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Lung Cancer

Safety and Success of Repeat Lung Needle Biopsies in Patients with Epidermal Growth Factor Receptor-Mutant Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Molecular targeted therapy • Disease progression • Needle biopsy • Complications

Abstract

Background. Postprogression repeat biopsies are critical in caring for patients with lung cancer with epidermal growth factor receptor (*EGFR*) mutations. However, hesitation about invasive procedures persists. We assessed safety and tissue adequacy for molecular profiling among repeat postprogression percutaneous transthoracic needle aspirations and biopsies (rebiopsies).

Materials and Methods. All lung biopsies performed at our hospital from 2009 to 2017 were reviewed. Complications were classified by Society of Interventional Radiology criteria. Complication rates between rebiopsies in *EGFR*-mutants and all other lung biopsies (controls) were compared using Fisher's exact test. Success of molecular profiling was recorded.

Results. During the study period, nine thoracic radiologists performed 107 rebiopsies in 75 *EGFR*-mutant patients and 2,635 lung biopsies in 2,347 patients for other indications. All biopsies were performed with computed tomography guidance, coaxial technique, and rapid on-site pathologic evaluation (ROSE). The default procedure was to take 22-gauge fine-needle aspirates (FNA) followed by 20-gauge tissue cores. Minor complications occurred in 9 (8.4%) rebiopsies and 503 (19.1%; $p = .004$) controls, including pneumothoraces not requiring chest tube placement (4 [3.7%] vs. 426 [16.2%] in rebiopsies and controls, respectively; $p < .001$). The only major complication was pneumothorax requiring chest tube placement, occurring in zero rebiopsies and 38 (1.4%; $p = .4$) controls. Molecular profiling was requested in 96 (90%) rebiopsies and successful in 92/96 (96%).

Conclusion. At our center, repeat lung biopsies for postprogression molecular profiling of *EGFR*-mutant lung cancers result in fewer complications than typical lung biopsies. Coaxial technique, FNA, ROSE, and multiple 20-gauge tissue cores result in excellent specimen adequacy. ***The Oncologist*** 2019;24:1570–1576

Implications for Practice: Repeat percutaneous transthoracic needle aspirations and biopsies for postprogression molecular profiling of epidermal growth factor receptor (*EGFR*)-mutant lung cancer are safe in everday clinical practice. Coaxial technique, fine-needle aspirates, rapid on-site pathologic evaluation, and multiple 20-gauge tissue cores result in excellent specimen adequacy. Although liquid biopsies are increasingly used, their sensitivity for analysis of resistant *EGFR*-mutant lung cancers remains limited. Tissue biopsies remain important in this context, especially because osimertinib is now in the frontline setting and *T790M* is no longer the major finding of interest on molecular profiling.

Introduction

Tyrosine kinase inhibitors (TKIs) have transformed the treatment of non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (*EGFR*) mutations and are the recommended first-line treatment for *EGFR*-mutant patients [1–3]. However, selective pressure imposed by TKIs unavoidably leads to drug resistance via outgrowth of preexisting resistant subclones or new mutations within the molecular target or bypass pathways [4]. Therefore, repeat molecular profiling is recommended to select the most appropriate therapy tailored to specific secondary aberrations [5].

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Although noninvasive molecular profiling based on plasma-derived circulating tumor DNA (ctDNA) has recently been developed, its most proven role in assessing acquired resistance to date is in testing for *T790M*, a mutation that will be less impactful moving forward because the *T790M*-inhibitor osimertinib is now standard of care for first-line therapy and *T790M* is not expected to develop in this scenario [3, 5–7]. Therefore, percutaneous transthoracic fine-needle aspiration and core biopsy (PTNAB) for postresistance molecular profiling of *EGFR*-mutant NSCLC (hereafter, rebiopsy) remains of great interest.

Our Thoracic Interventional Radiology practice at Massachusetts General Hospital currently performs approximately 400 percutaneous lung biopsies annually and has been doing repeat lung biopsies for molecular testing in patients with *EGFR*-mutant lung cancer with acquired resistance for more than 8 years. We sought to evaluate complications, technical success, and tissue adequacy for molecular profiling of rebiopsies in *EGFR*-mutant patients and to compare this with typical lung biopsies within our practice.

Materials and Methods

The institutional review board approved this retrospective study. All consecutive PTNAB procedures performed at Massachusetts General Hospital between January 2009 and December 2017 were reviewed: Those that were performed for molecular re-evaluation in patients with an established diagnosis of *EGFR*-mutant NSCLC and at least one previous PTNAB documented in the electronic medical record were included in the rebiopsy cohort, and PTNAB cases performed for other indictions were considered controls.

Data Collection and Definitions

Age and gender were retrospectively abstracted from the medical record for all subjects. Complication rates were extracted from a prospectively maintained departmental database. Complications were classified as major (including all cases that required a medical intervention greater than observation; hospitalization; unplanned increase in level of care; permanent adverse sequelae; death) or minor (all others) [8].

For the rebiopsy/case cohort, procedural details were also collected and included target lesion characteristics and lung parenchyma along the needle trajectory, which were classified on pre- and intraprocedural computed tomography (CT) images according to the Fleischner Society glossary of terms by a fellowship-trained radiologist with 5 years of experience in thoracic interventions (F.J.F.) [9]. Lesion size, aerated lung traversed [10], shortest skin-to-target distance [11], and needle-pleural angle [12] were measured with electronic calipers. If present on postprocedural chest radiographs (CXR), pneumothorax size was measured at the largest separation between the visceral and parietal pleura. Procedures were considered to be technically successful if the biopsy needle was placed into the target lesion (radiologic assessment) and cells were harvested (pathologic assessment). Histopathology diagnosis and success of molecular profiling were abstracted from the pathology report.

Biopsy Technique and Periprocedural Management

The performing radiologist had prospectively determined the feasibility of each rebiopsy and control biopsy after review of CT examinations and the medical record. Rebiopsy cases selectively favored lesions that were growing despite current therapy and safe for tissue sampling, with a high likelihood of yielding enough tissue for molecular analysis based on size and imaging features [13]. If extrathoracic targets were available, these were favored over lung lesions if there was a risk for pneumothorax. According to institutional practice, accepted coagulation parameters included platelet levels of at least 100,000/μL and an international normalized ratio of prothrombin time lower than 1.5. A combination of fentanyl and midazolam was administered intravenously (moderate sedation) unless contraindicated or refused.

All biopsy procedures were performed under conventional CT image guidance (Advantage; GE Healthcare, Chicago, IL) with the following techniques, all of which comprise our standard operating procedures in order to minimize the risk of complications. Coaxial technique with a 19-gauge thin-walled introducer needle (Chiba; Cook Medical, Bloomington, IN or Bard Biopsy Systems, Tempe, AZ), a 22-gauge needle for fine-needle aspiration (Chiba; Cook Medical), and a 20-gauge spring-loaded core biopsy device (Bard Mission; Bard Biopsy Systems or Temno Evolution; Merit Medical Systems, South Jordan, UT) was used [13]. The shortest suitable transthoracic needle trajectory was chosen, while avoiding crossing of pleural fissures and large vessels [13]. Patients were placed in a supine, prone, or lateral decubitus position, depending on target lesion location [13]. The skin entry site was marked with indelible ink and cleaned with antiseptic solution. The introducer needle was advanced in small increments through chest wall soft tissues. The introducer needle was aligned with the target before puncturing the pleura with a single deliberate motion. Once in the lung, readjustments were made without retracting the needle beyond the pleura.

After advancing the needle into the lesion, fine-needle aspirates (FNA) for slides were obtained and handed to an on-site cytopathologist, who immediately evaluated the specimens for diagnostic adequacy (rapid on-site pathologic evaluation [ROSE]). Additional FNAs were submitted in saline to be processed as a paraffin-embedded cellblock. Once tumor was confirmed on slides, 20-gauge tissue core samples were obtained. The number of cores acquired varied depending on the clinical judgement of the operator and the needs for standard and/or research tests for the patients. Tissue cores were preserved in formalin and sent to pathology for standard processing (hematoxylin and eosin staining, with immunohistochemistry as needed). Molecular testing (SNaPshot; Archer, Boulder, CO) was performed on either tissue cores or the cellblock obtained from FNAs.

In the event that a small pneumothorax was detected during the procedure, air was aspirated from the pleural space during removal of the introducer needle. Immediately after needle removal, patients were transferred to a stretcher and positioned puncture-site-down. Patients were monitored in this position and received nasal oxygen for at least 3 hours in the radiology recovery unit. CXRs were obtained in puncture-site-down position at 1 hour and upright at 3 hours after the procedure to assess for delayed pneumothorax. Following uneventful recovery, patients were discharged home in the care of an escort. As per institutional protocol, all patients

who either lived alone or lacked support at home, traveled from out of state, or had severe comorbidities were observed for 23 hours following the procedure. Occasional deviations from this standard procedure protocol are detailed in Results.

Statistical Analysis

Complication rates of *EGFR*-mutant rebiopsy cases were compared with those of lung biopsies for other indications. Fisher's exact test was used to assess for differences between groups with regard to pneumothorax, chest tube placement, and hemoptysis. Statistical analyses were performed with STATA software (version 13.0; StataCorp, College Station, TX). A type-I error rate of 5% was used for all hypothesis tests. Descriptive statistics were reported as mean ± SD for normally distributed data and as median and interquartile range for non-normally distributed data, as appropriate.

Results

A total of 2,742 consecutive CT-guided PTNAB procedures were performed by a group of nine thoracic radiologists with 1–29 years of experience in image-guided thoracic interventions between January 2009 and December 2017. Of these procedures, 107 performed in 75 patients constituted the rebiopsy/case cohort (Fig. 1). Rebiopsies included second, third, fourth, and even fifth biopsies, with two thirds of procedures being second-time biopsies. The control group included 2,635 biopsies performed in 2,347 patients. Patients in the rebiopsy cohort were 62% female with a median age of 60 (54–67) years, whereas patients in the control group were 53% female with a median age of 68 (58–76) years (Table 1).

Rebiopsy Cohort

Lesions targeted for rebiopsy were located in all lobes of the lung as well as pleura and were predominantly solid (Table 2). The smallest biopsied lesion measured 13 mm in maximum diameter. Pleural thickening was present in 23 cases, accompanied by a small pleural effusion in 7 instances. Only a minority of biopsied lungs demonstrated scarring from prior resection or radiation therapy. All but one patient underwent the procedure as an outpatient; one patient was an inpatient at the time of rebiopsy. Trainees were involved in 55 of 107 rebiopsies (51.4%), but it was a different trainee in nearly every case. Moderate sedation was administered for all but one procedure, which was performed using only local anesthesia at the patient's request. In 90 of 107 procedures, the same lobe was targeted during rebiopsy. In 15 of 107 rebiopsies, the target was in a different lobe on the same side, whereas the target was in a contralateral lobe in 2 of 107 procedures. The pleura was punctured only once during each procedure except for one case requiring placement of two 19-gauge introducer needles to manage an intraprocedural pneumothorax. Aerated lung was traversed in 70 of 107 cases (65.4%) and free of emphysema along the needle path in all but 3 instances. FNAs were obtained in all cases. Tissue cores were obtained in 104 of 107 cases (97.2%) and omitted in 3 cases for patient safety concerns (target lesion abutting large vessels and intractable coughing following fine-needle aspiration). Additional procedural details may be found in supplemental online Table 1.

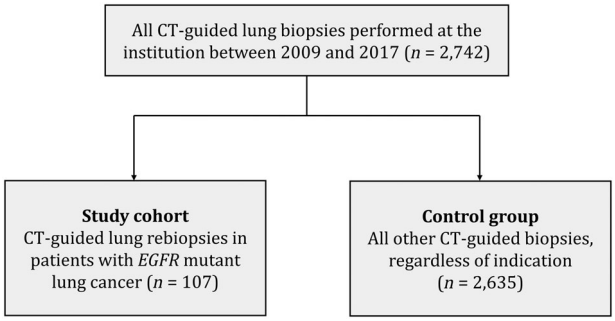

Figure 1. Consolidated Standards of Reporting Trials diagram of patient selection.
Abbreviations: CT, computed tomography; *EGFR*, epidermal growth factor receptor.

Table 1. Characteristics of patients in rebiopsy cohort at time of each procedure

Characteristics	*n* = 107
Age, median (IQR), years	60.0 (54–67)
Gender, *n* (%)	
Male	41 (38)
Female	66 (62)
Smoking status, *n* (%)	
Never	72 (67)
Former smoker	35 (33)
Number of previous lung biopsies, *n* (%)[a]	
1	71 (66)
2	26 (24)
3	8 (8)
4	2 (2)
Time interval between biopsies, median (IQR), months	10.4 (3.3–21.5)
ECOG performance status at time of procedure, *n* (%)	
0	40 (37)
1	53 (50)
2	14 (13)

[a]Including documented first-time biopsies and rebiopsies at outside institutions.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Complications

Minor complications occurred in 9 (8.4%) rebiopsy cases and 503 (19.1%) controls (Table 3). The rebiopsy minor complications included four postprocedural pneumothoraces that remained subcentimeter on serial CXR and did not require intervention, and mild hemoptysis in five patients, which also did not require intervention. Rebiopsies did not result in any major complications, air embolus, or death. In the control group, minor complications included 426 postprocedural pneumothoraces that required chest tube placement in 38 instances. Hemoptysis occurred in 77 instances. There were no instances of death or clinically significant air embolus in the control group.

Compared with controls, the pneumothorax rate was significantly lower in the rebiopsy cohort (3.7% vs. 16.2%,

Table 2. Characteristics of lesions and lung targeted for rebiopsy

Characteristics	*n* = 107
Target lesion location, *n* (%)	
Left lower lobe	31 (29)
Left upper lobe	22 (21)
Right lower lobe	21 (12)
Right middle lobe	6 (6)
Right upper lobe	23 (22)
Left lung (extending across major fissure)	1 (1)
Pleura	3 (3)
Target lesion characteristics	
Consistency	
Solid, *n* (%)	101 (94)
Consolidation, *n* (%)[a]	4 (4)
Ground glass, *n* (%)	2 (2)
Size, median (IQR), mm	
Long axis	37 (26–53)
Short axis	28 (20–44)
Distance from pleura, median (IQR), mm	2 (0–9)
Emphysma along needle trajectory, *n* (%)	
No	67 (63)
Yes	3 (3)
No aerated lung traversed	37 (35)
Pleural abnormalities, *n* (%)	
No	75 (70)
Pleural thickening only	16 (15)
Pleural effusion only	9 (8)
Both pleural effusion and pleural thickening	7 (7)
Prior surgery or radiation to biopsied lung, *n* (%)	16 (15)

[a]Consolidation is defined as a parenchymal opacity with air bronchograms.
Abbreviation: IQR, interquartile range.

Table 3. Lung biopsy complication rates, rebiopsies versus controls

Complication	Rebiopsies (*n* = 107)	Controls (*n* = 2,635)	*p* value (Fisher's)
Postprocedural pneumothorax, *n* (%)[a,b]	4 (4)	426 (16)	<.001
Chest tube placement, *n* (%)[a]	0 (0)	38 (1)	.401
Hemoptysis (mild), *n* (%)	5 (5)	77 (3)	.251
Air embolus, *n* (%)	0 (0)	0 (0)	-
Death, *n* (%)	0 (0)	0 (0)	-

[a]One patient was referred for lung biopsy with a chest tube in place and was not included in this category.
[b]Including two cases of postprocedural pneumothorax following intraprocedural aspiration of air from the pleural space.

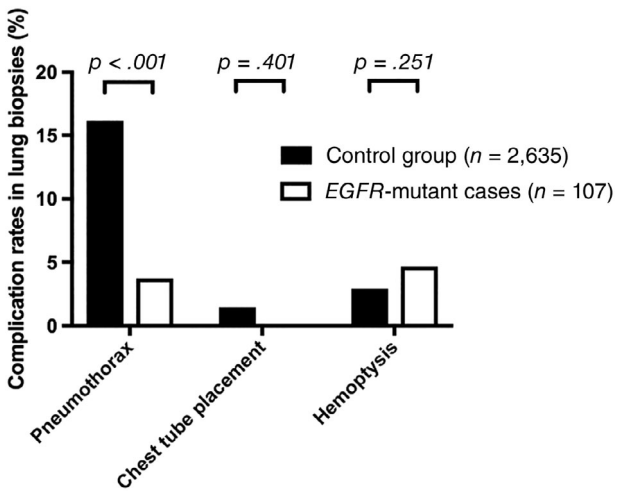

Figure 2. Comparison of lung biopsy complication rates, rebiopsies versus controls. Bar graph illustrates complication rates in rebiopsies performed in patients with *EGFR*-mutant non-small cell lung cancer compared with controls. Fisher's exact test was used to assess for differences.
Abbreviation: EGFR, epidermal growth factor receptor.

$p < .001$). There was no incidence of chest tube placement in the rebiopsy cohort, compared with 1.4% in the control group ($p = .401$). Although hemoptysis was more frequently observed in the rebiopsy cohort compared with the control group (4.7% vs. 2.9%), the difference was not statistically significant ($p = .251$; Fig. 2).

Biopsy Results and Molecular Profiling

Technical success rate in the rebiopsy cohort was 100%. Histopathology diagnosis of lung cancer was made by ROSE in 106 of 107 cases (99.1%), whereas only benign cells were present on fine-needle aspiration in the patient with intractable coughing following fine-needle aspiration.

Molecular profiling was attempted in 96 of 107 cases (89.7%). Molecular profiling was not attempted in 10 research rebiopsies scheduled either prior to ($n = 1$) or during a clinical trial ($n = 9$) if the trial protocol rather than disease progression dictated the biopsy. One case of transformation to small cell lung cancer ($n = 1$) also did not undergo molecular profiling.

In 4 of 96 cases (4.2%), harvested tissue was of insufficient quality for molecular profiling because of the low number of malignant cells. Instances included the above-described case of coughing following fine-needle aspiration ($n = 1$), as well as tissue cores demonstrating necrosis ($n = 1$) or abundant fibrous stroma ($n = 2$). Molecular profiling was successful in 92 of 96 cases (95.8%), including two instances in which only cellblocks created from FNAs were submitted because proximity of the target lesion to critical structures precluded harvesting of tissue cores.

Discussion

Our study demonstrates that postprogression rebiopsies in patients with *EGFR*-mutant NSCLC are safe and likely to be successful for molecular profiling, not only in patients with one prior biopsy but also in those with multiple (up to four) prior biopsies. No major complications occurred in 107 repeat lung biopsies performed in 75 consecutive patients. Furthermore, there were significantly fewer complications associated with rebiopsies compared with the 2,635 PTNAB procedures in the control group. Patients with *EGFR*-mutant NSCLC are a

unique population in that they tend to be younger and never-smokers compared with all patients with lung cancer.

This study documented successful molecular profiling in 95.8% of rebiopsies, whereas previously reported values range from 74% to 89% [10, 14–16]. This high success rate is attributed to the routine use of coaxial technique, FNAs, and ROSE, which have not been reported in the context of rebiopsies [10, 11]. ROSE of FNAs provides intraprocedural assessment of the tissue quality in the location of the introducer needle [17]. Although ROSE is used for all cases at our institution, this service may not be available elsewhere. ROSE allows the operator to reposition the introducer needle prior to harvesting tissue cores in case of suboptimal tissue quality (i.e., necrosis). Furthermore, aspirates were not only used for slides but also submitted in saline and processed into a paraffin-embedded cellblock. These cellblocks can be used for molecular profiling if tissue cores cannot be obtained or are of insufficient quality [18].

Although liquid biopsies have been a major advance in the analysis of resistant *EGFR*-mutant lung cancers in recent years, ctDNA analysis has several key limitations and should not replace tissue biopsy in this context. First, currently available ctDNA assays are limited in sensitivity [19]. In up to ~30% of cases, circulating tumor DNA content in the plasma is below the current limits of detection of currently available assays. Moreover, histologic transformations, in particular transformation to small cell carcinoma, are seen in a subset of *EGFR*-mutant lung cancers that progress on all classes of *EGFR* inhibitors and have important therapeutic implications [20–22]. The diagnosis of a change in histology requires tissue assessment and cannot be achieved by ctDNA. Finally, we have observed significant heterogeneity of resistant *EGFR*-mutant lung cancers, highlighting the often complementary data afforded by both tissue and liquid biopsies [23]. These factors emphasize the continued relevance and important role of tissue biopsies in this patient population and underline the importance of the current study, especially because osimertinib is now in the frontline setting and *T790M* is no longer the major finding of interest on molecular profiling.

In terms of other biopsy targets in the thorax, endobronchial ultrasound-guided transbronchial biopsy (EBUS) could sample mediastinal and hilar lymph nodes, and pleural effusions may be amenable to aspiration. However, a 2017 meta-analysis reported lower sensitivity of EBUS for lung cancer diagnosis compared with PTNAB (0.69 vs. 0.94) [24]. Because molecular profiling requires more tissue than histological diagnosis, needle biopsy can be expected to outperform EBUS for the indication of molecular profiling. However, complications are slightly higher with PTNAB compared with EBUS [24]. Although thoracentesis is safer than PTNAB, the yield of pleural fluid for molecular profiling compared with PTNAB in NSCLC is lower (30% vs. 34%, respectively) [25]. In terms of extrathoracic targets, safety and adequacy has been reported for percutaneous needle biopsies of liver, adrenal gland, and bone [26]. Focal liver core needle biopsy is a safe procedure [27, 28]. Although also safe, the yield of FNA from adrenal metastases for next-generation sequencing was only 40%, and core needle biopsy could be expected to produce a higher yield of molecular profiling [26]. Complications associated with bone biopsies are very low [29]. However, in the absence of a soft tissue component, the required decalcification of the specimen is known to decrease the yield for molecular profiling [30].

The lung biopsies reported in this study were performed and supervised by a group of thoracic radiologists with a wide range of experience. As a result, our study reflects everday clinical practice whereas other reports rely on a single experienced operator to perform or supervise all procedures [10, 11]. Interestingly, despite the heterogeneity of operators and trainee involvement in about half of the cases, our rebiopsy pneumothorax rate of 3.7% and absence of chest tube placement in the rebiopsy cohort are lower than those previously reported for rebiopsies [10]. These data support the safety of repeat biopsies in patients with *EGFR*-mutant NSCLC in everday clinical practice.

It is also noteworthy that complication rates in both our rebiopsy cohort and control group were lower than those in a recent meta-analysis of 8,133 CT-guided PTNAB procedures, which reported a pneumothorax rate of 25.3%, a chest tube rate of 5.6%, and a hemoptysis rate of 4.1% [31]. In contrast, the rate of postprocedure pneumothorax was 16% among our 2,635 control cases, with only 1% requiring chest tube placement. The increased rate of mild hemoptysis in our rebiopsy cohort (3%) compared with controls (5%) was not statistically significant and could be explained by the fact that more tissue was generally being sought during rebiopsies [31].

Several reasons may explain why patients in the rebiopsy cohort had fewer complications than controls. The rebiopsy cohort was younger than controls and likely also had less emphysema because patients with *EGFR*-mutant lung cancer are commonly light- or never-smokers as compared with a general patient population undergoing lung biopsies. Lastly, patients deemed appropriate for repeat biopsy by their treating physicians could have been biased toward improved performance status. Contrary to surgical biopsies, pleural scarring and adhesion formation are not know to occur following PTNAB and would not decrease the risk of pneumothorax during repeat biopsy.

We hypothesize that low complication rates in both groups may be explained by several elements of our uniform PTNAB technique that all operators adhered to, regardless of their level of experience. First, all patients were rolled over to a puncture-site-down position immediately after removal of the introducer needle at the end of the procedure [32]. Minimizing needle-out patient-rollover time has been shown to significantly decrease rates of chest tube placement for pneumothorax [33]. Second, use of smaller biopsy devices has been shown to reduce risk of complications in both fine-needle and core biopsy procedures [31, 34]. This study used only 20-gauge core biopsy devices. Whereas larger-sized biopsy devices have been found to increase nucleic acid yield in a prospective study by Jamshidi et al. [35], Cheung et al. [36] reported equal tissue adequacy but slightly higher complication rates with 18-gauge compared with 20-gauge biopsy needles. Third, coaxial technique was used in all instances to enable repeated sampling with a single pleural puncture [37]. Coaxial technique seems to be better suited for biopsies performed to obtain tissue for molecular profiling because both number of tissue cores [35, 38] and total amount of harvested tissue [10, 16, 39] are known to correlate with specimen adequacy. Although coaxial technique may result in increased hemorrhage [40], blood

products may reduce the incidence of pneumothorax because they are thought to seal the biopsy tract [41, 42]. Fourth, a saline drip was used to prevent air from entering the introducer hub during needle exchanges, thus minimizing the risk of air embolus [43]. Fifth, no breath hold maneuvers were used to minimize the risk of pleural tearing [44]. On the contrary, patients were given strict instructions to not talk or move during the procedure and during the recovery period and moderate sedation was administered whenever possible in order to facilitate immobilization and reduce respiratory excursions [12, 43, 45].

There are several limitations inherent in this study design. First, this is a retrospective study at a single tertiary academic medical center. Larger studies with data from other centers are required to determine the generalizability of these findings. Second, selection bias is inherent in the study design because patients who experienced complications after first-time PTNAB may not have been deemed amenable for rebiopsy by the referring oncologist. However, a history of complications during the initial biopsy was in and of itself not a reason for the radiologist to refuse the procedure. Last, the retrospective design does not allow for a precisely matched control group, which could be constituted of initial biopsies in patients with *EGFR*-mutant NSCLC.

Conclusion

Repeat lung biopsies for postprogression molecular profiling of *EGFR*-mutant lung cancer are safe in everday clinical practice. Coaxial technique, fine-needle aspirates, rapid on-site cytopathology evaluation, and multiple 20-gauge tissue cores result in excellent specimen adequacy.

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Disclosures

Lecia V. Sequist: AstraZeneca, Genentech, Pfizer, Blueprint Medicines, Merrimack Pharmaceuticals, Bristol-Myers Squibb, Novartis, Boehringer Ingelheim (C/A). **Zofia Piotrowska:** AstraZeneca, ImmunoGen, Guardant Health, Spectrum (C/A). The other authors indicated no financial relationships.

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