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The role of T2-FLAIR mismatch sign in the diagnosis of adult gliomas

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TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

The role of T2-FLAIR mismatch sign in the diagnosis of adult glioma.

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Faculdade de Medicina da Universidade do Porto, 22/03/2023

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Aos meus avós, ao meu pai, à minha mãe, a toda a família que mais pilar foi que as duas pernas que me movem. Aos amigos, que mais não são que família sem o sangue. Aos professores, aos colegas, a toda uma instituição que permitiu matar um sonho e renascer uma realidade. A ti que me lês, pois se o fazes do meu círculo partilhas. Do fundo, obrigado.

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The role of T2-FLAIR mismatch sign in the diagnosis of adult gliomas

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Highlights

- T2-FLAIR mismatch sign showed 100% specificity and 100% positive predictive value for IDH-mutated diffuse gliomas;
- T2-FLAIR mismatch has prognostic relevance;
- T2-FLAIR mismatch sign was significantly associated with the involvement of the subventricular zone.

Abstract

T2-FLAIR mismatch sign is a highly specific radiological sign for IDH mutation, specifically IDH-mutated 1p19q non-codeleted gliomas. The aim of this study was to evaluate the diagnostic performance of this sign and possible association with other tumor imaging features in gliomas. We retrospectively selected 49 adult patients with histopathologic diagnosis of diffuse glioma and available pre-operative MRI. T2-FLAIR mismatch sign was observed in 6 cases (12,2%): two grade 2 astrocytomas, two grade 4 astrocytomas and two grade 2 oligodendrogliomas. T2-FLAIR mismatch sign was a marker for IDH mutation with 54.5% sensitivity, 100% specificity, 100% positive predictive value and 88%

negative predictive value; subventricular zone involvement was significantly associated with T2-FLAIR mismatch sign (p=0.010). This study reinforces the diagnostic potential and clinical applicability of the T2-FLAIR mismatch sign, especially in combination with other radiological tools, and reveals a possible connection between T2-FLAIR mismatch-positive gliomas, subventricular zone involvement and a different origin stem cell.

Introduction

The classification of gliomas has evolved over the years, trying to incorporate a grading system that allows predicting the biological behavior of the tumor. Genetic characteristics were added to histological and immunohistochemical aspects, increasing diagnostic robustness and introducing prognostic guidance. [1,2,3,4]

Nowadays, after successive cIMPACT-NOW updates and 2021 WHO revision, further clarification has been achieved, mainly through new genetic typing/subtyping, and despite histology's longstanding dominance, molecular markers are now abreast in glioma grading.[5,6]

One molecular biomarker that stands out is IDH (isocitrate dehydrogenase). It has a recognized role in early gliomagenesis[7-9], and IDH mutation is associated with lower tumor aggressiveness, significantly prolonged survival and better overall prognosis in comparison to IDH-wild type glioma patients. [10-13]

Recently, a radiological sign known as T2-FLAIR mismatch was described as 100% specific for detection of IDH 1/2 mutation and highly specific for IDH-mutated, 1p19q non-codeleted gliomas, although rather insensitive.[14]

T2-FLAIR mismatch sign may allow IDH mutation identification in diffuse gliomas when histologic confirmation is unavailable.

This mismatch may occur due to microcystic changes and enlarged intercellular spaces within the IDH-mutant tumoral parenchyma [15,16], which result in extremely high T1 and T2 relaxation times, in contrast to IDH-wildtype gliomas (very low relaxation times).[17]

The aim of this study is to evaluate the performance of the T2-FLAIR mismatch sign in the diagnosis of adult-type IDH-mutant diffuse gliomas.

Methods

We conducted a retrospective study, by consecutively selecting patients from the histopathologic and imaging databases, from July 2012 to January 2022. Inclusion criteria: adult patients (≥ 18 years old) with diffuse glioma with known IDH and 1p19q codeletion status (respectively by immunohistochemistry and fluorescent in-situ hybridization), tumor grade and available pre-operative MRI (including at least post-contrast T1 weighted image (WI), T2WI and FLAIR (fluid attenuated inversion recovery sequences). The Ethical Board approved this study.

Tumors were re-classified according to the 2021 WHO Diffuse Glioma Classification. Pre-operative MRIs were reviewed by 2 neuroradiologists (2 years and 10 years of experience, respectively J.M.M.S. and L.S.), blinded to molecular tumor status.

Tumor imaging features were recorded according to a Modified VASARI set (https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project). Modified VASARI set features evaluated were as follows: (1) tumor location ("lesion geographic epicenter" – frontal temporal, insular, parietal, brainstem and callosal); (2) side of tumor epicenter (right, left, central, bilateral) ; (3) size of signal change (largest perpendicular (x-y) cross-sectional area of T2 signal abnormality measured on a single axial image); (4) proportion of enhancement (portion of tumor that demonstrated significantly higher signal on the postcontrast T1-WI compared to precontrast T1-WI - <5%, 6-33%, 34-67%, 68-95%); (5) proportion of necrosis (proportion of tumor region that does not enhance or shows markedly diminished enhancement, is hyperintense on T2-WI, is hypointense on T1-WI, and has an irregular border – none, <5%, 6-33%, >34%) and deep white matter invasion (internal capsule, brainstem or corpus callosum).

T2-FLAIR mismatch sign was defined as areas with T2-WI hyperintensity and a relatively hypointense signal on FLAIR except for a hyperintense peripheral rim[18]; predominantly cystic areas of tumor were not considered.

Subventricular zone (SVZ) involvement and presence of the T2-FLAIR mismatch sign were also evaluated. SVZ involvement was defined as signal change that involves the anatomically defined region within 3-5mm of the lateral wall of the lateral ventricle.

Descriptive and analytic statistics were performed using SPSS (Statistical Program for the Social Sciences, v29.0.0.0 (241)).

The interobserver agreement was calculated using Cohen's κ. In case of disagreement, cases were reviewed to achieve consensus.

Diagnostic performance of T2-FLAIR mismatch sign for IDH-mutated gliomas was characterized by determining the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Fisher's exact test was used for discrete variables. Kolmogorov-Smirnov and Shapiro-Wilk tests revealed a non-normal distribution ($p=0.014/p=0.047$), so we executed the Mann-Whitney U non-parametric test.

Results

A total of 49 patients with gliomas were selected; 57.1% were male (n=28) with a mean age of 60.5 years (SD = 13.2 years). Eleven tumors had IDH mutation (22.4%), and six had 1p19q codeletion (12.2%). Regarding tumor types, the most common was grade 4 glioblastoma (n=29; 59.2%), followed by grade 4 diffuse midline glioma (n=5; 10.2%), glioblastoma NOS (n=4; 8.2%), grade 4 astrocytoma (n=3; 6.1%), and grade 2 oligodendroglioma (n=3; 6.1%), grade 3 oligodendroglioma (n=3; 6.1%), grade 2 astrocytoma (n=2; 4.1%).

Table 1. Diffuse gliomas, IDH status, SVZ Involvement and T2-FLAIR mismatch sign

Diffuse Gliomas	n (%)	IDH-mutation		SVZ involvement		T2-FLAIR mismatch	
		mutated	wildtype	+	-	+	-
Glioblastoma (G4)	29 (59.2)	0	29	14	15	0	29
Diffuse midline glioma (G4)	5 (10.2)	0	5	1	4	0	5
Astrocytoma (G4)	3 (6.1)	3	0	3	0	2	1
Glioblastoma NOS	4 (8.2)	0	4	1	3	0	4
Oligodendroglioma (G3)	3 (6.1)	3	0	1	2	0	3
Astrocytoma (G2)	2 (4.1)	2	0	2	0	2	0
Oligodendroglioma (G2)	3 (6.1)	3	0	2	1	2	1

(G - grade)

T2-FLAIR mismatch was observed in six cases (12.2%): two grade 2 astrocytomas, two grade 4 astrocytomas and two grade 2 oligodendrogliomas.

Tumor imaging features – VASARI, T2-FLAIR mismatch sign and SVZ involvement are described in Table 3.

κ values were interpreted as follows: ≤ 0: no agreement, 0.01–0.20: none to slight agreement, 0.21–0.40: fair agreement, 0.41–0.60: moderate agreement, 0.61–0.80: substantial agreement, and 0.81–1.00: almost perfect agreement.

Table 2 – Tumor imaging features (VASARI, T2-FLAIR mismatch and Subventricular Zone Involvement

Variable	n (%)	Kappa (p)
Tumor Location		
Frontal	12 (24.5%)	0.908 (p < 0.001)
Parietal	3 (6.1%)	
Temporal	8 (16.3%)	
Brainstem	3 (6.1%)	
Callosal	2 (4.1%)	
2 locations	12 (24.5%)	
≥ 3 locations	5 (10.2%)	
Thalamic	1 (2%)	
Infratentorial	3 (6.1%)	
Side of Tumor Epicenter		
Right	24 (49%)	1 (p < 0.001)
Left	20 (40.8%)	
Central	4 (8.2%)	
Bilateral	1 (2%)	
Size of Signal Change		
Maximum	117x77.5mm	
Minimum	26x9.25mm	
Proportion of Enhancement		
<5%	18 (36.7%)	0.596 (p < 0.001)
5-33%	13 (26.5%)	
34-66%	14 (28.6%)	
67-100%	4 (8.2%)	
Proportion of Necrosis		
<5%	22 (44.9%)	0.905 (p < 0.001)
6-33%	13 (26.5%)	
>34%	14 (28.6%)	
Deep White Matter Invasion		
No invasion	14 (28.6%)	0.792 (p < 0.001)
Internal Capsule	11 (22.4%)	
Brainstem	2 (4.1%)	
Corpus Callosum	15 (30.6%)	
SVZ		
Involvement	24 (49%)	1 (p < 0.001)
T2-FLAIR Mismatch		
Mismatch	6 (12.2%)	1 (p < 0.001)

T2-FLAIR mismatch sign and VASARI analysis

T2-FLAIR mismatch sign showed 54.5% sensitivity and 100% specificity for IDH-mutation (PPV = 100% and NPV = 88%); it showed 80% sensitivity and 95.5% specificity for IDH-mutated astrocytomas (high and low grade).

No correlation was found between T2-FLAIR mismatch and VASARI variables. Only SVZ involvement was found to have a statistically significant association with T2-FLAIR mismatch; 100% (n=6) of the T2-FLAIR mismatch-positive cases showed SVZ involvement.

Discussion

Knowledge of IDH-status is paramount in creating an accurate prognostic picture and developing a solid treatment plan. IDH-mutation in both low and high-grade gliomas represents an independent factor for increased progression-free survival (PFS).[18-20] This may be related to a NADPH consumption in IDH1 mutated gliomas; subsequent impairment in the reduction of glutathione and increased oxidative stress due to oxygen radicals induces tumor cell apoptosis [21,22]. The prognosis for diffuse lower grade gliomas varies widely, from a few years to decades – quality-of-life and neurological deficits become increasingly relevant as overall survival increases with better surgical techniques, radiotherapy and chemotherapy schemes.[23]

Multiple studies have attempted to identify glioma's molecular status through radiological features, such as tumor location (TERTp and IDH mutations are more frequent in frontal lobe tumors)[24], tumor margins, ADC values (1p19q codeletion is related to less defined tumor margins and lower ADC values, IDH mutation is associated with higher diffusion than IDH-wildtype)[25,26], tumor volume and contrast enhancement (1p19q codeletion with specific chromosome 9p loss in anaplastic oligodendrogliomas results in increased contrast enhancement)[27]. Nonetheless, these features have not yet proved specific enough to accurately predict a specific molecular subtype in individual patients.[28]

T2-FLAIR mismatch sign, on the other hand, exhibited in our results 100% specificity for the identification of IDH-mutated gliomas and 95% specificity in the

diagnosis of IDH-mutated astrocytomas, despite its lower sensitivity; this signal can therefore provide significant diagnostic information when present, even in the absence of histopathological specimens.

As previously reported, we found that T2-FLAIR mismatch sign had high interobserver agreement. Its identification only requires conventional MRI sequences (particularly, T2WI and T2-FLAIR), which makes it extremely useful in clinical practice.[28-32]

For maximum performance, its criteria must be carefully met, otherwise false positives quickly add up and reduce specificity.[31,32] Furthermore, although no false-positives were identified in our study regarding IDH mutation, distinction between IDH-mutated astrocytomas and IDH-mutated oligodendrogliomas still benefits from use of other imaging characteristics, such as intralesional calcifications, ADC values, cerebral blood volume (perfusion-MR) and MR spectroscopy.[16] This evidence is corroborated by previous studies, in which T2-FLAIR mismatch sign was found in oligodendrogliomas.[33-35] Presence of T2-FLAIR mismatch sign in both types of gliomas may be explained by the unspecific nature of microcystic changes, which can be present in both astrocytomas and oligodendrogliomas and have been strongly linked to T2-FLAIR mismatch.[15,16,36]

Besides the aforementioned glial neoplasms, glioneuronal tumors such as dysembryoplastic neuroepithelial tumors (DNETs), more common in the pediatric population, are seldom included in previous studies and are a potential source of false positives.[37] Reports of H3 K27M-mutant midline glioma exhibiting T2-FLAIR mismatch should raise further caution when using this sign in younger patients.[38,39] Our study included five diffuse midline gliomas, all H3 K27M mutated, but none showed positive T2-FLAIR mismatch.

According to the European Association for Neuro-Oncology (EANO), the main pillar of low-grade diffuse glioma treatment is complete surgical resection. Watch-and-wait approaches without histological confirmation should only be considered in exceptional situations.[40] Chemotherapy and radiotherapy are used as adjuvant treatments, rescue treatments or palliation in irresectable tumors and are dependent on age, tumor grade, tumor residue and presence of neurological deficits; the value of T2-FLAIR mismatch becomes elusive when deciding about

these treatments. Novel therapies are being tested on clinical trials such as immunotherapy, antiangiogenic agents like bevacizumab and tumor treating fields, some yielding promising results.[41-43] Mutant IDH inhibitor (mIDH), vorasidenib, was recently granted a fast-track designation by the FDA after it met both primary and secondary endpoints on phase III of the INDIGO trial.[44] A positive T2-FLAIR mismatch sign may have an important role concerning patients with irresectable gliomas – in these patients, besides prognostic value, it may put to consideration the choice of secondary novel treatments without the need for biopsy.

Analysis of the VASARI glioma characteristics did not reveal any significant relation with the presence of T2-FLAIR mismatch, findings which are consistent with previous reports [16,45], except for SZI (p=0.010).

The fact that all six (100%) T2-FLAIR mismatch-positive cases showed SVZ involvement, whereas only 42% of mismatch-negative gliomas involved the same area remains unclear. The stem cell theory entails that two neurogenic foci exist in the brain: the SVZ and the subgranular zone (SGZ), in the hippocampus.[46] One previous study indicated that lower-grade gliomas are usually closer to the SVZ than higher grade gliomas, which are usually closer to the SGZ.[46]

SVZ involvement might represent initial origin or latter invasion. It usually entails a poorer prognosis in high grade gliomas; however, in lower grade gliomas it is not associated with worse outcomes and has demonstrated positive association with T2 signal homogeneity.[47-49] As IDH mutation status has been directly correlated to low-grade glioma location, low grade gliomas that involve the SVZ may therefore not only have distinctive molecular and genetic characteristics from its counterparts, but a different origin stem cell altogether. [46]

Our study has several limitations. Its retrospective nature introduces a patient selection bias, as we only included patients who had available information about IDH and 1p19q codeletion status and brain MRI imaging with T1WI, T2WI and FLAIR sequences. Furthermore, the reduced number of cases lowers the study's statistical power. The retrospective nature of this study led to inclusion of diffuse gliomas classified according to different criteria. Classification according to the 5th WHO classification was dubious in four IDH-wildtype gliomas histologically

classified as astrocytomas, due to lack of information about complete IDH sequencing and TERT/EGFR mutations – they were ultimately classified as glioblastomas NOS.

Conclusion

T2-FLAIR mismatch is a radiological sign with 100% specificity for IDH-mutation in diffuse gliomas, with strict criteria that should be thoroughly fulfilled to minimize false positives. It is recommended to use this sign in combination with other radiological signs for presumptive diagnosis of IDH-mutated astrocytomas and low-grade gliomas in general, maximizing diagnostic performance. Associated low cost and high interrater agreement ensure its clinical applicability. Besides being a marker of good prognosis, future treatment algorithms involving new therapies such as mIDH inhibitors might benefit from an initial non-invasive diagnostic approach, where the mismatch sign may play a central role. Relationship with SVZ may theoretically be related to a different origin stem cell, however further investigation is needed.

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43. Lin, Y. & Chen, B. Case report: tumor-treating fields prolongs IDH-mutant anaplastic astrocytoma progression-free survival and pathological evolution to glioblastoma. *Ann Transl Med* **9**, 1804 (2021).
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46. Skjulsvik, A.J.*, et al.* Is the anatomical distribution of low-grade gliomas linked to regions of gliogenesis? *J Neurooncol* **147**, 147-157 (2020).
47. Chiang, G.C.*, et al.* The Prognostic Value of MRI Subventricular Zone Involvement and Tumor Genetics in Lower Grade Gliomas. *J Neuroimaging* **30**, 901-909 (2020).
48. Zhao, K.*, et al.* The imaging features and prognosis of gliomas involving the subventricular zone: An MRI study. *Clin Neurol Neurosurg* **222**, 107465 (2022).
49. Tejada Neyra, M.A.*, et al.* Voxel-wise radiogenomic mapping of tumor location with key molecular alterations in patients with glioma. *Neuro-Oncology* **20**, 1517-1524 (2018).

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1,2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1,2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	3
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	3
Participants	**6**	Eligibility criteria	3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	3
	8	Where and when potentially eligible participants were identified (setting, location and dates)	3
	9	Whether participants formed a consecutive, random or convenience series	3
Test methods	**10a**	Index test, in sufficient detail to allow replication	4
	10b	Reference standard, in sufficient detail to allow replication	3
	11	Rationale for choosing the reference standard (if alternatives exist)	NA
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	4
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	3
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	3
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	NA
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	4
	15	How indeterminate index test or reference standard results were handled	10
	16	How missing data on the index test and reference standard were handled	NA
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	NA
	18	Intended sample size and how it was determined	NA
RESULTS			
Participants	**19**	Flow of participants, using a diagram	NA
	20	Baseline demographic and clinical characteristics of participants	5
	21a	Distribution of severity of disease in those with the target condition	5
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	NA
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	5
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	7
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	9,10
	27	Implications for practice, including the intended use and clinical role of the index test	9
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	10

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

(Foi utilizada numeração de linha continua)

Item 1: Página 1; Linha 22 e 23 (“The aim of this study was to evaluate the diagnostic performance of this sign”)

Página 2; Linha 28, 29 e 30 (“T2-FLAIR mismatch sign was a marker for IDH mutation with 54.5% sensitivity, 100% specificity, 100% positive predictive value and 88% negative predictive value”)

Item 2: Página 1 e 2; Linhas 21-35 (“T2-FLAIR mismatch sign is a highly specific radiological sign for IDH mutation, specifically IDH-mutated 1p19q non-codeleted gliomas…”)

Item 3: Página 2; Linhas 54 e 55 (“T2-FLAIR mismatch sign may allow IDH mutation identification in diffuse gliomas when histologic confirmation is unavailable”)

Item 4: Página 3; Linhas 60 e 61 (“The aim of this study is to evaluate the performance of the T2-FLAIR mismatch sign in the diagnosis of adult-type IDH-mutant diffuse gliomas.”)

Item 5: Página 3; Linhas 64 e 65 (“We conducted a retrospective study, by consecutively selecting patients from the histopathologic and imaging databases, from July 2012 to January 2022”)

Item 6: Página 3; Linhas 66-70 (“Inclusion criteria: adult patients (≥ 18 years old) with diffuse glioma, known IDH and 1p19q codeletion status (respectively by immunohistochemistry and fluorescent in-situ hybridization), tumor grade and pre-operative MRI (including at least post-contrast T1 weighted image (WI), T2WI and FLAIR (fluid attenuated inversion recovery sequences)”)

Item 7: Página 3; Linhas 66-69 (“adult patients (≥ 18 years old) with diffuse glioma, known IDH and 1p19q codeletion status (respectively by immunohistochemistry and fluorescent in-situ hybridization), tumor grade and pre-operative MRI (including at least post-contrast T1 weighted image (WI), T2WI and FLAIR”)

Item 8: Página 3; Linhas 64 e 65 (“by consecutively selecting patients from the histopathologic and imaging databases, from July 2012 to January 2022”)

Item 9: Página 3; Linha 64 e 65 (“…by consecutively selecting patients from the histopathologic and imaging databases, from July 2012 to January 2022.”)

Item 10a: Página 4; Linhas 89-91 (“T2-FLAIR mismatch sign was defined as the “presence of areas with T2-weighted image hyperintensity and a relatively hypointense signal on FLAIR except for a hyperintense peripheral rim”.18; predominantly cystic areas of tumor were not considered”)

Item 10b: Página 3; Linhas 72 e 73 (“Tumors were re-classified according to the 2021 WHO Diffuse Glioma Classification”)

Item 11: Foi utilizado como teste de referência o gold-standard na prática clínica.

Item 12a: Página 4; Linhas 89-91 (“T2-FLAIR mismatch sign was defined as the “presence of areas with T2-weighted image hyperintensity and a relatively hypointense signal on FLAIR except for a hyperintense peripheral rim”.18; predominantly cystic areas of tumor were not considered”)

Item 12b: Página 4; Linhas 72-73 (“Tumors were re-classified according to the 2021 WHO Diffuse Glioma Classification”)

Item 13a: Página 4; Linhas 73-75 (“Pre-operative MRIs were reviewed by 2 neuroradiologists (2 years and 10 years of experience, respectively J.M.M.S. and L.S.), blinded to molecular tumor status.”)

Item 13b: NA – A análise do teste de referência não foi feita de forma controlada pelo estudo; quaisquer vieses da classificação histopatológica são desconhecidos e potenciais limitações deste estudo.

Item 14: Página 4; Linhas 100-102 (“Diagnostic performance of T2-FLAIR mismatch sign for IDH-mutated gliomas was characterized by determining the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).”)

Item 15: Páginas 10 e 11; Linhas 253-257 (“Classification according to the 5th WHO classification was dubious in four IDH-wildtype gliomas histologically classified as astrocytomas, due to lack of information about complete IDH sequencing and TERT/EGFR mutations – they were ultimately classified as glioblastomas NOS.”)

Item 16: NA – Tendo em conta a amostragem consecutiva, não existiram dados omissos.

Item 17: NA – Apenas foi realizado cálculo dos parâmetros de acuidade diagnóstica para IDH status vs IDH-mut astrocitomas, que era um dos objetivos do estudo.

Item 18: NA – O tamanho amostral encontra-se limitado pelo número de casos existentes nas bases de dados com as patologias em estudo.

Item 19: NA – Não houve exclusão de casos, pelo que se dispensou a elaboração de um flow chart.

Item 20: Página 5; Linhas 116-122 (“57.1% were male (n=28) with a mean age of 60.5 years (SD = 13.2 years). Eleven tumors had IDH mutation (22.4%), and six had 1p19q codeletion (12.2%). Regarding tumor types, the most common was grade 4 glioblastoma (n=29; 59.2%), followed by grade 4 diffuse midline glioma (n=5; 10.2%), glioblastoma NOS (n=4; 8.2%), grade 4 astrocytoma (n=3; 6.1%), and grade 2 oligodendroglioma (n=3; 6.1%), grade 3 oligodendroglioma (n=3; 6.1%), grade 2 astrocytoma (n=2; 4.1%).”)

Item 21a: Página 5; Linhas 116-122 (“57.1% were male (n=28) with a mean age of 60.5 years (SD = 13.2 years). Eleven tumors had IDH mutation (22.4%), and six had 1p19q codeletion (12.2%). Regarding tumor types, the most common was grade 4 glioblastoma (n=29; 59.2%), followed by grade 4 diffuse midline glioma (n=5; 10.2%), glioblastoma NOS (n=4; 8.2%), grade 4 astrocytoma (n=3; 6.1%), and grade 2 oligodendroglioma (n=3; 6.1%), grade 3 oligodendroglioma (n=3; 6.1%), grade 2 astrocytoma (n=2; 4.1%).”)

Item 21b: NA – Não existiu amostragem de diagnósticos alternativos; ter glioma era critério de inclusão no estudo, e a amostragem foi feita de modo seriado.

Item 22: NA – O interval de tempo era irrelevante e não existiram intervenções clínicas entre os dois testes, tendo em conta o algoritmo de diagnóstico.

Item 23: Página 5; Tabela 1

Item 24: Página 7; Linhas 158-160 (“T2-FLAIR mismatch sign showed 54.5% sensitivity and 100% specificity for IDH-mutation (PPV = 100% and NPV = 88%); it showed 80% sensitivity and 95.5% specificity for IDH-mutated astrocytomas (high and low grade)”)

Item 25: NA – Quaisquer efeitos adversos que pudessem ocorrer encontravam-se fora do espectro deste estudo e não eram esperados

Item 26: Páginas 9 e 10; Linhas 245-254 (“Our study has several limitations. Its retrospective nature introduces a patient selection bias, as we only included patients who had available information about IDH and 1p19q codeletion status and brain MRI imaging with T1WI, T2WI and FLAIR sequences. Furthermore, the reduced number of cases lowers the study’s statistical power. The retrospective nature of this study led to inclusion of diffuse gliomas classified according to different criteria. Classification according to the 5th WHO classification was dubious in four IDH-wildtype gliomas histologically classified as astrocytomas, due to lack of information about complete IDH sequencing and TERT/EGFR mutations – they were ultimately classified as glioblastomas NOS.”)

Item 27: Página 9; Linhas 224-228 (“A positive T2-FLAIR mismatch sign may have an important role concerning patients with irresectable gliomas – in these patients, besides prognostic value, it may put to consideration the choice of secondary novel treatments without the need for biopsy.”)

Item 28: À data do preenchimento destas guidelines, o artigo ainda não foi publicado.

Item 29: NA – Nenhum artigo paralelo foi elaborado em relação ao protocol de estudo complete, visto que o estudo é retrospectivo e os métodos são simples. O artigo ainda não foi publicado à data de preenchimento destas guidelines.

Item 30: Página 10; Linhas 270 e 271 (“This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.”)

NEUROIMAGE: CLINICAL

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 2213-1582

DESCRIPTION

NeuroImage: Clinical,, a companion title to the highly-respected NeuroImage, is a journal of diseases, disorders and syndromes involving the Nervous System, provides a vehicle for communicating important advances in the study of abnormal structure-function relationships of the human nervous system based on imaging.

The focus of *NeuroImage: Clinical* is on defining changes to the brain associated with primary neurologic and psychiatric diseases and disorders of the nervous system as well as behavioral syndromes and developmental conditions. The main criterion for judging papers is the extent of scientific advancement in the understanding of the pathophysiologic mechanisms of diseases and disorders, in identification of functional models that link clinical signs and symptoms with brain function and in the creation of image based tools applicable to a broad range of clinical needs including diagnosis, monitoring and tracking of illness, predicting therapeutic response and development of new treatments. Papers dealing with structure and function in animal models will also be considered if they reveal mechanisms that can be readily translated to human conditions.

The journal welcomes original research articles as well as papers on innovative methods, models, databases, theory or conceptual positions provided that they involve imaging approaches and demonstrate significant new opportunities for understanding clinical problems.

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INTRODUCTION

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The journal welcomes original research articles as well as papers on innovative methods, models, databases, theory or conceptual positions provided that they involve imaging approaches and demonstrate significant new opportunities for understanding clinical problems.

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