Transthoracic Imaging-Guided Biopsy of Lung Lesions: Evaluation of Benign Non-specific Pathologic Diagnoses

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Objective: *Explore the definitive diagnoses of imaging-guided transthoracic needle biopsies (TNB) with a pathological result of benign non-specific diagnosis in a tuberculosis-endemic area. The secondary goal was to characterize the initial CT imaging findings between malignancy and benign lesions.*
Material and Method: *All TNB diagnoses considered to have benign non-specific features at the Radiology Department between January 2007 and December 2011 were retrospectively reviewed for definitive diagnosis based on clinical impressions and for CT imaging characteristics.*
Results: *Sixty-seven cases with TNB were given a benign non-specific diagnosis and had complete pathologic or radiologic follow-ups. Of these 67 cases, 16 (23.9%) were malignant and 51 were benign. Two main definitive diagnoses of benign cases were pulmonary tuberculosis (32.8%) and pneumonia/lung abscess (23.9%). On the CT images, most of lesions in the group of pulmonary tuberculosis (14/22, 63.6%) were not enhanced after contrast administration ($p<0.005$), and necrotic mediastinal lymph nodes were significantly found more in final malignancy diagnoses ($p<0.005$).*
Conclusion: *The definitive diagnoses of benign non-specific diagnoses based on TNB in this tuberculosis-endemic area had a high rate of both malignancy and pulmonary tuberculosis. Hence, repeated biopsies or radiological follow-ups are advised.*

Keywords: *Benign non-specific diagnosis, Transthoracic needle biopsy (TNB), Pulmonary lesions*

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Pulmonary lesions pose challenge to clinicians and radiologists. Therapy for pulmonary lesions depends on an accurate pathologic diagnosis. In tuberculosis-endemic areas, differentiation between pulmonary tuberculosis and lung cancer by diagnostic imaging sometimes proves difficult. Nowadays, imaging-guided transthoracic needle biopsy (TNB) is widely performed to determine the patient's definite diagnosis, as it is a simple and cost-effective diagnostic tool. Previous studies have reported that TNB has high accuracy rate, ranging from 86% to 93%[1-4]. In a pathologic diagnosis of malignancy and benign specific, TNB has a specificity approaching 100%[1,5]. However, the final diagnoses of pathologic benign non-specific features include findings such as fibrosis, inflammation, and necrosis, which vary widely. Thirteen percent of cases have been reported to be malignant at excisional biopsy or radiologic follow-up[5]. Most of the previous studies were performed in non-endemic areas of tuberculosis; therefore, the main purpose of the present study was to explore the definite diagnosis of TNB with a pathological result of a benign nonspecific diagnosis in the tuberculosis-endemic area. Its secondary purpose was to characterize imaging findings between malignant and benign lesions.

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Material and Method

Patients

This retrospective study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. The medical records of 551 patients underwent TNB at the Radiology Department, Songklanagarind Hospital, between January 2007 and December 2011, were reviewed from

the hospital database. All cases needed to meet the following criteria, age >15 years, underwent TNB and the pathological report was a benign non-specific diagnosis, and had pre-procedure chest computed tomography (CT) images available. A benign non-specific diagnosis was defined as pathological findings such as fibrosis, inflammation without identification of specific microorganisms, and necrosis[5]. The exclusion criteria were a biopsy diagnosis of or suspicious for malignancy, definite benign diagnosis, or inadequate sample for evaluation. A benign specific diagnosis was defined as a pathological report of a benign neoplasm or specific infection[5]. Of the 551 total cases, 67 benign non-specific diagnoses were included in the study (ages ranged from 21 to 87 years, with a mean of 57 years).

Biopsy technique

Written informed consents for biopsy were obtained from all patients at the time of procedure. Every patient underwent a diagnostic CT scan with 3 to 5 mm contiguous slices prior to the decision regarding the most appropriate imaging modality for the guided biopsy. Fluoroscopic guidance was considered initially in all patients, but, if the lesion was not seen on both frontal and lateral chest radiographs, or was close to the heart or major vessels, a CT-guided procedure was preferred. If the lesion was in contact with the chest wall or a subpleural location, as demonstrated by ultrasonography, an ultrasound-guided biopsy was preferred. All TNBs were performed by experienced interventional radiologists or radiology residents. The latter were supervised by attending interventional radiologists.

Biopsies were performed with the use of single-pass or coaxial techniques. In a large majority of cases, the size of the coaxial needle was 19-gauge in order to accommodate a 20-gauge core biopsy. The number of core biopsies depended on the quality of the tissue produced and the ability of the patient co-operation. The specimen was sent for histopathological study in a formalin specimen container.

Endpoints

Surgical resection provided the definitive diagnosis for benignity or malignancy. Patients who did not undergo resection were considered to have malignant lesions in accordance with the following criteria: biopsy diagnosis of or suspicious for malignancy on repeat TNB or bronchoscopy, evidence of interval increase in size of the lesion on follow-up images, or clinical and/or radiographic evidence of extrapulmonary spread of the disease.

Lung lesions were deemed to be benign if decreasing in size, or rapid growth on follow-up images was observed, or when they remained stable or regressed during at least a 2-year follow-up period.

The final clinical diagnoses such as lung cancer, pulmonary tuberculosis, and bacterial pneumonia/lung abscess were determined based on clinical impression.

CT technique

Before 2009, CT examinations were performed with a single-slice CT scanner (Tomoscan M Single Slice CT, Philips Healthcare). After 2009, a 64-slice CT scanner (Brilliance CT 64-slice, Philips Healthcare) was used. The CT parameters were as follow: slice thickness = 3 to 7 mm, reconstruction interval = 1.5 to 7 mm, tube voltage = 80 to 120 kVp, and tube current-exposure time product = 100 to 240 mAs. About 80 to 120 mL of nonionic iodinated contrast material was administrated at a rate of 1.5 to 2.0 mL/sec. Images were obtained before contrast medium injection and 60 to 70 seconds after the initiation of the contrast medium intravenous injection, which represented the venous phase. Unenhanced images were unavailable in 19 patients.

Imaging analysis

Two radiologists reviewed all initial CT images at a PACS workstation, and the interpretation was done on a consensus basis. Lung lesions were investigated in terms of size, number, morphology, enhancement, and location. The lesions were considered enhanced if the extent of their enhancement was more than 15 HU[6]. Associated findings like pleural and mediastinal involvement, and evidence of extrapulmonary spreading were also analyzed.

Statistical analysis

Continuous variables were reported as mean ± SD and compared across outcome groups using a simple linear regression. Categorical variables were reported as number and percent and compared using Fisher's exact test. Statistical significance was defined as $p<0.05$.

Results

Over a period of five years, 67 cases (15 women, 52 men) that met the inclusion criteria were included in the present study. The mean (± SD) time of the follow-up images was 21 (±18) months.

Twenty-nine patients underwent ultrasound-guided biopsy, others 24 underwent fluoroscopic-guided biopsy, and 14 underwent CT-guided biopsy. Thirty-seven cases had repeat biopsy; five of them underwent surgical resection.

Concerning the definitive diagnoses of the 67 cases, there were 16 malignant and 51 benign lesions. Among the 51 benign cases, two main final diagnoses was pulmonary tuberculosis (22/67, 32.8%) and pneumonia/lung abscess (16/67, 23.9%) (Table 1).

The mean (± SD) age of our study population was 57 (±14) years. Regarding smoking history, seven cases had an unknown smoking history, 25 had never smoked, 15 were current smokers, and 20 were former smokers. In terms of underlying diseases, 16 cases were immunocompromised, seven had an underlying malignancy, and five had active pulmonary tuberculosis. Forty-nine (73.1%) patients had the following clinical symptoms, cough (22/49, 44.9%), chest pain (8/49, 16.3%), dyspnea (6/49, 12.2%), hemoptysis (8/49, 16.3%), fever (3/49, 6.1%), and others (2/49, 4.1%). The studied cases were divided into three groups: definitive diagnosis of malignancy, pulmonary tuberculosis, and other benign diagnoses. The comparison of the three groups is shown in Table 2. The pulmonary tuberculosis group included significantly higher number of nonsmokers ($p = 0.021$). The number of cases with clinical symptoms in the malignancy group was significantly higher than those of the two groups with benign final diagnoses ($p = 0.002$).

The imaging characteristics in the three groups of patients are presented in Table 3. The occurrence of an emphysematous background was significant less often in the pulmonary tuberculosis group ($p = 0.008$). The mean size of lesions presenting as masses in malignancy group was significantly larger than those of the two benign groups ($p = 0.002$). The mean (±SD) diameter of masses in malignancy group, pulmonary tuberculosis group, and other benign diagnoses were 63±32 mm, 33±14 mm, and 42±25 mm, respectively.

The characteristics of the malignant and benign lesions such as edge and components such as fat, calcium, necrosis, and cavity were not significantly

Table 1. Definitive diagnosis of the lesions

Diagnosis	No. of lesions
Malignant lesions	
Lung cancer	12
Metastasis	4
Benign lesions	
Pulmonary tuberculosis	22
Other benign lesions	
Pneumonia/abscess	16
Hamartoma	1
Fibrosis	1
Bronchiectasis	2
Granuloma	1
Benign lesion of unknown histology	8
Total	67

Table 2. Patient characteristics of the 3 groups: definitive diagnosis of malignancy, pulmonary tuberculosis, and other benign diagnoses

Patient characteristics	Malignancy (n = 16), n (%)	Pulmonary tuberculosis (n = 22), n (%)	Other benign lesions (n = 29), n (%)	*p*-value
Age (year), mean ± SD	63±15	52±13	58±13	0.076
Smoking				0.021
Never	5 (31.2)	14 (63.6)	6 (20.7)	
Current smoker	2 (12.5)	5 (22.7)	8 (27.6)	
Ex-smoker	7 (43.8)	3 (13.6)	10 (34.5)	
Unknown	2 (12.5)	-	5 (17.2)	
Immunocompromised host	1 (6.2)	8 (36.4)	7 (24.1)	0.1
Pre-exiting cancer	4 (25.0)	1 (4.5)	2 (6.9)	0.143
Steroid use	-	1 (4.5)	4 (13.8)	0.183
Pulmonary tuberculosis				0.471
No	13 (81.3)	15 (68.2)	25 (86.2)	
Active disease	1 (6.2)	3 (13.6)	1 (3.4)	
Non-active disease	1 (6.2)	4 (18.2)	2 (6.9)	
Unknown	1 (6.2)	-	1 (3.4)	
Presenting symptoms	16 (100)	11 (50.0)	22 (76.0)	0.002

Table 3. Imaging characteristics in the 3 groups: definitive diagnosis of malignancy, pulmonary tuberculosis, and other benign diagnoses

CT features	Malignancy (n = 16), n (%)	Pulmonary tuberculosis (n = 22), n (%)	Other benign lesions (n = 29), n (%)	*p*-value
Emphysema	7 (43.7)	1 (4.5)	10 (34.5)	0.008
Contour				0.067
Mass	16 (100)	20 (90.9)	22 (75.9)	
Consolidation	-	2 (9.1)	7 (24.1)	
Enhancement	16 (100)	8 (36.4)	23 (79.3)	<0.005
Location				0.223
Right upper lobe	6 (37.6)	12 (54.5)	8 (27.6)	
Right middle lobe	1 (6.2)	4 (18.2)	5 (17.2)	
Right lower lobe	4 (25.0)	1 (4.5)	2 (6.9)	
Left upper lobe	2 (12.5)	4 (18.2)	8 (27.6)	
Left lower lobe	3 (18.8)	1 (4.5)	6 (20.7)	
Satellite nodules	5 (31.2)	11 (50.0)	11 (37.9)	0.482
Number				0.193
1	10 (62.5)	9 (40.9)	18 (62.1)	
2-5	3 (18.8)	6 (27.3)	9 (31.0)	
>5	3 (18.8)	7 (31.8)	2 (6.9)	
Pleural effusion	5 (31.2)	1 (4.5)	5 (17.2)	0.088
Pleural nodule	1 (6.2)	1 (4.5)	4 (13.8)	0.555
Pericardial effusion	-	2 (9.1)	-	0.159
Necrotic lymph node	9 (56.2)	-	2 (6.9)	<0.005
Calcified lymph node	-	-	3 (10.3)	0.248

different. After contrast administration, all of the malignant lesions were enhanced, but most of the lesions in the pulmonary tuberculosis group (14/22, 63.6%) were not enhanced ($p<0.005$). Among enhanced lesions, there was no significant difference in enhancement pattern between malignant and benign groups ($p = 0.433$), most of them showed heterogeneous enhancement rather than homogeneous enhancement.

Necrotic mediastinal lymph nodes were found significantly more often in a final malignant diagnosis rather than a benign diagnosis ($p<0.005$). The extrathoracic manifestations of the three categorized lesions like abdominal lymph node involvement, liver nodules, adrenal gland lesions, splenic lesions, and bone lesions were not significantly different.

Discussion

Nowadays, TNB is commonly performed in order to determine the definite diagnosis of lung lesions because of its high accuracy rate[1-3]. However, the final diagnosis for pathologically-benign non-specific diagnoses varies. In the present study, the three main final diagnoses were malignancy (23.9%), pulmonary tuberculosis (32.8%), and pneumonia/lung abscess (23.9%). A sampling error was a cause of benign non-specific diagnoses[7]; the tissue undergoing biopsy represents necrosis in the lesions or surrounding inflammation that is present in the specimen. The false-negative rate in benign non-specific pathologic diagnoses has been reported to vary from 13% to 63%[1,5,8]. It was 23.9% in the present study. Therefore, patients with a high index for suspicion of malignancy should be subject to repeat biopsy, surgical resection or close follow-up.

In tuberculosis-endemic areas, pulmonary tuberculosis poses as a major problem in distinguishing it from lung cancer or other pulmonary diseases since radiographic appearances such as mass-like forms may imitate cancerous diseases. Thus, histopathological studies are of a considerable importance to reach a definite diagnosis. However, the present study found that pulmonary tuberculosis was another factor leading to a benign non-specific pathologic diagnosis. This was true in up to one third of our cases. The finding was higher than those of previous studies conducted in the tuberculosis non-endemic areas[5,9].

The present study found that smoking and pulmonary emphysema were more prevalent in malignancy than pulmonary tuberculosis cases. Consequently, for patients with a risk for lung cancer, physicians should beware of false-negative results by TNB. The mean size of the mass in malignancy group was also significant larger than benign groups ($p = 0.002$) and the previous study supported that the likelihood of malignancy increased with the mass diameter[10].

Concerning CT imaging features, the present study showed that contrast enhancement was significant different between malignant and benign lesions. All malignant lesions (100%) showed enhancement and most lesions in the pulmonary tuberculosis group (63.6%) were not enhanced after contrast administration. The evaluation of lesion vascularity using contrast-enhanced CT imaging has proven to be useful for differentiating between malignant and benign nodules[6,11]. A previous study has reported that the absence of a significant lung nodule enhancement (≤15 HU) on CT is strongly predictive of benign etiology[6]. However, benign lesions show a variable contrast-enhancement pattern, depending on the inflammatory processes such as those associated with pneumonia and tuberculoma[12-15].

Lymphadenopathy is the most characteristic radiological feature in children with primary tuberculosis[16,17], but is rare in post-primary tuberculosis[18,19]. The present study supports the view that necrotic mediastinal lymph nodes are significantly more frequently found in the final malignancy diagnosis than in pulmonary tuberculosis and/or other benign lesions ($p<0.005$). Hence, pulmonary lesions that are associated with necrotic mediastinal lymph nodes should be taken into consideration for potential malignancy; repeated biopsy or radiologic follow-up is recommended.

As this was a retrospective study, some limitations should be noted. First, information on all potential confounders may not be complete. Second, there was moderate variation in the CT techniques used to obtain the images. Subtle findings might have been missed or misinterpreted because of thick sections. However, the use of thick sections was unlikely to have significantly affected the manifestation or interpretation of the main imaging findings.

In conclusion, the definitive etiology for a benign non-specific diagnosis based on TNB in an endemic area of tuberculosis had a high rate of both malignancy and pulmonary tuberculosis. Regarding CT imaging, emphysema, enhanced lung lesions, and necrotic mediastinal nodes were significantly more commonly found in the malignancy group. The present study suggested that a non-specific benign diagnosis by means of TNB should warrant a repeat biopsy or radiological follow-up.

What is already known on this topic?

The false-negative rate in benign non-specific pathologic diagnoses has been reported to vary from 13% to 63%. However, most of the previous studies were performed in non-endemic areas of tuberculosis.

What this study adds?

In a tuberculosis-endemic area, the definitive diagnoses of benign nonspecific diagnoses based on TNB had a high rate of both malignancy and pulmonary tuberculosis. Therefore, a repeat biopsy or radiological follow-up is recommended.

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Potential conflicts of interest

None.

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การตัดชิ้นเนื้อปอดผ่านทางผนังทรวงอกนำทางด้วยภาพรังสี: การประเมินผลชิ้นเนื้อจากผลพยาธิวิทยาที่ไม่ใช่มะเร็งและมีลักษณะไม่เฉพาะเจาะจง

นันทกา กิระนันทวัฒน์, นราพงศ์ ศรีศาลา, จิตต์ปรีดี สังข์ศิริ, ศรายุทธ ลูเซียน กีเตอร์, วิวัฒนา ถนอมเกียรติ

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อสำรวจผลการวินิจฉัยขั้นสุดท้ายของผลชิ้นเนื้อปอด ที่ตัดผ่านทางผนังทรวงอกนำทางด้วยภาพรังสีที่ผลพยาธิวิทยารายงานว่าไม่ใช่มะเร็งและมีลักษณะไม่เฉพาะเจาะจงในพื้นที่ระบาดของวัณโรค วัตถุประสงค์รองเพื่อหาลักษณะเฉพาะของภาพเอกซเรย์คอมพิวเตอร์ระหว่างรอยโรคที่เป็นมะเร็งและไม่ใช่มะเร็ง*

วัสดุและวิธีการ: *ผลชิ้นเนื้อปอดที่ตัดผ่านผนังทรวงอกนำทางด้วยภาพรังสีทุกรายที่รายงานผลว่าไม่ใช่มะเร็งและมีลักษณะไม่เฉพาะเจาะจง ที่แผนกรังสีวิทยา ตั้งแต่มกราคม พ.ศ. 2550 ถึง ธันวาคม พ.ศ. 2554 นำมาศึกษาย้อนหลังเพื่อหาผลการวินิจฉัยขั้นสุดท้าย ที่ตั้งอยู่บนอาการและลักษณะทางภาพรังสีเอกซเรย์คอมพิวเตอร์*

ผลการศึกษา: *ผู้เข้าร่วมการศึกษาทั้งหมด 67 ราย มีผลชิ้นเนื้อปอดที่ตัดผ่านผนังทรวงอกนำทางด้วยภาพรังสีรายงานผลว่าไม่ใช่มะเร็งและมีลักษณะไม่เฉพาะเจาะจง ที่มีการติดตามผลพยาธิวิทยาหรือการติดตามภาพรังสีครบถ้วน ในจำนวนนี้ 16 ราย (ร้อยละ 23.9) เป็นมะเร็ง และ 51 ราย ไม่ใช่มะเร็ง สองโรคหลักของการวินิจฉัยขั้นสุดท้ายในกลุ่มที่ไม่ใช่มะเร็ง คือ วัณโรคปอด (ร้อยละ 32.8) และปอดบวมหรือฝีในปอด (ร้อยละ 23.9) จากภาพเอกซเรย์คอมพิวเตอร์พบว่ารอยโรคในกลุ่มที่เป็นวัณโรคปอดส่วนใหญ่จะไม่มีการเพิ่มขึ้นของสารทึบรังสีในรอยโรค ($p<0.005$) ส่วนกลุ่มที่เป็นมะเร็งจะพบหย่อมเนื้อตายในต่อมน้ำเหลืองช่องทรวงอกอย่างมีนัยสำคัญทางสถิติ ($p<0.005$)*

สรุป: *ผลชิ้นเนื้อปอดที่ตัดผ่านผนังทรวงอกนำทางด้วยภาพรังสี ที่รายงานผลพยาธิวิทยาว่าไม่ใช่มะเร็งและมีลักษณะไม่เฉพาะเจาะจงในพื้นที่ระบาดของวัณโรค เมื่อติดตามไปพบว่ามีอัตราการวินิจฉัยขั้นสุดท้ายว่าเป็นมะเร็งและวัณโรคปอดที่สูง ดังนั้น จึงแนะนำให้ทำการตรวจชิ้นเนื้อซ้ำหรือติดตามภาพทางรังสี*