Original Article

# Clinical value of alveolar lavage supernatant specimens in the detection of the *EGFR* gene mutation in patients with non-small cell lung carcinoma

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**Background:** This study sought to compare the consistency of the epidermal growth factor receptor (*EGFR*) gene mutation detection results in the supernatant of alveolar lavage specimens to the tissue sample results, and the consistency of the blood *EGFR* gene mutation detection results to the tissue detection results.

**Methods:** In total, 29 patients with non-small cell lung carcinoma (NSCLC) were selected, and their bronchoalveolar lavage fluid (BALF) was collected. The supernatant and precipitate were separated by centrifugation. Deoxyribonucleic acid (DNA) was extracted from the supernatant, and blood and tumor tissues were collected to detect patients' *EGFR* gene mutation status.

**Results:** Of the 29 enrolled patients, 12 of the 23 tissue-biopsy patients (52.2%) were positive for *EGFR* mutations, 11 of the 28 blood-test patients (39.2%) were positive for *EGFR* mutations, and 13 of the 29 cases of the BALF-test patients (44.8%) were positive for *EGFR* mutations. The most common mutations were the exon 19 deletion mutation and the L858R point mutation. The *EGFR* gene mutation rate was higher in female, young, non-smoker, and stage IIIB patients (than stage IV patients), but the differences were not statistically significant (all P>0.05). Of the 29 NSCLC patients tested for the *EGFR* gene mutation, the BALF supernatant and blood results were the same for 27 patients (coincidence rate: 93.10%). Of the 23 of the 29 enrolled patients tested for the *EGFR* gene mutation, the BALF supernatant and tissue test results were the same for 21 patients (coincidence rate: 91.30%). Further,the blood-test and the tissue test results were the same for 20 patients (coincidence rate:86.96%).

**Conclusions:** The *EGFR* gene mutation rate was high in NSCLC patients. The coincidence rate of the *EGFR* gene mutation detection results between BALF supernatant and tumor tissues was slightly higher than that of the blood and tumor tissue *EGFR* gene mutation detection results.

**Keywords:** Bronchoalveolar lavage fluid (BALF); non-small cell lung carcinoma (NSCLC); epidermal growth factor receptor (*EGFR*)

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## Introduction

Lung carcinoma is the most common malignant tumor. Advanced non-small cell lung carcinoma (NSCLC) is the most common type of lung carcinoma, and has a high mortality rate and poor prognosis (1). The epidermal growth factor receptor (*EGFR*) is a tyrosine kinase type receptor, which leads to receptor dimerization, tyrosine kinase activation, the phosphorylation of specific tyrosine residues, and ultimately, also activates the mitogen-activated protein kinase, protein kinase B, and c-Jun N-terminal kinase, signaling pathways, leading to deoxyribonucleic acid (DNA) synthesis, cell proliferation, and differentiation (2).

The overexpression, abnormal expression, and mutation of the *EGFR* gene are closely related to NSCLC. The frequency of EGFR mutation in China, is higher than that in Europe, which is about 50% in China (3), and about 15% in Europe (4). The most common *EGFR* gene mutations in NSCLC patients are exon 19 deletion (19del) and exon 21 arginine substitution leucine (L858R) point mutations, which account for 90% of the *EGFR* gene mutations in NSCLC patients (5). Through the competitive binding of *EGFR*, tyrosine kinase inhibitors (TKIs) inhibit the *EGFR* signaling pathway, promote apoptosis, inhibit tumor cell proliferation and metastasis, prolong the survival time of patients, and improve their quality of life (6). Thus, it is of great clinical significance to detect the mutation status of the *EGFR* gene in patients with NSCLC, which is a prerequisite for determining whether patients can undergo targeted therapy.

Chemotherapy is the traditional treatment for NSCLC patients with positive *EGFR* gene mutation detection results, but it has severe side effects. Large clinical trials at home and abroad have compared the efficacy of chemotherapy and TKI-targeted therapy in NSCLC patients with positive tissue *EGFR* gene mutation detection results, and found that after TKI-targeted therapy, advanced patients with *EGFR* mutation positive results have prolonged progression free survival and an improved objective response rate (7,8). Consequently, the detection of the *EGFR* gene mutation before NSCLC treatment has gradually become routine.

The detection of *EGFR* mutations in tumor tissues is the gold-standard method for determining whether patients are likely to benefit from *EGFR* TKI-targeted therapy. The clinical application of tissue, which is the main material for detecting the *EGFR* gene mutation in NSCLC patients, is limited by various factors, such as the limitation of advanced stage and insufficient source of tumor tissue, the heterogeneity of the *EGFR* gene mutation, and the long detection cycle. Additionally, for NSCLC patients with multiple metastases undergoing TKI-targeted therapy, it is necessary to detect early evidence of recurrence or find the mechanism of potential drug resistance. Tissue biopsies are expensive. Conversely, peripheral blood detection is a simple, rapid and practical method with high specificity that overcomes tumor heterogeneity to a certain extent (9). Additionally, the consistency of tissue detection results can reach >80% (10). Blood sample plays a supplementary role in tissue detection and represents an important development direction with clinical application in the future.

In 2015, China's State Food and Drug Administration proposed that if the *EGFR* gene status of tumor samples could not be evaluated, circulating tumor DNA (ctDNA) obtained from blood (plasma) could be used for the evaluations (11). However, most of the techniques for detecting plasma *EGFR* gene mutations are not sensitive, and there are differences in sensitivity among tumor patients at different stages. Additionally, the sensitivity of the detection technique needs to be high (12), as the proportion of ctDNA adopted for *EGFR* gene detection in plasma cell-free DNA (cfDNA) is <1%.

The cytological examination of bronchoalveolar lavage fluid (BALF) has been widely adopted in the screening and diagnosis of lung tumors. However, the supernatant of BALF has not yet been used to detect the *EGFR* gene mutation in patients with NSCLC. For advanced patients, it is difficult to get the tissue sample, however because of the character of cancer rapid evolution during the treatment, we can't use tissue samples from a few years ago. BALF analysis may replace cancer tissue examination, which is of limited access in advanced stages. Though study has showed that BALF can be used to detect EGFR mutation and guide target therapy, but we do not get enough information about its sensitivity and specify, and if it's better than the tissue and plasma (13). This study sought to explore the feasibility and application value of the BALF supernatant in the diagnosis of the *EGFR* gene mutation in NSCLC patients by means of polymerase chain reaction detection to determine if it could be adopted as a supplement or substitute for tissue detection to improve the overall detection rate of the *EGFR* gene and the positive detection rate of the *EGFR* gene mutation in NSCLC patients.

This study also sought to provide more evidence for the clinical guidance of the individualized treatment of NSCLC. We present the following article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-681/rc).

## Methods

### *General data*

In total, 29 patients with NSCLC diagnosed at the Shanxi Province Cancer Hospital from March 2016 to May 2019 were enrolled in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by the ethics committee of Chinese Academy of Medical Sciences/ Cancer Hospital Affiliated to Shanxi Medical University (No. 201636). All patients have signed informed consent to enroll in this study. To be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) be newly diagnosed with NSCLC; or (II) have recurrent NSCLC. Patients were excluded from the study if they met any of the following exclusion criteria: (I) the pathological type of lung carcinoma could not be identified; and/or (II) the NSCLC patients could not tolerate a fiberoptic bronchoscopy.

Based on the inclusion and exclusion criteria, a total of 29 patients with NSCLC were included in the study. Of the 29 patients, 18 were male (62.1%) and 11 were female (37.9%). The patients had a mean age of 63.0 (range: 47.8–67.0) years, but the ages of 3 patients were unknown. Among the patients, 11 had a history of smoking (64.7%), but 16 had an unknown smoking history, and 9 had clinical stage ⅢB, 8 had stage IV, but the clinical stage of 12 was unknown.

### *Main reagents and instruments*

The nucleic acid extraction reagents (circulating DNA), human *EGFR* gene mutation detection reagents (Super-ARMS method), nucleic acid extraction reagents (tissue, pleural effusion DNA), and human *EGFR* gene mutation detection reagents (ADxARMS®) were all purchased from Xiamen Biopharmaceutical Technology Co. Ltd.

### *Research methods*

#### Sample collection and DNA extraction of BALF

The location of each lesion was determined by chest imaging examination. The site with the most significant lesion or the site with the fastest progression was selected for lavage. Lidocaine (2%; 1–2 mL) was injected into the lavaged lung segment through the biopsy hole, and local anesthesia was performed in the lavaged lung segment. At 37 ℃ or room temperature, aseptic saline was quickly injected through the operating channel, and after the top of the bronchoscope had been embedded in the target bronchial segment or sub-end opening, the BALF was immediately obtained by negative pressure suction. On the day on which the BALF samples were collected, 30 mL of BALF was taken into the centrifuge tube, and the supernatant and precipitate were separated by 2-stage centrifugation (i.e., 2,000 ×g centrifugation for 10 min, and 8,000 ×g centrifugation of the supernatant for 10 min ). The supernatant was transferred to a test tube, and cfDNA in the supernatant was extracted using an Ed biological cfDNA extraction kit, and stored in a refrigerator at 20 ℃. The remaining precipitated DNA in BALF after centrifugation was extracted using a biological tissue and pleural effusion DNA separation kit, and stored in a refrigerator at –20 ℃.

#### Collection of blood samples (9,11) and extraction of DNA

Whole blood (10 mL) was collected during the morning following hospitalization. A 2-stage centrifugation method was adopted (centrifugation for 10 min at 800 ×g, centrifugation for 5 min at 16,000 ×g, transference of the supernatant to the test tube), and the sample was isolated for <2 hours. The sample size was about 4–5 mL. A cfDNA extraction kit was used to extract the cfDNA from the plasma.

#### Collection of tissue specimens and extraction of DNA

The tumor tissue samples were obtained by endobronchial ultrasound-guided fine-needle biopsy, fiberoptic bronchoscopic biopsy, and percutaneous lung biopsy. The DNA was extracted from the tissue samples using a biological tissue and pleural effusion DNA separation kit.

#### EGFR test after DNA extraction

The *EGFR* in the BALF supernatant and the *EGFR* in the blood were detected using the Super-ARMS (amplification refractory mutation system, ARMS) method, and the *EGFR* in the tumor tissue was detected by ADx-ARMS®. Additionally, the mutation of the *EGFR* gene was detected according to the operating procedures of the instructions, and the results were interpreted according to the instructions.

### *Statistical analysis*

All the data were statistically analyzed using SPSS25.0 software. The measurement data with a normal distribution

 

and uniform variance are expressed as the x±s, and the *t*-test was used for comparisons between the groups. The data with a non-normal distribution are expressed as the median (first quartile, third quartile). The counting data are expressed as the case and rate (%). For the comparisons between groups, Fisher's exact probability method was used. A P value <0.05 indicated a statistically significant difference.

## Results

### *Results of EGFR gene mutation detection*

Of the 23 patients who underwent tissue examinations, 12 (52.2%) were positive for the *EGFR* gene mutation, 8 (66.7%) for the 19del mutation, and 4 (33.3%) for the L858R mutation. Additionally, of the 28 patients who had blood tests, 11 (39.2%) were positive for the *EGFR* gene mutation, 7 (63.6%) for the 19del mutation, and 4 (36.4% for the L858R mutation. Further, of the 29 patients who underwent BALF supernatant examinations, 13 (44.8%) were positive for the *EGFR* gene mutation, 8 for the (61.5%) 19del mutation, and 5 (38.5%) for the L858R mutation.

### *The results of the EGFR gene mutation detection in the different samples were consistent*

Of the 29 NSCLC patients tested for the *EGFR* gene mutation, the BALF supernatant and blood-test results were the same for 27 patients (coincidence rate: 93.10%). Of the 23 of the 29 patients tested for the *EGFR* gene mutation, the BALF supernatant and tissue test results were the same for 21 patients (coincidence rate: 91.30%). Further,the blood-test and the tissue test results were the same for 20 patients (coincidence rate:86.96%). The coincidence rate for the BALF supernatant and the tissue *EGFR* gene status was slightly higher than that of the blood and tissue *EGFR* gene status.

### *Relationship between EGFR gene mutation and clinicopathological features*

Among the 23 patients who underwent tissue examination, 8 of the patients were female, 6 of whom had the *EGFR* gene mutation (75.0%), and 15 were male, 6 of whom had the *EGFR* gene mutation (40.0%). The mutation rate in females was higher than that in males, but there was no significant difference between the 2 groups (P>0.05). Among the 10 patients aged >60 years, 5 (50.0%) were positive for the *EGFR* gene mutation, and among the 11 patients aged <60 years, 5 (45.5%) were positive for the *EGFR* gene mutation, but the difference between the 2 groups was not statistically significant (P>0.05). Among the 5 non-smoking patients, 4 (80.0%) had the *EGFR* gene mutation, and among the 9 smoking patients, 4 (44.4%) had the *EGFR* gene mutation. The mutation rate of the non-smoking patients was higher than that of the smoking patients, but the difference was not statistically significant (P>0.05). Among the 9 patients with clinical stage IIIB, 5 (55.6%) were positive for the *EGFR* gene mutation, and among the 6 patients with clinical stage IV, 3 (50.0%) were positive for the *EGFR* gene mutation, but the difference was not statistically significant (P>0.05; see *Table 1*).

## Discussion

TKI-targeted therapy based on EGFR gene detection has brought accuracy to the medical treatment of lung carcinoma. And now many target drugs like osimertinib, erlotinib, afatinib, gefitinib, dacomitinib have approved by FDA, and osimertinib as the first line used for patients with EGER mutation, the OS has achieved 33.1 months in China (14). Consequently, understanding the status of the EGFR mutation is of great significance to clinical decision making for patients with advanced NSCLC (especially lung adenocarcinoma) (15).

This study showed that the coincidence rate between the supernatant of the BALF and tissue *EGFR* gene status (91.3%) was slightly higher than that of the blood and tissue *EGFR* gene status (86.96%). *EGFR* gene mutation detection has become a key measure for the clinical treatment and efficacy evaluation of NSCLC patients. Tissue detection, which is the gold standard for determining the *EGFR* gene status, is limited by various factors in clinical practice, and its actual application rate is low. It is necessary to seek other biological samples that can be adopted for *EGFR* gene status detection to make up for the deficiency of tissue detection. BALF obtained by fiberoptic bronchoscope has been adopted as a new biological sample for *EGFR* detection. Compared to tissue detection, the detection results have high consistency, and have great potential for development. However, it is still necessary to overcome the problem of the low sensitivity of the detection and analysis techniques for the detection of the *EGFR* gene in non-tissue samples.

The common EGFR mutations are more likely to be associated with female patients or never-smokers, but a few

 

**Table 1** Relationship between *EGFR* gene mutation and clinicopathological features in patients with NSCLC

| Clinical features | Total | Detection results of tissue *EGFR* gene | | P |
|---|---|---|---|---|
| | | Mutation positive | Mutation negative | |
| Gender | | | | 0.193 |
| Male | 15 | 6 (40.0%) | 9 (60.0%) | |
| Female | 8 | 6 (75.0%) | 2 (25.0%) | |
| Age[a] (years) | | | | 1.000 |
| >60 | 10 | 5 (50.0%) | 5 (50.0%) | |
| ≤60 | 11 | 5 (45.5%) | 6 (54.5%) | |
| Smoking[b] | | | | 0.301 |
| No | 5 | 4 (80.0%) | 1 (20.0%) | |
| Yes | 9 | 4 (44.4%) | 5 (55.6%) | |
| Clinical staging[c] | | | | 1.000 |
| IIIB | 9 | 5 (55.6%) | 4 (44.4%) | |
| IV | 6 | 3 (50.0%) | 5 (50.0%) | |

Of the 23 patients who underwent tissue examinations, 12 (52.2%) were positive for the *EGFR* gene mutation, 8 (66.7%) for the 19del mutation, and 4 (33.3%) for the L858R mutation. [a], except for 21 patients with exact age information, the age of the other 2 patients is unknown; [b], except for 14 patients with smoking, smoking history of the other 9 patients is unknown; [c], except for 15 patients with definite clinical stage, 8 patients with unknown clinical stage.

rare mutations, like exon 20 mutations, are not associated with any clinicopathological features (16). This study showed that the gene mutation rate of female patients with NSCLC was higher than that of male patients, and the gene mutation rate of elderly patients was higher than that of younger patients. Additionally, the gene mutation rate of non-smoking patients was higher than that of smoking patients, and the gene mutation rate of stage IIIB patients was higher than that of stage IV patients, but the difference was not statistically significant (P>0.05). The results of this study differ to those of previous study (15). This may be because (I) this study is an observational study and had fewer patients than the multicenter prospective studies; (II) the results of the study may have been affected by underreporting, as some patients concealed their smoking history; and (III) the air pollution in Shanxi Province, which is serious due to its geographical location and industrial production, led to an increase in the incidence of the inhalation of harmful substances in patients with no history of smoking. However, both previous studies and our studies suggest that more attention should be paid to the status of the *EGFR* gene in women and patients with no history of smoking.

## Conclusions

The detection of the *EGFR* gene mutation is a key prerequisite for TKI-targeted therapy among NSCLC patients. The selection of suitable non-tissue biological samples for detection can improve the overall *EGFR* gene detection rate and the positive detection rate of *EGFR* gene mutations in NSCLC patients; thus, promoting the progress of individualized therapy in NSCLC patients. The coincidence rate of the *EGFR* gene mutation detection in the BALF supernatant and tissue *EGFR* gene mutation detection was slightly higher than that of the plasma and tissue *EGFR* gene mutation detection, which makes BALF a better genetic testing sample. However, to ensure more NSCLC patients can benefit from TKI-targeted therapy, further research needs to be conducted to improve the detection sensitivity and analysis technology, and standardize the relevant clinical operation. Currently, there is no standard method and operation flow for detecting the *EGFR* gene mutation in BALF in clinical practice.

 

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## Footnote

*Reporting Checklist:* The authors have completed the MDAR reporting checklist Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-681/rc

*Data Sharing Statement:* Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-681/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-681/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by the ethics committee of Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University (No. 201636). All patients have signed informed consent to enroll in this study.



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