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Imaging growth and isocitrate dehydrogenase 1 mutation are independent predictors for diffuse low-grade gliomas

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Background. We explored whether spontaneous imaging tumor growth (estimated by the velocity of diametric expansion) and isocitrate dehydrogenase 1 (IDH1) mutation (estimated by IDH1 immunoexpression) were independent predictors of long-term outcomes of diffuse low-grade gliomas in adults.

Methods. One hundred thirty-one adult patients with newly diagnosed supratentorial diffuse low-grade gliomas were retrospectively studied.

Results. Isocitrate dehydrogenase 1 mutations were present in 107 patients. The mean spontaneous velocity of diametric expansion was 5.40 ± 5.46 mm/y. During follow-up (mean, 70 ± 54.7 mo), 56 patients presented a malignant transformation and 23 died. The median malignant progression-free survival and the overall survival were significantly longer in cases of slow velocity of diametric expansion (149 and 198 mo, respectively) than in cases of fast velocity of diametric expansion (46 and 82 mo; $P < .001$ and $P < .001$, respectively) and in cases with IDH1 mutation (100 and 198 mo, respectively) than in cases without IDH1 mutation (72 mo and not reached; $P = .028$ and $P = .001$, respectively). In multivariate analyses, spontaneous velocity of diametric expansion and IDH1 mutation were independent prognostic factors for malignant progression-free survival ($P < .001$; hazard ratio, 4.23; 95% CI, 1.81–9.40 and $P = .019$; hazard ratio, 2.39; 95% CI, 1.19–4.66, respectively) and for overall survival ($P < .001$; hazard ratio, 26.3; 95% CI, 5.42–185.2 and $P = .007$; hazard ratio, 17.89; 95% CI, 2.15–200.1, respectively).

Conclusions. The spontaneous velocity of diametric expansion and IDH1 mutation status are 2 independent prognostic values that should be obtained at the beginning of the management of diffuse low-grade gliomas in adults.

Keywords: isocitrate dehydrogenase 1, low-grade glioma, prognosis, velocity of tumor expansion.

Supratentorial hemispheric diffuse low-grade gliomas (LGGs; World Health Organization [WHO] grade II)[1] are a heterogeneous group of tumors with distinct clinical, histopathological, and molecular characteristics and prognosis. These tumors grow continuously and progress to a higher grade of malignancy, leading to neurological disability and death.[2] Several risk factors allow prognostic refinements for LGGs: clinical parameters (age, preoperative neurological deficit, increased intracranial pressure, seizures), neuroimaging findings (tumor volume, tumor crossing the midline, contrast enhancement, relative cerebral blood volume on dynamic susceptibility contrast MRI), and histopathological and molecular findings (tumor subtype, *TP53* mutation, 1p loss, 1p19q codeletion, proliferation rates).[2–6] More recently, 2 additional prognostic factors have shown a strong and independent prognostic significance on overall survival for LGG: the isocitrate dehydrogenase (*IDH*) 1 gene mutation[7–9] and the spontaneous tumor growth on imaging quantified by the velocity of diametric expansion (VDE) of the tumor.[10–14] *IDH1* mutation

status has been shown to correlate independently with overall survival in gliomas whatever their histopathological grade.[8,9,15] The spontaneous VDE has been shown to correlate independently with malignant progression-free survival and with overall survival.[11,12] In addition, the spontaneous VDE has been shown to reflect the imaging, histopathological, and molecular risk factors for LGGs: LGGs with 1p19q codeletion grow slower and those with p53 overexpression grow faster than those without such abnormalities.[12,16,17] By contrast, IDH1 mutation status has no significant impact on spontaneous VDE.[12,17] Because IDH1 mutations occur at an early stage of the development of LGG[9,18] and are not significantly involved in tumor growth,[17] we hypothesized that spontaneous VDE and IDH1 mutation status are independent predictors of outcomes. The aim of the present retrospective study was to explore (i) whether IDH1 mutation status impacted the spontaneous VDE and (ii) whether the spontaneous VDE and IDH1 mutation status were independent predictors of long-term outcomes of supratentorial LGG in adults.

Methods

Selection Criteria

We searched the databases of a French glioma study group (Réseau d'Etude des Gliomes, Sainte-Anne Hospital, Nancy Hospital, Montpellier Hospital) for cases of adult patients with an LGG from 1992 to 2012. The following minimal criteria were required: (i) patients older than 15 years at histopathological diagnosis; (ii) histopathological diagnosis of WHO grade II glioma (gemistocytic histology excluded)[1]; (iii) supratentorial hemispheric location (gliomatosis cerebri excluded); (iv) available imaging follow-up before first-line oncological treatment (at least 2 MR examinations, minimum 6-wk interval) to estimate spontaneous VDE[10,14]; and (v) available IDH1 mutation status at histopathological diagnosis.

Procedures

The recorded variables gathered from clinical reports at histopathological diagnosis included sex (male vs female), age (<40 y vs ≥40 y), seizure (presence vs absence), neurological deficit (presence vs absence), increased intracranial pressure (presence vs absence), and Karnofsky performance status (>70% vs ≤70%). The recorded imaging characteristics gathered from MRI follow-up included main anatomic location of tumor (frontal vs temporal vs parietal vs insular vs occipital vs deep-seated), number of cerebral lobes involved (<2 vs ≥2), corpus callosum involvement (presence vs absence), tumor volume at diagnosis (<100 cc vs ≥100 cc), spontaneous VDE (<8 mm/y vs ≥8 mm/y), and contrast enhancement (presence with faint and patchy or nodular-like patterns vs absence according to Pallud et al.[6]). The recorded neuropathological characteristics included histopathological subtype (oligodendroglioma vs astrocytoma vs mixed glioma), oligodendroglial component (presence vs absence), proliferation rates (<5% vs ≥5%), 1p19q codeletion status (presence vs absence), TP53 mutation status (assessed by presence vs absence of overexpression of p53 protein), and IDH1 mutation status (presence vs absence) assessed by the research of IDH1 gene mutations in 77 cases (58.8%) and by the research restricted to IDH1 R132H mutation by immunohistochemistry in 54

cases (41.2%). The recorded therapeutic characteristics gathered from clinical reports included treatments (surgical resection, chemotherapy, and radiotherapy), extent of resection (biopsy vs partial removal with residual tumor ≥10 cc vs subtotal removal with residual tumor <10 cc vs total removal with no residual tumor, according to Berger et al.[19]), based on 3-month postoperative MRIs on T2-weighted or fluid attenuated inversion recovery sequences.[19]

Overall survival was defined as the time from histopathological diagnosis to death. Malignant progression-free survival was defined as the time from histopathological diagnosis to demonstration of evidence of malignant transformation or death. Malignant transformation was considered when new contrast enhancement appeared (nodular-like pattern) or progressed if originally present (progressive over time pattern) or when histologically proven.[6] These intervals were censored at the date of last follow-up for survivors.

Estimation of the Individual Velocities of Diametric Expansion on Imaging

The spontaneous imaging tumor growth (ie, the VDE) was measured on serial MR images (various MR techniques, various MR machines) before first-line oncological treatment. The VDE was determined on T2-weighted and fluid attenuated inversion recovery sequences using a methodology detailed elsewhere.[10,14] Tumor volumes were computed on digitized images or calculated using an ellipsoid approximation (volume = D1 × D2 × D3/2) after manual measurements of the 3 largest tumor diameters in 3 orthogonal planes (axial, coronal, and sagittal). The mean tumor diameter (MTD) was deduced from the tumor volume (V) through the formula: $MTD = (2 \times V)^{1/3}$. The VDE (ie, the glioma growth curve) was plotted as a function of MTD over time.

Statistical Analyses

Descriptive results are presented as means ± SD (median, range) for continuous data and percentages for categorical data. Analyses were tailored to address associations among clinical, imaging, histopathological, molecular, and treatment-related variables, spontaneous VDE, and outcomes. Univariate analyses were performed using χ^2 or Fisher's exact tests for categorical variables and the unpaired t-test or Mann–Whitney rank-sum test for continuous variables, as appropriate. Kaplan–Meier analysis was performed for unadjusted survival curves, using log-rank tests to assess significance. Cox proportional hazards models were constructed, adjusting for predictors associated with mortality or malignant transformation in univariate analyses. Variables associated at the $P < .2$ level in unadjusted analysis were then entered into models, with the final model retaining only the variables significant at the $P < .05$ level. $P < .05$ was considered statistically significant. All statistical analyses were performed using JMP version 11.0.0 (SAS Institute).

Results

Patient and Tumor Characteristics

One hundred thirty-one patients (79 males, 52 females) fulfilled eligibility criteria. They were previously reported separately in 4

different series.[12,17,20,21] The mean age at histological diagnosis was 38.0 ± 10.8 years (median, 38.0; range, 15–66), and the mean tumor volume at histological diagnosis was 65.0 ± 50.7 cc (median, 50.0; range, 5–220). Clinical, imaging, histopathological, molecular, and therapeutic findings are summarized in Table 1.

IDH1 mutations were present in 107 cases (81.7%). Distribution of IDH1 mutation status by clinical, imaging, molecular, and therapeutic findings is summarized in Table 1. Codeletion of 1p19q was present in 38 (31.9%) of the 119 available cases. Codeletion of 1p19q was more frequent in tumors with an oligodendroglial component (40.9%) than in astrocytomas (0%; $P <$ .001). Overexpression of p53 was present in 65 (52%) of the 125 available cases. In the same way, p53 overexpression was more frequent in both astrocytomas (73.9%) and oligoastrocytomas (60%) than in oligodendrogliomas (40.3%; $P =$ .009).

Spontaneous Tumor Velocities of Diametric Expansion

The mean number of MRIs performed before treatment was 3.1 ± 1.3 (median, 3.0; range, 2–7) per patient. The mean duration of repeated measurements before treatment was 20.2 ± 30.2 months (median, 9.6; range, 1.6–152.0). The MTD measurements were performed using the ellipsoid approximation in 117 cases (89.3%)[12,17,20] and using the segmentation method in 14 cases (10.7%).[21] The mean tumor spontaneous VDE before first oncological treatment was 5.40 ± 5.46 mm/y (median, 3.75 mm/y; range, 0–31.0 mm/y). When applying the cutoff previously described, 108 patients (82.4%, the slow VDE subgroup) presented a spontaneous VDE slower than 8 mm/y, and 23 patients (17.6%, the fast VDE subgroup) presented a spontaneous VDE equal to or faster than 8 mm/y (Fig. 1).[11,12]

Distribution of spontaneous VDE by clinical, imaging, molecular, and therapeutic findings is summarized in Table 1. Spontaneous VDE tended to be slower in tumors with 1p19q codeletion and tended to be faster in tumors with p53 overexpression without reaching significance (Fig. 1). Spontaneous VDE was not significantly different in tumors with IDH1 mutation (mean, 5.4 ± 5.6 mm/y; median, 3.8; range, 0–31.0) and without IDH1 mutation (mean, 5.2 ± 5.0 mm/y; median, 3.8; range, 0–19.2) ($P =$ .823). Interestingly, there were significantly more tumors with a fast spontaneous VDE in the subgroup of patients who underwent only a biopsy (27.1%) than in the subgroup of patients who underwent a resection (12.1%; $P =$ .032).

Velocity of Diametric Expansion, IDH1 Mutation Status, and Outcomes

The mean follow-up was 70 ± 54.7 months since histological diagnosis (median, 55; range, 3.6–262).

During the follow-up period, 56 patients (42.7%) presented with a malignant progression (histologically proven in 20 cases [35.7%] and suspected on imaging in the remaining 36 cases [64.3%]) at a mean 63.8 ± 50.7 months (median, 51; range, 1.7–233). A malignant progression was observed in 17 of the 23 patients (73.9%) of the fast VDE subgroup at a mean 47.1 ± 42.2 months (median, 36; range, 1.7–163) and in 39 of the 108 patients (36.1%) of the slow VDE subgroup at a mean 71.2 ± 52.9 months (median, 58; range, 5–233). Malignant progression-free survival was significantly longer in the slow VDE subgroup

(median, 149 mo; mean, 142) than in the fast VDE subgroup (median, 46 mo; mean, 56.2) ($P <$ .001; Fig. 2). A malignant progression was observed in 45 of the 107 patients (42.1%) of the subgroup with IDH1 mutation at a mean 70.0 ± 53.6 months (median, 55; range, 1.7–233) and in 11 of the 24 patients (45.8%) of the subgroup without IDH1 mutation at a mean 38.4 ± 24.8 months (median, 30; range, 5–88.5). Malignant progression-free survival was significantly longer in the subgroup with IDH1 mutation (median, 100 mo; mean, 131.2) than in the subgroup without IDH1 mutation (median, 72 mo; mean, 60.6) ($P =$ .028; Fig. 2). In the subgroup of 107 patients with IDH1 mutation, malignant progression-free survival remained significantly longer in the slow VDE subgroup (median, 169 mo; mean, 149.3) than in the fast VDE subgroup (median, 46 mo; mean, 54.4) ($P <$ .001; Fig. 2). In the subgroup of 108 patients with a slow VDE, malignant progression-free survival remained significantly longer in the subgroup with IDH1 mutation (median, 169 mo; mean, 149.3) than in the subgroup without IDH1 mutation (median, 72 mo; mean, 53.0) ($P =$ .009). When compiling the 2 parameters, malignant progression-free survival was significantly longer in the subgroup with IDH1 mutation and slow VDE (median, 169 mo; mean, 149.2) than in the subgroup with IDH1 mutation only or with slow VDE only (median, 58.3 mo; mean, 67.2) and in the subgroup without IDH1 mutation and with fast VDE (median, 46 mo; mean, 56.0) ($P <$ .001).

During the follow-up period, 23 patients (17.6%) died at a mean 77.3 ± 59.6 months (median, 111; range, 5–198). A death was observed in 10 of the 23 patients (43.5%) of the fast VDE subgroup at a mean 57.2 ± 48.1 months (median, 38; range, 5–163) and in 13 of the 108 patients (12.0%) of the slow VDE subgroup at a mean 92.8 ± 64.6 months (median, 91; range, 12–198). Overall survival was significantly longer in the slow VDE subgroup (median, 198 mo; mean, 166.1) than in the fast VDE subgroup (median, 82 mo; mean, 73.6) ($P <$ .001; Fig. 2). Death was observed in 18 of the 107 patients (16.8%) of the subgroup with IDH1 mutation at a mean 94.0 ± 56.7 months (median, 87.5 mo; range, 20–198) and in 5 of the 24 patients (20.8%) of the subgroup without IDH1 mutation at a mean 17.4 ± 11.0 months (median, 12 mo; range, 5–30). Overall survival was significantly longer in the subgroup with IDH1 mutation (median, 198 mo; mean, 159.3) than in the subgroup without IDH1 mutation (median, not reached; mean, 27.0 mo) ($P =$ .001; Fig. 2). In the subgroup of 107 patients with IDH1 mutation, overall survival remained significantly longer in the slow VDE subgroup (median not reached; mean, 172.9 mo) than in the fast VDE subgroup (median, 84 mo; mean, 96.3) ($P <$ .001; Fig. 2). In the subgroup of 108 patients with a slow VDE, overall survival remained significantly longer in the subgroup with IDH1 mutation (median not reached; mean, 172.9 mo) than in the subgroup without IDH1 mutation (median not reached; mean, 27.8 mo) ($P =$ .014). When compiling the 2 parameters, overall survival was significantly longer in the subgroup with IDH1 mutation and slow VDE (median not reached; mean, 172.9 mo) than in the subgroup with IDH1 mutation only or with slow VDE only (median, 92 mo; mean, 103.4) and in the subgroup without IDH1 mutation and with fast VDE (median not reached; mean, 22.3 mo) ($P <$ .001).

In univariate analysis (Table 2), predictors of malignant progression-free survival were spontaneous VDE ($P <$ .001), tumor volume ($P =$ .022), IDH1 mutation status ($P =$ .042), first-line resection ($P =$ .018), and extent of surgical resection ($P =$ .038).

Table 1. Patient and tumor characteristics

Parameters	n	Spontaneous VDE (mm/y)				IDH1 Mutation Status		
		Mean ± SD	Median	Range	P	IDH1 +	IDH1−	P
Clinical parameters								
Sex	131				.592			.477
Male	79	5.2 ± 4.4	3.7	0–22.6		79.8%	20.2	
Female	52	5.7 ± 6.8	3.8	0–31.0		84.6	15.4	
Age	131				.887			**.031**
<40	75	5.8 ± 6.4	3.7	0–31.0		88.0	12.0	
≥40	56	4.9 ± 4.0	3.9	0–19.2		73.2	18.3	
Increased intracranial pressure	109				.973			.343
Yes	2	11.0 ± 15.8	11.0	0–31.0		50.0	50.0	
No	107	5.0 ± 5.1	3.6	0–22.0		80.4	19.6	
Neurological deficit	109				.271			.180
Yes	20	6.5 ± 7.0	4.6	0–27.9		90.0	10.0	
No	89	4.8 ± 4.9	3.5	0–31.0		77.5	22.5	
Seizures	109				.156			.365
Yes	78	5.6 ± 5.9	3.1	0–31.0		82.1	17.9	
No	31	3.8 ± 3.2	3.8	0–15.0		74.2	25.8	
KPS	131				**.005**			.114
>70%	125	5.1 ± 5.3	3.7	0–31.0		80.8	19.2	
≤70%	6	11.4 ± 6.6	9.9	4.7–22.0		100.0	0	
Imaging parameters								
Cerebral lobes involved	118				.119			.054
<2	79	4.8 ± 5.3	3.5	0–31.0		88.6	11.4	
≥2	39	6.5 ± 5.7	4.7	0–22.6		74.4	25.6	
Corpus callosum involvement	117				.434			.410
No	105	5.0 ± 5.3	3.7	1.1–31.0		84.8	15.2	
Yes	12	7.6 ± 7.0	6.8	0–22.6		75.0	25.0	
Tumor location	131				.666			.509
Frontal	62	5.2 ± 5.9	3.4	0–31.0		80.7	19.4	
Temporal	22	6.7 ± 7.1	3.9	0–28.0		77.3	22.7	
Insular	31	5.0 ± 3.5	4.7	0.4–14.2		80.7	19.3	
Parietal	16	5.1 ± 4.1	3.7	0.6–16.9		93.8	6.2	
Contrast enhancement	131				.582			.449
No	121	5.2 ± 5.0	3.8	0–31.0		81.0	19.0	
Yes	10	7.5 ± 9.9	2.4	0–27.9		90.0	10.0	
Tumor volume	131				.778			.589
<100 cc	104	5.2 ± 5.3	5.8	0–31.0		80.8	19.2	
≥100 cc	27	6.4 ± 6.1	3.6	0–22.6		85.2	14.8	
Spontaneous VDE	131							.898
<8 mm/y	108					81.5	18.5	
≥8 mm/y	23					82.6	17.4	
Histopathological and molecular parameters								
Histopathological diagnosis	131				.536			.087
Astrocytoma	25	5.5 ± 5.5	4.0	0.4–27.9		72.0	28.0	
Oligodendroglioma	71	5.3 ± 5.8	3.7	0–31.0		88.6	11.4	
Mixed glioma	35	5.6 ± 4.9	4.6	0–22.9		75.0	25.0	
Oligodendroglial component	131				.526			.222
Yes	106	5.4 ± 5.5	3.7	0–31.0		83.8	18.2	
No	25	5.5 ± 5.5	4.0	0.4–27.9		72.0	28.0	
Proliferation rates	115				.888			.914
<5%	70	5.4 ± 5.9	3.5	0–31.0		81.4	18.6	
≥5%	45	5.1 ± 4.7	3.7	0–22.0		82.2	17.8	

Continued

Table 1. *Continued*

Parameters	n	Spontaneous VDE (mm/y)				IDH1 Mutation Status		
		Mean ± SD	Median	Range	P	IDH1 +	IDH1−	P
1p19q Codeletion	119				.077			.497
Yes	38	5.0 ± 6.0	3.1	0–31.0		79.0	20.1	
No	81	5.6 ± 5.0	4.4	0–27.9		84.2	15.8	
p53 Overexpression	125				.202			.250
Yes	65	5.8 ± 5.2	4.4	0–27.9		86.2	13.8	
No	60	5.0 ± 5.6	3.5	0–31.0		78.3	21.7	
IDH1 mutation	131				.823			
Yes	107	5.4 ± 5.6	3.8	0–31.0				
No	24	5.2 ± 5.0	3.8	0–19.2				
First-line oncological treatments								
Surgical resection	131				.236			.574
Yes	83	4.5 ± 4.2	3.6	0–31.0		83.1	16.9	
No	48	6.8 ± 6.9	4.0	0.5–27.9		79.2	20.8	
Extent of surgical resection	131				.396			.339
Biopsy	48	6.9 ± 7.7	4.0	0.5–27.9		79.2	20.8	
Partial removal	16	4.4 ± 3.2	3.7	0–12.3		87.5	12.5	
Subtotal removal	49	4.5 ± 3.1	4.0	0–15.0		83.7	16.3	
Total removal	18	4.8 ± 7.1	3.2	0–31.0		77.8	22.2	
Radiation therapy	131				.467			.158
Yes	23	6.7 ± 5.8	4.5	0.6–22.6		91.3	8.7	
No	108	5.1 ± 5.4	3.6	0–31.0		79.6	20.4	
Chemotherapy	131				**.040**			.099
Yes	14	3.7 ± 4.6	2.6	0.4–19.2		64.3	35.7	
No	117	5.6 ± 5.5	4.0	0–31.0		83.8	16.2	

Boldface indicates statistically significant.

Predictors of overall survival were sex ($P = .002$), presence of seizures at diagnosis ($P = .011$), contrast enhancement ($P = .001$), tumor volume ($P = .022$), corpus callosum involvement ($P = .042$), spontaneous VDE ($P < .001$), 1p19q codeletion ($P = .031$), *IDH1* mutation status ($P = .044$), first-line resection ($P = .042$), and extent of surgical resection ($P = .031$). In multivariate analysis (Table 2), independent prognostic factors for malignant progression-free survival were increased intracranial pressure ($P = .024$), parietal tumor location ($P = .019$), spontaneous VDE ($P = .001$), *IDH1* mutation status ($P = .019$), surgical resection ($P = .015$), and extent of surgical resection (partial, $P = .021$; total, $P = .025$). Independent factors for overall survival were male sex ($P = .001$), tumor volume ($P = .017$), spontaneous VDE ($P < .001$), *IDH1* mutation status ($P = .007$), and extent of surgical resection (subtotal, $P = .038$).

Discussion

We show for the first time in a retrospective exploratory dataset of 131 homogeneous cases that *IDH1* mutation status represents an independent prognostic factor for LGG clinical outcome among adult patients, together with the spontaneous VDE that reflects the imaging tumor growth. Specifically, we find that they are associated, independently from each other, with better malignant progression-free survival and overall survival, whatever the clinical, imaging, histopathological, and molecular findings,

including 1p19q codeletion and *p53* overexpression. Thus, the determination of spontaneous VDE and *IDH1* mutation status adds to the 1p19q codeletion status in determining outcomes of adult patients harboring an LGG.

In LGGs, *IDH1* mutation proved to have significant impact on overall survival only,[8,17,22–25] although with contradictory results,[26,27] which may be explained by the heterogeneity of the histopathological LGG subgroup. Here, we confirm that *IDH1* mutation impacts both malignant progression-free survival and overall survival of LGGs. However, the small number of observed deaths in the present study limits the observation. Further study with a longer follow-up period is needed. *IDH1* mutation and 1p19q codeletion are independent favorable prognostic factors for LGGs, but previous studies showed that these molecular parameters are closely associated.[15,17] Moreover, 1p19q codeletion status affects the imaging tumor growth, although *IDH1* mutation does not. Thus, ignoring the effects of 1p19q codeletion, of *IDH1* mutation status, and of spontaneous VDE, along with their interactions, while estimating their prognostic significance could lead to serious bias. We thus incorporated these parameters in the statistical modeling. In addition, we confirmed these results obtained on the whole series by performing complementary statistical analyses on the subgroup of LGGs with an *IDH1* mutation ($n = 107$) and on the subgroup of LGGs with a slow VDE ($n = 108$).

In addition, we confirm that *IDH1* mutation status does not significantly impact the spontaneous VDE, in accordance with
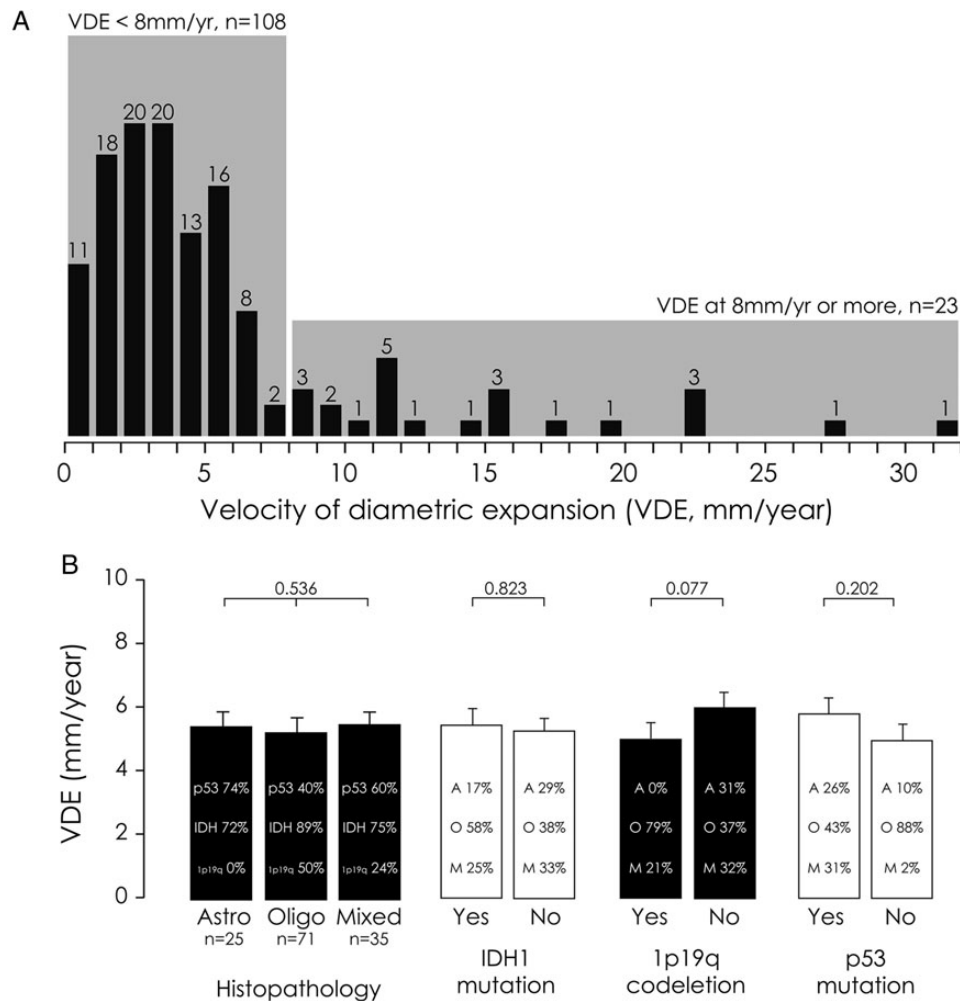
Fig. 1. (A) Distribution of the 131 patients by individual spontaneous VDEs (mm/y). (B) Molecular factors influencing the spontaneous VDE of LGGs.

previous reports[12,17] and in accordance with the conflicting results of the effects of *IDH1* mutation on glioma cell proliferation in experimental preparations.[28–30] These findings reinforce the hypothesis that *IDH* mutations, because of their precocity, might be considered instead as a causative link between early cellular metabolism disturbances and the emergence of other driving molecular events in gliomagenesis[15,17] in accordance with particular associations of gene mutations in brain tumors.[31–33]

The main limitation of the present retrospective study is the use of different techniques to assess *IDH1* mutation status. The research of *IDH1* gene mutations was the most frequent technique, performed in 77 cases (58.8%),[17,21] and the research restricted to *IDH1* R132H mutation by immunohistochemistry was performed in only 54 cases (41.2%).[12,20] *IDH2* mutations, present in only 2%–3% of gliomas,[34] are unlikely to alter the present results. Of note, an *IDH2* mutation was present in 3 cases of the subgroup of LGGs without *IDH1* mutation (3.8%), 1 of them corresponding to the unique patient of this subgroup who is alive without malignant transformation at 130 months follow-up (see Fig. 2).[17,21] Altogether, these findings should be interpreted with caution, given the inherent limitations arising from the retrospective study design and the possible bias resulting from the *IDH* mutation screening in this exploratory dataset.

Outcomes of LGGs vary considerably; the wide ranges of prognoses reflect the heterogeneity of LGGs and could be explained by the limitations of the histopathological diagnosis. Molecular markers, particularly 1p19q codeletion, *p53* expression, and *IDH1* mutation status, have improved diagnostic accuracy and refined prognosis. Although spontaneous VDE was shown to correlate with molecular markers, it represents an independent prognostic parameter for overall survival and for malignant progression-free survival and may help in predicting the natural history of LGGs.[11,12] As the spontaneous VDE adds to *IDH1* mutation status and to 1p19q codeletion status in determining outcomes, we propose that the spontaneous VDE could be integrated together with the other known prognostic parameters, including *IDH1* mutation status, 1p19q codeletion status, and *p53* overexpression, in a multidimensional approach to better predict the outcomes of an LGG at the individual level. Finally, the assessment of the prognostic significance of the spontaneous VDE is clinically relevant and would require prospective validation within the context of multicenter clinical trials.
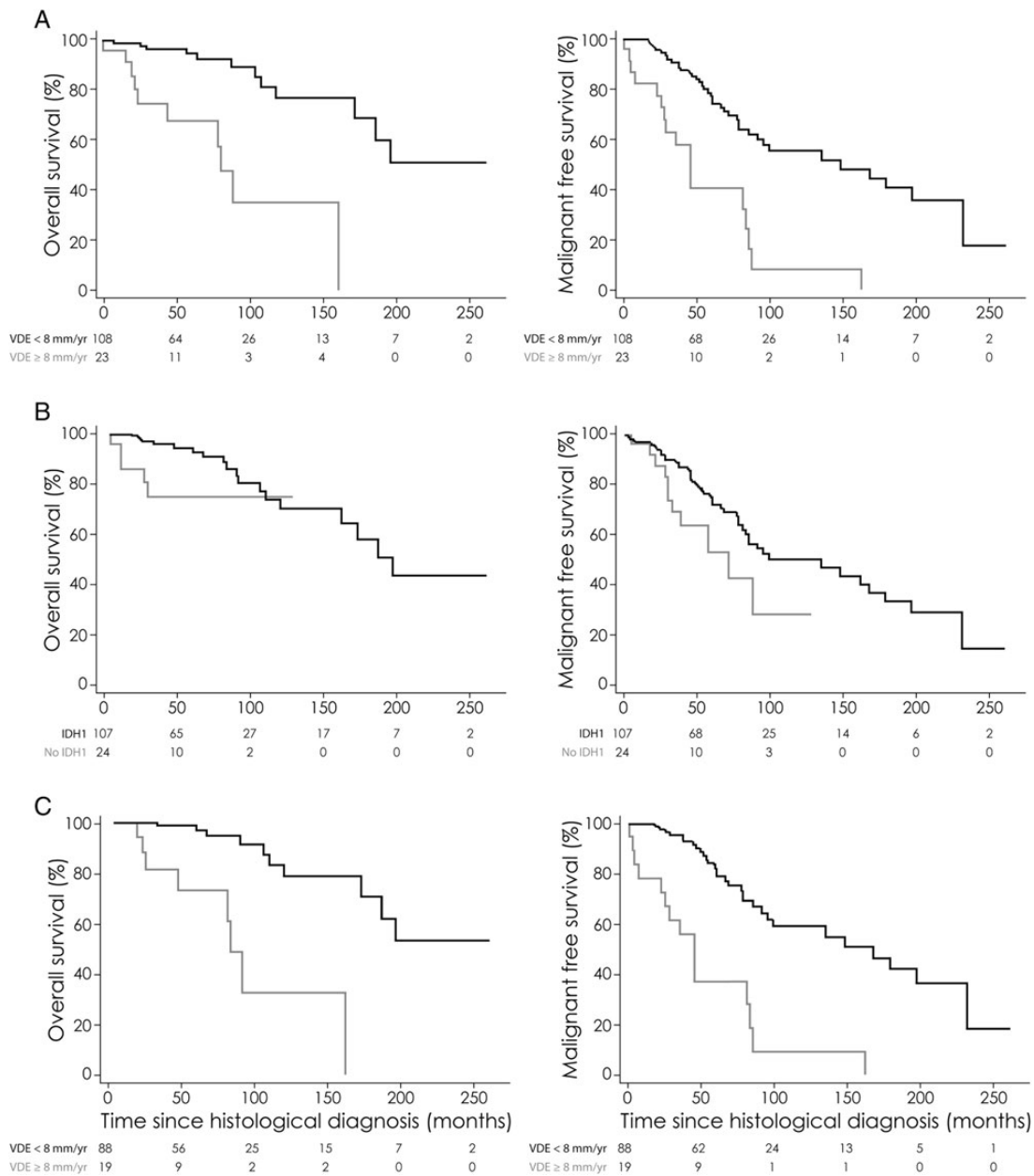
Fig. 2. Kaplan–Meier estimates of overall survival and malignant progression-free survival according to spontaneous VDE and *IDH1* mutation status. (A) Overall survival and malignant progression-free survival according to VDE (cutoff at 8 mm/y) ($n = 131$). The unadjusted hazard ratio for death among patients harboring an LGG with a spontaneous VDE ≥8 mm/y compared with those harboring an LGG with a spontaneous VDE <8 mm/y was 6.61 (95% CI, 2.69–12.2; $P < .001$). The unadjusted hazard ratio for death or malignant progression among patients harboring an LGG with a spontaneous VDE ≥8 mm/y compared with those harboring an LGG with a spontaneous VDE <8 mm/y was 4.18 (95% CI, 2.30–7.35; $P < .001$). (B) Overall survival and malignant progression-free survival according to *IDH1* mutation status ($n = 131$). The unadjusted hazard ratio for death among patients harboring an LGG without an *IDH1* mutation compared with those harboring an LGG with an *IDH1* mutation was 3.27 (95% CI, 1.03–8.84; $P = .044$). The unadjusted hazard ratio for death or malignant progression among patients harboring an LGG without an *IDH1* mutation compared with those harboring an LGG with an *IDH1* mutation was 2.05 (95% CI, 1.03–3.79; $P = .042$). (C) Overall survival and malignant progression-free survival according to VDE (cutoff at 8 mm/y) in the subgroup of patients with an *IDH1* mutation ($n = 107$). The unadjusted hazard ratio for death among patients harboring an LGG with a spontaneous VDE ≥8 mm/y compared with those harboring an LGG with a spontaneous VDE <8 mm/y was 8.49 (95% CI, 3.01–24.4; $P < .001$). The unadjusted hazard ratio for death or malignant progression among patients harboring an LGG with a spontaneous VDE ≥8 mm/y compared with those harboring an LGG with a spontaneous VDE<8 mm/year was 5.16 (95% CI, 2.64–9.73; $P < .001$).

Table 2. Survival analyses

Parameters	Overall Survival						Malignant Progression-free survival					
	Unadjusted Hazard Ratio (HR)			Adjusted Hazard Ratio			Unadjusted Hazard Ratio			Adjusted Hazard Ratio		
	HR	95% CI	*P*	HR$_a$	95% CI	*P*	HR	95% CI	*P*	HR$_a$	95% CI	*P*
Clinical parameters												
Sex												
Female	1 (ref)						1 (ref)					
Male	5.06	1.72–21.5	**.002**	10.22	2.58–17.8	**.001**	162	0.94–2.88	.082	1.77	0.88–3.74	.108
Age												
<40	1 (ref)						1 (ref)					
≥40	1.10	0.48–2.60	.821				1.26	0.74–2.18	.389			
Increased intracranial pressure												
No	1 (ref)						1 (ref)					
Yes	1.58	0.79–2.09	.667				5.33	0.85–17.9	.067	11.31	1.44–59.7	**.024**
Neurological deficit												
No	1 (ref)						1 (ref)					
Yes	1.03	0.26–5.18	.964				1.25	0.56–2.52	.562			
Seizures												
Yes	1 (ref)						1 (ref)					
No	4.13	1.40–11.6	**.011**	3.69	0.56–20.4	.161	1.12	0.58–2.38	.752			
KPS												
>70	1 (ref)						1 (ref)					
≥70	2.84	0.44–10.1	.224				2.32	0.70–5.76	.151	1.30	0.18–5.38	.745
Imaging parameters												
Cerebral lobes involved												
1	1 (ref)						1 (ref)					
≥2	1.99	0.84–4.7	.113	2.31	0.37–16.1	.373	1.36	0.73–2.42	.314			
Corpus callosum involvement												
No	1 (ref)						1 (ref)					
Yes	4.69	1.07–14.6	**.042**	1.35	0.19–7.83	.743	2.03	0.61–5.02	.220			
Anatomic location												
Frontal	1 (ref)						1 (ref)					
Temporal	1.63	0.57–4.32	.352				1.94	0.93–3.83	.074	2.05	0.63–5.95	.215
Parietal	1.43	0.31–4.69	.599				1.92	0.84–4.01	.116	4.20	1.28–12.99	**.019**
Insular	0.92	0.21–2.99	.896				1.53	0.72–3.07	.252	2.29	0.53–8.12	.069
Contrast enhancement												
No	1 (ref)						1 (ref)					
Yes	1.79	0.03–2.67	**.001**	2.29	0.02–21.5	.774	1.95	0.74–4.24	.159	1.98	0.67–5.04	.206
Tumor volume, cm^3												
<100	1 (ref)						1 (ref)					
≥100	2.44	1.15–4.72	**.0022**	9.69	1.49–70.1	**.017**	2.44	1.14–4.72	**.022**	1.41	0.47–3.76	.514
VDE												
<8 mm/y	1 (ref)						1 (ref)					
≥8 mm/y	6.61	2.69–12.2	**<.0001**	26.3	5.42–185.2	**<.0001**	4.18	2.30–7.35	**<.0001**	4.23	1.81–9.40	**.001**
Histopathological parameters												
Histological subtype												
Astrocytoma	1 (ref)						1 (ref)					
Oligodendroglioma	0.94	0.31–4.09	.926				0.92	0.45–2.05	.819			
Mixed glioma	0.88	0.22–4.35	.873				1.09	0.48–2.67	.826			
Oligodendroglial component												
Yes	1 (ref)						1 (ref)					
No	1.41	0.40–3.81	.549				0.91	0.47–1.94	.806			
Proliferation rates												
<5%	1 (ref)						1 (ref)					
≥5%	1.28	0.53–3.27	.577				1.13	0.62–2.02	.684			

Continued

Table 2. *Continued*

Parameters	Overall Survival						Malignant Progression-free survival					
	Unadjusted Hazard Ratio (HR)			Adjusted Hazard Ratio			Unadjusted Hazard Ratio			Adjusted Hazard Ratio		
	HR	95% CI	*P*	HR$_a$	95% CI	*P*	HR	95% CI	*P*	HR$_a$	95% CI	*P*
1p19q Codeletion												
Yes	1 (ref)						1 (ref)					
No	3.91	1.11–24.7	**.031**	2.92	0.35–60.9	.353	1.50	0.80–2.87	.220			
p53 Overexpression												
No	1 (ref)						1 (ref)					
Yes	2.42	0.95–7.41	.062	1.38	0.26–11.32	.720	1.33	0.77–2.34	.307			
IDH1 expression												
Yes	1 (ref)						1 (ref)					
No	3.27	1.03–8.84	**.044**	17.86	2.15–200.1	**.007**	2.05	1.03–3.79	**.042**	2.39	1.19–4.66	**.019**
Therapeutic parameters												
First-line surgery												
No	1 (ref)						1 (ref)					
Yes	0.41	0.16–0.97	**.042**	2.05	0.57–7.83	.270	0.53	0.31–0.90	**.018**	0.40	0.20–0.83	**.015**
First-line surgery												
Biopsy	1 (ref)						1 (ref)					
Partial removal	0.18	0.01–0.88	**.031**	0.21	0.04–1.52	.088	0.44	0.15–1.05	.067	0.27	0.07–0.83	**.021**
Subtotal removal	0.59	0.21–1.47	.265	0.22	0.05–0.91	**.038**	0.64	0.34–1.14	.127	0.51	0.24–1.11	.091
Total removal	0.31	0.02–1.58	.188	0.23	0.02–6.99	.349	0.34	0.08–0.94	**.038**	0.25	0.05–0.85	**.025**

Boldface indicates statistically significant.

As a practical consequence, the spontaneous VDE should be measured systematically[10,12,14] at the beginning of the management of an LGG without delaying treatment and should be added to the other known risk parameters (Pignatti and Chang prognostic scores, contrast enhancement, astrocytoma subtype, 1p19q codeletion, *p53* overexpression, *IDH1* mutation)[2,4–6,8] to adapt treatment and follow-up on an individual basis. Patients with a fast VDE should be considered as "high-risk," with an increased risk of early malignant transformation, particularly in cases where only a biopsy has been performed due to the possible risk of undergrading. Because these LGGs share outcomes similar to those of malignant gliomas, treatment modalities should be selected accordingly, and a 3-month follow-up should be preferred.[12]

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