

Extrapleural locating method in computed tomography-guided needle biopsies of 1,106 lung lesions

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Abstract. Transthoracic needle biopsy is considered to be safe and effective for the diagnosis of focal lung lesions. The aim of the present study was to evaluate factors affecting the accuracy and safety of automated cutting needle lung biopsy (ACNB) using a new extrapleural locating (EPL) method. Computed tomography (CT)-guided needle biopsies were performed on 1,065 patients between March 2005 and May 2012 using the EPL method. The locating needle remained in the chest following extrapleural positioning, while the radiologist confirmed the puncture angle and distance between the locating needle and lesion. The biopsy instrument was advanced into the lung, and the core needle was subsequently fired into the lesion based on the direction indicated by the locating needle. Univariate and multivariate regression analyses were used to evaluate the diagnostic accuracy and safety of the procedure. The sensitivity, specificity, positive predictive value and negative predictive value of the extrapleural method were 91.9, 100, 100 and 82.9%, respectively, and the overall diagnostic accuracy was 94.2%. Significant risk factors affecting accuracy were younger age, atelectasis, hemoptysis and lesion depth ($P < 0.03$). Multivariate logistic regression analysis revealed that the risk of malignant lesions receiving a false-negative diagnosis decreased for each additional year of subject age [odds ratio (OR), 0.97; $P = 0.027$] and increased with each millimeter increase in lesion depth (OR, 1.03; $P = 0.008$).

Among the 1,106 lesions biopsied, 207 were associated with pneumothorax, 251 with hemorrhage and 58 with hemoptysis. Multivariate analysis revealed that lesion size and emphysema affected pneumothorax incidence, while age, lesion location and depth and emphysema significantly affected hemorrhage incidence ($P < 0.05$). In conclusion, low-dose, CT-guided ACNB with the EPL method provides a safe and accurate diagnosis.

Introduction

Computed tomography (CT)-guided transthoracic needle biopsy is a well-established, effective and safe technique for the diagnosis of focal lung lesions (1,2) and has exhibited high diagnostic accuracy and specificity (3). No differences have been detected between single-needle transthoracic needle biopsy and a coaxial technique with regard to diagnostic accuracy (4). Conventional CT-guided transthoracic needle biopsy, however, is a method for locating lesion-edges that increases the dwell time of the needle within the lung while scanning prior to biopsy (3,5-8). The reported dwell times during conventional CT range between 29 and 41 min (4,6,9,10). Longer dwell times are believed to result in greater needle motion during respiration, leading to the widening of the pleural puncture site (2,11-13). Pneumothorax and hemorrhage are the most frequent complications associated with the procedure (11,14-17). Other potential factors affecting the rate of complications include lesion depth and size, presence of atelectasis and patient age (13-16,18-22).

In order to reduce the needle dwell time in the lungs and reduce complications, we have established an extrapleural locating (EPL) method that maintains the needle tip outside the visceral pleura prior to biopsy. Our previous pilot studies have involved only small sample sizes (23,24); however, the preliminary results of these studies indicated that the EPL method was accurate and safe, and decreased the dwell time compared with conventional techniques (4,6,9,10). Furthermore, EPL was shown to improve the false-negative rate (23,24). Factors that affected accuracy included lesion depth and size, necrosis and the number of pleural passes (9,22,25,26).

The aim of the present study was to assess the efficacy of the low-dose, CT-guided EPL method and extrapleural percutaneous lung biopsy on a larger cohort of patients. We

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Abbreviations: ACNB, automated cutting needle lung biopsy; EPL, extrapleural locating; CT, computed tomography; OR, odds ratio; ED, effective dose; DLP, dose-length product

Key words: computed tomography scan, biopsy, atelectasis, hemoptysis, pneumothorax

hypothesized that this novel technique would reduce complications during low-dose, CT-guided automated cutting needle biopsy (ACNB), compared with results from previously published studies. Thus, a range of factors affecting accuracy and safety were evaluated during ACNB using a new EPL method.

Subjects and methods

Subjects. The Ethics Committee of the Zhongnan Hospital of Wuhan University (Wuhan, China) approved the study protocol and provided permission to perform this study. Each patient provided signed informed consent prior to participation.

This study was a retrospective analysis of 1,106 percutaneous CT-guided ACNBs with EPL performed on 1,065 patients between March 2005 and May 2012. All procedures were performed by the two radiologists that were experienced in performing CT-guided lung biopsies. Percutaneous CT-guided ACNB with an EPL technique was indicated in any patient with a lung lesion requiring biopsy. Patients with pleural-based tumors, such as mesothelioma, or pleural-based metastases were excluded, as this study reported only the results of percutaneous lung biopsy.

EPL method. A CT scan of the chest using a conventional CT Scanner (Somatom Sensation 16; Siemens Healthcare, Forchheim, Germany) was initially performed to identify the lesion (Fig. 1A). Prior to the biopsy, patients with deep intraparenchymal lesions or lesions adjacent to blood vessels received 1 KU hemocoagulase (H20041730; Jinzhou Ahon Pharmaceuticals Co., Ltd., Jinzhou, China) intramuscularly, as previously described (27).

Prior to the procedure, the radiologist described the biopsy process to the patient and positioned the patient in supine, prone or lateral positions to minimize puncture depth, and to avoid contact with bone and large blood vessels. After placing the patient in the scanner, the patient was trained in the breath-holding technique to ensure they were able to maintain the required magnitude of breath-hold during the CT scans and biopsy.

An initial localization scan with a low-dose technique (Lung CARE Series, Siemens Sensation 16 CT scan: 20-50 mA; 120 kV; scan field, 30-60 mm) through the region of interest was performed at a slice thickness of 5 mm and viewed on lung and soft-tissue windows. Localization was performed following a review of conventional CT images and by using laser positioning and metal skin markers (Biopsy single series: 50 mA; 120 kV; 10-mm thickness) to indicate the site of needle entry and direction of approach for biopsy. During the procedure, the ribs, lung bullae, vessels, fissures and low-density areas were avoided and the amount of aerated lung tissue traversed was minimized.

After ensuring that the direction of needle approach was perpendicular to the chest wall, the thickness of the thoracic wall was measured from the skin marker to the pleural surface (Fig. 1B) to determine the depth of anesthesia required and the depth of needle insertion. Using an aseptic technique with a 23-gauge needle, local anesthetic (lidocaine 1%) was administered. The anesthetic needle was inserted into the

chest wall pleura as the locating needle. In patients with a thin chest wall, in which the anesthetic needle was unable to be fixed automatically, the operator directly applied a biopsy needle (Bard® Max-Core® Core Needle Biopsy Instrument; Bard Biopsy Systems, Tempe, AZ, USA) for positioning. Once the core gun had been inserted into the chest wall, the radiology assistant, wearing X-ray protective gear, fixed the core gun manually and the low-dose CT scan, with a dose-length product (DLP) of 6 mGy/cm, was performed for EPL positioning (Fig. 1C). The radiologist confirmed the puncture angle and distances between the locating pin and lesion based on the CT data. The position of the lesion in relation to the tip of the locating needle, the precise distance to the margin of the lesion and the needle-pleura angle (defined as the angle between the locating needle and the line vertical to pleural surface) (Fig. 1D and E) were optimized using sequential CT scanning (Biopsy single series: 50 mA; 120 kV; scan field, 13.5 mm).

According to the data obtained from the repeat CT scan, the trajectory of the locating needle was adjusted under the chest wall pleura. The Bard Max-Core Core Needle was directly advanced into the lung and fired to obtain a core of tissue (typically 2-cm in length) from the lesion, based on data including direction, angle and depth obtained using the locating needle, following which the needle gun was withdrawn. The needle dwell time within the lung was measured, as the time between the biopsy needle puncturing the lung and its withdrawal from the lungs by the radiologist. The extracted tissue was examined by the naked eye. If soft tissue was evident in the sample, the biopsy was considered successful and the specimens obtained were placed in formalin solution using a saline-filled syringe. In general, to ensure that the tissue block was sufficient for histological examination, the biopsy was repeated 2-3 times, with slight adjustment of the transthoracic puncture angle and depth used. If pneumothorax occurred and caused the lesion to shift, or if adequate tissue was not obtained during the procedure, a repeat localization CT scan with EPL was performed. In order to avoid air embolism, the procedure was terminated if the patient coughed or hemoptysis ensued. Following completion of the biopsy, the biopsy area was scanned using conventional CT guidance (Biopsy single series: 50 mA; 120 kV; thickness, 4.5 mm; scan field, 13.5 mm) to exclude pneumothorax or hemorrhage (Fig. 1F). The biopsy gun should advance to the depth displayed in Fig. 2.

Final diagnosis. The final diagnosis for each patient was based on the results of the surgery, response to relevant therapy, or clinical observations at month 24 of clinical follow-up. The biopsy specimens were evaluated by an experienced pathologist and the final diagnosis was confirmed by surgery. Histological findings obtained by biopsy were compatible with the patient's clinical disease manifestations. Atypical adenomatous hyperplasia was defined as malignancy in this series, as previously described (28).

Data collection. Data collected included details regarding patient information (gender, age), nature of the lesion (location, type, depth, size, presence of emphysema, contrast enhancement) and the presence of atelectatic lung tissue

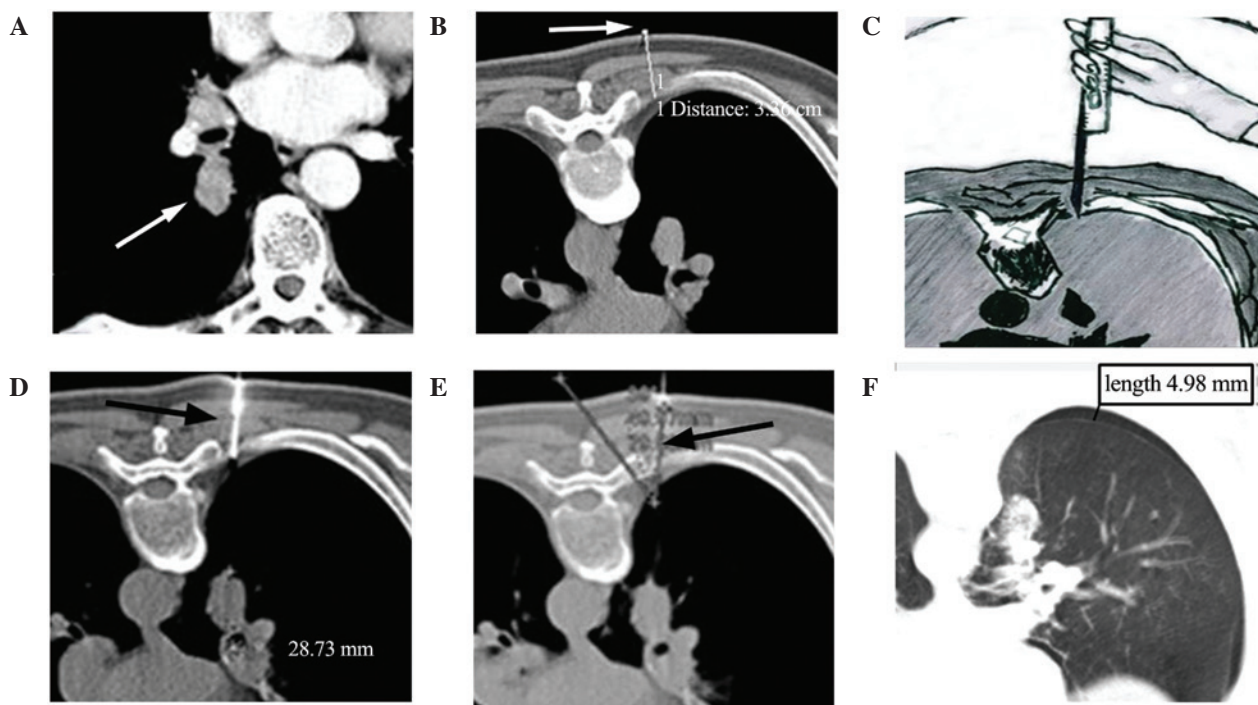


Figure 1. A 67-year-old man with a single, solid pulmonary nodule underwent automated cutting needle lung biopsy with extrapleural locating. (A) Pre-operative CT scan with enhancement demonstrating a nodule in the right lower lobe (arrow). (B) The patient was placed in the prone position. Axial CT imaging showed a skin marker (arrow) indicating the most favorable needle entry point; the thoracic wall thickness was 3.36 cm. (C) A core gun had been inserted into the chest wall outside the pleural area, the radiology assistant, wearing X-ray protective gear, fixed the core gun manually and performed the low-dose CT scan. (D) Introduction of the biopsy needle (arrow) into the soft tissues up to the pleural surface; the lesion depth from the needle tip to the lesion margin was 28.73 mm. (E) The needle-pleural angle was defined as the intersection angle between biopsy needle and the line which vertical to pleural, which is 34° (arrow). (F) Axial CT image acquired immediately after biopsy demonstrating the onset of pneumothorax. CT, computed tomography.

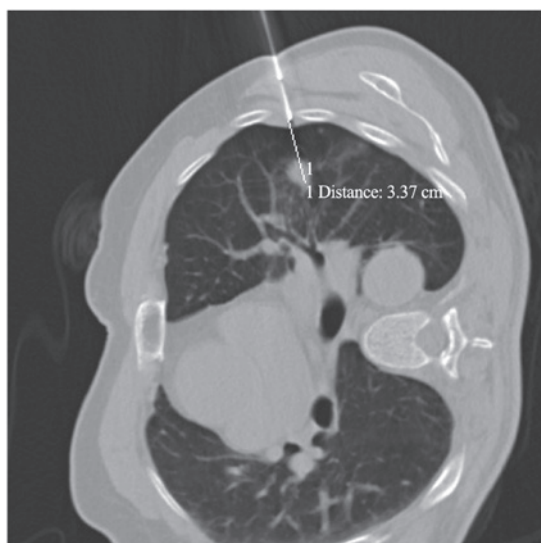


Figure 2. A 55-year-old man with adenocarcinoma, diagnosed using automated cutting needle lung biopsy with EPL. The upper left lung lesion size measured 12 mm. During pre-positioning for EPL biopsy, the distance between the biopsy gunpoint and the proximal edge of the lesion measured 34 mm. The gun was known to advance 22 mm due to the trigger of the biopsy gun; thus, the radiologist aimed to use the biopsy gun to enter the lung to a depth of 12 mm. EPL, extrapleural locating.

adjacent to the lesion, which could increase the difficulty of distinguishing between healthy and tumor tissue. In addition, details of the procedure (position, needle size, number of EPL attempts, needle-pleura angle), complications (pneumothorax,

hemorrhage, hemoptysis) and the histological results (benign versus malignant) were collected.

Potential complications of the EPL method included the presence of an immediate pneumothorax or hemorrhage on the post-biopsy CT images, the presence of a pneumothorax on the chest radiograph at 4 h post-biopsy and hemoptysis. Hemorrhage was also graded using the following criteria: i) Mild, hemorrhage presenting as haziness along the needle tracks or in adjacent air spaces on the CT scan; ii) moderate, occurrence of fewer than five episodes of hemoptysis estimated at <30 ml blood or minimal hemothorax; and iii) severe, hemoptysis or hemothorax associated with hemodynamic instability (13).

The presence of pneumothorax was assessed by a low-dose CT technique immediately subsequent to biopsy while the patient was on the CT scan table. Pneumothorax was graded using the following criteria: i) Mild, lung surface retraction of ≤ 2 cm; ii) moderate, lung surface retraction of between 2 and 4 cm; and iii) severe, lung surface retraction of ≥ 4 cm (13). Patients that were clinically stable remained under medical observation for 12 h prior to discharge (29). A chest radiograph was performed for all patients at 4 h after the procedure or sooner if they exhibited symptoms before this time.

Lesion size was measured along the needle path maximum long-axis diameter on the mediastinal windows. Lesion depth was measured from the point of pleural puncture to the nearest edge of the lung lesion along the needle path. Lesion type was divided into central versus peripheral. The definitions of



Figure 3. A 45-year-old man with well-differentiated adenocarcinoma, diagnosed using automated cutting needle lung biopsy with EPL. (A) An initial scan obtained prior to the biopsy showed a central lesion in the left lower lobe (white arrow). (B) Computed tomography scan obtained following the biopsy showed the needle point positioned outside the pleural surface (using the EPL method) to obtain the minimal distance from the nodule (black arrow). (C) High-power view of the nodule showed neoplastic gland formation (black arrows) (hematoxylin and eosin stain; magnification, $\times 100$). EPL, extrapleural locating.

central and peripheral lesions were based on imaging observation. Lesions that originated in the segmental bronchi or above bronchial lesions were graded as central lesions (Fig. 3), whereas lesions that originated in the lower bronchi were graded as peripheral lesions.

Emphysema was defined as ≤ 900 HU, in which ≤ 900 HU was used as the threshold for determining emphysema (30). The emphysema status was classified as follows: Group 1, no emphysemic tissue surrounding the lesion; group 2, emphysemic tissue surrounding the lesion, but distant from the needle tract; and group 3, prominent emphysemic tissue in the needle tract.

The Somatom Sensation 16 CT biopsy scanner was able to record the radiation dose administered throughout the entire scanning process. Total effective dose (ED) for all procedures was obtained directly from the CT station. Theoretically, $ED \text{ (mSv)} = DLP \times k$, where $k=0.014 \text{ (mSv/mGy/cm)}$ (31). Procedural duration was defined as the time between the first and last CT slice performed during the procedure.

Statistical analysis. Distributions of quantitative data were compared using the Student's *t*-test or the Mann-Whitney *U*-test, for analyzing the factors with or without a normal distribution, respectively. Distribution of qualitative data was compared using a χ^2 test or a bilateral Fisher's exact test. Categorical variables are presented as counts and percentages, with χ^2 tests for group comparisons. Logistic regression models were performed to detect the risk factors for diagnostic accuracy and complications. Continuous variables were stratified into groups for logistic regression analyses of complications. Using a forward procedure, only variables considered to be significant on univariate analysis ($P<0.05$) were subsequently introduced to multivariate logistic regression modeling to assess their contribution to diagnostic accuracy and the risk of pneumothorax, hemorrhage and hemoptysis. A two-sided $P<0.05$ was considered to indicate a statistically significant difference. SAS statistics software, version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

General data. A total of 1,106 percutaneous ACNBs were performed in 1,065 patients (733 men and 332 women) with

a mean age of 59 ± 12 years, including 290 outpatients and 775 inpatients. Among these, 198 cases underwent the procedure using a biopsy needle as a locating needle for EPL. The patients were primarily inpatients requiring pathological evaluation of their lesions. Among the 1,106 biopsies performed, 794 lesions were malignant and 312 were benign (Table I).

The overall diagnostic accuracy was 94.2%. A specific diagnosis was achieved in 81.4% of the benign and 84.5% of the malignant lesions (Table I). The overall specific diagnostic rate was 83.6%.

Risk factors affecting accuracy. The risk factors affecting accuracy are presented in Table II. Results of the univariate logistic regression analysis indicated that younger age, lesion type and depth, atelectasis and hemoptysis significantly affected accuracy ($P<0.05$; Table II). Factors that were significant on the univariate analyses were included in the multivariate model.

Results of the multivariate analysis suggested that the significant risk factors affecting accuracy included younger age, atelectasis, hemoptysis and lesion depth ($P<0.03$; Table II). In the 794 cases of malignant lesions, there were 64 false-negative results, including 15 false-negative cases in patients ≤ 50 years old (15/113, 13.27%), 19 false-negative cases in patients 51-60 years old (19/238, 8.00%), 22 false-negative cases in patients 61-70 years old (22/264, 8.33%) and 8 false-negative cases in patients aged >70 years (8/179, 4.47%). Among the 64 cases of malignant lesions, atelectasis was present in 24 cases (24/93, 25.81%), while there were 40 false-negative cases with no atelectasis (40/701, 5.71%); hemoptysis appeared in 10 cases (10/38, 26.32%), while there was no hemoptysis in 54 cases (54/756, 7.14%). Combining the malignant and benign lesions, hemorrhage occurred in 28 subjects (28/251, 11.16%) that had been administered hemocoagulase and 5 of the 58 subjects (8.62%) with hemoptysis had received hemocoagulase.

Lesion size had no effect on the false-negative results. Among the 64 false-negative cases, there were 17 cases with a lesion size measuring ≤ 20 mm, 11 measuring 21-30 mm, 9 measuring 31-40 mm, 12 measuring 41-50 mm and 15 measuring 51-88 mm.

Table I. Characteristics of malignant (n=794) and benign (n=312) lesions.

Characteristic	Total, n (%)	Malignant, n (%)	Benign, n (%)	P-value
Gender				0.017 ^a
Male	757 (68.44)	560 (70.53)	197 (63.14)	
Female	349 (31.56)	234 (29.47)	115 (36.86)	
Age, years				<0.001 ^a
≤50	236 (21.34)	113 (14.23)	123 (39.42)	
51-60	331 (29.93)	238 (29.97)	93 (29.81)	
61-70	330 (29.84)	264 (33.25)	66 (21.15)	
>70	209 (18.9)	179 (22.54)	30 (9.62)	
Lesion location, lobe				0.012 ^a
Right upper	333 (30.11)	251 (31.61)	82 (26.28)	
Right middle	46 (4.16)	24 (3.02)	22 (7.05)	
Right lower	242 (21.88)	169 (21.28)	73 (23.4)	
Left upper	273 (24.68)	203 (25.57)	70 (22.44)	
Left lower	212 (19.17)	147 (18.51)	65 (20.83)	
Lesion type				<0.001 ^a
Central	265 (23.96)	247 (31.11)	18 (5.77)	
Peripheral	841 (76.04)	547 (68.89)	294 (94.23)	
Lesion depth, mm				<0.001 ^a
0	521 (47.11)	348 (43.83)	173 (55.45)	
1-10	195 (17.63)	117 (14.74)	78 (25)	
11-20	216 (19.53)	175 (22.04)	41 (13.14)	
21-30	108 (9.76)	94 (11.84)	14 (4.49)	
>30	66 (5.97)	60 (7.56)	6 (1.92)	
Lesion size, mm				<0.001 ^a
≤10	57 (5.15)	22 (2.77)	35 (11.22)	
11-20	213 (19.26)	132 (16.62)	81 (25.96)	
21-30	273 (24.68)	171 (21.54)	102 (32.69)	
31-40	227 (20.52)	174 (21.91)	53 (16.99)	
>40	336 (30.38)	295 (37.15)	41 (13.14)	
Emphysema				0.063
0 ^b	423 (38.25)	287 (36.15)	136 (43.59)	
1 ^c	450 (40.69)	337 (42.44)	113 (36.22)	
2 ^d	233 (21.07)	170 (21.41)	63 (20.19)	
Contrast enhancement				0.087
Yes	336 (30.38)	253 (31.86)	83 (26.60)	
No	770 (69.62)	541 (68.14)	229 (73.40)	
Atelectasis				0.005 ^a
Yes	112 (10.13)	93 (11.71)	19 (6.09)	
No	994 (89.87)	701 (88.29)	293 (93.91)	
Position				0.665
Lateral	240 (21.7)	176 (22.17)	64 (20.51)	
Prone	586 (52.98)	414 (52.14)	172 (55.13)	
Supine	280 (25.32)	204 (25.69)	76 (24.36)	
Needle size, G				0.008 ^a
16	105 (9.49)	87 (10.96)	18 (5.77)	
18	1,001 (90.51)	707 (89.04)	294 (94.23)	
Number of attempts				0.034 ^a
≤2	396 (35.8)	277 (34.89)	119 (38.14)	
3	581 (52.53)	412 (51.89)	169 (54.17)	
≥4	129 (11.66)	105 (13.22)	24 (7.69)	

Table I. Continued.

Characteristic	Total, n (%)	Malignant, n (%)	Benign, n (%)	P-value
Needle-pleura angle, degrees				0.071
≤15	923 (83.45)	672 (84.63)	251 (80.45)	
16-30	110 (9.95)	78 (9.82)	32 (10.26)	
>30	73 (6.60)	44 (5.54)	29 (9.29)	
Pneumothorax				0.783
Yes	207 (18.72)	147 (18.51)	60 (19.23)	
No	899 (81.28)	647 (81.49)	252 (80.77)	
Hemorrhage				0.003 ^a
Yes	251 (22.69)	199 (25.06)	52 (16.67)	
No	855 (77.31)	595 (74.94)	260 (83.33)	
Hemoptysis				0.276
Yes	58 (5.24)	38 (4.79)	20 (6.41)	
No	1,048 (94.76)	756 (95.21)	292 (93.59)	
Diagnosis				<0.001 ^a
Positive	730 (66.00)	730 (91.94)	0 (0.00)	
Negative	376 (34.00)	64 (8.06)	312 (100.00)	
Specific diagnosis				0.245
Yes	925 (83.63)	671 (84.51)	254 (81.41)	
No	181 (16.37)	123 (15.49)	58 (18.59)	
False negative				
Yes	64 (8.06)	64 (8.06)		
No	730 (91.94)	730 (91.94)		

^aSignificant differences between groups. ^bNo emphysemic tissue surrounding the lesions; ^csome emphysemic tissue surrounding the lesions, but distant from the needle tract; ^dprominent emphysemic tissue in the needle tract.

The results of the multivariate logistic regression model showed that the risk of malignant lesions receiving a false-negative diagnosis decreased for every year increase in patient age [odds ratio (OR), 0.97; P=0.027] and increased with every millimeter increase in lesion depth (OR, 1.03; P=0.008) (Table II). The false-negative rates were 6.9% for a lesion depth of 0 mm, 2.56% for a lesion depth of 1-10 mm, 10.8% for 11-20 mm, 11.70% for 21-30 mm and 11.67% for a lesion depth >30 mm from the pleural surface. Additional significant risk factors affecting accuracy (false-negative diagnosis) included the presence of hemoptysis (OR, 5.06) and atelectasis (OR, 6.53) (Table II).

False-negative results occurred in 64 malignant cases (8.06%) (Table I). Among the 64 false-negative cases, a final diagnosis was confirmed by clinical manifestation of disease in 26 cases (40.6%), by definitive histology obtained at surgery in 18 cases (28%), by a secondary biopsy in 15 cases (23.4%) and by bronchofibroscope in 3 cases (4.0%). One case (2%) was confirmed by the detection of cancer cells in the hydrothorax, and one case was confirmed via thoracoscopy (2%) (Table III).

Complications of the procedure: Risk factors affecting pneumothorax. The incidence and distribution of pneumothorax, hemorrhage and hemoptysis are presented in Table IV. Among the 1,106 lesions biopsied, 207 (18.71%) biopsies

caused pneumothorax, 251 biopsies were associated with hemorrhage and 58 biopsies were associated with hemoptysis. The risk factors affecting complication rates are presented in Table V.

Table IV shows that lesion location, depth and size, as well as emphysema, atelectasis, position, needle size, number of attempts and hemostasis, had significant effects on the incidence of pneumothorax. The 207 cases of pneumothorax included 192 mild, 11 moderate and 4 severe pneumothoraces that required chest tube drainage.

A higher frequency of pneumothorax was observed in patients with CT evidence of emphysema (75.54%) in the needle tract (Table IV). The pneumothorax rate increased with increasing lesion depth. The pneumothorax rate was 4.61, 26.15, 31.02, 33.33 and 43.94% for the five groups of lesion depth (0, 1-10, 11-20, 21-30 and >30 mm, respectively) (Fig. 4).

Increasing lesion size >10 mm was inversely correlated with the incidence of pneumothorax. In the five groups of lesion size (≤10, 11-20, 21-30, 31-40 and >40 mm), the pneumothorax rate was 33.33, 29.58, 21.98, 15.42 and 8.93%, respectively (Table IV).

From multivariate logistic regression analysis, only lesion size and emphysema appeared to significantly affect the incidence of pneumothorax (P<0.05; Table V). The odds of pneumothorax were significantly reduced in subjects with

Table II. Univariate and multivariate analysis of risk factors affecting accuracy (false-negative rate).

Risk factor/reference	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender/female	1.54 (0.83-2.85)	0.167		
Age, years	0.97 (0.95-0.99)	0.009 ^a	0.97 (0.95-1.00)	0.027
Lesion location/right upper lobe				
Right middle lobe	0.86 (0.19-3.88)	0.844		
Right lower lobe	0.72 (0.35-1.49)	0.379		
Left upper lobe	0.81 (0.42-1.57)	0.531		
Left lower lobe	0.69 (0.32-1.49)	0.344		
Lesion type/central	0.34 (0.2-0.57)	<0.001 ^a	0.72 (0.37-1.39)	0.321
Lesion depth, mm	1.03 (1.01-1.05)	0.007 ^a	1.03 (1.01-1.05)	0.008 ^a
Lesion size, mm	1.00 (0.99-1.02)	0.894		
Emphysema/0 ^b	1.06 (0.61-1.82)	0.847		
1 ^c	0.65 (0.37-1.15)	0.142		
2 ^d	0.68 (0.34-1.36)	0.273		
Contrast enhancement/no	1.05 (0.61-1.81)	0.865		
Atelectasis/no	5.75 (3.27-10.1)	<0.001 ^a	6.53 (3.12-13.67)	<0.001 ^a
Position/lateral				
Prone	0.87 (0.46-1.65)	0.668		
Supine	1.04 (0.51-2.13)	0.917		
Needle size/16 G	2.64 (0.81-8.61)	0.107		
Number of attempts/≤2				
3	0.68 (0.38-1.21)	0.196		
≥4	1.76 (0.88-3.50)	0.109		
Needle-pleura angle/≤15°				
16-30°	0.95 (0.4-2.3)	0.916		
>30°	1.14 (0.4-3.32)	0.804		
Hemostatic/no	0.89 (0.31-2.54)	0.824		
Pneumothorax/no	1.52 (0.84-2.77)	0.166		
Hemorrhage/no	1.29 (0.74-2.26)	0.374		
Hemoptysis/no	4.64 (2.14-10.06)	<0.001 ^a	5.06 (2.19-11.70)	<0.001 ^a

^aP<0.05. ^bNo emphysemic tissue surrounding the lesions; ^csome emphysemic tissue surrounding the lesions, but distant from the needle tract; ^dprominent emphysemic tissue in the needle tract. OR, odds ratio; CI, confidence interval.

Table III. Distribution of diagnostic methods used to confirm the false-negative results.

Confirmation method	False-negative rate, n (%)
Clinical manifestations of disease	26 (40.6)
Surgery	18 (28.0)
Secondary biopsy	15 (23.4)
Bronchofibroscope	3 (4.0)
Thoracoscope	1 (2.0)
Cancer cell in hydrothorax	1 (2.0)
Total	64 (100)

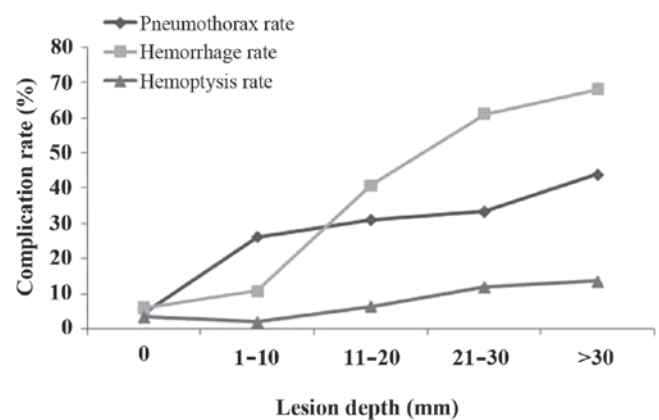


Figure 4. Association between lesion depth and complication rate.

Table IV. Complications.

Parameter	Pneumothorax, n (%)			Hemorrhage, n (%)			Hemoptysis, n (%)		
	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value
Total, n	899	207	-	855	251	-	1,048	58	-
Gender			0.060			0.033			0.005
Male	604 (79.79)	153 (20.21)		599 (79.13)	158 (20.87)		727 (96.04)	30 (3.96)	
Female	295 (84.53)	54 (15.47)		256 (73.35)	93 (26.65)		321 (91.98)	28 (8.02)	
Age, years			0.274			0.003			0.265
≤50	195 (82.63)	41 (17.37)		189 (80.08)	47 (19.92)		228 (96.61)	8 (3.39)	
51-60	266 (80.36)	65 (19.64)		244 (73.72)	87 (26.28)		308 (93.05)	23 (6.95)	
61-70	260 (78.79)	70 (21.21)		243 (73.64)	87 (26.36)		312 (94.55)	18 (5.45)	
>70	178 (85.17)	31 (14.83)		179 (85.65)	30 (14.35)		200 (95.69)	9 (4.31)	
Lesion location, lobe			0.004			0.021			0.147
Right upper	287 (86.19)	46 (13.81)		238 (71.47)	95 (28.53)		311 (93.39)	22 (6.61)	
Right middle	31 (67.39)	15 (32.61)		38 (82.61)	8 (17.39)		43 (93.48)	3 (6.52)	
Right lower	184 (76.03)	58 (23.97)		185 (76.45)	57 (23.55)		225 (92.98)	17 (7.02)	
Left upper	223 (81.68)	50 (18.32)		221 (80.95)	52 (19.05)		263 (96.34)	10 (3.66)	
Left lower	174 (82.08)	38 (17.92)		173 (81.60)	39 (18.40)		206 (97.17)	6 (2.83)	
Lesion type			0.121			0.414			0.974
Central	224 (84.53)	41 (15.47)		200 (75.47)	65 (24.53)		251 (94.72)	14 (5.28)	
Peripheral	675 (80.26)	166 (19.74)		655 (77.88)	186 (22.12)		797 (94.77)	44 (5.23)	
Lesion depth, mm			<0.001			<0.001			<0.001
0	497 (95.39)	24 (4.61)		490 (94.05)	31 (5.95)		503 (96.55)	18 (3.45)	
1-10	144 (73.85)	51 (26.15)		174 (89.23)	21 (10.77)		191 (97.95)	4 (2.05)	
11-20	149 (68.98)	67 (31.02)		128 (59.26)	88 (40.74)		202 (93.52)	14 (6.48)	
21-30	72 (66.67)	36 (33.33)		42 (38.89)	66 (61.11)		95 (87.96)	13 (12.04)	
>30	37 (56.06)	29 (43.94)		21 (31.82)	45 (68.18)		57 (86.36)	9 (13.64)	
Lesion size, mm			<0.001			0.001			0.052
≤10	38 (66.67)	19 (33.33)		44 (77.19)	13 (22.81)		55 (96.49)	2 (3.51)	
11-20	150 (70.42)	63 (29.58)		156 (73.24)	57 (26.76)		199 (93.43)	14 (6.57)	
21-30	213 (78.02)	60 (21.98)		194 (71.06)	79 (28.94)		253 (92.67)	20 (7.33)	
31-40	192 (84.58)	35 (15.42)		175 (77.09)	52 (22.91)		213 (93.83)	14 (6.17)	
>40	306 (91.07)	30 (8.93)		286 (85.12)	50 (14.88)		328 (97.62)	8 (2.38)	
Emphysema			<0.001			<0.001			0.030
0 ^a	406 (95.98)	17 (4.02)		309 (73.05)	114 (26.95)		392 (92.67)	31 (7.33)	
1 ^b	436 (96.89)	14 (3.11)		398 (88.44)	52 (11.56)		435 (96.67)	15 (3.33)	

Table IV. Continued.

Parameter	Pneumothorax, n (%)		P-value	Hemorrhage, n (%)		P-value	Hemoptysis, n (%)		P-value
	No	Yes		No	Yes		No	Yes	
2°	57 (24.46)	176 (75.54)		148 (63.52)	85 (36.48)		221 (94.85)	12 (5.15)	
Atelectasis			0.001			0.001			0.696
Yes	104 (92.86)	8 (7.14)		100 (89.29)	12 (10.71)		107 (95.54)	5 (4.46)	
No	795 (79.98)	199 (20.02)		755 (75.96)	239 (24.04)		941 (94.67)	53 (5.33)	
Position			<0.001			0.422			0.691
Lateral	156 (65.00)	84 (35.00)		193 (80.42)	47 (19.58)		230 (95.83)	10 (4.17)	
Prone	497 (84.81)	89 (15.19)		449 (76.62)	137 (23.38)		554 (94.54)	32 (5.46)	
Supine	246 (87.86)	34 (12.14)		213 (76.07)	67 (23.93)		264 (94.29)	16 (5.71)	
Needle size, G			<0.001			<0.001			0.488
16	102 (97.14)	3 (2.86)		98 (93.33)	7 (6.67)		101 (96.19)	4 (3.81)	
18	797 (79.62)	204 (20.38)		757 (75.62)	244 (24.38)		947 (94.61)	54 (5.39)	
Number of attempts			<0.001			<0.001			<0.001
≤2	296 (74.75)	100 (25.25)		262 (66.16)	134 (33.84)		360 (90.91)	36 (9.09)	
3	496 (85.37)	85 (14.63)		485 (83.48)	96 (16.52)		563 (96.90)	18 (3.10)	
≥4	107 (82.95)	22 (17.05)		108 (83.72)	21 (16.28)		125 (96.90)	4 (3.10)	
Needle-pleura angle, degrees			0.632			0.900			0.064
≤15	746 (80.82)	177 (19.18)		714 (77.36)	209 (22.64)		877 (95.02)	46 (4.98)	
16-30	91 (82.73)	19 (17.27)		86 (78.18)	24 (21.82)		106 (96.36)	4 (3.64)	
>30	62 (84.93)	11 (15.07)		55 (75.34)	18 (24.66)		65 (89.04)	8 (10.96)	
Hemostatic			<0.001			<0.001			0.381
Yes	40 (60.61)	26 (39.39)		38 (57.58)	28 (42.42)		61 (92.42)	5 (7.58)	
No	859 (82.60)	181 (17.40)		817 (78.56)	223 (21.44)		987 (94.90)	53 (5.10)	

P-values show the statistical significance of the univariate analysis of risk factors affecting complications. ^aNo emphysemic tissue surrounding the lesions; ^bsome emphysemic tissue surrounding the lesions, but distant from the needle tract; ^cprominent emphysemic tissue in the needle tract. Percentages for pneumothorax, hemorrhage and hemoptysis were calculated using the formula % = Y/(Y + N).

Table V. Statistical analysis of risk factors for complications (pneumothorax, hemorrhage and hemoptysis).

Risk factor/reference	OR (95% CI)	P-value
Pneumothorax		
Lesion size/≤10 mm		
11-20	1.25 (0.46-3.37)	0.662
21-30	0.64 (0.23-1.73)	0.377
31-40	0.48 (0.17-1.35)	0.162
>40	0.32 (0.11-0.95)	0.040 ^a
Emphysema/0 ^b		
1 ^c	1.00 (0.47-2.12)	0.999
2 ^d	72.11 (37.35-139.22)	<0.001 ^a
Hemorrhage		
Age/ ≤50 years		
51-60	1.68 (1.03-2.75)	0.038 ^a
61-70	1.75 (1.05-2.90)	0.031 ^a
>70	0.99 (0.53-1.82)	0.961
Lesion location/right upper lobe		
Right middle lobe	0.39 (0.15-1.00)	0.050
Right lower lobe	0.54 (0.33-0.88)	0.014 ^a
Left upper lobe	0.61 (0.38-0.99)	0.044
Left lower lobe	0.48 (0.29-0.80)	0.005 ^a
Lesion depth/0 mm		
1-10	1.62 (0.88-2.98)	0.122
11-20	9.56 (5.83-15.68)	<0.001 ^a
21-30	24.49 (13.36-44.87)	<0.001 ^a
>30	31.51 (15.22-65.24)	<0.001 ^a
Emphysema/0 ^b		
1 ^c	0.55 (0.35-0.87)	0.010 ^a
2 ^d	0.51 (0.33-0.80)	0.004 ^a
Hemoptysis		
Gender/female	0.55 (0.31-0.96)	0.036 ^a
Lesion depth/0 mm		
1-10	0.50 (0.16-1.53)	0.226
11-20	1.70 (0.79-3.66)	0.174
21-30	3.10 (1.35-7.12)	0.008 ^a
>30	3.85 (1.49-10.00)	0.006 ^a
Number of attempts/≤2		
3	0.40 (0.21-0.73)	0.003 ^a
≥4	0.42 (0.14-1.25)	0.118

^aP<0.05. ^bNo emphysemic tissue surrounding the lesions; ^csome emphysemic tissue surrounding the lesions, but distant from the needle tract; ^dprominent emphysemic tissue in the needle tract. OR, odds ratio; CI, confidence interval.

a lesion size of >40 mm (OR, 0.32; P=0.04) compared with those in subjects with a lesion size of <10 mm and were significantly higher in subjects with prominent emphysemic tissue in the needle tract (OR, 72.11; P<0.001) (Table V) compared with those in subjects with no emphysemic tissue surrounding the lesions. As shown in Fig. 4, the pneumothorax rates increased with increasing lesion depth (P<0.001), as did the rates of hemorrhage and hemoptysis (P<0.001).

Complications of the procedure: Risk factors affecting hemorrhage. A total of 251 biopsies (22.7%) caused perifocal and needle track hemorrhages, including 193 mild, 50 moderate and 8 severe, of which 52 were hemopneumothoraces. Gender, age, emphysema, atelectasis, needle size, number of attempts and hemostasis, as well as lesion location, depth and size, appeared to have a significant effect on the incidence of hemorrhage (Table IV). Lesions

Table VI. Number of biopsy attempts required for each lesion depth range.

Lesion depth, mm	Number of biopsy attempts, n (%)			P-value
	≤2	3	≥4	
0	9 (50.00)	9 (50.00)	0 (0.00)	0.003
1-10	2 (50.00)	2 (50.00)	0 (0.00)	
11-20	5 (35.71)	5 (35.71)	4 (28.57)	
21-30	12 (92.31)	1 (7.69)	0 (0.00)	
>30	8 (88.89)	1 (11.11)	0 (0.00)	

>10 mm in depth were associated with an increased incidence of hemorrhage (Table IV). Lesions in the right upper lobe were more prone to hemorrhage compared with those in other locations (28.53%, Table IV). The hemorrhage rate in the group that had emphysemic tissue in the needle tract (36.48%) was markedly increased compared with the bleeding rate from the needle pathway without emphysema (26.95%) (Table IV). Based on multivariate logistic regression analysis, age, lesion location and depth and emphysema all had a significant effect on the incidence of hemorrhage ($P<0.05$). The odds of hemorrhage were significantly higher in patients in the 61-70-year-old group (OR, 1.75; $P=0.031$) compared with those in patients aged ≤ 50 years and were significantly lower in those with lesions located in lobes other than the right upper lobe (all $P<0.05$). The odds of hemorrhage were significantly higher in subjects with lesion depths of 11-20, 21-30 and >30 mm (ORs of 9.56, 24.49 and 31.51, respectively; $P<0.001$) compared with those in subjects with a lesion depth of 0 mm. Multivariate analysis, following adjustment for confounding factors, showed that the odds of hemorrhage were significantly reduced in lesions with some or prominent emphysemic tissue compared with those in lesions without surrounding emphysemic tissue (ORs of 0.55 and 0.51, respectively; $P=0.010$ and 0.004, respectively; Table V).

Complications of the procedure: Risk factors affecting hemoptysis. The hemoptysis rate was 5.2% (Table IV). Gender, lesion depth, emphysema and number of attempts appeared to have a significant effect on the incidence of hemoptysis (Table IV). Based on multivariate logistic regression analysis, gender, lesion depth and number of biopsy attempts had a significant effect on the incidence of hemoptysis ($P<0.05$). The odds of hemoptysis were significantly lower in males compared with those in females (OR, 0.55; $P=0.036$); were significantly higher in subjects with lesion depths of 21-30 and >30 mm compared with those in patients with a lesion depth of 0 mm (ORs of 3.1 and 3.85, respectively; $P=0.008$ and 0.006, respectively); and were significantly lower in subjects with 3 biopsy attempts compared with those in subjects with ≤ 2 attempts (OR, 0.4; $P=0.003$; Table V).

Total ED and needle dwell time. The total mean ED was 0.54 ± 0.14 mSv (range, 0.21-0.95 mSv). The mean duration of the procedure was 16 ± 2 min and the mean time spent by the needle in the parenchyma (mean needle dwell time) was

5 ± 3 sec (range, 3-8 sec) per biopsy. A total of 396 patients (35.8%) each received 2 biopsy attempts and 581 patients (52.53%) each received 3 attempts (Table I).

Discussion

Low-dose, CT-guided ACNB of pulmonary lesions with EPL has high diagnostic accuracy and improved safety compared with conventional CT-guided biopsy. The sensitivity, specificity, positive predictive value and negative predictive value of the EPL method were 91.9, 100, 100 and 82.9%, respectively, and showed improvements compared with the values obtained in previous studies (13,18-24). The overall diagnostic accuracy of EPL in the present study was 94.2%. Results of multivariate analysis demonstrated that significant risk factors affecting accuracy included younger age, atelectasis, hemoptysis and lesion depth (all $P<0.03$). Younger age (≤ 50 years old) has not been investigated in previously published studies as a risk factor affecting accuracy and is, therefore, a novel finding. Among the 1,106 lesions biopsied, 207 resulted in pneumothorax, 251 in hemorrhage and 58 in hemoptysis. Lesion size and emphysema were demonstrated to exert a significant influence on the incidence of pneumothorax. Age, lesion location and depth and emphysema significantly affected the incidence of hemorrhage. In addition, gender, lesion depth and number of attempts had a significant effect on the incidence of hemoptysis.

With regard to the risk factors affecting accuracy, the results of multivariate analysis showed that significant risk factors affecting accuracy included younger age, atelectasis, hemoptysis and lesion depth (all $P<0.03$). Younger age (≤ 50 years old) has not previously been reported in the literature as a risk factor affecting accuracy and is, therefore, a novel finding. To the best of our knowledge, this is the first study to show a correlation between younger age and diagnostic accuracy. Other studies have investigated the effect of age on accuracy using various lung biopsy techniques (26,32,33). All three of these studies, however, failed to find any correlation between accuracy and age (26,32,33). The reason for the discrepancy between previously published results and the present findings may be associated with the high false-negative rate in the younger patients in the malignant group. This high false-negative rate may have been due to the increased inflammation and necrosis in the tumors of younger patients, which increased the difficulty of confirming a malignant diagnosis. Among the 15 false-negative cases in the malignant group of patients aged ≤ 50 years, 4 cases exhibited obvious necrosis

and 3 cases exhibited a combination of inflammation and necrosis. The final diagnoses included 8 cases of lung cancer, 5 cases of metastatic tumor, one malignant lesion and one case of malignant fibrous histiocytoma (data not shown).

The effect of atelectasis on accuracy may have been due to difficulty in distinguishing lesions from atelectasis, as the majority of lesions complicated with atelectasis were of a central type and exhibited necrosis. In addition, enhancement on CT scan appeared to exert no effect on diagnostic accuracy in the present study. The effect of hemoptysis on accuracy may have been due to the fact that the procedure was terminated due to the risk of air embolism if the patients developed serious cough or hemoptysis (25). Finally, it appeared that diagnostic accuracy decreased in proportion to increasing lesion depth >10 mm; this finding was expected, as deeper lesions are more difficult to biopsy.

The EPL method exhibits an acceptable complication rate. Among the 1,106 lesions biopsied, 207 biopsies (18.71%) led to pneumothorax. The EPL method appears to reduce damage to the visceral pleura, which may partly explain the reduced pneumothorax rate in the present study compared with rates reported using other techniques (13-15,19-21). Furthermore, the pneumothorax rate was relatively low despite multiple needle passes, which may have been due to the breath-hold training undergone by the patients at the beginning of the procedure.

As reported in previous studies, deeper lesions were associated with a higher rate of pneumothorax (10,14,34). The pneumothorax rates in the present study increased with increasing lesion depth ($P<0.001$). Furthermore, the pneumothorax rate in the present study was elevated in patients with emphysemic tissue surrounding the lesions, which increased the possibility of pulmonary vascular tearing, while it remained relatively low in the group without emphysema, younger patients or lesions situated in superficial parts.

For conventional CT-guided ACNB, the incidence of pulmonary hemorrhage reported in the literature varies between 4 and 42%, and the hemoptysis rate varies between 2 and 25% (13,14,18,19,22,24,28). In the present study, 251 biopsies (22.69%) were associated with hemorrhage and 58 biopsies (5.24%) were associated with hemoptysis (Table IV). Few reports have described an association between lesion location and hemorrhage (35,36). Analysis of the present data showed that right upper lobe lesions had a higher rate of hemorrhage; however, this finding may have been due to random error. Furthermore, the rates of hemorrhage and hemoptysis increased significantly with increasing lesion depth ($P<0.001$). The risk of hemorrhage was significantly lower in lesions with some or prominent emphysemic tissue compared with that in lesions with no surrounding emphysemic tissue (OR, 0.55 and 0.51, respectively; Table V). The risk of hemoptysis was also significantly lower in subjects with 3 biopsy attempts compared with that in patients that underwent ≤ 2 attempts, which may have been due to the fact that fewer deep-lesion biopsy attempts were made than superficial-lesion biopsy attempts (Table VI). Biopsy duration can increase if the surgeon considers more tissue biopsy specimens are required, which can result in a relatively high rate of bleeding. In addition, the administration of hemostatic drugs can reduce the rate of hemoptysis.

The present study contained several limitations, including its retrospective nature and the fact that the study was conducted at a single hospital and included primarily inpatients. In addition, hemocoagulase was used in patients with a high risk of bleeding prior to surgery, as it has been demonstrated to reduce bleeding from our clinical observations, particularly the incidence of hemoptysis. The injection of hemocoagulase was not randomized or controlled and was used only in certain cases. Thus, the inconsistent application of hemocoagulase may have affected the assessment of hemorrhage and hemoptysis (i.e., without the benefit of a randomized control, it may have affected the statistical results). As this study was retrospective, this limitation could not be altered.

In conclusion, the present EPL method for performing CT-guided ACNB is a novel technique that has been described in one previous study in the literature (24). This EPL method has been demonstrated to be a safe, fast and accurate diagnostic method with reduced dwell time compared with conventional techniques. The EPL method maintains the needle tip outside the visceral pleural prior to biopsy. Consequently, the time spent by the needle within the parenchyma (dwell time) is significantly decreased compared with that associated with conventional methods (2,19,22,27). In addition, the entire procedure, on average, has a duration of 16 ± 2 min, and requires a lower dose of radiation compared with those employed in previous studies (37,38). The results of the multivariate analysis indicated that significant risk factors affecting accuracy included younger age, atelectasis, hemoptysis and lesion depth ($P<0.03$). To the best of our knowledge, younger age (≤ 50 years old) has not been previously reported in the literature as a risk factor affecting accuracy and is therefore a novel observation.

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