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Original Article

Incidence and Risk Factors for Late Postoperative Seizures in Patients Who Underwent Intracranial Tumor Removal

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Abstract

Objective: **To estimate the incidence of late postoperative seizure (beyond 1 week to 2 years after surgery) in patients undergoing intracranial surgery for brain tumors and to identify risk factors for late postoperative seizure (POSz).**

Method: **A retrospective review of 252 patients who underwent intracranial brain surgery from June 2006 to April 2008 was done. Data were collected including the demographics, clinical onset, neurosurgical procedure, pathology report, postoperative antiepileptic drug (AED), and occurrence of POSz. The incidence of late POSz at one and two years was estimated. Demographic and clinical factors possibly associated with the occurrence of late postoperative seizure were identified using univariable and multivariable logistic regression analysis.**

Results: **The overall incidence of late POSz (at 1 year) was 11% (28/252). The incidence of late POSz in the supratentorial extra-axial group was 16% (12/77), 48% (16/33) in the intra-axial group, and none for other locations. In terms of tumor pathology, the incidence of late POSz was 46% (12/26) in the low grade glioma (LGG) group, 40% (4/10) in the high grade glioma (HGG) group, 8% (11/130) in meningioma group, while other pathology groups had no occurrence of seizures. Factors significantly associated with late POSz on univariable analysis included pathology of tumor, location of tumor, cortical incision and dissection, history of previous seizures, as well as early POSz and radiation therapy (RT). However, on multivariable analysis only early POSz was independently and significantly related to late POSz. The overall incidence of late POSz at 2 years was also 11% (20/191). The incidences of late POSz at two years subclassified according to location and pathology were similar to those at one year. Factors significantly associated with late POSz within two years were also similar to those at one year.**

Conclusion: **Patients with intracranial glioma and meningioma, located in the supratentorial cortical and subcortical areas, having a history of previous seizures, having early POSz, as well as RT and STR, are at high risk for late POSz. Approximately 97% of late POSz occurred within 1 year. Careful follow up and monitoring of AED levels in patients with a high risk for late POSz in first year after surgery should be done.**

Keywords: **brain tumor removal, late postoperative seizure**

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Background

Seizure is a common symptom in patients with brain tumors. Approximately 30% of patients with brain tumors develop epilepsy and in 30 to 50% of these patients, seizure heralds the clinical onset of the tumor[1]. The use of antiepileptic drug (AED) in patients with brain tumors who present with seizure is generally recommended. However, AED prophylaxis in patients with brain tumors who have no history of seizure is controversial. In the year 2000, the American Academy of Neurology stated that prophylactic AED is of no benefit in patients with brain tumors who have no history of seizures, and to withdraw these drugs in the first week after surgery if patients have never had a seizure[2]. AED associated side effect is especially common and occasionally life threatening[2].

Postoperative seizure (POSz) is a common problem in patients with brain tumors who have undergone intracranial surgery. There are two types of POSz: early onset and late onset POSz. Early onset seizures occur within one week after surgery, and late onset seizures occur beyond one week. The incidence of seizures in patients who underwent supratentorial surgery for non-traumatic pathology is estimated to be from 15 to 20%[3,4,5], and between 1 to 5% for infratentorial operations[6,7]. One randomized controlled study reported the incidence of early seizures after surgery for supratentorial brain tumors to be about 12%[5]. A recent study from Prasat Neurological Institute (PNI) reported an incidence of early POSz of 9.7 %[8]. But the incidence of late POSz after brain tumor surgery has never been reported from the Institute.

Many factors have been shown to have an association with the risk of late POSz, such as a previous history of seizures before surgery, pathology of the tumor, and cortical incision or dissection. However, location of the tumor, onset of early postoperative seizures, adjuvant radiation, and complications after surgery have not been reported to be associated with POSz[9,10]. The aims of the present study are to assess the incidence of late POSz in patients undergoing surgery for intracranial brain tumors at PNI, and to identify factors that may be associated with late POSz.

Patients and Methods

We reviewed the medical records of patients who underwent intracranial surgery for brain tumors at PNI from June 2006 to April 2008. Inpatient admission notes, daily progress notes, operative record, pathologic reports and outpatient notes were reviewed and data of interest were abstracted. These included demographic data such as age and gender. We also included the pathology of the tumors, classified as meningioma, glioma, and others (e.g., pituitary adenoma, schawannoma, metastasis, and craniopharyngioma). History of previous surgery (yes/no) was obtained. Location of the tumors was recorded and classified as supratentorial cortical (or extra axial), supratentorial subcortical (or intra axial), posterior fossa (include brainstem and fourth ventricular tumor), sellar and parasellar, intraventricular (lateral and third ventricle), pineal region, and others (including cavernous sinus location).

Other factors were also examined and abstracted, including duration of surgery (classified as less than or more than six hours); performance of cortical incision and dissection (yes/no); postoperative surgical complications such as hematoma at surgical site, ischemia, hydrocephalus, and meningitis (yes/no); extent of tumor removal reported in the operative notes (gross total removal or subtotal or partial tumor removal); history of preoperative clinical seizure (yes/no), early POSz (yes/no), tumor recurrence (yes/no), administration of radiotherapy (yes/no). Patients were excluded if they underwent stereotactic or opened biopsy, and if the follow-up time was less than one year. Postoperative information was gathered from one week to two years, or to the last follow up. We recorded time of onset of late POSz, the type of seizure, and the details of AED used. The use of prophylactic AED, and duration of postoperative AED, depended on the judgment of the risk of seizures made by individual surgeons.

Statistical analysis was done with the SPSS 16.0 for Windows. Tests for differences between patients with late POSz and those without POSz were done using Mann-Whitney U test for continuous variables, and chi-square test or Fisher's exact test for categorical variable. *P*-values < 0.05 were considered statistically significant. Odds ratios and 95% Confidence Intervals (95% CI) were obtained from logistic regression analyses. Factors which were significantly associated with late POSz on univariable analysis were tested in a multivariable model.

Results

Overall 252 consecutive cases of brain tumor surgery were seen at PNI from June 2006 to April 2008. All 252 patients were followed for more than 1 year. There were 90 men and 162 women. The mean age was 44.4 years (ranged from 9 to 83 years). Forty three patients (17%) had a history of previous seizures and 17/43 (39%) of these had late POSz. Twenty six patients (10%) developed early POSz and 10/26 (39%) of these had subsequent late POSz. The overall incidence of POSz (early and late onset seizures) was 44/252 (18%). See Table 1 for further details.

The overall incidence of late POSz within 1 year was 28/252 (11%). The incidence of late POSz in cortical (extra-axial), and subcortical (intra-axial) groups were 16% and 48%, respectively. Patients who had posterior fossa, sellar and parasellar, pineal, intraventricular, or cavernous sinus tumors did not develop late POSz. The incidence of POSz was 46% (12/26) for low-grade gliomas, 40% (4/10) for high-grade gliomas, and 8% (11/130) for meningiomas. There were no late POSz for patients with craniopharyngioma and pituitary tumors (Table 2).

We examined the univariable association between potential factors and late POSz. These included age, sex, tumor pathology, previous surgery, tumor location, cortical incision and dissection, duration of surgery, extent of tumor removal, complications of surgery, history of previous seizures, early POSz, tumor recurrence, and radiotherapy (RT), presented in Table 3. Six factors were significantly associated with the late POSz: pathology of tumor, tumor location, cortical incision and dissection, history of previous seizures, early POSz, and postoperative RT. On multivariable analysis, only early POSz was significantly and independently associated with late POSz.

At 2 years after operation, 61 patients were lost to follow up, thus only 191 patients were available for analysis. There were 62 men and 129 women. There were only 20 patients remaining who had late POSz, giving the incidence of late POSz at two years as 11% (20/191), similar to that at one year, because only one patient had further late POSz after one year. All estimates of the incidence of late POSz at two years were similar to those at one year, when subclassified in terms of location and pathology of tumor. Within statistical errors the result of univariable analysis of risk factors for late POSz at two years was similar to that at one year. Notable differences included the lack of association between RT and late POSz at two years, but a significant association between subtotal resection and POSz was seen at two years. Multivariable analysis was not done for the risk at two years because of the small number of outcomes.

Of the 29 patients who had late POSz, 69% (20/29) occurred within 6 months, 97% (28/29) occurred within one year, while only one patient had seizures occurring at 20 months of follow up (see Figure1). Nine of these patients were lost to follow up at two years, thus only 20 patients with late POSz remained at two years. Of the 29 patients with late POSz, the seizures were de novo in 7 patients, in 11 patients the seizures begun before surgery, in 4 patients the seizures

Table 1 Incidence of late postoperative seizures, classified by tumor location, at 1 year and 2 years.

Location	Incidence at 1year (%)	Incidence at 2 years (%)
Cortical (extra-axial)	12/77 (15.58)	9/58 (15.52)
Subcortical (intra-axial)	16/33 (48.48)	11/22 (50)
Posterior fossa	0/57 (0)	0/50 (0)
Sellar / parasellar lesion	0/59 (0)	0/43 (0)
Pineal location	0/2 (0)	0/2 (0)
Intraventricular lesion	0/10 (0)	0/7 (0)
Others	0/14 (0)	0/9 (0)

Table 2 Incidence of late postoperative seizures, classified by tumor pathology, at 1 year and 2 years.

Type of tumor	Incidence at 1 year (%)	Incidence at 2 years (%)
Meningioma	11/130 (8.5)	8/101 (7.9)
Previous seizure	5/19 (26.3)	2/12 (16.6)
New onset seizure	6/111 (5.4)	6/89 (6.7)
Low grade glioma	12/26 (46.2)	10/19 (52.6)
Previous seizure	10/17 (58)	9/14 (64.3)
New onset seizure	2/9 (22.2)	1/5 (20)
High grade glioma	4/10 (40)	2/5 (40)
Pituitary adenoma	0/21 (0)	0/16 (0)
Schawannoma	0/31 (0)	0/27 (0)
Metastasis	0/1 (0)	(0)
Craniopharyngioma	0/15 (0)	0/9 (0)
Others	0/18 (0)	0/14 (0)

Table 3 Association between potential risk factors and late postoperative seizures within 1 year.

Variable factor	Seizure (n = 28) (%)	Non seizure (n = 224) (%)	*P* value	OR	95%CI
Age (mean)	49.3	43.8	0.099	1.03	0.99 to1.057
Sex female	22/28 (78.6)	140/224 (62.5)	0.094	2.2	0.86 to 5.65
Previous surgery	5/28 (17.9)	15/224 (6.7)	0.055	3.03	1.01 to 9.10
Pathology of tumor			<0.001		
Meningioma	11/28 (39.3)	119/224 (53.1)			
Glioma	16/28 (57.1)	20/224 (8.9)		8.66	3.51 to 21.33
Others	1/28 (3.6)	85/224 (37.9)		0.13	0.16 to 1.01
Location of tumor			<0.001		
Cortical [extra axial]	12/28 (42.9)	65/224 (29.0)			
Subcortical [intra axial]	16/28 (57.1)	17/224 (7.6)		5.1	2.03 to 12.785
Others	0/28 (0)	142/224 (58.7)			
Location in cortex (n = 71)	0.362				
Occipital	1/26 (3.8)	6/45 (13.3)			
Frontal	12/26 (46.2)	25/45 (55.6)		2.88	0.31 to 26.68
Temporal and insular	5/26 (19.2)	5/45 (11.1)		6.00	0.52 to 69.754
Parietal	8/26 (30.8)	9/45 (20.0)		5.33	0.52 to 54.34
Cortical incision and dissection	25/28 (89.3)	49/224 (21.9)	<0.001	29.76	8.62 to 102.72
Duration of surgery [> 6 hr]	10/28 (35.7)	93/224 (41.5)	0.556	1.28	0.56 to 2.89
Extent of tumor removal [STR]	11/28 (39.3)	58/224 (25.9)	0.134	1.85	0.82 to 4.19
Complication	3/28 (10.7)	31/224 (13.8)	0.999	0.75	0.21 to 2.62
Previous seizure	17/28 (60.7)	26/224 (11.6)	<0.001	11.77	4.97 to 27.86
Early postoperative seizure	10/28 (35.7)	16/224 (7.1)	<0.001	7.22	2.83 to 18.22
Recurrence	3/28 (10.7)	21/224 (9.4)	0.737	1.16	0.32 to4.17
RT	10/28 (35.7)	33/224 (14.7)	0.013	3.22	1.37 to 7.57

Table 4 Multivariable analysis of risk factors for late postoperative seizures within 1 year.

Variablefactor	OR	95% CI	*p*-value
Pathology of tumor			0.479
Meningioma	0.60	0.14 to 24.79	
Glioma	3.84	0.23 to 63.10	
Others	-	-	
Location of tumor			0.797
Cortical [extra-axial]	-	-	
Subcortical [intra-axial]	0.32	0.11 to 9.10	
Others	-	-	
Cortical incision and dissection	3.30	0.77 to 14.10	0.108
History of previous seizure	1.67	0.54 to 5.15	0.372
Early postoperative seizure	4.64	1.21 to 17.71	0.025
RT	1.50	0.36 to 6.26	0.578

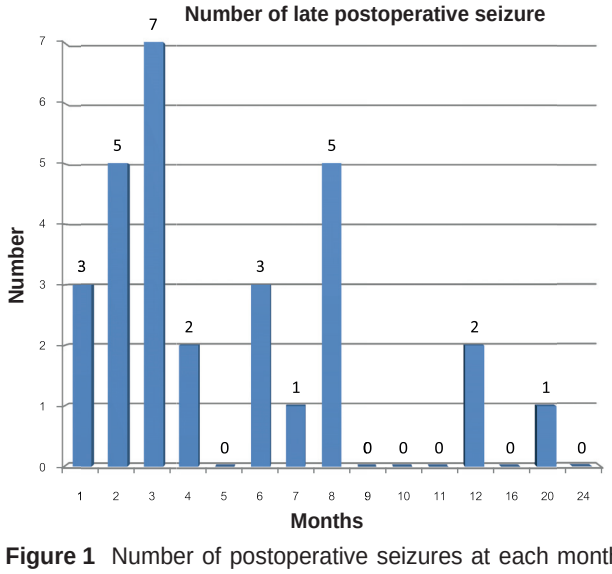

Figure 1 Number of postoperative seizures at each month of follow-up within 2 years after surgery.

were early onset, and in 7 patients these seizures occurred both before surgery and early after surgery. Types of late POSz included simple partial seizures in 6 patients, complex partial seizure in 5 patients, generalized tonic clonic seizures in 15 and unspecified type in 3.

Five patients with late POSz did not receive antiepileptic drugs (AED). Seven patients had AED

but at a subtherapeutic level, eight patients who received AED did not have their AED levels checked, while three patients received AED at the therapeutic level but had tumor recurrence.

Discussion

The present study is probably the first to estimate the incidence of, and to identify risk factors for, late POSz in Thai patients who underwent craniotomy for tumor removal, at one year and two years of follow-up. The overall incidence of late POSz both at one and two years was 11%. The incidence of late POSz in the supratentorial location was 14% in the present study, which was similar to a previous study of POSz after supratentorial surgery of non-trauma pathology (15 to 20%) but the latter included early and late POSz[3,4]. In a subgroup analysis, the incidence of late POSz was 16% in the supratentorial extra-axial, and 49% in supratentorial intra-axial, groups. Other groups had no late POSz. Again, this result was similar to those of previous studies which showed the incidence of early seizures following posterior fossa surgery to be 0.7 to 5.9 %, with no reported incidence of late POSz[6,7]. The present study showed that tumors located only at the supratentorial area were related to late POSz.

Hwang et al. found the incidence of postoperative seizures in patients with astrocytic tumors and a history of previous seizures to be 54%, while those who had no previous seizures had an incidence of 8%[11]. Pace et al. found that 56% of patients had recurrent seizures and 23% had late-onset seizures[12]. These findings are similar to those of the present study. However, the incidences of late POSz in the meningioma group (8%), in patients who have a history of previous seizures (26%), and in patients with new onset seizures (5%) in the present study, were lower than those in a previous study[10]. In that study, patients with meningioma who had a history of previous seizures had postoperative seizures in 37%, and 5% of patient had new onset seizures.

Of the 29 patients who had late POSz, 69% occurred within 6 months, and 97% occurred within 1 year. This tendency for seizures to occur relatively soon after craniotomy was in agreement with previous studies. Hwang et al. reported that patients with gliomas and a history of previous seizures had the occurrence of seizures in 59% within 6 months, with new onset seizures occurring in 64% within 6 months[11]. Pace et al. reported that postoperative seizures occurred within 6 months in 67% of patients with gliomas[12].

The present study showed that in patients with late POSz most within one year and patients had either discontinue AED, had subtherapeutic level of AED, or tumor recurrence. This emphasized the need for close follow-up, and to monitor AED levels in patients undergoing surgery and at high risk for developing postoperative seizures within one year after operation.

The present study showed that late POSz only occurred in patients with gliomas (both high and low grade) and meningiomas. This is in accord with previous studies which demonstrated high incidence of seizures in patients with gliomas and meningiomas, with no seizures in patients with hemangioblastoma, schawannoma and pituitary tumors[1,13]. This finding emphasized the need to prevent postoperative seizures in patients with gliomas and meningiomas.

We found significantly higher rates of late POSz in patients with supratentorial tumors, whereas those with posterior fossa, pineal, intraventricular, sellar and parasellar areas did not have late POSz. This was a similar finding to that of a review by Shamji et al., which showed a high incidence of seizures in tumors near the cortical area, and that tumors at the infratentorial and sellar regions had low incidence of seizures[13].

Corticotomy and dissection significantly increased the risks for developing POSz. Similar results were reported in Foy et al., who presented a high incidence of seizures in patients undergoing corticotomy and cortical dissection[4,14]. This increased incidence probably occurred because of extensive cortical damage and cortical injuries may lead to epilepto-genicity[4,14].

Patients with a history of previous seizures had significantly higher risk of late POSz than patients with no previous history, a similar finding to that reported in the literature[9,11,15,16]. Furthermore, Hwang et al. reported that a duration of preoperative seizures longer than six months increases the incidence of post-operative seizures[11].

Postoperative RT was significantly related to late POSz within one year but not within two years. This is likely a statistical artifact. Whether such an association truly exists is controversial. Khan and Onar reported that whole brain RT increased the risk for recurrence seizures[20]. Other studies of adjuvant RT did not find an increased risk of late POSz[11,15], while 2 small series[18,19]

showed a seizure frequency reduction of 75% or greater after RT. Nevertheless, seizure frequency may increase occasionally after RT, secondary to complication such as bleeding, edema and radiation necrosis[21]. Further studies of the effect of postoperative RT on post-operative seizures should be done.

Subtotal tumor removal was significantly related to late POSz only at two years, not at one year. This result was similar to that of a previous study[15]. But a statistical chance finding may explain this association as well. Patients who had early onset seizures had a higher rate of late POSz. A previous study by Foy et al. reported that early seizures were frequently followed by late seizures, in 41%[3]. Other studies also reported that early POSz is a risk factor for developing late POSz[17].

One risk factor which was not statistically significant but should be mentioned is location of the tumor within the cortex. The present study showed that late POSz occurred more often, but not significantly so, when the tumor was located in temporal and insular lobe, and parietal lobe, but less often when located in the frontal and occipital lobes. This result was similar to those of previous studies, which reported higher incidence of postoperative seizures for tumors located at the temporal and parietal lobes[1,5,13]. The lack of statistical significance in the present study could be due to the smaller sample size and fewer number of outcomes, being a subgroup analysis.

The present study was retrospective and observational, so the decision to continue or discontinue AED was not controlled. Because many patients were lost to follow up and excluded from the study, especially patients with glioblastoma multiforme and brain metastasis, and many patients were referred for follow-up or RT elsewhere. It was unclear whether patients excluded from the study were similar or different from those in the study (selection bias). Thus, a prospective study should be done.

Conclusion

Late POSz is a common problem in patients undergoing surgery for intracranial brain tumors, with an incidence of approximately 11% both within 1 year and within 2 years. Most late POSz (97%) occurred within 1 year. The incidence of late POSz varied according to tumor location and pathology. Tumors in the supratentorial cortical and subcortical locations have a high risk for late POSz. Gliomas and meningiomas also have a high risk for late POSz. Patients who have a history of previous seizures, early POSz, have higher risks for postoperative seizures as well. Patients with a high risk for late POSz should be closely followed, with serum AED level monitoring, especially during the first year after surgery.

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