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# Postoperative epileptic seizures after brain tumor surgery

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ABSTRACT

*Background:* We sought to examine the incidence of postoperative epileptic seizures, particularly nonconvulsive status epilepticus (NCSE), in brain tumor patients after craniotomy surgery.

*Methods:* This was a retrospective, single-center study of 388 patients who underwent brain tumor surgery via craniotomy at our hospital from January 2015 to August 2017. We used medical charts to retrospectively select patients with postoperative epileptic seizures (ES) and examined the incidence of postoperative ES, generalized convulsive status epilepticus (GCSE), and NCSE.

*Results:* Nineteen patients (4.9%) were diagnosed as having postoperative ES. The number of patients who had NCSE (14 cases) was larger than the number of those who had GCSE (3 cases) or focal aware seizures (2 cases). In most of the 19 seizure cases, the tumors were located in the intraparenchymal area (17 cases) or the frontal lobe (13 cases).

*Conclusions:* Postoperative ES was diagnosed in 4.9% of patients after brain tumor surgery, and NCSE constituted the overwhelming majority of postoperative ES.

## 1. Introduction

Patients with brain tumors frequently suffer from epileptic seizures (ES). For example, previous research showed that 78% of such patients have seizures throughout their lives [4]. Antiepileptic drugs (AEDs) are effective for ES after neurosurgical interventions for brain tumors performed via craniotomy for tumor removal or via trepanation for tumor biopsy [14]. However, according to a previous study of glioma patients, 9.1% of those patients had ES within 1 week of surgery and 48% had ES during the whole follow-up period [7]. The risk factors for postoperative ES were an intraparenchymal lesion, younger age (< 50 years), tumor location in the frontal lobe, and multiple lesions. In the subanalysis of the glioma patients, oligodendroglioma and low-grade gliomas were considered to be risk factors [7].

Although postoperative ES are theoretically focal (localization-related), status epilepticus (SE) is categorized as generalized convulsive SE (GCSE) or nonconvulsive SE (NCSE), which is defined as SE without prominent motor symptoms, often arising because of secondary generalization. NCSE is more difficult to diagnose than GCSE because it is often hard to distinguish the clinical signs owing to NCSE from transient (or permanent) neurological deficits after tumor removal. In the present retrospective study, we sought to examine the incidence of postoperative ES, especially of NCSE, in brain tumor patients after surgery via craniotomy.

## 2. Patients and methods

This study was a retrospective, single-center study. Of 1400 consecutive patients who underwent neurosurgical intervention in our hospital from January 2015 to August 2017, 574 brain tumor patients underwent neurosurgery via craniotomy. After excluding those who underwent endonasal surgery for pituitary adenoma or other diseases,

*Abbreviations:* AED, antiepileptic drug; CT, computed tomography; ED, epileptiform discharge; EEG, electroencephalography; ES, epileptic seizures; fPHT, fosphenytoin; GCSE, generalized convulsive status epilepticus; Gd, gadolinium; LEV, levetiracetam; MRI, magnetic resonance imaging; NCSE, nonconvulsive status epilepticus; PB, phenobarbital; PHT, phenytoin; POD, postoperative day; RDT, rhythmic delta/theta activity; SE, status epilepticus; SMA, supplementary motor area; WI, weighted imaging; IV, intravenous

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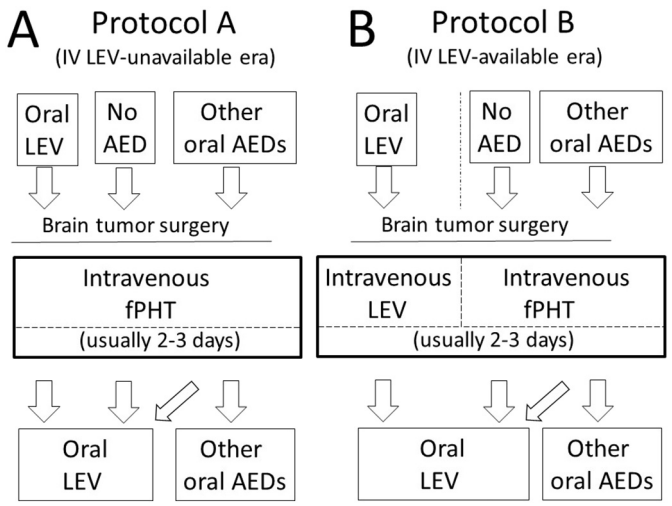


**Fig. 1. A**. Protocol A, intravenous fos-Phenytoin (fPHT) was chosen for preventing postoperative epileptic seizures for all high-risk patients (intravenous levetiracetam [LEV]-unavailable protocol, available before March 2016). **B**. Protocol B, intravenous LEV for patients with oral LEV before surgery and intravenous fPHT for other high-risk patients (intravenous LEV-available protocol, available after April 2016). In these protocols, the patients typically received these intravenous medications for fewer than 4 days, followed by oral AEDs.

388 patients were included in the study.

We prefer to use AEDs for brain tumor patients that are available both for intravenous (IV) and for oral administration during the perioperative period. AEDs currently available in Japan are phenytoin (PHT), its pro-drug fos-phenytoin (fPHT), phenobarbital (PB), and levetiracetam (LEV). Before March 2016, fPHT was chosen according to the clinical protocol of our neurosurgical department for preventing postoperative ES for all high-risk patients including patients who had any history of ES, patients who received any AEDs including oral LEV before surgery, and patients who had intraparenchymal tumor or intraparenchymal injury due to the tumor or the surgery but did not receive any AEDs (Fig. 1A, IV LEV-unavailable protocol). After April 2016, IV LEV was used for high-risk patients with oral LEV before surgery and IV fPHT was used for other high-risk patients without oral LEV (Fig. 1B, IV LEV-available protocol). The patients following a normal postoperative course with no postoperative ES received IV LEV or fPHT for fewer than 4 days, followed by oral AEDs. On the other hand, the patients with postoperative ES received IV medications for 4 days or more, including both LEV and fPHT and/or benzodiazepine. Therefore, in this study, we automatically selected candidate ES patients whose electronic records showed that they used IV LEV for no < 4 total days during hospitalization, fPHT for no < 4 total days, or a combination of IV LEV and fPHT. The use of benzodiazepine was excluded from this automatic selection algorithm since it was also used for sedation of patients during postoperative MRI, etc. After 56 patients were screened according to this algorithm, those with postoperative ES were selected retrospectively, by use of the medical charts. NCSE was suspected in patients with clinical features that were not explained by neurological deficits due to resection of the tumor-surrounding brain tissue, such as consciousness disturbance, catatonia, psychotic symptoms, speech disorders, and other subtle motor signs such as automatisms, cyclonic jerks, eye twitching, and eye deviation. Although several electroencephalography (EEG) criteria have been proposed for the definitive diagnosis of NCSE [1,2,5,11,13,17], we used the Salzburg criteria, which have high diagnostic accuracy for NCSE [1,13]. Namely, the following criteria were applied to the EEG of patients without preexisting epileptic encephalopathy: (1) > 25 epileptiform discharges (ED) per 10-second epoch (i.e., > 2.5/s) and (2) patients with 2.5 ED per second or fewer, or rhythmic delta/theta activity (RDT) exceeding 0.5/s AND at least 1 of the following criteria: (2a) clinical and EEG improvements from IV AEDs, (2b) subtle clinical phenomena, and (2c) typical spatiotemporal evolution [1,13]. All the patterns had to have lasted at least 10 s to qualify for consideration. Other parts of the EEG were also abnormal, but “at least 10 seconds” was the minimal duration in which the abnormalities were severe enough to fulfill the criteria [13].

The IV LEV-available and -unavailable protocols were evaluated in terms of the incidence rate of postoperative ES, GCSE, and NCSE. The chi-square test was performed to compare the proportions of the categorical variables between the groups. The threshold for significance was $P < 0.05$. All statistical analyses were conducted using Statcel 3 software (OMS Publishing, Tokorozawa, Japan).

## 3. Results

In 388 patients who underwent brain tumor surgery via craniotomy, 57 (15.9%) received IV LEV treatment and 208 (58.1%) received IV fPHT treatment. Postoperative ES was diagnosed in 19 patients (4.9%; Table 1). The number of patients who had NCSE (14 patients: 10 patients with suspected NCSE and 4 patients with definitive NCSE) was larger than the number of those who had GCSE (3 patients) or focal aware seizures (2 patients). In most of the 19 seizure cases, the tumors were located in the intraparenchymal area (17 patients) or the frontal lobe (13 patients). One hundred sixty-five patients underwent brain tumor surgery from January to March 2016 (IV LEV-unavailable group), and 223 patients underwent the surgery from April 2016 to August 2017 (IV LEV-available group). In those series, 6 patients in the IV LEV-unavailable group and 13 patients in the IV LEV-available group had postoperative ES. No significant difference was found in the occurrence of postoperative ES between those groups ($P = 0.32$). The number of patients who had postoperative NCSE in the former group accounted for 5 of the 6 seizure cases (83%); on the other hand, the number of patients in the latter group accounted for 9 of the 13 seizure cases (69%). No significant difference was found in the occurrence of postoperative NCSE between the 2 groups ($P = 0.60$).

In all 388 brain tumor cases, the number of patients who had postoperative seizures after receiving IV LEV treatment accounted for 3 of the 57 patients (4.8%); on the other hand, the number of patients who had postoperative seizures after receiving IV fPHT treatment accounted for 12 of the 208 patients (5.3%) ($P = 0.86$). One patient who had postoperative seizures was considered a low-risk case and received no AEDs intravenously after surgery, and the other 3 patients with suspected seizures just after surgery had both LEV and fPHT intravenously soon after the surgery.

As a representative case, a 60-year-old man who presented with a sustained aphasia attack of a few minutes was referred to our hospital. Magnetic resonance imaging (MRI) showed a high-intensity mass lesion in the left frontal region, including the left supplementary motor area (SMA), on T2-weighted imaging (WI) and no enhancement on T1WI with Gd administration, (Fig. 2A, B). He underwent awake surgery to remove the brain tumor whilst at the same time saving his motor and language functions, and received IV LEV after the surgery. The pathological diagnosis was oligodendroglioma, World Health Organization grade II. During the postoperative course, he had an SMA syndrome consisting of transient mild right hemiparesis and speech delay on postoperative days (POD) 0 to 4, although the postoperative MRI did not show any complications (Fig. 2C). After recovering from the SMA syndrome on POD 5, he had disturbance of consciousness and worsening aphasia on POD 9, whilst computed tomography (CT) showed no new lesions (Fig. 2D). EEG showed rhythmic sharp waves occurring in both hemispheres with dominance in the left one, and NCSE was diagnosed (Fig. 3).

**Table 1**
Characteristics of 19 patients with epileptic seizures after brain tumor surgery.

| Case | Age/sex | Diagnosis | Side | Location | Maximum diameter (mm) | Oral AEDs before surgery | Intravenous AEDs after surgery | Type of seizure | Symptoms | Interval from surgery to seizure diagnosis (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| A1 | 13/M | Anaplastic ependymoma | Bil | F | 61 | LEV | fPHT | NCSE | Abnormal hand movement | 3 |
| A2 | 47/M | AOD | R | F | 42 | PHT | fPHT | NCSE | Somnolence | 5 |
| A3 | 52/F | Inflammation with necrosis | Multi | F,P,O | < 10 | LEV | fPHT | NCSE | DOC, aphasia | 4 |
| A4 | 66/M | Meningioma | L | F | 39 | PB | fPHT | NCSE | DOC, aphasia | 2 |
| A5 | 68/F | AOD | L | F + P | 42 | PHT | fPHT | NCSE | DOC, aphasia | 4 |
| A6 | 73/F | GBM | Bil | F | 51 | PHT | fPHT | GCSE | Generalized convulsions | 4 |
| B1 | 9/F | GCT | R | BG | 29 | None | fPHT | NCSE | DOC, aphasia | 0 |
| B2 | 51/F | Met | L | F | 34 | LEV | fPHT[a] | NCSE | DOC, aphasia | 5 |
| B3 | 53/F | Meningioma | R | F | 29 | None | fPHT | NCSE | DOC, perseveration | 0 |
| B4 | 69/M | HGG | Multi | T + P | 17 | None | fPHT | Focal aware | Muscle cramps | 1 |
| B5 | 73/F | AA | L | F | 43 | None | fPHT | NCSE | Consciousness transformation | 2 |
| B6 | 81/M | GBM | L | T | 64 | LEV | fPHT[a] | NCSE | DOC, restlessness | 1 |
| B7 | 60/M | OD | L | F | 49 | LEV | LEV | NCSE | DOC, aphasia | 9 |
| B8 | 64/M | Pineoblastoma | L | P | 38 | LEV | LEV | NCSE | DOC, concomitant deviation | 3 |
| B9 | 68/M | GBM | Multi | F + P | 20 | LEV | LEV | GCSE | Generalized convulsions | 1 |
| B10 | 71/M | GBM | R | O | 40 | CBZ | None[a] | NCSE | DOC, automatism, concomitant deviation | 2 |
| Suppl. 1 | 34/F | AOA | R | F | 33 | LEV | None[b] | focal aware | Lt arm cramps | 0[b] |
| Suppl. 2 | 48/M | DLBCL | Multi | F | 40 | LEV | None[b] | NCSE | Aphasia, hemiparesis | 0[b] |
| Suppl. 3 | 66/M | GBM | L | P + O | 55 | VPA | None[b] | GCSE | Generalized convulsions | 0[b] |

AED, antiepileptic drugs; AOD, anaplastic oligodendroglioma; GBM, glioblastoma; GCT, germ cell tumor; HGG, high-grade glioma; GBM, glioblastoma; AA, anaplastic astrocytoma; OD, oligodendroglioma; AOA, anaplstic oligoastrocytoma; Met, metastatic brain tumor; DLBCL, diffuse large B cell lymphoma; R, right; L, left; Bil, bilateral; BG, basal ganglia; F, frontal; P, parietal; O, occipital; T, temporal; CBZ, carbamazepine; fPHT, fosphenytoin; PB, phenobarbital; PHT, phenytoin; LEV, levetiracetam; NCSE, nonconvulsive status epilepticus; GCSE, generalized convulsive status epilepticus; DOC, disturbance of consciousness.

[a] AED was changed from the protocol-based drug at the physician's discretion.

[b] Epileptic seizures occurred before protocol-based administration of intravenous AED, and fPHT and LEV were used after the seizures.

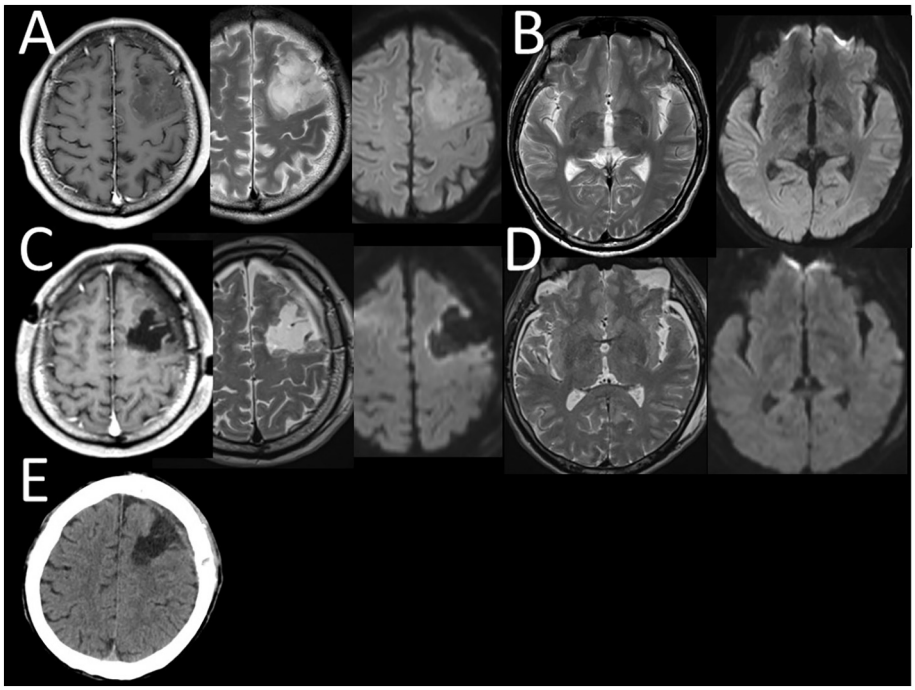


**Fig. 2.** A 60-year-old man with oligodendroglioma. Magnetic resonance imaging (MRI) before the surgery showed that the tumor was located in the left supplementary motor area (A: axial imaging at high convexity level. Left; T1WI with gadolinium [Gd] administration, middle; T2-weighted imaging [WI], right; diffusion-weighted imaging [DWI] and B: axial imaging at low convexity level. Left; T2WI, right; DWI). MRI at postoperative day (POD) 1 shows the tumor cavity after removal without massive hemorrhage or infarction (C: axial imaging at high convexity level. Left; T1WI with Gd, middle; T2WI, right; DWI and D: axial imaging at low convexity level. Left; T2WI, right; DWI). Although the patient had disturbance of consciousness and transient aphasia on POD 9, computed tomography (CT) showed no new lesions (E).

## 4. Discussion

In this study, postoperative ES was diagnosed in 4.9% of the patients after brain tumor surgery, and NCSE constituted the overwhelming majority of postoperative SE. Although the incidence of ES was similar to those in previous studies [7,8,10], this study was carried out in a retrospective manner and all the data were obtained from medical charts. Therefore, the possibility remains of underestimated diagnosis of postoperative seizures in patients with mild symptoms that were ignored by clinicians. It is also possible that some mild ES patients who received IV medication for < 4 total days were excluded since we selected the candidates automatically, as mentioned in the Patients and

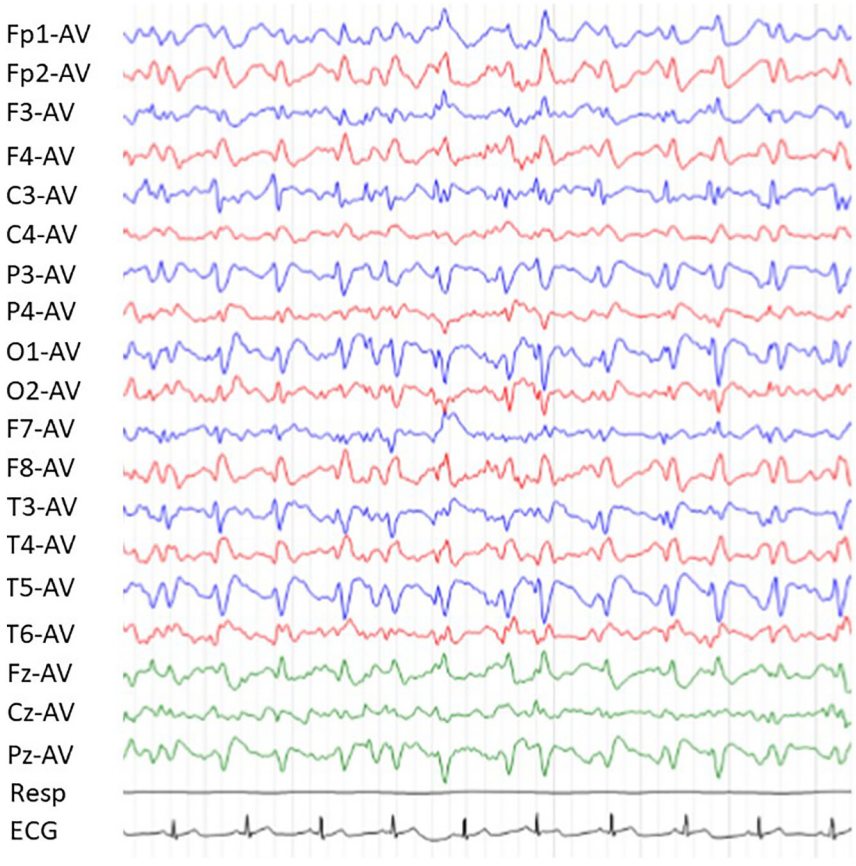


**Fig. 3.** Electroencephalography (EEG) was performed on day 9 after tumor removal in the left supplementary motor area. Rhythmic sharp waves are seen in both hemispheres with the left one being dominant, which is compatible with nonconvulsive status epilepticus (NCSE). Sensitivity = 10 μV, high cut filter = 120 Hz, time constant = 0.3 s.

Methods. Moreover, the initial time of the postoperative AED administration was not strict in our study; for instance, AEDs were administered immediately after the operation in some patients and a few hours later in others. The timing could have affected the occurrence of postoperative seizures. Our results showed that the tumors were located in the intraparenchymal area and/or the frontal lobe in most of the SE cases. So, we should pay attention to occurrence of NCSE especially in frontal intraparenchymal tumor cases. Our study showed that frontal lobe tumors rather than tumors in other areas were the most common factor of NCSE. As we mentioned above, NCSE is characterized mainly by changes in consciousness and non-motor symptoms. Although frontal lobe epilepsy is most likely to produce hypermotor symptoms, it may also produce psychiatric symptoms or language dysfunction [3,9]. Given this semiology, these symptoms may depend on the area in the frontal lobe. We suppose this is why the NCSE patients in our study did not present motor symptoms despite having frontal lobe lesions.

In this study, we investigated postoperative ES after intravenous AEDs in surgical patients with brain tumors. The results showed no significant difference in the incidence of seizures, not only in patients of both the IV LEV-unavailable and the IV LEV-available groups, but also in those of the IV LEV and fPHT groups. Previous studies have shown debatable results on postoperative use of AEDs. A double-blind study showed a significantly reduced incidence of perioperative seizures after craniotomy with PHT [16]. In contrast, a prospective randomized trial reported no significant effect of PHT on seizure prophylaxis in patients with intraparenchymal brain tumors [12]. Recent studies showed that LEV was more suitable than PHT as a prophylactic AED after craniotomy. A retrospective review showed a lower incidence of perioperative seizures in patients receiving LEV (2.5%) than in those receiving PHT (4.5%) without the difference being significant [10]. A randomized prospective study showed that the incidence of perioperative seizures was significantly lower for LEV (1.4%) than for PHT (15.1%) and that LEV was safe, with the treatment being completed in all patients; on the other hand, PHT was withdrawn because of adverse effects in 6.8% of the patients [8]. A meta-analysis also reported that the incidence of perioperative seizures was significantly lower in the LEV group (8/158) than in the PHT group (22/137) and moreover that the frequency of severe adverse effects was significantly lower in the LEV group than in the PHT group [6]. In contrast to these recent studies, our study showed no significant difference in the incidence rate of postoperative seizures between the IV LEV-unavailable and -available groups or between the IV LEV and fPHT groups (power analysis was performed to minimize type II error). We presumed that possible reasons for this lack of difference in our study were the use of fPHT instead of PHT, because fPHT, a water-soluble pro-drug of PHT, has less adverse effects such as arrhythmia, blood pressure changes, and phlebitis than does PHT [15], and the proactive diagnosis of NCSE. In some of these previous studies, there is a possibility that NCSE was underdiagnosed because the diagnosis was more difficult than for GCSE or other seizures. And as a further possible reason, the patients' backgrounds were different, for example, age, sex, pathology, location, tumor grade, preoperative seizure, and operative data (operative time, blood loss, intraoperative AED administration, intraoperative seizure, awake surgery, extent of resection).

## 5. Conclusion

In summary, postoperative ES was diagnosed in about 5% of patients after brain tumor surgery regardless of the types of postoperative AEDs used in this study, and NCSE constituted the overwhelming majority of postoperative ES. Since the tumors were located in the intraparenchymal area and the frontal lobe in most of the ES cases, we should pay attention to occurrence of NCSE especially in cases of frontal intraparenchymal tumor.

## Disclosures

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

E.I. has received management expenses grants for this study from University of Tsukuba.

## Ethical standards and informed consent

This manuscript was submitted to and approved by the ethics committee of the University of Tsukuba Hospital (H29-222). An opt-out format was used in the study instead of informed consent from each patient. Informed consent was obtained from each patient for the brain tumor surgery and for the clinical use of perioperative drugs including AEDs.

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