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Diagnostic Utility of Integration of Dynamic Contrast-Enhanced and Dynamic Susceptibility Contrast MR Perfusion Employing Split Bolus Technique in Differentiating High-Grade Glioma

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Abstract

Background: Despite documented correlation between glioma grades and dynamic contrast-enhanced (DCE) magnetic resonance (MR) perfusion-derived parameters, and its inherent advantages over dynamic susceptibility contrast (DSC) perfusion, the former remains underutilized in clinical practice. Given the inherent spatial heterogeneity in high-grade diffuse glioma (HGG) and assessment of different perfusion parameters by DCE (extravascular extracellular space volume [Ve] and volume transfer constant in unit time [k-trans]) and DSC (rCBV), integration of the two into a protocol could provide a holistic assessment. Considering therapeutic and prognostic implications of differentiating WHO grade 3 from 4, we analyzed the two grades based on a combined DCE and DSC perfusion.

Methods: Perfusion sequences were performed on 3-T MR. Cumulative dose of 0.1 mmol/kg of gadodiamide, split into two equal boluses, was administered with an interval of 6 minutes between the DCE and DSC sequences. DCE data were analyzed utilizing commercially available GenIQ software.

Results: Of the 41 cases of diffuse gliomas analyzed, 24 were WHO grade III and 17 grade IV gliomas (2016 WHO classification). To differentiate grade III and IV gliomas, Ve cut-off value of 0.178 provided the best combination of sensitivity (88.24%) and specificity (87.50%; AUC: 0.920; $p < 0.001$). A relative cerebral blood volume (rCBV) of value 3.64 yielded a sensitivity of 70.59% and specificity of 62.50% ($p = 0.018$). The k-trans value, although higher in grade III than in grade IV gliomas, did not reach statistical significance ($p = 0.108$).

Keywords
- combined perfusion technique
- split bolus contrast
- grade III from grade IV glioma

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Conclusion: Uniqueness of employed combined perfusion technique, treatment naïve patients at imaging, user-friendly postprocessing software utilization, and ability of Ve and rCBV to differentiate between grade III and IV gliomas ($p < 0.05$) are the strengths of the present study, contributing to the existing literature and moving a step closer to achieving accurate MR perfusion-based glioma grading.

Introduction

Dynamic susceptibility contrast (DSC) and dynamic contrast-enhanced (DCE) magnetic resonance (MR) perfusion techniques study the different perfusion parameters in brain tumors, with relative cerebral blood volume (rCBV) derived from the former, while volume transfer constant in unit time (k-trans) and extravascular extracellular space volume (Ve) from the latter.[1,2]

The DSC-derived rCBV is accepted by most authors as a time-tested, robust analysis technique and the most widely used perfusion parameter in assessment of brain tumors. However, a few drawbacks of this technique include the difficulty in determining absolute quantification and permeability assessment, presence of susceptibility artefacts, and invalid assumption of BBB integrity.[3] The DCE, "permeability," or "T1 perfusion" are considered synonymous, and it measures vessel permeability and provides absolute quantification of perfusion parameters. The leaky neoangiogenic vessels and increased necrotic areas that characterize high-grade diffuse glioma (HGG) may accurately correspond with the maximal K-trans and Ve values, respectively, hence providing accurate glioma grading.[3,4]

Considering the marked spatial heterogeneity (documented in HGG) and that DCE and DSC perfusion assess different perfusion parameters, the integration of both techniques into the protocol could provide a holistic assessment of brain tumor, compared to either perfusion technique in isolation.[5] Such integration of perfusion parameters, especially with no additional contrast dose administered, appears a more pragmatic and acceptable approach to a reliable grading of diffuse gliomas. Our study is designed to evaluate the efficacy of perfusion parameters (k-trans, Ve, and rCBV) derived from DCE and DSC MR perfusion in differentiating WHO grade III diffuse gliomas from glioblastomas (GBs).

Material and Methods

Subjects

Institutional Ethics Committee (IEC) approval was obtained for this retrospective study. The imaging and histopathological examination (HPE) data of all patients older than 18 years with brain tumor, who underwent both DCE and DSC MR perfusion between August 2016 and June 2018, were retrieved. Patients having received steroids, surgery, radiation, or chemotherapy prior to MR perfusion study were not included in the current study. The patients with HPE results other than diffuse glioma of WHO grade III or a GB were excluded. Of the 41 treatment naive patients analyzed in the present study, 24 had WHO grade III diffuse gliomas and the rest had GBs.

Data Acquisition

These patients underwent magnetic resonance imaging (MRI) study with a predetermined protocol at our institute (including conventional sequences, DCE and DSC perfusion).

MR study was performed on a 3-T scanner equipped with a standard 24-channel head coil. Precontrast T1-weighted, T2-weighted, T2-FLAIR (T2 fluid attenuated inversion recovery), diffusion, and susceptibility weighted images were acquired. A cumulative dose of 0.1 mmol/kg body weight of gadodiamide (Omniscan, 0.5 mmol/mL) was administered, split into two equal boluses. The initial contrast bolus was administered following commencement of the DCE sequence with a power injector at 3 mL/s. The second contrast bolus was injected following the third dynamic acquisition of DSC sequence, utilizing the power injector at 5 mL/s. Approximately 20 mL saline flush was injected following each of the two boluses of contrast administration. An interval of 6 minutes was maintained between the two boluses. After completion of the DSC MR sequence, standard postcontrast 3D brain volume imaging (BRAVO) data and MR spectroscopy were acquired. DCE-MRI was acquired using a 3D fast spoiled gradient echo sequence (FSPGR). The MR parameters employed in this study for DCE and DSC perfusion are summarized in ►**Table 1**.

Data Analysis

Imaging data were transferred to a workstation and the DCE data were analyzed utilizing a user-friendly software "GenIQ" (GE Medical Systems), based on the Tofts model. The 3D, rigid motion correction was employed in all patients. The pixels considered to be arteries or veins based on the temporal changes in signal intensity of the voxels were automatically extracted by the utilized software. Fixed T1 method and default T10 value (T10 = 1,000 milliseconds) were used in the analysis. The regions of interest (ROI) were defined by the neuroradiologist on axial postcontrast and FLAIR datasets, specifically avoiding the cystic, necrotic, and hemorrhagic areas. On each parametric map (k-trans and Ve), the hotspot (region of maximal abnormality) within the lesion volume was determined with visual inspection, 5 to 10 ROIs were then positioned serially within the hotspots, and the maximal quantitative value documented. The rCBV was obtained by dividing the maximum CBV value in the tumor volume to the CBV value of an ROI positioned in the contralateral normal-appearing white matter.

Table 1 Imaging parameters of MRI perfusion acquisition protocol DCE and DSC perfusion

Parameters	DCE perfusion	DSC perfusion
TR/TE (ms)	4.3/0.8	2,000/30
Slice thickness (mm)	5	5
Flip angle (degrees)	25	60
Matrix	128×128	96×96
Measurements	50	42
Temporal spacing (s)	6.48	2
Time duration (s)	324	84

Abbreviations: DCE, dynamic contrast enhanced; DSC, dynamic susceptibility contrast; MRI, magnetic resonance imaging; TE, echo time; TR, repetition time.

Following MRI, these patients underwent a surgical procedure, either tumor resection or biopsy. The histologic examination and tumor grading were performed by an experienced neuropathologist. Hematoxylin and eosin staining and immunohistochemistry for R132H-mutant IDH1, ATRX, p53, and proliferation marker Ki-67 were performed on all tumors using routing protocols established in the laboratory. IDH (isocitrate dehydrogenase) status was assessed based on R132H-mutant IDH1 immunohistochemistry. Sequencing for IDH1 and IDH2 genes and fluorescence in situ hybridization for 1p/19q co-deletion were not performed in any of the tumors. The diffuse gliomas were classified as per 2016 WHO classification of tumors of the central nervous system.[6]

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY). For all statistical tests, $p < 0.05$ was considered statistically significant. Quantitative variables were expressed as mean, standard deviation median, and interquartile range (IQR). Qualitative variables were expressed as frequency and percentage. Comparison of quantitative variables between two groups was analyzed by an independent sample *t*-test. Receiver operating characteristic (ROC) curve analysis was done to assess the performance of k-trans, Ve, and rCBV in differentiating WHO grade III gliomas from grade IV gliomas by measuring the areas under the curve (AUC). The optimum cut-off value, sensitivity, and specificity were calculated accordingly to differentiate WHO grade III from grade IV gliomas.

Results

Among the 41 cases analyzed in our study, the HPE documented 24 WHO grade III (58.5%) gliomas and 17 WHO grade IV (GB) diffuse gliomas (41.5%). Of the 17 GBs, 14 (82.4%) were IDH wild type and 3 (17.6%) were IDH mutants. The WHO grade III tumors included 16 cases of anaplastic astrocytoma (AA; 66.7%) and 8 cases of anaplastic oligodendroglioma (AODG; 33.3%). WHO grade III tumors comprised 9 cases of IDH-mutant AA, 7 cases of AA not otherwise specified (NOS), and 8 cases of AODG NOS.

The median Ve value observed in WHO grade III glioma was 0.051 with IQR of 0.023 to 0.106, whereas grade IV gliomas demonstrated median Ve of 0.318 with IQR of 0.205 to 0.443, difference between the two groups being statistically significant ($p < 0.001$). The median rCBV values observed in grade III and IV gliomas were 2.705 (IQR: 1.345–4.925) and 4.350 (IQR: 0.3.495–6.905), respectively, the difference between the two groups being statistically significant ($p = 0.018$). Grade III and IV gliomas demonstrated median k-trans values of 0.128 (IQR: 0.053–0.370) and 0.282 (IQR: 0.116–0.485), respectively, with the observed difference not being statistically significant ($p = 0.108$). The quantitative variables and perfusion parameter values derived from DSC (rCBV) and DCE (K-trans, Ve) among grade III and IV gliomas are summarized in ►**Table 2**. Scatter plot shows distribution of k-trans (►**Fig. 1**), Ve (►**Fig. 2**), and rCBV (►**Fig. 3**) parametric values for grade III and IV gliomas.

To differentiate WHO grade III gliomas from IV diffuse gliomas, within the independent parametric variables, the AUC was observed to be the highest for Ve (0.920), followed by rCBV (0.716) and K-trans (0.649). To differentiate grade III from grade IV diffuse gliomas, a Ve cut-off value of 0.178 provided the best combination of sensitivity (88.24%) and specificity (87.50%; AUC: 0.920; $p < 0.001$). An rCBV cutoff value of 3.645 provided the best combination of sensitivity (70.59%) and specificity (62.50%; AUC: 0.716; $p = 0.018$) for differentiating grade III from grade IV gliomas. A k-trans

Table 2 Quantitative variables and perfusion parameter values derived from DSC (rCBV) and DCE (K-trans, Ve) among grade III and IV gliomas

Parameter	Grade	*N*	Mean	SD	Min	Max	Median	Q1	Q3	*p*-Value
K-trans	Grade III	24	0.221	0.201	0.033	0.680	0.128	0.053	0.370	0.108
	Grade IV	17	0.326	0.274	0.048	1.176	0.282	0.116	0.485	
Ve	Grade III	24	0.1139	0.2048	0.007	1.000	0.0510	0.0238	0.1060	< 0.001
	Grade IV	17	0.3636	0.2142	0.1370	1.000	0.3180	0.2050	0.4435	
rCBV	Grade III	24	3.535	2.656	0.58	10.79	2.705	1.345	4.925	0.018
	Grade IV	17	5.456	2.770	2.730	12.09	4.350	3.495	6.905	

Abbreviations: DCE, dynamic contrast enhanced; DSC, dynamic susceptibility contrast; K-trans, volume transfer constant in unit time; rCBV, relative cerebral blood volume; SD, standard deviation; Ve, extravascular–extracellular space volume.

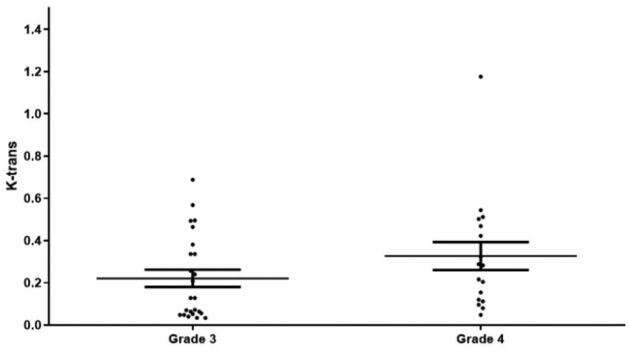

Fig. 1 Scatter plot shows distribution of volume transfer constant in unit time (k-trans) parametric value for grade III and IV gliomas.

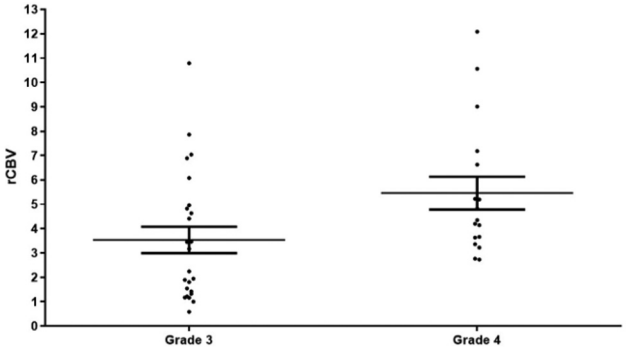

Fig. 3 Scatter plot shows distribution of relative cerebral blood volume (rCBV) parametric value for grade III and IV gliomas.

cut-off value of 0.221 was found to differentiate grade III gliomas and grade IV gliomas, with 58.82% sensitivity and 58.33% specificity (AUC: 0.649; p 0.108). ►**Fig. 4** depicts a comparison of the ROC curves of k-trans, rCBV, and Ve for differentiating grade III gliomas from grade IV gliomas.

Discussion

The characterization of tumor grade is crucial to both the decision-making about the mode of treatment and prognostication.[7] Although differentiating between low-grade gliomas (WHO grade I and II) and HGGs (grade III–IV) is of the utmost priority, differentiating between WHO grade III and IV gliomas also holds importance, both in terms of treatment and prognostication. Conventionally, patients with AA (WHO grade III) receive radiotherapy or temozolomide (TMZ), whereas GB (WHO grade IV) patients are usually managed with radiotherapy plus concurrent TMZ, followed by adjuvant TMZ.[8] Although 2016 WHO classification has incorporated molecular information into diagnoses, the importance of accurate assignation of histological grade cannot be underscored.[9]

The histologically heterogeneous nature of the HGG is a major hindrance to obtaining a true representative sample and hence to assigning accurate histologic grading. Targeting enhancing areas to obtain representative sample has proved useful; however, areas with the most dedifferentiation are not necessarily the most enhancing areas.[10–13] Targeting areas with the highest MR perfusion-derived parametric values (rCBV and K-trans) would yield a better representative sample in comparison to areas with maximum enhancement.[4] Also, given the good correlation between MR perfusion-derived parameters and the histologic grading, the invasive nature of biopsy and the inherent sampling errors, the acceptance of MR-based tumor grading and avoiding the latter are pragmatic in certain clinical scenarios.[14]

MRI is unambiguously the modality of choice for characterization of brain tumors, providing exquisite details of the morphological features.[15] However, lack of functional information with the conventional MR sequences warrants inclusion of advanced MR techniques as MR perfusion for the holistic assessment of a brain tumor.[16,17] The DSC and DCE MR perfusion are based on susceptibility and relaxivity effects of administered gadolinium-based contrast agents, respectively.[1,2]

Given the large amount of published works showing strong correlation between tumor grade and the rCBV,

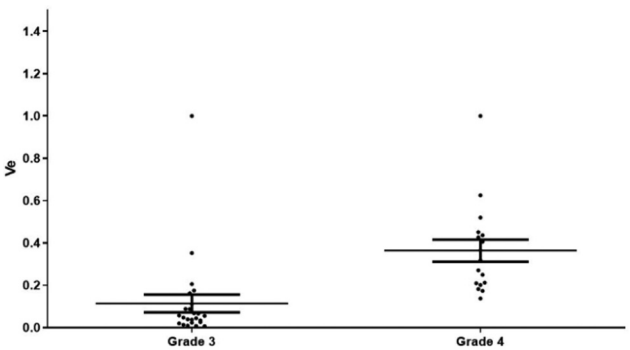

Fig. 2 Scatter plot shows distribution of extravascular–extracellular space volume (Ve) parametric value for grade III and IV gliomas.

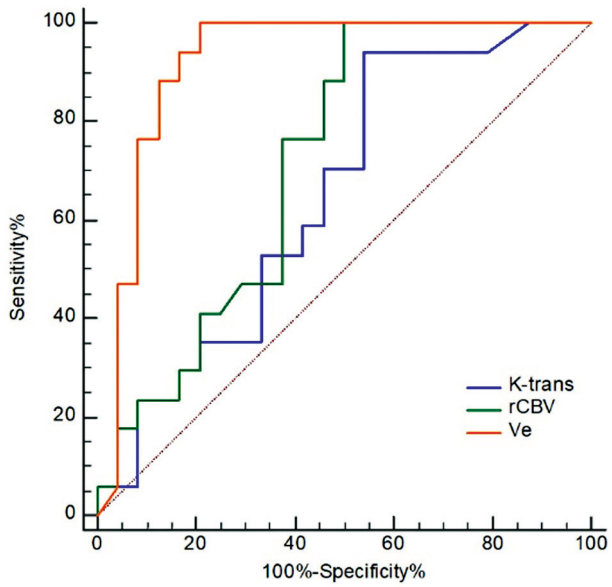

Fig. 4 Comparison of receiver operating characteristic (ROC) curves of volume transfer constant in unit time (k-trans), relative cerebral blood volume (rCBV), and extravascular–extracellular space volume (Ve) for differentiating grade III from grade IV gliomas.

robust acquisition protocol and analysis technique, the role of DSC MR perfusion in grading glioma and patient prognostication is acceptable to most authors. Despite studies showing encouraging results and good correlation between tumor grade and the DCE-derived parameters, it is underutilized in clinical practice.[4] The dependence of DCE-derived perfusion values on multiple parameters, such as MR field strength, precontrast longitudinal relaxation time of tissue, hematocrit, type of gadolinium contrast agent, arterial input function (AIF) assessment method, pharmacokinetic model applied, and longer postprocessing duration contribute to the technique's lesser adoption in clinical practice.[18,19]

However, considering the advantages of DCE over DSC in providing absolute quantification parameters, accurate perfusion assessment in the setting of cortical based tumor such as oligodendroglioma (ODG), higher spatial resolution, less susceptibility artifacts, and information about tissue permeability, the former appears to be an effective alternative method to DSC.[14,20] The DCE MRI overcomes vessel-induced susceptibility effects and therefore has the potential to reduce the rCBV value overlap between low- and high-grade ODG.[21]

k-trans represents the transfer of contrast medium from the vessel into extravascular extracellular space (EES), reflecting the intratumoral microvascular permeability. The increased expression of vascular endothelial growth factor by HGGs promotes endothelial proliferation, proportion of immature vessels, and consequently endothelial permeability.[22,23] Ve represents the volume fraction of contrast medium leaking into the EES and can be expressed mathematically as the ratio of contrast agent quantity that leaked into the EES to the contrast agent quantity that returned to the plasma space.[23] Although, the true physiological meaning of Ve remains debatable, it is considered an index of tumor necrosis and an inverse index of tumor cellularity.[24] Although both DSC (rCBV) and DCE (k-trans, Ve, and plasma volume [Vp]) derived parameters are increased with progressive higher grades of glioma, there is variable degree of correlation on voxel-by-voxel comparison of these parameters, suggesting the different physiological information provided by these parametric maps.[25] The representative cases from our study are illustrated in ►**Figs. 5** and **6**.

No universally agreeable rCBV threshold exists to differentiate low-grade diffuse gliomas from HGGs, with Shin et al,[26] Bulakbasi et al,[27] Law et al,[28] Al-Okaili et al,[29] and Aydin et al[30] suggesting rCBV cut-off values of 2.93, 2.60, 1.75, 1.85, 1.75, and 3.25, respectively. Gliomas with high rCBV, specifically more than 1.75, progress faster and are associated with a poor prognosis.[28]

Most DCE studies show increasing K-trans and Ve values with progressive tumor grade.[31–33] However, the K-trans, Ve, and Vp cut-off values differ markedly among studies, emphasizing the need to consider various confounding

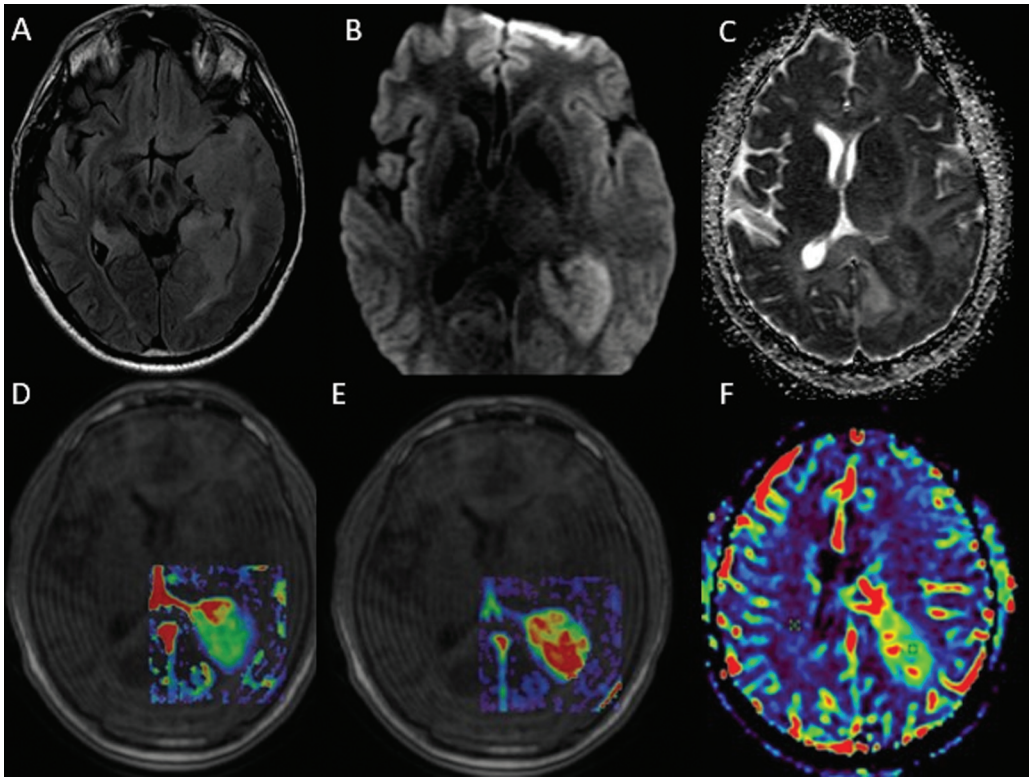

Fig. 5 (**A**) Fluid attenuated inversion recovery (FLAIR) demonstrates hyperintense intra-axial lesion involving the left peritrigonal and medial temporal lobe. Most part of the lesion appears hyperintense on (**B**) diffusion weighted imaging (DWI) and (**C**) hypointense on apparent diffusion coefficient (ADC), consistent with diffusion restriction. (**D**) Increased values of volume transfer constant in unit time (k-trans) 0.120, (**E**) extravascular–extracellular space volume (Ve) 0.209, and (**F**) rCBV 6.63 are noted on magnetic resonance (MR) perfusion. Histopathological diagnosis: glioblastoma, isocitrate dehydrogenase (IDH) mutant, and WHO grade IV.

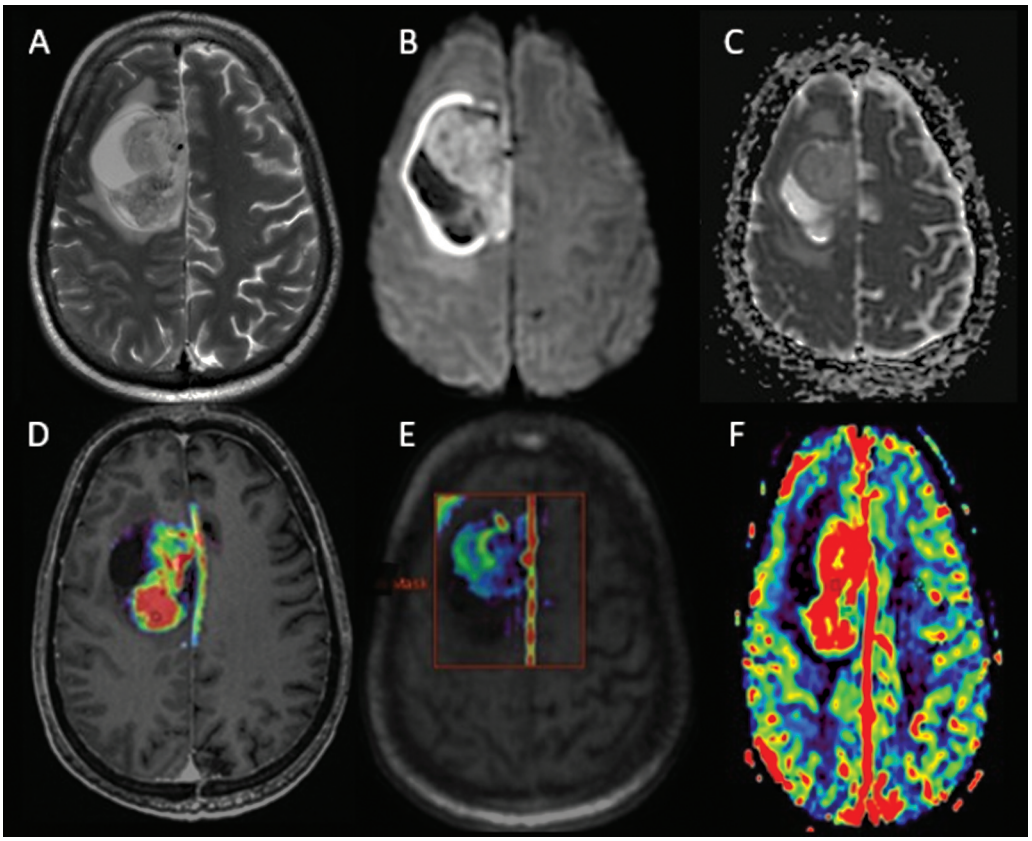

Fig. 6 (**A**) T2-weighted imaging (T2WI) demonstrate a heterogeneously hyperintense mixed solid and cystic intra-axial lesion epicentered in the right superior frontal gyrus region. Most part of the lesion appears markedly hyperintense on (**B**) diffusion weighted imaging (DWI) and (**C**) iso- to mildly hypointense on apparent diffusion coefficient (ADC), consistent with diffusion restriction. Increased values of (**D**) volume transfer constant in unit time (k-trans) 0.381 and (**E**) rCBV 7.86 are noted with (**F**) no significant increase in extravascular–extracellular space volume (Ve) 0.066. Histopathological diagnosis: anaplastic astrocytoma, not otherwise specified, and WHO grade III.

factors (type of pharmacokinetic model, contrast agent, and T10, among others) while comparing results among the studies.[31–33] The literature search reveals varying degrees of correlation between the rCBV and k-trans values with glioma grade.[28] Santarosa et al found a highly significant positive correlation of tumor grade with k-trans, Vp, and rCBV, with the highest correlation noted for Vp.[14] Although differentiating low-grade diffuse gliomas from HGGs is relatively easy with MR perfusion, studies show substantial overlap in differentiating WHO grade III from grade IV diffuse gliomas.[34] Li et al observed that although the mean K-trans and Ve values of grade III/IV gliomas were significantly higher than those of grade II gliomas, no statistically significant differences were observed between grade III and IV gliomas.[34]

Considering that differentiating between WHO grade III and IV gliomas also holds importance, both in terms of treatment and prognostication, we attempted to differentiate the two grades based on combined DCE and DSC perfusion studies. Considering the longer acquisition time as one of the important reasons to less acceptance of DCE-MRI in clinical practice, Abe et al utilized short acquisition time for DCE and confirmed comparable diagnostic performance to previous studies with longer acquisition times.[35] Similarly, we analyzed DCE perfusion efficacy using a short acquisition time, hence documenting its feasibility in clinical setting.

The newer introduced MR perfusion methods include dual-temporal resolution scanning and combined and consecutive DCE and DSC MR perfusion.[36–39] In our study, we administered gadolinium contrast dose split into two boluses (without increasing the cumulative contrast dose) in a sequential manner, with an interval of 6 minutes, allowing optimal contrast extravasation into the EES, hence permitting accurate Ve assessment. With this method of split contrast administration, the initial injection not only served as a preload to compensate for leakage correction for DSC perfusion but also provided dynamic data for permeability metric assessment.[5]

In our study, the Ve cut-off value of 0.178 provided the best combination of sensitivity (88.24%) and specificity (87.50%; AUC: 0.920; $p < 0.001$) in differentiating grade III gliomas from grade IV diffuse gliomas. Aydin et al demonstrated a Ve value of greater than 0.49 to predict a grade IV glioma with sensitivity and specificity of 87.5% and 78.57%, respectively.[30] In our study, an rCBV cut-off value of 3.65 provided the best combination of sensitivity (70.59%) and specificity (62.50%; AUC: 0.716; $p = 0.018$) for differentiating grade III from grade IV gliomas. The literature search documented a similar study employing a combined and consecutive DCE and DSC MR perfusion with contrast administration split into two boluses, where an rCBV value of more than 3.25 and 5.67 predicted an HGG and grade IV glioma, respectively,

with 100% specificity and sensitivity.[30] The available data, pertaining to employing this unique technique of combined DCE and DSC MR perfusion with split contrast administration method, are at best sparse.[5,30] Besides the uniqueness of MR perfusion technique employed, treatment naïve patients at imaging, user-friendly DCE postprocessing software utilization, availability of adequate tissue to analyze inherent heterogeneity in HGG (surgical resection specimen for HPE in 39 of 41 cases), and results documenting the ability of the Ve and rCBV to differentiate between grade III and IV diffuse gliomas ($p < 0.05$) are the strengths of the present study. The limitations of the present study include a retrospective design, a relatively small sample size, and additional requisite genetic tests not performed (assessment for 1p19q co-deletion and sequencing for IDH1/2 genes in R132H-mutant IDH1 negative gliomas). Our study contributes valuable information to the existing literature and is a step closer to achieving accurate, MR perfusion-based glioma grading.

Conclusion

Given the inherent spatial heterogeneity in HGG and assessment of different perfusion parameters by DCE (Ve, K-trans) and DSC (rCBV) perfusion, integration of the two into a protocol provides a holistic assessment, compared to either technique in isolation. Our study documented the ability of Ve and rCBV to differentiate between WHO grade III and IV gliomas ($p < 0.05$) and is a valuable contribution to the existing literature, moving a step closer to achieving accurate MR perfusion-based glioma grading. Further prospective studies employing combined DSC and DCE perfusion techniques with an emphasis on incorporation of genetic features (based on WHO 2021 classification) need to be carried out to identify the molecular characteristics of the primary brain tumors, and thus determine the aggressiveness and grading of tumors noninvasively.

Note
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Conflict of Interest
None declared.

References

1 Jahng GH, Li KL, Ostergaard L, Calamante F. Perfusion magnetic resonance imaging: a comprehensive update on principles and techniques. Korean J Radiol 2014;15(05):554–577
2 Singh IN, Sullivan PG, Hall ED. Peroxynitrite-mediated oxidative damage to brain mitochondria: Protective effects of peroxynitrite scavengers. J Neurosci Res 2007;85(10):2216–2223
3 Lacerda S, Law M. Magnetic resonance perfusion and permeability imaging in brain tumors. Neuroimaging Clin N Am 2009;19 (04):527–557
4 Patankar TF, Haroon HA, Mills SJ, et al. Is volume transfer coefficient (K(trans)) related to histologic grade in human gliomas? Am J Neuroradiol 2005;26(10):2455–2465
5 Essig M, Shiroishi MS, Nguyen TB, et al. Perfusion MRI: the five most frequently asked technical questions. Am J Roentgenol 2013; 200(01):24–34
6 Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. WHO Classification of Tumours of the Central Nervous System. Rev. 4th ed. Geneva: World Health Organization; 2016
7 Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114(02):97–109
8 Weller M, van den Bent M, Hopkins K, et al; European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol 2014;15(09):e395–e403
9 Johnson DR, Guerin JB, Giannini C, Morris JM, Eckel LJ, Kaufmann TJ. 2016 updates to the WHO brain tumor classification system: what the radiologist needs to know. Radiographics 2017;37(07): 2164–2180
10 Barker FG II, Chang SM, Huhn SL, et al. Age and the risk of anaplasia in magnetic resonance-nonenhancing supratentorial cerebral tumors. Cancer 1997;80(05):936–941
11 Spampinato MV, Smith JK, Kwock L, et al. Cerebral blood volume measurements and proton MR spectroscopy in grading of oligodendroglial tumors. Am J Roentgenol 2007;188(01):204–212
12 Batra A, Tripathi RP, Singh AK. Perfusion magnetic resonance imaging and magnetic resonance spectroscopy of cerebral gliomas showing imperceptible contrast enhancement on conventional magnetic resonance imaging. Australas Radiol 2004;48 (03):324–332
13 Calli C, Kitis O, Yunten N, Yurtseven T, Islekel S, Akalin T. Perfusion and diffusion MR imaging in enhancing malignant cerebral tumors. Eur J Radiol 2006;58(03):394–403
14 Santarosa C, Castellano A, Conte GM, et al. Dynamic contrast-enhanced and dynamic susceptibility contrast perfusion MR imaging for glioma grading: preliminary comparison of vessel compartment and permeability parameters using hotspot and histogram analysis. Eur J Radiol 2016;85(06):1147–1156
15 Kimura M, da Cruz LCH Jr. Multiparametric MR imaging in the assessment of brain tumors. Magn Reson Imaging Clin N Am 2016; 24(01):87–122
16 Jain R, Gutierrez J, Narang J, et al. In vivo correlation of tumor blood volume and permeability with histologic and molecular angiogenic markers in gliomas. Am J Neuroradiol 2011;32(02): 388–394
17 Jiang W, Huang Y, An Y, Kim BYS. Remodeling tumor vasculature to enhance delivery of intermediate-sized nanoparticles. ACS Nano 2015;9(09):8689–8696
18 Armitage P, Behrenbruch C, Brady M, Moore N. Extracting and visualizing physiological parameters using dynamic contrast-enhanced magnetic resonance imaging of the breast. Med Image Anal 2005;9(04):315–329
19 Armitage PA, Farrall AJ, Carpenter TK, Doubal FN, Wardlaw JM. Use of dynamic contrast-enhanced MRI to measure subtle blood-brain barrier abnormalities. Magn Reson Imaging 2011;29(03): 305–314
20 Artzi M, Liberman G, Nadav G, et al. Human cerebral blood volume measurements using dynamic contrast enhancement in comparison to dynamic susceptibility contrast MRI. Neuroradiology 2015;57(07):671–678
21 Lev MH, Ozsunar Y, Henson JW, et al. Glial tumor grading and outcome prediction using dynamic spin-echo MR susceptibility mapping compared with conventional contrast-enhanced MR: confounding effect of elevated rCBV of oligodendrogliomas [corrected]. Am J Neuroradiol 2004;25(02):214–221
22 Hoefnagels FW, Lagerwaard FJ, Sanchez E, et al. Radiological progression of cerebral metastases after radiosurgery:

assessment of perfusion MRI for differentiating between necrosis and recurrence. J Neurol 2009;256(06):878–887
23 Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging 1999;10(03):223–232
24 Mills SJ, Soh C, Rose CJ, et al. Candidate biomarkers of extravascular extracellular space: a direct comparison of apparent diffusion coefficient and dynamic contrast-enhanced MR imaging: derived measurement of the volume of the extravascular extracellular space in glioblastoma multiforme. AJNR Am J Neuroradiol 2010; 31(03):549–553
25 Alcaide-Leon P, Pareto D, Martinez-Saez E, Auger C, Bharatha A, Rovira A. Pixel-by-pixel comparison of volume transfer constant and estimates of cerebral blood volume from dynamic contrast-enhanced and dynamic susceptibility contrast-enhanced MR imaging in high-grade gliomas. Am J Neuroradiol 2015;36(05): 871–876
26 Shin JH, Lee HK, Kwun BD, et al. Using relative cerebral blood flow and volume to evaluate the histopathologic grade of cerebral gliomas: preliminary results. Am J Roentgenol 2002;179(03):783–789
27 Bulakbasi N, Kocaoglu M, Farzaliyev A, Tayfun C, Ucoz T, Somuncu I. Assessment of diagnostic accuracy of perfusion MR imaging in primary and metastatic solitary malignant brain tumors. Am J Neuroradiol 2005;26(09):2187–2199
28 Law M, Yang S, Babb JS, et al. Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade. AJNR Am J Neuroradiol 2004;25(05):746–755
29 Al-Okaili RN, Krejza J, Woo JH, et al. Intraaxial brain masses: MR imaging-based diagnostic strategy—initial experience. Radiology 2007;243(02):539–550
30 Aydin S, Fatihoğlu E, Koşar PN, Ergün E. Perfusion and permeability MRI in glioma grading. Egypt J Radiol Nucl Med 2020;51(02): 1–8
31 Zhang Y, Wang J, Wang X, Zhang J, Fang J, Jiang X. Feasibility study of exploring a T_1-weighted dynamic contrast-enhanced MR approach for brain perfusion imaging. J Magn Reson Imaging 2012; 35(06):1322–1331
32 Xyda A, Haberland U, Klotz E, et al. Diagnostic performance of whole brain volume perfusion CT in intra-axial brain tumors: preoperative classification accuracy and histopathologic correlation. Eur J Radiol 2012;81(12):4105–4111
33 Jia ZZ, Gu HM, Zhou XJ, et al. The assessment of immature microvascular density in brain gliomas with dynamic contrast-enhanced magnetic resonance imaging. Eur J Radiol 2015;84(09): 1805–1809
34 Li X, Zhu Y, Kang H, et al. Glioma grading by microvascular permeability parameters derived from dynamic contrast-enhanced MRI and intratumoral susceptibility signal on susceptibility weighted imaging. Cancer Imaging 2015;15(01):4
35 Abe T, Mizobuchi Y, Nakajima K, et al. Diagnosis of brain tumors using dynamic contrast-enhanced perfusion imaging with a short acquisition time. Springer Plus. Springer Plus 2015;4(88):1–6 PubMed
36 Jelescu IO, Leppert IR, Narayanan S, Araújo D, Arnold DL, Pike GB. Dual-temporal resolution dynamic contrast-enhanced MRI protocol for blood-brain barrier permeability measurement in enhancing multiple sclerosis lesions. J Magn Reson Imaging 2011;33 (06):1291–1300
37 Li KL, Buonaccorsi G, Thompson G, et al. An improved coverage and spatial resolution: using dual injection dynamic contrast-enhanced (ICE-DICE) MRI: a novel dynamic contrast-enhanced technique for cerebral tumors. Magn Reson Med 2012;68(02): 452–462
38 Miyati T, Banno T, Mase M, et al. Dual dynamic contrast-enhanced MR imaging. J Magn Reson Imaging 1997;7(01):230–235
39 Thompson EM, Guillaume DJ, Dósa E, et al. Dual contrast perfusion MRI in a single imaging session for assessment of pediatric brain tumors. J Neurooncol 2012;109(01):105–114

