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Early View

Original research article

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Please cite this article as: Lissavalid E, Khalil A, Soussi G, *et al*. Transthoracic lung biopsy for pulmonary nodules ≤20mm in the routine clinical care. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00562-2021).

Transthoracic Lung Biopsy for Pulmonary Nodules ≤20mm in the routine clinical care

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CONFLICTS OF INTEREST:

Emilie Lissavalid, Antoine Khalil, and Ghassen Soussi report no conflicts of interest. Marie-Pierre Debray reports personal fees and non-financial support from Boehringer Ingelheim, Roche, Boston Scientific, all outside the submitted work. Alice Guyard reports personal fees from Diaceutics, all outside the submitted work. Vincent Bunel reports no conflicts of interest. Raphael Borie reports grants and personal fees from Roche, Boerhinger Ingelheim, and Sanofi, all outside the submitted work. Pierre Mordant reports no conflicts of interest. Gérard Zalcman reports personal fees from BMS, MSD, and Boehringer; non-financial support and other from Roche and Astra-Zeneca, as well as other from Abbvie, all outside the submitted work. Valérie Gounant reports personal fees from MSD, Chugai, Novartis, and Boehringer; personal fees and non-financial support from Astra Zeneca, BMS, Takeda, and Pfizer; grants, personal fees, and non-financial support from Roche, all outside the submitted work. Aurélie Cazes reports personal fees from AstraZeneca, Boehringer, and Roche, all outside the submitted work.

FUNDING: None.

ABBREVIATIONS: CT = computed tomography; FNA = fine needle aspiration; IQR = interquartile range; NPV = negative predictive value; PPV = positive predictive value; TTLB = transthoracic lung biopsy

TAKE HOME MESSAGE

Lung cancer screening led to high rate of ≤20mm nodules discovery. Small nodules transthoracic biopsy had 84% sensitivity with 70% negative predictive for cancer diagnosis. 9.6% of pneumothorax needing chest tube insertion occurred. No death was observed.

Abstract

BACKGROUND: Computed tomography (CT) screening has improved lung cancer survival, yet increasingly detected small lung lesions. The number of transthoracic lung biopsies (TTLB) for small nodules is thus expected to rise significantly.

RESEARCH QUESTION: To evaluate the diagnostic accuracy and safety of CT-guided TTLB for nodules ≤20mm versus nodules >20mm.

STUDY DESIGN AND METHODS: Data for CT-guided TTLBs from 474 consecutive patients were prospectively collected over a 3-year period (198 lesions ≤20mm and 276 lesions >20mm) in a teaching hospital and analysed in terms of diagnostic performance and complications.

RESULTS: There were more conclusive biopsies in the >20mm lesion group (n=236; 85.5%) than in ≤20mm 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% for ≤20mm lesions and 94.2%, 93%, 100%, and 74.6% for >20mm lesions, respectively. Pneumothorax requiring drainage was significantly more common for ≤20mm lesions, compared to TTLB of larger lesions (9.6% *vs.* 4.3%; p=0.02). Prolonged hospital stay due to pneumothorax occurred in 27 (17.4%) TTLBs of ≤20mm lesions and 15 (7%) TTLBs of >20mm lesions (p=0.002). There were no deaths. The only variable significantly associated with diagnostic failure in the ≤20mm lesion group was the radiologist's experience.

INTERPRETATION: TTLBs for lesions ≤20mm 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 in a curative intent. Recent studies have revealed that lung cancer computed tomography (CT) screening in populations at high risk for 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 vs. 13.5% in control groups [3]).

In direct relation to CT screening, an increasing number of small lesions detected require histological confirmation. The number of transthoracic lung biopsies (TTLB) for small nodules (≤20mm) is thus expected to rise significantly, although the invasive procedure rate remained low (1.2%) in the randomized 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 (US) insurance databases reported a 22.2% complication rate for individuals aged 55 to 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 & Encounters database captured data on invasive diagnostic

procedures performed in 2008-2013. Nevertheless, CT-guided TTLB has significantly evolved over the last 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 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 (<20mm). 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 ≤20mm versus those >20mm, 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 in University Hospital Bichat-Claude Bernard, Paris, France, from January 2015 to December 2017. Data about inpatient duration stay were retrospectively collected from computed patients 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 greater than 10 mm (more than 500 mm^3) and nodules with a volume-doubling time less than 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 preoperative diagnosis of cancer, before the lung resection. Pure ground glass nodules were not biopsied by TTLB. Only GGO with features of consolidation exceeding 10 mm large during follow-up, were operated, with or without preoperative TTLB, according to estimated risk of the procedure by the seniors 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 hospitalized in an in-patient hospitalization unit at the time of the TTLB is performed. Antivitamin K or new oral anticoagulants were replaced by low molecular weight Heparin at least 7 days before the procedure, and LMWH was suspended for at least 12 hours. Anti-agregant therapy was interrupted at least 5 days before the procedure whenever possible, after a systematic cardiologist advice. According to most international recommendations, patients were not asked to discontinue low-dose ASA.

All procedures were performed by one of six chest radiologists, including two seniors with >10-year experience in CT-guided biopsies, and four juniors. The junior radiologist, having obtained a supervised training with more than 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 minutes after last puncture to detect complications (pneumothorax, intra-alveolar haemorrhage, or air embolism).

Standardized Operating Protocol regarding complications management

If a pneumothorax was detected in an asymptomatic patient with a <3cm distance between lung and chest wall, another whole-lung CT was performed 10 minutes 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 hospitalized for 24- to 36-hour monitoring. We attempted to remove the chest tube 24 hours post-TTLB, carrying out a control chest X-ray to ascertain lung re-expansion. In all cases, chest X-rays were performed 5 hours 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 X-Ray, seven days later.

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

Primary Endpoint: Diagnostic Performance and Diagnostic Outcomes

The pathological results were classified according to two lesion size groups: ≤20mm and >20mm. 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 extra-pulmonary lesion biopsy), clinical and radiological follow-up, or second TTLB.

Lesions with one of the following characteristics were defined malignant: (1) malignant surgical pathology; (2) malignant CT-guided biopsy pathology; (3) enlarged lesion with distant organ or lymph node metastasis during follow-up. Lesions with one of the following characteristics was defined benign: (1) benign surgical pathology; (2) significantly smaller or lesions disappearing on follow-up, without treatment; (3) specific benign diagnosis (tuberculosis, fungal infection, and organizing pneumonia) confirmed by biopsy pathology with marked improvement after targeted treatment; (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 Endpoint: 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 haemorrhaging, and air embolisms were analysed using CT images. Pulmonary haemorrhaging 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 that occurring in patients with pulmonary dysfunction (chronic obstructive

pulmonary disease [COPD]; lung fibrosis), though asymptomatic, a large (one pulmonary segment or more) CT-revealed haemorrhage or haemoptysis $\geq 10cm^3$ (total volume emitted once or on repeated times) occurring within one post-procedural hour. The impact of TTLB-induced pneumothorax on hospitalization 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 Corp., Armonk, N.Y., USA). TTLB diagnostic performance in each group was determined in terms of sensitivity (recall), specificity (selectivity), accuracy, positive predictive value (PPV), 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 Student's t-test (two independent samples) for continuous variables (or Mann-Whitney U test if not applicable or when comparing medians). Odds ratios (OR) and their respective 95% confidence intervals (95% CI) were calculated using contingency tables.

All hypothesis testing was two-tailed, with p values <0.05 considered statistically significant. Multicollinearity 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 trans-thoracic procedures, 59 of whom were excluded from analysis. Of these, 40 did not exhibit parenchymal pulmonary lesions, four were admitted for coil localization before surgery, and 15 experienced a decrease in lesion size while waiting for biopsy (Figure 1). The study thus concerned 474 consecutive patients that underwent TTLB. The characteristics of patients, lesions, and biopsy procedures are summarized in Table 1. The study population included 311 men and 163 women, with a mean age of 65.5 years (median: 65, interquartile range [IQR]: 57–73). The median lesion diameter was 25mm, (IQR: 15–40mm). There were 198 lesions ≤20mm, with a median 15mm (IQR: 12–17mm) diameter and 276 lesions >20mm, with a median 38mm (IQR: 28–50.8mm) diameter. Overall, 368 TTLBs were conducted as outpatient procedures (77.6% of all TTLBs; 155 [78.3%] for lesions ≤20mm and 213 [77.2%] for lesions >20mm).

Diagnostic Performances

Statistically, there were more conclusive biopsies in the >20mm group versus ≤20mm groups: 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 6 [15.4%], patients in >20mm and ≤20mm groups, respectively. Two

procedures in ≤20mm group were stopped prematurely because of pneumothorax. Eleven procedures were non-conclusive due to target failure. Another TTLB was performed in both patients a few days later, which ultimately revealed malignancies (Figure 1).

For non-conclusive TTLBs, final diagnosis was based on surgical resection (17 [29.3%] for nodules ≤20mm; 10 [25%] for nodules >20mm), clinical and radiological follow-up (13 [22.4%]; 10 [25%], respectively), other techniques (10 [17.2%]; 5 [12.5%], respectively), or a second TTLB. Second TTLBs were performed in five at first non-conclusive TTLBs for nodules ≤20mm (4/5 were contributory) and eight at first non-conclusive TTLBs for nodules >20mm (4/8 were contributory) (Figure 1).

Overall, 83 (17.5%) final diagnoses of benign lesions (43 [21.7%]; 40 [14.5%], respectively) and 371 (78.3%) final diagnoses of malignant lesions were established (142 [71.7%]; 229 [83%], respectively), whereas 20 (4.2%) final diagnoses remained unknown (13 [6.6%]; 7 [2.5%], respectively) (Figure 1).

There were no false-positives, but 21 and 16 non-conclusive TTLBs were ultimately proven malignant among ≤20mm and >20mm 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%, respectively, for lesions ≤20mm. The respective figures for lesions ≤20mm when TTLB was repeated after diagnostic failure were 90.4%, 86.8%, 100%, and 74% (Supplementary Table 1).

TTLB overall accuracy, sensitivity, specificity, and NPV for diagnosing malignant lesions were 94.2%, 93%, 100%, and 74.6%, respectively, for lesions >20mm. The respective

figures for lesions >20mm when TTLB was repeated after diagnostic failure were 95.7%, 94.8%, 100%, and 79.7% (Supplementary Table 1).

TTLB Complications

Complications detailed according to lesion size are provided in Table 2.

Pneumothorax (based on the CT and chest X-rays data) was the most frequent complication, occurring in 78 (39.4%) and 56 (20.3%) patients with ≤20mm and >20mm lesions, respectively (p <0.001). Most of the pneumothorax was asymptomatic (92 asymptomatic pneumothorax/134 pneumothorax (69%)). A chest tube was inserted in 31 (6.5%) TTLB procedures (19 [9.6%] for ≤20mm and 12 [4.3%] for >20mm lesions; p=0.023). Only 19 pneumothorax required immediate chest-tube insertion post-TTLB procedure in the radiology unit, because of dyspnea and a > 3cm distance between lung and chest wall. There was not between-group difference in indication of immediate chest insertion according to nodule size (*≤20mm versus >20mm)*. In 12 cases, the chest tube insertion was performed after the follow-up Chest X-Ray the same day.

Statistically more intra-parenchymal haemorrhages occurred for ≤20mm versus >20mm lesions (81 [40.9%]); 42 [15.2%], respectively) (p<0.001).

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

TTLB Complications' Impact on Stay Length in Outpatient Procedures

Among the initially performed TTLBs as outpatient procedures, 42 patients (11.4% of all outpatient procedures) required full hospitalization because of pneumothorax: 27

(64.3%) patients with ≤20mm and 15 (35.7%) with >20mm 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 in-patient 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 ≤20mm lesion group (Table 3A). Conversely, needle size was the only predictor of diagnostic failure of first TTLB in >20mm lesion group (Table 3B).

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 need count ≥2 in ≤20mm lesion group (Table 4A). The distance from entry point to target or contact with lung fissure were the only predictors of such pneumothorax in >20mm lesion group (Table 4B).

Discussion

Diagnostic Performances

Although TTLB is a safe and accurate procedure, only few studies have focused on TTLB diagnostic performance for small nodules (≤20mm), 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 between 78.8%–99.3% [8–10, 14, 15], sensitivity between 67.7%–96.8% [10, 14, 15], and specificity between 98.6%–98.8% [10, 15]. Our study has estimated overall TTLB accuracy at 88.4% for ≤20mm and 94.2% for >20mm 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 ≤20mm nodules, 19 initial biopsies (9.6% of nodules ≤20mm) 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 non-diagnostic procedure (overall accuracy: 90.4% for ≤20mm versus 95.7% for >20mm 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, FNA, or both techniques combined). Ng et al. [14] reported a 78.8% diagnostic accuracy, the lowest literature-reported rate, which can be explained by their series' FNA use. Notably, Choi et al. [10] reported FNA tended to be

associated with diagnostic failure. In our study, the chest radiologist's experience was significantly associated with diagnostic failure for ≤20mm nodules, yet not for larger nodules. TTLB actually requires learning, training, and experience, particularly as regards small nodules. Such 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 performances: 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). ^{18}F-FDG PET/CT could be helpful in this regard for necrotic tumors to select a non-necrotic area for the biopsy.

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 FNA, 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 need for needle repositioning count ≥2 as significantly associated with pneumothorax requiring chest tube drainage for ≤20mm nodules. Conversely, the only factor identified for >20mm 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, 3 times 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 A, et al report the PEARL approach showing such method significantly reduced the frequency of pneumothorax requiring drainage [18]. The PEARL approach combines patient positioning biopsy-side down, needle removal during expiration, autologous blood patch sealing, rapid rollover, and pleural patching.

Only 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 ≤20mm and 20.3% for >20mm 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 ≤20mm and 4.3% for all biopsies). Our TTLBs were mostly performed in outpatient procedures. Only 27 (17.4%) patients had an extended hospitalization stay due to pneumothorax occurring upon TTLBs of ≤20mm lesions, which further supports the procedure's safety. There is variation in clinical practice about management of pneumothorax and significant differences in international guidelines. However, manual aspiration should be preferred over chest tube drainage and hospitalization. An alternative is an 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 ≤20mm and >20mm lesions, respectively ($p<0.001$), which aligns with Heerink et al meta-analysis [5] and Tai et al study [20].

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

A large retrospective study extrapolating complications rates of invasive diagnostic procedures for lung nodules, based on U.S. 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 likely suggests that the patients from such databases likely exhibited larger nodules discovered due to respiratory symptoms as compared to high-risk asymptomatic individuals undergoing CT-screening programs. Our study supports Huo's 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 nodule size ≤20mm 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 specializes in thoracic interventional radiology. Overall, more than 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 Greater Paris area. Yet, our population comprised 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 ≤20mm lesions, it could still represent a method of choice for sampling ≤20mm nodules. The reason for this is the increasing detection rates of such small nodules on account of lung cancer screening programs. 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.

Acknowledgements Not applicable

Author contributions:

EL, AK, GZ, and VG: conceptualization, data curation, investigation, methodology, project administration, supervision, validation, and writing.

GS: methodology, formal analysis, data curation, writing - review & editing

MPD, AG, VBG, RB, PM, and AC: investigation.

All authors have read and approved the final manuscript.

Table 1 - Patient, lesion, and procedure characteristics by nodule size

Variables	N (data missing)	All patients	Nodule size		P
			≤20 mm	>20 mm	
Patient variables					
Age (years) Median (IQR)	474	65.5 (57.6-73.2)	63.9 (56.5-72.5)	66.3 (58.3-74.1)	0.177
Gender Male Female	474	311 (65.6) 163 (34.4)	121 (61.1) 77 (38.9)	190 (68.8) 86 (31.2)	0.081
PFT results Normal Obstructive or restrictive	325 (149 missing)	145 (44.6) 18 (55.4)	62 (43.7) 80 (56.3)	83 (45.4) 100 (54.6)	0.761
Emphysema Yes No	474	200 (42.2) 274 (57.8)	87 (43.9) 111 (56.1)	113 (40.9) 163 (59.1)	0.515
Lesion variables					
TTLB indication Suspicion of malignancy Suspicion of infection Re-biopsy Other	474	423 (89.2) 29 (6.1) 13 (2.7) 9 (1.9)	181 (91.4) 10 (5.1) 3 (1.5) 4 (2.0)	242 (87.7) 19 (6.9) 10 (3.6) 5 (1.8)	0.451
Nodule size (mm) Median (IQR)	474	25.0 (15.0-40.0)	15.0 (12.0-17.0)	38.0 (28.0-50.8)	**$< 10^{-12}$**
Nodule location RUL or LUL RML, RLL, or LLL	474	261 (55.1) 213 (44.9)	111 (56.1) 87 (43.9)	150 (54.3) 126 (45.7)	0.712
Contact with lung fissure Yes No	474	90 (19) 384 (81)	23 (11.6) 175 (88.4)	67 (24.3) 209 (75.7)	**< 0.001**
Distance from entry point (mm) Median (IQR)	474	11.0 (0-30.0)	17.0 (5.0-33.0)	0 (0-25.75)	**$< 10^{-7}$**
Distance from entry	474				

point (mm) ≤20 >20		305 (64.3) 169 (35.7)	111 (56.1) 87 (43.9)	194 (70.3) 82 (29.7)	**0.001**
Procedure variables					
Needle brand Bard Tenor Cook-Quick core Argon	430 (44 missing)	183 (42.6) 161 (37.4) 77 (17.9) 9 (2.1)	90 (48.6) 47 (25.4) 45 (24.3) 3 (1.6)	93 (38.0) 114 (46.5) 32 (13.1) 6 (2.4)	**< 10^{-4}**
Needle size 18G 20G	438 (38 missing)	121 (27.6) 317 (72.4)	25 (13.3) 163 (86.7)	96 (38.4) 154 (61.6)	**< 10^{-9}**
Needle-entry angle (degrees) 0-70 or 110-180 71-109	464 (10 missing)	242 (52.2) 222 (47.8)	103 (53.1) 91 (46.9)	139 (51.5) 131 (48.5)	0.732
Number of pleura crossings Median (IQR)	459 (15 missing)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.724
Number of samples Median (IQR)	392 (82 missing)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	3.0 (2.0-3.0)	**< 10^{-5}**
Number of samples <4 4+	392 (82 missing)	329 (83.9) 63 (16.1)	152 (90.5) 16 (9.5)	177 (79.0) 47 (21.0)	**0.002**
Procedure duration (min) Mean (SD)	466 (8 missing)	11.3 (7.3)	12.3 (7.3)	10.5 (7.2)	**< 10^{-5}**
Procedure duration (min) ≤10 >10	466 (8 missing)	261 (56.0) 205 (44.0)	99 (50.5) 97 (49.5)	162 (60.0) 108 (40.0)	**0.042**
Modality of hospital stay Full-hospital Day-hospital	474	106 (22.4) 368 (77.6)	43 (21.7) 155 (78.3)	63 (22.8) 213 (77.2)	0.775
Radiologist Senior	462 (12 missing)	395 (85.5)	176 (89.8)	219 (82.3)	**0.024**

Junior		67 (14.5)	20 (10.2)	47 (17.7)	

SD, standard deviation; IQR, interquartile range; 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; PTX, pneumothorax.

Table 2 – Procedure conclusiveness, performance and complications

Variable / Performance measure	N	All patients	Nodule size		P
			≤20 mm	>20 mm	
Procedure conclusiveness					
Conclusive pathology results following one TTLB Yes No	474	376 (79.3) 98 (20.7)	140 (70.7) 58 (29.3)	236 (85.5) 40 (14.5)	**$< 10^{-4}$**
Diagnosis of malignancy in conclusive first TTLB Yes No	376	334 (88.8) 42 (11.2)	121 (86.4) 19 (13.6)	213 (90.3) 23 (9.7)	0.255
Performance for malignancy diagnosis following first TTLB					
Se (%)		89.5	84.0	93.0	NA
Sp (%)		100	100	100	
Acc (%)		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 Yes No	474	134 (28.3) 340 (71.7)	78 (39.4) 120 (60.6)	56 (20.3) 220 (79.7)	**$< 10^{-5}$**
PTX requiring chest tube drainage Yes No	474	31 (6.5) 443 (93.5)	19 (9.6) 179 (90.4)	12 (4.3) 264 (95.7)	**0.023**
IAH occurrence Yes No	474	123 (25.9) 351 (74.1)	81 (40.9) 117 (59.1)	42 (15.2) 234 (84.8)	**$< 10^{-10}$**
Hemoptysis occurrence Yes	461 (13	20 (4.3)	13 (6.7)	7 (2.6)	**0.03**

No	missing)	441 (95.7)	180 (93.3)	261 (97.4)	**2**
Length of stay in patients planned as outpatient procedures (days) Mean (SD)	368 (6 missing)	2.3 (6.4)	1.9 (2.6)	2.6 (0.6)	0.054
Extended stay duration due to PTX in outpatient procedures Yes No	368 (6 missing)	42 (11.4) 326 (88.6)	27 (17.4) 128 (82.6)	15 (7.0) 198 (93.0)	**0.002**

TTLB, transthoracic lung biopsy; NA, not applicable; NS, not significant; Se, sensitivity / recall; Sp, specificity / selectivity; Acc, accuracy; PPV, positive predictive value / precision; NPV, negative predictive value; F1 score, harmonic mean of sensitivity and precision; PTX, pneumothorax; IAH, intra-alveolar hemorrhage.

Table 3A – Predictors of diagnostic failure of first TTLB for nodules ≤20mm

		Univariable analysis					Multivariable analysis		
		Procedure outcome							
Variables	N (missing data)	Conclusive	Non-conclusive	OR	95% CI	P	aOR	95% CI	P
Patient variables									
Age (years)									
≤50 or ≥75	198	43 (74.1)	15 (25.9)	1	-	-			
51-74		97 (69.3)	43 (30.7)	1.3	0.6-2.5	0.495			
Gender									
Male	198	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								
Normal	(56	44 (71.0)	18 (29.0)	1	-	-			
Obstructive or restrictive	missing)	56 (70.0)	24 (30.0)	1.1	0.5-2.2	0.900			
Emphysema									
Yes	198	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									
RML, RLL, or LLL	198	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	124 (70.9)	51 (29.1)	1	-	-			
No		16 (69.6)	7 (30.4)	1.1	0.4-2.7	0.898			
Yes									
Distance from entry point (mm)	198	64 (73.6)	26 (26.4)	1	-	-			
>20		76 (68.5)	35 (31.5)	1.3	0.7-2.4	0.435			
≤20									

Procedure variables									
Needle size 18G 20G	188 (10 missing)	20 (80.0) 110 (67.5)	5 (20.0) 53 (32.5)	1 1.9	- 0.7-5.4	- 0.213			
Needle-entry angle (degrees) 71-109 0-70 or 110-180	194 (4 missing)	69 (75.8) 69 (67.0)	22 (24.2) 34 (33.0)	1 1.5	- 0.8-2.9	- 0.177			
Needle repositioning count <2 2+	192 (6 missing)	118 (73.8) 19 (59.4)	42 (26.3) 13 (40.6)	1 1.9	- 0.9-4.2	- 0.104			
Number of pleura crossings 2+ 1	193 (5 missing)	11 (73.3) 127 (71.3)	4 (26.7) 51 (28.7)	1 1.1	- 0.3-3.6	- 0.870			
Number of samples <4 4+	168 (30 missing)	102 (67.1) 15 (93.8)	50 (32.9) 1 (6.3)	1 0.1	- 0-1.1	- 0.057			
Procedure duration (min) >10 ≤10	196 (2 missing)	69 (71.1) 69 (69.7)	28 (28.9) 30 (30.3)	1 1.1	- 0.6-2.0	- 0.826			
Radiologist Senior Junior	196 (2 missing)	129 (73.3) 9 (45.0)	47 (26.7) 11 (55.0)	1 3.4	- 1.3-8.6	- **0.012**	1 2.7	- 1.0-7.3	- **0.045**

TTLB, transthoracic lung biopsy; OR, odds ratio; 95% CI, 95% confidence interval; PFT, pulmonary function testing; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; PTX, pneumothorax.

Table 3B – Predictors of diagnostic failure of first TTLB for nodules >20mm

		Univariable analysis					Multivariable analysis		
		Procedure outcome							
Variables	**N** (missing data)	Conclusive	Non-conclusive	OR	95% CI	P	aOR	95% CI	P
Patient variables									
Age (years) 51-74 ≤50 or ≥75	276	156 (86.7) 80 (83.3)	24 (13.3) 16 (16.7)	1 1.3	- 0.7-2.6	- 0.455			
Gender Male Female	276	164 (86.3) 72 (83.7)	26 (13.7) 14 (16.3)	1 1.2	- 0.6-2.5	- 0.571			
PFT results Obstructive or restrictive Normal	183 (93 missing)	85 (85.0) 69 (83.1)	15 (15.0) 14 (16.9)	1 1.2	- 0.5-2.5	- 0.731			
Emphysema No Yes	276	141 (86.5) 95 (84.1)	22 (13.5) 18 (15.9)	1 1.2	- 0.6-2.4	- 0.573			
Lesion variables									
Location RUL or LUL RML, RLL or LLL	276	133 (88.7) 103 (81.7)	17 (11.3) 23 (18.3)	1 1.7	- 0.9-3.4	- 0.107	1 2.0	- 0.9-4.3	- 0.072
Contact with a lung fissure Yes No	276	58 (86.6) 178 (85.2)	9 (13.4) 31 (14.8)	1 1.1	- 0.5-2.5	- 0.777			
Distance from entry point (mm) >20 ≤20	276	75 (91.5) 161 (83.0)	7 (8.5) 33 (17.0)	1 2.2	- 0.9-5.2	- 0.073	1 2.4	- 1.0-5.9	- 0.059
Procedure variables									
Needle size	250								

18G 20G	(26 missing)	88 (91.7) 127 (82.5)	8 (8.3) 27 (17.5)	1 2.3	- 1.01-5.4	- **0.046**	1 2.6	- 1.1-6.1	- **0.033**
Needle-entry angle (degrees) 71-109 0-70 or 110-180	270 (6 missing)	119 (90.8) 112 (80.6)	12 (9.2) 27 (19.4)	1 2.4	- 1.2-4.9	- **0.019**			
Needle repositioning count <2 2+	265 (11 missing)	210 (86.4) 19 (86.4)	33 (13.6) 3 (13.6)	1 1.01	- 0.3-3.6	- 0.994			
Number of pleura crossings 2+ 1	266 (10 missing)	16 (88.9) 213 (85.9)	2 (11.1) 35 (14.1)	1 1.3	- 0.3-6.0	- 0.723			
Number of samples <4 4+	224 (52 missing)	153 (86.4) 40 (85.1)	24 (13.6) 7 (14.9)	1 1.1	- 0.4-2.8	- 0.814			
Procedure duration (min) >10 ≤10	270 (26 missing)	94 (87.0) 138 (85.2)	14 (13.0) 24 (14.8)	1 1.2	- 0.6-2.4	- 0.668			
Radiologist Senior Junior	266 (10 missing)	189 (86.3) 38 (80.9)	30 (13.7) 9 (19.1)	1 1.5	- 0.7-3.4	- 0.340			

TTLB, transthoracic lung biopsy; OR, odds ratio; 95% CI, 95% confidence interval; PFT, pulmonary function testing; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; PTX, pneumothorax.

Table 4A – Predictors of pneumothorax requiring chest tube drainage following TTLB for nodules ≤20mm

		Univariable analysis					Multivariable analysis		
		PTX requiring chest tube drainage		OR	95% CI	P	aOR	95% CI	P
Variables	**N** (missing data)`	No	Yes						
Patient variables									
Age groups (years) ≤50 or ≥75 51-74	198	57 (98.3) 122 (87.1)	1 (1.7) 18 (12.9)	1 8.4	- 1.1-64.6	- **0.041**	1 7.7	- 1.0-60.6	- 0.054
Gender Female Male	198	72 (93.5) 107 (88.4)	5 (6.5) 14 (11.6)	1 1.9	- 0.7-5.5	- 0.243			
PFT results Normal Obstructive or restrictive	142 (56 missing)	58 (93.5) 69 (86.3)	4 (6.5) 11 (13.8)	1 2.3	- 0.7-7.6	- 0.170			
Emphysema No Yes	198	106 (95.5) 73 (83.9)	5 (4.5) 14 (16.1)	1 4.1	- 1.4-11.8	- **0.010**	1 3.3	- 1.1-10.0	- **0.034**
Lesion variables									
Location RML, RLL, or LLL RUL or LUL	198	81 (93.1) 98 (88.3)	6 (6.9) 13 (11.7)	1 1.8	- 0.7-4.9	- 0.259			
Contact with a lung fissure Yes No	198	23 (100) 156 (89.1)	0 (0) 19 (10.9)	1 1.1	- 1.0-1.2	- 0.136			
Distance from entry point (mm) ≤20	198	104 (93.7) 75 (86.2)	7 (6.3) 12 (13.8)	1 2.4	- 0.9-6.3	- 0.083			

>20									
Procedure variables									
Needle size 18G 20G	188 (10 missin	24 (96.0) 148 (90.8)	1 (4.0) 15 (9.2)	1 2.4	- 0.3- 19.3	- 0.400			
Needle-entry angle (degrees) 71-109 0-70 or 110-180	194 (4 missing)	83 (91.2) 92 (89.3)	8 (8.8) 11 (10.7)	1 1.2	- 0.5-3.2	- 0.659			
Needle repositioning count <2 2+	192 (6 missing)	149 (93.1) 25 (78.1)	11 (6.9) 7 (21.9)	1 3.8	- 1.3- 10.7	- **0.012**	1 3.4	- 1.6- 10.2	- **0.026**
Number of pleura crossings 1 2+	193 (5 missing)	162 (91.0) 12 (80.0)	16 (9.0) 3 (20.0)	1 2.5	- 0.6-9.9	- 0.183			
Number of samples <4 4+	168 (30 missing)	141 (92.8) 13 (81.3)	11 (7.2) 3 (18.8)	1 3.0	- 0.7- 12.0	- 0.128			
Procedure duration (min) ≤10 >10	196 (2 missing)	92 (92.9) 86 (88.7)	7 (7.1) 11 (11.3)	1 1.7	- 0.6-4.5	- 0.305			
Radiologist Senior Junior	196 (2 missing)	159 (90.3) 18 (90.0)	17 (9.7) 2 (10.0)	1 1.0	- 0.2-4.9	- 0.961			

TTLB, transthoracic lung biopsy; PTX, pneumothorax; OR, odds ratio; 95% CI, 95% confidence interval; PFT, pulmonary function testing; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe.

Table 4B – Predictors of pneumothorax requiring chest tube drainage following TTLB for nodules >20mm

		Univariable analysis					Multivariable analysis		
		PTX requiring chest tube drainage							
Variables	**N** (missing data)	No	Yes	OR	95% CI	P	aOR	95% CI	P
Patient variables									
Age groups (years) ≤50 or ≥75 51-74	276	92 (95.8) 172 (95.6)	4 (4.2) 8 (4.4)	1 1.1	- 0.3-3.6	- 0.914			
Gender Female Male	276	83 (96.5) 181 (95.3)	3 (3.5) 9 (4.7)	1 1.4	- 0.4-5.2	- 0.639			
PFT results Obstructive or restrictive Normal	183 (93 missing)	96 (96.0) 77 (92.8)	4 (4.0) 6 (7.2)	1 1.9	- 0.5-6.9	- 0.345			
Emphysema No Yes	276	158 (96.9) 106 (93.8)	5 (3.1) 7 (6.2)	1 2.1	- 0.6-6.7	- 0.219			
Lesion variables									
Location RUL or LUL RML, RLL, or LLL	276	144 (96.0) 120 (95.2)	6 (4.0) 6 (4.8)	1 1.2	- 0.4-3.8	- 0.757			
Contact with lung fissure No Yes	276	202 (96.7) 62 (92.5)	7 (3.3) 5 (7.5)	1 2.3	- 0.7-7.6	- 0.161	1 3.6	- 0.9-13.4	- 0.060
Distance from entry point (mm) ≤20	276	190 (97.9) 74 (90.2)	4 (2.1) 8 (9.8)	1 5.1	- 1.5-	- **0.009**	1 9.7	- 2.0-	- **0.005**

>20					17.6			47.1	
Procedure variables									
Needle size 18G 20G	250 (26 missing	95 (99.0) 145 (94.2)	1 (1.0) 9 (5.8)	1 5.9	- 0.7-47.3	- 0.095			
Needle-entry angle (degrees) 71-109 0-70 or 110-180	270 (6 missing)	128 (97.7) 131 (94.2)	3 (2.3) 8 (5.8)	1 2.6	- 0.7-10.0	- 0.164			
Needle repositioning count 2+ <2	265 (11 missing)	22 (100) 232 (95.5)	0 (0) 11 (4.5)	1 1.1	- 1.0-1.1	- 0.607			
Number of pleura crossings 1 2+	266 (10 missing)	239 (96.4) 16 (88.9)	9 (3.6) 2 (11.1)	1 3.3	- 0.7-16.7	- 0.145			
Number of samples 4+ <4	224 (52 missing)	45 (95.7) 169 (95.5)	2 (4.3) 8 (4.5)	1 1.1	- 0.2-5.2	- 0.938			
Procedure duration (min) ≤10 >10	270 (6 missing)	158 (97.5) 101 (93.5)	4 (2.5) 7 (6.5)	1 2.7	- 0.8-9.6	- 0.115			
Radiologist Junior Senior	266 (10 missing)	45 (95.7) 209 (95.4)	2 (4.3) 10 (4.6)	1 1.1	- 0.2-5.1	- 0.926			

TTLB, transthoracic lung biopsy; PTX, pneumothorax; OR, odds ratio; 95% CI, 95% confidence interval; PFT, pulmonary function testing; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe.

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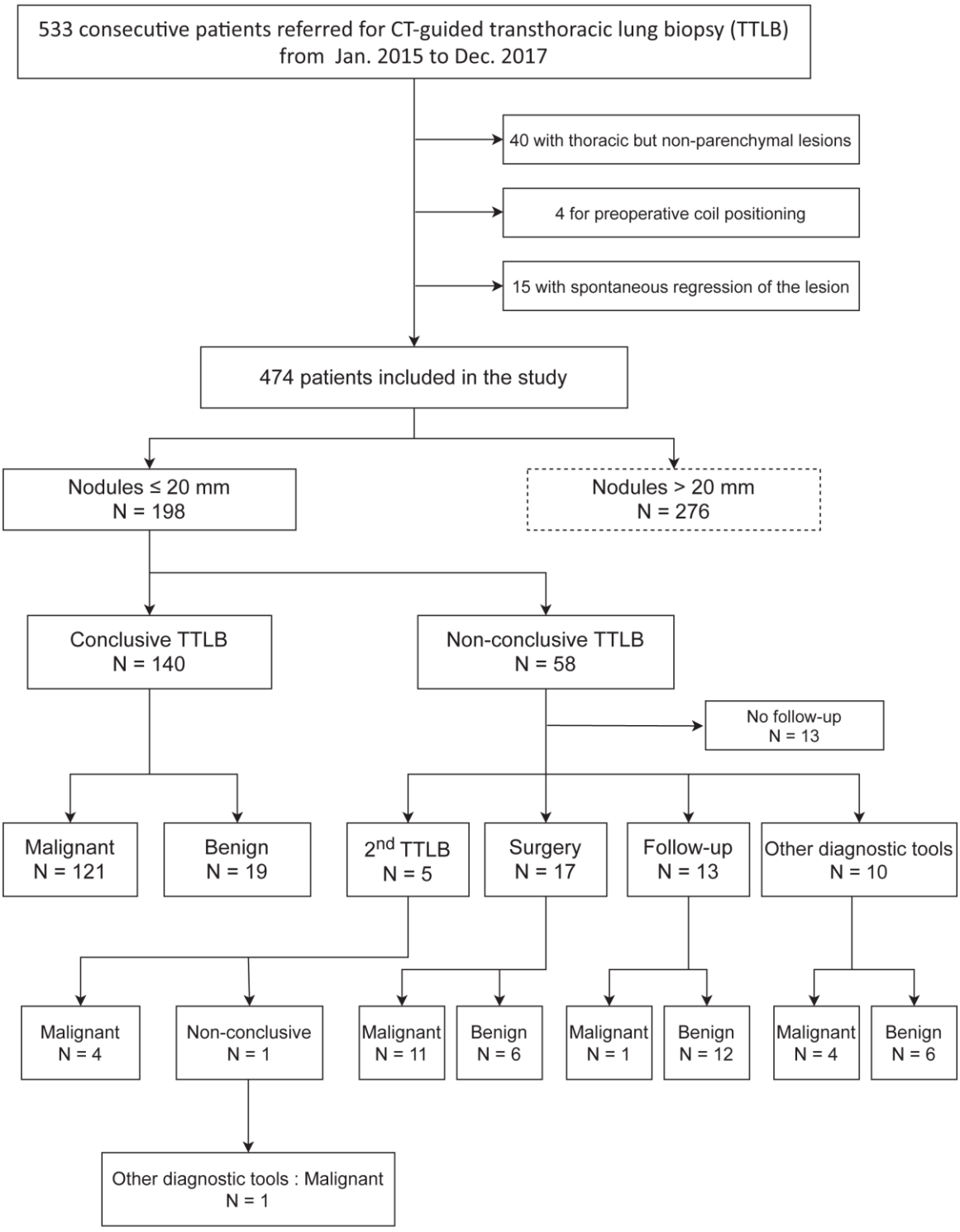
Figure Legend



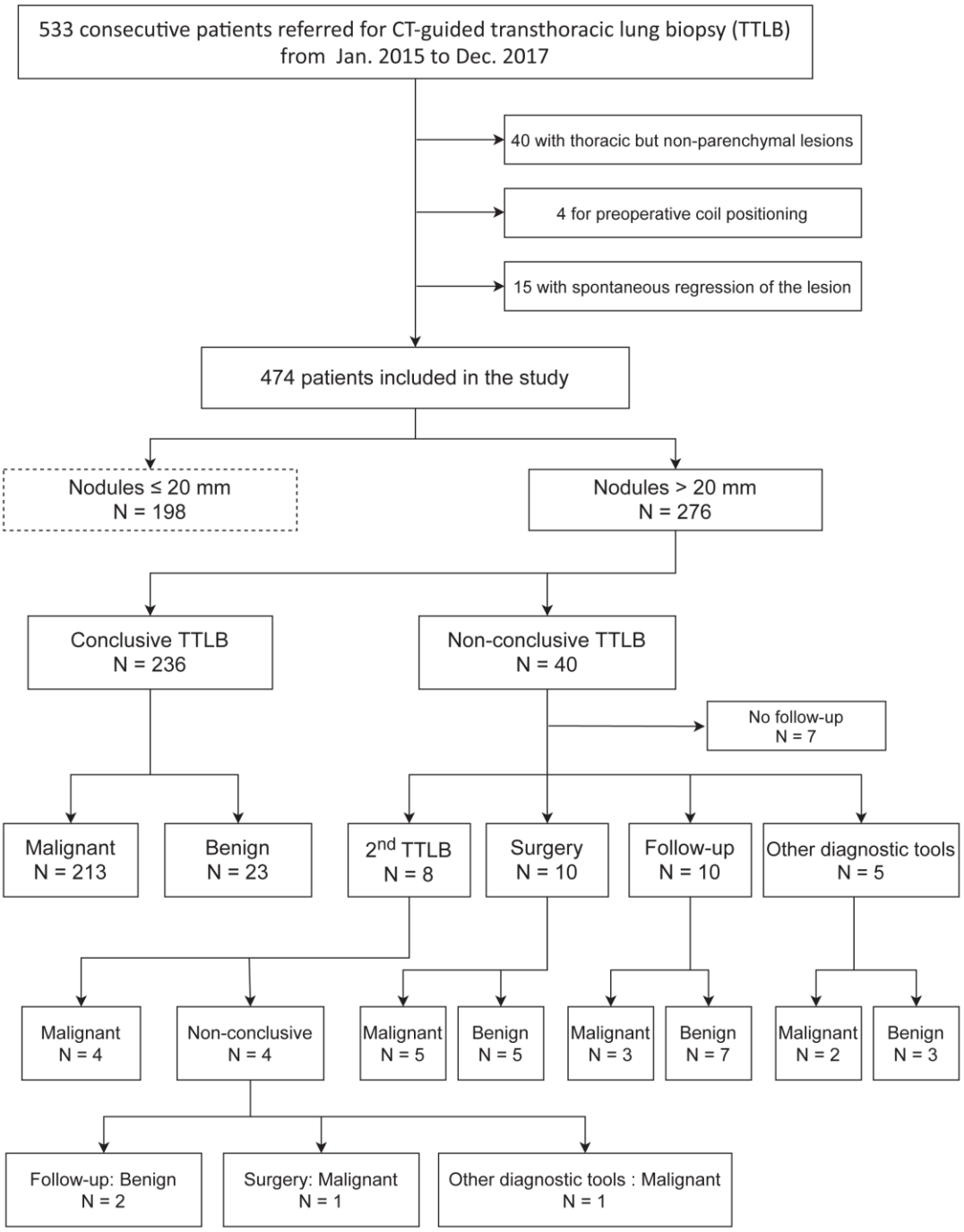


Figure 1 – *Patient disposition.*

Supplementary Table 1 – Procedure conclusiveness and performance following second TTLB

Variable / Performance measure	N	All patients	Nodule size		P
			≤ 20 mm	> 20 mm	
Procedure conclusiveness					
Conclusive pathology results following two TTLBs Yes No	474	384 (81.0) 90 (19.0)	144 (72.7) 54 (27.3)	240 (87.0) 36 (13.0)	**$< 10^{-4}$**
Diagnosis of malignancy following two TTLBs (when either TTLB is conclusive) Yes No	384	342 (89.1) 42 (10.9)	125 (86.8) 19 (13.2)	217 (90.4) 23 (9.6)	0.272
Performance for the diagnosis of malignancy following two TTLBs					
Se (%)		91.7	86.8	94.8	NA
Sp (%)		100	100	100	
Acc (%)		93.5	90.4	95.7	
PPV (%)		100	100	100	
NPV (%)		76.5	74.0	79.7	
F1 score (%)		95.7	92.9	97.3	

TTLB, transthoracic lung biopsy; NA, not applicable; NS, not significant; Se, sensitivity / recall; Sp, specificity / selectivity; Acc, accuracy; PPV, positive predictive value / precision; NPV, negative predictive value; F1 score, harmonic mean of sensitivity and precision; PTX, pneumothorax; IAH, intra-alveolar hemorrhage.