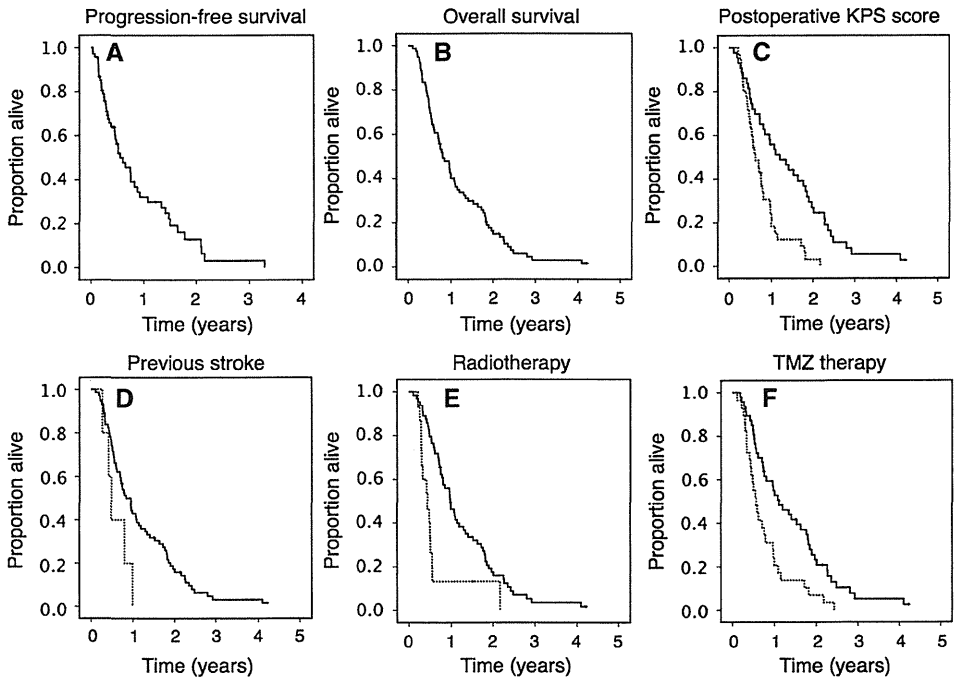

Fig. 1 Kaplan–Meier survival curves. **a** Progression-free survival. **b** Overall survival (OS). **c** OS in patients with a postoperative KPS score of ≥60 (*solid line*) and <60 (*dotted line*) ($p < 0.001$). **d** OS in patients without a previous stroke (*solid line*) and with a previous stroke (*dotted line*) ($p = 0.048$). **e** OS in patients who received radiotherapy (*solid line*) and who did not receive radiotherapy (*dotted line*) ($p = 0.001$). **f** OS in patients who received TMZ (*solid line*) and who did not receive TMZ (*dotted line*) ($p < 0.001$). All these factors were significantly associated with OS according to the log-rank test

Table 4 Multivariate analyses of factors associated with overall survival

	p value	Odds ratio	95 % CI
Postoperative KPS	0.017*	0.531	0.315–0.894
Radiotherapy	0.142	0.615	0.321–1.178
TMZ therapy	0.005*	0.442	0.25–0.784
Stroke	0.213	1.822	0.709–4.679

* $p < 0.05$

Some reports have indicated that elderly patients should be treated as aggressively as younger patients [13–20], especially patients with a favorable PS [13, 16, 17]. Minniti et al. [21] conducted a prospective trial of 32 primary glioblastoma patients aged ≥70 years. These patients received a combination of surgery, radiotherapy (total of 60 Gy), and chemotherapy with TMZ, and the mOS was 10.6 months. Multivariate analysis identified only preoperative KPS score as an independent prognostic factor. They concluded that elderly patients with a favorable preoperative KPS score should receive multidisciplinary treatment.

The previously reported prognostic factors for elderly glioblastoma patients are preoperative KPS score, extent of tumor resection, radiotherapy, chemotherapy, and O^6-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) activity [1, 2, 8, 12, 15–17, 19–24]. In our study of patients of a more advanced age, multivariate analyses identified postoperative KPS score and TMZ therapy as independent prognostic factors. It is interesting that prognosis was correlated with postoperative but not preoperative KPS score, suggesting that selection of treatment strategies based on preoperative KPS score may be less suitable in glioblastoma patients aged ≥76 years.

In the current study, the prognosis tended to be more favorable in patients who underwent ≥95 % resection than patients who underwent <95 % resection, but this difference was not significant ($p = 0.052$). However, a larger extent of tumor resection has been reported to contribute to improved outcomes in elderly glioblastoma patients [15, 17]. Chaichana et al. [23] examined risk factors to identify patients who would benefit from surgical resection. They suggested that surgery would be less beneficial in patients with one or more of the following factors: a low preoperative KPS score, chronic obstructive pulmonary disease, neurological symptoms, or a large tumor. As these factors are common in elderly patients, the benefits of aggressive surgery should be considered carefully.

Chemotherapy with TMZ is reported to be relatively safe and effective for the treatment of elderly glioblastoma patients [4, 8, 12, 14, 17, 21–30]. In our study, 31 patients received TMZ. Of the 19 patients (21.1 %) with CTCAE grade 3 myelosuppression, 4 received TMZ concomitantly with radiotherapy. Of the 27 patients (3.7 %) who received maintenance chemotherapy, one received TMZ as maintenance chemotherapy. The adverse reactions to TMZ are generally tolerable, and using TMZ as aggressively as possible may contribute to improved outcomes. Gállego Pérez-Larraya et al. [4] administered TMZ alone to

glioblastoma patients aged ≥70 years with postoperative KPS scores of ≤70, and reported that the adverse reactions were tolerable and patient outcomes were improved.

Some studies have reported low efficacy of radio-chemotherapy using TMZ and severe adverse reactions among elderly patients. In the European Organization for the Research and Treatment of Cancer (EORTC)–National Cancer Institute of Canada (NCIC) study, the HRs for death in patients receiving TMZ were 0.5 in patients aged <50 years ($p = 0.001$), 0.63 in patients aged 50–60 years ($p < 0.05$), 0.64 in patients aged 61–65 years ($p = 0.096$), and 0.78 in patients aged 66–70 years ($p = 0.34$), indicating that improvement of outcomes due to TMZ therapy decreased as patient age increased [2, 31]. Minniti et al. [21] conducted a prospective study of primary glioblastoma patients aged ≥70 years who received a combination of surgery, radiotherapy, and TMZ, and found grade 3–4 hematologic toxicity in 28 % of patients. Although the results of our study suggest that TMZ should be used aggressively, it is also necessary to be aware that TMZ may cause more severe adverse reactions in elderly patients than in younger patients. The Neuro-Oncology Working Group (NOA) 08 trial reported that postoperative monotherapy with TMZ is not inferior to radiotherapy in elderly patients, but the effects of TMZ are greatly affected by the methylation status of the MGMT promoter [30]. In the future, different treatment strategies may be employed according to the methylation status of the MGMT promoter.

A randomized phase III trial (NCT00482677) conducted by the NCIC Clinical Trials Group is currently ongoing. This study compares TMZ and short-course radiation with short-course radiation alone for the treatment of newly diagnosed glioblastoma in elderly (≥65 years) patients. The results of this study may strongly influence the treatment strategy for elderly glioblastoma patients.

This study has several limitations, including its retrospective design, reliance on questionnaire surveys for data, variation in radiotherapy regimens, and imprecise assessment of the extent of tumor resection. However, our results elucidate the present status and treatment outcomes of glioblastoma patients aged ≥76 years, which is an age group that has rarely been studied to date. Our findings may provide important information for the planning of future prospective clinical studies, which will be needed to establish a standard of treatment for elderly glioblastoma patients.

Conclusions

This study found that glioblastoma patients aged ≥76 years had an mPFS of 6.8 months and mOS of 9.8 months. Our findings suggest that the postoperative KPS score is an important prognostic factor in glioblastoma patients aged ≥76 years, and that these patients may benefit from TMZ therapy.

Acknowledgments We are grateful to Dr. Haruyasu Fujita, Department of Socio-Environmental Medicine, Public Health Division, Gunma University Graduate School of Medicine, Gunma, Japan, for his advice on the statistical analyses.

Conflict of interest There are no conflicts of interest to declare.

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Clinical significance and limitations of repeat resection for pediatric malignant neuroepithelial tumors

Clinical article

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Object. Maximized tumor resection and minimized surgical morbidity are extremely important in the treatment of children with malignant neuroepithelial tumors. However, the indications for repeat surgery for these tumors remain unclear. The present study investigated the clinical significance and limitations of repeat resection for these tumors.

Methods. This study included 61 consecutive pediatric patients with malignant neuroepithelial tumor, histologically diagnosed as WHO Grades III and IV. All patients were initially treated between January 1997 and March 2011 and had follow-up of more than 2 years. The number of surgeries, presence of leptomeningeal dissemination, survival, WHO grade, and Eastern Cooperative Oncology Group performance status before and after surgery were retrospectively reviewed.

Results. Repeat resections were performed for 21 patients (34.4%). Eastern Cooperative Oncology Group performance status was not aggravated by surgery, even after multiple operations. The 5-year survival rates of patients who received single and repeat surgery were 58.6% and 38.7%, respectively ($p = 0.12$). The mean interval between initial surgery and leptomeningeal dissemination detection was 331 ± 108 days in the single-surgery group and 549 ± 122 days in the repeat-surgery group ($p = 0.19$). The median survival time after leptomeningeal dissemination was 580 days in the single-surgery group and 890 days in the repeat-surgery group ($p = 0.74$).

Conclusions. Repeat resection with minimized surgical morbidity is an effective method to achieve better local control of pediatric malignant neuroepithelial tumors. Leptomeningeal dissemination was a leading cause of death, but repeat surgery did not increase the frequency of death.

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Key Words • **pediatric malignant neuroepithelial tumor** • **reoperation** • **resection** • **performance status** • **dissemination** • **oncology**

Pediatric malignant brain tumors are the most common solid tumors in children and are a leading cause of death.[15,20] The ultimate goal of treatment of patients with these tumors is to prolong the patient's life without causing neurological deficit. Recent advances in the treatment of patients with pediatric malignant brain tumors have increased the survival rate of patients, and advances in surgical techniques have improved the rate of complete resection and decreased surgical morbidity. However, local relapse and leptomeningeal dissemination are still challenging problems that need to be solved.[11,21,22,24,29]

Local recurrence is a well-known indicator of a poor prognosis after brain tumor surgery. In fact, treatment failure can predominantly occur at the local site, rather than distant locations.[24,27–29] To achieve better local control, repeat surgery should be considered, but this approach carries a higher risk of inducing neurological deficits and dissemination, which may impair a patient's PS.[18] Leptomeningeal dissemination is also a strong indicator of a poor prognosis.[21,22] Disseminated lesions sometimes occur in multiple locations, and surgery is not indicated in these cases. Radiation therapy and/or chemotherapy are the indicated interventions but are not always effective, resulting in an unsatisfying clinical outcome. Repeat surgery should be performed for local recurrence after gross-total tumor removal as well as for regrowth after

Abbreviations used in this paper: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

partial removal of the tumor. Low-grade malignant tumors in eloquent areas, such as hypothalamic/chiasmatic gliomas, sometimes require repeat surgery. However, leptomeningeal dissemination is less likely to occur with these low-grade malignant tumors.[6,26] Since the prognostic factors are different for high-grade and low-grade tumors, the indications for intervention for treatment failure in high-grade tumors remain important.

The present study retrospectively investigated the outcomes of consecutive patients with pediatric malignant neuroepithelial tumors treated in our department to evaluate the clinical significance and limitations of repeat resection for local tumor control and prognosis.

Methods

This study included 61 consecutive patients with pediatric neuroepithelial tumors admitted for treatment, including resection, chemotherapy, or radiation therapy, at Tohoku University Hospital, between January 1997 and March 2011. Some of these patients have been described previously.[1,10,22,23] All patients were under 15 years of age at the time of initial surgery and were followed up in our outpatient department for at least 2 years. The histological diagnosis was based on the WHO classification.[14] Patients who had a metastatic brain tumor, a non-neuroepithelial tumor such as meningioma or germ cell tumor, or a spinal cord tumor were excluded. Patients who underwent a stereotactic biopsy without radical resection were also excluded. The present study excluded patients with WHO Grade I and II neuroepithelial tumors, such as pilocytic astrocytoma, to evaluate the impact of repeat surgery on the clinical outcome of patients with an unsatisfactory prognosis. Informed consent was obtained from the patient or guardian at admission, prior to CT or MR imaging with contrast medium, and before resection or radiation or chemotherapy.

Data Collection and Analysis

The following variables were recorded in a database and analyzed: age, sex, histological diagnosis (WHO grade), presence of leptomeningeal dissemination, survival, and ECOG PS before and after surgery. Neuroimaging findings, including CT and MRI, were also recorded.

Clinical Management

All patients initially underwent radical surgery. As much of the tumor was removed as possible. Neuromonitoring, such as motor evoked potential, cortical and subcortical stimulation mapping, and neuronavigation, was used during resection if necessary. Adjuvant radiation or chemotherapy was performed as needed based on the histological diagnosis and clinical course. Patients were followed up at our outpatient department with MRI at 3-month intervals or more frequently. If a local recurrence was apparent, resection was considered. In our facility, the following precautions are taken to prevent wound-related complications: 1) the patient's head around the skin incision is always shaved immediately before the operation; 2) the skin is washed using chlorhexidine soap and is disinfected with alcohol followed by iodine solution; 3) after removing the bone flap, all granulation tissues and residual titanium plates and screws are completely removed; 4) the surgical field outside the dura mater is brushed and irrigated with iodine solution followed by normal saline solution; 5) the free bone flap is also brushed and irrigated with iodine solution followed by normal saline solution and is maintained in normal saline solution; 6) complete closure is performed to prevent CSF leakage; 7) the surgical field is irrigated with normal saline solution before wound closure;[8] and 8) prophylactic antibiotic administration is continued until 6 days after surgery (3 days for initial surgeries). Repeat surgery was not performed for patients with diffuse subarachnoidal or subependymal dissemination. Distant lesions with local recurrence, accessible via the same surgical approach, were not considered to be contraindicated for repeat surgery and were actively removed.

Statistical Analysis

Statistical analysis was performed on March 31, 2013. Estimates of overall survival from the time of initial surgery to death and survival times from the detection of leptomeningeal dissemination to death were calculated using the Kaplan-Meier method. Differences in characteristics between patients who underwent single surgery (single-surgery group) and who required repeat surgery (repeat-surgery group) were examined by Fisher exact test, Student t-test, or chi-square test. Probability values $\leq$ 0.05 were considered statistically significant; SPSS software (IBM Japan) was used for statistical analysis.

Results

Clinical Characteristics and Course

The clinical characteristics of the 61 patients with neuroepithelial tumors are shown in Tables 1 and 2. Forty patients (65.6%) underwent surgery once (single-surgery group), and 21 patients (34.4%) underwent repeat surgery during their entire clinical course (repeat-surgery group). Thirteen patients (21.3%) underwent surgery 2 times, 3 (4.9%) underwent surgery 3 times, and 4 (6.6%) underwent surgery 4 times. One patient with an ependymoblastoma underwent radical resection 6 times during 8.5 years and maintained full PS.[1] Among patients with local recurrent disease, 11 did not undergo surgery. This was due to concurrent leptomeningeal dissemination in 7 patients, the tumor being located in a surgically inaccessible region in 3 patients, and a complete response obtained by additional chemotherapy and radiation therapy in 1 patient.

Survival

Overall and progression-free survival times of patients in each WHO grade category are compared in Figs. 1 and 2, respectively. The 5-year overall survival rates were 48.1% in patients with WHO Grade III tumors and 56.9% in patients with WHO Grade IV tumors ($p = 0.91$). The 5-year progression-free survival rates were 35.9% in patients with WHO Grade III tumors and 45.8% in pa-

TABLE 1: Histological diagnosis in the 61 patients

Histology	No. of Patients	Single Op	Repeat Op	Rate of Repeat Op (%)
WHO Grade III	20	12	8	
anaplastic ependymoma	9	5	4	44.4
anaplastic astrocytoma	5	4	1	20.0
choroid plexus carcinoma	4	1	3	75.0
anaplastic oligoastrocytoma	1	1	0	0
anaplastic pilocytic astrocytoma	1	1	0	0
WHO Grade IV	41	28	13	
medulloblastoma	26	22	4	15.4
glioblastoma	5	1	4	80.0
primitive neuroectodermal tumor	6	3	3	50.0
pineoblastoma	2	2	0	0
ependymoblastoma	1	0	1	100
atypical teratoid/rhabdoid tumor	1	0	1	100

tients with WHO Grade IV tumors ($p = 0.57$). The 5-year overall survival rate was 58.6% for patients in the single-surgery group and 38.7% for patients in the repeat-surgery group, with no significant difference ($p = 0.12$) (Fig. 3). The median survival time of patients in the single-surgery group could not be calculated, but that of patients in the repeat-surgery group was 1716 days. During the observation period, 30 patients died, 22 (73.3%) of leptomeningeal dissemination, 7 (23.3%) of uncontrollable local recurrence, and 1 (3.3%) of sepsis during intensive chemotherapy.[10]

Dissemination

Leptomeningeal dissemination was observed in 18 patients (45.0%) in the single-surgery group and 14 (66.7%) in the repeat-surgery group (Table 2). The median survival time after leptomeningeal dissemination was 580 days in the single-surgery group and 890 days in the repeat-surgery group, with no significant difference ($p = 0.74$) (Fig. 4). The mean time interval (± SD) between initial surgery and detection of leptomeningeal dissemination was 331 ± 108 days in the single-surgery group and 549 ± 122 days in the repeat-surgery group, with no significant difference ($p = 0.19$). Also, the mean interval after second surgery to dissemination in the repeat-surgery group was 260 ± 84 days, with no significant difference compared with the time interval after initial surgery to dissemination ($p = 0.68$) (Fig. 5).

Eastern Cooperative Oncology Group Performance Status

The clinical condition was evaluated using the ECOG PS. There was no significant difference between the PS before the initial surgery and the PS before the second, third, and fourth surgeries (Fig. 6). We calculated the changes in PS after each surgery with the following formula: ΔPS = (preoperative PS) – (postoperative PS). Positive and negative values indicate improvement and aggravation of the clinical condition, respectively. Figure 7 shows that the maximum improvement was at the initial surgery, and that PS was not aggravated by surgery.

Surgical Complications

Unexpected incidents of neurological deterioration after surgical intervention are listed in Table 3. Surgical complications occurred in 13 patients (21.3%) at initial surgery and 2 patients (9.5%) at repeat surgery. Cerebellar mutism after removal of a medulloblastoma was the most frequent complication (7 cases). Infection and bleeding complications were not observed even with repeat surgery.

Representative Case

A 1-year-old boy suffered severe nausea and vomiting, and deterioration of general response. A CT scan of the head demonstrated a mass lesion in the fourth ventricle with ventricular dilation. The patient was referred to our department in July 2007. Magnetic resonance imaging on admission demonstrated that the tumor was heterogeneously enhanced with gadolinium (Fig. 8A). No other intracranial or spinal lesions were found. The PS score on admission was 4. Intraoperative examination revealed a very thin membranous tumor invading the medulla oblongata, which was preserved to avoid surgery-related

TABLE 2: Baseline demographic characteristics of 61 patients

Characteristic	Single Op	Repeat Op	p Value
no. of cases	40	21	
male/female ratio	26:14	14:7	0.90
mean age ± SD (yrs)	6.9 ± 4.4	5.2 ± 4.6	0.17
leptomeningeal dissemination (%)	18 (45)	14 (66.7)	0.11

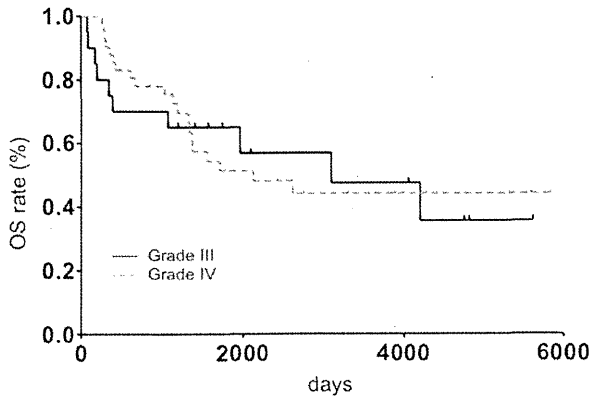

FIG. 1. Overall survival (OS) times in patients with WHO Grade III *(solid line)* and IV *(dashed line)* tumors plotted using the Kaplan-Meier method. The 5-year overall survival rates were 48.1% and 56.9% in patients with WHO Grade III and IV tumors, respectively (log-rank test, p = 0.91).

neurological deficit (1st surgery). The histological diagnosis was an anaplastic ependymoma.[22] Postoperative MR imaging detected no residual enhanced lesions (Fig. 8B), but adjuvant chemotherapy with ifosfamide, cisplatin, and etoposide was subsequently performed. The PS was 0 after the 1st surgery. The patient was discharged and had a good quality of life. One year after the initial surgery, a small mass lesion in the fourth ventricle was detected (Fig. 8C), and a reoperation was performed (second surgery) and followed by radiotherapy and chemotherapy with ifosfamide, cisplatin, and etoposide (Fig. 8D). The PS score was 1 before the second surgery and did not change after surgery. One year after second surgery, a right cerebellar mass lesion beside the fourth ventricle was detected (Fig. 8E), and a reoperation was performed (third surgery) and followed by chemotherapy with carboplatin (Fig. 8F). The PS score was 1 before the third surgery and 2 following it. Two years after the 3rd surgery, a small enhanced lesion was detected in the left lateral

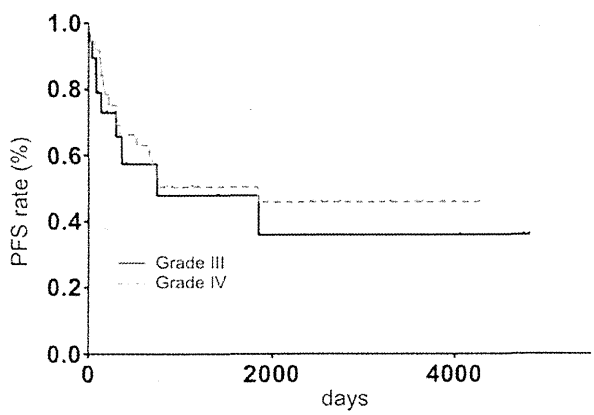

FIG. 2. Progression-free survival (PFS) times in patients with WHO Grade III *(solid line)* and IV *(dashed line)* tumors plotted using the Kaplan-Meier method. The 5-year PFS rates were 35.9% and 45.8% in patients with WHO Grade III and IV tumors, respectively (log-rank test, p = 0.57).

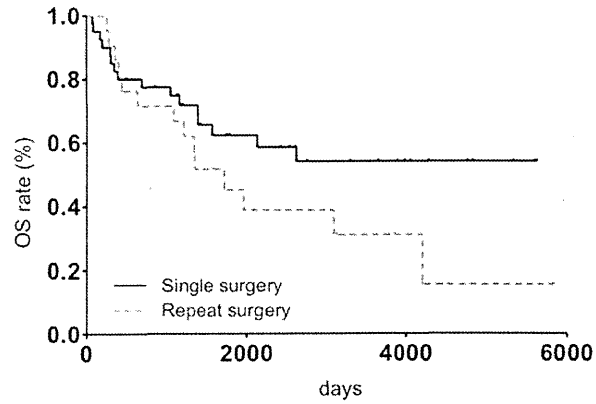

FIG. 3. Overall survival times in the single- *(solid line)* and repeat- *(dashed line)* surgery groups plotted using the Kaplan-Meier method. The 5-year overall survival rates were 58.6% and 38.7% in the single- and repeat-surgery groups, respectively, with no significant difference (log-rank test, p = 0.12). The median survival time in the single-surgery group could not be calculated and that in the repeat-surgery group was 1716 days.

recess and a fourth surgery was performed (Fig. 8G and H). The PS score before fourth surgery was 1 and did not change after surgery. The patient was still alive 5 years after the initial surgery with good neurological condition (PS score of 1) without leptomeningeal dissemination. He has been treated with nimustine hydrochloride bimonthly in our outpatient clinic.

Discussion

This study investigated the clinical effectiveness of repeat radical resection for pediatric patients with a malignant neuroepithelial tumor. The overall survival rate of the patients who received repeat surgery was not inferior to the survival rate of the patients who underwent a single surgery. Although the tumors in the present patient

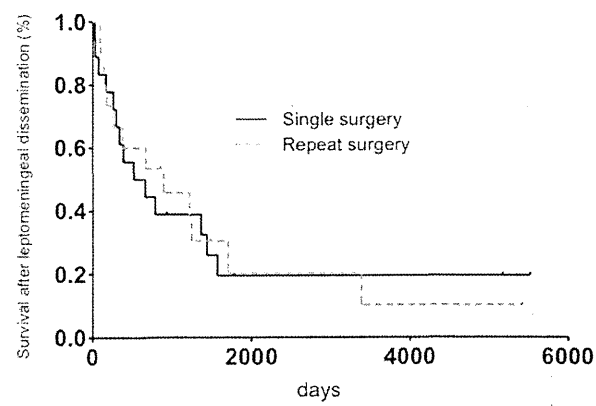

FIG. 4. Survival time after detection of leptomeningeal dissemination in the single- *(solid line)* and repeat- *(dashed line)* surgery groups plotted using the Kaplan-Meier method. The median survival time after leptomeningeal dissemination was 580 days in the single-surgery group and 890 days in the repeat-surgery group, with no significant difference (p = 0.74).

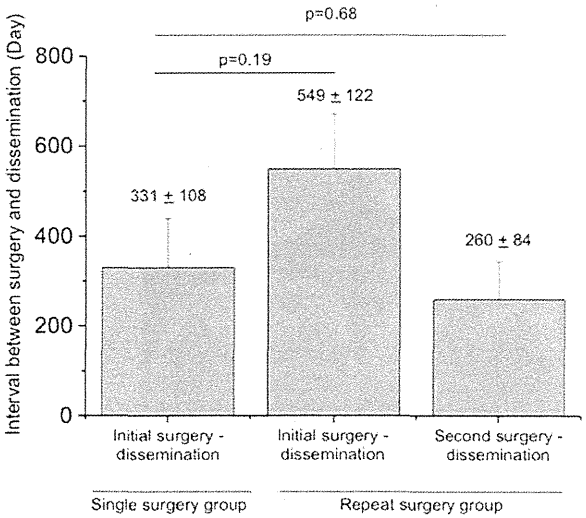

Fig. 5. Interval between surgery and detection of leptomeningeal dissemination. The mean interval (± SD) between initial surgery and leptomeningeal dissemination was 331 ± 108 days in the single-surgery group and 549 ± 122 days in the repeat-surgery group, with no significant difference ($p = 0.19$). The mean interval after second surgery to dissemination was 260 ± 84 days in the repeat-surgery group, with no significant difference compared with the time interval after initial surgery to dissemination ($p = 0.68$).

population were histologically heterogeneous, our results indicated that repeat surgery can achieve better local control of the tumor.

During the observation period, 30 patients died, mainly of leptomeningeal dissemination. Multivariate analysis was not possible because of the small sample size, but leptomeningeal dissemination certainly affected the prognosis. In fact, survival after detection of leptomeningeal dissemination was short, and this poor prognosis was the same for patients who had undergone single and repeat surgery (Fig. 4, $p = 0.74$). Advanced surgical techniques have significantly reduced the complication rate.

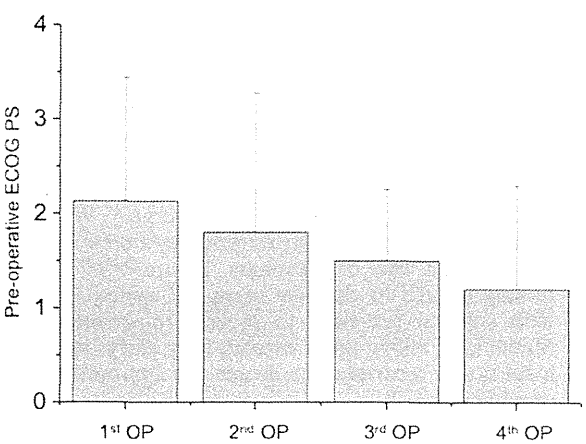

Fig. 6. Preoperative ECOG PS scores before each operation. There was no significant difference between the PS score before initial surgery and that before second, third, and fourth surgeries.

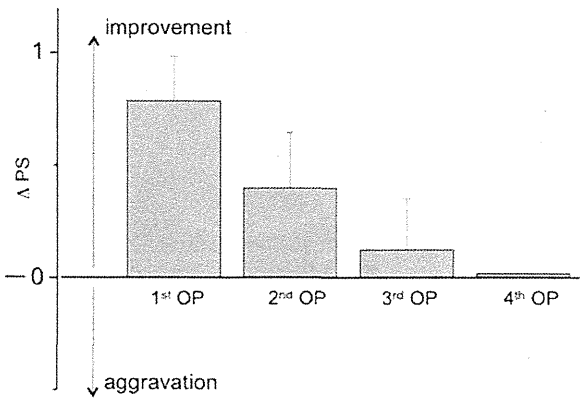

Fig. 7. Performance status improvement (ΔPS) after each surgery. Maximum improvement was obtained at the initial surgery, and PS was not aggravated after repeat surgery.

However, surgery-related tumor cell seeding remains as a possible cause of leptomeningeal dissemination.[3,4,12,19] Although patients who receive repeat surgery may face a higher risk of leptomeningeal dissemination, our study showed that the interval between initial surgery and detection of leptomeningeal dissemination was similar in the single- and repeat-surgery groups. Moreover, there was no difference between the interval after initial surgery to dissemination in the single-surgery group and the interval after second surgery to dissemination in the repeat-surgery group (Fig. 5, $p = 0.68$). These results indicate that surgical intervention, even repeat surgeries, may not result in leptomeningeal dissemination. Taken together, the findings of this study revealed that leptomeningeal dissemination might limit survival, but repeat surgery did not worsen the clinical course after initial surgery for pediatric neuroepithelial tumors.

As in most institutions, our surgical strategy is to resect tumors as completely as possible without causing new neurological deficits, to maximize the quality of functional survival.[2,16] More extensive resection has become possible with significant improvements in intraoperative neurophysiological monitoring, such as motor evoked potential or cortical and subcortical stimulation mapping, and neuronavigation.[13,25] The extent of resection is directly correlated with survival in patients with malignant gliomas.[16] Extensive resection may also provide increased symptomatic relief and neurological improvement.[9] Interestingly, surgically acquired motor and

TABLE 3: Surgical complications at initial and repeat surgery

Complication	Initial Op	Repeat Op
cerebellar mutism	7	0
focal damage/ischemia	3	2
cranial nerve symptoms	2	0
diabetes insipidus	1	0
infection	0	0
bleeding	0	0
total no. (complication rate)	13 (21.3%)	2 (9.5%)

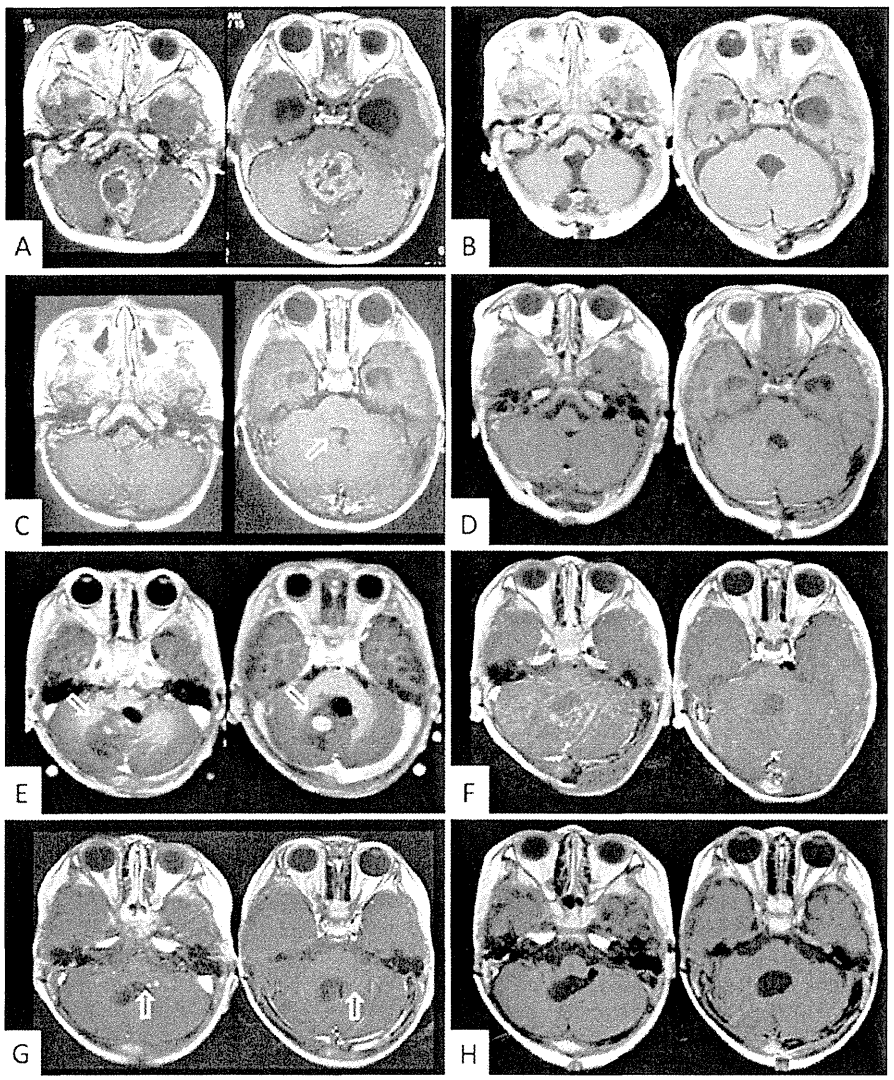

FIG. 8. Representative case of a 1-year-old boy with an anaplastic ependymoma successfully treated with 4 surgeries. Admission Gd-enhanced T1-weighted MR images showing a heterogeneously enhanced tumor located in the fourth ventricle **(A)** and after the first surgery resulting in gross-total removal **(B)**. Gadolinium-enhanced T1-weighted MR images 1 year after the first surgery showing local recurrence (**C**, *open arrow*) and after the second surgery resulting in gross-total removal **(D)**. Gadolinium-enhanced T1-weighted MR images 1 year after the second surgery showing another mass lesion in the right cerebellum (**E**, *open arrows*) and after the third surgery resulting in gross-total removal **(F)**. Follow-up Gd-enhanced T1-weighted MR images 2 years after the third surgery revealing a small enhanced lesion in the left lateral recess (**G**, *open arrows*) and after fourth surgery resulting in gross-total removal **(H)**.

language deficits are associated with a poor prognosis in patients with malignant gliomas.[17] Nevertheless, extensive resection is sometimes not easy to achieve because these tumors are frequently invasive and often involve eloquent areas.[5] In our study, the maximum improvement of PS was at the initial surgery (Fig. 7). However, the most remarkable and important finding was that PS was not worsened by surgery, even after multiple operations.

Our results indicate that surgical intervention, even repeat surgery, will not impair neurological condition or survival. Local recurrence can occur with malignant tumors such as anaplastic ependymoma, even if gross-total removal was achieved at the initial surgery. Previous reports have indicated that the primary tumor site is the predominant site of treatment failure.[25,27–29] However, tumors located in eloquent areas are sometimes treated with subtotal resection to prevent impairment of PS. Meticulous follow-up is essential for early detection of local tumor recurrence to decide the appropriate timing of reoperation.[22]

Since additional treatment including surgery, radiotherapy, and chemotherapy can be accompanied by serious adverse effects, careful decision making is required. In our series, cerebellar mutism was the most frequent

surgical complication, because medulloblastoma was the most common tumor in this study. In fact, 7 (26.9%) of 26 patients who had a medulloblastoma had cerebellar mutism after the initial surgery. The incidence of cerebellar mutism after medulloblastoma surgery is reported to range from 11% to 39%,[7,30] which is compatible with our findings. Moreover, none of our patients developed meningitis or required surgical treatment for wound infection. This infection rate was particularly low. Recently, surgical-site infection was observed in 15.4% of patients after surgery for pediatric brain tumors, and wound-related complications were more common in patients undergoing repeat surgery.[18] Patients who previously underwent surgery, radiotherapy, and chemotherapy are clearly likely to have a higher risk of wound complications, including infection. To prevent such complications of infection, we routinely performed the various preventative procedures described in the *Methods* section. Presumably, these intensive procedures are responsible for our low infection rate.

The present report has limitations. First, the number of cases is limited. More cases are required for better understanding of the prognostic factors. Second, this is a single-institution study. Surgical outcome is highly dependent on the operator's skill, so our results cannot be directly compared with other reports. However, we believe it is important to demonstrate the possibility that strict surgery and adjuvant therapy with meticulous follow-up can lead to a better prognosis even if repeat surgery is required.

Conclusions

Repeat surgery is the preferred and most effective method for local tumor control in patients with pediatric malignant neuroepithelial tumors, although additional radiochemotherapy should be performed. Maximized tumor resection and minimized surgical morbidity are essential for good outcome and preserved PS. Repeat surgery for local tumor control should be considered unless leptomeningeal dissemination is evident. In pediatric patients with malignant neuroepithelial tumors who died after receiving intensive treatment with surgery and adjuvant therapy, the most frequent cause of death was leptomeningeal dissemination.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kumabe. Acquisition of data: Kumabe, Kawaguchi, Saito, Kanamori, Yamashita, Sonoda. Analysis and interpretation of data: Kumabe, Kawaguchi, Saito, Kanamori, Yamashita, Sonoda. Drafting the article: Kawaguchi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kumabe. Statistical analysis: Kawaguchi. Administrative/technical/material support: Tominaga. Study supervision: Kumabe, Tominaga.

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The 71st Annual Meeting Special Topics — Part III: Treatment Strategy of Low Grade Glioma

Summary of 15 Years Experience of Awake Surgeries for Neuroepithelial Tumors in Tohoku University

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Abstract

We retrospectively analyzed 15 years experience of awake surgeries for neuroepithelial tumors in Tohoku University. Awake surgeries mostly for language mapping were performed for 42 of 681 newly diagnosed cases (6.2%) and 59 of 985 surgeries including for recurrence (6.0%). When the same histologies and locations as cases resected under awake condition are selected from the parent population treated by radical resection, awake surgeries were most frequently performed for 14 of 55 newly diagnosed cases (25.5%) and 14 of 62 surgeries (22.6%) with grade II gliomas. In the results, 8 of 59 surgeries (13.6%) could not achieve complete language monitoring until the final stage of tumor resection, considered as failed awake surgery. Gross total resection was accomplished in 20 of 42 newly diagnosed cases (47.6%) and 32 of 59 surgeries (54.2%). Mortality rate was 0%. Late severe deficits were observed in 2 of 42 newly diagnosed cases (4.8%) and 3 of 59 surgeries (5.1%). Negative language mapping cases did not suffer severe deficits in both early and late stages. In contrast, high incidence of severe deficits, 3 as early and 2 as late of 8 cases, were identified with failed awake surgery. The overall survival of patients treated by awake surgery compared favorably with those treated without stimulation mapping and with stimulation mapping under general anesthesia. Awake surgery may contribute to improve the outcome of gliomas near eloquent areas by maximizing the tumor resection and minimizing the surgical morbidity.

Key words: awake surgery, electrical stimulation, glioma, language mapping, outcome

Introduction

Awake surgeries provide an opportunity for mapping sensorimotor, language, and cognitive functions in order to maximize tumor resection and minimize surgical morbidity. Propofol, which is the essential sedative for awake surgery, became commercially available in December 1995 in Japan. Professor Tomokatsu Hori at Tottori University first reported awake surgery for meningioma using propofol in 1996.[12] We first resected glioma under the awake condition with neurophysiological

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monitoring on December 5, 1996, as reported in 1997.[21] These surgeries were the predawn of awake surgery in Japan. Thereafter, the Japan Awake Surgery Conference was established in 2002 for the purpose of continuing research into neurocognitive functions as well as establishing and promoting safe methods of awake craniotomy. Finally, guidelines for awake craniotomy for brain lesions near language areas were published in 2012.[11] Therefore, 15 years have passed since the introduction of awake surgery for resection of gliomas in Japan.

In this paper, we would like to summarize our experiences of awake surgery in Tohoku University for 15 years, and try to answer the following questions: 1) What does awake surgery bring to glioma surgery? 2) What is the frequency of awake surgery? 3) What was the outcome?

Materials and Methods

I. Patient population

We retrospectively analyzed 42 newly diagnosed consecutive patients, 31 males and 11 females aged 22 to 70 years (mean ± standard deviation [SD] 44.4 ± 14.5 years, median 45 years) with neuroepithelial tumors located near/within the motor and/or language areas, radically resected under the awake condition with intraoperative stimulation mapping/monitoring at Tohoku University Hospital between December 1996 and December 2011 by the same neurosurgeon (first author T.K.) These areas consisted of the sensorimotor strip (precentral and postcentral gyri), dominant hemisphere perisylvian language areas (superior and middle temporal, inferior and middle frontal, and inferior parietal areas) including their connecting fibers. The results of preoperative functional imaging, such as functional magnetic resonance (MR) imaging and magnetoencephalography, were also taken into consideration. Fifty-nine awake surgeries were performed for newly diagnosed and recurrent tumors (n = 17) during this period. Four patients were treated under the awake condition for both newly diagnosed and recurrent tumors. We had limited experience of awake surgery for language mapping except during the first 15 years, because motor mapping and monitoring can be performed using simulation mapping under general anesthesia. During the same period, 681 newly diagnosed neuroepithelial tumors were surgically treated, and 985 surgeries including biopsy were performed in our hospital. Decisions regarding patient treatment were made by the same neurosurgeon (first author T.K.) The histopathological diagnosis was based on the World Health Organization (WHO) classification. Informed consent was obtained from each patient or guardian on admission, prior to computed tomography or MR imaging with contrast medium and surgical resection/radiochemotherapy. Institutional Review Board approval was waived because of the retrospective nature of the study.

II. Surgical procedure

Patients were positioned with a large roll under the shoulder and with the head lying on a soft rest without rigid pin fixation. Neuronavigation systems could be used without pin fixation using skull reference tools.[1,14] The bipolar stimulator with 5-mm spacing between the electrodes was used. Under monitoring of after-discharge using electrocorticography, cortical and subcortical mapping was performed using electric stimuli of 3–16 mA (average 7.3 mA, median 8 mA), train of square waves, and biphasic pulses of 0.3-millisecond phase duration at a frequency of 50 Hz, to identify the sensorimotor and language cortices and their connection fibers, according to the method described previously.[2-6,15,24] Speech arrest was defined as a discontinuation in number counting without simultaneous motor responses. For sites associated with naming, stimulation was applied for 3 seconds at sequential cortical sites during a slide presentation of line drawings. All cortical sites were stimulated three times.

Two different anesthesiology protocols for awake surgery have been applied. In the early stage, spontaneous ventilation was maintained without the laryngeal mask throughout the surgical procedures (21 newly diagnosed cases and 2 recurrent cases). During this early stage, awake surgery was also applied purely for motor mapping in the 5 gliomas in the non-dominant hemisphere, but since then the indicator for awake surgery has been confined to identify the language function. We did not map the subcortical white matter for language at this stage, but only for motor pathways under prescribed sedative. After January 2005 (late stage), we routinely applied the asleep-awake-asleep (AAA) technique,[10] intermittent general anesthesia with controlled ventilation using the laryngeal mask (21 newly diagnosed cases and 15 recurrent cases) (Fig. 1). In general, the patients remained fully awake from the beginning of cortical mapping until the completion of tumor removal to obtain complete functional mapping for both cortical and subcortical regions. The tumor resection was carried out while the patients continued to perform the language tasks including free speech and conversation with the observer, and the surgeon modified the resection and the electrical subcortical stimulation. An awake craniotomy was

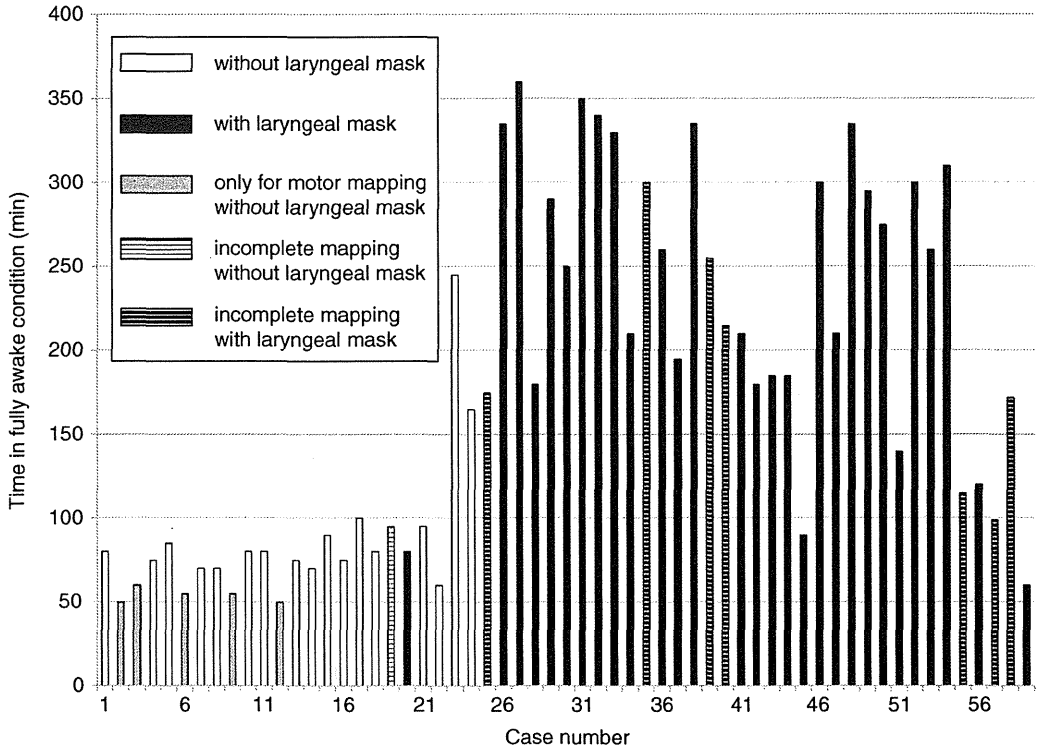

Fig. 1 Time in fully awake condition for each awake surgery. Each bar is arranged in chronological order. *White, black, and gray bars* indicate the different protocols for awake surgery, such as language mapping/monitoring without using the laryngeal mask (n = 18), language mapping/monitoring with the laryngeal mask (n = 36), and performing only motor mapping/monitoring without the laryngeal mask (n = 5), respectively. *Crossed bars* indicate the cases with incomplete language mapping (failed awake surgery) without (n = 1) and with the laryngeal mask (n = 7).

considered a failure if cortical and subcortical mapping or awake monitoring were either aborted prematurely or not performed successfully.

III. Extent of resection

In order to assess the effectiveness of awake surgery for maximizing tumor resection, the extent of surgical resection was evaluated with quantitative volumetric analysis using postoperative MR imaging performed within 72 hours of surgery. If the tumor was enhanced on the preoperative MR images, gross total resection (GTR) of the tumor was defined as resection with no residual enhanced tumor, subtotal resection (STR) as over 75% resection, and partial resection (PR) as under 75% resection. If the tumor was not enhanced on the preoperative MR images, resection was evaluated based on the residual high intensity lesion on the T_2-weighted MR images. Sometimes, the high intensity lesion was difficult to define on the T_2-weighted MR images as a residual tumor, so 98% or more resection was identified as GTR. STR and PR were considered as unsatisfactory resection.

IV. Postoperative neurological outcomes

The postoperative neurological outcome was recorded and confirmed by retrospective review of all hospital records and physician notes. Radiographic lesions without neurological symptoms were not defined as surgical complications. The primary outcome measure was the event rate of new postoperative neurological deficits. Deficits were categorized according to severity (severe or less severe) and timing of assessment (early and late), as proposed by De Witt Hamer et al.[9] Mortality from any cause within 30 days after resection was included. Deficits were considered severe if involving muscle strength grades 1 to 3 on the Medical Research Council Scale, aphasia or severe dysphasia, hemianopsia, or vegetative state. All other neurological deficits were considered less severe, including grade 4 monoparesis, isolated central facial palsy or other cranial nerve deficits, dysnomia, somatosensory syndrome, or parietal syndrome. Deficits at 7 days after surgery were defined as early, and deficits at 3 months were defined as late.

V. Statistical analysis

Statistical analysis was performed on December 31, 2012. Mean ± SD and median follow-up periods for 42 newly diagnosed cases were 2072 ± 1468 and 1652 days, respectively (range 357–5590 days). Estimate of overall survival (OS) from the time of initial surgery to death was calculated with the Kaplan-Meier method. Log rank test was used to compare the differences between groups. Qualitative variables were compared using the chi-square test, and analysis of variance (ANOVA) was used for continuous variables. Probability values ≤ 0.05 were considered statistically significant. JMP Pro 9.0.2 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analyses.

Illustrative Case

A 30-year-old female presented with glioblastoma that manifested as generalized tonic-clonic convulsion. T_2-weighted MR imaging demonstrated a hyperintense lesion in the left frontal lobe, infiltrating into the anterior parts of both the insula and basal ganglia, and the corpus callosum. Administration of contrast medium caused heterogeneous enhancement (Fig. 2A). Neurological and neuropsychological examination revealed no abnormality. Functional MR imaging revealed that her language dominancy was located in the left hemisphere (Fig. 2I).

We planned to resect the tumor using the AAA protocol with intraoperative neurophysiological

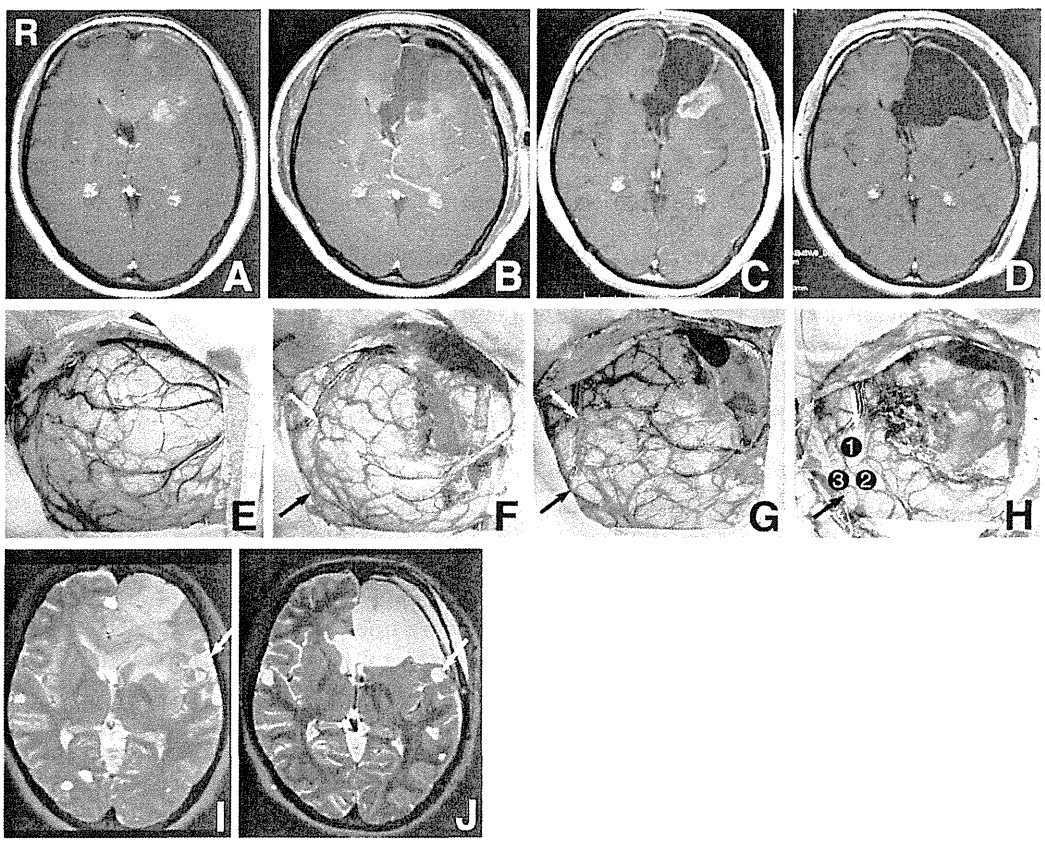

Fig. 2 Illustrative case of a 30-year-old female with left frontal glioblastoma. A–D: Axial T_1-weighted magnetic resonance (MR) images with contrast medium preoperatively (A), immediately after the first resection under general anesthesia (B), 3 months after the first surgery (C), and immediately after the second resection with stimulation mapping under awake condition (D). E–H: Intraoperative photographs just after opening of the dura mater (E) and tumor removal (F) at the first surgery, and just after reopening of the dura mater (G) and tumor removal (H) at the second surgery, demonstrating total resection of the tumor including the inferior and middle frontal gyri after the second surgery. *Arrows* indicate the central sulcus. *Three circles* depict the primary sensory sites of the tongue (1) and orofacial area (2), and the motor area of the tongue (3), respectively. I, J: Functional MR images before the first surgery (I) and after the second surgery (J). Activated areas through the verb generation task were superimposed on the axial T_2-weighted MR images, depicting the frontal language area was preserved just behind the resection cavity (*arrows*).

monitoring to maximize tumor resection and minimize surgical morbidity. However, Dr. Kiyotaka Sato, who was our only neuro-anesthesiologist, suddenly became ill on that day. Thus, we had no other choice than to resect only the medial part of tumor located in the inferior and middle frontal gyri to avoid language dysfunction under general anesthesia (Fig. 2E, F). Postoperatively, no new neurological deficits were observed, but MR imaging disclosed PR of the tumor (Fig. 2B). The histopathological diagnosis was glioblastoma. Adjuvant therapy consisted of 60 Gy of fractionated radiation and concomitant administration of temozolomide. However, the tumor progressed without neurological deterioration (Fig. 2C).

Three months after the initial operation, we tried to resect the tumor under the awake condition as in the original plan (Fig. 2G). We identified the primary sensory sites of the tongue and orofacial area, and the motor area of the tongue using direct cortical stimulation. Positive language sites could not be detected within the cortical exposure (negative language mapping), so we removed the inferior and middle frontal gyri and anterior parts of both the insula and basal ganglia with neuronavigational assistance (Fig. 2H). The patient's motor and language functions were maintained without interruption until the end of tumor resection. Postoperatively, neurological and neuropsychological examination revealed no abnormality, and MR imaging depicted GTR of the tumor (Fig. 2D). Functional MR imaging demonstrated that the frontal language area was preserved just behind the resection cavity (Fig. 2J). She returned to work as a home economics teacher. OS was 1124 days and she remains alive at this time.

Results

I. Frequency of awake surgery

Awake surgeries were performed for 42 of 681 newly diagnosed cases of glioma (6.2%) and 59 of 985 cases (6.0%) with neuroepithelial tumors. One hundred and eight newly diagnosed cases (15.9%) and 167 surgeries (17.0%) required radical resection with stimulation mapping techniques (Table 1). When the same histologies and locations as cases resected under awake condition are selected from the parent patient population undergoing radical resection, awake surgeries were performed for 14 of 55 newly diagnosed cases (25.5%) and 14 of 62 surgeries (22.6%) with grade II gliomas (diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas), and 20 of 129 newly diagnosed cases (15.5%) and 30 of 189 surgeries (15.9%) with grade III gliomas. Twenty-five of 55 newly diagnosed cases (45.5%) and 29 of 62 surgeries (46.8%) with grade II gliomas, and 45 of 129 newly diagnosed cases (34.9%) and 66 of 189 surgeries (34.9%) with grade III gliomas were radically resected with stimulation mapping. Among glioblastomas treated by radical resection, awake surgeries were performed only for 6 of 197 newly diagnosed cases (3.0%) and 11 of 323 total surgeries (3.4%), whereas 26 newly diagnosed cases (13.2%) and 53 surgeries (16.1%) were radically resected with stimulation mapping (Table 2).

Table 1 Surgical procedures for newly diagnosed patients and for all patients including with recurrence

Surgery	Newly diagnosed	All
Biopsy	126 (18.5%)	173 (17.6%)
Radical resection		
Without stimulation mapping	447 (65.6%)	645 (65.5%)
With stimulation mapping	108 (15.9%)	167 (17.0%)
under awake condition	42 (6.2%)	59 (6.0%)
under general anesthesia	66 (9.7%)	108 (11.0%)
Total	681	985

II. Resection rates and mapping results

GTR was accomplished in 20 of 42 newly diagnosed cases (47.6%) and 32 of 59 surgeries (54.2%). During the same period, the same histopathological tumors treated by awake surgeries were resected totally in 289 of 462 radical surgeries excluding biopsies (62.6%) without stimulation mapping, and 66 of 99 radical surgeries excluding biopsies (66.7%) with simulation mapping under general anesthesia. There was no significant difference (chi-square test, $p = 0.298$). GTR could be performed in only 2 of 8 failed awake surgeries (25.0%) (Table 3). Except for these 8 failed awake surgeries, GTR was achieved in 16 of 30 surgeries with positive language mapping (53.3%) and 10 of 16 surgeries with negative language mapping (62.5%), which could maintain the fully awake condition until the end of tumor removal. Four of 5 surgeries without language mapping (only motor mapping) (80.0%) could be resected totally. There was no significant difference between these four groups (chi-square test, $p = 0.209$).

III. Intraoperative events

Mean times in the fully awake condition in the early and late stages were 85 ± 42 and 231 ± 86 (mean $\pm$ SD) minutes, respectively (ANOVA, $p < 0.0001$) (Fig. 1). Eight of 59 surgeries (13.6%) could not undergo complete language mapping and monitoring until the final stage of tumor resection, considered as failed awake craniotomy. Times in

Table 2 Surgical procedures for patients with the same histologies and locations as patients treated by radical surgery under awake condition

WHO grade	Histology	With stimulation mapping				Without stimulation mapping		Total radical surgery	
		Under awake condition		Under general anesthesia					
		Newly diagnosed	All	Newly diagnosed	All	Newly diagnosed	All	Newly diagnosed	All
I		2	3	5	7	27	30	34	40
	Pilocytic astrocytoma (supratentorial type excluding optic/hypothalamic and brain stem tumor)	1	1	0	0	9	12	10	13
	Ganglioglioma	1	2	5	7	18	18	24	27
II		14	14	11	15	30	33	55	62
	Diffuse astrocytoma	3	3	6	7	8	9	17	19
	Oligodendroglioma	8	8	3	6	13	15	24	29
	Oligoastrocytoma	3	3	2	2	9	9	14	14
III		20	30	25	35	84	124	129	189
	Anaplastic astrocytoma	11	15	11	15	33	55	55	85
	Anaplastic oligodendroglioma	5	7	8	10	27	34	40	51
	Anaplastic oligoastrocytoma	1	3	4	7	13	16	18	26
	Anaplastic ganglioglioma	1	3	0	0	6	10	7	13
	Atypical central neurocytoma (lobar type)	1	1	0	0	0	0	1	1
	Anaplastic ependymoma (lobar type)	1	1	2	3	5	9	8	13
IV		6	12	20	42	171	275	197	329
	Glioblastoma	6	11	20	42	171	270	197	323
	Medulloblastoma supratentorial metastasis	0	1	0	0	0	5	0	6
	Total	42	59	61	99	312	462	415	620

All: all patients including with recurrence, WHO: World Health Organization.

Table 3 Correlations between the results of intraoperative mapping and resection rates

	Number	Resection rates		p Value
		Gross total	Subtotal/partial	
Negative language mapping	16	10 (62.5%)	6 (37.5%)	0.437
Positive language mapping	30	16 (53.3%)	14 (46.7%)	0.887
Failed awake surgery	8	2 (25.0%)	6 (75.0%)	0.074
Only motor mapping	5	4 (80.0%)	1 (20.0%)	0.227
Total	59	32 (54.2%)	27 (45.8%)	

fully awake condition of 8 failed awake surgeries ranged from 95 to 300 (average 178 ± 75, median 175) minutes. There was no significant difference in fully awake time between failed and successful (range 50–360, average 173 ± 105, median 165 minutes) awake surgeries (ANOVA, p = 0.8978). All intraoperative seizures (3/59 surgeries, 5.1%) could be easily controlled with cold saline irrigation,[20] and did not correlate with awake surgery failure. The reasons for incomplete language mapping and monitoring were as follows: further deterioration of preoperative language dysfunction influenced by prescribed propofol and remifentanil until the awake condition prevented naming objects under electrical stimulation (free conversation and checking whether patients could obey simple commands were maintained for preserving disturbed language functions) in 3 cases; developing lethargy during language subcortical mapping despite even complete withdrawal of propofol and remifentanil in 3 cases; patient's refusal to maintain the awake condition from fear during the cortical mapping in 1 case; and emotional incontinence during the final stage of subcortical mapping in 1 case.

IV. Postoperative neurological events and mapping results

Mortality rate was 0%. Early severe deficits were

observed in 15.3% (9/59 surgeries), and early deficits of any severity were observed in 32.2% (19/59 surgeries) (Table 4). In the newly diagnosed cases, early severe deficits were observed in 16.7% (7/42 surgeries), and early deficits of any severity were observed in 35.7% (15/42 surgeries). Late severe deficits were observed in 5.1% (3/59 surgeries), and late deficits of any severity were observed in 22.0% (13/59 surgeries) (Table 4). In the newly diagnosed cases, late severe deficits were observed in 4.8% (2/42 surgeries), and late deficits of any severity were observed in 26.2% (11/42 surgeries). Both of these cases with severe late deficits were progressive and highly infiltrative anaplastic astrocytomas. Their preoperative language deficits (severe dysarthria and anomia, respectively) deteriorated postoperatively into motor aphasia, and were not improved with progressive disease. Negative language mapping[18] cases did not suffer severe deficits in both the early (chi-square test, $p = 0.047$) and late (chi-square test, $p = 0.278$) stages (Table 4). In contrast, high incidence of severe deficits, 3 as early (chi-square test, $p = 0.060$) and 2 as late (chi-square test, $p = 0.006$) of 8 cases, occurred after failed awake surgery.

V. Outcomes

Fifteen of 42 patients with newly diagnosed cases had died by December 31, 2012. Fourteen patients died of disease progression. One patient with left premotor anaplastic oligodendroglioma died of bladder cancer, resulting in survival period of 41 months. Eastern Cooperative Oncology Group performance status of the surviving 27 patients was grade 0 for 22, grade 1 for 4, and grade 3 for 1 because of complicated cerebral infarction during the long-term follow-up period. Thus, 96.3% of surviving patients could live independent lives.

With the same histologies and locations as cases resected under awake condition selected from the parent population with radical resection, the OS of each WHO grade is summarized in Table 5 and Fig. 3. There was no statistical significance between

Table 4 Correlations between the results of intraoperative mapping and neurological outcome

	Number	Early neurological outcome		Late neurological outcome	
		Any deficits	Severe deficits	Any deficits	Severe deficits
Negative language mapping	16	4 (25.0%, p=0.470)	0 (0%, p=0.047*)	2 (12.5%, p=0.281)	0 (0%, p=0.278)
Positive language mapping	30	10 (33.3%, p=0.850)	5 (16.7%, p=0.759)	7 (23.3%, p=0.807)	1 (3.3%, p=0.533)
Failed awake surgery	8	3 (37.5%, p=0.730)	3 (37.5%, p=0.060)	3 (37.5%, p=0.256)	2 (25.0%, p=0.006*)
Only motor mapping	5	2 (40.0%, p=0.697)	1 (20.0%, p=0.758)	1 (20.0%, p=0.909)	0 (0%, p=0.559)
Total	59	19 (32.2%)	9 (15.3%)	13 (22.0%)	3 (5.1%)

*Significant difference, $p < 0.05$.

Table 5 Overall survival of newly diagnosed patients with the same histologies and locations as patients treated by radical surgery under awake condition

	Number	Median survival time (day)	Overall survival probability (%)		
			2 Years	5 Years	10 Years
Radical resection without stimulation mapping					
WHO grade I	27	NR	100	100	90.9
WHO grade II	30	NR	96.7	96.7	82.9
WHO grade III	84	NR	79.5	60.9	53.8
WHO grade IV	171	606	39.8	16.8	7.3
Radical resection with stimulation mapping under awake condition					
WHO grade I	2	807	100	50	NA
WHO grade II	14	3666	100	100	100
WHO grade III	20	2683	84.4	66.7	46.2
WHO grade IV	6	860	66.7	33.3	33.3
Radical resection with stimulation mapping under general anesthesia					
WHO grade I	5	NR	100	100	100
WHO grade II	11	NR	90.9	72.7	72.7
WHO grade III	25	4773	92.0	87.2	71.3
WHO grade IV	20	1160	64.3	40.1	10.0

NA: not available, WHO: World Health Organization.

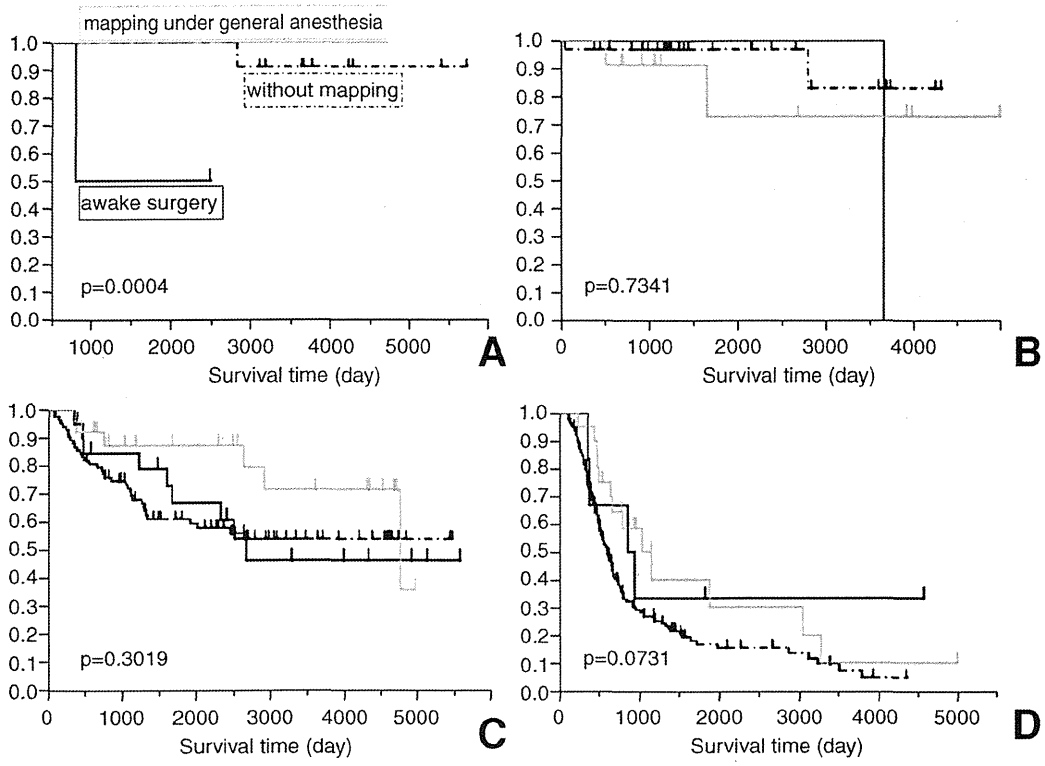

Fig. 3 Kaplan-Meier survival curves of the newly diagnosed patients who underwent awake surgery (*solid black line*), radical resection with stimulation mapping techniques under general anesthesia (*solid gray line*), and radical resection without stimulation mapping techniques (*solid dashed line*). The same histologies and locations as cases resected under awake condition are selected from the parent population undergoing radical resection (Table 2). A: World Health Organization (WHO) grade I, B: WHO grade II, C: WHO grade III, D: WHO grade IV.

patients treated under the awake condition, with stimulation mapping under general anesthesia, and without stimulation mapping, except for between awake surgery (n = 2) and without stimulation mapping (n = 27) for WHO grade 1 (log rank test, p = 0.0004). This difference was caused by the death of a 30-year-old male who had pilocytic astrocytoma in the left premotor area, which was totally resected under the awake condition in November 2002. The histopathological diagnosis was pilocytic astrocytoma with 3% of Ki-67 labeling index. His postoperative course was uneventful, but rapid local relapse was observed. This recurrent lesion was resected totally under general anesthesia. The tumor transformed into a glioblastoma. Although additional radiochemotherapies and reoperation were performed, the tumor disseminated throughout the leptomeningeal space. He died of disease progression, not due to local control failure but through dissemination, in January 2005 (OS 807 days).

Discussion

Intraoperative electrical cortico-subcortical mapping under the awake condition is crucial to allowing the most extensive removal of glioma with maximum functional preservation. Our ultimate goal during the awake condition is to obtain patient comfort to undergo the mapping in a positive manner, maximizing the functional information. The utilization of this technique is likely to vary with the surgeon. All the present series and parent populations were operated by a single neurosurgeon (first author T.K.), who was taught all the procedures for awake surgery by Dr. Berger. The present analyses may make meaningful contributions to evaluate how much impact awake surgery has for the treatment of gliomas, because all the surgeries had been performed by a single neurosurgeon, and the results including survival data were analyzed with the parent population.

I. What does awake surgery bring to glioma surgery?

The illustrative case demonstrates how important awake surgery is for glioma surgery. In this case, negative language mapping permitted this tumor to be aggressively resected without language deficits. Neurosurgeons are unable to perform GTR or maximize resection without this information for gliomas near/adjacent to eloquent areas. Awake surgery has brought "logic" into glioma surgery.

II. What is the frequency of awake surgery?

We had limited experience of awake surgery for language mapping except during the first 15 years, because motor mapping and monitoring can be performed using simulation mapping under general anesthesia. Thus, the frequency of awake surgeries might be relatively low compared to other institutes universally applying awake surgery to motor mapping and monitoring. If all simulation mapping surgeries including under general anesthesia are included, 15.9% of initial cases and 17.0% of surgeries had to be performed under the awake condition (Table 1). If cases treated by biopsy are excluded from the parent population, these frequencies were 19.5% and 20.6%, respectively. Around 20% of radical surgery procedures for gliomas required stimulation mapping techniques. Those patients most in need had WHO grade II gliomas, diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas, who required intraoperative stimulation mapping up to around 50% (Fig. 3, Table 2).

It is not so clear how often awake surgery is necessary for resection of gliomas. Bernstein in Toronto Western Hospital routinely performed 610 awake craniotomies as an adjunct for supratentorial tumor resection between 1991 and 2006,[22] and 367 of 610 cases (60.2%) were diagnosed as gliomas. Between 1993 and 2006, a total of 310 consecutive awake craniotomy procedures for the removal of intra-axial tumors near and/or within eloquent cortices were performed at the University of Texas MD Anderson Cancer Center,[13] and 284 of 310 procedures (91.6%) were performed for gliomas. Ram et al. performed 424 awake craniotomies including 313 gliomas (73.8%) at Tel Aviv Medical Center between 2003 and 2010.[16] Duffau performed 140 awake craniotomies for resection of glioma in an eloquent area of the brain in Montpellier University Hospital between 2008 and 2010.[10] Between 1997 and 2005, a total of 250 patients with gliomas underwent surgery at the University of California at San Francisco (UCSF) Medical Center, with the use of intraoperative language mapping while the patients were awake.[18] Awake surgeries were performed for a large number of gliomas, but there is no information about the parent populations in these series.

Between 1997 and 2009, 500 consecutive adult patients with newly diagnosed supratentorial glioblastoma underwent radical surgical removal at the UCSF.[19] Intraoperative motor mapping was conducted in 116 patients (23%), language mapping in 43 patients (9%), and subcortical mapping in 34 patients (7%). This paper did not mention how often they applied awake surgery for resection of glioblastomas, but at least 9% (language mapping) must have been resected under the awake condition. In excess of 800 patients with low-grade gliomas were treated at the UCSF between 1989 and 2005.[23] Of these, 216 patients were radically resected, and motor and speech mapping were performed in 154 (71%) and 75 (35%) cases, respectively. The majority of surgical procedures (74%) were performed by Dr. Berger himself. By estimate, under 10% (75/>800) of all low grade gliomas, including those treated by biopsy, were radically resected under the awake condition with language mapping. Chacko et al. reported that 883 patients underwent craniotomies for supratentorial tumors in Christian Medical College in India between 2002 and 2010.[7] Of these, 84 (9.5%) were chosen for awake craniotomy, and 67 were histologically verified as gliomas. From these results, awake surgery for gliomas may be necessary for around 10% of all gliomas.

In contrast, Sacko et al. reported that 356 patients collected prospectively with supratentorial gliomas underwent open brain surgery between 2002 and 2007 in the Institut National de la Santé et de la Recherche Médicale.[17] Awake craniotomy with intraoperative brain mapping was used in 143 of 356 patients (40%). They performed awake surgeries in 45 of 137 glioblastomas (32.8%), much higher than the results of UCSF and ours. The frequency of awake surgery must depend on the indications and the characteristics of their parent populations.

III. Intraoperative events

Duffau et al. reported that the patients remained fully awake for a mean time of 98 minutes for resection of 140 gliomas in an eloquent area using the AAA protocol.[10] A total of 139 patients (99.2%) were considered fully cooperative during the awake phase. The reasons for this high success rate were as follows: rigorous selection of patients; quality of the information given by each team member the day before surgery; and strong motivation of the patients who are aware of their disease and its outcome. In contrast, our mean time was 231 minutes with the same AAA protocol, and 29 of 36 patients (80.6%) were considered as successful awake surgeries. Suc-

cess rate of awake surgery might depend on the definition itself. In our cases, only 1 of 24 awake surgeries (4.2%) to obtain only the cortical function (early stage) was considered as a failure. One of the reasons for our relatively low incomplete language mapping rate might be the much longer awake time. It is a matter of speculation but longer awake time might lower brain temperature resulting in lethargy and functional deterioration. I tried to reduce the time for the fully awake state (Fig. 1), but complete subcortical functional data and resection of the tumor are still difficult to obtain in a short time.

IV. Postoperative neurological events and resection rates

De Witt Hamer et al. reviewed 90 reports published between 1990 and 2010 with 8091 patients who underwent surgery for supratentorial glioma with or without intraoperative stimulation mapping.[9] They categorized new postoperative neurological deficits on the basis of timing and severity. Early and late severe neurological deficits were observed in 36.0% and 3.4% of patients after resection with intraoperative stimulation mapping, respectively. Their conclusion was that reversible temporary loss of function of critical brain structures is more frequent with intraoperative stimulation mapping, but irreversible neurological damage is more effectively avoided, in comparison to surgery without mapping. In the present report, we evaluated the same criteria, and early and late severe neurological deficits were observed in 15.3% and 5.1%, respectively (Table 4). The relationship between resection rate and intraoperative functional information obtained under the awake condition confirms that awake surgery contributes to maximize resection of gliomas within/adjacent eloquent areas by minimizing the rate of severe deficits.

Nossek and Ram et al. reported that a significantly lower rate of GTR (54% vs 83%) with a higher incidence of short-term speech deterioration postoperatively (23.5% vs 6.1%) as well as at 3 months postoperatively (15.4% vs 2.3%) was observed in 27 patients with failed awake craniotomy (6.4%) compared with patients with successful awake craniotomy (n = 397).[16] They concluded that failures of awake craniotomy were associated with lower incidence of GTR and increased postoperative morbidity. Their cases included 313 gliomas (73.8%) and other 111 lesions. In contrast, negative mapping of eloquent areas provides a safe margin for surgical resection with a low incidence of neurological deficits.

Of the 200 patients in whom eloquent areas were identified, 86 (43%) experienced worsened neurological deficits in the immediate postoperative period, and 42 patients (21%) continued to have worsened deficits at the 1-month follow up. In contrast, of the 109 patients in whom eloquent areas were not localized, only 25 (23%) had deficits in the immediate postoperative period, and only 10 patients (9%) had deficits at the 1-month follow-up.[13] Kim et al. concluded that positive cortical mapping was a statistically significant predictor of worsened neurological deficits both in the immediate postoperative period and at the 1-month follow up.[13] Their different results from ours showed neither positive mapping nor intraoperative neurological changes had a significant impact on the overall extent of resection.

V. Outcomes

Unfortunately, little survival data of gliomas treated by awake surgery has been reported.[9] Sacko et al. disclosed survival data about glioblastoma and low-grade gliomas (n = 48/109) in a figure without discussion.[17] In glioblastomas, there was no significant difference in OS between patients who underwent awake surgery (n = 45) and patients who underwent surgery under general anesthesia (n = 92) ($p = 0.06$). In low-grade gliomas, there was a significant difference in OS between these patients (n = 48 vs n = 61, $p < 0.001$). Chang et al. retrospectively analyzed 281 cases with supratentorial low-grade gliomas treated in the UCSF, and categorized 4 groups, non-eloquent, no mapping, false-eloquent (all patients with tumors presumed to involve eloquent areas but which were found to spare eloquent brain based on intraoperative mapping), and true-eloquent (all patients in whom the presumption of eloquent brain involvement was confirmed through intraoperative mapping).[8] A major finding was that patients in the false-eloquent group had excellent survival outcomes, which suggests that mapping can drastically change the long-term progress for patients with low-grade gliomas through extensive resection. In contrast, the true-eloquent group did not have better survival even with intraoperative mapping.

At this point, it is not entirely convincing that awake surgery had improved the survival outcomes of patients with gliomas. At least in our cases, we could confirm that the OS of patients with glioma in or near eloquent areas resected using awake surgery compared favorably with those in other regions.

Conclusions

We retrospectively analyzed 15 years experience of awake surgeries with neurophysiological monitoring for neuroepithelial tumors in Tohoku Univer-