Original Article

Clinical model to predict progression-free survival in EGFR-mutant lung adenocarcinoma patients treated with first-generation EGFR-TKIs

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Background: Albeit epidermal growth factor receptor (EGFR) mutation status might be superior to other clinical and pathological factors for predicting response to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), the efficacy might differ a lot in patients with the same EGFR sensitive mutations. Thus, exploring factors associated with EGFR-TKIs efficacy other than EGFR mutation status is vital, especially in patients with EGFR-activating mutations.

Methods: The present study retrospectively collected clinical and pathological data on a total of 128 patients with EGFR-activating lung adenocarcinoma who received first-generation EGFR-TKIs (including gefitinib, erlotinib or icotinib). Kaplan-Meier and Cox regression methods were applied to identify independent factors associated with progression-free survival (PFS) and to generate a prognostic index (PI) model.

Results: The median PFS of the 128 patients was 14.9 months (95% CI, 13.2–16.5 months). A non-smoking history [hazard ratio (HR) =2.896; 95% CI, 1.501–5.558; P=0.002] and first-line EGFR-TKIs treatment (HR, 1.544; 95% CI, 0.999–2.386; P=0.05) were found to be independent predictive factors of a longer PFS with EGFR-TKIs therapy. Predictive model can be established as PI =1.063 × Smoking + 0.434 × Timing according to the results of Cox regression. Further analysis using the PI model indicated that there are differences of three groups in PFS: non-smoking and first-line therapy, non-smoking and non-first-line therapy, smoking regardless of treatment timing.

Conclusions: The findings of the present study suggest that a non-smoking history and a first-line EGFR-TKIs treatment timing are independent predictors of a longer PFS in EGFR-mutant lung adenocarcinoma patients treated with first-generation EGFR-TKIs. PFS is longer for those who are never smokers and receive first-line EGFR-TKIs, compared with other groups.

Keywords: Model; epidermal growth factor receptor (EGFR); tyrosine kinase inhibitors (TKIs); lung adenocarcinoma; progression-free survival (PFS)

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Introduction

The discovery of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) is a landmark event for survival improvement of non-small cell lung cancer (NSCLC) patients (1). In early studies, gefitinib and erlotinib showed promising efficacy in unselected NSCLC patients. However, differences in outcome were soon recognized after receiving these drugs. Subsequent clinical studies revealed that factors, such as East-Asian origin, female sex, adenocarcinoma histology, a non-smoking history were found to be predictors for a favorable response to EGFR-TKIs in unselected NSCLC (2-4). Mechanistic studies demonstrated that the above characteristics were more likely found in patients harboring specific mutations in the tyrosine kinase domain of EGFR (5-8). At the same time, these mutations were found to be oncogenic driver mutations by two study groups (1,6). Exon 19 deletions (19del) and a point mutation in exon 21 (21L858R) were the most commonly found EGFR mutations, comprising approximately 85% of lung-cancer-specific EGFR sensitive mutations (9).

Gefitinib showed a significant higher response and longer progression-free survival (PFS) compared with traditional chemotherapy (10). Based on the evidence, EGFR-TKIs are now recommended as a first-line treatment for NSCLC patients harboring EGFR sensitive mutations (11,12).

EGFR mutation status is widely acknowledged as the best predictor for EGFR-TKIs efficacy. Albeit it may be superior to other clinical and pathological factors for predicting response to EGFR-TKIs (13,14), the efficacy might differ a lot in patients with the same EGFR sensitive mutations (15). Thus, exploring factors associated with EGFR-TKIs efficacy other than EGFR mutation status is vital, especially for patients with EGFR-activating mutations.

In the current retrospective research, we first collected and analyzed clinicopathologic data on Chinese lung adenocarcinoma patients harboring EGFR-activating mutations after they were treated with EGFR-TKIs to identify independent factors of PFS, and then established a predictive model to further discover the implications of these factors.

Methods

Patients

The present study collected data on a total of 128 patients with EGFR-activating mutations who received first-generation EGFR-TKIs (including gefitinib, erlotinib or icotinib) between July 1, 2010 and December 1, 2013 at the Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University. All patients were diagnosed as lung adenocarcinoma with IIIB or IV stages according to the TNM system set by the International Association for the Study of Lung Cancer (IASLC). Patients with symptomatic brain metastases, an Eastern Cooperative Oncology Group performance status (ECOG PS) of more than 2, or with missing data were not included in the study. Those who received sequential chemotherapy during the course of targeted therapies were also excluded.

Clinical factors, such as age, sex, smoking history, EGFR mutation sites, clinical stages, metastatic sites, pulmonary surgical history, tumor differentiation, tumor locations, pretreatment (within 2 weeks) levels of six serum tumor markers [including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cancer antigen 125 (CA125), squamous cell carcinoma (SCC) antigen, cytokeratin-19 fragments (CYFRA21-1), and lactate dehydrogenase (LDH)], ECOG PS, and treatment timing with EGFR-TKIs were all collected and analyzed, along with the patients' PFS times.

This study was approved by the Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai. The Approval Number is K(P)15-04. The participants of the present study did not write informed consent before taking part since this was a retrospective study.

Detection of EGFR and serum tumor markers

ADx EGFR Mutation Detection Kit (Amoy Diagnostics, Xiamen, China), which has been approved by China's Food and Drug Administration (CFDA) was used to detect EGFR mutations. Serum tumor markers were detected by radioimmunoassay. The cut-off values for levels of CEA, NSE, CA125, SCC, CYFRA21-1 and LDH were: 5 ng/mL, 25 ng/mL, 35 U/mL, 1.5 μg/L, 5 ng/mL, and 250 U/L, respectively.

Administration of EGFR-TKIs, response assessment and follow-up

Gefitinib and erlotinib were administered in dosages of 250 and 150 mg once daily, respectively, while icotinib was administered in a dosage of 125 mg 3 times daily. All patients received 1 of the 3 EGFR-TKIs in a 28-day cycle.

All patients were evaluated by computed tomography (CT) of the thorax to acquire tumor baseline information before the administration of EGFR-TKIs. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 after the first cycle of therapy and subsequently after every two cycles. Routine thorax CT scan and abdominal ultrasound was carried out every time a patient came to follow-up. Bone scan and enhanced magnetic resonance imaging (MRI) of the brain was also performed when necessary. The cutoff date for the study was April 1, 2015.

Statistical analysis

All statistical analyses in this study were performed using SPSS® software, version 13.0 (SPSS Inc., Chicago, IL, USA). PFS was calculated as the time from the date EGFR-TKIs were first administered until the date of discontinuation or until the death of a patient.

Firstly, a Kaplan-Meier method and log-rank tests were used to analysis PFS. Factors with P values no more than 0.05 in different levels were selected to entera Cox proportional hazards model to identify the independent prognostic factors associated with PFS. Subsequently, a prognostic index (PI) model was generated according to the results of Cox regression analysis. Finally, each patient of the study was calculated a PI based on the model, and then was divided into different groups according to the quartiles of PI to further compare PFS using log-rank tests and a pairwise over strata method.

All confidence intervals reported in the present study were 2-sided, and P values no more than 0.05 were considered statistically significant.

Results

Patient characteristics and response assessment

Table 1 summaries the baseline characteristics of the 128 lung adenocarcinoma patients collected in the present study. These patients tended to be young (<60 years of age, 57.8%), female sex (61.7%), non-smokers (71.1%) and stage IV (91.4%). Sixty-five patients (50.8%) harbored EGFR 19del while 63 (49.2%) harbored a 21L858R mutation. The numbers of patients who received gefitinib, erlotinib, and icotinib were 69 (53.9%), 22 (17.2%) and 37 (28.9%), respectively.

At the study cutoff date, 110 of the 128 patients (85.9%) discontinued EGFR-TKIs therapy, while 18 (14.1%) did not stop taking EGFR-TKIs. The median PFS for all 128 patients was 14.9 months (95% CI, 13.2–16.5 months) (*Figure 1*).

Univariate survival analysis

Table 2 shows the results of the univariate survival analysis by the Kaplan-Meier method. The analyses suggested that female sex (PFS 17.8 *vs.* 12.4 months for males; P<0.001), a non-smoking history (PFS 17.4 *vs.* 9.9 months for a history of smoking; P<0.001), a surgical history of lung cancer (PFS 17.3 *vs.* 13.7 months for no surgical history; P=0.029), tumor located in the right lung (PFS 16.0 *vs.* 13.2 months for the left lung; P=0.038), a first-line EGFR-TKIs administration (PFS 18.9 *vs.* 13.0 months for other lines; P=0.001), ECOG PS 1 (PFS 15.8 *vs.* 10.0 months for PS 2; P=0.004), and a normal pretreatment CA125 level (PFS 17.4 *vs.* 13.2 months for a high level; P=0.019) were all predictors of a longer PFS. No statistically significant differences in PFS were found for age, first findings, tumor gross type, tumor differentiation, clinical stages, metastatic sites, EGFR mutation sites, EGFR-TKIs, and pretreatment serum levels of CEA, NSE, CYFRA21-1, SCC and LDH.

Multivariate regression analysis and modeling

Table 3 lists the outcomes of multivariate survival analysis by Cox regression methods. A non-smoking history [hazard ratio (HR), 2.896; 95% CI, 1.501–5.558; P=0.002] and first-line EGFR-TKIs treatment (HR, 1.544; 95% CI, 0.999–2.386; P=0.05) were found to be independent predictive factors of a longer PFS with EGFR-TKIs therapy. However, other factors including sex, surgical history, tumor locations, ECOG PS and pretreatment CA125 levels were not independent predictors of PFS. The PFS curves regarding smoking history and treatment timing are showed in *Figure 2*.

Based on the results of Cox regression, a PI model can be established as: PI =1.063 × Smoking + 0.434 × Timing. In our subsequent analysis, value assignments of smoking and treatment timing were defined as: for smoking, 1= non-smoking, 2= smoking; for treatment timing, 1= first-line therapy, 2= non-first-line therapy.

Further analysis according to the established PI model

Each patient was calculated a PI according to the above

Table 1 Baseline characteristics of the 128 patients

Characteristic	No. (%)
Age, years	
<60	74 (57.8)
≥60	54 (42.2)
Sex	
Male	49 (38.3)
Female	79 (61.7)
First findings	
Examination	37 (28.9)
Symptoms	91 (71.1)
Smoking history	
None	91 (71.1)
Yes	37 (28.9)
Surgical history	
No	83 (64.8)
Yes	45 (35.2)
Tumor location	
Right lung	75 (58.6)
Left lung	53 (41.1)
Gross type	
Central	34 (26.6)
Peripheral	94 (73.4)
Differentiation	
Low	97 (75.8)
Moderate and high	31 (24.2)
Clinical stage	
IIIB	11 (8.6)
IV	117 (91.4)
Treatment line	
First-line	60 (46.9)
Other line	68 (53.1)
EGFR status	
19del	65 (50.8)
L858R	63 (49.2)
ECOG PS	
1	111 (86.7)
2	17 (13.3)
EGFR-TKI therapy	
Gefitinib	69 (53.9)
Erlotinib	22 (17.2)
Icotinib	37 (28.9)
CEA	
Normal	68 (53.1)
High	60 (46.9)
NSE	
Normal	114 (89.1)
High	14 (10.9)
CYFRA21-1	
Normal	97 (75.8)
High	31 (24.2)
CA125	
Normal	82 (64.1)
High	46 (35.9)
SCC	
Normal	119 (93.0)
High	9 (7.0)
LDH	
Normal	99 (77.3)
High	29 (22.7)

CA125, cancer antigen 125; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin-19 fragments; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; SCC, squamous cell carcinoma.

model. The 25%, 50% and 75% quartiles of PI were 1.479, 1.931, and 2.560, respectively. Firstly, we divided patients into four groups according to the quartiles. As the model contains two factors with two levels each, the four groups were group A (PI =1.497), group B (PI =1.913), group C (PI =2.560) and group D (PI =2.994). The implication of each group has been listed in *Table 4*. *Table 5* and *Figure 3A* shows PFS comparisons of the four groups. Generally, there is a significant statistical difference among four groups in PFS. However, pairwise comparisons regarding PFS of different groups suggested that there was no statistical difference in two comparisons: group B

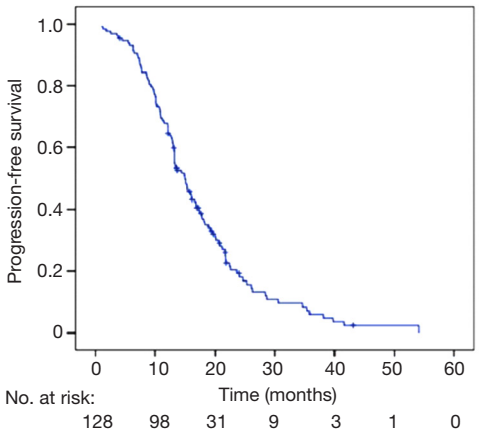

Figure 1 Kaplan-Meier curve for progression-free survival of the 128 EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs (tick marks represent censored observations). EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors.

and group C, group C and group D.

As we considered the reason might be due to the small sample size of group C, we merged group C and group D into group E (PI ≥2.560). Then the statistical analysis was repeated. The implication of group E is "smoking regardless of treatment timing" (*Table 4*). *Table 5* and *Figure 3B* shows PFS comparisons of the three groups. Pairwise comparisons regarding PFS suggested that statistical difference existed in group A, group B and group E indicating that there were differences between the three groups in PFS: non-smoking and first-line therapy, non-smoking and non-first-line therapy, smoking regardless of treatment timing.

Discussion

In this study, we found that a non-smoking history and first-

Table 2 Univariate survival analysis by Kaplan-Meier methods

Covariates	Comparisons	Median PFS in months (95 % CI)	P value
Age	≤60 *vs.* >60 years	13.2 (11.0–15.5) *vs.* 16.0 (13.3–18.7)	0.248
Sex	Male *vs.* female	12.4 (10.7–14.2) *vs.* 17.8 (15.0–20.7)	<0.001*
First findings	Examination *vs.* symptoms	16.0 (11.6–20.4) *vs.* 14.4 (12.6–16.2)	0.296
Smoking history	None *vs.* yes	17.4 (14.6–20.2) *vs.* 9.9 (7.8–12.0)	<0.001*
Surgical history	No *vs.* yes	17.3 (13.9–20.7) *vs.* 13.7 (11.7–15.6)	0.029*
Tumor location	Right *vs.* left	16.0 (13.7–18.3) *vs.* 13.2 (11.7–14.8)	0.038*
Gross type	Central *vs.* peripheral	13.2 (8.9–17.6) *vs.* 15.0 (11.9–18.1)	0.392
Differentiation	Low *vs.* moderate and high	15.0 (13.3–16.7) *vs.* 13.2 (3.6–22.9)	0.070
Clinical stage	IIIB *vs.* IV	21.7 (12.6–30.9) *vs.* 14.9 (13.1–16.7)	0.613
Metastatic sites	Brain *vs.* brain and other *vs.* other	15.0 (11.3–18.7) *vs.* 13.2 (11.8–14.6) *vs.* 19.6 (15.8–23.4)	0.114
Treatment timing	First-line *vs.* other line	18.9 (16.0–21.7) *vs.* 13.0 (12.1–13.8)	0.001*
EGFR mutation sites	19del *vs.* 21L858R	15.3 (13.6–17.0) *vs.* 13.2 (11.1–15.4)	0.619
ECOG PS	1 *vs.* 2	15.8 (14.1–17.6) *vs.* 10.0 (6.4–13.7)	0.004*
EGFR-TKIs	Gefitinib *vs.* erlotinib *vs.* icotinib	14.4 (11.6–17.2) *vs.* 15.0 (12.0–18.0) *vs.* 15.2 (11.6–18.9)	0.186
CEA	Normal *vs.* high	13.0 (11.8–14.3) *vs.* 17.4 (14.6–20.2)	0.092
NSE	Normal *vs.* high	15.8 (14.1–17.6) *vs.* 12.7 (7.9–17.5)	0.067
CYFRA21-1	Normal *vs.* high	15.3 (13.1–17.6) *vs.* 13.7 (9.4–17.9)	0.517
CA125	Normal *vs.* high	17.4 (13.4–21.4) *vs.* 13.2 (11.1–15.4)	0.019*
SCC	Normal *vs.* high	15.0 (12.4–17.7) *vs.* 15.3 (10.3–20.3)	0.805
LDH	Normal *vs.* high	15.3 (12.4–18.1) *vs.* 13.0 (11.7–18.3)	0.811

*, P≤0.05; 95% CI, 95% confidence interval; CA125, cancer antigen 125; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin-19 fragments; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; PFS, progression-free survival; SCC, squamous cell carcinoma. The cut-off values for judging normal or high levels of CEA, NSE, CA125, SCC, CYFRA21-1 and LDH were: 5 ng/mL, 25 ng/mL, 35 U/mL, 1.5 μg/L, 5 ng/mL, and 250 U/L, respectively.

Table 3 Multivariate survival analysis by Cox regression analysis

Covariates	B	SE	Wald	P value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Sex	−0.063	0.296	0.045	0.833	0.939	0.526	1.678
Smoking history	1.063	0.335	10.059	0.002*	2.896	1.501	5.558
Surgical history	−0.392	0.233	2.837	0.092	0.676	0.428	1.066
Tumor locations	0.231	0.221	1.097	0.295	1.260	0.818	1.942
Treatment timing	0.434	0.222	3.830	0.050*	1.544	0.999	2.386
ECOG PS	0.212	0.318	0.443	0.506	1.236	0.662	2.306
CA125	0.347	0.222	2.441	0.118	1.415	0.915	2.186

*, P≤0.05; B, partial regression coefficients; SE, standard error; Exp, exponential function; CA125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group performance status.

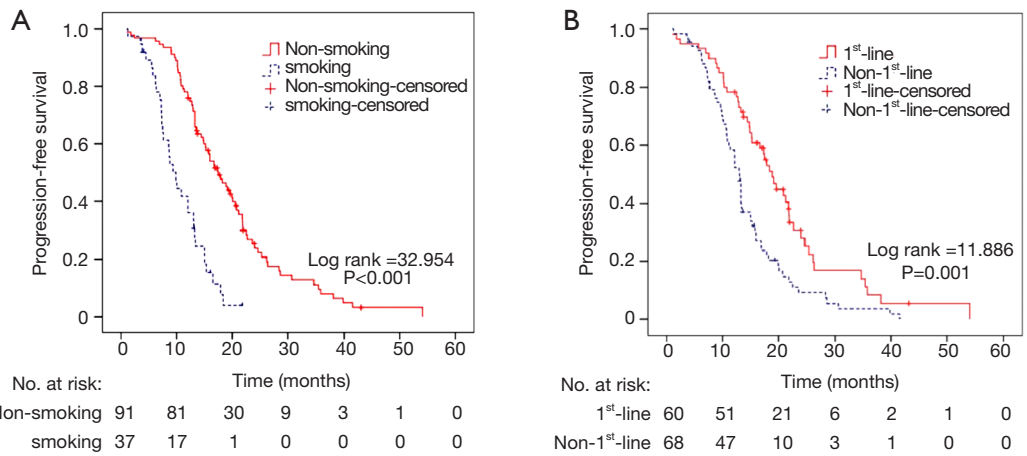

Figure 2 Kaplan-Meier curves for progression-free survival in smoking and treatment timing. (A) Kaplan-Meier curve for progression-free survival of the 128 EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs in smoking (tick marks represent censored observations). P<0.001, Log rank test; (B) Kaplan-Meier curve for progression-free survival of the 128 EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs in treatment timing (tick marks represent censored observations). P=0.001, Log rank test. EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors.

Table 4 PFS comparisons of different groups according to PI

Groups	PI	n	Meanings	Median of PFS		
				Months	SE	95% CI
Group A	1.497	50	Non-smoking and first-line therapy	20.8	1.7	17.5, 24.1
Group B	1.913	41	Non-smoking and other-line therapy	13.4	1.1	11.4, 15.5
Group C	2.560	10	Smoking and first-line therapy	9.3	3.5	2.4, 16.3
Group D	2.994	27	Smoking and other-line therapy	9.9	1.5	7.0, 12.8
Group E (C and D)	≥2.560	37	Smoking regardless of treatment timing	9.9	1.1	7.8, 12.0
Total	–	128	–	14.9	0.8	13.2, 16.5

PFS, progression-free survival; PI, prognostic index; SE, standard error; 95% CI, 95% confidence interval.

Table 5 Pairwise comparisons regarding PFS of different groups according to PI

Comparisons	Chi-Square (Log rank)	P values
Group A *vs.* group B	4.729	0.030*
Group A *vs.* group C	6.541	0.011*
Group A *vs.* group D	39.356	<0.001*
Group B *vs.* group C	1.352	0.245
Group B *vs.* group D	19.644	<0.001*
Group C *vs.* group D	3.629	0.057
Group A *vs.* group E (C and D)	32.715	<0.001*
Group B *vs.* group E (C and D)	13.620	<0.001*

*, P≤0.05; PFS, progression-free survival; PI, prognostic index.

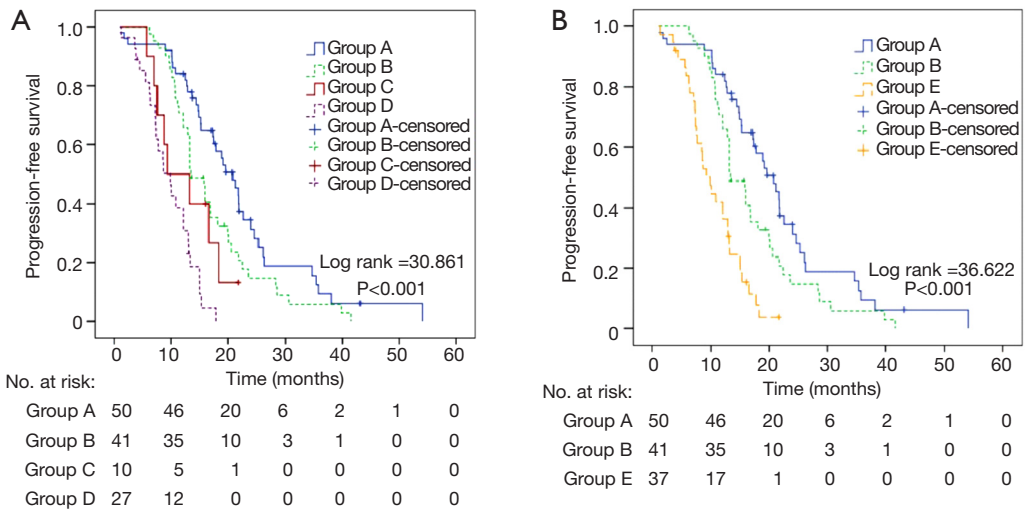

Figure 3 Kaplan-Meier curves for progression-free survival according to prognostic index. (A) Kaplan-Meier curve for progression-free survival of the 128 EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs according to Prognostic Index in 4 groups (tick marks represent censored observations). P<0.001, Log rank test; (B) Kaplan-Meier curve for progression-free survival of the 128 EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs according to Prognostic Index in three groups (after merging group C and group D into group E) (tick marks represent censored observations). P<0.001, Log rank test.

line EGFR-TKIs treatment were independent predictive factors of a longer PFS with EGFR-TKIs therapy by analyzing the data in our institute. According to the results of Cox regression analysis, a predictive model was established as PI =1.063 × Smoking + 0.434 × Timing. Based on the model, we further discovered the PFS differences among the three groups: non-smoking and first-line therapy, non-smoking and non-first-line therapy, smoking regardless of treatment timing.

Existing data showed that never smokers might have a favorable response to EGFR-TKIs since these patients are more likely to harbor EGFR sensitive mutations than ever smokers (16,17). Interestingly, in patients with EGFR-activating mutations, smoking was also a factor related to EGFR-TKIs efficacy. Our study indicated that a non-smoking history was an independent predictor of a longer PFS in EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs, which is consistent with previous

findings (18). However, we did not analyze the impact of smoking dosages due to the small sample size of our study. It has been reported that smoking dosage of more than 30 pack-years is an independent predictor for poor efficacy of EGFR-TKIs in EGFR-mutant lung adenocarcinoma patients (15). Specific molecular mechanisms about this phenomenon remain unknown. Some possible explanations include cigarette smoking-induced EGFR post-translational changes, activation of the nicotinic acetylcholine receptor, promotion of EGFR signal or epithelial-mesenchymal transition (19-22).

As we know, first-line EGFR-TKIs therapy in patients with EGFR-activating mutations achieves a longer PFS, compared with first-line standard chemotherapy (23-25). Previous data revealed that response rate of first-line gefitinib treatment was higher than that of non-first-line patients; however, there is no difference in OS (26). Our data showed that first-line EGFR-TKIs treatment was an independent predictor of a longer PFS. However, this result should be interpreted with caution since P value for comparison of different levels in treatment line was just 0.05. To date, views on treatment timing of EGFR-TKIs are not completely uniform albeit EGFR-TKIs are recommended as a first-line therapy. However, numerous opinions, including assurance on drug exposure, improvement in quality of life, better tolerance by patients with poor PS support the general application of first-line EGFR-TKIs (27).

It has been reported that pretreatment serum tumor markers are associated with EGFR-TKIs efficacy in patients with EGFR sensitive mutations. Higher pretreatment CEA levels may be associated with a worse outcome in EGFR-mutant patients treated with first-line EGFR-TKIs (28). Low pretreatment CYFRA21-1 levels were found to be an independent favorable predictor for longer OS in lung adenocarcinoma patients with EGFR mutations (29). In addition, EGFR-mutant NSCLC patients with an elevated serum NSE level might have significantly shorter PFS and OS after EGFR-TKIs therapy (30). However, our study did not show these serum tumor markers could influence the PFS of EGFR-TKIs in EGFR-mutant Chinese lung adenocarcinoma patients. The design of the previous studies differed from our study, and many studies with small sample size, and were retrospectively conducted in NSCLC patients instead of lung adenocarcinoma patients. We hypothesized that these factors might affect the outcomes.

In multivariate regression analysis, sex, surgical history, tumor locations, ECOG PS and pretreatment CA125 levels were not independent predictors of PFS although these factors could affect PFS in univariate analysis by Kaplan-Meier methods. The possible reason may be that these factors are more important as prognostic factors rather than predictive factors in EGFR-mutant lung adenocarcinoma patients receiving EGFR-TKIs (31).

The predictive model established in the study: PI =1.063 × Smoking + 0.434 × Timing can be used as a reference for clinical practice. By further analyzing the model, we found that patients with a smoking history had a shorter PFS regardless of treatment timing. The results of Cox regression analysis and PI model indicated that smoking might affect PFS more than treatment timing. Thus, EGFR-mutant lung adenocarcinoma patients who have a smoking history are more likely to acquire a relatively short PFS according to our findings.

This study has some limitations. First of all, many confounders might be inevitably introduced to the study due to its retrospective nature. For example, three EGFR-TKIs were not randomly assigned, but allocated mainly as the physicians' recommendation. Side effects were not collected in this study for its retrospective nature, but previous study has indicated that skin rash might be a predictor of erlotinib efficacy (32). Secondly, as a single center study, EGFR-TKIs might show larger treatment efficacy than multicenter studies. Moreover, the sample size of our study was relatively small, especially when we use these data to establish the PI model. Last but not least, the model we established should be interpreted with caution since P value for treatment timing was just 0.05 in Cox analysis.

In conclusion, findings of the present study suggest that a non-smoking history and a first-line EGFR-TKIs treatment timing are independent predictors of a longer PFS in EGFR-mutant lung adenocarcinoma patients treated with first-generation EGFR-TKIs. PFS is longer for those who are never smokers and receive first-line EGFR-TKIs, compared with other groups. However, taking the limitations of this study and the importance of exploring factors associated with EGFR-TKIs efficacy in EGFR-mutant patients into account, subsequent prospective analyses with larger sample sizes are needed to confirm the results.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.07.08). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai. The Approval Number is K(P)15-04. The participants of the present study did not write informed consent before taking part since this was a retrospective study.

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