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Computed tomography-guided biopsy of small lung nodules: diagnostic accuracy and analysis for true negatives

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Abstract

Objective: We evaluated the diagnostic accuracy of computed tomography (CT)-guided transthoracic core needle biopsy (TCNB) for small (≤20-mm) lung nodules and identified predictive factors for true negatives among benign biopsy results.

Methods: From March 2010 to June 2015, 222 patients with small lung nodules underwent CT-guided TCNB. We retrospectively analysed data regarding technical success, diagnostic accuracy, and predictors of true negatives.

Results: The technical success rate was 100%. The TCNB results of the 222 lung nodules included malignancy (n = 136), suspected malignancy (n = 8), specific benign lesion (n = 17), and nonspecific benign lesion (n = 61). The final diagnosis of 222 lung nodules included malignant (n = 160), benign (n = 60), and nondiagnostic lesions (n = 2). The sensitivity, specificity, and overall diagnostic accuracy of CT-guided TCNB for small lung nodules were 90.0%, 100%, and 92.7%, respectively. Pneumothorax and haemoptysis occurred in 23 and 41 patients, respectively. Based on the Cox regression analysis, the significant independent predictive factor for true negatives was a biopsy result of chronic inflammation with fibroplasia.

Conclusions: CT-guided TCNB offers high diagnostic accuracy for small lung nodules, and a biopsy result of chronic inflammation with fibroplasia can predict a true-negative result.

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Introduction

Lung nodules are usually incidentally discovered by chest computed tomography (CT). At present, low-dose CT is widely used in physical examinations, and the detection rate for lung nodules is increasing.[1] Differentiation of benign and malignant lung nodules is critical to minimise unnecessary operations.

Although various prediction models of lung nodules have been established, diagnosis of lung nodules is still challenging.[2–5] Although the size of the lung nodule is an independent risk factor for malignancy,[4,5] approximately 64% to 75% of small (≤20-mm) lung nodules are malignant.[6–8] Thus, accurate pathological diagnosis is a vital step in the management of small lung nodules. CT-guided transthoracic core needle biopsy (TCNB) has been widely used for the diagnosis of lung lesions because of its simplicity, minimal invasiveness, and high diagnostic accuracy.[8–11] The diagnostic accuracy of CT-guided TCNB for lung lesions ranges from 51.4% to 95.8%.[8–11] However, small lung nodules of <20 mm remain very challenging for radiologists, and research on TCNB of small (≤20-mm) lung nodules is lacking.

Another concern is the false-negative rate among nonspecific benign biopsy results because nonspecific benign biopsy results cannot necessarily guarantee a lesion's benignity.[12] The false-negative rate of TCNB ranges from 5% to 12%.[12] The predictive factors for true negatives among benign biopsy results are still unclear.

In this study, we aimed to determine the diagnostic accuracy of CT-guided TCNB of small lung nodules and identify predictive factors for true negatives among nonspecific benign biopsy results.

Materials and methods

Patients

This single-centre retrospective study was approved by our institutional review board, and the requirement for written informed consent was waived.

From March 2010 to June 2015, 222 consecutive patients with small lung nodules underwent CT-guided TCNB in our centre. The baseline data on these 222 patients are shown in Table 1. The indication for lung biopsy was determined from a multidisciplinary discussion among oncologists, respiratory physicians, and interventional radiologists. The inclusion criteria were newly discovered or enlarging lung nodules on chest CT and a lung nodule size of ≤20 mm. The exclusion criteria were a nodule size of <5 mm and blood coagulation dysfunction. The lesion size was measured as the maximal transverse diameter on CT.

TCNB procedure

All procedures were performed by two interventional radiologists and a pathologist. TCNB was guided by the use of a 16-detector CT device (Brilliance CT scanner; Philips Healthcare, Cleveland,

Table 1. Baseline data of the 222 patients and biopsy procedures.

Patients' characteristics	
Number of patients	222
Sex (male/female)	119/103
Age (years)	60.5 ± 11.8
Smoking history	91
Emphysema on computed tomography	50
Nodule size (mm)	16.6 ± 3.6
Nature of nodule	
Solid	217
Sub-solid	5
Nodule location	
Right upper lobe	37
Right middle lobe	13
Right lower lobe	66
Left upper lobe	46
Left lower lobe	60
Biopsy procedure	
Nodule number	222
Patient position	
Prone	142
Supine	71
Lateral	9
Lesion–pleura distance (mm)	17.6 ± 13.5
Needle–pleura angle (degrees)	66.6 ± 18.5
Number of needle pathways	1.7 ± 0.7
Number of specimens	1.4 ± 0.5
Procedure time (min)	15.9 ± 5.0

Data are presented as n or mean ± standard deviation.

OH, USA). The imaging parameters of the scanner were 120 kV, 150 mAs, and 2- to 5-mm section thickness.

The patients were placed in the prone, supine, or lateral decubitus position according to the location of the lesion. A thoracic CT scan was performed first to evaluate the needle pathway and distance from the puncture site to the lesion. The needle pathway was selected to avoid bone, visible vessels, bullae, and fissures. The puncture site was chosen by the CT gantry laser lights and landmarks using a homemade radiopaque grid on the patient's skin. Local anaesthesia was induced with 5 mL of 2% lidocaine. An 18-G coaxial needle (Precisa; H.S. Hospital Service S.p.A., Rome, Italy or Wego; Jierui Medical Products Co., Ltd., Weihai, China) was used to puncture the lung, and a repeat CT scan was performed to evaluate the site of the needle. Multiplanar reformation of the punctured image was established for lesions of <10 mm. When the needle tip reached the lesion, the specimen was obtained by pressing the trigger of the needle (Figure 1). The specimen was reviewed by the pathologist. If the specimen quantity was sufficient, the procedure was completed. Otherwise, another specimen was obtained. The specimen was placed in 10% formaldehyde for pathological examination.

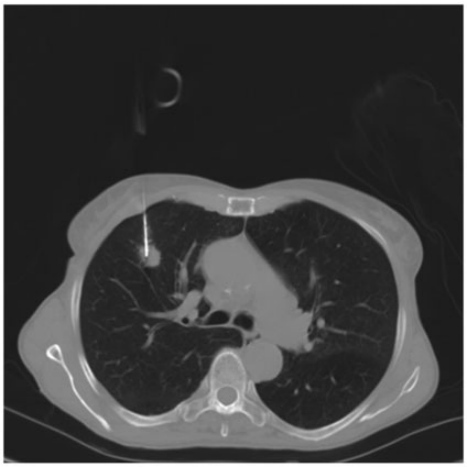

Figure 1. Imaging of computed tomography-guided transthoracic core needle biopsy for a small lung nodule.

After the TCNB procedure, chest CT was immediately performed to detect pneumothorax or lung haemorrhage. All patients were observed for 24 hours after TCNB, and a follow-up chest X-ray was performed to confirm whether delayed pneumothorax had occurred.

TCNB diagnosis

The TCNB results were divided into the following five diagnostic categories: malignancy,

suspected malignancy, specific benign lesion (such as hamartoma, mycotic infection, or tuberculosis), nonspecific benign lesion, or invalid diagnosis (necrotic tissue).[11–13] Malignancy and suspected malignancy were considered TCNB-positive results. Specific and nonspecific benign lesions were considered TCNB-negative results. An invalid diagnosis was considered neither positive nor negative.[11]

Final diagnosis

A final diagnosis of malignancy was established based on either the surgical or pathological results from the TCNB specimen.

A final diagnosis could be established based on one of the following four criteria: surgical results; pathological results from the TCNB specimen revealing a specific benign lesion, which was accepted as the final diagnosis of a benign lesion;[12,13] a lesion that decreased in size by $\geq$20% without anticancer treatment;[12,13] or a lesion that remained stable in size for at least 24 months without anticancer treatment.[12–16]

If the lung nodule did not meet any of the above-mentioned diagnostic criteria, the final diagnosis was listed as a nondiagnostic lesion.

Definitions

Technical success of TCNB was defined as obtaining an adequate tissue sample for visual inspection.[11–13] TCNB-positive results were considered true positive if the lesions were shown to be malignant on final diagnosis. TCNB-negative results were considered true negative if the lesions were shown to be benign on final diagnosis. An invalid diagnosis based on TCNB and nondiagnostic lesions on final diagnosis were not included in the calculation of the diagnostic accuracy.

True-negative analysis

The false-positive rate of TCNB is extremely low (0.00%–0.02%), and these positive biopsy results for malignancies using TCNB can have a direct impact on clinical decision-making.[12] Therefore, we only performed a true-negative analysis.

The nodules with nonspecific benign results on TCNB were included in the true-negative analysis. The nondiagnostic nodules were excluded from the true-negative analysis. The included nodules were divided into true-negative and false-negative groups. Data on baseline characteristics, imaging features, TCNB details, and pathological features of biopsy were compared between the two groups.

Statistical analysis

The statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are summarised as the mean or median and were analysed with the t-test. Categorical data were analysed using the χ^2 test or Fisher's exact probability test. The nonspecific benign results from TCNB were collected for analysis of the predictors of true-negative cases. The predictors of true-negative cases were determined using stepwise univariate and multivariate logistic regression analyses. The univariate analysis of each variable was performed first. The variables with a P-value of <0.1 in the univariate analysis were then used as input variables for the multivariate analysis. A P-value of <0.05 was considered statistically significant.

Results

Technical success

The technical success of CT-guided TCNB for small lung nodules was 100%. The details of the TCNB procedure are shown in Table 1.

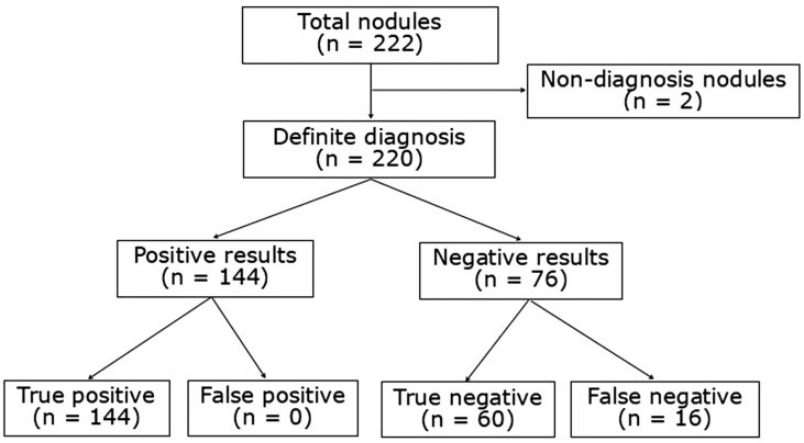

Figure 2. Flow diagram of diagnostic accuracy.

TCNB results

The TCNB results from the 222 lung nodules included malignancy (n = 136), suspected malignancy (n = 8), specific benign lesions (n = 17), and nonspecific benign lesions (n = 61). The eight suspected malignancies included heterocysts (n = 6) and atypical hyperplasia (n = 2). The 17 specific benign lesions included tuberculosis (n = 12), hamartomas (n = 3), and mycotic infection (n = 2).

Final results and diagnostic accuracy

Based on the final diagnosis, the 136 malignant and 17 specific benign lesions according to the TCNB results were directly considered the final results. The eight suspected malignant lesions were confirmed to be malignant (adenocarcinoma) by surgical resection. Among the 61 nonspecific lesions according to the TCNB results, 43 lesions were confirmed to be benign (surgical resection, n = 18; follow-up, n = 25), 16 lesions were confirmed to be malignant by surgical resection or a second TCNB, and the remaining 2 lesions were considered nondiagnostic because of anticancer treatment for previous malignancy.

Therefore, the final diagnosis of the 222 lung nodules included malignant (n = 160), benign (n = 60), and nondiagnostic lesions (n = 2) (Figure 2). The eight nondiagnostic lung nodules were not included in the calculation of the diagnostic accuracy. Therefore, the sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy of CT-guided TCNB for small lung nodules were 90.0% (144/160), 100% (60/60), 100% (144/144), 78.9% (60/76), and 92.7% (204/220), respectively.

Complications

Pneumothorax occurred in 23 (10.4%) patients. Among these 23 patients, 11 were managed with chest tube insertion and 12 were managed with conservative treatment. Haemoptysis occurred in 41 (18.5%) patients. These 41 patients were successfully managed with conservative treatment.

Prediction of true-negative cases

Among the 61 nodules with nonspecific benign results on biopsy, the 2 nondiagnostic nodules were excluded when determining the predictors of true-negative cases. All of the

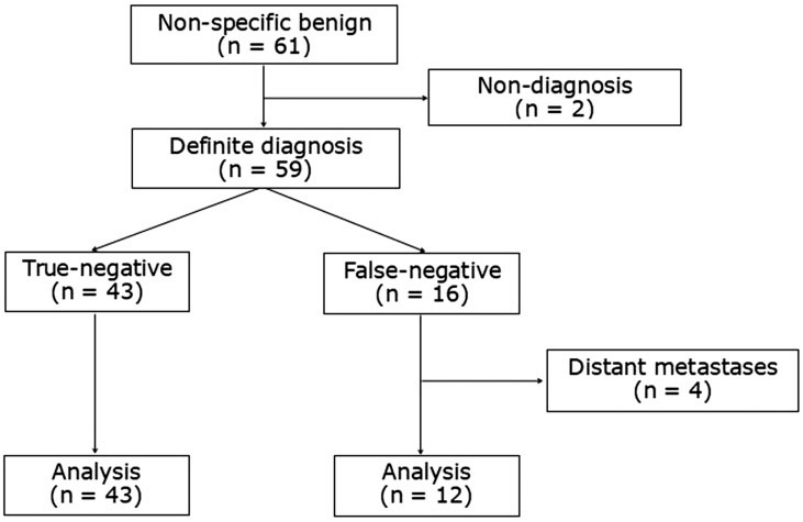

Figure 3. Flow diagram of analysis of true negatives.

remaining 59 nodules showed chronic inflammation on biopsy. Among these nodules, 43 were true-negative and 16 were false-negative cases. Among the 16 false-negative nodules, 4 included distant metastases (bone, n = 3; brain, n = 1), which were excluded when determining the predictive factors of true-negative cases because metastases strongly indicate a false-negative result. Finally, 55 nodules were included to determine the predictors of true-negative cases (Figure 3). Pathologic examination of the biopsy of these 55 nodules revealed chronic inflammation with fibroplasia in 27, chronic inflammation with alveolar epithelial hyperplasia in 8, granulomatous inflammation in 6, and only chronic inflammation in 14. The baseline data on the 55 patients are shown in Table 2.

In the univariate logistic regression analysis, the predictors of true-negative results from TCNB for small lung nodules included a shorter lesion–pleura distance [hazard ratio (HR), 3.730; 95% confidence interval (CI), 0.964–14.462], a lower carcinoembryonic antigen level (HR, 1.300; 95% CI, 1.034–1.636; $P = 0.025$), a lower squamous cell carcinoma antigen level (HR, 2.428; 95% CI, 0.965–6.105), a smaller hilar or mediastinal lymph nodule (HR, 4.620; 95% CI, 1.200–17.789; $P = 0.026$), and a biopsy result of chronic inflammation with fibroplasia (HR, 0.059; 95% CI, 0.007–0.503; $P = 0.016$). When these variables were entered into the multivariate logistic regression analysis, the only independent predictive factor of a true-negative result was a biopsy result of chronic inflammation with fibroplasia (HR, 0.024; 95% CI, 0.001–0.505; $P = 0.017$) (Table 3).

Discussion

This study was performed to evaluate the feasibility and diagnostic accuracy of CT-guided TCNB for small ($\leq$20-mm) lung nodules. The technical success rate and overall diagnostic accuracy were 100% and 92.7%, respectively. These rates may indicate that CT-guided TCNB is a simple and highly accurate method for diagnosis of small lung nodules. The present overall diagnostic rate is comparable with those in previous studies of CT-guided TCNB for lung nodules (92.9%–93.5%).[8,9] Previous studies

Table 2. Comparison of baseline data between true and false negatives.

	True negative	False negative	P value
Number of patients	43	12	–
Age (years)	57.6 ± 12.1	63.3 ± 5.4	0.025
Sex (male/female)	23/20	7/5	0.766
Smokers	20	7	0.469
Imaging features			
Size (mm)	15.8 ± 4.0	17.3 ± 3.8	0.233
Solid/sub-solid	42/1	10/2	0.117
Spiculation	19	6	0.224
Pleural retraction sign	15	4	1.000
Cavity	6	0	0.572
Calcification	4	0	0.583
Enlarged hilar or mediastinal lymph nodule (≥15 mm)	10	7	0.049
Emphysema	9	5	0.279
Nodule location			0.857
Right upper lobe	8	2	
Right middle lobe	3	1	
Right lower lobe	8	3	
Left upper lobe	10	4	
Left lower lobe	14	2	
Details of biopsy procedure			
Lesion–pleura distance (mm)	16.3 ± 14.5	23.3 ± 12.5	0.135
Needle–pleura angle (degrees)	68.3 ± 18.9	65.3 ± 21.7	0.640
Number of specimens	1.4 ± 0.5	1.3 ± 0.5	0.220
Pneumothorax	5	2	1.000
Haemoptysis	10	4	0.738
Tumour markers			
Carcinoembryonic antigen (μg/L)	2.3 ± 2.4	5.0 ± 3.8	0.045
Cyfra21-1 (ng/mL)	2.3 ± 1.2	2.8 ± 1.7	0.233
Squamous cell carcinoma antigen (μg/L)	0.9 ± 0.6	1.3 ± 0.9	0.137
Neuron-specific enolase (ng/mL)	12.6 ± 2.6	12.4 ± 1.1	0.787
Pathological feature of biopsy			
Chronic inflammation with fibroplasia	26	1	0.001
Chronic inflammation with alveolar epithelial hyperplasia	5	3	0.485
Granulomatous inflammation	6	0	0.397

Data are presented as n or mean ± standard deviation.

of CT-guided fine-needle aspiration biopsy (FNAB) for small lung nodules demonstrated that the diagnostic accuracy was only 77.2% to 89.9%.[6,7] Choi et al.[17] performed CT-guided aspiration or cutting biopsies for 305 supraclavicular lymph nodes and found that aspiration alone was a significant independent risk factor associated with diagnostic failure ($P = 0.001$).

FNAB usually shows the cytological features but not the tissue architecture of the lesion.[8] Furthermore, FNAB carries a risk of insufficient tissue sampling.[17] TCNB is a more accurate tissue sampling method than

Table 3. Predictors of true negatives.

	Univariate analysis			Multivariate analysis		
Variables	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Lesion–pleura distance of ≥2 cm	3.730	0.964–14.462	0.057	3.568	0.660–19.303	0.140
Carcinoembryonic antigen	1.300	1.034–1.636	0.025	1.292	0.889–1.879	0.180
Squamous cell carcinoma antigen	2.428	0.965–6.105	0.059	2.410	0.683–9.106	0.195
Hilar or mediastinal lymph nodule of ≥15 mm	4.620	1.200–17.789	0.026	0.560	0.044–7.070	0.654
Chronic inflammation with fibroplasia	0.059	0.007–0.503	0.016	0.024	0.001–0.505	0.017

CI, confidence interval.

FNAB because it can obtain a sufficient specimen for pathological diagnosis.[17] Ocak et al.[10] compared the diagnostic accuracy of TCNB and FNAB for lung lesions, and although they found no significant difference in overall diagnostic accuracy between the two groups (90% vs. 82%, respectively), TCNB provided a well-defined cancer type/subtype. In addition, TCNB specimens can provide adequate tissues for molecular testing, which can guide treatment strategies for lung cancer.[18]

Some researchers have performed CT fluoroscopy or C-arm cone-beam CT-guided TCNB for lung lesions, showing that the overall diagnostic accuracy can reach 98%.[13–15] However, both CT fluoroscopy and C-arm cone-beam CT require real-time monitoring, thus exposing the operators to radiation.

Both malignant results and specific benign results (such as hamartoma, mycotic infection, or tuberculosis) on TCNB can be directly accepted as the final diagnosis.[12] However, nonspecific benign biopsy results do not exclude malignancy. Evaluation of nonspecific benign results on TCNB is difficult.

The most frequent nonspecific benign lesion in the present study was chronic inflammation (49/55, 89.1%). The independent predictor of true-negative cases was a biopsy result of chronic inflammation with fibroplasia. Fibrosis is an important component of the inflammatory response.[19] Fibrosis is a dominant clinical feature in many diseases, including proliferative vitreoretinopathy, mucous membrane pemphigoid, cirrhosis, scleroderma, idiopathic pulmonary fibrosis, and retroperitoneal fibrosis.[19] A biopsy sample that exhibits chronic inflammation with fibroplasia may indicate that the punctured nodule is a benign lesion.

Fibrosis is also closely associated with various benign lung diseases, such as granuloma and sarcoidosis.[20] Thus, it is reasonable that the TCNB result of chronic inflammation with fibroplasia indicates a true-negative result.

Previous studies have also indicated that the lesion size is associated with the diagnostic accuracy of lung biopsy.[21,22] These studies included patients with lung nodules and masses, and misdiagnosis may often occur in larger lesions.[21,22] In the present study, the nodule size was not a predictive factor of true-negative results. This finding may be attributed to our restriction of the sample to TCNB of small lung nodules.

Pneumothorax and haemoptysis occurred in 23 (10.4%) and 41 (18.5%) patients, respectively. These rates are comparable with those in previous studies of CT-guided lung biopsy for lung nodules

or small lung nodules.[7–9] Most of these patients were managed with conservative treatment, and only 11 (4.9%) patients required chest tube insertion.

This study had several limitations. First, this study was retrospective; therefore, selection bias was present. Second, 2 of 222 lung nodules (0.9%) were nondiagnostic lesions. Although nondiagnostic lesions have also been reported in previous studies,[11–13] they definitely influenced the diagnostic accuracy and prediction of true negatives. Third, there was no control group in this study. Therefore, we have no means of comparing this approach with fluoroscopy-guided CT or C-arm cone-beam CT-guided TCNB for small lung nodules. Further prospective controlled trials should be performed.

In conclusion, CT-guided TCNB is a safe and high accurate method for the diagnosis of small (≤20-mm) lung nodules. When the biopsy diagnosis indicates a nonspecific benign result, a biopsy result of chronic inflammation with fibroplasias may indicate a true-negative result.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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