Outcomes according to initial and subsequent therapies following intracranial progression in patients with EGFR-mutant lung cancer and brain metastasis

Dong-gon Hyun1, Chang-Min Choi1,2, Dae Ho Lee2, Sang-We Kim2, Shinkyo Yoon2, Woo Sung Kim1, Wonjun Ji1*, Jae Cheol Lee2*

1 Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Songpa-Gu, Seoul, Republic of Korea, 2 Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Songpa-Gu, Seoul, Republic of Korea

* jack1097@naver.com (WJ); jclae@amc.seoul.kr (JCL)

Abstract

In patients with epidermal growth factor receptor (EGFR)-mutant non–small-cell lung cancer (NSCLC) with brain metastases, it remains controversial whether the use of EGFR-tyrosine kinase inhibitor (TKI) alone without radiotherapy (RT) is an optimal approach. Here, we investigated the clinical outcomes according to the use of upfront RT as well as the subsequent therapy following intracranial progression. This single-centre retrospective study included a total of 173 patients who were treated with EGFR-TKI alone (TKI alone group) or with upfront whole-brain RT (WBRT) or stereotactic radiosurgery (SRS) followed by EGFR-TKI (RT plus TKI group). Clinical outcomes according to initial and subsequent therapies following intracranial progression were analysed. There was no significant difference in OS according to the use of upfront RT (TKI alone group, 24.5 months vs. WBRT group, 20.0 months vs. SRS group, 17.8 months; P = 0.186). Intracranial progression was found in 35 (32.7%) of 107 patients in the TKI alone group. Among them, 19 patients who received salvage RT had the better prognosis than others [median overall survival (OS); 28.6 vs. 11.2 months; P = 0.041]. In the RT plus TKI group, 12 (18.1%) of the 66 patients experienced intracranial progression and 3 of them received salvage RT (median OS; 37.4 vs. 20.0 months; P = 0.044). In multivariate analysis, upfront WBRT was associated with trends towards a lower probability of intracranial progression, whereas upfront SRS was found to be an independent risk factor for poor OS. In conclusion, using EGFR-TKI alone for brain metastasis in EGFR-mutant lung cancer patients showed outcomes comparable to those using upfront RT followed by EGFR-TKI. Patients who could not receive salvage RT following intracranial progression had the worst survival regardless of the type of initial treatment.
Introduction

In patients with non–small-cell lung cancer (NSCLC), the incidence of initial brain metastases at the time of lung adenocarcinoma diagnosis is approximately 20% [1]; furthermore, patients with brain metastases have poor outcomes compared with those without brain metastases [2]. Although radiotherapy (RT) or surgical resection has been the conventional treatment for brain metastases, patient survival rate remains unsatisfactory and severe deterioration of general condition has often been observed owing to neurotoxicity after RT [3,4]. However, the median overall survival (OS) has recently been increasing in patients with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma and brain metastases due to the introduction of targeted therapy [5].

Although EGFR-tyrosine kinase inhibitor (TKI) has low cerebrospinal fluid penetration rates [6], it may result in good intracranial response rates due to a high sensitivity of EGFR-mutant tumour to EGFR-TKI [7]. Therefore, upfront EGFR-TKI alone without local RT has been used [8–11] with the advantage of avoiding radiation-induced neurotoxicity until tumour progression [12,13]. However, several studies have shown that upfront RT plus EGFR-TKI could produce a favourable outcome [14,15]. Furthermore, a recent multi-institutional retrospective analysis has revealed that stereotactic radiosurgery (SRS) followed by EGFR-TKI is associated with the longest OS [16]. Thus, proper management of EGFR-mutant NSCLC with brain metastases remains controversial.

Most studies have focused on outcomes according to the presence or absence of RT in initial treatment [14,16]. Hence, it is difficult to find data on the progression pattern after initial treatment and the effects of the subsequent treatments. To determine the optimal management of patients with EGFR-mutant NSCLC with brain metastases, this study investigated the clinical outcomes according to the use of upfront RT (WBRT or SRS) as well as the disease progression pattern and subsequent therapy following intracranial progression.

Material and methods

Study design and patients

This retrospective study included patients who were initially diagnosed with EGFR-mutant lung adenocarcinoma and brain metastases between 1st January 2011 and 31st December 2016. Data were collected from patients’ medical records. Inclusion criteria were as follows: 1) patients pathologically diagnosed with EGFR-mutant lung adenocarcinoma; 2) brain metastases confirmed using magnetic resonance imaging (MRI) or computed tomography (CT) scan at the time of initial diagnosis; 3) patients who received EGFR-TKI therapy with or without RT. Patients were excluded if they reported prior EGFR-TKI use, received conventional chemotherapy, underwent surgical resection or brain RT to the lung cancer before study enrolment or had an EGFR-TKI–resistant mutation. Patients were treated with EGFR-TKI alone (TKI alone group) or with upfront whole-brain RT (WBRT) or stereotactic radiosurgery (SRS) followed by EGFR-TKI (RT plus TKI group). This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2018–0240) and performed in accordance with the amended Declaration of Helsinki. Because this study was the retrospective analysis, IRB confirmed the requirement for informed consent was waived.

Data variables and response assessment

The following variables were collected for analysis: age, sex, TNM stage (8th edition) [17], smoking history, EGFR mutation, Eastern Cooperative Oncology Group (ECOG) performance status at the time of initial diagnosis, number of brain metastases, size of the largest
brain metastasis, presence or absence of extracranial metastases, symptoms associated with brain metastases, type of RT, pattern of progression (intracranial progression vs. systemic) and presence or absence of salvage RT after intracranial progression. EGFR mutations were detected using polymerase chain reaction amplification from the paraffin-embedded tumour samples.

Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours, version 1.1, using MR images of the brain; CT scans of the chest, abdomen and pelvis and positron emission tomography images. Objective response rate was defined as complete response (CR; the best tumour response) and partial response (PR), and disease control rate was defined as the sum of CR, PR and stable disease.

**Statistical methods**

All the available patient data were compared using $\chi^2$ test or Fisher’s exact test for categorical variables. OS was calculated from the date of lung adenocarcinoma diagnosis until the date of death due to any cause. Progression-free survival (PFS) was defined as the duration from the date of lung adenocarcinoma diagnosis until the date of growth of a previous lesion, development of a new lesion, death without documented progression or last follow-up. The primary outcome of this study was the comparison of OS in patients according to the type of initial treatment (EGFR-TKI alone, WBRT followed by EGFR-TKI and SRS followed by EGFR-TKI) or the presence of salvage RT. The secondary outcome included PFS, response rate and risk factors associated with death. Kaplan–Meier analysis was used to estimate OS and PFS, whereas log-rank test was used to test the significance of differences. Furthermore, cumulative incidence curves were generated for intracranial progression. Univariable and multivariable Cox proportional hazards regression models identified risk factors associated with death and intracranial progression. A final model was constructed using a stepwise method with backward selection; $p$ values $< 0.15$ in univariate analysis were set for the entry of variables. Two-sided $p$ values $< 0.05$ were considered to indicate significance. All analyses were performed using SPSS ver. 24.0 (IBM Corporation, USA) software.

**Results**

**Patient characteristics**

We identified 173 eligible patients after applying the exclusion criteria. Of the 173 patients, 107 (61.8%) received EGFR-TKI alone, 36 (20.8%) were treated with WBRT followed by EGFR-TKI and 30 (17.3%) were treated with SRS followed by EGFR-TKI. All of 173 patients were evaluated by MRI scan for CNS metastasis at the time of initial diagnosis. Patient characteristics are shown in Table 1. There were no differences between the TKI alone and RT plus TKI groups regarding age, sex, ECOG performance status, smoking status, number of brain metastases, extracranial metastases at the time of brain metastases, EGFR mutation and EGFR-TKIs. Patients treated with EGFR-TKI alone were more likely to have a N2–3 (51.4% TKI alone vs. 31.8% upfront RT; $P = 0.018$) and M1a (18.7% TKI alone vs. 0% upfront RT; $P < 0.0001$) stage tumour at diagnosis. The TKI alone group was less likely to have symptomatic brain metastases (8.4% TKI alone vs. 37.9% upfront RT; $P < 0.0001$) and largest brain metastases measuring $\leq 1$cm (67.3% TKI alone vs. 25.8% upfront RT; $P < 0.0001$). In the RT plus TKI group, the number of patients with $\geq 5$ brain metastases was higher in the upfront WBRT group (77.8%) than in the upfront SRS group (6.7%).

**Disease progression pattern and treatment outcomes**

The median follow-up duration was 18.7 (range 1.6–76.8) months. The median count of CNS imaging after initial treatment was 3.0 (range 1.0–24.0) and the median first, second interval
Table 1. Patient characteristics.

| Characteristic, No. (%) | TKI alone (n = 107) | RT plus TKI (n = 66) | WBRT (n = 36) | SRS (n = 30) | p-value |
|------------------------|---------------------|---------------------|---------------|--------------|---------|
| Sex                    |                     |                     |               |              |         |
| Male                   | 37 (34.6)           | .402               | 11 (30.6)     | 16 (53.3)    | .061    |
| Female                 | 70 (65.4)           |                     | 25 (69.4)     | 14 (46.7)    |         |
| Age (years)            |                     |                     |               |              |         |
| <65                    | 65 (60.7)           | .162               | 29 (80.6)     | 18 (60.0)    | .066    |
| ≥65                    | 42 (39.3)           |                     | 7 (19.4)      | 12 (40.0)    |         |
| T stage at diagnosis   |                     |                     |               |              |         |
| T1–3                   | 69 (64.5)           | .181               | 21 (58.3)     | 28 (93.3)    | .001    |
| T4                     | 38 (35.5)           |                     | 15 (41.7)     | 2 (6.7)      |         |
| N stage at diagnosis   |                     |                     |               |              |         |
| N0–1                   | 52 (48.6)           | .018               | 23 (63.9)     | 22 (73.3)    | .412    |
| N2–3                   | 55 (51.4)           |                     | 13 (36.1)     | 8 (26.7)     |         |
| M1a stage at diagnosis | 20 (18.7)           | < .0001            | 0 (0.0)       | 0 (0.0)      |         |
| ECOG                   | .251                |                     |               |              |         |
| 0–1                    | 77 (72.0)           |                     | 20 (55.6)     | 22 (73.3)    | .135    |
| 2–4                    | 30 (28.0)           |                     | 16 (44.4)     | 8 (26.7)     |         |
| Smoking status         |                     |                     |               |              |         |
| Current/former         | 36 (33.6)           | .505               | 10 (27.8)     | 9 (30.0)     | .843    |
| Never                  | 71 (66.4)           |                     | 26 (72.2)     | 21 (70.0)    |         |
| Symptomatic brain metastases |               |                     |               |              |         |
| No                     | 98 (91.6)           | < .0001            | 22 (61.1)     | 21 (70.0)    | .853    |
| Yes                    | 9 (8.4)             |                     | 14 (38.9)     | 11 (36.7)    |         |
| No. of brain metastases|                     |                     |               |              |         |
| 1                      | 24 (22.4)           | .791*              | 3 (8.3)       | 10 (33.3)    | < .0001 |
| 2–4                    | 30 (28.0)           |                     | 5 (13.9)      | 18 (60.0)    |         |
| 5–9                    | 23 (21.5)           |                     | 10 (27.8)     | 2 (6.7)      |         |
| ≥10*                   | 30 (28.1)           |                     | 18 (50.0)     | 0 (0.0)      |         |
| Size of largest brain metastases |                 |                     |               |              |         |
| ≤1 cm                  | 72 (67.3)           | < .0001*           | 10 (27.8)     | 7 (23.3)     | .574*   |
| >1 cm                  | 35 (32.7)           |                     | 26 (72.2)     | 23 (76.6)    |         |
| Extracranial metastases at time of brain metastases |     |                     |               |              |         |
| No                     | 24 (22.4)           | .713               | 8 (22.2)      | 9 (30.0)     | .575    |
| Yes                    | 83 (77.6)           |                     | 28 (77.8)     | 21 (70.0)    |         |
| EGFR mutation          |                     |                     |               |              |         |
| Exon 18                | 4 (3.7)             | .573*              | 1 (2.8)       | 3 (10.0)     | .429*   |
| Exon 19                | 68 (63.6)           |                     | 23 (63.9)     | 17 (56.6)    |         |
| Exon 21                | 35 (32.7)           |                     | 12 (33.3)     | 10 (33.3)    |         |
| EGFR-TKIs              |                     |                     |               |              |         |
| Gefitinib              | 77 (72.0%)          | .239               | 27 (75.0%)    | 21 (70.0%)   | .078*   |
| Erlotinib              | 16 (15.0%)          | 5 (13.9%)          | 9 (30.0%)     |             |         |
| Afatinib               | 14 (13.1%)          | 4 (11.1%)          | 0 (0.0%)      |             |         |

* Fisher’s exact test.

**Abbreviations:** ECOG; Eastern Cooperative Oncology Group. EGFR; Epidermal growth factor receptor. TKI; Tyrosine kinase inhibitor. RT; Radiotherapy. WBRT; Whole-brain radiotherapy. SRS; Stereotactic radiosurgery

https://doi.org/10.1371/journal.pone.0231546.t001
between response evaluations was 3.4 (range 0.6–28.6), 2.8 (range 0.0–37.0) months. The median OS for the TKI alone, WBRT and SRS groups was 24.5 months (95% CI, 18.1–30.8), 20.0 months (95% CI, 14.6–25.4) and 17.8 months (95% CI, 13.9–21.8), respectively (log-rank P = 0.186; Fig 1). The median time to intracranial progression for the TKI alone, WBRT and SRS groups was 13.6 months (95% CI, 11.6–15.5), 15.3 months (95% CI, 7.1–23.5) and 15.8 months (95% CI, 10.6–21.0), respectively (log-rank P = 0.389). Intracranial progression developed in 35 (32.7%) of the 107 patients who received EGFR-TKI alone, whereas it developed in 12 (18.1%) of the 66 patients who were treated with upfront RT followed by EGFR-TKI (P = 0.036) (Fig 2). Similar intracranial PFS (10.4 months vs. 10.8 months; P = 0.945) and extracranial PFS (11.6 months vs. 10.6 months; P = 0.754) were observed between patients treated with TKI alone and those who received RT plus TKI. The median OS for patients who received EGFR-TKI alone without and with salvage RT was 11.2 months (95% CI, 2.1–20.4) and 28.6 months (95% CI, 19.8 to 37.4), respectively (log-rank P = 0.041; Fig 3). Furthermore, there was a significant difference in OS according to the presence or absence of subsequent RT in the RT plus TKI group (37.4 months; 95% CI, 5.6–69.2 vs. 15.6 months; 95% CI, 8.6–22.6) (log-rank P = 0.044). Most patients without salvage RT could not undergo RT due to their deteriorating general condition. Regarding intracranial response at 1st evaluation, no significant difference in the intracranial objective response rate was observed among the three groups (TKI alone group, 62.6% vs. WBRT group, 72.2% vs. SRS group, 60.0%; P = 0.508) (Table 2). However, intracranial disease control rate was higher in the RT plus TKI group than in the TKI alone group (WBRT group, 94.4% vs. SRS group, 83.3% vs. TKI alone group, 72.0%; P = 0.014).

**Prognostic factors**

Multivariable model controlling for significant covariables such as age, ECOG performance status, upfront WBRT or SRS, smoking status, salvage RT and extracranial metastases at the time of brain metastases revealed that upfront SRS (HR 1.67; 95% CI, 1.08–2.58; P = 0.022), age < 65 years (HR 0.60; 95% CI, 0.42–0.84, P = 0.004), ECOG performance status 2–4 (HR 1.80; 95% CI, 1.24–2.61, P = 0.002) and extracranial metastases at time of brain metastases (HR 2.01; 95% CI, 1.27 to 3.17; P = 0.003) were independent risk factors for predicting OS.
Upfront WBRT was also associated with trends towards a lower probability of intracranial progression (HR 0.55; 95% CI, 0.33–0.91; P = 0.021). However, other variables such as sex, EGFR mutation and number of intracranial metastases did not influence OS and intracranial PFS.

Discussion

In this study, the use of upfront RT was not associated with a better prognosis than treatment with EGFR-TKI alone, although patients who received upfront RT followed by EGFR-TKI had a high disease control rate at the initial evaluation of treatment response. In addition, among...
patients who developed intracranial progression, OS improved in patients in whom salvage RT was applied to the intracranial lesions compared with that in patients without salvage RT.

Several mechanisms have been proposed for the progression of intracranial lesions. First, resistant mutations against TKI resistance could induce intracranial progression [18]. The p. Thr790Met point mutation (T790M) in the gene encoding EGFR is the most common cause of TKI resistance in lung cancer; it can reduce binding of TKIs to EGFR [19]. MET gene amplification [20] and transformation into small-cell lung cancer [21] are also associated with TKI resistance. Concurrent progression of both intracranial and extracranial lesions may be caused by these mechanisms, whereas only intracranial progression would occur due to different causes [22,23]. The altered penetration of TKI into the central nervous system across the blood–brain barrier has been considered as the one of mechanisms [24]. A decreased concentration of TKI in cerebrospinal fluid provokes the reduction of TKI-mediated inhibition of downstream signalling on the intracranial lesions, causing intracranial progression [22]. Through a similar mechanism, increased p-glycoprotein may lead to intracranial progression via a decrease in intracranial TKI concentration [25]. There were many patients with intracranial progression in this study; in them, the progression was likely related to a change in the intracerebral TKI concentration.

Table 2. Comparison of the response among the three groups at 1st evaluation after treatment.

| Variable, No. (%) | EGFR-TKI (n = 107) | Upfront WBRT (n = 36) | Upfront SRS (n = 30) | p-value |
|------------------|--------------------|-----------------------|---------------------|---------|
| Intracranial Response |                    |                       |                     | < .0001* |
| CR               | 20 (18.7)          | 0 (0.0)               | 0 (0.0)             |         |
| PR               | 47 (43.9)          | 26 (72.2)             | 18 (60.0)           |         |
| SD               | 10 (9.3)           | 8 (22.2)              | 7 (23.3)            |         |
| PD               | 30 (28.0)          | 2 (5.6)               | 5 (16.7)            |         |
| Intracranial ORR | 67 (62.6)          | 26 (72.2)             | 18 (60.0)           | .508    |
| Intracranial DCR | 77 (72.0)          | 34 (94.4)             | 25 (83.3)           | .014    |

* Fisher’s exact test.

**Abbreviations:** EGFR; Epidermal growth factor receptor. TKI; Tyrosine kinase inhibitor. WBRT; Whole-brain radiotherapy. SRS; Stereotactic radiosurgery. CR; Complete response. PR; Partial response. SD; Stable disease. PD; Progression disease. ORR; Objective response rate. DCR; Disease control rate.
In the present study, no significant differences in intracranial progression and survival benefit were observed between patients treated with EGFR-TKI alone and those who received upfront RT followed by EGFR-TKI. Because there were significantly more patients who had large and symptomatic brain metastases in the RT plus TKI group than in the TKI alone group, these results must be carefully interpreted. Moreover, approximately half the patients in the TKI alone group received salvage RT, but only a few patients in the RT plus TKI group received it. This difference might have influenced the clinical outcomes because an analysis of patients who had intracranial progression showed that patients who received salvage RT had a longer median OS than those who did not, regardless of the initial treatment. The third-generation EGFR-TKI commonly used nowadays can be considered as a treatment option instead of salvage RT because of its much better intracranial effect than that of previous EGFR-TKIs [26]. However, it is very difficult to obtain brain tissues for the identification of T790M in patients with intracranial progression. Although a liquid biopsy using a blood sample recently has been introduced into the test for T790M, the result through liquid biopsy occasionally seems to show discrepancy of T790M expression between actual tissue sample and blood sample. Therefore, salvage RT is more likely chosen to manage intracranial progression in real practice. Further study will be needed for EGFR mutant NSCLC patients with initially brain metastasis who received the third generation TKIs as the first line treatment to investigate the clinical outcomes according to the use of upfront RT as well as the salvage RT following intracranial progression. Because there could be a selection bias that patients without salvage RT might have poorer performance than those with salvage RT, further prospective randomised trials are needed to investigate the effect of salvage RT in patients with intracranial progression.

The clinical outcomes in this study seem to be consistent with those reported by prior studies evaluating the use of EGFR-TKI alone or of upfront RT followed by EGFR-TKI [16,27–35]. Although the disease control rate after the 1st treatment was higher in RT plus TKI groups than in the TKI alone group, the median OS of patients who received EGFR-TKI alone, upfront WBRT and upfront SRS in the present study was 24.5, 20.2 and 18.5 months, respectively, showing no significant differences. In two studies conducted in South Korea, the use of upfront RT did not provide more beneficial outcomes than the use of EGFR-TKI alone [27,33]. Other retrospective studies have also reported similar outcomes, with OS ranging

Table 3. Multivariable model of risk factors to predict intracranial progression-free survival and overall survival.

| Variable                                      | Progression-free survival | Overall survival |
|-----------------------------------------------|---------------------------|-----------------|
|                                               | HR  | 95% CI | p-value  | HR  | 95% CI | p-value |
| Upfront WBRT v EGFR-TKI                       | 0.55 | 0.33 to 0.91 | .021     | 1.08 | 0.70 to 1.67 | .723   |
| Upfront SRS v EGFR-TKI                        | 0.95 | 0.56 to 1.60 | .832     | 1.67 | 1.08 to 2.58 | .022   |
| Age (years)                                   |     |        |          | 0.60 | 0.42 to 0.84 | .004   |
| <65 vs. ≥65                                    |     |        |          | 1.92 | 1.28 to 2.90 | .002   |
| ECOG performance status                        |     |        |          | 1.80 | 1.24 to 2.61 | .002   |
| 2–4 vs. 0–1                                    |     |        |          | 1.40 | 0.98 to 2.02 | .064   |
| Smoking status                                 |     |        |          | 1.49 | 0.95 to 2.31 | .080   |
| Yes vs. No                                     |     |        |          | 2.01 | 1.27 to 3.17 | .003   |
| Extracranial metastases at time of brain metastases |     |        |          | 1.49 | 0.95 to 2.31 | .080   |

Abbreviations: EGFR; Epidermal growth factor receptor. TKI; Tyrosine kinase inhibitor. RT; Radiotherapy. WBRT; Whole-brain radiotherapy. SRS; Stereotactic radiosurgery. ECOG; Eastern Cooperative Oncology Group. HR; Hazard ratio. CI; confidence interval.

https://doi.org/10.1371/journal.pone.0231546.t003
from 21.6 months to 31.9 months according to the type of treatment, despite the higher intracranial PFS with upfront RT [30–32]. In addition, a meta-analysis that analysed the 5 studies for the comparison of WBRT plus EGFR-TKIs and EGFR-TKIs alone in Cerebral metastatic NSCLC patients has presented that EGFR-TKIs provides similar clinical outcomes compared with WBRT plus EGFR-TKIs [35]. These studies are likely to support the non-inferiority of EGFR-TKIs alone treatment. Conversely, a retrospective multi-institutional analysis has shown a better prognosis than that observed in the present study; in that study, the median OS of patients treated with SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI and EGFR-TKI followed by SRS or WBRT was 47, 31 and 25 months, respectively [16]. We believe that accumulating more data in the near future can help explain this issue.

This study has several limitations. First, it was a single-centre retrospective study, which would lead to all of the inherent biases in such a study. There were significantly different baseline characteristics between the groups. The RT plus TKI group had more patients with CNS symptom and > 1cm size of brain metastasis than the TKI alone group, which might have resulted in better prognostic effects on patients in the TKI alone group. However, a tumor burden such as N2-3 and M1a of the TKI alone group was larger than the RT plus TKI group. Considering these factors, the results that there were no significant differences from clinical outcomes between the two groups in rear world practice could be reasonable and meaningful. In addition, this study had the homogeneity of the patient population with confounding factors including age, ECOG to affect the clinical outcomes and we also tried to minimize bias by using multivariate model. Further prospective studies with well-balanced cohort are needed in the future. Second, the evaluation of intracranial disease using brain imaging was not regularly performed. Approximately 40% patients received CNS evaluation only 1 time, while some patient was evaluated by maximal 24 times for CNS metastasis. A differential bias might have resulted from missing asymptomatic brain metastases. Nevertheless, most patients in this study were evaluated for CNS metastasis every approximately three months. Also, the strength of this study is that we analysed all patients’ pattern of cancer progression and subsequent treatment course according to the progression pattern. Third, we did not account for several RT-induced neurotoxicities, which is one of the most important reasons for the deterioration of patients’ quality of life. Despite of this missing data, it is important to note that we evaluated the impact of salvage RT, the statistically significant finding, on the final outcome. Considering these limitations, the findings in this study need to be validated in prospective trials with large scale.

Conclusions

Although EGFR-TKI alone for brain metastasis in EGFR-mutant lung cancer showed outcomes comparable to those obtained with upfront RT followed by EGFR-TKI, a proportion of patients who could not receive RT following intracranial progression had the worst survival in this study. In patients with only intracranial progression, salvage RT to the intracranial lesions might have survival benefits. Further prospective studies are needed to determine the optimal management of patients with EGFR-mutant NSCLC who initially develop brain metastases.

Author Contributions

Conceptualization: Dong-gon Hyun, Chang-Min Choi, Sang-We Kim, Woo Sung Kim, Wonjun Ji, Jae Cheol Lee.

Data curation: Dong-gon Hyun, Sang-We Kim, Shinkyo Yoon, Wonjun Ji.
Formal analysis: Dong-gon Hyun, Chang-Min Choi, Sang-We Kim, Shinkyo Yoon, Wonjun Ji, Jae Cheol Lee.

Funding acquisition: Chang-Min Choi, Wonjun Ji, Jae Cheol Lee.

Methodology: Dong-gon Hyun, Dae Ho Lee, Shinkyo Yoon, Wonjun Ji, Jae Cheol Lee.

Visualization: Dae Ho Lee.

Writing – original draft: Dong-gon Hyun, Shinkyo Yoon, Woo Sung Kim, Wonjun Ji, Jae Cheol Lee.

Writing – review & editing: Chang-Min Choi, Dae Ho Lee, Wonjun Ji.

References

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol. 2004; 22: 2865–2872. https://doi.org/10.1200/JCO.2004.12.149 PMID: 15254054

2. Noronha V, Joshi A, Gokarn A, Sharma V, Patil V, Janu A, et al. The importance of brain metastasis in EGFR mutation positive NSCLC patients. Chemother Res Pract. 2014; 2014: 856156. https://doi.org/10.1155/2014/856156 PMID: 25548673

3. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004; 363: 1665–1672. https://doi.org/10.1016/S0140-6736(04)16250-8 PMID: 15158627

4. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet. 2016; 388: 2004–2014. https://doi.org/10.1016/S0140-6736(16)30825-X PMID: 27604504

5. Bai H, Han BH. The effectiveness of erlotinib against brain metastases in non-small cell lung cancer patients. Am J Clin Oncol Cancer Clin Trial. 2013; 36: 110–115. https://doi.org/10.1097/COC.0b013e3182438c91 PMID: 22391431

6. Zhao J, Chen M, Zhong W, Zhang L, Li L, Xiao Y, et al. Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. Clin Lung Cancer. 2013; 14: 188–193. https://doi.org/10.1016/j.clclc.2012.06.004 PMID: 22846582

7. Iuchi T, Shingyoji M, Sakaida T, Hatano K, Nagano O, Itakura M, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer. 2013; 82: 282–287. https://doi.org/10.1016/j.lungcan.2013.08.016 PMID: 24021541

8. Bai H, Xiong L, Han B. The effectiveness of EGFR-TKIs against brain metastases in EGFR mutation-positive non-small-cell lung cancer patients. Onco Targets Ther. 2017; 10: 2335–2340. https://doi.org/10.2147/OTT.S129809 PMID: 28490892

9. Jiang T, Su C, Li X, Zhao C, Zhou F, Ren S, et al. EGFR TKIs plus WBRT demonstrated no survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. J Thorac Oncol. 2016; 11: 1718–1728. https://doi.org/10.1016/j.jtho.2016.05.013 PMID: 27237825

10. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer. 2012; 77: 556–560. https://doi.org/10.1016/j.lungcan.2012.05.092 PMID: 22677429

11. Kim JE, Lee DH, Choi Y, Yoon DH, Kim SW, Suh C, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer. 2009; 65: 351–354. https://doi.org/10.1016/j.lungcan.2008.12.011 PMID: 19157632

12. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Korn Ruth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009; 10: 1037–1044. https://doi.org/10.1016/S1470-2245(09)70263-3 WOS:000271852800012 PMID: 19801201
13. Soon YY, Leong CN, Koh WY, Tham IW. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: a systematic review and meta-analysis. Radiother Oncol. 2015; 114: 167–172. https://doi.org/10.1016/j.radonc.2014.12.011 PMID: 25583566

14. Du XJ, Pan SM, Lai SZ, Xu XN, Deng ML, Wang XH, et al. upfront cranial radiotherapy vs. EGFR tyrosine kinase inhibitors alone for the treatment of brain metastases from non-small-cell lung cancer: a meta-analysis of 1465 patients. Front Oncol. 2018; 8: 603. https://doi.org/10.3389/fonc.2018.00603 PMID: 30619745

15. Wang C, Lu X, Lyu Z, Bi N, Wang L. Comparison of up-front radiotherapy and TKI with TKI alone for NSCLC with brain metastases and EGFR mutation: a meta-analysis. Lung Cancer. 2018; 122: 94–99. https:// doi.org/10.1016/j.lungcan.2018.05.014 PMID: 30032853

16. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine kinase inhibitor-naive epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. J Clin Oncol. 2017; 35: 1070–1077. https://doi.org/10.1200/JCO.2016.69.7144 PMID: 28113019

17. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016; 11: 39–51. https://doi.org/10.1016/j.jtho.2015.09.009 PMID: 26762738

18. Sequist LV, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. Clin Cancer Res. 2011; 17: 1616–1622. https://doi.org/10.1186/1753-4658-15-587820 PMID: 21135146

19. Tartarone A, Lerose R. Clinical approaches to treat patients with non-small cell lung cancer and epidermal growth factor receptor tyrosine kinase inhibitor acquired resistance. Ther Adv Respir Dis. 2015; 9: 242–250. https://doi.org/10.1177/1753465815587820 PMID: 26016841

20. Lee JK, Lee J, Kim S, Kim S, Youk J, Park S, et al. Clonal history and genetic predictors of transformation into small-cell carcinomas from lung adenocarcinomas. J Clin Oncol. 2017; 35: 3065–3074. https://doi.org/10.1200/JCO.2016.71.9096 PMID: 28498782

21. Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borras AM, et al. Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. J Clin Oncol. 2006; 24: 4517–4520. https://doi.org/10.1200/JCO.2006.06.6126 PMID: 16983123

22. How J, Mann J, Lacznik AN, Baggstrom MQ. Pulsatile erlotinib in EGFR-positive non-small-cell lung cancer patients with leptomeningeal and brain metastases: review of the literature. Clin Lung Cancer. 2017; 18: 354–363. https://doi.org/10.1016/j.cllc.2017.01.013 PMID: 28245967

23. Omuro AM, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT, et al. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. Cancer. 2005; 103: 2344–2348. https://doi.org/10.1002/cncr.21033 PMID: 15844174

24. de Vries NA, Buckle T, Zhao J, Beijnen JH, Schellens JH, van Tellingen O. Restricted brain penetration of the tyrosine kinase inhibitor erlotinib due to the drug transporters P-gp and BCRP. Invest New Drugs. 2012; 30: 443–449. https://doi.org/10.1007/s10637-010-9569-1 PMID: 20963470

25. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol. 2018. https://doi.org/10.1200/JCO.2018.78.3118 PMID: 30153097

26. Byeon S, Ham JS, Sun JM, Lee SH, Ahn JS, Park K, et al. Analysis of the benefit of sequential cranial radiotherapy in patients with EGFR mutant non-small cell lung cancer and brain metastasis. Med Oncol. 2016; 33: 97. https://doi.org/10.1007/s12032-016-0811-3 PMID: 27477111

27. Wang W, Song Z, Zhang Y. Efficacy of brain radiotherapy plus EGFR-TKI for EGFR-mutated non-small cell lung cancer patients who develop brain metastasis. Arch Med Sci. 2018; 14: 1298–1307. https://doi.org/10.5114/ams.2018.78939 PMID: 30393484

28. Chen Y, Yang J, Li X, Hao D, Wu X, Yang Y, et al. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma. Cancer Sci. 2016; 107: 1800–1805. https://doi.org/10.1111/cas.13079 PMID: 27627582
30. Fan Y, Xu Y, Gong L, Fang l, Lu H, Qin J, et al. Effects of icotinib with and without radiation therapy on patients with EGFR mutant non-small cell lung cancer and brain metastases. Sci Rep. 2017; 7: 45193. https://doi.org/10.1038/srep45193 PMID: 28332624

31. Liu YM, Deng L, Zhou XJ, Gong YL, Xu Y, L, et al. Concurrent brain radiotherapy and EGFR-TKI may improve intracranial metastases control in non-small cell lung cancer and have survival benefit in patients with low DS-GPA score. Oncotarget. 2017; 8: 111309–111317. https://doi.org/10.18632/oncotarget.22785 WOS:000419567000048 PMID: 29340055

32. Doherty MK, Korpanty GJ, Tomasini P, Alizadeh M, Jao K, Labbe C, et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. Radiother Oncol. 2017; 123: 195–202. https://doi.org/10.1016/j.radonc.2017.03.007 PMID: 28363487

33. Sung S, Lee SW, Kwak YK, Kang JH, Hong SH, Kim YS. Intracranial control and survival outcome of tyrosine kinase inhibitor (TKI) alone versus TKI plus radiotherapy for brain metastasis of epidermal growth factor receptor-mutant non-small cell lung cancer. J Neurooncol. 2018; 139: 205–213. https://doi.org/10.1007/s11060-018-2861-1 PMID: 29644484

34. Wang C, Lu X, Zhou Z, Wang J, Hui Z, Liang J, et al. The efficacy of upfront intracranial radiation with TKI compared to TKI alone in the NSCLC patients harboring EGFR mutation and brain metastases. J Cancer. 2019; 10: 1985–1990. https://doi.org/10.7150/jca.30131 PMID: 31205558

35. Zheng H, Liu QX, Hou B, Zhou D, Li JM, Lu X, et al. Clinical outcomes of WBRT plus EGFR-TKIs versus WBRT or TKIs alone for the treatment of cerebral metastatic NSCLC patients: a meta-analysis. Oncotarget. 2017; 8: 57356–57364. https://doi.org/10.18632/oncotarget.19054 PMID: 28915676