doi:10.1093/brain/awt345 Brain 2014: 137; 449–462 | 449

BRAIN
A JOURNAL OF NEUROLOGY

Epileptic seizures in diffuse low-grade gliomas in adults

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Diffuse low-grade gliomas are highly epileptogenic brain tumours. We aimed to explore the natural course of epileptic seizures, their predictors and the prognostic significance of their occurrence in adult patients harbouring a diffuse low-grade glioma. An observational retrospective multicentre study examined 1509 patients with diffuse low-grade gliomas to identify mutual interactions between tumour characteristics, tumour course and epileptic seizures. At diagnosis, 89.9% of patients had epileptic seizures. Male gender ($P = 0.003$) and tumour location within functional areas ($P = 0.001$) were independent predictors of a history of epileptic seizures at diagnosis. Tumour volume, growth velocity, cortical location, histopathological subtype or molecular markers did not significantly affect epileptic seizure occurrence probability. Prolonged history of epileptic seizures ($P < 0.001$), insular location ($P = 0.003$) and tumour location close to functional areas ($P = 0.038$) were independent predictors

Received August 9, 2013. Revised October 15, 2013. Accepted October 27, 2013. Advance Access publication December 27, 2013

of uncontrolled epileptic seizures at diagnosis. Occurrence of epileptic seizures ($P < 0.001$), parietal ($P = 0.029$) and insular ($P = 0.002$) locations were independent predictors of uncontrolled epileptic seizures after oncological treatment. Patient age ($P < 0.001$), subtotal ($P = 0.007$) and total ($P < 0.001$) resections were independent predictors of total epileptic seizure control after oncological treatment. History of epileptic seizures at diagnosis and total surgical resection were independently associated with increased malignant progression-free ($P < 0.001$ and $P < 0.001$) and overall ($P < 0.001$ and $P = 0.016$) survivals. Epileptic seizures are independently associated with diffuse low-grade glioma prognosis. Patients diagnosed with epileptic seizures and those with complete and early surgical resections have better oncological outcomes. Early and maximal surgical resection is thus required for diffuse low-grade gliomas, both for oncological and epileptological purposes.

Keywords: diffuse low-grade gliomas; epileptic seizures; prognosis; predictors; surgery

Introduction

Epileptic seizures are one of the most relevant symptomatic expressions of diffuse gliomas in the brain, so that epileptic seizures contribute to glioma diagnosis and impair its evolution (van Breemen *et al*., 2007; Ruda *et al*., 2012). Epileptic seizure incidence varies with tumour type, grade and location and low-grade tumours are more epileptogenic than high-grade tumours (van Breemen *et al*., 2007; Chang *et al*., 2008*a*; Sherman *et al*., 2011). Among these, WHO classified diffuse low-grade gliomas are one of the most highly epileptogenic (Fig. 1A) (van Breemen *et al*., 2007; Chang *et al*., 2008*a*; Sherman *et al*., 2011). Epileptic seizures are the most common presenting sign, occurring in >80% of cases (van Breemen *et al*., 2007; Soffietti *et al*., 2010; Ruda *et al*., 2012) but epileptic seizure history and control rates vary among patients. Identification of predictors of epileptic seizure and of their control in patients with diffuse low-grade glioma is valuable as epilepsy significantly impacts quality of life (Klein *et al*., 2003; Chang *et al*., 2008*a*; Sherman *et al*., 2011). Indeed, both epileptic seizure and antiepileptic drugs predispose patients to cognitive impairments, a central concern during the comparatively long survival of diffuse low-grade glioma, and may impact the oncological outcomes because of possible interactions with chemotherapy and possible direct oncological effects (Klein *et al*., 2003; Ruda *et al*., 2012). In addition to delaying diffuse low-grade glioma progression, oncological treatments [surgery (Chang *et al*., 2008*a*; Jakola, 2012), radiotherapy (Rogers *et al*., 1993; van den Bent *et al*., 2005); and chemotherapy (Brada *et al*., 2003; Pace *et al*., 2003; Hoang-Xuan *et al*., 2004; Frenay *et al*., 2005)] may influence epileptic seizure, particularly in combination with antiepileptic drugs (Fig. 1B) (Soffietti *et al*., 2010). Complete surgical resection is a predictor of epileptic seizure control (Chang *et al*., 2008*a*; You *et al*., 2012) and survival (Sanai and Berger, 2008; Smith *et al*., 2008). However, predictors of epileptic seizure control after oncological treatment are partially unknown and would contribute to improving patient's management during the oncological evolution (Chang *et al*., 2008*a*; Englot *et al*., 2011*a*).

Better understanding the links between epileptic seizure and diffuse gliomas requires studying large series since the dynamic and prolonged interactions between brain, diffuse low-grade glioma and epileptic seizure patterns are highly variable among patients. Systematic literature reviews regarding epileptic seizures and diffuse low-grade glioma are limited by the variability of the data sources and by the number of variables of interest (Englot *et al*., 2011*a*, *b*).

We report our experience of diffuse low-grade glioma-related epilepsy in a large retrospective multicentre series of 1509 adult patients. In this analysis, we studied (i) the prevalence and predictors of epileptic seizure at diagnosis; (ii) the evolution of epileptic seizure during the natural course of the tumour; (iii) epileptic seizure control rates and predictors of epileptic seizure control after first-line oncological treatment; and (iv) the prognostic significance of epileptic seizure on malignant progression-free survival and overall survival. Such information could be of clinical relevance to refine patients' oncological management on an individual basis.

Materials and methods

Data source

We searched the database of a French glioma cooperative study group (Réseau d'Etude des Gliomes) for cases of diffuse low-grade glioma included from 1992 to 2011 and followed until March 2012. Inclusion criteria were (i) patients >18 years of age at diagnosis; (ii) histopathological diagnosis of WHO grade II gliomas, with a neuropathological reassessment for all cases diagnosed before 2007; (iii) supratentorial hemispheric location; and (iv) available follow-up to estimate epileptic seizure history. Although no central pathology review was performed for all patients in the present study, 767 (50.8%) cases had previously been centrally reviewed in the framework of previous studies.

Data collection

Clinical characteristics systematically gathered at the time of histopathological diagnosis from medical records were: gender, age (cut-offs at 30 and 45 years), time to diagnosis (from first symptom to histopathological diagnosis), neurological deficit (absence versus presence), increased intracranial pressure (absence versus presence), Karnofsky performance status (cut-off at 70), history of epileptic seizure at imaging discovery and at histopathological diagnosis (presence versus absence), and first-line oncological treatment modalities. Imaging characteristics systematically gathered at the time of histopathological diagnosis from preoperative MRI were: number of cerebral lobes involved (cut-off at two), corpus callosum involvement (absence versus presence), tumour main anatomical location (frontal versus temporal versus parietal versus insular versus other), tumour

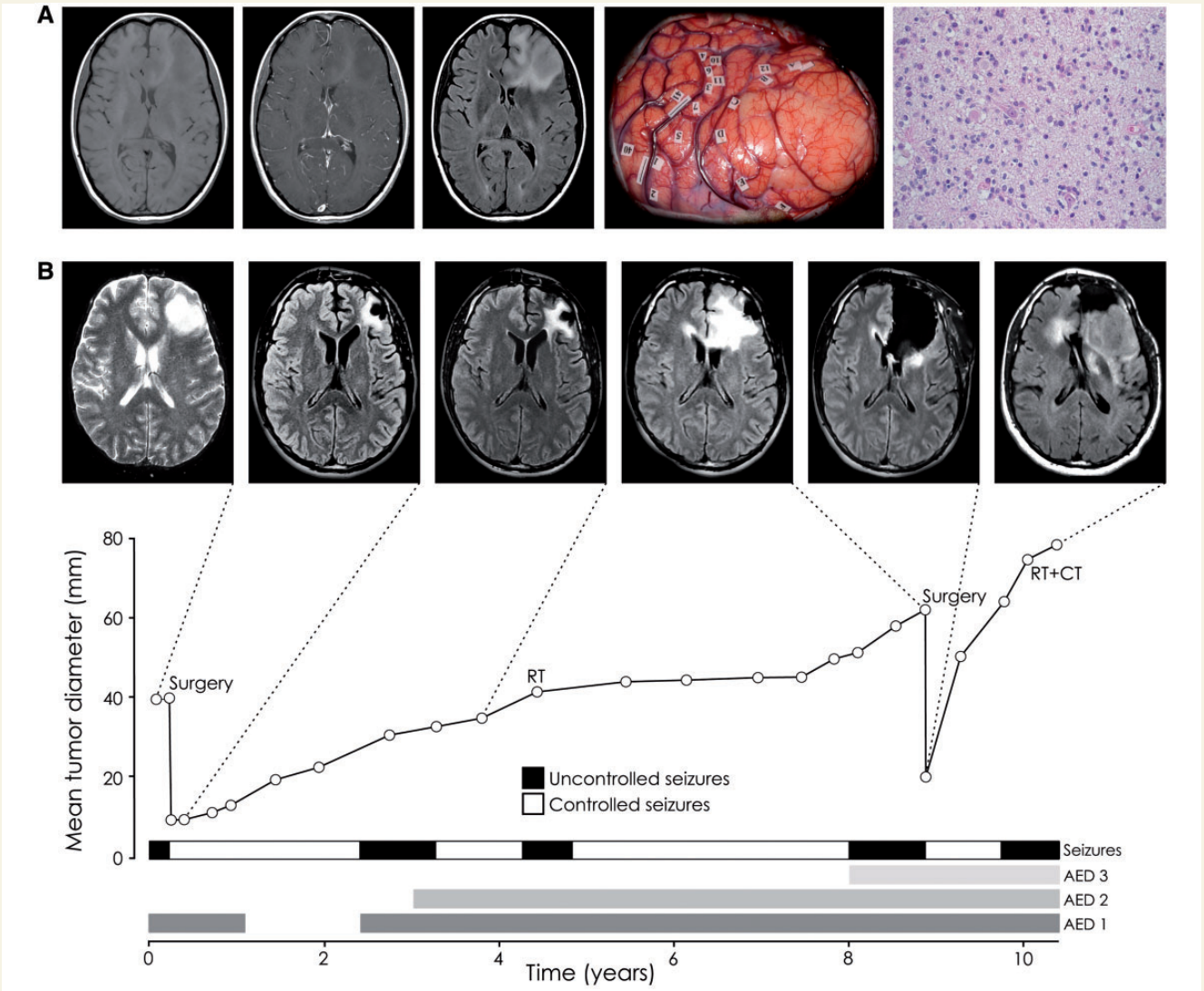

Figure 1 (**A**) Example of a left frontal diffuse low-grade glioma (WHO grade II astrocytoma). The tumour appears as a hypointense region on T_1-weighted imaging (*left*) without contrast enhancement (*mid-left*) and a hyperintense region on FLAIR image (*middle*) (Courtesy of Dr. Raphaëlle Souillard Scemama) and as pale, hypertrophied and infiltrated gyri on intraoperative photographs (*mid-right*) (Courtesy of Dr Edouard Dezamis). The histopathological analysis demonstrates tumour infiltration of cortex by isolated tumour cells (haematoxylin and eosin staining, magnification $\times 100$) (Courtesy of Dr Pascale Varlet). **(B)** Example of the epileptic seizure history along the natural course of a diffuse low-grade glioma. The evolution of the radiographic mean tumour diameter is plotted over time. A 27-year-old right-handed patient presented with simple partial aphasic epileptic seizures controlled with one antiepileptic drug (AED) and a left frontal non-enhanced mass with spontaneous growth on MRI (velocity of diametric expansion at 4.0 mm/year). A subtotal resection was performed and confirmed the diagnosis of a WHO grade II oligodendroglioma. Antiepileptic Drug 1 was stopped ~1 year after this initial operation. The residual tumour progressed (velocity of diametric expansion at 7.8 mm/year) and epileptic seizures recur 2 years post-operatively, requiring the introduction of antiepileptic Drug 2. A conformational external radiotherapy was performed at epileptic seizure recurrence 4 years after surgery, allowing epileptic seizure control and imaging tumour control (velocity of diametric expansion at 0.2 mm/year) over >3 years. Then, epileptic seizures recurred concomitantly to an imaging progression (velocity of diametric expansion at 8.3 mm/year). Epileptic seizures remained uncontrolled despite the introduction of antiepileptic Drug 3 and their control required a second surgery. The patient refused further oncological treatment until epileptic seizures recurred in association with language disturbances and with evidence of a malignant transformation on imaging (velocity of diametric expansion at 47.8 mm/year). Despite aggressive treatment with external conformational radiotherapy (RT) plus concomitant and adjuvant chemotherapy with temozolomide (CT), the tumour progressed and death occurred 10 years after histopathological diagnosis.

main functional location (distant versus close versus within cortical functional areas versus deep-seated extensions, according to Sawaya *et al*. (1998), tumour cortical involvement (presence versus absence), tumour volume (as a continuous or binary variable, $<$ or $\geqslant 100\,cm^3$) based on pretreatment MRI on FLAIR sequences, contrast enhancement (absence versus presence, according to Pallud *et al*., 2009) extent of surgical resection (biopsy versus partial removal with residual tumour $\geqslant 10\,cm^3$ versus subtotal removal with residual tumour

$<10\,cm^3$ versus total removal with no residual tumour, according to Berger *et al*., 1994) based on 3-month postoperative MRIs on FLAIR sequences. Finally, histopathological subtype was collected (astrocytoma versus oligodendroglioma versus mixed glioma) from histopathological report.

We collected supplementary variables to conduct complementary exploratory analyses, based on varying number of patients depending on the missing data patterns. Additional characteristics at the time of histopathological diagnosis were: time to discovery (from first symptom to imaging discovery), time to oncological treatment (from first symptom to first oncological treatment), prognostic scores for diffuse low-grade glioma (Pignatti *et al*., 2002; Chang *et al*., 2008*b*), tumour midline crossing (absence versus presence), spontaneous imaging tumour growth (velocity of diametric expansion on MRI as a continuous or binary variable, $<$ or $\geqslant$8 mm/year; Pallud *et al*., 2006, 2012), tumour cystic component (presence versus absence), proliferation rates (cut-off at 5%), and biomolecular markers (1p19q codeletion, p53 expression, isocitrate deshydrogenase 1 expression, 1p deletion, 19q deletion, 10q deletion, epidermal growth factor receptor amplification).

Endpoints

According to the International League Against Epilepsy, diffuse low-grade glioma-related epilepsy is defined as a history of at least one epileptic seizure with the presence of an enduring alteration in the brain (i.e. the diffuse low-grade glioma) (Fisher *et al*., 2005). History of epileptic seizure and epileptic seizure control status were evaluated at the time of discovery and of diagnosis, at 6 months after first-line oncological treatment and at malignant transformation. The epileptic seizure control was defined as a patient completely free of any epileptic seizure with or without antiepileptic drugs, i.e. Class Ia of Engel Classification and outcome Class 1 of the International League Against Epilepsy classification (Wieser *et al*., 2001).

Overall survival was measured from the date of histopathological diagnosis to the date of death. Malignant progression-free survival was measured from the date of histopathological diagnosis to the date of evidence of malignant transformation or to the date of death. Malignant transformation towards a higher grade of malignancy was considered when contrast enhancement appeared or progressed on MRI or when histopathologically proven (WHO grade III or IV). For surviving patients, these intervals were censored at the date of last follow-up. In addition to calculating the time to assessed endpoints on the basis of the date of histological diagnosis, we also calculated survival times on the basis of the start of symptoms, of the radiological discovery and of the first treatment. The results were not substantially different from those using outcomes measures based on the date of histological diagnosis. Therefore, only the results based on the date of histological diagnosis are presented.

Statistical analyses

To determine factors associated with a history of epileptic seizure or with the epileptic seizure control status after oncological treatment, univariate analyses were carried out, computing unadjusted odds ratios and using the chi-square or Fisher's exact tests for comparing categorical variables, and the unpaired *t*-test or Mann–Whitney rank-sum test for continuous variables, as appropriate. Variables associated at the $P < 0.2$ level in unadjusted analysis were then entered into backward stepwise logistic regression models, with the final model retaining only the variables significant at the $P < 0.05$ level. Unadjusted survival curves for overall survival and malignant progression-free survival were plotted by the Kaplan-Meier method, using log-rank tests to assess significance for group comparison. Cox proportional hazards models were constructed using a backward stepwise approach, adjusting for predictors previously associated with mortality and malignant transformation in univariate analysis. The proportional-hazards assumption was tested with Schoenfeld residuals and was found to hold. Considering the mostly exploratory nature of this study investigating several different outcomes and predictors of various nature, no power calculation had previously been performed and no correction for multiple statistical comparisons was made. Missing data were considered as a specific category in all analyses to ensure stability in sample sizes, a two-tailed *P*-value of < 0.05 was considered significant. Statistical analyses were performed using Stata software version 11.0 (StataCorp).

Results

History of epileptic seizures at histopathological diagnosis

The main characteristics of the population are detailed in Table 1 and in Supplementary Table 1. Of the 1509 patients harbouring a diffuse low-grade glioma that met our selection criteria, 1251 (82.9%) and 1355 (89.8%) had a history of epileptic seizure at discovery and at diagnosis, respectively (Fig. 2A). Only 5.3% of the patients with a history of epileptic seizure at diagnosis presented with apparently primary or secondary generalized epileptic seizure. Other presenting symptoms were increased intracranial pressure (6.3%), neurological deficit (6.0%), and incidental discovery (4.8%). Seizure control status was known in 1031 patients with a history of seizures at diagnosis: 868 (84.2%) patients had controlled seizures that were obtained using antiepileptic drug therapy after a unique seizure in 302 (29.4%) cases and after recurrent seizures in 568 (57.0%) cases (Fig. 2A). Up to 161 (15.6%) patients had uncontrolled seizures at diagnosis despite antiepileptic drug therapy.

Time to discovery was significantly longer in patients presenting with epileptic seizure (mean, 13.9 ± 38.7 months), with (mean, 14.8 ± 27.4 months) and without (mean, 13.9 ± 39.2 months) generalization, than in those presenting with others symptoms (mean, 6.8 ± 16.9 months) ($P = 0.025$). In patients with controlled epileptic seizure, the time to diagnosis was significantly shorter in patients with a single epileptic seizure (mean, 10.2 ± 38.6 months) than in those with recurrent epileptic seizure before antiepileptic drugs (mean, 15.6 ± 41.0 months) ($P = 0.039$). The time to oncological treatment was significantly shorter in patients without epileptic seizure (mean, 11.8 ± 16.1 months) than in those with a history of epileptic seizure at diagnosis (mean, 30.1 ± 51.7 months) ($P < 0.001$). In this latter subgroup, the time to oncological treatment was shorter in patients with controlled epileptic seizure (mean, 30.9 ± 50.4 months) than in those with uncontrolled epileptic seizure despite antiepileptic drugs (mean, 33.1 ± 30.6 months) ($P = 0.050$).

These data confirm that epileptic seizure are the main presenting symptoms for diffuse low-grade glioma and that their overall prevalence increases, together with those of uncontrolled epileptic

Table 1 Main characteristics of the study sample ($n = 1509$)

Clinical parameters		*n*	%
Gender	Female	652	43.2
	Male	857	56.8
Age	<30	390	25.8
	30 to 45	726	48.1
	>45	393	26.0
Time to histological diagnosis	<1 year	1160	76.9
	⩾1 year	305	20.2
	Missing	44	2.9
Karnofsky performance status	>70	1402	92.9
	⩽70	30	2.0
	Missing	77	5.1
Increased intracranial pressure		188	12.5
Neurological deficit		367	24.3
History of seizures at histological diagnosis		1355	89.8
Uncontrolled epileptic seizures after oncological treatment	⩾1	371	24.6
	Missing	521	34.5
Imaging and histopathological parameters at histological diagnosis			
Number of cerebral lobes involved	1	822	54.5
	⩾2	687	45.5
Corpus callosum involvement		281	18.6
Anatomic location	Frontal	759	50.3
	Temporal	274	18.2
	Parietal	142	9.4
	Insular	241	16.0
	Other	93	6.2
Functional location	Distant	186	12.3
	Close	520	34.5
	Within	683	45.3
	Deep-seated	120	8.0
Contrast enhancement	No	1053	69.8
	Yes	306	20.3
	Missing	150	9.9
Cortex involvement	No	126	8.3
	Yes	1080	71.6
	Missing	303	20.1
Tumour volume, cm^3	<100	808	53.5
	⩾100	346	22.9
	Missing	355	23.5
Tumour volume, cm^3 (mean ± SD)		1154	84.4 ± 72.2
Histopathological subtype	Astrocytoma	327	21.7
	Oligodendroglioma	781	51.8
	Mixed glioma	280	18.6
	Missing	121	8.0
Therapeutic parameters			
First-line surgery	Biopsy	619	41.0
	Partial removal	427	28.3
	Subtotal removal	313	20.7
	Total removal	150	9.9
Radiotherapy		424	28.1
Chemotherapy		251	16.6

SD = standard deviation.

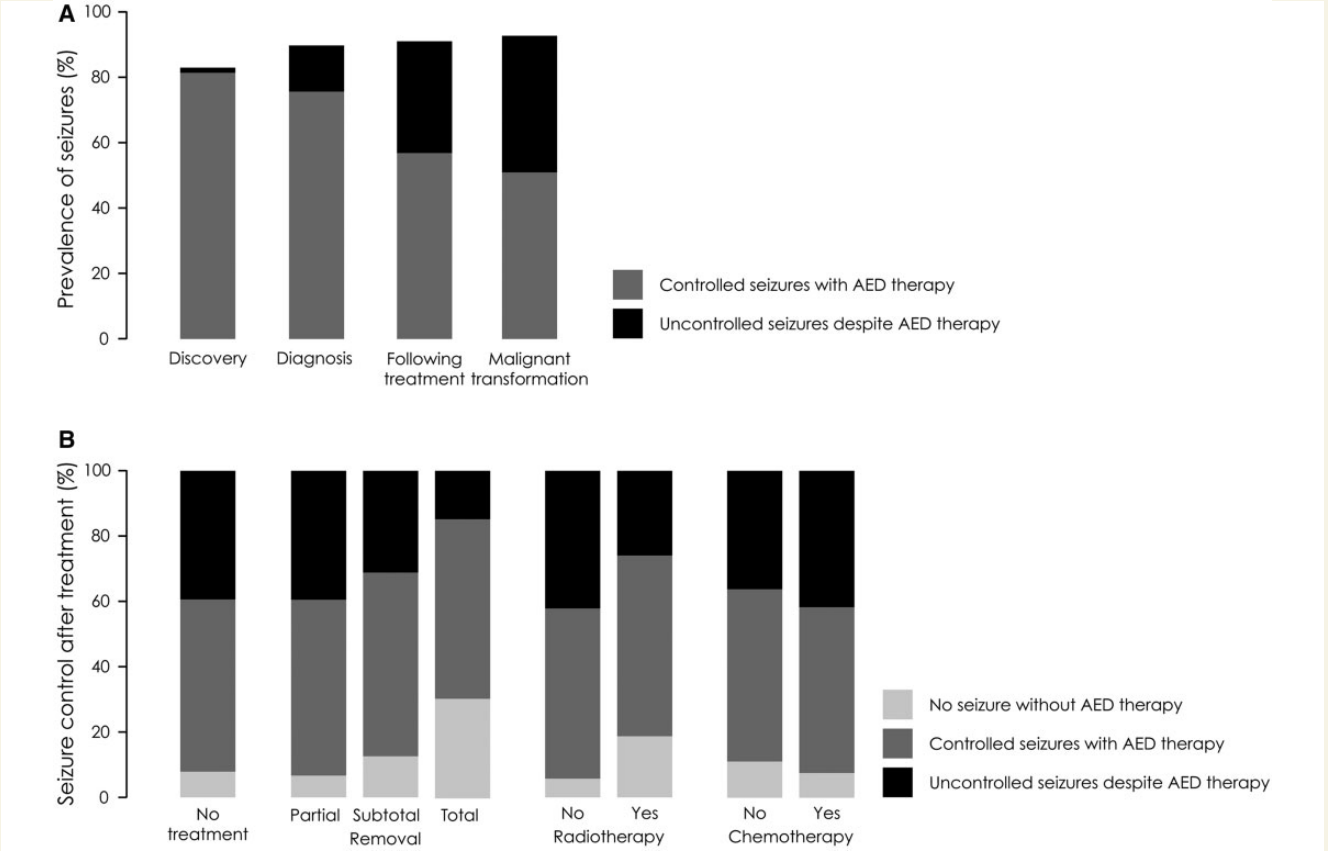

Figure 2 (**A**) Prevalence (%) of controlled (grey) and uncontrolled (black) epileptic seizures with antiepileptic drug (AED) therapy at the time of imaging discovery ('Discovery'), at the time of histopathological diagnosis ('Diagnosis'), at 6 months after first-line oncological treatment ('Following treatment'), and at malignant transformation ('Malignant transformation'). (**B**) Distribution of epileptic seizure control rates at 6 months after first-line oncological treatment (light grey, no epileptic seizure without antiepileptic drugs; dark grey, controlled epileptic seizures with antiepileptic drugs; black, uncontrolled epileptic seizures despite antiepileptic drugs) by first-line oncological treatments [no treatment, surgical removal (partial, subtotal, total), radiotherapy, chemotherapy].

seizure, during the tumour natural course before oncological treatment, from discovery to diagnosis.

Risk factors of epileptic seizures at histopathological diagnosis

Risk factors of a history of epileptic seizure at diagnosis are detailed in Table 2. In multivariate analysis ($n = 1509$, 1355 patients with epileptic seizure), male gender ($P = 0.003$), and tumour close to functional areas ($P = 0.001$) were independently associated with a history of epileptic seizure at diagnosis. An increased intracranial pressure ($P < 0.001$) and a patient age >45 years ($P = 0.007$) were independently associated with no history of epileptic seizure at diagnosis. No significant association was observed for tumour volume, cortical involvement on MRI, tumour growth speed, histopathological subtype, proliferation rates or the expression of biomolecular markers (including 1p19q codeletion, p53 expression and isocitrate dehydrogenase 1 expression).

Risk factors of uncontrolled epileptic seizure at diagnosis are detailed in Supplementary Tables 2 and 3. In multivariate analysis ($n = 1509$, 161 patients with uncontrolled epileptic seizure), prolonged time to diagnosis ($P < 0.001$), insular location ($P = 0.003$) and tumour within functional areas ($P = 0.038$) were independently associated with uncontrolled epileptic seizure at diagnosis.

Taken together, this suggests that the risk factors of epileptic seizure at diagnosis are related to the time interval before management, to the tumour anatomical location and to the presence of other presenting symptoms (particularly increased intracranial pressure).

Epileptic seizures course in oncologically untreated patients

No oncological treatment was administered after stereotactic biopsy in 208 patients because of different oncological management strategies between centres or patients decisions. As compared to oncologically treated patients, this cohort did not significantly differ regarding clinical, imaging and histopathological findings, with the exception of a higher age at discovery in untreated patients (40.5 ± 13.2 versus 37.1 ± 11.8; $P < 0.001$). Among them, 190 (91.8%) had a history of epileptic seizures at

Table 2 Risk factors of a history of epileptic seizures at histological diagnosis

Parameters		History of epileptic seizures at histological diagnosis							
		Yes		Unadjusted odds ratio			Adjusted odds ratio*		
		n	%	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Clinical parameters									
Gender	Female	559	85.7	1 (ref)					
	Male	797	93.0	2.21	1.57–3.11	**$<10^{-3}$**	1.77	1.21–2.58	**0.003**
Age	<30	358	91.8	1 (ref)					
	30 to 45	655	90.2	0.82	0.53–1.28	0.387	1.03	0.63–1.68	0.905
	>45	343	87.3	0.61	0.38–0.98	**0.040**	0.49	0.29–0.83	**0.007**
Time to histological diagnosis	<1 year	1032	89.0	1 (ref)					
	⩾1 year	285	93.4	1.77	1.08–2.88	**0.022**			
	Missing	39	88.6	0.97	0.37–2.50	0.945			
Karnofsky performance status	>70	1273	90.8	1 (ref)					
	⩽70	21	70.0	0.24	0.11–0.53	**$<10^{-3}$**			
	Missing	62	80.5	0.42	0.23–0.76	**0.004**			
Increased intracranial pressure		110	58.5	0.08	0.06–0.12	**$<10^{-3}$**	0.08	0.06–0.13	**$<10^{-3}$**
Neurological deficit		301	82.0	0.38	0.27–0.53	**$<10^{-3}$**			
Imaging and histopathological parameters									
Corpus callosum involvement		232	82.6	0.44	0.30–0.63	**$<10^{-3}$**			
Anatomic location	Frontal	665	87.6	1 (ref)					
	Temporal	251	91.6	1.54	0.96–2.49	0.076			
	Parietal	133	93.7	2.09	1.03–4.24	**0.042**			
	Insular	223	92.5	1.75	1.03–2.97	**0.037**			
	Other	84	90.3	1.32	0.64–2.71	0.451			
Functional location	Distant	160	86.0	1 (ref)					
	Close	491	94.4	2.75	1.57–4.81	**$<10^{-3}$**	2.89	1.57–5.35	**0.001**
	Within	613	89.8	1.42	0.88–2.31	0.152	1.35	0.79–2.31	0.27
	Deep-seated	92	76.7	0.53	0.30–0.97	**0.038**	0.62	0.32–1.23	0.172
Cortex involvement	No	105	83.3	1 (ref)					
	Yes	978	90.6	1.92	1.15–3.20	0.013			
	Missing	273	90.1	1.82	1.00–3.32	0.051			
Tumour volume, cm^3	<100	736	91.1	1 (ref)					
	⩾100	300	86.7	0.64	0.43–0.95	0.025			
	Missing	320	90.1	0.89	0.58–1.37	0.607			

Unadjusted and adjusted odds ratios by logistic regression model ($n = 1509$).
CI = confidence interval; OR = odds ratio.
*Multivariate backward stepwise logistic regression model.
Also tested but not significant in univariate analysis: cerebral lobes involved, contrast enhancement, histopathological subtype.

diagnosis. At that time, 87.3% of the epileptic patients had controlled epileptic seizures obtained using antiepileptic drugs after a single epileptic seizure in 35.1% of cases and after recurrent epileptic seizures in 64.9% of cases. Only 12.7% of them had uncontrolled epileptic seizures despite antiepileptic drugs. At a mean 33.8 ± 46.4 months of follow-up without oncological treatment, 39.4% of patients had uncontrolled epileptic seizures despite antiepileptic drugs and 60.6% of patients had controlled epileptic seizures with and without antiepileptic drugs in 84.1% and 15.9% of cases, respectively. In this subgroup of oncologically untreated patients, there were significantly more uncontrolled epileptic seizures despite antiepileptic drugs after follow-up than at diagnosis ($P < 0.001$). At the end of follow-up without oncological treatment, patients with controlled epileptic seizures at diagnosis remained epileptic seizure-controlled in 89.5% and patients with uncontrolled epileptic seizures at diagnosis remained epileptic seizure-uncontrolled in all cases.

Taken together, these data suggest that epileptic seizure occurrence, epileptic seizure control and medically-refractory status worsen despite antiepileptic drugs during the natural course of untreated diffuse low-grade glioma.

Effects of oncological treatments on epileptic seizures

For 1301 patients, a first oncological treatment was started at a mean interval of 16.0 ± 32.0 months after diagnosis, of which 1164 (89.5%) had a history of epileptic seizure at diagnosis. Seizure control status at 6 months after oncological treatment was known for 988 patients. Among them, seizure control was achieved in 617 (62.4%) cases, using antiepileptic drug therapy in 515 (52.1%) cases and without antiepileptic drug therapy in 102 (10.3%) cases. Three hundred and seventy-one (37.6%) patients had uncontrolled seizures despite antiepileptic drug therapy. After oncological treatment, 70.6% of patients with controlled epileptic seizures at diagnosis remained seizure-free, whereas 29.4% of patients with uncontrolled epileptic seizure at diagnosis became

seizure-free. The time to discovery and the time to diagnosis were longer in patients with uncontrolled epileptic seizures after oncological treatment (mean, 20.7 ± 46.6 and 42.2 ± 66.7 months, respectively) than in those with controlled epileptic seizures after oncological treatment (mean 8.3 ± 19.3 and 16.8 ± 21.8 months, respectively) ($P = 0.047$ and $P = 0.077$, respectively).

The effects of specific oncological treatments on epileptic seizure control status at 6 months after oncological treatment are detailed in Fig. 2B and in Supplementary Table 4. There was no significant difference in epileptic seizure total control status with or without chemotherapy ($P = 0.193$) or radiotherapy ($P = 0.126$). There were significantly more patients with controlled seizures after total and subtotal surgical resections than after partial resection and biopsy in the whole series ($P < 0.0001$). In the subgroup of patients with controlled epileptic seizures after oncological treatment, there were significantly more patients that were seizure-free without antiepileptic drugs after total surgical resection than after subtotal, partial resection and biopsy ($P < 0.001$). Taken together, this suggests that highest rates of controlled epileptic seizures after oncological treatment are obtained by therapeutic modalities including a subtotal or a total surgical resection.

Risk factors of epileptic seizures after oncological treatment

Risk factors of uncontrolled epileptic seizure after oncological treatment are detailed in Table 3 and in Supplementary Table 5. Complete data on epileptic seizure control following oncological treatment were missing for 521 patients (34.5%): when compared with those with a known epileptic seizure control status, patients with missing data for this criterion did not significantly differ on age, gender, clinical symptoms, and tumour location, but had a higher frequency of astrocytoma histopathological subtype ($P < 0.001$), and shortened malignant progression-free survival and overall survival [hazard ratio (HR) = 1.20, $P = 0.013$ and HR = 1.68, $P < 0.001$, respectively), indicating a likely poorer prognosis for these patients.

In multivariate analysis ($n = 988$, 371 patients with uncontrolled epileptic seizure), history of epileptic seizure at diagnosis ($P < 0.001$), tumour parietal ($P = 0.029$) and insular ($P = 0.002$) locations were independently associated with uncontrolled epileptic seizure despite antiepileptic drug therapy after oncological treatment. Age >30–45 years ($P = 0.010$) and >45 years at diagnosis ($P < 0.001$), subtotal ($P = 0.007$) and total ($P < 0.001$) surgical resections were independently associated with controlled epileptic seizure after oncological treatment. Taken together, this suggests that the main prognostic parameters of epileptic seizure control after oncological treatment are age, tumour location and extent of resection.

Oncological prognostic significance of epileptic seizures

Survival curves are detailed in Fig. 3. During the follow-up period (mean 82 ± 65 months from diagnosis), 708 (45.8%) patients presented a malignant transformation [mean 63 ± 54 months, median malignant progression-free survival 99 months (95% confidence interval (CI) 91–107) since diagnosis] that was histopathologically proven in 357 cases (50.4%, 313 grade III, 44 grade IV), the remaining 351 cases were diagnosed on clinical and imaging follow-up. Analyses are detailed in Table 4 and Supplementary Table 6. In multivariate analysis ($n = 1509$), male gender ($P = 0.001$), increased intracranial pressure ($P = 0.016$), contrast enhancement ($P < 0.001$), cortex involvement ($P = 0.004$) and tumour volume ($P = 0.007$) were independently associated with shorter malignant progression-free survival. History of epileptic seizure at diagnosis ($P < 0.001$), partial ($P < 0.001$), subtotal ($P < 0.001$) and total ($P < 0.001$) surgical resections, chemotherapy ($P < 0.001$) and radiotherapy ($P < 0.001$) were independently associated with longer malignant progression-free survival. Thus, a history of epileptic seizure at diagnosis was a strong independent protective prognostic parameter for malignant transformation: it occurred at a mean time from diagnosis of 65.1 ± 54.8 and 39.5 ± 28.3 months, respectively, for the subgroup of patients with and without a history of epileptic seizure at diagnosis.

During the follow-up period, 370 (24.0%) patients died [mean 91 ± 68 months, median overall survival 182 months (95% CI, 168–203) since diagnosis]. Analyses are detailed in Table 4 and Supplementary Table 6. In multivariate analysis ($n = 1509$), male gender ($P = 0.001$), age > 45 years at diagnosis ($P = 0.005$), tumour temporal ($P = 0.024$) and insular ($P < 0.0001$) locations, tumour volume ($P < 0.001$), and radiotherapy ($P = 0.010$) were independently associated with shorter overall survival. History of epileptic seizure at diagnosis ($P < 0.001$) and total surgical resection ($P = 0.016$) were independently associated with longer overall survival. Thus, a history of epileptic seizure at diagnosis was a strong independent protective prognostic parameter for overall survival: patients died at a mean time from histopathological diagnosis of 92.3 ± 69.1 and 51.1 ± 38.0 months, respectively, for the subgroup of patients with and without a history of epileptic seizure at diagnosis.

Discussion

Supratentorial diffuse low-grade gliomas are one of the most epileptogenic cerebral lesions and share long survivals. The evaluation of the prognostic significance of seizures and the identification of predictors of their occurrence and control in patients with diffuse low-grade glioma is essential and requires studies based on large series of patients over a long follow-up. However, the available recent literature contains sparse studies on that topic, including two monocentric studies of 332 and 508 patients, respectively, and a systematic literature review with meta-analysis, pooling 773 patients from 20 small-sized studies (Chang *et al.*, 2008*a*; Englot *et al.*, 2011*a*; You *et al.*, 2012). Though well conducted and interesting, the contribution of these studies is limited by their restriction to postoperative seizure control, the lack of long-term follow-up, and the heterogeneity of the data sources used. There is a general agreement from those previous reports on the need for a multi-institutional study pooling a large number of cases. The present study explored data on epilepsy during the natural course of diffuse low-grade gliomas in a large observational multicentre investigation. The strength of this study lies in: (i) its large

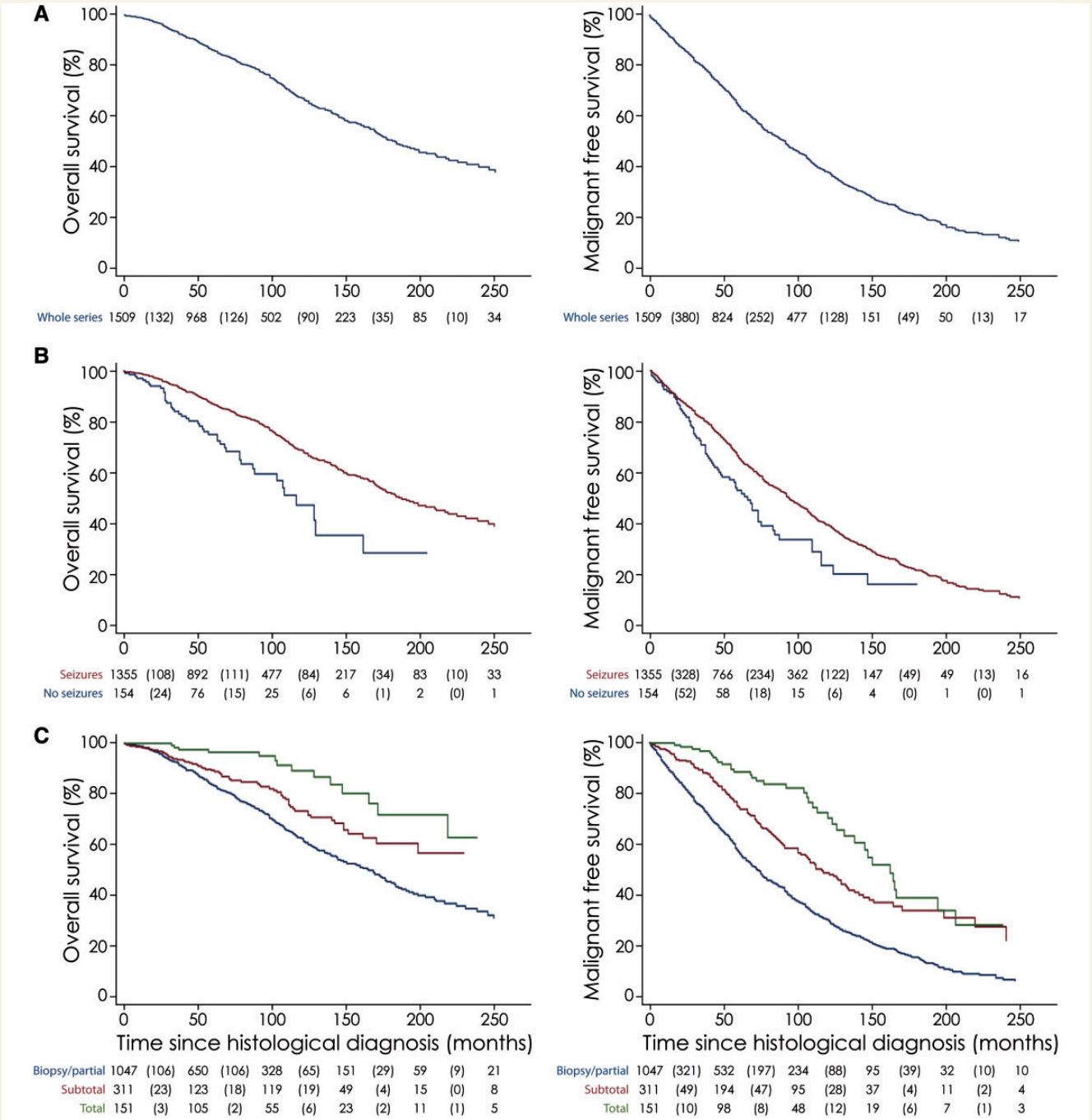

Figure 3 Kaplan-Meier estimates of overall survival and malignant progression-free survival according to history of epileptic seizures and to extent of surgical resection. (**A**) Overall survival and malignant progression-free survival in the series of 1509 diffuse low-grade gliomas. (**B**) Overall survival and malignant progression-free survival according to history of epileptic seizures. The hazard ratio for death among patients with a history of epileptic seizures at histopathological diagnosis, as compared with those without a history of epileptic seizures was 0.39 (95% CI, 0.28–0.54; $P < 0.001$). The hazard ratio for death or malignant progression among patients with a history of epileptic seizures at histopathological diagnosis, as compared with those without a history of epileptic seizures was 0.60 (95% CI, 0.46–0.77; $P < 0.001$). (**C**) Overall survival and malignant progression-free survival according to the extent of surgical resection. The hazard ratio for death among patients that underwent a total surgical resection and a subtotal surgical resection, as compared with those that underwent a partial surgical resection or a biopsy were 0.51 (95%CI, 0.30–0.88; $P = 0.016$) and 0.81 (95% CI, 0.59–1.10; $P = 0.169$), respectively. The hazard ratio for death or malignant progression among patients that underwent a total surgical resection and a subtotal surgical resection, as compared with those that underwent a partial surgical resection or a biopsy were 0.22 (95% CI, 0.16-0.32; $P < 0.001$ and 0.43 (95% CI, 0.35–0.53), respectively.

Table 3 Risk factors of uncontrolled epileptic seizures after first-line oncological treatment

Parameters		Uncontrolled epileptic seizures after oncological treatment							
		Yes		Unadjusted odds ratio			Adjusted odds ratio*		
		n	%	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Clinical parameters									
Age	<30	114	44.2	1 (ref)					
	30 to 45	179	36.9	0.74	0.54–1.00	0.054	0.65	0.47–0.90	**0.010**
	>45	78	31.8	0.59	0.41–0.85	**0.005**	0.50	0.34–0.74	**$<10^{-3}$**
Time to diagnosis	<1 year	274	36.0	1 (ref)					
	⩾1 year	89	45.9	1.51	1.10–2.08	**0.011**			
	Missing	8	25.0	0.59	0.26–1.34	0.209			
Karnofsky performance status	>70	357	37.4	1 (ref)					
	⩽70	6	27.3	0.63	0.24–1.62	0.334			
	Missing	8	66.7	3.34	1.00–11.19	**0.050**			
Increased intracranial pressure		30	26.8	0.57	0.37–0.89	**0.013**			
History of seizures at histological diagnosis		362	40.7	6.87	3.42 - 13.81	**$<10^{-3}$**	5.73	2.82–11.63	**$<10^{-3}$**
Imaging and pathological parameters									
Cerebral lobes involved	1	182	33.2	1 (ref)					
	⩾2	189	43.0	1.51	1.17–1.96	**0.002**			
Anatomic location	Frontal	162	32.5	1 (ref)					
	Temporal	67	38.3	1.29	0.90–1.85	0.162	1.17	0.80–1.70	0.414
	Parietal	42	47.2	1.86	1.18–2.93	**0.008**	1.71	1.06–2.75	**0.029**
	Insular	84	51.2	2.18	1.53–3.13	**$<10^{-3}$**	1.79	1.23–2.62	**0.002**
	Other	16	26.2	0.74	0.41–1.35	0.325	0.66	0.35–1.22	0.185
Functional location	Distant	23	21.7	1 (ref)					
	Close	138	40.2	2.43	1.46–4.04	**0.001**			
	Within	189	40.3	2.44	1.48–4.01	**$<10^{-3}$**			
	Deep-seated	21	30.0	1.55	0.78–3.08	0.215			
Tumour volume, cm^3	<100	197	34.7	1 (ref)					
	⩾100	99	43.0	1.42	1.04–1.95	**0.027**			
	Missing	75	39.5	1.23	0.88–1.72	0.234			
Therapeutic parameters									
First-line surgery	Biopsy	186	44.3	1 (ref)					
	Partial removal	110	39.9	0.83	0.61–1.13	0.248	0.82	0.59–1.14	0.232
	Subtotal removal	58	31.7	0.58	0.40–0.84	**0.004**	0.59	0.40–0.87	**0.007**
	Total removal	17	15.6	0.23	0.13–0.40	**$<10^{-3}$**	0.25	0.14–0.44	**$<10^{-3}$**

Unadjusted and adjusted odds ratios by logistic regression model ($n = 988$).
CI = confidence interval; OR = odds ratio.
*Multivariate backward stepwise logistic regression model.
Also tested but not significant in univariate analysis: gender, age, neurological deficit, corpus callosum involvement, contrast enhancement, cortex involvement, histopathological subtype, radiotherapy, chemotherapy.

population of 1509 patients, the largest ever studied on diffuse low-grade glioma in adults to our knowledge; (ii) the homogeneous data collection from an observational French multicentre database; (iii) the long-term follow-up allowing the assessment of the independent role of epilepsy within a survival analysis framework; (iv) the inclusion of multiple variables of interest, including novel ones (molecular markers, tumour growth speed); (v) the concomitant search for spontaneous risk factors of epileptic seizure, risk factors of epileptic seizures after treatment and prognostic significance of epileptic seizures; and (vi) the potential bias induced by data missing was limited by their systematic incorporation in each statistical analysis as a specific category. Our findings should be interpreted with full consideration of the retrospective and exploratory nature of the analyses and thus should be validated within other prospective large databases.

We studied both the effects of epileptic seizures on diffuse low-grade glioma diagnosis and evolution, and the effects of diffuse low-grade glioma on tumour-related epilepsy in an observational retrospective multicentre study of 1509 supratentorial hemispheric cases in adults. Our findings suggest that (i) risk factors of epileptic seizure at diagnosis are related to the anatomical and functional tumour locations and to the presence of competitive other symptoms (neurological deficit, increased intracranial pressure); (ii) control of epileptic seizures and their medically-refractory status worsen during the natural course of diffuse low-grade glioma; (iii) epileptic seizure control after oncological treatment is related to the tumour's anatomical findings and to the extent of surgical resection; and (iv) a history of epileptic seizures at diagnosis is a strong favourable independent prognostic parameter for malignant progression-free survival and overall survival, suggesting that that the epileptic seizure status may contribute to adapt the treatment procedure.

We confirm that epileptic seizures are the primary symptom for diffuse low-grade glioma in adults and progress during the natural

Table 4 Univariate and multivariate predictors of malignant progression-free survival and overall survival

Parameters		Overall survival (months)						Malignant progression free survival (months)					
		Unadjusted Hazard Ratio			Adjusted Hazard Ratio			Unadjusted Hazard Ratio			Adjusted Hazard Ratio		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Clinical parameters													
Gender	Female	1 (ref)						1 (ref)					
	Male	1.34	1.09–1.64	**0.005**	1.44	1.17–1.78	**0.001**	1.25	1.09–1.44	**0.002**	1.28	1.11–1.48	**0.001**
Age	<30	1 (ref)						1 (ref)					
	30 to 45	1.31	1.02–1.67	**0.035**	1.22	0.95–1.58	0.124	1.12	0.95–1.33	0.171			
	>45	1.64	1.24–2.16	**0.001**	1.51	1.13–2.01	**0.005**	1.23	1.01–1.49	**0.038**			
Time to diagnosis	<1 year	1 (ref)						1 (ref)					
	⩾1 year	0.92	0.72–1.18	0.535				0.96	0.81–1.14	0.654			
	Missing	0.82	0.42–1.60	0.566				1.02	0.69–1.49	0.937			
Karnofsky performance status	>70	1 (ref)						1 (ref)					
	⩽70	1.62	0.87–3.05	0.131				1.61	1.04–2.49	**0.032**			
	Missing	1.98	1.41–2.78	**$<10^{-3}$**				1.34	1.01–1.78	**0.043**			
Increased intracranial pressure		1.58	1.19–2.09	**0.002**				1.57	1.28–1.92	**$<10^{-3}$**	1.31	1.05–1.63	**0.016**
Neurological deficit		1.40	1.12–1.73	**0.003**				1.23	1.05–1.44	**0.010**			
History of seizures at histological diagnosis		0.48	0.35–0.66	**$<10^{-3}$**	0.39	0.28–0.54	**$<10^{-3}$**	0.67	0.53–0.85	**0.001**	0.60	0.46–0.77	**$<10^{-3}$**
Uncontrolled seizures after oncological treatment	None	1 (ref)						1 (ref)					
	⩾1	1.23	0.94–1.61	0.126	1.20	0.91–1.59	0.206	1.10	0.92–1.31	0.287			
	Missing	1.84	1.46–2.32	**$<10^{-3}$**	1.80	1.42–2.29	**$<10^{-3}$**	1.25	1.06–1.46	**0.008**			
Imaging and pathological parameters													
Cerebral lobes involved	1	1 (ref)						1 (ref)					
	⩾2	1.58	1.30–1.92	**$<10^{-3}$**				1.50	1.31–1.72	**$<10^{-3}$**			
Corpus callosum involvement		1.36	1.06–1.74	**0.015**	1.54	1.11–2.14	**0.01**	1.52	1.28–1.80	**$<10^{-3}$**			
Anatomic location	Frontal	1 (ref)						1 (ref)					
	Temporal	1.25	0.95–1.64	0.112	1.40	1.05–1.87	**0.024**	1.01	0.83–1.22	0.958			
	Parietal	1.18	0.83–1.68	0.347	1.12	0.78–1.61	0.537	1.06	0.83–1.36	0.632			
	Insular	1.92	1.48–2.50	**$<10^{-3}$**	1.71	1.28–2.28	**$<10^{-3}$**	1.38	1.14–1.67	**0.001**			
	Other	1.38	0.93–2.06	0.112	1.19	0.78–1.82	0.413	1.42	1.09–1.86	**0.010**			
Functional location	Distant	1 (ref)						1 (ref)					
	Close	1.36	0.96–1.94	0.086				1.38	1.08–1.77	**0.010**			
	Within	1.81	1.29–2.53	**0.001**				1.66	1.31–2.11	**$<10^{-3}$**			
	Deep-seated	1.45	0.91–2.30	0.119				1.74	1.27–2.39	**0.001**			
Contrast enhancement	No	1 (ref)						1 (ref)					
	Yes	1.29	1.01–1.64	**0.041**				1.42	1.20–1.67	**$<10^{-3}$**	1.37	1.15–1.63	**$<10^{-3}$**
	Missing	1.73	1.28–2.33	**$<10^{-3}$**				1.57	1.26–1.96	**$<10^{-3}$**	1.16	0.88–1.53	0.284
Cortex involvement	No	1 (ref)						1 (ref)					
	Yes	0.95	0.69–1.31	0.746				1.34	1.05–1.70	**0.018**	1.44	1.13–1.84	**0.004**
	Missing	1.12	0.78–1.59	0.539				0.95	0.72–1.26	0.739	1.17	0.83–1.63	0.369
Tumour volume, cm^3	<100	1 (ref)						1 (ref)					
	⩾100	1.80	1.40–2.30	**$<10^{-3}$**	1.31	1.00–1.71	0.052	1.62	1.37–1.90	**$<10^{-3}$**	1.27	1.07–1.51	**0.007**
	Missing	2.04	1.62–2.57	**$<10^{-3}$**	1.84	1.45–2.34	**$<10^{-3}$**	1.10	0.92–1.30	0.288	1.24	0.95–1.61	0.111
Histological subtype	Astrocytoma	1 (ref)						1 (ref)					
	Oligodendroglioma	0.77	0.61–0.98	**0.035**	1.02	0.86–1.20	0.849	1.02	0.86–1.20	0.849	1.07	0.90–1.28	0.453
	Mixed glioma	0.69	0.50–0.96	**0.026**	1.01	0.82–1.26	0.910	1.01	0.82–1.26	0.910	1.13	0.90–1.41	0.292
	Missing	1.31	0.96–1.78	0.089	0.59	0.44–0.78	**0.001**	0.59	0.44–0.78	**$<10^{-3}$**	0.64	0.44–0.92	**0.017**

(continued)

Table 4 Continued

Parameters		Overall survival (months)						Malignant progression free survival (months)					
		Unadjusted Hazard Ratio			Adjusted Hazard Ratio			Unadjusted Hazard Ratio			Adjusted Hazard Ratio		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Therapeutic parameters													
First-line surgery	Biopsy	1 (ref)						1 (ref)					
	Partial removal	0.95	0.76–1.19	0.663	1.10	0.87–1.40	0.409	0.83	0.71–0.97	**0.019**	0.68	0.58–0.81	$< 10^{-3}$
	Subtotal removal	0.62	0.47–0.82	**0.001**	0.81	0.59–1.10	0.169	0.51	0.42–0.62	$< 10^{-3}$	0.43	0.35–0.53	$< 10^{-3}$
	Total removal	0.32	0.20–0.53	$< 10^{-3}$	0.51	0.30–0.88	**0.016**	0.29	0.21–0.41	$< 10^{-3}$	0.22	0.16- 0.32	$< 10^{-3}$
Radiotherapy		1.60	1.31–1.96	$< 10^{-3}$	1.31	1.07–1.60	**0.010**	0.88	0.76–1.03	0.104	0.71	0.61–0.83	$< 10^{-3}$
Chemotherapy		0.92	0.69–1.22	0.553				0.81	0.67–0.99	**0.040**	0.54	0.44–0.67	$< 10^{-3}$

Unadjusted hazard ratios (HR) by logrank tests and adjusted hazard ratios by Cox proportional hazards model ($n = 1509$).
CI = confidence interval; HR = hazard ratio.

course of the tumour (Hildebrand *et al*., 2005; Bauman *et al*., 2009; Danfors *et al*., 2009). We observe that (i) seizure rates increased from 83% at discovery to 90% at diagnosis; and (ii) seizure control rates decreased during the natural course of both treated and untreated diffuse low-grade gliomas, suggesting the delayed occurrence of epileptic seizure and of uncontrolled epileptic seizure. In accordance, the epileptic seizure control rates at diagnosis and at 6 months after oncological treatment relate to the timing of oncological management. These findings emphasize the value of an early oncological intervention for an improved epileptic seizure control.

We found no significant association between epileptic seizure and tumour volume, tumour growth speed, histopathological findings, tumour growth speed and molecular correlates. Regarding molecular markers, it has been previously suggested that diffuse low-grade gliomas without 19q deletion were most likely to present with epileptic seizures in a series of 103 patients and that proliferation rates were associated with epileptic seizure outcomes in two series of 508 and 93 patients, respectively (Huang *et al*., 2011; You *et al*., 2012; Yuan *et al*., 2013). We failed to find such associations in our complementary analyses performed on 527 and 427 patients, respectively. These findings should be interpreted with caution, given the low statistical power and potential bias resulting from the high rate of missing data for the molecular parameters in our database, particularly for the *IDH1* mutation status. The study of the possible links between molecular markers and epileptic seizures remains of paramount importance. In accordance with an emerging hypothesis regarding glioma-related epileptogenicity, we found no association between epileptic seizure history and histopathological findings, tumour growth speed and molecular correlates, suggesting that glioma-related epileptic seizures may not be triggered by specific intrinsic tumour properties (de Groot *et al*., 2011; Pallud *et al*., 2013). Conversely, our data also demonstrated that tumour anatomical and functional locations were predictive of epileptic seizure incidence, suggesting that glioma-related epileptic seizures may be triggered by interactions between glioma and neocortex. Electrophysiological recordings and histopathological analyses support this hypothesis by demonstrating that epileptic seizures arise from the peritumoral neocortex and not from the tumour core and that infiltrated isolated glioma cells permeate the peritumoral neocortex (Haglund *et al*., 1992; Berger *et al*., 1993; Senner *et al*., 2004; Pallud *et al*., 2010, 2013; Buckingham *et al*., 2011; de Groot *et al*., 2011; Gerin *et al*., 2013).

Additionally, we confirm that the extent of surgical resection is an independent predictor of controlled epileptic seizures at 6 months after oncological treatment (Chang *et al*., 2008*a*; Englot *et al*., 2011*a*; You *et al*., 2012). Consequently, a maximal resection may not only provide an oncological benefit, but impacts epileptological outcome of patients with diffuse low-grade glioma. It should be noted that surgical resection was performed using intraoperative functional cortical and subcortical mapping allowing extensive resection while preserving eloquent brain areas but without the use of intraoperative electrophysiology such as electrocorticography, which may affect the epileptological outcomes (Berger *et al*., 1993; Englot *et al*., 2011*a*; De Witt Hamer *et al*., 2012). Interestingly, adjuvant chemotherapy and radiotherapy were not independent predictors of total seizure control, although they both reduce seizure frequency. We examined seizure control rates at

6 months after treatment, but did not quantify changes in seizure frequency beyond this interval, as seizure freedom, alone, appears to determine quality of life (Klein *et al*., 2003). Therefore, our results do not necessarily contradict other known effects of radiotherapy (Rogers *et al*., 1993; Soffietti *et al*., 2010) and chemotherapy (Brada *et al*., 2003), which have been associated with a decrease in seizure frequency (Hildebrand *et al*., 2005; van den Bent *et al*., 2005; Sherman *et al*., 2011).

Occurrence of epileptic seizure independently impacted diffuse low-grade glioma prognosis, as both malignant progression-free survival and overall survival were longer in patients with a history of epileptic seizures. This effect was not related to the time to oncological treatment as it was paradoxically delayed in patients presenting with epileptic seizures.

In conclusion, epileptic seizure progression during the natural course of diffuse low-grade glioma and the effects of surgical resection on seizure control rates argue for early neurosurgical intervention and maximal resection. Moreover, epileptic seizure status at diagnosis can help clinical follow-up, as patients without a history of seizures, and particularly those with neurological deficit and with increased intracranial pressure, are at higher risk for worsened oncological outcomes.

Acknowledgements

These physicians are greatly acknowledged (in alphabetical order): Georges Abi-Lahoud, Valérie Bernier, Françine Chassoux, Philippe Colin, Fabrice Chrétien, Frédéric Dhermain, Julien Domont, Marc Frenay, Maria Koziak, Elisabeth Landre, Michael Mann, Jean-François Meder, Charles Mellerio, Charles Mellerio, Karima Mokhtari, François Nataf, Catherine Oppenheim, François-Xavier Roux, Raphaëlle Souillard-Scemama, Baris Turak, Pascale Varlet.

Supplementary material

Supplementary material is available at *Brain* online.

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