

CT-Guided Core Needle Biopsy of Peripheral Lung Lesions with Onsite Adequate Evaluation: Review of 215 Cases

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Abstract

Background: CT-guided core biopsy and fine needle aspiration have been used for diagnosis of peripheral lung lesions, and both methods have advantages and disadvantages. In our institution, CT-guided core needle biopsy with onsite cytology adequacy evaluation of touch preparations is the standard method for evaluation of peripheral lung lesions.

Methods: The study was approved by Institutional Review Board. We retrospectively reviewed the cytology reports of all lung core needle biopsies during 2009-2012. The clinical information was collected from chart review.

Results: There were total 215 cases during the study period. The average lesion size (in 190 available cases) was 3.46 cm. The average passes were 3.3/lesion. The final diagnoses included 132 malignancies, 70 benign and 13 atypical. Twenty-four cases had follow-up resections. There were two false negative diagnoses due to sample errors and there was no false positive case with a positive predictive value of 100%. The final adequate rate was 99.5% (214/215), and only one case was unsatisfactory. In the 204 patients with available information of post-procedure chest X-ray, 140 (68.6%) had no pneumothorax, and 64 (31.4%) had pneumothorax including 48 mild (23.5%), 3 moderate (1.5%), 2 severe (1%), 3 tension pneumothorax (1.5%), and 8 with chest tubes placed during procedure (3.9%).

Conclusions: Our study showed that CT-guided core biopsy with onsite cytology evaluation has high adequate and low atypical rates. Lung core biopsy can provide more accurate tumor classification and specific diagnoses for non-neoplastic lesions. Adequate tissue is often available for molecular study. The complication rate of pneumothorax in core needle biopsy is compatible to that of fine needle aspiration.

Keywords: Computed tomography; Core needle biopsy; Rapid onsite evaluation; Lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death in the United States for both males and females. According to United States Cancer Statistics (USCS), in 2009, 205,974 people in the United States were diagnosed with lung cancer, including 110,190 men and 95,784 women and 158,081 people died from lung cancer, including 87,694 men and 70,387 women [1]. Lung is also one of the most common metastatic sites of many other primary cancers. Tissue is often required to differentiate primary from metastasis, benign lesions from malignant lesions, and further classify a primary lung cancer for treatment. Tissue can be either cytology or histology specimens. The cytology specimens include sputum, bronchial brushing, washing, alveolar lavage, and fine needle aspiration (FNA). FNA includes CT guided (CT-FNA), Wang needle and endobronchial ultrasound guided (EBUS). CT-FNA is often used for peripheral lung lesions and CT-guided core needle (CT-CN) biopsy can also be used for that purpose. Both CT-FNA and CT-CN have been documented to be effective for malignancy diagnosis. The most common complication is pneumothorax, and hemorrhage while air embolism and tumors seeding are rare in both fine needle aspiration and core needle biopsies [2-7].

CT-CN may have advantage over CT-FNA for obtaining more tissue to perform immunohistochemistry and/or molecular studies [2,3]. A specific lung cancer classification is often mandatory using the limited tissue material, because of the availability of variable targeted treatments. In addition, some treatment may improve outcome in a patient subpopulation, but contraindicated in patients with other type of tumor. For example, Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) can only be used in patients with non-squamous cell lung carcinoma, due to fatal hemorrhagic events

in patients with squamous cell lung carcinoma [8]. With the demands of personalized medicine and improved understanding of the molecular pathways of different lung cancers, multiple analyses are needed, such as *EGFR* and *KRAS* mutation analysis and *ALK* translocation [9,10]. In 2011, a multidisciplinary expert panel representing the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a major revision of lung cancer classification, which also emphasizes that the tissue sample should be preserved for not only morphological diagnosis, but also molecular testing [11]. Furthermore, CT-CN may provide more specific diagnosis for non-neoplastic lesions than CT-FNA.

Touch preparation from CT-CN with onsite rapid cytology evaluation can provide adequate assessment and triage specimens for appropriate studies such as flow cytometry or microbiology culture. The onsite cytology evaluation also can reduce unnecessary passes, improve the diagnostic rate and provide a preliminary cytologic diagnosis. In our institution, CT-CN with onsite cytology adequate evaluation is the standard method for evaluation of peripheral lung lesions, and here we report our institutional experience.

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Materials and Methods

Institutional Review Board approval for this study was obtained. The cytopathology archives of Memorial Hermann Hospital were retrospectively searched for CT-CN of peripheral lung lesions between January 1, 2009 and December 31, 2012. There were 215 cases during this four-year period. Chest wall, pleural or mediastinal biopsies were not included in this study. All the procedures were performed by radiologists. A pathologist was present during the procedure for rapid on-site cytology evaluation (ROSA). For preparing touch preparation cytology for the on-site evaluation, the cores were gently rolled against glass slides to obtain imprint smears. The slides were air-dried and stained with Diff-Quik for immediate on-site evaluation to determine the adequacy of the specimen. Additional slides of touch preparation were fixed in cytology preservative (CytoLyt) and later stained with Papanicolaou stain for further cytological assessment. The core biopsies were fixed in formalin and embedded in paraffin for routine H&E evaluation.

Information including age, lesion size, number of passes, immunohistochemistry, histochemical stains, onsite adequate assessment and final diagnosis was collected from the cytopathology reports. Clinical information including patients' history, imaging

Diagnosis	Number of cases
I. Benign	70
Granulomatous inflammation	10
Organizing pneumonia	10
Fungal infection	3
Acid fast bacilli infection	1
Amyloidoma	1
Lung elastosis	1
Nonspecific	44
II. Malignant	132
Squamous cell carcinoma	25
Adenocarcinoma	40
NSCLS with both adeno and squamous components	10
NSCLS, favor adenocarcinoma	7
NSCLS, favor squamous	3
NSCLS, NOS	2
Small cell carcinoma or neuroendocrine	11
Metastatic carcinoma	26
Metastatic melanoma	2
Metastatic sarcoma	2
Malignant spindle cell neoplasm	1
Mesothelioma	1
B-cell lymphoma	1
Thymoma	1
III. Atypical	13

Table 1: Classification of benign, malignant and atypical lesions.

Case	Age	Lesion size (cm)	Core needle biopsy diagnosis	Follow-up procedure	Resection Diagnosis
1	65	1.4	Negative for malignancy	Lobectomy	Squamous cell carcinoma
2	75	1.9	Negative for malignancy	Wedge resection	Adenocarcinoma
3	73	5.3	Atypical	Lobectomy	Inflammatory pseudotumor
4	80	1.0	Atypical	Pneumectomy	Adenocarcinoma
5	80	2.3	Atypical	Wedge resection	Adenosquamous carcinoma
6	63	1.1	Atypical	Wedge resection	Metastatic hepatocellular carcinoma
7	68	2.5	Atypical	Lobectomy	Adenocarcinoma

Table 2: Summary of false negative cases and cases that definite diagnosis cannot be made on core needle biopsy (only cases with follow-up resections included).

studies was collected from Electronic Medical Records (EMR). The follow-up surgical pathology diagnosis in EMR was reviewed.

Statistical analyses were performed using SPSS Software. Chi-square tests were used to compare lesions with different sizes and pass numbers. P-values less than 0.05 were considered statistically significant.

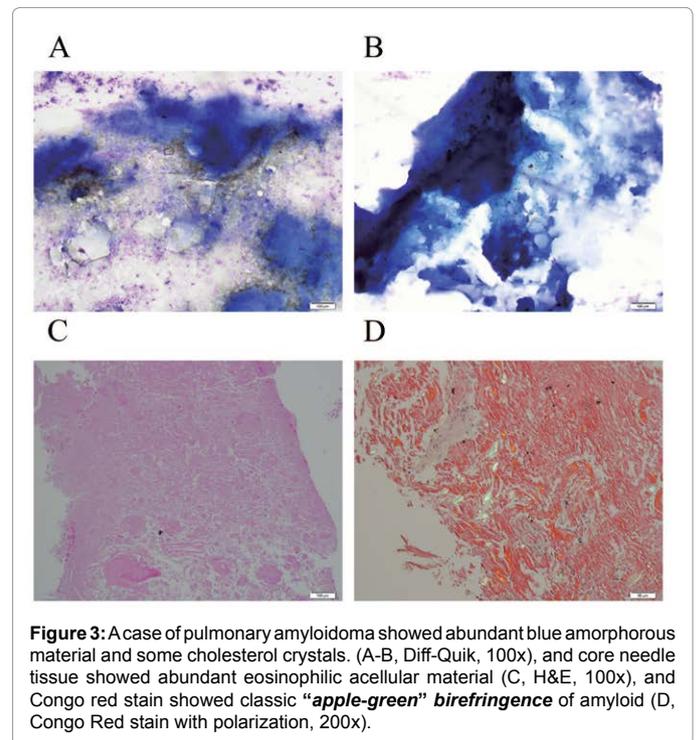
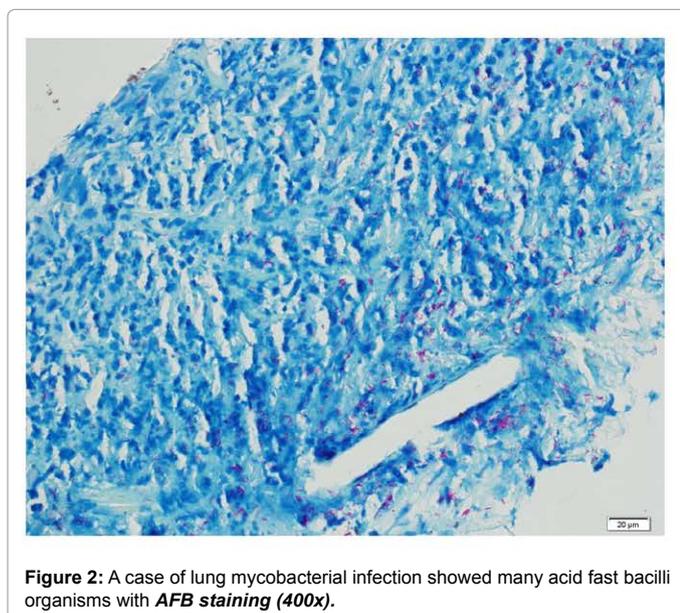
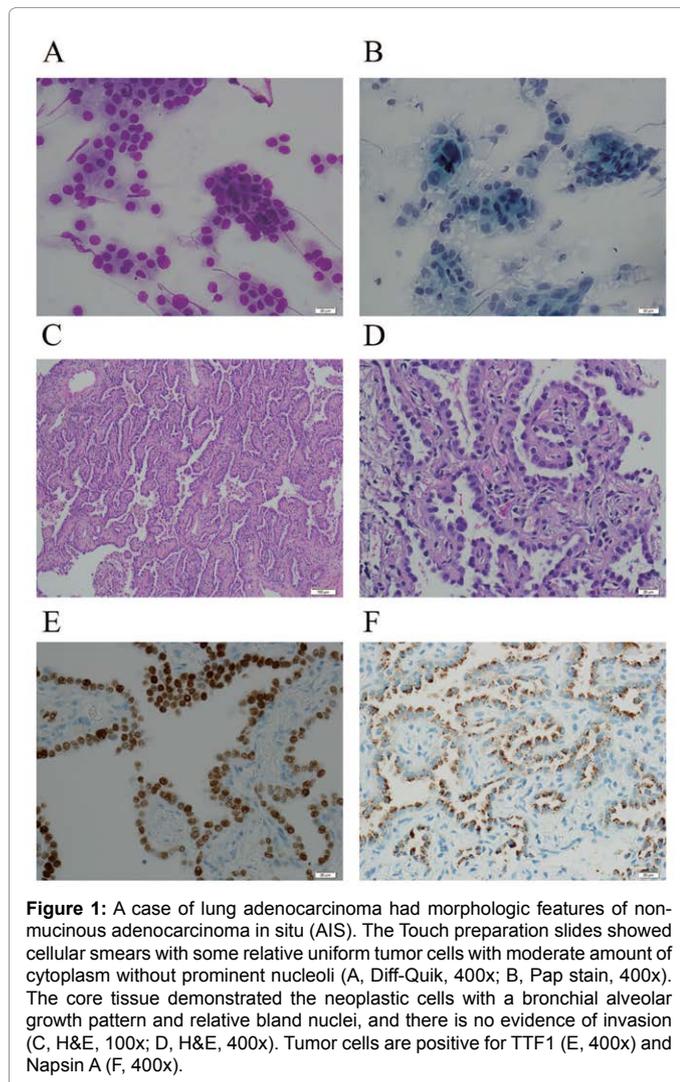
Results

There were a total of 215 specimens during the study period obtained from 207 patients (119 male and 88 female). The mean age of patients was 66 years (11 to 94 years). The average lesion size was 3.46 centimeters (0.4 to 20 centimeters) in 190 cases with available information. The average passes were 3.3 per lesion (1 to 10 passes per lesion). The average number of total slides submitted was 3.9 (1 to 19). The average number of Diff-Quick slides was 2.6 (1 to 10). The average number of Papanicolaou slides was 1.3 (0 to 9).

The final cytology diagnoses included 132 malignancies, 70 benign diagnoses, and 13 atypical diagnoses (Table 1). Twenty-four cases had follow-up surgical resections (11.2%). There were two false negative diagnoses due to sampling errors (Table 2). There was no false positive diagnosis. The positive predictive value was 100% (16/16 cases). Five cases with diagnosis of "atypical" had follow-up surgical resections. One lesion was diagnosed as inflammatory pseudotumor, and the other four lesions were diagnosed as malignant neoplasm in the follow-up resection specimen, including three primary lung neoplasms and one metastatic carcinoma (Table 2).

Immunohistochemistry was performed in 137 cases, including 111 malignant, 11 atypical and 15 benign. The average number of immunostains performed per case was 5 (2 to 21). The commonly used markers include CK7, CK20, TTF-1, p63, CK5/6, and Napsin A (Figure 1). Histochemical stains were performed in 53 cases. The most common histochemical stains were *acid fast bacilli (AFB)*, and *Grocott's Methenamine Silver (GMS) stain*. Fungal infection was confirmed by GMS stain in three cases, including one coccidioidomycosis, one cryptococcus and one fungus not specified. One case of mycobacterial infection was confirmed by AFB stain (Figure 2). One case of pulmonary amyloidosis was confirmed by Congo red stain, and both touch preparation and CT-CN showed amorphous paucicellular material that stained orange with *Congo red* and exhibited *apple-green birefringence* under polarized light (Figure 3). Of note, electron microscopy was performed in two cases, and molecular tests were performed in 15 cases. Flow cytometry and FISH were performed in one case of B cell lymphoma.

In the 204 patients with available information of post-CT-CN chest X-ray, 140 (68.6%) had no pneumothorax, and 64 (31.4%) had pneumothorax including 48 mild (23.5%), 3 moderate (1.5%), 2 severe (1%), 3 tension pneumothorax (1.5%), and 8 with chest tubes placed during procedure (3.9%). Two patients had pre-existing pneumothorax



and chest tube placement before the procedure and weren't included here. Mild pneumothorax was defined as tiny apical or 10%- 20% lung compression; moderate pneumothorax was defined as 30%-40% lung compression; severe pneumothorax was defined as 50%-60% lung compression; tension pneumothorax was diagnosed by the clinician and documented in the radiological reports or clinical notes. During the core needle biopsy procedures, the radiologists decided to insert a chest tube in 8 patients to prevent severe pneumothorax.

The cases were divided into three groups according to the lesion sizes (≤ 2.0 cm, 2.1-5 cm, > 5.0 cm). There was no statistically significant difference in pneumothorax rate among these three groups (Table 3, $p > 0.05$). When the cases were divided into three groups according to the number of passes (1 to 2 passes, 3 to 4 passes, and 5 passes or more). There was no statistically significant difference in pneumothorax rate among these three groups (Table 4, $p > 0.05$).

In addition, molecular test results were available in 15 cases, including successful testing ($n=11$) and quantity not sufficient ($n=4$).

Lesion size (cm)	Number of cases	Pneumothorax			
		Negative	Positive	NA	Rates of pneumothorax
≤ 2.0	69	42	24	3	36.4% (24/66)
2.1 to 5.0	83	53	26	4	32.9% (26/79)
> 5.0	38	26	9	3	25.7% (9/35)

Table 3: Comparison of core needle biopsies with different lesion sizes (in 190 cases).

Number of passes	Number of cases	Pneumothorax			
		Negative	Positive	NA	Rates of pneumothorax
1 or 2	79	53	22	4	29.3% (22/75)
3 or 4	94	60	28	6	31.8% (28/88)
5 or above	42	27	14	1	34.1% (14/41)

Table 4: Comparison of core needle biopsies with different number of passes.

Discussion

CT-CN with onsite cytology adequacy assessment using touch preparation has a low unsatisfactory rate [2,9,12,13]. In our study, the final adequate rate in our study was 99.5% with only one unsatisfactory case, and the satisfactory rates of the onsite evaluation were variable depending on the cytology diagnosis. The onsite evaluation satisfactory rates were 99.2% (131/132) for malignant diagnosis, 88.6% (62/70) for benign diagnosis, and 76.9% (10/13) for atypical diagnosis. A definite diagnosis (either positive or negative for malignancy) was made in 94% of the cases in our study and the atypical rate was 6%. CT-CN with onsite cytology adequate assessment also provided more accurate classification of malignant tumors (Table 1). Furthermore, a specific diagnosis was made in 37% of cases in the benign category, including granulomatous inflammation, organizing pneumonia, fungal and mycobacterial infection, amyloidoma and lung elastosis.

CT-CN and surgical resection correlation was performed in 24 cases (11.2%). There were two false negative diagnoses due to sampling errors (Table 2). There was no false positive diagnosis. In these two false negative cases, the malignant cells were not present in the touch preparation slides and the cores. So, a negative result of CT-CN does not totally exclude malignancy due to sampling error. Lesion size is a significant factor contributing to diagnostic accuracy in both FNA and biopsies [14-19]. Multiple studies reported higher rates and of false negative diagnosis of malignancy by FNA in relatively smaller lesions (equal or smaller than 1-3 cm). Mukherjee et al. [16] reported a negative predictive value of 66.67%, and Montaudon et al. [19] reported a negative predictive value of 73.3%. Kothary et al. [18] reported an accurate rate of 69.6%. However, Gelbman et al. [14] reported that those with false negative results had significantly larger nodules compared with true negative cases (mean, 27 mm versus 17 mm, $p = 0.04$). In our study, both lesions in the false negative cases were less than 2.0 cm. Extensive necrosis can also lead to false negative in core needle biopsies, which wasn't identified in our two cases. It is crucial to correlate with clinical and radiological information and decide which patients need a follow-up resection. In addition, there were five patients with the core needle biopsy diagnosis in the "atypical" category underwent follow-up resections. The resection diagnosis were positive for malignant in four cases (80%). Interestingly, the lesion sizes in all four cases were less than 3.0 cm (Table 2). This suggested that the patients in the "atypical" category needed to be followed up more carefully.

The core needle biopsy often has enough tissue for ancillary studies, including immunohistochemistry, histochemical stains, electron microscopy and molecular analysis, which makes it easier for tumor diagnosis and subclassification. In our study, immunohistochemistry was performed in 63% (136/215) of the cases and histochemical study was performed in 24.7% (53/215) of the cases. In two cases, electron microscopy was performed and contributed to the diagnosis of mesothelioma and metastatic melanoma respectively. Molecular study was successfully performed in 73.3% (11/15) of the cases.

In the current study, we reported a pneumothorax rate of 31.4%. Beslic et al. [2] compared the complication rate in CT-guided percutaneous trans-thoracic fine needle aspiration biopsies and core needle biopsies. They found that pneumothorax was detected in 9.7% of the patients with fine needle biopsy and 31.5% of the patients with the core needle biopsy respectively. However, other authors reported the pneumothorax rate was variable, ranging from less than 10% to more than 60% in fine needle aspiration and biopsies [19-25]. Wallace et al. [23] reported the highest rate of pneumothorax (62%) in lung nodules

1.0 cm or smaller underwent CT-guided transthoracic fine needle aspiration biopsy using either aspiration or capillary (nonaspiration) technique. Laspas et al. [24] reported a low pneumothorax rate (4%) in fine needle aspiration (size of the lesions biopsied was from 0.6 to 10 cm, mostly between 2 and 5 cm). Poulou et al. [25] recently published a study of 1000 patients underwent fine needle biopsy, needle core biopsy or both, and found complication rate reached 9.7%, including hemorrhage (6.2%), pneumothorax (2.8%), both hemorrhage and pneumothorax (0.5%) and hemoptysis (0.2%). Even though the incidence of pneumothorax is very low in their study, the incidence of hemorrhage is high, which was different from most other studies.

There are several other factors that can affect complication rate other than lesion size. Tachibana et al. [13] reported that core needle biopsy with immediate cytology evaluation can improve diagnostic performance and decrease the complication rate. Another possible cause of the big difference in complication rate is how the patients were monitored after the procedures. According to some authors, they observed the patients and post-procedure imaging studies were performed only when the patients developed symptoms, such as dyspnea, chest pain, or hemoptysis [24]. Some authors observed the inpatients in the ward, while the outpatients had CT scan or X-ray before they were dismissed from the hospital [24]. In our institution, post-procedure three-hour chest X-ray was routinely performed in all the patients, which identified more patients with mild pneumothorax. Since the clinical significant pneumothorax may take time to develop, we believe it may be beneficial for the patients to undergo routine post-procedure three-hour chest X-ray. In our study, the overall pneumothorax rate is about 31.4%, but the majority of these patients had mild pneumothorax (23.5%). The high rate in our study may be related to the close follow-up and the mandatory chest X-ray few hours after the procedure. In 3.9% of the patients, the radiologists decided to insert chest tubes during the procedure to prevent a significant pneumothorax from developing. It depended on the radiologists' experience which patient was treated with chest tube placement. Even though we observe a possible "trend" that the pneumothorax rates slightly increase with more number of passes, the difference was not statistically significant. Rizzo et al. [26] reported small lesions were significantly associated with the onset of parenchymal hemorrhage and pneumothorax. On the contrary, Kotharya et al. [18] studied 139 patients underwent CT-guided percutaneous fine-needle aspiration biopsy or 20-gauge core biopsy using an automated biopsy gun and found no correlation between nodule size and the incidence of complications. In our study, there was no significant difference in pneumothorax rate within three groups with different lesion sizes.

In 2011, a multidisciplinary expert panel representing the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a major revision of lung classification [11]. Since we retrospectively studied cases from 2009 and 2012, the majority of the cases were signed out before the new classification was implemented. In the future, it will be useful to further study the diagnosis and subclassification of lung cancers using the 2011 IASLC/ATS/ERS Classification. Also recently, National Lung Screening Trial (NLST), a randomized trial funded by National Cancer Institute (NCI) published its available data and showed that lung cancer death rates can be reduced by 20% when a high-risk group is screened with a low-dose computer tomography (CT) scan compared to chest radiography [27]. It is still too early to tell if low-dose computer tomography (CT) should be used to screen the high risk patients in the general population without carefully considering the cost-effectiveness and possibility of

overdiagnosis [28]. However, it is possible that, in the near future, more lung cancers will be diagnosed at an early stage and more core needle biopsies will be performed in small lesions.

In summary, CT-CN with onsite cytology evaluation of touch preparation is a valuable tool in the initial diagnosis of peripheral lung lesions and it provides more accurate classification of malignant tumors and more specific diagnosis on non-neoplastic lung lesions.

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