Effect of Intraoperative Ventricular Opening on Recurrence Patterns Following Bis-Chloroethyl-Nitrosourea Wafer Implantation for Newly Diagnosed Glioblastoma

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Objective: To evaluate the effect of ventricular opening (VO) on recurrence patterns in patients with newly diagnosed glioblastoma (GBM) treated with bis-chloroethyl-nitrosourea (BCNU) wafer implantation.

Methods: This single-center retrospective study included 40 patients with newly diagnosed GBM who received BCNU wafer implantation after tumor resection between March 2013 and February 2022. The patients were categorized into two groups based on whether VO occurred during the GBM resection. While 18 patients had VO, 22 did not have VO. In cases with VO, the ventricular wall defect is closed with gelatin or oxidized regenerated cellulose and fibrin glue before BCNU wafer implantation. Recurrence patterns—classified as local, diffuse, distant, or multifocal—and time to recurrence were compared between patients with and without VO.

Results: The median follow-up period for the entire cohort was 32.2 months (interquartile range, 16.7–38 months). Median survival time was comparable between patients with VO and patients without VO (38 vs. 26 months, \( p = 0.53 \)). Recurrence occurred in 31/40 patients (77.5%) in entire cohort. The incidence of recurrence was comparable between patients with VO and patients without VO (14 [77.8%] vs. 17 [77.3%], \( p = 1.0 \)). No significant differences were seen between the two groups in time to recurrence (\( p = 0.59 \)) or recurrence patterns (\( p = 0.35 \)).

Conclusion: Ventricular opening during surgery with BCNU wafer implantation does not seem to influence the recurrence patterns. Ventricular opening does not induce distant recurrence if appropriate ventricular closure is performed.

Key Words: Carmustine · Gliadel · Glioblastoma · Ventricles · Recurrence.

INTRODUCTION

Glioblastoma (GBM) is the most common and most aggressive form of glioma, a brain tumor that originates from glial cells. Even with the best treatment, which involves maximal surgical resection followed by adjuvant radiotherapy, chemotherapy, and tumor-treating fields (TTF), the median survival time (MST) of patients with GBM is only about 2 years.\(^4,20,21\)
Checkpoint inhibitors such as nivolumab and pembrolizumab have shown limited effectiveness in the treatment of GBM in clinical trials. The antitumor agent bis-chloroethyl-nitrosourea (BCNU) has been found to be effective in clinical trials, but because intravenous administration is associated with side effects such as lung damage and myelosuppression, it is currently used in the form of BCNU wafers implanted into resected tumor cavity. For newly diagnosed GBM, the Stupp regimen with/without TTF is administered after BCNU wafer implantation. A recent meta-analysis showed that BCNU wafer implantation could significantly improve MST.

The ventricles are often opened during the latter part of surgery for GBM. In cases with ventricular opening (VO), previous reports including our recent study, the ventricular wall defect is closed with gelatin or oxidized regenerated cellulose and fibrin glue. Our recent study showed that intraoperative VO does not affect complications after BCNU wafer implantation; this is consistent with an earlier report by Bettag et al. Therefore, even if the ventricles are opened during surgery for GBM, BCNU wafer implantation is not contraindicated. However, it should be noted that even with BCNU wafer implantation in the resected cavity, tumor recurrence is inevitable. The prognosis is particularly poor in cases where VO has been performed. Most commonly, recurrence occurs around the resected cavity. However, it is not clear whether VO increases risk of intraventricular seeding during tumor resection or of distant recurrence. This retrospective study aimed to identify the recurrence patterns associated with VO after BCNU wafer implantation for GBM.

### MATERIALS AND METHODS

#### Patients

The Ethics Committee of Nara Medical University approved this retrospective study (approval No. 3334). The clinical data of 44 consecutive patients with newly diagnosed GBM treated with BCNU wafer implantation at our hospital between March 2013 and February 2022 were retrospectively reviewed. Four patients who did not undergo appropriate radiological examinations during the follow-up period were excluded. Finally, 40 patients were included in this study.

#### Surgical procedure and postoperative follow-up

The surgical protocol and procedure for BCNU wafer implantation in patients with newly diagnosed GBM have been described in detail previously. Briefly, the procedure is as follows: patients are administrated 5-aminolevulinic acid (20 mg/kg) orally on the surgery day. After craniotomy and dural opening, the tumor is delineated by ultrasonography and a neuronavigation system (Brainlab, Munich, Germany). After intraoperative pathology confirms the diagnosis of malignant glioma, BCNU wafer placement is generally considered when it is determined that at least 90% of the tumor has been removed. The resection cavity is covered with up to eight BCNU wafers. In cases with VO, the ventricular wall defect is closed with gelatin or oxidized regenerated cellulose and fibrin glue before BCNU wafer implantation. The wafers are covered with oxidized regenerated cellulose to prevent dislocation. BCNU wafer implantation is not performed in cases where the VO is so large that proper closure would be difficult.

All patients included in this study underwent computed tomography on the day after the surgery and magnetic resonance imaging (MRI) within 72 hours after surgery. Follow-up contrast-enhanced MRI was performed every 3 months if possible. Tumor volume was evaluated before and after surgery using iPlan RT (Brainlab). In this study, gross total removal was defined as ≥95% removal on postoperative MRI, subtotal removal as >90% and <95%, and partial removal as <90%. If disease progression was detected on MRI, a Brain Tumors Review Board—comprising neurosurgeons, neurooncologists, neuroradiologists, and radiation oncologists—reviewed the imaging findings and degree of clinical deterioration and proposed any additional treatment; the options included reoperation, radiation therapy, rechallenge chemotherapy, or palliative treatment.

#### Recurrence patterns

Recurrence after BCNU wafer implantation was defined as per the criteria reported by Shimato et al. Briefly, recurrence is defined as the new appearance of T1-gadolinium enhancement or enlargement of T1-gadolinium enhancement of residual enhanced lesion observed on postoperative MRI. If pseudo-progression was suspected, MRI was repeated at short intervals to monitor the changes in contrast enhancement.

Recurrence patterns were classified into four different types: as “local” if the recurrence was in continuity with...
the wall of resection cavity and within 1.5 cm from the resection cavity; as “diffuse” if the recurrence was in continuity with the wall of resection cavity but extended more than 1.5 cm from the margin of resection cavity; as “distant” if the recurrence was not contiguous with the resection cavity; or as “multifocal” if there was a mixture of “distant” and “local” or “diffuse” patterns (Supplementary Figs. 1-4).

**Statistical analysis**

MST was calculated using the Kaplan-Meier method. The log-rank test was used for univariate analysis. The t-test, Fisher exact test, and Mann-Whitney U test were used to compare characteristics between patients with and without VO. All analyses were performed using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and p<0.05 was considered statistically significant.

**RESULTS**

**Patient characteristics**

The study cohort comprised 25 males and 15 females, with mean age of 65.6±11.8 years. According to the World Health Organization criteria, the pathological grade of the resected tumors was grade 4 in all cases. While 18 patients underwent VO, 22 patients did not. There were no significant differences between the two groups in sex composition, age, Charlson comorbidity index, pre-treatment and post-treatment Karnofsky performance status scores, number of wafers implanted, and extent of resection (Table 1).

**Samples of recurrence patterns**

Recurrence was divided into four patterns; Supplementary Figs. 1-4 show representative cases of each type. All patients with recurrence underwent second surgery, and pathology confirmed recurrent of GBM in all.

**Recurrence after BCNU wafer implantation**

The median follow-up period for the entire cohort was 32.2 months (interquartile range, 16.7–38 months); median follow-up was for 30 months (interquartile range, 18.3–36.5 months) in patients with VO and 34.1 months (interquartile range, 16.3–39.5 months) in patients without VO. The MST for the entire cohort was 32 months (Fig. 1A). The MST was comparable in patients with VO and without VO (38 vs. 26 months, p=0.532; Fig. 1B).

Recurrence after BCNU wafer implantation occurred in 31/40 patients (77.5%). The incidence of recurrence was comparable between patients with VO and patients without VO (14 [77.8%] vs. 17 [77.3%], p=1.0). Among the patients with VO, six had local recurrence, five had diffuse recurrence, and three had distant recurrence. Among the patients without VO, three had local recurrence, six had diffuse recurrence, two had multifocal recurrence, and six had distant recurrence.
The recurrence patterns were not significantly different between the two groups \((p=0.354)\). The time to recurrence after BCNU wafer implantation was also comparable between patients with VO and without VO \((607 \text{ vs. } 493 \text{ days}, p=0.562; \text{Table 2})\).

During the same period, BCNU wafer implantation was not performed in 12 cases. One of these 12 patients did not undergo appropriate radiological examinations (Supplementary Table 1). In the remaining 11 patients, the VO was so large that proper closure would be difficult. Among these 11 patients, recurrence after surgery without BCNU wafer implantation occurred in nine cases \((81.8\%);\) among those nine patients, six had distant recurrence and three had diffuse recurrence (Supplementary Table 2). The MST of the patients with VO and without BCNU wafer implantation and the patients with VO and BCNU wafer implantation was 20 and 38 months, respectively \((p=0.008)\) (Fig. 1C). Even in a comparison between cases with the same VO, MST was significantly longer in cases that BCNU wafer could be implanted.
DISCUSSION

GBM is the most aggressive among all primary brain tumors in adults. Even with multidisciplinary treatment, which includes surgical resection, radiation therapy, chemotherapy, and TTF, the 5-year survival rate is poor. BCNU is a chemotherapeutic agent used to treat various types of cancer. It belongs to a class of drugs called alkylating agents, which kill cancer cells by interfering with the DNA replication process.

BCNU wafer implantation in the tumor resection cavity bridges the treatment gap between surgery and the start of radiotherapy or chemotherapy. Wafer implantation allows a high concentration of BCNU to be achieved within the tumor and helps in local control of the tumor by affixing it to the resection cavity; thus, it helps prolong survival. BCNU wafer implantation in the tumor resection cavity bridges the treatment gap between surgery and the start of radiotherapy or chemotherapy. Wafer implantation allows a high concentration of BCNU to be achieved within the tumor and helps in local control of the tumor by affixing it to the resection cavity; thus, it helps prolong survival.

In the current study, we included only newly diagnosed GBM treated with BCNU wafer implantation and evaluated the recurrence patterns. Recurrence occurred in 31/40 patients in entire cohort, with the frequency of recurrence being similar in patients with and without VO. The pattern of recurrence was also similar in patients with and without VO. We had 11 cases without BCNU wafer implantation, where VO was so large that proper closure would be difficult; among these 11 patients, six had distant recurrence and three had diffuse recurrence. There was a trend toward more distant recurrences in this group than in patients treated with BCNU wafer implantation. We had anticipated that intraoperative VO would result in tumor seeding within the ventricles and increase possibility of distant recurrence; however, the study results suggest that VO does not increase risk of distant recurrence if the ventricles are properly closed. In addition, comparing the OS of the same VO cases in which BCNU wafer implantation was performed, it was found that the OS was significantly longer in patients with local recurrence than in patients with non-local recurrence. If VO during surgery for GBM could lead to distant recurrence or dissemination, VO should be avoided. However, it is not yet known whether tumor cells can stray into the ventricles during VO and result in intraventricular seeding or distant recurrence.

In the study by Dörner et al., 80% of patients treated with BCNU wafer implantation developed local or diffuse recurrence during follow-up, and the authors therefore concluded that BCNU wafer implantation does not provide lasting local tumor control. Shimato et al. reported better local tumor control in patients with BCNU wafer implantation than patients without BCNU wafer implantation; however, their study included only eight patients with BCNU wafer implantation. As Piper et al. pointed out, studies on GBM use different criteria to classify recurrence patterns as local, diffuse, multifocal, and distant, and so comparison between studies is very difficult.

Shibahara et al. followed up 64 patients with BCNU wafer implantation and reported recurrence in 55 patients, with 33 (60%) developing local recurrence, 13 (23.6%) developing distant recurrence, and nine (16.3%) developing multifocal recurrence. MST was significantly longer in patients with local recurrence than in patients with non-local recurrence. If VO during surgery for GBM could lead to distant recurrence or dissemination, VO should be avoided. However, it is not yet known whether tumor cells can stray into the ventricles during VO and result in intraventricular seeding or distant recurrence.

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Table 2. Recurrence patterns in patients with and without VO

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All cases (n=40)</th>
<th>Ventricle opening (n=18)</th>
<th>Ventricle intact (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence patterns</td>
<td>No</td>
<td>9</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>31</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Local</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Multifocal</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Median time to recurrence (days)</td>
<td>539</td>
<td>607</td>
<td>493</td>
<td>0.562</td>
</tr>
</tbody>
</table>

VO: ventricular opening

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BCNU wafer could be implanted and those in which BCNU wafer could not be implanted due to large VO, the MST was significantly prolonged in those cases in which BCNU wafer could be implanted. The results may be due to the anti-tumor effect of BCNU wafer itself or to the widespread periventricular invasion of GBM, which may have influenced the poor prognosis. However, the small number of cases in both cases limits the interpretation of these results. Our previous study demonstrated that VO during surgery with BCNU wafer implantation does not increase the occurrence of postoperative adverse effects as long as the ventricles are accurately closed. In the present study, we show that BCNU wafer implantation has no effect on recurrence patterns and time to recurrence even if VO has been performed. Thus, BCNU wafer implantation is an alternative treatment option that should be considered among the limited treatment options for newly diagnosed GBM.

The primary limitations of this study are its retrospective design and the small sample size. In addition, the decision to implant BCNU wafers was at the discretion of the treating neurosurgeon. All these factors may have introduced a selection bias. Large well-designed prospective studies are needed to verify our findings.

CONCLUSION

Recurrence patterns in patients with newly diagnosed GBM treated with BCNU wafer implantation appear to be uninfluenced by intraoperative VO as long as appropriate ventricular closure is achieved during surgery.

AUTHORS’ DECLARATION

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Informed consent
This type of study does not require informed consent.

Author contributions
Conceptualization : R Matsuda; Data curation : R Matsuda, R Maeoka, TN; Formal analysis : R Matsuda, R Maeoka, TN; Funding acquisition : R Matsuda; Methodology : R Matsuda, R Maeoka, TN, NT; Project administration : R Matsuda; Visualization : R Matsuda; Writing - original draft : R Matsuda, R Maeoka, TN, NT; Writing - review & editing : R Matsuda, R Maeoka, TM, TN

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Data sharing
None

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