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ORIGINAL ARTICLE

Safety and diagnostic accuracy of percutaneous CT-guided transthoracic biopsy of small lung nodules (≤20 mm) adjacent to the pericardium or great vessels

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PURPOSE
We aimed to evaluate the safety and diagnostic accuracy of computed tomography (CT)-guided transthoracic biopsy of small lung nodules (≤20 mm) adjacent to the pericardium or great vessels.

METHODS
This retrospective study examined the safety and diagnostic accuracy of percutaneous CT-guided biopsy for small lung nodules (≤20 mm) located within 10 mm of the pericardium or great vessels. Technical aspects and factors influencing complications were assessed, and diagnostic accuracy was calculated.

RESULTS
A total of 168 biopsies were performed in 168 patients. The complications were mainly pneumothorax (34.5%; 58 of 168 patients), chest tube insertion (5.3%; 9 of 168 patients), and pulmonary hemorrhage (61.3%; 103 of 168 procedures), with no patient mortality. One patient (0.6%) was admitted because of hemorrhage complications. Significant independent risk factors for pneumothorax were nodules resided in upper or middle lobes and lateral patient position, and for hemorrhage, longer distance from structures and longer needle trajectory through the lung parenchyma. Overall, the sensitivity, accuracy, and specificity were 91.0%, 92.2%, and 100%, respectively.

CONCLUSION
Percutaneous CT-guided transthoracic biopsy was highly accurate in small lung nodules (≤20 mm) adjacent to the pericardium or great vessels. Complications are common, but most were minor and self-limited.

In recent years, with wide availability of computed tomography (CT) and the development of low-dose CT screening techniques, more small lung nodules (≤20 mm) have been detected (1–3). Lee et al. (4) reported that small lung nodules were detected at a rate of 44.5%, and that 39.7% of lung cancers were found in small nodules. Accurate histopathological diagnosis is of great importance in management of these nodules, but biopsy via fluoroscopy or ultrasound guidance is technically more difficult, and CT guidance is usually required (5).

Percutaneous CT-guided transthoracic lung biopsy is a reasonably safe and accurate approach to the histological diagnosis of primary and secondary lung nodules (4, 6, 7). However, nodule size is the major determinant of diagnostic accuracy, which reached 96.9% for larger nodules (7), but ranged from 52% to 78.8% for small nodules (8, 9).

Biopsy of small lung nodules close to proximity to the pericardium or great vessels is particularly challenging, and precise needle placement is essential to avoid complications resulting from non-target tissue injury near vital mediastinal or vascular structures. Hsu et al. (10) suggested that CT-guided lung biopsy should be avoided if the adjacent nodule is within 10 mm of the pericardium.

The authors know of no related studies of biopsy of small lung nodules close to the pericardium or great vessels. This study, therefore, was conducted to examine the safety and diagnostic accuracy of CT-guided transthoracic biopsy of small lung nodules (≤20 mm) within 10 mm of the pericardium or great vessels.

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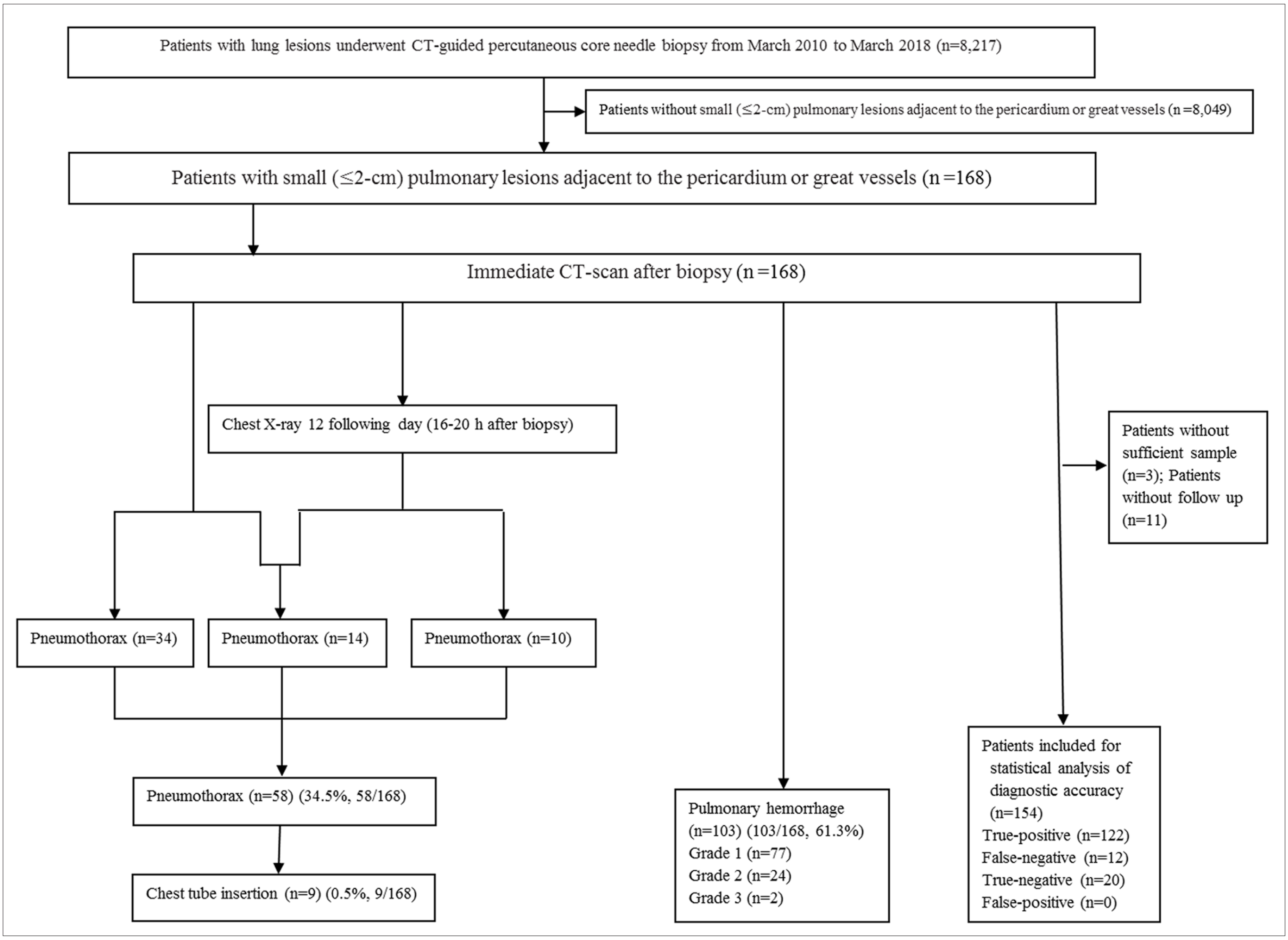

Figure 1. Flow diagram of patient management, interventions, and sample size for analyses.

Methods

Data were collected retrospectively from the institutional departmental database, and the study protocol and waiver of informed consent were approved by the Institutional Review Board (decision/protocol number 1904159-3-1905&1904159-3-1906). Patient management and intervention are summarized by the flow diagram shown in Fig. 1.

Main points

- Nodule in the upper or middle lobe was a significant risk factor for pneumothorax.
- Lateral position was a significant risk factor for pneumothorax.
- Longer transparenchymal needle trajectory increased the risk of hemorrhage.
- CT-guided biopsy was highly accurate for diagnosing small lung nodules near the pericardium or great vessels.

Patients

Between March, 2010, and March, 2018, 8217 patients underwent CT-guided transthoracic biopsy at our hospital. Patients were included if they had lung nodules measuring ≤20 mm in standard lung windows and adjacent to the pericardium or great vessels. Adjacent nodules were defined as index tumors seen at any distance within 10 mm of the pericardium or great vessels on axial CT images.

Biopsy procedures

CT-guided transthoracic lung biopsies were performed using a 64-slice spiral CT scanner (120 kV, 250 mA; Philips Healthcare) with 3 mm slice thickness by one of five interventional radiologists with more than 5-year experience.

Previous diagnostic images were reviewed to confirm the general location of the target lung nodule, and a planning CT scan was then performed to determine the best patient position for the procedure: prone, supine, or lateral (biopsy side up; contralateral dependent), to optimize guided needle placement while ensuring the patient's safety and comfort. The most effective needle track was selected to approach the nodule, while avoiding crossing the adjacent large pulmonary vessels, visible airways, or fissures if possible. If feasible, a needle entry site as close as possible to the superior aspect of the rib was chosen to avoid intercostal vasculature. When possible, the needle track was kept parallel to the surface of the pericardium or great vessels, avoiding puncture of the pericardium or great vessel. The patients received local anesthesia, and the biopsies were performed using either a coaxial or non-coaxial technique, depending on a) whether or not immunohistochemical or molecular analysis was planned, and b) operator preference following risk/benefit analysis. For the coaxial technique, either a 17-gauge coaxial

Table 1. Final diagnoses

Core needle biopsy histological results	Final diagnosis		
	Malignant	Benign	Total
Malignant	122	0	122
Benign	12	20	32
Total	134	20	154

needle with an 18-gauge semi-automated core biopsy needle or a 19-gauge coaxial needle with a 20-gauge semi-automated core biopsy needle was used (SuperCore; Argon Medical Devices). The needles were pushed into the peripheries of the lung nodules using a step-by-step technique under CT guidance. CT images were used to confirm the correct position of the needle tip. Great care was taken to puncture pleura only once during procedure. When the nodule was along the projected course of the needle, the procedure was continued. Otherwise, the needle was repositioned or the puncture site was changed. If the needle tip was located correctly within the target lesion, the biopsy was performed.

CT images were acquired immediately after the biopsy for checking any procedure-related complications. Patients were then positioned with the puncture site down and admitted for 4-hour continuous observation. The biopsies were always performed after 2:00 PM on Mondays to Thursdays, and all patients had erect anteroposterior chest radiographs 16 to 20 hours postbiopsy and were evaluated by the interventional radiologists. Our standard threshold for chest tube placement for pneumothorax was symptomatic pneumothorax, or at least 30% to 40% involvement of the hemithorax. Chest tubes were kept in place until air leakage stopped.

Data review

We recorded nodule size (0–15 mm, and 15.1–20 mm), nodule location (upper and middle lobes, lower lobes), pericardium vs. great vessel adjacent to the target nodule, and distance from pericardium or great vessel (0 mm, and 0.1–10 mm). Nodule size was determined by the maximum diameter measured on CT image.

Procedure data included position of patient (supine or prone vs. lateral), angle of pleural puncture, number of pleural punctures, and the length of needle trajectory through lung parenchyma (0–30 mm vs. >30 mm). Axial CT-images of needle placement into the nodule were used to measure the angle of pleural puncture, that is, the lesser of the two angles between them, and to measure the length of the needle trajectory.

Complications were graded according to the Cardiovascular and Interventional Radiology Society of Europe (CIRSE) Classification System (11). Postprocedure pneumothorax was based on the immediate postbiopsy CT images or the chest X-ray at 16 to 20 hours postbiopsy. Pulmonary hemorrhage was defined by any new ground-glass opacity or consolidation on the immediate postbiopsy CT scan, and its severity was graded according to published methods (12, 13): 0, no hemorrhage; 1, hemorrhage along the needle tract less than 2 cm wide; 2, hemorrhage along the needle tract more than 2 cm wide but sublobar; 3, lobar hemorrhage or greater; or 4, hemothorax with hemodynamic instability.

We reviewed postbiopsy and post-resection pathologic reports and serial CT scans monitoring nodules over time. The CT-guided biopsy diagnoses of malignancy were classified as true positive (i.e., surgical confirmation of malignancy or same results of the known primary malignancy or postprocedural clinical evidence of malignancy) and false positive (i.e., no evidence of malignancy in surgical specimens). Postprocedural clinical evidence of malignancy was defined as fulfilling at least one of three criteria during the follow-up period: 1) increase in nodule size; 2) other proven metastases; 3) decrease in nodule size after radiotherapy, chemotherapy, or targeted therapy (14, 15). Benign CT-guided biopsy diagnoses were classified as true negative (i.e., surgical confirmation of benign nodule, subsequent disappearance or significant decrease in size of the nodule, or no change for at least 12 months postbiopsy) and false negative (i.e., subsequent proof of malignancy).

Statistical analysis

The data were grouped according to presence or absence of complications (pneumothorax, pulmonary hemorrhage) after the biopsy procedure, and continuous and categorical variables were respectively compared between groups with and without complications by independent sample t test and Pearson chi-square test. Significant differences identified by univariate analysis were then analyzed with multivariate analysis by the use of logistic regression with forward selection. Based on the histopathologic diagnoses of the biopsy specimens with the final surgical, clinical, or follow-up radiologic findings, the sensitivity, specificity, and diagnostic accuracy of CT-guided biopsy for benign vs. malignant diagnoses were calculated by using 2×2 tables (Table 1). Statistical analysis using a commercially available statistical program was performed (IBM SPSS 20, IBM). Values of $p < 0.05$ were statistically significant.

Results

There were 168 biopsies in 168 patients (67 men, 101 women; mean age, 59±11 years). The characteristics of patients, lung nodules, and biopsy procedures are presented in Table 2. Cardiac chambers adjacent to the nodules were: left atrium (n=6; Fig. 2a), left ventricle (n=36; Fig. 2b), right atrium (n=26; Fig. 2c), and right ventricle (n=4; Fig. 2d). Great vessels adjacent to the nodules were: aorta (n=59; Fig. 3a), innominate artery (n=4; Fig. 3b), pulmonary artery shunt (n=12; Fig. 3c), subclavian artery (n=1; Fig. 3d), superior vena cava (n=13; Fig. 3e), inferior vena cava (n=2; Fig. 3f), innominate vein (n=1; Fig. 3g), and subclavian vein (n=4; Fig. 3h). No procedure-related mortality was recorded. One patient had CIRSE grade 2 pulmonary hemorrhage with hemoptysis (Fig. 4). The remaining complications, including pneumothorax in 58 cases and pulmonary hemorrhage in 102 cases, were categorized as grade 1.

The overall pneumothorax rate was 34.5% (58/168); pneumothorax was detected on the immediate postpuncture CT in 28.6% (10/58) and on chest X-ray the following morning in 6% (10/168) (Fig. 1). The placement of chest tube was required in 15.5% (9/58) of the pneumothorax cases, representing 5.4% (9/168) of the total study population. On univariate analysis, the significant risk factors for pneumothorax were nodule location ($p = 0.020$) and patient position ($p = 0.017$). Patient age, sex, nodule size, nodule adjacent to the pericardium or great vessels, distance from pericardium or great vessels to target nod-

Table 2. Characteristics of patients, lung nodules, and biopsy procedures

Characteristics		Data
Age (years), mean±SD (range)		59±11 (15–79)
Sex, n (%)	Male	67 (39.9)
	Female	101 (60.1)
Nodule size, n (%)	0–15 mm	60 (35.7)
	15.1–20 mm	108 (64.3)
Nodule location, n (%)	Upper or middle lobe	117 (69.6)
	Lower lobe	51 (30.4)
Pericardium adjacent to the target nodule, n (%)	Left atrium	6 (8.3)
	Left ventricle	36 (50.0)
	Right atrium	26 (36.1)
	Right ventricle	4 (5.6)
Great vessel adjacent to the target nodule, n (%)	Aorta	59 (61.5)
	Innominate artery	4 (4.2)
	Pulmonary artery	12 (12.5)
	Subclavian artery	1 (1.0)
	Superior vena cava	13 (13.5)
	Inferior vena cava	2 (2.1)
	Innominate vein	1 (1.0)
	Subclavian vein	4 (4.2)
Distance from pericardium or great vessels, n (%)	0 mm	53 (31.5)
	0.1–10 mm	115 (68.5)
Patient position, n (%)	Supine and prone	145 (86.3)
	Lateral	23 (13.7)
Angle of pleural puncture, n (%)	≤50°	51 (30.4)
	>50°	117 (69.6)
Number of pleural punctures, n (%)	1	166 (98.8)
	2	2 (1.2)
Length of needle path through the lung parenchyma, n (%)	0–30 mm	63 (37.5)
	>30 mm	105 (62.5)

ule, angle of pleural puncture, and length of needle trajectory through the lung parenchyma were not significantly different between groups (Table 3). Multivariate analysis revealed nodules residing in the upper or middle lobes ($p = 0.012$) and lateral position ($p = 0.011$) as significant independent risk factors for pneumothorax (Table 4).

Pulmonary hemorrhage occurred in 103 procedures (61.3%) among 168 patients (Fig. 1). Two (1.2%) of the 168 biopsies caused grade 3 hemorrhage, 24 (14.3%) caused grade 2 hemorrhage, and 77 (45.8%) caused grade 1 hemorrhage. Univariate analysis demonstrated that closer proximity to great vessels, longer distance (0.1–10 mm) from pericardium or great vessels, and longer transparenchymal needle trajectory possessed significant risk of pulmonary hemorrhage ($p = 0.022$, $p = 0.027$, and $p < 0.001$, respectively), while patient age, sex, nodule size, nodule location, patient position, and angle of pleural puncture were not significant (Table 3). On multivariate analysis, longer distance (0.1–10 mm) from pericardium or great vessels and longer needle trajectory (>30 mm) through the lung parenchyma remained as significant independent risk factors for pulmonary hemorrhage ($p = 0.049$ and $p < 0.001$, respectively) (Table 5).

The biopsy results were considered nondiagnostic if the sample was not sufficient or if patient follow-up information was not available (n=14). Therefore, the statistical analysis of diagnostic performance included 154 of 168 patients (Fig. 1). Malignancy was finally diagnosed according to the gold standard in 134 patients. Among these, the diagnosis by CT-guided biopsy was true-positive in 122 patients and false-negative in 12 patients. Revisions in diagnosis of malignancy were based on surgical confirmation (n=13), histological findings that were similar to those of the known primary malignancy (n=46), and a postprocedural clinical course consistent with an obvious malignant process (n=75). Twenty nodules were identified as benign masses (true negative, n=20; false negative, n=0). Benign nodules were confirmed by surgical specimen (n=8), subsequent disappearance of the nodule (n=3), significant reduction in nodule size (n=7) in follow-up, or by stable status for more than 12 months postbiopsy (n=2). Overall, the sensitivity, accuracy, and specificity of CT-guided biopsy for diagnosis in small lung nodules were 91% (122 of 134), 92.2% (142 of 154), and 100% (20 of 20) (Table 1). The 95% confidence intervals were calculated as 0.846–0.951 for sensitivity and 0.800–1 for specificity.

Discussion

Percutaneous transthoracic needle biopsy with CT and CT-fluoroscopy guidance has proved to be an accurate and safe diagnostic procedure for small lung nodules (5, 16, 17). Beyond conventional CT, CT-fluoroscopy allows real-time visualization as the needle is advanced (18) , and more recently, C-arm cone beam CT provides both real-time fluoroscopy and three-dimensional (3D) CT reconstruction images (19). However, both of these techniques impose significant radiation burden for patients and operators (20), and although navigation systems are now being incorporated to assist with image-guided percutaneous biopsy (21), those that have been tested *in vivo* thus far are few, and most of the trials have been conducted in small, heterogeneous cohorts (18, 19, 21). As such, even when real-time control is not available, conventional CT is still universally adopted in clinical practice for imaging-guided percutaneous needle biopsy of masses in lung.

The potential complications of CT-guided biopsy in close proximity to the pericardium or great vessels include cardiac tamponade, hemopericardium, pneumopericardium, right ventricular perforation, and great vessel laceration (22–24). These complications are rare but potentially fatal and of primary concern to the interventional radiologist. It is important that a step-by-step technique is used to monitor the relative position of the needle tip to the pericardium or great vessel. Once the correct needle trajectory, toward the lung nodule and avoiding puncture of the pericardium or great vessel, is confirmed, the needle is advanced incrementally until the tip lies within the nodule. If possible, the needle is positioned parallel to the surface of the pericardium or great vessels. Notwithstanding the recommendation that transcutaneous CT-guided biopsy should be avoided when the adjacent nodule is within 10 mm of the pericardium (10), there were no fatal complications recorded in our study of 168 patients with small lung nodules (≤20 mm) adjacent to the pericardium or great vessels.

In our cohort, 10 patients who did not have noticeable pneumothorax immediately postoperatively had pneumothorax detected by chest X-ray the following morning, and these accounted for 17% of 54 patients with pneumothorax. In other studies, chest-X rays have been obtained at 1 to 4 hours after biopsy (5, 25, 26). To our knowledge, no consensus exists regarding the most appropriate timing for post-biopsy chest X-rays. The overall rate of pneumothorax in our study was 34.5% and is well within the range of 12.8% to 62.0% reported in similar studies (3–5, 25–28). Nodule location in the upper or middle lobe is an

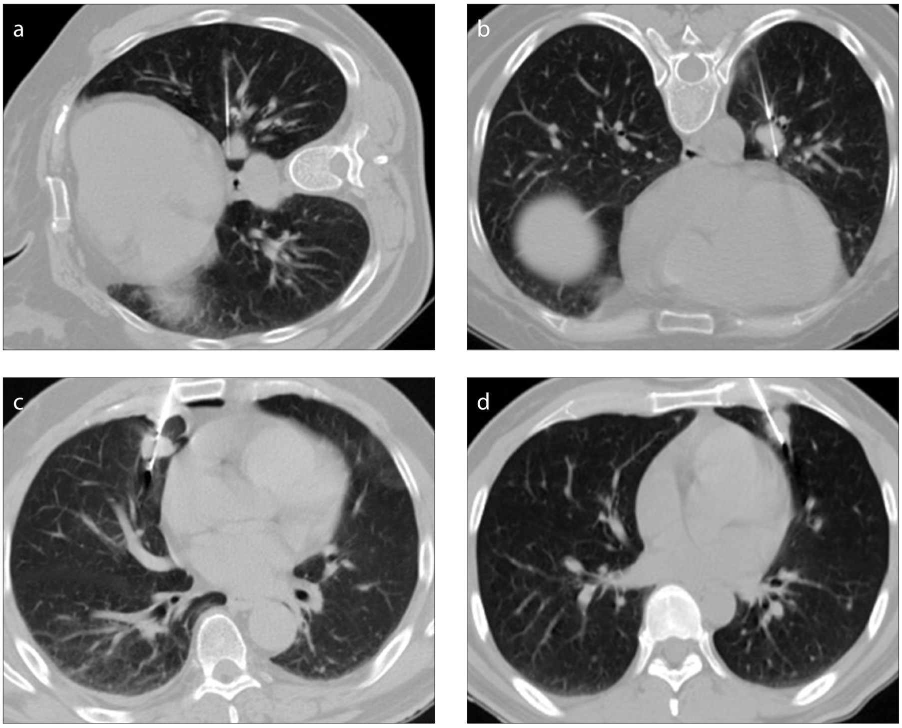

Figure 2. a–d. Representative CT images show lung nodules located within 10 mm of left atrium **(a)**, left ventricle **(b)**, right atrium **(c)**, and right ventricle **(d)**.

Table 3. Univariate analysis for risk factors associated with pneumothorax and pulmonary hemorrhage

Characteristics		Pneumothorax Yes	Pneumothorax No	*p*	Pulmonary hemorrhage Yes	Pulmonary hemorrhage No	*p*
Age (years)	Mean±SD	57±10	58±11	0.448[a]	58±11	57±11	0.496[a]
Sex, n (%)	Male	28 (41.8)	39 (58.2)	0.107[b]	42 (62.7)	25 (37.3)	0.765[b]
	Female	30 (29.7)	71 (70.3)		61 (60.4)	40 (39.6)	
Nodule size, n (%)	0–15 mm	20 (33.3)	40 (66.7)	0.809[b]	37 (61.7)	23 (38.3)	0.944[b]
	15.1–20 mm	38 (35.2)	70 (64.8)		66 (61.1)	42 (38.9)	
Nodule location, n (%)	Upper or middle lobe	47 (40.2)	70 (59.8)	0.020[b]	71 (60.7)	46 (39.3)	0.801[b]
	Lower lobe	11 (21.6)	40 (78.4)		32 (62.7)	19 (37.3)	
Nodule adjacent to, n (%)	Pericardium	27 (37.5)	45 (62.5)	0.482[b]	37 (51.4)	35 (48.6)	0.022[b]
	Great vessel	31 (32.3)	65 (67.7)		66 (68.8)	30 (31.2)	
Distance from pericardium or great vessels to target nodule, n (%)	0 mm	20 (37.7)	33 (62.3)	0.552[b]	26 (49.1)	27 (50.9)	0.027[b]
	0.1–10 mm	38 (33.0)	77 (67.0)		77 (67.0)	38 (33.0)	
Patient position, n (%)	Supine or prone	45 (31.0)	100 (69.0)	0.017‡	89 (61.4)	56 (38.6)	0.963[b]
	Lateral	13 (56.5)	10 (43.5)		14 (60.9)	9 (39.1)	
Angle of pleural puncture, n (%)	≤50°	14 (27.5)	37 (72.5)	0.286[b]	29 (56.9)	22 (43.1)	0.435[b]
	>50°	42 (35.9)	75 (64.1)		74 (63.2)	43 (36.8)	
Length of needle path through the lung parenchyma, n (%)	0-30 mm	18 (28.6)	45 (71.4)	0.209[b]	25 (39.7)	38 (60.3)	<0.001[b]
	>30 mm	40 (38.1)	65 (61.9)		78 (74.3)	27 (25.7)	

[a]Independent sample t test.
[b]Pearson chi-square test.

independent risk factor for pneumothorax, as previous data attest (5). Reported findings of the influence of nodule location on the pneumothorax rate are conflicting. In some studies, a nodule in the lower lobe increased the pneumothorax rate (4, 29, 30), whereas in others this was not an independent risk factor for pneumothorax (3, 8, 16, 31–33). The difference between our study and prior similar studies may be explained by the fact that a small nodule in upper and middle lobe is difficult to sample because of closely spaced ribs and the frequent proximity of such small nodules to the pericardium or great vessels. These conditions theoretically require more redirection and adjustment of the needle trajectory, causing longer operative time and higher pneumothorax rate.

The finding of a higher rate of pneumothorax in association with lateral dependent position does not contradict prior studies (25, 29). Rozenblit et al. (25) and Mills et al. (29) found that using the ipsilateral dependent position could reduce the rate of pneumothorax. For biopsies

Table 4. Multivariate analysis to identify independent risk factors for pneumothorax

Characteristics	B coefficient	*p*	OR	95% CI
Nodule location	-1.016	0.012	0.362	0.164–0.801
Patient position	1.220	0.011	3.387	1.327–8.648

OR, odds ratio; CI, confidence interval.
p value for Hosmer-Lemeshow test was 0.738.

Table 5. Multivariate analysis to identify independent risk factors for pulmonary hemorrhage

Characteristics	B coefficient	*p*	OR	95% CI
Nodule adjacent to pericardium or great vessels	0.593	0.089	1.809	0.914–3.578
Distance from pericardium or great vessels	0.724	0.049	2.063	1.003–4.240
Length of needle path through the lung parenchyma	1.476	<0.001	4.375	2.200–8.703

OR, odds ratio; CI, confidence interval.
p value for Hosmer-Lemeshow test was 0.913.

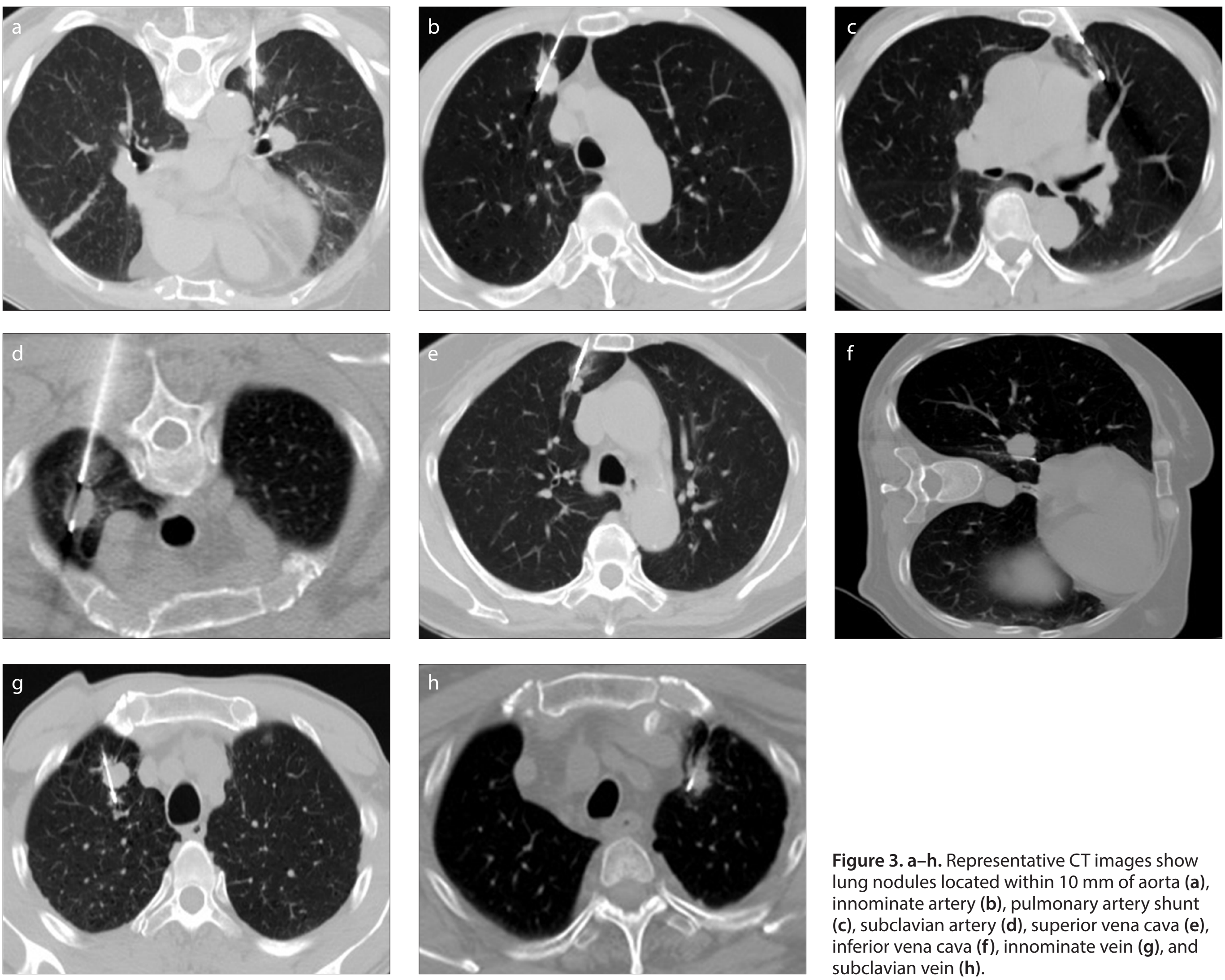

Figure 3. a–h. Representative CT images show lung nodules located within 10 mm of aorta **(a)**, innominate artery **(b)**, pulmonary artery shunt **(c)**, subclavian artery **(d)**, superior vena cava **(e)**, inferior vena cava **(f)**, innominate vein **(g)**, and subclavian vein **(h)**.

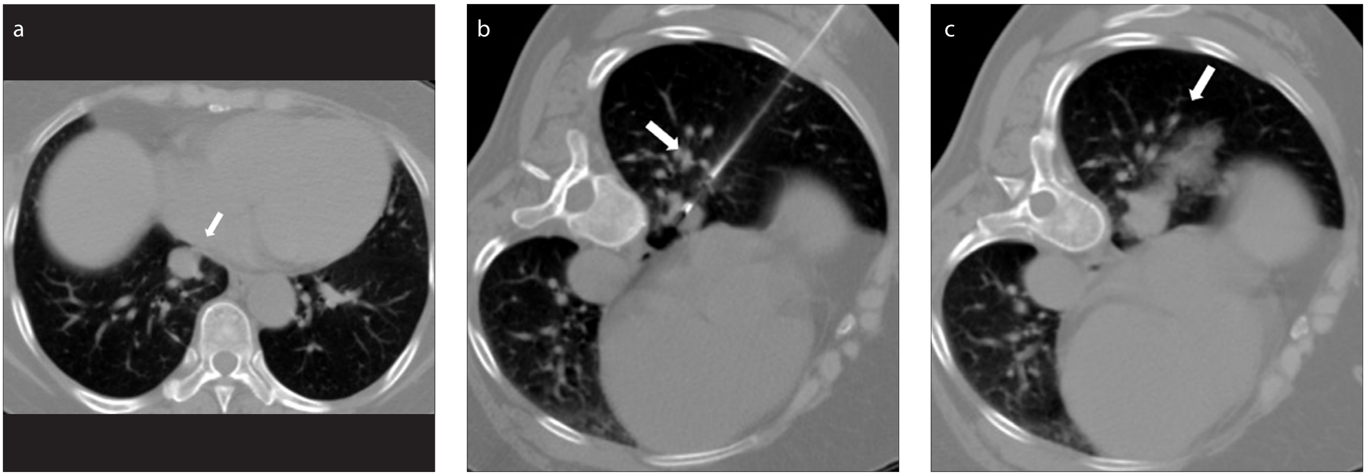

Figure 4. a–c. CT-guided core biopsy of a small nodule in a 58-year-old woman. CT image **(a)** obtained before biopsy with patient in supine position shows a 17 mm lung nodule in the right lower lobe. The nodule is within 10 mm of the right atrium. CT image **(b)** obtained after needle placement shows the precise localization of the tip of the biopsy needle in the nodule. The length of needle trajectory through the lung parenchyma is 100 mm. CT image **(c)** obtained after needle removal shows grade 2 hemorrhage along the needle tract. The core biopsy diagnosis was adenocarcinoma, which was the final diagnosis after surgical resection.

performed in the contralateral dependent position, the patient is positioned with the nodule in the nondependent portion of the chest. Therefore, the relative hyperinflation and increased rib excursion of the nondependent lung may contribute to the development of pneumothorax (25).

The rate of pulmonary hemorrhage of 61.3% in our study is higher than the 30% to 42.4% range reported in other studies (12, 13, 34). This is probably because all of the CT-guided biopsies were performed in small lung nodules. Previous studies involving lung nodules ≤20 mm have registered higher rates of hemorrhage (12, 35, 36). Yeow et al. (12) had a rate of pulmonary hemorrhage of 66% for small (≤20 mm) lung nodules. The independent predictor of higher risk of pulmonary hemorrhage was a longer (>30 mm) needle trajectory through the lung parenchyma, which compliments previous reports (36) maintaining that longer transparenchymal needle paths increase the risk of vessel puncture and hemorrhage. In addition, the pulmonary vessels enlarge when lung nodules are close to pericardium or great vessels, further increasing the incidence of major pulmonary hemorrhage. Nonetheless, the majority of the postprocedure pulmonary hemorrhages in our group were relatively minor and self-limited, requiring hospital admission in only one case (0.5%), similar to the result of Tai et al. (13), who had an admission rate of 0.4%.

It appears that the smaller the lung nodule, the more difficult inserting the needle into the nodule using CT-guidance. Several studies reported decreased biopsy accuracy associated with decreasing nodule size (37, 38), whereas others have reported similar success rates in small and large nodules (35, 39). The diagnostic accuracy of biopsy of small lung nodules (≤20 mm) has been reported as 77.2%–98.2% (3, 8, 16, 38, 40), and the overall accuracy of diagnosis in our study was 92.2%. These variable results may be attributable to many study differences, including imaging guiding system, biopsy approach, nodule location, surgeon's skill, and patient characteristics.

Our present study had important limitations. First, the study was retrospective. A randomized controlled trial would clearly be preferable. Second, the definition of small lung nodules (≤20 mm) adjacent to the pericardium or great vessels was arbitrary. Third, the likely correlation between risk factors was not analyzed. Fourth, the 12-month follow-up period may be not sufficiently long, and there is still controversy about whether a 12- or 24-month follow-up period is optimal (3, 4, 40). For now, this study and others (3, 40) rely on a 12-month follow-up period for confirming the nature of nodules, while the 24-month follow-up period has prevailed elsewhere (4).

In conclusion, we found that percutaneous CT-guided transthoracic biopsy was highly accurate for the diagnosis of small lung nodules (≤20 mm) adjacent to the pericardium or great vessels. Complications were common, but mostly self-limited.

Financial disclosure

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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