Retraction Notice

Title of retracted article:	**Mutation Analysis of EGFR Gene in Patients with Non-Small Cell Lung Cancer in Xinjiang**
Author(s):	Yi Shi*, Xuelian Pang, Zhiping Ma, Wenli Cui, Yuqing Ma, Wei Zhang
* Corresponding author.	Email: sy_0201@163com
Journal:	International Journal of Clinical Medicine
Year:	2020
Volume:	11
Number:	4
Pages (from - to):	144-153
DOI (to PDF):	https://doi.org/10.4236/ijcm.2020.114015
Paper ID at SCIRP:	2101974
Article page:	https://www.scirp.org/journal/paperinformation.aspx?paperid=99226
Retraction date:	2020-06-05

Retraction initiative (multiple responses allowed; mark with **X**):

✘ All authors
☐ Some of the authors:
☐ Editor with hints from
- ○ Journal owner (publisher)
- ○ Institution:
- ○ Reader:
- ○ Other:

Date initiative is launched: 2020-06-03

Retraction type (multiple responses allowed):

☐ Unreliable findings
- ○ Lab error
- ○ Inconsistent data
- ○ Analytical error
- ○ Biased interpretation
- ○ Other:

☐ Irreproducible results
☐ Failure to disclose a major competing interest likely to influence interpretations or recommendations
☐ Unethical research

☐ Fraud
- ○ Data fabrication
- ○ Fake publication
- ○ Other:

☐ Plagiarism
☐ Self plagiarism
☐ Overlap
☐ Redundant publication *
☐ Copyright infringement
☐ Other legal concern:

☐ Editorial reasons
- ○ Handling error
- ○ Unreliable review(s)
- ○ Decision error
- ○ Other:

✘ Other:

Results of publication (only one response allowed):

✘ are still valid.
☐ were found to be overall invalid.

Author's conduct (only one response allowed):

☐ honest error
☐ academic misconduct
✘ none (not applicable in this case – e.g. in case of editorial reasons)

* Also called duplicate or repetitive publication. Definition: "Publishing or attempting to publish substantially the same work more than once."

History
Expression of Concern:
☐ yes, date: yyyy-mm-dd
✘ no

Correction:
☐ yes, date: yyyy-mm-dd
✘ no

Comment:

The authors have more requirements on indexing.

This article has been retracted to straighten the academic record. In making this decision the Editorial Board follows COPE's Retraction Guidelines. Aim is to promote the circulation of scientific research by offering an ideal research publication platform with due consideration of internationally accepted standards on publication ethics. The Editorial Board would like to extend its sincere apologies for any inconvenience this retraction may have caused.

Editor guiding this retraction: The IJCM Editorial Board

Scientific Research Publishing

International Journal of Clinical Medicine, 2020, 11, 144-153
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

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

How to cite this paper: Shi, Y., Pang, X.L., Ma, Z.P., Cui, W.L., Ma, Y.Q. and Zhang, W. (2020) Mutation Analysis of EGFR Gene in Patients with Non-Small Cell Lung Cancer in Xinjiang. *International Journal of Clinical Medicine*, **11**, 144-153.
https://doi.org/10.4236/ijcm.2020.114015

Received: February 11, 2020
Accepted: March 28, 2020
Published: March 31, 2020

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 postoperative 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 lis 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-

cording to their tobacco consumption, in pack-year.

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 χ^2 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	%
		766	241	31.5%	525	68.5%
Age group	<65	426	144	33.8%	282	66.2%
	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%
	Mongolian	8	1	12.5%	7	87.5%
	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%
Histology	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%
Sample type	Tissue	675	206	30.5%	469	69.5%
	Thoracic water Precipitation	83	31	37.3%	52	62.7%
	Blood	8	4	50.0%	4	50.0%
Tumour grade	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%

Adenosquamous Cell Carcinoma (ADSC), Adenocarcinoma (AD), Squamous Cell Carcinoma (SCC), Small Cell Lung Cancer (SCLC).

(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		Negative		95% CI	p-value
			Number	%	Number	%		
		766	241	31.5%	525	68.5%		
Gender	Men	487	112	23.0%	375	77.0%	−1.902 - 0.143	0.0001**
	Women	279	129	46.2%	150	53.8%		
Smoking	Yes	481	111	23.1%	370	76.9%	−0.625 - 1.439	0.001**
	No	285	130	45.6%	155	54.4%		
Histology	AD	511	214	41.9%	297	58.1%	−1.029 - −0.159	0.0001**
	SCC	227	18	7.9%	209	92.1%		
	ADSC	10	5	50.0%	5	50.0%		
	SCLC	18	4	22.2%	14	77.8%		
Sample type	Tissue	675	206	30.5%	469	69.5%	−0.500 - 0.706	0.236
	Thoracic water Precipitation	83	31	37.3%	52	62.7%		
	Blood	8	4	50.0%	4	50.0%		
Tumor grade	I	108	29	26.9%	79	73.1%	−0.360 - −0.003	0.228
	II	136	33	24.3%	103	75.7%		
	III	223	73	32.7%	150	67.3%		
	IV	285	92	32.3%	193	67.7%		

*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							Total	Chi-squared statistic	p
		19 DEL	20 INS	Combined mutations	G719X	L858R	L861Q	T790M			
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%)		
	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 < 0.05, **p < 0.01.

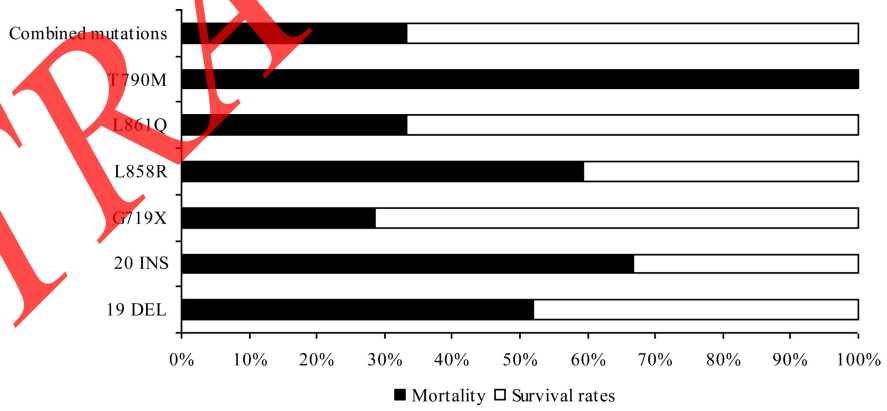

Figure 1. Survival function curve.

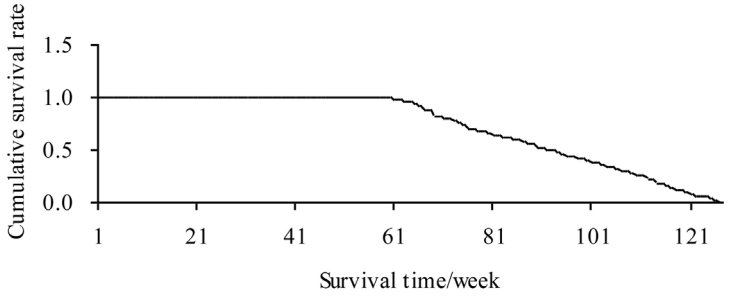

Figure 2. Survival function curve.

4. Discussion

Xinjiang Uyghur 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 lis 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.

Funding

This research is supported by Xinjiang Uygur Autonomous Region Natural Science Foundation (No. 2019D01C306).

Conflicts of Interest

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

References

[1] Seow, W.J., Matsuo, K., Hsiung, C.A., *et al.* (2017) Association between GWAS-Identified Lung Adenocarcinoma Susceptibility Loci and EGFR Mutations in Never-Smoking Asian Women, and Comparison with Findings from Western Populations. *Human Molecular Genetics*, **26**, 454-465.

[2] Da Cunha Santos, G., Shepherd, F.A. and Tsao, M.S. (2011) EGFR Mutations and Lung Cancer. *Annual Review of Pathology*, **6**, 49-69. https://doi.org/10.1146/annurev-pathol-011110-130206

[3] Bao, M.X., Jing, C. and Duan, D. (2005) Identification of EGFR Kinase Domain Mutations among Lung Cancer Patients in China: Implication for Targeted Cancer Therapy. *Cell Research*, **15**, 212. https://doi.org/10.1038/sj.cr.7290289

[4] Yuh, M. (2013) Usage of EGFR-TKI and WBRT in NSCLC Patients with Brain Metastases. *Annals of Palliative Medicine*, **2**, 108-110.

[5] Fan, Y., Xu, X. and Xie, C. (2014) EGFR-TKI Therapy for Patients with Brain Metastases from Non-Small-Cell Lung Cancer: A Pooled Analysis of Published Data. *OncoTargets and Therapy*, **7**, 2075-2084. https://doi.org/10.2147/OTT.S67586

[6] Roskoski, R. (2019) Small Molecule Inhibitors Targeting the EGFR/ErbB Family of Protein-Tyrosine Kinases in Human Cancers. *Pharmacological Research*, **139**, 395-411. https://doi.org/10.1016/j.phrs.2018.11.014

[7] Li, Y., Appius, A., Pattipaka, T., *et al*. (2019) Real-World Management of Patients with Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Non-Small-Cell Lung Cancer in the USA. *PLoS ONE*, **14**, e0209709. https://doi.org/10.1371/journal.pone.0209709

[8] Ahn, M.J., Kim, S.W., Cho, B.C., *et al*. (2014) Phase II Study of Afatinib as Third-Line Treatment for Patients in Korea with Stage IIIB/IV Non-Small Cell Lung Cancer Harboring Wild-Type EGFR. *Oncologist*, **19**, 702-703. https://doi.org/10.1634/theoncologist.2013-0419

[9] Schuette, W., Schirmacher, P., Eberhardt, W.E., *et al*. (2015) EGFR Mutation Status and First-Line Treatment in Patients with Stage III/IV Non-Small Cell Lung Cancer in Germany: An Observational Study. *Cancer Epidemiology, Biomarkers & Prevention*, **24**, 1254-1261. https://doi.org/10.1158/1055-9965.EPI-14-1149

[10] Chen, W., Zheng, R., Zeng, H., *et al*. (2015) Epidemiology of Lung Cancer in China. *Thoracic Cancer*, **6**, 209-215. https://doi.org/10.1111/1759-7714.12169

[11] Agustoni, F., Suda, K., Yu, H., *et al*. (2019) EGFR-Directed Monoclonal Antibodies in Combination with Chemotherapy for Treatment of Non-Small-Cell Lung Cancer: An Updated Review of Clinical Trials and New Perspectives in Biomarkers Analysis. *Cancer Treatment Reviews*, **72**, 15-27. https://doi.org/10.1016/j.ctrv.2018.08.002

[12] Takanashi, Y., Tajima, S., Hayakawa, T., *et al*. (2016) Pulmonary Micropapillary-Type Adenosquamous Carcinoma Sharing Epidermal Growth Factor Receptor Mutation in Adenocarcinoma and Squamous Cell Carcinoma. *Respirology Case Reports*, **4**, e00179. https://doi.org/10.1002/rcr2.179

[13] Wang, Z., Li, Z., Ding, X., *et al*. (2015) ERbeta Localization Influenced Outcomes of EGFR-TKI Treatment in NSCLC Patients with EGFR Mutations. *Scientific Reports*, **5**, 11392. https://doi.org/10.1038/srep11392

[14] Sasaki, H., Endo, K., Mizuno, K., *et al*. (2006) EGFR Mutation Status and Prognosis for Gefitinib Treatment in Japanese Lung Cancer. *Lung Cancer*, **51**, 135-136. https://doi.org/10.1016/j.lungcan.2005.09.004

[15] Zhong, W.-Z., Wang, Q., Mao, W.-M., *et al*. (2018) Gefitinib versus Vinorelbine plus Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFR-Mutant NSCLC (ADJUVANT/CTONG1104): A Randomised, Open-Label, Phase 3 Study. *The Lancet Oncology*, **19**, 139-148. https://doi.org/10.1016/S1470-2045(17)30729-5

[16] Kuiper, J.L., Hashemi, S.M., Thunnissen, E., *et al*. (2016) Non-Classic EGFR Mutations in a Cohort of Dutch EGFR-Mutated NSCLC Patients and Outcomes Following EGFR-TKI Treatment. *British Journal of Cancer*, **115**, 1504-1512. https://doi.org/10.1038/bjc.2016.372

[17] Soo, R.A., Kubo, A., Ando, M., *et al*. (2017) Association between Environmental Tobacco Smoke Exposure and the Occurrence of EGFR Mutations and ALK Rearrangements in Never-Smokers with Non-Small-Cell Lung Cancer: Analyses from a Prospective Multinational ETS Registry. *Clinical Lung Cancer*, **18**, 535-542. https://doi.org/10.1016/j.cllc.2017.01.005

[18] Kawaguchi, T., Ando, M., Kubo, A., *et al*. (2011) Long Exposure of Environmental Tobacco Smoke Associated with Activating EGFR Mutations in Never-Smokers with Non-Small Cell Lung Cancer. *Clinical Cancer Research*, **17**, 39-45. https://doi.org/10.1158/1078-0432.CCR-10-1773

[19] Shi, Y., Siu-Kie Au, J., Thongprasert, S., Chun-Ming, T.M., Karin Heeroma, T.K., *et al*. (2014) A Prospective, Molecular Epidemiology Study of EGFR Mutations in Asian Patients with Advanced Non-Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER). *Journal of Thoracic Oncology*, **9**, 154-156. https://doi.org/10.1097/JTO.0000000000000033

[20] Chen, W., Zheng, R., Baade, P.D., *et al*. (2016) Cancer Statistics in China, 2015. *CA*: *A Cancer Journal*, **66**, 115-132. https://doi.org/10.3322/caac.21338

[21] Penault-Llorca, F. and Radosevic-Robin, N. (2018) Tumor Mutational Burden in Non-Small Cell Lung Cancer-The Pathologist's Point of View. *Translational Lung Cancer Research*, **7**, 716-721. https://doi.org/10.21037/tlcr.2018.09.26

[22] Li, M., Zhang, Q., Liu, L., *et al*. (2011) The Different Clinical Significance of EGFR Mutations in Exon 19 and 21 in Non-Small Cell Lung Cancer Patients of China. *Neoplasma*, **58**, 74-81. https://doi.org/10.4149/neo_2011_01_74

[23] Wu, Y.-L., Lee, V., Liam, C.-K., *et al*. (2018) Clinical Utility of a Blood-Based EGFR Mutation Test in Patients Receiving First-Line Erlotinib Therapy in the ENSURE, FASTACT-2, and ASPIRATION Studies. *Lung Cancer*, **126**, 1-8. https://doi.org/10.1016/j.lungcan.2018.10.004

[24] Benbrahim, Z., Antonia, T. and Mellas, N. (2018) EGFR Mutation Frequency in Middle East and African Non-Small Cell Lung Cancer Patients: A Systematic Review and Meta-Analysis. *BMC Cancer*, **18**, 891. https://doi.org/10.1186/s12885-018-4774-y

[25] Yang, M.Z., Zhang, L., Bai, J., *et al*. (2016) The Difference of EGFR Mutation in Uygur and Han's Non-Small Cell Lung Cancer in Xinjiang, China. *Modern Oncology*, **24**, 404-406.

[26] Gu, G.D., Wang, X. and Liu, C. (2014) Clinical Feature Analysis of 254 Cases of Uygur Lung Cancer Patients in Xinjiang Area. *Journal of Clinical Medicine in Practice*, **18**, 37-38.