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Review Article

Seizures in Patients with Brain Metastases: A Literature Review

Reverberi C[1], Rees J[2], Welsh L[3], Brewer M[3], Creak A[3], Solda F[3] and Rosenfelder N[3]*

[1]*Radiation Oncologist, Radiotherapy Department, Azienda Sanitaria Friuli Centrale (ASUFC), Italy*

[2]*Department of Neurology, National Hospital for Neurology and Neurosurgery, UK*

[3]*Department of Neuro-Oncology, The Royal Marsden Hospital, London*

***Corresponding author:** Niocla Rosenfelder, Department of Neuro-Oncology, The Royal Marsden Hospital, London

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Introduction

The number of patients living with brain metastases (BMs) has increased significantly over the last 5-10 years. This is due to a combination of improved survival resulting from better systemic treatment options for many of the primary cancers most commonly associated with BM, and better treatment of intracranial disease. In addition, the increased availability of magnetic resonance imaging (MRI) and better quality of imaging has resulted in more asymptomatic patients being diagnosed with small volume intracranial disease.

Many patients with BM have a limited prognosis of <6 months and are treated with best supportive care with or without whole brain radiotherapy. However, an increasing number of fit patients with controlled, controllable or absent systemic disease are being referred for surgical resection and/or stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) for BM. The median survival for these patients is 12-15 months, but with improved control of extracranial disease in many subtypes of cancer, the population of patients with BMs is recognised as a heterogeneous group with some patient subgroups living for years with BM, and consideration of the longer-term side effects of treatments is increasingly important.

Seizures are one of the most common presenting symptoms of BM [1-5] and may be the presenting symptom of intracranial disease or even of the underlying cancer. A further cohort of patients develops de novo seizures following treatment [6]. However, much of the seizure incidence data comes from patients treated prior to the availability of newer systemic treatments such as immunotherapy and targeted therapies.

The development of seizures, or even just the awareness of being at increased risk of seizures, can have a devastating effect on patients, causing considerable fear, anxiety, and loss of confidence leading to the inability to carry out normal day-to-day activities. In the United Kingdom, all patients with BMs are told at the time of diagnosis that they need to stop driving immediately and inform the Driver & Vehicle Licensing Agency (DVLA) of their situation. The ban on driving is usually upheld for at least 1-2 years and this driving ban is the single most difficult issue for patients with BM in clinic. The majority of patients do not have seizures at presentation nor following treatment and, with the increasing inclusion of cranial imaging in staging asymptomatic patients, the proportion of patients with BM who experience seizures is likely to be significantly smaller than previous estimates.

In this paper, we review published literature on seizure incidence in patients with BMs and discuss the possible pathogenesis of seizures in this cohort in comparison with primary brain tumour-associated seizures. We also present the literature discussing risk factors for development of seizures before and after treatment.

Incidence of Seizure - Variations in Estimates

It is estimated that 10-30% of patients with extra-cranial malignancy develop BM. This number is likely to increase with improved extracranial disease control from better systemic treatments, giving additional time for BM to develop, either at the time of extracranial progression or as a sanctuary site of uncontrolled disease. At the time of diagnosis of BM, many patients have multiple intracranial lesions [7-10].

Although only 5% of patients with extra-cranial malignancy develop seizures, estimates in the population with BM range from 10-40% [2,5,6,8,11,12] similar to the incidence reported in patients with primary brain tumours [13]. Higher rates of up to 67% have been reported in patients with BM from melanoma [4].

Pathophysiology of Seizure Development with Different Tumours

The pathophysiology of seizure development ('epileptogenesis') in patients with primary or metastatic brain tumours is not fully understood but is likely to be multifactorial. Different pathogenic processes may play a role in seizure development for BM from different primary tumour types, and for those developing seizures at diagnosis versus post-treatment. These differences may explain the variation in seizure frequency between primary tumour types [14-16].

Tumours such as intrinsic glioneuronal tumours (e.g. gangliogliomas and dysembryoplastic neuroepithelial tumours, DNTs) exhibit intrinsic epileptogenesis which is believed to arise from overexpression of neurotransmitters and neuropeptides causing a hyper-excitable neuronal component and disruption of the normal balance between inhibitory and excitatory stimuli [17]. The disorganisation of the adjacent cortex may also contribute to seizure generation.

For slower-growing low-grade primary brain tumours, which cause seizures in approximately 60-88% of patients [18,19], seizure activity may be caused by hypersensitivity of surrounding brain tissue [20-22]. Disruption to the balance of the normal neural networks is thought to contribute to the epileptogenesis with the formation of 'random networks' with lower seizure thresholds [15,23]. Epileptogenic foci may also be found distal to the primary tumour and 'secondary epileptogenesis' may arise from alterations in peritumoral tissue [20].

In de novo high grade primary brain tumours such as glioblastoma multiforme, the risk of seizures is lower than for low-grade tumours at 30-50% [24,25]. The mechanism of seizure development is thought to be through the abrupt tissue damage with necrosis, oedema, bleeding and haemosiderin deposition. In the peri-tumour microenvironment, reduction of glutamate synthetase may lead to impaired metabolism of the excitatory neurotransmitter glutamate to glutamine, resulting in enhanced excitation of surrounding neural networks [26]. The additional burden from tumour growth and aberrant angiogenesis could lead to hypoxia, acidosis, free radical generation and downstream damage to alterations in gene expression, unstable cell turnover and seizures. In extrinsic tumours such as meningiomas, the mechanism of epilepsy development is thought to be due to peritumoral oedema [27].

In BM, the pathogenesis is most likely to be similar to that of high-grade gliomas with the hyper-excitability state arising from the effects of the tumour on the adjacent neural tissue, although the precise mechanism is poorly understood and a number of factors may contribute to the risk. Extrapolating possible mechanisms from the evidence from primary brain tumours, there may be altered expression of neurotransmitters and receptors in peritumoral tissue and high levels of the excitatory neurotransmitter glutamate has been found in the brain tumours of patients with epilepsy. Activation of glutamate receptors may down-regulate γ-aminobutyric acid (GABA)-mediated inhibitory stimuli which may contribute to tumour-related seizures. The difference in seizure incidence between BM subtypes and sites is not understood and causative factors remain unknown.

Following SRS for BM, both the development of radionecrosis and tumour progression are considered to be risk factors for post-treatment de novo seizures. The role of tissue necrosis, oedema and other such tissue responses may increase the likelihood of seizures, although the role of parenchyma versus the vasculature versus inflammatory cell infiltrates in the pathophysiology is not clear. Treatments including resection or steroids play a key role in seizure control by stopping tumour growth or by shrinking metastatic volume or oedema, respectively. Local spread and uncontrolled disease are recognized risk factors for the development of neurological symptoms.

Prognostic Factors for Epilepsy Pre-treatment

A number of clinical factors have been suggested to be important for seizure development in BM, although data are mainly from retrospective studies, some of which include a diverse population of patients with primary and metastatic intracranial tumours. Findings have not been entirely consistent across studies, which may be related to confounding factors from the retrospective analyses.

The largest retrospective study to date identified 15,863 seizure-naïve patients with BM from SEER-Medicare data (2008-2016) and 1453 patients from a single institution (2000-2015) and examined risk factors in both cohorts. In the SEER-Medicare cohort, Black race, urban residence, melanoma and stereotactic brain radiation were associated with greater seizure risk. In the institutional cohort, melanoma, more than 4 BM, BM in a high-risk location and lack of brain-directed therapy were important risk factors and the authors suggest prophylactic anti-epileptic drugs (AEDs) be considered in patients with melanoma metastases, a large intracranial disease burden or metastases in high-risk locations [11].

A retrospective study investigating tumour-related epilepsy in 799 patients with BM found that unprovoked seizures occurred

in 28% of patients (226/799); for most, seizure was the first sign of intracranial disease1. In the sub-group of un-operated patients (n=242), solitary BM and haemorrhage were both significant prognostic factors. Neither primary tumour histology nor supratentorial location was associated with seizure risk. However, in the patients who underwent surgery (n=557), pre-operative seizure risk was associated with lung cancer primary (p=0.022, HR 2.0, 95% CI 1.1-3.6), and supratentorial location (p=0.003, HR 20.78, 95% CI 2.8-153.4). Differences between the un-operated group and the pre-operative group would be unexpected as both groups have untreated BM, and thus are likely to be due to factors which also influence selection of patients for surgery; for example, patients with solitary tumours in highly eloquent areas would not be offered surgery but may be more likely to develop seizures. Post-operatively, seizures were associated with supratentorial location and incomplete resection [1].

In a separate retrospective study of 565 patients undergoing surgical resection, 20% presented with seizures at diagnosis. In this population, headache, cognitive decline, the number of BM (≥ 2), tumour location (temporal lobe and occipital lobe), and bone involvement were associated with increased seizure risk at presentation [2].

Results from other reviews show a variation in seizure incidence with primary tumour histology with the highest incidence in those with melanoma, followed by lung cancer and gastrointestinal cancer and breast cancer, although results vary between series' [4,8] and this may reflect changes in imaging and treatments available over the years. As well as being at higher risk of developing multiple BMs, itself a possible risk factor for seizure development, patients with melanoma and lung cancer are considered at higher risk of seizure due to the increased risk of haemorrhage, independently thought to be associated with seizure. However, much of the data is from patients treated prior to the availability of immunotherapy and the relevance of the data to today's patients is questionable.

As mentioned above, tumour location may also affect seizure-risk but this too has not been demonstrated consistently between studies, with some suggesting the frontal lobe as having the highest risk, whilst others report the temporal lobe, insula and/or occipital lobe as being important for seizure-development [1,2,28].

The number of BM may also be important with increased seizure incidence reported in patients with multiple BM in some retrospective reviews [2,29], although here too results are inconsistent with some studies reporting increased incidence with a solitary metastasis1. In patients with 1-3 BMs, the prevalence of epilepsy prior to SRS or FRSRT was 33/195 (16.9%) with a significantly higher risk in patients ≤61years old, with trends (although not significant) in those with primary NSCLC and controlled extracranial disease [30]. Interestingly, symptoms and seizures prior to radiotherapy do not appear to be related to survival.

Other factors, not directly related to the presence of BMs may influence seizure activity, including systemic treatment, metabolic disturbance, opportunistic infection and paraneoplastic encephalitis. The number of cases of status epilepticus was found to have increased significantly in one single-centre retrospective study since the introduction of immune checkpoint inhibitors (ICIs) in 2014. However, the number of cases was small and further larger prospective studies are required [31].

Seizure Activity Post-Radiosurgery

It has been suggested that radiotherapy, whether whole brain, partial brain or SRS, may provoke seizure activity by increasing brain oedema (acute adverse event) or as a manifestation of radiation necrosis (late toxicity). A few limited retrospective studies have investigated the relationship between BM, its treatment, and the development of seizures but much of the literature also includes patients with primary brain tumours, and in particular low grade glioma [13-15,28].

There are limited data for seizure activity post SRS. In a review on outcomes post-SRS in 316 lesions treated in 273 patients, new neurological complications were seen in 101/316 (32%) lesions treated, but of these only 41/316 (13%) were new seizures. On multivariate analysis, tumour location in the eloquent cortex (HR=2.5, 95% CI 1.6-3.8, p<0.001) and progressing primary cancer (HR=1.6, 95% CI 1.1-2.5, p=0.03) were significantly associated with new neurological complications. The median onset complication was at 20 months after SRS [32].

In a separate retrospective study, 32/258 (12.4%) patients with lung cancer BMs, treated with gamma knife radiosurgery developed de novo seizure activity after treatment [33].

The reported incidence of radionecrosis in a cohort of 206 patients with single or multiple BMs treated with SRS was 24% (75/310 treated lesions), with symptomatic radio-necrosis reported in 10%. Reported symptoms were: seizure (5.2%, 16 patients), motor deficits (2.9%), cognitive deficits (1.0%), sensory deficits (1.3%) and speech deficits (1.3%). Three patients developed epilepsy without radionecrosis. The authors suggest hypofractionated stereotactic radiotherapy may be a better option for patients if the normal brain volume receiving 12Gy (V12Gy) was greater than 8.5cc, as the risk of radio-necrosis was nearly 10% [34].

Seizure Activity Post-Craniotomy

The incidence of seizure post-craniotomy is thought to be 15-20% with most events occurring within the first month after surgery. Although prophylactic AEDs may be used temporarily

in the immediate peri-operative period, there is no evidence to support their use in reducing the risk of seizures at other times.

In the series by Wolpert discussed above, the incidence of seizures post-operatively was 15.4% [1]. Factors associated with post-operative seizures were supratentorial disease (p=0.012), occipital location (p=0.027), venous thrombosis (p=0.03) and single versus more than one brain surgery in the disease course (p=0.00001). Gross total resection was favourable but brain irradiation increased seizure risk (p=0.013), as did chemotherapy (p=0.002). Interestingly there was no association between pre-operative and post-operative seizures (p=0.077). In contrast to pre-operative findings, tumour histology was not associated with post-operative seizures (p=0.479). On mulitvariate analysis, supratentorial disease and subtotal resection were independently associated with post-operative seizures, although the risk was not statistically significant for multiple surgeries (p=0.095).

In the series by Wu described above, post-operative seizures occurred in 5.3%, but here the risk of seizures was increased by pre-operative seizures, temporal lobe location, absence of systemic therapy after surgery, subtotal resection and local relapse [2]. New onset seizure occurred in only 1.8% of patients after surgery. Although Wolpert et al found that chemotherapy increased the risk of post-operative seizures, Wu et al. [2] found the risk increased in those who did not receive post-operative systemic therapy, although again this may be because of a different factor such as uncontrolled disease.

Seizure Treatment and Prevention

Monotherapy with AEDs is recommended for those patients with brain tumours who have had at least one seizure event. The preferred first line AED is Levetiracetam given its tolerability, effectiveness and lack of drug interactions [35]. A prospective observational trial evaluated the safety and efficacy of levetiracetam, oxcarbazepine and topiramate as monotherapy in 48 patients with brain metastases and found that 63% of patients remained seizure free after a mean follow up of 6 months [36].

Approximately 50% of people with tumour-related epilepsy may respond to monotherapy with AEDs [37]. Retrospective analysis of the risk of seizures in patients with melanoma BMs from a single centre showed that seizure led to the diagnosis of BM in 13% (14/109) and a further 20% (22/109) developed seizures later. In those without a seizure at diagnosis prophylactic AEDs significantly decreased the risk of seizure with 3-month seizure rate of 0% compared to 17% without prophylactic AEDs. Univariate analysis demonstrated that haemorrhage and multiple supratentorial metastases were associated with increased seizure risk and the authors suggest that prophylaxis may be beneficial in selected patients, and this should be addressed in a randomized controlled trial [38].

Guidelines recently published by the Congress of Neurological Surgeons and endorsed by the American Society of Clinical oncology (ASCO) and Society for Neuro-Oncology (SNO) recommend that prophylactic AEDs are not used routinely in patients with BMs who did not undergo surgical resection and are seizure free, nor for those post-craniotomy who remain seizure-free except for a short period of use perioperatively for seizure control [39-43]. However, as discussed by Goldlust et al. [38] the data available when designing these guidelines included heterogenous patient populations and among the 4 randomised controlled trials, only one considered BM as a distinct cohort from primary brain tumours, and the systemic management will be outdated [38,44-47].

Conclusion

At the time of diagnosis of BM, all patients in the UK are informed that they are no longer allowed to drive because of an increased risk of developing a seizure. In many other countries the treating doctor decides whether an individual with BM who is currently seizure-free should continue to drive or not, but there are few data to support specific patient-tailored and evidence-based recommendations.

Improved systemic and targeted intracranial treatments have significantly prolonged survival in cohorts of patients with BM. Retrospective reviews suggest a number of factors may influence seizure risk including tumour location, number of metastases, primary melanoma histology, presence of haemorrhage, and systemic disease control. Prospective evaluation of a cohort of BM patients will allow identification of factors that increase the seizure risk.

To date there is no evidence to support the use of prophylactic anti-epileptic drugs in patients with BM. However, here too the current data available are based on limited data; and there may be subgroups of patients with BM who would benefit from AEDs. If those at high seizure risk can be identified, further trials can specifically assess the benefit of AEDs in this population, and thereby potentially reduce the seizure rate in those most at risk. Furthermore, whilst it is imperative that public and individual patient safety is paramount, the current driving guidelines in the UK may be stricter than required for safe practice. The threshold seizure risk that is usually set for patients with Group 1 licences i.e. non-professional drivers is 20% per annum and therefore any study that can demonstrate a lower risk than this will potentially advise the next guidelines so that a larger number of patients with BM can continue driving, with a significant improvement in their quality of life.

References

1. Wolpert F, Lareida A, Terziev R, Grossenbacher B, Neidert MC, et al. (2020) Risk factors for the development of epilepsy in patients with brain metastases. Neuro Oncol 22(5): 718-728.

2. Wu A, Weingart JD, Gallia GL, Lim M, Brem H, et al. (2017) Risk Factors for Preoperative Seizures and Loss of Seizure Control in Patients Undergoing Surgery for Metastatic Brain Tumors. World Neurosurg 104: 120-128.
3. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, et al. (2019) Brain metastases. Nat Rev Dis Primers 5(1): 5.
4. Oberndorfer S, Schmal T, Lahrmann H, Urbanits S, Lindner K, et al. (2002) [The frequency of seizures in patients with primary brain tumors or cerebral metastases. An evaluation from the Ludwig Boltzmann Institute of Neuro-Oncology and the Department of Neurology, Kaiser Franz Josef Hospital, Vienna]. Wien Klin Wochenschr 114(21-22): 911-916.
5. Skardelly M, Brendle E, Noell S, Behling F, Wuttke TV, et al. (2015) Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: A retrospective observational single center study. Ann Neurol 78(6): 917-928.
6. Rudà R, Mo F, Pellerino A (2020) Epilepsy in brain metastasis: an emerging entity. Curr Treat Options Neurol 22(2): 6.
7. Louis DN, Perry A, Reifenberger G, Deimling AV, Figarella-Branger D, et al. (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131(6): 803-820.
8. Chan V, Sahgal A, Egeto P, Schweizer T, Das S (2017) Incidence of seizure in adult patients with intracranial metastatic disease. J Neurooncol 131(3): 619-624.
9. Tsao MN (2015) Brain metastases: advances over the decades. Ann Palliat Med 4(4): 225-32.
10. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, et al. (2012) International practice survey on the management of brain metastases: Third International Consensus Workshop on Palliative Radiotherapy and Symptom Control. Clin Oncol (R Coll Radiol) 24(6): e81-e92.
11. Lamba N, Catalano PJ, Cagney DN, Haas-Kogan DA, Bubrick EJ, et al. (2021) Seizures Among Patients with Brain Metastases: A Population- and Institutional-level Analysis. Neurology 6(8): e1237-e1250.
12. Rostami R, Mittal S, Rostami P, Tavassoli F, Jabbari B (2016) Brain metastasis in breast cancer: a comprehensive literature review. J Neurooncol 127(3): 407-414.
13. Avila EK, Graber J (2010) Seizures and epilepsy in cancer patients. Curr Neurol Neurosci Rep 10(1): 60-67.
14. Rossetti AO, Stupp R (2010) Epilepsy in brain tumor patients. Curr Opin Neurol 23(6): 603-609.
15. Rudà R, Trevisan E, Soffietti R (2010) Epilepsy and brain tumors. Curr Opin Oncol 22(6): 611-620.
16. Lee JW, Wen PY, Hurwitz S, Black P, Kesari S, et al. (2010) Morphological characteristics of brain tumors causing seizures. Arch Neurol 67(3): 336-342.
17. Ferrier CH, Aronica E, Leijten FS, Spliet WGM, Huffelen ACV, et al. Electrocorticographic discharge patterns in glioneuronal tumors and focal cortical dysplasia. Epilepsia 47(9): 1477-1486.
18. Brogna C, Gil Robles S, Duffau H (2008) Brain tumors and epilepsy. Expert Rev Neurother 8(6): 941-955.
19. Danfors T, Ribom D, Berntsson SG, Smits A (2009) Epileptic seizures and survival in early disease of grade 2 gliomas. Eur J Neurol 16(7): 823-831.
20. Van Breemen MS, Wilms EB, Vecht CJ (2007) Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 6(5): 421-430.
21. Bartolomei F, Bosma I, Klein M, Johannes C Baayen, et al. (2006) Disturbed functional connectivity in brain tumour patients: evaluation by graph analysis of synchronization matrices. Clin Neurophysiol 117(9): 2039-2049.
22. Bartolomei F, Bosma I, Klein M, Baayen JC, Reijneveld JC, et al. (2006) How do brain tumors alter functional connectivity? A magnetoencephalography study. Ann Neurol 59(1): 128-138.
23. Ponten SC, Bartolomei F, Stam CJ (2007) Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. Clin Neurophysiol 118(4): 918-927.
24. Moots PL, Maciunas RJ, Eisert DR, Parker RA, Laporte K, et al. (1995) The course of seizure disorders in patients with malignant gliomas. Arch Neurol 52(7): 717-724.
25. Riva M, Salmaggi A, Marchioni E, Silvani A, Tomei G, et al. (2006) Tumour-associated epilepsy: clinical impact and the role of referring centres in a cohort of glioblastoma patients. A multicentre study from the Lombardia Neurooncology Group. Neurol Sci 27(5): 345-351.
26. Rosati A, Marconi S, Pollo B, Tomassini A, Lovato L, et al. (2009) Epilepsy in glioblastoma multiforme: correlation with glutamine synthetase levels. J Neurooncol 93(3): 319-324.
27. Lieu AS, Howng SL (2000) Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. Epilepsy Res 38(1): 45-52.
28. Englot DJ, Chang EF, Vecht CJ (2016) Epilepsy and brain tumors. Handb Clin Neurol 134: 267-285.
29. Rades D, Witteler J, Dziggel L, Kjaer TW, Tvilsted S, et al. (2020) Seizures Prior to Whole-brain Irradiation for Metastatic Disease: Prevalence, Risk Factors and Association With Survival. Anticancer Res 40(6): 3429-3434.
30. Rades D, Witteler J, Kjaer TW, Tvilsted S, Schild SE (2020) Occurrence of Seizures Prior to Single-fraction Radiosurgery or Multi-fraction Stereotactic Radiotherapy in Patients With Very Few Brain Metastases. Anticancer Res 40(6): 3499-3504.
31. Urban H, Willems LM, Ronellenfitsch MW, Rosenow F, Steinbach JP, et al. (2020) Increased occurrence of status epilepticus in patients with brain metastases and checkpoint inhibition. Oncoimmunology 9(1): 1851517.
32. Williams BJ, Suki D, Fox BD, Pelloski CE, Maldaun MVC, et al. (2009) Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications. J Neurosurg 111(3): 439-448.
33. Lee MH, Kong DS, Seol HJ, Nam DH, Lee JI (2013) Risk of seizure and its clinical implication in the patients with cerebral metastasis from lung cancer. Acta Neurochir (Wien) 155(10): 1833-1837.
34. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, et al. (2011) Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiat Oncol 6: 48.
35. Nasr ZG, Paravattil B, Wilby KJ (2016) Levetiracetam for seizure prevention in brain tumor patients: a systematic review. J Neurooncol 129(1): 1-13.
36. Maschio M, Dinapoli L, Gomellini S, V Ferraresi, F Sperati, et al. (2010) Antiepileptics in brain metastases: safety, efficacy and impact on life expectancy. J Neurooncol 98(1): 109-116.
37. Van Breemen MS, Wilms EB, Vecht CJ (2012) Seizure control in brain tumors. Handb Clin Neurol 104: 381-389.
38. Goldlust SA, Hsu M, Lassman AB, Panageas KS, Avila EK (2012) Seizure prophylaxis and melanoma brain metastases. J Neurooncol 108(1): 109-114.
39. Sirven JI, Wingerchuk DM, Drazkowski JF, Lyons MK, Zimmerman RS (2004) Seizure prophylaxis in patients with brain tumors: a meta-analysis. Mayo Clin Proc 79(12): 1489-1494.
40. Chang SM, Messersmith H, Ahluwalia M, Andrews D, Brastianos PK, et al. (2019) Anticonvulsant Prophylaxis and Steroid Use in Adults With Metastatic Brain Tumors: ASCO and SNO Endorsement of the Congress of Neurological Surgeons Guidelines. J Clin Oncol 37(13): 1130-1135.

41. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR (2008) Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev 2: CD004424.

42. Mikkelsen T, Paleologos NA, Robinson PD, Ammirati M, Andrews DW, et al. (2010) The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96(1): 97-102.

43. Olson JJ, Kalkanis SN, Ryken TC (2019) Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With Metastatic Brain Tumors: Executive Summary. Neurosurgery 84(3): 550-552.

44. North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB (1983) Phenytoin and postoperative epilepsy. A double-blind study. J Neurosurg 58(5): 672-677.

45. Franceschetti S, Binelli S, Casazza M, Lodrini S, Panzica F, et al. (1990) Influence of surgery and antiepileptic drugs on seizures symptomatic of cerebral tumours. Acta Neurochir (Wien) 103(1-2): 47-51.

46. Forsyth PA, Weaver S, Fulton D, Brasher PMA, Sutherland G, et al. (2003) Prophylactic anticonvulsants in patients with brain tumour. Can J Neurol Sci 30(2): 106-112.

47. Glantz MJ, Cole BF, Friedberg MH, Lathi E, Choy H, et al. (1996) A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. Neurology 46(4): 985-991.