphasizes how advanced MRI techniques, including DSC-MRI, ASL, and MRS, can overcome these limitations by offering quantitative imaging of cerebral blood volume, metabolic activity, and tissue composition, which are crucial for glioma classification. The use of DSC-MRI to measure rCBV has proven particularly valuable in distinguishing between low-grade and high-grade gliomas, with higher rCBV correlating with greater tumor malignancy and worse prognosis. Additionally, methods like MR elastography and MR spectroscopy provide further information on tumor stiffness and metabolic properties, which can complement traditional imaging techniques in determining tumor aggressiveness. Despite these advantages, the clinical implementation of these advanced methods remains challenging due

to the need for specialized hardware, software, and expertise. The lack of standardized protocols and validation across different institutions also hampers their widespread adoption. The review highlights the importance of an expert consensus approach in evaluating the clinical readiness of these MRI techniques, which have shown strong potential in improving the accuracy of glioma diagnosis and treatment planning. While the validation of these methods continues, their integration into clinical practice will require overcoming technical and practical barriers. Future advancements in MRI technology, coupled with the development of standardized protocols and robust clinical evidence, are essential to enhance the diagnostic capabilities of glioma imaging. Ultimately, the successful incorporation of these advanced MRI techniques could lead to more personalized treatment approaches, improving patient outcomes by enabling more accurate preoperative assessments and tailored therapies based on tumor characteristics.

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