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Original Article

Clinical outcome analysis of non-small cell lung cancer patients with brain metastasis receiving metastatic brain tumor resection surgery: a multicenter observational study

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Abstract: Brain metastasis is most common in primary non-small cell lung cancer (NSCLC), and some patients require neurosurgical resection for intracranial disease control. Because advances in systemic therapies for metastatic NSCLC have been developed in the past decade, we aimed to analyze and determine clinical factors associated with the postresection survival of NSCLC patients with brain metastasis who underwent neurosurgery followed by systemic therapy. Between January 2017 and December 2021, data for 93 NSCLC patients with brain metastasis treated with neurosurgery followed by systemic therapy at Linkou, Kaohsiung and Chiayi Chang Gung Memorial Hospitals were retrospectively retrieved for analysis. For all study patients, median postresection survival was 34.36 months (95% confidence interval (CI), 28.97-39.76), median brain metastasis (BM)-free survival was 26.90 months (95% CI, 22.71-31.09), and overall survival (OS) was 41.13 months (95% CI, 34.47-47.52). In multivariate analysis, poor performance status (Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2) and concurrent liver metastasis were identified as independent unfavorable factors associated with significantly shortened postresection survival (P<0.001). The histological type adenocarcinoma was associated with significantly longer postresection survival (P = 0.001). The median postresection survival for adenocarcinoma and nonadenocarcinoma patients was 36.23 and 10.30 months, respectively (hazard ratio (HR) = 0.122; 95% CI, 0.035-0.418; P<0.001); that for patients with and without concurrent liver metastasis was 11.43 and 36.23 months, respectively (HR = 22.18; 95% CI, 5.827-84.459; P<0.001). Patients with preserved ECOG PS, adenocarcinoma histology type and no concurrent liver metastasis appeared to have better postresection survival than nonadenocarcinoma patients. Our results provide counseling and decision-making references for neurosurgery feasibility in NSCLC patients with brain metastasis.

Keywords: Non-small cell lung cancer (NSCLC), brain tumor, brain metastasis, neurosurgery, adenocarcinoma

Introduction

Brain metastatic tumors from primary non-small cell lung cancer (NSCLC) are frequent malignant brain metastatic tumors, and approximately 40%-50% of NSCLC patients experience brain metastasis throughout their whole disease course [1, 2]. Brain metastasis is a major morbidity associated with unfavorable prognosis in NSCLC, and patient survival is

shorter than 3 months if no treatment is administered [1-3]. In recent decades, there have been advances in systemic treatments for metastatic lung cancer. Several drugs targeting specific cancer driver mutations as well as immune checkpoint inhibitor (ICI) immunotherapy have been developed and have improved the survival of NSCLC patients with metastasis [4-9]. For example, previous clinical studies have shown that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) inhibitors are effective in controlling brain metastatic NSCLC harboring EGFR or ALK mutations [6, 10]. Anti-programmed death receptor-1 (PD-1)/programmed death ligand 1 (PD-L1) ICIs have also been reported to be effective for treatment of brain metastasis in lung cancer [11, 12].

Despite advances in targeted therapies and immunotherapy, local therapies such as surgical resection, stereotactic body radiation therapy (SBRT), and whole-brain radiotherapy (WBRT) have been primarily used as treatment modalities for brain metastasis of NSCLC [12, 13]. Brain tumor resection surgery plays a key role in various cancer patients with brain metastasis, especially for those with undetermined primary sites, large intracranial tumor burdens, or neurologic symptoms due to mass effects and vasogenic edema. Surgery can provide tissue samples for molecular testing and immediately address brain metastasis-related neurologic symptoms [14, 15]. Despite such recent advances in anticancer systemic therapy for NSCLC, resection surgery is performed for some NSCLC patients with brain metastasis in clinical practice, but the outcome of these patients is not clear.

In this study, we sought to perform a retrospective analysis of the clinical outcome of NSCLC patients with brain metastasis receiving neurosurgery followed by systemic therapy. We aimed to determine clinical factors associated with postresection survival and identify NSCLC brain metastatic patients whose survival may benefit from neurosurgery.

Methods

Patients and follow-up

Between January 2017 and December 2021, 106 patients with histologically diagnosed primary lung cancer with brain metastasis who underwent brain metastatic tumor resection surgery were screened retrospectively from the cancer center database at Linkou, Chiayi and Kaohsiung Chang Gung Memorial Hospitals (CGMHs). Ninety-three patients were ultimately included in the study for analysis. The inclusion criteria were as follows: (1) non-small cell lung cancer (NSCLC) histological type in primary lung cancer; (2) metastatic NSCLC histological type of the resected brain tumor; (3) brain metastasis-induced symptom relief through surgery; and (4) systemic treatment (targeted therapy, immunotherapy or chemotherapy) after surgery. The exclusion criteria were as follows: (1) primary histological type of small cell lung cancer (SCLC); (2) SCLC or non-NSCLC histological type for the resected brain metastatic tumor; (3) diagnostic surgery (e.g., biopsy and not for symptomatic treatment); and (4) no systemic treatment (targeted therapy, immunotherapy or chemotherapy) after surgery. The screening of study subjects and the inclusion and exclusion criteria are summarized in **Figure 1**.

All study patients usually received whole-body contrast medium enhancement computed tomography (CT) every 3 to 4 months to evaluate response to systemic therapy and underwent brain magnetic resonance imaging (MRI) to determine brain metastasis before brain tumor resection surgery. After the operation, all study patients received brain MRI as follow-up imaging every 3 to 6 months to evaluate the status of the brain metastasis. Additional brain MRIs were ordered based on clinical need or the decision of surgeons and physicians. Other imaging studies, such as fluorodeoxyglucose (FDG) positron emission tomography (PET) scans, chest plain films, and sonograms, were ordered during treatment follow-up to assist in evaluation of the disease status, as needed.

Treatment responses to systemic therapy in this study, including partial response (PR), stable disease (SD), and progressive disease (PD), were defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Postresection survival was defined as the duration of time from the first date of the brain metastasis resection surgery to the recorded date of death. Overall survival (OS) was defined as the time duration from the date of NSCLC diagnosis to the date of mortality event record-

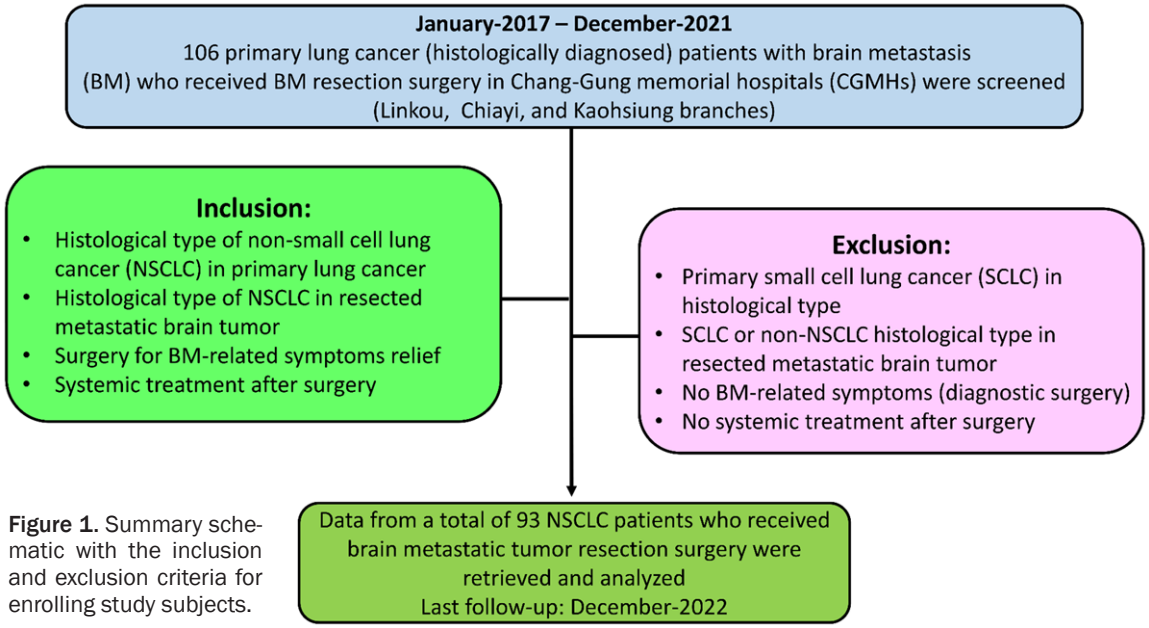

Figure 1. Summary schematic with the inclusion and exclusion criteria for enrolling study subjects.

ed. If the patient was alive through the last follow-up time-point of this study (December 31, 2022), survival (postresection survival and OS) was censored at the recorded last clinical visit date. Brain metastasis-free (BM-free) survival was defined as the duration from the first date of brain metastasis resection surgery to the first date of brain metastasis progression detected by images; censoring was at the date of recorded mortality event.

For analysis of driver mutations, EGFR mutations were detected by conducting amplified refractory mutation system-Scorpion (ARMS/S) assays or next-generation sequencing (NGS) on the resected brain tumor tissues. All the remaining driver mutations other than EGFR mutations were detected by NGS.

Statistical analysis

The baseline clinical characteristics and treatment information of the patients in this study are presented as quantitative variables; age is shown as the mean ± standard deviation (SD). Univariate and multivariate Cox regression analyses were used to analyze postresection survival according to different clinical variables. Kaplan-Meier survival curves were applied to calculate postresection survival, OS and brain metastasis-free survival between the study groups. Statistical significance was defined when the two-sided *P* values were lower than 0.05. All statistical analyses in this study were performed by using IBM SPSS Statistics version 22.0 (SPSS Corp., Chicago, IL, USA). Survival curve figures, including postresection survival and OS, were plotted with GraphPad Prism (Version 5.0; GraphPad Software, San Diego, CA, USA).

Results

Baseline demographic characteristics and associated treatment information of study patients

A total of 93 patients were ultimately included and analyzed in the present study. The baseline demographic characteristics and information on treatment modalities after brain tumor resection surgery are shown in **Tables 1** and **2**. Among the 93 patients, adenocarcinoma accounted for most of the histological types (88.2%), and 2 patients (2.2%) had adenosquamous mixed type. Fifty-nine patients (63.4%) received surgery at the initial diagnosis of NSCLC, and 34 (36.6%) received surgery when brain metastasis occurred during prior systemic therapy. Five patients (5.4%) experienced surgery-related complications, including hemorrhage, infection and edema, but all complications were manageable, and no serious sequelae or deaths related to surgery were recorded.

Table 1. Baseline clinical characteristics of the study patients

Total	N = 93 (%)
Sex	
Male	45 (48.4%)
Female	48 (51.6%)
Age in years (mean ± SD)	67.4 ± 11.2
ECOG PS at surgery	
1	68 (73.1%)
2	25 (26.9%)
Smoking status	
Nonsmoker	56 (60.2%)
Former/current smoker	37 (39.8%)
Histology	
Adenocarcinoma	82 (88.2%)
Squamous cell carcinoma	2 (2.2%)
Adenosquamous	2 (2.2%)
Large cell neuroendocrine carcinoma	4 (4.2%)
NSCLC*	3 (3.2%)
Initial timing of brain metastasis resection	
Synchronous	59 (63.4%)
Metachronous	34 (36.6%)
Driver mutations (After surgery)	
EGFR mutations	56 (60.2%)
ALK-EML4	2 (2.2%)
ROS-1	2 (2.2%)
KRAS	5 (5.3%)
RET fusion	2 (2.2%)
HER2	2 (2.2%)
FGFR3-TACC3 fusion	1 (1.0%)
Wild-type and unknown	23 (24.7%)
Number of brain metastasis	
Single	50 (53.8%)
2-3	32 (34.4%)
>3	11 (11.8%)
Diameter of the resected metastatic tumor (cm)	
≤3	59 (63.4%)
>3	34 (36.6%)
Concurrent metastatic sites other than the brain	
Bone	22 (23.7%)
Liver	9 (9.7%)
Neurological symptoms at surgery	
Headache	22 (23.7%)
Dizziness & Vertigo	29 (63.4%)
Hemiplegia	24 (25.8%)
Conscious disturbance	2 (2.2%)
Seizure and convulsion	6 (6.5%)
Visual disorder	3 (3.2%)
Unsteady gait	7 (7.5%)
Slurred speech	2 (2.2%)

Most patients (89 (95.7%)) in this study received adjuvant radiation therapy to the brain after surgery, though 4 did not receive adjuvant radiation because of personal reasons or the decision of the physician. Among the 89 (95.7%) patients, 38 (40.9%) received WBRT, and the other 51 (54.8%) received SBRT. Cancer driver mutations of NSCLC were detected in seventy patients (75.3%) after brain metastasis resection surgery.

EGFR-TKI-based targeted therapy accounted for the majority of systemic therapies after surgery in this study (52 (57.0%)). The ALK inhibitor taken by 2 study patients and the ROS-1 inhibitors described in this study were both crizotinib. Regarding treatment responses to postresection systemic therapy, 58 patients (62.4%) had PR, 23 (24.7%) had SD, and 12 (12.9%) had PD. Among the 36 (38.7%) patients receiving non-targeted postresection systemic therapy, 23 (24.7%) received chemotherapy alone; 2 (2.2%) received chemotherapy combined with bevacizumab. Five patients (5.4%) received single pembrolizumab (anti-PD-1 ICI) because of strong positive PD-L1 expression in their resected tumor (tumor proportion score (TPS) ≥50%). Four (4.3%) patients received chemotherapy combined with anti-PD-1/PD-L1 ICIs, and the other 2 (2.2%) received chemotherapy plus bevacizumab and nivolumab per the protocol of a clinical trial.

Clinical outcomes after BM resection surgery

The clinical outcomes of the patients receiving brain metastasis resection surgery were analyzed as postresection survival, BM-free survival and OS, and the results are shown in **Figure 2**. The median postresection survival of all study patients was 34.36 months (95% confidence interval (CI), 28.97-39.76; **Figure 2A**), the median BM-free survival 26.90 months (95% CI, 22.71-31.09; **Figure 2B**), and the median OS 41.13 months (95% CI, 34.47-47.52; **Figure 2C**).

Complications of surgery	
Hemorrhage	2 (2.2%)
Infection	2 (2.2%)
Brain edema	1 (1.0%)

Abbreviations: SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK-EML4, anaplastic lymphoma kinase-echinoderm microtubule-associated protein-like 4; ROS-1, Proto-Oncogene 1; KRAS, Kirsten rat sarcoma virus; HER2, human epidermal growth factor receptor 2; FGFR3, Fibroblast Growth Factor Receptor 3. *not otherwise specified.

Table 2. Information on treatments administered after brain metastasis resection surgery

Treatments	
Radiation therapy	
None	4 (4.3%)
Whole brain radiotherapy (WBRT)	38 (40.9%)
Stereotactic body radiation therapy (SBRT)	51 (54.8%)
Systemic therapies after surgery	
Targeted therapy	57 (61.3%)
EGFR-TKI-based	52 (57.0%)
EGFR-TKI alone	46 (49.5%)
EGFR-TKI + bevacizumab	6 (6.5%)
ALK inhibitor	2 (2.2%)
ROS-1 inhibitor	2 (2.2%)
Other targeted drug (DZD9008)	1 (1.0%)
Nontargeted therapy	36 (38.7%)
Chemotherapy alone	23 (24.7%)
Immunotherapy alone	5 (5.4%)
Chemotherapy + bevacizumab	2 (2.2%)
Chemotherapy + immunotherapy	4 (4.3%)
Chemotherapy + immunotherapy + bevacizumab	2 (2.2%)
Response to systemic therapy after surgery	
Partial response (PR)	58 (62.4%)
Stable disease (SD)	23 (24.7%)
Progressive disease (PD)	12 (12.9%)

Abbreviations: EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; ROS-1, proto-oncogene 1.

Analysis of predictive factors associated with median postresection survival

Median postresection survival according to different clinical factors was analyzed by Cox regression; the results are shown in **Table 3**. In univariate analysis, poor performance (Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2), large tumor size (diameter >3 cm), and concurrent bone and liver metastases were associated with significantly shorter median postresection survival (P<0.05). Adenocarcinoma histological type was significantly associated with longer median postresection survival (P<0.05). Multivariate analysis was performed to identify independent predictors associated with median postresection survival. ECOG PS ≥2 and concurrent liver metastases were independent unfavorable predictors of median postresection survival (P<0.05). Adenocarcinoma histological type was an independent predictive factor associated with better median postresection survival than other histological types (P<0.05). In addition, median postresection survival associated with adenocarcinoma histology and concurrent liver metastasis was analyzed by Kaplan-Meier survival curves. Patients with adenocarcinoma histology had significantly longer postresection survival than those with nonadenocarcinoma histology (36.23 VS. 10.30 months; hazard ratio (HR) = 0.122; 95% CI, 0.035-0.418; P<0.001; **Figure 3A**). Moreover, patients with concurrent liver metastasis had significantly shorter postresection survival than those without liver metastasis (36.23 VS. 11.43 months; HR = 22.18; 95% CI, 5.827-84.459; P<0.001; **Figure 3B**).

Discussion

In this study, we provide updated and important clinical information on NSCLC patients with symptomatic brain metastasis who underwent brain tumor resection surgery. Our results showed that NSCLC patients receiving brain tumor resection followed by systemic therapy had an approximate 3-year median postresection survival (34.36 months) and a median BM-free survival of over 2 years (26.90 months). Moreover, we identified that poor performance status, nonadenocarcinoma histology and concurrent liver metastasis were associated with unfavorable outcomes regarding postresection survival.

Two previous studies analyzed clinical factors associated with survival in brain metastatic NSCLC patients who underwent neurosurgery,

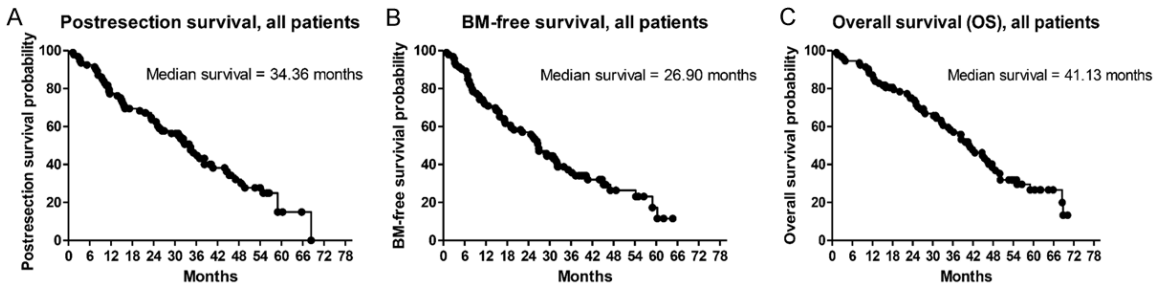

Figure 2. Clinical outcomes of all study patients after BM resection surgery. A. Median postresection survival was 34.36 months (95% CI, 28.97-39.76). B. Median BM-free survival was 39.06 months (95% CI, 27.56-50.57). C. Median OS was 41.13 months (95% CI, 34.47-47.52).

Table 3. Cox proportional hazard regression analysis of predictive factors associated with postresection survival

Variables	Median postresection survival (months)	Univariate analysis *P* value HR (95% CI)	Multivariate analysis	
			HR (95% CI)	*P* value
Age (years)				
>60	29.03	0.318		
≤60	35.23	0.764 (0.451-1.295)		
Sex				
Female	36.23	0.837		
Male	32.76	0.947 (0.564-1.591)		
ECOG PS				
1	49.04	<0.001	1	
≥2	15.87	11.110 (5.692-21.672)	8.196 (3.984-16.949)	<0.001
Smoking status				
Nonsmoker	38.33	0.767		
Former/current smoker	32.76	1.084 (0.636-1.847)		
Histology			1	0.001
Adenocarcinoma	36.23	0.002	3.877 (1.746-8.606)	
Nonadenocarcinoma	10.03	3.406 (1.585-7.319)		
Timing of brain metastasis resection				
Synchronous	37.00	0.949		
Metachronous	29.03	1.078 (0.604-1.604)		
Driver mutation				
Wild-type and unknown	25.20	0.311		
With driver mutation	34.40	0.758 (0.443-1.295)		
Number of brain metastasis				
Single	35.23	0.383		
2-3	34.36	1.184 (0.810-1.731)		
>3	23.30			
Diameter of resected metastatic tumor (cm)				
≤3	38.33	0.005		
>3	13.80	2.178 (1.279-3.709)		
Bone metastasis				
Without bone metastasis	38.33	0.016		
With bone metastasis	23.30	1.995 (1.136-3.505)		
Liver metastasis				
Without liver metastasis	36.23	0.001	1	<0.001
With liver metastasis	11.43	5.012 (2.319-10.831)	4.566 (2.024-10.309)	

Brain radiation therapy after surgery		
None	23.50	0.152
Whole-brain radiotherapy (WBRT)	24.66	0.703 (0.434-1.138)
Stereotactic body radiation therapy (SBRT)	38.33	
Systemic therapy after surgery		
Nontarget therapy	32.76	0.183
Target therapy-based	34.36	0.696 (0.410-1.181)

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; EGFR, epidermal growth factor.

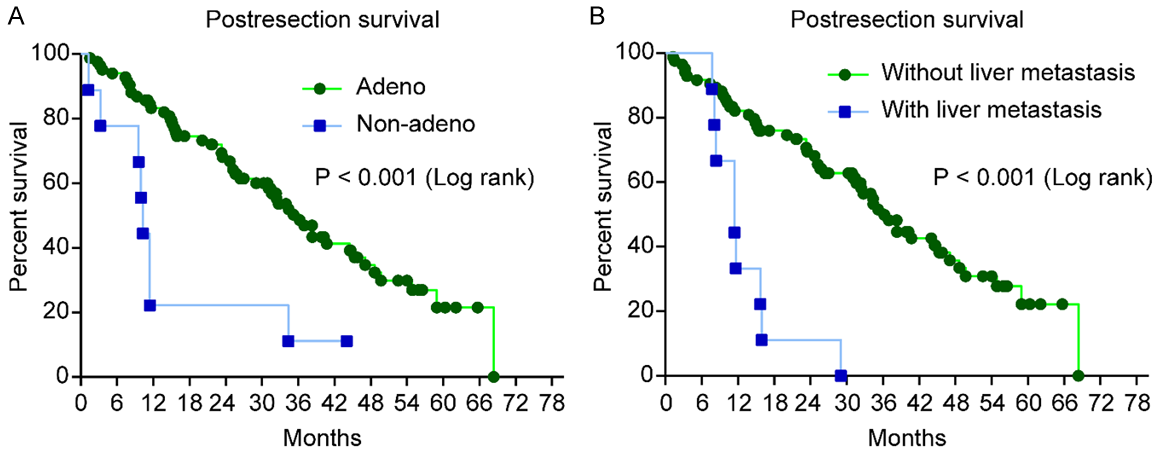

Figure 3. Comparisons of median postresection survival with different predictive factors. A. Comparison of median postresection survival between patients with adenocarcinoma and nonadenocarcinoma histological types (HR = 0.122; 95% CI, 0.035-0.418; P<0.001). B. Comparison of median postresection survival between patients with and without liver metastasis (HR = 22.18; 95% CI, 5.827-84.459; P<0.001).

and both studies found that poor performance status was significantly associated with shorter postresection survival [16, 17]. Similar to these previous studies, our results showed that NSCLC patients with preserved performance status (ECOG PS = 1) had a 4-year median postresection survival but that those with ECOG PS ≥2 had approximately 16 months of postresection survival. Performance status has been frequently reported to be a predictive factor associated with treatment efficacy and survival in NSCLC, and patients with better performance status have more effective treatment responses and longer survival times than those with poor performance status [18-20].

Furthermore, in the same two previous studies, NSCLC patients with EGFR mutation who received EGFR-TKIs as postresection systemic therapy had significantly longer survival than those with wild-type EGFR [16, 17]. Our study showed no significant difference in postresection survival in patients receiving targeted therapies compared with those not receiving targeted therapy, which differs from the findings of the two previous studies. In the study by Shah et al., patients with EGFR-mutated NSCLC taking EGFR-TKIs were analyzed, but 3 patients with ALK/ROS-1 mutation were not included in the analysis [16]. Another study by Perng et al. mainly focused on the correlation between EGFR mutation status and postresection survival, but the authors did not show data on EGFR-TKI therapy [17]. In these two previous studies, data on other systemic therapies, including chemotherapy, other targeted therapies or immunotherapy, administered after brain metastasis resection in their study patients were not clearly reported. In addition, recruitment of study patients was completed in a time frame of over 10 years [16, 17], whereas the time range of our study was only 5 years. Our study included subjects who were treated after 2017 when anti-PD-1/PD-L1 ICIs and the third-generation EGFR-TKI osimertinib had been approved for treatment of metastatic NSCLC [21, 22]. All the patients in our study received systemic therapy after brain metasta-

sis resection. A previous study reported that advances in anticancer therapies and increasing treatment options have significantly prolonged the survival of metastatic NSCLC patients in recent decades [23]. In addition, small patient numbers (36 for nontargeted therapy and 57 for targeted therapy) may lead to unachieved clinical significance in analyses. The power calculation performed (not shown in the results) by us indicated that statistical significance could be achieved when the patient number in each group was more than 70. Taken together, these findings may explain why the postresection survival in our study was longer than that in the two previous studies (Shah et al. and Perng et al.).

Among the 57 (61.3%) patients who received targeted therapy after surgery, 56 had the adenocarcinoma histological type, and only 1 (1.1%) had not otherwise specified histological type NSCLC with exon 19-deletion EGFR mutation. Among the other 8 (8.6%) nonadenocarcinoma patients, 7 (7.5%) received platinum-based doublet chemotherapy and 1 single pembrolizumab therapy. Four (4.3%) adenocarcinoma patients in this study received bevacizumab (a humanized anti-angiogenesis monoclonal antibody) in addition to chemotherapy or chemotherapy combined with immunotherapy. Previous clinical studies have shown that bevacizumab in addition to targeted therapy or chemotherapy significantly improves treatment efficacy and progression-free survival (PFS) in lung adenocarcinoma patients with brain metastasis [24, 25], and anti-PD-1/PD-L1 ICIs alone or in combination with chemotherapy have been shown to improve survival in metastatic NSCLC in clinical studies [26, 27]. The diverse treatments that lung adenocarcinoma patients received in this study suggest that adenocarcinoma histological type is an independent favorable factor associated with postresection survival.

The liver is another site of distant metastasis frequently observed in advanced NSCLC patients. The molecular and pathophysiological mechanisms of NSCLC liver metastasis are more complex than those of distant metastasis at other sites [28]. Although patients with NSCLC liver metastasis respond to systemic therapies, including chemotherapy, immunotherapy and targeted therapies, patients with liver metastasis are reported to have shorter PFS and OS than those without liver metastasis in several previous studies [28-30]. The patients with concurrent liver metastasis in our study had a postresection survival shorter than 1 year (11.43 months), and concurrent liver metastasis was identified as an independent predictive factor associated with unfavorable outcome in brain metastatic NSCLC patients receiving resection neurosurgery. In general, development of a new therapeutic strategy for NSCLC liver metastasis is needed to improve the survival of this group of patients.

Previous studies have shown that more than half of NSCLC patients with brain metastasis experience local brain tumor recurrence after resection within 1-2 years if no postresection adjuvant radiation therapy is administered. Adjuvant radiation therapy after NSCLC brain metastatic tumor resection surgery has been shown in several previous studies to reduce local recurrence [31-33]. Most patients (89 (95.7%)) in our study had received adjuvant radiation therapy, either WBRT or SBRT, after neurosurgery, with only 4 (4.3%) not receiving adjuvant radiation therapy. Symptomatic intracranial radiation necrosis occurs in some patients after radiation therapy, and additional intervention, such as systemic steroid administration, is needed for symptom relief [31]. Regarding the concern of adverse effects induced by radiation therapy, a few patients decided not to receive this therapy after surgical resection. However, most of the patients in our study did receive adjuvant radiation therapy after resection, and the median brain metastasis-free survival of our study patients was as long as 39.06 months.

There are some limitations of this study that should be noted. The patients included were all East Asian, and the lung adenocarcinoma driver mutation profile in this study was different from that of other ethnic groups. In a previous study conducted by Shah et al., KRAS mutations accounted for most driver mutations (22/84 = 26.2%), followed by EGFR mutations (19/84 = 22.6%), in the study subjects [16]. Differences in driver mutation profiles and postresection targeted therapies may lead to different survival outcomes. The first KRAS inhibitor sotorasib was approved by the United States (US) Food and Drug Administration (FDA)

in 2021, after the study of Shah et al. [16, 34] was conducted. Future studies with different ethnic groups and driver mutation profiles are warranted for prognostic analysis of NSCLC patients with brain metastasis who undergo neurosurgery.

Conclusion

Brain metastasis resection surgery followed by systemic therapy is feasible and may benefit survival in NSCLC patients with brain metastasis and favorable clinical factors. For NSCLC patients with reserved ECOG PS, adenocarcinoma histology type and no concurrent liver metastasis, neurosurgery may be considered a prior treatment modality for brain metastasis and then followed by systemic therapy.

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Disclosure of conflict of interest

None.

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