Am J Cancer Res 2021;11(12):6160-6172
www.ajcr.us /ISSN:2156-6976/ajcr0137278

Original Article

Surgical resection of brain metastases prolongs overall survival in non-small-cell lung cancer

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Received July 12, 2021; Accepted November 15, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: It remains unclear whether surgical resection of brain metastases prolongs overall survival in patients with non-small-cell lung cancer (NSCLC). A retrospective study was designed to evaluate the benefits of surgical resection for 296 patients with NSCLC and brain metastases. Patients were grouped into those who underwent craniotomy (brain surgery group) and those who did not (non-surgery group). Characteristics, survival, and *EGFR* mutation status were compared between the two groups. We found that the clinical characteristics were similar between the two groups. However, patients in the brain surgery group had metastases of larger diameters (3.67 cm vs. 2.06 cm, P<0.001) and a lower rate of extracranial metastasis (8.7% vs. 45.5%, P=0.001). Overall survival was significantly longer for those who underwent brain surgery (40.3 months vs. 8.4 months, P<0.001). The adjusted hazard ratio of craniotomy was 0.30 (95% confidence interval [CI], 0.15-0.62). The survival benefit of brain surgery was observed in both *EGFR* mutation-positive and *EGFR* mutation-negative sub-populations; the adjusted hazard ratios [aHRs] were 0.34 [95% CI, 0.11-1.00] and 0.26 [95% CI, 0.09-0.73] for *EGFR* mutation-positive and mutation-negative sub-populations, respectively. We concluded that for patients with NSCLC and brain metastases, surgical resection of brain metastases improved overall survival. This survival benefit was particularly evident in cases with large-sized metastases limited to the brain.

Keywords: Non-small cell lung cancer, metastasectomy, brain metastases, EGFR, adenocarcinoma, ERBB receptors, brain neoplasms, operation, surgical procedures

Introduction

Brain metastases are a major problem in non-small cell lung cancer (NSCLC). Approximately 30% of patients with NSCLC develop brain metastases; about half of these patients have brain metastases at the time of diagnosis, while others develop brain metastases during periods of treatment [1, 2]. The incidence of brain metastases increases as patients live longer and is probably higher among those resistant to targeted therapies such as with gefitinib, erlotinib, afatinib, and crizotinib [3-6]. Targeted therapies have proved beneficial and improved overall survival of late-stage NSCLC over the past several decades [7, 8], and immune checkpoint inhibitors are expected to have similar benefits [9]. Hence, brain metastases are expected to increase following prolonged overall survival in the future.

Most patients with brain metastases have oligometastases [10]. For these patients, local treatment of brain metastases improves symptom control, quality of life, and survival time [11-13]. Currently, local treatments for brain metastases include whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection, either alone or in combination. The Radiation Therapy Oncology Group (RTOG) 9508 trial showed that the addition of SRS to WBRT improved the quality of life and

overall survival compared to WBRT alone [14]. Another study showed that the addition of WBRT to SRS did not improve overall survival [15]. Based on the above studies, SRS alone was considered the treatment of choice for brain metastases. However, not all patients are suitable for SRS. Only patients with 1-3 brain metastases and all lesions <3 cm benefited from SRS [15]. The role of SRS in patients with brain metastases larger than 3 cm or more than four in number is unclear.

A randomized case-control study in 1990 reported that surgical resection improved the survival of patients with single brain metastasis [16]. Hence, surgical resection of brain metastases may be beneficial for lesions with larger diameters. Compared to WBRT or SRS, surgical resection of brain metastases may not be restricted to the lesion diameter. However, the study population in the above study was heterogeneous and did not focus exclusively on NSCLC. Furthermore, other studies on surgical resection of brain metastases lacked comparison with control groups and showed no survival benefit.

The aim of this study was to evaluate the benefits of brain surgery for lung cancer with brain metastases. Hence, in this study, a retrospective observational design was undertaken to evaluate the survival benefit of surgical resection of brain metastases in patients with NSCLC.

Materials and methods

Study design and study population

This was a retrospective observational study. Consecutive patients were enrolled from January 1, 2011, to December 31, 2017, in MacKay Hospital, Taipei, Taiwan. Patients diagnosed before January 2011 were not included because of the unavailability of electronic medical records from the hospital. Medical records from the Lung Cancer Registry were reviewed; the data of all patients with pathologically diagnosed lung cancer are recorded in this registry. Among these patients, those with brain metastases were included in our study. The exclusion criteria were as follows: 1. patients who were lost to follow-up within 30 days after the initial diagnosis of brain metastasis; 2. cases with incomplete information, for example, because some patients were not initially diagnosed in our hospital, we could not obtain their formal pathology report and brain image; 3. patients with brain tumors that were immeasurable through imaging; and 4. patients with leptomeningeal metastasis, sarcoma, mesothelioma, or sarcomatoid cancer because the clinical courses of these cancers differ from that of other NSCLCs. The study protocol was approved by the institutional review board.

Measurements

For each patient, medical records including age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, presence of symptoms related to brain metastases, histology type, staging T and N at the time of brain metastasis, *EGFR* mutation status, size of brain tumor, number of brain tumors, presence of extracranial metastases, therapy administered, and clinical outcomes were recorded. *EGFR* positivity was defined as the presence of *EGFR* mutations that were sensitive to tyrosine kinase inhibitors (TKIs) whereas *EGFR* negativity was defined as the absence of *EGFR* mutation or presence of *EGFR* mutations that were not sensitive to TKI. The size of the brain tumor was defined as the largest diameter of the largest brain tumor in the brain images. The overall survival time in months was defined from the date of the diagnosis of brain metastasis to the date of death or the date of the last outpatient follow-up visit before September 10, 2019.

Statistical analysis

The Mann-Whitney U test and chi-square test were performed to compare the differences between groups for continuous and categorical data, respectively. Survival curves were derived using the Kaplan-Meier method, and the log-rank test was used to evaluate differences between curves. The adjusted hazard ratio (aHR) of brain surgery was estimated using multivariate Cox proportional hazards regression analysis. The Cox proportional hazards model with a stepwise selection method for optimizing the combination of variables was performed. The full model included all variables such as age (continuous data, directly used in the model), sex (female vs. male), smoking (Ever vs. Never), histology type (adenocarcinoma vs. non-adenocarcinoma), ECOG perfor-

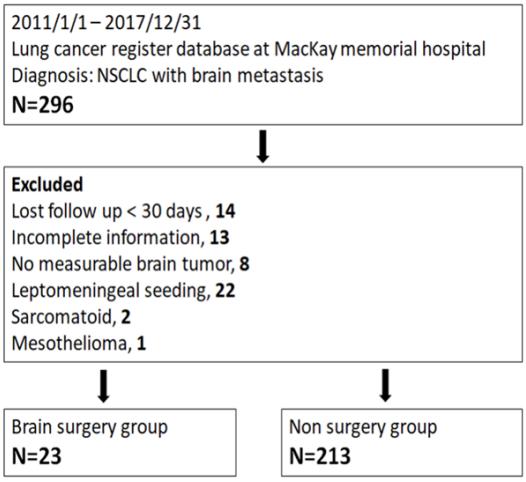

Figure 1. Flowchart for patient selection.

mance status (≥2 vs. <2), brain tumor size (continuous data, directly used in the model), number of brain tumors (>3 vs. ≤3), presence of symptoms caused by brain tumor (presence vs. absence), extra-CNS metastasis (presence vs. absence), history of brain surgery (yes vs. no), systemic treatment after brain metastasis, T stage representing the size and extent of metastatic tumor (T1-T2 vs. T3-T4), and N stage representing nodal involvement (N0-N1 vs. N2-N3). *EGFR*-positive and *EGFR*-negative patients were analyzed separately.

In addition, the nearest matching method for propensity score matching was also performed. We used 1:2 matching with matching factors, such as *EGFR* mutation status and the factors used in the Cox model selection.

All statistical analyses were performed using R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and *P*-values <0.05, were considered statistically significant.

Results

Patient characteristics

Data of 296 consecutive lung cancer patients with brain metastases were extracted from the Lung Cancer Registry database at MacKay Memorial Hospital (**Figure 1**). Among these patients, 60 were excluded from further analysis because 14 of them were lost to follow-up within 30 days, 13 were not diagnosed at our hospital and had incomplete pathological information, 8 had no measurable brain tumors in brain images upon review, 22 had leptomeningeal metastases, 2 had sarcomatoid lung cancer, and 1 had malignant mesothelioma. Ultimately, 236 patients were included in the study. Of which, 23 had undergone brain surgery for tumor resection (the brain surgery group), while 213 had not undergone brain surgery (the non-surgery group).

The characteristics of patients in both groups are presented in **Table 1**. The distributions of age, sex, smoking status, ECOG performance status, *EGFR* mutation status, radiation therapy for brain tumor, histology types, number of brain tumors, rate of symptoms related to brain tumor, and systemic treatments were not significantly different between the two groups. However, patients in the brain surgery group had larger brain tumor size (3.67 cm vs. 2.06 cm, P<0.001), lower rate of extracranial metastases (8.6% vs. 45.5%, P=0.001), lower T stage (T3-T4: 34.8% vs. 65.7%, P=0.007), and lower N stage (N2-N3: 39.1% vs. 69.5%, P=0.007) (**Table 1**).

In the *EGFR*-positive subgroup, those who had undergone brain surgery had larger brain tumor size (3.96 cm vs. 1.91 cm, P<0.001) and lower rate of extracranial metastasis (9.1% vs. 49.0%, P=0.002). In the *EGFR*-negative subgroup, patients who had undergone brain surgery had lower T stage (T3-T4: 16.7% vs. 65.8%, P=0.003) and N stage (N2-N3: 33.3% vs. 70.9%, P=0.02) (**Table 3**).

Complications after brain surgery

Among the 23 patients underwent brain surgery, one (4.3%) developed intracranial hemorrhage (ICH) after surgery. The patient died 26 days after brain surgery. Another patient (4.3%) developed vomiting 3 days after the surgery. The vomiting recovered after supportive treatment.

Survival of patients in brain surgery group vs. non-brain surgery group

Patients in the brain surgery group had significantly longer survival than those in the non-surgery group (40.3 months vs. 8.4 months, P<0.001, **Figure 2A**). The patients in the brain surgery group also had higher 1-year (78.378%

Table 1. Demographic data of patients in brain surgery group vs. non-surgery group

	Brian surgery group (n=23)	Non-surgery group (n=213)	*P*-value
Age, years (range)	60.0 (41-77)	62.7 (31-85)	0.25
Male sex, n (%)	13 (56.5)	114 (53.5)	0.96
Smoking, n (%)			0.85
Never	12 (52.2)	124 (58.2)	
Current	9 (39.1)	74 (34.7)	
Former	2 (8.7)	15 (7.0)	
ECOG Performance score, n (%)			1
<2	16 (69.6)	150 (70.4)	
≥2	7 (30.4)	63 (29.6)	
Histology, n (%)			0.30
Adenocarcinoma	22 (95.7)	182 (85.4)	
Non-adenocarcinoma	1 (4.3)	31 (14.6)	
T stage, n (%)			0.007
T1-T2	15 (65.2)	73 (34.3)	
T3-T4	8 (34.8)	140 (34.3)	
N stage, n (%)			0.007
N0-N1	14 (60.9)	65 (30.5)	
N2-N3	9 (39.1)	148 (69.5)	
EGFR mutation, n (%)			0.97
Positive	11 (47.8)	96 (45.0)	
Negative	12 (52.2)	117 (54.9)	
Brain lesion size (cm), mean (range)	3.67 (0.5-7.4)	2.06 (0.3-6.6)	<0.001
Brain lesion number, n (%)			0.47
≤3	19 (82.6)	156 (73.2)	
>3	4 (17.4)	57 (26.8)	
Extracranial metastasis, n (%)			0.001
Yes	2 (8.7)	97 (45.5)	
No	21 (91.3)	116 (54.5)	
Symptoms related to brain tumor, n (%)			0.05
Yes	23 (100)	174 (81.7)	
No	0 (0)	39 (18.3)	
Brain RT, n (%)			0.61
No	2 (8.7)	12 (5.6)	
WBRT	20 (87.0)	197 (92.5)	
SRS	1 (4.3)	4 (1.9)	
Systemic treatment after brain metastasis, n (%)			0.18
No	2 (8.7)	49 (23.1)	
Chemotherapy/Other*	9 (39.1)	87 (41.0)	
Targeted therapy	12 (52.2)	76 (35.8)	

*other: includes one immunotherapy and one clinical trial in the non-surgery group. Non-adenocarcinoma histology types included squamous cell carcinoma, adenosquamous carcinoma, pleomorphic carcinoma, large cell carcinoma, and carcinoma not otherwise specified. Positive EGFR mutations included EGFR L858R, del19, E746G + L861Q, L861Q, C719S, and G719A + I706T. RT, radiation therapy; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery.

[95% CI: 55.4%-90.3%]) and 5-year (45.76% [95% CI: 17.2%-70.5%]) survival than those in the non-surgery group (1-year: 36.3% [95% CI: 29.4%-43.2%]; 5-year: 8.79% [95% CI: 4.2%-15.2%]). After stepwise model selection, the covariates: age, sex, smoking status, T stage, symptoms related to brain tumor, extracranial metastasis, brain surgery, and systemic treat-

Table 2. Cox proportional hazards regression analysis for the overall survival

	aHR	95% CI	*P*-value
Age	1.02	1.01-1.04	0.006
Sex (Female)	1.50	1.02-2.22	0.04
Smoking (Ever vs. Never)	1.44	0.98-2.12	0.06
T stage (T3-4 vs. T1-2)	1.40	1.00-1.97	0.05
Presence of symptoms related to brain tumor	1.57	1.01-2.43	0.04
Presence of extracranial metastasis	1.45	1.05-1.99	0.02
History of brain surgery	0.36	0.18-0.72	0.004
Systemic treatment after brain metastasis			
Chemotherapy vs. no therapy	1.47	0.18-0.43	<0.001
TKI vs. no therapy	0.30	0.12-0.33	<0.001

Under "Smoking", the category "Ever smoker" includes both current and former smokers. Brain RT included whole brain RT and stereotactic radiosurgery. aHR, adjusted hazard ratio; CI, confidence interval; RT, radiation therapy; TKI, tyrosine kinase inhibitor.

ment after brain metastasis were included in the Cox proportional hazard regression analysis. Older age (aHR=1.02 [95% CI, 1.01-1.04], P=0.006), female sex (aHR=1.5 [95% CI, 1.02-2.22], P=0.04), history of brain surgery (aHR=0.36 [95% CI, 0.18-0.72], P=0.004), presence of symptoms related to brain tumor (aHR=1.57 [95% CI, 1.01-2.43], P=0.04), presence of extracranial metastasis (aHR=1.45 [95% CI, 1.05-1.99], P=0.02), and systemic treatment after brain metastasis (chemotherapy vs. no therapy, aHR=0.27 [95% CI, 0.18-0.43], P<0.001; TKI vs. no therapy, aHR=0.20 [95% CI, 0.12-0.33], P<0.001) emerged as significant factors (**Table 2**).

To consolidate the selection bias from the non-brain surgery group, propensity score matching was performed. After propensity score matching, all the matching factors were balanced (**Table 5**). The benefits of brain surgery were robust. The median survival time of patients who had undergone brain surgery was 40.3 months (95% CI: 16.3-not determined), which was significantly longer than the median survival time of patients who had not undergone brain surgery (10.1 months [95% CI: 3.87-16.8], P<0.001). The hazard ratio of brain surgery was 0.25 (95% CI: 0.12-0.54, P<0.001) (**Figure 3A**).

Patients in EGFR mutation-positive and EGFR mutation-negative subgroups

Because clinical courses and treatment responses differ with *EGFR* mutation positivity or negativity, patients were stratified into *EGFR* mutation-positive and negative groups for further analysis.

In both groups, patients who had undergone brain surgery group had longer survival (40.3 months vs. 11.3 months, P=0.024 in *EGFR* mutation-positive group; 37.6 months vs. 5.8 months, P<0.001 in *EGFR* mutation-negative group) (**Figure 2B** and **2C**). The aHR for brain surgery significant for both groups (aHR=0.33 [95% CI, 0.12-0.89], P=0.03 for *EGFR* mutation-positive group; aHR=0.34 [95% CI, 0.13-0.93], P=0.04 for *EGFR* mutation-negative group) (**Table 4**). In the *EGFR* mutation-positive group, older age was negatively associated with survival (aHR=1.03 [95% CI, 1.01-1.06]). In both *EGFR* mutation-positive and mutation-negative groups, systemic treatment with TKI after discovery of brain metastasis was associated with better survival.

After propensity score matching, the brain lesion size in the EGFR mutation-positive group was significantly larger among those who had undergone brain surgery (n=11) than among those who had not undergone brain surgery (n=25) (3.96 cm vs. 2.54 cm, P=0.006). All other factors were balanced. In the *EGFR* mutation-negative subgroups, all factors were balanced (**Table 6**). Survival analysis of both *EGFR* mutation-positive and mutation-negative subgroups after propensity score matching was performed using the Cox proportional hazards model. Brain surgery showed a statistically significant survival benefit (HR=0.25 [95% CI: 0.12-0.54]) (**Figure 3B** and **3C**).

Discussion

In this study, 23 and 213 NSCLC patients, with and without a history of brain surgery, respectively, were enrolled, and their prognoses were compared. Results showed that overall survival was prolonged in the brain surgery group (40.3 months vs. 8.4 months, P<0.001) and the aHR of craniotomy was 0.36 ([95% CI, 0.11-1.00], P=0.004). The survival benefit of brain surgery

Table 3. Demographic data of patients in brain surgery group vs. non-surgery group in EGFR mutation-positive and mutation-negative subgroups

	EGFR mutation-positive (n=107)		*P*-value	*EGFR* mutation-negative (n=129)		*P*-value
	Brian surgery group (n=11)	Non-surgery group (n=96)		Brian surgery group (n=12)	Non-surgery group (n=117)	
Age (range)	63.1 (51-74)	40 (33-84)	0.77	57.1 (41-77)	63.0 (31-85)	0.09
Male sex, n (%)	3 (27.3)	40 (41.7)	0.55	10 (83.3)	74 (63.2)	0.28
Smoking, n (%)			0.79			0.56
Never	8 (72.7)	67 (69.8)		4(33.3)	57 (48.7)	
Current	2 (18.2)	24 (25.0)		7 (58.3)	50 (42.7)	
Former	1 9.1	5 (5.2)		1 (8.3)	10 (8.5)	
ECOG performance score, n (%)			0.48			0.66
<2	7 (63.6)	75 (78.1)		9 (75)	75 (64.1)	
≥2	4 (36.4)	21 (21.9)		3 (25)	42 (35.9)	
Histology, n (%)			1			0.33
Adenocarcinoma	11 (100)	95 (99.0)		11 (91.7)	87 (74.4)	
Non-adenocarcinoma	0 (0)	1 (1)		1 (8.3)	30 (25.6)	
T stage, n (%)			0.69			0.003
T1-T2	5 (45.5)	33 (34.4)		10 (83.3)	40 (34.2)	
T3-T4	6 (54.5)	63 (65.6)		2 (16.7)	77 (65.8)	
N stage, n (%)			0.26			0.02
N0-N1	6 (54.5)	31 (32.3)		8 (66.7)	34 (29.1)	
N2-N3	5 (45.5)	65 (67.7)		4 (33.3)	83 (70.9)	
Brain lesion size, mean (range)	3.96 (2.5-6)	1.91 (0.4-5.7)	<0.001	3.39 (0.5-7.4)	2.19 (0.3-6.6)	0.05
Brain lesion number, n (%)			1			0.33
≤3	8 (72.7)	69 (71.9)		11 (91.7)	87 (74.4)	
>3	3 (27.3)	27 (28.1)		1 (8.3)	30 (25.6)	
Extracranial metastasis, n (%)			0.002			0.06
Yes	1 (9.1)	49 (49.0)		11 (91.7)	69 (59.0)	
No	10 (90.9)	47 (51.0)		1 (8.3)	48 (41.0)	
Symptoms related to brain tumor, n (%)			0.17			0.33
Yes	11 (100)	74 (77.1)		12 (100)	100 (85.5)	
No	0 (0)	22 (22.9)		0 (0)	17 (14.5)	
Brain RT, n (%)			1			0.32
No	0 (0)	4 (4.2)		2 (16.7)	8 (6.8)	
WBRT	11 (100)	92 (95.8)		9 (75.0)	105 (89.7)	
SRS				1 (8.3)	4 (3.4)	
Systemic treatment after brain surgery, n (%)			0.22			0.59
No	0 (0)	14 (14.7)		2 (16.7)	35 (29.9)	
Chemotherapy/Other	1 (9.1)	18 (18.9)		8 (66.7)	69 (59.0)	
Targeted therapy	10 (90.9)	63 (66.3)		2 (16.7)	13 (11.1)	

RT, radiation therapy; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery.

was observed in both *EGFR* mutation-positive and mutation-negative sub-populations (aHR= 0.33 [95% CI, 0.12-0.89], P=0.03 and aHR= 0.34 [95% CI, 0.13-0.93], P=0.04 for EGFR mutation-positive and mutation-negative groups, respectively). Our study showed that surgical resection of metastatic lesions in the brain greatly improved overall survival in patients with NSCLC who developed brain metastases. This benefit was more obvious for patients with T1-T2 and N0-N1 disease, less than three brain tumors, and metastases limited to the brain.

Three randomized control trials (RCTs) have been previously conducted to compare outcomes of brain surgery plus WBRT with those of WBRT alone in the treatment of single brain metastasis. The overall survival benefit of brain surgery noted in two of these three RCTs is consistent with our results. However, these trials were not specific for lung canc-

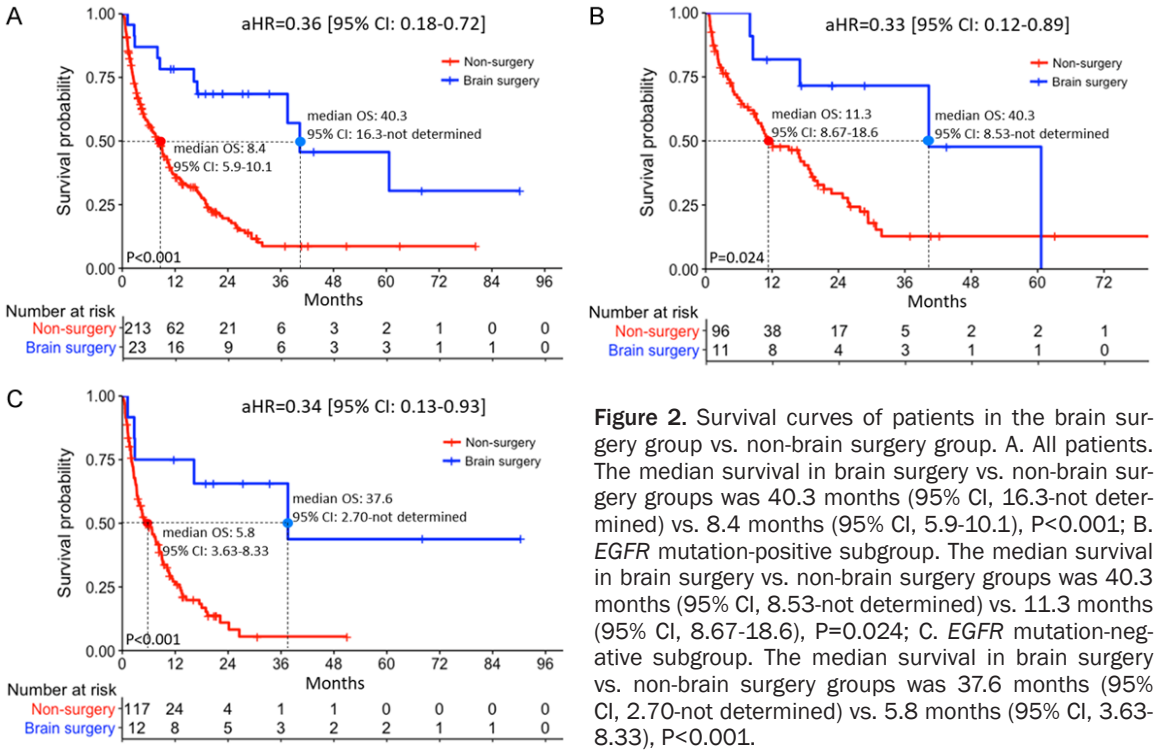

Figure 2. Survival curves of patients in the brain surgery group vs. non-brain surgery group. A. All patients. The median survival in brain surgery vs. non-brain surgery groups was 40.3 months (95% CI, 16.3-not determined) vs. 8.4 months (95% CI, 5.9-10.1), P<0.001; B. *EGFR* mutation-positive subgroup. The median survival in brain surgery vs. non-brain surgery groups was 40.3 months (95% CI, 8.53-not determined) vs. 11.3 months (95% CI, 8.67-18.6), P=0.024; C. *EGFR* mutation-negative subgroup. The median survival in brain surgery vs. non-brain surgery groups was 37.6 months (95% CI, 2.70-not determined) vs. 5.8 months (95% CI, 3.63-8.33), P<0.001.

Table 4. Cox proportional hazards regression analysis for comparing overall survival in EGFR mutation-positive and mutation-negative subgroup

	EGFR mutation-positive			*EGFR* mutation-negative		
	aHR	95% CI	*P*-value	aHR	95% CI	*P*-value
Age	1.03	1.01-1.06	0.005	1.01	0.99-1.03	0.29
Sex (Female vs. male)	1.37	0.76-2.48	0.30	1.59	0.94-2.70	0.08
Smoking (Ever vs. Never)	1.57	0.87-2.83	0.13	1.32	0.80-2.20	0.28
T stage (T1-2 vs. T3-4)	1.68	0.98-2.89	0.06	1.26	0.79-2.01	0.33
Presence of symptoms related to brain tumor	1.97	1.00-3.87	0.05	1.34	0.74-2.44	0.33
Presence of extra-cranial metastasis	1.57	0.93-2.65	0.09	1.48	0.97-2.25	0.07
Receiving brain surgery	0.33	0.12-0.89	0.03	0.34	0.13-0.93	0.04
Systemic treatment after brain metastasis						
Chemotherapy vs. no therapy	0.22	0.09-0.55	0.001	0.28	0.17-0.46	<0.001
TKI vs. no therapy	0.24	0.11-0.55	<0.001	0.31	0.14-0.68	0.003

aHR, adjusted hazard ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor.

er, and they were reported in 1990s when *EGFR* TKIs were still not a treatment choice [16-18].

Even in the era of *EGFR* TKIs, stage IV lung cancer has a very poor prognosis and is considered incurable. The 5-year survival rate is reported to be less than 5% for stage IV patients not treated with EGFR-TKI therapy and approximately 15% for those treated with gefitinib or erlotinib, which are first-generation TKIs [19, 20]. Moreover, the 5-year survival rate is noticeably worse for patients with brain metastases [21, 22]. The majority of NSCLC patients with brain metastases are treated systemically and palliatively, while brain surgery is seldom considered as a treatment option. For patients with targetable *EGFR* mutations, TKI has shown a favorable intracranial response rate from 33% to 88% [1]. However, despite the favorable response rate, the 5-year survival rate remains low [21, 22]. Although second-generation TKIs

Table 5. Demographic data of patients in the brain surgery group vs. non-surgery group after propensity score matching (1:2 matching)

	Brian surgery group (n=23)	Non-surgery group (n=46)	*P*-value
Age (range)	60.0 (41-77)	61.7 (31-82)	0.53
Male sex, n (%)	13 (56.5)	29 (63.0)	0.79
Smoking, n (%)			0.80
Never	12 (52.2)	21 (45.7)	
Ever	11 (47.8)	25 (54.3)	
ECOG performance score, n (%)			0.77
<2	16 (69.6)	35 (76.1)	
≥2	7 (30.4)	11 (23.9)	
Histology, n (%)			0.87
Adenocarcinoma	22 (95.7)	42 (91.3)	
Non-adenocarcinoma	1 (4.3)	4 (8.7)	
T stage			0.44
T1-T2	15 (65.2)	24 (52.2)	
T3-T4	8 (34.8)	22 (47.8)	
N stage			0.35
N0-N1	14 (60.9)	21 (45.7)	
N2-N3	9 (39.1)	25 (54.3)	
EGFR mutation status			0.80
Positive	11 (47.8)	25 (54.3)	
Negative	12 (52.2)	21 (45.7)	
Brain lesion size, mean (range)	3.67 (0.5-7.4)	2.93 (0.8-6.6)	0.09
Brain lesion number, n (%)			1
≤3	19 (82.6)	38 (82.6)	
>3	4 (17.4)	8 (17.4)	
Extracranial metastasis, n (%)			1
Yes	2 (8.7)	5 (10.9)	
No	21 (91.3)	41 (89.2)	
Symptoms related to brain tumor, n (%)			NA
Yes	23 (100)	46 (100)	
No	0 (0)	0 (0)	
Brain RT, n (%)			1
No RT	2 (8.7)	4 (8.7)	
Brain RT	21 (91.3)	42 (91.3)	
Systemic treatment after brain metastasis, n (%)			0.39
No	2 (8.7)	10 (21.7)	
Chemotherapy	9 (39.1)	14 (30.4)	
Targeted therapy	12 (52.2)	22 (47.8)	

RT, radiation therapy; Brain RT included whole brain radiation therapy and stereotactic radiosurge.

like afatinib can bind to *EGFR* irreversibly, their superiority to first-generation TKIs (for e.g., gefitinib) in prolonging OS was not observed in the LUX-Lung 7 randomized control trial. In a subgroup analysis of 26 patients with brain metastasis in the LUX-Lung 7 trial, there was no statistically significant benefit of afatinib to gefitinib [23]. These results were consistent with those of a real-world study wherein the OS benefit of afatinib to gefitinib or erlotinib for *EGFR*-mutated lung cancer with brain metastasis could not be demonstrated [24]. It has been

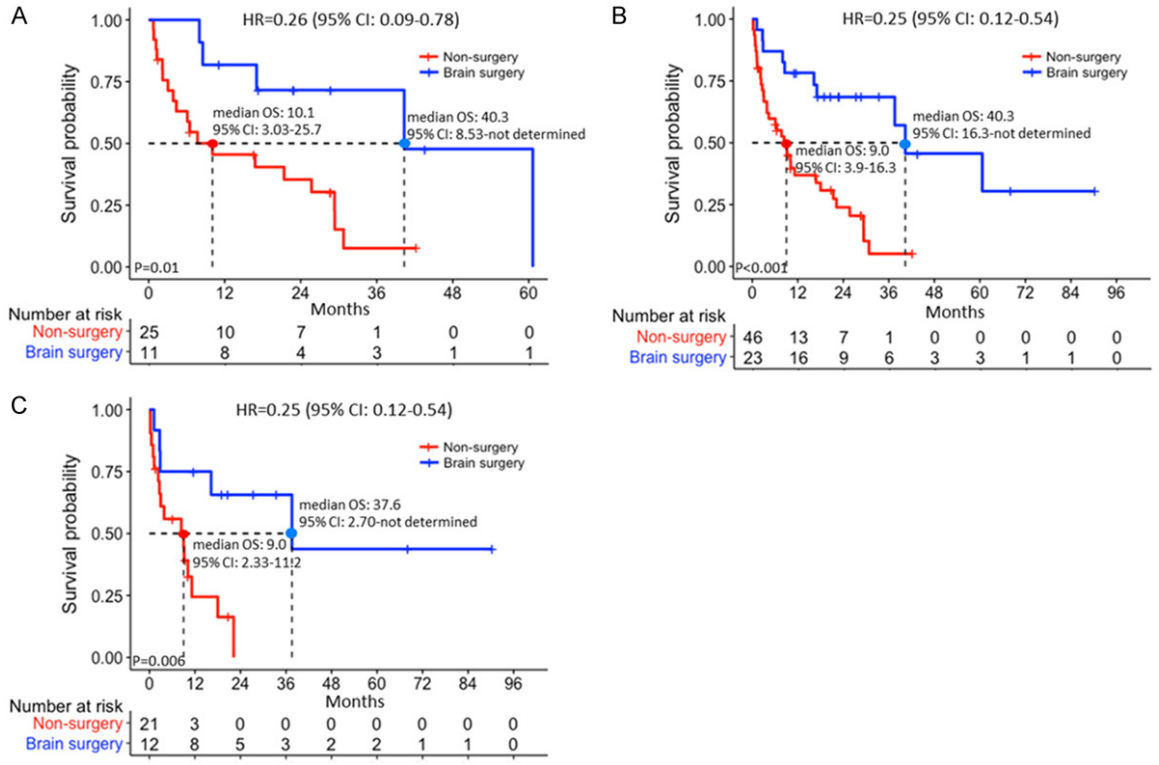

Figure 3. Survival curves of patients in the brain surgery group vs. non-brain surgery group after propensity score matching. A. All matched patients. 23 patients had undergone brain surgery, while 46 patients had not undergone brain surgery. The median survival in brain surgery vs. non-brain surgery groups was 40.3 months (95% CI, 16.3-not determined), vs. 9.0 months (95% CI, 3.87-16.8), P<0.001. Hazard ratio =0.25 (95% CI: 0.12-0.54). B. EGFR mutation-positive subgroup. 11 patients had undergone brain surgery while 25 had not undergone brain surgery. The median survival in brain surgery vs. non-brain surgery groups was 40.3 months (95% CI, 8.53-not determined), vs. 10.1 months (95% CI, 3.03-25.7), P=0.01. Hazard ratio =0.26 (95% CI: 0.09-0.78). C. EGFR mutation-negative subgroup. 12 patients had undergone brain surgery while 21 patients had not undergone brain surgery. The median survival in brain surgery vs. non-brain surgery groups was 37.6 months (95% CI, 2.70-not determined) vs. 9.0 months (95% CI, 2.33-11.2), P=0.006, hazard ratio =0.22 (95% CI: 0.07-0.70).

shown that osimertinib, a third-generation TKI, had a superior overall survival benefit than did a first-generation TKI (gefitinib) for treatment of *EGFR*-mutated lung cancer with brain metastasis [25]. The use of third-generation TKI is an important confounding factor in the outcome of brain metastasis. However, no patients in the present study had received osimertinib because during the study period, osimertinib was still not reimbursed by the general health insurance in Taiwan.

Local brain therapies, including surgery, are generally used only in patients with symptoms related to metastases but could provide more than just symptom relief. Studies have shown that local brain therapies improve survival in patients with lung cancer and brain metastasis, especially in those with oligometastasis [11, 13, 26]. The findings of our study corroborate those of previous studies. However, the mainstay of local brain therapy in previous studies was SRS. Our study focused on surgery as a local therapy and showed that the surgical treatment of brain metastases improved survival in NSCLC with brain metastases, achieving a 5-year survival rate of 46%. Regardless of *EGFR* mutation status, brain surgery remains a strong prognostic factor for better survival. Local therapy for intracranial tumor control should thus be considered an important treatment to prolong survival. Whether SRS or surgery is better for local control of brain metastases remains debatable; nonetheless, surgery should at least be considered for those cases not suitable for SRS.

In the *EGFR* mutation-negative subgroup, we found that TKI use for brain metastasis is also an independent prognostic factor associated

Table 6. Demographic data of patients in brain surgery group vs. non-surgery group in EGFR mutation-positive and mutation-negative subgroup after propensity score matching

	EGFR mutation-positive (n=36)		*P*-value	EGFR mutation-negative (n=33)		*P*-value
	Brain surgery group (n=11)	Non-surgery group (n=25)		Brain surgery group (n=12)	Non-surgery group (n=21)	
Age (range)	63.1 (51-74)	63.5 (50-82)	1	57.1 (41-77)	59.7 (31-79)	0.52
Male sex, n (%)	3 (27.3)	11 (44.0)	0.56	10 (83.3)	18 (85.7)	1
Smoking, n (%)			0.72			1
Never	8 (72.7)	15 (60.0)		4 (33.3)	6 (28.6)	
Ever	3 (27.3)	10 (40.0)		8 (66.7)	15 (71.4)	
ECOG performance status, n (%)			0.72			1
<2	7 (63.6)	19 (76.0)		9 (75)	16 (76.2)	
≥2	4 (36.4)	6 (24.0)		3 (25)	5 (23.8)	
Histology, n (%)			NA			0.75
Adenocarcinoma	11 (100.0)	25 (100.0)		11 (91.7)	17 (19.0)	
Non-adenocarcinoma	0 (0)	0 (0)		1 (8.3)	4 (81.0)	
T stage, n (%)			1			0.16
T1-T2	5 (45.5)	13 (52.0)		10 (83.3)	11 (52.4)	
T3-T4	6 (54.5)	12 (48.0)		2 (16.7)	10 (47.6)	
N stage, n (%)			1			0.22
N0-N1	6 (54.5)	13 (52.0)		8 (66.7)	8 (38.1)	
N2-N3	5 (45.5)	12 (48.0)		4 (33.3)	13 (61.9)	
Brain lesion size, mean (range)	3.96 (2.5-6)	2.54 (0.8-5.7)	0.006	3.39 (0.5-7.4)	3.39 (1.1-6.6)	0.82
Brain lesion number, n (%)			0.96			1
≤3	8 (72.7)	20 (80)		11 (91.7)	18 (85.7)	
>3	3 (27.3)	5 (20)		1 (8.3)	3 (14.3)	
Extracranial metastasis, n (%)			0.98			1
Yes	1 (9.1)	4 (16.0)		11 (91.7)	20 (95.2)	
No	10 (90.9)	21 (84.0)		1 (8.3)	1 (4.8)	
Symptoms related to brain tumor, n (%)			NA			NA
Yes	11 (100)	25 (100)		12 (100)	21 (100)	
No	0 (0)	0 (0)		0 (0)	0 (0)	
Brain RT, n (%)			0.86			0.32
No	0 (0)	2 (8)		2 (16.7)	2 (9.5)	
WBRT	11 (100)	23 (92)		9 (75.0)	19 (90.5)	
SRS				1 (8.3)	0 (0)	
Systemic treatment after brain surgery, n (%)			0.30			0.41
No	0 (0)	3 (12)		2 (16.7)	7 (33.3)	
Chemotherapy	1 (9.1)	5 (20)		8 (66.7)	9 (42.9)	
Targeted therapy	10 (90.9)	17 (68)		2 (16.7)	5 (23.8)	

with longer survival. In the TAILOR trial, a 26% disease control rate of TKI was still observed in the *EGFR* mutation-negative group [27]. Contrastingly, EGFR-mutated NSCLCs have a predilection to spread to the brain. Considering the tumor heterogeneity and the fact that many brain metastases in our study population developed after first-line treatment, using brain surgery plus TKI may lead to a higher response rate and better survival.

There are some limitations to our study. First, it was a retrospective study and was prone to selection bias. We believe that it is quite difficult to conduct a randomized controlled trial in such cases particularly because brain tumor resection is a highly invasive technique. Patients with lung cancer tend to be older, have poor ECOG performance, and may not be suitable for surgery. The sample sizes populations of previously published RCTs on brain surgery were also small. However, further clarifications are needed to determine cases in which brain surgery is a suitable and unsuitable treatment option. Second, most of the patients in the surgery group had less than or equal to three brain

tumors and had metastases limited to the brain. Our findings may not be applicable to patients with extracranial metastases or more than three brain metastases. Hong et al. reported the outcomes of 51 NSCLC patients with symptomatic brain metastases who underwent resection of cerebral lesions. Thirteen of these patients had total resections and 38 had resections of symptomatic lesions only. There was no difference in survival between the two groups [28]. Hence, for patients with more than three brain lesions, it may be beneficial to remove some of the tumors if complete resection is not feasible. Third, we did not include brain tumor volume as a prognostic confounding factor. The total brain tumor volume and the largest brain tumor volume have been considered prognostic factors in patients with brain metastasis [29, 30]. Instead, we included the largest brain tumor diameter and number of brain metastases in our analysis because metastatic brain tumors tend to be round or ovoid [31], and the largest brain tumor diameter reflects the brain disease burden.

Patients without extracranial metastases and good ECOG performance have been found to live longer after resection of brain metastases [32]. Generally, patients are considered unsuitable for SRS if the largest brain tumor is larger than 3 cm. As mentioned above, surgical resection can be performed in patients with brain tumors larger than 3 cm, good ECOG performance, and no extracranial metastases. Thus, it may be possible to resolve the limitations of the SRS. Of the 213 patients in the non-surgery group in this study, 36 fulfilled those criteria, suggesting that the resection of brain tumors is probably underutilized in our institution. Meanwhile, multidisciplinary team management has been shown to improve survival in NSCLC and is recommended as a key part of the best cancer care [33-35]. However, neurosurgeons are usually not included in the multidisciplinary team. This could be one of the reasons why surgical resection of brain metastases is underutilized. Our study showed, however, that neurosurgeons can play a critical role in improving the survival of NSCLC patients with brain metastases. The findings of this study suggest that neurosurgeons should participate in multidisciplinary cancer care management of patients with NSCLC and brain metastases.

In conclusion, this study showed that surgical resection of brain metastases may improve overall survival in NSCLC patients with brain metastases regardless of *EGFR* mutation status, especially among patients with no extracranial metastases. Neurosurgeons are recommended to play a role in making treatment decisions to manage brain metastases in such patients.

Acknowledgements

This research was supported by Academia Sinica, the Ministry of Science and Technology (AS-GC-110-MD06, AS-KPQ-107-TCPMP, AS-104-TP-A07, MOST 104-0210-01-09-02, MOST 105-0210-01-13-01, MOST 106-0210-01-15-02, MOST 105-2314-B-008-002), and the Taiwan Biosignature Project of Lung Cancer. The authors thank the National Center for High-performance Computing (NCHC) of the National Applied Research Laboratories (NARLabs) in Taiwan for providing computational and storage resources (MOST108-2319-B-492-001), the Pharmacogenomics Laboratory (PGL) of National Research Program for Biopharmaceuticals (NRPB) for provision of materials, and the Mathematics in Biology Group of Institute of Statistical Science AS for aiding with biostatistics.

Disclosure of conflict of interest

None.

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