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Effects of different brain surveillance strategies on outcomes for patients with EGFR-mutant metastatic lung adenocarcinoma under targeted therapy

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ABSTRACT

Objectives: Brain metastasis (BM) is common in patients with epidermal growth factor receptor (EGFR)-mutant lung cancer. However, the brain surveillance strategy during treatment in advanced lung cancer patients varies, and the impact on clinical outcome is unclear. Here we aimed to evaluate the effect of different brain surveillance strategies on the clinical characteristics and treatment outcome in patients with EGFR-mutant lung adenocarcinoma treated with first-line EGFR tyrosine kinase inhibitors (EGFR-TKIs).

Materials and methods: This is a retrospective observational study conducted in a medical center in an area with high prevalence of EGFR mutation. Patients with initially diagnosed stage IV EGFR-mutant lung adenocarcinoma were included. Patients undergoing regular brain magnetic resonance imaging (MRI) every 3-6 months were categorized in the regular follow-up (RFU) group, and the rest were categorized in the liberal follow-up (LFU) group. Clinical outcomes were collected and analyzed.

Results: A total of 310 patients were included, and 43.5% initially had brain metastases. Patients in the LFU group were significantly older than those in the RFU group (median age: 67 vs 62, $p < 0.001$). The overall survival and time-to-treatment failure of patients with initial EGFR-TKIs treatment showed no statistical difference between the two groups. However, the intracranial progression free survival was significantly shorter in the RFU group than in the LFU group ($p = 0.009$). The risk of mortality was similar in the LFU and RFU groups. There was no difference in the intracranial progression patterns and cause of death between the two groups.

Conclusions: For EGFR-mutant lung adenocarcinoma patients who used EGFR-TKIs as the frontline therapy, regular or liberal brain MRI follow-up showed no significant impact on the outcome, irrespective of initial brain metastasis.

1. Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality around the world. Brain metastasis (BM) is seen in up to 20-40% patients with NSCLC [1,2]. Patients with EGFR mutation have a higher likelihood of BM because of prolonged survival by EGFR tyrosine kinase inhibitors (EGFR-TKIs) [3–5]. Further, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and surgical excision are options for local control, and each shows different treatment benefit in selected subgroups [6]. However, the staging and follow-up strategies of brain metastasis in NSCLC patients remain inconclusive. According to the National Comprehensive Cancer Network (NCCN) guidelines, newly diagnosed NSCLC patients with the stage IB or above were recommended to undergo brain magnetic resonance imaging (MRI) during the initial evaluation [7]. Meanwhile, National Institute for Health and Care Excellence (NICE) guidelines recommend brain computed tomography or MRI evaluation for patients with curative intent [8,9]. There is no consensus regarding the brain surveillance protocol during treatment. In clinical practice, the brain surveillance strategy in advanced lung cancer patients during treatment varies, and the impact on the clinical outcome is unclear [8,10]. Our study aimed to determine the effects of different brain surveillance strategies on the

Abbreviation: BM, Brain metastasis; RFU, Regular follow-up; LFU, Liberal follow-up; EGFR, Epidermal growth factor receptor; EGFR-TKIs, Epidermal growth factor receptor tyrosine kinase inhibitors; WBRT, Whole-brain radiotherapy; SRS, Stereotactic radiosurgery; TTF, Time-to-treatment failure; icPFS, Intracranial progression free survival; OS, Overall survival; LOS, Length of stay

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clinical outcome of patients with EGFR-mutant lung adenocarcinoma treated with first-line EGFR-TKIs.

2. Material and methods

2.1. Patient cohort

This retrospective observational cohort study was conducted in a tertiary medical center in Taiwan. All patients with EGFR-mutant stage IV lung adenocarcinoma diagnosed between January 1, 2013, and December 31, 2015, were identified. All patients received the 1 st or 2nd generation EGFR-TKIs (gefitinib, erlotinib, or afatinib) as their first-line systemic treatment. Patients were excluded if they had been diagnosed with other cancers, had incomplete medical records, had been enrolled in prospective clinical trials, had received less than 3 months of follow-up, or had no contrast-enhanced brain MRI study at baseline or follow-up. To remove potentially confounding variables, patients who underwent surgical resection for BM or had significant neurologic symptoms at initial presentation were also excluded. The data cut-off date was December 31, 2017.

2.2. Study design

The following variables were collected for analysis: gender, age, ECOG performance status, smoking history, EGFR mutation type, brain imaging study, and cancer-related treatment and disease outcomes. We used AJCC 7th edition for lung cancer staging. Patients with contrast-enhanced brain MRI at baseline and follow-up were divided into two groups according to their brain surveillance strategies. Patients with regular brain MRI scanning every 3-6 months were defined as the regular follow-up (RFU) group. Patients who received follow-up brain MRI scanning due to the presence of neurologic symptoms or systemic disease progression, or at a frequency longer than 6 months, were defined as the liberal follow-up (LFU) group. We collected clinical data and correlated with the treatment outcome. Time-to-treatment failure (TTF) was defined as the period from the date of dosing EGFR-TKIs to the date of withholding EGFR-TKIs. Intracranial progression free survival (icPFS) was defined as the period from the date of diagnosis to the date of imaging-confirmed-intracranial progression or death. Disease progression and intracranial disease progression were defined by the judgement of the clinical physician. Overall survival (OS) was defined from the date of diagnosis to death. This study was approved by the Institution Review Board at Taipei Veterans General Hospital.

2.3. Statistics

Pearson's chi-square or Fisher's exact test was performed to compare categorical variables. Continuous variables were compared using the Student t-test for normally distributed variables. Kaplan-Meier survival curves were plotted for time-to-treatment-failure, intracranial progression survival, and overall survival. Univariate and multivariate associations of clinical features and outcome were analyzed with Cox proportional hazards regression model. A p-value < 0.05 was considered statistically significant, and all p-values were two-sided. We used SPSS software (version 24.0) for all analysis.

3. Results

3.1. Patient characteristics

A total of 310 patients (41.3% male and 58.7% female) were identified initially. All of them had stage IV, EGFR-mutant lung adenocarcinoma, had no significant neurologic symptoms at baseline, and were treated with first-line EGFR-TKIs (Fig. 1). The median age was 65 (30-94) years. Most patients were non-smokers (72.3%), had ECOG 0-1 (88.1%), and were stage M1b disease (70.6%). One hundred and thirty-five (43.5%) patients had brain metastases at their initial presentation. Half of the patients showed EGFR L858R mutation (50%), 41.3% patients had exon 19 deletion, and 8.7% patients had uncommon mutations. The majority of patients (85.5%) received EGFR-TKIs alone as the first-line treatment; 8.4% received WBRT first; and 6.1% patients received SRS at the start. In this cohort, as of the data cutoff date, 15.2% patients have received 3rd generation EGFR-TKIs in their following treatment after disease progression.

Overall, 137 patients underwent regular brain MRI surveillance during treatment (RFU group, 44.2%) and 173 were followed-up liberally by the treating physicians (LFU group, 55.8%). Patients in the LFU group (median age, 67) were significantly older than those in the RFU group (median age, 62) ($p < 0.001$). Over half of patients (59.9%) in RFU group had initial brain metastasis, whereas only 30.6% patients in LFU group had initial brain metastasis ($p < 0.001$). Patients in the RFU group conducted more upfront brain-focus therapy than those in the LFU group (24% vs. 7%, $p < 0.001$). There was no statistical difference in sex, smoking history, ECOG performance status, EGFR mutation types, and types of first-line EGFR-TKIs between the two follow-up groups. Patients in the LFU group were older, having less brain metastases, but more extracranial metastases. The results are summarized in Table 1. For further evaluation of treatment outcome, we excluded patients with uncommon mutations since they responded differently to standard EGFR-TKIs treatment and therefore presented with heterogeneous clinical outcome. We also excluded patients who received upfront brain-focus therapy for they had a different surveillance strategy compared to that with EGFR-TKIs treatment alone. Finally, 240 patients were identified with common EGFR mutations and started the treatment with upfront EGFR-TKIs (Supplementary Table 1).

3.2. Survival

In the 240 patients with common EGFR mutations and initial EGFR-TKIs therapy, we founded no statistically significant OS difference between the two follow-up strategies ($p = 0.577$). One-year cumulative probability of survival in the RFU and LFU groups were 0.933 and 0.923, respectively; two year cumulative probability of survival in the RFU and LFU groups were 0.817 and 0.711, respectively (Fig. 2). The TTF of first-line EGFR-TKIs in the RFU and LFU groups also revealed no difference (median, RFU 12.6 months, LFU 12.4 months; $p = 0.924$) (Fig. 3a). However, the icPFS was significantly shorter in the RFU than LFU group ($p = 0.004$) (Fig. 3b). In patients without initial BM, there was no icPFS difference between RFU and LFU groups ($P = 0.639$). However, in patients with initial BM, there was a trend that RFU group had inferior icPFS compared to the LFU group ($P = 0.058$) (Supplementary Fig. 1a and b).

3.3. Risk factors of survival

Age, smoking, ECOG, EGFR mutation types, and follow-up strategies were included in the multivariate analysis. LFU strategy was not associated with OS and TTF in univariate analysis. Smoking and initial BM were independent predictors of OS after adjustment with certain clinical variables in multivariate analysis. Both smoking history (HR 1.73 (95% C.I. 1.10-2.73), $p = 0.018$) and initial BM (HR 1.91 (95% C.I. 1.23-2.96), $p = 0.004$) showed noticeable effect on OS (Table 2). Initial BM was associated with unfavorable TTF, while age older than 65 was associated with better TTF in multivariate analysis. The hazard ratio of initial BM was 1.94 (95% C.I. 1.43-2.64, $p < 0.001$) and hazard ratio of age older than 65 was 0.66 (95% C.I. 0.49-0.88, $p = 0.004$). Table 3 presents the results of Cox regression analysis of TTF. Variables including initial staging M1b (HR 1.85 (95% C.I. 1.06-3.20), $p = 0.03$) and initial BM (HR 2.55 (95% C.I. 1.64-3.98), $p < 0.001$) were independent factors in multivariate analysis for icPFS. However, smoking history and LFU were not predictable factors of TTF after adjustment. Details of risk factors of icPFS are presented in Supplementary Table 2.

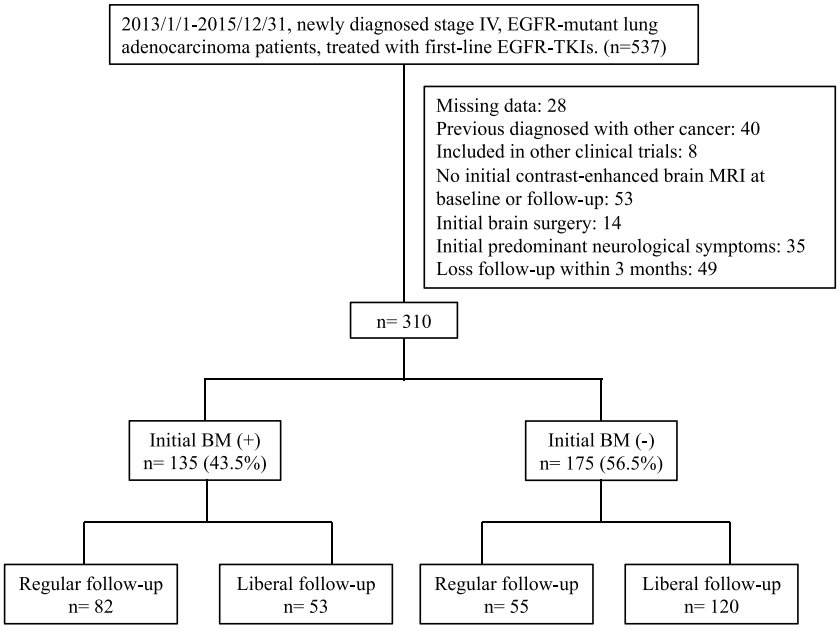

Fig. 1. Patient deposit.
Brain metastasis: BM.

Table 1
Patient characteristics.

	All participants (310)	RFU (137)	LFU (173)	P value
Gender				
Male	128 (41.3)	56 (40.9)	72 (41.6)	0.908
Female	182 (58.7)	81 (59.1)	101 (58.4)	
Age				
Median (range)	65 (30-94)	62 (30-91)	67 (34-94)	< 0.001
Smoking				
Never	224 (72.3)	99 (72.3)	125 (72.3)	1.00
Ever	86 (27.7)	38 (27.7)	48 (27.7)	
ECOG				
0-1	273 (88.1)	123(89.8)	150 (86.7)	0.482
> =2	37 (11.9)	14 (10.2)	23 (13.3)	
M stage				
M1a	91 (29.4)	27 (19.7)	64 (37.0)	0.001
M1b	219 (70.6)	110(80.3)	109 (63.0)	
Extracranial metastasis				
No	37 (11.9)	23 (16.8)	14 (8.1)	0.02
Yes	273 (88.1)	114 (83.2)	159 (91.9)	
Brain metastasis at initial presentation				
No	175 (56.5)	55 (40.1)	120 (69.4)	< 0.001
Yes	135 (43.5)	82 (59.9)	53 (30.6)	
Number of brain metastases				
Median (range)	0 (0-4)	1 (0-1)	0 (0-3)	< 0.001
Number of brain MRI before intracranial progression				
Median (range)	0 (0-4)	6 (2-17)	2 (1-7)	< 0.001
EGFR mutation				
Exon 19 del	128 (41.3)	54 (39.4)	74 (42.8)	0.64
L858R	155 (50.0)	69 (50.4)	86 (49.7)	
Others	27 (8.7)	14 (10.2)	13 (7.5)	
Initial Treatment				
EGFR-TKIs alone first	265 (85.5)	104 (75.9)	161 (93.1)	< 0.001
SRS first	19 (6.1)	18 (13.1)	1 (0.6)	
WBRT first	26 (8.4)	15 (10.9)	11 (6.4)	
EGFR-TKIs				
Gefitinib	158 (51.0)	67 (48.9)	91 (52.6)	0.427
Erlotinib	106 (34.2)	52 (38.0)	54 (31.2)	
Afatinib	46 (14.8)	18 (13.1)	28 (16.2)	

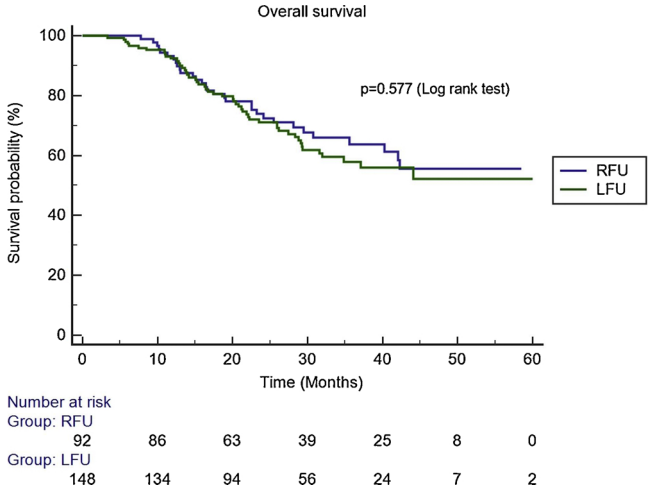

Fig. 2. Overall survival.
Regular follow-up: RFU; Liberal follow-up: LFU.

3.4. Number of brain MRI before intracranial progression

We also analyzed subgroup outcomes. For patients without an initial BM (n = 159), patients in the RFU group underwent significantly more brain MRIs before first-time of intracranial progression. The median times of MRI before intracranial progression in the RFU group was 6, and 2 in the LFU group ($p < 0.001$, Wilcoxon signed rank test). The cost of brain imaging per patient per year before intracranial progression, based on Taiwan National Health Insurance, was estimated at about 1575 USD for RFU group and 676 USD for LFU group ($p < 0.001$). Comparing the types of intracranial progression and incidence of leptomeningeal carcinomatosis, there was no difference between two surveillance strategies (progression due to leptomeningeal carcinomatosis: RFU 4.1%, LFU 3.6%, p = 0.82). Comparing the cause of death, the LFU group did not have more death related to intracranial progression (RFU: intracranial progression related death 32.3%, extracranial progression related death 41.9%; LFU intracranial progression related death 19.6%, extracranial progression related death 47.1%). However, the patient number was small (n = 82). For patients

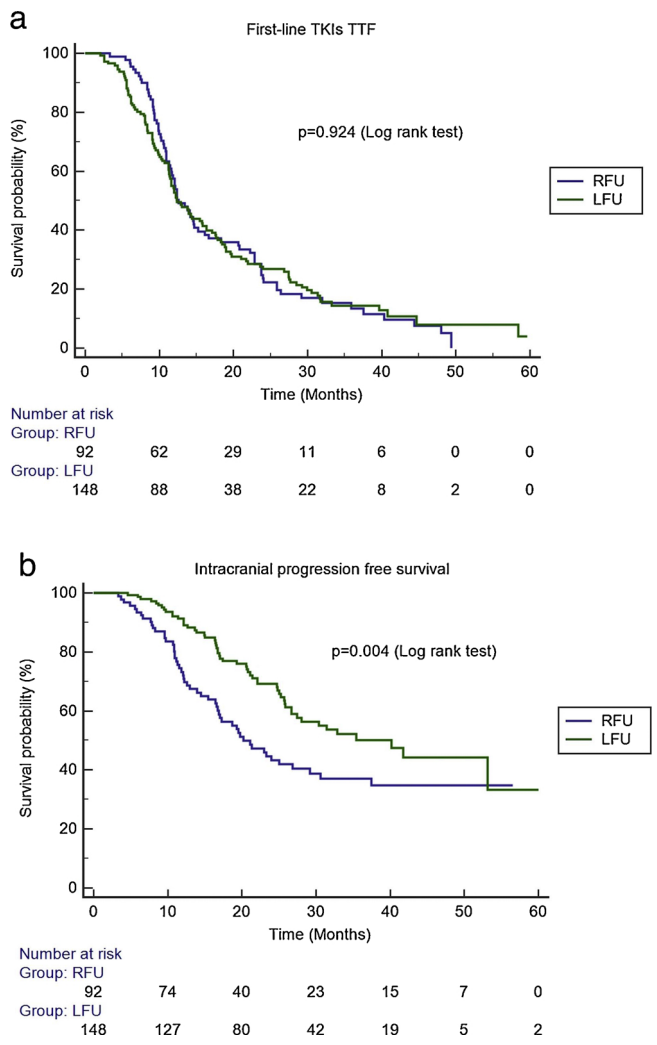

Fig. 3. Time-to-treatment failure and intracranial progression free survival.
(3a) Time-to-treatment failure (TTF) of first-line EGFR-TKIs.
(3b) Intracranial progression free survival.
Regular follow-up: RFU; Liberal follow-up: LFU.

Table 2
Cox proportional hazards model for OS (n = 240).

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR(95%CI)	P value
Age > 65	1.01 (0.66-1.56)	0.955		
Ever smoker	1.81(1.15-2.84)	0.011	1.73 (1.10-2.73)	0.018
Female	0.81 (0.52-1.25)	0.337		
ECOG > =2	1.68 (0.91-3.09)	0.099	1.80 (0.97-3.32)	0.063
M1b	1.53 (0.95-2.46)	0.082		
Initial BM(+)	1.93 (1.24-2.99)	0.003	1.91 (1.23-2.96)	0.004
EGFT-TKIs				
Gefitinib	Reference			
Erlotinib	0.99 (0.61-1.62)	0.980		
Afatinib	0.96 (0.47-1.96)	0.909		
L858R	0.97 (0.63-1.50)	0.905		
LFU	1.14 (0.73-1.78)	0.578		

presented with intracranial progression during follow-up period (n = 108), the median times of hospitalization after intracranial progression showed no significant difference between two groups (p = 0.80). The mean length of stay (LOS) after intracranial progression in RFU group was 27.4 days and LFU 30.1 days (p = 0.70). After adjusting with the length of survival after intracranial progression, there was still no difference in LOS. Furthermore, the median lines of systemic treatment, times of WBRT and times of SRS after intracranial progression were all of insignificant difference (Supplementary Table 3).

Table 3
Cox proportional hazards model for TTF (n = 240).

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR(95%CI)	P value
Age > 65	0.64 (0.48-0.85)	0.002	0.66 (0.49-0.88)	0.004
Ever smoker	1.09 (0.79-1.52)	0.594		
Female	1.01 (0.75-1.36)	0.949		
ECOG > =2	0.72 (0.43-1.20)	0.201		
M1b	1.60 (1.18-2.17)	0.002		
Initial BM(+)	1.98 (1.46-2.69)	< 0.001	1.94 (1.43-2.64)	< 0.001
EGFT-TKIs				
Gefitinib	Reference			
Erlotinib	1.35 (0.98-1.84)	0.064		
Afatinib	0.78 (0.48-1.27)	0.319		
L858R	1.02 (0.76-1.36)	0.894		
LFU	1.01 (0.76-1.36)	0.924		

4. Discussion

Whether to follow brain MRI regularly or not in patients with metastatic NSCLC during treatment is still controversial. Current guidelines, including NCCN, ESMO and NICE, have no consensus on brain surveillance strategy [7,9,11]. Patients receiving radiotherapy were suggested an intensive routine follow-up protocol for clinical benefits and cost-effectiveness [12]. However, those data focused on general cancer patients with previous radiotherapy and routine follow-up protocol showed inconsistent impact on OS [13]. A recent retrospective cohort study of melanoma showed that brain MRI was cost-effective only during the first year after melanoma treatment in patients with AJCC stage IIC and III [14,15]. Considering the prolonged survival of cancer patients and the burden of the health care system, risk evaluation with specific cancer type and staging surveillance protocol should be developed. Our study focused on the EGFR-mutant adenocarcinoma and patients all received first-line EGFR-TKIs. This specific group of patients have high incidence of BM during disease course [3,16]. We retrospectively collected patients' clinical data and their serial intracranial condition. We found that the two surveillance strategies had no indicative effects on OS and the first-line EGFR-TKIs TTF irrespective of initial BM. However, the icPFS was statistically shorter in patients with RFU.

There are two possible reasons for no statistical significance in OS and TTF. First, we use RFU and LFU for classification of surveillance strategy rather than the traditional definition. Previous studies divided strategies by whether to follow-up regularly or follow-up by neurological symptoms [17]. Neurological symptoms and signs are non-specific in clinical practice and may restrict the indication for brain MRI evaluation. In our study, opting for a LFU strategy means to follow up patients by symptoms or any clinical purposes such as re-staging. Physicians had more flexibility in judging the timing of imaging and then adjust their treatment strategy. Interestingly, even under LFU protocol, the mean brain MRI times of LFU was still significantly lower than RFU (RFU: 6 times of MRI, Liberal FU: 2 times of MRI, p < 0.001). Secondly, there is no consistent evidence supporting that EGFR mutant patients with asymptomatic BM have benefit from intervention such as SRS and WBRT. Some studies showed that the addition of WBRT to EGFR-TKIs did not bring additional survival benefit compared to EGFR-TKIs alone [18]. Some research revealed no superior OS of SRS in patients with asymptomatic BM [12]. Patients with RFU protocol may receive more imaging evaluation for asymptomatic BM with uncertain benefit [13]. The management of BM remains varied worldwide [10,19]. Our results confirmed above findings while the

icPFS was statistically shorter in patients with RFU and no difference in OS between RFU and LFU. We also analyzed the intracranial progression pattern, cause of death, times of hospitalization, LOS, systemic and local treatment after intracranial progression; all revealed no statistical significance in different groups. The finding is compatible with current evidence [13,20]. A more delicate patients' BM risk evaluation should be constructed for further patient-centered and precision medicine.

With the improved OS and better quality of imaging, more and more asymptomatic BM will be detected. An intensive routine brain imaging brings more economic burden to the health care system [21]. Close surveillance may also induce anxiety and stress to patients [22]. Furthermore, patients with different histology, mutation types, initial brain condition, and even different treatment strategy may need different surveillance protocols. New technology such as radiomics combined with machine learning has shown some promising data in predicting tumor types [23]. Comparing the intracranial condition, the RFU group had shorter icPFS. It is under our expectation because frequent brain imaging may detect more intracranial change. However, the difference was insignificant after adjustment with older age, ECOG, M1b stage, and initial BM in multivariate analysis. This finding indicated that the icPFS may be more associated to clinical characteristics rather than follow-up strategies alone. Initial BM and distant metastases were more important factors in disease outcome. Based on our findings, we suggested further prospective study to set up a model in predicting the BM incidence and progression. This may help us to develop a personal clinical pathway rather than a fixed protocol surveillance. We believe a flexible and individualized follow-up strategy should be constructed in the immediate future.

There are several strengths of our study. We focus on the cohort of EGFR-mutant lung adenocarcinoma in an area of high prevalence of EGFR mutation. In this cohort, patients received EGFR-TKIs as their first systemic treatment. This is a clear stratified study group with effective systemic treatment for intracranial control. Besides, all enrolled patients received contrast MRI in the same radiology department of a tertiary medical center. The study protocol and imaging quality were more homogeneous with less confounding factors. However, our research still had some limitations. First, this is a retrospective observational study. Even though all the data were carefully examined and recorded, retrospective study shows restrictions. Secondly, the definition of LFU was to arrange brain MRI after documented neurologic symptoms, re-staging due to evidence of disease progression, or any clinical considerations. This definition allowed physicians to judge the timing by clinical evidences. However, the bias between individual physicians was inevitable. In this cohort, we found that clinical physicians tended to use RFU strategy for younger patients, an initial staging of M1b, initial BM, and those with upfront brain-focus therapy. Thirdly, it is believed that 3rd generation EGFR-TKIs may have a better intracranial control rate [24]. Some patients received the 3rd generation EGFR-TKIs as their following treatment after disease progression in our cohort. However, the patient number is too small for analysis. With a better systemic treatment such as 3rd generation EGFR-TKIs, the clinical pathway and surveillance strategy might change.

Our finding suggests that RFU and LFU of brain MRI have no difference in OS and TTF of first-line EGFR-TKIs of patients with advanced EGFR-mutant lung adenocarcinoma. Although RFU may detect BM earlier with shorter icPFS, the strategy did not show impact on cause of death and pattern of intracranial progression.

5. Conclusion

For EGFR-mutant lung adenocarcinoma patients who used EGFR-TKIs as the frontline therapy, regular or liberal brain MRI follow-up showed no significant difference in OS and TTF irrespective of initial brain metastasis. Although regular brain MRI follow-up can detect BM earlier (shorter icPFS), this aggressive surveillance strategy did not result in OS benefit. A further prospective study should be done for better clinical strategy development since frequent brain imaging is a huge burden for the health system and patients.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

C.H.C and C.L.C had received honoraria from AstraZeneca, Boehringer Ingelheim, and Roche. Other authors had no conflicts of interest to disclose.

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Appendix A. Supplementary data

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