Postoperative survival of EGFR-TKI-targeted therapy in non-small cell lung cancer patients with EGFR 19 or 21 mutations: a retrospective study

Wenjing Yang, Yibo Gao*, Xuelian Li, Jing Zhang, Tiejun Liu, Xiaoli Feng, Hao Pan, Xiaofan Yang, Shuanghua Xie, Xiaoshuang Feng, Zhangyan Lv, Yonggang Wang, Zhaoli Chen and Jie He*

Abstract

Background: The aim of this retrospective study is to identify epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer patients and to compare the long-term postoperative outcomes in different EGFR-TKI-targeted therapy effects between the different EGFR mutation groups.

Methods: A total of 2094 postoperative non-small cell lung cancer (NSCLC) patients with EGFR gene detection were collected in the Department of Pathology in the Cancer Hospital Chinese Academy of Medical Sciences from January 2003 to January 2014. Three hundred sixty-three patients were treated with EGFR tyrosine kinase inhibitor (TKI) after surgery: 184 harbored the exon 19 deletion mutation and 179 cases carried the exon 21 L858R point mutation. The end points included progression-free survival (PFS), overall survival (OS), and the response rate.

Results: OS was increased in the EGFR exon 19 deletion group compared with the exon 21 L858R point mutation group (92 vs. 65 months; \( P < 0.001 \)). But the median PFS did not differ between two groups (12 vs 14 months). The objective response rate (ORR) in 19 deletion group was increased compared with L858R mutation patients (28.35 vs. 22.73%). The disease control rate (DCR) of patients with 19 deletion benefited more from targeted therapy, compared with L858R group (93.71 vs. 84.31%, \( P = 0.014 \)). In 19 deletion group, a high ORR and DCR were noted in patients treated with icotinib, 16 out of 18 achieved stable disease (SD), and the DCR in this population was 100%.

Conclusions: EGFR subtypes could influence the postoperative survival of NSCLC patients with TKI-targeted therapy.

Keywords: EGFR subtypes could influence the postoperative survival of NSCLC patients with TKI-targeted therapy.

Background

Non-small cell lung cancer (NSCLC) accounts for 80 to 85% of all common types of lung cancer, and NSCLC exhibits the highest morbidity and mortality rate, which is still increasing [1]. Fortunately, developments in lung cancer research over the past decade have codified major advances in the pathogenesis and management of lung cancer, especially adenocarcinoma. The identification of epidermal growth factor receptor (EGFR) mutations in NSCLC and the association between EGFR mutations and gefitinib sensitivity have changed the way lung cancer is diagnosed and treated [2]. Previous retrospective and prospective trials reported that in patients with EGFR mutations, gefitinib or erlotinib produces response rates of 70 to 80%, especially in advanced NSCLC patients with activating EGFR mutations [3, 4]. Furthermore, patients with EGFR mutations have significantly longer survival than those with wild-type EGFR when treated with EGFR tyrosine kinase inhibitors (TKIs) [4–7]. Testing for EGFR mutations is now recommended to guide patient selection for therapy involving an EGFR...
inhibitor and a routine postoperative examination, especially in Chinese NSCLC patients [8, 9]. However, published results have often been inconsistent and occasionally contradictory regarding the efficacy of targeted therapy as an independent treatment for NSCLC patients [10]. Most previous studies focus on the efficacy of TKI compared with chemotherapy drugs in patients with EGFR mutations, and there are also conflicting reports on whether patients with EGFR mutations are sensitive to this type of treatment [10, 11]. How to address the clinical utility and predict the benefit of taking EGFR-TKI is still unanswered.

The aim of this retrospective study is to identify EGFR mutations in NSCLC patients and to compare the long-term postoperative outcomes in different EGFR-TKI-targeted therapy effects between the different EGFR mutation groups.

Methods

General materials

All consecutive lung cancer subjects who underwent EGFR mutation testing in the Department of Pathology in the Cancer Hospital Chinese Academy of Medical Sciences were collected from January 2003 to January 2014. A total of 2094 postoperative NSCLC patients with EGFR gene detection were retrospectively reviewed. Then, patients meeting the following criteria for inclusion were enrolled in the present retrospective study: (i) NSCLC with a histopathological diagnosis, (ii) harboring a specific EGFR mutation (the exon 19 deletion mutation or the L858R point mutation), (iii) treated with EGFR-TKI until the disease progressed or toxicity was intolerable, and (iv) clinical and survival data of all patients were complete and up to date on January 1, 2015. Patients with a secondary lung tumor combined with tuberculosis, tuberculosis pleural effusion, and other types of tumors or carriers of other types of EGFR mutations were excluded. In total, 363 patients aged 46 to 75 years (average age of 59.7 ± 11.6 years) were available for the present analysis. Of these patients, 184 harbored the exon 19 deletion mutation and 179 cases carried the exon 21 L858R point mutation. A total of 16 (4.41%) patients had squamous cell lung carcinoma or large cell lung cancer, whereas 347 (95.59%) patients had adenocarcinoma.

General data, including gender, age, tumor type, tumor stage, and TNM stage, and diameter of the tumor were collected as baseline information. After the subjects were enrolled, the patients were followed up every 6 months until progression; thereafter, they were observed every 6 months for survival. The primary end point of the study was progression-free survival (PFS, referred to the time span from surgery to tumor progression or death). Secondary end points included overall survival (OS) and the response rate. Four response categories included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the effective evaluation criteria from the Response Evaluation Criteria in Solid Tumors.

EGFR mutation testing

PCR was used for amplification and sequencing of the EGFR 19 and 21 exons. ABI Sequencing Analysis v 5.4 software (Applied Biosystems, Foster City, CA, USA) was used to analyze the sequencing results to identify EGFR mutations. A search was conducted for the following mutations: (i) EGFR exon 19 deletions and (ii) the L858R mutation (amino acid substitution at position 858 in EGFR, from a leucine to an arginine) in exon 21. EGFR 19 and 21 sites were detected in all of the cases participating in this study. TKI medicine was administered to patients with mutant EGFR, qd, or po for a duration of 4 to 8 months.

The routine follow-up procedures included a physical examination, hematological examination, computed tomography (CT) of the chest, and ultrasound of the neck and abdomen. Magnetic resonance imaging (MRI) of the head and whole-body bone scans were performed every 1 or 2 years or when recurrent disease was suspected. Routine blood examinations, heart, liver, and kidney functions, and coagulation indicators were monitored periodically. Fever, white blood cell reduction, and other complications were treated symptomatically.

Statistical analysis

Normally distributed data are reported as the mean ± SD or as the median and interquartile range (data which deviated from the normal distribution), and the t test or Mann–Whitney test was used for comparisons between groups, as appropriate. Survival curves were estimated by the Kaplan–Meier product-limit method and compared with the Mantel (log-rank) test. The independent prognostic power of variances for OS and PFS was analyzed by the Cox proportional hazard method by the introduction of all covariates that were related to OS or PFS on univariate analysis or traditional confounding factors (age, sex). Hazard ratios (HR) and their 95% CIs were calculated with the estimated regression coefficients and their standard errors in the Cox regression analysis. A P value less than 0.05 was considered to be statistically significant. All analyses were performed using SPSS version 19.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 363 NSCLC patients were identified with activating mutations in EGFR (exon 19 deletions or exon 21 L858R point mutations). At the data cutoff point (December 31, 2014), the median follow-up period was 72 months, with
a range of 5 to 134 months. Of these, 184 cases had an EGFR 19 site mutation, and 179 had an EGFR 21 site mutation. The main demographic and clinical characteristics are listed in Table 1. Patients with an exon 19 deletion were diagnosed at a younger age than exon 21 L858R point mutation patients ($58.69 \pm 10.19$ vs. $60.87 \pm 10.33$). Striking differences in the distribution of the clinical stage were noted in the two EGFR mutation groups (Table 1).

**Comparison of survival**
Superior survival was observed with younger (age at diagnosis is less than 45 years) lung cancer patients (adjusted hazard ratio, 0.246; 95% confidence interval, 0.098 to 0.621) compared with patients diagnosed at over 45 years of age. Other types of NSCLC were associated with an increased hazard ratio for death compared with lung adenocarcinoma (adjusted HR 3.279, 95% CI 1.558

| Table 1 Baseline patient characteristics in the EGFR 19 and 21 mutation groups |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age (mean ± SD)                 | 363             | $58.69 \pm 10.19$ | $60.87 \pm 10.33$ | 0.044           |
| Gender, n (%)                   |                 |                 |                 |                 |
| Male                            | 137             | 75 (40.76)      | 62 (34.64)      | 0.229           |
| Female                          | 226             | 109 (59.24)     | 117 (65.36)     |                 |
| Smoking, n (%)                  |                 |                 |                 |                 |
| Yes                             | 83              | 47 (25.54)      | 36 (20.11)      | 0.218           |
| No                              | 280             | 137 (74.46)     | 143 (79.89)     |                 |
| Family history, n (%)           |                 |                 |                 |                 |
| Yes                             | 62              | 27 (14.67)      | 35 (19.55)      | 0.174           |
| No                              | 301             | 157 (85.79)     | 144 (80.45)     |                 |
| Type, n (%)                     |                 |                 |                 |                 |
| AD                              | 347             | 175 (95.11)     | 172 (96.09)     | 0.649           |
| Other                           | 16              | 9 (4.89)        | 7 (3.91)        |                 |
| Differentiation, n (%)          |                 |                 |                 |                 |
| High                            | 49              | 23 (12.85)      | 26 (15.29)      | 0.663           |
| Middle                          | 246             | 130 (72.63)     | 116 (68.24)     |                 |
| Low                             | 54              | 26 (14.53)      | 28 (16.47)      |                 |
| Stage, n (%)                    |                 |                 |                 | 0.026           |
| I                               | 87              | 52 (28.26)      | 35 (19.55)      |                 |
| II                              | 52              | 26 (14.13)      | 26 (14.53)      |                 |
| III                             | 168             | 72 (39.13)      | 96 (53.63)      |                 |
| IV                              | 56              | 34 (18.48)      | 28 (16.47)      |                 |
| Operation, n (%)                |                 |                 |                 | 0.302           |
| Radical                        | 288             | 142 (77.17)     | 146 (81.56)     |                 |
| Palliative                      | 75              | 42 (22.83)      | 33 (18.44)      |                 |
| Adjuvant chemotherapy           |                 |                 |                 | 0.157           |
| Yes                             | 285             | 150 (81.52)     | 135 (75.42)     |                 |
| No                              | 78              | 34 (18.48)      | 44 (24.58)      |                 |
| Adjuvant radiation              |                 |                 |                 | 0.395           |
| Yes                             | 111             | 60 (32.61)      | 51 (28.49)      |                 |
| No                              | 252             | 124 (67.39)     | 128 (71.51)     |                 |
| TKI                             |                 |                 |                 | 0.886           |
| Gefitinib                       | 237             | 123 (66.85)     | 114 (63.69)     |                 |
| Erlotinib                       | 55              | 28 (15.22)      | 27 (15.08)      |                 |
| Icotinib                        | 58              | 27 (14.67)      | 31 (17.32)      |                 |
| Others                          | 13              | 6 (3.26)        | 7 (3.91)        |                 |
to 6.900). Patients with a high histological grade of differentiation had a longer median survival time than those with a low or middle differentiation (72 vs. 68 months), but survival according to the differentiation revealed no significant difference. The EGFR 19 deletion mutation is associated with prolonged survival in patients with lung cancer, with a median survival of approximately 92 months. Icotinib provides superior efficacy to gefitinib in NSCLC patients in this study, with an adjusted HR of 0.316 (95% CI, 0.137 to 0.731) (Table 2).

Overall survival was significantly increased in the EGFR exon 19 deletion group compared with the exon 21 L858R point mutation group (median, 92 vs. 65 months; hazard ratio for death, 1.265; 95% CI, 1.041 to 1.538; \( P = 0.018 \)) (Fig. 1).

The data on progression-free survival for these patients were censored at the time of the last CT evaluation at which they did not yet have evidence of disease progression. In total, there were 177 patients with exon 19 deletions, and 169 patients with exon 21 L858R mutations had disease progression. In total, 48.48% of patients (176 patients) had disease progression within 12 months after surgery. Specifically, 96 (26.45%) patients exhibited 13 to 24 months of PFS, whereas 49 (13.50%) patients experienced 25 to 36 months of PFS. The median progression-free survival did not differ significantly between patients with

| Table 2 HRs for overall survival by subgroup |
|---------------------------------------------|
| Groups                                      |
| OS  | P  | chHR | 95% CI  | aHR  | 95% CI  |
|-----|----|------|---------|------|---------|
| Age | > 45 | 71   | 1.000   | 1.000 |         |
|     | ≤ 45 | –    | 0.022   | 0.349 | 0.142   | 0.859   | 0.246   | 0.098   | 0.621   |
| Gender | Male | 68   | 1.000   |       |         |
|     | Female | 92   | 0.400   | 1.087 | 0.895   | 1.320   |         |         |
| Smoking | No | 76   | 1.000   |       |         |
|     | Yes | 72   | 0.968   | 1.009 | 0.647   | 1.574   |         |         |
| Family history | No | 71   | 1.000   |       |         |
|     | Yes | 83   | 0.350   | 0.750 | 0.410   | 1.372   |         |         |
| Disease history | No | 72   | 1.000   |       |         |
|     | Yes | –    | 0.724   | 0.777 | 0.191   | 3.161   |         |         |
| Histopathologic type | AD | 76   | 1.000   |       |         |
|     | Non AD | 53   | 0.027   | 2.260 | 1.097   | 4.659   | 3.279   | 1.558   | 6.900   |
| Differentiation | High | 72   | 1.000   |       |         |
|     | Middle | 68   | 0.300   | 1.484 | 0.703   | 3.131   |         |         |
|     | Low | –    | 0.320   | 1.325 | 0.746   | 2.452   |         |         |
| Stage | I | 83   | 1.000   |       |         |
|     | II | 68   | 0.209   | 1.507 | 0.795   | 2.857   | 1.455   | 0.751   | 2.282   |
|     | III | –    | 0.037   | 1.706 | 1.032   | 2.821   | 1.621   | 0.968   | 2.715   |
|     | IV | 65   | 0.095   | 1.750 | 0.908   | 3.372   | 1.748   | 0.905   | 3.337   |
| Operation | Radical | 68   |        |       |         |
|     | Palliative | 72   | 0.762   | 1.086 | 0.637   | 1.852   |         |         |
| Adjuvant chemotherapy | No | 76   | 1.000   |       |         |
|     | Yes | 67   | 0.688   | 0.904 | 0.554   | 1.477   |         |         |
| Adjuvant radiation | No | 81   | 1.000   |       |         |
|     | Yes | 68   | 1.356   | 1.356 | 0.917   | 2.006   |         |         |
| TKI | Gefitinib | 72   | 1.000   |       |         |
|     | Erlotinib Hydrochloride | 68   | 0.889   | 1.038 | 0.613   | 1.759   | 0.956   | 0.562   | 1.627   |
|     | Icotinib | –    | 0.022   | 0.379 | 0.165   | 0.871   | 0.316   | 0.137   | 0.731   |
|     | Others | 45   | 0.183   | 1.761 | 0.765   | 4.054   | 1.433   | 0.618   | 3.327   |
| EGFR mutation | 19 del | 92   | 1.000   |       |         |
|     | 21 L858R | 65   | 0.018   | 1.265 | 1.041   | 1.538   | 1.275   | 1.040   | 1.563   |
the EGFR exon 19 deletion (12 months) and those with the L858R point mutation (14 months) (Table 3). Young patients were more likely to experience progression.

Comparison of response
Owing to a lack of progression information, 83 patients (57 patients with the exon 19 deletion and 26 patients with the exon 21 L858R mutation) were excluded from the analysis of responses. The objective response rate in the exon 19 deletion group was increased compared with exon 21 L858R mutation patients (28.35 vs. 22.87%). Patients with the EGFR 19 deletion benefitted more from treatment with EGFR tyrosine kinase inhibitor (TKI) therapy (DCR 93.70 vs. 84.31%, \( P = 0.014 \)). The differences identified were statistically significant (\( P < 0.05 \); Table 2). The objective response and disease control rate were similar in each TKI group in exon 21 L858R mutation patients (Table 4). In contrast, in the exon 19 deletion group, a high ORR and DCR were noted in patients treated with icotinib. In this patient group, 16 out of 18 achieved SD, and the DCR in this population was 100%.

Discussion
In this study, we retrospectively collected survival data of NSCLC cases to explore the impact on the postoperative survival of NSCLC patients with an EGFR mutation. The EGFR exon 19 deletion that eliminates a leucine–arginine–glutamate–alanine motif in the tyrosine kinase domain of EGFR and the thymine-to-guanine transversion that results in an arginine for leucine substitution at amino acid 858 (L858R) were the two most common EGFR mutations in NSCLC. These mutations represented 85 to 90% of EGFR mutations [12, 13]. In this population, EGFR mutations were identified in 50.33% (1054) of 2094 surgically resected non-small cell lung cancers, and 321 patients with an EGFR exon 19 deletion and 372 patients with exon 21 L858R were identified. These drug-sensitive mutations are noted in approximately 10% of Caucasian patients and up to 50% of Asian patients with NSCLC. In addition, the finding that 33.09% (95%CI, 31.09 to 35.16%) of patients harbored one of the two most common EGFR mutation genotypes was consistent with previous studies in Chinese [14] but was relatively high compared with other Asian populations (Korean population, 27.8%) [15]. In an unselected population-based cohort, 5.4% of the patients had EGFR mutation (4.3% men/6.7% women). Eighty-seven percent were activating mutations. Eight percent of adenocarcinomas and 1.9% of squamous cell carcinomas were mutated. [16] The frequency of EGFR mutations in black patients across all of these studies range from 2 to 19% [17].

Previous studies have suggested that EGFR tyrosine kinase inhibitors are highly effective against mutated-EGFR non-small cell lung cancer given that TKI may increase the binding affinities to these mutant EGFR proteins [18]. Patients with EGFR exon 19 deletions had significantly longer overall survival compared with patients with EGFR L858R after treatment with erlotinib or gefitinib [19]. Our findings confirm the benefit in OS attained with EGFR-targeted agents in Asian patients.
Why do people with exon 19 del have better survival than people with L858R? Firstly, one of the reasons was that EGFR subtype exon 19 del had higher affinities to TKIs than L858R. A study by Carey et al. [20] showed that relative binding affinity of TKI to the EGFR kinase domain was 23 times higher in the EGFR 19 deletion mutation subtype compared with EGFR L858R subtype. Another study of in vitro kinetic assay by Mulloy et al. [21] also indicated a higher affinity of TKI for exon 19 deletion than L858R mutation. Secondly, another reason of better survival with EGFR exon 19 than exon 21 L858R mutations is due to differential inhibition of downstream signals. In the study by Okabe et al. [22], TKI inhibited the phosphorylation of EGFR, Akt and Erk, to a greater degree in exon 19 deletion cells than in L858R cells. Zhu et al. [23] indicated that cell proliferation was inhibited more significantly in EGFR 19 del cells than in EGFR L858R cells in the presence of TKI. Lastly, EGFR-TKI resistant T790M mutation is more frequently encountered in pretreatment samples from patients with the L858R mutation than those with the exon 19 mutation [24]. This result suggests another possible mechanism to explain the better efficacy of EGFR-TKI in deletion 19 patients.

In this retrospective study, we also review the correlation between EGFR mutations and clinical factors that

| Groups               | PFS | P    | cHR | 95% CI       | aHR | 95% CI       |
|----------------------|-----|------|-----|--------------|-----|--------------|
| Age                  |     |      |     |              |     |              |
| > 45                 | 12  | 1.000| 1.000|              |     |              |
| ≤ 45                 | 16  | 0.006| 0.611| 0.429 0.870 | 0.569| 0.398 0.814 |
| Gender               |     |      |     |              |     |              |
| Male                 | 12  | 1.000|     |              |     |              |
| Female               | 14  | 0.577| 1.064| 0.855 1.324 |     |              |
| Smoking              |     |      |     |              |     |              |
| No                   | 13  | 1.000|     |              |     |              |
| Yes                  | 12  | 0.962| 1.006| 0.780 1.297 |     |              |
| Family history       |     |      |     |              |     |              |
| No                   | 12  | 1.000|     |              |     |              |
| Yes                  | 13  | 0.313| 0.864| 0.651 1.148 |     |              |
| Disease history      |     |      |     |              |     |              |
| No                   | 13  | 1.000|     |              |     |              |
| Yes                  | 10  | 0.158| 1.578| 0.838 2.972 |     |              |
| Histopathologic type |     |      |     |              |     |              |
| AD                   | 12  | 1.000|     |              |     |              |
| Non AD               | 11  | 0.988| 1.004| 0.583 1.730 |     |              |
| Differentiation      |     |      |     |              |     |              |
| High                 | 13  | 1.000|     |              |     |              |
| Middle               | 12  | 0.730| 0.948| 0.701 1.282 |     |              |
| Low                  | 12  | 0.470| 0.864| 0.582 1.283 |     |              |
| Stage                |     |      |     |              |     |              |
| I                    | 15  | 1.000|     |              |     |              |
| II                   | 12  | 0.209| 1.507| 0.795 2.857 | 1.039| 0.729 1.481 |
| III                  | 12  | 0.037| 1.706| 1.032 2.821 | 1.232| 0.943 1.610 |
| IV                   | 13  | 0.095| 1.750| 0.908 3.372 | 1.585| 0.975 2.579 |
| Operation            |     |      |     |              |     |              |
| Radical              | 18  | 1.000|     |              |     |              |
| Palliative           | 12  | 0.023| 1.369| 1.044 1.794 | 1.816| 1.217 2.711 |
| Adjuvant chemotherapy|     |      |     |              |     |              |
| No                   | 13  | 1.000|     |              |     |              |
| Yes                  | 12  | 0.624| 0.936| 0.720 1.218 |     |              |
| Adjuvant radiation   |     |      |     |              |     |              |
| No                   | 13  | 1.000|     |              |     |              |
| Yes                  | 12  | 0.723| 1.042| 0.830 1.309 |     |              |
| TKI                  |     |      |     |              |     |              |
| Gefitinib            | 13  | 1.000|     |              |     |              |
| Erlotinib Hydrochloride| 12  | 0.303| 1.171| 0.867 1.581 |     |              |
| Icotinib             | 13  | 0.177| 1.225| 0.912 1.646 |     |              |
| Others               | 11  | 0.200| 1.489| 0.810 2.735 |     |              |
| EGFR mutation        |     |      |     |              |     |              |
| 19 del               | 12  | 1.000|     |              |     |              |
| 21 L858R             | 14  | 0.302| 0.946| 0.851 1.052 |     |              |
are predictive of response to TKI treatment. Patients with EGFR exon 19 deletions had significant improvements in DCR compared with patients with EGFR L858R after TKI treatment (93.70 vs. 84.31%, \( P = 0.018 \)), but they had similar response rates (28.35 vs. 22.87%, \( P = 0.281 \)). DCR may more accurately reflect drug efficacy and be a good candidate for one of the surrogate markers for novel types of anticancer agents in first-line and second-line or later settings [25]. Our findings strengthen this rationale. Previous randomized trials reported that the response rates to EGFR-TKIs exceed 60 to 70% in US patients [26]. However, in postoperative patients in this study, we only observed an ORR of 25%.

Gefitinib and erlotinib are first-line EGFR-TKIs that are effective at treating NSCLC. In our study, the response rates to gefitinib were 27.91 and 23.47% in the EGFR exon 19 deletion group and EGFR L858R group, respectively. The response rates to erlotinib were 47.62 and 18.18%, respectively. Significant differences in response rates determined by different mutations were observed with erlotinib. Icotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, is a new treatment option for pretreated patients with advanced non-small cell lung cancer [26, 27]. A randomized, double-blind, phase 3 non-inferiority trial with 400 patients demonstrated that icotinib was non-inferior to gefitinib in terms of PFS but had less drug-related adverse events compared with gefitinib [27]. Our result was consistent with this study, which showed that no prolonged PFS in patients treated with icotinib were found. It showed a higher DCR and a longer OS after EGFR-TKI treatment than gefitinib and erlotinib in both exon 19 deletion and EGFR L858R group. In most studies [27, 28], icotinib have less adverse effect than other TKIs. Maybe this could improve the integrated state of patients and has better results. Moreover, the higher dose of icotinib was also well tolerated [28].

Several limitations should be taken into account when considering the results of this study. First, it was a retrospective study, not a randomized trial, and lacked a placebo control. Furthermore, all patients were postoperative patients with lung cancer who received an EGFR mutation test, and our study population may not represent the general population. Additionally, a sample size of 363 patients was sufficient to provide representative and reliable results, but it may not be sufficient for subgroup analysis. These observations warrant further confirmation in prospective studies. Further investigation is also needed to clarify the molecular mechanisms behind the varying efficacies of EGFR-TKI treatment in patients with these mutations. The efficacy of a new generation of EGFR-TKIs targeting these mutations also should be elucidated.

**Conclusions**

EGFR mutations in exons 19 or 21 are correlated with clinical factors that are predictive of the response to TKI and postoperative survival in NSCLC. Patients with EGFR exon 19 deletion mutations had a longer median overall survival time compared with patients with exon 21 L858R point mutations, but the median progression-free survival time did not differ significantly. Significant variability in the DCR was noted for the different EGFR tyrosine kinase inhibitors (TKI) in patients with EGFR exon 19 deletion mutations, but not in patients with L858R point mutations. Icotinib is a new treatment option for NSCLC, which may offer survival benefits.

**Acknowledgements**

We are grateful to Tian Qiu and Jianming Ying, Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, for their support to this study.

**Funding**

There is no funding support in this study.
Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors’ contributions
JH, WY, YG, ZC, and YW have made substantial contributions to the design of this study. WY, XL, and YG have been involved in drafting the manuscript and revising it critically for important intellectual content. HP and XY analyzed and interpreted the patient data. WY, JZ, and TL have made contributions to acquiring the data of 2094 NSCLC patients; SX, XF (Xiaoshuang Feng), and ZL have analyzed and interpreted these data. XF (Xiaoli Feng) performed the histological examination of the lung. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All participants who attended the study provided written informed consent. The study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
1Department of Thoracic Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. 2Department of Epidemiology, School of Public Health, China Medical University, Shenyang, Liaoning Province, China. 3Department of Pathology, National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China. 4Program Office for Cancer Screening in Urban China, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.

Received: 31 December 2016 Accepted: 26 September 2017
Published online: 06 November 2017

References
1. Ambra J, Baselga J. Who will benefit from treatment against EGFR? Lancet Oncol. 2005;6(5):257–8.
2. Heinrich MC, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21(23):4342–9.
3. Tamura K, et al. Multicentre prospective phase II trial of gefitinib for advanced non-small cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). Br J Cancer. 2008;98(S):907–14.
4. Rosell R, et al. Screening for epidermal growth factor receptor mutations: the other side of the coin. J Clin Oncol. 2011;29(28):3835–7. author reply 3837–9.
5. Yang SH, et al. Mutations in the tyrosine kinase domain of the epidermal growth factor receptor in non-small cell lung cancer. Clin Cancer Res. 2005; 11(6):2106–10.
6. da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. Ann Rev Pathol. 2013;8:49–69.
7. Lee VHF, et al. Association of exon 19 and 21 EGFR mutation patterns with treatment outcome after first-line tyrosine kinase inhibitor in metastatic non-small-cell lung cancer. J Thorac Oncol. 2013;8(9):1148–55.
8. Baek JH, et al. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small cell lung cancer except both exon 19 deletion and exon 21 L858R: a retrospective analysis in Korea. Lung Cancer. 2015;87(2):148–54.
9. Skov BG, et al. The prevalence of EGFR mutations in non-small cell lung cancer in an unselected Caucasian population. APMS. 2015;123(2):108–15.
10. Araujo LH, Lammers PE, Matthews-Smith V, et al. Somatic mutation spectrum of non-small-cell lung cancer in African Americans: a pooled analysis. J Thorac Oncol. 2015;10(10):1430–6.
11. Maemondo M, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380–8.
12. Riely GJ, et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. Clin Cancer Res. 2006;12(3 Pt 1):839–44.
13. Carey KD, Garton AJ, Romero MS, et al. Kinetic analysis of epidermal growth factor receptor somatic mutant proteins shows increased sensitivity to the epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib. Cancer Res. 2006;66(136):1–71.
14. Mulloy R, Ferrand A, Kim Y, et al. Epidermal growth factor receptor mutations from human lung cancers exhibit enhanced catalytic activity and increased sensitivity to gefitinib. Cancer Res. 2007;67:2325–30.
15. Okabe T, Okamoto I, Tamura K, et al. Differential constitutive activation of the epidermal growth factor receptor in non-small cell lung cancer cells bearing EGFR gene mutation and amplification. Cancer Res. 2007;67:2046–53.
16. Zhu JQ, Zhong WZ, Zhang GC, et al. Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals. Cancer Lett. 2008;265:307–17.
17. Chen YF, Molina-Wa MA, Ruan SY, et al. Coexistence of EGFR T790M mutation and common activating mutations in pretreatment non-small cell lung cancer: a systematic review and meta-analysis. Lung Cancer. 2016;94:46–53.
18. Hotta K, et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials. J Thorac Oncol. 2007;2(5):402–7.
19. Gaughan EM, Costa DB. Genotype-driven therapies for non-small cell lung cancer: focus on EGFR, KRAS and ALK gene abnormalities. Ther Adv Med Oncol. 2011;3(3):113–25.
20. Shi Y, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol. 2013;14(10):953–61.
21. Xingsheng H, et al. A single-arm, multicentre, safety-monitoring, phase IV study of icotinib in treating advanced non-small cell lung cancer (NSCLC). Lung Cancer. 2014;86(2):207–12.