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CT-Guided Core-Needle Biopsy of Pulmonary Lesions Associated With Cystic Airspaces: A Case-Control Study

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Abstract

Background: Concern may exist that pulmonary lesions associated with cystic airspaces are at risk of increased biopsy complications or lower biopsy accuracy given challenges in targeting tissue abutting or intermingled with the cystic airspaces.

Objective: To evaluate the safety and diagnostic performance of CT-guided core-needle biopsy (CNB) of pulmonary lesions with cystic airspaces.

Methods: This retrospective study included 90 patients (median age, 69.5 years; 28 female, 62 male) who underwent CT-guided CNB of pulmonary lesions associated with cystic airspaces (based on review of procedural images) from February 2010 to December 2022 and a matched control group (2:1 ratio) of 180 patients (median age, 68.0 years; 56 female, 124 male) who underwent CNB of noncystic noncavitary lesions during the same period. The groups were compared in terms of complications, nondiagnostic biopsies (i.e., nonspecific benignities, atypical cells, or insufficient specimens), and CNB diagnostic performance for detecting malignancy using as reference the final diagnosis from a joint review of all available records. For lesions associated with cystic airspaces that underwent surgical resection after CNB, histologic slides were re-reviewed to assess cystic airspace etiology.

Results: The final diagnosis was malignant in 90% (81/90) of lesions associated with cystic airspaces and 92% (165/180) of noncystic noncavitary lesions. Patients with lesions associated with cystic airspaces and patients with

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noncystic noncavitary lesions showed no significant difference in frequencies of complication (all: 40% [36/90] vs 38% [68/180], p=.79; major: 4% [4/90] vs 6% [10/180], p=.78; minor: 36% [32/90] vs 32% [58/180], p=.59), frequency of nondiagnostic biopsies (12% [11/90] vs 9% [16/180], p=.40), or diagnostic performance (accuracy: 94.% [85/90] vs 97% [175/180], p=.50; sensitivity: 94% [76/81] vs 97% [160/165], p=.50; specificity: 100% [9/9] vs 100% [15/15]; p>.99), respectively. All false-negative results for malignancy in both groups occurred in patients with nondiagnostic CNB results. Among lesions associated with cystic airspaces that were resected after CNB (all malignant), the cystic airspaces most commonly represented tumor degeneration (22/31, 71%).

Conclusion: CT-guided CNB is safe and accurate for assessing pulmonary lesions associated with cystic airspaces.

Clinical Impact: CNB may help avoid a missed or delayed cancer diagnosis in pulmonary lesions with cystic airspaces.

Highlights

- *Key finding:* CT-guided CNBs of pulmonary lesions associated with cystic airspaces and of noncystic noncavitary lesions showed no significant differences in complications (overall: 40% vs 38%, *p*=.79; major: 4% vs 6%, *p*=.78), nondiagnostic biopsies (12% vs 9%, *p*=.40), or diagnostic performance (sensitivity: 94% vs 97%, *p*=.50; specificity: 100% vs 100%, *p*>.99), respectively.
- *Importance:* CNB can establish a diagnosis for pulmonary lesions associated with cystic airspaces with safety and accuracy comparable to that found for biopsied noncystic noncavitary lesions.

Introduction

Pulmonary lesions associated with cystic airspaces encompass a broad spectrum of benign and malignant entities, including primary lung cancer, metastasis, infection, and any of a number of autoimmune disorders [1,2]. Determining the diagnosis noninvasively is challenging, as clinical and imaging characteristics overlap between benign and malignant lesions with cystic airspaces [3,4].

A uniform strategy for managing pulmonary lesions with cystic airspaces is lacking. Clinical and laboratory data, serial CT examinations, and FDG PET/CT can contribute to lesion assessment [1–4]. Nevertheless, tissue sampling may be required, for instance, when clinical and radiologic workup cannot establish a benign diagnosis [5,6]. The presence of cystic airspaces has been recognized as a factor contributing to a missed or delayed cancer diagnosis in a screening setting [7], and Lung-RADS version 2022 (v2022) indicated that suspicious atypical cysts require further investigation, including possible tissue sampling [8].

CT-guided transthoracic core needle biopsy (CNB) is a widely accepted procedure to evaluate pulmonary lesions [9–12], yet scarce data describe its safety and diagnostic performance in lesions with cystic airspaces. Indirect evidence may stem from pulmonary cavities, which also contain an air component and for which CNB has shown high diagnostic accuracy, sensitivity, and specificity, with acceptable complication rates [13,14]. However, these entities are distinct: cavitation represents progressive gas-filled spaces within an initially solid lesion due to cell loss; lesions with cystic airspaces are thought to result from various other causative mechanisms, such as tissue formation around a preexisting bulla or a check-valve bronchiolar obstruction secondary to an inflammatory or neoplastic process [1,2]. When a pulmonary lesion's air component predominates over its soft-tissue component–a condition primarily ascribed to lesions with cystic airspaces rather than to cavitation–operators considering biopsy may have concerns for an increased risk of procedural complications, including pneumothorax, air embolism, parenchymal hemorrhage, or hemoptysis, and possibly of lower biopsy accuracy due to challenges in targeting the pathologic tissue abutting or intermingled with the cystic airspaces [1,15–18].

The aim of this study was to evaluate the safety and diagnostic performance of CT-guided CNB of pulmonary lesions with cystic airspaces.

Methods

The institutional review board (Comitato Etico Territoriale Interaziendale AOU Città della Salute e della Scienza di Torino) approved this retrospective observational case-control study (protocol n. 0116967) and waived the requirement for written informed consent.

Study Population

The PACS was searched for all patients who underwent CT-guided transthoracic biopsy of a pulmonary lesion in the radiology unit at the San Luigi Gonzaga Hospital (Orbassano, Italy) from February 2010 to December 2022. Records of identified patients, including procedural CT images, were reviewed in consensus by a thoracic radiologist (MBi) with 3 years of posttraining experience, a fourth-year radiology resident (MBa), and a third-year radiology resident (NCC), to identify those who underwent CNB of a pulmonary lesion with cystic airspaces, defined as any solid or subsolid lesion abutting or intermingled with cystic airspaces at the time of biopsy. In the presence of circumferentially thickened air lucency, a pulmonary lesion with cystic airspaces was differentiated from cavitation based on the lesion's longitudinal evolution over the course of prior examinations; if prior examinations were limited or unavailable, then the lesion was classified as a pulmonary lesion with cystic airspaces if its dominant feature was air, and as cavitation if its dominant feature was soft tissue, consistent with Lung-RADS v2022 [8]. Additionally, the readers did not deem a lesion to be a pulmonary lesion with cystic airspaces if the cystic airspace could be confidently considered an ancillary rather than a substantial component of the lesion (e.g., limited bubble-like lucencies in a nodule or mass). Morphologic characteristics of pulmonary lesions with cystic airspaces and of other air-containing entities are illustrated in **Figure 1**. Patients were then excluded if having incomplete imaging data or if having an indeterminate final diagnosis. The remaining patients formed the final sample of patients who underwent CNB of a pulmonary lesion with cystic airspaces.

A control group of patients who underwent CNB for noncystic noncavitary lesions was identified from the same set of patients identified by the initial PACS search, at a 2:1 ratio to the final number of patients with a lesion with cystic airspaces. Control patients were matched to patients with a pulmonary lesion with cystic airspaces by age (±5 years), sex, lesion depth (±5 mm), whole-lesion dimension (±5 mm), and emphysema (at most one category difference), assessing these features as described later in the Methods. When multiple potential patients fulfilled the matching criteria, matching patients were selected at random. The same group of three investigators reviewed the images in the selected control patients to ensure that the biopsied lesion was noncavitary.

The institutional CNB protocol is described in the **Supplemental Methods**.

Data Collection

The previously noted group of investigators reviewed patients' records, including procedural images, to assess for emphysema severity (graded as absent, trace, mild, moderate, confluent, or advanced destructive [19]), presence of interstitial lung disease (ILD), evidence (by imaging or other records) of prior thoracic surgery, as well as lesion and procedure information.

Lesion information included lesion lobe, depth (distance from the pleura to the lesion's outer margin), cystic airspace type, consistency, cystic airspace loculation, and dimension measurements (**Fig. 1**). Cystic airspace type,

consistency, and loculation were classified using a modification of the approach described by Fintelmann et al. [20]. In particular, cystic airspace type was classified as 0 [≤1 mm in wall thickness (i.e., thin-walled) without overt nodule], 1 (endophytic nodule), 2 (exophytic nodule), or 3 [>1 mm in wall thickness (i.e., thick-walled) without overt nodule]; consistency was classified as solid or subsolid; and loculation was classified as unilocular or multilocular. Three dimensions were measured for each lesion: dimension of the whole lesion; dimension of the cystic airspace; and dimension based on wall thickness and, if present, the dominant mural nodule. These dimension measurements were performed using electronic calipers and recorded (aside from wall-thickness measurement) as the mean of the maximal long axis and maximal perpendicular short axis in the axial plane.

Procedure information included the number of pleural passes, needle size, transpulmonary needle path length, patient position (prone, supine, oblique, or lateral decubitus), needle traversal through emphysema (yes vs no), needle traversal through fissures (yes vs no), pleural angle, needle angle to gravity, needle intralesional trajectory (i.e., needle traversal through the cystic airspace) (yes vs no), use of a tangential approach (i.e., needle targeted to the lesion wall) (yes vs no) [17], and procedure time. The pleural angle was computed as the deviation angle between the needle's longitudinal axis and a line drawn perpendicularly to the tangent to the pleura at the needle's entry point, as illustrated in a previous study [21]. The needle angle to gravity was calculated using the CT table as a horizontal frame of reference and classified as closer to vertical (+45° to +135°) or closer to horizontal (-45° to +45°) [22]. The procedure time was defined as the time elapsed from the procedure start, when a scout CT image was obtained, to the time of the last CT acquisition before needle removal [23]. The senior operator and that operator's years of posttraining experience in pulmonary biopsy were also recorded; the involvement of a trainee in the procedure was not recorded.

Factors assessed in noncystic noncavitary lesions included emphysema severity, lesion depth, lesion consistency, and whole-lesion dimension.

Complications

For all patients in both groups, complications were extracted from the records and classified as minor or major, consistent with guidelines [24]. Specifically, transient hemoptysis not requiring treatment, self-limiting hemothorax not requiring treatment, pneumothorax without chest tube placement, and pulmonary hemorrhage measuring >20 mm in width not requiring treatment, were classified as minor complications; pneumothorax with chest tube placement, bleeding requiring treatment, air embolism, and death were classified as major complications. Hemorrhage measuring ≤20 mm in width along the needle tract and pneumothorax measuring ≤ 1 cm were considered normal postprocedural findings [25,26].

Pathology Review of Biopsy Results and Resection Specimens

Two pathologists (LR and FF, with 13 and 5 years of posttraining experience, respectively, in thoracic pathology) reviewed in consensus the clinical pathology reports from biopsy procedures in both groups and classified each biopsy result into one of the following five pre-specified categories [11,27]: malignancy, specific benignity (e.g., hamartoma), nonspecific benignity (e.g., granulomatous inflammation), atypical cells, or insufficient specimen (i.e., inadequate because of cellular paucity). The pathology reports from the biopsy procedures were also classified as diagnostic (i.e., category of malignancy or specific benignity) or nondiagnostic (i.e., category of nonspecific benignity, atypical cells, or insufficient specimen) [28]. For pulmonary lesions with cystic airspaces that were resected after CNB and for which the histologic slides from the resection specimen were available for re-review, the two pathologists reviewed the slides in consensus to qualitatively explore the nature of the cystic airspace.

Determination of Final Diagnoses

For all patients in both groups, the previous radiologist (MBi) and one of the previously noted pathologists (LR) jointly reviewed all available records, including surgical information and postsurgical follow-up data, to determine a final diagnosis. The criteria for determining a final diagnosis were based on prior literature [27, 29] and are summarized in the **Supplemental Methods**. Based on the final diagnosis, each lesion was classified as benign or malignant. Pulmonary lesions with cystic airspaces that were resected after CNB and for which the histologic slides were available for re-review were assessed for concordance between the biopsy diagnosis and final diagnosis.

Statistical Analysis

Patients who underwent biopsy of pulmonary lesions with cystic airspaces and patients who underwent biopsy of noncystic noncavitary lesions were compared in terms of the frequency of complications, the proportion of biopsies that were nondiagnostic, and the diagnostic performance of CNB. The diagnostic performance of CNB was assessed in terms of the accuracy, sensitivity, and specificity for detecting malignancy, using the final diagnosis as the reference standard. For these calculations, all categories of CNB results other than malignancy (including nondiagnostic biopsy results) were considered negative, consistent with a prior study [14]. Univariable logistic regression analyses were performed to compare patients who underwent biopsy of pulmonary lesions with cystic airspaces and patients who underwent biopsy of noncystic noncavitary lesions in terms of risk of complications (multinomial analysis) and risk of nondiagnostic biopsy (binomial analysis).

In the analyses, dichotomization was performed of lesion lobe as lower versus other; of number of pleural passes as 1 versus more than 1; of needle size as 20-gauge versus 18-gauge; and of patient position as supine or prone versus other positions. Previously reported thresholds were used to dichotomize age (<65 years vs ≥65 years), needle angle to gravity (closer to vertical vs closer to horizontal), and dimension based on wall thickness and dominant mural nodule (classification of a lesion as small if both the maximum wall thickness was <5 mm and the dominant mural nodule, if present, was ≤20 mm; classification as not small otherwise) [13,22,30,31]. Otsu's method [32] was used to dichotomize the other continuous variables, including transpulmonary needle path (<20 mm vs ≥20 mm), pleural angle (<28° vs ≥28°), procedure time (<45 minutes vs ≥45 minutes), lesion depth (<12 mm vs ≥12 mm), whole-lesion diameter (<30 mm vs ≥30 mm), and cystic airspace dimension (<23 mm vs ≥23 mm).

For biopsy of pulmonary lesions with cystic airspaces, univariable and multivariable logistic regression analyses were performed to identify risk factors for the occurrence of no, minor, or major complications (multinomial logistic regression analysis), and for a nondiagnostic result (binomial logistic regression analysis). The univariable analyses included all patient, procedure, and lesion factors. Only factors with $p<.10$ in univariable analysis were initially tested in the multivariable model. The multivariable model used stepwise regression analysis with bidirectional elimination, guided by the Akaike information criterion (AIC), to identify the most relevant predictors for the final model. Assessments related to diagnostic yield excluded patients with more than one pleural pass because it was not possible to determine the specific specimen that was used for diagnosis.

Due to unequal sample sizes, pairwise comparisons were performed by the nonparametric rank-sum Wilcoxon test (continuous variables) or Fisher's exact test (discrete variables); overall comparisons were performed by Kruskal-Wallis test (continuous variables) or Fisher's exact test (discrete variables). In the presence of overall statistically significant differences between patients with no, minor, and major complications, post-hoc pairwise comparisons were performed between patients with major versus with minor or no complications, as well as between patients with no versus with major or minor complications.

Statistical significance was set at $p<.05$. All statistical analyses were performed using R software (R Core Team, Vienna, Austria; https://www.r-project.org/), version 4.2.2.

Results

The initial search identified 3069 patients who underwent CT-guided transthoracic biopsy during the study period. Of these patients, 95 underwent CNB of a pulmonary lesion with cystic airspaces. Of these patients, one was excluded due to incomplete imaging information, and four were excluded due to an indeterminate final diagnosis, resulting in 90 patients who underwent CNB of a pulmonary lesion with cystic airspaces in the final sample. Thus,

180 matched patients who underwent CNB of a noncystic noncavitary lesion were selected as control patients. **Figure 2** shows the flow of patient selection. Patients who underwent biopsy of a pulmonary lesion with cystic airspaces versus who underwent biopsy of a noncystic noncavity lesion showed no significant difference in median age (69.5 vs 68.0 years, p=.71); sex [31% (28) women and 69% (62) men vs 31% (56) women and 69% (124) men; p>.99], median lesion depth (0 mm [IQR, 0-5 mm] vs 1 mm [IQR, 0-8 mm]; *p*=.21), median whole-lesion dimension (26 mm [IQR, 20.3-35 mm] vs 24 mm [IQR 16.0-34.3 mm]; *p*=.12); and emphysema severity (e.g., advanced destructive emphysema in 6% vs 3%, p=.76) (**Table 1**).

Pulmonary lesions with cystic airspaces were most commonly classified as type 3 (thick-walled without overt nodule) (51/90, 57%) or type 2 (exophytic nodule) (36/90, 40%), solid (86/90, 96%), and multilocular (50/90, 56%). Among noncystic noncavitary lesions, 94% (170/180) were solid, and 6% (10/180) were subsolid.

Pulmonary lesions with cystic airspaces underwent biopsy by one of three interventional radiologists with 7, 11, and 15 years of posttraining experience in pulmonary biopsy. For these procedures, the median transpulmonary needle path was 12.0 mm [IQR, 0.0-28.8 mm], and the median procedure time was 37.0 minutes [IQR, 28.3-44.8 minutes].

Complications

Patients who underwent biopsy of pulmonary lesions with cystic airspaces, in comparison with patients who underwent biopsy of noncystic noncavity lesions, showed no significant difference in the frequencies of any complication [36/90 (40%) vs 68/180 (38%)] (*p*=.79), of a major complication (regardless of concomitant minor complications) [4/90 (4%) vs 10/180 (6%)] (*p*=.78), or of only a minor complication [32/90 (36%) vs 58/180 (32%)] (*p*=.59). The frequencies of individual complications were also not significantly different between the two groups (**Table 1**). The major complications after biopsy of pulmonary lesions with cystic airspaces and of noncystic noncavitary lesions were all cases of pneumothorax requiring chest tube placement (n=3 and 9, respectively) and major bleeding (n=1 and 1, respectively). Biopsy of a pulmonary lesion with cystic airspaces, with respect to biopsy of noncystic noncavitary lesions, was not a significant risk factor for occurrence of a complication (OR = 0.93 [95% CI, 0.56-1.56]; *p*=.79).

Table 2 compares patient, procedure, and lesion factors between patients with major, minor, and no complications, among those who underwent biopsy of a pulmonary lesion with cystic airspaces. The frequency of a transpulmonary needle path ≥20 mm was significantly higher in patients with a major complication [4/4 (100%)] than in patients with a minor complication [13/32 (41%)] or no complication [16/54 (30%)] (*p*=.02). The frequency of a procedure time ≥45 minutes was significantly lower in patients with no complication [4/54 (7%)] than in patients with a major complication [2/4 (50%)] or minor complication [16/32 (50%)] (p=.007). No other

factor was significantly different between groups based on complication presence and severity (all p>.05). **Figure 3** illustrates the distribution of the transpulmonary needle path length and procedure time in patients grouped by complication presence and severity.

In the final model from multivariable analysis (**Table 3**), risk of complications showed significant independent associations with a transpulmonary needle path ≥20 mm (OR=2.86 [95% CI, 1.08-7.80]; *p*=.04), procedure time ≥45 minutes (OR=10.93 [95% CI, 3.77-35.85]; *p*<.001), and needle traversal of emphysema (OR=3.04 [95% CI, 0.67-13.67]; *p*=.14).

Nondiagnostic Specimens

CNB of pulmonary lesions with cystic airspaces had a result of malignancy in 85% (76/90), specific benignity in 3% (3/90), and a nondiagnostic specimen in 12% (11/90); the latter category included nonspecific benignity in 9% (8/90) and atypical cells in 3% (3/90) (**Table 1**). These frequencies were not significantly different in comparison with biopsy of noncystic noncavitary lesions (p=.21). No biopsy in either group yielded an insufficient specimen. The frequency of a nondiagnostic specimen was not significantly different between patients with a pulmonary lesion with cystic airspaces (11/90, 12%) and patients with a noncystic noncavitary lesion (16/180, 9%) (*p*=.40). Biopsy of a pulmonary lesion with cystic airspaces, with respect to biopsy of noncystic noncavitary lesions, was not a significant risk factor for a nondiagnostic specimen (OR=0.63 [95% CI, 0.29-1.43]; *p*=.26).

In 10 patients who underwent biopsy of a pulmonary lesion with cystic airspaces, the biopsy entailed multiple pleural passes. In the remaining 80 patients in whom such lesions were biopsied by a single pleural pass, those with diagnostic and nondiagnostic results showed no significant difference for any patient, procedure, or lesion factor (**Table 2**). In multivariable analysis, no factor was independently associated with risk of nondiagnostic specimen (**Table 3**).

Final Diagnoses and Nature of Cystic Airspace

The final diagnoses of pulmonary lesions with cystic airspaces and of noncystic noncavitary lesions are summarized in **Table 4** and **Table 5**, respectively. The final diagnosis was malignant in 90% (81/90) of pulmonary lesions with cystic airspaces and 92% (165/180) of noncystic noncavitary lesions. In both groups, based on final diagnoses, the two most common malignancies were adenocarcinoma (pulmonary lesions with cystic airspaces: 49/81, 60%; noncystic noncavitary lesions: 105/165, 64%) and squamous cell carcinoma (pulmonary lesions with cystic airspaces: 24/81, 30%; noncystic noncavitary lesions: 22/165, 13%).

A total of 42/90 (47%) pulmonary lesions with cystic airspaces were surgically resected. Of these, the histologic slides from the resection specimens were available for re-review in 31/42 (74%) patients. All 31 of these patients

had a final diagnosis of malignancy (squamous cell carcinoma in 15, adenocarcinoma in 16) that was consistent with the biopsy result. Pathologic review demonstrated cystic airspace surrounded by fibroelastotic walls lined by thick layers of tumor cells (i.e., tumor degeneration) in 71% (22/31), tumor foci growing along emphysematous alveolar walls in 10% (3/31), and a lack of recognizable cystic airspace in 19% (6/31).

Figure 4, **Figure 5**, and **Figure S1** show CT images in three representative resected pulmonary lesions with cystic airspaces and corresponding histologic findings.

Diagnostic Performance

In both groups, all patients with a biopsy diagnosis of malignancy had a malignant final diagnosis, and all patients with a biopsy diagnosis of specific benignity had a benign final diagnosis. Thus, all false-negative results for malignancy occurred in patients with nondiagnostic CNB results (nonspecific benign findings or atypical cells). In patients with a pulmonary lesion with cystic airspaces, a final diagnosis of malignancy was observed in 2/8 (25%) lesions with nonspecific benign findings on CNB and in 3/3 (100%) lesions with atypical cells on CNB. In patients with a noncystic noncavitary lesion, a final diagnosis of malignancy was observed in 4/15 (27%) lesions with nonspecific benign findings on CNB and in 1/1 (100%) lesion with atypical cells on CNB.

CNB of pulmonary lesions with cystic airspaces versus of noncystic noncavitary lesions was associated with an accuracy of 94% (85/90) versus 97% (175/180) (p=.50), sensitivity of 94% (76/81) versus 97% (160/165) (p=.50), and specificity of 100% (9/9) versus 100% (15/15) (p>.99), for the detection of malignancy using the final diagnoses as the reference standard.

Discussion

Limited evidence describes the safety and diagnostic performance of CT-guided CNB in pulmonary lesions with cystic airspaces, a group of lesions that deserve particular attention in order to avoid a missed or delayed lung cancer diagnosis. The present study found CT-guided CNB of such lesions to have high safety and diagnostic performance, with no significant difference in the frequency of minor or major complications; in the frequency of nondiagnostic results; or in accuracy, sensitivity, or specificity for malignancy, in comparison with CNB of noncystic noncavitary lesions. For biopsy of lesions with cystic airspaces, a long transpulmonary needle path (≥20 mm) and a prolonged procedure time (≥45 minutes) showed significant independent associations with the occurrence of complications, while no factors were independently associated with a nondiagnostic specimen. Malignant pulmonary lesions with cystic airspaces were most commonly adenocarcinoma (60%), and, in resected specimens for such lesions, the cystic airspace most commonly corresponded to tumor degeneration (71%).

The results suggest that CNB can contribute to managing pulmonary lesions with cystic airspaces by safely and accurately reaching a diagnosis. Operators may have concerns that the air component in lesions with cystic airspaces leads to an increased risk of biopsy complications such as air embolism (induced by simultaneous needle passage through the cystic airspace and vessels) or pneumothorax (from cystic airspace communication with the pleural cavity) [15,17]. Nonetheless, the frequency of complications after biopsy of pulmonary lesions with cystic airspaces was within previously reported ranges for CT-guided lung biopsy in general [12]. In both groups, complications were most commonly minor events (e.g., pneumothorax or perilesional hemorrhage not requiring treatment), supporting CT-guided CNB as an overall safe and well-tolerated procedure. The diagnostic performance was also comparable with other studies of CNB that reported an accuracy of 89-95% [11,15,27,33]. Moreover, CNB approached or exceeded the accuracy of other techniques previously proposed to evaluate pulmonary lesions with air lucencies, such as fine-needle aspiration biopsy or percutaneous needle washing [14,34–36], suggesting that CNB is a suitable option to maximize tissue sampling of pulmonary lesions with cystic airspaces, without detrimental impact on safety.

For pulmonary lesions with cystic airspaces, small dimensions were not associated with a higher risk of complications nor of a nondiagnostic specimen. This result is in accordance with Shin et al., who found CNB to be safe and accurate in thin-walled (i.e., <5 mm) cavitations, although they only evaluated lesions with unilocular cystic airspaces [13]. The diagnostic utility of CNB in small pulmonary lesions with cystic airspaces may impact the management of patients undergoing lung cancer screening since atypical cysts, a recently acknowledged Lung-RADS category that overlaps with such lesions, may require biopsy when exhibiting malignant behavior (e.g., increased density or loculation over time), regardless of dimensions [8]. Although promising, the finding should be interpreted cautiously because of the single-center design. Further evidence is warranted to assess the results' dependence on operator expertise, a factor associated with complications and diagnostic yield in prior studies of biopsy of small pulmonary nodules [30].

The literature provides inconsistent results regarding associations of various factors with complications from CNB of pulmonary lesions. For instance, Heerink et al. identified no significant risk factor in a meta-analysis of 8133 CNB procedures [12]. Yet, in a recent large single-center retrospective study of 1430 patients undergoing CNB or fine-needle aspiration, Lee et al. found the most significant risk factors for complications to be a prolonged procedure time and a long transpulmonary needle path, consistent with the present results [22]. Compared with that previous sample, we observed a similar transpulmonary needle path (mean, 12.1 mm in the earlier study) yet a larger procedure time (mean, 14.6 minutes in the earlier study). This latter discrepancy is likely to be related to a methodologic difference; Lee et al. determined procedure time based on the time between needle insertion and its withdrawal, whereas we determined procedure time based on the time between the scout CT image and

the last CT acquisition before needle removal. Needle traversal of emphysema was significantly associated with complications in univariable analysis but not in multivariable analysis, suggesting a lesser contribution of this variable in predicting complications. Other risk factors highlighted in previous studies, such as multiple pleural passes or needle traversal of fissures [22,30,37], were uncommon in the present sample, possibly affecting the model's generalizability. Although no particular type of pulmonary lesion with cystic airspaces was associated with an increased risk of complications, a larger sample size could help determine whether any distinct morphologic feature of these lesions affects CNB and personalize biopsy procedures in this patient group.

The histologic types of malignant pulmonary lesions with cystic airspaces found in the present study are consistent with prior literature [38,39]. In a meta-analysis of 328 patients with lung cancers associated with cystic airspaces and available histologic data, most were adenocarcinoma (88.1%), followed by squamous cell carcinoma (9.1%), adenosquamous carcinoma (1.2%), and poorly differentiated carcinoma (0.6%) [39]. Similarly, in the present sample, malignant pulmonary lesions with cystic airspaces were most commonly adenocarcinoma, followed by squamous carcinoma. In the majority of resected lesions with cystic airspaces, the findings suggested an underlying mechanism of tumor degeneration—possibly matching the cystification process hypothesized by Fintelmann et al. [20]—while the presence of tumor cells along emphysematous walls was relatively uncommon. Prior work described two additional histologic patterns in lung cancers associated with cystic airspaces [20]–check-valve obstruction and lepidic growth along the wall of a pre-existing bulla–that, for unclear reasons, were not observed in the present study.

This study had limitations. First, it was retrospective and included a small number of cases. However, in earlier years during the study period, awareness of the risk of malignancy in lesions with cystic airspaces was relatively low, and some such lesions may not have undergone biopsy until the lesion developed a solid appearance with soft tissue overall replacing the air component at the time of biopsy. Second, we could not reliably explore the impact of operator experience, a factor affecting safety and diagnostic accuracy in previous studies [30]. Third, we were unable to determine the causal link between prolonged procedure time and increased frequency of complications after biopsy of pulmonary lesions with cystic airspaces; larger prospective studies exploring possible intervening pathways of damage not assessed by the present design may help to explain this association. Fourth, cases of mild self-limiting hemoptysis may have been underreported in the medical records; however, all complications requiring treatment are expected to have been documented. Fifth, nondiagnostic biopsies were classified as true-negative results in patients with benign final diagnoses, although the management of patients with such results on biopsy is variable in practice. Sixth, multiple investigators performed the data collection process in consensus; interreader agreement was not assessed for characteristics of lesions with cystic airspaces.

Finally, a limited number of resected specimens were evaluated, hampering a comprehensive correlation between histopathology and imaging findings.

In conclusion, the results suggest that transthoracic CT-guided CNB is a safe and accurate procedure for evaluating pulmonary lesions with cystic airspaces. Procedure time ≥45 minutes and transpulmonary needle path ≥20 mm were independently associated with a greater risk of complications. The results support CNB as a useful diagnostic tool in this group of lesions at risk of a missed or delayed cancer diagnosis.

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Table 1. Comparison of patients with pulmonary lesions with cystic airspaces and patients with noncystic noncavitary lesions, in terms of variables used for matching, complications, and CNB results

Variable	Patients With Pulmonary Lesions with Cystic Airspaces (n=90)	Patients With Noncystic Noncavitary Lesions (n=180)	*p*
Patient age (y)	69.5 [62.0 – 75.0]	68.0 [61.0 – 74.3]	.71
Patient sex			>.99
Female	28/90 (31)	56/180 (31)	
Male	62/90 (69)	124/180 (69)	
Lesion whole dimension (mm)	26.0 [20.3 – 35.0]	24.0 [16.0 – 34.3]	.12
Lesion depth (mm)	0.0 [0.0 – 5.0]	1.0 [0.0 – 8.0]	.21
Emphysema severity[a]			.76
Absent	35/90 (39)	73/180 (41)	
Trace	18/90 (20)	39/180 (22)	
Mild	16/90 (18)	33/180 (18)	
Moderate	7/90 (8)	18/180 (10)	
Confluent	9/90 (10)	12/180 (7)	
Advanced destructive	5/90 (6)	5/180 (3)	
Complications[b]			
Pneumothorax	21/90 (23)	33/180 (18)	.34
With chest tube	3/90 (3)	9/180 (5)	.33
Any bleeding	21/90 (23)	44/180 (24)	.88
Hemoptysis	1/90 (1)	2/180 (1)	>.99
Hemothorax	1/90 (1)	6/180 (3)	.43
Parenchymal hemorrhage	21/90 (23)	43/180 (24)	>.99
Major bleeding	1/90 (1)[c]	1/180 (180)[d]	>.99
CNB results			.21
Malignancy	76/90 (85)	160/180 (89)	
Specific benignity	3/90 (3)	4/180 (2)	
Nondiagnostic specimen	11/90 (12)	16/180 (9)	.40
Nonspecific benignity	8/90 (9)	15/180 (8)	
Atypical cells	3/90 (3)	1/180 (1)	
Insufficient specimen	0/90 (0)	0/180 (0)	

Data are shown as median [IQR] or as number/total (%).
P values were computed by the Wilcoxon rank sum test (continuous variables) or Fisher's exact test (binary or categorical variables).
[a]Graded according to the Fleischner Society [19].
[b]Sum for types of bleeding is larger than value for any bleeding because some patients experienced multiple forms of bleeding.
[c]Single case of pneumothorax, hemothorax, and extensive parenchymal hemorrhage requiring emergency department referral.
[d]Single case of parenchymal hemorrhage, hemoptysis, and hemothorax requiring emergency department referral.
CNB, core-needle biopsy

Table 2. Comparison of patient with major complications, minor complications, and no complications, as well as of patients with diagnostic and nondiagnostic biopsy results (among patients with a single needle plural pass), among patients with pulmonary lesions with cystic airspace

Variable	Complications					Diagnostic Yield			
	All (n=90)	Major Complications (n=4)	Minor Complications (n=32)	No Complications (n=54)	*p*	All (n=80)	Diagnostic Results (n=71)	Nondiagnostic Results (n=9)	*p*
Patient factors									
Age, < 65 y	30/90 (33)	0/4 (0)	11/32 (34)	19/54 (35)	.50	27/80 (34)	22/71 (31)	5/9 (56)	.16
Sex, female	28/90 (31)	0/4 (0)	9/32 (28)	19/54 (35)	.41	24/80 (30)	22/71 (31)	2/9 (22)	.72
Emphysema, yes	55/90 (61)	2/4 (50)	23/32 (72)	30/54 (56)	.28	51/80 (64)	44/71 (62)	7/9 (78)	.48
ILD, yes	4/90 (4)	0/4 (0)	1/32 (3)	3/54 (6)	>.99	2/80 (3)	2/71 (3)	0/9 (0)	>.99
Prior thoracic surgery, yes	14/90 (16)	0/4 (0)	4/32 (13)	10/54 (19)	.78	13/80 (16)	11/71 (15)	2/9 (22)	.63
Procedure factors									
No. of pleural passes, > 1	10/90 (11)	2/4 (50)	3/32 (9)	5/54 (9)	.10	---	---	---	---
Needle size, 20 Gauge	7/90 (8)	0/4 (0)	4/32 (13)	3/54 (6)	.58	6/80 (8)	4/71 (6)	2/9 (22)	.13
Transpulmonary needle path, ≥ 20 mm	33/90 (37)	4/4 (100)[a]	13/32 (41)	16/54 (30)	**.02**	30/80 (37)	26/71 (37)	4/9 (44)	.72
Patient position, supine or prone	83/90 (92)	3/4 (75)	28/32 (88)	52/54 (96)	.11	73/80 (91)	65/71 (92)	8/9 (89)	.58
Needle traversal of fissure, yes	1/90 (1)	0/4 (0)	0/32 (0)	1/54 (2)	>.99	1/80 (1)	1/71 (1)	0/9 (0)	>.99
Needle traversal of emphysema, yes	9/90 (10)	2/4 (50)	4/32 (13)	3/54 (6)	.05	7/80 (9)	5/71 (7)	2/9 (22)	.18
Pleural angle, ≥ 28°	45/90 (50)	3/4 (75)	16/32 (50)	26/54 (48)	.07	39/80 (49)	36/71 (51)	3/9 (33)	.48
Needle angle to gravity, closer to vertical	67/90 (74)	3/4 (75)	24/32 (75)	40/54 (74)	>.99	59/80 (74)	52/71 (79)	7/9 (78)	>.99
Needle intralesional trajectory, traversal of the cystic airspace	49/90 (54)	3/4 (75)	18/32 (56)	28/54 (52)	.71	45/80 (56)	41/71 (58)	4/9 (44)	.49
Tangential approach, no	27/90 (30)	2/4 (50)	11/32 (34)	14/54 (26)	.41	21/80 (26)	18/71 (25)	3/9 (33)	.69
Procedure time, ≥ 45 min	22/90 (24)	2/4 (50)	16/32 (50)	4/54 (7)[a]	**.007**	15/80 (19)	13/71 (18)	2/9 (22)	.67
Lesion factors									
Lung lobe, lower lobes	42/90 (47)	1/4 (25)	12/32 (38)	29/54 (54)	.26	39/80 (49)	37/71 (52)	2/9 (22)	.16
Depth, ≥ 12 mm	15/90 (17)	2/4 (50)	6/32 (19)	7/54 (13)	.14	15/80 (19)	14/71 (20)	1/9 (11)	>.99
Cystic airspace type[b]					.31				.12
Type 0	0/90 (0)	0/4 (0)	0/32 (0)	0/54 (0)					
Type 1	3/90 (3)	0/4 (0)	1/32 (3)	2/54 (4)		3/80 (4)	3/71 (4)	0/9 (0)	
Type 2	36/90 (40)	0/4 (0)	16/32 (50)	20/54 (37)		33/80 (41)	32/71 (45)	1/9 (11)	
Type 3	51/90 (57)	4/4 (100)	15/32 (47)	32/54 (59)		44/80 (55)	36/71 (51)	8/9 (89)	
Consistency, subsolid	4/90 (4)	0/4 (0)	2/32 (6)	2/54 (4)	.69	3/80 (4)	3/71 (4)	0/9 (0)	>.99
Cystic airspace loculation, multilocular	50/90 (56)	2/4 (50)	21/32 (66)	27/54 (50)	.32	49/80 (61)	43/71 (61)	6/9 (67)	>.99
Whole dimension, < 30 mm	54/90 (60)	3/4 (75)	23/32 (72)	28/54 (52)	.13	43/80 (54)	41/71 (58)	2/9 (22)	.07
Dimension based on wall thickness and dominant mural nodule, small[c]	38/90 (42)	2/4 (50)	17/32 (53)	19/54 (35)	.24	37/80 (46)	34/71 (48)	3/9 (33)	.55
Cystic airspace dimension, < 23 mm	65/90 (72)	3/4 (75)	24/32 (75)	38/54 (70)	.92	58/80 (73)	51/71 (72)	7/9 (78)	>.99

The first column presents categorical variables along with their respective level for purposes of data reporting (aside from cystic airspace type, for which all levels are reported).
Data are reported as number/total (%).
P values were computed using the Fisher's exact test. In the presence of a significant overall difference (highlighted in bold), post-hoc pairwise comparisons were also performed between major versus minor or no complications, as well as between no complications versus major or minor complications.
[a]Denotes a statistically significant ($p < .05$) post-hoc pairwise comparison; single group in comparison is indicated.
[b]Based on the Fintelmann et al. classification [20].
[c]Maximum wall thickness <5 mm and, if present, a dominant mural nodule ≤20 mm.
ILD, interstitial lung disease

Table 3. Results of logistic regression analyses for identifying factors associated with CNB complications and nondiagnostic results in patients with pulmonary lesions with cystic airspaces

Variable	Complications (n=90)				Nondiagnostic Results (n=80)			
	Univariable LR		Multivariable LR		Univariable LR		Multivariable LR	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Patient factors								
Age, < 65 y	1.35 (0.56 – 3.36)	.51			0.36 (0.08 – 1.48)	.15		
Sex, female	1.75 (0.71 – 4.58)	.24			0.64 (0.09 – 2.89)	.59		
Emphysema, yes	1.70 (0.71 – 4.20)	.24			2.14 (0.48 – 15.13)	.36		
ILD, yes	0.47 (0.02 – 3.69)	.52			NA	NA		
Prior thoracic surgery, yes	0.53 (0.14 – 1.70)	.31			1.56 (0.21 – 7.54)	.61		
Procedure factors								
No. of pleural passes, > 1	0.45 (0.11 – 1.84)	.26			---	---		
Needle size, 20 Gauge	1.78 (0.39 – 7.74)	.44			4.79 (0.59 – 29.71)	.10		
Transpulmonary needle path, ≥ 20 mm	2.50 (1.05 – 6.07)	**.04**	2.86 (1.08 – 7.80)	**.04**	1.38 (0.32 – 5.69)	.65		
Patient position, supine or prone	0.23 (0.05 – 1.08)	**.07**			0.74 (0.11 – 14.87)	.79		
Needle trespassing fissure, yes	NA	NA			NA	NA		
Needle trespassing emphysema, yes	4.75 (1.14 – 21.83)	**.04**	3.04 (0.67 – 13.67)	.14	3.77 (0.48 – 21.59)	.15		
Pleural angle, ≥ 28°	1.28 (0.55 – 2.96)	.56			0.49 (0.10 – 1.99)	.33		
Needle angle to gravity, closer to vertical	1.05 (0.41 – 2.81)	.92			0.78 (0.11 – 3.58)	.77		
Needle intralesional trajectory, traversal of the cystic airspace	1.36 (0.59 – 3.18)	.48			0.59 (0.13 – 2.39)	.45		
Tangential approach, no	1.67 (0.68 – 4.13)	.26			1.47 (0.29 – 6.21)	.61		
Procedure time, ≥ 45 min	9.81 (3.51 – 30.99)	**<.001**	10.93 (3.77 – 35.85)	**<.001**	1.27 (0.18 – 6.04)	.78		
Lesion data								
Lung lobe, lower lobes	0.48 (0.20 – 1.12)	**.09**			0.23 (0.03 – 1.05)	.11		
Depth, ≥ 12 mm	2.23 (0.73 – 6.90)	.16			0.51 (0.03 – 3.12)	.54		
Cystic airspace type[a]								
Type 2	1.54 (0.15 – 34.26)	.73			NA	NA		
Type 3	1.33 (0.13 – 29.26)	.82			NA	NA		
Consistency, subsolid	1.35 (0.16 – 9.26)	.76			NA	NA		
Whole dimension, < 30 mm	2.40 (1.00 – 6.06)	**.06**			1.30 (0.31 – 6.57)	.72		
Cystic airspace loculation, multilocular	1.68 (0.72 – 4.02)	.24			0.21 (0.03 – 0.94)	**.06**	0.21 (0.03 – 0.94)	.06
Dimension based on wall thickness and dominant nodular component, small[b]	2.00 (0.86 – 4.72)	.11			0.54 (0.36 – 2.23)	.42		
Cystic airspace dimension, < 23 mm	1.26 (0.50 – 3.34)	.64			1.37 (0.30 – 9.74)	.71		

All factors, other than cystic airspace type, are reported in binary manner, with respective level for purposes of regression analysis listed after comma. For cystic airspace type, type 1 served as the reference level.

ORs, 95% CI, and p values were computed by univariable ordinal logistic regression models. Variables found to be significant in the univariable analysis (p<.10, in bold) were included in the multivariable ordinal logistic model, which was further reduced using AIC stepwise model selection technique. Variables found to be significant in the multivariable model (p<.05) are indicated in bold.

NA means that calculation was not feasible due to limited counts and an imbalanced distribution between patient subgroups.

[a]Based on the Fintelmann et al. classification [20].

[b]Maximum wall thickness <5 mm and, if present, a dominant mural nodule ≤20 mm.

AIC, Akaike's information criterion; CNB, core-needle biopsy; ILD, interstitial lung disease; LR, logistic regression

Table 4. Final diagnoses of biopsied pulmonary lesions with cystic airspaces

Final Diagnosis	Value
Malignancy	81/90 (90)
Adenocarcinoma	49/81 (60)
Squamous cell carcinoma	24/81 (30)
Undifferentiated carcinoma	3/81 (4)
Metastasis from extrapulmonary tumor	2/81 (2)
Pleomorphic carcinoma	1/81 (1)
Malignancy of unknown histology[a]	2/81 (2)
Benign finding	9/90 (10)
Mycobacterial infection	2/9 (22)
Leiomyoma	1/9 (11)
Nonspecific inflammatory process	6/9 (67)

Data are reported as number/total (%).

[a]Occurrence of metastases at follow-up.

Table 5. Final diagnoses of biopsied noncystic noncavitary pulmonary lesions

Final Diagnosis	Value
Malignancy	165/180 (92)
Adenocarcinoma	105/165 (64)
Squamous cell carcinoma	22/165 (13)
Undifferentiated carcinoma	19/165 (11)
Metastasis from extrapulmonary tumor	6/165 (4)
Carcinoid	4/165 (2)
Adenosquamous carcinoma	1/165 (1)
Small cell lung carcinoma	5/165 (2)
Leiomyosarcoma	1/165 (1)
Giant cell carcinoma	1/165 (1)
Malignant germinal tumor	1/165 (1)
Benign finding	15/180 (8)
Mycobacterial infection	1/15 (7)
Hamartoma	2/15 (13)
Hamartochondroma	2/15 (13)
Sarcoidosis	1/15 (7)
Nonspecific inflammatory process	9/15 (60)

Data are reported as number/total (%).

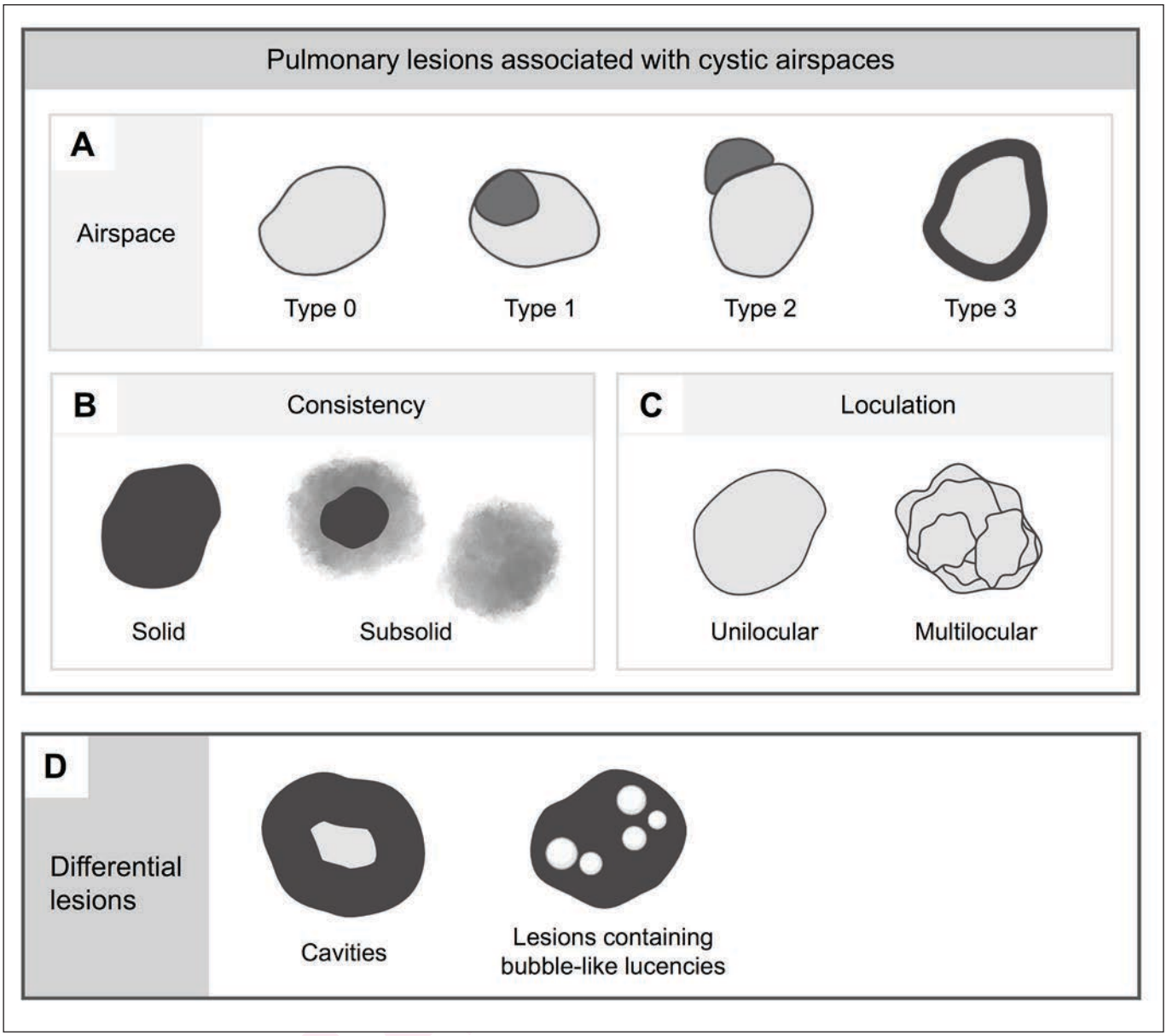

Fig. 1—(A-D) Illustration of pulmonary lesions associated with cystic airspaces, showing classification of lesion type (A), classification of consistency (B), and classification of loculation (C), representing modification of approach used by Fintelmann et al. [20]. (D) Illustration of air-containing lesions not classified as pulmonary lesions associated with cystic airspaces.

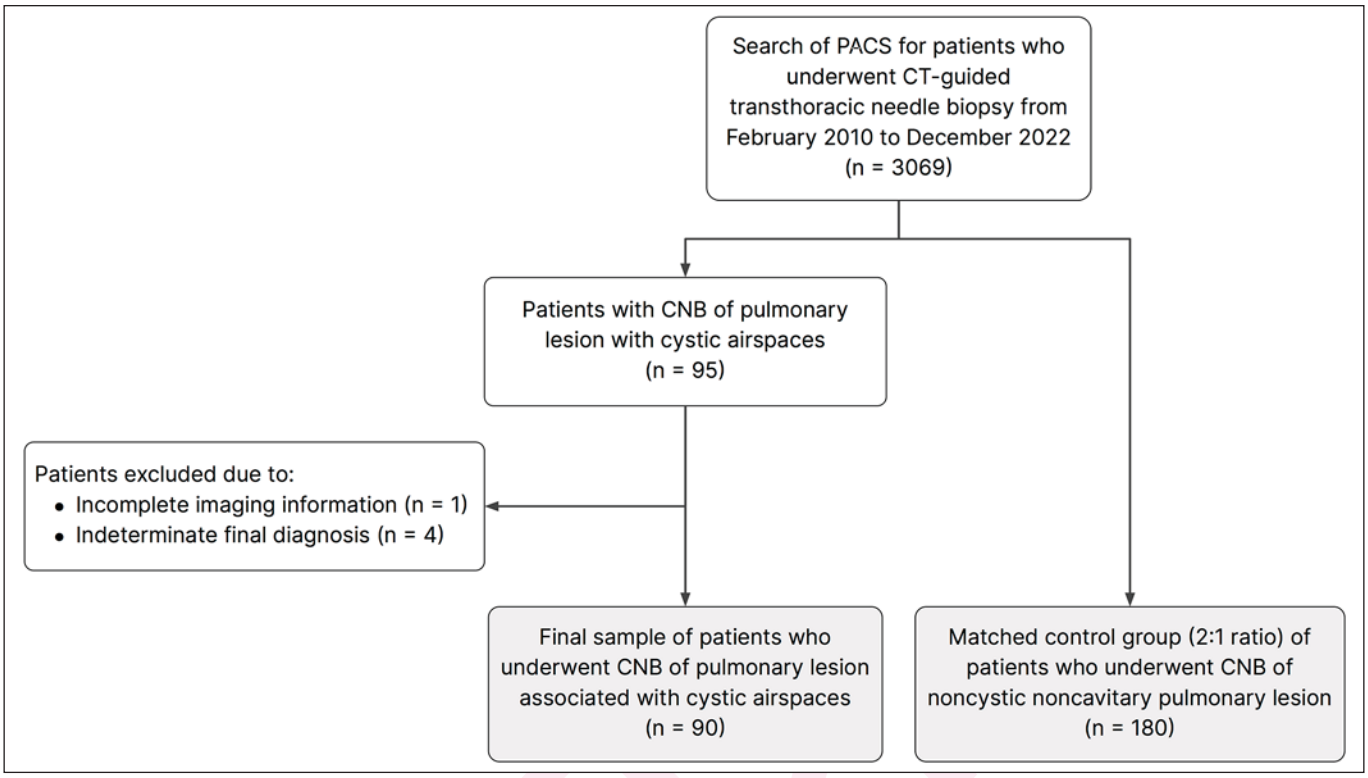

Fig. 2—Flowchart of patient selection process. Grey boxes indicate final study groups. CNB, core-needle biopsy.

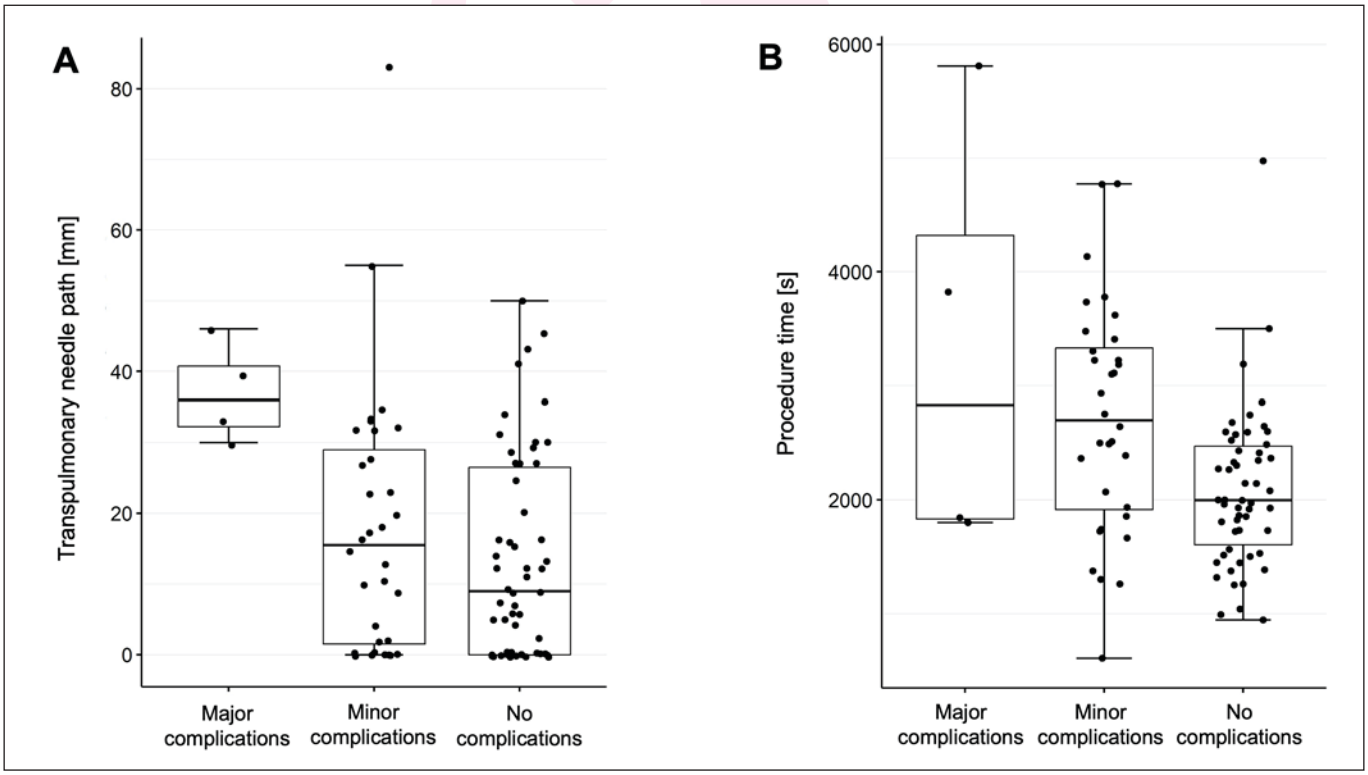

Fig. 3—Box-and-whisker plots showing distributions of transpulmonary needle path length (A) and procedure time (B) for core-needle biopsies of pulmonary lesions associated with cystic airspaces, stratified as major complications (n = 4), minor complications (n = 32), and no complications (n = 54). Horizontal lines in centers of boxes indicate medians, ends of boxes indicate IQRs, whiskers represent greatest or least point within 1.5 times IQR, and points represent individual patients.

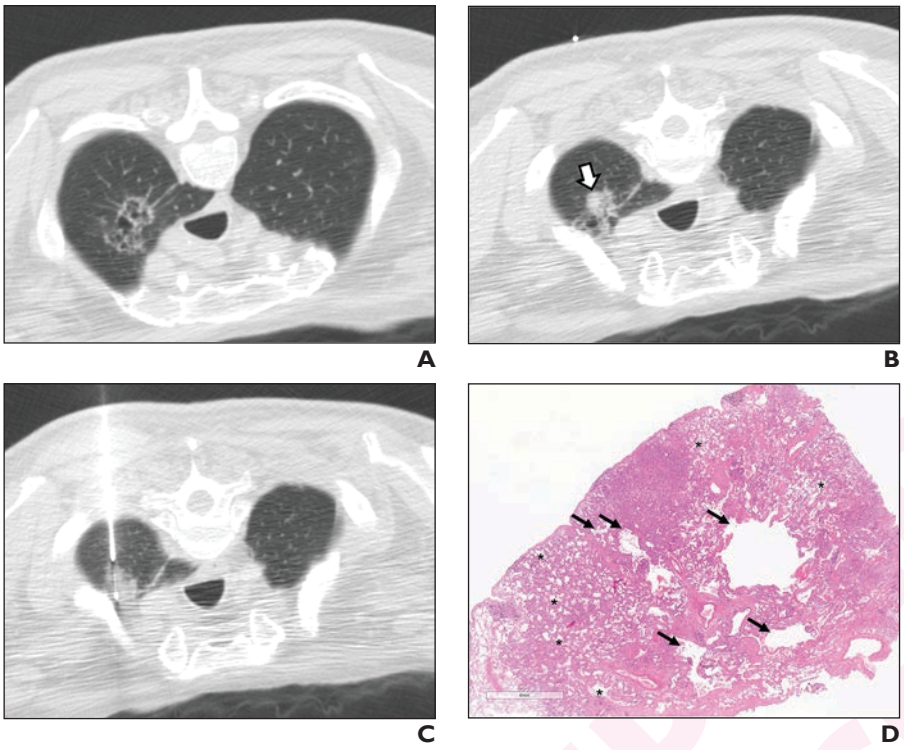

Fig. 4—69-year-old man who underwent core-needle biopsy (CNB) of pulmonary lesion associated with cystic airspace. (A, B) Axial CT images acquired before needle insertion show lesion associated with cystic airspaces in right upper lobe. Lesion was multilocular and showed cranial solid nodular component (arrow, B). (C) Intraprocedural axial CT image. CNB was performed using posterior approach with patient lying prone, targeting cranial solid nodular component. Biopsy specimen revealed adenocarcinoma. Lesion subsequently underwent surgical resection, yielding final diagnosis of adenocarcinoma. (D) Photomicrograph (H and E, 20X magnification) of specimen shows centrally located cystic spaces (arrows), with tumor foci growing along emphysematous alveolar walls at periphery (asterisks).

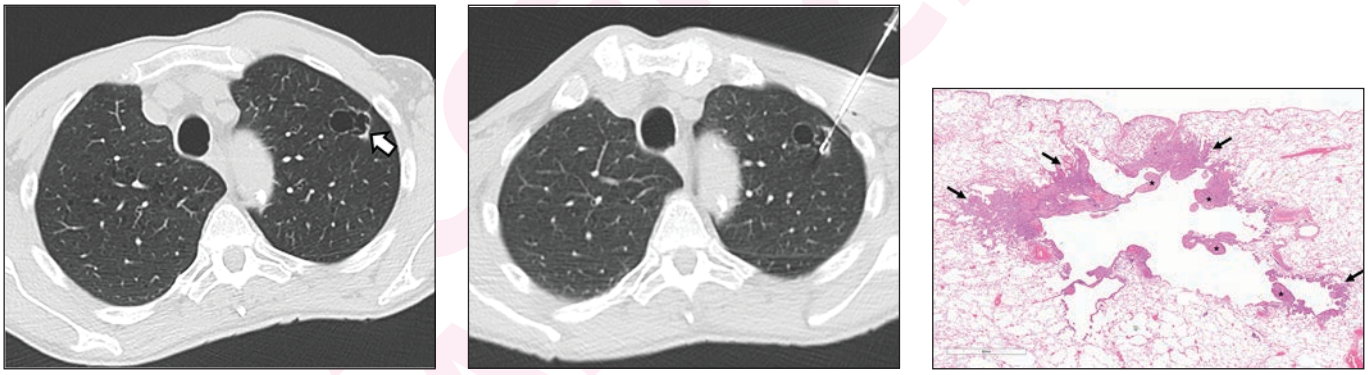

Fig. 5—69-year-old man who underwent core-needle biopsy (CNB) of pulmonary lesion associated with cystic airspace. (A) Axial CT image acquired before needle insertion shows lesion in left upper lobe. Lesion showed few septa and asymmetric nodular wall thickening (arrow). (B) Intraprocedural axial CT image. Procedure was performed using anterior approach with patient lying supine, targeting wall thickening. Biopsy specimen revealed squamous cell carcinoma. Lesion subsequently underwent surgical resection, yielding final diagnosis of squamous cell carcinoma. (C) Photomicrograph (H and E, 20X magnification) of specimen shows tumor lining cystic airspace (arrows); cystic airspaces are bordered by thick ruptured emphysematous alveolar walls (asterisks).

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