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Neuro-Oncology

25(4), 701–709, 2023 | https://doi.org/10.1093/neuonc/noac197 | Advance Access date 16 August 2022

IDH1/2 wildtype gliomas grade 2 and 3 with molecular glioblastoma-like profile have a distinct course of epilepsy compared to *IDH1/2* wildtype glioblastomas

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Abstract

Background. *IDH1/2* wildtype (IDHwt) glioma WHO grade 2 and 3 patients with p*TERT* mutation and/or *EGFR* amplification and/or + 7/–10 chromosome gain/loss have a similar overall survival time as IDHwt glioblastoma patients, and are both considered glioblastoma IDHwt according to the WHO 2021 classification. However, differences in seizure onset have been observed. This study aimed to compare the course of epilepsy in the 2 glioblastoma subtypes.

Methods. We analyzed epilepsy data of an existing cohort including IDHwt histologically lower-grade glioma WHO grade 2 and 3 with molecular glioblastoma-like profile (IDHwt hLGG) and IDHwt glioblastoma patients. Primary outcome was the incidence proportion of epilepsy during the disease course. Secondary outcomes included, among others, onset of epilepsy, number of seizure days, and antiepileptic drug (AED) polytherapy.

Results. Out of 254 patients, 78% (50/64) IDHwt hLGG and 68% (129/190) IDHwt glioblastoma patients developed epilepsy during the disease ($P = .121$). Epilepsy onset before histopathological diagnosis occurred more frequently in IDHwt hLGG compared to IDHwt glioblastoma patients (90% vs 60%, $P < .001$), with a significantly longer median time to diagnosis (3.5 vs 1.3 months, $P < .001$). Median total seizure days was also longer for IDHwt hLGG patients (7.0 vs 3.0, $P = .005$), and they received more often AED polytherapy (32% vs 17%, $P = .028$).

Conclusions. Although the incidence proportion of epilepsy during the entire disease course is similar, IDHwt hLGG patients show a significantly higher incidence of epilepsy before diagnosis and a significantly longer median time between first seizure and diagnosis compared to IDHwt glioblastoma patients, indicating a distinct clinical course.

Key Points

- IDHwt hLGG patients presented more often with epilepsy as IDHwt glioblastoma.
- Course of epilepsy is more protracted in IDHwt hLGG compared to IDHwt glioblastomas.
- Earlier recognition of epilepsy might result in earlier treatment of IDHwt hLGG.

Importance of the Study

According to the latest WHO 2021 Classification criteria, glioblastomas IDHwt comprise both IDHwt glioblastoma and histologically WHO grade 2 and 3 IDHwt glioma with molecular glioblastoma-like profile (IDHwt hLGG). Despite their comparable overall survival time, we observed a distinct course of epilepsy in patients with IDHwt hLGG. Although, the proportion of patients with epilepsy was similar, IDHwt hLGG had a significantly longer history of seizures before histopathological diagnosis compared to IDHwt glioblastoma patients. This distinct clinical course of epilepsy is further illustrated by our findings that IDHwt hLGG patients presented more often with epilepsy, had more seizure days before diagnosis and were prescribed more often antiepileptic drug polytherapy compared to IDHwt glioblastoma patients. Early recognition of epilepsy could expedite tumor diagnosis in this subtype of glioblastoma with histological characteristics of LGG.

Epilepsy is frequently observed in patients with a glioma, with prevalence up to 90%, depending on histological tumor grade, tumor location, and type of antitumor treatment.[1,2] The occurrence of seizures is inversely correlated with the growth rate of the tumor, for example, glioneural tumors and diffuse low-grade gliomas show the highest seizure prevalence.[3,4] In patients with a glioblastoma, epilepsy has been shown an independent, favorable prognostic factor for survival.[5] Nowadays, the role of specific molecular-genetic tumor markers is of increasing importance in this patient population. Recent studies showed that tumor location, telomerase reverse transcriptase promotor (*pTERT*) mutation, 1p/19q co-deletion status, p53 expression, and Alpha Thalassemia/Mental Retardation Syndrome X-Linked (*ATRX*) loss are not associated with the occurrence of preoperative seizures in glioma patients.[6,7] Isocitrate dehydrogenase 1 and 2 (*IDH1/2*) mutated tumors have been associated with seizures, both in patients with low-grade and high-grade gliomas.[8–12] The product (D2HG) of the mutant IDH has a structural similarity to the excitatory glutamate, thereby possibly increasing the neuronal activity and, as a consequence, provoking epileptic seizures.[13] However, for the most common *IDH1/2* wildtype (IDHwt) subtypes of glioblastomas, including gliomas with molecular but not histological characteristics of a glioblastoma, the course of epilepsy is still largely unknown.

Molecular profiling of central nervous system tumors has led to a reclassification of IDHwt lower-grade gliomas (LGGs) of World Health Organization (WHO) grade 2 and 3 to WHO grade 4 tumors under the condition that they have a *pTERT* mutation, and/or gain of chromosome 7 combined with loss of chromosome 10 (7+/10–), and/or epidermal growth factor receptor (*EGFR*) amplification.[14–16] Consequently, the 2021 WHO Classification of Tumors of the Central Nervous System has reclassified both "classic" IDHwt glioblastoma and IDHwt glioma WHO grade 2 and 3 with molecular glioblastoma-like profile (IDHwt hLGG), as glioblastomas IDHwt.[17] This reclassification was supported by the finding that the median overall survival time of IDHwt hLGG was comparable to IDHwt glioblastomas (23.8 vs 19.2 months, $P = .242$).[18] Remarkably, seizures appear to be more frequently observed as a presenting symptom in patients with IDHwt hLGG compared to patients with IDHwt glioblastoma (65% vs 27%, respectively, $P < .001$), which may be an indication of a distinct symptomatology, particularly in the prediagnostic stage.[18] Despite their similar survival times, it is insufficiently known whether the clinical course of epilepsy differs pre- and postoperatively between these glioblastoma subtypes. This study aimed to gain additional insight into the clinical behavior of IDHwt hLGG and IDHwt glioblastoma tumors. To do so, we determined the incidence proportion of epilepsy during the disease course in the 2 glioblastoma subtypes, as well as epilepsy characteristics.

Materials and Methods

Patient Population

For this retrospective, multicenter, descriptive analysis, data from a previously published cohort study from Erasmus Medical Center Cancer Institute, Haaglanden Medical Center, and Leiden University Medical Center was used.[18] Adult patients with a newly diagnosed IDHwt histologically LGG (WHO grade 2 or 3), diagnosed between 2003 and 2019, were identified. The *IDH1/2* mutation status, the presence of 7+/10–, *pTERT* status and *EGFR* status was assessed in these patients with a glioma-tailored next-generation sequencing panel. Patients with a histological diagnosis of LGG but presenting with ring-like contrast enhancement with evidence of central necrosis on magnetic resonance imaging (MRI) at the time of histological diagnosis were excluded to avoid sampling error. A historical cohort from the Erasmus Medical Center of IDHwt glioblastoma patients diagnosed with the next-generation sequencing panel between 2013 and 2019 was used to compare outcomes. For the current study, additional epilepsy data were collected directly from patients' medical charts. The International League Against Epilepsy (ILAE) criteria were used to define epilepsy, in which (1) 2 unprovoked seizures occurring more than 24 h apart, or (2) a single unprovoked seizure in case the seizure recurrence risk is high are considered epilepsy.[19] Since the latter criterium generally applies to patients with a high-grade glioma, patients with 1 seizure were also considered to have epilepsy. Patients were eligible if data on epilepsy was present (patients were classified as having "no seizures" or having "at least one seizure" during the disease trajectory). In case a patient experienced at least 1 seizure, the date of the first seizure, the total number of seizures between the first

seizure and end of follow-up, and the total number of seizure days (ie, days when there was at least 1 seizure) was collected. When exact dates could not be reliably extracted, an estimation was made based on data on the frequency of outpatient contacts, description of seizure frequency, and other reported information. The dominant seizure type was used in analyses for patients who experienced different types of seizures during the course of their disease. The institutional review boards of the participating centers approved the study and consent of patients was obtained following the institutions' policy.

Outcomes

The primary outcome was the incidence proportion of epilepsy during the entire disease course (starting from the date of the first symptom indicative for a brain tumor), separately for the 2 glioblastoma subgroups. Secondary outcomes included the onset of epilepsy (before or after histopathological diagnosis), epilepsy as a first symptom, number of seizure days (ie, days when at least 1 seizure occurred, irrespective of the duration of the seizure) between the first seizure and end of follow-up, type of seizures, and use of antiepileptic drugs (AEDs) (yes/no, type, and polytherapy, defined as the concomitant use of more than 1 AED at the same time). In addition, we evaluated whether the overall survival time was different for patients with epilepsy as a first symptom and those with other symptoms. Overall survival was defined as the time between the first MRI and death, and the analysis was performed irrespective of tumor subtype.

Statistical Analysis

Sociodemographic and clinical characteristics between patients with IDHwt hLGG and IDHwt glioblastoma were compared using the chi-square test for categorical variables and the *t*-test or Mann–Whitney *U* test for continuous variables, depending on the distribution of the variable. The primary outcome, for example, the incidence proportion of epilepsy, was not only calculated for the entire disease course, but also for 2 distinct time periods: incidence proportion of epilepsy before and after the histopathological diagnosis. Multivariable logistic regression was used to assess if the histological subgroup was independently associated with presence of epilepsy at presentation, thereby adjusting for factors including frontal lobe involvement, temporal lobe involvement, gender, and age at diagnosis. The median time between the first seizure and histopathological diagnosis was also calculated separately for the 2 time periods. The median follow-up time was calculated from date of histopathological diagnosis to date of last follow-up or death. Median overall survival was calculated for patients who presented with epilepsy and patients who did not, and Kaplan–Meier curves were created. Patients for whom the date of death was unknown were censored at the moment of last follow-up. *p*-values < .05 were considered to be statistically significant. Statistical analyses were performed using statistical package *IBM SPSS Statistics for Windows* version 28.0.

Results

Cohort Sociodemographics

Of the 284 patients in the original cohort, information with respect to the presence of epilepsy was available in 254 patients: 64 IDHwt hLGG patients (25%) and 190 IDHwt glioblastoma patients (75%). The median follow-up time was 14.5 months (Interquartile Range [IQR] 8.3–22.9): 12.8 (IQR 6.2–20.3) for the IDHwt hLGG patients and 15.6 months (IQR 8.7–24.2) for the IDHwt glioblastoma patients ($P = .041$). The median age at histopathological diagnosis was comparable between both groups: 58.0 (IQR = 50.3–67.8) years for the patients with an IDHwt hLGG compared to 54.5 (IQR = 47.0–62.0) years in IDHwt glioblastoma patients ($P = .051$). Gender was equally divided between the 2 groups: 67% (43/54) of the IDHwt hLGG patients were male versus 68% (130/190) in the IDHwt glioblastoma patients ($P = .855$). The tumor showed significantly more often involvement in the temporal lobe in IDHwt hLGG (75% [48/64]) compared to IDHwt glioblastoma patients (40% [76/190], $P < .001$), but also more often multilobar involvement (92% [59/64] vs 40% [75/190], $P < .001$, respectively). Biopsy was performed significantly more often in IDHwt hLGG patients (78% vs 17%, $P < .001$). Table 1 shows all sociodemographic characteristics of the 2 groups.

Incidence Proportion of Epilepsy

Of the IDHwt hLGG patients, 78% (50/64) developed epilepsy during the course of the disease, versus 68% (129/190) of the IDHwt glioblastoma patients ($P = .121$). See Figure 1 for the incidence proportion of epilepsy in the twenty-four months before and after histopathological diagnosis. Patients with an IDHwt hLGG presented with epilepsy significantly more often compared to patients with an IDHwt glioblastoma: odds ratio (OR) 3.90 (95% confidence interval [CI] 2.03–7.48, $P < .001$). This association was not dependent on other factors, because no significant associations were observed between epilepsy at presentation and gender (OR 0.58 for females, $P = .084$), age at diagnosis (OR 1.01, $P = .358$), frontal tumor involvement (OR 1.08, $P = .801$), and temporal tumor involvement (OR 1.06, $P = .859$). Details on presenting symptoms can be found in Table 1.

Of the patients with epilepsy, significantly more IDHwt hLGG patients had their first seizure before histopathological diagnosis compared to IDHwt glioblastoma patients: 90% (45/50) versus 60% (77/129), respectively ($P < .001$). The median time between the first seizure and histopathological diagnosis was 3.5 months (IQR 2.0–7.3) in IDHwt hLGG patients and 1.3 months (IQR 0.8–2.8) in IDHwt glioblastoma patients ($P < .001$). Similarly, the median time between the first seizure and radiological diagnosis was 0.9 months (IQR 0.1–2.1) in IDHwt hLGG patients and 0.1 months (IQR 0.0–1.0) in IDHwt glioblastoma patients ($P = .026$). In the group of patients who developed epilepsy after the histopathological diagnosis, a statistically significant difference could not be demonstrated for the median time between diagnosis and first seizure for the remaining

Table 1 Study characteristics

Characteristics	IDHwt hLGG *n* = 64	IDHwt glioblastoma *n* = 190	Total cohort *n* = 254	*P*-Value
Gender, male, no. (%)	43 (67%)	130 (68%)	173 (68%)	.855
Median age at diagnosis, years (IQR)	58.0 (50.3–67.8)	54.5 (47.0–62.0)	55.0 (48.8–63.0)	.051
Median follow-up, months (IQR)	12.8 (6.2–20.3)	15.6 (8.7–24.2)	14.5 (8.3–22.9)	.041
Presenting symptom, no. (%)				<.001
Epilepsy	39 (61%)	53 (28%)	92 (36%)	
Motor impairment	3 (5%)	16 (8%)	19 (8%)	
Speech disorder	4 (6%)	18 (10%)	22 (9%)	
Cognitive disorder	5 (8%)	23 (12%)	28 (11%)	
Behavioral changes	2 (3%)	8 (4%)	10 (4%)	
Visual loss	0 (0%)	7 (4%)	7 (3%)	
Headache	5 (8%)	53 (28%)	58 (23%)	
Sensibility disorder	4 (6%)	2 (1%)	6 (2%)	
Reduced GCS score	0 (0%)	2 (1%)	2 (1%)	
Incidental finding	2 (3%)	8 (4%)	10 (4%)	
Hemisphere, no. (%)				<.001
Left	30 (47%)	69 (36%)	99 (39%)	
Right	22 (34%)	106 (56%)	128 (50%)	
Bilateral	12 (19%)	10 (5%)	21 (9%)	
Midline	0 (0%)	5 (3%)	5 (2%)	
Tumor lobe involvement, no. (%)				
Frontal lobe	30 (47%)	60 (32%)	90 (36%)	.068
Parietal lobe	31 (48%)	56 (30%)	87 (34%)	.019
Temporal lobe	47 (73%)	76 (40%)	123 (48%)	<.001
Occipital lobe	16 (25%)	33 (17%)	49 (19%)	.314
Insula	38 (59%)	11 (6%)	49 (19%)	<.001
Corpus callosum	21 (33%)	18 (10%)	39 (15%)	<.001
Basal ganglia	31 (48%)	11 (6%)	42 (17%)	<.001
Thalamus	23 (36%)	4 (2%)	27 (11%)	<.001
Brainstem	5 (8%)	4 (2%)	9 (4%)	.067
Cerebellar	2 (3%)	3 (2%)	5 (2%)	.253
Multilobar involvement, no. (%)	59 (92%)	75 (40%)	134 (53%)	<.001
Surgery modality, no. (%)				<.001
Biopsy	51 (80%)	33 (17%)	84 (33%)	
Partial resection	11 (17%)	136 (72%)	147 (58%)	
Total resection	2 (3%)	21 (11%)	23 (9%)	
Primary treatment, no. (%)				<.001
Watchful waiting	8 (13%)	8 (4%)	16 (6%)	
Radiotherapy	17 (27%)	8 (4%)	25 (10%)	
Chemotherapy	12 (19%)	4 (2%)	16 (6%)	
Chemoradiation	27 (42%)	170 (90%)	197 (78%)	

Abbreviations: GCS, Glasgow Coma Scale; IDHwt hLGG, IDHwt glioma WHO grade 2 and 3 with molecular glioblastoma-like profile, IQR, interquartile range; no., number of patients; SD, standard deviation.

5/50 (10%) IDHwt hLGG patients and the 52/129 (40%) IDHwt glioblastoma patients: 8.9 months (IQR 1.5–10.2) versus 5.7 months (IQR 2.8–13.1) respectively, $P = .967$ (Table 2).

Seizure Characteristics

Patients with IDHwt hLGG who developed epilepsy before histopathological diagnosis had significantly more seizure

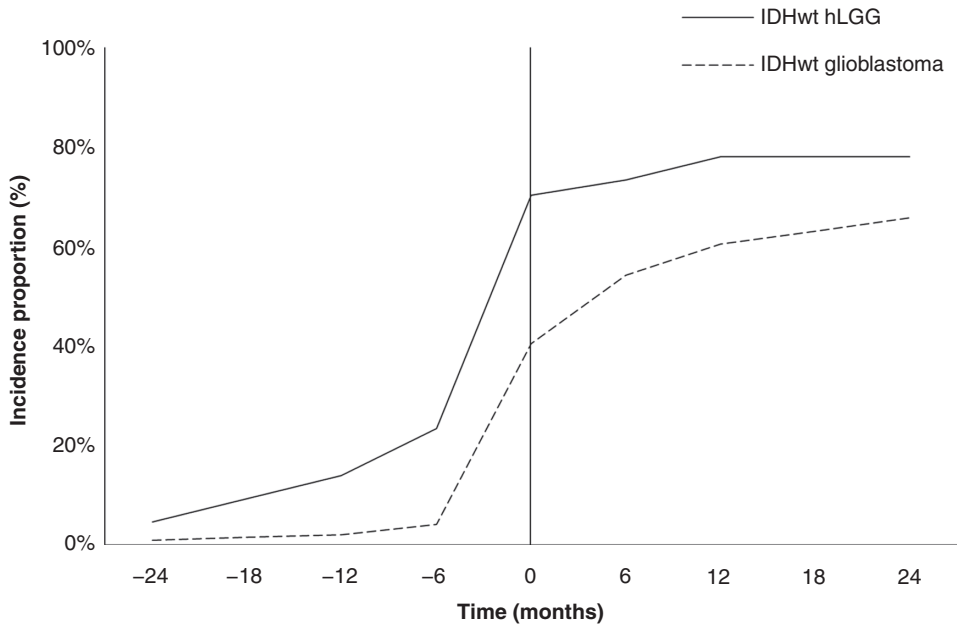

Fig. 1 Incidence proportion of epilepsy 24 months before and after histopathological diagnosis. Outliers more than the 24 months were omitted.

Table 2 Epilepsy before and after histopathological diagnosis

Characteristics	IDHwt hLGG *n* = 50	IDHwt glioblastoma *n* = 129	Total epilepsy cohort *n* = 179	*P*-Value
First seizure before diagnosis, no. (%)	45 (90%)	77 (60%)	122 (68%)	<.001
Median time to diagnosis, months (IQR)	3.5 (2.0–7.3)	1.3 (0.8–2.8)	2.1 (0.9–3.9)	<.001
First seizure after diagnosis, no. (%)	5 (10%)	52 (40%)	57 (32%)	<.001
Median time to first seizure, months (IQR)	8.9 (1.5–10.2)	5.7 (2.8–13.1)	6.0 (2.8-11.9)	.967

Abbreviations: IDHwt hLGG, IDHwt glioma WHO grade 2 and 3 with molecular glioblastoma-like profile; IQR, interquartile range; no., number of patients.

days before diagnosis (median 4.0, IQR 1.0–8.5) compared to IDHwt glioblastoma patients with epilepsy before diagnosis (median 1.0, IQR 1.0–2.0), $P < .001$. This difference was not observed in patients who developed epilepsy after histopathological diagnosis: median of 2.0 days (IQR 1.0–7.5) for IDHwt hLGG patients and 3.0 days (IQR 1.0–5.8) for IDHwt glioblastoma patients ($P = .708$). No differences in seizure days were found for *EGFR* amplification status, *pTERT* mutation status and 7+/10– status in IDHwt hLGG patients with epilepsy.

Of patients with IDHwt hLGG and epilepsy, 46% (23/50) had tonic-clonic seizures compared to 35% (45/129) of IDHwt glioblastoma patients with epilepsy, while this type was unknown in 2% (1/50), and 12% (15/129), respectively ($P = .085$). For the other patients, one or more seizures with impaired consciousness occurred in 60% (30/50) of patients with IDHwt hLGG compared to 50% (64/129) of patients with IDHwt glioblastoma, and was unknown in 4% (2/50) and 12% (16/129), respectively ($P = .191$). See Table 3 for the details on epileptic seizures.

AEDs

Patients with IDHwt hLGG were prescribed AED polytherapy significantly more often compared to patients with IDHwt glioblastoma: 32% (16/50) versus 17% (22/129), respectively ($P = .028$). Regarding the type of AEDs, there were significant differences in the type of first-line AED. In IDHwt hLGG with epilepsy, 44% (22/50) of the patients received levetiracetam as first-line treatment, compared to 71% (91/129) of patients with IDHwt glioblastoma and epilepsy ($P < .001$). Valproic acid was prescribed as first-line AED in 38% (19/50) of IDHwt hLGG patients compared to 23% (29/129) of IDHwt glioblastoma patients ($P = .035$). See Table 4 for the details on AEDs.

Table 3 Detailed epilepsy characteristics for the patients with epilepsy

Characteristics	IDHwt hLGG *n* = 50	IDHwt glioblastoma *n* = 129	Total epilepsy cohort *n* = 179	*P*-Value
Seizure days patients with epilepsy before diagnosis, median (IQR)	4.0 (1.0–8.5)	1.0 (1.0–2.0)	2.0 (1.0–5.0)	<.001
Seizure days patients with epilepsy after diagnosis, median (IQR)	2.0 (1.0–7.5)	3.0 (1.0–5.8)	3.0 (1.0–5.5)	.708
Seizure days, total, median (IQR)	7.0 (2.8–20.0)	3.0 (1.0–7.0)	4.0 (2.0–10.0)	.005
Seizure days within 3 months before last follow-up, median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	.851
Motor seizures*[a]				.081
Motor, no. (%)	31 (62%)	77 (60%)	108 (60%)	
Nonmotor, no. (%)	17 (34%)	32 (25%)	49 (27%)	
Unknown, no. (%)	2 (4%)	20 (16%)	22 (12%)	
Impaired awareness[a]				.191
Aware, no. (%)	18 (37%)	49 (38%)	67 (37%)	
Impaired, no.(%)	30 (60%)	64 (50%)	94 (53%)	
Unknown, no. (%)	2 (4%)	16 (12%)	18 (10%)	
Bilateral tonic-clonic seizures[a]				.085
Yes, no. (%)	23 (46%)	45 (35%)	68 (38%)	
No, no. (%)	26 (52%)	69 (54%)	95 (53%)	
Unknown, no. (%)	1 (2%)	15 (12%)	16 (9%)	

Abbreviations: IDHwt hLGG, IDHwt glioma WHO grade 2 and 3 with molecular glioblastoma-like profile; IQR, interquartile range; no., number of patients.
[a]Dominant seizure type was used in patients who experienced different types during the course of disease.

Table 4 Antiepileptic drug characteristics

Characteristics	IDHwt hLGG *n* = 50	IDHwt glioblastoma *n* = 129	Total epilepsy cohort *n* = 179	*P*-Value
First AED ≤ 2014, no. (%)[a]	31 (63%)	40 (33%)	71 (42%)	<.001
Polytherapy, no. (%)	16 (32%)	22 (17%)	48 (27%)	.028
Type of first AED				<.001
Levetiracetam, no. (%)	22 (44%)	91 (71%)	113 (63%)	
Valproic acid, no. (%)	19 (38%)	29 (23%)	48 (27%)	
Other, no. (%)	8 (16%)	4 (3%)	12 (7%)	
Clonazepam	0 (0%)	1 (1%)	1 (1%)	
Phenytoin	1 (2%)	1 (1%)	2 (1%)	
Clobazam	0 (0%)	1 (1%)	1 (1%)	
Carbamazepine	4 (8%)	0 (0%)	4 (2%)	
Phenytoin	2 (4%)	0 (0%)	2 (1%)	
Lamotrigine	1 (2%)	0 (0%)	1 (1%)	
Unknown	0 (0%)	1 (1%)	1 (1%)	

Abbreviations: AED, antiepileptic drug; IDHwt hLGG, IDHwt glioma WHO grade 2 and 3 with molecular glioblastoma-like profile; no., number of patients.
[a]Cut-off based on changed policies as a result of updated evidence.[20]

Overall Survival

Taking the two histology groups together, the median overalls survival time for patients who had epilepsy as the first presenting symptom indicative for a brain tumor was 20.7 months (95% CI 18.2–23.1), which is comparable to the 17.4 months (95% CI 15.5–19.3) for patients who did not present with epilepsy (log-rank test: $P = .091$). The survival curves reflecting these numbers can be seen in Figure 2. Stratification by histology group showed no differences in survival functions (data not shown).

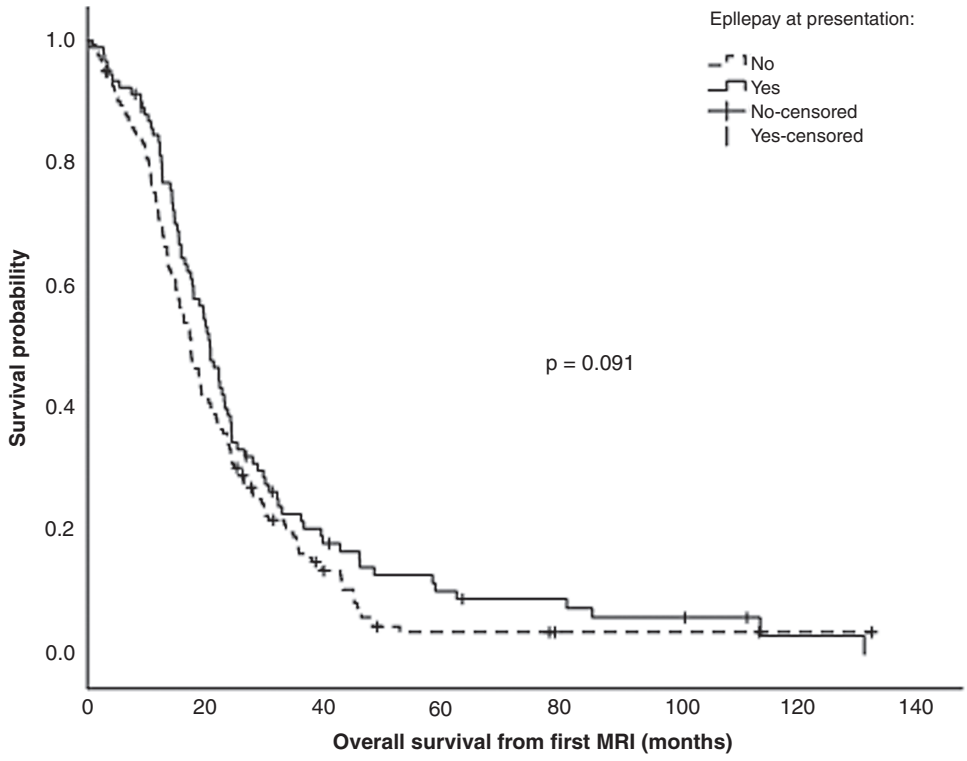

Fig. 2 Overall survival time (months) for patients with and without epilepsy at presentation. Dashed lines represent the median overall survival.

Discussion

According to the latest WHO 2021 Classification criteria, glioblastomas IDHwt comprise both IDHwt glioblastomas and histologically grade 2 and 3 astrocytic IDHwt gliomas with molecular features of a glioblastoma. Despite their comparable overall survival time,[18] we observed a distinct course of epilepsy in patients with IDHwt hLGG, not only including a higher proportion of patients presenting with epilepsy, but also a significantly longer history of seizures before histopathological diagnosis compared to IDHwt glioblastoma patients. However, during the course of the disease, these 2 subtypes of glioblastoma converge in terms of seizure incidence proportion, with eventually approximately 3 out of 4 patients developing epilepsy. The results of this study, comprising differences in radiological characteristics, tumor distribution, epilepsy, and other symptomatology between IDHwt hLGG and IDHwt glioblastoma patients, may ultimately indicate a further example of tumor heterogeneity of glioblastoma.

Several mechanisms may underlie the higher incidence proportion and prolonged history of preoperative seizures in patients with an IDHwt hLGG. First, the prolonged history of seizures before both the radiological and histopathological diagnosis in patients with IDHwt hLGG might be a reflection of a truly prolonged presence and hence lower initial growth rate of these tumors, allowing time to develop functional changes in the peritumoral cortex that eventually lead to epileptogenesis.[21] In contrast, patients with an IDHwt hLGG were prescribed significantly less often levetiracetam compared to IDHwt glioblastoma patients, although this seems to be a more effective AED than valproic acid in this patient population.[22] However, formal analysis on seizure control after AED treatment could not be performed as firm conclusions are hampered by the long interval between different treatment policies together with the absence of a standardized AED treatment protocol. The difference in prescriptions could be explained by the differences in year of prescription: valproic acid was more often the AED of first choice before 2015, and significantly more patients with IDHwt hLGG were prescribed AEDs before 2015 compared to IDHwt glioblastoma (63% vs 33%, $P < .0001$, Table 4). Third, nonmotor seizures, which tended to be more prevalent in IDHwt hLGG (34% vs 25%, $P = .216$, see Table 3), appeared to have been overlooked by the patient at the early stage. In retrospect, seizures had started months before the tumor diagnosis in some patients with IDHwt hLGG, but were not recognized as such at the time of seizure onset. In patients with nonmotor seizures, this delayed diagnosis also leads to a delayed initiation of AED treatment.[23] However, findings on seizure types have to be interpreted with caution due to missing data on this characteristic. Fourth, the time between the first MRI-scan and first surgery was slightly longer in patients with IDHwt hLGG compared to IDHwt glioblastoma

(1.3 vs 0.5 months, respectively).[18] Due to the radiologically lower-grade appearance of IDHwt hLGG, these tumors can be misdiagnosed for glioma mimics such as an encephalitis or ischemic stroke, which could result in an initial wait-and-see policy, leading to an additional diagnostic delay of the malignant brain tumor. Fourth, the need of early recognition of IDHwt hLGG is supported by the fact that, in this study cohort, relatively more patients with IDHwt hLGG initially underwent a biopsy and received no subsequent antitumor treatment, reflecting limited treatment options at the time of histopathological diagnosis. Finally, multilobar involvement of the tumor was more often seen in the IDHwt hLGG patients compared to the IDHwt glioblastoma patients, which can play a role in the distinct course of epilepsy, although the proportion of epilepsy during the entire course of disease was not different between the 2 groups.

Interestingly, besides differences in seizure-related outcomes, the 2 tumor subtypes in this study also showed differences with respect to other tumor- and treatment-related variables. Differences in multilobar involvement, tumor localization, surgery modality, and primary treatment together point to distinct clinical phenotypes of glioblastoma. Moreover, the IDHwt hLGG group showed some similarities with LGG with frequent involvement of the insula, which is known to be a predominant location for classical LGG.[24] Nonetheless, the association between a decreased time to definitive diagnosis, treatment, and better outcomes is not straightforward.[25] Both low-grade and high-grade gliomas presenting with seizures have been associated in previous studies with a significantly favorable survival time compared to patients without epilepsy before diagnosis.[26] It is suggested that this survival benefit, among other factors, may be the result of early diagnosis. However, we did not find indications for a difference in survival in our cohort between patients who had epilepsy as presenting symptom and those who had not. Notwithstanding, survival as well as overall well-being might have been better when seizures had been recognized at an earlier stage, something which patients with IDHwt hLGG would particularly benefit from, given their relatively long history of seizures before a final histopathological diagnosis is obtained.

This study has several limitations that are primarily related to its retrospective design. First, assessing accurate numbers of seizures and seizure days is highly dependent on patient and physician reporting, which is subject to recall bias, documentation bias, and recognition of all seizures.[27] Also, glioma patients are known to experience a wide range of symptoms in the year before diagnosis, however, these symptoms are often nonspecific and generally do not distinguish from other patients with central nervous system disorders.[28] In addition, patients may not visit a healthcare professional, such as the general practitioner, for each symptom they experience. As new-onset seizures may represent one of the most specific warning signs of a brain tumor, their immediate recognition could be the key to prevent delay in tumor diagnosis. Nevertheless, most likely because of the impact of the event, the date of the first seizure was clearly defined in the medical charts in all patients or could be extracted with a margin of error of a few days. Second, some patients underwent postoperative care in another hospital, therefore being lost to follow-up during the postoperative disease trajectory. Third, since only 5 patients with an IDHwt hLGG developed epilepsy after histopathological diagnosis, analyses performed on this small group have to be interpreted with caution.

In conclusion, this study shows that IDHwt hLGG patients present more often with epilepsy and have a longer history of seizures before histopathological diagnosis, indicating a distinct clinical course compared to IDHwt glioblastoma patients. Although it is unknown whether a prolonged history of seizures is a reflection of a prolonged presence of the tumor before definitive diagnosis, precious time might be gained by earlier recognition of seizures as a sign of a malignant brain tumor. This may particularly expedite tumor diagnosis in patients with this subtype of glioblastoma with histological characteristics of LGG, and subsequently result in earlier initiation of antitumor treatment, which might in the end positively affect their survival time as well as their functioning and well-being.

Keywords

epilepsy | glioblastoma | glioma | IDHwt | seizure

Funding: None.

Conflicts of interest statement. M.J.v.d.B. has received speaker honoraria from Astra Zeneca, Boehringer, Agios, Genenta, Nerviano, Carthera, and Chimerix. None of the other authors declare a conflict of interest.

Authorship statement: Study concept and design: M.P.v.O., L.D., M.J.B.T., J.A.F.K. Material preparation, data collection, and analysis: M.P.v.O. C.M.S.T., L.D., H.J.D., P.N.A., J.M.K., S.G.v.D., M.S., J.A.F.K. Statistical analysis: M.P.v.O., L.D., J.A.F.K. Writing and revision of manuscript: M.P.v.O., C.M.S.T., L.D., P.B.v.d.M., M.M.J.W., A.J.P.E.V., M.L.D.B., H.J.D., P.N.A., J.M.K., S.G.v.D., M.S., P.J.F., M.J.v.d.B., M.J.B.T., J.A.F.K.

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