Original Article

Nonspecific benign pathological results on computed tomography-guided lung biopsy: A predictive model of true negatives

Yu-Fei Fu*, Li-Hua Jiang[1]*, Tao Wang, Guang-Chao Li, Wei Cao, Yi-Bing Shi

Department of Radiology, Xuzhou Central Hospital, Xuzhou, [1]Department of Clinical Laboratory, Clinical Laboratory, Yuhuangding Hospital, Yantai, China

For correspondence:
Dr. Wei Cao, Department of Radiology, Xuzhou Central Hospital, 199 South Jiefang Road, Xuzhou, 221009, China.
E-mail: xzcaowei@126.com
Dr. Yi-Bing Shi, Department of Radiology, Xuzhou Central Hospital, 199 South Jiefang Road, Xuzhou 221009, China.
E-mail: ctsyb@163.com

*Yu-Fei Fu and Li-Hua Jiang, contributed equally to this work.

ABSTRACT

Objective: The aim of this study is to develop a predictive model for identifying true negatives among nonspecific benign results on computed tomography-guided lung biopsy.

Materials and Methods: This was a single-center retrospective study. Between December 2013 and May 2016, a total of 126 patients with nonspecific benign biopsy results were used as the training group to create a predictive model of true-negative findings. Between June 2016 and June 2017, additional 56 patients were used as the validation group to test the constructed model.

Results: In the training group, a total of 126 lesions from 126 patients were biopsied. Biopsies from 106 patients were true negatives and 20 were false-negatives. Univariate and multivariate logistic regression analyses were identified a biopsy result of "chronic inflammation with fibroplasia" as a predictor of true-negative results ($P = 0.013$). Abnormal neuron-specific enolase (NSE) level ($P = 0.012$) and pneumothorax during the lung biopsy ($P = 0.021$) were identified as predictors of false-negative results. A predictive model was developed as follows: Risk score = −0.437 + 2.637 × NSE level + 1.687 × pneumothorax - 1.82 × biopsy result of "chronic inflammation with fibroplasia." The area under the receiver operator characteristic (ROC) curve was 0.78 ($P < 0.001$). To maximize sensitivity and specificity, we selected a cutoff risk score of −0.029. When the model was used on the validation group, the area under the ROC curve was 0.766 ($P = 0.005$).

Conclusions: Our predictive model showed good predictive ability for identifying true negatives among nonspecific benign lung biopsy results.

KEYWORDS: False-negative, lung biopsy, nonspecific benign, true-negative

INTRODUCTION

Computed tomography (CT)-guided lung biopsy is a safe, accurate, and minimally invasive approach for determining the benign or malignant nature of lung masses or nodules.[1-4] The overall diagnostic accuracy of a CT-guided lung biopsy ranges from 90% to 94%.[1,4] A malignant diagnosis obtained from a lung biopsy facilitates direct clinical decision-making because of an extremely low rate of false-positives (0%–0.2%).[5] A specific benign diagnosis (e.g., tuberculosis, fungal infection, or hamartoma) from lung biopsy can also be accepted as a final diagnosis,[6-8] enabling patients with suspicious lung lesions to avoid unnecessary surgery. However, a nonspecific benign diagnosis (e.g., chronic inflammation) from a lung biopsy is challenging to manage because of a high rate of false-negatives, with reports indicating a range of 7.1%–16.4%.[9-11] Furthermore, a nonspecific benign biopsy result does not preclude further assessment with more invasive diagnostic methods and treatments.

A previous study by Kim *et al.* identified several predictors of false-negative findings from nonspecific benign lung biopsy results.[11] However, this study did not combine predictors into an integrated predictive model. The purpose of our study was to develop a predictive model for identifying true negatives among nonspecific benign results from a CT-guided lung biopsy.

MATERIALS AND METHODS

This retrospective study was approved by the Local Institutional Review Board, and the requirement of written informed consent was waived.

Submitted: 12-Feb-19
Revised: 12-Jun-19
Accepted: 01-Jul-19
Published: 13-Jan-20

Access this article online
Website: www.cancerjournal.net
DOI: 10.4103/jcrt.JCRT_109_19
Quick Response Code:

Cite this article as: Fu YF, Jiang LH, Wang T, Li GC, Cao W, Shi YB. Nonspecific benign pathological results on computed tomography-guided lung biopsy: A predictive model of true negatives. J Can Res Ther 2019;15:1464-70.

Study design

A total of 716 patients underwent CT-guided lung biopsy at our hospital between December 2013 and May 2016. All patients had lung lesions that were suspicious for malignancies. The indication for lung biopsy was determined from a multidisciplinary discussion between oncologists, respiratory physicians, and interventional radiologists. Among the 716 patients, we included 126 patients with nonspecific benign biopsy results as the training group to create a predictive model of true-negative findings among nonspecific benign lung biopsy results. The exclusion criteria were as follows: (a) lesions without a final diagnosis, (b) chronic granulomatous inflammation on lung biopsy results (because several studies had found that biopsy result of granulomatous inflammation was a robust indicator of true negatives.[10,11]), and (c) patients with distant metastases. A study diagram of the training group is shown in Figure 1. Baseline data of these patients included age, gender, patients' history, imaging examination, details of biopsy, and laboratory examination.

Clinical data were also collected from an additional 73 patients with nonspecific benign biopsy results between June 2016 and June 2017. Among the 73 patients, 17 patients were excluded because they were missing a final diagnosis ($n = 12$) or presented with distant metastases ($n = 5$). Therefore, 56 patients were included in a validation group that tested the constructed model.

Biopsy needles

Biopsy needles were 18G semi-automatic cutting needles (Precisa, Roma, Italy, or Wego, Weihai, China). All needles were 100 or 150 mm long, and consisted of an outer needle and an inner stylet. The stylet contains a 20 mm sample notch. The end of the needle is a trigger, which allowed the outer needle to advance. The outer needle was used to localize the lesion, and the stylet was used to obtain the samples.

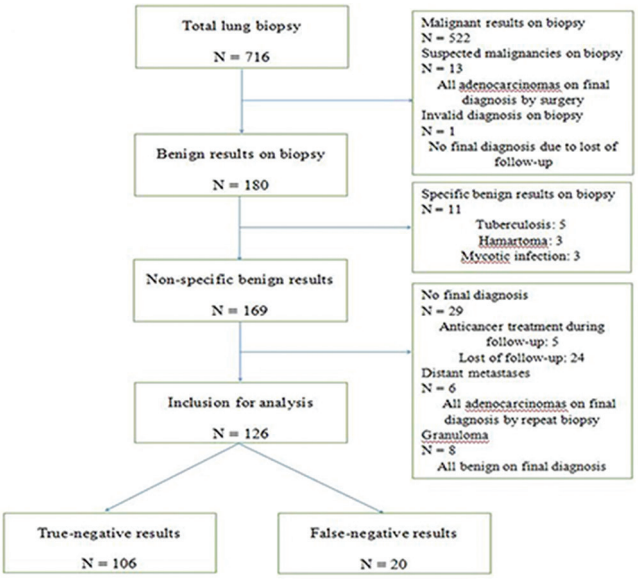

Figure 1: The flowchart of the training group

Lung biopsy procedure

All procedures were performed by an interventional radiologist with 10 years of experience. Lung biopsy was guided by a 16-detector CT (Philips, Cleveland, Ohio, USA). The tube voltage and current were 120 kV and 150 mA/s, respectively.

Patients were placed in the prone, supine, or lateral position in accordance with the location of the target lesion. The needle pathway was evaluated by a preoperative chest CT using a routine section thickness of 5 mm. A section thickness of 2 mm was used if an appropriate pathway could not be determined based on a section thickness of 5 mm. The needle pathway was selected with the intention of avoiding bone, visible vessels, bullae, and fissures. The puncture site was selected by CT gantry laser lights and landmarks using a radiopaque grid on the patient's skin.

The coaxial system was not used during the procedure. After administering 5 ml of 2% lidocaine as a local anesthetic, an 18G cutting needle was used to puncture the lung and additional CT scanning was performed to evaluate the needle puncture site. A specimen was obtained with the needle tip in superficial contact with the lesion. If the lesion diameter was larger than 20 mm, the required sample length was 10–20 mm. If the lesion diameter was <20 mm, the required sample length was 5–10 mm. Samples were placed into 10% formaldehyde until pathological examination.

Definitions

Technical success of a lung biopsy was defined as obtaining an adequate tissue sample upon visual inspection.[6] Pathological results of lung biopsies were classified into 1 of 4 groups: (a) malignancy or suspected malignancy; (b) specific benign; (c) nonspecific benign; or (d) invalid diagnosis (necrotic tissue or alveolus tissue). Diagnoses of malignancy and suspected malignancy were considered positive results; diagnoses of specific and nonspecific benign were considered negative results. An invalid diagnosis was neither positive nor negative.[7]

Specific benign results were defined as benign tumors (e.g., hamartoma and leiomyoma) or infectious diseases with identified pathogens (e.g., fungal, bacterial, and mycobacterial infections).[11] Nonspecific benign results were defined as the presence of benign pathological features such as inflammatory cells or fibrosis that was insufficient to render a specific diagnosis.[11]

Nonspecific benign results on lung biopsy were considered to be true negatives if the lesions were benign on final diagnosis. A final benign diagnosis could be made in 1 of the 3 ways: (a) surgical resection; (b) determination of a specific benign lesion upon pathological analysis of the lung biopsy

sample;[11] or (c) a decrease of 20% or more in lesion diameter, stability in size (without anticancer treatment) over minimum of 2 years.[6,11] If nonspecific benign lesions did not meet the third criterion, or if patients underwent anticancer treatment during the follow-up period, final diagnoses were listed as nondiagnostic lesions.

Statistical analysis

The statistical analysis was performed using the SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the mean or median. Numeric data were analyzed using the Chi-squared tests or Fisher's exact probability tests. Predictors of true-negative findings were identified using univariate and multivariate logistic regression analyses. The covariates incorporated into the multivariate analysis were variables with $P < 0.05$ in the univariate analysis. Receiver operator characteristic (ROC) curves were created and areas under the curves were calculated. A value of $P < 0.05$ was considered as statistically significant.

RESULTS

Training group

A total of 126 patients with 126 nonspecific benign biopsy results were included in training group. Biopsy results for 106 patients were true-negative and 20 were false-negative [Table 1]. The negative predictive value (NPV) of the nonspecific benign biopsy was 84.1% (106/126).

Complications

Among the 126 patients, 36 patients (28.6%) experienced procedure-related complications (hemoptysis: 19; pneumothorax: 16; hemoptysis with pneumothorax: 1). According to the Society of Interventional Radiology classification,[12,13] 27 patients experienced major complication and 9 patients experienced minor complication. All patients with hemoptysis were successfully treated by appropriate hemostasis. The pneumothorax was managed by chest tube insertion in 8 patients and the remaining 9 patients did not undergo special treatment.

During the lung biopsy procedure, 79, 40, and 7 patients were placed in prone, supine, and lateral positions, respectively. There were no significant differences in hemoptysis (prone: 11/79; supine: 9/40; lateral: 0/7, $P = 0.239$) and pneumothorax (prone: 10/79; supine: 5/40; lateral: 2/7, $P = 0.486$) between patients with different positions.

True negatives

Among the 106 true-negative lesions, 78 had their final diagnosis confirmed by clinical follow-up, and 28 were

Table 1: Comparison of baseline data between true-and false-negative lesions in training group

	True-negative (*n*=106)	False-negative (*n*=20)	*P*
Age (years)	58.2±11.4	63.3±6.1	0.006
Gender			
Male	63	14	0.374
Female	43	6	
Smoking history	51	13	0.166
Tumor history	2	0	1.00
Imaging features			
Diameter (mm)	31.8±19.2	38.8±26.9	0.28
Side			
Left	46	11	0.339
Right	60	9	
Lobe			
Upper	47	12	0.198
Nonupper	59	8	
Nature			
Solid	105	18	0.065
Sub-solid	1	2	
Location			
Hilar	23	9	0.071
Peripheral	83	11	
Tumor markers			
Abnormal CEA (range: 0-5 ng/ml)	7	4	0.13
Abnormal Cyfra211 (range: 0-3.3 ng/ml)	12	6	0.066
Abnormal SCC (range: 0-2.5 ng/ml)	3	4	0.011
Abnormal NSE (range: 0-16.3 ng/ml)	4	5	0.005
Details of biopsy procedure			
Lesion-pleura distance (mm)	14.3±15.2	18.2±14.6	0.303
Needle-pleura angle (°)	67.3±17.1	65.7±20.7	0.71
Number of samples	1.6±0.7	1.3±0.5	0.051
Pneumothorax	11	6	0.046
Hemoptysis	14	6	0.121
Pathological features from biopsy			
Chronic inflammation with fibroplasia	58	5	0.015
Chronic inflammation with alveolar epithelial hyperplasia	17	5	0.317

CEA=Carcinoembryonic antigen, SCC=Squamous cell carcinoma antigen, NSE=Neuron-specific enolase

confirmed by surgery. Among the 28 cases whose diagnoses were confirmed by surgery. Among the 28 cases who were confirmed by surgery, 23 cases were confirmed as chronic inflammation, 2 cases were confirmed as hamartoma, 1 case was confirmed as fungus, 1 case was confirmed as tuberculosis, and 1 case was confirmed as a bronchial cyst.

False-negatives

Among 20 false-negative lesions, 12 had their final diagnoses confirmed by surgery, 7 were confirmed by repeat lung biopsy, and 1 was confirmed by bronchoscopy. The final diagnoses of the 20 lesions included adenocarcinoma (n = 12), squamous cells carcinoma (n = 5), and small-cell lung cancer (n = 3).

Predictors

Table 2 summarizes the predictors of true-negative and false-negative results. Univariate and multivariate logistic regression analyses revealed that a biopsy result of "chronic inflammation with fibroplasia" was a predictor of true negatives (P = 0.013, hazard ratio (HR) =0.2, 95% confidential interval (CI) =0.0–0.7), while abnormal NSE (normal range: 0–16.3 ng/ml) level (P = 0.012, HR = 14.0, 95% CI = 1.8–108.4), and pneumothorax during the lung biopsy (P = 0.021, HR = 5.4. 95% CI = 1.3–22.6) were predictors of false-negatives. The number of samples was not associated with true-negative results (P = 0.055, HR = 0.3. 95% CI = 0.1–1.1).

Risk scores were calculated for individual patients by combining the above-mentioned three prognostic values as follows: $-0.437 + 2.637 \times$ NSE level (0: NSE $\leq$ 16.3; 1: NSE >16.3) $+1.687 \times$ pneumothorax (0: no pneumothorax; 1: pneumothorax present) - $1.82 \times$ biopsy result of "chronic inflammation with fibroplasia" (0: no present; 1: present).

An ROC curve was used to determine the predictive value of this risk score for true-negative results. The area under the ROC curve was 0.78 [95% CI = 0.65–0.91, $P < 0.001$, Figure 2a]. To maximize sensitivity and specificity, we selected a cutoff risk score of -0.029 (sensitivity = 50%, specificity = 97.2%). If the score was ≥ -0.029, the biopsy result was considered to be false-negative. If the score was < -0.029, the biopsy result was considered to be true-negative.

Validation group

Clinical data of the patients in the validation group were used to test the accuracy of the predictive model. The baseline data of the validation group are demonstrated in Table 3. A total of 56 patients with 56 nonspecific benign biopsy results were included in the validation group. Biopsy results for 44 patients were true-negative and 12 were false-negative. The NPV of the nonspecific benign biopsy was 78.6% (44/56). When this risk score was used on the validation group, the area under the ROC curve was 0.766 [95% CI = 0.61–0.93, P = 0.005, Figure 2b].

DISCUSSION

This study identified two significant predictors of false-negative biopsies and one significant predictor of true-negative biopsies. Furthermore, we developed an integrated risk score that combines these three predictors to identify true negatives. These findings might help in further analyzing lung lesions with nonspecific benign biopsy results.

CT-guided lung biopsy is widely used to diagnose lung lesions, and lung biopsy samples can provide adequate tissues for molecular testing that can guide treatment in lung cancer cases.[14] Previous studies have investigated predictors or factors that influence the overall diagnostic accuracy of lung biopsy;[8,15] however, a major problem that limits the accuracy of a lung biopsy is differentiating true negatives in cases of a nonspecific benign biopsy result. In fact, there is no consensus regarding a standard or recommended diagnostic approach after an initial lung biopsy yields a nonspecific benign result, although options include repeated biopsy, surgery, and follow-up.[11]

In the present study, the NPV of 84.1% in the training group was comparable to that in previous studies.[10,11] Abnormal NSE level, and pneumothorax during the biopsy were predictors of a false-negative result. In a previous study, Kim *et al.* found that a partial-solid lesion on biopsy was a significant predictor of a false-negative result (HR = 3.95, P = 0.022).[11] However, there was only three subsolid lesions in the training group and they did not have the statistical effect. Nonetheless, two (66.7%) of the three sub-solid lesions were false-negative. We still believe that a nonspecific benign result from a partial-solid lesion biopsy should prompt immediate additional evaluation in order to exclude the possibility of a false-negative malignancy.

Table 2: Predictors of true negatives

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Hilar lesion	3.1	1.2-8.5	0.025	2.5	0.7-8.8	0.163
Abnormal Cyfra211	3.4	1.1-10.4	0.036	1.9	0.4-8.7	0.396
Abnormal SCC	8.6	1.8-42.0	0.008	4.5	0.6-34.4	0.15
Abnormal NSE	8.5	2.1-35.2	0.003	14.0	1.8-108.4	0.012
Number of specimen	0.4	0.1-1.0	0.049	0.3	0.1-1.0	0.055
Pneumothorax	4.1	1.3-13.1	0.017	5.4	1.3-22.6	0.021
Chronic inflammation with fibroplasia	0.3	0.1-0.8	0.020	0.2	0.0-0.7	0.013

CI=Confident interval, SCC=Squamous cell carcinoma antigen, NSE=Neuron-specific enolase

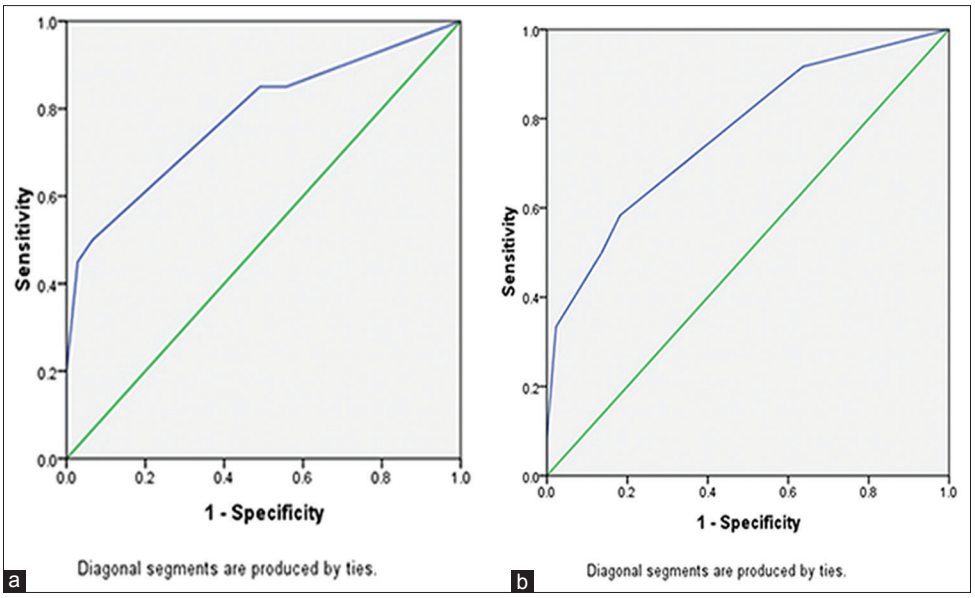

Figure 2: The receiver operator characteristic curve generated using the risk scores from training (a) and validation (b) groups

Table 3: Comparison of baseline data between training and validation groups

	Training group (*n*=126)	Validation group (*n*=56)	*P*
Age (years)	59.0±10.9	59.4±14.1	0.856
Gender			
Male	77	36	0.684
Female	49	20	
Smoking history	64	27	0.748
Tumor history	2	3	0.345
Imaging features			
Diameter (mm)	32.9±20.6	39.6±17.6	0.035
Side			
Left	57	23	0.601
Right	69	33	
Lobe			
Upper	59	29	0.537
Nonupper	67	27	
Nature			
Solid	123	55	1.000
Sub-solid	3	1	
Location			
Hilar	32	24	0.018
Peripheral	94	32	
Tumor markers			
Abnormal CEA (range: 0-5 ng/ml)	11	4	1.000
Abnormal Cyfra211 (range: 0-3.3 ng/ml)	18	11	0.362
Abnormal SCC (range: 0-2.5 ng/ml)	7	7	0.186
Abnormal NSE (range: 0-16.3 ng/ml)	9	8	0.126
Details of biopsy procedure			
Lesion-pleura distance (mm)	14.9±15.1	13.0±17.0	0.454
Needle-pleura angle°	67.1±17.6	69.1±16.0	0.450
Number of samples	1.6±0.6	1.6±0.7	0.404
Pneumothorax	17	8	0.886
Hemoptysis	20	8	0.784
Pathological features from biopsy			
Chronic inflammation with fibroplasia	63	20	0.074
Chronic inflammation with alveolar epithelial hyperplasia	22	9	0.818

CEA=Carcinoembryonic antigen, SCC=Squamous cell carcinoma antigen, NSE=Neuron-specific enolase

NSE is a common tumor maker for lung cancer.[16] The false-negative group had a significantly higher rate of abnormal NSE than the true-negative group (25% vs. 3.8%, respectively; $P = 0.005$). Pneumothorax during the lung biopsy was also a predictor of false-negatives in this study. This result may be attributed to that pneumothorax may disturb the biopsy procedure. Although the number of samples was not associated with the true- or false-negatives, pneumothorax

also could reduce the quality of the samples. Gelbman *et al.* also found that procedure-related pneumothorax was the main factor predicting false-negative biopsy results because it limited needle insertion into the lesion and the number of passes.[17]

In a previous study, the pathological diagnosis of granulomatous inflammation on biopsy was a robust indicator of true negatives.[11] In this study, we excluded the cases with granulomatous inflammation and found that chronic inflammation with fibroplasia was a predictor of true-negative results ($P = 0.013$). The true-negative group had a significantly higher rate of cases with chronic inflammation with fibroplasia than the false-negative group (54.7% vs. 25%, respectively; $P = 0.015$). Similarly, Doxtader *et al.* found that 1of 16 cases (6.3%) with nonspecific chronic inflammation and fibrosis on biopsy was ultimately a false-negative.[18]

Fibrosis is an important component of the inflammatory response and is a dominant clinical feature in many diseases, including proliferative vitreoretinopathy, mucous membrane pemphigoid, cirrhosis, scleroderma, idiopathic pulmonary fibrosis, and retroperitoneal fibrosis.[18-20] A biopsy sample that presents with chronic inflammation with fibroplasia may indicate that the punctured lesion is true-negative.

Finally, we developed an integrated risk score that combined the above three predictors in order to identify true negatives. The area under the ROC curve showed good predictive ability, and a cut-off value of −0.029 was obtained by calculating the optimum sensitivity and specificity. This predictive model was well fitted to the independent validation group of 56 patients from April 2016 to June 2017, which demonstrates the accuracy of the model.

The present study had some limitations. First, a retrospective design led to some selection bias. Second, there is no unified criterion for the quantity of a biopsy sample needed for collection. Instead, we collected biopsy samples in accordance with our experience. Although the number of samples was not associated with true-negative results, it may have otherwise biased our findings. Third, 29 and 12 lesions were classified as nondiagnostic lesions in training and validation groups, respectively. Although nondiagnostic lesions have also been reported in previous studies of lung biopsy,[6,11] they surely influenced predictive values in this study. Fourth, there is no PET-CT data in this study. Due to the high cost of PET-CT, only a few patients underwent PET-CT examination.

CONCLUSIONS

A biopsy result of "chronic inflammation with fibroplasia" might indicate the true negatives in nonspecific benign biopsy results. Abnormal NSE level and pneumothorax during the lung biopsy might indicate the false-negatives. Using these factors, we generated a combined risk score that had a good predictive ability for identifying true negatives among nonspecific benign lung biopsy results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Li Y, Du Y, Yang HF, Yu JH, Xu XX. CT-guided percutaneous core needle biopsy for small (≤20 mm) pulmonary lesions. Clin Radiol 2013;68:e43-8.
2. Ji Z, Wang G, Chen B, Zhang Y, Zhang L, Gao F, *et al.* Clinical application of planar puncture template-assisted computed tomography-guided percutaneous biopsy for small pulmonary nodules. J Cancer Res Ther 2018;14:1632-7.
3. Yu H, Zhang C, Liu S, Jiang G, Li S, Zhang L, *et al.* Application value of coaxial biopsy system in needle cutting biopsy for focal ground glass-like density nodule. J Cancer Res Ther 2018;14:1509-14.
4. Tai R, Dunne RM, Trotman-Dickenson B, Jacobson FL, Madan R, Kumamaru KK, *et al.* Frequency and severity of pulmonary hemorrhage in patients undergoing percutaneous CT-guided transthoracic lung biopsy: Single-institution experience of 1175 cases. Radiology 2016;279:287-96.
5. Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: Summary of published evidence. Chest 2003;123:115S-128S.
6. Choo JY, Park CM, Lee NK, Lee SM, Lee HJ, Goo JM. Percutaneous transthoracic needle biopsy of small (≤ 1 cm) lung nodules under C-arm cone-beam CT virtual navigation guidance. Eur Radiol 2013;23:712-9.
7. Kim GR, Hur J, Lee SM, Lee HJ, Hong YJ, Nam JE, *et al.* CT fluoroscopy-guided lung biopsy versus conventional CT-guided lung biopsy: A prospective controlled study to assess radiation doses and diagnostic performance. Eur Radiol 2011;21:232-9.
8. Lee SM, Park CM, Lee KH, Bahn YE, Kim JI, Goo JM. C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of lung nodules: Clinical experience in 1108 patients. Radiology 2014;271:291-300.
9. Yaffe D, Koslow M, Haskiya H, Shitrit D. A novel technique for CT-guided transthoracic biopsy of lung lesions: Improved biopsy accuracy and safety. Eur Radiol 2015;25:3354-60.
10. Rui Y, Han M, Zhou W, He Q, Li H, Li P, *et al.* Non-malignant pathological results on transthoracic CT guided core-needle biopsy: When is benign really benign? Clin Radiol 2018;73:757.e1-7.
11. Kim JI, Park CM, Kim H, Lee JH, Goo JM. Non-specific benign pathological results on transthoracic core-needle biopsy: How to differentiate false-negatives? Eur Radiol 2017;27:3888-95.
12. Veltri A, Bargellini I, Giorgi L, Almeida PA, Akhan O. CIRSE guidelines on percutaneous needle biopsy (PNB). Cardiovasc Intervent Radiol 2017;40:1501-13.
13. Leoni CJ, Potter JE, Rosen MP, Brophy DP, Lang EV. Classifying complications of interventional procedures: A survey of practicing radiologists. J Vasc Interv Radiol 2001;12:55-9.
14. Tian P, Wang Y, Li L, Zhou Y, Luo W, Li W. CT-guided transthoracic core needle biopsy for small pulmonary lesions: Diagnostic performance and adequacy for molecular testing. J Thorac Dis 2017;9:333-43.
15. Yeow KM, Tsay PK, Cheung YC, Lui KW, Pan KT, Chou AS. Factors affecting diagnostic accuracy of CT-guided coaxial cutting needle lung biopsy: Retrospective analysis of 631 procedures. J Vasc Interv Radiol 2003;14:581-8.
16. Jiang ZF, Wang M, Xu JL. Thymidine kinase 1 combined with CEA,

CYFRA21-1 and NSE improved its diagnostic value for lung cancer. Life Sci 2018;194:1-6.
17. 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;7:815-20.
18. Doxtader EE, Mukhopadhyay S, Katzenstein AL. Core needle biopsy in benign lung lesions: Pathologic findings in 159 cases. Hum Pathol 2010;41:1530-5.
19. Rosenbaum JT, Choi D, Wilson DJ, Grossniklaus HE, Harrington CA, Dailey RA, *et al.* Fibrosis, gene expression and orbital inflammatory disease. Br J Ophthalmol 2015;99:1424-9.
20. Bonham CA, Strek ME, Patterson KC. From granuloma to fibrosis: Sarcoidosis associated pulmonary fibrosis. Curr Opin Pulm Med 2016;22:484-91.