Patterns of Intracranial Glioblastoma Recurrence After Aggressive Surgical Resection and Adjuvant Management: Retrospective Analysis of 43 Cases

Yoshiyuki KONISHI,¹ Yoshihiro MURAGAKI,^{1,2} Hiroshi ISEKI,^{1,2}
Norio MITSUHASHI,³ and Yoshikazu OKADA²

¹Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science,
and Departments of ²Neurosurgery and ³Radiation Oncology,
Tokyo Women's Medical University, Tokyo

Abstract

The present retrospective study evaluated the recurrence patterns after aggressive surgical removal of intracranial glioblastomas in 43 consecutive adult patients. The resection rate of the enhanced lesion on magnetic resonance imaging was 100% and 95–99% in 22 and 21 cases, respectively. All patients received postoperative fractionated radiotherapy (60 Gy in 30 fractions) with additional chemotherapy (25 cases) or vaccine therapy (18 cases). During follow-up (median 17 months), tumor recurrence was identified in 33 patients, most frequently regional within the wall of the resection cavity (20 cases). No clinical factor differed significantly between the groups of patients with regional or marginal tumor progression (N = 22) and patients with distant or multiple recurrences (N = 8). Progression-free survival did not differ significantly between these two groups ($p = 0.27$). However, overall survival was significantly longer ($p = 0.04$) in patients with regional or marginal tumor progression, and constituted 90% and 54% at 1 and 2 years after surgery, respectively, compared to 75% and 0% in patients with distant or multiple recurrences. Aggressive surgical resection and adjuvant management of intracranial glioblastoma may change its recurrence pattern. Tumor progression appears in the wall of the resection cavity or within 2 cm from its margin in approximately half of patients.

Key words: glioblastoma, gross total resection, progression, recurrence, survival

Introduction

Glioblastoma is the most common primary brain tumor in adults and carries an extremely grim prognosis. Management usually includes surgical resection followed by postoperative fractionated radiotherapy (FRT) as well as concomitant and adjuvant chemotherapy. Nevertheless, the incidences of recurrence, regrowth, and dissemination of the tumor are very high due to the well-known infiltrative extension far beyond the boundaries of the localized lesion identifiable with neuroimaging.^{4,20,33,37,48)} The progression of glioblastoma after treatment in up to 97% of cases occurs either from the bulk of the mass or within 20 mm from the border of its enhanced part identifiable on T₁-weighted magnetic resonance (MR) imaging, and the presence of such local recurrence may be associated with impaired

prognosis.^{2,3,12,13,23,25,32,34,35,43,44,54)} Therefore, various methods for improvement of tumor control at the time of both initial and salvage treatment have been proposed, such as inclusion of the marginal brain tissue in the high dose area during FRT,^{4,17,20,26,31–33,35,49,50)} additional dose boost with stereotactic radiosurgery,^{14,18,41)} brachytherapy,^{10,36,43)} implantation of Gliadel wafers (Guilford Pharmaceuticals Inc., Baltimore, Maryland, USA),⁵³⁾ or various types of intralesional immunotherapy.^{7,42)}

The majority of studies on progression of intracranial gliomas after initial treatment have included many cases with incomplete surgical tumor removal. Contemporary advances in neurosurgical technique and introduction of modern intraoperative technologies now permit attain gross total resection of the brain tumor in many cases.^{16,19,24,28,30,39,45)} Surgical treatment in the vast majority of gliomas could not be considered as curative, but more complete removal of the localized part of the neoplasm may change the dynamics of further growth and

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related prognosis.^{11,31)}

The present retrospective analysis tried to evaluate the recurrence patterns of intracranial glioblastomas after aggressive surgery.

Materials and Methods

This retrospective study was initiated in September 2009. There were two initial selection criteria: surgery for newly diagnosed glioma performed in the intelligent operating theater of Tokyo Women's Medical University with the use of intraoperative MR (iMR) imaging; and final histopathological diagnosis of glioblastoma. Retrospective backward selection of cases from the constantly maintained computer database was started from June 2008 to allow a minimum of 12-month follow up after completion of postoperative FRT in surviving patients. Case selection was limited to the beginning of 2004, since the initial period after installation of iMR imaging in our clinic (2000) was completed by this time, significant improvement of the intraoperative image quality had succeeded, and the surgical algorithm of glioma treatment in this facility was fully established.^{16,27,28,30)} All selected cases were checked for resection rate. The established cut-off level of 95% or greater tumor removal was chosen, because this value corresponds to the grading of resection of malignant gliomas used by The Committee of Brain Tumor Registry of Japan.⁵⁾

A total of 65 consecutive patients underwent craniotomy and removal of the newly diagnosed intracranial glioblastoma in the intelligent operating theater of the Tokyo Women's Medical University from January 2004 to June 2008. Resection of 95% or greater was attained in 47 patients. Four patients from this cohort were excluded from further analysis due to omission of postoperative FRT. The remaining 43 patients were included in the present study. The 29 men and 14 women were aged from 18 to 79 years (median 43 years). Eighteen patients were less than 50 years old. Karnofsky performance scale (KPS) score before surgery was 100–80 in 31 patients, 70–60 in 6, and 50 or less in 6. The tumor was predominantly located within the frontal (19 cases), temporal (12 cases), parietal (7 cases), and occipital (3 cases) lobes. Other locations were encountered in only 2 patients. The left hemisphere was affected slightly more often than right (23 vs. 20 cases). According to recursive partitioning analysis classification⁶⁾ 12 patients had class III, 21 had class IV, and 10 had class V.

Tumor removal was performed according to our concept of information-guided surgery^{17,28,30)} with the use of iMR imaging, updated neuronavigation,

comprehensive neurophysiological monitoring, neurochemical monitoring with 5-aminolevulinic acid (5-ALA), and histopathological monitoring with multiple microscopic investigations of the resected tissue using frozen sections. Awake craniotomy and/or intraoperative cortical and subcortical brain mapping were performed if indicated. The main goal of surgery was defined as maximum possible removal of the contrast-enhanced area identified on preoperative T₁-weighted MR imaging without the risk of postoperative major permanent neurological morbidity. The final histopathological diagnosis of glioblastoma was established according to the current World Health Organization criteria²¹⁾ using paraffin-embedded tissue sections stained with hematoxylin and eosin and appropriate antibodies for immunohistochemistry.

Evaluation of the resection rate was based on visual side-by-side comparison of the preoperative and postoperative MR images obtained within 3 days after the surgery, using a 1.5 T clinical scanner (ExcellArt; Toshiba Medical Systems, Tokyo). Any contrast-enhanced area on T₁-weighted images was considered to be residual tumor.⁸⁾ In the analyzed cohort, the resection rate was 100% in 22 patients, and between 95% and 99% in the other 21 patients.

All patients underwent postoperative FRT, which was initiated within 2 to 3 weeks after surgical removal of the tumor. The treatment protocol was based on the three-dimensional planning system. The total dose was 60 Gy delivered in 30 fractions (2 Gy per fraction) in all cases. During the initial 25 fractions (up to 50 Gy of irradiation), the clinical target volume (CTV) was defined as the hyperintense area on T₂-weighted MR images and the 15 mm marginal area of the adjacent cerebral tissue. From 26 to 30 fractions (from 52 to 60 Gy of irradiation), the CTV was reduced to the resection cavity and the 15 mm marginal area of the adjacent cerebral tissue. Any contrast-enhanced area on T₁-weighted MR images was always included in the irradiation field. Concomitant and adjuvant chemotherapy was administered in 25 patients according to the standard protocols for nimustine (ACNU)^{40,48)} (9 cases) or temozolomide^{46,47)} (16 cases). Chemotherapy was omitted in 18 patients, but treatment with autologous formalin-fixed tumor vaccine (AFTV) concomitant with FRT was performed.²⁹⁾

Follow-up evaluations were performed by the attending neurosurgeon, starting 2 weeks after completion of FRT, and scheduled every 2–3 months thereafter. Additional examinations were done if required by the clinical condition of the patient. The regular investigations included physical testing with evaluation of KPS score and determination of the

Medical Research Council neurological functional grade, blood and urinary tests, and brain MR imaging with contrast medium. Other investigations were not performed unless were clinically indicated. The length of follow up varied from 3 to 71 months (median 17 months).

The diagnosis of tumor recurrence was based on the joint opinions of the neurosurgeon and neuroradiologist, and was defined as appearance of new contrast-enhanced lesion(s) on T₁-weighted MR images, or 25% or more increase of the volume of the previous enhanced lesion(s). Patterns of recurrence were considered as regional (in the wall of the resection cavity), marginal (within 20 mm from the margin of the resection cavity), distant (more than 20 mm from the margin of the resection cavity), multiple (several recurrences in various brain areas), and subarachnoid dissemination (Fig. 1). At the time of tumor recurrence the patients usually underwent salvage treatment, which included re-resection of the tumor, stereotactic radiosurgery, chemotherapy, vaccine therapy, or various combinations.

Clinical factors in the defined groups of patients were compared with the chi-square test or Mann-Whitney test. Overall (OS) and progression-free survival (PFS) were evaluated from the day of surgery and were compared with the log-rank test after construction of the Kaplan-Meier curves.

Fig. 1 T₁-weighred magnetic resonance images with contrast medium illustrating the patterns of glioblastoma recurrence (arrows and circles) after aggressive surgery and adjuvant management. A: regional, in the wall of the resection cavity; B: marginal, within 20 mm from the margin of the resection cavity; C: distant, more than 20 mm from the margin of the resection cavity; D: multiple, several recurrences in various brain areas; and E: subarachnoid dissemination.

Results

Tumor recurrence was observed during the follow-up period in 33 of 43 patients. Incidences of various recurrence patterns are presented in Table 1. Overall tumor progression within the wall of the resection cavity or within 20 mm from the margin accounted for 51% of cases. Subarachnoid dissemination was evident in 5 patients and was isolated pattern of recurrence in 3 of them. It was identified in 3 of 25 cases when the cerebral ventricle was opened during surgery, and in 2 of 18 cases when this was not done ($p = 0.78$). Spinal dissemination was evident in 1 patient, and no case of glioblastoma metastasis outside the central nervous system was identified.

PFS did not differ significantly between patients with regional or marginal progression of glioblastoma (22 cases) and patients with distant or multiple recurrences (8 cases), as shown in Fig. 2. Comparison of the investigated clinical factors did not differ

Table 1 Incidence of various recurrence patterns after aggressive surgery and adjuvant management of intracranial glioblastoma

Recurrence pattern	No. of cases*
Regional (in the wall of the resection cavity)	20 (46.5%)
Marginal (within 20 mm from the margin of the resection cavity)	2 (4.7%)
Distant (more than 20 mm from the margin of the resection cavity)	4 (9.3%)
Multiple (several recurrences in various brain areas)	4 (9.3%)
Subarachnoid dissemination	3 (6.9%)

*In 10 cases, recurrence of the tumor was not observed during follow-up period.

Fig. 2 Comparison of progression-free survival from the time of surgery in patients with different recurrence patterns of intracranial glioblastoma. There is no significant difference ($p = 0.27$).

Table 2 Comparison of clinical factors and outcome variables in patients with different recurrence patterns of intracranial glioblastoma

Clinical factors and outcome variables	Patients with regional or marginal progression (N = 22)	Patients with distant or multiple recurrences (N = 8)	p Value
Sex			0.35*
men	15	5	
women	7	3	
Age			0.70*
< 50 yrs	10	3	
≥ 50 yrs	12	5	
Median age (range), yrs	52 (18–68)	56 (36–79)	0.16**
KPS score			0.21*
80–100	18	4	
60–70	1	2	
≤ 50	3	2	
Tumor location			0.24*
frontal	11	2	
temporal	6	4	
parietal	2	2	
occipital	1	0	
other	2	0	
Tumor side			0.23*
left	12	2	
right	10	6	
RPA class			0.29*
III	7	2	
IV	11	2	
V	4	4	
Resection rate			0.41*
100%	10	5	
95–99%	12	3	
Adjuvant treatment			0.70*
chemotherapy (ACNU or TMZ)	10	3	
vaccine therapy	12	5	
Salvage treatment			
any	14	6	0.56*
re-resection	8	0	0.05*
gamma knife radiosurgery	0	1	0.09*
chemotherapy (TMZ)	13	6	0.42*
vaccine therapy	1	0	0.54*
Outcome			0.29*
dead	15	7	
alive	7	1	
Overall survival			0.04***
median (range), mos	27 (3–57)	14 (6–23)	
actuarial 1-yr rate (95% CI)	90% (78–100%)	75% (45–100%)	
actuarial 2-yr rate (95% CI)	54% (32–76%)	0%	
Progression-free survival			0.27***
median (range), mos	10 (2–41)	8 (4–20)	
actuarial 1-yr rate (95% CI)	36% (16–56%)	25% (0–55%)	
actuarial 2-yr rate (95% CI)	14% (0–28%)	0%	

According to *chi-square test, **Mann-Whitney test, and ***log-rank test. ACNU: nimustine, CI: confidence interval, KPS: Karnofsky performance status, RPA: recursive partitioning analysis, TMZ: temozolomide.

significantly between the two defined groups (Table 2). No correlation between tumor location and recurrence pattern was found, but the recurrent tumor affected genu of the corpus callosum in all 4 patients with glioblastoma initially located in the prefrontal region (Fig. 3). In contrast, no neoplasm located in the parietal and/or occipital lobes recurred in the splenium of the corpus callosum.

Salvage treatment was performed in 14 of 22 patients with regional or marginal tumor progression and in 6 of 8 patients with distant or multiple recurrences ($p = 0.56$). However, re-craniotomy and additional lesion resection were done only in 8 cases of the former group ($p = 0.05$). Histopathological investigation revealed pure recurrence of the neoplasm in 6 cases, and intermixture with radiation necrosis in 2. Patients with regional or marginal progression of glioblastoma, who underwent re-resection of the neoplasm, had a mild tendency to better OS (median 13 vs. 10 months after diagnosis of recurrence), but the difference did not reach statistical significance (Fig. 4).

At the time of data analysis, 18 patients remained alive, whereas 25 had died, all of the intracranial tumor. OS was longer in patients with regional or marginal progression of glioblastoma compared to patients with distant or multiple recurrences ($p = 0.04$), as shown in Fig. 5.

Discussion

The conventional objectives of resective surgery for malignant glioma include relief of compression of the tumor bulk on the surrounding brain (important for neurological improvement), reduction of the volume of the neoplasm (increases the efficacy of adjuvant postoperative treatment), and establishment of the precise histopathological diagnosis (required for choice of the appropriate therapy, optimal follow up, and prediction of prognosis).¹⁾ Additionally, extensive removal of the neoplasm may positively influence the survival. While the latter has not been formally proved to date,³⁸⁾ there is a growing agreement that total resection of the lesion is associated with better long-term outcome. Adjustment for biases of age and eloquent area location in the dataset of randomized study on use of neurochemical navigation with 5-ALA during resection of glioblastoma found that median OS after complete removal of the enhanced lesion was significantly longer compared to cases with incomplete resection (17 months vs. 12 months).⁴⁵⁾ In concordance, the report on European Organisation for Research and Treatment of Cancer randomized trial of combined chemotherapy for anaplastic gliomas showed the OS

Fig. 3 Follow-up images in 4 patients with glioblastoma initially located in the prefrontal region showing the recurrent tumor affected the genu of the corpus callosum (arrows).

Fig. 4 Comparison of the overall survival from the time of regional or marginal tumor progression relative to re-resection. There is no significant difference ($p = 0.20$).

Fig. 5 Comparison of the overall survival from the time of surgery in patients with different recurrence patterns of intracranial glioblastoma. There is a significant difference ($p = 0.04$).

was better after complete tumor removal compared to partial removal or biopsy.⁵¹⁾ Resection of 98% or more of glioblastoma is associated with significant improvement of the long-term outcome,¹⁹⁾ whereas the same trend was recently revealed even at 78% resection rate.³⁹⁾ Concordant results were reported by The Committee of Brain Tumor Registry of Japan: analysis of 5,328 cases of glioblastoma showed that more than 95% tumor removal is associated with survival advantage, but such resection rate was attained in only 31.4% of cases.⁵⁾ In our series, 95% and more resection was achieved in 47 of 65 consecutive patients (72%). After aggressive surgery and adjuvant management 23% of patients remained free of tumor progression within the median follow-up period of 17 months. Such beneficial results may reflect the advantages of our treatment concept of information-guided surgery for brain tumors based on the constant use of advanced intraoperative technologies.^{17,28,30)}

Our surgical strategy for information-guided management of intracranial gliomas with the use of iMR imaging has been described in detail elsewhere.^{27,28,30)} It is based on the integration of various intraoperative anatomical, functional, and histological data to attain maximal surgical resection of the tumor with minimal risk of postoperative neurological morbidity. It should be specifically emphasized that complete removal is highly desirable, but is not the ultimate goal of surgery for glioma. In our practice, the procedure is usually directed to the maximal possible resection of the enhanced area in cases of high-grade glioma, which might be radiologically total as well as subtotal, leaving the residual lesion within the functioning eloquent brain structures identified with neurophysiological monitoring and/or brain mapping.^{27,28,30)}

In the majority of reported series, local progression of intracranial glioblastoma after initial

Table 3 Recurrence rates of intracranial glioblastoma after treatment

Author (Year)	No. of analyzed cases	Cohort characterization	Length of follow-up (mos)	Total recurrence rate	Local recurrence rate
Hochberg and Pruitt (1980) ¹²⁾	42	CT-based delineation of the tumor recurrence after irradiation and/or chemotherapy (CCNU); Anaplastic astrocytomas might be included	ND	ND	80%
Nagashima et al. (1989) ³²⁾	48	Comparison of 3 FRT techniques with irradiation dose > 45 Gy in each case: WBRT, generous local irradiation (complete coverage of the area of hypodensity on CT), and restricted local irradiation (within 2 cm of the CT-defined tumor margin)	ND	100%	85%
Sneed et al. (1994) ⁴³⁾	25	Surgery, FRT (59.4–60 Gy) with concomitant oral hydroxyurea followed by brachytherapy with high-activity (50 Gy) iodine-125 sources and 6 cycles of chemotherapy (procarbazine, lomustine, and vincristine)	ND	88%	68%
Nakagawa et al. (1998) ³³⁾	38	Surgical resection or biopsy in all cases (gross total resection 8%), followed by FRT (60–90 Gy in 20 cases and ≥90 Gy in 16) concurrent with chemotherapy (ACNU and vincristine)	ND	84%	53%
Oppitz et al. (1999) ³⁵⁾	34	CT-based analysis of recurrence after FRT (range of total doses 45–68 Gy, median 60 Gy)	ND	100%*	97%
Wick et al. (2008) ⁵⁴⁾	63	Comparison of recurrence patterns in only radiotherapy group (33 cases) and TMZ-based chemoradiotherapy group (30 cases); “Debulking surgery” was done in 37 patients	ND	100%*	80%
Brandes et al. (2009) ²⁾	95	Total or subtotal surgical resection followed by TMZ-based chemoradiotherapy (irradiation dose 60 Gy)	median 18.9; range 6.6–44.8	83%	72%
Milano et al. (2010) ²⁵⁾	54	Surgical resection or biopsy (gross total resection 31%), followed by TMZ-based chemoradiotherapy (irradiation dose 60 Gy); Additional SRS boost in 3 patients	median 17	72%	67%
Chamberlain (2011) ³⁾	70	Initial treatment with FRT with concurrent and adjuvant TMZ followed by bevacizumab at first recurrence	ND	100%*	80%
McDonald et al. (2011) ²³⁾	62	Evaluation of the limited margin FRT (total dose 60 Gy); Gross total tumor resection in 45% of patients; Concurrent and adjuvant chemotherapy with TMZ (97% of patients) or concurrent arsenic trioxide (3% of patients)	median 12; maximal 28	69%	68%
Oh et al. (2011) ³⁴⁾	67	Evaluation of recurrence patterns after TMZ-based chemoradiotherapy; Tumor “resection” in 13% of patients	ND	100%*	87%
Murakami et al. (2012) ³¹⁾	138	Maximal possible tumor removal (gross total resection in 28% of patients) followed by FRT (dose 60 Gy) with concurrent and adjuvant chemotherapy	ND	96%	88%
Pan et al. (in press) ³⁶⁾	31	Overall 10 patients underwent total surgical resection; In 10 cases maximal tumor removal followed by FRT (59.4–60.0 Gy) with concurrent and adjuvant TMZ was done; 12 patients were treated with intracavitary brachytherapy after maximal surgical debulking followed by FRT (45 Gy) with concurrent and adjuvant TMZ; 9 patients had unresectable disease and underwent hypofractionated radiotherapy (50–66 Gy in 10 fractions) followed by adjuvant TMZ or bevacizumab	median 12.6; range 3.5–50.6	100%	52%
Present series	43	≥ 95% surgical resection in all cases (total resection 51%) followed by FRT (60 Gy) with chemotherapy (ACNU or TMZ) or vaccine therapy	median 17; range 3–71	77%	51%

*Series included only cases with recurrences. ACNU: nimustine, CT: computed tomography, CCNU: lomustine, FRT: fractionated radiotherapy, ND: no data, SRS: stereotactic radiosurgery, TMZ: temozolomide, WBRT: whole brain radiation therapy.

management was encountered in 67% to 97% of cases (Table 3),^{2,3,12,23,25,31,32,34,35,43,54)} but comparison of different studies is difficult due to differences in treatment strategy, proportion of patients with total

surgical tumor removal, postoperative surveillance, length of follow-up, as well as definition and categorization of the tumor progression. Nevertheless, aggressive resection of the neoplasm may

change its recurrence pattern.^{11,31)} In a recent study, regional re-growth of glioblastoma after surgery and chemoradiotherapy was noted in 100% of biopsied and 97% of partially removed lesions, but in just 62% of lesions after gross total resection.³¹⁾ Moreover, in 10% of the latter cases, PFS for more than 24 months was marked, which is more or less comparable to the present results. We were able to identify two other series which demonstrated similar outcomes. High-dose FRT (from 60 to more than 90 Gy) concurrent with chemotherapy (ACNU, vincristine) resulted in 53% local recurrence rate.³³⁾ In another series aggressive management, including total tumor removal (32% of cases), brachytherapy, and hypofractionated radiotherapy, resulted in 52% local tumor progression within a median follow up of 12.6 months.³⁶⁾ Based on these findings, we suggest that aggressive management with gross total resection and/or high dose irradiation may result in improvement of local control of intracranial glioblastoma.

In cases of malignant glioma infiltration of the tumor cells can be identified far beyond the localized contrast-enhanced area identifiable on MR imaging. Therefore, comprehensive evaluation of the distant spread of neoplasm is necessary in each individual case,³⁶⁾ and can be possibly attained with detailed analysis of fluid-attenuated inversion recovery or T₂-weighted MR images, as well as functional and metabolic information obtained with perfusion-weighted, diffusion-weighted, and diffusion tensor imaging, or with ¹H-MR spectroscopy.^{13,54)} Such distant tumor spread may vary from one patient to another, and aggressive local management, including surgery and irradiation, can be expected to have greater efficacy for more localized disease. Correspondingly, regional or marginal tumor progression after initial total or nearly total resection of glioblastoma followed by postoperative FRT should appear later compared to distant recurrences, which are affected only by systemic therapy. However, this was not confirmed in the present study, since PFS did not differ significantly between the two groups of patients. Previously, similar PFS was found in patients with local and distant recurrences of glioblastoma,³⁴⁾ whereas some series demonstrated that time to regional tumor progression might be even shorter compared to distant failure.^{25,31,36)}

At present, the standard management of glioblastoma includes chemotherapy with temozolomide concomitant and adjuvant to FRT.^{46,47)} This treatment is not complication-free,¹⁵⁾ which is enforcing the search for novel therapeutic options for malignant gliomas. Interest is growing in modalities based on tumor-specific immune reactions, which

have potentially high benefit-to-risk ratio. Our recent prospective study on the use of AFTV concomitant with FRT for management of newly diagnosed glioblastoma showed very promising results.²⁹⁾ In the present analysis, the recurrence patterns did not differ between patients, who underwent chemotherapy or vaccine therapy, so both types of adjuvant management may have comparable efficacy in control of the tumor progression after initial treatment. However, systemic therapy in general may have rather limited effect on the recurrence pattern of glioblastoma, as distant failure was noted in 18% of patients in the temozolomide-based chemoradiotherapy group, and 23% of those ones in FRT only group.⁵⁴⁾

The present study did not identify any clinical factor associated with specific recurrence patterns of intracranial glioblastoma. However, all tumors initially located in the prefrontal region at the time of further progression invariably affect the genu of the corpus callosum. Therefore, routine inclusion of this area into the irradiation field after total or near total surgical resection of such neoplasms might be reasonable. Several previous studies found that local recurrence of glioblastoma was associated with impaired prognosis.^{2,12,25,44)} In particular, the median survival was 17.3, 14.8, and 26.1 months in patients with recurrence inside, at the margin, and outside the irradiation field.²⁾ In contrast, our 22 patients with regional or marginal progression of the tumor had significantly longer ($p = 0.04$) OS compared to patients with distant or multiple recurrences. Corresponding OS rates were 90% vs. 75% at 1 year and 54% vs. 0% at 2 years after surgery. Such trends might reflect selection bias with more aggressive salvage treatment, particularly re-resection, or inclusion of some cases with pseudoprogression erroneously interpreted as local recurrence, which might result in survival advantage.

Modifications of clinical practice during the study period represent unavoidable pitfall of any retrospective investigation, but seemingly did not affect the results of the present study. On the other hand, absence of volumetric tumor assessment might lead to somewhat inaccurate estimation of the resection rate. Nevertheless, the criteria for total removal were rather strict, since any contrast-enhanced area on postoperative MR imaging obtained within 3 days after surgery was considered to be residual neoplasm.⁸⁾ In fact, visual side-by-side comparison of MR images still represents a rather common method for the evaluation of treated intracranial tumors, but is less accurate compared to more sophisticated tools.⁹⁾ According to recent recommendations of the Response Assessment in Neuro-Oncology Working

Group, volumetric methods for postoperative evaluation of gliomas are not ultimately required at present and still considered as a field of major research.^{22,52)}

In conclusion, aggressive surgical resection and adjuvant management of intracranial glioblastoma may change its recurrence patterns. Further tumor progression appears in the wall of the resection cavity or within 2 cm from its margin in approximately half of such patients. This group has a trend for longer OS compared to patients with distant or multiple recurrences.

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Address reprint requests to: Yoshihiro Muragaki, MD, PhD, Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
e-mail: ymuragaki@abmes.twmu.ac.jp