Transthoracic lung biopsy for pulmonary nodules ⩽20 mm in routine clinical care

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Shareable abstract (@ERSpublications)
Lung cancer screening led to high rate of ⩽20 mm nodule discovery. Small-nodule TTLB had 84% sensitivity with 70% NPV for cancer diagnosis. Pneumothorax needing chest tube insertion occurred in 9.6% of TTLBs for lesions ⩽20 mm. No death was observed. https://bit.ly/3ohTd7f

Abstract

Background Computed tomography (CT) screening has improved lung cancer survival, yet increasingly detects small lung lesions. Thus, the number of transthoracic lung biopsies (TTLB) for small nodules is expected to rise significantly. The aim of the present study was to evaluate the diagnostic accuracy and safety of CT-guided TTLB for nodules ⩽20 mm *versus* nodules >20 mm.

Study design and methods Data for CT-guided TTLBs from 474 consecutive patients were prospectively collected over a 3-year period (198 lesions ⩽20 mm and 276 lesions >20 mm) in a teaching hospital and analysed in terms of diagnostic performance and complications.

Results There were more conclusive biopsies in the >20 mm lesion group (n=236, 85.5%) than in ⩽20 mm lesion group (n=140, 70.7%; p<0.001). The overall accuracy, sensitivity, specificity and negative predictive value for diagnosing malignant lesions after first TTLB were 88.4%, 84%, 100% and 70.1%, respectively, for ⩽20 mm lesions, and 94.2%, 93%, 100% and 74.6%, respectively, for >20 mm lesions. Pneumothorax requiring drainage was significantly more common for ⩽20 mm lesions, compared to TTLB of larger lesions (9.6% *versus* 4.3%; p=0.02). Prolonged hospital stay due to pneumothorax occurred in 27 (17.4%) TTLBs of ⩽20 mm lesions and 15 (7%) TTLBs of >20 mm lesions (p=0.002). There were no deaths. The only variable significantly associated with diagnostic failure in the ⩽20 mm lesion group was the radiologist's experience.

Interpretation TTLBs for lesions ⩽20 mm were associated with slightly lower diagnostic performance, whereas the higher rate of major complications was still inferior to that extrapolated from United States insurance databases.

Introduction

While lung cancer is the second most frequent cancer in males and females, it is the deadliest cancer in both genders worldwide [1]. Since half of lung cancers are diagnosed at an advanced stage [1], the major challenge is to diagnose early-stage cancer, when surgery or ablative radiotherapy can still be proposed with a curative intention. Recent studies have revealed that computed tomography (CT) lung cancer screening in populations at high risk of lung cancer could reduce lung cancer related mortality by 20–26% [2, 3]. In the CT screening group, cancers were diagnosed at an earlier stage (40.4% stage I cancers in CT screening *versus* 13.5% in control groups [3]).

In direct relation to CT screening, an increasing number of small lesions detected require histological confirmation. Thus, the number of transthoracic lung biopsies (TTLB) for small nodules (⩽20 mm) is expected to rise significantly, although the invasive procedure rate remained low (1.2%) in the randomised National Lung Screening Trial (NLST) and NELSON studies, since most uncovered nodules underwent radiological observation. However, NLST authors reported a 9.8% complication rate (providing only few details on the invasive procedures causing such complications), while recent data extrapolated from United States insurance databases reported a 22.2% complication rate for individuals aged 55–77 years [4]. Any-grade complication rates of transthoracic biopsies were estimated at 18.7%, with only 4.0% considered major complications. Such retrospective studies extrapolated from insurance databases did not report nodule sizes or the precise techniques used (core biopsy or fine needle aspiration). NLST patients were enrolled in the early 2000s, while the MarketScan Commercial Claims and Encounters Database captured data on invasive diagnostic procedures performed in 2008–2013. Nevertheless, CT-guided TTLB has evolved significantly over recent decades.

Safety is a major concern when selecting diagnostic interventional procedures. Common TTLB complications include pneumothorax (8–45.3%) and pulmonary haemorrhage (2.9–54%) [5], both of which are relatively unthreatening.

Accuracy is another issue, yet TTLB has proven a reliable procedure for accurate histological diagnosis [6]. Its sensitivity, specificity and accuracy for diagnosing malignancy were estimated at 85.7–97.4%, 88.6–100% and 89–96.9%, respectively [7].

Although TTLB is probably as effective and safe as when applied to larger lesions [8–17], only few studies have evaluated the risk factors of TTLB failure for small lesions (<20 mm). These are the lesions most likely discovered upon lung cancer CT screening [10].

This study sought to compare the accuracy, diagnostic outcome and safety of TTLBs using core biopsies for lung nodules ⩽20 mm *versus* those >20 mm, in a tertiary university hospital.

Materials and methods

According to French observational study regulations, all patients received a printed information sheet explaining procedure, complication risk and data collection, before providing their oral consent. This study was approved by Bichat-Claude Bernard Hospital institutional review board (CRM-1909-029).

Study population

Data from all consecutive patients who underwent TTLB were collected constituting a prospective database of all interventional CT-scan procedures performed at the University Hospital Bichat-Claude Bernard (Paris, France), from January 2015 to December 2017. Data about inpatient duration stay were collected retrospectively from patients' computer files.

Nodule review and CT scan data

Demographic and lung function test data were collected. CT scan analysis assessed emphysema (absence or presence) in the whole area of the lung and not specifically around the nodule, and lesion characteristics including size, lobe location, distance from pleural puncture site and contact with a fissure.

Biopsy procedure

The lung biopsy indications were validated at weekly thoracic oncology multidisciplinary tumour boards. Using the criteria of the NELSON study, solid nodules with diameter >10 mm (>500 mm^3) and nodules with a volume-doubling time <400 days were considered as high-risk nodules justifying further histological exploration, including TTLB. Whenever possible, an invasive biopsy (mainly TTLB) was performed in such high-risk nodules, to obtain a pre-operative diagnosis of cancer, before the lung resection. Pure ground-glass nodules were not biopsied by TTLB. Only ground-glass opacities with features of consolidation >10 mm during follow-up were operated upon, with or without pre-operative TTLB, according to estimated risk of the procedure by the senior radiologists.

TTLB procedures were conducted under CT guidance (Brillance 40 Phillips or Aquilion PRIME Canon) with core biopsy sizes (18G or 20G semi-automated cutting needle: Temno, Cook, Bard, Argon) specified. TTLB procedures were performed in the outpatient clinic (without overnight stay) at the exception of patients already hospitalised in an inpatient hospitalisation unit at the time the TTLB was performed. Antivitamin K or new oral anticoagulants were replaced by low molecular weight heparin (LMWH) ⩾7 days before the procedure, and LMWH was suspended for ⩾12 h. According to most international

recommendations, patients were not asked to discontinue low-dose acetylsalicylic acid. Other anti-aggregant therapy was interrupted >5 days before the procedure whenever possible, after the agreement of the cardiologist.

All procedures were performed by one of six chest radiologists, including two seniors with >10 years' experience in CT-guided biopsies, and four juniors. A junior radiologist, having completed supervised training with >30 TTLBs, under the supervision of a senior radiologist for the puncture path and patient positioning, is allowed to perform the procedure alone, after having clarified with the senior doctor both the position of the patient and the path of the puncture, for each procedure and patient.

Multiple samples (at least three whenever possible) were taken with a coaxial needle using slightly different angles.

Post-procedural whole-lung ultra-low-dose CT scans were systematically performed within 5 min after the last puncture to detect complications (pneumothorax, intra-alveolar haemorrhage or air embolism).

Standardised operating protocol regarding management of complications

If a pneumothorax was detected in an asymptomatic patient with a <3 cm distance between lung and chest wall, another whole-lung CT was performed 10 min later to check on any further expansion. If the patient was symptomatic or if the pneumothorax was even greater, a chest tube was inserted under CT-scan control. In this case, the patient was hospitalised for 24–36 h monitoring. We attempted to remove the chest tube 24 h post-TTLB, performing control chest radiography to ascertain lung re-expansion. In all cases, chest radiography was performed 5 h after completing TTLB to check for late pneumothorax occurrence or worsening when a chest tube was not immediately inserted.

In case of asymptomatic pneumothorax and without indication of chest tube insertion, the patient was discharged with a planned outpatient visit and chest radiography, 7 days later.

In case of haemoptysis, patients underwent close monitoring in the outpatient clinic or inpatient unit according to the importance of the haemorrhage and the clinical repercussions.

Primary end-point: diagnostic performance and diagnostic outcomes

The pathological results were classified according to two lesion size groups: ⩽20 mm and >20 mm. For each group, the histological results were classified as malignant, benign or diagnostic failure. A conclusive biopsy was a TTLB that enabled diagnosing a malignant or benign lesion. A diagnostic failure was a TTLB that did not enable any formal histological diagnosis.

The final diagnosis was based on subsequent surgery (biopsy or lung resection), other diagnostic tools (bronchoscopy, endobronchial ultrasonography or extrapulmonary lesion biopsy), clinical and radiological follow-up, or second TTLB.

Lesions with one of the following characteristics were defined as malignant: 1) malignant surgical pathology; 2) malignant CT-guided biopsy pathology; or 3) enlarged lesion with distant organ or lymph node metastasis during follow-up. Lesions with one of the following characteristics was defined as benign: 1) benign surgical pathology; 2) significantly smaller or lesions disappearing on follow-up, without treatment; 3) specific benign diagnosis (tuberculosis, fungal infection and organising pneumonia) confirmed by biopsy pathology with marked improvement after targeted treatment; or 4) no lesion enlargement upon follow-up. Biopsy pathologies were divided into true positive (biopsy pathology and final diagnosis were both malignant), false positive (biopsy pathology evoking malignancy, yet benign final diagnosis), true negative (biopsy pathology and final diagnosis both benign) and false negative (benign biopsy pathology, yet malignant final diagnosis). Primary outcomes were TTLB diagnostic performances according to lesion sizes.

Secondary end-point: complications and associated risk factors

CT-scan images and clinical follow-ups were analysed retrospectively with a minimal 12-month follow-up. Pneumothorax, intra-alveolar haemorrhage and air embolisms were analysed using CT images. Pulmonary haemorrhage was defined as new consolidative or ground-glass opacity on post-biopsy images. Newly developed haemoptysis post-biopsy cases were collected from TTLB CT reports. Complications requiring further on-site follow-up included pneumothorax needing immediate chest tube insertion or occurring in patients with pulmonary dysfunction (COPD, lung fibrosis); although asymptomatic, a large (one or more pulmonary segments) CT-revealed haemorrhage or haemoptysis ⩾10 cm^3 (total volume emitted once or

repeatedly) occurring within 1 h post-procedure. The impact of TTLB-induced pneumothorax on hospitalisation length was collected from computed files and analysed retrospectively. Collected patient-related variables included age, chronic lung disease and emphysema. Lesion-related variables included size, location, distance to pleura, procedure indication and pathological diagnosis. Technique-related variables included needle gauge, needle brand, pass numbers, pleura-needle angle, pleural crossing, needle reposition, duration and physician.

Statistical analysis

Data were exported from Microsoft Excel (version 2013 for Windows; Microsoft Corporation, 2013) to IBM SPSS Statistics for Windows (version 25.0; IBM, Armonk, NY, USA). TTLB diagnostic performance in each group was determined in terms of sensitivity (recall), specificity (selectivity), accuracy, positive predictive value, negative predictive value (NPV) and F1 score. Between-group comparisons were performed using Pearson's Chi-squared test or Fisher's exact test for discrete variables, and the t-test (two independent samples) for continuous variables (or Mann–Whitney U-test if not applicable or when comparing medians). Odds ratios and their 95% confidence intervals were calculated using contingency tables.

All hypothesis testing was two-tailed, with $p<0.05$ considered statistically significant. Multicolinearity and assumptions required for running the logistic regression were verified. Multivariable analysis was conducted using stepwise binary logistic regression with variables exhibiting a significance threshold $p<0.20$ included in the modelling procedure.

Results

Over a 3-year period, overall 533 consecutive patients were referred for CT-guided transthoracic procedures, 59 of whom were excluded from analysis. Of these, 40 did not exhibit parenchymal pulmonary lesions, four were admitted for coil localisation before surgery and 15 experienced a decrease in lesion size while waiting for biopsy (figure 1). Thus, the study concerned 474 consecutive patients who underwent TTLB. The characteristics of patients, lesions and biopsy procedures are summarised in table 1. The study population included 311 men and 163 women, with a mean age of 65.5 years (median 65 years, interquartile range (IQR) 57–73 years). The median (IQR) lesion diameter was 25 mm (15–40 mm). There were 198 lesions ⩽20 mm, with a median (IQR) 15 mm (12–17 mm) diameter and 276 lesions >20 mm, with a median (IQR) 38 mm (28–50.8 mm) diameter. Overall, 368 TTLBs were conducted as outpatient procedures (77.6% of all TTLBs; 155 (78.3%) for lesions ⩽20 mm and 213 (77.2%) for lesions >20 mm).

Diagnostic performance

Statistically, there were more conclusive biopsies in the >20 mm group *versus* ⩽20 mm group: 236 (85.5%) *versus* 140 (70.7%) conclusive biopsies along with 40 (14.5%) *versus* 58 (29.3%) diagnostic failures, respectively (p<0.001) (table 2).

Diagnostic failure was due to insufficient sampling with low assessable cell content in 14 (24.6%) and six (15.4%) patients in the >20 mm and ⩽20 mm groups, respectively. Two procedures in the ⩽20 mm group were stopped prematurely because of pneumothorax. 11 procedures were nonconclusive due to target failure. Another TTLB was performed in both patients a few days later, which ultimately revealed malignancies (figure 1).

For nonconclusive TTLBs, final diagnosis was based on surgical resection (n=17, 29.3% and n=10, 25% for nodules ⩽20 mm and >20 mm, respectively), clinical and radiological follow-up (n=13, 22.4% and n=10, 25%, respectively), other techniques (n=10, 17.2% and n=5, 12.5%, respectively), or a second TTLB. Second TTLBs were performed in five initially nonconclusive TTLBs for nodules ⩽20 mm (four out of the five were finally conclusive) and eight initially nonconclusive TTLBs for nodules >20 mm (four out of the eight were finally conclusive) (figure 1).

Overall, 83 (17.5%) final diagnoses of benign lesions (n=43, 21.7% and n=40, 14.5%, for nodules ⩽20 mm and >20 mm, respectively) and 371 (78.3%) final diagnoses of malignant lesions were established (n=142, 71.7% and n=229, 83%, respectively), whereas 20 (4.2%) final diagnoses remained unknown (n=13, 6.6% and n=7, 2.5%, respectively) (figure 1).

There were no false-positives, but 21 and 16 nonconclusive TTLBs were ultimately proven malignant among ⩽20 mm and >20 mm lesions, respectively, constituting false-negatives (figure 1).

TTLB diagnostic performances according to lesion size are shown in table 2. TTLB overall accuracy, sensitivity, specificity and NPV for diagnosing malignant lesions were 88.4%, 84%, 100% and 70.1%,
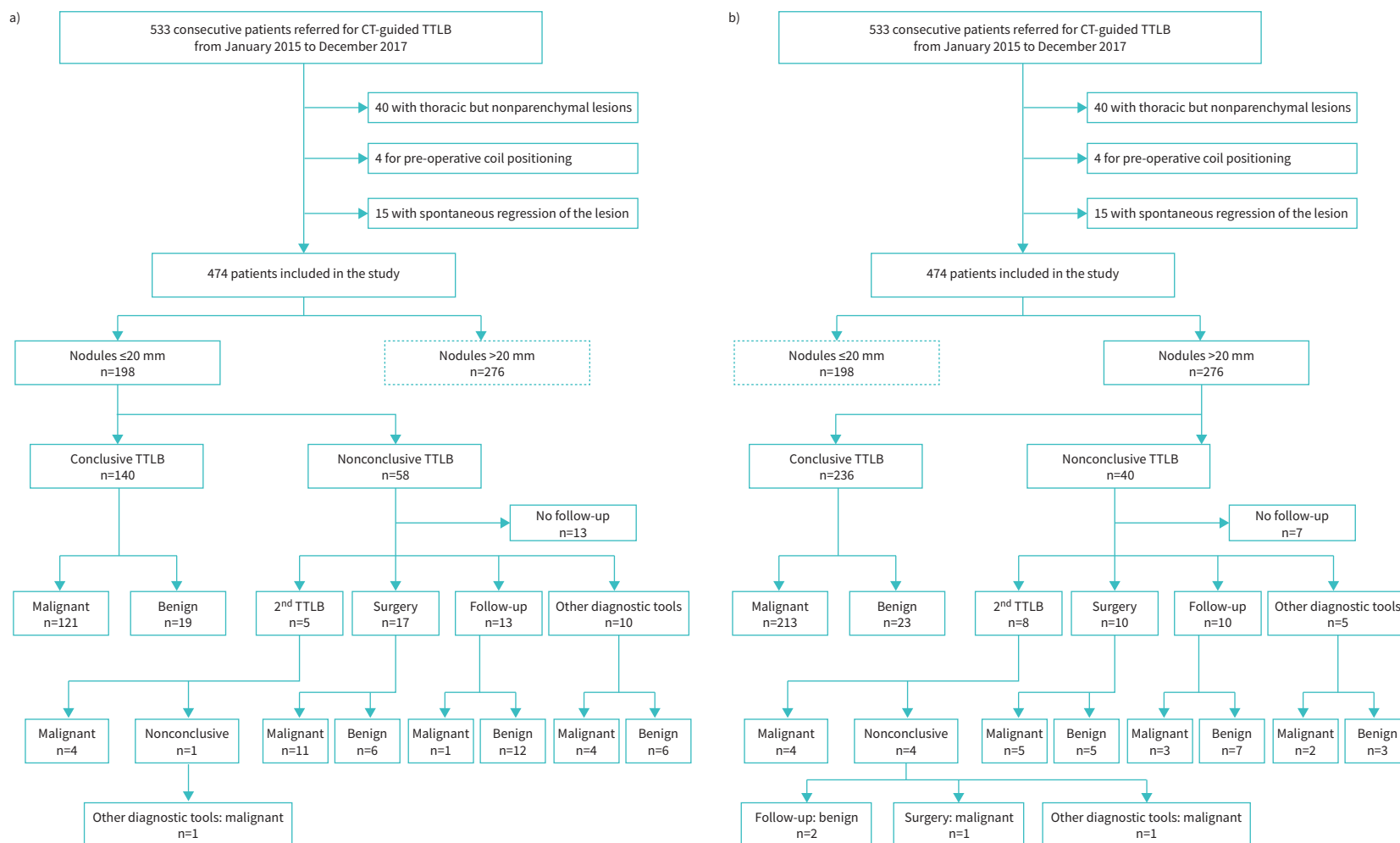
FIGURE 1 Patient disposition. a) Nodules ⩽20 mm; b) nodules >20 mm. CT: computed tomography; TTLB: transthoracic lung biopsy.

TABLE 1 Patient, lesion and procedure characteristics by nodule size

	Patients (data missing) (n)	All patients	Nodule size		p-value
			≤20 mm	>20 mm	
Patient variables					
Age (years)	474	65.5 (57.6–73.2)	63.9 (56.5–72.5)	66.3 (58.3–74.1)	0.177
Gender	474				0.081
Male		311 (65.6)	121 (61.1)	190 (68.8)	
Female		163 (34.4)	77 (38.9)	86 (31.2)	
PFT results	325 (149)				0.761
Normal		145 (44.6)	62 (43.7)	83 (45.4)	
Obstructive or restrictive		18 (55.4)	80 (56.3)	100 (54.6)	
Emphysema	474				0.515
Yes		200 (42.2)	87 (43.9)	113 (40.9)	
No		274 (57.8)	111 (56.1)	163 (59.1)	
Lesion variables					
TTLB indication	474				0.451
Suspicion of malignancy		423 (89.2)	181 (91.4)	242 (87.7)	
Suspicion of infection		29 (6.1)	10 (5.1)	19 (6.9)	
Re-biopsy		13 (2.7)	3 (1.5)	10 (3.6)	
Other		9 (1.9)	4 (2.0)	5 (1.8)	
Nodule size (mm)	474	25.0 (15.0–40.0)	15.0 (12.0–17.0)	38.0 (28.0–50.8)	$<10^{-12}$
Nodule location	474				0.712
RUL or LUL		261 (55.1)	111 (56.1)	150 (54.3)	
RML, RLL or LLL		213 (44.9)	87 (43.9)	126 (45.7)	
Contact with lung fissure	474				**<0.001**
Yes		90 (19)	23 (11.6)	67 (24.3)	
No		384 (81)	175 (88.4)	209 (75.7)	
Distance from entry point (mm)	474	11.0 (0–30.0)	17.0 (5.0–33.0)	0 (0–25.75)	$<10^{-7}$
≤20		305 (64.3)	111 (56.1)	194 (70.3)	**0.001**
>20		169 (35.7)	87 (43.9)	82 (29.7)	
Procedure variables					
Needle brand	430 (44)				$<10^{-4}$
Bard		183 (42.6)	90 (48.6)	93 (38.0)	
Tenor		161 (37.4)	47 (25.4)	114 (46.5)	
Cook-Quick core		77 (17.9)	45 (24.3)	32 (13.1)	
Argon		9 (2.1)	3 (1.6)	6 (2.4)	
Needle size	438 (38)				$<10^{-9}$
18G		121 (27.6)	25 (13.3)	96 (38.4)	
20G		317 (72.4)	163 (86.7)	154 (61.6)	
Needle-entry angle (°)	464 (10)				0.732
0–70 or 110–180		242 (52.2)	103 (53.1)	139 (51.5)	
71–109		222 (47.8)	91 (46.9)	131 (48.5)	
Number of pleura crossings	459 (15)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.724
Number of samples	392 (82)	3.0 (2.0–3.0)	2.0 (2.0–3.0)	3.0 (2.0–3.0)	$<10^{-5}$
<4		329 (83.9)	152 (90.5)	177 (79.0)	**0.002**
≥4		63 (16.1)	16 (9.5)	47 (21.0)	
Procedure duration (min)	466 (8)	11.3±7.3	12.3±7.3	10.5±7.2	$<10^{-5}$
≤10		261 (56.0)	99 (50.5)	162 (60.0)	**0.042**
>10		205 (44.0)	97 (49.5)	108 (40.0)	
Modality of hospital stay	474				0.775
Full-hospital		106 (22.4)	43 (21.7)	63 (22.8)	
Day-hospital		368 (77.6)	155 (78.3)	213 (77.2)	
Radiologist	462 (12)				**0.024**
Senior		395 (85.5)	176 (89.8)	219 (82.3)	
Junior		67 (14.5)	20 (10.2)	47 (17.7)	

Data are presented as median (interquartile range), n (%) or mean±SD, unless otherwise stated. Bold type represents statistical significance. PFT: pulmonary function testing; TTLB: transthoracic lung biopsy; RUL: right upper lobe; LUL: left upper lobe; RML: right middle lobe; RLL: right lower lobe; LLL: left lower lobe.

TABLE 2 Procedure conclusiveness, performance and complications					
	Patients (data missing) (n)	All patients	Nodule size		p-value
			≤20 mm	>20 mm	
Procedure conclusiveness					
Conclusive pathology results following one TTLB	474				**<10⁻⁴**
Yes		376 (79.3)	140 (70.7)	236 (85.5)	
No		98 (20.7)	58 (29.3)	40 (14.5)	
Diagnosis of malignancy in conclusive first TTLB	376				0.255
Yes		334 (88.8)	121 (86.4)	213 (90.3)	
No		42 (11.2)	19 (13.6)	23 (9.7)	
Performance for malignancy diagnosis following first TTLB					
Sensitivity/recall (%)		89.5	84.0	93.0	NA
Specificity/selectivity (%)		100	100	100	
Accuracy (%)		91.8	88.4	94.2	
PPV (%)		100	100	100	
NPV (%)		72.1	70.1	74.6	
F1 score (%)		94.5	91.3	96.4	
Complications					
PTX occurrence	474				**<10⁻⁵**
Yes		134 (28.3)	78 (39.4)	56 (20.3)	
No		340 (71.7)	120 (60.6)	220 (79.7)	
PTX requiring chest tube drainage	474				**0.023**
Yes		1 (6.5)	19 (9.6)	12 (4.3)	
No		443 (93.5)	179 (90.4)	264 (95.7)	
IAH occurrence	474				**<10⁻¹⁰**
Yes		123 (25.9)	81 (40.9)	42 (15.2)	
No		351 (74.1)	117 (59.1)	234 (84.8)	
Haemoptysis occurrence	461 (13)				**0.032**
Yes		20 (4.3)	13 (6.7)	7 (2.6)	
No		441 (95.7)	180 (93.3)	261 (97.4)	
Length of stay in patients planned as outpatient procedures (days)	368±6	2.3±6.4	1.9±2.6	2.6±0.6	0.054
Extended stay duration due to PTX in outpatient procedures	368 (6)				**0.002**
Yes		42 (11.4)	27 (17.4)	15 (7.0)	
No		326 (88.6)	128 (82.6)	198 (93.0)	

Data are presented as n (%) or mean±SD, unless otherwise stated. Bold type represents statistical significance. TTLB: transthoracic lung biopsy; PPV: positive predictive value/precision; NPV: negative predictive value; F1 score: harmonic mean of sensitivity and precision; PTX: pneumothorax; IAH: intra-alveolar haemorrhage; NA: not applicable.

respectively, for lesions ≤20 mm. The respective figures for lesions ≤20 mm when TTLB was repeated after diagnostic failure were 90.4%, 86.8%, 100% and 74% (supplementary table S1).

TTLB overall accuracy, sensitivity, specificity and NPV for diagnosing malignant lesions were 94.2%, 93%, 100% and 74.6%, respectively, for lesions >20 mm. The respective figures for lesions >20 mm when TTLB was repeated after diagnostic failure were 95.7%, 94.8%, 100% and 79.7% (supplementary table S1).

TTLB complications
Complications detailed according to lesion size are provided in table 2.

Pneumothorax (based on the CT and chest radiography data) was the most frequent complication, occurring in 78 (39.4%) and 56 (20.3%) patients with ≤20 mm and >20 mm lesions, respectively (p<0.001). Most of the pneumothoraces were asymptomatic (92 (69%) out of 134 asymptomatic pneumothorax). A chest tube was inserted in 31 (6.5%) TTLB procedures (n=19, 9.6% for ≤20 mm and n=12, 4.3% for >20 mm lesions; p=0.023). Only 19 pneumothoraces required immediate chest-tube insertion post-TTLB procedure in the radiology unit, because of dyspnoea and a >3 cm distance between lung and chest wall. There was no between-group difference in indication of immediate chest insertion according to nodule size (≤20 mm versus >20 mm). In 12 cases, the chest tube insertion was performed after the follow-up chest radiography the same day.

Statistically more intraparenchymal haemorrhages occurred for ⩽20 mm *versus* >20 mm lesions (n=81, 40.9% and n=42, 15.2%, respectively) (p<0.001).

Small-volume haemoptysis (<10 cm^3) occurred in 13 (6.7%) patients for ⩽20 mm and seven (2.6%) for >20 mm lesions (p=0.032). No large-volume haemoptysis required treatment, as all resolved spontaneously within hours, without further recurrence. No air embolism occurred.

Impact of TTLB complications on length of stay in outpatient procedures

Among the initially performed TTLBs as outpatient procedures, 42 patients (11.4% of all outpatient procedures) required full hospitalisation because of pneumothorax: 27 (64.3%) patients with ⩽20 mm and 15 (35.7%) with >20 mm lesions. Regardless of lesion size, 31 (73.8%) patients underwent chest tube drainage and 11 (26.2%) were admitted for clinical follow-up. The length of stay among these patients did not differ depending on lesion size. The mean stay length for patients requiring extended inpatient follow-up was 2 days for both groups (table 2).

Predictors of diagnostic failure

In multivariate analysis, only the chest radiologist's experience was significantly associated with diagnostic failure of first TTLB in ⩽20 mm lesion group (table 3). Conversely, needle size was the only predictor of diagnostic failure of first TTLB in >20 mm lesion group (table 4).

Predictors of pneumothorax requiring chest tube drainage

In multivariate analysis, the factors statistically associated with pneumothorax requiring chest tube drainage were emphysema and needle repositioning count of at least two in the ⩽20 mm lesion group (table 5). The distance from entry point to target or contact with lung fissure were the only predictors of such pneumothorax in >20 mm lesion group (table 6).

Discussion
Diagnostic performance

Although TTLB is a safe and accurate procedure, few studies have focused on TTLB diagnostic performance for small nodules (⩽20 mm), and even fewer have done it solely using core biopsies. Conversely, lung cancer CT screening has caused small-sized nodules to be increasingly detected.

Several previous studies have reported overall estimates of accuracy 78.8–99.3% [8–10, 14, 15], sensitivity 67.7–96.8% [10, 14, 15] and specificity 98.6–98.8% [10, 15]. Our study has estimated overall TTLB accuracy at 88.4% for ⩽20 mm nodules and 94.2% for >20 mm nodules, in line with previous reports on lower-size series, while such performance remains unknown in lung cancer screening settings. TTLB thus appears to be an accurate technique for small nodules, even though its accuracy is slightly lower for small *versus* larger nodules. Among the 198 biopsies of ⩽20 mm nodules, 19 initial biopsies (9.6% of nodules ⩽20 mm) enabled benign lesion diagnosis, thereby avoiding unnecessary surgery.

In our study, its diagnostic performance was increased when a second TTLB was performed following an initial nondiagnostic procedure (overall accuracy 90.4% for ⩽20 mm lesions *versus* 95.7% for >20 mm lesions).

Comparing these results with published data proves difficult, given that the number of biopsies was smaller in other publications than in ours, and that biopsy techniques often differed, as well (core biopsy, fine needle aspiration or both techniques combined). NG *et al*. [14] reported a 78.8% diagnostic accuracy, the lowest literature-reported rate, which can be explained by the use of fine needle aspiration in their series. Notably, CHOI *et al*. [10] reported that fine needle aspiration tended to be associated with diagnostic failure. In our study, the chest radiologist's experience was significantly associated with diagnostic failure for ⩽20 mm nodules, yet not for larger nodules. TTLB requires learning, training and experience, particularly as regards small nodules. Such a requirement for trained and experienced radiologists is paramount upon further implementing CT-scan lung cancer screening from clinical trial to real-life settings. Expertise is the crucial point. However, many techniques could be proposed to increase diagnostic performance: particularly the control of the needle deployed inside the nodule to check the site of the cutting part (which is feasible with semi-automatic biopsy needles) and the guidance according to respiration cycle with control of the needle always at the same time (generally expiration). Fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography CT could be helpful in this regard for necrotic tumours, to select a non-necrotic area for the biopsy.

TABLE 3 Predictors of diagnostic failure of first transthoracic lung biopsy for nodules ⩽20 mm

	Patients (missing data) (n)	Univariable analysis				Multivariable analysis	
		Procedure outcome		OR (95% CI)	p-value	aOR (95% CI)	p-value
		Conclusive	Nonconclusive				
Patient variables							
Age (years)	198						
⩽50 or ⩾75		43 (74.1)	15 (25.9)	1			
51–74		97 (69.3)	43 (30.7)	1.3 (0.6–2.5)	0.495		
Gender	198						
Male		91 (75.2)	30 (24.8)	1			
Female		49 (63.6)	28 (36.4)	1.7 (0.9–3.2)	0.083		
PFT results	142 (56)						
Normal		44 (71.0)	18 (29.0)	1			
Obstructive or restrictive		56 (70.0)	24 (30.0)	1.1 (0.5–2.2)	0.900		
Emphysema	198						
Yes		63 (72.4)	24 (27.6)	1			
No		77 (69.4)	34 (30.6)	1.2 (0.6–2.2)	0.640		
Lesion variables							
Location	198						
RML, RLL or LLL		63 (72.4)	24 (27.6)	1			
RUL or LUL		77 (69.4)	34 (30.6)	1.2 (0.6–2.2)	0.640		
Contact with lung fissure	198						
No		124 (70.9)	51 (29.1)	1			
Yes		16 (69.6)	7 (30.4)	1.1 (0.4–2.7)	0.898		
Distance from entry point (mm)	198						
>20		64 (73.6)	26 (26.4)	1			
⩽20		76 (68.5)	35 (31.5)	1.3 (0.7–2.4)	0.435		
Procedure variables							
Needle size	188 (10)						
18G		20 (80.0)	5 (20.0)	1			
20G		110 (67.5)	53 (32.5)	1.9 (0.7–5.4)	0.213		
Needle-entry angle (°)	194 (4)						
71–109		69 (75.8)	22 (24.2)	1			
0–70 or 110–180		69 (67.0)	34 (33.0)	1.5 (0.8–2.9)	0.177		
Needle repositioning count	192 (6)						
<2		118 (73.8)	42 (26.3)	1			
⩾2		19 (59.4)	13 (40.6)	1.9 (0.9–4.2)	0.104		
Number of pleura crossings	193 (5)						
⩾2		11 (73.3)	4 (26.7)	1			
1		127 (71.3)	51 (28.7)	1.1 (0.3–3.6)	0.870		
Number of samples	168 (30)						
<4		102 (67.1)	50 (32.9)	1			
⩾4		15 (93.8)	1 (6.3)	0.1 (0–1.1)	0.057		
Procedure duration (min)	196 (2)						
>10		69 (71.1)	28 (28.9)	1			
⩽10		69 (69.7)	30 (30.3)	1.1 (0.6–2.0)	0.826		
Radiologist	196 (2)						
Senior		129 (73.3)	47 (26.7)	1		1	
Junior		9 (45.0)	11 (55.0)	3.4 (1.3–8.6)	**0.012**	2.7 (1.0–7.3)	**0.045**

Data are presented as n (%), unless otherwise stated. Bold type represents statistical significance. aOR: adjusted odds ratio; PFT: pulmonary function testing; RML: right middle lobe; RLL: right lower lobe; LLL: left lower lobe; RUL: right upper lobe; LUL: left upper lobe.

Complications
Pneumothorax

In their meta-analysis, HEERINK *et al.* [5] reported a statistically different overall complication rate of 38.8% for core biopsy *versus* 24% for fine needle aspiration, along with major complication rates of 5.7% and 4.4%, respectively. These authors did not identify significant risk factors for complications when using core biopsy. In our study, only core biopsy was used. We identified emphysema and the at least two instances of need for needle repositioning count as significantly associated with pneumothorax requiring

TABLE 4 Predictors of diagnostic failure of first transthoracic lung biopsy for nodules >20 mm

	Patients (missing data) (n)	Univariable analysis				Multivariable analysis	
		Procedure outcome		OR (95% CI)	p-value	aOR (95% CI)	p-value
		Conclusive	Nonconclusive				
Patient variables							
Age (years)	276						
51–74		156 (86.7)	24 (13.3)	1			
⩽50 or ⩾75		80 (83.3)	16 (16.7)	1.3 (0.7–2.6)	0.455		
Gender	276						
Male		164 (86.3)	26 (13.7)	1			
Female		72 (83.7)	14 (16.3)	1.2 (0.6–2.5)	0.571		
PFT results	183 (93)						
Obstructive or restrictive		85 (85.0)	15 (15.0)	1			
Normal		69 (83.1)	14 (16.9)	1.2 (0.5–2.5)	0.731		
Emphysema	276						
No		141 (86.5)	22 (13.5)	1			
Yes		95 (84.1)	18 (15.9)	1.2 (0.6–2.4)	0.573		
Lesion variables							
Location	276						
RUL or LUL		133 (88.7)	17 (11.3)	1		1	
RML, RLL or LLL		103 (81.7)	23 (18.3)	1.7 (0.9–3.4)	0.107	2.0 (0.9–4.3)	0.072
Contact with a lung fissure	276						
Yes		58 (86.6)	9 (13.4)	1			
No		178 (85.2)	31 (14.8)	1.1 (0.5–2.5)	0.777		
Distance from entry point (mm)	276						
>20		75 (91.5)	7 (8.5)	1		1	
⩽20		161 (83.0)	33 (17.0)	2.2 (0.9–5.2)	0.073	2.4 (1.0–5.9)	0.059
Procedure variables							
Needle size	250 (26)						
18G		88 (91.7)	8 (8.3)	1		1	
20G		127 (82.5)	27 (17.5)	2.3 (1.01–5.4)	**0.046**	2.6 (1.1–6.1)	**0.033**
Needle-entry angle (°)	270 (6)						
71–109		119 (90.8)	12 (9.2)	1			
0–70 or 110–180		112 (80.6)	27 (19.4)	2.4 (1.2–4.9)	**0.019**		
Needle repositioning count	265 (11)						
<2		210 (86.4)	33 (13.6)	1			
⩾2		19 (86.4)	3 (13.6)	1.01 (0.3–3.6)	0.994		
Number of pleura crossings	266 (10)						
⩾2		16 (88.9)	2 (11.1)	1			
1		213 (85.9)	35 (14.1)	1.3 (0.3–6.0)	0.723		
Number of samples	224 (52)						
<4		153 (86.4)	24 (13.6)	1			
⩾4		40 (85.1)	7 (14.9)	1.1 (0.4–2.8)	0.814		
Procedure duration (min)	270 (26)						
>10		94 (87.0)	14 (13.0)	1			
⩽10		138 (85.2)	24 (14.8)	1.2 (0.6–2.4)	0.668		
Radiologist	266 (10)						
Senior		189 (86.3)	30 (13.7)	1			
Junior		38 (80.9)	9 (19.1)	1.5 0.7–3.4	0.340		

Data are presented as n (%), unless otherwise stated. Bold type represents statistical significance. aOR: adjusted odds ratio; PFT: pulmonary function testing; RUL: right upper lobe; LUL: left upper lobe; RML: right middle lobe; RLL: right lower lobe; LLL: left lower lobe.

chest tube drainage for ⩽20 mm nodules. Conversely, the only factor identified for >20 mm nodules was the distance from entry point to target. Many techniques have been proposed to decrease the rate of pneumothorax before (needle track/approach) and during the procedure (blood patch, three instances of withdrawal, removal of the needle during expiration and rapid needle-out patient-rollover time approach defined as the time between removal of the biopsy needle and placing the patient biopsy-side down). Recently, NAJAFI et al. [18] reported the PEARL approach showing that such a method significantly

TABLE 5 Predictors of pneumothorax (PTX) requiring chest tube drainage following transthoracic lung biopsy for nodules ⩽20 mm

	Patients (missing data) (n)	Univariable analysis				Multivariable analysis	
		PTX requiring chest tube drainage		OR (95% CI)	p-value	aOR (95% CI)	p-value
		No	Yes				
Patient variables							
Age groups (years)	198						
⩽50 or ⩾75		57 (98.3)	1 (1.7)	1		1	
51–74		122 (87.1)	18 (12.9)	8.4 (1.1–64.6)	**0.041**	7.7 (1.0–60.6)	0.054
Gender	198						
Female		72 (93.5)	5 (6.5)	1			
Male		107 (88.4)	14 (11.6)	1.9 (0.7–5.5)	0.243		
PFT results	142 (56)						
Normal		58 (93.5)	4 (6.5)	1			
Obstructive or restrictive		69 (86.3)	11 (13.8)	2.3 (0.7–7.6)	0.170		
Emphysema	198						
No		106 (95.5)	5 (4.5)	1		1	
Yes		73 (83.9)	14 (16.1)	4.1 (1.4–11.8)	**0.010**	3.3 (1.1–10.0)	**0.034**
Lesion variables							
Location	198						
RML, RLL or LLL		81 (93.1)	6 (6.9)	1			
RUL or LUL		98 (88.3)	13 (11.7)	1.8 (0.7–4.9)	0.259		
Contact with a lung fissure	198						
Yes		23 (100)	0 (0)	1			
No		156 (89.1)	19 (10.9)	1.1 (1.0–1.2)	0.136		
Distance from entry point (mm)	198						
⩽20		104 (93.7)	7 (6.3)	1			
>20		75 (86.2)	12 (13.8)	2.4 (0.9–6.3)	0.083		
Procedure variables							
Needle size	188 (10)						
18G		24 (96.0)	1 (4.0)	1			
20G		148 (90.8)	15 (9.2)	2.4 (0.3–19.3)	0.400		
Needle-entry angle (°)	194 (4)						
71–109		83 (91.2)	8 (8.8)	1			
0–70 or 110–180		92 (89.3)	11 (10.7)	1.2 (0.5–3.2)	0.659		
Needle repositioning count	192 (6)						
<2		149 (93.1)	11 (6.9)	1		1	
⩾2		25 (78.1)	7 (21.9)	3.8 (1.3–10.7)	**0.012**	3.4 (1.6–10.2)	**0.026**
Number of pleura crossings	193 (5)						
1		162 (91.0)	16 (9.0)	1			
⩾2		12 (80.0)	3 (20.0)	2.5 (0.6–9.9)	0.183		
Number of samples	168 (30)						
<4		141 (92.8)	11 (7.2)	1			
⩾4		13 (81.3)	3 (18.8)	3.0 (0.7–12.0)	0.128		
Procedure duration (min)	196 (2)						
⩽10		92 (92.9)	7 (7.1)	1			
>10		86 (88.7)	11 (11.3)	1.7 (0.6–4.5)	0.305		
Radiologist	196 (2)						
Senior		159 (90.3)	17 (9.7)	1			
Junior		18 (90.0)	2 (10.0)	1.0 (0.2–4.9)	0.961		

Data are presented as n (%), unless otherwise stated. Bold type represents statistical significance. aOR: adjusted odds ratio; PFT: pulmonary function testing; RML: right middle lobe; RLL: right lower lobe; LLL: left lower lobe; RUL: right upper lobe; LUL: left upper lobe.

reduced the frequency of pneumothorax requiring drainage. The PEARL approach combines patient positioning biopsy-side down, needle removal during expiration, autologous blood patch sealing, rapid rollover and pleural patching.

Few studies have focused on TTLB complications in the event of small nodules, especially in lung cancer CT-screening settings. The TTLB-associated pneumothorax rate we observed was 39.4% for ⩽20 mm and

TABLE 6 Predictors of pneumothorax (PTX) requiring chest tube drainage following transthoracic lung biopsy for nodules >20 mm

	Patients (missing data) (n)	Univariable analysis			Multivariable analysis	
		PTX requiring chest tube drainage		OR (95% CI)	p-value	aOR (95% CI)	p-value
		No	Yes				
Patient variables							
Age groups (years)	276						
⩽50 or ⩾75		92 (95.8)	4 (4.2)	1			
51–74		172 (95.6)	8 (4.4)	1.1 (0.3–3.6)	0.914		
Gender	276						
Female		83 (96.5)	3 (3.5)	1			
Male		181 (95.3)	9 (4.7)	1.4 (0.4–5.2)	0.639		
PFT results	183 (93)						
Obstructive or restrictive		96 (96.0)	4 (4.0)	1			
Normal		77 (92.8)	6 (7.2)	1.9 (0.5–6.9)	0.345		
Emphysema	276						
No		158 (96.9)	5 (3.1)	1			
Yes		106 (93.8)	7 (6.2)	2.1 (0.6–6.7)	0.219		
Lesion variables							
Location	276						
RUL or LUL		144 (96.0)	6 (4.0)	1			
RML, RLL or LLL		120 (95.2)	6 (4.8)	1.2 (0.4–3.8)	0.757		
Contact with lung fissure	276						
No		202 (96.7)	7 (3.3)	1		1	
Yes		62 (92.5)	5 (7.5)	2.3 (0.7–7.6)	0.161	3.6 (0.9–13.4)	0.060
Distance from entry point (mm)	276						
⩽20		190 (97.9)	4 (2.1)	1		1	
>20		74 (90.2)	8 (9.8)	5.1 (1.5–17.6)	**0.009**	9.7 (2.0–47.1)	**0.005**
Procedure variables							
Needle size	250 (26)						
18G		95 (99.0)	1 (1.0)	1			
20G		145 (94.2)	9 (5.8)	5.9 (0.7–47.3)	0.095		
Needle-entry angle (°)	270 (6)						
71–109		128 (97.7)	3 (2.3)	1			
0–70 or 110–180		131 (94.2)	8 (5.8)	2.6 (0.7–10.0)	0.164		
Needle repositioning count	265 (11)						
⩾2		22 (100)	0 (0)	1			
<2		232 (95.5)	11 (4.5)	1.1 (1.0–1.1)	0.607		
Number of pleura crossings	266 (10)						
1		239 (96.4)	9 (3.6)	1			
⩾2		16 (88.9)	2 (11.1)	3.3 (0.7–16.7)	0.145		
Number of samples	224 (52)						
⩾4		45 (95.7)	2 (4.3)	1			
<4		169 (95.5)	8 (4.5)	1.1 (0.2–5.2)	0.938		
Procedure duration (min)	270 (6)						
⩽10		158 (97.5)	4 (2.5)	1			
>10		101 (93.5)	7 (6.5)	2.7 (0.8–9.6)	0.115		
Radiologist	266 (10)						
Junior		45 (95.7)	2 (4.3)	1			
Senior		209 (95.4)	10 (4.6)	1.1 (0.2–5.1)	0.926		

Data are presented as n (%), unless otherwise stated. Bold type represents statistical significance. aOR: adjusted odds ratio; PFT: pulmonary function testing; RUL: right upper lobe; LUL: left upper lobe; RML: right middle lobe; RLL: right lower lobe; LLL: left lower lobe.

20.3% for >20 mm lesions (p<0.001). These figures align with previously reported rates [5, 15] Although core biopsies have been associated with a higher risk of pneumothorax [19], our current study shows that the actually observed cases were indeed manageable, rarely requiring chest-tube insertion (9.6% for ⩽20 mm and 4.3% for all biopsies). Our TTLBs were mostly performed in outpatient procedures. Only 27 (17.4%) patients had an extended hospitalisation stay due to pneumothorax occurring upon TTLBs of ⩽20 mm lesions, which further supports the safety of the procedure. There is variation management of

pneumothorax in clinical practice and significant differences in international guidelines. However, manual aspiration should be preferred over chest tube drainage and hospitalisation. An alternative is a Heimlich valve for chest drainage to maintain outpatient care.

Intrapulmonary haemorrhage and haemoptysis

Intrapulmonary haemorrhage, mostly asymptomatic, occurred in 40.9% and 15.2% of ≤20 mm and >20 mm lesions, respectively (p<0.001), which aligns with the meta-analysis by HEERINK et al. [5] and the study by TAI et al. [20].

Low-volume haemoptysis occurred in 6.7% and 2.6% of ≤20 mm and >20 mm lesions, respectively (nonsignificant), in line with previous studies [5, 8]. Since they resolved spontaneously without respiratory impairment, neither oxygen supply nor arterio-embolisation procedures were needed.

A large retrospective study extrapolating complications rates of invasive diagnostic procedures for lung nodules, based on United States insurance databases, revealed a 4.0% TTLB rate for major complications and 13.6% and 13.9% rates for minor and intermediate complications, respectively, without mentioning technical issues or nodule sizes. This observation suggests that the patients from such databases probably exhibited larger nodules discovered due to respiratory symptoms as compared to high-risk asymptomatic individuals undergoing CT-screening programmes. Our study supports Huo et al.'s [4] data analysis. Indeed, despite a 39.4% pneumothorax rate and 6.7% small-volume haemoptysis rate, no death occurred, with only few patients requiring chest tube insertion (9.6%), only few requiring extended complication-related inpatient stay (17.4%) of short duration (mean 1.9 days). It must be stressed that the ≤20 mm nodule size considered in our series is precisely the size of nodules that are mostly detected in asymptomatic individuals undergoing CT screening.

Limitations

This study has several limitations. Data about inpatient duration stay were retrospective, which may be a source of bias. Yet, such bias may have been limited through a systematic review of the data from all consecutive patients who had undergone TTLB, which were included in the prospective database of interventional CT-scan procedures performed in our radiology department.

Our results should be interpreted cautiously, as they were dependent on technical facilities and local expertise. Indeed, our study was conducted in a tertiary teaching hospital with extensive thoracic expertise, which includes three pulmonology departments, one thoracic surgery department and a radiology department that specialises in thoracic interventional radiology. Overall, >150 TTLBs are performed each year.

This study's findings may not be applicable to areas with high incidence rates of tuberculosis or histoplasmosis, because most patients referred to perform TTLB in our study were Caucasian and living in the Greater Paris area. Yet, our population included a high percentage of patients originating from North Africa, where tuberculosis incidence is high.

In conclusion, although core TTLB displays a slightly lower diagnostic performance and higher complication rates for ≤20 mm lesions, it could still represent a method of choice for sampling ≤20 mm nodules. The reason for this is the increasing detection rates of such small nodules on account of lung cancer screening programmes. Indeed, TTLB was associated with a formal diagnosis in 70.7% of patients, avoiding surgery for 9.6% of them, with an acceptable rate of low-grade complications, mainly consisting of easily manageable pneumothorax.

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