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Exploring Brain Metastasis in EGFR-Mutated Non-Small Cell Lung Cancer Patients: Correlation, Detection and Treatment Strategies

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Abstract

Non-Small Cell Lung Cancer (NSCLC) is a common type of lung cancer, and Epidermal Growth Factor Receptor (EGFR) mutation is a key subtype. NSCLC patients with EGFR mutations generally show better responses to targeted therapy; however, brain metastasis remains a clinical challenge in this patient population. This review aims to delve into the correlation, diagnostic methods, and treatment strategies of EGFR mutations and brain metastasis in NSCLC patients. Firstly, we discuss the correlation between EGFR mutations and the incidence of brain metastasis as well as the survival time of NSCLC patients. We analyze the differences that EGFR mutations bring to the detection of NSCLC patients currently. In terms of treatment, we discuss various options such as surgical resection, radiotherapy, and drug therapy, as well as the pros and cons and potential side effects of these treatment methods. Overall, the management of brain metastasis in NSCLC patients with EGFR mutations faces multiple challenges, but through in-depth research into the specificity of the EGFR signaling pathway and the molecular mechanisms of brain metastasis, we can move towards more effective prevention and treatment strategies.

Introduction

Lung cancer remains a significant global health challenge. Among malignant tumor patients, lung cancer is one of the most common primary tumors with Central Nervous System (CNS) metastasis, constituting 50% of cases [1]. In Non-Small Cell Lung Cancer (NSCLC) patients, approximately 20% to 40% will experience brain metastasis during the course of the disease. Tumors with activating mutations in the Epidermal Growth Factor Receptor (EGFR+) have a higher incidence of brain metastasis, but a longer overall survival [2]. Tumors carrying activating mutations in the Epidermal Growth Factor Receptor (EGFR+) show a higher incidence of brain metastasis, yet they have an extended overall survival period [3]. Treatment modalities for Non-Small Cell Lung Cancer (NSCLC) with Central Nervous System (CNS) metastasis include surgery, Stereotactic Radiosurgery (SRS), Whole-Brain Radiotherapy (WBRT), chemotherapy, and tyrosine kinase inhibitors [4].

Among Non-Small Cell Lung Cancer (NSCLC) patients with brain metastasis, those with EGFR mutations exhibit differences in incidence, detection, treatment strategies and more. This article aims to briefly elucidate the characteristics of NSCLC with EGFR mutations in brain metastasis, focusing on mechanisms, clinical manifestations, differential diagnosis, and treatment.

The Correlation Between EGFR Mutations and Brain Metastasis in NSCLC

EGFR mutation is an independent predictor of brain metastasis

Lung cancer is one of the leading causes of cancer-related deaths worldwide [5]. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85% of all lung cancers. The brain is one of the major sites of metastasis in lung cancer patients, with Brain Metastasis (BMs) remaining a primary cause of its incidence and mortality rates. Throughout the course of the disease, nearly 50% of NSCLC patients will experience distant metastasis, often accompanied by the occurrence of brain metastasis [6]. Non-Small Cell Lung Cancer (NSCLC) has a high incidence of Brain Metastasis (BM), with 10% to 20% diagnosed with brain metastasis at an early stage and 40% diagnosed during the course of the disease [7].

Research has confirmed that many NSCLC brain metastasis patients harbor mutations in EGFR, ALK and KRAS [8]. Among patients experiencing brain metastasis, there are significant differences

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between groups with different mutated genes. A study involving 9,058 NSCLC patients and encompassing 45 studies revealed that EGFR and KRAS mutations are most significantly associated with the incidence of brain metastasis, with rates of 0.16 and 0.17, respectively [9].

Among East Asian patients, Matsumoto et al. [10] conducted testing on 19 cases of brain metastatic lung adenocarcinoma, revealing EGFR mutations in 12 cases (63%). In contrast, Gow et al. detected EGFR mutations in 44% of brain metastasis patients [11,12].

A retrospective analysis by Han et al. [13] concluded that EGFR mutation is an independent predictor and prognostic risk factor for brain metastasis in lung adenocarcinoma patients. It is also a positive predictor for the Overall Survival (OS) of patients with brain metastasis. Whether at the time of diagnosis or during the course of the disease, the incidence of Brain Metastasis (BM) in patients with EGFR mutant tumors is higher than in those with EGFR wild-type tumors. Shuo et al. study indicates that the proportion of patients with EGFR mutant tumors (26 cases; 44.8%) who died from brain metastasis is significantly higher than that of patients with EGFR wild-type tumors (3 cases; 8.3%) ($P<0.001$) [14]. Research by Mitra et al. [15] suggests that the probability of brain metastasis significantly increases in NSCLC patients after standard combination therapy, but this is unrelated to a longer overall survival.

Relevant *in vitro* experiments suggest several possible reasons: 1) EGFR mutations induce morphological changes in lung cancer cells from an epithelial phenotype to a spindle-shaped morphology; 2) Mutated EGFR inhibits the barrier properties of lung cancer cells; 3) Compared to wild-type EGFR, mutated EGFR increases the expression of vimentin, thereby promoting cell migration [16]. Analysis of two different lung adenocarcinoma cohorts also indicates that mutated EGFR promotes the dissemination of lung cancer cells and is correlated with the expression of vimentin [17,18].

Meanwhile, EGFR mutation is also associated with a longer median survival. Eichler et al. [19] reported that brain metastasis patients with EGFR mutations have a longer survival period compared to those with wild-type EGFR (20.2 *vs.* 17.9 months).

EGFR mutation is correlated with the symptoms of Brain Metastasis (BM)

Depending on the mutation status of NSCLC patients, there are differences in the spatial distribution of brain metastasis, which may impact clinical presentations. Takono et al. [20] first revealed the relationship between EGFR mutation status and the spatial distribution of lung cancer brain metastasis. Compared to EGFR wild-type or EGFR exon 19 deletion mutations, the intracranial lesions with EGFR L858R mutations were significantly closer to the brain surface ($P=0.0032$, $P<0.0001$); the occurrence rate of L858R mutation brain metastasis in the occipital lobe, cerebellum and temporal lobe was higher than that of EGFR exon 19 mutations. In lung adenocarcinoma patients with a history of chemotherapy but without molecular targeted therapy, brain metastases were notably located deeper from the brain surface ($P=0.0002$) [20]. In a study by Chen et al. involving 110 NSCLC patients and a total of 1,386 brain metastases, the results revealed that the high-incidence areas of EGFR-driven brain metastases include three clusters located in the left cerebellum, the left portion of the occipital lobe, the left precuneus, and the central anterior gyrus of the right frontal lobe. Moreover, brain metastases in the EGFR group tended to prioritize distribution to the medial frontal gyrus, possibly associated with brain functions like memory and decision-making. Compared to patients with wild-type EGFR, those with mutated EGFR were more inclined to develop multiple brain metastases [21].

In NSCLC brain metastasis patients with EGFR mutations, different types of mutations may lead to different subsequent clinical symptoms. Heon et al. [22] found that patients with exon 19 deletions had a higher incidence of central nervous system impairment compared to those with L858R mutations. Sekine et al. [23] found that Brain Metastases (BM) in NSCLC with EGFR exon 19 deletions are more numerous, smaller in volume, and have less edema compared to BM in wild-type or L858R-mutated NSCLC. These characteristics resemble granular-type brain metastases. The authors suggest that the deletion of exon 19 may reduce the growth capacity of tumor cells, leading to smaller metastatic lesions [23].

Detection of Brain Metastasis in NSCLC Patients with EGFR Mutations

Radiological examinations

Given the high risk of brain metastasis in the EGFR mutation population, regular brain MRI monitoring is considered beneficial for this population, allowing for early intervention through targeted systemic and/or radiation therapy. Mitra et al. [15] study indicates that the risk of brain metastasis increases most rapidly in the first year after the initial 5 years of treatment. Therefore, they recommend performing brain MRI monitoring every 6 months, starting 1 year after the initiation of treatment and continuing until the end of 5 years. Hsiao et al. [16] study indirectly supports this view, suggesting that non-small cell lung cancer patients with mutated EGFR may require more frequent brain imaging assessments than patients with wild-type EGFR to facilitate the early detection of secondary brain metastasis during follow-up.

Genetic testing

Due to the difficulty in obtaining live biopsies from brain metastatic lesions, it is often assumed in clinical practice that the gene mutations in extracranial lesions are consistent with those in brain metastatic lesions. Therefore, when NSCLC patients with EGFR mutations develop brain metastasis, the clinical significance of whether the gene types in metastatic lesions are consistent with those in the primary lesions is crucial.

Several studies have revealed heterogeneity in cancer cells and different metastatic sites. Kuukasjärvi et al. [24] analyzed the genomic composition of 29 primary breast cancers and their paired asynchronous metastatic tumors. They found that the genetic composition of 9 cases (31%) of metastatic tumors was almost completely different from that of the paired primary tumors. A case report from 2007 also identified different k-Ras genotypes in distinct lesions of the same patient. Moreover, the lesions exhibited different patterns of chromosomal aberrations, suggesting they might involve distinct underlying tumorigenic pathways [25].

In Gow et al. [26] study, among 18 patients with EGFR mutation-positive primary lung tumors, 9 cases (50%) lost the mutation during metastasis. Among 26 metastatic tumors, 17 cases (65%) were EGFR mutation-positive, while the primary tumors were EGFR mutation-negative. After analyzing these paired tissues with different EGFR mutations, the inconsistency rate reached 27% (18 out of 67 cases). In Han et al. [27] study, the inconsistency rate of EGFR mutations

Table 1: Prospective trials of TKIs in brain metastasis.

Data source	Medicine	Dose	Pathological feature	Number of patients	PFS	OS
Marinis et al. [73]	afatinib	40 mg qd	EGFR +	479 (17% BM)	13.4m (11.8-14.5m)	NM
LUX-Lung 3 [74]	afatinib	40 mg qd	EGFR+	20	11.14m (3.98-19.12m)	19.78m (16.36-41.66m)
LUX-Lung 6 [74]	afatinib	40 mg qd	EGFR+	28	8.21m (4.76-19.35m)	22.44m (10.51-35.55m)
Togashi et al. [75]	erlotinib	1500 mg qw	EGFR+	9	2.7m (0.8-14.5 m)	12m (2.5m-)
Park et al. [76]	erlotinib or gefitinib	gefitinib 250 mg qd or erlotinib 150 mg qd	EGFR+	28	6.6m (3.8-9.3m)	15.9m (7.2-24.6m)
Kim et al. [77]	erlotinib or gefitinib	gefitinib 250 mg qd or erlotinib 150 mg qd	AC	23	7.1m	18.8m
Iuchi et al. [78]	gefitinib	250 mg qd	EGFR+	41	14.5m (10.2-18.3m)	21.9m (18.5-30.3m)
Cho et al. [79]	lazertinib	240 mg qd	EGFR T790M	78	11.1m (5.5-16.4)	NR
Tan et al. [80]	nazartinib	150 mg qd	EGFR+	18	17m (11-21m)	NE
Park et al. [81]	osimertinib	160 mg qd	EGFR T790M	40	7.6 m (5.0-16.6)	16.9 ms (CI 7.9-)
Yamaguchi et al. [82]	osimertinib	80 mg qd	T790M	39	25.2m (7.0-34.5m)	19.8m (10.9-34.5m)

NR: Not Reach; NM: Not Mention; NE: Not Estimable; AC: Adenocarcinoma of the Lung

Table 2: Blood-Brain Barrier (BBB) penetration capabilities of EGFRs in human.

EGFR-TKIs	Doses	Penetration	Concentration	Data source
Erlotinib	150 mg qd	2.80%	66.9 ± 39.0 nM (CSF)	Togashi et al. [83]
Erlotinib	150 mg qd	2.15%	1981.50 ng/ml (plasma)	Chen et al. [84]
Gefitinib	250 mg qd	1.10%	8.2 ± 4.3 nM (CSF)	Togashi et al. [83]
Gefitinib	1250 mg qd	-	39 nM (CSF)	Katayama et al. [85]
Gefitinib	500 mg qd	-	6.2 nM (CSF)	Katayama et al. [85]
Afatinib	40 mg qd	0.59%	40.27 ng/ml (plasma)	Chen et al. [84]
Osimertinib	80 mg qd	0.08 ~ 1.12%	340.92 ng/ml (plasma)	Chen et al. [84]
Osimertinib	160 mg qd	2.18%	-	Chen et al. [84]

between primary lung adenocarcinomas and corresponding metastatic tumors was 16.2% (6 cases out of 37 patients). With an increasing number of considered mutated genes, the inconsistency becomes more apparent. In a study by Wang et al. [28], which included 61 patients undergoing surgical resection for primary Non-Small Cell Lung Cancer (NSCLC) and brain metastasis, next-generation sequencing of 416 cancer-related genes revealed that approximately 30% of patients (18 cases out of 61) had brain-specific mutations in addition to those found in the primary lung tumors. However, mutations in major driver genes, including EGFR, KRAS, TP53, and ALK, were highly consistent (>80%).

In more studies, EGFR mutations in primary lesions and brain metastatic lesions are consistent. In a retrospective study by Luo et al. [29], the consistency of EGFR mutation status between primary lung lesions and corresponding brain metastatic tumors was 93.3% (14 cases out of 15 patients). The difference was not statistically significant (McNemar test, P=1.000; Kappa test, κ=0). According to Matsumoto et al. [10] study, mutation analysis was conducted on the corresponding primary lung tumors of 6 cases with EGFR mutations in brain metastatic lung adenocarcinoma patients. The results showed the detection of the same type of EGFR mutations in all cases. Meanwhile, Fan conducted paired testing of the primary tumor tissue and Cerebrospinal Fluid (CSF) of NSCLC patients with EGFR-positive brain leptomeningeal metastasis, and the activating mutation status in the two was highly consistent (90.9%) [30]. In Huang et al. [31] study, paired assessment of the EGFR mutation status in cfDNA from cerebrospinal fluid and plasma samples of lung adenocarcinoma brain metastasis patients showed a high consistency (73.5%). This suggests that determining the EGFR status of brain metastatic lesions through cerebrospinal fluid testing is feasible.

After analyzing the mutation status of 2,781 tumors, Yatabe et al. [32] suggested that the heterogeneous distribution of EGFR mutations is extremely rare, and invasive adenocarcinomas carrying EGFR mutations carry mutations throughout the entire tumor tissue. They pointed out that the occurrence of pseudo-heterogeneity may be due to several reasons, including Mutation Allele-Specific Imbalance (MASI), heterogeneous distribution of EGFR amplification within the tumor, and the lower sensitivity of detection methods.

Treatment of NSCLC Brain Metastasis Patients with EGFR Mutations

Localized therapy

The most common local treatment for brain metastasis is Radiotherapy (RT), including Whole-Brain Radiotherapy (WBRT) and Stereotactic Radiosurgery (SRS), as well as surgical resection [33].

Surgical resection of metastatic brain tumors is typically used for larger brain lesions, when patients exhibit symptoms due to increased intracranial pressure, and when the tumor is preferably located in non-functional areas [34]. Compared to conventional treatment approaches for brain metastasis, it is more of an emergency measure.

Whole-Brain Radiotherapy (WBRT) has long been the standard treatment for multiple brain metastases in non-small cell lung cancer, relieving symptoms and extending survival [35]. When WBRT is used alone, it is associated with an increase in median survival from 4 to 6 months [36]. However, WBRT typically leads to neurological sequelae, such as neurocognitive dysfunction [37]. Stereotactic Radiosurgery (SRS) has become a primary alternative treatment for

limited brain metastasis, allowing precise targeting of tumors with minimal invasiveness [38,39]. There are reports that in a series of patients undergoing SRS treatment, the median Overall Survival (OS) exceeds 12 months [38,40]. However, after the use of SRS alone, frequent intracranial tumor progression occurs, primarily due to the development of new metastatic lesions [41,42].

There has been extensive research on whether to use WBRT alone or in combination with SRS. The QUARTZ trial conducted in 2016 is a well-powered randomized controlled trial specifically designed to study the efficacy of supportive care plus WBRT versus supportive care alone in patients with non-small cell lung cancer. The trial indicated that for younger patients, WBRT may offer a survival advantage, but for all other groups, omitting WBRT did not significantly impact Quality-Adjusted Life Years (QALY) or overall survival [4]. In the randomized controlled trial RTOG 9508 led by Andrews et al. [43], only patients with solitary brain metastasis obtained statistically significant survival benefits when WBRT was combined with local (surgical or stereotactic) treatment for intracranial disease. A systematic review organized by Patil et al. [44] found no difference in Overall Survival (OS) between the WBRT + SRS group and the WBRT alone group (Hazard Ratio (HR) 0.82, 95% Confidence Interval (CI) 0.65-1.02; 2 studies, 358 subjects; moderate-quality evidence). However, the performance status and local control were significantly better in the SRS plus WBRT group.

The potential side effects of WBRT or SRS treatment need to be considered. According to the ALLIANCE study report, brain metastasis patients receiving WBRT + SRS had poorer quality of life and functional health compared to those receiving SRS alone, suggesting that WBRT itself may lead to a decrease in quality of life [45]. Within 3 months, WBRT resulted in less cognitive decline compared to WBRT plus SRS, and the difference was significant. Therefore, in patients with 1-3 brain metastases, stereotactic radiosurgery may be the preferred strategy [46]. However, there are also studies with opposite conclusions. In a randomized controlled trial conducted by Aoyama et al. [47] involving 132 patients, they found no difference in radiation-induced side effects or survival rates between SRS alone and WBRT plus SRS. For patients with 1-4 brain metastases, neither SRS alone nor WBRT plus SRS improved survival, but the frequency of intracranial recurrence was significantly higher in those not receiving WBRT. This suggests that WBRT may significantly reduce the number of brain metastasis recurrences without apparent neurotoxicity.

In practical application, the choice of specific treatment methods often depends on the location and number of lesions [33]. Considering that WBRT may cause long-term cognitive impairment, it is suggested to use smaller daily doses (e.g., <3 Gy/d) to potentially reduce this risk [48]. The use of drugs such as memantine during and after WBRT, or the use of donepezil after cranial radiotherapy, may improve long-term cognitive outcomes [49,50].

Systemic treatment

Chemotherapy: Chemotherapy has always been a recognized treatment strategy for advanced non-small cell lung cancer, with responses observed in all subgroups, including the EGFR mutation subgroup [51]. Pemetrexed is particularly effective against adenocarcinoma and shows a response to brain metastases, as confirmed in a small trial of 39 patients [52]. Ortuzar and colleagues conducted a retrospective analysis of two randomized controlled trials of pemetrexed in the treatment of NSCLC (total of 2296 patients), revealing an odds ratio of 0.49 (95% CI 0.32-0.76, p=0.001) for the association between pemetrexed exposure and brain metastasis [53]. However, due to the limited permeability of the Blood-Brain Barrier (BBB) and the risk of toxicity to surrounding healthy brain tissue, systemic treatment has limited efficacy in the treatment of brain metastasis [3]. Conventional treatment regimens with platinum-based double chemotherapy, such as cisplatin and paclitaxel, typically have poor efficacy [54].

Immunotherapy: For patients with driver gene-positive Non-Small Cell Lung Cancer (NSCLC), there is currently insufficient evidence to support the effectiveness of combined immunotherapy and targeted therapy. Due to the "target-first" principle, patients with stage IV NSCLC-carrying mutations that can be targeted by therapy are typically prioritized for first-line targeted treatment. As a result, these patients are often excluded from studies testing combinations of immunotherapy [55]. However, early research results on the combination of pembrolizumab and Lenvatinib indicate improved efficacy and sustained response in various advanced solid tumors, including preliminary data in patients with refractory NSCLC [56]. Zhou et al. [57] study suggests that in NSCLC patients with EGFR mutations and brain metastases, combination therapy of immunotherapy and chemotherapy exhibits significant efficacy within the intracranial compartment. This approach can be considered as an option after the failure of EGFR-TKI treatment.

EGFR-TKIs: Significant progress has been made in improving the prognosis of Non-Small Cell Lung Cancer (NSCLC) patients with driver gene-positive molecular targeted therapy [58]. According to the joint recommendations of the European Neurological Society-European Medical Oncology Society and experts, the use of EGFR-Tyrosine Kinase Inhibitors (TKIs) should be considered for patients with advanced NSCLC and brain metastases who are positive for Epidermal Growth Factor Receptor Mutations (EGFRm) [59]. The efficacy of the first-generation EGFR Tyrosine Kinase Inhibitors (TKIs) in intracranial lesions is limited, possibly due to their lower permeability through the Blood-Brain Barrier (BBB). However, newly developed TKIs have improved penetration through the BBB, and third-generation targeted drugs like Osimertinib have demonstrated significant intracranial activity.

Compared to their concentrations in plasma, first-generation drugs like gefitinib and erlotinib have limited concentrations in cerebrospinal fluid [60]. However, intermittent (pulsed) high-dose administration (1000-1500 mg per week) can achieve higher concentrations in cerebrospinal fluid than standard doses [61]. Pulsed high-dose and dose-escalation erlotinib are more effective in controlling brain metastases [62].

In contrast to the first-generation (erlotinib or gefitinib) EGFR TKIs, the second-generation (afatinib and dacomitinib) ErbB family inhibitors bind irreversibly to EGFR, ErbB2, and ErbB4, blocking phosphorylation of ErbB3, thereby inhibiting all ErbB family signaling [63,64]. In patients with brain metastases and common (Del19/L858R) EGFR mutations, afatinib significantly improves PFS compared to chemotherapy [65]; studies suggest that, compared to chemotherapy, afatinib is associated with quality-of-life benefits [66].

Preclinical data have indicated that Osimertinib can penetrate the blood-brain barrier and has anti-tumor [67]. In the AURA3 and FLAURA phase III studies, in a subgroup assessing central nervous system responses (n=46), the Response Rate (OR) for Osimertinib was 70%, while the chemotherapy group was 31%. Osimertinib significantly improves PFS compared to chemotherapy [68].

Compared to the first-generation drugs erlotinib and gefitinib, the higher blood-brain barrier penetration of afatinib and Osimertinib may lead to greater central nervous system efficacy [69,70]. Osimertinib has shown remarkable clinical activity in patients with T790M-positive tumors after failure with erlotinib, gefitinib, or afatinib [71]. While T790M is the major mechanism of acquired resistance to first- and second-generation EGFR TKIs (50-70%) [72].

The prospective studies of EGFR-TKI in patients with brain metastases are shown in Table 1. The concentrations of different EGFR-TKI in plasma and cerebrospinal fluid are shown in Table 2.

Conclusion

There are significant differences in brain metastasis between EGFR mutation-positive and wild-type Non-Small Cell Lung Cancer (NSCLC). This article primarily discusses the incidence, clinical features, monitoring strategies, and treatment methods for brain metastasis in patients with EGFR mutations. Further clinical data are needed to assist in the treatment of NSCLC patients with EGFR mutations. We hope this article contributes to the management of patients with brain metastasis.

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