new brain lesions. At the time of recurrence the salvage treatment was applied according to the preference of the individual doctors and usually included a combination of re-resection, second-line chemotherapy, and/or vaccine therapy.

End Point Evaluation

The primary end point of the study was overall survival (OS) rate at 12 months after PDT. Secondary end points were progression-free survival (PFS) and local PFS rates at 6 months after PDT. The OS, PFS, and local PFS were all estimated from the date of surgery. Additionally, in cases with a maximal diameter of the residual neoplasm of 16 mm or more, the overall tumor response to treatment was evaluated. All brain MRI data before surgery and during follow-up were assessed by review board members. Safety end points included rates of adverse events, side effects, and results of skin photosensitivity testing.

Data Analysis

Analysis of the treatment efficacy was done in all patients who underwent PDT based on administration of talaporfin sodium and intraoperative laser irradiation of the residual neoplasm and/or resection cavity if the diagnosis of primary malignant parenchymal brain tumor was confirmed by the pathology review board after investigation of the permanent formalin-fixed tissue sections (study cohort). Separate analysis of the treatment efficacy was also done in the subgroup of patients with newly diagnosed GBMs. Survival was assessed using the Kaplan-Meier method. Analysis of the treatment safety was done in all patients initially enrolled into the study who received talaporfin sodium.

Results

Patient Characteristics

Detailed characteristics of patients enrolled in the study are presented in Table 1. In all, 27 patients initially received talaporfin sodium. However, 3 patients were deemed ineligible for study participation during surgery and did not receive irradiation with the laser based on the results of the intraoperative histopathological investigation of the resected tissue on the frozen sections, which revealed lymphoma, low-grade glioma, and cavernoma (1 case each). Additionally, 2 patients were excluded from the study later on because the pathology review board did not confirm the diagnosis of a primary malignant parenchymal brain tumor based on the postoperative examination of the permanent formalin-fixed tissue sections. Therefore, the study cohort included 22 patients with a male/female ratio of 1:1 and a median age of 50.5 years (range 24–69 years). The frontal lobe was affected most frequently (59.1% of cases). In 72.7% of patients the tumor was located within or close to eloquent brain areas. Total, subtotal (> 90% of the lesion volume), and partial resections of the neoplasm were performed in 36.4%, 50%, and 13.6% of cases, respectively. No significant differences in clinical characteristics were observed between the entire group of initially enrolled patients (n = 27) and the study cohort (n = 22). Thirteen (59.1%) of 22 patients included in the study cohort had newly diagnosed GBMs and corresponded to recursive partitioning analysis Classes III (4 cases), IV (5 cases), and V (4 cases).[6]

Treatment Efficacy

Among all 22 patients included in the study cohort, 1 death occurred within 12 months after surgery. This patient died 3.4 months after resection and PDT of a newly diagnosed gliosarcoma due to local progression of the tumor. Therefore, the 12-month OS rate was 95.5%. Two tumors demonstrated progression despite treatment within 6 months after surgery, and both recurrences were local. Therefore, the 6-month PFS and local PFS rates were 91%. The maximum length of follow-up was 38.6 months. The median OS was 27.9 months (95% CI lower, 24.8 months; upper, not estimated), the median PFS was 20 months (95% CI lower, 10.3 months; upper, not estimated), and the median local PFS was 22.5 months (95% CI lower, 17.2 months; upper, not estimated).

Among 13 patients with newly diagnosed GBM, the 12-month OS, 6-month PFS, and 6-month local PFS rates after surgical removal of the tumor and PDT were all 100% (Fig. 1). In this subgroup the maximum length of follow-up was 32.0 months. The median OS was 24.8 months (95% CI 18.5–32.0 months), the median PFS was 12.0 months (95% CI 10.3–24.2 months), and the median local PFS was 20.0 months (95% CI 16.2–32.0 months).

In only 1 patient was it possible to evaluate the overall tumor response to treatment. In this case, a newly diagnosed GBM showed complete response 4 months after surgery and PDT.

Treatment Safety

Among all 27 patients who received talaporfin sodium the day before surgery, serious adverse events were noted postoperatively in 6 patients (22.2%). These included aphasia (2 cases) and hemiplegia, hemiparesis, unilateral blindness, visual field defect, homonymous hemianopia, postoperative pyrexia, and infection (1 case each). The overall frequency and distribution of postoperative adverse events were within the range of our usual neurosurgical practice in cases of primary malignant parenchymal brain tumors, and their causal relationships with administration of talaporfin sodium and/or intraoperative laser irradiation were very unlikely. None of these adverse events resulted in the death of a patient.

The laboratory test results in all patients were abnormal, most frequently with an increase in γ-glutamyltransferase (59.3%), alanine aminotransferase (48.1%), aspartate aminotransferase (37.0%), blood alkaline phosphatase (25.9%), and blood lactate dehydrogenase (22.2%). In 18 (66.7%) of 27 patients such abnormalities could be considered as side effects after administration of talaporfin sodium. Postoperative adverse events by system organs, particularly abnormal liver function, were relatively frequent but never exceeded Grade 3 toxicity (Table 2). Only 2 patients (7.4%) had skin disorders, which could be con-

TABLE 1: Characteristics of patients enrolled into study

Demographics & Clinical Characteristics	Value*		
	Initially Enrolled Patients (n = 27)	Study Cohort	
		Total (n = 22)	Newly Diagnosed GBM (n = 13)
age in yrs			
mean ± SD	47.1 ± 13.5	48.1 ± 13.5	46.0 ± 14.1
median (range)	50.0 (24–69)	50.5 (24–69)	49.0 (24–69)
sex			
male	13 (48.1)	11 (50.0)	6 (46.2)
female	14 (51.9)	11 (50.0)	7 (53.8)
histopathological type of tumor†			
GBM	13 (48.1)	13 (59.1)	13 (100.0)
gliosarcoma	1 (3.7)	1 (4.5)	0 (0)
anaplastic astrocytoma	3 (11.1)	3 (13.6)	0 (0)
anaplastic oligoastrocytoma	2 (7.4)	2 (9.1)	0 (0)
anaplastic oligodendroglioma	2 (7.4)	2 (9.1)	0 (0)
pilocytic astrocytoma w/ anaplastic features	1 (3.7)	1 (4.5)	0 (0)
oligodendroglioma	2 (7.4)	0 (0)	0 (0)
central review not performed‡	3 (11.1)	0 (0)	0 (0)
WHO grade†			
IV	14 (51.9)	14 (63.6)	13 (100.0)
III	8 (29.6)	8 (36.4)	0 (0)
II	2 (7.4)	0 (0)	0 (0)
central review not performed‡	3 (11.1)	0 (0)	0 (0)
tumor status			
newly diagnosed	26 (96.3)	21 (95.5)	13 (100.0)
recurrent	1 (3.7)	1 (4.5)	0 (0)
tumor location			
frontal lobe	16 (59.3)	13 (59.1)	7 (53.8)
temporal lobe	5 (18.5)	3 (13.6)	2 (15.4)
parietal lobe	4 (14.8)	4 (18.2)	3 (23.1)
occipital lobe	2 (7.4)	2 (9.1)	1 (7.7)
tumor side			
rt	13 (48.1)	12 (54.5)	8 (61.5)
lt	14 (51.9)	10 (45.5)	5 (38.5)
tumor functional grade			
located in eloquent area	13 (48.1)	12 (54.5)	7 (53.8)
adjacent to eloquent area	6 (22.2)	4 (18.2)	2 (15.4)
located in noneloquent area	8 (29.6)	6 (27.3)	4 (30.8)
PS before treatment§			
0	14 (51.9)	10 (45.5)	3 (23.1)
1	10 (37.0)	9 (40.9)	8 (61.5)
2	0 (0)	0 (0)	0 (0)
3	3 (11.1)	3 (13.6)	2 (15.4)
extent of tumor resection			
total	9 (33.3)	8 (36.4)	5 (38.5)
subtotal (>90% of lesion vol)	13 (48.1)	11 (50.0)	8 (61.5)
partial	5 (18.5)	3 (13.6)	0 (0)

* Unless otherwise stated, values represent cases (%).

† According to central review based on WHO criteria.

‡ These patients did not receive laser irradiation during surgery due to results of the intraoperative histopathological investigation of the resected tissue on the frozen sections and exclusion of the diagnosis of primary malignant parenchymal brain tumor.

§ According to the Eastern Cooperative Oncology Group Performance Status Scale.

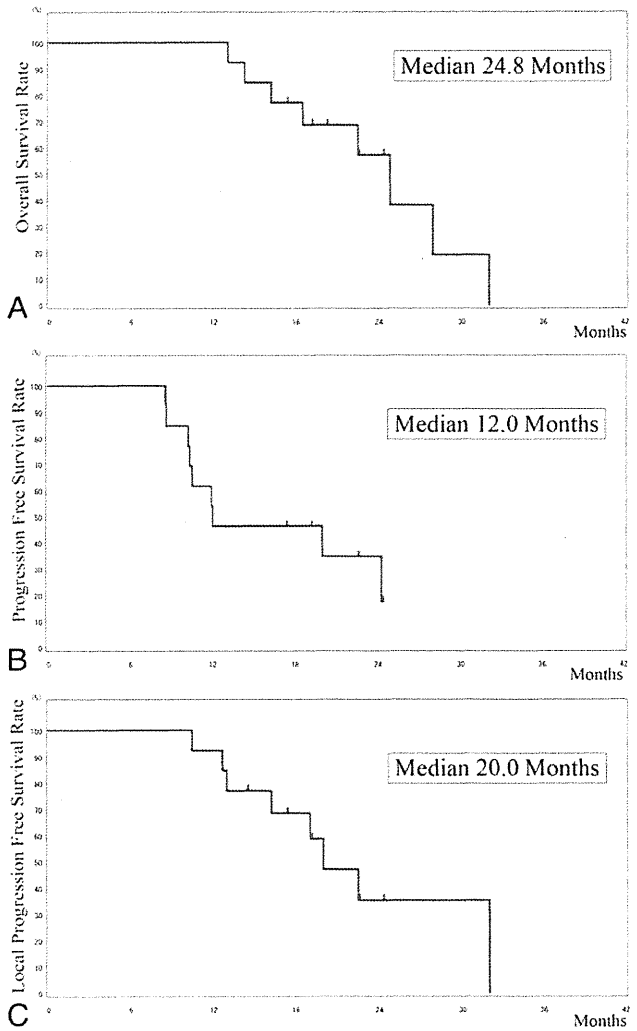

Fig. 1. Kaplan-Meier curves for OS **(A)**, PFS **(B)**, and local PFS **(C)** in the subgroup of patients with newly diagnosed GBM included in the study cohort. Censored observations are marked.

sidered as side effects after administration of talaporfin sodium. It included rash (2 cases), blister (1 case), and erythema (1 case).

Photosensitivity test results were relatively mild and most patients had a score of 1 (barely perceptible erythema) or 2 (distinct erythema); no patient had a score of 3 (marked erythema or edema). These reactions completely disappeared within 4, 8, and 15 days after administration of talaporfin sodium in 55.6%, 77.8%, and 100% of patients, respectively (Table 3).

Discussion

Management of primary malignant parenchymal brain tumors represents a significant challenge. According to the latest edition of the Japan Brain Tumor Registry, 1-, 2-, and 3-year survival rates of patients with high-grade gliomas constitute 64%, 37%, and 28%, respectively.[5] The poor survival rates are mainly due to an inability to perform complete removal of the neoplasm due to its infiltrative growth into functionally important neuronal structures, as well as the limited effectiveness of the postoperative radiotherapy and chemotherapy. Therefore, finding additional effective and safe treatment options in such cases is required.

As a highly selective treatment with minimal injury to the adjacent normal structures, PDT has demonstrated promising potential for management of the various cancers and nonneoplastic disorders, such as age-related macular degeneration, local infection, dermatological diseases, arteriosclerosis, and rheumatoid arthritis.[7] However, despite a large amount of basic and clinical research conducted during several decades and directed on testing of the various photosensitizers, light sources, irradiation types, and treatment regimens, PDT still was not approved to be used as a standard treatment for malignant brain tumors.[2,10] During the last decade there was considerable interest in the use of 5-aminolevulinic acid (5-ALA) in the surgical management of gliomas. Nevertheless, while its application for photodynamic diagnosis and fluorescence-guided resection was associated with a significant impact on effectiveness of tissue sampling, tumor resection rates, and clinical outcomes,[4,17] the attempts to use this photosensitizer for PDT were not so impressive.[2] These unimpressive results might be particularly caused by insufficient incorporation of the drug in the neoplastic cells, especially in necrotic regions and at the periphery of the neoplasm.[2]

In the present study PDT was based on administration of the relatively novel second-generation photosensitizer talaporfin sodium. This water-soluble compound is derived from plant chlorophyll. In the living body it binds to albumin and does not pass the blood-brain barrier. In neoplastic cells it is primarily distributed in the lysosomes.[14] Compared with conventional photosensitizers, talaporfin sodium is activated by light with longer wavelengths; therefore, its light absorption is not affected by hemoglobin and penetrates deeper.[13] Additionally, talaporfin sodium more selectively accumulates in glioma tissue, is rapidly eliminated from the normal tissues, and is less likely to cause adverse reactions.[14] It was demonstrated that PDT based on administration of talaporfin sodium with subsequent irradiation using a 664-nm laser led to necrosis and apoptosis of cultured human glioblastoma cells[13] and experimental tumors[14] in a dose- and time-dependent fashion. The adverse effects on the peritumoral brain were limited to mild temporary edema, and no damage to neurons or the myelin sheath was observed.[14] A pilot clinical study on 14 adult patients with unresectable malignant gliomas showed a median PFS of 23 months in newly diagnosed neoplasms.[1] In concordance, in our present prospective investigation, which included 21 patients with newly diagnosed high-grade gliomas treated according to strict research protocol, the median local PFS constituted 22.5 months.

The most impressive results of our study were obtained in patients with a newly diagnosed GBM. In this subgroup, the 12-month OS and 6-month PFS rates were 100%, and the median OS and median PFS were 24.8 and 12.0 months, respectively. These rates compare favorably

TABLE 2: Frequency of adverse events and side effects by grade*

System Organ Class†	No. of Patients (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (n = 27)
adverse events						
investigations	3 (11.1)	12 (44.4)	10 (37.0)	2 (7.4)	0 (0.0)	27 (100.0)
gastrointestinal disorders	5 (18.5)	16 (59.3)	0 (0.0)	0 (0.0)	0 (0.0)	21 (77.8)
general disorders & administration site conditions	15 (55.6)	6 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	21 (77.8)
nervous system disorders	1 (3.7)	17 (63.0)	2 (7.4)	0 (0.0)	0 (0.0)	20 (74.1)
skin & subcutaneous tissue disorders	10 (37.0)	8 (29.6)	0 (0.0)	0 (0.0)	0 (0.0)	18 (66.7)
injury, poisoning, & procedural complications	9 (33.3)	6 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	15 (55.6)
eye disorders	7 (25.9)	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	9 (33.3)
infections & infestations	1 (3.7)	3 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	6 (22.2)
renal & urinary disorders	3 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (18.5)
psychiatric disorders	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.8)
respiratory, thoracic, & mediastinal disorders	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.8)
vascular disorders	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	0 (0.0)	4 (14.8)
musculoskeletal & connective tissue disorders	1 (3.7)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.1)
blood & lymphatic system disorders	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)
metabolism & nutrition disorders	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	2 (7.4)
cardiac disorders	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
ear & labyrinth disorders	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
side effects						
investigations	7 (25.9)	6 (22.2)	5 (18.5)	0 (0.0)	0 (0.0)	18 (66.7)
skin & subcutaneous tissue disorders	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)

* According to the Cancer Therapy Evaluation Program.[3]

† According to the Medical Dictionary for Regulatory Activities version 14.1 (http://www.meddra.org).

with contemporary results obtained in such tumors with standard treatment. In a global Phase III randomized controlled study on radiotherapy with concomitant and adjuvant temozolomide for GBM, Stupp et al.[18] demonstrated a 12-month OS rate of 61%, a 6-month PFS rate of 54%, a median OS of 14.6 months, and a median PFS of 6.9 months. In the series by Stummer et al.[17] on fluorescence-guided resection of malignant gliomas with the use of 5-ALA, the 6-month PFS rate was 41% and the median PFS period was 5.1 months. Moreover, in our patients with a newly diagnosed GBM, the median local PFS was nearly two times longer than the median PFS (20.0 vs 12.0 months). It can therefore be speculated that prolonged survival was caused by improved local tumor growth control due to intraoperative PDT. It should be emphasized that in the present series all patients with newly diagnosed GBM underwent either total or subtotal resection. Aggressive removal of the tumor may be an important prerequisite for clinical effectiveness of intraoperative PDT, since the penetration depth of a laser is approximately 2.5–5 mm; therefore, the corresponding effective distance for irradiation is limited to 0.75–1.5 cm.[1,2] The limitations of the efficacy of PDT in bulky target tissues and recurrent tumors have been demonstrated.[1] It is also possible that metabolically active infiltrating tumor cells in the periphery of the GBM may be more sensitive to PDT because of incorporation of a greater amount of photosensitizer. It was reported that the tissue concentration of a photosensitizer directly correlates with the grade of malignancy of the neoplasm.[2]

In the present study PDT showed a high level of safe-

TABLE 3: Skin photosensitivity test results in 27 patients*

No. of Days†	No. of Patients (%)	Cumulative No. of Patients (%)
3	4 (14.8)	4 (14.8)
4	11 (40.7)	15 (55.6)
8	6 (22.2)	21 (77.8)
10	1 (3.7)	22 (81.5)
13	2 (7.4)	24 (88.9)
14	1 (3.7)	25 (92.6)
15	2 (7.4)	27 (100)

* For the skin photosensitivity test, between 11 a.m. and 2 p.m., the back of the individual's hand was exposed to direct sunlight for 5 minutes, and the occurrence of any photosensitivity reaction, such as erythema, was assessed. In cases in which photosensitivity reactions were detected, the subject was kept shielded from light until the reaction disappeared, and the skin photosensitivity test was subsequently repeated.

† From administration of talaporfin sodium to disappearance of reaction.

ty. While laboratory investigations have frequently revealed abnormalities likely attributable to the administration of talaporfin sodium, only 2 patients (7.4%) had definite symptoms on the skin, which did not exceed Grade 2 toxicity. In no case did we encounter brain edema or cerebral infarction, which may complicate PDT.[1,2] Therefore, the risk of clinically significant side effects caused by the administration of talaporfin sodium and intraoperative irradiation of the residual tumor and peritumoral brain with a 664-nm laser 22–27 hours thereafter may be considered low. Moreover, according to photosensitivity test results, any reactions completely disappeared in all patients within 15 days after administration of the drug.

The main limitations of the present study are related to its design. A nonrandomized noncontrolled prospective investigation was performed in just 2 neurosurgical centers with well-established neurooncology programs and enrolled a limited number of highly selected cases with rather heterogeneous histopathological diagnoses of malignant parenchymal brain tumors. It is evident that to prove clinical efficacy of the intraoperative PDT with talaporfin sodium and a semiconductor laser, further carefully designed Phase III studies should be performed in a sufficiently large number of patients with possible initial stratification according to tumor resection rate. Testing of the proposed treatment method is also planned in cases of low-grade gliomas and in incompletely resected benign extraaxial neoplasms, such as pituitary adenomas and meningiomas. Since appropriate use of equipment for PDT requires specific skills, the dedicated training program for neurosurgeons is currently under organization. Finally, advanced experimental investigations directed at further understanding the basic mechanisms of the therapeutic effectiveness of intraoperative PDT are also required, and additional studies to search for the most optimal treatment regimens should be continued as well.

Conclusions

The results of the present study demonstrate that novel PDT based on administration of talaporfin sodium and subsequent irradiation with a 664-nm semiconductor laser may provide an additional benefit to the combined management of primary malignant parenchymal brain tumors through possible improvement of their local growth control, which, in turn, may lead to prolongation of the patient's survival. The therapy seems sufficiently safe with a minimal risk of serious side effects. Therefore, application of the intraoperative PDT along with aggressive resection, radiotherapy, and chemotherapy may be of clinical significance, particularly in patients with newly diagnosed GBM.

Disclosure

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References

1. Akimoto J, Haraoka J, Aizawa K: Preliminary clinical report on safety and efficacy of photodynamic therapy using talaporfin sodium for malignant gliomas. **Photodiagn Photodyn Ther 9:**91–99, 2012
2. Bechet D, Mordon SR, Guillemin F, Barberi-Heyob MA: Photodynamic therapy of malignant brain tumours: a complementary approach to conventional therapies. **Cancer Treat Rev** [epub ahead of print], 2012
3. Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events v3.0 (CTCAE). **ctep.cancer.gov.** (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) [Accessed July 22, 2013]
4. Colditz MJ, Jeffree RL: Aminolevulinic acid (ALA)-protoporphyrin IX fluorescence guided tumour resection. Part 1: Clinical, radiological and pathological studies. **J Clin Neurosci 19:**1471–1474, 2012
5. Committee of Brain Tumor Registry of Japan: Report of brain tumor registry of Japan (1984–2000), 12 edition. **Neurol Med Chir (Tokyo) 49 (Suppl):**1–101, 2009
6. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. **J Natl Cancer Inst 85:**704–710, 1993
7. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, et al: Photodynamic therapy. **J Natl Cancer Inst 90:**889–905, 1998
8. Juzeniene A, Peng Q, Moan J: Milestones in the development of photodynamic therapy and fluorescence diagnosis. **Photochem Photobiol Sci 6:**1234–1245, 2007
9. Konishi Y, Muragaki Y, Iseki H, Mitsuhashi N, Okada Y: Patterns of intracranial glioblastoma recurrence after aggressive surgical resection and adjuvant management: retrospective analysis of 43 cases. **Neurol Med Chir (Tokyo) 52:**577–586, 2012
10. Kostron H: Photodynamic diagnosis and therapy and the brain. **Methods Mol Biol 635:**261–280, 2010
11. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds): **WHO Classification of Tumours of the Central Nervous System, ed 4.** Lyon: IARC Press, 2007
12. Matsumura H, Akimoto J, Haraoka J, Aizawa K: Uptake and retention of the photosensitizer mono-L-asparthyl chlorine e6 in experimental malignant glioma. **Lasers Med Sci 23:**237–245, 2008

13. Miki Y, Akimoto J, Yokoyama S, Homma T, Tsutsumi M, Haraoka J, et al: Photodynamic therapy in combination with talaporfin sodium induces mitochondrial apoptotic cell death accompanied with necrosis in glioma cells. **Biol Pharm Bull 36:**215–221, 2013
14. Namatame H, Akimoto J, Matsumura H, Haraoka J, Aizawa K: Photodynamic therapy of C6-implanted glioma cells in the rat brain employing second-generation photosensitizer talaporfin sodium. **Photodiagn Photodyn Ther 5:**198–209, 2008
15. Palumbo G: Photodynamic therapy and cancer: a brief sightseeing tour. **Expert Opin Drug Deliv 4:**131–148, 2007
16. Petrecca K, Guiot MC, Panet-Raymond V, Souhami L: Failure pattern following complete resection plus radiotherapy and temozolomide is at the resection margin in patients with glioblastoma. **J Neurooncol 111:**19–23, 2013
17. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. **Lancet Oncol 7:**392–401, 2006
18. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. **N Engl J Med 352:**987–996, 2005

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ORIGINAL ARTICLE

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

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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 T_1-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 classification[6] 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 T_1-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 criteria[21] 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 T_1-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 T_2-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 T_1-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 T_1-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.

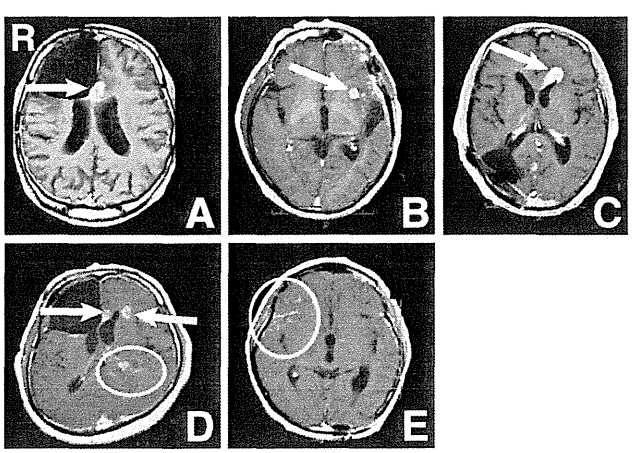

Fig. 1 T_1-weighred magnetic resonance images with contrast medium illustrating the patterns of glioblastoma recurrence (*arrows and circles*) after aggressive surgery and adjuvant management. A: regional, in the wall of the resection cavity; B: marginal, within 20 mm from the margin of the resection 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.

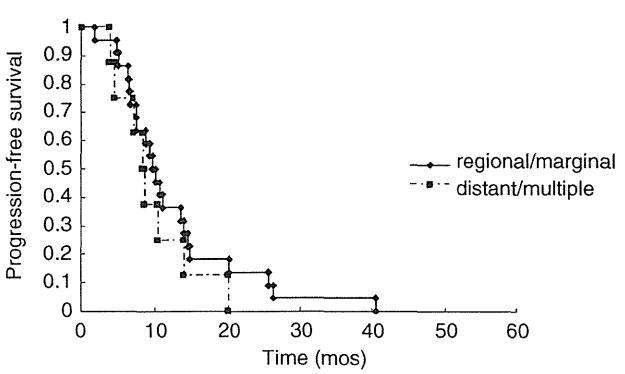

Fig. 2 Comparison of progression-free survival from the time of surgery in patients with different recurrence patterns of intracranial glioblastoma. There is no significant difference ($p = 0.27$).

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

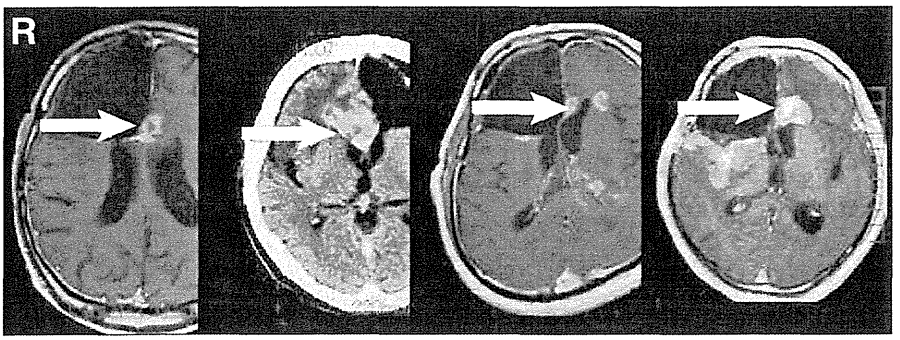

Fig. 3 Follow-up images in 4 patients with glioblastoma initially located in the prefrontal region showing the recurrent tumor affected the genu of the corpus callosum (*arrows*).

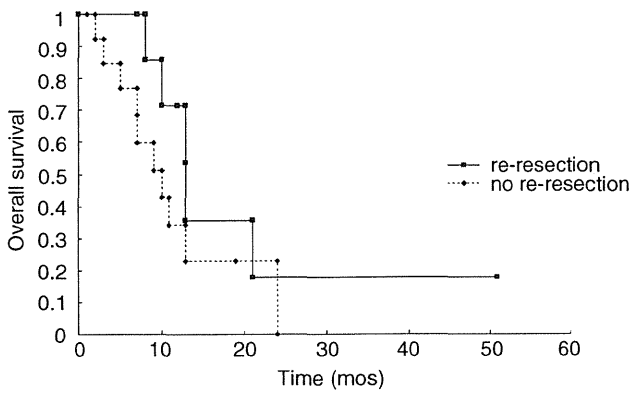

Fig. 4 Comparison of the overall survival from the time of regional or marginal tumor progression relative to re-resection. There is no significant difference (p = 0.20).

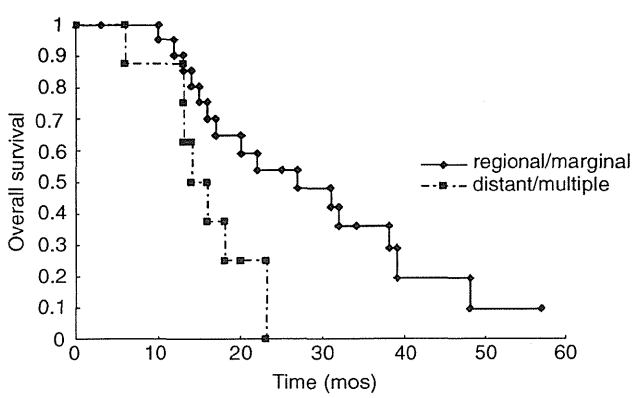

Fig. 5 Comparison of the overall survival from the time of surgery in patients with different recurrence patterns of intracranial glioblastoma. There is a significant difference (p = 0.04).

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 T_2-weighted MR images, as well as functional and metabolic information obtained with perfusion-weighted, diffusion-weighted, and diffusion tensor imaging, or with ^{1}H-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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References

1) Albert FK, Forsting M, Sartor K, Adams HP, Kunze S: Early postoperative magnetic resonance imaging after resection of malignant glioma: Objective evaluation of residual tumor and its influence on regrowth and prognosis. *Neurosurgery* 34: 45–61, 1994
2) Brandes AA, Tosoni A, Franceschi E, Sotti G, Frezza G, Amista P, Morandi L, Spagnolli F, Ermani M: Recurrence pattern after temozolomide concomitant with and adjuvant to radiotherapy in newly diagnosed patients with glioblastoma: Correlation with MGMT promoter methylation status. *J Clin Oncol* 27: 1275–1279, 2009
3) Chamberlain MC: Radiographic patterns of relapse in glioblastoma. *J Neurooncol* 101: 319–323, 2011
4) Chan JL, Lee SW, Fraass BA, Normolle DP, Greenberg HS, Junck LR, Gebarski SS, Sandler HM: Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. *J Clin Oncol* 20: 1635–1642, 2002
5) The Committee of Brain Tumor Registry of Japan: Report of brain tumor registry of Japan (1984–2000), 12th edition. *Neurol Med Chir (Tokyo)* 49 Suppl: 1–101, 2009
6) Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krisch RE, Nelson DF: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 85: 704–710, 1993
7) Dillman RO, Duma CM, Ellis RA, Cornforth AN, Schiltz PM, Sharp SL, DePriest MC: Intralesional lymphokine-activated killer cells as adjuvant therapy for primary glioblastoma. *J Immunother* 32: 914–919, 2009
8) Ekinci G, Akpinar IN, Baltacioglu F, Erzen C, Kilic T, Elmaci I, Pamir N: Early-postoperative magnetic resonance imaging in glial tumors: prediction of tumor regrowth and recurrence. *Eur J Radiol* 45: 99–107, 2003
9) Erickson BJ, Wood CP, Kaufmann TJ, Patriarche JW, Mandrekar J: Optimal presentation modes for detecting brain tumor progression. *AJNR Am J Neuroradiol* 32: 1652–1657, 2011
10) Fabrini MG, Perrone F, De Franco L, Pasqualetti F, Grespi S, Vannozzi R, Cionini L: Perioperative high-dose-rate brachytherapy in the treatment of recurrent malignant gliomas. *Strahlenther Onkol* 185: 524–529, 2009
11) Forsting M, Albert FK, Kunze S, Adams HP, Zenner D, Sartor K: Extirpation of glioblastomas: MR and CT follow-up of residual tumor and regrowth patterns. *AJNR Am J Neuroradiol* 14: 77–87, 1993
12) Hochberg FH, Pruitt A: Assumptions in the radiotherapy of glioblastoma. *Neurology* 30: 907–911, 1980
13) Hou LC, Veeravagu A, Hsu AR, Tse VCK: Recurrent glioblastoma multiforme: a review of natural history and management options. *Neurosurg Focus* 20(4): E3, 2006
14) Hsieh PC, Chandler JP, Bhangoo S, Panagiotopoulos K, Kalapurakal JA, Marymont MH, Cozzens JW, Levy RM, Salehi S: Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery* 57: 684–692, 2005
15) Ikuta S, Muragaki Y, Maruyama T, Ogata H, Iseki H: [Assessment of effect and toxicity of temozolomide combined with radiation therapy for newly-diagnosed glioblastoma in Japan]. *Tokyo Joshi Ika Daigaku Zasshi* 79: 510–515, 2009 (Japanese)
16) Iseki H, Nakamura R, Muragaki Y, Suzuki T, Chernov M, Hori T, Takakura K: Advanced computer-aided intraoperative technologies for information-guided surgical management of gliomas: Tokyo Women's Medical University experience. *Minim Invasive Neurosurg* 51: 285–291, 2008
17) Iuchi T, Hatano K, Narita Y, Kodama T, Yamaki T, Osato K: Hypofractionated high-dose irradiation for the treatment of malignant astrocytomas using simultaneous integrated boost technique by IMRT. *Int J*

Radiat Oncol Biol Phys 64: 1317–1324, 2006
18) Kondziolka D, Flickinger JC, Bissonette DJ, Bozik M, Lunsford LD: Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. *Neurosurgery* 41: 776–785, 1997
19) Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 95: 190–198, 2001
20) Laperriere N, Zuraw L, Cairncross G: Radiotherapy for newly diagnosed malignant glioma in adults: A systematic review. *Radiother Oncol* 64: 259–273, 2002
21) Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (*eds*): *WHO Classification of Tumours of the Central Nervous System*. Lyon, IARC, 2007
22) Lutz K, Radbruch A, Wiestler B, Baumer P, Wick W, Bendszus M: Neuroradiological response criteria for high-grade gliomas. *Clin Neuroradiol* 21: 199–205, 2011
23) McDonald MW, Shu HKG, Curran WJ Jr, Crocker IR: Pattern of failure after limited margin radiotherapy and temozolomide for glioblastoma. *Int J Radiat Oncol Biol Phys* 79: 130–136, 2011
24) Mikuni N, Miyamoto S: Surgical treatment of glioma: extent of resection applying functional neurosurgery. *Neurol Med Chir (Tokyo)* 50: 720–726, 2010
25) Milano MT, Okunieff P, Donatello RS, Mohile NA, Sul J, Walter KA, Korones DN: Patterns and timing of recurrence after temozolomide-based chemoradiation for glioblastoma. *Int J Radiat Oncol Biol Phys* 78: 1147–1155, 2010
26) Monjazeb AM, Ayala D, Jensen C, Case LD, Bourland JD, Ellis TL, McMullen KP, Chan MD, Tatter SB, Lesser GJ, Shaw EG: A Phase I dose escalation study of hypofractionated IMRT field-in-field boost for newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 82: 743–748, 2012
27) Muragaki Y, Iseki H, Maruyama T, Kawamata T, Yamane F, Nakamura R, Kubo O, Takakura K, Hori T: Usefulness of intraoperative magnetic resonance imaging for glioma surgery. *Acta Neurochir Suppl* 98: 67–75, 2006
28) Muragaki Y, Iseki H, Maruyama T, Tanaka M, Shinohara C, Suzuki T, Yoshimitsu K, Ikuta S, Hayashi M, Chernov M, Hori T, Okada Y, Takakura K: Information-guided surgical management of gliomas using low-field-strength intraoperative MRI. *Acta Neurochir Suppl* 109: 67–72, 2011
29) Muragaki Y, Maruyama T, Iseki H, Tanaka M, Shinohara C, Takakura K, Tsuboi K, Yamamoto T, Matsumura A, Matsutani M, Karasawa K, Shimada K, Yamaguchi N, Nakazato Y, Sato K, Uemae Y, Ohno T, Okada Y, Hori T: Phase I/IIa trial of autologous formalin-fixed tumor vaccine concomitant with fractionated radiotherapy for newly diagnosed glioblastoma. *J Neurosurg* 115: 248–255, 2011
30) Muragaki Y, Maruyama T, Nakamura R, Iseki H, Kubo O, Takakura K, Hori T: [Information-guided surgery for glioma removal]. *No Shinkei Geka Journal* 15: 384–395, 2006 (Japanese)
31) Murakami R, Hirai T, Nakamura H, Furusawa M, Nakaguchi Y, Uetani H, Kitajima M, Yamashita Y: Recurrence patterns of glioblastoma treated with postoperative radiation therapy: relationship between extent of resection and progression-free interval. *Jpn J Radiol* 30: 193–197, 2012
32) Nagashima T, Matsutani M, Nakamura O, Tanaka Y: [Regrowth pattern of glioblastoma multiforme after radiotherapy]. *Gan No Rinsho* 35: 1272–1276, 1989 (Japanese)
33) Nakagawa K, Aoki Y, Fujimaki T, Tago M, Terahara A, Karasawa K, Sakata K, Sasaki Y, Matsutani M, Akanuma A: High-dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 40: 1141–1149, 1998
34) Oh J, Sahgal A, Sanghera P, Tsao MN, Davey P, Lam K, Symons S, Aviv R, Perry JR: Glioblastoma: patterns of recurrence and efficacy of salvage treatments. *Can J Neurol Sci* 38: 621–625, 2011
35) Oppitz U, Maessen D, Zunterer H, Richter S, Flentje M: 3D-recurrence-patterns of glioblastomas after CT-planned postoperative irradiation. *Radiother Oncol* 53: 53–57, 1999
36) Pan H, Alksne J, Mundt AJ, Murphy KT, Cornell M, Kesari S, Lawson JD: Patterns of imaging failures in glioblastoma patients treated with chemoradiation: a retrospective study. *Med Oncol* Epub 2011 Nov 23
37) Paravati AJ, Heron DE, Landsittel D, Flickinger JC, Mintz A, Chen YF, Huq MS: Radiotherapy and temozolomide for newly diagnosed glioblastoma and anaplastic astrocytoma: Validation of Radiation Therapy Oncology Group—recursive partitioning analysis in the IMRT and temozolomide era. *J Neurooncol* 104: 339–349, 2011
38) Proescholdt MA, Macher C, Woertgen C, Brawanski A: Level of evidence in the literature concerning brain tumor resection. *Clin Neurol Neurosurg* 107: 95–98, 2005
39) Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg* 115: 3–8, 2011
40) Shibui S: Randomized controlled trial on malignant brain tumors—activities of the Japan Clinical Oncology Group-Brain Tumor Study Group. *Neurol Med Chir (Tokyo)* 44: 220–221, 2004
41) Shuto T, Matsunaga N, Suinaga J, Yoshizumi T, Tuzuki S, Ootake M: [Role of gamma knife treatment for glioblastoma]. *Nippon Kagaku Ryoho Gakkai Zasshi* 37: 1024–1026, 2010 (Japanese)
42) Smith MM, Thompson JE, Castillo M, Cush S, Mukherji SK, Miller CH, Quattrocchi KB: MR of recurrent high-grade astrocytomas after intralesional immunotherapy. *AJNR Am J Neuroradiol* 17: 1065–1071,

1996
43) Sneed PK, Gutin PH, Larson DA, Malec MK, Phillips TL, Prados MD, Scharfen CO, Weaver KA, Wara WM: Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. *Int J Radiat Oncol Biol Phys* 29: 719–727, 1994
44) Stewart LA: Chemotherapy in adult high-grade glioma: A systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 359: 1011–1018, 2002
45) Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T: Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery* 62: 564–576, 2008
46) Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 10: 459–466, 2009
47) Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987–996, 2005
48) Takakura K, Abe H, Tanaka R, Kitamura K, Miwa T, Takeuchi K, Yamamoto S, Kageyama N, Handa H, Mogami H, Nishimoto A, Uozumi T, Matsutani M, Nomura K: Effects of ACNU and radiotherapy on malignant glioma. *J Neurosurg* 64: 53–57, 1986
49) Tanaka M, Ino Y, Nakagawa K, Tago M, Todo T: High-dose conformal radiotherapy for supratentorial malignant glioma: A historical comparison. *Lancet Oncol* 6: 953–960, 2005
50) Tsien C, Moughan J, Michalski JM, Gilbert MR, Purdy J, Simpson J, Kressel JJ, Curran WJ, Diaz A, Mehta MP: Phase I three-dimensional conformal radiation dose escalation study in newly diagnosed glioblastoma: Radiation Therapy Oncology Group trial 98–03. *Int J Radiat Oncol Biol Phys* 73: 699–708, 2009
51) van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, Haaxma-Reiche H, Kros JM, van Kouwenhoven MC, Vecht CJ, Allqeier A, Lacombe D, Gorlia T: Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organization for Research and Treatment of Cancer phase III trial. *J Clin Oncol* 24: 2715–2722, 2006
52) Vogelbaum MA, Jost S, Aghi MK, Heimberger AB, Sampson JH, Wen PY, Macdonald DR, Van den Bent M, Chang SM: Application of novel response/progression measures for surgically delivered therapies for gliomas: Response Assessment in Neuro-Oncology (RANO) Working Group. *Neurosurgery* 70: 234–244, 2012
53) Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jaaskelainen J, Ram Z: A Phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 5: 79–88, 2003
54) Wick W, Stupp R, Beule AC, Bromberg J, Wick A, Ernemann U, Platten M, Marosi C, Mason WP, van den Bent M, Weller M, Rorden C, Karnath HO: A novel tool to analyze MRI recurrence patterns in glioblastoma. *Neuro Oncol* 10: 1019–1024, 2008

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The Guidelines for Awake Craniotomy

Guidelines Committee of The Japan Awake Surgery Conference

Preface

Cortical mapping by awake craniotomy has become frequently used worldwide as part of the treatment strategy for brain lesions located near language areas. However, no systematic guidelines have been established for this surgery. The Japan Awake Surgery Conference has now created guidelines for awake craniotomy for brain lesions near language areas.

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. The 4th annual meeting of this conference decided to establish guidelines for awake craniotomy and organized a guidelines committee. Members specializing in the fields of neurosurgery, neurology, and anesthesiology took part in discussions, a systematic review was carried out, and the guidelines committee attempted to create guidelines in compliance with evidence-based medicine methods as far as possible. However, the absence of randomized control trials of awake craniotomy forced the guidelines committee to use "de facto standards" to create the guidelines.

The guidelines consist of three parts: 1) Surgical maneuvers for awake craniotomy, 2) Anesthetic management for awake craniotomy, and 3) Language assessment during awake craniotomy. The guidelines are not intended to override the methods of experienced practitioners, and are not intended to exclude methods other than those included. We hope that these guidelines will improve the safety of awake surgeries and promote the development of the neuroscience of neurocognitive function.

President of The Japan Awake Surgery Conference
Takamasa KAYAMA, MD

I. SURGICAL MANEUVERS FOR AWAKE CRANIOTOMY

Indications

1. Age

[Recommendation]

While there is no specific upper age limit, an anesthesiologist, surgeon, and speech therapist should consider the condition of each patient carefully. Surgeons with little experience of awake craniotomy should try to perform awake surgery only in patients aged from 15 to 65 years.

[Commentary]

Awake surgery is usually performed in patients aged from 15 to 65 years. However, patients indicated for such surgery are not only specified by age. If the required tasks can be handled correctly, awake surgery can be performed in persons younger than 15 years and older than 65 years. Patients can undergo such surgery at any age if they are considered to be suitable candidates after other factors have been assessed. The cortex is difficult to excite by electrical stimulation in children aged 7 years or younger, so they do not fulfill the criteria for cortical electrical stimulation.[1] Patients older than 70 years, who may develop delirium or marked emergent increase in blood pressure, require especial attention.

Reference

1) Berger MS, Ojemann GA, Lettich E: Neurophysiological monitoring during astrocytoma surgery. *Neurosurg Clin N Am* 1: 65–80, 1990

These guidelines are approved by The Japan Neurosurgical Society. The part on anesthetic management is approved by the Japan Society of Anesthesiology and the part on language assessment during awake craniotomy is approved by the Neuropsychology Association of Japan.

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2. Diseases

[Recommendation]

In principle, the indication is for intramedullary diseases that can be treated surgically.

[Commentary]

Epilepsy without macroscopic demarcation between the normal brain tissue and the lesion, gliomatosis with indistinct borders, and cavernous hemangiomas that can only be reached through normal brain regions are typical indications.[1] Metastatic brain tumors are sometimes an indication. Extramedullary tumors such as meningioma are a less common indication, depending on the case.[2] For example, extramedullary tumor corresponding to brain disease with extended motor nerve involvement may be an indication.

References

1) Muragaki Y, Maruyama T, Iseki H, Takakura K, Hori T: [Functional brain mapping and electrophysiological monitoring during awake craniotomy for intraaxial brain lesions]. *No Shinkei Geka Journal* 17: 38–47, 2008 (Japanese)
2) Shinoura N, Yoshida M, Yamada R, Tabei Y, Saito K, Suzuki Y, Takayama Y, Yagi K: Awake surgery with continuous motor testing for resection of brain tumors in the primary motor area. *J Clin Neurosci* 16: 188–194, 2009

3. Sites

[Recommendation]

Areas indicated for awake surgery are locations where surgical procedures may lead to worsening of neurological symptoms, but can be assessed by the performance of intraoperative tasks.

[Commentary]

Lesions in and around the anatomical language areas, lesions in the lateral parietal lobe of the dominant hemisphere (mainly including the angular gyrus), lesions adjacent to the arcuate fibers (superior longitudinal fasciculus), lesions adjacent to the motor cortex, etc.

Awake surgery is indicated for lesions affecting the triangular and opercular regions of the posterior part of the inferior frontal gyrus (Brodmann's areas 44 and 45) or the inferior part of the precentral gyrus with respect to the language motor center, as well as lesions in the posterior half of the superior, middle, and inferior temporal gyri of the temporal lobe (areas 41, 42, 22, and 37) or the supramarginal and angular gyri of the parietal lobe (areas 40 and 39) with respect to the sensory language center. Awake surgery is also indicated for lesions adjacent to the arcuate fibers (superior longitudinal fasciculus) that appear to connect the motor and sensory language areas. The hippocampus is located deep inside the temporal lobe, and is associated with verbal memory, and includes the insular gyri.[1] If a lesion is located near any of the above sites in the dominant hemisphere or if the lesion cannot be confirmed to affect the nondominant hemisphere, identify the functional areas by stimulation.

Reference

1) Muragaki Y, Maruyama T, Iseki H, Takakura K, Hori T: [Functional brain mapping and electrophysiological monitoring during awake craniotomy for intraaxial brain lesions]. *No Shinkei Geka Journal* 17: 38–47, 2008 (Japanese)

4. Other indications such as neurological symptoms

[Recommendation and commentary]

The patient has to participate in awake surgery, so the patient, assessors, surgeons, and anesthesiologists must all fully understand the meaning of aggressive resection and possible complications, and be able to recognize whether or not the patient can tolerate awake anesthesia.

If patients have already developed moderate or severe symptoms, mapping and monitoring are difficult to perform. For example, patients with impairment of language functions, such as understanding, reading, repetition, and object naming, are not suitable for awake surgery. Among patients who cannot speak fluently but have no disorders of understanding, those with minor naming disorders and decreased word enumeration are candidates, although severe disorders may develop during surgery.[1]

Patients with serious intracranial hypertension and those with serious systemic complications are not suitable.

Reference

1) Berger MS, Ojemann GA, Lettich E: Neurophysiological monitoring during astrocytoma surgery. *Neurosurg Clin N Am* 1: 65–80, 1990

5. Determination of the dominant hemisphere

[Recommendation]

Performance of a provocation test (Wada test) by cerebral angiography is desirable. If determination of the dominant hemisphere is done by noninvasive tests such as functional magnetic resonance imaging (fMRI), the therapeutic strategy should be defined after considering the possibility of pseudolocalization.

[Commentary]

Various advanced procedures such as fMRI, mag-

netoencephalography (MEG), and near infrared spectroscopy (NIRS) have been developed as functional tests. These procedures are noninvasive and have made substantial contributions to neuroscience and neurology. However, for decision-making about surgical resection, the "gold standard," which is the most reliable procedure available (the procedure used to define the "correct answer" as the standard for comparison with new procedures), should be used. The gold standards for identification of the dominant hemisphere, functional areas, and neuronal functions are the provocation test (Wada test), that involves infusion of anesthetic during cerebral angiography, identification of functional sites by electrical stimulation, and neurological testing, respectively. Although the anesthetic for the Wada test was amobarbital in the original proposal, propofol is primarily used these days because amobarbital is not currently marketed in Japan.[3] These "gold standard" procedures should be used despite being more invasive because, if less invasive but less reliable procedures are used and an incorrect result is obtained, the invasiveness of surgery may become greater than necessary. Determination of the dominant hemisphere in patients with tumors causing compression based on fMRI may have left-right errors (pseudolocalization) in 14%.[4] The surgical strategy largely depends on whether or not a lesion affects the dominant hemisphere and incorrect information naturally increases the risk, so performing the Wada test (the gold standard preoperative procedure) is considered to be necessary. Although textbooks state that 99% of right-handed persons are left hemisphere dominant, a meta-analysis of 734 patients undergoing the Wada test (including 121 of our patients)[2] revealed that the dominant hemisphere for right-handed persons was the left hemisphere in 88%, the right in 5%, and both in 7%.[1] The dominant hemisphere determined by electrical stimulation is the left hemisphere in 91% and the right in 9%. Thus, around 90% of right-handed persons are left hemisphere dominant and around 10% are right hemisphere dominant, which is not a low prevalence, suggesting that careful attention should be paid during surgery to lesions in functional areas of the dominant hemisphere. The results of the Wada test in left-handed people have shown that the left dominant:right dominant ratio ranges from 1:1 to 3:1, with a slightly higher rate of left dominance.

In recent years, the increasing accuracy of noninvasive procedures such as fMRI, MEG, and NIRS has provided us with more and more knowledge. In addition, when a gradual transition from invasive to noninvasive procedures occurs because of the risk of complications of cerebral angiography, including the Wada test, the risk of pseudolocalization should be accepted. Feedback with respect to comparison of the results of the Wada test and those of mapping by electrical stimulation is needed.

References

1) Ishikawa T, Muragaki Y, Maruyama T, Ono Y, Abe K, Tanaka M, Amano K, Inoue T, Kubo O, Iseki H, Hori T, Sakai K: [Efficacy of the determination of the dominant hemisphere by Wada test and functional MRI for tumors around language areas]. Presented at the 65th Annual Meeting of the Japan Neurosurgical Society; October 18-20, 2006; Kyoto (Japanese)
2) Medina LS, Bernal B, Ruiz J: Role of functional MR in determining language dominance in epilepsy and nonepilepsy populations: a Bayesian analysis. *Radiology* 242: 94-100, 2007
3) Takayama M, Miyamato S, Ikeda A, Mikuni N, Takahashi JB, Usui K, Satow T, Yamamoto J, Matsuhashi M, Matsumoto R, Nagamine T, Shibasaki H, Hashimoto N: Intracarotid propofol test for speech and memory dominance in man. *Neurology* 63: 510-515, 2004
4) Ulmer JL, Hacein-Bey L, Mathews VP, Mueller WM, DeYoe EA, Prost RW, Meyer GA, Krouwer HG, Schmainda KM: Lesion-induced pseudo-dominance at functional magnetic resonance imaging: implications for preoperative assessments. *Neurosurgery* 55: 569-581, 2004

Methods

1. Preoperative treatment

1-1. Status and details of simulation

[Recommendation]

The tasks that will be performed during surgery should be preoperatively rehearsed in the ward. Simulation of the surgical posture, equipment set-up, and role sharing, as well as rehearsal of the tasks for the patient, surgeons, anesthesiologists, and other surgical staff (such as nurses) should also be performed in the operating room.

[Commentary]

For successful intraoperative mapping with awake anesthesia, it is important to reduce the patient's anxiety as much as possible by maintaining a comfortable environment during surgery. Bring the patient to the operating room on the day before surgery, and take enough time to explain what will be done on the next day (including the posture that the patient will be placed in by the surgeon, anesthesiologists, and nurses). Then have the patient actually adopt that posture. If possible, show the patient a video of surgery on previous patients for better understanding. If functional language mapping is performed, conduct higher function exami-

nation before surgery, perform the tasks that will done during surgery in the ward in advance, and select intraoperative tasks, for example, by showing the patient pictures or photographs of common objects used in object naming and selecting some that the patient can answer correctly. If there has been a long interval between examination and surgery in a patient with progressive symptoms due to a tumor adjacent to the language areas, the tasks should be selected immediately before surgery.

1-2. Monitoring of anticonvulsants

[Recommendation]

In patients who are scheduled to undergo awake surgery, it is desirable to initiate the administration of anticonvulsants in advance and maintain effective blood concentrations if enough time is available. Phenytoin can be administered and the concentration increased to the upper limit of the effective range (target level 20 mg/dl) by the day before surgery.

[Commentary]

Even if an effective blood concentration of an anticonvulsant has been maintained since before surgery, there is some risk of convulsions during awake surgery (as described below). Therefore, sufficient preoperative antiepileptic drug saturation is desirable to prevent intraoperative convulsions and for easy drug loading after the onset of convulsions. Regarding the selection of drugs, phenytoin is recommended, since intravenous administration can be performed immediately before or during surgery when oral administration is not possible, rapid saturation is easy, a steady-state blood concentration can be obtained after a relatively short time (4-5 days), and regulation of the blood concentration is easy.

The bioavailability of phenytoin is high (98%) and there is little difference between systemic absorption after intravenous and oral administration. If there are 3 or more days before surgery, it is desirable to achieve the target blood concentration by oral administration to reduce patient discomfort. If rapid saturation immediately before surgery is selected, the target blood concentration can be obtained promptly by intravenous administration of phenytoin.

Especially for patients with tumors located near the motor cortex, after obtaining an adequate preoperative blood concentration of phenytoin, the blood level should be monitored every 2 hours during surgery. If the concentration is low, intravenous administration of 250 mg of phenytoin should be given to raise the concentration to the normal upper limit (this dose increases the blood level by approximately 6 mg/dl in a patient weighing 60 kg), or 100-200 mg of phenytoin should be given every 4 hours during surgery (this dose will increase the blood level by approximately 2.4-4.7 mg/dl in a patient weighing 60 kg).

Sixteen (16%) of the 100 patients who underwent awake surgery at Tokyo Women's Medical University from 2004 to the present developed seizures under awake conditions, whereas 48 (48%) of these 100 patients had a history of seizures before surgery. Twelve (24.5%) of the 49 patients with tumors near the motor cortex developed seizures during awake surgery and this rate was higher than at other sites. Occurrence of seizures during awake surgery is defined as clinically obvious convulsions and does not include patients who only have afterdischarges.

Among the 80% or more of our 100 patients who had received preoperative antiepileptic drug therapy, patients with lesions near the motor cortex and a preoperative blood level within or above the effective range accounted for 70% of patients both with and without intraoperative convulsions, although the blood level was not measured in all patients. Thus, even if the blood level of an antiepileptic drug is within the effective concentration range, there is no improvement of the preventative effect against intraoperative seizures, which is more likely to depend on the conditions of electrical stimulation.

Preoperative phenytoin loading is not performed at Tokyo Women's Medical University, so its efficacy has not been demonstrated there. Therefore, the frequency of intraoperative convulsions in patients with brain lesions at each site should be compared with that determined at institutions where rapid preoperative phenytoin saturation is performed to assess the usefulness of this procedure. It may also be necessary to assess the conditions employed for electrical stimulation, especially for the motor cortex, as well as the use of rapid anticonvulsant saturation.

[Saturation][1,2]

Initial loading dose [mg]: target blood concentration [mg/dl] × volume of distribution Vd [l/kg] × body weight [kg] = 20 × 0.7 × body weight [kg]..(a)

Additional loading dose [mg]: {target blood concentration − measured value [mg/dl]} × volume of distribution Vd [l/kg] × body weight [kg] = (20 − measured value) × 0.7 × body weight [kg].....(b)

Where target blood concentration is 20 mg/dl, and Vd is specific value for each drug: phenytoin 0.6-0.8 (approximately 0.7) l/kg.

For example, in a patient weighing 60 kg, the initial loading dose calculated using (a) is 840 mg, which is administered as three divided doses every 2