



Original Article

# Preoperative imaging features: Are they useful tools for predicting IDH1 mutation status in gliomas Grades II–IV?

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## ABSTRACT

**Background:** It is already known that gliomas biomolecular parameters have a reliable prognostic value. However, an invasive procedure is required to determine them. Our aim was to better understand the clinical characteristics of gliomas Grades II–IV and to assess the usefulness of imaging features in magnetic resonance imaging (MRI) to predict the isocitrate dehydrogenase one (IDH1) mutation.

**Methods:** Preoperative MRI characteristics were retrospectively reviewed and molecular diagnosis of gliomas was tested in adult patients between 2014 and 2021 in two institutions. We applied a biological criterion to divide the brain in cerebral compartments.

**Results:** A total of 108 patients met the inclusion criteria. Contrast enhancement (CE) in MRI was significantly associated with wild-type IDH1 (IDH1-Wt) ( $P < 0.00002$ ). Furthermore, the positive predictive value of CE for IDH1-Wt was of 87.1%. On the other hand, the negative predictive value of non-CE for mutated IDH1 (IDH1-Mut) was of 52.6%; 60.2% of gliomas were located in the neocortical and 24.1% in the allocortical/mesocortical telencephalon. Considering gliomas Grades II–III, 66.7% of IDH1-Mut and 28.6% of IDH1-Wt gliomas were located in the neocortex, without statistical significance.

**Conclusion:** Our research revealed that CE is useful for predicting IDH1-Wt in gliomas. On the contrary, non-CE is not useful for predicting IDH1-Mut gliomas. Thus, the traditional concept of associating non-CE MRI with a low-grade glioma should be reviewed, as it can lead to an underestimation of the potential aggressiveness of the tumor. If this association was validated with the future prospective studies, a noninvasive tool would be available for predicting gliomas IDH1 mutation status.

**Keywords:** Glioma, Isocitrate dehydrogenase, Limbic system, Molecular diagnosis, Paralimbic system, Radiological features

## INTRODUCTION

The 2016 and 2021 World Health Organization (WHO) central nervous system (CNS) tumor classification generated a conception shift on how to diagnose and understand gliomas by adding molecular diagnosis, such as isocitrate dehydrogenase (IDH) mutation or 1p19q codeletion

status, to the classic histologic classification. It is already known that these biomolecular parameters have a reliable prognostic value.<sup>[11,22,26]</sup> However, an invasive procedure is required to determine them. Finally, these biomarkers are still not widely available in middle- and low-income countries.<sup>[12,18]</sup>

There is evidence that gliomas have a predilection for the frontal, temporal, and insular lobe.<sup>[3,7,8,14,16,20]</sup> In turn, it was also determined that the molecular profiles of gliomas varied from one cerebral lobule to another.<sup>[2,3,5,13,19,20,27]</sup> However, since the 19<sup>th</sup> century, the location of tumors was considered following a descriptive criterion of a lobar division of the brain whose limits were arbitrary. Yasargil *et al.* proposed that the location of neoplastic lesions in the CNS should be understood following a biological cerebral division. In this way, he defined functional compartments by their embryological, metabolic, and cytoarchitectural characteristics, among others.<sup>[24,25]</sup> Furthermore, several studies have suggested associations between specific contrast enhancement (CE) patterns and IDH mutation status.<sup>[1,9,14,23]</sup> However, to the best of our knowledge, there are no widely accepted results. The use of neuroimaging features for prediction of the molecular diagnosis of gliomas according to the 2021 WHO classification is still in process of validation.

We hypothesize that imaging characteristics correlate with biological behavior of gliomas which is, in turn, strongly related to their genotype. In this study, we investigate whether there is an association between IDH1 mutation status and several radiological characteristics. The location of the lesions was defined in a novel way according to the division in cerebral functional compartments proposed by Yasargil,<sup>[25]</sup> an approach seldom used in the previous reports.<sup>[10]</sup> Our purpose is to better understand gliomas clinical characteristics and to evaluate the usefulness of imaging features in presurgical magnetic resonance imaging (MRI) to predict the R132H mutation in the IDH1 gene in patients with Grades II–IV gliomas.

## MATERIALS AND METHODS

The study has been approved by both Institutional Research Ethics Committees before experiment was started and has been conducted in accordance with the principles set forth in the Helsinki Declaration of 1975, as revised in 2000.

### Patients' selection and study design

An observational, epidemiological, retrospective, and multicenter study was designed.

Patients with a diagnosis of cerebral glioma between January 2014 and December 2021 were identified and analyzed. All the data were obtained from the records of both institutions,

which are publicly funded. All patients included were adults, underwent biopsy or tumor resection, and had an MRI (1.5 or 3T) available for review done before their first surgery. Patients' age was considered at the date of their first surgery. Accessible neuroimaging consisted of at least T2-weighted, FLAIR, T1-weighted, and T1-weighted postcontrast sequences. Patients with ependymomas and choroid plexus tumors were excluded from the study.

The cases diagnosed between 2014 and 2020 according to the 2007 or 2016 WHO classification were reviewed at the Institute of Oncology "Ángel H. Roffo" by a single neuropathologist (JIGE). Molecular testing was done and the diagnosis was reclassified according to the 2021 WHO classification.

### Molecular analysis

All genetic testing was done at the Department of Diagnosis of the Institute "Roffo." IDH1 mutation analysis was performed by immunohistochemistry using a monoclonal antibody against IDH1-R132H (H09, Dianova, Hamburg, Germany) in all specimens. Furthermore, by immunohistochemistry, alpha-thalassemia/mental retardation X-linked (ATRX) expression (AX1 clon, Dianova, Hamburg, Germany), p53 staining (D07 clon, Leica, Buffalo Grove, United States of America), and glial fibrillary acidic protein (EP672Y clon, Roche-Ventana, Oro Valley, United States of America) were tested. Finally, CDKN2A homozygous deletion and 1p/19q codeletion analysis were performed by fluorescence *in situ* hybridization by means of double detection with a specific DNA molecular probe (ZytoLight SPEC CDKN2A/CEN 9 and 1p36/1q25 and 19q13/19q13 dual color probe, Bremerhaven, Germany). The latter was tested in all gliomas except in glioblastomas (GBMs). This decision was based on the diagnostic algorithm proposed by the WHO.<sup>[11]</sup> If despite histological analysis and biomolecular testing, an uncertain diagnosis was rendered, the tumor was classified as "Diffuse Glioma, not otherwise specified (NOS)."

### Imaging characteristics

Preoperative contrast-enhanced MRIs were reviewed. Patients' images were classified as "CE" or "non-CE" according to the T1-weighted postcontrast sequences. **"CE" was defined as any contrast-enhancing nonvascular lesion, when compared with the noncontrast T1 images, regardless of its pattern of enhancement or appearance.** In addition, tumor borders were categorized as "sharp" or "indistinct."

Two of the authors evaluated the images independently, and when their decisions were not concordant, they met to discuss and agreed on the final classification.

## Topography

Due to the infiltrative nature of gliomas, when there was a single lesion that did not enhance with contrast, the tumor topography was considered where the epicenter of the lesion in the T2-weighted and FLAIR sequences was located. In gliomas that did enhance with gadolinium, their location was considered according to the epicenter of the tumor in the T1-weighted postcontrast sequences.<sup>[4]</sup> The classification method was the same as explained above for other imaging characteristics.

The tumors' cerebral topography was classified as follows, according to the functional compartments proposed by Yasargil *et al.*:<sup>[24,25]</sup> **(A) neocortical telencephalon:** comprised by structures with six cortical layers. (a) Frontal lobe: superior, middle, and inferior frontal gyrus; (b) central lobe: precentral, paracentral, and postcentral gyrus; (c) parietal lobe: superior and inferior parietal lobe and precuneus; (d) occipital lobe: cuneus, superior, middle, and inferior occipital gyrus, lingual, and temporo-occipital gyrus (posterior third); (e) temporal lobe: superior, middle, and inferior temporal gyrus and temporo-occipital gyrus (anterior two-thirds). **(B) Mesocortical telencephalon (paralimbic system):** comprised by structures with 3–5 cortical layers, which include the insular lobe, cingulate gyrus, parahippocampal gyrus, temporal pole, and orbital gyri. **(C) Allocortical telencephalon (limbic system):** comprised by structures with no definite lamination to two-layered cortex, which include the amygdala, hippocampal and piriform cortex, septal regions, and substantia innominata. **(D) Central nuclei:** diencephalon, basal ganglia, and brainstem. **(E) Ventricles.**

If one lesion occupied two or more compartments, approximately equal in volume, without normal brain interposed, the topography was named “**combined**.”

A glioma was classified as “**multicentric**” if the patient presented two or more lesions in any given compartment with normal brain interposed between them.

An “**eloquent area**” was defined as a cortical cerebral area whose function cannot be replaced in case of injury (e.g., the primary sensorimotor area, speech centers, or insula).

Finally, the side of the lesion was systemized as “left,” “right,” or “bilateral.”

## Statistical analysis

Data were analyzed through a descriptive analysis. The association between imaging features and IDH1 mutation status was tested using the Chi-squared test or Fisher's exact test on occasions when frequencies were <5. In all tests, a two-tailed  $P < 0.05$  was considered statically significant.

## RESULTS

Of 111 patients initially evaluated, 108 met the inclusion criteria, 55.6% were male, with a mean age of 50.1 years (19–84 years). About 75.9% of the samples were obtained by resection, 24.1% by biopsy. The most frequent diagnosis was GBM IDH1-Wt (58/108 = 53.7%). Only considering gliomas Grades II–III, diffuse astrocytoma, IDH1-Mut/ATRX-Mut (11/108 = 10.2%) was the most frequent. There were 13 cases categorized as diffuse gliomas NOS, all of them Grade II and IDH1-Wt. Five of them were midline gliomas, located in the central nuclei compartment. The other Grade II ( $n = 20$ ) gliomas were IDH1-Mut. Finally, 9/15 (60%) of the Grade III gliomas were IDH1-Mut. The patients' characteristics and neuroimaging findings are summarized in Table 1.

Regarding tumor topography, 60.2% were localized in the neocortical telencephalon (23.1% in the frontal lobe and 11.1% in the temporal lobe), 24.1% in the paralimbic and limbic system, and 7.4% were multicentric. Only 4.6% of all gliomas involved two or more different compartments. In our investigation, no cerebellar gliomas were reported.

Addressing the hypothesis of our research, we looked for an association between the molecular profile and imaging characteristics in presurgical MRI. In Table 2, it is observed that gliomas Grades II–III (33 Grade II and 15 Grade III cases, considering the integrated diagnosis) were very heterogeneous without any significant association. On the other hand, GBM presented more homogeneous characteristics, with a preponderance of CE and sharp borders. Of the 55 CE GBM, 25 were ring-enhancing lesions with the central necrosis. Considering all of the gliomas, CE was significantly associated with IDH1-Wt ( $P < 0.00002$ ). In addition, the positive predictive value of CE for IDH1-Wt was of 87.1% (95%CI: 77.1–93.3%). Furthermore, the negative predictive value of non-CE for IDH1-Mut was of 52.6% (95%CI: 37.3–67.5%). We observed that 33.3% ( $n = 5/15$  cases) of Grade III gliomas and that 5.2% ( $n = 3/58$ ) of GBM did not enhance with gadolinium. There were 5 (15.2%) Grade II gliomas that did enhance with contrast. Three of them were IDH1-Wt and their diagnosis was diffuse glioma NOS.

When analyzing a possible association between genotype and topography, considering Grades II–III gliomas [Table 3], 66.7% (18/27) with IDH1-Mut were located in the neocortex (13 Grade II and five Grade III). In contrast, only 28.6% (6/21) IDH1-Wt (three Grade II and three Grade III cases) were located in that compartment. Moreover, 75% of gliomas Grades II–III localized in the neocortex were IDH1-Mut, but 61.5% (8/13) of the ones localized in the meso/allocortex were IDH1-Mut (six Grade II and two Grade III). These results did not achieve a statistical significance [Table 3].

## DISCUSSION

In this investigation, we found that CE is statistically associated with an IDH1-Wt, in low- and high-grade

**Table 1:** Clinical and neuroimaging characteristics,  $n=108$ .

Sex, $n$ (%)	
Male	60 (55.6)
Female	48 (44.4)
Age, mean (range), years	50.1 (19-84)
Type of surgery, $n$ (%)	
Surgical excision	82 (75.9)
Stereotactic biopsy	26 (24.1)
Brain side, $n$ (%)*	
Right hemisphere	49 (45.4)
Left hemisphere	50 (46.3)
Bilateral	9 (8.3)
Topography, $n$ (%)*	
Neocortical telencephalon	65 (60.2)
Frontal lobe	25 (23.1)
Temporal lobe	12 (11.1)
Parietal lobe	13 (12.0)
Central lobe	9 (8.3)
Occipital lobe	3 (2.8)
Temporo-occipital	1 (0.9)
Parietotemporal	1 (0.9)
Parieto-occipital	1 (0.9)
Mesocortical telencephalon	20 (18.5)
Allocortical telencephalon	6 (5.6)
Central nuclei	6 (5.6)
Ventricles	1 (0.9)
Multicentric	8 (7.4)
Combined	2 (1.8)
Eloquence, $n$ (%)	
Eloquent	42 (38.9)
Noneloquent	66 (61.1)
MRI – borders, $n$ (%)	
Sharp	74 (68.5)
Indistinct	34 (31.5)
MRI – contrast enhancement, $n$ (%)	
No	38 (35.2)
Yes	70 (64.8)

\*Percentages may not add up to 100% due to rounding. MRI: Magnetic resonance imaging

gliomas. Given its positive predictive value of 87.1%, it can be considered a useful characteristic for predicting an IDH1-Wt. On the contrary, according to our results, non-CE is not a good predictor of an IDH1-Mut. This is because the negative predictive value, that is, the probability that the patient has a mutated IDH1 tumor since the MRI does not show CE, was of 52.6%. This is relevant given the general impression of inferring a low-grade glioma from lesions that do not enhance with gadolinium in the MRI. Taking this evidence into account is that this concept should be reviewed and that gliomas that do not enhance with contrast should not be underestimated. In summary, no CE is not a good feature for predicting IDH1-Mut gliomas.

It is already known that the presence of CE in gliomas is an imaging characteristic of aggressive tumors<sup>[6,17]</sup> and also that it could be an independent prognostic factor, associated with worse total survival.<sup>[1,14]</sup> However, the evidence available at the moment on the capacity of prediction of the IDH mutation status by CE in MRI is contradictory. We found investigations that report that there is no significant association,<sup>[1]</sup> while others report that it is a good predictor. In a recent meta-analysis,<sup>[21]</sup> it is asserted that IDH-mutant gliomas showed less CE than IDH-Wt. Our research revealed that CE is more useful for predicting an IDH1-Wt in gliomas Grades II–IV, than for suggesting a mutation in IDH1, in accordance with other reports.<sup>[9,14,23]</sup> We decided to analyze gliomas Grades II–IV altogether, to look for tools that would serve in the presurgical stage, when the patients still do not have a definitive diagnosis that enables to differentiate them into high- or low-grade gliomas. Michiwaki *et al.*<sup>[14]</sup> reported that gliomas with ring enhancement can be predicted as GBM IDH-Wt with high sensitivity (0.89) and specificity (0.91), and also that ring-enhanced tumors present an unfavorable course. Certainly, prospective studies with more statistical power are needed to continue studying this topic.

We observed that most of the gliomas ( $65/108 = 60.2\%$ ) have their epicenter in the neocortical telencephalic compartment, keeping this distribution even considering Grades II–III and GBM separately. It is known that gliomas have a predilection

**Table 2:** Relationship between the WHO grades, molecular factors, contrast enhancement, and tumor borders.

Histology and WHO grade	IDH1 status	Contrast enhancement			Tumor borders	
		Yes	No	<i>P</i> -value	Sharp	Indistinct
Gliomas, Grade II, $n=33$	IDH1-Mut	2	17	0.35	12	7
	IDH1-Wt	3	11		5	9
Gliomas, Grade III, $n=15$	IDH1-Mut	7	1	0.1	4	4
	IDH1-Wt	3	4		4	3
Astrocytoma Grade IV, $n=2$	IDH1-Mut	-	2	-	2	-
Glioblastoma, $n=58$	IDH1-Wt	55	3	-	47	11
All, $n=108$	IDH1-Mut	9	20	0.00002	18	11
	IDH1-Wt	61	18		56	23

IDH: Isocitrate dehydrogenase, Mut: Mutated, WHO: World Health Organization, Wt: Wild type

**Table 3:** Correlations between the WHO grades, molecular factors, and topography.

Histology and WHO grade	IDH1 status, n (%)	Topography, n (%)*		
		Neocortical telencephalon	Meso-/allocortical telencephalon	Others
Gliomas Grades II–III, n=48	IDH1-Mut, 27 (100)	18 (66.7)	8 (29.6)	1 (3.7)
	IDH1-Wt, 21 (100)	6 (28.6)	5 (23.8)	10 (47.6)
Astrocytoma Grade IV, n=2	IDH1-Mut (100)	1 (50)	-	1 (50)
Glioblastoma, n=58	IDH1-Wt, 58 (100)	40 (69)	13 (22.4)	5 (8.6)

\*Percentages may not add up to 100% due to rounding. IDH: Isocitrate dehydrogenase, Mut: Mutated, WHO: World Health Organization, Wt: Wild type

for the frontal, temporal, and insular lobe.<sup>[3,7,8,14,16,20]</sup> Although it may be because these cerebral lobes represent more brain volume than the rest, there are reports that assert that gliomas are located in certain brain regions more frequently than expected even after adjusting this difference to tissue volume.<sup>[8]</sup> To the best of our knowledge, our research is one of the few epidemiological reports that account for this asymmetry in tumor topography using the biological criteria described previously.<sup>[24,25]</sup> Furthermore, Yasargil observed that tumors that arise in a compartment grow within its limits except for very aggressive exceptions. In our work, only 4.6% of the gliomas occupied two or more different compartments, in accordance with the 10% reported.<sup>[25]</sup>

We highlight an investigation that compares the molecular profile of gliomas located in the temporal lobe neocortex with others located in the meso- and allocortex of the mentioned lobule.<sup>[10]</sup> There are methodological differences with our study that should be mentioned when comparing results. Li *et al.*<sup>[10]</sup> did not include all the functional brain compartments, as in our work, but only the telencephalon; nor was it carried out in South-American patients. Leaving these differences aside, the investigation carried out by Li *et al.*<sup>[10]</sup> concludes that gliomas Grades II–IV located in the neocortex have a slightly higher incidence of mutated IDH, than those located in the limbic and paralimbic system.

This finding, without having statistical power, is also observed in our research when we found that IDH1-Mut Grades II–III glial tumors have a higher prevalence in the neocortical compartment than in other compartments and that IDH1-Wt, a lower prevalence. One possible explanation proposes that since the glia of different brain regions expresses different growth factors, and oncogenesis occurs in cells that overexpress a specific growth factor, then tumors would only grow in a particular region.<sup>[27]</sup> A vision based on biological characteristics for division of the brain may contribute to elucidate in the future the pathophysiology of gliomas.

This study has several limitations. The first is that only the IDH1-R132H mutation was evaluated due to the lack of availability in publicly funded institutions in Argentina of the specific techniques for evaluation of other IDH1 and IDH2 mutations. Fortunately, the R132H mutation in the IDH 1

gene represents 95%<sup>[9]</sup> of IDH1/2 mutations in GBM and 80% in Grades II–III gliomas,<sup>[15]</sup> so the error that can induce in our results is small or without clinical consequences. Second, the patient sample was sparse to perform statistical analysis to all the tumoral characteristics examined. Finally, the retrospective nature of the work brings several biases inherent to the design. We believe that continuing the investigation prospectively, increasing the number of patients, and evaluating all mutations in IDH1 and IDH2 could contribute to reducing the above-mentioned limitations.

Despite the potential limitations, we consider that the greatest value of this work is focused on the positive finding of CE as a predictor of IDH1-Wt. Furthermore, we highlight the questioning of the concept of inferring a good prognosis glioma due to the fact that the lesion does not enhance with contrast in the MRI. Therefore, continuing in the future, the investigation of a possible association between gliomas genotype and radiological features would allow us to provide a noninvasive clinical prognosis instrument that could also have an impact on therapeutic strategies.

## CONCLUSION

CE was a reliable imaging feature for predicting IDH1-Wt gliomas. On the other hand, non-CE did not allow predicting with certainty the IDH1 status. According to our study, the concept that if a glioma does not enhance with contrast which is of good prognosis should be reviewed. Furthermore, most gliomas were located in the neocortical telencephalon. In addition, with the exception of very aggressive tumors, gliomas grew within the limits of a single brain compartment.

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## Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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## Conflicts of interest

There are no conflicts of interest.

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