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Endobronchial ultrasound-guided re-biopsy of non–small cell lung cancer with acquired resistance after EGFR tyrosine kinase inhibitor treatment

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Abstract

Background: Few studies assessed the use of endobronchial ultrasound (EBUS)-guided re-biopsy for detecting the T790M mutation after epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) failure.

Methods: A total of 2996 EBUS procedures were performed during the study period (January 2019–June 2022). In total, 44 consecutive patients who underwent EBUS-guided re-biopsy (56 procedures) for detecting the T790M mutation were analyzed. The success rates and T790M mutation frequencies were analyzed according to the re-biopsy site and EBUS method. Multivariate logistic regression analyses were used to identify factors affecting the likelihood of the T790M mutation.

Results: The success rates for the mutation analyses using EBUS with a guide-sheath (EBUS-GS), EBUS guided transbronchial needle aspiration (EBUS-TBNA), and EBUS-GS with EBUS-TBNA for re-biopsy were 80.6% (29/36), 93.3% (14/15), and 100% (5/5), respectively. Patients who underwent lymph node biopsy using EBUS-TBNA had an increased rates of the T790M mutation compared with those undergoing lung biopsy using EBUS-GS (EBUS-TBNA, 60.0%; EBUS-GS with EBUS-TBNA, 40.0%; EBUS-GS, 11.1%; $p < 0.001$). In multivariate analysis, the use of a first-generation EGFR-TKI (odds ratio [OR], 4.29; 95% confidence interval [CI], 1.05–17.58; $p = 0.043$) was associated with occurrence of the T790M mutation. Re-biopsy of the metastatic site tended to be associated with a higher T790M mutation rate. Mild hemoptysis occurred in 3.6% (2/56) of the patients.

Conclusions: EBUS-guided re-biopsy can be used for detecting the T790M mutation in patients who failed EGFR-TKI therapy. The T790M mutation frequency differed according to the re-biopsy site. The use of a first-generation EGFR-TKI was an independent predictor of the T790M mutation.

KEYWORDS
bronchoscopy, re-biopsy, ultrasonography

INTRODUCTION

Lung cancer is a major cause of cancer-related deaths worldwide, including in Korea. According to the 2014 report of the Korean Association of Lung Cancer Registry, 45% of non–small cell lung cancer (NSCLC) patients had stage IV disease at the initial diagnosis, and 36.8% of stage IV adenocarcinomas harbored the epidermal growth factor receptor (EGFR) mutation. EGFR mutation-positive NSCLC patients have a better prognosis than wild-type EGFR patients.[1]

EGFR tyrosine kinase inhibitor (TKI) treatment produces favorable clinical responses in most patients

Kyung Soo Hong and Jinmo Cho contributed equally to this work.

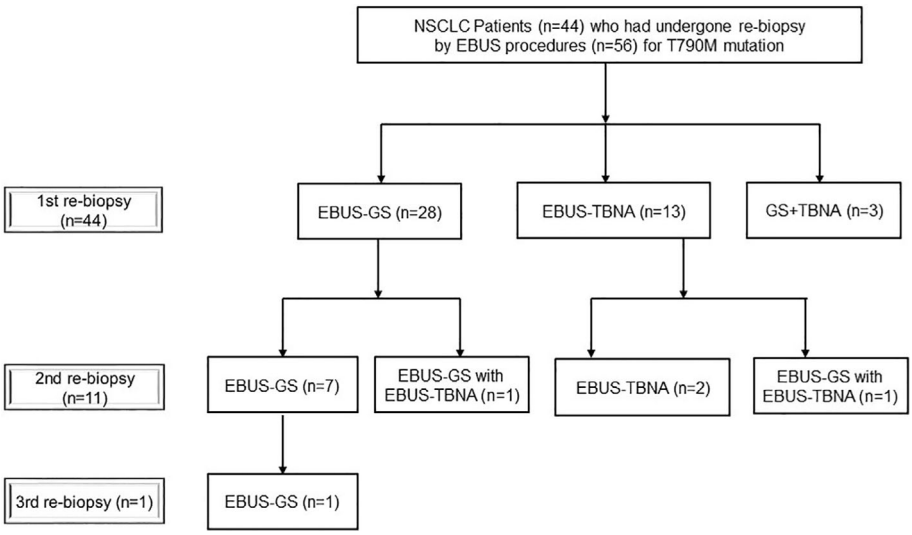

FIGURE 1 Study flowchart. EBUS, endobronchial ultrasound; EBUS-GS, EBUS with a guide sheath; EBUS-TBNA, EBUS-guided transbronchial needle aspiration; NSCLC, non–small cell lung cancer

who harbor the sensitizing EGFR mutation, prolonging survival. However, most patients develop resistance after 9–13 months.[2–4] Several mechanisms of acquired resistance to EGFR-TKIs have been reported, and about half of the resistance is attributed to the occurrence of the EGFR T790M mutation in exon 20.[5] Osimertinib, a third-generation EGFR-TKI, is selective for T790M resistance mutations and showed greater efficacy in patients with T790M-positive NSCLC in the AURA3 study.[6]

Among patients initially treated with first or second-generation EGFR-TKIs showing disease progression, progression-free survival was significantly longer in T790M-positive than T790M-negative cases at re-biopsy.[7] It is important to collect adequate cancer tissue to analyze the T790M mutation. Although percutaneous core needle biopsy has a high sample adequacy rate at re-biopsy, complications occur frequently.[8]

Endobronchial ultrasound with a guide sheath (EBUS-GS) and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) are widely used to obtain samples of peripheral pulmonary lesions and mediastinal and hilar lymph nodes, respectively.[9] However, only one previous study with a small number of patients focused on the efficacy and safety of EBUS-guided re-biopsy after failed EGFR-TKI therapy.[10] In this study, we evaluated the efficacy of EBUS-guided re-biopsy according to the re-biopsy site and identified factors affecting the likelihood of the T790M mutation.

METHODS

Study design, subjects, and equipment

We performed a retrospective observational study of 44 consecutive EGFR mutation (T790M)-positive NSCLC patients who underwent re-biopsy via EBUS procedures at Yeungnam University Hospital, a tertiary referral hospital in Daegu, South Korea, from January 2019 to June 2022. During the study period, 2996 EBUS procedures (1836 EBUS-GS and 1160 EBUS-TBNA) were performed. More specifically, EBUS-GS, EBUS-TBNA, or EBUS-GS with EBUS-TBNA was used according to the attending physicians' decision. Forty-four patients underwent their first re-biopsy. Second re-biopsies were performed in 11 T790M-negative patients at the initial re-biopsy. One patient underwent re-biopsy three times. Ultimately, data from 44 patients and 56 EBUS procedures were included in the analyses (Figure 1).

All bronchoscopic procedures were performed by three pulmonologists (K.S.H., J.G.J., and J.H.A.). All patients underwent thin-section chest computed tomography (CT) (0.75-mm slice thickness with a 0.75-mm interval; SOMATOM Definition AS 64-slice CT scanner; Siemens Healthcare).

EBUS-GS was performed to obtain cancer tissue from peripheral lesions. A 4-mm bronchoscope (BF P260F; Olympus) was used to reach the target lesion. After the lesion was detected using a radial probe (UM S20-17 S; Olympus), a bronchial brush and biopsy forceps were introduced into the GS, and brushings and biopsy specimens were collected without X-ray fluoroscopy. All EBUS-GS techniques were detailed previously.[9] EBUS-TBNA was performed to obtain cancer tissue from the mediastinal and hilar lymph nodes using a linear array ultrasonic bronchoscope (EB-1970UK; Pentax) and a single-use 22-gauge aspiration needle (SonoTip EBUS Pro Flex needle; Medi-Globe).

The re-biopsy success rate was defined as the number of EBUS procedures in which sufficient tumor tissue was acquired for the EGFR mutation test divided by the total number of EBUS procedures.

EGFR mutation analysis

Amplifiable DNA from cancer tissue was purified from formalin-fixed paraffin-embedded sections of tumor tissues using the Maxwell CSC DNA FFPE kit (Promega). EGFR

mutations were detected by real-time polymerase chain reaction assay, performed using the PANAMutyper EGFR Mutation Detection Kit (Panagene).

Statistical analyses

Continuous variables are expressed as medians (range). Categorical variables were compared using the χ^2 or Fisher's exact tests and are described as frequencies (percentages). Univariate and multivariate logistic regression analyses including factors with p-values <0.1 in univariate analyses were performed, to identify predictors of the T790M mutation. In all analyses, a two-tailed p-value <0.05 was considered significant. All statistical procedures were performed with SPSS software (version 24.0; IBM).

Ethics statement

This study followed the tenets of the Declaration of Helsinki, and the study protocol was reviewed and approved by the institutional review board of Yeungnam University Hospital (Yeungnam University Hospital IRB 2022-09-057). The requirement for informed consent was waived because of the retrospective study design.

RESULTS

Baseline characteristics and EGFR mutation profiles

The baseline demographic and clinical characteristics of the 44 patients are listed in Table 1. Their median age was 60 years, and 31 (70.5%) patients were women. Forty-two (95.4%) patients were histologically diagnosed with adenocarcinoma, and 16 (36.4%) had brain metastasis at the initial diagnosis. Twenty (45.4%) and 23 (52.3%) patients harbored the activating EGFR exon 19 deletion and exon 21 L858R mutations, respectively. Of the 44 patients, three had received erlotinib, 17 had received gefitinib, and 24 had received afatinib as their initial EGFR-TKI regimens.

The EGFR mutation was initially detected in 44 cases (exon 19 deletion in 20, exon 19 insertion in one, and exon 21 L858R mutation in 23). Twelve patients harbored the T790M mutation at the first re-biopsy, and three harbored the T790M mutation at the second re-biopsy. A total of 15 (34.1%) patients harbored the T790M mutation (Table 2).

TABLE 1 Patient demographic and clinical characteristics ($n = 44$)

Characteristic	
Patients	
Age, years	60 (42–85)
Sex	
Male	13 (29.5)
Female	31 (70.5)
Smoking status	
Never smoker	28 (63.6)
Ex-smoker	8 (18.2)
Current smoker	8 (18.2)
Histology	
Adenocarcinoma	42 (95.4)
Adenosquamous cell carcinoma	1 (2.3)
Non–small cell lung cancer, NOS	1 (2.3)
Stage	
IIIA	5 (11.3)
IIIB	1 (2.3)
IIIC	1 (2.3)
IV	37 (84.1)
Brain metastasis	16 (36.4)
Initial EGFR mutation profile	
Exon 19 del	20 (45.4)
Exon 19 ins	1 (2.3)
Exon 21 L858R	23 (52.3)
Initial EGFR-TKI regimen	
Erlotinib	3 (6.8)
Gefitinib	17 (38.6)
Afatinib	24 (54.5)
EGFR-TKI days	404 (82–1305)
Diagnosis to re-biopsy days	498 (130–2142)
Best response of EGFR-TKI	
PR	35 (79.5)
SD	8 (18.2)
PD	1 (2.3)

Note: Data are presented as median (range) or number (%).
Abbreviations: EGFR, epidermal growth factor receptor; NOS, not otherwise specified; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Diagnostic performance, re-biopsy success, and T790M mutation rates

Table 3 shows the diagnostic performance of EBUS-guided re-biopsy, and Table 4 shows the re-biopsy success and T790M mutation rates according to the EBUS method and biopsy site.

Thirty-six patients underwent EBUS-GS, 15 underwent EBUS-TBNA, and five underwent EBUS-GS with EBUS-TBNA for re-biopsy. The success rates of mutation analyses using EBUS-GS, EBUS-TBNA, and EBUS-GS with EBUS-TBNA for re-biopsy were 80.6% (29/36), 93.3% (14/15), and 100% (5/5), respectively. Patients who underwent EBUS-TBNA for lymph node biopsy had higher rates of T790M mutation compared with those who underwent EBUS-GS lung biopsy (EBUS-TBNA, 60.0%; EBUS-GS with EBUS-TBNA, 40.0%; EBUS-GS, 11.1%; $p < 0.001$). The rate of

TABLE 2 EGFR mutation profiles

Initial EGFR mutation profile ($n = 44$)		EGFR mutation profile on re-biopsy ($n = 56$)	1st re-biopsy ($n = 44$)	2nd re-biopsy ($n = 11$)	3rd re-biopsy ($n = 1$)
19 del	20	19 del alone	12	3	
		19 del + T790M	5	2	
		Re-biopsy failure	2	1	
		Wild-type	1		
19 ins	1	Wild-type	1		
21 L858R	23	L858R alone	8	2	1
		L858R + T790M	7	1	
		19 del	1		
		Re-biopsy failure	3	2	
		Wild-type	4		
T790M mutation rate, *n* (%)			12 (27.3)	3 (27.3)	0 (0)

Abbreviation: EGFR, epidermal growth factor receptor.

TABLE 3 Diagnostic performance of EBUS-guided re-biopsy

Parameter	EBUS-GS ($n = 36$)	EBUS-TBNA ($n = 15$)	EBUS-GS with EBUS-TBNA ($n = 5$)	Overall ($n = 56$)
True-positive, *n*	29	14	5	48
True-negative, *n*	0	0	0	0
False-positive, *n*	0	0	0	0
False-negative, *n*	7	1	0	8
Sensitivity, %	80.56	93.33	100	85.71
Specificity, %	Unmeasurable	Unmeasurable	Unmeasurable	Unmeasurable
PPV, %	100	100	100	100
NPV, %	0	0	0	0
No. of core tissues obtained by forceps	7 (4–20)		8 (7–10)	8 (4–20)
No. of core tissues obtained by needle		2 (1–6)	2 (1–3)	2 (1–6)

Note: Data are presented as number, %, or median (range).
Abbreviations: EBUS, endobronchial ultrasound, GS, guide-sheath, NPV, negative predictive value, PPV, positive predictive value, TBNA, transbronchial needle aspiration.

TABLE 4 Re-biopsy success and T790M mutation rates according to the EBUS method and biopsy site ($n = 56$)

	Total ($n = 56$)	%	Success ($n = 48$)	%	*p*-value	T790M ($n = 15$)	%	*p*-value
Site of re-biopsy								
Lung	36	64.3	29	80.6	0.399	4	11.1	0.001
Lymph node	15	26.8	14	93.3		8	60.0	
Lung with lymph node	5	8.9	5	100		3	40.0	
EBUS methods								
EBUS-GS	36	64.3	29	80.6	0.399	4	11.1	0.001
EBUS-TBNA	15	26.8	14	93.3		8	60.0	
EBUS-GS with EBUS-TBNA	5	8.9	5	100		3	40.0	
Re-biopsy sites (primary vs. metastatic)								
Primary	34	60.7	28	82.4	0.840	4	11.8	0.003
Metastatic	18	32.1	16	88.9		10	55.6	
Primary with metastatic	4	7.1	4	100.0		1	25.0	

Abbreviations: EBUS, endobronchial ultrasound, GS, guide-sheath, TBNA, transbronchial needle aspiration.

T790M mutation was highest in metastatic lesions, followed by primary lesions with metastasis and primary lesions (11.8, 55.6% and 25.0%, respectively; $p < 0.001$). Case series of patients who were T790M negative at first re-biopsy, but T790M positive on additional re-biopsy are shown in Table 5.

TABLE 5 Case series of patients who were T790M negative at first re-biopsy, but T790M positive on additional re-biopsy ($n = 3$)

	First re-biopsy				Second re-biopsy				
Case	Method	Site	Biopsy result	T790M result	Method	Site	Biopsy result	T790M result	Different lesion from the first re-biopsy
1	EBUS-TBNA	LN	ADC (a few cancer cells)	Negative	EBUS-TBNA	LN	ADC	Positive	No
2	EBUS-GS	Lung	ADC	Negative	EBUS-GS with EBUS-TBNA	Lung, LN	ADC	Positive	Yes
3	EBUS-GS	Lung	ADC (a few cancer cells)	Negative	EBUS-GS	Lung	ADC	Positive	Yes

Abbreviations: ADC, adenocarcinoma, EBUS, endobronchial ultrasound, GS, guide-sheath, LN, lymph node, TBNA, transbronchial needle aspiration.

TABLE 6 Multivariate analyses of factors affecting the occurrence of T790M mutation ($n = 44$)

			Univariate analyses		Multivariate analyses	
	T790M positive ($n = 15$)	T790M negative ($n = 29$)	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age, years	60 (42–78)	69 (45–85)		0.393		
Male	3 (20.0%)	10 (34.5%)	0.48 (0.11–2.08)	0.488		
Smoking status						
Never smoker	9 (60.0%)	19 (65.5%)	0.79 (0.22–2.86)	0.718		
Current or ex-smoker	6 (40.0%)	10 (34.5%)				
Initial EGFR mutation profile						
19 del	8 (53.3%)	12 (41.3%)	1.62 (0.46–5.68)	0.450		
Others	7 (46.7%)	17 (58.6%)				
Brain metastasis				0.105		
Yes	3 (20.0%)	13 (44.8%)	0.31 (0.71–1.33)			
No	12 (80.0)	16 (55.2%)				
Initial EGFR-TKI regimen						
1st generation (erlotinib, gefitinib)	10 (66.7%)	10 (34.5%)	3.80 (1.02–14.21)	0.042	4.29 (1.05–17.58)	0.043
2nd generation (afatinib)	5 (33.3%)	19 (65.5%)				
Best response				1.000		
PR	12 (80.0%)	23 (79.3%)				
SD	3 (20.0%)	5 (17.2%)				
PD	0 (0.0%)	1 (3.4%)				
EGFR-TKI days	400 (242–1069)	405 (82–1305)		0.656		
Diagnosis to re-biopsy days	485 (276–2142)	510 (130–1834)		0.544		
No. of repeat biopsies						
1	11 (73.3%)	22 (75.9%)	0.88 (0.21–3.64)	1.000		
≥2	4 (26.7%)	7 (24.1%)				
Re-biopsy sites						
Metastatic	8 (53.3%)	7 (24.1%)	3.59 (0.96–13.50)	0.053	4.10 (0.98–17.11)	0.053
Primary only	7 (46.7%)	22 (75.9%)				

Abbreviations: EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Factors affecting the likelihood of the T790M mutation

We investigated factors affecting the likelihood of the T790M mutation (Table 6). Univariate analyses revealed that the use of a first-generation EGFR-TKI (odds ratio [OR], 3.80; 95% confidence interval [CI], 1.02–14.21; $p = 0.042$) was associated with occurrence of the T790M mutation. Re-biopsy of the metastatic site (OR, 3.59; 95% CI, 0.96–13.50; $p = 0.053$) tended to increase the T790M

mutation rate. Multivariate analysis revealed that the use of a first-generation EGFR-TKI (OR, 4.29; 95% CI, 1.05–17.58; $p = 0.043$) was associated with occurrence of the T790M mutation. Re-biopsy of the metastatic site (OR, 4.10; 95% CI, 0.98–17.11; $p = 0.053$) tended to increase the T790M mutation rate.

Complications

Among the 44 patients who underwent EBUS-GS and/or EBUS-TBNA (56 procedures), two had mild hemoptysis that spontaneously resolved with supportive care (3.6%).

DISCUSSION

This study confirmed that EBUS-guided re-biopsy for detecting the T790M mutation is a useful diagnostic method for patients who failed EGFR-TKI therapy. The success rates for mutation analyses using EBUS-GS, EBUS-TBNA, and EBUS-GS with EBUS-TBNA for re-biopsy were 80.6%, 93.3%, and 100%, respectively. Patients who underwent lymph node biopsy using EBUS-TBNA showed higher rates of T790M mutation compared with those who underwent lung biopsy using EBUS-GS. The use of a first-generation EGFR-TKI was associated with occurrence of the T790M mutation, and re-biopsy of the metastatic site showed a trend toward an association with a higher T790M mutation rate. Complication rates (mild hemoptysis in 3.6% of patients) were acceptable. To the best of our knowledge, this is the largest study to analyze the use of EBUS-guided re-biopsy in patients with EGFR-TKI failure.

The importance of re-biopsy after EGFR-TKI treatment is increasing because T790M mutation-positive patients exhibited improved survival compared with T790M mutation-negative patients in several studies.[7,11] Clinically, third-generation EGFR-TKIs, such as osimertinib and lazertinib, show promise in patients with progressive T790M mutation-positive NSCLC after EGFR-TKI treatment.[6,12] Percutaneous core needle biopsy of the lung lesion is widely used to obtain an adequate sample to analyze the T790M mutation. One meta-analysis including five studies showed that the pooled adequacy rate of samples was 86.92%, and the pooled T790M detection rate was 46.0%. However, complication rates of up to 20% have been reported.[8]

EBUS-TBNA has been widely used for sampling mediastinal and hilar lymph nodes. The sensitivity, specificity, and accuracy of EBUS-TBNA for diagnosing malignant lymph nodes are 95.7%, 100%, and 97.1%, respectively.[13,14] There has been little research on the use of EBUS-TBNA for detecting the T790M mutation. One study focusing on the role of EBUS for re-biopsy after EGFR-TKI failure enrolled 44 patients undergoing nine EBUS-TBNA procedures. The success of re-biopsy using EBUS-TBNA was 100% (9/9) by cytology and 88.9% (8/9) by histology. The T790M mutation rate for EBUS-TBNA was not analyzed in that study and there were no severe complications.[10] Another study focusing on the usefulness of bronchoscopic re-biopsy investigated 139 patients who underwent bronchoscopic re-biopsy and EBUS-TBNA. Successful pathological diagnoses were made in 102 (73.4%) patients and 18 (43.9%) of the 41 EGFR mutant adenocarcinoma patients were positive for the T790M mutation. In that study, 16 EBUS-TBNA procedures were done, but the rates of diagnostic success and T790M mutation were not analyzed.[15] Hong et al.[7] reported 14 EBUS-TBNA re-biopsy cases; the re-biopsy success rate was 78.6% (11/14) and the T790M mutation rate was 42.9% (6/14). There were no complications.[7]

Only one study used EBUS-GS, Izumo et al.[10] enrolled 44 patients undergoing 44 EBUS-GS procedures. In that study, the success of re-biopsy using EBUS-GS was 72.7% (32/44) by cytology and 75.0% (33/44) by histology. There were no severe complications. Factors affecting diagnostic success were a central location and acquisition of an EBUS image within the lesion. The T790M mutation rate was not analyzed by EBUS-GS, but was 41.5% according to EBUS-TBNA/EBUS-GS (22/53).[10] In our study, the success rates of EBUS-GS (80%), EBUS-TBNA (93.3%), and EBUS-GS with EBUS-TBNA (100%) re-biopsy were similar or superior to other studies, and the complication rates were low. However, the T790M mutation rate (34.1%, 15/44) was lower than in other studies. A meta-analysis revealed that T790M was more frequent in the exon 19 deletion than L858R among patients with acquired resistance to EGFR-TKIs.[16] Therefore, the low T790M mutation rates in our study are thought to be because of the relatively small proportion of patients with the exon 19 deletion (45.4%) in our study compared to other studies (56.1%–58%).[7,10,15]

The pharmacological profiles of first- and second-generation EGFR-TKIs are different, which leads to different clonal acquired resistance mechanisms.[17] One retrospective study analyzed the T790M mutation in cases with disease progression using cell-free DNA, according to the generation of EGFR-TKIs. In that study, T790M-positive clones were more frequently seen in patients taking first- (79%) than second-generation EGFR-TKIs (34%).[18] In our study, the use of a first-generation EGFR-TKI (50.0%) resulted in a higher frequency of the T790M mutation than use of a second-generation EGFR-TKI (20.8%).

In our study, re-biopsy of the metastatic site tended to result in a higher T790M mutation rate. EBUS-TBNA showed a trend of higher re-biopsy success rates, however it was not significant. Patients who underwent EBUS-TBNA for lymph node biopsy showed significant higher rates of T790M mutation. Therefore, in addition to the factors of higher re-biopsy success rates, it is thought that the characteristics of metastatic site itself are related with the expression of T790M mutation. A previous study also showed that re-biopsy at the metastatic site was associated with a higher likelihood of harboring the T790M mutation. Heterogeneity between the primary and metastatic lesions could explain this result.[19] Another study showed that re-biopsy of a metastatic mediastinal lymph node resulted in

a trend toward a higher T790M mutation rate compared with the primary tumor in multivariate analysis (63.6% vs. 36.7%, $p = 0.123$).[15] As there have been few studies in which lesions were related to a high T790M mutation rate, further studies are needed.

Among the 11 patients who were T790M negative at first re-biopsy and had undergone repeated re-biopsy, three patients showed T790M positive (Table 5). Of the three patients, two showed a few cancer cells in the first re-biopsy, and second re-biopsy showed sufficient cancer cells with T790M positive. If sufficient cancer cells are not obtained for genetic testing at first re-biopsy, repeated re-biopsy can be helpful. Additionally, two of the three patients had undergone second re-biopsy in different lesion from the first re-biopsy. Considering the tumor heterogeneity, it is helpful to get tissue in diverse locations at repeated re-biopsy.

This study had several limitations. First, because it was a retrospective study conducted at a single center, selection bias cannot be ruled out. Re-biopsy methods and sites can differ between institutions depending on the protocols and facilities. Our study focused on the use of EBUS during re-biopsy. Second, the T790M mutation rates were somewhat lower than in other studies; patients who harbor T790M-negative tissue may become plasma T790M-positive as the disease progresses. Third, EGFR mutation analyses were performed by mixing EBUS-GS tissue and EBUS-TBNA tissues in our center. Mixing tissues can increase the diagnosis rate of EGFR, but it is impossible to clearly describe in which site of biopsy was positive for T790M. Nevertheless, our study highlights that EBUS-guided re-biopsy techniques are accurate and safe for detecting the T790M mutation.

CONCLUSIONS

The use of EBUS re-biopsy to detect the T790M mutation proved accurate and safe for patients showing progressive disease after EGFR-TKI therapy. T790M mutation frequencies differed according to the re-biopsy site. The use of a first-generation EGFR-TKI was an independent predictor of the T790M mutation.

AUTHOR CONTRIBUTIONS

Conceptualization: June Hong Ahn. Data curation: Kyung Soo Hong, Jinmo Cho, Jong Geol Jang, Min Hye Jang, and June Hong Ahn. Investigation: Kyung Soo Hong, Jinmo Cho, and June Hong Ahn. Supervision: Kyung Soo Hong, Jinmo Cho, Jong Geol Jang, Min Hye Jang, and June Hong Ahn. Writing–original draft: Kyung Soo Hong and June Hong Ahn. Writing–review and editing: June Hong Ahn.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted following the tenets of the Declaration of Helsinki, and the study protocol was reviewed and approved by the institutional review board of Yeungnam University Hospital (Yeungnam University Hospital IRB 2022–09-057). The requirement for informed consent was waived because of the retrospective study design.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data set supporting the conclusions of this article is available from the corresponding author on reasonable request.

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