9. Emergence and discharge

i) After the completion of surgery, discontinue sedatives and analgesics.

ii) Confirm emergence and the return of spontaneous respiration, remove the LMA if used, and transfer the patient to the intensive care unit.

[Commentary]

Follow the regular procedures for neurosurgical anesthetic management of emergence and discharge.

III. LANGUAGE ASSESSMENT DURING AWAKE CRANIOTOMY

1. Methods of language mapping by cortical electrical stimulation during awake craniotomy

[Recommendation]

Indications: Patients with lesions around the perisylvian language areas of the dominant hemisphere. Patients without apparent aphasia who are able to fully understand the language tasks and cooperate with them.

Preoperative preparation: Set language tasks that can easily be performed by patients and fully familiarize them with the tasks.

Electrical stimulation: A stronger stimulus intensity (6–12 mA) and longer duration (2–4 sec) are required than for motor and sensory mapping. Initiate electrical stimulation immediately before presenting the language stimulus (line drawing or question) and continue it during presentation.

Language tasks: Perform counting, visual naming, and listening comprehension tasks for cortical mapping. If electrical stimulation reveals any dysfunction, assess reproducibility. Monitor language functions primarily on the basis of spontaneous speech during resection. If an abnormality is suspected, perform language mapping with visual naming and/or listening comprehension.

[Commentary]

Purpose: The purpose of language mapping is to identify the language areas and to avoid postoperative aphasia by preserving these areas. Because the extent of the language areas varies among individuals and it is difficult to accurately identify them anatomically, the areas should be determined for each individual.[5] If language areas are identified outside the resection zone and language functions are confirmed to be localized away from the lesion to be resected, the neurosurgeon can resect the lesion with confidence.

Indications: Because patients must have full understanding and good cooperation to perform language mapping, we should consider the preoperative cognitive level and mental maturity of the patient. Because some patients cannot adapt to the special circumstances of the operating room environment, after providing sufficient explanation and practice of the tasks, determine whether they are suitable candidates for awake surgery or not. Be especially careful with young and elderly persons. Children and patients with obvious aphasia before surgery are not suitable for language mapping. Patients showing slight anomia or word finding difficulty (poor word production by category or initial phonemes) during preoperative examination may attempt language mapping, but their language function can become worse than preoperatively because of drowsiness, which can make language mapping difficult.

Preoperative preparation: Examination: Perform neurological and neuropsychological testing. Explanation: Fully explain the language tasks that will be used for mapping. Establishment of tasks: After performing the standard tasks once, exclude stimuli that evoke unstable responses, leaving only the stimuli for which the patient can definitely provide correct answers. Determine the rate of presenting line drawings at which the patient can answer comfortably (2–5 sec intervals). Practice: The selected tasks should be practiced several times until the patient can answer with confidence. If examination reveals suspected decrease of language function, perform the standard aphasia tests to measure the severity of aphasia. Identification of language-related sites by fMRI might be useful to limit the area that has to be explored by intraoperative mapping.[6]

Electrical stimulation: Follow the usual standards, but remember that stronger and longer stimulation is required for language mapping. Employ a stimulus intensity of 6–12 mA if no afterdischarge is evoked. Because electrical stimulation is initiated immediately before presenting a line drawing or question and is continued during presentation, stimulation needs to be applied for between 3 and 4 seconds (Fig. 5). It is desirable to present the language tasks at regular intervals so that the neurosurgeons get used to the timing of electrical stimulation. Also, adjust the location of the screen so the surgeons are able to monitor stimulation during the language tasks.

Language tasks: Language tasks to be performed: For all areas to be tested, counting and visual nam-

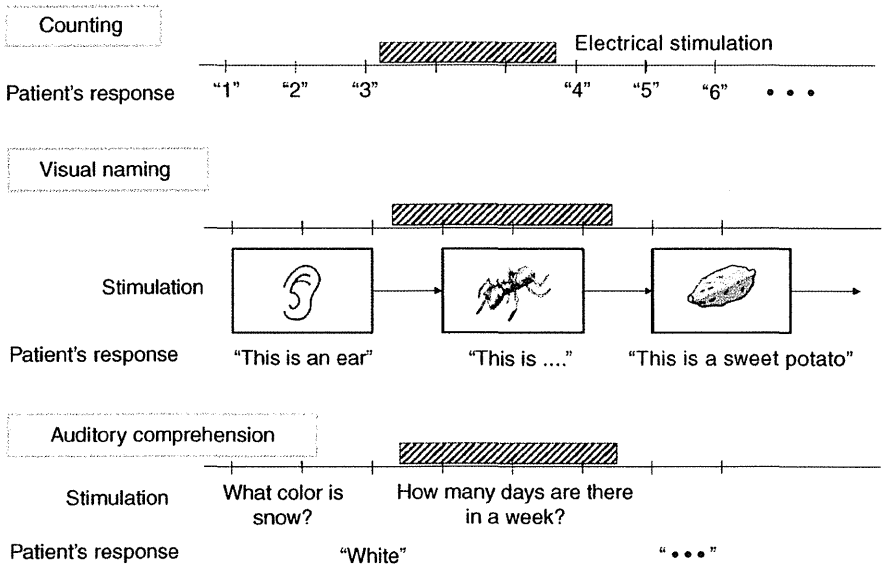

Fig. 5 Flow chart of language tasks. Initiate electrical stimulation before presenting the language tasks.

ing should be performed. With counting, check speech arrest and delay. Confirm that the site of speech arrest does not correspond to the negative motor area. During the visual naming task (picture naming), record slips of the tongue (errors), delayed responses, or no response. Words for the naming task are selected from among high-frequency words, such as cat, knife, desk etc. For the temporal lobe, also perform auditory comprehension. Frequency: Stimulate each site twice or more with the maximum current to check whether a language abnormality is detected. If any language abnormality is detected, stimulate the site twice or more again to check reproducibility. Interpretation of results: If three stimuli induce at least two incorrect responses, the site should be designated as a language-related site (Fig. 5).

Cortical mapping: Counting (from 1 to 30): Perform electrical stimulation while asking the patient to count from 1 to 30 at approximately one number per second. After the patient reaches 30, he/she starts from 1 again. Identify the sites where stimulation leads to abnormalities of speech (arrest, delay, dysarthria). Regarding the sites associated with these abnormalities, ask about the patient's subjective symptoms (e.g., inability to move the tongue). Then, assess whether or not the sites are primary motor areas or negative motor areas related to articulation. Visual naming[7]: Present line drawings (on paper or a monitor) at the interval predetermined for each patient and instruct the patient to name them using a carrier phrase like "This is...". Anomia or paraphasia: After saying "This is" fluently, patients cannot recall the name or substitute one word for another. Speech arrest: The patient cannot say "This is". Auditory comprehension: The patient answers an easy question with a single word. Because this involves both word recall and listening comprehension, electrical stimulation at sites different from those related to visual naming induces abnormalities.[3] Language mapping is based on the above three tasks. If time permits, other language tasks can be added as required.

Subcortical mapping: This is required if nerve fibers immediately below or adjacent to the language areas are to be resected. Continue conversation between the patient and examiner during resection and perform mapping with electrical stimulation at the sites with possible abnormalities. Use visual naming and, for the posterior language areas, listening comprehension as well. The intensity of electrical stimulation should be equal to or slightly greater than that for cortical stimulation. Identification of nerve fascicles by preoperative tractography might be useful to determine the sites for subcortical mapping.[1,2,4]

References

1) Berman JI, Berger MS, Chung SW, Nagarajan SS, Henry RG: Accuracy of diffusion tensor magnetic resonance imaging tractography assessed using intraoperative subcortical stimulation mapping and magnetic source imaging. *J Neurosurg* 107: 488–494, 2007
2) Duffau H: The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. *Neuropsychologia*

Table 1 Examples of line drawings used in the visual naming task

Grape	Ear	Ant	Potato	Train	Strawberry	Eye	Cat	Truck	Rabbit
Bus	Scissors	Patrol car	Carrot	Plane	Chicken	Pencil	Motorcycle	Apple	Cup

Words are selected from among high-frequency words in the vocabulary test for aphasia and color drawings without copyright are used.

46: 927–934, 2008
3) Hamberger MJ, Seidel WT: Auditory and visual naming tests: normative and patient data for accuracy, response time, and tip-of-the-tongue. *J Int Neuropsychol Soc* 9: 479–489, 2003
4) Henry RG, Berman JI, Nagarajan SS, Mukherjee P, Berger MS: Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping. *Neuroimage* 21: 616–622, 2004
5) Ojemann G, Ojemann J, Lettich E, Berger M: Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 108: 411–421, 2008
6) Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW: Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 51: 350–360, 2002
7) Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. *N Engl J Med* 358: 18–27, 2008

2. Task details

Examples of line drawings used in the visual naming task and questions used to treat auditory comprehension are shown in Tables 1 and 2, respectively.

Table 2 Examples of questions used to test auditory comprehension

1. What is your name?
2. What color is snow?
3. What color is a sunflower?
4. What color is a crow?
5. What color is a banana?
6. What color is a fire truck?
7. How many days are there in a week?
8. How many minutes are there in an hour?
9. How many legs has a dog?
10. What day is after Tuesday?
11. What season is after spring?
12. What month is New Year's Day in?
13. What month is the Bon Festival in?
14. Which direction the sun sets in?
15. What is the offspring of a frog called?
16. What is the offspring of a chicken called?
17. A mother is a woman. What is a father?
18. A brother is a man. What is a sister?
19. The sun shines during the daytime. When do the stars come out?
20. Cherry blossom is seen in spring. How about red leaves?
21. Where do you buy postage stamps?
22. What do you use to cut vegetables?
23. What do you use to cut paper?
24. What do you use to tell the time?
25. Hot water is hot. How about ice?
26. Iron is heavy. How about feathers?
27. The sea is deep. How about mountains?
28. You wear clothes. How about shoes?
29. Birds fly. How about fish?
30. You listen to music. How about paintings?

Questions that can be answered within approximately 2 seconds are prepared based on the Wechsler Intelligence Scale for Children-Revised, Illinois Test of Psycholinguistic Abilities, Western Aphasia Battery test, etc.

Appendix: GUIDELINES COMMITTEE OF THE JAPAN AWAKE SURGERY CONFERENCE

Chairman of the Committee

Takamasa KAYAMA (National Cancer Center & Dept. of Neurosurgery, Yamagata University Faculty of Medicine)

Co-Chairman of the Committee

Hiroshi ISEKI (Tokyo Women's Medical University, Faculty of Advanced Techno-Surgery)

Yoshitsugu YAMADA (Dept. of Anesthesiology, Faculty of Vital Care Medicine, The Graduate School of Medicine, The University of Tokyo)

Committee Members

Tatsuya ABE (Dept. of Neurosurgery, Oita University Faculty of Medicine)

Chikashi FUKAYA (Dept. of Neurosurgery and Applied System Neuroscience, Nihon University School of Medicine)

Hidekatsu FURUTANI (Dept. of Anesthesia, Kyoto University Hospital)

Kazuhiro HONGO (Dept. of Neurosurgery, Shinshu University School of Medicine)

Tohru ITAKURA (Wakayama Medical University)

Koji KAJIWARA (Dept. of Neurosurgery, Yamaguchi University Graduate School of Medicine)

Kyosuke KAMADA (Dept. of Neurosurgery, Asahikawa Medical University)

Masahiko KAWAGUCHI (Dept. of Anesthesiology, Nara Medical University)

Mikito KAWAMATA (Dept. of Anesthesiology and Resuscitology, Shinshu University School of Medicine)

Toshihiro KUMABE (Dept. of Neurosurgery, Tohoku University Graduate School of Medicine)

Junichi KURATSU (Dept. of Neurosurgery, Kumamoto University School of Medicine)

Masanori KURIMOTO (Dept. of Neurosurgery, University of Toyama, Faculty of Medicine)

Nobuhiro MIKUNI (Dept. of Neurosurgery, Sapporo Medical University, School of Medicine)

Yasuhiro MORIMOTO (Dept. of Anesthesiology, Yamaguchi University Graduate School of Medicine)

Yoshihiro MURAGAKI (Tokyo Women's Medical University, Faculty of Advanced Techno-Surgery)

Osamu NAGATA (Dept. of Anesthesiology, Tokyo Women's Medical University)

Kaori SAKURADA (Dept. of Neurosurgery, Yamagata University Faculty of Medicine)

Kiyotaka SATO (Dept. of Anesthesiology, Kohnan Hospital)

Shinya SATO (Dept. of Neurosurgery, Yamagata University Faculty of Medicine)

Nobusada SHINOURA (Dept. of Neurosurgery, Komagome Metropolitan Hospital)

Morihiro SUGISHITA (Institute of Brain Vessels)

Masahiko SUMITANI (Dept. of Anesthesiology and Pain Relief Center, The University of Tokyo)

Kyoko SUZUKI (Dept. of Clinical Neuroscience, Yamagata University Faculty of Medicine)

Seiji TAKAOKA (Dept. of Anesthesiology, Yamagata City Hospital Saiseikan)

ORIGINAL ARTICLE

Neurol Med Chir (Tokyo) 52, 577 ~ 586, 2012

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 OKADA[2]

[1]*Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science, and Departments of* [2]*Neurosurgery and* [3]*Radiation 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 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

Received November 28, 2011; Accepted February 27, 2012

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.

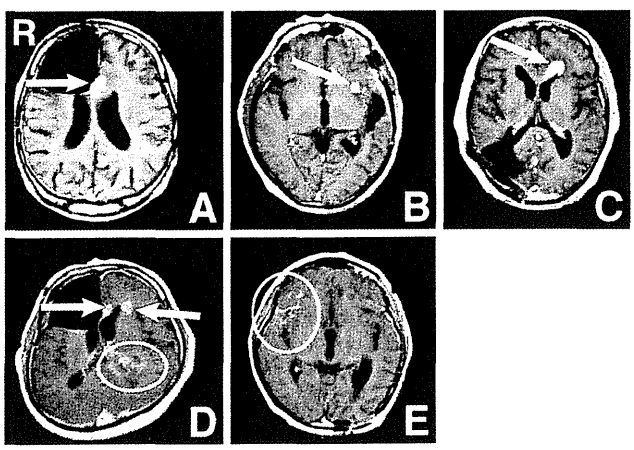

Fig. 1 T_1-weighred magnetic resonance images with contrast medium illustrating the patterns of glioblastoma recurrence (*arrows* and *circles*) after aggressive surgery and adjuvant management. A: regional, in the wall of the resection cavity; B: marginal, within 20 mm from the margin of the resection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

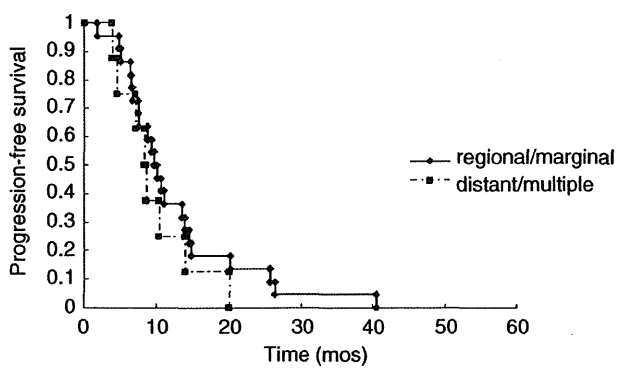

Fig. 2 Comparison of progression-free survival from the time of surgery in patients with different recurrence patterns of intracranial glioblastoma. There is no significant difference ($p = 0.27$).

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

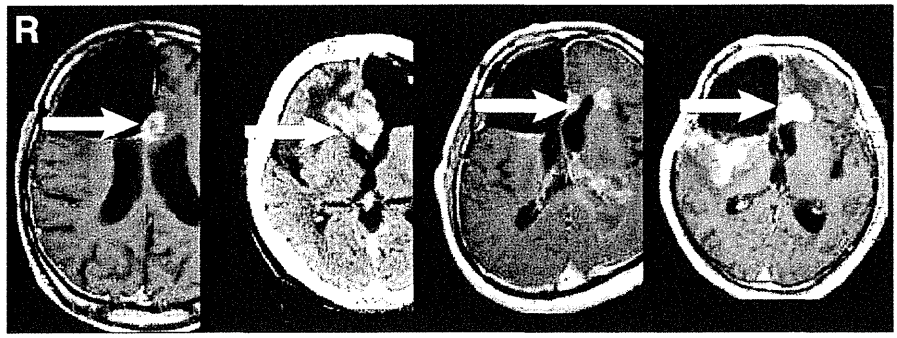

Fig. 3 Follow-up images in 4 patients with glioblastoma initially located in the prefrontal region showing the recurrent tumor affected the genu of the corpus callosum (*arrows*).

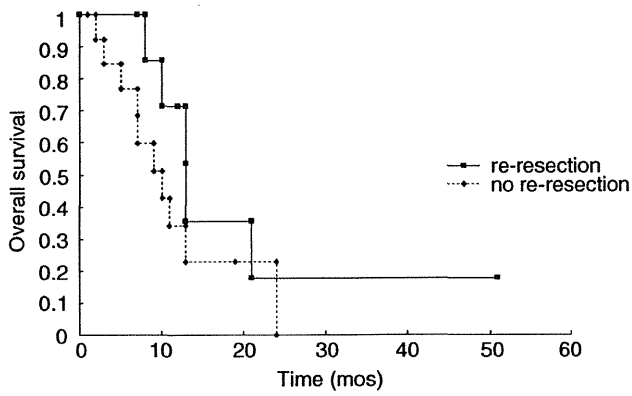

Fig. 4 Comparison of the overall survival from the time of regional or marginal tumor progression relative to re-resection. There is no significant difference (p = 0.20).

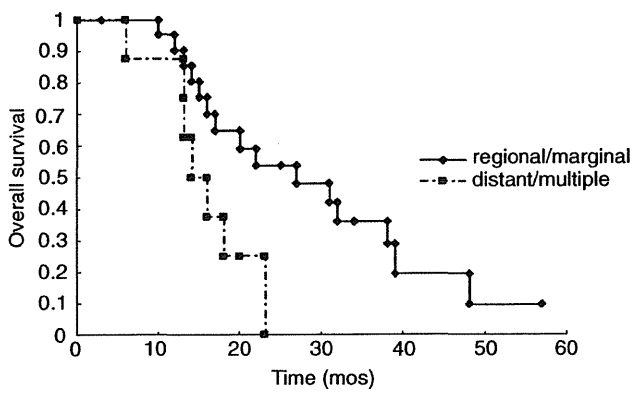

Fig. 5 Comparison of the overall survival from the time of surgery in patients with different recurrence patterns of intracranial glioblastoma. There is a significant difference (p = 0.04).

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.

Acknowledgements

The authors are grateful to Drs. Takashi Maruyama, Masahiko Tanaka, Masayuki Nitta, Katsuya Maebayashi, Soko Ikuta, and Mikhail Chernov (Departments of Neurosurgery and Radiation Oncology, and Faculty of Advanced Techno-Surgery, Tokyo Women's Medical University) for help provided with data collection and analysis. This study was supported by the Japan Society for the Promotion of Science (JSPS) through the "Funding Program for World-Leading Innovative Research and Development on Science and Technology" (FIRST Program), initiated by the Council for Science and Technology Policy (CSTP). Partial support from Research Committee of Intractable Pancreatic Diseases (Principal Investigator Dr. Toru Shimosegawa) was provided by Ministry of Health, Labor and Welfare of Japan.

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

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 Kawadacho, Shinjuku-ku, Tokyo 162-8666, Japan.
e-mail: ymuragaki@abmes.twmu.ac.jp

Letter to the Editor

Stereotactic and Functional Neurosurgery

Received: November 5, 2011
Accepted: November 16, 2011
Published online: January 24, 2012

Stereotact Funct Neurosurg 2012;90:63–65
DOI: 10.1159/000335168

^{1}H-MRS-Guided Stereotactic Brain Biopsy

Mikhail Chernov, Yoshihiro Muragaki, Takaomi Taira, Hiroshi Iseki

Faculty of Advanced Techno-Surgery and Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

The recently published article by Frati et al. [1] regarding frameless stereotactic brain biopsy was read with great interest. One of the objectives of that study was the evaluation of the usefulness of proton magnetic resonance spectroscopy (^{1}H-MRS) for guidance of tissue sampling in 296 brain lesions, including 211 gliomas. In 37 cases, contrast enhancement of the mass was absent. Before the stereotactic procedure, a multivoxel spectroscopic examination was performed, metabolic data were incorporated into the neuronavigation system and fused with the structural MR images, and a target was selected in the area of the lesion corresponding to the highest value of the choline-containing compounds to N-acetylaspartate (Cho/NAA) ratio, which was identified on the visualized grid of the spectroscopic voxels showing automatically calculated numerical values. Three targets were used in each case, and the number of obtained tissue specimens varied from 4 to 12 (average, 6). Overall, a diagnosis was established in all but one case (diagnostic yield 99.7%). It was found that histopathological grades within the tissue samples taken from the same tumor are well associated with the values of Cho/NAA ratios ($p < 0.01$). Regrettably, no results are presented on the correlation of the metabolic data with the MIB-1 index, while immunostaining for Ki-67 was regularly done. However, the authors concluded that spectroscopic guidance may be very useful for appropriate targeting of the stereotactic brain biopsy, particularly in cases of nonenhancing lesions.

Certainly, the use of metabolic and functional data for target selection during both frame-based and frameless stereotactic tissue sampling seems very promising. The application of chemical shift imaging is especially attractive, because it can be easily attained at the time of routine MRI, is fully noninvasive and highly sensitive to the presence of pathology. Indeed, the reported diagnostic yield of ^{1}H-MRS-guided brain biopsy typically attains 100% [2–5]. Moreover, according to our own experience, spectroscopic support may facilitate histopathological diagnosis both on frozen and permanent tissue sections [5]. However, we were not able to demonstrate a greater diagnostic yield of ^{1}H-MRS-guided procedures (100% in 30 patients) compared to MRI-based ones (90% in 39 patients), seemingly due to a relatively small sample size of our series [5]. In fact, a subsequent analysis revealed that with the same parameters of the study, it would be necessary to have 85 and 111 patients in the case and control groups, respectively, to prove the presence of a difference in the diagnostic yield with a power of 0.8 and type I error probability of 0.05. Anyway, in our opinion, metabolic guidance may be rather useful during stereotactic biopsy of parenchymal brain tumors, and may be especially recommended for recurrent, particularly previously irradiated, neoplasms, or for sampling of the highly vascular lesions since in the latter cases, detection of the spectroscopic abnormalities outside the contrast-enhanced area may permit a surgeon to obtain a representative tissue specimen with reduced risk of hemorrhagic complications [6].

On the other hand, it is clear that just a confirmation of the presence of glioma with stereotactic biopsy is not sufficient enough for modern treatment objectives. These neoplasms are well known for their heterogeneity; therefore, the main requirement for tissue sampling in such cases is detailed characterization of the tumor type and histopathological grade. However, in the series of the MD Anderson Cancer Center, 63% of gliomas designated after stereotactic biopsy as being of low or intermediate grade and 60% of anaplastic astrocytomas were found to be more malignant after open surgery [7]. In our analysis, just 36% of the patients diagnosed as having low-grade glioma after stereotactic biopsy had complete diagnostic agreement in tumor typing and grading compared to subsequent resection [8]. Certainly, the diagnostic accuracy of the stereotactic procedure may be improved by multiple tissue sampling; however, it is not clear, whether or not metabolic guidance may also be helpful. Unfortunately, the referenced study by Frati et al. [1] does not provide reliable information on this issue. From our experience, addition of spectroscopic support with targeting the area of the lesion characterized by the lowest NAA/Cho ratio did not result in improved diagnostic accuracy of the stereotactic procedures [5]. Major diagnostic disagreement between biopsy and subsequent surgical resection was observed in 6 out of 18 cases and was most frequently related to initial undergrading of the nonenhancing WHO grade III gliomas [5]. Others demonstrated that the direction of tissue sampling on the area with the lowest NAA/Cho ratio may lead to erroneous diagnosis of anaplastic astrocytoma in cases of glioblastoma [9].

The NAA/Cho ratio is widely recognized as a marker of glioma presence, proliferative activity, and growth characteristics, but it seems that stereotactic targeting of the tumor area with its lowest value does not necessarily result in the precise determination of the histopathological grade. Further studies are needed to identify the optimal metabolic target during spectroscopy-guided stereotactic procedures. Presence and distribution of other metabolites, particularly lactate and mobile lipids [9], should also be taken into consideration (fig. 1). ^{1}H-MRS is intrinsically a multiparameter investigation and limitation of its evaluation to only one metabolite content or single ratio does not seem reasonable. Therefore, at present, during the evaluation of the spectroscopic data in addition to calculation of the various metabolite contents and ratios, we are constantly performing pattern analysis of the whole pathological ^{1}H-MR spectrum as well (fig. 2).

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1011–6125/12/0901–0063$38.00/0

Accessible online at:
www.karger.com/sfn

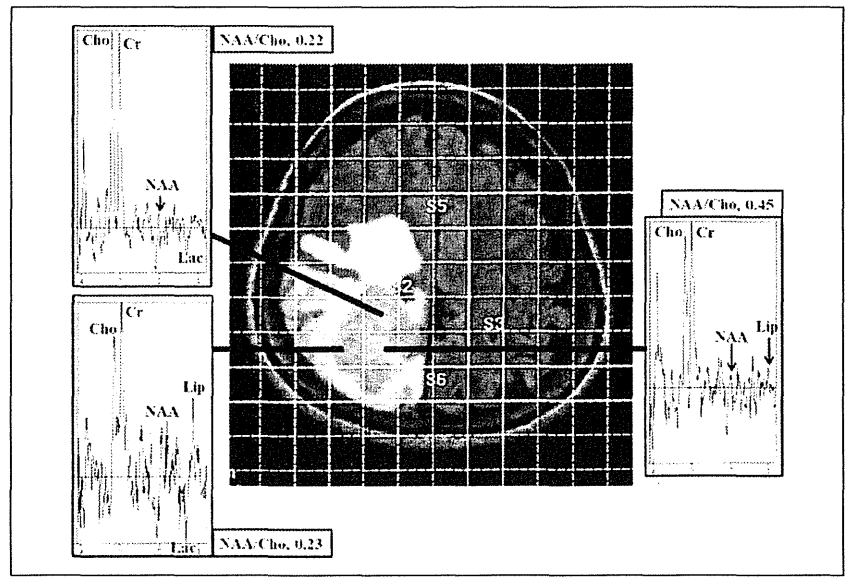

Fig. 1. Slightly different ^{1}H-MR spectra in the various parts of glioblastoma. The area of the tumor corresponding to the spectrum with the moderate elevation of mobile lipids (Lip) seems most suitable for biopsy targeting (lower left). Cr = Creatine; Lac = lactate. Automatically calculated values of the NAA/Cho ratio are presented. Figures on the horizontal axes correspond to resonance frequency.

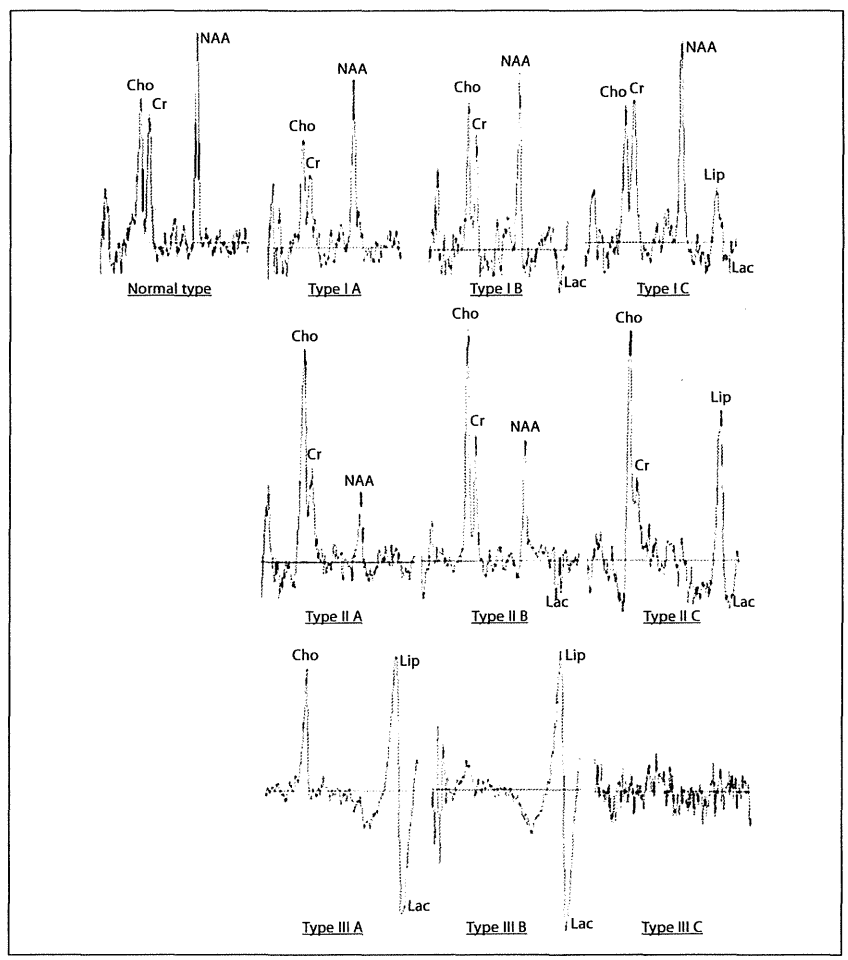

Fig. 2. Classification of the pathological ^{1}H-MR spectra based on determination of the main metabolites, namely NAA, Cho, lactate (Lac), and mobile lipids (Lip). Types I C and II C are further subdivided in cases with mild and moderate elevation of Lip. From Chernov et al. [10].

References

1 Frati A, Pichierri A, Bastianello S, Raco A, Santoro A, Esposito V, Giangaspero F, Salvati M: Frameless stereotactic cerebral biopsy: our experience in 296 cases. Stereotact Funct Neurosurg 2011;89:234–245.
2 Son BC, Kim MC, Choi BG, Kim EN, Baik HM, Choe BY, Naruse S, Kang JK: Proton magnetic resonance chemical shift imaging (^{1}H CSI)-directed stereotactic biopsy. Acta Neurochir (Wien) 2001;143:45–50.
3 Hall WA, Truwit CL: 1.5 T: spectroscopy-supported brain biopsy. Neurosurg Clin N Am 2005;16:165–172.
4 Hermann EJ, Hattingen E, Krauss JK, Marquardt G, Pilatus U, Franz K, Setzer M, Gasser T, Tews DS, Zanella FE, Seifert V, Lanfermann H: Stereotactic biopsy in gliomas guided by 3-tesla ^{1}H-chemical-shift imaging of choline. Stereotact Funct Neurosurg 2008;86:300–307.
5 Chernov MF, Muragaki Y, Ochiai T, Taira T, Ono Y, Usukura M, Maruyama T, Nakaya K, Nakamura R, Iseki H, Kubo O, Hori T, Takakura K: Spectroscopy-supported frame-based image-guided stereotactic biopsy of parenchymal brain lesions: comparative evaluation of diagnostic yield and diagnostic accuracy. Clin Neurol Neurosurg 2009;111:527–535.
6 Burtscher IM, Skagerberg G, Geijer B, Englund E, Stahlberg F, Holtas S: Proton MR spectroscopy and preoperative diagnostic accuracy: an evaluation of intracranial mass lesions characterized by stereotactic biopsy findings. AJNR Am J Neuroradiol 2000;21:84–93.
7 Jackson RJ, Fuller GN, Abi-Said D, Lang FF, Gokaslan ZL, Shi WM, Wildrick DM, Sawaya R: Limitations of stereotactic biopsy in the initial management of gliomas. Neuro Oncol 2001;3:193–200.
8 Muragaki Y, Chernov M, Maruyama T, Ochiai T, Taira T, Kubo O, Nakamura R, Iseki H, Hori T, Takakura K: Low-grade glioma on stereotactic biopsy: how often is the diagnosis accurate? Minim Invasive Neurosurg 2008;51:275–279.
9 Ng WH, Lim T: Targeting regions with highest lipid content on MR spectroscopy may improve diagnostic yield in stereotactic biopsy. J Clin Neurosci 2008;15:502–506.
10 Chernov M, Hayashi M, Izawa M, Nakaya K, Ono Y, Usukura M, Yoshida S, Kato K, Muragaki Y, Nakamura R, Iseki H, Hori T, Takakura K: Metabolic characteristics of intracranial metastases, detected by single-voxel proton magnetic resonance spectroscopy, are seemingly not predictive for tumor response to gamma knife radiosurgery. Minim Invasive Neurosurg 2007;50:233–238.

Mikhail Chernov, MD
Faculty of Advanced Techno-Surgery and
Department of Neurosurgery, Tokyo Women's Medical University
8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666 (Japan)
Tel. +81 3 3353 8111, ext. 66003, E-Mail m_chernov@yahoo.com

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(11)1066–1072
doi:10.1093/jjco/hys136
Advance Access Publication 22 August 2012

Characteristics of Lymph Node Metastases Defining the Outcome After Radical Cystectomy of Urothelial Bladder Carcinoma

Tohru Nakagawa[1,*], Yae Kanai[2], Hiroyuki Nakanishi[1], Motokiyo Komiyama[1] and Hiroyuki Fujimoto[1]

[1]Department of Urology, National Cancer Center Hospital and [2]Division of Molecular Pathology, National Cancer Center Research Institute, Tokyo, Japan

*For reprints and all correspondence: Tohru Nakagawa, Department of Urology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tohru-tky@umin.ac.jp

Received June 10, 2012; accepted July 29, 2012

Objective: The aim of this study was to identify clinicopathological variables associated with the clinical outcomes of patients with lymph node metastasis-positive urothelial bladder carcinoma after radical cystectomy.
Methods: Forty-six patients who underwent radical cystectomy without preoperative chemotherapy and had histologically proven nodal metastasis were included in the study. The status of lymph nodes and primary lesion was analyzed in terms of disease-specific survival and recurrence-free survival.
Results: The 5-year disease-specific survival and recurrence-free survival for the 46 patients overall were 41.3 and 32.2%, respectively. Univariate analysis showed that pN status, the total number of involved lymph nodes, lymph node density and extranodal invasion were statistically significant variables predictive of disease-specific survival. Multivariate analysis revealed that the total number of involved lymph nodes, extranodal invasion and diameter of the metastatic lesion were statistically significant variables predictive of disease-specific survival. Interestingly, the diameter of metastatic lesions was inversely correlated with poorer survival. Patients with large ($\geq$10 mm) metastatic lesions and no extranodal invasion (expansive growth) had significantly better disease-specific survival than those with multiple small ($<$10 mm) metastatic lesions and no extranodal invasion (highly spreading) ($P = 0.0156$) or those with extranodal invasion (infiltrative growth) ($P = 0.0181$).
Conclusions: Our data indicate that the clinical outcome of node-positive patients is not only stratified according to the tumor burden reflected in the total number of involved lymph nodes, but also affected by tumor biology including invasiveness and potential for metastasis, which is reflected in pathological characteristics such as extranodal invasion and the diameter of metastatic lesions.

Key words: bladder cancer – extranodal invasion – lymph node – metastasis – radical cystectomy

INTRODUCTION

Radical cystectomy with pelvic lymph node (LN) dissection is a gold standard treatment for muscle-invasive bladder cancer (1); 18–28% of the patients who undergo radical cystectomy are found to have LN metastases upon histological examination of their surgically resected specimens (1). The 5-year overall survival and recurrence-free survival (RFS) of patients with LN metastases (pN1–3) are reported to be 25–31 and 20–35%, respectively (2), and their clinical outcomes are highly variable.

Several clinicopathological factors that can further stratify the risk of recurrence and death in node-positive patients have been identified: the number of LNs involved with the tumor (3–7), the number of LNs removed (5,7), the ratio (percentage) of the number of involved nodes divided by the total number of nodes removed (LN density) (4,5,8–11), primary pathological stage (pT) (3–5), extranodal invasion

(ENI) of LN metastases (12–14) and the use of adjuvant chemotherapy (6,15).

Among these variables, the significance of the total number of LNs involved with the tumor and LN density have been well examined and are becoming accepted as prognostic variables, although the use of LN density in a practical setting is still debatable (16).

On the other hand, the significance of the diameter of metastatic lesions in LNs and ENI for survival prediction remains to be clarified. Although Mills et al. (12) reported that metastatic lesions in LNs <0.5 cm in diameter were associated with better clinical outcome, no subsequent studies have validated such an association. Moreover, the conclusions of previous studies that examined the significance of ENI for predicting the survival of patients with bladder cancer were inconsistent. Although three papers from a single center (the University of Bern, Switzerland) have suggested that ENI is the strongest independent prognostic factor for disease-specific survival (DSS) (12–14), Kassouf et al. (15) reported that ENI was associated with neither DSS nor RFS.

The aim of this study was to assess the significance of several clinicopathological variables including ENI and the diameter of metastatic lesions for the prediction of outcome in patients with LN metastasis-positive urothelial carcinoma of the urinary bladder after cystectomy.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 611 consecutive patients who underwent radical cystectomy and pelvic LN dissection for invasive bladder cancer with curative intent at the National Cancer Center Hospital between January 1986 and April 2008. During this period, radical cystectomy was abandoned in 25 patients intraoperatively due to advanced local disease. Patients included in the study were those for whom LN metastases were confirmed histologically in their surgically resected specimens. Patients were excluded if they had received neoadjuvant chemotherapy before surgery, had pure non-urothelial carcinomas histologically (i.e. squamous cell carcinoma and adenocarcinoma), had remote metastases at the time of surgery or had synchronous or metachronous invasive upper urinary tract cancers. On this basis, 46 patients were included in the present study, which comprised 7.5% of the 611 patients who underwent radical cystectomy. This study was approved for analysis by the institutional review board.

All cystectomy specimens were subjected to routine pathological examination. The LN specimen from each anatomical location was separately examined visually and by manual palpation without fat clearing solution, and all macroscopically detected LNs were completely embedded. One hematoxylin- and eosin-stained section was taken per tissue block, and no immunostains were routinely performed. A single pathologist (Y.K.) reviewed the specimens microscopically for this study in a blinded manner. The primary tumors and LNs were staged based on the 2009 UICC TNM system (17) and were evaluated for the diameter of metastatic lesions in the LNs, and the presence or absence of ENI. ENI was defined as obvious disruption of the microscopically visible LN capsule by tumor cells infiltrating into the perinodal tissue (Fig. 1).

All patients were followed routinely after surgery every 3 months in the first year, at 3- to 6-month intervals in years 2–3, every 6 months in years 4–5 and annually thereafter. Follow-up consisted of physical examination, serum biochemical profile, urine cytology, chest X-ray or computed tomography (CT) imaging of the chest and CT imaging of the abdomen–pelvis.

Survival data were analyzed using the Kaplan–Meier method, and log-rank tests were used to evaluate associations between survival and the variables studied. The duration of follow-up was calculated from the date of surgery to the date of death or last follow-up. Univariate and multivariate Cox

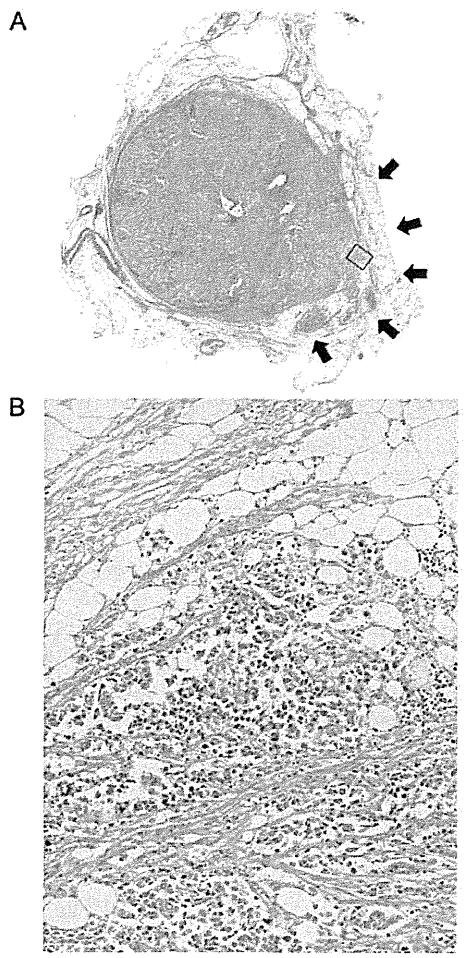

Figure 1. A representative photograph of lymph node (LN) metastasis with extranodal invasion. LN capsule is disrupted by tumor cells infiltrating into the perinodal tissue (arrows). (A) Scanning magnification. (B) Higher magnification of the boxed area in (A) (reduced from ×200).

proportional hazard models were employed to assess which clinicopathological features were associated with death due to, or recurrence of, bladder cancers. The relationships between the clinicopathological features studied and outcome were summarized in terms of risk ratios and 95% confidence intervals (95% CI). Differences with P values of <0.05 were considered significant.

RESULTS

The clinicopathological features of the 46 patients included in the study are shown in Table 1. There were 37 male and 9 female patients, with a median age of 66 (range: 46–83) years at the time of surgery. The median follow-up duration was 32 (range: 3–272) months for the patients as a whole and 110.5 (range: 26–272) months for the 14 patients who were alive at the final follow-up.

Thirty-three patients suffered from disease recurrence, and 28 of them died of metastatic bladder cancer during follow-up. The 5-year DSS and RFS for the 46 patients overall were 41.3 and 32.2%, respectively (Fig. 2). The median DSS and RFS were 34 (95% CI: 25–154) and 11.5 (95% CI: 10–46) months, respectively (Fig. 2).

Due to the retrospective nature of this study, the extent of LN dissection was variable; 36 patients underwent limited pelvic lymphadenectomy below the bifurcation of common iliac arteries, whereas 7 and 3 cases up to the level of aortic bifurcation and inferior mesenteric artery, respectively.

Adjuvant systemic chemotherapy was considered for all cases with LN metastasis. However, it was not administered in 28 patients because of impaired performance status and/or high age, or no consent from the patients. The regimens of chemotherapy were two courses of MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) in 16 cases, MEP (methotrexate, etoposide and cisplatin) in 1 and CAP (cyclophosphamide, doxorubicin and cisplatin) in 1.

The results of univariate analysis to examine the contribution of each clinicopathological factor to DSS and RFS are shown in Table 2. Whereas pT3–4 tumors did not show significant difference compared with pT2 tumors in terms of DSS and RFS, several LN-related variables were found to be significantly associated with patient prognosis. Therefore, further analyses focused on these LN-related variables. pN status according to the TNM classification, the total number of involved LNs, LN density and ENI were statistically significant variables predictive of DSS, and the total number of involved LNs and LN density were significant variables predictive of RFS. Figure 3 shows DSS of the patients with or without ENI and of the patients with less than five involved LNs or with five or more, analyzed using the Kaplan–Meier method.

Multivariate analysis revealed that the total number of involved LNs, ENI and the diameter of the metastatic lesion

Table 1. Clinicopathological characteristics of the 46 patients with lymph node metastasis at radical cystectomy

Sex	
Male	37 (80.4%)
Female	9 (19.6%)
Age	
Median	66
Range	46–83
Extent of LN dissection	
Below bifurcation of CIA	36 (78.3%)
Up to aortic bifurcation	7 (15.2%)
Up to the level of IMA	3 (6.5%)
Histological type	
UC	38 (82.6%)
UC with other components (i.e. squamous cell carcinoma and adenocarcinoma)	8 (17.4%)
Nuclear grade	
G3	46 (100%)
pT stage	
pT2	6 (13.0%)
pT3	26 (56.5%)
pT4	14 (30.5%)
pN stage	
pN1	16 (34.8%)
pN2	25 (54.3%)
pN3	5 (10.9%)
Total number of involved LNs	
Median	2
Range	1–13
Number of LNs resected	
Median	12.5
Range	4–36
LN density	
Median	17%
Range	3–67
Maximum diameter of metastatic lesions in LNs	
Median	9 mm
Range	1–28
ENI of LN metastases	
Negative	27 (58.7%)
Positive	19 (41.3%)
Adjuvant chemotherapy	
No	28 (60.9%)
Yes	18 (39.1%)

LN, lymph node; CIA, common iliac artery; IMA, inferior mesenteric artery; UC, urothelial carcinoma; ENI, extranodal invasion.