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Radiographic assessment of contrast enhancement and T2/FLAIR mismatch sign in lower grade gliomas: correlation with molecular groups

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Abstract

Purpose: With the updated World Health Organization (WHO) 2016 neuropathological diagnostic criteria, radiographic prognostic associations in lower-grade gliomas (LGG, WHO grade II and III) are undergoing re-evaluation.

Methods: We identified 316 LGG patients (151 grade II and 165 grade III) for a combined cohort from three independent databases. We analyzed the preoperative axial FLAIR, axial T2-weighted and post-gadolinium volumetric T1-weighted MR images. The molecular data collected included the status of *IDH1/2, TP53, TERT* promoter and *ATRX* mutations, in addition to 1p/19q co-deletions. In a subset of cases (n=133), we assessed the "T2-FLAIR mismatch" sign.

Results: Gliomas were assigned to one of the three molecular groups: Group O (*IDH*-mutant, 1p/19q co-deleted oligodendrogliomas, n=95), Group A (*IDH*-mutant, *ATRX* inactivated astrocytomas, n=175) and Group G (*IDH* wild-type, GBM-like, n=46). A contrast-enhancing tumor was seen in 98 patients (31%), most frequently in Group G (n=28/45, 57%), when

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compared to Group A (n= 49/175, 28%) and Group O (n= 24/95, 25.3%) tumors (p=0.008 and p=0.0011, respectively). Consistent with previous reports, T2-FLAIR mismatch was preferentially found in Group A tumors (73.1%, 60 of 82), although its presence was not associated with survival, after controlling for molecular group. False positive mismatch sign was noted in 28.5% (12/42) Group O tumors, but none of the tumors in Group G. A combination of all three factors: age under 40 years at first diagnosis, a tumor size larger than 6 cm and T2-FLAIR mismatch was highly specific for *IDH* mutant astrocytoma (Group A).

Conclusion: We identify radiographic correlates of molecular groups in lower-grade gliomas, which join clinical demographic features in defining the characteristic presentation of these tumors. Radiographic correlates of prognosis in LGG require re-evaluation within molecular group.

Keywords

Glioma; *IDH* mutation; contrast enhancement; T2-FLAIR mismatch; radiographic correlates

Introduction

Imaging plays an essential role in the management of lower-grade gliomas (LGG). Indeed, magnetic resonance imaging (MRI) represents the first-line modality in the diagnosis of these tumors, and in the assessment of response to treatment. Recent advances in MRI techniques have allowed for an improved, non-invasive, pre-therapeutic characterization of LGG, expanding our knowledge beyond the historical view of LGG as non-enhancing areas of increased signal on T2-weighted imaging [1–3]. Moreover, the legacy classification of adult diffuse LGG as a homogenous group of neoplasms is shifting as evidence has emerged that emphasizes the distinct origin of tumors with differing molecular subtypes, and the subsequent impact on response to treatment and patient outcomes [4–9]. Codified in the recent 2016 update to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System [10], this has resulted in an ongoing re-evaluation of the radiographic assessment of LGG patients [11, 12].

In the era preceding WHO 2016, well-established clinical and radiographic features, such as contrast enhancement, mass effect and necrosis were used to correlate MRI features to pathological grade in gliomas and, consequently, to predict outcome [13–16]. In addition, contrast enhancement was routinely used to predict higher grade or progressive malignant transformation and was associated with poor overall survival. Radiologic features such as tumor size and midline infiltration were synthesized into the widely used Pignatti criteria for prognostic assessment[17]. However, the significant overlap of imaging characteristics between different histological entities, limited the utility of MRI as a definitive predictor of grade – some higher-grade lesions were non-enhancing, some lower-grade tumors had enhancing components.

With the new WHO 2016 criteria enforcing a molecular homogeneity within these previously mixed histologic cohorts, recent studies have identified specific radiographic features that are characteristic of certain molecular groups, most notably the “T2-FLAIR mismatch” sign, which is reported to be highly specific for *IDH*-mutant, *TP53/ATRX*

inactivated astrocytic gliomas [18, 19]. We hypothesized that a combined “radio-genomic” approach composed of clinical and pre-operative radiographic features could prove useful in the diagnosis and survival prediction of LGG patients. Here, we aim to establish a radiographic score that facilitates identifying patients within certain molecular classifications.

Methods

Patient selection and clinical data

Our retrospective study was reviewed and approved by the human subjects’ institutional review board of the Dana-Farber Cancer Institute/Harvard Cancer Center and complied with HIPAA guidelines, protocol number 2011P002334. The study utilized three separate databases to develop a combined cohort of 316 patients who underwent surgical resection of a WHO grade II/III glioma with available imaging and molecular data. Patient data was acquired from The Cancer Genome Atlas (TCGA) (n=162), a National Cancer Institute-supported publicly available dataset derived from de-identified patients, the Department of Neurosurgery at Massachusetts General Hospital (n=87) and the Department of Neurosurgery at University Hospital Dresden (n=69). Included cases met the following criteria: (1) Tumors were WHO grade II or WHO grade III, (2) preoperative imaging data with fluid-attenuated inversion recovery (FLAIR), T2-weighted and post-gadolinium T1 contrast sequences was available, and (3) tumors had known *IDH* mutation status. The primary reason for patient ineligibility (n=127) was due to lack of preoperative MR scans acquired from the Cancer Imaging Archive (TCIA).

Molecular analysis

The molecular data collected from the TCGA cohort included the status of *IDH1/2, TP53* and *ATRX* mutations, in addition to 1p/19q co-deletions. In the remaining cohorts, *IDH* mutations were assessed using either Next Generation Sequencing (MGH Cohort)[20] or Sanger sequencing (Dresden cohort)[21] or Immunohistochemistry (MGH and Dresden) [22]. *ATRX* inactivation was evaluated using Immunohistochemistry[23]. *TERT* promoter (*TERT*p) mutations were assessed either by amplification using Sanger sequencing performed with ABI Prism 3730 DNA Analyzer or using the fluorescence PCR technique, as previously described [24, 25]. 1p/19q co-deletions were detected by fluorescence-in situ hybridization analysis on samples of paraffin-embedded tumor tissues [26, 27]

Radiographic Annotation

MR images from the TCGA cohort were obtained from The Cancer Imaging Archive (TCIA), a National Cancer Institute-supported imaging network that provides radiographic data corresponding to the de-identified patients from the TCGA. The MR images from the remaining two datasets were locally performed and included preoperative axial FLAIR (3-5 mm sections, 1 mm interslice gaps), axial T2-weighted images (5 mm sections, 1 mm interslice gaps), coronal T1 (5 mm sections, 1 mm interslice gaps) as well as post-gadolinium T1-weighted MR images. All images were analyzed in accordance with the Response Assessment in Neuro-Oncology (RANO) guideline [12].

Using Osirix, a DICOM image processing application, we scored the preoperative axial FLAIR, axial T2-weighted and post-gadolinium volumetric T1-weighted MR images. Tumor size was measured as the largest orthogonal cross product of the tumor on the axial T2/FLAIR scans. Similarly, enhancing volume was measured as the largest orthogonal cross product of the enhancing tumor on axial T1-post gadolinium scans. For the purposes of the study, tumor enhancement was defined as present in cases with enhanced cross product greater than or equal to 10% of the overall tumor size demonstrated on the T2/FLAIR images (examples in Supplemental Figure 1).

T2-FLAIR mismatch sign

Preoperative MR scans from 133 patients were assessed for mismatched T2-weighted ("hyper-intense") and the FLAIR ("hypo-intense") signals, using a previously reported approach [19]. The assessment was performed by two independent clinically experienced reviewers (D.D., a neuroradiologist and T.A.J., a neurosurgeon). The reviewers were blinded to molecular status and diagnosis. In cases of disagreement (n=4), a third experienced reviewer (J.J.M.) was involved in the assessment. Inter-reviewer agreement was evaluated using the Kappa statistic (κ = 0–0.40, poor; κ = 0.41–0.60, moderate; κ = 0.61–0.80, good; κ = 0.81–1.00, excellent).

Statistical Analysis

The Kaplan-Meier method was used to estimate progression free survival (PFS) and overall survival (OS). Differences in survival were assessed using the log-rank test. PFS was defined as the interval between the day of first surgery to MRI-confirmed tumor progression, death or end of follow-up. OS was defined as the interval from the day of first surgery until death or the end of follow-up. The Mann-Whitney U and Fisher's exact tests were used to test for association of radiographic variables and the three molecular subgroups. A multivariate Cox proportional hazards model was constructed to assess the impact of radiographic features on patient outcome. A p value (two-sided) of less than 0.05 was considered significant. All analyses were conducted using the SPSS software package (Version 21.0 SPSS Inc., Chicago, IL, USA).

Results

Molecular classification

The 2016 World Health Organization (WHO) classification of central nervous system tumors was used to categorize tumors [28]. Based on the presence or absence of *TERT*p mutations, *IDH* mutations, *ATRX* inactivation and lp/19q co-deletion, the vast majority of adult diffuse gliomas can be clustered into three distinct molecular subgroups [9]: Group O, Group A and Group G. The molecular oligodendroglial "Group O" is defined by the presence of *IDH* and *TERT*p mutations and 1p/19q co-deletions. The molecular astrocytic "Group A" is characterized by *IDH* mutation with concomitant *TP53/ATRX* inactivation, or the absence of lp/19q co-deletions and/or *TERT*p mutations. Group G ("glioblastoma-like") can then be defined by the absence of a mutation in an *IDH* gene. In our cohort, a total of 316 WHO grade II/III gliomas (151 WHO grade II and 165 WHO grade III) were assigned to one of the three molecular groups: Group O (n=95), Group A (n=175) and Group G

(n=46). Table 1 provides a summary of the clinical characteristics of the three molecular subgroups.

The median age for all of the patients at the time of diagnosis was 44 years (range 19 - 86 years). The median age of patients in Group A was 36.7 years (range 19-74), which is significantly younger than patients in Group G (54 years, range 23-72) and Group O (43.1 years, range 20-86) ($p<0.0001$). The median PFS and OS of all patients were 5.06 years (95% CI 4.2 – 5.8) and 11.3 years (95% CI 9.2 – 13.4 years), respectively. During the follow-up time, 144 patients (45.5%) experienced progressive disease and 72 patients (22.8%) died. As expected, patients in Groups A and O had a significantly longer PFS (5.3 years, 95% CI 4.6 -6.1 years for Group A and 6.1 years, 95% CI 4.3 – 8.0 years for Group O, respectively) than their counterparts in Group G (1.3 years, 95% CI 0.9 – 1.7 years, $p < 0.0001$) (Figure 1).

Tumor Size

Analyses were performed to determine if tumor size varied by molecular group. Gliomas in Group A had the largest tumor diameter, with a median size of 26.4 mm^2 (range 3.2-84 mm^2). In accordance with the Pignatti criteria [17], gliomas in Group A were more likely to have at least one diameter equal to or larger than 6 cm (Fisher's exact p=0.044 and p=0.045 compared to Group G and Group O, respectively). In aggregate however, Group A gliomas were comparable in size to those in Group O (median size 19.6 mm^2, range 2.9 – 87.8); a difference in tumor diameter which was not significant (p=0.2). Interestingly, LGG in Group G were significantly smaller at first presentation than those in Group A (median 18.2 mm^2, range 1.8-49.5, p = 0.002). We speculate that because *IDH* mutant tumors have a slower growth trajectory, they are able to achieve a larger size prior to becoming clinically symptomatic and then being diagnosed for the first time [29]. Furthermore, while patients with *IDH*-mutant WHO grade II and III gliomas had similar age at first diagnosis (median 40.1 years, 95% CI 18 – 86 years), *IDH* mutant WHO grade III gliomas had a significantly larger size at diagnosis than *IDH* mutant WHO grade II tumors ($p< 0.01$) (Table 1).

Moreover, a multivariate Cox regression analysis revealed molecular Group G status and larger tumor size as factors that are significantly associated with worse PFS (Table 2).

Contrast enhancement

Out of 316 patients, 98 patients (31%) showed a contrast-enhancing tumor on their preoperative MR scans (see Methods). The inter-reviewer agreements were excellent (κ = 0.93, 95% CI, 0.89 – 0.95). Based on the molecular analysis, enhancing gliomas were found to be significantly more common in Group G (n=28/45, 57%), when compared to Group A (n= 49/175, 28%) and Group O (n= 24/95, 25.3%) tumors (p=0.008 and p=0.0011, respectively). Strikingly, we did not observe a significant difference in PFS when comparing the enhancing and non-enhancing gliomas (Figure 2).

Notably, although we observed a significantly higher rate of gadolinium enhancement in *IDH*-mutant WHO grade III gliomas (50/131, 38.2%) compared to their WHO II counterparts (23/139, 16.5%, $p< 0.0001$), this did not clearly influence prognosis as there was no significant difference in PFS between *IDH*-mutant WHO grade II and grade III

gliomas (median PFS of 5.5 years (95% CI 4.6-6.4) for WHO grade II and median 5.9 years (95% CI 4.8-7.1) for WHO grade III, p = 0.65.)

Likewise, the OS of patients with enhancing gliomas was nearly identical to those with non-enhancing gliomas [11.3 years (95% CI 8.0 -14.3) vs. 11.3 years (95% CI 8.3 – 14.3), p = 0.2]. We hypothesized that this lack of association reflects the molecular heterogeneity of the overall cohort, and therefore examined the molecular subgroups separately. We did not observe an association between contrast enhancement and prognosis after stratification within molecular group. Accordingly, although there were 22 deaths in the Group G cohort, only 12 of them demonstrated enhancing features on their MRI scans, suggesting that the poor prognosis commonly associated with *IDH* wild-type LGG is not necessarily correlated with contrast-enhancement.

T2-FLAIR Mismatch analysis

In a recently published study, Broen et al. confirmed a strong association between the T2-FLAIR mismatch sign and classification as an *IDH*-mutant astrocytoma[19]. While this study exclusively included non-enhancing gliomas, we analyzed the mismatch signal in our multi-institutional cohort, which included contrast-enhancing gliomas as well. The results of the analysis are shown in Table 3. Consistent with the prior reports, T2-FLAIR mismatch was preferentially found in Group A tumors, 68.7% and 76% of WHO grades II and III, respectively. Additionally, we observed a mismatch sign in 28% of WHO grade II and 29.5% of WHO grade III oligodendrogliomas (Group O), but none of the tumors in Group G. Furthermore, we evaluated the inter-reviewer consensus with the kappa statistic. The inter-reviewer agreement for T2-FLAIR mismatch was largely consistent ($\kappa = 0.86$, 95% CI, 0.79 – 0.91). We did not observe a difference in PFS of patients in Groups A and O with and without a T2-FLAIR mismatch sign, (Figure 3) suggesting that T2-FLAIR mismatch does not identify cases with different prognosis, within the A and O groups.

Group A probability criteria

We considered that radiographic correlates could be combined with clinical demographic features to robustly identify typical presentations of molecular categories of glioma. In particular, a radiographic method of confidently identifying patients with a Group A glioma preoperatively would have significant clinical utility, as these patients tend to benefit most from aggressive upfront surgical resection [30, 31]. Considering the potential combination of features, we noted that patients younger than 40 years of age with a tumor larger than 6cm in diameter that displays T2-FLAIR mismatch were highly likely to have an *IDH* mutant astrocytoma (Group A), with a specificity of 96% and a positive predictive value of 88% when all three criteria were fulfilled. However, it should be noted that many group A tumors did not fulfill all of these criteria, as there was only 27% sensitivity (Table 4).

Discussion

With the updated WHO 2016 diagnostic criteria, modernization of the radiographic clinical heuristics for decision-making is undergoing re-evaluation, as the relationship between imaging characteristics and the underlying molecular features remains to be fully elucidated.

Utilizing a large cohort of WHO grade II and grade III glioma, our study provides evidence that the conventional MR features of low-grade gliomas do not seamlessly correspond with the new molecular WHO 2016 classification of brain tumors. The evaluation of radiographic metrics in the WHO 2016 era is complex, since many prior metrics were initially developed using mixed molecular cohorts, in populations enriched for *IDH* wild-type high-grade gliomas [32].

Contrast enhancement is one of the most common radiographic features used in clinical practice for prediction of malignant behavior. In addition, it has historically thought to serve as a strong negative prognostic factor [14–16]. In our cohort, although enhancement was present within each molecular subgroup in our study, the *IDH* wild-type Group G, a biologically more aggressive group, exhibited the highest prevalence of contrast enhancement compared with gliomas in Groups A and O (*IDH*-mutant). Interestingly, despite this finding, we did not observe significant outcome differences when comparing enhancing and non-enhancing tumors within each molecular subgroup, suggesting that the prognostic significance of contrast enhancement may lose its impact after controlling for molecular subclass. Thus, contrary to the prevailing assumption, our analysis suggests that contrast enhancement may prove to be a less useful marker of prognosis for LGG. This finding partly confirms the results of a previous study that showed no significant survival differences between patients with and without enhancing *IDH*-mutant gliomas but reported longer survival in patients without gadolinium enhancement in the *IDH* wild-type glioblastomas group [33]. In contrast, we did not detect an improved survival in patients in Group G harboring LGG with no contrast enhancement when compared with their counterparts with enhancement. The difference between our findings and those of Hemple et al. could be explained by the fact that our Group G included exclusively WHO grades II/III gliomas and no glioblastomas. Moreover, we cannot completely exclude the possibility that some of the patients included- in Group G may have actually had other enhancing *IDH* wild-type subtypes of LGGs, such as gangliogliomas or pilocytic astrocytomas.

In contrast to the clinical similarities that have been previously described [34, 35], we did note distinct radiographic differences between *IDH*-mutant WHO grade II and grade III gliomas. *IDH* mutant grade III gliomas were significantly larger at diagnosis and were more likely to exhibit enhancement when compared with their WHO grade II counterparts. On one hand, this finding shows substantial differences in radiologic appearance between grades, corresponding with the histological grading of these tumors. On the other hand, this higher rate of gadolinium enhancement in *IDH*-mutant WHO grade III gliomas does not correspond with a more aggressive clinical course or a higher recurrence rate. Indeed, the PFS of patients with WHO grade II and III gliomas were almost identical (Supplementary Figure 2). This finding further aligns with our observation that the presence of contrast enhancement in *IDH*-mutant gliomas is not an obligate surrogate for poor outcome.

Overall, these observations further highlight the need for improved imaging surrogate biomarkers of prognosis. In keeping with this intention, we expanded upon the recently reported studies that utilized the T2-FLAIR mismatch sign as a diagnostic marker in *IDH*-mutant astrocytic LGGs [18, 19]. We detected the presence of the mismatch sign in a considerably higher rate of gliomas than previously reported [18, 19], potentially explained

by inclusion of *IDH*-mutant WHO grade III and more contrast-enhancing gliomas in our series. Moreover, we were able to detect the T2-FLAIR mismatch sign in a substantial subset of WHO grades II and III oligodendrogliomas, which has not been yet reported. While the mismatch sign was validated in non-enhancing WHO grade II gliomas in the study by Broen et al., our dataset included contrast enhancing tumors. Though useful for predicting which tumors are *IDH*-mutant, the presence of the mismatch sign in either oligodendrogliomas or astrocytomas was not associated with a difference in PFS, limiting its utility as a prognostic tool. Our data nevertheless further validate the specificity of the T2-FLAIR mismatch sign and suggest that it can be applied as a diagnostic tool in both *IDH*-mutant WHO grade II and III gliomas. Since diffusion-weighted imaging (DWI) is considered a valuable MRI tool in the clinical setting, Wu et al. have recently demonstrated that ADC values obtained from DWI correlate with *IDH* mutation status and overall survival in adult diffuse gliomas [36]. The authors concluded that preoperative ADC estimates may corroborate with molecular subtypes as a prognostic marker and potentially enhance risk stratification, especially within *IDH*-mutant gliomas [36].

Finally, we established clinical-radiographic criteria that are specific to patients with *IDH*-mutant astrocytoma, by combining three parameters: age younger than 40 years, large tumor size defined as greatest diameter larger than 6 cm, and the presence of T2-FLAIR mismatch sign. These clinical and radiographic data are straightforward to determine and may find utility in clinical scenarios due to its high specificity. In addition, the predictive positive value of our score rule (88.6%) can be applied to identify patients with *IDH*-mutant astrocytoma in the preoperative setting. With 96% specificity (likelihood ratio of 5.7) for predicting an *IDH*-mutant astrocytoma (Group A), such criteria could be useful for prioritizing patients who will maximally benefit from surgical resection adjuncts, such as intraoperative MRI scanning, since an individual tumor's molecular classification is not typically available at the time of the initial operative procedure [30, 31].

Taken together, our findings demonstrate that the relationship between imaging features and molecular classification is complex, providing evidence that the long-standing usage of contrast enhancement as a marker of prognosis in LGG needs to be re-evaluated. As molecular characterization now plays an instrumental role in predicting tumor behavior, careful clinical and radiologic assessment within specific molecular subgroups may result in the emergence of a prognostic radio-genomic signature in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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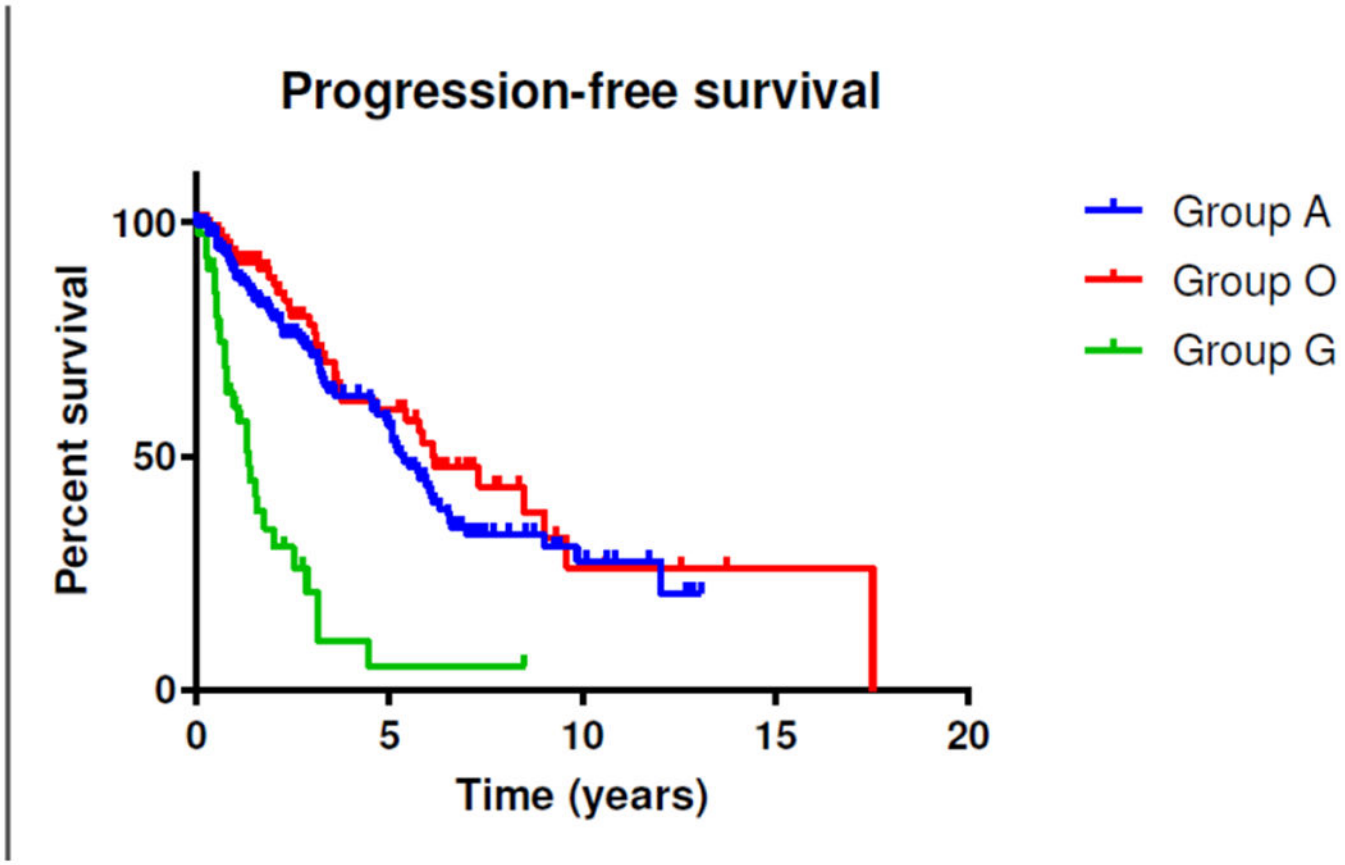

Figure 1:

Kaplan-Meier estimates of progression-free survival in LGG in relation to the molecular groups. Patients in Groups A and O had a significantly longer PFS (5.3 years, 95% CI 4.6 -6.1 years for Group A and 6.1 years, 95% CI 4.3 – 8.0 years for Group O, respectively) than their counterparts in Group G (1.3 years, 95% CI 0.9 – 1.7 years, $p < 0.0001$).

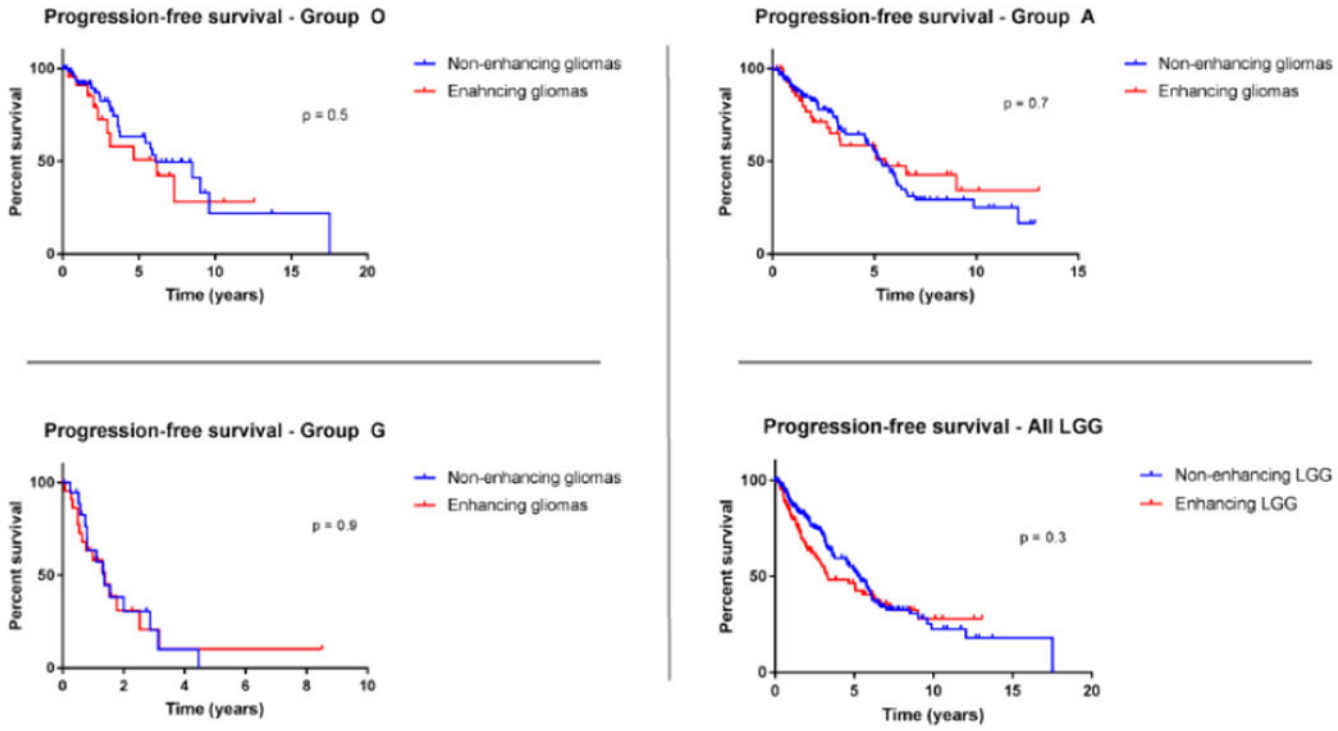

Figure 2:

Kaplan-Meier estimates of progression-free survival in all three LGG molecular groups (A/O/G) in relation to contrast enhancement. Out of 316 patients, 98 patients (31%) showed a contrast-enhancing tumor on their preoperative MR scans. No significant differences in PFS were observed when comparing the enhancing and non-enhancing gliomas.

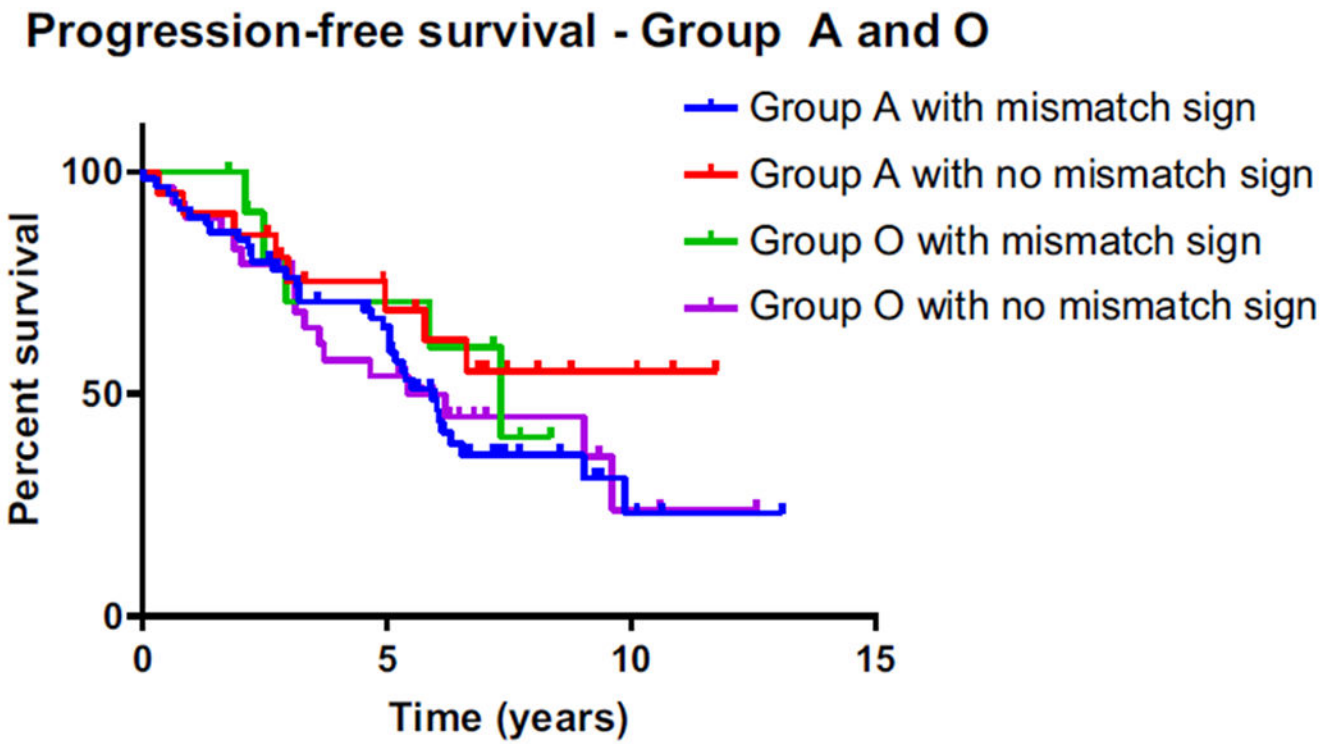

Figure 3:
Kaplan-Meier estimates of progression-free survival in the molecular groups A and O in relation to the T2-FLAIR mismatch sign. The PFS of patients in Groups A and O with and without a T2-FLAIR mismatch sign were similar.

Table 1:

Clinical characteristics of the study patients according to the molecular groups

Characteristic	Total (n=316)	Group O (n=95)	Group A (n=175)	Group G (n=46)
WHO grade				
Grade II	151 (47.8%)	59 (62.1%)	80 (45.7%)	12 (26.1%)
Grade III	165 (52.2%)	36 (37.9%)	95 (54.3%)	34 (73.9%)
Age at diagnosis (years)				
Median	40	43	37	54
Range	18-86	20-86	18-74	23-72
Tumor size				
x-dimension (cm)				
Median	4	3.73	4.24	3.53
Range	1-9.5	1-9.5	1.3-8.4	1-7.4
y-dimension (cm)				
Median	5.9	5.3	6.2	5.2
Range	1.38-12.3	2.3-11.6	1.9-12.3	1.38-10.5
Total area (cm2)				
Median	24.25	19.6	276.46	18.22
Range	1.87-87.87	2.9-87.87	3.23-84	1.87-49.56
Largest tumor diameter				
< 6 cm	163 (51.6%)	53 (55.8%)	82 (46.9%)	28 (60.9%)
≥ 6 cm	153 (48.4%)	42 (44.2%)	93 (53.1%)	18 (39.1%)
Crossing midline				
Yes	56 (17.7%)	23 (24.2%)	28 (16%)	5 (10.9%)
No	260 (82.3%)	72 (75.8%)	147 (84%)	41 (89.1%)

Table 2:

Multivariate Cox regression analysis associated with progression-free survival.

	Hazard ration (HR)	95% CI	p-value
Molecular group (G vs. A/O)	5.2	3.2-7.1	0.000
Tumor size (>6cm vs. < 6cm)	1.6	1.3-2.2	0.007

Further tested variables which were not independent factors were: patients' age at first diagnosis, contrast enhancement in the MRI, tumor crossing the midline and WHO grade II vs. III.

Table 3:

Analysis of the T2-FLAIR mismatch signal in 133 cases from two cohorts (MGH and Dresden)

Molecular group	WHO grade	T2-FLAIR mismatch sign (n=133)
Group A (n=82)	Grade II	22/32 (68.7%)
	Grade III	38/50 (76%)
Group O (n=42)	Grade II	7/25 (28%)
	Grade III	5/17 (29.5%)
Group G (n=9)	Grades II/III	0/9

Table 4:

Group A probability criteria: Patients who were younger than 40 years of age at first diagnosis, with a tumor larger than 6cm in diameter that displays T2-FLAIR mismatch were most likely (96% specificity and likelihood ratio of 5.7) to have an *IDH* mutant astrocytoma (Group A).

Statistic	Value	95% CI
Sensitivity	27.1%	17.99% to 37.79%
Specificity	94.3%	84.34% to 98.82%
Positive Likelihood Ratio	4.7	1.51 to 15.15
Negative Likelihood Ratio	0.77	0.67 to 0.89
Positive Predictive Value	88.4%	70.76% to 96.05%
Negative Predictive Value	44.6%	41.09% to 48.26%
Disease Prevalence	61.6%	52.4% to 69.74%