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► To cite this version:

J. Brioulet, A. David, C. Sagan, L. Cellerin, E. Frampas, et al.. Percutaneous CT-guided lung biopsy for the diagnosis of persistent pulmonary consolidation. *Diagnostic and Interventional Imaging*, 2020, 101, pp.727 - 732. 10.1016/j.diii.2020.07.007 . hal-03493415

HAL Id: hal-03493415

<https://hal.science/hal-03493415>

Submitted on 7 Nov 2022

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Percutaneous CT-guided lung biopsy for the diagnosis of persistent pulmonary consolidation

Short title:

CT-guided biopsy of pulmonary consolidation

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None of the authors have any conflict of interest related or unrelated to the study to disclose.

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List of abbreviations

BAL: bronchoalveolar lavage

CI: confidence intervals

CT: computed tomography

PET/CT: Positron emission tomography/Computed tomography

SD: standard deviation

Abstract

Purpose: The primary objective of this study was to determine the diagnostic accuracy of percutaneous computed tomography (CT)-guided biopsy of persistent pulmonary consolidations. The secondary objective was to determine the complication rate and identify factors affecting diagnostic yield.

Materials and methods: Two radiologists retrospectively reviewed 98 percutaneous CT-guided biopsies performed in 93 patients (60 men, 33 women; mean age, 62 ± 14.0 (SD) years; range: 18-88 years) with persistent pulmonary consolidations. Final diagnoses were based on surgical outcomes or 12 months clinical follow-up findings. Biopsy results were compared to the final diagnosis to estimate diagnostic yield.

Results: A final diagnosis was obtained for all patients: 51/93 (54.8 %) had malignant lesions, 12/93 (12.9%) specific definite benign lesions (including 9 infections, two pneumoconiosis and one lipoid pneumonia) and 30/93 (32.3%) non-specific benign lesions. CT-guided biopsy had an overall diagnostic yield of 60 % (59/98) with a correct diagnosis for 50/51 malignant lesions (diagnostic yield of 98.0% for malignancy) and for 9/47 benign lesions (diagnostic yield of 19.1% for benign conditions). Major complications occurred in 4/98 (4 %) of lung biopsies (four pneumothoraxes requiring chest tube placement).

Conclusion: Percutaneous CT-guided biopsy is an alternative to endoscopic or surgical biopsy for the diagnosis of persistent consolidation with a low risk of severe complication.

Keywords: Lung diseases; Pneumonia; Tomography, X-ray computed (CT); Image-guided biopsy.

Introduction

Pulmonary consolidation is a non-specific pattern on computed tomography (CT) that is mostly due to acute pulmonary infection [1]. Consolidation is considered to be persistent when the opacity has failed to resolve by 50% in 2 weeks or completely in 4 weeks [1]. Consolidation may be caused by various disorders including atypical infections, malignancy, vasculitis and organizing pneumonia [2].

When clinical, radiological, and bacteriological results do not provide a definite diagnosis of persistent pulmonary consolidation, an invasive approach is often needed to determine the underlying disease. There is no consensus guideline, but bronchoscopy used in association with bronchoalveolar lavage (BAL) and transbronchial biopsy is the preferred approach, allowing a definite diagnosis for most patients with persistent pulmonary consolidation [3]. However, surgical biopsy may be needed in a subset of patients, but is associated with non-negligible morbidity and mortality [4].

Percutaneous CT-guided biopsy of persistent pulmonary consolidation can be an alternate option when bronchoscopy and BAL do not provide a definite diagnosis. Percutaneous CT-guided biopsy is effective and safe for the diagnosis of pulmonary nodules [5, 6] but only four previous studies [7-10] have evaluated CT-guided biopsy for pulmonary consolidations.

The primary objective of this study was to determine the diagnostic accuracy of percutaneous CT-guided biopsy of persistent pulmonary consolidations. The secondary objective was to determine the complication rate and identify factors affecting diagnostic yield.

Materials and methods

Study design

This retrospective single-center study was conducted in our University Hospital and approved by our Institutional Review Board. Between September 1st, 2010 and July 31st, 2019 inclusively, 1676 CT-guided biopsies of lung lesions were performed in our institution. Two radiologists, with respectively 4- (J.B.) and 10 years (O.M.) of experience, reviewed procedural images to include all biopsies of persistent pulmonary consolidations.

The inclusion criterion was a pulmonary consolidation on CT presenting as a homogeneous increase in pulmonary parenchymal attenuation that obscured the margins of vessels and airways wall according to the Fleischner Society definition [11]. Exclusion criteria were: (i), consolidation presenting as a mass on CT, and (ii), no standard of reference available for inconclusive biopsy (*i.e.*, no histopathological confirmation or no 12-month clinical follow up).

Ninety-six patients underwent CT-guided biopsy of persistent pulmonary consolidation. Three patients were excluded (1 death and 2 lost to follow-up without final diagnosis). Four consolidations were biopsied several times because of a non-contributive biopsy and an unfavorable clinico-radiological evolution (3 patients underwent two biopsies and 1 patient underwent three biopsies). A repeated biopsy was considered a new procedure in order to calculate diagnostic accuracy.

Interventional procedure

After checking the coagulation factors, percutaneous CT-guided biopsies were performed under local anesthesia (10 mL of 1% lidocaine). Biopsies were performed under CT guidance by trained operators (10 to 20 years of experience) or by a resident (4 to 5 years of experience) under their supervision. A path was planned to cross a little of pleural surface as possible and to avoid areas of necrosis, excavation or visible bullae. When a positron emission tomography/CT (PET/CT) examination had been previously obtained, targeting of the zone with maximal metabolic activity was attempted. A 17-Gauge coaxial Temno™ introducer needle (Merit Medical) was used and core needle biopsies were obtained with an 18-Gauge semi-automatic cutting needle Temno™ (Figure 2). A minimum of two biopsies were performed and additional samples were obtained if there was a suspicion of infection or for molecular testing. After biopsy, a final CT examination was performed to search for potential complications.

Data analysis

The electronic medical records of the patients were reviewed to retrieve clinical characteristics of the patients who had CT-guided biopsy of consolidations and to determine the final diagnosis. CT images and procedural reports of all CT-guided biopsies were reviewed to determine CT features and periprocedural complications.

Post intervention complications were classified into major or minor categories according to the CIRSE classification system [12]. Pneumothorax (with or without a chest tube placement), hemoptysis, gas embolism and broncho-pleural fistula were also documented. Hospitalization in intensive care unit and length of hospital stay were listed.

Biopsy results, classification and definitions

The classification described by Kiranantawat et al. was used for histopathological analyses [9]. According to the results of histopathological and microbiological analysis of pulmonary biopsy specimens, pulmonary consolidations were classified into malignant, specific benign, non-specific benign and no definite cause.

The diagnosis of malignant tumor was considered when histopathological analysis confirmed malignant cells. Specific benign category was considered when histopathological analysis and/or microbiological analysis revealed benign tumors, infections or benign non neoplastic conditions (such as pneumoconiosis, lipoid pneumonia, vasculitis). Non-specific benign category was considered when histopathological analysis and/or microbiological analysis revealed fibrosis, necrosis or inflammation without identification of a specific disease. Finally, biopsy was considered as non-diagnostic when only normal parenchymal cells and no infectious agents were found.

Diagnostic yield was defined as the percentage of tissue samples obtained from core needle-biopsy resulting in the diagnosis of malignancy, or benign specific lesion. For benign specific lesions, the initial histopathological diagnosis was confirmed using surgical findings or 12-month clinical follow-up findings. Diagnostic failure included non-diagnostic, non-specific benign and misdiagnosis biopsies.

Non-specific benign, specific benign and non-diagnostic biopsies were considered as a negative result for malignancy, and it was considered as misdiagnosis when surgical resection or clinical follow-up proved malignancy.

The biopsy result was considered positive for benign category when a specific infectious organism, a benign tumor or a specific benign non neoplastic condition was identified, and it was considered as a true positive according to the clinico-radiological evolution or surgical correlation.

Non-specific benign category was considered as a benign lesion on final diagnosis in case of spontaneous resolution, resolution after treatment other than chemotherapy or stability

in size after 12 months, but was considered as diagnostic failure of percutaneous CT-guided biopsy.

Finally, patients were classified into two groups to determine risk factors for diagnostic failure. The diagnostic failure group included patients with erroneous diagnosis and those with non-diagnostic and non-specific benign biopsies.

Statistical analysis

Sensitivity, specificity and accuracy for the diagnosis of malignancy and benignity were calculated with the corresponding proportions and 95% confidence intervals (CI). Continuous variables were compared using Student *t* test. Categorical variables were compared using Fisher exact test. Significance was set at $P < 0.05$.

Results

Among 1676 CT-guided biopsies of pulmonary lesions, 98 (98/1676; 6%) were performed for the diagnosis of pulmonary consolidations. Clinical characteristics of the patients and CT patterns are summarized in Tables 1 and 2. Ninety-three patients were included; there were 60 men and 33 women, with a mean age of 62 ± 14.0 (SD) years (range: 18-88 years). Figure 1 shows the flow chart of patients who met inclusion/exclusion criteria for the study population. Of these, 37/93 (40 %) patients had a history of malignancy and 48/93 (52 %) were current or former smokers. In 58/93 patients (62 %) an inconclusive bronchoscopy had been previously performed and 48 patients (52%) had received antibiotic or antifungal empiric therapy before lung biopsy.

Consolidations were limited to one lobe in 78/93 patients (84%), 50/93 (54%) were associated with a ground-glass component, 17/93 (18%) with cavitation and 14/93 (15%) with necrosis.

Biopsy outcome

A final diagnosis was obtained for all patients including 51 malignant lesions, 12 benign lesions with a specific diagnosis and 30 non-specific benign lesions (Table 3). CT-guided biopsy had a diagnostic yield of 60 % (95% CI: 50.3-69.3%) per procedure ($n = 98$) and 62 % (95% CI: 52.2-71.5%) per patient ($n = 93$), with a correct diagnosis of 50/51 malignant lesions (resulting in a sensitivity and specificity of 98% (95% CI: 89.7-99.7%) and 100% (95% CI: 92.4-100%) for malignancy and 9/47 (19%) benign specific lesions.

Histopathological analysis of biopsy specimens revealed malignancy in 50 patients, with 43 primitive lung cancer including 40 adenocarcinomas. There was only one misdiagnosed malignant lesion, initially diagnosed as a benign tumor (papillary adenoma) on CT-biopsy and proved malignant (papillary adenocarcinoma) after surgical resection.

The biopsy result was specific benign in 10 biopsies with 1 benign tumor (that was finally malignant), 6 infections (1 *Mycobacterium*, 2 *Mucormycosis*, 1 *Klebsiella* and 2 *Pseudomonas Aeruginosa*), 2 pneumoconiosis and 1 lipid pneumonia. Finally, 3 additional infections were diagnosed consisting in one infection due to *Atypical Mycobacterium*, one due to *Bacteroides fragilis* diagnosed with BAL and one due to *T. Pallidum* diagnosed with VDRL-TPHA serology.

The biopsy result was benign non-specific in 36 patients and in 3 biopsies a germ was finally found and a final diagnosis for infection was established. Only 2 biopsy samples were considered unrepresentative and classified as non-diagnostic, they were finally reclassified as non-specific benign lesions after clinico-radiological follow-up.

Repeat biopsies have been taken into account: four revealed benign non-specific lesions on the first biopsy, which were confirmed as benign on final diagnosis, and one consolidation initially diagnosed as benign non-specific on the first biopsy proved to be a bacterial infection.

Complications

Thirty-nine CT-guided lung biopsies (39/98; 40%) resulted in complications, including 32 pneumothoraxes (32/98; 32%), and 7 minor hemoptysis (7/98; 7%) resolving spontaneously. Only 4 pneumothoraxes (4/32; 12%) in four patients required chest tube placement and short hospitalization stay (*i.e.*, < 48 hours).

Comparison between success and failure group

A comparison of variables between the diagnostic success group and failure groups is summarized in Table 4. A final diagnosis of benign lesion (38/39; 97.4%), presence of cavitation on CT images (11/39; 28.2%) and post biopsy pneumothorax (17/39; 43.6%) were significantly more frequent in the failure group.

Discussion

The results of our study confirm that CT-guided biopsy is a useful approach to consolidation when bronchoscopy failed, with a diagnostic yield of 60 % and high sensitivity and specificity for the diagnosis of malignant condition in patients with persistent pulmonary consolidation. Only 4 studies have previously analyzed the diagnostic accuracy of percutaneous CT-guided biopsy in the evaluation of consolidations, reviewing 48, 23, 30 and 56 patients respectively [7-10]. To our knowledge, with 98 percutaneous CT-guided biopsies of consolidation our study represents the largest series to date. Our study confirms the efficacy of CT-guided biopsy to diagnose malignant consolidations, with excellent sensitivity and specificity as reported in other series (87% and 100%, respectively) [8] and (95% and 100%, respectively) [9].

In our study, most malignant lesions were lung cancers, including mostly adenocarcinomas which are well known mimickers of pneumonia [13]. A recent study demonstrated the potential of CT-texture analysis in differentiating in-situ and minimally-invasive from invasive adenocarcinomas for subsolid lung nodules [14]. In patients with lung cancer, CT-guided lung biopsy may be useful not only for the diagnosis but also for molecular testing, which is increasingly used for targeted-therapy [15].

In our study, the second cause of malignancy was primary lymphoma whereas it represents only 0.5% of all lung neoplasms [16]. Consolidation is one of the most frequent imaging manifestations of pulmonary lymphoma [17] and the diagnosis is rarely possible with bronchoscopy [18,19]. Percutaneous CT-guided lung biopsy is less invasive than surgical biopsy and allows obtaining large tissue samples to diagnose pulmonary lymphoma.

In most of patients, the diagnosis of benign lesion is clinical and clinico-radiological follow up is reassuring. However, it may be necessary to perform invasive procedure to obtain a histological or microbiological diagnosis. Bronchoscopy is widely performed as the initial procedure for pathologic diagnosis because of its advantages, especially its relative safety but CT-guided biopsy can be useful in second intention. In our study, the diagnostic yield of CT-guided biopsy for benign lesion was significantly lower than that for malignant lesions. This was mostly due to a high rate of non-specific benign lesions which were considered as negative results.

In patients with infections, lung biopsy is rarely performed. Indeed, the diagnosis of pneumonia is usually made on the basis of clinical findings and treated using empiric

antibiotic therapy. A germ is identified, generally by sputum culture, blood culture, antigen testing or rarely by bronchoscopy with BAL [20]. However, it may be important to identify the causative germ in selected patients. In this regard, for immunocompromised patients early and accurate diagnosis is crucial because of high morbidity and mortality rates [21]. Identifying the germ is also necessary in patients with persistent lung consolidation when slow-growing germs such as *Mycobacterium* or *Actinomyces* are suspected before initiating prolonged treatment [22,23]. In our study all patients with pulmonary infection were immunocompromised, with a prior negative BAL.

In our cohort CT-guided biopsy of persistent lung consolidation is safe with a low rate of adverse events, mostly minor pneumothorax and minor hemoptysis that resolved spontaneously. We had a rate of severe complication similar to that of other studies (8.3 - 43%) [8-10]. It appears that CT-guided biopsies of consolidation convey the same rate of adverse events as CT-guided biopsies of lung nodules, with 23-26% of pneumothorax [24,25] and 4% of hemoptysis [25]. Other complications such as air embolism or broncho-pleural fistula are described in large series of biopsies of lung nodule but are extremely rare and were not observed in our study [24,25].

We found that consolidations with cavitation are associated with a high rate (11/39; 28.2%) of diagnostic failure. This may be explained by the difficulty to obtain large samples and the higher probability to retrieve non-specific material like necrosis when biopsying a cavitating lesion [26]. Other studies also found an association between diagnostic failure and necrosis or ground glass component [27]. Consequently, it seems appropriate to avoid the focal zones of cavitation, necrosis or ground glass opacities when performing a biopsy of lung consolidation. PET/CT might help differentiate between tumor and postobstructive atelectasis and, therefore, essential in those situations to avoid false-negative biopsies by targeting a focal zone with hypermetabolic activity among a consolidation [28,29] but we had not enough data to confirm this hypothesis.

CT fluoroscopy-guided biopsy with real-time imaging could be an interesting alternative, with high diagnostic yield and consequent reduction in complications by reducing procedure time. Iguchi et al. reported 97.2% diagnostic yield for mediastinal masses using this technique [30].

Our study has several limitations. It is a retrospective study performed in a single center, thus introducing selection bias. The duration of follow-up was arbitrarily set at 12 months, but is similar to other studies [8,9]. Diagnosis was uncertain in 39 % of the patients, and there was

probably a significant number of undiagnosed infections. Indeed, many of these patients received an empirical antibiotic or antifungal therapy, which was probably involved in the resolution of pulmonary consolidation.

In conclusion, percutaneous CT-guided biopsy is a promising alternative technique for the diagnosis of persistent lung consolidation. It appears as an accurate technique for a definite diagnosis of malignant lesions presenting as persistent lung consolidations. For infections, the diagnostic yield is lower but CT-guided biopsy can enable to identify pathogen germs even when previous bronchoscopy has failed. The complications of percutaneous lung biopsy are limited and generally minor, including pneumothorax and minor hemoptysis resolving spontaneously.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal

Editors (ICMJE) criteria for Authorship.

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Legends

Figure 1. Studyflow chart.

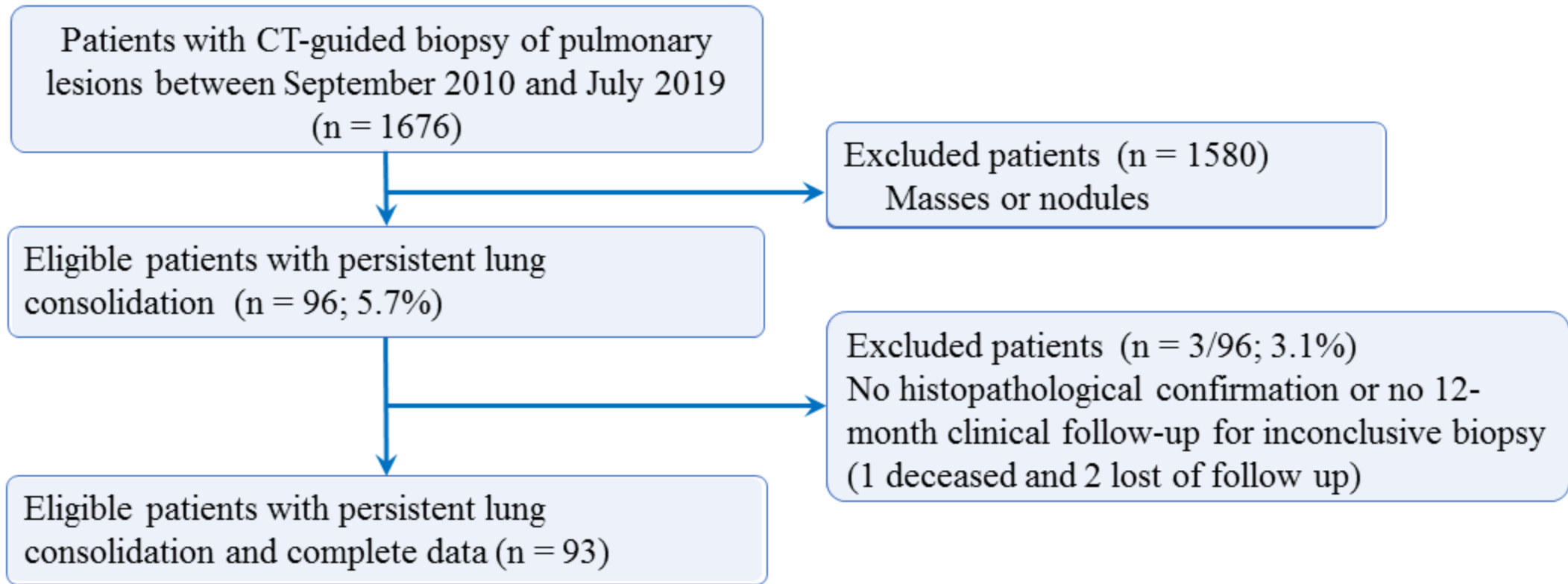
Figure 2. A 63-year-old man with persistent lung consolidation. A. Computed tomography image in the axial plane shows pulmonary consolidation of the middle lobe, surrounded by ground glass opacification. B. Computed tomography image in the axial plane during percutaneous CT-guided biopsy shows a 17-Gauge coaxial introducer needle (arrow) within lung consolidation. C. Computed tomography image in the axial plane shows an 18-Gauge semi-automatic needle biopsy (arrow). Primary pulmonary lymphoma was identified at histopathological analysis of percutaneous biopsy specimens.

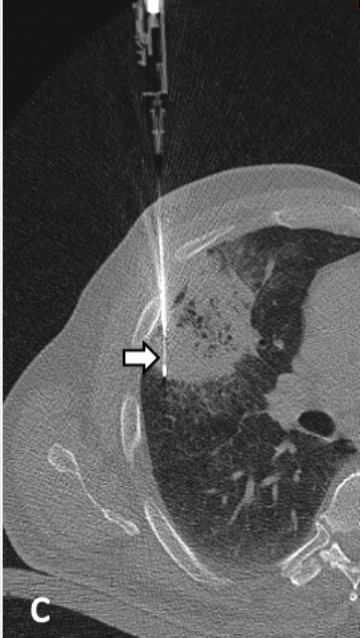
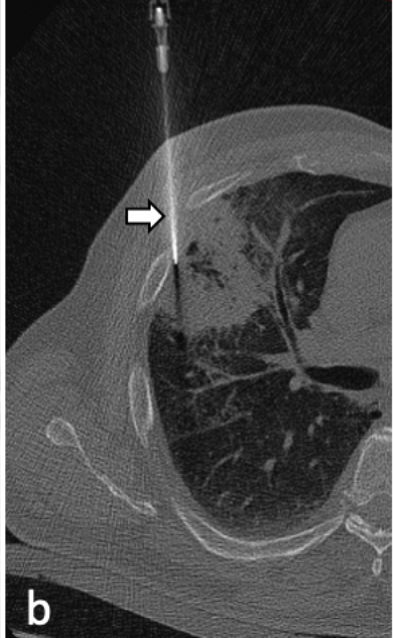
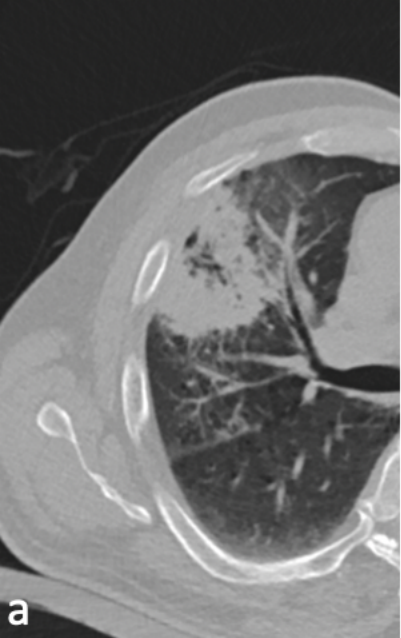
Table 1. Prebiopsy clinical characteristics in 93 patients.

Table 2. CT imaging features in 93 patients who underwent CT-guided lung biopsy for persistent pulmonary consolidation.

Table 3. Outcome and final diagnosis of 98 percutaneous CT-guided lung biopsies in 93 patients.

Table 4. Characteristics of patients, consolidations and complications related to the procedure in diagnostic success group and failure group.





Variable	
Sex	
<i>Male</i>	60 (60/93; 65%)
<i>Female</i>	33 (33/93; 35%)
Age (years)	62 ± 14 [18 - 88]
Smoking history	
<i>Non-smoker</i>	30 (30/93; 32%)
<i>Current smoker</i>	22 (22/93; 23%)
<i>Former smoker</i>	26 (26/93; 27%)
<i>Unknow</i>	15 (15/93; 16%)
Indication for biopsy	
<i>Cancer</i>	51 (51/93; 52%)
<i>Cancer or infection</i>	43 (43/93; 44%)
<i>Infection</i>	4 (4/93; 4%)
Treatment before biopsy	
<i>None</i>	23 (23/93; 25%)
<i>Antibiotic/Antifungals</i>	48 (48/93; 52%)
<i>Antibiotic/Antifungals and steroids</i>	3 (3/93; 3%)
<i>Chemotherapy/radiotherapy</i>	2 (2/2; 2%)
<i>Unknow</i>	17 (17/93; 18%)
Underlying disease	
<i>None</i>	38 (38/93; 41 %)
<i>Lung cancer</i>	3 (3/93; 3%)
<i>Other malignancy</i>	
<i>Other solid cancer</i>	15 (15/93; 16%)
<i>Leukemia</i>	8 (8/93; 9%)
<i>Lymphoma</i>	11 (11/93; 12%)
<i>Pulmonary disease</i>	11 (11/93; 12%)
<i>Vasculitis</i>	1 (1/93; 1%)
<i>Unknow</i>	6 (6/93; 6%)
Bronchoscopy prior to PTNB	
<i>Yes</i>	58 (58/93; 62%)
<i>No</i>	20 (20/93; 22%)
<i>Unknow</i>	15 (15/93; 16%)

Qualitative variables are expressed as raw numbers; numbers in parentheses are proportions followed by percentages. Quantitative variables are expressed as means ± standard deviations; numbers in brackets are ranges

PTNB indicates percutaneous transthoracic needle biopsy

CT finding		
Emphysema		
	<i>Absent</i>	60 (60/93; 65%)
	<i>Present</i>	38 (38/93; 41%)
Ground glass component		
	<i>Absent</i>	48 (48/93; 52%)
	<i>Present</i>	50 (50/93; 54%)
Pleural effusion		
	<i>Absent</i>	68 (68/93; 73%)
	<i>Present</i>	30 (30/93; 32%)
Cavitation		
	<i>Absent</i>	81 (81/93; 87%)
	<i>Present</i>	17 (17/93; 18%)
Necrosis		
	<i>Absent</i>	84 (84/93; 90%)
	<i>Present</i>	14 (14/93; 15%)
Air bronchogram		
	<i>Absent</i>	17 (17/93; 18%)
	<i>Present</i>	81 (81/93; 87%)

Qualitative variables are expressed as raw numbers; numbers in parentheses are proportions followed by percentages. CT: computed tomography

Lung lesion	Biopsy outcome	Final diagnosis
Malignant lesions		
<i>Lung cancer</i>	43 (43/98; 44%)	44 (44/93; 47%)
<i>Metastasis</i>	1 (1/98; 1%)	1 (1/93; 1%)
<i>Lymphoma</i>	5 (5/98; 5%)	5 (5/93; 5%)
<i>Leukemia</i>	1 (1/98; 1%)	1 (1/93; 1%)
Benign lesions		
<i>Benign tumor</i>	1 (1/98; 1%)	0
<i>Bacterial infection</i>	3 (3/98; 3%)	5 (5/93; 5%)
<i>Fungal infection</i>	2 (2/98; 2%)	2 (2/93; 2%)
<i>Mycobacterial infection</i>	1 (1/98; 1%)	2 (2/93; 2%)
<i>Pneumoconiosis</i>	2 (2/98; 2%)	2 (2/93; 2%)
<i>Lipoid pneumonia</i>	1 (1/98; 1%)	1 (1/93; 1%)
Non-specific (fibrosis/inflammation/necrosis)	36 (36/98; 37%)	30 (30/93; 32%)
Non diagnosis	2 (2/98; 2%)	0 (0/93; 0%)
Total	98	93

Variables are expressed as raw numbers; numbers in parentheses are proportions followed by percentages.

Variable	Success group (n = 59 patients) <i>Total (59/98; 60%)</i>	Failure group (n = 39 patients) <i>Total (39/98; 40%)</i>	<i>P</i> value
Male	36 (36/59; 61.0%)	29 (29/39; 74.4%)	0.195
Malignant History	20 (20/59; 34.0%)	17 (17/39; 43.6%)	0.196
Ground glass component	29 (29/59; 49.1%)	21 (21/39; 53.8%)	0.684
Emphysema	24 (24/59; 40.7%)	11 (11/39; 28.2%)	0.676
Pleural effusion	16 (16/59; 27.1%)	14 (14/39; 35.9%)	0.378
Cavitation	6 (6/59; 10.2%)	11 (11/39; 28.2%)	0.029
Necrosis	5 (5/59; 8.5%)	9 (9/39; 23.1%)	0.076
Intra parenchymal needle track	32 (32/59; 54.2%)	19 (19/39; 48.7%)	0.680
Final diagnosis			< 0.001
	Malignant 50 (50/59; 84.7%)	1 (1/39; 2.6%)	
	Benign 9 (9/59; 15.2%)	38 (38/39; 97.4%)	
Not drained pneumothorax	11 (11/59; 18.6%)	17 (17/39; 43.6%)	0.011
Drained pneumothorax	2 (2/59; 3.4%)	2 (2/39; 5.1%)	> 0.999
Hemoptysis	3 (3/59; 5.1%)	4 (4/39; 10.6%)	0.431

Variables are expressed as raw numbers; numbers in parentheses are proportions followed by percentages. Bold indicates significant *P* value