Received: 2 November 2023 | Revised: 4 March 2024 | Accepted: 5 March 2024

DOI: 10.1111/epi.17956

Epilepsia®

RESEARCH ARTICLE

Motor seizures confer overall survival benefit in who grade 2 glioma

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Abstract

Objective: The prevalence of epilepsy in World Health Organization (WHO) grade 2 glioma is high, with seizures being the presenting symptom in 60%–90%. We explore the epidemiology of seizures in this patient population in a regional neurosurgical center.

Methods: Electronic health records of patients with histologically-proven WHO grade 2 glioma ($n = 228$) were reviewed between 1997 and 2021, with data collected including patient demographics, epilepsy prevalence, and seizure semiology. The influence of seizure type on overall survival was calculated using a Cox proportional hazards model.

Results: Overall, 197 of 228 patients (86.4%) were diagnosed with epilepsy—either at presentation or during the course of their disease. Male patients were more likely than female patients to be diagnosed with epilepsy (91.1% vs 77.1%, $p = .003$) and, in those with epilepsy, more likely to experience at least one focal to bilateral tonic–clonic seizure (69.4% vs 54.1%, $p = .05$). Patients with left-sided tumors were twice as likely to have experienced a focal to bilateral tonic–clonic seizure ($p = .02$, odds ratio [OR] = .47). Predominantly experiencing seizures with motor activity appeared to confer better overall survival, with a 65% decrease in the risk of death 10 years post diagnosis (hazard ratio [HR] = .35, $p = .02$). This is despite accounting for previously described prognostic markers including tumor histology/genetics, time from diagnosis to surgery, and the extent of tumor resection.

Significance: Motor seizure activity is a frequent feature in WHO grade 2 glioma and appears to confer a survival benefit regardless of histology or surgical factors. Seizures due to dominant hemisphere tumors may be more likely to propagate and cause bilateral tonic–clonic activity.

KEYWORDS

epilepsy, glioma, motor, seizures, survival

Melissa Maguire and Ryan K. Mathew are co-senior authors.

1 | INTRODUCTION

Seizures are a common and often early manifestation in patients with a brain tumor. Gliomas are a group of tumors arising from the glial cell type. Glioma grading follows the World Health Organization (WHO) classification for brain tumors and runs from grades 1–4.[1] In particular, lower grades of glioma (grades 1 and 2) are associated with a very high incidence of seizures in comparison with those of a high grade.[2] The incidence of tumor-related epilepsy in WHO grade 2 glioma is reported to be between 60% and 90%.[3,4]

Grade 2 gliomas are usually slow growing tumors and, despite most eventually progressing to a higher grade, overall survival from diagnosis is often several years.[5] This is in stark contrast to high-grade tumors such as glioblastoma (WHO grade 4), where overall survival is almost universally very poor, averaging about 12–15 months despite treatment. The two most commonly encountered grade 2 gliomas in adults are diffuse astrocytoma and oligodendroglioma. Even within the same grade, survival can vary depending on the specific tumor subtype. One large epidemiological study shows that in patients with an oligodendroglioma, 5-year survival was 80%, whereas in those with a diffuse astrocytoma, survival at 5 years was 47%.[6]

The recent rise in tumor molecular subtyping now complements histological appearances. Accordingly, tumor classification is now an integrated molecular and histological diagnosis.[1] The use of tumor molecular markers to better classify grade 2 gliomas has helped to improve our understanding of the heterogenous outcomes seen previously in this patient population and critically helps better predict overall survival. Diffuse astrocytomas with the isocitrate dehydrogenase-1 (*IDH1*) mutation show better overall survival than those returning as wild-type (and in fact, as of the 2021 WHO classification, wild-type astrocytomas are now classified as glioblastoma).[7] In addition, the 1p19q codeletion is considered the genetic hallmark of an oligodendroglioma, thereby also inferring a better prognosis.[8] Molecular markers may also predict better overall survival by way of response to treatment. Methylation of the promoter region of *O*-6-methylguanine-DNA methyltransferase (MGMT) is associated with a favorable response to the chemotherapy agent temozolomide, thought to be due to methylation hampering tumor self-repair mechanisms.[9] This association is stronger in glioblastoma and less clear in grade 2 glioma.[10]

Other prognostic factors in grade 2 glioma include age, performance status, and the extent of surgical resection. Increasing age infers a worse prognosis in grade 2 glioma, and overall survival in adults 40 years of age or older is lower than in those below 40.[6] A higher Karnofsky performance status at diagnosis has also been correlated with better outcomes.[11] Surgical resection is now undertaken in the majority of patients with grade 2 glioma, although a watch-and-wait policy was often used in the past. Despite resection not being a curative treatment, it has been shown that earlier resection may delay malignant transformation and improve survival outcomes.[12] The extent of resection is important, with gross total resection more likely to result in longer progression-free survival compared with sub-total resection or less.[13] A feature of all gliomas is that their spread within the brain often extends beyond the apparent tumor margins delineated on conventional neuroimaging. For this reason, supra-total surgical resection (resection beyond the perceived radiological margins) is often advocated and may lead to even better outcomes.[14] Because the peri-tumoral margin is often thought to be the instigator of seizures in glioma-related epilepsy, it is perhaps not surprising that a greater extent of resection is also associated with better seizure outcomes post-operatively.[15,16]

Grade 2 gliomas can occur in most parts of the brain. They are most frequent in the frontal lobes, followed by the parietal and then temporal lobes. Tumor size and location can inform prognosis. Patients with a glioma in a frontal cortical region have long been thought to display an improved overall survival, and this may be due in part to the higher likelihood of tumors in these areas being an oligodendroglioma, and more amenable to greater extents of resection.[17] A smaller tumor volume at presentation is also associated with better overall survival. The development of tumor-related epilepsy appears more likely with frontal location and oligodendroglioma histology, with the exception of tumors situated in the midline.[4,18]

The presence of epilepsy at diagnosis may influence survival. Several studies report improved outcomes in patients who present with epilepsy vs those who do not.[19] The exact mechanisms underpinning this

Key points

- Experiencing predominantly motor seizure activity appears to confer an overall survival benefit accounting for histology and surgical factors.
- Left hemisphere gliomas are twice as likely to ever cause a focal to bilateral tonic–clonic seizure than right hemisphere gliomas.
- Male sex is an independent risk factor for the development of epilepsy in grade 2 glioma.

correlation are not clear. It may be that seizures lead to an earlier presentation and therefore earlier intervention. Others have looked to tumor physiology for an explanation. As noted previously, the presence of an *IDH1* mutation is associated with an improved prognosis. IDH1 is an enzyme which normally catalyzes the conversion of isocitrate to α-ketoglutarate. Mutant IDH1 has altered enzymatic activity, reducing α-ketoglutarate to 2-hydroxyglutarate (2HG). 2HG is structurally similar to glutamate, the primary excitatory neurotransmitter in the central nervous system (CNS), and it is hypothesized that it may mimic its excitatory action in vivo or alternatively cause local disruption via mammalian target of rapamycin hyperactivation, resulting in seizures.[20] Patients with differing glioma grades have been shown to be more likely to experience seizures if they possess the *IDH1* mutation compared to wild-type.[21] As the majority of patients with grade 2 glioma possess both the *IDH1* mutation and usually develop seizures, this probable relationship does little to help prognosticate within the grade.

The International League Against Epilepsy (ILAE) provides a framework to classify seizure type in all forms of epilepsy.[22] This framework organizes seizures by their onset (generalized or focal), level of awareness (aware or unaware), and additional descriptors such as the presence of motor activity (motor or non-motor). Seizures that are focal in onset but progress to a generalized tonic–clonic seizure (previously termed secondary generalized) are now referred to as "focal to bilateral tonic-clonic." Previous studies of low-grade gliomas have often reported the seizure onsets of patients using older seizure terminology.[18,23] Focal seizures appear to dominate and some studies do not use the notion of generalized onset at all in this patient group, terming all apparently generalized seizures as focal to bilateral tonic–clonic.[23] This approach seems reasonable given that these patients have a focal epileptogenic lesion, focal seizures appear to be the norm, and seizures reported as generalized onset may simply have an unwitnessed or subtle focal onset. Seizure characteristics have been used to infer the likelihood of seizure freedom, with Chang et al. (2008) demonstrating in a cohort of 332 patients with low-grade glioma that both focal aware seizures preoperatively and a temporal lobe location increased the likelihood that seizures would be pharmaco-resistant.[18] Focal aware seizures also predicted poorer seizure outcomes post-operatively.

Little is known about whether these seizure types reflect something more fundamental regarding the tumor and its likely course. We sought to explore in more detail whether bilateral generalized tonic–clonic seizure spread, seizure awareness, or motor activity was associated with improved survival outcomes in a population of patients who had undergone surgery for diagnostically proven grade 2 glioma. We also assess how patient demographics and tumor laterality may influence the seizure type experienced.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We undertook a retrospective observational study of patients presenting to a multi-disciplinary low-grade glioma clinic at a UK National Health Service (NHS) regional neurosurgical center. Patients included in the study were required to have diagnostically proven WHO grade 2 diffuse astrocytoma or oligodendroglioma. Of an initial 412 patients attending a low-grade clinic, 228 were ultimately included. The effect of histology, presenting complaint, tumor genetics, sex, and tumor laterality on survival (primary analysis) was analyzed. A subgroup was then created that included only those patients with a diagnosis of epilepsy and in whom seizure semiology was evident. The effect of seizure semiology on survival was assessed in this smaller group of 185 (secondary analysis). Patient selection is depicted in Figure 1.

2.2 | Data collection and study design

This was a retrospective observational study that examined the electronic medical records of patients between January 1997 and December 2021. Data collected included: patient demographics, tumor laterality, extent of surgical resection, disease course information (age at diagnosis, survival time, dates of surgery, follow up period), an integrated tissue/molecular diagnosis (according to WHO 2021 Tumors of the CNS criteria), and epilepsy descriptors (whether present at glioma diagnosis and seizure semiology including whether bilateral generalized tonic–clonic spread, awareness, and activity). Extent of resection was categorized on post-operative MRI (within 72 h) as either gross total (apparent complete resection), near-total (<3 mm rim residual only), sub-total (nodular residual), or biopsy/gross residual. This was done by reviewing the neuroradiologist's report and, where there was uncertainty, the view of the multidisciplinary team with the hindsight of the next follow-up MRI. Whether a resection was supra-total (beyond visible pre-operative radiological margin) was not reported and so this was not considered. Seizure semiology information was extracted from clinic letters, pre-hospital/ambulance sheets, in-hospital notes, and electroencephalography/video-telemetry recordings. For each patient, the predominant (most typical/frequent)

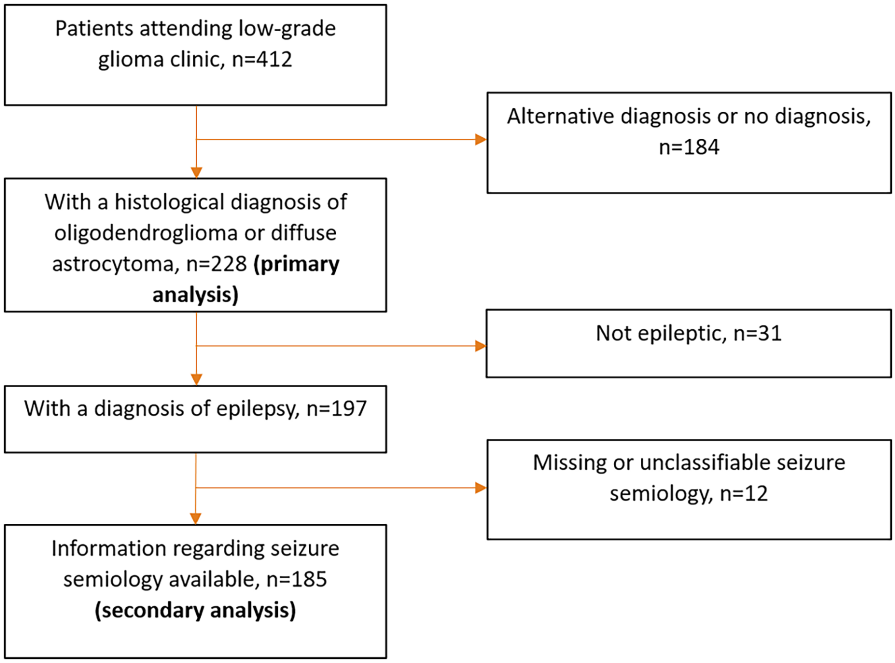

FIGURE 1 Flow chart demonstrating the patient selection process for both the primary and secondary analyses.

seizure type that they experienced was recorded. Records were searched between January 1997 and December 2021.

2.3 | Statistical analysis software

Study data was anonymized at collection. It was then coded to allow analysis using the statistical software '*R*' (available via https://www.r-project.org/, version 4.1.2). Most analysis was performed using base '*R*' and the 'survival' package. The synthetic minority oversampling technique (SMOTE) sub-analysis was performed using the '*ROSE*' package, also available in '*R*'.

2.4 | Model and variable selection

For the primary analysis, Kaplan–Meier analysis was conducted in *R* to provide a visual depiction and *p*-values via chi-square testing. This was done for several variables including tumor diagnosis (astrocytoma vs oligodendroglioma) and presenting complaint. Patients were censored if lost to follow-up. Fisher's exact test ($p < .05$) was used to assess the influence of tumor laterality on the risk of a focal to bilateral seizure. In the secondary analysis, a Cox-proportional hazards (CPH) model was applied to the data allowing the calculation of hazard ratios and *p*-values to assess the influence of each variable on 10-year overall survival. Variable selection was honed by performing analysis of variance (ANOVA) testing ($p < .05$) using the likelihood ratio test (LRT) to see whether inclusion of specific variables led to an overall improvement in the model's predictive power. The likelihood ratio tests indicated that the CPH model needed to include the histology result, the time from diagnosis to surgery (to the nearest year), and the extent of tumor resection (coded as biopsy, subtotal, near total, and gross total), as these all had a significant influence on 10-year overall survival. Both the time from diagnosis to surgery variable and the extent of resection variable were stratified to allow their inclusion. There was no significant difference in the extent of resection variable between the motor seizure vs non-motor seizure groups ($p = .85$) with chi-square testing ('biopsy' 15.4% vs 16.7%, 'subtotal' 47.7% vs 52.8%, 'near-total' 23.5% vs 16.7%, and 'gross total' 13.4% vs 13.9%, respectively). Other variables (sex, awake or asleep resection, *TERT* mutation status, patient age at diagnosis, and tumor laterality) were discarded at this stage due to them not significantly improving the model when included. The MGMT methylation status variable contained too much missing data to be included. Patient age at diagnosis was omitted from the model having returned a *p*-value of .29 when included and not statistically improving the model (LRT $p = .29$). Even when included, no change in the significance values returned for both tumor histology or seizure type on survival was observed. All patients had *IDH1* mutation positivity at some point, although occasionally, after subsequent operations, their *IDH1* status changed. This was felt to be most likely due to surgical factors (normal brain tissue being sent for analysis) or laboratory factors such as tests/reagents failing. Patients with changing *IDH1* status were rare in our group. A sub-analysis, in which a variable

stating whether or not *IDH1* mutation status changed, was temporarily added to the Cox model and this again did not change the significance of other variables or significantly contribute to the predicting power of the model ($p > .05$). Schoenfeld residuals were calculated to ensure that the CPH model assumptions were met and these were appropriately non-significant.

3 | RESULTS

3.1 | Primary analysis group ($n = 228$)

Presenting complaint and tumor diagnosis on survival: A Kaplan–Meier analysis comparing the 10-year overall survival of patients presenting with seizures ($n = 180$) vs those with other presenting complaints ($n = 48$) did not demonstrate a benefit to seizures at presentation on chi-square testing ($p = .6$, 1*df*). This is shown in Figure 2.

Although our patient cohort of 228 is a reasonable size, the high incidence of seizures in grade 2 glioma leads to the "no seizures at presentation" group (21.2% of patients) still being relatively small ($n = 48$). It may be that a much larger, national patient cohort is required to properly assess this relationship. In total, 197 of 228 patients (86.4%) received a diagnosis of epilepsy, either at presentation or during follow-up. Ever having a diagnosis of epilepsy, either before or after glioma diagnosis, also failed to show any significant overall survival benefit ($p = .5$, 1*df*). We performed a sub-analysis in which this "never epileptic" population was oversampled using SMOTE. In this 'SMOTE'd' data set, a Cox-proportional hazards analysis controlling for histology still demonstrated no significant survival benefit for the epileptic group ($p = .87$). Patients with a confirmed oligodendroglioma were significantly more likely to be alive at 10 years than those with an astrocytoma ($p < .001$, 1*df*). *TERT* status did not significantly influence 10-year survival ($p = .2$, 1df). Where tested, methylation of the MGMT promoter region (>15% methylation) was associated with increased overall survival compared with patients with an unmethylated (<10%) or equivocal (10%–15%) result ($p = .03$, 2*df*). The findings correlate with previously published literature and validate our data as representative of WHO Grade 2 glioma.

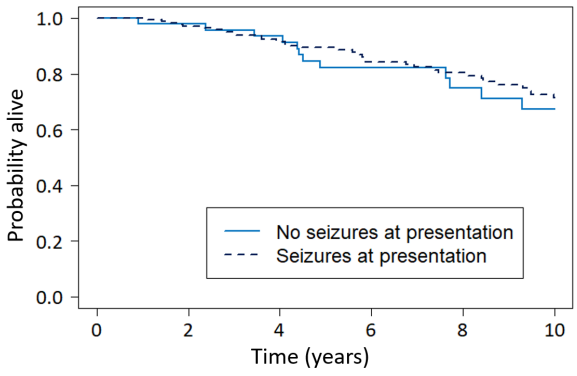

FIGURE 2 Kaplan–Meier analysis of overall survival from diagnosis depending on presenting complaint.

Risk of experiencing focal to bilateral seizures by sex and tumor laterality: Whether a patient had ever experienced a focal to bilateral seizure was coded as yes or no. Using Fisher's exact test, it was found that male patients (133/146, 91.1%) were more likely to be diagnosed with epilepsy than female patients (64/83, 77.1%, $p = .003$). In those with epilepsy and an auditable medical record ($n = 185$, 12 patients had incomplete seizure data), male patients were more likely to have ever experienced a focal to bilateral seizure ($p = .05$, 69.4% vs 54.1%). There was no difference in overall survival between the sexes.

Each tumor was assigned a laterality (left or right), with 18 patients omitted due to having either a midline or diffusely bilateral lesion (leaving $n = 210$; 94 left-sided, 116 right-sided). Tumor laterality did not influence 10-year overall survival (Kaplan–Meier chi-square, $p = .4$) or the risk of developing epilepsy ($p = .84$). The left/right distribution of tumors was similar in male and female patients ($p = .33$). Patients with epilepsy with left-sided tumors were twice as likely to have ever experienced a focal to bilateral seizure than those with right-sided tumors (Fisher's exact test, $p = .02$, OR = .47, CI .24–.91). The proportion of patients ever experiencing a focal to bilateral seizure by tumor laterality is displayed in Figure 3. Tumor histology did not influence the risk of focal to bilateral seizures ($p = .21$).

3.2 | Secondary analysis group ($n = 185$)

Seizure semiology and 10-year overall survival: A subanalysis was undertaken to assess whether certain features of seizure activity were associated with a change in 10-year overall survival. Initial Kaplan–Meier models with chi-square testing did not show a significant difference in survival based on seizure type (focal vs focal to bilateral, $p = .3$) or seizure awareness (aware vs unaware, $p = .5$). Seizure activity (motor vs non motor) did show a significant difference, with motor seizures associated with better overall survival ($p = .05$). Oligodendrogliomas were not more likely to cause motor seizures than astrocytomas (chi-square, $p = .99$). Ever having a focal to bilateral seizure did not influence survival ($p = .7$).

To investigate this relationship further, with a wider selection of variables thought to influence overall survival, a CPH model was produced using only variables that contributed to the model's predictive power as per a likelihood ratio test. This included the tumor histology as per genetic

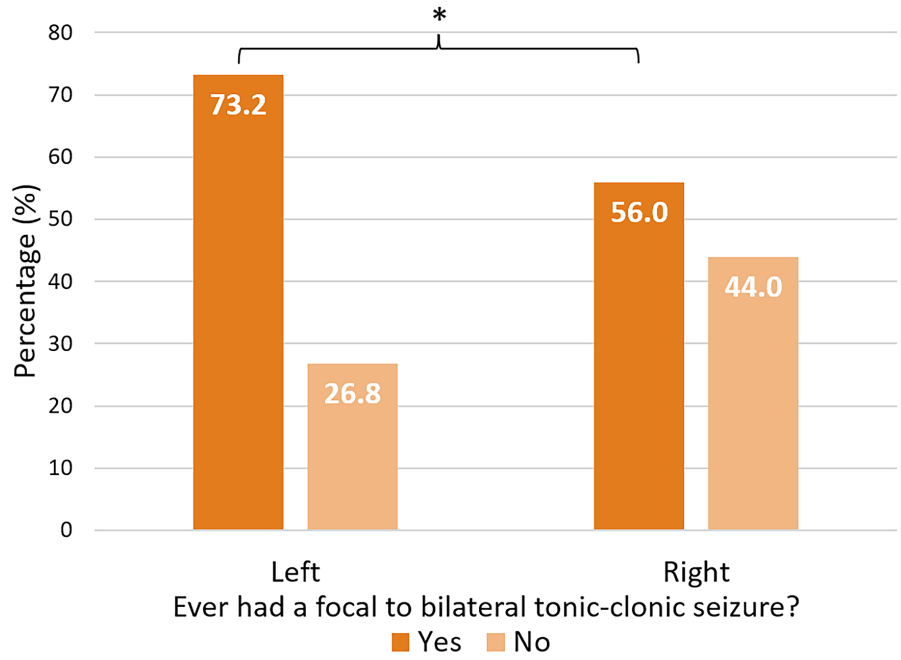

FIGURE 3 Bar chart comparing left- and right-sided tumors and the percentage of patients with each to have ever experienced a focal to bilateral tonic–clonic seizure.

TABLE 1 The influence of histology and seizure activity type on overall 10-year survival as calculated by a Cox proportional hazards model.

	p-value	Hazard ratio	95% Confidence interval
Oligodendroglioma on biopsy	.002	.21	.07–.56
Motor seizure activity	.02	.35	.15–.83

testing and the seizure activity type. In addition, both the time from diagnosis to surgery and the extent of tumor resection were accounted for using appropriate stratification methods (see Section 2.4). A summary of the CPH model results is displayed in Table 1.

Confirmed astrocytoma resulted in a fourfold increase in the risk of death in 10 years ($p = .002$) compared with oligodendroglioma at first biopsy. Having predominantly motor seizure activity showed a survival advantage with a 65% decrease in the risk of death at 10 years.

4 | DISCUSSION

To our knowledge, a correlation between the predominant seizure activity type that a patient experiences and overall survival has not been demonstrated or looked for previously. That patients with motor seizures are twice as likely to survive within a 10-year timeframe, controlling for histology, tumor diagnosis, extent of resection, and time to surgery, raises questions as to whether this effect is due to the seizure activity type itself or related to another attribute of this patient group.

One possible explanation could come from tumor location. As discussed previously, the location of grade 2 gliomas may sometimes be difficult to categorize, especially when they span multiple lobes. Using simple methods to categorize these tumors (deciding in a binary fashion whether or not a tumor is involved in a particular region or lobe) proves challenging in such circumstances. It also does not reflect what we believe to be happening in these tumors with regard to seizure generation, namely, that the tumor margin is the site of epileptogenesis rather than the core. It may be that future studies could better describe tumor location using volumetric measurements or by estimating tumor surface area within each region of interest. This may also be a flawed methodology, however, as proximity in the brain does not necessarily equate to connectivity. All of our patient cohort underwent a surgical procedure, with the vast majority undergoing maximal safe tumor debulking rather than biopsy alone. It may be the case that patients with motor seizures have a tumor in a more frontal location, which in turn allows for a more aggressive surgical resection than a tumor closer to more eloquent areas. Our model was set up to account for the extent of resection (albeit with only four categories) and yet seizure activity still appeared to be a significant factor in predicting survival.

An alternative hypothesis may come from the differing timeframes with which patients present with motor vs non-motor seizures. Some of the non-motor seizure patients in our cohort manifested as intermittent sensory symptoms or emotional/behavioral phenomena. Both of these presentations could easily be labeled as alternative diagnoses in this relatively young patient cohort such as migrainous aura or psychiatric complaints. Frank motor seizures on the other hand are likely to be a greater cause for concern for neurological disease among both patients and the primary care clinicians they initially present to, likely resulting in earlier neuroimaging and a comparatively earlier diagnosis. Although we know that seizures are a very frequent occurrence, and often the first symptom to manifest clinically in grade 2 glioma, it is not clear how early they occur in tumourigenesis. It may be that although seizures are the first clinical manifestation, their appearance is still several years after the onset of tumourigenesis, negating the impact of slightly earlier discovery due to overt seizures. It does not appear from our modeling that experiencing a focal to bilateral seizure either regularly or at least once influences survival.

We found that patients with left-sided tumors were more likely to have experienced at least one focal to bilateral seizure. In our study, we were not able to record whether patients were right- or left-handed due to a lack of clinical information. We did not infer from functional imaging their dominant hemisphere. However, one would assume that the vast majority of patients within our cohort would be left hemisphere dominant, much like the general population. Our results suggest that dominant hemisphere tumors are more likely to result in seizure generalization than those in the non-dominant hemisphere. The higher likelihood of generalization suggests that there may be faster propagation of seizures from dominant to non-dominant hemispheres or a greater ability of the dominant hemisphere to resist involvement when there is uncontrolled activity in the non-dominant side. A recent study suggested that left hemisphere, focal-onset seizures may have a longer duration than right, and this increased seizure duration may increase the risk of generalization proportionately.[24] This may also be the case in tumor-related epilepsy and many other lesional epilepsies. However, seizure length is not something we were able to measure within the scope of this study.

Improved survival outcomes in patients with oligodendroglioma have been reported previously. We redemonstrate these in our grade 2 glioma cohort. The significance of seizures at presentation on overall survival has remained controversial and, at least in this analysis, no significant link was demonstrated. This may be due simply to this being a relatively small effect and requiring a larger sample size than the one we present here. Patient sex appears to influence both the likelihood of epilepsy in grade 2 glioma as well as the risk of seizure generalization, with males more likely to have epilepsy and less likely to have only focal seizures. It is possible that seizures are underdiagnosed in females with glioma if they are more likely to have purely focal seizures that are perhaps less apparent to the clinician. Neither of these findings appear to impact upon overall survival, however, perhaps implying more fundamental differences in seizure generation and propagation in tumor-affected brain between sexes.

5 | CONCLUSIONS

The presence of motor as opposed to non-motor seizures appears to infer an overall survival advantage in grade 2 glioma, independent of diagnosis, time to surgery from diagnosis, and extent of resection. This correlation may be explained by tumor location within the electrical geography of the brain, motor seizures alerting a clinician earlier to their cause, or something more fundamental about tumor biology and neurophysiology. Left (and likely dominant) hemisphere seizures may increase the risk of seizure generalization, either reflecting greater connectivity between the peri-tumoral margin and the rest of the brain or a tendency to provoke focal seizures of a greater duration. Further work is needed to better understand the complex biology and neurophysiology of tumor epileptogenesis and how this translates to the clinical course.

AUTHOR CONTRIBUTIONS

The study was designed by S.F., R.M., and M.M. S.F., J.G., P.C., and R.M. collected the data. Data analysis was performed by S.F. and interpreted by S.F., R.M., and M.M. All authors were involved in drafting the manuscript and have read and approved the final version.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

S.F. is a post-doctoral researcher funded by Leeds Teaching Hospitals NHS Trust. R.K.M. receives research funding from Yorkshire's Brain Tumor Charity and Candlelighters.

CONFLICT OF INTEREST STATEMENT

S.F. has delivered a paid lecture of his own work for UCB Pharma. All other authors have no declarations to make in relation to this work.

DATA AVAILABILITY STATEMENT

Anonymised data will be made available by the authors at reasonable request.

ETHICS STATEMENT

This study received approval from our center's research & innovation/information governance departments. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Fairclough S, Chumas P, Goodden J, Maguire M, Mathew RK. Motor seizures confer overall survival benefit in who grade 2 glioma. Epilepsia. 2024;65:1679–1686. https://doi.org/10.1111/epi.17956