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Retrospective Study

Accuracy of endoscopic ultrasound-guided needle aspiration specimens for molecular diagnosis of non-small-cell lung carcinoma

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Abstract

BACKGROUND

Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are highly sensitive for diagnosing and staging lung cancer. In recent years, targeted therapy has shown great significance in the treatment of non-small cell lung carcinoma (NSCLC). Using these minimally invasive techniques to obtain specimens for molecular testing will provide patients with a more convenient diagnostic approach.

AIM

To evaluate the feasibility and accuracy of tissue samples obtained using EUS-FNA and EBUS-TBNA for molecular diagnosis of NSCLC.

METHODS

A total of 83 patients with NSCLC underwent molecular testing using tissues obtained from EUS-FNA or EBUS-TBNA at the Tianjin Medical University Cancer Hospital from January 2017 to June 2019. All enrolled patients underwent chest computed tomography or positron emission tomography/computed tomography prior to puncture. We detected abnormal expression of *EGFR*, *KRAS*, *MET*, *HER2*, *ROS1* and anaplastic lymphoma kinase protein. Two patients failed to complete molecular testing due to insufficient tumor tissue. The clinical features, puncture records, molecular testing results and targeted treatment in the remaining 81 patients were summarized.

RESULTS

In a total of 99 tissue samples obtained from 83 patients, molecular testing was

study because the analysis used anonymous clinical data that were obtained after patient had agreed to treatment with written consent.

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successfully completed in 93 samples with a sample adequacy ratio of 93.9% (93/99). Biopsy samples from two patients failed to provide test results due to insufficient tumor tissue. In the remaining 81 patients, 62 cases (76.5%) were found to have adenocarcinoma, 11 cases (13.6%) had squamous cell carcinoma, 3 cases (3.7%) had adenosquamous carcinoma and 5 cases (6.2%) had NSCLC-not otherwise specified. The results of molecular testing showed *EGFR* mutations in 21 cases (25.9%), *KRAS* mutations in 9 cases (11.1%), *ROS-1* rearrangement in 1 case (1.2%) and anaplastic lymphoma kinase-positive in 5 cases (6.2%). Twenty-four patients with positive results received targeted therapy. The total effectiveness rate of targeted therapy was 66.7% (16/24), and the disease control rate was 83.3% (20/24).

CONCLUSION

Tissue samples obtained by EUS-FNA or EBUS-TBNA are feasible for the molecular diagnosis of NSCLC and can provide reliable evidence for clinical diagnosis and treatment.

Key Words: Endobronchial ultrasound-guided transbronchial needle aspiration; Endoscopic ultrasonography-guided fine-needle aspiration; Non-small cell lung carcinoma; Molecular diagnosis; Targeted therapy

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Core Tip: The purpose of this retrospective study was to evaluate the feasibility and reliability of tissue samples obtained using endoscopic ultrasonography-guided fine-needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration for molecular diagnosis of non-small cell lung carcinoma. In the study, 93.9% of the puncture samples could be used for molecular testing. The proportion of patients with positive results corresponds to the frequency of molecular mutations. Patients receiving targeted therapy responded well to treatment. The samples obtained by the two techniques can be used for molecular diagnosis of lung cancer. They can provide reliable evidence for clinical diagnosis and treatment.

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INTRODUCTION

According to the latest cancer statistics released in 2018, lung cancer still has the highest morbidity and mortality worldwide. Most patients have locally advanced tumors or distant metastasis at diagnosis. The 5-year survival rate is only 16.1%^[1,2]. At present, the treatment of advanced lung cancer mainly depends on comprehensive treatment and individualized treatment strategies that are formulated according to pathological types, molecular genetic characteristics and patient condition^[3]. In recent years, targeted therapy for non-small cell lung cancer (NSCLC) has played an important role in clinical applications. Therefore, obtaining tumor tissue or metastatic lymph node tissue for molecular testing before first-line treatment is essential for timely and effective individualized treatment. In China, NSCLC accounts for 80%-85% of all lung cancer cases^[1]. The National Comprehensive Cancer Network guidelines clearly indicate that molecular testing should be undertaken in all cases of NSCLC, including lung adenocarcinoma, large cell carcinoma and NSCLC-not otherwise specified^[4]. For squamous cell carcinoma, molecular testing is recommended for nonsmokers, patients with small biopsy specimens or mixed histological types^[4]. *EGFR*, *KRAS* and anaplastic lymphoma kinase (ALK) should be routinely tested. It has been suggested that more extensive molecular testing is a key factor in NSCLC therapy.



Endoscopic ultrasound-guided minimally invasive diagnosis and treatment technology has been widely used in many diseases in recent years^[5-8]. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) have high sensitivity and specificity for diagnosing and staging lung cancer^[9,10] and have become safe and effective methods to establish diagnosis for patients with clinically suspected advanced-stage disease. Due to the different accessibility of lung and mediastinal lesions, the two biopsy methods are considered to be complementary. They can puncture almost all of the mediastinal lymph nodes^[11]. The purpose of this retrospective study was to evaluate the feasibility and reliability of EUS-FNA and EBUS-TBNA in obtaining tissue for the molecular diagnosis of NSCLC.

MATERIALS AND METHODS

Patients

A total of 83 patients with NSCLC underwent molecular testing using tissues obtained from EUS-FNA or EBUS-TBNA at the Tianjin Medical University Cancer Hospital from January 2017 to June 2019. Two patients failed to complete the molecular testing due to insufficient tumor tissue. We summarized the molecular testing results and targeted treatment in the remaining 81 patients. All enrolled patients underwent chest computed tomography or positron emission tomography/computed tomography prior to puncture. The results showed a highly suspicious malignant lung mass or metastatic lymph node. In addition, we reviewed the targeted therapy of patients with positive molecular testing results and evaluated tumor response after 3 mo of targeted therapy. Clinical efficacy was evaluated according to the response evaluation criteria in solid tumors. All patients signed an informed consent before examination. The ethics committee of our institution approved the study.

EUS-FNA and EBUS-TBNA

EBUS-TBNA was performed with a convex probe endobronchial ultrasound for line array scanning (BF-UC206FW, Olympus) and a 22-gauge ultrasound bronchial biopsy needle for tissue aspiration (ECHO-HD-22-EBUS-O, Cook). We performed EUS-FNA with a convex ultrasound endoscope (EG-3870UTK, Pentax) and a 22-gauge ultrasound biopsy needle (ECHO-3-22, Cook). The biopsy specimens were collected for cytology, histopathology and molecular testing. Rapid on-site evaluation of cytopathology was not performed.

Pathology and molecular analysis of specimens

The collected specimens were fixed with 40 g/L formaldehyde solution and were embedded in paraffin. Processed samples were used for histopathological diagnosis and classification by hematoxylin eosin staining and immunohistochemistry (IHC). If the number of tumor cells exceeded 100 in the paraffin section, they were considered feasible for molecular testing. Following a definite diagnosis, we extracted DNA from paraffin tissue blocks and used Sanger sequencing for mutation analysis of *EGFR* exons 18-21, *KRAS* exon 2, *MET* exon 14 and *HER2* exon 20. The expression of ALK protein was detected by Ventana ALK (D5F3) IHC. The expression of ROS1 protein was preliminarily determined by IHC. Further fluorescence *in situ* hybridization testing was required in patients with IHC results of + to +++. The positive criteria on fluorescence *in situ* hybridization detection were more than 50 tumor cells in the tissue sections and more than 15% of the counted cells showing a separation signal.

Statistical analysis

IBM SPSS Statistics (v24.0; IBM Corp., United States) were used for data analysis. Continuous variables are presented as mean \pm standard deviation and categorical variables as the frequency (*n*) and percentage (%).

RESULTS

Clinical characteristics of the patients

In this study, molecular testing was performed in 83 patients. At least one suspected malignant lung lesion or one suspected metastatic lymph node was biopsied in each patient. In a total of 99 lesion samples obtained from 83 patients, molecular testing was

successfully performed in 93 samples with a sample adequacy ratio of 93.9% (93/99). Molecular testing failed in two patients due to insufficient biopsied tumor tissue. The clinical characteristics of the remaining 81 patients who completed the molecular testing are summarized in Table 1. Of these patients, 59 were male (72.8%), and 22 were female (27.2%) with a mean age of 59.1 ± 9.4 years (28-76 years). Forty-two patients (51.9%) had a history of smoking, and 39 (48.1%) were nonsmokers. Fifteen patients (18.5%) had a family history of lung cancer. Histopathological analysis revealed that 62 cases (76.5%) had adenocarcinoma, 11 cases (13.6%) had squamous cell carcinoma, 3 cases (3.7%) had adenosquamous carcinoma and 5 cases (6.2%) had NSCLC-not otherwise specified. All patients were at an intermediate or advanced stage (stage III-IV). We performed EUS-FNA on 44 patients (54.3%) and EBUS-TBNA on 37 patients (45.7%).

A total of 97 lesion samples were obtained from 81 patients. One patient underwent biopsy of 3 lesions, and 14 patients underwent biopsy of 2 lesions. The location and size of the lung lesions and lymph nodes sampled are shown in Table 2. The specific conditions of multifocal biopsy are shown in Table 3. Each lesion was punctured 2-4 times with an average of 2.7 ± 0.6 times. In patients with multifocal biopsy, one sample did not provide a reliable malignant diagnosis in two patients. In another two patients, molecular testing was not completed due to insufficient tumor tissue.

Molecular analysis of the samples

Of the 81 patients with NSCLC, 21 (25.9%) had *EGFR* mutations, 9 (11.1%) had *KRAS* mutations, 1 (1.2%) had *ROS-1* rearrangements and 5 (6.2%) were ALK positive. However, the detection of *MET* and *HER2* did not yield a positive result. Data analysis showed that genetic mutations were still concentrated in patients with lung adenocarcinoma. Among the 62 patients with lung adenocarcinoma and 3 patients with adenosquamous carcinoma, there were 21 cases (32.3%) of *EGFR* mutations, 8 cases (12.3%) of *KRAS* mutations, 1 case (1.5%) of *ROS-1* rearrangements and 5 cases were ALK positive (7.7%). However, in eleven patients with lung squamous cell carcinoma, only one *KRAS* mutation was detected, and in five patients with NSCLC-not otherwise specified, there were no positive results. Table 4 lists the results of molecular testing.

Of the 15 patients who underwent multifocal sampling, 4 patients had positive results. These four patients underwent biopsy of two lesions. One of the patients had insufficient tumor tissue in one of the samples, and in the other three patients we found that different lesions in the same patient had consistent mutation results (Table 5).

Evaluation of the efficacy of targeted therapy

A total of 36 patients had positive molecular testing results, 24 of them received targeted therapy, including 19 cases of *EGFR* mutations, 1 case of *ROS-1* rearrangement and 4 ALK-positive cases. Therapeutic drugs included gefitinib, erlotinib, alectinib and crizotinib. The evaluation of tumor response after 3 mo of treatment is shown in Table 6. The total effectiveness rate of targeted therapy was 66.7% (16/24), and the disease control rate was 83.3% (20/24).

DISCUSSION

Due to limited cancer screening and other reasons, approximately 70% of lung cancer patients are diagnosed at a late stage of the disease^[12]. Therefore, they have missed or lost the best surgical opportunity. These patients usually have a poor prognosis and a high mortality rate. In recent years, EUS-FNA and EBUS-TBNA have been widely used in the diagnosis and staging of lung cancer, which has greatly shortened the time for treatment decision-making compared with conventional techniques such as thoracoscopic surgery^[13]. In addition, because of their high sensitivity and specificity, they can improve the accuracy of lymph node staging, thereby reducing the number of unnecessary surgical interventions and have become the preferred methods for diagnosis and lymph node evaluation in patients with advanced lung cancer^[14,15].

With the advancement of targeted therapy for lung cancer, more convenient, rapid and accurate acquisition of patients' molecular testing results can greatly improve the efficiency of clinical diagnosis and treatment. Based on relevant guidelines and listed targeted drugs, our center provides a molecular testing platform for the corresponding targets. Our research involved the analysis of tumor tissue obtained using EUS-FNA or EBUS-TBNA for molecular testing in NSCLC. We tested *EGFR*, *KRAS*, *MET*, *HER2*,

Table 1 Clinical characteristics of the 81 patients, *n* (%)

| Characteristics | Patients, <i>n</i> = 81 |
|----------------------------|-------------------------|
| Gender | |
| Male | 59 (72.8) |
| Female | 22 (27.2) |
| Smoking status | |
| Nonsmoker | 39 (48.1) |
| Former or current smoker | 42 (51.9) |
| Pathological type | |
| Adenocarcinoma | 62 (76.5) |
| Squamous cell carcinoma | 11 (13.6) |
| Adenosquamous carcinoma | 3 (3.7) |
| NSCLC-NOS | 5 (6.2) |
| Clinical stage | |
| IIIA | 15 (18.5) |
| IIIB | 28 (34.6) |
| IIIC | 3 (3.7) |
| IV | 35 (43.2) |
| Distant metastasis | |
| Malignant pleural effusion | 3 (3.7) |
| Pleura | 4 (4.9) |
| Contralateral lung | 9 (11.1) |
| Bone | 14 (17.3) |
| Brain | 9 (11.1) |
| Liver | 3 (3.7) |
| Adrenal gland | 5 (6.2) |

NSCLC-NOS: Non-small cell lung carcinoma-not otherwise specified.

ROS1 and *ALK* simultaneously. If the amount of tumor tissue was insufficient and all molecules could not be detected, the sample was considered invalid. A total of 99 tissue samples were obtained from 83 patients, of which 93 samples provided sufficient tumor tissue for molecular detection with a sample adequacy ratio of 93.9%. In a meta-analysis of 28 studies evaluating EBUS-TBNA for the identification of *EGFR* and *ALK* mutations, the pooled probability of obtaining a sufficient sample for the *EGFR* assay was 94.5% [95% confidence interval, 93.2%-96.4%], and the pooled probability was 94.9% for *ALK* mutations (95% confidence interval, 89.4-98.8%)^[16]. Folch *et al*^[17] obtained lung cancer tissue samples from the hilum pulmonis or mediastinal lymph nodes *via* convex probe-EBUS for *EGFR*, *KRAS* and *ALK* gene detection with a success rate of over 90%. Our research had approximate success rates compared to similar types of studies and completed the detection of multiple molecular targets. Most incomplete molecular diagnostic samples were due to the puncture site containing a large amount of necrotic tumor tissue or blood loss. Research has shown that selecting larger lymph nodes and at least three punctures per lesion may result in a higher success rate in molecular testing^[18].

Due to differences in the number of samples, smoking history, ratio of male to female patients and the sensitivity of detection methods, there are differences in the frequencies of abnormal molecules in different studies. Available related studies and reviews concluded that the mutation frequencies of *EGFR*, *KRAS*, *ALK*, *ROS1*, *MET* and *HER2* in Asian lung adenocarcinoma are approximately 30%-50%, 8%-16%, 3%-7%, 1%-3%, 3%-4% and 1%-3%, respectively^[19-24]. In the present study, gene mutations

Table 2 Puncture site and lesion size

| Location of sample | Patients, <i>n</i> | Minimum, mm | Maximum, mm |
|--------------------|--------------------|-------------|-------------|
| Primary tumor | | | |
| Right | 18 | 24 | 65 |
| Left | 7 | 28 | 91 |
| Lymph node | | | |
| 2R | 2 | 10 | 21 |
| 4R | 19 | 9 | 34 |
| 4L | 4 | 27 | 28 |
| 5 | 2 | 19 | 38 |
| 7 | 35 | 15 | 70 |
| 8 | 2 | 12 | 20 |
| 10R | 5 | 24 | 26 |
| 10L | 3 | 23 | 45 |

2R: Right upper paratracheal; 4R: Right lower paratracheal; 4L: Left lower paratracheal; 5: Subaortic; 7: Subcarinal; 8: Paraesophageal; 10R: Right hilar; 10L: Left hilar.

Table 3 Puncture of multiple lesions

| Location of sample | Patients, <i>n</i> |
|---------------------|--------------------|
| 4R, 4L, 7 | 1 |
| 4R, 7 | 7 |
| 5, 7 | 1 |
| 7, 8 | 1 |
| Left lung mass, 7 | 1 |
| Right lung mass, 4R | 2 |
| Right lung mass, 7 | 2 |

4R: Right lower paratracheal; 4L: Left lower paratracheal; 5: Subaortic; 7: Subcarinal; 8: Paraesophageal.

mainly occurred in patients with lung adenocarcinoma. In 62 patients with lung adenocarcinoma and 3 patients with adenosquamous carcinoma, there were 21 cases (32.3%) of *EGFR* mutations, 8 cases (12.3%) of *KRAS* mutations, 1 case (1.5%) of *ROS-1* rearrangements and 5 cases were *ALK* positive (7.7%). These results are broadly similar to those observed in the above studies. In addition, mutation-positive patients responded well to targeted therapy in this study with a total effectiveness rate of 66.7% (16/24) and a disease control rate of 83.3% (20/24). It can be seen that tissue samples obtained by EUS-FNA and EBUS-TBNA for molecular detection are reliable. In addition, we did not obtain positive results for *MET* and *HER2* mutations, and there were no multiple mutations due to an insufficient number of cases.

Of the fifteen patients who underwent multifocal sampling, four patients had positive results. One sample had insufficient tumor tissue, and in the other three patients it was found that different lesions in the same patient had consistent mutation results. Kang *et al*^[25] compared the *EGFR* mutation status of lymph node samples obtained by EBUS-TBNA and primary tumor samples and found that the discordance rate in major mutations between matched primary tumor and lymph node specimens was 4.1% (3/74). Ito *et al*^[26] compared the *EGFR* and *ALK* mutation status of lymph node samples and primary tumor samples and found that the concordance rate was 96.7%. Due to the limitations of this retrospective study, we did not have enough data on molecular testing to compare matched primary tumor and lymph node specimens. Further research should be performed in the future. In addition, suspected lesions

Table 4 Molecular analysis of all patients

| | Adenocarcinoma, <i>n</i> = 62 | Squamous cell carcinoma, <i>n</i> = 11 | Adenosquamous carcinoma, <i>n</i> = 3 | NSCLC-NOS, <i>n</i> = 5 |
|-----------------------------------|-------------------------------|--|---------------------------------------|-------------------------|
| EGFR mutation | | | | |
| Exon 19 | | | | |
| E746-A750del (1) | 2 | 0 | 0 | 0 |
| E746-A750del (2) | 4 | 0 | 0 | 0 |
| L747-T751del | 2 | 0 | 0 | 0 |
| L747-S752del | 1 | 0 | 0 | 0 |
| L747-A750del | 1 | 0 | 0 | 0 |
| Exon 21 | | | | |
| L858R | 8 | 0 | 1 | 0 |
| L861Q | 2 | 0 | 0 | 0 |
| KRAS mutation | | | | |
| Exon 2 | | | | |
| G12C | 3 | 1 | 0 | 0 |
| G12D | 2 | 0 | 0 | 0 |
| G12V | 2 | 0 | 0 | 0 |
| G12L | 1 | 0 | 0 | 0 |
| ROS-1 (FISH) positive | 1 | 0 | 0 | 0 |
| ALK (Ventana IHC) positive | 5 | 0 | 0 | 0 |

NSCLC-NOS: Non-small cell lung carcinoma-not otherwise specified; ALK: Anaplastic lymphoma kinase; FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemistry.

Table 5 Molecular analysis of patients with multiple lesions

| Type | Puncture site | Mutation | Puncture site | Mutation |
|---------------------------|-----------------|---------------------|---------------|---------------------|
| 1 Adenocarcinoma | 5 | Insufficient sample | 7 | EGFR, exon 21 L858R |
| 2 Adenocarcinoma | Right lung mass | EGFR, exon 21 L858R | 7 | EGFR, exon 21 L858R |
| 3 Adenocarcinoma | 4R | EGFR, exon 21 L858R | 7 | EGFR, exon 21 L858R |
| 4 Squamous cell carcinoma | 4R | KRAS, exon 2 G12C | 7 | KRAS, exon 2 G12C |

4R: Right lower paratracheal; 5: Subaortic; 7: Subcarinal.

should be sampled as much as possible in clinical applications to obtain a more comprehensive and reliable diagnosis.

CONCLUSION

In conclusion, from this analysis, it is believed that the molecular diagnosis of NSCLC patients following the evaluation of tissue samples obtained by EUS-FNA or EBUS-TBNA is reliable. At present, our center provides patients with a next-generation sequencing detection platform, which requires fewer specimens and can detect multiple genes at the same time^[27]. EUS-FNA and EBUS-TBNA will provide more efficient help for patients with lung cancer.

Table 6 Response to targeted therapy

| | Drugs | CR, <i>n</i> | PR, <i>n</i> | SD, <i>n</i> | PD, <i>n</i> |
|----------------|--------------------------------|--------------|--------------|--------------|--------------|
| EGFR mutation | Gefitinib, erlotinib, exitinib | 0 | 13 | 3 | 3 |
| ROS-1 positive | Crizotinib | 0 | 0 | 1 | 0 |
| ALK positive | Crizotinib | 0 | 3 | 0 | 1 |

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

ARTICLE HIGHLIGHTS

Research background

Endoscopic ultrasound-guided needle aspiration technology is applied to the diagnosis of lung cancer, which exempts many patients from undergoing more traumatic examinations. It has been gradually promoted in clinical practice. Whether the limited puncture tissue can be used for pathological diagnosis, molecular diagnosis, *etc.* and obtain reliable results, is the question we wanted to clarify in order to help us understand whether the technology can efficiently assist clinical diagnosis and treatment.

Research motivation

To evaluate the value of endoscopic ultrasound-guided needle aspiration in the diagnosis of lung cancer.

Research objectives

Through retrospective research to understand the success rate of molecular diagnosis of non-small cell lung carcinoma with puncture specimens. To evaluate the reliability of the diagnosis results through follow-up of clinical treatment effects.

Research methods

According to the location of the patient's lesion, we choose to use endoscopic ultrasonography-guided fine-needle aspiration or endobronchial ultrasound-guided transbronchial needle aspiration. Due to the different accessibility of lung and mediastinal lesions, the two puncture methods are considered to be complementary. We used Sanger sequencing for mutation analysis of *EGFR*, *KRAS*, *MET* and *HER2*. This is not the most advanced detection method, but the test results are reliable. Moreover, it does not require high costs, so more patients can benefit from it.

Research results

In this study, 93.9% of the punctured tissues met the molecular test standards. The test results were in line with the mutation frequency of the patient population. The patients who received targeted therapy according to the test results responded well. These results add evidence to support the application value of this technology in diagnosis of non-small cell lung carcinoma. However, this study lacks comparison data between this technique and other methods, so it cannot prove that it is the first choice for clinical diagnosis.

Research conclusions

The two puncture methods are considered to be complementary. They can puncture almost all the mediastinal lymph nodes. This technique obtains diseased tissue under minimally invasive conditions, thus reducing unnecessary surgical intervention. The diagnosis results are reliable and can effectively guide clinical treatment.

Research perspectives

Advantages and problems of endoscopic ultrasound in diagnosis and treatment of lung cancer and gastrointestinal tumors.

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