

# Double-edged Sword in the Placement of Carmustine (BCNU) Wafers along the Eloquent Area: A Case Report

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Although direct Gliadel® wafer implantation into the resection cavity has been shown to significantly improve survival in patients with high-grade gliomas, several complications have been associated with the implantations of Gliadel wafers, including brain edema, healing delay, cerebral spinal fluid leak, intracranial infections, and cyst formation. The brain edema that is associated with Gliadel wafer implantation might result in neurological deficits and significant morbidities and mortalities. In particular, it is not clear if they should be placed in the eloquent areas, such as language areas, motor areas, and areas related to cognitive function, even if these areas contain a remnant tumor. Here, we present a case of profound brain edema along the pyramidal tract due to Gliadel wafer implantation, which resulted in severe neurological deficits. This treatment represents a double-edged sword due to the possibility of severe symptomatic brain edema along the eloquent area, even though Gliadel wafers might be effective in controlling local tumor growth. We should keep in mind that Gliadel wafer placement in eloquent areas may result in severe disadvantages to patients and a loss of their quality of life.

**Keywords:** Gliadel wafer, brain edema, eloquent area, pyramidal tract

## Introduction

Malignant gliomas are the most common brain tumors in the primary central nervous system in adults.<sup>1</sup> An international randomized trial comparing treatments with radiotherapy alone or with concomitant radiotherapy and temozolomide for high-grade gliomas has demonstrated a significant improvement in median survival with temozolomide.<sup>2,3</sup> Since then, the systemic administration of temozolomide has been the current first-line chemotherapeutic agent for high-grade gliomas.<sup>2</sup> Nevertheless, the prognosis remains very poor due to the limited therapeutic efficacy.

Adjuvant local chemotherapy has been increasingly used to treat high-grade gliomas. Gliadel® wafers (Eisai Co., Ltd., Tokyo) that are loaded with carmustine (bis-chloroethylnitrosourea, BCNU) are often lined along the wall of the resection cavity following tumor resection. Carmustine is released continuously, and it diffuses into the parenchyma with a peak release in one week.<sup>4-7</sup> Gliadel wafers implanted during

surgery have a statistically significant survival advantage as shown in the placebo-controlled study by Brem et al.<sup>8</sup> Whestphal et al. also demonstrated the overall survival in patients with Gliadel wafer implantation for primary malignant gliomas was 13.9 months compared to 11.6 months in the placebo group.<sup>9</sup>

The principle advantages of local drug administration are higher local drug concentrations and fewer systemic side effects. However, several studies have reported the risk of local complications, such as wound healing delay, brain edema, convulsions, and cyst formation.<sup>10-16</sup> While the introduction of Gliadel wafers into the tumor resection cavity has been shown to be a beneficial therapy for malignant gliomas, it should be recognized that clinically significant brain edema is one of the potential adverse effects. This brain edema that is associated with the implantation of Gliadel wafers might lead to neurological deficits and significant morbidities and mortalities.<sup>17</sup> In particular, it is unclear if they should be placed in the eloquent areas, such as language areas and motor areas,<sup>8,9,17-19</sup> if a tumor was left in those regions after surgery. Many neurosurgeons will want to put them in the eloquent areas after tumor resection because tumors left in these areas cannot be removed later.

Here, we describe a clinical case who demonstrated profound brain edema in the precentral gyrus and pyramidal tract that was apparently caused by Gliadel wafer implantation. This brain edema led to extended hospitalization and transient significant motor dysfunction. Gliadel wafer-induced brain edema might cause the severe morbidity that has been observed after tumor resections of eloquent areas, even though the Gliadel wafers themselves might provide better local tumor control.

## Case Report

### I. History and neuroimaging findings

A 47-year-old right-handed woman presented in August 2008 due to occasional seizure attacks. She was admitted to the neurosurgical department at a nearby hospital. Magnetic resonance imaging (MRI) of her brain disclosed a marked tumor lesion that was located in the right superior frontal gyrus, which involved mainly the supplementary motor area (SMA) and the white matter beneath it. She underwent the first surgery while she was under general anesthesia at that hospital in September 2008. The tumor was completely resected, and she was diagnosed with a World Health Organization grade-II diffuse astrocytoma. Subsequently, she was followed at an outpatient ward, and she did not receive any

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Received: January 30, 2014; Accepted: June 22, 2014

chemoradiotherapy because gross total resection of the tumor had been achieved.

Five years after the first surgery, however, areas of high intensity on T<sub>2</sub>-weighted images were observed to be gradually progressing, and they extended around the tumor resection cavity. Therefore, she was referred to our department because recurrence of the tumor was strongly suspected. No apparent neurological deficits were observed in the physical examination that was performed at the time of admission. Further review of her systems, previous medical history, and family history were noncontributory. In addition, postoperatively, the patient developed a seizure disorder that was well controlled with medical management with antiepileptic drugs.

An MRI study confirmed the presence of a well-defined area of high intensity on T<sub>2</sub>-weighted images, and the area contacted the margin of the right precentral gyrus (Fig. 1A). A significant and partially enhanced lesion was found in the SMA-proper area with T<sub>1</sub>-weighted MRI with gadolinium enhancement (arrow in Fig. 1B). The area with the highest uptake in a positron emission tomography (PET) scan with L-[methyl-11C] methionine (11C-MET) was in the superficial and medial part of the lesion (arrowhead in Fig. 1C), which corresponded largely with the enhanced area that was seen on MRI.

## II. Surgery

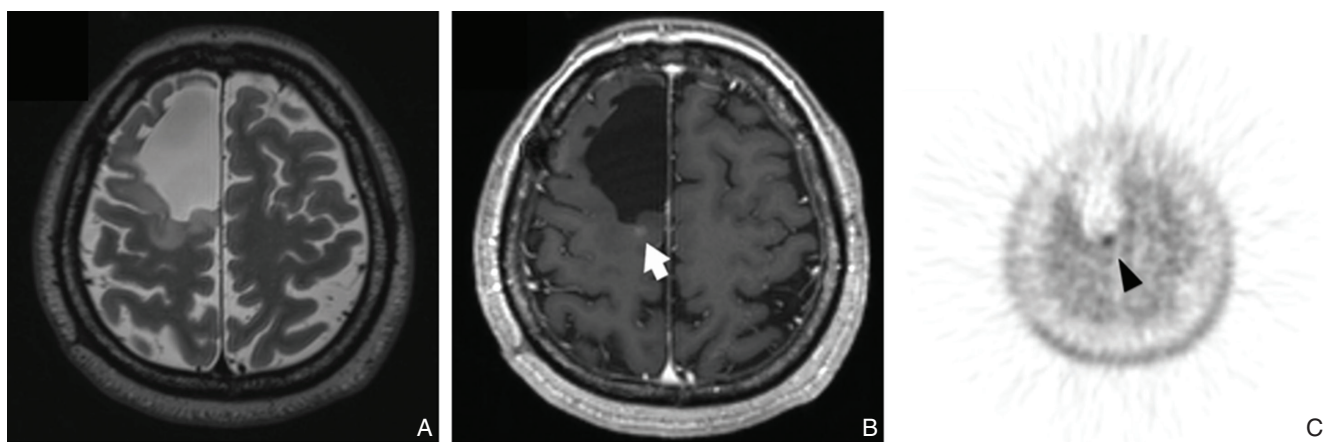
In June 2013, tumor removal was performed through the same approach that was used in the first surgery. Electrophysiological monitoring systems, which included somatosensory-evoked potential (SEP) monitoring and intermittent motor-evoked potential (MEP) monitoring, were used in this patient.

First, we removed the tumor at the anterior and lateral parts of the cavity wall, as these regions are relatively safer to resect compared to sites that are close to the pyramidal tract. Next, we carefully resected the tumor along the

precentral gyrus and pyramidal tract with the frequent use of direct subcortical MEP monitoring with a bipolar stimulator (Unique Medical Co., Ltd., Osaka). Similar to the cortical stimulation, a short train of high-frequency pulses was used (500 Hz; duration, 0.4 ms; train, 5). When direct subcortical stimulation with a 10-mA amplitude produced responses in the left four muscles of the upper and lower extremities, tumor resection was stopped, and the first intraoperative MRI was performed. We made use of an operation theater (Brain THEATER) that was equipped with a 0.4-Tesla intraoperative MRI and neuronavigational system. Because of the small remnants of the tumor that were in the deep side of the cavity, tumor resection was performed until a response was identified by direct subcortical stimulation with a 5-mA amplitude. A second intraoperative MRI demonstrated gross total removal of the tumor and no other ischemic abnormalities around the tumor cavity. Therefore, five Gliadel wafers were implanted on the precentral gyrus and anterior side of the pyramidal tract because we concluded that further resection of these areas would not be possible if tumor recurrence occurred (Fig. 2). Transcortical MEP monitoring with 20-mA stimulation showed a continuously favorable response until the end of the surgical resection. The intraoperative histologic examinations of the resected tumor resulted in a diagnosis of a World Health Organization grade-III anaplastic astrocytoma, which suggested that malignant transformation of the grade-II diffuse astrocytoma had occurred.

## III. Postoperative course

Postoperative MRI showed that localized areas of high intensity on T<sub>2</sub>-weighted images appeared along the pyramidal tracts where the Gliadel wafers had been placed (Fig. 3A). Because these areas did not exhibit high intensity on diffusion-weighted MRI scans (Fig. 3B), focal edema was strongly suspected to have been directly caused by the Gliadel wafer placement and not by ischemic changes resulting from the surgical procedure. Subsequently,



**Fig. 1** Preoperative axial T<sub>2</sub>- (A) and axial T<sub>1</sub>-weighted magnetic resonance imaging (MRI) with gadolinium enhancement (B) show a high-intensity area around the resection cavity of the first surgery and enhanced areas (arrow) inside the mass lesion, respectively. (C) L-[methyl-11C] methionine (11C-MET) positron emission tomography (PET) clearly shows relatively regular high uptake inside the superficial and medial parts of the lesion (arrowhead).

intensive treatment with corticosteroids and osmotic diuretic glycerol was immediately started. However, the severe left hemiplegia was not changed despite the intensive treatment. On postsurgical MRIs that were performed on postoperative days 4, 20, 29, 36, and 47 (Figs. 3, 4), the focal edema that was localized to the precentral gyrus reduced gradually. At the same time, her hemiparesis recovered by slow degrees. Almost one and a half months after the surgery, she eventually was able to walk and raise her left hand without any help and she was discharged by herself after 2 months.

**Discussion**

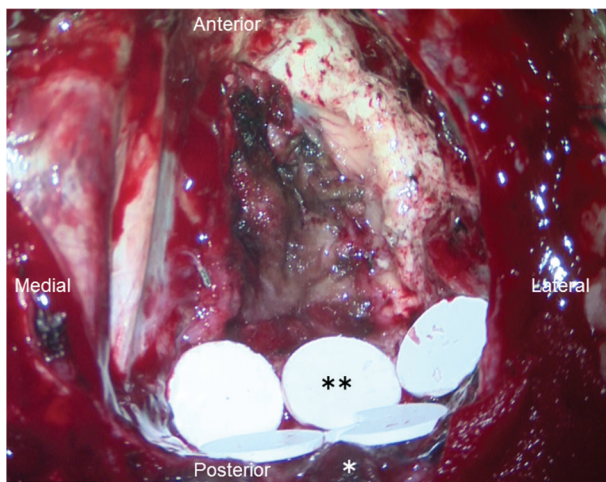
The goal of malignant glioma surgery is to achieve the maximum extent of surgical resection (cytoreduction, reduction in mass) without causing new neurological deficits. In particular, tumor resections in eloquent brain areas are frequently terminated before total tumor removal in order

to reduce the risks of neurological deficits. From a neuro-oncological point of view, however, remnant tumors in eloquent areas should be controlled by other treatments, such as radiation or chemotherapy. Although malignant gliomas are a diffuse disease process, most recurrences occur within 2 cm of the resection margin.<sup>20,21</sup> Local tumor control may not provide a cure, but it may extend the survival term and even improve the quality of life. Gliadel wafer therapy has been devised as a way to treat the tumor resection cavity and the adjacent infiltrated brain directly. Implantable chemotherapeutic devices, such as Gliadel wafers, allow for continuous local chemotherapeutic agent delivery within the blood-brain barrier, thus avoiding adverse systemic reactions.

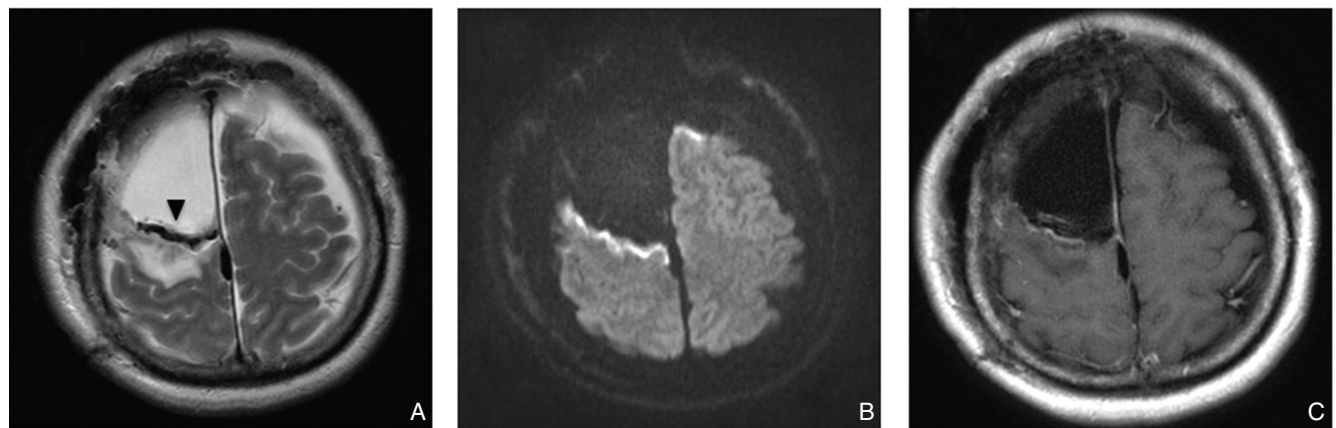
Gliadel wafer implantation directly into the tumor resection cavity and subsequent radiation therapy have been shown to significantly improve survival in patients with newly diagnosed malignant gliomas.<sup>9</sup> However, several complications have been associated with the implantation of Gliadel wafers, including brain edema, healing abnormalities, cerebral spinal fluid leaks, intracranial infections, seizures, hydrocephalus, and cyst formation.<sup>4-6,10,11,13,16</sup> The rate of these adverse events have been well established in the following randomized phase-III trials that tested Gliadel wafers compared to placebo wafers.<sup>8,9</sup>

In a phase-III study of 222 patients with recurrent malignant gliomas, Brem et al.<sup>8</sup> have reported that all patients experienced cerebral edema during the study, as is typical for postoperative craniotomy patients, and that all patients received postsurgical corticosteroid treatment. There were no significant differences in the steroid requirements among the three groups: patients in Group 1 were treated with 3.85 mg of BCNU/wafer, those in Group 2 were treated with 7.7 mg of BCNU/wafer, and those in Group 3 were treated with 12.7 mg of BCNU/wafer.

However, in the phase-III trial of Whestphal et al., which enrolled 240 patients with primary malignant gliomas, the overall incidence of serious brain edema was more common with BCNU wafer treatment (27 out of 120; 22.5%)

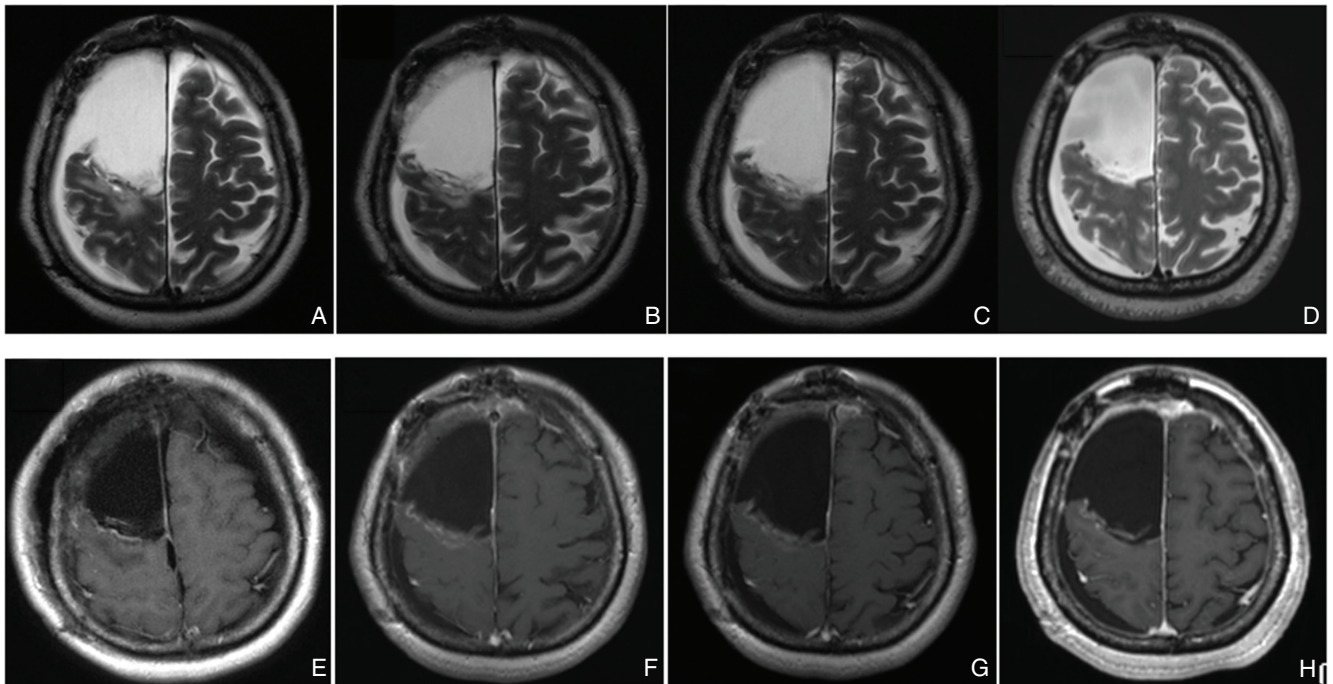


**Fig. 2** Intraoperative photograph taken after tumor resection and placement of the Gliadel wafers. The Gliadel wafers (\*\*\*) were implanted on the precentral gyrus and anterior side of the pyramidal tract (\*).



**Fig. 3** Postoperative day 4 axial T<sub>2</sub>-weighted magnetic resonance imaging (MRI) scans (A) show localized high intensity areas along the pyramidal tracts where Gliadel wafers were placed and a very low-intensity area (arrowhead) that was suspected to be Gliadel wafers. Postoperative day 4 diffusion-weighted MRI scans (B) and T<sub>1</sub>-weighted MRI with gadolinium enhancement (C) show areas of high intensity in the anterior part of the right precentral gyrus.





**Fig. 4** Postoperative axial T<sub>2</sub>-weighted magnetic resonance imaging (MRI) scans and T<sub>1</sub>-weighted MRI with gadolinium enhancement performed on day 20 (A, E), day 29 (B, F), day 36 (C, G), and day 47 (D, H). The high-intensity area of T<sub>2</sub>-weighted images in the right precentral gyrus gradually reduced and disappeared on day 47. T<sub>1</sub>-weighted MRI with gadolinium enhancement show that enhancing areas also gradually reduced through the postoperative course.

compared to placebo (23 out of 120, 19.2%), although the difference was not statistically significant.<sup>9)</sup> In contrast, a study that was published by Olivi et al. has assessed the effects of escalating doses (ranging from 6.5% to 28% BCNU) of BCNU wafers on recurrent malignant gliomas in 44 adults. Only at the level of 28% BCNU did severe morbidity result as an individual developed anoxic brain injury. As dosing levels were increased, the complications of cerebral edema increased. One patient required reoperation and polymer removal with subsequent clinical improvement of the brain edema. It appeared clear that the dose was associated with dose-limiting toxicity.

These three studies, however, never described the details of the frequency of symptomatic brain edema and the timing of this edema occurrence relative to Gliadel wafer placement. Moreover, there were no data on whether they should be placed in the eloquent areas, such as language areas, motor areas, and areas related to cognitive function.<sup>8,9,17–19)</sup>

Although few studies have reported serious symptomatic brain edema that was due to Gliadel wafer placement, Weber et al.<sup>17)</sup> have reported cases with malignant brain edema that was associated with significant ipsilateral cerebral edema and progressive neurological deficits. Two clinical cases that demonstrated profound cerebral edema that was associated with the implantation of Gliadel wafers have been reported. As a result, one of these individuals had premature death. This study might assist in explaining the mechanisms by which clinically significant cerebral edema may develop. Eventually, this cerebral edema resulted in repeated and extended hospitalizations, significant morbidity, neurological

deficits, and delays in subsequent therapeutic modalities, such as chemoradiotherapy. In our case, brain edema by Gliadel wafer placement also resulted in extended hospitalization and transient significant motor dysfunction. Like the reports on malignant brain edema, our case also showed resistance to intensive therapy with corticosteroids and osmotic diuretic glycerol. Recently, anti-vascular endothelial growth factor (VEGF)-A molecule bevacizumab, which has the effect of down-regulating angiogenesis, has been used for malignant gliomas and shown progression-free survival benefit.<sup>22–25)</sup> Furthermore, its efficacy for peritumoral edema is also reported.<sup>26)</sup> However, the drug should be used cautiously immediately after surgery because there are reports of severe complications such as hypertension, thromboembolic events, and wound dehiscence at a constant rate even when administered 4 weeks after surgery.<sup>25,27)</sup> Therefore, we refrained from using bevacizumab for this patient although the symptomatic brain edema was refractory to steroids.

Surgical resection injury alone leads to vasogenic brain edema, which is due to abnormally large amounts of fluid in the extracellular space of the brain, because the blood vessels near the surgical cavity become very leaky and the blood–brain barrier (BBB) is damaged.<sup>28)</sup> In our case, however, the brain edema was apparently limited to only the areas where the Gliadel wafers were placed. Furthermore, T<sub>1</sub>-weighted MRI with gadolinium enhancement showed enhancing lesions in the areas where the Gliadel wafers were placed through the postoperative course (Figs. 2C, 3E–H), indicating that the disruption of BBB due to the placement of Gliadel wafers might have caused the brain edema. In order

to understand the mechanism by which carmustine might elicit brain edema, understanding the pharmacokinetics of Gliadel and the mechanisms of drug delivery is extremely crucial. Drug distribution within the brain has several basic patterns, which include “diffusion” and “bulk flow.”<sup>29)</sup> The distribution of carmustine within the brain is actually dependent upon the state of the brain parenchyma, that is, whether it is in a nontraumatized or in a traumatized state. In the tissue of the tumor resection wall that consisted of traumatized brain parenchyma, “bulk flow” is the predominant mechanism by which carmustine distributes, rather than “diffusion,” which leads to long penetration distances of carmustine.<sup>6)</sup> The early penetration distances of carmustine (one to three days after implantation) are enhanced relative to later distances, which occur as a result of the enhanced interstitial fluid convection arising from postoperative edema.<sup>30)</sup>

Based on the above findings, it is likely that the toxicity of BCNU in the Gliadel wafers is enhanced in early postoperative period. In our case, brain edema was identified on the postoperative day-4 MRI, even though there were no abnormalities on the intraoperative MRI. Because this brain edema area did not exhibit high intensity on diffusion-weighted MRI scans, it was thought to not merely be vasogenic brain edema that was caused by surgical injury but malignant brain edema that was caused by the toxicity of BCNU.

Our report demonstrated postoperative symptoms that fit well with the potential cytotoxic effects of Gliadel wafer. It has been shown that carmustine distributes directly along the pyramidal tract for several days after implantation. As this patient eventually did not respond to intensive corticosteroid therapy, the edema was initially refractory, and it produced profound disability and a delay of further treatment modalities.

## Conclusion

Although the use of Gliadel wafers for the treatment of malignant gliomas has been shown in some studies to be effective with minimal adverse effects, it sometimes causes malignant symptomatic edema, which results in severe neurological deficits. In fact, Gliadel wafer treatment is a double-edged sword as it has both anti-tumorigenic activities and severe adverse effects. As such, further attention is needed when Gliadel wafers are placed on eloquent areas that are related to motor and language function. Therefore, we should retain that Gliadel wafer placement in eloquent area as may possibly result in severe disadvantages to patients and a decrease of their quality of life.

## Acknowledgments

The authors would like to thank Mr. Takashi Mizuguchi (Department of Neurosurgery, Nagoya University School of Medicine, Nagoya, Japan) for his wonderful technical assistance.

## Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs or materials in the article.

All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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