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ORIGINAL ARTICLE

Oncological and functional outcomes support early resection of incidental IDH-mutated glioma

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Abstract

Purpose The main objective was to assess the neuropsychological, epileptical, and oncological outcomes in a series of patients operated on for a IDH-mutated diffuse low-grade glioma (DLGG) of incidental discovery (iDLGG).

Methods We retrospectively reviewed a consecutive series of surgically treated adults with DLGG and selected cases incidentally discovered. Tumor volumes, growth rates, and extents of resection (EOR) were assessed by volumetric measures of fluid-attenuated inversion recovery magnetic resonance imaging. The data on oncological, functional, and epileptical results were retrieved from the patients' digital files.

Results Among all patients with DLGG resected at our center between June 2011 and April 2022, we found eleven cases with an incidental discovery. Resection was supratotal, gross total, and subtotal in 45.5%, 26.4%, and 18.1% of cases, respectively. The rate of epileptic seizures after the surgery was 9.1%. There were 45.4% of patients that had tumor progressions and the overall mean time to tumor progression was 42 months. After the surgery, 3 (27.3%) patients had mild neurocognitive deteriorations, which impeded the return to work in one patient (9.1%). There were no differences with previous series regarding clinical, radiological, and molecular characteristics. Similar results were also found for functional, surgical, epileptical, and oncological outcomes.

Conclusion Although the right approach for iDLGG is still a matter of debate, our data support the safety and effectiveness of early surgical resection. More studies are needed to firmly ground this early "preventive" surgery approach.

Keywords Incidental diffuse low-grade glioma · IDH mutated · Awake surgery · Neuropsychological assessment · Return to work

Introduction

Due to the wider access to MRI nowadays, IDH-mutated glioma (aka diffuse low-grade glioma, DLGG) are more frequently incidentally diagnosed [17]. The long period of asymptomatic evolution of DLGG explains their significant prevalence in the healthy adult population, close to 0.04% [32]. These incidental DLGG (iDLGG), albeit detected in a clinically silent stage [30], are slowly but continuously growing tumors, with growth rates (around 3.5 mm/year) very close to those of symptomatic DLGG (sDLGG) [34, 37, 38]. Nevertheless, their management is still a matter of debate. There has been a recent shift from a wait-and-watch paradigm to a "preventive" surgery, arguing that early and radical surgical resection should enable to increase survival [10]. Hence, a maximal surgical resection according to functional boundaries is recommended [23, 39]. There are several series in the literature that already assessed separately the functional, epileptical, and oncological outcomes of patients with a surgically treated iDLGG, sustaining the feasibility and safety of this preventive surgery approach [18]. In the present series, we aimed to report the functional, epileptical, and oncological results of all iDLGG surgically treated at our institution and to compare the results with other available series.

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Methods

Data source

This retrospective study examined a consecutive series of 107 adult patients who underwent a surgical resection of a DLGG between June 2011 and April 2022 at Lariboisière Hospital, Paris, France. Histological diagnosis was made according to the WHO 2016 classification [25].

From this series, we selected the 11 patients in whom the glioma was incidentally discovered, that is in whom the glioma was considered as an unexpected finding on an MRI performed for another purpose.

The following parameters were collected from the digitalized medical files: gender, age at the surgery, sex, handedness, reason for initial MRI, tumor location and side, time interval between radiological diagnosis and surgery, preoperative tumor volume and surgically resected volume—evaluated on preoperative and postoperative MRI using fluid attenuated inversion recovery (FLAIR) sequence—, time interval between radiological diagnosis and tumor growth confirmation, number of MRIs until tumor growth demonstration, histopathological diagnosis according to the WHO 2016, postoperative oncological treatment, time interval from surgery to tumor progression, follow-up since diagnosis and surgery, the return to work after surgery and its mode (part/full time), delay for resuming work, early and delayed postoperative epileptic seizures (within first month and after), oncological adjuvant treatment, delay to antiepileptic drug (AED) withdrawal, and finally, the survival. Handedness was assessed by the speech therapist using the Oldfield Coefficient (Edinburgh Inventory).

Surgical technique

All the patients but one were operated on under awake conditions (patient #4 was operated on under general anesthesia at first surgery, and under local anesthesia at second surgery). All the surgeries were performed by the senior author of the study.

Neuronavigation (S7, Medtronic, Minneapolis, MN, USA) was used in all patients at the beginning of the surgery for the planification of the incision and the bone flap.

Resection was performed using the surgical microscope (Pentero, Zeiss, Jena, Germany) before 2018 (cases #1 to #6) or surgical loops (Zeiss) after 2018 (cases #7 to #11). Awake surgery was performed using the same protocol as previously reported [2, 26]. The cortical and axonal electrical stimulation (Nimbus iCare light, Innopsys, Carbonne, France) was used with the following settings: frequency = 60 Hz, biphasic pulses of 500 µs each, and intensity between 1 and 3 mA. In addition to the standard sensorimotor and picture naming testing, several other cognitive tasks were also intraoperatively monitored [2]. The set of intraoperative tasks were selected by the surgeon, depending on the location of the tumor and the patient's job/hobbies [28], among the following tasks: pyramid and palm tree test (PPTT), double task (repetitive movement of contralateral superior limb + picture naming or picture naming in 1-back), read the mind in the eyes test (RMET), and trail making test (TMT).

Imaging

All the patients had a first postoperative MRI within 48 h, then a second 4-month follow-up MRI. Preoperative and early postoperative FLAIR recovery volumes were manually segmented using Carestream software (Onex, Toronto, Ontario, Canada). The extent of resection (EOR) was calculated as follows: (100-[postoperative tumor volume/preoperative tumor volume]*100), with 100% indicating gross total resection. Resection was deemed subtotal when residual tumor volume was less than 10 cm^3 [4, 42]. When no residual tumor was seen on postoperative MRI, we further assessed whether the resection was supratotal. To this end, we applied the standard definition used in previous studies [20]: the resection was deemed supratotal whenever the volume of the surgical cavity on the follow-up MRI was larger than the preoperative FLAIR tumor volume. For those patients, EOR was calculated as (volume of the surgical cavity / preoperative tumor volume) *100.

Molecular biology

The IDH1 and IDH2 mutations were assessed by polymerase chain reaction, as previously described [1]. The 1p19q codeletion was determined by comparative genomic hybridization (CGH) array technique on frozen samples using a SurePrint G3 human comparative genomic hybridization Microarray Kit 4 × 180 K (Agilent Technologies, Inc.).

Analysis of neurocognitive status

For all the patients, the neurocognitive status was assessed by a speech therapist preoperatively, 3 to 5 days postoperatively, and 3 to 4 months after the surgery. Preoperative and postoperative long-term (3-4 months) testing assessed the following cognitive domains, as previously detailed [3, 26]:

- Language functions, including naming 80 black and white pictures (DO [Denomination Orale d'Images] 80) [31] and literal and categorical word fluencies,
- Mathematics: 3 basic arithmetic mental computations,

- Praxis: copy of the Rey figure [40],
- Memory: forward and backward digital span, verbal span, free and cued selective (16 items or 48 items) reminding test (FCSRT) [15]; delayed copy of the Rey figure [40],
- Attention: d2 attention test [7],
- Executive functions: Stroop test [43], trail-making test (TMT) parts A and B [13].

For each task, cognitive deterioration was defined as a decrement of more than one unit of the *z*-score. One domain was considered as impaired whenever at least one of the *z*-scores decreased by more than one unit.

Analysis of postoperative employment activity

Patients were scheduled for consultation every 3 months in the first year after the surgery and systematically questioned about their employment activity. For patients resuming professional activity, the date of the return was noted, as well as the mode of work (full time, part time).

Results

Descriptive clinical and radiological data

A detailed description of the 11 included cases is given in Table 1. There were 7 males and 4 females. The median age at the surgery was 37 years (range 25 to 58 years). Nine patients were right-handed, and two were ambidextrous. Headaches were the main reason for MRI examination, found in five patients (45.4%). Other reasons were follow-up for another tumor, cranial trauma, familial screening, and neurological symptoms non-related to the glioma.

In nine patients, the localization of the glioma was frontal, fronto-insular in one, and parietal in another one. The tumor was right-sided in 6 patients and left-sided in the other five (see Fig. 1 & 2). The mean tumor volume at surgery was 18 cm^3, with a range between 1 and 79 cm^3. On histopathological analysis, all the gliomas were IDH-mutated (10 grade 2 and one grade 4); 5 tumors were 1p/19q co-deleted (oligodendroglioma) and 6 non-co-deleted (astrocytoma).

Time from radiological diagnosis to evidence of tumor growth and surgery

On the majority of cases, more than 1 year was needed to prove that the tumor was growing, using the methodology previously described [29]. Average number of MRIs before surgery was 2.7 (Fig. 2). The overall mean time from radiological diagnosis until surgery was 25 months (range 3–68). Only one patient (case #4) needed a biopsy to confirm the diagnosis of glioma before resection, because of the complexity of the case: MRI showed a right frontal lesion strongly suggestive of a DLGG but the patient also had a diagnosis of multiple sclerosis (MS) (see Fig. 3). The patient #2 had an unusual evolution: his follow-up MRIs never showed tumor growth on FLAIR sequences but, on the third follow-up MRI, a contrast enhancement was detected (see Fig. 1) that prompted the surgery. Another case that is worth to detail is the patient #8, referred to us from another center, for which the tumor growth over the first year of follow-up was missed by the former clinician in charge. As he came to our clinics 1 year later, the tumor had already undergone a malignant transformation (see Fig. 4). At that stage, the patient had a generalized seizure and surgery was offered straight away.

Extent of resection

The overall mean extent of resection (EOR) in our series was 99.1%, with supratotal, gross total, and subtotal resection in 45.4%, 27.4%, and 18.1% of cases, respectively (see Table 1). The subtotal resections were both observed when the glioma was situated near eloquent brain areas: premotor/SMA cortex.

Immediate post-op complications

Patient #1 presented a hemiparesis at postoperative day (POD) 2 that was caused by an epidural hematoma (see Fig. 5), requiring a surgical evacuation. Subsequent evolution was favorable with complete recovery. Patient #8 presented at 1 month after the surgery a wound infection that required surgical revision under local anesthesia and a 6-week treatment with antibiotics. Patient #3 presented immediately after the surgery a slight motor aphasia, a right neglect, and a slight weakness of the right superior limb that was attributed to a small venous ischemia (see Fig. 6) and that fully resolved after rehabilitation.

Neurological and neurocognitive outcomes

None of the patients suffered permanent neurological deficits. Nevertheless, there were 3 patients that had slight deteriorations on neurocognitive status assessed at the 4-month follow-up. The cognitive changes after the surgery are shown by domains in Table 2, while the full data on preoperative and follow-up performances are exposed in Table 3.

Deficits of attention and executive functions were found at follow-up for patient #1 with a right frontal glioma. Interestingly, an area of diffusion hypersignal in the deep white matter of the middle frontal gyrus was observed for this patient on his immediate postop MRI (see Fig. 5). Patient #5 with a right fronto-insular glioma worsened his deficits on attention, executive functions, and processing speed after the

Table 1 Descriptive data for the 11 patients. *R*, right; *L*, left; *AD*, ambidextrous; *MS*, multiple sclerosis; *FGT*, full time; *PT*, part time; *NA*, not applicable

Patient	Sex	Age	Handedness	Reason for MRI	Tumor localization	Tumor side	Pre-op tumor volume (cc)	Post-op tumor volume (cc)	Extent of resection, EOR (%)	Grade	IDH status	1p/19q co-deletion status	Time from radiological diagnosis to surgery (months)
1	M	58	R	Screening for other ENT tumor	Middle frontal gyrus	R	13.5	0.25	98	2	1	1	3
2	M	32	R	Sensation of facial muscle spasm	Middle frontal gyrus	L	1	0	900	2	1	1	42
3	F	43	R	Follow-up for another tumor	Superior and middle frontal gyrus	L	9	0	520	2	1	0	50
4	M	27	R	Headache	Medial frontal gyrus	R	1.7	0	100	2	1	0	14
5	M	47	R	Headache	Fronto-insular	R	42	0	100	2	1	1	68
6	M	40	AD	Familial screening: sister with MS	Middle frontal gyrus	R	13	0	200	2	1	1	13
7	M	40	AD	Rotational vertigo	Frontal basal-pars orbitalis	L	8	0	100	2	1	1	16
8	M	26	R	Headache	Superior, middle and medial frontal gyrus	R	79	6	92	4	1	0	18
9	F	37	R	Cranial trauma	Frontal superior-medial gyrus	L	18	0	230	2	1	0	4
10	F	28	R	Headache	Middle frontal gyrus	R	10.4	0	233	2	1	0	22
11	F	28	R	Headache	Parietal (precuneus)	L	2.4	0	100	2	1	0	25

Patient	Number of MRIs until surgery	Time from first MRI to growth evidence (months)	Early post-op seizures	Delayed post-op seizures	Time until AED withdrawal (months)	Return to work	Mode of return to work, FT/PT	Time between surgery and return to work (months)	Adjuvant oncological treatment, modality, time from surgery	Second surgery	Deaths	Follow-up since radiological diagnosis (months)	Follow-up since surgery (months)
1	1	132	No	No	6	No	0	0	Yes (P CV), 66 months	0	0	256	133
2	3 (no growth)	38	Yes	No	33	Yes	FT	3	No	0	0	148	106
3	3	34	No	No	NA	Yes	FT	8	No	1 (42 months)	0	134	84
4	4	11	No	Yes (21 months)	1.5	Yes	FT	1.5	No	1 (36 months)	0	88	80
5	2 (claustrophobia)	66	No	No	5	Yes	FT	1	Yes (2nd surgery and SRT), 30 and 35 months)	1 (24 months)	0	140	72

Table 1 (continued)

Patient	Number of MRIs until surgery	Time from first MRI to growth evidence (months)	Early post-op seizures	Delayed post-op seizures	Time until AED withdrawal (months)	Return to work	Mode of return to work, FT/PT	Time between surgery and return to work (months)	Adjuvant oncological treatment, modality, time from surgery	Second surgery	Deaths	Follow-up since radiological diagnosis (months)	Follow-up since surgery (months)
6	4	11	No	No	14	Yes	PT/FT	5	No	0	0	73	60
7	3	11	No	No	11	Yes	FT	5	No	0	0	80	64
8	3 (2)	17	No	Yes (36 months)	Not stopped	No	0	0	Yes (RT + CT, SRT × 2, CT)	0	1	57	39 (death)
9	1	4	No	No	6	Yes	FT	3	No	0	0	22	18
10	3	17	No	Yes (7 months)	Not stopped	Yes	PT/FT	3	No	0	0	12	10
11	3	22	No	No	6	Yes	FT	6	No	0	0	28	6

first surgery. Of note, he subsequently improved with rehabilitation program, and 2 years later, when he was reevaluated preoperatively to the second surgery, his functions had returned back to normal. Finally, patient #8 slightly deteriorated on the memory and executive functions. It is worth to note that this patient was the only one who received (because of a diagnosis of grade 4 astrocytoma) radiation therapy with concomitant chemotherapy straight after the surgery.

Employment activity

We found 2 patients (#1 and #8) who did not resume their previous work. For the patients that did return to work, the sick leave period lasted 3.7 months (range 1–8 months). The two patients who resumed their work the most rapidly were both self-employed workers. All patients resumed their job full time, after a short period of half-time in two of them.

Epileptical status

All patients were put on anti-epileptic drugs after the surgery: levetiracetam for a couple of months and clobazam for 2 weeks. The levetiracetam was withdrawn progressively, within 12 months in the vast majority of cases. There were 2 patients that stopped the AED by themselves before 6 months, without presenting any epileptic seizure. One patient (case #2) with suboptimal compliance developed an early partial seizure 1 month after the surgery. He thus needed an increase of the dosage and, finally, after a period of 33 months, the AED could be withdrawn. There were 3 patients that manifested late seizures, and in one of them, the seizure could be directly imputed to the surgery: patient #10 had several partial seizures 7 months after the surgery, during the period she was diminishing progressively the levetiracetam. Seizures were stopped by re-increasing the dosage of levetiracetam. The other two patients developed seizures much later, one at 21 months, attributed by the neurologist to MS relapse; and the other one at 36 months, in keeping with the tumor progression towards a multifocal disease.

Subsequent treatments

In our series, there were in total 5 patients that had radiological progressions and the overall mean time to progression was 42 months. Three patients had a redo surgery for recurrences (patient #3 at 42 months, patients #4 at 36 months and #5 at 24 months, see Figs. 1 and 2). Unexpectedly, histopathological examination did not find any tumor but only gliosis in patient #3. Patient #5 had a second recurrence 3 years later that was treated by stereotactic radiotherapy.

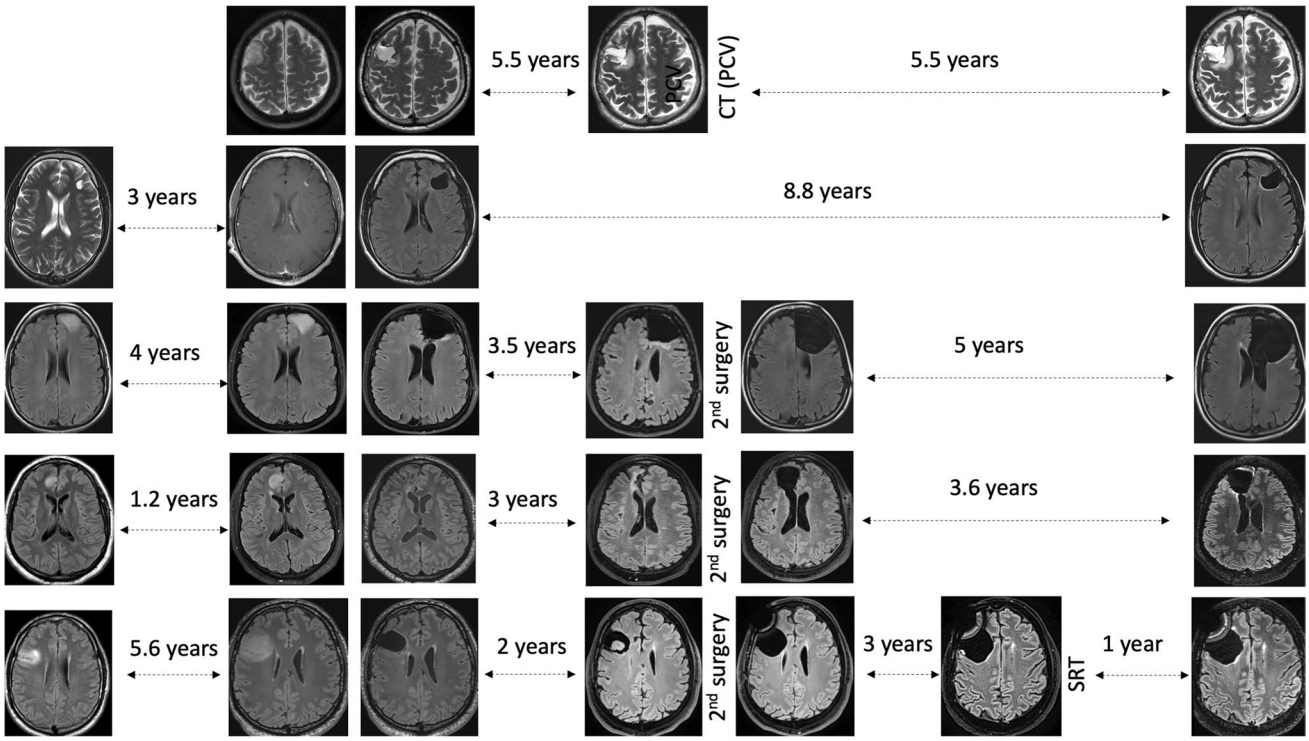

Fig. 1 Serial MRI panels for patients #1 to #5. First column: radiological diagnosis; 2nd column: preoperative MRI; 3rd column: postoperative MRI

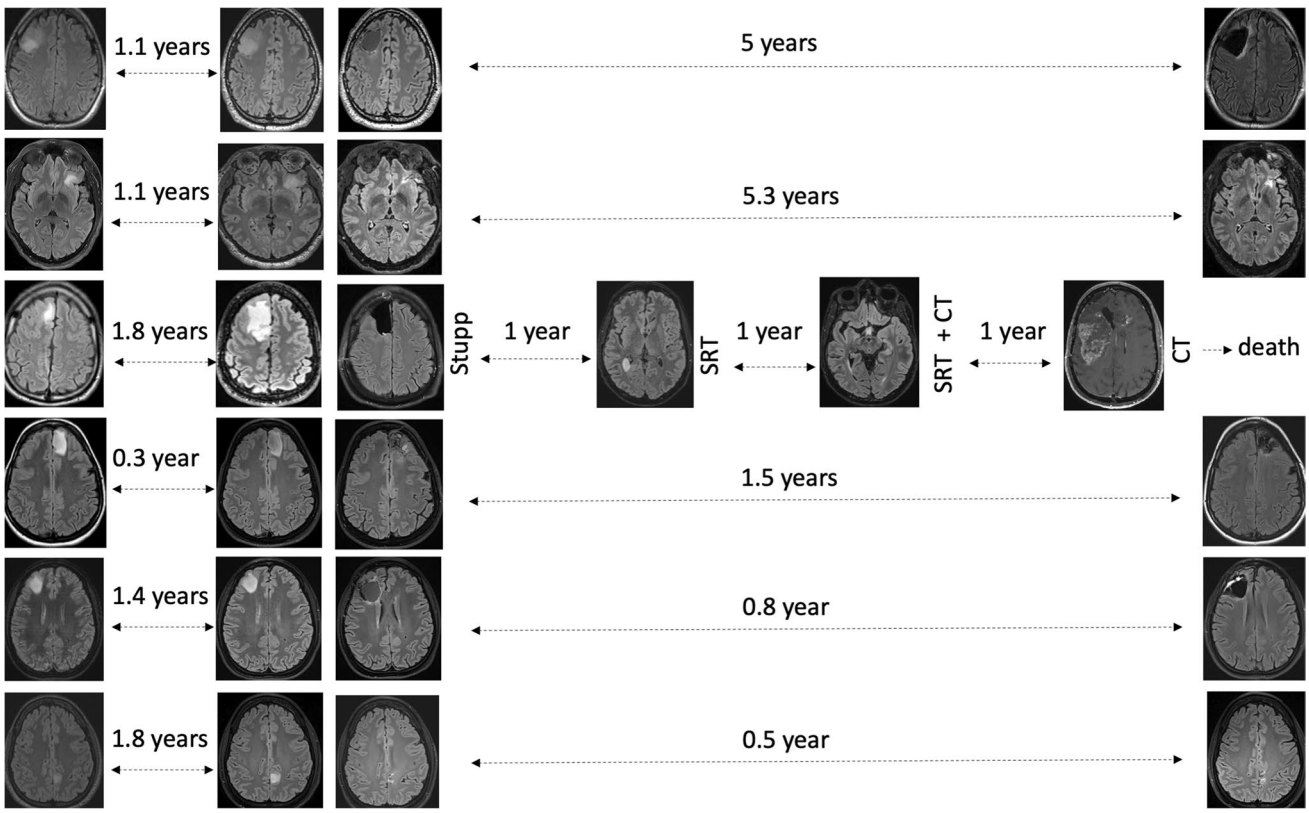

Fig. 2 Serial MRI panels for patients #6 to #11. First column: radiological diagnosis; 2nd column: preoperative MRI; 3rd column: postoperative MRI

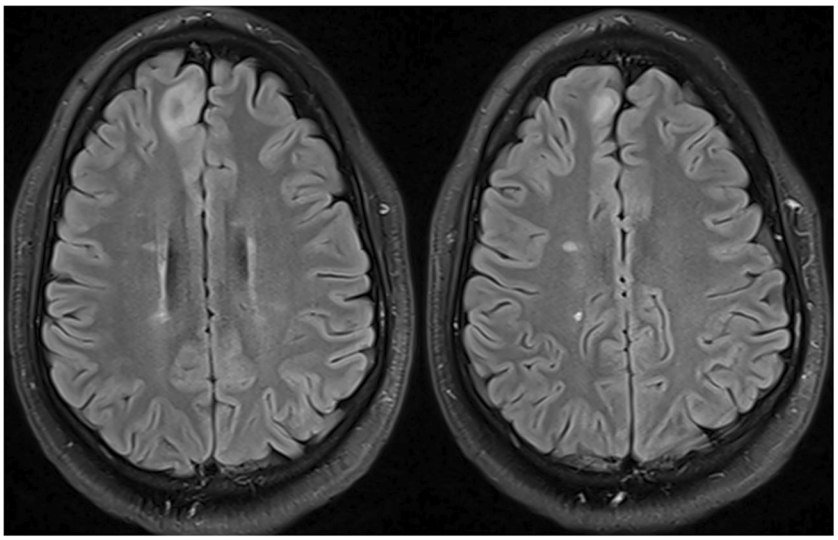

Fig. 3 Concomitant diagnosis of incidental diffuse low-grade glioma and multiple sclerosis in patient #4. Axial FLAIR images showing the frontal-mesial glioma but also multiples foci of hyperintensities in bilateral white matter typical of MS lesions

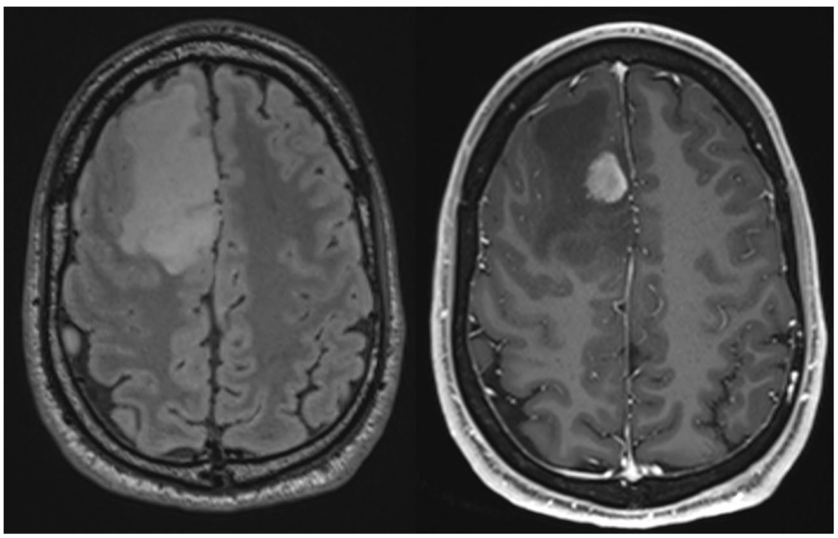

Fig. 4 Malignant transformation in patient #8. Axial flair and T1 gadolinium-enhanced images

Two other patients needed adjuvant oncological treatment. Patient #1 recurred more than 5 years after surgery and received a chemotherapy by PCV. Patient #8 underwent the STUPP protocol, and then multiple additional lines of chemotherapy and stereotactic radiation therapy for multiple remote recurrences.

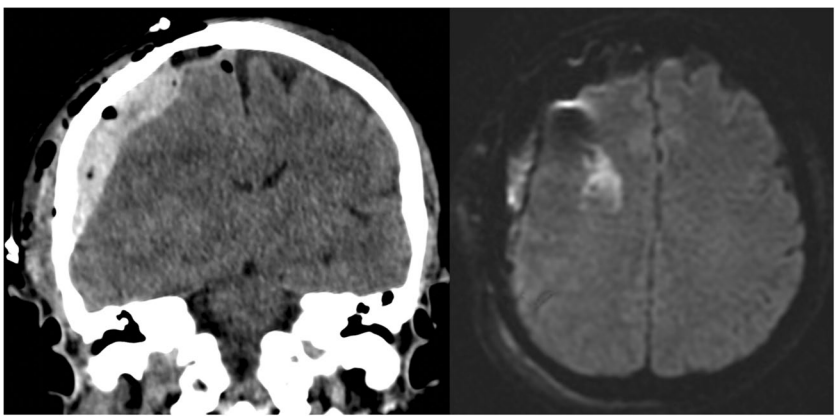

Fig. 5 Post-operative complications in patient #1. Left: coronal CT showing an epidural hematoma at POD 2. Right: Axial diffusion weighted MRI at POD 1 showing a small stroke

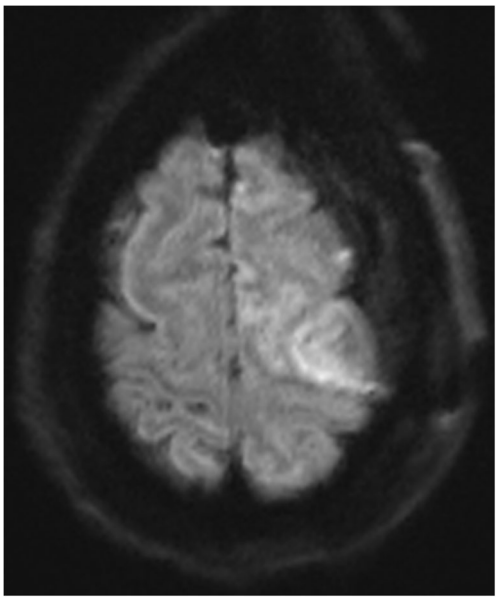

Fig. 6 Post-operative complications in patient #3. Axial diffusion-weighted MRI showing cortical diffuse foci of ischemia of venous origin

Follow-up and survival analysis

The mean follow-up from radiological discovery for our series was 83.4 months (range from 12 to 148). The mean follow-up after surgery was 60.2 months (with a range between 6 and 133 months). Patient #8 died at 39 months after surgery. All other patients had a stable disease on last MRI and were alive at last follow-up.

Discussion

In the present work, we provided oncological, cognitive, epileptical, and professional outcomes in a consecutive series of 11 patients operated on for a DLGG of incidental discovery. We propose to put our results in perspective with the existing literature and to highlight some lessons learned from the present series.

Characteristics of iDLGG

In Tables 4 and 5, we summarized the main findings of the 12 series of iDLGG that we selected and reviewed (see flowchart in supplementary materials and references [8, 14, 17, 18, 21, 22, 33, 35, 37, 38, 45, 46]). All studies including ours converged to establish that the following characteristics of iDLGG are similar to those observed in sDLGG (see [14] in particular): mean age of 40 years, predominance of frontal location, and weighted proportions of astrocytoma (1p19q no codel) and oligodendroglioma (1p19q codel). On the contrary, compared to sDLGG, iDLGG shows a slight female predominance and smaller volume. Not surprisingly, this latter characteristic likely explains the higher rates of complete resection in iDLGG.

The challenge of optimizing onco-functional balance in iDLGG patients

Even if their incidence is growing, iDLGG are still a rare entity nowadays. Because of this rarity, the management remains unclear and debatable [39]. Preventive surgery for iDLGG has been proposed, arguing that the earlier the surgery, the higher the chances to achieve a total or even supratotal tumor resection without permanent deficits [10, 14, 17, 18, 21, 36].

In our center, we sticked to the principle of offering surgery only once tumor growth could be demonstrated on serial MRIs, which might take some time considering the slow growth of these tumors. Accordingly, in our series, the time interval between radiological diagnosis and surgery was 25 months, in line with previous studies (see Tables 4 and 5). This policy is rooted in the observation that up to 18.8% of cases did not show any radiological evolution after a mean follow-up of 46.9 ± 34.9 months in a large series of patients with a suspected iDLGG [6].

In general, the principle of DLGG surgery is to optimize the "onco-functional balance" [11, 27], a challenge particularly difficult for incidentally discovered lesions, as it should always be kept in mind that patients would enjoy a strictly normal life if an MRI would not have been performed for another purpose. Therefore, the bar regarding cognitive and

Table 2 Follow-up changes in main cognitive domains for the 11 patients

	1	2	3	4	5	6	7	8	9	10	11
Language	=	=	=	=	=	=	↘	=	=	=	=
Praxies	=	=	=	=	↘	↗	=	=	=	=	=
Calculus	=	=	=	=	=	↗	NA	=	=	=	=
Memory	=	=	=	=	↘	=	↘	↘	=	=	=
Attention	↘	=	=	=	↘	=	↗	=	=	=	=
Executive functions	↘	=	=	=	↘	↗	↗	↘	=	=	=
Processing speed	=	=	=	=	↘	=	↗	↘	=	=	=

Table 3 Complete raw scores of cognitive testing for the 11 patients, before and 4 months after surgery

		1	2	3	4	5	6	7	8	9	10	11
Language	DO80	80/79	76/NA	73/73	79/78	78/80	79/78	78/80	78/78	77/79	77/79	7/80
	LWF	30/22	34/NA	16/16	40/22	32/34	31/22	38/38	32/32	38/38	39/34	50/51
	CWF	51/35	31/NA	5/3	26/23	36/32	14/14	20/15	15/20	24/23	18/25	28/33
Praxies (Rey figure copy)	Type	IV/II	IV/NA	NA	I	I/I	I/TAYLOR	I/I	NA/I	I/I	IV	I/I
	Score	36/36	34/NA	NA	36/33	35/31	27/33	36/36	NA/36	36/35	35/36	36/36
Calculus		3/3	11:19/NA	NA	11/11.5	0/2	0:1	NA	NA	9/12 vs 6.5/12	NA/NA	6:6/6:6
Memory	WM	6:4/6:3	6/NA	4:2/3:2	4:4/5:6	7:5/6:3	5:3/5:2	6:5/6:6	4:3/4:3	4:3/5:4	5:3/5:3	6:5/7:5
	VEM	28:19/37:10	NA	NA	16:19/16:13	44:27/46:37	16:13/16:15	15:9/15:9	16:30/16:39	16:15/16:15	16:14/16:15	16:15/16:5
Attention and executive functions	PASAT	-/47	NA/NA	NA	52/54	58/57	NA	55/56	48/48	NA	48/44	59/60
	TMT B-A	35″/24″	NA/NA	NA	1″/19″	28″/71″	NA/171″	31″/43″	26″/22″	22″/44″	60″/49″	13″/12″
	Stroop-c	55″/67″	49″/NA	NA	102″/92	74″/77″	173″/162″	125″/148″	112″/65″	117″/89″	111″/99″	68″/65″
	d2—KL	92/90	NA	61″/66″	180″/182″	249/162	113/165	188/181	160″/217″	156″/169″	90/122	234/248
Processing speed	TMT A	32″/43″	12″/NA	82″/80″	24″/22″	34″/28″	42″/32″	26″/33″	18″/15″	39″/19″	22″/31″	19″/17″
	Rey	-/-	120″/NA	NA	NA/58″	56″/62″	88″/92″	128″/82″	NA	119″/97″	134″/126″	100″/145″
	Stroop-n	53″/57″	23″/NA	NA	56″:58″	40″/41″	83″/63″	71″/95″	58″/44″	49″/39″	61″/55″	40″/37″
	d2-GZ	78″/78″	NA/NA	188″/224″	461″/451″	579″/519″	514″/420″	507″/455″	398″/217″	453″/450″	287″/348″	562″/573″

functional outcomes after surgery of iDLGG should be significantly raised.

In the present series, it is demonstrated that the risk of long-term cognitive deficits directly imputable to neural tissue resection is virtually null. Indeed, among the three patients (#1, #5, #8) with cognitive impairments at 4-month follow-up, the deficit could be attributed to the resection of functional connectome in patient #5 only, but this patient fully recovered at 2 years. In patient #8, we suppose the deterioration could be more related to the aggressive nature of the tumor and treatments, hampering optimal reshaping of functional networks thanks to neural plasticity. In patient #1, the suboptimal cognitive outcome might be explained by a small deep stroke (see Fig. 5) within the so-called minimal common brain [16] in a 57 years of age patient. Such mini-strokes have been previously reported in several studies of glioma surgery [5, 12, 19, 24, 41, 44] and they may currently pose a limitation in attaining optimal cognitive outcomes. Indeed, it has been shown that their occurrence correlates with some slight neurocognitive impairments [5, 24]. All in all, the good cognitive results plaids in favor of awake surgery, a methodology that allows to closely monitor cognitive abilities intraoperatively and to tailor the resection according to the brain functional networks of each patient.

Surgery-induced epilepsy represents another caveat. In the present series, one patient developed partial seizures that were a likely consequence of the surgery. This low rate of 9.1% is in good agreement with recent larger series [22, 33].

Nonetheless, these small risks of mini-strokes and epileptogenicity appear to be largely counterbalanced by the risk of a rapid malignant transformation under wait-and-watch policy, as illustrated by patient #8 in the present study and as previously described by others [9].

Accordingly, the oncological outcome of iDLGG was demonstrated to be better than the sDLGG, showing larger delays until tumor progression, with a mean delay of 43.4 months (see Tables 4 and 5). In our series, there were 5 patients that had tumor progressions with an overall mean time to tumor progression of 42 months, very close to previous series. In the largest surgical series comparing iDLGG with sDLGG, it was reported that median survival was not reached for iDLGG versus 14.6 years for sDLGG [14]. However, the true survival advantage remains difficult to estimate, as the analysis should also account for the lead-time bias.

Cognitive assessments in relation to return to work

In a large series of iDLGG patients, Cocherau et al. reported that almost half of the patients with iDLGG had preoperatively a slight cognitive deficit. Thus, the preop neuropsychological assessment is a useful tool for selecting the tasks to be tested during the awake surgery, according to the tumor

Table 4 Comparative series on iLGG: literature review (1)

	N°	Mean age (years)	Sex ratio (female/male)	Tumor localization	Tumor side (right/left)	Pre-op tumor volume (cc)	Time to surgery Mean, range (months)	Reason for MRI
Pallud et al., 2010 (37)	47	35.5	58%/42%	Frontal 68%	51%/49%	Median 17.2	NA	Headache 42.5% Trauma 4.2%
Lima et al., 2017 (22)	11	31.6 (18–50)	73%/27%	Frontal 54.6%	0%/100%	Mean 32.6 (range 2–140)	20.1 (range 3–71)	Headache 45.4% Trauma 9.1%
M.B. Potts et al., 2012 (38)	35	38.4 ± 1.8	57.1%/42.9%	Frontal 65.7%	42.9%/57.1%	Mean 20.2 ± 2.9	10.4 ± 2.3	Headache 31.4% Trauma 20%
Zhang ZY et al., 2014 (46)	23	41.9 ± 2.6	43.5%/56.5%	Frontal 65.3%	NA	Mean 23.8 ± 5.1	NA	Headache 21.7% Trauma 47.8%
Lima GL, Dufau H, 2015 (23)	21	35	71.4%/28.6%	Frontal 52.5%	NA	Mean 39.6 (range 2–142)	11.5 (range 3–42)	Headache 57.1% Trauma 4.8%
Cochereau et al., 2016 (10)	15	38.5 (24–64)	53%/47%	Frontal 46.7%	73.3%/26.7%	Mean 32.6 (range 1–100)	NA	Headache 40% Trauma 6.7%
M. Opoku-Darko et al., 2017 (35)	34	40.8	50%/50%	Frontal 52.9%	56%/44%	57.2	27.6	Headache 26% Trauma 15%
Ng et al., 2019 (41)	74	35.7 ± 9.7	58.1%/41.8%	Frontal/frontoopercular 45.9%	41.9%/58.1%	28.1 ± 27.3 2	34.4 ± 41.1	NA
Ius et al., 2020 (18)	34	37.5 (18–71)	55.8%/44.2%	Frontal 61.8%	58.82%/14.18%	Median 15 (5–40)	NA	Headache 35.3% Trauma 23.5%
Zeng et al., 2021 (45)	49	20–29—14.3% 30–39—36.7% 40–49—46.9% 50–59—2.1%	59.2%/40.8%	Frontal 42.9%	NA	Less than 2:26.5% 2 to 3:59.2% More than 3:14.3%	30 (range 12–60)	Headache 19% Trauma 16%
Gogos et al., 2020 (15)	113	39.4 (18.9–71.3)	55.8%/44.2%	Frontal 58.4%	40.7%/59.3%	Mean 22.5	Median 3.1 (range 1–144)	Headache 34.5% Trauma 16.8%
Ius et al., 2022 (19)	267	39.19 (18–71)	58%/42%	Frontal 52.44%	55.4%/44.6%	Median 15 (1–189)	Median 22 (1–170)	Headache 33% Trauma 13%
Present series	11	36.9	36.4%/63.6%	Frontal 81.8%	54.5%/45.5%	Mean 18 (range 1–79)	Mean 25 (range 3–68)	Headache 45.4% Trauma 9.1%

location and patient expectations regarding their job and hobbies (see [28]). The late cognitive assessments helped us to better guide the rehabilitation program, with the aim to give to the patients the best chances to return to work within the shortest delay.

In this sense, and although it is a multifactorial endpoint, the rate of return to work is an interesting proxy of a cognitively successful surgery. The rate of 90% found in our series is comparable to the 97% reported in the sole other series of the literature in which this parameter was assessed [33]. It is worth noting that it is the cognitive deficit which impeded patient #1 to resume his work, emphasizing the strong link that exists between cognitive evaluations and capability to go back to work.

Strengths and limitations

The main limitation of the study is the small number of patients in the series that is understandable giving the rarity of this neurooncological entity. Moreover, the well-known test–retest effect might have led to underestimate the true rate of cognitive deterioration. Nonetheless, it is anticipated that the 4-month period separating the two evaluations strongly reduced this effect.

Table 5 Comparative series on iLGG: literature review (2)

	EOR:GTR and STR/PR (mean, %)	IDH status	1p/19q co-deletion status	Follow-up since diagnosis/surgery (mean, months)	Post-operative seizures (%)	Time to progression (% and mean period, months)	Return to work (%)
Pallud et al., 2010 (24)	TR—38% STR—26% PR—2% Biopsy—34%	NA	NA	Since diagnosis-mean—91.2	NA	27.6 months	NA
Lima et al., 2017 (2)	Mean—97.3% TR and SupraTR—63.6% STR—36.4%	NA	NA	Since diagnosis—60.3 Since surgery—40.6	0.00%	52 months (28–65)	NA
M.B. Potts et al., 2012 (31)	95.7 ± 1.3 GTR—60% STR—40%	NA	NA	61.2 ± 7.2	NA	34.3%—progression 11.4%—malignant progression 33.9 months	NA
Zhang ZY et al., 2014 (27)	GTR—91.3% STR and PR—8.7%	IDH mutated 95.6%	1p/19q co-deletion 69.6%	Median—111.6	NA	NA	NA
Lima GL, Duffau H, 2015 (25)	Mean—97.3% GT and SupraTR—67% ST—33%	NA	NA	Since surgery—49	Early 4.8% (because of stopping the AED)	33.3% progression 39.9 months	NA
Cochereau et al., 2016 (36)	NA	NA	NA	NA	NA	NA	NA
M. Opoku-Darko et al., 2017 (5)	Mean—81.03%	17.6%—NA or NS* IDH mutated 73.5% IDH wt—8.8%	1p/19q co-deletion—38%	Since diagnosis—61.2	Early 17.6% Late 29.4%	43.8 months (range 3–105 months) RR—23.5% CT—8.8% RT—11.8%	NA
NG et al., 2019 (28)	Mean—95.7 ± 8.2 SupraTR—28.4%	NS* 9.4% IDHwt 12.2% IDH mutated 78.4%	1p19q co-deletion—48.6%	Since surgery—67	Early and late 17.6%	CT 32.4% RT 9.5% RR 32.4% 63.1 months	Before 12 months—86.1% After 12 months—13.9%
Ius et al., 2020 (1)	Median range—100%	IDH1/2 mutated 82.35%	1p/19q codeletion—41.18%	Since diagnosis—70	0.00%	NA	NA
Zeng et al., 2021 (26)	TR—83.7% STR—12.2% PR—4.1%	NA	NA	NA	Early and late—10.2%	NA	NA
Gogos et al., 2020 (37)	Median—100% (90.4–100%) GTR—57.1%	(From 85 available) IDHwt—12.9% IDH mutated—87.1%	1p/19q + —55.3% 1p/19q intact—30.6% Other 1p19q status—1.2%	Since diagnosis—90	Early and late—2.7%	CT 23.9% including 8% CT and RT RR 23.9% 9.7%—malignant progression	NA
Present series	Mean—99.1% GTR—81.8% STR—18.2%	IDH mutated 100%	1p/19q co-deletion—45.4% No–co-deletion—54.6%	Since diagnosis—83.4 Since surgery—60.2	Early 9.1% Late 9.1%	42 months	90%

The strength of the study is that we tried to give a holistic view of postoperative outcomes, including the oncological, neurocognitive, epileptical, and professional status.

Conclusions

The results of this small study are similar with the results of other series in the field and suggest that preventive surgery in iLGG is an available and safe therapeutic option. The earlier the surgery is done, the smaller the tumor and the greater the extent of resection, resulting in better oncological, epileptical, and functional results. The high rate of work resumption combined with the high proportion of supratotal resections in the present series gives further support to this proactive attitude.

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Data Availability Data can be made available upon reasonable request.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee of Lariboisière Hospital and with the 1964 Helsinki declaration and its later amendments. Oral consent to use clinical datas for research purpose was collected in written by the clinicians.

Conflict of interest The authors declare no competing interests.

References

1. Amelot A, De Cremoux P, Quillien V et al (2015) IDH-mutation is a weak predictor of long-term survival in glioblastoma patients. PLoS ONE 10(7):e0130596
2. Aubrun S, Poisson I, Barberis M, Draou C, Toure M, Madadaki C, Froelich S, Gayat E, Mandonnet E (2020) The challenge of overcoming the language barrier for brain tumor awake surgery in migrants: a feasibility study in five patient cases. Acta Neurochir (Wien) 162(2):389–395
3. Barberis M, Poisson I, Facque V, Letrange S, Prevost-Tarabon C, Houdart E, Froelich S, Levy R, Mandonnet E (2022) Group-level stability but individual variability of neurocognitive status after awake resections of right frontal IDH-mutated glioma. Sci Rep 12(1):6126
4. Berger MS, Deliganis AV, Dobbins J, Keles GE (1994) The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer 74(6):1784–1791
5. Berger A, Tzarfati G, Costa M et al (2019) Incidence and impact of stroke following surgery for low-grade gliomas. J Neurosurg 134:1–9
6. Boetto J, Ng S, Duffau H (2021) Predictive evolution factors of incidentally discovered suspected low-grade gliomas: results from a consecutive series of 101 patients. Neurosurgery 88(4):797–803
7. Brickenkamp R (1981) Test d2: Aufmerksamkeits-Belastungs-Test (Test d2: Concentration-Endurance Test: Manual). Verlag fur Psychologie, Gotteningen
8. Cochereau J, Herbet G, Duffau H (2016) Patients with incidental WHO grade II glioma frequently suffer from neuropsychological disturbances. Acta Neurochir (Wien) 158(2):305–312
9. Cochereau J, Herbet G, Rigau V, Duffau H (2016) Acute progression of untreated incidental WHO grade II glioma to glioblastoma in an asymptomatic patient. J Neurosurg 124(1):141–145
10. Duffau H (2013) The rationale to perform early resection in incidental diffuse low-grade glioma: toward a "preventive surgical neurooncology." World Neurosurg 80(5):e115-117
11. Duffau H, Mandonnet E (2013) The "onco-functional balance" in surgery for diffuse low-grade glioma: integrating the extent of resection with quality of life. Acta Neurochir (Wien) 155(6):951–957
12. Gempt J, Förschler A, Buchmann N, Pape H, Ryang Y-M, Krieg SM, Zimmer C, Meyer B, Ringel F (2013) Postoperative ischemic changes following resection of newly diagnosed and recurrent gliomas and their clinical relevance. J Neurosurg 118(4):801–808
13. Godefroy O, Azouvi P, Robert P, Roussel M, LeGall D, Meulemans T, Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group (2010) Dysexecutive syndrome: diagnostic criteria and validation study. Ann Neurol 68(6):855–864
14. Gogos AJ, Young JS, Pereira MP, Morshed RA, Potts MB, Hervey-Jumper SL, Berger MS (2020) Surgical management of incidentally discovered low-grade gliomas. J Neurosurg 1–8. https://doi.org/10.3171/2020.6.JNS201296
15. Grober E, Buschke H, Crystal H, Bang S, Dresner R (1988) Screening for dementia by memory testing. Neurology 38(6):900–903
16. Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H (2011) Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a "minimal common brain." Neuroimage 56(3):992–1000
17. Ius T, Cesselli D, Isola M et al (2020) Incidental low-grade gliomas: single-institution management based on clinical, surgical, and molecular data. Neurosurgery 86(3):391–399
18. Ius T, Ng S, Young JS, Tomasino B, Polano M, Ben-Israel D, Kelly JJP, Skrap M, Duffau H, Berger MS (2022) The benefit of early surgery on overall survival in incidental low-grade glioma patients: a multicenter study. Neuro Oncol 24(4):624–638
19. Jakola AS, Berntsen EM, Christensen P, Gulati S, Unsgård G, Kvistad KA, Solheim O (2014) Surgically acquired deficits and diffusion weighted MRI changes after glioma resection–a matched case-control study with blinded neuroradiological assessment. PLoS One 9(7):e101805
20. Kreatsoulas D, Damante M, Gruber M, Duru O, Elder JB (2023) Supratotal surgical resection for low-grade glioma: a systematic review. Cancers 15(9):2493
21. Lima GLO, Dezamis E, Corns R, Rigaux-Viode O, Moritz-Gasser S, Roux A, Duffau H, Pallud J (2017) Surgical resection of incidental diffuse gliomas involving eloquent brain areas. Rationale, functional, epileptological and oncological outcomes. Neurochirurgie 63(3):250–258
22. de Lima GL, O, Duffau H, (2015) Is there a risk of seizures in "preventive" awake surgery for incidental diffuse low-grade gliomas? J Neurosurg 122(6):1397–1405
23. de Lima GLO, Zanello M, Mandonnet E, Taillandier L, Pallud J, Duffau H (2016) Incidental diffuse low-grade gliomas: from early detection to preventive neuro-oncological surgery. Neurosurg Rev 39(3):377–384
24. Loit M-P, Rheault F, Gayat E, Poisson I, Froelich S, Zhi N, Velut S, Mandonnet E (2019) Hotspots of small strokes in glioma surgery: an overlooked risk? Acta Neurochir (Wien) 161(1):91–98
25. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131(6):803–820
26. Mandonnet E, De Witt Hamer P, Poisson I et al (2015) Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. Neurosurgery 76(4):382–389 (discussion 389)
27. Mandonnet E, Duffau H (2018) An attempt to conceptualize the individual onco-functional balance: why a standardized treatment is an illusion for diffuse low-grade glioma patients. Crit Rev Oncol Hematol 122:83–91
28. Mandonnet E, Herbet G (eds) (2021) Intraoperative mapping of cognitive networks: which tasks for which locations. https://doi.org/10.1007/978-3-030-75071-8
29. Mandonnet E, Pallud J, Clatz O, Taillandier L, Konukoglu E, Duffau H, Capelle L (2008) Computational modeling of the WHO grade II glioma dynamics: principles and applications to management paradigm. Neurosurg Rev 31(3):263–269

30. Mandonnet E, de Witt HP, Pallud J, Bauchet L, Whittle I, Duffau H (2014) Silent diffuse low-grade glioma: toward screening and preventive treatment? Cancer 120(12):1758–1762
31. Metz-Lutz M, Kremin H, Deloche G, Hannequin D, Ferrand L, Perrier D (1991) Standardisation d'un test de dénomination orale: Contrôle des effets de l'âge, du sexe et du niveau de scolarité chez les sujets adultes normaux. Rev Neuropsychol 1:73–95
32. Morris Z, Whiteley WN, Longstreth WT Jr et al (2009) Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 339:b3016
33. Ng S, Herbet G, Moritz-Gasser S, Duffau H (2020) Return to work following surgery for incidental diffuse low-grade glioma: a prospective series with 74 patients. Neurosurgery. https://doi.org/10.1093/neuros/nyz513
34. Opoku-Darko M, Eagles ME, Cadieux M, Isaacs AM, Kelly JJP (2019) Natural history and growth patterns of incidentally discovered diffusely infiltrating low-grade gliomas: a volumetric study. World Neurosurg 132:e133–e139
35. Opoku-Darko M, Lang ST, Artindale J, Cairncross JG, Sevick RJ, Kelly JJP (2018) Surgical management of incidentally discovered diffusely infiltrating low-grade glioma. J Neurosurg 129(1):19–26
36. Pallud J, Capelle L, Taillandier L, Badoual M, Duffau H, Mandonnet E (2013) The silent phase of diffuse low-grade gliomas. Is it when we missed the action? Acta Neurochir (Wien) 155(12):2237–2242
37. Pallud J, Fontaine D, Duffau H et al (2010) Natural history of incidental World Health Organization grade II gliomas. Ann Neurol 68(5):727–733
38. Potts MB, Smith JS, Molinaro AM, Berger MS (2012) Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg 116(2):365–372
39. Pradhan A, Mozaffari K, Ghodrati F, Everson RG, Yang I (2022) Modern surgical management of incidental gliomas. J Neurooncol 159(1):81–94
40. Rey A (1941) L'examen psychologique dans les cas d'encéphalopathie traumatique. Arch Psychol 28:328–336
41. Smith JS, Cha S, Mayo MC, McDermott MW, Parsa AT, Chang SM, Dillon WP, Berger MS (2005) Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury. J Neurosurg 103(3):428–438
42. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, Tihan T, Vandenberg S, McDermott MW, Berger MS (2008) Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 26(8):1338–1345
43. Stroop J (1935) Studies of interference in serial verbal reactions. J Exp Psychol 6:643–662
44. van der Boog ATJ, Rados M, Akkermans A, Dankbaar JW, Kizilates U, Snijders TJ, Hendrikse J, Verhoeff JJC, Hoff RG, Robe PA (2023) Occurrence, risk factors, and consequences of postoperative ischemia after glioma resection: a retrospective study. Neurosurgery 92(1):125–136
45. Zeng L, Mei Q, Li H, Ke C, Yu J, Chen J (2021) A survival analysis of surgically treated incidental low-grade glioma patients. Sci Rep 11(1):8522
46. Zhang Z-Y, Chan AK-Y, Ng H-K et al (2014) Surgically treated incidentally discovered low-grade gliomas are mostly IDH mutated and 1p19q co-deleted with favorable prognosis. Int J Clin Exp Pathol 7(12):8627–8636

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