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

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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 everyday clinical practice. Coaxial technique, fine-needle aspirates, rapid on-site pathologic evaluation, and multiple 20-gauge tissue cores result in excellent specimen adequacy. The Oncologist 2019;24:1570–1576

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 pre-existing 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].

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
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 indications 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 hand 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 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.

**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%,
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**

Biopsy 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 intra-cavity 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

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**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)      |
| Emphysemia 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) |

^aConsolidation is defined as a parenchymal opacity with air bronchograms. Abbreviation: IQR, interquartile range.

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**Table 3. Lung biopsy complication rates, rebiopsies versus controls**

| Complication                              | Rebiopsies \( ( n = 107 ) \) | Controls \( ( n = 2,635 ) \) | \( p \) value (Fisher’s) |
|-------------------------------------------|-------------------------------|-------------------------------|-------------------------|
| Postprocedural pneumothorax, \( n (%) \)^ab | 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)                         | -                       |

^aOne patient was referred for lung biopsy with a chest tube in place and was not included in this category.

^bIncluding two cases of postprocedural pneumothorax following intraprocedural aspiration of air from the pleural space.
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 everyday 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 biopsy 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 everyday 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 known 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-rollerover 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 PTNB 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 cancer are safe in everyday clinical practice. Coaxial technique, fine-needle aspirates, rapid on-site cytopathology evaluation, and multiple 20-gauge tissue cores result in excellent specimen adequacy.

**References**

1. Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–246.
2. Sequist LV, Yang JC, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with non-small-cell lung cancer: Status in 2016. J Thorac Oncol 2016;11:399–409.
3. Ramalingam SS, Yang JC, Lee CK et al. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. J Clin Oncol 2018;36:841–849.
4. Sacks D, McClenny TE, Cardella JF et al. Society of Interventional Radiology clinical practice guidelines. J Vasc Inter Radiol 2003;14:S199–S202.
5. Hansell DM, Bankier AA, MacMahon H et al. Fleischner Society: Glossary of terms for thoracic radiology. Radiology 2008;246:697–722.
6. Yoon HJ, Lee HY, Lee KS et al. Repeat biopsy for mutational analysis of non-small cell lung cancer resistant to previous chemotherapy: Adequacy and complications. Radiology 2012;265:939–948.
7. Kim H, Chae KJ, Yoon SH et al. Repeat biopsy of patients with acquired resistance to EGFR TKIs: Implications of biopsy-related factors on T790M mutation detection. Eur Radiol 2018;28:861–868.
8. Ko JP, Shepard JD, Drucker EA et al. Pneumothorax rate at lung biopsy: Are dwell time and angle of pleural puncture contributing factors? Radiology 2001;218:491–496.
9. Wu CC, Maher MM, Shepard JA. CT-guided percutaneous needle biopsy of the chest: Pre-procedural evaluation and technique. AJR Am J Roentgenol 2011;196:W51–W54.
10. Yu HA, Arcila ME, Rekhtman N et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240–2247.
11. Chousid C, Dujon C, Do P et al. Feasibility and clinical impact of re-biopsy in advanced non-small-cell lung cancer: A prospective multicenter study in a real-world setting (GFPC study 12-01). Lung Cancer 2014;86:170–173.
12. Tam AL, Kim ES, Lee JJ et al. Feasibility of image-guided transthoracic core-needle biopsy in the BATTLE lung trial. J Thorac Oncol 2013;8:436–442.
13. Azabdatari D, Goldberg SN, Wang HH. Efficacy of on-site specimen adequacy evaluation of image-guided fine and core needle biopsies. Acta Cytol 2010;54:132–137.
14. Billah S, Stewart J, Staerkel G et al. EGFR and KRAS mutations in lung carcinoma: Molecular testing by using cytology specimens. Cancer Cytopathol 2011;119:111–117.
15. Thress KS, Brant R, Carr TH et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291. Lung Cancer 2015;90:509–515.
16. Sequist LV, Waltman BA, Dias-Santagata D et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3:75ra26.
21. Piotrowska Z, Isozaki H, Lennerz JK et al. Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and the Royal College of Physicians of London. Gut 1995;36:437–441.

22. Marcoux N, Gettinger SN, O’Kane G et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: Clinical outcomes. J Clin Oncol 2019;37:278–285.

23. Piotrowska Z, Hazar-Rethinam M, Rizzo C et al. Heterogeneity and coexistence of T790M and T790 wild-type resistant subclones drive mixed response to third-generation epidermal growth factor receptor inhibitors in lung cancer. JCO Precis Oncol 2018;2018.

24. Zhan P, Zhu QQ, Miu YY et al. Comparison between endobronchial ultrasound-guided transbronchial biopsy and CT-guided transthoracic lung biopsy for the diagnosis of peripheral lung cancer: A systematic review and meta-analysis. Transl Lung Cancer Res 2017;6:23–34.

25. Guan Y, Wang ZJ, Wang LQ et al. Comparison of EGFR mutation rates in lung adenocarcinoma tissue and pleural effusion samples. Genet Mol Res 2016;15.

26. Glesson FC, Kipp BR, Levy MJ et al. Lung cancer adrenal gland metastasis: Optimal fine-needle aspirate and touch preparation smear cellularity characteristics for successful theranostic next-generation sequencing. Cancer Cytopathol 2014;122:822–832.

27. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.

28. Gilmore IT, Burroughs A, Murray-Lyon IM et al. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: An audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut 1995;36:437–441.

29. Matsumoto T, Hasebe T, Baba Y et al. Feasibility and safety of CT-guided intrathoracic and bone re-biopsy for non-small cell lung cancer. Anticancer Res 2018;38:3587–3592.

30. Singh VM, Salunga RC, Huang VI et al. Analysis of the effect of various decalcification agents on the quantity and quality of nucleic acid (DNA and RNA) recovered from bone biopsies. Ann Diagn Pathol 2013;17:322–326.

31. Heerink WJ, de Bock GH, de Jonge GJ et al. Complication rates of CT-guided transthoracic lung biopsy: Meta-analysis. Eur Radiol 2017;27:138–148.

32. Moore EH, LeBlanc I, Montesi SA et al. Effect of patient positioning after needle aspiration lung biopsy. Radiology 1991;181:385–387.

33. O’Neill AC, McCarthy C, Ridge CA et al. Rapid needle-out patient-rollover time after percutaneous CT-guided transthoracic biopsy of lung nodules: Effect on pneumothorax rate. Radiology 2012;262:314–319.

34. Geraghty PR, Kee ST, McFarlane G et al. CT-guided transthoracic needle aspiration biopsy of pulmonary nodules: Needle size and pneumothorax rate. Radiology 2003;229:475–481.

35. Sharma A, Shepard JO et al. Frequency and severity of pulmonary hemorrhage in patients undergoing percutaneous CT-guided transthoracic lung biopsy: Single-institution experience of 1175 cases. Radiology 2016;279:287–296.

36. Gouveia AM, Gandhi R, Brody LA et al. Factors associated with pneumothorax and pneumothorax requiring treatment after percutaneous lung biopsy in 443 consecutive patients. J Vasc Inter Vasc Radiol 2010;31:1713.

37. Cheung YC, Chang JW, Hsieh JJ et al. Adequacy and complications of computed tomography-guided core needle biopsy of ex vivo tissue and in vivo lung. Radiology 2017;282:903–912.

38. Zhu QQ, Miu YY et al. Comparison of EGFR mutation rates in lung adenocarcinoma tissue and pleural effusion samples. Genet Mol Res 2016;15.

39. Wu CC, Maher MM, Shepard JA. Complications of CT-guided cutting needle biopsy of the chest: Prevention and management. AJR Am J Roentgenol 2011;196:W678–W682.