# Cerebral Edema Due to Chemotherapeutic Wafer Implantation for Malignant Glioma: Registry Study of Correlation with Perioperative Epileptic Seizures

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## Abstract

**Factors predicting adverse events following implantation with wafers containing 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU), which is used in local chemotherapy for malignant gliomas (MGs), are unknown. The association between cerebral edema (CE), which often occurs after implantation, and perioperative seizures, which are often observed in MG cases, is under debate. This study investigated risk factors for CE associated with BCNU wafer implantation and their relationship with perioperative seizures. A total of 31 surgical cases involving 28 adult patients who underwent BCNU wafer implantation for MGs were investigated and classified into those with and without postoperative transient CE. We assessed the correlations between CE caused by BCNU implantation and various factors, including postoperative epileptic seizures. World Health Organization (WHO) grade III MGs significantly affected postoperative CE ($p$ = 0.003) and the occurrence of seizures ($p$ = 0.0004). Factors predictive of postoperative seizures were WHO grade III MGs ($p$ = 0.0026), increased postoperative CE ($p$ = 0.0272), and history of preoperative seizures ($p$ = 0.0316). Postoperative CE, WHO grade III MGs, and a history of preoperative seizures might predict the postoperative occurrence of seizures, necessitating stringent management of seizures and CE in the affected patients.**

Keywords: BCNU wafer, cerebral edema, glioma, seizure

## Introduction

Malignant gliomas (MGs) are one of the most common neoplasms affecting the central nervous system. The current standard therapy for MGs includes the Stupp protocol, which prescribes maximal safe resection of the tumor followed by radiotherapy and concomitant administration of temozolomide (TMZ).[1] However, the outcomes are unfavorable despite the implementation of all these treatment modalities. Recently, various trials have been conducted for the development of adjuvant therapy for MGs, including implantation of wafers releasing 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU), bevacizumab, tumor-treating fields, and photodynamic therapy, which have contributed to the improvement in outcomes of patients with MGs.[2] The BCNU wafer is inserted into the tumor bed after MG resection and is considered a local chemotherapeutic regimen effective against tumor cells invading the normal brain tissues around the resection cavity.[3] Some studies have found that the implantation of BCNU wafers confers a survival benefit compared with placebo wafers.[3,4] However, studies have reported some adverse events, such as brain edema, seizures, abnormal healing, infection, cerebrospinal fluid leakage, and thrombosis related to the implantation of BCNU wafers.[2,3,5-11] Postoperative edema and seizures have a major impact on the patient's prognosis

and activities of daily living. To the best of our knowledge, no study has investigated the relationship between cerebral edema (CE) caused by BCNU wafer implantation and perioperative epileptic seizures in MG. Here we focused on postoperative brain edema caused by the implantation of BCNU wafers and its relationship with the occurrence of postoperative seizures.

## Materials and Methods

### Patient population

Clinical and radiological data of consecutive patients diagnosed with MG based on intraoperative frozen sections, who underwent BCNU implantation between March 2013 and March 2019 at Shinshu University Hospital, was retrospectively extracted from our institutional database. Data on 35 surgical cases (32 patients) were collected initially. Three patients with insufficient postoperative magnetic resonance imaging (MRI) scans and one with cerebellar glioblastoma multiforme were excluded. Finally, 31 cases (28 patients: 18 men and 10 women) were analyzed. The tumor grade and pathological diagnoses were confirmed based on the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[12] The cases were divided into two groups based on the presence of CE (+, n = 9), caused by BCNU wafer implantation or absence (CE−, n = 22). CE was defined as a transient increase in high-intensity areas adjacent to the wares on fluid-attenuated inversion recovery (FLAIR) MRI within 2 months following surgery. Cases with progressive enlargement of the FLAIR abnormality more than 2 months following surgery were suspected of relapse and were included in the CE− group. Various factors, including age, sex, laterality, location, primary or secondary diagnosis, tumor pathology, frequency, duration of relapse, and occurrence of seizures, were compared between the CE+ and CE− groups to investigate each correlation. Patients with newly diagnosed MGs received adjuvant radiotherapy (60 Gy in 30 fractions) and concomitant TMZ therapy (75 mg/m$^2$/day) for 6 weeks, followed by maintenance TMZ therapy (150-200 mg/m$^2$/day for 5 consecutive days of a 28-day cycle), in accordance with the Stupp regimen.[1] Patients with recurrent MG received maintenance TMZ therapy. Dexamethasone and glycerol were administered until amelioration was achieved if the high-intensity area on the FLAIR image appeared aggravated on postoperative MRI. Perioperative antiepileptic therapy was routinely administered, irrespective of a history of epileptic seizures. Moreover, the study population was divided into patients who did or did not experience postoperative seizures to analyze the association between the occurrence of postoperative seizures and several factors such as preoperative seizure, WHO grade, CE, tumor location, number of BCNU wafers used, first/revision surgery, and extent of tumor resection. The clinical data were obtained from medical records. This study was approved by the institutional review board of Shinshu University (approval number: 4777), and informed consent was obtained from all patients or their families.

### Quantitative analysis of cerebral edema

MRI was performed before surgery, within 72 h after surgery, and at 2 weeks, 1 month, and 2 months after surgery. Volumetric analysis for CE was conducted using a dedicated workstation (iPlan Station, Cranial surgical planning software; Brainlab AG, Feldkirchen, Germany). Manual segmentation was performed with region-of-interest analysis to measure tumor volumes in cm$^3$ based on the axial FLAIR and contrast-enhanced T1-weighted MRI scans (Fig. 1). CE volume was calculated by subtracting the volume of the tumor or resection cavity from the volume of the high-intensity region on FLAIR. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf) was used to assess the adverse clinical events related to BCNU wafer implantation.

### Statistical analyses

All statistical analyses were performed using the free EZR statistical software (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html). All $p$-values <0.05 were considered significant.

## Results

### Patient presentation and clinical data

The participants' clinical status and surgical results are presented in Table 1. Cerebral edema occurred due to BCNU wafer implantation in nine cases, which were classified into the CE+ group. All CE+ cases had a CTCAE grade of 3. The age of patients ranged from 30 to 91 years (mean ± standard deviation, 56.2 ± 17.4 years). Of the 31 cases, 12 (39%) were observed in women. Histopathologically, the tumors included glioblastoma IDH wild type (n = 15), glioblastoma IDH mutant (n = 4), glioblastoma NOS (n = 4), anaplastic astrocytoma IDH mutant (n = 1), anaplastic astrocytoma IDH wild type (n = 3), anaplastic astrocytoma NOS (n = 1), anaplastic oligodendroglioma IDH mutant, 1p/19q codeleted (n = 2), and anaplastic oligodendroglioma NOS (n = 1). Nineteen tumors revealed MGMT methylation and four tumors were unmethylated (data not available of the four tumors). The chief sites of the tumors were in the frontal (16; 51.6%), temporal (9; 29.0%), parietal (4; 12.9%), and occipital lobes (2; 6.5%). The number of implanted BCNU wafers ranged from 1 to 8 (mean, 6.1). Twenty-four cases (77.4%) were initially diagnosed as high-grade gliomas and seven (22.6%) as recurrent high-grade gliomas. Complete tumor resection was performed during 20 (64.5%) surgeries, subtotal resection during 7 (22.6%), and partial resection during 4 (12.9%). Relapse of the tu-
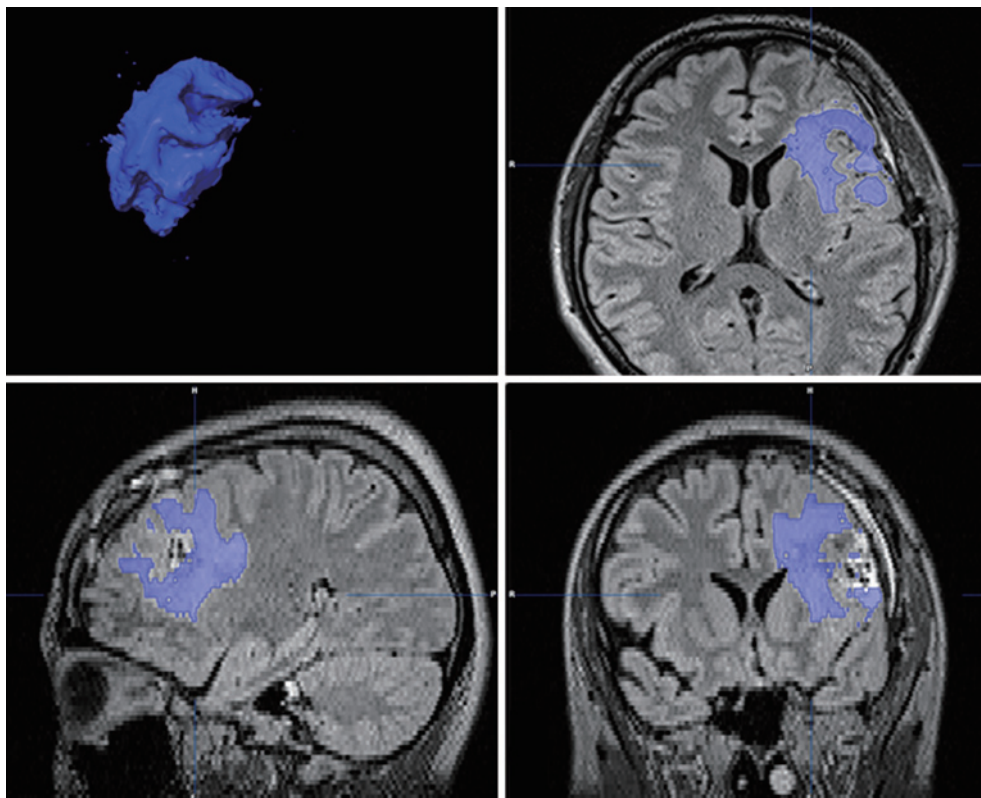
**Fig. 1 Volumetric analysis of cerebral edema (blue) by segmentation of the high-intensity volume surrounding the tumor on FLAIR MRI. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.**

mor was observed in 19 cases (61.3%), and the mean duration to relapse was 7.7 months. WHO grade III MGs significantly affected postoperative CE ($p$ = 0.003). On the other hand, neither status of the IDH mutation ($p$ = 1) nor MGMT methylation ($p$ = 0.273) affected the postoperative CE.

**Correlation between postoperative cerebral edema and seizures**

In the CE+ group, there were five cases (55.6%) of postoperative partial seizures, all of which had a history of preoperative seizures (Table 2). In these five cases, the types of preoperative seizure were partial seizures in three cases and generalized seizures in the remaining two cases. In the CE+ group, new-onset seizures did not occur after surgery. One patient with a history of preoperative general seizures did not experience any postoperative seizures. In the CE– group, there were three cases (13.6%) of postoperative seizures, although only one of these had a history of preoperative seizures. The case with preoperative and postoperative seizures had both partial seizures. On the other hand, two cases with only postoperative seizures experienced generalized seizures. Thus, there were two cases (9.1%) of new seizures after surgery and five cases (22.7%) of preoperative seizures without postoperative seizures. Therefore, although the occurrence of preoperative seizures was

higher in the CE+ group than in the CE– group, the difference was not significant ($p$ = 0.051). However, the occurrence of postoperative seizures was significantly higher in the CE+ group than in the CE– group ($p$ = 0.0272). Although generalized seizures were frequently observed postoperatively in the CE+ group, all the postoperative seizures were partial seizures. Levetiracetam was mainly used as the antiepileptic drug. In the two cases of CE+ group with refractory epilepsy, perampanel was added.

**Comparison between seizures and histopathology**

As shown in Table 3, a comparison revealed that perioperative seizures occurred in all 8 cases (100%) with WHO grade III tumors and in 6 (26.1%) of 23 cases with WHO grade IV tumors, and this difference was significant ($p$ = 0.0004). All cases with WHO grade III tumor and postoperative seizures experienced preoperative seizures. None of the cases in this group experienced new seizures after surgery. However, postoperative seizures were observed in three cases (13.0%) with WHO grade IV tumors, of which two (8.7%) experienced new seizures after surgery. The occurrence of postoperative seizures was significantly higher in grade III MGs than in grade IV MGs ($p$ = 0.0135).

**Table 1**  Demographic data in patients with or without postoperative cerebral edema due to BCNU wafer implantation

| | Number N = 31 | Cerebral edema | | p-value |
| --- | --- | --- | --- | --- |
| | | CE+ (N = 9) | CE− (N = 22) | |
| Sex | | | | 0.253 |
| Male (%) | 19 (61) | 4 | 15 | |
| Female (%) | 12 (39) | 5 | 7 | |
| Mean age (years) | 56.2 | 49.0 | 59.1 | 0.122 |
| Laterality | | | | 1 |
| Right (%) | 18 (58.1) | 5 | 13 | |
| Left (%) | 13 (41.9) | 4 | 9 | |
| Tumor location | | | | 0.113 |
| Frontal lobe (%) | 16 (51.6) | 7 | 9 | |
| Temporal lobe (%) | 9 (29.0) | 0 | 9 | |
| Parietal lobe (%) | 4 (12.9) | 2 | 2 | |
| Occipital lobe (%) | 2 (6.5) | 0 | 2 | |
| Tumor grade | | | | 0.003* |
| WHO grade III (%) | 8 (25.8) | 6 | 2 | |
| WHO grade IV (%) | 23 (74.2) | 3 | 20 | |
| No. of BCNU wafers used (sheets, range) | 6.1 | 6.2 (4–8) | 6.3 (2–8) | 0.822 |
| Diagnosis | | | | 1 |
| Initial (%) | 24 (77.4) | 7 | 17 | |
| Recurrent (%) | 7 (22.6) | 2 | 5 | |
| Relapse (%) | 19 (61.3) | 6 | 13 | 1 |
| Duration of relapse (months) | 7.7 | 8.8 | 7.2 | 0.478 |

\* $p < 0.05$, Fisher's exact test
Abbreviations: BCNU, 1,3-bis [2-chloroethyl]-1-nitrosourea; CE, cerebral edema; WHO, World Health Organization

**Table 2**  Comparison of seizure with or without cerebral edema

| | Cerebral edema | | p-value |
| --- | --- | --- | --- |
| | CE+ (N = 9) | CE− (N = 22) | |
| Without seizure | 3 | 14 | |
| With seizure | 6 | 8 | 0.233 |
| Preoperative | 6 | 6 | 0.051 |
| Postoperative | 5 | 3 | 0.0272* |

\*$p < 0.05$, Fisher's exact test
Abbreviations: CE, cerebral edema

**Table 3**  Comparison of seizures between WHO grades III and IV

| | WHO grade | | p-value |
| --- | --- | --- | --- |
| | Grade III (N = 8) | Grade IV (N = 23) | |
| Without seizure | 0 | 17 | |
| With seizure | 8 | 6 | 0.0004* |
| Preoperative | 8 | 4 | 0.0001* |
| Postoperative | 5 | 3 | 0.0135* |

\* $p < 0.05$, Fisher's exact test
Abbreviations: WHO, World Health Organization

**Relationship between rate of change of cerebral edema and seizures**

In the CE+ group, there were five cases of perioperative seizures and four cases of no seizures (Table 4 and Fig. 2). The mean rate of increase in the severity of CE was 354% in cases with seizures and 212% in cases without seizures, although this difference was not significant ($p = 0.866$).

**Predictive factors associated with postoperative seizures**

The WHO grade ($p = 0.0135$) and history of preoperative seizures ($p = 0.0316$) were significantly correlated with the occurrence of postoperative seizures (Table 5). However, the other factors we examined were not significantly correlated with the occurrence of postoperative seizures.

**Table 4 Increase in cerebral edema and perioperative seizures**

| | CE with seizure (N = 5) | CE without seizure (N = 4) | *p*-value* |
|---|---|---|---|
| POD 1 FLAIR HIA (mean, cm³) | 25.4 | 45.6 | |
| Maximum FLAIR HIA (mean, cm³) | 61.1 | 84.1 | |
| Increase rate (mean, %) | 354 | 212 | 0.886 |

*Mann–Whitney U test
Abbreviations: CE, cerebral edema; FLAIR, fluid-attenuated inversion recovery; POD, postoperative day; HIA, high-intensity area

## Discussion

**Brain edema due to implantation of BCNU wafers**

The implantation of BCNU wafers following tumor resection is an approved treatment modality for newly diagnosed or recurrent MG that can prolong a patient's survival.[6] However, the occurrence of adverse events related to the procedure is well established.[2,3,5-11] CE is the most frequent of these events, although its incidence varies across several studies, ranging from 2.1% to 37.5%. Moreover, 3%-17% of patients with BCNU wafer implantation have marked symptoms such as new neurological deficits, altered mental status, and newly diagnosed seizures or require readmission.[3,5-7]

Risk factors for postoperative CE caused by BCNU wafer implantation have not been elucidated. In this study, postoperative brain edema was not correlated with sex, age, tu-
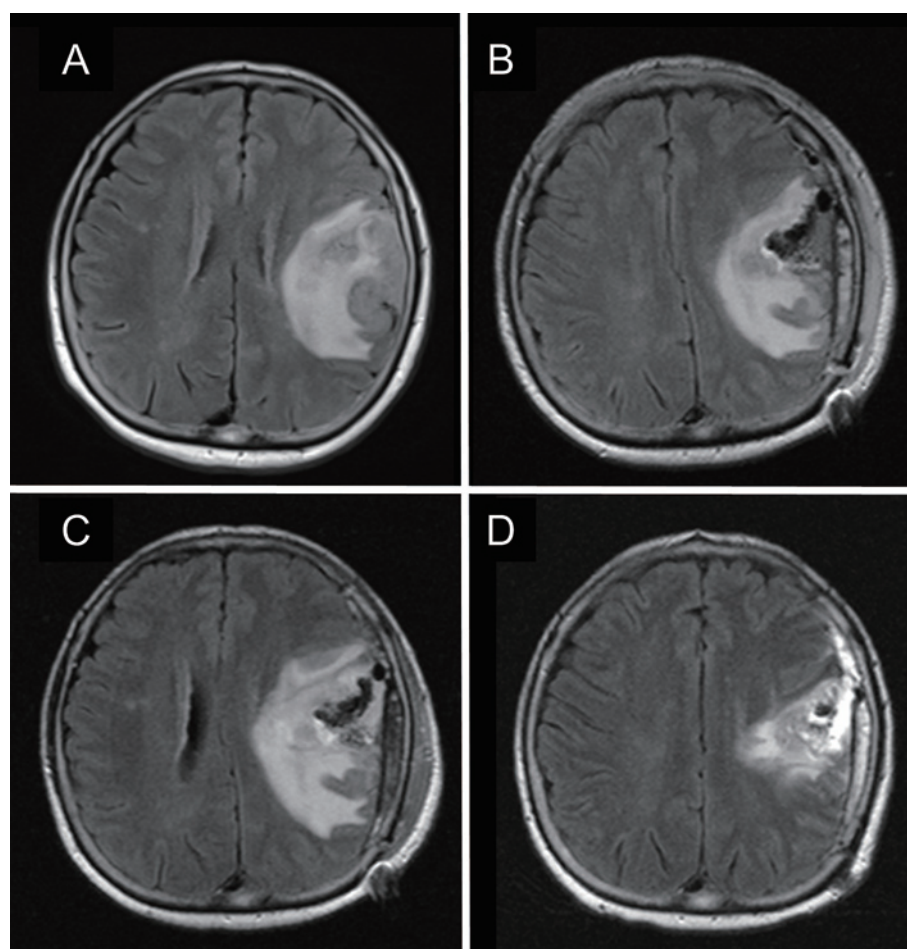


**Fig. 2 FLAIR MRI of an illustrative case featuring prolongation of cerebral edema (CE). (a) The patient is a 65-year-old woman presenting with right hemiparesis; MRI reveals a left parietal tumor with CE. (b) Two days after partial resection of the tumor and implantation of eight sheets of carmustine (BCNU) wafers, FLAIR reveals a residual high-intensity area (volume = 78.3 cm³) around the resection cavity. (c) MRI acquired 7 days after surgery reveals an increase in the area of high-intensity FLAIR (volume = 127.9 cm³, 163% of baseline). (d) Follow-up MRI acquired 45 days after surgery reveals a reduction in the volume of the CE. Neither preoperative nor postoperative seizures were observed in this patient. FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; BCNU, 1,3-bis (2-chloroethyl)-1-nitrosourea.**

**Table 5   Demographic data in patients with or without postoperative seizure**

|  | Number (N = 31) | With postoperative seizure (N = 8) | Without postoperative seizure (N = 22) | p-value |
|---|---|---|---|---|
| Sex |  |  |  | 0.206 |
|   Male (%) | 19 (61) | 3 | 16 |  |
|   Female (%) | 12 (39) | 5 | 7 |  |
| Mean age (years) | 56.2 | 51.9 | 57.7 | 0.425 |
| Side of tumor |  |  |  | 0.689 |
|   Right (%) | 18 (58.1) | 4 | 14 |  |
|   Left (%) | 13 (41.9) | 4 | 9 |  |
| Tumor location |  |  |  | 0.685 |
|   Frontal lobe (%) | 16 (51.6) | 5 | 11 |  |
|   Temporal lobe (%) | 9 (29.0) | 1 | 8 |  |
|   Parietal lobe (%) | 4 (12.9) | 2 | 2 |  |
|   Occipital lobe (%) | 2 (6.5) | 0 | 2 |  |
| Tumor grade |  |  |  | 0.0135* |
|   WHO grade III (%) | 8 (25.8) | 5 | 3 |  |
|   WHO grade IV (%) | 23 (74.2) | 3 | 20 |  |
| Number of BCNU wafer (sheets, range) | 6.1 | 5.5 (4–8) | 6.3 (2–8) | 0.317 |
| Diagnosis |  |  |  | 1 |
|   Initial (%) | 24 (77.4) | 6 | 18 |  |
|   Recurrent (%) | 7 (22.6) | 2 | 5 |  |
|   Relapse (%) | 19 (61.3) | 5 | 14 | 1 |
| Duration of relapse (months) | 7.7 | 7.2 | 7.9 | 0.87 |
| With preoperative seizure (%) | 12 (38.7) | 6 (75.0) | 6 (27.3) | 0.0316* |

* $p < 0.05$, Fisher's exact test

Abbreviations: BCNU, 1,3-bis [2-chloroethyl]-1-nitrosourea; WHO, World Health Organization

mor location, or the number of BCNU wafers implanted; this result is consistent with previous studies.[3,6] Moreover, patients with non-glioblastomatous MGs (i.e., anaplastic astrocytoma and anaplastic oligodendroglioma) were significantly more likely to develop postoperative CE than were the patients with glioblastomas in our study. van Breemen et al. reported that slow-growing tumors might induce epileptogenesis by causing partial deafferentation of the nearby brain cortex (denervation hypersensitivity) and altering neurotransmitter release and local metabolism. Moreover, rapidly progressive brain tumors presumably induce epilepsy through abrupt methods of tissue damage, such as tissue necrosis or hemosiderin deposition. However, they could not find a clear association between seizure frequency and CE owing to tumor mass.[13] Therefore, the histopathology of the lesion might be associated with CE caused by BCNU wafer implantation, which should be investigated in further research.

Although brain edema is clearly exacerbated following BCNU wafer implantation, two different underlying mechanisms have been postulated; however, they remain unclear: (1) the formation of necrotic debris induced by carmustine and convective flow and (2) vasogenic edema induced by surgery causing an enhanced distribution of carmustine with subsequent cytotoxicity.[3] Therefore, appropriate management of brain edema is essential. Brain edema is often controlled using intensive perioperative treatment with diuretics and corticosteroids; however, severe delayed CE often causes permanent morbidity even with intensive care. In our study, postoperative CE was observed in 9 of 31 cases (29.0%); however, the condition of all patients improved with the administration of dexamethasone and glycerol without any morbidity related to CE. Although this type of edema is usually well controlled with preoperative and postoperative medical management, there are side effects of the long-term use of corticosteroids, including an immunocompromised state, hypertension, and hyperglycemia. Moreover, the implantation of BCNU wafers in eloquent areas is controversial, and we believe that tumors located in these areas are unfavorable for BCNU wafer implantation due to the possibility of brain swelling. Conversely, some studies have reported that with strict management, BCNU wafer implantation can be recommended even in eloquent areas.[3]

Although the quantitative measurement of high-intensity areas on FLAIR was a valuable method to determine the

volume of CE in our study, the area of high-intensity FLAIR is not always representative of the CE caused by BCNU wafer implantation due to confounders such as cerebral contusion, venous edema, and tumor infiltration. Therefore, the difficulty in assessing postoperative CE is a major hurdle in studies on this subject. Moreover, brain edema can be caused by tumor resection, the MGs themselves, and steroids; therefore, a meticulous evaluation of brain edema is necessary. Such difficulties and limitations on CE research should be addressed in future studies.

**Seizures in glioma surgery**

The prevalence of epilepsy in patients with gliomas has varied across studies. Lote et al.[14] reported that the prevalence of epilepsy in patients with histological intracranial gliomas varied with patient age and tumor histology, and prevalence was greatest in low-grade tumors. However, Yoshida et al.[8] found no association between seizure incidence and glioma grade. We focused on the correlations between postoperative CE caused by BCNU wafer implantation and seizures. Moreover, the occurrence of perioperative seizures was significantly higher in patients with WHO grade III tumors than in those with glioblastoma in our study.

Postoperative seizures associated with BCNU wafer implantation are among the drawbacks of MG therapy. Seizures are reported in 5.8% (range, 1.0%-43.0%) of MG cases during the postoperative period.[15] Della Puppa et al.[15] stated that preoperative epilepsy could be a risk factor for seizures in patients treated with BCNU wafers, and some studies have reported that seizure risk is >30% in these patients. Anticonvulsant therapy is usually recommended for all patients scheduled to undergo BCNU wafer implantation. Aoki et al.[2] reported that seizures are complications of brain tumors and neurosurgical interventions but found no difference between the BCNU-implant and placebo groups with respect to the overall incidence of seizures. Although our study did not investigate a direct relationship between BCNU implantation and epileptic seizures, 8 of 31 cases (25.8%) of BCNU implantation during tumor resection included patients who experienced postoperative epileptic seizures, despite the administration of anticonvulsant medication before surgery.

Della Puppa et al.[15] also failed to find a significant association between seizures and the extent of resection, first versus revision surgery, type of antiepileptic drug administered (old-generation versus new-generation antiepileptic drugs), or the median number of implanted wafers. We found that the presence of WHO grade III tumors, postoperative CE, and a history of preoperative seizures were significant predictive factors for the occurrence of postoperative seizures. Other factors were not significantly correlated in our study. Despite the importance of the occurrence of perioperative seizures in MG surgery, studies that specifically focus on seizures and their possible risk factors

among BCNU wafer-treated patients are lacking. We believe that this study is valuable because we investigated perioperative seizures occurring in MG surgery in greater detail than did previous research by studying preoperative and postoperative seizures separately.

This study has some limitations. The small sample size may have affected the results. Moreover, the dose or type of antiepileptic drug administered (old versus new generation) was not considered here, despite a difference in the pharmacotherapeutic effect. Further, it was difficult to determine whether the FLAIR abnormality represented brain edema or an infiltrative tumor; however, we judge that the volumetric analysis of CE employed in our study was valuable. Moreover, the patients in our study were not uniform. Our cohort included WHO grade III and IV and initial and recurrent cases. Nevertheless, the patients in the previous reports were also heterogeneous. Further studies with larger cohorts are needed to confirm the precise correlations between CE caused by BCNU wafer implantation and perioperative epileptic seizures in MG cases.

In conclusion, the presence of WHO grade III tumors, postoperative CE, and a history of preoperative seizures may be predictors of the occurrence of postoperative seizures in patients with BCNU wafer implants. WHO grade III tumors were also an important factor associated with postoperative CE due to BCNU wafer implantation. Therefore, such patients require stringent management of seizures and CE.

## Abbreviations

BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea
CE, cerebral edema
CTCAE, Common Terminology Criteria for Adverse Events
FLAIR, fluid-attenuated inversion recovery
MG, malignant glioma
MRI, magnetic resonance imaging
TMZ, temozolomide
WHO, World Health Organization

## Funding Information

## Data Availability

Not applicable

## Ethics Declarations

All procedures performed in this study were in accordance with the ethical standards of the institutional and/

or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the institutional review board of Shinshu University (approval number: 4777), and informed consent was obtained from all patients or their families.

## Author Contributions

Yu Fujii and Toshihiro Ogiwara contributed equally to this work.

## Conflicts of Interest Disclosure

The authors declare no competing interests.

## References

1) Stupp R, Mason WP, van den Bent MJ, et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987-996, 2005
2) Aoki T, Nishikawa R, Sugiyama K, et al.: A multicenter phase I/II study of the BCNU implant (Gliadel(Ⓡ) Wafer) for Japanese patients with malignant gliomas. *Neurol Med Chir (Tokyo)* 54: 290-301, 2014
3) Murai S, Ichikawa T, Kurozumi K, et al.: Quantitative analysis of brain edema in patients with malignant glioma treated with BCNU wafers. *J Clin Neurosci* 33: 148-153, 2016
4) McGirt MJ, Than KD, Weingart JD, et al.: Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. *J Neurosurg* 110: 583-588, 2009
5) Bock HC, Puchner MJA, Lohmann F, et al.: First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: a multicenter experience. *Neurosurg Rev* 33: 441-449, 2010
6) Masuda Y, Ishikawa E, Yamamoto T, et al.: Early postoperative expansion of parenchymal high-intensity areas on T2-weighted imaging predicts delayed cerebral edema caused by carmustine wafer implantation in patients with high-grade glioma. *Magn Reson Med Sci* 15: 299-307, 2016
7) Sabel M, Giese A: Safety profile of carmustine wafers in malignant glioma: a review of controlled trials and a decade of clinical experience. *Curr Med Res Opin* 24: 3239-3257, 2008
8) Yoshida M, Yamaguchi S, Ishi Y, et al.: Risk factors for adverse events after implantation of BCNU wafers in high-grade gliomas. *No Shinkei Geka* 43: 603-610, 2008
9) Nishikawa R, Iwata H, Sakata Y, Muramoto K, Matsuoka T: Safety of Gliadel implant for malignant glioma: report of post-marketing surveillance in Japan. *Neurol Med Chir (Tokyo)* 61: 536-548, 2021
10) Della Puppa A, Rossetto M, Ciccarino P, et al.: The first 3 months after BCNU wafers implantation in high-grade glioma patients: clinical and radiological considerations on a clinical series. *Acta Neurochir (Wien)* 152: 1923-1931, 2010
11) Giese A, Bock HC, Kantelhardt SR, Rohde V: Risk management in the treatment of malignant gliomas with BCNU wafer implants. *Cent Eur Neurosurg* 71: 199-206, 2010
12) Louis DN, Perry A, Reifenberger G, et al.: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 131: 803-820, 2016
13) van Breemen MS, Wilms EB, Vecht CJ: Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol* 6: 421-430, 2007
14) Lote K, Stenwig AE, Skullerud K, Hirschberg H: Prevalence and prognostic significance of epilepsy in patients with gliomas. *Eur J Cancer* 34: 98-102, 1998
15) Della Puppa A, Denaro L, Rosetto M, et al.: Postoperative seizure in high grade glioma patients treated with BCNU wafers. A mono-institutional experience. *J Neurooncol* 105: 275-280, 2011

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