Incidental Low-Grade Gliomas: Single-Institution Management Based on Clinical, Surgical, and Molecular Data

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BACKGROUND: Incidentally discovered diffuse low-grade gliomas (iLGG) are poorly documented in the literature. They are diagnosed by chance during radiological examinations.

OBJECTIVE: To review a cohort of patients with iLGG surgically treated in our institution, analyzing clinical, molecular, and surgical aspects.

METHODS: Clinical, radiological, and treatment data of iLGG were retrieved and compared with those of symptomatic diffuse LGGs (sLGG). Histological and molecular review was carried out as well. The extent of resection was evaluated on preoperative and postoperative T2-weighted magnetic resonance imaging.

RESULTS: Thirty-four iLGG cases were identified within a monoinstitutional cohort of 332 patients operated for low-grade gliomas from 2000 to 2017. Clinically, patients with iLGG had higher preoperative karnofsky performance scale (KPS) ($P = .003$), smaller tumor volume ($P = .0001$), lower frequency of eloquent areas involvement ($P = .0001$), and higher rate of complete resection ($P = .0001$) compared to those with sLGG. No differences in the molecular profile and O^6-methylguanine-DNA-methyltransferase promoter methylation were detected between iLGG and sLGG. Importantly, patients with iLGG had longer overall survival than those with sLGG ($P = .0001$), even when a complete surgical resection was achieved ($P = .001$).

CONCLUSION: Although the therapeutic strategy of iLGG is still a matter of debate, our data support the safety and the effectiveness of early surgical resection. The favorable prognosis of iLGG may be due to the higher practicability of extensive resection, noneloquent tumor location, and smaller tumor volume.

KEY WORDS: Low-grade gliomas, Incidental findings, Molecular pattern, Extension of resection, Brain mapping

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In recent years, advances in tumor biology, neuroimaging, and treatment paradigms have completely changed the management of low-grade gliomas. Whereas surgical resection is recognized as the first treatment option for the symptomatic diffuse low-grade glioma (sLGG), surgery for incidental low-grade gliomas (iLGG) remains a controversial issue.[1-11] These lesions are generally discovered as incidental findings during brain imaging for unrelated complaints, head trauma, or research studies and represents 3.8% to 9.6% of the LGGs.[9,12] The natural history of iLGG prior to discovery is poorly understood,[3,9,13-15] and the question of management is a recent topic.[2,4-6,8-11,14,16,17]

Based on the role of extent of resection (EOR) as an independent prognostic factor for overall survival (OS) and tumor recurrence,[18-24] the management of iLGG is changing from a "watch and wait" approach toward preventive surgery and individualized oncological treatments.[18-27]

ABBREVIATIONS: EOR, extent of resection; **FISH,** fluorescence in Situ hybridization; **H-MRS,** hydrogen-magnetic resonance spectroscopy; **IDH,** isocitrate dehydrogenase; **iLGG,** incidental low-grade gliomas; **KPS,** karnofsky performance scale; **MGMT,** O^6-methylguanine-DNA-methyltransferase; **MRI,** magnetic resonance imaging; **NAA,** N-acetylaspartate; **OS,** overall survival; **PFS,** progression-free survival; **sLGG,** symptomatic diffuse LGGs; **sTR,** supratotal resection; **WHO,** World Health Organization

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Previous studies have indeed shown that iLGG proliferate at similar rates to sLGG, with both tumor sets having a median Ki67 proliferative index of 5.0%, suggesting that iLGG represent an earlier phase in the natural history of LGGs.[6,15] Therefore, early and radical surgical resection should be advocated to increase the chance of a better prognosis and an increased survival rate.

For this reason, this retrospective investigation aimed at reviewing a cohort of patients with iLGG surgically treated comparing, for the first time, to the best of our knowledge, clinical, molecular, radiological, and surgical aspects with those of sLGG treated in our center within the same timeframe.

METHODS

Study Population

In this study, we retrospectively reviewed adult Caucasian patients (age ≥ 18 yr) who underwent surgery for infiltrative LGGs between 2000 and 2017, with at least 12 mo of follow-up. iLGG were defined as gliomas found on imaging studies obtained for a reason unrelated to the underlying tumor, including headache (during the diagnostic workup of episodic primary headache, mainly migraine-like), trauma, otolaryngology disorders, or magnetic resonance imaging (MRI) studies in healthy volunteers.

sLGG patients were defined and based on the presence of neurological deficits or epilepsy at the onset of the disease.

The present study was approved by the local ethics committee. Written informed consent was obtained for surgery. Considering that the study was retrospective, written consent to participate in the study was not applicable.

MRI and Spectroscopy

All patients underwent a diagnostic brain MRI before surgery, including a hydrogen-magnetic resonance spectroscopy (H-MRS) examination in 29 cases.

Single-section, 2-dimensional multivoxel or single-voxel H-MRS was performed using a point-resolved spectroscopy sequence (PRESS) before contrast medium administration on a 3.0 T magnet (Achieva, Philips Medical System, Best, The Netherlands) in 25 cases. In 4 cases, a single-voxel H-MRS was performed on a 1.5-T magnet (Avanto, Siemens, Erlangen, Germany). The volume of interest was selected on FLAIR or T2W images to include the area of altered signal and the contralateral, apparently, normal brain tissue in the same plane by carefully avoiding the areas of skull base, sinuses, and scalp.

Surgical Technique

The surgical procedures were conducted under cortical and subcortical white matter brain mapping, according to the intraoperative technique previously described by Berger et al.[28,29]

The awake surgery protocol was selected in all cases with lesions of the dominant hemisphere, following the standard protocol in use at our institution.[19,29]

When functionally possible, the resection was extended beyond the tumor limits visible on preoperative MRI (supratotal resection [sTR]), as reported by Duffau et al.[30]

Volumetric Analysis

The EOR was evaluated using MRI images acquired 4 mo after surgery. It was calculated on T2-weighted MRI axial images as follows: (preoperative tumor volume postoperative tumor volume)/(preoperative tumor volume).[19] To define the tumor growth pattern (infiltrative vs expansive), the infiltration index ΔVT2T1 was computed on MRI images as follows: preoperative volumetric tumor volume segmented on T2-weighted MRI images – preoperative volumetric tumor volume segmented on T1-weighted images.[27]

Histological and Molecular Analysis

All histological samples were reviewed by 2 expert neuropathologists according to the 2016 World Health Organization (WHO) classification of the tumors of the central nervous system.[31]

Histological examination, immunohistochemistry, fluorescence in Situ hybridization (FISH), and analysis of the genetic status of O^6-methylguanine-DNA-methyltransferase (MGMT) promoter and isocitrate dehydrogenase (IDH1/2) genes were performed as previously described.[32] Ki-67 (1:200, clone Mib-1; Dako) and $IDH1^{R132H}$ (1:150, clone H09; Dianova) were detected using the EnVision™ FLEX system (Dako). FISH analysis for 1p36 and 19q13 deletions was performed using dual-color 1p36/1q25 and 19q13/19p13 probes (Vysis).[32,33] Codeletion status, IDH gene mutation, and MGMT promoter methylation were assessed as before.[32] Gliomas were defined as methylated when the average percentage of methylation of CpG islands was ≥8%.[34]

Statistical Analysis

Characteristics of the study population were described using the median and range for continuous variables and percentages for categorical variables. Data were tested for normal distribution using the Shapiro–Wilk test. The Student's *t*-test or Mann–Whitney *U*-test were used to compare continuous variables between groups, as appropriate. Comparison of categorical variables was performed by chi-squared analysis or Fisher's exact test, as appropriate.

OS was defined as the time between the dates of surgery and death. Progression-free survival (PFS) was defined as the time from initial resection to the demonstration of unequivocal tumor enlargement on follow-up imaging or death. Analysis of survival was done using the Kaplan–Meier approach, and analyzed by Cox proportional hazard models after the proportional hazard assumption had been verified. Log-rank test was used to compare survival curves.

All analyses were conducted using Stata/SE (version 14.0 Stata Corp.) for Mac. All 2-tailed statistical significance levels were set at $P < .05$.

RESULTS

Three hundred and thirty-two adult patients underwent surgery at our institution for primary LGGs located in the supratentorial hemispheres. Thirty-four patients (10.24%) met the criteria for iLGG. No incidental cases were observed before 2005. The comparison between the iLGG and sLGG groups was thus made by selecting sLGG operated from 2005 to 2017 (298 cases) to have the same timeframe of analysis. Molecular analyses were available in 223 sLGG.

The baseline characteristics of iLGG and sLGG are summarized in Table 1. Among iLGG cases, the MRI was performed for headache, head trauma, research MRI studies in healthy

TABLE 1. Comparison of Demographic, Surgical Radiological, and Molecular Data between iLGG and sLGG

Variable	Value *n* (%) in 34 iLGG	Value *n* (%) in 223 sLGG	*P*
Sex			
Male	15 (44.12%)	135 (60.54%)	.070
Female	19 (55.8%)	88 (39.46%)	
Age (yr)			
Median (range)	37.5 (18-71)	39 (19-75)	.320
Tumor site			
Frontal	21 (61.76%)	88 (39.46%)	**.0001**
Insular	2 (5.88%)	68 (30.49%)	
Occipital	1 (2.94%)	0 (.00)	
Parietal	2 (5.88%)	31 (13.90%)	
Temporal	8 (23.53%)	36 (16.14%)	
Tumoral side			
Right	20 (58.82%)	103 (46.19%)	.169
Left	14 (14.18%)	120 (53.81%)	
Neurological onset			
n (%)	Headache 12 (35.30%)	Seizure 214 (96%)	n.a.
	Head trauma 8 (23.53%)	Neurological deficits 9 (4%)	
	Otolaryngology disorders 8 (23.53%)		
	Research MRI studies 3 (8.82%)		
	Others 3 (8.82%)		
Eloquent area involvement			
n (%)	4 (11.76%)	203 (91.03%)	**.0001**
Preoperative KPS			
Median (range)	100 (100-100)	97 (80-100)	**.003**
Preoperative tumoral volume (cm^3) T2-weighted MRI			
Median (range)	15 (5-40)	44 (6-200)	**.0001**
EOR			
Median (range)	100	85 (28-100)	**.0001**
Preoperative ΔT2T1 value (cm^3)			
Median (range)	0	14 (range 0-95)	**.0001**
Transient postoperative deficits *n* (%)	3 (8.82%)	41 (18.39%)	.224
Motor deficits	1 (2.94%)	21 (9.42%)	
Language deficits	2 (5.88%)	20 (8.96%)	
Permanent postoperative deficits *n* (%)	0 (.00%)	7 (3.14%)	.599
Motor deficits		3 (1.34%)	
Language deficits		4 (1.80%)	
Mib1-Ki67 (%)			
Median (range)	4 (1-9)	5 (1-22)	.0027
IDH1/2 mutant *n* (%)	28 (82.35%)	193 (86.55%)	.335
MGMT promoter methylation *n* (%)	30 (88.24%)	191 (85.65)	.831
1p/19q codeletion *n* (%)	14 (41.18%)	67 (30.04%)	.175
Molecular class *n* (%)			
Astrocytomas, IDH1/2 mutant	14 (41.2%)	130 (58.3%)	.210
Oligodendrogliomas, IDH1/2 mutant 1p/19q codeleted	14 (41.2%)	67 (30%)	
Astrocytomas, IDH1/2 wild type	6 (17.6%)	26 (11.7%)	

EOR = extent of resection; iLGG = incidental diffuse low-grade gliomas; IDH = isocitrate dehydrogenase; MGMT = O^6-methylguanine-DNA-methyltransferase; n.a. = not appliable; sLGG = symptomatic diffuse low-grade gliomas; MRI, magnetic resonance imaging. Boldfacing represent statistical significant results ($p < .05$).

volunteers, otolaryngology disorders, and others medical reasons in cases 12, 8, 3, 8, and 3, respectively.

No adjuvant treatments were administered immediately after surgery in either iLGG or sLGG. Patients underwent chemo- and/or radiotherapy only at tumor progression.

iLGG Volumetric Analysis and Spectroscopy MRI

The median preoperative tumor volume computed on T2-weighted images was 15 cm^3. Regarding the tumor growth pattern, no iLGG showed an expansive pattern; rather, an infiltrative one, being the median difference in the tumor volume,

was calculated between T2- and T1-weighted MRI sequences, of 2 cm^3. In all iLGG analyzed cases, there was a reduction of N-acetylaspartate (NAA) peak and a slight or moderate increase of the choline peak, with NAA/Cho ratios ranging from 0.07 vs 2.08 to 0.52 vs 0.70 and Cho/Cr ratios ranging from 3.24 vs 1.21 to 1.67 vs 0.99. In 15 cases, we also noticed a slight increase of the myo-inositol peak at short time of echo. In all cases, the spectrum analysis was considered suggestive for LGG nature (Figure 1).

iLGG Postoperative Course

In iLGG, new immediate postoperative deficits were detected in 3 patients as follows: motor deficits developed in 1 case with lesion in the supplementary motor area, whereas speech disorders (dysarthria) occurred in 2 patients with lesions close to the Broca's area. Three months after surgery, there were no permanent neurological deficits, and all iLGG patients returned to a normal life. None of the iLGG patients experienced epilepsy in the follow-up.

Comparative Analysis between iLGG and sLGG

The clinical, radiological, surgical, and pathological characteristic of the entire cohort have been summarized in Table 1.

Patients with iLGG had higher preoperative KPS ($P = .003$), smaller tumor volume ($P = .0001$), and higher rate of complete resection ($P = .0001$) compared to those with sLGG.

The EOR was 100% in all iLGG, whereas the median EOR was 85% in sLGG.

Regarding the tumor growth, iLGG were significantly more compact than sLGG, with a median ΔVT2T1 of 14 cm^3 ($P = .0001$). iLGG were much less likely to involve eloquent areas, such as cortices of motor, sensory, or language areas, like the insular lobe ($P = .0001$). Only 4 cases of iLGG (11.76%) were close to functional areas, as demonstrated by the preoperative functional MRI and intraoperative intraoperative electrical stimulation, whereas sLGG were close or within functional areas in 91.03% of cases. Regarding the molecular subtype, iLGG and sLGG did not significantly differ, showing a similar distribution in the 3 major diffuse glioma entities ($P = .176$). Conversely, the median fraction of Ki67 expression was significantly higher ($P = .0027$) in sLGG with respect to iLGG.

Differently from iLGG, transient and permanent deficits occurred in 18.39% and 3.14% of sLGG. Regarding the prognosis in the iLGG population, the median survival time has not been reached because of the fact that no deaths occurred in this cohort (median follow-up of 70 mo; range, 12-144). In the median, follow-up in living patients in sLGG group was 66 mo (range, 12-144). The estimated 5- and 10-yr OSs of the sLGG group were 69.58% and 25.37%, respectively (Figure 2A). In the iLGG group, the PFS was observed in 4 cases (mean PFS, 74 mo; range, 38-98), and among these, only 1 case was IDH1/2 wild type. The estimated 5- and 10-yr PFS of the iLGG and sLGG groups were 90.91% and 51.65%, and 36.38% and 5.47%, respectively.

To determine if the outcome of iLGG patients is merely a consequence of the degree of resection, we also compared completely resected sLGG patients ($n = 40$ with EOR = 100%) with incidental iLGG patients. As shown by the Kaplan-Meier survival curves (Figure 2B), the 5- and 10-yr-estimated OSs of these groups were significantly different ($P = .001$), being of 97.2% and 48.1% in sLGG, and 100% and 100% in iLGG. Additionally, in sLGG with complete resection, the prognostic role of IDH1/2 mutation was demonstrated by Kaplan–Meier curves (log rang test $P = .028$) (Figure 2C).

DISCUSSION

Key Results

In this retrospective study, including 34 adult patients harboring iLGG, we analyzed clinical, radiological, and molecular data in comparison with those of sLGG. This comparative investigation evidence of the following: (1) patients with iLGG had higher preoperative KPS, smaller tumor volume, lower frequency of eloquent areas involvement and higher rate of complete resection compared to those with sLGG. (2) No differences in the molecular profile and MGMT promoter methylation were detected between iLGG and sLGG. (3) Patients with iLGG had longer OS than those with sLGG, even when a complete surgical resection was achieved.

Interpretation

Diffuse LGGs are a heterogeneous population of intrinsic brain tumors whose natural history is characterized by an initial indolent growth with an intrinsic tendency for recurrence and malignant transformation.[6,8]

Although early and maximal resection is, at present, the first-line treatment for sLGG,[18-23,25,35-38] as recommended by the current European Guidelines,[39] the best management of iLGG remains unclear and debatable because of the rarity of iLGG and difficulty in long-term follow-up.[1-11,14-17] The natural history of iLGG has been recently investigated, with studies that have shown a progressive growth with a median velocity of diametric expansion close to the growth rate of sLGG.[9,15] Preventive surgery for iLGG has been proposed, arguing that the earlier the surgery, the higher the possibility to achieve a total or supratotal tumor resection without permanent deficits[1,5,7,9-11,15] (Table 2). Here, we presented our experience with 34 iLGG patients, surgically treated, comparing clinical, radiological, surgical, and molecular results with those related to sLGG. According to the literature we identified, in iLGG, higher preoperative KPS, smaller tumor volumes, absence of postoperative permanent neurological deficits, and more extensive EOR. All these features are considered favorable prognostic factors significantly influencing the survival.[19,23,35,36,38,40,41]

Previous retrospective studies revealed that 3.8% to 9.6% of supratentorial hemispheric LGGs were iLGG, which were associated with smaller tumor volumes, higher rates of complete resection, and better prognosis compared to sLGG.[9,15] The higher incidence reported in our study compared to those in the

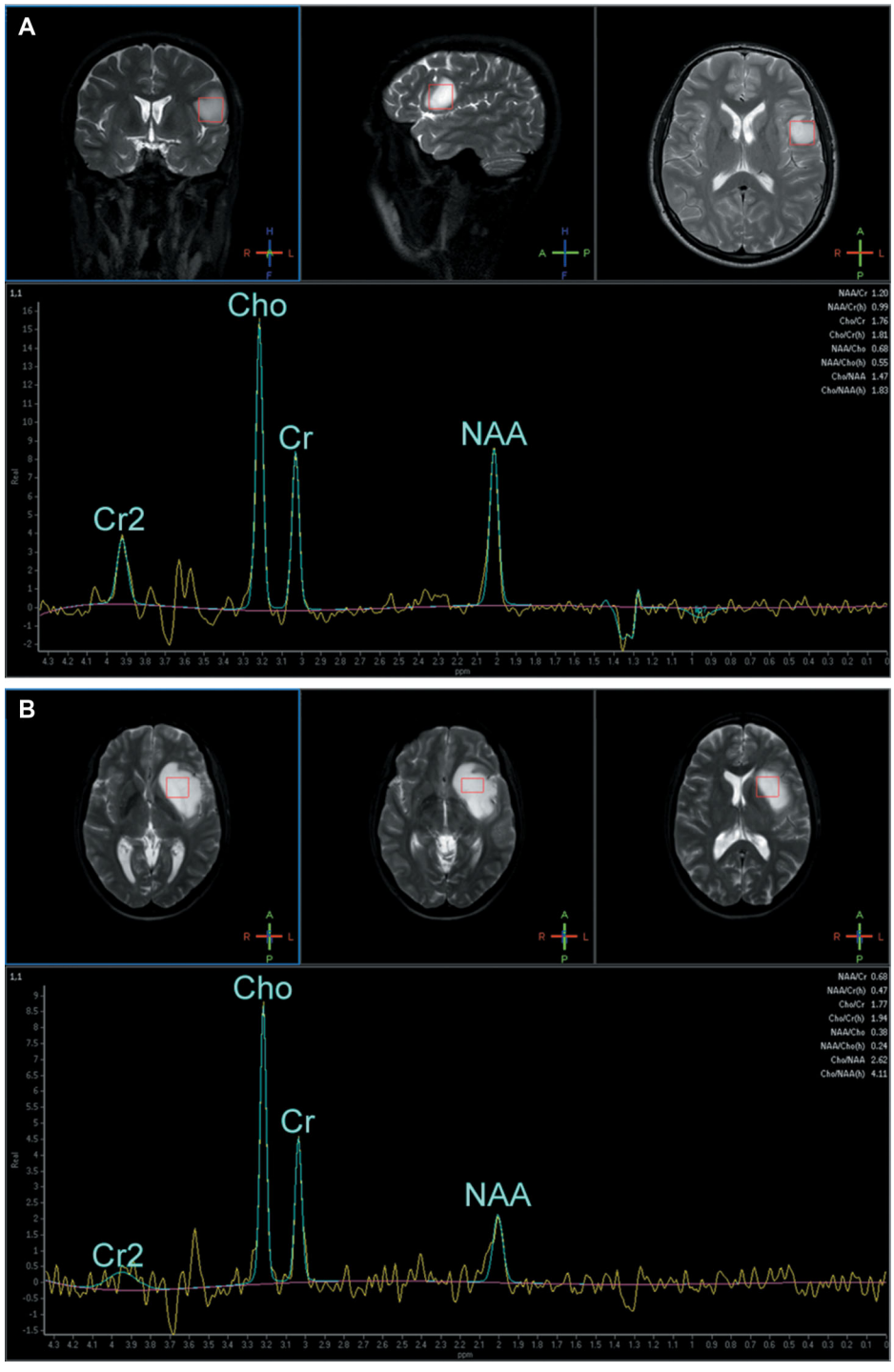

FIGURE 1. *Two representative cases of nonenhancing LGG. Presurgical SSh-TSE T2-weighted images and single-voxel MRS analyses were included.* **A**, *An iLGG involving the left fronto-opercular region with preoperative tumor volume on T2-weighted images of 15 cm^3.* **B**, *A left insular sLGG with a preoperative tumor volume on T2-weighted images of 30 cm^3. In both cases, the MRS data demonstrated a reduction of NAA and a slight increase of Cho peak with inversion of the normal NAA/Cho ratio. The main difference of neuroradiological study consisted in an asymptomatic case having a significant smaller size.*

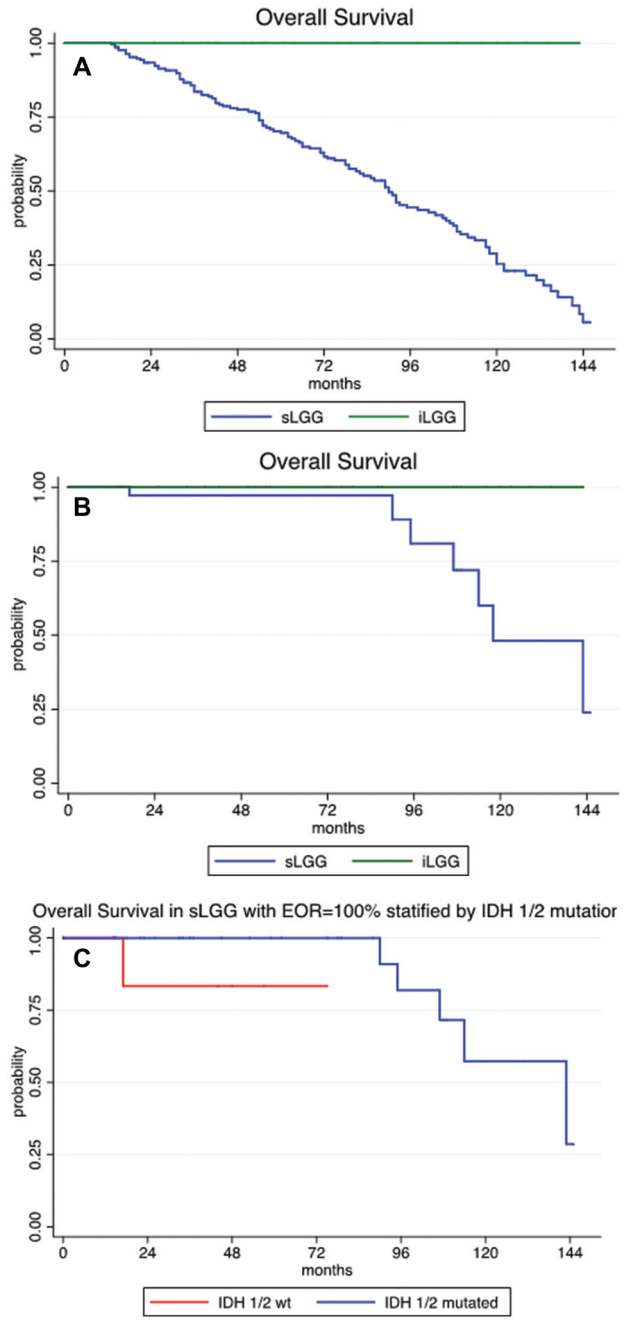

FIGURE 2. **A**, *OS rates in iLGG and sLGG. Kaplan–Meier curves revealing that patients with iLGG were found to be alive at the last follow-up (median follow-up of 70 mo; range, 12-144). The estimated 5- and 10-yr OS of the sLGG group were, instead, 69.58% and 25.37%, respectively (median follow-up of 66 mo; range, 12-144) (log rang test; P = .0001).* **B**, *sLGG patients with complete resection (EOR = 100%) had a different prognoses in comparison with iLGG with complete resection. As shown by the Kaplan–Meier survival curves, the 5- and 10-yr estimated OS of this group was, respectively, of 97.2% and 48.1% in sLGG, significantly different from that of iLGG (log rang test; P = .0001).* **C**, *In sLGG with complete resection, the prognostic role of IDH1/2 mutation was demonstrated by Kaplan–Meier curves (log rang test; P = .028).*

current literature may be due to the increased use of MRI in screening.

Additionally, iLGG, in our cohort, presented a median preoperative tumor volume of 15 cm^3 and involved functional areas in only 4 cases, in accordance with previous series.[9,10,15] In these latter cases, the EOR was functionally limited by the proximity of the tumor to eloquent areas, reducing the possibility to obtain an sTR. Interestingly, only these patients presented tumor progression, independently from their molecular features, which strongly supports the role of early preventive surgery for iLGG. Consistently, we observed that sLGG with a complete resection, in comparison with iLGG, were characterized by a significant lower OS. Because the molecular features of the 2 groups are the same, we can hypothesize that although the macroscopic EOR is similar in the 2 groups, we cannot exclude the presence of a microscopic infiltration in the symptomatic group, a peculiar feature of the intrinsic behavior of LGGs,[42-44] that can be responsible for the relapse and malignant transformation of the tumor, despite a first radical surgery. Indeed, only in the sLGG, IDH1/2 mutation resulted to have a prognostic role.

The decision to postpone surgical treatment and follow the patient by MRI, waiting for a tumor volume increase, could favor the development of more aggressive intratumoral foci or the microscopic tumor infiltration. In fact, in all iLGG cases, the tumor growth pattern was expansive, rather than infiltrative. These radiological characteristics of iLGG (smaller tumor volume, expansive growth pattern, and noneloquent areas) may be correlated with the absence of symptoms when the tumors were discovered. Another interesting result is that iLGG are much more amenable to be completely resected than sLGG, in accordance with the conclusions of other authors who support the early surgery as the first option in iLGG management.[3,10,15,37] Moreover, data in our previous studies confirmed that expansive tumors are significantly associated with greater EOR.[19,27]

None of the patients experienced epilepsy in the years following the glioma removal as previously reported by Duffau et al.[37] This could be explained by the theory according to which glioma-related epileptic seizure may be correlated with the infiltrating residuum of the tumor,[19] triggered by the interaction between glioma and neocortex.[45]

The 2016 WHO classification of gliomas recognizes 3 major groups on the basis of IDH1/2 gene mutation and 1p/19q co-deletion.[31] Data describing the molecular characteristics of iLGG are very rare. Zhang et al. reported a systematic revision of the molecular profile in 23 iLGG, concluding that the iLGG have a better prognosis because they are predominantly *IDH1* mutated and 1p/19q codeleted.[10] Conversely, in the present investigation, iLGG presented an IDH1/2 frequency similar to those of sLGG, suggesting that iLGG were not a unique entity different from other LGGs. The high percentage of IDH1/2 mutation both in iLGG and sLGG supports the possibility that IDH mutations occurred early in the natural history of glioma development.[46,47] Consequently, these molecular data further strengthen the evidence that the better prognosis of iLGG is not

TABLE 2. Incidental Diffuse Low-Grade Gliomas: Literature Review

Authors	*n* of cases	Histological diagnosis	Preoperative tumoral volume (cm^3)	EOR	PFS (mo) median (range)	Dead patients (*n*)	IDH1/2 mutation	1p/19q codeletion	MGMT methylation
Pallud et al 2010[15]	47	Astrocytoma = 7 Oligodendroglioma = 31 Oligoastrocytoma = 9	17.2	GR = 14 STR = 12 PR = 1 Biopsy = 16	68 (8-152)	4	n/a	n/a	n/a
Potts et al 2012[9]	35	Astrocytoma = 16 Oligodendroglioma = 12 Oligoastrocytoma = 6 Ganglioglioma = 1	20.2	GTR = 21 STR = 14	29 (5-70)	1	n/a	n/a	n/a
Duffau et al 2012[11]	11	Glioma WHO II	32.6	sTR = 3 GTR = 4 STR = 4	64 (28-73)	0	n/a	n/a	n/a
Zhang et al 2014[10]	23	Astrocytoma = 6 Oligodendroglioma = 6 Oligoastrocytoma = 11	23.8	GTR = 21 PR = 2	85 (34-108)	5	95.6%	69.6%	n/a
Lima et al 2016[5]	19	Glioma WHO II	51.4	sTR = 5 GTR = 4 STR = 7 PR = 2	28 (3-79)	0	n/a	n/a	n/a
Cochereau et al 2016[1]	15	Astrocytoma = 11 Oligodendroglioma = 4	33.4	n/a	n/a	0	n/a	n/a	n/a
Opoku-Darko et al 2017[7]	34	Astrocytoma = 44% Oligodendroglioma = 47%	57.2	81.03%	72	1	74%	38.2%	n/a

EOR = extent of resection; GTR = gross-total resection; IDH = isocitrate dehydrogenase; MGMT = O^6-methylguanine-DNA-methyltransferase; n/a = not available; PFS = progression free survival; PR = partial resection; STR = subtotal resection; sTR = supratotal resection.
This table summarizes the major studies reported in the literature regarding iLGG, specifying histological, surgical, survival, and molecular data. Only original articles have been included. Single-case publications were excluded.

exclusive due to the expression of different molecular patterns but to an early, preventive, and radical surgery.[5,17]

Although this study suggests both safety and clinical utility of an early surgical resection in treating patients with iLGG, a multi-institution study, allowing the enrollment of an increased number of patients, would be recommended to overcome the epidemiological issue of iLGG rarity. Moreover, our results reinforce the proposal of a screening policy for LGG to evolve toward a "preventive treatment."[5,6,37] Considering the elevate costs for MRI screening,[5,6] advances in developing cell-free plasma DNA techniques to early detect tumor biomarkers could be an option in the new challenging screening frontiers.[48]

Generalizability

The strength of the present study is in the following: (1) the homogeneous data collection both in iLGG and sLGG groups; (2) the statistical analysis of all radiological and molecular clinical variables between iLGG and sLGG; (3) the survival comparison between iLGG and sLGG, with a total resection to reinforce the indication of early surgery even in iLGG; and (4) the exclusion of patients without surgical resection as first-line treatment, and with oncological treatment (chemotherapy and radiotherapy), to decrease confounding factors.

Limitations

There are several limitations in our retrospective investigation, which should be acknowledged. The study is based on a small number of iLGG patients, which, in turn, can be due to the rarity in discovering this disease in an early phase.

A relatively short follow-up time could represent another limitation. However, the comparison of iLGG and sLGG strengthened the conclusions that patients with iLGG survived significantly longer than those with symptomatic LGGs if surgically treated.[5,9,10,15,17] Nonetheless, a more prolonged follow-up time could also contribute to exclude the hypothesis that the prolonged survival time seen in incidental gliomas may represent a lead-time bias.[49]

A neuropsychological assessment of iLGG has not been included in this study, which has been proven to be useful in sLGG studies.[50] This component has been implemented in our ongoing future studies currently underway.

In addition, spectroscopic data was used in the decision-making process of iLGG. It could be of clinical use to compare

spectroscopic data of iLGG and sLGG in future studies to better understand the natural history of LGG.

CONCLUSION

The results of this study suggest that preventive surgery in iLGG should be considered as a therapeutic option, because it tends to be a safer surgery and is associated with a better prognosis in comparison to sLGG management. The favorable prognosis of iLGG may be due to the higher practicability of extensive resection, noneloquent tumor location, and smaller tumor volume. A multicentric study based on iLGG is strongly required to increase the statistical power of this investigation.

Disclosures

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COMMENTS

The authors present a retrospective review of 34 incidental low-grade gliomas (LGGs) within areas of the brain undergoing surgical resection and discuss the clinical and biological characteristics. In this study, the authors sought to evaluate the effect of extent of resection on quality of life postsurgery, using cognitive evaluation and return to work as surrogates for quality of life outcomes. Previous studies have demonstrated the positive impact of surgical intervention in these cases on survival, Karnofsky performance status, and seizure control. Limitations of the study include the small cohort, retrospective data, and the selection bias because of the surgical series. Despite the presence of these inherent limitations, the study adds to the existing literature and provides insight into the management of patients with this condition and could potentially provide clinical use. In addition, this study adds to the observation vs intervention debate pertaining to incidental LGGs. The results emphasize the role of preventive surgery for incidental LGG and highlight the lower risks compared to surgery for symptomatic LGG. Molecular analysis illustrates the congruence in molecular features between the incidental diffuse LGGs (iDLGGs) and symptomatic diffuse LGGs (SDLGGs). In addition, analysis of survival data in symptomatic patients by molecular profile supports pre-existing literature and illustrates differences in survival between diffuse LGGs (DLGGs) IDH1/2 wild type and IDH1/2 mutated. As the authors stated, the similarity in these molecular features highlights that incidental LGGs could perhaps be representative of an earlier stage of symptomatic LGG. In conclusion, the study provides clinical and molecular insight that emphasizes the necessity for early preventive surgery. Furthermore, this study paves the way for future research in a multicenter study to validate the findings.

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The authors have provided a review of their institutional experience with patients harboring an incidentally discovered LGG. They identified 34 cases of iDLGG among the cohort of 332 patients who underwent surgery for LGG from 2000–2017 at their institution for study. As might be expected, patients with iDLGG harbored smaller tumors with a lower frequency of involvement of eloquent areas, had a higher preoperative Karnofsky performance status, and more commonly had complete resection, when compared with patients with SDLGGs. The authors found no difference in the molecular profile and O^6-methylguanine-DNA-methyltransferase promoter methylation status between tumors from the 2 groups. Patients with iDLGG had longer survival than patients with SDLGG. The conclusions reached by the authors are fair and guarded.

These valuable data speak to a problem that is not uncommon in neurosurgical (and, particularly, neuro-oncologic) practice, for which we have little data to guide us. The authors have performed surgery in this cohort without inciting a permanent neurological cost. The fundamental question is, and still remains, do we improve upon the natural history of this disease by performing early cytoreductive surgery?

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