Improved Survival with Decreased Wait Time to Surgery in Glioblastoma Patients Presenting with Seizure

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BACKGROUND: Preoperative seizure is reported to confer favorable prognosis in glioblastoma patients, but studies to date have not investigated how broadly applicable seizure is as a prognostic factor.

OBJECTIVE: To investigate if prompt surgical intervention affects the relationship between preoperative seizure and prognosis in glioblastoma patients, focusing on the development of tumor growth and/or additional preoperative symptoms after seizure.

METHODS: Retrospective analysis of 443 patients (mean age = 60.2; 60% male) undergoing first glioblastoma resection at our institution (2005-2011).

RESULTS: Preoperative seizure(s) occurred in 28% of patients (n = 124), of which 63 (51%) had only seizure at presentation. Patients experiencing seizure as their only preoperative symptom ("seizure-only"; n = 45) survived over twice as long as patients who presented with seizure and then later developed additional preoperative symptoms (n = 18; "other symptoms postseizure"; 26.8 vs 10.2 months, $P < .001$) and patients without preoperative seizure ("no seizure"; 26.8 vs 13.1 months, $P < .001$). Multivariate stepwise analysis revealed preoperative seizures only (hazard ratio 0.54 [0.37-0.75]; $P < .001$) to be independently associated with increased survival. Longer wait time from presentation (ie, diagnostic magnetic resonance imaging) to surgery was a risk factor for developing additional symptoms. Eleven "other symptoms postseizure" patients (69%) vs 6 of the "seizure-only" patients (15%) had wait times >45 days ($P < .001$).

CONCLUSION: Seizure as the only preoperative symptom independently improved survival, however, when patients developed additional preoperative symptoms, typically due to surgical delay, no prognostic benefit was observed. Prompt diagnosis and neurosurgical intervention is warranted in patients with seizures without other preoperative symptoms to preserve their favorable prognosis.

KEY WORDS: Elderly, Glioblastoma, Oncology, Prognostic factors, Seizure

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Glioblastoma is the most common primary malignant brain tumor with a median survival of less than 2 years, which represents only a modest improvement from previous decades.^{1,2} Currently, very few factors have been identified that contribute to improving survival rates in glioblastoma patients with the best-known prognostic factors being extensive resection, diagnosis in adults

under age 65, and radio-oncologic treatment.³ Accordingly, identification of prognostic factors that strongly predict survival in patients with glioblastoma is paramount, especially when this knowledge can lead to improvements in clinical management. A few studies have reported that history of seizure prior to diagnosis of glioblastoma predicts longer survival,⁴⁻⁶ but the relationship between preoperative seizure and glioblastoma prognosis is not well understood.

While seizure is more commonly a feature of lower grade gliomas, occurring in over 80% of patients,⁷ seizures do occur quite frequently in glioblastoma and are the first symptom in 20% to 40% of cases.^{8,9} Interestingly, seizures might

ABBREVIATIONS: CCI, Charlson Co-morbidity Index; CI, confidence interval; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; MRI, magnetic resonance imaging

occur via different mechanisms in low- vs high-grade gliomas. Lee et al (2010),¹⁰ through use of a retrospective imaging survey, found that the influence of location and size of gliomas on their tendency to cause seizures varies with tumor grade. In low-grade gliomas, tumors presenting with seizures were larger than tumors presenting with other symptoms, whereas in high-grade gliomas, tumors producing seizures were smaller and less likely to be deep-seated in the pericallosal regions compared to tumors presenting with other symptoms. Although not fully understood, brain-tumor related epilepsy is thought to occur via excretion of molecules by the tumor itself to make the tumor or peritumoral tissue more epileptogenic¹¹ and/or via the mechanical compression of normal tissue leading to its ischemia and hypoxia, making it more epileptogenic. The dominant mechanism of epileptogenesis in glioblastoma is likely disruption of the subcortical electrical network due to its fast-growth and infiltrative nature, causing an imbalance between inhibitory and excitatory neural networks.¹²

While seizures occurring in lower grade gliomas have been well described, few studies have investigated seizure as a prognostic factor in glioblastoma, and no studies have investigated seizures in the context of other preoperative symptoms. Preoperative symptoms can reflect the tumor characteristics (eg, size, growth rate) and also can influence clinical course (eg, how early a glioblastoma is detected) and thus can give insight into prognosis. By examining the multiple differences that exist between patients with tumors that cause only seizures preoperatively vs those that cause seizures than other symptoms preoperatively, we sought to provide information that might define the importance of prompt surgical intervention in the management of glioblastoma patients with preoperative seizures.

METHODS

Patient Cohort

We retrospectively analyzed data from patients with newly diagnosed glioblastoma undergoing first resection between 2005 and 2011 at our tertiary care specialized brain tumor center. Any patient who was under the age of 18 had been previously diagnosed with a lower grade glioma, or had previous resection and/or adjuvant therapy was excluded. In total, 443 patients met inclusion criteria. Our Institutional Committee on Human Research reviewed and approved this study. Because our study did not use or collect information beyond what was in the medical record, informed consent of patients was not required.

Recorded Variables

Radiographic reports from MR scans were used to determine size (ie, tumor's largest dimension) (as measured by T1 postgadolinium enhancement) and location of the tumor according to the lobe (frontal, temporal, parietal, and occipital), or "other surgical location" (eg, thalamus, basal ganglia, and cerebellum). To determine location, computed tomography scan reports were used when MR scans were not available (occurred in less than 2% of cases). Preoperative scan reports were also used to determine if tumors were multifocal and/or bilateral. Extent of resection was divided into 2 groups based on radio-

logical reports: the first group consisted of patients in whom "gross total" or "near total" resection (>95%) was achieved, and the second group included patients in whom "subtotal resection" was achieved. Epileptic seizures were classified according to the categories set by the International League Against Epilepsy, as focal with or without impairment of consciousness, or evolving to a bilateral convulsive seizure.¹³ Patients were considered as having a preoperative seizure in cases where they suffered at least 1 seizure during the preoperative period that was not attributable to other etiologies such as subdural hematoma, increased intracranial pressure, electrolyte disturbances, or metabolic/toxic causes.

Other preoperative symptoms were determined through corroboration of all preoperative patient charts. Other than seizures, preoperative symptoms included headache, visual disturbances, facial weakness, gait instability, focal weakness, cognitive disturbances (eg, confusion, memory decline), and sensory disturbances. In addition, preoperative patient medical comorbidities were recorded using the Charlson comorbidity index,¹⁴ which assigns a weighted score using a range of comorbid conditions (22 in total). Postresection in-hospital morbidities (eg, delirium, deep venous thrombosis, seizure) as well as length of postresection hospital stay were recorded. All postoperative treatments after first resection (even after subsequent resections) were recorded including standard of care Stupp protocol¹⁵ (radiation and temozolomide) and additional agents (eg, bevacizumab, lomustine). Survival (in months) was calculated by subtracting date of death (found through the Social Security Death Index or medical records) from the date of first resection.

For patients who had seizure as their only symptom at presentation, the time from presentation to surgery was recorded. Date of presentation occurred when patients presented to a hospital after having one or more seizures and received imaging demonstrating a mass suggestive of high-grade glioma (ie, date of diagnostic magnetic resonance imaging [MRI]). All preoperative radiographic scans and medical records were reviewed to determine if tumor growth (based on tumor volume increase >20% [ie, likely not due to measurement error] and/or radiologist impressions) and new symptoms other than seizure occurred in the interval between the first preoperative scan and the scan immediately prior to surgery. Interval tumor growth was based on increase in dimensions of the T1-gadolinium enhancement on MRI scans. The degree of tumoral edema was assessed in the MRI taken immediately prior to resection using a binary classification method¹⁶ whereby minor vs major edema designations were based upon the maximal extension of bright T2-weighted signal beyond the tumor margins. If the T2-weighted signal extended >1 cm in any direction beyond the tumor margin, this was considered major edema and if not, the tumor was said to have minor edema. The location of initial presentation was also recorded for this group and was categorized as either "emergency room presentation" or "outpatient clinic presentation."

Statistics

The Wilcoxon rank-sum and chi-square tests were used for continuous and categorical variable comparison, respectively. We used univariate Cox proportional hazards methods to assess how prognostic factors, such as extent of resection, tumor size, and adjuvant radiotherapy impacted overall survival. Stepwise multivariate Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to investigate variables independently predicting overall survival. A *P*-value of <.1 was required for variable entry and retention in all stepwise multivariate models. In our study, all *P*-values < .05 were considered

statistically significant. All analyses were performed through use of JMP Statistical Software version 12 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient Cohort

Data from the electronic medical record of a total of 443 patients who met inclusion criteria were analyzed. The median age of the entire cohort was 60.2 years, and 40.0% of patients were female (Table 1). One hundred sixty-one patients (36%) were 65 years or older. The frontal lobe was the most common lobe in which the tumor was centered (ie, majority of tumor mass in frontal lobe; 37% of cases, $n = 163$). Tumors were centered in the temporal lobe in 36% of cases ($n = 158$), the parietal lobe in 20% of cases ($n = 90$), occipital in 5% of cases ($n = 21$), and other location (eg, cerebellum, thalamus, basal ganglia) in 3% of cases ($n = 11$). Tumor involvement of the temporal lobe, a purported risk factor for tumor-related epilepsy,⁹ was present in about half of patients (51%, $n = 228$). Preoperative seizure(s) occurred in 28% of patients ($n = 124$), of which 63 (51%) had only seizure at presentation. The mean tumor size was 4.7 cm. About half of the patients underwent gross total resection ($n = 219$, 49%). A large majority underwent the postoperative adjuvant standard of care Stupp protocol consisting of radiation therapy with concurrent temozolomide (>90%).

Preoperative Seizure Classification

Ninety-five of the 124 patients (77%) with preoperative seizures had reliable accounts of their epileptic seizure characteristics that permitted classification by seizure type (Table 2).

The most common seizure types were “focal without consciousness impairment” (35%) and “focal evolving to a bilateral convulsive” (35%) and the least common type was “focal with consciousness impairment” (10%). About half of patients (51%) with preoperative seizures had more than 1 seizure event before surgery.

Other Preoperative Symptoms

Descriptive data were collected on the frequency of various common preoperative symptoms occurring in the context of glioblastoma. The most common symptoms in patients without preoperative seizure were headache (47%) and cognitive difficulty (43%), whereas headache (23%) and language deficit (23%) were most common in patients with preoperative seizure (Table 3). When seizure was included as a symptom, the mean number of symptoms in patients with and without preoperative seizure was 2.2 and 2.1, respectively ($P = .84$). Furthermore, 92 of the 313 patients (29%) without preoperative seizure experienced only 1 preoperative symptom.

Patient Subgroups

The patient cohort was divided into 3 groups for most analyses: patients without preoperative seizures (“no seizure,” $n = 313$),

patients with seizure as their only preoperative symptom (“seizure only,” $n = 45$), and patients who presented with seizure and then later developed additional preoperative symptoms (“other symptoms postseizure,” $n = 18$). Patients with nonepileptic seizures ($n = 4$; eg, seizure due to hemorrhage or toxic/metabolic causes) and baseline seizure disorders ($n = 2$) were excluded from comparative analyses. Breakdown of these groups is represented in Figure 1.

Subgroup Analyses

Several significant differences in tumor characteristics between groups were noted. First, tumors in patients with preoperative seizure were more likely to be centered in the temporal lobe compared to tumors in patients without preoperative seizure ($P = .033$). Tumors in “seizure-only” patients were smaller than tumors in “other symptoms postseizure” patients (3.5 vs 4.8 cm; $P = .0033$) and tumors in “no seizure” patients (3.5 vs 4.7 cm; $P < .001$). Furthermore, radiographic preoperative tumor growth occurred more frequently in “other symptoms postseizure” than it did in “seizure-only” patients (79% vs 13%, $P < .001$; Table 1). When compared to “other symptoms postseizure” patients, “seizure-only” patients had shorter hospital stays (4.6 vs 6.1 days, $P < .001$) and were less like to develop postresection morbidities (eg, delirium, hemiplegia; 4% vs 28%, $P = .008$).

Impact of Time From Presentation to Surgery

Longer wait time from presentation (ie, diagnostic MRI) to surgery was a risk factor for developing additional symptoms in patients initially presenting with seizure only ($n = 63$). Patients with “other symptoms postseizure” had longer wait times from presentation to surgery than “seizure-only” patients (median wait times = 83 vs 18 days, $P < .001$). Furthermore, 11 “other symptoms postseizure” patients (69%) vs 6 “seizure-only” patients (15%) had wait times >45 days ($P < .001$). Patients with wait times >45 days were more likely to exhibit radiographic preoperative tumor growth than patients with shorter wait times (71% vs 15%, $P < .001$).

We found that site of initial presentation impacted wait time to surgery. Wait times were significantly shorter when initial presentation was to the emergency room vs outpatient clinic (18 vs 56 days, $P = .002$), and patients were more likely to present to emergency room when they had generalized seizures vs other types (90% vs 50%, $P = .029$). Wait time was not influenced by distance between the patient’s residence and our medical center (using analysis of distance between zip codes); patients living >100 miles away ($n = 26$) had a median wait time to surgery of 26 vs 21 days in patients living <100 miles away ($n = 37$; $P = .72$).

Increased peritumoral edema has been associated with development of seizures in gliomas,¹⁶ although this link has not been thoroughly established. Using the previously mentioned binary categorization method to assess the degree of edema present on the 63 patients’ MRIs taken immediately prior to surgery, we found that wait time to surgery was significantly longer in patients with

TABLE 1. Patient, Tumor, and Treatment Characteristics in 443 Patients Undergoing Resection for Primary Glioblastoma

Characteristic	All patients (n = 443)	No seizure (n = 313)	Seizures (n = 124)	P-value (seizures vs no seizures)	Seizure only pre-op (n = 45)	Symptoms postseizure (n = 18)	P-value (no seizure vs seizure only preop vs symptoms postseizure)
Patient characteristics							
Age	60.2 ± 12.4	60.6 ± 12.6	59.1 ± 11.6	.20	55.7 ± 10.9	59.3 ± 11.3	.024
% age 65 or older	161 (36%)	119 (38%)	40 (32%)	.67	9 (20%)	5 (28%)	.049
Gender (% male)	266 (60%)	191 (61%)	73 (59%)	.27	28 (62%)	12 (67%)	.86
Charlson comorbidity score >0	127 (29%)	88 (28%)	37 (30%)	.70	9 (20%)	6 (33%)	.44
Tumor characteristics							
Primary tumor location							
F—frontal	F: 163 (37%)	F: 114 (36%)	F: 48 (39%)	.10 (overall)	F: 20 (44%)	F: 5 (28%)	.68 (overall)
T—temporal	T: 158 (36%)	T: 100 (32%)	T: 53 (43%)		T: 18 (40%)	T: 10 (56%)	
P—parietal	P: 90 (20%)	P: 71 (23%)	P: 19 (15%)	.033 (temporal lobe)	P: 5 (11%)	P: 2 (11%)	.11 (temporal lobe)
O—occipital	O: 21 (5%)	O: 19 (6%)	O: 2 (2%)		O: 1 (2%)	O: 1 (6%)	
Other location	Other: 11 (3%)	Other: 9 (3%)	Other: 2 (2%)		Other: 1 (2%)	Other: 0 (0%)	
Temporal lobe involvement	228 (51%)	157 (50%)	66 (53%)	.61	22 (49%)	14 (78%)	.076
Bilateral	61 (14%)	47 (15%)	13 (11%)	.20	3 (7%)	1 (6%)	.18
Multifocal	88 (20%)	62 (20%)	25 (20%)	.97	10 (22%)	3 (17%)	.87
Largest tumor dimension (in cm)	4.7 ± 1.5	4.9 ± 1.4	4.1 ± 1.5	<.001	3.5 ± 1.4	4.8 ± 1.4	<.001
Radiographic evidence of preoperative tumor growth	NA	NA	NA	NA	5 (13%)	11 (79%)	<.001
Postresection in-hospital course							
Length of in-hospital postresection stay	5.9 ± 3.6	6.1 ± 3.9	5.5 ± 2.6	.20	4.6 ± 3.0	6.1 ± 2.8	<.001
Postresection morbidities	60 (14%)	46 (15%)	14 (11%)	.33	2 (4%)	5 (28%)	.042
Treatment characteristics							
Radiotherapy	382 (95%)	268 (94%)	110 (97%)	.14	43 (98%)	13 (93%)	.56
Temozolomide	363 (91%)	252 (89%)	107 (95%)	.08	42 (95%)	12 (86%)	.38
Adjuvant agents (eg, bevacizumab)	182 (46%)	127 (45%)	55 (50%)	.43	28 (63%)	5 (38%)	.053
Clinical trial participation	119 (29%)	84 (29%)	34 (30%)	.85	19 (43%)	2 (13%)	.055
Gross total resection	219 (49%)	149 (48%)	67 (54%)	.25	31 (69%)	13 (72%)	.0054
Median survival (months; 95% CI)	13.7 (12.3-14.9)	13.1 (11.1-14.7)	15.1 (13.0-18.1)		26.8 (19.5-35.4)	10.2 (7.7-15.1)	

Of the 443 Patients Undergoing First Resection for Primary Glioblastoma, 124 (28%) had Preoperative Seizure. The 63 Patients with Seizure Only at Presentation Were Divided in to Those Experiencing Additional Preoperative Symptoms (n = 18) vs Those not Experiencing Preoperative Symptoms (n = 45). Patient, Tumor, And Treatment Characteristics were Compared: "Seizure" vs "No Seizure" as well as "Seizure" vs "Seizure Only" vs "Seizure Then Symptoms" Were the 2 Comparisons Performed. P-Values are Listed in the Columns to the Right of the Groups Compared and Those <.05 are in Bold.

TABLE 2. Seizure Characteristics in 124 Patients With Preoperative Seizures

Seizure type	Number of patients (% of patients)
Focal without consciousness impairment	43 (35%)
Focal with consciousness impairment	13 (10%)
Focal evolving to a bilateral convulsive	43 (35%)
Unspecified seizure type	29 (23%)
Multiple seizure types	4 (3%)
Multiple seizure events	63 (51%)
Status epilepticus	3 (2%)
Total patients with seizures	124

Seizures Were Classified Into 3 Groups Based on Type (Focal Without Consciousness Impairment, Focal With Consciousness Impairment, and Focal Evolving to a Bilateral Convulsive). If Patient Records Were not Clear as to the Type of Seizure, it was Designated as Unspecified.

minor edema vs major edema (40 vs 21 days, $P = .024$). Having major edema (vs minor edema) was not associated with a significantly increased overall survival in these patients (20.2 vs 15.9 months, HR = 0.58 [0.30-1.12]).

Survival

The median survival for all patients was 13.7 months. “Seizure-only” patients ($n = 45$) survived more than twice as long as “other symptoms postseizure” patients (26.8 vs 10.1 months, HR = 0.21 [0.11-0.43], $P < .001$) and patients without preoperative seizure (“no seizure”; 26.8 vs 13.1 months, HR = 0.50 [0.35-0.70], $P < .001$; Figure 2). Preoperative seizure (vs no preoperative seizure) was not associated with a statistically significant

increased survival in patients with glioblastoma (15.1 vs 13.1 months, HR = 0.81[0.65-1.01], $P = .07$).

The 92 patients without preoperative seizure who only had 1 preoperative symptom did not have increased survival compared to patients without preoperative seizure who experienced more than 1 preoperative symptom (12.2 vs 13.1 months, HR = 1.10 [0.84-1.42], $P = .48$), suggesting that there was no prognostic benefit of having only 1 preoperative symptom in patients whose sole preoperative symptom was not seizure.

Univariate survival analyses were conducted (Table 4). A variety of factors were found to be associated with decreased survival in patients with glioblastoma undergoing first resection including age at surgery (>65 years), Charlson comorbidity (score ≥ 1 and ≥ 2 vs 0), preoperative cognitive disturbances, preoperative motor weakness, subtotal resection, postresection morbidities, and development of preoperative symptoms after presenting with only seizure, whereas radiation, temozolomide, additional chemotherapeutic agents, clinical trial participation, and seizure as the only preoperative symptom were associated with increased survival. Interestingly, postresection (in-hospital) seizure was not associated with a survival difference ($P = .92$). However, when patients with postresection (in-hospital) seizure were subdivided into nonelderly (age ≤ 65 years, $n = 10$) and elderly (age > 65 years, $n = 7$), postresection seizure in elderly patients (vs all other elderly patients) was associated with a significant decreased in overall survival (2.0 vs 8.7 months, [HR] 4.37 [95% CI 1.69-9.27], $P = .0044$).

Univariate survival analyses were conducted on the 63 patients who presented with only preoperative seizure (Table 5). Wait time (from presentation to surgery) greater than 45 days (as well as wait time as a continuous variable), radiographic evidence of preoperative tumor growth (after presentation before surgery),

TABLE 3. Percentage of Other Symptoms in Glioblastoma Patients With Preoperative Seizure ($n = 124$) vs Percentage of Symptoms in Patients Without Preoperative Seizure ($n = 313$)

Symptom	Percentage of symptoms in patients with preoperative seizure (%)	Percentage of symptoms in patients without preoperative seizure (%)	P-value
Visual symptoms	5	14	.0052
Headache	23	47	<.001
Cognitive difficulty	20	43	<.001
Sensory disturbance	10	11	.82
Language deficit	23	36	.013
Weakness	22	28	.18
Facial weakness	10	16	.085
Gait disturbances	5	18	<.001
Average number of symptoms per patient (including seizures)	2.2	2.1	.84

Percentages of Preoperative Symptoms Other Than Seizure Were Listed for Patients With Seizure vs Patients Without. Significant Differences in Proportions of Patients With a Given Preoperative Symptom Were Listed as well as P-Values in the Rightmost Column Comparing Proportions Between Groups ($P < .05$ in Bold). There was not a Significant Difference in Number Of Symptoms Experienced by Patients With Seizure vs Those Without When Seizure was Included as a Preoperative Symptom. Pearson's Chi-Square Test was Used to Compare Proportions Between Groups; Wilcoxon Rank-Sum Test was Used for Comparing Number of Symptoms Between Groups.

and development of preoperative symptoms after presenting with only seizure were associated with decreased survival. Site of presentation (emergency department vs outpatient) was not associated with a statistically significant difference in overall

survival in patients presenting with only preoperative seizure ($P = .19$).

Multivariate analysis of the 63 patients presenting with seizure only revealed that after controlling for a variety of factors known to influence survival in glioblastoma (ie, age, temozolomide administration, preoperative Charlson Comorbidity Index (CCI) score, adjuvant therapies, and extent of resection), increased wait time from presentation to surgery was independently associated with decrease survival ([HR] 1.36 [95% CI 1.08-1.69], $P = .011$; HR reported as unit regressor equal to 1 month increased wait time).

Multivariate stepwise analysis was used to identify independent predictors of survival in all patients in our study ($n = 443$). Consistent with previous studies, younger age at diagnosis (≤ 65 years; [HR] 0.69 [95% CI 0.54-0.88], $P = .0034$), Charlson comorbidity score = 0 ([HR] 0.75 [95% CI 0.59-0.98], $P = .032$), gross total resection ([HR] 0.68 [95% CI 0.54-0.84], $P < .001$), postoperative temozolomide ([HR] 0.35 [95% CI 0.21-0.63], $P < .001$), postoperative radiation ([HR] 0.39 [95% CI 0.19-0.77], $P = .0075$), and use of other adjuvant agents (eg, bevacizumab; anytime after first resection; [HR] 0.67 [95% CI 0.53-0.83], $P < .0001$) were associated with improved survival. Additionally, in this multivariate analysis, the presence of preoperative seizures without other symptoms was independently associated with significantly improved survival ([HR] 0.54 [95% CI 0.37-0.75], $P < .0001$; Table 6).

When the patient groups were subdivided into nonelderly vs elderly patients (≥ 65 years old), seizure in the absence of other

TABLE 4. Univariate Analysis of Overall Survival in 443 Patients Undergoing First Resection for Primary Glioblastoma (389 Deaths and 54 Censored)

Factor	Median Survival Time (months) with 95% CI	P-values and HR
Sex		.076
Male	13.4 (11.7-14.9)	1
Female	14.3 (11.5-17.3)	.83 (0.68-1.02)
Age at surgery		<.001
<65 years	16.5 (14.8-18.2)	1
≥65 years	8.5 (6.9-10.1)	1.97 (1.59-2.43)
Charlson index		<.001
0 (vs ≥1)	15.3 (14.1-16.9)	1
≥1 (vs 0)	9.4 (7.4-11.5)	1.68 (1.35-2.09)
≥2 (vs 0)	7.6 (4.9-11.2)	1.84 (1.36-2.44)
Preoperative language disturbances		.59
No language disturbances	13.4 (11.5-14.8)	1
Language disturbances	14.2 (11.6-16.6)	1.06 (0.86-1.30)
Preoperative cognitive disturbances		.0011
No cognitive disturbances	14.9 (13.1-16.5)	1
Cognitive disturbances	10.9 (9.1-14.2)	1.41 (1.14-1.72)
Preoperative motor weakness		.017
No motor weakness	14.5 (13.4-15.9)	1
Motor weakness	9.9 (7.7-13.1)	1.32 (1.05-1.65)
Preoperative seizure		.067
No seizure	13.1 (11.1-14.7)	1
Seizure	15.1 (13.0-18.1)	0.81 (0.65-1.01)
Tumor size		.062
≤4 cm	15.4 (12.9-17.6)	1
>4 cm	12.9 (10.4-14.3)	1.23 (0.99-1.55)
EOR		<.001
GTR	17.0 (14.8-19.0)	0.60 (0.49-0.73)
STR	10.4 (8.6-12.7)	1
Postresection morbidities		.012
No morbidities	14.7 (13.3-15.8)	1
Morbidities	6.4 (3.3-10.5)	1.50 (1.10-2.01)
Postresection (in-hospital) seizure		.92
No seizure	13.8 (12.3-14.9)	1
Seizure	10.5 (2.0-16.8)	0.97 (0.53-1.62)
Postoperative therapy		
Radiation		<.001
No radiation	1.0 (0.2-5.3)	1
Radiation	14.9 (13.7-16.3)	0.16 (0.10-0.26)
Temozolomide		<.001
No temozolomide	4.3 (2.5-6.1)	1
Temozolomide	15.6 (14.3-17.2)	0.17 (0.12-0.25)
Additional agents other than temozolomide (eg, bevacizumab)		<.001
No additional agents	9.0 (7.2-10.7)	1
Additional agents	18.8 (17.3-21.6)	0.56 (0.46-0.70)
Clinical Trial Participation		<.001
No clinical trial	10.7 (9.3-13.0)	1
Clinical trial	18.7 (17.3-21.1)	0.61 (0.49-0.77)
Symptoms postseizure (initially presenting with seizure only)		.0433
Symptoms postseizure	10.2 (6.7-16.6)	1.76 (1.02-2.81)
All other patients	14.3 (13.1-15.6)	1

TABLE 4. Continued.

Factor	Median Survival Time (months) with 95% CI	P-values and HR
Preoperative seizure only		<.001
Preoperative seizure only	26.8 (18.2-34.2)	0.48 (0.34-0.67)
All other patients	12.9 (11.1-14.2)	1

Median Survival (With 95% CIs) was Listed for Various Factors With the Potential to Influence Survival. HRs and P-Values Associated With Each Comparison are Listed in the Rightmost Column and P-Values <0.05 are in Bold.

TABLE 5. Univariate Factors Predicting Survival in 63 Patients Presenting With Seizure Only (11 Censored, 52 Deaths)

Characteristic	Median survival time (months) with 95% CI	P-values and HR
Wait time from presentation to surgery		
Wait time (binary cut-off)		.025
Wait time ≤45 days (n = 39, 70%)	22.0 (18.1-40.2)	1
Wait time >45 days (n = 17, 30%)	12.9 (8.4-16.8)	2.17 (1.11-4.05)
Wait time (in months)		.0018
Unit increase in wait time (in months)	NA	1.43 (1.16-1.74)
Site of initial presentation		0.19
Outpatient (n = 14, 41%)	16.6 (10.1-33.7)	1
ED (n = 20, 59%)	28.2 (15.2-48.8)	0.57 (0.25-1.35)
Radiographic evidence of preoperative tumor growth		.043
No evidence of growth (n = 34, 63%)	26.1 (15.7-43.3)	1
Evidence of growth (n = 20, 37%)	15.0 (7.9-18.8)	1.94 (1.00-3.66)
Development of additional preoperative symptoms		<.001
Symptoms postseizure (n = 18, 29%)	10.1 (6.7-16.6)	4.7 (2.31-9.31)
Seizure only (n = 45, 71%)	26.8 (18.2-34.2)	1

Factors Influencing the Survival of the 63 Patients With Only Seizure At Presentation Were Explored. Median Survival Of Each Group (with 95% CIs) was reported. Hazard Ratios and P-Values Comparing Groups are Listed in the Rightmost Column and P-Values <0.05 are in Bold. Complete Data was not Available for Every Patient. For example, not Every Patient had Sufficient Documentation to Conclude Their Exact Date of Presentation, Disallowing Calculation of Wait Time From Presentation to Surgery.

TABLE 6. Stepwise Multivariate Analysis of Various Patient, Treatment, and Tumor Characteristic That Affected Overall Survival in Patients With Glioblastoma

Characteristic	Hazard ratios	P-values
Temozolomide (vs no temozolomide)	0.35 [0.21-0.63]	<.001
Radiation (vs no radiation)	0.39 [0.19-0.77]	.0075
'Seizure only' (vs all other patients)	0.54 [0.37-0.75]	<.001
Adjuvant agents (eg, bevacizumab; vs no adjuvant agent)	0.67 [0.53-0.83]	<.001
Gross total resection (vs subtotal resection)	0.68 [0.54-0.84]	<.001
Younger age (≤65 years old; vs >65 years old)	0.69 [0.54-0.88]	.0034
Charlson comorbidity score = 0 (vs CCI>0)	0.75 [0.59-0.98]	.032

Univariate Factors Known to Influence Survival Were Included in a Stepwise Multivariate Analysis of Survival in 443 Patients With Primary Glioblastoma Undergoing First Resection. Seven Variables Were Retained in the model, Including "Seizure Only" (vs All Other Patients; HR 0.54 [0.37-0.75], $P < .001$).

symptoms remained a significant prognostic factor, especially in the elderly (Figure 3). The elderly patients in the "seizure-only" (n = 9) group lived more than twice as long (30.4 vs 8.6 months, HR = 0.42 [0.20-0.80], $P = .0062$) as elderly patients in the "no

seizure" group (n = 117), and there was no statistically significant difference in the survival of elderly patients vs nonelderly patients in the "seizure-only" group (n = 36; 30.4 vs 26.8 months, HR = 1.31 [0.57-2.71], $P = .50$).

FIGURE 3. Elderly patients with “seizure-only” experience substantially increased survival. The elderly patients in the “seizure-only” ($n = 9$) group lived more than twice as long (30.4 vs 8.6 months, $HR = 0.42$ [0.20-0.80], $P = .0062$) as elderly patients in the “no seizure” group ($n = 117$), and there was no statistically significant difference in the survival of elderly patients vs nonelderly patients in the “seizure-only” group ($n = 36$; 30.4 vs 26.8 months, $HR = 1.31$ [0.57-2.71], $P = .50$).

DISCUSSION

A number of prognostic factors have been suggested for glioblastoma, a devastating cancer with a median survival of less than 2 years. The most validated factors for improving glioblastoma patient prognosis include diagnosis in adults under age 65, extensive resection, and use of adjuvant radiation and chemotherapy.^{3,17} We sought to further characterize the prognostic significance of preoperative seizure in glioblastoma. The prevalence of preoperative seizure in our patient cohort was consistent with previous literature, which cites that about 25% of patients with glioblastoma will experience seizure as the first symptom of the disease.⁵

Preoperative seizure has previously been found to predict increased survival in glioblastoma, although there is not an overwhelming consensus about this association.^{4,5,18} Ozbek et al (2004)⁴ was the first article to report on the prognostic significance of preoperative seizure in glioblastoma and found the variable of “seizure at diagnosis” to be associated with increased survival in multivariate analysis. Similarly, Toledo et al (2015)⁵ found seizures as a presentation symptom independently predicted increased survival, whereas postresection seizures tended to signal tumor progression or end of life stages. Most recently, Shin et al (2016)¹⁸ found that seizures (at any time during the course of glioblastoma) were not associated with significantly increased survival. We are first to report the significance of wait time from presentation to surgery in the context of patients presenting with preoperative seizure. Our data suggest that the prognostic benefit of preoperative seizure occurs because seizures typically arise from small lesions, but that this prognostic benefit only occurs when surgical intervention is prompt and timely

before other symptoms, a surrogate marker of subsequent tumor growth, occur.

We attempted to identify possible reasons for decreased wait times in patients presenting with only seizure and found that patients presenting to the emergency room instead of an outpatient presentation had decreased wait times to surgery. This was presumably due to patients being admitted to the hospital from the emergency room and undergoing more prompt surgical intervention than a patient needing to await a spot on the elective surgical schedule from the clinic. Regardless of whether they present through the emergency room or clinic, we hope that our findings will imbue a sense of immediacy in this process for patients presenting with seizure as their only symptom.

In our cohort of patients with preoperative seizure alone, those who went to surgery quickly such that seizure remained their only symptom had better survival than those with greater delay to surgery, which was associated with the emergence of other symptoms. A longer wait time allows for tumor growth (which we detected radiographically) and might also allow for glioblastoma to evolve more aggressive biology, either of which could lead to the development of other symptoms after an initial seizure. Development of this aggressive biology¹⁹ might render this tumor less responsive to treatment, which would mean a poorer survival for these patients harboring these tumors. Further prospective investigation would be helpful to validate our retrospective observation that more immediate surgical intervention improves survival in patients who initially present with seizure as their only preoperative symptom.

Limitations

Limitations of this study include its retrospective nature, which could affect the accuracy of information on time from diagnostic MRI to surgery if some images failed to be archived or recorded, which could lead to underestimation. Also, the nature of reporting in the electronic medical record as well as patients’ illness perceptions could lead to a confounding effect if patients or clinicians did not endorse or record other potentially subtle presenting symptoms given the overwhelming influence of a seizure presentation. In addition, the majority of the time period during which these cases were pulled occurred before our institution began routine analysis of modern molecular markers such as Isocitrate dehydrogenase 1 (IDH1), a molecular marker that is associated with lower grade gliomas and secondary glioblastomas (those arising from lower grade gliomas) and, accordingly, portends a favorable prognosis.²⁰ However, a recent study found no significant association ($P = .9$) between preoperative seizures in glioblastoma and IDH mutation status,²¹ suggesting that our results about the importance of prompt surgical resection in patients presenting with seizure only were not confounded by the IDH status of these tumors. Nonetheless, the molecular biology and genetics of epileptogenic glioblastomas is believed to be different from nonepileptogenic glioblastomas. For example, glioblastomas with oligodendroglial

components reduced EAAT2 expression, and higher glutamate concentrations have been shown to be associated with the development of tumor-associated epilepsy in glioblastoma.^{8,11} Biological differences between epileptogenic and nonepileptogenic glioblastomas could account for differences in survival, and this relationship is an area for further research.

CONCLUSION

Seizure as the only preoperative symptom independently improved survival; however, when patients developed additional preoperative symptoms, typically due to delay in surgery, no prognostic benefit was observed. Tumors in patients with preoperative seizure were smaller than tumors in patients without preoperative seizure. Seizure as the only preoperative symptom was especially predictive of increased survival in elderly patients. Taken together, our results suggest that the prognostic benefit of preoperative seizure in glioblastoma patients is only realized with prompt neurosurgical intervention and that failure to do so can lead to the development of other symptoms causing these patients to lose their favorable prognosis.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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