Journal of Clinical Neuroscience 134 (2025) 111113

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.journals.elsevier.com/journal-of-clinical-neuroscience

Outcomes of awake surgery for recurrent glioblastoma: A single-institution retrospective analysis

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ARTICLE INFO

Keywords:
Awake surgery
Glioblastoma
Recurrence

ABSTRACT

Background: Awake surgery facilitates maximal safe resection of brain tissue in cases of glioma, but its effectiveness for recurrent glioblastoma (GBM) remains unestablished. In this study, we investigate the safety, success rate of mapping, and surgical outcomes of awake surgery for recurrent GBM.
Methods: This study included glioma cases that underwent awake surgery at our hospital between March 2010 and February 2023 and met the following criteria: (1) cases with a pathologic diagnosis of glioblastoma or astrocytoma, isocitrate dehydrogenase-mutant, WHO grade 4 at recurrence, and (2) cases in which this was the second surgery in the course of treatment. We retrospectively analyzed the clinical features, mapping response, resection rate, postoperative complications, overall survival (OS), and progression-free survival (PFS).
Results: Forty-one cases were analyzed. The median age was 47 years, and 24 patients (58.5 %) were male. Awake mapping was successfully completed in 35 cases (85.4 %). A positive response to mapping was observed in 20 cases (48.8 %), which limited resection in 15 cases (36.6 %). The extent of resection was gross total resection in 20 cases (48.8 %), subtotal resection in 11 cases (26.8 %), partial resection in 8 cases (19.5 %), and biopsy in 2 cases (4.9 %). Acute-phase neurological deficits developed in 10 cases (24.4 %), but sequelae or symptom exacerbations were observed in 2 cases (4.9 %). The median post-recurrence OS and PFS were 18.7 months and 7.2 months, respectively.
Conclusions: Awake mapping for recurrent GBM demonstrated a low complication rate and facilitated tumor resection without exacerbating neurological symptoms. Awake surgery for recurrent GBM may contribute to prolonged survival.

1. Introduction

Glioblastoma (GBM), the most common type of adult malignant brain tumor, has a poor prognosis, with a 5-year survival rate of 16 % [1]. Since GBM infiltrates normal brain tissue, total surgical resection is impossible. However, maximal safe resection of GBM has been reported to contribute to prolonged survival [2–7]. Further, for GBM developing in eloquent areas, performing resection while monitoring neurological function through awake surgery has been reported to improve the extent of resection, reduce the complication rate, and prolong overall survival [8–11]. Recurrence after standard treatment is unavoidable, and the median survival time after recurrence is 7–10 months [12–14]. Standard treatment for recurrence has not been established. Although repeat resection has been suggested to prolong survival in cases of recurrence in certain regions [15–21], the effectiveness of awake surgery for recurrent GBM developing in or adjacent to eloquent areas has not been reported. In this study, we investigated the safety, success rate of mapping and surgical outcomes of awake surgery performed at our hospital for the first recurrence of GBM.

2. Material and Methods

2.1. Participants

This study included cases of recurrent glioma that underwent awake craniotomy for tumor resection at our hospital between March 2010 and

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https://doi.org/10.1016/j.jocn.2025.111113
Received 25 September 2024; Accepted 6 February 2025
Available online 13 February 2025

March 2023, meeting the following criteria: (1) cases with a pathologic diagnosis of GBM or astrocytoma, isocitrate dehydrogenase (IDH)-mutant, WHO grade 4 at recurrence, and (2) cases in which this was the second surgery in the course of treatment. Cases where the tumor was located in or adjacent to language areas of the cortex, language-related association fibers, the primary motor cortex, primary somatosensory cortex, or premotor cortex, and with mild to moderate symptoms were eligible for awake surgery. Mild symptoms were defined as abnormal language or motor function that did not interfere with social life, whereas moderate symptoms were defined as difficulties in social life but with the ability to perform language or motor tasks. Cases with multifocal lesions were excluded.

Anesthesia and the surgical procedure were performed as previously described [22]. Briefly, anesthesia was induced using propofol in combination with remifentanil. Local anesthetics were administered around the pin fixation and skin incision sites and selective nerve blocks were performed. Counting, visual naming, and auditory comprehension were conducted as language tasks depending on the participant's condition. Voluntary movements of the upper and lower extremities were observed to evaluate motor function. Bipolar stimulation was performed at 2–10 mA for cortical and subcortical lesions. If language or motor arrest occurred during tumor removal, bipolar stimulation was performed along the removal site to determine its proximity to functional areas. Mapping failure was defined as the inability to perform tasks intraoperatively. A positive response to mapping was defined as the cessation of speech, dysarthria, or paraphasia during language mapping and the cessation of movement during motor function.

The following variables were analyzed: age, sex, and Karnofsky Performance Status (KPS) at admission and 3 months postoperatively; tumor site, maximum diameter; final pathologic diagnosis; IDH 1/2 status; response to intraoperative stimulation; response to mapping findings; resection rate; development of convulsive seizure intraoperatively or up to 1 week postoperatively, postoperative neurological deficits; overall survival; post-recurrence overall survival (OS); and progression-free survival (PFS). The resection rate was calculated using pre and postoperative T1 gadolinium enhanced magnetic resonance imaging (MRI) and classified as follows: gross total resection (GTR), extent of resection (EOR) = 100 %; subtotal resection (STR), EOR = 95–99 %; partial resection (PR), EOR < 95 %; biopsy; and collection of tissue for diagnostic purposes only. The calculation used fluid-attenuated inversion recovery hyperintensity lesions in cases with no contrast enhancement. Postoperative neurological deficits were defined as early if they developed within 3 months of surgery and as late if they persisted >3 months after surgery [23]. Post-recurrence overall survival was defined as the period from the first surgery post-recurrence to death or the last follow-up. PFS was the period from the first surgery post-recurrence to the second recurrence, death, or the last follow-up. OS was the period from the initial diagnosis to death or the last follow-up. OS and PFS were analyzed using a Kaplan–Maier curve. Survival times are shown as the median and 95 % confidence interval.

This study was approved by the Research Ethics Review Committee of our hospital (research project no: 2013–042).

2.2. Statistical analysis

Baseline patient characteristics were summarized using descriptive statistics. Continuous variables were presented as the median and interquartile range. Differences in median continuous variable were examined using the Mann–Whitney *U* test. Nominal variables were analyzed using Fisher's exact test. OS and PFS estimates were obtained using the Kaplan–Meier method and compared using log-rank tests. Statistical analyses were conducted using EZR [24]. A p-value of <0.05 was considered statistically significant.

3. Results

Forty-one cases were analyzed. Their clinical characteristics are shown in Table 1. The median age was 47 years (range, 39–59); 24 patients (58.5 %) were male, and the median KPS at admission was 80 (range, 70–90). Post-recurrence pathologic diagnosis included glioblastoma, IDH-wild type in 22 cases (53.7 %); glioblastoma, IDH-mutant/astrocytoma, IDH-mutant WHO grade 4 in 15 cases (36.6 %); glioblastoma, not otherwise specified (NOS) in 3 cases (7.3 %); and gliosarcoma in 1 case (2.4 %). The lesion was in the left hemisphere in 29 cases (70.7 %), the right hemisphere in 11 cases (26.8 %), and a butterfly glioma in 1 case (2.4 %). The location was the frontal lobe in 23 cases (56.1 %), the temporal lobe in 8 cases (19.5 %), the parietal lobe in 3 cases (7.3 %), the basal ganglia in 1 case (2.4 %), and multilobular in 6 cases (14.6 %).

Details of the treatments are shown in Table 2. Before secondary surgery, temozolomide, bevacizumab, and other drugs were administered in 36 cases (87.8 %), 7 cases (17.1 %), and 10 cases (24.4 %), respectively. Tumor treating fields were used in 3 cases (7.3 %). Gamma knife and boron neutron capture therapy were each used in one case (2.4 %). Photodynamic therapy was performed in 8 cases (19.5 %), and carmustine wafers were placed in 5 cases (12.2 %). After secondary surgery, temozolomide, bevacizumab, and other drugs were administered in 31 cases (75.6 %), 31 cases (75.6 %), and 16 cases (39.0 %), respectively. Radiotherapy was administered in 17 cases (41.5 %), and repeat surgery was performed in 9 cases (22.0 %).

Surgical outcomes are shown in Table 3. Surgery using mapping was successfully completed in 35 cases (85.4 %), but tasks could not be performed or evaluated in 6 cases (14.6 %). Mapping failure was attributed to a drowsy state and restlessness in four and two cases, respectively. A positive response to mapping was observed in 20 cases

Table 1
Clinical characteristics of Glioblastoma Patients.

Characteristics		
Age, years, median, (IQR)	47	(39–59)
Men, (%)	24	(58.5)
KPS on admission, median, (IQR)	80	(70–90)
Comorbidities, (%)		
Hypertension	3	(7.3)
Diabetes mellitus	2	(4.9)
Dyslipidemia	1	(2.4)
Preoperative neurological morbidity, (%)		
Hemiparesis	15	(36.6)
Sensory disturbance	5	(12.2)
Aphasia	11	(26.8)
Homonymous hemianopsia	1	(2.4)
Pathological diagnosis at recurrence, (%)		
Glioblastoma, IDH-wild	22	(53.7)
Glioblastoma, IDH mutant/Astrocytoma grade 4	15	(36.6)
Glioblastoma, NOS	3	(7.3)
Gliosarcoma	1	(2.4)
Location, (%)		
Frontal	23	(56.1)
Temporal	8	(19.5)
Parietal	3	(7.3)
Multilobular	6	(14.6)
Basal ganglia	1	(2.4)
Laterality, (%)		
Left	29	(70.7)
Right	11	(26.8)
Bilateral (butterfly glioma)	1	(2.4)
Preoperative vomule, median (IQR)	24.0	(9.5–56.4)
Extent of resection at first surgery, (%)		
Gross toral resection	13	(31.7)
Subtotal resection	5	(12.2)
Partial resection	18	(43.9)
Biopsy	3	(7.3)
Unknown	2	(4.9)

IDH = Isocitrate dehydrogenase. IQR = Interquartile range. KPS = Karnofsky Performance Status. NOS=Not otherwise specified.

Table 2
Details of the treatment.

Before secondary surgery, (%)			Intraoperative local therapy, (%)			After secondary surgery, (%)		
Temozolomide	36	(87.8)	PDT	8	(19.5)	Temozolomide	31	(75.6)
Bevacizumab	7	(17.1)	Carmustine wafer	5	(12.2)	Bevacizumab	31	(75.6)
Other drugs	10	(24.4)				Other drugs	16	(39.0)
TTF	3	(7.3)				Radiotherapy	17	(41.5)
Radiotherapy (GKS, BNCT)	2	(4.9)				Repeat surgery	9	(22.0)

BNCT= Boron neutron capture therapy. GKS= Gamma knife surgery. PDT=Photodynamic therapy. TTF=Tumor treating fields.

Table 3
Surgical outcomes of awake surgery for glioblastoma patients.

Surgical Outcomes		
Awake mapping, (%)		
Successfully completed	35	(85.4)
Failure	6	(14.6)
Drowsy state	4	(9.8)
Restlessness	2	(4.9)
Response to awake mapping, (%)		
Positive response to cortical mapping	4	(9.8)
Positive response to subcortical mapping	18	(43.9)
Negative	15	(36.6)
Response to mapping results, (%)		
Stop resection	15	(36.6)
Extent of Resection, (%)		
Gross toral resection	20	(48.8)
Subtotal resection	11	(26.8)
Partial resection	8	(19.5)
Biopsy	2	(4.9)
Seizure, (%)		
Intraoperative	4	(9.8)
Postoperative acute periods	4	(9.8)
Early neurological deficits, (%)	10	(24.4)
Hemiparesis	6	(14.6)
Sensory disturbance	1	(2.4)
Aphasia	2	(4.9)
Aprosexia and Dysmensia	1	(2.4)
Late neurological deficits, (%)	2	(4.9)
Aprosexia and Dysmensia	1	(2.4)
Vegetative state (due to disease progression)	1	(2.4)
Median KPS 3 months after 2nd surgery, (IQR)	80	(70–90)
Median OS after 2nd surgery, months, (95 % CI)	18.7	(12.5–36.2)
Median PFS after 2nd surgery, months, (95 % CI)	7.2	(5.3–10.2)

CI=Confidence interval. IQR==Interquartile range. KPS = Karnofsky Performance Status. OS=Overall survival. PFS= Progression free survival.
Early neurological deficits: Deficits that developed within 3 months of surgery. Late neurological deficits: Deficits that lasted > 3 months after surgery.

(48.8 %). Among these, 4 (9.8 %) showed a positive response to cortical stimulation, and 18 (43.9 %) showed a positive response to white matter stimulation. In 15 cases (36.6 %), resection of mapping positive sites was not performed. The EOR was GTR in 20 cases (48.8 %), STR in 11 cases (26.8 %), PR in 8 cases (19.5 %), and biopsy in 2 cases (4.9 %). Functional shift was observed in one case 12 months after the initial surgery. 5-aminolevulinic acid and intraoperative ultrasound were used in all cases, while intraoperative MRI was performed in 22 cases (53.7 %). Intraoperative seizures occurred in 4 cases (9.8 %), but cooling with artificial cerebrospinal fluid stopped the seizures in all cases. Seizures occurred within 1 week postoperatively in 4 cases (9.8 %) but did not lead to status epilepticus in any case. Early neurological deficits developed in 10 cases (24.4 %), but late neurological deficits were observed in only 2 cases (4.9 %). Among the two cases exhibiting late neurological deficits, tumor progression was observed in one case, and cerebral edema, believed to result from a carmustine wafer, persisted 3 months postoperatively in the other. Postoperative pneumonia and deep venous thrombosis were not observed.

The median post-recurrence PFS and OS were 7.2 months (95 % confidence interval [CI], 5.3–10.2) and 18.7 months (95 % CI, 12.5–36.2), respectively (Fig. 1A and 1B). PFS and OS were analyzed for the 37 cases in which IDH status analysis was performed. PFS was 9.3 months (95 % CI, 3.9–15.6) for the IDH-wildtype and 7.2 months (95 % CI, 3.3–12.2) for the mutant type; the difference was not significant ($p = 0.477$) (Fig. 1C). Post-recurrence OS was 28.9 months (95 % CI, 11.4–37.4) for the IDH-wild type and 16.7 months (95 % CI, 11.7–not applicable [NA]) for the mutant type, and the difference was not significant ($p = 0.754$) (Fig. 1D). The survival curve based on secondary surgery EOR is shown in Fig. 2. Post-recurrence OS was 21.1 months (95 % CI, 16.7–NA) with GTR, 12.5 months (95 % CI, 8.6–NA) with STR, and 13.5 months (95 % CI, 5.5–NA) with PR or biopsy. The survival time was significantly prolonged in cases where GTR was achieved ($p = 0.049$). The stratified survival curves for IDH mutation status on secondary surgery EOR are shown in supplementary Fig. S1. Post-recurrence OS of glioblastoma, IDH-wildtype was 37.4 months (95 % CI, 10.7–NA) with GTR, 12.5 months (95 % CI, 8.8–NA) with non-GTR ($p = 0.013$). Post-recurrence OS of astrocytoma, IDH-mutant, WHO grade 4, was 19.2 months (95 % CI, 11.8–NA) with GTR, 16.6 months (95 % CI, 9.3–NA) with non-GTR ($p = 0.646$).

Treatment outcomes for the 16 cases with an initial pathologic diagnosis of glioblastoma, IDH-wild type, are shown in Fig. 3. Post-recurrence PFS was 7.6 months (95 % CI, 3.0–15.6), post-recurrence OS was 21.1 months (95 % CI, 10.7–37.4), and median OS from the time of initial diagnosis was 42.7 months (95 % CI, 24.8–59.1) (Fig. 3A–C).

4. Discussion

This is the first report on the treatment outcomes of awake surgery for recurrent GBM. Gross total resection was achieved in 48.8 % of cases, and complications lasting at least 3 months were infrequent occurring in 4.9 % of cases. The OS and PFS after the first recurrence were favorable at 18.7 months (95 % CI, 12.5–36.2) and 7.2 months (95 % CI, 5.3–10.2), respectively. A significantly prolonged survival time was observed in cases where GTR was achieved.

Although various treatments have been attempted for recurrent GBM, none have been established to contributes to prolonged survival. Molecular targeted therapies are recommended for cases with mutations in genes such as BRAF and NTRK [25]. For unresectable lesions, temozolomide rechallenge, bevacizumab, radiation, and TTF are recommended, but none have been shown to contribute to prolonged survival [25,26]. For resectable lesions, re-resection is recommended. The EOR of contrast-enhanced lesions in the newly diagnosed GBM has been reported to affect prognosis [2–7]. While there is no standard treatment for recurrent GBM, resection of contrast-enhancing lesions has been reported to improve the prognosis. Repeat resection should, therefore, be actively considered, depending on the disease status [15–21].

Awake surgery for gliomas, particularly low-grade gliomas, has been reported to be effective for preserving function and achieving maximal resection, and the utility has been established [27]. Recent studies have shown that awake surgery for GBM also improves resection rates and prolongs the survival time [8–11]. Prospective cohort studies and randomized controlled trials evaluating the utility of awake surgery for GBM and malignant gliomas are underway [28,29]. No reports have been made on the utility of awake surgery for recurrent GBM. The median overall survival for recurrent GBM is reported to be 7–10 months

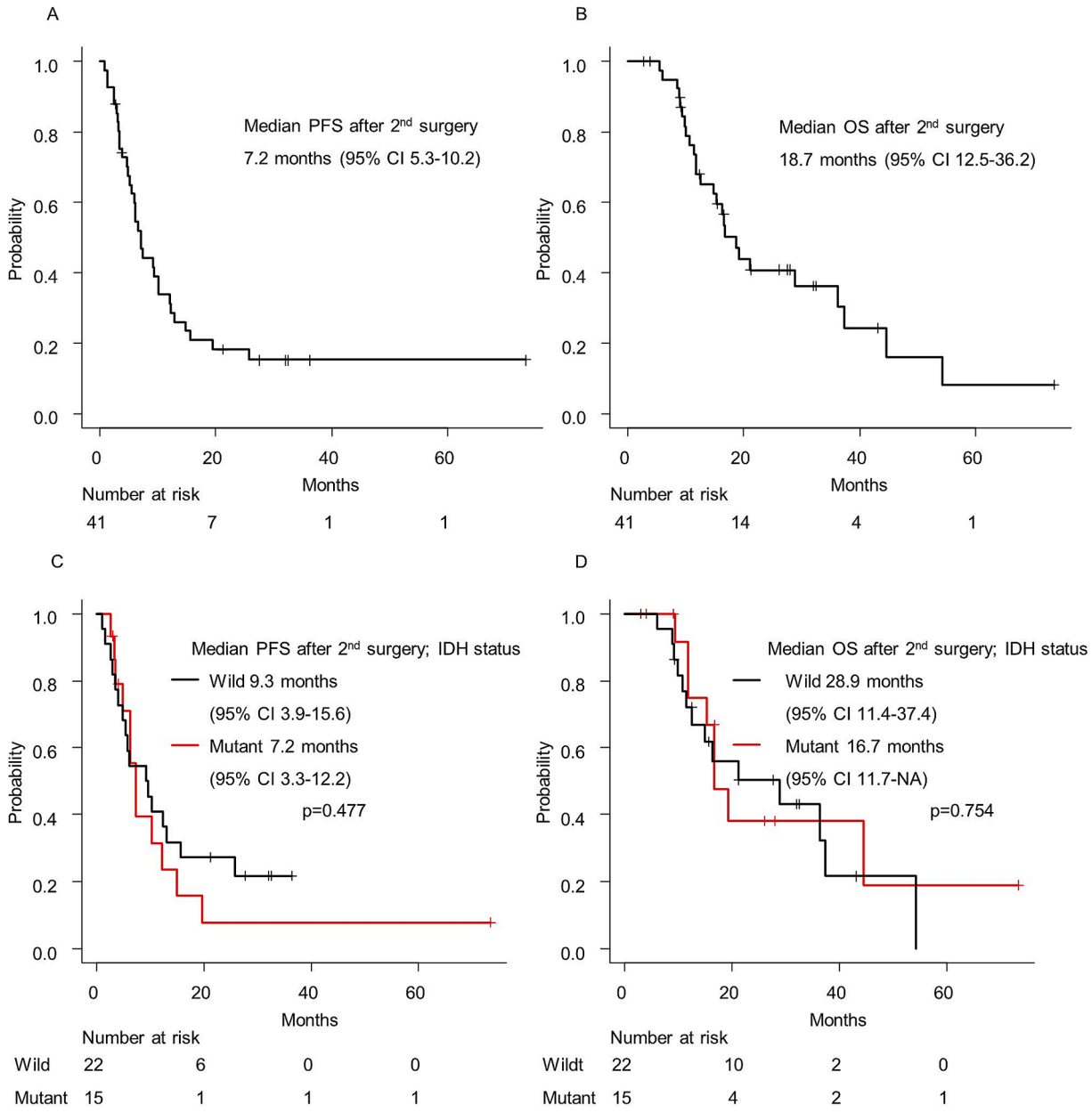

Fig. 1. (A, B) Post-recurrence progression-free survival and overall survival. (C, D) Post-recurrence progression-free survival and overall survival for IDH-wild type and IDH-mutant type. NA = not applicable. OS = overall survival. PFS = progression free survival.

[12–14], while this number is 13–20 months in cases that achieve total resection of the contrast-enhancing lesion at the time of recurrence [15,16,19,20]. Although the definition of GTR varies across studies, Karschnia et al. from the RANO resect group reported that a post-operative contrast-enhanced lesion smaller than 1 cm^3 improves survival outcomes [16]. Our results are consistent with this finding, and total resection of contrast-enhanced lesions should be pursued for recurrent GBM. In this study, survival time was longer than that reported in previous studies, with a median survival time of 18 months after the first recurrence and 21 months in cases with total resection of contrast-enhancing lesions. This may have been influenced by the fact that the 3-month postoperative median KPS was high (80 points) and many patients were young. Differences in postoperative treatment could also contribute to the prognosis. Especially, bevacizumab and repeat surgery, which contribute to prolonging the survival of GBM, may have influenced outcomes.

The complication rate was low, with only two cases (4.9 %) experiencing complications lasting >3 months. One of these cases exhibited tumor progression, and brain edema due to a carmustine wafer was suspected in the other. No permanent sequelae from surgical hemorrhage, contusion, or infarction were observed. The complication rate was low compared to past studies, which reported permanent sequelae from surgery for recurrent GBM at a rate of 7.6–11.1 % [17,19]. Therefore, it can be concluded that awake mapping preserved neurological function in recurrent GBM. In this study, the positive response to mapping was particularly high in deep white matter at 43.9 %, while the positive response to cortical mapping was 9.8 %. Association fibers and projection fibers lie within deep white matter, and preserving these structures is reported to be effective in preserving brain function [30]. It was suggested that awake surgery enables the identification and preservation of these functionally important white matter structures in recurrent GBM as well. Postoperative neurological complications are a prognostic factor for GBM [31], and performing maximal safe resection while preserving function through awake surgery is expected to be of

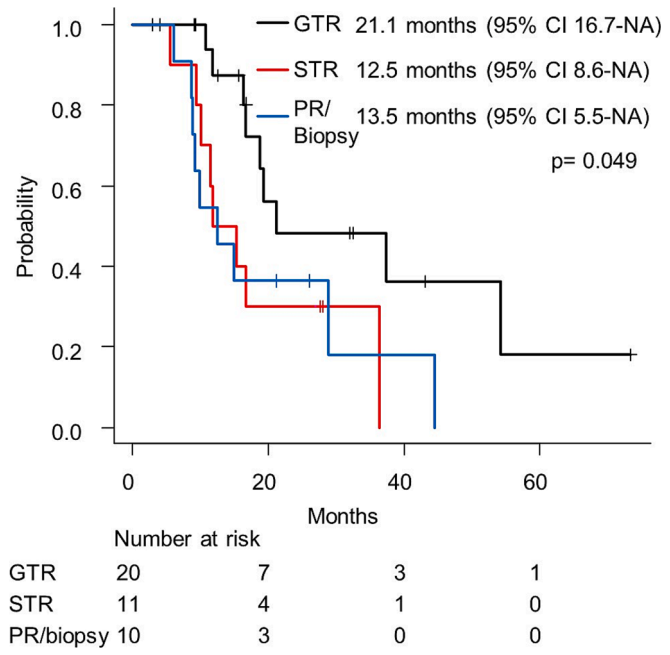

Fig. 2. Impact of extent of resection on overall survival GTR = gross total resection. NA = not applicable. STR = subtotal resection. PR = partial resection.

highly beneficial.

In this study, mapping failure due to insufficient consciousness was observed in 14.6 % of cases. Previous studies reported that insufficient consciousness occurred in 5.2 % to 19.1 % of cases [32,33]. Since this study specifically involves glioblastoma, many cases presented with severe brain edema, which might lead to insufficient consciousness at a relatively high rate. We previously reported that the time from anesthetic induction to extubation was correlated with successful awake mapping [22]. Moreover, insufficient consciousness during awake surgery is associated with an age of ≥70 years, uncontrolled epileptic seizures, previous oncological treatment, hyperperfusion on MRI, mass effect on the midline, and a left-sided lesion [32–34]. Individuals aged ≥70 years are considered to be at high risk of intraoperative delirium [34]In the future, it will be necessary to identify the risk factors for insufficient consciousness during awake surgery for GBM.

There are several clinical specificities of awake surgery in recurrent GBM, including cortical adhesions to the previous surgical site, reduced network plasticity, and a lower KPS score compared to lower-grade gliomas. While cortical adhesions were observed in many cases, no brain damage associated with the dissection was noted. Although little is known about neural plasticity in GBM, Gibb et al. and Price et al. reported cases in which functional shift was observed [35,36]. Similar to their studies, one case in this study presented a functional shift 12 months after the first surgery. In this case, resection, including the areas identified as functional regions during the first surgery, was successfully performed, and no neurological deficits were observed. Further studies are needed to explore neural plasticity in GBM, which has a shorter recurrence period compared to lower-grade gliomas. Since GBM is a rapidly progressing disease, many cases show a lower KPS score at recurrence. As awake surgery requires the ability to perform tasks, cases with a lower KPS score are generally not considered suitable for awake surgery. Although there are challenges that remain to be addressed regarding awake surgery for recurrent GBM, this study indicated that awake surgery was able to safely detect functional areas, similar to our report on newly diagnosed GBM [22]. Therefore, awake surgery should be considered for recurrent GBM in selected cases that are eligible for resection.

This study is limited in that it was a single-arm, retrospective analysis. Additionally, this study contains a significant selection bias, as the indication for awake surgery in recurrent glioblastoma is constrained by the location, number of lesions, symptoms, and KPS. We acknowledge that our results need to be confirmed in larger studies.

5. Conclusions

Awake mapping for recurrent GBM enabled tumor resection with a low neurological complication rate. Total resection of contrast-enhancing lesions was suggested to lead to prolonged overall survival. Although there is currently no established treatment for recurrent GBM, awake surgery may contribute to prolong survival time.

Funding source

This study was supported by grants from the AMED under Grant Number 23ck0106865h0001.

CRediT authorship contribution statement

Sho Osawa: Writing – original draft, Investigation, Data curation, Conceptualization. **Daisuke Kawauchi:** Data curation, Writing – review & editing. **Makoto Ohno:** Writing – review & editing. **Yasuji Miyakita:** Writing – review & editing. **Masamichi Takahashi:** Writing – review & editing. **Shunsuke Yanagisawa:** Writing – review & editing. **Shohei Fujita:** Writing – review & editing. **Takahiro Tsuchiya:** Writing –

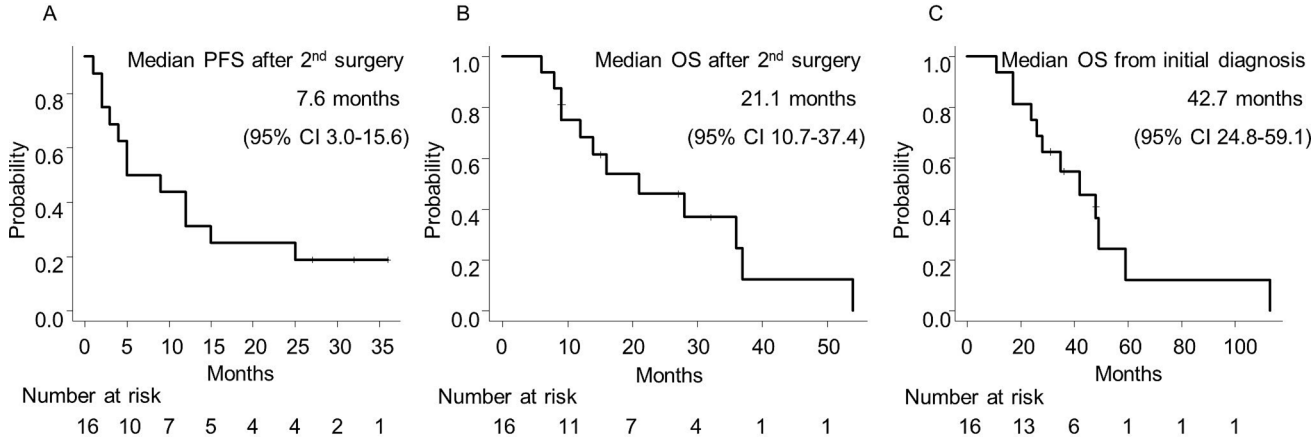

Fig. 3. (A) Post-recurrence progression-free survival, (B) Post-recurrence overall survival, and (C) Overall survival since initial diagnosis of initially diagnosed Glioblastoma, IDH-wild type. OS = overall survival. PFS = progression free survival.

review & editing. **Junya Matsumi:** Writing – review & editing. **Tetsufumi Sato:** Writing – review & editing. **Yoshitaka Narita:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2025.111113.

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