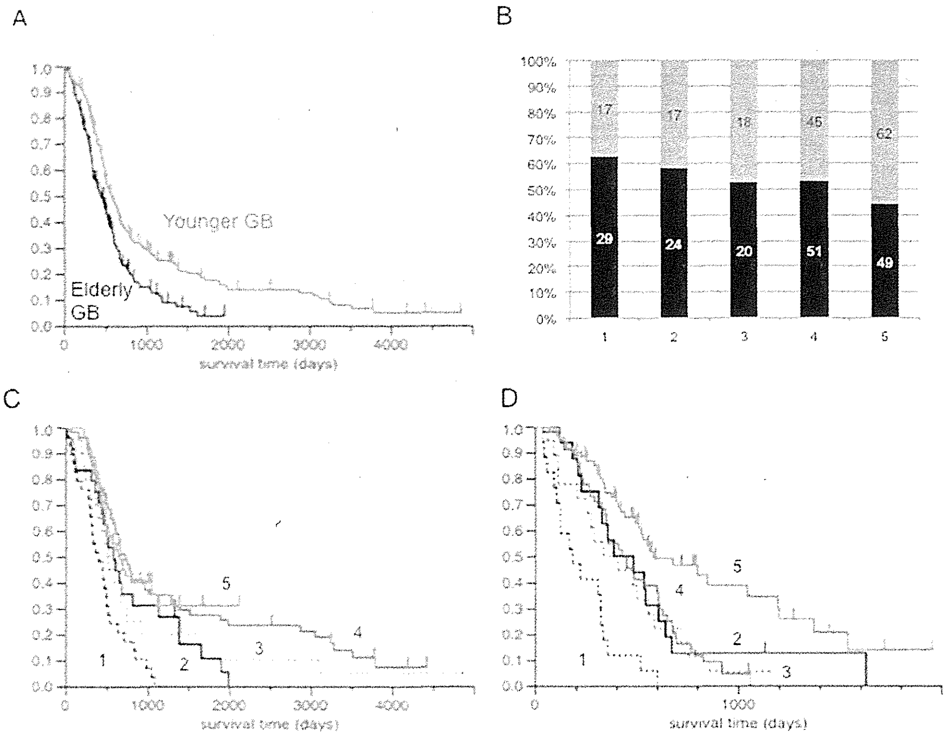

Fig. 3 A: Kaplan-Meier analysis of overall survival (OS) for histologically proven glioblastoma (GB) in Tohoku University between 1982 and 2011, stratified by the age groups. Younger and elderly GB were defined as patients aged below 60 years and those aged 60 years or over, respectively. There was a significant difference of OS between these two age groups ($p < 0.0001$, logrank test). B: Historical change of these two age groups stratified by the treatment eras. Numbers 1 through 5 correspond to Groups 1 through 5, respectively. In Group 5 (temozolomide era), more than half of the patients belong to the elderly GB. Younger and elderly GBs are indicated in gray and black, respectively. C: Kaplan-Meier analysis of OS for the younger GB, stratified by the treatment eras. Significantly increased OS was demonstrated between Groups 1 and 2 ($p = 0.0065$, logrank test). D: Kaplan-Meier analysis of OS for the elderly GB, stratified by the treatment eras. Significantly increased OS was demonstrated between Groups 1 and 2 ($p = 0.0014$, logrank test), and between Groups 4 and 5 ($p = 0.0005$, logrank test).

Table 2 Survival of patients with glioblastoma stratified by age group

Age group	No. of patients	Median survival time (day)	Overall survival rate (%) 2-Year	5-Year	10-Year	Probability
Younger	173	592	39	17.4	6.6	] $p < 0.0001$
Elderly	159	449	23.4	3.6	NR	

NR: not reached.

Table 3 Survival of younger patients with glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%) 2-Year	5-Year	10-Year	Probability			
1	29	399	17.2	0.0	0.0	] p = 0.0065			
2	24	582	35.7	10.7	0.0		] NS		
3	20	518	30.0	10.0	5.0			] NS	
4	51	736	51.0	27.5	11.0				] NS
5	49	671	45.2	31.0	NR				

NR: not reached, NS: not significant.

Table 4 Survival of elderly patients with glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
1	17	184	0.0	0.0	0.0	] p = 0.0014 (1–2)
2	17	436	12.5	0.0	0.0	] NS (2–3)
3	18	373	16.7	0.0	0.0	] NS (3–4)
4	45	449	16.0	0.0	0.0	] p = 0.0005 (4–5)
5	62	581	46.4	13.8	NR	

NR: not reached, NS: not significant.

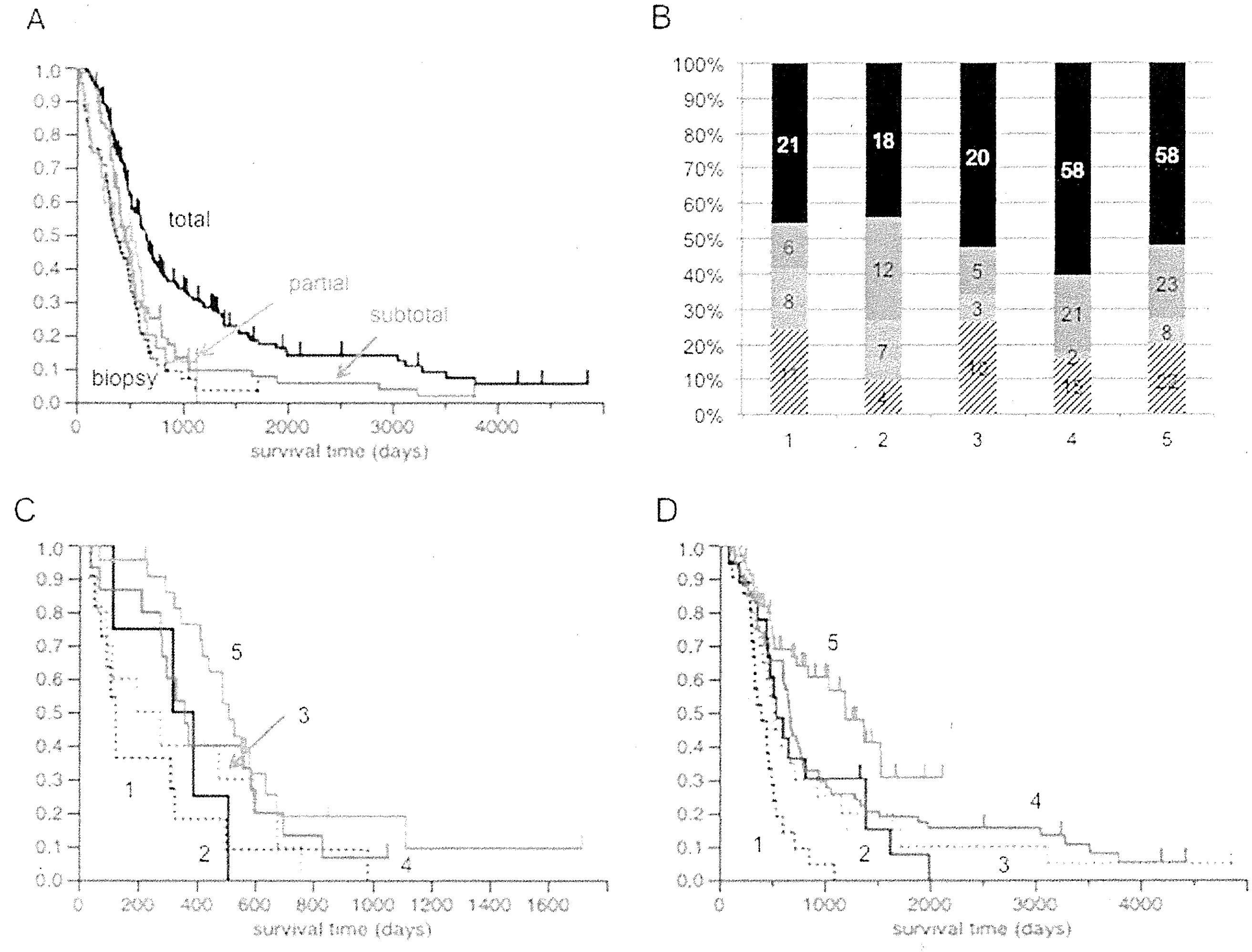

Fig. 4 A: Kaplan-Meier analysis of overall survival (OS) for histologically proven glioblastoma in Tohoku University between 1982 and 2011, stratified by the resection rate. Total, subtotal, and partial resection and biopsy are indicated in black, dark gray, light gray solid line, and black dashed line, respectively. There was a significant difference of OS between total and subtotal resection (p = 0.0011, logrank test). B: Historical change of resection rate stratified by the treatment eras. Total, subtotal, and partial resection and biopsy are indicated in black, dark gray, light gray, and black diagonal line, respectively. Numbers 1 through 5 correspond to Groups 1 through 5, respectively. C: Kaplan-Meier analysis of OS for the biopsied glioblastoma, stratified by the treatment eras. There was no significant difference. D: Kaplan-Meier analysis of OS for the totally resected glioblastoma, stratified by the treatment eras. Significantly increased OS was demonstrated between Groups 1 and 2 (p = 0.0002, logrank test), and between Groups 4 and 5 (p = 0.0194, logrank test).

Table 5 Survival of patients with glioblastoma stratified by surgical resection rate

Resection rate	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
Biopsy	62	369	13.0	NR	NR	] NS
Partial	28	520	20.0	0.0	0.0	] NS
Subtotal	67	451	24.9	7.7	1.9	] p = 0.0011
Total	175	657	42.9	17.4	7.3	

NR: not reached, NS: not significant.

Table 6 Survival of patients with biopsied glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
1	11	125	9.1	0.0	0.0	] NS
2	4	352	0.0	0.0	0.0	] NS
3	10	235	10.0	0.0	0.0	] NS
4	15	357	13.3	NR	NR	] NS
5	22	510	19.1	NR	NR	

NR: not reached, NS: not significant.

Table 7 Survival of patients with totally resected glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
1	21	399	9.5	0.0	0.0	] p = 0.0002
2	18	545	36.4	7.6	0.0	] NS
3	20	518	30.0	10.0	5.0	] NS
4	58	670	41.4	19.0	8.0	] p = 0.0194
5	58	1198	66.5	30.1	NR	

NR: not reached, NS: not significant.

Discussion

Definitive conclusions are always difficult to establish based on retrospective analyses because of the heterogeneous clinical materials and treatments. But the present study strongly suggests improvement of outcomes for patients with GB in Tohoku University during the last 30 years. In particular, the MST has doubled, and the 5-year OS of patients aged below 60 years and with total tumor resection after introduction of TMZ exceeded 30%. In our department, 30 of 332 patients with GB lived for more than 5 years.

Heterogeneous populations of patients containing various prognostic factors can be adjusted using the RPA classification to some extent in comparison with the other institutional results of GB. However, many more factors are clearly involved with the prognosis of GB, for example, O^6-methylguanine deoxyribonucleic acid methyltransferase promoter methylation status.[8] In addition, race is a factor affecting the survival of patients with GB. A significant difference in survival was seen in the Asian population compared to white, black, and other populations. Racial differences in survival are known in patients diagnosed with GB, with the Asian race having increased survival when compared to other races.[13] The reason for this are

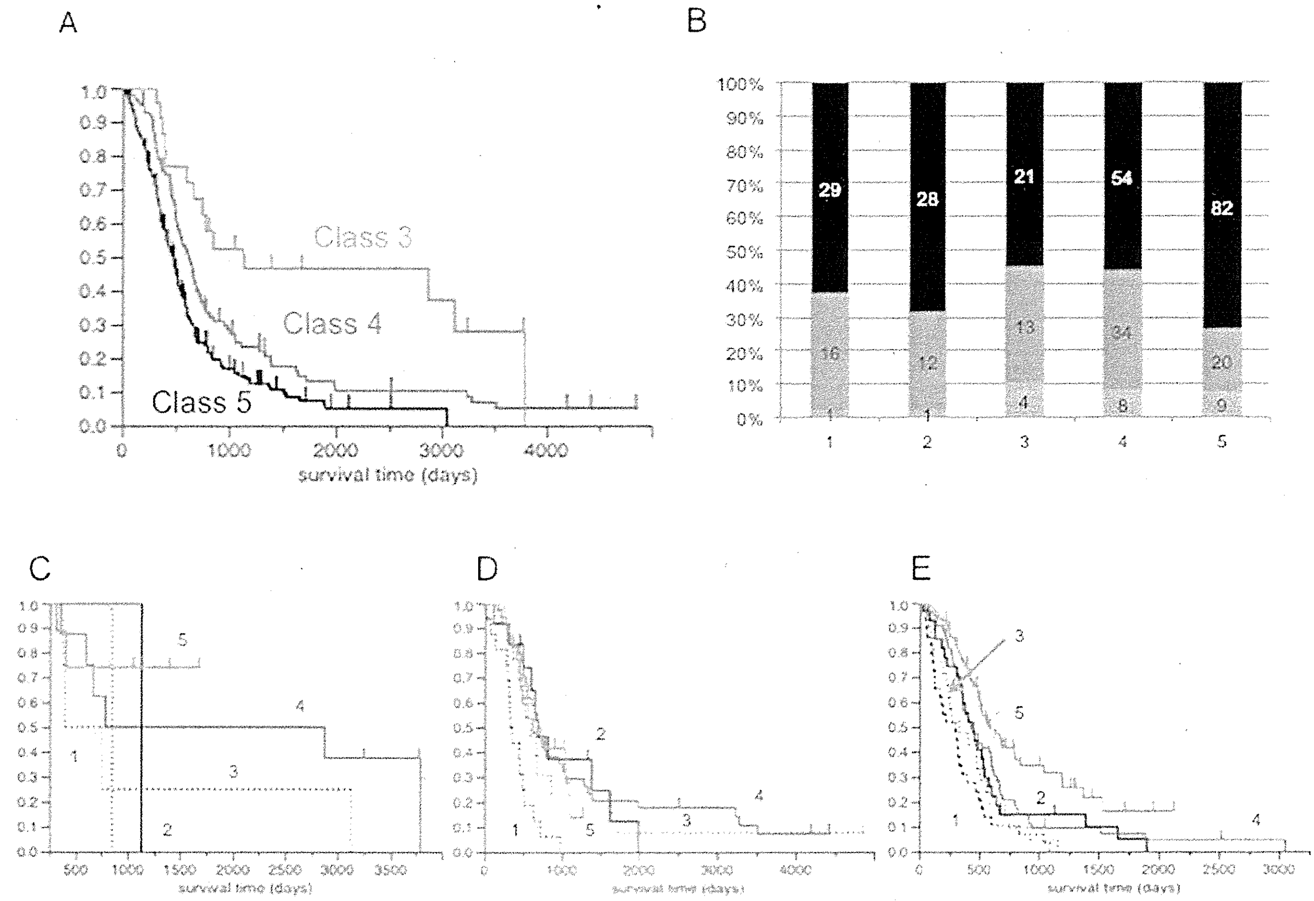

Fig. 5 **A: Kaplan-Meier analysis of overall survival (OS) for histologically proven glioblastoma in Tohoku University between 1982 and 2011, stratified by the recursive partitioning analysis (RPA) classification. RPA classes 3, 4, and 5 are indicated in light gray, dark gray, and black, respectively. There was a significant difference of OS between RPA classes 3 and 4 (p = 0.0144, logrank test), and between classes 4 and 5 (p = 0.0024, logrank test). B: Historical change of resection rate stratified by the RPA classification. Numbers 1 through 5 correspond to Groups 1 through 5, respectively. C: Kaplan-Meier analysis of OS for the RPA class 3 glioblastoma, stratified by the treatment eras. There was no significant difference. D: Kaplan-Meier analysis of OS for the RPA class 4 glioblastoma, stratified by the treatment eras. Significantly increased OS was demonstrated between Groups 1 and 2 (p = 0.0026, logrank test). E: Kaplan-Meier analysis of OS for the RPA class 5 glioblastoma, stratified by the treatment eras. Significantly increased OS was demonstrated between Groups 1 and 2 (p = 0.0217, logrank test), and between Groups 4 and 5 (p = 0.0085, logrank test).**

Table 8 **Survival of patients with glioblastoma stratified by RPA classification**

RPA class	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability	
			2-Year	5-Year	10-Year		
3	23	1136	67.1	46.5	27.9	] p = 0.0144	
4	95	615	38.9	13.2	5.1		] p = 0.0024
5	214	474	24.7	7.3	0		

RPA: recursive partitioning analysis.

Table 9 Survival of patients with RPA class 3 glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
1	1	853	100.0	0.0	0.0	] NS
2	1	1136	100.0	0.0	0.0	] NS
3	4	577	50.0	25.0	0.0	] NS
4	8	1829	62.5	50.0	37.5	] NS
5	9	NR	74.1	NR	NR	

NR: not reached, NS: not significant, RPA: recursive partitioning analysis.

Table 10 Survival of patients with RPA class 4 glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
1	16	348	6.3	0.0	0.0	] p = 0.0026
2	12	687	46.3	12.4	0.0	] NS
3	13	592	30.8	7.7	7.7	] NS
4	34	715	50.0	20.6	7.1	] NS
5	20	628	47.6	NR	NR	

NR: not reached, NS: not significant, RPA: recursive partitioning analysis.

Table 11 Survival of patients with RPA class 5 glioblastoma stratified by treatment era

Group (treatment era)	No. of patients	Median survival time (day)	Overall survival rate (%)			Probability
			2-Year	5-Year	10-Year	
1	29	301	10.3	0.0	0.0	] p = 0.0217
2	28	449	14.8	5.0	0.0	] NS
3	21	336	14.3	0.0	0.0	] NS
4	54	427	20.8	7.1	0.0	] p = 0.0085
5	82	581	41.6	16.1	NR	

NR: not reached, NS: not significant, RPA: recursive partitioning analysis.

Table 12 Multivariate hazard ratios, confidence intervals, and p values for survival of patients with glioblastoma

Factor	Hazard ratio	95% Confidence intervals	p Value
MR imaging	0.426	0.302–0.602	< 0.0001
Total resection	0.587	0.458–0.751	< 0.0001
Temozolomide	0.590	0.434–0.793	0.0004
Age (below 60 years)	0.636	0.475–0.851	0.0022
RPA class 5	1.460	1.082–1.973	0.0132

MR: magnetic resonance, RPA: recursive partitioning analysis.

not clearly defined.

Previously, our retrospective study investigated the outcome in elderly patients aged 60 years or over with malignant astrocytic tumor treated in Tohoku University before (1982–1988) and after (1989–1999) the adoption of routine clinical use of MR imaging.[3] This study demonstrated that preoperative MR imaging contributed to longer survival time by providing earlier diagnosis in patients with better performance status, by allowing more thorough surgical resection, and resulting in better performance status after the treatment.

In the present study, the outcome of both younger and elderly GB was significantly improved after the introduction of MR imaging. Elderly GB, RPA class 5, and totally resected GB were associated with significantly improved prognosis after the introduction of TMZ, as follows: MST/2-year OS/5-year OS in Group 4 (n = 45, 449 days (15.0 months)/16.0/0) vs Group 5 (n = 62, 581 days (19.4 months)/46.4%/13.8%) for elderly GB ($p = 0.0005$), Group 4 (n = 54, 427 days (14.2 months)/20.8%/7.1%) vs Group 5 (n = 82, 581 days (19.4 months)/41.6%/16.1%) for RPA class 5 ($p = 0.0085$), and Group 4 (n = 58, 670 days (22.3 months)/41.4%/19.0%) vs Group 5 (n = 58, 1198 days (39.9 months)/66.5%/30.1%) for totally resected GB ($p = 0.0194$). Multivariate analysis showed that introduction of MR imaging and TMZ, and total resection of the tumor were highly significant as survival factors.

No chemotherapeutic agents were used for elderly GB in Group 4, so the improvement in outcome of elderly GB after the introduction of TMZ might represent the difference in therapeutic effectiveness between only RT and RT plus TMZ. In contrast, patients aged below 60 years showed no difference in prognosis between management by ACNU and after the introduction of TMZ. In the present study, TMZ was much more effective in totally resected GB, as already been demonstrated.[9,10]

The prognosis for patients with GB has improved during the last 30 years in Tohoku University, even with the aging population. This retrospective analysis showed that the introduction of MR imaging and TMZ, and total resection of the tumor have had significant impacts on improving the outcomes of GB treatment. The MST has doubled during these 30 years, and the 5-year OS of patients aged below 60 years and with total tumor resection has exceeded 30% after the introduction of TMZ.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. T. Kumabe, R. Saito, M. Kanamori, M. Chonan, Y. Mano, I. Shibahara, T. Kawaguchi, H. Kato, Y. Yamashita, Y. Sonoda, J. Kawagishi, R. Katakura, T. Kayama, and T. Tominaga have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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Address reprint requests to: Toshihiro Kumabe, MD, PhD, Department of Neurosurgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan.
e-mail: kuma@kitasato-u.ac.jp

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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

Toshihiro KUMABE,[1] Kiyotaka SATO,[†] Masaki IWASAKI,[1] Ichiyo SHIBAHARA,[1] Tomohiro KAWAGUCHI,[1] Ryuta SAITO,[1] Masayuki KANAMORI,[1] Yoji YAMASHITA,[1] Yukihiko SONODA,[1] Osamu IIZUKA,[2] Kyoko SUZUKI,[3] Ken-ichi NAGAMATSU,[1] Shintaro SEKI,[1] Nobukazu NAKASATO,[4] and Teiji TOMINAGA[1]

Departments of [1]Neurosurgery, [2]Behavioral Neurology & Cognitive Neuroscience, and [4]Epileptology, Tohoku University Graduate School of Medicine, Sendai, Miyagi; [3]Department of Clinical Neuroscience, Yamagata University, Graduate School of Medical Science, Yamagata, Yamagata; [†]Department of Neuroanesthesiology, Kohnan Hospital, Sendai, Miyagi (Died May 30, 2012)

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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Author's present address: T. Kumabe, MD, Department of Neurosurgery, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan.

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

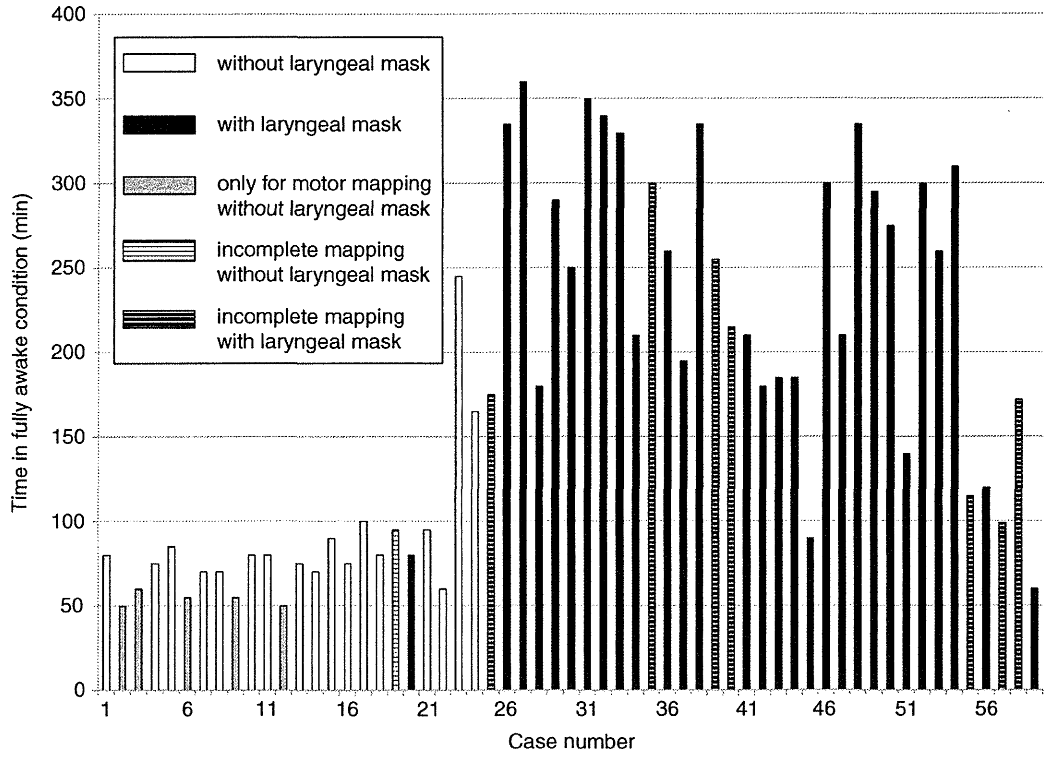

Fig. 1 Time in fully awake condition for each awake surgery. Each bar is arranged in chronological order. *White, black, and gray bars* indicate the different protocols for awake surgery, such as language mapping/monitoring without using the laryngeal mask (n = 18), language mapping/monitoring with the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

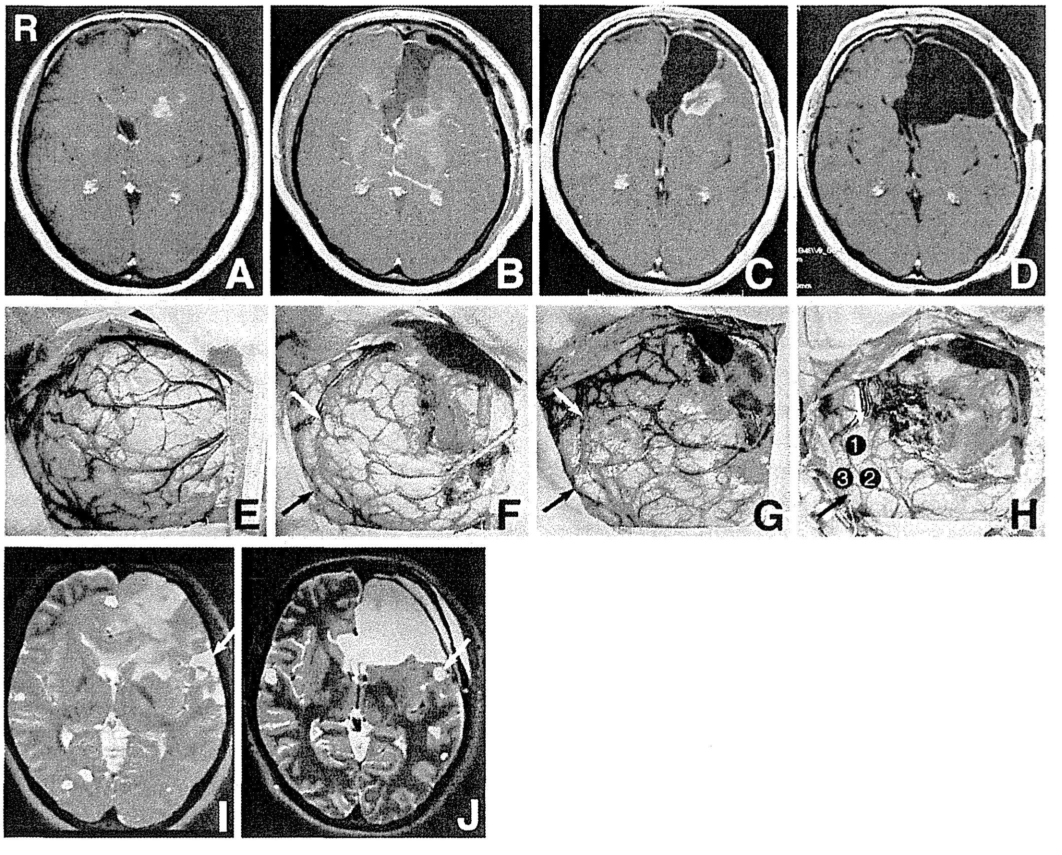

Fig. 2 Illustrative case of a 30-year-old female with left frontal glioblastoma. A–D: Axial T_1-weighted magnetic resonance (MR) images with contrast medium preoperatively (A), immediately after the first resection under general anesthesia (B), 3 months after the first surgery (C), and immediately after 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%)

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

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).

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.

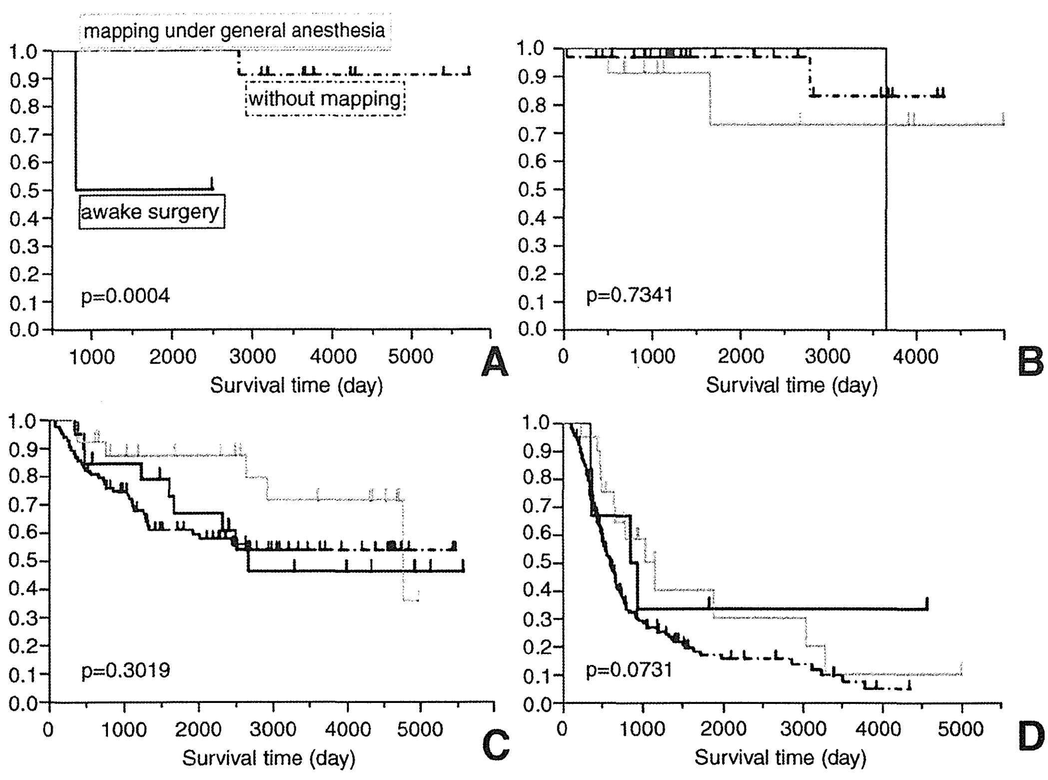

Fig. 3 Kaplan-Meier survival curves of the newly diagnosed patients who underwent awake surgery (*solid black line*), radical resection with stimulation mapping techniques under general anesthesia (*solid gray line*), and radical resection without stimulation mapping techniques (*solid dashed line*). 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. Success 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 University. Awake surgery with intraoperative stimulation mapping may contribute to improve the outcome of gliomas by maximizing the tumor resection and minimizing the surgical morbidity. The biggest benefit of this procedure is thought to be the identification and total resection of tumor in the false-eloquent group, which can be found as negative mapping results. It is still difficult to confirm the survival benefit using awake surgery for infiltrative gliomas in the true-eloquent group, but further investigations of much larger sets of meticulous retrospective data or prospective studies will reveal this assignment.

Acknowledgment

We express our grief at the death of Dr. Kiyotaka Sato. We would like to dedicate this manuscript to him.

Conflicts of Interest Disclosure

All authors have already declared conflicts of interest (COI) status to the Japan Neurosurgical Society. This manuscript has no COI that should be disclosed.

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Address reprint requests to: Toshihiro Kumabe, MD, Department of Neurosurgery, Kitasato University School of Medicine, 1–15–1 Kitasato, Minami-ku, Sagamihara 252–0374, Japan.
e-mail: kuma@kitasato-u.ac.jp

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Treatment of Malignant Brain Tumor

New Treatment Strategies to Eradicate Cancer Stem Cells and Niches in Glioblastoma

Takuichiro HIDE,[1] Keishi MAKINO,[1] Hideo NAKAMURA,[1] Shigetoshi YANO,[1] Shigeo ANAI,[1] Tatsuya TAKEZAKI,[1] Jun-ichiro KURODA,[1] Naoki SHINOJIMA,[1] Yutaka UEDA,[1] and Jun-ichi KURATSU[1]

[1]*Department of Neurosurgery, Kumamoto University Graduate School of Medical Science, Kumamoto, Kumamoto*

Abstract

Glioblastoma multiforme (GBM) harbors are not only rapidly dividing cells but also small populations of slowly dividing and dormant cells with tumorigenesity, self-renewal, and multi-lineage differentiation capabilities. Known as glioblastoma stem cells (GSCs), they are resistant to conventional chemo- and radiotherapy and may be a causative factor in recurrence. The treatment outcome in patients with GBM remains unsatisfactory and their mean survival time has not improved sufficiently. We studied clinical evidence and basic research findings to assess the possibility of new treatment strategies that target GSCs and their specific microenvironments (GBM niches) and raise the possibility of adding new treatments to eradicate GSCs and GBM niches.

Key words: glioblastoma, stem cells, niches, treatment, cancer stem cells

Introduction

Glioblastoma multiforme (GBM) is one of the most malignant tumors in humans. Despite postoperative chemo- and radiotherapy the mean survival time of GBM patients is 12–14 months and only a few survive for more than 5 years.[74,75] Cancers are comprised of heterogeneous populations of cancer cells and include specific subpopulations that possess stem cell-like characteristics. They are known as cancer stem cells (CSCs) and they can produce CSCs and differentiated non-CSCs.[65] Singh et al.[69,70] who proposed the "cancer stem cell hypothesis" in human brain tumors reported that they contain small populations of cells that can initiate brain tumors and that they are concentrated in the $CD133^+$ fraction. Vescovi et al.[78] defined brain tumor stem cells as cells with cancer initiation and extensive self-renewal ability, karyotypic or genetic alterations, aberrant differentiation properties, and the capacity to generate non-tumorigenic end cells.

It is now known that specific microenvironments (niches) play an important role in maintaining the stemness of normal somatic stem cells and CSCs, and that, changes in the niches lead to the differentiation of stem cells. Cell-cell- and cell extracellular matrix (ECM) interactions take place in niches and several secreting molecules are involved.[25,61] Glioblastoma stem cells (GSCs) and GBMs niches play a pivotal role in the initiation, progression, resistance to therapy, and recurrence of GBM.

The standard treatment for GBM consists of a combination of surgical resection and chemo-radiotherapy. Attempts are made to remove the tumor mass as thoroughly as possible. Neuronavigation systems, intraoperative magnetic resonance (MR) imaging, neurological monitoring, and photodynamic diagnosis using 5-aminolevulinic acid may facilitate maximal tumor removal and avoid the induction of neurological deficits.[19,46,77] However, GBM tumor cells migrate into the brain parenchyma far from the tumor mass[80] and recurrence is commonly seen along the periphery of the tumor removal cavity even

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