CT-guided percutaneous core needle biopsy of pulmonary nodules smaller than 2 cm: technical aspects and factors influencing accuracy

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of CT-guided percutaneous core needle biopsy (CT-CNB) of pulmonary nodules ≤ 2 cm, as well as to identify factors influencing the accuracy of the procedure and its morbidity. **Methods:** This was a retrospective, single-center study of 170 consecutive patients undergoing CT-CNB of small pulmonary nodules (of ≤ 2 cm) between January of 2010 and August of 2015. **Results:** A total of 156 CT-CNBs yielded a definitive diagnosis, the overall diagnostic accuracy being 92.3%. Larger lesions were associated with a higher overall accuracy (OR = 1.30; p = 0.007). Parenchymal hemorrhage occurring during the procedure led to lower accuracy rates (OR = 0.13; p = 0.022). Pneumothorax was the most common complication. A pleura-to-lesion distance > 3 cm was identified as a risk factor for pneumothorax (OR = 16.94), whereas performing a blood patch after biopsy was a protective factor for pneumothorax (OR = 0.18). **Conclusions:** Small nodules (of < 2 cm) represent a technical challenge for diagnosis. CT-CNB is an excellent diagnostic tool, its accuracy being high.

Keywords: Image-guided biopsy; Neoplasms; Lung.

INTRODUCTION

Recent widespread availability of CT and advances in low-dose CT screening techniques have enabled the identification of an increasing number of small pulmonary nodules (of ≤ 2 cm).[1-3] These small nodules represent a diagnostic challenge. In addition, stage IA lesions represent an excellent opportunity to perform lung-sparing resections for non-small cell lung cancer, with excellent 5-year survival and low local recurrence rates.[4]

Lung lesions can be considered benign when imaging findings suggest stability or when consistent clinical and laboratory findings are available. In contrast, lesions that have CT features suggestive of malignancy require further investigation. The options for managing such lesions include surveillance CT imaging, CT-guided biopsy, (navigational or non-navigational) bronchoscopic biopsy, and surgical resection.[5-7] Follow-up CT requires ionizing radiation and provides results after considerable delay. This can cause anxiety in some patients, a more rapid diagnostic method therefore being preferable. CT-guided biopsy can be performed on an outpatient basis and constitutes a viable option in such cases.[8]

CT-guided percutaneous transthoracic core needle biopsy (CNB) is a safe and accurate technique that has been widely used in order to evaluate pulmonary nodules.[9-11] Although some studies have evaluated the accuracy of CT-guided CNB of pulmonary nodules,[12-15] only a few have tested the accuracy of 20-gauge coaxial CNB performed exclusively for lesions of ≤ 2 cm in size.[16,17]

The primary objective of the present study was to evaluate the overall diagnostic accuracy of CT-guided percutaneous 20-gauge CNB of small pulmonary nodules, as well as to identify factors influencing the accuracy of the procedure. A secondary objective was to evaluate morbidity and the factors influencing it.

METHODS

Patients

This was a retrospective, single-center study. The study was approved by the local research ethics committee. Between January of 2010 and August of 2015, 174 CT-guided percutaneous CNBs of small pulmonary

nodules (of ≤ 2 cm) were performed in 170 patients, all of whom gave written informed consent before the procedure.

All 170 patients had undergone CT before recommendation of CT-guided CNB. Platelet count and prothrombin time were determined before the procedure, which was not performed if the platelet count was < 50,000 or if the international normalized ratio was > 1.5. Patients were admitted to the interventional radiology department on the same day of the procedure.

Biopsy procedure

Patients underwent local anesthesia, sedation, or general anesthesia depending on the size and location of the lesion. Lower lobe lesions were most commonly biopsied under general anesthesia, whereas large lesions were most commonly biopsied under local anesthesia. Therefore, the type of anesthesia used varied according to the nodule features and the professional team. The choice of patient position was made in order to facilitate access to the target lesion and avoid target lesion motion, given that lying on the side of the lung to be biopsied reduces the respiratory motion of the lung.

All biopsies were guided by a multislice CT scanner (Somatom Definition AS 40-slice; Siemens Healthcare GmbH, Erlangen, Germany). Each biopsy was performed by one of seven interventional radiologists with more than 5 years of experience.

An initial ultra-low-dose noncontrast chest CT was performed for biopsy planning. The imaging parameters were as follows: tube voltage, 80 kVp; tube current, 8 mA; collimation, 1.2 mm; and slice thickness, 2.4-3.0 mm. The CT scanner gantry laser lights and radiopaque landmarks indicated the site of needle entry on the patient's skin. After needle insertion through the thoracic wall, thin-section CT images were obtained in order to guide the needle. All biopsies were performed by using a coaxial technique with a 19-gauge introducer needle (Argon Medical Devices Inc., Frisco, TX, USA or Cook Medical LCC, Bloomington, IN, USA). With the introducer needle in the correct position, samples were collected through a 20-gauge semiautomatic core needle (SuperCore™; Argon Medical Devices Inc., or Quick-Core®; Cook Medical LCC), which can obtain specimens of 10 or 20 mm in length. Initially, one to three specimens were collected. One of five on-site pathologists with more than 5 years of experience was present for all biopsies. The specimens were gently rolled onto a glass slide and immediately sent for cytopathology (imprint cytology). If the specimen was insufficient, another specimen was taken until a diagnosis was made. When pathology showed that the specimens contained cells consistent with the lesion (sufficient for later analysis), at least three more nodule samples were obtained through the coaxial needle. At the end of the biopsy, all specimens were placed in a container with 10% formalin.

Prior to removal of the coaxial needle, a CT scan of the chest was performed to assess immediate complications. When no pneumothorax was present, a blood patch was performed in the biopsy path, at the discretion of the interventional radiologist, by injecting 1 ml of patient peripheral blood for every 1 cm of needle withdrawn. Immediately after biopsy, a follow-up CT scan of the chest was performed to detect complications. After recovery from anesthesia, all patients were monitored closely, and an expiratory posteroanterior chest X-ray was obtained 1 h after the procedure. After 4-6 h, patients with no complaints or complications were discharged.

Cases of pneumothorax during or after biopsy were classified as mild, moderate, or severe on the basis of the extent of retraction of the lung parenchyma from the chest wall: < 2 cm, mild; 2-4 cm, moderate; and > 4 cm, severe. Symptomatic or increasing pneumothorax despite monitoring or aspiration was treated with placement of a 14-French chest tube (Cook Medical LCC) connected to a Heimlich valve. Hemodynamically stable patients were discharged and returned 2-3 days later for chest tube removal. Parenchymal hemorrhage was classified as mild when it compromised the same lung segment as the nodule; moderate when it compromised distant segments or when associated with small-volume hemoptysis; and severe when associated with large-volume hemoptysis or hemodynamic instability.

Histopathological findings

Final pathology results were used in order to evaluate the accuracy of the CNBs. Because the surgical management of premalignant lesions (such as atypical adenomatous hyperplasia) and malignant lesions is similar, they were grouped together.

CNB findings of malignancy were considered true positives when 1) there was surgical confirmation; 2) the histological findings were consistent with the known primary malignancy; and 3) the subsequent clinical course was consistent with malignancy. Malignant CNB findings were considered false positives when 1) there was no surgical confirmation; and 2) the subsequent clinical course was inconsistent with malignancy. Benign CNB findings were considered true positives when 1) there was surgical confirmation; 2) the lesion disappeared or decreased in size with or without antibiotics; and 3) the lesion remained stable for at least 1 year after biopsy. Benign CNB findings were considered false positives when 1) surgical findings showed malignancy; and 2) the subsequent clinical course was inconsistent with a benign diagnosis. Finally, inadequate or paucicellular CNB specimens were considered false negatives (nondiagnostic). No lesions were classified as true negatives, because the CT findings were conclusive. Patients without a final diagnosis (because of cancer-unrelated death during follow-up, loss to follow-up, or a follow-up period of < 1 year) were excluded. Diagnostic accuracy was

calculated as the sum of all true positives divided by the sum of all included patients.

Statistical analysis

Categorical variables were described as absolute and relative frequencies. Nodule size was described as median and interquartile range. In order to analyze the association between dichotomous outcomes and other study variables, we used generalized estimating equations to take into account the dependence between measurements on each individual. Binomial distribution and exchangeable correlation structure were used. Initially, crude adjustments were made, variables being compared two by two. Associations showing p < 0.200 were considered for inclusion in the multiple regression model, and, after a stepwise process of exclusion and inclusion of variables, only variables that had a significant association with the outcome remained in the model. All statistical analyses were performed with the R software, version 3.1.3 (The R Foundation for Statistical Computing,

Vienna, Austria), and the level of significance was set at 5%.

A safety analysis was conducted in all of the patients who underwent CNB. An accuracy analysis was conducted in all of the patients in whom the CNB diagnosis was confirmed by surgery or clinical follow-up (≥ 1 year).

RESULTS

A total of 174 CNBs were performed in 170 patients, for whom there were data available for safety analysis. Of the 170 patients analyzed, 89 were male and 81 were female, their mean age being 61.5 years (range, 4-87). The mean lesion size was 1.25 cm (range, 0.4-2.0). Most (80.4%) of the lesions were predominantly solid. Eighteen patients with nonmalignant results were excluded for the following reasons: no follow-up (in 9), less than 1 year of follow-up after biopsy (in 8), and death from other causes during the first year of follow-up (in 1). Lesion size was associated with increased accuracy

Table 1. Variables associated with the overall diagnostic accuracy of CT-guided percutaneous core needle biopsy of small pulmonary nodules.[a]

Variable		Total	Overall diagnostic accuracy		p*
			No	Yes	
		(N = 156)	(n = 12)	(n = 144)	
Nodule density	Predominantly solid	124 (79.5)	7 (58.3)	117 (81.2)	
	Pure ground-glass opacity	32 (20.5)	5 (41.7)	27 (18.8)	0.056
Lesion size	1-10 mm	58 (37.2)	8 (66.7)	50 (34.7)	
	11-20 mm	98 (62.8)	4 (33.3)	94 (65.3)	0.037
Pleura-to-lesion distance	0-10 mm	87 (55.8)	9 (75.0)	78 (54.2)	
	11-30 mm	49 (31.4)	1 (8.3)	48 (33.3)	0.122
	> 30 mm	20 (12.8)	2 (16.7)	18 (12.5)	0.959
Proximity to pulmonary fissures	No	134 (85.9)	11 (91.7)	123 (85.4)	
	Yes	22 (14.1)	1 (8.3)	21 (14.6)	0.583
Length of needle trajectory through the lung parenchyma	0-10 mm	47 (30.1)	5 (41.7)	42 (29.2)	
	11-20 mm	42 (26.9)	3 (25.0)	39 (27.1)	0.553
	21-30 mm	23 (14.7)	1 (8.3)	22 (15.3)	0.385
	> 30 mm	44 (28.2)	3 (25.0)	41 (28.5)	0.484
Type of anesthesia	General anesthesia	117 (75.0)	9 (75.0)	108 (75.0)	
	Conscious sedation or local anesthesia	39 (25.0)	3 (25.0)	36 (25.0)	0.941
Number of specimens obtained	1-2	6 (3.8)	1 (8.3)	5 (3.5)	
	3-4	26 (16.7)	2 (16.7)	24 (16.7)	0.437
	5 or more	124 (79.5)	9 (75.0)	115 (79.9)	0.428
Pneumothorax during the procedure	No	143 (91.7)	10 (83.3)	133 (92.4)	
	Yes	13 (8.3)	2 (16.7)	11 (7.6)	0.447
Alveolar hemorrhage during the procedure	No	141 (90.4)	9 (75.0)	132 (91.7)	
	Yes	15 (9.6)	3 (25.0)	12 (8.3)	0.065
Malignancy	Yes	108 (69.2)	7 (58.3)	101 (70.1)	
	No	48 (30.8)	5 (41.7)	43 (29.9)	0.343
Lesion size, mm[b]		13.00 [9.00-16.00]	8.50 [7.75-12.50]	13.00 [9.75-16.00]	0.006

[a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as median [interquartile range]. *Logistic regression model.

(p = 0.037), whereas pleura-to-lesion distance, proximity to pulmonary fissures, length of needle trajectory through the lung parenchyma, and number of specimens obtained were not. Table 1 shows all of the variables analyzed for their effect on diagnostic accuracy. Accuracy analysis was possible in 156 CNBs (Figure 1). The histopathological findings of the CNBs are shown in Table 2. The overall diagnostic accuracy of those 156 CNBs was 92.3%. All 144 conclusive CNB results were confirmed as benign or malignant by follow-up imaging or surgery. In the multivariate analysis, larger lesions were associated with higher overall accuracy (OR = 1.30; 95% CI: 1.08-1.57; p = 0.007), whereas parenchymal hemorrhage during the procedure had lower accuracy rates (OR = 0.13; 95% CI: 0.02-0.75; p = 0.022). Some of the features of the 12 biopsied nodules that were misdiagnosed are shown in Table 3.

Pneumothorax was the most common complication, having occurred in 25 (16.0%) of 156 CNBs. Pneumothorax was mild in 5 cases, moderate in 13, and severe in 7. Of the 25 pneumothoraces, 10 decreased in size or remained stable, whereas 15 moderate-to-severe pneumothoraces required chest tube placement. Of those, 1 occurred before biopsy, i.e., during intubation, being associated with massive mediastinal emphysema secondary to tracheal injury, and 3 were delayed pneumothoraces, which were identified 24 h after the procedure.

In the multivariate analysis, a pleura-to-lesion distance > 3 cm was identified as a risk factor for pneumothorax (OR = 16.94; 95% CI: 2.39-120.26), whereas performing a blood patch after biopsy (n = 88/156; 56.4%) was a protective factor for pneumothorax (OR = 0.18; 95% CI: 0.04-0.86).

With regard to bleeding complications of the procedure, alveolar hemorrhage occurred in 15 CNBs (9.6%), being mild in 10 and moderate in 5. In addition, there was 1 case of mild hemothorax. No additional treatment was required in any of the aforementioned cases. In the multivariate analysis, there were no risk factors associated with bleeding complications.

Uncommon complications included myocardial infarction, in 1 patient, and cerebral air embolism, in 1 patient (Figure 2). The former was due to the anesthetics, and the patient made a full recovery; the latter was possibly due to positive pressure ventilation during biopsy, and the patient developed cognitive dysfunction despite having received specialized treatment.

DISCUSSION

Recent advances in imaging techniques and screening protocols have allowed the identification of an increasingly large number of small nodules in many parts of the body, such as the prostate, breasts, and lungs.[16] CT-CNB plays a key role in the evaluation of small pulmonary nodules. Several studies using different guidance techniques and needle sizes have shown that CNB has a high diagnostic accuracy.[9,15-21]

In the present study, 170 patients underwent CT-guided 20-gauge CNB. Eighteen patients were lost to follow-up or were followed for less than 1 year, which is one of the limitations of the study. The diagnostic accuracy of CT-CNB in the present study was 92.3%. This finding is similar to those of other studies reporting the diagnostic accuracy of CNBs of nodules smaller than 2 cm (i.e., 87-95%).[12,16,17] Unlike most other studies, in which accuracy was measured for malignancy only, our study measured "overall accuracy", which includes accuracy for benign CNB results. This is especially important in Brazil, where tuberculosis remains a health problem. CNB can provide a definitive diagnosis in cases of infection or benign disease, avoiding an unnecessary pulmonary resection and its associated morbidity.

There are several reasons why diagnostic accuracy was high in the present study. First, we used a coaxial technique, which allows multiple biopsies once the lesion has been targeted. Second, we performed CNB rather than fine-needle biopsy. Third, we had an experienced pathologist in our team. Finally, we used a biopsy protocol that consisted of an additional three biopsies after adequate diagnostic tissue had been obtained (as determined by the pathologist).

The coaxial technique is the most widely recommended technique for percutaneous lung biopsy[16] because it has been shown to reduce procedure time and complications. In addition, larger specimens can be collected with core needles that are inserted into the coaxial introducer, thus facilitating histopathology.[22] Finally, the presence of an experienced pathologist is extremely helpful because it ensures that the biopsy is performed in the target lesion and that the specimen collected is sufficient for diagnosis, especially when the lesion has a necrotic component.

With regard to the coaxial introducer and core needles, we always use 19- and 20-gauge needles, respectively. For percutaneous biopsies, the smallest gauge needle that can obtain sufficient tissue for diagnosis should be used. It has been reported that a larger gauge needle translates to a higher risk of complications.[8] We found that, for small pulmonary nodules, 20-gauge core needles can be used not only for histopathology and immunohistochemistry but also for simultaneous molecular and genetic analyses. This finding is important because of the ever-growing trend toward personalized cancer therapies.

Pneumothorax and bleeding were the most common complications in our sample, with an incidence of 14.3% and 7.4%, respectively. A chest tube was placed in 8.7% of the patients in our sample. These results are similar to those of previous studies.[12,16] According to the guidelines proposed by Gupta et al.,[8] all except one of the complications observed in the present study were minor. The only major complication was
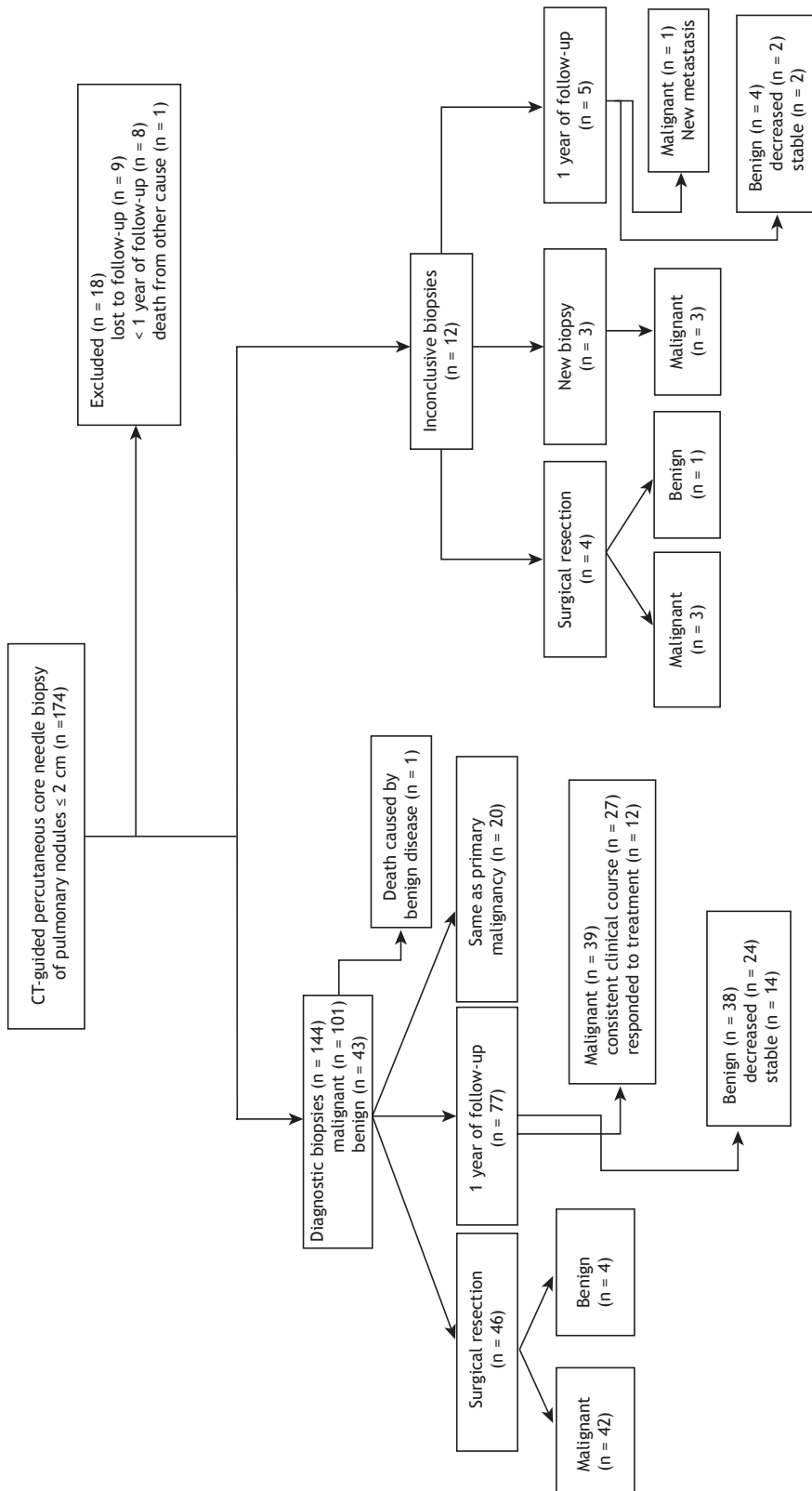
Figure 1. Flow chart of 174 patients undergoing CT-guided percutaneous core needle biopsy of pulmonary nodules of ≤ 2 cm in size, together with the final diagnosis.

Table 2. Histopathological findings of 156 biopsied lesions.

Biopsy diagnosis	Patients, n (%)
Malignant/premalignant	100 (64.1)
Primary adenocarcinoma	48
Metastatic adenocarcinoma	21
Other metastasis	13
Carcinoid tumor	7
Primary squamous cell carcinoma	6
Atypical adenomatous hyperplasia	5
Benign	44 (28.2)
Fungal infection	12
Organizing pneumonia	10
Caseating granuloma	5
Noncaseating granuloma	5
Other non-specific chronic inflammation	5
Hamartoma	4
Abscess	1
Fibrosis	1
Pulmonary infarction	1
Inconclusive/insufficient material	12 (7.7)
Total	156 (100)

Table 3. Features of the nodules that were initially misdiagnosed, together with the final diagnosis.

Case	Size, mm	Density	Distance from the pleura, mm	Specimen, n	Complications during biopsy	Final diagnosis
1	4	subsolid	3	> 7	none	Benign - unknown
2	7	solid	2	> 7	mild pneumothorax	Benign - unknown
3	7	subsolid	6	6	none	Primary adenocarcinoma
4	8	subsolid	8	7	none	Primary adenocarcinoma
5	8	solid	7	> 7	none	Metastasis
6	8	subsolid	2	> 7	none	Benign - fibrosis
7	9	solid	4	1	mild bleeding	Metastasis
8	10	solid	2	> 7	moderate pneumothorax	Metastasis
9	12	solid	0	3	hemodynamic instability*	Metastasis
10	14	solid	31	3	moderate bleeding	Benign - unknown
11	14	subsolid	15	> 7	moderate bleeding	Benign - unknown
12	14	solid	35	7	none	Carcinoid tumor

*The patient presented with myocardial infarction during biopsy, which was immediately interrupted.
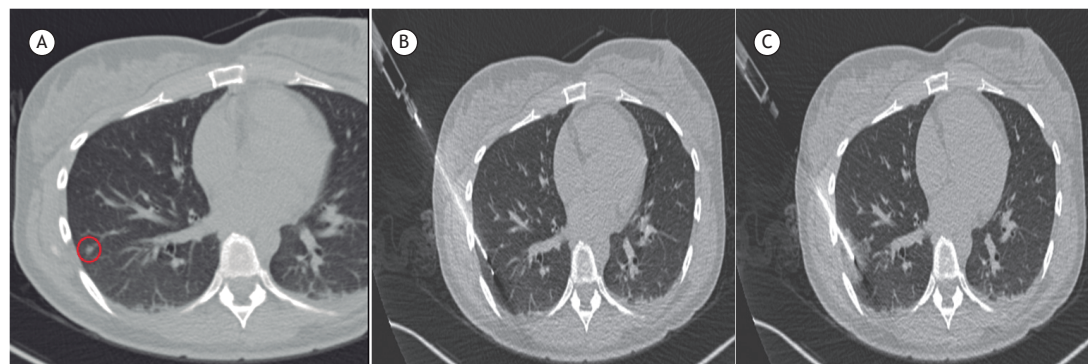

Figure 2. In A, pulmonary nodule with slightly jagged edges, measuring 0.6 cm and located in the lateral basal segment of the right lower lobe. In B, coaxial needle placement guided by CT. In C, alveolar hemorrhage after collection of the first specimen.

cerebral air embolism (in 1 patient), a relatively rare complication.[23]

Several factors have been found to affect the accuracy of CT-guided CNB of pulmonary lesions, including lesion size ≤ 1 cm,[9] lesion size ≤ 1.5 cm,[24] lower lobe lesions,[9] ≤ 2 specimens,[9] and malignant lesions.[9] In studies analyzing the aforementioned factors in patients with nodules of ≤ 2.0 cm in size, the only factor that was found to have a positive influence on the diagnostic accuracy of CT-CNB was a lesion size ≥ 0.8 cm.[17] In the present study, two factors were found to have influenced the overall diagnostic accuracy of CT-CNB: lesion size and parenchymal hemorrhage. To the best of our knowledge, ours is the first study in which parenchymal hemorrhage was associated with a lower diagnostic accuracy.

Some studies have shown that smaller lesions lead to lower biopsy accuracy,[9-12] whereas others have not.[1,25] In the present study, a smaller lesion translated to a lower diagnostic accuracy. Given that biopsies of pulmonary nodules smaller than 1 cm are challenging, our choice of patient position was made so as to minimize target lesion motion and provide greater stability to the coaxial and biopsy needles.

This is particularly advantageous for nodules of < 1 cm in size.

Parenchymal hemorrhage was another factor that negatively influenced the overall diagnostic accuracy. We found that parenchymal hemorrhage usually occurs after the first sample collection and results in poor visualization on subsequent imaging and biopsy. On CT, alveolar hemorrhage has an attenuation coefficient that is very similar to that of a pulmonary nodule, which is therefore obscured by it. An attempt should therefore be made to obtain the best possible specimen at the first collection, with CT confirmation of the cutting needle crossing the largest diameter of the target lesion.

In conclusion, the overall diagnostic accuracy of CT-guided percutaneous 20-gauge CNB of pulmonary nodules smaller than 2 cm is high. Lesion size and parenchymal hemorrhage are associated with reduced accuracy. Pneumothorax is the most common complication of CT-CNB, being associated with a pleura-to-lesion distance > 3 cm, whereas performing a blood patch after biopsy appears to be a protective factor in selected cases.

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