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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.
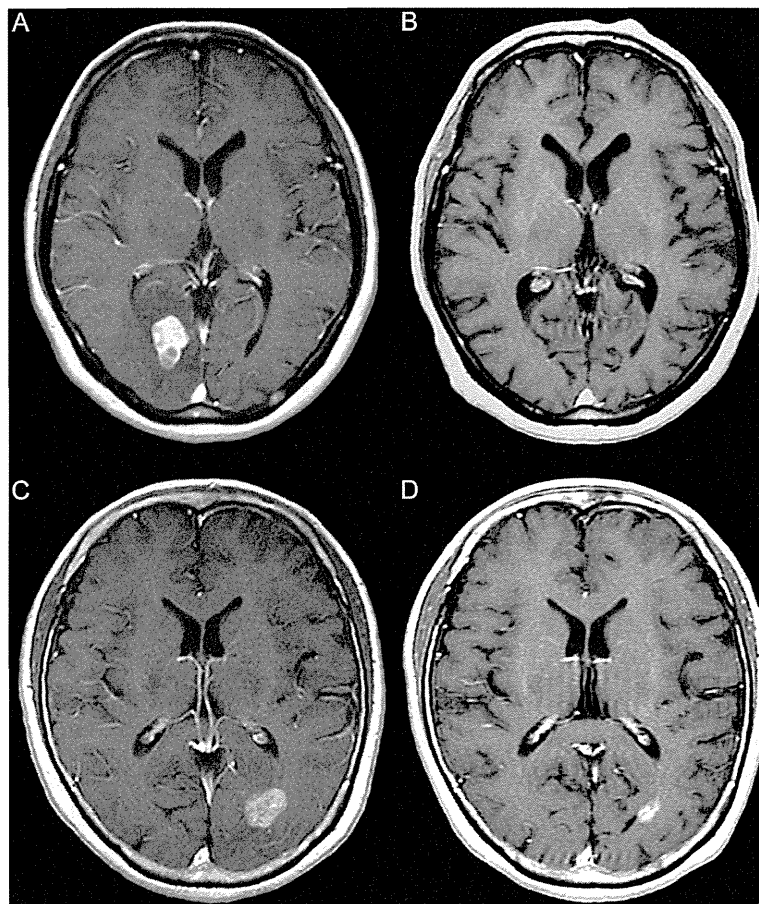
Fig. 1. Axial sections of contrast enhanced T1-weighted magnetic resonance imaging studies of the brain in representative cases. (A) Baseline study of a 53-year-old female with lung adenocarcinoma harboring exon 21 L858R showed right occipital lesion. (B) The study taken after 14 months of gefitinib 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.
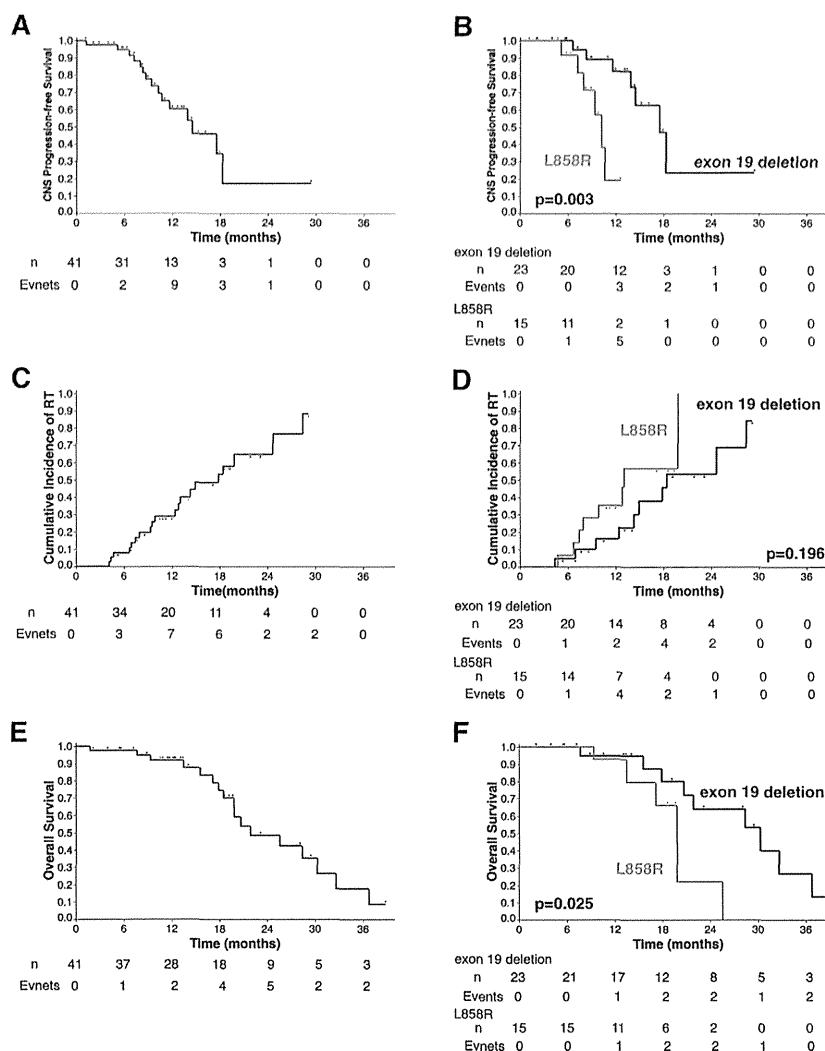
A

CNS Progression-free Survival vs Time (months)

| n | 41 | 31 | 13 | 3 | 1 | 0 | 0 |
| Evnets | 0 | 2 | 9 | 3 | 1 | 0 | 0 |

B

CNS Progression-free Survival — L858R, exon 19 deletion, p=0.003

exon 19 deletion
| n | 23 | 20 | 12 | 3 | 1 | 0 | 0 |
| Events | 0 | 0 | 3 | 2 | 1 | 0 | 0 |

L858R
| n | 15 | 11 | 2 | 1 | 0 | 0 | 0 |
| Evnets | 0 | 1 | 5 | 0 | 0 | 0 | 0 |

C

Cumulative Incidence of RT vs Time (months)

| n | 41 | 34 | 20 | 11 | 4 | 0 | 0 |
| Evnets | 0 | 3 | 7 | 6 | 2 | 2 | 0 |

D

Cumulative Incidence of RT — exon 19 deletion, L858R, p=0.196

exon 19 deletion
| n | 23 | 20 | 14 | 8 | 4 | 0 | 0 |
| Events | 0 | 1 | 2 | 4 | 2 | 0 | 0 |

L858R
| n | 15 | 14 | 7 | 4 | 0 | 0 | 0 |
| Evnets | 0 | 1 | 4 | 2 | 1 | 0 | 0 |

E

Overall Survival vs Time (months)

| n | 41 | 37 | 28 | 18 | 9 | 5 | 3 |
| Evnets | 0 | 1 | 2 | 4 | 5 | 2 | 2 |

F

Overall Survival — exon 19 deletion, L858R, p=0.025

exon 19 deletion
| n | 23 | 21 | 17 | 12 | 8 | 5 | 3 |
| Events | 0 | 0 | 1 | 2 | 2 | 1 | 2 |

L858R
| n | 15 | 15 | 11 | 6 | 2 | 0 | 0 |
| Evnets | 0 | 0 | 1 | 2 | 2 | 1 | 0 |

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.

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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 cm³, 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.
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KEY WORDS • brain metastases • radiation therapy • stereotactic radiosurgery • Gamma Knife • tumor number • oncology

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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. 1–4 (Group A)	Tumor Nos. ≥5 (Group B)	p Value*
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 (cm³)				
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).[9,11,26] 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 cm³, 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 (cm³)				
>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. 1–4 (Group A)	Tumor Nos. ≥5 (Group B)	p Value*
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 (cm³)				
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)

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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
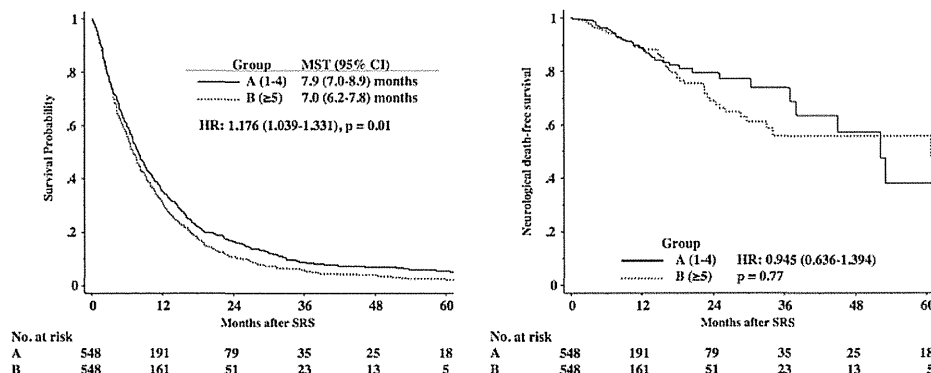

Fig. 1. Overall survival **(left)** and neurological death–free survival **(right)**, based on a subset of 1096 case-matched patients according to tumor number (1–4 [Group A] and ≥ 5 [Group B]), estimated using the standard Kaplan-Meier method.

TABLE 4: Summary of treatment results after SRS

| Incidences | Total | Tumor Nos. | | p Value |
		1-4 (Group A)	≥5 (Group B)	
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 deterio-ration	125	72 (13.1%)	53 (9.7%)	0.09
SRS-related compli-cations	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
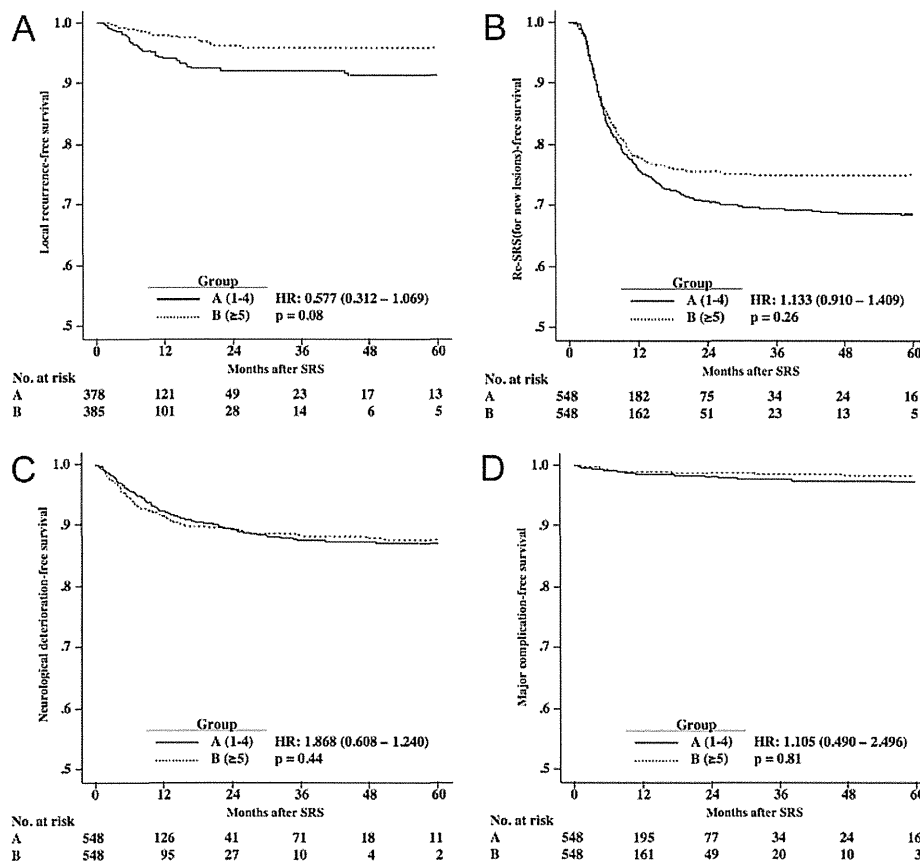

FIG. 2. Local recurrence–free survival (A), repeat SRS (for new lesions)–free survival (B), neurological deterioration–free survival (C), and major complication–free survival (D) according to tumor number (1–4 [Group A] and ≥ 5 [Group B]) estimated using competing risk analysis (see text).

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 en-

titled "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.

Radiosurgery for 1–4 vs ≥ 5 brain metastases

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Direct comparison of radiation dosimetry of six PET tracers using human whole-body imaging and murine biodistribution studies

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Abstract

Objective We investigated the whole-body biodistributions and radiation dosimetry of five ^{11}C-labeled and one ^{18}F-labeled radiotracers in human subjects, and compared the results to those obtained from murine biodistribution studies.

Methods The radiotracers investigated were ^{11}C-SA4503, ^{11}C-MPDX, ^{11}C-TMSX, ^{11}C-CHIBA-1001, ^{11}C-4DST, and ^{18}F-FBPA. Dynamic whole-body positron emission tomography (PET) was performed in three human subjects after a single bolus injection of each radiotracer. Emission scans were collected in two-dimensional mode in five bed positions. Regions of interest were placed over organs identified in reconstructed PET images. The OLINDA program was used to estimate radiation doses from the number of disintegrations of these source organs. These results were compared with the predicted human radiation doses on the basis of biodistribution data obtained from mice by dissection.

Results The ratios of estimated effective doses from the human-derived data to those from the mouse-derived data ranged from 0.86 to 1.88. The critical organs that received the highest absorbed doses in the human- and mouse-derived studies differed for two of the six radiotracers. The differences between the human- and mouse-derived dosimetry involved not only the species differences, including faster systemic circulation of mice and differences in the metabolism, but also measurement methodologies.

Conclusions Although the mouse-derived effective doses were roughly comparable to the human-derived doses in most cases, considerable differences were found for critical organ dose estimates and pharmacokinetics in certain cases. Whole-body imaging for investigation of radiation dosimetry is desirable for the initial clinical evaluation of new PET probes prior to their application in subsequent clinical investigations.

Keywords Radiation dosimetry · PET · Whole-body distribution

Introduction

The estimation of human radiation doses is mandatory for the development of new radiotracers used in positron emission tomography (PET). For this purpose, various animal species, such as rodents, dogs, rabbits, and non-human primates, have been used to perform preclinical biodistribution studies. Human radiation dosimetry of radiotracers was initially performed using these experimental animal data to determine the maximum allowable injection activity in clinical studies. Tissue dissection using rodents was the most popular method used for this purpose with extrapolation of animal data to human data to normalize interspecies variations. This classical dissection method is easily employed in many facilities at a relatively low cost.

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With advances in equipment enabling whole-body imaging, PET imaging of non-human primates is preferred in several well-equipped institutes because there are fewer interspecies differences. In the last decade, radiation dosimetry using whole-body PET and PET/CT in human subjects has been applied to several newly developed tracers and others that have proven to be clinically useful. Recently, human radiation dosimetry studies were extensively reviewed, and the use of dosimetry was subsequently recommended during the early course of clinical trials [1, 2]. In a previous study, van der Aart et al. [2] summarized the dosimetry of 38 ^{11}C-labeled PET tracers after researching MEDLINE literature. On the basis of rodent versus human data, several tracers demonstrated substantial differences between the calculated effective doses. In the review, Zanotti-Fregonara and Innis compared monkey- and human-derived radiation dosimetry studies that had used whole-body PET imaging for nine ^{11}C-labeled tracers. It was observed that the effective dose extrapolated from monkeys was greater than that estimated from human subjects [1]. The animal- and human-derived radiation dosimetry studies for several PET tracers were compared; however, these reports summarized previously published data, most of which involved different protocols, apparatus, and calculation methods. Dosimetry estimates are known to be affected by both biological and methodological sources of variability. Therefore, species differences are best evaluated by direct comparisons using the same protocols, apparatus, and calculation methods.

To date, there have been only a limited number of studies that have compared rodent-derived dosimetry of PET radiotracers with human-derived dosimetry. Santens et al. [3] reported similar effective doses of ^{11}C-methoxy-progabidic acid for the gamma-amino-butyric acid (GABA) receptor determined from biodistribution data obtained by tissue dissection in mice and by whole-body PET scans in human subjects. The effective dose of ^{11}C-CP-126-998, acetylcholine esterase inhibitor, evaluated by human PET imaging was 50 % of that evaluated by dissection of mice; i.e., 3.85 versus 7.68 μSv/MBq [4]. However, this study was insufficient because absorbed doses only from the liver, small intestine, kidney, and brain were used in the human study. The effective dose of ^{11}C-choline on the basis of the rat imaging study was 64 % of the effective dose determined by human PET imaging [5]. Recently, we found that an α7 nicotinic receptor tracer, 4-^{11}C-methylphenyl 1,4-diazabicyclo[3.2.2.]nonane-4-carboxylate (^{11}C-CHIBA-1001), had different pharmacokinetics in mice and human subjects, which led to an underestimation of the human data obtained from the results in mice; i.e., 3.8 versus 6.9 μSv/MBq [6]. Most of these studies compared only the effective doses; however, for effective dose estimation of radiotracers, several

technical problems and assumptions are present in the evaluation of their biodistribution and in the extrapolation of animal data to human data. To date, the predicated radiation dosimetry in human from animal-derived data has not been validated sufficiently. Furthermore, the maximum injected activity per study may be limited by the critical organ rather than the effective dose. Organ perfusion and mechanism of clearance are major determinants of tracer biokinetics in the body and critical organ. Therefore, detailed direct comparisons between rodent- and human-derived organ dosimetry are also important.

In this study, human biodistribution measurements and radiation dosimetry dose estimations of six PET tracers were determined by whole-body PET scans. Organ-absorbed doses and effective doses were compared with those estimated in murine studies that used the dissection method. The radiotracers investigated were ^{11}C-1-(3, 4-dimethoxyphenethyl)-4-(3-phenylprophyl)piperazine (^{11}C-SA4503) for sigma$_1$ receptor; ^{11}C-8-dicyclopropylmethyl-1-methyl-3-propylxanthine (^{11}C-MPDX) for adenosine A$_1$ receptor; ^{11}C-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine (^{11}C-TMSX) for adenosine A$_{2A}$ receptor; ^{11}C-CHIBA-1001, ^{11}C-4'-thiothymidine (^{11}C-4DST) for DNA synthesis; and 4-borono-2-^{18}F-fluoro-L-phenylalanine (^{18}F-FBPA) for boron neutron capture therapy. The mouse- and human-derived dosimetry studies of ^{11}C-CHIBA-1001 and the human-derived study of ^{11}C-4DST were reported previously [6, 7]. The mouse-derived dosimetry studies of four of the other radiotracers (excluding ^{11}C-4DST) were also reported [8–11]. All biodistribution studies of the six radiotracers in mice, including ^{18}F-FBPA, were accomplished by the same dissection method used by Ishiwata et al. However, the organ-absorbed doses and effective doses of ^{11}C-SA4503, ^{11}C-MPDX, ^{11}C-TMSX, and ^{18}F-FBPA were re-calculated from their biodistribution data for the present purposes.

Materials and methods

Radiotracers

Five ^{11}C-labeled radiotracers, ^{11}C-SA4503, ^{11}C-MPDX, ^{11}C-TMSX, ^{11}C-CHIBA-1001, and ^{11}C-4DST, were prepared as described previously [7–10, 12–14]. The mean specific activity of the five radiotracers in the human PET studies was 70.4 ± 53.0 GBq/μmol at the time of injection, and the radiochemical purity was >97 %.

^{18}F-FBPA was prepared as described previously [11] with several modifications using a multi-purpose synthesizer CFN-MPS100, including an ^{18}F-F$_2$/acetyl ^{18}F-hypofluorite production system [15] (Sumitomo Heavy Industries, Tokyo, Japan). In brief, acetyl ^{18}F-hypofluorite in Ne was bubbled at a flow rate of 500–1000 mL/min at room temperature into