CASE STUDY

Impact of seizures and antiseizure medication on survival in patients with glioma

Thinisha Sathis Kumar¹,⁴ · Wan Muhammad Afnan²,⁴ · Chet-Ying Chan²,⁴ · Christine Audrey²,⁴ · Si-Lei Fong²,⁴ · Retnagowri Rajandram³,⁴ · Kheng-Seang Lim²,⁴ · Vairavan Narayanan¹,⁴

Received: 14 July 2022 / Accepted: 27 July 2022 / Published online: 29 August 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Purpose Seizures are a common presenting symptom among patients with low- and high-grade glioma. However, the impact and inter-relationship between the presence of seizures, anti-seizure medication (ASM) and survival are unclear. We retrospectively analyzed the incidence of seizures and identified the pattern and relationship of anti-seizure medication on survival in our cohort of patients with glioma.

Methods We evaluated all glioma patients who underwent treatment at the University of Malaya Medical Centre (UMMC) between 2008 and 2020. Demographic and clinical data of seizures and pattern of ASM administration in comparison to overall survival were analyzed.

Results A total of 235 patients were studied, with a minimum of one year clinical follow-up post-treatment. The median survival for low-grade glioma was 38 months whereas high-grade glioma was 15 months. One-third of our glioma patients (n = 74) presented with seizures. All patients with seizures and a further 31% of patients without seizures were started on anti-seizure medication preoperatively. Seizure and Levetiracetam (LEV) were significantly associated with OS on univariate analysis. However, only LEV (HR 0.49; 95% CI 0.23-0.87; p=0.02) was significantly associated with improving overall survival (OS) on multivariate analysis. Once ASM was adjusted for relevant factors and each other, LEV was associated with improved survival in all grade gliomas (HR 0.52; 95% CI 0.31-0.88; p=0.02) and specifically high-grade gliomas (HR 0.53; 95% CI 0.30-0.94; p=0.03).

Conclusions Pre-operative seizures among patients with glioma indicated a better overall prognosis. The administration of ASM, specifically LEV was associated with a significant survival advantage in our retrospective cohort of patients.

Keywords Antiseizure medication · Glioma · Levetiracetam · Seizure · Survival

Introduction

Gliomas account for more than 65% of all primary brain tumors. Glioblastoma is the most common (65%) and most malignant histopathological type [1]. Survival of patients varies significantly by grade across all glioma subtypes. There is a striking contrast when comparing survival rates in low and high-grade glioma patients. Patients with low-grade gliomas (LGG) have longer survival compared to patients with high-grade gliomas, with a median survival of 14 years with optimal treatment [2, 3].

Seizure is the most common presenting symptom among 15 to 50% of newly diagnosed glioma patients, and 83% among low-grade glioma (LGG) patients [4, 5]. History of seizures was suggested as a good prognostic factor in both low and high-grade gliomas (HGG) as early as 1980 by Scott et al. [6–9]. Since seizures are directly linked to a patient's quality of life, it's important to control the clinical seizure manifestation throughout glioma treatment [10]. Complete seizure control achieved with a single drug is the aim of seizure therapy in patients with LGG. Currently

Vairavan Narayanan
nvairavan@um.edu.my

¹ Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
² Division of Neurology, Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
³ Department of Surgery, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
⁴ Hospital Tanah Merah Kelantan, Tanah Merah, Malaysia
available anti-seizure medication (ASMs) are quite effective in this aspect, whereas the main treatment methods for LGG (surgery and radiation therapy) have a beneficial impact on seizure control [11]. On the other hand, antiseizure drugs remain the primary modality of seizure control in HGG [12]. The impact on survival was more significant in low-grade glioma, especially those with focal seizures without impairment of consciousness. [13]. Nevertheless, the management of seizures in these patients is often opportunistic and not evidence-based or uniform.

Anti-seizure medicine (ASM) has shown variable effectiveness in treating seizures in patients with glioma [14, 15]. While there are many ASM routinely used by clinicians, the common drugs prescribed to glioma patients include Phenytin (PHT), Valproic acid (VPA), Carbamazepine (CBZ), Lamotrigine (LTG), and Levetiracetam (LEV) [16–18]. Some clinical studies imply that patients with glioblastoma multiforme (GBM) who are treated with VPA have better outcomes than those treated with other ASM [19–22]. Other papers have suggested that combined treatment of LEV and Temozolomide has reduced seizures [23–25], improved the efficacy of chemotherapy and prolonged the survival of GBM patients [26–28]. In contrast to these studies, Knudsen-Baas KM and Hirotomo Tanaka et al. found that ASMs had no significant effect on OS in GBM patients [26, 29].

The current literature on seizures and ASM in glioma patients has shown a somewhat mixed picture of the impact of seizures and the utility of ASM beyond seizure control in patients with glioma. This study identifies the impact of seizures and ASM in relation to survival in our cohort of glioma patients.

Methodology

Study design

This is a retrospective single-centre cohort study of glioma patients who underwent treatment at the University of Malaya Medical Centre (UMMC) between 2008 and 2020. Ethical approval was obtained from the Medical Research Ethics Committee, UMMC (No. 2020930-9118). Informed consent was not required as this was a retrospective anonymous design study.

Sample recruitment

Glioma patients were identified from the neurosurgical patient database. A total of 235 patients with histopathologically confirmed glioma diagnosed between January 2008 and December 2020, were included in this study. Of which 221 were on ASM regardless of having seizures and 14 had unavailable information on the use of ASM and the date of diagnosis. A neurologist or a neurosurgeon confirmed the pre-operative diagnosis of seizures based on a documented clinical history of seizures or electroencephalographic (EEG) findings. Clinical data of the included patients were collected using electronic medical records. Patients with a single ASM were defined as monotherapy while patients with more than one ASM at any one time were defined to be on polytherapy.

Statistical analyses

All statistical evaluations were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. The univariate analysis evaluated age, gender, ethnicity, tumor grade, epileptic seizures, tumor site, and the type of anti-seizure medication (ASM). Cox proportional hazards model and hazard ratios (HR) with a 95% confidence interval (CI) were used in the multivariate analysis. A p-value of 0.05 or less was regarded as significant. The correlation between the use of ASM and survival was examined using the Kaplan Meier method, and the findings were compared using the log-rank test. In this analysis, not all patients had full ASM data. From the final study, 14 patients having insufficient ASM data were left out. Overall survival was determined as the time from diagnosis to the final check-up or the time until death from any cause. Using Cox regression, the impact of ASMs like VPA, LEV, and PHT on survival was evaluated. Due to a lack of data, other ASMs weren’t examined.

Results

A total of 235 patients with gliomas were recruited for this study. Of these, 221 were on ASM regardless of the presence of clinical seizures while 14 had unavailable information on the use of ASM. Table 1 summarizes the baseline characteristics of this study cohort. Younger glioma patients (< 65 years old) were more likely to present with seizures preoperatively. Patients with GBM were more prone to develop seizures preoperatively (51%) compared to lower-grade gliomas. Most of our patients (n=173) had their tumor confined to a single lobe while 59 and 3 patients respectively had tumor involving two lobes and three lobes each. The most common location in relation to presentation with seizures was the frontal lobe n=40 (54%, p=0.00), followed by parietal n=20 (27%, p=0.53), temporal n=12 (16.2%, p=0.89), occipital n=5 (6.8%, p=0.87). All patients who presented with seizures were started on ASM, while 50 patients (32%) without seizures were started on ASM prophylactically. The majority of our patients were on monotherapy (n = 69) whereas patients with highly resistant seizures (n = 48) were started on polytherapy, ranging between 2 and 4 ASMs.
According to our analysis of the effect of seizures on overall survival, patients with seizures have significantly longer median overall survival than patients without seizures (Fig. 1) i.e., 124 and 29 months with seizures and without seizures respectively. Using the log-rank approach, a Kaplan-Meier survival analysis revealed a statistically significant difference (p=0.01) for this comparison.

A wide variety of ASM was used by patients in our cohort. 48 patients with polytherapy were administered between 2 to 4 ASMs throughout their treatment (Table 2). In total, 55 PHT, 53 LEV, 34 VPA, and 7 CBZ were administered to the patients while the other less common ASM ranged from 1 to 7 occurrences. PHT was the most common ASM prescribed followed by LEV. Most patients were on monotherapy versus polytherapy (n=69 versus n=48) in our cohort whereas the total number of drugs that had been prescribed for polytherapy was n=85.

Older age (HR 2.42; 95% CI 1.57-3.72; p= 0.00), high grade glioma (HR 2.01; 95% CI 1.62-2.49; p=0.00), tumor location in the parietal lobe (HR 1.51; 95% CI 1.04-2.17; p=0.03), patients with seizure (HR 0.58; 95% CI 0.38-0.88; p=0.01), and LEV administration (HR 0.56; 95% CI 0.33-0.94; p=0.03) were correlated with the overall survival on univariate analysis. Further multivariate analysis between these factors revealed high grade glioma (HR 3.42; 95% CI 2.18-5.39; p=0.00) and LEV administration (HR 0.49; 95% CI 0.23-0.87; p=0.02) to be significantly associated with OS (Table 3).

Kaplan Meier survival analysis for all grade glioma based on the 3 most common anti-seizure medication used in our cohort is presented in Fig. 2. LEV (Fig. 2a) showed a significant survival benefit (HR 1.32; 95% CI 1.04-1.68; p=0.02) with a median survival of 62 months while PHT

---

**Table 1** Baseline clinical characteristics of glioma patients

| Variables          | Total (n=74), N (%) | Seizure (n=161), N (%) | P value |
|--------------------|---------------------|------------------------|---------|
| Sex                |                     |                        |         |
| Male               | 123 (55)            | 82 (50.9)              | 0.52    |
| Female             | 112 (44.6)          | 79 (49.1)              |         |
| Ethnic             |                     |                        |         |
| Malay              | 77 (27)             | 50 (31.1)              | 0.42    |
| Indian             | 57 (21.3)           | 39 (24.2)              |         |
| Chinese            | 96 (29.2)           | 67 (41.6)              |         |
| Others             | 5 (0)               | 5 (3.1)                |         |
| Age group          |                     |                        |         |
| <65 years old      | 198 (70)            | 128 (79.5)             | 0.03    |
| ≥65 years old      | 37 (4.5)            | 33 (20.5)              |         |
| Grade              |                     |                        |         |
| Low grade          | 96 (36.5)           | 60 (37.3)              | 0.09    |
| High grade         | 139 (51.4)          | 101 (62.7)             |         |
| Administration of  |                     |                        |         |
| ASM                |                     |                        |         |
| Yes                | 117 (70)            | 50 (32.5)              | 0.00    |
| No                 | 104 (4)             | 104 (67.5)             |         |
| ASM                |                     |                        |         |
| Monotherapy        | 69 (56.7)           | 31 (62.0)              | 0.57    |
| Polytherapy        | 48 (43.3)           | 19 (38)                |         |
| Frequently used ASM|                     |                        |         |
| LEV                | 53 (50.7)           | 19 (12.3)              | 0.00    |
| No                 | 168 (49.3)          | 135 (87.7)             |         |
| PHT                | 55 (35.8)           | 31 (20.1)              | 0.13    |
| No                 | 166 (64.2)          | 123 (79.9)             |         |
| VPA                | 34 (34.3)           | 11 (7.1)               | 0.00    |
| No                 | 187 (65.7)          | 143 (92.9)             |         |

**Abbreviations:** ASM, antiseizure medication; LEV, levetiracetam; PHT, phenytoin; VPA, valproate.

ASM data is available in 221 cases only.

Table 2 Type and number of anti-seizure medications prescribed to patients

| ASMs            | Monotherapy | Polytherapy | Total |
|-----------------|-------------|-------------|-------|
| Phenytoin       | 26          | 29          | 55    |
| Levetiracetam   | 20          | 33          | 53    |
| Sodium Valproate| 15          | 19          | 34    |
| Carbamazepine   | 5           | 2           | 7     |
| Gabapentin      | 1           | 1           | 2     |
| Lamotrigine     | 0           | 1           | 1     |
| Zonisamide      | 1           | 0           | 1     |
| Oxycarbamazepine| 1           | 0           | 1     |
(Fig. 2b) (HR 1.08; 95% CI 0.86-1.36; p=0.50), VPA (Fig. 2c) (HR 1.23; 95% CI 0.95-1.59; p=0.11) with a median survival of 60 and 42 months respectively were not significant. Based on cox regression analysis, in LGG (Fig 2d) LEV (HR 0.52; 95% CI 0.31-0.88; p=0.02) was the most favorable ASM in terms of survival compared to VPA (HR 0.79; 95% CI 0.47-1.33; p=0.38) and PHT (HR 1.35; 95% CI 0.89-2.07; p=0.15). LEV (HR 0.53; 95% CI 0.30-0.94; p=0.03) also showed similar results for HGG (Fig 2e) compared to other VPA (HR 0.87; 95% CI 0.46-1.65; p=0.66), and PHT (HR 1.05; 95% CI 0.66-1.67; p=0.83).

| Table 3 | Associated factors for glioma patients’ overall survival |
|---|---|---|---|
| Variables | Univariate | Multivariate |
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Sex | | | | |
| Male | 1 | | | |
| Female | 1.31 (0.92-1.88) | 0.14 | | |
| Ethnic | | | | |
| Malay | 1 | | | |
| Indian | 1.36 (0.86-2.15) | 0.19 | | |
| Chinese | 0.99 (0.64-1.51) | 0.94 | | |
| Others | 0.74 (0.18-3.05) | 0.67 | | |
| Age group | | | | |
| < 65 years old | 1 | | | |
| ≥ 65 years old | 2.42 (1.57-3.72) | 0.00 | 1.64 (1.03-2.62) | 0.04 |
| Grade | | | | |
| Low grade | 1 | | | |
| High grade | 2.01 (1.62-2.49) | 0.00 | 3.42 (2.18-5.37) | 0.00 |
| Tumor location | | | | |
| Frontal | 0.96 (0.66-1.40) | 0.83 | | |
| Temporal | 1.54 (0.98-2.42) | 0.6 | | |
| Parietal | 1.51 (1.04-2.17) | 0.03 | 1.19 (0.81-1.74) | 0.34 |
| Occipital | 1.22 (0.62-2.41) | 0.56 | | |
| Preoperative seizure | | | | |
| No | 1 | | | |
| Yes | 0.58 (0.38-0.88) | 0.01 | 0.94 (0.58-1.52) | 0.79 |
| Administration of ASM | | | | |
| No | 1 | | | |
| Yes | 1.34 (0.93-1.93) | 0.11 | | |
| ASM | | | | |
| Monotherapy | 1 | | | |
| Polytherapy | 0.63 (0.36-1.11) | 0.11 | | |
| Types of ASM | | | | |
| LEV | 0.56 (0.33-0.94) | 0.03 | 0.49 (0.23-0.87) | 0.02 |
| PHT | 1.17 (0.78-1.77) | 0.44 | | |
| VPA | 0.80 (0.48-1.34) | 0.40 | | |
Our study showed that glioma patients with seizures had significantly longer survival compared to patients without seizures. In the current era of modern ASM, there is a variety of medications that can provide patients with greater seizure control while not compromising the quality of life or concurrent adjuvant treatment for glioma patients. Our findings suggest that treatment with LEV was associated with longer survival compared to other ASMs that are available, irrespective of whether ASM monotherapy or polytherapy was utilized.

The risk of seizures in glioma patients is generally assumed to be high. In our study we accumulated data on 239 patients with glioma, spanning 12 years between 2008 and 2020, diagnosed and treated in a single centre. Of these 235 patients, 31% patients had seizure onset at presentation or some point in their pre-surgical period. All patients with seizures were started on at least one ASM among a variety that was available in our centre. The choice of ASM was variable, depending on familiarity and ease of prescription by the treating clinician. Of the remaining 68.5% with no seizures, one-third (31%) were also started on ASM pre-operatively. Thus, most patients with glioma in our cohort

![Fig. 2 Kaplan–Meier survival curves show the overall survival of patients.](image)

(A) K-M plot of patients with LEV, other ASM and no ASM. Survival was significantly different between the 3 groups (p=0.02). (B) K-M plot of glioma patients treated with PHT. (C) K-M plot of glioma patients treated with VPA. (D) K-M survival plot shows ASMs in all grade glioma and LEV is significant compared to other drugs (p=0.02). (E) K-M survival plot shows ASM in only high-grade glioma. The plot shows that LEV is significant compared to other drugs (p=0.03).

Abbreviations: ASM, antiseizure medication; CI, confidence interval; HR, hazard ratio; LEV, levetiracetam; PHT, phenytoin; VPA, valproate
received ASM irrespective of the seizure status. Current existing guidelines do not favour the administration of prophylactic ASM in the perioperative period [30–32].

There has been discussion on whether and why seizures may improve overall survival in glioma patients [33, 34]. In our cohort, the presence of presurgical seizures was a protective factor (HR 0.58) in univariate analysis for survival. While this has been established in patients from high-income countries, similar data have been lacking in low- and middle-income countries where access to medical facilities and optimal medical diagnosis may not be as easily available [33, 35–37]. The reason for the protective nature of seizures in patients with glioma is still not established. Among the postulated hypothesis include early tumor detection due to the visible physical manifestation that may lead to early treatment and longer survival time [34, 38, 39]. Glutamate, an excitatory neurotransmitter, is crucial for the emergence of seizures [40]. Increased expression of particular glutamate receptor subtypes, low glutamine synthetase activity, high glutamate concentrations in glioma cells, essentially nonexistent intracellular uptake, and excessive extracellular glutamate levels are all abnormalities. These modifications may have an impact on tumor and are correlated with increased seizure frequency [37].

For glioma patients with epilepsy, the choice of an ASM is influenced by a number of variables, including accessibility, tolerability, effectiveness, comorbidity, costs, the convenience of administration, titration plans, and finally, the preference of the treating physician [41]. In our cohort, PHT and LEV were commonly used to treat seizure patients with glioma. PHT was widely used as it is affordable although it has side effects such as headache, nausea, vomiting, constipation, dizziness, or nervousness. On the other hand, LEV is being used with increasing frequency in these patients due to the expected low side effect profile, fewer interactions with other medications and simplicity of dose titration [42, 43].

The grade of glioma, specifically high-grade glioma had a significant impact on survival as expected. More interestingly, we found the use of LEV had a significant impact on survival in both univariate and multivariate analyses among patients with glioma. This was confirmed by cox regression analysis which revealed a significantly lower hazard ratio for the use of LEV compared to three other commonly used ASM. Previous papers have alluded to possible mechanisms of action in which LEV may provide a beneficial effect including as a temozolomide chemosensitizer or by repressing the MGMT expression [29]. VPA has been previously suggested to carry a potential anti-tumor effect. However, we did not find a similar effect in our cohort of patients.

While ASM may indeed have a causative role in the prolongation of survival among patients with glioma, it must be stressed that this current study only establishes an association between LEV and prolonged survival in glioma. Among the many non-causative factors that may have led to these results include the continued improvement of surgical skills in the period studied and increasing availability and affordability of Temozolomide, both of which coincided with the availability and increased awareness of the advantages of using LEV in tumor related seizures compared with older drugs like PHT or CBZ.

The use of ASM seems to be very varied among our cohort of patients, with 8 different ASM being used in various permutations of monotherapy and polytherapy. Tumor-related epilepsy is frequently drug-resistant and may require higher doses as well as multiple drugs to achieve reasonable control [44]. Furthermore, this variability in its use, especially in a prophylactic fashion is due to the lack of clear guidelines on tumor-related epilepsy management.

**Limitations of the study**

The findings in this study are limited by the small sample size and heterogeneity of associated factors. Some data were not available due to the retrospective nature of the data collected. The impact of individual ASMs could not definitively be determined because many patients were on ASM polytherapy. These limitations can be overcome with a prospectively designed study that may be able to determine the impact and benefit of ASMs in patients with glioma.

**Conclusion**

The presence of preoperative seizures among patients with glioma indicated a better overall prognosis. The administration of ASM preoperatively, especially LEV demonstrated a significant survival advantage in our cohort of patients. The findings in this study improve our understanding of the impact of seizures, the pattern of ASM usage and its association with survival in glioma patients in our cohort. Further large prospective randomized trials should be conducted taking into account all the prognostic factors for validating the benefits of LEV on survival in glioma.

**Acknowledgements** This study is sponsored by an Impact-oriented Interdisciplinary Research Grant (IIRG) (reference no: IIRG003-2020HWB).

**Author contributions** Conception and design of original study was by VN; Material preparation, data collection and analysis were performed by TS, WMA, Vanessa, CA, SLF, and RR. The first draft of manuscript was written by TSK. Approval of final manuscript was done by KSL and VN.

**Funding** This work was supported by Impact-oriented Interdisciplinary Research Grant (IIRG) (reference no: IIRG003-2020HWB).
Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Competing interest The authors have no relevant financial or non-financial interest to disclose.

Ethical approval Ethical approval was obtained from the Medical Research Ethics Committee, UMMC (No. 2020930-9118).

Consent to participate Informed consent was not required as this was a retrospective anonymous design study.

Consent to publish No individual data was used in this paper.

References

1. Ohgaki H, Kleihues P (2005) Epidemiology and etiology of gliomas. Acta Neuropathol 109:93–108
2. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, Coons S, Ricci P, Bullard D, Brown PD (2016) Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 374:1344–1355
3. Bush NAO, Chang S (2016) Treatment strategies for low-grade glioma in adults. J Oncol Pract 12:1235–1241. https://doi.org/10.1097/JOP.0000000000000092
4. Pace A, Bove L, Innocenti P, Pietrangeli A, Carapella C, Oppido P, Raus L, Occhipinti E, Jandolo B (1998) Epilepsy and gliomas: incidence and treatment in 119 patients. J Exp Clin Cancer Res 17:479–482
5. Iuchi T, Hasegawa Y, Kawasaki K, Sakaida T (2015) Epilepsy in patients with gliomas: incidence and control of seizures. J Clin Neurosci 22:87–91
6. Scott G, Gibberd F (1980) Epilepsy and other factors in the prognosis of gliomas. Acta Neurol Scand 61:227–239
7. Chaichana KL, Halthore AN, Parker SL, Olivi A, Weingart JD, Scott G, Gibberd F (2016) Survival analysis for valproic acid use in adult glioblastoma multiforme: a meta-analysis of individual patient data and a systematic review. Seizure 23:830–835
8. Chang CY, Li JR, Wu CC, Ou YC, Chen WY, Kuan YH, Wang WW, Chen CJ (2015) Valproic acid sensitizes human glioma cells to gefitinib-induced autophagy. IUBMB Life 67:869–879
9. SmiNia MF (2015) Abdel Nasser Hosein, Yi Chieh Lim, Bryan Day, Brett Stringer, Stephen Rose, Richard Head, Leah Cosgrove, Peter J Neurooncol 122:263–271
10. Krawczuk AV, Myrehaug SD, Chang MG, Holdford DJ, Smith S, Shih J, Tofilon PJ, Fine HA, Camphausen K (2015) A phase 2 study of concurrent radiation therapy, temozolomide, and the histone deacetylase inhibitor valproic acid for patients with glioblastoma. J Natl Cancer Inst 107:61–67
11. Knudsen-Baas KM, Engeland A, Gilhus NE, Storstein AM, Owe E, Hovig E, Ulvestad R (2015) Does the choice of antiepileptic drug affect survival in patients with brain tumors: new insights and evidence-based management. Seizure 23:830–835
12. Sminia P, Stalpers LJ (2012) Valproic acid sensitizes human glioma cells for temozolomide and γ-radiation. J Neurooncol 109:325–335
13. Dobran M, Nasi D, Chiariotti S, Gladi M, Di Somma L, Iacoangeli M, Scerrati M (2018) Prognostic factors in glioblastoma: is there a role for epilepsy? Neurol Med Chir 58:110–115
14. Talati R, Scholle MJ, Pugh OJ, Baker WL, Baker EL, Ashaye A, Kluger J, Quercia R, Mather J, Giovenale S, Coleman CI, White CM (2011) Effectiveness and safety of antiepileptic medications in patients with epilepsy. Agency for healthcare research and quality (US). Rockville (MD)
15. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, Shinnar S, Conwit R, Meinzer C, Cock H (2019) Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 381:2103–2113
16. Bracken MS, Wilms EB, Vecht CJ (2007) Epilepsy in patients with brain tumors: epidemiology, mechanisms, and management. The Lancet Neurology 6:421–430
17. SmiNia MF (2015) Abdel Nasser Hosein, Yi Chieh Lim, Bryan Day, Brett Stringer, Stephen Rose, Richard Head, Leah Cosgrove, Peter J Neurooncol 122:263–271
18. Vecht CJ, Wagner GL, Wilms EB (2003) Treating seizures in patients with brain tumors: drug interactions between antiepileptic and chemotherapeutic agents. Sem Oncol. https://doi.org/10.1053/j.semoncol.2003.11.030
19. Yuan Y, Xiang W, Qing M, Yanhui L, Jiewen L, Yunhe M (2014) Survival analysis for valproic acid use in adult glioblastoma multiforme: a meta-analysis of individual patient data and a systematic review. Seizure 23:830–835
20. Chang CY, Li JR, Wu CC, Ou YC, Chen WY, Kuan YH, Wang WW, Chen CJ (2015) Valproic acid sensitizes human glioma cells to gefitinib-induced autophagy. IUBMB Life 67:869–879
21. SmiNia MF (2015) Abdel Nasser Hosein, Yi Chieh Lim, Bryan Day, Brett Stringer, Stephen Rose, Richard Head, Leah Cosgrove, Peter J Neurooncol 122:263–271
22. Krawczuk AV, Myrehaug SD, Chang MG, Holdford DJ, Smith S, Shih J, Tofilon PJ, Fine HA, Camphausen K (2015) A phase 2 study of concurrent radiation therapy, temozolomide, and the histone deacetylase inhibitor valproic acid for patients with glioblastoma. J Natl Cancer Inst 107:61–67
23. Knudsen-Baas KM, Engeland A, Gilhus NE, Storstein AM, Owe E, Hovig E, Ulvestad R (2015) Does the choice of antiepileptic drug affect survival in patients with brain tumors: new insights and evidence-based management. Seizure 23:830–835
24. Sciuettichiano BM, Sorrentino S, Proietti G, Lama G, Dobrowolsn G, Catizone A, Binda E, Larocca LM, Sica G (2018) Levetiracetam enhances the temozolomide effect on glioblastoma stem cell proliferation and apoptosis. Cancer Cell Int 18:1–18
25. Van Nijkerk KA, Van den Berg J, Slotman BJ, Lalefleur MV, SmiNia P, Stalpers LJ (2012) Valproic acid sensitizes human glioma cells for temozolomide and γ-radiation. J Neurooncol 107:61–67
26. Knudsen-Baas KM, Engeland A, Gilhus NE, Storstein AM, Owe E, Hovig E, Ulvestad R (2015) Does the choice of antiepileptic drug affect survival in patients with brain tumors: new insights and evidence-based management. Seizure 23:830–835
27. Vecht CJ, Kerkhof M, Duran-Pena A (2014) Seizure prognosis in brain tumors: new insights and evidence-based management. Oncologist 19:751
28. Kim YH, Kim T, Joo JD, Han JH, Kim YJ, Kim LA, Yun CH, Kim CY (2015) Survival benefit of levetiracetam in patients treated with concomitant chemoradiotherapy and adjuvant chemotherapy with temozolomide for glioblastoma multiforme. Cancer 121:2926–2932
29. Tanaka H, Sasayama T, Nishihara M, Morikawa M, Ikeda M, Tanaka K, Kohmura E (2017) NCMP-10 Survival Benefit of Antiepileptic Drugs in Patients with Glioblastoma. Neuro-Oncol 19:v1136

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
30. Chandra V, Rock AK, Opalak C, Stary JM, Sima AP, Carr M, Vega RA, Broadus WC (2017) A systematic review of perioperative seizure prophylaxis during brain tumor resection: the case for a multicenter randomized clinical trial. Neurosurg Focus 43:E18. https://doi.org/10.3171/2017.8.Focus17442

31. Lockney D, Vaziri S, Walch F, Kubilis P, Neal D, Murad G, Rahman M (2016) Prophylactic antiepileptic drug use in brain tumor patients undergoing craniotomy. World Neurosurg. https://doi.org/10.1016/j.wneu.2016.10.079

32. Lockney DT, Vaziri S, Walch F, Kubilis P, Neal D, Murad GJ, Rahman M (2017) Prophylactic antiepileptic drug use in patients with brain tumors undergoing craniotomy. World Neurosurg 98:28–33. https://doi.org/10.1016/j.wneu.2016.10.079

33. Berendsen S, Varkila M, Kroonen J, Seute T, Snijders TJ, Kauw F, Spliet WG, Willems M, Poulet C, Broekman ML (2016) Prognostic relevance of epilepsy at presentation in glioblastoma patients. Neuro Oncol 18:700–706

34. Toledo M, Sarria-Estrada S, Quintana M, Maldonado X, Martinez-Ricarte F, Rodon J, Auger C, Salas-Puig J, Santamarina E, Martinez-Saez E (2015) Prognostic implications of epilepsy in glioblastomas. Clin Neurol Neurosurg 139:166–171

35. Fan X, Li Y, Shan X, You G, Wu Z, Li Z, Qiao H, Jiang T (2018) Seizures at presentation are correlated with better survival outcomes in adult diffuse glioma: a systematic review and meta-analysis. Seizure 59:16–23

36. Toledo M, Sarria-Estrada S, Quintana M, Maldonado X, Martinez-Ricarte F, Rodon J, Auger C, Aizpurua M, Salas-Puig J, Santamarina E (2017) Epileptic features and survival in glioblastomas presenting with seizures. Epilepsy Res 130:1–6

37. Rosati A, Poliani PL, Todeschini A, Cominelli M, Medicina D, Cenzato M, Simoncini EL, Magrini SM, Buglione M, Grisanti S (2013) Glutamine synthetase expression as a valuable marker of epilepsy and longer survival in newly diagnosed glioblastoma multiforme. Neuro Oncol 15:618–625

38. Ozbek N, Cakir S, Gursel B, Meydan D (2004) Prognostic significance of seizure in patients with glioblastoma multiforme. Neurol India 52:76–78

39. Flanigan PM, Jahangiri A, Kuang R, Truong A, Choi S, Chou A, Rick JW, Chang SM, Molinaro AM, McDermott MW, Berger MS, Agli MK (2017) Improved survival with decreased wait time to surgery in glioblastoma patients presenting with seizure. Neurosurgery 81:824–833. https://doi.org/10.1093/neuros/nyx084

40. Huberfeld G, Vecht CJ (2016) Seizures and gliomas—towards a single therapeutic approach. Nat Rev Neurol 12:204–216. https://doi.org/10.1038/nrneurol.2016.26

41. Armstrong TS, Grant R, Gilbert MR, Lee JW, Norden AD (2016) Epilepsy in glioma patients: mechanisms, management, and impact of anticonvulsant therapy. Neuro Oncol 18:779–789

42. Fonkem E, Bricker P, Mungall D, Aceves J, Ebwe E, Tang W, Kirmani B (2013) The role of levetiracetam in treatment of seizures in brain tumor patients. Front Neurol 4:153. https://doi.org/10.3389/fneur.2013.00153

43. van Breemen MS, Vecht CJ (2005) Optimal seizure management in brain tumor patients. Curr Neurol Neurosci Rep 5:207–213

44. Maschio M (2012) Brain tumor-related epilepsy. Curr Neuropharmacol 10:124–133. https://doi.org/10.2174/157015912800604470

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.