Is there a risk of seizures in “preventive” awake surgery for incidental diffuse low-grade gliomas?

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OBJECT Although a large amount of data supports resection for symptomatic diffuse low-grade glioma (LGG), the therapeutic strategy regarding incidental LGG (ILGG) is still a matter of debate. Indeed, early “preventive” surgery has recently been proposed in asymptomatic patients with LGG, after showing that the extent of resection was larger than in symptomatic patients with LGG. However, the quality of life should be preserved by avoiding both neurological deficit and epilepsy. The aim of this study was to determine the risk of seizures related to such a prophylactic surgical treatment in ILGG.

METHODS The authors report a prospective series of 21 patients with ILGG who underwent awake surgery with a minimum follow-up of 20 months following resection. Data regarding clinicoradiological features, surgical procedures, and outcomes were collected and analyzed. In particular, the eventual occurrence and type of seizures in the intra- and postoperative periods were studied, as follows: early (< 3 months) and long-term (until last follow-up) periods.

RESULTS There were no intraoperative seizures in this series. During the early postoperative period, the authors observed only a single episode of partial seizures in a patient with no antiepileptic drug (AED) prophylaxis—all other patients were given antiepileptic treatment following resection. The AEDs were discontinued in all cases, with a mean delay of 8 months after surgery (range 3–24 months). No patient had permanent neurological deficits. All 21 patients returned to an active familial, social, and professional life (working full time in all cases). Total or even “supratotal” resection (the latter meaning that a margin around the tumor visible on FLAIR-weighted MRI was removed) was achieved in 14 cases (67%). In 7 patients (33%) subtotal resection was performed, with a mean residual tumor volume of 1.5 ml (range 1–7 ml). No oncological treatment was administered in the postsurgical period. The mean follow-up after surgery was 49 months (range 20–181 months). Only 2 patients had seizures during the long-term follow-up. Indeed, due to tumor progression after incomplete resection, seizures occurred in 2 cases, 39 and 78 months postsurgery, leading to administration of AEDs and adjuvant treatment. So far, all patients are still alive and enjoy a normal life.

CONCLUSIONS The risk of inducing seizures is very low in ILGG, and it does not represent an argument against early surgery. These data strongly support the proposal of a screening policy for LGG that will evolve toward a preventive treatment in a more systematic manner.

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KEY WORDS diffuse low-grade glioma; awake surgery; incidental tumor; epilepsy; outcome; oncology

A WHO Grade II glioma (diffuse low-grade glioma [LGG]) is a continuously growing lesion that migrates along white matter pathways and that will inescapably evolve toward a higher grade of malignancy.³⁹ This tumor is usually revealed by inaugural seizures in young adults with no or only mild neurological deficits.¹¹ Despite the lack of prospective randomized trials, a large

amount of data reported in the modern literature strongly supports the impact of early and maximal resection on the natural history of the disease, by delaying malignant transformation and thus by significantly increasing survival.^{1,15,20,21,30,46,49} Recently the French Glioma Network published the largest surgical series of LGG ever reported, in which multivariate analysis was used to show that extent

ABBREVIATIONS AED = antiepileptic drug; EOR = extent of resection; ILGG = incidental low-grade glioma; KPS = Karnofsky Performance Scale.

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of resection (EOR) as well as postsurgical residual volume were independent prognostic factors significantly associated with a longer survival—overall survival was approximately 15 years in this series.^{5,36} As a consequence, according to the current European guidelines, tumor resection represents the first therapeutic option in LGG.⁵¹

The management is nonetheless more controversial concerning incidental LGG (ILGG). In the healthy population, the incidence of ILGG is currently estimated to be between 0.025% and 0.3%.^{23,35,53,54} In a series of 4309 gliomas from the French Brain Tumor Databank, 130 cases of incidentally diagnosed gliomas (3%) have been reported.² Due to the rapid development of neuroimaging, the probability of encountering ILGG will increase in the near future. Interestingly, the natural course of ILGG has been investigated by several authors.^{37,40} They showed that ILGG was a progressive tumor in all cases (with a growth rate of approximately 3.5 mm/year; i.e., very close to the growth rate of symptomatic LGG), leading to clinical transformation toward symptomatic LGG at a median interval of 48 months after radiological discovery. In addition, the risk of malignant transformation of the lesion was evaluated at approximately 30% at a median interval of 5.7 years after its radiological discovery.³⁷

This is the reason the concept of “prophylactic surgery” has recently been proposed in the treatment of ILGG.^{9,12} Indeed, due to a smaller tumor volume in ILGG in comparison with symptomatic LGG, early surgical management allows the achievement of a greater rate of both total and “supratotal” resections^{9,37,40} (supratotal resection meaning that a margin around the tumor visible on FLAIR-weighted MRI was removed). This is an important issue, because such a supratotal resection has been demonstrated as preventing malignant transformation in LGG.⁵⁷ Of note, neuropathological examination has nonetheless revealed that microfoci with endothelial proliferation were already present in the middle of the tumor in up to 27% of ILGG, showing that the beginning of anaplastic transformation may occur before any symptoms appear.⁹ Finally, patients undergoing surgery for ILGG have improved overall survival in comparison with a control group of patients with symptomatic LGG.^{37,40} Therefore, from an oncological point of view, these results support the concept of preventive maximal resection for ILGG, before glioma progression and malignant transformation.^{11,12} Given this state of affairs, it has been recently proposed to the neuro-oncological community to envision a screening policy for LGG.²⁷

On the other hand, ILGG surgery can be considered only on the condition that quality of life is preserved. In a previous preliminary surgical series with a selected subgroup of patients with ILGG involving eloquent areas, all resections were performed using intraoperative electrostimulation mapping in awake patients. Despite frequent immediate postoperative neurological worsening, all patients recovered their preoperative neurological status within a few weeks after surgery thanks to a specific functional rehabilitation program, and they returned to a normal social and professional life.⁹ Yet, beyond the risk of neurological deficits, resection by itself may induce seizures, even for lesions far from eloquent regions.^{26,58}

Epilepsy could be a possibly serious complication, especially in previously asymptomatic patients, with major consequences on quality of life (e.g., driver’s license suspension).

In this study our aim was to investigate the risk of seizures related to surgical treatment in a prospective series of asymptomatic patients who underwent awake surgery for ILGG.

Methods

Selection of Patients

We prospectively collected cases of asymptomatic adult patients (older than 18 years at the time of radiological discovery of the lesion) who underwent surgery for an ILGG (i.e., unexpectedly discovered and unrelated to the purpose of the MRI examination) by the senior author (H.D.) between December 1998 and September 2012, with a minimum follow-up of 20 months.

From a series of 25 patients with ILGG selected according to these criteria, we excluded 4 because they experienced seizures in the period between the diagnosis and surgery (mean interval 36 months, range 18–54 months). Indeed, the goal was to study whether “preventive” resective surgery may generate epilepsy in asymptomatic patients.

Evaluation Methods

Information concerning the following parameters was obtained for all patients: sex, age at diagnosis, reason initial radiological examination was performed, tumor location and growth rate, interval between diagnosis and surgery, tumor volumes (evaluated on pre- and postoperative MRI), surgical procedure with eventual occurrence of intraoperative seizures, postsurgical course with eventual onset of seizures in the early (< 3 months) and long-term (until last follow-up) periods, neurological outcomes, neuropathological results, adjuvant treatment (chemotherapy and/or radiotherapy), and survival.

Preoperative Clinical and Radiological Examination

In addition to preoperative neurological examination, handedness was assessed using a standardized questionnaire (Edinburgh inventory).³⁴ Moreover, the Karnofsky Performance Scale (KPS) score was evaluated for each patient.²²

The topography of the tumor was accurately analyzed on a preoperative MR image (T1-weighted and spoiled-gradient images obtained before and after Gd enhancement, and T2- and FLAIR-weighted images). In the first period of this series, the preoperative tumor volume was calculated on the basis of the 3 largest diameters (D1, D2, and D3) of areas of signal abnormality on FLAIR-weighted MR images according to the 3 orthogonal planes (axial, sagittal, and coronal). An estimation of tumor volume was calculated by the ellipsoid approximation ($[D1 \times D2 \times D3]/2$), as already reported.^{28,29} Postoperatively, the volume of the residual tumor (if any) was calculated using the same method on the FLAIR-weighted MR images obtained 3 months after surgery. In the second period of the series, both pre- and postsurgical volumes were cal-

culated using dedicated software (Myrian, Intrasure). In all cases, at least 2 MRIs spaced 3 months apart were performed before surgery to calculate tumor growth by using a previously described methodology.^{28,29,37}

Surgical Procedure

All surgical procedures were performed using an asleep-awake-asleep technique with intraoperative direct electrical mapping for cortical and subcortical eloquent structures.^{10,13,14} Technical details of our functional mapping-guided surgical procedure have been described in previous reports.⁵² Prior to tumor resection, stimulation of the entire exposed cortical surface was performed using a bipolar electrode with 5-mm spacing (60 Hz, 1-msec pulse width, current amplitude 1–4 mA). First, after determining real-time tumor and sulcal/gyral anatomy with intraoperative ultrasound, motor and sensory mapping was performed starting at 1 mA and increasing up to a maximum of 4 mA until reliable motor and/or sensory changes were elicited. Once the sensorimotor threshold was determined, that amplitude was used for the remainder of the cortical and subcortical mapping.

Intraoperative tasks included counting, DO (dénomination orale) 80 picture naming,³¹ and a double task (picture naming in concert with contralateral arm movement) while receiving systematic stimulation throughout the cortex. For the picture-naming task, the patient was asked to start with “This is a...” to distinguish anomia from speech arrest. The DO 80 picture-naming task uses a set of 80 common black-and-white pictures that has been validated in clinical populations to assess anomias and naming impairment.^{14,31} Further tasks may be added according to the location of the tumor and the quality of life of the patient (defined on the basis of his/her job and hobbies); e.g., semantic association tasks, double task, visuospatial tasks, judgment, mentalizing, and so on (for a recent review on this topic, see Fernández Coello et al.⁷). Intraoperative evaluation of patient function was assessed by a licensed speech therapist and/or neuropsychologist blinded to stimulation. Sites that elicited errors in the aforementioned functional tasks at 3 nonsequential stimulations followed by normalization after stimulation ceased were marked with tags on the cortical surface, and the specifics of the error were recorded (semantic paraphasia, speech arrest, dysarthria, and so on). To avoid seizures, the same site was never stimulated twice in succession. Numbered sterile tags marked the eloquent areas. A photograph was taken before resection to capture the cortical map and was subsequently analyzed offline.

After the completion of cortical mapping, glioma resection was started and subcortical structures were systematically stimulated to identify critical pathways. Indeed, using the same parameters of stimulation as at the cortical level, the functional fibers were followed progressively from the eloquent cortical sites already mapped to the depth of the resection. During the resection and stimulation of subcortical tracts, the patient continued with the same tasks, and the speech therapist and/or neuropsychologist analyzed the functional disturbances in real time. To perform an optimized tumor removal while preserving eloquent areas, all resections were pursued until critical net-

works were encountered around the surgical cavity; i.e., resections were achieved according to functional boundaries. This means that there was no margin left around the eloquent areas, either within the gray or white matter.¹⁷ As a consequence, when possible, the resection was extended beyond the tumor's visible limits on preoperative FLAIR-weighted MRI (Fig. 1).⁵⁷ After tumor removal, a photograph of the subcortical maps was taken.

Postoperative Course

Immediate postoperative assessment, in which the same tests were used as were done preoperatively, was achieved 3–5 days after surgery, at 3 months, and then every 6 months in the outpatient clinic. The KPS score was also evaluated 3 months after surgery.

All patients received systematic postoperative prophylaxis with antiepileptic drugs (AEDs) for at least 3 months. We analyzed the type of drug, duration, possible side effects, and the occurrence (or not) of seizures.

Postoperative MRI (T1-, T2-, and FLAIR-weighted imaging) was performed within 24 hours after surgery, at 3 months to assess the EOR, and then every 6 months thereafter. The resection was defined as “subtotal” when the residual tumor was less than 10 ml (with calculation of the percentage of resection); as “total” when no residual signal abnormalities were present; and as “supratotal” when a margin of parenchyma was removed around the preoperative FLAIR-weighted signal abnormality (that is, when there was a larger volume of the surgical cavity as compared with the presurgical tumor volume).⁵⁷ All other cases were considered a partial resection.

In long-term follow-up, the eventual regrowth of the tumor and its possible correlation with seizures was collected.

Results

Patient Population

The series consisted of 21 patients (6 men and 15 women), with a mean age of 35 years (range 18–57 years) at diagnosis. Nineteen patients were right-handed and 2 were left-handed. Clinicoradiological features, therapeutic management, and outcome in the 21 patients are summarized in Table 1.

The reasons for initial MRI examination were headaches in 12 cases, dizziness in 2 cases, tinnitus in 2 patients, other symptomatic diseases in 2 cases (1 multiple sclerosis and 1 Chiari malformation), and mood disorders, head trauma, and investigation protocol in 1 case each.

The average time between the diagnosis and surgery was 11.5 months (range 3–42 months). No patient underwent a biopsy before surgery. No patient had undergone previous medical oncological treatment (chemotherapy or radiotherapy). No patient used AEDs before surgery. Preoperatively, none of the patients had neurological deficits, and the preoperative KPS score was 100 in all cases.

The tumor was located in the left hemisphere in 15 cases, and in the right hemisphere in 6 cases. Eleven gliomas involved the frontal lobe, 7 the paralimbic system (4 frontoinsular, 1 insular, 1 temporoinsular, 1 frontotemporoinsular), and 3 the temporal lobe.

FIG. 1. Case 5. **a:** Preoperative axial FLAIR-weighted MRI, coronal T2-weighted MRI, and sagittal enhanced T1-weighted MRI studies showing a right frontomesial diffuse LGG incidentally discovered while investigating headache in a 21-year-old right-handed woman with normal neurological examination results and enjoying a normal life. Due to a slow but objective tumor growth calculated on serial MR images, surgery was proposed 42 months after the diagnosis. **b:** Intraoperative photograph taken during awake surgery showing the view after glioma removal, which was achieved according to functional boundaries detected by intraoperative electrical mapping at both cortical and subcortical levels throughout the resection. The tags mark the pyramidal pathways eliciting involuntary movements and the negative motor network inducing arrest of movement when stimulated, in an awake patient who was performing a continuous double task combining regular movement and a language task (as described in Fernández Coello et al.⁷). There were no intraoperative seizures. **c:** Postoperative axial FLAIR-weighted MRI, coronal T2-weighted MRI, and sagittal enhanced T1-weighted MRI studies demonstrating a supratotal resection of the diffuse LGG (histologically confirmed), beyond the preoperative FLAIR signal abnormality. The patient totally recovered, with no postoperative seizures, and returned to a normal social and professional life (full-time work) 3 months after surgery, with no symptoms. An AED was given in the postsurgical period, and it was discontinued after 3 months. No adjuvant oncological treatments were administered. There was no tumor relapse during a follow-up period of 40 months. A = anterior; P = posterior. Figure is available in color online only.

A volume increase was demonstrated in all patients on serial MRIs, that is, on at least 2 MRIs spaced 3 months apart. The mean preoperative volume was 39.6 ml (range 2–142 ml).

Intraoperative Findings

In all patients, the cortical and subcortical eloquent areas were detected by intraoperative stimulation. These cortical and subcortical functional structures represented the limits of resection in the 21 patients (Fig. 1). There were no intraoperative seizures.

Postoperative Neurological Results

There were no deaths in the series. In the immediate postsurgical period, a transient neurological worsening was noted in 7 patients. There were 5 mild language disorders and 2 supplementary motor area syndromes (with

akinesia and mutism). All patients improved after a personalized functional rehabilitation. Three months after surgery, all 21 patients had totally recovered, with no permanent neurological deficit. The 21 patients returned to a normal social and professional life (working full time in all cases). The KPS score was 100 in all cases.

Postoperative Epileptological Results

During the early postoperative period (within 3 months after surgery), an AED was administered in all cases (carbamazepine in the first part of this series, then levetiracetam in the second part of the series). This treatment was well tolerated by 19 patients. However, 2 patients reported mild side effects (intolerance in one case and fatigue in the other case). The patient with fatigue abruptly discontinued the AED and experienced a partial motor seizure (dysarthria with facial movement) that was controlled by

TABLE 1. Summary of clinicoradiological features, therapeutic management, and outcomes in 21 patients who underwent awake surgery for ILGG

Case No.	Age (yrs), Sex	Reason for MRI	Preop FU (mos)	Vol at Op (ml)	EOR (%)/ Residue (ml)	Early Postop Szs	Delayed Szs (mos postop)	Long-Term AEDs	Adjuvant Therapy (mos postop)	FU Post-Dx/ Postop (mos)
1	26, F	Headache	6	20	95/1	No	No	No	RT (65)	187/181
2	32, F	Headache	3	35	97/1	No	Yes (78)	Yes	Chemo (79)	107/104
3	30, F	Headache	3	34	80/7	No	No	No	Chemo (28)	70/67
4	29, M	Headache	7	25	TR	No	No	No	No	80/73
5	21, F	Headache	42	8	SupraTR	No	No	No	No	82/40
6	57, F	Mood Dis	4	60	TR	No	No	No	No	66/62
7	47, F	Dizziness	26	10	TR	No	No	No	No	55/29
8	18, F	Head trauma	23	11	91/1	Yes	Yes (39)	Yes	Chemo (40)	78/55
9	30, M	Chiari control	6	25	TR	No	No	No	No	55/49
10	36, M	Headache	4	20	TR	No	No	No	No	55/51
11	26, F	Headache	32	2	SupraTR	No	No	No	No	67/35
12	30, F	Headache	7	142	97/4	No	No	No	Chemo (20)	67/60
13	31, M	Headache	11	110	98/2	No	No	No	Chemo (24)	45/34
14	53, F	Headache	6	39	SupraTR	No	No	No	No	34/28
15	38, F	Headache	7	14	86/1	No	No	No	Chemo (23)	38/31
16	30, M	Protocol	13	8	TR	No	No	No	No	42/29
17	49, F	Dizziness	8	91	TR	No	No	No	No	33/25
18	41, F	Tinnitus	20	7	TR	No	No	No	No	42/22
19	36, M	Tinnitus	3	109	TR	No	No	No	No	25/22
20	42, F	MS control	7	32	SupraTR	No	No	No	No	29/22
21	31, F	Headache	6	31	TR	No	No	No	No	26/20

chemo = chemotherapy; Dx = diagnosis; FU = follow-up; mood dis = mood disorders; MS = multiple sclerosis; RT = radiotherapy; SupraTR = supratotal resection (EOR > 100%, including margin around tumor); Szs = seizures; TR = total resection (EOR 100%).

readministration of levetiracetam. No other patient experienced seizures in this early postsurgical period.

There were no seizures in the long-term postoperative period. The AEDs were discontinued in all cases with a mean delay of 8 months after surgery (range 3–24 months), after a slow decrease of dosages.

Postoperative Oncological Results

Total or supratotal resection was achieved in 14 cases (67%). In 7 patients (33%) subtotal resection was performed, with a mean residual tumor volume of 1.5 ml (range 1–7 ml). Pathological results revealed WHO Grade II glioma in all 21 cases. No postoperative adjuvant oncological treatment was administered in the postsurgical period.

Follow-Up and Outcome

During the follow-up, in the 7 cases with residual tumor, a volumetric increase was demonstrated, leading to the administration of chemotherapy (temozolomide) in 6 cases and radiotherapy in 1 patient (initial period of this study). The stabilization of the tumor was achieved in the 7 cases.

In the years following surgery, of these 7 cases, 2 patients experienced epilepsy. In both patients only subtotal removal was initially achieved, with subsequent tumor regrowth. First, the patient who had partial seizures dur-

ing the immediate postoperative period again experienced partial seizures after the delivery of her baby (39 months after surgery). An acceleration of the tumor growth rate was noted during her pregnancy, and temozolomide was administered following delivery and this episode of seizures. In addition, 1 patient had a single episode of generalized seizures 78 months after surgery. Again, temozolomide was given due to glioma regrowth. In both cases, levetiracetam was administered (1 g/day), with a total control of seizures.

With a mean follow-up of 49 months after surgery (range 20–181 months), all patients are still alive and enjoy a normal familial, social, and professional life.

Discussion

Many surgical studies in the recent literature support the significant impact of early and maximal resection in patients with LGG, both for oncological and epileptological purposes.^{1,5,15,20,21,30,46,49} Indeed, in a large series based on 1509 patients, Pallud et al. showed that total and subtotal resections were independent prognostic factors of overall survival as well as total epilepsy control.³⁶ Recently, due to the demonstration that ILGG is also a growing tumor in all cases, with a risk of malignant transformation (as in symptomatic LGG),³⁷ the same principle of early and radical surgery has been proposed.^{9,40} Because the volume is smaller in ILGG due to earlier discovery,

“preventive” surgical management allows the achievement of a higher EOR.^{9,37,40} In addition, thanks to the use of intraoperative functional mapping, which in a recent meta-analysis has been demonstrated as optimizing EOR while significantly decreasing postoperative permanent deficit in glioma, ILGG surgery is a safe procedure—this has been supported by a preliminary study in which no permanent postoperative deficits occurred following resection of ILGG involving eloquent areas.⁹

However, although the high rate of seizures generated by the tumor is well established in LGG,^{3,4,6,44,50} the risk of inducing seizures by the surgery itself is not well known in ILGG. Epilepsy could nonetheless be a potentially devastating complication after tumor resection,²⁶ especially in asymptomatic patients. Indeed, postoperative seizures play an important role in quality of life, from the subjective acceptance of a chronic disease such as LGG to practical social behavior—in particular driver’s license suspension and work issues.

Here, for the first time to our knowledge, we analyzed the risk of developing seizures during and after resection (in the immediate and long-term postoperative periods) in a prospective series of 21 asymptomatic patients who underwent awake surgery for ILGG.

Of note, because ILGG is a rare entity, the vast majority of patients (all but 2) were diagnosed in other departments with a more conservative attitude than in our institute. As a consequence, patients were generally referred to us only when a significant growth was demonstrated on repeat MR images, explaining the delay between diagnosis and surgery (11.5 months on average). This reflects the current management of ILGGs by neuro-oncologists and neurosurgeons.

Intraoperative Seizure Risk

According to a recent series by Nossek et al., the risk of inducing seizures during electrical mapping in awake patients would be approximately 12.6%, with a rate up to 86% in young patients with frontal tumors.^{32,33} This is a very high rate in comparison with our own results. Indeed, in a recent prospective series of 140 awake procedures for glioma involving eloquent areas, our team showed that no seizures occurred intraoperatively.⁸ In the present series, again we observed no intraoperative seizures, despite a mean age at time of surgery of 35 years and despite a majority of patients (16 of 21) with frontal lobe involvement.

Several hypotheses can be considered to explain this discrepancy. First, in our experience, we use a low intensity of electrical stimulation (i.e., between 1 and 4 mA), whereas Nossek et al. reported the use of stimulation intensity up to 10 mA.^{32,33} Nonetheless, we were able to detect cortical and subcortical eloquent structures in all cases. This is due to the fact that we create a wide bone flap, with the aim of avoiding negative mapping before the start of resection. Indeed, if one does not expose a critical cortical epicenter because of a “minimally invasive approach,” the risk could be that of increasing the intensity of stimulation and thus eliciting intrasurgical epilepsy. In addition, because negative mapping can be due to false negatives for methodological reasons, it does not guarantee the absence of eloquent sites. In the study reported by

Sanai et al.,⁴⁵ the 4 patients with permanent postoperative deficits had no positive sites detected prior to their resections. Moreover, a positive mapping finding might also allow an optimization of the EOR, because this resection can be pursued until eloquent areas are encountered (that is, with no margin around the functional structures).^{13,17,57} Finally, it is worth noting that we use the same electrical parameters at the subcortical level as those selected at the cortical level (with no increase of the intensity). Thanks to this very rigorous methodology, in our experience based on hundreds of procedures,^{13,17,52} no awake surgeries were aborted due to intraoperative seizures—as confirmed in the present series with asymptomatic LGG patients.

Risk of Seizures in the Early Postoperative Period

Early postoperative seizures are thought to occur at a frequency between 1% and 12% for all intracranial tumors.⁵⁵ In astrocytic tumor series of patients with LGG, approximately 20%–23% had postoperative seizures; more than half of these occurred within 3 months after surgery.^{18,19} The presence of irritative substances in the first weeks following surgery, such as hemosiderin deposits, inflammatory substances, edema, and/or electrolytic disturbances might explain the appearance of seizures in this critical time.^{25,41} However, in the current literature, there are no clear data with regard to the epilepsy risk related to surgery in ILGG. In our series, we observed that only 1 patient (4.7%) experienced a single partial seizure after ILGG resection.

The prophylactic use of AEDs in patients with no preoperative seizures is still a controversial issue. Nonetheless, it seems that prophylactic AEDs could reduce the risk for early seizures by 40%–50% in patients with brain tumors undergoing intracranial surgery.²⁴ In addition, the choice of AED and duration of postcraniotomy prophylaxis are not clearly defined and remain an individual decision in each institution.^{16,43} Recently, a prospective study of incidental brain tumors in which phenytoin was used for perioperative seizure prophylaxis failed to demonstrate protection.⁵⁶ Such data were in agreement with a meta-analysis of studies in which other old-generation AEDs were used, which was not able to show the usefulness of prophylactic treatment.⁴⁸ On the other hand, levetiracetam, a new-generation AED, was demonstrated to be effective in patients with brain tumors by decreasing the frequency of postoperative seizures, with minor reversible side effects.⁵⁹ Additionally, its lack of potential drug interactions makes levetiracetam an ideal candidate for oncology patients who can receive chemotherapeutic agents.⁵⁹

In our experience, the 21 patients benefited from prophylactic AEDs (carbamazepine in the first period of this series, and then levetiracetam in the second period). Indeed, because early surgical management of ILGG is still a matter of debate, it was important to decrease the risk of generating possible seizures in the immediate postoperative period. This attitude is supported by the fact that there was excellent tolerance in all but 2 cases, and those 2 patients experienced side effects (intolerance in one case and fatigue in the other case). In addition, it is worth noting that the patient with fatigue abruptly discontinued AEDs and was the only patient who had 1 episode of partial sei-

zures after resection. Interestingly, epilepsy was controlled by readministration of levetiracetam. Therefore, even though there is no control group without administration of prophylactic AEDs, these findings support the use of these drugs following ILGG surgery, with a slow decrease of dosages before discontinuation of treatment.

Risk of Seizures During the Long-Term Follow-Up

Seizures could be observed in up to 20% of patients during the 1st year after resection of LGG.⁵⁸ In our series, AEDs were discontinued in all cases, with a mean delay of 8 months after surgery (range 3–24 months), after a slow reduction of dosages. There was no epilepsy in the late postoperative period, and the 21 patients returned to normal familial, social, and professional lives (working full time and driving), with no negative impact of surgery on their quality of life (no adjuvant oncological treatment). Such favorable outcomes confirm the results detailed in our preliminary report, i.e., that the risk of generating a permanent neurological deficit is very low in ILGG surgery, even for tumors located within eloquent areas.⁹

With a long-term follow-up, it has been suggested that seizures almost never occurred (with a few exceptions) when the tumor was stabilized, especially after total glioma resection.⁴² On the contrary, regrowth of incompletely removed LGG can often cause epilepsy.⁵⁰ In our series, 2 patients experienced delayed seizures 39 months and 78 months after subtotal resection and subsequent glioma regrowth. Therefore, due to the long interval between the awake procedure and epilepsy, seizures can reasonably be attributed to tumor progression rather than to the surgery itself. Indeed, because LGG is a continuously growing tumor,³⁹ in the 7 patients with residual tumor that was deliberately left for functional reasons, a volumetric increase was observed on regular MR images, including in these 2 patients with late seizure. This progression led to the administration of chemotherapy (temozolomide) in 6 cases—including both patients with epilepsy—and radiotherapy in 1 patient (in the initial period of this series). Stabilization of the tumor was achieved in all cases. Moreover, in both patients with delayed epilepsy, levetiracetam was administered (1 g/day), with total control of seizures. Interestingly, in the patient who was pregnant, an acceleration of the growth rate of the residual tumor was observed during pregnancy, in agreement with previous reports that showed an increase of the glioma kinetics in pregnant patients.³⁸ Thus, we could hypothesize that acceleration of the rapidity of tumor growth and migration might have facilitated seizure onset after delivery. Finally, this patient had an LGG involving the central area, i.e., a region known to generate frequent seizures when invaded by a diffuse glioma.⁴⁷

It is worth noting that 4 patients were excluded from this series because they experienced seizures in the period between the diagnosis and surgery, with a mean interval of 36 months, confirming the risk of seizure onset if no surgery is performed in ILGG. Indeed, these 4 patients were followed in another institution, with a wait-and-see attitude. They were referred to our department only when they became symptomatic. Of note, only 2 became seizure free after resection. This is in agreement with a previous

observation made by Pallud et al., who reported that in nontreated ILGG, clinical transformation toward symptomatic LGG (consisting of seizures in the vast majority of cases) occurred at a median interval of 48 months after radiological discovery.³⁹ Moreover, once the patients are symptomatic, seizures are intractable in approximately 50% of those with LGG, preventing these patients from having a normal life.⁵¹ Interestingly, in our present series in which there was a mean follow-up of 60.5 months after radiological discovery (49 months after surgery, including patients with more than 15 years of postoperative follow-up), all patients are still alive and enjoy a normal familial, social, and professional life, with no seizures (in 2 cases under levetiracetam) and with control of the glioma in all 21 patients (after adjuvant treatment in 7 cases). Thus, based on these favorable outcomes, we might suggest that preventive surgery in patients with ILGG could preserve quality of life for a long time.

Limitations of the Study

First, we should acknowledge the small number of patients in the study. However, it is worth noting that, today, only 3 studies have been published on the surgical management of LGGs, in all cases with a limited number of patients due to the rarity of this entity: 11 prospective cases,⁹ 35 retrospective cases,⁴⁰ and 47 retrospective cases.³⁷ Here we describe the largest prospective study ever reported, with 21 cases, demonstrating that resection of ILGGs is not associated with increased risk of epilepsy. Given these unique findings, it seems important for neurosurgeons to propose earlier surgery in the context of emerging data that indicate that early resection may increase survival by delaying malignant degeneration.

Second, we must also acknowledge the limitation of the length of mean follow-up, i.e., 49 months after surgery. Nonetheless, we should insist on the fact that, in 8 patients, the follow-up was between 51 and 181 months after resection. When the follow-up is longer, the risk of seizures increases due to an increased risk of tumor relapse. As a consequence, beyond oncological considerations, 49 months of mean follow-up seems sufficient to support the finding that resection by itself is not associated with an increased risk of epilepsy in patients with ILGG.

Conclusions

In a prospective study with 21 patients who underwent awake surgery for ILGG, we have demonstrated for the first time that the risk of inducing seizures is very low; that is, only a single episode of partial seizures occurred in a patient who abruptly discontinued AEDs in the early postoperative period. No patients experienced epilepsy in the long-term follow-up except in 2 cases, several years after surgery, due to tumor regrowth. In addition, a total or supratotal resection was achieved in 67% of cases (no partial resections), with no permanent neurological deficits, confirming the data reported in previous surgical series for ILGG—i.e., that early resection could increase the EOR (because the tumors are in essence smaller) while preserving the quality of life.^{9,37,40}

In summary, it seems that the theoretical risk of gen-

erating epilepsy does not represent an argument against early surgery in patients with ILGG. These data strongly reinforce the proposal of a screening policy for LGG that will evolve toward preventive treatment in a more systematic manner.²⁷

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