Table 1 Patient characteristics (N=46)

Characteristics	n
Age, y	
<60/≤60	14/32
Sex	
Female/Male	16/30
KPS (%)	
<70/≤70	23/23
Extent of resection	
<95%/≤95%	17/29
RPA class	
III/IV/V/VI	2/17/16/11
MGMT	
Met/UnMet	11/34*

Abbreviations: KPS = Karnofsky performance status; Met = methylated; MGMT = *O-6-methylguanine-DNA methyltransferase* gene; RPA = recursive partitioning analysis; UnMet = unmethlylated.
* *MGMT* methylation status was not available in 1 case.

patients, but TMZ was withdrawn because of tumor progression in 23. The median number of TMZ cycles was 5.

Local control

Progression of enhancing lesions at the original tumor site was observed in 19 patients. Among these lesions, 13 were diagnosed as tumor progression: high methionine uptake in 5 and continuous progression on MRI in 8. Removal of these lesions was performed in 9 patients, including 5 diagnosed by Met-PET, and a viable tumor was found in all patients. The remaining 6 lesions were diagnosed as necrosis because of low methionine uptake on PET images. Among these 6 patients, second surgery was performed in 1, and no viable cells were found. Pathologic evaluation was not available for the remaining 5 patients, but the enhanced lesion shrank on MRI by dexamethasone in all patients.

Among these 13 tumor progressions, 4 recurrences were diagnosed after diagnosis of other types of failures: after distant failure in 2 and after dissemination in 2.

The 2- and 5-year local progression-free survival was 63.9% and 57.5%, respectively (Fig. 2A). We found no clinical variables that were significantly associated with local lesion control.

Other types of failures

Distant failure was observed in 10 patients during the course of their disease (Fig. 2B). Half of these distant failures appeared after other types of failures, and distant failure was the primary failure pattern in 5 patients. No clinical variable significantly affected distant failure-free survival.

Dissemination was more common in our series. This type of failure was diagnosed in 21 patients and before other types of failure in 14 patients (Fig. 2C). These disseminated lesions were located at the lateral ventricle wall in 14 patients, surrounding the brain stem in 2, at the surface of the brain convexity in 2, in the fourth ventricle in 2, and in the spinal canal in 1. We found no clinical variables that were significantly associated with dissemination.

Consequently, the dominant failure pattern in our patients was dissemination: the primary site of failure was local in 11 patients, distant in 5, and beside the CSF space in 14. The median time to any type of failure was 9.7 months after treatment (Fig. 2D).

Survival

At the time of the last follow-up visits, 37 patients had died. The cause of death was disseminated disease progression in 15, local tumor progression in 9, distant lesion progression in 1, radiation

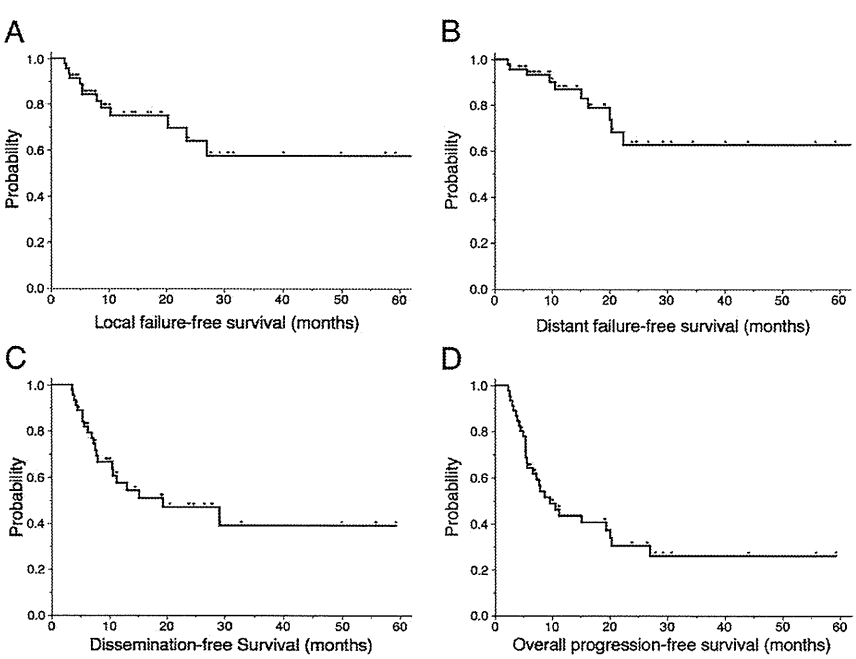

Fig. 2. Progression-free survival. The times to progression were analyzed differently according to the failure site: failure at the original tumor site (A), distant failure (B), and disseminated failure (C). The time to the first progression regardless of the pattern of failure was also demonstrated (D).

necrosis in 4, pneumonia in 1, lung embolism in 1, and pneumonitis in 1. The median OS of all patients was 20.0 months. The 1-, 2-, 3-, 4-, and 5-year survival rates were 69.6%, 42.8%, 26.5%, 13.3%, and 6.6%, respectively (Fig. 3A). The presence of a methylated *MGMT* gene promoter was significantly correlated with longer patient survival (HR, 2.42; 95% CI, 1.10-6.08; $P=.026$) (Fig. 3B), but no other patient- or treatment-related variables were associated with survival (Table 2). Subgroup analyses of patient survival are summarized in Table 3.

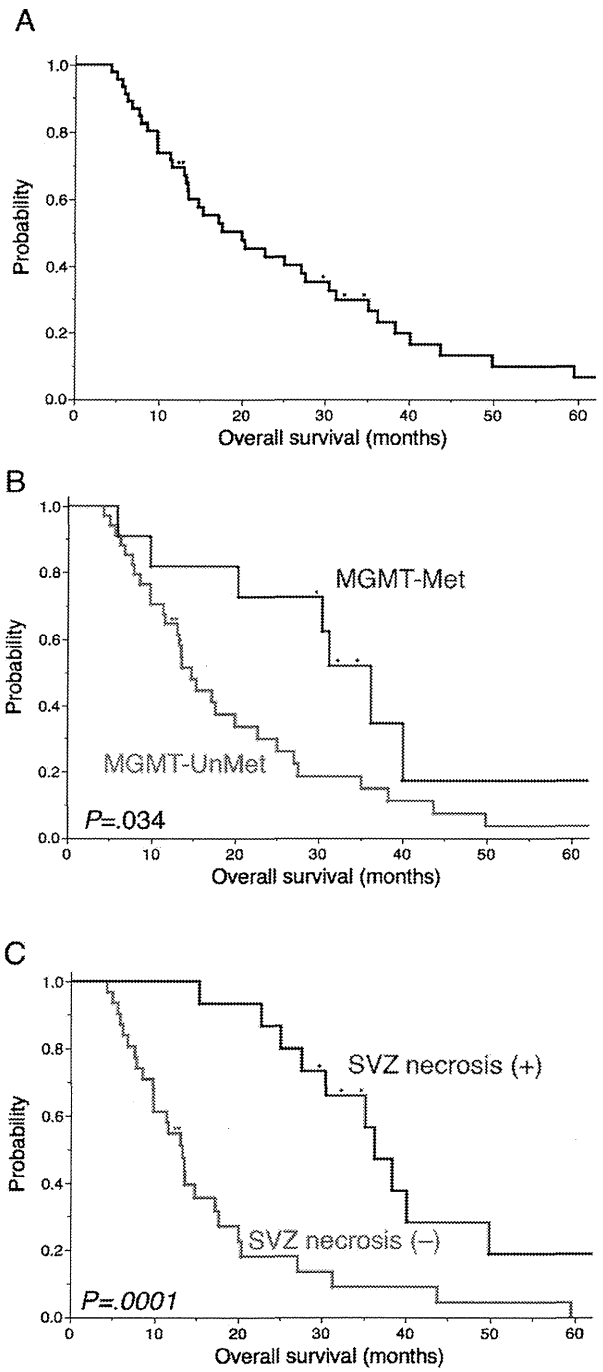

Fig. 3. Overall survival of the 46 patients. The median survival time was 20.0 months (A). Methylation (Met) of the *O-6-methylguanine-DNA methyltransferase* (MGMT) gene promoter (B) and necrosis in the subventricular zone (SVZ) (C) were significantly correlated with better survival (log–rank $P=.034$ and .0001, respectively).

Toxicity

No grade ≥3 adverse events were observed during IMRT. However, during and after treatment, radiation necrosis was frequently observed. This necrosis arose not only surrounding the original tumor site (Fig. 1D) but also in the SVZ, although this area was not included in the high-dose field (Fig. 1E). The incidence of radiation necrosis was 10.9% surrounding the original tumor, 21.7% in the SVZ, and 10.9% in both. The median time to necrosis was 42.0 months (95% CI, 28.1 months to not reached) at the original tumor site and 16.1 months (95% CI, 12.2 months to not reached) in the SVZ. The occurrence of radiation necrosis was not associated with the methylation status of the *MGMT* gene promoter: the HR was 1.40 at the original tumor site ($P=.641$) and 0.57 in the SVZ ($P=.278$).

Radiation necrosis in the SVZ was strongly associated with prolonged patient survival. The median OS was 36.2 and 13.3 months in patients with and without SVZ necrosis, respectively (HR, 4.08; 95% CI, 1.97-9.10; $P=.0001$) (Fig. 3C). Radiation necrosis at the original tumor site also showed a tendency to correlate with better survival, but this difference was not statistically significant (HR, 1.94; 95% CI, 0.91-4.61; $P=.089$). In multivariate analysis, SVZ necrosis was the only variable significantly associated with prolonged survival after hypofractionated high-dose IMRT (Table 2).

Hematologic toxicities secondary to chemotherapy or antiepileptic drugs were also observed during the treatment, as follows: grade 3 liver dysfunction in 8 patients (17.8%), grade 3 or 4 anemia in 8 (17.8%), grade 3 or 4 lymphocytopenia in 21 (45.7%), grade 3 or 4 neutropenia in 3 (6.5%), and grade 3 thrombocytopenia in 1 (2.2%).

Discussion

Nakagawa et al (5) reported alteration of the failure pattern of GBM from local to disseminated by dose escalation to 90 Gy by 3-dimensional conformal radiation therapy (3D-CRT), which indicated better local tumor control by high-dose radiation therapy. However, Chan et al (6) reported no local control benefit with 90 Gy by 3D-CRT. Several other investigators also failed to prove a survival benefit of dose escalation with 70 Gy (7), 78 Gy (8), and 84 Gy (9) by 3D-CRT. Therefore, the effect of dose escalation with conventional 1.8- to 2.0-Gy fractions is still being debated.

Hypofractionation is a different approach to increase the biological effect of irradiation (10). It has several advantages over conventional fractionation. First, increased cell damage by a higher dose per fraction is expected from a linear-quadratic (LQ) model. Second, the shortened treatment time may reduce the effect of rapid tumor repopulation during treatment (11). In GBM, the potential tumor-doubling time is reportedly ≤10 days (12, 13), and the effect of repopulation cannot be ignored. In addition to these advantages, the shortened treatment time may contribute to fewer hospitalized days.

However, hypofractionation has an increased risk of late toxicity of normal brain tissue. Therefore, recent trials have attempted to deliver doses focusing on a limited area using IMRT. Sultanem et al

Table 2 Survival analyses

Variables	High-risk group	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, y	<60	1.32 (0.64-2.60)	.441		
Sex	Male	1.51 (0.75-3.29)	.261		
KPS (%)	<70	1.42 (0.74-2.75)	.291		
Extent of resection	<95%	1.44 (0.71-2.82)	.303		
RPA class (III/IV vs (V/VI)	V/VI	1.52 (0.79-3.05)	.215		
MGMT	UnMet	2.42 (1.10-6.08)	.026	1.57 (0.68-4.11)	.305
Necrosis (regional)	No	1.94 (0.91-4.61)	.089	1.70 (0.76-4.33)	.205
Necrosis (paraventricular)	No	4.08 (1.97-9.10)	.007	4.71 (2.08-11.55)	.0002

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; MGMT = *O-6-methylguanine-DNA methyltransferase* gene; RPA = recursive partitioning analysis; UnMet = unmethlylated.

(14) reported on their hypofractionated IMRT with 60 Gy in 3.0-Gy fractions. IMRT with 50 Gy in 5.0-Gy fractions was also reported by Floyd et al (15). In the above 2 trials, hypofractionation contributed to a shortened treatment period, but the biologically effective doses (BEDs) calculated based on the LQ model (alpha/beta = 10; 78 Gy in the trial by Sultanem et al [14], 75 Gy in the trial by Floyd et al [15]) were equivalent to that of conventional irradiation (72 Gy), and failed to improve patient survival. In contrast to these reports, we previously reported the benefits of dose escalation using hypofractionated IMRT (16). In that report, the dose for the central lesion was escalated from 48 Gy (BED, 77 Gy) to 68 Gy (BED, 126 Gy), and we demonstrated a favorable effect on local control without severe early toxicities. From these results, we fixed the dose at 68 Gy and used the same fractionation scheme: 8 fractions during 10 treatment days.

More recently, trials of dose escalation using hypofractionated IMRT with concurrent and adjuvant TMZ have been reported. In a study by Chen et al (17), all patients received a total dose of 60 Gy, but the dose per fraction was escalated from 3.0 to 6.0 Gy in 1.0-Gy increments. Their median patient survival was 16.2 months, and acute toxicity secondary to irradiation was extremely rare. A recent report by Tsien et al (18) also demonstrated the safety of hypofractionated IMRT. In our current series, we experienced no acute toxicity related to irradiation. In contrast to previous reports, our hypofractionated high-dose IMRT altered the dominant failure pattern from local to disseminated. A decreased incidence of local failure after high-dose irradiation has also been reported by several investigators. In addition to the report by Nakagawa et al (5) noted earlier, Tsien et al (18) reported a decreased probability of central failure with increased radiation doses. Intensive IMRT targeting regional tumors prolonged the time to local failure, but not to dissemination, resulting in earlier appearance of dissemination rather than local progression and alteration of the dominant failure pattern. Although our treatment still had limitations, the median patient survival was 20.0 months, and the 2- and 3-year survival rates were 42.8% and 26.5%, respectively. These survival results indicate the potential benefit of hypofractionated high-dose IMRT.

Late toxicities after our treatment were more frequent than early toxicities, and careful observation was required. Radiation necrosis was the most frequent late toxicity, and symptomatic necrosis requiring necrotomy developed in 5 patients. Surprisingly, these necroses progressed more frequently and much earlier in the SVZ than at the original tumor site, although SVZ was not included in the high-dose field. The irradiated doses to the SVZ were equivalent to 50 to 60 Gy of conventional radiation (alpha/beta = 3). Hypofractionated radiation might have a higher risk of SVZ injury than expected by the LQ model.

Table 3 Subgroup analyses of patient survival

	Median, mo (95% CI)	2 y (%)	3 y (%)	4 y (%)	5 years (%)
Overall (46)	20.0 (13.3-27.6)	42.8	26.5	13.3	6.6
Extent of surgery					
Complete resection (29)	20.0 (13.6-30.4)	46.1	26.3	13.2	8.8
Partial resection (17)	11.4 (5.9-38.3)	39.2	29.4	14.7	0.0
Age, y					
<50 (3)	20.4 (11.4-49.9)	33.3	33.3	33.3	0.0
50-60 (11)	20.0 (11.6-25.1)	31.8	0.0	0.0	0.0
>60 (32)	17.2 (9.8-36.2)	47.5	35.9	15.4	10.3
RPA					
Class IV (17)	25.1 (11.4-59.6)	51.3	36.7	24.5	12.2
Class V (16)	21.4 (7.9-36.2)	43.8	29.2	7.3	7.3
MGMT methylation					
Unmethylated (34)	14.8 (11.4-22.8)	29.9	15.0	7.5	3.7
Methlyated (11)	36.2 (9.8-not reached)	72.7	52.0	17.3	17.3

Abbreviations: CI = confidence interval; MGMT = *O-6-methylguanine-DNA methyltransferase* gene; RPA = recursive partitioning analysis.

On the other hand, the SVZ is believed to harbor cancer stem cells (CSCs) in patients with GBM (19, 20). Increased dose delivery to the SVZ (≥59.4 Gy) has recently been reported to correlate with better tumor control (21-23). However, CSCs may reportedly be resistant to radiation therapy because of preferential activation of the DNA damage checkpoint and DNA repair response (24). It is difficult to believe that conventional radiation may directly control CSCs in the SVZ, but impairment of CSC niches may sterilize the function of CSCs and decrease the supply of mature glioblastoma cells. In our current series, SVZ injury was strongly associated with patient survival. Hypofractionated radiation had a higher risk of SVZ injury, but it also had a stronger effect on impairment of CSC niches, which resulted in better patient outcomes. However, the SVZ also harbors neural stem cells, and injury to this area may increase the risk of neurocognitive sequelae. Several studies have recently reported a positive correlation between the radiation dose to the hippocampus and cognitive function in series of pediatric brain tumors (25-27). In our series, hippocampus injury was observed in only 1 patient, and the majority of necroses were observed in the SVZ of the anterior horn (6 patients), body (7 patients), and occipital horn of the lateral ventricle (1 patient). However, SVZ necrosis progressed after irradiation, and the performance status of the patients was impaired as necrosis progressed. Although it progressed very slowly, SVZ injury was the major cause of deterioration in the performance status of long-term survivors. Whether we should escalate the irradiation dose to the SVZ to control CSCs or spare this area to protect neural stem cells remains controversial.

Recent reports have indicated the usefulness of Met-PET to distinguish tumor recurrence from necrosis with excellent sensitivity (75%-100%) and specificity (60%-100%), although different T/N cutoff ratios (1.58-1.90) have been used (28-31). In this study, Met-PET was available in 22 cases; 16 lesions were diagnosed as necrosis, and the remaining 6 were diagnosed as tumor recurrence with a T/N threshold of 1.8. Among these lesions, the pathologic diagnosis was confirmed in 9 cases: 3 SVZ necroses, 1 regional necrosis, 2 local recurrences, and 3 disseminated diseases. No discrepancies in diagnosis were observed between Met-PET and pathologic analysis. However, another patient experienced regrowth of the lesion even though it had been diagnosed as necrosis by Met-PET 8 months before progression. We should be aware of the limitation of tracer imaging in that it reflects only the dominant features of lesions.

This single-institution prospective study demonstrated a satisfactory effect of hypofractionated high-dose IMRT on local control and survival in patients with GBM in the TMZ era. Despite the significant effect on control of GBM, this method still has some limitations. First, our IMRT contributed to local tumor control but not to prevention of dissemination. Second, our treatment increased the risk of radiation injury to the SVZ. The SVZ injury was associated with better patient survival but with impairment of patients' performance status. Third, this was a single-institution, small, nonrandomized study. Larger multiinstitutional randomized trials are required to validate our results and to confirm the efficacy of hypofractionated high-dose IMRT on control of GBM.

References

1. Stupp R, Hegi ME, Mason WP, et al. 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* 2009;10:459-466.
2. Sherriff J, Tamangani J, Senthil L, et al. Patterns of relapse in glioblastoma multiforme following concomitant chemoradiotherapy with temozolomide. *Br J Radiol* 2013;86:20120414.
3. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005;352:997-1003.
4. Lim DA, Cha S, Mayo MC, et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. *Neuro Oncol* 2007;9:424-429.
5. Nakagawa K, Aoki Y, Fujimaki T, et al. High-dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 1998;40:1141-1149.
6. Chan JL, Lee SW, Fraass BA, et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. *J Clin Oncol* 2002;20:1635-1642.
7. Graf R, Hildebrandt B, Tilly W, et al. Dose-escalated conformal radiotherapy of glioblastomas: results of a retrospective comparison applying radiation doses of 60 and 70 Gy. *Onkologie* 2005;28:325-330.
8. Watkins JM, Marshall DT, Patel S, et al. High-dose radiotherapy to 78 Gy with or without temozolomide for high grade gliomas. *J Neurooncol* 2009;93:343-348.
9. Tsien C, Moughan J, Michalski JM, et al. 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* 2009;73:699-708.
10. Hingorani M, Colley WP, Dixit S, et al. Hypofractionated radiotherapy for glioblastoma: Strategy for poor-risk patients or hope for the future? *Br J Radiol* 2012;85:e770-e781.
11. Wang JZ, Li XA. Impact of tumor repopulation on radiotherapy planning. *Int J Radiat Oncol Biol Phys* 2005;61:220-227.
12. Hlatky L, Olesiak M, Hahnfeldt P. Measurement of potential doubling time for human tumor xenografts using the cytokinesis-block method. *Cancer Res* 1996;56:1660-1663.
13. Furneaux CE, Marshall ES, Yeoh K, et al. Cell cycle times of short-term cultures of brain cancers as predictors of survival. *Br J Cancer* 2008;99:1678-1683.
14. Sultanem K, Patrocinio H, Lambert C, et al. The use of hypofractionated intensity-modulated irradiation in the treatment of glioblastoma multiforme: Preliminary results of a prospective trial. *Int J Radiat Oncol Biol Phys* 2004;58:247-252.
15. Floyd NS, Woo SY, Teh BS, et al. Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 2004;58:721-726.
16. Iuchi T, Hatano K, Narita Y, et al. Hypofractionated high-dose irradiation for the treatment of malignant astrocytomas using simultaneous integrated boost technique by IMRT. *Int J Radiat Oncol Biol Phys* 2006;64:1317-1324.
17. Chen C, Damek D, Gaspar LE, et al. Phase I trial of hypofractionated intensity-modulated radiotherapy with temozolomide chemotherapy for patients with newly diagnosed glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 2011;81:1066-1074.
18. Tsien CI, Brown D, Normolle D, et al. Concurrent temozolomide and dose-escalated intensity-modulated radiation therapy in newly diagnosed glioblastoma. *Clin Cancer Res* 2012;18:273-279.
19. Barani IJ, Benedict SH, Lin PS. Neural stem cells: Implications for the conventional radiotherapy of central nervous system malignancies. *Int J Radiat Oncol Biol Phys* 2007;68:324-333.
20. Li SC, Vu LT, Ho HW, et al. Cancer stem cells from a rare form of glioblastoma multiforme involving the neurogenic ventricular wall. *Cancer Cell Int* 2012;12:41.
21. Evers P, Lee PP, DeMarco J, et al. Irradiation of the potential cancer stem cell niches in the adult brain improves progression-free survival of patients with malignant glioma. *BMC Cancer* 2010;10:384.
22. Lee P, Eppinga W, Lagerwaard F, et al. Evaluation of high ipsilateral subventricular zone radiation therapy dose in glioblastoma: A pooled analysis. *Int J Radiat Oncol Biol Phys* 2013;86:609-615.

23. Chen L, Guerrero-Cazares H, Ye X, et al. Increased subventricular zone radiation dose correlates with survival in glioblastoma patients after gross total resection. *Int J Radiat Oncol Biol Phys* 2013;86:616-622.
24. Bao S, Wu Q, McLendon RE, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 2006;444:756-760.
25. Armstrong GT, Jain N, Liu W, et al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. *Neuro Oncol* 2010;12:1173-1186.
26. Jalali R, Mallick I, Dutta D, et al. Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;77:974-979.
27. Redmond KJ, Mahone EM, Terezakis S, et al. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: A prospective study. *Neuro Oncol* 2013;15:360-369.
28. Tripathi M, Sharma R, Varshney R, et al. Comparison of F-18 FDG and C-11 methionine PET/CT for the evaluation of recurrent primary brain tumors. *Clin Nucl Med* 2012;37:158-163.
29. Glaudemans AW, Enting RH, Heesters MA, et al. Value of 11C-methionine PET in imaging brain tumours and metastases. *Eur J Nucl Med Mol Imaging* 2013;40:615-635.
30. Terakawa Y, Tsuyuguchi N, Iwai Y, et al. Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. *J Nucl Med* 2008;49:694-699.
31. Okamoto S, Shiga T, Hattori N, et al. Semiquantitative analysis of C-11 methionine PET may distinguish brain tumor recurrence from radiation necrosis even in small lesions. *Ann Nucl Med* 2011;25: 213-220.

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Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma

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ABSTRACT

Background: Brain metastases (BM) are a common in patients with lung cancer. Although whole-brain radiation therapy (WBRT) is the standard therapy, it may have a risk of decline in cognitive function of patients. In this study, we evaluated the efficacy of gefitinib alone without radiation therapy for the treatment of patients with BM from lung adenocarcinoma.
Materials and methods: Eligible patients had BM from lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations. Gefitinib was given at 250 mg orally once a day until tumor progression or unacceptable toxicity.
Results: Forty-one patients were enrolled. The response rate was 87.8%. No patient experienced grade ≥4 toxicity. The median progression-free survival time was 14.5 months (95% CI, 10.2–18.3 months), and the median overall survival time was 21.9 months (95% CI, 18.5–30.3 months). In compared with L858R, exon 19 deletion was associated with better outcome of patients after treatment with gefitinib in both progression-free ($p = 0.003$) and overall survival ($p = 0.025$).
Conclusion: Favorable response of BM to gefitinib even without irradiation was demonstrated. Exon 19 deletion was both a predictive and prognostic marker of patients with BM treated by gefitinib.

1. Introduction

Approximately 10% of patients with non-small cell lung cancer (NSCLC) have brain metastases at diagnosis, and another 15% of patients develop them during the course of their disease. These rates of clinically-diagnosed brain metastases are, however, inferior to the rate in autopsy, and nearly half of patients with lung cancer may have brain metastases [1]. Selected patients may be treated by stereotactic radiosurgery (RS) alone, but the increased risk of brain recurrence after RS alone had been reported [2]. The effect of whole-brain radiation therapy (WBRT) on prevention of recurrence both at the initial site and at new sites after RS had been also reported [3]. Furthermore, more than half of the patients with brain metastases from NSCLC have multiple intracranial lesions [4]. Therefore, the standard treatment for brain metastases is surgical removal or RS followed by WBRT [5], even though the neurocognitive toxicity of WBRT is still debated [6–8].

A considerable proportion of patients with brain metastases also have extracranial lesions, and require systemic chemotherapy after treatment of brain metastases. However, delivery of anti-cancer agents to the intracranial tumors penetrating brain–blood barriers (BBBs) has been believed to be limited. This is the reason why radiation therapy is still the current standard of care for patients with brain metastases.

Recently, some reports indicated the safety of chemotherapy without radiation therapy for unselected NSCLC patients with brain metastases [9,10]. If chemotherapy has sufficient effect on control of intracranial lesions, it may replace WBRT and patients can avoid the risk of their neurocognitive deterioration related to irradiation. Furthermore, small lesions may be controlled by chemotherapy alone without RS.

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The aim of this study is to evaluate the safety and effect of gefitinib without radiation therapy for the selected patients whose tumors are expected to be sensitive to tyrosine kinase inhibitors (TKIs), and to clarify how long can TKIs delay irradiation for these patients.

2. Patients and methods

2.1. Patients

Eligibility criteria included newly radiographically diagnosed brain metastasis from lung adenocarcinoma with mutations of epidermal growth factor receptor (EGFR), without history of chemotherapy using TKIs, with active extracranial lesions which required chemotherapy, age > 18 years, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤2. Smoking history was not included in eligibility criteria but obtained during the patient's first evaluation. The mutation status of EGFR gene was evaluated by direct DNA sequencing using the original (primary) lung tumor. This study did not consider the types of EGFR-mutations. Surgical resection of brain metastasis which caused the neurological symptoms did not preclude participation. All patients provided written informed consent. This study has been approved by the Ethical Review Board of our institution.

2.2. Treatment

In this study, consecutive patients with brain metastases received gefitinib at the daily dose of 250 mg given until disease progression or unacceptable toxicity. Baseline evaluation included a total-body computed tomography (CT) and contrast-enhanced magnetic resonance images (MRIs) of brain. All baseline images were taken within 4 weeks before systemic therapy. After the initiation of treatment, toxicity and disease-related symptom assessment were performed every 4 weeks. Toxic effects were assessed according to the Common Terminology Criteria for adverse Events V3.0 [11]. For the evaluation of response to chemotherapy, brain MRI was performed 1 month following the initiation of chemotherapy and every 2 months thereafter, or at the time of neurological deterioration.

After withdrawal of gefitinib owing to tumor progression or toxicity, erlotinib with the daily dose of 150 mg was administrated. In cases, progression of the tumors regardless of the site of the tumors was observed after erlotinib, irradiation was performed for salvage treatment. RS was selected for patients with small (<20 mm) and a few numbers (≤4) of intracranial lesions, while WBRT was performed for the others. In cases whose extracranial lesions disappeared radiographically after TKIs and lost the need of systemic chemotherapy for extracranial lesions, TKIs was discontinued and irradiation was performed if the brain metastases were still remained.

2.3. Statistical methods

The primary endpoint of this study was survival of patients after diagnosis of brain metastases. The secondary endpoints included progression-free survival, time to salvage radiation therapy, radiologic response, and safety. We used Fisher's exact test and Chi-square test to compare patients with different types of EGFR mutations with respect to clinical and demographic factors. Response rates were analyzed according to the following variables: age (<60 yeas versus 60≤), gender, types of mutations (exon 19 deletion versus L858R), number of intracranial lesions (<4 versus 4≤) and maximum size of lesions (<15 mm versus 15 mm≤). All parameters were analyzed as categorical variables. Univariate and multivariate analyses were performed using a logistic regression model. The impact of these variables on progression-free survival, time to irradiation and overall survival was evaluated univariate analysis using log-rank test, and survival curves were drawn by Kaplan–Meier method. The independent value of variables was assessed in multivariate analysis using the Cox proportional hazard model. All statistical analyses were performed by using JMP 8.0 for Mac (SAS Institute, Cary, NC).

3. Results

3.1. Patients

Between January 2007 and August 2012, 41 patients entered onto this study at Chiba Cancer Center. All of the patients were Asian Japanese and their characteristics were provided in Table 1.

Neurological deficit owing to brain metastasis was the primary symptom in only 3 cases (7.3%), and majority of the intracranial lesions were diagnosed by systemic evaluation at diagnosis of lung cancer (28 cases, 68.3%). Overall, brain metastases were diagnosed prior to initiation of any treatments in 31 cases (75.6%). The remaining 10 intracranial lesions (24.4%) were diagnosed during or after treatment of systemic disease. Female patients were more frequently included (70.7%), and majority of the patients (78.0%) had no smoking history. The median age of patients was 65 years (range 46–81). Most patients had a good PS (0-1 ECOG), but all patients had extracranial active disease and classified into poor prognostic group by Diagnosis-Specific Graded Prognostic

Table 1
Patient characteristics ($n = 41$).

	n	%
Gender		
Male	12	29.3
Female	29	70.7
Age		
<60 years	10	24.4
60 years≤	31	75.6
Smoking status		
Active	3	7.3
Former	6	14.6
Negative	32	78.0
ECOG performance status		
0	15	36.6
1	19	46.3
2	7	17.1
Number of intracranial lesions		
1	12	29.3
2	5	12.2
3	6	14.6
4	18	43.9
Tumor size		
<15 mm	32	78.0
15 mm≤	9	22.0
DS-GPA		
0	2	4.9
0.5	4	9.8
1	11	26.8
1.5	12	29.3
2	12	29.3
EGFR-mutation		
Ex18 G718A	1	2.4
Ex18 G719X	1	2.4
Ex18 L861Q	1	2.4
Ex19 deletion	23	56.1
Ex21 L858R	15	36.6

ECOG, Eastern Cooperative Oncology Group; DS-GPA, Diagnosis-Specific Graded Prognostic Assessment; EGFR, epidermal growth factor receptor; Ex, exon.

Table 2
Types of EGFR-mutations.

	Ex19 deletion	Ex21 L858R	p	Test
Gender			0.087	Fisher's exact
Male	9	2		
Female	14	13		
Age			0.228	Fisher's exact
<60 years	4	5		
60 years≤	19	10		
Smoking status			0.202	Chi-square
Active	3	0		
Former	3	2		
Never	17	13		
ECOG performance status			0.921	Chi-square
0	8	6		
1	11	7		
2	4	2		
Number of lesions			0.462	Chi-square
1	8	4		
2	2	2		
3	5	1		
4≤	8	8		
Tumor size			0.772	Fisher's exact
<15 mm	18	11		
15 mm≤	5	4		
DS-GPA			0.522	Chi-square
0	2	0		
0.5	2	1		
1	4	5		
1.5	8	4		
2	7	5		

Assessment (DS-GPA) score [4]. Solitary metastasis was rare (29.3%), and 43.9% of patients had 4 or more metastases in the brain, although the majority of the lesions (78.0%) were small (<15 mm). Large lesions which caused neurological symptoms required surgical removal prior to chemotherapy in 5 cases (12.2%).

3.2. EGFR mutation

Among the 41 cases, 5 types of EGFR mutation were observed. Deletion of exon 19 was most frequently observed (23 cases), and exon 21 L858R was the next (15 cases). Point mutations which caused change of single nucleotide in exon 18 were rare but also observed in 3 cases (L861Q, G718A, G719A).

When we compared the clinical backgrounds of tumors with exon 19 deletion and L858R, female patients was more frequently included in both types of mutations, but this tendency was more clearly found in L858R tumors with borderline significance ($p = 0.087$, Fisher's exact method). No other difference was observed among the types of mutations (Table 2).

Table 3
Response of brain metastases to gefitinib.

	All patients	Ex19 deletion	Ex21 L858R
Patients number	41	23	15
CR	13(31.7%)	10(43.5%)	3(20.0%)
PR	23(56.1%)	13(56.5%)	9(60.0%)
CR+PR	36(87.8%)	23(100.0%)	12(80.0%)
SD	4(9.8%)	0(0.0%)	3(20.0%)
PD	1(2.4%)	0(0.0%)	0(0.0%)

Ex, exon; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

3.3. Response to chemotherapy and control of tumors

All patients were evaluable for response to chemotherapy. The responses to gefitinib were summarized in Table 3. The objective response rate of all patients was 87.8%, with complete response of the brain metastases in 13 cases (31.7%) and partial response in 23 (56.1%). Representative cases of brain response to gefitinib are shown in Fig. 1. The response rate of tumors with exon 19 deletion (100.0%) was superior to those with L858R (80.0%) with borderline significance ($p = 0.054$, Fisher's exact test). No other patient or treatment variable was related to response of intracranial lesions.

The median time to withdrawal of gefitinib from diagnosis was 10.6 (95% CI 8.3–14.3) months. Among the 41 patients, this agent was discontinued in 32 patients. The most common cause of withdrawal was progression of brain metastases (15 cases) and the secondary cause was progression of extracranial disease (12 cases). Other causes of withdrawal were unacceptable toxicity in 3 cases, deterioration of patient's performance status in 1 and disappearance of extracranial lesions in 1.

Erlotinib was administrated as second line chemotherapy in 13 cases. In one case, this agent was discontinued only one week after initiation owing to the Grade 3 anorexia, and response to erlotinib was not evaluable. Among the remaining 12 cases, complete response was observed in 3 (25.0%), partial response in 4 (33.3%) and stable disease in 3 cases (25.0%), while only 2 case (16.7%) showed progressive disease. The objective response rate was 58.3%. The median time to progression of intracranial lesions was 11.9 months after initiation of erlotinib.

Among the 41 cases, salvage irradiation was required in 20 cases (48.8%). WBRT was performed for 14 patients and RS for 6. Among the 17 patients whose death was observed during the follow-up, salvage irradiation was performed for 12 patients, while the remaining 5 patients did not require radiation therapy during their course of disease.

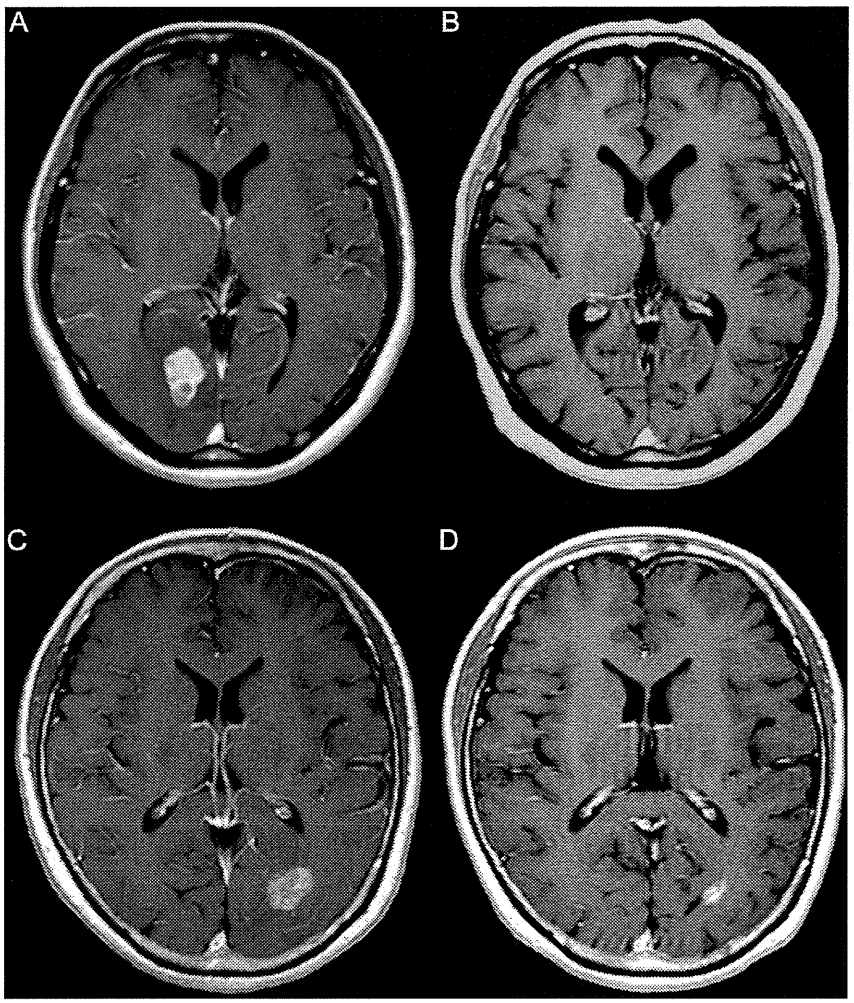

Fig. 1. Axial sections of contrast enhanced T1-weighted magnetic resonance imaging studies of the brain in representative cases. (A) Baseline study of a 53-year-old female with lung adenocarcinoma harboring exon 21 L858R showed right occipital lesion. (B) The study taken after 14 months of gefitinib therapy demonstrated complete response to chemotherapy. (C) Baseline study of a 64-year-old female with exon 19 deletion showed left occipital lesion. (D) Marked decrease of the lesion was observed after 3 months of treatment with gefitinib.

3.4. Duration of survival

During the treatment with gefitinib, central nervous system (CNS)-failure was observed in 15 cases (36.6%). The median time to progression of intracranial lesions was 14.5 (95% CI 10.2–18.3) months from diagnosis of brain metastases (Fig. 2A). The progression-free survival time of tumors with exon 19 deletion (17.5 months, 95% CI 13.9 – not reached) was significantly longer than that with L858R (10.2 months, 95% CI 7.2 – not reached, log rank $p = 0.003$, Fig. 2B). Male patients also showed better control of brain disease in compared with females ($p = 0.007$), but this better control in male patients was probably owing to the different distribution of gender among the types of EGFR mutations. No other patient- or treatment-related variable was statistically correlated with progression-free survival of patients.

After withdrawal of gefitinib, 10 more CNS-failures were observed. Overall, 25 patients (61.0%) experienced progression of brain metastases at some point during or after treatment.

TKIs delayed irradiation, and the median time to salvage irradiation was 17.9 (95% CI 12.4–24.7) months from diagnosis (Fig. 2C). TKIs delayed the irradiation longer in patients with exon 19 deletion (18.4 months) in compared with those with L858R (13.1 months), but this difference was not significant ($p = 0.196$, Fig. 2D).

At the time of the last follow-up, 24 patients were still alive. The 6-months, 1-year, and 2-year overall survival rates were 97.6%, 91.9%, and 48.6%. The median survival was 21.9 (95% CI 18.5–30.3) months after diagnosis of brain metastases (Fig. 2E). The dominant cause of deaths was progression of extracranial disease (76.5%). Neurological deaths were observed in only 4 cases, and leptomeningeal carcinomatosis was the cause of death in all cases. The median overall survival times were significantly different according to the types of EGFR mutations: 30.3 months for the exon 19 deletion group and 19.8 months for the L858R group (log rank $p = 0.025$, Fig. 2F). This survival difference between the two major types of EGFR mutation was also proven with Cox's proportional hazard model. Patients' age, and performance status also showed significant correlation with overall survival by univariate analysis, but independent significance of EGFR genotypes on patients' survival was proven by multivariate analysis (Table 4).

3.5. Toxicity

Side effects were consisted mainly of skin toxicity. Skin disorders occurred in 27 (65.9%) cases. Grade 3 rash was progressed in 6 patients (14.6%), but skin disorders were not causes of discontinuity in any case. Liver dysfunction was also common after gefitinib.

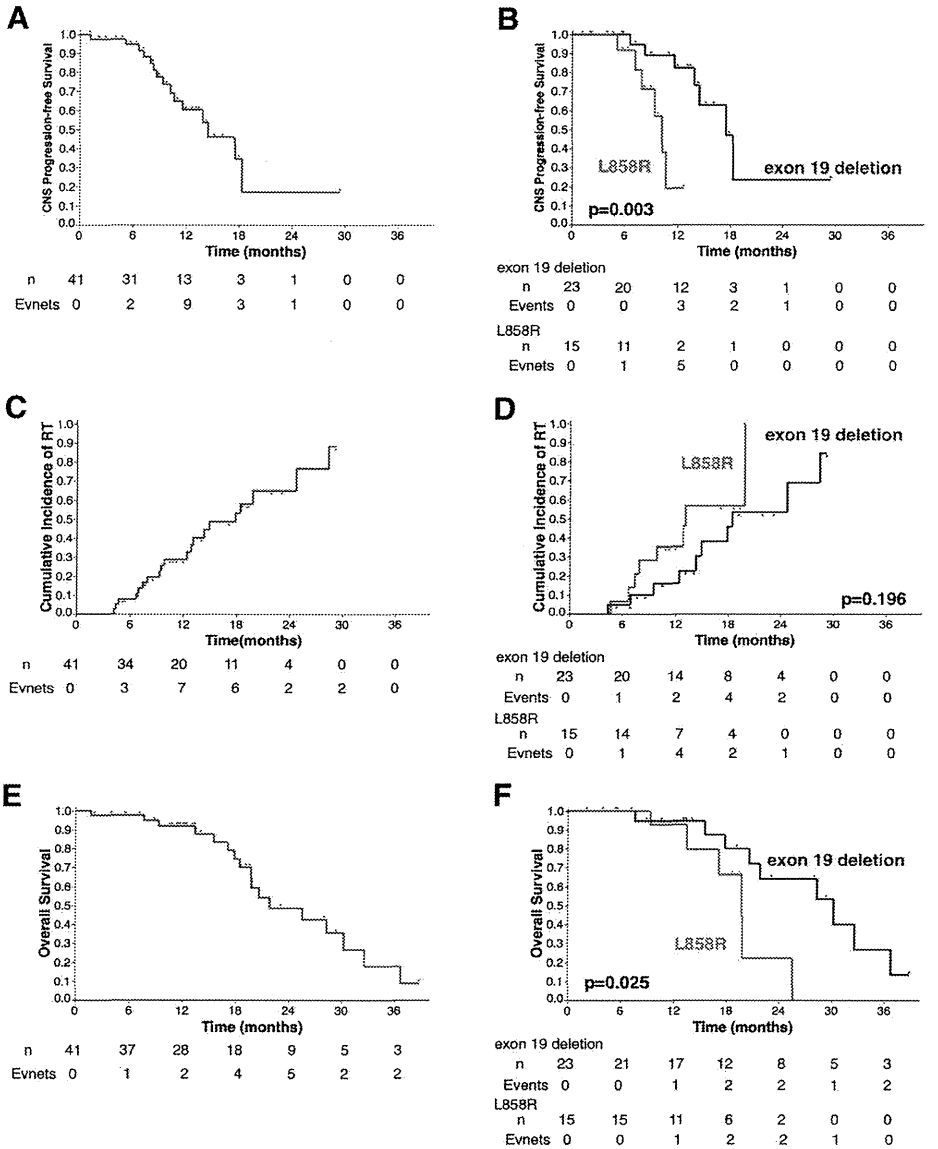

Fig. 2. CNS progression-free and overall survival after treatment of brain metastases with gefitinib alone. CNS progression-free survival for (A) all patients ($n=41$) and (B) by epidermal growth factor receptor (EGFR) mutation genotypes (23 cases with exon 19 deletion and 15 with L858R). Cumulative incidence of salvage radiation therapy for (C) all patients and (D) by EGFR mutation genotypes. Overall survival for (E) all patients and (F) by EGFR mutation genotypes.

Grade 3 hepatobiliary events were observed in 5 (12.2%) cases, and chemotherapy was withdrawn in 1 case. Pulmonary events were very rare, but Grade 3 pneumonitis caused discontinuity of gefitinib in 1 case.

4. Discussion

Gefitinib is a large molecule and a substrate of p-glycoprotein [12]. These suggested the inadequate delivery of this agent

Table 4
Overall survival.

	Risk group	Relative risk (95% CI)	p	Relative risk (95% CI)	p
Sex	Female	2.60 (0.90–9.37)	0.078		
Age	<60 y.o.	0.29 (0.08–1.02)	0.053	0.72 (0.18–3.17)	0.646
Smoking status[a]	Never	1.14 (0.41–3.72)	0.805		
ECOG PS	0 or 1	0.15 (0.04–0.52)	0.004	0.06 (0.01–0.34)	0.002
Number of lesions	≤4	1.69 (0.64–4.54)	0.287		
Tumor size	15 mm≤	1.32 (0.44–3.62)	0.600		
GPA	1.5≤	0.93 (0.32–2.75)	0.897		
EGFR-mutation[b]	Ex19 deletion	0.26 (0.06–0.91)	0.036	0.10 (0.02–0.46)	0.003

ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor; Ex, exon.
[a] Never versus active or former.
[b] Ex19 deletion versus Ex21 L858R.

penetrating BBBs to the intracranial lesions and disappointed response of brain metastases. However, gefitinib showed favorable effect on control of brain metastases in this study. The excellent response of brain metastases to gefitinib indicated the permeability of this agent to the brain metastases which showed enhancement by contrast medium on MRIs. The response rate of our patients was similar to previously reported results after erlotinib concurrent with WBRT [13], even though gefitinib is larger molecule than erlotinib and our patients did not treated with irradiation. Previously, Ceresoli et al. also reported the active response of intracranial metastases to gefitinib, but their results were inferior to ours; response and disease control rates in their series were 10% and 27%, respectively [14]. One reason of these differences was the selection of patients. The previous reports enrolled patients regardless of the EGFR mutation status, while only EGFR-mutant patients were selected in our study. Kim et al. also reported the efficacy of TKIs without WBRT on brain metastases [15]. They selected non-smoking Asian patients but mutation status of EGFR was not evaluated. Gefitinib or erlotinib was administrated, and response rate was reported as 69.6%, which was still inferior to ours. These data indicated the significance of gene diagnosis to decide the treatment strategy of brain metastases.

Nearly half of our patients delayed radiation therapy for more than 1.5 years after diagnosis of brain metastases by TKIs. Furthermore, the median overall survival of our patients reached 21.9 months, even though all patients had active extracranial lesions at diagnosis and classified in poor prognostic groups: DS-GPA score of 0–2.0. The median survival of our patients with DS-GPA score 0–1.0 was 19.8 months and that with DS-GPA score 1.5–2.5 was 21.9 months. These data was superior to previously reported survival of patients after irradiation: 3.02 months for DS-GPA score 0–1.0, and 6.53 months for score 1.5–2.5 [4]. These findings validated the adequate effect of TKIs and safety to withhold radiation therapy to avoid neurocognitive deterioration for selected patients.

In this study, we also demonstrated the difference in response of brain metastases to gefitinib according to EGFR genotypes. In the current study group of Asian patients, exon 19 deletion was the most frequently observed genotype (56%) and L858R was the next (37%). Furthermore, in compared with L858R, exon 19 deletion was correlated with better response of brain metastases to gefitinib, and better survival of patients. The predominance of exon 19 deletion and its' association with better response of lung lesion to TKIs were also reported previously [16–18]. This tendency was also preserved in intracranial lesions.

This single institutional prospective study demonstrated the sufficient effect of gefitinib alone on control of brain metastases which harbored EGFR mutation and its' association with satisfied outcome of patients. Despite clinically significant findings, it still has some limitations. First, genetic evaluation of EGFR was confirmed using samples from primary lung lesion and not with intracranial lesions. Recently, discordance in EGFR mutation status between primary and metastatic tumors had been reported [19,20]. However, high response rate of intracranial lesions in the current study indicated the proper selection of patients. Second, this was single institutional, small-sized and non-randomized study. Larger multi-institutional randomized trials are required to validate our results, and to confirm the efficacy of gefitinib on control of brain metastases.

Conflict of interest

The authors have declared no conflict of interest.

References

[1] Sørensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. J Clin Oncol 1988;6:1474–80.

[2] Regine WF, Hubn JL, Patchell RA, St Clair WH, Strottmann J, Meigooni A, et al. Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastases: results and implications. Int J Radiat Oncol Biol Phys 2002;52:333–8.

[3] Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29:134–41.

[4] Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010;77:655–61.

[5] Tsao MN, Rades K, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2012;2:210–25.

[6] Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 2007;68:1388–95.

[7] Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts or sensitivity [Editorial]. J Clin Oncol 2003;21:3557–8.

[8] Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomized controlled trial. Lancet Oncol 2009;10:1037–44.

[9] Moscetti L, Nelli F, Felici A, Rinaldi M, De Santis S, D'Auria C, et al. Up-front chemotherapy and radiation treatment in newly diagnosed nonsmall cell lung cancer with brain metastases. Cancer 2007;109:274–81.

[10] Lee DH, Han JY, Kim HT, Yoon SJ, Pyo HR, Cho KH, et al. Primary chemotherapy for newly diagnosed non-small cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first: result of a randomized pilot study. Cancer 2008;113:143–9.

[11] European Organization for Research and Treatment of Cancer: Common Toxicity Criteria (CTC). http://www.eortc.be/services/doc/ctc/default.htm

[12] Agarwal S, Sane R, Gallardo JL, Ohlfest JR, Elmquist WF. Distribution of gefitinib to the brain is limited by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2)-mediated active efflux. J Pharmacol Exp Ther 2010;334:147–55.

[13] Welsh JW, Komaki R, Amini A, Munsell MF, Unger W, Allen PK, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. J Clin Oncol 2013;31:895–902.

[14] Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crinò L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. Ann Oncol 2004;15:1042–7.

[15] Kim JE, Lee DH, Choi Y, Yoon DH, Kim SW, Suh C, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer 2009;65:351–4.

[16] Riely GJ, Pao W, Pham D, Li AR, Rizvi N, Venkatraman ES, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. Clin Cancer Res 2006;12:839–44.

[17] Jackman DM, Yeap BY, Sequist LV, Lindeman N, Homes AJ, Joshi VA, et al. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. Clin Cancer Res 2006;12:3908–14.

[18] Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958–67.

[19] Kalikaki A, Koutsopoulos A, Trypaki M, Souglakos J, Stathopoulos E, Georgoulias V, et al. Comparison of EGFR and K-RAS gene status between primary tumours and corresponding metastases in NSCLC. Br J Cancer 2008;99:923–9.

[20] Gow CH, Chang YL, Hsu YC, Tsai MF, Wu CT, Yu CJ, et al. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol 2009;20:696–702.

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A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1–4 vs ≥ 5 tumors

Clinical article

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Object. Although stereotactic radiosurgery (SRS) alone for patients with 4–5 or more tumors is not a standard treatment, a trend for patients with 5 or more tumors to undergo SRS alone is already apparent. The authors' aim in the present study was to reappraise whether SRS results for ≥ 5 tumors differ from those for 1–4 tumors.

Methods. This institutional review board–approved retrospective cohort study used the authors' database of prospectively accumulated data that included 2553 consecutive patients who underwent SRS, not in combination with concurrent whole-brain radiotherapy, for brain metastases (METs) between 1998 and 2011. These 2553 patients were divided into 2 groups: 1553 with tumor numbers of 1–4 (Group A) and 1000 with ≥ 5 tumors (Group B). Because there was considerable bias in pre-SRS clinical factors between Groups A and B, a case-matched study was conducted. Ultimately, 1096 patients (548 each in Groups A and B) were selected. The standard Kaplan-Meier method was used to determine post-SRS survival and the post-SRS neurological death–free survival times. Competing risk analysis was applied to estimate cumulative incidences of local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-induced complications.

Results. The post-SRS median survival time was significantly longer in the 548 Group A patients (7.9 months, 95% CI 7.0–8.9 months) than in the 548 Group B patients (7.0 months 95% [CI 6.2–7.8 months], HR 1.176 [95% CI 1.039–1.331], p = 0.01). However, incidences of neurological death were very similar: 10.6% in Group A and 8.2% in Group B (p = 0.21). There was no significant difference between the groups in neurological death–free survival intervals (HR 0.945, 95% CI 0.636–1.394, p = 0.77). Furthermore, competing risk analyses showed that there were no significant differences between the groups in cumulative incidences of local recurrence (HR 0.577, 95% CI 0.312–1.069, p = 0.08), repeat SRS (HR 1.133, 95% CI 0.910–1.409, p = 0.26), neurological deterioration (HR 1.868, 95% CI 0.608–1.240, p = 0.44), and major SRS-related complications (HR 1.105, 95% CI 0.490–2.496, p = 0.81).

In the authors' cohort, age ≤ 65 years, female sex, a Karnofsky Performance Scale score ≥ 80%, cumulative tumor volume ≤ 10 cm^3, controlled primary cancer, no extracerebral METs, and neurologically asymptomatic status were significant factors favoring longer survival equally in both groups.

Conclusions. This retrospective study suggests that increased tumor number is an unfavorable factor for longer survival. However, the post-SRS median survival time difference, 0.9 months, between the two groups is not clinically meaningful. Furthermore, patients with 5 or more METs have noninferior results compared to patients with 1–4 tumors, in terms of neurological death, local recurrence, repeat SRS, maintenance of good neurological state, and SRS-related complications. A randomized controlled trial should be conducted to test this hypothesis.
(http://thejns.org/doi/abs/10.3171/2013.3.JNS121900)

Key Words • **brain metastases** • **radiation therapy** • **stereotactic radiosurgery** • **Gamma Knife** • **tumor number** • **oncology**

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; MET = metastasis; MST = median survival time; RPA = recursive partitioning analysis; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

Current evidence-based guidelines have supported the use of SRS for patients with 1–4 brain metastases (METs).[21] However, as Sheehan and Schlesinger[29] very recently stated, such guidelines frequently lag behind contemporary clinical practice because

several years, at least, are required for conducting rigorous prospective clinical trials. In fact, as we reported previously[36,37] and as described by Knisely et al.,[20] a trend for patients with ≥ 5, or even ≥ 10, tumors to be potential candidates for SRS alone had already become apparent in the early 21st century. Tsao et al.[33] recently stated, in the American Society for Radiation Oncology evidence-based guideline, that "when new brain METs are seen on the planning scan the day of SRS, it may be reasonable to proceed and complete the SRS procedure for all of the lesions visualized even if they exceed a total of 4 brain METs." Also, Grandhi et al.[10] very recently reported that SRS can be used to safely and effectively treat intracranial disease with a high rate of local control in patients with ≥ 10 brain METs.

In 1997, the first author (M.Y.) reported 2 lung cancer patients in whom more than 30 brain METs were successfully controlled for 4.5 and 5.5 months (the respective remaining survival periods after SRS alone).[35] Although retrospective studies of SRS-treated patients with many brain METs have since been reported, these studies were based on small patient numbers.[3,6,14,19,30,32] Therefore, the role of SRS for patients with ≥ 5 brain METs has not yet been sufficiently analyzed based on databases with a large sample size. The goals of this retrospective cohort study, based on our patients with SRS-treated brain METs, were to reappraise whether treatment results were truly inferior for tumor numbers of ≥ 5 versus 1–4 and to identify factors determining inferiority and/or noninferiority.

Methods

Patient Population

This institutional review board–approved, retrospective cohort study used our prospectively accumulated database at Tokyo Women's Medical University, including 2553 consecutive patients. Patients in our series underwent SRS alone, not in combination with concurrent WBRT, for brain METs during the 13-year period between July 1998 and June 2011. As all patients had been referred to us for SRS, their primary physicians had mostly made the patient selections. Patient selection criteria may thus have differed among referring physicians. Therefore, one author (M.Y.) decided whether to accept a patient. We did not perform SRS on patients with low KPS[18] scores due to systemic diseases (< 70%), a uncooperative state due to poor neurocognitive function, meningeal dissemination, or an anticipated survival period of 3 months or less. Therefore, only 173 patients (6.8%) were categorized into RPA Class 3.[8] Table 1 summarizes clinical characteristics of the entire cohort and also for Group A (1–4 tumors, 1553 patients) and Group B (≥ 5 tumors, 1000 patients). Because all patients had been referred to us for SRS by other facilities, the primary physicians responsible for each patient decided the indications for both surgery and radiotherapy. Therefore, prior to SRS, 18.3% of the 2553 patients had undergone surgical removal of brain METs and 4.8% had undergone WBRT (Table 1).

The treatment strategy was explained in detail to each patient, and at least one adult relative, by the first author (M.Y.) before SRS. Written informed consent was obtained from all patients. Our previous report described our radiosurgical techniques in detail.[37] Briefly, standard SRS procedures were performed using a Leksell Gamma Unit model B before June 2003 and thereafter a Leksell Gamma Unit model C (Elekta AB). Regarding dose selection in cases with multiple METs, total absorbed energy to the whole skull < 15 Joules was considered to be safe, as we have reported elsewhere.[36,37] According to this upper limit criterion, a peripheral dose of 22 ± 3 Gy was applied to cases in which cumulative tumor volumes did not exceed 10.0 cm^3, while those > 10.0 cm^3 received 18 ± 3 Gy. Furthermore, a tumor with a maximum lesion volume > 10.0 cm^3 was irradiated with 18 Gy or less. Irradiation doses to the optic apparatus should not exceed 10–12 Gy. In cases with brainstem lesions, a peripheral dose of 18–20 Gy can be used for tumor volumes < 1 cm^3, 16–18 Gy for 1–4 cm^3, and no more than 15 Gy for > 4 cm^3. In the few patients (4.8%) who had undergone WBRT, peripheral doses were decreased by 10%–15%. After SRS, all cases were routinely managed by referring physicians, and patients were recommended to have clinical and neuroimaging examinations at an approximately 2- to 3-month interval. However, in 760 (29.8%) of the 2553 patients, neuroimaging follow-up could not be performed due to early post-SRS death or remarkable deterioration of general condition. Approximately 50% of patients came to our outpatient clinic periodically, while clinical and/or neuroimaging data were sent to us by mail in about 25%. The first author (M.Y.) called the remaining 25% of patients or their relatives to confirm patients' conditions. For cases in which patients had died, the day of death, cause of death, and detailed information on condition changes were surveyed by telephone.

Case Matching

As shown in Table 1, there was considerable bias between Groups A and B. Therefore, a case-matched study was conducted by one of the authors (Y.S.), who did not participate in other aspects of this study and was blinded to final outcomes. Patient selection was performed by employing the propensity score matching method with a Greedy 5-To-1 Digit-Matching algorithm for clinical factors, (that is, age, sex, primary tumor state, extracerebral METs, KPS score, neurological symptoms, prior procedures [surgery and WBRT], volume of the largest tumor, and peripheral doses).[5,25]

Clinical Outcomes

The primary end point was overall survival, and the secondary end points were neurological death, neurological deterioration, local recurrence of the treated tumor, repeat SRS for new lesions, and SRS-induced major complications. For each end point, failures were regarded as events and any others as censored. Overall survival time was defined as the interval between the first SRS and death due to any cause (that is, progression of systemic and/or brain METs, other cancer-unrelated diseases, accident, suicide, and so on, or the day of the last follow-up). Neurological death was defined as death caused by any

TABLE 1: Summary of clinical characteristics of 2553 patients with brain METs

Characteristic	Total	Tumor Nos.		p Value*
		1–4 (Group A)	≥5 (Group B)	
no. of patients	2553	1553	1000	
tumor no.				
median	3	2	10	
range	1–89	1–4	5–89	
age (yrs)				
median	64.0	64.7	63.0	0.001
range	19–96	19–96	19–91	
sex				
female	1004	557	447	
male	1549	996 (64.1%)	553 (55.3%)	<0.001
primary cancer sites				
lung	1658	974 (62.7%)	684 (68.4%)	0.011†
alimentary tract	302	225 (14.5%)	76 (7.6%)	
breast	279	131 (8.4%)	148 (14.8%)	
kidney	103	79 (5.1%)	24 (2.4%)	
melanoma	15	10 (0.6%)	5 (0.5%)	
others	169	134 (8.6%)	63 (6.3%)	
primary cancer status				
controlled	738	493	245	
not controlled	1815	1060 (68.3%)	755 (75.5%)	0.001
extracerebral METs				
no	1332	848	484	
yes	1221	705 (45.4%)	516 (51.6%)	0.002
KPS score				
≥80%	1945	1209	736	
≤70%	608	344 (22.2%)	264 (26.4%)	0.015
RPA class				
1	195	145	50	
2	2185	1324 (85.3%)	861 (86.1%)	0.42‡
3	173	84	89	
neurological symptoms				
no	1234	742	510	
yes	1319	829 (53.4%)	490 (49.0%)	0.031
prior surgery				
no	2085	1226	859	
yes	468	327 (21.1%)	141 (14.0%)	<0.001
prior WBRT				
no	2429	1496	933	
yes	122	57 (3.7%)	65 (6.5%)	0.001
tumor vol (cm^3)				
cumulative				
mean	9.92	8.71	11.80	<0.001
range	0.01–126.2	0.01–126.2	0.10–115.3	
largest tumor				
mean	6.92	7.55	5.93	<0.001
range	0.01–94.2	0.01–89.3	0.03–94.2	

(continued)

TABLE 1: Summary of clinical characteristics of 2553 patients with brain METs *(continued)*

Characteristic	Total	Tumor Nos.		p Value*
		1–4 (Group A)	≥5 (Group B)	
peripheral dose (Gy)				
mean	21.14	21.67	20.33	<0.001
range	10.00–32.00	10.00–32.00	10.00–27.00	

* Student t-test was used for continuous variables and Fisher exact test for pairs of categorical variables.
† Lung versus nonlung.
‡ RPA Class 2 versus Classes 1 and 3.

intracranial disease (that is, tumor recurrence, carcinomatous meningitis, cerebral dissemination, and progression of other untreated intracranial tumors).

Local recurrence–free survival time was defined as the interval between the first SRS and the day when follow-up MR imaging demonstrated local recurrence (at the irradiated lesion). Generally, local recurrence criteria were increased size of an enhanced area on post-Gd T1-weighted MR images and enlarged tumor core on T2-weighted MR images.[15] However, in 115 cases in which MRI alone was not sufficient to confirm recurrence, ^{11}C methionine PET was used to distinguish tumor recurrence from necrotic lesions.[22,23,34,38] Positron emission tomography was performed, and the results were evaluated by one author (T.N.) not involved in either SRS treatment or patient follow-up. Thus, all findings of recurrence on MRI and/or PET were regarded as events and any others as censored. Also, repeat SRS–free survival time was defined as the interval between the first SRS and the day the second SRS was performed for new METs; all repeat SRS procedures for newly developed lesions were regarded as events and any others as censored. For patients developing new brain METs after the first SRS, our approach is similar to that in patients with initially diagnosed brain METs. As to tumor size, if follow-up MRI demonstrates tumors with diameters of 2–3 mm in the brainstem or optic apparatus, we perform repeat SRS without further observation. Otherwise, repeat SRS is usually postponed with close MRI follow-up until the tumor diameter exceeds approximately 1 cm.

Neurological deterioration-free survival time was defined as the interval between the first SRS and the day that any brain disease–caused neurological worsening manifested (that is, local recurrence, progression of new lesions, and SRS-induced complications). Decreases in KPS scores, in patients with scores ≥ 20%, due to neurological worsening were regarded as events and any others as censored. Major complication–free survival time was taken as the interval between the first SRS and the day major SRS-induced complications occurred. Patients with major complications included those with RTOG neurotoxicity grades of 2 or worse and, even if the grade was either 0 or 1, those in whom surgical intervention was required based on sequential MRI follow-up demonstrating progressive enlargement of a cyst and/or a mass lesion with further observation thus being regarded as excessively high risk; all of these conditions were regarded as events and any others as censored.[24]

Statistical Analysis

All data were analyzed according to the intention-to-treat principle. For the baseline variables, summary statistics were constructed by using frequencies and proportions for categorical data and means ± SD for continuous variables. We compared patient characteristics using the Fisher exact test for categorical outcomes and t-tests for continuous variables, as appropriate. The standard Kaplan-Meier method was used for overall and neurological death–free survivals.[16] Also, univariate analysis using the Cox proportional hazard model was performed to determine pre-SRS clinical factors favoring longer survival.[4]

For time-to-event outcomes, the cumulative incidences of local recurrence, repeat SRS, neurological deterioration, and major complications were estimated by a competing risk analysis, because death is a competing risk for loss to follow-up (that is, patients who die can no longer become lost to follow-up).[9,11,25] Also, to identify baseline and clinical variables associated with the 4 aforementioned outcomes, competing risk analyses were performed with the Fine-Gray generalization of the proportional hazards model accounting for death as a competing risk.[7] Fine-Gray generalization makes use of the subdistribution hazard to model cumulative incidence, thereby quantifying the overall benefit or harm of an exposure.[2]

All comparisons were planned, and the tests were 2-sided. A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed by one of the authors (Y.S.) using SAS software version 9.2 (SAS Institute) and the R statistical program, version 2.13. Before statistical analyses, the database was cleaned (by Y.H.). These two authors were not involved in either SRS treatment or patient follow-up.

Results

Cohort Study

Four patients (0.15%; 1 in Group A and 3 in Group B) were lost to follow-up. As of the end of December 2011, 201 patients (7.9%) were confirmed to be alive (censored observation) and the remaining 2348 (92.0%) had died (event). The mean post-SRS follow-up periods were 36.1 months (95% CI 31.6–40.5 months) in the censored subgroup and 10.4 months (95% CI 10.0–10.9 months) in the event subgroup; the overall mean post-SRS follow-up du-

ration was 12.5 months (95% CI 11.8–13.1 months). The MST after SRS was 7.4 months (95% CI 7.1–7.9 months). Cumulative post-SRS survival rates were 57.6%, 33.7%, 15.0%, 8.3%, and 4.5% at the 6th, 12th, 24th, 36th, and 60th post-SRS month, respectively. Causes of death could not be determined in 106 patients but were confirmed in the remaining 2242 to be nonbrain diseases in 1983 (88.4%) and brain diseases in 259 (11.6%).

Among various pre-SRS clinical factors, univariate analysis demonstrated age ≤ 65 years, female sex, KPS score ≥ 80%, cumulative tumor volume ≤ 10 cm^3, controlled primary cancer, no extracerebral METs, and neurologically asymptomatic status to be significant factors favoring longer survival, as shown in Table 2. For all clinical factors significantly impacting survival, both hazard ratios and probability values were very similar in the 2 groups.

Case-Matched Study

As described above, after all the propensity-score matches had been performed, we compared baseline covariates between the 2 groups. Ultimately, 1096 patients (548 with 1–4 tumors [Group A] and 548 with ≥ 5 tumors [Group B]) were selected. The p values after matching were > 0.05 for all clinical factors (Table 3).

As shown in Fig. 1 left, MST after SRS was significantly longer in the 548 patients in Group A than in the 548 in Group B (7.9 vs 7.0 months, HR 1.176, 95% CI 1.039–1.331, p = 0.01). However, incidences of death caused by progression of brain disease were very similar: 10.6% in Group A and 8.2% in Group B (p = 0.21) (Table 4). Furthermore, there was no significant difference between the 2 groups in neurological death–free survival intervals (HR 0.945, 95% CI 0.636–1.394, p = 0.77) (Fig. 1 right).

Post–stereotactic radiosurgery follow-up MRI examinations were available in 763 patients (69.6%): 378 in Group A and 385 in Group B. Among these 763 patients, the incidence of local recurrence was significantly higher in the Group A than in the Group B patients (8.5% vs 3.9%, p = 0.01) (Table 4). Nevertheless, there was no significant difference between the 2 groups in local recurrence–free survival intervals (HR 0.577, 95% CI 0.312–1.069, p = 0.08) (Fig. 2A).

As shown in Table 4, there were no significant differences between Groups A and B in the incidences of salvage WBRT (3.7% vs 5.8%, p = 0.11), salvage surgery (2.2% vs 1.1%, p = 0.23), repeat SRS for new lesions (30.3% vs 29.0%, p = 0.69), neurological deterioration (13.1% vs 9.7%, p = 0.09), or SRS-related complications (2.7% vs 2.0%, p = 0.55). Also, there were no significant differences between the 2 groups in the repeat SRS–free survival intervals (HR 1.133, 95% CI 0.910–1.409, p = 0.26) (Fig. 2B), neurological deterioration–free survivals (HR 1.868, 95% CI 0.608–1.240, p = 0.44) (Fig. 2C), or SRS-related complication-free survival intervals (HR 1.105, 95% CI 0.490–2.496, p = 0.81) (Fig. 2D), all of which were estimated using competing risk analysis.

Discussion

Do Tumor Numbers Impact Post-SRS Treatment Results?

At present, the majority of physicians consider patients with 1–4 METs to be good candidates for SRS with or without WBRT. Debate continues as to how many brain METs make a patient ineligible for SRS alone. Karlsson et al.[17] reported, based on 1921 MET patients who underwent SRS, that despite patients with a single MET sur-

TABLE 2: Clinical factors before SRS impacting post-SRS survival period in 2549 patients*

	Tumor Nos.			
	1–4 (Group A)		≥5 (Group B)	
Factors	HR (95% CI)	p Value	HR (95% CI)	p Value
no. of patients	1552		997	
age (yrs)				
>65 vs ≤65	1.214 (1.092–1.350)	<0.001	1.181 (1.040–1.341)	0.01
sex				
male vs female	1.437 (1.287–1.607)	<0.001	1.307 (1.150–1.487)	<0.001
KPS score				
≤70% vs ≥80%	2.223 (1.958–2.517)	<0.001	2.682 (2.309–3.106)	<0.001
cumulative tumor vol (cm^3)				
>10 vs ≤10	1.439 (1.280–1.614)	<0.001	1.469 (1.289–1.673)	<0.001
primary cancer status				
not controlled vs controlled	2.418 (2.159–2.725)	<0.001	2.320 (1.987–2.721)	<0.001
extracerebral metastases				
yes vs no	1.470 (1.322–1.634)	<0.001	1.420 (1.250–1.615)	<0.001
neurological symptoms				
yes vs no	1.242 (1.118–1.380)	<0.001	1.274 (1.121–1.448)	<0.001

* Cohort excludes 4 patients lost to follow-up.

TABLE 3: Summary of clinical characteristics of 1096 case-matched patients with brain METs

Characteristic	Total	Tumor Nos.		p Value*
		1–4 (Group A)	≥5 (Group B)	
no. of patients	1096	548	548	
tumor no.				
median	4	2	8	
range	1–51	1–4	5–51	
age (yrs)				
median	63.8	63.7	63.9	0.7
range	19–91	19–88	19–91	
sex				
female	465	240	225	
male	631	308 (56.2%)	323 (58.9%)	0.36
primary cancer sites				
lung	737	366 (66.8%)	371 (67.7%)	0.75†
alimentary tract	108	55 (10.0%)	53 (9.7%)	
breast	135	68 (12.4%)	67 (12.2%)	
kidney	34	15 (2.7%)	19 (3.5%)	
melanoma	6	2 (0.4%)	4 (0.7%)	
others	76	42 (7.7%)	34 (6.2%)	
primary cancer status				
controlled	299	145	154	
not controlled	797	403 (73.5%)	394 (71.9%)	0.54
extracerebral METs				
no	575	283	292	
yes	521	265 (48.4%)	256 (46.7%)	0.59
KPS score				
≥80%	848	412	436	
≤70%	248	136 (24.8%)	112 (20.4%)	0.08
RPA class				
1	75	43	32	
2	949	468 (85.4%)	481 (87.8%)	0.19‡
3	72	37	35	
neurological symptoms				
no	561	286	275	
yes	535	262 (47.8%)	273 (49.8%)	0.51
prior surgery				
no	914	461	453	
yes	182	87 (15.9%)	95 (17.3%)	0.52
prior WBRT				
no	1048	524	524	
yes	46	24 (4.4%)	22 (4.0%)	0.24
tumor vol (cm^3)				
cumulative				
mean	9.02	9.12	8.92	0.79
range	0.01–122.2	0.01–122.0	0.10–115.3	
largest tumor				
mean	6.39	6.84	5.95	0.09
range	0.01–94.2	0.01–89.3	0.03–94.2	

(continued)

TABLE 3: Summary of clinical characteristics of 1096 case-matched patients with brain METs *(continued)*

Characteristic	Total	Tumor Nos.		p Value*
		1–4 (Group A)	≥5 (Group B)	
peripheral dose (Gy)				
mean	21.51	21.44	21.58	0.42
range	10.00–27.00	12.00–25.00	10.00–27.00	

* Student t-test was used for continuous variables and Fisher exact test for pairs of categorical variables.
† Lung versus nonlung.
‡ RPA Class 2 versus Classes 1 and 3.

viving longer than those with multiple METs, there were no significant MST differences among individuals with 2, 3–4, 5–8, or > 8 metastases. Chang et al.[3] recently reported, based on 323 SRS-treated patients with brain METs, that there were no significant MST differences among 4 tumor number groups (that is, 1–5, 6–10, 11–15, and > 15). The first author (M.Y.) has described elsewhere that the Kaplan-Meier method was used to compare 15 pairs of groups based on tumor numbers: 1 vs ≥ 2, ≤ 2 vs ≥ 3, and so on through ≤ 15 vs ≥ 16. In each of the 15 pairs, the MSTs in patients with lower tumor numbers were significantly longer than those in patients with higher tumor numbers ($p < 0.0001$).[37] Furthermore, 14 other pairs of groups, based on tumor numbers, were also assessed by this method (1 vs 2, 2 vs 3, 3 vs 4, and so on through 14 vs 15). Among the 14 pairs, only 1 vs 2 showed a significant MST difference ($p = 0.0002$); no significant differences were detected for the other 13 pairs.[37]

In our present study, although the post-SRS MST difference, 0.9 months, between the 2 groups was statistically significant, this difference was not clinically meaningful. Furthermore, approximately 90% of patients with brain METs died of causes other than brain disease progression, regardless of tumor number, when only carefully selected patients were treated. Also, as mentioned, the Group B patients were demonstrated to have noninferior results compared with the Group A patients, in terms of neurological death, local recurrence, repeat SRS required for new tumors, maintenance of good neurological state, and SRS-related complications. Particularly, as reported previously,[36] SRS for patients with multiple METs was not found to be excessively high risk in carefully selected patients. Furthermore, we also reported very recently that, based on 167 patients surviving more than 3 years after SRS, tumor numbers did not impact the incidence of SRS-induced complications (HR 1.066, 95% CI 0.968–1.131, $p = 0.1567$).[38] Our current results showed no apparent increase in the risk of complications with SRS for ≥ 5 METs compared with 1–4 METs. Furthermore, post-SRS MRI confirmed the absence of leukoencephalopathy in patients receiving SRS alone.

Because approximately 90% of patients died due to extracerebral diseases, it is clearly crucial for brain MET treatments to maintain a good neurological state in those patients treated. We thus consider it to be very important that the currently reported SRS results of good neurological status maintenance in patients with ≥ 5 tumors were clearly noninferior to those in patients with 1–4 tumors.

Is WBRT Necessary for All Patients With Multiple METs?

The central criticism of using SRS alone for multiple METs is the assumption that frequent microscopic tumors will soon require salvage SRS or other treatment. Thus, WBRT has generally been advocated. However, WBRT can be expected to prevent new tumors arising within 6–8 post-WBRT months at the longest, as shown in Fig. 2 of the article written by Aoyama et al.[1] We should remember that considerable numbers of patients with brain METs can survive more than 1 year, outliving the effects of

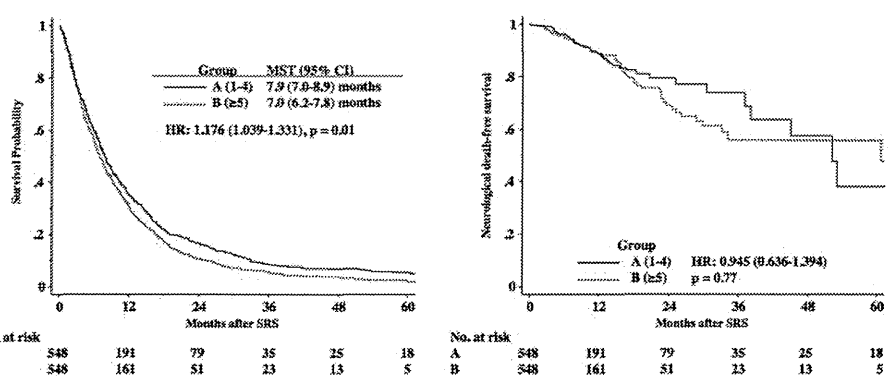

FIG. 1. Overall survival **(left)** and neurological death–free survival **(right)**, based on a subset of 1096 case-matched patients according to tumor number (1–4 [Group A] and ≥ 5 [Group B]), estimated using the standard Kaplan-Meier method.

TABLE 4: Summary of treatment results after SRS

Incidences	Total	Tumor Nos. 1–4 (Group A)	≥5 (Group B)	p Value
no. of patients	1096	548	548	
neurological death	103	58 (10.6%)	45 (8.2%)	0.21
salvage WBRT	52	20 (3.7%)	32 (5.8%)	0.11
salvage surgery	18	12 (2.2%)	6 (1.1%)	0.23
local recurrence*	47	32 (8.5%)	15 (3.9%)	0.01
repeat SRS	325	166 (30.3%)	159 (29.0%)	0.69
neurological deterioration	125	72 (13.1%)	53 (9.7%)	0.09
SRS-related complications	26	15 (2.7%)	11 (2.0%)	0.55

* Based on 763 patients (378 in Group A and 385 in Group B; 333 were excluded because neuroimaging results were not available).

WBRT. Most fortunately, we already live in an era when an MET with a diameter of 2 mm or even slightly smaller can be detected using thin-slice, postenhanced MR images.[13] Hanssens et al.[12] recently reported that SRS alone based on high-resolution MRI decreased the incidence of and lengthened the time to distant recurrences. In fact, although data on periods between SRS and the appearance of new lesions were not available, the present study showed that the repeat-SRS rate in our Group B patients (29.0%) was very similar to that in our Group A patients (30.3%, p = 0.69), as shown in Table 4. Furthermore, we found that the repeat-SRS–free intervals (when SRS was performed for new lesions) were almost the same for our Group A and Group B patients (Fig. 2B). Therefore, the availability of an alternative treatment for multiple brain METs allows WBRT to be reserved for subsequent treatment attempts (that is, for meningeal dissemination or miliary METs treatable only with WBRT).

Most physicians consider current evidence to clearly support WBRT use over SRS for patients with poor performance status and progressive/uncontrolled systemic disease and, ultimately, a relatively short survival expectancy.[1] Therefore, as described in *Patient Population*, we usually do not perform SRS in patients with low KPS[18] scores due to systemic diseases (< 70%) and an anticipated survival period of 3 months or less. However, in other patients, the availability of an alternative treatment for brain METs allows WBRT to be postponed relative to the course of another management strategy, such as very extensive chemotherapy and/or radiation therapy for spinal

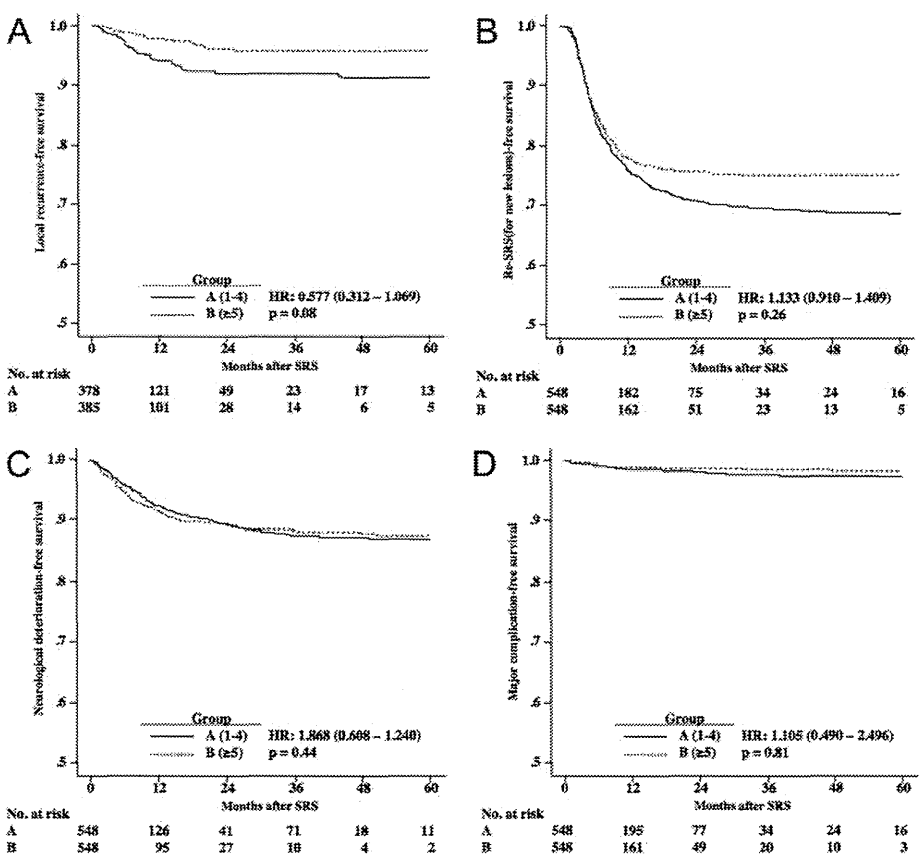

FIG. 2. Local recurrence–free survival (A), repeat SRS (for new lesions)–free survival (B), neurological deterioration–free survival (C), and major complication–free survival (D) according to tumor number (1–4 [Group A] and ≥ 5 [Group B]) estimated using competing risk analysis (see text).

lesions or other organ involvement, which are also urgent. Furthermore, SRS takes only 1 day, whereas 2–3 weeks are necessary for completing WBRT. Thus, SRS allows patients, and this is especially important for those with a short survival expectancy, to maximize any remaining time with their families.

The North American Gamma Knife Consortium is currently conducting a prospective randomized study entitled "Neurocognitive outcomes in patients treated with radiotherapy for five or more brain metastases (NAGKC-Rand)" (Identifier NCI01731704; http://www.clinicaltrials.gov/). The primary aim of this study is to compare the change in neurocognitive function outcomes between baseline and 6 months in WBRT versus SRS treatment groups. Patients with ≥ 5 METs are selected for this study. The results of this study are expected to clarify the role of SRS alone versus WBRT.

Weaknesses of the Present Study

As mentioned in our previous article,[39] in general the major weakness of a retrospective study might be that clinical factors are obviously heterogeneous. In fact, there was considerable bias between Groups A and B in our cohort (Table 1). Greater patient group homogeneity makes a study more scientific. However, heterogeneity actually reflects clinical settings rather closely, as we physicians often deal with inhomogeneous clinical factors. In particular, our database included some patients whose brain METs were not newly diagnosed tumors. However, proportions of such patients in the 2 groups were very small and did not differ significantly (Table 3). Thus, this heterogeneity had only a minimal impact on our results, as we reported very recently.[31] Nevertheless, treatment selection is considered to be largely influenced by the characteristics of patients receiving a particular treatment regimen. This is an important issue when estimating the effect of treatments or exposures on outcomes using observational data. One approach to reducing or eliminating the effect of treatment selection bias and confounding effects is to use propensity score matching, which allows one to design and analyze an observational (nonrandomized) study that mimics some of the characteristics of a randomized controlled trial. Therefore, in the present investigation, a case-matched study was also conducted by one of the authors (Y.S.), who did not participate in other aspects of this study and was blinded to final outcomes.

Only patients with RTOG neurotoxicity Grade 2 or worse were counted in this study because, if severe problems, not only those that were symptomatic but also those shown only on MRI, occurred in SRS-treated patients, every physician, without exception, consulted the first author. In fact, some busy physicians actually forgot to report minor problems like RTOG neurotoxicity Grade 0 or 1 to us. Therefore, a weakness of this study is that all patients with minor complications were not surveyed.

Ongoing Prospective Cohort Study

The Japanese Leksell Gamma Knife Society is currently conducting a prospective observational study entitled "Gamma knife treatment results for patients with multiple brain metastases: A multi-institutional prospective study" (abbreviation JLGK0901; trial no. 1812; http://www.umin.ac.jp/)." This investigation was designed to examine whether SRS alone for patients with 5–10 brain METs is not inferior to SRS alone for patients with 2–4 METs in terms of overall survival and other clinical results. Although the final result of this ongoing study is due in early 2013, based on our previous retrospective investigations, the JLGK0901 study is anticipated to show noninferiority of SRS as the sole treatment for patients with 5–10 brain METs compared with 2–4 METs in terms of overall survival.[27,28] However, a randomized controlled trial, in the near future, is necessary to clarify the most appropriate role for SRS alone in patients with ≥ 5 METs.

How Should Good Candidates for SRS Alone Be Selected From Among Patients With ≥ 10 METs?

The selection of good candidates for SRS alone, even from among patients with ≥ 5 METs, is a very important issue. As shown in Table 2, we identified pre-SRS clinical factors that significantly favored longer survival after SRS. Among these factors, KPS score ≥ 80% and controlled primary cancer were regarded as the 2 major prognostic factors for selecting good candidates. It must be noted that both hazard ratios and probability values for the 7 clinical factors were very similar in the 2 groups. This means that it is not necessary for physicians to use different patient selection criteria when they manage patients with ≥ 5 METs.

Conclusions

Although our retrospective study suggests increased tumor number to be an unfavorable factor for longer survival, the post-SRS MST difference, 0.9 months, between the 2 groups is not clinically meaningful. Furthermore, patients with ≥ 5 METs have noninferior results compared with patients with 1–4 METs, in terms of neurological death, local recurrence, repeat SRS, maintenance of a good neurological state, and SRS-related complications. A randomized controlled trial should be conducted to test this hypothesis.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Yamamoto. Acquisition of data: Yamamoto, Kawabe. Analysis and interpretation of data: Yamamoto. Drafting the article: Yamamoto, Barfod. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Yamamoto. Statistical analysis: Sato, Higuchi. Study supervision: Yamamoto, Kasuya. Evaluation of PET findings: Nariai. Checked English in manuscript: Barfod. General patient care: Urakawa.

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