LOMBOK HEALTH and SCIENCE JOURNAL
No. ISSN 2964-5239
https://journal.unram.ac.id/index.php/lhsj/index

Vol.2 (2024) : LHSJ February 2024 (42-52)

Factors Predicting Seizure Outcome After Surgical Excision Of Meningioma : A Systematic Review

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Abstract

Background Seizures in meningiomas occur in approximately 30% of patients. Meningiomas that press on the cortical area, as well as larger meningiomas have a greater tendency to cause focal or generalized seizures. The risk of seizures is increased in tumors that grow along the surface of the brain compared to the base of the calvaria because these tumors are more often located in areas where they can compress cortical tissue that is susceptible to epileptogenesis. The study also aimed to discuss the predictors of seizure/epilepsy in post-operative patients.

Methods We searched PubMed gateway database and searched the studies published between the years 2020 and 2023. The following keywords were used to search for the specific article, single and/or in combination: meningioma, seizure, epilepsy, primary brain tumor, craniotomy, predictor, and surgery. the inclusion criteria for the studies were published in English and with “human” specified as the study category. We excluded review articles, expert opinions, and other language articles.

Results We included 10 studies we found that most seizures in meningioma post-operative patients are male gender, size > 8 cm, cortical location, peritumoral edema, and history of previous seizures. The occurrence of early in-hospital seizures was associated with motor cortex involvement, postoperative Karnofsky performance score <70, postoperative complications, and preoperative seizures

Conclusion This systematic review shows are several predictors that can used to predict the seizure/epilepsy outcome in patients who underwent surgery for meningioma

Keywords: meningioma, post-operative, seizure, epilepsy, predictors

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Introduction

Meningiomas are the most common central nervous system tumors, accounting for 36% of all brain tumors overall with an incidence of 4.2 and 8.6 per 100,000 people. Although many meningiomas are asymptomatic and discovered incidentally, overall 10%-50% of meningioma patients experience seizures, thus representing the majority of brain tumor-related epilepsy. Meningioma-associated epilepsy is a cause of significant morbidity, including cognitive deficits, depression, and impaired ability to drive and perform other tasks of daily living, which generally reduces quality of life. Patients with meningioma who experience seizures have a significantly worse progression-free survival rate compared with those who do not experience seizures, suggesting that meningioma-associated epilepsy signals the presence of a more aggressive tumor.[1,2]

Seizures in meningiomas occur in approximately 30% of patients. Meningiomas that press on the cortical area, as well as larger meningiomas, have a greater tendency to cause focal or generalized seizures. In addition, the risk of seizures is increased in tumors that grow along the surface of the brain compared to the base of the calvaria because these tumors are more often located in areas where they can compress cortical tissue that is susceptible to epileptogenesis. Risk factors for seizures in meningioma preoperatively, perioperatively, and postoperatively are male gender, tumor size > 8cm, cortical location, peritumoral edema, and previous seizures.[3] Symptomatic meningiomas can usually be resolved and treated with surgical resection. Tumor excision results in seizure freedom in 53-90% of meningioma patients with seizures before surgery, so seizure freedom is the primary goal of surgery. However, the incidence of post-operative seizures still ranges between 26%-60% in the literature, which includes patients who are not seizure-free, as well as those who are seizure naïve and then experience post-operative seizures.[1,2] In this article, we would like to discuss about the predictors of seizure/epilepsy in post-operative patients.[2,3]

Methods

This systematic review was performed a literature search using the PubMed gateway database and searched the studies published between the years 2020 and 2023. The following keywords were used to search for the specific article, single and/or in

combination: meningioma, seizure, epilepsy, primary brain tumor, craniotomy, predictor, and surgery. the inclusion criteria for the studies were published in English and with "human" specified as the study category. We excluded review articles, expert opinions, and other language articles.

We found 10 studies that meet the inclusion criteria. The results of each study are summarized in Table 1.

Results

Author, year	Type of Study	Result of study
Chen et al., 2017	Retrospective chart review of 1033 subjects who underwent supratentorial meningioma resection between 1991 and 2014.	Fifty-four (5.9%) patients experienced acute postoperative seizures before discharge (mean duration of postoperative hospitalization: 4 days, 5.72±6.63), which was significantly associated with weakness as an initial symptom, location calvarial base, and the occurrence of medical/surgical complications. The presence of preoperative seizures, the occurrence of postoperative seizures in hospital and medical/surgical complications are significant predictors of postoperative seizures after discharge from the hospital.
Englot et al., 2016	Meta-analysis of 39 observational case series (4709 patients undergoing	Among patients with preoperative seizures, there is a strong association between persistent postoperative seizures and

	meningioma surgery) published between January 1980-September 2014	peritumoral edema. Tumor progression after surgery is associated with recurrence of seizures. Postoperative de-novo seizures occur more frequently in patients with a history of previous radiation or gross-total resection.
Gadot, 2021	Retrospective review of 384 patients who underwent meningioma resection from 2008-2020	Postoperative ischemia, higher WHO score, increased MIB-1 index, and disease recurrence independently predicted postsurgical seizures.
Li et al., 2020	Retrospective study of 778 patients who underwent surgery for supratentorial meningioma between 2011 and 2012.	The occurrence of medical/surgical complications is a significant risk factor for postoperative in-hospital seizures. Postoperative seizures after discharge from the hospital were associated with maximum tumor diameter ≥3.5 cm, preoperative seizures, in-hospital postoperative seizures, and tumor recurrence/progression. Tumor recurrence/progression is the only predictor of postoperative seizures.
Lu et al., 2019	Meta-analysis, searching 4 electronic databases from inception to February 2019, yielded 430 reports with 5,581 patients with meningioma	Independent predictors of postoperative seizures identified were preoperative seizure history, non-skull base location, postoperative complications, and meningioma recurrence.
Morsy et al, 2019	Prospective study of 40 patients with group A intracranial meningioma with preoperative seizures	Postoperative complications were significantly associated with de-novo epilepsy and poor seizure control.

	and group B without preoperative epilepsy.	
Seyedi et al, 2018	Retrospective cohort study of 295 patients who underwent supratentoral meningioma resection between 2007-2015	Postoperative seizures increased in left-sided meningiomas, and decreased in convexity/parasagittal/falx meningiomas and there were no postoperative complications.
Wirsching et al., 2016	Retrospective study of 779 patients treated for histologically confirmed intracranial meningiomas in 2000-2013	Predictors of postoperative epilepsy were preoperative epilepsy, major surgical complications including central nervous system infection, hydrocephalus, repeat craniotomy, and symptomatic intracranial hemorrhage, as well as potential postoperative EEG epilepsy, younger age, and tumor progression.
Xue et al, 2018	Retrospective study of 113 adult patients (>18 years) with newly diagnosed meningiomas undergoing surgery between 2006-2008	Larger tumor size (diameter ≥3.5 cm) and preoperative seizures were associated with postoperative seizures.
Zheng et al., 2013	Retrospective study of 97 patients with supratentorial meningiomas plus preoperative seizures	Factors associated with late postoperative seizures include tumor progression and new postoperative neurologic deficits. Reduced intraoperative brain/vascular injury may result in fewer postoperative neurologic deficits and better seizure outcomes

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Discussion

According to The International League Against Epilepsy (ILAE) defines acute postoperative seizures as seizures that occur within seven days after craniotomy. Late postoperative seizures were defined as epileptic clusters occurring after the first week of surgery. Some studies categorize postoperative seizures into early seizures, late seizures, in-hospital seizures, and seizures after discharge from the hospital. Identifying possible predictors of postoperative seizures can help control seizures and minimize complications associated with long-term use of anticonvulsant medications.[14]

Tumor location, size, grade, motor area involvement and Karnofsky performance score have all been studied as predictors of postoperative seizures. The occurrence of early in-hospital seizures was associated with motor cortex involvement, postoperative Karnofsky performance score <70, postoperative complications, and preoperative seizures. It is suggested that reduced thresholds and increased cortical sensitivity during the immediate postoperative period are important factors to consider, and the use of anticonvulsant drugs may be justified in this period. A Karnofsky performance score <80 is an independent predictor of postoperative seizures, with an almost threefold higher risk of preoperative seizures. This explains further the impact of seizures on quality of life.[1,2,14]

Calvarial base lesions were associated with a decreased incidence of seizures before surgery, with an opposite trend and increased incidence in the postoperative period. Chen et al., reported a reduced incidence of seizures in non-skull base lesions. Tumor location is an important risk factor for postoperative seizures. Patients with convexity/parasagittal/parafalcine tumors experience a 3-6-fold increase in postoperative seizures. In contrast to preoperative seizures, Englot et al., found that postoperative seizures generally occurred in calvarial base tumors, possibly due to the difficult location of the tumor and vital neovascular structures, thereby limiting the extent of resection.[5] In addition, calvarial base lesions require more brain retraction, which further increases brain edema. In a radiology study analyzing 3D magnetic resonance imaging (MRI) imaging in meningioma patients to identify seizure-prone spots, the results showed a higher likelihood of seizures when the lesion was

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located in the motor cortex of the frontal lobe.[1,14,15]

WHO grade 2 and 3 CNS meningiomas had an increased risk of postoperative seizures on univariate statistical analysis. Anaplastic or malignant tumors (CNS WHO grade 3) tended to lead to worse seizure outcomes compared with lower grade tumors, but this was not statistically significant. Although in general it can be said that higher grade meningiomas indirectly increase the risk of postoperative seizures through increased peritumoral edema and brain invasion, but this is more related to the preoperative outcome.[5,6,7]

Chen et al., demonstrated that postoperative peritumoral edema >1 cm was associated with seizures, but this significant effect was lost in multivariate analysis when including patients with a history of preoperative seizures. Likewise brain invasion does not appear to directly influence postoperative seizures. These findings suggest that preoperative peritumoral edema and brain invasion may be sufficient to induce epileptogenesis but are not necessary once the epileptogenic area within the cortex is established.[1,2,14,15]

A history of meningioma-related epilepsy before surgery is the most significant predisposing factor for postoperative seizures, with studies showing a nearly 6-fold increased risk in patients experiencing postoperative seizures. For patients with and without preoperative seizures, the 5-year seizure-free status was 60% and 90%, respectively. Patients with uncontrolled preoperative seizures had reduced postoperative seizure-free events and were more than 2 times more likely to experience postoperative seizure recurrence. Vocal seizures and generalized seizures have not been shown to affect the risk of postoperative seizures. Preoperative seizures are a strong predictor of postoperative seizures, especially uncontrolled seizures. There are contradictions in the literature regarding neurological deficits as a presenting symptom. In some studies, it was associated with fewer preoperative seizures, and in others, it was found to be significantly associated with postoperative seizures before discharge.[1,2,14] In univariate analysis, Chen et al. found that neurologic deficits in the form of new-onset weakness, pneumonia, hematoma, and infarction with edema were significantly associated with in-hospital seizures. In their study, weakness was a predictor for in-hospital seizures but not for preoperative or post-discharge seizures.[4]

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Interestingly, Wirsching et al., found that postoperative improvement and recovery from preoperative neurological deficits were associated with a lower risk of postoperative seizures and better control.[11]

Postoperative complications are an independent predictor of postoperative seizures. In the period immediately after surgery, the brain is more sensitive with a decreased seizure threshold. Any irritation of the highly sensitive and possibly still edematous neocortex can aggravate seizures immediately after surgery. A positive correlation has been found between postoperative complications such as hematoma, hydrocephalus, infection, and edema. New, permanent neurologic deficits postoperatively, especially in patients with vascular injuries, significantly increase the risk of postoperative seizures. Wirshing et al., mentioned major surgical complications such as central nervous system infection, hydrocephalus, repeat craniotomy, and symptomatic intracranial hemorrhage as risk factors for postoperative seizures.[11]

For seizures after hospital discharge, Li et al., identified tumor size > 3.5 cm, seizures before surgery, and tumor progression as strong predictors. In the same study, postoperative complications were associated with acute postoperative seizures, but there was no correlation with postoperative seizures at long-term follow-up.[7] In this study, surgical complications were associated with in-hospital seizures and post-discharge seizures in patients who did not experience seizures. Chen et al., did not find tumor recurrence or subtotal resection to be strong predictors of postoperative seizures. Englot et al., found a strong association between cranial nerve deficits and post-discharge seizures in univariate analysis.[5,8,9]

Age and gender were not associated with postoperative seizures. One 2018 literature review by Baumgaurten et al., found that 1 in 6 studies showed an increased risk of seizures in younger adult patient populations. Likewise gender plays an important role in postoperative seizures. Men had twice the risk of experiencing postoperative seizures on univariate analysis in the Baumgaurten review weakened by the failure to support an association between age group or gender and postoperative seizures in most other studies.[1]

The extent of resection plays an important role in achieving spasm resection and is likely related to other factors, including residual tumor volume and tumor location. Gross Total Resection (GTR) has been shown to significantly reduce the rate of

postoperative seizures. However, certain tumor locations preclude gross total resection, resulting in residual tumor volume. The extent of resection, preoperative tumor volume and residual tumor volume are predictors of preoperative seizures. In patients who do not experience seizures, gross total resection is associated with an increased risk of postoperative seizures. In addition, residual tumor size > 3-4 cm in diameter is associated with postoperative seizures.[1,2,10]

The risk of residual tumor in postoperative seizures is directly and indirectly related to postoperative seizures. Residual tumor may directly increase the risk of postoperative seizures through cortical irritation because in general the relatively larger volume of residual tumor may exacerbate its effect on the cortex and may be associated with other surgical risk factors, such as increased manipulation or retraction of the brain, leading to ischemia as well as affects postoperative epileptogenesis.[1,11]

Conclusion

Meningioma characteristics associated with a high risk of preoperative, perioperative and postoperative seizures are male gender, size > 3,5 cm, cortical location, peritumoral edema, and history of previous seizures. Peritumoral edema and tumor location are associated with seizures in meningiomas. Peritumoral edema is the strongest predictor of seizures in the preoperative and postoperative periods. Further analysis need to be done to measure the effect size of each predictor for post-operative seizure.

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