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Prognostic relevance of epilepsy at presentation in glioblastoma patients

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Background. Epileptogenic glioblastomas are thought to convey a favorable prognosis, either due to early diagnosis or potential antitumor effects of antiepileptic drugs. We investigated the relationship between survival and epilepsy at presentation, early diagnosis, and antiepileptic drug therapy in glioblastoma patients.

Methods. Multivariable Cox regression was applied to survival data of 647 consecutive patients diagnosed with de novo glioblastoma between 2005 and 2013 in order to investigate the association between epilepsy and survival in glioblastoma patients. In addition, we quantified the association between survival and valproic acid (VPA) treatment.

Results. Epilepsy correlated positively with survival (HR: 0.75 (95% CI: 0.61–0.92), $P < .01$). This effect is independent of age, sex, performance status, type of surgery, adjuvant therapy, tumor location, and tumor volume, suggesting that this positive correlation cannot be attributed solely to early diagnosis. For patients who presented with epilepsy, the use of the antiepileptic drug VPA did not associate with survival when compared with patients who did not receive VPA treatment.

Conclusion. Epilepsy is an independent prognostic factor for longer survival in glioblastoma patients. This prognostic effect is not solely explained by early diagnosis, and survival is not associated with VPA treatment.

Keywords: epilepsy, glioblastoma, prognosis, survival, valproic acid.

Glioblastoma (GBM) is the most malignant form of primary brain tumors, and 30%–40% of GBM patients initially present with epileptic seizures.[1,2] It has been hypothesized that seizures may convey a more favorable prognosis,[3] although this latter assertion remains controversial,[4–7] and potential mechanisms that would underlie a survival advantage remain speculative. At the most trivial level, seizures could trigger earlier presentation for care, thus accelerating diagnosis and initiating earlier treatment of smaller GBMs.[8] Epileptogenic GBMs may have distinct biological characteristics, such as a higher expression of glutamate and the $X_{(c)(-)}^{-}$ system[9] and lower contents of glutamine synthetase,[7,10] which have been proposed to be oncogenic.[11,12] In addition, the IDH1 R132H mutation is frequently identified in proneural GBMs[13] and is reported to be associated with epilepsy in low-grade glioma[14] and be a favorable prognostic factor in GBM patients.[15,16] However, the correlation between these biological differences reported for epileptogenic GBMs and patient survival still awaits demonstration.

In vitro data suggest that antiepileptic drugs (AEDs) such as valproic acid (VPA) can alter glioma tumor growth and treatment resistance. VPA is believed to slow tumor growth through inhibition of a subset of histone deacetylases and modulation of the expression and activity of key transcription factors and cell-cycle regulators such as NF-κB, STAT3, p53, p21 and TCF/β-catenin. VPA was further shown to reduce angiogenesis, tumor invasion, and DNA repair caused by chemotherapies (eg, temozolomide and etoposide) or radiation therapy (reviewed in[17]). Consistent with these in vitro data, some retrospective studies suggest a correlation between VPA and the overall survival of GBM patients.[1,18,19] These studies, however, fail to differentiate the proper role of epilepsy from that of its treatment, and others do not observe this effect.[20]

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In this study, we assessed the prognostic relevance of epileptic onset and subsequent VPA treatment in a cohort of 647 consecutive de novo GBM patients.

Materials and Methods

Patient Cohort

All adult patients ($n = 647$) with histologically confirmed de novo supratentorial GBM (WHO grade IV) diagnosed at the University Medical Center Utrecht between 2005 and 2013 were retrospectively included in this study. Hospital records of all patients were screened for the presence of at least one de novo epileptic seizure at symptom onset (ie, prior to the surgery that obtained tissue for histological diagnosis), resulting in subgroups of patients with and without epilepsy at presentation. In addition, all patients were screened for treatment with AEDs at the time of surgery. For analysis of the effect of AEDs on patient survival, we included patients who continued to use the specific AED for at least 2 months or until death. Other characteristics such as age, sex, KPS, tumor volume, type of surgery (biopsy or resection), the contrast-enhancing lesion on the presurgical MRI scan (T1 weighted + gadolinium) with use of OsiriX version 4.1.2 (Pixmeo). These scans were also used to determine the location of the contrast-enhancing lesion.

Ethics Statement

This study was conducted following approval by the ethical committee and institutional review board of the University Medical Center Utrecht (protocols 09-420 and 14-225).

Tissue Microarrays, Immunohistochemistry, and Scoring

Archival formalin-fixed, paraffin-embedded tumor tissue was available and collected retrospectively for 360 of the 647 GBM patients treated in the University Medical Center Utrecht between 2005 and 2013. The histology of each specimen was reviewed by a senior clinical neuropathologist and marked on hematoxylin-and-eosin stained sections. For each patient, 2–3 tissue cores were placed on recipient arrayed paraffin blocks using a manual arrayer (Beecher Instruments). Immunohistochemical staining was performed on 4 μm sectioned TMA slides, which were deparaffinated in xylene and rehydrated with graded alcohol solutions. After peroxidase blocking, antigen retrieval was achieved by incubation in citrate buffer (pH 6) for 12 minutes at 126°C. Slides were incubated with anti-IDH1 R132H (Immunologic) for 1 hour at room temperature. Protein expression evaluation was blinded to the clinical data and scored as negative (0% of cells expressing IDH1 R132H) or positive (>0% of cells expressing IDH1 R132H).

Statistical Analysis

Statistical analyses were performed with the use of SPSS 22.0 (IBM). P values $<.05$ were considered significant. Differences in baseline characteristics were analyzed with chi-square tests or Fisher exact tests and independent t tests or Mann-Whitney U tests, according to the distribution of data. We analyzed differences in IDH1 R132H expression between subgroups using the chi-square test. Kaplan-Meier curves were analyzed with use of the log-rank test. Cox regression was used for the survival analyses. Since the Cox model assumes that survival curves of 2 strata follow hazard functions that are proportional over time, this proportional hazards (PH) assumption was checked for each variable in the model with log-minus-log plots and time-dependent variables and did not hold for the variables KPS and tumor volume. Extension of the model with time-dependent variables for KPS and tumor volume resulted in a significantly better model fit, and these time-dependent variables (KPS*time and tumor volume*time) were therefore included in the final model. These time-dependent variables represent the changing association of the variable as time progresses.

The PH assumption held for the epilepsy variable for patients with survival up to 1000 days after surgery but was not valid after this point. Therefore, in addition to performing the survival analyses with the unadjusted follow-up time, the analyses were restricted to a maximal follow-up time of 1000 days after surgery. All patients who survived beyond this point were censored at 1000 days.

Univariable Cox regression was performed to assess the effect of epilepsy on GBM patient survival. Next, multivariable Cox regression was performed, including other prognostic factors and baseline variables that differed across the subgroups. The following variables were included in the multivariable model: epilepsy, age at diagnosis, KPS, tumor volume, KPS*time, tumor volume*time, type of surgery, postsurgical treatment, tumor location, and sex.

Next, we evaluated the effect of VPA treatment compared with treatment with other AEDs on patient survival using Kaplan-Meier curves and univariate analysis. The effect was also corrected for age at diagnosis, KPS, KPS*time, tumor volume, tumor volume*time, type of surgery, surgery*time, postsurgical treatment, tumor location, and sex.

Results

Epilepsy and Survival in Glioblastoma Patients: Univariable Analysis

All adult patients with de novo supratentorial GBM diagnosed at the University Medical Center Utrecht between 2005 and 2013 ($n = 647$) were retrospectively included in this study. Baseline characteristics of the subgroups are described in Table 1.

The median overall survival in the total cohort of patients was 9.9 months (range: 0–>103 mo) from surgery. One hundred twenty-three patients were still alive and censored at the time of analysis. A total of 212 GBM patients presented with epileptic seizures, of which 191 received AED treatment. Twenty-one patients with epileptic seizures were not treated with an AED. One patient without epilepsy at presentation received carbamazepine for treatment of neuropathic pain. None of the patients without epilepsy received prophylactic AED treatment. Epilepsy was significantly associated with longer overall survival, with a median survival in the epilepsy group of 13.2 months (95% CI: 11.4–14.9) versus 8.4 months for patients without epilepsy (95% CI: 7.4–9.5; log-rank $P < .0001$) (Supplementary Fig. S1).

Table 1. Baseline characteristics of total cohort and subgroups analyzed in this study

Patient Characteristics *n* (%)	Total Cohort 647 (100)	Epilepsy 212 (32.9)	No Epilepsy 435 (67.1)	VPA 55 (8.5)	Epilepsy, Not Treated with VPA 157 (24.3)
Age (mean ± SD)	61.5 ± 12.3	59.3 ± 12.8	62.5 ± 11.9	57.9 ± 13.7	59.7 ± 12.5
Sex, % male	59.8	68.4	55.6	61.8	70.7
KPS, *n* (%)					
<70	182 (28.1)	47 (22.2)	135 (31.0)	12 (21.8)	35 (22.3)
≥70	461 (71.3)	163 (76.9)	298 (68.5)	43 (78.2)	120 (76.4)
	Missing: 4 (0.6)	*Missing: 2 (0.9)*	*Missing: 2 (0.5)*		*Missing: 2 (1.3)*
Tumor volume cm^3 (median (range))	34.3 (0.1–204.2)	17.8 (0.1–201.6)	40.7 (0.4–204.2)	17.0 (0.8–201.6)	18.6 (0.1–111.8)
	Missing: 19 (2.9)	*Missing: 9 (4.2)*	*Missing: 10 (2.3)*	*Missing: 3 (5.5)*	*Missing: 6 (3.8)*
Tumor location, *n* (%)[a]					
Left					
Frontal	106 (16.4)	37 (17.5)	69 (15.9)	11 (20.0)	26 (16.6)
Parietal	93 (14.4)	27 (12.7)	66 (15.2)	3 (5.5)	24 (15.3)
Temporal	124 (19.2)	43 (20.3)	81 (18.6)	14 (25.5)	29 (18.5)
Occipital	46 (7.1)	7 (3.3)	39 (9.0)	1 (1.8)	6 (3.8)
Right					
Frontal	113 (17.5)	51 (24.1)	62 (14.3)	11 (20.0)	40 (25.5)
Parietal	125 (19.3)	49 (23.1)	76 (17.5)	12 (21.8)	37 (23.6)
Temporal	168 (26.0)	54 (25.5)	114 (26.2)	13 (23.6)	41 (26.1)
Occipital	61 (9.4)	15 (7.1)	46 (10.6)	0 (0)	15 (9.6)
Bilateral	109 (16.8)	16 (7.5)	93 (21.4)	3 (5.5)	13 (8.3)
	Missing: 11 (1.7)	*Missing: 3 (0.5)*	*Missing: 8 (1.8)*	*Missing: 1 (1.8)*	*Missing: 2 (1.3)*
Extent of surgery, *n* (%)					
Biopsy	223 (34.5)	59 (27.8)	164 (37.7)	16 (29.1)	43 (27.4)
Debulking	424 (65.5)	153 (72.2)	271 (62.3)	39 (70.9)	114 (72.6)
Postsurgical treatment, *n* (%)					
None	147 (22.7)	30 (14.2)	117 (26.9)	6 (10.9)	24 (15.3)
Monotherapy RT or TMZ	163 (25.2)	44 (20.8)	119 (27.4)	9 (16.4)	35 (22.3)
RT + TMZ	332 (51.3)	136 (64.2)	196 (45.1)		96 (61.1)
	Missing: 5 (0.8)	*Missing: 2 (0.9)*	*Missing: 3 (0.7)*	40 (72.7)	*Missing: 2 (1.3)*
Treatment with AED, *n* (%)[a]					
None	455 (70.3)	21 (9.9)	433 (99.8)	–	21 (13.4)
Valproic acid	55 (8.5)	55 (25.9)	–	55 (100)	–
Levetiracetam	92 (14.2)	92 (43.4)	–	9 (16.4)	83 (52.9)
Carbamazepine	26 (4.0)	25 (11.8)	1 (0.2)	2 (3.6)	23 (14.6)
Phenytoin	37 (5.7)	37 (17.5)	–	2 (3.6)	35 (22.3)
Other	3 (0.5)	3 (1.4)	–	1 (1.8)	2 (1.3)
Combination of AEDs	21 (3.2)	21 (9.9)	–	14 (25.5)	7 (4.5)

Abbreviations: AED: antiepileptic drug; RT: radiotherapy, TMZ: temozolomide; VPA, valproic acid.
[a]Percentages do not add up to 100% for these variables due to possible multilobar tumor locations and multiple AED treatments per patient.

As mentioned above, the PH assumption of the Cox model did not hold for the entire range of the follow-up period. The analysis was thus restricted to the period of time when this assumption was valid by censoring all survival data that surpassed 1000 days. Epileptic GBM presentation remained significantly associated with an increased overall survival compared with GBM patients without epilepsy, as tested both with the log-rank test (median: 13.2; 95% CI: 11.4–14.9; versus median: 8.4; 95% CI: 7.4–9.5; $P < .00005$; Fig. 1A) as well as with univariable Cox regression (crude HR: 0.68; 95% CI: 0.56–0.82; $P < .001$; Table 2).

Epilepsy and Survival in Glioblastoma Patients: Multivariable Analysis

The epilepsy and nonepilepsy subgroups showed evident differences with respect to age, sex, KPS, type of surgery, and postsurgical treatment. Lobar involvement differed notably, with left occipital, right frontal, and bilateral tumor locations observed more in the nonepilepsy subgroup (Table 1). These locations were therefore included in the multivariable model. We also found epileptogenic GBMs to be significantly smaller than nonepileptogenic ones (17.8 cm^3 [0.1–201.6] vs 40.9 cm^3 [0.4–204.2]; Mann-Whitney U test; $P < .0005$), which has been reported by others as well.[21]

Despite these differences, epilepsy remained significantly associated with survival of GBM patients (HR: 0.75 [95% CI: 0.61–0.92]; $P < .01$) after correcting for age, sex, type of surgery, postsurgical treatment, tumor volume, affected lobes, bilateral tumor involvement, and KPS (Table 2). Mutation of the IDH1 R132H allele was observed in 8 of 136 patients in the epilepsy subgroup, compared with 13 of 224 for the patients without epilepsy (difference not significant; chi-square test; $P = .98$). The baseline characteristics for the patients included in this analysis are described in Supplementary Table S1.

Prognostic Relevance of Valproic Acid in Glioblastoma Patients

Although several previous studies have suggested a favorable effect of the AED VPA on the overall survival of GBM patients,[1,18,19] we did not find evidence for this. Within the epileptic GBM group, the survival of patients who received VPA ($n = 55$; median survival: 13.8 mo; 95% CI: 10.1–17.4) did not differ significantly from those with seizures who did not receive VPA ($n = 157$; median survival: 12.7 mo; 95% CI: 10.6–14.8; log-rank test; $P = .55$; crude HR: 0.90; 95% CI: 0.62–1.29; $P = .55$; Fig. 1B, Supplementary Table S2). Baseline characteristics of these subgroups are described in Table 1. In multivariable analysis, the association between VPA treatment and survival remained nonsignificant (adjusted HR: 0.99; 95% CI: 0.65–1.50; $P = .95$, Supplementary Table S2).

Discussion

Our study demonstrates a favorable association between epilepsy at presentation and prolonged survival of GBM patients in the largest consecutive cohort studied to this end so far ($n = 647$). With a hazard ratio of 0.75 in multivariable Cox regression (95% CI: 0.61–0.92; $P < .01$), our results build upon existing smaller studies[5–7] to firmly establish this correlation. Furthermore, we show that the improved prognosis of patients with epileptic GBM is independent of the age, sex, or performance status of the patients as well as the location of their tumors or the surgical and adjuvant treatments they received.

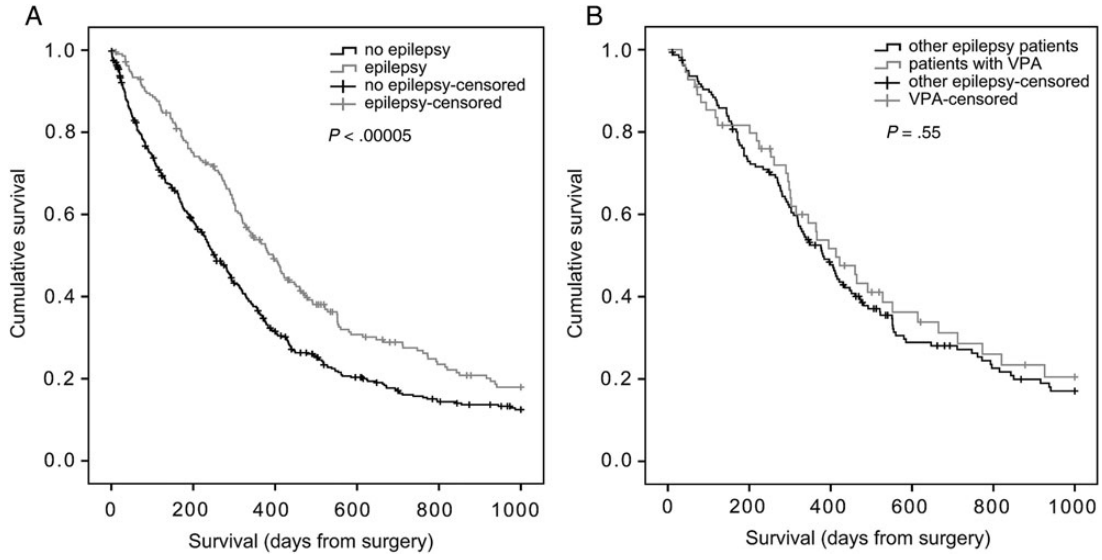

Fig. 1. Effect of epilepsy and valproic acid (VPA) on glioblastoma patient survival. (A) Kaplan-Meier plot of patients with (grey, $n = 212$) and without epilepsy (black, $n = 435$). Patients with survival >1000 days from surgery were censored. Survival was significantly different between the 2 groups (log-rank test, $P < .00005$). (B) Kaplan-Meier plot of glioblastoma patients treated with VPA (grey, $n = 55$) or all other patients with epilepsy (black, $n = 157$). Patients with survival >1000 days from surgery were censored. Survival was not significantly different between the 2 groups (log-rank test, $P = .55$).

Table 2. Univariable and multivariable Cox proportional hazard regression analysis

Variable	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Epilepsy	0.68 (0.56–0.82)	<.001	0.75 (0.61–0.92)	<.01
Sex (male)	1.05 (0.88–1.26)	.57	0.93 (0.82–1.20)	.94
Age	1.03 (1.03–1.04)	<.0005	1.011 (1.002–1.019)	<.05
KPS <70	1.00		1.00	
KPS ≥70	0.24 (0.17–0.32)	<.0005	0.61 (0.43–0.86)	<.01
KPS * time	1.003 (1.002–1.004)	<.0005	1.002 (1.001–1.003)	<.005
Biopsy	1.00		1.00	
Resection	0.40 (0.33–0.48)	<.005	0.71 (0.57–0.89)	<.005
Postoperative treatment				
None	1.00		1.00	
Monotherapy RT or TMZ	0.17 (0.13–0.22)	<.0005	0.20 (0.15–0.27)	<.0005
RT + TMZ	0.06 (0.05–0.08)	<.0005	0.08 (0.06–0.12)	<.0005
Tumor location				
Left occipital	1.03 (0.74–1.43)	.46	1.7 (0.75–1.51)	.72
Right frontal	0.73 (0.57–0.93)	<.05	0.80 (0.61–1.03)	.09
Bilateral	2.54 (2.02–3.18)	<.0005	1.62 (1.23–2.14)	<.005
Tumor volume	1.006 (1.002–1.011)	<.005	1.003 (0.999–1.007)	.11
Tumor volume * time	1.000 (1.000–1.000)	<.005	1.000 (1.000–1.000)	<.005

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiotherapy, TMZ, temozolomide.
Epilepsy remains significantly associated with survival of glioblastoma patients in multivariable analysis. Time-dependent variables (KPS * time and tumor volume * time) are included to correct for violation of the proportional hazards assumption and represent changes in the association between the variable and survival over time.

Consistent with previous observations,[21] the volume of epileptogenic tumors was significantly smaller than that of nonepileptogenic ones. However, epilepsy remained a significant prognostic factor independent of tumor size in multivariable analysis, suggesting that mechanisms other than early detection may also contribute to the better outcome of epileptogenic tumors.

AEDs have been postulated to alter the outcome of epileptic GBM patients. An analysis of the survival of nonepileptic GBM patients treated prophylactically with nonenzyme-inducing AEDs pointed to a survival advantage for these patients.[22] VPA treatment was also reported to enhance survival in a few retrospective studies of high-grade glioma patients[1,19,23] and in a post-hoc analysis of the EORTC 26981/NCIC 3.E trial.[18] The actual therapeutic benefit is still being debated,[20,24] and the antitumoral mechanisms of therapeutic doses of VPA in GBMs have yet to be demonstrated in patients. In our retrospective cohort, however, VPA usage at the time of GBM diagnosis was not associated with any survival advantage when compared with all other patients with epileptic seizures. Previous studies have examined the effect of VPA on survival by including only GBM patients treated with radiotherapy[19] or chemoradiation,[1,18] whereas our analysis also included patients who did not receive any adjuvant treatment. When we restricted our comparison to epileptic GBM patients treated with chemoradiation, there was no survival difference among those who received VPA ($n = 40$) and those who did not ($n = 96$; log-rank test; $P = .88$). Similarly, for epileptic GBM patients who received radiotherapy (with or without chemotherapy), there was no difference in survival between patients treated with VPA ($n = 49$) and those who did not receive VPA ($n = 131$; log-rank test; $P = .76$). However, the limited statistical power of these latter subanalyses (due to fewer patients contributing to the measure) should be taken into consideration, since small but meaningful differences might become apparent in larger cohorts.

Detangling the independent relationship between AED use and presence of seizures is problematic because no patients received prophylactic AEDs in the absence of clinical seizures, and few patients with seizures did not receive AEDs. Since there are no patients without epilepsy who received prophylactic AED treatment in this study, we cannot completely rule out an association of VPA with survival of GBM patients, which might be overshadowed by the more profound prognostic effect of epilepsy per se. To be solved, this question would likely require a randomized prospective trial with AED administration to patients both with and without epilepsy.

Even though VPA has received the most attention in literature for its possible antitumor effects, some studies have investigated the effects of other AEDs. For instance, levetiracetam has been reported to chemosensitize glioma cells to temozolomide treatment, possibly by inhibition of MGMT expression.[25] A recent study reported a survival benefit for GBM patients receiving chemoradiation therapy and treatment with levetiracetam compared with those who were not treated with levetiracetam. However, the majority of patients in that study received seizure prophylaxis and did not present with epilepsy at diagnosis.[26] Guthrie et al reported a survival benefit for GBM patients receiving carbamazepine or phenytoin compared with patients receiving no AED treatment.[27] However, the epilepsy status was not included in the multivariable analyses in both studies. In our cohort, we analyzed the survival of patients who presented with epilepsy and were treated with

levetiracetam, carbamazepine, or phenytoin to the survival of other patients who presented with epilepsy. The baseline characteristics of the analyzed subgroups were comparable (Supplementary Tables S3–S5), and we did not observe any association between specific AED use and survival using Kaplan-Meier analysis (Supplementary Fig. S2A–C) and univariable Cox regression (Supplementary Table S6).

A potential limitation of this study remains its retrospective nature. As a result, medical imaging to assess the extent of resection was incomplete for patients diagnosed in the first years of the cohort. This presents a challenge because the surgeon's perception of the estimated extent of resection does not always correspond strictly to quantitative radiological assessment of the pre- and postoperative tumor burden.[28] Furthermore, surgical resection of >78% of the tumor volume can provide a survival benefit compared with biopsy alone, with further significant increments for additional tumor debulking.[29] Despite this, the differentiation between biopsy and resection (whether for debulking or gross-total resection) has been proven to have a significant effect on prognosis,[30] and we used this for our survival analyses.

The observed prognostic effect might result from distinct biological features of epileptogenic tumors. For instance, the IDH1 R132H mutation has been reported to occur frequently in proneural GBMs,[13] to correlate with epilepsy in low-grade glioma patients,[14] and to confer a more favorable prognosis in GBM patients.[15,16] In our series, however, the IDH1 mutational status did not correlate with epilepsy status at all (chi-square test; $P = .98$). This finding should, however, be nuanced. Indeed, the subset of patients included in our histochemical IDH1 analysis was enriched in patients who underwent debulking rather than biopsy due to tissue availability constraints. They likewise presented a higher average age, a larger median tumor volume, more involvement of the right hemisphere and less bilateral tumor location, and involved more patients treated with chemoradiation and more patients presenting with epilepsy than our complete patient population (Supplementary Table S1).

Previous reports also suggested some gene expression alterations in epileptogenic gliomas such as higher expression of glutamate and the $X_{(c)(-)}^{-}$ system[9] and lower expression of glutamine synthetase.[7,10] Our laboratory is currently investigating whether such biological differences are indeed present in our cohort of patients.

Collectively, our results show that epilepsy at presentation is associated with prolonged survival of GBM patients independent of age, sex, performance status, type of surgery, postsurgical treatment, and tumor volume and location. This prognostic effect cannot be solely explained by early diagnosis, and survival was not associated with VPA treatment.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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