# Romanian NEUROSURGERY

The T2FLAIR mismatch novel radiogenomic marker in the newly suspected low-grade gliomas. Implications for grading and neurosurgical management in light of the 2021 WHO Classification of Tumours of the Central Nervous System (WHOCNS5)

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**ABSTRACT**

**Background.** The T2-FLAIR (fluid-attenuated inversion recovery) mismatch sign has been defined over the last few years as an important novel radiogenomic marker highly suggestive of isocitrate dehydrogenase mutated (IDH-mut) 1p19q non-codeleted gliomas (astrocytomas). Existing studies have demonstrated that this has good specificity but limited sensitivity for IDH-mut astrocytomas. The new 2021 WHO Classification of Tumors of the Central Nervous System (WHO CNS5) has introduced a layered grading system in which all IDH mutant diffuse astrocytic tumours are considered a single type (Astrocytoma, IDH-mutant) and are graded as CNS WHO grade 2, 3, or 4. Because of the growing importance of molecular information in CNS tumour classification, diagnoses and diagnostic reports need to combine different data types into a single diagnosis. Whether the T2FLAIR mismatch sign is of clinical relevance for the management of low-grade gliomas still needs to be further determined.

**Methods.** We included histologically verified supratentorial low-grade gliomas (LGG) WHO grade 2-3 retrospectively during the period 2013–2018 (n=18). For the period 2019–2023 (n=27), patients with a radiological presumptive diagnosis of low-grade glioma were prospectively included, and we took into consideration the fact that in this group we could encounter other diagnoses than glioma. Clinical, radiological and histology data were collected. We aimed to examine the association of the T2-FLAIR mismatch sign (where identified) with clinical factors and outcomes. We evaluated the diagnostic reliability of the mismatch sign and its

relation to the definitive histological diagnosis, the co-existence of an MR spectroscopy signature; we have also tried to determine whether the identification of the radiogenomic marker had any impact on the clinical outcome through the decision-making in neurosurgical management.

**Results.** Out of 45 patients with radiological suspected glioma, 30 had a definitive diagnosis of diffuse astrocytoma grade 2 and 3 (Astrocytoma, IDH-mutant according to WHOCNS5). 6 patients had a diagnosis of glioblastoma (Glioblastoma, IDH-wildtype according to WHOCNS5). 8 patients have been diagnosed with oligodendroglioma (Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted according to WHOCNS5) and 1 case had a definitive histology of cerebral abscess. Out of the 30 patients with IDH-mut astrocytoma, 6 (20.0%) showed a mismatch sign. The sensitivity and specificity of the mismatch sign for IDH-mut astrocytoma detection were 20% and 98.6%, respectively. There were no differences between patients with an IDH-mut astrocytoma with or without T2FLAIR mismatch sign when grouped according to this with related to baseline characteristics, clinical outcome and presenting symptoms. MR spectroscopy sequences were analyzed where available for the retrospective and prospective cohort. There were 7 cases where MR spectroscopy was performed and, for the IDH-mut astrocytoma cases (n=4) it showed a persistent high Cho/NAA ratio without any difference between the patients with or without the T2FLAIR mismatch sign.
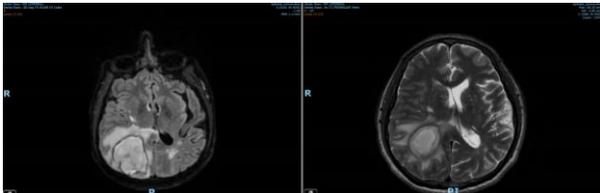


**Figure 1** (Left). Axial T2FLAIR images of 50M with final histology brain abscess.
**Figure 2** (Right). Axial T2W images of 50M with final histology brain abscess.

**Conclusion.** In our relatively small retrospective and prospective cohorts, the T2-FLAIR mismatch sign, where identified, was not correlated with clinical features at presentation, prognosis or outcome. Until recently, the grading of CNS tumours has been focusing mainly on histology characteristics, but specific molecular markers can now be used for valuable prognostic information. For this reason, molecular-specific information has been added as an essential feature in grading and it is considered very useful for further estimation of prognosis within variable tumor types. We could not determine if the IDH-mut astrocytomas with mismatch sign represent a specific subgroup. Our study has confirmed that the T2-FLAIR mismatch sign is a reliable and specific marker of IDH-mut astrocytomas.

## Background

The T2-FLAIR (fluid attenuated inversion recovery) mismatch sign has been defined over the last few years as an important novel radiogenomic marker highly suggestive of isocitrate dehydrogenase mutated (IDH-mut) 1p19q non-codeleted gliomas (astrocytomas)[7]. Existing studies have demonstrated that this has a good specificity but limited sensitivity for IDH-mut astrocytomas. The new 2021 WHO Classification of Tumors of the Central Nervous System (WHO CNS5) has introduced a layered grading system in which all IDH mutant diffuse astrocytic tumors are considered a single type (Astrocytoma, IDH-mutant) and are graded as CNS WHO grade 2, 3, or 4 [10]. Because of the growing importance of molecular information in CNS tumor classification, diagnoses and diagnostic reports need to combine different data types into a single diagnosis.

Whether the T2FLAIR mismatch sign is of clinical relevance for the management of low-grade gliomas still needs to be further determined [11].
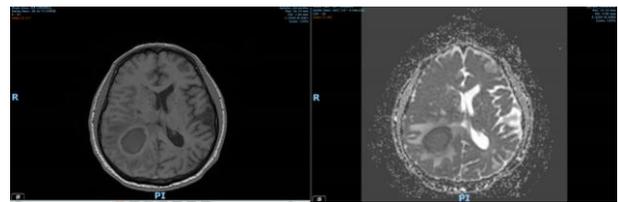


**Figure 3** (Left). Axial T1W non-contrast images of 50M with final histology brain abscess.
**Figure 4** (Right). ADC map images of 50M with final histology brain abscess.

Several recent studies have recently demonstrated that the IDH mutation and 1p/19q non co- deletion status can be predicted by conventional and advanced MRI [13].



**Figure 5.** Brain MRI Spectroscopy images of 50M with final histology brain abscess.

MRI with gadolinium contrast is the main imaging investigation of election for diagnosis and management [11]. Diffuse astrocytoma IDH-mut involves the white matter and causes expansion of the surrounding cortex. On conventional MRI, the T2-FLAIR mismatch sign is an easily identifiable imaging finding that has been studied in extensor recently [11, 12, 13]. Few studies in the last couple of years have validated the idea that this radiogenomic marker plays a relevant role in making preoperative diagnosis and treatment planning [6, 7, 8].



**Figure 6.** AxialT2W images of 61F with final histology WHO grade 3 astrocytoma.

The T2-FLAIR mismatch sign is defined by a homogenously hyperintense signal on T2Weighted Imaging and a central hypointensity with peripheral hyperintensity on FLAIR. This constitutes a radiogenomic marker regarded as highly specific for IDH-mutant and 1p/19q non-co-deleted gliomas (astrocytomas). There is a strong possibility that it reflects microcystic changes in IDH- mutant astrocytomas [14].



**Figure 7** (Left). Axial non-contrast T1W images of 61F with final histology WHO grade 3 astrocytoma.
**Figure 8** (Right). Coronal FLAIR images of 61F with final histology WHO grade 3 astrocytoma.

Biomarkers are the essential elements of patient-specific management strategies, but the commonly analyzed histological biomarkers are available only after the surgical procedure [Correll et all. (2020)]. Therefore, in the neurosurgical management and decision making, radiogenomic biomarkers are of great interest to help identify relevant subgroup of patients. The newly described imaging feature of T2-FLAIR (fluid attenuation inversion recovery) mismatch sign has attracted increased interest, since it is a widely available and simple potential imaging marker to predict IDH- mutated (IDH-mut) 1p19q non-codeleted (non-codel) gliomas (astrocytoma) with high specificity [16].



**Figure 9** (Left). Axial non-contrast T1W images of 61F with final histology WHO grade 3 astrocytoma.
**Figure 10** (Right). Coronal FLAIR images of 61F with final histology WHO grade 3 astrocytoma.

The tumors showing a T2FLAIR mismatch sign on MRI are different radiologically from gliomas without the mismatch sign with their distinct features. This raises questions regarding underlying biology. Until recently existing studies have not indicated that this radiogenomic marker is reflected by a specific biological feature [17].

We aimed to evaluate demographic, clinical, radiological and histological parameters with regard to mismatch sign and we have tried to redefine the diagnosis in conformity with the new 2021 WHOCNS5 classification of CNS tumors. In addition, we analyzed if IDH-mut astrocytomas with mismatch sign had similar MR spectroscopy features compared to samples without the mismatch sign.



**Figure 11** (Left). Axial T2FLAIR images of 61M with final histology WHO grade 3 astrocytoma.
**Figure 12** (Right). Axial T1W non contrast images of 61M with final histology WHO grade 3 astrocytoma.

**Figure 13.** Coronal T2FLAIR images of 61M with final histology WHO grade 3 astrocytoma.

## METHODS

We included histological verified supratentorial low-grade gliomas (LGG) WHO grade 2-3 retrospectively during the period 2013–2018 (n=18). For the period 2019–2023 (n=27), patients with a radiological presumptive diagnosis of low grade glioma were prospectively included, and we took into consideration the fact that in this group we could encounter other diagnoses than glioma. Clinical, radiological and histology data were collected.

We centralized and redefined the perspective on the histological diagnosis of all the patients in both the prospective and retrospective cohorts in line with new 2021 WHO Classification of Tumors of the Central Nervous System (**WHO CNS5**).

We aimed to examine the association of the T2-FLAIR mismatch sign (where identified) with clinical factors and outcomes. We evaluated the diagnostic reliability of the mismatch sign and its relation to the definitive histological diagnosis, the co-existence of an MR spectroscopy signature; we have also tried to determine whether the identification of the radiogenomic marker had any impact on the clinical outcome through the decision making in the neurosurgical management.

The Neurosurgical department at the Emergency University Hospital in Bucharest covers the population of approximately 1 million inhabitants.

The patients in the Bucharest region in Romania with newly diagnosed primary intracranial intra-axial tumors are referred either through the GP (General Practitioner) service or by direct presentation in the Accident and Emergency Department. From the moment of clinical and radiological presumptive diagnosis of CNS tumor they enter a clinical pathway involving Neurosurgery, Neuroradiology, Oncology,

being managed in a multidisciplinary team (MDT) with weekly meetings ("Tumor Board") at the Emergency University Hospital Bucharest.

Our patients groups consisted of two components; one retrospective group (2013-2018) and one prospective (2019-2023).

We performed a retrospective analysis of clinical and imaging data between 2013 and 2018, including surgical procedure logs, patients clinical notes and histology results, including all patients with a histology result diagnosis of a supratentorial infiltrating WHO grade 2 or 3 glioma with available magnetic resonance imaging (MRI) (n=18).
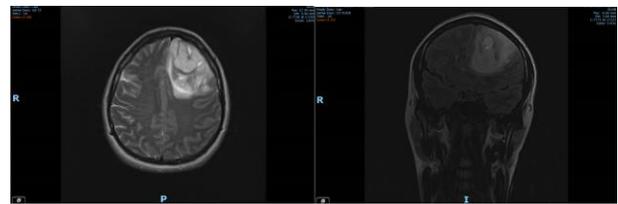


**Figure 14** (Left)**.** Axial T2W images of 37F with final histology WHO grade 3 oligodendroglioma.
**Figure 15** (Right)**.** Coronal FLAIR images of 37F with final histology WHO grade 3 oligodendroglioma.
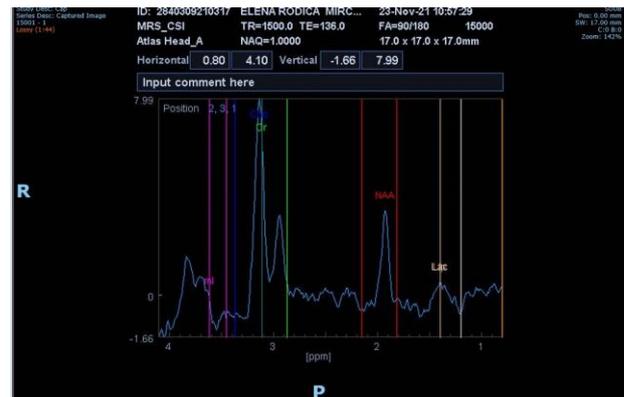


**Figure 16.** MR Spectroscopy of 37F with final histology WHO grade 3 oligodendroglioma.

Between 2019 and 2023, we worked prospectively on a cohort including patients with a suspected diagnosis of diffuse low grade glioma, referred either through the GP or presenting directly to our Emergency Department (n=27).

This prospective group of patients consisted of intraaxial space-occupying lesions suggestive of primary brain tumor with a hyperintense signal in T2W images, with or without significant contrast enhancement. We took into consideration the fact

that we might encounter other histopathological diagnoses (e.g. cerebral abscess or other tumors). The main reason for including these patients was to enable the evaluation of the mismatch sign in a group with mostly similar MRI appearance, but also potential different diagnoses than low grade glioma, as opposed to previous studies that used tissue diagnosis as inclusion criteria [7, 17].

We used MRI images from all patients in the both retro- and prospective groups to identify the T2-FLAIR mismatch sign (N = 45).

We included parameters such as patient age, gender, presenting symptom, localisation of the lesion, eloquence. We separated further the patients with IDH-mut astrocytomas (n=30) divided into two subgroups, with and without mismatch sign.
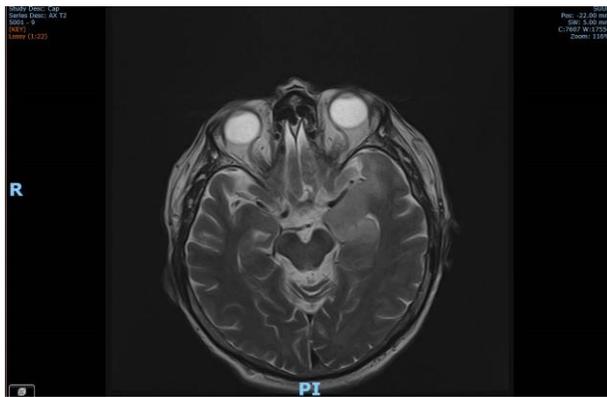


**Figure 17.** Axial T2W images of 69M with final histology WHO grade 2 diffuse astrocytoma.

MRI examinations reviewed in this study were performed in the Radiology Department of the Emergency University Hospital Bucharest as part of the pre-operative work-up investigation. MRI images were analyzed for: main part of the brain involved (frontal, temporal, parietal, occipital, insula), side (right, left, bilateral), eloquence [14], T2-FLAIR mismatch (yes/no) and MR spectroscopy sequences characteristic features (Cho/NAA high ratio) correlated with the presence or absence of the T2FLAIR mismatch sign.

Evaluation was performed independently by a neurosurgical specialist, a neurosurgical resident, a senior neurosurgeon and a neuroradiologist [14, 16, 17].

## RESULTS

Out of 45 patients with radiological suspected glioma, 30 had a definitive diagnosis of diffuse astrocytoma grade 2 and 3 (Astrocytoma, IDH-mutant according to WHOCNS5). 6 patients had a diagnosis of glioblastoma (Glioblastoma, IDH-wildtype according to WHOCNS5). 8 patients have been diagnosed with oligodendroglioma (Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted according to WHOCNS5) and 1 case had a definitive histology of cerebral abscess.

Out of the 30 patients with IDH-mut astrocytoma, 6 (20.0%) showed a mismatch sign. The sensitivity and specificity of the mismatch sign for IDH-mut astrocytoma detection were 20% and 98.6%, respectively. There were no differences between patients with an IDH-mut astrocytoma with or without T2FLAIR mismatch sign when grouped according to this with related to baseline characteristics, clinical outcome and presenting symptoms. MR spectroscopy sequences were analyzed where available for the retrospective and prospective cohort; a number of n=4 MRI spectroscopy images were available for the IDH-mut astrocytoma group (n=30). In all the cases of MR spectroscopy from the IDH-mut astrocytoma group, this showed a persistent high Cho/NAA ratio without any difference between the patients with or without the T2FLAIR mismatch sign.

**Table 1.** Demographic, clinical and radiological characteristics of patients diagnosed between 2013 and 2023 with low grade glioma (N = 30), analyzed comparing the T2-FLAIR mismatch sign presence or absence and the MR spectroscopy high Cho/NAA ratio.

| | T2 FLAIR mismatch sign present n=6 | T2 FLAIR mismatch sign absent n=24 | High Cho/NAA ratio on MR spectroscopy n=4 |
|---|---|---|---|
| Age (median) | 51 | 52 | 51.5 |
| Gender (F) n | 4 (66.6%) | 16 (67%) | 3 |
| **Location of the tumor (lobe) n** | | | |
| Frontal | 3 (50%) | 16 (67%) | 2 |
| Temporal | 0 | 1 (4%) | 0 |
| Parietal | 2 (33%) | 6 (25%) | 2 |
| Insular | 1 (16%) | 1 (4.6%) | 0 |
| **Lateralisation and eloquence n** | | | |
| Right side | 2 (33.3%) | 13 (54.16%) | 3 |
| Left side | 3 (50%) | 8 (33.3%) | 1 |
| Bilateral | 1 (16%) | 3 (12.5%) | 0 |
| Functional area | 4 (75%) | 11 (45.83%) | 1 |
| **Presenting symptoms n** | | | |
| Asymptomatic | 0 | 3 (12.5%) | 0 |
| Motor deficits | 3 (50%) | 12 (50%) | 2 |
| Dysphasia | 3 (50%) | 7 (29.17%) | 1 |

| | | | |
|---|---|---|---|
| Visual disturbance | 0 | 2 (8.33%) | 0 |
| Cognitive impairment | 1 (16%) | 5 (20.83%) | 0 |
| Seizures | 3 (50%) | 14 (58.33%) | 3 |
| Intracranial hypertension | 1 (16%) | 3 (12.5%) | 0 |
| **Surgical procedure** | | | |
| Biopsy only | 1 (16%) | 4 (16.67%) | 1 |
| Resection | 5 (84%) | 20 (83.3%) | 3 |
| **WHOCNS5 grade** | | | |
| 2 | 2 (33.3%) | 11 (45.83%) | 1 |
| 3 | 4 (66.6%) | 13 (54.17%) | 3 |

Our patient cohort included retro- and prospectively 45 patients with available MRI images. The retrospective part of the cohort included 18 patients with mean age of 47 years and 11 patients (61%) were females. The majority of this group underwent biopsy followed by resection, as opposed to biopsy only (n=15, 83.33%).

In the prospective part, we evaluated 27 patients with a suspected diffuse IDH-mut astrocytoma. This included both tumor and non-tumor diagnoses, such as an atypical cerebral abscess. In this cohort, 18 patients were female (66.6%) and the mean age was 49.2 years.

The most common surgical procedure was resection (83.3%). Out of the 45 patients, the majority were diagnosed with WHO grade 2 or 3diffuse astrocytoma (N = 30), oligodendroglioma (N = 8) and glioblastoma (N = 6). Other diagnoses included non-neoplastic lesions such as cerebral abscess (N=1). The mismatch sign was not present in the non-tumor diagnosis.

In total there were 30 patients with IDH-mut diffuse astrocytoma. These were separated based upon the presence of T2- FLAIR mismatch sign (N = 6) or absence (N = 24). In Table 1 we elaborate on comparison between these groups in regards to clinical features, imaging variables (including MR spectroscopy) and clinical aspects.

There were no differences regarding lobe involvement, presenting symptoms or surgical procedure employed. There was no difference between groups with respect to the extent of resection, with mismatch sign and without mismatch sign) [14].

In six patients (20%) from both groups the T2FLAIR mismatch sign was identified and all of them had IDH-mutated diffuse astrocytomas. We have not identified any patient with positive T2FLAIR

mismatch sign in the IDH-wild type group (glioblastoma).

From the retrospective and prospective groups, 7 cases had available MR spectroscopy images. From the total number of MR spectroscopy performed (n=7), 4 patients were diagnosed with IDH- mut diffuse astrocytoma, 1 patient was diagnosed with IDH-mut 1p19q co-deleted glioma (oligodendroglioma), 1 patient was diagnosed with IDH-wild type glioblastoma and 1 with cerebral abscess. In all of the cases of MR spectroscopy and IDH-mut astrocyoma, a persistent high Cho/ NAA ratio, without any difference between the patients with or without the T2FLAIR mismatch sign was present.

## DISCUSSION

Until recently, the grading of CNS tumors has been focusing mainly on histology characteristics, but specific molecular markers can now be used for valuable prognostic information. For this reason, molecular specific information has been added as an essential feature in grading and it is considered very useful for further estimation of prognosis within variable tumor types. See tables 2-4 [10]

**Table 2.** World Health Organisation Classification of Tumors of the Central Nervous System, fifth edition (WHO CNS5) [10].

| 2021 WHO Classification of Tumors of the Central Nervous System |
|---|
| Gliomas<br><br>• Adult-type diffuse gliomas;<br>• Astrocytoma, IDH-mutant;<br>• Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted;<br>• Glioblastoma, IDH-wildtype. |

In this relatively small study we found no difference between diffuse IDH-mut astrocytomas with or without the mismatch sign with regards to extent of resection or any other clinical variable. We reconfirmed that the T2- FLAIR mismatch sign has a good specificity for diffuse IDH-mut astrocytomas.
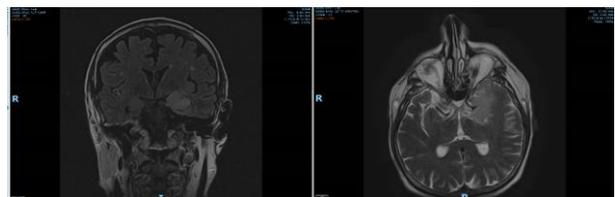
**Figure 18** (Left)**.** COR FLAIR images of 69M with final histology WHO grade 2 diffuse astrocytoma.
**Figure 19** (Right)**.** MR Spectroscopy images of 69M with final histology WHO grade 2 diffuse astrocytoma.

As reiterated in many previous studies, it is well known that gliomas may vary in consistency and their macroscopic aspect, and with the radiological image of homogenous signal on T2-weighted sequences and infiltrative tumor border, the question was raised whether the extent of the resection is related to the mismatch sign. This may be of particular importance, since the IDH-mut astrocytoma group seems to be the one where extensive surgery is of definite benefit [11, 12, 14].

**Table 3.** Key Diagnostic Genes, Molecules, Pathways, and/or Combinations in Major Primary CNS Tumors (WHO CNS5) [10]

| Tumor Type | Genes/Molecular Profiles Characteristically Altered |
|---|---|
| Astrocytoma, IDH-mutant | IDH1, IDH2, ATRX, TP53, CDKN2A/B |
| Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted | IDH1, IDH2, 1p/19q, TERT promoter, CIC, FUBP1, NOTCH1 |
| Glioblastoma, IDH-wildtype | IDH-wildtype, TERT promoter, chromosomes 7/10, EGFR |

In our study, the extent of resection was not different between groups, therefore the T2FLAIR mismatch sign should probably not be considered a factor influencing the extent of resection in diffuse IDH-mut astrocytomas. Patel et all. had evaluated the association between survival and the mismatch sign, with a median follow-up of 65.7 months, and found no differences in overall survival between groups [17].

**Table 4.** CNS WHO Grades of Selected Types, Covering Entities for Which There Is a New Approach to Grading, an Updated Grade, or a Newly Recognised Tumor That Has an Accepted Grade (WHO CNS5) [10]

| CNS WHO Grades of Selected Types | |
|---|---|
| Astrocytoma, IDH-mutant | 2, 3, 4 |
| Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted | 2, 3 |
| Glioblastoma, IDH-wildtype | 4 |

Broen et al and Patel et al have reported a 100% specificity for IDH-mut astrocytomas [6, 17]. More recent studies have found overall specificity in the range of 96.0–100.0% [6, 17, 18]. The T2 FLAIR mismatch sign has been found rarely in IDH-mut codel gliomas (oligodendrogliomas), but also in pediatric low-grade brain tumors. Until now, the mismatch sign has been reported in pilomyxoid astrocytoma, low grade glioma with MYB rearrangement, oligodendroglioma (IDH- mut co-del) [11].

One previous study (Correll et all.) has reported a patient with T2-FLAIR mismatch sign had a diagnosis of IDH-mut glioblastoma, suggesting that the mismatch sign is not grade specific [11]. Importantly, there were no other differential diagnoses beyond diffuse gliomas that presented with the mismatch sign. Although of low sensitivity (27.1–51.0%), the specificity for IDH-mut astrocytomas makes the evaluation of mismatch sign useful in a clinical setting for individual cases [6, 11, 17, 18]. Adding advanced imaging characteristic sequences like apparent diffusion coefficient (ADC) and cerebral blood volume (CBV) to the mismatch sign may further improve the diagnostic capabilities of IDH-mut astrocytomas[11].

Foltyn et all. (2022) have hypothesised that the higher ADC value in IDH-mutant gliomas with a T2/FLAIR-mismatch sign (as compared to those without) translate into a measurable prognostic effect, although this requires investigation in future studies. The same study affirms that spatial differences in ADC values between the core and rim of tumors with a T2/FLAIR-mismatch sign potentially reflect specific distinctions in tumor cellularity and microenvironment [12].

## CONCLUSION

In our relatively small retrospective and prospective cohorts, the T2-FLAIR mismatch sign, where identified, was not correlated with clinical features at presentation, prognosis or outcome. We could not determine if the IDH-mut astrocytomas with mismatch sign represent a specific subgroup. Our study has confirmed that the T2-FLAIR mismatch sign is a reliable and specific marker of IDH-mut astrocytomas. MR spectroscopy, where available, has proven a very useful imaging investigation with a high value for management of these CNS neoplastic tumors.

Fast progress in identification of more pre-operative non-invasive tumor markers represents the way forward in the context of rapid evolution of the complexity and transformation of the whole concept of cancer treatment; advanced imaging characteristic sequences like apparent diffusion coefficient (ADC), cerebral blood volume (CBV) and identification of the T2FLAIR mismatch will improve the pre-operative diagnostic possibilities [11].

It is also of crucial importance that the new WHOCNS5 grading system will be integrated into our standard clinical practice, with the main purpose being a more adaptable and reliable, also more practical diagnosis and management tool.

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