Mutation Analysis of EGFR Gene in Patients with Non-Small Cell Lung Cancer in Xinjiang

Yi Shi*, Xuelian Pang, Zhiping Ma, Wenli Cui, Yuqing Ma, Wei Zhang

Pathology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China
Email: *sy_0201@163.com

Abstract
The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (RTK) that links extracellular signals to the control of cell survival, growth, proliferation and differentiation. EGFR has been a therapeutic target for human malignancies, due to its frequent hyperactivation, therefore, it is necessary to investigate the characteristics of EGFR mutation, and identify patients who are likely to benefit from EGFR mutation. In this study, we examined 766 non-small cell lung cancer (NSCLC) patients (675 tissue, 83 thoracic water precipitation and 8 plasma samples) tested in pathology department of First Affiliated Hospital of Xinjiang Medical University from 2013 to 2017 by using ARMS-PCR method. The correlation between EGFR mutations and clinical pathological features was further explored. Subgroup analyses according to ethnicity, histological type, sample type, and tumour grade were done. Subgroup analyses showed the mutation rate of tumor tissue, thoracic water precipitation and plasm was 30.5%, 37.3%, 50.0% respectively. We found female (p < 0.0001), no smoking (p < 0.001), adenocarcinoma (p < 0.0001), and tissue specimens (Tobacco use) were associated with higher EGFR mutation rate. The most common mutations were exon 19 deletions (47.30%) and L858R point (42.32%) mutation. We have not found any differences between EGFR mutations and ethnic groups especially. In addition, we did not find differences in common mutations and rare sensitive mutations in the survival of targeted therapies.

Keywords
Non-Small, Cell, Lung, Cancer, EGFR, Mutations, Survival

1. Introduction
Lung cancer is the leading cause of cancer-related death in the world [1]. Plati-
num-based chemotherapy remains the main treatment choice for advanced non-small-cell lung cancer (NSCLC) [2]. However, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) therapy recently achieved promising successes in NSCLC patients harboring EGFR active mutations [3] [4] [5] significantly prolonging patients’ survival. Therefore, it is of great importance to determine the prevalence of EGFR mutations frequency.

EGFR as a driving gene, plays an important role in the treatment of advanced lung cancer, and EGFR-TKIs significantly prolongs the progression-free survival (PFS) of patients with advanced NSCLC who are positive for EGFR mutations [6], and it has become a first-line standard treatment for patients with advanced EGFR mutant positive NSCLC. For early NSCLC patients, there is still a high risk of disease recurrence after radical resection [7] [8] [9]. A large proportion of patients die from the recurrence of lung cancer [10] [11]. With the rapid development of targeted therapy, more and more studies have begun to explore the application of EGFR-TKIs in the adjuvant therapy of early NSCLC after operation [12] [13] [14]. Research proved that EGFR patients with mutations who received EGFR-TKIs targeted therapy after radical surgery for lung cancer and after completing adjuvant chemotherapy were less able to reduce the risk of post-operative recurrence than those who were not accepted EGFR-TKIs; there is also a trend to extend the overall survival (OS) (41.6 months vs 32.6 months, P = 0.76) [15] [16].

Research also reported that EGFR has a mutation rate of about 30% in late-Asian NSCLC patients, but the mutation rate can be as high as 60% in patients who do not smoke, women, and pathological types of adenocarcinoma [17] [18] [19]. Based on this background, investigating the difference of EGFR mutation rate and mutation spectrum in patients with NSCLS is necessary [20] [21].

2. Materials and Methods

2.1. Data Collection

We collected 766 non-small cell lung cancer (NSCLC) specimens from the system of pathology department of First Affiliated Hospital of Xinjiang Medical University from 2013 to 2017, including 675 tissue samples, 83 thoracic water precipitation samples and 8 plasma samples. All patients’ information were collected, including gender, age, and smoking status. Disease data included date of first NSCLC diagnosis, histological type, AJCC stage, nodal status, and distant metastases. Standardized case report forms were used to record the data in accordance with the protocol’s instructions. Smoking was assessed using two ways. First, patients were classified according to their actual smoking status (never-smoked means that the subject smoked no cigarettes during his entire lifetime; ex-smoker means that the subject no longer smokes; occasional smoker means that the subject smokes, but not every day; and regular smoker means that the subject smokes every day). Second, smoking patients were classified ac-
2.2. EGFR Mutation Analysis

Tumor samples were obtained from primary or metastatic lesions, and were handled and stored following laboratories’ quality control requirements. Biopsy site and technique were recorded. Cytological samples were accepted only when histological material was unavailable.

After tumor DNA extraction, EGFR mutation was analyzed at Laboratory of First Affiliated Hospital, Xinjiang Medical University, tested by an amplification refractory mutation system (ARMS)-based EGFR mutation detection kit (EGFR 18 - 21 exon PCR kit, Yakangbo, Beijing, China). This kit allows the detection of 32 mutations in the EGFR gene.

2.3. Statistical Analyses

Statistical analysis was performed by the IBM SPSS Statistics. The per protocol analysis (PPS) set was used for all statistical analyses. Mutations prevalence and corresponding 95% confidence intervals (95% CI) were calculated using the Wilson score method. Associations between mutations and demographic and clinical characteristics were analyzed by χ² tests or Fisher’s exact tests, as appropriate. Characteristics associated with mutations with a P-value < 0.05 were included in a multivariate logistic model. All analyses were two-sided and a P-value < 0.05 was considered significant. In the multivariate analysis, a P-value < 0.01 was considered significant.

3. Results

3.1. Baseline Characteristics of the Study Population

The clinical baseline characteristics of 766 patients in this study are shown in Table 1. Seven clinical characteristics of patients are analyzed in this study, including age, sex, smoking, ethnicity, histological type, sample type and tumor grade. In the age statistics, according to the median, the patients are divided into three groups: <65 years, 65 - 74.9 and >75 years old. In ethnic statistics, because of the diversity of ethnic minorities in Xinjiang, and the study covered 10 ethnic groups of patients, therefore, the results of the study have a strong individualized guiding role in the treatment of lung cancer among ethnic minorities in Xinjiang.

3.2. Correlation between EGFR Mutation and Clinicopathological Features

A total of 766 patients were enrolled in the study group, and the correlation between EGFR mutation and clinicopathological features were shown in Table 2. Of the 766 cases, 241 (31.5%, 241/766) were EGFR mutation-positive. Among them, 129 (46.2%, 129/279) were female, 112 (23.0%, 112/487) were male, 130 (45.6%, 130/285) were non-smoking, 111 (23.1%, 111/481) were smoking, 5
Table 1. Baseline characteristics of the study population.

| Baseline Characteristic | EGFR gene mutation Positive | EGFR gene mutation Negative |
|-------------------------|-----------------------------|-----------------------------|
|                         | Total | Number | %   | Number | %   |
| Age group               |       |        |     |        |     |
| <65                     | 766   | 241    | 31.5% | 525   | 68.5% |
| 65 - 74.9               | 238   | 68     | 28.6% | 170   | 71.4% |
| >75                     | 102   | 29     | 28.4% | 73    | 71.6% |
| Gender                  |       |        |     |        |     |
| Men                     | 487   | 112    | 23.0% | 375   | 77.0% |
| Women                   | 279   | 129    | 46.2% | 150   | 53.8% |
| Smoking                 |       |        |     |        |     |
| Yes                     | 481   | 111    | 23.1% | 370   | 76.9% |
| No                      | 285   | 130    | 45.6% | 155   | 54.4% |
| Ethnic                  |       |        |     |        |     |
| Han                     | 647   | 203    | 31.4% | 444   | 68.6% |
| Uygur                   | 61    | 20     | 32.8% | 41    | 67.2% |
| Kazak                   | 19    | 5      | 26.3% | 14    | 73.7% |
| Hui                     | 23    | 10     | 43.5% | 13    | 56.5% |
| Ethnic                  | 8     | 1      | 12.5% | 7     | 87.5% |
| Mongolian               | 2     | 0      | 0.0%  | 2     | 100.0% |
| Kirgiz                  | 2     | 0      | 0.0%  | 2     | 100.0% |
| Manchu                  | 2     | 0      | 0.0%  | 2     | 100.0% |
| Tujia                   | 2     | 0      | 0.0%  | 2     | 100.0% |
| Tatar                   | 1     | 1      | 100.0% | 0  | 0.0% |
| Xibe                    | 1     | 1      | 100.0% | 0  | 0.0% |
| AD                      | 511   | 214    | 41.9% | 297   | 58.1% |
| SCC                     | 227   | 18     | 7.9%  | 209   | 92.1% |
| ADSC                    | 10    | 5      | 50.0% | 5     | 50.0% |
| SCLC                    | 18    | 4      | 22.2% | 14    | 77.8% |
| Tissue                  | 675   | 206    | 30.5% | 469   | 69.5% |
| Sample type             |       |        |     |        |     |
| Thoracic water Precipitation | 83     | 31     | 37.3% | 52    | 62.7% |
| Blood                   | 8     | 4      | 50.0% | 4     | 50.0% |
| I                       | 108   | 29     | 26.9% | 79    | 73.1% |
| II                      | 136   | 33     | 24.3% | 103   | 75.7% |
| III                     | 223   | 73     | 32.7% | 150   | 67.3% |
| IV                      | 285   | 92     | 32.3% | 193   | 67.7% |

(50%, 5/10) were Adenosquamous cell carcinoma (ADSC), 214 (41.9%, 214/511) were adenocarcinoma (AD), 18 (7.9%, 18/227) were squamous cell carcinoma (SCC), and 4 (22.2%, 4/18) were small cell lung cancer (SCLC). Statistical analysis showed that the distribution of EGFR gene mutation positive cases in patients with gender, smoking status and histological type were statistically significant (p < 0.01), while the distribution of age, ethnicity, sample type and tumor grade were not statistically significant (p > 0.05).
Table 2. Correlation between EGFR mutation and clinicopathological features.

| Characteristic | Total | Total Positive | Total Negative | 95% CI     | p-value |
|----------------|-------|----------------|----------------|------------|---------|
|                | Number | %              | Number         |            |         |
| Number %       | Total  | Positive %     | Negative %     |            |         |
| Gender         | 766    | 241 (31.5%)    | 525 (68.5%)    |            |         |
| Men            | 487    | 112 (23.0%)    | 375 (77.0%)    | -1.902     | 0.0001**|
| Women          | 279    | 129 (46.2%)    | 150 (53.8%)    | 0.143      |         |
| Smoking        | 481    | 111 (23.1%)    | 370 (76.9%)    | -0.625     | 0.001** |
| Yes            | 285    | 130 (45.6%)    | 155 (54.4%)    | 1.439      |         |
| No             | 214    | 79 (37.3%)     | 135 (62.7%)    |            |         |
| Histology      | 511    | 214 (41.9%)    | 297 (58.1%)    |            |         |
| AD             | 227    | 18 (7.9%)      | 209 (92.1%)    | -1.029     | 0.0001**|
| SCC            | 500    | 18 (3.6%)      | 482 (96.4%)    | -0.159     |         |
| ADSC           | 10     | 5 (50.0%)      | 5 (50.0%)      |            |         |
| SCLC           | 18     | 4 (22.2%)      | 14 (77.8%)     |            |         |
| Sample type    | 675    | 206 (30.5%)    | 469 (69.5%)    |            |         |
| Tissue         | 83     | 31 (37.3%)     | 52 (62.7%)     | -0.500     | 0.236   |
| Blood          | 8      | 4 (50.0%)      | 4 (50.0%)      |            |         |
| I              | 10     | 29 (26.9%)     | 79 (73.1%)     |            |         |
| II             | 136    | 33 (24.3%)     | 103 (75.7%)    |            |         |
| III            | 223    | 73 (32.7%)     | 150 (67.3%)    | -0.360     | 0.228   |
| IV             | 285    | 92 (32.3%)     | 193 (67.7%)    | -0.003     |         |

*p < 0.05, **p < 0.01.

3.3. Differences in Survival between Different Mutation Types

There were 241 EGFR mutation positive cases in 766 patients in this study. The mutation types were classified into 8 types, L858R, 19 DEL, L861Q, G719X, S768I, 20INS, T790M and Combined mutations, respectively, in which L858R (42.32%, 102/241) at exon 21 and 19DEL (47.30%, 114/241) at exon 19 were significantly more than other types of mutations in the cases. We assessed the association between different EGFR mutation types and patients’ survival. The results showed that different types of EGFR mutations had no significant effect on the survival of patients (p > 0.05) (Table 3). In comparison, patients with combined mutations (median survival, 158) and G719X (median survival, 155) mutations had a longer survival, while patients with 20 INS (median survival, 90) had a shorter survival (Figure 1), but the difference was not significant.

The relationship between mutation types of EGFR gene and patients’ mortality also studied, the results showed that 96 patients died and 81 patients were still alive, regardless of the number of lost patients. Chi-square test showed that different mutation types of EGFR gene had no significant effect on patients’ mortality (p > 0.05) (Table 4).

Cox proportional hazard model (Figure 2) showed that different types of EGFR did not affect the survival of patients in our study: the regression coefficient was 0.106 (p > 0.05).
Table 3. Correlation analysis between EGFR gene mutation type and patient survival.

| EGFR mutation type | Number | %     | Survival median/weeks | z-value | p-value |
|--------------------|--------|-------|------------------------|---------|---------|
| L858R              | 102    | 42.32%| 125                    |         |         |
| 19 DEL             | 114    | 47.30%| 149                    |         |         |
| L861Q              | 3      | 1.24% | 146                    |         |         |
| G719X              | 8      | 3.32% | 155                    |         |         |
| S768I              | 3      | 1.24% | Lost contact           | −0.042  | 0.966   |
| 20 INS             | 5      | 2.07% | 90                     |         |         |
| T790M              | 1      | 0.41% | 129                    |         |         |
| Combined mutations | 5      | 2.07% | 158                    |         |         |
| None               | 525    |       | 96                     |         |         |
| Total              | 766    |       |                        |         |         |

*p < 0.05, **p < 0.01.

Table 4. The chi-square test of EGFR mutation type and mortality.

| Item            | Mark | Molecular diagnosis | 19 DEL | 20 INS | Combined mutations | G719X | L858R | L861Q | T790M | Total | Chi-squared statistic | p    |
|-----------------|------|---------------------|--------|--------|--------------------|-------|-------|-------|-------|-------|-----------------------|------|
| Death or not    | 0    | 41 (51.90%)         | 2 (66.67%) | 1 (33.33%) | 2 (28.57%) | 48 (59.26%) | 1 (33.33%) | 1 (100.00%) | 96 (54.24%) | 4.942 | 0.551               |      |
|                 | 1    | 38 (48.10%)         | 1 (33.33%) | 2 (66.67%) | 5 (71.43%) | 33 (40.74%) | 2 (66.67%) | 0 (0.00%) | 81 (45.76%) | 4.942 | 0.551               |      |
| Total           | 79   | 3                   | 3       | 7       | 81                 | 3     | 1     | 177   | **p < 0.01.** **p < 0.01.**

Figure 1. Survival function curve.

Figure 2. Survival function curve.
4. Discussion

Xinjiang Uighur Autonomous Region is a provincial-level autonomous region of China. It is the largest Chinese administrative division and it is home to a number of ethnic groups. Whether the difference of life reflects the difference of mechanism or genetic background has to be studied in depth and detail, especially in Xinjiang where a few ethnic minorities are numerous. It is necessary to study EGFR fusion according to local characteristics. Gene incidence for future selection of inhibitors of EGFR genes to provide clinical Basis. And China’s domestic study of EGFR mutations to guide individualized treatment, the study of most of the subjects are Han, Xinjiang Uygur Research is less. So study EGFR mutations are more individual in guiding the treatment of NSCLC in Xinjiang.

In this paper, a total of 766 initially diagnosed NSCLC patients (675 tissue, 83 thoracic water precipitation and 8 plasm samples) of NSCLC specimens were selected, in which Han were 647 cases, Uygur were 61 cases, basic information of patients such as sex, pathology, age and smoking or not, the baseline level was consistent. All the 766 samples were detected by arms PCR method, the results showed that 241 cases with EGFR mutation, the mutation rate was 31.5%, in which 203 cases were Han, the mutation rate in Han was 31.4%, and 20 cases were Uygur, the mutation rate in Uygur was 32.8%, but there were no statistical differences.

EGFR mutation hotspots are mainly concentrated on exon 19th and 21st [22]. The EGFR mutations detected in this paper are mainly 19 DEL mutation and 21 exon L858R mutation. There are reports showing that the EGFR mutation rate of lung cancer has ethnic differences, in Japanese the EGFR mutations in 94 patients with NSCLC were studied and analyzed [23], the total mutation rate was found to be 33%, and the mutations detected were 19 exon missing mutation and 21 exon L858R mutation. Another study in Europe about the EGFR mutations in 162 patients with NSCLC were analyzed, and the results showed that the mutation rate of EGFR is 24.7%. By comparing similar studies at home and abroad, it was found that the mutation rate in Chinese patients with NSCLC was higher than that in Europe and the United States [24], but the mutation rate in patients with NSCLC is similar with Asia and Japan.

The lung cancer of Uygur population in Xinjiang has its own pathogenic characteristics, ShenHongli and others in 2013 detected the dimension In the case of man and Han EGFR mutations [25], Uygur mutation rate was 10.8%, With the Han mutation rate of 44%. Guo and others [26] detected 76 cases of Uygur NSCLC in Xinjiang in 2014, from their research, the mutation rate of EGFR were 15.79%. In our study, the mutation rate of EGFR in Uygur was much higher compared with the previous researches, but the mutation rate was still low compared with Han. Uygur belongs to the Caucasian race, but Han belongs to the Mongolian race, the race difference may lead to this difference. In addition, two ethnic groups in the social culture, living areas, lifestyle also exist different, the reasons may lead to different genetic status. However, molecular genetics and
epidemiological investigations are still needed for further verification.

All in all, this paper compares Han and Uygur NSCLC in the case of EGFR mutations, it is concluded that the mutation rate of EGFR in Han was a little lower than that of Uygur, but there was no statistical difference, the distribution of age, ethnicity, sample type and tumor grade were not statistically significant also (p > 0.05), while the distribution of EGFR gene mutation positive cases in patients with gender, smoking status and histological type were statistically significant (p < 0.05).

In this study, the specimens of EGFR mutations in NSCLC were collected from the system of pathology department of First Affiliated Hospital of Xinjiang Medical University from 2013 to 2017, there was no criterion for the selection of samples, and there were only 61 Uygur cases in the total specimens, so there may be some limits of the study that may affect the outcome of the study, We need more detailed researches to reveal the differences of races in Xinjiang, identifying which patients may benefit from the research of EGFR mutations is our final goal.

5. Conclusion

In conclusion, our study characterized the distributions of EGFR mutations in NSCLC patients in Xinjiang and investigated the relevance of gender, smoking status, histology type, sample type, tumor grade, race, and mutation type. Statistical analysis showed that the distribution of EGFR gene mutation positive cases in patients with gender, smoking status and histological type was statistically significant (p < 0.01). Although these outcomes have some statistical significance, they cannot perfectly elucidate the EGFR-mediated molecular basis of tumorigenesis, development and therapeutic resistance and identify potential therapeutic targets. More extensive studies are therefore needed.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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