Natural History and Growth Patterns of Incidentally Discovered Diffusely Infiltrating Low-Grade Gliomas: A Volumetric Study

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■ BACKGROUND: **Incidentally discovered diffusely infiltrating low-grade gliomas (iDLGGs) are rare findings on neuroimaging that pose a challenge to neurosurgeons. There is a paucity of data regarding the natural history of these lesions, and thus management is controversial. We characterize the growth rates and patterns of iDLGGs in a cohort of patients who underwent serial magnetic resonance imaging before surgical treatment.**

■ METHODS: **We performed a retrospective review of all adult patients (≥18 years old) with diffuse low-grade glioma diagnosed at our institution between April 2004 and April 2016. iDLGG was defined as any lesion discovered on computed tomography or magnetic resonance imaging performed for reasons and/or symptoms not attributable to the lesion and confirmed on histopathology as low-grade glioma. Tumor growth rates and patterns of growth were analyzed in patients who had serial imaging available.**

■ RESULTS: **Inclusion criteria were met by 15 patients. Mean velocity of diametric expansion was 2.93 mm/year. Of 15 patients, 11 (73.3%) had tumors with an exponential growth pattern, and 4 (26.7%) had a linear growth pattern. Initial tumor volume was positively correlated ($r = 0.78$) with velocity of diametric expansion.**

■ CONCLUSIONS: **iDLGGs grow over time, and most exhibit an exponential pattern of growth. Tumor volume at the time of diagnosis is predictive of a faster growth rate, but not the pattern of growth.**

INTRODUCTION

Historically, the World Health Organization (WHO) classification of central nervous system (CNS) tumors was based on histopathologic features predicated on cell type and features of malignancy. Diffuse low-grade gliomas (DLGGs) were conventionally defined as WHO grade II CNS tumors that arise from astrocytic and oligodendrocytic precursors with only atypia, but without high mitotic activity, microvascular proliferation, or necrosis.[1,2] However, over the past few decades, there has been a paradigm shift in CNS tumor nomenclature, as mounting evidence underscores the role of molecular genetics in tumor characteristics, response to treatment, and prognosis. A 2016 WHO update has subsequently redefined DLGGs based on molecular features and is based on genetic alterations of the *IDH1/2*, *ATRX*, and *TP53* genes together with chromosomes 1p and 19q codeletion.[3]

DLGGs were traditionally considered as slowly progressing benign lesions[4] and were typically managed conservatively with serial imaging, especially if the associated symptoms (i.e., controlled seizures) were tolerable by the patient. Gui et al.[5] recently reported a series of 10 patients with DLGG who underwent at least 8 magnetic resonance imaging (MRI) scans of the brain to monitor disease progression and found that tumor diameter increased in a linear fashion, at an average rate of 2.17 mm per year. However, other clinical and experimental studies have demonstrated that untreated DLGGs can undergo malignant differentiation into higher grade neoplasms,[6] often with extensive infiltration that precludes curative surgery.[7,8] Other studies have also shown that early surgical intervention with maximal safe resection of DLGGs improves overall survival.[7,9] Thus, this raises concerns with the dogma of a wait-and-see treatment approach, and some centers have been proactive in resecting DLGGs on discovery.

Key words
- Asymptomatic
- Growth rate
- Incidental
- Low-grade glioma
- Natural history

Abbreviations and Acronyms
CNS: Central nervous system
DLGG: Diffuse low-grade glioma
D_{mean}: Mean tumor diameter
iDLGG: Incidentally discovered diffusely infiltrating low-grade glioma
MRI: Magnetic resonance imaging
VDE: Velocity of diametric
WHO: World Health Organization

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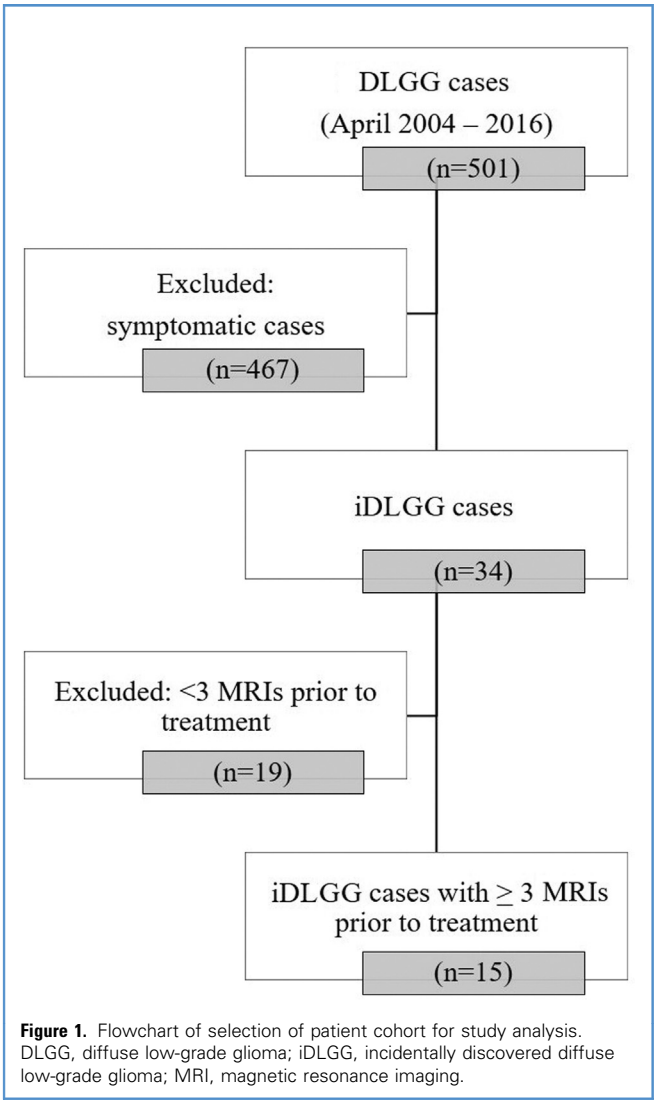

Figure 1. Flowchart of selection of patient cohort for study analysis. DLGG, diffuse low-grade glioma; iDLGG, incidentally discovered diffuse low-grade glioma; MRI, magnetic resonance imaging.

Patients harboring DLGGs usually present with associated symptoms, such as headaches, seizures, focal neurologic deficits, and cognitive difficulties. However, in the present era of easy accessibility to neuroimaging, incidentally discovered DLGGs (iDLGGs) are becoming more prevalent.[10] iDLGGs pose a unique management challenge to patients and treating physicians in light of the current evidence, as most iDLGGs are small and discovered in young patients.[11,12] To inform appropriate treatment approaches to iDLGGs, adequate understanding of the natural history of these tumors is an imperative first step. Using a cohort of patients who underwent serial imaging at our institution, we set out to 1) assess tumor growth rates, 2) assess growth patterns, and 3) elucidate any factors that may be predictive of the growth and natural history of iDLGGs.

MATERIALS AND METHODS

Patient Selection

This study was approved by the Conjoint Health Research Ethics Board. Individual patient consent was not required, as this was a retrospective study and some of the patients involved were not alive. Adult patients (≥18 years old) with DLGG diagnosed and treated at our institution between April 2004 and April 2016 were retrospectively reviewed. An iDLGG was defined as a DLGG identified on computed tomography or MRI that was performed for reasons and/or symptoms not attributable to the lesion. All iDLGGs were confirmed by histopathologic and molecular genetic diagnosis based on WHO 2016 CNS tumor classification system. Only patients with at least 3 consecutive MRI scans were included in the analysis. All symptomatic patients and patients with radiographic or histopathologic suggestion of high-grade glioma at the time of initial presentation were excluded. Patients' demographic information and general medical comorbidities were assessed.

Tumor Volumetric Analysis

Digital Imaging and Communications in Medicine images were obtained for all patients with iDLGGs with at least 3 consecutive MRI scans from the time of diagnosis until surgery or biopsy was performed. Tumor volumetric analysis of fluid attenuated inversion recovery or T2-weighted MRI sequences was performed using OsiriX software (Pixmeo SARL, Bernex, Switzerland). Regions of interest were manually segmented around the borders of the tumor to compute tumor volumes (cm^3). The mean tumor diameter (D_{mean}) was calculated from the tumor volume (V) as: $D_{mean} = (2 \cdot V)^{1/3}$.[13] Tumor growth curves were then plotted. For consistency, all measurements were done by 1 author (M.C.).

Evaluation of Growth Rate and Pattern

Tumor growth rates were determined by plotting a D_{mean}—time graph and computing the slope of the graph as ($\Delta D_{mean}/\Delta$time). This is reported as the velocity of diametric expansion (VDE) (mm/year) for each patient. Correlation between VDE and characteristics such as initial tumor volume at time of diagnosis, age, sex, and tumor histology was performed. Tumor volume calculated at each follow-up examination was plotted on volume-time coordinates for each patient. Growth curves were fitted to both exponential and linear growth. A regression analysis was then performed for the growth. Tumor growth pattern was categorized as linear or exponential based on the larger R^2 value.[14]

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad Software, San Diego, California, USA). Regression analysis and other statistical analyses, such as Fisher exact test and Mann-Whitney U test for independence, were performed. A P value <0.05 was considered statistically significant.

RESULTS

Patient Population

Of the 501 cases of newly diagnosed DLGGs over a 12-year period, 34 (6.8%) were incidentally discovered (iDLGGs). Of the 34 iDLGG cases, 15 (44%) had at least 3 consecutive MRI scans performed and were used for our analysis (Figure 1). Of the 15 patients, 7 were men and 8 were women. The mean age at presentation was 43 years (range, 20—62 years). The mean initial tumor volume was 25.07 cm^3 (range, 2.31—121 cm^3) with a mean

Table 1. Patient Characteristics and Regression Analysis with Growth Patterns

Case	Age at Diagnosis (Years)/Sex	Mode of Discovery	2016 WHO Diagnosis	Vdx (cm^3)	R^2 (Expo.)	R^2 (Linear)	Growth Pattern	VDE (mm/Year)	Follow-Up (Months)
1	44/M	Hearing loss	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	2.31	0.887*	0.811	Expo.	0.44	161
2	46/M	Headaches	Oligodendroglioma, NOS	4.11	0.870	0.903*	Linear	0.85	60
3	57/F	Screening	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	7.43	0.777*	0.744	Expo.	0.89	35
4	20/F	Headaches	Diffuse astrocytoma, *IDH* mutant	2.31	0.951*	0.834	Expo.	1.62	60
5	62/F	Facial tics	Diffuse astrocytoma, *IDH* wild-type	35.4	0.932	0.944*	Expo.	1.73	25
6	47/M	Screening	Diffuse astrocytoma, *IDH* mutant	11.1	0.978*	0.957	Linear	1.75	95
7	34/M	Nonspecific symptoms	Diffuse astrocytoma, *IDH* mutant	2.67	0.924	0.956*	Expo.	2.04	37
8	36/F	Dizziness	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	4.28	0.933*	0.922	Linear	2.35	45
9	34/M	Nonspecific symptoms	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	40.5	0.994*	0.965	Expo.	3.06	133
10	32/M	Screening	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	5.78	0.998*	0.988	Expo.	3.38	14
11	32/F	Screening	Diffuse astrocytoma, *IDH* mutant	40.4	0.907*	0.884	Expo.	3.70	24
12	62/F	Nonspecific symptoms	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	27.4	0.970*	0.955	Expo.	4.54	10
13	55/F	Headaches	Oligodendroglioma, *IDH* mutant and 1p19q codeleted	27.8	0.977	0.991*	Expo.	4.77	23
14	41/M	Trauma	Diffuse astrocytoma, *IDH* mutant	43.6	0.979*	0.975	Linear	5.88	11
15	49/F	Nonspecific symptoms	Diffuse astrocytoma, *IDH* mutant	121	0.987*	0.981	Expo.	6.90	19

WHO, World Health Organization; Vdx, volume at diagnosis; Expo., exponential growth; VDE, velocity of diametric expansion; M, male; NOS, not otherwise specified; F, female.
*Predominant growth pattern.

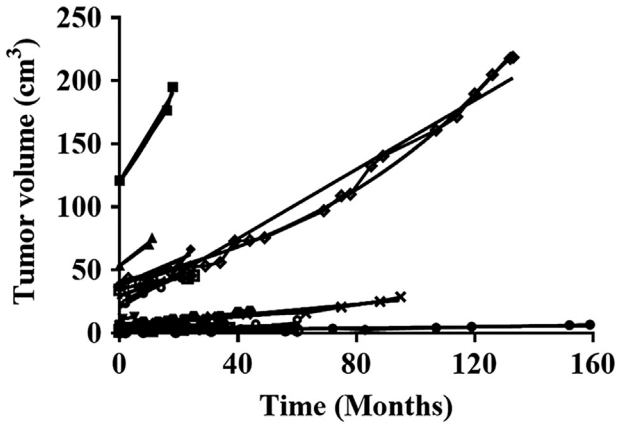

Figure 2. Graph of time course of tumor volumes in all 15 patients. Each curve starts at the first magnetic resonance imaging scan obtained at diagnosis and ends at the last follow-up or preoperative magnetic resonance imaging scan.

follow-up period of 50 months (range, 10–61 months). The most common reasons for obtaining neuroimaging were screening for other neurologic diseases (e.g., aneurysms) and nonspecific symptoms. Other reasons included mild headaches and trauma. Nine (60%) patients had right hemispheric tumors. Localized anatomic locations were the frontal lobe (n = 7; 46.7%), parietal lobe (n = 3; 20%), frontotemporal lobe (n = 2; 13.3%), insular lobe (n = 2; 13.3%), and thalamus (n = 1; 6.7%). Seven (46.7%) patients had diffuse astrocytoma, *IDH* mutant; 7 (46.7%) had oligodendroglioma, *IDH* mutant with 1p19q codeletion, and 1 (6.6%) had oligodendroglioma, not otherwise specified (*IDH* and 1p19q indeterminate). Patient clinical characteristics are shown in Table 1.

Volumetric Analysis and Tumor Growth Pattern

Best-fit tumor volume-time curves for all 15 patients were constructed (Figure 2). Tumor-volume curves fit to both exponential and linear curves, and the larger R^2 value determined growth pattern. Of 15 patients, 11 (73.3%) demonstrated exponential growth patterns, and 4 (26.7%) demonstrated linear growth

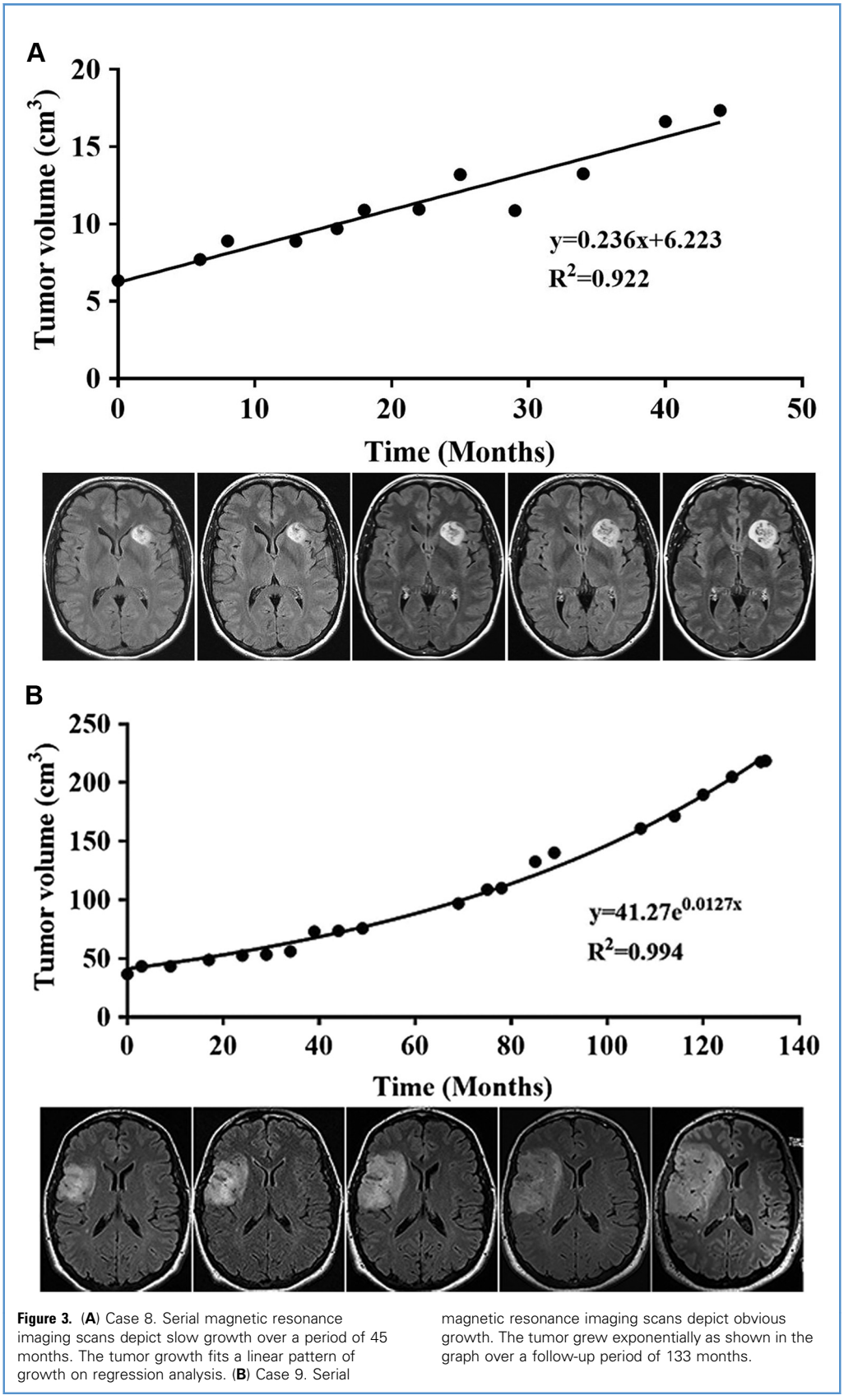

Figure 3. (**A**) Case 8. Serial magnetic resonance imaging scans depict slow growth over a period of 45 months. The tumor growth fits a linear pattern of growth on regression analysis. (**B**) Case 9. Serial magnetic resonance imaging scans depict obvious growth. The tumor grew exponentially as shown in the graph over a follow-up period of 133 months.

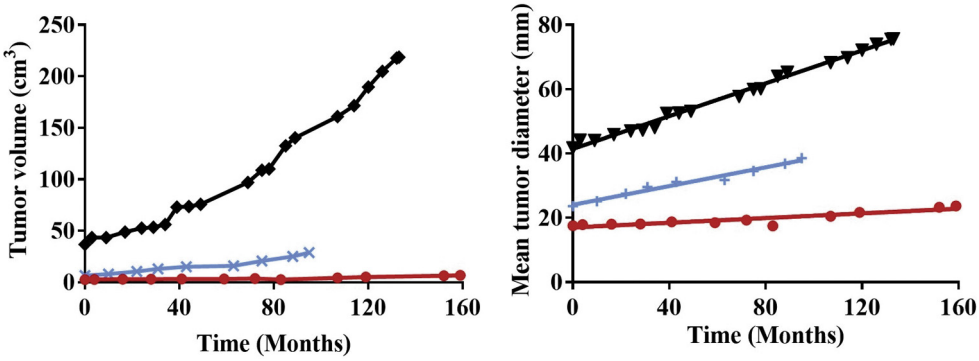

Figure 4. Volume-time curves and their corresponding mean tumor diameter—time curves in 3 patients. Whereas volume-time curves were either linear or exponential, mean tumor diameter—time curves all were linear.

patterns. Serial changes in tumor volume (both radiologically and graphically) in illustrative cases of linear (Figure 3A) and exponential (Figure 3B) growth patterns are shown.

Determination of Tumor Growth

Tumor volumes of each follow-up MRI scan were converted to D_{mean}. D_{mean}—time curves followed a linear curve and hence were more accurate in determining tumor growth rate as computed from the slope of the curves (Figure 4). VDE was variable as shown in Figure 5. Mean ± SD VDE was 2.93 ± 1.92 mm/year. Regression analyses were performed to determine factors that might influence VDE, including initial tumor volume, age at presentation, sex, and tumor histology as shown in Table 2. Initial tumor volume at the time of diagnosis was positively correlated ($r = 0.78$) with VDE (Figure 6).

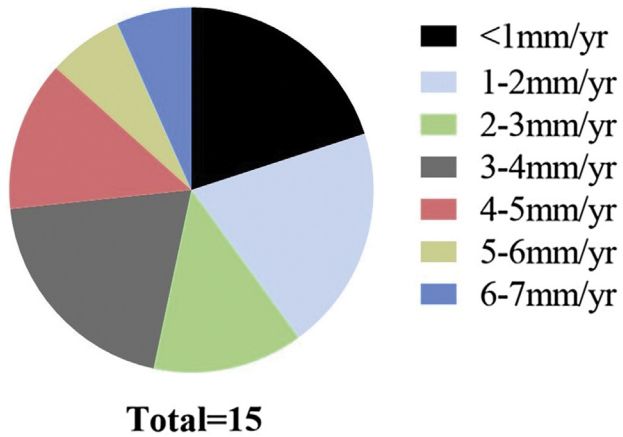

Figure 5. Chart showing variability in the velocity of diametric expansion of all 15 patients with incidentally discovered diffusely infiltrating low-grade glioma.

DISCUSSION

Incidentally diagnosed DLGGs present significant challenges for patients, their families, and neurosurgeons when determining a treatment plan and deciding between conservative management or a potentially morbid surgical resection.[15] It behooves us to identify the growth patterns of these tumors to inform treatment recommendations. In our study, iDLGGs showed growth over time usually in an exponential fashion, and initial tumor volume at diagnosis predicted faster growth.

iDLGGs are discovered on imaging that is performed for signs or symptoms not directly attributable to the patient's tumor; according to the literature, the most common reason for this is a nonspecific headache.[12,15] These lesions typically affect young patients thought to have no focal neurologic deficits.[4] However, there is some evidence that these patients may be more affected than previously thought, as some recent studies suggest that patients with iDLGGs may have cognitive disorders on neuropsychological testing.[16,17] As such, there may not be a significant difference between iDLGGs and symptomatic lesions, other than that the symptoms associated with iDLGGs are

Table 2. Predictors of Growth in Incidentally Discovered Low-Grade Glioma

	r	*P* Value
VDE vs. variable (Spearman correlation)		
Age, years	0.10	0.72
Initial tumor volume, cm^3	0.78	0.0006*
VDE vs. variable (Mann-Whitney)		
Sex		0.46
Histology, Oligo. vs. Astro.		0.57

VDE, velocity of diametric expansion; Oligo., oligodendroglioma; Astro., astrocytoma.
*Statistically significant.

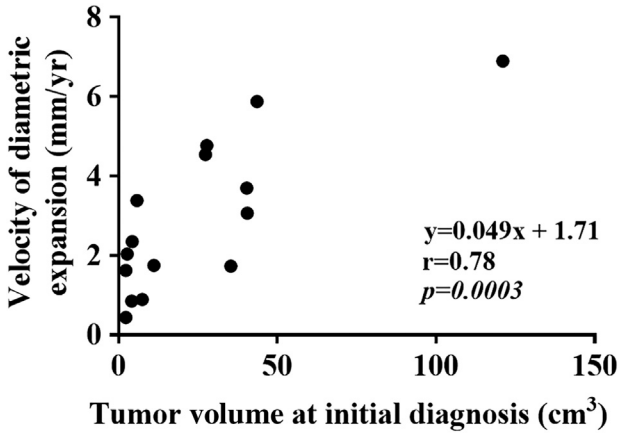

Figure 6. Significant positive correlation between velocity of diametric expansion and tumor volume at initial diagnosis.

subclinical. Clinical practice guidelines published in 2015 support early surgery in the treatment of iDLGGs.[18] However, these guidelines conceded there are no studies directly comparing surgery with expectant management for incidental lesions suggestive of iDLGGs, and other authors have suggested a watchful waiting approach.[15,19]

The literature on the natural history of iDLGGs is limited. A review of the studies on this topic found only 2 articles that examined it.[11,12] In these articles, the most common indication for imaging was a nonspecific headache. Patients with iDLGGs were more likely to undergo gross total resection and had a survival benefit compared with symptomatic DLGGs. Whereas the focus of these studies was comparing incidental and symptomatic DLGGs, our study sought to emphasize the natural history of patients with incidental lesions. Importantly, our results suggest there is a difference in the growth rate and pattern based on the size of the iDLGG at the time of discovery, something that has not been reported previously. Furthermore, our volumetric growth analysis demonstrated an exponential pattern of growth in most tumors, which is also a novel and important finding. R^2 values for linear and exponential growth regressions were close in some patients, and the better fit of the two was assigned as the pattern of growth. A larger sample size is necessary to definitively say that these lesions grow in an exponential, as opposed to linear, fashion.

Owing to the lack of evidence guiding management of iDLGGs, neurosurgeons are often required to base their decision making on tumor imaging characteristics. In the seminal article by Pignatti et al.,[20] tumors with a maximal cross-sectional diameter >6 cm had a worse prognosis than smaller tumors. Our results support this. Patients with larger tumors at diagnosis had a greater increase in mean cross-sectional diameter and had an exponential pattern of volume increase. The reason for this is unclear but may be due to areas of early malignant dedifferentiation in larger tumors.

Mathematical modeling of glioma behavior has demonstrated that growth rates are based on 2 fundamental properties: cell proliferation and diffusion.[21] High-grade gliomas have increased mitotic rates and are highly invasive, allowing them to grow up 10 times faster than DLGGs.[22] Therefore, our results suggest that larger tumors are likely to have increased cell proliferation and infiltrative potential, which may be predictive of faster growth and malignant transformation. This information weakens the case for watchful waiting in the case of incidental lesions concerning for DLGGs, especially larger ones.

The main limitation of our work is the small sample size. However, this is to be expected because iDLGGs are quite rare with a prevalence of 0.05% in asymptomatic individuals according to 1 systematic review and meta-analysis.[10] Thus, iDLGGs regardless of location or molecular characteristics were used in this study. Furthermore, this study included only cases with serial imaging. We believe that our study is an important contribution to the literature on iDLGGs, as it is the first study to our knowledge that demonstrates variable growth patterns based on the size of the lesion at the time of discovery.

CONCLUSIONS

Our study demonstrates that there may be a relationship between the size of an incidentally discovered DLGG and its rate of growth. Perhaps more importantly, there appears to be a difference in the pattern of growth, with most tumors exhibiting exponential volume of expansion. Whereas size is an established risk factor for poor prognosis in these tumors,[20,23,24] rate of growth may also herald malignant transformation.[23-25] Taken together, our results support earlier surgical intervention for DLGGs, especially larger tumors.

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