

# Factors that predict progression-free survival in Chinese lung adenocarcinoma patients treated with epidermal growth factor receptor tyrosine kinase inhibitors

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**Background:** Although first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have shown efficacy in patients with advanced lung cancers, survival predictors with these drugs have not been extensively investigated. This study was performed to explore factors that may predict progression-free survival (PFS) in Chinese lung adenocarcinoma patients treated with EGFR-TKIs.

**Methods:** We retrospectively collected clinicopathologic data on 208 patients who received either gefitinib, erlotinib or icotinib, including the patients' EGFR mutation status and levels of six serum tumor markers [carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cancer antigen 125 (CA125), squamous cell carcinoma antigen (SCC), cytokeratin-19 fragments (CYFRA21-1) and lactate dehydrogenase (LDH)]. Univariate and multivariate survival analyses were performed to identify independent prognostic factors associated with PFS.

**Results:** At the study cutoff date, 189 (90.9%) of the patients met the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria for progressive disease (PD), while 19 (9.1%) had stable disease (SD). The median PFS of the 208 patients was 12.4 months (95% CI, 11.0–13.8 months). In the multivariate analysis using a Cox proportional hazard model, a non-smoking history [hazard ratio (HR) =2.460; 95% CI, 1.484–4.079;  $P<0.001$ ], first-line treatment (HR =1.500; 95% CI, 1.062–2.119;  $P=0.021$ ), and a high pretreatment serum level of CEA (HR =1.424; 95% CI 1.026–1.977;  $P=0.035$ ) were found to be significant predictors of a longer PFS.

**Conclusions:** In Chinese lung adenocarcinoma patients treated with EGFR-TKIs, a non-smoking history, first-line EGFR-TKIs treatment and a high serum level of CEA were independent predictors of a longer PFS along with an EGFR-activating mutation.

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

Submitted Jul 23, 2015. Accepted for publication Dec 13, 2015.

doi: 10.3978/j.issn.2072-1439.2016.01.12

**View this article at:** <http://dx.doi.org/10.3978/j.issn.2072-1439.2016.01.12>

## Introduction

Targeted molecular therapy is playing an increasingly important role in the treatment of non-small cell lung cancer (NSCLC). In advanced disease settings, first-generation epidermal growth factor receptor tyrosine kinase

inhibitors (EGFR-TKIs) such as gefitinib, erlotinib and icotinib have demonstrated good clinical efficacy.

Several studies with EGFR-TKIs have revealed that factors such as East-Asian ethnicity, female sex, adenocarcinoma histology, and a non-smoking history are

predictors of a favorable response in advanced NSCLC (1-3). Subsequent studies have shown that EGFR-activating mutations such as deletions in exon 19 (19del) and L858R point mutation in exon 21 are strong predictors of a favorable response to EGFR-TKIs (4-7). Consequently, for NSCLC patients with activating EGFR mutations, EGFR-TKIs are now recommended as the standard first-line therapy (8-10). However, in China, the EGFR mutation status is often unknown for patients when they receive treatment. Firstly, sometimes small specimens acquired by biopsies (e.g., bronchoscopy or lung biopsy) cannot meet the requirements for both diagnosis and EGFR detection, and thus EGFR mutation status is yet available (11). Secondly, elderly people or patients with poor physical conditions are intolerable to biopsy or secondary biopsy for the purpose of diagnosis and EGFR detection. In addition, despite Chinese patients with lung adenocarcinoma having a higher EGFR mutation rate (about 60%) than people of other ethnicities, the detection rate of EGFR mutations is still only about 30% in China. Additionally, some patients with advanced stage whose tumor specimens have been sent for EGFR detection cannot wait to receive first-line chemotherapy because they believe the duration waiting for the results is too long. Therefore, identifying factors other than the EGFR mutation status that will predict greater efficacy and survival in Chinese lung adenocarcinoma populations is vital.

Currently, few studies have focused on clinical factors other than the EGFR mutation status that can potentially influence survival in Chinese patients with advanced lung adenocarcinoma treated with EGFR-TKIs (12). Therefore, exploring factors that may have major roles in determining survival in these patients would help clinicians determine appropriate treatment strategies. In this study, we retrospectively collected clinicopathologic data on Chinese lung adenocarcinoma patients treated with EGFR-TKIs to identify clinical factors that may predict progression-free survival (PFS).

## Patients and methods

### Patients

A total of 208 patients treated with EGFR-TKIs (gefitinib, erlotinib or icotinib) between July 01, 2010 and December 01, 2013 at the Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, were retrospectively registered in this study. All were

histologically diagnosed and staged as clinically advanced (stage IIIB or stage IV) lung adenocarcinoma. Prior to initiation of therapy, all patients were evaluated by computed tomography (CT) of the thorax.

Age, gender, smoking status, EGFR mutation status, clinical stage, surgical history, differentiation, tumor location, pretreatment levels of serum tumor markers [including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cancer antigen 125 (CA125), squamous cell carcinoma antigen (SCC), cytokeratin-19 fragments (CYFRA21-1), and lactate dehydrogenase (LDH)], the Eastern Cooperative Oncology Group performance status (ECOG PS), and the treatment line with EGFR-TKIs (first-line or other line) were all analyzed, along with the patients' PFS times.

The study was approved by the Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai [Approval number: K(P)15-04].

### Detection methods

To determine the patients' EGFR mutation status, we used the ADx EGFR Mutation Detection Kit (Amoy Diagnostics, Xiamen, China), which has been approved by China's Food and Drug Administration (CFDA). The principle of amplification refractory mutation system (ARMS) was used in the kit. Serum tumor markers were detected by radioimmunoassay. 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.

### Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment, response evaluation and follow-up

All patients received 1 of the 3 EGFR-TKIs in 28-day cycles. 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. The tumor response was assessed after the first cycle of therapy and subsequently after every 2 cycles using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (13). CT scans were performed to assess the response to EGFR-TKIs as clinically indicated or until discontinuation of treatment. Patients continued to receive EGFR-TKIs as long as they did not have progressive disease (PD) or intolerable adverse effects. The final cutoff date for the study was April 01, 2015.

### Statistical analysis

Pearson  $\chi^2$  tests were used for comparing characteristics between patients with 19del and L858R mutations. PFS was defined as the time from the date EGFR-TKIs were first administered until the date of objective PD according to RECIST version 1.0 or until the death of a patient. The Kaplan-Meier method and log-rank tests were used to analysis PFS and select factors with P values less than 0.05 in different levels, and then a Cox proportional hazards model was used to further identify the independent prognostic factors associated with PFS. All confidence intervals reported were 2-sided, and P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS® software, version 13.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

The demographic and clinicopathologic characteristics of the 208 patients registered in the study are summarized in *Table 1*. The patients tended to be young (<60 years of age, 58.2%), female (57.7%), and never-smokers (64.4%). Most patients (73.6%) sought medical attention because of symptoms such as cough, expectoration, chest pain, tightness, and shortness of breath; 67 (32.2%) had a history of surgery for lung cancer, and the majority (73.6%) had peripheral tumors. Most patients (79.3%) had tumors that were poorly differentiated; 190 (91.3%) had clinical IV stage disease and 18 (8.7%) had clinical stage IIIB disease according to the International Association for the Study of Lung Cancer Staging Project (7<sup>th</sup> edition). EGFR mutations were identified in 128 patients (61.5%), 65 of whom harbored 19del mutations while 63 harbored L858R mutations; 8 patients (3.8%) had a negative EGFR status and 72 (34.6%) had an unknown status. Most patients (87.0%) were in good physical condition, with an ECOG PS of 0 to 1. The numbers of patients who received gefitinib, erlotinib, and icotinib were 107 (51.4%), 33 (15.9%) and 68 (32.7%), respectively.

### Response evaluation

At the study date cutoff, 189 of the 208 patients (90.9%) met the RECIST criteria for disease progression, while

**Table 1** Demographic and clinicopathologic characteristics of the patients (n=208)

Characteristic	N (%)
Age (years)	
<60	121 (58.2)
≥60	87 (41.8)
Sex	
Male	88 (42.3)
Female	120 (57.7)
First findings	
Examination	55 (26.4)
Symptoms	153 (73.6)
Smoking history	
None	134 (64.4)
Yes	74 (35.6)
Surgical history	
No	141 (67.8)
Yes	67 (32.2)
Tumor location	
Right lung	118 (56.7)
Left lung	90 (43.3)
Gross type	
Central	55 (26.4)
Peripheral	153 (73.6)
Differentiation	
Low	165 (79.3)
Moderate and high	43 (20.7)
Clinical stage	
IIIB	18 (8.7)
IV	190 (91.3)
Treatment line	
First-line	82 (39.4)
Other line	126 (60.6)
Epidermal growth factor receptor (EGFR) status	
19del	65 (31.3)
L858R	63 (30.3)
Negative	8 (3.8)
Unknown	72 (34.6)
Eastern Cooperative Oncology Group performance status (ECOG PS)	
0–1	181 (87.0)
2–3	27 (13.0)

**Table 1** (continued)

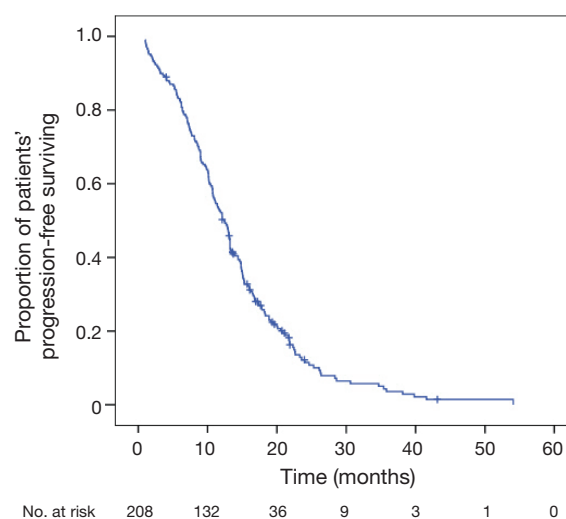
**Table 1** (continued)

Characteristic	N (%)
Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy	
Gefitinib	107 (51.4)
Erlotinib	33 (15.9)
Icotinib	68 (32.7)
Carcinoembryonic antigen (CEA)	
Normal	102 (49.0)
High	106 (51.0)
Neuron-specific enolase (NSE)	
Normal	188 (90.4)
High	20 (9.6)
Cytokeratin-19 fragments (CYFRA21-1)	
Normal	151 (72.6)
High	57 (27.4)
Cancer antigen 125 (CA125)	
Normal	126 (60.6)
High	82 (39.4)
Squamous cell carcinoma antigen (SCC)	
Normal	192 (92.3)
High	16 (7.7)
Lactate dehydrogenase (LDH)	
Normal	147 (70.7)
High	61 (29.3)

19 (9.1%) were found to have stable disease (SD). Six patients had to discontinue EGFR-TKIs treatment due to severe adverse effects (SAEs, 3 for AST or ALT elevation, 1 for vomiting, 1 for severe rash and 1 for interstitial lung disease). For these patients, we calculated the PFS from the day they were first administrated EGFR-TKIs to the day they were found SAEs. The median PFS for all 208 patients was 12.4 months (95% CI, 11.0–13.8 months) (*Figure 1*); 19 patients (9.1%) were censored at the study cutoff date.

### Univariate survival analysis

The results of the univariate survival analysis by the Kaplan-Meier method are shown in *Table 2*. The analyses suggested that female sex (PFS 14.4 *vs.* 9.0 months for males;  $P<0.001$ ), a non-smoking history (PFS 14.8 *vs.* 8.1 months for a history of smoking;  $P<0.001$ ), a history of surgery for lung cancer (PFS 13.3 *vs.* 11.1 months for no surgical history;  $P=0.004$ ), tumor located in the right lung (PFS 13.1 *vs.* 10.8 months



**Figure 1** Kaplan-Meier curve for progression-free survival of the 208 patients treated with EGFR-TKIs (tick marks represent censored observations). EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

for the left lung;  $P=0.027$ ), first-line EGFR-TKI therapy (PFS 15.3 *vs.* 10.7 months for other lines;  $P<0.001$ ), EGFR sensitive mutation status (PFS 14.9 *vs.* 3.2 months for a negative status;  $P<0.001$ ), ECOG PS 0–1 (PFS 13.0 *vs.* 7.4 months for PS 2–3;  $P=0.001$ ), and a high pretreatment CEA level (PFS 14.8 *vs.* 10.9 months for a normal level;  $P=0.044$ ) were all predictors of a longer PFS. No statistically significant differences in PFS were found for age, the first finding (examination *vs.* symptoms), gross type, differentiation, clinical stage, EGFR-TKIs, and pretreatment serum levels of NSE, CYFRA21-1, CA125, SCC and LDH. We did not include the EGFR mutation status in the subsequent Cox multivariate regression analysis since the EGFR mutation status could influence the other two factors (sex and smoking history) in predicting PFS.

The demographic and clinicopathologic characteristics of 128 patients with EGFR sensitive mutations (19del or L858R) are shown in *Table 3*. Although PFS was longer in patients with 19del mutations (15.3 months; 95% CI, 13.6–17.0 months) compared with those with L858R mutations (13.2 months; 95% CI, 11.1–15.4 months), the difference between the 2 groups was not statistically significant ( $P=0.619$ , log-rank test) (*Figure 2*).

### Cox multivariate regression analysis

In the multivariate analysis using a Cox proportional

**Table 2** Univariate survival analysis by the Kaplan-Meier method

Covariates	Comparison	Median PFS in months (95 % CI)	P value
Age	≤60 vs. >60 years	11.0 (9.8–12.2) vs. 13.3 (11.2–15.4)	0.234
Sex	Male vs. female	9.0 (7.5–10.6) vs. 14.4 (12.7–16.1)	<0.001*
First findings	Examination vs. symptoms	13.2 (12.5–13.9) vs. 11.6 (10.0–13.1)	0.174
Smoking history	None vs. yes	14.8 (13.3–16.4) vs. 8.1 (7.0–9.2)	<0.001*
Surgical history	No vs. yes	11.1 (9.6–12.6) vs. 13.3 (11.1–15.5)	0.004*
Tumor location	Right vs. left	13.1 (10.9–15.3) vs. 10.8 (9.6–12.1)	0.027*
Gross type	Central vs. peripheral	11.4 (8.6–14.2) vs. 12.8 (11.6–14.1)	0.364
Differentiation	Low vs. moderate and high	12.1 (10.2–14.0) vs. 12.4 (9.5–15.4)	0.080
Clinical stage	IIIB vs. IV	13.1 (12.8–13.5) vs. 12.1 (10.6–13.6)	0.821
Treatment line	First-line vs. other line	15.3 (12.9–17.7) vs. 10.7 (9.8–11.7)	<0.001*
EGFR status	Sensitive mutation <sup>a</sup> vs. negative vs. unknown	14.9 (13.2–16.5) vs. 3.2 (1.3–5.1) vs. 9.0 (7.0–11.0)	<0.001*
ECOG PS	0–1 vs. 2–3	13.0 (12.0–14.0) vs. 7.4 (6.4–8.4)	0.001*
EGFR-TKI	Gefitinib vs. erlotinib vs. icotinib	12.9 (11.7–14.1) vs. 14.9 (10.2–20.0) vs. 10.2 (8.4–12.0)	0.193
CEA	Normal vs. high	10.9 (9.1–12.6) vs. 14.8 (13.1–16.5)	0.044*
NSE	Normal vs. high	13.0 (11.5–14.6) vs. 9.0 (2.6–15.4)	0.164
CYFRA21-1	Normal vs. high	13.0 (11.7–14.4) vs. 13.0 (9.0–17.0)	0.685
CA125	Normal vs. high	13.0 (11.8–14.2) vs. 13.2 (10.3–16.1)	0.159
SCC	Normal vs. high	13.0 (11.7–14.3) vs. 13.2 (4.8–21.7)	0.736
LDH	Normal vs. high	13.0 (11.7–14.3) vs. 13.2 (8.4–18.1)	0.971

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. <sup>a</sup>, sensitive mutation: EGFR 19 deletion or 21 L858R; \*, P<0.05. PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CYFRA21-1, cytokeratin-19 fragments; CA125, cancer antigen 125; SCC, squamous cell carcinoma antigen; LDH, lactate dehydrogenase.

hazard model, a non-smoking history [hazard ratio (HR) =2.460; 95% CI, 1.484–4.079; P<0.001], first-line treatment (HR =1.500; 95% CI, 1.062–2.119; P=0.021), and a high pretreatment serum level of CEA (HR =1.424; 95% CI, 1.026–1.977; P=0.035) were independent predictors of a longer PFS with EGFR-TKI therapy. Female sex, tumor location in the right lung, a history of surgery for lung cancer, and ECOG PS 0–1 were not independent predictors of PFS (Table 4).

## Discussion

The present study retrospectively analyzed clinical factors associated with PFS in Chinese patients with lung adenocarcinoma who were treated with EGFR-TKIs. We found that a non-smoking history, first-line EGFR-TKIs treatment and a high pretreatment serum level of CEA were independent predictors of a longer PFS by means

of a univariate survival analysis and a Cox multivariate regression analysis. This suggests that in addition to patients with an EGFR mutation status, patients who receive first-line EGFR-TKIs, with a non-smoking history and a high pretreatment serum level of CEA may also benefit from treatment with EGFR-TKIs.

Previous studies have shown that first-line therapy with first-generation EGFR-TKIs in patients harboring tumors with EGFR-activating mutations achieves a longer PFS, with acceptable toxicity, in comparison with standard platinum-based chemotherapy (9,14–16). Our results revealed that first-line EGFR-TKIs treatment was an independent predictor of a longer PFS. However, some studies hold that EGFR-TKIs showed similar efficacy in patients with EGFR mutation-positive adenocarcinoma in terms of PFS regardless of treatment timing (17). Taking the assurance on drug exposure, improvement in quality of life, better tolerance by patients with poor PS, and deferral

**Table 3** Demographic and clinicopathologic characteristics of 128 patients with EGFR sensitive mutations (19del or L858R)

Characteristic	19del (n=65)	%	L858R (n=63)	%	P value
Age (years)					0.113
<60	42	64.6	32	50.8	
≥60	23	35.4	31	49.2	
Sex					0.684
Male	26	40.0	23	36.5	
Female	39	60.0	40	63.5	
First findings					0.934
Examination	19	29.2	18	28.6	
Symptoms	46	70.8	45	71.4	
Smoking history					0.758
None	47	72.3	44	69.8	
Yes	18	27.7	19	30.2	
Surgical history					0.057
No	37	56.9	46	73.0	
Yes	28	43.1	17	27.0	
Tumor location					0.296
Right lung	41	63.1	34	54.0	
Left lung	24	36.9	29	46.0	
Gross type					0.769
Central	18	27.7	16	25.4	
Peripheral	47	72.3	47	74.6	
Differentiation					0.929
Low	52	80.0	50	79.4	
Moderate and high	13	20.0	13	20.6	
Clinical stage					0.794
IIIB	6	9.2	5	7.9	
IV	59	90.8	58	92.1	
Treatment line					0.851
First-line	31	47.7	29	46.0	
Other line	34	52.3	34	54.0	
ECOG PS					0.742
0-1	57	87.7	54	85.7	
2-3	8	12.3	9	14.3	
EGFR-TKI					0.522
Gefitinib	32	49.2	37	58.7	
Erlotinib	13	20.0	9	14.3	
Icotinib	20	30.8	17	27.0	
CEA					0.730
Normal	30	46.2	31	49.2	
High	35	53.8	32	50.8	

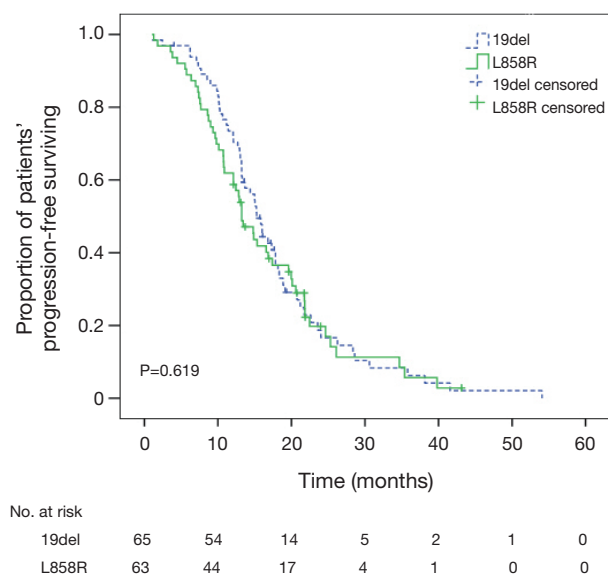
**Table 3** (continued)



Table 3 (continued)

Characteristic	19del (n=65)	%	L858R (n=63)	%	P value
NSE					0.507
Normal	60	92.3	56	88.9	
High	5	7.7	7	11.1	
CYFRA21-1					0.915
Normal	48	73.8	46	73.0	
High	17	26.2	17	27.0	
CA125					0.560
Normal	38	58.5	40	63.5	
High	27	41.5	23	36.5	
SCC					0.794
Normal	59	90.8	58	92.1	
High	6	9.2	5	7.9	
LDH					0.637
Normal	45	69.2	46	73.0	
High	20	30.8	17	27	

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



**Figure 2** Kaplan-Meier curves for progression-free survival of patients with EGFR 19del and L858R mutations treated with EGFR-TKIs (P=0.619; log-rank test). EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

of whole-brain radiation therapy for patients with brain metastasis into account, the general application of first-line EGFR TKIs was recommended (18). In addition, EGFR-TKIs are currently recommended as the standard first-line therapy for patients with activating EGFR mutations (8-10). In contrast, EGFR-TKIs are not suitable for patients with no EGFR sensitive mutations. The TORCH study revealed that if the EGFR mutation status is unknown or there is no mutation, administration of EGFR-TKIs instead of chemotherapy is associated with a deleterious effect in terms of the response rate, PFS, and overall survival (19).

In this study, we confirmed that an EGFR sensitive mutation status was a predictor of a longer PFS. However, our findings did not indicate a statistically significant difference in PFS between patients with EGFR 19del and L858R mutations. Other investigations have reported clinical differences in both the response rate and survival between patients with different EGFR mutations (5,20-22). These studies have shown that patients with the EGFR 19del mutation have a longer survival following treatment with gefitinib or erlotinib than those with the L858R

**Table 4** Cox multivariate regression analysis

Covariates	B	SE	Wald	P value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Sex	-0.123	0.241	0.262	0.608	0.884	0.551	1.417
Smoking history	0.900	0.258	12.178	<0.001*	2.460	1.484	4.079
Surgical history	-0.425	0.180	1.667	0.196	1.385	0.847	2.270
Tumor location	0.126	0.168	0.559	0.455	1.134	0.816	1.576
Treatment line	0.405	0.176	5.289	0.021*	1.500	1.062	2.119
ECOG PS	0.325	0.252	1.666	0.197	1.384	0.845	2.269
CEA	0.354	0.167	4.470	0.035*	1.424	1.026	1.977

\*, P<0.05. B, partial regression coefficients; SE, standard error; Exp, exponential function. ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen.

mutation, indicating that the mutation itself could possibly have an effect on outcomes. This has been demonstrated in a study of patients with surgically-resected, early-stage NSCLC who did not receive EGFR-TKIs (6). Existing data also suggest that the survival advantage found after treatment with gefitinib or erlotinib reflects an even more significant alteration in the potential disease course for patients with the 19del mutation (5,22). However, the sample sizes of these studies were relatively small. While our study did not find a statistically significant difference in PFS with EGFR-TKI treatment between patients with the 19del and L858R mutations, we cannot be certain that the effect of the EGFR mutation on outcomes in patients with advanced lung adenocarcinoma will be the same as that observed in patients with surgically-resected, early-stage disease.

NSCLC patients with a smoking history may have a poorer response and shorter PFS with EGFR-TKI treatment (23-25). Consistent with these findings, our study showed that a non-smoking history was an independent predictor of a longer PFS. Specific reasons for this phenomenon remain unclear, but several mechanisms have been proposed to explain the poorer response to EGFR-TKIs in patients with a smoking history, such as cigarette smoking-induced EGFR post-translational changes, and activation of the nicotinic acetylcholine receptor by cigarette smoking-induced EGFR-TKI resistance (26,27).

Several studies have suggested that levels of serum tumor markers may affect the survival of patients treated with EGFR-TKIs (28-34). In a multivariate regression analysis, we found that patients with a high serum level of CEA before EGFR-TKI treatment achieved a longer PFS compared with those with a normal serum level of CEA.

Previous studies have also reached this conclusion (28,29). A recent study revealed that pre-treatment higher CEA (>5 ng/mL) was associated significantly with a higher overall survival (30). The reason maybe that high serum CEA levels are possibly associated with sensitive mutations of the EGFR gene in patients with lung adenocarcinomas (34). In clinical practice, patients with poor PS are intolerance to invasive procedures such as bronchoscopy, thus their EGFR mutation status remains unknown. Additionally, EGFR detection was always limited by the insufficient tissue acquired by biopsies, especially for the advanced stage. Peripheral blood samples are easily obtained for all patients. Therefore, serum CEA levels of these people could be used as a reference of EGFR-TKIs treatment. For patients with a high serum CEA level, it is worth attempting EGFR-TKI treatment, as this may achieve a better clinical response and survival. In addition, one recent study showed that in patients with wild-type/unknown EGFR mutation status, CEA response was significantly correlated with disease control rate and resulted as a significant predictor of PFS (31). Hence, according to this study, CEA response after 1 month of EGFR-TKIs therapy could be used as an early predictor of PFS in EGFR wild-type/unknown NSCLC for which EGFR status is not available.

Although some studies have shown that patients with a high CYFRA 21-1 level have a significantly shorter PFS (31,33), we found that the serum level of CYFRA21-1 was not a predictor for PFS. However, the previous studies were retrospective in design and had small sample sizes, and the patients either received chemotherapy before EGFR-TKI treatment or had EGFR mutations, which differs from our study. We hypothesize that these factors may, to some extent, have influenced the outcome.



It is worth noting that female sex was not a significant factor in predicting a longer PFS in the multivariate analysis of our study, although it is a well-known clinical factor for predicting a better PFS with EGFR-TKIs. In a recent large sample study analyzing gender-based impact of EGFR mutation in NSCLC, gender were not independent prognostic factors of 2-year overall survival (35). The reason may be that in Chinese adenocarcinoma patients, gender may not be an independent factor associated with EGFR mutation status, and thus, was not an independent predictor of PFS in this study.

Our study has some limitations. Firstly, it was a retrospective study conducted at a single center. Due to its retrospective nature, three EGFR-TKIs were not randomly assigned to patients and this may introduce some bias to the study. Most of the registered patients (107 cases) received gefitinib, while 33 patients received erlotinib. Although the three drugs may have a balanced efficacy and some analogous toxic profiles, heterogeneities exist among them. In addition, single center studies might show larger treatment effects than multicenter ones (36). Secondly, the sample size of the study was relatively small, and the associations reported as statistically significant require validation in larger patient cohorts in future studies. Thirdly, the results should be interpreted with caution as many patients with an unknown EGFR mutation status (34.6% of the population evaluated) were registered in the study. In addition, it should be noted that treatments administered before EGFR-TKI therapy may have influenced the EGFR mutation status, and influenced the survival of patients subsequently treated with EGFR-TKIs (37,38). Many of the patients registered had received chemotherapy and radiotherapy before EGFR-TKIs treatment, and not all of them had EGFR mutations that were detected only a short time before receiving EGFR-TKIs. This may have introduced some confounding factors into the study.

In conclusion, the findings of this study indicate that a non-smoking history, first-line EGFR-TKIs treatment and a high pretreatment serum level of CEA are independent predictors of a longer PFS in Chinese lung adenocarcinoma patients treated with EGFR-TKIs. However, due to the study's limitations, prospective, multicenter analyses with larger sample sizes are needed to confirm these findings.

## Acknowledgements

Editorial assistance with the manuscript was provided by

Content Ed Net, Shanghai Co. Ltd.

**Funding:** This project was supported by the National Nature Science Foundation of China (Grant No. 81472175) and Shanghai Municipal Commission of Health and Family Planning Key Projects (Grant No. 20134007).

## Footnote

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

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**Cite this article as:** Cui S, Xiong L, Lou Y, Shi H, Gu A, Zhao Y, Chu T, Wang H, Zhang W, Dong L, Jiang L. Factors that predict progression-free survival in Chinese lung adenocarcinoma patients treated with epidermal growth factor receptor tyrosine kinase inhibitors. *J Thorac Dis* 2016;8(1):68-78. doi: 10.3978/j.issn.2072-1439.2016.01.12