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Feasibility of Image-Guided Transthoracic Core Needle Biopsy in the BATTLE Lung Trial

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Abstract

Purpose—As therapy for non-small cell lung cancer (NSCLC) patients becomes more personalized, additional tissue in the form of core needle biopsies (CNBs) for biomarker analysis is increasingly required for determining appropriate treatment and for enrollment into clinical trials. We report our experience with small-caliber percutaneous transthoracic (PT) CNBs for the evaluation of multiple molecular biomarkers in BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination), a personalized, targeted therapy NSCLC clinical trial.

Methods—The medical records of patients who underwent PTCNB for consideration of enrollment in BATTLE, were reviewed for diagnostic yield of 11 predetermined molecular markers, and procedural complications. Univariate and multivariate analyses of factors related to patient and lesion characteristics were performed to determine possible influences on diagnostic yield.

Results—One hundred and seventy PTCNBs were performed using 20-gauge biopsy needles in 151 NSCLC patients screened for the trial. 82.9% of the biopsy specimens were found to have adequate tumor tissue for analysis of the required biomarkers. On multivariate analysis, metastatic lesions were 5.4 times more likely to yield diagnostic tissue as compared to primary tumors ($p = 0.0079$). Pneumothorax and chest tube insertion rates were 15.3% and 9.4%, respectively.

Conclusions—Image-guided 20-gauge PTCNB is safe and provides adequate tissue for analysis of multiple biomarkers in the majority of patients being considered for enrollment into a personalized, targeted therapy NSCLC clinical trial. Metastatic lesions are more likely to yield diagnostic tissue as compared to primary tumors.

Keywords

research biopsy; biomarker analysis; percutaneous transthoracic biopsy

INTRODUCTION

Lung cancer is the most common cause of cancer-related death for men and women and represents about 28% of all cancer deaths.^{1,2} Despite advances in cancer therapy, the overall 5-year survival rate remains poor with less than 30% of patients being eligible for curative resection at the time of diagnosis.^{3,4,5} Treatment advances for cancer therapy are now predicated on an understanding of the molecular basis of cancer which may provide the opportunity to develop novel treatment strategies. Since targeted agents are known to be effective against specific mutations, molecular characterization of the tumor and the development of prognostic and predictive biomarkers are critical to guiding clinical decision-making in the pursuit of personalized cancer therapy. As a result, tissue, sufficient not only for tumor classification by cytology, histology, but also molecular characteristics (e.g. epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) translocation), is important to determine whether standard chemotherapy versus targeted therapy would be the most appropriate treatment for the patients.⁶

Image-guided percutaneous transthoracic core needle biopsy (PTCNB) is a standard diagnostic procedure which is now being used to obtain tissue for research protocols where molecular biomarker analysis rather than histology is the ultimate goal.⁷⁻¹⁰ However, little has been written about the safety and adequacy of the techniques used for tissue acquisition in research biopsies.^{11,12,13} In addition, factors such as tumor histology and previous anti-cancer treatments, that could potentially influence the diagnostic yield in a research setting have not been studied. The BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial was the first completed prospective, biopsy-mandated, biomarker-based, adaptively randomized phase II clinical trial in patients with pretreated, advanced lung cancer.¹⁴ This study demonstrated for the first time that PTCNBs of non-small cell lung cancers (NSCLCs) could provide biomarker information that may be used to predict response to a particular targeted therapy. The purpose of this paper is to report on the safety and reliability of using image-guided small-caliber PTCNBs for multiple molecular marker analysis in patients with NSCLC being considered for enrollment in the BATTLE trial. We also analyzed the patient and biopsy-related factors to determine possible influences on diagnostic yield.

MATERIALS AND METHODS

This was a HIPPA compliant, subset analysis of patients who underwent PTCNB for consideration of enrollment in the BATTLE trial; the study was approved by the institutional review board, and we followed the recommendations of the Declaration of Helsinki for biomedical research. Of the total 324 patients who were biopsied in the BATTLE trial, 151 patients (not all of whom were randomized to treatment) underwent 170 PTCNBs and represent the subset of BATTLE patients analyzed in this study.¹⁴ Nineteen patients underwent a repeat biopsy: eighteen patients who were assigned to a treatment arm and progressed while on protocol underwent repeat biopsy for consideration of re-enrollment into the trial. The last patient underwent a second optional biopsy for investigational purposes of the protocol.

The medical records of these patients were reviewed for the following parameters: biopsy site, imaging findings, needle size, image-guidance, diagnostic yield, previous treatments, and procedural complications. Univariate and multivariate analyses of following factors were performed to determine possible influences on diagnostic yield: age, gender, tumor histology, history of previous radiation treatment to biopsied lesion, primary versus metastatic nature of the biopsied lesion, lesion depth from the pleura, lesion size (maximum diameter on computed tomography (CT) images with standard lung window settings),

location and morphology, availability of a fluorodeoxyglucose positron-emission tomography/computed tomography (FDG-PET/CT) within 6 months prior to biopsy. A biopsy that yielded sufficient tumor tissue for evaluation of all 11 biomarkers required for enrollment in the protocol was considered a diagnostic biopsy. Lesion morphology was categorized as solid mass, consolidation (areas of parenchymal opacification obscuring underlying lung markings with or without air bronchograms), or cavitory lesion (presence of air-filled cavity within lung lesion). Bivariate analyses were conducted using Fisher's exact tests to explore the association of diagnostic yield with several patient and lesion characteristics. A multivariate logistic regression was fitted to the data to investigate the presence of higher dimension associations (SAS 9.2, SAS Institute Inc., Cary, NC). A p-value ≤ 0.05 was considered statistically significant.

The BATTLE trial required patients to undergo a mandatory baseline biopsy consisting of at least 2 fresh PTCNBs prior to treatment randomization. The samples were assessed visually by the interventional radiologist (IR) performing the procedure, and if the initial two specimens were small or fragmented, additional samples were obtained if the size and location of the lesion permitted additional sampling in a safe manner.

The tumor tissue was immediately fixed in formalin and embedded in paraffin within 24-hours. A hematoxylin-and-eosin-stained histological section was used to assess the presence, quantity, quality and histological type of tumor tissue. Each histology section considered adequate for biomarker analysis had at least 200 malignant cells.¹⁴ Using at least 12 histology sections, the tumor tissue was tested for 11 different biomarkers: gene mutation analysis by polymerase chain reaction based sequencing for *EGFR* exons 18–21, *KRAS* codons 12, 13, and 61 and *BRAF* exons 11 and 15; two copy number analyses by fluorescent in situ hybridization of *EFGR* and *Cyclin D1*; and, six protein analyses (vascular endothelial growth factor (*VEGF*), *VEGFR-2*, retinoid X receptors (*RXRs*) α , β and γ , and *Cyclin D1*) by immunohistochemistry. Confirmation of the presence of adequate tumor tissue in the formalin-fixed and paraffin-embedded tissue specimens by histology examination was performed within 24–48 hours, and analysis of the 11 molecular biomarkers was performed, completed and reported within 14 days. Based on the molecular characteristics, patients were assigned to one of four biomarker groups (*EGFR*, *KRAS/BRAF*, *VEGF* or *RXR/Cyclin D1*) to receive different therapies (erlotinib, vandetanib, erlotinib and bezarotene or sorafenib).¹⁴

All PTCNB procedures were performed under CT guidance by a board-certified IR. Written informed consent for the procedure was obtained. Accepted coagulation parameters included platelet levels of at least $75 \times 10^9/L$ and an INR ≤ 1.5 . All biopsies were performed using a coaxial technique which allowed acquisition of multiple biopsy samples using only one transgression through the pleura: an 18- or 19-gauge guide needle (Cook Inc., Bloomington IN) was inserted through the skin and directed to the periphery of the lesion; subsequently, a 20-gauge core biopsy needle (Quikcore, Cook Inc., Bloomington IN) was inserted through the guide needle, and samples obtained after CT confirmation of the needle tip's position. Following the biopsy, serial inspiratory chest radiographs with the patient in an erect position were obtained over a three-hour observation period. A chest tube with a Heimlich valve was inserted if the pneumothorax size was $>30\%$ of lung volume, the pneumothorax increased in size, or patients experienced pain, dyspnea or a decrease in oxygen saturation. Patients who had chest tubes placed were treated as outpatients, returning the next day for chest tube removal.¹⁵ Patients with persistent air leaks or those with severe pain were admitted to the hospital for management.

RESULTS

All patients had a diagnosis of metastatic NSCLC and had been previously treated with chemotherapy (Table 1). All patients underwent PTCNB successfully and at least 2 PTCNBs of the tumor were obtained in each patient: 82.9% (n=141) of the biopsy samples had sufficient tissue for the required biomarker analysis. Univariate analyses showed biopsy of metastatic lesions were more likely to yield diagnostic tissue than biopsy of primary tumors (Table 2) (94.7% versus 76.9%; $p = 0.0042$). Biopsy of cavitory lesions were less likely to yield diagnostic tissue as compared to biopsy of masses or consolidations (50% versus 86.7% and 77.8%, respectively, $p = 0.0315$). The diagnostic yield was 73%, 84% and 84% for lesions <2 cm, 2–5 cm, and >5 cm in size, respectively; the differences in size were not statistically significant. There was no difference ($p=0.54$) in diagnostic yield between the cases that had a FDG-PET/CT within 6 months of biopsy versus those that did not. On multivariate logistic regression analysis, only one of the variables evaluated was found to be predictive: metastatic lesions were 5.4 times more likely to yield diagnostic tissue as compared to primary tumors ($p = 0.0079$).

Review of the imaging data in the 29 cases with non-diagnostic samples (Table 3) revealed that tissue yield in 23 of these cases potentially could have been improved. Sampling error was identified in 9 cases where a different portion of the lesion should have been sampled (Figure 1). Lesion selection was not optimal in fourteen cases: five cases demonstrated a change to the morphology of the lesion following systemic or radiation therapy with three lesions becoming smaller and two lesions obscured by the development of adjacent consolidative changes or pneumonitis in the lung parenchyma. The remaining nine cases had either a large lesion or multiple lesions. In these patients, it is possible that presence of a recent FDG-PET/CT could have helped in selecting the best lesion (lesion with highest standardized uptake value in patients with multiple lesions) or the most viable area within a large lesion for biopsy. A review of the images for the last six cases with non-diagnostic biopsies revealed that both lesion selection and biopsy technique were appropriate. In these patients, we believe that on-site cytopathologic evaluation of fine-needle aspirations or touch-preparations of core samples has the potential to improve the diagnostic yield. None of the 14 cases in which lesion selection was identified as the error category had a FDG-PET/CT within 6 months of the biopsy. Similarly, 4 cases of sampling error and 3 cases of unknown error had not had a FDG-PET/CT within 6 months of the biopsy.

The overall complication rate was 15.9% (n=27), consisting of 26 cases of pneumothorax and one case of subcutaneous emphysema following lung biopsy. Chest tube placement was needed in 16 (59.2%) of 27 cases (9.4% of all biopsies). All but three of the patients requiring chest tube placement were treated as outpatients and had the chest tubes removed the next day, resulting in a minor (CTCAE Gr 2) complication rate of 14.1% (n=24). The major (all CTCAE Gr 3) complication rate was 1.8% (n=3): Two patients who required prolonged chest tube drainage for treatment of pneumothorax, one of whom required pleurodesis, and the patient who required chest tube placement for subcutaneous emphysema were admitted to the hospital.

DISCUSSION

Patients with NSCLC have therapies that can be tailored based on their molecular markers. This study demonstrates that 20-gauge PTCNB is safe and provides adequate tissue for the analysis of multiple biomarkers in 83% of patients enrolled into a personalized, targeted therapy NSCLC clinical trial. While success rates and acceptable thresholds for diagnostic yield have been well defined in the setting of diagnostic biopsy, these guidelines have yet to be established in the research setting.¹⁶ The lower diagnostic yield (83%) in this research

clinical trial as compared to average yield of around 93% reported in a diagnostic setting is not surprising, since the purpose of the biopsy in a research setting is to get enough tissue sufficient not only for tumor classification by cytology and histology, but also for multiple biomarker analyses. Few studies have been conducted to analyze the adequacy of CNB for molecular profiling, and most of these studies have been limited to breast or liver tissue and 14-gauge needles.^{11,17,18} However, large-caliber needles are generally not used for PTCNB because of the potential for higher risk of pneumothorax and chest tube insertion. It remains questionable as to whether PTCNB using standard 20-gauge needles yields sufficient and reliable material for mutational analysis.^{13,19}

Our experience with this study demonstrates that standard biopsy tools and techniques can be applied to acquiring tissue for research purposes. Table 4 represents a compilation of more recent experiences in using small tissue samples for the detection of mutations in NSCLC and shows a wide variation and lack of standardization with respect to the type of tissue sampled, the technique by which the tissue is acquired and the methodology used for mutation analysis.^{12,13,19,20–23} The current standard of practice for lung cancer clinical trials is to take samples from the original tumor for molecular analysis however, this may not be an accurate representation of the current biomarkers of the treated tumor.^{24–27} Furthermore, a recent article reviewing tissue sampling in lung cancer reported bronchoscopic biopsy in the MarkER Identification Trial (MERIT) yielded evaluable tissue for molecular profiling in only 50% of samples and had limited utility in other large NSCLC trials (BR.21 trial, ISEL, TRIBUTE and IPASS).^{7, 24–27} PTCNB offers several advantages over that of bronchoscopic biopsy: all areas of the thorax, including the mediastinum and peripheral lesions, are accessible and multiple core biopsies are possible. Three studies, only one of which was in the setting of a clinical trial,¹³ address the utility of percutaneous, PTCNB for mutation analysis in NSCLC.^{12,13,23} In comparison, our study is unique because PTCNBs of the tumor were acquired for the purpose of using the molecular profile to individualize patient therapy in a clinical trial.¹⁴ The 83% diagnostic yield seen in the current study is lower than the 90–100% yield reported in some other studies on biopsies in a research setting;^{12,13,23} this is most likely related to the fact that 11 different biomarkers were analyzed in our study whereas the other studies reported on the adequacy of CNB for the analyses of one or two mutations.

This study demonstrates the risks associated with transthoracic research biopsy are similar to those reported for transthoracic diagnostic biopsy. Pneumothorax is a common complication of transthoracic diagnostic biopsy and reported rates have ranged from 0% to 61% with most large series reporting pneumothorax rates in the range of 20–25%, with pneumothorax aspiration or chest tube insertion rates ranging from 0–17%.^{28–32} Our pneumothorax rate of 15.3% and chest tube insertion rate of 9.4% fall within these accepted ranges and demonstrate that patients who undergo transthoracic research biopsies are not subject to increased risk for complications.

Previous studies dealing with PTCNB in a diagnostic setting have suggested that small lesion size (lesions < 1cm) is associated with a poor diagnostic yield.^{32–35} Lesion size, however, was not found to be a predictive factor in our study; this could be related to the fact that all of the lesions biopsied were larger than 1cm in size. In the current study, metastatic lesions were more likely to yield adequate tissue for biomarker analyses as compared to primary tumors. In addition, presence of cavitation in the biopsied lesion was associated with a poor diagnostic yield; however, on multivariate analyses this was not found to be predictive. The cases in the lesion selection problem error category represented 48% of the non-diagnostic biopsies. Although we did not find a difference in the diagnostic yield between patients with or without a recent FDG-PET-CT, we believe that FDG-PET-CT, with its ability to distinguish metabolically active disease from normal tissue, necrosis,

fibrosis, or atelectasis, may be useful for optimizing lesion selection in unclear cases both by determining the best lesion for biopsy and by defining the most viable area of tumor to target during biopsy. The fact that none of the 14 cases in which lesion selection was identified as the error category had a FDG-PET/CT within 6 months of the biopsy indirectly supports this hypothesis. Emerging research where FDG-PET/CT guidance is used during biopsy to target the most avid regions may help to clarify this issue further.^{36–40} Sampling error was the second category affecting diagnostic yield; and, careful, pre-procedural review of the diagnostic and functional imaging, critical to procedural planning and acquiring diagnostic specimen, should be emphasized. In the six cases with no obvious source of error, the presence of on-site cytopathology assessment at the time of the biopsy procedure, for evaluation of either a fine needle aspiration sample or a touch prep of a CNB, may be helpful to determine tissue viability and predict the adequacy of subsequent CNBs taken from the area.^{41–45} Based on this error analysis, forthcoming clinical trials (BATTLE-2 and BATTLE-FL) have incorporated the use of real-time cytopathology assessment to determine tissue viability; and, if no clear lesion can be selected for biopsy based on the available diagnostic imaging, the IR has been requesting a FDG-PET/CT to optimize lesion selection prior to biopsy. It remains to be seen whether the implementation of these measures will improve diagnostic yield. In the future, the development of FDG-PET/CT guided biopsy techniques, the routine use of navigation devices and fusion of diagnostic and procedural images in the interventional radiology suite may also improve the likelihood of sampling viable tumor tissue.^{36–40}

This study has limitations. First, despite the large number of biopsy cases, this study represents data from a single institution, a well-established cancer center with the requisite infrastructure and experience capable of coordinating this endeavor. Second, the error categories were assigned based on a retrospective review of the imaging of the biopsy cases making it difficult to truly establish cause and effect. In addition, our recommendations for improving the diagnostic yield in a research setting are not supported by numbers and statistical evidence. However, the purpose of analyzing the interventional radiology experience in the setting of this first large clinical trial using integral biomarker analysis from research biopsies to drive patient accrual and randomization, is in part hypothesis generating, and these ideas will be evaluated in future iterations of the BATTLE trials. Our recommendations are based partly on the results of the current study and partly on applying principles, such as on-site cytopathology assessment to improve yield, that have been tested previously in the diagnostic setting.^{41–45}

The era of personalized therapy for lung cancer is here; and, while histological diagnosis remains important, molecular profiling, both for current treatment and most certainly for research, requires more robust tumor sampling. This study demonstrates small caliber core biopsy needles can be used to collect tissue safely and reliably during image-guided PTCNB for biomarker analysis in a clinical trial setting and validates this new paradigm for translational research in NSCLC patients.¹⁴ Multivariate analyses suggests that metastatic lesions are more likely to yield diagnostic tissue as compared to primary tumors. We believe that careful review of imaging data, especially PET-CT, if available for selecting the most appropriate biopsy site, and use of on-site cytopathology assessment have the potential of improving the diagnostic yield; however, these recommendations need to be validated in future studies.

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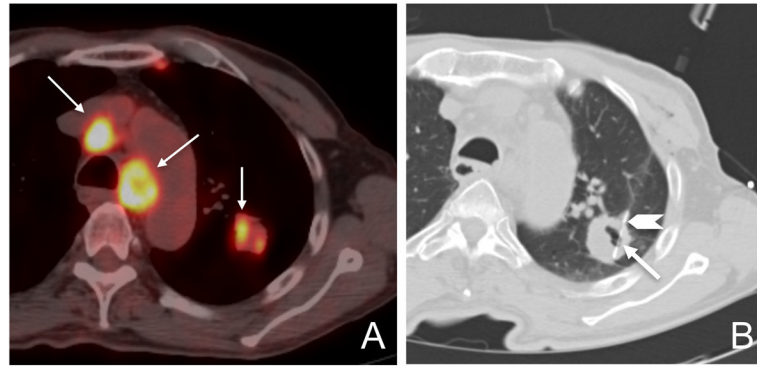


Figure 1. Case of sampling error resulting in insufficient tissue for biomarker analysis. Axial fused PET/CT image demonstrates FDG activity (arrows) within the mediastinal nodes and the inferior, medial border of the left upper lobe lung mass (A). Axial CT image during lung biopsy to acquire tumor tissue for enrollment into BATTLE demonstrates a coaxial technique with the tip of the 19-gauge guide needle located at the periphery of the lesion (arrowhead) and the 20-gauge core biopsy needle located in the lateral edge of the cavity mass (arrow), an area which does not correspond to the highest area of FDG uptake on the pre-biopsy diagnostic PET/CT (B).

Table 1

Patient Demographics

		n (%)
Age (mean 61 years, range 34–81 years)	<50	31 (20.5)
	51–60	33 (21.9)
	61–70	56 (37.1)
	>70	31 (20.5)
Gender	Male	86 (57)
	Female	65 (43)
Ethnicity	Caucasian	125 (82.8)
	Hispanic	6 (4)
	African American	9 (6)
	Asian	11 (7.2)
Smoker	Current	12 (8)
	Former	108 (71.5)
	Never	31 (20.5)
ECOG	0	27 (17.9)
	1	101 (66.9)
	2	23 (15.2)
Total Patients		151 (100)

Table 2

Influence of patient, lesion and biopsy variables on likelihood of obtaining diagnostic tissue sufficient for biomarker analyses: Univariate analysis

Characteristic	Number of Biopsies, (n)	Diagnostic n, (%)	Non-Diagnostic n, (%)	P-value
Size				0.5842
<2 cm	11	8 (72.7)	3 (27.3)	
2–5 cm	135	112 (82.9)	23 (17.1)	
>5 cm	24	21 (87.5)	3 (12.5)	
Lesion Biopsied				0.0042
Primary Tumor	113	87 (77)	26 (23)	
Metastatic Focus	57	54 (94.7)	3 (5.3)	
History of Prior Radiation Therapy to the Lesion Biopsied				0.5820
Yes	28	22 (78.6)	6 (21.4)	
No	142	119 (83.8)	23 (16.2)	
Lesion Morphology				0.0315
Mass/Nodule	153	130 (84.9)	23 (15.1)	
Consolidation	9	7 (77.8)	2 (22.2)	
Cavitation	8	4 (50)	4 (50)	
Lesion Location				0.1969
Lung	150	123 (82)	27 (18)	
Hilum/Mediastinum	8	6 (75)	2 (25)	
Pleura	12	12 (100)	0 (0)	
Lesion Depth				0.1763
0–2 cm	82	72 (87.8)	10 (12.2)	
2–4 cm	66	53 (80.3)	13 (19.7)	
>4 cm	22	16 (72.7)	6 (27.3)	
Tumor Histology				0.3427
NSCLC-NOS	31	28 (90.3)	3 (9.7)	
NSCLC-SCC	26	20 (76.9)	6 (23.1)	
NSCLC-Adenocarcinoma	103	86 (83.5)	17 (16.5)	
Other	10	7 (70)	3 (30)	
PET-CT within 6 months				0.5391
Yes	76	65 (85.5)	11 (14.5)	
No	94	76 (80.8)	18 (19.2)	

NSCLC-non-small cell lung cancer; SCC-squamous cell carcinoma; NOS-not otherwise specified

Table 3

Patients with Inadequate Tissue Samples

No. of Patients	Descriptive Reasons for Inadequate Tissue Sampling	Error Category	Recommendations
14	Large mass without recent PET/CT (n=4). Multiple lesions without recent PET/CT (n=5). Lesion response to therapy (radiation or chemotherapy) without recent PET/CT (n=5).	A: Lesion selection problem	Recent functional imaging (PET/CT) would improve lesion selection: <ul style="list-style-type: none"> determine best lesion for biopsy (highest SUV) determine most viable area within tumor for biopsy distinguish between residual tumor versus pneumonitis or parenchymal collapse following radiation therapy
9	Area sampled did not show FDG activity on pre-biopsy PET/CT (n=3). Area sampled did not show contrast enhancement on pre-biopsy contrast-enhanced CT (n=3). Needle not in lesion, edge of lesion biopsied (n=3).	B: Sampling error	Pre-biopsy review of available cross-sectional and preferably functional imaging (PET/CT) is essential to procedural planning. Areas suspected to have the most viable tumor should be targeted.
6	Needle in appropriate position within the lesion-reason for inadequate tissue sampling unknown (n=6).	C: Unknown	On-site cytologic assessment of a fine needle biopsy from the area may help to determine tissue viability and predict the adequacy of subsequent core biopsies taken from the area.

Table 4

Studies Using Small Tissue Specimens for Mutation Evaluation in NSCLC

Author, Year	Number of Samples	Sample Type	Sample Size	Number of Samples Acquired	Mutations Evaluated	Complications	% Samples with Tissue Adequate for Mutation Analysis
Shih et al. 2006 ¹⁹	63	Formalin-fixed, paraffin embedded needle biopsy/ aspiration ^d	NR	NR	<i>EGFR</i> by PCR analysis	NR	100%
Orani et al. 2008 ²⁰	53	Wash fluid from PTNB	NR	NR	<i>EGFR</i> by PCR analysis	NR	100%
Zudaire et al. 2008 ²¹	33	Paraffin embedded FNA	NR	NR	5p15, <i>EGFR</i> , <i>MYC</i> , <i>CEP70</i> , <i>P53</i> , <i>K1-67</i> by FISH and immunocytochemistry	NR	94%
Savic et al. 2008 ^{b, 22}	84	Cytological specimens	NR	NR	<i>EGFR</i> by FISH	NR	95%
Chen et al. 2008 ^{a, 23}	17	Core needle biopsy (fresh frozen)	18-gauge	3	<i>EGFR</i>	Pneumothorax 17.6% Hemoptysis 11.8% Chest tube insertion rate 6%	100%
Solomon et al. 2009 ^{a, 13}	18	Core needle biopsy	18-gauge (n=15) 20-gauge (n=3)	Median =2	<i>EGFR</i> by direct sequencing or PCR <i>KRAS</i> by direct sequencing	Pneumothorax 16.7% Chest tube insertion rate 0%	88.9%
Cheung et al. 2010 ¹²	47	Core needle biopsy	18-gauge (n=32) 20-gauge (n=15)	3	<i>EGFR</i> by PCR analysis	Pneumothorax 12.8% Hemoptysis 6.4% Chest tube insertion rate 5.6%	100%
Current Study Tam et al. 2012 [*]	170	Core needle biopsy	20-gauge	Median =3	<i>EGFR</i> , <i>KRAS</i> , <i>BRAF</i> by PCR, <i>EGFR</i> and <i>Cyclin D1</i> by FISH and six protein analyses by immunohistochemistry	Pneumothorax 15.3% Hemoptysis 0% Chest tube insertion rate 9.4%	83%

^a Samples taken from image guided core needle biopsies, endoscopic guided aspiration biopsies and effusion cell blocks. Tissues analysed included lung, liver, stomach, subcutaneous soft tissue metastasis and ascites.

^b Samples taken from transbronchial fine needle aspirations, bronchial washings, bronchial brushes, bronchoalveolar lavages and pleural effusions.

* Indicates prospective study

NR-not reported, PTNB-percutaneous transthoracic needle biopsy, PCR-polymerase chain reaction, FNA-fine needle aspiration, FISH-fluorescent in situ hybridization