Original Article

Impact of pulmonary interstitial lesions on efficacy and prognosis of EGFR-TKI-treated advanced non-small cell lung cancers

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Background: This study aimed to assess the impact of pre-existing pulmonary interstitial lesions (PIL) on the efficacy and prognosis of patients with epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) treated with EGFR tyrosine kinase inhibitor (TKI).

Methods: Patients with advanced NSCLC harboring EGFR exon 19 deletion (E19 del) or exon 21 (E21) L858R were enrolled in this study. All patients underwent high resolution computed tomography (HRCT) chest scans prior to EGFR-TKI treatment. Pre-existing PIL was graded according to HRCT imaging (PIL 0, 1, 2, and 3). Cox proportional-hazards regression models were used to identify the prognostic factors for progression-free survival (PFS).

Results: A total of 134 eligible patients were enrolled. The overall objective response rate (ORR) and median PFS were 73.1% and 10.0 months (95% CI: 7.51–12.49), respectively. There were 62 (46.3%), 25 (18.7%), 28 (20.9%), and 19 (14.1%) cases of PIL grade 0, 1, 2, and 3, respectively, with median PFS and ORR of 12.9 months and 80.6%, 11.0 months and 72.0%, 10.0 months and 71.4%, and 7.0 months and 52.6%, respectively. Multivariate analysis showed that squamous cell carcinoma (*vs.* adenocarcinoma, HR =4.33), E21 L858R (*vs.* E19 del, HR =1.57), and PIL grade 3 (*vs.* grade 0–2, HR =1.60–2.48) were poor prognostic factors for PFS (P<0.05 for all).

Conclusions: Pre-existing PIL grade is an independent prognostic factor for predicting resistance to EGFR-TKIs in patients with EGFR-mutant advanced NSCLC. Higher PIL grade suggests higher risk of early progression.

Keywords: Epidermal growth factor receptor (EGFR); non-small cell lung cancer (NSCLC); prognosis; pulmonary interstitial lesions (PIL); tyrosine kinase inhibitors (TKIs)

Introduction

Lung cancer is the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases (1). For advanced NSCLC with epidermal growth factor receptor (EGFR) mutation, EGFR tyrosine kinase inhibitors (EGFR-TKIs) serve as standard first-line therapies with a response rate of over 70% and a median progression-free survival (PFS) of 9–13 months (2,3). However, patients receiving the EGFR-TKI treatment almost inevitably develop disease progression due to primary or secondary drug resistance. The mechanism of

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resistance is complicated, with EGFR T790M accounting for approximately 50% of its emergence. Mesenchymal-epithelial transition amplification, epithelial-mesenchymal transition (EMT), and small cell transformation can also lead to drug resistance (4). Once tumor cells acquire the properties of EMT, their invasive ability and metastasis will be enhanced, thereby resulting in drug resistance (5).

EMT is also a mode of interstitial cell production in the process of pulmonary fibrosis and is significantly related to interstitial lung disease (ILD) (6). TGF-β is a fibrogenic cytokine that can induce EMT and is closely related to pulmonary fibrosis (7-9). Furthermore, previous studies have shown that ILD is closely related to carcinogenesis in lung cancer and that the incidence of ILD upon lung cancer diagnosis varied between 2.4–10.9% (10-12). ILD patients with lung cancer had a poor prognosis (10).

Based on the relationship of EMT with pulmonary fibrosis and EGFR-TKI resistance, it is worth investigating whether there is a connection between pulmonary fibrosis and EGFR-TKI resistance. Therefore, this study evaluated the effect of pre-existing pulmonary interstitial lesions (PIL) based on high-resolution computed tomography (HRCT) imaging on the efficacy and prognosis of EGFR-TKIs for advanced EGFR-mutant NSCLC and explored the relationship between the extent of PIL and EGFR-TKI resistance.

Methods

Patient selection

We retrospectively reviewed patient records at the Cancer Center in the Shengjing Hospital of China Medical University between January 2016 and April 2018. Patients who met the following inclusion criteria were enrolled: (I) histologically or cytologically confirmed NSCLC; (II) recurrence or unresectable stage III or IV, according to the seventh edition of the tumor-node-metastasis (TNM) classification for lung cancer by the American Joint Committee on Cancer; (III) EGFR exon 19 deletion (E19 del) or exon 21 (E21) L858R mutation; (IV) received first-generation EGFR-TKI monotherapy; (V) HRCT imaging (256-section CT scanner, Brilliance iCT®; Philips Healthcare, Cleveland, OH, USA) and follow-up information before and after EGFR-TKI treatment was available. Patients were excluded if they had one of the following exclusion criteria: (I) received chemotherapy or other targeted therapy during EGFR-TKI treatment;

(II) EGFR-TKIs were only used as consolidation or maintenance therapy; (III) harbored rare or co-mutated EGFR mutations; (IV) previously received EGFR-TKI treatment; (V) second- or third-generation EGFR-TKIs; (VI) had a history of chest radiotherapy before or during EGFR-TKI treatment.

Eligible patients' clinicopathological characteristics were collected and included age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), Charlson comorbidity index (CCI), pathological type, clinical stage, EGFR mutation type, EGFR-TKI category, PIL grade, and follow-up information. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1. PFS was defined as the time in months from the initiation of EGFR-TKI treatment to disease progression.

Grading criteria for PIL

HRCT imaging PIL features included ground-glass opacity, interlobular septal thickening, interstitial hyperplasia, honeycomb sign, reticulation, consolidation, patchy shadow, tractive bronchiectasis, and bullae (13,14). Referring to the HRCT features for usual interstitial pneumonia in the ATS/ERS/JRS/ALAT International Guidelines and previous studies of ILD (14-16), grading criteria for PIL based on chest HRCT imaging were proposed (*Table 1* and *Figure 1*). Each patient's PIL grade was independently verified by two chest radiologists, according to the chest HRCT before the EGFR-TKI treatment. In cases of disagreement between radiologists, another radiologist was consulted until a consensus was reached.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software version 21.0 (IBM Corporation, Armonk, NY, USA). In this study, continuous variables were statistically analyzed using the median binary classification. A chi-squared test was used for categorical variable correlation analysis. Median PFS was estimated using the Kaplan-Meier method, where curves were compared using the log-rank test. Potential prognostic factors were identified by univariate analysis, where $P<0.1$ was considered statistically significant. Multivariable Cox proportional hazard models were used to calculate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs), where $P<0.05$ was considered statistically significant.

Table 1 PIL grading criteria based on HRCT imaging

PIL grade	Description
Grade 0 (no interstitial change)	No signs of interstitial lesions
Grade 1 (mild interstitial change)	Ground glass opacification, focal or non-segmental distribution, without reticular abnormalities, honeycombing and traction bronchiectasis
Grade 2 (moderate interstitial change)	Reticular abnormalities in one or two lobes, without honeycombing and traction bronchiectasis
Grade 3 (severe interstitial change)	Reticular abnormalities in more than two lobes, and/or honeycombing with or without traction bronchiectasis

PIL, pulmonary interstitial lesions; HRCT, high resolution computed tomography.
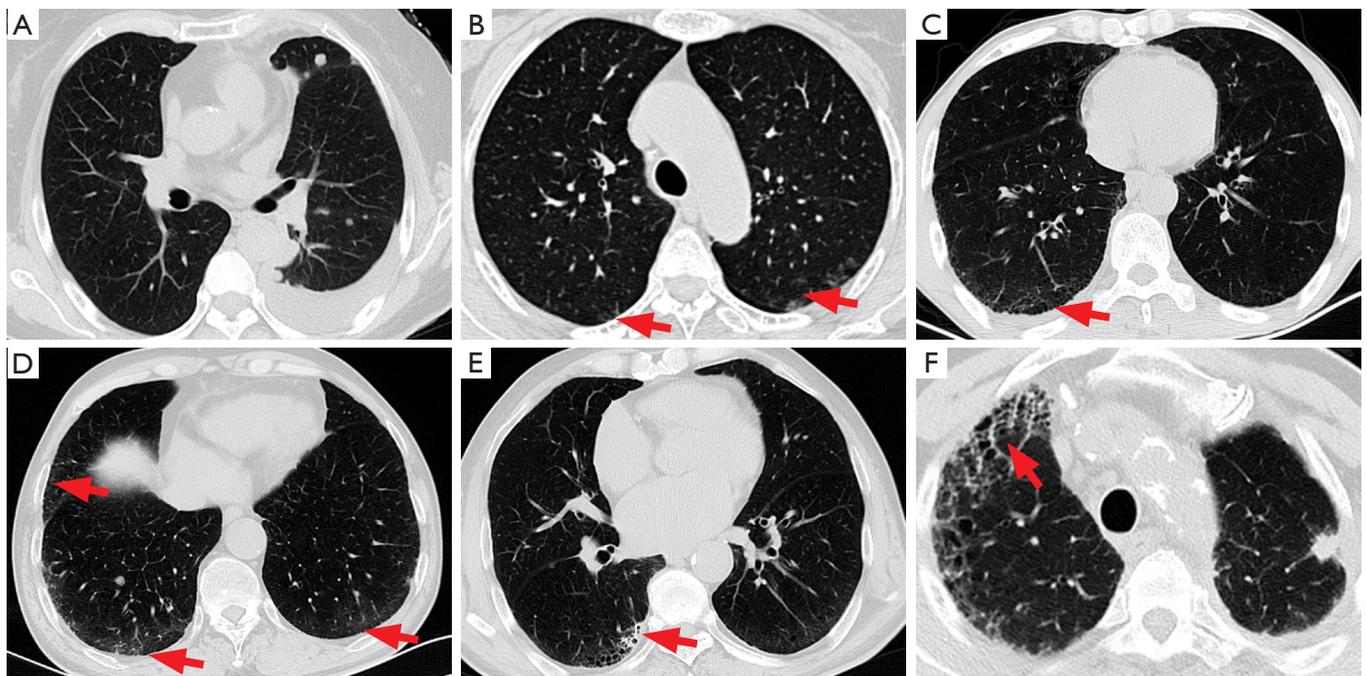

Figure 1 Grading criteria for PIL based on chest HRCT imaging. (A) Grade 0: no interstitial lung abnormalities; (B) grade 1: scattered ground-glass opacification in bilateral upper lobes; (C) grade 2: reticulation changes in right lower lobe; (D) grade 3: reticular abnormalities in three lobes (right middle and bilateral lower lobes) and (E) honeycombing in right lower lobe; and (F) grade 3: honeycombing with traction bronchiectasis in right upper lobe. PIL, pulmonary interstitial lesions; HRCT, high resolution computed tomography.

Results

Patient characteristics

Patient characteristics are summarized in *Table 2*. A total of 134 eligible patients were enrolled in this study. The median age was 61 years (range, 37–86 years), 85 patients were female (63.4%), 101 patients had ECOG PS 1 (75.4%), 129 patients had adenocarcinoma (96.3%), 128 patients had stage IV disease (95.6%), 58 patients had EGFR E19

del (43.3%), 29 patients had surgical history of lung cancer (21.6%), and 94 patients had first-line treatment (70.1%).

PIL grade and correlation analysis

According to the PIL grading criteria based on CT imaging, there were 62 patients with PIL grade 0 (46.3%), 25 patients with PIL grade 1 (18.7%), 28 patients with PIL grade 2 (20.9%), and 19 patients with PIL grade 3 (14.1%,

Table 2 Clinicopathological characteristics of the included patients

Characteristics	Number (%)
Age	
≤60	65 (48.5)
>60	69 (51.5)
Gender	
Male	49 (36.6)
Female	85 (63.4)
Smoking	
Never	106 (79.1)
Current/former	28 (20.9)
ECOG PS	
1	101(75.4)
2	20 (14.9)
3	13 (9.7)
CCI score	
≤8	101 (75.4)
>8	33 (24.6)
Pathological type	
Adenocarcinoma	129 (96.3)
Squamous cell carcinoma	5 (3.7)
EGFR mutation type	
E19 del	58 (43.3)
E21 L858R	76 (56.7)
TNM stage (AJCC 7th)	
IIIA	3 (2.2)
IIIB	3 (2.2)
IVA	46 (34.4)
IVB	82 (61.2)
History of chemotherapy	
No	75 (54.6)
Yes	59 (45.4)
Surgical history of lung	
No	105 (78.4)
Yes	29 (21.6)

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Number (%)
EGFR-TKI category	
Gefitinib	66 (49.3)
Icotinib	31 (23.1)
Erlotinib	37 (27.6)
Treatment line	
First-line	94 (70.1)
≥ Second-line	40 (19.9)
PIL grade	
PIL0	62 (46.3)
PIL1	25 (18.7)
PIL2	28 (20.9)
PIL3	19 (14.1)

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PIL, pulmonary interstitial lesions; ECOG PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson comorbidity index; TNM, tumor-node-metastasis.

Table 2). Correlation analysis between PIL grade and other variables showed that only surgical history of lung cancer was weakly correlated with PIL grade, while age, sex, smoking history, CCI, EGFR mutation type, pathological type, and clinical stage were not related to PIL grade (*Table 3*).

Independent risk factors for disease progression

The objective response rate (ORR) and median PFS of the patients receiving EGFR-TKI treatment were 73.1% and 10.0 months (95% CI: 7.51–12.49), respectively. PFS rates for 1, 2, and 3 years were 45%, 20%, and 5%, respectively. Univariate analysis showed that sex, age, clinical stage, smoking history, ECOG PS, CCI, EGFR-TKI category, history of chemotherapy, and treatment lines were not significantly associated with PFS (P>0.1 for all). In turn, pathological type, EGFR mutation type, surgical history of lung cancer, and PIL grade were associated with PFS (P<0.1 for all).

Multivariate analysis showed that there was no significant association between surgical history of lung cancer and PFS, while pathological type, EGFR mutation type, and

Table 3 The correlations between pulmonary interstitial lesions (PIL) and other clinicopathological factors

Variables	P	Correlation coefficient(r)
Age	0.131	0.087
Gender	0.550	0.087
Smoking	0.799	0.085
ECOG PS	0.487	0.085
CCI	0.187	0.078
Pathology type	0.659	0.083
EGFR mutation type	0.593	0.091
TNM stage	0.522	−0.055
History of chemotherapy	0.639	−0.105
Surgical history of lung	0.051	−0.21
EGFR-TKI category	0.507	0.062
Treatment line	0.907	−0.032

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson comorbidity index; TNM, tumor-node-metastasis.

PIL grade were significantly associated with PFS. The clinicopathological factors significantly associated with shorter PFS included squamous cell carcinoma, E21 L858R, and higher PIL grade, which were independent risk factors for disease progression. Median PFS and ORR of squamous cell carcinoma *vs.* adenocarcinoma were 3.0 *vs.* 10.0 months (HR =4.34; 95% CI: 1.52–12.42, P=0.006) and 40% *vs.* 74.4%, respectively. Median PFS and ORR for E21 L858R *vs.* E19 del were 8.0 *vs.* 14.5 months (HR =1.57; 95% CI: 1.00–2.46, P=0.049) and 64.5% *vs.* 84.5%, respectively. Median PFS and ORR for PIL grade 0, 1, 2, and 3 were 12.9 months and 80.6%, 11.0 months and 72.0%, 10.0 months and 71.4%, and 7.0 months and 52.6% (P=0.031), respectively. Compared to PIL grade 3, HRs for PFS of PIL grade 0, 1, and 2 were 0.40 (95% CI: 0.21–0.76, P=0.005), 0.46 (95% CI: 0.23–0.93, P=0.029), and 0.63 (95% CI: 0.30–1.29, P=0.20, respectively) (*Table 4*, *Figure 2*).

Discussion

EGFR-TKIs greatly improve survival and quality of life for patients with EGFR-mutant advanced NSCLC. However, acquired drug resistance impedes long-term clinical benefits and poses new challenges for treatment. Moreover, the time and patterns of recurrence among individuals are not the same. This study investigated the relationship between pre-existing PIL and EGFR-TKI resistance. The results showed that pre-existing PIL grade was an independent risk factor besides pathological type and EGFR mutation type for predicting disease progression in patients with EGFR-mutant advanced NSCLC treated with EGFR-TKIs. It suggested that the presence of higher PIL grade before EGFR-TKI treatment implied shorter PFS, which might be related to early resistance to EGFR-TKIs.

Epidemiological data shows that the incidence of lung cancer in patients with pulmonary interstitial fibrosis is 3.34–7.30 times higher than in healthy people and that pulmonary interstitial fibrosis is considered an independent risk factor affecting prognosis and survival (10-12,17,18). A retrospective analysis reported by Kanaji *et al.* showed that in advanced NSCLC patients who received first-line chemotherapy or EGFR-TKI treatment, median PFS was significantly shorter in patients with ILD (118 days) or idiopathic pulmonary fibrosis (92 days) than in those with non-ILD (196 days) (19). A previous study has shown that alveolitis was the earliest manifestation of ILD in pathology, mainly presenting as ground-glass opacity in HRCT (20). Reticulation was defined as small linear opacities that represent thickened intralobular or interlobular septa (14), while honeycomb signs represented end-stage parenchymal

Table 4 Variables in univariate and multivariate analysis

Variables	PFS (months)	Univariate	Multivariate		
		P	HR	95% CI	P
Pathology					
SCC	3.0	0.002			1.000
Ade	10.0		0.23	0.08–0.66	0.006
Surgery history of lung					
Yes	15.0	0.092			1.000
No	8.0		1.33	0.80–2.21	0.27
EGFR mutation type					
E21 L858R	8.0	0.028			1.000
E19 del	14.5		0.64	0.41–0.99	0.049
PIL grade					
PIL3	7.0	0.003			1.000
PIL2	10.0		0.63	0.30–1.29	0.203
PIL1	11.0		0.46	0.23–0.93	0.029
PIL0	12.9		0.40	0.21–0.76	0.005

PFS, progression-free survival; HR, hazard ratio; CI, confidence intervals; SCC, squamous cell carcinoma; Ade, adenocarcinoma; PIL, pulmonary interstitial lesions.

fibrosis (16). Therefore, the present study classified PIL into grades 0 to 3 according to HRCT manifestations of the range and extent of ground-glass opacity, abnormal reticulation, and honeycomb signs in both lungs. The findings indicated that higher PIL grade was associated with shorter PFS, leading to earlier acquired EGFR-TKI resistance. Median PFS was only 7.0 months in patients with PIL grade 3 *vs.* 12.9 months in those with PIL grade 0, suggesting that PIL grade may be a predictor of early resistance to EGFR-TKIs.

The mechanisms of EGFR-TKI resistance are complex. Preclinical studies have shown that EMT plays an important role in both the EGFR-TKI resistance and formation of pulmonary fibrosis (5,6). TGF-β is the main inducer in the process of EMT and is highly expressed in patients with ILD (7,8,17). Persistent exposure to TGF-β1 is necessary for tumor cells to maintain their mesenchymal phenotype and the state of EGFR-TKI resistance (21). Progression and completion of EMT processes are associated with cell invasion and drug resistance (22). EMT is a process in which epithelial cells lose their polarity and adherence, while gaining migratory ability and adopting a mesenchymal phenotype, manifesting as a loss of E-cadherin

and accompanied by an increase in N-cadherin, vimentin, and fibronectin expression (6). *In vitro* studies have reported that NSCLC cells resistant to gefitinib exhibit EMT features and their mesenchymal phenotype is more resistant than the epithelial phenotype (23). With these results in mind, it is possible that there might be different expression levels of TGF-β or EMT-related proteins in pulmonary interstitial and serum of lung cancer patients with different PIL grades, which may be related to acquired resistance to EGFR-TKIs. Specific mechanisms are being studied to provide more effective predictors or monitoring indicators for early clinical evaluation of the EGFR-TKI efficacy.

EGFR-TKI-induced ILD is a rare but severe adverse effect, which may exacerbate pulmonary fibrosis, leading to a life-threatening acute event. The incidence of ILD with EGFR-TKIs is about 1.2–6.5% and the mortality rate is 13.0–40.0% among EGFR-TKI-treated patients with ILD, mostly occurring within 4 weeks of treatment initiation (24-27). Johkoh *et al.* reported that ILD exacerbation occurred in 10.6% of the erlotinib-treated patients (24). In the present study, on the basis of clinical and radiological manifestations, no patients experienced acute exacerbation of pulmonary fibrosis and resulting treatment interruption
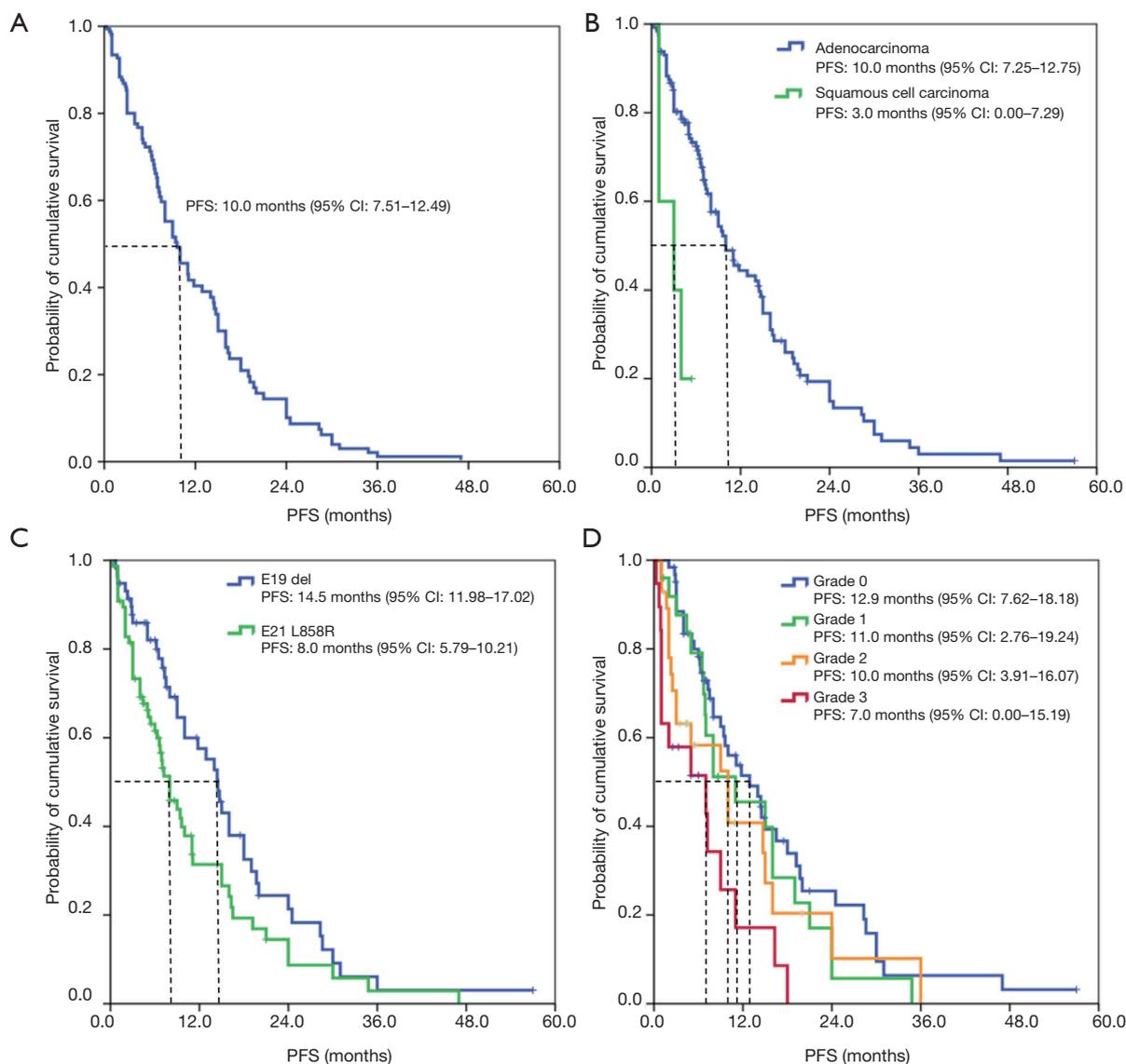
Figure 2 Curves of PFS. (A) Kaplan-Meier curves for PFS in all patients; (B) PFS in subgroups of adenocarcinoma *vs.* squamous cell carcinoma; (C) E19 del *vs.* E21 L858R; and (D) PIL grades 0, 1, 2, and 3. PFS, progression free survival; PIL, pulmonary interstitial lesions.

regardless of PIL grade. No lethal ILD outcomes were observed at the end of the last follow-up.

Furthermore, based on the conclusion between pre-existing PIL grade and resistance to EGFR-TKIs, we speculate that the combination of EGFR-TKIs and anti-pulmonary fibrosis agents might delay or prevent the onset of EGFR-TKI resistance. Nintedanib is a triple angiokinase inhibitor that binds to the intracellular tyrosine kinase domain of angiogenesis-related receptors, including FGFR, PDGFR, and VEGFR. *In vitro* cell experiments have demonstrated that nintedanib can inhibit early TGF-β1 signaling

transduction events, downregulate expression of fibronectin, and inhibit the differentiation of myofibroblast (28). Of note, nintedanib is also able to inhibit TGF-β1-induced phenomena of increased vimentin and decreased E-cadherin expression in A549 cells, while reversing TGF-β1-induced EMT and resistance to gefitinib (29). However, there are few clinical trials on combination therapy with nintedanib. In the LUME-Lung 1 controlled trial, docetaxel and nintedanib group significantly improved overall survival in the second-line treatment of lung adenocarcinoma compared to docetaxel and placebo group (12.6 *vs.*

10.3 months) (30). In a phase I clinical trial assessing the efficacy of afatinib combined with nintedanib, the disease control rate in 18 NSCLC patients was 83%, with one complete response and three partial responses (31). Thus, whether EGFR-TKIs in combination with nintedanib can delay the emergence of acquired drug resistance in patients with pulmonary interstitial fibrosis, especially with higher PIL grades, remains to be studied further.

Generally, squamous cell lung carcinoma has a lower EGFR mutation rate (2.7–9.6%) (32-35), so that routine testing for all squamous cell carcinoma types is not recommended by the NCCN guidelines. Nevertheless, gene testing for squamous cell carcinoma can be recommended for select patients, including light or never-smokers, patients diagnosed with small biopsy specimens, or those with mixed lung squamous cell carcinoma (36,37). Our results showed that median PFS of squamous cell carcinoma was significantly shorter than that of adenocarcinoma (3.0 *vs.* 10.0 months), although only five cases (3.7%) of lung squamous cell carcinoma were included in this study, which is not sufficient to evaluate the prognostic impact of squamous cell carcinoma. Previous studies also reported that EGFR-TKIs were less effective in EGFR-mutant non-adenocarcinoma than in adenocarcinoma. The difference in their efficacy may be related to lower levels of EGFR mutations and higher proportion of other genetic mutations in squamous cell carcinoma. PIK3CA mutation and copy number gains are more frequent in squamous cell carcinoma than in adenocarcinoma (30 *vs.* 3%) (38).

This study also found that patients with E19 del had a significantly better PFS than those with E21 L858R (14.5 *vs.* 8.0 months), which is consistent with previous studies (39,40). A meta-analysis showed that treatment with EGFR-TKIs compared to chemotherapy was significantly associated with a 63% reduction in the risk of disease progression or death. For tumors with E19 del, the benefit was greater than for tumors with E21 L858R, with unadjusted pooled HR of 0.26 and 0.45, respectively (41).

There are some limitations to this study. First, this was a single center retrospective study with a limited number of cases that needs to be validated by well-designed prospective studies. Second, the enrolled patients received different first-generation EGFR-TKIs. Although multiple randomized controlled trials have suggested that there is a small difference in efficacy among gefitinib, erlotinib and icotinib (42), the difference in efficacy caused by the drug itself will be magnified due to the study's small sample size. Third, HRCT cannot completely distinguish atypical

interstitial-like manifestations from other lung diseases (e.g., atypical adenomatous hyperplasia, adenocarcinoma *in situ*, and minimally invasive adenocarcinoma) and even misdiagnose physiological gravity-dependent opacification as pulmonary interstitial diseases, although dynamic follow-up CT can help identify these conditions to some extent. In the present study, radiologists reached a consensus on diagnosis and grade of PIL according to baseline HRCT before treatment or in combination with review of follow-up CT (if needed) to minimize diagnostic errors.

Conclusions

Our study suggested that pre-existing PIL might affect the efficacy of EGFR-TKIs in patients with advanced EGFR-mutant NSCLC. The higher the PIL grade, the shorter the PFS, which is related to early resistance of the EGFR-TKI treatment. Further clinical trials are needed to verify whether the combination of EGFR-TKI and anti-pulmonary fibrosis drugs can delay or prevent the occurrence of EGFR-TKI resistance.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of Shengjing Hospital of China Medical University (No. 2015PS167K). The requirement for patient consent was waived because this was a retrospective cohort study.

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