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Accuracy of transbronchial biopsy as a rebiopsy method for patients with relapse of advanced non-small-cell lung cancer after systemic chemotherapy

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ABSTRACT

Introduction: Rebiopsy in patients with advanced non-small-cell lung cancer (NSCLC) resistant to systemic chemotherapy may yield information on the mechanisms of resistance and planning of subsequent treatment. Transbronchial biopsy (TBB) using a flexible bronchoscope has been commonly used for establishing the initial diagnosis of lung cancer. The aim of this study was to assess the accuracy and safety of TBB in patients with NSCLC relapse, and the factors affecting its diagnostic yield.

Methods: We retrospectively screened patients with advanced NSCLC who underwent TBB for rebiopsy after developing resistance to systemic chemotherapy at Kurume University Hospital between January 2012 and June 2016. A positive diagnostic result obtained by TBB was defined as malignancy determined on the basis of histological features that were adequate for mutational analysis or immunohistochemistry. Severe postprocedural complications were defined as those requiring invasive medical procedures or prolonged hospitalisation.

Results: 109 patients were enrolled in this retrospective study. Adequate tumour samples were collected from 88 of these patients, giving a high diagnostic yield of 80.7%. The diagnostic yield of TBB was not associated with tumour mutational status, the previous treatment regimen, or efficacy of the previous treatment. There were no severe postprocedural complications such as pneumothorax or serious haemorrhage.

Conclusions: TBB is considered one of the safest and most useful procedures for rebiopsy of NSCLC that has relapsed after chemotherapy, regardless of patient background and treatment history.

KEY MESSAGES

- Therapeutic strategies for non-small-cell lung cancer (NSCLC) have focused on next-generation EGFR-TKIs and immunotherapies.
- Rebiopsy is required to evaluate the T790M mutation or programmed cell death-ligand 1 expression.
- The aim of this study was to assess the feasibility and safety of transbronchial biopsy (TBB) in patients with NSCLC relapse.
- We demonstrated that TBB for rebiopsy has a high diagnostic yield without severe complications.
- The diagnostic yield was not associated with patient background and treatment history.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of death worldwide due to cancer.[1] Transbronchial biopsy (TBB) using a flexible bronchoscope has been commonly used for establishing a diagnosis of lung cancer, having a more favourable safety profile than transthoracic needle aspiration or surgical procedures.[2–4] Although the diagnostic yield of TBB has not been satisfactory, especially for small peripheral lesions, recent technical advances have improved its diagnostic accuracy.[4]

Therapeutic strategies for NSCLC over the past few decades have focused on overcoming resistance to molecular targeted therapies and development of immunotherapies.[5–14] It has been suggested that expression of programmed cell death-ligand 1 (PD-L1) in tumours may predict a favourable response to immune checkpoint inhibitors.[13 14] In order to evaluate the mechanisms of resistance to molecular targeted therapies, immunostaining for PD-L1 is necessary using tumour samples obtained after disease progression. Rebiopsy is performed for this purpose, and TBB seems to be the safest method for doing so, except for cases of skin, muscle or superficial lymph node metastasis. However, the utility of TBB as a rebiopsy method and the impact of

previous treatment on its diagnostic yield are unknown. Here, we retrospectively evaluated the accuracy and safety of TBB as a rebiopsy method in patients with advanced NSCLC that had relapsed after systemic chemotherapy, and the factors influencing its diagnostic yield.

MATERIALS AND METHODS

Patients

We retrospectively screened 2126 consecutive patients who underwent bronchoscopy at Kurume University Hospital between January 2012 and June 2016. Among these patients, 109 with advanced NSCLC who underwent TBB for rebiopsy after developing resistance to systemic chemotherapy were enrolled. These patients underwent TBB for enrolment in clinical trials that required rebiopsy, further investigation of tumour mutations, or assessment of whether TKI treatment should be continued. In patients who underwent multiple rebiopsies, the result of the initial rebiopsy was selected. The clinical characteristics of the patients, including age, sex, smoking status, histology, mutational status, tumour size, previous treatment and efficacy of the previous treatment, were recorded. Tumour response was examined by CT and evaluated using the Response Evaluation Criteria for Solid Tumors V.1.0 (RESIST V.1.0).[15] The present study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University Hospital (IRB No. 12029). Informed consent was obtained from the patients.

Procedure of TBB

For TBB, a conventional flexible bronchoscope (BF-260, P260F, P290 or 1T240 Bronchovideoscope, Olympus, Tokyo, Japan) was used after spraying the pharynx with 2% xylocaine. Procedures were performed under conscious sedation with midazolam. TBB was performed under guidance with a radial ultrasound probe (UM-S20-17S, Olympus, Tokyo, Japan) and a guide sheath kit (K-201, Olympus, Tokyo, Japan) in patients with peripheral pulmonary lesions. A positive diagnostic result obtained by TBB was defined as malignancy determined on the basis of histological features that were adequate for mutational analysis or immunohistochemistry. Severe postprocedural complications were defined as those requiring invasive medical procedures or prolonged hospitalisation.

Statistical analysis

Correlations between patient characteristics and the success of rebiopsy were analysed using Fisher's exact test for categorical variables. All tests were two-sided, and differences were considered statistically significant at $p<0.05$. All of the statistical analyses were conducted using JMP V.10 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient characteristics

The clinical characteristics of the 109 patients are shown in table 1. The median age of the patients at the time of rebiopsy was 67 years (range 33–85 years), and 50 of the patients were men. One hundred and one patients had adenocarcinoma, and 59 patients had no smoking history. Sixty-two of the patients had epidermal growth factor receptor (EGFR) mutation, five had anaplastic lymphoma kinase (ALK) rearrangement, and 42 were negative for both EGFR and ALK anomaly. Rebiopsy was performed after first-line treatment in 61 patients, after second-line treatment in 24, and after third-line or further treatment in 24. The mean diameter of the target lesions for rebiopsy was 34.6 mm (range 10–89 mm). Ten patients had lung metastasis that was targeted for rebiopsy. Tumour or bronchial mucosal infiltration was visible on bronchoscopy in 25 patients, and invisible in 84 patients who had only peripheral lung lesions. The overall rate of response to the previous treatment before rebiopsy was 55.0%.

Results of rebiopsy and postprocedural complications

Adequate tumour samples were obtained from 88 patients, giving an overall diagnostic yield of 80.7% (figure 1A). Among these patients with positive diagnostic results, 64 were analysed by predesigned mutational testing and 24 by immunohistochemistry. In 21 patients, the tumour samples collected were inadequate. Although the pathological features of the specimens

Table 1 Patient characteristics

Patient characteristics	Number	Per cent
Age		
Median	67	
Range	33–85	
Sex		
Male	50	45.9
Female	59	54.1
Smoking status		
Never	59	54.1
Former/current	50	45.9
Histology		
Adenocarcinoma	101	92.7
Squamous cell carcinoma	8	7.3
Mutational status		
EGFR	62	56.9
ALK	5	4.6
Wild	42	38.5
Pretreatment line		
First	61	56.0
Second	24	22.0
Third or further	24	22.0
Tumour size (mm)		
Mean	34.6	
Range	10–89	

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.

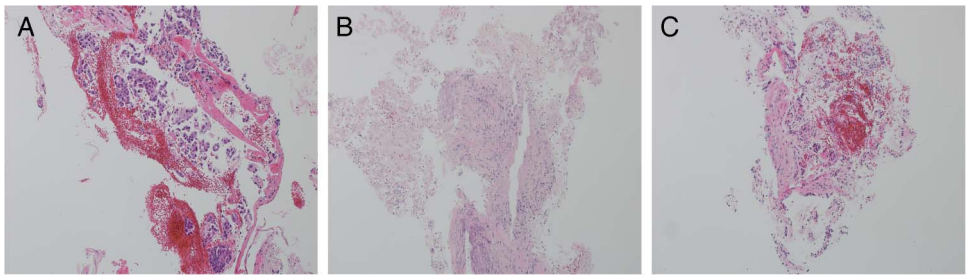

Figure 1 Pathological findings of rebiopsy. (A) Positive diagnostic result, showing tubular adenocarcinoma. (B) Negative diagnostic result, showing necrotic tissue without viable tumour cells. (C) Negative diagnostic result, showing fibrosis and infiltration of inflammatory cells.

Table 2 Results of rebiopsy and association between diagnostic yield and factors

Patient characteristics	Tissue obtained		p Value
	Success	Failure	
Age			
<70	51	13	0.81
≥70	37	8	
Sex			
Male	42	8	0.47
Female	46	13	
Smoking status			
Never	45	14	0.23
Former/current	43	7	
Histology			
Adenocarcinoma	82	19	0.65
Squamous cell carcinoma	6	2	
Mutational status			
EGFR/ALK	53	14	0.63
Wild	35	7	
Tumour size			
<30 mm	29	15	<0.01
≥30 mm	59	6	
Rebiopsy site			
Primary	80	19	1.00
Metastatic	8	2	
Previous treatment			
Platinum-based			
Received	63	14	0.79
Not received	25	7	
Antiangiogenesis agent			
Received	29	8	0.80
Not received	59	13	
Molecular targeting agent			
Received	48	14	0.34
Not received	40	7	
Response of last treatment			
CR/PR	50	10	0.47
SD/PD	38	11	

ALK, anaplastic lymphoma kinase; CR, complete response; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease.

suggested possible malignancy in four patients, these samples were inadequate for mutational analysis or immunostaining because of fragmentation or low numbers of cells. Furthermore, one patient had only a necrotic tissue without viable tumour cells (figure 1B). The specimen from the remaining patients showed normal lung tissue and fibrosis in 13 and 3 patients, respectively (figure 1C).

Postprocedural complications were observed in 12 cases. Four patients developed transient fever, and haemorrhage during the biopsy, requiring haemostasis, occurred in eight patients. However, none of these events required inpatient hospitalisation or prolongation of existing hospitalisation. There were no cases of pneumothorax or massive haemoptysis.

Association between diagnostic yield and clinicopathological features

The factors affecting the diagnostic yield of TBB for rebiopsy are shown in table 2. The diagnostic yield of TBB for mass lesions was significantly higher than that for nodular lesions (≥30 mm: 59 of 65 lesions; 90.1% vs <30 mm: 29 of 44 lesions; 65.9%, p<0.01). There was no significant correlation between diagnostic yield and other clinicopathological features including tumour mutational status, previous treatment and efficacy of the previous treatment before rebiopsy.

DISCUSSION

With the development of new therapeutic strategies for NSCLC, including next-generation EGFR-TKIs or blockade of immune checkpoints with monoclonal antibodies, the importance of rebiopsy has increased.[11–14] Any method for tissue collection in this setting should be reliable and safe. In the present study, we investigated TBB as a method for rebiopsy in patients with advanced NSCLC that had relapsed after systemic chemotherapy. We found that TBB had a high diagnostic yield of 80.7% and was not associated with severe complications. As far as we are aware, no previous study has investigated the utility of TBB for rebiopsy in NSCLC patients, or the factors influencing its diagnostic yield. Some previous studies have investigated the feasibility of rebiopsy in NSCLC patients. Chouaid *et al*[16] and Bosc *et al*[17] reported that an adequate tissue sample was obtained in 74.4% (61/82) and 89.7% (35/39) of cases, the proportions of patients undergoing TBB for rebiopsy being 52% (43/

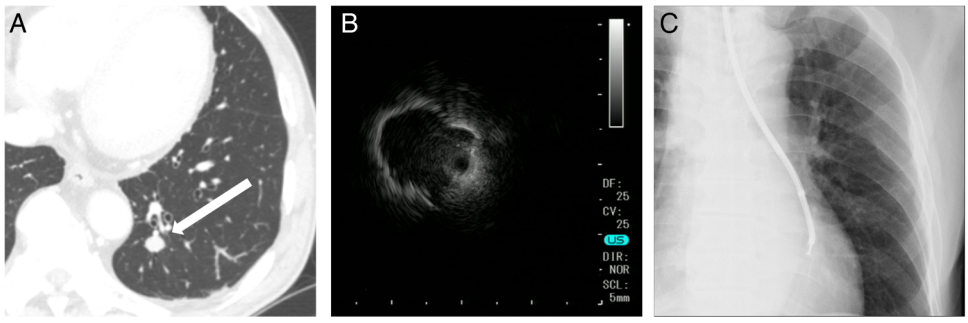

Figure 2 Successful tissue collection in patients with relapse of EGFR-positive adenocarcinoma after EGFR-TKI treatment. (A) Chest CT demonstrates a nodular lesion 12 mm in diameter in S10 of the left lung. (B) EBUS image shows a hypoechoic nodule with an irregular margin. (C) Transbronchial biopsy of the lesion detected by EBUS. EBUS, endobronchial ultrasound; EGFR, epidermal growth factor receptor.

82) and 28% (11/39), respectively. Yoon *et al*[18] reported a diagnostic yield of 80% (75/94) for chest CT-guided transthoracic lung biopsy, with a postprocedural serious complication rate of 14%. Although the present study was limited to only TBB, the diagnostic yield compared favourably with those of previous studies.

Recently, endobronchial ultrasound-guided TBB with a guide sheath (EBUS-GS) has been used to improve the diagnostic yield for small peripheral pulmonary lesions.[19–26] Wang Memoli *et al*[27] reported the results of a meta-analysis of diagnostic yield for several bronchoscopy modalities. The pooled diagnostic yield was 70% for all modalities, and the highest diagnostic yield for bronchoscopic evaluation (73.2%) appeared to be associated with the use of EBUS-GS. EBUS-GS-guided TBB was also shown to have a quite favourable safety profile, with a pneumothorax rate of 1.5% and no episodes of severe bleeding. Consistent with previous reports, we found that TBB had a high diagnostic yield, even for small peripheral pulmonary lesions, as long as the tumour was detectable by EBUS-GS (figure 2). Furthermore, there were no severe complications such as pneumothorax or serious haemorrhage. In comparison with core needle biopsy or surgical biopsy, which have higher accuracy for rebiopsy but are more invasive, TBB is a safer method with equivalent diagnostic ability.

We initially hypothesised that a dramatic reduction of tumour volume resulting from previous treatment might have a negative impact on the diagnostic yield of TBB. Use of the antiangiogenic agent bevacizumab for non-squamous cell NSCLC and molecular targeting inhibitors for EGFR/ALK-positive NSCLC has yielded relatively high response rates in comparison with conventional systemic chemotherapies.[5–9 28 29] We investigated the association between diagnostic yield and several factors, including the previous treatment regimen or response to the previous treatment before rebiopsy. However, the success of tissue collection by TBB was not associated with tumour mutational status, previous treatment or efficacy of the previous treatment before rebiopsy. Our findings indicated that in a rebiopsy setting, the diagnostic yield and safety profile of TBB are adequate.

This study had several limitations. First, the number of patients included was relatively small. Second, the information was collected retrospectively. Third, the indication of TBB for rebiopsy was determined by individual attending physicians. Also, as TBB was performed for pulmonary lesions considered to have sufficient tissue for biopsy based on CT findings, this may have resulted in selection bias.

In conclusion, we have demonstrated that TBB for rebiopsy of NSCLC that has relapsed after chemotherapy is not associated with severe complications and has a high diagnostic yield, regardless of tumour mutational status, previous treatment or efficacy of the previous treatment before rebiopsy. Our results suggest that TBB is one of the safest and most accurate procedures for rebiopsy, and can yield information useful for decision-making about possible next-line treatment.

Contributors HI and KA contributed to the study concept design and drafting of the manuscript. KY, NM, MN, TT, TK and TH contributed to data analysis and interpretation, study design, statistical analysis, and review of the manuscript. All authors had full access to the data of the study, take responsibility for the integrity and accuracy of data analysis, critically reviewed the manuscript, and approved the final version of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The present study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University Hospital (IRB number 12029).

Provenance and peer review Not commissioned; externally peer reviewed.

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