



# Non-Diagnostic CT-Guided Percutaneous Needle Biopsy of the Lung: Predictive Factors and Final Diagnoses

Thanisa Tongbai, MD<sup>1</sup>, Shaunagh McDermott, MD<sup>2</sup>, Nantaka Kiranantawat, MD<sup>3</sup>, Victorine Vining Muse, MD<sup>2</sup>, Carol Chia-chia Wu, MD<sup>2</sup>, Jo-Anne O'Malley Shepard, MD<sup>2</sup>, Matthew David Gilman, MD<sup>2</sup>

<sup>1</sup>Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; <sup>2</sup>Department of Radiology, Massachusetts General Hospital, Boston, MA, USA; <sup>3</sup>Department of Radiology, Songklanagarind Hospital, Prince of Songkhla University, Hat Yai, Thailand

**Objective:** To investigate the predictive factors for a non-diagnostic result and the final diagnosis of pulmonary lesions with an initial non-diagnostic result on CT-guided percutaneous transthoracic needle biopsy.

**Materials and Methods:** All percutaneous transthoracic needle biopsies performed over a 4-year period were retrospectively reviewed. The initial pathological results were classified into three categories—malignant, benign, and non-diagnostic. A non-diagnostic result was defined when no malignant cells were seen and a specific benign diagnosis could not be made. The demographic data of patients, lesions' characteristics, technique, complications, initial pathological results, and final diagnosis were reviewed. Statistical analysis was performed using binary logistic regression.

**Results:** Of 894 biopsies in 861 patients (male:female, 398:463; mean age 67, range 18–92 years), 690 (77.2%) were positive for malignancy, 55 (6.2%) were specific benign, and 149 (16.7%) were non-diagnostic. Of the 149 non-diagnostic biopsies, excluding 27 cases in which the final diagnosis could not be confirmed, 36% revealed malignant lesions and 64% revealed benign lesions. Predictive factors for a non-diagnostic biopsy included the size  $\leq 15$  mm, needle tract traversing emphysematous lung parenchyma, introducer needle outside the lesion, procedure time  $> 60$  minutes, and presence of alveolar hemorrhage. Non-diagnostic biopsies with a history of malignancy or atypical cells on pathology were more likely to be malignant ( $p = 0.043$  and  $p = 0.001$ ).

**Conclusion:** The predictive factors for a non-diagnostic biopsy were lesion size  $\leq 15$  mm, needle tract traversing emphysema, introducer needle outside the lesion, procedure time  $> 60$  minutes, and presence of alveolar hemorrhage. Thirty-six percent of the non-diagnostic biopsies yielded a malignant diagnosis. In cases with a history of malignancy or the presence of atypical cells in the biopsy sample, a repeat biopsy or surgical intervention should be considered.

**Keywords:** Adults; Lungs; Biopsy/needle aspiration; Non-diagnostic; Complications

## INTRODUCTION

Computed tomography-guided percutaneous transthoracic needle biopsy (PTNB) has become a widely accepted technique for establishing a diagnosis in patients with

pulmonary lesions due to its high accuracy, ranging from 83–97% (1-3). This procedure is minimally invasive, safe, and has a short recovery time and a low complication rate (4-7).

When a diagnosis of malignancy is established by PTNB, the management algorithm is usually straightforward because of the low false-positive rate (0–0.2%) (8). When a specific benign diagnosis is rendered, such as hamartoma or granuloma, the result is usually considered a true reflection of the biopsied lesion. The presence of a positive biopsy culture (when there is no suspicion of post-obstructive pneumonia) supports the likelihood of a benign lesion due to the low likelihood of a false positive culture (9). However, when a non-diagnostic result is obtained, uncertainty may arise over how to proceed.

Received January 9, 2019; accepted after revision July 17, 2019.

**Corresponding author:** Shaunagh McDermott, MD, Department of Radiology, Massachusetts General Hospital, 55 Fruit Street, Founders 202, Boston, MA 02114, USA.

• Tel: (1617) 7244254 • Fax: (1617) 7240046

• E-mail: [mcdermott.shaunagh@mg.harvard.edu](mailto:mcdermott.shaunagh@mg.harvard.edu)

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Although PTNB is widely performed in daily practice, only a limited number of studies have analyzed the final diagnoses of non-diagnostic biopsies. Prior studies have reported a high percentage of non-diagnostic cases, up to 15% (10), which may result in a delay in diagnosis and treatment. Most of these prior studies were limited by a small number of cases or were focused on specific lesions, such as ground glass lesions or suspected infection. One of the largest studies included patients from three different centers and samples from lung, mediastinal, and pleura to achieve a study group of 980 cases (9). A more recent multicenter study examining the malignancy risk of non-diagnostic PTNB of lung lesions included patients from eight different centers and utilized many different imaging modalities to obtain a study group of 9384 cases (11).

We therefore performed a large single-center analysis of PTNB of lung-only lesions to determine the predictive factors for a non-diagnostic result and the final diagnosis of pulmonary lesions with an initial non-diagnostic CT-guided PTNB result.

## MATERIALS AND METHODS

This study was designed as a retrospective single-center study and performed in accordance with the Health Insurance Portability and Accountability Act. Due to the retrospective nature of the study protocol, the Institutional ethical Review Board waived the need for informed consent.

### Medical Record Review

Medical records and chest CT images of all patients who underwent a CT-guided PTNB between July 2009 to June 2013 were retrospectively reviewed by two board certified chest radiologists, both with 3 years of experience in chest radiology. A total of 894 consecutive CT- PTNBs were performed over the 4-year period in a single academic thoracic radiology institution.

The patients' records were reviewed to determine the histologic interpretation of the PTNB. The biopsy results were classified into the following three categories: malignancy, benign, and non-diagnostic. Malignancy included cases where malignant cells or cell suspicious for malignancy were described. Benign disease was defined as a benign neoplasm, such as hamartoma, a granulomatous lesion, such as sarcoidosis, a benign process, such as organizing pneumonia, or inflammatory cells with positive bacterial, fungal, or mycobacterial cultures. A

non-diagnostic result was defined as the presence of normal respiratory elements, atypical cells, nonspecific inflammatory cells, blood, inadequate for interpretation, and cases where no specific diagnoses had been made.

The clinical variables, including age, sex, and history of prior malignancy, were also extracted from the patients' records. The radiologic variables analyzed for each patient included the size of the biopsied nodule, and whether the nodules were solid, part-solid, pure ground glass, or cavitory, or if a consolidation was biopsied. CT images obtained at the time of biopsy were reviewed. The biopsy-related variables included distance between the pleura and the nodule along the needle path, presence of emphysema along the needle path, whether the needle tip was in the lesion, and the procedure time (which was from the time of the initial localizing scan to the time when the last image was obtained prior to removing the needle). Any complications during or after the procedure were also recorded.

In the non-diagnostic cases, the final diagnosis was established either through surgical resection, repeat biopsy, or clinical and radiologic follow-up for least two years after the biopsy. A final diagnosis of benignity was made if 1) a specific benign diagnosis was made by pathology on the initial biopsy, re-biopsy, or surgical resection; 2) the lesion spontaneously resolved without chemotherapy or radiation; or 3) the lesion remained stable or decreased in size on imaging follow-up of at least two years. Those with imaging follow-up less than 2 years were excluded.

### Needle Biopsy Technique

All biopsies were performed by one of six dedicated interventional thoracic radiologists with 10–25 years of experience. All procedures were performed under CT guidance using a 16-multidetector CT scanner (Lightspeed, GE Healthcare, Milwaukee, WI, USA). Patients were placed in the prone, supine, or oblique position, depending on the location of the lesion, to avoid crossing bullae, emphysema, and fissures. A localizing CT scan was performed using initially 5-mm and then 2.5-mm slices to decide on the point of entry and perform the biopsy.

The biopsies were performed under local anesthesia (1% xylocaine without epinephrine) and moderate sedation with intravenous midazolam and fentanyl. All biopsies were performed with a 19-gauge thin-walled coaxial introducer needle (Chiba Ultrathin, Cook Medical, Bloomington, IN, USA). Once the needle was in the lesion, the inner stylet was removed and the 22-gauge Chiba needle

(Cook Medical) was advanced through the lumen of the 19-gauge introducer-needle. Tissue samples were obtained in quick, short movements while suction was applied with an attached 10-mL syringe. To reduce the risk of air embolization, saline solution was placed in the well of the introducer needle during needle exchanges to provide a water seal (12).

Aspirates on sterile glass slides were reviewed by on-site cytopathologists to determine if diagnostic material was present. If infection was suspected or if malignancy was not confirmed by the on-site cytopathologist, further aspirates were obtained and sent to a microbiology laboratory. When appropriate and safe, core biopsy specimens were obtained using a 20-gauge biopsy needle (Cook Medical) with a 1- or 2-cm needle throw.

When an intraprocedural pneumothorax was present, if feasible, air would be aspirated as the needle was withdrawn. After removal of the biopsy needle, the patient was immediately rolled over to place the puncture site in the dependent position to minimize the risk of pneumothorax (13). The patient was encouraged to lie still and breathe gently during the 3-hour recovery period. Chest radiographs were obtained at 1 and 3 hours after the procedure.

Complications were categorized in accordance with the Society of Interventional Radiology clinical practice guidelines (14).

### Statistical Analysis

Patients were classified into two groups according to the diagnostic performance (diagnostic vs. non-diagnostic) and final diagnosis of initially non-diagnostic biopsies (benign vs. malignant). We included all patients who underwent a CT-guided PTNB in the evaluation of predictive factors for a non-diagnostic biopsy. For the evaluation of final diagnosis of initially non-diagnostic biopsy, we excluded patients with a non-diagnostic biopsy and those in whom a final diagnosis could not be made, either because there was no diagnostic pathology by resection or repeat biopsy, or with imaging follow-up of less than two years.

Comparison of demographic data and target characteristics between the two groups was performed using binary logistic regression. Multivariable logistic regression, using variables yielding a  $p$  value of  $< 0.1$  in the univariable logistic regression analysis, was performed to identify independent risk factors for diagnostic success. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A  $p$  value

less than 0.05 was considered statistically significant. All statistical calculations were performed using StataCorp. 2013. Stata Statistical Software (Release 13, StataCorp LP, College Station, TX, USA).

## RESULTS

### Demographic Information

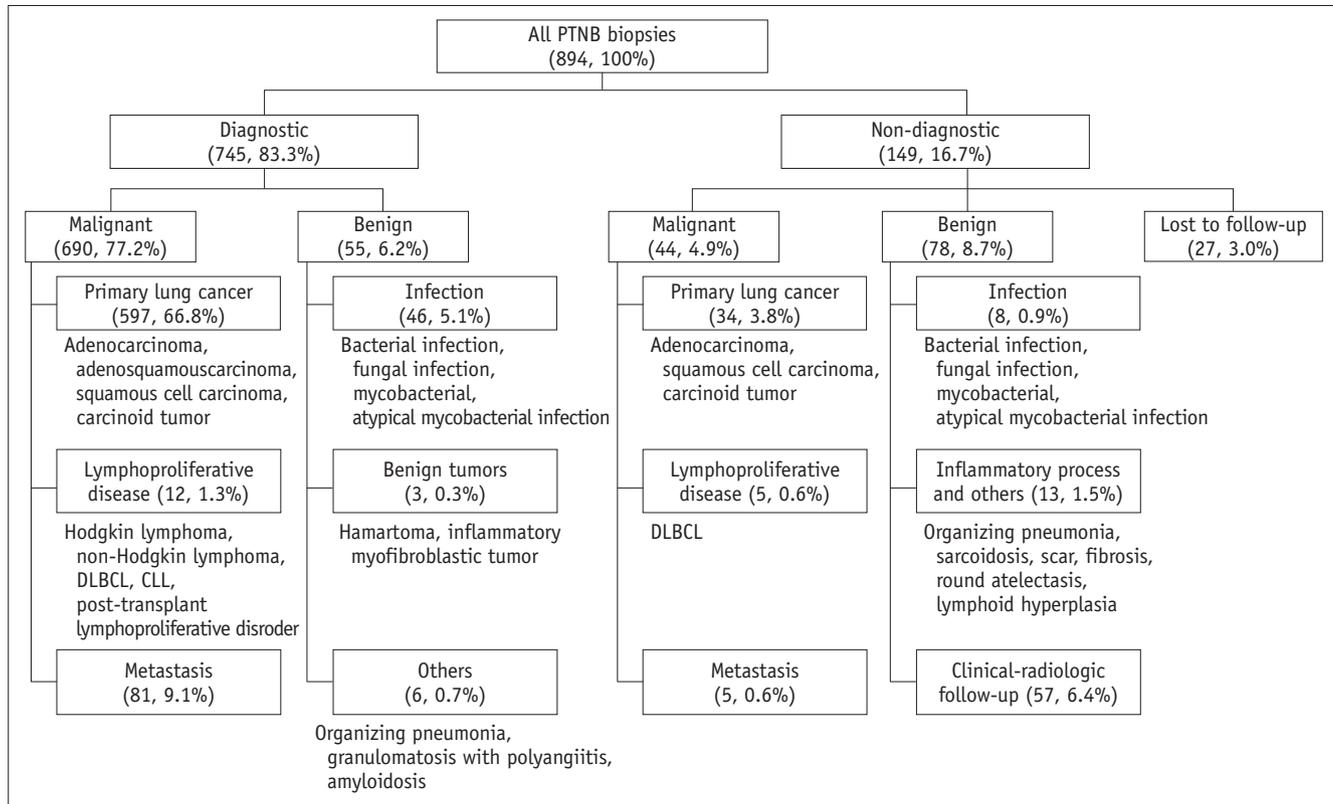
Between July 1, 2009 and June 30, 2013, 894 consecutive CT-guided PTNBs were performed in 861 patients. There were 149 non-diagnostic biopsies, yielding an overall non-diagnostic rate of 16.7% (149/894). Of 149 non-diagnostic biopsies, 27 were excluded because of follow-up less than 2 years. Thus, there were 867 biopsies which had been performed in 834 patients, 122 of which were non-diagnostic. Thirty-three patients had two biopsies of the same lesion, which were counted as separate events. There were 383 males and 451 females with patient ages ranging from 18 to 92 years (mean age,  $67 \pm 26$  years). The distribution of all biopsy results is detailed in Figure 1. The final diagnosis was malignancy in 85% (734/867) (Fig. 2) and benign disease in 15% (133/867) of all biopsies (Fig. 3). The distribution of malignancy, including primary lung cancer, lymphoproliferative disease, and metastasis in both diagnostic and non-diagnostic biopsies is detailed in Table 1.

### Diagnostic Versus Non-Diagnostic Biopsies

The difference in non-diagnostic biopsy rates for patients with a malignant final diagnosis (44/734, 6%) and benign lesions (78/133, 59%) was statistically significant ( $p = 0.001$ ). The differences in the non-diagnostic biopsy rates in the malignant group for primary lung cancer (34/631, 5%), lymphoproliferative disease (5/17, 29%), and metastasis (5/86, 6%) were statistically significant ( $p = 0.001$ ). Among the lung cancers, carcinoid tumor had a higher percentage of non-diagnostic biopsy; however, the number of patients with carcinoid tumors was small.

There was a statistically significant difference in the non-diagnostic rates according to the lesion size, which were 19% (32/166) for lesions  $\leq 15$  mm and 13% (90/701) for lesions  $> 15$  mm ( $p = 0.032$ ). There were no statistically significant differences between the initially diagnostic and non-diagnostic groups in demographic data including age, sex, and lesion characteristics including attenuation, location, necrosis, and pleural contact.

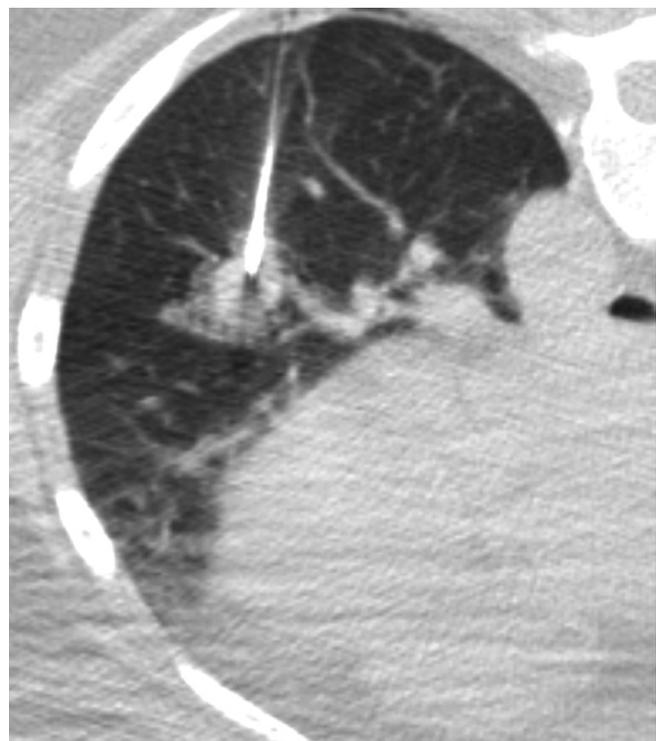
There was a higher non-diagnostic rate when the biopsy needle traversed emphysematous lung parenchyma (18/74,



**Fig. 1.** Flow diagram shows diagnoses and distribution of initial biopsy results of 894 consecutive biopsies. CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, PTNB = percutaneous transthoracic needle biopsy

25%) compared to when it did not (104/793, 13%) ( $p = 0.008$ ). The non-diagnostic rate was significantly higher when the introducer needle was outside the lesion (7/10, 70%) compared with when it was at the edge or within the lesion (115/857, 13%) ( $p = 0.001$ ). There was also a significant difference in the non-diagnostic rates stratified by procedure time, which were 10% (48/504) for procedure time  $\leq 60$  minutes and 20% (74/363) for procedure time  $> 60$  minutes ( $p = 0.001$ ). There were no statistically significant differences between the initial diagnostic and non-diagnostic groups in other aspects of the biopsy technique, including the patient position, needle traversing aerated lung, and needle path length. There was also no statistically significant difference between these two groups based on the operator's experience ( $p = 0.907$ ).

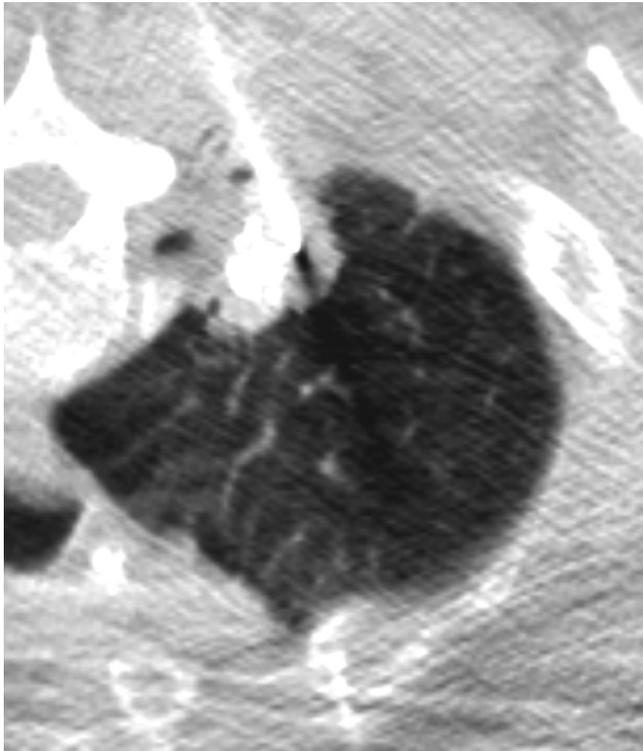
Among the 867 biopsies, 100% (867/867) had fine needle aspiration (FNA), 43% (371/867) had core needle biopsy (CNB), and 27% (230/867) had microbiology. The differences in the non-diagnostic biopsy rates for patients undergoing FNA with CNB (48/371, 13%) and FNA without CNB (74/496, 15%) were not statistically significant ( $p = 0.406$ ). This remained true when the malignant final diagnosis and benign final diagnosis groups were reviewed



**Fig. 2.** 61-year-old woman with carcinoid tumor. Prone unenhanced chest CT scan obtained during PTNB revealed left lower lobe nodule surrounded with minimal alveolar hemorrhage. Diagnosis was made on FNA. FNA = fine needle aspiration

separately ( $p = 0.551$  and  $p = 0.521$ , respectively).

A pneumothorax was detected in 207 cases (24%) and 20 cases (2%) required chest tube drainage. There was a significant difference in pneumothorax rate between cases in which the needle traversed emphysema (33/74, 45%)



**Fig. 3.** 77-year-old man with amyloidoma. Prone unenhanced chest CT scan obtained during PTNB revealed right upper lobe nodule with calcification. Diagnosis was made on CNB. CNB = core needle biopsy

and cases in which it did not (174/793, 22%), respectively ( $p = 0.001$ ) (Fig. 4). However, there was no statistically significant difference in the non-diagnostic rate between the presence (18%, 37/207) or absence (13%, 85/660) of pneumothorax ( $p = 0.071$ ).

Mild perilesional hemorrhage was seen in the majority of cases (55%); however, self-limiting hemoptysis was seen in only 17 cases (2%). Non-diagnostic rates in patients with alveolar hemorrhage (83/478, 17%) were significantly higher than those in patients without alveolar hemorrhage (39/389, 10%) ( $p = 0.002$ ) (Fig. 5). Hemothorax was detected in eight cases (1%), only one case (0.001%) required chest tube drainage and a blood transfusion. Table 2 details the demographic data, lesion characteristics, technique of PTNB and complications of initially diagnostic and non-diagnostic groups of 867 biopsies.

A multivariable regression model was made including sex, lesion size, pleural contact, procedure length, needle traversing emphysema, needle within the lesion, pneumothorax and alveolar hemorrhage as significant univariate regression variables. In this model, we could demonstrate that smaller lesion size (OR 1.027; 95% CI 1.011–1.044;  $p = 0.001$ ), the presence of pleural contact (OR 0.359; 95% CI 0.277–0.568;  $p = 0.001$ ), needle traverse emphysema (OR 0.424; 95% CI 0.229–0.785;  $p = 0.006$ ), needle not within the lesion (OR 12.562; 95% CI 3.167–49.829;  $p = 0.001$ ) and longer procedure time (OR 0.983; 95% CI 0.974–0.992;  $p = 0.001$ ) were independent risk factors for a non-diagnostic biopsy in our study.

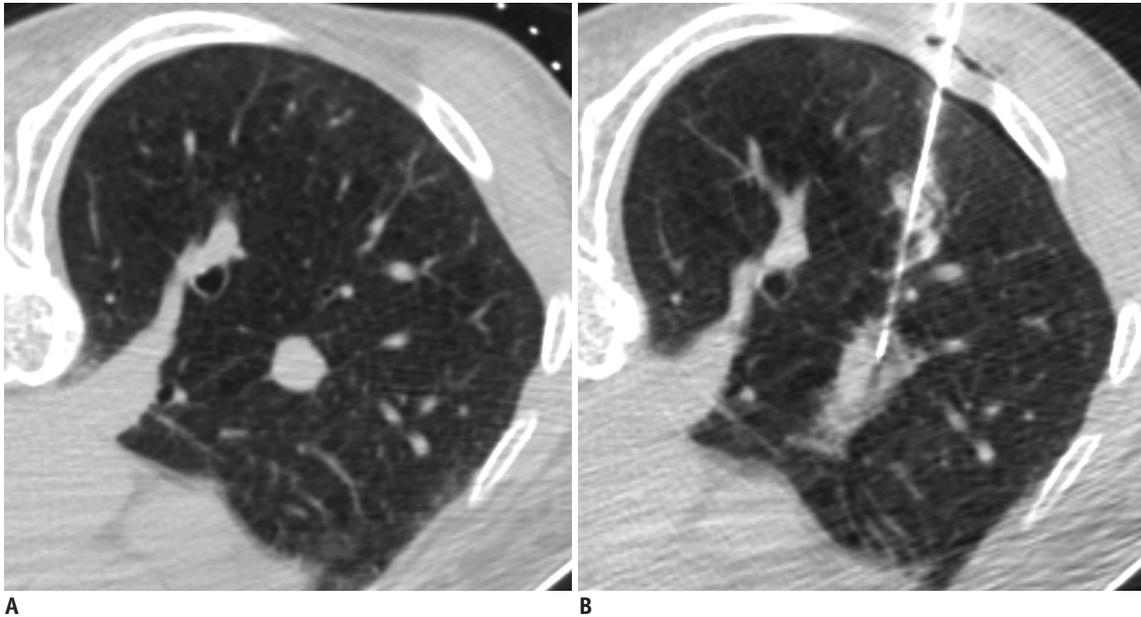
**Table 1. Distribution of Malignant Diagnoses for Both Diagnostic and Non-Diagnostic Biopsies**

Category of Malignancy	Diagnostic Biopsies	Non-Diagnostic Biopsies	Total
	n (%)	n (%)	
Primary lung cancer	597 (95)	34 (5)	631
Adenocarcinoma	416 (96)	19 (4)	435
Squamous cell carcinoma	84 (92)	7 (8)	91
Large cell carcinoma	1 (100)	0 (0)	1
Small cell lung cancer	19 (100)	0 (0)	19
Carcinoid tumor	10 (83)	2 (17)	12
Others	67 (92)	6 (8)	73
Lymphoproliferative disease	12 (71)	5 (29)	17
Non-Hodgkin lymphoma	8 (73)	3 (27)	11
Hodgkin lymphoma	1 (100)	0 (0)	1
Chronic lymphocytic leukemia	1 (100)	0 (0)	1
Lymphoproliferative disorder	2 (67)	1 (33)	3
Not otherwise specified	0 (0)	1 (100)	1
Metastasis	81 (94)	5 (6)	86
Total	690 (94)	44 (6)	734

**Non-Diagnostic Biopsies**

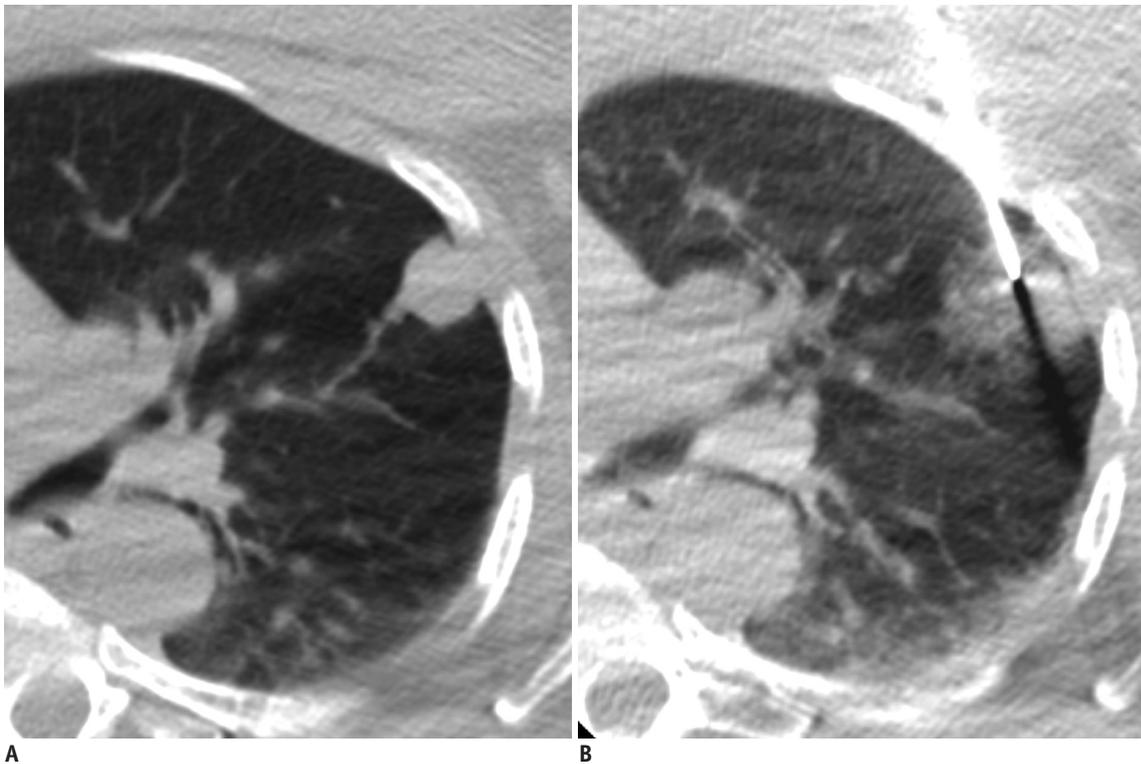
Thirty-six percent (44/122) of non-diagnostic biopsies ultimately yielded a diagnosis of malignancy. The only

statistically significant difference in the demographic data between the benign and malignant groups was the age ( $p = 0.027$ ). There were no statistically significant differences in



**Fig. 4. 77-year-old woman with final diagnosis of squamous cell carcinoma.**

(A) Localizing CT scan showed 1.4-cm central right lower lobe nodule (B) CT scan during biopsy revealed small pneumothorax and minimal alveolar hemorrhage around nodule and along needle tract. Fine needle aspirate was non-diagnostic and CNB was not performed. Final diagnosis was made at surgery.



**Fig. 5. 56-year-old woman with final diagnosis of histoplasmoma.**

(A) Localizing CT scan revealed 1.6-cm peripheral nodule in left upper lobe (B) CT scan obtained during biopsy revealed minimal alveolar hemorrhage around nodule. PTNB (both FNA and CNB) was non-diagnostic and final diagnosis was made at surgery.

**Table 2. Demographics, Characteristics, Technique of PTNB and Complications Associated with Initial Diagnostic and Non-Diagnostic Results**

	Diagnostic Group (n = 745)		Non-Diagnostic Group (n = 122)		P
	n	%	n	%	
<b>Demographics</b>					
Age, years					0.893
Mean	67.2		66.8		
Range	18.1–91.9		25.4–88.7		
<b>Sex</b>					
Male/female	354/391		47/75		0.065
<b>Lesion characteristics</b>					
Size of nodule, mm					0.001*
Mean	34.3		25.2		
Range	7.6–159.3		6.9–84.9		
≤ 15	134	18	32	26	0.032*
<b>Morphology</b>					
Solid	598	80	93	76	
GGO	27	4	8	7	
Part-solid	48	6	5	4	
Consolidation	28	4	5	4	
Cavity	44	6	11	9	
Necrosis	46	6	9	7	0.614
Pleural contact	391	52	75	61	0.065
<b>Procedure techniques</b>					
Patient position					0.900
Supine	160	21	28	23	
Prone	493	66	78	64	
Oblique	92	12	16	13	
<b>Needle approach</b>					
Anterior	196	26	35	29	0.943
Posterior	509	68	78	64	
Lateral	40	5	9	7	
Needle traverse aerated lung	539	72	89	73	0.915
Needle traverse emphysema	56	8	18	15	0.008*
Needle path length, mm (mean, range)	28 (0–110.6)		30.8 (5–79.7)		0.456
Needle within lesion	742	100	115	94	0.001*
Needle crossed fissure	24	3	4	3	0.974
Total time, mins (mean, range)	58 (21–175)		68 (20–141)		
Total time ≤ 60 mins	456	61	48	39	0.001*
<b>Complications</b>					
Pneumothorax	170	23	37	30	0.080
Air aspiration	34	5	11	9	
Chest tube drainage	16	2	4	3	
Alveolar hemorrhage	395	53	83	68	0.002*
Hemoptysis	10	1	7	6	
Hemothorax	5	1	3	2	
Need treatment	1	0.001	0	0	
Air embolism	0	0	0	0	
Death	0	0	0	0	

\*p values are significant. GGO = ground glass opacity, PTNB = percutaneous transthoracic needle biopsy

the other demographic data, including sex, smoking history, and lesion characteristics and how the nodule behaved on imaging prior to the PTNB. Table 3 details the demographic data and lesion characteristics of malignant and benign groups in the 122 non-diagnostic cases.

Of 60 patients with a history of prior malignancy (60/122, 49%), 27 cases were malignant (45%) and 33 were benign (55%). In the 62 patients without a prior history of malignancy, 17 cases were malignant (27%) and 45 were benign (73%). This difference in final diagnosis of malignancy between those with a history of malignancy and those without history of malignancy was statistically significant ( $p = 0.043$ ).

Of the 122 non-diagnostic biopsies, 42% (51/122) had

insufficient tissue for diagnosis, 23% (28/122) had atypical cells present, and 35% (43/122) described normal tissue elements in the pathology report. In cases where atypical cells were present, 64% (18/28) had a final diagnosis of malignancy, compared to 39% (20/51) of cases where there was insufficient tissue for diagnosis and 14% (6/43) in cases where normal respiratory tissue was obtained ( $p = 0.001$ ).

Another multivariable regression model was constructed including age, sex, history of prior malignancy and non-diagnostic pathology result as significant univariate regression variables. In this model we could demonstrate that female gender (OR 0.382; 95% CI 0.161–0.905;  $p = 0.029$ ), history of prior malignancy (OR 2.756; 95% CI

**Table 3. Characteristics Associated with Final Malignant and Benign Diagnoses of 122 Non-Diagnostic Biopsies**

	Malignant (n = 44)		Benign (n = 78)		P
	n	%	n	%	
<b>Demographics</b>					
Age, years					0.027*
Mean	68		66.1		
Range	33.2–85.3		25.4–88.7		
<b>Sex</b>					
Male/female	12/32		35/43		0.056
Smoker <sup>†</sup>	32	76	45	63	0.756
History of prior malignancy	27	61	33	42	0.043*
<b>Lesion characteristics</b>					
Size of nodule, mm					0.408
Mean	26.1		24.6		
Range	6.9–73.2		8.4–84.9		
Morphology					0.923
Solid	34	77	59	76	
GGO	3	7	5	6	
Part-solid	3	7	2	3	
Consolidation	1	2	4	5	
Cavity	3	7	8	10	
Necrosis	2	5	7	9	0.373
Pleural contact	26	59	49	63	0.687
How does nodule behave prior to bx					0.980
Increased	17	39	37	47	
Decreased	0	0	1	1	
Unchanged	3	7	10	13	
New	5	11	8	10	
No prior study	19	43	22	28	
<b>Non-diagnostic pathology result</b>					
Insufficient	20	45	31	40	0.018*
Atypical cell present	18	41	10	13	
Normal respiratory tissue	6	14	37	47	

\* $p$  values are significant. <sup>†</sup>Smoking status was only known for 42 with final diagnosis of malignancy and 71 with final benign diagnosis. bx = biopsy

**Table 4. Non-Diagnostic Biopsies and Methods by Which Their True Diagnoses Were Determined**

	Surgery n (%)	Repeat PTNB n (%)	Clinical-Radiologic Follow-Up n (%)	Total
Benign	22 (28)	0	56 (72)	78
Malignancy	26 (59)	10 (23)	8 (18)	44
Primary lung cancer	23 (68)	6 (18)	5 (15)	34
Metastasis	2 (40)	1 (20)	2 (40)	5
Lymphoproliferative disease	1 (20)	3 (60)	1 (20)	5
Total	48 (39)	10 (8)	64 (52)	122

Calculated percentages are from within each diagnostic category.

1.212–6.627;  $p = 0.016$ ), and presence of atypical cells (OR 0.541; 95% CI 0.334–0.877;  $p = 0.013$ ) were significant independent risk factors for a final diagnosis of malignancy.

In the 44 cases of malignancy initially found to be non-diagnostic on PTNB, the final diagnosis was made at surgery in 26 cases, with re-biopsy in 10 cases, and clinical-radiologic follow-up in 8 cases. In the 78 benign cases initially found to be non-diagnostic on PTNB, the final diagnosis was made at surgery in 22 cases, and clinical-radiologic follow-up in 56 cases. The median and interquartile range of follow-up duration of all 122 initially non-diagnostic biopsies was 227 days and 1161 days, respectively, and for the 64 cases in which the final diagnosis was made by clinical-radiologic follow-up was 1164 and 1080, respectively. Table 4 details the main method by which the final diagnosis was determined after the initial non-diagnostic biopsy.

## DISCUSSION

PTNB of the thorax is commonly performed to obtain the diagnosis of pulmonary lesions discovered on imaging. However, when the PTNB result is non-diagnostic, a clinical decision must be made as to whether the patient needs repeat PTNB, surgical intervention, bronchoscopy, serial imaging, or empiric therapy. Knowledge of the outcome and predictive factors of non-diagnostic biopsies can help inform such patient management decisions.

Prior studies have calculated that the non-diagnostic rate of CT-guided PTNB ranges from 1.3–15% (2, 10, 11, 15–17). Studies evaluating outcomes after a benign nonspecific biopsy found that false negative rates varied between 7–29% (18–21). The sensitivity of FNA (with or without CNB) in evaluating benign thoracic diseases varied from 17–91% (22–24).

In our four-year retrospective analysis of 894 CT-guided PTNBs, there were 149 non-diagnostic biopsies for a non-

diagnostic rate of 16.7%. Our slightly higher non-diagnostic rate may be due to a broader definition of a non-diagnostic biopsy compared to that in prior studies. Quint et al. (15) categorized biopsy results into malignant, benign specific, benign nonspecific, and non-diagnostic categories. In their study, non-diagnostic was defined as a case with only normal pulmonary tissue and/or insufficient tissue to render a diagnosis. We considered the benign nonspecific group also as a non-diagnostic result because the management and clinical implications of benign nonspecific and non-diagnostic categories were similar. Our non-diagnostic rate was lower than that in a recently published study of malignancy risk of non-diagnostic PTNB of lung lesions in which 27.6% of cases were non-diagnostic (11). This difference may be related to their inclusion of patients who underwent fluoroscopy- and ultrasound-guided biopsy, as well as CT-guided biopsy. The difference in the non-diagnostic rate may also be explained by their categorizing granulomatous inflammation, abscess or organizing pneumonia as nonspecific benign results. The availability of onsite cytopathology may also explain our lower non-diagnostic rate.

Our total study population of 894 patients had a high rate of malignancy (85%). This is similar to the findings of Fontaine-Delaruelle et al. (10) who also reported a high rate of malignancy (79%) in a series of 980 PTNBs. In our initially non-diagnostic PTNBs, we found a 36% rate of malignancy underscoring the need for further evaluation and follow-up of non-diagnostic biopsies. Prior studies also showed a 29–50% rate of malignancy on initially non-diagnostic biopsies (10, 15, 20). In our study, the false negative cases for malignancy were proven by surgery (59%), repeat biopsy (23%) or clinicoradiologic follow-up (18%). Repeat biopsy was performed in 16 patients of which 10 (63%) yielded a final diagnosis of malignancy. In prior studies, Fontaine-Delaruelle et al. (10) found that repeat PTNBs of the same target provided a final diagnosis

in 95% of cases and Montaudon et al. (25) found a 100% negative predictive value on second biopsy. In our non-diagnostic cases, a malignant final diagnosis was more likely in patients with a history of malignancy and patients with atypical cells reported on pathology. Lee et al. (11) also reported a higher likelihood of malignancy in lesions categorized as atypical cell lesions, compared to that for lesions with insufficient specimens and nonspecific benign categories.

Of the patients with a malignant final diagnosis, we found that lymphoproliferative disease had a statistically higher non-diagnostic rate. Of the 17 patients ultimately diagnosed with a lymphoproliferative disease, the initial biopsy diagnosed only 71% (12/17), compared to 95% of primary lung cancers (597/631), and 94% of metastasis (81/86). The difficulty in diagnosing lymphoma on PTNB is consistent with a prior report of PTNB of mediastinal lymphoma (26). For patients with benign lesions, the rate of non-diagnostic PTNB was significantly higher (59%, 78/133) than that in patients with malignant lesions (6%, 44/734).

Predictive factors of non-diagnostic results included lesion size  $\leq 15$  mm, an introducer needle outside the lesion, a needle tract traversing emphysematous lung parenchyma, the presence of alveolar hemorrhage during the procedure, and a total procedure time  $> 60$  minutes. A target  $\leq 15$  mm was also found to be predictive of a non-diagnostic biopsy result by Fontaine-Delaruelle et al. (10). An introducer needle inside the target is obviously important to achieve diagnostic material as reported by Klein and Zarka (27). Biopsy complications have also been previously reported to increase the likelihood of a non-diagnostic result (10). We found that the presence of alveolar hemorrhage independently increased the risk of a non-diagnostic result, possibly due to hemorrhage obscuring the lesion or early termination of the biopsy. Our study and prior studies showed that the presence of emphysema around a lesion increased the risk of pneumothorax (28); however, our study also showed an increased likelihood of a non-diagnostic result when the needle tract traversed emphysema ( $p = 0.008$ ). There was also a higher rate of non-diagnostic biopsy when the total procedure time  $> 60$  minutes. This longer procedure time may reflect the greater difficulty due to small size, difficult location, development of a complication, and/or the additional time required for the cytopathologist to process additional passes that are often required in non-diagnostic cases.

Some studies have found increased accuracy in both malignant and benign lesions when core biopsy is obtained in addition to FNA (29, 30). However, we found no statistically significant difference in the diagnostic performance between FNA alone and FNA with core biopsy. This is consistent with a systemic review by Yao et al. (30) which concluded there was insufficient evidence to support a difference in the diagnostic yield between FNA alone and FNA with core biopsy when diagnosing malignancy; however, they did comment that it appeared that core biopsy may be superior to FNA for classifying benign disease.

Our rate of pneumothorax was similar to that in prior reports ranging between 11.7–34% (7, 10, 20, 22, 31), with a low rate of chest tube drainage (2%) compared to prior studies (25, 31). Our incidence of mild perilesional hemorrhage (55%) was slightly higher than previously reported values (23, 25); however only 2% developed self-limited hemoptysis. Eight patients developed hemothoraces (1%), with chest tube drainage required in one patient (0.001%).

Our study has several limitations, the first of which is the retrospective design. Second, we were required to exclude 27 non-diagnostic biopsies (18%) due to the absence of a 2-year follow-up to determine a final diagnosis. Finally, our study was based on the experience of a single academic medical center with dedicated thoracic interventional radiologists and thoracic cytopathologists which may be different than practice at other medical institutions.

In conclusion, the predictive factors for a non-diagnostic biopsy were lesion size  $\leq 15$  mm, needle tract traversing emphysema, introducer needle outside the lesion, procedure time  $> 60$  minutes, and presence of alveolar hemorrhage. Thirty-six percent of the non-diagnostic cases yielded a malignant diagnosis. In non-diagnostic cases with a history of malignancy, pathology showing atypical cells, or in cases where lymphoma is suspected, a repeat biopsy or surgical intervention should be considered due to the higher rate of malignancy. In cases where further intervention is not performed, we recommend repeat imaging to document stability or resolution of the lesion. If a lesion demonstrates growth, then a repeat biopsy or surgical intervention should be considered.

#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Shaunagh McDermott

<https://orcid.org/0000-0003-0200-9159>

Thanisa Tongbai

<https://orcid.org/0000-0003-4010-4376>

Nantaka Kiranantawat

<https://orcid.org/0000-0003-0828-8486>

Victorine Vining Muse

<https://orcid.org/0000-0001-9004-6624>

Carol Chia-chia Wu

<https://orcid.org/0000-0003-1005-0995>

Jo-Anne O'Malley Shepard

<https://orcid.org/0000-0003-1932-7620>

Matthew David Gilman

<https://orcid.org/0000-0002-2972-5684>

REFERENCES

1. Tsukada H, Satou T, Iwashima A, Souma T. Diagnostic accuracy of CT-guided automated needle biopsy of lung nodules. *AJR Am J Roentgenol* 2000;175:239-243
2. Takeshita J, Masago K, Kato R, Hata A, Kaji R, Fujita S, et al. CT-guided fine-needle aspiration and core needle biopsies of pulmonary lesions: a single-center experience with 750 biopsies in Japan. *AJR Am J Roentgenol* 2015;204:29-34
3. Poulou LS, Tsagouli P, Ziakas PD, Politi D, Trigidou R, Thanos L. Computed tomography-guided needle aspiration and biopsy of pulmonary lesions: a single-center experience in 1000 patients. *Acta Radiol* 2013;54:640-645
4. Manhire A, Charig M, Clelland C, Gleeson F, Miller R, Moss H, et al.; BTS. Guidelines for radiologically guided lung biopsy. *Thorax* 2003;58:920-936
5. Laurent F, Montaudon M, Latrabe V, Bégueret H. Percutaneous biopsy in lung cancer. *Eur J Radiol* 2003;45:60-68
6. Birchard KR. Transthoracic needle biopsy. *Semin Intervent Radiol* 2011;28:87-97
7. Yoon SH, Park CM, Lee KH, Lim KY, Suh YJ, Im DJ, et al. Analysis of complications of percutaneous transthoracic needle biopsy using CT-guidance modalities in a multicenter cohort of 10568 biopsies. *Korean J Radiol* 2019;20:323-331
8. Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. *Chest* 2003;123(1 Suppl):115S-128S
9. Gelbman BD, Cham MD, Kim W, Libby DM, Smith JP, Port JL, et al. Radiographic and clinical characterization of false negative results from CT-guided needle biopsies of lung nodules. *J Thorac Oncol* 2012;7:815-820
10. Fontaine-Delaruelle C, Souquet PJ, Gamondes D, Pradat E, De Leusse A, Ferretti GR, et al. Negative predictive value of transthoracic core-needle biopsy: a multicenter study. *Chest* 2015;148:472-480
11. Lee KH, Lim KY, Suh YJ, Hur J, Han DH, Kang MJ, et al. Nondiagnostic percutaneous transthoracic needle biopsy of lung lesions: a multicenter study of malignancy risk. *Radiology* 2019;290:814-823
12. Wu CC, Maher MM, Shepard JA. CT-guided percutaneous needle biopsy of the chest: preprocedural evaluation and technique. *AJR Am J Roentgenol* 2011;196:W511-W514
13. O'Neill AC, McCarthy C, Ridge CA, Mitchell P, Hanrahan E, Butler M, 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
14. Gupta S, Wallace MJ, Cardella JF, Kundu S, Miller DL, Rose SC; Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for percutaneous needle biopsy. *J Vasc Interv Radiol* 2010;21:969-975
15. Quint LE, Kretschmer M, Chang A, Nan B. CT-guided thoracic core biopsies: value of a negative result. *Cancer Imaging* 2006;6:163-167
16. Priola AM, Priola SM, Cataldi A, Errico L, Di Franco M, Campisi P, et al. Accuracy of CT-guided transthoracic needle biopsy of lung lesions: factors affecting diagnostic yield. *Radiol Med* 2007;112:1142-1159
17. Minot DM, Gilman EA, Aubry MC, Voss JS, Van Epps SG, Tuve DJ, et al. An investigation into false-negative transthoracic fine needle aspiration and core biopsy specimens. *Diagn Cytopathol* 2014;42:1063-1068
18. Anderson JM, Murchison J, Patel D. CT-guided lung biopsy: factors influencing diagnostic yield and complication rate. *Clin Radiol* 2003;58:791-797
19. Calhoun P, Feldman PS, Armstrong P, Black WC, Pope TL, Minor GR, et al. The clinical outcome of needle aspirations of the lung when cancer is not diagnosed. *Ann Thorac Surg* 1986;41:592-596
20. Savage C, Walser EM, Schnadig V, Woodside KJ, Ustuner E, Zwischenberger JB. Transthoracic image-guided biopsy of lung nodules: when is benign really benign? *J Vasc Interv Radiol* 2004;15(2 Pt 1):161-164
21. Wang Y, Li W, He X, Li G, Xu L. Computed tomography-guided core needle biopsy of lung lesions: diagnostic yield and correlation between factors and complications. *Oncol Lett* 2014;7:288-294
22. Greif J, Marmor S, Schwarz Y, Staroselsky AN. Percutaneous core needle biopsy vs. fine needle aspiration in diagnosing benign lung lesions. *Acta Cytol* 1999;43:756-760
23. Klein JS, Salomon G, Stewart EA. Transthoracic needle biopsy with a coaxially placed 20-gauge automated cutting needle: results in 122 patients. *Radiology* 1996;198:715-720
24. Yeow KM, Su IH, Pan KT, Tsay PK, Lui KW, Cheung YC, et al. Risk factors of pneumothorax and bleeding: multivariate analysis of 660 CT-guided coaxial cutting needle lung biopsies. *Chest* 2004;126:748-754
25. Montaudon M, Latrabe V, Pariente A, Corneloup O, Begueret H, Laurent F. Factors influencing accuracy of CT-guided

- percutaneous biopsies of pulmonary lesions. *Eur Radiol* 2004;14:1234-1240
26. Petranovic M, Gilman MD, Muniappan A, Hasserjian RP, Digumarthy SR, Muse VV, et al. Diagnostic yield of CT-guided percutaneous transthoracic needle biopsy for diagnosis of anterior mediastinal masses. *AJR Am J Roentgenol* 2015;205:774-779
27. Klein JS, Zarka MA. Transthoracic needle biopsy: an overview. *J Thorac Imaging* 1997;12:232-249
28. Topal U, Ediz B. Transthoracic needle biopsy: factors effecting risk of pneumothorax. *Eur J Radiol* 2003;48:263-267
29. Choi SH, Chae EJ, Kim JE, Kim EY, Oh SY, Hwang HJ, et al. Percutaneous CT-guided aspiration and core biopsy of pulmonary nodules smaller than 1 cm: analysis of outcomes of 305 procedures from a tertiary referral center. *AJR Am J Roentgenol* 2013;201:964-970
30. Yao X, Gomes MM, Tsao MS, Allen CJ, Geddie W, Sekhon H. Fine-needle aspiration biopsy versus core-needle biopsy in diagnosing lung cancer: a systematic review. *Curr Oncol* 2012;19:e16-e27
31. Lucidarme O, Howarth N, Finet JF, Grenier PA. Intrapulmonary lesions: percutaneous automated biopsy with a detachable, 18-gauge, coaxial cutting needle. *Radiology* 1998;207:759-765