Trials

STUDY PROTOCOL

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A multi-center, open-label, randomized clinical trial evaluating the preventive effect of perampanel on craniotomy-induced epileptogenesis in seizure-naive patients with supratentorial brain tumors: study protocol for a GRAMPAS trial

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Abstract

Background Early seizures after craniotomy are significant perioperative complications that can adversely impact patient outcomes. Despite current guidelines advising against the routine use of antiseizure drugs for seizure after craniotomy prevention due to limited efficacy data, many clinicians continue prescribing them. This discrepancy highlights the need for robust evidence to guide clinical practice. This multi-center, randomized clinical trial was designed to investigate the efficacy of perampanel in preventing early seizures after craniotomy.

Method This multi-center, open-label, randomized clinical trial will be conducted across five hospitals in Nagoya, Japan, from February 2024 to December 2026. A total of 142 seizure-naive patients with supratentorial brain tumors will be recruited and randomized (1:1) into the treatment and control groups. The treatment group will receive 2 mg of perampanel starting 2 days preoperatively and continuing for 28 days postoperatively, while the control group will receive no antiseizure drugs. The primary outcome is the incidence of seizures within 28 days after craniotomy. Secondary outcomes are length of hospital and intensive care unit stays and postoperative complications.

Discussion This study addresses the critical need for evidence-based recommendations regarding antiseizure drug use for preventing early seizures after craniotomy. As the first multi-center, randomized trial evaluating perampanel's efficacy in this setting, the findings may significantly influence clinical guidelines and perioperative practices.

Trial registration This trial was registered with the Japan Registry of Clinical Trials (approval number: jRCTs041230117) on December 18, 2023, a member of the Primary Registry Network of the World Health Organization's International Clinical Trials Registry Platform.

Keywords Perampanel, Brain tumor, Early seizures after craniotomy, Prophylaxis

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Background

In Japan, 14.1 cases of brain tumors are reported to occur in 100,000 people per year [1]. Seizures often trigger the discovery of brain tumors, and 30–40% of patients with brain tumors experience seizures at the time of diagnosis, for which antiseizure drugs are prescribed [2–4]. Although many patients with brain tumors undergo craniotomy, this procedure increases the risk of seizures after craniotomy, with an incidence of approximately 20% in glioma cases within 30 days post-craniotomy [5]. Retrospective studies report postoperative seizure rates ranging from 2.9 to 20%, typically occurring within 1 week to 1 month after craniotomy [6–9]. The occurrence of seizures after craniotomy is detrimental to the patient, causing increased cerebral pressure, worsening neurological symptoms, aspiration pneumonia, and prolonged intensive care unit (ICU) stay [10–12]. Seizures after craniotomy frequently occur during the early postoperative phase (within 7 days) and are less likely to progress to epilepsy, whereas later seizures (beyond 30 days) carry a higher risk of evolving into epilepsy [5]. Despite randomized clinical trials and guidelines advising against routine antiseizure drug prophylaxis after craniotomy [5, 6, 13], many clinicians continue to prescribe antiseizure drugs, particularly levetiracetam (LEV), as reflected in a survey by the American Association of Neurological Surgeons/Congress of Neurological Surgeons [14]. The duration of antiseizure drug administration after craniotomy varied widely, with approximately 50% of cases involving usage for 2 weeks or less. This gap between guideline recommendations and clinical practice has persisted for nearly two decades, underscoring clinicians' concern over seizure risks [15]. In Japan, fosphenytoin, a prodrug of phenytoin, is approved for perioperative seizure management in seizure-naive patients undergoing craniotomy. However, evidence supporting its efficacy for preventing seizures after craniotomy in seizure-naive patients with brain tumors remains insufficient. In a domestic phase III trial pivotal to its approval in Japan, only nine seizure-naive patients were enrolled, four of whom had brain tumors [16].

In recent years, novel antiseizure drugs with improved seizure suppression profiles and fewer adverse events (AEs) have emerged. For instance, a retrospective study utilizing LEV for postoperative seizure prevention reported a seizure incidence of approximately 5%, lower than previously observed rates [17, 18]. Notably, previous clinical trials primarily used phenytoin, an older antiseizure drug, suggesting that newer antiseizure drugs may offer improved seizure control after craniotomy.

Perampanel (PER), a selective inhibitor of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid receptors, is a novel antiseizure drug developed and manufactured by Eisai Co. in Japan. It has demonstrated efficacy across various seizure types [19]. Its primary clinical indications include focal onset seizures and tonic–clonic seizures. Compared to other antiseizure drugs, rapid and high transfer from the blood to the central nervous system has been reported and its pharmacologic half-life is approximately 105 h [20, 21]. While a gradual increase in dosage from an initial dosage of 2 mg to a maintenance dosage of 4–10 mg is recommended, the low dose of 2 mg has also been shown to be effective [22, 23]. Furthermore, this recommended maintenance dose was established in a study of patients diagnosed with epilepsy; hence, low-dose PER may be sufficient for seizure prophylaxis in "seizure-naive" patients [24]. Additionally, retrospective studies have reported a 5% incidence of seizures with a prophylactic 2 mg dose of PER; however, data on its efficacy for seizure prevention after craniotomy are lacking. Therefore, a prospective study is warranted to assess its effectiveness in this context [22]. Should this trial demonstrate low-dose PER's preventive effectiveness, a larger-scale trial will be conducted to confirm the findings.

Here, we designed a clinical trial to evaluate the efficacy of low-dose PER for seizure prevention after craniotomy. Given the absence of prospective validation for LEV's prophylactic efficacy after craniotomy and its exclusion from guidelines, our study's control group will receive no antiseizure drug treatment. We named the study the GRAMPAS trial, an acronym derived from the title of the research project: a randomized trial of preventive effect on craniotomy-induced epileptoGenesis by peRAMPAnel in Seizure-naive patients with supratentorial brain tumor.

Methods/design

Study design

This multi-center, open-label, randomized clinical trial will be conducted at five hospitals in Nagoya, Japan (Nagoya University Hospital, Nagoya Central Hospital, Aichi Cancer Center, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital and Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital), from February 2024 to December 2026. These hospitals were selected based on their high annual caseloads of craniotomies for brain tumors (exceeding 20 cases) and their comprehensive medical teams, which include at least three neurosurgeons and adequate support staff for intensive postoperative care. Each principal investigator at these sites is a neurosurgeon with over 20 years of experience as neurosurgeons, possess extensive knowledge, and expertise in managing brain tumors. Ethical approval was granted by the Ethics Committee of Nagoya University Hospital on December 7, 2023 (Approval number: 2023–0348). This

study has been registered and published in the Japan Registry of Clinical Trials (jRCT) (Approval number: jRCTs041230117). The jRCT is an approved member of the Primary Registry Network of the World Health Organization's International Clinical Trials Registry Platform. The study protocol adheres to the SPIRIT guideline [25]. Following SPIRIT's recommendations, the schedule of enrolment, intervention, and assessment is summarized in Table 1, and a schematic representation of the study design is shown in Fig. 1.

Informed consent

Each participant will receive a detailed description of the study from their investigator-in-charge and express their willingness to participate in the clinical trial by signing an institutional review board-approved consent form. The consent includes authorization for the collection and use of patient data and biological specimens in ancillary studies.

Patient selection

Patients will be selected based on the following inclusion and exclusion criteria, with only those treated according to standard clinical practice at the participating hospitals eligible for recruitment. Preclinical safety studies in patients without a history of epilepsy were conducted in adults, and this trial includes participants aged 18 years and older [26]. The upper age limit is set at 80 years to reduce the risks of AEs. A patient with "no history of seizures" in the inclusion criteria is defined as one who has no documented seizures and is not taking antiseizure drugs at the time of trial enrollment.

Inclusion criteria

- Patients with supratentorial brain tumors scheduled for craniotomy
- Patients with intra-axial tumors, extra-axial tumors with brain edema, or extra-axial tumors without brain edema compressing the motor cortex, diagnosed by the physicians in charge to be at high risk for early seizures after craniotomy

Table 1 Timeline summary of enrolment, intervention, and assessments for the study

	Enrolment	Allocation	Post allocation							Withdrawal	First seizure onset
Timepoint	**By −2**		**−2**	**0**	**1**	**7**	**14**	**21**	**28**		
Enrolment											
Eligibility screen	X										
Informed consent	X										
Allocation		X									
Intervention											
Surgery (craniotomy)				X							
Oral 2 mg perampanel (treatment group)											
No treatment (control group)											
Data collection											
Basic patient background data	X										
Vital sign	X									X	X
ECG	X										
Chest X-ray	X										
Laboratory data	X			X[1]	X	X	X		X	X	X
Measurement of blood concentration of perampanel				X[1]							
Clinical examination										X	X
Head CT[a]					X						X
Head MRI[a]					X[2]						X[3]
Adverse events[b]										X	X

X[1], perform within 3 h of intensive care unit admission (only treatment group); X[2], perform within 72 h after surgery; X[3], perform if necessary

Abbreviations: *PER*, perampanel; *AE*, adverse event

[a] Head CT and MRI are performed as a routine preoperative evaluation at each facility and are not specified as a trial protocol

[b] Collect grade 1 or higher liver enzyme abnormalities (AST, ALT, γGTP), clinical symptoms (rotational dizziness, floating dizziness, somnolence, irritability), and other grade 3 or higher abnormalities in CTCAE

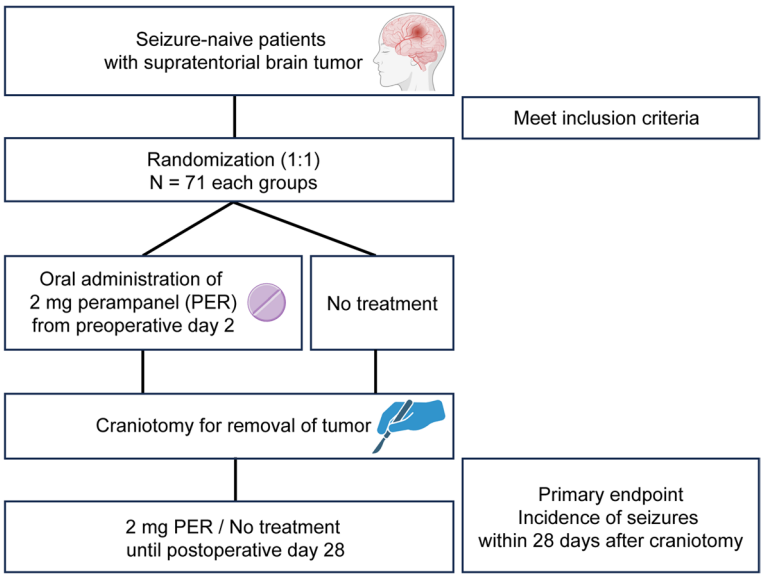

Fig. 1 Schematic representation of the study design

- Karnofsky Performance Scale above 70
- Ages from 18 to 80 years
- No documented history of seizures
- No contraindications to PER use
- Written consent by the individual, a designated relation, attendant, next of kin, or surrogate

Exclusion criteria

- Patients unable to take tablets orally
- Patients indicated for awake surgery
- Patients with central nervous system diseases other than brain tumors
- Patients with a history of treatment for central nervous system diseases
- Patients with a history of antiseizure drug use other than PER within 1 week of surgery
- Patients deemed unsuitable for trial enrollment by the physicians in charge

Sample size

The sample size was determined using a one-sided significance level of 5%, a power of 80%, and an assumed dropout rate of 5%. We assumed an incidence rate of 20% in the control group and 5% in the PER group, requiring a total of 142 patients (71 per group). The assumed 20% incidence rate in the control group was based on the only prospective study examining the effect of antiseizure drugs on preventing early seizures after craniotomy, which reported an 18% incidence rate in the observation group [8]. For the assumed 5% incidence rate in the PER group, we referred to studies evaluating LEV, a relatively newer antiseizure drug, for seizure prophylaxis. In these retrospective studies, the incidence rate of early seizures after craniotomy ranged from 1.6 to 4.6% [12, 13]. Similarly, a retrospective study specifically investigating the prophylactic use of 2 mg PER reported a seizure incidence rate of 5% [17].

Randomization

Patients will be assigned (1:1) to either the treatment or control group using the minimization method in the web registration system and issued case numbers. Adjustment factors for allocation will be tumor type (primary brain tumor, metastatic brain tumor, or extra-axial tumor), sex, age (over or under 65 years), and institution. The physicians in charge will register and assign patients using this system.

Basic data collection

Demographic and clinical characteristics of the patients, including age, sex, medical history, family history of epilepsy, laboratory data, pre- and post-operative head magnetic resonance imaging reports, computed tomography findings, and pathological findings, will be recorded.

Treatment and measurement

Patients in the treatment group will take 2 mg of PER tablets before sleep for 2 days prior to surgery and for 28 days after surgery. Eight 2 mg PER tablets are individually packaged on a single drug sheet. To facilitate patient compliance and adherence to the treatment protocol,

patients will be instructed to continue taking the medication until day 28, the last day of the observation period. PER administration will be omitted on the day of surgery to minimize the risk of aspiration and account for variable dosing times due to surgery schedules. Postoperative blood PER levels will be measured. Patients in the control group will not receive any antiseizure drugs before or after surgery, as current guidelines do not recommend prophylactic antiseizure drug use in the perioperative period. If seizures occur in the PER group, the PER dose will be increased, or another antiseizure drug will be introduced at the discretion of the physicians in charge. In the control group, the antiseizure drugs use is prohibited until a seizure occurs. However, if a seizure does occur, an antiseizure drug will be administered according to standard clinical practice, with the specific drug choice left to the physician in charge. However, if a seizure occurs during the observation period, the patient will discontinue protocol treatment and any scheduled interventions.

Seizures will be diagnosed based on clinical manifestations, including involuntary movements, alterations in consciousness, or abnormal motor, sensory, or psychosensory phenomena. If the occurrence of a seizure is uncertain, an electroencephalogram will be performed, and a blinded adjudicating physician will make the final decision.

Postoperative follow-up

During hospitalization, the physicians in charge will conduct daily safety assessments and monitor for seizure occurrences. Nurses will ensure that patients adhere to the prescribed PER tablet regimen by collecting empty drug sheets as evidence of compliance throughout the study. Blood tests for safety assessment will be performed on postoperative days 1, 7, 14, and 28. Patients may be discharged after day 7 if recovery is satisfactory. Upon discharge, an outpatient consultation will be scheduled for postoperative day 28, marking the final day of the protocol period, during which patients will undergo a blood test and submit empty drug sheets. Patients will also self-report their adherence to PER and their physical condition. Adherence during home care will primarily be based on patient self-reporting, ideally during outpatient visits, although telephone interviews or reports from next to kin are also acceptable. If a noticeable seizure occurs during home care, the physicians in charge will request the patient's return to the hospital. For patients discharged between days 7 and 14, an additional outpatient consultation will be scheduled for postoperative day 14, where they will undergo a blood test, submit empty drug sheets, and self-report adherence to PER and physical condition.

Safety assessment

AEs will be recorded according to the Common Terminology Criteria for Adverse Events version 5.0. The number and incidence rates of AEs, along with the number of affected patients, will be summarized by AE type. Comparative analyses of AE incidence between the treatment and control groups will be conducted using Fisher's exact test for each AE category. AEs will also be assessed for their relationship to the treatment (e.g., possibly, probably, or definitely related to PER). Serious adverse events (SAEs) will be reported separately. Regular monitoring will ensure patient safety and accurate data collection, as outlined in the protocol's "Monitoring" section. Any grade 3 or higher AEs attributed to the treatment will be immediately reported to the monitoring committee for evaluation. Hematologic abnormalities (AST, ALT, γGTP) and clinical symptoms (dizziness, somnolence, irritability) potentially associated with PER will be recorded as grade 1 or higher, while all other AEs will be recorded as grade 3 or higher. Clinical symptoms will be documented based on patient-reported complaints from the initiation of PER administration. If a grade 3 or higher AE attributable to PER is identified, PER administration will be discontinued.

Handling of deaths

Although deaths are not expected given the patient population and the nature of the intervention, the study protocol includes provisions for their occurrence. Any death occurring within the trial period will be thoroughly investigated to determine the potential association with the study intervention. Causes of death will be categorized (e.g., tumor progression, perioperative complications, or unknown). The incidence of death will be reported descriptively for each group. Suppose an unexpected death potentially related to PER occurs, it will be reported as a SAE and reviewed by the monitoring committee to ensure patient safety. Statistical analysis of mortality rates will not be conducted unless an unexpectedly high incidence of death occurs.

Planned outcomes

The primary outcome is the incidence of seizures within 28 days postoperatively. Secondary outcomes include the length of hospital stay, ICU stay, and incidence of postoperative complications.

Data management

Researchers will enter data collected during the observation period into an electronic data capture system (REDCap). The trial system was developed at a data center (Department of Advanced Medicine, Nagoya University

Graduate School of Medicine). Data entered into REDCap will be monitored by the main data manager and maintained for 10 years post-study completion.

Data analysis

All collected data will be analyzed after the observation period for all cases by the main data-management manager, who will remain blinded to the treatment group. Patients who receive at least one dose of PER will be analyzed as the treatment group. The primary efficacy analysis population will be the Full Analysis Set (FAS), including all patients in the safety analysis population, excluding those with serious protocol violations (e.g., lack of consent, serious violations of study procedures) or without any post-treatment data. The primary analysis will follow the intention-to-treat principle, adhering closely to the FAS approach as recommended by ICH E9 guidelines. All patients who receive at least one dose of PER will be included in the treatment group analysis, regardless of adherence or protocol deviations. A per-protocol analysis will also be conducted as a secondary analysis to assess the efficacy of PER in patients who strictly adhered to the study protocol. These complementary analyses will strengthen the robustness of our findings.

For the primary endpoint, seizure incidence will be compared between groups using Fisher's exact test within the FAS population. Hospital and ICU stays, measured from surgery day to discharge (with surgery day designated as day 0), will be analyzed using the Mann–Whitney U test. Postoperative complications, defined as surgery-attributable events, and their incidences will be analyzed using Fisher's exact test. In case of missing, unused, or abnormal data, available data will be utilized. If substantial missing data is identified, exploratory analyses will be conducted to estimate its impact. A one-sided significance level of 0.05 will be used to test the superiority of the PER group over the control group for the primary endpoint. This study is designed as a superiority trial to assess the PER's preventive effect on seizures after craniotomy. The primary objective is to demonstrate the PER's superiority over the control group in reducing seizure incidence. Specifically, statistical significance will be declared if seizure incidence is significantly lower in the PER group compared to the control group. For all other analyses, a two-sided significance level of 0.05 will be used.

Confidentiality

Identifying information about individual patients will be removed, and each patient will be assigned a research registration ID. A list linking the research registration IDs to the original pre-processing information will be maintained by the principal investigator on a network-disconnected computer. Data will be retained for 10 years post-study completion, accessible only to the principal investigator and the main data manager.

Plans to promote patient retention and complete follow-up

Post-discharge medical interview appointments will be scheduled for all patients. If a patient does not attend the follow-up appointment, a telephone interview with the patient or family member will be conducted to gather the necessary information.

Composition of the coordinating center and the data management team

The coordinating center for the clinical trial is located at Nagoya University Hospital consists of members from the Department of Neurosurgery, the Department of Advanced Medicine, and the Department of Pharmacy. This center is responsible for ensuring trial safety, verifying data accuracy, and distributing study drugs to other participating hospitals. The data management team, located within the Department of Advanced Medicine, handles system registration, data management, and final statistical analyses.

Monitoring

A monitoring committee for this study has been established at Nagoya University Hospital. An individual who is not involved in the study and is accredited by Nagoya University Hospital is designated as the monitor. Monitors will conduct regular on-site or off-site monitoring and report the results to the principal investigator.

Interim analysis

No interim analysis is planned for this study. Therefore, the study will not be terminated based on interim findings.

AEs reporting

AEs will be documented and assessed based on patient complaints and blood test results, as specified in the protocol. In the event of SAEs, physicians in charge will promptly provide necessary treatments and report them to the principal investigator. SAEs are defined as follows: death, life-threatening conditions, conditions requiring hospitalization or prolonged hospitalization for treatment, and permanent or serious disability/incapacity. For unintended SAEs, the principal investigator will report to the Pharmaceuticals and Medical Devices Agency.

Provisions for ancillary and post-trial care

Any harms resulting from this clinical trial will be covered by clinical research insurance.

Auditing

No auditing is planned for this clinical trial.

Plans for communicating important protocol amendments to relevant parties

All protocol amendments will be reviewed and approved by the Ethics Committee of Nagoya University Hospital. Approved amendments will be registered with the jRCT. The latest version of the protocol will be promptly distributed to all investigators.

Dissemination policy

The results of this clinical trial will be published in a peer-reviewed journal and made accessible to all interested parties. There are no plans to publish the full protocol or final dataset.

Discussion

For the results of this trial to be robust, it is essential to correctly assess the primary endpoint, which is the occurrence of seizures. Convulsive seizures are notably easier to identify, while nonconvulsive seizures are more difficult to detect and could impact the accuracy of the primary endpoint. To enhance objectivity, the study design includes an adjudicating physician blinded to the treatment allocation. Although daily assessments by the primary physician are essential, the open-label nature of this trial requires heightened vigilance to minimize assessment bias. In setting the inclusion criteria, extra-axial tumors were limited to those with brain edema and those without brain edema but with compressing the motor cortex and high seizure risk judged by the surgeon, but this had the potential for introducing selection and observer bias. Additionally, tumor pathology and location may influence trial outcomes. With patient enrollment underway, a planned protocol revision will include subgroup analyses to evaluate potential bias impacts.

Although this trial focuses on preventing clinical seizures after craniotomy, subclinical seizures may also occur. The benefit of preventing subclinical seizures after craniotomy remains unclear. However, if this trial demonstrates the efficacy of PER in preventing clinical seizures, it would be valuable to design a future trial investigating the efficacy of PER in preventing subclinical seizures after craniotomy.

In contrast to prior studies on antiseizure drugs for seizures after craniotomy, this trial initiates PER administration preoperatively. Consequently, it is essential to monitor preoperative AEs closely to ensure they do not interfere with surgery. Furthermore, since this trial compares PER against no antiseizure drug treatment, there is potential for bias, especially with subjective AEs, such as dizziness and somnolence. Thus far, 15 patients have been enrolled, and the protocol has been successfully followed without any AEs affecting surgery or necessitating PER discontinuation.

To our knowledge, the GRAMPAS trial is the first randomized trial investigating the preventive effect of oral PER administration on seizures after craniotomy. This trial introduces a novel approach to seizure prevention after craniotomy: the preoperative and postoperative use of oral antiseizure drugs. Regardless of efficacy confirmation, this trial will provide valuable evidence to re-evaluate the current habitual use of antiseizure drugs prophylactically, with potential benefits in terms of health economics.

Trial status

This manuscript is based on protocol version 1.2 (last updated on November 1, 2023). The first patient was enrolled on February 29, 2024, and case enrollment is ongoing. Recruitment is anticipated to conclude by December 2025.

Abbreviations

ICU	Intensive care unit
LEV	Levetiracetam
PER	Perampanel
jRCT	The Japan Registry of Clinical Trials
AE	Adverse event
SAE	Serious adverse events
FAS	Full Analysis Set

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Authors' contributions

Conceptualization; JY and RS. Project administration; RS. Data curation and investigation; FO, KM, TI, NN, TI, SF, MO, and RS. Methodology and resources; JY, YY, MA, KN, and RS. Formal analysis; KN. Writing—review and editing; JY and RS. All authors were involved in the drafting and the protocol manuscript. All those involved in the management of this clinical trial have authorship.

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Data availability

The final dataset will be accessible to the principal investigator and the main data-management manager.

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of Nagoya University Hospital on December 7, 2023 (approval number: 2023-0348). This study has been registered and jRCT (approval number: jRCTs041230117). jRCT is an

approved member of the Primary Registry Network of WHO ICTRP. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Nakamura H, Makino K, Yano S, Kuratsu J. Epidemiological study of primary intracranial tumors: a regional survey in Kumamoto prefecture in southern Japan–20-year study. Int J Clin Oncol. 2011;16(4):314–21.
2. Rossetti AO, Stupp R. Epilepsy in brain tumor patients. Curr Opin Neurol. 2010;23(6):603–9.
3. Rudà R, Bello L, Duffau H, Soffietti R (2012) Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro Oncol;14 Suppl 4(Suppl 4):iv55–64.
4. Shaw MD, Foy PM. Epilepsy after craniotomy and the place of prophylactic anticonvulsant drugs: discussion paper. J R Soc Med. 1991;84(4):221–3.
5. Wu AS, Trinh VT, Suki D, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. J Neurosurg. 2013;118(4):873–83.
6. Dewan MC, White-Dzuro GA, Brinson PR, et al. Perioperative seizure in patients with glioma is associated with longer hospitalization, higher readmission, and decreased overall survival. J Neurosurg. 2016;125(4):1033–41.
7. Garbossa D, Panciani PP, Angeleri R, et al. A retrospective two-center study of antiepileptic prophylaxis in patients with surgically treated high-grade gliomas. Neurol India. 2013;61(2):131–7.
8. Lapointe S, Florescu M, Nguyen DK, et al. Prophylactic anticonvulsants for gliomas: a seven-year retrospective analysis. Neurooncol Pract. 2015;2(4):192–8.
9. Lwu S, Hamilton MG, Forsyth PA, et al. Use of peri-operative anti-epileptic drugs in patients with newly diagnosed high grade malignant glioma: a single center experience. J Neurooncol. 2010;96(3):403–8.
10. Neal A, Morokoff A, O'Brien TJ, Kwan P. Postoperative seizure control in patients with tumor-associated epilepsy. Epilepsia. 2016;57(11):1779–88.
11. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. Ann Neurol. 2003;54(4):514–20.
12. Jacoby A, Gamble C, Doughty J, et al. Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures. Neurology. 2007;68(15):1188–96.
13. Walbert T, Harrison RA, Schiff D, et al. SNO and EANO practice guideline update: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro Oncol. 2021;23(11):1835–44.
14. Dewan MC, Thompson RC, Kalkanis SN, et al. Prophylactic antiepileptic drug administration following brain tumor resection: results of a recent AANS/CNS Section on Tumors survey. J Neurosurg. 2017;126(6):1772–8.
15. Siomin V, Angelov L, Li L, Vogelbaum MA. Results of a survey of neurosurgical practice patterns regarding the prophylactic use of anti-epilepsy drugs in patients with brain tumors. J Neurooncol. 2005;74(2):211–5.
16. Inoue Y, Otsuki T, Nakamura H, et al. Efficacy, safety, and pharmacokinetics of fosphenytoin injection in Japanese patients. Rinshouiyaku. 2012;28(7):623–33.
17. Oushy S, Sillau SH, Ney DE, et al. New-onset seizure during and after brain tumor excision: a risk assessment analysis. J Neurosurg. 2018;128(6):1713–8.
18. Iuchi T, Kuwabara K, Matsumoto M, et al. Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study. J Neurol Neurosurg Psychiatry. 2015;86(10):1158–62.
19. Potschka H, Trinka E. Perampanel: does it have broad-spectrum potential? Epilepsia. 2019;60(Suppl 1):22–36.
20. Hibi S, Ueno K, Nagato S, et al. Discovery of 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (perampanel): a novel, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) receptor antagonist. J Med Chem. 2012;55(23):10584–600.
21. Patsalos PN. The clinical pharmacology profile of the new antiepileptic drug perampanel: a novel noncompetitive AMPA receptor antagonist. Epilepsia. 2015;56(1):12–27.
22. Kusakabe K, Inoue A, Watanabe H, et al. Perioperative perampanel administration for early seizure prophylaxis in brain tumor patients. Surg Neurol Int. 2023;14:287.
23. Chonan M, Saito R, Kanamori M, et al. Experience of low dose perampanel to add-on in glioma patients with levetiracetam-uncontrollable epilepsy. Neurol Med Chir (Tokyo). 2020;60(1):37–44.
24. French JA, Krauss GL, Wechsler RT, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial. Neurology. 2015;85(11):950–7.
25. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346: e7586.
26. (2020) Pharmaceuticals and Medical Devices Agency (PMDA). Fycompa prescribing information [Japanese].

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