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ABSTRACT

Purpose: While the T2-FLAIR mismatch sign is highly specific for isocitrate dehydrogenase (IDH)-mutant, 1p/19q-noncodeleted astrocytomas among lower-grade gliomas, its utility in WHO grade 4 gliomas is not well-studied. We derived the partial T2-FLAIR mismatch sign as an imaging biomarker for IDH mutation in WHO grade 4 gliomas.

Methods: Preoperative MRI scans of adult WHO grade 4 glioma patients (n=2165) from the multi-institutional ReSPOND (Radiomics Signatures for PrecisiON Diagnostics) consortium were analyzed. Diagnostic performance of the partial T2-FLAIR mismatch sign was evaluated. Subset analyses were performed to assess associations of imaging markers with overall survival (OS).

Results: 121 (5.6%) of 2165 grade 4 gliomas were IDH-mutant. Partial T2-FLAIR mismatch was present in 40 (1.8%) cases, 32 of which were IDH-mutant, yielding 26.4% sensitivity, 99.6% specificity, 80.0% positive predictive value, and 95.8% negative predictive value. Multivariate logistic regression demonstrated IDH mutation was significantly associated with partial T2-FLAIR mismatch (odds ratio [OR] 5.715, 95% CI [1.896, 17.221], p=0.002), younger age (OR 0.911 [0.895, 0.927], p<0.001), tumor centered in frontal lobe (OR 3.842, [2.361, 6.251], p<0.001), absence of multicentricity (OR 0.173, [0.049, 0.612], p=0.007), and presence of cystic (OR 6.596, [3.023, 14.391], p<0.001) or non-enhancing solid components (OR 6.069, [3.371, 10.928], p<0.001). Multivariate Cox analysis demonstrated cystic components (p=0.024) and non-enhancing solid components (p=0.003) were associated with longer OS, while older age (p<0.001), frontal lobe center (p=0.008), multifocality (p<0.001), and multicentricity (p<0.001) were associated with shorter OS.

Conclusion: Partial T2-FLAIR mismatch sign is highly specific for IDH mutation in WHO grade 4 gliomas.

KEYWORDS

glioblastoma; astrocytoma; isocitrate dehydrogenase; magnetic resonance imaging; T2-FLAIR mismatch

INTRODUCTION

Identification of isocitrate dehydrogenase (IDH) mutation in adult-type diffuse gliomas on pre-treatment imaging remains a clinically important challenge, particularly in WHO grade 4 tumors. The latest 2021 update of the WHO classification of CNS tumors emphasizes the importance of this distinction by IDH status by classifying all IDH-wildtype tumors as grade 4 glioblastomas and grade 4 IDH-mutant gliomas as grade 4 astrocytomas (formerly IDH-mutant glioblastoma).[1] Accurate noninvasive identification could aid diagnosis, management, and prognostication as IDH mutation in high-grade gliomas is associated with greater extent of surgical resection and with longer survival compared to IDH-wildtype tumors.[1-3]

The T2-FLAIR (Fluid Attenuation Inversion Recovery) mismatch sign has been shown to be a highly specific imaging biomarker for IDH mutation and 1p/19q-noncodeleted status in lower-grade gliomas.[4-8] Previous studies attempting to extend the T2-FLAIR mismatch sign to predict

IDH mutation in grade 4 gliomas report mixed success, in part due to the heterogeneous imaging appearance of high-grade gliomas and the low prevalence of IDH mutation in this population.[9,10] Building on this previous work, we propose the "partial T2-FLAIR mismatch sign" as a specific marker of IDH mutation in grade 4 gliomas. To help overcome the relatively low prevalence of grade 4 astrocytomas, we leveraged data collected by the multi-institutional ReSPOND (Radiomics Signatures for PrecisiON Diagnostics) consortium, an international collaboration dedicated to improving glioblastoma prognostication.[11]

MATERIALS & METHODS

Data

In this HIPAA-compliant retrospective study, we analyzed a cohort of pathologically confirmed, newly diagnosed WHO grade 4 gliomas with preoperative MRI and known IDH mutation status from the ReSPOND consortium. 2331 patients were initially identified. 160 patients were excluded from analysis: 127 were missing demographic data (age or gender), 24 were duplicates, 5 did not have baseline scans, 3 had evidence of prior intracranial surgery, 1 had excess artifacts, and 6 were younger than 18 years old. The final sample (n=2165) consisted of data from the following institutions (sample size in parentheses): University of Pennsylvania (641), University of California-San Francisco (377), Washington University School of Medicine in St. Louis (245), University of Pittsburgh Medical Center (151), Catalan Institute of Oncology (133), Yonsei University/Severance Hospital (118), Case Western Reserve University/University Hospitals (103), The Cancer Imaging Archive (93), Kings College London (58), New York University Langone Health (54), Thomas Jefferson University (49), Henry Ford Health (47), Ivy Glioblastoma Atlas Project (33), Ohio State University (25), Tata Memorial Centre (22), and University Hospital Río Hortega (16). IDH mutation status was determined by immunohistochemistry and/or genomic sequencing, according to institutional protocols. Analyses of subsets with data for overall survival (OS; length of time between grade 4 glioma diagnosis and death) and O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status were performed.

All MRI scans contained T2-weighted, T2-FLAIR, and T1-weighted sequences before and after the administration of gadolinium-based contrast, obtained according to institutional protocols. All scans were preprocessed according to a harmonization protocol that has been previously described[12,13] and included deidentification, rigid registration to the SRI24 atlas[14], resampling to isotropic 1 mm^3-voxel resolution, and skull stripping/brain extraction.

The tumor nomenclature used in this study is consistent with the 2021 WHO Classification of Tumors of the CNS, which consolidated all IDH-mutant diffuse astrocytic tumors under a single type (astrocytoma, IDH-mutant, grades 2-4).[1]

Imaging Analysis

MRI scans were analyzed in consensus by a radiology resident with 3 years of neuroimaging experience (M.D.L.) and a board-certified neuroradiologist with 20 years of post-fellowship experience (R.J.); both were blinded to IDH mutation status during the initial imaging review. The presence of partial T2-FLAIR mismatch (homogeneously T2-hyperintense signal in a non-

enhancing solid portion of the tumor with corresponding FLAIR suppression, not necessarily involving the entire tumor volume; Figure 1) was recorded. The presence of cystic components (smooth well-defined inner wall with no/minimal peripheral enhancement around a region of homogeneously T2-hyperintense and homogeneously FLAIR-hypointense signal, distinct from ventricles and perivascular spaces, and more homogeneous on FLAIR than regions of partial mismatch; Figure 2) and presence of non-enhancing solid-appearing components that were not considered partial T2-FLAIR mismatch (T2/FLAIR-hyperintense signal less intense than cerebrospinal fluid with corresponding T1-hypointensity and associated mass effect, without the characteristic appearance and distribution of vasogenic edema; this definition was based on previous studies[15] and the VASARI feature set[16]; Figure 3) were also recorded. To approximate "fluid attenuation in non-contrast-enhancing tumor (nCET),"[10] cases with partial T2-FLAIR mismatch or cystic components were considered.

Additionally, the primary lobe/region of involvement (tumor center), multifocality (enhancing lesions connected by a region of T2/FLAIR-hyperintense edema/infiltrative tissue), and multicentricity (separate lesions not connected by T2/FLAIR-hyperintense signal) were noted.

Statistical Analysis

Statistical analysis was conducted in MATLAB version 9.13.0, R2022b (MathWorks, Natick, Massachusetts). Continuous variables are presented as means and standard deviations (SD). Categorical variables are presented as counts (and proportions). Fisher's exact test was performed to assess univariate associations between imaging variables and genetic status (IDH mutation or MGMT methylation). Multivariate associations between imaging variables and genetic status were assessed using logistic regression. Cox proportional hazard models were developed to evaluate associations between variables and OS. $P<0.05$ was considered significant.

RESULTS

Imaging Analysis

Table 1 summarizes demographic and imaging data by IDH status. IDH mutation was present in 121 of 2165 cases (5.6%). IDH-mutant cases were significantly younger than IDH-wildtype cases and more likely to exhibit partial T2-FLAIR mismatch, tumors centered in the frontal lobe, cystic components, and non-enhancing solid components (all $p<0.001$). Multivariate logistic regression demonstrated that younger age, the presence of partial T2-FLAIR mismatch, tumor centered in the frontal lobe, absence of multicentricity, and the presence of cystic or non-enhancing solid components were significant predictors of IDH mutation (Table 2).

Partial T2-FLAIR mismatch was present in 40 of 2165 (1.8%) cases, 32 of which were IDH-mutant. One IDH-mutant case exhibited complete T2-FLAIR mismatch (Figure 4), while the rest of these cases exhibited partial mismatch. 30 of 32 (93.8%) IDH-mutant and 4 of 8 (50%) IDH-wildtype patients with partial T2-FLAIR mismatch were younger than 55 years of age. Over the total cohort of 2165 patients, partial T2-FLAIR mismatch as a predictor for IDH mutation yielded a sensitivity of 26.4%, specificity 99.6%, positive predictive value 80.0%, and negative predictive value 95.8%.

To approximate "fluid attenuation in non-contrast-enhancing tumor (nCET),"[10] we identified 49 of 121 (40.5%) IDH-mutant and 50 of 2044 (2.4%) IDH-wildtype cases with partial T2-FLAIR mismatch or cystic components ($p<0.001$), yielding a sensitivity of 40.5%, specificity 97.6%, positive predictive value 49.5%, and negative predictive value 96.5% for predicting IDH mutation.

Subset analysis for IDH-wildtype cases with known MGMT methylation status (n=1196) showed that none of the recorded MRI characteristics were statistically significant predictors of MGMT methylation (Table S1).

Survival Analysis

OS was known for 1915 patients, 92 (4.8%) of which were IDH-mutant. OS was significantly longer for IDH-mutant cases than IDH-wildtype cases (mean±SD, 28.2±21.0 v. 15.5±13.2 months, $p<0.001$).

Univariate age-adjusted Cox analysis revealed IDH mutation ($p=0.004$), cystic components ($p=0.003$), and non-enhancing solid components ($p=0.022$) were associated with longer OS. Multifocality and multicentricity were associated with shorter OS ($p<0.001$). Partial T2-FLAIR mismatch was not a statistically significant predictor ($p=0.457$), even when stratified by IDH status (IDH-mutant with vs. without partial mismatch: 27.5±24.1 v. 28.4±19.8 months, $p=0.901$; IDH-wildtype with vs. without partial mismatch: 19.3±20.6 v. 15.4±13.2 months, $p=0.659$).

Multivariate Cox analysis demonstrated cystic and non-enhancing solid components were associated with longer OS, while older age, tumor centered in the frontal lobe, multifocality, and multicentricity were associated with shorter OS (Table 3).

Multivariate subset analyses by IDH status demonstrated that longer OS was associated with the presence of non-enhancing solid components in IDH-wildtype cases (Table S2) and with the presence of cystic components in IDH-mutant cases (Table S3). IDH-mutant cases with cystic components had OS of 35.8±26.1 months, whereas IDH-mutant cases without cystic components had OS of 25.8±18.7 months ($p=0.029$).

DISCUSSION

We present the partial T2-FLAIR mismatch sign as a highly specific imaging biomarker for IDH-mutant grade 4 astrocytoma in a large cohort of adult-type WHO grade 4 diffuse gliomas from the multi-institutional ReSPOND consortium. Partial T2-FLAIR mismatch describes a region of homogenous T2-hyperintense and FLAIR-hypointense signal within a non-enhancing, solid-appearing portion of tumor, not necessarily involving the entire tumor volume. The partial T2-FLAIR mismatch sign is derived from the T2-FLAIR mismatch sign, which is a highly specific marker for lower-grade IDH-mutant 1p/19q-noncodeleted/intact astrocytomas and applies to an entire tumor volume with homogeneously T2-hyperintense signal and corresponding near-complete FLAIR suppression, except for a thin peripheral FLAIR-hyperintense rim.[4-6] These signs are clinically practical because they rely solely on the visual evaluation of routinely acquired MRI sequences.

The partial T2-FLAIR mismatch sign had 99.6% specificity, 95.8% negative predictive value, and 80% positive predictive value. In contrast, the positive predictive value of the T2-FLAIR mismatch sign for low-grade astrocytoma has been reported to be 100%.[4-6] The 26.4% sensitivity of partial T2-FLAIR mismatch was low but similar to that of the T2-FLAIR mismatch sign.[4-6] Average OS in IDH-mutant cases was longer than IDH-wildtype cases in our study (28.2±21.0 v. 15.5±13.2 months), consistent with prior studies.[2] IDH mutation was a statistically significant factor in univariate analysis but not multivariate analysis of survival because the other factors (i.e., age, frontal lobe center, multifocality, multicentricity, cystic components, and non-enhancing solid components) were even more significant. Like the T2-FLAIR mismatch sign, partial T2-FLAIR mismatch was not a statistically significant predictor of OS, although there was a trend toward slightly longer survival among patients with partial T2-FLAIR mismatch.

Our results extend previous work based on the T2-FLAIR mismatch sign in grade 4 gliomas. Using the definition of T2-FLAIR mismatch as in lower-grade gliomas, Foltyn et al. analyzed 295 glioblastomas, none of which had T2-FLAIR mismatch, though only 5 cases were IDH-mutant.[9] Deriving a novel imaging biomarker from T2-FLAIR mismatch, Patel et al. identified "fluid attenuation in nCET" in 11 of 16 IDH-mutant as well as 3 of 183 IDH-wildtype glioblastomas, which was associated with longer survival.[10] Fluid attenuation in nCET is similar to partial T2-FLAIR mismatch described in the current work but was not distinguished from cysts. To approximate fluid attenuation in nCET, we identified cases with partial T2-FLAIR mismatch or cystic components. The presence of either of these features resulted in a higher sensitivity but lower specificity and positive predictive value compared to partial T2-FLAIR mismatch alone. To help overcome the low prevalence of IDH mutation as seen in these prior studies, we analyzed more than 2000 cases from the 15 institutional datasets in the ReSPOND consortium, making the present study the largest investigation of its kind to date.

Machine learning approaches using radiomics or deep learning for determining IDH mutation status from MRI have yielded promising results.[17-20] However, most of these studies are based on small samples, reproducibility is variable, and the clinical applicability of these methods remains limited. In contrast, the partial T2-FLAIR mismatch sign is a robust visual imaging biomarker identified using conventional MRI sequences and is highly specific. Future studies on the quantification and automated detection of partial T2-FLAIR mismatch may allow more objective identification of this sign. For example, geographically weighted regression has been shown to accurately identify T2-FLAIR mismatch in lower-grade gliomas[21] and may potentially be extendable to grade 4 gliomas.

We evaluated additional imaging features beyond partial T2-FLAIR mismatch. Cystic components and non-enhancing solid components were considered distinct from partial T2-FLAIR mismatch and were more often seen in IDH-mutant than IDH-wildtype cases. Although these features were not as specific or predictive as partial T2-FLAIR mismatch for IDH mutation, they were associated with longer OS. Subset analyses based on IDH status revealed the presence of non-enhancing solid components was associated with longer survival in IDH-wildtype cases, whereas cystic components were associated with longer survival in IDH-mutant cases. Non-enhancing tumor has been associated with longer survival in high-grade gliomas in some prior studies[22], though others report shorter survival, possibly related to residual viable tumor cells after initial resection of enhancing tumor.[15,23] Further investigation is warranted to determine whether the presence of these features corresponds to underlying molecular

differences beyond IDH mutation. Our finding that IDH-mutant tumors were more likely to be centered in the frontal lobe is consistent with prior studies.[10,24] While the proportions of multifocal IDH-mutant and IDH-wildtype tumors were similar, multicentricity was predictive of IDH-wildtype status. Multifocal and multicentric tumors were associated with shorter OS overall and among IDH-wildtype cases, also consistent with prior studies.[10,24]

IDH mutations in gliomas affect cellular metabolism and oncogenesis by leading to the accumulation of the oncometabolite 2-hydroxyglutarate as well as changes in DNA methylation and signaling pathways.[25] However, the biological mechanisms underlying T2-FLAIR mismatch remain incompletely elucidated. Differences in cellular proliferation and tumor microenvironment, such as the suppression or immune cells[25] and the presence of microcystic changes on histopathology[4,26], may influence the diffusion of water molecules and contribute to T2-FLAIR mismatch. Increased expression of genes and proteins in the mechanistic target of rapamycin (mTOR) pathway may also contribute.[4] Future studies with genetic and metabolic correlation may help explain why only a subset of IDH-mutant gliomas harbor partial T2-FLAIR mismatch. Decoding the metabolic pathways in gliomas and their corresponding imaging appearances could also provide a potential approach for future novel molecular targeted therapies.

While the main purpose of our study was to evaluate the association of the described imaging markers with IDH mutation, we also performed a subset analysis to explore associations with MGMT promoter methylation status. None of the examined MRI features were associated with MGMT status. MRI prediction of MGMT status remains challenging, though recent machine learning approaches have shown some success.[20,27,28]

Limitations of this study include its retrospective design, subjective assessment of the imaging markers without quantification of the degree or extent of partial T2-FLAIR mismatch, and consensus as opposed to independent review. Variable MRI acquisition protocols may have affected evaluation for partial T2-FLAIR mismatch. Specifically, the degree of T2 weighting may have differed between conventional 2D and 3D pulse sequences. Inversion time for FLAIR has also been shown to influence T2-FLAIR mismatch detection.[29] Methods of IDH testing were institution-dependent, genomic sequencing was unavailable for all cases, and some noncanonical IDH mutations may have not been identified.

CONCLUSION

Partial T2-FLAIR mismatch is a highly specific and clinically practical imaging sign for IDH mutation status in WHO grade 4 gliomas.

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TABLES

Table 1. Comparison of demographic and imaging variables by IDH mutation status.

Variable	**IDH-mutant**	**IDH-wildtype**	**P-value**
N	121	2044	
Female	46 (38.0%)	841 (41.1%)	
Age (years), mean±SD [min, max]	*41.4±13.2 [19, 79]*	*61.9±11.8 [18, 94]*	*<0.001*
Partial T2-FLAIR mismatch	*32 (26.4%)*	*8 (0.4%)*	*<0.001*
Centered in frontal lobe	*74 (61.2%)*	*621 (30.4%)*	*<0.001*
Multifocal	17 (14.0%)	391 (19.1%)	0.189
Multicentric	4 (3.3%)	194 (9.5%)	0.022
Cystic component	*24 (19.8%)*	*44 (2.2%)*	*<0.001*
Non-enhancing solid component	*62 (51.2%)*	*151 (7.4%)*	*<0.001*

Table 2. Multivariate logistic regression for prediction of IDH mutation status.

Variable	**Odds Ratio**	**95% Confidence Interval**	**P-value**
Age	*0.911*	*[0.895, 0.927]*	*<0.001*
Partial T2-FLAIR mismatch	*5.715*	*[1.896, 17.221]*	*0.002*
Centered in frontal lobe	*3.842*	*[2.361, 6.251]*	*<0.001*
Multifocal	0.839	[0.439, 1.602]	0.595
Multicentric	*0.173*	*[0.049, 0.612]*	*0.007*
Cystic component	*6.596*	*[3.023, 14.391]*	*<0.001*
Non-enhancing solid component	*6.069*	*[3.371, 10.928]*	*<0.001*

Table 3. Multivariate Cox proportional hazards model for overall survival prediction (n=1915).

Variable	**Hazard Ratio**	**95% Confidence Interval**	**P-value**
Age	*1.021*	*[1.016, 1.025]*	*<0.001*
IDH mutation	0.798	[0.614, 1.038]	0.092
Partial T2-FLAIR mismatch	1.263	[0.823, 1.940]	0.286
Centered in frontal lobe	*1.141*	*[1.035, 1.258]*	*0.008*
Multifocal	*1.308*	*[1.164, 1.470]*	*<0.001*
Multicentric	*1.418*	*[1.204, 1.671]*	*<0.001*
Cystic component	*0.735*	*[0.562, 0.961]*	*0.024*
Non-enhancing solid component	*0.763*	*[0.637, 0.913]*	*0.003*

FIGURE CAPTIONS

Figure 1. Partial T2-FLAIR mismatch sign in IDH-mutant cases with T2-weighted (A, D, G), FLAIR (B, E, H), and postcontrast T1-weighted images (C, F, I). Each case has T2-hyperintense signal corresponding to FLAIR-hypointense signal in non-enhancing portions of the tumors.

Figure 2. A cystic component (arrow) coexists in an IDH-mutant tumor with partial T2-FLAIR mismatch with T2-weighted (A), FLAIR (B), and postcontrast T1-weighted images (C).

Figure 3. A non-enhancing solid component that does not meet the criteria for partial T2-FLAIR mismatch extends to the right frontal cortical gray matter anteriorly (arrow) in an IDH-mutant case on T2-weighted (A), FLAIR (B), and postcontrast T1-weighted images (C).

Figure 4. Complete T2-FLAIR mismatch sign in a 25-year-old patient with a left frontoparietal IDH-mutant WHO grade 4 astrocytoma that shows homogeneous T2-hyperintense signal (A), FLAIR suppression except for a thin hyperintense rim (B), and no enhancement on postcontrast T1-weighted images (C).