Optimal Sequence of Local and EGFR-TKI Therapy for EGFR-Mutant Non-Small Cell Lung Cancer With Brain Metastases Stratified by Number of Brain Metastases

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Optimal Sequence of Local and EGFR-TKI Therapy for EGFR-Mutant Non-Small Cell Lung Cancer With Brain Metastases Stratified by Number of Brain Metastases

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Summary

This was a retrospective comparison of upfront epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and upfront local therapy to brain metastases for patients with EGFR-mutant non-small cell lung cancer and brain metastases. We found a longer overall survival among patients treated with upfront local therapy than in those treated with upfront EGFR tyrosine kinase inhibitor in patients with 1 to 4 brain metastases, although there was no significant difference in overall survival between groups in those with ≥5 brain metastases.

Purpose: It is unclear whether local therapy (LT) or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) should take precedence for patients with EGFR-mutant non-small cell lung cancer (NSCLC) and brain metastases (BMs). The number of BMs is important in the choice of LT, including whole-brain radiation therapy, stereotactic radiosurgery, and surgery.

Methods: We retrospectively evaluated cases of EGFR-mutant non-small cell lung cancer with BMs from a single site. Patients were divided into 2 groups based on upfront therapy—EGFR-TKI (TKI) or LTs—and subsequently stratified by the number of BMs.

Results: Among 176 patients, 61% received upfront EGFR-TKI, and 39% received upfront LT. The number of patients with 1 to 4 BMs was similar (56% vs 52%; $P = .61$). All patients with 1 to 4 BMs in the LT group, except for surgical cases, received stereotactic radiosurgery (n = 31). Among those with ≥5 BMs, most (n = 27; 82%) received whole-brain radiation therapy. There was no significant difference in OS between LT and TKI groups (median overall survival, 28 vs 23 months; hazard ratio, 0.75; 95% confidence interval, 0.52-1.07). In patients with 1 to 4 BMs, the LT group showed significantly better OS compared with the TKI group (median overall survival, 35 vs 23 months; hazard ratio, 0.54; 95% confidence interval, 0.32-0.90). There was no difference in OS between the LT and TKI groups for patients with ≥5 BMs. Multivariable analysis showed that upfront LT yielded significantly better OS for patients with 1 to 4 BMs.

Conclusion: Upfront LT followed by EGFR-TKI is more effective than upfront EGFR-TKI for the survival of untreated patients harboring EGFR mutations with 1 to 4 BMs.

Introduction

A frequent and serious complication for non-small cell lung cancer (NSCLC) is brain metastasis. Approximately 20% to 40% of patients with NSCLC develop brain metastases (BMs) at some point in their disease course.[1-3] The prognosis for patients with BMs has been poor, with an overall survival (OS) of less than 3 months without treatment.[4] However, advances in systemic therapy and radiation therapy have resulted in median OS ranging from 3 to 15 months in patients treated for their BMs.[5] Whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgery are standard therapies for BM. WBRT is usually recommended for multiple BMs.[6,7] SRS reduces the radiation damage to the surrounding normal brain tissue, thereby resulting in less neurologic toxicity; it is recommended for a limited number of BMs (1-4), with a maximum diameter of no more than approximately 3 cm.[8,9]

Patients with epidermal growth factor receptor (EGFR)-mutant NSCLC more frequently develop BM than patients without EGFR mutations.[3,10] However, patients with NSCLC who also harbor EGFR alterations with BM have markedly improved survival compared with those without alterations, probably in part because of the development of treatment by EGFR tyrosine kinase inhibitor (TKI).[3,11] EGFR-TKI is the first-line treatment for patients with advanced NSCLC with EGFR mutations.[12] Their median OS after BM development is 23 months, with some reaching nearly 4 years.[11,13] EGFR-TKI monotherapy without radiation therapy can offer 75% to 88% response rates to intracranial disease in patients with EGFR-mutant NSCLC with BM.[14-16]

In contrast, Magnuson et al[17] reported that the use of upfront EGFR-TKI, followed by radiation therapy to BM including SRS or WBRT, was associated with inferior OS in patients with EGFR-mutant NSCLC with BM compared with upfront radiation therapy to BM followed by EGFR-TKI. They also showed that SRS followed by EGFR-TKI resulted in the longest OS.[17] A phase 3 trial revealed that upfront SRS followed by chemotherapy did not improve OS in NSCLC with asymptomatic 1 to 4 BMs compared with upfront chemotherapy, although the cohort included patients with and without EGFR mutations.[18] Jiang et al[19] reported that the addition of WBRT to EGFR-TKIs did not appear to have survival benefit compared with EGFR-TKIs alone in patients with EGFR-mutated NSCLC with BM.[19] In addition, WBRT can sometimes cause crucial complications related to quality of life, including moderate-to-severe dementia that occurs several months to years after WBRT consequent to neurocognitive toxicity, whereas the negative impact of BM progression on neurocognitive function when omitting WBRT is debatable.[20] With the longer survival of patients with EGFR mutations after EGFR-TKI approval,[21] these late toxicities of WBRT, especially for EGFR mutation with BM, are important considerations.

Thus, the optimal treatment sequence for untreated EGFR-mutated NSCLC with BM remains controversial. Moreover, some retrospective studies included patients who

received SRS and those who received WBRT. The number of BMs is an important factor influencing the physician's decision, and stratification by the number of BMs can therefore be useful to examine the treatment sequence for such patients. This retrospective study aims to evaluate the optimal treatment sequence for untreated EGFR-mutated NSCLC with BM by comparing 2 groups divided by the upfront therapy including EGFR-TKI or local therapy (LT) for BM, with a focus on patient subgroups stratified by the number of BMs.

Methods and Materials

Patient cohort

We retrospectively collected measurements from the medical records of patients with EGFR-mutated NSCLC with synchronous BM and treated with EGFR-TKIs as first-line treatment between October 2007 and April 2018 at our institution. BMs were confirmed with magnetic resonance imaging. Patients were included in this study even if they did not receive EGFR-TKI as a sequential treatment with LT for BM. Patients were excluded from this study if they had prior EGFR-TKI use before diagnosis of BM. Patients enrolled into this study were divided into 2 groups by the upfront therapy. The TKI group comprised those with upfront EGFR-TKI, and the LT group comprised upfront LT.

The following characteristics were collected for analysis: age; sex; Eastern Cooperative Oncology Group performance status (ECOG PS) at diagnosis; smoking history; stage at diagnosis; the Charlson comorbidity index, which has been proven to be a valid and reliable method of measuring comorbidity[22,23]; EGFR mutation status; EGFR-TKI drugs (gefitinib, erlotinib, or afatinib); asymptomatic or symptomatic BM; presence of meningitis at diagnosis; number of BMs; size of the largest BM; existence of extracranial metastasis; and type of local BM therapy (WBRT, SRS, or surgery). The start date of initial LTs, start of EGFR-TKI, disease progression, intracranial progression, most recent follow-up, and death were recorded. Intracranial progression was defined as radiographic progression of pre-existing BM, the development of new BM, or both. Diagnosis of intracranial progression was performed by neuro-oncologists based on enhanced magnetic resonance imaging and/or perfusion computed tomography.[24] The tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1).

EGFR genotyping

Materials for bronchoscopy, percutaneous needle biopsy, or surgical resection were used for extraction of genomic DNA. EGFR mutations were evaluated using polymerase chain reaction amplification with commercially available methods.

Radiation therapy

Both linear accelerators and Gamma Knife devices were allowed as SRS. Fractionated stereotactic radiation therapy was also included in SRS. In SRS using Gamma Knife, the median prescribed dose was 18 Gy (range, 16-22 Gy) at the lesion periphery. In SRS using linear accelerators, the median prescribed dose was 25 Gy (range, 20-25 Gy) in a single fraction, or 30 Gy (range, 28-35 Gy) in 4 to 5 fractions. WBRT was applied using standard techniques. As standard techniques, the prescribed dose was 30 Gy in 10 fractions of 3 Gy at the midline, 5 fractions per week. If a patient underwent radiation therapy in combination with surgery, we categorized the patient into the surgery group.

Statistical methods

Patient characteristics of each group were compared both descriptively and with the χ^2 test for categorical variables. Continuous variables were analyzed using analysis of variance. The primary outcome was OS measured from the earlier date (start of EGFR-TKI or start of LTs for BM) to death or censored at the last follow-up date. Progression-free survival (PFS) was evaluated in patients receiving EGFR-TKI treatment. PFS was measured from the start of EGFR-TKI to disease progression or death and censored at the date of last follow-up date. The time to intracranial progression was calculated from the earlier date (start of EGFR-TKI or start of LTs for BM) to the date of intracranial progression, and patients with no radiologically intracranial progression were considered censored cases. Median survival estimates were calculated using the Kaplan-Meier method. The standard log-rank tests were used to compare groups. The Cox proportional hazard model was used for univariate and multivariate survival analyses to calculate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The variables associated with the OS in univariate analyses ($P \leq .25$) were included in the multivariate logistic regression model. $P < .05$ (two-sided) was considered statistically significant. Analyses were performed with JMP version 11 (SAS Institute, Cary, NC, USA). This study protocol was approved by the institutional review board of our institution.

Results

Patient characteristics

Between October 2007 and April 2018, 230 patients were identified with EGFR-mutated NSCLC and newly diagnosed BM. Fifty-four patients were excluded for the following reasons: administration of cytotoxic chemotherapy as first line (n = 36), participation in clinical trials (n = 6), impossibility to evaluate BM radiologically before

treatment (n = 4), best supportive care (n = 1), and hospital transfer before first evaluation (n = 7).

Of the 176 patients enrolled in this study, 107 (61%) patients received upfront EGFR-TKI (TKI group), and 69 (39%) patients underwent upfront LT (LT group). In the TKI group, 36 (34%) patients were examined by neuro-oncologists at diagnosis of BM. In the LT group, 27 patients were treated with WBRT, 36 patients were treated with SRS, and 6 patients were treated with surgery. Twenty-six patients did not receive EGFR-TKI as a sequential treatment with LT. Of the 26 patients, 8 patients failed to receive EGFR-TKI after LT, and 18 patients started EGFR-TKI at the point of progression after the LT. The median follow-up time was 23 months (range, 2.3-91 months). The LT group had symptomatic BM (39% vs 9%; $P < .01$) and BM diameters $\geq$1 cm (78% vs 40%; $P < .01$) more frequently than the TKI group did, and had extracranial metastases (64% vs 94%; $P < .01$) less frequently than the TKI group.

Table 1 Patient characteristics

Characteristic	TKI group (n = 107)	LT group (n = 69)	*P* value	WBRT (n = 27)	SRS (n = 36)	Surgery* (n = 6)
Median age, years (range)	67 (41-88)	69 (32-85)	.55	-	-	-
Sex, n (%)						
Female	78 (73)	44 (64)	.20	-	-	-
Male	29 (27)	25 (36)		-	-	-
ECOG PS, n (%)						
0-1	74 (69)	48 (70)	.95	-	-	-
2-4	33 (31)	21 (30)		-	-	-
Stage at diagnosis, n (%)						
IV	90 (84)	44 (64)	<.01	-	-	-
I-III	17 (16)	25 (36)		-	-	-
Smoking status, n (%)						
Current or former	39 (36)	32 (46)	.19	-	-	-
Never	68 (64)	37 (54)		-	-	-
CCI, n (%)						
0	83 (77)	53 (77)	.54	-	-	-
1-2	21 (20)	15 (22)		-	-	-
3-4	2 (2)	0 (0)		-	-	-
≥5	1 (1)	1 (1)		-	-	-
EGFR mutation, n (%)						
Exon19 deletion	50 (47)	31 (45)	.06	-	-	-
Exon21 L858R	54 (50)	30 (43)		-	-	-
Others	3 (3)	8 (12)		-	-	-
EGFR-TKI, n (%)						
Gefitinib	71 (66)	40 (58)	—	-	-	-
Erlotinib	30 (28)	18 (26)		-	-	-
Afatinib	6 (6)	3 (4)		-	-	-
None	—	8 (12)		-	-	-
Symptom of BM, n (%)						
Yes	10 (9)	27 (39)	<.01	13 (48)	9 (25)	5 (83)
No	97 (91)	42 (61)		14 (52)	27 (75)	1 (17)
Meningitis, n (%)						
Yes	6 (6)	5 (7)	.66	5 (18)	0 (0)	0 (0)
No	101 (94)	64 (93)		22 (82)	36 (100)	6 (100)
Number of BMs, n (%)						
1-4	60 (56)	36 (52)	.61	0 (0)	31 (86)	5 (83)
≥5	47 (44)	33 (48)		27 (100)	5 (14)	1 (17)
Size of the largest BM, n (%)						
≥1 cm	43 (40)	54 (78)	<.01	23 (85)	25 (69)	6 (100)
<1 cm	64 (60)	15 (22)		4 (15)	11 (31)	0 (0)
Extracranial metastasis, n (%)						
Yes	102 (95)	44 (64)	<.01	23 (85)	18 (50)	3 (50)
No	5 (5)	25 (36)		4 (15)	18 (50)	3 (50)

Abbreviations: BM = brain metastasis; CCI = Charlson Comorbidity Index; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; LT = local therapy; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; WBRT = whole-brain radiotherapy; — = not detectable.

* Of 6 patients receiving surgery, 4 patients underwent adjuvant WBRT and 1 patient underwent adjuvant SRS.

Clinicopathological characteristics, age, sex, ECOG PS, smoking status, Charlson comorbidity index, EGFR mutation status, and EGFR-TKI drug use were not significantly different between groups (Table 1). Although the proportion of patients with 1 to 4 BMs was similar in both arms (52% vs 56%; $P = .61$), all patients with 1 to 4 BMs in the LT group, except for surgical cases, received SRS (n = 31); among those with ≥5 BMs, most patients (n = 27; 82%) received WBRT.

Survival outcomes

For the entire cohort, the median OS from the start of treatment was 26 months (95% CI, 21-28 months). OS did not significantly differ between the LT and TKI groups, with a respective median OS of 28 months and 23 months (HR, 0.75; 95% CI, 0.52-1.07; $P = .12$; Fig. 1A). In patients receiving EGFR-TKI as first-line treatment, PFS was also similar between groups (median PFS, 9.0 vs 8.3 months; HR, 0.85; 95% CI, 0.61-1.17; $P = .32$; Fig. 1B). In patients with 1 to 4 BMs, the LT group (n = 36) showed significantly better PFS than the TKI group did (n = 60; median PFS, 14 vs 9.1 months; HR, 0.57; 95% CI, 0.34−0.91; $P = .02$; Fig. 2A). There was no difference in PFS between groups in patients with ≥5 BMs (median PFS, 8.4 vs 7.4 months; HR, 1.13; 95% CI, 0.70-1.80; $P = .61$; Fig. 2B). The LT group showed significantly better OS than the TKI group did for those with 1 to 4 BMs (median OS, 35 vs 23 months; HR, 0.54; 95% CI, 0.32-0.90; $P = .02$; Fig. 2C). OS was similar between groups for patients with ≥5 BMs (median OS, 22 vs 27 months; HR, 1.08; 95% CI, 0.64-1.81; $P = .76$; Fig. 2D).

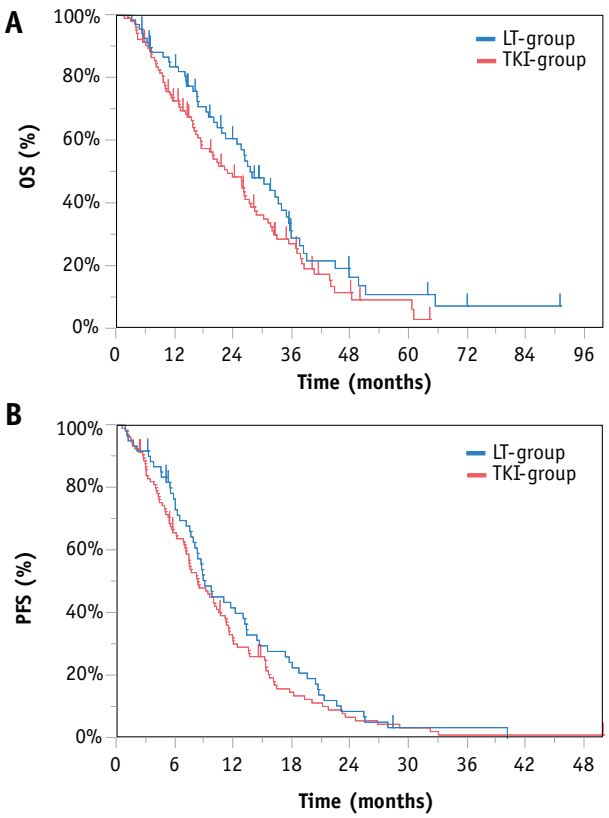

Fig. 1. (A) Kaplan-Meier curves of overall survival (OS) in patients treated with upfront local therapy for brain metastases and upfront epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). (B) Kaplan-Meier curves of progression-free survival (PFS) in patients treated with upfront local therapy for brain metastases and upfront EGFR-TKI.

Intracranial progression

Among patients who had progression (n = 155), the frequency of failure in the brain as a first failure site did not differ between groups (LT group [48%] vs TKI group [46%]; $P = .78$). For modality of LTs, 68% of SRS-treated patients, 35% of WBRT-treated patients, and 33% of surgery-treated patients had progression in the brain as a first progression site. The median time to intracranial progression was 22 months in the LT group versus 12 months in the TKI group (HR, 0.54; 95% CI, 0.36-0.79; $P < .01$). In patients with 1 to 4 BMs, frequency of progression in the brain as a first failure site was similar, and time to intracranial progression was 24 months in the LT group and 15 months in the TKI group (HR, 0.39; 95% CI, 0.22-0.67; $P < .01$).

Subgroup analysis in patients with 1 to 4 brain metastases

For patients with 1 to 4 BMs, stage IV at diagnosis (80% vs 47%; $P < .01$) and extracranial metastases (92% vs 50%; $P < .01$) were more frequently observed in the TKI group (Table 2), whereas symptomatic BM (12% vs 28%; $P = .05$) and BM diameter ≥1 cm (33% vs 72%: $P < .01$) were more frequently observed in the LT group. After adjusting for age, sex, ECOG PS, stage, symptomatic BM, size of the largest BM, and presence of extracranial metastasis, which were covariates influencing the selection of radiation therapy for BM, multivariate analysis also showed that upfront LT yielded significantly better OS than did upfront EGFR-TKI for patients with 1 to 4 BMs (adjusted HR, 0.36; 95% CI, 0.19-0.66; $P < .01$; Table 3). For the entire cohort, multivariate analysis also showed that upfront LT yielded better OS than upfront EGFR-TKI did (Table E3; available online at https://doi.org/10.1016/j.ijrobp.2019.02.051).

Subsequent cancer therapies

For patients with 1 to 4 BMs, 34 of 55 patients (62%) in the TKI group and 16 of 29 patients (55%) in the LT group subsequently received second-line chemotherapy. Twenty-five (45%) patients in the TKI group had been treated with LTs for BMs (8 with SRS alone, 14 with WBRT alone, 2

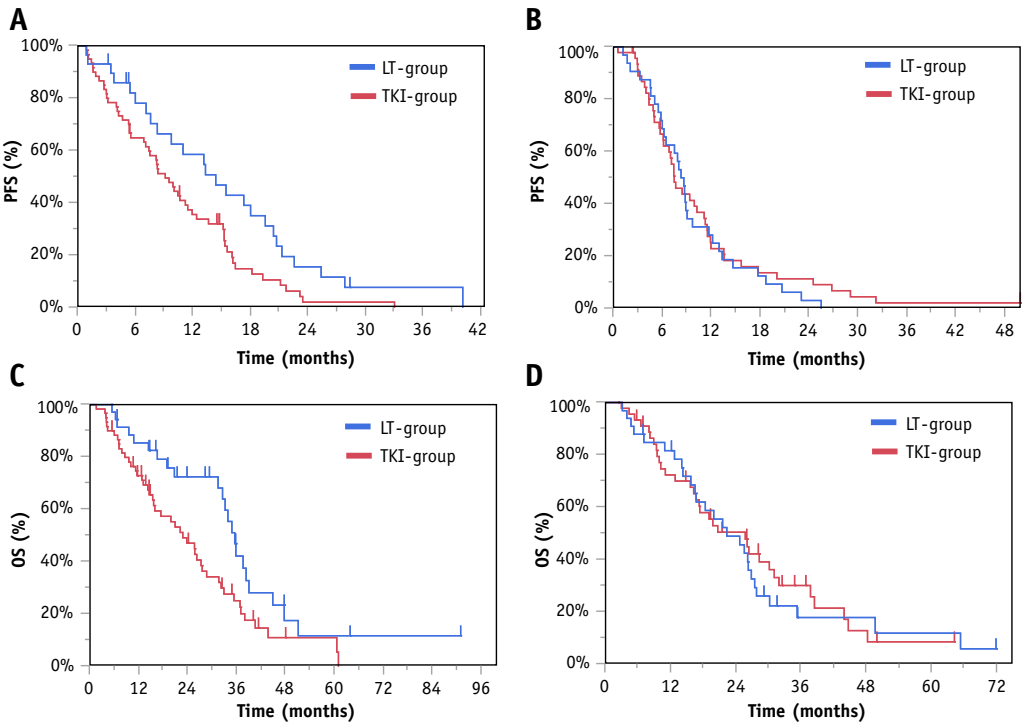

Fig. 2. Analysis stratified by number of brain metastases (BMs): 1 to 4 BMs and ≥5 BMs. (A) Kaplan-Meier curves of progression-free survival (PFS) in patients treated with upfront local therapy (LT) for BM and upfront epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in the subgroup of 1 to 4 BMs. (B) Kaplan-Meier curves of PFS in patients treated with upfront local therapy for BM and upfront EGFR-TKI in the subgroup of ≥5 BMs. (C) Kaplan-Meier curves of overall survival (OS) in patients treated with upfront local therapy for BM and upfront EGFR-TKI in the subgroup of 1 to 4 BMs. (D) Kaplan-Meier curves of OS in patients treated with upfront local therapy for BM and upfront EGFR-TKI in the subgroup of ≥5 BMs.

with surgery, and 1 with SRS and WBRT). Of the 29 patients in the LT group, 12 (41%) required additional LTs (8 with SRS alone, 3 with WBRT alone, 1 with surgery). Eight patients (15%) in the TKI group and 4 patients (14%) in the LT group were treated with osimertinib. Both TKI and LT groups were similar in the number of patients receiving subsequent chemotherapy, osimertinib, and additional LTs. Patients in the TKI group were more frequently treated with other extracranial LTs than those in the LT group (51% vs 24%; $P = .02$; Table 4). A similar result for subsequent cancer therapies was seen in the entire cohort (Table E4; available online at https://doi.org/10.1016/j.ijrobp.2019.02.051).

Discussion

Although this study cohort did not show superior outcome of LTs followed by EGFR-TKI over upfront EGFR-TKI for OS and PFS, we have shown that LTs including SRS or surgery followed by EGFR-TKI yield significantly better survival in patients with 1 to 4 BMs.

Magnuson et al[17] reported that the SRS followed by EGFR-TKI was associated with longer OS in patients with EGFR-mutant NSCLC with BM compared with EGFR-TKI alone (median OS, 47 vs 25 months; adjusted HR, 0.39; 95% CI, 0.26-0.58; $P < .001$).[17] Gerber et al[25] showed that the median OS of upfront SRS was 64 months compared with 26 months in patients with EGFR-TKI alone (HR, 0.26; 95% CI, 0.09-0.78; $P = .02$).[25] A systematic review and meta-analysis of 12 studies has also upheld the view that upfront cranial radiation therapy can improve survival outcomes compared with TKI alone.[26] However, because SRS is commonly used for a limited number of BMs (ie, 1-4), the influence of the number of BMs in this retrospective study might have resulted in selection bias. Our study was designed to remove the selection bias by stratification based on the number of BMs. Our results suggest that upfront SRS followed by EGFR-TKI is recommended for patients with EGFR-mutant NSCLC with BM if the number of BMs is limited. Notably, Magnuson et al[17] and Gerber et al[25] have demonstrated that patients with a more favorable disease-specific graded prognostic assessment who received upfront SRS had a longer median OS, which might indicate that the number of BMs is still a material factor in a subpopulation that could benefit from SRS; disease-specific graded prognostic assessment consists of age, Karnofsky performance status, extracranial metastases, and number of BMs.[5] Surgery also has been reported to extend survival in patients with EGFR-mutant NSCLC with limited BMs,

Table 2 Patient characteristics in the subgroup of 1 to 4 brain metastases

Characteristic	TKI group (n = 60)	LT group (n = 36)	*P* value	SRS (n = 31)	Surgery (n = 5)*
Median age (range), y	69 (41-87)	71 (40-85)	.95	-	-
Sex, n (%)					
Female	44 (73)	20 (56)	.08	-	-
Male	16 (27)	16 (44)		-	-
ECOG PS					
0-1	46 (77)	29 (81)	.65	-	-
2-4	14 (23)	7 (19)		-	-
Stage at diagnosis					
IV	48 (80)	17 (47)	<.01	-	-
Postoperative recurrence	12 (20)	19 (53)		-	-
Smoking status					
Current or former	22 (37)	18 (50)	.20	-	-
Never	38 (63)	18 (50)		-	-
CCI					
0	45 (75)	27 (75)	.62	-	-
1-2	14 (23)	9 (25)		-	-
3-4	0 (0)	0 (0)		-	-
≥5	1 (2)	0 (0)		-	-
EGFR mutation					
Exon19 deletion	27 (45)	16 (45)	.29	-	-
Exon21 L858R	32 (53)	17 (47)		-	-
Others	1 (2)	3 (8)		-	-
EGFR-TKI					
Gefitinib	43 (72)	17 (47)	—	-	-
Erlotinib	13 (22)	9 (26)		-	-
Afatinib	4 (6)	3 (8)		-	-
None	0 (0)	7 (19)		-	-
Symptom of BM					
Yes	7 (12)	10 (28)	.05	6 (19)	4 (80)
No	53 (88)	26 (72)		25 (81)	1 (20)
Meningitis					
Yes	3 (5)	0 (0)	.09	0 (0)	0 (0)
No	57 (95)	36 (100)		31 (100)	5 (100)
Size of the largest BM					
≥1 cm	20 (33)	26 (72)	<.01	21 (68)	5 (100)
<1 cm	40 (67)	10 (28)		10 (32)	0 (0)
Extracranial metastasis					
Yes	56 (93)	18 (50)	<.01	15 (48)	3 (60)
No	4 (7)	18 (50)		16 (52)	2 (40)

Abbreviations: BM = brain metastasis; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; LT = local therapy; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; WBRT = whole-brain radiotherapy; — = not detectable.

* Of 5 patients receiving surgery, 4 patients underwent adjuvant WBRT.

which corroborates our findings.[27] Recently, a meta-analysis of 7 studies has shown that patients with EGFR-mutant NSCLC and a limited number of BMs (ie, 1-4) receiving up-front cranial radiation therapy had longer OS compared with those receiving EGFR-TKI alone (HR, 0.54; 95% CI, 0.41-0.72; $P < .001$).[28] This meta-analysis excluded patients who failed to receive EGFR-TKI after local radiation therapy. The exclusion seemed to affect the meta-analysis result as a selection bias, eliminating those whose post−radiation therapy courses were eventful and not applicable for EGFR-TKI. However, our study results suggest that the exclusion would not affect the fact that up-front local radiation therapy followed by EGFR-TKI would bring about positive outcome; 81% of patients with 1 to 4 BMs could receive EGFR-TKI after local radiation therapy in our study.

Conversely our results suggest that the benefit of LTs is not shown in patients with >4 BMs. Because almost all patients with more than 5 BMs received WBRT, this might indicate that WBRT followed by EGFR-TKI is not an optimal treatment for BM of EGFR-mutant NSCLC, in concurrence with the proposal made by several reports.[19,25,29] Jiang et al[19] reported that 91 of 157 patients with EGFR-mutant NSCLC with BM at diagnosis received EGFR-TKIs, and 30 of them received EGFR TKIs plus

Table 3 Univariate and multivariate analysis of covariables associated with OS in the subgroup of 1 to 4 brain metastases

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Upfront therapy (LT vs EGFR-TKI)	0.54	0.32-0.90	.02	0.36	0.19-0.66	<.01
Age (<75 vs ≥ 75 y)	0.74	0.44-1.24	.24	0.77	0.45-1.33	.34
Sex (female vs male)	0.74	0.46-1.24	.25	0.46	0.26-0.80	<.01
ECOG PS (0-1 vs 2-4)	0.33	0.19-0.60	<.01	0.44	0.21-0.90	.03
Stage at diagnosis (I-III vs IV)	0.61	0.35-1.04	.07	0.77	0.39-1.42	.41
Smoking status (never vs current or former)	0.98	0.62-1.65	.94	—	—	—
CCI (0 vs ≥ 1)	0.80	0.48-1.40	.42	—	—	—
EGFR mutation (activating vs uncommon*)	1.00	0.61-1.62	.99	—	—	—
Symptom of BM (no vs yes)	0.50	0.29-0.92	.03	0.42	0.21-0.89	.02
Size of the largest BM (<1 vs ≥1 cm)	0.67	0.41-1.10	.11	0.67	0.36-1.26	.22
Extracranial metastasis (no vs yes)	0.60	0.32-1.07	.09	0.61	0.27-1.28	.20

Abbreviations: BM = brain metastasis; CCI = Charlson comorbidity index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HR = hazard ratio; LT = local therapy; OS = overall survival; TKI = tyrosine kinase inhibitor.

* *Activating* was defined as EGFR exon 19 deletion or EGFR exon 21 L858R. *Uncommon* was defined as other EGFR mutations.

WBRT as first-line therapy. For first-line treatment, the PFS and OS were similar between patients who received EGFR-TKIs plus WBRT and those who received EGFR TKIs alone (median PFS, 8.0 vs 8.1 months, $P = .71$; median OS, 22.3 vs undefined months; $P = .22$).[19] In another retrospective study, intracranial disease progression was less likely to be detected as a first progression site in patients treated with WBRT (24%) compared with 58% of patients treated with EGFR-TKI, whereas 71% of patients treated with SRS showed intracranial disease progression ($P = .004$).[25]

These findings could indicate that LT is a cornerstone of treatment for patients with EGFR-mutant NSCLC with limited BM, as borne out by their oligometastatic state. Hellman and Weichselbaum[30] first established a concept of the oligometastatic state, which can be improved by LT with radiation therapy or surgical resection in patients with limited metastases.[31,32] In a study of NSCLC in patients harboring EGFR mutations with oligometastases, LT was associated with longer PFS and OS.[33] Al-Halabi et al showed that almost 50% of EGFR-mutant patients experienced isolated failure of sites of original disease (primary/metastatic) after first-line EGFR-TKI, and PFS was longer in patients who experienced new-site failure compared with those with original-site failure.[34] Given that their data suggest that pre-existing site progression is likely to occur before new distant metastasis, LT could be effective.

Our results and those of previous studies also suggest that WBRT cannot give a survival benefit while being effective in controlling intracranial progression. In addition, WBRT to control brain metastasis can cause deterioration in cognitive functions and health-related quality of life.[9,20,35] The hallmarks of radiation-induced cognitive impairment are decrements in memory, attention, and executive function,[35,36] all with increased incidence and severity over time.[37] Cognitive impairments can cause earlier discontinuation of a systemic therapy. WBRT-treated patients tend to start EGFR-TKI treatment later than those treated with SRS because WBRT needs 2 to 3 weeks for completion. Mulvenna et al reported that WBRT was regarded as being of little use compared with the best supportive care in patients with NSCLC irrespective of EGFR mutation.[38] Therefore, physicians should give careful consideration to WBRT as an initial treatment, especially for NSCLC in patients harboring EGFR mutations.

This study has some limitations. First, conclusions are limited because of our small-cohort, retrospective study in a single institution, and the efficacies might be influenced by selection of upfront treatment. Complications or adverse

Table 4 Subsequent therapies in the subgroup of 1 to 4 brain metastases

Subsequent therapy	TKI group (N = 60)	LT group (N = 36)	*P* value
Patients with disease progression	55 (92%)	29 (81%)	—
Patients treated with second-line chemotherapy	34 (62%)	16 (55%)	.56
Patients treated with additional local therapies	25 (45%)	12 (41%)	.72
Patients treated with osimertinib	8 (15%)	4 (14%)	.93
Patients treated with other extracranial local therapies	28 (51%)	7 (24%)	.02

Abbreviations: LT = local therapy; TKI = tyrosine kinase inhibitor.

events could not be sufficiently evaluated because tools of cognitive function were not used. However, our study is one of few retrospective studies evaluating the treatment sequence for NSCLC with BM. Second, imaging and clinical evaluation frequency and the length of follow-up to BM were dependent on physicians' decisions. Third, LTs for BMs or other extracranial lesions were performed without EGFR-TKI in some patients with oligometastatic disease or oligorecurrence, and the inclusion of those patients could result in a bias in survival analysis. Finally, we could not compare modality of LTs because the choice of the modality was based on the number of BMs. At present, SRS alone can be considered in patients with more than 4 metastatic brain lesions, although there has been no randomized trial evaluating SRS efficacy for multiple BMs.[39] It is crucial to prospectively evaluate the optimal procedure for patients with EGFR-mutant NSCLC with BMs, with particular attention paid to the modality of LTs and number of BMs.

Conclusion

The present study suggests that upfront LT followed by EGFR-TKI is more effective for the survival of patients with untreated NSCLC who harbor EGFR mutations with 1 to 4 BMs compared with upfront EGFR-TKI, and that upfront LT has no survival benefit for those with $\geq$5 BM. LT for a limited number of BMs might be undertaken before EGFR-TKI in untreated patients with EGFR mutation with BM.

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和文要約

論文題名：Optimal Sequence of Local and EGFR-TKI Therapy for EGFR-Mutant Non-small cell lung cancer With Brain Metastases Stratified by Number of Brain Metastases
（**和訳：**脳転移を有するEGFR遺伝子変異陽性非小細胞肺癌に対する、局所療法とEGFR－TKIの最適な治療シーケンスについての、脳転移の個数による層別化による検討）

［背景］

非小細胞肺癌では脳転移をしばしば認め、その予後は不良である。このため脳転移に対する治療（全脳照射(WBRT)、定位照射(SRS)、手術）が標準治療となっている。EGFR遺伝子変異陽性の非小細胞肺癌では脳転移の発症頻度が高いことが知られているが、EGFRチロシンキナーゼ阻害薬(EGFR-TKI)が奏効するため脳転移を有していても数年の予後が見込める。しかしながら、EGFR-TKIの先行により、脳転移に対する治療先行よりも生存期間が劣ることが報告された。一方で、WBRTは時としてQOLに関連した重大な合併症を引き起こす可能性があるため、適応には慎重な判断が必要である。本研究は、脳転移を有する未治療のEGFR遺伝子変異陽性非小細胞肺癌患者を対象に、脳転移に対する治療の選択バイアスとなる脳転移の個数で層別化(一般的にSRSの適応となる1-4個と、≥5個で層別化)したサブグループを中心に、EGFR-TKI先行群と脳転移対する治療先行群の2群を比較することで最適な治療シーケンスを評価する。

［方法］

静岡がんセンターで2007年10月から2018年4月に初回化学療法としてEGFR-TKIで治療された脳転移を有するEGFR遺伝子変異陽性非小細胞肺癌患者の診療録を後方視的に検討した。
（補足１）OSは全患者で治療開始日を起点日として評価し、PFSはEGFR-TKIを投与された患者のみでEGFR-TKI開始日を起点日として評価した。

（補足2） SRSを中心とした脳転移に対する治療をEGFR-TKIに先行することが予後良好因子であるという過去の報告があるが、SRSが適応となるような症例は脳転移個数がそもそも少数である。脳転移の個数によって治療選択のバイアスが生じていると考え、脳転移個数を層別化した解析を行う必要性があると考え、本研究はSRSの適応となる1-4個を層別化因子とした。SRSの適応については、本文中のReference 8, 9と本邦の肺癌診療ガイドライン2019年版における「脳転移対する放射線治療の選択については、4個以下で腫瘍径3㎝程度であれば定位照射、それ以外の脳転移については全脳照射を行うのが基本的な考え方である」という記載を根拠とした。

(補足3)腫瘍の最大径も治療の選択バイアスとなる。しかしながら、本研究のコホート全体(176人)で、最大腫瘍径が2.5㎝以上となるのは15人、肺癌診療ガイドライン2019においてSRSが適応

外となる最大腫瘍径 3 ㎝以上となるのは8人と少数であるため検討ができないと判断した。このため、本研究では腫瘍径のカットオフ値を 1 ㎝(Reference 17. Magnuson et al の研究でのカットオフ値を参考)とした。本文中に腫瘍径の記載はしていないが論文の Supplementary Data 内の Table S2 で最大腫瘍径を記載した(添付資料③)。手術例では最大腫瘍径が WBRT・SRS 施行例と比較し有意に大きかったが、WBRT、SRS 間では大きな偏りはなかった。

[結果]

患者背景

176 人が本試験へ登録され、107 人(61%)が EGFR-TKI 先行(TKI 群)、69 人(39%)が脳転移に対する治療を先行(LT 群)していた。LT 群では症候性脳転移(39% vs 9%, p <0.01)、脳転移の腫瘍径 1 ㎝以上(78%vs40%, P <0.01)が TKI 群よりも多く、頭蓋外病変の頻度は低かった(64% vs 94%, P<0.01)。その他の患者背景は両群間で有意差はなかった。

（補足） 患者背景の表(Table 1)に記載のある Stage at diagnosis の項の I-III は術後再発を意味する。術後再発例(根治術後の脳転移再発例)も本研究では対象患者として含まれている。

生存結果

全生存期間(OS)は両群間で有意差を認めなかった(LT 群 28 ヵ月、TKI 群 23 ヵ月、HR 0.75、95% CI, 0.52-1.17, p=0.12)。脳転移の個数が 1-4 個の患者においては、LT 群は有意に TKI 群よりも良好な PFS(14 vs 9.1 ヵ月、HR 0.57、95% CI, 0.34-0.91, p=0.02)と OS(35 vs 23 ヵ月、HR 0.54、95% CI, 0.32-0.90, p=0.02)を示した。脳転移個数が 5 個以上の場合は PFS・OS ともに両群間で有意差はなかった。

(補足) 追加解析として、stage IV のみで両群間の OS・PFS を比較した。本研究と同様にコホート全体では両群間で OS・PFS ともに有意差は認めなかった(添付資料①)。脳転移個数 1-4 個と≥5 個での層別化解析では、1-4 個のサブループにおいて、OS では有意差はないものの LT 群で良好な傾向が示され、PFS では有意に LT 群が良好な結果となった。一方、脳転移≥5 個のサブグループでは OS・PFS ともに両群間に有意差は認めなかった(添付資料②)。

脳転移の病勢進行

病勢進行を認めた患者の内、初回増悪部位が脳の割合は両群間で有意差はなかった(LT 群 48% vs TKI 群 46%, p=0.78)。脳転移増悪までの期間中央値は LT 群で 22 ヵ月、TKI 群で 12 ヵ月であり、LT 群で有意に長かった(0.54、95% CI, 0.36-0.79, p<0.01)。

脳転移の個数が 1-4 個のサブグループ解析

脳転移の個数が 1-4 個のサブグループにおいて、年齢、性別、PS、脳転移の症候性、脳転移腫瘍径、頭蓋外病変の有無で調整した多変量解析においても脳転移に対する治療の先行が TKI

先行と比較し有意に良好な OS を示した(調整 HR 0.36, 95% CI, 0.19-0.66, p<0.01, Table 3)。(補足)コホート全体でも同様に多変量解析を行い、 脳転移に対する治療の先行が TKI 先行と比較し良好な OS である傾向があった(調整 HR 0.63, 95% CI, 0.40-1.00, p＝0.05, Table S3)。

[考察]

本研究は OS・PFS ともにコホート全体では、EGFR-TKI 先行に対する脳転移に対する治療先行の有効性を示すことはできなかったが、脳転移の個数が 1-4 個のサブグループにおいては脳転移に対する治療先行が有効であることを示した。これまでの先行研究においても、脳転移に対する治療の先行は EGFR-TKI 単独での治療と比較して生存を延長することが報告されている。しかしながら、SRS は脳転移の個数が限られた(一般的には 1-4 個)症例に適応があるため、過去の研究は選択バイアスの結果であった可能性がある。本研究は脳転移の個数別のサブグループ解析を行うことで、選択バイアスを除き、個数が限られる場合には脳転移に対する治療先行が有効であることを示した。

本研究と過去の研究いずれにおいても WBRT は頭蓋内病変の病勢制御は良好であるにも関わらず延命効果を示すことが出来ていない。しかも WBRT は認知機能の低下や QOL の低下をもたらすことが知られている。治療医は WBRT の適応については慎重に検討する必要がある。

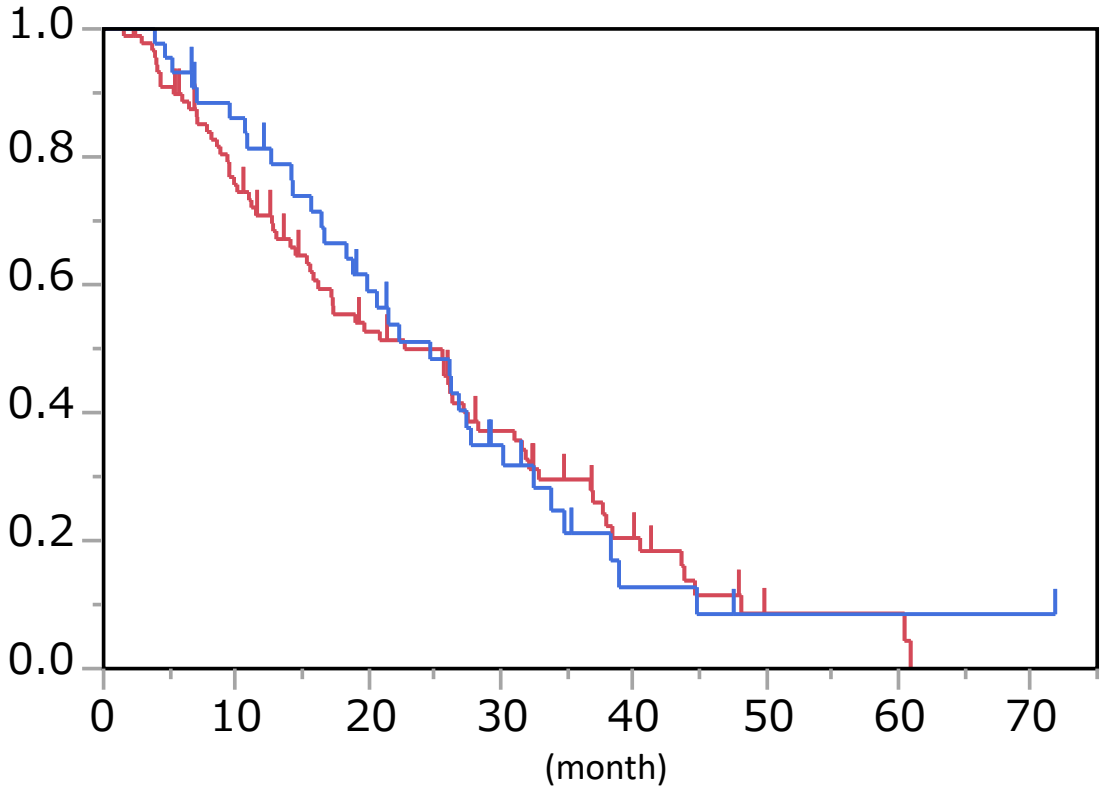
本研究にはリミテーションがいくつかある。単施設の後方視的研究であること、画像や臨床的評価の間隔に規定がないこと、脳転移に対する治療先行群には EGFR-TKI が投与されていない患者も含まれていること、脳転移に対する治療の方法についての比較ができていないことが挙げられる。

[結論]

1-4 個の脳転移を有する EGFR 遺伝子変異陽性肺癌において、EGFR-TKI に先行して脳転移に対する治療を行うことの有効性を示した。また、脳転移が 5 個以上の場合には脳転移に対する治療先行の有効性がないことも示した。

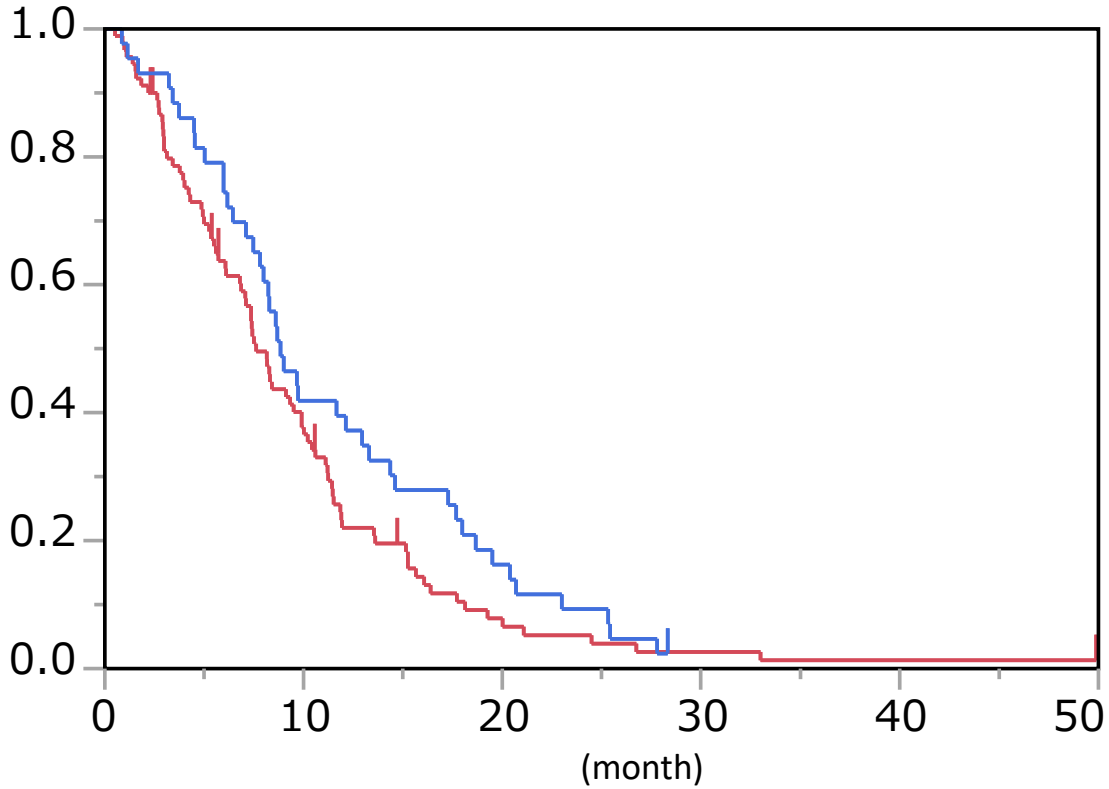
添付資料①

Figure. OS



	n	median	HR (95%CI)	*p*
LT-group	44	25 mo	0.95 (0.62 – 1.44)	0.80
TKI-group	90	23 mo		

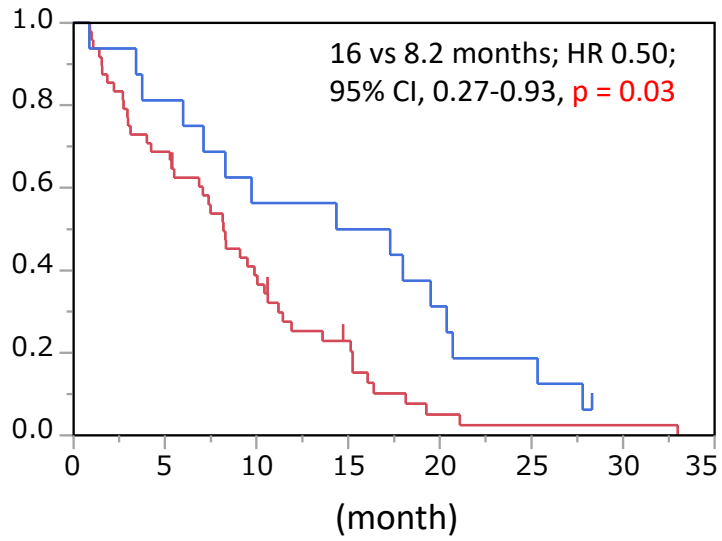
Figure. PFS



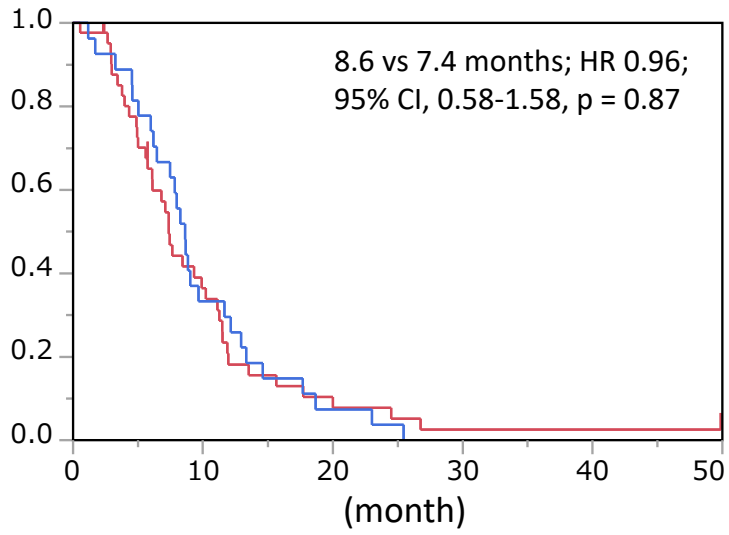
	n	median	HR (95%CI)	*P*
LT-group	44	8.8 mo	0.75 (0.51 – 1.09)	0.13
TKI-group	90	7.6 mo		

添付資料②

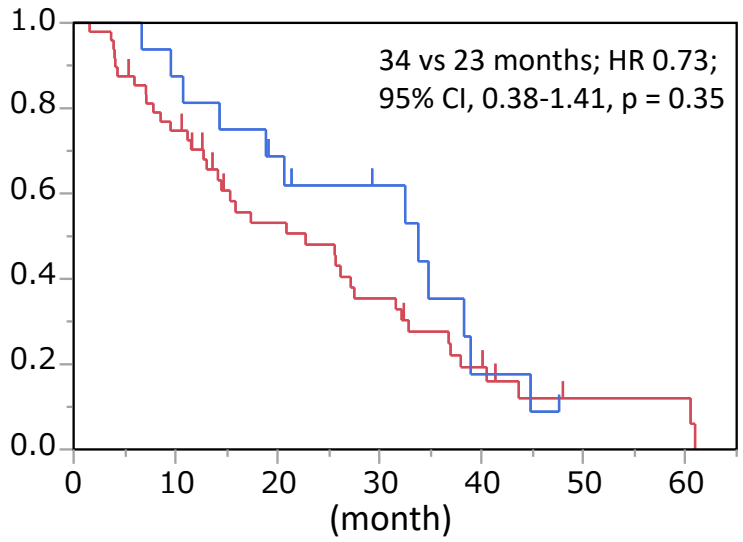
BM1-4個. PFS



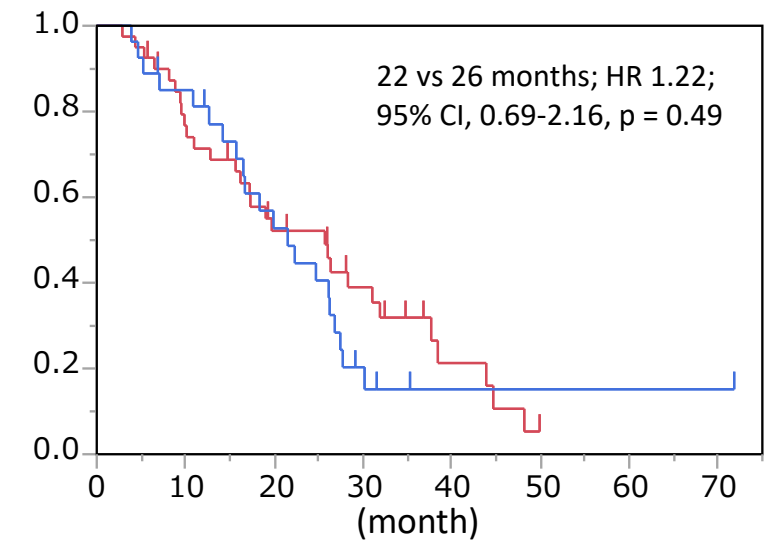
BM≥5個. PFS



BM1-4個. OS



BM≥5個. OS



添付資料③

Supplement

Table S1. stereotactic radiosurgery dose

	Whole patients (n = 36)	**Subgroup of 1 -4 BMs (n=31)**
GKS	14 (39%)	9 (29%)
18Gy	7	4
20Gy	4	4
21Gy	1	1
22Gy	1	0
N/D	1	0
Linear accelerators	12 (33%)	12 (39%)
20Gy	1	1
24Gy	3	3
25Gy	7	7
N/D	1	1
SRT	10 (28%)	10 (32%)
35Gy	2	2
30Gy	7	7
28Gy	1	1

Abbreviation: BM, brain metastasis; GKS, gamma-knife surgery; N/D, no data; SRT, stereotactic radiotherapy.

Table S2. Size of largest brain metastases

	TKI-group (n = 107)	**LT-group (n = 69)**	***P*-value**
Median (Range) (mm)	8 (1-35)	17 (3-56)	< .01

	WBRT (n = 27)	**SRS (n = 36)**	**Surgery (n = 6)**	***P*-value**
Median (Range) (mm)	16 (5-35)	14 (3-29)	34 (20-56)	< .01

Abbreviation: LT, local therapy; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiotherapy.

Table S3. Univariate and Multivariate Analysis of Covariables Associated with OS

Variable	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	***P-value***	**HR**	**95% CI**	***P-value***
Upfront therapy (LT vs EGFR-TKI)	0.75	0.52 – 1.07	.12	0.63	0.40 – 1.00	.05
Age (< 75 years vs ≥ 75 years)	0.76	0.52 – 1.13	.17	0.85	0.57 – 1.27	.41
Gender (female vs male)	0.79	0.86 – 1.82	.23	0.54	0.37 – 0.81	< .01
ECOG PS (0-1 vs 2-4)	0.44	0.30 – 0.64	< .01	0.49	0.33 – 0.73	< .01
Stage at diagnosis (I-III vs IV)	0.63	0.41 – 0.96	.03	0.94	0.57 – 1.50	.80
Smoking status (never vs current / former)	0.89	0.63 – 1.28	.54			
CCI (0 vs ≥ 1)	0.85	0.57 – 1.30	.45			
EGFR mutation (activating vs uncommon*)	1.00	0.70 – 1.42	.99			
Symptom of BM (no vs yes)	0.44	0.25 – 0.82	.01	0.47	0.29 – 0.78	< .01
Size of the largest BM (< 1cm vs ≥ 1cm)	0.63	0.43 – 0.96	.03	0.77	0.52 – 1.15	.20
Extracranial metastasis (no vs yes)	0.51	0.30 – 0.81	< .01	0.44	0.24 – 0.79	< .01

Abbreviation: BM, brain metastasis; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor - tyrosine kinase inhibitor; HR, hazard ratio; LT, local therapy.

* Activating was defined as EGFR exon 19 deletion or EGFR exon 21 L858R. Uncommon was defined as other EGFR mutations.

Table S4. Subsequent Therapies in whole patients

	TKI-group (n = 107)	**LT-group (n = 69)**	***P*-value**
Patients with disease progression	98 (92%)	62 (90%)	-
Patients treated with 2nd line chemotherapy	60 (61%)	35 (56%)	.55
Patients treated with additional local therapies	52 (53%)	25 (40%)	.12
Patients treated with osimertinib	19 (19%)	9 (15%)	.42
Patients treated with other extracranial local therapies	50 (51%)	21 (34%)	.03

Abbreviation: LT, local therapy; TKI, tyrosine kinase inhibitor.